Pharmaceutical Press

Martindale

Thirty-sixth edition

THE COMPLETE DRUG REFERENCE

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Martindale

The Complete Drug Reference

Thirty-sixth edition

Edited by

Sean C Sweetman

BPharm, FRPharmS

London • Chicago **Pharmaceutical Press**

Published by the Pharmaceutical Press
An imprint of RPS Publishing

1 Lambeth High Street, London SEl 7JN, UK
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

RPS Publishing is the publishing organisation of the Royal Pharmaceutical Society of Great Britain

First edition of *Martindale: The Extra Pharmacopoeia* was published in 1883. *Squire's Companion* was incorporated in the twenty-third edition in 1952.

Thirty-sixth edition published 2009

Printed in China by Everbest Printing Co. Ltd

ISBN 978 0 85369 840 1

ISSN 0263-5364

A catalogue record for this book is available from the British Library

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Preface

The aim of Martindale is to provide healthcare professionals with unbiased evaluated information on drugs and medicines used throughout the world. It therefore has to develop as the body of knowledge on existing drugs grows, new drugs emerge, new preparations are launched, and old preparations are abandoned, reformulated, or redefined. It also has to reflect the changing needs of those practising pharmacy and medicine. We try to ensure that each new edition continues to meet all these needs.

In order to provide more up-to-date information the interval between the publication of the printed versions of Martindale has been reduced over successive editions and the book is now produced about every 2 years. For those who require even more up-to-date information from Martindale there are various electronic versions, sections of which are updated more frequently.

The year 2008 saw the publication of the third Spanish edition of Martindale, the translation having again been undertaken by our colleagues at Grupo Ars XXI, and also saw the appearance of the first edition of a Chinese language version of Martindale.

Martindale has been continuously expanded since it was first published in 1883, and to present all the extra information this edition of Martindale maintains the recent return to a two-volume publication. The first volume contains this preface and the drug monographs, and the second holds the proprietary preparations and the index, as well as manufacturers' contact information.

As always the contents have been extensively revised, with all the text scanned and revalidated where necessary by a team of experienced pharmacists. Over 260 monographs have been added, and 89 removed from the book (abbreviated information on the latter remains available in the electronic versions). In our continuing attempts to improve the clinical relevance of the book, the chapters on Prostaglandins and Hypothalamic and Pituitary Hormones have been split up and most of their contents added to new chapters on Obstetric Drugs and Growth Hormone and its Modulators. The chapter on Sex Hormones has been reorganised and renamed Sex Hormones and their Modulators.

The disease treatment reviews, 668 in all and generally located in the chapter introductions, have also been revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

Martindale contains much nomenclature information intended to assist the reader in identifying a particular drug or compound, and for this edition we have again greatly expanded our coverage of synonyms, with the addition of names from Poland and Turkey, and increased coverage of Russian synonyms and 'street names' for substances of abuse. Coverage of ATC codes has been expanded to include codes assigned to veterinary medicines

This edition of Martindale also sees the number of graphical representations of the chemical structures increased.

The information on proprietary preparations, an important feature of Martindale, has been updated and more countries have been covered for this edition.

Martindale is based on published information and more than 47 700 selected references are included. The amount of drug information now published electronically has increased significantly since the last printed edition of Martindale and this edition now includes nearly 2700 citations to material available on the Internet as web pages. Because of the nature of the Internet, there is no way to guarantee that the material referred to by a URL will remain at that location, as many sites are subject to periodic reorganisation; additionally, the content of Internet documents may change without warning. All URLs in Martindale are rechecked shortly before publication to ensure that a document is present. The accession date given in the citation represents the last date on which the content of the document referred to was revalidated.

Our objective is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. Multicentre studies, meta-analyses, and systematic reviews play an important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate. In compiling the text of a Martindale monograph extensive use is made of the drug's licensed product information as published in various countries and approved by the relevant regulatory health bodies. Acknowledgement is also given to information referenced from a number of authoritative sources including the *British National Formulary*, the *British National Formulary for Children*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, the *United States National Formulary*, and the *United States Pharmacopeia*.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Philosophy and methodology

Martindale's uses are as varied as its users. However, our primary aims are:

- to summarise clinically useful information on all drugs and medicines around the world
- to provide accurate, unbiased, reasonably comprehensive, and regularly re-evaluated information in a concise format
- to provide a lead-in to the published evidence base from which we derive our information

In order to achieve the aims specified above, our working practices have to optimise internal knowledge management.

MARTINDALE STAFF. Martindale is currently produced by a team of 21 people, 18 of whom are pharmacists or pharmacy technicians with relevant expertise. The team is divided into 5 revising groups each of 2 staff editors, as well as 5 assistant editors, 1 editor-in-chief, a co-ordinator for the processing of information on proprietary medicines, and 4 clerical and support staff. A number of pharmacists work as external evaluators to maintain coverage of non-UK preparations.

Staff editors receive formal training in literature evaluation and searching techniques, as well as specific, 'on-the-job' training in internal procedures. Each revision team has responsibility for the re-evaluation and update of a particular group of chapters. Senior editorial staff edit and approve the output of the teams. Staff are responsible for ongoing data collection as well as the revision process.

DATA COLLECTION. In order to reduce the amount of formal data collection required at revision, a prospective data-collection roster is in operation. This involves all staff members in hand-searching selected major medical journals, as well as regular searches of the internet sites of regulatory authorities (EMEA, FDA, and MHRA), and sources of high-quality systematic reviews and guidelines (such as Bandolier, Clinical Evidence, Cochrane, and NICE), for drug information. In addition, pharmacopoeial, governmental and WHO publications are hand-searched for information relating to drugs and drug therapy.

The list of sources used has been iteratively developed over many years by analysis of previous citations, and is reviewed and updated regularly.

PROPRIETARY PREPARATIONS. The Martindale proprietary preparations team evaluate licensed product information for 40 countries and regions, in order to maintain the widest possible coverage of drugs in use internationally. Preparation names, manufacturers, ingredients, and licensed uses are included in the internal Martindale database for review during the revision process, and any significant additional information is forwarded to the relevant revision team.

REVISION. In order to maintain the quality and currency of our content, it is constantly revised and updated. Our revision processes cover both scheduled, in-depth revision of the content of every chapter in the book on a chapter-by-chapter basis, and updates in reaction to new information as it arrives. The revision procedure involves the formalised re-evaluation of all standing information, the assessment of new collected references for quality and relevance, and the selective use of search techniques on bibliographic databases and the Internet to identify further candidate information.

CHECKING. Once the material for a given chapter has been re-evaluated and updated it undergoes a rigorous check, designed to ensure not only that all changes are valid and appropriate, but also that important points have not been missed.

EDITING. The chapter is then passed to a member of the senior editorial staff, who performs a second check and preliminary editing of the data. This process is designed to ensure consistency of approach and style, as well as offering an opportunity to pick up any errors missed at the first check. Changes and questions are fed back to the revision team in an iterative process that may involve more than one cycle. Once past its preliminary edit the chapter is sent to the Editor for a final check and approval, which again may require changes to be made and checked, before passing it to the next stage.

KEYING, PROOF-READING, AND DOSE-CHECKING. Once approved by the Editor, amendments can be incorporated into the database, which remains untouched until this stage as a security measure. These changes are then proofread for errors, corrected if necessary, and any corrections checked. Extensive electronic testing for spelling, style, and format is also carried out at all stages. The amended chapter then undergoes an independent check of the dose information against its recorded sources. This check is performed by a member of staff outside the original revising and editing team, and is an additional safeguard against the inadvertent introduction of potentially dangerous dose errors. Once past these stages the data are cleared for release, and can be published in the next update of the Martindale electronic products, and, at appropriate points in the publishing cycle, in the book.

ADDITIONAL CHECKS FOR PUBLICATION. Some additional checks are made before publishing a print edition of Martindale. An second independent dose check of all chapters is made by an external expert, all cross-references are revalidated, and tests of the typesetting and page structure are made. In addition our extensive index is generated and carefully checked for accuracy, order, and consistency.

FEEDBACK. We are always grateful to get feedback from our users and, whenever possible, we try to incorporate information or suggestions that help us to improve Martindale. Anyone wishing to comment on the editorial content of Martindale can contact us at the following e-mail address: martindale@rpsgb.org

Arrangement

VOLUME 1: • MONOGRAPHS ON DUGS AND ANCILLARY SUBSTANCES (pages 1–2418). This section contains 5827 monographs arranged in 54 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease may contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments.The last chapter in this section consists of a series of monographs arranged in the alphabetical order of their main titles. It includes monographs on drugs not easily classified, on herbals, and on drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

VOLUME 2: • PREPARATIONS (pages 2191–2880). This section contains over 146 000 proprietary preparations from a range of countries and regions. For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, the United Arab Emirates, UK, USA, and Venezuela. We have also included some proprietary preparations from Japan. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.

• DIRECTORY OF MANUFACTURERS (pages 3205–3274). In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address and website if it is available. This directory contains nearly 13 000 entries.

• GENERAL INDEX (pages 3275–3694). To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from 153 000 entries, includes entries for drugs (approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page. To improve clarity and the ease of location of index entries long chemical names have been omitted from the index.

This edition includes both nonproprietary and proprietary names in Russian, and these names may be found in Russian alphabetical order in the Cyrillic section of the index immediately following the entries in the Latin alphabet.

Nomenclature

TITLES AND SYNONYMS. The title of each monograph is in English, with preference usually being given to International Nonproprietary Names (INN), British Approved Names (BAN), and United States Adopted Names (USAN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requires the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Community and where the BAN and INN differed in the past the BAN has been changed to accord with the rINN. The major exception to this convention is the retention of the names adrenaline and noradrenaline, these being the terms used as the titles of the monographs in the European Pharmacopoeia and therefore the official names in the member states. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. Inevitably there may be some inconsistencies of style with older approved names but wherever possible the names used for drugs or radicals in Martindale have been altered in accordance with the guidelines on the use of INNs for pharmaceutical substances. A table of contracted names for ions and groups used in approved names and titles is given on page xi. INNs in the four other main official languages (French, Latin, Russian, and Spanish) have also been included in the list of synonyms where these differ from the English INN. BAN names for substance combinations and United States Pharmacy Equivalent Names (PEN) for dosage forms containing two or more active ingredients are given in the text of the relevant monographs; these names start with the prefix 'Co-'.

This section also includes names given as synonyms such as commonly used abbreviated names; Latin versions of the titles in the European Pharmacopoeia; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. Official titles and synonyms used in the British, European, and US Pharmacopoeias are given in the section on pharmacopoeias where the relevant pharmacopoeial substance is described.

STREET NAMES. This edition of Martindale once again includes greatly expanded coverage of 'street names' for substances of abuse. Street terms and other slang names for drugs of abuse are included for guidance only and should be used with caution. Because of the very nature of their origin they cannot be relied upon for definitive identification of a substance. The use of such terms changes rapidly, and can vary between different geographical locations, and any given name may potentially be applied to more than one substance or even to a mixture of substances. Furthermore, established or well recognised generic drug names or herbal names have sometimes been misused as street terms for completely unrelated substances. In order to enable the reader to distinguish them from better validated synonyms, in the index, such names are included in italics and in quotation marks.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

ATC CODES. Codes from the Anatomical Therapeutic Chemical (ATC) classification system (see http://www.whocc.no) have been provided, where available, for each monograph substance to help readers refer to other information systems. The codes assigned in the equivalent classification system for veterinary medicines (ATC Vet—see http://www.whocc.no/atcvet) have been included where possible.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 2007 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry (IUPAC) and based on the ^{12}C scale (see page xiii). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. A description of the substance and a summary of the pharmaceutical information (see below) that appears in the British, European, or US Pharmacopoeias is also included. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: *British, British Veterinary, Chinese, European, French, German, International, Italian, Japanese, Polish, Spanish, Swiss, United States* (including the *National Formulary*), and *Vietnamese*. The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page viii, which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the Former Yugoslav Republic of Macedonia. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British, European, and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. The term ‘a cool place’ is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Drugs in Sport

Wherever possible we have attempted to indicate those drugs and substances that may be subject to restriction in some or all sports, either in their own right, or because they are a derivative of a restricted substance or a member of a prohibited group. Proprietary preparations containing such compounds are also marked in the preparation section in Volume 2. The definitive guide used for identifying restricted drugs for this edition is the 2008 Prohibited List issued by the World Anti-Doping Agency (WADA—see www.wada-ama.org). However, these regulations, which are issued annually, are subject to interpretation and therapeutic exemption, and may vary from sport to sport; particular sporting authorities may also issue additional restrictions, and competitors should always check with the appropriate body. The rules are constantly evolving and the absence of any indication of restriction in Martindale should not be taken as absolute confirmation that the substance may legitimately be taken by a competitor.

Pharmacological and Therapeutic Information

Information on adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains about 15 000 such abstracts or reviews based on information in an ever widening range of publications.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Licensed product information and manufacturers' literature has been considered in the light of other available information.

The risks of giving drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Some drugs given to the mother are distributed into breast milk and therefore may pose a risk to a breast-fed infant. Whenever possible, information has been included to help determine the safety of continuing to breast feed while the mother is receiving a particular drug. Safety during breast feeding should not be inferred from the absence of a statement for any drug.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when given by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are also due to K Baxter, M Jane, CR Lee, DK Mehta, F Post, and AB Prasad, for advice and comments on specific issues during revision. The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization, the British Pharmacopoeia Commission, and our Spanish colleagues at Grupo Ars XXI.

Martindale staff have been able to call on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to J Martin and the staff of the British National Formulary, and the staff of the library and information department. Thanks are due to I Baxter, M Davis, S Driver, EJ Laughton, R McLarney, and SJ Shankie for their editorial tasks. Thanks are also due to PJ Weller, C Fry and the staff of the Pharmaceutical Press for their support.

The contents of this 36th edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor is pleased to acknowledge the skills and commitment of all the Martindale staff and to record his gratitude: to Christine Iskandar for clerical assistance; to Michael Evans for Knowledge Systems support; to Chloë Hatwal, Elizabeth King, James O’Reilly, and Elen Shute for editorial assistance; to the Staff Editors Catherine Cadart, Kathleen Eager, Sue Handy, Fauziah Hashmi, Sue Ho, Joanna Humm, Jean Macpherson, Melissa Siew, Sandra Sutton, and Gerda Viedge; to the Assistant Editors Alison Brayfield, Julie McGlashan, Gail Neathercoat, and Anne Parsons; and to the Senior Assistant Editor Paul Blake.

London October 2008

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, page 3205.

ACE—angiotensin-converting enzyme.
ADHD—attention deficit hyperactivity disorder.
agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.
AIDS—acquired immunodeficiency syndrome.
a.m.—*ante meridiem*, 'before noon'.
ARC—AIDS-related complex.
Arg.—Argentina.
ATC—Anatomical Therapeutic Chemical classification.
AUC—area under the concentration-time curve.
Austral.—Australia.
AV—atrioventricular.
BAN—British Approved Name.
BANM—British Approved Name Modified.
Belg.—Belgium.
BMA—British Medical Association.
BMI—body mass index.
BNF—British National Formulary.
BNFC—British National Formulary for Children.
b.p.—boiling point.
BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 2008 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2008.
BPC—British Pharmaceutical Codex.
Br.—British.
Braz.—Brazil.
Bulg.—Bulgaria.
BUN—Blood-urea-nitrogen.
°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.
Canad.—Canada.
CAPD—continuous ambulatory peritoneal dialysis.
CAS—Chemical Abstracts Service.
CCPD—continuous cycle peritoneal dialysis.
CDC—Centers for Disease Control and Prevention (USA) (formerly Centers for Disease Control).
Chin. P.—Chinese Pharmacopoeia 2005.
CHM—Commission on Human Medicines (UK).
CI—Colour Index.
CMV—cytomegalovirus.
CNS—central nervous system.
cP—centipoise(s).
CPMP—Committee on Proprietary Medicinal Products of the European Union.
CSF—cerebrospinal fluid.
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines).
cSt—centistokes.
Cz.—Czech Republic.
D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.
d.c.—direct current.
DEFRA—Department for Environment, Food, and Rural Affairs (UK).
Denm.—Denmark.
DHSS—the former Department of Health and Social Security (UK).
dL—decilitre(s).
DNA—deoxyribonucleic acid.
DoH—Department of Health (UK).
DTF—Drug Tariff Formulary.
ECG—electrocardiogram.
ECT—electroconvulsive therapy.
Ecuad.—Ecuador.
ed.—editor(s) *or* edited by *or* edition.
EEC—European Economic Community, now the European Union.
EEG—electro-encephalogram.
e.g.—*exempli gratia* 'for example'.
EMEA—European Medicines Agency.
ENL—erythema nodosum leprosum.
ESRD—end-stage renal disease.
et al.—*et alii*, 'and others': for three or more co-authors or co-workers.
et seq.—and what follows.
EU—European Union.
Eur. P.—see Ph. Eur.
Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.
°F—degrees Fahrenheit.
FAC—Food Additives and Contaminants Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FAO—Food and Agriculture Organization of the United Nations.
FAO/WHO—Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FDA—Food and Drug Administration of USA.
FdAC—Food Advisory Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FEV_1—forced expiratory volume in 1 second.
Fin.—Finland.
FIP—Fédération Internationale Pharmaceutique.
f.p.—freezing point.
FPA—Family Planning Association (UK).
Fr.—France.
Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Francaise, X^e Edition) and updates up to 2003.
g—gram(s).
Ger.—Germany.
Ger. P.— German Pharmacopoeia (Deutsches Arzneibuch, 2007).
GFR—glomerular filtration rate.
G6PD—glucose-6-phosphate dehydrogenase.
Gr.—Greece.
HAART—highly active antiretroviral therapy.
Hb— haemoglobin.
Hib—*Haemophilus influenzae* type b.
HIV—human immunodeficiency virus.
HLA—human lymphocyte antigens.
HLB—hydrophilic-lipophilic balance.

HRT—hormone replacement therapy.
HSE—Health and Safety Executive (UK).
Hung.—Hungary.
IARC—International Agency for Research on Cancer.
ibid.—*ibidem*, 'in the same place (journal or book)'.
idem—'the same': used for the same authors and titles.
i.e.—*id est*, 'that is'.
Ig—immunoglobulin.
Indon.—Indonesia.
INN—International Nonproprietary Name.
INNM—International Nonproprietary Name Modified.
Int. P.—International Pharmacopoeia 4th ed., 2006.
IPCS—International Programme on Chemical Safety.
IQ—intelligence quotient.
Irl.—Ireland.
ISH—International Society of Hypertension.
It. P.—Italian Pharmacopoeia 11th ed., 2002 (Farmacopea Ufficiale della Repubblica Italiana, XI Edizione, 2002).
Ital.—Italy.
IUD—intra-uterine device.
IUPAC—International Union of Pure and Applied Chemistry.
IVF—*in-vitro* fertilisation.
J—joule(s).
Jpn—Japan.
Jpn P.—The Pharmacopoeia of Japan, 15th ed., 2006.
K—kelvin.
kcal—kilocalorie(s).
kg—kilogram(s).
kJ—kilojoule(s).
lb—pound(s) avoirdupois.
LD50—a dose lethal to 50% of the specified animals or micro-organisms.
m—metre(s).
m^2—square metre(s).
m^3—cubic metre(s).
M—molar.
MAFF—the former Ministry of Agriculture, Fisheries and Food (UK), now Department of Environment, Food, and Rural Affairs (DEFRA).
MAOI—monoamine oxidase inhibitor.
max.—maximum.
MBC—minimum bactericidal concentration.
MCA—Medicines Control Agency, now MHRA (UK).
mEq—milliequivalent(s).
Mex.—Mexico.
mg—milligram(s).
MHRA—Medicines and Healthcare products Regulatory Agency (UK).
MIC—minimum inhibitory concentration.
min—minute.
min.—minimum.
MJ—megajoule(s).
mL—millilitre(s).
mm—millimetre(s).
mm^2—square millimetre(s).
mm^3—cubic millimetre(s).
mmHg—millimetre(s) of mercury.
mmol—millimole.
mol—mole.
mol. wt—molecular weight.
Mon.—Monaco.
mosmol—milliosmole.
m.p.—melting point.
MRC—Medical Research Council (UK).
MRSA—meticillin-resistant *Staphylococcus aureus*.
μg—microgram(s).
μm—micrometre(s).
Neth.—The Netherlands.
NICE—National Institute for Health and Clinical Excellence (formerly the National Institute for Clinical Excellence) (UK).
NIH—National Institutes of Health (USA).
nm—nanometre(s).
NMDA—*N*-methyl-D-aspartate.
NNRTI—non-nucleoside reverse transcriptase inhibitor.
Norw.—Norway.
NRTI—nucleoside reverse transcriptase inhibitor.
NSAID—nonsteroidal anti-inflammatory drug.
NYHA—New York Heart Association.
NZ—New Zealand.
OP—over proof.
o/w—oil-in-water.
P—probability.
Pa—pascal(s).
pCO_2—plasma partial pressure (concentration) of carbon dioxide.
p_aCO_2—arterial plasma partial pressure (concentration) of carbon dioxide.
PEN—Pharmacy Equivalent Name, see page vi.
pg—picogram(s).
pH—the negative logarithm of the hydrogen ion concentration.
Ph. Eur.—European Pharmacopoeia, 6th ed., 2008 and Supplements 6.1 and 6.2.
Pharm. Soc. Lab. Rep.—Royal Pharmaceutical Society's Laboratory Report.
Philipp.—Philippines.
PHLS—Public Health Laboratory Service (UK).
pINN—Proposed International Nonproprietary Name.
pINNM—Proposed International Nonproprietary Name Modified.
pK_a—the negative logarithm of the dissociation constant.
p.m.—*post meridiem*, 'afternoon'.
pO_2—plasma partial pressure (concentration) of oxygen.
p_aO_2—arterial plasma partial pressure (concentration) of oxygen.
Pol.—Poland.
Pol. P.—Polish Pharmacopoeia 6th ed., 2002 (Farmakopea Polska VI, 2002) and Supplement 2005.
Port.—Portugal.
ppm—parts per million.
PSGB—The Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society of Great Britain.
PUVA—psoralen with UVA light irradiation.
PVC—polyvinyl chloride.
RCGP—Royal College of General Practitioners (UK).
RIMA—reversible inhibitor of monoamine oxidase type A.
rINN—Recommended International Nonproprietary Name.
rINNM—Recommended International Nonproprietary Name Modified.
RNA—ribonucleic acid.
RPSGB—The Royal Pharmaceutical Society of Great Britain.
RSV—respiratory syncytial virus.
S. Afr.—South Africa.
SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).

SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).
SI—Statutory Instrument *or* Système International d'Unités (International System of Units).
sic—written exactly as it appears in the original.
SLE—systemic lupus erythematosus.
sp.—species (plural spp.).
sp. gr.—specific gravity.
Span.—Spanish.
Span. P.—Spanish Pharmacopoeia 2nd ed., 2002 (Real Farmacopoea Española, Segunda Edición, 2002) and Supplement 2.1.
SSRI—selective serotonin reuptake inhibitor.
St—stokes.
subsp.—subspecies.
suppl—supplement(s).
Swed.—Sweden.
Swiss P.—Swiss Pharmacopoeia 2006 (Pharmacopoea Helvetica, 10 Ausgabe, Deutsche Ausgabe).
Switz.—Switzerland.
Thai.—Thailand.
TNF—tumour necrosis factor.
TPN—total parenteral nutrition.
Turk.—Turkey.
UAE—United Arab Emirates.
UK—United Kingdom.
UNICEF—United Nations Children's Fund.
UP—under proof.
Urug.—Uruguay.
US and ***USA***—United States of America.
USAN—United States Adopted Name.
USNF—The United States 'National Formulary 26', 2008, and Supplements 1 and 2.
USP—The United States Pharmacopeia 31, 2008, and Supplements 1 and 2.
UV—ultraviolet.
var.—variety.
Venez.—Venezuela.
Viet.—Vietnamese.
Viet. P.—Vietnamese Pharmacopoeia 2002 (Pharmacopoeia Vietnamica, Editio III).
vol.—volume(s).
v/v—volume in volume.
v/w—volume in weight.
WHO—World Health Organization.
w/o—water-in-oil.
wt—weight.
wt per mL—weight per millilitre.
w/v—weight in volume.
w/w—weight in weight.

Contracted Names for Ions and Groups

Contracted Name	Chemical Name
acefurate	acetate (ester) and furan-2-carboxylate (ester)
aceglumate	*rac*-hydrogen *N*-acetylglutmate
aceponate	acetate (ester) and propionate (ester)
acetonide	isopropylidenedioxy or propane-2,2-diylbis(oxy)
aceturate	*N*-acetylglycinate
acibutate	acetate (ester) and 2-methylpropanoate (ester)
acistrate	acetate (ester) and stearate (salt)
acoxil	acetoxymethyl or (acetyloxy)methyl
alfoscerate	(2*R*)-2,3-dihydroxypropyl hydrogen phosphate
alideximer	poly([oxy(2-hydroxyethane-1,1-diyl)]{oxy[1-(hydroxymethyl)ethane-1,2-diyl]}) partly *O*-etherified with carboxymethyl groups with some carboxy groups amide linked to the tetrapeptide residue (glyglyglycyl-L-phenylalanylglycyl)
amsonate	4,4′-diaminostilbene-2,2′-disulfonate or 2,2′-ethene-1,2-diylbis(5-aminobenzene-1-sulfonate)
anisatil	2-(4-methoxyphenyl)-2-oxoethyl or *p*-methoxyphenacyl
arbamel	2-(dimethylamino)-2-oxoethyl or ester with *N*,*N*-dimethylglycolamide
argine	30^{B}α–L-argine-30^{B}β-L-argine
aritox	ricin A chain-MAB immunotoxine
aspart	28^{B}-L-aspartic acid-
axetil	(*RS*)-1-acetoxyethyl or *rac*-1-(acetyloxy)ethyl
beloxil	benzyloxy
benetonide	*N*-benzoyl-2-methyl-β-alanine (ester) and acetonide
besilate (besylate)	benzenesulfonate
betadex	β-cyclodextrin
bezomil	(benzoyloxy)methyl
buciclate	*trans*-4-butylcyclohexanecarboxylate
bunapsilate	3,7-di-*tert*-butylnaphthalene-1,5-disulfonate
buteprate	butyrate (ester) and propionate (ester)
camsilate (camsylate)	camphor-10-sulfonate or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate
caproate	hexanoate
carbesilate	4-sulfobenzoate
ciclotate (cyclotate)	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate
cilexetil	(*RS*)-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl or *rac*-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl
cipionate (cypionate)	cyclopentanepropionate or 3-cyclopentylpropanoate
cituxetan	*rac*-*N*-(4-{2-[bis(carboxymethyl)amino]-3-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)propyl}phenyl)thiocarbamoyl
clofibrol	2-(4-chlorophenoxy)-2-methylpropyl
closilate (closylate)	4-chlorobenzene-1-sulfonate
crobefate	*rac*-{3-[(3*E*)-4-methoxybenzylidene]-2-(4-methoxyphenyl)chroman-6-yl phosphate(2-)}
cromacate	2-[(6-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate
cromesilate	6,7-dihydroxycoumarin-4-methanesulfonate or (6,7-dihydroxy-2-oxo-2*H*-chromen-4-yl)methanesulfonate
crosfumaril	(2*E*)-but-2-enedioyl
cyclamate	cyclohexylsulfamate
daloxate	L-alaninate (ester) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
daropate (dapropate)	*N*,*N*-dimethyl-β-alaninate or 3-(dimethylamino)propanoate
deanil	2-(dimethylamino)ethyl
decil	decyl
defalan	des-1^{B}-L-phenylalanine-insulin
detemir	tetradecanoyl
dibudinate	2,6-di-*tert*-butylnaphthalene-1,5-disulfonate
dibunate	2,6-di-*tert*-butylnaphthalene-1-sulfonate
dicibate	dicyclohexylmethyl carbonate
diftitox	*N*-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388→2′)-protein
digolil	2-(2-hydroxyethoxy)ethyl
diolamine	2,2′-azanediyldiethanol or diethanolamine
docosil	docosyl
dofosfate	octadecyl hydrogen phosphate
ecamate	*N*-ethylcarbamate
edamine	ethane-1,2-diamine or ethylenediamine
edetate	ethylenediamine-*NNN′N′*-tetra-acetate
edisilate (edisylate)	ethane-1,2-disulfonate
embonate	4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate) or 4,4′-methylenebis(3-hydroxy-2-naphthoate) (=pamoate)
enantate (enanthate)	heptanoate
enbutate	acetate (ester) and butanoate (ester)
epolamine	1-pyrrolidineethanol or 2-(pyrrolidin-1-yl)ethanol
erbumine	*tert*-butylamine or 2-methylpropan-2-amine
esilate (esylate)	ethanesulfonate
estolate	propanoate (ester) and dodecyl sulfate (salt) or propionate dodecyl sulfate
etabonate	(ethoxycarbonyl)oxy (=ethyl carbonate)
etilsulfate	ethyl sulfate
farnesil	(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl
fendizoate	2-(6-hydroxybiphenyl-3-carbonyl)benzoate
fostedate	tetradecyl hydrogen phosphate
furetonide	1-benzofurane-2-carboxylate (ester) and propane-2,2-diylbis(oxy)
gamolenate	(6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate
glargine	21^{A}-glycine-30^{B}α-L-arginine-30^{B}β-L-arginine
gluceptate	D-*glycero*-D-*gulo*-heptanoate or D-*glycero*-D-*gulo*-heptonate
glulisine	[3^{B}-L-lysine,29^{B}-L-glutamic acid]
glutamer	glutaraldehyde polymer
guacil	2-methoxyphenyl
hemisuccinate	hydrogen butanedioate

Contracted Name	Chemical Name
hexacetonide	3,3-dimethylbutanoate (ester) and propan-2,2-diylbis(oxy) or 3,3-dimethylbutyrate (ester) and acetonide
hibenzate (hybenzate)	2-(4-hydroxybenzoyl)benzoate
hyclate	monohydrochloride hemi-ethanolate hemihydrate
hydroxynaphtoate	3-hydroxynapthalene-2-carboxylate
isetionate (isethionate)	2-hydroxyethane-1-sulfonate
laurate	dodecanoate
lauril	dodecyl
laurilsulfate (lauryl sulphate)	dodecyl sulfate
lisetil	L-lysinate (ester) and diethyl (ester)
lisicol	{*N*-[(5*S*)-5-carboxy-5-(3α,7α,12α-trihydroxy-5β-cholan-24-amido)pentyl]carbamothioyl}amino
lispro	28^{B}-L-lysine-29^{B}-L-proline
mafenatox	enterotoxin A (227-alanine) (*Staphylococcus aureus*)
medoxomil	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
megallate	3,4,5-trimethoxybenzoate
meglumine	*N*-methylglucamine
merpentan	4,5-bis(2-mercaptoacetamido) valeric acid or {*N*,*N*′-[1-(3-oxopropyl)ethane-1,2-diyl]bis(2-sulfanylacetamidato)}(4-)
mertansine	tetrakis{(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl}
mesilate (mesylate)	methanesulfonate
metembonate	4,4′-methylenebis(3-methoxynaphthalene-2-carboxylate)
methonitrate	*N*-methyl, nitrate (salt)
metilsulfate	methyl sulfate
metiodide	*N*-methyl, iodide (salt)
methylbromide	*N*-methyl, bromide (salt)
mofetil	2-(morpholino)ethyl or 2-(morpholin-4-yl)ethyl
napadisilate	naphthalene-1,5-disulfonate
napsilate (napsylate)	naphthalene-2-sulfonate
nicotinate	pyridine-3-carboxylate
octil	octyl
olamine	2-aminoethanol or ethanolamine
oleate	(9*Z*)-octadec-9-enoate
oxoglurate	hydrogen 2-oxopentanedioate
palmitate	hexadecanoate
pamoate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=embonate)
pegol	α-(2-carboxyethyl)-ω-methoxypoly(oxyethane-1,2-diyl)
pendetide	N^6-{*N*-[2-({2-[bis(carboxymethyl)amino]-ethyl}(carboxymethyl)amino)ethyl]-*N*-(carboxymethyl)glycyl}-N^2-(*N*-glycyl-L-tyrosyl)-L-lysine
pentexil	(*RS*)-1-[(2,2-dimethylpropanoyl)oxy]ethyl
phenpropionate	3-phenylpropionate
pivalate	2,2-dimethylpropanoate (ester) or trimethylacetate
pivoxetil	*rac*-1-[(2-methoxy-2-methylpropanoyl)oxy]ethyl or 1-(2-methoxy-2-methylpropionyloxy)ethyl
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or [(2,2-dimethylpropanoyl)oxy]methyl or (pivaloyloxy)methyl
poliglumex	[poly(L-glutamic acid)$_z$—(L-glutamate-γ-ester)—poly(L-glutamic acid)$_y$]$_n$
probutate	17-(1-oxobutoxy) (ester) and 21-(1-oxopropoxy) (ester) or propionate (ester) and butyrate (ester)
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl or *rac*-1-{[(propan-2-yloxy)carbonyl]oxy}ethyl
raffimer	(2*S*,4*R*,6*R*,8*S*,11*S*,13*S*)-2,4,8,13-tetrakis(hydroxymethyl)-4,6,11-tris(ylomethyl)-3,5,7,10,12-pentaoxatetradecane-1,14-diyl
salicylate	2-hydroxybenzoate
sesquioleate	(9*Z*)-octadec-9-enoate(1.5)
soproxil	{[(propan-2-yloxy)carbonyl]oxy}methyl
steaglate	2-(octadecanoyloxy)acetate (ester)
stearate	octadecanoate
stinoprate	*N*-acetylcysteinate (salt) and propanoate (ester)
succinil	3-carboxypropanoyl
sudotox	248-L-histidine-249-L-methionine-250-L-alanine-251-L-glutamic acid-248-613-endotoxin A (*Pseudomonas aeruginosa* reduced)
suleptanate	monosodium 8-[methyl(2-sulfoethyl)amino]-8-oxooctanoate or monosodium 7-[methyl(2-sulfonatomethyl)carbamoyl]heptanoyl
sulfoxylate	sulfinomethyl, monosodium salt
tafenatox	enterotoxin A (*Staphylococcus aureus*)
tartrate	(2*R*,3*R*)-2,3-dihydroxybutanedioate
tebutate	*tert*-butylacetate or 3,3-dimethylbutyrate
tenoate	thiophene-2-carboxylate
teoclate	8-chloro-1,3-dimethyl-2,6-dioxo-3,6-dihydro-1*H*-purin-7-(2*H*)-ide or 8-chlorotheophyllinate
teprosilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propane-1-sulfonate
tidoxil	*rac*-2-(decyloxy)-3-(dodecylsulfanyl)propyl
tiuxetan	*N*-(4-{(2*S*)-2-[bis(carboxymethyl)amino]-3-[(2*RS*)-{2-[bis(carboxymethyl)amino]propyl}(carboxymethyl)amino]propyl}phenyl) thiocarbamoyl
tocoferil	*rac*-(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-yl
tofesilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)ethane-1-sulfonate
tosilate (tosylate)	4-methylbenzene-1-sulfonate or toluene-4-sulfonate
triclofenate	2,4,5-trichlorophenolate
triflutate	trifluoroacetate
trioleate	(9*Z*)-octadec-9-enoate(3) or tris[(9*Z*)-octadec-9-enoate]
tristearate	octadecanoate(3) or tris(octadecanoate)
trolamine	2,2′,2″-nitrilotriethanol or triethanolamine
troxundate	[2-(2-ethoxyethoxy)ethoxy]acetate or 3,6,9-trioxaundecanoate
undecylate	undecanoate
undecylenate	undec-10-enoate
valerate	pentanoate
xinafoate	1-hydroxynaphthalene-2-carboxylate or 1-hydroxy-2-naphthoate

Atomic Weights of the Elements— $^{12}C=12$

Atomic Number	Name	Symbol	Atomic Weight
89	Actinium	Ac	*
13	Aluminium	Al	26.9815386
95	Americium	Am	*
51	Antimony	Sb	121.760
18	Argon	Ar	39.948
33	Arsenic	As	74.92160
85	Astatine	At	*
56	Barium	Ba	137.327
97	Berkelium	Bk	*
4	Beryllium	Be	9.012182
83	Bismuth	Bi	208.98040
107	Bohrium	Bh	*
5	Boron	B	10.811
35	Bromine	Br	79.904
48	Cadmium	Cd	112.411
55	Caesium	Cs	132.9054519
20	Calcium	Ca	40.078
98	Californium	Cf	*
6	Carbon	C	12.0107
58	Cerium	Ce	140.116
17	Chlorine	Cl	35.453
24	Chromium	Cr	51.9961
27	Cobalt	Co	58.933195
29	Copper	Cu	63.546
96	Curium	Cm	*
110	Darmstadtium	Ds	*
105	Dubnium	Db	*
66	Dysprosium	Dy	162.500
99	Einsteinium	Es	*
68	Erbium	Er	167.259
63	Europium	Eu	151.964
100	Fermium	Fm	*
9	Fluorine	F	18.9984032
87	Francium	Fr	*
64	Gadolinium	Gd	157.25
31	Gallium	Ga	69.723
32	Germanium	Ge	72.64
79	Gold	Au	196.966569
72	Hafnium	Hf	178.49
108	Hassium	Hs	*
2	Helium	He	4.002602
67	Holmium	Ho	164.93032
1	Hydrogen	H	1.00794
49	Indium	In	114.818
53	Iodine	I	126.90447
77	Iridium	Ir	192.217
26	Iron	Fe	55.845
36	Krypton	Kr	83.798
57	Lanthanum	La	138.90547
103	Lawrencium	Lr	*
82	Lead	Pb	207.2
3	‡Lithium	Li	6.941
71	Lutetium	Lu	174.9668
12	Magnesium	Mg	24.3050
25	Manganese	Mn	54.938045
109	Meitnerium	Mt	*
101	Mendelevium	Md	*
80	Mercury	Hg	200.59
42	Molybdenum	Mo	95.96
60	Neodymium	Nd	144.242
10	Neon	Ne	20.1797
93	Neptunium	Np	*
28	Nickel	Ni	58.6934
41	Niobium	Nb	92.90638
7	Nitrogen	N	14.0067

Atomic Number	Name	Symbol	Atomic Weight
102	Nobelium	No	*
76	Osmium	Os	190.23
8	Oxygen	O	15.9994
46	Palladium	Pd	106.42
15	Phosphorus	P	30.973762
78	Platinum	Pt	195.084
94	Plutonium	Pu	*
84	Polonium	Po	*
19	Potassium	K	39.0983
59	Praseodymium	Pr	140.90765
61	Promethium	Pm	*
91	†Protactinium	Pa	231.03588
88	Radium	Ra	*
86	Radon	Rn	*
75	Rhenium	Re	186.207
45	Rhodium	Rh	102.90550
111	Roentgenium	Rg	*
37	Rubidium	Rb	85.4678
44	Ruthenium	Ru	101.07
104	Rutherfordium	Rf	*
62	Samarium	Sm	150.36
21	Scandium	Sc	44.955912
106	Seaborgium	Sg	*
34	Selenium	Se	78.96
14	Silicon	Si	28.0855
47	Silver	Ag	107.8682
11	Sodium	Na	22.98976928
38	Strontium	Sr	87.62
16	Sulfur	S	32.065
73	Tantalum	Ta	180.94788
43	Technetium	Tc	*
52	Tellurium	Te	127.60
65	Terbium	Tb	158.92535
81	Thallium	Tl	204.3833
90	†Thorium	Th	232.03806
69	Thulium	Tm	168.93421
50	Tin	Sn	118.710
22	Titanium	Ti	47.867
74	Tungsten	W	183.84
112	Ununbium	Uub	*
116	Ununhexium	Uuh	*
118	Ununoctium	Uuo	*
115	Ununpentium	Uup	*
114	Ununquadium	Uuq	*
113	Ununtrium	Uut	*
92	†Uranium	U	238.02891
23	Vanadium	V	50.9415
54	Xenon	Xe	131.293
70	Ytterbium	Yb	173.054
39	Yttrium	Y	88.90585
30	Zinc	Zn	65.38
40	Zirconium	Zr	91.224

Elements marked (*) have no stable nuclides and IUPAC states "there is no general agreement on which of the isotopes of the radioactive elements is, or is likely to be judged 'important' and various criteria such as 'longest half-life', 'production in quantity', 'used commercially', etc., have been applied in the Commission's choice." However, atomic weights are given for radioactive elements marked (†) as they do have a characteristic terrestrial isotopic composition. Commercially available lithium (‡) materials have atomic weights ranging from 6.939 to 6.996; if a more accurate value is required, it must be determined for the specific material.

IUPAC Commission on Atomic Weights and Isotopic Abundances. Atomic Weights of the Elements 2007. Available at http://www.chem.qmul.ac.uk/iupac/AtWt/

Volume 1

Monographs on Drugs and Ancillary Substances

Analgesics Anti-inflammatory Drugs and Antipyretics

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The drugs described in this chapter are used mainly in the relief of pain, inflammation and, in some cases, fever. They can be grouped broadly into one of the categories briefly described below.

Aspirin and other salicylates

Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties. Like other NSAIDs (see below) they are inhibitors of the enzyme cyclo-oxygenase; however, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

For further discussion of the actions and uses of salicylates, see Aspirin, p.20.

Described in this chapter are

Aloxiprin, p.18
Aluminium Aspirin, p.19
Ammonium Salicylate, p.19
Amyl Salicylate, p.19
Aspirin, p.20
Bornyl Salicylate, p.28
Carbasalate Calcium, p.33
Choline Magnesium Trisalicylate, p.36
Choline Salicylate, p.36
Diethylamine Salicylate, p.47
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Ethyl Salicylate, p.52
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Glycol Salicylate, p.62
Imidazole Salicylate, p.66
Lithium Salicylate, p.77
Lysine Aspirin, p.79
Magnesium Salicylate, p.79
Methyl Butetisalicylate, p.85
Methyl Salicylate, p.85
Morpholine Salicylate, p.91
Salamidacetic Acid, p.121
Salicylamide, p.121
Salix, p.121
Salol, p.122
Salsalate, p.122
Sodium Salicylate, p.124
Sodium Thiosalicylate, p.124
Thurfyl Salicylate, p.129
Trolamine Salicylate, p.132

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory properties thought to be mediated, in some cases, by the inhibition of the release or activity of cytokines. They are used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis; some are also of benefit in ankylosing spondylitis and psoriatic arthritis. Many DMARDs also possess other therapeutic properties and are used in non-rheumatic conditions. The DMARD gold is referred to below; other DMARDs include sulfasalazine (p.1773), penicillamine (p.1456), the antimalarials chloroquine (p.599) and hydroxychloroquine (p.604), rituximab (p.767), and the immunosuppressants azathioprine (p.1818), ciclosporin (p.1822), cyclophosphamide (p.702), and methotrexate (p.745).

Described in this chapter are

Abatacept, p.14
Actarit, p.15
Adalimumab, p.15
Anakinra, p.19
Etanercept, p.50
Golimumab, p.62
Infliximab, p.69
Leflunomide, p.75

Gold compounds

Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p.122.

Described in this chapter are

Auranofin, p.25
Aurothioglucose, p.26
Aurotioprol, p.26
Gold Keratinate, p.62
Sodium Aurothiomalate, p.122
Sodium Aurotiosulfate, p.124

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of structurally unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties (see p.96). NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.2374). There are 2 forms of cyclo-oxygenase (COX), COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastrointestinal tract. Most of the NSAIDs currently available for clinical use inhibit both COX-1 and COX-2, although selective COX-2 inhibitors such as celecoxib are now available.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Indometacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders. Aspirin (see above) is considered to be an NSAID, although it also has other properties.

Described in this chapter are

Aceclofenac, p.14
Acemetacin, p.15
Alminoprofen, p.18
Aminophenazone, p.19
Aminopropylone, p.19
Ampiroxicam, p.19
Amtolmetin Guacil, p.19
Azapropazone, p.26
Bendazac, p.27
Benoxaprofen, p.27
Benzydamine, p.27
Beta-aminopropionitrile, p.28
Bromfenac, p.28
Bufexamac, p.28
Bumadizone, p.28
Butibufen Sodium, p.31
Carprofen, p.34
Celecoxib, p.34
Clofexamide, p.37
Clofezone, p.37
Clonixin, p.37
Dexibuprofen, p.39
Diclofenac, p.44
Dipyrone, p.49
Eltenac, p.50
Epirizole, p.50
Etodolac, p.52
Etofenamate, p.53
Etoricoxib, p.53
Felbinac, p.54
Fenbufen, p.54
Fenoprofen, p.55
Fentiazac, p.60
Fepradinol, p.60
Feprazone, p.60
Firocoxib, p.60
Floctafenine, p.60
Flufenamic Acid, p.60
Flunixin, p.61
Flurbiprofen, p.61
Furprofen, p.62
Glafenine, p.62
Glucametacin, p.62
Ibuprofen, p.64
Ibuproxam, p.66
Indometacin, p.66
Isonixin, p.72
Kebuzone, p.72
Ketoprofen, p.73
Ketorolac, p.74
Lonazolac, p.77
Lornoxicam, p.77
Loxoprofen, p.78
Lumiracoxib, p.78
Meclofenamic acid, p.79
Mefenamic Acid, p.80
Meloxicam, p.80
Mofebutazone, p.86
Mofezolac, p.86
Morniflumate, p.86
Nabumetone, p.91
Naproxen, p.92
Nepafenac, p.95
Niflumic Acid, p.95
Nimesulide, p.95
Oxaprozin, p.105
Oxyphenbutazone, p.107
Parecoxib, p.111
Phenazone, p.116
Phenylbutazone, p.117
Piketoprofen, p.117
Piroxicam, p.117
Pranoprofen, p.119
Proglumetacin, p.119
Propyphenazone, p.119
Proquazone, p.119
Ramifenazone, p.120
Rofecoxib, p.121
Sulindac, p.126
Suprofen, p.128
Suxibuzone, p.128
Tenoxicam, p.128
Tepoxalin, p.129
Tetridamine, p.129
Tiaprofenic Acid, p.129
Tiaramide, p.129
Tolfenamic Acid, p.130
Tolmetin, p.130
Valdecoxib, p.132
Vedaprofen, p.133
Zaltoprofen, p.133

Opioid analgesics

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors (see p.101). The term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesics has legal connotations and is no longer used pharmacologically or clinically.

Most opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine or dextropropoxyphene are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, including cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug.

Some opioids are rarely if ever used as analgesics and are described elsewhere; they include the antitussives dextromethorphan (p.1555) and pholcodine (p.1570), and the antidiarrhoeals diphenoxylate (p.1724) and loperamide (p.1741).

Opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. They are also subject to abuse.

Described in this chapter are

Alfentanil, p.16
Anileridine, p.20
Buprenorphine, p.29
Butorphanol, p.32
Carfentanil, p.34
Codeine, p.37
Dextromoramide, p.39
Dextropropoxyphene, p.40
Diamorphine, p.42
Dihydrocodeine, p.48
Dipipanone, p.49
Embutramide, p.50
Ethoheptazine, p.52
Ethylmorphine, p.52
Etorphine, p.54
Fentanyl, p.55
Hydrochlorides of Mixed Opium Alkaloids, p.105
Hydrocodone, p.63
Hydromorphone, p.63
Ketobemidone, p.73
Levacetylmethadol, p.77
Levomethadone, p.77
Levorphanol, p.77
Meptazinol, p.81
Methadone, p.82
Morphine, p.86
Nalbuphine, p.91
Nicomorphine, p.95
Opium, p.105
Oxycodone, p.106
Oxymorphone, p.107
Papaveretum, p.105
Pentazocine, p.112
Pethidine, p.113
Piritramide, p.117
Remifentanil, p.120
Sufentanil, p.124
Tilidine, p.129
Tramadol, p.130
Trimeperidine, p.132

Paracetamol and other para-aminophenols

Paracetamol is the principal para-aminophenol derivative in use. Acetanilide and phenacetin have generally been replaced by safer analgesics. Propacetamol is hydrolysed to paracetamol in the plasma.

Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains to be fully elucidated, but may be due to inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used for the relief of mild to moderate pain and minor febrile conditions.

Described in this chapter are

Acetanilide, p.15
Paracetamol, p.108
Phenacetin, p.115
Propacetamol, p.119

Analgesia and Pain

Pain is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

Under normal circumstances pain is the result of stimulation of peripheral receptors that transmit impulses through pain pathways to the brain. Pain receptors or nociceptors are of two basic types:

- *mechanoheat receptors* have a high stimulation threshold and respond to intense or potentially damaging noxious stimuli. These receptors are associated with rapidly conducting, thinly myelinated Aδ fibres, and their stimulation produces rapid sharp localised pain that serves to activate withdrawal reflexes
- *polymodal nociceptors* respond to mechanical, thermal, or chemical insults. These receptors are also activated by cellular components that are released after tissue damage. Their impulses are transmitted slowly along unmyelinated C type fibres and produce dull, aching, and poorly localised pain with a slower onset

Nerve fibres from nociceptors terminate in the dorsal root of the spinal cord before transmission by ascending pathways to the brain. There have been many theories on the processing of pain signals at the spinal level but the 'gate theory' proposed by Melzack and Wall is one of the best known. This theory postulates that the transmission of impulses to the brain is modulated by a gate mechanism in the substantia gelatinosa. Stimulation of small fibres opens the gate and facilitates transmission whereas stimulation of large fibres, which normally carry non-painful sensory input, can close the gate and inhibit transmission. Transmission also appears to be modulated by several other mechanisms which can influence the sensitivity of the gate.

Inflammatory mediators such as bradykinin, histamine, serotonin, and prostaglandins produced in response to tissue damage can produce peripheral sensitisation so that receptors respond to low intensity or innocuous stimuli; central sensitisation also occurs. Pain associated with tissue damage hence results in increased sensitivity of the sensory system so that the pain can occur in the absence of a clear stimulus. There may be a reduction in the pain threshold (*allodynia*) resulting in an exaggerated response (*hyperalgesia*) or a prolonged effect (*hyperpathia*).

Pain is often classified as being acute or chronic in nature.

- **Acute pain** is associated with trauma or disease and usually has a well-defined location, character, and timing. It is accompanied by symptoms of autonomic hyperactivity such as tachycardia, hypertension, sweating, and mydriasis.
- **Chronic pain** is usually regarded as pain lasting more than a few months. It may not be clearly associated with trauma or disease or may persist after the initial injury has healed; its localisation, character, and timing are more vague than with acute pain. Furthermore, as the autonomic nervous system adapts, the signs of autonomic hyperactivity associated with acute pain disappear. Some forms of pain regarded as being chronic may consist of intermittent attacks of pain followed by relatively long pain-free periods. Patients with chronic pain experience physical, psychological, social, and functional deterioration which contributes towards exacerbation of the pain.

Physiologically, pain may be divided into nociceptive pain and neuropathic pain.

- **Nociceptive pain** follows activation of nociceptors by noxious stimuli as described above but is not associated with injury to peripheral nerves or the CNS. It may be somatic or visceral, depending on which receptors or nerves are involved. *Somatic pain* is usually well localised and may be described as deeply located, sharp or dull, nagging, stabbing, throbbing, or pressure-like. *Visceral pain* is generally less localised and more diffuse than somatic pain and may be referred to remote areas of the body. Depending on the structure involved it is variously described as deeply located, aching, nagging, cramping, or pressing and may be accompanied by nausea and vomiting. Nociceptive pain usually responds to treatment with conventional analgesics.
- Pain resulting from damage or dysfunction of peripheral nerves/receptors or of the CNS is known as **neuropathic pain** (or neurogenic pain). The term covers *sympathetically maintained pain* including causalgia and reflex sympathetic dystrophy, and painful conditions such as postherpetic and trigeminal neuralgia, and diabetic neuropathy. Neuropathic pain associated with central nervous tissue, such as in central post-stroke pain (the thalamic syndrome) is referred to as *central pain*. The clinical signs of neuropathic pain can vary greatly. Some of the more common features include heightened pain sensitivity and sensations of superficial burning or stabbing (lancinating) pain. The pain may be associated with areas of sensory deficit or some form of autonomic instability. Neuropathic pain responds poorly to conventional analgesics and can be difficult to treat.

Early **treatment** of pain is important as unrelieved pain can have profound psychological effects on the patient, and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is a mainstay of pain treatment (see below), physical methods such as physiotherapy (including massage and the application of heat and cold), surgery, and nervous system stimulation techniques such as acupuncture and transcutaneous electrical nerve stimulation (TENS) are also used.

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Choice of analgesic

Paracetamol and **NSAIDs** are the first choice analgesics for treating mild to moderate pain and are also used in moderate to severe pain to potentiate the effects of opioids. They are suitable for use in acute or chronic pain. Effective relief of acute pain can be achieved with oral NSAIDs and with paracetamol (particularly in combination with an opioid—see below). Dependence and tolerance are not a problem with non-opioid analgesics but they have a rather flat dose-response curve: as the dose is increased, the increase in pain relief may be quite small. Aspirin and other non-selective NSAIDs inhibit blood platelet function, adversely affect the gastrointestinal tract, and can precipitate hypersensitivity reactions including asthma. The risk of severe upper gastrointestinal adverse effects may be less with selective inhibitors of cyclo-oxygenase-2 (COX-2) such as the coxibs, but their use has been greatly restricted by concerns about serious cardiovascular effects. Paracetamol does not have the haematological or gastrointestinal adverse effects of aspirin but large doses can produce severe or sometimes fatal hepatotoxicity. Giving paracetamol with an NSAID improves analgesia.

For the treatment of moderate or moderate to severe opioid-sensitive pain **codeine** is the traditional choice; alternatives include **dihydrocodeine** and **tramadol**. They are often given with non-opioid analgesics. Combinations of codeine with paracetamol at full doses produce a small but significant increase in analgesia compared with paracetamol alone and are one of the most effective options for acute pain, but the incidence of adverse effects increases with repeated use. Combinations of **dextropropoxyphene** with paracetamol or aspirin are no more effective in acute pain than the non-opioid alone; efficacy in chronic pain is unclear and adverse effects may become troublesome. The combination preparation co-proxamol (dextropropoxyphene with paracetamol) has been gradually withdrawn from the UK market because of poorly established efficacy and the risk of toxicity in overdose.

More potent opioids such as **morphine** are mainly used in the treatment of severe acute non-malignant pain and cancer pain (see below). Their use in chronic non-malignant pain is somewhat controversial because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. Opioids may also be of value in neuropathic pain in some patients.

Morphine is the opioid of choice in severe pain. It is absorbed when given orally and has a short half-life so that the use of immediate-release oral preparations offers a flexible means of dosage titration in, for example, palliative care. Once initial pain relief has been achieved, administration of a modified-release preparation every 12 or 24 hours is more convenient for maintenance of analgesia in severe chronic pain. It may also be given parenterally (e.g. for control of acute severe pain in emergency departments or in patient-controlled analgesia—see also below), or rectally or transdermally, where there would be problems with the oral route.

Occasionally **other opioids** may be useful. Switching to an alternative opioid may be effective in patients who have inadequate pain control or intolerable adverse effects with morphine. Methadone (which also acts as an NMDA antagonist) or oxycodone have a longer duration of action than morphine, but it should be noted that methadone, which has a long half-life, should not be given more than twice daily when used long term because of the risk of progressive CNS depression and overdosage. A rapid onset of action is provided by alfentanil and fentanyl but use of pethidine is no longer recommended. Diamorphine or hydromorphone may be preferred to morphine when the parenteral route has to be used because they are more soluble and can be given in a smaller volume. Tramadol, which may impair respiratory and gastrointestinal function less than other opioids at equianalgesic doses, is also of benefit in neuropathic pain.

Adverse effects of opioids include sedation, nausea, vomiting, constipation, and, most seriously, respiratory depression. Tolerance generally develops to all of these effects except constipation, which may be prevented by regular use of laxatives.

A number of other groups of drugs have significant roles in pain management either alone or as **analgesic adjuvants**.

Subantidepressant doses of tricyclic **antidepressants** (usually amitriptyline) are considered to be useful in refractory chronic pain, including neuropathic pain of the burning, dysaesthetic type such as postherpetic neuralgia and diabetic neuropathy; shooting pain has also been reported to respond. They may be used in addition to conventional analgesics, notably in the treatment of cancer pain of mixed aetiology. There is little evidence for benefit in acute pain although musculoskeletal pain has sometimes responded. Amitriptyline has also been found to be useful for tension-type headache and for the prophylaxis of migraine. The role of other antidepressants in the treatment of neuropathic pain is less clear although venlafaxine may be useful.

Antiepileptics (often carbamazepine and, more recently, gabapentin and pregabalin) have been found useful in the relief of neuropathic pain, especially when there is a stabbing (lancinating) element, as in trigeminal neuralgia; there have also been reports of efficacy in the treatment of diabetic neuropathy and for migraine prophylaxis.

Benzodiazepines and **other muscle relaxants** such as baclofen or dantrolene are useful for relieving painful muscle spasm in acute or chronic conditions.

Bone modulating drugs such as calcitonin and bisphosphonates may be useful in cancer pain arising from bone metastases (see below) but have a slow onset of action and are second choice to NSAIDs. Bisphosphonates may cause an initial transient increase in bone pain.

Caffeine has been used with the aim of enhancing the effects of non-opioid and opioid analgesics but is of debatable benefit. There are similar doubts about whether caffeine enhances the effect of ergotamine in the treatment of migraine (see Pharmacokinetics, p.621); it may also add to gastrointestinal adverse effects and in large doses can itself cause headache.

Corticosteroids have produced improvement, often substantial, in neuropathic pain. They can also relieve headache caused by raised intracranial pressure and refractory pain caused by bone metastases, and have the added benefits of increasing well-being and appetite.

Some **inhalational anaesthetics** are used in subanaesthetic doses as inhalation analgesics for acute pain. In particular, nitrous oxide is given with oxygen for pain relief in obstetrics and during dental and other procedures, and in emergency management. Isoflurane, enflurane, and in some countries methoxyflurane or trichloroethylene have been used similarly.

Miscellaneous drugs. Following the discovery that epidural or intrathecal injection of opioids can produce effective analgesia many other drugs have been tried by these routes, either alone or with opioids or local anaesthetics, but their role, if any, in the management of pain remains to be determined. Some of these drugs, such as clonidine and ketamine, also appear to have analgesic properties when given by other routes, and ketamine may be useful in reducing opioid requirements. Some antiarrhythmics (including systemic lidocaine) may be effective in chronic neuropathic pain, but must be used with extreme caution. The use of antipsychotics, such as the phenothiazines, as adjuvant analgesics is controversial; levomepromazine is sometimes used as an adjunct in palliative care.

See below for discussions of the use of patient-controlled analgesia, and rubefacients and topical analgesics. Nerve blocks are discussed under Pain, on p.1852.

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Choice of analgesics in children

Pain has often been undertreated in infants and children because of fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness, and addiction with potent opioid analgesics. Assessment of pain is also a problem in children of all ages[1-3] and it is not that long since it was widely believed that neonates were incapable of feeling pain.

Non-opioid analgesics are used in ***infants and children***, either alone for minor pain or as an adjunct to opioid analgesics in severe pain,[4,5] (they can reduce opioid requirements,[1,6] perhaps by up to 40%[5]). Paracetamol is frequently used but it lacks any anti-inflammatory effect. NSAIDs such as ibuprofen are useful for minor pain,[4,5,7] especially when associated with inflammation or trauma. The use of aspirin is greatly restricted by its association with Reye's syndrome.

The **opioids** are still the mainstay of analgesia for moderate to severe pain in paediatric patients, and morphine is the standard against which the others are compared. It is given intravenously for rapid relief of severe pain (for example after burns, fractures or other injuries), and is titrated to achieve a suitable analgesic dose.[4,5,7,8] Where intravenous access is not readily achievable, oral morphine may be given but its onset is slower and less predictable; some favour intranasal diamorphine as an alternative to intravenous morphine.[4] Continuous intravenous morphine infusion with or without initial loading doses has become popular for postoperative pain relief,[6,8] but titration of the infusion rate is necessary to achieve a balance between analgesia and respiratory depression (particular care is needed in neonates, see below). Subcutaneous infusions of morphine have also been used,[5] mostly for the relief of terminal cancer pain in children. Intramuscular injections are painful[7-10] and therefore probably only suitable for short-term use. Fentanyl has also been widely used for short-term analgesia in surgical procedures,[6-8,10,11] and other opioids such as buprenorphine, hydromorphone, oxycodone, and tramadol have been given.[5] Patient-controlled analgesia using morphine has been tried in children (see below).

Morphine has also been given to children by the epidural route;[8] experience with the intrathecal route is more limited. Other methods of opioid drug delivery of possible value in paediatric analgesia include transmucosal,[6,11] nasal,[4,7] and transdermal[6,9] dosage.

Cancer pain in children may be treated using the analgesic ladder scheme described under Cancer Pain (see below).

Inhaled **nitrous oxide** and oxygen mixtures may be useful for preliminary pain relief and short, painful procedures.[4,7,8,10]

Local anaesthetics are especially suitable for the management of acute pain in day-care situations. Single injections given by the epidural route are often used to provide analgesia during and after surgery. Continuous epidural infusions of local anaesthetics have also been used. However, simpler techniques such as wound infiltration or peripheral nerve blocks can also provide effective analgesia for some procedures and are free of the problems of lower limb weakness or urinary retention associated with caudal blocks.[5,7,8,10] Application of eutectic creams (see Surface Anaesthesia, p.1866) containing lidocaine with prilocaine to intact skin, to produce surface anaesthesia, may be sufficient for some minor painful procedures in children.[6-9,11]

Ketamine is used in outpatients for brief, painful procedures such as fracture reduction and to provide immobility for repair of facial lacerations in young children.[11,12] The emergence reactions that limit its use in adults are less common in children,[11] and can be ameliorated by benzodiazepines.[7,10]

Most ***neonates*** requiring analgesia and receiving respiratory support can be managed with an infusion of morphine but in neonates who are breathing spontaneously there is a substantial risk of respiratory depression. Morphine has been used in such neonates[8] but should be limited to those under intensive care, as for example after major surgery (see also Intensive Care, p.957). Fentanyl citrate[1] and codeine phosphate have also been used in neonates. **Sucrose** and other sweet tasting solutions have been shown to reduce physiologic and behavioural indicators of stress and pain in neonates undergoing painful procedures[9] although there had been some doubt expressed over whether this indicates effective analgesia.[13] The American Academy of Pediatrics has suggested that oral sucrose together with other non-pharmacological methods such as swaddling should be used for minor routine procedures; topical local anaesthetics may be used for more painful procedures such as venepuncture if time permits. Opioids should be the basis of postoperative analgesia after major surgery in the absence of regional anaesthesia; a rapidly acting opioid such as fentanyl is advocated, together with infiltration of the site with a local anaesthetic where time permits, for insertion of a chest drain.[14] Similar recommendations for painful procedures in neonates have been made by an international consensus group.[15]

The use of **analgesic adjuncts** (see Choice of Analgesic, above) has also been advocated in some children.[16]

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Nerve blocks

For a discussion of the use of nerve blocks in the management of pain, see under Pain, p.1852.

Patient-controlled analgesia

Patient-controlled analgesia (PCA) involves the use of automated delivery systems that enable patients to receive doses of an analgesic on demand. The technique is now widely favoured in the management of acute pain,[1-3] and appears to produce slightly better analgesia, and greater patient acceptance, than conventional analgesic methods.[4,5] It has been used successfully in children as young as 4 years, and in elderly patients.[6] Most experience relates to systems using intravenous opioids.

Initial analgesia must be established by giving the patient bolus doses of the analgesic, to achieve effective blood concentrations.[2,3] In the simplest type of PCA the patient is then able to self-administer a small fixed dose on demand; further doses are not permitted until a pre-programmed lockout interval has expired. The demand dose should be large enough to produce an appreciable analgesic effect, but not large enough to lead readily to toxic concentrations; the lockout period should also be long enough for the maximum analgesic effect to be felt before another dose is permitted, and should therefore relate to the speed of onset of action of the drug.[2] Some devices allow the dose to be given as a short infusion[2] to reduce adverse effects associated with high peak concentrations of opioids. In another commonly used method, sometimes described as patient-augmented analgesia, the patient is given a continuous background infusion which is supplemented by self-administered bolus doses.[2,3,6] However, with this method patients may receive more opioids without any improvement in analgesia;[6,7] There is also a greater risk of adverse effects, including respiratory depression.[2,3,7] It remains to be seen if there is any advantage with the more sophisticated devices that can be programmed to adjust the background infusion according to the frequency of the bolus demands.[6,7]

Most of the common opioids have been used successfully for PCA.[2] Morphine remains the gold standard, and fentanyl, hydromorphone, or tramadol are widely used alternatives.[2,3] Use of pethidine is no longer advised because of the risk of accumulation of its toxic metabolite, norpethidine.[2] Drugs with very short (remifentanil) or very long (methadone) half-lives may be less suitable for use.

Although generally perceived as safer than conventional opioid analgesia, occasional serious adverse effects and fatalities have resulted from errors in programming, or incorrect or inappropriate use (including operation by persons other than the patient). These risks can be minimised by safety features built into the PCA device itself, and by the development of standard protocols for the use of the technique.[2,3]

Most experience relates to the use of the intravenous route. However, epidural PCA is also used. It appears to be as effective, or more effective, than intravenous PCA,[2,3] although it may not be suitable in all cases, and carries additional risks to do with the placement of the epidural catheter.[3] Epidural PCA generally produces analgesia with a combination of a lipid-soluble opioid such as fentanyl or sufentanil plus a long-acting local anaesthetic such as bupivacaine or ropivacaine; the optimum combination has yet to be defined.[2,3] In addition, unlike intravenous PCA, the use of a background infusion is recommended.

Other routes have been investigated, including intranasal[7] and, in particular, transdermal[2,8] PCA. An iontophoretic patient-controlled delivery system for transdermal fentanyl has been developed,[8,9] and allows PCA to be given in a non-invasive manner.

Although it is not always considered in terms of PCA, inhaled nitrous oxide in oxygen also has a long history of effective use as a patient-controlled analgesic during childbirth; opioid PCA may not be suitable for such pain although local anaesthetics have been used with satisfactory results.[10]

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Postoperative analgesia

Pain relief after surgery has often been inadequate and it is now recognised that pain control should be adjusted for each patient and each situation.[1-3] Multimodal regimens, using several classes of analgesic, and ideally more than one route, are now generally favoured.[3-5] Pre-operative evaluation of the patient,[2,4] and frequent assessment of pain intensity after surgery (both to allow appropriate analgesia, and to detect possible complications)[3] are fundamental. Evidence-based procedure-specific guidelines are under development.[6] Giving pain control on a preventative basis (pre-emptive analgesia) has been recommended, and may be more effective than conventional management, at least for some regimens, although results have varied.[7,8]

Patients undergoing minor surgery can be adequately managed with oral analgesics, such as paracetamol, NSAIDs, tramadol, and oxycodone. Those undergoing more extensive surgery usually require parenteral opioids or local analgesic techniques such as regional block, sometimes in combination.[3]

- **Opioid analgesics**, in particular morphine, are the mainstay of treatment for moderate to severe postoperative pain.[3] Opioid dose should be individually titrated; they may be given by numerous routes, but intravenous doses give more predictable results than intramuscular or subcutaneous doses and are widely favoured.[2,3,9] Intravenous *patient-controlled analgesia* (see above) is now a standard method of management for postoperative pain.[3,4] Where it is unavailable, intramuscular or subcutaneous dosage every 2 hours as needed for 24 to 72 hours, followed by conversion to an oral analgesic regimen, may be an alternative.[3] Careful monitoring for potential adverse effects, in particular respiratory depression, is needed.[3]

  Opioids injected centrally via the epidural and intrathecal routes provide effective regional analgesia[2,4,9] (and may be more effective than intravenous opioids,[10] although whether this improves the ultimate outcome is unclear[3]). Morphine is the opioid most commonly given centrally, but others such as fentanyl, which is more lipid soluble, may be preferable in the case of epidural injection. The epidural and intrathecal routes have also been used for patient-controlled analgesia.

  Oral opioids may not be suitable in the immediate postoperative period, but oral regimens are generally preferred if the patient can swallow and gastrointestinal function has recovered.[1,3] Tramadol is useful in patients undergoing minor or intermediate surgery.[3]

  Management of postoperative pain in patients who have been receiving long-term opioids before surgery may be particularly difficult.[3,11] Baseline requirements should be calculated for each patient, but may go up or down after surgery; typically, at least 50% of the baseline dose will be needed postoperatively, with additional opioids titrated according to pain requirements. Such patients may thus require larger than normal doses of opioids to be given, and a balanced multimodal approach to analgesia is particularly important.[11]
- **NSAIDs** and **paracetamol** are useful analgesic adjuncts that can improve pain relief,[3] but are not suitable alone after major surgery.[2] After minor or intermediate surgery an oral regimen of paracetamol plus an NSAID such as naproxen may be adequate, with oxycodone or tramadol being given for breakthrough pain.[3] NSAIDs can be used effectively with other drugs, and use of an NSAID with an opioid after major surgery enables the dose of the opioid to be reduced without loss of analgesic effect.[1-5,9] However, the risk of gastric ulceration, impaired coagulation, and reduced renal function may limit the use of NSAIDs in some patients,[3,9] and the potential cardiovascular effects of the selective inhibitors of cyclo-oxygenase-2 (COX-2) have also been a cause of great concern.[3]

  Diclofenac, flurbiprofen, ketoprofen, ketorolac, lornoxicam, and naproxen are among the NSAIDs used for postoperative pain; the COX-2 inhibitors including parecoxib have also been used. Diclofenac, ketoprofen, ketorolac, and parecoxib may be given by injection, and a parenteral formulation of paracetamol is available in some countries.
- Infiltration of **local anaesthetics** at the site of operation is a simple method of preventing postoperative wound pain.[1,4] Central nerve blocks obtained with epidural or intrathecal local anaesthetics produce excellent analgesia,[1,2,4] although again, whether this improves outcome is unclear.[2,3] Insertion of a catheter during the operation allows subsequent infusion or bolus injection.[9] However, there may be complications related to both the procedure and the drugs used (see also Adverse Effects of Central Block, p.1850). Local anaesthetics are rarely used alone, as a mixture of an opioid and a local anaesthetic produces effective analgesia using relatively smaller doses of each drug.[9] Such combinations are also used in patient-controlled epidural analgesia (see above).
- There is growing interest in the use of **analgesic adjuvants**, including antiepileptics such as gabapentin or pregabalin,[12] or the NMDA antagonist ketamine,[13,14] to modulate opioid dosage and efficacy for postoperative pain. (For further discussion of analgesic adjuvants see Choice of Analgesic, above.)

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Rubefacients and topical analgesia

Substances applied topically can relieve local pain through a number of different mechanisms.[1] Rubefacients or counter-irritants can relieve superficial or deep-seated local pain probably by producing counter stimulation, which according to the 'gate theory' of pain (see Analgesia and Pain, above) helps to inhibit the transmission of pain signals. Their topical application produces hyperaemia or irritation of the skin and they are used alone or as an adjunct to massage in the management of a variety of painful musculoskeletal conditions.[2] Some are also traditionally used in preparations for the symptomatic relief of minor peripheral vascular disorders such as chilblains. Substances commonly used in **rubefacient** preparations include nicotinate and salicylate compounds, essential oils, capsicum, solutions of ammonia, camphor, and nonivamide. They may be of benefit in acute pain, but seem to be less effective in chronic arthritic and rheumatic pain.[3]

Capsaicin, which is one of the active ingredients of capsicum, is used alone as a topical analgesic in a range of painful conditions, including neuropathic pain and rheumatic disorders; its benefits are modest though it may be useful in some patients.[4] It does not rely on vasodilatation in the skin and it is therefore not considered to be a traditional counter-irritant.

Some **NSAIDs** have been used topically in the treatment of soft-tissue injuries and inflammatory musculoskeletal conditions, although this route does not necessarily avoid the adverse effects of systemic treatment. There is some evidence[5] to suggest that topical NSAIDs might be more effective than placebo.

Other agents used as topical analgesics include compounds such as ethyl chloride and the halogenated hydrocarbon propellants; their evaporation produces an intense cold that numbs the tissues. Transdermal clonidine has been used in the treatment of chronic pain. Ketamine also appears to have some local analgesic effect when applied topically.[1]

Local anaesthetics are sometimes included in topical preparations used for the relief of painful skin and musculoskeletal disorders.

Application of heat to the skin can also help to relieve pain and melted hard paraffin has been used in wax baths as an adjunct to physiotherapy for painful joints and sprains. Warm kaolin poultices have also been used as a means of applying heat for pain relief.

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Specific pain states

Biliary and renal colic. Gallstones (see Ursodeoxycholic Acid, p.2409) or other biliary disorders that result in obstruction of the bile ducts may produce **biliary colic**. Morphine may relieve the accompanying pain, but as it can also produce spasm of the sphincter of Oddi it can raise intrabiliary pressure and exacerbate the pain. It is therefore usually recommended that morphine and its derivatives should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Historically, pethidine has been regarded as a more suitable choice because it was thought to have less smooth muscle activity than morphine; however, this has been questioned. Prostaglandins have also been implicated in the aetiology of biliary colic and NSAIDs such as diclofenac or ketorolac have been successfully used to relieve the pain.[1-3] Antimuscarinic antispasmodics have been tried for their action on biliary smooth muscle and the sphincter of Oddi.

Ureteral obstruction, such as in the formation and passage of renal calculi (see p.2181), produces painful **renal** or **ureteral colic**.[4-6] The acute pain of renal or ureteral colic has been traditionally relieved using opioid analgesics such as pethidine that have a minimal effect on smooth muscle, although morphine has also been used.[4,6] However, opioids, and especially pethidine, are particularly associated with nausea and vomiting,[5,7] and NSAIDs are increasingly used in their place; they appear to be at least comparable with the opioids in terms of efficacy.[4-7] They can be given intramuscularly, intravenously, orally, and rectally, although the best route is unclear.[5,8] Diclofenac sodium given intramuscularly is recommended as first-line treatment by some authors.[6] Parenteral ketorolac also seems to be effective.[5] The use of intranasal desmopressin is also being studied.[4,5]

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Cancer pain. The pain cancer patients experience may be acute, chronic, or intermittent. It may result from tumour involvement of the viscera and extension into soft tissues, tumour-induced nerve compression and injury, raised intracranial pressure, or bone metastases. Pain may also arise as a result of adverse effects of treatment, or from a concurrent disease, and may be exacerbated by emotional or mental changes. Many patients will have more than one type of pain. There may also be exacerbations due to movement (incident pain) or worsening of cancer: pain occurs in about a quarter of patients with newly diagnosed malignancies, but in up to three-quarters of those with advanced disease.

Pain relief involves the treatment of the cause of the pain as well as treatment of the pain itself, together with explanation, reassurance, and supportive care to improve any mental and social complicating factors. The mainstay of cancer pain management is drug treatment with non-opioid or opioid analgesics, or both together, plus adjuvant analgesics if necessary. A small proportion of patients (about 10 to 20%) may experience pain that responds poorly or not at all to opioid analgesics given at tolerable doses, e.g. neuropathic pain resulting from nerve destruction or compression, incident bone pain, pancreatic pain, and muscle spasm.

In the management of cancer pain the aim is to achieve adequate continuous pain relief with the minimum of adverse effects and this calls for appropriate assessment of the intensity and quality of pain, and regular monitoring of the treatment. Guidelines for the relief of cancer pain, published by WHO in 1986[1] and revised in 1996,[2] are widely endorsed by specialists in pain relief and the care of the terminally ill[3-7] despite some questions about the robustness of supporting studies.[7] Subsequent guidelines[8] issued by the Scottish Intercollegiate Guidelines Network in 2000 and the annually updated guidelines of the US National Comprehensive Cancer Network (NCCN)[9] are also widely referred to. Specific guidelines for the relief of cancer pain in children have also been published.[10,11]

Treatment should be given regularly, by mouth if possible, and should follow the accepted three-step **'analgesic ladder'**.[1,2] This approach is often described as treatment 'by mouth, by the clock, and by the ladder'. Regular dosage rather than treatment as required aims to prevent pain re-emerging and to minimise the expectation of pain. The analgesic ladder consists of 3 stages, treatment beginning at step 1 and progressing to step 3 if pain is uncontrolled or increases. The stages are as follows:

1. a non-opioid analgesic such as aspirin, other NSAIDs, or paracetamol; an adjuvant (see below) may also be given if necessary to tackle specific pain or associated symptoms
2. an opioid analgesic such as codeine, dihydrocodeine, or tramadol plus a non-opioid analgesic; an adjuvant may also be given
3. a potent opioid analgesic such as oral morphine; a non-opioid analgesic may also be given, as may an adjuvant.

Combining analgesics with different pharmacological actions can produce additive or synergistic increases in analgesia but only one analgesic from each of the 3 groups (non-opioid, less potent opioid, potent opioid) should be used at the same time.

Evidence to support the **choice of analgesic** is often scanty. A systematic review[12] found some evidence of benefit from the use of NSAIDs to treat cancer pain, and supported their use in mild pain (WHO step 1), but there was little to support the choice of one NSAID over another, and little evidence for the addition of an opioid to an NSAID in moderate pain (WHO step 2).

In moderate to severe pain (WHO step 3), morphine is generally held to be the opioid of choice;[5] alternatives include fentanyl, hydrocodone, and oxycodone.[5,9] Partial agonists or opioids with long half-lives (such as methadone or levorphanol) are less suitable for treatment than pure opioid agonists with less prolonged actions.[9] In patients who do not achieve effective analgesia at an acceptable level of adverse effects with one opioid, **opioid rotation**, switching to an alternative opioid at an equivalent dose, may enable pain control.[9,13]

The optimal **route** for use is by mouth. For best effect, both conventional (for dose titration) and modified-release (for maintenance) dosage forms are required. The European Association for Palliative Care (EAPC) suggests[5] that the simplest method of dose titration is with conventional morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue' dose may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take account of the amount needed for breakthrough pain. If pain returns consistently before the next dose is due the regular dose should be increased. Conventional formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain. For patients taking conventional morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep.

Similar recommendations are given by the NCCN.[9] They advise that the oral rescue dose for breakthrough pain should be calculated as 10 to 20% of the total 24-hour requirement; this may then be increased by 50 to 100% in patients who still have increased pain, with hourly reassessment of efficacy and adverse effects. If inadequate response is still seen after 2 or 3 cycles, a change of route (e.g. intravenous titration) may be considered.

If patients are unable to take morphine orally the EAPC considers the preferred alternative route to be subcutaneous,[5] and the NCCN suggests either continuous parenteral infusion, intravenous, or subcutaneous dosage.[9] There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful.[5] In the UK diamorphine hydrochloride is often preferred to morphine sulfate for parenteral use because it is more soluble and allows a smaller dose volume; hydromorphone hydrochloride is an alternative to diamorphine.

Epidural or intrathecal opioids, either by injection or infusion, have been used when conventional routes have failed.[9,14] Some advocate the use of these routes because smaller doses may produce analgesia equivalent to that of larger doses given orally or parenterally, although there has been little conclusive evidence for a lower incidence of adverse effects or a better quality of analgesia.

The buccal, sublingual, and nebulised routes have been investigated, but these are not recommended for morphine because there is no current evidence of clinical advantage over conventional routes.[5] However, buprenorphine is given sublingually and although may be a useful alternative in patients with dysphagia, although experience of long-term use in cancer pain is limited. Buprenorphine or fentanyl can be given via a transdermal system that provides continuous and controlled delivery for up to 72 hours. Calculating an appropriate conversion regimen for transfer of patients from oral or parenteral therapy to transdermal can be difficult,[15] but the NCCN suggests that the total daily requirement of oral morphine is equivalent to about 2000 times the hourly dose of transdermal fentanyl.[9] An oral transmucosal dosage form of fentanyl is also available for the management of breakthrough cancer pain.[9]

Automated delivery systems for self-administration of parenteral analgesics (patient-controlled analgesia) have been used to administer opioid analgesics (see above).

Adjuvant drugs that may be necessary at any stage include antidepressants, antiepileptics, and class I antiarrhythmics for neuropathic pain, corticosteroids for nerve compression and headache resulting from raised intracranial pressure, and muscle relaxants for muscle spasm. Radiotherapy and radioisotopes such as strontium-89 may be of use when the bone pain of metastases is unresponsive to NSAIDs alone. Bone modulating drugs such as calcitonin and bisphosphonates may be of additional benefit but have a slow onset of action and bisphosphonates may cause an initial transient increase in pain. Corticosteroids have been used as an alternative to NSAIDs in refractory bone pain but long-term use should be avoided. Nerve blocks with local anaesthetics or neurolytic solutions may benefit a few patients, in particular those with sympathetically maintained pain or specific localised pain (see under Pain, p.1852). Topical local anaesthetics or capsaicin may also be of use in some patients.[9] Physiotherapy and relaxation techniques may be useful for painful muscle spasm. The addition of an NMDA antagonist such as dextromethorphan or ketamine to conventional analgesic regimens has been tried with some success in patients with refractory pain.[13] Adjuvant therapy should be fully explored before moving on to the next 'rung' of the treatment ladder or increasing the dosage of an opioid analgesic.[16] For further details of analgesic adjuvants, see Choice of Analgesic, above.

Management of cancer pain also requires monitoring to prevent and reduce **adverse effects** of therapy, particularly of opioids. Appropriate bowel regimes to manage constipation should be started at the same time as opioid therapy, as should antiemetic therapy; sedation and nausea usually become less marked as treatment progresses,[5] and warrant reassessment if they persist for longer than a week.[9] Concerns about respiratory depression and dependence should not be allowed to interfere with appropriate treatment: patients whose pain ameliorates can generally reduce and stop opioid treatment without difficulty.[5]

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Central post-stroke pain. Central pain is a neuropathic pain arising from lesions of the CNS.[1-4] Pain following a cerebrovascular accident has been referred to as thalamic syndrome but is now commonly known as central post-stroke pain and may arise not only from classical stroke but also from surgery or trauma to the head. The pain, which has been described as burning, stabbing, and aching, may be mild to intolerable and occurs spontaneously or in response to a mild stimulus.

As in other types of neuropathic pain, whether opioid analgesics can be of benefit is controversial: it has been suggested that the value of conventional opioids such as high-dose morphine is modest, but that NMDA receptor antagonists such as methadone may be of more benefit.[2] Ketamine, another NMDA antagonist, may also be of value. Conventional management of central post-stroke pain involves the use of antidepressants such as amitriptyline and antiepileptics including lamotrigine or gabapentin. Early peripheral sympathetic blockade may produce temporary relief in some cases. Mexiletine may be of use in patients with refractory pain; it has often been given with amitriptyline. Oral or intrathecal baclofen may be tried. Transcutaneous electrical nerve stimulation (TENS) may occasionally be of help but some advocate brain or spinal cord stimulation. Surgical treatment generally gives disappointing results.

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Complex regional pain syndrome. Complex regional pain syndrome (CRPS) is a regional, post-traumatic neuropathic pain that generally affects the limbs. CRPS has also been referred to as reflex sympathetic dystrophy, post-traumatic dystrophy, causalgia, Sudeck's atrophy, and shoulder-hand syndrome. Causalgia has also been used to describe the burning pain that follows a penetrating injury. Historically, it was considered that the pain was maintained by the sympathetic nervous system and the term 'reflex sympathetic dystrophy' was commonly used to describe the syndrome (although recent studies have shown that the sympathetic nervous system is not always involved). However, the terms given above are now considered to be inappropriate and CRPS is now broadly classified as:

- Type I: (previously reflex sympathetic dystrophy) which develops after tissue trauma, such as that accompanying myocardial infarction, stroke, burns, frostbite, fractures, and shoulder or limb injury, but where there is no identifiable nerve lesion
- Type II: (previously causalgia) which develops after trauma to a major peripheral nerve

Clinically the two subsets are identical and typical symptoms include pain, allodynia, and hyperalgesia; as the syndrome becomes chronic, trophic changes to the bone, muscles, and skin may occur. Sympathetic dysfunction may also be present. If the pain is relieved by a sympathetic block (see below), this pain is regarded as 'sympathetically-maintained', if not it is known as 'sympathetically-independent' pain.

The treatment of CRPS is difficult especially in chronic disorders and is usually aimed at pain control and restoring limb function. The cornerstone of treatment is physiotherapy, with pain relief provided in order to allow physical exercise. Patients with mild disease may not require pain management; those with moderate pain should be tried with a tricyclic antidepressant, an antiepileptic such as gabapentin, or a less potent opioid. Oral or intravenous bisphosphonates have also produced some promising results. A sympathetic nerve block with bretylium or perhaps a local anaesthetic may be useful in carefully selected patients with sympathetically-maintained pain; those who do not respond to a sympathetic nerve block may be given an epidural block. Other methods that have been tried in refractory pain include spinal cord stimulation and intrathecal baclofen or opioids. There are small studies or anecdotal reports of the use of a variety of other drugs and interventions.

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Diabetic neuropathy. Sensory polyneuropathy, a complication of diabetes mellitus, is the commonest of the neuropathies producing neuropathic pain. The pain is mainly experienced as a burning sensation, sometimes accompanied by shooting, or aching pain. Painful neuropathy may benefit from optimal diabetic control (see under Diabetic Complications, p.433). Non-opioid analgesics such as aspirin or other NSAIDs, or paracetamol may be tried, although neuropathic pain is often resistant to conventional analgesics, and the treatment of painful diabetic neuropathy is generally as for postherpetic neuralgia (see below). Relief may be obtained using tricyclic antidepressants and the *BNF* considers them to be the drugs of choice. SSRIs have been tried but studies suggest that they are ineffective or less effective than tricyclic antidepressants. Duloxetine, a serotonin and noradrenaline reuptake inhibitor, is licensed for use in diabetic neuropathy. Antiepileptics such as carbamazepine, gabapentin, phenytoin, and pregabalin can be used to control any shooting or stabbing components of the pain; lamotrigine and topiramate are also under investigation. Antiarrhythmics such as lidocaine given intravenously or mexiletine given orally have been shown to be effective against some components of the pain. Topical application of capsaicin or lidocaine may have some effect. Neuropathic pain may respond partially to some opioid analgesics and they may be of use when other treatments are ineffective.

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Dysmenorrhoea. Dysmenorrhoea is painful menstruation. The primary form arises from uterine contractions produced by release of prostaglandins from the endometrium in the luteal phase of the menstrual cycle. For this reason, drugs that inhibit ovulation or prostaglandin production are often effective treatments.[1] NSAIDs inhibit cyclo-oxygenase (prostaglandin synthetase) and are usually the drugs of first choice.[1-3] They are taken at the onset of discomfort and continued for a few days while symptoms persist. Those most commonly used have included aspirin, diflunisal, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, naproxen, and piroxicam. Theoretically, mefenamic acid has the advantage of inhibiting both the synthesis and the peripheral action of prostaglandins, but clinical studies have not consistently shown fenamates to be more effective than other cyclo-oxygenase inhibitors. Paracetamol has also been given for pain relief. A systematic review[2] comparing several of these drugs concluded that ibuprofen appeared to have the best risk-benefit ratio in dysmenorrhoea and was the preferred analgesic; naproxen, mefenamic acid, and aspirin were also effective, but the limited data on paracetamol did not show such clear benefits. Another such review considered that there was insufficient evidence to determine which NSAID should be preferred.[3]

Patients who fail to respond to analgesics may benefit from the use of progestogens either alone for part of the cycle or more usually together with oestrogens in the form of oral contraceptive preparations.

Antispasmodic drugs such as hyoscine butylbromide are included in some preparations promoted for the relief of spasm associated with dysmenorrhoea but the *BNF* considers that they do not generally provide significant relief. There is limited evidence[4] that vitamin B_1 may be effective and some consider[1] that it may be worth trying; evidence of benefit from other therapies such as magnesium or vitamin E is considered to be weaker.[1,4,5]

Secondary dysmenorrhoea is associated with various other disorders such as endometriosis, and treatment is primarily aimed at the underlying cause.

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Headache. Aspirin and other NSAIDs, or paracetamol are often tried first for the symptomatic treatment of various types of headache including migraine (p.616) and tension-type headache (p.617). NSAIDs may also be effective for the prophylaxis of migraine, although they are not considered first-line options.

Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine or tension-type headache, but are best avoided, especially in patients who have frequent attacks.

Labour pain. It is important to assess the adverse effects, on both the mother and the fetus, when selecting any method for the management of labour pain. Non-pharmacological methods of pain relief may include relaxation techniques, transcutaneous electrical nerve stimulation (which is popular with patients, although there is no robust evidence of benefit[1]), and various other complementary therapies: of the latter, there is some evidence of benefit with the use of acupuncture and hypnosis.[2] Water immersion (use of a birthing pool) during the first stage of labour has been shown to reduce reported maternal pain.[3] Subcutaneous or intradermal injection of sterile water into the back has also been used for the relief of low back pain during labour.[4,5]

However, at some point during labour many women will request some sort of pharmacological analgesia.

The inhalational anaesthetic **nitrous oxide**, given with oxygen, is suitable for self-administration and is commonly used to relieve labour pain. It is relatively safe and can produce substantial analgesia in most patients.[6] Other inhalational analgesics such as isoflurane or sevoflurane are also sometimes used[7] (see Choice of Analgesic, above).

Opioid analgesics have been given systemically in the management of labour pain for many years, although they do not appear to provide adequate analgesia in most patients at a tolerable dosage.[8,9] There is no clear evidence to favour one opioid over another.[10] Morphine is considered unsuitable,[7] and the widest experience has been with pethidine.[7,10] However, its effectiveness has been queried,[7,10] and its use has declined in many countries.[7] Fentanyl and its derivatives sufentanil and alfentanil have been used, particularly when given as intravenous patient-controlled analgesia,[7] but it is not clear that they have any great advantages, and as with other opioids they may cross the placenta and produce respiratory depression and other adverse effects in the newborn. The use of the very short-acting opioid remifentanil for patient-controlled analgesia during labour has been investigated, with some benefit,[11] but although it is less likely to produce effects on neonatal respiration it is not clear that the degree of supervision required to guard against unacceptable respiratory depression in the mother can be widely achieved on busy labour wards.[7] Nalbuphine has been used in some countries because of its mixed agonist/antagonist action,[7] although there does not seem to be clear evidence that it conveys any substantial benefit.

Epidural analgesia with a *local anaesthetic* is now considered the gold standard for treatment and provides the most effective pain relief during labour.[9,12-14] Medical indications may include a history of malignant hyperthermia, certain cardiovascular or respiratory disorders, or pre-eclampsia, but the primary indication is the patient's desire for pain relief.[9,13] Bupivacaine is one of the local anaesthetics most often used in epidural analgesia; others include ropivacaine and lidocaine.[14]

Epidural block has few contra-indications and serious adverse events are rare. Nonetheless, it has been associated with an increased risk of prolonged second-stage labour, forceps delivery, and caesarean section[9,13,14] (although meta-analysis[8] and a systematic review[14] refute the latter), and it may not improve maternal experience of childbirth. Many centres stop epidural analgesia for the second stage of labour to reduce the incidence of forceps delivery but substantive evidence for this is lacking.[15] Central blocks may also produce adverse effects including shivering, post-puncture headache, and hypotension (for further details of the adverse effects of and precautions for epidural block see p.1850 and p.1851, respectively). Occasionally epidural local anaesthetic does not produce adequate analgesia due to patchy or incomplete block.

Some of the adverse effects associated with epidural analgesia are associated with the motor block and profound analgesia resulting from traditional techniques using relatively high concentrations of local anaesthetic. There has therefore been an increasing trend to the use of lower-dose techniques. Although *opioid analgesics* are not particularly effective for labour analgesia when given systemically (see above), addition of a small amount of an opioid to epidural solutions enables effective analgesia to be achieved with lower concentrations of local anaesthetic, and with less motor block;[9,12,16,17] however, the incidence of pruritus (a known effect of opioids) is greater than with a local anaesthetic alone.[18] There is no standard combination of local anaesthetic and opioid, although one large study used bupivacaine 0.1% with fentanyl 2 micrograms/mL.[16] Sufentanil is also widely used with either bupivacaine[18] or ropivacaine. The epidural use of other adjuvants such as clonidine and neostigmine is also being studied.[19] Low-dose techniques are the basis of so-called 'ambulatory' or 'walking' epidural management, although it is unclear to what extent this mobility improves outcomes or patient satisfaction.[20]

Once an initial block is established, additional analgesia can be provided through a catheter by intermittent 'top-up' doses or by a continuous epidural infusion; a combination of the two methods forms the basis of some types of patient-controlled epidural analgesia.

Another method of reducing the adverse effects of traditional epidural techniques is to combine a spinal block, which is quick acting but not long lasting enough to be used alone for analgesia in labour, with epidural delivery. Although studies have reported superior pain relief[17] with such **combined spinal-epidural analgesia**, a systematic review[18] considered that there was no overall benefit with the technique when compared with low-dose epidural techniques, although onset of analgesia was faster.

The use of **spinal blocks** in obstetrics has been more commonly associated with anaesthesia and management of postoperative pain in caesarean section.[12] Spinal blocks with local anaesthetics have a greater tendency to produce hypotension and headache than epidural blocks (for further details of the adverse effects of and precautions for spinal block see p.1850 and p.1851, respectively).

Pudendal nerve blocks with lidocaine followed by a local anaesthetic given into the perineum provide pain relief during labour.[12] However, the technique of paracervical local anaesthetic block is now largely of historic interest in labour analgesia[21] because of reports of fetal arrhythmias, acidosis, and asphyxia and isolated reports of fetal death.

Local anaesthetics have been applied topically for **perineal pain** caused by tearing or episiotomy in women who have given birth. However, a systematic review[22] considered that the evidence of effectiveness was not compelling.

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Low back pain. Low back pain (sometimes referred to as lumbago), is a common complaint but only a small percentage of patients suffer from a recognised organic disease, most frequently disc disease. In patients with a lumbar disc prolapse or herniation, the rupture of one of the fibrocartilagenous intervertebral discs can exert pressure on spinal nerve roots and produce a condition characterised by severe and often acute pain radiating from the back along the distribution of the nerves affected (radiculopathy). The sciatic nerve may be involved and patients experience pain (sciatica), usually in one leg along the typical distribution of the nerve. Non-specific back pain (back pain of unknown origin) is usually self-limiting with a good prognosis, although recurrence is common.[1-3] Back pain is considered to be acute if it lasts for less than 6 weeks, sub-acute if it lasts for 6 to 12 weeks, or chronic if it persists for more than 12 weeks.[4]

Treatment for **acute back pain** should be given early to prevent the condition becoming chronic. For simple back pain (in the absence of nerve root symptoms or signs of serious spinal pathology) paracetamol should be tried first. NSAIDs are probably more effective,[1,5] but are associated with a higher frequency of adverse effects and should be reserved for those in whom paracetamol is ineffective.[1,4-7] If these treatments fail, muscle relaxants, including baclofen or tizanidine, may be added to therapy, although adverse effects may limit their usefulness;[1-6,8,9] benzodiazepines such as diazepam (which should only be given for a short period because of the risk of dependence)[1] are among the most effective muscle relaxants, but there is little comparative evidence, and some suggest that they act primarily as sedatives.[6] Opioids have moderate benefits in severe or disabling pain not relieved by paracetamol or NSAIDs,[1,5,6] but again should only be used in the short term.[3] There is strong evidence that remaining active speeds recovery and reduces the risk of chronicity, even if pain or discomfort is caused; bed rest delays recovery and is not recommended.[2-4,8,10,11] Other non-pharmacological approaches that have evidence of a benefit include topical heat wraps and spinal manipulation.[1,2,4,12,13] There is little or no clinical evidence that acupuncture, transcutaneous electrical nerve stimulation (TENS), massage, traction, specific back exercises, or lumbar support are beneficial.[1,2,4,10,12] However, patient expectations of benefit from different therapies may influence outcomes, and this should be taken into consideration.[1]

Sciatica usually resolves with conservative management including analgesics and continued activity; however, if sciatic pain persists for longer than 6 to 8 weeks, surgery may be indicated.[14] Dissolution of the disc by injection of enzymes (chemonucleolysis) such as chymopapain or collagenase has been used as an effective alternative to surgery, but concerns about its safety have led to a decline in use, and discectomy is often preferred.[15]

Epidural injections of corticosteroids, using either the caudal or lumbar route, have been given to patients with sciatica; any relief is temporary only, the evidence of a benefit is conflicting, and their use is no longer recommended.[14,16] There is no evidence of benefit in patients with non-specific acute or chronic back pain.[2,4,17]

About 2 to 7% of patients with acute lower back pain go on to develop **chronic** pain,[4] and in the majority of cases, the source of the pain cannot be identified. Chronic pain is not necessarily the same as prolonged acute back pain and treatment is difficult. Conservative treatment is as for acute pain (see above);[1,2,5,17,18] tricyclic antidepressants may also be tried[1-3,5,17,18] although a systematic review found the evidence of benefit to be lacking.[19] Topical application of capsaicin may be considered for short-term relief.[17] Surgery may be indicated for disc disease (see above) or spondylosis,[20] although it is not recommended for non-specific chronic back pain until conservative treatments have been tried for at least 2 years.[17] Epidural corticosteroids, intra-articular corticosteroid injections, local facet nerve blocks, trigger point injections, and spinal cord stimulation also lack evidence of efficacy.[17] Other methods that may be tried for intractable chronic back pain include multidisciplinary physical and psychological approaches;[1-3,12,17] evidence for TENS, massage, acupuncture, laser therapy, and traction is scant, however.[2,17,18,21]

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Myocardial infarction pain. The severe pain of acute myocardial infarction is located in the retrosternal area with radiation to the arms, neck, jaw, and epigastrium. Pain relief is of benefit not only in its own right but also because pain may cause adverse haemodynamic effects such as increases in blood pressure, heart rate, and stroke volume. Although early treatment of the myocardial infarction (p.1175) may relieve pain dramatically, opioid analgesics are the first-line treatment for pain and should be given intravenously as soon as possible, that is before hospital admission, to patients with suspected infarction.[1-4] Opioids can also help to reduce anxiety. An inhaled mixture of nitrous oxide and oxygen has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given.

Diamorphine or morphine given by slow intravenous injection have generally been the opioids of choice, partly because of a better haemodynamic profile, but pethidine has also been used. An intravenous antiemetic such as metoclopramide or, if left ventricular function is not compromised, cyclizine, should also be given. The intramuscular route should only be used if venous access is unobtainable since it is relatively ineffective in shocked patients, complicates the enzymatic assessment of the infarction, and may result in large haematomas when patients are given thrombolytics. Alternative analgesics include nalbuphine or buprenorphine, although the latter may not produce pain relief as quickly as diamorphine. The cardiovascular effects of pentazocine make it unsuitable for use during or after myocardial infarction. Selective cyclo-oxygenase-2 (COX-2) inhibitors and non-selective NSAIDs (other than aspirin) should not be used in patients with acute myocardial infarction because of their known cardiovascular risks[5] (see Thrombotic Events under Adverse Effects of NSAIDs, p.97).

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Neuropathic pain syndromes. The definition and characteristics of neuropathic pain are described under Analgesia and Pain, above. Treatment can be difficult and is best undertaken in specialist pain clinics, since neuropathic pain often responds poorly to conventional analgesics.[1-5] The painful disorders characterised by neuropathic pain (either as the predominant form of pain or as one component of the overall pain) discussed in this section are:

- Central Post-stroke Pain
- Complex Regional Pain Syndromes
- Diabetic Neuropathy
- Phantom Limb Pain
- Postherpetic Neuralgia
- Trigeminal Neuralgia

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Orofacial pain. Orofacial pain may arise from a wide range of disorders so its effective management depends very much on the correct identification and treatment of any underlying cause, which may include:

- dental disease
- cluster headache (p.616)
- migraine (p.616)
- trigeminal neuralgia (see below)
- sinusitis (p.193)
- ear disease such as otitis media (p.182)
- giant cell arteritis (p.1503)
- aneurysms
- neoplasms

In the treatment of dental pain, analgesics are used judiciously as a temporary measure until the underlying cause has been effectively managed. Paracetamol or aspirin or other NSAIDs are adequate for most purposes. Opioid analgesics are relatively ineffective and are rarely needed.

Burning mouth syndrome (stomatodynia; glossodynia) is characterised by a burning sensation or other dysaesthesias of the oral mucosa in the absence of specific oral lesions. It is often accompanied by xerostomia and altered taste. Those treatments for which there is the best evidence of efficacy include topical therapy with clonazepam, systemic treatment with thioctic acid, SSRIs, or amisulpride, and cognitive therapy. Other treatments that may produce some benefit include capsaicin used topically or systemically, topical lidocaine, or systemic therapy with other antidepressants.

In addition, a large number of patients have a type of facial pain of unknown cause which is typically exacerbated by stress and can develop into a chronic debilitating disorder. Many patients with such idiopathic facial pain respond to non-opioid analgesics, explanation, and reassurance. Antidepressants such as the tricyclics are often of value. Antiepileptics, including carbamazepine and sodium valproate, and the oral lidocaine analogue mexiletine have been used as adjuncts to the tricyclics. Topical treatment with capsaicin has also been tried. Treatment needs to be continued for several months to avoid pain recurrence on withdrawal. Psychological treatments can also be helpful.

Botulinum A toxin has been tried for the relief of facial pain associated with some disorders of the orofacial muscles.

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Pancreatic pain. Pain in pancreatitis (p.2361) can be severe and may require opioid analgesics. Concerns over the long-term use of opioids in non-malignant pain should not prevent the patient being given effective analgesia which may be achieved by following the general principles recommended by the WHO for treatment of cancer pain (see above); this involves giving non-opioid analgesics such as NSAIDs for mild attacks, with or without antispasmodics such as antimuscarinics, and progressing to 'weak' opioids such as codeine, and 'strong' opioids including morphine according to the severity of pain.

There has been some controversy about the appropriate choice of opioid: traditionally, morphine and its derivatives have been avoided in favour of pethidine, in the belief that they are more likely to cause spasm of the sphincter of Oddi. However, the evidence supporting this has been questioned. Some suggest that κ-receptor agonists such as oxycodone may be of value. In addition, there is some evidence that pancreatic pain may have a neuropathic element, and the use of an antiepileptic such as gabapentin, or an SSRI such as paroxetine, may be considered for pain syndromes associated with chronic pancreatitis.

Analgesics are given before meals to help to alleviate the postprandial exacerbation of pain. They should be given on a regular basis and doses titrated for each patient. Pancreatic extracts may ease the pain but are otherwise reserved for those with symptomatic malabsorption. Coeliac plexus block has been used for the relief of severe intractable pain in some patients with chronic pancreatitis; it has also been used similarly in patients with cancer of the pancreas. However, the benefits of such a block are unclear.

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Phantom limb pain. Phantom limb pain is associated with an amputated limb and is more common when there has been severe pre-amputation pain. It is frequently a mixture of neuropathic and other types of pain. Management may be difficult[1-7] but in a survey of war veteran amputees, for those who took any form of treatment for phantom limb pain, conventional analgesics such as NSAIDs or paracetamol with or without opioid analgesics were reported as being satisfactory.[1] The use of the WHO analgesic ladder, as in cancer pain (see p.5) may guide the choice of analgesic;[7] although the use of opioids has been questioned in what is essentially a neuropathic pain syndrome, many consider them of potential value in phantom limb pain.[6,7] Transcutaneous electrical nerve stimulation (TENS) was another method used by some and considered to be at least as effective as other therapies.[1] Tricyclic antidepressants and antiepileptics may be of help for the neuropathic components of the pain[2,3,5] and some relief may be obtained with sympathetic blocks. Intravenous ketamine may also be of use.[2,4,5] From a review[8] of studies investigating the effect of regional anaesthesia in preventing phantom limb pain in patients undergoing lower-limb amputation it appeared that epidural blockade started before and continuing for the duration of surgery or for several days after amputation conferred more protection from long-term pain than blockade begun late intra-operatively or postoperatively. However, a randomised, double-blind, controlled study[9] failed to show any benefit of pre-emptive analgesia using epidural blockade in such patients. A subsequent review[4] that included this study concluded that the pre-emptive use of epidural block was of limited success.

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Postherpetic neuralgia. About 10% of patients who have had acute herpes zoster still experience neuropathic pain resulting from peripheral nerve injury one month or more after the rash has healed. The elderly are the most susceptible. The affected area (commonly head, neck, and limbs) is extremely sensitive to any stimuli; even the pressure of clothing can produce unbearable pain. Spontaneous remission occurs in many patients within a few months. However, in a small percentage of patients the pain can last for several years.

Attempts have been made to **prevent** the development of postherpetic neuralgia. A meta-analysis[1] concluded that, if started within 72 hours of the onset of rash, aciclovir might reduce the incidence of residual pain at 6 months in some patients. A subsequent analysis[2] considered that there was only marginal evidence of a decreased incidence of postherpetic neuralgia with aciclovir treatment and that there was no reduction in incidence with either famciclovir or valaciclovir treatments. It is, however, generally agreed that antiviral treatment does reduce the duration of postherpetic neuralgia.[2-4] Epidural injection of methylprednisolone with bupivacaine has been shown to reduce short-term pain from herpes zoster, but was ineffective in preventing postherpetic neuralgia in the longer term,[5] and evidence of the preventive value of corticosteroids is generally lacking.[6]

Various **treatments** have been tried once neuralgia develops.[2-4,7-12] The value of conventional analgesics is limited because of the neuropathic character of the pain although opioid analgesics have been used in refractory cases (see below). Low-dose tricyclics such as amitriptyline, or in particular nortriptyline, have been widely used for treatment, and appear to be of benefit in about half of all cases;[4] however, the antiepileptics gabapentin and pregabalin may now be preferred, and gabapentin is licensed for this indication in a number of countries. A comparative study has suggested that gabapentin is as effective as nortriptyline and better tolerated.[13] Topical lidocaine has also been licensed for treatment of postherpetic neuralgia, but the evidence for such use has been questioned.[14] However, it is likely to be better tolerated than the other main topical alternative, capsaicin.[4] Opioids, including methadone, morphine, and oxycodone, are usually reserved for patients who fail to respond to tricyclics or gabapentin.[9] Nerve blocks and surgical techniques may provide temporary pain relief, but results have generally been disappointing. Transcutaneous electrical nerve stimulation (TENS) has also been tried. Topical preparations of aspirin or indometacin, have shown some promise.

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Sickle-cell crisis. The management of pain of sickle-cell crisis (p.1044) is similar to that of other forms of acute pain. The pain of mild crises may be controlled using oral analgesics such as paracetamol, an NSAID, codeine, or dihydrocodeine. Partial agonist and antagonist opioids such as buprenorphine are not recommended to treat acute pain before transfer to hospital.[1] Crises severe enough to need hospital admission usually require the use of more potent parenteral opioid analgesics but NSAIDs may be useful as an adjunct for bone pain. In most centres, morphine is the opioid of choice for moderate to severe pain. Some patients appear to prefer pethidine but many clinicians[2-7] avoid its use if possible as control of pain may be inadequate and doses of pethidine needed to manage crises can lead to accumulation of its neuroexcitatory metabolite norpethidine and precipitate seizures (see also Effects on the Nervous System, p.114). UK guidelines[8] recommend that pethidine should only be used in exceptional circumstances such as in patients hypersensitive to other opioids. Diamorphine, fentanyl, hydromorphone, and methadone have been used as alternatives to morphine. Nalbuphine may also be suitable.[9] As the dose of opioid required to control the pain can vary considerably, not only during each episode but also from one episode to another and between individual patients, patient-controlled analgesia (see above) may be of help to manage the pain once initial pain relief has been obtained with loading doses of parenteral opioids;[4,10,11] opioids used have included morphine and fentanyl. The use of continuous epidural analgesia with local anaesthetics alone or with opioids has been tried. However, a randomised study[12] of morphine for the management of severe painful sickle-cell crises in children showed that oral modified-release morphine was a safe and effective alternative to continuous intravenous morphine. Inhalation of a mixture of nitrous oxide and oxygen may be a useful analgesic during transfer to hospital.[1,8]

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Trigeminal neuralgia. Trigeminal neuralgia (tic douloureux) is a neuropathic pain characterised by sudden, brief, sharp, agonising, episodic pain in the distribution of one or more branches of the fifth cranial nerve. There may be several episodes (lasting several seconds or minutes) a day over a number of weeks, followed by a pain-free interval which may last for weeks or years. Trigeminal neuralgia generally has a 'trigger zone' in which even a very light stimulus such as a draught of air produces pain. In some cases firm pressure applied around but not to the zone itself may help to relieve pain. Trigeminal neuralgia may be idiopathic or may be secondary to nerve compression (such as that caused by a tumour), facial injury, or multiple sclerosis.

Carbamazepine is the drug of choice for the management of trigeminal neuralgia and initially may produce satisfactory pain relief in 70% or more of patients, although increasingly large doses may be required.[1-7] If pain relief is inadequate phenytoin or baclofen may be added to carbamazepine therapy; these drugs may also be used alone in patients intolerant of carbamazepine.[4] Other antiepileptics such as gabapentin, lamotrigine, oxcarbazepine, valproate, and clonazepam have also been used in patients intolerant of, or resistant to, carbamazepine.[1-6] Evidence for the value of non-antiepileptic drugs in trigeminal neuralgia is mostly poor.[8]

In some patients drug therapy eventually fails to control the pain or produces unacceptable adverse effects and invasive procedures become necessary. These may include the selective destruction of pain bearing nerve fibres with radiofrequency thermocoagulation, instillation of glycerol (although the efficacy and safety of the procedure is debatable), gamma knife radiation, and microvascular decompression of the trigeminal nerve root.[2,3,6,7]

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Increased Body Temperature

The hypothalamus is the centre of the thermoregulatory system and is responsible for maintaining the body temperature at a set point (known as the set-point temperature) which is normally 37°. Mechanisms that produce or conserve body heat include passive heat absorption from the environment, peripheral vasoconstriction, and thermogenic processes such as metabolic reactions and shivering. Heat loss is achieved mainly through sweating and peripheral vasodilatation. Various states may lead to an abnormal increase in body temperature.

Fever and hyperthermia

As mentioned above, body temperature is normally regulated by the hypothalamus. *Fever* (pyrexia) is a controlled increase in body temperature due to an elevated hypothalamic set-point temperature. Common reasons for this include infections, inflammatory disorders, neoplastic disease, and some drug treatment. *Hyperthermia* (hyperpyrexia) implies a disturbance of thermoregulatory control. It is caused by external factors such as injury to the hypothalamus, heat stroke following defective heat loss (as occurs in dehydration or excessive heat production following strenuous activities), excessive dosage of some drugs, or a reaction to certain drugs such as anaesthetics (malignant hyperthermia, p.1896) or antipsychotics (neuroleptic malignant syndrome, p.972). Underlying thermoregulatory defects may be a particular problem in sedentary elderly subjects.

Whenever possible the underlying cause of **fever** should be identified and treated.[1] Body temperatures up to 41° are relatively harmless[2] and it is not clear if there is any value in treating fever at lower temperatures,[1] but some groups may be more vulnerable, such as young children, pregnant women, or patients who are already dehydrated or malnourished or those with cardiac, respiratory, or neurological diseases.

Both physical means and antipyretics may be used to reduce body temperature in fever. Maintaining an adequate fluid intake is important. Fanning, removal of clothing, and tepid sponging are often used,[1-3] but they do not reduce the set-point of the hypothalamus, and lead to shivering (rigor) or other adverse effects as the body tries to meet the raised set-point, and their value is therefore questionable;[1] similarly, cold baths should not be used as they may actually increase body temperature by inducing vasoconstriction, and the risks of a cold-induced pressor response should be borne in mind. Antipyretics appear mostly to help return the set-point temperature to normal by inhibiting central synthesis and release of prostaglandin E_2, which mediates the effect of endogenous pyrogens in the hypothalamus.[4] This mechanism cannot lower the body temperature below normal, and antipyretics are ineffective against raised body temperature not associated with fever.

Choice of antipyretic in children has been widely debated. The drugs most commonly used are paracetamol and ibuprofen; salicylates (including aspirin) are generally contra-indicated because of the possible link between their use and the development of Reye's syndrome. A systematic review[5] found inconsistent evidence to support the use of paracetamol to reduce fever in children, since the number of reliable studies was too low to be sure that it was effective. Although studies have found that ibuprofen was superior to paracetamol in terms of both efficacy and duration of action, some of the doses of paracetamol were below those recommended in the UK and NICE did not consider that either drug had a significant advantage over the other.[1] Alternation of the two may be more effective than either alone[6] but again this is controversial.[1,7,8]

Antipyretics should not be given to all children with fever, but only to those in obvious discomfort or distress.[1,9] It has been suggested that the use of antipyretics might prolong infection,[2] and that in severe infection the use of antipyretics might increase mortality:[10] WHO has[10] recommended that in developing countries antipyretics should not be given routinely to children with fever but should be reserved for those with severe discomfort or high fever. In the UK, the Joint Committee on Vaccination and Immunisation recommends antipyretic therapy to treat post-immunisation fever developing after some vaccines. However, if the fever persists after the second dose of antipyretic medical advice should be sought.

Antipyretics have also been given as *prophylaxis* against febrile convulsions, especially in those with a history of such seizures or in those with epilepsy. However, antipyretic therapy does not appear to prevent recurrence of febrile convulsions (p.470).[1,11,12] There is also little to support the use of antipyretics for prophylaxis of post-immunisation fever although some suggest offering it to infants at higher risk of seizures receiving diphtheria-tetanus-pertussis or polio immunisation.[13]

Recommendations for management of fever in adults are similar to those for children,[2,4] although aspirin may also be used.

Hyperthermia may produce body temperatures greater than 41°. These high temperatures are life-threatening and need to be lowered immediately. Antipyretics are ineffective since the high temperatures are a result of thermoregulatory failure. One of the most rapid and effective means of cooling is to immerse the patient in very cold water but core temperature should be monitored to avoid inducing hypothermia.[14] Evaporative cooling methods may be more efficient.[15] Intravenous or intraperitoneal administration of cool fluids, gastric lavage or enemas with ice water have also been used.[14,16]

When hyperthermia is associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, as in the neuroleptic malignant syndrome and malignant hyperthermia, temperature reductions may be obtained using the muscle relaxant dantrolene. There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents. However, dantrolene is not an effective treatment for all types of hyperthermia and rigidity accompanying poisoning. Although dantrolene has been tried in patients with heat stroke, there is no evidence that it affects outcome.[17] In severe cases of hyperthermia when neuromuscular hyperactivity may also impair ventilation, a neuromuscular blocker has been used, although suxamethonium is best avoided as it can itself precipitate malignant hyperthermia.

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Musculoskeletal and Joint Disorders

The **rheumatic disorders** are painful disorders affecting primarily the joints and related structures of the musculoskeletal system, but there may also be widespread involvement of other systems. The term arthritis is used when the disease is largely confined to the joints. Some of the most common forms of arthritis are discussed in this section and these include rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, and the spondyloarthropathies such as ankylosing spondylitis. Other conditions that are associated with arthritis and which are discussed elsewhere include gout (p.552) and SLE (p.1513).

The names **soft-tissue rheumatism** (see below) and **non-articular rheumatism** have been used to describe a number of painful conditions associated with disease of the structures that surround a joint. For a discussion of the management of **low back pain**, see above.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (juvenile chronic arthritis) is a term used to describe a clinically heterogeneous group of idiopathic arthritides occurring in children under 16 years of age; subtypes include systemic arthritis, oligoarthritis (particularly of leg joints), and polyarthritis, either positive or negative for rheumatoid factor.[1,2]

Treatment involves many of the same drugs used for rheumatoid arthritis in adults (see below), although there may be limited evidence for their use in children.[1-8] Appropriate management will depend on the subtype of disease, but there is no definitive consensus on the drugs of choice.

- The **NSAIDs** have been a mainstay of treatment for many years, and continue to be important.[1,2] Most children begin therapy with an NSAID,[1] and they may be particularly useful in oligoarthritis.[2] Naproxen, ibuprofen, or indometacin are among the most often used.[1] Aspirin is now rarely prescribed,[8] although in many countries juvenile idiopathic arthritis remains one of its few licensed indications in children.
- Intra-articular injections of a **corticosteroid** (often triamcinolone hexacetonide) are rapidly effective, and well tolerated, and are often used in oligoarthritis with, or instead of, NSAIDs;[1,2,5] they may reduce the development of deformity secondary to contracture.[1] They also have a role in the management of disease flare in

patients already taking second-line drugs, although it is unclear whether multiple intra-articular injections would be preferable to systemic corticosteroids in patients with polyarthritis.[5]

Moderate or high-dose systemic corticosteroids are more generally reserved for patients with systemic arthritis whose disease is not controlled by NSAIDs. In other subtypes, the adverse effects of systemic therapy are likely to outweigh the benefits. A course of low-dose prednisone might be considered for reduction of pain and stiffness in patients with severe polyarthritis who are unresponsive to other drugs, or awaiting response to slow-acting second-line treatments.[1]

- The second-line treatment of choice in children with persistent active arthritis is **methotrexate**.[1,2,6,8] Like several other second-line drugs it is of less benefit in systemic arthritis than in polyarthritis or refractory oligoarthritis.[8] Improvement may take up to 12 weeks to be seen.[1]
- The so-called **biological therapies** have become increasingly important in managing more severe or refractory forms of juvenile idiopathic arthritis.[1,2,4,8] The tumour necrosis factor inhibitor etanercept, which is licensed for paediatric use in many countries, produces excellent responses in many patients with polyarthritis, particularly those who are rheumatoid-factor positive.[8] Like methotrexate, it may be less effective in those with systemic juvenile idiopathic arthritis.[2] Infliximab, although unlicensed, also seems to be of benefit,[1,2,8] and may be more effective than etanercept in the treatment of associated uveitis.[2] Other drugs that have been tried with some evidence of benefit include abatacept, adalimumab, tocilizumab, and anakinra;[1,2,8] there is some evidence that the latter, an interleukin-1 receptor antagonist, may be more effective than the tumour necrosis factor inhibitors in treating patients with systemic arthritis.[2]
- Many **other drugs** have been tried in juvenile idiopathic arthritis, often on the basis of effectiveness in adults. Sulfasalazine may be of benefit in late-onset oligoarthritis[1] but adverse effects are often troublesome.[8] Concern about adverse effects may also have limited the use of cytotoxic and immunosuppressant drugs other than methotrexate, and there are few controlled studies,[8] although benefit has been reported with leflunomide in polyarticular disease.[1,8] Thalidomide has been suggested for treatment-resistant systemic arthritis.[1] In very severe unremitting disease, autologous bone marrow transplantation has been tried.[1,7,8]

Drug treatment aimed at the complications of disease, rather than the disease process itself, may be needed. There is some evidence that bisphosphonates may be useful in controlling low bone mineral density and fragility fractures associated with juvenile idiopathic arthritis.[1,9] Growth hormone has also been widely used to moderate the severe growth retardation that is often seen.[1] Topical treatment with glucocorticoids and mydriatics may be needed for eye disease.[1]

Physiotherapy and occupational therapy are also important components of disease management, and surgery may be needed in selected cases.[1]

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Osteoarthritis

Osteoarthritis is the clinical and pathological outcome of a range of disorders that cause structural and functional failure of synovial joints. It is characterised by involvement of the entire joint, with loss and erosion of articular cartilage, subchondral bone changes, meniscal degeneration, mild to moderate synovial inflammation, and outgrowth of bone and cartilage at the joint margins (osteophytes).[1-4] These changes result in pain, stiffness (especially after inactivity) and reduced mobility,[1-6] although patients with changes characteristic of osteoarthritis are often asymptomatic.[4,6] Increased loading of the joint, and mechanical factors such as misalignment and muscle weakness, contribute to joint damage and loss of function.[1,2,4] The joints most often affected are hands, hips, and knees.[4,6]

Current treatment for osteoarthritis is not curative, and management is largely concerned with relief of pain and maintenance of joint function.[1-6]

Physical methods of treatment may be preferred initially, and include physiotherapy, heat and cold therapy, exercises, splinting, correction of misalignment, and weight reduction in the obese.[1-8] Acupuncture may also be tried, and appears to be of benefit in improving pain and functionality in knee osteoarthritis.[9] Transcutaneous electrical nerve stimulation (TENS) may also be of benefit.[8,10]

For the management of pain, paracetamol is recommended as the drug of first choice.[1-6,8] Despite its benefits it has been shown to be less effective than an NSAID in patients with osteoarthritis,[11] and the latter may therefore be considered as an alternative first-line treatment.[2,4] However, because of the risk of potentially serious toxicity in a predominantly elderly group of patients, it is generally considered that a low-dose NSAID should only be added or substituted in patients with an inadequate response to paracetamol alone,[2,4,5] and the long-term use needed for osteoarthritis management may be problematic.[12] Like other treatments NSAIDs do not slow the disease process, and there has even been a concern that some NSAIDs such as indometacin might accelerate it.[6]

In order to reduce the risk of gastrointestinal toxicity with NSAIDs, use of a gastroprotective drug such as a proton pump inhibitor or misoprostol has been recommended.[1-5,8] The use of topical NSAIDs has also been advocated,[4,6,8] although a meta-analysis[13] in 2004 found little evidence of long-term benefit. In the light of concerns about cardiovascular safety, treatment with NSAIDs such as celecoxib that are selective inhibitors of cyclo-oxygenase-2 (COX-2) is limited[14] to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see p.97).

In patients in whom paracetamol and/or NSAIDs are ineffective or not tolerated, addition of an opioid analgesic may be appropriate;[2,3,5,8,15] codeine or dihydrocodeine are often used as combinations with paracetamol, and there is evidence of benefit with tramadol, but more potent opioids such as hydrocodone, oxycodone, transdermal fentanyl, or morphine, may have a role in a selected subgroup of patients.[15]

The anthraquinone derivative diacerein has been widely used in some countries, and appears to produce a small but consistent benefit in the treatment of osteoarthritis.[16] Topical capsaicin also produces some relief of pain.[1,4,5,8] There are some interesting data[17] to suggest that doxycycline may have a favourable effect on the progression of osteoarthritis, which might open the way for the development of disease-modifying drugs. Experimental therapies include anakinra[18] and the combined cyclo-oxygenase/lipoxygenase inhibitor licofelone.[19]

Systemic corticosteroids have no place in the management of osteoarthritis. Intra-articular injection of a corticosteroid produces short-term relief of pain and inflammation,[2-4,8,20,21] and may be useful for acute exacerbations. Triamcinolone hexacetonide appears to be more effective than betamethasone.[21] There may also be some benefit from intra-articular injection of hyaluronic acid, to improve the viscosity and elasticity of the synovial fluid;[22,23] improvement may be longer lasting than with intra-articular corticosteroids.[21]

Alternative and complementary therapies have been widely used in osteoarthritis.[2] Powdered rose hip has been reported to be of benefit,[24] as has a mixture of unsaponifiable fractions from avocado and soya oils (avocado-soybean unsaponifiables; ASU).[25] Particular attention has focused on the use of oral glucosamine and chondroitin. Results, however, have been ambiguous:[26-29] overall it is not clear to what extent these therapies have a benefit over placebo, but there is some evidence that combined treatment may be useful in the subset of patients with moderate to severe knee pain.[26] Evidence for chondroitin seems particularly weak.[29]

Surgery, including joint replacement, is of great benefit to patients with severe osteoarthritis that cannot be effectively managed by physical or medical therapy.[2-6,8]

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Rheumatoid arthritis

Rheumatoid arthritis is a common chronic systemic inflammatory disease that results in progressive disability and increased mortality. Early disease is characterised primarily by inflammation of the synovium (the inner membrane of the capsule of synovial joints); as the disease progresses the patient suffers destruction of cartilage and bone. Extra-articular features commonly include general malaise, fatigue, weight loss, fever, and anaemia. More severe disease may be associated with vasculitis, pericarditis, pleurisy, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules, scleritis, and Sjögren's syndrome. Palindromic rheumatism is characterised by repeated episodes of arthritis and periarthritis without fever; the joints appear normal between attacks.

The severity and course of rheumatoid arthritis varies greatly between patients. Some have brief attacks with little or no disease progression, but the majority will have slowly progressive joint destruction and deformity despite intermittent relapses and remissions; a few patients may have very severe and rapidly progressive disease. Because irreversible joint damage occurs early in the course of disease, rapid diagnosis and institution of treatment aimed at preventing progression is crucial.[1-3] Although there is no cure, remission or substantial slowing of the disease process is increasingly seen as an achievable goal in the majority of patients.[4,5]

The choice of **drugs for relief of pain** depends upon the severity of symptoms. In mild cases an analgesic such as paracetamol (with codeine if needed) may be all that is required but most patients prefer an NSAID; although these are thought to have an advantage because of their anti-inflammatory effects, the clinical evidence for this has been questioned.[6] There is little apparent difference between the various NSAIDs in terms of anti-inflammatory activity, but patient responses vary widely. When starting an NSAID the dose is gradually increased to the recommended maximum over 1 to 2 weeks; if the response is inadequate after a total of about 4 weeks, or if adverse effects are intolerable, other NSAIDs are tried. In the light of concerns about cardiovascular safety, treatment with NSAIDs such as celecoxib that are selective inhibitors of cyclo-oxygenase-2 (COX-2) is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors[7] (see p.97). Topical analgesics such as NSAIDs or capsaicin, or rubefacients may provide slight relief of pain but their role, if any, is unclear.

Once the diagnosis is confirmed and severity and progression of the disease have been assessed, introduction of a **disease-modifying antirheumatic drug** (DMARD) should take place as early as possible.[1-4,8] Although opinions vary, there is an increasing trend to aggressive management in early disease, with tight control of the disease process.[4,5,9]

Available DMARDs include antimalarials (hydroxychloroquine), sulfasalazine, gold compounds (auranofin, sodium aurothiomalate), penicillamine, conventional immunosuppressants (methotrexate, azathioprine, ciclosporin, cyclophosphamide, and leflunomide), and so-called biological therapies, including the tumour necrosis factor-α (TNF-α) inhibitors (adalimumab, etanercept, and infliximab), co-stimulation blockers (abatacept), interleukin-1 receptor antagonists (anakinra), and B-cell-targeted antibodies (rituximab). It is thought that most DMARDs inhibit the release or activity of cytokines involved in maintaining the inflammatory process, although other actions may also contribute. Since any therapeutic effect may not be apparent for 4 to 6 months, treatment should continue for at least 6 months before considered ineffective.

There is evidence of disease modifying effect for methotrexate, sulfasalazine, leflunomide, and intramuscular gold, with less compelling data for hydroxychloroquine, penicillamine, oral gold, ciclosporin, and azathioprine.[9-15] Concerns about toxicity or effectiveness mean that gold compounds and penicillamine seem now to be less widely used. There is good evidence of the effectiveness of the TNF-α inhibitors,[4,5,9,15-17] and some in favour of anakinra,[16] but good evidence of an effect of other biological therapies on disease progression is currently scanty, although clinical benefit has been found with, for example, abatacept and rituximab.[5,16,18]

The choice of DMARD to begin treatment is based on the risk/benefit ratio, with the antimalarial hydroxychloroquine an option in mild disease, and sulfasalazine or methotrexate preferred in those with moderate to severe disease, or judged likely to progress.[9] Methotrexate has become the DMARD of first choice in the majority of patients.[1,2,8,9] Subcutaneous or intramuscular methotrexate may be an option in patients who cannot be satisfactorily managed with weekly oral dosage.[1,9] Addition of sulfasalazine, hydroxychloroquine, or both may be a suitable option in patients refractory to optimal methotrexate therapy,[1,9] and addition of corticosteroids or leflunomide are also options, although evidence for combining methotrexate with ciclosporin is not entirely convincing.[9] At what stage biological therapies are to be recommended remains a matter of debate. In the UK, official recommendations are still that TNF-α inhibitors should be reserved for patients who have failed treatment with two conventional DMARDs,[17,19] but others permit earlier introduction, for example after failure of the first conventional DMARD.[8,16,20] Other classes of biological therapy are likely to be reserved for patients in whom TNF-α inhibitors are ineffective or contra-indicated, as is currently the case with rituximab.[18,21]

There is also some evidence in favour of beginning therapy with a combination of DMARDs, and subsequently 'stepping down' once control is achieved.[1,4,5,8,9,22,23] The large, multicentre BeSt study found that although initial combination therapy (methotrexate and infliximab, or methotrexate, sulfasalazine, and tapered high-dose prednisone) produced earlier clinical improvement and less progression of joint damage, the ultimate clinical improvement was similar in patients assigned to sequential monotherapy or 'step-up' therapy.[24] There is a concern that combination therapy may expose patients to an increased risk of toxicity,[22] although the BeSt study did not find this to be the case.[24] Combinations of TNF-α inhibitors with other biological response modifiers such as anakinra or abatacept are not advisable, because of an increased risk of serious infection.[5,16]

Since rheumatoid arthritis is a chronic disease, treatment may need to be very prolonged, but evidence of the long-term tolerability and efficacy of DMARDs is patchy. Studies have suggested that many DMARDs are stopped after a few years, usually because of a decline in efficacy rather than adverse events.[25]

Addition of **corticosteroids** to DMARD therapy may be useful in early disease to control synovitis, or as bridging therapy when starting or increasing DMARDs, since they produce rapid symptomatic control.[9] Although they produce bone loss, this may be outweighed (at least short-term) by their beneficial effects on the disease process: there is good evidence that adding a corticosteroid to treatment reduces the progression of joint erosion.[26] Short-term and moderate-term intermittent use of relatively low doses has therefore been suggested (not exceeding the equivalent of 15 mg of prednisolone daily).[27,28] However, prolonged therapy is associated with significant adverse effects, and long-term use is not considered justified.[9] Intra-articular injection is recommended for acute flares, and may be particularly effective when combined with aggressive DMARD therapy.[9]

There is little good evidence to support most **other drugs** tried in rheumatoid arthritis.[8] Meta-analysis[29] has confirmed that tetracyclines, and in particular minocycline, can produce some reduction in disease activity; effects on serological markers appear to be more marked than clinical improvements in tender and swollen joints. The effects may be greater in patients with early disease. Much research has been conducted into immunomodulators and immunotherapy. Although alternative immunosuppressants such as mycophenolate mofetil and tacrolimus have been tried, most interest in recent years has surrounded new biological therapies. Matrix metalloproteinase inhibitors have proved disappointing, but new TNF-α inhibitors such as certolizumab pegol and golimumab, the interleukin-6 receptor antagonist tocilizumab, and modulators of B-cell function such as atacicept, belimumab, and epratuzumab are under investigation. In addition, denosumab is of interest for its potential to control joint destruction.[5] Other methods of treatment that are being or have been investigated include gene therapy and autologous bone marrow transplantation. A rheumatoid arthritis vaccine is also in clinical trials. Induction of tolerance with collagen and other antigens given orally has also been tried, but results are reported to be variable.[30]

Some studies suggest that addition of fish oils[31] and/or evening primrose oil to standard antirheumatic therapy might help to reduce pain and joint swelling. Many alternative and herbal therapies have been tried, although good evidence of benefit is scanty.

There has been considerable interest in the possibility that statins such as atorvastatin may produce clinical improvements, albeit modest, in symptoms of rheumatoid arthritis,[32] as well as in any accompanying cardiovascular risk factors.

The importance of managing co-morbidity in patients with rheumatoid arthritis has been emphasised;[1] in particular infection (especially pulmonary infection), cardiovascular disease, and osteoporosis require appropriate management and action to reduce risk factors.

The treatment of rheumatoid arthritis during **pregnancy** presents its own problems; some of the most effective DMARDs such as methotrexate and leflunomide have teratogenic properties, and for others, including the biological therapies, there is little evidence.[33,34] Hydroxychloroquine, and perhaps azathioprine and sulfasalazine, may be relatively safe to use, but it is important to weigh benefit against risk for each individual case.[33]

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Soft-tissue rheumatism

Soft-tissue rheumatism includes conditions such as:

- bursitis (e.g. housemaid's knee)
- fasciitis
- fibromyalgia (fibrositis, muscular rheumatism, myofascial pain)
- frozen shoulder
- humeral epicondylitis (e.g. tennis or golfer's elbow)
- sprains and strains
- tendinitis
- tenosynovitis
- Tietze's syndrome

Inflamed or displaced tissue may also impinge on nearby nerves and produce compression neuropathies such as carpal tunnel syndrome.

Some forms of soft-tissue rheumatism respond to selective rest of the affected region, massage, splinting, or application of heat, cold, or rubefacients.[1-3] Exercise is of value in neck pain,[3,4] fibromyalgia,[5,6] and frozen shoulder,[7] but its benefit in epicondylitis is unclear.[4]

For patients with epicondylitis oral or topical NSAIDs may offer short-term pain relief, but it is unclear if they are effective in producing longer term benefit.[4] They are of unknown benefit in frozen shoulder,[7] and are not thought to be helpful in fibromyalgia,[5] although some benefit has been reported with paracetamol and tramadol.[8]

Corticosteroid injections produce dose-dependent benefit for up to 9 months in shoulder pain such as that associated with rotator cuff tendinitis or frozen shoulder,[9] and oral corticosteroids may be of benefit for up to 6 weeks although it is not clear that benefit is subsequently maintained[10] (a study[11] in patients with epicondylitis suggested that benefits of corticosteroid injection in this group were paradoxically reversed after 6 weeks). Corticosteroid injections are often combined with a local anaesthetic; injection of a local anaesthetic alone has been shown to be of benefit in chronic neck pain.[4]

Botulinum toxin has been tried in epicondylitis[12] and myofascial pain.[13] There is evidence that nitric oxide plays a role in healing in patients with tendinitis, and topical application of a patch containing glyceryl trinitrate has proved of benefit in patients with epicondylitis or tendinitis.[14]

Fibromyalgia appears to be associated with abnormal pain responses, and some consider it a central pain syndrome rather than a rheumatic syndrome. There is strong evidence that low-dose tricyclic antidepressants are of benefit in many patients, as is the tricyclic compound cyclobenzaprine. Combination of amitriptyline with the SSRI fluoxetine also appears beneficial, although SSRIs alone have produced equivocal results; serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine, milnacipran, or venlafaxine have also been reported to be of value. Pregabalin and gabapentin have been shown to be of benefit in controlled studies.[5,6,8]

Surgery may be of benefit in some conditions such as epicondylitis and possibly shoulder pain.[4] Surgical decompression is also the definitive treatment for carpal tunnel syndrome,[15] although there is also evidence of benefit from splinting[16] and local corticosteroid injection[17] (although benefit may not be long term, and the procedure carries some risks[18]). Oral corticosteroids and ultrasound have also demonstrated benefit in patients with carpal tunnel syndrome.[16]

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Spondyloarthropathies

The spondyloarthropathies are a group of seronegative arthritides which include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disorders (enteropathic arthritis), and arthritis associated with infection as in reactive arthritis (aseptic arthritis).

Ankylosing spondylitis is characterised by arthritis of the spine and sacroiliac joints and sometimes there is also asymmetrical peripheral involvement. Males under 40 years of age are mainly affected. The aim of management of the disease is to reduce pain and stiffness and to prevent spine and joint deformity, which is accomplished using a combination of active physical therapy and drug therapy. Exercises are used to strengthen muscles and to maintain a good posture and range of movement in joints. NSAIDs are used to relieve pain and inflammation, thus allowing the exercises to be performed; they do not influence the progression of the disease. Some patients may need to add other non-opioid analgesics such as paracetamol for additional pain control. Systemic corticosteroids are rarely indicated but intra-articular injections of corticosteroids may be beneficial when one or two peripheral joints are severely affected. The disease-modifying antirheumatic drug (DMARD) sulfasalazine is of benefit for peripheral arthritis, but not for spinal symptoms. The efficacy of most other DMARDs used in rheumatoid arthritis (see above) remains to be demonstrated. However, the tumour necrosis factor-α (TNF-α) inhibitors adalimumab, etanercept, and infliximab improve spinal pain, function, and peripheral joint disease. They produce rapid benefit (usually within 12 weeks) although most patients relapse once they are withdrawn. Treatment with a TNF-α inhibitor should be considered in patients with active disease despite conventional treatments. There is some evidence that early intervention may produce better remission rates, but it is yet unknown if this results in longer-lasting remission on withdrawal. Evidence is mostly lacking for other biological therapies, but no marked benefit has been seen in conflicting studies with the interleukin-1 receptor antagonist anakinra.

Psoriatic arthritis (or psoriatic arthropathy) is an inflammatory seronegative arthritis occurring in patients with psoriasis. In some patients the spine may be involved when the condition may be indistinguishable from ankylosing spondylitis. Less frequently some patients have a form of symmetrical arthritis resembling rheumatoid arthritis. The psoriasis (p.1583) and the arthritis usually require separate treatment. Treatment of the arthritis is initially as for ankylosing spondylitis with NSAIDs and physical therapy. If these methods fail treatment with a DMARD may be instituted, although chloroquine and hydroxychloroquine should be avoided since they may precipitate skin reactions (see Psoriatic Arthritis, p.601). There is most evidence to support the use of sulfasalazine or methotrexate. Leflunomide may be effective but is likely to be restricted by its toxicity and prolonged half-life. Ciclosporin is also restricted by its toxicity. As in ankylosing spondylitis, however, significant benefit has now been found with the TNF-α inhibitors, and treatment with these is recommended in patients with active disease despite treatment with NSAIDs and/or DMARDs. In the UK, etanercept or adalimumab are preferred to infliximab, but treatment should be individualised; a monoclonal antibody such as adalimumab or infliximab is advocated by others in patients who also have inflammatory bowel disease. There is some suggestion that alefacept may also be of benefit in psoriatic arthritis. Systemic corticosteroids have little or no place in the management of psoriatic arthritis.

Reactive arthritis is characterised by sterile synovitis following 1 to 4 weeks after an infection, most commonly of the gastrointestinal or genito-urinary tract. Extra-articular features involving the skin, eyes, or genito-urinary tract may or may not be present. Reactive arthritis is also a feature of Reiter's syndrome. Reactive arthritis is treated with physical therapy and NSAIDs and, if indicated, intra-articular injections of corticosteroids; the role of antibacterials is less certain (see Bone and Joint Infections, p.164).

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Still's disease

Adult-onset Still's disease is a syndrome characterised by high fever, with body temperature classically spiking daily or twice daily, an evanescent pink maculopapular rash, and arthritis (usually oligoarthritis initially). It is most common in patients aged 16 to 35 years.

Treatment has traditionally relied on NSAIDs, corticosteroids, and immunosuppressants or other DMARDs similar to those used in rheumatoid arthritis (above).[1-3] A trial of NSAIDs is worthwhile in patients with mild disease, but most patients cannot be managed with NSAIDs alone.[2,3] Corticosteroids may be needed for initial therapy if manifestations are severe, but will eventually be needed in about 80% of cases.[2] DMARDs (generally methotrexate) are introduced when corticosteroid therapy fails to control the disease or when their adverse effects become problematic. Most patients will respond to methotrexate although liver function must be closely monitored. The value of other DMARDs is uncertain. Intravenous immunoglobulin is also frequently tried, although supporting evidence is lacking.[2,3]

The TNF-α inhibitors have also been tried,[2,3] but results have been variable.[2] There is, however, some evidence that interleukin-1 and interleukin-6 play a role in pathogenesis of the condition, and there have been a few reports of dramatic improvement with anakinra (an interleukin-1 receptor antagonist) in resistant disease, while tocilizumab (an interleukin-6 receptor antagonist) has also been suggested as an investigational therapy.[2,3]

The name Still's disease has also been used rather inconsistently to describe some types of juvenile idiopathic arthritis (above).

1. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. *Semin Arthritis Rheum* 2006; **36:** 144–52.
2. Pouchot J. How can we improve the management of adult-onset Still's disease? *Joint Bone Spine* 2007; **74:** 117–19.
3. Kontzias A, Efthimiou P. Adult-onset Still's disease : pathogenesis, clinical manifestations and therapeutic advances. *Drugs* 2008; **68:** 319–337.

Abatacept *(BAN, USAN, rINN)*

Abataceptum; BMS-188667; CTLA4-Ig. 1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment), bimolecular (146→146′)-disulfide.

Абатацепт

CAS — 332348-12-6.
ATC — L04AA24.
ATC Vet — QL04AA24.

Adverse Effects and Precautions

Acute infusion reactions occurring within 1 hour of starting an infusion are common with abatacept use. The most frequently reported infusion events are dizziness, headache, and hypertension; hypotension and dyspnoea occur less commonly. Other acute events include nausea, flushing, pruritus, rash, and wheezing. Most events are usually mild to moderate although stopping treatment may be necessary in a few patients.

Other common adverse effects include headache, nasopharyngitis, nausea, dyspepsia, diarrhoea, dizziness, back pain, fatigue, cough, and abnormal liver function values. Antibodies to abatacept may develop and anaphylaxis or anaphylactic reactions have been reported rarely. Uncommon adverse reactions include paraesthesia, thrombocytopenia, and leucopenia.

Infections are frequent in patients treated with abatacept and most often affect the respiratory and urinary tracts. More serious infections such as pneumonia, sepsis, cellulitis, bronchitis, diverticulitis, and acute pyelonephritis have also been rarely associated with abatacept treatment. Treatment should be stopped in patients who develop a serious infection. Abatacept should not be given to patients with severe and uncontrolled infections such as sepsis and opportunistic infections. It should be used with caution in patients with a history of recurrent infections, with underlying conditions that may predispose to infections, or with chronic, latent, or localised infections. Patients should be screened for latent tuberculosis before starting treatment; those testing positive should be treated with standard chemoprophylaxis before beginning abatacept.

Some disease-modifying antirheumatic drugs have been associated with hepatitis B reactivation; licensed product information for abatacept recommends screening for viral hepatitis before starting treatment.

Adverse effects of abatacept are more frequent in patients with chronic obstructive pulmonary disease and may include a worsening of their respiratory symptoms.

Carcinogenicity. The role of abatacept in the onset of malignancies such as lymphoma in humans is not known.

In placebo-controlled studies the overall frequency of malignancies in patients treated with abatacept compared to those that received placebo was similar (1.4% and 1.1%, respectively). However, there were more cases of lung cancer and lymphomas in those given abatacept. In *animal* studies in mice, increases in lymphomas and mammary tumours have been noted, although these increases have not been seen in some studies with other mammals.

Interactions

Live vaccines should not be given with abatacept, or within 3 months of stopping it, as its effect on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with abatacept may increase the risk of serious infections (see p.71); such combinations are not recommended. Use with anakinra or rituximab is also not recommended because of insufficient evidence to assess safety.

Pharmacokinetics

Abatacept is reported to have linear pharmacokinetics at usual dosages. After repeated intravenous doses, its mean terminal half-life is about 13 days.

Studies in *animals* suggest that abatacept is distributed into breast milk.

Uses and Administration

Abatacept, a fusion protein, is a co-stimulation blocker. It prevents the activation of T-cells; activated T-cells have been found in the synovium of patients with rheumatoid arthritis. It is used in the treatment of moderate to severe active rheumatoid arthritis to delay structural damage and improve physical function. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor; in the USA, it may be used to reduce the signs and symptoms of early disease.

Abatacept is given by intravenous infusion over a period of 30 minutes in the following doses, based on body-weight:

- 500 mg for patients weighing less than 60 kg
- 750 mg for those weighing 60 to 100 kg
- 1 g for those over 100 kg.

The dose is repeated at 2 and 4 weeks, then every 4 weeks thereafter. If a response to treatment is not seen within 6 months, the benefits of continuing abatacept may need to be considered. In the UK, abatacept is licensed for use with methotrexate; however, in the USA it may be given alone or with other DMARDs (but see Interactions, above).

For the use of abatacept in children, and recommended doses, see below.

Abatacept is also being studied for other auto-immune diseases such as inflammatory bowel disease, psoriatic arthritis, and SLE.

Administration in children. In the USA, abatacept is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 6 years and above; it may be used alone or with methotrexate. The dose is calculated according to body-weight and is given as an intravenous infusion over 30 minutes; those weighing less than 75 kg should be given 10 mg/kg initially, while heavier children may receive the appropriate adult dose (see above). Doses should be repeated at 2 and 4 weeks, and then every 4 weeks thereafter.

Rheumatoid arthritis. References to the use of abatacept in rheumatoid arthritis (p.11).

1. Kremer JM, *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003; **349:** 1907–15.
2. Genovese MC, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. *N Engl J Med* 2005; **353:** 1114–23. Correction. *ibid.*; 2311.
3. Kremer JM, *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; **144:** 865–76.
4. Weinblatt M, *et al.* Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006; **54:** 2807–16.
5. Nogid A, Pham DQ. Role of abatacept in the management of rheumatoid arthritis. *Clin Ther* 2006; **28:** 1764–78.
6. Pollard LC. Inhibiting costimulatory activation of T cells: a viable treatment option for rheumatoid arthritis? *Drugs* 2007; **67:** 1–9.
7. Lundquist L. Abatacept: a novel therapy approved for the treatment of patients with rheumatoid arthritis. *Adv Therapy* 2007; **24:** 333–45.
8. Russell AS, *et al.* Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007; **66:** 189–94.
9. Bruce SP, Boyce EG. Update on abatacept: a selective costimulation modulator for rheumatoid arthritis. *Ann Pharmacother* 2007; **41:** 1153–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Orencia; ***Cz.:*** Orencia; ***Fr.:*** Orencia; ***Port.:*** Orencia; ***UK:*** Orencia; ***USA:*** Orencia.

Aceclofenac *(BAN, rINN)*

Acéclofénac; Aceclofenaco; Aceclofenacum; Aceklofenák; Aceklofenak; Aceklofenakas; Aseklofenaakki; Aseklofenak. [o-(2,6-Dichloroanilino)phenyl]acetate glycolic acid ester; 2-(2,6-Dichloroanalino)phenylacetoxyacetic acid.

Ацеклофенак

$C_{16}H_{13}Cl_2NO_4$ = 354.2.
CAS — 89796-99-6.
ATC — M01AB16; M02AA25.
ATC Vet — QM01AB16; QM02AA25.

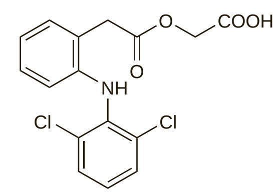

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Aceclofenac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Hypersensitivity. Leukocytoclastic vasculitis, a type III hypersensitivity reaction, has been reported after therapy with aceclofenac.[1,2] Anaphylaxis has also occurred.[3]

1. Epelde F, Boada L. Leukocytoclastic vasculitis and hemoptysis after treatment with aceclofenac. *Ann Pharmacother* 1995; **29:** 1168.
2. Morros R, *et al.* Hypersensitivity vasculitis related to aceclofenac. *Br J Rheumatol* 1997; **36:** 503–4.
3. Rojas-Hijazo B, *et al.* Anaphylactic reaction after aceclofenac intake. *Allergy* 2006; **61:** 511.

Precautions

As for NSAIDs in general, p.98.

Aceclofenac should be avoided in patients with moderate to severe renal impairment.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Aceclofenac is well absorbed from the gastrointestinal tract; peak plasma concentrations are reached 1 to 3 hours after an oral dose. Aceclofenac is more than 99% bound to plasma proteins. The plasma-elimination half-life is about 4 hours. About two-thirds of a dose is excreted in the urine, mainly as hydroxymetabolites. A small amount is converted to diclofenac.

◊ It has been suggested[1] that low concentrations of diclofenac, a minor metabolite, may account for some of the actions of aceclofenac.

1. Hinz B, *et al.* Aceclofenac spares cyclooxygenase 1 as a result of limited but sustained biotransformation to diclofenac. *Clin Pharmacol Ther* 2003; **74:** 222–35.

Uses and Administration

Aceclofenac, a phenylacetic acid derivative, is an NSAID (see p.99) related to diclofenac (p.44). It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, in usual oral doses of 100 mg twice daily. Reduced doses should be used in patients with hepatic impairment, see below.

◊ Reviews.

1. Dooley M, *et al.* Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. *Drugs* 2001; **61:** 1351–78.
2. Reginster JY, *et al.* Comment positionner l'acéclofénac au sein de l'arsenal thérapeutique des pathologies ostéo-articulaires chroniques? *Rev Med Liege* 2001; **56:** 484–8.
3. Legrand E. Aceclofenac in the management of inflammatory pain. *Expert Opin Pharmacother* 2004; **5:** 1347–57.
4. Lee J, *et al.* Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch Pharm Res* 2005; **28:** 1097–1102.

Administration in hepatic impairment. The initial oral dose of aceclofenac should be reduced to 100 mg daily in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Berlofen; Bristaflam†; ***Austria:*** Beofenac†; ***Belg.:*** Air-Tal; Biofenac; ***Braz.:*** Aceflan†; Cecoflan†; Proflam; ***Chile:*** Airtal†; Bristaflam†; ***Denm.:*** Barcan; ***Fin.:*** Barcan; ***Fr.:*** Cartrex; ***Ger.:*** Beofenac; ***Gr.:*** Aceclonac; Arlina; Biofenac; Sovipan; ***Hung.:*** Aflamin; ***India:*** Aceclo; Arrestin; Movon; Zerodol; ***Ital.:*** Airtal; Gladio; Kafenac; ***Mex.:*** Bristaflam; ***Neth.:*** Biofenac; ***Norw.:*** Barcan; ***Philipp.:*** Clanza; ***Port.:*** Airtal; Biofenac; ***Rus.:*** Airtal (Аэртал); ***Spain:*** Airtal; Airtal Difucrem; Falcol; Gerbin; Sanein; ***Swed.:*** Barcan; ***Switz.:*** Locomin†; ***UAE:*** Aceclofar; ***UK:*** Preservex; ***Venez.:*** Airtal†; Bristaflam.

Multi-ingredient: ***India:*** Kinectine; Kinectine P; Kinectine-MR; Movon-MR; Movon-P†; Zerodol-MR; Zerodol-P.

Acemetacin *(BAN, rINN)*

Acemetacina; Acémétacine; Acemetacinum; Asemetasin; Bay-f-4975; Indometasinin Glikolik Asit Esteri; TVX-1322. *O*-[(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-yl)acetyl]glycolic acid.

Ацеметацин

$C_{21}H_{18}ClNO_6$ = 415.8.

CAS — 53164-05-9.

ATC — M01AB11.

ATC Vet — QM01AB11.

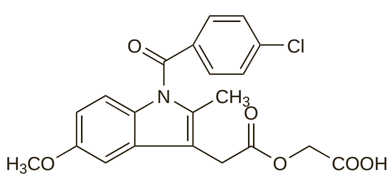

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Acemetacin). A yellow or greenish-yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous alcohol; soluble in acetone. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Acemetacin is well absorbed after oral dosage. Its major metabolite is indometacin (p.66) which, after repeated doses, is present at higher concentrations than those of acemetacin. Acemetacin is bound to plasma proteins to a slightly lesser extent than indometacin. It is eliminated via both the liver and the kidneys.

Uses and Administration

Acemetacin, a glycolic acid ester of indometacin, is an NSAID (p.99). Its pharmacological activity is due to both acemetacin and its major metabolite, indometacin (p.66). Acemetacin is used in rheumatoid arthritis, osteoarthritis, and low back pain, and for postoperative pain and inflammation. Usual oral doses are 120 to 180 mg daily in divided doses. Acemetacin is eliminated by both hepatic and renal routes, although pharmacokinetics are not affected by moderate renal or hepatic impairment and appear to be unchanged in the elderly.

◊ References.

1. Jones RW, *et al.* Comparative pharmacokinetics of acemetacin in young subjects and elderly patients. *Br J Clin Pharmacol* 1991; **31:** 543–5.
2. Hazleman B, Bernstein RM. Acemetacin in the long-term therapy of rheumatoid arthritis. *Curr Med Res Opin* 1993; **13:** 119–26.
3. Chou CT, Tsai YY. A double-blind, randomized, controlled parallel group study evaluating the efficacy and safety of acemetacin for the management of osteoarthritis. *Int J Clin Pharmacol Res* 2002; **22:** 1–6.
4. Leeb BF, *et al.* Behandlung der Gonarthrose: Wirksamkeit und Verträglichkeit von retardiertem Acemetacin im Vergleich zu Celecoxib. *Orthopade* 2004; **33:** 1032–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Rheutrop; ***Cz.:*** Rantudil; ***Ger.:*** Acemetadoc; Acephlogont†; Rantudil; ***Gr.:*** Gamespir†; Rantutal; ***Hung.:*** Rantudil; ***Ital.:*** Acemix; Solart†; ***Jpn:*** Rantudil; ***Mex.:*** Rantudil; ***Philipp.:*** Rantudil; ***Pol.:*** Rantudil; ***Port.:*** Rantudil; ***Spain:*** Espledol; Oldan; ***Switz.:*** Tilur; ***Turk.:*** Rantudil; ***UK:*** Emflex; ***Venez.:*** Mostanol†; Pranex.

Multi-ingredient: ***Arg.:*** Rucaten Forte; Rucaten Prednisolona.

Acetanilide

Acetanilida; Antifebrin. *N*-Phenylacetamide.

Антифебрин; Ацетанилид

C_8H_9NO = 135.2.

CAS — 103-84-4.

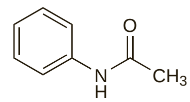

Pharmacopoeias. In *Fr.*

Profile

Acetanilide, a para-aminophenol derivative related to paracetamol (p.108), has analgesic and antipyretic properties. It was replaced by safer analgesics.

Actarit *(rINN)*

Actaritum; MS-932. (*p*-Acetamidophenyl)acetic acid.

Актарит

$C_{10}H_{11}NO_3$ = 193.2.

CAS — 18699-02-0.

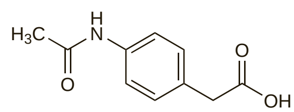

Profile

Actarit is reported to be a disease-modifying antirheumatic drug. It has been given in the treatment of rheumatoid arthritis in a usual oral dose of 100 mg three times daily.

Adverse effects. A photosensitivity reaction developed in a 52-year-old woman one month after starting actarit and doxycycline.[1] Photopatch tests for both drugs were only positive for the patches containing actarit.

1. Kawada A, *et al.* Photosensitivity due to actarit. *Contact Dermatitis* 1997; **36:** 175–6.

Use. References.

1. Nakamura H, *et al.* Clinical effects of actarit in rheumatoid arthritis: improvement of early disease activity mediated by reduction of serum concentrations of nitric oxide. *Clin Exp Rheumatol* 2000; **18:** 445–50.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Mover†; Orcl.

Adalimumab *(BAN, USAN, rINN)*

Adalimumabum; D2E7; LU-200134. Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer.

Адалимумаб

CAS — 331731-18-1.

ATC — L04AB04.

ATC Vet — QL04AB04.

Adverse Effects and Precautions

As for Infliximab, p.69.

Injection site reactions including erythema, itching, pain, and swelling are the most common adverse reactions with adalimumab; however, most reactions are mild and do not result in drug withdrawal. Other common reactions include headache, rashes, back pain, hypertension, paraesthesias, increased alkaline phosphate levels, and cough.

Autoantibodies to adalimumab have been detected.

Interactions

As for Infliximab, p.71.

Methotrexate is reported to reduce the clearance of adalimumab by up to 44% but licensed product information for the latter states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Adalimumab is reported to have linear pharmacokinetics at usual dosages. After subcutaneous injection peak concentrations are reached in about 3 to 8 days and bioavailability is estimated to be 64%. The mean terminal half-life is about 2 weeks.

◊ References.

1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; **74** (suppl): 13–18.

Uses and Administration

Adalimumab is a recombinant human monoclonal tumour necrosis factor (TNF) antibody that binds specifically to TNF-α and blocks its interaction with endogenous cell-surface TNF receptors. It also modulates biological responses that are induced or regulated by TNF. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and Crohn's disease.

Adalimumab is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active and progressive **psoriatic arthritis** to delay structural damage and improve physical function. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs), although in severe progressive rheumatoid arthritis it may be used in patients not previously treated with methotrexate; in the USA, it may be used to reduce the signs and symptoms of early disease. Adalimumab is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used to reduce signs and symptoms in early disease. For all the above indications, it is given by subcutaneous injection in a dose of 40 mg every other week. In the treatment of rheumatoid arthritis, UK licensed product information recommends that adalimumab should be given with methotrexate, although monotherapy may be used where treatment with methotrexate would be inappropriate. When used as monotherapy in rheumatoid arthritis, some patients may benefit from increasing the dose to 40 mg every week. Clinical response is usually achieved within 12 weeks of treatment.

Adalimumab is also used in the treatment of moderate to severe, active **Crohn's disease** unresponsive to conventional treatment; it may also be used in patients who have relapsed while taking infliximab. Patients may be given an initial dose of 160 mg on day 1 (given as four 40-mg injections in one day or two 40-mg injections daily for 2 consecutive days), followed by 80 mg two weeks later (day 15). After a further two weeks (day 29), a maintenance dose of 40 mg every other week may be started. Alternatively, UK licensed product information advises that patients at risk of adverse effects may be given 80 mg initially, followed by 40 mg 2 weeks later; thereafter, usual maintenance doses may be given. A clinical response is usually seen within 12 weeks of starting treatment; those patients who relapse while on adalimumab may benefit from increasing the maintenance dose to 40 mg every week.

In the treatment of moderate to severe chronic **plaque psoriasis** in patients unresponsive to, or intolerant of, conventional systemic therapy including phototherapy, the recommended initial dose of adalimumab is 80 mg subcutaneously; this may be followed by a maintenance dose of 40 mg subcutaneously on alternate weeks, starting 1 week after the initial dose. A clinical response is usually seen within 16 weeks of starting treatment.

For the uses of adalimumab in children, and recommended doses, see below.

Administration in children. In the USA, adalimumab is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 4 years and above: it may be used alone or with methotrexate. The dose is calculated according to weight and is given subcutaneously: those weighing 15 kg to less than 30 kg should be given 20 mg every other week, while heavier children may receive 40 mg every other week.

Inflammatory bowel disease. Adalimumab is used in the management of Crohn's disease[1-4] (p.1697), including in patients who are intolerant of, or relapse on, infliximab treatment.[5-8] It has also been tried in the treatment of ulcerative colitis (p.1697).[9]

1. Hanauer SB, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130:** 323–33.
2. Sandborn WJ, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56:** 1232–9.
3. Colombel JF, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132:** 52–65.
4. Plosker GL, Lyseng-Williamson KA. Adalimumab: in Crohn's disease. *BioDrugs* 2007; **21:** 125–32.
5. Sandborn WJ, *et al.* An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004; **99:** 1984–9.
6. Papadakis KA, *et al.* Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. *Am J Gastroenterol* 2005; **100:** 75–9.
7. Peyrin-Biroulet L, *et al.* Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. *Aliment Pharmacol Ther* 2007; **25:** 675–80.
8. Sandborn WJ, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007; **146:** 829–38.
9. Peyrin-Biroulet L, *et al.* Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol* 2007; **13:** 2328–32.

Psoriasis. Adalimumab is used in the treatment of plaque psoriasis (p.1583).

References.

1. Gordon KB, *et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55:** 598–606.
2. Papoutsaki M, *et al.* Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. *J Am Acad Dermatol* 2007; **57:** 269–75.
3. Menter A, *et al.* Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58:** 106–15.
4. Revicki D, *et al.* Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008; **158:** 549–57.
5. Saurat J-H, *et al.* CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. *Br J Dermatol* 2008; **158:** 558–66.
6. NICE. Adalimumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 146 (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA146Guidance.pdf (accessed 25/07/08)

Rheumatoid arthritis. References to the use of adalimumab in rheumatoid arthritis (p.11).

1. den Broeder AA, *et al.* Long-term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. *Ann Rheum Dis* 2002; **61**: 311–18.
2. Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. *Ann Rheum Dis* 2002; **61** (suppl 2): 70–3.
3. Weinblatt ME, *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; **48:** 35–45.
4. Furst DE, *et al.* Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; **30:** 2563–71.
5. van de Putte LB, *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; **63:** 508–16.
6. Keystone EC, *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; **50:** 1400–11.
7. Wick MC, *et al.* Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. *Scand J Rheumatol* 2005; **34:** 353–8.
8. Navarro-Sarabia F, *et al.* Adalimumab for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 13/06/08).
9. Weinblatt ME, *et al.* Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. *Ann Rheum Dis* 2006; **65:** 753–9.
10. Breedveld FC, *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; **54:** 26–37.
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12. Cvetković RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. *BioDrugs* 2006; **20:** 293–311.
13. Burmester GR, *et al.* Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis* 2007; **66:** 732–9.
14. Bombardieri S, *et al.* Research in Active Rheumatoid Arthritis (ReAct) Study Group. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 2007; **46:** 1191–9.
15. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)

Spondyloarthropathies. References to the use of adalimumab in ankylosing spondylitis and psoriatic arthritis (see Spondyloarthropathies, p.13).

1. Chew A-L, *et al.* Successful treatment of severe psoriasis and psoriatic arthritis with adalimumab. *Br J Dermatol* 2004; **151:** 492–6.
2. Mease PJ, *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 3279–89.
3. van der Heijde D, *et al.* Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54:** 2136–46.
4. van der Heijde D, *et al.* ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54:** 2136–46.
5. Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. *Drugs* 2006; **66:** 1487–96.
6. Gladman DD, *et al.* Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. *Ann Rheum Dis* 2007; **66:** 163–8.
7. Gladman DD, *et al.* Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007; **56:** 476–88.
8. Genovese MC, *et al.* M02-570 Study Group. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007; **34:** 1040–50. Correction. *ibid.*; 1439.
9. Davis JC, *et al.* Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. *Arthritis Rheum* 2007; **57:** 1050–7.
10. NICE. Adalimumab for the treatment of psoriatic arthritis: Technology Appraisal Guidance 125 (issued August 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA125guidance.pdf (accessed 13/06/08)

Uveitis. Adalimumab has been tried with some success in the treatment of idiopathic uveitis (p.1515). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with adalimumab may improve ocular symptoms in addition to its effect on the primary disorder.

References.

1. Vazquez-Cobian LB, *et al.* Adalimumab therapy for childhood uveitis. *J Pediatr* 2006; **149:** 572–5.
2. Biester S, *et al.* Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007; **91:** 319–24.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Humira; ***Austral.:*** Humira; ***Belg.:*** Humira; ***Braz.:*** Humira; ***Canad.:*** Humira; ***Chile:*** Humira; ***Cz.:*** Humira; ***Denm.:*** Humira; ***Fin.:*** Humira; ***Fr.:*** Humira; ***Ger.:*** Humira; ***Gr.:*** Humira; ***Hong Kong:*** Humira; ***Hung.:*** Humira; ***Irl.:*** Humira; ***Israel:*** Humira; ***Ital.:*** Humira; ***Malaysia:*** Humira; ***Mex.:*** Humira; ***Neth.:*** Humira; Trudexa; ***Norw.:*** Humira; ***NZ:*** Humira; ***Pol.:*** Humira; ***Port.:*** Humira; ***Singapore:*** Humira; ***Spain:*** Humira; ***Swed.:*** Humira; ***Switz.:*** Humira; ***UK:*** Humira; ***USA:*** Humira; ***Venez.:*** Humira.

Alfentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

Alfentaniilihydrokloridi; Alfentanil, chlorhydrate d'; Alfentanil Hidroklorür; Alfentanil-hidroklorid; Alfentanil-hydrochlorid; Alfentanilhydroklorid; Alfentanili hydrochloridum; Alfentanilio hidrochloridas; Hidrocloruro de alfentanilo; R-39209. *N*-{1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl}propionanilide hydrochloride.

Альфентанила Гидрохлорид

$C_{21}H_{32}N_6O_3,HCl = 453.0.$

CAS — 71195-58-9 (alfentanil); 69049-06-5 (anhydrous alfentanil hydrochloride); 70879-28-6 (alfentanil hydrochloride monohydrate).

ATC — N01AH02.

ATC Vet — QN01AH02.

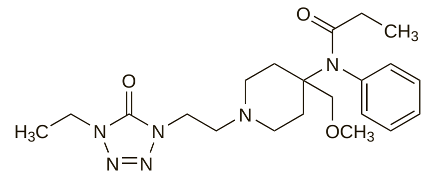

(alfentanil)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Alfentanil Hydrochloride). A white or almost white powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 31 (Alfentanil Hydrochloride). A white to almost white powder. Soluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in acetone. Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102, and for Fentanyl, p.56.

Effects on the cardiovascular system. Sinus arrest had occurred[1] during intubation in 2 patients given alfentanil 30 micrograms/kg.

1. Maryniak JK, Bishop VA. Sinus arrest after alfentanil. *Br J Anaesth* 1987; **59:** 390–1.

Effects on mental function. Like fentanyl, alfentanil 7.5 or 15 micrograms/kg intravenously had no effect on memory in healthy subjects.[1] In another study impairment of memory for new facts did occur 2 hours after operation in patients anaesthetised with alfentanil 7.5 micrograms/kg, but not in those given fentanyl;[2] methohexital might have contributed to the impairment.

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kennedy DJ, Ogg TW. Alfentanil and memory function: a comparison with fentanyl for day case termination of pregnancy. *Anaesthesia* 1985; **40:** 537–40.

Effects on the respiratory system. Alfentanil, like other opioid agonists, causes dose-related respiratory depression; it is significant with doses of more than 1 mg. Recovery has been reported to be faster after alfentanil than after fentanyl (see p.56),[1,2] possibly reflecting the shorter elimination half-life of alfentanil. Even so, accumulation of alfentanil is possible with large doses over a prolonged period. Profound analgesia is accompanied by marked respiratory depression which may persist or recur postoperatively.

Sudden respiratory arrest usually within an hour after the end of alfentanil infusion has been reported in patients who initially appeared to have made a rapid recovery from anaesthesia;[3-5] all responded to treatment with naloxone. Close monitoring of respiration in the initial postoperative period was recommended and this was reinforced by the manufacturers;[6] factors such as hyperventilation and the use of opioid premedication might enhance or prolong the respiratory depressant effects of alfentanil.

1. Andrews CJH, *et al.* Ventilatory effects during and after continuous infusion of fentanyl or alfentanil. *Br J Anaesth* 1983; **55:** 211S–16S.
2. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
3. Sebel PS, *et al.* Respiratory depression after alfentanil infusion. *BMJ* 1984; **289:** 1581–2.
4. Krane BD, *et al.* Alfentanil and delayed respiratory depression: cases studies and review. *Anesth Analg* 1990; **70:** 557–61.
5. Sternlo JEG, Sandin RH. Recurrent respiratory depression after total intravenous anaesthesia with propofol and alfentanil. *Anaesthesia* 1998; **53:** 378–81.
6. Waldron HA, Cookson RF. Respiratory depression after alfentanil infusion. *BMJ* 1985; **290:** 319.

Precautions

As for Opioid Analgesics in general, p.103.

Children. Alfentanil given to preterm infants undergoing paralysis and mechanical ventilation for respiratory distress syndrome resulted in a rapid and significant fall in heart rate and blood pressure, emphasising that proper evaluation of the pharmacological and clinical effects was necessary.[1]

The *BNFC* states that the half-life of alfentanil is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required.

1. Marlow N, *et al.* Hazards of analgesia for newborn infants. *Arch Dis Child* 1988; **63:** 1293.

The elderly. EEG changes suggested that elderly patients had increased brain sensitivity to alfentanil,[1] and that lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons. See also under Pharmacokinetics, below.

1. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.

Handling. Avoid contact with the skin and the inhalation of particles of alfentanil hydrochloride.

Inflammatory bowel disease. Patients with Crohn's disease required higher doses of alfentanil than control patients[1] although there were no differences in alfentanil pharmacokinetics between the 2 groups of patients.

1. Gesink-van der Veer BJ, *et al.* Influence of Crohn's disease on the pharmacokinetics and pharmacodynamics of alfentanil. *Br J Anaesth* 1993; **71:** 827–34.

Pregnancy. UK licensed product information contra-indicates the use of alfentanil in labour, or before clamping of the cord during caesarean section, because placental transfer means there is a risk of neonatal respiratory depression.

Interactions

For interactions associated with opioid analgesics, see p.103.

Drugs that depress the heart or increase vagal tone, such as beta blockers and anaesthetic drugs, may predispose patients given alfentanil to develop bradycardia and hypotension. Use of alfentanil with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

The metabolism of alfentanil via the cytochrome P450 isoenzyme CYP3A4 may be reduced by potent inhibitors of this isoenzyme, resulting in a risk of prolonged or delayed respiratory depression. Reduced doses of alfentanil may be required if given with a CYP3A4 inhibitor such as cimetidine, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, or ritonavir.

Antibacterials. The elimination half-life of alfentanil was increased and clearance decreased when given after a 7-day course of oral *erythromycin* in healthy subjects.[1] Prolonged respiratory depression has also occurred in a 32-year-old man given alfentanil during anaesthesia after three 1-g doses of erythromycin in the 24 hours before surgery.[2] In another study of healthy subjects, the clearance (three-compartment model) of alfentanil was reduced by 70% in those given oral *troleandomycin*.[3]

Other hepatic enzyme inhibitors and drugs interfering with hepatic blood flow might also affect the clearance of alfentanil.

1. Bartkowski RR, *et al.* Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; **46:** 99–102.
2. Bartkowski RR, McDonnell TE. Prolonged alfentanil effect following erythromycin administration. *Anesthesiology* 1990; **73:** 566–8.
3. Kharasch ED, *et al.* The role of cytochrome P450 3A4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997; **87:** 36–50.

Antifungals. Azole antifungals such as *fluconazole*, *ketoconazole*, or *voriconazole* can inhibit the metabolism of alfentanil. In a study,[1] giving alfentanil 1 hour after intravenous or oral fluconazole decreased the clearance of alfentanil by 60 and 55%, respectively and increased the mean half-life of alfentanil from 1.5 hours to 2.7 and 2.5 hours, respectively. Similarly, another study[2] found that giving alfentanil 1 hour after oral voriconazole decreased the clearance of alfentanil by 85% and increased the mean half-life of alfentanil to 6.6 hours.

1. Palkama VJ, *et al.* The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. *Anesth Analg* 1998; **87:** 190–4.
2. Saari TI, *et al.* Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. *Clin Pharmacol Ther* 2006; **80:** 502–8.

Pharmacokinetics

After parenteral doses alfentanil hydrochloride has a rapid onset and short duration of action. Alfentanil is about 90% protein bound and has a small volume of distribution. Its terminal elimination half-life is about 1 to 2 hours. It is metabolised in the liver; oxidative *N*- and *O*-dealkylation by the cytochrome P450 isoenzyme CYP3A4 leads to inactive metabolites, which are excreted in the urine. Alfentanil crosses the blood-brain barrier and the placenta and has been detected in colostrum.

◊ Alfentanil is less lipid-soluble than fentanyl, but more so than morphine. It is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. Decreased lipid solubility can be expected to limit penetration of the blood-brain barrier when compared with fentanyl, but the majority of unbound alfentanil is unionised and can rapidly gain access to the CNS. Alfentanil has a smaller volume of distribution than fentanyl and its elimination half-life is shorter. The manufacturers have given values for a three-compartment pharmacokinetic model with a distribution half-life of 0.4 to 3.1 minutes, a redistribution half-life of 4.6 to 21.6 minutes, and a terminal elimination half-life of 64.1 to 129.3 minutes after single bolus injections of 50 or 125 micrograms/kg. Accumulation is less likely than with fentanyl, but can occur after repeated or continuous dosage especially in patients with reduced clearance. The mean elimination half-life reported is usually about 90 minutes, but this is reduced in children and increased in the elderly and neonates, in hepatic impairment, in the obese, and during cardiopulmonary bypass (see below).

◊ Reviews.

1. Hull CJ. The pharmacokinetics of alfentanil in man. *Br J Anaesth* 1983; **55** (suppl 2): 157S–164S.
2. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
3. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
4. Bodenham A, Park GR. Alfentanil infusions in patients requiring intensive care. *Clin Pharmacokinet* 1988; **15:** 216–26.
5. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. *Clin Pharmacokinet* 1996; **31:** 275–92.

Administration. *CONTINUOUS INTRAVENOUS INFUSION.* Small studies of alfentanil by continuous intravenous infusion[1-3] have found pharmacokinetic parameters to be similar to those after a single bolus injection, but with some conflicting results. In 29 patients undergoing orthopaedic surgery an initial bolus intravenous injection of alfentanil 50 micrograms/kg was followed by intravenous infusion of 1 microgram/kg per minute, continued for 44 to 445 minutes; a second bolus injection of 50 micrograms/kg was given immediately before incision and an additional bolus injection of 1 mg given if necessary.[4] The time course of the plasma-alfentanil concentration fitted a two-compartmental model in 26 patients. Terminal half-lives varied widely from 56 to 226 minutes (mean 106 minutes), the highest values being mainly in patients over 60 years. There was no significant correlation between pharmacokinetic parameters and the duration of the infusion or the total dose. Plasma clearance and volumes of distribution did not correlate significantly with body-weight although steady-state volume of distribution was enlarged with increasing age. The mean estimated steady-state concentration was 293 nanograms/mL (range 147 to 636 nanograms/mL).

1. Fragen RJ, *et al.* Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983; **55:** 1077–81.
2. Shafer A, *et al.* Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986; **65:** 1021–8.
3. Reitz JA, *et al.* The pharmacokinetics of alfentanil in gynecologic surgical patients. *J Clin Pharmacol* 1986; **26:** 60–4.
4. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.

INTRAMUSCULAR. See The Elderly, below.

Burns. The volume of distribution and total clearance of alfentanil were reduced and its elimination half-life prolonged in patients with burns.[1] This was due, in part, to raised concentrations of α_1-acid glycoprotein leading to increased protein binding.

1. Macfie AG, *et al.* Disposition of alfentanil in burns patients. *Br J Anaesth* 1992; **69:** 447–50.

Cardiopulmonary bypass. The elimination half-life of alfentanil increased from 72 minutes before cardiopulmonary bypass to 195 minutes afterwards in 5 patients.[1] This was attributed to an increase in volume of distribution, based in part on a dilution-induced decrease in plasma protein binding. Others[2,3] found that on starting cardiopulmonary bypass total serum concentrations of alfentanil were halved, mainly because of dilution of α_1-acid glycoprotein and an increase in unbound alfentanil.

1. Hug CC, *et al.* Alfentanil pharmacokinetics in patients before and after cardiopulmonary bypass. *Anesth Analg* 1983; **62:** 266.
2. Kumar K, *et al.* The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. *Eur J Clin Pharmacol* 1988; **35:** 47–52.
3. Hynynen M, *et al.* Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *Br J Anaesth* 1994; **72**: 571–6.

Children. Alfentanil has been shown to have a shorter elimination half-life (about 40 minutes) and a smaller volume of distribution in children than in adults.[1] However, the half-life of alfentanil is prolonged in neonates. See also Hepatic Impairment, below.

1. Meistelman C, *et al.* A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; **66:** 13–16.

The elderly. Plasma clearance of alfentanil after a single intravenous dose of 50 micrograms/kg was reduced in patients more than 65 years old when compared with that in healthy young adults.[1] Mean elimination half-life was 137 minutes in the elderly and 83 minutes in the young adults. Volumes of distribution were similar and it was considered that reduced clearance might be due to decreased hepatic metabolism in the elderly. In a study in male patients the terminal elimination half-life of alfentanil increased with age, although clearance was not significantly affected.[2] In patients given alfentanil 1 microgram/kg per minute by continuous intravenous infusion during orthopaedic surgery,[3] terminal half-life increased linearly with age in those older than 40 years and steady-state volume of distribution was enlarged with increasing age; clearance did not correlate significantly with age and was thought to be more variable during a continuous infusion in long-term surgery than after a single bolus injection. Others have reported[4] that the effects of age on alfentanil pharmacokinetics are dependent on gender. In this study total plasma clearance decreased and terminal half-life increased with increasing age in women, but not in men. It has been suggested that this effect in women may be more dependent on menopausal status than on age.[5]

In a study[6] in elderly patients plasma concentrations of alfentanil were greater and the maximum concentration occurred earlier when alfentanil was injected into the deltoid muscle compared with injection into the gluteal muscle.

1. Helmers H, *et al.* Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984; **36:** 239–43.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.
3. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.
4. Lemmens HJM, *et al.* Influence of age on the pharmacokinetics of alfentanil: gender dependence. *Clin Pharmacokinet* 1990; **19:** 416–22.
5. Rubio A, Cox C. Sex, age and alfentanil pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 81.
6. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.

Hepatic impairment. Total plasma clearance and protein binding of alfentanil were decreased in patients with alcoholic cirrhosis when compared with control subjects. Elimination half-life was prolonged from 90 to 219 minutes in the cirrhotic patients following a single intravenous dose of 50 micrograms/kg and was attributed in part to alterations in binding sites of α_1-acid glycoprotein.[1] There might be different effects on alfentanil disposition in patients with non-alcoholic cirrhosis or other liver disorders.[2] The pharmacokinetics of alfentanil were apparently not affected in children with cholestatic hepatic disease whereas clearance was reduced postoperatively in 3 patients who had undergone liver transplantation.[3]

1. Ferrier C, *et al.* Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985; **62:** 480–4.
2. Bower S, *et al.* Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. *Br J Anaesth* 1992; **68:** 462–5.
3. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.

Obesity. The pharmacokinetics of alfentanil are reportedly altered in obesity.[1] Elimination half-life was 172 minutes in 6 obese patients compared with 92 minutes in 7 who were not obese. Plasma clearance of alfentanil was also decreased, although others[2] found that obesity had no effect on clearance, but it did have a direct relationship with the volume of the central compartment.

1. Bentley JB, *et al.* Obesity and alfentanil pharmacokinetics. *Anesth Analg* 1983; **62:** 251.
2. Maitre PO, *et al.* Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; **66:** 3–12.

Renal impairment. The pharmacokinetics of alfentanil were not affected significantly in adults[1] or children[2] with chronic renal failure. In another study[3] increased volume of distribution of alfentanil at steady state was associated with decreased plasma protein binding in patients with chronic renal failure.

1. Van Peer A, *et al.* Alfentanil kinetics in renal insufficiency. *Eur J Clin Pharmacol* 1986; **30:** 245–7.
2. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.
3. Chauvin M, *et al.* Pharmacokinetics of alfentanil in chronic renal failure. *Anesth Analg* 1987; **66:** 53–6.

Uses and Administration

Alfentanil is a short-acting opioid analgesic (p.104) related to fentanyl (p.58).

Alfentanil is used in surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. It is also used as an analgesic and respiratory depressant in the management of mechanically ventilated patients under intensive care.

Alfentanil is given intravenously as the hydrochloride although doses are expressed in terms of the base. Alfentanil hydrochloride 108.8 micrograms is equivalent to about 100 micrograms of alfentanil. A peak effect may be seen within 1.5 to 2 minutes of an injection and analgesia can be expected to last for up to 10 minutes; dose supplements are therefore required if it is to be used for more prolonged surgical procedures. It may be given by continuous intravenous infusion in ventilated patients.

The dosage of alfentanil used depends on whether the patient has spontaneous respiration or assisted ventilation and on the expected duration of anaesthesia. Doses are adjusted according to the needs of the patient. Children may require higher or more frequent doses than adults, whereas the elderly or debilitated patients may require lower or less frequent doses. Obese patients may require doses based on their ideal (lean) body-weight.

When used as an adjunct in the **maintenance of general anaesthesia** the initial licensed dose in the UK is as follows:

- in patients with *spontaneous respiration*, up to 500 micrograms may be given slowly over about 30 seconds with supplementary doses of 250 micrograms
- *ventilated* patients may be given 30 to 50 micrograms/kg with supplements of 15 micrograms/kg. When given by infusion to ventilated patients there is an initial loading dose of 50 to 100 micrograms/kg given as a bolus or by infusion over 10 minutes, followed by infusion at a rate of 0.5 to 1 microgram/kg per minute

Typical doses that have been used in the USA are as follows:

- for *short surgical procedures of less than 1 hour* in patients with spontaneous respiration or assisted ventilation, the dose is 8 to 20 micrograms/kg; this may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.5 to 1 microgram/kg per minute. Alternatively patients with assisted or controlled ventilation may be given an initial dose of 20 to 50 micrograms/kg, followed by supplementary doses of 5 to 15 micrograms/kg every 5 to 20 minutes
- in *general surgical procedures* in patients with assisted or controlled ventilation, an initial dose of 50 to 75 micrograms/kg may be followed by an infusion of 0.5 to 3 micrograms/kg per minute. If alfentanil has been given in anaesthetic doses (see below) for the induction of anaesthesia, infusion rates may need to be reduced by 30 to 50% during the first hour of maintenance

Maintenance infusions of alfentanil should be stopped 10 to 30 minutes before the anticipated end of surgery.

For details of doses in children, see below.

The dose for the **induction of anaesthesia** in patients with assisted ventilation undergoing procedures of at least 45 minutes is 130 to 245 micrograms/kg, followed by an inhalation anaesthetic or maintenance doses of alfentanil of 0.5 to 1.5 micrograms/kg per minute.

In the UK, *ventilated* patients in **intensive care** may be given alfentanil initially at an infusion rate of 2 mg/hour or a loading dose of 5 mg may be given in divided doses over 10 minutes or more slowly if hypotension or bradycardia occur. Thereafter a suitable rate of infusion should be determined for each patient (rates of 0.5 to 10 mg/hour have been used); patients should be carefully monitored and the duration of treatment should not generally exceed 4 days. During continuous infusion additional bolus injections of 0.5 to 1 mg may be given if required to provide analgesia for short painful procedures that may be carried out in intensive care.

Alfentanil is also used as an analgesic in patients with *spontaneous respiration* receiving monitored anaesthesia care; in the USA, an initial dose of 3 to 8 micrograms/kg may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.25 to 1 microgram/kg per minute.

Administration. Alfentanil is usually given by intravenous injection or infusion, but has also been given intramuscularly,[1,2] intrathecally,[3] or epidurally (see Pain, below).

1. Arendt-Nielsen L, *et al.* Analgesic efficacy of im alfentanil. *Br J Anaesth* 1990; **65:** 164–8.
2. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.
3. Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour. *Anaesthesia* 2000; **55:** 1116–21.

Administration in children. Alfentanil is licensed in the UK for use in ventilated children during surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. When used as an adjunct in the **maintenance of general anaesthesia** licensed product information states that ventilated children may be given the usual intravenous *injection* doses as for ventilated adults (see above). However, the *BNFC* suggests that neonates may be given 5 to 20 micrograms/kg initially and children aged from 1 month to 18 years, 10 to 20 micrograms/kg initially; supplementary doses of up to 10 micrograms/kg may be given. When given by *infusion* the *BNF* states that ventilated children may be given the usual doses as for ventilated adults (see above); the *BNFC* suggests that usual adult doses may be given to those aged as young as 1 month. The *BNFC* also suggests that neonates may be given an initial loading dose of 10 to 50 micrograms/kg over 10 minutes followed by infusion at a rate of 0.5 to 1 microgram/kg per minute.

Anaesthesia. Alfentanil, like fentanyl (p.59), appears to produce fewer circulatory changes than morphine and may be preferred for anaesthetic use, especially in cardiovascular surgery. It is generally considered to have a shorter duration of action than fentanyl. It has been used with propofol to facilitate intubation, and for total intravenous anaesthesia.

For a discussion of the drugs used to facilitate intubation and of opioids such as alfentanil used to control the pressor response and the rise of intra-ocular pressure associated with intubation, see Anaesthesia, p.1900. For reference to a study indicating that pretreatment with alfentanil can reduce the pain associated with injection of propofol, see p.1791.

CAESAREAN SECTION. UK licensed product information contra-indicates the use of alfentanil before clamping the cord during caesarean section because of the risk of respiratory depression in the neonate. A study of alfentanil 30 micrograms/kg in women undergoing caesarean section was abandoned after massive respiratory depression had occurred in 4 of 5 neonates.[1] Another study[2] in patients undergoing elective caesarean section found that although maternal haemodynamic responses to intubation were minimised when alfentanil 10 micrograms/kg was given intravenously immediately before induction, neonates in the alfentanil group had lower Apgar scores compared with those in the placebo group.

However, alfentanil has been used successfully to minimise haemodynamic responses to intubation and surgery in patients with severe cardiovascular disorders undergoing caesarean section.[3,4] A baby delivered after the successful use of alfentanil 35 micrograms/kg in a mother with severe aortic stenosis[3] was apnoeic and unresponsive with poor muscle tone; the baby responded rapidly to naloxone. Alfentanil 10 micrograms/kg immediately before induction attenuated the cardiovascular response to intubation in patients with severe pregnancy-induced hypertension[4] and was considered a suitable alternative to fentanyl 2.5 micrograms/kg; no effect on neonatal mortality could be attributed to anaesthetic technique. However, it has been suggested that the use of smaller doses of alfentanil of 7.5 micrograms/kg with magnesium sulfate 30 mg/kg may provide better cardiovascular control.[5]

1. Leuwer M, *et al.* Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during caesarean section. *Br J Anaesth* 1990; **64:** 398P–9P.
2. Gin T, *et al.* Alfentanil given immediately before the induction of anesthesia for elective cesarean delivery. *Anesth Analg* 2000; **90:** 1167–72.
3. Redfern N, *et al.* Alfentanil for caesarean section complicated by severe aortic stenosis: a case report. *Br J Anaesth* 1987; **59:** 1309–12.
4. Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *Br J Anaesth* 1990; **65:** 468–74.
5. Ashton WB, *et al.* Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. *Br J Anaesth* 1991; **67:** 741–7.

PHAEOCHROMOCYTOMA. Alfentanil does not release histamine and was of value in the anaesthetic management of patients with phaeochromocytoma.[1] It has a very rapid onset of action, good vasodilating properties, and a relatively short elimination half-life. These patients are often very somnolent for the first 48 hours after surgery and postoperative opioid dosage requirements may be less than expected. Alfentanil infusion continued into the postoperative period allows careful titration of dosage.

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

Pain. ***POSTOPERATIVE ANALGESIA.*** Continuous on-demand epidural infusions of alfentanil 200 micrograms/hour or fentanyl 20 micrograms/hour provided comparable analgesia to morphine 200 micrograms/hour in the early postoperative period;[1] alfentanil (16 minutes) and fentanyl (13 minutes) had the advantage of more rapid onset of analgesia than morphine (44 minutes). However, some considered that there was no overall advantage of epidural over intravenous alfentanil either as patient-controlled analgesia[2] or by continuous infusion.[3]

1. Chrubasik J, *et al.* Relative analgesic potency of epidural fentanyl, alfentanil, and morphine in treatment of postoperative pain. *Anesthesiology* 1988; **68:** 929–33.
2. Chauvin M, *et al.* Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; **76:** 1251–8.
3. van den Nieuwenhuyzen MCO, *et al.* Epidural vs intravenous infusion of alfentanil in the management of postoperative pain following laparotomies. *Acta Anaesthesiol Scand* 1996; **40:** 1112–18.

Preparations

USP 31: Alfentanil Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Brevafen; ***Austral.:*** Rapifen; ***Austria:*** Rapifen; ***Belg.:*** Rapifen; ***Braz.:*** Alfast; Rapifen; ***Canad.:*** Alfenta; ***Chile:*** Rapifen; ***Cz.:*** Rapifen; ***Denm.:*** Rapifen; ***Fin.:*** Rapifen; ***Fr.:*** Rapifen; ***Ger.:*** Rapifen; ***Gr.:*** Rapifen; ***Hong Kong:*** Rapifen; ***Hung.:*** Rapifen; ***Irl.:*** Rapifen; ***Israel:*** Rapifen; ***Ital.:*** Fentalim; ***Malaysia:*** Rapifen†; ***Mex.:*** Rapifen; ***Neth.:*** Rapifen; ***Norw.:*** Rapifen; ***NZ:*** Rapifen; ***S.Afr.:*** Rapifen; ***Spain:*** Fanaxal; Limifen; ***Swed.:*** Rapifen; ***Switz.:*** Rapifen; ***Turk.:*** Rapifen; ***UK:*** Rapifen; ***USA:*** Alfenta; ***Venez.:*** Rapifen.

Alminoprofen *(rINN)*

Alminoprofène; Alminoprofeno; Alminoprofenum. 4-[(2-Methylallyl)amino]hydratropic acid.

Альминопрофен

$C_{13}H_{17}NO_2$ = 219.3.
CAS — 39718-89-3.
ATC — M01AE16.
ATC Vet — QM01AE16.

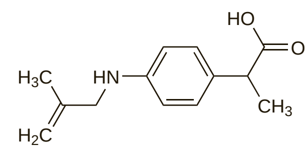

Profile

Alminoprofen, a propionic acid derivative related to ibuprofen (p.64), is an NSAID (p.96). It has been used in inflammatory and rheumatic disorders in oral doses of up to 900 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Minalfene.

Aloxiprin *(BAN, rINN)*

Acetilsalicilato de polioxoaluminio; Aloksipriini; Aloxiprina; Aloxiprine; Aloxiprinum.

Алоксиприн

CAS — 9014-67-9.
ATC — B01AC15; N02BA02.
ATC Vet — QB01AC15; QN02BA02.

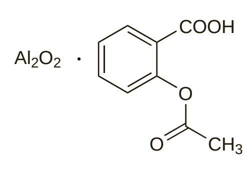

Pharmacopoeias. In *Br.*

BP 2008 (Aloxiprin). A polymeric condensation product of aluminium oxide and aspirin. A fine, white or slightly pink powder, odourless or almost odourless. It contains not less than 7.5% and not more than 8.5% of aluminium and not less than 79.0% and not more than 87.4% of total salicylates, calculated as aspirin, $C_9H_8O_4$, both calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in ether; slightly soluble in chloroform.

Profile

Aloxiprin, a polymeric condensation product of aluminium oxide and aspirin, has actions similar to those of aspirin (p.20); aloxiprin 600 mg is equivalent to about 500 mg of aspirin. Aloxiprin has been used as an analgesic and anti-inflammatory in musculoskeletal and joint disorders. It has also been used in the treatment and prevention of thromboembolic disorders.

Preparations

BP 2008: Aloxiprin Tablets.

Proprietary Preparations (details are given in Part 3)
Cz.: Superpyrin.

Multi-ingredient: ***UK:*** Askit.

Aluminium Aspirin

Acetilsalicilato de aluminio; Aluminum Acetylsalicylate; Aluminum Aspirin; Aluminum Bis(acetylsalicylate); Aspirin Aluminium. Bis(2-acetoxybenzoato-*O*′)hydroxyaluminium.

Алюминий Аспирина; Аспирин Алюминий

$C_{18}H_{15}AlO_9$ = 402.3.

CAS — 23413-80-1.

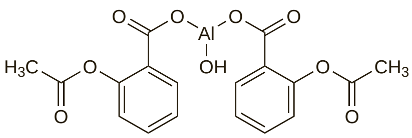

Pharmacopoeias. In *Jpn.*

Profile

Aluminium aspirin is a salicylic acid derivative (see Aspirin, p.20) that has been given orally in the management of fever, pain, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Remasal; ***S.Afr.:*** Analgen-SA†.

Aminophenazone *(rINN)*

Amidazofen; Amidopyrine; Amidopyrine-Pyramidon; Aminofenatsoni; Aminofenazon; Aminofenazona; Aminophénazone; Aminophenazonum; Aminopyrine; Dimethylaminoantipyrine; Dimethylaminophenazone. 4-Dimethylamino-1,5-dimethyl-2-phenyl-4-pyrazolin-3-one.

Аминофеназон

$C_{13}H_{17}N_3O$ = 231.3.

CAS — 58-15-1.

ATC — N02BB03.

ATC Vet — QN02BB03.

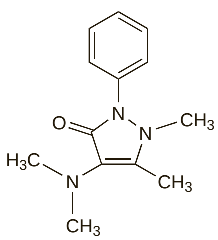

Pharmacopoeias. In *It.*

Profile

Aminophenazone, a pyrazolone derivative, is an NSAID (p.96), but the risk of agranulocytosis is sufficiently great to render it unsuitable for systemic use. Onset of agranulocytosis may be sudden and unpredictable. Aminophenazone has been used as salts or complexes, including topically as the salicylate.

Precautions. CARCINOGENICITY. Some[1] consider that aminophenazone should be regarded as a potential carcinogen because it reacted readily with nitrous acid to form dimethylnitrosamine. The reaction was catalysed by thiocyanate present in the saliva particularly in smokers.

1. Boyland E, Walker SA. Catalysis of the reaction of aminopyrine and nitrite by thiocyanate. *Arzneimittelforschung* 1974; **24:** 1181–4.

PORPHYRIA. Aminophenazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Gineburno†; ***Cz.:*** Dinyl†; Eunalgit†; ***Hung.:*** Antineuralgica; Demalgon; Demalgonil; Dolor; Germicid-C; Germicid†; Kefalgin; Meristin; ***Ital.:*** Virdex; ***Mex.:*** Flumil; ***Switz.:*** Thermocutan†; ***Venez.:*** Flexidone†.

Aminopropylone

Aminopropilona; Aminopropylon. *N*-(2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)-2-(dimethylamino)propanamide.

Аминопропилон

$C_{16}H_{22}N_4O_2$ = 302.4.

CAS — 3690-04-8.

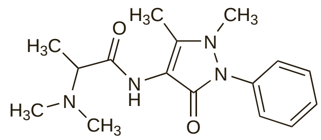

Profile

Aminopropylone is an NSAID (p.96) that has been used in topical preparations, for the local treatment of pain and inflammatory conditions. The hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Vessiflex†.

Ammonium Salicylate

Salicilato de amonio.

Аммоний Салицилат

$C_7H_9NO_3$ = 155.2.

CAS — 528-94-9.

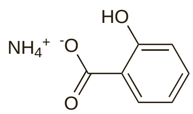

Profile

Ammonium salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p.85) for the relief of pain in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Radian-B†; ***Irl.:*** Radian-B†; ***UK:*** Radian-B.

Ampiroxicam *(BAN, rINN)*

Ampiroxicamum; CP-65703. 4-[1-(Ethoxycarbonyloxy)ethoxy]-2-methyl-N^2-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Ампироксикам

$C_{20}H_{21}N_3O_7S$ = 447.5.

CAS — 99464-64-9.

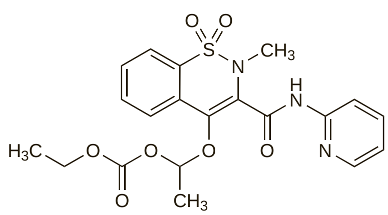

Profile

Ampiroxicam is an NSAID (p.96) that is reported to be metabolised to piroxicam (p.117). It has been given orally for the relief of pain and inflammation particularly in musculoskeletal disorders such as rheumatoid arthritis and osteoarthritis.

Adverse effects. Photosensitivity reactions have occurred during ampiroxicam treatment.[1-3]

1. Kurumaji Y. Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; **34:** 298–9.
2. Toyohara A, *et al.* Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; **35:** 101–2.
3. Chishiki M, *et al.* Photosensitivity due to ampiroxicam. *Dermatology* 1997; **195:** 409–10.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Flucam†.

Amtolmetin Guacil *(rINN)*

Amtolmetina guacilo; Amtolmétine Guacil; Amtolmetinum Guacilum; MED-15; ST-679. *N*-[(1-Methyl-5-*p*-toluoylpyrrol-2-yl)acetyl]glycine *o*-methoxyphenyl ester.

Амтолметин Гуацил

$C_{24}H_{24}N_2O_5$ = 420.5.

CAS — 87344-06-7.

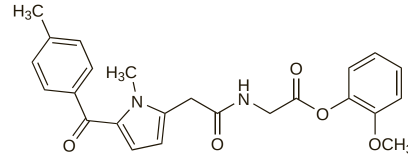

Profile

Amtolmetin guacil is an NSAID (p.96) that is an ester prodrug of tolmetin (p.130). It is used in painful and inflammatory disorders in oral doses of 600 to 1200 mg daily.

◊ References.

1. Biasi G, Marcolongo R. Efficacia e tollerabilità dell'amtolmetina guacil nel trattamento dell'artrosi in fase di riacutizzazione. *Minerva Med* 2001; **92:** 315–24.
2. Jajic Z, *et al.* Gastrointestinal safety of amtolmetin guacyl in comparison with celecoxib in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; **23:** 809–18.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Articol; Artromed; Eufans.

Amyl Salicylate

Isoamyl Salicylate; Isopentyl Salicylate; Salicilato de isoamilo; Salicilato de isopentilo. 3-Methylbutyl 2-hydroxybenzoate.

Амилсалицилат

$C_{12}H_{16}O_3$ = 208.3.

CAS — 87-20-7.

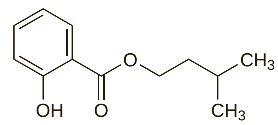

Pharmacopoeias. In *Fr.*

Profile

Amyl salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p.85) for its analgesic and anti-inflammatory actions. It has also been used in perfumery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Atomo Desinflamante; Atomo Desinflamante C; Atomo Desinflamante Familiar; Rati Salil Crema; ***Fr.:*** Sedartryl†; ***Spain:*** Linimento Klari†.

Anakinra *(BAN, USAN, rINN)*

Anakinrum; rhIL-1ra; r-metHuIL-1ra. N^2-L-methionylinterleukin 1 receptor antagonist (human isoform x reduced).

Анакинра

CAS — 143090-92-0.

ATC — L04AC03.

ATC Vet — QL04AC03.

```
                                                       M
RPSGRKSSKM  QAFRIWDVNQ  KTFYLRNNQL  VAGYLQGPNV  NLEEKIDVVP
IEPHALFLGI  HGGKMCLSCV  KSGDETRLQL  EAVNITDLSE  NRKQDKRFAF
IRSDSGPTTS  FESAACPGWF  LCTAMEADQP  VSLTNMPDEG  VMVTKFYFQE
DE
```

Adverse Effects and Precautions

Mild to moderate injection site reactions with symptoms of erythema, bruising, swelling, and pain are common with anakinra particularly in the first month of treatment. Other common reactions include headache, nausea, diarrhoea, and abdominal pain. Antibodies to anakinra may develop. Allergic reactions such as rashes have been reported rarely; if a severe allergic reaction occurs, anakinra should be stopped and appropriate treatment given.

Serious infections have been reported with anakinra, particularly in patients with asthma. These infections are mainly bacterial, such as cellulitis, pneumonia, and bone and joint infections. More rarely, opportunistic infections involving fungal, mycobacterial, and viral pathogens have also been seen. Anakinra should be stopped in those who develop a serious infection. In addition, therapy should not be started in patients with active infections, including chronic or localised infections; caution is recommended in those with a history of recurrent infections or with underlying conditions that may predispose to infections.

A small decrease in absolute neutrophil count (ANC) is commonly seen with anakinra treatment; however, true neutropenia

(ANC <1500 cells/mm^3) is rare. Licensed product information recommends that neutrophil counts should be taken before starting anakinra and periodically throughout treatment. UK licensed information recommends monthly monitoring during the first 6 months and then quarterly thereafter; US licensed information requires monthly monitoring for the first 3 months and then quarterly monitoring for a period of up to 1 year. Anakinra should not be started in patients with neutropenia. Small reductions in the total white blood cell and platelets counts and a small increase in eosinophils have also been noted. Anakinra is also associated with an increased incidence of lymphoma in patients with rheumatoid arthritis.

For caution in patients with renal impairment see under Uses and Administration, below.

Effects on the cardiovascular system. A 29-year-old woman with refractory adult-onset Still's disease developed shortness of breath, which progressed to cardiorespiratory failure, 3 months after being started on anakinra;[1] although resuscitation was tried, the patient died. The authors considered that the role of anakinra in this event was unclear, particularly as the patient had shown some evidence of myocardial or pulmonary dysfunction before starting the drug.

1. Ruiz PJ, *et al.* Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra. *Ann Rheum Dis* 2007; **66:** 422–3.

Effects on the skin. Inflammatory lesions at injection sites were reported in 5 patients after anakinra use.[1] The lesions were erythematous, oedematous, painful, and itchy plaques, and were seen within 16 days of starting treatment. Treatment with anakinra was completely stopped in 1 patient and interrupted in 2 other patients; when reintroduced, one patient developed abdominal pain, dyspnoea, and facial and abdominal erythema with pruritus.

1. Vila AT, *et al.* Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; **153:** 417–23.

Interactions

Live vaccines should not be given with anakinra as its effect on vaccine efficacy or the risk of infection transmission is unknown.

The risk of serious infection and neutropenia is increased when anakinra and etanercept are used together (see under Infliximab, p.71); a similar effect may occur with other TNF antagonists. The use of anakinra with etanercept or other TNF inhibitors is not recommended.

Pharmacokinetics

After subcutaneous doses, peak plasma concentrations of anakinra are reached in 3 to 7 hours. Its terminal half-life is about 4 to 6 hours. Anakinra is excreted mainly in the urine.

Uses and Administration

Anakinra is a recombinant receptor antagonist of interleukin-1 (p.2325), an inflammatory mediator found in the plasma and synovial fluid of patients with rheumatoid arthritis.

Anakinra is used for the treatment of the signs and symptoms of moderate to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate or another disease-modifying antirheumatic drug (DMARD) alone (but see below). In the UK, it is only licensed for use with methotrexate; however, in the USA, it may be given either alone or with another DMARD, although not one that inhibits TNF (see Interactions, above). The usual dose in adults is 100 mg once daily by subcutaneous injection. The dose should be given at about the same time each day.

Anakinra has been tried in septic shock and graft-versus-host disease in transplant recipients, but results were disappointing.

Administration in renal impairment. Caution may be advisable if anakinra is used in patients with renal impairment. A study[1] in patients with varying degrees of renal function indicated that no dosage adjustment was needed for anakinra in patients with mild or moderate renal impairment but dosage on alternate days appeared advisable in those with severe renal impairment. US licensed product information also recommends alternate-day dosing in patients with severe impairment or end-stage disease (creatinine clearance less than 30 mL/minute). However, in the UK, licensed product information contra-indicates use in those with this degree of impairment.

Dialysis does not affect anakinra concentrations to any significant degree.

1. Yang B-B, *et al.* Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; **74:** 85–94.

Familial Mediterranean fever. For mention of anakinra having been tried in familial Mediterranean fever, see p.557.

Rheumatoid arthritis. In the UK, anakinra is licensed for the treatment of rheumatoid arthritis (p.11) in patients with an inadequate response to methotrexate alone; however, NICE does not recommend its use except in the context of a controlled, long-term clinical study.

References.

1. Bresnihan B, *et al.* Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; **41:** 2196–2204.
2. Cohen S, *et al.* Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 614–24.
3. Nuki G, *et al.* Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 2838–46.
4. Fleischmann RM, *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; **48:** 927–34.
5. NICE. Anakinra for rheumatoid arthritis: Technology Appraisal Guidance 72 (issued November 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA072guidance.pdf (accessed 22/06/07)
6. Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. *Drugs* 2004; **64:** 2493–2501.
7. Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. *BioDrugs* 2005; **19:** 189–202.
8. Reiff A. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005; **7:** 434–40.
9. den Broeder AA, *et al.* Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; **65:** 760–2.
10. Burger D, *et al.* Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; **20:** 879–96.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Kineret; ***Canad.:*** Kineret; ***Cz.:*** Kineret; ***Denm.:*** Kineret; ***Fin.:*** Kineret; ***Fr.:*** Kineret; ***Ger.:*** Kineret; ***Gr.:*** Kineret; ***Irl.:*** Kineret; ***Ital.:*** Kineret; ***Neth.:*** Kineret; ***Norw.:*** Kineret; ***Pol.:*** Kineret; ***Port.:*** Kineret; ***Spain:*** Kineret; ***Swed.:*** Kineret; ***UK:*** Kineret; ***USA:*** Kineret.

Anileridine *(BAN, rINN)*

Anileridiini; Anileridin; Anileridina; Aniléridine; Anileridinum. Ethyl 1-(4-aminophenethyl)-4-phenylpiperidine-4-carboxylate.

Анилеридин

$C_{22}H_{28}N_2O_2$ = 352.5.
CAS — 144-14-9.
ATC — N01AH05.
ATC Vet — QN01AH05.

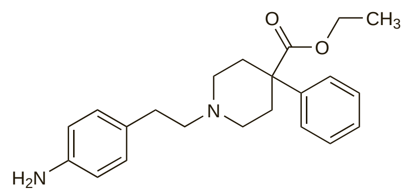

Pharmacopoeias. In *US.*

USP 31 (Anileridine). A white to yellowish-white, odourless or practically odourless, crystalline powder. When exposed to light and air it oxidises and darkens in colour. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80° and the other at about 89°. Very slightly soluble in water; soluble 1 in 2 of alcohol and 1 in 1 of chloroform; soluble in ether but solutions may be turbid. Store in airtight containers. Protect from light.

Anileridine Hydrochloride *(BANM, rINNM)*

Aniléridine, Chlorhydrate d'; Anileridini Hydrochloridum; Hidrocloruro de anileridina.

Анилеридина Гидрохлорид

$C_{22}H_{28}N_2O_2,2HCl$ = 425.4.
CAS — 126-12-5.

Pharmacopoeias. In *US.*

USP 31 (Anileridine Hydrochloride). A white or nearly white odourless crystalline powder. Soluble 1 in 5 of water and 1 in 80 of alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is 2.5 to 3.0. Store in airtight containers. Protect from light.

Anileridine Phosphate *(BANM, rINNM)*

Aniléridine, Phosphate d'; Anileridini Phosphas; Fosfato de anileridina.

Анилеридина Фосфат

$C_{22}H_{28}N_2O_2,H_3PO_4$ = 450.5.
CAS — 4268-37-5.

Profile

Anileridine, a phenylpiperidine derivative, is an opioid analgesic (p.101) chemically related to pethidine (p.113) and with similar actions. It has been used as the hydrochloride in the management of moderate to severe pain. Anileridine has also been given by injection as the phosphate.

Preparations

USP 31: Anileridine Hydrochloride Tablets; Anileridine Injection.

Aspirin *(BAN)*

Acetilsalicílico, ácido; Acetilsalicilo rūgštis; Acetilszalicilsav; Acetylsal. Acid; Acetylsalicylic Acid; Acetylsalicylsyra; Acide acétylsalicylique; Acidum acetylsalicylicum; Asetilsalisilik Asit; Asetyylisalisyylihappo; Kwas acetylosalicylowy; Kyselina acetylsalicylová; Polopiryna; Salicylic Acid Acetate. *O*-Acetylsalicylic acid; 2-Acetoxybenzoic acid.

Аспирин

$C_9H_8O_4$ = 180.2.
CAS — 50-78-2.
ATC — A01AD05; B01AC06; N02BA01.
ATC Vet — QA01AD05; QB01AC06; QN02BA01.

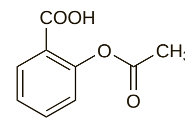

NOTE. The use of the name Aspirin is limited; in some countries it is a trade-mark.

Compounded preparations of aspirin may be represented by the following names:

- Co-codaprin (*BAN*)—aspirin 50 parts and codeine phosphate 1 part (w/w)
- Co-codaprin (*PEN*)—aspirin and codeine phosphate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Acetylsalicylic Acid; Aspirin BP 2008). White or almost white, crystalline powder or colourless crystals. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 31 (Aspirin). White crystals, commonly tubular or needle-like, or white crystalline powder; odourless or has a faint odour. Is stable in dry air; in moist air it gradually hydrolyses to salicylic and acetic acids. Soluble 1 in 300 of water, 1 in 5 of alcohol, 1 in 17 of chloroform, and 1 in 10 to 15 of ether; sparingly soluble in absolute ether. Store in airtight containers.

Adverse Effects and Treatment

Aspirin has many properties in common with the non-aspirin NSAIDs, the adverse effects of which are described on p.96.

The most common adverse effects of therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia, and vomiting. Gastrointestinal symptoms may be minimised by giving aspirin with food. Irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur. Histamine H_2-antagonists, proton pump inhibitors, and prostaglandin analogues such as misoprostol may be used in the management of NSAID-induced ulceration (see Peptic Ulcer Disease, p.1702), including that caused by aspirin. Slight blood loss, which is often asymptomatic, may occur in about 70% of patients; it is not usually of clinical significance but may, in a few patients, cause iron-deficiency anaemia during long-term therapy. Such occult blood loss is not affected by giving aspirin with food but may be reduced by use of enteric-coated or other modified-release tablets, H_2-antagonists, or high doses of antacids. Major upper gastrointestinal bleeding occurs rarely.

Some persons, especially those with asthma, chronic urticaria, or chronic rhinitis, exhibit notable hypersensitivity to aspirin (see also below), which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often exhibit cross-sensitivity to other NSAIDs.

Aspirin increases bleeding time, decreases platelet adhesiveness, and, in large doses, can cause hypoprothrombinaemia. It may cause other blood disorders, including thrombocytopenia.

Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. For further details see under Reye's Syndrome, below.

Aspirin given rectally may cause local irritation; anorectal stenosis has been reported.

Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at the plasma concentrations of 150 to 300 micrograms/mL required for optimal anti-inflammatory activity; more serious adverse effects occur at concentrations above 300 micrograms/mL. Symptoms of more severe intoxication or of acute poisoning following overdosage include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis. Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe.

In acute oral salicylate overdosage the UK National Poisons Information Service recommends that repeated oral doses of activated charcoal be given if the patient is suspected of ingesting more than 125 mg/kg of salicylate within 1 hour of presentation. Activated charcoal not only prevents the absorption of any salicylate remaining in the stomach but also aids the elimination of any that has been absorbed.

Measurement of plasma-salicylate concentration should be carried out in patients who have ingested more than 125 mg/kg of salicylate, although the severity of poisoning cannot be estimated from plasma concentrations alone. Absorption of aspirin can be delayed by reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. In consequence, plasma concentrations should be measured at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion and repeated 2 hours later. Patients who overdose with enteric preparations require continual monitoring of plasma concentrations.

Fluid and electrolyte management is essential to correct acidosis, hyperpyrexia, hypokalaemia, and dehydration. Intravenous sodium bicarbonate is given to enhance urinary salicylate excretion if plasma salicylate concentrations exceed 500 micrograms/mL (350 micrograms/mL in children under 5 years). Haemodialysis or haemoperfusion are also effective methods of removing salicylate from the plasma. The *BNF* considers haemodialysis the method of choice in severe poisoning; it should be seriously considered when the plasma salicylate concentration is more than 700 micrograms/mL or if there is severe metabolic acidosis. Vulnerable patients such as children or the elderly may require dialysis at an earlier stage.

◊ References to salicylate toxicity and its management.

1. Notarianni L. A reassessment of the treatment of salicylate poisoning. *Drug Safety* 1992; **7:** 292–303.
2. Woods D, *et al.* Acute toxicity of drugs: salicylates. *Pharm J* 1993; **250:** 576–8.
3. Collee GG, Hanson GC. The management of acute poisoning. *Br J Anaesth* 1993; **70:** 562–73.
4. Watson JE, Tagupa ET. Suicide attempt by means of aspirin enema. *Ann Pharmacother* 1994; **28:** 467–9.
5. Dargan PI, *et al.* An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J* 2002; **19:** 206–9.
6. Rivera W, *et al.* Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. *Ann Pharmacother* 2004; **38:** 1186–8. Correction. *ibid.* 2006; **40:** 999.

Effects on the blood. Although it has beneficial effects on platelets, aspirin can cause adverse blood effects. An indication of this toxicity is given by an early reference[1] to reports submitted to the UK CSM. There were 787 reports of adverse reactions to aspirin reported to the CSM between June 1964 and January 1973. These included 95 reports of blood disorders (17 fatal) including thrombocytopenia (26; 2 fatal), aplastic anaemia (13; 7 fatal), and agranulocytosis or pancytopenia (10; 2 fatal). Aspirin has also been associated with haemolytic anaemia in patients with G6PD deficiency.[2]

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–9.
2. Magee P, Beeley L. Drug-induced blood dyscrasias. *Pharm J* 1991; **246:** 396–7.

Effects on the cardiovascular system. Salicylate poisoning may result in cardiovascular collapse but details of such cases have not been widely reported. In 2 patients with salicylate intoxication asystole developed after intravenous diazepam.[1] It was suggested that diazepam-induced respiratory depression affected the acid–base balance so that the concentration of non-ionised membrane-penetrating fraction of salicylate was increased. Fatal aspirin intoxication in a 5-year-old child was marked by hypotension and rapidly progressive cardiac symptoms including ventricular tachycardia and AV block.[2] Extensive myocardial necrosis was found at autopsy.

For reference to the effects of aspirin on blood pressure compared with other NSAIDs, see p.96.

1. Berk WA, Andersen JC. Salicylate-associated asystole: report of two cases. *Am J Med* 1989; **86:** 505–6.
2. Peña-Alonso YR, *et al.* Aspirin intoxication in a child associated with myocardial necrosis: is this a drug-related lesion? *Pediatr Dev Pathol* 2003; **6:** 342–7.

Effects on the gastrointestinal tract. Clinical and epidemiological evidence suggests that aspirin produces dose-related gastrointestinal toxicity[1,2] that is sometimes, but rarely, fatal.[2] Meta-analysis[3] suggests that the risk of gastrointestinal bleeding is not significantly lowered with the use of oral low-dose aspirin (less than 300 mg daily). A systematic review[4] of observational epidemiologic studies also concurred with this finding. More recently, a systematic review[5] of randomised, controlled studies found that although low-dose aspirin (up to 325 mg daily) increased the risk of major bleeding including gastrointestinal bleeding by twofold when compared to placebo, the actual risk of bleeding was modest; for every 833 patients taking low-dose aspirin for cardiovascular prophylaxis only 1 additional major bleeding episode will occur annually. In another, population-based study,[6] the annual excess risk of upper gastrointestinal complications was about an extra 5 cases per 1000 patients; however, the excess risk varied with underlying gastrointestinal risk factors such as old age and might exceed an extra 10 cases per 1000 patients in a higher risk group comprising over 10% of aspirin users. It has been suggested that very small doses of aspirin can produce prophylactic benefits in cardiovascular disease without the risk of gastrointestinal toxicity,[7] although others have reported gastric injury even with doses of 10 mg daily.[8]

There appears to be no convincing evidence that the risk of major gastrointestinal bleeding associated with a 75-mg dose is reduced by using enteric-coated or modified-release formulations rather than soluble aspirin,[3,4,9] although individual studies have reported a reduction in acute mucosal injury with enteric coating.[10] All known NSAIDs have the potential for causing acute damage to the gastric mucosa (see p.97), and comparative studies of acute gastric mucosal damage caused by such drugs consistently associate aspirin with the most severe lesions.[1] Gastric mucosal injury can occur even with cutaneous application.[11]

1. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986; **104:** 390–8.
2. Roderick PJ, *et al.* The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993; **35:** 219–26.
3. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; **321:** 1183–7.
4. García Rodríguez LA, *et al.* Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001; **52:** 563–71.
5. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119:** 624–38.
6. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006; **4:** 22. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-22.pdf (accessed 11/12/06)
7. Lee M, *et al.* Dose effects of aspirin on gastric prostaglandins and stomach mucosal injury. *Ann Intern Med* 1994; **120:** 184–9.
8. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; **117:** 17–25.
9. Anonymous. Which prophylactic aspirin? *Drug Ther Bull* 1997; **35:** 7–8.
10. Cole AT, *et al.* Protection of human gastric mucosa against aspirin—enteric coating or dose reduction? *Aliment Pharmacol Ther* 1999; **13:** 187–93.
11. Cryer B, *et al.* Effects of cutaneous aspirin on the human stomach and duodenum. *Proc Assoc Am Physicians* 1999; **111:** 448–56.

Effects on hearing. Studies have shown that tinnitus develops at serum-salicylate concentrations above 200 micrograms/mL.[1] However, there appears to be considerable intersubject variation in the response of the ear to salicylate;[2] tinnitus may occur at lower concentrations, whereas patients with pre-existing hearing loss may not experience tinnitus despite serum-salicylate concentrations of 311 to 677 micrograms/mL.[1] A graded increase in intensity of ototoxicity with increasing salicylate dose and plasma concentration has been demonstrated.[2] For example, at an average total plasma-salicylate concentration of 110 micrograms/mL, the hearing loss at any given frequency was about 12 decibels; such a deficit might be relevant to patients with pre-existing hearing impairment.[2]

1. Mongan E, *et al.* Tinnitus as an indication of therapeutic serum salicylate levels. *JAMA* 1973; **226:** 142–5.
2. Day RO, *et al.* Concentration-response relationships for salicylate-induced ototoxicity in normal volunteers. *Br J Clin Pharmacol* 1989; **28:** 695–702.

Effects on the kidneys. Although abuse of combined analgesic preparations containing aspirin has been implicated in the development of analgesic nephropathy, kidney damage associated with the therapeutic use of aspirin alone appears to be comparatively rare. Many studies have failed to find an increased risk of renal damage in patients taking aspirin.[1-9]

1. New Zealand Rheumatism Association Study. Aspirin and the kidney. *BMJ* 1974; **1:** 593–6.
2. Walker BR, *et al.* Aspirin and renal function. *N Engl J Med* 1977; **297:** 1405.
3. Akyol SM, *et al.* Renal function after prolonged consumption of aspirin. *BMJ* 1982; **284:** 631–2.
4. Bonney SL, *et al.* Renal safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1986; **40:** 373–7.
5. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
6. Pommer W, *et al.* Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989; **9:** 403–12.
7. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
8. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.
9. Rexrode K, *et al.* Analgesic use and renal function in men. *JAMA* 2001; **286:** 315–21.

Effects on the liver. Aspirin-induced hepatic injury is generally mild and manifests as a mild to moderate elevation in aminotransferase values; however, there is a risk of severe liver injury.[1] One review[2] reported an increase in aminotransferase values in 59 of 439 patients given aspirin; the increase was considered to be probably related to aspirin in 23. Hepatotoxicity appears to be correlated with serum-salicylate concentrations greater than 150 micrograms/mL and with active rheumatoid disease. Aspirin-induced liver injury is usually reversible on stopping the drug.[2]

See also under Reye's Syndrome, below.

1. Lewis JH. Hepatic toxicity of nonsteroidal anti-inflammatory drugs. *Clin Pharm* 1984; **3:** 128–38.
2. Freeland GR, *et al.* Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1988; **43:** 473–9.

Effects on the mouth. Aspirin burn (ulceration of the mucosal layer of the lips) developed in a 26-year-old woman after taking an aspirin-containing powder for a migraine.[1] The woman had swallowed the powder undissolved rather than adding to water.

1. Dellinger TM, Livingston HM. Aspirin burn of the oral cavity. *Ann Pharmacother* 1998; **32:** 1107.

Hypersensitivity. The main clinical features of patients who have aspirin hypersensitivity include middle-age, female sex, diagnoses of asthma or rhinitis, a personal or family history of atopy, and a history of nasal polyps.[1,2] Aspirin sensitivity occurring with asthma and nasal polyps has been referred to in some reports as the 'aspirin triad'. Other sensitivities often found concomitantly include allergy to food dyes such as tartrazine and to drugs such as other NSAIDs.

The prevalence of aspirin-induced asthma can vary according to the method used to measure it. A systematic review[3] calculated the prevalence of aspirin-induced asthma to be 21% in the general adult asthma population and 5% in children when determined by oral provocation testing. However, when based on medical history alone it was only 2.7% in adults and 2% in children. In another study[4] using data from patient questionnaires the prevalence of aspirin-induced asthma was 10 to 11% in patients with asthma and 2.5% in non-asthmatics.

There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. In a systematic review[3] cross-sensitivity to other NSAIDs (ibuprofen, diclofenac, and naproxen) occurred in over 90% of those patients with aspirin-induced asthma. Paracetamol is usually safe in patients sensitive to aspirin and cross-sensitivity to paracetamol has been calculated as about 7%.[3] Based on these figures, it is considered that less than 2% of asthmatic patients would be likely to react to both paracetamol and aspirin.

The response to individual NSAIDs is believed to be closely linked to the extent to which they inhibit prostaglandin synthesis.[5,6] There may be a dose threshold below which no detectable symptoms occur and patients who may be tolerant of regular low-dose aspirin can develop symptoms when they take larger doses.[6] Some[6] use a formal challenge with a 300-mg oral dose of aspirin to confirm a diagnosis of NSAID sensitivity but others[7] consider this to be a dangerous technique and use inhalation of lysine aspirin which they consider to be a safer and more predictable alternative. Intranasal challenge with lysine aspirin has also been used.[8,9]

1. Kwoh CK, Feinstein AR. Rates of sensitivity reactions to aspirin: problems in interpreting the data. *Clin Pharmacol Ther* 1986; **40:** 494–505.
2. Schiavino D, *et al.* The aspirin disease. *Thorax* 2000; **55** (suppl 2): S66–S69.
3. Jenkins C, *et al.* Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328:** 434–7.
4. Vally H, *et al.* The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002; **57:** 569–74.

5. Power I. Aspirin-induced asthma. *Br J Anaesth* 1993; **71:** 619–21.
6. Frew A. Selected side-effects: 13. non-steroidal anti-inflammatory drugs and asthma. *Prescribers' J* 1994; **34:** 74–7.
7. Davies BH. NSAIDs and asthma. *Prescribers' J* 1994; **34:** 163–4.
8. Casadevall J *et al*. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax* 2000; **55:** 921–4.
9. Alonso-Llamazares A, *et al.* Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy* 2002; **57:** 632–5.

DESENSITISATION. Successful desensitisation has been achieved using oral aspirin challenge protocols.[1-5] Incremental doses of aspirin (traditionally starting at 30 mg) are given until an allergic response occurs; aspirin is readministered at the dose that caused the response and again incremental doses are given until finally a 650-mg dose is tolerated.[1,2] After desensitisation, an interruption of continuous aspirin dosage results in the reappearance of sensitivity.

1. Asad SI, *et al*. Effect of aspirin in "aspirin sensitive" patients. *BMJ* 1984; **288:** 745–8.
2. Stevenson DD. Desensitization of aspirin-sensitive asthmatics: a therapeutic alternative? *J Asthma* 1983; **20:** 31–8.
3. Gollapudi RR, *et al.* Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004; **292:** 3017–23.
4. Cormican LJ, *et al.* Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity. *Clin Exp Allergy* 2005; **35:** 717–22.
5. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. *Curr Opin Allergy Clin Immunol* 2006; **6:** 161–6.

Hypoglycaemia. A review of the literature[1] on drug-induced hypoglycaemia highlighted the fact that overdosage with salicylates could produce hypoglycaemia in children. Although therapeutic doses of salicylates in adults can lower blood-glucose concentrations in diabetic and non-diabetic subjects alike, opinion on the clinical significance of this effect varies. Salicylates have been implicated in a few cases of hypoglycaemia in adults[1] and some[2] suggest that patients with renal impairment or those receiving large doses, such as in the treatment of rheumatoid arthritis, may be at risk. Hypoglycaemia has been reported in a patient with renal failure after excessive application of a topical preparation containing salicylic acid.[3]

1. Seltzer HS. Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
2. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
3. Raschke R, *et al.* Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991; **151:** 591–3.

Reye's syndrome. Reye's syndrome is a disorder characterised by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children although cases have been seen[1] in patients over the age of 12. Many factors may be involved in its aetiology but it typically occurs after a viral infection such as chickenpox or influenza and may be precipitated by a chemical trigger. Several large studies, as well as individual case reports, have found a link between Reye's syndrome and the prior ingestion of aspirin.[2-6] The evidence for other salicylates could not be adequately evaluated.[4] Although the role of aspirin and possibly other salicylates in the pathogenesis of Reye's syndrome remains to be determined, the use of aspirin and other acetylated salicylates as analgesics or antipyretics is generally considered contra-indicated in children under the age of 12 years and, in some countries, in teenagers. For example, the UK CSM has recommended that all children under 16 should not take aspirin.[7] (This advice superseded their earlier recommendations to avoid aspirin during fever or viral infection in children under 16 years; the Committee felt that this advice was too complex for products on general sale and, given the wide availability of other analgesic preparations, there was no need to expose this age group to any risk.) Some countries also extend these recommendations to non-acetylated salicylates. One group of workers[8] who re-examined some of the original studies suggested that there might also be a link between Reye's syndrome and the use of antiemetics, phenothiazines, and some other antihistamines, but their conclusions have been criticised.[9] More recently, others[10] have suggested that Reye's syndrome was caused by a viral mutation or the result of misdiagnoses of metabolic disorders but again these conclusions have been questioned.[6,11]

1. Hall SM, Lynn R. Reye's syndrome. *N Engl J Med* 1999; **341:** 845–6.
2. Waldman RJ, *et al.* Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; **247:** 3089–94.
3. Halpin TJ, *et al.* Reye's syndrome and medication use. *JAMA* 1982; **248:** 687–91.
4. Hurwitz ES, *et al.* Public health service study of Reye's syndrome and medications: report of the main study. *JAMA* 1987; **257:** 1905–11.
5. Hall SM, *et al.* Preadmission antipyretics in Reye's syndrome. *Arch Dis Child* 1988; **63:** 857–66.
6. Glasgow JFT. Reye's syndrome: the case for a causal link with aspirin. *Drug Safety* 2006; **29:** 1111–21.
7. MHRA. Aspirin and Reye's syndrome: questions and answers (issued 4th April, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019512&RevisionSelectionMethod=LatestReleased (accessed 29/11/06)
8. Casteels-Van Daele M, Eggermont E. Reye's syndrome. *BMJ* 1994; **308:** 919–20.
9. Hall SM. Reye's syndrome. *BMJ* 1994; **309:** 411.
10. Orlowski JP, *et al.* Is aspirin a cause of Reye's syndrome? A case against. *Drug Safety* 2002; **25:** 225–31.
11. Waller P, Suvarna R. Is aspirin a cause of Reye's syndrome? *Drug Safety* 2004; **27:** 71–3.

Precautions

Aspirin has many properties in common with the non-aspirin NSAIDs, the precautions of which are described on p.98.

Aspirin should be used cautiously, if at all, in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be given to patients with haemophilia or other haemorrhagic disorders, nor to treat patients with gout (since low doses increase urate concentrations).

Aspirin should be used with caution in patients with asthma or allergic disorders. It should not be given to patients with a history of sensitivity reactions to aspirin or other NSAIDs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by such drugs (for further details of risk factors see Hypersensitivity under Adverse Effects, above).

Caution is necessary when renal or hepatic function is impaired; aspirin should be avoided in severe renal or hepatic impairment. Aspirin should be used cautiously in dehydrated patients and in the presence of uncontrolled hypertension.

High doses may precipitate acute haemolytic anaemia in patients with G6PD deficiency. Aspirin may interfere with insulin and glucagon control in diabetics (see Hypoglycaemia under Adverse Effects, above).

The use of aspirin in children is extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above, and under Uses and Administration, below).

Although low-dose aspirin might be used in some pregnant patients, analgesic doses of aspirin should not be used at term as they may be associated with delayed onset and prolongation of labour and with maternal and neonatal bleeding. High doses may cause closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the newborn (but see Pregnancy, below); kernicterus may occur in jaundiced neonates.

Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding.

Aspirin should be stopped several days before scheduled surgical procedures (see below).

Aspirin and other salicylates can interfere with thyroid function tests.

Breast feeding. The American Academy of Pediatrics[1] considers that salicylates should be given with caution to breast-feeding mothers, since aspirin has been associated with metabolic acidosis in the infant.[2] The *BNF* also recommends that aspirin should be avoided in breast-feeding mothers because of the possible risk of Reye's syndrome in nursing infants; they also advise that infants with neonatal vitamin K deficiency may be at risk of hypoprothrombinaemia after the regular use of high doses of aspirin in breast-feeding mothers. However, a prospective study[3] found no adverse effects in 15 breast-fed infants whose mothers were receiving aspirin.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/11/06)
2. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)* 1981; **20:** 53–4.
3. Ito S, *et al.* Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168:** 1393–9.

Pregnancy. The potential adverse effects of aspirin when used during pregnancy have been reviewed.[1] Salicylates readily cross the placenta and have been shown to be teratogenic in *animals*. Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, most large studies[2-4] have failed to find any significant risk or evidence of teratogenicity. Analysis of data collected by the Slone Epidemiology Unit Birth Defects Study suggests that use of aspirin during the early months of pregnancy, when the fetal heart is developing, is not associated with an increased risk of cardiac defects.[5] The ability of aspirin, however, to alter platelet function may be a potential risk. There have been a few reports of haemorrhagic disorders in infants whose mothers had consumed aspirin during pregnancy[6] and of salicylate-associated haemorrhagic complications in mothers.[7] However, no clinically significant adverse effects on maternal or neonatal bleeding or on fetal ductus flow were reported in a meta-analysis[8] of 6 controlled studies which evaluated low-dose aspirin (less than 325 mg daily) in pregnancy-induced hypertension. Two more recent placebo-controlled studies[9,10] have also observed no clinically significant adverse effects on neonatal bleeding with low-dose aspirin. It appeared that the degree of cyclo-oxygenase inhibition produced by aspirin was unlikely to be great enough to cause premature closure of the ductus arteriosus or to affect the pulmonary blood vessels.[1] See also under Surgical Procedures, below. However, in some studies in patients considered to have high-risk pregnancies the risk of abruptio placentae[11] or consequent perinatal death[12] was increased by maternal dosage with aspirin. For reference to a possible association between aspirin and other NSAIDs and persistent pulmonary hypertension of the newborn, see under NSAIDs, p.99.

Although aspirin has the potential to inhibit uterine contractions of labour it was considered that intermittent or low-dose aspirin was unlikely to inhibit cyclo-oxygenase for long enough to prolong pregnancy or labour.[1]

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Resistance. Some patients given aspirin for the management of cardiovascular disease do not respond to treatment, a phenomenon that has been described as aspirin resistance. At present, aspirin resistance is poorly understood and further studies are needed to define it.

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Surgical procedures. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation. This effect is irreversible and new platelets must be released into the circulation before bleeding time can return to normal. Therefore aspirin therapy should be stopped several days before surgical procedures. In some clinical situations, aspirin may have been given shortly before a surgical procedure. When emergency coronary bypass surgery is required for myocardial infarction, most patients would have received aspirin as part of the initial treatment for infarction. Perioperative bleeding, transfusion requirements, and surgical re-exploration rates may be increased when aspirin is given.[1] However, some studies[2,3] have shown that the increase in bleeding is not significant; in addition, there have been reports that pre-operative aspirin may reduce the rate of perioperative myocardial infarction (with aprotinin),[4] improve oxygenation,[5] and even decrease mortality.[3,6] Desmopressin may reduce the risk of perioperative bleeding (see under Haemorrhagic Disorders, p.2187).

Aspirin is sometimes given during the second and third trimester for the prevention of pregnancy-induced hypertensive disease (see under Hypertension, p.1171). Studies indicate that when given in a dose of 325 mg daily or less, clinically significant effects on maternal or neonatal bleeding do not occur.[7] Some have suggested that aspirin therapy may increase the risk of formation of extradural haematoma thus making epidural anaesthesia inadvisable[8] but a subsequent study[9] found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia.

Patients on low-dose aspirin, in whom tourniquets are used for nerve blocks or other procedures, may be at increased risk of developing purpuric rash.[10]

It has been suggested that in patients undergoing dermatological,[11] or minor dental[12] surgery, aspirin need only be stopped before surgery in those patients with a prolonged bleeding time, whereas patients with a normal bleeding time could continue therapy.

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Interactions

Aspirin has many properties in common with the non-aspirin NSAIDs, the interactions of which are described on p.99.

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. Use of gold compounds with aspirin may exacerbate aspirin-induced liver damage.

Use of aspirin with dipyridamole may result in an increase in plasma-salicylate concentrations. Drugs such as metoclopramide in patients with migraine headache result in earlier absorption of aspirin and higher peak plasma-salicylate concentrations. Metoprolol may also increase peak plasma-salicylate concentrations. Salicylate intoxication has occurred in patients on high-dose salicylate regimens and carbonic anhydrase inhibitors.

Plasma-salicylate concentrations may be reduced by corticosteroids. This interaction is likely to be important in patients receiving high-dose long-term salicylate treatment. Conversely, salicylate toxicity may occur if corticosteroids are withdrawn. Also the risk of gastrointestinal bleeding and ulceration associated with aspirin is increased when used with corticosteroids. Antacids may increase the excretion of aspirin in alkaline urine.

Aspirin may increase the activity of coumarin anticoagulants, sulfonylurea hypoglycaemic drugs, zafirlukast, methotrexate, phenytoin, and valproate. Aspirin diminishes the effects of uricosurics such as probenecid and sulfinpyrazone. The manufacturer of mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by aspirin or NSAIDs may alter the efficacy of mifepristone.

Use of aspirin with other NSAIDs should be avoided because of the increased risk of adverse effects; the cardioprotective effects of aspirin may be abolished by ibuprofen and possibly other NSAIDS. Aspirin may decrease the plasma concentration of some other NSAIDs, for example, fenbufen, indometacin, and piroxicam.

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ACE inhibitors. For a discussion of aspirin and other NSAIDs reducing the activity of ACE inhibitors, see p.1197.

Antiepileptics. Aspirin may inhibit the metabolism of *valproate*; for further details, see Analgesics, p.510.

Antifungals. Plasma-salicylate concentrations in an 8-year-old child receiving long-term aspirin therapy for rheumatic heart disease were markedly reduced when treatment with *griseofulvin* was started.[1] It was suggested that griseofulvin might interfere with absorption of aspirin.

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Calcium-channel blockers. The antiplatelet effects of aspirin and calcium-channel blockers may be increased when they are used together; there have been isolated reports[1,2] of disturbed haemostasis including abnormal bruising, prolonged bleeding times and ecchymosis in patients taking aspirin and *verapamil* concurrently.

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General anaesthetics. For the effect of aspirin on *thiopental* anaesthesia, see p.1796.

NSAIDs. It has been suggested that *ibuprofen* and possibly other *NSAIDs* may reduce the cardioprotective effect of aspirin. A study[1] involving 7107 patients found that cardiovascular mortality was increased in patients taking low-dose aspirin for cardiovascular disease when also taking ibuprofen (adjusted hazard ratio 1.73 times that of patients not taking ibuprofen). Another study[2] found that although taking low-dose aspirin or NSAIDs alone decreased the incidence of myocardial infarction, there was a non-significant increase in the risk of myocardial infarction when both were taken. Another large study also found the risk to be increased in those taking regular rather than intermittent NSAID treatment with aspirin.[3] However, a study[4] involving 14 098 patients concluded that the risk of myocardial infarction was reduced in patients taking ibuprofen with aspirin when compared to those taking aspirin alone. Furthermore, a study[5] in 70 316 patients found that the risk of death in patients prescribed aspirin and ibuprofen was comparable to that of patients prescribed aspirin alone or with another NSAID.

The timing of doses may be important; a study[6] has shown that irreversible platelet aggregation occurred when a single daily dose of ibuprofen was given 2 hours after aspirin; however, when ibuprofen was given before aspirin as a single daily dose or given three times daily, platelet aggregation was reversible which may limit the cardioprotective effects of aspirin.

There are limitations to all these studies and further studies are needed before any recommendations can be made.[7-11]

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Spironolactone. For the effect of aspirin in patients taking spironolactone, see p.1401.

Pharmacokinetics

Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin.

After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylate appears in breast milk and crosses the placenta.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325-mg aspirin dose, elimination is a first-order process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

Salicylate is removed by haemodialysis.

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Uses and Administration

Aspirin is a salicylate NSAID and has many properties in common with non-aspirin NSAIDs (p.99). Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties; they act as inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.2374). Aspirin also inhibits platelet aggregation; non-acetylated salicylates do not.

Aspirin is used for the relief of mild to moderate pain such as headache, dysmenorrhoea, myalgias, and dental pain. It has also been used in the management of pain and inflammation in acute and chronic rheumatic disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the treatment of minor febrile conditions, such as colds or influenza, aspirin can reduce temperature and relieve headache and joint and muscle pains.

Aspirin is also used for its antiplatelet activity in the initial treatment of cardiovascular disorders such as angina pectoris and myocardial infarction and for the prevention of cardiovascular events in patients at risk. Other such uses include the treatment and prevention of cerebrovascular disorders such as stroke. For further details see under Antiplatelet Therapy, below.

Aspirin is usually taken by mouth. Gastric irritation may be reduced by taking doses after food. Various dosage forms are available including plain uncoated tablets, buffered tablets, dispersible tablets, enteric-coated tablets, and modified-release tablets. In some instances aspirin may be given rectally by suppository.

The usual oral dose of aspirin as an analgesic and antipyretic is 300 to 900 mg, repeated every 4 to 6 hours according to clinical needs, to a maximum of 4 g daily. The dose as suppositories is 450 to 900 mg every 4 hours to a maximum of 3.6 g daily.

Plasma-salicylate concentrations of 150 to 300 micrograms/mL are required for optimal anti-inflammatory activity (but see also Adverse Effects, above). Doses need to be adjusted individually to achieve optimum concentrations. Generally doses of about 4 to 8 g daily in divided doses are used for acute rheumatic disorders such as rheumatoid arthritis or osteoarthritis. Doses of up to 5.4 g daily in divided doses may be sufficient in chronic conditions.

Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above), but include Kawasaki disease (see below), and juvenile idiopathic arthritis and Still's disease (see Rheumatic Disorders, below).

Sodium aspirin has also been used for the treatment of pain and fever.

Administration in children. Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above). For further information, including some doses, see Antiplatelet Therapy, Kawasaki Disease, and Rheumatic Disorders, below.

Antiplatelet therapy. Aspirin is an inhibitor of the enzyme cyclo-oxygenase, the **action** being considered to be due to an irreversible acetylation process.

- In blood platelets such enzyme inhibition prevents the synthesis of thromboxane A_2, a compound which is a vasoconstrictor, causes platelet aggregation, and is thus potentially thrombotic.
- In blood vessel walls the enzyme inhibition prevents the synthesis of prostacyclin, which is a vasodilator, has anti-aggregating properties, and is thus potentially anti-thrombotic.

Aspirin therefore appears to have paradoxical biological effects. The duration of these effects, however, may differ, with the *effects on the vascular tissue generally being shorter than the effects on the platelets* (although the *animal* species studied, the type of blood vessel used, and the prevailing experimental conditions may alter the results). The difference may be explained by the fact that vascular cells regain the ability to regenerate prostacyclin in a few hours but platelets are unable to re-synthesise cyclo-oxygenase, which results in no new thromboxane A_2 being produced for about 24 hours until more platelets are released by the bone marrow; as platelet activity in bone marrow may also be affected by aspirin it is generally considered that aspirin only needs to be given once daily for inhibition of platelet aggregation to occur. The inhibitory effect on thromboxane is rapid and unrelated to serum concentrations of aspirin, probably because of the inactivation of cyclo-oxygenase in platelets in the presystemic circulation. Since the effect is unrelated to systemic bioavailability, modified-release and dermal delivery preparations which do not achieve high systemic concentrations of aspirin are being developed to limit extraplatelet effects of aspirin. Inhibition is cumulative on repeated dosage, and it has been estimated that a daily dose of 20 to 50 mg will result in virtually complete suppression of platelet thromboxane synthesis within a few days. Large doses of 150 to 300 mg can produce maximum suppression almost instantaneously.

Uses. Aspirin's antiplatelet activity has led to its use for the treatment or prevention of a variety of disorders.[1-6]

- It is used as part of the initial **treatment** of unstable *angina* (p.1157) and is given in the early treatment of *myocardial infarction* (p.1175); it is also of benefit in the initial treatment of acute *ischaemic stroke* (p.1185).
- Aspirin is used for its combination of anti-inflammatory, antipyretic, and antiplatelet activity in the treatment of *Kawasaki disease* (see below). It is also used to treat thrombotic symptoms associated with *antiphospholipid syndrome*, such as occurs in patients with SLE (p.1513), and has been recommended for prophylactic use in pregnant patients with antiphospholipid antibodies who are at risk of fetal loss. The thrombolytic action of aspirin has also led to its use in thrombotic thrombocytopenic purpura (see Thrombotic Microangiopathies, p.1076). Aspirin has been tried in *pregnancy-induced hypertension* (see under Hypertension, p.1171) for the prevention of pre-eclampsia and intra-uterine growth retardation and may provide a small to moderate benefit in some women.
- It is of value for the **prevention** of cardiovascular events in patients at high risk, including those with stable or unstable angina, current or previous myocardial infarction, ischaemic stroke, or transient ischaemic attack (see Cardiovascular Risk Reduction, p.1164). It has also been used in the long-term management of atrial fibrillation (see under Cardiac Arrhythmias, p.1160) for the prevention of stroke in patients with contra-indications to warfarin or if there are no other risk factors for stroke.
- The value of aspirin for **primary prevention** of cardiovascular events, particularly *myocardial infarction* and *stroke* depends upon the accurate estimation of overall cardiovascular risk but is probably not justified in healthy individuals.[7-9]

  Although aspirin may prevent *venous thromboembolism* (p.1189) after surgery, other treatments have been preferred. However, it is recommended for use in preventing thrombotic complications associated with procedures such as angioplasty and coronary bypass grafting (see under Reperfusion and Revascularisation Procedures, p.1181). Aspirin is often given as an adjunct to patients with *peripheral arterial thromboembolism* (p.1178) to prevent propagation of the clot and also to prevent postoperative complications. It may have some effect in delaying disease progression and reducing vascular events in patients with *peripheral arterial disease* (p.1178) but an analysis[10] concluded that there was insufficient evidence to support its prophylactic use in patients with intermittent claudication but no additional cardiovascular risk factors.

  The benefit of aspirin for the primary prevention of cardiovascular events in patients with *diabetes mellitus* (see under Diabetic Complications, p.433) and who have no other cardiovascular risk factors remains to be determined.[8] Use is recommended in all those at increased risk, which includes (in the USA) all diabetics over 40 years of age,[11] or those aged 50 and over or with existing atherosclerosis or hypertension or a history of diabetes for over 10 years (in the UK).[12]

  The value of adding aspirin to anticoagulants for the prophylaxis of thromboembolism in patients with *prosthetic heart valves* (see p.1187) is also still to be firmly established. It is usually recommended as an adjunct in patients with other risk factors. Aspirin alone may be considered in patients with bioprosthetic valves who do not require anticoagulation.

Several pharmacological studies have attempted to find a **dose** of aspirin that would inhibit synthesis of platelet thromboxane A_2 while sparing the effect on prostacyclin production[13-15] but it has been pointed out[3] that in patients with vascular disease accompanying or caused by endothelial dysfunction, such as in atherosclerosis, a selective sparing of vascular prostacyclin production may not be obtained at any effective antiplatelet dose. However, the clinical relevance of inhibiting the synthesis of prostacyclin may have been exaggerated.[16] Experimental evidence indicates that aspirin is thrombogenic only at extremely high doses (200 mg/kg), far exceeding the minimum dose required to inhibit prostacyclin production. Also aspirin is clinically effective as an antithrombotic drug at doses that inhibit the synthesis of prostacyclin. Further support for the lack of importance of inhibition of prostacyclin synthesis comes from epidemiological studies in patients with arthritis given large doses of aspirin and patients with congenital cyclo-oxygenase deficiency; neither of these groups of patients have experienced an excess of thrombotic episodes.

In a meta-analysis conducted by the Antithrombotic Trialists' Collaboration[8] daily doses of 75 to 325 mg appeared to be equally effective for their antiplatelet effect; doses greater than 500 mg did not appear to be superior and caused more gastrointestinal adverse effects. Whether doses less than 75 mg offer the same efficacy with reduced gastrointestinal toxicity remains to be determined (see Effects on the Gastrointestinal Tract, above). The meta-analysis concluded that for the long-term prevention of serious vascular events in high-risk patients, a daily dose of aspirin in the range of 75 to 150 mg should be effective; if an immediate effect is required as in the initial treatment of acute myocardial infarction, acute ischaemic stroke, or unstable angina, a loading dose of 150 to 300 mg may be given. Other analyses[10,17] have made similar dose recommendations. However, another review[18] has suggested that doses as low as 75 or 80 mg daily may be inadequate for the primary prevention of stroke and myocardial infarction; it was considered that the most appropriate dose of aspirin for primary prevention was 160 mg daily. Aspirin should be chewed or dispersed in water; chewing a tablet of aspirin ensures that some buccal absorption occurs.

The use of aspirin in **children** is limited because of the risk of Reye's syndrome (see under Adverse Effects, above); however, it may be specifically indicated in those at risk of clot formation after cardiac surgery or for the prophylaxis of stroke in high-risk children. The *BNFC* has suggested oral doses of 1 to 5 mg/kg (up to a usual maximum of 75 mg) once daily in neonates and children up to 12 years of age; older children may be given 75 mg daily.

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Behçet's syndrome. For reference to the use of aspirin in the management of vasculitic symptoms of Behçet's syndrome, see p.1499.

Cataract. Evidence to support or disprove the hypothesis that aspirin has a protective effect against cataract formation is considered inconclusive. A study in the US in over 22 000 males concluded that low-dose aspirin (325 mg on alternate days) for 5 years was unlikely to have a major effect on cataract formation but that a slightly decreased risk for cataract extraction could not be excluded.[1] In a later study[2] in the UK ophthalmic examination of over 1800 patients who were receiving 300 mg to 1.2 g of aspirin daily for transient ischaemic attacks failed to confirm any protective effect. Re-analysis[3] of the results of the original US study identified additional cases of cataract formation or extraction although these cases did not affect the overall conclusions of the original study. However, when the study patients were followed up over 15 years, observational data[4] suggested that the use of low-dose aspirin may, in fact, increase the risk of cataract development. It was considered that further trials were needed to establish the role of long-term aspirin in cataract prevention.

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4. Christen WG, *et al.* Aspirin use and risk of cataract in posttrial follow-up of Physicians' Health Study I. *Arch Ophthalmol* 2001; **119:** 405–12.

Dysmenorrhoea. Drugs such as aspirin and other NSAIDs that inhibit prostaglandin production through inhibition of cyclo-oxygenase are effective drugs in the treatment of dysmenorrhoea (p.6).

Fever. Methods for controlling fever (see p.10) include the use of antipyretics and/or physical cooling methods (although the value of the latter is questionable). Paracetamol, salicylates such as aspirin, and some other NSAIDs are the main antipyretics used. However, salicylates are generally contra-indicated for the management of fever in children because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects, above).

Headache. Aspirin is often used for the symptomatic treatment of various types of headache including migraine (see p.616) and tension-type headache (see p.617). Aspirin given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.

1. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. *Cephalalgia* 1984; **4:** 107–11.
2. Buring JE, *et al.* Low-dose aspirin for migraine prophylaxis. *JAMA* 1990; **264:** 1711–13.
3. MacGregor EA, *et al.* Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002; **42:** 249–55.
4. Steiner TJ, *et al.* Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003; **23:** 59–66.
5. Lipton RB, *et al.* Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005; **45:** 283–92.
6. Diener HC, *et al.* Aspirin in the treatment of acute migraine attacks. *Expert Rev Neurother* 2006; **6:** 563–73.

Kawasaki disease. Aspirin has been given in regimens with normal immunoglobulins to children with Kawasaki disease (p.2228) because of its anti-inflammatory, antipyretic, and antiplatelet activity.[1-4]

The usual practice is to use an anti-inflammatory regimen until the fever has settled and then convert to an antithrombotic regimen. The *BNFC* recommends an oral dose of 30 to 50 mg/kg daily in 4 divided doses in children aged 1 month and over (neonates may be given 32 mg/kg daily in 4 divided doses); this should be continued until the patient is afebrile or for the first 14 days after the onset of symptoms. Once fever and signs of inflammatory disease resolve, the aspirin dose is reduced to 2 to 5 mg/kg daily (neonates may be given 5 mg/kg daily) as a single dose for its antiplatelet effect. Aspirin may be stopped 6 to 8 weeks after the onset of illness but is usually continued for at least one year if coronary abnormalities are present and is continued indefinitely if coronary aneurysms persist. Similar regimens[3,4] are used in the USA although the initial dose of aspirin is more usually 80 to 100 mg/kg daily.

Despite this widespread use the optimum dose and duration of treatment have not been clearly established, and the value of aspirin in the initial management of Kawasaki disease has been questioned. In a meta-analysis[5] fever duration was significantly shorter in those on high-dose aspirin; however, other studies[6] have not shown such a benefit. Meta-analyses[5,7] have also shown that the incidence of coronary artery abnormalities is not significantly different for regimens using high (over 80 mg/kg daily) or low doses of aspirin. Furthermore, a retrospective study[8] suggested that aspirin use (irrespective of dose) in the acute phase of the disease may be unnecessary as its addition to immunoglobulin treatment had no effect on the rate of coronary artery abnormalities. A more recent review[9] found that evidence from comparative studies failed to show that aspirin reduced the rate of coronary artery abnormalities; a lack of good quality randomised controlled trials prevented any recommendations on the use of aspirin in the treatment of Kawasaki disease.

1. Williams RV, *et al.* Pharmacological therapy for patients with Kawasaki disease. *Paediatr Drugs* 2001; **3:** 649–60.
2. Brogan PA, *et al.* Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002; **86:** 286–90.
3. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114:** 1708–33. Correction. *ibid.* 2005; **115:** 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 12/04/07) Also published in *Circulation* 2004; **110:** 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
4. Freeman AF, Shulman ST. Kawasaki disease: summary of the American Heart Association guidelines. *Am Fam Physician* 2006; **74:** 1141–8.
5. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; **131:** 888–93.
6. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. *Clin Pediatr (Phila)* 2002; **41:** 597–601.
7. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; **96:** 1057–61.
8. Hsieh K-S, *et al.* Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. *Pediatrics* 2004; **114:** 689. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/6/e689 (accessed 27/11/06)
9. Baumer JH, *et al.* Salicylate for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/11/06).

Leg ulcers. A 4-month placebo-controlled study[1] in 20 patients suggested that aspirin 300 mg daily aided healing of chronic venous leg ulcers; the mechanism of action was unclear.[2] However, the validity of the findings has been challenged.[3] The management of leg ulcers is discussed on p.1585.

1. Layton AM, *et al.* Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet* 1994; **344:** 164–5.
2. Ibbotson SH, *et al.* The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. *Br J Dermatol* 1995; **132:** 422–6.
3. Ruckley CV, Prescott RJ. Treatment of chronic leg ulcers. *Lancet* 1994; **344:** 1512–13.

Malignant neoplasms. For references to studies suggesting that regular use of aspirin and other NSAIDs may reduce the risk of developing malignant neoplasms of the gastrointestinal tract, see under NSAIDs, p.100.

Myeloproliferative disorders. Aspirin in low doses may be used to provide symptomatic relief for erythromelalgia (burning pain and erythema of the hands and feet) in patients with polycythaemia vera (p.654) and primary thrombocythaemia (p.654).

Pain. Aspirin, along with other NSAIDs and paracetamol, may be used for treating mild or moderate pain (see Choice of Analgesic, p.2) and is also used in moderate or severe pain to potentiate the effects of opioids. It is suitable for use in acute or chronic pain. Aspirin should not be used for pain relief in children because of its association with Reye's syndrome (see under Adverse Effects, above).

Dependence and tolerance are not a problem with non-opioid analgesics such as aspirin, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

References.

1. Edwards JE, *et al.* Single dose oral aspirin for acute pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/11/06).
2. Hersch EV, *et al.* Over-the-counter analgesics and antipyretics: a critical assessment. *Clin Ther* 2000; **22:** 500–48.
3. Vergne P, *et al.* Aspirine, douleurs et inflammation. *Rev Med Interne* 2000; **21** (Suppl 1): 89s–96s.

Rheumatic disorders. Aspirin was once widely used in the treatment of rheumatoid arthritis (p.11) but has been superseded by better tolerated NSAIDs; however, juvenile idiopathic arthritis including Still's disease (p.10) are among the limited number of indications for aspirin use in children. The *American Hospital Service Formulary* suggests that children weighing 25 kg or less may be given an initial oral dose of 60 to 130 mg/kg daily in divided doses; heavier children should be started on 2.4 to 3.6 g daily. The usual maintenance dose is 80 to 100 mg/kg daily although up to 130 mg/kg daily may be required in some children; however, because of the risk of toxicity, it is recommended that children weighing over 25 kg should not receive doses of 100 mg/kg daily or above.

Preparations

BP 2008: Aspirin and Caffeine Tablets; Aspirin Tablets; Co-codaprin Tablets; Dispersible Aspirin Tablets; Dispersible Co-codaprin Tablets; Effervescent Soluble Aspirin Tablets; Gastro-resistant Aspirin Tablets;
USP 31: Acetaminophen and Aspirin Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Aspirin and Codeine Phosphate Tablets; Aspirin Capsules; Aspirin Delayed-release Capsules; Aspirin Delayed-release Tablets; Aspirin Effervescent Tablets for Oral Solution; Aspirin Extended-release Tablets; Aspirin Suppositories; Aspirin Tablets; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Buffered Aspirin Tablets; Butalbital and Aspirin Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol and Aspirin Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Oxycodone and Aspirin Tablets; Pentazocine and Aspirin Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Aspirin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Adiro†; Aspimed†; Aspirina; Aspirinetas; Ball†; Bayaspirina; Bufferin†; Cardioaspirina; Desenfriolito; Ecotrin; Geniol AP†; Geniol Prevencion; Geniol SC sin Cafeina; Geniolito†; Lacefal†; Lafeaspirina; Nuevapina; ***Austral.:*** Aspro; Astrix; Bex†; Cardiprin; Cartia; Disprin; Disprin Direct; Ecotrin†; Solprin; Spren†; Vincent's Powders†; ***Austria:*** Acekapton; Aspiricor; Aspro; ASS; Herz ASS; Herzschutz ASS; Salimont; Thrombo ASS; Thrombostad; Togal Mono; ***Belg.:*** Acenterine; Asaflow; Asarid†; Aspirine; Aspro; Cardioaspirine; Cardiphar; Dispril; Sedergine; Therasa†; ***Braz.:*** AAS; Aasedatil†; Aceticil; Analgesin; Antifebrin†; Ascedor†; Asetisin†; Aspirina; Bufferin; Caas†; Cardio AAS; Cimaas; Ecasil†; Hipotermal; Salicil; Salicin; Salitil; Somalgin; ***Canad.:*** Asaphen; Aspergum; Aspirin with Stomach Guard; Bufferin; Entrophen; Equate; Novasen; Rivasa; Tri-Buffered ASA; ***Chile:*** Aspirina; Cardioaspirina; Disgren; Ecotrin; Fluicor; Hassapirin Puro; Thrombo AS; ***Cz.:*** Acylpyrin; Anopyrin; Apo-Asa†; Aspro†; Godasal; Upsarin†; ***Denm.:*** Hjerdyl; Hjertemagnyl; Idotyl; Magnyl; ***Fin.:*** Aspirin Cardio; Aspirin Zipp; Disperin; Primaspan; ***Fr.:*** Aspirine; Aspirine pH8†; Aspirisucre; Aspro; Catalgine†; Claragine; ***Ger.:*** Acesal; Acetylin†; Aspro; ASS; Godamed; HerzASS; Miniasal; Santasal N; Thomapyrin akut†; Togal ASS; ***Gr.:*** Salospir; Upsalgin-N; ***Hong Kong:*** Aspilets; Astrix; Bokey; Cardiprin; Cartia; Disprin; Ecotrin; Glyprin; LAsprin; Propirin; ***Hung.:*** Aspirin Protect; Astrix; Colfarit; Istopirin†; Kalmopyrin; ***India:*** ASA; Aspicot; Colsprin; CV-Sprin; Delisprin; Disprin; Ecosprin; ***Indon.:*** Aptor; Ascardia; Aspilets; Astika; Bodrexin; Cardio Aspirin; Contrexyn; Farmasal; Inzana; Minigrip; Naspro; Procardin; Restor; Rheumapill; Thrombo Aspilets; ***Irl.:*** Aspro; Caprin; Disprin; Lowasa; Nu-Seals; Resprin; ***Israel:*** Acetosal; Alka-Seltzer; Ascriptin†; Buffered Pirin; Cartia; Ecoprin; Godamed; Micropirin; Tevapirin; ***Ital.:*** Acesal†; ASA-ratio; Ascriptin; Aspiglicina; Aspirina; Aspirina 03; Aspirinetta; Aspro; Bufferin†; Cardioaspirin; Cemirit; Kilios†; ***Malaysia:*** Aceprin; Bufferin Low Dose†; Cardiprin; Casprin; Disprin; Dusil†; Glyprin; ***Mex.:*** Acetil-A; Acetin; Acitab; Adiro†; Antacsal; ASA; Ascriptin; Aspirina Protect; Axal†; Disprina; Doloquim; Ecotrin; Midolen; Vastecel; ***Neth.:*** Asacard; Aspirine Protect; Aspro; Bisolgripin†; Darosal; Togal; ***Norw.:*** Albyl-E; Dispril; Globoid; ***NZ:*** Aspec; Aspro; Cardiprin†; Cartia; Disprin; Ecotrin; Solprin; ***Philipp.:*** Anthrom; Asaprim; Aspec; Aspilets; Cor-30, Cor-80; Cortal; Enteroprin; Tromcor; ***Pol.:*** Acard; Acesan; Alka-Prim; Alka-Seltzer; ASA; Aspimag; Aspirin Protect; Asprocard; Asprocol; Bestpirin; Calcipiryna; Cardiofil; Encopirin; Galocard; Nipas; Polocard; Polopiryna; Polopiryna S; Proficar; Upsarin; ***Port.:*** AAS; Asacard; ASP; Aspirina; Aspro†; Cartia; Melhoral Infantil†; Migraspirina; Salycilina†; Toldex; Tromalyt; ***Rus.:*** Aspinat Cardio (Аспинат Кардио); Aspirin Cardio (Аспирин Кардио); CardiASK (КардиАСК); Thrombo ASS (Тромбо АСС); ***S.Afr.:*** Disprin; Ecotrin; Myoprin; ***Singapore:*** Aspro; Astrix; Bokey; Bufferin†; Cardiprin; Disprin; Dusil; Glyprin; ***Spain:*** AAS; Adiro; Aspinfantil†; Aspirina; Bioplak; Helver Sal†; Mejoral†; Okal; Orravina†; Rhonal; Saspryl†; Sedergine; Tromalyt; ***Swed.:*** Albyl minor; Bamycor†; Bamyl; Bamyl S; Emotpin†; Magnecyl; Trombyl; ***Switz.:*** ASA; Asperivo†; Aspirine Cardio; Aspro; ASS; Juridin; Thrombace Neo; Tiatral 100 SR; Togal ASS; ***Thai.:*** Actorin; Anassa; Asatab; Ascot†; Aspent; Aspilets; Asrina; Caparin; Cardiprin; Comoprin†; Entrarin; Seferin; V-AS; ***Turk.:*** Algo; Algo Bebe; Asabrin; Asinpirine; Aspapirine; Aspinal; Ataspin; Babyprin; Coraspin; Dispril; Ecopirin; Notras; Opon; ***UAE:*** Jusprin; ***UK:*** Alka; Angettes; Aspro; Caprin; Disprin; Disprin Direct; Enprin; Micropirin; Nu-Seals; PostMI†; Pure Health; ***USA:*** Adprin-B; Arthritis Pain Formula; Ascriptin; Aspergum; Asprimox†; Bayer Low Adult Strength; Bufferin; Buffex; Cama Arthritis Pain Reliever; Easprin; Ecotrin; Empirin; Extra Strength Bayer Plus; Genprin; Halfprin; Magnaprin†; Norwich Extra Strength; Norwich Regular Strength; Regular Strength Bayer; St. Joseph Adult Chewable; ZORprin; ***Venez.:*** Asaprol; Ascriptin; Aspiretina†; Azacard; Cardipirina; Coraspirina.

Multi-ingredient: numerous preparations are listed in Part 3.

Auranofin *(BAN, USAN, rINN)*

Auranofiini; Auranofina; Auranofine; Auranofinum; Oranofin; SKF-39162; SKF-D-39162. (1-Thio-β-D-glucopyranosato)(triethylphosphine)gold 2,3,4,6-tetra-acetate.

Ауранофин

$C_{20}H_{34}AuO_9PS = 678.5.$

CAS — 34031-32-8.

ATC — M01CB03.

ATC Vet — QM01CB03.

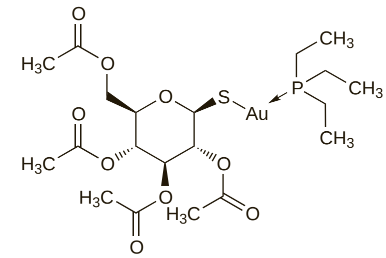

Adverse Effects and Treatment

The most common adverse effects of auranofin involve the gastrointestinal tract and include nausea, abdominal pain, and sometimes vomiting, but most often diarrhoea, which can affect up to 50% of patients and may be severe enough to cause patients to withdraw from treatment. Other adverse effects are similar to those experienced with sodium aurothiomalate (p.122), although they appear to be less troublesome since fewer patients stop treatment with auranofin than with injectable gold. As with other gold salts, treatment of adverse effects is generally symptomatic (see p.123). Modifying the diet to increase bulk, use of a bulking agent such as bran, or a temporary reduction in auranofin dosage, may help the diarrhoea (but see Effects on the Gastrointestinal Tract, below).

◊ Reviews.

1. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2:** 177–89.

Effects on the gastrointestinal tract. Diarrhoea and abdominal pain are common with auranofin. The mechanism of gastrointestinal toxicity has not been established but may be associated with a reversible defect in intestinal permeability.[1] Although some have suggested that diarrhoea may occur in up to 50% of patients taking auranofin, a study in 269 patients given the drug for rheumatoid arthritis found that only about 15% experienced loose and watery stools over a six-month period.[2] Although bulking agents have been recommended in the management of auranofin-induced diarrhoea, no overall difference in incidence was seen between patients given prophylactic psyllium and those given placebo; however, patients given psyllium had slightly fewer days with loose and watery stools.

Gold-induced colitis has also been reported in patients taking auranofin.[3,4]

1. Behrens R, *et al.* Investigation of auranofin-induced diarrhoea. *Gut* 1986; **27:** 59–65.
2. van Beusekom HJ, *et al.* The moderate intestinal side effects of auranofin do not require prophylactic therapy with a bulkforming agent. Dutch Ridaura Study Group. *Clin Rheumatol* 1997; **16:** 471–6.
3. Michet CJ, *et al.* Auranofin-associated colitis and eosinophilia. *Mayo Clin Proc* 1987; **62:** 142–4.
4. Langer HE, *et al.* Gold colitis induced by auranofin treatment of rheumatoid arthritis: case report and review of the literature. *Ann Rheum Dis* 1987; **46:** 787–92.

Effects on the kidneys. In a retrospective review[1] of 1283 patients who had received auranofin for treatment of rheumatoid arthritis 41 (3.2%) were found to have developed proteinuria. In most cases proteinuria was treated by stopping auranofin therapy. Long-term follow-up of 36 patients indicated that proteinuria had resolved in 31 within 2 years and in 29 within 1 year. Seven of 8 patients later rechallenged with auranofin had no relapses. In a further review of 2 comparative double-blind studies using gold compounds in the treatment of rheumatoid arthritis, proteinuria was found to have developed in 27% (23 of 85) of patients treated with sodium aurothiomalate, in 17% (42 of 247) of those treated with auranofin, and in 17% (36 of 210) of those receiving placebo. All patients were receiving NSAIDs.

1. Katz WA, *et al.* Proteinuria in gold-treated rheumatoid arthritis. *Ann Intern Med* 1984; **101:** 176–9.

Precautions

As for Sodium Aurothiomalate, p.123. Urine and blood tests should be carried out before starting auranofin and monthly thereafter; licensed product information advises that auranofin should be withdrawn if the platelet count falls below 100 000 cells/mm^3 or if signs and symptoms suggestive of thrombocytopenia, leucopenia or aplastic anaemia occur. US licensed product information states that baseline renal and liver function levels should also be established before starting auranofin therapy. Auranofin should be used with caution in patients with inflammatory bowel disease.

Porphyria. Auranofin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Sodium Aurothiomalate, p.123.

Pharmacokinetics

Auranofin is incompletely absorbed from the gastrointestinal tract, only about 25% of the gold being absorbed. Gold from auranofin is bound to plasma proteins as well as to red blood cells. After 2 to 3 months of treatment the steady-state concentration of gold in the blood is reported to be about 0.7 micrograms/mL. The average terminal plasma half-life of gold at steady state is about 26 days while the biological half-life is 80 days. Tissue retention and total gold accumulation in the body are less than with intramuscular gold. Gold from auranofin penetrates into synovial fluid.

Most of a dose of auranofin appears in the faeces due to its poor absorption. About 60% of the absorbed gold from auranofin is excreted in the urine and the remainder in the faeces.

◊ Reviews.

1. Blocka KLN, *et al*. Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11:** 133–43.
2. Benn HP, *et al.* Pharmacokinetics of auranofin: a single dose study in man. *J Rheumatol* 1990; **17:** 466–8.

Uses and Administration

Auranofin is a gold compound with a gold content of about 29%; it has similar actions and uses to those of sodium aurothiomalate (p.123). It is given orally in active progressive rheumatoid arthritis (below); such oral treatment is less toxic than intramuscular gold but is also much less effective. The usual initial dose of auranofin is 6 mg daily given in two divided doses at first, then, if tolerated, as a single dose. Treatment should be continued for at least 6 months to assess the response; the dose may be increased after 6 months, if the response is inadequate, to 3 mg three times daily. If the response is still inadequate after 3 months at this dosage, then treatment should be stopped.

Asthma. A systematic review[1] found that oral or parenteral gold compounds reduced corticosteroid requirements in the management of asthma (p.1108); however, it was considered that the effect was probably of limited clinical significance and, given the adverse effects and monitoring requirements of gold compounds, their use in asthma could not be recommended.

1. Evans DJ, *et al.* Gold as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 25/10/06).

Lupus. Since the introduction of less toxic drugs gold compounds are now rarely used in the treatment of SLE, however, there have been anecdotal reports suggesting that auranofin may still be of use in patients with discoid lupus erythematosus[1] or cutaneous lupus erythematosus[2] refractory to conventional treatment.

1. Dalziel K, *et al.* Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; **115:** 211–16.
2. Farrell AM, Bunker CB. Oral gold therapy in cutaneous lupus erythematosus (revisited). *Br J Dermatol* 1996; **135** (suppl 47): 41.

Pemphigus. A patient with long-standing pemphigus foliaceus being treated with prednisolone and hydroxychloroquine had healing of his lesions within 6 months of auranofin being substituted for the hydroxychloroquine.[1]

1. Bagheri MM, *et al.* Pemphigus foliaceus presenting as eruptive seborrheic keratosis and responding to oral gold treatment. *J Drugs Dermatol* 2002; **1**:333–4.

Psoriasis. Although topical auranofin has been shown in a placebo-controlled study[1] to be effective in the treatment of plaque-type psoriasis (p.1583) the high incidence of adverse skin reactions, such as contact dermatitis, was thought to outweigh any benefit.

1. Helm KF, *et al.* Topical auranofin ointment for the treatment of plaque psoriasis. *J Am Acad Dermatol* 1995; **33:** 517–19.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p.11). Oral gold is less toxic than intramuscular gold but is also much less effective. Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p.13) and have been used in juvenile idiopathic arthritis (p.10).

References.

1. Suarez-Almazor ME, *et al.* Auranofin versus placebo in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 09/05/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Ridaura; ***Austria:*** Ridaura; ***Belg.:*** Ridaura; ***Braz.:*** Ridaura†; ***Canad.:*** Ridaura†; ***Denm.:*** Ridaura†; ***Fin.:*** Ridaura; ***Fr.:*** Ridauran; ***Ger.:*** Ridaura; ***Gr.:*** Ridaura; ***Hong Kong:*** Ridaura; ***India:*** Goldar; ***Irl.:*** Ridaura; ***Israel:*** Ridaura; ***Ital.:*** Ridaura; ***Neth.:*** Ridaura; ***Norw.:*** Ridaura; ***NZ:*** Ridaura; ***Port.:*** Ridaura; ***Rus.:*** Auropan (Ауропан); ***S.Afr.:*** Ridaura; ***Spain:*** Ridaura; ***Swed.:*** Ridaura†; ***Switz.:*** Ridaura; ***UK:*** Ridaura; ***USA:*** Ridaura.

Aurothioglucose

1-Aurothio-D-glucopyranose; Aurotioglucosa; (D-Glucosylthio)-gold; Gold Thioglucose. (1-Thio-D-glucopyranosato)gold.

Ауротиоглюкоза

$C_6H_{11}AuO_5S$ = 392.2.

CAS — 12192-57-3.

ATC — M01CB04.

ATC Vet — QM01CB04.

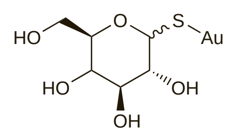

Pharmacopoeias. In *US.*

USP 31 (Aurothioglucose). A yellow odourless or practically odourless powder. An aqueous solution is unstable on long standing. It is stabilised by the addition of a small amount of sodium acetate. pH of a 1% solution in water is about 6.3. Freely soluble in water; practically insoluble in alcohol, in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Sodium Aurothiomalate, p.122.

Effects on the blood. Thrombocytopenia developed in 2 patients treated with intramuscular aurothioglucose.[1]

1. Levin M-D, *et al.* Two patients with acute thrombocytopenia following gold administration and five-year follow-up. *Neth J Med* 2003; **61:** 223–5.

Interactions

As for Sodium Aurothiomalate, p.123.

Pharmacokinetics

As for Sodium Aurothiomalate, p.123; absorption is slower and more irregular.

Uses and Administration

Aurothioglucose is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p.123). It is used in the treatment of active rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10). Aurothioglucose is given intramuscularly as a suspension in oil in an initial weekly dose of 10 mg increasing gradually to up to 50 mg weekly. Therapy is continued at weekly intervals until a total dose of 0.8 to 1 g has been given; if improvement has occurred with no signs of toxicity 50 mg may then be given at intervals of 3 to 4 weeks. Children aged 6 to 12 years have been given one-quarter the adult dose, to a maximum of 25 mg per dose.

◊ For comment on the relative efficacy and tolerability of aurothioglucose and aurothiomalate see Rheumatic Disorders, under Sodium Aurothiomalate, p.124.

Preparations

USP 31: Aurothioglucose Injectable Suspension.

Proprietary Preparations (details are given in Part 3)

Canad.: Solganal†; ***Israel:*** Solganal; ***Neth.:*** Auromyose†; ***USA:*** Solganal.

Aurotioprol

Sodium 3-aurothio-2-hydroxypropane-1-sulphonate.

Ауротиопрол

$C_3H_6AuNaO_4S_2$ = 390.2.

CAS — 27279-43-2.

ATC — M01CB05.

ATC Vet — QM01CB05.

Profile

Aurotioprol is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p.122). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p.11). The initial dose is 25 mg weekly, increased to 50 to 100 mg weekly, until a total dose of 1.2 to 1.5 g has been given. If improvement has occurred with no signs of toxicity, this may be followed by a dose of 50 to 100 mg intramuscularly every month.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Allochrysine†; ***Fr.:*** Allochrysine.

Azapropazone *(BAN, rINN)*

AHR-3018; Apazone *(USAN)*; Atsapropatsoni; Azapropazon; Azapropazona; Azapropazonum; Mi85; NSC-102824. 5-Dimethylamino-9-methyl-2-propylpyrazolo[1,2-*a*][1,2,4]benzotriazine-1,3(2*H*)-dione.

Азапропазон

$C_{16}H_{20}N_4O_2$ = 300.4.

CAS — 13539-59-8.

ATC — M01AX04.

ATC Vet — QM01AX04.

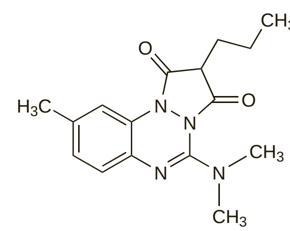

Pharmacopoeias. *Br.* includes the dihydrate.

BP 2008 (Azapropazone). The dihydrate is a white to pale yellow crystalline powder. Very slightly soluble in water and in chloroform; soluble in alcohol; dissolves in solutions of alkali hydroxides.

Profile

Azapropazone is an NSAID (see p.96), structurally related to phenylbutazone (p.117). It also has uricosuric properties. Because azapropazone appears to be associated with a higher incidence of adverse effects than with some other NSAIDs, its use has been restricted to the treatment of rheumatoid arthritis, ankylosing spondylitis, and acute gout in patients for whom other NSAIDs have been ineffective.

Azapropazone is used as the dihydrate and doses are expressed in terms of this hydrated form. For the treatment of rheumatoid arthritis or ankylosing spondylitis the usual oral dose was up to 1.2 g daily in 2 divided doses. Patients *over 60 years of age* have been given 300 mg twice daily. Reduced doses were also recommended in patients with renal impairment, see below.

Administration in renal impairment. In the treatment of *rheumatoid arthritis* or *ankylosing spondylitis* in patients with reduced renal function the usual dose was reduced according to creatinine clearance (CC) as follows:

- CC 50 to 75 mL/minute: reduce usual dose (see above) by one-third to one-half
- CC less than 50 mL/minute: reduce usual dose by one-half to two-thirds

Breast feeding. Small quantities of azapropazone are excreted into breast milk.[1] However, the American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of azapropazone by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Bald R, *et al.* Excretion of azapropazone in human breast milk. *Eur J Clin Pharmacol* 1990; **39:** 271–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)

Effects on the blood. Auto-immune haemolytic anaemia, occasionally fatal, often with pulmonary infiltration, allergic alveolitis, pulmonary fibrosis, or fibrosing alveolitis, has been reported in patients receiving azapropazone.[1-3]

1. Chan-Lam D, *et al.* Red cell antibodies and autoimmune haemolysis after treatment with azapropazone. *BMJ* 1986; **293:** 1474.

2. Albazzaz MK, *et al.* Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1986; **293:** 1537–8.
3. Montgomery RD, Babb RG. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.

Effects on the gastrointestinal tract. In a review[1] of the relative safety of 7 oral NSAIDs, the UK CSM commented that azapropazone was associated with the highest risk of gastrointestinal reactions in both epidemiological studies and an analysis of spontaneous reporting of adverse reactions. Although it appeared that some patients over 60 years of age had received doses exceeding those recommended for this age group, it was considered that even when this was taken into account a marked difference remained between gastrointestinal reactions for azapropazone compared with other NSAIDs.

The CSM recommended that azapropazone should be restricted to use in rheumatoid arthritis, ankylosing spondylitis, and acute gout and only when other NSAIDs have been ineffective. Its use in patients with a history of peptic ulceration was contra-indicated. It was also recommended that when used in patients over 60 years of age for rheumatoid arthritis or ankylosing spondylitis the dose should be restricted to a maximum of 600 mg daily.

Azapropazone has been withdrawn in many countries including the UK.

1. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Effects on the skin. Of 917 reports of adverse reactions associated with azapropazone forwarded to the WHO Collaborating Centre for International Drug Monitoring[1] before September 1984, 190 (21%) were of photosensitivity. Of 154 reports of photosensitivity evaluated a causal relationship to use of azapropazone was considered certain in 6, probable in 138, and possible in 10. In May 1994 the UK CSM stated[2] that since 1976 they had received 464 reports of photosensitivity reactions associated with azapropazone and commented that, when corrected for prescription volume, reporting of this reaction was 50 times greater than with other commonly prescribed NSAIDs. They recommended that patients should be advised to avoid direct exposure to sunlight or to use sunblock preparations.

1. Olsson S, *et al.* Photosensitivity during treatment with azapropazone. *BMJ* 1985; **291:** 939.
2. CSM/MCA. Photosensitivity associated with azapropazone (Rheumox). *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Porphyria. Azapropazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

BP 2008: Azapropazone Capsules; Azapropazone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Debelex†; ***Austria:*** Prolixan†; ***Gr.:*** Prolixan†; ***Hung.:*** Prolixan†; ***Irl.:*** Rheumox†; ***Port.:*** Prolixan†; ***S.Afr.:*** Rheumox; ***Turk.:*** Prodisan; ***UK:*** Rheumox†.

Bendazac *(BAN, USAN, rINN)*

AF-983; Bendazaco; Bendazacum; Bindazac. (1-Benzyl-1*H*-indazol-3-yloxy)acetic acid.

Бендазак

$C_{16}H_{14}N_2O_3$ = 282.3.
CAS — 20187-55-7.
ATC — M02AA11; S01BC07.
ATC Vet — QM02AA11; QS01BC07.

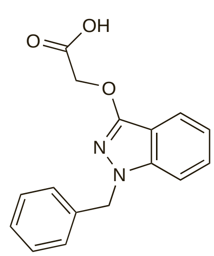

Bendazac Lysine *(BANM, rINNM)*

AF-1934; Bendazac lisina; Bendazacum Lysinum. L-Lysine-(1-benzyl-1*H*-indazol-3-yloxy)acetic acid.

Бендазак Лизин

$C_{22}H_{28}N_4O_5$ = 428.5.
CAS — 81919-14-4.
ATC — S01BC07.
ATC Vet — QS01BC07.

Pharmacopoeias. In *Chin.*

Profile

Bendazac is an NSAID (p.96) structurally related to indometacin (p.66). It has been used topically in preparations containing 1 or 3% for the treatment of various inflammatory skin disorders.

Bendazac lysine has been used in the management of cataract, eye drops containing 0.5% being instilled three times daily.

Hepatotoxicity has been reported.

◊ References.

1. Balfour JA, Clissold SP. Bendazac lysine: a review of its pharmacological properties and therapeutic potential in the management of cataracts. *Drugs* 1990; **39:** 575–96.
2. Prieto de Paula JM, *et al.* Hepatotoxicidad por bendazaco: análisis de 16 casos. *Rev Clin Esp* 1995; **195:** 387–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Versus; ***Gr.:*** Versalba; ***Ital.:*** Bendalina; Versus; ***Philipp.:*** Bendalina; ***Port.:*** Bendalina; ***Venez.:*** Bendalina.

Benorilate *(BAN, rINN)*

Benorilaatti; Benorilat; Bénorilate; Benorilato; Benorilatum; Benorylate; FAW-76; Fenasprate; Win-11450. 4-Acetamidophenyl *O*-acetylsalicylate.

Бенорилат

$C_{17}H_{15}NO_5$ = 313.3.
CAS — 5003-48-5.
ATC — N02BA10.
ATC Vet — QN02BA10.

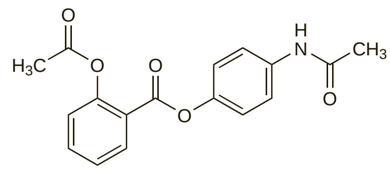

Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Benorilate). A white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in chloroform.

Profile

Benorilate is an aspirin-paracetamol ester with analgesic, anti-inflammatory, and antipyretic properties. After absorption, it is rapidly metabolised to salicylate and paracetamol. It has been used orally in the treatment of mild to moderate pain (see Choice of Analgesic, p.2) and fever (p.10). It has also been used in osteoarthritis, rheumatoid arthritis, and soft-tissue rheumatism.

When an overdose of benorilate is suspected, it has been suggested that plasma concentrations of both salicylate and paracetamol should be measured since a normal plasma-paracetamol concentration cannot necessarily be assumed from a normal plasma-salicylate measurement.

◊ References.

1. Aylward M. Toxicity of benorylate. *BMJ* 1973; **2:** 118.
2. Symon DNK, *et al.* Fatal paracetamol poisoning from benorylate therapy in child with cystic fibrosis. *Lancet* 1982; **ii:** 1153–4.

Preparations

BP 2008: Benorilate Oral Suspension; Benorilate Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Duvium†; ***Fr.:*** Salipran†; ***Irl.:*** Benoral†; ***Switz.:*** Duvium†; ***UK:*** Benoral†.

Benoxaprofen *(BAN, USAN, rINN)*

Benoksaprofeeni; Bénoxaprofène; Benoxaprofeno; Benoxaprofenum; Compound 90459; LRCL-3794. 2-[2-(4-Chlorophenyl)benzoxazol-5-yl]propionic acid.

Беноксапрофен

$C_{16}H_{12}ClNO_3$ = 301.7.
CAS — 51234-28-7.
ATC — M01AE06.
ATC Vet — QM01AE06.

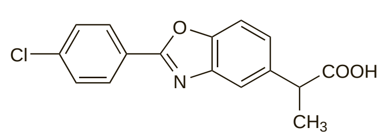

Profile

Benoxaprofen is an NSAID (p.96) structurally related to ibuprofen (p.64). It was formerly given orally in rheumatoid arthritis and osteoarthritis but because of reports of adverse reactions and fatalities the manufacturers halted worldwide marketing of the preparation known as *Opren* in the early 1980s. Adverse effects that have occurred with benoxaprofen include skin disorders, notably photosensitivity reactions but also erythema multiforme and the Stevens-Johnson syndrome, onycholysis and other nail disorders, gastrointestinal disturbances including peptic ulceration and bleeding, blood disorders such as thrombocytopenia, cholestatic jaundice and other liver or biliary disorders, and renal failure.

Benzydamine Hydrochloride *(BANM, USAN, rINNM)*

AF-864; Benzidamin Hidroklorür; Benzindamine Hydrochloride; Benzydamine, Chlorhydrate de; Benzydamini Hydrochloridum; Benzydaminy chlorowodorek; Hidrocloruro de bencidamina. 3-(1-Benzyl-1*H*-indazol-3-yloxy)-*NN*-dimethylpropylamine hydrochloride.

Бензидамина Гидрохлорид

$C_{19}H_{23}N_3O,HCl$ = 345.9.
CAS — 642-72-8 (benzydamine); 132-69-4 (benzydamine hydrochloride).
ATC — A01AD02; G02CC03; M01AX07; M02AA05.
ATC Vet — QA01AD02; QG02CC03; QM01AX07; QM02AA05.

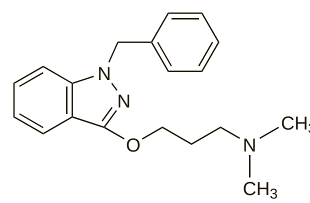

(benzydamine)

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Benzydamine Hydrochloride). A white crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 5.5.

Adverse Effects

After topical application to the skin local reactions such as erythema or rash may occur and photosensitivity has been reported. After use as mouth and throat preparations, numbness or stinging sensations of the oral mucosa have been reported; hypersensitivity reactions including urticaria, photosensitivity, and bronchospasm may also occur rarely.

Effects on the kidneys. A 57-year-old woman who had used 400 g of a topical cream containing benzydamine hydrochloride 3% over a period of 4 months was found to have raised plasma concentrations of creatinine and urea consistent with a substantial reduction in glomerular filtration rate.[1]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.

Effects on the skin. Photoallergic contact dermatitis developed on the hands of a 65-year-old woman after the use of a genital wash containing benzydamine 0.1% for several years.[1] The lesions disappeared once the patient stopped using the solution.

1. Lasa Elgezua O, *et al.* Photoallergic hand eczema due to benzydamine. *Eur J Dermatol* 2004; **14:** 69–70.

Overdose. A 6-year old girl had hallucinations[1] after receiving 500 mg of benzydamine orally; it had been intended as a vaginal douche for pruritus vulvae; recovery was spontaneous.

1. Gómez-López L, *et al.* Acute overdose due to benzydamine. *Hum Exp Toxicol* 1999; **18:** 471–3.

Uses and Administration

Benzydamine hydrochloride is an NSAID (p.99). It is used topically on the skin in concentrations of 3 to 5% in painful musculoskeletal and soft-tissue disorders. Benzydamine hydrochloride is also used as a mouthwash or spray in concentrations of 0.15% for the relief of inflammatory conditions of the mouth and throat. It has been given orally or rectally for the relief of painful and inflammatory conditions, and as a topical solution for vaginal irrigation.

Benzydamine salicylate (benzasal) has been used topically on the skin as a 6% cream or spray.

Mouth disorders. Results of a randomised placebo-controlled study in patients undergoing radiotherapy for oropharyngeal cancer indicated that benzydamine as an oral rinse was effective in reducing the area and severity of mucositis.[1] Benzydamine is also used locally for the management of mouth ulcers (p.1700) although an early study[2] found it no more useful than placebo.

1. Epstein JB, *et al.* Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer* 2001; **92:** 875–85.
2. Matthews RW, *et al.* Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; **63:** 189–91.

Preparations

BP 2008: Benzydamine Cream; Benzydamine Mouthwash; Benzydamine Oromucosal Spray.

Proprietary Preparations (details are given in Part 3)
Arg.: Actifedrin; Bencifem; Ernex; Sandival Desleible; ***Austral.:*** Difflam; Difflam Anti-inflammatory Throat Spray; Difflam Solution; ***Austria:*** Tantum; Tantumar; ***Braz.:*** Benflogin; Benzitrat; Ciflogex; Eridamin†; Flogin-Ped†; Flogo Rosa; Flogolab; Flogoral; Fonergoral; Neoflogin; ***Canad.:*** Sun-Benz†; Tantum; ***Cz.:*** Rosalgin; Tantum; ***Denm.:*** Andolex; ***Fr.:*** Opalgyne; ***Ger.:*** Tantum Rosa; Tantum Verde; ***Gr.:*** Tantum; ***Hong Kong:*** Dantum; Difflam; Verax; ***Hung.:*** Tantum Verde; ***Indon.:*** Tanflex; Tantum; ***Irl.:*** Difflam; ***Israel:*** Easy gel; ***Ital.:*** Afloben; Benzirin; Ginesal; Lagin†; Multum†; Saniflor Collutorio; Tantum; Verax; Xentafid; ***Malaysia:*** Difflam Anti-inflammatory Lozenges; Difflam Solution; ***Mex.:*** Artroben; Lonol; Vantal; ***Neth.:*** Tantum; ***NZ:*** Difflam; ***Philipp.:*** Difflam; ***Pol.:*** Hascosept; Tantum; ***Port.:*** Flogoral; Momen; Rosalgin; Tantum; Tantum Rosa; Tantum Verde; ***Rus.:*** Tantum Rose (Тантум Роза); Tantum Verde (Тантум Верде); ***S.Afr.:*** Andolex; ***Singapore:*** Difflam; ***Spain:*** Agilona; Fulgium; Rosalgin; Tantum; Tantum Verde; ***Swed.:*** Andolex; ***Switz.:*** Bucco-Tantum; ***Thai.:*** Difflam; ***Turk.:*** Benzidan; Tanflex; Tantum; Ternex; ***UK:*** Difflam; ***Venez.:*** Azutan; Bevi Dam; Biozendi; Flodont; Ginacol; Tantum; Tantum Verde; Zydan.

Multi-ingredient: ***Arg.:*** Buchex; Dresan Biotic†; Dresan†; Ernex Duo; Espectocural; Pentadent†; ***Austral.:*** Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; ***Braz.:*** Angino-Rub; ***Hong Kong:*** Difflam Anti-inflammatory Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; ***Hung.:*** Tantum Rosa; ***Ital.:*** Algolisina†; Gola Action; Linea F; Mediplus; ***Malaysia:*** Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Difflam-C; ***Mex.:*** Lonol Sport; ***NZ:*** Difflam Cough; Difflam Mouth Gel; Difflam-C; ***Port.:*** Benoral; Gartun; Tantum Verde; ***S.Afr.:*** Andolex-C; ***Singapore:*** Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Mouth Gel; Difflam-C; ***Spain:*** Bristaciclina Dental; Dolosarto†; Etermol Antitusivo; Mentamida; Prosturol; Tantum; Vinciseptil Otico; ***Turk.:*** Kloroben; ***Venez.:*** Amicets; Gencivol Compuesto; Solunovar Compuesto.

Benzyl Nicotinate

Bensylnikotinat; Bentsyylinikotinaatti; Benzil Nikotinat; Benzyli Nicotinas; Nicotinato de bencilo. Benzyl pyridine-3-carboxylate.
$C_{13}H_{11}NO_2$ = 213.2.
CAS — 94-44-0.

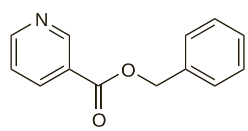

Pharmacopoeias. In *Ger.*

Profile

Benzyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Leukona-Aktiv-Rheumabad†; Pernionin Thermo Teilbad; Pernionin Thermo Vollbad; Pykaryl T; Rubriment; Rubriment-BN.

Multi-ingredient: ***Arg.:*** Butidiona†; Oxa Sport; Pergalen; ***Austria:*** Ambenat; Derivon; Expectal-Balsam; Igitur-antirheumatische; Igitur-Rheumafluid; Menthoneurin; Mobilisin plus; Rheumex; Rubizon-Rheumagel; Rubriment; Thermo-Rheumon; Thrombophob; ***Braz.:*** Etrat†; Trombofob; ***Chile:*** Bayro-Therm†; ***Cz.:*** Dolo-Rubriment†; Rheuma-Salbe†; Rubriment-N†; Thermo-Rheumon†; ***Fin.:*** Trombosol; ***Fr.:*** Lumbalgine; ***Ger.:*** ABC Warme-Salbe†; Ambene N; Arthrodestal N†; Auroanalin Thermo; Camphopin; Capsamol N†; Caye Rheuma-Balsam; Cor-Select†; DoloVisano Salbe†; Emasex-N†; Forapin E†; Hot Thermo; Lomazell forte N†; Lumbinon Thermo†; mikanil†; Ostochont†; Pelvichthol N; Phardol Rheuma†; Phardol Warme-Balsam†; Phlogont-Thermal; Praecordin S†; Rheubalmin Thermo†; Rheuma-Salbe N; Rheuma-Salbe†; Rheumasalbe†; Rheumasan N†; Rheumasit†; Rubriment; Rubriment-N†; Tachynerg Campher Herzsalbe; Thermo-Menthoneurin†; Thermo-Rheumon N†; Thermo-Rheumon†; Thermosenex; Togal Mobil-Gel†; Warme-Gel†; zuk thermo†; ***Gr.:*** Bayolin; Ehrlich; Striafissan†; Thermo-Roiplon; ***Hong Kong:*** Salomethyl; ***Hung.:*** Bayolin†; Thermo-Rheumon†; ***India:*** Beparine; K5 Hair Tincture†; Thrombophob; ***Indon.:*** Stop X; Thrombophob; Zeropain; ***Ital.:*** Salonpas; Sloan; ***Mex.:*** Bayro Termo; ***Pol.:*** Lumbolin; Thermo-Rheumon; ***Port.:*** Adrinex†; Balsamo Analgesico; Medalginan; ***Rus.:*** Capsicam (Капсикам); Heparin Ointment (Гепариновая Мазь); ***Switz.:*** Assan thermo; Demotherm Pommade contre le rhumatisme†; Dolo Demotherm; Forapin†; Histalgane; Marament-N; Thermocutan†; ***Turk.:*** Thermo-Doline; Thermo-Rheumon; Thermoflex; ***UK:*** Salonair; ***Venez.:*** Ehrlich Balsamo.

Beta-aminopropionitrile

Aminopropionitrile; β-Aminopropionitrile; β-Aminopropionitrilo; BAPN. 3-Aminopropionitrile.
Бета-аминопропионитрил
$C_3H_6N_2$ = 70.09.
CAS — 151-18-8 (beta-aminopropionitrile); 1119-28-4 (beta-aminopropionitrile fumarate).
ATC Vet — QM01AX91.

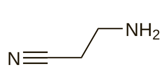

Profile

Beta-aminopropionitrile, a lysyl oxidase inhibitor, is an anti-inflammatory used as the fumarate in veterinary medicine for the treatment of tendinitis.

Bicifadine Hydrochloride *(USAN, rINNM)*

Bicifadina, hidrocloruro de; Bicifadine, Hydrochloride de; Bicifadini Hydrochloridum; CL-220075. (±)-1-*p*-Tolyl-3-azabicyclo-[3.1.0]hexane hydrochloride.
Бицифадина Гидрохлорид
$C_{12}H_{15}N,HCl$ = 209.7.
CAS — 71195-57-8 (bicifadine); 66504-75-4 (bicifadine hydrochloride).

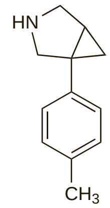

(bicifadine)

Profile

Bicifadine hydrochloride is a novel analgesic under investigation for the treatment of painful conditions including postoperative dental pain.

Bornyl Salicylate

Borneol Salicylate; Salicilato de bornilo. 2-Hydroxybenzoic acid 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester.
Борнилсалицилат
$C_{17}H_{22}O_3$ = 274.4.
CAS — 560-88-3.

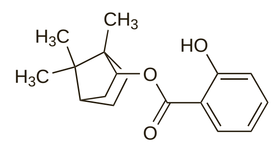

Profile

Bornyl salicylate is a salicylic acid derivative that has been used topically in rubefacient preparations similarly to methyl salicylate (p.85) for the relief of pain in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Forapin E†; ***Switz.:*** Forapin†; Hygiodermil.

Bromfenac Sodium *(USAN, rINNM)*

AHR-10282; AHR-10282B; Bromfénac Sodique; Bromfenaco sódico; Natrii Bromfenacum. Sodium [2-amino-3-(*p*-bromobenzoyl)phenyl]acetate sesquihydrate.
Натрий Бромфенак
$C_{15}H_{11}BrNNaO_3,1\frac{1}{2}H_2O$ = 383.2.
CAS — 91714-94-2 (bromfenac); 91714-93-1 (bromfenac sodium); 120638-55-3 (bromfenac sodium).

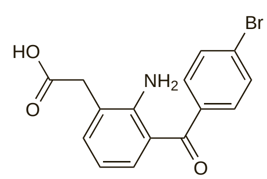

(bromfenac)

Profile

Bromfenac sodium, a phenylacetic acid derivative related to diclofenac (p.44), is an NSAID (p.96). It is instilled twice daily as 0.1% eye drops for ocular pain and inflammation including postoperative inflammation in patients who have undergone cataract extraction. When used postoperatively, it may be started 24 hours after surgery and continued for the next 14 days.

It was formerly given orally in the management of acute pain but was withdrawn from the market after reports of severe and sometimes fatal hepatic failure.

Effects on the eyes. Severe corneal melting (ulceration) was seen in 3 patients after topical use of bromfenac sodium.[1] All patients recovered after bromfenac was withdrawn. Similar effects have been reported with other ophthalmic NSAID preparations; for further details see under Adverse Effects of Diclofenac, p.45.

1. Asai T, *et al.* Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea* 2006; **25:** 224–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Bronuck; ***USA:*** Xibrom.

Bufexamac *(BAN, rINN)*

Bufeksamaakki; Bufeksamakas; Bufexamaco; Bufexamacum; Bufexamák; Bufexamak. 2-(4-Butoxyphenyl)acetohydroxamic acid.
Буфексамак
$C_{12}H_{17}NO_3$ = 223.3.
CAS — 2438-72-4.
ATC — M01AB17; M02AA09.
ATC Vet — QM01AB17; QM02AA09.

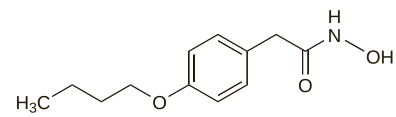

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Bufexamac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dimethylformamide; slightly soluble in ethyl acetate and in methyl alcohol. Protect from light.

Profile

Bufexamac is an NSAID (p.96) that is applied topically in concentrations of 5% in various skin disorders. Stinging and burning may occur after application; hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Parfenac†; ***Austral.:*** Paraderm†; ***Austria:*** Bufex; Bufexan; Droxaryl; Parfenac; ***Belg.:*** Bufexine†; Droxaryl†; ***Cz.:*** Droxaryl†; ***Fr.:*** Parfenac; ***Ger.:*** Bufederm†; duradermal; Haemo-Exhirud Bufexamac; Jomax; Malipuran; Parfenac; Windol; ***Ital.:*** Fansamac; Viafen; ***Neth.:*** Droxaryl; Parfenac; ***Port.:*** Parfenac; ***Switz.:*** Parfenac.

Multi-ingredient: ***Austral.:*** Paraderm Plus; Resolve; ***Austria:*** Droxaryl; ***Cz.:*** Mastu S; ***Ger.:*** Faktu akut; Hamo-ratiopharm N; Hamoagil plus; Mastu S; ***Hong Kong:*** Fungo Soothing Balm; Mastu S; ***Hung.:*** Mastu S; ***NZ:*** Paraderm Plus; ***Rus.:*** Proctosan (Проктозан); ***Thai.:*** Mastu S.

Bumadizone Calcium *(rINNM)*

Bumadizona cálcica; Bumadizone Calcique; Calcii Bumadizonum. Calcium 2-(1,2-diphenylhydrazinocarbonyl)hexanoate hemihydrate.
Кальций Бумадизон
$(C_{19}H_{21}N_2O_3)_2Ca,\frac{1}{2}H_2O$ = 699.8.
CAS — 3583-64-0 (bumadizone); 34461-73-9 (bumadizone calcium).
ATC — M01AB07.
ATC Vet — QM01AB07.

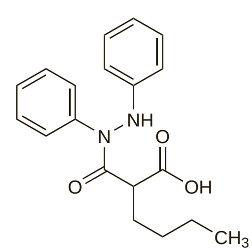

(bumadizone)

Profile

Bumadizone calcium is an NSAID (p.96) that is metabolised to phenylbutazone (p.117) and oxyphenbutazone (p.107). Use has been limited by the risk of agranulocytosis and other haematological adverse effects.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Desflam.

Buprenorphine *(BAN, rINN)* ⊗

Buprenorfiini; Buprenorfin; Buprenorfina; Buprenorfinas; Buprénorphine; Buprenorphinum; RX-6029-M. (6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-*O*-methyl-6,14-ethano-17-normorphine; (2*S*)-2-[(−)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3,3-dimethylbutan-2-ol.

Бупренорфин

$C_{29}H_{41}NO_4$ = 467.6.

CAS — 52485-79-7.

ATC — N02AE01; N07BC01.

ATC Vet — QN02AE01; QN07BC01.

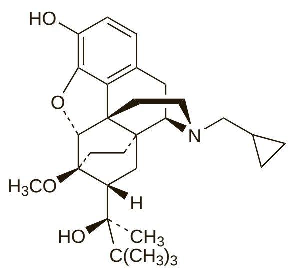

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of buprenorphine: TEM; Tems.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Buprenorphine). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in acetone; slightly soluble in cyclohexane; soluble in methyl alcohol. It dissolves in dilute solutions of acids. Protect from light.

Buprenorphine Hydrochloride

(BANM, USAN, rINNM) ⊗

Buprenorfiinihydrokloridi; Buprenorfin-hidroklorid; Buprenorfin-hydrochlorid; Buprenorfinhydroklorid; Buprenorfino hidrochloridas; Buprénorphine, chlorhydrate de; Buprenorphini hydrochloridum; CL-112302; Hidrocloruro de buprenorfina; NIH-8805; UM-952.

Бупренорфина Гидрохлорид

$C_{29}H_{41}NO_4$,HCl = 504.1.

CAS — 53152-21-9.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Buprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in cyclohexane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Buprenorphine Hydrochloride). pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Buprenorphine may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, below). Abrupt withdrawal of buprenorphine is said to produce only a mild abstinence syndrome, which may be delayed in onset.

Buprenorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Acute hepatotoxicity, including elevated liver enzyme values, hepatitis with jaundice, hepatic failure, necrosis, and encephalopathy, and hepatorenal syndrome, has been reported in opioid-dependent addicts; these reactions have also occurred after the misuse of buprenorphine, particularly after high doses or intravenous use.

Local reactions such as rash, erythema, and itching have been reported with the transdermal patches. In isolated cases delayed local allergic reactions with marked signs of inflammation have occurred; the patches should be withdrawn in such cases.

Treatment of adverse effects is similar to that for other opioid analgesics (p.102). The effects of buprenorphine are only partially reversed by naloxone (see Effects on the Respiratory System, below) but use of the latter is still recommended.

Incidence of adverse effects. Adverse effects reported[1] after *parenteral* buprenorphine in 8187 patients were nausea (8.8%), vomiting (7.4%), drowsiness (4.3%), sleeping (1.9%), dizziness (1.2%), sweating (0.98%), headache (0.55%), confusion (0.53%), lightheadedness (0.38%), blurred vision (0.28%), euphoria (0.27%), dry mouth (0.11%), depression (0.09%), and hallucinations (0.09%). Some studies[2,3] have reported nausea, vomiting, and dizziness to be more troublesome with buprenorphine than with morphine.

In a study[4] of *sublingual* buprenorphine, 50 of 141 cancer patients withdrew because of adverse effects, especially dizziness, nausea, vomiting, and drowsiness; constipation was not reported. A woman developed[5] a painless ulcer on the upper surface of her tongue after she had put sublingual buprenorphine tablets on rather than under her tongue.

Shock occurred[6] in 2 patients 2 hours after receiving *epidural* buprenorphine 300 micrograms; treatment with naloxone was unsuccessful but symptoms disappeared spontaneously after 2 to 3 hours.

In a multicentre study[7] of *transdermal* buprenorphine, 252 of 1223 patients with moderate to severe cancer pain or non-cancer pain withdrew due to adverse effects. The most commonly reported were nausea (11%), vomiting (9.2%), constipation (7.8%), dizziness (7.5%), drowsiness (4.0%), retching (3.7%), generalised pruritus (2.0%), and headache (1.6%); local adverse effects included pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%). Another study[8] reported oedema, headache, nausea, palpitation, and difficulty concentrating as causes for therapy withdrawal in 4 out of 90 patients.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Sear JW, *et al.* Buprenorphine for postoperative analgesia. *Br J Anaesth* 1979; **51:** 71.
3. Kjaer M, *et al.* A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. *Br J Clin Pharmacol* 1982; **13:** 487–92.
4. Robbie DS. A trial of sublingual buprenorphine in cancer pain. *Br J Clin Pharmacol* 1979; **7** (suppl 3): 315S–317S.
5. Lockhart SP, Baron JH. Tongue ulceration after lingual buprenorphine. *BMJ* 1984; **288:** 1346.
6. Christensen FR, Andersen LW. Adverse reaction to extradural buprenorphine. *Br J Anaesth* 1982; **54:** 476.
7. Muriel C, *et al.* Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther* 2005; **27:** 451–62.
8. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; **26:** 1808–20.

Effects on the heart. For a report of myocardial infarction associated with abuse of buprenorphine, see Abuse under Precautions, below.

Effects on mental function. Psychotomimetic effects have been relatively uncommon with buprenorphine. Hallucinations were reported[1] in only 7 of 8147 patients (0.09%) given buprenorphine by injection. There have been reports of hallucinations after sublingual[2] or epidural[3] use.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; **2:** 163–5.
2. Paraskevaides EC. Near fatal auditory hallucinations after buprenorphine. *BMJ* 1988; **296:** 214.
3. MacEvilly M, O'Carroll C. Hallucinations after epidural buprenorphine. *BMJ* 1989; **298:** 928–9.

Effects on the respiratory system. There have been varying reports on the occurrence of respiratory depression with buprenorphine. It may be subject to a 'ceiling effect' in which respiratory depression does not increase further above doses of about 3 micrograms/kg.[1] However, high doses of 30 or 40 micrograms/kg given as sole intravenous analgesic in balanced anaesthesia have been associated with severe respiratory depression.[2]

Respiratory depression may be delayed in onset and more prolonged than with morphine and is only partially reversed by naloxone, possibly because buprenorphine is very firmly bound to opioid receptors. A study of sublingual buprenorphine for postoperative pain relief was abandoned when 3 of the first 16 patients showed signs of late-onset respiratory depression after the second dose of buprenorphine; the respiratory depression did not respond to naloxone.[3] Successful reversal has been shown in healthy subjects with buprenorphine-induced respiratory depression given large doses of naloxone 5 or 10 mg, but not with 1 mg; reversal was gradual in onset and decreased the duration of the normally prolonged respiratory depression.[4] Other studies found that lower doses of naloxone 2 to 4 mg given over 30 minutes,[5,6] or bolus doses of 2 to 3 mg followed by a continuous infusion of 4 mg/hour,[6] were effective in reversing buprenorphine-induced respiratory depression. The authors of both these studies suggested that a longer duration of naloxone infusion may be needed for reversal of respiratory depression caused by high doses of buprenorphine. The respiratory depressant and analgesic effects of buprenorphine were decreased by the *concomitant* use of naloxone.[7] It should be noted that a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

1. Dahan A, *et al.* Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; **94:** 825–34.
2. Schmidt JF, *et al.* Postoperative pain relief with naloxone: severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia* 1985; **40:** 583–6.
3. Thörn S-E, *et al.* Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet* 1988; **i:** 179–80.
4. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 1989; **45:** 66–71.
5. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med* 2006; **20** (Suppl 1): s3–s8.
6. van Dorp E, *et al.* Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 2006; **105:** 51–7.
7. Lehmann KA, *et al.* Influence of naloxone on the postoperative analgesic and respiratory effects of buprenorphine. *Eur J Clin Pharmacol* 1988; **34:** 343–52.

Overdosage. A small case series reported[1] acute buprenorphine intoxication in 5 children, aged from 15 to 22 months, after accidental ingestion of sublingual tablets; of these, 4 had ingested a combined preparation containing naloxone (*Suboxone; Reckitt Benckiser, USA*). Symptoms included drowsiness and miosis; decreased respiratory rates were reported in 4. All 5 children required hospital admission; 4 were treated with naloxone and 1 needed mechanical ventilation. Accidental poisoning has also been reported[2] in a 9-month-old infant who ingested *Suboxone*; his symptoms were reversed by naloxone. A retrospective review[3] of buprenorphine overdoses in children under 6 years of age reported by US poison centres to a national surveillance system from November 2002 to December 2005 concluded that overdosage is generally well tolerated. Out of 86 reports, 54 children developed symptoms of toxicity. Such symptoms included: drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities, and significant CNS and respiratory depression occurred in 7%. *Suboxone* preparations were the most commonly ingested products. The authors considered that any child who has ingested more than 2 mg and any aged under 2 years who has had more than a lick or taste should be referred to the emergency department.

During the years 1980 to 2002, buprenorphine was mentioned in 43 cases of adult fatalities in the UK.[4] Of these, 27 deaths were confirmed to have involved buprenorphine including 7 cases where it was taken alone. In those deaths where multiple drugs were involved sedatives or benzodiazepines were detected in 23 cases and other opioids were found in 17 cases; alcohol had also been taken in 10 cases. The authors also found an increase in buprenorphine-related fatalities since 1999 when the high-dose formulation became available.

1. Geib A-J, *et al.* Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics* 2006; **118:** 1746–51.
2. Cho CS, *et al.* Exploratory buprenorphine ingestion in an infant. *Ann Emerg Med* 2006; **48:** 109.
3. Hayes BD, *et al.* Toxicity of buprenorphine overdoses in children. *Pediatrics* 2008; **121:** 807–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/4/e782 (accessed 22/07/08)
4. Schifano F, *et al.* Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. *Hum Psychopharmacol* 2005; **20:** 343–8.

Precautions

As for Opioid Analgesics in general, p.103.

Buprenorphine has opioid antagonist actions and may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

Respiratory depression, if it occurs, is relatively slow in onset and of prolonged duration; it may be only partially reversed by naloxone.

Licensed product information states that baseline liver function levels should be established before starting buprenorphine therapy, and periodic monitoring of liver function should be performed throughout therapy in patients being treated for opioid dependence. It should be used with caution in all patients with pre-existing hepatic impairment.

Absorption of buprenorphine from transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take up to 30 hours for plasma concentrations of buprenorphine to decrease by 50% after removal of a patch; patients who have had adverse effects should be monitored during this period.

Abuse. A 22-year-old man had chest pains on each of two occasions after he had inhaled crushed buprenorphine tablets.[1] An ECG taken after the second episode suggested that the patient had suffered a myocardial infarction. Intravenous injection of crushed sublingual tablets was associated with rhabdomyolysis and sciatic neuropathy in 2 patients.[2] A case series[3] of 4 patients reported severe limb and digit complications, such as ischaemia and gangrene, from parenteral abuse of sublingual buprenorphine tablets; intra-arterial injection in 2 cases resulted in amputation of the affected digits or limb. The use of adulterants in illicit preparations may also cause adverse effects: 4 patients on substitution treatment developed candida endophthalmitis after intravenously injecting sublingual buprenorphine diluted with lemon juice.[4]

Hepatotoxicity has been seen in opioid-dependent addicts after buprenorphine abuse (see Adverse Effects and Treatment, above).

1. Cracowski J-L, *et al.* Myocardial infarction associated with buprenorphine. *Ann Intern Med* 1999; **130:** 537.
2. Seet RCS, Lim ECH. Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy. *Ann Emerg Med* 2006; **47:** 396–7.
3. Loo HW, *et al.* Severe upper limb complications from parenteral abuse of Subutex. *Ann Acad Med Singapore* 2005; **34:** 575–8.
4. Cassoux N, *et al.* Presumed ocular candidiasis in drug misusers after intravenous use of oral high dose buprenorphine (Subutex). *Br J Ophthalmol* 2002; **86:** 940–1.

Breast feeding. From a study[1] of a breast-feeding mother who was receiving buprenorphine 4 mg daily, it was estimated that at the age of 4 weeks the total amount ingested by the infant during a 24-hour period was 3.28 micrograms for buprenorphine and 0.33 micrograms for norbuprenorphine. Another study[2] found that buprenorphine was present in the breast milk of a breast-feeding mother with a maternal milk-to-plasma ratio of about one. The authors of both studies considered the amount absorbed through breast feeding to be low.

The *BNF* and some licensed product information states that buprenorphine should not be given to mothers who are breast feeding.

Studies in *rats* have shown that it may inhibit lactation.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Johnson RE, *et al.* Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001; **63:** 97–103.

Pregnancy. An infant born to a mother who was being treated with buprenorphine 4 mg daily for diamorphine addiction suffered a minor withdrawal syndrome 2 days after birth.[1] The infant rapidly recovered without any treatment. No further signs of withdrawal occurred when breast feeding was abruptly stopped at the age of 8 weeks. In another report[2] of 15 opioid-dependent mothers who had received buprenorphine maintenance during their pregnancies, withdrawal symptoms were either absent or mild in 12 of the neonates. The remaining 3 neonates required treatment with morphine. There appeared to be no correlation between the buprenorphine dose and the degree of withdrawal symptoms. A literature review[3] found that of about 309 infants born to opioid-dependent mothers maintained on buprenorphine (sublingual dose range: 0.4 to 24 mg daily), 193 developed neonatal abstinence syndrome; of these, 149 required treatment. More than 40% of treated cases were confounded by misuse of other drugs. Onset of symptoms occurred within the first 12 to 48 hours and peaked within about 72 to 96 hours; duration of symptoms was about 120 to 168 hours although in some infants, it was reported to last for 6 to 10 weeks.

The 67 pregnancies of 66 women using buprenorphine have been followed in a prospective study.[4] The incidences of premature birth, caesarean section, and low Apgar scores in buprenorphine-exposed neonates were no greater than those seen in the general population although the mean birth-weight of the exposed neonates was significantly lower. In the exposed group, 91% of neonates needed intensive care treatment: 76% had neonatal abstinence syndrome and 57% needed opioid replacement therapy. There were also 2 cases of sudden infant deaths in the exposed group, which was considered to be higher than that generally expected.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Fischer G, *et al.* Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 2000; **95:** 239–44.
3. Johnson RE, *et al.* Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 2003; **70** (suppl 2): S87–S101.
4. Kahila H, *et al.* A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. *Acta Obstet Gynecol Scand* 2007; **86:** 185–90.

Interactions

For interactions associated with opioid analgesics, see p.103.

Buprenorphine is metabolised by the cytochrome P450 isoenzyme CYP3A4; consequently, use with other drugs that induce or inhibit this isoenzyme may result in changes in plasma concentrations of buprenorphine and, possibly adverse effects. Some manufacturers state that dosage adjustment of buprenorphine may be necessary when used with such drugs. The UK licensed product information for one sublingual formulation (*Subutex; Schering-Plough*) recommends that the dose of buprenorphine should be halved when starting treatment with the potent CYP3A4 inhibitor, ketoconazole.

There have been reports of respiratory and cardiovascular collapse in patients given therapeutic doses of intravenous buprenorphine and diazepam.

Use with other potentially hepatotoxic drugs may increase the risk of liver damage.

Analgesics. There is a risk that, with opioid agonist-antagonists such as buprenorphine, their antagonistic effects might impair more effective analgesic therapy. This appeared to happen in 2 cancer patients both of whom were given sublingual buprenorphine that was later substituted by *morphine*.[1] Conventional doses of morphine were inadequate and in one patient raising the dose of morphine proved fatal.

1. Overweg-van Kints J, Stricker BHC. Falende pijnbestrijding tijdens sublinguaal gebruik van buprenorfine. *Ned Tijdschr Geneeskd* 1987; **131:** 1973–4.

Antivirals. Various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and most are also substrates for CYP3A4; thus, they have the potential to interact with buprenorphine. A pharmacokinetic study[1] found that usual doses of *nelfinavir*, *ritonavir*, and *lopinavir-ritonavir* given to HIV-negative patients taking buprenorphine with naloxone for opiate dependence did not produce any clinically significant interactions: ritonavir increased the area under the concentration-time curve (AUC) of buprenorphine by about 57%, although no adverse effects were seen. Another pharmacokinetic study[2] in a similar group of patients also found no clinically significant interactions between buprenorphine with naloxone and *delavirdine* or *efavirenz*: delavirdine increased the AUC of buprenorphine fourfold, and efavirenz decreased it by about 50%, but no adverse effects were seen. However, a small case series[3] of 3 opioid-dependent patients reported symptoms of buprenorphine toxicity, such as dizziness, daytime somnolence, and decreased mental functioning, with concomitant *atazanavir* and ritonavir therapy.

Buprenorphine does not appear to significantly affect the pharmacokinetics of antiretrovirals.[1,2]

1. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: I—The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis* 2006; **43** (suppl 4): S224–S234.
2. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: II—The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. *Clin Infect Dis* 2006; **43** (suppl 4): S235–S246.
3. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. *AIDS* 2006; **20:** 783–4.

Pharmacokinetics

After intramuscular injection, buprenorphine rapidly reaches peak plasma concentrations. Absorption also takes place through the buccal mucosa after sublingual doses and peak plasma concentrations are achieved after 90 minutes. Transdermal application results in absorption through the skin; the minimum effective concentration is reached in 12 to 24 hours and peak plasma concentrations are achieved after about 60 hours. However, there is a lack of correlation between plasma concentrations and analgesic activity. Buprenorphine is about 96% bound to plasma proteins.

Elimination of buprenorphine is bi- or triphasic; metabolism takes place in the liver by oxidation via the cytochrome P450 isoenzyme CYP3A4 to the pharmacologically active metabolite *N*-dealkylbuprenorphine (norbuprenorphine), and by conjugation to glucuronide metabolites. Buprenorphine is subject to considerable first-pass metabolism after oral doses. However, when given by the usual routes buprenorphine is excreted mainly unchanged in the faeces; there is some evidence for enterohepatic recirculation. Plasma elimination half-lives have ranged from 1.2 to 7.2 hours after intravenous injection; elimination half-lives after sublingual or transdermal use are longer and may range from 20 to 36 hours or more. Metabolites are excreted in the urine, but very little unchanged drug is excreted in this way. Buprenorphine crosses the placenta and small amounts are distributed into breast milk.

◊ References.

1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005; **44:** 661–80.

Administration. *BUCCAL ROUTE.* Absorption of sublingual buprenorphine is relatively slow. In a 10-hour study[1] plasma concentrations after 400 or 800 micrograms given sublingually peaked at about 200 minutes (range 90 to 360 minutes) and buprenorphine was still detected in plasma at the end of the study. Systemic availability was about 55% (range 16 to 94%) and absorption was more or less complete 5 hours after a dose. However, the authors of a subsequent study[2] considered that this was an overestimation, possibly due to methodological flaws. The later study results indicated that the bioavailability of sublingual buprenorphine is about 30% and that sublingual holding times between 3 and 5 minutes are bioequivalent. Another single-dose study[3] found that the bioavailability of sublingual buprenorphine was 50% less from a tablet than from a liquid formulation. Later studies[4,5] noted that the bioavailability of buprenorphine from a sublingual tablet relative to a sublingual liquid formulation was about 70% after daily dosing for 7 days. One of these studies[4] also found that the bioavailability of sublingual buprenorphine from a tablet formulation containing naloxone was higher than from a single-ingredient tablet formulation and similar to that seen with liquid formulations.

1. Bullingham RES, *et al.* Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982; **13:** 665–73.
2. Mendelson J, *et al.* Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; **37:** 31–7.
3. Nath RP, *et al.* Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol* 1999; **39:** 619–23.
4. Strain EC, *et al.* Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend* 2004; **74:** 37–43.
5. Compton P, *et al.* Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug Alcohol Depend* 2006; **82:** 25–31.

Children. The terminal elimination half-life of buprenorphine was only about 1 hour in small children aged 4 to 7 years given 3 micrograms/kg intravenously as premedication, but could not be estimated reliably because of the rapid decline in plasma-buprenorphine concentrations.[1] Clearance values did, however, appear higher than in adults; steady-state volume of distribution was similar. Premature neonates (gestational age 27 to 32 weeks) given a similar dose followed by an infusion of 0.72 micrograms/kg per hour had a considerably lower clearance rate and had a mean elimination half-life of 20 hours.[2] Although this dosing regimen appeared to be safe, sedation was judged to be inadequate in 4 of the 12 neonates studied. It was suggested that as buprenorphine given by infusion might not produce consistent sedation and analgesia in premature neonates, it could not be recommended for use in neonatal care.

1. Olkkola KT, *et al.* Pharmacokinetics of intravenous buprenorphine in children. *Br J Clin Pharmacol* 1989; **28:** 202–4.
2. Barrett DA, *et al.* The pharmacokinetics and physiological effect of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol* 1993; **36:** 215–19.

Renal impairment. Buprenorphine clearance appears to occur mainly by hepatic extraction and metabolism and would not be expected to be related to renal function, whereas metabolites are excreted in urine. In a study, buprenorphine kinetics were similar in anaesthetised healthy patients to those in patients with renal impairment, with a mean elimination half-life of 398 and 239 minutes, respectively.[1] Plasma concentrations of the metabolites norbuprenorphine and buprenorphine-3-glucuronide were increased about 4 times and 15 times, respectively in patients with renal impairment,[1] but significant pharmacological activity was unlikely since norbuprenorphine has little analgesic activity compared with the parent compound and buprenorphine-3-glucuronide has none.

1. Hand CW, *et al.* Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 1990; **64:** 276–82.

Uses and Administration

Buprenorphine is an opioid analgesic (p.104) classified as an opioid agonist and antagonist. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Buprenorphine is also used in the treatment of opioid dependence.

Buprenorphine has a relatively slow onset but prolonged duration of action. On intramuscular injection analgesia is apparent within 15 minutes and lasts up to 6 hours. A slower, more prolonged response is achieved after sublingual doses. The analgesic effects of buprenorphine after transdermal application may not be seen for at least 12 to 24 hours or up to 72 hours in the case of the once-weekly patch.

Buprenorphine is usually given by intramuscular or intravenous injection or sublingually as the hydrochloride or as transdermal patches as the base. For all routes doses are expressed in terms of the base. Buprenorphine hydrochloride 107.8 micrograms is equivalent to about 100 micrograms of buprenorphine.

Buprenorphine is given by all the above routes for opioid analgesia in moderate to severe **pain**.

- The dose by intramuscular or slow intravenous injection is 300 to 600 micrograms repeated every 6 to 8 hours as required
- By the sublingual route, doses of 200 to 400 micrograms may be repeated every 6 to 8 hours as required
- For opioid treatment of chronic pain in patients aged 18 years and over transdermal patches delivering varying amounts of buprenorphine are available. Doses should be individually titrated for each patient according to previous opioid usage. During transfer to treatment with buprenorphine patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-buprenorphine concentrations. Depending on dose required up to 2 patches may be applied, however, this should be done at the same time to avoid confusion. Buprenorphine patches are not appropriate for acute pain. In the UK, transdermal buprenorphine patches are available as follows:

  Transtec (*Napp, UK*) delivering buprenorphine in a range of 35 to 70 micrograms/hour. Initial dosages should not exceed 35 micrograms/hour in *opioid-naive* patients. For *patients who have been receiving a strong opioid analgesic* the initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 35 micrograms/hour of buprenorphine is roughly equivalent to 30 to 60 mg daily of oral morphine sulfate. Patches should be replaced every 96 hours at the latest with the new patch being applied to a different site; use of the same area of the skin should be avoided for at least the next 2 applications.

  BuTrans (*Napp, UK*) delivering buprenorphine in a range of 5 to 20 micrograms/hour. Initial dosages should not exceed 5 micrograms/hour in *all* patients. Patches should be replaced every 7 days with the new patch being applied to a different site; use of the same area of the skin should be avoided for the next 3 to 4 weeks.

When used in balanced **anaesthesia** 300 micrograms may be given intramuscularly or 400 micrograms sublingually for premedication; 300 to 450 micrograms may be given intravenously as a perioperative analgesic supplement.

For the treatment of **opioid dependence** in patients aged 16 years and over, the initial dose is 0.8 to 4 mg sublingually once daily. The dose may be increased as necessary but maintenance doses should not exceed 32 mg daily. Once the patient has been stabilised, the dosage should be reduced gradually to a lower maintenance dose; treatment may eventually be stopped if appropriate. For addicts who have not undergone opioid withdrawal before starting buprenorphine, the first dose of buprenorphine should not be given until the first signs of craving appear or until at least 4 (USA) or 6 (UK) hours after the last opioid use. In those already receiving methadone replacement, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine therapy. As a deterrent to abuse, a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

For details of doses in **children**, see below.

Action. Buprenorphine is generally described as a mixed agonist-antagonist acting mainly as a partial agonist at μ opioid receptors, with some antagonist activity at κ receptors. It has also been shown to bind at μ, δ, and κ opioid binding sites and to have high affinity for the μ and δ receptors and lesser affinity for the κ receptor.[1] Buprenorphine, like fentanyl, has high lipid solubility, but has a lower intrinsic activity than fentanyl. Differences between buprenorphine and pure μ opioid agonists such as fentanyl, including relatively slow onset of action, prolonged duration of action, resistance to antagonism by naloxone, and lack of correlation between plasma concentrations and analgesic effects, have been explained by differences in the way buprenorphine binds to opioid receptors. In a study *in vitro* buprenorphine had slow rates of association and dissociation from the opioid receptor when compared with fentanyl.[2]

1. Bovill JG. Which potent opioid? Important criteria for selection. *Drugs* 1987; **33:** 520–30.
2. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine: the significance of receptor binding. *Br J Anaesth* 1985; **57:** 192–6.

Administration in children. Buprenorphine is used for the relief of moderate to severe **pain** in children. In the UK, those aged from 6 months to 12 years may be given 3 to 6 micrograms/kg by *intramuscular* or slow *intravenous* injection every 6 to 8 hours; up to 9 micrograms/kg may be given if required in refractory cases. In the USA, parenteral buprenorphine is licensed in children aged 2 years and over; usual doses of 2 to 6 micrograms/kg may be given intramuscularly or intravenously every 4 to 6 hours to those up to 12 years old. The *sublingual* route is licensed in the UK in children aged from 6 to 12 years and the following doses are given every 6 to 8 hours according to body-weight: 16 to 25 kg, 100 micrograms; 25 to 37.5 kg, 100 to 200 micrograms; 37.5 to 50 kg, 200 to 300 micrograms. Older children requiring pain relief may be given the usual adult dose (see above) for all the above routes.

Buprenorphine is also used in the treatment of **opioid dependence**; adolescents aged 16 years and over may be given the usual adult dose (see above).

Opioid dependence. Buprenorphine is used in the treatment of opioid dependence (p.101). Its agonist-antagonist properties may mean that it has a lower potential for dependence and a lower risk of respiratory depression in overdose than pure agonists such as methadone. Buprenorphine can be used as substitution therapy in patients with moderate opioid dependence for acute management of withdrawal and in maintenance treatment as an alternative to or together with methadone. However, in patients dependent on high doses of opioids buprenorphine may precipitate withdrawal due to its partial antagonist properties; the daily opioid dose should be reduced gradually in such patients before beginning buprenorphine. Abuse of the preparation, as with other substitution therapies, may be a problem. A combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries as a deterrent to abuse.

References.

1. Kakko J, *et al.* 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003; **361:** 662–8.
2. Fudala PJ, *et al.* Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003; **349:** 949–58.
3. Montoya ID, *et al.* Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 2004; **75:** 34–48.
4. Fiellin DA, *et al.* Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J Subst Abuse Treat* 2004; **27:** 153–9.
5. Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. *Am Fam Physician* 2006; **73:** 1573–8.
6. Sung S, Conry JM. Role of buprenorphine in the management of heroin addiction. *Ann Pharmacother* 2006; **40:** 501–5.
7. Robinson SE. Buprenorphine-containing treatments: place in the management of opioid addiction. *CNS Drugs* 2006; **20:** 697–712.
8. Gowing L, *et al.* Buprenorphine for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 26/06/08).
9. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)
10. Boothby LA, Doering PL. Buprenorphine for the treatment of opioid dependence. *Am J Health-Syst Pharm* 2007; **64:** 266–72.
11. Mattick RP, *et al.* Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 26/06/08).
12. Sullivan LE, Fiellin DA. Narrative review: buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med* 2008; **148:** 662–70.

Pain. ***ACUTE PAIN.*** The *BNF* considers that buprenorphine may antagonise the analgesic effect of other opioids and is generally not recommended for the management of *postoperative* pain. Nonetheless, it can be given intramuscularly, intravenously, or sublingually for this purpose, although the intravenous route may be preferred for acute pain relief. The epidural route[1] and continuous subcutaneous infusion[2] have also been used; an intranasal formulation of buprenorphine is under investigation for the management of postoperative pain.[1] Patient-controlled analgesia with intravenous[3] and intramuscular[4] buprenorphine has been effective although its long half-life may limit such use.

Buprenorphine had no adverse cardiovascular effects when given intravenously after open-heart surgery,[5] suggesting that it was a suitable analgesic for patients with unstable circulation. Epidural analgesia with buprenorphine has also been used after cardiac surgery.[6] Buprenorphine was also considered suitable for the relief of pain in *myocardial infarction*.[7]

1. Miwa Y, *et al.* Epidural administered buprenorphine in the perioperative period. *Can J Anaesth* 1996; **43:** 907–13.
2. Kawamata T, *et al.* Pain management after lumbar spinal fusion surgery using continuous subcutaneous infusion of buprenorphine. *J Anesth* 2005; **19:** 199–203.
3. Dingus DJ, *et al.* Buprenorphine versus morphine for patient-controlled analgesia after cholecystectomy. *Surg Gynecol Obstet* 1993; **177:** 1–6.
4. Harmer M, *et al.* Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine, and meptazinol. *BMJ* 1983; **286:** 680–2.
5. Rosenfeldt FL, *et al.* Haemodynamic effects of buprenorphine after heart surgery. *BMJ* 1978; **2:** 1602–3.
6. Mehta Y, *et al.* Lumbar versus thoracic epidural buprenorphine for postoperative analgesia following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand* 1999; **43:** 388–93.
7. Hayes MJ, *et al.* Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction. *BMJ* 1979; **2:** 300–2.

CHRONIC PAIN. Transdermal buprenorphine is used for chronic intractable cancer pain.[1-4] It has also been used successfully in chronic non-cancer pain including neuropathic pain;[1,2,4-6] however, licensed product information states that this route is not suitable for the treatment of acute pain.

1. Böhme K. Buprenorphine in a transdermal therapeutic system—a new option. *Clin Rheumatol* 2002; **21** (suppl 1): S13–S16.
2. Evans HC, Easthope SE. Transdermal buprenorphine. *Drugs* 2003; **63:** 1999–2010.
3. Sittl R. Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med* 2006; **20** (suppl 1): S25–S30.
4. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Rev Neurother* 2005; **5:** 315–23.
5. Bálint G. Buprenorphine treatment of patients with non-malignant musculoskeletal diseases. *Clin Rheumatol* 2002; **21** (suppl 1): S17–S18.
6. Hans G. Buprenorphine—a review of its role in neuropathic pain. *J Opioid Manag* 2007; **3:** 195–206.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Magnogen†; Temgesic†; ***Austral.:*** Norspan; Subutex; Temgesic; ***Austria:*** Subutex; Temgesic; Transtec; Tridol; ***Belg.:*** Subutex; Temgesic; Transtec; ***Braz.:*** Temgesic; ***Chile:*** Transtec; ***Cz.:*** Norspan; Suboxone; Subutex; Temgesic; Transtec; ***Denm.:*** Anorfin; Norspan; Subutex; Temgesic; Transtec; ***Fin.:*** Subutex; Temgesic; ***Fr.:*** Suboxone; Subutex; Temgesic; ***Ger.:*** Subutex; Temgesic; Transtec; ***Gr.:*** Subutex; ***Hong Kong:*** Subutex; Temgesic; ***Hung.:*** Bupren; Transtec; ***India:*** Norphin; Pentorel; Tidigesic†; ***Indon.:*** Subutex; ***Irl.:*** BuTrans; Temgesic; Transtec; ***Israel:*** Nopan; Subutex; ***Ital.:*** Subutex; Temgesic; Transtec; ***Malaysia:*** Suboxone; Subutex†; Temgesic†; ***Mex.:*** Brospina; Temgesic; Transtec; ***Neth.:*** Temgesic; ***Norw.:*** Subutex; Temgesic; ***NZ:*** Suboxone; Temgesic; ***Pol.:*** Bunondol; Transtec; ***Port.:*** Buprex; Norspan; Suboxone; Subutex; Transtec; ***Rus.:*** Nopan (Нопан)†; Transtec (Транстек); ***S.Afr.:*** Subutex; Temgesic; ***Singapore:*** Subutex†; Temgesic†; ***Spain:*** Buprex; Prefin†; Subutex; Transtec; ***Swed.:*** Norspan; Subutex; Temgesic; ***Switz.:*** Subutex; Temgesic; Transtec; ***Thai.:*** Buprine; Temgesic†; ***UK:*** BuTrans; Suboxone; Subutex; Temgesic; Transtec; ***USA:*** Buprenex; Suboxone; Subutex.

Butibufen Sodium *(rINNM)*

Butibufén sódico; Butibufène Sodique; FF-106 (butibufen); Natrii Butibufenum. Sodium 2-(4-isobutylphenyl)butyrate.

Натрий Бутибуфен

$C_{14}H_{19}NaO_2$ = 242.3.

CAS — 55837-18-8 (butibufen); 60682-24-8 (butibufen sodium).

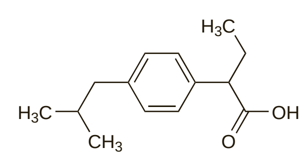

(butibufen)

Profile

Butibufen sodium is an NSAID (p.96) that has been used orally in inflammatory and rheumatic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Mijal†.

The symbol † denotes a preparation no longer actively marketed

Butorphanol Tartrate *(BANM, USAN, rINNM)*

levo-BC-2627 (butorphanol); Butorfanolitartraatti; Butorfanoltartrat; Butorphanol, Tartrate de; Butorphanoli Tartras; Tartrato de butorfanol. (−)-17-(Cyclobutylmethyl)morphinan-3,14-diol hydrogen tartrate.

Буторфанола Тартрат

$C_{21}H_{29}NO_2,C_4H_6O_6$ = 477.5.
CAS — 42408-82-2 (butorphanol); 58786-99-5 (butorphanol tartrate).
ATC — N02AF01.
ATC Vet — QN02AF01.

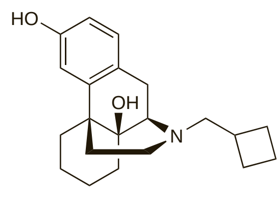

(butorphanol)

Pharmacopoeias. In *US.*

USP 31 (Butorphanol Tartrate). A white powder. Its solutions are slightly acidic. Sparingly soluble in water; insoluble in alcohol, in chloroform, in ether, in ethyl acetate, and in hexane; slightly soluble in methyl alcohol; soluble in dilute acids. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Butorphanol may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, below). Abruptly stopping chronic butorphanol has produced a less severe withdrawal syndrome than with morphine.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102, and for Pentazocine, p.112.

Headache, and feelings of floating may also occur. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. In addition insomnia and nasal congestion may occur frequently when butorphanol is given intranasally.

Because butorphanol has opioid agonist and antagonist activity, naloxone is the recommended antagonist for the treatment of overdosage.

Effects on the respiratory system. Butorphanol 2 mg produces a similar degree of respiratory depression to morphine 10 mg, but a ceiling effect is apparent with higher doses of butorphanol.[1] It has been reported to be a less potent respiratory depressant than fentanyl,[2] but more potent than nalbuphine.[3]

1. Nagashima H, *et al.* Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin Pharmacol Ther* 1976; **19:** 738–45.
2. Dryden GE. Voluntary respiratory effects of butorphanol and fentanyl following barbiturate induction: a double-blind study. *J Clin Pharmacol* 1986; **26:** 203–7.
3. Zucker JR, *et al.* Respiratory effects of nalbuphine and butorphanol in anesthetized patients. *Anesth Analg* 1987; **66:** 879–81.

Precautions

As for Opioid Analgesics in general, p.103.

Although cardiovascular effects may be less than with pentazocine, butorphanol should generally be avoided after myocardial infarction.

Butorphanol may precipitate withdrawal symptoms if given to patients physically dependent on opioids. The dosage regimen of butorphanol may need to be adjusted in the elderly and in patients with hepatic or renal impairment.

Abuse. A WHO expert committee considered in 2006 that the likelihood of butorphanol abuse was low and was not great enough to warrant international control.[1] Abuse had been reported infrequently and only in a few countries. The committee also commented that, pharmacologically, intranasal preparations of butorphanol do not appear to differ in their abuse potential from parenteral preparations; however, other factors such as availability and usage patterns may affect the likelihood of abuse. Indeed, US licensed product information states that there have been more reports of abuse with intranasal preparations than with injectable ones.

Cases of butorphanol abuse have been published[2,3] including a report of fibrous myopathy associated with chronic intramuscular abuse.

1. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
2. Wagner JM, Cohen S. Fibrous myopathy from butorphanol injections. *J Rheumatol* 1991; **18:** 1934–5.
3. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia* 2006; **26:** 89–97.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given butorphanol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In a study[2] of 12 women, butorphanol was detected in breast milk after both intramuscular and oral doses. However, the milk-to-plasma ratio after a 2-mg intramuscular dose (0.7) was significantly less than that after an 8-mg oral dose (1.9). Although the mothers were not breast feeding at the time of the study, the authors concluded that the potential for any adverse effects on nursing infants after maternal butorphanol use would be minimal.

1. American Academy of Pediatrics The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Pittman KA, *et al.* Human perinatal distribution of butorphanol. *Am J Obstet Gynecol* 1980; **138:** 797–800.

Pregnancy. Two instances of sinusoidal fetal heart rate pattern were noted out of 188 consecutive cases of butorphanol use in active-phase labour.[1] Visual hallucinations and paranoid delusions developed in a woman on receiving a 1-mg intravenous injection of butorphanol early in labour; the psychosis had resolved 40 hours after the injection and was not noted on follow-up 2 weeks later.[2]

1. Welt SI. Sinusoidal fetal heart rate and butorphanol administration. *Am J Obstet Gynecol* 1985; **152:** 362–3.
2. Davis A, *et al.* Acute psychosis associated with butorphanol. *J Neuropsychiatr Clin Neurosci* 1998; **10:** 236–7.

Interactions

For interactions associated with opioid analgesics, see p.103.

Antimigraine drugs. No pharmacokinetic interactions were reported when butorphanol nasal spray and subcutaneous *sumatriptan* were used together within a minute of each other in healthy subjects.[1] However, another study[2] in healthy subjects found that the AUC and maximum plasma concentration of intranasal butorphanol were reduced by about 29% and 38%, respectively when given 1 minute after intranasal sumatriptan. No such effect was noted when administration was separated by 30 minutes. It was suggested that sumatriptan may reduce butorphanol absorption by inducing transient nasal vasoconstriction.

1. Srinivas NR, *et al.* Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; **35:** 432–7.
2. Vachharajani NN, *et al.* A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* 2002; **22:** 282–7.

Pharmacokinetics

Butorphanol is absorbed from the gastrointestinal tract but it undergoes extensive first-pass metabolism. Peak plasma concentrations occur 0.5 to 1 hour after intramuscular and intranasal doses and 1 to 1.5 hours after oral doses. Butorphanol has a plasma elimination half-life of about 4.5 hours. About 80% is bound to plasma proteins.

Butorphanol is extensively metabolised in the liver through hydroxylation, *N*-dealkylation, and conjugation, only 5% being excreted unchanged. Excretion is mainly in the urine; about 15% of a parenteral dose is excreted in the bile. It crosses the placenta and is distributed into breast milk.

Administration. INTRANASAL ROUTE. References.

1. Davis GA, *et al.* Pharmacokinetics of butorphanol tartrate administered from single-dose intranasal sprayer. *Am J Health-Syst Pharm* 2004; **61:** 261–6.
2. Davis GA, *et al.* Bioavailability of intranasal butorphanol administered from a single-dose sprayer. *Am J Health-Syst Pharm* 2005; **62:** 48–53.
3. Wermeling DP, *et al.* Pharmacokinetics, bioequivalence, and spray weight reproducibility of intranasal butorphanol after administration with 2 different nasal spray pumps. *J Clin Pharmacol* 2005; **45:** 969–73.

Uses and Administration

Butorphanol tartrate, a phenanthrene derivative, is an opioid analgesic (p.104) with opioid agonist and antagonist properties; it is pharmacologically similar to pentazocine (p.113). Butorphanol is used for the relief of moderate to severe pain, including the pain of labour, and as an adjunct to anaesthesia. Onset of analgesia occurs within 15 minutes of intramuscular injection or an intranasal dose and may last for 3 to 4 hours after parenteral doses or for 4 to 5 hours after intranasal doses.

For the relief of moderate to severe **pain**, butorphanol tartrate is given in doses of 1 to 4 mg (usually 2 mg) by intramuscular injection or in doses of 0.5 to 2 mg (usually 1 mg) by intravenous injection every 3 to 4 hours. It may also be given as a nasal spray, in usual doses of 1 mg (1 spray in 1 nostril), repeated after 60 to 90 minutes, if necessary. This sequence may be repeated after 3 to 4 hours as needed. An initial dose of 2 mg (1 spray in each nostril) may be given for severe pain, but should not be repeated until 3 to 4 hours later.

In *obstetric analgesia* 1 to 2 mg may be given by intramuscular or intravenous injection during early labour in women at term. This dose may be repeated after 4 hours if necessary but an alternative analgesic should be used if delivery is expected within 4 hours.

In **anaesthesia**, 2 mg may be given intramuscularly for premedication 60 to 90 minutes before surgery. For use in balanced anaesthesia, a usual dose is 2 mg given intravenously shortly before induction and/or 0.5 to 1 mg given intravenously in increments during anaesthesia. The total dose needed varies but most patients require 4 to 12.5 mg.

Dosage adjustment may be needed in the elderly. When given by injection the initial dose of butorphanol for pain should be half the usual initial adult dose. Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours. Similar recommendations have also been made for patients with hepatic or renal impairment, see below.

◊ References.

1. Atkinson BD, *et al.* Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol* 1994; **171:** 993–8.
2. Gillis JC, *et al.* Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995; **50:** 157–75.
3. Commiskey S, *et al.* Butorphanol: effects of a prototypical agonist-antagonist analgesic on κ-opioid receptors. *J Pharmacol Sci* 2005; **98:** 109–16.

Administration in hepatic or renal impairment. The dosage of butorphanol may need to be adjusted in patients with hepatic or renal impairment. When given by injection the initial dose for pain should be half the usual initial adult dose (see above). Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours.

Headache. Butorphanol has been advocated for use as a nasal spray in the treatment of migraine, but there have been problems with abuse and dependence (see above) and its place in therapy, if any, still remains to be established. See also Antimigraine Drugs, under Interactions, above.

References.

1. Freitag FG. The acute treatment of migraine with transnasal butorphanol (TNB). *Headache Q* 1993; **4** (suppl 3): 22–8.
2. Hoffert MJ, *et al.* Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; **35:** 65–9.
3. Melanson SW, *et al.* Transnasal butorphanol in the emergency department management of migraine headache. *Am J Emerg Med* 1997; **15:** 57–61.

Pruritus. Results from a small study[1] of 6 patients with severe opioid-induced pruritus unresponsive to diphenhydramine, and from a case series of 5 patients with intractable pruritus from other causes,[2] suggest that intranasal butorphanol may be an effective treatment. Doses have ranged from 1 mg every other day to 2 mg every 4 to 6 hours.

1. Dunteman E, *et al.* Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage* 1996; **12:** 255–60.
2. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; **54:** 527–31.

Preparations

USP 31: Butorphanol Tartrate Injection; Butorphanol Tartrate Nasal Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Stadol†; ***Chile:*** Stadol†; ***Cz.:*** Beforal†; Moradol†; ***India:*** Butrum; ***Mex.:*** Stadol; ***Philipp.:*** Stadol; ***Rus.:*** Stadol (Стадол); ***USA:*** Stadol.

Capsaicin

Capsaicina; Capsaicinum; Kapsaicin; Kapsaicyna; Kapsaisiini. (*E*)-8-Methyl-*N*-vanillylnon-6-enamide.

$C_{18}H_{27}NO_3$ = 305.4.
CAS — 404-86-4.
ATC — N01BX04.
ATC Vet — QN01BX04.

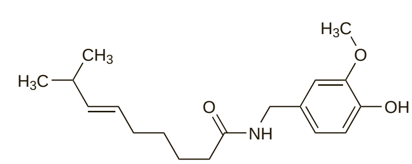

NOTE. Do not confuse capsaicin with capsicin, which is capsicum oleoresin (see Capsicum, p.2276).

Pharmacopoeias. In *US.*

USP 31 (Capsaicin). An off-white powder. M.p. 57° to 66°. Practically insoluble in cold water; soluble in alcohol, in chloroform, and in benzene; slightly soluble in carbon disulfide. Store in a cool place in airtight containers. Protect from light.

Adverse Effects

A warm, stinging, or burning sensation may occur at the site of application; this usually disappears after a few days of use but may persist longer if applications are less frequent than recommended (see Uses and Administration, below). Coughing, sneezing, or other signs of respiratory irritation may occur if dried residue from topical preparations is inhaled.

Precautions

Capsaicin should be handled with care. Particles should not be inhaled nor come into contact with any part of the body.

For topical application, contact with eyes and broken or irritated skin should be avoided. The hands should be washed after application of the cream, unless the hands are the treated areas, in which case, they should be washed 30 minutes after application. If bandages are used to cover treated areas they should not be wound too tightly. Heating pads should not be used with capsaicin, and patients should avoid taking a hot bath or shower immediately before or after application, as the burning sensation may be exacerbated. Thick applications of the cream should be avoided.

Uses and Administration

Capsaicin is the active principle of the dried ripe fruits of *Capsicum* spp. It is used as a topical analgesic (p.5) in painful conditions such as postherpetic neuralgia after the lesions have healed, diabetic neuropathy, osteoarthritis, and rheumatoid arthritis. Capsaicin is usually applied sparingly 3 or 4 times daily (and not more often than every 4 hours) as a 0.025% or 0.075% cream; in the UK these creams are not licensed for use in children, but in the USA they may be used in children over 2 years of age. A more concentrated cream containing 0.25% capsaicin is available in some countries.

Capsaicin cream should be rubbed well into the skin until little or no residue is left on the surface. Therapeutic response may not be evident for 1 to 2 weeks for arthritic disorders, or 2 to 4 weeks for neuralgias (or even longer if the head or neck are involved). For the management of painful diabetic neuropathy, licensed UK product information recommends that capsaicin should only be used under specialist supervision and that treatment should be reviewed after the first 8 weeks and regularly re-evaluated thereafter.

Although not a counter-irritant itself, capsaicin has been included in rubefacient preparations for the relief of muscular and rheumatic pain.

Action. The action of capsaicin and related compounds (vanilloids) are complex and still being investigated. Capsaicin has been found to produce burning pain[1,2] by activating specific vanilloid receptors such as TRPV1 (transient receptor potential channel, vanilloid subfamily member 1) which are also stimulated by heat and acids. TRPV1 is expressed by nerves and other tissues such as the keratinocytes of the epidermis, bladder urothelium and smooth muscle, and liver.

The analgesic effect of capsaicin has been suggested to be due to both depletion of substance P from local sensory C-type nerve fibres[3-7] and to the desensitisation of vanilloid receptors.[1,2,8] Since the effect of capsaicin does not rely on vasodilatation in the skin it is therefore not considered to be a traditional counter-irritant.

1. Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51:** 159–211.
2. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1: an update. *Eur J Biochem* 2004; **271:** 1814–19.
3. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991; **25:** 381–7.
4. Cordell GA, Araujo OE. Capsaicin: identification, nomenclature, and pharmacotherapy. *Ann Pharmacother* 1993; **27:** 330–6.
5. Winter J, *et al.* Capsaicin and pain mechanisms. *Br J Anaesth* 1995; **75:** 157–68.
6. Del Bianco E, *et al.* The effects of repeated dermal application of capsaicin to the human skin on pain and vasodilatation induced by intradermal injection of acid and hypertonic solutions. *Br J Clin Pharmacol* 1996; **41:** 1–6.
7. Fusco BM, Giacovazzo M. Peppers and pain: the promise of capsaicin. *Drugs* 1997; **53:** 909–14.
8. Tominaga M, Julius D. Capsaicin receptor in the pain pathway. *Jpn J Pharmacol* 2000; **83:** 20–4.

Headache. Prevention of attacks of *cluster headache* (p.616) by repeated application of capsaicin to the nasal mucosa has been reported.[1] The *Z*-isomer (zucapsaicin; civamide) has also been found to be modestly effective.[2]

Repeated nasal application of capsaicin has also been found to be effective in *chronic migraine*.[3]

1. Fusco BM, *et al.* Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994; **59:** 321–5.
2. Saper JR, *et al.* Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002; **59:** 990–4.
3. Fusco BM, *et al.* Repeated intranasal capsaicin applications to treat chronic migraine. *Br J Anaesth* 2003; **90:** 812.

Micturition disorders. Intravesical capsaicin has been tried for painful bladder disorders and to treat bladder detrusor hyperreflexia.[1-9] Results have been variable, and the characteristic sensory effects of capsaicin make blinding of studies difficult, but some patients have reported benefit particularly those with neurological bladder disorders. Instillation into the ureter has also been tried in the management of the loin pain/haematuria syndrome.[10]

1. Lazzeri M, *et al.* Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. *J Urol (Baltimore)* 1996; **156:** 947–52.
2. de Sèze M, *et al.* Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. *Neurourol Urodyn* 1998; **17:** 513–23.
3. Petersen T, *et al.* Intravesical capsaicin in patients with detrusor hyper-reflexia: a placebo-controlled cross-over study. *Scand J Urol Nephrol* 1999; **33:** 104–10.
4. de Sèze M, *et al.* Intravesical instillation of capsaicin in urology: a review of the literature. *Eur Urol* 1999; **36:** 267–77.
5. de Sèze M, *et al.* Capsaïcine intravésicale et hyperréflexie du détrusor: expérience de 100 instillations sur une période de cinq ans. *Ann Readapt Med Phys* 2001; **44:** 514–24.
6. Szallasi A, Fowler CJ. After a decade of intravesical vanilloid therapy: still more questions than answers. *Lancet Neurol* 2002; **1:** 167–72.
7. de Sèze M, *et al.* Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. *J Urol (Baltimore)* 2004; **171:** 251–5.
8. Lazzeri M, *et al.* Intravesical vanilloids and neurogenic incontinence: ten years experience. *Urol Int* 2004; **72:** 145–9.
9. El-Mahrouky AS, *et al.* The effect of intravesical capsaicin and resiniferatoxin in neurogenic bladder dysfunction. *Adv Exp Med Biol* 2003; **539:** 359–79.
10. Bultitude MI. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet* 1995; **345:** 921–2.

Neuropathic pain. Capsaicin has been tried topically in various types of pain including neuropathic pain, which does not generally respond to conventional systemic analgesics. Topical capsaicin is used in the management of diabetic neuropathy (p.6) and postherpetic neuralgia (p.9), but while a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2] suggested that it is effective in painful diabetic neuropathy the evidence for efficacy in postherpetic neuralgia was considered[1] to be less convincing. Another meta-analysis[3] and a systematic review[4] have suggested that capsaicin was of benefit in neuropathic pain, although this effect may be modest.[4] The difficulty of blinding in placebo-controlled trials of capsaicin has also been noted, because of the burning sensation it produces. Other types of pain syndrome for which capsaicin has been tried include reflex sympathetic dystrophy (see Complex Regional Pain Syndrome, p.6), postmastectomy neuroma, amputation stump pain, chronic neck pain, and the pain of oral mucositis.[5]

See also Rheumatic Disorders, below for use in musculoskeletal pain.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46:** 517–22.
2. Biesbroeck R, *et al.* A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. *Adv Therapy* 1995; **12:** 111–20.
3. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73:** 123–39.
4. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328:** 991–4.
5. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Pruritus. Substance P is a possible mediator of itch sensations and since capsaicin acts as a depletor of substance P it has been tried in the relief of pruritus (p.1582) associated with various diseases and haemodialysis.[1-7] It has also been used to provide relief from pruritus induced by hetastarch[8] and for the itch and pain associated with PUVA therapy.[9,10]

1. Breneman DL, *et al.* Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; **26:** 91–4.
2. Leibsohn E. Treatment of notalgia paresthetica with capsaicin. *Cutis* 1992; **49:** 335–6.
3. Fölster-Holst R, Brasch J. Effect of topically applied capsaicin on pruritus in patients with atopic dermatitis. *J Dermatol Treat* 1996; **7:** 13–15.
4. Hautmann G, *et al.* Aquagenic pruritus, PUVA and capsaicin treatments. *Br J Dermatol* 1994; **131:** 920–1.
5. Ständer S, *et al.* Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; **44:** 471–8.
6. Lysy J, *et al.* Topical capsaicin— a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003; **52:** 1323–6.
7. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.
8. Szeimies R-M, *et al.* Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; **131:** 380–2.
9. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
10. Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. *Br J Dermatol* 1997; **137:** 152.

Psoriasis. Since substance P has been implicated in the pathophysiology of several inflammatory dermatological processes, capsaicin, a substance P depletor, has been tried with some benefit in a number of skin disorders including psoriasis.[1-3]

The usual management of psoriasis is discussed on p.1583.

1. Bernstein JE, *et al.* Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. *J Am Acad Dermatol* 1986; **15:** 504–7.
2. Ellis CN, *et al.* A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993; **29:** 438–42.
3. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Rheumatic disorders. Topical capsaicin is used for the temporary relief of the pain of arthritis. From the results of a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2,3] it appears that capsaicin is effective in easing the pain of osteoarthritis (p.11) but its role, if any, is unclear; published evidence[4] for efficacy in rheumatoid arthritis (p.11) appears to be limited. A review of use in both neuropathic and musculoskeletal chronic pain concluded that its benefits were at best moderate, but noted that in a minority of patients unresponsive to, or intolerant of, other treatments it might be useful.[5] Capsaicin may be a useful therapy for pain associated with primary fibromyalgia[6] (see under Soft Tissue Rheumatism, p.13), which responds poorly to conventional treatment.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46:** 517–22.
2. Altman RD, *et al.* Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 25–33.
3. McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000; **4:** 355–60.
4. Deal CL, *et al.* Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991; **13:** 383–95.
5. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328:** 991–4.
6. McCarty DJ, *et al.* Treatment of pain due to fibromyalgia with topical capsaicin: a pilot study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 41–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Zostrix; ***Belg.:*** Hansamedic Warmtepleister; ***Braz.:*** Moment; ***Canad.:*** Antiphlogistine Rub A-535 Capsaicin; Arthricare for Women Extra Moisturizing†; Zostrix; ***Chile:*** Presyc; ***Gr.:*** Gelcen; Zacin; ***Indon.:*** Capzacin; ***Irl.:*** Axsain; Zacin; ***Israel:*** Zostrix; ***Mex.:*** Capsidol; ***Norw.:*** Capsina; ***NZ:*** Zostrix; ***Port.:*** Hansaplast Emplastro Termico; Hansaterm; ***Spain:*** Capsicin; Capsicum Farmaya; Capsidol; Gelcen; Hansaterm; Katrum; ***Swed.:*** Capsina; ***Switz.:*** Emplatre antirhumatismal Isola Capsicum N; Emplatre Etoile†; ***UK:*** Axsain; Zacin; ***USA:*** Axsain; Capsin; Capzasin-HP; Capzasin-P; Dolorac; Doublecap; No Pain-HP; R-Gel; Rid-a-Pain HP; Theragen; Zostrix.

Multi-ingredient: ***Arg.:*** Atomo Desinflamante C; Rati Salil Crema; Rati Salil Flex; ***Austria:*** Rubizon-Rheumagel; ***Canad.:*** Arthricare for Women Multi-Action†; Heet; Menthacin; Midalgan†; ***Cz.:*** Capsicolle; Dr Theiss Rheuma Creme†; ***Fr.:*** Capsic; Cliptol Sport†; ***Ger.:*** Capsamol N†; ***Gr.:*** Ponostop; ***Hong Kong:*** Salomethyl; ***Hung.:*** Nicoflex; ***India:*** Nimulid Nugel; ***Irl.:*** Algipan; Radian-B†; ***Ital.:*** Disalgil†; ***Pol.:*** Capsigel N; Neo-Capsiderm; ***Switz.:*** Emplatre antirhumatismal Isola Capsicum N a l'huile essentielle de Gaultherie; Emplatre Etoile salicyle†; ***UK:*** NatraFlex; ***USA:*** Arthricare Odor Free; Heet; Menthacin; Pain Doctor; Ziks.

Carbasalate Calcium *(BAN, rINN)*

Calcium Acetylsalicylate Carbamide; Calcium Carbaspirin; Carbasalate calcique; Carbasalato cálcico; Carbasalatum calcicum; Carbasalatum Calcium; Carbaspirin Calcium *(USAN)*; Karbasalaattikalsium; Karbasalát vápenatá sůl; Karbasalatkalcium; Karbasalato kalcio druska; Karbaszalát-kálcium. Calcium bis[2-(acetoxy)benzoate]—urea.

Карбасалат Кальций

$C_{19}H_{18}CaN_2O_9$ = 458.4.
CAS — 5749-67-7.
ATC — B01AC08; N02BA15.
ATC Vet — QB01AC08; QN02BA15.

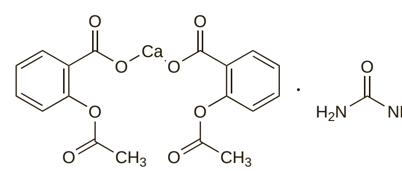

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Carbasalate Calcium). A white or almost white, crystalline powder. It contains not less than 99.0% and not more than the equivalent of 101.0% of an equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea, calculated with reference to the anhydrous substance. Freely soluble in water and in dimethylformamide; practically insoluble in acetone and in anhydrous methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

Carbasalate calcium, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Effects on hearing. As of June 2006 the Netherlands Pharmacovigilance Centre[1] database contained 8 reports of tinnitus and 1 of ototoxicity associated with use of low oral doses of carbasalate calcium (38 or 100 mg usually once daily). The association between low-dose carbasalate calcium and tinnitus was considered to be disproportional.

1. Nederlands Bijwerkingen Centrum. Low dosage carbasalate calcium and tinnitus. Available at: http://www.lareb.nl/documents/kwb_2006_3_carbas.pdf (accessed 12/04/07)

Interactions

For interactions associated with aspirin, see p.23.

Uses and Administration

Carbasalate calcium is a 1:1 complex of calcium acetylsalicylate and urea. It is metabolised to aspirin after absorption and thus has the actions of aspirin (p.23). Carbasalate calcium is given in oral doses equivalent to about 400 to 800 mg of aspirin every 4 to 8 hours up to a maximum of about 3 g daily for pain or fever. Carbasalate calcium has also been used in the management of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Iromin; Vascal; ***Neth.:*** Ascal; ***Port.:*** Ascal; ***Spain:*** Ascal; ***Switz.:*** Alcacyl.

Multi-ingredient: ***Austria:*** Irocopar c C; Irocophan; Iromin-Chinin-C; ***Cz.:*** Cephalgan†; ***Fr.:*** Cephalgan†; ***Switz.:*** Alca-C.

Carfentanil Citrate *(USAN, rINNM)* ⊗

Carfentanil, Citrate de; Carfentanili Citras; Citrato de carfentanilo; R-33799. Methyl 1-phenethyl-4-(*N*-phenylpropionamido)isonipecotate citrate.

Карфентанила Цитрат

$C_{24}H_{30}N_2O_3,C_6H_8O_7$ = 586.6.
CAS — 59708-52-0 (carfentanil); 61380-27-6 (carfentanil citrate).

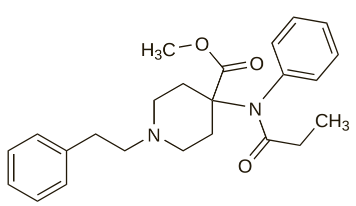

(carfentanil)

Profile

Carfentanil citrate is an opioid analgesic related to fentanyl (p.55). It is used in veterinary medicine.

Carprofen *(BAN, USAN, rINN)*

C-5720; Carprofène; Carprofeno; Carprofenum; Karprofeeni; Karprofen; Ro-20-5720/000. (±)-2-(6-Chlorocarbazol-2-yl)propionic acid.

Карпрофен

$C_{15}H_{12}ClNO_2$ = 273.7.
CAS — 53716-49-7.
ATC Vet — QM01AE91.

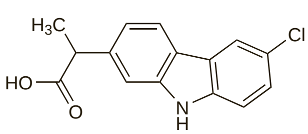

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Carprofen for Veterinary Use). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol; slightly soluble in isopropyl alcohol. It exhibits polymorphism. Protect from light.

USP 31 (Carprofen). A white crystalline powder. Practically insoluble in water; freely soluble in acetone, in ether, in ethyl acetate, and in solutions of sodium carbonate and of sodium hydroxide. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Carprofen, a propionic acid derivative, is an NSAID (p.96) used in veterinary medicine.

Adverse effects. A pruritic, erythematous, eczematous eruption developed in a 27-year-old woman after occupational exposure to carprofen.[1] Patch testing showed a strong positive photoallergic reaction to carprofen.

1. Walker SL, *et al.* Occupational photoallergic contact dermatitis in a pharmaceutical worker manufacturing carprofen, a canine nonsteroidal anti-inflammatory drug. *Br J Dermatol* 2006; **154:** 569–70.

Preparations

USP 31: Carprofen Tablets.

Celecoxib *(BAN, USAN, rINN)*

Célécoxib; Celecoxibum; Celekoxib; SC-58635; Selekoksib; Selekoksibi; YM-177. *p*-[5-*p*-Tolyl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide.

Целекоксиб

$C_{17}H_{14}F_3N_3O_2S$ = 381.4.
CAS — 169590-42-5.
ATC — L01XX33; M01AH01.
ATC Vet — QL01XX33; QM01AH01.

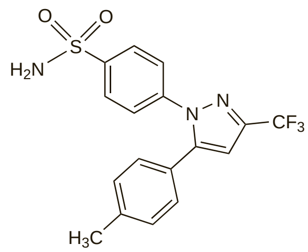

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with celecoxib. Other hypersensitivity reactions, including anaphylaxis and angioedema, have also occurred. Celecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions have been seen in patients with a history of allergic reactions to sulfonamides and the use of celecoxib is contra-indicated in such patients.

Celecoxib should not be used after coronary artery bypass surgery as there may be an increased risk of adverse effects such as myocardial infarction and stroke. It should be used with caution, if at all, in patients with a history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; it should also be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. For further details see Effects on the Cardiovascular System, below.

Therapy is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), inflammatory bowel disease, and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Celecoxib should also not be used in patients with severe hepatic impairment (Child-Pugh category C). Caution is recommended when using celecoxib in dehydrated patients; rehydration may be advisable before giving celecoxib.

Celecoxib treatment may need to be stopped if signs or symptoms of organ toxicity develop.

Incidence of adverse effects. A prescription-event monitoring study[1] conducted after the introduction of celecoxib in England in May 2000 found that the most common adverse events reported were gastrointestinal effects including dyspepsia (4.7% of all events), abdominal pain (1.8%), nausea or vomiting (1.6%), and diarrhoea (1.4%). Rash (1.2%) was also common. Uncommon events included anaemia, cough, anxiety, hypertension, visual disturbances, and insomnia. Blood dyscrasias, gastrointestinal bleeds, myocardial infarction, heart failure, abnormal liver function tests, nephritis, confusion, hallucinations, serious skin disorders, anaphylaxis, and bronchospasm were rare.

1. Layton D, *et al.* Safety profile of celecoxib as used in general practice in England: results of a prescription-event monitoring study. *Eur J Clin Pharmacol* 2004; **60:** 489–501.

Breast feeding. Licensed product information recommends that celecoxib should not be used in breast-feeding women because of the potential for serious adverse effects in nursing infants.

No adverse effects were noted in 2 older infants (aged 17 and 22 months) whose mothers took celecoxib while breast feeding.[1] The authors of this report also measured celecoxib plasma concentrations in 2 other women; from these values, the average milk-to-plasma ratio was calculated to be 0.23 and infant exposure was estimated at about 0.3% of the weight-adjusted maternal dose. Similar values have also been estimated from a study of blood and milk concentrations of celecoxib in 6 women.[2]

1. Hale TW, *et al.* Transfer of celecoxib into human milk. *J Hum Lact* 2004; **20:** 397–403.
2. Gardiner SJ, *et al.* Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol* 2006; **61:** 101–4.

Effects on the blood. Severe methaemoglobinaemia has been reported in an elderly patient after taking celecoxib for 1 month.[1]

1. Kaushik P, *et al.* Celecoxib-induced methemoglobinemia. *Ann Pharmacother* 2004; **38:** 1635–8.

Effects on the cardiovascular system. Prelicensing studies did not report any increased risk of serious cardiovascular effects in patients given celecoxib.[1,2] Nonetheless, by February 2001 the UK CSM had received a small number of reports[3] of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors. There have also been 3 cases of *torsade de pointes* associated with celecoxib use.[4] Subsequently, in September 2004, the COX-2 inhibitor rofecoxib was generally withdrawn worldwide by the manufacturer after further reports of cardiovascular adverse effects (see p.121) and this has prompted re-evaluation of the safety of other selective COX-2 inhibitors.

In December 2004 a large study of celecoxib for prevention of colon polyps (the APC study) was halted because of an increased risk of cardiovascular events (including death from cardiovascular causes, myocardial infarction, stroke, and heart failure) in patients receiving the drug compared with those receiving placebo.[5] The results of this long-term study suggested that there was a 2.8-fold increase in the risk of such events in patients taking either celecoxib 400 or 800 mg daily and that the increase was dose-related. The possibility of a dose-adverse effect relationship was supported by some at-the-time unpublished studies, the PreSAP and ADAPT studies, that showed no increase in the risk of cardiovascular effects with celecoxib 400 mg daily when compared with placebo.[6] These studies[7,8] have since been published and their finished reports were less reassuring than initially thought. The risk of serious cardiovascular events was found to be increased in the celecoxib group when compared with the placebo group although the difference was not significant. In addition, an update[9] of the original APC study confirmed that the risk of adverse cardiovascular events was significantly increased for both high-dose (800 mg daily) and low-dose (400 mg daily) celecoxib when compared with placebo treatment; however, high-dose treatment was associated with the greatest risk. Increases in blood pressure were also more likely with both celecoxib groups than with placebo. An analysis[10] using pooled data from the APC and PreSAP studies provides further evidence of an increased cardiovascular risk with celecoxib.

Based on the findings of the above studies, EU regulatory authorities[11-13] recommend that:

- selective COX-2 inhibitors should not be used in patients with established ischaemic heart disease or cerebrovascular disease; they are also contra-indicated in those with peripheral arterial disease
- patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes, and smoking should be carefully monitored if given selective COX-2 inhibitors
- all patients should be assessed individually on the risks and benefits of selective COX-2 inhibitor treatment, particularly cardiovascular and gastrointestinal risk factors, and alternative treatments considered

Similar advice has also been issued by the FDA;[14] however, the only absolute contra-indication is in the immediate postoperative period after coronary artery bypass surgery. (In the USA celecoxib is currently the only available selective COX-2 inhibitor.)

COX-2 inhibitors such as celecoxib do not possess the intrinsic antiplatelet activity associated with aspirin and possibly other non-selective NSAIDs and consequently do not provide protection against ischaemic cardiac events.[3,15]

1. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
2. White WB, *et al.* Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002; **89:** 425–30.
3. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
4. Pathak A, *et al.* Celecoxib-associated torsade de pointes. *Ann Pharmacother* 2002; **36:** 1290–1.
5. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
6. FDA. Celecoxib (marketed as Celebrex) (issued 7th April 2005). Available at: http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf (accessed 01/11/07)
7. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.
8. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Available at: http://clinicaltrials.plosjournals.org/archive/1555-5887/1/7/pdf/10.1371_journal.pctr.0010033-L.pdf (accessed 01/11/07)
9. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.

10. Solomon SD, *et al.* Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006; **114:** 1028–35.
11. MHRA. Updated advice on the safety of selective COX-2 inhibitors. Message from Professor G Duff, Chairman of CSM (issued 17th February, 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
12. EMEA. European Medicines Agency announces regulatory action on COX-2 inhibitors (issued 17th February, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/6275705en.pdf (accessed 29/08/08)
13. EMEA. European Medicines Agency concludes action on COX-2 inhibitors (issued 27th June, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/20776605en.pdf (accessed 01/11/07)
14. FDA. FDA issues public health advisory recommending limited use of cox-2 inhibitors: agency requires evaluation of prevention studies involving cox-2 selective agents. (issued 23rd December, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html (accessed 01/11/07)
15. Bing RJ, Lomnicka M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? *J Am Coll Cardiol* 2002; **39:** 521–2.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as celecoxib may cause less gastrotoxicity than the non-selective inhibition of the traditional NSAIDs.

Results from controlled studies suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a placebo-controlled study[1] the incidence of endoscopically determined gastroduodenal ulcers in patients taking celecoxib for rheumatoid arthritis (dose range 200 to 800 mg daily) was not significantly different to that seen with the placebo group. Another study[2] in patients taking celecoxib at supratherapeutic doses (800 mg daily) concluded that there was a lower combined incidence of symptomatic gastrointestinal ulcers and ulcer complications (bleeding, perforation, and obstruction) after 6 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or diclofenac 150 mg daily). However, the incidence of ulcer complications alone was not significantly different to that seen with other NSAIDs. A re-analysis of the study by the FDA, including both the 6-month and full-term data, also found that there was no significant reduction in the rate of ulcer complications with celecoxib compared with the non-selective NSAIDs although, in subjects not taking aspirin, there was a strong trend in favour of celecoxib compared to ibuprofen.[3] The risk of ulcer complications was also significantly increased in celecoxib users taking concomitant low-dose aspirin.[2] A later systematic review[4] of studies of patients receiving celecoxib or NSAIDs for at least 12 weeks claimed to show improved gastrointestinal safety and tolerability in those receiving celecoxib (including in patients also taking low-dose aspirin) but this has been criticised on grounds of data selection.[5,6]

It has been noted that the use of aspirin appears to nullify any potential protective effect of COX-2 selectivity by celecoxib.[7,8]

There have been individual case reports of gastrotoxicity with celecoxib.[9-11]

1. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–8.
2. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
3. FDA. Celebrex capsules (celecoxib) NDA 20-998/S009—Medical Officer Review. 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 01/11/07)
4. Deeks JJ, *et al.* Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; **325:** 619–23.
5. Jüni P, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: problems compromise review's validity. *BMJ* 2003; **326:** 334.
6. Metcalfe S, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: celecoxib's relative gastrointestinal safety is overstated. *BMJ* 2003; **326:** 334–5.
7. Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs: new and improved? *JAMA* 2000; **284:** 1297–9.
8. Bates DE, Lemaire JB. Possible celecoxib-induced gastroduodenal ulceration. *Ann Pharmacother* 2001; **35:** 782–3.
9. Mohammed S, Croom DW. Gastropathy due to celecoxib, a cyclooxygenase-2 inhibitor. *N Engl J Med* 1999; **340:** 2005–6.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Celecoxib: early Australian reporting experience. *Aust Adverse Drug React Bull* 2000; **19:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0006.pdf (accessed 29/08/08)
11. Adverse Drug Reactions Advisory Committee (ADRAC). Serious gastrointestinal effects with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 01/11/07)

Effects on the kidneys. Increasing evidence suggests that selective cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib appear to have adverse effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Some references to the adverse renal effects of celecoxib.

1. Boyd IW, *et al.* COX-2 inhibitors and renal failure: the triple whammy revisited. *Med J Aust* 2000; **173:** 274.
2. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
3. Graham MG. Acute renal failure related to high-dose celecoxib. *Ann Intern Med* 2001; **135:** 69–70.
4. Alkhuja S, *et al.* Celecoxib-induced nonoliguric acute renal failure. *Ann Pharmacother* 2002; **36:** 52–4.
5. Ahmad SR, *et al.* Renal failure associated with the use of celecoxib and rofecoxib. *Drug Safety* 2002; **25:** 537–44.
6. Alper AB, *et al.* Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 2002; **40:** 1086–90.
7. Akhund L, *et al.* Celecoxib-related renal papillary necrosis. *Arch Intern Med* 2003; **163:** 114–15.
8. Markowitz GS, *et al.* Membranous glomerulopathy and acute interstitial nephritis following treatment with celecoxib. *Clin Nephrol* 2003; **59:** 137–42.
9. Brewster UC, Perazella MA. Acute tubulointerstitial nephritis associated with celecoxib. *Nephrol Dial Transplant* 2004; **19:** 1017–18.
10. Clifford TM, *et al.* Celecoxib-induced nephrotoxicity in a renal transplant recipient. *Pharmacotherapy* 2005; **25:** 773–7.

Effects on the liver. Cholestatic hepatitis developed in a 54-year-old woman taking celecoxib;[1] her liver function tests improved and her symptoms resolved after drug withdrawal. Despite the temporal relationship between celecoxib use and the onset of hepatotoxicity, the manufacturers have stated that current evidence does not support such a relationship.[2] Other cases[3,4] have since been reported.

For a case of acute hepatitis with pancreatitis, see Pancreatitis, below.

1. O'Beirne JP, Cairns SR. Cholestatic hepatitis in association with celecoxib. *BMJ* 2001; **323:** 23.
2. Arellano FM, *et al.* Case of cholestatic hepatitis with celecoxib did not fulfil international criteria. *BMJ* 2002; **324:** 789–90.
3. Grieco A, *et al.* Acute cholestatic hepatitis associated with celecoxib. *Ann Pharmacother* 2002; **36:** 1887–9.
4. Chamouard P, *et al.* Prolonged cholestasis associated with short-term use of celecoxib. *Gastroenterol Clin Biol* 2005; **29:** 1286–8.

Effects on the lungs. Report of a case of pulmonary oedema and possible pneumonitis in a patient taking celecoxib.[1]

1. Olin JL, *et al.* Pulmonary edema and possible pneumonitis associated with celecoxib. *Ann Pharmacother* 2004; **38:** 1086.

Effects on the nervous system. Acute neuropsychiatric reactions such as confusion, somnolence, and insomnia, have occurred after celecoxib use.[1] There has also been a case report of aseptic meningitis.[2]

1. Adverse Drug Reations Advisory Committee (ADRAC). Acute neuropsychiatric events with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 01/11/07)
2. Papaioannides DH, *et al.* Aseptic meningitis possibly associated with celecoxib. *Ann Pharmacother* 2004; **38:** 172.

Hypersensitivity. A 52-year-old man suffered an allergic vasculitis after 8 days of treatment with celecoxib.[1] Despite intensive treatment the patient died from multiple organ failure and diffuse cutaneous necrolysis. The authors noted that potentially fatal skin reactions have occurred with other sulfa-containing drugs, although there is some evidence suggesting that the potential for cross-reactivity in patients sensitive to sulfonamides is relatively low;[2] nonetheless, licensed product information contra-indicates the use of celecoxib in such patients.

1. Schneider F, *et al.* Fatal allergic vasculitis associated with celecoxib. *Lancet* 2002; **359:** 852–3.
2. Shapiro LE, *et al.* Safety of celecoxib in individuals allergic to sulfonamide: a pilot study. *Drug Safety* 2003; **26:** 187–95.

Pancreatitis. Acute hepatitis and pancreatitis developed in an elderly patient with a reported history of hypersensitivity to sulfonamides who was given celecoxib.[1] Symptoms resolved on stopping the drug. Pancreatitis has also been reported in a patient known to be tolerant of sulfonamides.[2]

Celecoxib was one of the more commonly implicated drugs cited in case reports of drug-induced pancreatitis received by the Adverse Drug Reactions Advisory Committee in Australia.[3]

1. Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: a case report. *Arch Intern Med* 2000; **160:** 553–4.
2. Baciewicz AM, *et al.* Acute pancreatitis associated with celecoxib. *Ann Intern Med* 2000; **132:** 680.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 01/11/07)

Interactions

The metabolism of celecoxib is mediated mainly by the cytochrome P450 isoenzyme CYP2C9. Use with other drugs that inhibit or induce or are metabolised by this isoenzyme may result in changes in plasma concentration of celecoxib; fluconazole has increased plasma concentrations of celecoxib and licensed product information recommends that the dose of celecoxib should be halved when given with fluconazole.

Celecoxib is an inhibitor of the isoenzyme CYP2D6 and the potential therefore exists for an effect on drugs metabolised by this enzyme.

For interactions associated with NSAIDs in general, see p.99.

Pharmacokinetics

Celecoxib is absorbed from the gastrointestinal tract, peak plasma concentrations being achieved after about 3 hours. Protein binding is about 97%. Celecoxib is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C9; the three identified metabolites are inactive as inhibitors of COX-1 or COX-2 enzymes. It is eliminated mainly as metabolites in the faeces and urine; less than 3% is recovered as unchanged drug. The effective terminal half-life is about 11 hours. Celecoxib is distributed into breast milk. The pharmacokinetics of celecoxib may vary in different ethnic groups; it has been stated that the area under the curve is elevated in patients of Afro-Caribbean origin, although any clinical significance is unclear.

◊ References.

1. Davies NM, *et al.* Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2000; **38:** 225–42.
2. Stempak D, *et al.* Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clin Pharmacol Ther* 2002; **72:** 490–7. Correction. *ibid.* 2006; **80:** 667.
3. Kirchheiner J, *et al.* Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* 2003; **13:** 473–80.
4. Lundblad MS, *et al.* Accumulation of celecoxib with a 7-fold higher drug exposure in individuals homozygous for CYP2C9*3. *Clin Pharmacol Ther* 2006; **79:** 287–8.

Uses and Administration

Celecoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the treatment of rheumatoid arthritis including juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis, and in the adjunctive treatment of adenomatous colorectal polyps. Celecoxib is also used in the management of acute pain and dysmenorrhoea.

For **osteoarthritis** the recommended oral dose is 200 mg daily given as a single dose or in 2 divided doses. If necessary a dose of 200 mg twice daily may be used. For **rheumatoid arthritis** the dose is 100 to 200 mg given twice daily. Celecoxib is also used for **ankylosing spondylitis** in an initial dose of 200 mg daily, as a single dose or in 2 divided doses. In the USA, the dose may be increased to 400 mg daily after 6 weeks, although if no response is seen at this dose after a further 6 weeks, alternative treatments should be considered. A similar increase is also permitted in UK licensed product information; however, it is recommended that if ineffective, the higher dose should only be continued for 2 weeks before considering alternative treatments. In elderly patients treatment should be begun at the lowest recommended dose.

For doses in children with **juvenile idiopathic arthritis**, see below.

In the treatment of **pain** and **dysmenorrhoea**, an initial dose of 400 mg followed by an additional dose of 200 mg, if necessary, is recommended on the first day; thereafter the dose is 200 mg twice daily.

Celecoxib is also used as an adjunct to standard therapy to reduce the number of adenomatous **colorectal polyps** in patients with familial adenomatous polyposis. For this purpose it may be given in doses of 400 mg twice daily with food.

Reduced doses are recommended in patients with hepatic impairment (see below).

◊ Reviews.

1. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; **59:** 957–80.
2. Frampton JE, Keating GM. Celecoxib: a review of its use in the management of arthritis and acute pain. *Drugs* 2007; **67:** 2433–72.

Administration in children. In the USA, celecoxib is licensed for the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral doses, based on body-weight, are:

- 10 kg to 25 kg: 50 mg twice daily
- over 25 kg: 100 mg twice daily

Licensed product information recommends that the contents of a celecoxib capsule may be sprinkled onto apple sauce if a patient has difficulty swallowing the capsules. The sprinkled capsule should be taken immediately; however, it remains stable at a temperature between 2° to 8° for up to 6 hours.

Administration in hepatic impairment. Licensed product information recommends that doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh category B); its use is contra-indicated in those with severe impairment (Child-Pugh category C or a score of 10 or more).

Familial adenomatous polyposis. Celecoxib is used in the treatment of familial adenomatous polyposis, an inherited syndrome known to predispose sufferers to the development of colonic cancer (see p.666). A randomised study[1,2] found that treatment with celecoxib reduced the number of colonic polyps; the authors considered celecoxib to be a useful adjunct to the standard therapy of colectomy.

1. Steinbach G, *et al.* The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342:** 1946–52.
2. Phillips RKS, *et al.* A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50:** 857–60.

Malignant neoplasms. Celecoxib is under investigation as adjuvant therapy in the treatment of cancer;[1-9] preliminary results have been variable. It has also been investigated for chemoprevention of malignancy[10-13] (see also Familial Adenomatous Polyposis, above), but a large study for the prevention of colon cancer was terminated early because of increased cardiovascular risk.[11,12]

1. Dang CT, *et al.* Phase II study of celecoxib and trastuzumab in metastatic breast cancer patients who have progressed after prior trastuzumab-based treatments. *Clin Cancer Res* 2004; **10:** 4062–7.
2. Reardon DA, *et al.* Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. *Cancer* 2005; **103:** 329–38.
3. Nugent FW, *et al.* Docetaxel and cyclooxygenase-2 inhibition with celecoxib for advanced non-small cell lung cancer progressing after platinum-based chemotherapy: a multicenter phase II trial. *Lung Cancer* 2005; **48:** 267–73.
4. Gasparini G, *et al.* The combination of the selective cyclooxygenase-2 inhibitor celecoxib with weekly paclitaxel is a safe and active second-line therapy for non-small cell lung cancer: a phase II study with biological correlates. *Cancer J* 2005; **11:** 209–16.
5. Prince HM, *et al.* A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. *Clin Cancer Res* 2005; **11:** 5504–14.
6. Pan CX, *et al.* A phase II trial of irinotecan, 5-fluorouracil and leucovorin combined with celecoxib and glutamine as first-line therapy for advanced colorectal cancer. *Oncology* 2005; **69:** 63–70.
7. Ferrari V, *et al.* Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: a phase II trial. *Cancer Chemother Pharmacol* 2006; **57:** 185–90.
8. Csiki I, *et al.* Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. *Clin Cancer Res* 2005; **11:** 6634–40.
9. Chow LWC, *et al.* Serum lipid profiles in patients receiving endocrine treatment for breast cancer—the results from the Celecoxib Anti-Aromatase Neoadjuvant (CAAN) Trial. *Biomed Pharmacother* 2005; **59** (suppl 2): S302–S305.
10. Limburg PJ, *et al.* Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. *Gastroenterology* 2005; **129:** 863–73.
11. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
12. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.
13. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.

Musculoskeletal and joint disorders. Celecoxib is used in the treatment of osteoarthritis (p.11) and rheumatoid arthritis (p.11) including juvenile idiopathic arthritis (p.10). However, in the UK it is recommended that the use of celecoxib and other selective cyclo-oxygenase-2 (COX-2) inhibitors be limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Adverse Effects, above).

Celecoxib is also used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p.13).

References.

1. Bensen WG, *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74:** 1095–1105.
2. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–28.
3. Emery P, *et al.* Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; **354:** 2106–11.
4. Dougados M, *et al.* Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 2001; **44:** 180–5.
5. Stengaard-Pedersen K, *et al.* Celecoxib 200 mg qd is efficacious in the management of osteoarthritis of the knee or hip regardless of the time of dosing. *Rheumatology (Oxford)* 2004; **43:** 592–5.
6. Schnitzer TJ, *et al.* VACT-1 and VACT-2 (Protocols 106 and 150) Study Groups. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. *J Rheumatol* 2005; **32:** 1093–1105.
7. Singh G, *et al.* Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med* 2006; **119:** 255–66.
8. Barkhuizen A, *et al.* Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol* 2006; **33:** 1805–12.
9. Luyten FP, *et al.* A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. *Ann Rheum Dis* 2007; **66:** 99–106.

Palmar-plantar erythrodysesthesia syndrome. Celecoxib has been investigated in the treatment of capecitabine-induced hand-foot (palmar-plantar erythrodysesthesia) syndrome; for references, see under Adverse Effects and Precautions of Capecitabine, p.692.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Algybrex; Celebrex; Celemax†; Cloxib†; Coxel†; Coxtenk; Niflam†; Radicacine; Tisorek†; ***Austral.:*** Celebrex; ***Austria:*** Celebrex; Solexa; ***Belg.:*** Celebrex; ***Braz.:*** Celebra; ***Canad.:*** Celebrex; ***Chile:*** Celebra; ***Cz.:*** Celebrex; Onsenal; ***Denm.:*** Celebra; ***Fin.:*** Celebra; ***Fr.:*** Celebrex; Onsenal; ***Ger.:*** Celebrex; ***Gr.:*** Aclarex; Celebrex; ***Hong Kong:*** Celebrex; ***Hung.:*** Celebrex; ***India:*** Celedol; Celib; Cobix; Orthocel; Ultracele†; Zycel; ***Indon.:*** Celebrex; ***Irl.:*** Celebrex; ***Israel:*** Celcox; Celebra; ***Ital.:*** Artilog†; Celebrex; Solexa†; ***Malaysia:*** Celebrex; ***Mex.:*** Celebrex; ***Neth.:*** Celebrex; Onsenal; Solexa; ***Norw.:*** Celebra; Onsenal; ***NZ:*** Celebrex; ***Philipp.:*** Celebrex; Flamar; ***Pol.:*** Celebrex; ***Port.:*** Celebrex; Onsenal; Solexa; ***Rus.:*** Celebrex (Целебрекс); ***S.Afr.:*** Celebrex; ***Singapore:*** Celebrex; ***Spain:*** Celebrex; Onsenal; ***Swed.:*** Celebra; Onsenal; ***Switz.:*** Celebrex; ***Thai.:*** Celebrex; ***UK:*** Celebrex; ***USA:*** Celebrex; ***Venez.:*** Celebrex†; Cexb.

Choline Magnesium Trisalicylate

Trisalicilato de colina y magnesio.

Холин Магнезиум Трисалицилаты

$C_{26}H_{29}O_{10}NMg$ = 539.8.

CAS — 64425-90-7.

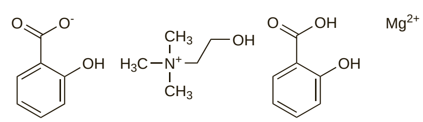

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

The use of aspirin and other acetylated salicylates is generally not recommended for children unless specifically indicated, because of the risk of Reye's syndrome. US licensing information extends this precaution to choline magnesium trisalicylate.

Effects on the liver. References.

1. Cersosimo RJ, Matthews SJ. Hepatotoxicity associated with choline magnesium trisalicylate: case report and review of salicylate-induced hepatotoxicity. *Drug Intell Clin Pharm* 1987; **21:** 621–5.
2. Nadkarni MM, *et al.* Eosinophilic hepatitis after ingestion of choline magnesium trisalicylate. *Am J Gastroenterol* 1992; **87:** 151–3.

Interactions

For interactions associated with salicylates, see Aspirin, p.23.

Uses and Administration

Choline magnesium trisalicylate is a combination of the salicylic acid derivatives choline salicylate (p.36) and magnesium salicylate (p.79). It has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p.23). After oral administration, choline magnesium trisalicylate dissociates and the salicylate moiety is rapidly absorbed. Each unit dose of 500 mg of salicylate is provided by about 293 mg of choline salicylate with 362 mg of magnesium salicylate (anhydrous). Choline magnesium trisalicylate has been used in osteoarthritis, rheumatoid arthritis, and other arthritides in oral doses equivalent to 1 or 1.5 g of salicylate twice daily; doses may also be given as a single daily dose if required. A dose of 750 mg given three times daily may be more suitable for elderly patients. Choline magnesium trisalicylate is also used in similar doses in the general management of other forms of pain and for fever.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Trilisate†; ***USA:*** Trilisate†.

Choline Salicylate *(BAN, USAN, rINN)*

Choline, Salicylate de; Cholini Salicylas; Koliinisalisylaatti; Kolinsalicylat; Salicilato de colina. (2-Hydroxyethyl)trimethylammonium salicylate.

Холина Салицилат

$C_{12}H_{19}NO_4$ = 241.3.

CAS — 2016-36-6.

ATC — N02BA03.

ATC Vet — QN02BA03.

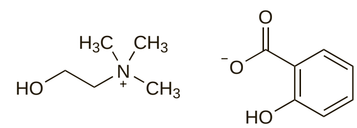

Pharmacopoeias. *Br.* includes a solution.

BP 2008 (Choline Salicylate Solution). An aqueous solution containing 47.5 to 52.5% of choline salicylate. It is a clear colourless liquid. It may contain a suitable antimicrobial preservative.

Profile

Choline salicylate is a salicylic acid derivative (see Aspirin, p.20) used in the treatment of pain and fever, and in the management of rheumatic disorders. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin. Choline salicylate is given orally in doses of 435 to 870 mg every four hours as necessary for pain and fever, and in doses of 4.8 to 7.2 g daily in divided doses for rheumatic disorders.

Choline salicylate is also used as a local analgesic. Solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa but are considered to be of doubtful value; they are also used to soften ear wax as an aid to removal (see p.1725). An 8.7% gel is used for lesions of the mouth (p.1700). Choline salicylate has also been applied topically in a rubefacient preparation for the relief of muscular and rheumatic pain.

Choline salicylate is also given in the form of choline magnesium trisalicylate (see above).

Adverse effects. A 21-month-old boy developed salicylate poisoning after his mother had rubbed the contents of 3 tubes of *Bonjela* teething ointment (containing a total of 2.61 g of choline salicylate) on his gums over 48 hours.[1]

In another case, an 8-year-old boy with G6PD deficiency developed an oral mucosal burn a few hours after application of about half a tube of *Teejel* oral gel.[2] He developed mouth ulcers and displayed signs of apathy, lethargy, and nasal congestion 3 days after exposure. His condition improved after a week. The authors felt that G6PD deficiency may have been a contributing factor in the occurrence of adverse effects.

1. Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. *Lancet* 1979; **ii:** 1132.
2. Sapir S, Bimstein E. Cholinsalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24:** 103–6.

REYE'S SYNDROME. The link between aspirin use in children and the development of Reye's syndrome is established although the evidence for other salicylates could not be adequately evaluated (see p.22). However, a 20-month-old boy who had received a teething gel containing choline salicylate (applied in doses of 1.31 g daily, equivalent to acetylsalicylate 100 mg/kg daily, which exceeds the recommended dose) developed Reye's syndrome following a viral illness.[1] The authors noted that the MHRA in the UK were aware of two earlier reports suggesting an association between choline salicylate and Reye's syndrome.

1. Oman TK, *et al.* Topical choline salicylates implicated in Reye's syndrome. *BMJ* 2008; **336:** 1376.

Preparations

BP 2008: Choline Salicylate Ear Drops; Choline Salicylate Oromucosal Gel.

Proprietary Preparations (details are given in Part 3)

Arg.: Dercolina; ***Austral.:*** Applicaine; Herron Baby Teething Gel; Ora-Sed Jel; ***Belg.:*** Teejel; ***Ger.:*** Audax†; ***Hong Kong:*** Ora-Sed; ***India:*** Gelora; Zytee; ***Irl.:*** Audax; Teejel; ***Israel:*** Teejel; ***NZ:*** Ora-Sed; ***Pol.:*** Cholinex; Otinum; ***Port.:*** Bucagel; ***Rus.:*** Otinum (Отинум); ***Singapore:*** Ora-Sed; ***UK:*** Audax†; Dinnefords Teejel†; ***USA:*** Arthropan†.

Multi-ingredient: ***Arg.:*** Pansoral; ***Austral.:*** Bonjela; Seda-Gel; ***Austria:*** Mundisal; ***Belg.:*** Givalex; ***Cz.:*** Mundisal; ***Fr.:*** Givalex; Pansoral; ***Ger.:*** Givalex†; Mundisal†; ***Gr.:*** Mundisal; ***Hong Kong:*** Bonjela; Dermojela; ***Hung.:*** Mundisal; ***Irl.:*** Bonjela; ***Israel:*** Baby Gum; Bonjela; ***Malaysia:*** Bonjela; Orregel; ***NZ:*** Bonjela; ***Pol.:*** Sachol zel Stomatologiczny; ***Rus.:*** Cholisal (Холисал); Pansoral (Пансорал); ***S.Afr.:*** Bonjela; ***Singapore:*** Bonjela; Soragel; ***Spain:*** Aldo Otico†; ***Switz.:*** Mundisal; Pansoral; Tenderdol; ***Thai.:*** Bonjela; ***UK:*** Bonjela; Earex Plus.

Clofexamide *(rINN)*

ANP-246; Clofexamida; Clofexamidum. 2-(4-Chlorophenoxy)-*N*-(2-diethylaminoethyl)acetamide.

Клофексамид

$C_{14}H_{21}ClN_2O_2$ = 284.8.

CAS — 1223-36-5.

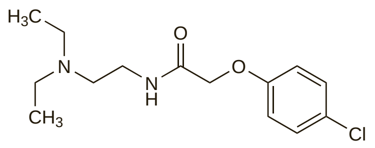

Profile

Clofexamide has been used topically as the hydrochloride in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clofezone *(rINN)*

ANP-3260; Clofezona; Clofézone; Clofezonum. An equimolar combination of clofexamide and phenylbutazone.

Клофезон

$C_{14}H_{21}ClN_2O_2,C_{19}H_{20}N_2O_2,2H_2O$ = 629.2.

CAS — 60104-29-2.

ATC — M01AA05; M02AA03.

ATC Vet — QM01AA05; QM02AA03.

Profile

Clofezone, a combination molecule containing clofexamide (above) and phenylbutazone (p.117), has been given orally and by rectal suppository and applied topically in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clonixin *(USAN, rINN)*

CBA-93626; Clonixine; Clonixino; Clonixinum; Sch-10304. 2-(3-Chloro-*o*-toluidino)nicotinic acid.

Клониксин

$C_{13}H_{11}ClN_2O_2$ = 262.7.

CAS — 17737-65-4.

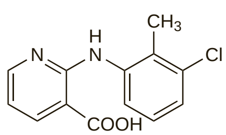

Clonixin Lysine *(rINNM)*

Clonixin Lysinate; Clonixine Lysine; Clonixino lisina; Clonixinum Lysinum; L-104; Lysine Clonixinate; R-173.

Клониксина Лизин

$C_{13}H_{11}ClN_2O_2$, $C_6H_{14}N_2O_2$ = 408.9.

CAS — 55837-30-4.

Profile

Clonixin is an NSAID (p.96). It has been used as the lysine salt in oral doses of up to 250 mg four times daily for the relief of pain. Clonixin lysine has also been given by intramuscular or intravenous injection and as a rectal suppository.

◊ References.

1. Eberhardt R, *et al.* Analgesic efficacy and tolerability of lysine-clonixinate versus ibuprofen in patients with gonarthrosis. *Curr Ther Res* 1995; **56:** 573–80.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Clonixil; Diclen; Dolex; Dolnot†; Dorixina; ***Braz.:*** Dolamin; ***Chile:*** Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon; Dolalgial†; Lafigesic; Medigesic; Nefersil; Traumicid; ***Mex.:*** Disinal; Donodol; Dorixina; Firac; Lonixer; Prestodol; Sedepron; ***Port.:*** Algimate; Clonix; ***Spain:*** Dolalgial; ***Venez.:*** Dorixina.

Multi-ingredient: ***Arg.:*** Amplibenzatin Bronquial; Aseptobron Ampicilinat†; Dorixina B1 B6 B12; Dorixina Forte; Dorixina Relax; Espasmo Dolex; Migra Dorixina; Mikesan; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; ***Braz.:*** Dolamin Flex; ***Chile:*** Clonalgin Compuesto; Ergonef; Migra-Nefersil; Nefersil B; Neurocam; ***Mex.:*** Donodol Compuesto; Espacil Compuesto; Firac Plus; Klonaza; Optium; Plidan Compuesto; Prestodol Compuesto; Yuredol; ***Venez.:*** Dologinex; Dorixina Flex; Migradorixina; Plidan Compuesto.

Codeine *(BAN)*

Codeína; Codéine; Codeinum; Codeinum Monohydricum; Kodeiini; Kodein; Kodein monohydrát; Kodeina; Kodeinas; Methylmorphine; Metilmorfina; Morphine Methyl Ether. 7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol monohydrate.

Кодеин

$C_{18}H_{21}NO_3,H_2O$ = 317.4.

CAS — 76-57-3 (anhydrous codeine); 6059-47-8 (codeine monohydrate).

ATC — R05DA04.

ATC Vet — QR05DA04.

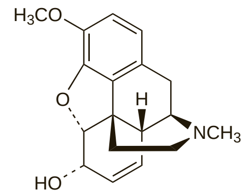

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of codeine:

AC/DC; Barr; Captain Cody; Cody; Coties; Cough Syrup; Down; Karo; Lean; Nods; School boy; Schoolboy; T3.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Codeine). White or almost white, crystalline powder or colourless crystals. Soluble in boiling water; freely soluble in alcohol. Protect from light.

USP 31 (Codeine). Colourless or white crystals or white crystalline powder. It effloresces slowly in dry air. Soluble 1 in 120 of water, 1 in 2 of alcohol, 1 in 0.5 of chloroform, and 1 in 50 of ether. Its saturated solution in water is alkaline to litmus. Store in airtight containers. Protect from light.

Codeine Hydrochloride *(BANM)*

Codeína, hidrocloruro de; Codéine (chlorhydrate de) dihydraté; Codeini hydrochloridum dihydricum; Kodeiinihydrokloridiidihydraatti; Kodein-hidroklorid-dihidrát; Kodein-hydrochlorid dihydrát; Kodeinhydrokloriddihydrat; Kodeino hidrochloridas dihidratas.

Кодеина Гидрохлорид

$C_{18}H_{21}NO_3,HCl,2H_2O$ = 371.9.

CAS — 1422-07-7 (anhydrous codeine hydrochloride).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Codeine Hydrochloride Dihydrate; Codeine Hydrochloride BP 2008). Small colourless crystals or a white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Protect from light.

Codeine Phosphate *(BANM)*

Codeína, fosfato de; Codéine, phosphate de; Codeine Phosphate Hemihydrate; Codeini phosphas; Codeini Phosphas Hemihydricus; Codeinii Phosphas; Kodeiinifosfaatti; Kodein-fosfát hemihydrát; Kodeinfosfathemi; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan półwodny; Methylmorphine Phosphate.

Кодеина Фосфат

$C_{18}H_{21}NO_3,H_3PO_4,\frac{1}{2}H_2O$ = 406.4.

CAS — 52-28-8 (anhydrous codeine phosphate); 41444-62-6 (codeine phosphate hemihydrate); 5913-76-8 (codeine phosphate sesquihydrate).

NOTE. Compounded preparations of codeine phosphate may be represented by the following names:

- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—codeine phosphate and paracetamol
- Co-codaprin (*BAN*)—codeine phosphate 1 part and aspirin 50 parts (w/w)
- Co-codaprin (*PEN*)—codeine phosphate and aspirin.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Pharmacopoeias may specify the hemihydrate, sesquihydrate, or both, either under one monograph or as separate monographs.

Ph. Eur. 6.2 (Codeine Phosphate Hemihydrate; Codeine Phosphate BP 2008). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble or very slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

Ph. Eur. 6.2 (Codeine Phosphate Sesquihydrate; Codeini Phosphas Sesquihydricus). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Codeine Phosphate). The hemihydrate occurs as fine, white, needle-shaped crystals or white crystalline powder; odourless. Soluble 1 in 2.5 of water, 1 in 0.5 of water at 80°, 1 in 325 of alcohol, and 1 in 125 of boiling alcohol. Its solutions are acid to litmus. Store in airtight containers at a temperature up to 40° as permitted by the manufacturer. Protect from light.

Incompatibility. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two drugs, even at a low moisture level.[1] *Animal* work suggested that the analgesic activity of codeine was not affected by acetylation.[2]

1. Galante RN, *et al.* Solid-state acetylation of codeine phosphate by aspirin. *J Pharm Sci* 1979; **68:** 1494–8.
2. Buckett WR, *et al.* The analgesic properties of some 14-substituted derivatives of codeine and codeinone. *J Pharm Pharmacol* 1964; **16:** 174–82.

Codeine Sulfate

Codeína, sulfato de; Codeine Sulphate *(BANM).*

Кодеина Сульфат

$(C_{18}H_{21}NO_3)_2,H_2SO_4,3H_2O$ = 750.9.

CAS — 1420-53-7 (anhydrous codeine sulfate); 6854-40-6 (codeine sulfate trihydrate).

Pharmacopoeias. In *US.*

USP 31 (Codeine Sulfate). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 30 of water, 1 in 6.5 of water at 80°, and 1 in 1300 of alcohol; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Codeine sulfate solutions appear to be intrinsically more stable than codeine phosphate solutions.[1]

1. Powell MF. Enhanced stability of codeine sulfate: effect of pH, buffer, and temperature on the degradation of codeine in aqueous solution. *J Pharm Sci* 1986; **75:** 901–3.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Codeine is subject to abuse (see under Precautions, below), but produces less euphoria and sedation than morphine.

Neonatal abstinence syndrome. Some of the symptoms characteristic of the neonatal abstinence syndrome were seen in a neonate whose mother had taken about 90 mg of codeine daily during the last 2 months of pregnancy.[1]

1. Khan K, Chang J. Neonatal abstinence syndrome due to codeine. *Arch Dis Child* 1997; **76:** F59–F60.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use. After large doses of codeine, excitement and convulsions may occur.

Codeine, like morphine, has a dose-related histamine-releasing effect. Anaphylactic reactions after intravenous use have been reported rarely.

Effects on mental function. Central effects of codeine phosphate appeared to be limited, but dose-related, in subjects given 30, 60, or 90 mg; visuo-motor coordination was altered with doses of 60 and 90 mg and dynamic visual acuity with 90 mg.[1] Drowsiness reported by subjects given 90 mg of codeine phosphate could not be linked with impaired performance whereas nausea could.

1. Bradley CM, Nicholson AN. Effects of a μ-opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man. *Br J Clin Pharmacol* 1986; **22:** 507–12.

Effects on the pancreas. A 26-year-old woman developed acute pancreatitis on 2 separate occasions a few hours after taking a single, 40-mg dose of codeine.[1] There was no history of alcohol consumption and her recovery was uneventful. Other cases have been reported.[2-5]

1. Hastier P, *et al.* Pancreatitis induced by codeine: a case report with positive rechallenge. *Gut* 1997; **41:** 705–6.
2. Locher C, *et al.* Pancréatite aiguë après la prise d'une association paracétamol-codéine. *Gastroenterol Clin Biol* 2003; **27:** 124–5.
3. Kohlen K, *et al.* Codein-induzierte Pankreatitis. *Dtsch Med Wochenschr* 2005; **130:** 878–9.
4. Moreno Escobosa MC, *et al.* Pancreatitis due to codeine. *Allergol Immunopathol (Madr)* 2005; **33:** 175–7.
5. Belhassen García M, *et al.* Pancreatitis secundaria a paracetamol-codeína. *An Med Interna* 2006; **23:** 400–401.

Effects on the skin. Pruritus and burning erythemato-vesicular plaques that developed in a patient in response to oral codeine were attributed to a fixed drug eruption.[1] A similar reaction occurred in another patient after taking various analgesics including a combined preparation of paracetamol and codeine;[2] patch testing showed a positive response for codeine only. Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate;[3] fever, splenomegaly, and lymphadenopathy also occurred.

1. Gonzalo-Garijo MA, Revenga-Arranz F. Fixed drug eruption due to codeine. *Br J Dermatol* 1996; **135:** 498–9.
2. Gastaminza G, *et al.* Erythrodermia caused by allergy to codeine. *Contact Dermatitis* 2005; **52:** 227–8.
3. Enomoto M, *et al.* Codeine phosphate-induced hypersensitivity syndrome. *Ann Pharmacother* 2004; **38:** 799–802.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Acute codeine intoxication in 430 children, due to accidental ingestion of antitussive preparations, was reviewed.[1] The children were nearly all between 1 and 6 years old. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting, itching, ataxia, and swelling of the skin. Respiratory failure occurred in 8 children and 2 died; all 8 had taken 5 mg/kg or more. Infants are at special risk and there have been fatalities[2,3] and severe adverse effects[4,5] after inappropriate treatment in infants given mixtures containing codeine.

Opioid toxicity, in addition to severe salicylate toxicity, has occurred in adults after overdoses of aspirin and codeine tablets.[6]

1. von Mühlendahl KE, *et al.* Codeine intoxication in childhood. *Lancet* 1976; **ii:** 303–5.
2. Ivey HH, Kattwinkel J. Danger of Actifed-C. *Pediatrics* 1976; **57:** 164–5.
3. Magnani B, Evans R. Codeine intoxication in the neonate. Abstract: *Pediatrics* 1999; **104:** 1379. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/6/e75 (accessed 26/06/08)
4. Wilkes TCR, *et al.* Apnoea in a 3-month-old baby prescribed compound linctus containing codeine. *Lancet* 1981; **i:** 1166–7.
5. Lee AC, *et al.* A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine. *Hong Kong Med J* 2004; **10:** 285–7.
6. Leslie PJ, *et al.* Opiate toxicity after self poisoning with aspirin and codeine. *BMJ* 1986; **292:** 96.

Precautions

As for Opioid Analgesics in general, p.103.

Abuse. Although the risk of dependence on codeine is low with normal use,[1] it is the subject of deliberate abuse. In France[2] and in the UK linctuses containing codeine have been particularly liable to abuse. Reports in the literature include the use in New Zealand of codeine-containing preparations to produce demethylated products known as "Homebake" containing variable amounts of morphine[3] and abuse of co-codaprin tablets for their codeine content.[4-6]

1. Rowden AM, Lopez JR. Codeine addiction. *DICP Ann Pharmacother* 1989; **23:** 475–7.
2. Armand C, *et al* 10 ans de détournement d'usage du Néocodion entre 1992 et 2002: Neocodion misuse: evolution between 1992 and 2002. *Therapie* 2004; **59:** 547–53.
3. Shaw JP. Drug misuse in New Zealand. *Pharm J* 1987; **238:** 607.
4. Sakol MS, Stark CR. Codeine abuse. *Lancet* 1989; **ii:** 1282.
5. Paterson JR, *et al.* Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.
6. Sakol MS, Stark CR. Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.

Breast feeding. Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultrarapid metaboliser of codeine. In a recent report,[1] a 13-day-old infant died from opioid toxicity after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30 mg twice daily as part of a combination preparation with paracetamol for about 2 weeks. Assayed morphine concentrations in the breast milk were found to be 87 nanograms/mL; the usual range is 1.9 to 20.5 nanograms/mL after repeated doses of codeine 60 mg four times daily. Subsequent investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 (the enzyme involved in the conversion of codeine to morphine) classified her as an ultrarapid metaboliser of codeine.

Based on this case, the FDA has advised[2] that nursing mothers taking codeine should be informed of the potential risk of morphine overdose and the need to monitor breast-fed infants for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Nursing mothers, themselves, may also experience overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation. Similar advice has also been issued by the MHRA in the UK.[3] Nonetheless, codeine appears to have been used safely for many years in breast-feeding mothers and several authorities including the American Academy of Pediatrics[4] and the *BNF* consider that it is usually compatible with breast feeding.

1. Koren G, *et al.* Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; **368:** 704.
2. FDA. Information for healthcare professional: use of codeine products in nursing mothers (issued 17th August, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm (accessed 26/06/08)
3. MHRA/CHM. Codeine: very rare risk of side-effects in breastfed babies. *Drug Safety Update* 2007; **1** (4): 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032917&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Children. See Overdosage, above, and under Uses and Administration, below.

Driving. Codeine phosphate 50 mg alone and with alcohol had a deleterious effect on driving skills in a simulated driving test.[1]

1. Linnoila M, Häkkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clin Pharmacol Ther* 1974; **15:** 368–73.

Genetic polymorphism. Life-threatening toxicity in a patient given moderate doses of codeine was thought to be due to a genotype predisposing him to ultrarapid metabolism of the drug into morphine by the cytochrome P450 isoenzyme CYP2D6, coupled with drug-induced inhibition of the usual major metabolic pathway mediated by CYP3A4, and transient reduction in renal function.[1] For a report of the effect of this genotype in a breast-feeding mother, see Breast Feeding, above.

1. Gasche Y, *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004; **351:** 2827–31. Correction. *ibid.* 2005; **352:** 638.

Pregnancy. See Neonatal Abstinence Syndrome under Dependence and Withdrawal, above.

Renal impairment. The renal clearance of codeine and its metabolites is significantly reduced in patients with end-stage renal disease on regular haemodialysis therapy. One such elderly patient developed tonic-clonic seizures 7 days after starting oral codeine phosphate 30 mg 4 times daily; no further seizures occurred after codeine was stopped and naloxone started.[1] The dosage of codeine should be reduced according to renal function in patients with renal impairment but no specific recommendations appear to be given in the literature.

1. Kuo S-C, *et al.* Probable codeine phosphate-induced seizures. *Ann Pharmacother* 2004; **38:** 1848–51.

Interactions

For interactions associated with opioid analgesics, see p.103.

Quinidine. For reference to a suggestion that quinidine can inhibit the analgesic effect of codeine, see Metabolism under Pharmacokinetics, below.

Pharmacokinetics

Codeine and its salts are absorbed from the gastrointestinal tract. Rectal absorption of codeine phosphate has been reported. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. Codeine is metabolised by *O*- and *N*-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

The plasma half-life has been reported to be between 3 and 4 hours after an oral or intramuscular dose.

Codeine crosses the placenta and is distributed into breast milk.

◊ References.

1. Guay DR, *et al.* Pharmacokinetics of codeine after single- and multiple-oral-dose administration to normal volunteers. *J Clin Pharmacol* 1987; **27:** 983–7.
2. Persson K, *et al.* The postoperative pharmacokinetics of codeine. *Eur J Clin Pharmacol* 1992; **42:** 663–6.
3. Lafolie P, *et al.* Urine and plasma pharmacokinetics of codeine in healthy volunteers: implications for drugs-of-abuse testing. *J Anal Toxicol* 1996; **20:** 541–6.
4. Kim I, *et al.* Plasma and oral fluid pharmacokinetics and pharmacodynamics after oral codeine administration. *Clin Chem* 2002; **48:** 1486–96.

Administration. In a comparative study[1] codeine had an oral/intramuscular analgesic relative potency ratio of 6:10. This was high compared with that of morphine and was attributed to protection from rapid first-pass metabolism rather than more efficient absorption after oral doses. In a comparative study in children[2] the absorption rate of codeine from a suppository was found to be similar to that from an intramuscular injection; however, peak plasma concentrations were not as high when given rectally.

1. Beaver WT, *et al.* Analgesic studies of codeine and oxycodone in patients with cancer I: comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J Pharmacol Exp Ther* 1978; **207:** 92–100.
2. McEwan A, *et al.* A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000; **10:** 189–93.

Metabolism. The analgesic effect of codeine may be partly due to its metabolite morphine and it has been suggested that its efficacy may be impaired in patients who are poor metabolisers of codeine[1-4] or in those who are also receiving drugs, such as quinidine, that impair its metabolism.[1] However, patients unable to demethylate codeine to produce detectable plasma concentrations of morphine obtained a similar analgesic effect to patients with detectable plasma morphine concentrations.[5] A study[6] involving infants aged 6 to 10 months has indicated that children were capable of demethylating codeine to morphine at the age of 6 months although glucuronidation of the morphine appeared to be impaired when compared with older children.

For a report of severe toxicity thought to be due to altered metabolism of codeine see Genetic Polymorphism, above.

1. Desmeules J, *et al.* Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; **41:** 23–6.
2. Chen ZR, *et al.* Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* 1991; **31:** 381–90.
3. Sindrup SH, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1991; **49:** 686–93.
4. Williams DG, *et al.* Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89:** 839–45.
5. Quiding H, *et al.* Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; **44:** 319–23.
6. Quiding H, *et al.* Infants and young children metabolise codeine to morphine: a study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992; **33:** 45–9.

Uses and Administration

Codeine, a phenanthrene derivative, is an opioid analgesic (p.104) obtained from opium or made by methylating morphine. It is much less potent as an analgesic than morphine and has relatively mild sedative effects.

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intramuscular or subcutaneous injection, in doses similar to those used orally, for the relief of pain; the intravenous and rectal routes have also been used.

For the relief of **pain** codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive **cough** codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of **acute diarrhoea** in doses of 15 to 60 mg given 3 or 4 times daily.

For details of doses in children, see below.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Administration in children. Licensed product information for codeine in the treatment of *pain* often restricts its use to those over 1 year of age, but some authorities consider codeine to be an effective analgesic in neonates and children.[1] In the UK, the *BNFC* suggests that neonates and children aged up to 12 years may be given codeine phosphate 0.5 to 1 mg/kg every 4 to 6 hours for mild to moderate pain up to the usual adult maximum dose of 240 mg daily; these doses can be given orally, rectally, or by the subcutaneous or intramuscular routes. Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of oral codeine as an alternative, or in addition, to diclofenac, for moderate pain such as that associated with small burns or scalds, finger tip injuries, or appendicitis. With a single dose of codeine phosphate 1 mg/kg given orally or by intramuscular injection there was a relatively small risk of respiratory depression in neonates, but significant respiratory depression has occurred with multiple doses and patients should be observed closely.[1] Case reports of adverse reactions such as vasodilatation, severe hypotension, and apnoea in infants and children after intravenous doses of codeine have precluded its use by this route in children of all ages.[3]

Antimotility drugs such as codeine should not be used in infants and young children with acute *diarrhoea*.[4,5]

The *BNFC* advises that *cough* suppressants containing pholcodine or similar opioids (such as codeine) are generally not recommended for children and should be avoided in those under 2 years of age. However, codeine phosphate is licensed to allay non-productive cough and children aged 1 to 5 years may be given 3 mg three or four times daily; and those aged 5 to 12 years, 7.5 to 15 mg three or four times daily.

Children and adolescents aged 12 years and over may be given the usual adult doses of codeine phosphate for all these indications (see above).

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.

2. British Association for Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in children (2004). Available at: http://www.emergencymed.org.uk/BAEM/CEC/assets/cec_pain_in_children.pdf (accessed 26/06/08)
3. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.
4. Anonymous. Drugs in the management of acute diarrhoea in infants and young children. *Bull WHO* 1989; **67:** 94–6.
5. Cimolai N, Carter JE. Antimotility agents for paediatric use. *Lancet* 1990; **336:** 874.

Administration in renal impairment. See under Precautions, above.

Cough. A systematic review[1] of over-the-counter preparations for acute cough concluded that codeine appeared no more effective than placebo in reducing cough symptoms in adults or children, although the number of patients in the studies considered was small.

See also Administration in Children, above.

1. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 26/06/08).

Pain. Systematic reviews[1,2] comparing paracetamol-codeine combinations versus paracetamol alone concluded that in single-dose studies addition of codeine to paracetamol produced a comparatively small but statistically significant increase in analgesic effect; however, there was an increased incidence of adverse effects with the combination.

1. de Craen AJM, *et al.* Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996; **313:** 321–5.
2. Moore A, *et al.* Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 26/06/08).

Preparations

BP 2008: Co-codamol Capsules; Co-codamol Tablets; Co-codaprin Tablets; Codeine Linctus; Codeine Phosphate Injection; Codeine Phosphate Oral Solution; Codeine Phosphate Tablets; Dispersible Co-codaprin Tablets; Effervescent Co-codamol Tablets; Paediatric Codeine Linctus;
USP 31: Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Aspirin and Codeine Phosphate Tablets; Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Codeine Phosphate Injection; Codeine Phosphate Tablets; Codeine Sulfate Tablets; Guaifenesin and Codeine Phosphate Syrup; Terpin Hydrate and Codeine Elixir.

Proprietary Preparations (details are given in Part 3)
Austral.: Actacode; ***Austria:*** Codipertussin; Codipront Mono; Coditard; Makatussin-Hustentropfen; Tricodein; ***Belg.:*** Bromophar; Bronchodine; Bronchosedal; Eulyptan†; Gloceda†; Glottyl; Toularynx; ***Canad.:*** Codeine Contin; ***Fr.:*** Codedrill; Codenfan; Neo-Codion; Paderyl; ***Ger.:*** Antitussivum Burger; Bronchicum Mono Codein; codi OPT; Codicaps mono; Codicaps N†; Codicaps Neo; Codicompren; Codipertussin; Codipront Mono†; Makatussin Codein; Melrosum Codein Hustensirup†; Neo-Codion NN†; Optipect Kodein; Tryasol; Tussoret; ***Gr.:*** Codipront N†; ***Hong Kong:*** Codipront N†; ***India:*** Codifos; ***Irl.:*** Codant; Codinex; ***Israel:*** Codical; Rekod; ***Malaysia:*** Setlinctus†; ***Neth.:*** Bronchicum Extra Sterk; ***Port.:*** Toseina; ***Rus.:*** Neo-Codion (Нео-Кодион); ***Spain:*** Bisoltus; Codeisan; Codulin; Fludan Codeina; Histaverin; Notusin; Perduretas Codeina; Toseina; ***Switz.:*** Makatussin nouvelle formule; Tricodein†; ***UK:*** Bepro; Galcodine; ***Venez.:*** Codipront Mono.

Multi-ingredient: numerous preparations are listed in Part 3.

Croton Oil

Aceite de crotón; Oleum Crotonis; Oleum Tiglii.
CAS — 8001-28-3.

Pharmacopoeias. *Chin.* includes fruits of *Croton tiglium.*

Profile

Croton oil is an oil expressed from the seeds of *Croton tiglium* (Euphorbiaceae). Externally, it is a powerful counter-irritant and vesicant. Croton oil is also used with phenol in cosmetic chemical peeling of the skin.

Croton oil has such a violent purgative action that it should not be used as a laxative. Croton oil contains phorbol esters, which are carcinogenic.

Homoeopathy. Croton has been used in homoeopathic medicines under the following names: Croton tiglium; Crot. tig.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Rheumalan†.

Devil's Claw Root

Djävulsklorot; Harpagofytový kořen; Harpagonjuuri; Harpagophyti radix; Harpagophyton; Harpagophyton, racine d'; Harpagophytum; Inkaruočių šaknys; Ördögcsáklya gyökér; Raíz de harpagofito; Teufelskrallenwurzel.
CAS — 19210-12-9 (harpagoside).

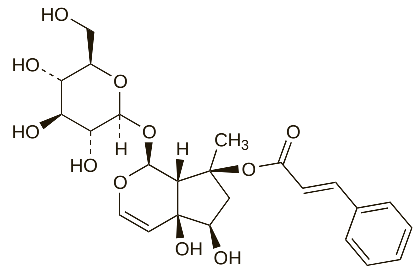

(harpagoside)

Pharmacopoeias. In *Eur.* (see p.vii), which also includes the dry extract.
Ph. Eur. 6.2 (Devil's Claw Root; Devil's Claw BP 2008). The cut and dried tuberous, secondary roots of *Harpagophytum procumbens* and/or *H. zeyheri*. Greyish-brown to dark brown with a bitter taste. Contains not less than 1.2% harpagoside ($C_{24}H_{30}O_{11}$ = 494.5), calculated with reference to the dried drug. Protect from light.

Profile

Devil's claw root is used in herbal remedies for musculoskeletal and joint disorders. Its activity is attributed in part to the plant's content of iridoid glycosides, notably harpagoside.

Pain. Preparations containing devil's claw root have been tried with some success in the treatment of musculoskeletal disorders such as low back pain and osteoarthritis. There is some evidence of efficacy for daily doses standardised to 50 to 100 mg harpagoside but the quality of reporting in trials is generally poor and further studies are needed to establish its place in therapy.[1,2]

1. Gagnier JJ, *et al.* Harpgophytum [sic] procumbens for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med* 2004; **4:** 13.
2. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Herbaccion Flex†; ***Braz.:*** Tenitrat; ***Fr.:*** Elusanes Harpagesic; Harpadol; Harpagocid; ***Ger.:*** Ajuta; Allya; Arthrosetten H; Arthrotabs; Bomarthros; Cefatec; Dolo-Arthrodynat†; Dolo-Arthrosetten H; Doloteffin; flexi-loges; Harpagoforte; HarpagoMega†; Harpagosan†; Herbadon†; Jucurba; Matai†; Pargo†; Rheuferm Phyto; Rheuma-Sern; Rivoltan; Sogoon; Teltonal; Teufelskralle; ***Pol.:*** Reumaphyt; ***Spain:*** Fitokey Harpagophytum; Harpagofito Orto; ***UK:*** Atrosan; Flexiherb.

Multi-ingredient: ***Austral.:*** Arthriforte; Arthritic Pain Herbal Formula 1; Bioglan Arthri Plus; Boswellia Compound; Devils Claw Plus; Extralife Arthri-Care; Guaiacum Complex†; Herbal Arthritis Formula†; Lifesystem Herbal Formula 1 Arthritic Aid†; Prost-1†; ***Belg.:*** Algi-Cool; ***Cz.:*** Antirevmaticky Caj; ***Fr.:*** Arkophytum†; ***Ger.:*** Dr Wiemanns Rheumatonikum; ***Ital.:*** Bodyguard; Cartago; Flodolor; Nevril; Pik Gel; Reumafort; ***Malaysia:*** Celery Plus†; ***Mex.:*** Rodan; ***Pol.:*** Reumaherb; ***Spain:*** Dolosul†; Natusor Harpagosinol†.

Dexibuprofen *(BAN, USAN, rINN)*

Deksibuprofeeni; Dexibuprofène; Dexibuprofeno; Dexibuprofenum; *S*-(+)-Ibuprofen.
Дексибупрофен
CAS — 51146-56-6.
ATC — M01AE14.
ATC Vet — QM01AE14.

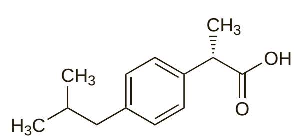

Profile

Dexibuprofen is the *S*(+)-enantiomer of ibuprofen (p.64) and is used similarly in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache, postoperative pain, dental pain, sprains, and soft-tissue rheumatism. It is also used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. It may be used as an antipyretic to reduce fever.

The usual adult dose is 600 to 900 mg daily by mouth in up to 3 divided doses, adjusted according to response, to a usual maximum of 1.2 g daily. Elderly patients should be started at the lower end of the dose range; dosage may then be increased according to tolerance. Dose reductions are also recommended in patients with hepatic or renal impairment, see below.

For doses in children, see below.

◊ References.

1. Phleps W. Overview on clinical data of dexibuprofen. *Clin Rheumatol* 2001; **20** (suppl 1): S15–S21.
2. Mayrhofer F. Efficacy and long-term safety of dexibuprofen [S(+)-ibuprofen]: a short-term efficacy study in patients with osteoarthritis of the hip and a 1-year tolerability study in patients with rheumatic disorders. *Clin Rheumatol* 2001; **20** (suppl 1): S22–S29.
3. Hawel R, *et al.* Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003; **41:** 153–64.

Administration in children. Although dexibuprofen is not licensed for use in children under 18 years of age in the UK, some countries permit such use. For example, in Switzerland, dexibuprofen has been given to children aged 6 years and over; usual oral doses are 10 to 15 mg/kg daily in 2 to 4 divided doses. Licensed product information for one preparation recommends a maximum dose of 300 mg daily for those weighing less than 30 kg.

Administration in hepatic and renal impairment. UK licensed product information specifies that the initial dose of dexibuprofen should be reduced in patients with mild to moderate hepatic or renal impairment; it should not be used in those with severe impairment.

Pharmacokinetics. For mention of the metabolism of dexibuprofen, see p.65.

Further references.

1. Eller N, *et al.* Pharmacokinetics of dexibuprofen administered as 200 mg and 400 mg film-coated tablets in healthy volunteers. *Int J Clin Pharmacol Ther* 1998; **36:** 414–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dextropirac†; Dolomin†; ***Austria:*** Actifen; Eu-Med Neu; Monactil; Movone; Seractil; ***Chile:*** Dexelle; ***Cz.:*** Seractil; ***Denm.:*** Seractiv; ***Fin.:*** Dexit; ***Ger.:*** Deltaran; ***Gr.:*** Seractil; ***Hung.:*** Seractil; ***India:*** Sibet; ***Ital.:*** Seractil; ***Neth.:*** Seractil; ***Norw.:*** Seractiv; ***Pol.:*** Dexprofen; Seractil; ***Port.:*** Seractil; ***Spain:*** Atriscal; Seractil; ***Swed.:*** Tradil; ***Switz.:*** DexOptifen; Seractil; ***UK:*** Seractil.

Dextromoramide *(BAN, pINN)* ⊗

Dekstromoramidi; Dextrodiphenopyrine; Dextromoramid; Dextromoramida; Dextromoramidum; *d*-Moramid; Pyrrolamidol. (+)-1-(3-Methyl-4-morpholino-2,2-diphenylbutyryl)pyrrolidine.
Декстроморамид
$C_{25}H_{32}N_2O_2$ = 392.5.
CAS — 357-56-2.
ATC — N02AC01.
ATC Vet — QN02AC01.

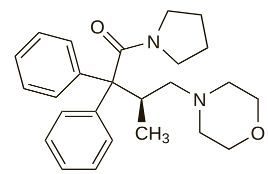

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextromoramide: Palf.

Dextromoramide Tartrate *(BANM, pINNM)* ⊗

Bitartrate de Dextromoramide; Dekstromoramiditartraatti; Dekstromoramido tartratas; Dextromoramide Acid Tartrate; Dextromoramide Hydrogen Tartrate; Dextromoramide, tartrate de; Dextromoramidi tartras; Dextromoramid-tartarát; Dextromoramidtartrat; Tartrato de dextromoramida.
Декстроморамида Тартрат
$C_{25}H_{32}N_2O_2,C_4H_6O_6$ = 542.6.
CAS — 2922-44-3.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dextromoramide Tartrate). A white or almost white, crystalline or amorphous powder. Soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 3.0 to 4.0.

Profile

Dextromoramide is an opioid analgesic (p.104) structurally related to methadone (p.82). It has been used in the treatment of severe pain although it was not recommended for use in obstetric analgesia because of an increased risk of neonatal depression. Dextromoramide is subject to abuse.

Dextromoramide has been given orally as the tartrate. It has also been given rectally as suppositories and by subcutaneous or intramuscular injection.

Preparations

BP 2008: Dextromoramide Tablets.

Proprietary Preparations (details are given in Part 3)
Irl.: Palfium; ***Neth.:*** Palface; Palfium.

Dextropropoxyphene *(BAN, pINN)*

Dekstropropoksifeeni; Dextropropoxifen; Dextropropoxifeno; Dextropropoxyphène; Dextropropoxyphenum; Propoxyphene. (+)-(1*S*,2*R*)-1-Benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate.

Декстропропоксифен

$C_{22}H_{29}NO_2$ = 339.5.

CAS — 469-62-5.

ATC — N02AC04.

ATC Vet — QN02AC04.

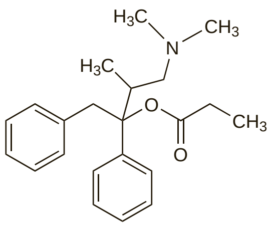

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextropropoxyphene: Dummies.

Dextropropoxyphene Hydrochloride

(BANM, pINNM)

Dekstropropoksifeenihydrokloridi; Dekstropropoksifeno hidrochloridas; Dextropropoxifén-hidroklorid; Dextropropoxifenhydroklorid; Dextropropoxyfen-hydrochlorid; Dextropropoxyphène, chlorhydrate de; Dextropropoxypheni hydrochloridum; Hidrocloruro de dextropropoxifeno; Propoxyphene Hydrochloride *(USAN)*.

Декстропропоксифена Гидрохлорид

$C_{22}H_{29}NO_2,HCl$ = 375.9.

CAS — 1639-60-7.

NOTE. Compounded preparations of dextropropoxyphene hydrochloride may be represented by the following names:

- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dextropropoxyphene Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Propoxyphene Hydrochloride). A white odourless crystalline powder. Freely soluble in water; soluble in alcohol, in acetone, and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers.

Dextropropoxyphene Napsilate *(BANM, pINNM)*

Dextropropoxyphène, Napsilate de; Dextropropoxyphene Napsylate; Dextropropoxypheni Napsilas; Napsilato de dextropropoxifeno; Propoxyphene Napsylate *(USAN)*. Dextropropoxyphene naphthalene-2-sulphonate monohydrate.

Декстропропоксифена Напсилат

$C_{22}H_{29}NO_2,C_{10}H_8O_3S,H_2O$ = 565.7.

CAS — 17140-78-2 (anhydrous dextropropoxyphene napsilate); 26570-10-5 (dextropropoxyphene napsilate monohydrate).

NOTE. Compounded preparations of dextropropoxyphene napsilate may be represented by the following names:

- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Dextropropoxyphene Napsilate). An odourless or almost odourless white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform.

USP 31 (Propoxyphene Napsylate). A white powder having essentially no odour. Very slightly soluble in water; soluble 1 in 15 of alcohol and 1 in 10 of chloroform; soluble in acetone and in methyl alcohol. Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dextropropoxyphene has been subject to abuse (see under Precautions, below).

◊ Reports of dextropropoxyphene dependence and its treatment.

1. Wall R, *et al.* Addiction to Distalgesic (dextropropoxyphene). *BMJ* 1980; **280:** 1213–14.
2. D'Abadie NB, Lenton JD. Propoxyphene dependence: problems in management. *South Med J* 1984; **77:** 299–301.

Adverse Effects

As for Opioid Analgesics in general, p.102.

In the recommended dosage the adverse effects of dextropropoxyphene are less marked than those of morphine. Gastrointestinal effects, dizziness, and drowsiness are the most common. Liver impairment, manifest as abnormal liver function tests and, more rarely, as reversible jaundice, has been reported.

There have been a large number of fatalities from either accidental or intentional overdosage with dextropropoxyphene. Many reports emphasise the rapidity with which death ensues; death within an hour of overdosage is not uncommon, and it can occur within 15 minutes. Overdosage is often complicated by patients also taking other CNS depressants such as alcohol and using mixed preparations such as dextropropoxyphene with paracetamol or aspirin.

Symptoms of overdosage are similar to those of opioid poisoning in general, but in addition patients may experience psychotic reactions. There may be cardiac conduction abnormalities and arrhythmias.

Dextropropoxyphene injections are painful and have a very destructive effect on soft tissues and veins when abused in this way.

Anorectal reactions have followed the prolonged use of suppositories containing dextropropoxyphene; the reactions appear to be dose dependent.

Effects on the blood. A 12-year history of haemolysis and subsequent significant haemolytic anaemia in an elderly woman[1] was associated with chronic, periodic, and occasionally excessive intake of co-proxamol.

1. Fulton JD, McGonigal G. Steroid responsive haemolytic anaemia due to dextropropoxyphene paracetamol combination. *J R Soc Med* 1989; **82:** 228.

Effects on the ears. A report of complete nerve deafness associated with chronic abuse of co-proxamol was made to the UK CSM.[1] The CSM had received 2 other reports of permanent hearing loss attributed to co-proxamol abuse; transient hearing loss had also been reported in 2 patients taking usual doses; 7 further reports described tinnitus.

1. Ramsay BC. Complete nerve deafness after abuse of co-proxamol. *Lancet* 1991; **338:** 446–7.

Effects on the liver. There have been occasional reports of jaundice in patients taking dextropropoxyphene alone but many of the 49 suspected hepatic reactions with dextropropoxyphene reported to the UK CSM by 1985[1] had involved use with paracetamol; clinical features including malaise, jaundice, raised serum transaminases, and sometimes fever, were however generally characteristic of dextropropoxyphene alone. Relapsing jaundice mimicking biliary disease was attributable to the dextropropoxyphene component of co-proxamol in 3 patients,[2] whereas there was no abnormality of liver function in 11 patients on long-term co-proxamol analgesia.[3] Another report of 9 cases found that the hepatotoxicity of dextropropoxyphene mimicked symptoms of large bile duct obstruction, and suggested that such toxicity might be misdiagnosed.[4] A more recent review[5] also concluded that hepatotoxicity with dextropropoxyphene might mimic a biliary tract disease, sometimes with few or no symptoms.

1. CSM. Hepatotoxicity with dextropropoxyphene. *Current Problems 17* 1986. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024424&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. Bassendine MF, *et al.* Dextropropoxyphene induced hepatotoxicity mimicking biliary tract disease. *Gut* 1986; **27:** 444–9.
3. Hutchinson DR, *et al.* Liver function in patients on long-term paracetamol (co-proxamol) analgesia. *J Pharm Pharmacol* 1986; **38:** 242–3.
4. Rosenberg WMC, *et al.* Dextropropoxyphene induced hepatotoxicity: a report of nine cases. *J Hepatol* 1993; **19:** 470–4.
5. Bergeron L, *et al.* Dextropropoxyphène et atteintes hépatiques: à propos de 4 cas et revue de littèrature. *Therapie* 2002; **57:** 464–72.

Effects on the lungs. Hypersensitivity pneumonitis and skin rash has been reported in a patient taking co-proxamol.[1] No such reaction occurred when the patient was subsequently given paracetamol alone.

1. Matusiewicz SP, *et al.* Hypersensitivity pneumonitis associated with co-proxamol (paracetamol + dextropropoxyphene) therapy. *Postgrad Med J* 1999; **75:** 475–6.

Hypoglycaemia. Hypoglycaemia has occasionally been reported with the use of dextropropoxyphene.[1-6]

1. Wiederholt IC, *et al.* Recurrent episodes of hypoglycemia induced by propoxyphene. *Neurology* 1967; **17:** 703–4.
2. Almirall J, *et al.* Propoxyphene-induced hypoglycemia in a patient with chronic renal failure. *Nephron* 1989; **53:** 273–5.
3. Laurent M, *et al.* Hypoglycémie sous dextropropoxyphène chez des grands vieillards: 7 cas. *Presse Med* 1991; **20:** 1628.
4. Lowenstein W, *et al.* Hypoglycémie au dextropropoxyphène: une urgence chez le toxicomane. *Presse Med* 1993; **22:** 133.
5. Santos Gil I, *et al.* Hipoglucemia secundaria a ingestión de dextropropoxifeno en un paciente adicto a drogas. *Med Clin (Barc)* 1998; **110:** 475–6.
6. Shah P, *et al.* Propoxyphene-induced hypoglycemia in renal failure. *Endocr Pract* 2006; **12:** 170–3.

Overdosage. There have been several reviews or retrospective studies of acute self-poisoning with dextropropoxyphene.[1-4] At a symposium on the safety and efficacy of dextropropoxyphene[5] many of the participants dealt with the problems of dextropropoxyphene overdosage, often in conjunction with paracetamol and sometimes with alcohol. Profound and even fatal CNS depression can develop rapidly as a result of the dextropropoxyphene content and in many cases death has occurred within an hour;[6] it was suggested that as few as 15 to 20 tablets of co-proxamol may be fatal.[7,8] Analysis of suicides involving drugs in England and Wales between 1997 and 1999 revealed that the odds of dying after overdose with co-proxamol were 2.3 times that for tricyclic antidepressant overdose, and 28.1 times greater than for paracetamol.[9] Another analysis of suicides due to poisoning in 3 areas of the UK between 2000 and 2001 identified 123 cases of fatal overdose with co-proxamol;[10] those who also consumed alcohol had generally taken fewer co-proxamol tablets than those who had not, emphasising the increased toxicity of the combination.

An analysis of overdosage involving combination analgesic preparations prescribed in Scotland between 2000 and 2002 also found that overdoses with co-proxamol were 10 times more likely to be fatal when compared with co-dydramol or co-codamol.[11] In the USA[12] the incidence of dextropropoxyphene-associated deaths reached a peak in 1977 and then fell at a rate that was not matched by a decline in prescribing.

It is not clear whether the metabolite, nordextropropoxyphene, plays an important role in fatalities.[12] However, nordextropropoxyphene, like dextropropoxyphene, is considered to have local anaesthetic activity and the membrane stabilising activity of dextropropoxyphene has been implicated as a major factor responsible for its severe cardiac depressant effect.[13]

In January 2005, the UK CSM found the risk of toxicity of co-proxamol in overdose to be unacceptable;[14] consequently, co-proxamol has been gradually withdrawn from the UK market. Fixed-dose combinations of dextropropoxyphene and paracetamol have also been withdrawn in several other countries including Sweden and Switzerland.

1. Young RJ. Dextropropoxyphene overdosage: pharmacological considerations and clinical management. *Drugs* 1983; **26:** 70–9.
2. Madsen PS, *et al.* Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand* 1984; **28:** 661–5.
3. Segest E. Poisoning with dextropropoxyphene in Denmark. *Hum Toxicol* 1987; **6:** 203–7.
4. Jonasson U, *et al.* Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings. *Forensic Sci Int* 1999; **103:** 125–32.
5. Bowen D, *et al.* (ed). Distalgesic; safety and efficacy. *Hum Toxicol* 1984; **3** (suppl): 1S–238S.
6. Proudfoot AT. Clinical features and management of Distalgesic overdose. *Hum Toxicol* 1984; **3** (suppl): 85S–94S.
7. Whittington RM. Dextropropoxyphene deaths: coroner's report. *Hum Toxicol* 1984; **3** (suppl): 175S–185S.
8. Young RJ, Lawson AAH. Distalgesic poisoning—cause for concern. *BMJ* 1980; **280:** 1045–7.
9. Hawton K, *et al.* Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. *BMJ* 2003; **326:** 1006–8.
10. Hawton K, *et al.* A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol* 2005; **59:** 207–12.
11. Afshari R, *et al.* Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol* 2005; **60:** 444–7.
12. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
13. Henry JA, Cassidy SL. Membrane stabilising activity: a major cause of fatal poisoning. *Lancet* 1986; **i:** 1414–17.
14. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)

Treatment of Adverse Effects

As for Opioid Analgesics in general, p.102.

Rapid treatment of overdosage with naloxone and assisted respiration is essential. Cardiac effects may not be reversed by naloxone. Gastric lavage and activated charcoal may be of value within 1 hour of ingestion, but dialysis is of little use.

Convulsions may require control with an anticonvulsant, bearing in mind that the CNS depressant effects of dextropropoxyphene can be exacerbated (see also Interactions, below). Stimulants should not be used because of the risk of inducing convulsions.

Patients taking overdoses of dextropropoxyphene with paracetamol will also require treatment for paracetamol poisoning (p.108). Mixtures of dextropropoxyphene and aspirin may be involved; the treatment of aspirin poisoning is described on p.20.

Precautions

As for Opioid Analgesics in general, p.103.

Abuse. There have been reports[1] of the abuse of dextropropoxyphene, and some[2] considered that the ready availability of dextropropoxyphene made it liable to abuse although it was a relatively weak opioid analgesic. However, others[3] thought there was no evidence that dextropropoxyphene was frequently associated with abuse, or concluded that, although there was abuse potential, it was of relatively low importance in terms of the community as a whole.[4]

A severe withdrawal syndrome has been reported[5] in an elderly patient who covertly consumed a daily dose of dextropropoxyphene of 1 to 3 g for at least 12 months. The patient was treated by a gradually decreasing dosage schedule of dextropropoxyphene over 9 weeks.

1. Tennant FS. Complications of propoxyphene abuse. *Arch Intern Med* 1973; **132:** 191–4.
2. Lader M. Abuse of weak opioid analgesics. *Hum Toxicol* 1984; **3** (suppl): 229S–36S.
3. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
4. Turner P. Final remarks. *Hum Toxicol* 1984; **3** (suppl): 237S–8S.
5. Hedenmalm K. A case of severe withdrawal syndrome due to dextropropoxyphene. *Ann Intern Med* 1995; **123:** 473.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving dextropropoxyphene, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of dextropropoxyphene in breast milk is too small to be harmful.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Porphyria. Dextropropoxyphene has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with opioid analgesics, see p.103.

Plasma concentrations of dextropropoxyphene are increased by ritonavir, with a resultant risk of toxicity; they should not be given together.

CNS depressants, including alcohol, may contribute to the hazards of dextropropoxyphene, see also Overdosage, above. The convulsant action of high doses of dextropropoxyphene may be enhanced by CNS stimulants.

Dextropropoxyphene interacts with several other drugs through inhibition of liver metabolism. Drugs reported to be affected include antidepressants (see p.379), benzodiazepines (see p.989), beta blockers (see p.1229), carbamazepine (see p.474), phenobarbital (see p.493), phenytoin (see p.497), and warfarin (see p.1427).

Antimuscarinics. A suggested interaction between *orphenadrine* and dextropropoxyphene has been questioned (see p.812).

Pharmacokinetics

Dextropropoxyphene is readily absorbed from the gastrointestinal tract, the napsilate tending to be more slowly absorbed than the hydrochloride, but both are subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 to 2.5 hours after ingestion. It is rapidly distributed and concentrated in the liver, lungs, and brain. About 80% of dextropropoxyphene and its metabolites are reported to be bound to plasma proteins. Dextropropoxyphene crosses the placenta. It has been detected in breast milk.

Dextropropoxyphene is *N*-demethylated to nordextropropoxyphene (norpropoxyphene) in the liver. It is excreted in the urine mainly as metabolites. It is now recognised that dextropropoxyphene and nordextropropoxyphene have prolonged elimination half-lives; values of 6 to 12 hours and 30 to 36 hours, respectively, have been reported. Accumulation of dextropropoxyphene and its metabolites may occur with repeated doses and nordextropropoxyphene may contribute to the toxicity seen with overdosage.

◊ Reviews.

1. Pearson RM. Pharmacokinetics of propoxyphene. *Hum Toxicol* 1984; **3** (suppl): 37S–40S.

The elderly. The elimination half-lives of dextropropoxyphene and its metabolite nordextropropoxyphene were prolonged in healthy elderly subjects when compared with young controls.[1] After multiple dosing median half-lives of dextropropoxyphene and nordextropropoxyphene were 36.8 and 41.8 hours, respectively in the elderly compared with 22.0 and 22.1 hours in the young subjects. In this study[1] there was a strong correlation between half-life of nordextropropoxyphene and estimated creatinine clearance.

1. Flanagan RJ, *et al.* Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989; **28:** 463–9.

Hepatic impairment. Plasma concentrations of dextropropoxyphene were higher in patients with cirrhosis given the drug than in healthy subjects whereas concentrations of nordextropropoxyphene were lower.[1]

1. Giacomini KM, *et al.* Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clin Pharmacol Ther* 1980; **28:** 417–24.

Renal impairment. Higher and more persistent plasma concentrations of dextropropoxyphene and nordextropropoxyphene in anephric patients when compared with healthy subjects[1] were attributed to decreased first-pass metabolism of dextropropoxyphene and decreased renal excretion of nordextropropoxyphene in the anephric patients.

1. Gibson TP, *et al.* Propoxyphene and norpropoxyphene plasma concentrations in the anephric patient. *Clin Pharmacol Ther* 1980; **27:** 665–70.

Uses and Administration

Dextropropoxyphene is an opioid analgesic (p.104) structurally related to methadone (p.82). It has mild analgesic activity and is given orally as the hydrochloride or napsilate to alleviate mild to moderate pain. Unlike the laevo-isomer (levopropoxyphene), dextropropoxyphene has little antitussive activity.

Dextropropoxyphene is mainly used with other analgesics that have anti-inflammatory and antipyretic effects, such as aspirin or paracetamol. In the USA the usual dose is 65 mg of the hydrochloride or 100 mg of the napsilate given every 4 hours up to a maximum total daily dose of 390 mg or 600 mg, respectively. In the UK similar doses have been given three or four times daily.

The combination preparation co-proxamol (dextropropoxyphene with paracetamol) has been gradually withdrawn from the UK market (see also Pain, below) although such combinations may remain available in a number of countries.

Pain. A detailed review[1] of the analgesic effectiveness of dextropropoxyphene suggested that with respect to single oral doses, recommended doses of dextropropoxyphene were no more (and probably less) effective than usual doses of paracetamol, aspirin, or other NSAIDs. However, the comparative effectiveness may vary substantially depending on the cause of the pain.

When it comes to comparative studies involving combinations of dextropropoxyphene with other analgesics, findings are even less clear-cut.[2] The effectiveness of co-proxamol has long been a matter of controversy yet despite this a survey[3] conducted in 30 UK teaching hospitals found that co-proxamol was the most widely used paracetamol-containing analgesic. It was suggested that the popularity of co-proxamol was purely down to prescribing habits passed on to new medical staff, rather than hard evidence regarding efficacy. This view has been refuted by others[4] who say that a large number of studies have shown clear analgesic effects for dextropropoxyphene. However, any assumption that the combination was widely used because it was more effective than paracetamol alone was not supported by a systematic overview of single-dose studies.[5] This concluded that while co-proxamol was indeed an effective analgesic it was no better than paracetamol alone. Although the evidence from this and other systematic reviews indicate that co-proxamol should be replaced by paracetamol alone for acute pain, the position for chronic use is considered to be not so clear (but see below).[6]

In January 2005, the UK CSM found the efficacy of co-proxamol to be poorly established and its risk of toxicity in overdose to be unacceptable;[7] they considered that there was no robust evidence of the superior efficacy of co-proxamol to full-strength paracetamol alone in either acute or chronic pain. Consequently, co-proxamol has been gradually withdrawn from the UK market. Fixed-dose combinations of dextropropoxyphene and paracetamol have also been withdrawn in several other countries including Sweden and Switzerland.

1. Beaver WT. Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review. *Hum Toxicol* 1984; **3** (suppl): 191S–220S.
2. Collins SL, *et al.* Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 26/06/08).
3. Haigh S. 12 Years on: co-proxamol revisited. *Lancet* 1996; **347:** 1840–1. Correction. *ibid.*; **348:** 346.
4. Sykes JV, *et al.* Coproxamol revisited. *Lancet* 1996; **348:** 408.
5. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997; **315:** 1565–71. Correction *ibid.* 1998; **316:** 116 and 656.
6. Anonymous. Co-proxamol or paracetamol for acute pain? *Drug Ther Bull* 1998; **36:** 80.
7. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)

Preparations

BP 2008: Co-proxamol Tablets; Dextropropoxyphene Capsules;
USP 31: Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Hydrochloride Capsules; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Acetaminophen Tablets; Propoxyphene Napsylate and Aspirin Tablets; Propoxyphene Napsylate Oral Suspension; Propoxyphene Napsylate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Gobbigesic; ***Austral.:*** Doloxene; ***Belg.:*** Depronal; ***Canad.:*** 642†; Darvon-N; ***Denm.:*** Abalgin; Doloxene; ***Fin.:*** Abalgin; ***Gr.:*** Romidon; Zideron; ***India:*** Parvodex; ***Irl.:*** Doloxene†; ***Ital.:*** Liberen†; ***Mex.:*** Darvon Simple; ***Neth.:*** Depronal; ***NZ:*** Doloxene†; ***S.Afr.:*** Doloxene; ***Spain:*** Darvon†; Deprancol; ***Swed.:*** Dexofen; Doloxene; ***USA:*** Darvon; Darvon-N.

Multi-ingredient: *Arg.:* Artifene; Calmopirin; Canovex†; D-P†; Dexprofeno; Dextro + Dipirona; Dextrodip; Dorixina Forte; Gobbicalm; Klosidol; Klosidol B1 B6 B12; Supragesic; Vicefeno; ***Austral.:*** Capadex; Di-Gesic; Paradex; ***Austria:*** APA; Contraforte†; Sigmalin B forte; ***Belg.:*** Algophene; Distalgic†; ***Braz.:*** Doloxene-A; ***Fin.:*** Paraflex comp†; ***Fr.:*** Dextroref; Di Dolko; Di-Antalvic; Diadupsan†; Dialgirex; Dioalgo; Propofan; ***Hong Kong:*** Cosalgesic; Distalgesic†; Dolocin; Dolpocetmol; Medonol; ***Hung.:*** Novopyrin; ***India:*** Buta-Proxyvon; Ibu-Proxyvon; Parvon; Parvon Forte; Parvon-N; Parvon-Spas; Proxytab; Proxyvon; Spasmo-Proxyvon; Spasmocip; Spasmocip Plus; Sudhinol; Walagesic†; Wygesic; ***Irl.:*** Distalgesic†; ***Israel:*** Algolysin; Proxol; Rogaan; ***Mex.:*** Darvon-N Compuesto†; Neo-Percodan; Qual; ***Norw.:*** Aporex; ***NZ:*** Apo-Paradex†; Capadex; Paradex; ***Port.:*** Algifene; ***S.Afr.:*** Distalgesic; Doloxene Co; Doxyfene; Lentogesic; Synap; ***Swed.:*** Distalgesic†; Doleron†; Paraflex comp†; ***Switz.:*** Distalgesic†; ***UK:*** Cosalgesic†; Distalgesic†; ***USA:*** Balacet; Darvocet; Darvocet-N; Darvon Compound†; PC-Cap; Propacet; Trycet; Wygesic†.

Diacerein *(rINN)*

Diacereína; Diacéréine; Diacereinum; Diacerhein; Diacetylrhein; 2,4-dichlorobenzylique, alcool; Rhein Diacetate; SF-277; SF-277. 9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthroic acid diacetate.

Диацереин

$C_{19}H_{12}O_8$ = 368.3.
CAS — 13739-02-1.
ATC — M01AX21.
ATC Vet — QM01AX21.

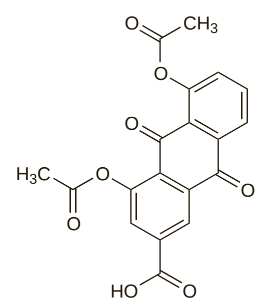

Profile

Diacerein is an anthraquinone derivative that is used in osteoarthritis (p.11) in oral doses of 50 mg twice daily. Doses should be halved in patients with creatinine clearance less than 30 mL/minute. Diarrhoea is a common adverse effect with diacerein. Its active metabolite, rhein, a constituent of rhubarb (p.1768), is reported to act as an interleukin-1 inhibitor.

Administration in renal impairment. See above and Pharmacokinetics, below.

Musculoskeletal and joint disorders. Diacerein is thought to act via inhibition of interleukin-1β,[1] which plays a role in inflammatory processes. Systematic reviews[2,3] on the use of diacerein in the treatment of osteoarthritis have indicated that diacerein produces a small, but consistent, improvement in pain. Further research is necessary to confirm its short- and long-term effectiveness and safety but there is some evidence of residual benefit on stopping treatment,[3] which has been postulated to represent an improvement in the disease process.

1. Van den Berg WB. Les mécanismes d'action de la diacerhéine, premier inhibiteur de l'interleukine 1 dans l'arthrose. *Presse Med* 2004; **33:** 10–12.
2. Fidelix TSA, *et al.* Diacerein for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 06/10/06).
3. Rintelen B, *et al.* A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 2006; **166:** 1899–1906.

Pharmacokinetics. References.

1. Debord P, *et al.* Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 13–19.
2. Nicolas P, *et al.* Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; **35:** 347–59.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Artrodar; Artroglobina†; ***Austria:*** Artrolyt; Verboril; ***Braz.:*** Artrodar; ***Chile:*** Artrizona; ***Cz.:*** Artrodar; ***Fr.:*** Art; Zondar; ***Gr.:*** Arthrofar; Arthrorein; Deserein; Diacer; Diaceril; Idealite; Inflabion; Myobloc; Ostirein; Pentacrin; Reumanisal; Verboril; ***Indon.:*** Artrodar; ***Israel:*** Art; Diatrim; ***Ital.:*** Fisiodar; ***Malaysia:*** Artrodar; ***Port.:*** Artrolyt; Cartivix; ***Spain:*** Galaxdar; Glizolan; ***Thai.:*** Artrodar; ***Venez.:*** Artrodar.

Multi-ingredient: *Mex.:* Dolocartigen.

Diamorphine Hydrochloride

(BANM) ⊗

Diacetilmorfina, hidrocloruro de; Diacetylmorphine Hydrochloride; Heroin Hydrochloride; Hidrocloruro de diamorfina; Hidrocloruro de heroína. 4,5-Epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate.

Героина Гидрохлорид; Диаморфина Гидрохлорид

$C_{21}H_{23}NO_5,HCl,H_2O = 423.9.$

CAS — 561-27-3 (diamorphine); 1502-95-0 (diamorphine hydrochloride).

ATC — N02AA09.

ATC Vet — QN02AA09.

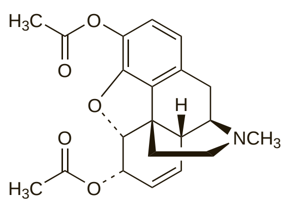

(diamorphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diamorphine:
57 Chevy; A Sidani; AIP; Al Capone; Amelia; Antifreeze; Aries; Aunt Hazel; Auntie Hazel; Aunty Hazel; Bacalhau; Bad bundle; Bad seed; Ball; Ballot; Bart Simpson; Batman; Beast; Big Bad Boy; Big bag; Big doodig; Big H; Big Harry; Bin laden; Bindle; Birdie powder; Black; Black Dragon; Black eagle; Black Girl; Black pearl; Black stuff; Black tar; Black tootsie roll; Blanche; Blanco; Blast; Bleue; Block busters; Blow; Blows; Blue bag; Blue hero; Blue star; Bobby Brown; Bomb; Bomba; Bombe; Bombido; Bombita; Bombitas; Bombs away; Bone; Bonita; Boy; Bozo; Brad; Brain damage; Brea; Brick gum; Broja; Brother; Brown; Brown crystal; Brown rhine; Brown sugar; Brown tape; Bugger; Bull dog; Bundle; Burra; Butu; Caballo; Caca; Calbo; Capital H; Caps; Captain Jack; Carga; Carne; Cavalo; Chang; Chapopote; Charley; Chatarra; Cheese; Cheva; Cheval; Chi; Chiba; Chick; Chicken; Chicle; Chieva; China cat; China white; Chinche; Chinese H; Chinese red; Chinese Rocks; Chinoise; Chip; Chiva; Chocofan; Choco-fan; Chueva; Chunks; Climax; Cocofan; Coffee; Cotics; Cotton Candy; Courage pills; Crank; Crap; Crop; Crown crap; Cura; Dead on arrival; Dead president; Deuce; Diesel; Diggidy; Dirt; DOA; Dog food; Doggee; Dogie; Doogie; Doojee; Dookey Rocks; Dooley; Doosey; Dope; Downtown; Dr. Feelgood; Dragon; Dreck; DT; Dugee; Dugie; Duji; Dujra; Dujre; Dust; Dyno; Dyno-pure; Eggs; Eight; Eighth; Elephant; Estuffa; Fachiva; Ferry dust; Fix; Flea powder; Foil; Foo foo stuff; Foolish powder; Furra; Galloping horse; Gallup; Gamot; Garbage; Gato; Gear; George; George smack; Ghost; Girl; Glacines; Glass; Goat; Gold; Golden Brown; Golden girl; Golpe; Goma; Good; Good H; Good Horse; Good and plenty; Goods; Goop; Grape Jolly Rancher; Gravy; Grey shields; H; H22; H-bomb; H Caps; Hache; Hair; Hairpiece; Hairy; Hammer; Hard candy; Hard stuff; Harriet Tubman; Harry; Harry Jones; Hayron; Hazel; Heaven; Heaven dust; Heavy stuff; Helen; Hell dust; Henry; Hera; Hero; Hero of the underworld; Heroa; Heroina; Heron; Herone; Hessle; Him; Holy terror; Hombre; Homebake; Homicide; Hong-yen; Hood; Hop; Horning; Horse; Horsebite; Hot dope; Hot heroin; HRN; Isda; Jack; Jee gee; Jerry Springer; Jesus; Jive; Jive doo jee; Joharito; Jojee; Jones; Joy; Joy dust; Joy flakes; Joy powder; Judas; Junco; Junk; Kabayo; Kaka Water; Karachi; Kermit the Frog; La Buena; La Chiva; Lady H; Layne; LBJ; Lemonade; Life saver; Little bomb; Man; Manteca; Matsakow; Mayo; Mexican Black Tar; Mexican brown; Mexican Dirt; Mexican horse; Mexican mud; Mister Brownstone; Mojo; Money talks; Monkey; Montego; Morse Code Features; Morotgara; Mortal combat; Mother pearl; Mr. Brownstone; Mud; Murotugora; Muzzle; Nanoo; Nice and easy; Nickel bag; Nickel deck; Nixon; Noddy Brown; Noise; Nose; Nose drops; Number 3; Number 4; Number 8; Nurse; Oddy Noddy; Of course my horse; Ogoy; Oil; Old garbage; Old navy; Old Steve; One way; Orange line; Outfit; Pack; Pakistanaise; Pako; Pangonadalot; Parachute; P-dope; Peg; Pepper; Perfect high; P-funk; Pluto; Po; Poeira; Poison; Polvo; Poppy; Poudre; Powder; Predator; Primo; Produto; Pulborn; Pure; Quill; Race horse Charlie; Racehorse Charlie; Ragweed; Rain; Rambo; Rane; Raw; Raw fusion; Raw hide; Raw Opportunities; Ready rock; Red chicken; Red devil; Red eagle; Red rock; Red rum; Reindeer dust; Rhine; Ring of Turd; Rob Flaherty; Rock; Rocks; Rush hour; Sack; Salt; Scag; Scat; Scate; Schmack; Schmeck; Schmeek; Scott; Scramble; Second to none; Shit; Shmeck; Shmeek; Shmek; Shoot; Silk; Skag; Skid; Skunk; Slack-dad-eat-your-heart-out; Slam; Sleeper; Sleepers; Slime; Slow; Sludge; Smack; Snotty; Snow; Spider; Spider blue; Stuff; Stunna; Sugar; Suicide; Sweet dreams; Sweet Jesus; Sweet stuff; Synthe; Tang; Tar; Taste; Tecata; Tecate; Thailandaise; Thanie; The beast; The fake throwdown; The Jack Bauer; The Loud-House Permadillo; The Nax; The witch; Thing; Thunder; Tiger; Tigre; Tigre Blanco; Tigre del Norte; Tits; TNT; T.N.T.; Tongs; Tootsie roll; Top drool; Train; Trash; Twin towers; Twists; Vidrio; Whack; Whicked; White; White Bitch; White boy; White dragon; White dynamite; White girl; White horse; White junk; White lady; White nurse; "White Pony"; White stuff; White Tiger; Wicked; Wings; Witch; Witch hazel; WTC; Zoquete.

Pharmacopoeias. In *Br.* and *Swiss. Swiss* also includes the anhydrous form.

BP 2008 (Diamorphine Hydrochloride). A white or almost white crystalline powder, odourless when freshly prepared but develops an odour characteristic of acetic acid on storage. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether. Protect from light.

Incompatibility. Diamorphine hydrochloride is incompatible with mineral acids and alkalis and with chlorocresol.[1]

The *BNF* notes that cyclizine may precipitate from mixtures with diamorphine hydrochloride at concentrations of cyclizine greater than 10 mg/mL, or in the presence of sodium chloride 0.9%, or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.

It also considers that mixtures of diamorphine and haloperidol are liable to precipitate after 24 hours if the haloperidol concentration is above 2 mg/mL. Under some conditions mixtures of metoclopramide and diamorphine may become discoloured and should be discarded.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.

Stability. Diamorphine is relatively unstable in aqueous solution and is hydrolysed to 6-*O*-monoacetylmorphine and then morphine to a significant extent at room temperature; 3-*O*-monoacetylmorphine is only occasionally detected. The rate of decomposition is at a minimum at about pH 4.[1,2]

In a study of the stability of aqueous solutions of diamorphine in chloroform water it was concluded that such solutions should be used within 3 weeks of preparation when stored at room temperature.[3] Another study[4] noted that the degradation products of diamorphine were not devoid of analgesic activity. Using a more sensitive analytical method it was reported that although the pH range of maximum stability of diamorphine in aqueous solution was 3.8 to 4.4, the addition of buffers reduced stability.[5] Simple unbuffered chloroform water gave maximum stability, the shelf-life of such a solution being 4 weeks at room temperature.

The BP 2008 recommends that solutions for injection be prepared immediately before use by dissolving Diamorphine Hydrochloride for Injection in Water for Injections. This may pose a problem with solutions for subcutaneous infusion when concentrated solutions may remain in infusion pump reservoirs for some time.[6] Investigation of 9 concentrations of diamorphine stored at 4 different temperatures for 8 weeks[7] revealed instability under conditions of concentration, time, and temperature prevalent during subcutaneous infusion. Degradation of diamorphine occurred at all concentrations (0.98 to 250 mg/mL) at temperatures of 4° and above; the effect of temperature was significant at 21° and 37°. The percentage fall in diamorphine concentration was directly related to initial concentration and was accompanied by a corresponding increase in 6-*O*-monoacetylmorphine and, to a lesser extent, morphine; other possible breakdown products such as 3-*O*-monoacetylmorphine were not present in detectable quantities. Diamorphine degradation was associated with a fall in pH and the development of a strong acetic acid-like odour. Precipitation and a white turbidity was seen in solutions of 15.6 mg/mL and above after incubation for 2 weeks at 21° and 37°. It has been noted that solutions for infusion are generally freshly prepared and used within 24 hours, but that signs of precipitation should be watched for, especially when using longer-term infusions and high concentrations of diamorphine.[7]

In another stability study[8] diamorphine hydrochloride in concentrations of both 1 and 20 mg/mL in sodium chloride 0.9% was stable for a minimum of 15 days at room temperature (23° to 25°) and 4° when stored in a PVC container. In one type of disposable infusion device (Infusor) similar solutions were stable for 15 days even at 31°. In another infusion device (Intermate 200) diamorphine was stable for a minimum of 15 days at both concentrations and all temperatures except for the 1 mg/mL solution kept at 31° when stability was only maintained for a minimum of 2 days. When stored in glass syringes both strengths of diamorphine hydrochloride were stable for 15 days at 4° and at room temperature the 1 mg/mL solution was stable for a minimum of 7 days and the 20 mg/mL solution was stable for a minimum of 12 days. There were no substantial changes in physical appearance or pH.

1. Davey EA, Murray JB. Hydrolysis of diamorphine in aqueous solutions. *Pharm J* 1969; **203:** 737.
2. Davey EA, Murray JB. Determination of diamorphine in the presence of its degradation products using gas liquid chromatography. *Pharm J* 1971; **207:** 167.
3. Cooper H, *et al.* Stability of diamorphine in chloroform water mixture. *Pharm J* 1981; **226:** 682–3.
4. Twycross RG. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 218.
5. Beaumont IM. Stability of diamorphine in chloroform water. *Pharm J* 1981; **227:** 41.
6. Jones VA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *Br J Clin Pharmacol* 1987; **23:** 651P.
7. Omar OA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; **41:** 275–7.
8. Kleinberg ML, *et al.* Stability of heroin hydrochloride in infusion devices and containers for intravenous administration. *Am J Hosp Pharm* 1990; **47:** 377–81.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Diamorphine is subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Diamorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, below).

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts. Nausea and hypotension are claimed to be less common than with morphine.

There are many reports of adverse effects associated with the abuse of diamorphine, usually obtained illicitly in an adulterated form.

Abuse. Most of the reports of adverse effects with diamorphine involve its abuse. In addition to the central effects, there are effects caused by the administration methods and by the adulterants.[1,2] Thus in many instances it is difficult to identify the factor causing the toxicity. Most body systems are involved including the immune system,[3] kidneys,[4,5] liver,[6] respiratory system,[7-10] and the nervous system.[11-16]

Other aspects of the illicit use of diamorphine include fatal overdose[17] and smuggling by swallowing packages of drug[18,19] or other methods of internal bodily concealment.

1. Hendrickse RG, *et al.* Aflatoxins and heroin. *BMJ* 1989; **299:** 492–3.
2. CDC. Atypical reactions associated with heroin use: five states, January–April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.*; 852.
3. Husby G, *et al.* Smooth muscle antibody in heroin addicts. *Ann Intern Med* 1975; **83:** 801–5.
4. Cunningham EE, *et al.* Heroin-associated nephropathy. *JAMA* 1983; **250:** 2935–6.
5. do Sameiro Faria M, *et al.* Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant* 2003; **18:** 2308–13.
6. Weller IVD, *et al.* Clinical, biochemical, serological, histological and ultrastructural features of liver disease in drug abusers. *Gut* 1984; **25:** 417–23.
7. Anderson K. Bronchospasm and intravenous street heroin. *Lancet* 1986; **i:** 1208.
8. Cygan J, *et al.* Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest* 2000; **117:** 272–5.
9. Boto de los Bueis A, *et al.* Bronchial hyperreactivity in patients who inhale heroin mixed with cocaine vaporized on aluminium foil. *Chest* 2002; **121:** 1223–30.
10. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest* 2001; **120:** 1628–32.
11. Sempere AP, *et al.* Spongiform leucoencephalopathy after inhaling heroin. *Lancet* 1991; **338:** 320.
12. Roulet Perez E, *et al.* Toxic leucoencephalopathy after heroin ingestion in a 2 ⁄ -year-old child. *Lancet* 1992; **340:** 729.
13. Zuckerman GB. Neurologic complications following intranasal administration of heroin in an adolescent. *Ann Pharmacother* 1996; **30:** 778–81.
14. Kriegstein AR, *et al.* Heroin inhalation and progressive spongiform leukoencephalopathy. *N Engl J Med* 1997; **336:** 589–90.
15. Long H, *et al.* A fatal case of spongiform leukoencephalopathy linked to "chasing the dragon". *J Toxicol Clin Toxicol* 2003; **41:** 887–91.
16. Dabby R, *et al.* Acute heroin-related neuropathy. *J Peripher Nerv Syst* 2006; **11:** 304–9.
17. Kintz P, *et al.* Toxicological data after heroin overdose. *Hum Toxicol* 1989; **8:** 487–9.
18. Stewart A, *et al.* Body packing—a case report and review of the literature. *Postgrad Med J* 1990; **66:** 659–61.
19. Traub SJ, *et al.* Pediatric "body packing". *Arch Pediatr Adolesc Med* 2003; **157:** 174–7.

Administration. Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous *subcutaneous* infusions.[1] Acute dysphoric reactions have been reported after the use of *epidural* diamorphine.[2]

1. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
2. Holder KJ, Morgan BM. Dysphoria after extradural diamorphine. *Br J Anaesth* 1994; **72:** 728.

Breast feeding. The American Academy of Pediatrics has stated[1] that, when used as a drug of abuse by breast-feeding mothers, diamorphine has caused adverse effects in the infant, notably tremors, restlessness, vomiting, and poor feeding. However, the *BNF* considers that diamorphine when given in therapeutic doses to a breast-feeding mother is unlikely to affect the breast-fed infant.

See also Opioid Dependence under Uses and Administration, below.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hypersensitivity. Anaphylaxis occurred in a patient given *intrathecal* diamorphine and bupivacaine for surgical anaesthesia;[1] the authors noted that the patient received patient-controlled analgesia with morphine shortly after the reaction without problem. Subsequent skin prick tests identified diamorphine as the likely causative agent.

1. Gooch I, Gwinnutt C. Anaphylaxis to intrathecal diamorphine. *Resuscitation* 2006; **70:** 470–3.

Phaeochromocytoma. Diamorphine can liberate endogenous histamine which may in turn stimulate release of catecholamines. Its use provoked hypertension and tachycardia in a patient with phaeochromocytoma.[1]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.

Pregnancy and the neonate. Some references to diamorphine dependence in pregnant women and the effects on the fetus and neonate.

1. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child* 1978; **132:** 360–6.
2. Ostrea EM, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 1979; **94:** 292–5.
3. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
4. Klenka HM. Babies born in a district general hospital to mothers taking heroin. *BMJ* 1986; **293:** 745–6.
5. Gregg JEM, *et al.* Inhaling heroin during pregnancy: effects on the baby. *BMJ* 1988; **296:** 754.
6. Little BB, *et al.* Maternal and fetal effects of heroin addiction during pregnancy. *J Reprod Med* 1990; **35:** 159–62.
7. Mur Sierra A, *et al.* Asociación entre el consumo de heroína durante la gestación y anomalías estructurales de los cilios respiratorios en el período neonatal. *An Esp Pediatr* 2001; **55:** 335–8.

Interactions

For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics

Diamorphine hydrochloride is well absorbed from the gastrointestinal tract, although this may be erratic, and after subcutaneous or intramuscular injection. On injection it is rapidly hydrolysed to the active metabolite 6-*O*-monoacetylmorphine (6-acetylmorphine) in the blood and then to morphine (p.88). Oral doses are subject to extensive first-pass metabolism to morphine; neither diamorphine nor 6-acetylmorphine have been detected in the blood after giving diamorphine by this route. Both diamorphine and 6-acetylmorphine readily cross the blood-brain barrier. Morphine glucuronides are the main excretion products in the urine. A small amount is excreted in the faeces.

◊ References.

1. Boerner U, *et al.* The metabolism of morphine and heroin in man. *Drug Metab Rev* 1975; **4:** 39–73.
2. Inturrisi CE, *et al.* The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984; **310:** 1213–17.
3. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
4. Barrett DA, *et al.* Morphine kinetics after diamorphine infusion in premature neonates. *Br J Clin Pharmacol* 1991; **32:** 31–7.
5. Girardin F, *et al.* Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. *Clin Pharmacol Ther* 2003; **74:** 341–52.

Administration. *INHALATIONAL ROUTE.* A literature review[1] found that intranasal diamorphine had a similar pharmacokinetic profile to that of intramuscular diamorphine. It is rapidly absorbed, as a dry powder, via the nasal mucosa although this is not as complete as by intramuscular injection; intranasal absorption appeared to be dose dependent.

The pharmacokinetics of inhaled diamorphine fumes ("chasing the dragon") has been studied[2] in diamorphine addicts receiving substitution therapy with diamorphine and methadone. Absorption through the lungs occurred very rapidly and was virtually complete immediately after inhalation; bioavailability was estimated to be about 53%.

1. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
2. Rook EJ, *et al.* Population pharmacokinetics of heroin and its major metabolites. *Clin Pharmacokinet* 2006; **45:** 401–17.

INTRASPINAL ROUTE. Diamorphine is much more lipid-soluble and has a more rapid onset and shorter duration of action than morphine. Although deacetylation to morphine occurs rapidly in the blood it occurs only slowly in the CSF after intraspinal injection of diamorphine.[1] After intrathecal injection diamorphine was removed from the CSF much more rapidly than morphine.[2] Peak plasma concentrations of morphine after epidural diamorphine injection were significantly higher and were achieved significantly faster than after epidural injection of morphine.[3]

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
3. Watson J, *et al.* Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesth Analg* 1984; **63:** 629–34.

Children. Loading doses of either 50 micrograms/kg or 200 micrograms/kg of diamorphine were given as an infusion over 30 minutes to 19 ventilated neonates followed by a continuous infusion of 15 micrograms/kg per hour, and the pharmacokinetics of the products of diamorphine metabolism (morphine, morphine-6-glucuronide, and morphine-3-glucuronide) studied.[1] Although the overall elimination of morphine was reduced compared with adults, the relative contributions of the various metabolic routes of morphine remained similar between neonates and adults. Data from this study did not indicate any advantage for the higher loading dose (see also under Uses and Administration, below).

1. Barrett DA, *et al.* Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996; **41:** 531–7.

Uses and Administration

Diamorphine hydrochloride is an acetylated morphine derivative and is a more potent opioid analgesic (p.104) than morphine (p.89). Diamorphine is used for the relief of severe pain especially in palliative care. It is also used similarly to morphine for the relief of dyspnoea due to pulmonary oedema resulting from left ventricular failure. Diamorphine has a powerful cough suppressant effect and has been given as Diamorphine Linctus (BPC 1973) to control cough associated with terminal lung cancer although morphine is now preferred.

In the treatment of **acute pain** usual doses of diamorphine hydrochloride by subcutaneous or intramuscular injection are 5 to 10 mg every 4 hours. Doses equivalent to one-quarter to one-half of the corresponding intramuscular dose may be given by slow intravenous injection.

For the pain of myocardial infarction doses of 5 mg are given by slow intravenous injection at a rate of 1 mg/minute with a further dose of 2.5 to 5 mg if required; doses may be reduced by one-half for elderly or frail patients. Doses of 2.5 to 5 mg may be given intravenously at the same rate for acute **pulmonary oedema**.

For **chronic pain** 5 to 10 mg may be given by subcutaneous or intramuscular injection every 4 hours; the dose may be increased according to needs. Similar doses may be given orally, although it is converted to morphine by first-pass metabolism (see Pharmacokinetics, above). Diamorphine hydrochloride may also be given by continuous subcutaneous or intravenous infusion or intraspinally.

For details of doses in children, see below.

Action. Because of its abuse potential, supply of diamorphine is carefully controlled and in many countries it is not available for clinical use; morphine can provide equivalent analgesia by dose adjustment. There has been much debate regarding the relative merits of analgesia with diamorphine or morphine. Many now regard oral morphine to be the opioid analgesic of choice although diamorphine hydrochloride may be preferred for injection because it is more soluble in water thus allowing the use of smaller dose volumes. Diamorphine hydrochloride may also be preferred to morphine salts for intraspinal use because it is more lipid-soluble.

As a guide to relative potency diamorphine hydrochloride 5 mg given intramuscularly is equivalent to about 10 mg given orally, which in turn is equivalent to about 15 mg of oral morphine sulfate. When given by subcutaneous infusion, diamorphine hydrochloride 10 mg every 24 hours is equivalent to about 15 mg every 24 hours of morphine sulfate.

Administration in children. In the treatment of acute or chronic pain in children, the *BNFC* suggests the following doses according to age:

by continuous intravenous infusion

- neonates with spontaneous respiration may be given 2.5 to 7 micrograms/kg per hour
- ventilated neonates may be given 50 micrograms/kg initially by intravenous injection over 30 minutes followed by 15 micrograms/kg per hour by continuous intravenous infusion
- 1 month to 12 years, 12.5 to 25 micrograms/kg per hour

by intravenous injection

- 1 to 3 months, 20 micrograms/kg every 6 hours if necessary
- 3 to 6 months, 25 to 50 micrograms/kg every 6 hours if necessary
- 6 to 12 months, 75 micrograms/kg every 4 hours if necessary
- 1 to 12 years, 75 to 100 micrograms/kg every 4 hours if necessary

by mouth

- 1 month to 12 years, 100 to 200 micrograms/kg (maximum of 10 mg) every 4 hours if necessary

In a study[1] of the effects of diamorphine in 34 premature infants (gestational age 26 to 40 weeks), a loading dose of 50 micrograms/kg given as an *intravenous* infusion over 30 minutes followed by a continuous infusion at a rate of 15 micrograms/kg per hour was considered to be safe and resulted in plasma concentrations of morphine comparable with those that usually produce adequate analgesia in children and adults; the duration of the infusion ranged from 14 to 149 hours. Small but significant reductions in heart rate and mean blood pressure were noted but these were not associated with any clinical deterioration. The fall in respiration rate reflected the desired intention to encourage synchronisation of the infants' breathing with the ventilator. The authors concluded that intravenous diamorphine could be given safely to neonates and would provide adequate analgesia. A later study[2] indicated that the use of a 200 micrograms/kg loading dose conferred no benefit over a 50 micrograms/kg dose and might produce undesirable physiological effects. In a comparative study[3] with morphine (200 micrograms/kg loading dose over 2 hours, followed by maintenance infusion of 25 micrograms/kg per hour) in ventilated preterm neonates requiring sedation, diamorphine (120 micrograms/kg over 2 hours and then 15 micrograms/kg per hour) was as effective as morphine in producing sedation and also had a faster onset of action. The small but significant drop in blood pressure noted during morphine infusions was not seen with diamorphine infusions.

The *subcutaneous* route appeared to be as effective and safe as the intravenous route for infusions in children for postoperative pain relief after elective abdominal surgery.[4] The dose of diamorphine used in both groups of children was 1 mg/kg given at a rate of 20 micrograms/kg per hour.

Intranasal diamorphine has been investigated in adults and children, and appears to be effective and well tolerated; because it does not require a needle it may offer particular advantages in children.[5] Guidelines[6] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intranasal diamorphine for severe pain such as that associated with large burns, long bone dislocation, appendicitis, or sickle-cell crisis. A suggested dose to be instilled into one nostril is 100 micrograms/kg given in 0.2 mL of sterile water.

1. Elias-Jones AC, *et al.* Diamorphine infusion in the preterm neonate. *Arch Dis Child* 1991; **66:** 1155–7.
2. Barker DP, *et al.* Randomised, double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants. *Arch Dis Child* 1995; **73:** F22–F26.
3. Wood CM, *et al.* Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F34–F39.
4. Semple D, *et al.* Comparison of iv and sc diamorphine infusions for the treatment of acute pain in children. *Br J Anaesth* 1996; **76:** 310–12.
5. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42:** 501–13.
6. British Association for Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in children (2004). Available at: http://www.emergencymed.org.uk/BAEM/CEC/assets/cec_pain_in_children.pdf (accessed 26/06/08)

Opioid dependence. The treatment of opioid dependence is discussed on p.101. Many opiate misusers have expressed a preference for withdrawal using diamorphine rather than methadone. In a comparative study stabilisation was achieved using either diamorphine or methadone 1 mg/mL oral solutions;[1] patients could not identify which they had been given. Whenever signs of physical withdrawal were seen 10 mL of either solution was given and the total amount over the first 24 hours taken as the patient's daily requirement. The mean dose of diamorphine required for stabilisation was 55 mg compared with 36 mg for methadone. Some centres have given diamorphine in the form of reefers. Diamorphine has also been prescribed with methadone in the management of addicts.[2] A systematic review[3] that included this study failed to produce conclusive results about the effectiveness of diamorphine (alone or with methadone) in maintenance treatment; however, since the studies were not directly comparable, continued evaluation in clinical studies is required. Oral tablets[4] and intravenous injection[5] of diamorphine have also been tried in severely dependent, treatment-resistant patients.

Breast feeding has been used to treat diamorphine dependence in the offspring of dependent mothers but this is no longer considered to be the best method and some authorities recommend that breast feeding should be stopped.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. van den Brink W, *et al.* Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Abridged version: *BMJ* 2003; **327:** 310–12. Correction. *ibid.*; 724. Full version: http://www.bmj.com/cgi/reprint/327/7410/310 (accessed 26/06/08)
3. Ferri M, *et al.* Heroin maintenance for chronic heroin dependents. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 26/06/08).
4. Frick U, *et al.* A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. *Addiction* 2006; **101:** 1631–9.
5. March JC, *et al.* Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 2006; **31:** 203–11.

Pain. *ACUTE PAIN.* Rapid pain relief may be obtained with the intravenous injection of diamorphine. Other routes include the intraspinal route for which diamorphine is well suited because of its lipid solubility and pharmacokinetics. Epidural doses of diamorphine have ranged from 0.5 to 10 mg.[1] Analgesia was significantly more prolonged and more intense after epidural rather than intramuscular injection of diamorphine 5 mg in women who had had caesarean section;[2] itching was reported by 50% of patients undergoing epidural analgesia. Epidural diamorphine alone[3] or with bupivacaine[4] has been used for analgesia during labour; addition of adrenaline appeared to improve the quality and duration of analgesia with diamorphine.[3] In another study addition of diamorphine to bupivacaine produced a high incidence of pruritus and drowsiness.[5] A study[6] of patient-controlled analgesia for postoperative pain found that although epidural diamorphine, used alone or with bupivacaine, reduced the analgesic dose requirement, there was little clinical advantage over the subcutaneous route.

Continuous epidural infusion of diamorphine 500 micrograms/hour in 0.125% bupivacaine provided postoperative analgesia superior to that with either drug alone in patients undergoing major abdominal gynaecological surgery.[7] A similar infusion produced analgesia superior to that with either epidural bolus injection or patient-controlled intravenous diamorphine in patients undergoing total abdominal hysterectomy.[8] However, more patients receiving the continuous epidural infusion were hypoxaemic than in the other 2 groups.

Diamorphine has also been given intrathecally for postoperative analgesia and should be effective at lower doses than with the epidural route because of greater CSF concentrations. Diamorphine 250 or 500 micrograms given intrathecally with bupivacaine spinal anaesthesia both provided greater postoperative analgesia than bupivacaine alone,[9] but the incidence of adverse effects, especially nausea, vomiting, and urinary retention, was still high with either dose and routine use of this technique was not recommended. Intrathecal diamorphine with bupivacaine has also been used for analgesia during labour[10,11] and caesarean section.[12-16] In a study[12] in patients undergoing caesarean section, intrathecal diamorphine 250 micrograms showed comparable postoperative analgesia with a 5-mg epidural dose and was associated with less postoperative nausea and vomiting. Other studies[13,14] found that intrathecal diamorphine reduced supplemental analgesic requirements during and after caesarean section when compared with intrathecal fentanyl. Intrathecal diamorphine 400 micrograms was considered by some[15] to be the lowest dose required to reduce intraoperative analgesic supplementation to below 5%; however, lower doses of 300 micrograms have been used in practice.[16]

Diamorphine has been extensively used by cardiologists in the UK for the management of pain in acute left ventricular failure, unstable angina, and myocardial infarction. It has been theorised that diamorphine may offer benefits over morphine because its stimulatory effects at opioid δ receptors on the myocardium may reduce the extent of myocardial damage.[17] Evidence to support this theory is, however, lacking.

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Macrae DJ, *et al.* Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and im diamorphine following caesarean section. *Br J Anaesth* 1987; **59:** 354–9.
3. Keenan GMA, *et al.* Extradural diamorphine with adrenaline in labour: comparison with diamorphine and bupivacaine. *Br J Anaesth* 1991; **66:** 242–6.
4. McGrady EM, *et al.* Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989; **44:** 400–3.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Gopinathan C, *et al.* A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17:** 189–96.
7. Lee A, *et al.* Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60:** 845–50.
8. Madej TH, *et al.* Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; **69:** 554–7.
9. Reay BA, *et al.* Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *Br J Anaesth* 1989; **62:** 248–52.
10. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
11. Vaughan DJA, *et al.* Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine. *Br J Anaesth* 2001; **86:** 567–9.
12. Hallworth SP, *et al.* Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82:** 228–32.
13. Cowan CM, *et al.* Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89:** 452–8.
14. Lane S, *et al.* A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60:** 453–7.
15. Saravanan S, *et al.* Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. *Br J Anaesth* 2003; **91:** 368–72.
16. Wrench IJ, *et al.* Dose response to intrathecal diamorphine for elective caesarean section and compliance with a national audit standard. *Int J Obstet Anesth* 2007; **16:** 17–21.
17. Poullis M. Diamorphine and British cardiology: so we are right! *Heart* 1999; **82:** 645–6.

CHRONIC PAIN. Patients with chronic opioid-sensitive pain are often treated with diamorphine given by continuous subcutaneous infusion using a small battery-operated syringe driver. The following technique has been described.[1] Diamorphine hydrochloride 1 g could be dissolved in 1.6 mL of water to give a solution with a volume of 2.4 mL (415 mg/mL), but the maximum suggested concentration was 250 mg/mL. If the analgesic requirement was not known the following protocol was recommended:

- Start injections every 4 hours of 2.5 or 5 mg diamorphine, or, if the patient has already been taking opioids, a dose that is equivalent to the last dose
- If this is unsatisfactory increase this dose in 50% increments until the patient reports even a little pain relief
- Calculate the 24-hour requirement by multiplying by six, and start the infusion at this level
- Increase the 24-hour dosage in the pump by 50% increments until the pain is controlled. Note that requirements may vary from less than 20 mg to more than 5 g per 24 hours

When starting an infusion it is important not to allow any breakthrough pain. This may be achieved either by starting the infusion more than 2 hours before the previous oral dose wears off or by giving a loading dose injection of the 4-hourly requirement.

Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous subcutaneous infusions.[2]

The intraspinal[3] and intraventricular[4] routes have also been used successfully in patients with intractable pain. Topical application of diamorphine has also been tried[5,6] for the control of pressure ulcer pain in a small number of palliative care patients.

1. Dover SB. Syringe driver in terminal care. *BMJ* 1987; **294:** 553–5.
2. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
3. Baker L, *et al.* Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; **18:** 507–15.
4. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; **65:** 544–7.
5. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25:** 547–54.
6. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage* 2004; **28:** 532–4.

Preparations

BP 2008: Diamorphine Injection;
BPC 1973: Diamorphine Linctus.

Proprietary Preparations (details are given in Part 3)
Switz.: Diaphin.

Diclofenac *(BAN, rINN)*

Diclofénac; Diclofenaco; Diclofenacum; Diklofenaakki; Diklofenak. [2-(2,6-Dichloroanilino)phenyl]acetic acid.

Диклофенак

$C_{14}H_{11}Cl_2NO_2$ = 296.1.
CAS — 15307-86-5.
ATC — D11AX18; M01AB05; M02AA15; S01BC03.
ATC Vet — QD11AX18; QM01AB05; QM02AA15; QS01BC03.

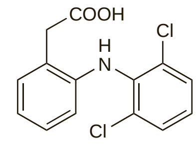

Diclofenac Diethylamine *(BANM)*

Diclofenac Diethylammonium; Diclofenaco dietilamina; Diklofenak Dietilamonyum.

Диклофенак Диэтиламин

$C_{18}H_{22}Cl_2N_2O_2$ = 369.3.
CAS — 78213-16-8.
ATC — D11AX18.
ATC Vet — QD11AX18.

Pharmacopoeias. In *Br.*

BP 2008 (Diclofenac Diethylamine). A white to light beige, crystalline powder. Sparingly soluble in water and in acetone; freely soluble in alcohol and in methyl alcohol; practically insoluble in 1M sodium hydroxide. The pH of a 1% solution in alcohol (10%) is between 6.4 and 8.4. Store in airtight containers. Protect from light.

Diclofenac Epolamine

DHEP; Diclofenac Hydroxyethylpyrrolidine.

Диклофенак Эполамин

$C_{14}H_{11}Cl_2NO_2,C_6H_{13}NO$ = 411.3.
CAS — 119623-66-4.
ATC — D11AX18.
ATC Vet — QD11AX18.

Diclofenac Potassium *(BANM, USAN, rINNM)*

CGP-45840B; Diclofénac potassique; Diclofenaco potásico; Diclofenacum kalicum; Diklofenaakkikalium; Diklofenak draselná sůl; Diklofenak Potasyum; Diklofenakkalium; Diklofenák-kálium; Diklofenako kalio druska; Kalii Diclofenacum. Potassium [o-(2,6-dichloroanilino)phenyl]acetate.

Калия Диклофенак

$C_{14}H_{10}Cl_2KNO_2$ = 334.2.
CAS — 15307-81-0.
ATC — D11AX18.
ATC Vet — QD11AX18.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Diclofenac Potassium). A white or slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Potassium). pH of a 1% solution in water is between 7.0 and 8.5. Store at a temperature of 20° to 25°. Protect from light.

Diclofenac Sodium *(BANM, USAN, rINNM)*

Diclofénac sodique; Diclofenaco sódico; Diclofenacum natricum; Diclophenac Sodium; Diklofenaakkinatrium; Diklofenak sodná sůl; Diklofenak Sodyum; Diklofenaknatrium; Diklofenák-nátrium; Diklofenako natrio druska; GP-45840; Natrii Diclofenacum. Sodium [2-(2,6-dichloroanilino)phenyl]acetate.

Натрий Диклофенак

$C_{14}H_{10}Cl_2NNaO_2$ = 318.1.
CAS — 15307-79-6.
ATC — D11AX18.
ATC Vet — QD11AX18.

NOTE. DICL is a code approved by the BP 2008 for use on single unit doses of eye drops containing diclofenac sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Diclofenac Sodium). A white to slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Sodium). A white to off-white, hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

There may be pain and, occasionally, tissue damage at the site of injection when diclofenac is given intramuscularly. Diclofenac suppositories can cause local irritation. Transient burning and stinging may occur with diclofenac ophthalmic solution; more serious corneal adverse effects have also occurred (see Effects on the Eyes, below). Topical preparations of diclofenac, such as plasters and gel, may cause application site reactions.

Incidence of adverse effects. A review of worldwide clinical studies with diclofenac[1] has reported the incidence of drug-associated adverse effects to be about 12%; about 16% of patients who had adverse effects stopped treatment (a figure corresponding to about 2% of the entire patient sample). The most frequently reported adverse effects were gastrointestinal and were reported in 7.6% of patients. CNS-related adverse effects were reported in 0.7% of patients and allergy or local reactions in 0.4%. This and other reviews[2] have shown that adverse effects associated with diclofenac are usually mild and transient and appear to be unrelated to the dose given.

1. Willkens RF. Worldwide clinical safety experience with diclofenac. *Semin Arthritis Rheum* 1985; **15** (suppl 1): 105–10.
2. Small RE. Diclofenac sodium. *Clin Pharm* 1989; **8:** 545–8.

Effects on the blood. Results of a large survey undertaken to assess the relation between agranulocytosis, aplastic anaemia, and drug exposure indicated that diclofenac was significantly associated with aplastic anaemia, providing an estimated tenfold increase in risk.[1] There are reports of other haematological abnormalities including haemolytic anaemia,[2,3] thrombocytopenia,[4,5] neutropenia,[5] and agranulocytosis[6] occurring in patients given diclofenac.

Localised spontaneous bleeding,[7] bruising,[8] inhibition of platelet aggregation,[7] and prolonged bleeding time[8] have been reported.

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. López A, *et al.* Autoimmune hemolytic anemia induced by diclofenac. *Ann Pharmacother* 1995; **29:** 787.
3. Ahrens N, *et al.* Misdiagnosis in patients with diclofenac-induced hemolysis: new cases and a concise review. *Am J Hematol* 2006; **81:** 128–31.
4. George S, Rahi AHS. Thrombocytopenia associated with diclofenac therapy. *Am J Health-Syst Pharm* 1995; **52:** 420–1.
5. Kim HL, Kovacs MJ. Diclofenac-associated thrombocytopenia and neutropenia. *Ann Pharmacother* 1995; **29:** 713–15.
6. Colomina P, Garcia S. Agranulocytosis caused by diclofenac. *DICP Ann Pharmacother* 1989; **23:** 507.
7. Price AJ, Obeid D. Spontaneous non-gastrointestinal bleeding associated with diclofenac. *Lancet* 1989; **ii:** 1520.
8. Khazan U, *et al.* Diclofenac sodium and bruising. *Ann Intern Med* 1990; **112:** 472–3.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including diclofenac, see p.96.

Effects on electrolytes. A syndrome resembling the syndrome of inappropriate antidiuretic hormone secretion has been reported in elderly women given diclofenac.[1,2] Also the UK CSM had received a report of fatal hyponatraemia in another elderly woman.[2]

1. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
2. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.

Effects on the eyes. A patient who had been taking oral diclofenac for several years and had increasingly complained of dry, gritty eyes noticed that eye irritation disappeared within 3 days when diclofenac had to be stopped because of gastrointestinal effects.[1]

Ocular diclofenac and related drugs have been implicated in reports of corneal toxicity. Ulceration of the conjunctiva or cornea, corneal or scleral melts, and perforations have been reported in patients using diclofenac eye drops, particularly after cataract surgery.[2-5] Keratitis and perforations were also reported with ketorolac eye drops,[4] although less frequently. For mention of corneal melting with bromfenac, see p.28.

1. Reid ALA, Henderson R. Diclofenac and dry, irritable eyes. *Med J Aust* 1994; **160:** 308.
2. Lin JC, *et al.* Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000; **118:** 1129–32.
3. Congdon NG, *et al.* Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2001; **27:** 622–31.
4. Guidera AC, *et al.* Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology* 2001; **108:** 936–44.
5. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc* 2001; **99:** 205–10.

Effects on the gastrointestinal tract. The most frequent adverse effects reported in patients given diclofenac systemically are gastrointestinal in nature. Typical reactions include epigastric pain, nausea, vomiting, and diarrhoea. Rarely peptic ulcer and gastrointestinal bleeding have occurred. Diclofenac has also been implicated as the causative agent in colonic ulceration,[1] small bowel perforation,[2] and pseudomembranous colitis.[3] Diclofenac suppositories may cause local reactions such as itching, burning, or exacerbation of haemorrhoids.

1. Carson J, *et al.* Colonic ulceration and bleeding during diclofenac therapy. *N Engl J Med* 1990; **323:** 135.
2. Deakin M, *et al.* Small bowel perforation associated with an excessive dose of slow release diclofenac sodium. *BMJ* 1988; **297:** 488–9.
3. Gentric A, Pennec YL. Diclofenac-induced pseudomembranous colitis. *Lancet* 1992; **340:** 126–7.

Effects on the kidneys. Renal papillary necrosis[1] and nephrotic syndrome[2-4] have been reported in patients taking diclofenac. See also Effects on Electrolytes, above.

1. Scott SJ, *et al.* Renal papillary necrosis associated with diclofenac sodium. *BMJ* 1986; **292:** 1050.
2. Beun GDM, *et al.* Isolated minimal change nephropathy associated with diclofenac. *BMJ* 1987; **295:** 182–3.
3. Yinnon AM, *et al.* Nephrotic syndrome associated with diclofenac sodium. *BMJ* 1987; **295:** 556.
4. Tattersall J, *et al.* Membranous nephropathy associated with diclofenac. *Postgrad Med J* 1992; **68:** 392–3.

Effects on the liver. Elevations of serum aminotransferase activity and clinical hepatitis,[1-8] including fatal fulminant hepatitis[2,5] have occurred in patients taking diclofenac. There has also been a case report of hepato-renal damage attributed to diclofenac.[9] Analysis[10] of 180 of the cases of diclofenac-associated hepatic injury received by the FDA between November 1988 and June 1991 suggested an increased risk of hepatotoxicity in female patients and those taking diclofenac for osteoarthritis. Hepatotoxicity had been detected within 6 months of starting diclofenac in 85% of the patients. The biochemical pattern of injury was hepatocellular or mixed hepatocellular in 66% of patients and cholestatic injury was found in 8% of patients. Signs of hypersensitivity were uncommon and it was considered that the mechanism of hepatic injury was likely to be a metabolic idiosyncratic reaction rather than due to intrinsic toxicity of diclofenac.

1. Dunk AA, *et al.* Diclofenac hepatitis. *BMJ* 1982; **284:** 1605–6.
2. Breen EG, *et al.* Fatal hepatitis associated with diclofenac. *Gut* 1986; **27:** 1390–3.
3. Schapira D, *et al.* Diclofenac-induced hepatotoxicity. *Postgrad Med J* 1986; **62:** 63–5.
4. Ryley NG, *et al.* Diclofenac associated hepatitis. *Gut* 1989; **30:** A708.
5. Helfgott SM, *et al.* Diclofenac-associated hepatotoxicity. *JAMA* 1990; **264:** 2660–2.
6. Purcell P, *et al.* Diclofenac hepatitis. *Gut* 1991; **32:** 1381–5.
7. Bhogaraju A, *et al.* Diclofenac-associated hepatitis. *South Med J* 1999; **92:** 711–13.
8. Greaves RRSH, *et al.* Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol* 2001; **13:** 71–3.
9. Diggory P, *et al.* Renal and hepatic impairment in association with diclofenac administration. *Postgrad Med J* 1989; **64:** 507–8.
10. Banks AT, *et al.* Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22:** 820–7.

Effects on the skin. Self-limiting skin reactions such as rash or pruritus may occur in patients given diclofenac. More serious skin reactions attributed to diclofenac include bullous dermatitis[1] and erythema multiforme.[2,3] Local irritation and necrosis has occurred on intramuscular injection of diclofenac.[4-7]

1. Gabrielsen TØ, *et al.* Drug-induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol (Stockh)* 1981; **61:** 439–41.
2. Morris BAP, Remtulla SS. Erythema multiforme major following use of diclofenac. *Can Med Assoc J* 1985; **133:** 665.
3. Young J. Erythema multiforme-like eruption as a result of 'Solaraze' treatment. *J Dermatol Treat* 2003; **14:** 189.
4. Stricker BHC, van Kasteren BJ. Diclofenac-induced isolated myonecrosis and the Nicolau syndrome. *Ann Intern Med* 1992; **117:** 1058.
5. Pillans PI, O'Connor N. Tissue necrosis and necrotising fasciitis after intramuscular administration of diclofenac. *Ann Pharmacother* 1995; **29:** 264–6.
6. Ezzedine K, *et al.* Nicolau syndrome following diclofenac administration. *Br J Dermatol* 2004; **150:** 385–7.
7. Mutalik S, Belgaumkar V. Nicolau syndrome: a report of 2 cases. *J Drugs Dermatol* 2006; **5:** 377–8.

Hypersensitivity. Aspirin-sensitive asthmatic patients have developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) when challenged with diclofenac in doses of 10 to 25 mg[1] and the UK CSM has received a report of an aspirin-sensitive patient who died from acute asthma 4 hours after a single 25-mg dose of diclofenac.[2]

Anaphylactic shock has been reported.[3]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. CSM/MCA. Avoid all NSAIDs in aspirin-sensitive patients. *Current Problems* 1993; **19:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
3. Dux S, *et al.* Anaphylactic shock induced by diclofenac. *BMJ* 1983; **286:** 1861.

Precautions

As for NSAIDs in general, p.98. Systemic diclofenac is contra-indicated in patients with severe hepatic or renal impairment.

In addition, use of intravenous diclofenac is contra-indicated in patients with moderate or severe renal impairment, hypovolaemia, or dehydration; it should also not be given intravenously in patients with a history of haemorrhagic diathesis, cerebrovascular bleeding (including suspected), or asthma nor in patients undergoing surgery with a high risk of haemorrhage.

Ophthalmic preparations containing diclofenac should not be used by patients who wear soft contact lenses.

Breast feeding. Diclofenac is distributed into breast milk although the *BNF* and some licensed product information consider the amount to be too small to be harmful to breast-fed infants.

Porphyria. Diclofenac sodium has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Veterinary use. Veterinary use of diclofenac in cattle in South Asia has been associated with severe decline in the numbers of vultures, to whom the residues are highly toxic if they consume the carcasses.[1,2] Meloxicam (p.80) has been suggested as an alternative.

1. Shultz S, *et al.* Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. *Proc Biol Sci* 2004; **271** (suppl 6): S458–S460.
2. Sharp D. Meloxicam to prevent rabies? *Lancet* 2006; **367:** 887–8.

Interactions

For interactions associated with NSAIDs, see p.99.

Diclofenac should not be given intravenously to patients already receiving other NSAIDs or anticoagulants including low-dose heparin.

Ciclosporin. Deterioration in renal function has been attributed to the use of diclofenac with ciclosporin.[1] Increased concentrations of diclofenac were also noted with ciclosporin;[2] licensed product information for ciclosporin recommends that the dosage of diclofenac should be reduced by about one-half when the two are given together.

1. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.
2. Kovarik JM, *et al.* Cyclosporine and nonsteroidal antiinflammatory drugs: exploring potential drug interactions and their implications for the treatment of rheumatoid arthritis. *J Clin Pharmacol* 1997; **37:** 336–43.

Diuretics. Deterioration in renal function has been attributed to the use of diclofenac with *triamterene*.[1]

1. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293:** 698–9.

Gastrointestinal drugs. A decrease in the plasma concentration of diclofenac has been reported[1] when given after *sucralfate*.

1. Pedrazzoli J, *et al.* Short-term sucralfate administration alters potassium diclofenac absorption in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 104–108.

Lipid regulating drugs. *Colestyramine* appears substantially to reduce the bioavailability of diclofenac when the two drugs are given together;[1] *colestipol* produces a similar but smaller effect.

1. al-Balla SR, *et al.* The effects of cholestyramine and colestipol on the absorption of diclofenac in man. *Int J Clin Pharmacol Ther* 1994; **32:** 441–5.

Misoprostol. The plasma concentration of diclofenac was reduced when it was given as a 100-mg dose daily in the form of a modified-release preparation to subjects receiving misoprostol 800 micrograms daily.[1] Use together was also associated with an increase in the incidence and severity of gastrointestinal effects. Studies by the manufacturer[2] had failed to find any significant pharmacokinetic interactions between diclofenac and misoprostol when given in a formulation containing diclofenac 50 mg and misoprostol 200 micrograms.

1. Dammann HG, *et al.* Differential effects of misoprostol and ranitidine on the pharmacokinetics of diclofenac and gastrointestinal symptoms. *Br J Clin Pharmacol* 1993; **36:** 345–9.
2. Karim A. Pharmacokinetics of diclofenac and misoprostol when administered alone or as a combination product. *Drugs* 1993; **45** (suppl 1): 7–14.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Diclofenac is rapidly absorbed when given as an oral solution, sugar-coated tablets, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although diclofenac given orally is almost completely absorbed, it is subject to first-pass metabolism so that about 50% of the drug reaches the systemic circulation in the unchanged form. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may persist even when plasma concentrations fall; small amounts are distributed into breast milk. The terminal plasma half-life is about 1 to 2 hours. Diclofenac is metabolised to 4′-hydroxydiclofenac, 5-hydroxydiclofenac, 3′-hydroxydiclofenac and 4′,5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulfate conjugates, mainly in the urine (about 60%) but also in the bile (about 35%); less than 1% is excreted as unchanged diclofenac.

◊ References.

1. Fowler PD, *et al.* Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol* 1983; **25:** 389–94.
2. Maggi CA, *et al.* Comparative bioavailability of diclofenac hydroxyethylpyrrolidine vs diclofenac sodium in man. *Eur J Clin Pharmacol* 1990; **38:** 207–8.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac: therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33:** 184–213.
4. Brenner SS, *et al.* Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet* 2003; **42:** 283–92.
5. Hinz B, *et al.* Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* 2005; **59:** 80–4.

Uses and Administration

Diclofenac, a phenylacetic acid derivative, is an NSAID (p.99). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, migraine, and after some surgical procedures. It has also been used in some countries for the management of actinic keratoses and fever. Eye drops of diclofenac sodium are used for the prevention of intra-operative miosis during cataract extraction, for the treatment of inflammation after surgery or laser treatment of the eye, for pain in corneal epithelial defects after surgery or accidental trauma, and for the relief of ocular signs and symptoms of seasonal allergic conjunctivitis.

The usual **oral** or **rectal** dose of diclofenac sodium is 75 to 150 mg daily in divided doses. In the UK the maximum dose regardless of route or indication is 150 mg daily; however, in the USA a maximum oral dose of 200 mg daily is allowed in the treatment of rheumatoid arthritis. Modified-release preparations of diclofenac sodium are available for oral use. Diclofenac has also been given in equivalent oral doses as the free acid in dispersible preparations for short-term treatment up to 3 months long. Diclofenac is also given orally as the potassium salt. Doses of the potassium salt are similar to those for diclofenac sodium. Diclofenac potassium is also used in the treatment of migraine in an initial dose of 50 mg taken at the first signs of an attack; an additional dose of 50 mg may be taken after 2 hours if symptoms persist. If necessary further doses of 50 mg may be taken every 4 to 6 hours to a maximum daily dose of 200 mg.

Diclofenac sodium may also be given by deep intramuscular **injection** into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. Diclofenac sodium may also be given as a continuous or intermittent intravenous infusion in glucose 5% or sodium chloride 0.9% (both previously buffered with sodium bicarbonate) or as a bolus intravenous injection.. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes or as a bolus injection. The dose may be repeated once after 4 to 6 hours if necessary. To prevent postoperative pain, an initial dose of 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. Alternatively, the initial dose may be given as a bolus injection over 5 to 60 seconds followed by additional injections up to the maximum daily dosage; this may be repeated after 4 to 6 hours if necessary although the *total* dose should not exceed the maximum daily dose of 150 mg. The maximum period recommended for parenteral use is 2 days. Diclofenac sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

For dosage details in children see below.

Diclofenac sodium is used as a 0.1% **ophthalmic solution** in a number of situations:

- for the prevention of intra-operative miosis during cataract surgery, it is instilled in the appropriate eye 4 times during the 2 hours before surgery
- for the treatment of postoperative inflammation after cataract surgery, it is instilled 4 times daily for up to 28 days starting 24 hours after surgery
- for the control of post-photorefractive keratectomy pain, it is instilled twice in the hour before surgery, then one drop twice at 5-minute intervals immediately after the procedure, and then every 2 to 5 hours while awake for up to 24 hours
- for pain control after accidental trauma one drop is instilled 4 times daily for up to 2 days
- in the treatment of inflammation and discomfort after strabismus surgery one drop is instilled 4 times daily for the first week; this is reduced to 3 times daily in the second week, twice daily in the third week, and as required for the fourth week
- for the control of inflammation after argon laser trabeculoplasty one drop is instilled 4 times during the 2 hours before the procedure followed by one drop 4 times daily for up to 7 days after the procedure
- for the treatment of pain and discomfort after radial keratotomy one drop is instilled before surgery followed by one drop immediately after surgery and then one drop 4 times daily for up to 2 days
- to relieve symptoms of seasonal allergic conjunctivitis one drop is instilled 4 times daily as necessary

Diclofenac diethylamine is used **topically** as a gel containing the equivalent of 1% of diclofenac sodium for the local symptomatic relief of pain and inflammation; it is applied to the affected site 3 or 4 times daily; treatment should be reviewed after 14 days or after 28 days if used for osteoarthritis. A topical solution of diclofenac sodium 1.6% is also available for the treatment of osteoarthritis in superficial joints such as the wrist or knee; it is applied in small aliquots to achieve a total of 20 or 40 drops, depending on the size of the joint, and repeated four times daily. Diclofenac is also used in the management of actinic keratoses; it is applied twice daily as diclofenac sodium gel 3% for 60 to 90 days but the optimum therapeutic effect may not be seen until 30 days after the end of treatment. Diclofenac epolamine is also used topically as a plaster containing the equivalent of 1% of diclofenac sodium for local symptomatic pain relief in ankle sprain and epicondylitis. In the treatment of ankle sprain, 1 plaster is applied once daily for a maximum of 3 days and for epicondylitis, 1 plaster is applied twice daily for a maximum of 14 days.

Diclofenac is available in combination with misoprostol (see p.2013) for patients at risk of NSAID-induced peptic ulceration.

Administration. ***IN CHILDREN.*** In children 1 to 12 years old the licensed UK *oral* or *rectal* dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses. In children 6 to 12 years old diclofenac sodium may also be given rectally for the treatment of acute postoperative pain, either alone or as an adjunct to opiate therapy; a usual dose is 1 to 2 mg/kg daily in divided doses for a maximum of 4 days. The *parenteral route* is not licensed for use in children although it has been used (see below).

The *BNFC* suggests slightly different doses of diclofenac sodium: in the management of rheumatic disease, including juvenile idiopathic arthritis, in children from 6 months of age, it recommends an oral dose of 3 to 5 mg/kg daily, in 2 or 3 divided doses, up to a maximum of 150 mg daily. For relief of pain and inflammation in, for example, soft-tissue disorders, the recommended oral or rectal dose in children from 6 months of age is 0.3 to 1 mg/kg given three times daily; children 2 years of age and older may be given a similar dose once or twice daily *by intravenous infusion* or *deep intramuscular (gluteal) injection* instead, for up to 2 days. Again, a maximum daily dose of 150 mg should not be exceeded.

Diclofenac potassium has also been used in children aged over 14 years for the treatment of rheumatic disease, musculoskeletal disorders, and postoperative pain; it is given in an *oral* dose of 75 to 100 mg daily in 2 to 3 divided doses.

TOPICAL. References to the use of plasters providing sustained topical release of diclofenac epolamine,[1-6] and a systematic review of the use of a topical solution of diclofenac with dimethyl sulfoxide to treat osteoarthritis.[7] The latter was found to be effective and better tolerated than oral use.

1. Galeazzi M, Marcolongo R. A placebo-controlled study of the efficacy and tolerability of a nonsteroidal anti-inflammatory drug, DHEP plaster, in inflammatory peri- and extra-articular rheumatological diseases. *Drugs Exp Clin Res* 1993; **19:** 107–15.
2. Dreiser RL, Tisne-Camus M. DHEP plasters as a topical treatment of knee osteoarthritis—a double-blind placebo-controlled study. *Drugs Exp Clin Res* 1993; **19:** 117–23.
3. Affaitati G, *et al.* Effects of topical diclofenac (DHEP plaster) on skin, subcutis and muscle pain thresholds in subjects without spontaneous pain. *Drugs Exp Clin Res* 2001; **27:** 69–76.
4. Jenoure P-J. Évaluation d'un anti-inflammatoire non stéroïdien topique dans le traitement de la douleur et de l'inflammation: exemple de Flector Tissugel 1% dispositif local bioadhésif de diclofénac épolamine. *Presse Med* 2004; **33:** 10–13.
5. Brühlmann P, *et al.* Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomised clinical studies. *Curr Med Res Opin* 2006; **22:** 2429–38.
6. Alessandri F, *et al.* Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol* 2006; **13:** 195–200.
7. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2006; **33:** 567–73.

Actinic keratoses. Diclofenac sodium 3% in hyaluronic acid gel is used[1-3] in the treatment of actinic keratoses (see Basal Cell and Squamous Cell Carcinoma, p.673), and a meta-analysis[4] found it to be of benefit, despite previous concerns that the preparation may not be significantly more effective than hyaluronic acid gel alone.[5] An open-label comparison involving 30 patients with multiple actinic keratoses suggested that 90 days of treatment with diclofenac sodium 3% gel (to lesions on one side of the face and scalp) was better tolerated, but slightly less effective, than 28 days of treatment with fluorouracil 5% cream (to lesions on the other side).[6]

1. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; **133:** 1239–42.
2. Rivers JK, *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146:** 94–100.
3. Ulrich C, *et al.* Treatment of multiple actinic keratoses with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol* 2007; **156** (suppl 3): 40–2.
4. Pirard D. *et al.* Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res* 2005; **297:** 185–9.
5. McEwan LE, Smith JG. Topical diclofenac/hyaluronic acid gel in the treatment of solar keratoses. *Australas J Dermatol* 1997; **38:** 187–9.
6. Smith SR, *et al.* Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol* 2006; **5:** 156–9.

Pain. Reviews.

1. Barden J, *et al.* Single dose oral diclofenac for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 07/11/06).

Preparations

BP 2008: Diclofenac Gel; Gastro-resistant Diclofenac Tablets; Prolonged-release Diclofenac Capsules; Prolonged-release Diclofenac Tablets;
USP 31: Diclofenac Potassium Tablets; Diclofenac Sodium Delayed-release Tablets; Diclofenac Sodium Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ainedif; Aktiosan†; Aldoron NF; Algicler; Algioxib; Anaflex; Atomo Desinflamante Geldic; Banoclus; Befol; Blokium; Calmoflex; Cataflam†; Curinflam; Damixa†; Desinflam†; DFN; Diastone; Diclac; Diclogesic; Diclogrand; Diclomar; Diclonex; Difenac; Difenac Forte; Dilam; Dioxaflex; Disipan; Dolo Tomanil; Dolofenac; Doloneitor; Dolvan; Doxtran; Faboflem; Flexin; Flexiplen; Flogenac†; Flogolisin; Flotac†; Fluxpiren; Gel Antiinflamatorio†; Gentisalyl; Iglodine; Imanol; Indofeno†; Ingeclof; Klonafenac; Lenitil†; Levedad; Lorbifenac; Metaflex NF; Miocalm; Nalgiflex; Natura Fenac; Norviken; Oxa; Oxaprost; Pronix; Quer-Out; Rati Salil D; Rodinac; Salicrem Forte; Silfox; Tomanil; Vesalion; Viartril NF; Vimultisa; Virobron Gel; Virobron NF; Volforte; Voltaren; Voltaren Colirio; Voltaren Migra; Xedenol; Xina†; ***Austral.:*** Arthrotec; Clonac; Dencorub Anti-Inflammatory†; Diclac; Diclohexal; Dinac; Fenac; Imflac; Solaraze; Voltaren; Voltaren Ophtha; ***Austria:*** Agilomed; Algefit; Arthrotec; Dedolor; Deflamat; Deflamm; Diclac; Diclaxol; Diclo-B; Diclobene; Diclomelan; Diclostad; Diclosyl; Difene; Dolo-Voltaren; Dolpasse; Fenaren; Flector; Magluphen†; Rheumabene†; Tratul; Voltaren; Zymamed; ***Belg.:*** Arthrotec; Cataflam; Diclofemed; Diclotop; Docdiclofe; Flector; Motifene; Polyflam; Voltapatch; Voltaren; ***Braz.:*** Ana-Flex; Artren; Augelit†; Bel-Gel†; Benevran; Biofenac; Cataflam; Cataflex; Cataflexym; Catalgem†; Cinaflan†; Clofaren†; Clofen†; Clofenak; Clofenid; Deltaflogin; Deltaren; Desinflex†; Diclac†; Diclo P; Diclof†; Diclofen†; Diclofenax†; Diclogenom; Diclokalium†; Diclonaco; Diclonatrium†; Diclonax; Diclonil; Diclosod†; Diclosodico; Difenan†; Dioxaflex; Dnaren; Dorflan; Dorgen; Doriflan†; Fenaflan; Fenaren; Fenburil; Fisioren; Fladon; Flamalgen†; Flanakin; Flanaren; Flexamina†; Flodin Duo; Flogan; Flogesic†; Flogiren; Flogonac†; Flotac; Infladoren†; Inflamax; Kindaren; Lifaren†; Luparen†; Maxilerg; Neocoflan; Neotaflan; Neotaren; Olfen; Optamax†; Ortoflan; Poltax; Probenxil; Prodofenaco; Profenac†; Sintofenac†; Sodix; Still; Tonaflan†; Tricin†; Vendrex; Voltaflan; Voltaflex; Voltaren; Voltaren Colirio; Voltrix; ***Canad.:*** Apo-Diclo; Arthrotec; Diclotec†; Novo-Difenac; Nu-Diclo; Pennsaid; Voltaren;

Voltaren Ophtha; ***Chile:*** 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclotaren; Dicogel; Dignofenac†; Elitiran; Exflam; Flector; Flotac; Lertus; Merpal; Noxiflex†; Oftic; Pirexyl; Piroflam; Pro Lertus; Spirac; Turbogesic; Voltaren; ***Cz.:*** Almiral; Apo-Diclo; Arthrotec†; Diclofen; Dicloreum; DIKY; Dolmina; Dorosan; Feloran†; Flector; Inflamac†; Monoflam; Myogit; Naclof†; Naklofen; Olfen; Rewodina; Uniclophen; Uno; Veral; Voltaren; ***Denm.:*** Arthrotec; Diclodan; Diclogea†; Diclon; Difenet; Flector; Modifenac; Solaraze; Voltaren; Vostar; ***Fin.:*** Arthrotec; Diclometin; Diclomex; Eeze; Flector; Motifene; Solaraze; Trabona†; Voltaren; ***Fr.:*** Artotec; Flector; Solaraze; Voldal; Voltarendolo; Voltarene; Xenid; ***Ger.:*** Allvoran; Arthotec; Benfofen†; Delphinac†; Diclac; Diclo; Diclo-Divido; Diclo-Gel; Diclo-Puren; Diclo-saar; Diclodoc; Diclofenbeta; Diclophlogont†; Difen; Dolgit-Diclo; duravolten†; Effekton; Jenafenac; Jutafenac; Lexobene†; Monoflam; Myogit; Rewodina; Sigafenac†; Solaraze; Voltaren; Voltaren Ophtha; ***Gr.:*** Anthraxiton; Arthrotec; Cataflam†; Clonac†; Declofon; Delimon; Denaclof; Diclofast; Diclophlogont†; Dicloplast; Difend†; Dinaclon†; Evinopon; Eyeclof; Fenoclof; Figrel†; Flefarmin; Optobet; Pengon†; Pennsaid; Relipain; Rheumavek; Ruvominox; Sfinac; Topalgon; Urigon; Vilacril†; Vilonit; Voltaren; Vurdon; ***Hong Kong:*** Almiral; Analpan; Apo-Diclo; Arthrotec; Cataflam; Clofec; Clofenac; Curinflam; Diclo-Denk; Diclofen; Diclogesic; Diclowal†; Difenac; Difenol; Erdon; Eurofenac; Flector; Flogofenac; Grofenac; Inflanac; Novo-Difenac†; Olfen; Remafen; Remethan; Ren; Rhemofenax; Uniren; Vartelon; Voltaren; Voltaren Ophtha; Votalen; Zolterol; ***Hung.:*** Cataflam; Diclac; Diclomel; Flameril; Flector; Fortedol; Huma-Difenac†; Olfen†; Veral†; Voltaren; Voltaren Ophta; ***India:*** Cofenac; Diclomol; Diclonac; Dicloran†; Doflex; Dolocide K; Dolocide Plus; Esgipyrin DS; Fenlodac†; Fensaide†; I-Gesic; Jonac; K-Fenac; Nac; Nac Gel; Oxalgin; Oxalgin-D; Oxalgin-SR; Profenac; Reactine; Relaxyl; Solunac; Tromagesic; Tromax; Voveran; ***Indon.:*** Abdiflam; Alflam; Atranac; Berifen; Cataflam; Catanac; Deflamat; Dicloflam; Diclomec; Diflam; Divoltar; Eflagen; Exaflam; Fenaren; Fenavel; Flamar; Flamenac; Kadiflam; Kaflam; Kamaflam; Klotaren; Laflanac; Linac; Matsunaflam; Merflam; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen; Prostanac; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Valto; Volmatik; Voltadex; Voltaren; Voltaren Ophtha; Voren; X-Flam; Xepathritis; Yariflam; Zegren; ***Irl.:*** Arthrotec; Cataflam; Diclac; Diclo; Diclomax; Diclomel; Difene; Solaraze; Vologen†; Voltarol; Voltarol Ophtha; ***Israel:*** Abitren; Arthrotec; Betaren; Cataflam; Dicloplast; Diclorengel; Olfen; Voltaren; Voltaren Ophtha; ***Ital.:*** Algosenac; Artrofenac†; Artrotec; Dealgic; Deflamat; Diclocular; Diclofan; Dicloftil; Dicloral; Dicloreum; Diclotears; Dolaut; Doroxan; Dropflam; Fenadol; Fender; Flector; Flogofenac; Forgenac; Itami; Leviogel; Lisiflen†; Misofenac; Molfenac; Novapirina; Pennsaid; Ribex Flu†; Solaraze; Topfans; Voltadol; Voltaren; Voltfast; Zeroflog; ***Jpn:*** Anavan; ***Malaysia:*** Almiral; Apo-Diclo†; Cataflam; Clofec; Clofenac; Difnal; Fenac; Fenadium†; Inflanac; Leslam; Neo-Pyrazon; Olfen; Remafen†; Remethan; Rhewlin†; Taks†; Uniren; Voltaren; Voren; Wari-Diclowal†; Zolterol; ***Mex.:*** 3A Ofteno; Alsidexten; Ariflam; Artrenac; Artrenac Pro; Artrene; Artrotec; Atalak; Cataflam; Clo-Far; Clonodifen; Coral; Deflox; Dicfafena; Diclac; Dicloran; Diclosol; Dioxaflex; Dirret; Docril; Dofen; Dolaren; Dolflam; Dolofenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren; Galedol; Hipo Sport; Lertus; Lifenac; Liroken; Lodyfen; Logesic†; Lonatec; Lufac-Z; Mafena; Manacon; Merxil; Metracin; Musol; Neciclon; Neo-Dolaren; Pharmaflam; Practiser; Precifenac; Selectofen; Solof; Still; Uni-Fenil†; Vicmafen; Volfenac; Voltaren; ***Neth.:*** Arthrotec; Artrotec; Cataflam; Itami; Misofenac; Naclof; Normulen; Otriflu; Voltaren; ***Norw.:*** Arthrotec; Cataflam; Modifenac; Otriflu; Solaraze; Voltaren; Voltaren Ophtha; ***NZ:*** Apo-Diclo; Cataflam; Diclax; Diclohexal; Flameril; Voltaren; Voltaren Ophtha; Voltfast; ***Philipp.:*** Acuflam; Cataflam; Clofenix; Clofil; Clonaren; Difenax; Diflapane; Doloflam; Dycon; Eslofen; Fenaspec; Lobafen; Lofenax; Neo-Pyrazon; Nepenthe; Parafortan; Rheuflam; Uniclonax; Volfenn; Voltaren; Voren; Zobid; ***Pol.:*** Apo-Diclo; Arthrotec; Cataflam; Diclac; Dicloberl; DicloDuo; Dicloratio; Dicloreum; Difadol; Diklonat P; Dikloziaja; Felogel; Majamil; Naclof; Naklofen; Olfen; Ratiogel; Rewodina; Veral; Voltaren; Voltenac; ***Port.:*** Arthrotec; Cataflam; Clofen; Dicloabak; Diclodent; Dicloftal; Diclospray; Diclotec; Difnan; Dofene; Dolacen; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Olfen; Otriflu; Painex; Pennsaid; Solaraze; Voltaren; ***Rus.:*** Almiral (Алмирал); Apo-Diclo (Апо-дикло); Arthrotec (Артротек)†; Diclac (Диклак); Diclo-F (Дикло-ф); Diclobene (Диклобене); Dicloberl (Диклоберл); Diclonat (Диклонат); Dicloran (Диклоран); Diclovit (Дикловит); Feloran (Фелоран)†; Naclof (Наклоф); Naklofen (Наклофен); Naklofen Duo (Наклофен Дуо); Rapten Rapid (Раптен Рапид); Voltaren (Вольтарен); ***S.Afr.:*** Adco-Clofelam; Arcanafenac; Arthrotec; Arthru-Derm; Cataflam; Dicloflam; Diclohexal; Dynak; Flexagen; Fortfen; Infla-Ban; K-Fenak; Panamor; Pharmaflam†; Veltex; Voltaren; Voltaren Ophtha; ***Singapore:*** Almiral; Cataflam; Clofec; Clofenac; Diclo; Diclo-Denk†; Dicloran; Diclowal†; Difenac; Difnal; Inac; Inflanac; Lesflam; Neo-Pyrazon†; Olfen; Pritaren; Remafen; Remethan†; Rhewlin; Ultrafen; Uniren; Voltaren; Voltaren Ophtha; Voren; Zolterol; ***Spain:*** Artrotec; Di Retard; Dolo Nervobion; Dolo-Voltaren; Dolotren; Luase; Normulen; Sulexon; Voltaren; ***Swed.:*** Arthrotec; Flector; Modifenac†; Solaraze; Voltaren; Voltaren Ophtha; Voltaren T; ***Switz.:*** Agofenac†; Arthrotec; Athrofen; Deflamat†; Diclac; diclo-basan; Diclo†; Diclosifar; Ecofenac; Effigel; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Tonopan; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophta; Voltarene; ***Thai.:*** Almiral†; Ammi-Votara; Amminac; Arclonac; Arthrotec†; Cataflam; Catanac; Cencenag; Chinclonac; Clofec; Clofon; Demac; Diclofen†; Diclogel; Diclolan; Diclomol; Diclosian; Difelene†; Difen; Difenac; Difengesic; Difeno; Dinac; Dinefec†; Dosanac; Fenac; Fenagel; Flexy; Inflanac; Lesflam; Lofenac; Masaren; Medaren†; Myfenax; Myonac; N-Zen; Naclof; Olfen†; Ostaren; Posnac; Putaren†; Remethan; Rhumanol; Rumatab†; Sefnac; Silflam†; Subsyde; Taks; Tarjen†; Tarjena; Uniren; Vasalen; Veenac; Ventarone; Volfenac; Volnac; Volta; Voltanac; Voltaren; Volverac; Votamed; ***Turk.:*** Actinoma; Cataflam; Deflamat; Dicloflam; Diclomec; Difenak; Dikloron; Dolorex; Inflased; Kalidren; Miyadren; Voltaren; Voltaren Ophta; ***UAE:*** Clofen; ***UK:*** Acoflam†; Arthrotec; Defanac; Defenac; Dexomon; Dicloflex; Diclomax; Diclovol; Diclozip; Dyloject; Econac; Fenactol; Flamatak; Flamrase; Lofensaid†; Motifene; Pennsaid; Rheumatac; Rhumalgan; Slofenac; Solaraze; Volraman; Volsaid; Voltarol; Voltarol Ophtha; ***USA:*** Arthrotec; Cataflam; Flector; Solaraze; Voltaren; ***Venez.:*** 3A Ofteno; Arthrotec; Artren; Campal; Cataflam; Clofen; Clofenac; Diagesic; Diclofen P; Diclosal; Diclostan†; Difenac; Diklason; Diralon; Dival; Doltren†; Flogaren; Flotac; Klafenac; Viavox; Voltaren; Volten; Votaxil.

Multi-ingredient: ***Arg.:*** Albesine Biotic; Algicler; Algio Nervomax; Algio Nervomax Fuerte; Amixen Plus; Befol Plus; Belmalen; Blokium B12; Blokium Flex; Blokium Gesic; Corteroid Gesic; Curinflam Plus; Delta Tomanil B12; Desinflam Biotic†; Diclogesic Forte; Diclogesic Plus B12; Diclogesic Relax; Diclomar Flex; Diclonex Relax; Dioxaflex B12; Dioxaflex Forte; Dioxaflex Gesic; Dioxaflex Plus; Dolo Nervobion; Dolo Nervobion 10000; Dolvan Flex; Doxtran B12; Doxtran Flex; Doxtran Gesic; Flaval; Glifapen; Hyanac†; Iglodine Flex; Ingebrax; Lertus Biotic†; Metaflex Gesic; Metaflex Plus NF; Meticil; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa B12; Oxa Forte; Oxa Sport; Oxadisten; Oxafem; Oxagesic; Pancloflex; Panclogesic; Rodinac B12; Rodinac Biotic; Rodinac Flex; Rodinac Gesic; Silfox Flex; Tafirol Artro; Tobradiclo; Tobratlas; Tomanil Flex; Vesalion B12; Vesalion Flex; Vesalion Gesic; Viartril Flex; Virobron B12 NF; Voltaren Flex; Voltaren Forte; Xedenol B12; Xedenol Flex; Xedenol Gesic; ***Austria:*** Diclovit; Dolo-Neurobion; Neodolpasse; Neurofenac; Voltamicin; ***Belg.:*** Ocubrax; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Codaten; Diclofetamol; Flexalgin; Mioflex A; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Neodolpasse; Voltamicin†; ***Ger.:*** Combaren; Voltaren Plus; ***Gr.:*** Tobrafen; ***Hong Kong:*** Neurofenac†; Vartelon-B; Vidaclofen-Plus; ***Hung.:*** Neodolpasse; Ocubrax†; Voltamicin†; ***India:*** Actimol; Buta-Proxyvon; Cip-Zox; Cipzen D; Cofenac; Diclogenta; Diclomol; Dicloran MS; Dicloran-A†; Diclospa; Diser; Doflex Plus; Dolocide KP; Dolocide MR; DP Gesic; Duoflam Gel; Esgipyrin; Fenaplus; Fenaplus-MR; Fensaide-P†; Flamar-MX; Flanzen-D; Inflazone; Myospaz Forte; New Panazox; Nicip D; Omnigel; Osteoflam-MR; Oxalgin-DP; Pacizox; Paracip Plus; Parvon Forte; Reactine Forte; Reactine Plus; Relaxyl Plus; Spasmo-Proxyvon Forte; Systaflam; ***Indon.:*** Dolofenac; ***Ital.:*** Voltamicin†; ***Malaysia:*** Voren Plus; ***Mex.:*** Ariflam Forte; Diclovith-B; Dolaren; Dolo-Neurobion; Dolo-Pangavit; Duciclon; Duoflex; Empatil; Lertus CD; Ortocol; Tafirol AC; Trazinac; Tribedoce Compuesto; Uni-Dox; Voltaren Forte; ***Pol.:*** Venozel; ***Rus.:*** Diclofenacol (Диклофенакол); Dicloran Plus (Диклоран Плюс); ***Singapore:*** Voltamicin†; ***Spain:*** Ocubrax; ***Switz.:*** Tobrafen; Voltamicin; ***Turk.:*** Ocubrax; ***Venez.:*** Combaren; Painfort; Todenac; Trazinac.

Diethylamine Salicylate

Diethylamini Salicylas; Dietylaminsalicylat; Dietyyliamiinisalisylaatti; Salicilato de dietilamina; Salisilat Dietilamin.

Диэтиламин Салицилат; Салицилат Диэтиламина

$C_{11}H_{17}NO_3 = 211.3.$

CAS — 4419-92-5.

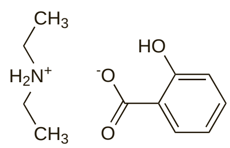

Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Diethylamine Salicylate). White or almost white, odourless or almost odourless crystals. Very soluble in water; freely soluble in alcohol and in chloroform. Protect from light. Avoid contact with iron or iron salts.

Profile

Diethylamine salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p.85) for rheumatic and muscular pain.

Preparations

BP 2008: Diethylamine Salicylate Cream.

Proprietary Preparations (details are given in Part 3)
Belg.: Algesal; ***Canad.:*** Physiogesic; ***Fin.:*** Algesal; ***Hung.:*** Aciphen; ***India:*** Multigesic†; ***Ital.:*** Algesal†; ***Neth.:*** Algesal; ***Norw.:*** Algesal; ***Pol.:*** Saldiam; ***Port.:*** Algicum; Algiderma; Massagim; ***Swed.:*** Algesal; ***Turk.:*** Algesal; Reparil N; ***UK:*** Algesal; Lloyd's Cream; ***Venez.:*** Alesal.

Multi-ingredient: ***Arg.:*** Algesal; Cartiflex; Crema Antiinflamatoria; Feparil†; Rati Salil Flex; Salicrem; ***Austral.:*** Rubesal; ***Austria:*** Algesal; Derivon; Dolo-Menthoneurin; Dolorex†; Igitur-antirheumatische; Igitur-Rheumafluid; Latesyl; Pasta rubra salicylata; Reparil; Rheugesal; Thermal; ***Belg.:*** Reparil; ***Braz.:*** Reparil; ***Chile:*** Repariven; ***Cz.:*** Algesal; Reparil-Gel N; ***Fr.:*** Algesal Suractive; Reparil; Traumalgyl; ***Ger.:*** Algesal; Algesalona†; Dolo-Menthoneurin†; Doloneuro†; Reparil-Gel N; ***Gr.:*** Algesal Suractive; Ponostop; ***Hong Kong:*** Reparil; Rubesal; ***Hung.:*** Algesal; Reparil N; ***Indon.:*** Algesal Suractive; ***Ital.:*** Edeven; Reparil; Sedalpan; Via Mal Traumagel; ***Mex.:*** Algesal†; ***Neth.:*** Algesal Forte; ***Norw.:*** Thermal†; ***Pol.:*** Reparil N; ***Port.:*** Algesal; Latesil; Medalginan; Venoparil; ***S.Afr.:*** Reparil; ***Spain:*** Algesal; Contusin; Doctomitil†; Dolmitin; Feparil; Radio Salil; ***Switz.:*** Algesal†; Algesalona†; Mavena Proctal-Gen; Reparil; ***Thai.:*** Reparil; Veno Gel; ***Turk.:*** Algesal Suractive; Prepagel; ***UAE:*** Rubicalm; ***UK:*** Fiery Jack; Transvasin Heat Spray; ***Venez.:*** Lemazol.

Diflunisal *(BAN, USAN, rINN)*

Diflunisaali; Diflunisalis; Diflunisalum; Difluniszal; MK-647. 5-(2,4-Difluorophenyl)salicylic acid.

Дифлунисал

$C_{13}H_8F_2O_3 = 250.2.$

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.

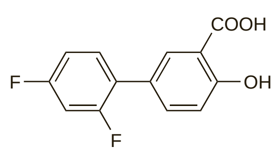

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Diflunisal). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Diflunisal). A white to off-white, practically odourless, powder. Insoluble in water and in hexane; freely soluble in alcohol and in methyl alcohol; soluble in acetone and in ethyl acetate; slightly soluble in carbon tetrachloride, in chloroform, and in dichloromethane.

Adverse Effects and Treatment

As for NSAIDs in general, p.96. The commonest adverse effects occurring with diflunisal are gastrointestinal disturbances, headache, and rash. Peptic ulceration and gastrointestinal bleeding have been reported. Dizziness, drowsiness, insomnia, and tinnitus may also occur.

Effects on the blood. Haematological adverse effects associated with diflunisal appear to be infrequent. Thrombocytopenia associated with diflunisal-induced peripheral platelet destruction has been reported in a patient with rheumatoid arthritis.[1] Heinz-body haemolytic anaemia has also been reported, see Hypersensitivity, below.

1. Bobrove AM. Diflunisal-associated thrombocytopenia in a patient with rheumatoid arthritis. *Arthritis Rheum* 1988; **31:** 148–9.

Effects on the kidneys. Acute interstitial nephritis, presenting as acute oliguric renal failure, erythroderma, and eosinophilia has followed the use of diflunisal.[1]

1. Chan LK, *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; **280:** 84–5.

Effects on the lungs. For reference to pneumonitis associated with diflunisal therapy, see Hypersensitivity, below.

Effects on the skin. Reports of Stevens-Johnson syndrome associated with diflunisal.[1,2] See also Hypersensitivity, below.

1. Hunter JA, *et al.* Diflunisal and Stevens-Johnson syndrome. *BMJ* 1978; **2:** 1088.
2. Grom JA, *et al.* Diflunisal-induced erythema multiforme major. *Hosp Formul* 1986; **21:** 353–4.

Hypersensitivity. Three cases of hypersensitivity to diflunisal in which the main clinical features were fever, elevated liver enzyme values, erythroderma, and eosinophilia, have been reported.[1] Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis[2] and fulminant necrotising fasciitis.[3]

1. Cook DJ, *et al.* Three cases of diflunisal hypersensitivity. *Can Med Assoc J* 1988; **138:** 1029–30.
2. Rich MW, Thomas RA. A case of eosinophilic pneumonia and vasculitis induced by diflunisal. *Chest* 1997; **111:** 1767–9.
3. Krige JEJ, *et al.* Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; **ii:** 1432–3.

Overdosage. Diflunisal poisoning has sometimes been fatal.[1,2] A dose of 15 g has been reported to have caused death when no other drugs were involved but a dose of 7.5 g has also been fatal when taken with other drugs.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Levine B, *et al.* Diflunisal related fatality: a case report. *Forensic Sci Int* 1987; **35:** 45–50.

Precautions

As for NSAIDs in general, p.98. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe. Aspirin and other acetylated salicylates are not recommended for use in children unless specifically indicated, because of the risk of Reye's syndrome. Although this precaution has not been specifically extended to diflunisal it is not generally licensed for use in children.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin may produce a small decrease in the plasma concentration of diflunisal. Diflunisal has been reported to increase the plasma concentrations of indometacin and paracetamol; diflunisal with indometacin has been associated with fatal gastrointestinal haemorrhage and therefore the combination should not be used. Regular use of antacids may reduce the absorption of diflunisal.

Benzodiazepines. For the effect of diflunisal on plasma concentrations of *oxazepam*, see p.989.

Probenecid. Average steady-state plasma concentrations of diflunisal were increased by 65% when it was given with probenecid.[1] This was due mainly to reduced formation of the phenolic and acyl glucuronides. However, plasma concentrations of these glucuronides and the sulfate conjugate were also increased even more because probenecid also reduced their renal clearance.

1. Macdonald JI, *et al.* Effect of probenecid on the formation and elimination kinetics of the sulphate and glucuronide conjugates of diflunisal. *Eur J Clin Pharmacol* 1995; **47:** 519–23.

Pharmacokinetics

Diflunisal is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 3 hours after ingestion of a single dose. It is more than 99% bound to plasma protein and has a plasma half-life of about 8 to 12 hours. Diflunisal exhibits non-linear pharmacokinetics so that doubling the dose more than doubles drug accumulation. Due to the long half-life and non-linear kinetics, several days are required to reach steady-state plasma concentrations after multiple dosing. The time to steady-state concentrations can be reduced by giving an initial loading dose. Concentrations of diflunisal in synovial fluid reach about 70% of those in plasma. Diflunisal is excreted in the urine mainly as glucuronide conjugates. Some biliary recycling may also occur. Diflunisal is distributed into breast milk with concentrations reported to be about 2 to 7% of those in plasma.

◊ References.

1. Loewen GR, *et al.* Effect of dose on the glucuronidation and sulphation kinetics of diflunisal in man: single dose studies. *Br J Clin Pharmacol* 1988; **26:** 31–9.
2. Eriksson L-O, *et al.* Influence of renal failure, rheumatoid arthritis and old age on the pharmacokinetics of diflunisal. *Eur J Clin Pharmacol* 1989; **36:** 165–74.
3. Verbeeck RK, *et al.* The effect of multiple dosage on the kinetics of glucuronidation and sulphation of diflunisal in man. *Br J Clin Pharmacol* 1990; **29:** 381–9.
4. Macdonald JI, *et al.* Sex-difference and the effects of smoking and oral contraceptive steroids on the kinetics of diflunisal. *Eur J Clin Pharmacol* 1990; **38:** 175–9.
5. Nuernberg B, *et al.* Pharmacokinetics of diflunisal in patients. *Clin Pharmacokinet* 1991; **20:** 81–9.

Uses and Administration

Diflunisal is a salicylic acid derivative (see Aspirin, p.23) but it is not hydrolysed to salicylate and its clinical effects resemble more closely those of propionic acid derivative NSAIDs such as ibuprofen (p.65). Diflunisal is given in the acute or long-term management of mild to moderate pain, and pain and inflammation associated with osteoarthritis and rheumatoid arthritis. The usual initial oral dose for pain relief is 1 g followed by a maintenance dose of 500 mg every 12 hours. In some patients 250 mg every 8 to 12 hours may be sufficient but others may require 500 mg every 8 hours. Maintenance doses greater than 1.5 g daily are not recommended. The usual oral dose for arthritis is 500 mg to 1 g daily in 2 divided doses. Doses may need to be reduced in patients with renal impairment, see below.

Diflunisal arginine has been used similarly given by mouth or by intramuscular or intravenous injection.

Administration in renal impairment. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe.

Preparations

BP 2008: Diflunisal Tablets;
USP 31: Diflunisal Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dolobid†; ***Austria:*** Fluniget; ***Belg.:*** Biartac†; Diflusal; ***Denm.:*** Donobid†; ***Fin.:*** Donobid†; ***Fr.:*** Dolobis†; ***Gr.:*** Analeric; ***Irl.:*** Dolobid†; ***Israel:*** Dolobid†; ***Ital.:*** Artrodol; Dolobid†; ***Mex.:*** Dolobid†; ***Neth.:*** Dolobid; Dolocid; ***Norw.:*** Donobid; ***Port.:*** Dolobid†; Flunidor†; ***Spain:*** Dolobid; ***Swed.:*** Donobid; ***Switz.:*** Unisal†; ***Thai.:*** Dolobid; ***Turk.:*** Dolphin; ***UK:*** Dolobid†; ***USA:*** Dolobid†; ***Venez.:*** Dolobid†.

Dihydrocodeine Phosphate

(BANM, rINNM)

Dihydrocodéine, Phosphate de; Dihydrocodeini Phosphas; Fosfato de dihidrocodeína; Hydrocodeine Phosphate.

Дигидрокодеина Фосфат

$C_{18}H_{23}NO_3,H_3PO_4 = 399.4.$

CAS — 24204-13-5.

ATC — N02AA08.

ATC Vet — QN02AA08.

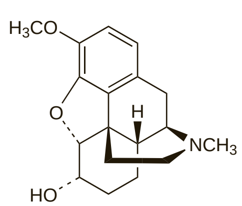

(dihydrocodeine)

Pharmacopoeias. In *Jpn.*

Dihydrocodeine Tartrate *(BANM, rINNM)*

Dihidrokodein-hidrogén-tartrát; Dihidrokodeino-vandenilio tartratas; Dihydrocodeine Acid Tartrate; Dihydrocodeine Bitartrate; Dihydrocodeine Hydrogen Tartrate; Dihydrocodéine, hydrogénotartrate de; Dihydrocodéine, Tartrate de; Dihydrocodeini Bitartras; Dihydrocodeini hydrogenotartras; Dihydrocodeini Tartras; Dihydrokodeiinivetytartratti; Dihydrokodein-tartarát; Dihydrokodeinvätetartrat; Dihydrokodeiny wodorowinian; Drocode Bitartrate; Hydrocodeine Bitartrate; Tartrato de dihidrocodeína. 4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol hydrogen tartrate.

Дигидрокодеина Тартрат

$C_{18}H_{23}NO_3,C_4H_6O_6 = 451.5.$

CAS — 125-28-0 (dihydrocodeine); 5965-13-9 (dihydrocodeine tartrate).

NOTE. Compounded preparations of dihydrocodeine tartrate may be represented by the following names:

- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w).

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dihydrocodeine tartrate:

DFs; Diffs; Duncan Flockharts.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dihydrocodeine Hydrogen Tartrate; Dihydrocodeine Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 3.2 to 4.2. Protect from light.

USP 31 (Dihydrocodeine Bitartrate). pH of a 10% solution in water is between 3.2 and 4.2. Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dihydrocodeine has been subject to abuse (see under Precautions, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102; adverse effects of dihydrocodeine are less pronounced than those of morphine.

Overdosage. A 29-year-old man who had taken 2.1 g of dihydrocodeine had biochemical evidence of acute renal and hepatic impairment when admitted 13 hours after the overdose.[1] Severe life-threatening respiratory depression subsequently developed 36 hours after the overdose and only responded to treatment with naloxone after large doses (a total of 46.6 mg of naloxone) over a long period (106 hours). Commenting on this report some questioned the evidence for hepatic impairment and considered that the raised liver enzyme values were of muscular origin as a result of rhabdomyolysis.[2-4] Rhabdomyolysis may also have contributed to renal failure.

An anaphylactoid reaction after an overdose with an unspecified number of dihydrocodeine tablets[5] appeared to respond to intravenous naloxone.

1. Redfern N. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 751–2.
2. Buckley BM, Vale JA. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
3. Blain PG, Lane RJM. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
4. Wen P. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1548.
5. Panos MZ, *et al.* Use of naloxone in opioid-induced anaphylactoid reaction. *Br J Anaesth* 1988; **61:** 371.

Pain. For reference to increased postoperative pain associated with the use of dihydrocodeine, see under Uses and Administration, below.

Precautions

As for Opioid Analgesics in general, p.103.

Abuse. Dihydrocodeine has been reported to be widely abused by opiate addicts.[1-4]

1. Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300:** 1313.
2. Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
3. Strang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
4. Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46:** 143–6.

The elderly. Despite some renal impairment an elderly group of patients[1] appeared to handle dihydrocodeine similarly to healthy young subjects. There was marked variability in all measurements and on the basis of this study no clear conclusions on guidelines for dosage in elderly patients could be drawn. However, the recommendation that small doses be given initially with subsequent doses according to response was endorsed.

1. Davies KN, *et al.* The effect of ageing on the pharmacokinetics of dihydrocodeine. *Eur J Clin Pharmacol* 1989; **37:** 375–9.

Renal impairment. Caution is necessary when giving dihydrocodeine to patients with severe renal impairment. Severe narcosis occurred in a patient with anuria and on maintenance haemodialysis after she had received dihydrocodeine orally for 4 days.[1] She responded to treatment with naloxone.

See also under Pharmacokinetics, below.

1. Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *BMJ* 1983; **286:** 438–9.

Interactions

For interactions associated with opioid analgesics, see p.103.

Quinidine. Dihydrocodeine is metabolised via the cytochrome P450 isoenzyme CYP2D6 to active metabolites, which may perhaps play a role in its analgesic activity in extensive metabolisers; quinidine impairs this metabolism, but a study in 11 healthy subjects did not find any reduced analgesic activity when dihydrocodeine was given with quinidine, despite a three- to fourfold reduction in plasma concentrations of the metabolite dihydromorphine.[1]

1. Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45:** 575–81.

Pharmacokinetics

After oral doses peak concentrations of dihydrocodeine occur after about 1.2 to 1.8 hours; oral bioavailability is only about 20%, probably because of substantial first-pass metabolism in the gut wall or liver. Dihydrocodeine is metabolised in the liver via the cytochrome P450 isoenzyme CYP2D6, to dihydromorphine, which has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be primarily due to the parent compound; some is also converted via CYP3A4 to nordihydrocodeine. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life is reported to range from about 3.5 to 5 hours.

◊ References.

1. Rowell FJ, *et al.* Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol* 1983; **25:** 419–24.
2. Fromm MF, *et al.* Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995; **58:** 374–82.
3. Ammon S, *et al.* Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple dosing. *Br J Clin Pharmacol* 1999; **48:** 317–22.
4. Webb JA, *et al.* Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; **52:** 35–43.

Renal impairment. The pharmacokinetics of dihydrocodeine tartrate, given as a single oral 60-mg dose, were affected in 9 patients with chronic renal failure treated with haemodialysis when compared with 9 healthy subjects.[1] Time to peak plasma concentration in those with renal failure was 3 hours compared with 1 hour in healthy subjects; the area under the plasma concentration-time curve was greater in those with renal failure; and after 24 hours dihydrocodeine was still detectable in the plasma of all renal failure patients, but in only 3 of the healthy subjects.

1. Barnes JN, *et al.* Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ* 1985; **290:** 740–2.

Uses and Administration

Dihydrocodeine is an opioid analgesic (p.104). It is related to codeine (p.38) and has similar analgesic activity. Dihydrocodeine is used for the relief of moderate to severe pain, often in combination preparations with paracetamol. It has also been used as a cough suppressant.

For **analgesia** the usual oral dose of dihydrocodeine tartrate is 30 mg after food every 4 to 6 hours; up to 240 mg daily may be given for severe pain. Modified-release preparations are available for twice daily dosage in patients with chronic severe pain.

Dihydrocodeine tartrate may also be given by deep subcutaneous or intramuscular injection in doses of up to 50 mg every 4 to 6 hours.

For details of doses in children, see below.

As a **cough suppressant** dihydrocodeine tartrate may be given in oral doses of 10 to 30 mg up to three times daily.

Dihydrocodeine phosphate has also been used. Other salts of dihydrocodeine used, mainly for their antitussive effects, include the hydrochloride, the polistirex, and the thiocyanate. Dihydrocodeine polistirex has also been used in modified-release preparations.

Administration in children. In the UK, dihydrocodeine tartrate may be given orally, or by deep subcutaneous or intramuscular injection, for analgesia in children aged from 4 to 12 years in usual doses of 0.5 to 1 mg/kg (to a maximum of 30 mg) every 4 to 6 hours; older children may be given the usual adult dose (see above). Although unlicensed in children under 4 years, the *BNFC* suggests giving those aged 1 to 4 years 500 micrograms/kg every 4 to 6 hours.

Dyspnoea. Dihydrocodeine has been reported[1] to have produced benefit in normocapnic patients severely disabled by breathlessness due to chronic airflow obstruction. A dose of

15 mg was taken 30 minutes before exercise up to three times a day.

1. Johnson MA, *et al.* Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983; **286:** 675–7.

Pain. Dihydrocodeine is used in the management of moderate to severe pain. However, dose-related increase in postoperative pain has been seen[1] in patients given 25 or 50 mg dihydrocodeine tartrate intravenously after dental surgery, and it has been proposed that dihydrocodeine might act as an antagonist in situations where acute pain was accompanied by high opioid activity.[2] Systematic review of the use of single oral doses of dihydrocodeine has indicated that these are insufficient to provide adequate relief of postoperative pain, and that dihydrocodeine is less effective than ibuprofen.[3]

1. Seymour RA, *et al.* Dihydrocodeine-induced hyperalgesia in postoperative dental pain. *Lancet* 1982; **i:** 1425–6.
2. Henry JA. Dihydrocodeine increases dental pain. *Lancet* 1982; **ii:** 223.
3. Edwards JE, *et al.* Single dose dihydrocodeine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 26/06/08).

Preparations

BP 2008: Co-dydramol Tablets; Dihydrocodeine Injection; Dihydrocodeine Oral Solution; Dihydrocodeine Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Paracodin; Rikodeine; ***Austria:*** Codidol; Dehace; Paracodin; ***Belg.:*** Codicontin; Paracodine; ***Cz.:*** DHC Continus; ***Fr.:*** Dicodin; ***Ger.:*** DHC; Paracodin; Paracodin N; Remedacen†; Tiamon Mono; ***Gr.:*** Condugesic†; ***Hong Kong:*** DF 118; ***Hung.:*** DHC; Hydrocodin; ***Irl.:*** DF 118; DHC Continus; Paracodin; ***Ital.:*** Paracodina; ***Malaysia:*** Codesic†; DF 118; ***NZ:*** DHC Continus; ***Pol.:*** DHC Continus; ***Port.:*** Didor†; ***S.Afr.:*** DF 118; Paracodin; ***Spain:*** Contugesic†; Paracodina; Tosidrin; ***Switz.:*** Codicontin; Paracodin; ***UK:*** DF 118; DHC Continus.

Multi-ingredient: ***Arg.:*** Lentusin; ***Austral.:*** Codox; ***Austria:*** Paracodin; ***Ger.:*** Antitussivum Burger N†; Makatussin Tropfen forte†; Paracodin retard†; ***Hong Kong:*** Codaewon; ***Irl.:*** Paramol; ***Ital.:*** Cardiazol-Paracodina; Paracodina; ***Jpn:*** Colgen Kowa IB Toumei; ***Malaysia:*** Dihydrocodeine P; ***Switz.:*** Escotussin; Makatussin Comp; Paracodin retard†; ***UK:*** Paramol; Remedeine; ***USA:*** DHC Plus; DiHydro-CP; DiHydro-GP; DiHydro-PE; Duohist DH; Novahistine DH; Pancof; Pancof PD; Pancof-EXP; Panlor; Synalgos-DC.

Dipipanone Hydrochloride *(BANM, rINNM)*

Dipipanone, Chlorhydrate de; Dipipanoni Hydrochloridum; Hidrocloruro de dipipanona; Phenylpiperone Hydrochloride; Piperidyl Methadone Hydrochloride; Piperidylamidone Hydrochloride. (±)-4,4-Diphenyl-6-piperidinoheptan-3-one hydrochloride monohydrate.

Дипипанона Гидрохлорид

$C_{24}H_{31}NO,HCl,H_2O$ = 404.0.

CAS — 467-83-4 (dipipanone); 856-87-1 (dipipanone hydrochloride).

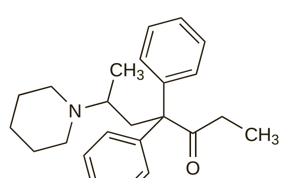

(dipipanone)

Pharmacopoeias. In *Br.*

BP 2008 (Dipipanone Hydrochloride). An odourless or almost odourless, white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in acetone; practically insoluble in ether. A 2.5% solution in water has a pH of 4.0 to 6.0.

Profile

Dipipanone hydrochloride is an opioid analgesic (p.101) structurally related to methadone (p.82). Used alone it is reported to be less sedating than morphine. It is used in the treatment of moderate to severe pain.

Dipipanone hydrochloride is usually given in combination preparations with the antiemetic cyclizine hydrochloride to reduce the incidence of nausea and vomiting, but the use of such preparations is not recommended for the management of chronic pain, as the antiemetic is usually only required for the first few days of treatment. The usual oral dose of dipipanone hydrochloride is 10 mg, repeated every 6 hours. The dose may be increased if necessary in increments of 5 mg; it is seldom necessary to exceed a dose of 30 mg. After an oral dose the analgesic effect begins within an hour and lasts about 4 to 6 hours.

Preparations of dipipanone hydrochloride with cyclizine hydrochloride are subject to abuse.

Preparations

BP 2008: Dipipanone and Cyclizine Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Wellconal†; ***Irl.:*** Diconal†; ***S.Afr.:*** Wellconal; ***UK:*** Diconal.

Dipyrone *(BAN, USAN)*

Metamizole Sodium *(pINN)*; Aminopyrine-sulphonate Sodium; Analginum; Dipiron; Dipyron; Dipyroni; Dipyronum; Metamitsolinatrium; Metamizol; Metamizol sódico; Metamizol sodná sůl monohydrát; Metamizol sodowy; Metamizol Sodyum; Métamizole sodique; Metamizolnatrium; Metamizol-nátrium; Metamizolo natrio druska; Metamizolum natricum; Metamizolum Natricum Monohydricum; Methampyrone; Methylmelubrin; Natrium Novaminsulfonicum; Noramidazophenum; Novamidazofen; Novaminsulfone Sodium; NSC-73205; Sodium Noramidopyrine Methanesulphonate; Sulpyrine. Sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N*-methylaminomethanesulphonate monohydrate.

Метамизол Натрий

$C_{13}H_{16}N_3NaO_4S,H_2O$ = 351.4.

CAS — 68-89-3 (anhydrous dipyrone); 5907-38-0 (dipyrone monohydrate).

ATC — N02BB02.

ATC Vet — QN02BB02.

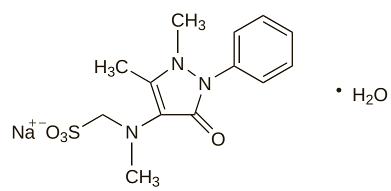

NOTE. Confusingly the term dipyrone sodium also appears to be used synonymously for dipyrone itself. Dipyrone is referred to in some countries by the colloquial name 'Mexican aspirin'. The names noraminophenazonum and novaminsulfon have apparently been applied to dipyrone, but it is not clear whether these are the sodium salt.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Metamizole Sodium; Dipyrone BP 2008). A white or almost white crystalline powder. Very soluble in water; soluble in alcohol. Protect from light.

Adverse Effects and Precautions

Use of dipyrone is associated with an increased risk of agranulocytosis and with shock.

◊ References.

1. Levy M. Hypersensitivity to pyrazolones. *Thorax* 2000; **55** (suppl 2): S72–S74.

Effects on the blood. Data collected from 8 population groups in Europe and Israel by the International Agranulocytosis and Aplastic Anemia Study[1] revealed that there was a significant regional variability in the rate-ratio estimate for agranulocytosis and dipyrone (0.9 in Budapest to 33.3 in Barcelona). Although a large relative increase in risk between agranulocytosis and use of dipyrone was found, the incidence was less than some previous reports had suggested.

Blood dyscrasias such as agranulocytosis and granulocytopenia have continued to be reported where dipyrone remains available.[2-7]

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002; **58:** 265–74.
3. Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res* 2002; **30:** 488–95.
4. Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004; **10:** PI93–PI95.
5. Ibanez L, *et al.* Agranulocytosis associated with dipyrone (metamizol). *Eur J Clin Pharmacol* 2005; **60:** 821–9.
6. Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J* 2005; **123:** 247–9.
7. Garcia S, *et al.* Dipyrone-induced granulocytopenia: a case for awareness. *Pharmacotherapy* 2006; **26:** 440–2.

Effects on the skin. Dipyrone has been considered responsible for a case of drug-induced toxic epidermal necrolysis.[1]

1. Roujeau J-C, *et al.* Sjögren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985; **i:** 609–11.

Hypersensitivity. Cross-sensitivity between aspirin and dipyrone occurred in a patient.[1] Dipyrone produced an exacerbation of dyspnoea, cyanosis, and respiratory arrest.

1. Bartoli E, *et al.* Drug-induced asthma. *Lancet* 1976; **i:** 1357.

Porphyria. Dipyrone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pharmacokinetics

After oral doses dipyrone is rapidly hydrolysed in the gastrointestinal tract to the active metabolite 4-methyl-amino-antipyrine, which after absorption undergoes metabolism to 4-formyl-amino-antipyrine and other metabolites. Dipyrone is also rapidly undetectable in plasma after intravenous doses. None of the metabolites of dipyrone are extensively bound to plasma proteins. Most of a dose is excreted in the urine as metabolites. Dipyrone metabolites are also distributed into breast milk.

◊ References.

1. Heinemeyer G, *et al.* The kinetics of metamizol and its metabolites in critical-care patients with acute renal dysfunction. *Eur J Clin Pharmacol* 1993; **45:** 445–50.
2. Levy M, *et al.* Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* 1995; **28:** 216–34.
3. Zylber-Katz E, *et al.* Dipyrone metabolism in liver disease. *Clin Pharmacol Ther* 1995; **58:** 198–209.

Uses and Administration

Dipyrone is the sodium sulfonate of aminophenazone (p.19) and has similar properties. Because of the risk of serious adverse effects, in many countries its use is considered justified only in severe pain or fever where no alternative is available or suitable. Dipyrone has been given orally in doses of 0.5 to 4 g daily in divided doses. It has also been given by intramuscular or intravenous injection and rectally as a suppository.

A magnesium congener of dipyrone, metamizole magnesium has been used similarly to dipyrone as has the calcium congener metamizole calcium.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Algiopiret†; Analgina; Dioxadol; Dipigrand; Ditral; Integrobe; Lisalgil; Novacler; Novalgina; Novemina; Unibios Simple; ***Austria:*** Inalgon Neu; Novalgin; Spasmo Inalgon Neu; ***Belg.:*** Analgine; Novalgine; ***Braz.:*** Algirona; Anador; Analgesil; Analgex†; Apiron; Baralgin; Conmel; Difebril; Dipimax; Dipirex†; Dipiron; Dipironax†; Dipix; Diprin; Doralex†; Dorfebril†; Dorilan†; Dornal†; Dorona; Dorpinon; DS500†; Findor†; Magnodor†; Magnopyrol; Maxiliv; Multiralgim†; Nofebrin; Novagreen; Novalgex†; Novalgina; Pirofebran†; Pirogina; Prodopirona; Sifpirona†; Termonal; Termopirona; Termoprin; Toloxin†; Zitalgin†; ***Chile:*** Baralgina M; Conmel; Novalgina†; ***Cz.:*** Novalgin; ***Fr.:*** Novalgine†; ***Ger.:*** Analgin; Berlosin; Metalgin†; Nopain; Novalgin; Novaminsulfon; ***Hong Kong:*** Metilon†; ***Hung.:*** Algopyrin; Algozone; Novalgin; Panalgorin; ***India:*** Novalgin; ***Indon.:*** Antalgin; Antrain; Cornalgin; Foragin; Licogin; Norages; Novalgin; Panstop; Pragesol; Pyronal; Ronalgin; Scanalgin; Unagen; ***Israel:*** Novalgin; Optalgin; Phanalgin; V-Talgin; ***Ital.:*** Novalgina; ***Mex.:*** Alnex; Anaprol; Anapyrol; Apixol†; Avafontan; Avaldrian†; Ayoral Simple†; Carofril†; Conmel; Dalmasin; Dalsin; Defin; Dimetirol; Dipydol; Dofisan; Dolgan; Dolizol; Dolofur; Domenal; Exalgin†; Exodalina; Fandall; Fardolpin; Farlin; Indigon; Lozima; Mach-2; Macodin; Magnil; Magnol; Magnolonas; Magnopyrol; Magsons; Mayoprina; Mecoten†; Medipirol; Mermid; Messelfenil; Metapirona; Midelin; Minoral; Mizoltec; Modimet; Neo-Melubrina; Neomelin; Neosedal; Paleodina; Pifrol; Piramagno†; Pirandall; Pirasod; Pirinovag; Piromebrina; Poloren†; Precidona; Prodolina; Prolubrin; Pyranol; Pyron; Suprin; Termonil; Utidol; Vegal; ***Neth.:*** Novalgin; ***Pol.:*** Pyrahexal; Pyralgin; Pyralginum; ***Port.:*** Conmel†; Dolocalma; Nolotil; Novalgina†; ***Rus.:*** Analgin (Анальгин); Baralgin M (Баралгин M); ***Spain:*** Algi; Citdolal†; Dolemicin; Lasain; Neo Melubrina; Nolotil; ***Switz.:*** Minalgine; Novalgine; ***Thai.:*** Acodon†; Centagin; Deparon; Genergin; Invoigin; Kno-Paine; Medalgin†; Mezabox; Nivagin; Novalgin; Olan-Gin; ***Turk.:*** Adepiron; Andolor; Baralgin M; Devaljin; Feninox; Geralgine; Kafalgin; Nogesic; Novakom-S; Novalgin; Novo-Plan; Novopyrine; Sebon; Veraljin; ***Urug.:*** Dolanet; ***Venez.:*** Bral; Buscadol†; Combanal†; Combaron†; Conmel; Delsal; Dipamona; Dipidol; Klinomel†; Nimel†; Noval†; Novalcina; Piradro†; Piradrops Simple†; Promel; Rosadol†.

Multi-ingredient: ***Arg.:*** Antispasmina; Apasmo; Apasmo Compuesto; Artifene; Bellatotal; Buscapina Compositum; Calmopirin; Canovex†; Cifespasmo Compuesto; Colobolina D; Craun†; Cronopen Balsamico; D-P†; Dentolina Plus; Dextro + Dipirona; Dextrodip; Dioxadol; Dresan Biotic†; Dresan†; Espasmo Biotenk; Espasmo Dioxadol; Fadagrip; Febrimicina†; Flexicamin A; Gastrolina Compuesta; Gobbicalm; Integrobe Plus; Keptan Compuesto†; Klosidol; Klosidol B1 B6 B12; Lisalgil Compuesto; Luar-G Compositum; Migra Dioxadol; Migral; Migral Compositum; Multin; Novopasmil Compuesto; Paratropina Compuesta; Pasmodina Compuesta; Pasmosedan Compuesto†; Rupe-N Compuesto; Saldeva†; Solacil; Sumal; Tetralgin; Tetralgin Novo; Vicefeno; ***Austria:*** Buscopan Compositum; Spasmium comp; ***Belg.:*** Buscopan Compositum; ***Braz.:*** Algexin; Algice; Aminocid†; Analgin C-R; Analgosedan†; Analverin Composto†; Analverin†; Anapirol†; Baldin-CE†; Banidor†; Bicavine; Binospan; Bioscina Composta†; Bromalgina†; Broncopinol†; Buscopan Composto; Buscoveran Composto; Butilamin; Cafalena†; Cefaldina; Cefaliv; Codeverin†; Dalgex; Dexalgen; Dimex†; Dipirol†; Disbuspan; Doralgex; Doralgina; Dorciflex; Dorflex; Doricin; Doridina; Dorilen; Doriless; Dorscopena†; Dorsedin; Dorspan; Dorzone; Ductopan†; Enxak; Espasmocron; Espasmodid Composto; Eucaliptan†; Flexalgex; Flexdor; Gripanil†; Gripion†; Gripomatine†; Griponia†; Gripsay; Hioariston; Hiospan Composto; Inib-Dor†; Itaiflex†; Killgrip†; Kindpasm; Lisador; Melpaz†; Migraliv; Migranette; Mionevrix; Miorrelax; Neocopan; Neomigran†; Neosaldina; Neuralgina; Nevralgex; Par; Pasmalgin†; Plenocedan†; Pulmorien†; Relaflex; Rielex; Sedabel†; Sedalene; Sedalex; Sedalgina; Sedalin; Sedol; Spasmotropin; Tensaldin; Tetrapulmo; Theopirina†; Tropinal; Uzara†; Veratropan Composto; ***Chile:*** Bramedil Compuesto; Buscapina Compositum; Cefalmin; Cinabel; Dioran†; Dolcopin; Dolnix; Dolo-Neurobionta†; Dolonase; Fredol; Migragesic; Migranol; Migratam; Neo Butartrol; Nospasmin Compuesto; Piretanyl; Scopanil; Silartrin†; Silrelax†; Sistalgina†; Ultrimin; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; ***Cz.:*** Algifen; Algifen Neo; Analgin; Quarelin†; ***Fin.:*** Litalgin; ***Fr.:*** Avafortan†; Cefaline-Pyrazole†; Salgydal a la noramidopyrine†; Visceralgine Forte†; ***Hung.:*** Algopyrin Complex; Quarelin; Ridol†; ***Indon.:*** Analsik; Arsinal; Biomega; Cetalgin; Cetalgin-T; Corsanural; Dactron; Danalgin; Deparon; Dolo Scanneuron; Dolo-Licobion; Foraneural; Goralgin; Hedix; Ikaneuron Plus; Neuralgin RX; Neuro Panstop; Neurobat A; Neurodial; Neurogen; Neurosanbe Plus; Neurotropic Plus; Neuroval; Opineuron; Penagon; Pritagesic; Procolic; Proneuron; Spaslic; Spasmal; Spasminal; Stileran; Supranal; Tropineuron; Unthecol; ***Ital.:*** Soma Complex†; ***Mex.:*** Algosfar; Anadil; Ayoral†; Benfol; Biomesina Compuesta; Bipasmin Compuesto; Bipasmin Compuesto N; Buscapina Compositum; Busconet; Busepan; Busprina; Colepren; Dolnefort; Dolo-Tiaminal; Espasmogress; Hiosinotil Compuesto†; Hiosultrina-F; Korifen; Neo-Brontyl; Neo-Pasmonal; Ortran†; Pasmodil; Pirobutil; Respicil; Retodol Compositum; Selpiran; Serralpina Compuesta; Singril; ***Pol.:*** Gardan P; Scopolan Compositum; Spasmalgon; Tolargin; ***Rus.:*** Analgin-Chinin (Анальгин-Хинин); Antigrippin-ANVI (Антигриппин-АНВИ); Baralgetas (Баралгетас)†; Benalgin (Бенальгин);

Maxigan (Максиган); Nebalgan (Небалган); Pentalgin-N (Пенталгин-Н); Revalgin (Ревалгин); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); Tempalgin (Темпалгин); Tempanginol (Темпангинол); ***S.Afr.:*** Baralgan†; Buscopan Compositum; Norifortan†; Scopex Co; ***Spain:*** Buscapina Compositum; Nolotil Compositum†; ***Thai.:*** Butarion; Novapam; ***Turk.:*** Buscopan Compositum; Peraljin; Skopolin; ***Venez.:*** Bort†; Buscapina Compositum; Butilamina Compuesta; Cotar†; Diezol Compuesto†; Flemibar; Hioscinol Compuesto†; Praxona; Sarifan Compuesto†; Sistalcin Compositum.

Eltenac *(rINN)*

Elténac; Eltenaco; Eltenacum. 4-(2,6-Dichloroanilino)-3-thiopheneacetic acid.

Эльтенак

$C_{12}H_9Cl_2NO_2S$ = 302.2.
CAS — 72895-88-6.

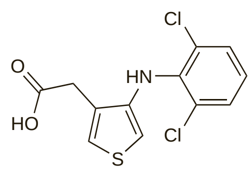

Profile

Eltenac is an NSAID (p.96) used in veterinary medicine.

Embutramide *(BAN, USAN, rINN)*

Embutramida; Embutramidum; Hoe-18-680. *N*-(β,β-Diethyl-*m*-methoxyphenethyl)-4-hydroxybutyramide.

Эмбутрамид

$C_{17}H_{27}NO_3$ = 293.4.
CAS — 15687-14-6.

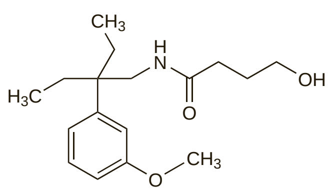

Profile

Embutramide is an opioid analgesic used in veterinary medicine for euthanasia.

Enoxolone *(BAN, rINN)*

Enoksolonas; Enoksoloni; Enoxolon; Enoxolona; Énoxolone; Enoxolonum; Glycyrrhetic Acid; Glycyrrhetinic Acid; Kwas glicyryzynowy. 3β-Hydroxy-11-oxo-olean-12-en-30-oic acid.

Эноксолон

$C_{30}H_{46}O_4$ = 470.7.
CAS — 471-53-4.
ATC — D03AX10.
ATC Vet — QD03AX10.

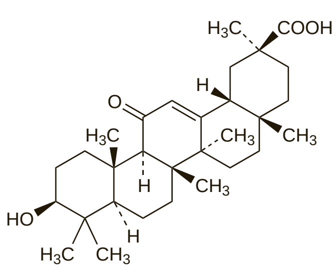

NOTE. Do not confuse with glycyrrhizic acid (p.2316).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Enoxolone). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Enoxolone is a complex triterpene prepared from glycyrrhizic acid (p.2316), a constituent of liquorice (p.1740). Enoxolone is used locally in preparations for the treatment of non-infective inflammatory disorders of the skin, mouth, throat, and rectum. Enoxolone potassium (potassium glycyrrhetinate) has been used similarly.

Derivatives of enoxolone, including its aluminium salt (p.1729) and carbenoxolone (p.1714) have been used in the treatment of benign peptic ulcer disease and other gastrointestinal disorders.

◊ Enoxolone is a potent inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase, which inactivates cortisol, and use with hydrocortisone has been shown in *animal* studies to potentiate the activity of hydrocortisone in skin.[1] Whether this also increased the systemic absorption and toxicity of hydrocortisone was unclear.[2] However, for reference to adverse effects attributed to systemic inhibition of cortisol when enoxolone (glycyrrhetinic acid) is produced during metabolism of ingested liquorice, see Effects on Fluid and Electrolyte Homoeostasis, p.1740.

A cream containing enoxolone with hyaluronic acid, telmesteine, and a grape extract, has been investigated with apparent benefit in the management of mild to moderate eczema.[3,4] However, topical application of enoxolone has been associated with contact dermatitis.[5]

1. Teelucksingh S, *et al.* Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. *Lancet* 1990; **335:** 1060–3.
2. Greaves MW. Potentiation of hydrocortisone activity in skin by glycerrhetinic acid. *Lancet* 1990; **336:** 876.
3. Belloni G, *et al.* A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair) in the treatment of mild to moderate atopic dermatitis. *Eur J Dermatol* 2005; **15:** 31–6.
4. Abramovits W, Boguniewicz M. Adult Atopiclair Study Group. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. *J Drugs Dermatol* 2006; **5:** 236–44.
5. Tanaka S, *et al.* Allergic contact dermatitis from enoxolone. *Contact Dermatitis* 2001; **44:** 192.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Dermanox; ***Fr.:*** Arthrodont; Moustidose; PO 12; ***S.Afr.:*** Arthrodont.

Multi-ingredient: *Arg.:* Anastim con RTH; Empecid Pie; ***Chile:*** Gingilacer†; Ruboril; Sebium AKN; Suavigel; ***Fr.:*** Apaisance; Erygine; Fluocaril dents sensibles; Hexalyse; Hyseke; Hyseke Solaire; Mousticologne; Moustidose Bebe-Nourrisson; Night Peel; Novophane; Novophane S; Photoderm Flush†; Photoderm Laser†; Pyreflor; Sebium AKN; Sedorrhoide; Tiq'Aouta; Vocadys; ***Hong Kong:*** Hexalyse; ***Indon.:*** Polik; ***Israel:*** Aphtagone; Aptha-X; Gelclair†; ***Ital.:*** Acnesan†; Bactilene; Benodent Gel Gengivale†; Biothymus DS; Eudent con Glysan†; Fluocaril; Lenipasta†; Lenirose†; Lisomucil Gola; Neo-Stomygen; Pastiglie Valda†; Prurex; Skab 2; Viderm†; ***Mex.:*** Angenovag; Periodentyl; ***Port.:*** Despigmentante; ***Rus.:*** Hexalyse (Гексализ); ***Spain:*** Angileptol; Anginovag; Roberfarin; ***UK:*** Atopiclair; Gelclair; Xclair; ***USA:*** Atopiclair; Gelclair; ***Venez.:*** Sebium AKN; Sensibio DS.

Epirizole *(USAN, pINN)*

DA-398; Epirizol; Épirizole; Epirizolum; Mepirizole. 4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine.

Эпиризол

$C_{11}H_{14}N_4O_2$ = 234.3.
CAS — 18694-40-1.

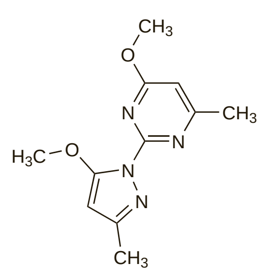

Pharmacopoeias. In *Jpn.*

Profile

Epirizole is an NSAID (p.96) that has been given in a usual oral dose of 150 to 450 mg daily in divided doses; larger doses of up to 600 mg daily have been used in patients with rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Mebron†; ***Jpn:*** Mebron; ***Venez.:*** Dalex.

Etanercept *(BAN, USAN, rINN)*

Étanercept; Etanerceptum; Etanersept; Etanersepti; rhu-TNFR:Fc; TNR-001. A dimer of 1-235 tumour necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment).

Этанерцепт

CAS — 185243-69-0.
ATC — L04AB01.
ATC Vet — QL04AB01.

Adverse Effects and Precautions

As for Infliximab, p.69.

Mild to moderate injection site reactions with symptoms of erythema, itching, pain, or swelling are common with etanercept. Other common reactions include headache, dizziness, asthenia, nausea and vomiting, abdominal pain, dyspepsia, and allergic reactions. Antibodies to etanercept may develop.

Etanercept should be used with caution in patients with heart failure.

◊ References.

1. Sánchez Carazo JL, *et al.* Safety of etanercept in psoriasis: a critical review. *Drug Safety* 2006; **29:** 675–85.

Wegener's granulomatosis. The addition of etanercept to standard therapy (including cyclophosphamide or methotrexate and corticosteroids) was not shown to be effective in patients with Wegener's granulomatosis and was associated with an increased incidence of various non-cutaneous malignancies.[1] Licensed product information recommends that etanercept should not be added to therapy in patients with Wegener's granulomatosis.

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; **352:** 351–61.

Interactions

As for Infliximab, p.71. The use of etanercept with sulfasalazine has resulted in decreased white blood cell counts; however, the clinical significance of this is unknown. For an increased incidence of malignancy when etanercept was added to standard immunosuppressive therapy in patients with Wegener's granulomatosis, see above.

Pharmacokinetics

After a single subcutaneous dose of etanercept, UK licensed product information states that the mean half-life is about 70 hours, and the time to peak serum concentration 48 hours. In contrast, US information gives the half-life as 102 hours and the time to peak concentration as about 70 hours, although with a considerable range. Repeated dosing was noted to result in a two- to sevenfold increase in serum levels of etanercept in some patients.

◊ References.

1. Korth-Bradley JM, *et al.* The pharmacokinetics of etanercept in healthy volunteers. *Ann Pharmacother* 2000; **34:** 161–4.
2. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J Clin Pharmacol* 2005; **45:** 490–7.
3. Yim D-S, *et al.* Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 246–56.
4. Don BR, *et al.* The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis. *J Pharm Pharmacol* 2005; **57:** 1407–13.
5. Sullivan JT, *et al.* Bioequivalence of liquid and reconstituted lyophilized etanercept subcutaneous injections. *J Clin Pharmacol* 2006; **46:** 654–61.
6. Nestorov I, *et al.* Pharmacokinetics of subcutaneously administered etanercept in subjects with psoriasis. *Br J Clin Pharmacol* 2006; **62:** 435–45.
7. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156:** 138–42.

Uses and Administration

Etanercept is a recombinant version of soluble human tumour necrosis factor (TNF) receptor that binds specifically to tumour necrosis factor (p.783) and blocks its interaction with endogenous cell-surface TNF receptors. This interaction prevents the important effect of TNF in the inflammatory processes of rheumatoid arthritis; elevated TNF levels are also found in psoriatic plaques, in the synovium of patients with psoriatic arthritis, and in the serum and synovium of patients with ankylosing spondylitis.

Etanercept is used in the treatment of moderately to severely active **rheumatoid arthritis** and active and progressive **psoriatic arthritis**. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs although, in severe rheumatoid arthritis, it may be used in patients not previously treated with methotrexate. In the USA, it is licensed to treat early rheumatoid arthritis or psoriatic arthritis, to reduce the signs and symptoms, delay structural damage, and improve physical function. In both indications, it is given as a subcutaneous injection in a dose of 25 mg twice weekly at intervals of 3 or 4 days. The equivalent weekly dose of 50 mg may also be given either as a single 50-mg injection or as two separate 25-mg injections (given at about the same time). In the UK, NICE recommends, based on guidelines from the British Society of Rheumatology, that treatment be stopped if there is no adequate response after 6 months. Etanercept is also indicated in the treatment of severely active **ankylosing spondylitis**; in the UK, its use is again limited to those who have had an inadequate response to conventional therapy. Doses are similar to those used for rheumatoid arthritis.

Etanercept is also used in the treatment of chronic, moderate to severe plaque **psoriasis**. In the UK, its use is usually limited to patients in whom other systemic treatments are not suitable. The recommended initial dose is 25 mg twice weekly. Alternatively, an initial dose of 50 mg twice weekly at intervals of 3 or 4 days may be given for 12 weeks; the dose should then be reduced to 25 mg twice weekly or 50 mg weekly. Initial doses of 25 or 50 mg once weekly have also been shown to be effective. Treatment should continue until remission is achieved, for up to 24 weeks. Etanercept should be stopped after 12 weeks in patients who show no response.

For details of uses and dosage in children, see below.

Administration in children. Etanercept is used in the treatment of moderately to severely active polyarticular **juvenile idiopathic arthritis**; UK licensed product information limits its use to those who have had an inadequate response to, or who are intolerant of, the disease-modifying antirheumatic drug methotrexate.

In the UK, it is given subcutaneously to children aged 4 years and over in a dose of 400 micrograms/kg (up to a maximum dose of 25 mg) twice weekly at intervals of 3 or 4 days. In the USA, etanercept is licensed for use in children as young as 2 years old. Similar doses are used although they are expressed as 800 micrograms/kg (up to a maximum dose of 50 mg) weekly: doses to be given as 2 separate injections may either be given on the same day or 3 to 4 days apart.

In the UK, NICE recommends, based on guidelines from the British Paediatric Rheumatology Group, that treatment be stopped in children if there is no response after 6 months, or an initial response is not maintained.

For references on the use of etanercept in juvenile idiopathic arthritis, see Rheumatoid Arthritis, below.

Asthma. TNF inhibitors such as etanercept have been investigated in the treatment of refractory asthma (p.1108).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[3]

1. Howarth PH, *et al.* Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; **60:** 1012–18.
2. Berry MA, *et al.* Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006; **354:** 697–708.
3. Brightling C, *et al.* Targeting TNF-α: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Dementia. A small pilot study[1] and individual case reports[2] have suggested that perispinal injection of etanercept, in doses of 25 to 50 mg weekly, may improve signs of dementia in patients with Alzheimer's disease. However, randomised controlled studies are required to confirm any benefit.

1. Tobinick E, *et al.* TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. *MedGenMed* 2006; **8:** 25. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16926764 (accessed 13/06/08)
2. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008; **5:** 2. Available at: http://www.jneuroinflammation.com/content/pdf/1742-2094-5-2.pdf (accessed 13/06/08)

Psoriasis. Etanercept is effective in patients with moderate to severe plaque psoriasis (p.1583).[1-9] It has also been successfully tried in the treatment of erythrodermic psoriasis,[10] and of plaque psoriasis in children and adolescents.[11]

Efficacy may be dose-related; in one study,[1] 25% of patients in the low-dose (25 mg once weekly) group showed at least a 75% improvement compared with 44% in the medium-dose group (25 mg twice weekly) and 59% in the high-dose group (50 mg twice weekly) after 24 weeks of etanercept treatment. However, a later multicentre study[2] in patients with chronic plaque psoriasis found that the therapeutic effect of etanercept was maintained when the dose was reduced after 12 weeks from 50 mg twice weekly to 25 mg twice weekly. An open-label extension[8] of these 2 studies found that efficacy was also sustained when patients who had received etanercept 25 mg twice weekly for at least 24 weeks had their dose altered to 50 mg once weekly.

1. Leonardi CL, *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349:** 2014–22.
2. Papp KA, *et al.* A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152:** 1304–12.
3. NICE. Etanercept and efalizumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 103 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA103guidance.pdf (accessed 13/06/08)
4. Boehncke W-H, *et al.* European Dermatology Expert Group. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 2006; **20:** 988–98.
5. Woolacott N, *et al.* NHS Health Technology Assessment Programme. Etanercept and efalizumab for the treatment of psoriasis: a systematic review (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1046.pdf (accessed 13/06/08)
6. Tyring S, *et al.* Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143:** 719–26.
7. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
8. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156:** 138–42.
9. Ahmad K, Rogers S. Two years of experience with etanercept in recalcitrant psoriasis. *Br J Dermatol* 2007; **156:** 1010–14.
10. Esposito M, *et al.* Treatment of erythrodermic psoriasis with etanercept. *Br J Dermatol* 2006; **155:** 156–9.
11. Paller AS, *et al.* Etanercept Pediatric Psoriasis Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; **358:** 241–51.

Rheumatoid arthritis. Some references to the use of etanercept in rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10).

1. Weinblatt ME, *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; **340:** 253–9.
2. Moreland LW, *et al.* Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999; **130:** 478–86.
3. Lovell DJ, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000; **342:** 763–9.
4. Bathon JM, *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1586–93. Correction. *ibid.* 2001; **344:** 76.
5. Johnson CJ, *et al.* Etanercept in juvenile rheumatoid arthritis. *Ann Pharmacother* 2001; **35:** 464–71.
6. Genovese MC, *et al.* Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; **46:** 1443–50.
7. NICE. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis: Technology Appraisal Guidance 35 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf (accessed 13/06/08)
8. Klareskog L, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363:** 675–81.
9. Genovese MC, *et al.* Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1232–42.
10. Bathon JM, *et al.* Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol* 2006; **33:** 234–43.
11. van Riel PLCM, *et al.* ADORE (Add Enbrel or Replace Methotrexate) Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis* 2006; **65:** 1478–83.
12. Moreland LW, *et al.* Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006; **33:** 854–61.
13. van der Heijde D, *et al.* Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; **54:** 1063–74.
14. Chen Y-F, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 13/06/08)
15. Weisman MH, *et al.* A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology (Oxford)* 2007; **46:** 1122–5.
16. Dhillon S, *et al.* Etanercept: a review of its use in the management of rheumatoid arthritis. *Drugs* 2007; **67:** 1211–41. Correction. *ibid.*; 1849.
17. van der Heijde D, *et al.* Etanercept Study 400 Investigators. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Ann Rheum Dis* 2008; **67:** 182–8.
18. van der Heijde D, *et al.* Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3928–39.
19. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)
20. Gartlehner G, *et al.* Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008; **27:** 67–76.

Spondyloarthropathies. References to the use of etanercept in the treatment of ankylosing spondylitis and psoriatic arthritis (p.13).

1. Mease PJ, *et al.* Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; **356:** 385–90.
2. Brandt J, *et al.* Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; **48:** 1667–75.
3. Davis JC, *et al.* Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; **48:** 3230–6.
4. Mease PJ, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; **50:** 2264–72.
5. Baraliakos X, *et al.* Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum* 2005; **53:** 856–63.
6. Mease PJ, *et al.* Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006; **33:** 712–21.
7. NICE. Etanercept and infliximab for the treatment of adults with psoriatic arthritis: Technology Appraisal Guidance 104 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA104guidance.pdf (accessed 13/06/08)
8. Woolacott N, *et al.* NHS Health Technology Assessment Programme. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation (issued September 2006). Available at: http://www.hta.ac.uk/fullmono/mon1031.pdf (accessed 13/06/08)
9. van der Heijde D, *et al.* Etanercept Study 314 Investigators. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 1572–7.
10. Cantini F, *et al.* Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum* 2006; **55:** 812–6.
11. Woolacott NF, *et al.* Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. *Clin Exp Rheumatol* 2006; **24:** 587–93.
12. Braun J, *et al.* Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology (Oxford)* 2007; **46:** 999–1004.
13. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
14. Frankel EH, *et al.* Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. *Cutis* 2007; **79:** 322–6.
15. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 13/06/08)
16. Gottlieb AB, *et al.* Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. *J Dermatolog Treat* 2006; **17:** 343–52.
17. Hoy SM, Scott LJ. Etanercept: a review of its use in the management of ankylosing spondylitis and psoriatic arthritis. *Drugs* 2007; **67:** 2609–33.

Vasculitic syndromes. For a preliminary report on the use of etanercept in Takayasu's arteritis, see p.1514.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Enbrel; ***Austral.:*** Enbrel; ***Belg.:*** Enbrel; ***Braz.:*** Enbrel; ***Canad.:*** Enbrel; ***Chile:*** Enbrel; ***Cz.:*** Enbrel; ***Denm.:*** Enbrel; ***Fin.:*** Enbrel; ***Fr.:*** Enbrel; ***Ger.:*** Enbrel; ***Gr.:*** Enbrel; ***Hong Kong:*** Enbrel; ***India:*** Enbrel; ***Indon.:*** Enbrel; ***Irl.:*** Enbrel; ***Israel:*** Enbrel; ***Ital.:*** Enbrel; ***Malaysia:*** Enbrel; ***Mex.:*** Enbrel; ***Neth.:*** Enbrel; ***Norw.:*** Enbrel; ***NZ:*** Enbrel; ***Philipp.:*** Enbrel; ***Pol.:*** Enbrel; ***Port.:*** Enbrel; ***S.Afr.:*** Enbrel; ***Singapore:*** Enbrel; ***Spain:*** Enbrel; ***Swed.:*** Enbrel; ***Switz.:*** Enbrel; ***Thai.:*** Enbrel; ***Turk.:*** Enbrel; ***UK:*** Enbrel; ***USA:*** Enbrel; ***Venez.:*** Enbrel.

Multi-ingredient: ***Hung.:*** Enbrel.

Ethenzamide *(BAN, rINN)*

Aethoxybenzamidum; Etentsamidi; Etenzamid; Etenzamida; Etenzamide; Éthenzamide; Ethenzamidum; Ethoxybenzamide; Ethylsalicylamide; HP-209. 2-Ethoxybenzamide.

Этензамид

$C_9H_{11}NO_2$ = 165.2.
CAS — 938-73-8.
ATC — N02BA07.
ATC Vet — QN02BA07.

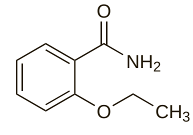

Pharmacopoeias. In *Jpn.*

Profile

Ethenzamide is a salicylic acid derivative (see Aspirin, p.20) given by mouth in painful and inflammatory conditions and to reduce fever.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Coldadolin; Dolmix; Helopyrin; Nisicur; Seltoc; ***Cz.:*** Cephyl†; ***Ger.:*** Glutisal†; Kolton grippale N†; ***Indon.:*** Farapon; Neo Novapon Plus; ***Jpn:*** Sin Colgen Kowa Kaze; ***Pol.:*** Erka; Etomar; Etopiryna; ***Port.:*** Cephyl; ***Rus.:*** Nextrim Aktiv (Некстрим Актив); ***Switz.:*** Nicaphlogyl†; Seranex sans codeine†.

Ethoheptazine Citrate *(BANM, rINNM)*

Citrato de etoheptacina; Éthoheptazine, Citrate d'; Ethoheptazini Citras; Wy-401. Ethyl 1-methyl-4-phenylperhydroazepine-4-carboxylate dihydrogen citrate.

Этогептазина Цитрат

$C_{16}H_{23}NO_2,C_6H_8O_7 = 453.5.$

CAS — 77-15-6 (ethoheptazine); 6700-56-7 (ethoheptazine citrate); 2085-42-9 ((±)-ethoheptazine citrate).

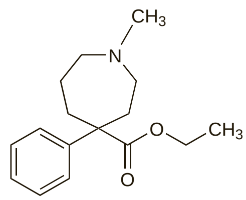

(ethoheptazine)

Profile

Ethoheptazine citrate is an opioid analgesic (p.101) structurally related to pethidine (p.113). It has been used as an analgesic in the short-term treatment of mild to moderate pain, usually with other drugs such as aspirin and meprobamate.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Equagesic; ***S.Afr.:*** Equagesic.

Ethyl Nicotinate

Nicotinato de etilo.

$C_8H_9NO_2 = 151.2.$

CAS — 614-18-6.

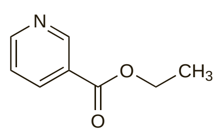

Profile

Ethyl nicotinate is used in concentrations of up to 2% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It has also been used as suppositories in anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Mucotherm.

Multi-ingredient: ***Austria:*** Percucor†; Thermal; ***Belg.:*** Transvane; ***Hung.:*** Nicoflex; ***Irl.:*** Transvasin; ***Norw.:*** Thermal†; ***Switz.:*** Baume Esco Forte; Frixo-Dragon Vert†; Knobel Huile N; Thermocutan†; Ziegella; ***UK:*** PR Heat Spray; Transvasin Heat Rub.

Ethyl Salicylate

Salicilato de etilo. Ethyl 2-hydroxybenzoate.

Этилсалицилат

$C_9H_{10}O_3 = 166.2.$

CAS — 118-61-6.

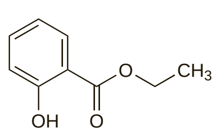

Profile

Ethyl salicylate is a salicylic acid derivative that is used similarly to methyl salicylate (p.85) in concentrations of up to 5% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Deep Heat; Radian-B†; ***Belg.:*** Rado-Salil; ***Israel:*** Deep Heat Spray; ***Ital.:*** Remy; ***Pol.:*** Deep Heat; ***S.Afr.:*** Deep Heat Spray; ***Singapore:*** Deep Heating Spray†; ***Switz.:*** Alginex†; ***UK:*** Deep Heat Spray; Dubam; Numark Muscle Spray; Ralgex.

Ethylmorphine Hydrochloride *(BANM)*

Aethylmorphinae Hydrochloridum; Aethylmorphini Hydrochloridum; Chlorhydrate de Codéthyline; Ethylmorfin-hydrochlorid dihydrát; Éthylmorphine, chlorhydrate d'; Ethylmorphini hydrochloridum; Ethylmorphini Hydrochloridum Dihydricum; Ethylmorphinium Chloride; Etilmorfina, hidrocloruro de; Etilmorfin-hidroklorid; Etilmorfino hidrochloridas; Etylmorfinhydroklorid; Etylomorfiny chlorowodorek; Etyylimorfiinihydrokloridi. 3-O-Ethylmorphine hydrochloride dihydrate; 7,8-Didehydro-4,5-epoxy-3-ethoxy-17-methylmorphinan-6-ol hydrochloride dihydrate.

$C_{19}H_{23}NO_3,HCl,2H_2O = 385.9.$

CAS — 76-58-4 (ethylmorphine); 125-30-4 (ethylmorphine hydrochloride).

ATC — R05DA01; S01XA06.

ATC Vet — QR05DA01; QS01XA06.

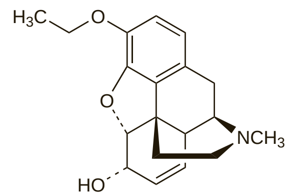

(ethylmorphine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Ethylmorphine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. A 2% solution in water has a pH of 4.3 to 5.7. Protect from light.

Profile

Ethylmorphine hydrochloride is an opioid analgesic (p.101) and has properties similar to those of codeine (p.37). It is used mainly as a cough suppressant. It has also been used for its analgesic and antidiarrhoeal properties. It was formerly given in eye drops as a lymphagogue.

Ethylmorphine free base and the camphorate and camsilate have also been used.

◊ References.

1. Aasmundstad TA, *et al.* Biotransformation and pharmacokinetics of ethylmorphine after a single oral dose. *Br J Clin Pharmacol* 1995; **39:** 611–20.
2. Jonasson B, *et al.* Fatal poisonings where ethylmorphine from antitussive medications contributed to death. *Int J Legal Med* 1999; **112:** 299–302.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dionina; ***Belg.:*** Codethyline; ***Cz.:*** Diolan; ***Fin.:*** Cocillana; ***Fr.:*** Dithiol†; ***UK:*** Collins Elixir.

Multi-ingredient: ***Austria:*** Modiscop; ***Belg.:*** Longbalsem; Saintbois; Tux†; ***Chile:*** Codelasa; ***Fin.:*** Indalgin; ***Fr.:*** Ephydion; Humex†; Tussipax; Vegetoserum; ***Hung.:*** Dolor; ***India:*** Bell Diono Resolvent; Bell Resolvent; ***Ital.:*** Mindol-Merck†; ***Norw.:*** Cosylan; Solvipect comp; ***Port.:*** Bronquiasmol†; Calmarum†; Xarope Antigripal†; ***Spain:*** Demusin; Sedalmerck†; ***Swed.:*** Cocillana-Etyfin; Lepheton; ***Switz.:*** Ipeca†; Phol-Tux; Saintbois; Sano Tuss; ***Turk.:*** Fenokodin; ***Venez.:*** Novacodin.

Etodolac *(BAN, USAN, rINN)*

AY-24236; Etodolaakki; Étodolac; Etodolaco; Etodolacum; Etodolák; Etodolak; Etodolakas; Etodolic Acid. 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

Этодолак

$C_{17}H_{21}NO_3 = 287.4.$

CAS — 41340-25-4.

ATC — M01AB08.

ATC Vet — QM01AB08.

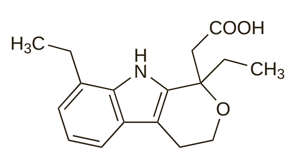

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Etodolac). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone.

USP 31 (Etodolac). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

The presence of phenolic metabolites of etodolac in the urine may give rise to a false-positive reaction for bilirubin.

Effects on the blood. Agranulocytosis has been reported in a patient receiving etodolac.[1] Coombs-positive haemolytic anaemia due to sensitivity to etodolac metabolites has also been reported.[2]

1. Cramer RL, *et al.* Agranulocytosis associated with etodolac. *Ann Pharmacother* 1994; **28:** 458–60.
2. Cunha PD, *et al.* Immune hemolytic anemia caused by sensitivity to a metabolite of etodolac, a nonsteroidal anti-inflammatory drug. *Transfusion* 2000; **40:** 663–8.

Effects on the gastrointestinal tract. Etodolac is reported to be a preferential inhibitor of cyclo-oxygenase 2 (COX-2) and consequently it may produce less gastric toxicity than the non-selective NSAIDs such as naproxen.[1-3]

1. Taha AS, *et al.* Effect of repeated therapeutic doses of naproxen and etodolac on gastric and duodenal mucosal prostaglandins (PGs) in rheumatoid arthritis (RA). *Gut* 1989; **30:** A751.
2. Bianchi Porro G, *et al.* A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991; **229:** 5–8.
3. Weideman RA, *et al.* Risks of clinically significant upper gastrointestinal events with etodolac and naproxen: a historical cohort analysis. *Gastroenterology* 2004; **127:** 1322–8.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Etodolac is a chiral compound given as the racemate. Peak plasma concentrations of the active (S)-enantiomer and of the inactive (R)-enantiomer are usually obtained within about 2 hours of a dose by mouth but plasma concentrations of the (R)-enantiomer have been reported to greatly exceed those of the (S)-enantiomer. Both enantiomers are highly bound to plasma proteins. Both are also distributed to the synovial fluid, although the difference in their concentrations may not be as marked as the difference in plasma concentrations. The plasma half-life of total etodolac has been reported to be about 7 hours; excretion is mainly in the urine as hydroxylated metabolites and glucuronide conjugates; some may be excreted in the bile.

◊ References.

1. Brocks DR, *et al.* Stereoselective disposition of etodolac enantiomers in synovial fluid. *J Clin Pharmacol* 1991; **31:** 741–6.
2. Brocks DR, *et al.* The stereoselective pharmacokinetics of etodolac in young and elderly subjects, and after cholecystectomy. *J Clin Pharmacol* 1992; **32:** 982–9.
3. Brocks DR, Jamali F. Etodolac clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 259–74.
4. Boni J, *et al.* Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. *J Clin Pharmacol* 1999; **39:** 729–37.
5. Boni JP, *et al.* Pharmacokinetics of etodolac in patients with stable juvenile rheumatoid arthritis. *Clin Ther* 1999; **21:** 1715–24.

Uses and Administration

Etodolac, a pyrano-indoleacetic acid derivative, is an NSAID (p.99) reported to be a preferential inhibitor of cyclo-oxygenase 2 (COX-2). It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, and osteoarthritis and for the treatment of acute pain.

For the treatment of rheumatoid arthritis and osteoarthritis, the recommended oral dose is initially 600 to 1000 mg daily in divided doses adjusted according to response; single daily doses of up to 600 mg may also be given. Modified-release preparations are available for once-daily use in these conditions. For doses in children, see below.

For the treatment of acute pain, the recommended dose is 200 to 400 mg every 6 to 8 hours to a maximum of 1 g daily.

Administration in children. In the USA modified-release preparations of etodolac may be given for the oral treatment of juvenile idiopathic arthritis in children aged 6 to 16 years. Doses are given once daily according to body-weight as follows:

- 20 to 30 kg: 400 mg
- 31 to 45 kg: 600 mg
- 46 to 60 kg: 800 mg
- over 60 kg: 1 g

Preparations

BP 2008: Etodolac Capsules; Etodolac Tablets;
USP 31: Etodolac Capsules; Etodolac Extended-Release Tablets; Etodolac Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Lodine†; ***Braz.:*** Flancox; ***Canad.:*** Ultradol†; ***Denm.:*** Todolac; ***Fin.:*** Lodine; ***Fr.:*** Lodine; ***Gr.:*** Ecridoxan†; Lonine; ***Hong Kong:*** Lodine; ***Indon.:*** Lonene; ***Israel:*** Etopan; ***Ital.:*** Lodine†; ***Jpn:*** Hypen; ***Mex.:*** Lodine†; ***Port.:*** Acudor; Articulan; Dualgan; Lodine†; Lodot†; Metazin†; Sodolac; ***Switz.:*** Lodine; ***Thai.:*** Etonox; ***Turk.:*** Edolar; Etodin; Etol; Lodine; Tadolak; ***UK:*** Eccoxolac; Etopan; Lodine; ***USA:*** Lodine†; ***Venez.:*** Lodine†.

Etofenamate *(BAN, USAN, rINN)*

B-577; Bay-d-1107; Etofenamaatti; Etofenamát; Etofenamat; Etofenamatas; Étofénamate; Etofenamato; Etofenamatum; TV-485; TVX-485; WHR-5020. 2-(2-Hydroxyethoxy)ethyl *N*-(ααα-trifluoro-*m*-tolyl)anthranilate.

Этофенамат

$C_{18}H_{18}F_3NO_4$ = 369.3.
CAS — 30544-47-9.
ATC — M02AA06.
ATC Vet — QM02AA06.

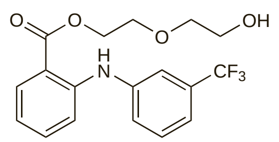

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Etofenamate). A yellowish viscous liquid. Practically insoluble in water; miscible with alcohol and with ethyl acetate.

Profile

Etofenamate is an NSAID (p.96) that has been applied topically in a concentration of 5 or 10% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. It has also been given by deep intramuscular injection in single doses of 1 g.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Bayrogel†; Contour†; Flogol; ***Austria:*** Rheumon; Traumon; ***Belg.:*** Flexium; ***Braz.:*** Bayro; ***Chile:*** Bayagel; Bayro†; Flogojet; Master-Gel†; Valorel; ***Cz.:*** Etogel†; Rheuma Denk†; Rheumon; Traumon; ***Ger.:*** Algesalona E†; Rheuma-Gel; Rheumon; Traumon; ***Gr.:*** Cimal†; Etofenol; Fenam†; Melferut; Pazergicel†; Radermin; Reumina; Roiplon; ***Hong Kong:*** Flogoprofen; ***Hung.:*** Activon Extra; Rheumon; Traumon†; ***Ital.:*** Bayro; ***Mex.:*** Bayro; ***Pol.:*** Rheumon; Traumon; ***Port.:*** Fenogel; Reumon; ***Spain:*** Aspitopic; Flogoprofen; Zenavan; ***Switz.:*** Activon†; Etofen†; Rheumon; Traumalix; ***Turk.:*** Doline; Flexo; Painex; Rheumon; ***Venez.:*** Traflan.

Multi-ingredient: ***Arg.:*** Bayagel; ***Austria:*** Thermo-Rheumon; ***Chile:*** Bayro-Therm†; ***Cz.:*** Thermo-Rheumon†; ***Ger.:*** Thermo-Rheumon†; ***Gr.:*** Thermo-Roiplon; ***Hung.:*** Thermo-Rheumon†; ***Mex.:*** Bayro Termo; ***Pol.:*** Thermo-Rheumon; ***Turk.:*** Thermo-Doline; Thermo-Rheumon; Thermoflex; ***Venez.:*** Reugel.

Etoricoxib *(BAN, USAN, rINN)*

Étoricoxib; Etoricoxibum; Etorikoksib; Etorikoksibi; Etorikoxib; L-791456; MK-0663; MK-663. 5-Chloro-6′-methyl-3-[*p*-(methylsulfonyl)phenyl]-2,3′-bipyridine.

Эторикоксиб

$C_{18}H_{15}ClN_2O_2S$ = 358.8.
CAS — 202409-33-4.
ATC — M01AH05.
ATC Vet — QM01AH05.

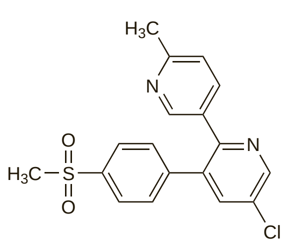

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving etoricoxib; it should be stopped at the first signs of hypersensitivity. Etoricoxib should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen.

Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective COX-2 inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled (see also Effects on the Cardiovascular System, below).

Etoricoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Caution is recommended when using etoricoxib in dehydrated patients; it may be advisable to rehydrate patients before giving etoricoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p.121). The cardiovascular safety of etoricoxib has been assessed in the MEDAL programme[1] which pooled data from 3 studies involving over 30 000 patients with either osteoarthritis or rheumatoid arthritis. Patients with osteoarthritis were given etoricoxib 60 or 90 mg daily; those with rheumatoid arthritis received 90 mg daily. In all studies, diclofenac 150 mg daily was given as the comparator; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After an average treatment duration of 18 months, the rates of thrombotic events such as myocardial infarction, stroke, and sudden or unexplained death with etoricoxib were similar to those for diclofenac. (It has been suggested that diclofenac itself may increase the risk of some thrombotic events; for further details, see p.97.) The programme also found that the rate of some other non-thrombotic cardiovascular events was increased with etoricoxib: one of the 3 studies showed that there was a non-significant increase in the rate of heart failure with etoricoxib 90 mg daily compared to diclofenac; withdrawals due to oedema were also more frequent with high-dose etoricoxib than with diclofenac or etoricoxib 60 mg daily. In addition, the number of patients stopping treatment because of hypertension was higher with both doses of etoricoxib than with diclofenac. Similar results were seen in the other 2 studies.

In another study[2] that pooled pre-licensing data, the risk of thrombotic events with etoricoxib, given at a dose of at least 60 mg daily, was also found to be similar to that for placebo treatment, ibuprofen (2.4 g daily), diclofenac (150 mg daily), and naproxen (1 g daily), although there was a trend towards more events with etoricoxib than with naproxen. For details on the relative risk of thrombotic events associated with non-selective NSAIDs, see p.97.

The EMEA's Committee for Medicinal Products for Human Use (CHMP)[3] has recommended the inclusion of a warning in the labelling of etoricoxib that it must not be given to patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled; in addition, high blood pressure should be controlled before starting treatment and monitored for 2 weeks afterwards then regularly thereafter.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p.34.

1. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368:** 1771–81.
2. Curtis SP, *et al.* Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. *Curr Med Res Opin* 2006; **22:** 2365–74.
3. EMEA. EMEA recommends strengthening warnings and contraindications for etoricoxib-containing medicines used in the treatment of rheumatoid arthritis and ankylosing spondylitis (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/33363608en.pdf (accessed 16/07/08)

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as etoricoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information states that upper gastrointestinal perforation, ulceration, and bleeds, in some cases fatal, have occurred with etoricoxib treatment; consequently, it should be used with caution in patients with a history of, or at risk of developing, such events. In addition, etoricoxib should not be used in patients with active gastrointestinal ulceration or bleeding.

Results from controlled studies have suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a study[1] of the pooled data from 3 randomised clinical studies, etoricoxib (in doses of 60 or 90 mg daily) was associated with significantly less frequent upper gastrointestinal clinical events than diclofenac (150 mg daily). The result was attributed to the lower rate of uncomplicated ulcers with etoricoxib compared with diclofenac; there was no difference in the rate of complicated gastrointestinal events between the 2 drugs. The lower rate of uncomplicated events with etoricoxib compared with diclofenac was not affected by treatment with low-dose aspirin or proton pump inhibitors. An analysis[2] by the manufacturer, of pooled data from 10 randomised clinical studies, found that etoricoxib (in daily doses of 60, 90, or 120 mg) was associated with a lower combined risk of upper gastrointestinal perforations and bleeding, and symptomatic gastroduodenal ulcers when compared with non-selective NSAIDs (diclofenac 150 mg daily, ibuprofen 2.4 g daily, or naproxen 1 g daily) as a group. This reduced risk was seen even in patients with known risk factors for such complications such as the elderly and those with a history of gastrointestinal reactions.

1. Laine L, *et al.* Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; **369:** 465–73.
2. Ramey DR, *et al.* The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; **21:** 715–22.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as etoricoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Interactions

The metabolism of etoricoxib is mediated by the cytochrome P450 isoenzyme CYP3A4. Use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of etoricoxib. In addition, *in vitro* studies suggest that several other isoenzymes may also mediate the main metabolic pathway of etoricoxib. Rifampicin, a potent inducer of CYP isoenzymes, has produced decreased plasma concentrations of etoricoxib.

Etoricoxib is an inhibitor of human sulfotransferase activity and has been shown to increase the plasma concentration of ethinylestradiol. Interactions with other drugs, such as oral salbutamol and minoxidil, also metabolised by this enzyme may be a possibility and licensed product information advises care with such combinations.

For interactions associated with NSAIDs in general, see p.99.

Pharmacokinetics

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations are reached in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption. Plasma protein binding is about 92%. At steady state the half-life of etoricoxib is about 22 hours. Etoricoxib is extensively metabolised with less than 2% of a dose recovered in the urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6′-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6′-carboxylic acid derivative, the major metabolite. Both are inactive or only weak cyclo-oxygenase-2 (COX-2) inhibitors. Excretion is mainly via the urine (70%) with only 20% of a dose appearing in the faeces. Studies in *animals* suggest that etoricoxib may cross the placenta and that some is distributed into breast milk.

◊ References.

1. Agrawal NGB, *et al.* Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *J Clin Pharmacol* 2003; **43:** 268–76.
2. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with hepatic impairment. *J Clin Pharmacol* 2003; **43:** 1136–48.
3. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with renal impairment. *J Clin Pharmacol* 2004; **44:** 48–58.

Uses and Administration

Etoricoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the symptomatic relief of rheumatoid arthritis, osteoarthritis, and acute gouty arthritis.

In osteoarthritis, etoricoxib is given orally in a usual dose of 30 mg once daily, increased to 60 mg once daily if necessary. The recommended dose in rheumatoid arthritis is 90 mg once daily; higher doses of 120 mg once daily are used in gouty arthritis although such doses should only be used for the acute symptomatic period and for a maximum of 8 days. For dosage recommendations in patients with hepatic impairment, see below.

◊ References.

1. Patrignani P, *et al.* Clinical pharmacology of etoricoxib: a novel selective COX2 inhibitor. *Expert Opin Pharmacother* 2003; **4:** 265–84.
2. Dallob A, *et al.* Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003 **43:** 573–85.
3. Martina SD, *et al.* Etoricoxib: a highly selective COX-2 inhibitor. *Ann Pharmacother* 2005; **39:** 854–62.

Administration in hepatic impairment. The maximum oral dose of etoricoxib in patients with mild hepatic impairment (Child-Pugh score of 5 to 6), regardless of indication, is 60 mg once daily; those with moderate impairment (Child-Pugh 7 to 9) should be given a maximum of 60 mg every other day or 30 mg once daily. Etoricoxib should not be given to patients with severe hepatic impairment (Child-Pugh 10 or more).

Musculoskeletal and joint disorders. The selective cyclo-oxygenase-2 (COX-2) inhibitor etoricoxib is used in the treatment of the musculoskeletal disorders osteoarthritis and rheumatoid arthritis (see p.11 and p.11, respectively). However, in the UK, it is recommended that the use of selective COX-2 inhibitors is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p.97).

Etoricoxib is also used in gouty arthritis (p.552) and has been tried in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p.13).

References.

1. Cochrane DJ, *et al.* Etoricoxib. *Drugs* 2002; **62:** 2637–51.
2. Schumacher HR, *et al.* Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002; **324:** 1488–92.
3. Gottesdiener K, *et al.* Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002; **41:** 1052–61.
4. Wiesenhutter CW, *et al.* Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 470–9.
5. van der Heijde D, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; **52:** 1205–15.
6. Curtis SP, *et al.* Etoricoxib in the treatment of osteoarthritis over 52-weeks: a double-blind, active-comparator controlled trial [NCT00242489]. *BMC Musculoskelet Disord* 2005; **6:** 58. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-6-58.pdf (accessed 01/11/07)
7. Bingham CO, *et al.* Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology (Oxford)* 2007; **46:** 496–507.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Arcoxia; ***Austria:*** Arcoxia; Auxib; ***Belg.:*** Arcoxia; ***Braz.:*** Arcoxia; ***Cz.:*** Arcoxia; ***Denm.:*** Arcoxia; ***Fin.:*** Arcoxia; ***Fr.:*** Arcoxia; ***Ger.:*** Arcoxia; ***Gr.:*** Arcoxia; ***Hong Kong:*** Arcoxia; ***India:*** Ebov; Ecoxib†; Etoxib; Etozox; Kretos†; Nucoxia; ***Indon.:*** Arcoxia; ***Irl.:*** Arcoxia; ***Israel:*** Arcoxia; ***Ital.:*** Algix; Arcoxia; Tauxib; ***Malaysia:*** Arcoxia; ***Mex.:*** Arcoxia; ***Neth.:*** Arcoxia; Auxib; ***Norw.:*** Arcoxia; ***NZ:*** Arcoxia; ***Philipp.:*** Arcoxia; ***Port.:*** Arcoxia; Exxiv; Turox; ***Singapore:*** Arcoxia; ***Spain:*** Arcoxia; ***Swed.:*** Arcoxia; ***Thai.:*** Arcoxia; ***UK:*** Arcoxia; ***Venez.:*** Arcoxia.

Etorphine Hydrochloride *(BANM, rINNM)*

Étorphine, Chlorhydrate d'; Etorphini Hydrochloridum; Hidrocloruro de etorfina; M-99; 19-Propylorvinol Hydrochloride. (6*R*,7*R*,14*R*)-7,8-Dihydro-7-[(1*R*)-1-hydroxy-1-methylbutyl]-6-*O*-methyl-6,14α-ethenomorphine hydrochloride; (2*R*)-2-[(−)-(5*R*,6*R*,7*R*,14*R*)-4,5-Epoxy-3-hydroxy-6-methoxy-9a-methyl-6,14-ethenomorphinan-7-yl]pentan-2-ol hydrochloride.

Эторфина Гидрохлорид

$C_{25}H_{33}NO_4,HCl = 448.0.$

CAS — 14521-96-1 (etorphine); 13764-49-3 (etorphine hydrochloride).

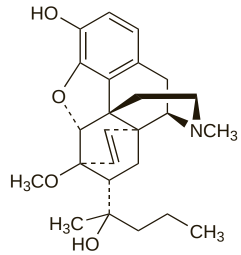

(etorphine)

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Etorphine Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.0 to 5.5. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102. Etorphine is not used therapeutically in humans.

Etorphine hydrochloride is highly potent and rapid acting; minute amounts can exert serious effects leading to coma. It may be absorbed through skin and mucous membranes. It is thus advisable to inject an antagonist *immediately* after contamination of skin or mucous membranes with preparations containing etorphine hydrochloride and to wash the affected areas copiously. Accidental injection or needle scratch injuries should also be treated immediately by injecting an antagonist. Naloxone is preferred as the antagonist in medical treatment. However, veterinary preparations of etorphine are supplied with a preparation (*Revivon*) containing diprenorphine hydrochloride (p.1445) and this should be used for immediate first-aid antagonism if naloxone is not available.

Uses and Administration

Etorphine hydrochloride is a highly potent opioid analgesic (p.104) used for reversible neuroleptanalgesia (see Anaesthetic Techniques, p.1780) in veterinary medicine. It is given with acepromazine maleate or levomepromazine (*Immobilon*) to restrain animals and before minor veterinary surgery. The duration of action of etorphine is up to about 45 to 90 minutes depending on the species but it may be longer in man, especially if the large animal preparation is involved.

Famprofazone *(BAN, rINN)* ⊗

Famprofazona; Famprofazonum. 4-Isopropyl-2-methyl-3-[methyl(α-methylphenethyl)aminomethyl]-1-phenyl-3-pyrazolin-5-one.

Фампрофазон

$C_{24}H_{31}N_3O = 377.5.$

CAS — 22881-35-2.

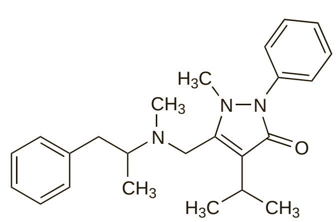

Profile

Famprofazone has analgesic and antipyretic properties and has been given orally, usually with other analgesics.

Pharmacokinetics. On ingestion, metabolic products of famprofazone include amfetamine and metamfetamine enantiomers,[1,2] which has led to false positive results on drug testing.[3] For sporting competition famprofazone was classified by the World Anti-Doping Agency as a stimulant.[4]

1. Greenhill B, *et al.* Metabolic profile of amphetamine and methamphetamine following administration of the drug famprofazone. *J Anal Toxicol* 2003; **27:** 479–84.
2. Rodriguez AT, *et al.* Metabolic profile of famprofazone following multidose administration. *J Anal Toxicol* 2004; **28:** 432–8.
3. Musshoff F, Kraemer T. Identification of famprofazone ingestion. *Int J Legal Med* 1998; **111:** 305–8.
4. World Anti-Doping Agency. The world anti-doping code: the 2008 prohibited list international standard. Available at: http://www.wada-ama.org/rtecontent/document/2008_List_En.pdf (accessed 24/07/08)

Felbinac *(BAN, USAN, rINN)*

CL-83544; Felbinaakki; Felbinaco; Felbinacum; Felbinak; LJC-10141. Biphenyl-4-ylacetic acid.

Фелбинак

$C_{14}H_{12}O_2 = 212.2.$

CAS — 5728-52-9.
ATC — M02AA08.
ATC Vet — QM02AA08.

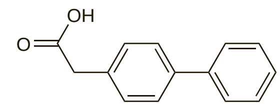

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Felbinac). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

Adverse Effects and Precautions

Mild local reactions such as erythema, dermatitis, and pruritus have occurred in patients using felbinac topically. More serious adverse effects including bullous dermatoses such as epidermal necrolysis and erythema multiforme, photosensitivity, anaphylaxis, and bronchospasm or wheeziness have also been reported. Gastrointestinal disturbances may occur.

Felbinac preparations should be avoided in patients with a history of hypersensitivity reactions to aspirin or other NSAIDs.

Incidence of adverse effects. The UK CSM had received 49 reports of adverse reactions associated with felbinac by October 1989, about 11 months after it was released on the UK market.[1] Bronchospasm or wheeziness was reported in 8 patients using felbinac gel. Four of these patients had a history of asthma of whom 3 were reported to have had a similar reaction to aspirin or other NSAIDs. Other reported reactions included skin rashes (17 cases), local application site reactions (7), and dyspepsia (6).

1. CSM. Felbinac (Traxam) and bronchospasm. *Current Problems 27* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024444&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Uses and Administration

Felbinac, an active metabolite of fenbufen (below), is an NSAID (p.99). It is used topically in the symptomatic treatment of musculoskeletal pain including that due to soft-tissue injuries. It is applied as a 3% gel or a 3.17% foam to unbroken skin over affected areas 2 to 4 times daily. The total daily dose of gel or foam should not exceed 25 g regardless of the size or number of affected areas. Therapy should be reviewed after 14 days.

Diisopropanolamine felbinac has been used similarly.

◊ References.

1. Hosie GAC. The topical NSAID, felbinac, versus oral ibuprofen: a comparison of efficacy in the treatment of acute lower back injury. *Br J Clin Res* 1993; **4:** 5–17.

Preparations

BP 2008: Felbinac Cutaneous Foam; Felbinac Gel.

Proprietary Preparations (details are given in Part 3)

Austria: Target†; ***Belg.:*** Flexfree; ***Ger.:*** Spalt Schmerz-Gel†; ***Irl.:*** Traxam; ***Ital.:*** Dolinac; Traxam; ***Jpn:*** Seltouch; ***Switz.:*** Dolo Target†; ***UK:*** Traxam.

Fenbufen *(BAN, USAN, rINN)*

CL-82204; Fenbufeeni; Fenbufén; Fenbufenas; Fenbufène; Fenbufenum. 4-(Biphenyl-4-yl)-4-oxobutyric acid.

Фенбуфен

$C_{16}H_{14}O_3 = 254.3.$

CAS — 36330-85-5.
ATC — M01AE05.
ATC Vet — QM01AE05.

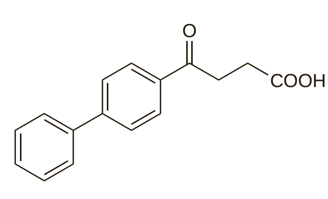

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Fenbufen). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in acetone, and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96, although the commonest adverse effects of fenbufen are skin rashes, usually occurring within the first 2 weeks of therapy, and particularly in women and in patients with sero-negative rheumatoid arthritis or psoriatic arthritis. Disorders such as epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have also been reported. A small number of patients who develop rash may go on to develop a severe illness characterised by pulmonary eosinophilia or allergic alveolitis. Treatment with fenbufen should be stopped immediately if a rash appears.

Breast feeding. UK licensed product information advises that fenbufen should be avoided in breast-feeding mothers, because of the presence of its metabolites in breast milk.

Effects on the blood. Haemolytic anaemia[1] and aplastic anaemia[2] have been reported in patients receiving fenbufen.

1. Martland T, Stone WD. Haemolytic anaemia associated with fenbufen. *BMJ* 1988; **297:** 921.
2. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the lungs. In January 1989 the UK CSM reported that it had received 7 reports of a suspected association between rash and an allergic interstitial lung disorder in patients receiving fenbufen.[1] In 5 patients, the lung disorder was diagnosed as pulmonary eosinophilia; in the 2 other patients the pulmonary component of the reaction was described as allergic alveolitis. Several of these reactions have been reported in the literature.[2,3]

1. CSM. Fenbufen, rash and pulmonary eosinophilia. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
2. Swinburn CR. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.
3. Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; **300:** 82–3.

Effects on the skin. In September 1988 the UK CSM reported[1] that it was still receiving large numbers of reports of adverse reactions to fenbufen when such reports were expected to have declined. Fenbufen was the most commonly reported suspect drug in 1986 and 1987. At the time of the report more than 6000 such reports had been received, 80% concerning mucocutaneous reactions and most involving a generalised florid erythematous rash, often with pruritus. There were 178 reports of erythema multiforme, 30 of Stevens-Johnson syndrome, and 2 fatalities.

1. CSM. Fenbufen and mucocutaneous reactions. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Hypersensitivity. See under Effects on the Lungs (above).

Interactions

For interactions associated with NSAIDs, see p.99.

Use of fenbufen with aspirin may result in decreased serum concentrations of fenbufen and its metabolites.

Pharmacokinetics

Fenbufen is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations are reached in about 70 minutes. Fenbufen is over 99% bound to plasma proteins. It is metabolised in the liver to the active metabolites, biphenylacetic acid and 4-hydroxy-biphenylbutyric acid. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine. Metabolites of fenbufen have been detected in breast milk in small amounts.

Uses and Administration

Fenbufen, a propionic acid derivative, is an NSAID (p.99). It is given for the relief of pain and inflammation associated with musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in oral doses of 900 mg daily; the dose may be either 450 mg in the morning and evening or 300 mg in the morning with 600 mg in the evening.

Preparations

BP 2008: Fenbufen Capsules; Fenbufen Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Lederfen†; ***Indon.:*** Cybufen; ***Irl.:*** Lederfen; ***Port.:*** Basifen; Reugast†; ***Thai.:*** Cepal; Cinopal†; ***Turk.:*** Cinopal; ***UK:*** Lederfen.

Fenoprofen Calcium *(BANM, USAN, rINNM)*

Calcii Fenoprofenum; Fénoprofène Calcique; Fenoprofeno cálcico; Lilly-69323; Lilly-53858 (fenoprofen); Lilly-61169 (fenoprofen sodium). Calcium (±)-2-(3-phenoxyphenyl)propionate dihydrate.

Кальций Фенопрофен

$(C_{15}H_{13}O_3)_2Ca,2H_2O = 558.6.$

CAS — 31879-05-7 (fenoprofen); 34597-40-5 (anhydrous fenoprofen calcium); 53746-45-5 (fenoprofen calcium dihydrate).

ATC — M01AE04.

ATC Vet — QM01AE04.

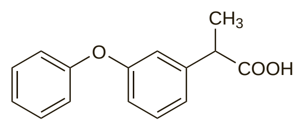

(fenoprofen)

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2008 (Fenoprofen Calcium). A white or almost white odourless or almost odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol.

USP 31 (Fenoprofen Calcium). A white crystalline powder. Slightly soluble in water, in methyl alcohol, and in n-hexanol; practically insoluble in chloroform. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Dysuria, cystitis, haematuria, interstitial nephritis, and acute renal insufficiency have been reported with fenoprofen. Nephrotic syndrome, which may be preceded by fever, rash, arthralgia, oliguria, azotaemia, and anuria, has also occurred. Upper respiratory-tract infection and nasopharyngitis have been reported. There have been reports of severe hepatic reactions, including jaundice and fatal hepatitis.

Breast feeding. Fenoprofen is distributed into breast milk although the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. In contrast, licensed product information does not recommend its use since safety has not been established.

Effects on the blood. Haematological adverse effects including agranulocytosis,[1] aplastic anaemia,[2] and thrombocytopenia[3,4] have been reported in patients taking fenoprofen; licensed product information also reports haemolytic anaemia.

1. Simon SD, Kosmin M. Fenoprofen and agranulocytosis. *N Engl J Med* 1978; **299:** 490.
2. Ashraf M, *et al.* Aplastic anaemia associated with fenoprofen. *BMJ* 1982; 284: 1301–2.
3. Simpson RE, *et al.* Acute thrombocytopenia associated with fenoprofen. *N Engl J Med* 1978; **298:** 629–30.
4. Katz ME, Wang P. Fenoprofen-associated thrombocytopenia. *Ann Intern Med* 1980; **92:** 262.

Effects on the liver. Cholestatic jaundice and hepatitis developed in a 68-year-old woman after receiving fenoprofen 600 mg four times daily for 7 weeks. Subsequent use of naproxen and indometacin did not result in hepatotoxicity.[1] However, there has been a report of cross-hepatotoxicity between fenoprofen and naproxen.[2]

1. Stennett DJ, *et al.* Fenoprofen-induced hepatotoxicity. *Am J Hosp Pharm* 1978; **35:** 901.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the skin. Toxic epidermal necrolysis was associated with fenoprofen in 2 patients.[1]

1. Stotts JS, *et al.* Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; **18:** 755–7.

Overdosage. A report of coma, respiratory depression, hypotension, and metabolic acidosis in a patient who had ingested between 24 and 36 g of fenoprofen.[1] The patient responded to gastric lavage and activated charcoal and intensive supportive care.

1. Kolodzik JM, *et al.* Nonsteroidal anti-inflammatory drugs and coma: a case report of fenoprofen overdose. *Ann Emerg Med* 1990; **19:** 378–81.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin is reported to reduce plasma concentrations of fenoprofen.

Antiepileptics. *Phenobarbital* might increase the rate of metabolism of fenoprofen.[1] US licensed product information suggests that dosage adjustment of fenoprofen may be required when given with phenobarbital.

1. Helleberg L, *et al.* A pharmacokinetic interaction in man between phenobarbitone and fenoprofen, a new anti-inflammatory agent. *Br J Clin Pharmacol* 1974; **1:** 371–4.

Pharmacokinetics

Fenoprofen is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations occur 1 to 2 hours after a dose. The plasma half-life is about 3 hours. Fenoprofen is 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours, chiefly as the glucuronide and the glucuronide of hydroxylated fenoprofen. Fenoprofen is distributed into breast milk.

Uses and Administration

Fenoprofen, a propionic acid derivative, is an NSAID (p.99) used in the management of mild to moderate pain and for the relief of pain and inflammation associated with disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is given as the calcium salt although doses are expressed in terms of the base; fenoprofen calcium (dihydrate) 1.2 g is equivalent to about 1 g of fenoprofen. A usual oral dose is the equivalent of 300 to 600 mg of fenoprofen three or four times daily, adjusted thereafter according to response. In the USA, lower doses of 200 mg every 4 to 6 hours are recommended for mild to moderate pain. It has been recommended that the total daily dose should not exceed 3 g (UK) or 3.2 g (USA).

Preparations

BP 2008: Fenoprofen Tablets;
USP 31: Fenoprofen Calcium Capsules; Fenoprofen Calcium Tablets.

Proprietary Preparations (details are given in Part 3)

Braz.: Trandor†; ***Canad.:*** Nalfon†; ***Denm.:*** Nalfon†; ***Fr.:*** Nalgesic; ***Gr.:*** Expron†; ***Mex.:*** Nalfon†; ***S.Afr.:*** Fenopron†; ***UK:*** Fenopron; ***USA:*** Nalfon; ***Venez.:*** Fenopron†.

Fentanyl *(BAN, rINN)* ⊗

Fentanil; Fentanilis; Fentanilo; Fentanylum; Fentanyyli. *N*-(1-Phenethyl-4-piperidyl) propionanilide.

Фентанил

$C_{22}H_{28}N_2O = 336.5.$

CAS — 437-38-7.

ATC — N01AH01; N02AB03.

ATC Vet — QN01AH01; QN02AB03.

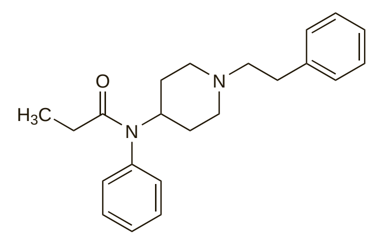

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fentanyl:

Apache; China girl; China town; China white; Dance fever; Fentanest; Friend; Goodfellas; Great bear; He-man; Jackpot; King ivory; Murder 8; Poison; Tango & Cash; TNT; T.N.T.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fentanyl). A white or almost white polymorphic powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Fentanyl Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de fentanilo; Fentanil-citrát; Fentanilio citratas; Fentanyl, citrate de; Fentanylcitrat; Fentanyl-citrát; Fentanyli citras; Fentanylu cytrynian; Fentanyylisitraatti; McN-JR-4263-49; Phentanyl Citrate; R-4263. *N*-(1-Phenethyl-4-piperidyl)propionanilide dihydrogen citrate.

Фентанила Цитрат

$C_{22}H_{28}N_2O,C_6H_8O_7 = 528.6.$

CAS — 990-73-8.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Fentanyl Citrate). White or almost white powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 31 (Fentanyl Citrate). A white crystalline powder or white glistening crystals. Sparingly soluble in water; slightly soluble in chloroform; soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Fentanyl Hydrochloride *(BANM, rINNM)* ⊗

Fentanyl, Chlorhydrate de; Fentanyli Hydrochloridum; Hidrocloruro de fentanilo.

Фентанила Гидрохлорид

$C_{22}H_{28}N_2O,HCl$ = 372.9.

CAS — 1443-54-5.

Incompatibility. Fentanyl citrate is incompatible with thiopental sodium and methohexital sodium.

A thick white precipitate formed in the intravenous tubing when fentanyl citrate with droperidol was given shortly after nafcillin sodium. There was no precipitate when fentanyl citrate alone was mixed with nafcillin sodium.[1]

Fentanyl citrate underwent rapid and extensive loss when admixed with fluorouracil in PVC containers.[2] The loss was due to sorption of fentanyl to the PVC as a result of the alkaline pH of the admixture, and presumably could occur from admixture of fentanyl citrate with any sufficiently alkaline drug.

See also Stability, below.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.
2. Xu QA, *et al.* Rapid loss of fentanyl citrate admixed with fluorouracil in polyvinyl chloride containers. *Ann Pharmacother* 1997; **31:** 297–302.

Stability. In a 48-hour study fentanyl citrate in glucose 5% or sodium chloride 0.9% was stable when stored at room temperature under usual light conditions in glass or PVC containers;[1] the concentration of fentanyl delivered by a patient-controlled system was relatively constant throughout a 30-hour study period. Fentanyl citrate injection diluted to 20 micrograms/mL with sodium chloride 0.9% was stable for 30 days at 3° or 23° in PVC reservoirs for portable infusion pumps.[2] In another study[3] fentanyl citrate diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.

An admixture of fentanyl citrate and bupivacaine in sodium chloride 0.9% appeared[4] compatible and stable when stored for up to 30 days at 3° or 23° in a portable infusion pump. In another study[5] the stability of solutions containing fentanyl, bupivacaine, and adrenaline, alone and in combination was studied over a period of 56 days when stored at various temperatures in the light or in the dark in PVC bags. Both fentanyl and bupivacaine were adsorbed from solution onto the PVC for the first 3 days but thereafter concentrations of these drugs remained relatively stable; freezing appeared to slow the concentration change for bupivacaine but not for fentanyl. Solutions containing adrenaline became more acidic during the study as the adrenaline progressively deteriorated but this was greatly reduced by freezing. Autoclaving produced a further reduction in the concentration of all drugs. There was no sign of precipitation from any of the solutions studied.

An admixture of fentanyl citrate, ketamine hydrochloride, and droperidol in sodium chloride 0.9% was stable[6] for at least 30 days when stored in glass bottles at 25°; the minor decrease in the concentrations of all 3 drugs was attributed to either hydrolytic degradation or adsorption. This admixture also appeared compatible when stored in PVC bags at 4° and 25°; the small increase in drug concentrations over 30 days may be a result of water permeation and evaporation through the bags.

Fentanyl is potentially unstable in PVC containers when admixed with alkaline drugs (see Incompatibility, above).

1. Kowalski SR, Gourlay GK. Stability of fentanyl citrate in glass and plastic containers and in a patient-controlled delivery system. *Am J Hosp Pharm* 1990; **47:** 1584–7.
2. Allen LV, *et al.* Stability of fentanyl citrate in 0.9% sodium chloride solution in portable infusion pumps. *Am J Hosp Pharm* 1990; **47:** 1572–4.
3. Chapalain-Pargade S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.
4. Tu Y-H, *et al.* Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. *Am J Hosp Pharm* 1990; **47:** 2037–40.
5. Dawson PJ, *et al.* Stability of fentanyl, bupivacaine and adrenaline solutions for extradural infusion. *Br J Anaesth* 1992; **68:** 414–17.
6. Lee DKT, *et al.* Compatibility of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% sodium chloride injection stored in polyvinyl chloride bags. *Am J Health-Syst Pharm* 2005; **62:** 1190–2.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Fentanyl and illicitly manufactured analogues are subject to abuse (see under Precautions, below).

◊ Plasma concentrations required to produce satisfactory sedation have been reported to increase steadily in neonates receiving continuous infusions, suggesting the development of *tolerance* to the sedating effects of fentanyl.[1]

Movement disorders, extreme irritability, and symptoms characteristic of *opioid abstinence syndrome* have been reported in children after withdrawal of prolonged fentanyl infusions.[2,3] Similarly, withdrawal symptoms and, in one case, myoclonus have occurred in adults when fentanyl transdermal patches have been stopped.[4,5] Acute opioid withdrawal syndrome has also been seen in cancer patients switched from modified-release oral morphine to transdermal fentanyl despite adequate analgesia being maintained.[6]

1. Arnold JH, *et al.* Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; **119:** 639–43.
2. Lane JC, *et al.* Movement disorder after withdrawal of fentanyl infusion. *J Pediatr* 1991; **119:** 649–51.
3. Dominguez KD, *et al.* Opioid withdrawal in critically ill neonates. *Ann Pharmacother* 2003 **37:** 473–7.
4. Han PKJ, *et al.* Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 2002; **23:** 66–72.
5. Ishihara C, *et al.* Withdrawal symptom after discontinuation of transdermal fentanyl at a daily dose of 0.6 mg. *Pharm World Sci* 2005; **27:** 13–15.
6. Anonymous. Opiate withdrawal with transdermal fentanyl. *Pharm J* 1995; **255:** 680.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Respiratory depression, which occurs especially with high doses of fentanyl, responds to naloxone (see also Effects on the Respiratory System, below). Atropine may be used to block the vagal effects of fentanyl such as bradycardia. Unlike morphine, fentanyl is reported not to cause significant histamine release. Transient hypotension may follow intravenous dosage. Muscle rigidity can occur and may require neuromuscular blockers.

Local reactions such as rash, erythema, and itching have been reported with transdermal use. Gum bleeding and irritation, and taste perversion have been reported with transmucosal use.

Effects on the cardiovascular system. For a reference to the effects of fentanyl on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on mental function. Fentanyl had some dose-related effects on mental function and motor activity in healthy subjects,[1] but immediate and delayed recall were not affected. See also under Alfentanil (p.16).

Acute toxic delirium has been reported after treatment with transdermal fentanyl.[2]

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kuzma PJ, *et al.* Acute toxic delirium: a uncommon reaction to transdermal fentanyl. *Anesthesiology* 1995; **83:** 869–71.

Effects on the nervous system. There have been reports of seizures with low and high doses of fentanyl or sufentanil.[1] There was, however, no EEG evidence of cortical seizure activity in a patient who had seizure-like muscle movements during a fentanyl infusion;[2] the muscle movements might have been due to myoclonus produced by depression of higher CNS inhibitory centres or to a pronounced form of opioid-induced muscle rigidity.

For a report of encephalopathy associated with prolonged use of fentanyl and midazolam in infants in intensive care, see Encephalopathy under Adverse Effects of Diazepam, p.988.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Scott JC, Sarnquist FH. Seizure-like movements during a fentanyl infusion with absence of seizure activity in a simultaneous EEG recording. *Anesthesiology* 1985; **62:** 812–14.

Effects on the respiratory system. Fentanyl, like other opioid agonists, causes dose-related respiratory depression; it is significant with *intravenous* fentanyl doses of more than 200 micrograms and may be more prolonged than analgesia. Anaesthesia with fentanyl may result in either prolonged or delayed respiratory depression postoperatively.[1] Consequently, patients should continue to be monitored postoperatively until spontaneous breathing has been re-established. Severe respiratory depression in a 14-month-old child after intravenous sedation with fentanyl and midazolam has also highlighted the necessity for careful monitoring when giving with other respiratory depressants.[2] If present at the end of operation respiratory depression may be reversed by an opioid antagonist such as naloxone; alternatively, a respiratory stimulant such as doxapram that does not reverse analgesia has been given.

Rigidity of the respiratory muscles (chest wall rigidity) may occur during fentanyl anaesthesia. The effects can be minimised by using a slow intravenous injection but a neuromuscular blocker may be required to allow artificial ventilation; rigidity has been reversed postoperatively by naloxone. Similar muscle rigidity induced by alfentanil could be attenuated by pretreatment with a benzodiazepine whereas small doses of neuromuscular blockers appeared to be ineffective.[3]

Coughing has been associated[4] with intravenous fentanyl; incidence was decreased with a longer injection time,[5] in light cigarette smokers,[5,6] and in older patients.[6] For the use of beclometasone and lidocaine to prevent cough associated with intravenous fentanyl in anaesthesia, see p.1518 and p.1852, respectively.

The risk of respiratory depression associated with *epidural* doses of fentanyl, a highly lipid-soluble opioid, has been considered relatively small and only slight ventilatory depression was noted[7] after a dose of 50 micrograms. However, profound delayed respiratory depression has been reported in 2 women 100 minutes[8] and 80 minutes,[9] respectively after fentanyl 100 micrograms had been given epidurally for caesarean section. No adverse effects on neonatal respiration or neurobehaviour were detected in a study[10] of neonates of mothers given epidural infusions of bupivacaine and fentanyl during labour. However, a later report[11] described 2 neonates who developed respiratory depression after their mothers were given epidural fentanyl during labour; the effect was reversed by intramuscular naloxone 400 micrograms. The authors noted that the doses of fentanyl used were higher than those in the previous study.

Respiratory depression is also a risk with *topically* applied fentanyl preparations. Severe hypoventilation with some fatalities has occurred in patients given fentanyl as a transdermal patch for minor painful conditions.[12] More recently, Health Canada had received 2 reports of fatal respiratory depression associated with the use of transdermal fentanyl patches in adolescents for relatively minor conditions (chronic headache and throat pain);[13] in both cases the respiratory depression developed within 24 hours of applying the first and only patch. See also Administration, Transdermal Route, under Precautions below.

1. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
2. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
3. Sanford TJ, *et al.* Pretreatment with sedative-hypnotics, but not with nondepolarizing muscle relaxants, attenuates alfentanil-induced muscle rigidity. *J Clin Anesth* 1994; **6:** 473–80.
4. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001; **92:** 1442–3.
5. Lin J-A, *et al.* Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. *Anesth Analg* 2005; **101:** 670–4.
6. Oshima T, *et al.* Identification of independent risk factors for fentanyl-induced cough. *Can J Anesth* 2006; **53:** 753–8.
7. Morisot P, *et al.* Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *Br J Anaesth* 1989; **63:** 97–102.
8. Brockway MS, *et al.* Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; **64:** 243–5.
9. Wang CY. Respiratory depression after extradural fentanyl. *Br J Anaesth* 1992; **69:** 544.
10. Porter J, *et al.* Effect of epidural fentanyl on neonatal respiration. *Anesthesiology* 1998; **89:** 79–85.
11. Kumar M, Paes B. Epidural opioid analgesia and neonatal respiratory depression. *J Perinatol* 2003; **23:** 425–7.
12. *FDC Reports Pink Sheet* 1994; January 24: 12.
13. Health Canada. Transdermal fentanyl (Duragesic): respiratory arrest in adolescents. *Can Adverse React News* 2004; **14** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 26/06/08)

Effects on the skin. A patient developed a macular rash covering the whole body, except for the face and scalp, while using transdermal fentanyl patches.[1]

1. Stoukides CA, Stegman M. Diffuse rash associated with transdermal fentanyl. *Clin Pharm* 1992; **11:** 222.

Effects on the urinary tract. Urinary retention developed in 2 premature infants after sedation with fentanyl infusion at a dose of 3 micrograms/kg per hour.[1] In both cases catheterisation relieved symptoms.

1. Das UG, Sasidharan P. Bladder retention of urine as a result of continuous intravenous infusion of fentanyl: 2 case reports. *Pediatrics* 2001; **108:** 1012–1015.

Precautions

As for Opioid Analgesics in general, p.103.

Caution is advised in patients with myasthenia gravis; the effects of muscular rigidity on respiration may be particularly pronounced in these patients.

US licensed product information contra-indicates the use of standard transdermal fentanyl patches in opioid-naive patients because of the risk of fatal respiratory depression (see Effects on the Respiratory System, above and Administration, Transdermal Route, below). Similar contra-indications apply to fentanyl buccal tablets (see Administration, Transmucosal Route, below).

Absorption of fentanyl from standard transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take 17 hours or longer for plasma concentrations of fentanyl to decrease by 50% after removal of a transdermal patch; patients who have had adverse effects should be monitored for up to 24 hours and those requiring replacement opioid therapy should initially receive low doses increased gradually thereafter. Similar advice is also given for patients receiving fentanyl via an iontophoretic drug delivery system; the mean half-life of fentanyl in this system is 11 hours.

The bioavailability of different transmucosal fentanyl preparations is not equivalent and consequently they should not be substituted on a dose-per-dose basis.

Abuse. Several synthetic analogues of fentanyl, so-called 'designer drugs', have been manufactured illicitly for recreational use, particularly in the USA. They are highly potent, and respiratory depression and death may occur very rapidly.[1] The 'fentanyls' have been smoked or snorted as well as injected intravenously.

Fentanyl analogues identified by WHO[2,3] as being subject to street abuse or likely to be abused include: alpha-methylfentanyl (also known as 'China white' or 'synthetic heroin'), 3-methylfentanyl, acetyl-alpha-methylfentanyl, alpha-methylthiofentanyl, para-fluorofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, thiofentanyl, and 3-methylthiofentanyl.

Fentanyl itself is also subject to illicit use. It is chemically unrelated to morphine and does not react in screening tests for morphine-related opioids. It has therefore been recommended[4] that fentanyl should be tested for specifically in cases with suspected opioid misuse.

Used fentanyl transdermal systems may contain significant amounts of fentanyl and have been subject to abuse. In some cases the contents of the patches have been injected intravenously; such abuse has resulted in death.[5,6] Licensed product information advises that used patches and iontophoretic transdermal systems should be folded firmly in half, adhesive side inwards to conceal the release membrane, and disposed of safely.

1. Buchanan JF, Brown CR. 'Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988.
3. WHO. WHO expert committee on drug dependence: twenty-sixth report. *WHO Tech Rep Ser 787* 1989.
4. Berens AIL, *et al.* Illicit fentanyl in Europe. *Lancet* 1996; **347:** 1334–5.
5. Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. *Med J Aust* 2002; **177:** 552–3.
6. Tharp AM, *et al.* Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. *Am J Forensic Med Pathol* 2004; **25:** 178–81.

Administration. *INTRAVENOUS ROUTE.* Fentanyl is much more lipid-soluble than morphine and after standard single intravenous doses has a rapid onset and short duration of action. However, fentanyl is rapidly redistributed in the body and has a longer elimination half-life than morphine (see under Pharmacokinetics, below). Hence, with high or repeated doses, fentanyl becomes a relatively long-acting drug; to avoid accumulation patients should be monitored and doses adjusted accordingly.

Repeated intra-operative doses of fentanyl should be given with care, since not only may the respiratory depression persist into the postoperative period but it may become apparent for the first time postoperatively when the patient is away from immediate nursing attention.

TRANSDERMAL ROUTE. Fatalities have been associated with the use of standard fentanyl transdermal patches (see Effects on the Respiratory System, above). Incorrect or inappropriate use resulting in serious adverse effects and fatalities had prompted regulatory authorities to issue warnings and recommendations for changes to product labelling; in particular transdermal fentanyl patches are not appropriate for the treatment of acute or postoperative pain. Nonetheless, reports of fatalities and life-threatening adverse reactions have continued to be received[1,2] and, in December 2007, the FDA[1] reiterated that:

- fentanyl patches are indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients
- licensed product information must be consulted when determining the initial dose as overestimating when converting patients from another opioid analgesic can result in fatal overdose with the first dose
- use with any inhibitors of the cytochrome P450 isoenzyme CYP3A4 may result in an increase in plasma-fentanyl concentrations, which may cause potentially fatal respiratory depression; patients who are taking CYP3A4 inhibitors and using fentanyl patches for an extended period of time should be monitored and the dose of fentanyl adjusted if necessary

1. FDA. Information for healthcare professionals: fentanyl transdermal system (marketed as Duragesic and generics) (issued 21st December, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fentanyl_2007HCP.htm (accessed 23/07/08)
2. Health Canada. Fentanyl transdermal patch and fatal adverse reactions. *Can Adverse React News* 2008; **18** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n3-eng.pdf (accessed 23/07/08)

TRANSMUCOSAL ROUTE. The FDA[1] has received reports of serious adverse effects, including fatalities, in patients who have taken the fentanyl buccal tablets, *Fentora* (*Cephalon, USA*), resulting from inappropriate use in patients who were not opioid tolerant, misunderstanding of dosing instructions, or inappropriate substitution for other fentanyl-containing formulations. The FDA reiterated that *Fentora*:

- should only be used for breakthrough pain in opioid-tolerant cancer patients
- should not be used in those who only need an opioid on an intermittent, or as required, basis and who are not on around-the-clock opioids
- should not be used for the management of acute or postoperative pain including headaches, migraines, and pain due to injury
- should not be directly substituted for other fentanyl-containing formulations

1. FDA. Information for healthcare professionals: fentanyl buccal tablets (marketed as Fentora) (issued 26th September, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fentanyl_buccal.htm (accessed 24/07/08)

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect in infants of breast-feeding mothers given fentanyl, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of fentanyl distributed into breast milk is too small to be harmful to a breast-fed infant. However, licensed product information states that, since fentanyl is distributed into breast milk, it should be avoided in nursing mothers because of the possibility of sedation or respiratory depression in breast-fed infants.

A study[2] using fentanyl 100 micrograms intravenously for induction of anaesthesia in 5 mothers concluded that the amount of fentanyl excreted into breast milk within 24 hours of induction was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Children. The *BNFC* states that the half-life of fentanyl is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required. See also under Pharmacokinetics, below.

Exercise. Opioid toxicity requiring naloxone treatment occurred in a patient who wore a fentanyl patch while engaging in vigorous outdoor exercise.[1] Physicians should be aware that along with fever and external heat sources, physical activity may cause increased absorption of transdermal fentanyl.

1. Carter KA. Heat-associated increase in transdermal fentanyl absorption. *Am J Health-Syst Pharm* 2003; **60:** 191–2.

Handling. Avoid contact with skin and the inhalation of fentanyl citrate particles.

Interactions

For interactions associated with opioid analgesics, see p.103. Use of fentanyl with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

Fentanyl is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with potent inhibitors of this isoenzyme, such as ritonavir and other HIV-protease inhibitors, may increase fentanyl plasma concentrations.

Antidepressants. For reference to a possible case of serotonin syndrome associated with use of fentanyl and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397.

Antivirals. *Ritonavir*, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, might prolong fentanyl-induced respiratory depression. The plasma clearance of fentanyl was decreased, and the elimination half-life and area under the plasma concentration-time curve increased, when given with ritonavir in a study in healthy subjects.[1]

1. Olkkola KT, *et al.* Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999; **91:** 681–5.

Benzodiazepines. For the effects of opioids such as fentanyl with benzodiazepines, see Analgesics under Interactions of Diazepam, p.989.

Propofol. For reference to the effect that fentanyl has on blood concentrations of propofol, see p.1792.

Pharmacokinetics

After parenteral doses fentanyl citrate has a rapid onset and short duration of action. After transmucosal delivery, up to 50% of the dose is rapidly absorbed from the buccal mucosa; the remainder is swallowed and slowly absorbed from the gastrointestinal tract. Some first-pass metabolism occurs via this route. The absolute bioavailability of transmucosal delivery is about half that for intravenous fentanyl but varies between formulations. Absorption is slow after transdermal application. Fentanyl is metabolised in the liver by *N*-dealkylation and hydroxylation via the cytochrome P450 isoenzyme CYP3A4. Metabolites and some unchanged drug are excreted mainly in the urine. The short duration of action is probably due to rapid redistribution into the tissues rather than metabolism and excretion. The relatively longer elimination half-life reflects slower release from tissue depots. About 80% has been reported to be bound to plasma proteins. Fentanyl appears in the CSF. It crosses the placenta and has been detected in breast milk.

◊ Marked differences in results of pharmacokinetic studies of fentanyl have been attributed[1] to differences in assay methods. The need for sensitive assay methods has been emphasised because the potency of fentanyl means that small doses are used. However, there are differences in pharmacokinetics between bolus doses and prolonged infusion with highly lipophilic drugs such as fentanyl.[2] Terminal half-lives ranging from 2 to 7 hours have been reported in healthy subjects and surgical patients. However, the duration of action of fentanyl after a single intravenous dose of up to 100 micrograms may be only 30 to 60 minutes as a result of rapid redistribution into the tissues. US licensed product information has given values for a three-compartment pharmacokinetic model with a distribution time of 1.7 minutes, a redistribution time of 13 minutes, and a terminal elimination half-life of 219 minutes. Giving repeated or large doses, or continuous infusions, may result in accumulation and a more prolonged action.

The clinical significance of secondary peak plasma-fentanyl concentrations and the possible role of entero-systemic recirculation[3] has been controversial, but some[4] considered that irregular decay curves were not unlikely for lipophilic compounds such as fentanyl, especially in patients undergoing operations and subject to large changes in blood flow. Unexpectedly high plasma-fentanyl concentrations in a patient following epidural use were thought to be a result of aortic clamping and might reflect the effect of changes in blood flow.[5]

The main metabolites of fentanyl, which are excreted in the urine, have been identified as 4-*N*-(*N*-propionylanilino) piperidine and 4-*N*-(*N*-hydroxypropionylanilino) piperidine; 1-(2-phenethyl)-4-*N*-(*N*-hydroxypropionylanilino) piperidine is a minor metabolite.[6] Fentanyl has no active or toxic metabolites.[4]

1. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
5. Bullingham RES, *et al.* Unexpectedly high plasma fentanyl levels after epidural use. *Lancet* 1980; **i:** 1361–2.
6. Goromaru T, *et al.* Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography-mass spectrometry. *Anesthesiology* 1984; **61:** 73–7.

Administration. Some references to the pharmacokinetics of fentanyl after constant rate intravenous infusion,[1] transdermal application,[2-5] use of the oral sublingual[6] and transmucosal[7-11] routes, intranasal dosage,[12] subcutaneous infusion,[13] and epidural use.[14-16]

1. Duthie DJR, *et al.* Pharmacokinetics of fentanyl during constant rate iv infusion for the relief of pain after surgery. *Br J Anaesth* 1986; **58:** 950–6.
2. Grond S, *et al.* Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. *Clin Pharmacokinet* 2000; **38:** 59–89.
3. Solassol I, *et al.* Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. *Ther Drug Monit* 2005; **27:** 491–8.

4. Marier J-F, *et al.* Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system of fentanyl relative to the commercially available reservoir formulation in healthy subjects. *J Clin Pharmacol* 2006; **46:** 642–53.
5. Marier J-F, *et al.* Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. *Br J Clin Pharmacol* 2007; **63:** 121–4.
6. Lennernäs B, *et al.* Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol* 2005; **59:** 249–53.
7. Streisand JB, *et al.* Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* 1991; **75:** 223–9.
8. Darwish M, *et al.* Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet* 2005; **44:** 1279–86.
9. Darwish M, *et al.* Comparison of equivalent doses of fentanyl buccal tablets and arteriovenous differences in fentanyl pharmacokinetics. *Clin Pharmacokinet* 2006; **45:** 843–50.
10. Darwish M, *et al.* Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 56–63.
11. Darwish M, *et al.* Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* 2007; **47:** 343–50.
12. Walter SH, *et al.* Pharmacokinetics of intranasal fentanyl. *Br J Anaesth* 1993; **70** (suppl 1): 108.
13. Miller RS, *et al.* Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients. *Br J Clin Pharmacol* 1995; **40:** 553–6.
14. Gourlay GK, *et al.* Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; **38:** 253–9.
15. Bader AM, *et al.* Maternal and neonatal fentanyl and bupivacaine concentrations after epidural infusion during labor. *Anesth Analg* 1995; **81:** 829–32.
16. Moises EC, *et al.* Pharmacokinetics and transplacental distribution of fentanyl in epidural anesthesia for normal pregnant women. *Eur J Clin Pharmacol* 2005; **61:** 517–22.

Cardiopulmonary bypass. In general, studies[1,2] indicate that serum concentrations of fentanyl during cardiopulmonary bypass decrease initially and then remain stable. The fall in concentrations has been attributed to haemodilution although adsorption to the bypass apparatus has also been found.

1. Buylaert WA, *et al.* Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1989; **17:** 10–26.
2. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.

Children. The disposition of intravenous fentanyl 10 to 50 micrograms/kg in 14 neonates undergoing various major surgical procedures was highly variable.[1] The mean elimination half-life of 317 minutes and other pharmacokinetic parameters including volume of distribution and total body clearance were greater than reported in adults, but both pharmacodynamic and pharmacokinetic mechanisms appeared responsible for the very prolonged respiratory depression that can occur in neonates after fentanyl anaesthesia. In 9 premature neonates given fentanyl 30 micrograms/kg intravenously for induction of anaesthesia[2] the elimination half-life ranged from 6 to 32 hours, but cautious interpretation was advised because of the method of calculation.

1. Koehntop DE, *et al.* Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986; **65:** 227–32.
2. Collins C, *et al.* Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesth Analg* 1985; **64:** 1078–80.

The elderly. In one study the elimination half-life of intravenous fentanyl increased from 265 minutes in patients with a mean age of 36 years to 945 minutes in those with a mean age of 67 years.[1] The authors of another study were critical of the relatively short sampling time used and in contrast found that major fentanyl pharmacokinetic parameters did not correlate with age.[2] However, elderly patients had increased brain sensitivity to intravenous fentanyl, as shown by EEG changes[2] and lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons.

1. Bentley JB, *et al.* Age and fentanyl pharmacokinetics. *Anesth Analg* 1982; **61:** 968–71.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.

Hepatic impairment. The pharmacokinetics of fentanyl were not affected significantly in surgical patients with cirrhosis of the liver.[1] A 1987 review[2] considered that fentanyl had not been associated with clinical problems when given to patients with liver dysfunction.

1. Haberer JP, *et al.* Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth* 1982; **54:** 1267–70.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Renal impairment. Clearance of fentanyl from plasma was reported to be enhanced in surgical patients with end-stage renal disease,[1] although clearance was reduced and elimination half-life increased in patients with renal failure undergoing transplantation,[2] possibly because of the influence of uraemia on metabolism in the liver. Nevertheless, a 1987 review[2] noted that fentanyl had no active or toxic metabolites and had not been associated with clinical problems when given to patients with renal dysfunction.

1. Corall IM, *et al.* Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease. *Br J Anaesth* 1980; **52:** 101P.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Uses and Administration

Fentanyl, a phenylpiperidine derivative, is a potent opioid analgesic (p.104) chemically related to pethidine (p.113) and is primarily a μ-opioid agonist.

Fentanyl is used as an analgesic, as an adjunct to general anaesthetics, and as an anaesthetic for induction and maintenance. It is also used as a respiratory depressant in the management of mechanically ventilated patients under intensive care. When used with an antipsychotic such as droperidol it can induce a state of neuroleptanalgesia in which the patient is calm and indifferent to his surroundings and is able to cooperate with the surgeon.

Fentanyl is usually given parenterally or by the transmucosal route as the citrate, in transdermal patches as the base, or by iontophoretic transdermal delivery as the hydrochloride. Fentanyl citrate 157 micrograms and fentanyl hydrochloride 111 micrograms are each equivalent to about 100 micrograms of fentanyl. Doses are expressed in terms of the base.

It is more lipid soluble than morphine and after an intravenous injection of 100 micrograms the effects of fentanyl begin almost immediately, although maximum analgesia and respiratory depression may not occur for several minutes; the duration of action of fentanyl depends on the dose and the intensity of the pain involved, and may vary from 10 minutes to several hours.

For **premedication** the equivalent of 50 to 100 micrograms of fentanyl may be given *intramuscularly* 30 to 60 minutes before the induction of anaesthesia.

As an **adjunct** to general anaesthesia, fentanyl is usually given by *intravenous* injection. Dosage recommendations show a wide range depending on the technique.

- *Patients with spontaneous respiration* may be given 50 to 200 micrograms as an initial dose with supplements of 50 micrograms. In the USA it is recommended that doses above 2 micrograms/kg be accompanied by assisted ventilation. Significant respiratory depression follows doses of more than 200 micrograms
- *Patients whose ventilation is assisted* may be given 300 micrograms to 3.5 mg (up to 50 micrograms/kg) as an initial dose, with supplements of 100 to 200 micrograms depending on the patient's response. High doses have been reported to moderate or attenuate the response to surgical stress (see Anaesthesia, below)

Fentanyl may also be given by intravenous infusion. In ventilated patients a loading dose of about 1 microgram/kg per minute is given for the first 10 minutes followed by an infusion of about 100 nanograms/kg per minute; alternatively, the loading dose may be given as a bolus. The infusion rate should be titrated according to response and rates of up to 3 micrograms/kg per minute have been used in cardiac surgery. Infusions should be stopped about 40 minutes before the end of surgery unless artificial ventilation is to be continued postoperatively. In patients with spontaneous respiration, lower infusion rates of 50 to 80 nanograms/kg per minute are used.

Reduced doses are used in *the elderly* or debilitated patients

Similar doses to those used for premedication may also be given by *intramuscular* injection **postoperatively**, and by *intramuscular* or *slow intravenous injection* as an adjunct to **regional anaesthesia**.

For the treatment of **intractable chronic pain** in adults when opioid analgesia is indicated *transdermal* patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour are available. In the UK, fentanyl patches may be used in strong opioid-naive patients; however, in the USA, use is restricted to patients who are already tolerant to opioid therapy of comparable potency.

- Doses should be individually titrated for each patient according to previous opioid usage. Initial dosages should not exceed 25 micrograms/hour in *opioid-naive* patients; in addition, it is recommended that these patients are initially titrated with low doses of short-acting opioids before transferring to fentanyl patches
- For *patients who have been receiving a strong opioid analgesic* the initial dose of the fentanyl patch should be based on the previous 24-hour opioid requirement. Use of a patch providing 25 micrograms of fentanyl per hour is equivalent to about 60 to 90 mg daily of oral morphine sulfate. During transfer to treatment with fentanyl patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-fentanyl concentrations
- More than one patch may be applied if doses greater than 100 micrograms/hour are required (applied at the same time to avoid confusion); additional or alternative analgesic therapy should be considered if doses greater than 300 micrograms/hour are required. Patches should be replaced every 72 hours with the new patch being applied to a different site; use of the same area of the skin should be avoided for several days
- *Elderly* or debilitated patients should be observed carefully for signs of toxicity and the dose reduced if necessary

Fentanyl patches are not appropriate for acute or postoperative pain.

A patient-activated *iontophoretic transdermal* fentanyl delivery system, *IONSYS* (*Janssen-Cilag, UK*; *Ortho-McNeil, USA*), is available for the management of acute moderate to severe **postoperative pain** in hospitalised patients. Patients should be titrated to an acceptable level of analgesia before starting therapy. *IONSYS* contains fentanyl hydrochloride and each system delivers an equivalent of 40 micrograms of fentanyl per dose over 10 minutes, to a maximum of 6 doses per hour, for 24 hours after the first dose or for 80 doses (maximum of 3.2 mg), whichever is reached first. The maximum duration of treatment is 72 hours, or 3 consecutive systems applied sequentially, with the new system being applied to a different site; only one system should be worn at a time. It should be applied to intact, non-irritated, and non-irradiated skin on the chest or upper outer arm.

A lozenge-on-a-stick dosage form of fentanyl citrate for *transmucosal* delivery is used as an analgesic in the management of **breakthrough cancer pain** in those already receiving and tolerant to opioid treatment. Lozenges containing the equivalent of 200 micrograms to up to 1.6 mg of fentanyl are available. An initial unit dose of 200 micrograms may be taken over 15 minutes for an episode of breakthrough pain and repeated once if necessary after a further 15 minutes. Doses are subsequently titrated according to response, up to a unit dose of 1.6 mg if necessary. Once the patient has been stabilised on an effective dose, no more than 4 unit doses should be taken daily.

In the USA, a buccal tablet containing fentanyl citrate for transmucosal delivery is also available and licensed for the same indication as the lozenge. Tablets containing the equivalent of 100 micrograms to up to 800 micrograms of fentanyl are available. An initial dose of 100 micrograms may be taken for an episode of breakthrough pain and repeated once if necessary after 30 minutes; thereafter, patients must wait at least 4 hours before treating another episode. Doses are subsequently titrated according to response. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain a day.

Caution must be exercised when switching between the lozenge and buccal tablet as the extent of absorption may be substantially different.

For details of doses in *children*, see below.

Administration. ***INHALATION ROUTE.*** In a study[1] inhaled fentanyl provided plasma concentrations similar to those after intravenous doses; use as patient-controlled analgesia was suggested. Inhaled formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain and acute pain.

1. Mather LE, *et al.* Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* 1998; **46:** 37–43.

INTRANASAL ROUTE. Studies[1-3] have shown that intranasal fentanyl is as effective as the intravenous route for postoperative pain management and that it can be used in a patient-controlled analgesia system. Intranasal fentanyl has also been studied[4-6] for the management of acute pain in children. Intranasal spray formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain.

1. Striebel HW, *et al.* Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia* 1993; **48:** 753–7.
2. Striebel HW, *et al.* Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* 1996; **83:** 548–51.
3. Toussaint S, *et al.* Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anesth* 2000; **47:** 299–302.
4. Manjushree R, *et al.* Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth* 2002; **49:** 190–3.
5. Borland ML, *et al.* Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* 2005; **31:** 831–7.
6. Borland M, *et al.* A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007; **49:** 335–40.

INTRASPINAL ROUTE. For a discussion on the intraspinal use of fentanyl, see Postoperative Pain, below.

TRANSDERMAL ROUTE. Transdermal fentanyl is used for chronic intractable cancer pain in adults and children.[1-5]

Transdermal fentanyl is also used in the treatment of chronic non-cancer pain;[4-6] however transdermal use is contra-indicated in the management of acute or postoperative pain because the problems of dose titration in the short term increase the possibility of development of significant respiratory depression[4] (see also under Adverse Effects and under Precautions, above).

Although the licensed dosage interval for transdermal patches of fentanyl is 72 hours studies have suggested that up to about 25% of cancer patients may require more frequent application with some patients requiring fresh patches every 48 hours.[7,8] Equally, in an attempt to supply lower doses than are allowed for by existing transdermal dosage forms, patches have sometimes been cut, folded, or partially masked with non-porous dressings; the manufacturers do not recommend such practices as they consider the dose supplied will be unreliable, and there is potential for overdosage.

An iontophoretic drug delivery system containing fentanyl hydrochloride is also available for the management of acute moderate to severe postoperative pain in a hospital setting (see Postoperative Pain, below for some references).

1. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* 1997; **53:** 109–38.
2. Muijsers RBR, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* 2001; **61:** 2289–2307.
3. Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; **2:** 165–72.
4. Kornick CA, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003; **26:** 951–73.
5. Zernikow B, *et al.* Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain* 2007; **8:** 187–207.
6. Allan L, *et al.* Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; **322:** 1154–8.
7. Radbruch L, *et al.* Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 2001; **15:** 309–21.
8. Donner B, *et al.* Long-term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998; **15:** 168–75.

TRANSMUCOSAL ROUTE. Transmucosal fentanyl has been tried for sedation and analgesia before anaesthesia or painful procedures in adults[1] and children[2,3] and is used for breakthrough cancer pain in opioid-tolerant patients.[4,5] It has been noted[6] that this dosage method can cause all the adverse effects of parenteral opioids; nausea and vomiting are common and potentially lethal respiratory depression can occur (see also under Precautions, above). Dosage guidelines have been suggested.[7]

1. Macaluso AD, *et al.* Oral transmucosal fentanyl citrate for premedication in adults. *Anesth Analg* 1996; **82:** 158–61.
2. Nelson PS, *et al.* Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. *Anesthesiology* 1989; **70:** 616–21.
3. Schechter NL, *et al.* The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* 1995; **95:** 335–9.
4. Blick SKA, Wagstaff AJ. Fentanyl buccal tablet: in breakthrough pain in opioid-tolerant patients with cancer. *Drugs* 2006; **66:** 2387–93.
5. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 26/06/08).
6. Anonymous. Oral transmucosal fentanyl citrate. *Med Lett Drugs Ther* 1994; **36:** 24–5.
7. Aronoff GM, *et al.* Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. *Pain Med* 2005; **6:** 305–14.

Administration in children. Indications for fentanyl therapy in children are similar to those in adults (see above).

Fentanyl is usually given by *intravenous* injection as an **adjunct** to general anaesthesia. In the UK recommended initial doses range from 2 to 3 micrograms/kg in children aged 2 to 12 years with *spontaneous respiration*; supplements of 1 microgram/kg may be given. (The *BNFC* suggests initial doses of 1 to 5 micrograms/kg for neonates and children up to 12 years of age.) When *ventilation* is *assisted*, the initial recommended dose is also 2 to 3 micrograms/kg, with supplements of 1 microgram/kg. (The *BNFC* suggests an initial dose of 5 to 10 micrograms/kg for neonates and children up to 12 years of age, with supplements of 1 to 3 micrograms/kg.) In the USA doses are similar to those licensed in the UK.

Children may also be given fentanyl by intravenous infusion: licensed product information implies that doses are similar to those used in adults (see above) although the *BNFC* recommends that the infusion rate in ventilated patients is 1.5 micrograms/kg per hour in neonates and is 1 to 6 micrograms/kg per hour in older children.

Transdermal patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour may be used for the treatment of **intractable chronic pain** in children aged 2 years and older who are already tolerant to opioid therapy of comparable potency. The initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 12 micrograms of fentanyl per hour is equivalent to about 30 to 44 mg daily of oral morphine sulfate. See Uses and Administration, above for further details. Patches should be applied to the upper backs of young children to minimise the potential for removal.

Although the *transmucosal* lozenge-on-a-stick formulation is not licensed for use in children, the *BNFC* suggests a single dose of 15 to 20 micrograms/kg (maximum of 400 micrograms) for the management of **breakthrough pain** and as **premedication** in those aged 2 years and older, and who weigh more than 10 kg.

Anaesthesia. Fentanyl and its congeners alfentanil and sufentanil are shorter-acting than morphine and appear to produce fewer circulatory changes; they are preferred for use as supplements during anaesthesia with inhalational or intravenous drugs. Fentanyl is widely used as the analgesic component of balanced anaesthesia. It has been used to attenuate cardiovascular stress responses to intubation (see Anaesthesia, p.1900), and may be used in higher doses in an attempt to reduce the cardiovascular, endocrine, and metabolic changes that may accompany surgery. When attenuation of surgical stress is especially important, for example in cardiac surgery, intravenous fentanyl 50 to 100 micrograms/kg in conjunction with oxygen and a neuromuscular blocker, and sometimes up to 150 micrograms/kg, may be used for general anaesthesia. Total intravenous anaesthesia with fentanyl and propofol has been successful.[1]

Satisfactory anaesthesia has been reported[2] with high-dose fentanyl citrate (30 to 50 micrograms/kg) in *premature infants* when used as sole anaesthetic, in conjunction with pancuronium, for ligation of patent ductus arteriosus; cardiovascular stability was maintained throughout the procedure. However, others[3] found significant hypotension in preterm infants given either fentanyl 20 micrograms/kg, isoflurane, halothane, or ketamine; systolic arterial pressure was best maintained with the ketamine technique. The surgical stress response in preterm babies was abolished by the addition of fentanyl 10 micrograms/kg intravenously to an anaesthetic regimen of nitrous oxide and tubocurarine.[4] Dose responses of fentanyl in *neonatal* anaesthesia have been discussed.[5]

For details of doses in neonates and children, see above.

Neuroleptanalgesia. An injection of short-acting fentanyl 50 micrograms/mL with the longer-acting antipsychotic droperidol 2.5 mg/mL has been used for neuroleptanalgesia, premedication, and as an adjunct to anaesthesia. However, the use of such a fixed-ratio combination cannot be recommended.

1. Jenstrup M, *et al.* Total iv anaesthesia with propofol-alfentanil or propofol-fentanyl. *Br J Anaesth* 1990; **64:** 717–22.
2. Robinson S, Gregory GA. Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. *Anesth Analg* 1981; **60:** 331–4.
3. Friesen RH, Henry DB. Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. *Anesthesiology* 1986; **64:** 238–42.
4. Anand KJS, *et al.* Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **i:** 243–8.
5. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; **66:** 433–5.

PHAEOCHROMOCYTOMA. Unlike morphine and some other opioids, fentanyl and alfentanil do not release histamine and may be used safely in the anaesthetic management of patients with phaeochromocytoma.[1]

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

POSTOPERATIVE SHIVERING. As pethidine appears to be effective in the treatment of postoperative shivering a number of other opioids including fentanyl have also been tried. Not all opioids are necessarily effective but fentanyl has been reported to be so,[1] although information is scanty.[2]

1. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; **70** (suppl 1): 38.
2. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; **94:** 453–60.

Intensive care. Despite the short duration of action of fentanyl after single doses, rapid redistribution in the body results in an elimination half-life longer than that of morphine. Consequently fentanyl is not a short-acting drug when used for analgesia in intensive care, and may offer little advantage over morphine.[1]

1. Aitkenhead AR. Analgesia and sedation in intensive care. *Br J Anaesth* 1989; **63:** 196–206.

Pain. ***CANCER PAIN.*** Transdermal fentanyl is used in the management of chronic intractable cancer pain; for references see Administration, Transdermal Route, above. For references to the use of transmucosal fentanyl in the management of breakthrough cancer pain, see Administration, Transmucosal Route, above.

LABOUR PAIN. Fentanyl has been reported to be an effective intravenous analgesic during active labour. Epidural fentanyl is unreliable when used alone,[1,2] although it does enhance the epidural analgesia achieved with the local anaesthetic bupivacaine. The reduction in the minimum local analgesic concentration of epidural bupivacaine for labour pain increased with increasing dose of fentanyl added to bupivacaine.[3] However, the incidence of pruritus increased significantly with fentanyl in a dose of 4 micrograms/mL and therefore the optimum dose of fentanyl may be 3 micrograms/mL for bupivacaine-sparing epidural analgesia during labour. Respiratory depression has also been reported with the combination.[4]

1. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
2. Lindow SW, *et al.* A randomised double-blind comparison of epidural fentanyl versus fentanyl and bupivicaine [sic] for pain relief in the second stage of labour. *Br J Obstet Gynaecol* 2004; **111:** 1075–80.
3. Lyons G, *et al.* Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. *Br J Anaesth* 1997; **78:** 493–7.
4. McClure JH, Jones G. Comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *Br J Anaesth* 1989; **63:** 637–40.

POSTOPERATIVE PAIN. Small intravenous bolus doses of an opioid analgesic may be injected immediately after surgery for postoperative analgesia and faster acting opioids such as fentanyl may be preferable to morphine.[1] Fentanyl has also been given by epidural injection in doses of 100 or 200 micrograms or by continuous epidural infusion in doses of 20 to 80 micrograms/hour; patient-controlled systems have been used.[2]

Epidural fentanyl or sufentanil provided effective postoperative analgesia after caesarean section with comparable adverse effect profiles.[3] The suggested optimal dose of fentanyl was 100 micrograms. For references comparing epidural fentanyl with alfentanil, see Postoperative Analgesia under Uses and Administration of Alfentanil, p.18. In a review[4] of perioperative pain management epidural opioids were considered to provide effective analgesia at lower doses than systemic opioids. Fentanyl may be given through a lumbar epidural catheter that is often inserted immediately postoperatively. After an initial loading dose of 1 to 1.5 micrograms/kg of fentanyl, infusion at the rate of 0.7 to 2 micrograms/kg per hour is begun and continued for about 48 hours on average. Some prefer to use intermittent injection. A small study[5] comparing 2 patient-controlled routes of administration found that cervical epidural fentanyl provided better postoperative pain relief at rest than intravenous fentanyl; however, there was no decrease in the total dose required and the authors considered that the benefits of epidural fentanyl did not outweigh its potential complications.

Combined opioid and local anaesthetic epidural infusions have also proved effective, for example fentanyl 1 microgram/mL with bupivacaine 0.1%; both could be infused at lower rates than either drug alone. Although a study[6] comparing bupivacaine-fentanyl combinations with each drug alone for epidural analgesia after caesarean section confirmed an additive analgesic effect for the combination, there was no demonstrable clinical benefit compared with fentanyl alone in this patient group who expect early mobilisation. However, the combination may be of greater benefit in patients for whom early ambulation is not routine.

Fentanyl has also been given by epidural injection to children for postoperative analgesia.[7]

Fentanyl has been tried by intrathecal injection for postoperative pain.[8]

As mentioned in Administration, Transdermal Route, above, an iontophoretic transdermal system for postoperative pain is also available.[9-11]

1. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; **63:** 147–58.
2. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
3. Grass JA, *et al.* A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
4. Swarm RA, *et al.* Pain treatment in the perioperative period. *Curr Probl Surg* 2001; **38:** 835–920.
5. Roussier M, *et al.* Patient-controlled cervical epidural fentanyl compared with patient-controlled i.v. fentanyl for pain after pharyngolaryngeal surgery. *Br J Anaesth* 2006; **96:** 492–6.
6. Cooper DW, *et al.* Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. *Br J Anaesth* 1996; **76:** 611–15.
7. Lejus C, *et al.* Postoperative extradural analgesia in children: comparison of morphine with fentanyl. *Br J Anaesth* 1994; **72:** 156–9.
8. Sudarshan G, *et al.* Intrathecal fentanyl for post-thoracotomy pain. *Br J Anaesth* 1995; **75:** 19–22.
9. Chelly JE. An iontophoretic, fentanyl HCl patient-controlled transdermal system for acute postoperative pain management. *Expert Opin Pharmacother* 2005; **6:** 1205–14.
10. Koo PJ. Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am J Health-Syst Pharm* 2005; **62:** 1171–6.
11. Mayes S, Ferrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *Ann Pharmacother* 2006; **40:** 2178–86.

Preparations

BP 2008: Fentanyl Injection;
USP 31: Fentanyl Citrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Durogesic; Fentax; Gray-F; Nafluvent; Sublimaze; Talnur; ***Austral.:*** Actiq; Durogesic; Sublimaze; ***Austria:*** Durogesic; ***Belg.:*** Durogesic; ***Braz.:*** Durogesic; Fentabbott; Fentanest; Fentatil; ***Canad.:*** Duragesic; ***Chile:*** Durogesic; ***Cz.:*** Durogesic; Fentagesic; Fentahexal; Fentalis; Ionsys; Matrifen; Wintanyl; ***Denm.:*** Actiq; Durogesic; Haldid; ***Fin.:*** Actiq; Durogesic; ***Fr.:*** Actiq; Durogesic; Ionsys; ***Ger.:*** Actiq; Durogesic; Fenta-Hameln†; ***Gr.:*** Actiq; Durogesic; Fentadur; Matrifen; ***Hong Kong:*** Durogesic; ***Hung.:*** Durogesic; Matrifen; Sedaton; ***India:*** Durogesic; Trofentyl; ***Indon.:*** Durogesic; ***Irl.:*** Actiq; Durogesic; Fental; Sublimaze; ***Israel:*** Durogesic; Tanyl; ***Ital.:*** Actiq; Durogesic; Fentanest; ***Jpn:*** Durotep; ***Malaysia:*** Durogesic; Talgesil; ***Mex.:*** Durogesic; Fenodid; Fentanest; ***Neth.:*** Actiq; Durogesic; ***Norw.:*** Actiq; Durogesic; Leptanal; ***NZ:*** Durogesic; Sublimaze; ***Philipp.:*** Durogesic; Sublimaze; ***Pol.:*** Durogesic; Fentahexal; ***Port.:*** Durogesic; Fentanest; Ionsys; Nilfene; ***Rus.:*** Durogesic (Дюрогезик); ***S.Afr.:*** Durogesic; Sublimaze; Tanyl; ***Singapore:*** Durogesic; ***Spain:*** Actiq; Durogesic; Fentanest; ***Swed.:*** Actiq; Durogesic; Leptanal; Matrifen; ***Switz.:*** Actiq; Durogesic; Sintenyl; ***Thai.:*** Durogesic; ***Turk.:*** Durogesic; ***UK:*** Actiq; Durogesic; Fentalis; Ionsys; Matrifen; Osmach; Sublimaze; Tilofyl; ***USA:*** Actiq; Duragesic; Fentora; Ionsys; Sublimaze; ***Venez.:*** Durogesic.

Multi-ingredient: Arg.: Disifelit; ***Austral.:*** Marcain with Fentanyl; Naropin with Fentanyl; ***Braz.:*** Nilperidol; ***Ital.:*** Leptofen; ***NZ:*** Bupafen; Marcain with Fentanyl; Naropin with Fentanyl.

Fentiazac *(BAN, USAN, rINN)*

BR-700; Fentiazaco; Fentiazacum; Wy-21894. [4-(4-Chlorophenyl)-2-phenylthiazol-5-yl]acetic acid.

Фентиазак

$C_{17}H_{12}ClNO_2S$ = 329.8.
CAS — 18046-21-4.
ATC — M01AB10; M02AA14.
ATC Vet — QM01AB10; QM02AA14.

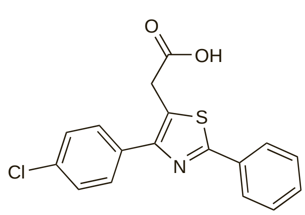

Profile

Fentiazac is an NSAID (p.96) that has been used for the relief of pain and inflammation associated with musculoskeletal, joint, peri-articular, and soft-tissue disorders. It has also been used in the treatment of fever. Fentiazac has been given in usual oral doses of 200 mg once or twice daily. Fentiazac has also been applied topically and has been given rectally as the calcium salt.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: O-Flam; ***Port.:*** Donorest†; IDR†; Norvedan†.

Fepradinol *(rINN)*

Fépradinol; Fepradinolum. (±)-α-{[(2-Hydroxy-1,1-dimethylethyl)amino]methyl}benzyl alcohol.

Фепрадинол

$C_{12}H_{19}NO_2$ = 209.3.
CAS — 63075-47-8.

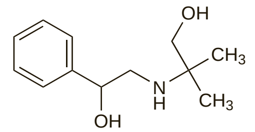

Profile

Fepradinol is an NSAID (p.96) that has been used topically in a concentration of 6% for the relief of pain and inflammation. The hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Sinalgia†; ***Mex.:*** Sinalgia; ***Spain:*** Dalgen; Flexidol†.

Feprazone *(BAN, rINN)*

DA-2370; Feprazona; Féprazone; Feprazonum; Phenylprenazone; Prenazone. 4-(3-Methylbut-2-enyl)-1,2-diphenylpyrazolidine-3,5-dione.

Фепразон

$C_{20}H_{20}N_2O_2$ = 320.4.
CAS — 30748-29-9 (feprazone); 57148-60-4 (feprazone piperazine salt 1:1).
ATC — M01AX18; M02AA16.
ATC Vet — QM01AX18; QM02AA16.

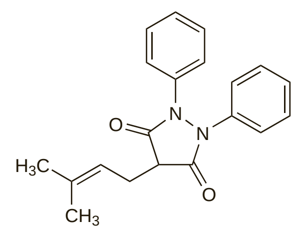

Profile

Feprazone, a phenylbutazone (p.117) derivative, is an NSAID (p.96). It has been given orally in the treatment of mild to moderate pain, fever, and inflammation associated with musculoskeletal and joint disorders. Feprazone has also been given rectally and used topically as a 5% cream.

Pinazone, the piperazine salt of feprazone, has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Zepelin; ***Spain:*** Brotazona; ***Venez.:*** Vapesin.

Firocoxib *(USAN, rINN)*

Firocoxibum; ML-1785713. 3-(Cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5*H*)-one.

Фирококсиб

$C_{17}H_{20}O_5S$ = 336.4.
CAS — 189954-96-9.
ATC Vet — QM01AH90.

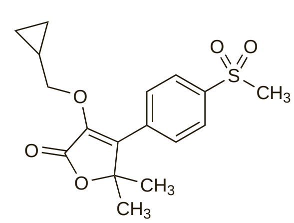

Profile

Firocoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, is an NSAID used in veterinary medicine for the treatment of inflammation and pain associated with osteoarthritis in dogs.

Floctafenine *(BAN, USAN, rINN)*

Floctafenina; Floctafénine; Floctafeninum; R-4318; RU-15750. 2,3-Dihydroxypropyl *N*-(8-trifluoromethyl-4-quinolyl)anthranilate.

Флоктафенин

$C_{20}H_{17}F_3N_2O_4$ = 406.4.
CAS — 23779-99-9.
ATC — N02BG04.
ATC Vet — QN02BG04.

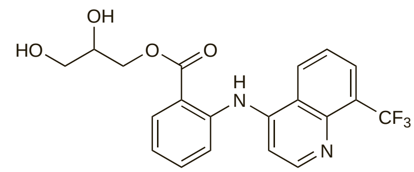

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Anaphylactic shock has been reported, and may be preceded by minor allergic manifestations; floctafenine should be stopped in any patient who develops signs suggestive of allergy (such as pruritus or urticaria). Reactions may also involve the liver. Floctafenine may cross-react with glafenine (p.62) and should not be given to patients who have had glafenine-associated reactions.

Porphyria. Floctafenine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Floctafenine is absorbed from the gastrointestinal tract; peak plasma concentrations are obtained 1 to 2 hours after ingestion. Its plasma half-life is about 8 hours. It is metabolised in the liver to floctafenic acid. It is excreted mainly as glucuronide conjugates in the urine and bile.

Uses and Administration

Floctafenine, an anthranilic acid derivative related to glafenine (p.62), is an NSAID (p.99) used in oral doses of up to 1.2 g daily, in divided doses, for the short-term relief of pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Idarac†; ***Fr.:*** Idarac; ***Irl.:*** Idarac†; ***Thai.:*** Idarac.

Flufenamic Acid *(BAN, USAN, rINN)*

Acide Flufénamique; Ácido flufenámico; Acidum Flufenamicum; CI-440; CN-27554; Flufenaamihappo; Flufenamsyra; INF-1837; Kwas flufenamowy; NSC-82699. *N*-(ααα-Trifluoro-*m*-tolyl)anthranilic acid.

Флуфенамовая Кислота

$C_{14}H_{10}F_3NO_2$ = 281.2.
CAS — 530-78-9 (flufenamic acid); 61891-34-7 (flufenamate aluminium); 16449-54-0 (flufenamate aluminium).
ATC — M01AG03.
ATC Vet — QM01AG03.

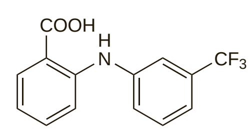

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving flufenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

An early study[2] found that only very small amounts of flufenamic acid were excreted into breast milk after oral doses.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)
2. Buchanan RA, *et al.* The breast milk excretion of flufenamic acid. *Curr Ther Res* 1969; **11:** 533–8.

Effects on the gastrointestinal tract. Acute proctocolitis associated with oral flufenamic acid in a patient.[1]

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.

Porphyria. Flufenamic acid has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Uses and Administration

Flufenamic acid, an anthranilic acid derivative related to mefenamic acid (p.80), is an NSAID (p.99). Flufenamic acid is mainly used topically in a concentration of 3 or 3.5% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. Flufenamic acid and its aluminium salt have also been given orally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Dignodolin†; ***Jpn:*** Opyrin.

Multi-ingredient: ***Austria:*** Mobilisin; Mobilisin plus; Rheugesal; ***Belg.:*** Mobilisin; ***Braz.:*** Mobilisin Composto; ***Ger.:*** Algesalona†; ***Hung.:*** Mobilisin†; ***Ital.:*** Mobilisin; ***Port.:*** Latesil; Mobilisin; ***Spain:*** Movilisin; ***Switz.:*** Algesalona†; Assan; Assan thermo; Mobilisin.

Flunixin Meglumine *(BANM, USAN, rINNM)*

Fluniksiinimeglumiini; Flunixin megluminová sůl; Flunixine méglumine; Flunixini megluminum; Flunixinmeglumin; Flunixino meglumina; Flunixinum Megluminicum; Meglumini Flunixinum; Sch-14714 (flunixin). 2-{[2-Methyl-3-(trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1); 2-(α^3,α^3,α^3-Trifluoro-2,3,-xylidino)nicotinic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1).

Меглумина Флуниксин

$C_{14}H_{11}F_3N_2O_2,C_7H_{17}NO_5 = 491.5.$

CAS — 38677-85-9 (flunixin); 42461-84-7 (flunixin meglumine).

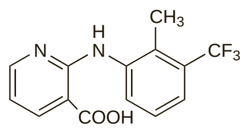

(flunixin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Flunixin Meglumine for Veterinary Use; Flunixin Meglumine BP(Vet) 2008). A white to almost white crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 7.0 to 9.0.

USP 31 (Flunixin Meglumine). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ethyl acetate. pH of a 5% solution in water is between 7.0 and 9.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Profile

Flunixin meglumine is an NSAID (p.96) used in veterinary medicine for the relief of pain and inflammation in acute and chronic disorders and as adjunctive therapy in the treatment of endotoxic or septic shock and mastitis.

Flupirtine Maleate *(BANM, USAN, rINNM)*

D-9998; Flupirtine, Maléate de; Flupirtini Maleas; Maleato de flupirtina; W-2964M. Ethyl 2-amino-6-(4-fluorobenzylamino)-3-pyridylcarbamate maleate.

Флупиртина Малеат

$C_{15}H_{17}FN_4O_2,C_4H_4O_4 = 420.4.$

CAS — 56995-20-1 (flupirtine); 75507-68-5 (flupirtine maleate).

ATC — N02BG07.

ATC Vet — QN02BG07.

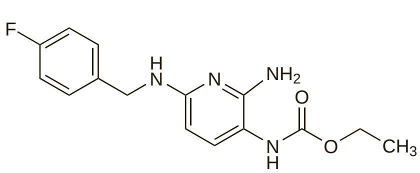

(flupirtine)

Profile

Flupirtine maleate is an analgesic that has been given for the relief of pain (see Choice of Analgesic, p.2) in usual doses of 100 mg three or four times daily by mouth, or 150 mg three or four times daily as a rectal suppository; daily doses of up to 600 mg by mouth or 900 mg rectally have been used where necessary. Flupirtine has also been given by intramuscular injection as the gluconate in the management of acute pain.

There has been some interest in the potential of flupirtine to treat prion diseases such as Creutzfeldt-Jakob disease (see below).

◊ References.

1. Friedel HA, Fitton A. Flupirtine: a review of its pharmacological properties, and therapeutic efficacy in pain states. *Drugs* 1993; **45:** 548–69.

Creutzfeldt-Jakob disease. A double-blind placebo-controlled study[1] in 28 patients with Creutzfeldt-Jakob disease (CJD) found flupirtine to have beneficial effects on cognitive function. However, further studies are needed to establish any place in therapy.

1. Otto M, *et al.* Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. *Neurology* 2004; **62:** 714–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Katadolon; ***Ger.:*** Katadolon; Trancopal Dolo; ***Port.:*** Metanor; Novocebrin; ***Rus.:*** Katadolon (Катадолон).

Flurbiprofen *(BAN, USAN, rINN)*

BTS-18322; Flurbiprofeeni; Flurbiprofén; Flurbiprofenas; Flurbiprofène; Flurbiprofeno; Flurbiprofenum; U-27182. 2-(2-Fluorobiphenyl-4-yl)propionic acid.

Флурбипрофен

$C_{15}H_{13}FO_2 = 244.3.$

CAS — 5104-49-4.

ATC — M01AE09; M02AA19; S01BC04.

ATC Vet — QM01AE09; QM02AA19; QS01BC04.

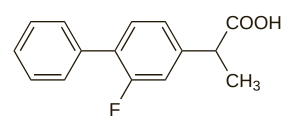

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Flurbiprofen). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane; dissolves in aqueous solutions of alkali hydroxides and carbonates.

USP 31 (Flurbiprofen). A white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in ether, and in methyl alcohol; soluble in acetonitrile. Store in airtight containers.

Flurbiprofen Sodium *(BANM, rINNM)*

Flurbiprofène Sodique; Flurbiprofeno sódico; Natrii Flurbiprofenum. Sodium (±)-2-(2-fluoro-4-biphenylyl)propionate dihydrate.

Натрий Флурбипрофен

$C_{15}H_{12}FNaO_2,2H_2O = 302.3.$

CAS — 56767-76-1.

Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Flurbiprofen Sodium). A white to creamy-white, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Minor symptoms of ocular irritation including transient burning and stinging have been reported on instillation of flurbiprofen sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation has also followed rectal use, and local effects including a sensation of warming or burning in the mouth may be seen after using flurbiprofen lozenges.

Incidence of adverse effects. Reports from the manufacturers on the range and incidence of the adverse effects of flurbiprofen.[1,2]

1. Sheldrake FE, *et al.* A long-term assessment of flurbiprofen. *Curr Med Res Opin* 1977; **5:** 106–16.
2. Brooks CD, *et al.* Clinical safety of flurbiprofen. *J Clin Pharmacol* 1990; **30:** 342–51.

Effects on the CNS. A severe symmetrical parkinsonian syndrome developed in a 52-year-old man who had taken flurbiprofen for 7 days.[1]

1. Enevoldson TP, *et al.* Acute parkinsonism associated with flurbiprofen. *BMJ* 1990; **300:** 540–1.

Effects on the kidneys. Renal papillary necrosis has been described in a patient who had used flurbiprofen for many years.[1] Acute flank pain and reversible renal dysfunction has been reported in 2 patients treated with flurbiprofen.[2,3] Membranous nephropathy also developed in a patient who took flurbiprofen daily for 12 to 18 months.[4]

1. Nafría EC, *et al.* Renal papillary necrosis induced by flurbiprofen. *DICP Ann Pharmacother* 1991; **25:** 870–1.
2. Kaufhold J, *et al.* Flurbiprofen-associated tubulointerstitial nephritis. *Am J Nephrol* 1991; **11:** 144–6.
3. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; **92:** 459–60.
4. MacKay K. Membranous nephropathy associated with the use of flurbiprofen. *Clin Nephrol* 1997; **47:** 279–80.

Effects on the liver. A case of cholestatic jaundice probably due to flurbiprofen has been reported.[1]

1. Kotowski KE, Grayson MF. Side effects of non-steroidal anti-inflammatory drugs. *BMJ* 1982; **285:** 377.

Effects on the skin. Cutaneous vasculitis apparently due to flurbiprofen occurred in a 59-year-old woman with long-standing rheumatoid arthritis.[1] Contact dermatitis has also been seen in a 22-year-old woman who applied a poultice containing flurbiprofen to her wrist.[2]

1. Wei N. Flurbiprofen and cutaneous vasculitis. *Ann Intern Med* 1990; **112:** 550–1.
2. Kawada A, *et al.* Contact dermatitis due to flurbiprofen. *Contact Dermatitis* 2000; **42:** 167–8.

Hypersensitivity. A diffuse, pruritic, maculopapular rash developed in a patient 48 hours after taking a second dose of flurbiprofen.[1] Two days later, the rash had become urticarial, and angioedema and hypotension were also noted. Patch testing with flurbiprofen powder was positive.

See also Effects on the Skin, above.

1. Romano A, Pietrantonio F. Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997; **241:** 81–3.

Precautions

As for NSAIDs in general, p.98.

Breast feeding. Flurbiprofen is distributed into breast milk; however, the *BNF* and licensed product information consider the amount to be too small to be harmful to a breast-fed infant.

Herpes simplex keratitis. Whether flurbiprofen can exacerbate infection when used to treat ocular herpes simplex is unclear from *animal* studies,[1,2] but licensed product information for flurbiprofen sodium eye drops recommends that they should not be used in patients with active epithelial herpes simplex keratitis. Patients with a history of herpes simplex keratitis should also be monitored closely when undergoing treatment with these eye drops.

1. Trousdale MD, *et al.* Effect of flurbiprofen on herpes simplex keratitis in rabbits. *Invest Ophthalmol Vis Sci* 1980; **19:** 267–70.
2. Hendricks RL, *et al.* The effect of flurbiprofen on herpes simplex virus type 1 stromal keratitis in mice. *Invest Ophthalmol Vis Sci* 1990; **31:** 1503–11.

Interactions

For interactions associated with NSAIDs, see p.99.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations and for flurbiprofen sodium eye drops states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Flurbiprofen is readily absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring about 1 to 2 hours after ingestion. Absorption after rectal doses may be more rapid. It is about 99% bound to plasma proteins and has a plasma half-life of about 3 to 6 hours. It is metabolised mainly by hydroxylation (via the cytochrome P450 isoenzyme CYP2C9) and conjugation in the liver and excreted in urine. Flurbiprofen is distributed into breast milk.

Flurbiprofen is a chiral compound given as the racemate and the above pharmacokinetic characteristics refer to the racemic mixture. Allowance may have to be made for the different activities of the enantiomers.

◊ References.

1. Aarons L, *et al.* Plasma and synovial fluid kinetics of flurbiprofen in rheumatoid arthritis. *Br J Clin Pharmacol* 1986; **21:** 155–63.
2. Smith IJ, *et al.* Flurbiprofen in post-partum women: plasma and breast milk disposition. *J Clin Pharmacol* 1989; **29:** 174–84.
3. Kean WF, *et al.* The pharmacokinetics of flurbiprofen in younger and elderly patients with rheumatoid arthritis. *J Clin Pharmacol* 1992; **32:** 41–8.
4. Davies NM. Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet* 1995; **28:** 100–14.

Uses and Administration

Flurbiprofen, a propionic acid derivative, is an NSAID (p.99). It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, and in mild to moderate pain including dysmenorrhoea and migraine. Flurbiprofen is also used as lozenges in the symptomatic relief of sore throat. Flurbiprofen sodium is used in eye drops to inhibit intra-operative miosis and to control postoperative inflammation of the anterior segment of the eye.

For **pain and inflammation**, flurbiprofen is given in usual oral doses of 150 to 200 mg daily in divided doses, increased to 300 mg daily in acute or severe conditions if necessary. A modified-release preparation for once-daily use is also available. Patients with dysmenorrhoea may be given an initial dose of 100 mg followed by 50 to 100 mg every four to six hours to a maximum total daily dose of 300 mg. Doses given rectally as suppositories are similar to those given by orally.

For the relief of **sore throat**, a lozenge containing 8.75 mg of flurbiprofen may be sucked or allowed to dissolve slowly in the mouth every 3 to 6 hours to a maximum daily dose of 5 lozenges. It is recommended that treatment should be limited to a maximum of 3 days.

To inhibit intra-operative miosis during **ocular surgery** one drop of flurbiprofen sodium 0.03% is instilled into the eye every 30 minutes beginning 2 hours before surgery and ending not less than 30 minutes before surgery. To control postoperative inflammation the same dosage regimen is used before ocular surgery followed 24 hours after surgery by the instillation of one drop 4 times daily for 1 to 3 weeks. Flurbiprofen sodium eye drops have also been used in the topical treatment of cystoid macular oedema.

Flurbiprofen axetil has been given in some countries by intravenous injection for severe pain.

The *R*-enantiomer, tarenflurbil, is under investigation in the management of Alzheimer's disease.

Preparations

BP 2008: Flurbiprofen Eye Drops; Flurbiprofen Suppositories; Flurbiprofen Tablets;
USP 31: Flurbiprofen Sodium Ophthalmic Solution; Flurbiprofen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Clinadol; Flurbic; Flurbid†; Luarprofeno; Tolerane; ***Austral.:*** Ocufen; Strepfen; ***Austria:*** Froben; Ocuflur†; ***Belg.:*** Froben; Ocuflur; ***Braz.:*** Ocufen; Targus; ***Canad.:*** Ansaid; Froben; Novo-Flurprofen; Ocufen; ***Chile:*** Ansaid; Distex; Ocufen; ***Cz.:*** Ansaid†; Flugalin†; Ocuflur†; Strepfen; Trans-ActLAT†; ***Denm.:*** Flurofen; ***Fr.:*** Cebutid; Ocufen; Strefen; ***Ger.:*** Dobendan Direkt; Dobrofen†; Ocuflur; ***Gr.:*** Bedice†; Bonatol-R; Fladolef-B†; Flurofen; Fluroptic; Inflaflur; Ocuflur; ***Hong Kong:*** Ocufen†; ***Hung.:*** Flugalin; Ocuflur†; Strepfen; ***India:*** Arflur†; Cadiflur; Froben; Ocuflur; ***Irl.:*** Froben; Ocufen†; Strepsils Intensive; ***Ital.:*** Benactiv; Froben; Ocufen; Tantum Activ Gola; Transact Lat; ***Jpn:*** Ropion; ***Malaysia:*** Acustop Cataplasma; ***Mex.:*** Ansaid; Ocufen; ***Neth.:*** Froben; ***NZ:*** Froben†; Ocufen†; Strepfen; ***Pol.:*** Flugalin; Strepsils Intensive; ***Port.:*** Edolfene; Froben; Ocuflur†; Reupax†; Strepfen; Transact Lat; ***Rus.:*** Strepfen (Стрепфен); ***S.Afr.:*** Froben; Ocufen; TransAct; ***Singapore:*** Acustop Cataplasma†; Ocufen†; ***Spain:*** Froben; Neo Artrol†; Ocuflur; ***Switz.:*** Froben; Ocuflur; ***Thai.:*** Flurozin; ***Turk.:*** Majezik; ***UK:*** Froben; Ocufen; Strefen; ***USA:*** Ansaid; Ocufen; ***Venez.:*** Flurben†; Ocufen†.

Fosfosal *(rINN)*

Fosfosalum; UR-1521. 2-Phosphono-oxybenzoic acid.

Фосфосал

$C_7H_7O_6P$ = 218.1.
CAS — 6064-83-1.

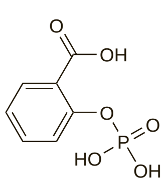

Profile

Fosfosal is a salicylic acid derivative (see Aspirin, p.20). It has been given in usual oral doses of up to 3.6 g daily for the treatment of pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Aydolid; Disdolen; Protalgia.

Multi-ingredient: ***Spain:*** Aydolid Codeina; Disdolen Codeina.

Furprofen

Furprofeno. 4-(2-Furanylcarbonyl)-α-methylbenzeneacetic acid.

Фурпрофен

$C_{14}H_{12}O_4$ = 244.2.
CAS — 66318-17-0.

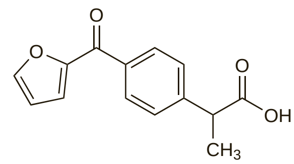

Profile

Furprofen, a propionic acid derivative, is an NSAID (p.96) that has been given by mouth for the relief of pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Dolex†.

Glafenine *(rINN)*

Glafenina; Glafénine; Glafeninum; Glaphenine. 2,3-Dihydroxypropyl *N*-(7-chloro-4-quinolyl)anthranilate.

Глафенин

$C_{19}H_{17}ClN_2O_4$ = 372.8.
CAS — 3820-67-5.
ATC — N02BG03.
ATC Vet — QN02BG03.

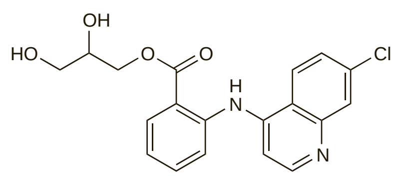

Profile

Glafenine, an anthranilic acid derivative, is an NSAID (p.96) that was used for the relief of all types of pain. However, its high incidence of anaphylactic reactions has led to its withdrawal from the market in most countries. Glafenine hydrochloride was also used.

Adverse effects and precautions. Glafenine is a common cause of anaphylaxis. There may be hepatotoxicity (sometimes fatal), nephrotoxicity, and gastrointestinal disturbances. It should be stopped at the first sign of any allergic reaction. Crystallisation of glafenine in the urinary tract has also occurred. Cross-reactivity with floctafenine has been reported.

Glucametacin *(rINN)*

Glucametacina; Glucamétacine; Glucametacinum. 2-{2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetamido}-2-deoxy-D-glucose.

Глюкаметацин

$C_{25}H_{27}ClN_2O_8$ = 518.9.
CAS — 52443-21-7.

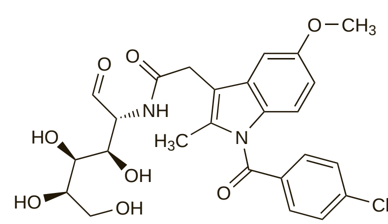

Profile

Glucametacin, a derivative of indometacin (p.66), is an NSAID (p.96) that has been given orally in musculoskeletal, joint, periarticular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Teoremin; ***Mex.:*** Teoremac.

Multi-ingredient: ***Chile:*** Fibrorelax.

Glycol Salicylate

Ethylene Glycol Monosalicylate; Glycoli Salicylas; Glykolisalisylaatti; Glykolsalicylat; Hidroksietilo salicilatas; Hidroxietil-szalicilát; Hydroksietyylisalisylaatti; Hydroxietylsalicylat; Hydroxyaethyli Salicylas; Hydroxyéthyle, salicylate d'; Hydroxyethylis salicylas; Hydroxyethyl-salicylát; Salicilato de glicol. 2-Hydroxyethyl salicylate.

Гликоль Салицилат

$C_9H_{10}O_4$ = 182.2.
CAS — 87-28-5.

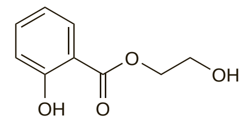

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hydroxyethyl Salicylate). An oily, colourless or almost colourless liquid or colourless crystals. M.p. about 21°. Sparingly soluble in water; freely soluble in alcohol; very soluble in acetone and in dichloromethane. Protect from light.

Profile

Glycol salicylate is a salicylic acid derivative used similarly to methyl salicylate (p.85) in topical rubefacient preparations in usual concentrations of 5 to 15% for the relief of muscular and rheumatic pain. Dipropylene glycol salicylate has been used in similar preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Lumbinon†; ***Ger.:*** Auroanalin N†; Dolo-Arthrosenex N; Dolo-Arthrosenex NH; Dolo-Rubriment H†; Etrat Sportgel HES; Kytta†; Lumbinon†; Mobilat Akut HES; Phardol mono; Phlogont Rheuma†; Phlogont†; Rheubalmin N†; Salhumin Gel; Traumasenex; zuk Schmerzgel, zuk Schmerzsalbe†.

Multi-ingredient: ***Arg.:*** Infrarub†; Venostasin; ***Austral.:*** Deep Heat; Goanna Analgesic Ice†; ***Austria:*** Ambenat; Etrat; Igitur-Rheumafluid; Menthoneurin; Mobilisin; Moviflex; Rheumex; Rubizon-Rheumagel; Rubriment; Sportino Akut†; Venostasin compositum; ***Belg.:*** Algipan; Emerxil; Mobilisin; Percutalgine; Rado-Salil; Rado-Spray†; Stilene; ***Braz.:*** Etrat†; Mobilisin Composto; Venostasin†; ***Canad.:*** Midalgan†; ***Cz.:*** Arnidol; Dolo-Rubriment†; Rheuma-Salbe†; Rubriment-N†; ***Fin.:*** Moviflex†; ***Fr.:*** Algipan; Cortisal; Le Thermogene†; Lumbalgine; Percutalgine; ***Ger.:*** ABC Warme-Salbe†; Ambene N; Arthrodestal N†; Auroanalin Thermo; Caye Rheuma-Balsam; Dolo Mobilat†; Doloneuro†; DoloVisano Salbe†; Essaven Sport†; Etrat Sportgel†; Heparin Plus†; Hot Thermo; Infrotto Ultra†; Lumbinon Thermo†; Menthoneurin-Salbe; mikanil†; Ostochont†; Phardol Rheuma†; Phardol Warme-Balsam†; Phlogont-Thermal; Rheubalmin Thermo†; Rheuma Bad; Rheuma-Salbe N; Rheuma-Salbe†; Rubriment-N†; Sportino Akut; Tetesept Badekonzentrat Rheuma Bad†; Thermo-Menthoneurin†; Thermo-Rheumon N†; Thermosenex; Togal Mobil-Gel†; Trauma-Puren†; Venoplant AHS†; Vertebralon N†; Warme-Gel†; zuk thermo†; ***Gr.:*** Bayolin; ***Hong Kong:*** New Patecs A; Prelloran†; Salomethyl; ***Hung.:*** Bayolin†; Mobilisin†; Nicoflex; ***India:*** Algipan; ***Irl.:*** Algipan; ***Israel:*** Deep Heat Spray; ***Ital.:*** Balsamo Sifcamina; Disalgil†; Mobilisin; Salonpas; Sloan; ***Malaysia:*** Salonpas; ***Neth.:*** Cremor capsici comp; Cremor Capsici compositus; Kruidvat Spierbalsem; ***Pol.:*** Deep Heat; Lumbolin; ***Port.:*** DM Creme; DM Gel; Midalgan†; ***S.Afr.:*** Deep Heat Spray; Infrarub; ***Singapore:*** Deep Heating Spray†; Saak†; ***Spain:*** Movilisin; ***Switz.:*** Assan; Assan thermo; Demotherm Pommade contre le rhumatisme†; Dolo Demotherm; Dolo-Arthrosenex; Dolo-Arthrosenex sine Heparino†; Dolo-Veniten†; Histalgane; Histalgane mite; Midalgan; Mobilisin; Phlebostasin compositum†; Prelloran†; Radalgin; Remexal; Sportusal; Sportusal Spray sine heparino; Venoplant comp; Venucreme; Venugel; ***Thai.:*** Percutalgine†; ***UK:*** Cremalgin; Deep Heat Spray; Dubam; Fiery Jack; Ralgex; Ralgex Freeze Spray; Ralgex Heat Spray (low-odour); Salonair; Salonpas; Transvasin Heat Spray.

Gold Keratinate

Aurothiopolypeptide; Queratinato de oro.

CAS — 9078-78-8.

Profile

Gold keratinate is a gold compound with a gold content of about 13%; It has similar actions and uses to those of sodium aurothiomalate (p.122). It has been given by intramuscular injection as the calcium salt for the treatment of rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aurochobet.

Golimumab *(USAN, rINN)*

CNTO-148; Golimumabum. Immunoglobulin G1, anti-(human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer.

Голимумаб

CAS — 476181-74-5.

Profile

Golimumab is a human monoclonal antibody to tumour necrosis factor α, a pro-inflammatory mediator (see Infliximab, p.71), that is being investigated in the management of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

◊ References.

1. Zhou H, *et al.* Pharmacokinetics and safety of golimumab, a fully human anti-TNF-α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007; **47:** 383–96.
2. Kay J, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; **58:** 964–75.

Hexyl Nicotinate

Heksyylinikotinaatti; Hexylnicotinatum; Hexylnikotinat; Nicotinato de hexilo. *n*-Hexyl nicotinate.

$C_{12}H_{17}NO_2$ = 207.3.

CAS — 23597-82-2.

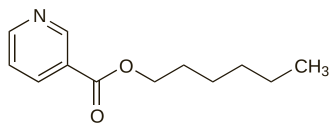

Profile

Hexyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Transvane; ***Irl.:*** Transvasin; ***Port.:*** Hipodor†; ***UK:*** Transvasin Heat Rub.

Hydrocodone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidrocodona; Hydrocodone, Chlorhydrate d'; Hydrocodoni Hydrochloridum.

Гидрокодона Гидрохлорид

$C_{18}H_{21}NO_3,HCl,2\frac{1}{2}H_2O$ = 380.9.

CAS — 25968-91-6 (anhydrous hydrocodone hydrochloride).

ATC — R05DA03.

ATC Vet — QR05DA03.

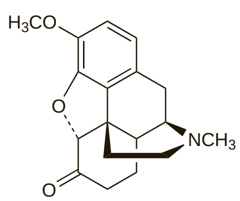

(hydrocodone)

Hydrocodone Tartrate *(BANM, rINNM)*

Dihydrocodeinone Acid Tartrate; Hydrocodone Acid Tartrate; Hydrocodone Bitartrate *(USAN)*; Hydrocodone, Tartrate d'; Hydrocodoni Bitartras; Hydrocodoni Tartras; Hydrocone Bitartrate; Tartrato de dihidrocodeinona; Tartrato de hidrocodona. 6-Deoxy-3-*O*-methyl-6-oxomorphine hydrogen tartrate hemipentahydrate; (−)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-one hydrogen tartrate hemipentahydrate.

Гидрокодона Тартрат

$C_{18}H_{21}NO_3,C_4H_6O_6,2\frac{1}{2}H_2O$ = 494.5.

CAS — 125-29-1 (hydrocodone); 143-71-5 (anhydrous hydrocodone tartrate); 34195-34-1 (hydrocodone tartrate hemipentahydrate).

ATC — R05DA03.

ATC Vet — QR05DA03.

NOTE. Compounded preparations of hydrocodone tartrate may be represented by the following names:

- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol.

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydrocodone tartrate:

Cough Syrup; Vikes.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Hydrocodone Hydrogen Tartrate 2.5-Hydrate). White or almost white, hygroscopic, crystalline powder. Freely soluble or soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 2% solution in water has a pH of 3.2 to 3.8. Store in airtight containers. Protect from light.

USP 31 (Hydrocodone Bitartrate). Fine, white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 2% solution in water is between 3.2 and 3.8. Store in airtight containers. Protect from light.

Profile

Hydrocodone, a phenanthrene derivative, is an opioid analgesic (p.101) related to codeine (p.37) and has similar actions, but is more potent on a weight-for-weight basis. Hydromorphone (below) is one of the metabolites of hydrocodone.

Hydrocodone is used mainly as the tartrate in combination preparations for the relief of irritant cough, though it has no particular advantage over codeine. Hydrocodone tannate has been used similarly. Hydrocodone tartrate is also used for the relief of moderate to moderately severe pain, usually with paracetamol. The usual oral dose of hydrocodone tartrate in such combination preparations is 5 to 10 mg every 4 to 6 hours.

For details of doses in children, see below.

Hydrocodone hydrochloride is given orally and also by injection. The polistirex derivative (a hydrocodone and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Hydrocodone has also been used in the treatment of dyspnoea.

Abuse. The abuse or overuse of preparations containing hydrocodone and paracetamol has been associated with *sensorineural hearing loss.*[1,2] Cochlear implants improved the hearing loss in some of the patients.

A case of *palatal perforation* associated with intranasal abuse of a crushed preparation of hydrocodone and paracetamol has also been reported.[3]

1. Friedman RA, *et al.* Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; **21:** 188–91.
2. Ho T, *et al.* Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; **10:** 467–72.
3. Jewers WM, *et al.* Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99:** 594–7.

Administration in children. Hydrocodone tartrate may be given as part of a combination preparation for the relief of irritant cough in children aged from 6 to 12 years in usual oral doses of 2.5 mg every 4 to 6 hours. Older children may be given the usual adult dose (see above).

Pharmacokinetics. References.

1. Hutchinson MR, *et al.* CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 2004; **57:** 287–97.

Preparations

USP 31: Hydrocodone Bitartrate and Acetaminophen Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets; Hydrocodone Bitartrate Tablets.

Proprietary Preparations (details are given in Part 3)

Belg.: Biocodone; ***Canad.:*** Hycodan; ***Ger.:*** Dicodid; ***Switz.:*** Dicodid†; Hydrocodeinon.

Multi-ingredient: ***Arg.:*** Hidronovag Complex; ***Canad.:*** Coristine-DH†; Dalmacol; Dimetane Expectorant DC; Hycomine; Novahistex DH; Novahistine DH; ratio-Calmydone; ratio-Coristex-DH; Tussionex; Vasofrinic DH; ***India:*** Cardiazol-Dicodid†; ***USA:*** Alor; Anaplex HD; Anexsia; Atuss EX†; Atuss G; Atuss HC; Atuss HD; Atuss HS; Atuss HX; Bancap HC; Ceta Plus; Co-Gesic; Co-Tuss V; Codal-DH; Codiclear DH; Codimal DH; Cophene XP; Cordron-HC; Cyndal HD†; Cytuss HC; Cytuss-HC NR; Damason-P; De-Chlor G; De-Chlor HC; De-Chlor HD†; De-Chlor MR; De-Chlor NX; Deconamine CX; Dolacet; Donatussin DC; Drocon-CS; Duocet; Duratuss HD; Dytan-HC; ED Tuss HC; ED-TLC; Endagen-HD; Endal-HD; Endal-HD Plus; Entex HC; Entuss Expectorant; Entuss-D; Entuss-D Jr; H-Tuss-D†; Histex HC; Histinex D; Histinex HC; Histinex PV; Histussin D†; Histussin HC; Hy-KXP; Hy-Phen; Hycet; HycoClear Tuss; Hycodan; Hycomine Compound; Hycotuss; Hydex PD; Hydro DP; Hydro PC†; Hydro-GP; Hydro-Tussin HD; Hydro-Tussin HG; Hydrocet; Hydrocodone CP; Hydrocodone GF; Hydrocodone HD; Hydrogesic; Hydromet; Hydron CP; Hydron EX; Hydron KGS; Hydron PSC; Hydropane; Hyphed; HyTan; Ibudone; Iodal; Iotussin HC; Kwelcof; Levall 5.0; Liquicet; Lorcet 10/650; Lorcet Plus; Lorcet-HD; Lortab; Lortab ASA; Lortuss HC; Marcof; Margesic H; Maxi-Tuss HCG; Maxi-Tuss HCX; Maxidone; Nalex DH; Nalex Expectorant; Narcof; Nariz HC; Neo HC; Norco; Notuss PD; Notuss-Forte; Oncet; P-V-Tussin; Pancof XP; Pancof-HC; Pancof-XL; Para-Hist HD; Pneumotussin; Poly-Tussin; Pro-Red; Protuss-D†; Protuss†; Relacon-HC; Relasin-HCX; Reprexain; S-T Forte 2; SRC Expectorant; Stagesic; Su-Tuss HD; T-Gesic; Tusana-D; Tusdec-HC; Tusnel-HC; Tussafed HC†; Tussafed-HCG; Tussafin Expectorant; Tussanil DH; Tussend; Tussigon; Tussionex Pennkinetic; Tusso-DF; Tusso-HC; Tussplex; Tyrodone; Unituss HC; Vanex Expectorant; Vanex-HD; Vazotuss HC; Vicodin; Vicodin Tuss; Vicoprofen; Vitussin; Xodol; Z-Cof HC; Zamicet; Zydone; Zymine HC.

Hydromorphone Hydrochloride

(BANM, rINNM) ⊗

Dihydromorphinone Hydrochloride; Hidrocloruro de dihidromorfinona; Hidrocloruro de hidromorfona; Hidromorfono hidrochloridas; Hydromorfon-hydrochlorid; Hydromorfonhydroklorid; Hydromorfonihydrokloridi; Hydromorphone, chlorhydrate d'; Hydromorphoni hydrochloridum. 6-Deoxy-7,8-dihydro-6-oxomorphine hydrochloride; (−)-(5*R*)-4,5-Epoxy-3-hydroxy-9a-methylmorphinan-6-one hydrochloride.

Гидроморфона Гидрохлорид

$C_{17}H_{19}NO_3,HCl$ = 321.8.

CAS — 466-99-9 (hydromorphone); 71-68-1 (hydromorphone hydrochloride).

ATC — N02AA03.

ATC Vet — QN02AA03.

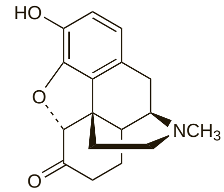

(hydromorphone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydromorphone:

Dillies; HillBilly Heroin; Hospital heroin.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Hydromorphone Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

USP 31 (Hydromorphone Hydrochloride). A fine white, or practically white, odourless, crystalline powder. Soluble 1 in 3 of water; sparingly soluble in alcohol; practically insoluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with hydromorphone hydrochloride in 5% glucose injection.[1] Mixtures of hydromorphone hydrochloride and dexamethasone sodium phosphate exhibited concentration-dependent incompatibility.[2] White cloudiness, haziness, or precipitation developed 4 hours after mixing thiopental sodium and hydromorphone hydrochloride.[3]

Stability of mixtures of fluorouracil and hydromorphone hydrochloride in 0.9% sodium chloride or 5% glucose depended on the concentration of fluorouracil present.[4] Hydromorphone hydrochloride 0.5 mg/mL with fluorouracil 1 mg/mL was stable for at least 7 days at 32° and for at least 35 days at 23°, 4°, or −20°. When the concentration of fluorouracil was increased to 16 mg/mL, hydromorphone was noted to decompose incurring unacceptable losses after 3 days at 32° or after 7 days at 23°, but was stable for at least 35 days at 4° or −20°.

1. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
2. Walker SE, *et al.* Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991; **48:** 2161–6.
3. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
4. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

UK licensed product information contra-indicates the use of hydromorphone hydrochloride in patients with hepatic impairment; however, product information in the USA permits its cautious use although doses may need to be reduced. It should also be used with caution and given in reduced doses to those with renal impairment.

Effects on the nervous system. Myoclonus has been reported[1] in a 55-year-old man given relatively low doses of intravenous hydromorphone with a total daily dose of 4 mg on day 1 and 6 mg on day 2; symptoms resolved when the drug was stopped on day 3. A chart review[2] for neuroexcitatory symptoms in 48 patients with terminal illnesses on hydromorphone found 13 cases of agitation, 9 of myoclonus, and 4 of seizures; maximal dose and treatment duration were noted to increase the risk of neurotoxicity.

1. Patel S, *et al.* A myoclonic reaction with low-dose hydromorphone. *Ann Pharmacother* 2006; **40:** 2068–70.
2. Thwaites D, *et al.* Hydromorphone neuroexcitation. *J Palliat Med* 2004; **7:** 545–50.

Interactions

For interactions associated with opioid analgesics, see p.103.

Alcohol. The FDA received data from pharmacokinetic studies in healthy subjects which showed that significantly higher peak plasma concentrations of hydromorphone were achieved, as a result of dose-dumping, when alcohol was ingested with once-daily hydromorphone modified-release capsules (*Palladone;*

Purdue Frederick, USA); these increases were considered potentially lethal, even in opioid-tolerant patients.[1] Subsequently, this formulation was voluntarily withdrawn by the US manufacturer in July 2005.

1. Food and Drug Administration. FDA alert for healthcare professionals: alcohol-Palladone interaction (issued 13th July, 2005). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/hydromorphoneHCP.pdf (accessed 26/06/08)

Pharmacokinetics

Hydromorphone hydrochloride is rapidly but incompletely absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations occur within 0.5 to 1 hour. Oral bioavailability is about 50% as it undergoes extensive first-pass metabolism. Hydromorphone is about 8 to 19% bound to plasma proteins. A plasma elimination half-life of about 2.5 hours has been reported after oral or intravenous doses. Hydromorphone appears to be widely distributed in the tissues; it crosses the placenta and is distributed into breast milk. It is extensively metabolised by glucuronidation in the liver and excreted in the urine mainly as conjugated hydromorphone, dihydroisomorphine, and dihydromorphine.

◊ References.

1. Vallner JJ, *et al.* Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *J Clin Pharmacol* 1981; **21:** 152–6.
2. Parab PV, *et al.* Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988; **9:** 187–99.
3. Vashi V, *et al.* Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol* 2005; **45:** 547–54.

Uses and Administration

Hydromorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.104). It is related to morphine (p.89) but with a greater analgesic potency. Hydromorphone hydrochloride is used for the relief of moderate to severe pain and for the relief of non-productive cough.

In the treatment of **pain**, hydromorphone hydrochloride is a useful alternative to morphine for subcutaneous use since its greater solubility in water allows a smaller dose volume. After injection onset of action usually occurs within 15 minutes and analgesia is reported to last for more than 5 hours; after oral doses onset of analgesia is usually within 30 minutes. It is given by subcutaneous or intramuscular injection in initial doses of 1 to 2 mg every 4 to 6 hours as necessary. It may also be given by slow intravenous injection or by intravenous or subcutaneous infusion, with doses adjusted according to individual requirements. Higher parenteral doses may be given to opioid-tolerant patients using a highly concentrated solution containing 10 mg/mL that allows smaller dose volumes. In the UK, the initial oral dose is 1.3 mg every 4 hours; thereafter the dose may be increased as necessary. In the USA, initial oral doses of 2 mg may be given every 4 to 6 hours; doses may be increased to 4 mg or more for severe pain. Modified-release preparations are available for less frequent administration, but see Alcohol, under Interactions, above. By rectum, the usual dose is 3 mg every 6 to 8 hours.

For the relief of non-productive **cough** hydromorphone hydrochloride is given, as a syrup, in doses of 1 mg repeated every 3 to 4 hours.

◊ References.

1. Bruera E, *et al.* A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. *J Clin Oncol* 1996; **14:** 1713–17.
2. Miller MG, *et al.* Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999; **18:** 9–16.
3. Quigley C. Hydromorphone for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 26/06/08).
4. Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage* 2005; **29** (suppl): S57–S66.
5. Grosset AB, *et al.* Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage* 2005; **29:** 584–94.
6. Du Pen S, *et al.* Intrathecal hydromorphone for intractable nonmalignant pain: a retrospective study. *Pain Med* 2006; **7:** 10–15.
7. Chang AK, *et al.* Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006; **48:** 164–72.

Preparations

USP 31: Hydromorphone Hydrochloride Injection; Hydromorphone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dolonovag; ***Austral.:*** Dilaudid; ***Austria:*** Dilaudid; Hydal; ***Belg.:*** Palladone; ***Canad.:*** Dilaudid; Hydromorph; ***Cz.:*** Jurnista; Palladone; ***Denm.:*** Opidol†; Palladon; ***Fin.:*** Palladon; ***Fr.:*** Sophidone; ***Ger.:*** Dilaudid; Palladon; ***Hung.:*** Palladone; ***Irl.:*** Palladone; ***Israel:*** Palladone; ***Mex.:*** Liberaxim; ***Neth.:*** Palladon; ***Norw.:*** Palladon; ***NZ:*** Dilaudid†; ***Port.:*** Jurnista; Palladone; ***Swed.:*** Opidol†; Palladon; ***Switz.:*** Palladon; ***UK:*** Palladone; ***USA:*** Dilaudid; Palladone†.

Multi-ingredient: ***Swed.:*** Dilaudid-Atropin; ***Switz.:*** Dilaudid-Atropin†; ***USA:*** Dilaudid Cough.

Ibuprofen *(BAN, USAN, rINN)*

Ibuprofeeni; Ibuprofén; Ibuprofenas; Ibuprofène; Ibuprofeno; Ibuprofenum; RD-13621; U-18573. 2-(4-Isobutylphenyl)propionic acid.

Ибупрофен

$C_{13}H_{18}O_2 = 206.3.$

CAS — 15687-27-1.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

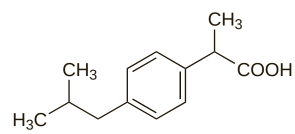

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Ibuprofen). A white or almost white, crystalline powder or colourless crystals. M.p. 75° to 78°. Practically insoluble in water; freely soluble in acetone, in dichloromethane, and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

USP 31 (Ibuprofen). A white to off-white crystalline powder having a slight characteristic odour. Practically insoluble in water; very soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate. Store in airtight containers.

Ibuprofen Lysine *(USAN)*

Ibuprofen Lysinate; Soluphene. Lysine 2-(4-isobutylphenyl)propionate.

Ибупрофен Лизин

$C_{19}H_{32}N_2O_4 = 352.5.$

CAS — 57469-77-9.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

Stability. Solutions of ibuprofen lysine in Water for Injections stored at room temperature were found to be most stable when protected from light.[1]

1. Volonté MG, *et al.* Stability of ibuprofen in injection solutions. *Am J Health-Syst Pharm* 2005; **62:** 630–3.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Ibuprofen may be better tolerated than other NSAIDs.

Adverse effects that may be associated with the use of ibuprofen injection in premature **neonates** include intraventricular haemorrhage, periventricular leucomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, necrotising enterocolitis, intestinal perforation, oliguria, fluid retention, and haematuria; hypoxaemia and gastrointestinal haemorrhage have also been reported. In addition ibuprofen injection should not be given to neonates with life-threatening infection, with significant renal impairment, or with known or suspected necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should also not be given parenteral ibuprofen, and those given it should be monitored during treatment for signs of bleeding. Renal function should be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

Symptoms of nausea, vomiting, and tinnitus have been reported after ibuprofen overdosage. More serious toxicity is uncommon, but gastric emptying followed by supportive measures is recommended if the quantity ingested within the previous hour exceeds 400 mg/kg.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ibuprofen, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount of ibuprofen distributed into breast milk to be too small to be harmful to a breast-fed infant. A study[2] estimated that a breast-fed infant would ingest about 0.0008% of the maternal dose. However, licensed product information for some preparations, including some topical preparations, recommends that breast feeding should be avoided during ibuprofen treatment.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)
2. Walter K, Dilger C. Ibuprofen in human milk. *Br J Clin Pharmacol* 1997; **44:** 211–12.

Children. An analysis[1] of the outcome of treatment of 83 915 children found that the risk of hospitalisation for gastrointestinal bleeding, renal failure, or anaphylaxis was no greater in children given ibuprofen than in those given paracetamol.

1. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995; **273:** 929–33.

Effects on the blood. Blood disorders including agranulocytosis, aplastic anaemia,[1] pure white-cell aplasia,[2] and thrombocytopenia[3] have been reported in patients taking ibuprofen. Fatal haemolytic anaemia occurred in a man taking ibuprofen and oxazepam.[4]

1. Gryfe CI, Rubenzahl S. Agranulocytosis and aplastic anemia possibly due to ibuprofen. *Can Med Assoc J* 1976; **114:** 877.
2. Mamus SW, *et al.* Ibuprofen-associated pure white-cell aplasia. *N Engl J Med* 1986; **314:** 624–5.
3. Jain S. Ibuprofen-induced thrombocytopenia. *Br J Clin Pract* 1994; **48:** 51.
4. Guidry JB, *et al.* Fatal autoimmune hemolytic anemia associated with ibuprofen. *JAMA* 1979; **242:** 68–9.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including ibuprofen, see p.96.

Effects on the CNS. Aseptic meningitis has occurred in patients taking NSAIDs. A review[1] of NSAID-related CNS adverse effects summarised 23 literature reports of NSAID-associated aseptic meningitis; 17 reports involved ibuprofen, 4 sulindac, 1 naproxen, and 1 tolmetin. Of the 23 reports, 11 were in patients with a diagnosis of SLE. Typically the reaction is seen in patients who have just restarted NSAID therapy after a gap in their treatment. Within a few hours of restarting the NSAID the patient experiences fever, headache, and a stiff neck; abdominal pain may be present. The patient may become lethargic and eventually comatose. Symptoms resolve if the NSAID is stopped. It is believed to be a hypersensitivity reaction but there does not appear to be cross-reactivity between NSAIDs.

Similar conclusions have also been reported more recently.[2] After experience of 2 cases, a review of the literature identified 71 episodes of ibuprofen-induced aseptic meningitis in 36 patients; 22 patients had recurrent episodes after repeated ibuprofen use. An underlying auto-immune connective tissue disorder was noted in 22 patients of whom 14 had SLE, 6 had an undifferentiated or mixed disorder, 1 had rheumatoid arthritis , and 1 had Sjögren's syndrome. In most cases, symptoms developed within 24 hours of starting ibuprofen although 1 patient had been taking ibuprofen for 2 years before the onset of symptoms. Cross-reactivity was reported in only 1 patient who had also developed aseptic meningitis with both naproxen and rofecoxib.

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Rodríguez SC, *et al.* Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine* 2006; **85:** 214–20.

Effects on electrolytes. Hyponatraemia has been described in patients receiving ibuprofen;[1-3] other risk factors such as pre-existing renal impairment or use with desmopressin were generally present.

1. Blum M, Aviram A. Ibuprofen induced hyponatraemia. *Rheumatol Rehabil* 1980; **19:** 258–9.
2. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; **305:** 318–20.
3. García EBG, *et al.* Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease. *Haemophilia* 2003; **9:** 232–4.

Effects on the eyes. Reversible amblyopia has been reported in patients receiving ibuprofen.[1,2] For reference to effects on the optic nerve associated with ibuprofen, see p.97.

1. Collum LMT, Bowen DI. Ocular side-effects of ibuprofen. *Br J Ophthalmol* 1971; **55:** 472–7.
2. Palmer CAL. Toxic amblyopia from ibuprofen. *BMJ* 1972; **3:** 765.

Effects on the gastrointestinal tract. Ibuprofen may be associated with a lower risk of upper gastrointestinal effects than some other NSAIDs, but nonetheless it can cause dyspepsia, nausea and vomiting, gastrointestinal bleeding, and peptic ulcers and perforation. Colitis and its exacerbation have occurred.[1,2]

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.
2. Clements D, *et al.* Colitis associated with ibuprofen. *BMJ* 1990; **301:** 987.

Effects on the kidneys. Reports of adverse renal effects with ibuprofen include an increase in serum creatinine concentration,[1] acute renal failure,[2-6] and nephrotic syndrome.[7] Cystitis, haematuria, and interstitial nephritis may occur. Acute flank pain and reversible renal dysfunction has been reported in some patients treated with ibuprofen.[8,9] See also Effects on Electrolytes, above.

1. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. *Ann Intern Med* 1990; **112:** 568–76.
2. Brandstetter RD, Mar DD. Reversible oliguric renal failure associated with ibuprofen treatment. *BMJ* 1978; **2:** 1194–5.
3. Kimberly RP, *et al.* Apparent acute renal failure associated with therapeutic aspirin and ibuprofen administration. *Arthritis Rheum* 1979; **22:** 281–5.
4. Spierto RJ, *et al.* Acute renal failure associated with the use of over-the-counter ibuprofen. *Ann Pharmacother* 1992; **26:** 714.
5. Fernando AHN, *et al.* Renal failure after topical use of NSAIDs. *BMJ* 1994; **308:** 533.
6. Moghal NE, *et al.* Ibuprofen and acute renal failure in a toddler. *Arch Dis Child* 2004; **89:** 276–7.
7. Justiniani FR. Over-the-counter ibuprofen and nephrotic syndrome. *Ann Intern Med* 1986; **105:** 303.
8. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; **92:** 459–60.
9. Wattad A, *et al.* A unique complication of nonsteroidal anti-inflammatory drug use. *Pediatrics* 1994; **93:** 693.

Effects on the liver. Raised liver transaminase values were noted in 3 patients with chronic hepatitis C infection after taking ibuprofen.[1] Values returned to normal on stopping the drug; the effect recurred in one patient who was re-exposed. Other hepatic adverse effects reported with ibuprofen include hepatitis[2] and liver failure.[3].

See also Effects on the Skin, below.

1. Riley TR, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series. *Am J Gastroenterol* 1998; **93:** 1563–5.
2. Borel I, *et al.* Hépatite aiguë sévère après prise d'ibuprofène. *Gastroenterol Clin Biol* 2001; **25:** 430–2.
3. Rodríguez-González FJ, *et al.* Orthotopic liver transplantation after subacute liver failure induced by therapeutic doses of ibuprofen. *Am J Gastroenterol* 2002; **97:** 2476–7.

Effects on the skin. Skin rashes may occur during hypersensitivity reactions although serious dermatological effects attributed to ibuprofen are rare. Reports of more serious effects have included Stevens-Johnson syndrome (often associated with hepatotoxicity),[1-4] photosensitivity,[5] and bullous leukocytoclastic vasculitis.[6]

1. Sternlieb P, Robinson RM. Stevens-Johnson syndrome plus toxic hepatitis due to ibuprofen. *N Y State J Med* 1978; **78:** 1239–43.
2. Srivastava M, *et al.* Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. *Gastroenterology* 1998; **115:** 743–6.
3. Health Canada. Ibuprofen: Stevens-Johnson syndrome. *Can Adverse React News* 2005; **15** (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3-eng.pdf (accessed 29/08/08)
4. Taghian M, *et al.* Acute vanishing bile duct syndrome after ibuprofen therapy in a child. *J Pediatr* 2004; **145:** 273–6.
5. Bergner T, Przybilla B. Photosensitization caused by ibuprofen. *J Am Acad Dermatol* 1992; **26:** 114–16.
6. Davidson KA, *et al.* Ibuprofen-induced bullous leukocytoclastic vasculitis. *Cutis* 2001; **67:** 303–7.

Hypersensitivity. A fatal asthma attack occurred in a 65-year-old woman, with adult-onset asthma, 30 minutes after ingestion of ibuprofen 800 mg.[1]

For other hypersensitivity reactions or possible reactions see also Effects on the CNS and Effects on the Skin, above.

1. Ayres JG, *et al.* Asthma death due to ibuprofen. *Lancet* 1987; **i:** 1082.

Meningitis. For reports of aseptic meningitis after use of ibuprofen, see Effects on the CNS, above.

Overdosage. There was a substantial increase in the number of cases of ibuprofen overdose reported to the National Poisons Information Service of the UK in the 2 years after its introduction as an 'over-the-counter' medication.[1] However, no concurrent increase in severity of poisoning was found and in only 1 of 203 cases was ibuprofen thought to have caused serious problems. It was concluded that ibuprofen appeared to be much less toxic in acute overdose than either aspirin or paracetamol. Current advice is that doses below 100 mg/kg are unlikely to cause toxicity in *children*, whereas clinical features will occur in children who have ingested more than 400 mg/kg. In *adults* the dose-response effect is less clear cut, but those who have ingested less than 100 mg/kg are unlikely to require treatment.

Nonetheless, reports illustrate the complexity of major overdosage with ibuprofen. A syndrome of coma, hyperkalaemia with cardiac arrhythmias, metabolic acidosis, pyrexia, and respiratory and renal failure was reported[2] in a 17-year-old man after major overdosage with ibuprofen and minor overdosage with doxepin. Hyperkalaemia was not evident until 14 hours after hospital admission and was thought to be due to a combination of potassium replacement for initial hypokalaemia, acidosis, muscle damage, and ibuprofen-induced renal failure. A 6-year-old child developed[3] shock, coma, and metabolic acidosis after ingestion of a dose of ibuprofen equivalent to 300 mg/kg. Treatment consisting of intubation, mechanical ventilation, fluid resuscitation, gastric lavage, and activated charcoal proved successful. In another report,[4] in which a 21-month-old child had ingested the equivalent of 500 mg/kg of ibuprofen, the presenting symptoms were acute renal failure with severe metabolic acidosis. The child developed tonic-clonic seizures 46 hours after ingestion, with significant hypocalcaemia and hypomagnesaemia, which may have been exacerbated by use of sodium polystyrene sulfonate and furosemide. The seizures, which could not be controlled with diazepam, phenytoin, and phenobarbital, ceased on correction of electrolyte balance.

1. Perry SJ, *et al.* Ibuprofen overdose: the first two years of over–the–counter sales. *Hum Toxicol* 1987; **6:** 173–8.
2. Menzies DG, *et al.* Fulminant hyperkalaemia and multiple complications following ibuprofen overdose. *Med Toxicol Adverse Drug Exp* 1989; **4:** 468–71.
3. Zuckerman GB, Uy CC. Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. *Ann Pharmacother* 1995; **29:** 869–71.
4. Al-Harbi NN, *et al.* Hypocalcemia and hypomagnesemia after ibuprofen overdose. *Ann Pharmacother* 1997; **31:** 432–4.

Interactions

For interactions associated with NSAIDs, see p.99.

Antineoplastics. For the effect of ibuprofen on the metabolism of *pemetrexed*, see p.762.

Aspirin. It has been suggested that ibuprofen may reduce the cardioprotective effect of aspirin but see NSAIDS under Interactions of Aspirin, p.23.

Lipid regulating drugs. For a report of rhabdomyolysis and renal failure attributed to an interaction between ibuprofen and *ciprofibrate*, see p.1233.

Muscle relaxants. *Baclofen* toxicity may develop after starting ibuprofen; for further details, see p.1888.

Pharmacokinetics

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is also absorbed on rectal use. It is partially absorbed after topical application to the skin; some licensed product information states that percutaneous absorption from topical gel is about 5% of that from an oral dose form. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little if any distribution into breast milk.

The above figures refer to racemic ibuprofen. However, ibuprofen's disposition is stereoselective and there is some metabolic conversion of the inactive *R*-(−)-enantiomer to the active *S*-(+)-enantiomer, dexibuprofen (p.39).

◊ References.

1. Davies NM. Clinical pharmacokinetics of ibuprofen: the first 30 years. *Clin Pharmacokinet* 1998; **34:** 101–54.
2. Sharma PK, *et al.* Pharmacokinetics of oral ibuprofen in premature infants. *J Clin Pharmacol* 2003; **43:** 968–73.
3. Gregoire N, *et al.* Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. *J Clin Pharmacol* 2004; **44:** 1114–24.
4. Han EE, *et al.* Pharmacokinetics of ibuprofen in children with cystic fibrosis. *Clin Pharmacokinet* 2004; **43:** 145–56.
5. Hao H, *et al.* Enantioselective pharmacokinetics of ibuprofen and involved mechanisms. *Drug Metab Rev* 2005; **37:** 215–-34.
6. Kyllonen M, *et al.* Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth* 2005; **15:** 566–73.

Uses and Administration

Ibuprofen, a propionic acid derivative, is an NSAID (p.99). Its anti-inflammatory properties may be weaker than those of some other NSAIDs.

Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen is also used as an alternative to indometacin in the treatment of patent ductus arteriosus.

The usual **oral** dose for painful conditions is 1.2 to 1.8 g daily in divided doses although maintenance doses of 600 mg to 1.2 g daily may be effective in some patients. If necessary the dose may be increased; in the UK the maximum recommended dose is 2.4 g daily whereas in the USA it is 3.2 g daily. Modified-release preparations of ibuprofen are available for once- or twice-daily dosing, although actual dosages vary with different preparations. Patients with rheumatoid arthritis generally require higher doses of ibuprofen than those with osteoarthritis. The recommended dose for fever reduction is 200 to 400 mg every 4 to 6 hours to a maximum of 1.2 g daily. For oral doses in children, see Administration in Children, below.

Ibuprofen may be given **parenterally** in the treatment of patent ductus arteriosus in preterm infants; for details of doses, see below.

Ibuprofen is applied **topically** as a 5% cream, foam, gel, or spray solution; a 10% gel is also available. It is also used topically as a dressing containing 500 micrograms/cm^2 of ibuprofen for the management of ulcers and superficial wounds.

Ibuprofen is usually given as the base but **derivatives**, including various salts, esters, and other complexes, have also been used. These include lysine (see Patent Ductus Arteriosus, below) and sodium salts, guaiacol and pyridoxine esters, and mabuprofen (ibuprofen aminoethanol), isobutanolammonium, and meglumine derivatives.

Ibuprofen is usually given as a racemic mixture but preparations containing only the *S*-(+)-isomer dexibuprofen (p.39) are available in some countries.

Administration in children. In the UK, the following oral doses of ibuprofen, given according to age, are recommended by the *BNFC* for the treatment of **pain**, **inflammation**, or **fever** in children:

- 1 to 3 months: 5 mg/kg 3 or 4 times daily
- 3 to 6 months: 50 mg 3 times daily
- 6 to 12 months: 50 mg 3 or 4 times daily
- 1 to 4 years: 100 mg 3 times daily
- 4 to 7 years: 150 mg 3 times daily
- 7 to 10 years: 200 mg 3 times daily
- 10 to 12 years: 300 mg 3 times daily
- 12 to 18 years: 200 to 400 mg 3 or 4 times daily increased, if necessary, to a maximum of 2.4 g daily
- in *severe* conditions in children aged between 3 months and 12 years, a dose of 30 mg/kg daily in 3 or 4 divided doses may be given

In the USA, suggested doses for children aged 6 months and over are: for fever, 5 to 10 mg/kg (depending on the severity of the fever) and for pain, 10 mg/kg; doses may be given every 6 to 8 hours up to a maximum daily dose of 40 mg/kg.

In the treatment of **rheumatic disease** including juvenile idiopathic arthritis, the *BNFC* recommends a dose of 10 mg/kg 3 or 4 times daily (maximum 2.4 g daily) in children aged 3 months and over; if necessary up to 60 mg/kg daily in 4 to 6 divided doses (maximum 2.4 g daily) may be given in systemic juvenile idiopathic arthritis.

Similar dosage regimens are also suggested by UK licensed product information; however, ibuprofen use is not generally recommended in children weighing less than 5 kg and some suggest a maximum daily dose of 500 mg in those weighing less than 30 kg. A usual daily dose in the USA for juvenile idiopathic arthritis is 30 to 40 mg/kg in divided doses.

For **post-immunisation pyrexia**, a dose of 50 mg has been recommended; a second dose may be given after 6 hours. If the pyrexia persists after the second dose, medical advice should be sought. Infants aged 2 to 3 months may also be given a 50-mg dose of ibuprofen for post-immunisation pyrexia on the advice of a doctor.

Ibuprofen or its lysine salt are also used in the treatment of **patent ductus arteriosus** in preterm infants; dosage details for this indication are given below.

Cachexia. For reference to the use of ibuprofen with megestrol to treat cancer cachexia, see p.2115.

Cystic fibrosis. In patients with cystic fibrosis (see p.166), the inflammatory response to chronic pulmonary infection with *Pseudomonas* organisms contributes to lung destruction. NSAIDs have been studied in patients with cystic fibrosis as an alternative to corticosteroids to reduce pulmonary inflammation. A systematic review[1] found evidence in support of using high-dose NSAIDs, most notably ibuprofen, to slow the progression of lung damage in patients with cystic fibrosis. However, there are limited data about the long-term safety of high doses[1] and some consider that this may have limited such use of NSAIDs;[2] others remain to be convinced that a benefit has been demonstrated.[3] The reviewers did consider that there were sufficient data to recommend that NSAIDs be temporarily stopped when intravenous aminoglycosides or other nephrotoxic drugs are used.[1]

1. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/11/07).
2. Fennel PB, *et al*. Use of high-dose ibuprofen in a pediatric cystic fibrosis center. *J Cyst Fibros* 2007; **6:** 153–8.
3. Bush A, Davies J. Non! to non-steroidal anti-inflammatory therapy for inflammatory lung disease in cystic fibrosis (at least at the moment). *J Pediatr* 2007; **151:** 228–30.

Pain. Findings from a long-term study[1] in 585 patients (mean age of 64 years) with knee pain suggested that oral and topical ibuprofen had an equivalent analgesic effect although the former was associated with more minor adverse effects; there was no difference in the rate of major adverse effects.

1. Underwood M, *et al*. Topical or oral ibuprofen for chronic knee pain in older people: the TOIB study. *Health Technol Assess* 2008; **12:** 1–176.

Patent ductus arteriosus. Ibuprofen or its lysine salt may be given **parenterally** for the treatment of patent ductus arteriosus (p.68) in preterm infants of less than 34 weeks' gestation; doses are expressed in terms of ibuprofen. Three intravenous doses (infused over 15 minutes) are given at 24-hour intervals; the initial dose is equivalent to 10 mg/kg of ibuprofen followed by two further doses of 5 mg/kg. If, 48 hours after this course of therapy the ductus remains open, a second course may be given, but if this produces no response surgery may be necessary. Ibuprofen injection, *when given as the base*, should be used undiluted, but if necessary it may be reconstituted with sodium chloride 0.9% or glucose 5% for injection. *When given as the lysine salt*, it should be diluted with sodium chloride 0.9% or glucose 5%.

For a suggestion that ibuprofen might be a better choice than indometacin for the treatment of patent ductus arteriosus, see p.68.

Preparations

BP 2008: Ibuprofen Cream; Ibuprofen Gel; Ibuprofen Oral Suspension; Ibuprofen Tablets;
USP 31: Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Ibuprofen Oral Suspension; Ibuprofen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Actron; Acuilfem; Afebril; Algioprofen†; Atomo Desinflamante Ibu; Bistryl†; Brunal†; Butidiona; Causalon Ibu; Copiron; Dolocox†; Dolorsyn; Druisel; Fabogesic; Febratic; Fontol; Ibu; Ibu Evanol; Ibu-Lady†; Ibu-Novalgina; Ibubenitol; Ibucalmin; Ibucler; Ibufabra; Ibufix; Ibulam; Ibumar; Ibumultin; Ibup; Ibupirac; Ibupiretas; Ibuprofenix; Ibuprofex; Ibusi; Ibusol; Ibusumal; Ibutenk; Ibuxim; Ibuzidine; Kesan†; Matrix; Motrax†; Novo Geniol; Oxibut; Pakurat; Paraflex Crema†; Ponstil Mujer; Ponstin; Ponstinetas; Salivia; Sindol; Teprix; Tonal; Vefren; ***Austral.:*** ACT-3; Actiprofen; Advil; Brufen; Bugesic†; Dimetapp Pain & Fever Relief; Hexal Compufen†; Nurofen; Proven; Rafen; Tri-Profen; ***Austria:*** Advil; Aktren; Avallone; Brufen; Dismenol Neu; Dolgit; Dolibu; Dolofort; Duafen; Ibu; Ibudol; Ibufem; Ibugel; Ibumetin; Ibupron; Iburem†; Ibutop; Imbun; Kratalgin; Momento; Nurofen; ratioDolor; Tabcin; Urem†; ***Belg.:*** Adulfen Lysine; Advil Mono; Brufen; Buprophar; Dolofin; Epsilon; Extrapan; Ibu-Slow†; Ibumed; Ibutop; Junifen; Malafene; Nurofebryl; Nurofen; Optalidon Nieuwe Formule; Perdofemina; Perdophen; Perviam; Provenol; Siprofen†; Spidifen; ***Braz.:*** Actiprofen; Advil; Algiflex; Algy-Flanderil†; Alivium; Artril; Dalsy; Doraplax†; Doretrim†; Dorigren; Frenador†; Ib-Profeno†; Ibufran; Ibupril; Ibuprofan; Lombalgina; Motrin; Parartrin; Spidufen; Uniprofen; ***Canad.:*** Advil; Motrin; Novo-Profen; ***Chile:*** Actron; Advil†; Bediatil; Bladex†; Deucodol; Dolorub; Fenpic†; Fortapal; Ibu; Ibu-4†; Ibu-6†; Ibupirac; Ipson; Kin; Motrin; Niofen; Pediaprofen; Pironal; Pyriped; Tifen†; ***Cz.:*** Advil; Baroc; Brufen; Dolgit; Ibalgin; Ibumax; Irfen†; Nurofen; Nurofen Advance; Nurofen Stopgrip; Pabiprofen; Panafen; Pedea; Solpaflex; Tomaflex; Urgo; ***Denm.:*** Apain; Brufen; Ibumetin; Ibureumin; Ibutop; Ipren; Pedea; Solpaflex†; ***Fin.:*** Brufen; Burana; Ibumax; Ibumetin; Ibusal; Ibuxin; ***Fr.:*** Advil; Anadvil; Antarene; Brufen; Dolgit; Doltaque; Ergix; Expanfen; Gelufene; Hemagene Tailleur; Ibualgic†; Ibutop; Intralgis; Nureflex; Nurofen; Nurofentabs; Nuroflash; Pedea; Solufen; Spedifen; Spifen; Upfen; ***Ger.:*** Advel; Aktren; Contraneural; Dismenol N; Dolgit; Dolo Sanol; Dolo-Puren; Dolodoc; Dolormin; Esprenit; Eudorlin Extra; Eudorlin Migrane; Gyno-Neuralgin; Gynofug†; Ibu; Ibu Benuron; ibu-Attritin; Ibu-ratiopharm; Ibubeta; Ibudolor; Ibuflam; Ibuhexal; Ibumerck; Ibuphlogont†; Ibuprof†; Ibutad; Ibutop; Ilvico grippal†; Imbun; Jenaprofen; Kontagripp; Mensoton; Migranin Ibuprofen; Novogent†; Nurofen; Optalidon; Opturem; Parsal; Pedea; Pfeil†; Phamoprofen†; ratioDolor†; Schmerz-Dolgit; Spalt; Tabalon; Tempil†; Tispol Ibu-DD; Togal Akut Ibuprofen; Trauma-Dolgit; Urem; ***Gr.:*** Advil; Algofren; Brufen; Buscofem; Nurofen; Rozovin†; ***Hong Kong:*** Advil; Bifen; Brufen†; Bupogesic; Dolo-Spedifen†; Ibufac; Ibupen; Neutropain; Nurofen; Perofen; Profen; Rupan†; Schufen; Spedifen; ***Hung.:*** Advil; Algoflex; Dolgit; Huma-Profen; Ibulos†; Ibumax; Ibutop; Melfen; Nurofen; Solpaflex; Spedifen; ***India:*** Brufen; Butafen†; Cipgesic; Emflam; Ibugesic; Ibupal; ***Indon.:*** Anafen; Arthrifen; Bufect; Dofen; Dolofen-F; Febryn; Fenris; Iprox; Lexaprofen; Nofena; Ostarin; Prifen; Profen; Proris; Rhelafen; Ribunal; Shelrofen; Spedifen; Yariven; ***Irl.:*** Advil; Brufen; Bufigen; Fenopine; Ibugel; Melfen; Nurofen; Phorpain; Proflex; Solfen†; ***Israel:*** Adex; Advil; Artofen; Ibufen; Ibuleve; Nurofen; ***Ital.:*** Algofen; Antalfebal; Antalfort; Antalgil; Antalisin; Arfen; Benflogin; Brufen; Buscofen; Calmine; Cibalgina Due Fast; Dolocyl; Dolofast; Edenil; Faspic; Ganaprofene†; Gineflor; Ginenorm; Moment; Nureflex; Nurofast; Nurofen; Nurosolv; Pedea; Subitene; Zafen†; ***Malaysia:*** Bifen; Brugesic†; Ibufac; Ibufen†; Nurofen; Perofen; Rupan†; Spedifen; ***Mex.:*** ABKI; Actron; Adivon; Advil; Aflusil; Ainex; Aldofen; Algidol; Bestafen; Carone; Citalgan; Dadicil; Days; Dibufen; Dipofen; Diprodol; Dolprin; Dolprofen; Dolval; Dolver; Eufenil; Febratic; Fidoin-Q; Flexafen; Gelidol; Gobrosan; Ibuflam; Ibuflex; Ifentil; Inpained; Maxifen; Medifen; Mejorultra†; Motrin; Natiken†; Novartril†; Offeno†; Pro-XB; Proartinal; Probuxil; Quadrax; Realdrax; Ribufen; Tabalon; ***Neth.:*** Advil; Brufen; Femapirin; Ibosure; Ibulgan†; Nurofen; Pedea; Roco; Sarixell; Spidifen; Zafen; ***Norw.:*** Brufen; Ibumetin; Ibuprox; Ibux; ***NZ:*** ACT-3; Brufen; Fenapaed; Ibucare; Nurofen; Panafen; ***Philipp.:*** Advil; Brufen; Dolan; Idyl; Medicol; Midol; Skelan; ***Pol.:*** Bolinet; Deep Relief†; Dolgit; Ibufen; Ibum; Ibupar; Ibuprom; Nurofen; Pedea; ***Port.:*** Anadvil; Arfen; Baroc; Brufen; Calbrun; Dolocyl; Dolomate; Dolormin; Faspic; Frenidor; Ibupax†; Junifen; Moment; Motrin†; Norvectan; Nuprilan†; Nurofen; Ozonol; Pedea; Plusofen; Seclodin; Solufen; Solvium; Spidifen; Sporfen; Trifene; Zafen; Zip-A-Dol; ***Rus.:*** Aldospray (Альдоспрей); Burana (Бурана); Dolgit (Долгит); Ibufen (Ибуфен); Nurofen (Нурофен); Solpaflex (Солпафлекс); ***S.Afr.:*** Advil; Antiflam†; Betagesic; Betaprofen; Brufen; Brugesic†; Iboflam; Ibugesic; Ibuleve; Ibumax; Ibumed; Inza; Lenafen†; Norflam T; Nurofen; Painil†; Ranfen; ***Singapore:*** Ampifen†; Bifen; Ibufen; Ibuloid†; Nurofen; ***Spain:*** Advil; Aldospray Analgesico; Algiasdin; Algidrin; Alogesia; Altior; Babypiril; Bexistar; Calmafher†; Dadosel; Dalsy; Diltix; Doctril; Dolbufen; Dolorac; Dorival; Espidifen; Factopan; Feminalin; Fiedosin; Frenatermin; Gelofeno; Ibubex; Ibufen; Ibumac; Ibuprox; Inadol†; Isdibudol†; Isdol†; Junifen; Narfen; Neobrufen; Nodolfen; Norvectan; Nurofen; Oberdol; Oltyl†; Optajun; Paidofebril; Pedea; Pirexin; Pocyl†; Ratiodol; Remidol†; Saetil; Solvium; Takigrip†; Tedifebrin; ***Swed.:*** Alindrin; Brufen; Ibumetin; Ipren; ***Switz.:*** Algifor; Artofen; Brufen; Dismenol; Dolo-Dismenol; Dolo-Spedifen; Dolocyl; Ecoprofen; Grefen; Ibufen-L; Ibusifar; Iproben; Iprogel†; Irfen; Melabon; Nurofen; Optifen; Perskindol Ibuprofen acute; Saridon N; Sinedol Ibuprofen; Spedifen; Treupel Dolo Ibuprofen; ***Thai.:*** Ambufen; Anbifen; Aprofen; Babefen Sus†; Borafen; Borakid; Brufen; Brumed†; Bruprin; Brusil; Bumed; Cefen; Cenbufen; Duran†; Faspic; G-Fen; Gesica; Greatofen; Heidi; Ibrofen; Ibu; Ibufac; Ibugan; Ibulan; Iburen†; Junifen†; Mano-Bruzone; Nurofen; Ostofen†; P-Fen; Perofen†; Pippen; Probue; Probufen; Profena†; Profeno; Rheumanox; Rumasian; Rumatifen; Rupan†; Schufen; Skelan IB; Tofen; Trofen; Umafen; ***Turk.:*** Advil; Artril; Bebol; Biophen; Brufen; Dolgit; Dolven; Gerofen; Ibu-600; Ibufen; Nurofen; Pedifen; Profen; Repozal; Rofen; Siyafen; Suprafen; Temsofen; Ultrafen; Upren; ***UAE:*** Profinal; ***UK:*** Advil; Anadin Ibuprofen; Anadin Joint Pain; Anadin Ultra; Arthrofen; Biatain-Ibu; Brufen; Calprofen; Cuprofen; Ebufac; Fenbid; Fenpaed; Feverfen; Galprofen; Hedex Ibuprofen; Ibrufhalal; Ibufem; Ibugel; Ibuleve; Ibumousse; Ibuspray; Ibutop Cuprofen; Ibutop Ralgex; Librofem; Mandafen; Manorfen; Mentholatum Ibuprofen; Migrafen; Motrin†; Novaprin; Nurofen; Nurofen Migraine; Obifen; Orbifen; Pacifene; Pedea; Phor Pain; Proflex; Radian-B Ibuprofen; Relcofen; Rimafen; ***USA:*** Advil; Anadar; Genpril†; Haltran†; Ibu; Ibu-Tab; Ibu-4, -6, -8; Ibutab; Menadol; Midol Cramp & Body Aches; Motrin; NeoProfen; Nuprin†; Saleto-200; ***Venez.:*** Advil; Brugesic; Buprifen†; Buprodol; Butilene†; Dologesic; Femicaps; Femmex Plus; Ibucaps; Ibufen; Ibufenac†; Ibuprin; Ibuprox†; Ibutan; Lumbax; Max; Maydol; Mestral; Motrin; Pedibu.

Multi-ingredient: ***Arg.:*** Aliviagrip; Bioneural B12†; Buscapina Fem; Butidiona†; Causalon Gesic†; Deep Relief†; Dexprofeno; Espasmo Ibupirac†; Espasmo Motrax†; Espasmofin; Ibu Evanol Plus; Ibu-Buscapina†; Ibu-Tetralgin; Ibudolofrix; Ibudristan; Ibumar Migra†; Ibunastizol; Ibupirac Fem; Ibupirac Flex; Ibupirac Migra; Mensalgin; Migral II; Novo Wilpan†; Roveril; Supragesic; ***Austral.:*** Dimetapp Headcold & Flu; Nurofen Cold & Flu; Nurofen Plus; Panafen Plus; Sudafed Sinus & Anti-inflammatory Pain Relief; Tri-Profen Cold & Flu†; ***Austria:*** Advil Cold; Ardinex; ***Belg.:*** Adulfen Codeine; ***Braz.:*** Algi-Itamanil†; Algi-Reumatril; Algifen†; Fymnal†; Reuplex; ***Canad.:*** Advil Cold & Sinus; Advil Cold & Sinus Plus; Childrens Advil Cold; Dristan Sinus†; Robax Platinum; Sudafed Sinus Advance; Vicks DayQuil Sinus & Pain Relief; ***Chile:*** Adona; Artritapsin; Butartrol; Deucodol Plus; Dioran†; Dolnix; Dolo Winasorb; Dolo-Niofen; Dolo-Octirona; Dolonase; Gedol†; Ibupirac Compuesto; Ibupirac Flu; Ipson-D; Midol†; Neo Butartrol; Niofen Flu; Predual DI†; Silartrin†; Termo-Niofen; ***Cz.:*** Advil Cold; Ardinex†; Ibu-Hepa; Ibufein†; Modafen; ***Fin.:*** Ardinex; Burana-C; ***Fr.:*** Anadvil Rhume; Cliptol; Nurofen Rhume; Rhinadvil; Rhinathiol Rhume†; Rhinureflex; Vicks Rhume†; ***Gr.:*** Nurofen CF; Vicks; ***Hung.:*** Advil Cold; Algoflex-M; Deep Relief; Nurofen Cold & Flu; Rhinathiol Cold; ***India:*** Acks; Anaflam; Answell; Bruace; Cipgesic Plus; Combiflam; Duoflam; Duoflam Plus; Emflam Plus; Flexon; Flexon-MR; Ibu-Proxyvon; Ibuflamar-P; Ibugesic Plus; Ibugesic-M; Reactine Forte; Reducin-A†; Robiflam; Somaflam; ***Indon.:*** Aknil; Axalan; Iremax; Limasip; Neo Rheumacyl; Neuralgin; Shelrod-Plus; ***Irl.:*** Advil Cold & Flu; Codafen Continus†; Nurofen Cold & Flu; Nurofen Plus; ***Israel:*** Nurofen Cold & Flu; ***Ital.:*** Solvifiu; Vicks Flu-Action; ***Jpn:*** Colgen Kowa IB Toumei; ***Mex.:*** Algitrin; Bipasmin Compuesto NF†; Carbager-Plus; Dualgos; Sinutab Advance; ***NZ:*** Nurofen Cold & Flu; Nurofen Plus; ***Philipp.:*** Alaxan; Anoflam; Brustan; Flexigesic; Muskelax; Restolax; Selxan; ***Pol.:*** Ardinex; Dip Rilif; Ibalgin Sport; Ibuprom Zatoki; Metafen; Modafen; Nurofen Antigrip; Nurofen Plus; ***Rus.:*** Brustan (Брустан); Ibuclin (Ибуклин); Novigan (Новиган); Nurofen Plus (Нурофен Плюс); ***S.Afr.:*** Advil CS; Dentopain; Gen-Payne; Ibucod; Ibumol; Ibupain; Ibupain Forte; Lotem; Mybucod; Mybulen; Mypaid; Myprodol; Nurofen Cold & Flu; Sinumax IB; ***Spain:*** Nurofen Complex; Salvarina; ***Swed.:*** Ardinex; ***Switz.:*** Ibufen-L; ***Thai.:*** Alaxan Pl; Brustan; Cetan; Dologen; Kintal†; Rumatifen-Plus; Skelan; ***Turk.:*** Nurofen Cold & Flu; ***UAE:*** Profinal Cold & Sinus; Profinal FM; Profinal XP; ***UK:*** Codafen Continus†; Cuprofen Plus; Deep Relief; Lemsip Flu 12Hr; Lemsip Pharmacy Powercaps; Non-Drowsy Sudafed Dual Relief Max; Nurofen Cold & Flu; Nurofen Plus; Nurofen Sinus; Orbifen Cold & Flu; Solpadeine Migraine; Solpaflex; ***USA:*** Advil Allergy Sinus; Advil Cold & Sinus; Advil PM; Anadar Cold & Flu; Childrens Advil Cold; Childrens Ibuprofen Cold; Childrens Motrin Cold; Combunox; Dimetapp Childrens Cold & Fever; Dimetapp Sinus; Dristan Sinus; Ibudone; Motrin IB Sinus; Reprexain; Sine-Aid IB; Vicoprofen; ***Venez.:*** Brudol; Brugesina; Colfene; Femmexultra; Ibucoden.

Ibuproxam *(rINN)*

Ibuproxamum. 4-Isobutylhydratropohydroxamic acid.

Ибупроксам

$C_{13}H_{19}NO_2$ = 221.3.
CAS — 53648-05-8.
ATC — M01AE13.
ATC Vet — QM01AE13.

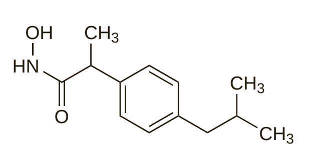

Profile

Ibuproxam is an NSAID (p.96) that has been used topically as a 5% ointment in musculoskeletal, joint, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Ibudros†; ***Spain:*** Nialen.

Imidazole Salicylate *(rINN)*

Imidazole, Salicylate d'; Imidazoli Salicylas; Salicilato de imidazol. Imidazole compounded with salicylic acid.

Имидазола Салицилат

$C_{10}H_{10}N_2O_3$ = 206.2.
CAS — 36364-49-5.
ATC — N02BA16.
ATC Vet — QN02BA16.

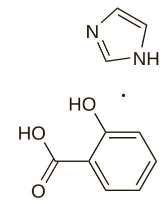

Profile

Imidazole salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used in the treatment of fever and inflammatory respiratory-tract and otorhinolaryngeal disorders. Imidazole salicylate has been given in oral doses of up to 2.25 g daily in divided doses. It has also been given as a rectal suppository and has been applied topically as a 5% gel for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Selezen.

Indometacin *(BAN, rINN)*

Indometacina; Indometacinas; Indométacine; Indometacinum; Indometacyna; Indometasiini; Indometasin; Indomethacin *(USAN)*. [1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

Индометацин

$C_{19}H_{16}ClNO_4$ = 357.8.
CAS — 53-86-1.
ATC — C01EB03; M01AB01; M02AA23; S01BC01.
ATC Vet — QC01EB03; QM01AB01; QM02AA23; QS01BC01.

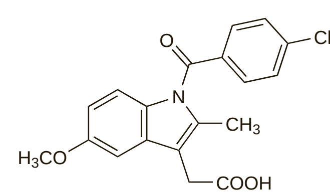

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Indometacin). A white or yellow, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Indomethacin). A pale yellow to yellow-tan, crystalline powder having not more than a slight odour. It exhibits polymorphism. Practically insoluble in water; soluble 1 in 50 of alcohol, 1 in 30 of chloroform, and 1 in 40 of ether. Protect from light.

Stability. Indometacin is unstable in alkaline solution.

Indometacin Sodium *(BANM, rINNM)*

Indometacina sódica; Indométacine Sodique; Indomethacin Sodium *(USAN)*; Indomethacin Sodium Trihydrate; Natrii Indometacinum. Sodium 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate, trihydrate.

Натрий Индометацин

$C_{19}H_{15}ClNNaO_4,3H_2O$ = 433.8.
CAS — 74252-25-8.

Pharmacopoeias. In *US.*

USP 31 (Indomethacin Sodium). Protect from light.

Incompatibility. Indometacin sodium injection is reconstituted with preservative-free sodium chloride for injection 0.9% or preservative-free water for injection. Preparations containing glucose should not be used; reconstitution at a pH below 6 may cause precipitation of indometacin. Visual incompatibility has been reported between indometacin sodium injection and tolazoline hydrochloride,[1] 7.5 and 10% glucose injection, calcium gluconate, dobutamine, dopamine, cimetidine,[2] gentamicin sulfate, levofloxacin,[3] and tobramycin sulfate.[4] A pH below 6 may account for the visual incompatibility of indometacin sodium and several of these drugs.

1. Marquardt ED. Visual compatibility of tolazoline hydrochloride with various medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 1802–3.
2. Ishisaka DY, *et al.* Visual compatibility of indomethacin sodium trihydrate with drugs given to neonates by continuous infusion. *Am J Hosp Pharm* 1991; **48:** 2442–3.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–90.
4. Thompson DF, Heflin NR. Incompatibility of injectable indomethacin with gentamicin sulfate or tobramycin sulfate. *Am J Hosp Pharm* 1992; **49:** 836–8.

Stability. A reconstituted solution of indometacin sodium 500 micrograms/mL was stable for 14 days when stored at 2° to 6° in either the manufacturer's original glass vial or in a polypropylene syringe.[1]

1. Walker SE, *et al.* Stability of reconstituted indomethacin sodium trihydrate in original vials and polypropylene syringes. *Am J Health-Syst Pharm* 1998; **55:** 154–8.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Adverse effects are more frequent with indometacin than with many other NSAIDs, the most common being gastrointestinal disturbances, headache, vertigo, dizziness, and lightheadedness. Gastrointestinal perforation, ulceration, and bleeding may also occur; rarely, intestinal strictures have been reported. Other adverse effects include depression, drowsiness, tinnitus, confusion, insomnia, psychiatric disturbances, syncope, convulsions, coma, peripheral neuropathy, blurred vision, corneal deposits and other ocular effects, oedema and weight gain, hypertension, haematuria, skin rashes, pruritus, urticaria, stomatitis, alopecia, and hypersensitivity reactions. Leucopenia, purpura, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, epistaxis, hyperglycaemia, hypoaldosteronism and hyperkalaemia, and vaginal bleeding have been reported. There have also been reports of hepatitis, jaundice, and renal failure. Hypersensitivity reactions may also occur in aspirin-sensitive patients. Rectal irritation and bleeding has been reported occasionally in patients who have received indometacin suppositories.

Adverse effects associated with the use of indometacin injection in premature **neonates** may also include haemorrhagic, renal, gastrointestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection may also occur.

Effects on the blood. There were 1261 reports of adverse reactions to indometacin reported to the UK CSM between June 1964 and January 1973. These included 157 reports of blood disorders (25 fatal) including thrombocytopenia (35; 5 fatal), aplastic anaemia (17; no fatalities), and agranulocytosis or leucopenia (21; 3 fatal).[1] Subsequently, the First Report from the International Agranulocytosis and Aplastic Anemia Study confirmed a significant relationship between the use of indometacin and agranulocytosis and aplastic anaemia.[2] Neutropenia has also been noted in a premature infant with patent ductus arteriosus after use of indometacin.[3]

Although use of indometacin in 20 women being treated for premature labour did not affect maternal prothrombin or activated partial thromboplastin time, maternal bleeding time during therapy was increased.[4] However, no cases of neonatal intraventricular haemorrhage or maternal postpartum haemorrhage were seen.

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–10.
2. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
3. Bengtsson B-OS, *et al.* Indomethacin-associated neutropenia with subsequent Gram-negative sepsis in a preterm infant: cause or coincidence? *J Perinatol* 2006; **26:** 381–3.
4. Lunt CC, *et al.* The effect of indomethacin tocolysis on maternal coagulation status. *Obstet Gynecol* 1994; **84:** 820–2.

Effects on cerebral blood flow. See Patent Ductus Arteriosus under Uses and Administration, below.

Effects on the eyes. Severe and irreversible retinopathy, presumably due to long-term ingestion of high doses of indometacin occurred in a 33-year-old man.[1] A summary of previous literature reports of indometacin-induced ocular effects indicated that indometacin was retinotoxic, although to what degree was uncertain. For reference to effects on the optic nerve associated with indometacin, see p.97.

1. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. *Br J Ophthalmol* 1988; **72:** 434–8.

Effects on the gastrointestinal tract. Nausea, vomiting, dyspepsia, gastrointestinal lesions, and serious reactions including gastrointestinal bleeding, ulceration, and perforation have occurred in patients receiving indometacin. Although it is well established that NSAIDs can produce adverse effects on the upper gastrointestinal tract, indometacin and other NSAIDs can also affect the large intestines.[1] Giving indometacin to preterm neonates increases the risk of small bowel perforation and necrotising enterocolitis.[2-4] Risk seems to be increased in very-low-birth-weight or extremely premature infants.

1. Oren R, Ligumsky M. Indomethacin-induced colonic ulceration and bleeding. *Ann Pharmacother* 1994; **28:** 883–5.
2. Grosfeld JL, *et al.* Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. *Ann Surg* 1996; **224:** 350–7.
3. Shorter NA, *et al.* Indomethacin-associated bowel perforations: a study of possible risk factors. *J Pediatr Surg* 1999; **34:** 442–4.
4. Fujii AM. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. *J Perinatol* 2002; **22:** 535–40.

Effects on the joints. For references to concern that NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis, see Effects on Bone, under NSAIDs, p.96.

Effects on the kidneys. Acute renal failure,[1] nephrotic syndrome,[2] and renal papillary necrosis[3] have been reported in patients given indometacin. There have been suggestions that misoprostol might reduce the risk of indometacin-induced renal toxicity.[4,5]

Renal impairment has also occurred in **neonates** given indometacin intravenously for patent ductus arteriosus. Although rare, and usually reversible, the effect may be serious in neonates with pre-existing renal disorders.[6] Serious or fatal renal toxicity has been reported in neonates exposed to indometacin due to maternal ingestion.[7] The renal effects of prenatal indometacin may be prolonged.[8]

1. Chan X. Fatal renal failure due to indomethacin. *Lancet* 1987; **ii:** 340.
2. Boiskin I, *et al.* Indomethacin and the nephrotic syndrome. *Ann Intern Med* 1987; **106:** 776–7.
3. Mitchell H, *et al.* Indomethacin-induced renal papillary necrosis in juvenile chronic arthritis. *Lancet* 1982; **ii:** 558–9.
4. Weir MR, *et al.* Minimization of indomethacin-induced reduction in renal function by misoprostol. *J Clin Pharmacol* 1991; **31:** 729–35.
5. Wong F, *et al.* The effect of misoprostol on indomethacin-induced renal dysfunction in well-compensated cirrhosis. *J Hepatol* 1995; **23:** 1–7.
6. Cuzzolin L, *et al.* NSAID-induced nephrotoxicity from the fetus to the child. *Drug Safety* 2001; **24:** 9–18.
7. van der Heijden BJ, *et al.* Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. *Am J Obstet Gynecol* 1994; **171:** 617–23.
8. Butler-O'Hara M, D'Angio CT. Risk of persistent renal insufficiency in premature infants following the prenatal use of indomethacin for suppression of preterm labor. *J Perinatol* 2002; **22:** 541–6.

Effects on the liver. Cholestasis occurred in a 52-year-old woman several days after starting indometacin;[1] liver function values returned to normal once indometacin was stopped.

1. Cappell MS, *et al.* Indomethacin-associated cholestasis. *J Clin Gastroenterol* 1988; **10:** 445–7.

Hypersensitivity. Hypersensitivity reactions including acute asthma have been reported after use of indometacin suppositories,[1] eye drops,[2] or capsules[3] by patients who were aspirin-sensitive or had a history of asthma.

1. Timperman J. A fatal asthmatic attack following administration of an indomethacin suppository. *J Forensic Med* 1971; **18:** 30–2.
2. Sheehan GJ, *et al.* Acute asthma attack due to ophthalmic indomethacin. *Ann Intern Med* 1989; **111:** 337–8.
3. Johnson NM, *et al.* Indomethacin-induced asthma in aspirin-sensitive patients. *BMJ* 1977; **2:** 1291.

Precautions

As for NSAIDs in general, p.98.

Indometacin should be used with caution in patients with epilepsy, parkinsonism, or psychiatric disorders. Dizziness may affect the performance of skilled tasks such as driving. Patients on long-term indometacin therapy should be examined regularly for adverse effects, and the *BNF* particularly recommends periodic blood and ophthalmic examinations. Rectal use should be avoided in patients with proctitis and haemorrhoids.

In addition indometacin should not be given to **neonates** with untreated infection, with significant renal impairment, or with necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should not be given indometacin and those receiving indometacin should be monitored during treatment for signs of bleeding. Electrolytes and renal function should also be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

False-negative results in the dexamethasone suppression test have been reported in patients taking indometacin.

Breast feeding. Convulsions in a one-week old breast-fed infant appeared to be associated with maternal ingestion of indometacin;[1] the child had normal motor and mental development at the age of 1 year and seizures had not recurred.

Indometacin has been detected in breast milk, but some workers[2,3] and the *BNF* consider that the amount is so small that it should not constitute a contra-indication to breast feeding. The American Academy of Pediatrics[4] also states that indometacin is usually compatible with breast feeding despite acknowledging the above case report of convulsions. However, licensed product information recommends that indometacin should not be used in nursing mothers.

1. Eeg-Olofsson O, *et al.* Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* 1978; **ii:** 215.
2. Beaulac-Baillargeon L, Allard G. Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. *Br J Clin Pharmacol* 1993; **36:** 413–16.
3. Lebedevs TH, *et al.* Excretion of indomethacin in breast milk. *Br J Clin Pharmacol* 1991; **32:** 751–4.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

The elderly. After a study[1] of the pharmacokinetics of indometacin in the elderly it was suggested that the maintenance dose of indometacin in elderly patients should be reduced by 25%. The total clearance of indometacin in elderly subjects had been reduced when compared with that in young subjects; this was thought to be due to reduced hepatic metabolism in the elderly.

1. Oberbauer R, *et al.* Pharmacokinetics of indomethacin in the elderly. *Clin Pharmacokinet* 1993; **24:** 428–34.

Pregnancy. See Premature Labour under Uses and Administration, below.

Interactions

For interactions associated with NSAIDs, see p.99.

Anti-inflammatory doses of aspirin decrease indometacin blood concentrations by about 20%. Diflunisal decreases the renal clearance and increases plasma concentrations of indometacin. Use of diflunisal with indometacin has also resulted in fatal gastrointestinal haemorrhage, and the two should not be used together. Plasma concentrations of indometacin are likely to be increased in patients receiving probenecid.

Antibacterials. Indometacin has been reported to increase plasma concentrations of *aminoglycosides*.

Antipsychotics. Severe drowsiness and confusion have been reported in patients given *haloperidol* with indometacin.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Bone modulating drugs. Indometacin has been reported to increase the bioavailability of *tiludronate*, see p.1106.

Desmopressin. The effect of desmopressin may be enhanced by indometacin.

Digoxin. In addition to increasing digoxin serum concentrations (see p.1263), combination of digoxin with indometacin has been reported to reduce the half-life of the latter in premature neonates (see Half-life under Pharmacokinetics, below).

Parasympathomimetics. The manufacturer of acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Indometacin is readily absorbed from the gastrointestinal tract in adults; peak plasma concentrations are reached about 2 hours after a dose. Absorption may be slowed by food or by aluminium- or magnesium-containing antacids. In premature neonates, absorption of oral indometacin is poor and incomplete. The bioavailability of rectal suppositories in adults has been reported to be comparable with or slightly less than the bioavailability with oral dosage forms.

Indometacin is about 99% bound to plasma proteins. It is distributed into synovial fluid, the CNS, and placenta. Low concentrations have been distributed into breast milk. The terminal plasma half-life has been reported to range from 2.6 to 11.2 hours in adults. The terminal half-life in neonates has been reported to be between 12 and 28 hours (see also below). Indometacin is metabolised in the liver to its glucuronide conjugate and to desmethylindomethacin, desbenzoylindomethacin, desmethyl-desbenzoylindomethacin, and to their glucuronides. Some indometacin undergoes N-deacylation. Indometacin and its conjugates undergo enterohepatic circulation. Excretion of indometacin and its metabolites is mainly in the urine with lesser amounts appearing in the faeces.

◊ References.

1. Moise KJ, *et al.* Placental transfer of indomethacin in the human pregnancy. *Am J Obstet Gynecol* 1990; **162:** 549–54.
2. Mannila A, *et al.* Plasma and cerebrospinal fluid concentrations of indomethacin in children after intravenous administration. *J Clin Pharmacol* 2007; **47:** 94–100.

Half-life. The plasma half-life of indometacin in premature infants can be variable but appears to be inversely proportional to post-natal age and weight.[1,2] One population model suggests that for an infant of 1.17 kg, half-life would be 22.3 hours at a post-natal age of 8 days, but 16.1 hours at 25 days (and only 11.2 hours if also receiving digoxin).[2]

1. Wiest DB, *et al.* Population pharmacokinetics of intravenous indomethacin in neonates with symptomatic patent ductus arteriosus. *Clin Pharmacol Ther* 1991; **49:** 550–7.
2. Smyth JM, *et al.* Intravenous indometacin in preterm infants with symptomatic patent ductus arteriosus: a population pharmacokinetic study. *Br J Clin Pharmacol* 2004; **58:** 249–58.

Uses and Administration

Indometacin, an indole acetic acid derivative, is an NSAID (p.99). It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gout, and in periarticular disorders such as bursitis and tendinitis. It may also be used in inflammation, pain, and oedema following orthopaedic procedures, in mild to moderate pain in conditions such as dysmenorrhoea, and it has been used in the management of postoperative pain as an adjunct to opioids, and in the treatment of fever. Indometacin is also used as the sodium salt to close patent ductus arteriosus in premature infants (see below).

The usual initial oral dose in **chronic musculoskeletal and joint disorders** is 25 mg two or three times daily increased, if required, by 25 to 50 mg at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffness, up to 100 mg of the total daily dose may be given orally, or rectally as a suppository, on retiring. Alternatively, the total daily dose may be given rectally as 100 mg in the morning and at night. The total daily combined oral and rectal dose should not exceed 200 mg. In acute gout the daily dose is 150 to 200 mg in divided doses until all symptoms and signs subside; in dysmenorrhoea up to 75 mg daily has been suggested. Modified-release preparations of indometacin are available for use once or twice daily. For doses in children, see below.

Indometacin has been used as eye drops, usually of 0.1 or 0.5%, to **prevent miosis during cataract surgery**; the usual dose is 2 drops, repeated after 2 hours, on the day before surgery, then 2 drops 3 hours before and 2 drops 1 hour before surgery. The eye drops may then be instilled up to 6 times daily postoperatively to prevent **cystoid macular oedema**; treatment should be continued until inflammatory signs have disappeared. Indometacin eye drops have also been used in other inflammatory eye disorders in doses similar to those used to prevent oedema.

Meglumine indometacin and indometacin farnesil, a lipid soluble ester of indometacin ($C_{34}H_{40}ClNO_4$ = 562.1), have also been given for painful and inflammatory conditions. A complex of indometacin and L-arginine, known as indoarginine, has also been used.

Administration in children. Although indometacin is not licensed in the UK for the treatment of **rheumatic diseases** such as juvenile idiopathic arthritis in children, the *BNFC* suggests an oral dose of 0.5 to 1 mg/kg twice daily in those aged 1 month to 18 years; higher doses may sometimes be required.

Indometacin is also used in the treatment of **patent ductus arteriosus** in premature infants; see below for further details including doses.

Bartter's syndrome. The treatment of Bartter's syndrome can often be difficult (see p.1670). Blocking the kinin-prostaglandin axis with a cyclo-oxygenase inhibitor such as indometacin improves hypokalaemia and other clinical features (including growth retardation) in children with the syndrome.[1-5]

1. Littlewood JM, *et al.* Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* 1976; **ii:** 795.
2. Seidel C, *et al.* Pre-pubertal growth in the hyperprostaglandin E syndrome. *Pediatr Nephrol* 1995; **9:** 723–8.
3. Craig JC, Falk MC. Indomethacin for renal impairment in neonatal Bartter's syndrome. *Lancet* 1996; **347:** 550.
4. Mourani CC, *et al.* Bartter syndrome in a neonate: early treatment with indomethacin. *Pediatr Nephrol* 2000; **14:** 143–5.
5. Vaisbich MH, *et al.* Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004; **19:** 858–63.

Diabetes insipidus. Indometacin and other prostaglandin synthetase inhibitors have been reported to decrease urine volume in all types of nephrogenic diabetes insipidus (p.2179).

References.

1. Rosen GH, *et al.* Indomethacin for nephrogenic diabetes insipidus in a four-week-old infant. *Clin Pharm* 1986; **5:** 254–6.
2. Libber S, *et al.* Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. *J Pediatr* 1986; **108:** 305–11.
3. Allen HM, *et al.* Indomethacin in the treatment of lithium-induced nephrogenic diabetes insipidus. *Arch Intern Med* 1989; **149:** 1123–6.
4. Martinez EJ, *et al.* Lithium-induced nephrogenic diabetes insipidus treated with indomethacin. *South Med J* 1993; **86:** 971–3.
5. Hohler T, *et al.* Indomethacin treatment in amphotericin B induced nephrogenic diabetes insipidus. *Clin Investig* 1994; **72:** 769–71.
6. Lam SS, Kjellstrand C. Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. *Ren Fail* 1997; **19:** 183–8.

Malignant neoplasms. In common with some other NSAIDs (see p.100) it has been suggested that indometacin might possess some antineoplastic activity.[1] Some NSAIDs such as indometacin may also be of value for the differential diagnosis and the management of neoplastic fever, as they appear to be more effective in reducing this type of fever than against fever associated with infections.[2] Indometacin has also been tried for the treatment of fever and flu-like symptoms associated with interleukin-2 therapy although there has been concern over exacerbation of renal toxicity (see NSAIDs, under Interactions, p.736).

1. Mertens WC, *et al.* Effect of indomethacin plus ranitidine in advanced melanoma patients on high-dose interleukin-2. *Lancet* 1992; **340:** 397–8.
2. Engervall P, *et al.* Antipyretic effect of indomethacin in malignant lymphoma. *Acta Med Scand* 1986; **219:** 501–5.

Neonatal intraventricular haemorrhage. Indometacin has been tried prophylactically to prevent the development of intraventricular haemorrhage in neonates at risk (see p.1050). Several mechanisms have been proposed for its possible action including reduction of cerebral flow as a result of vasoconstriction, reduction of oxygen free-radical damage, and accelerated maturation of blood vessels around the ventricles. Early studies[1-3] of the use of indometacin for prevention of intraventricular haemorrhage produced conflicting results. A subsequent large multicentre study[4] (the Indomethacin Intraventricular Haemorrhage Prevention Trial, IIHP) suggested that indometacin could reduce the incidence and severity of intraventricular haemorrhage, especially for the more severe forms. Neonates with a birth-weight of 600 to 1250 g were given indometacin in a dose of 100 micrograms/kg intravenously at 6 to 12 hours after delivery and then every 24 hours for 2 additional doses. There was, however, concern[5] that an unusually large number of neonates with severe intraventricular haemorrhage in the control group might have biased the findings.

A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps. Follow-up at 3 years,[6] at 4⁄ years,[7] and at 8 years of age[8] in the infants included in the IIHP study reported no adverse effects on cognitive or motor development. However, another large multicentre study[9] (the Trial of Indomethacin Prophylaxis in Preterms, TIPP) in extremely-low-birth-weight infants (less than 1000 g) found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[10] also concluded that indometacin prophylaxis did not improve survival free of neurosensory disability although, again, the incidence of severe intraventricular haemorrhage was reduced.

Further analysis of the data from the IIHP study has suggested that indometacin might reduce intraventricular haemorrhage in boys but have little effect in girls;[11] verbal scores at ages 3 to 8 years were also higher in those boys treated with indometacin when compared to a control group of boys treated with saline; no differences in scores were noted in indometacin-treated girls and their control group. Re-analysis of data from the TIPP study[12] in extremely-low-birth-weight neonates suggested a weak gender difference in the effect of indometacin treatment when all primary outcomes such as death, cerebral palsy, cognitive delay, and severe intraventricular haemorrhage were considered; however, when outcomes were considered individually, there was a significant reduction in intraventricular haemorrhage in boys when compared with girls. The authors considered the results to be a consequence of an unfavourable effect of indometacin in girls rather than any positive effects in boys. Any true difference in effect between the sexes remains to be confirmed.

Indometacin does not appear to prevent the progression of existing haemorrhage.[13]

1. Ment LR, *et al.* Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. *J Pediatr* 1985; **107:** 937–43.
2. Rennie JM, *et al.* Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986; **61:** 233–8.
3. Bada HS, *et al.* Indomethacin reduces the risks of severe intraventricular hemorrhage. *J Pediatr* 1989; **115:** 631–7.
4. Ment LR, *et al.* Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994; **93:** 543–50.
5. Volpe JJ. Brain injury caused by intraventricular hemorrhage: is indomethacin the silver bullet for prevention? *Pediatrics* 1994; **93:** 673–7.
6. Ment LR, *et al.* Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 1996; **98:** 714–18.
7. Ment LR, *et al.* Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000; **105:** 485–91.
8. Vohr BR, *et al.* School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Abstract: *Pediatrics* 2003; **111:** 874. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/4/e340 (accessed 07/11/07)
9. Schmidt B, *et al.* Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 1966–72.
10. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F464–F466.
11. Ment LR, *et al.* Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004; **145:** 832–4.
12. Ohlsson A, *et al.* Male/female differences in indomethacin effects in preterm infants. *J Pediatr* 2005; **147:** 860–2.
13. Ment LR, *et al.* Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994; **124:** 951–5.

Patent ductus arteriosus. In the fetal circulation the ductus arteriosus connects the pulmonary artery and the descending aorta. After birth, various mechanisms, including a fall in prostaglandin concentration, trigger its closure but in some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. This condition may be found in infants with congenital heart defects but is more commonly seen in premature neonates, especially those with respiratory distress syndrome.

- Some infants may be asymptomatic or have only slight clinical symptoms and no immediate intervention is required. In many cases spontaneous closure will occur after several months, or else surgical ligation may be performed if clinical symptoms persist.
- In some infants a patent ductus arteriosus is necessary for maintaining some oxygenation of the blood, for example in pulmonary artery atresia or transposition of the great arteries. These infants require treatment with a prostaglandin such as *alprostadil* or *dinoprostone* to maintain patency of the ductus arteriosus until surgery can be performed to correct the malformation.
- Infants with haemodynamically significant ductus arteriosus, signs of heart failure, and who require ventilation should undergo treatment to close the patent ductus arteriosus.

Initial **management** involves fluid restriction, diuretics, correction of anaemia, and support of respiration. *Chlorothiazide* and *furosemide* are diuretics commonly used. There has been concern that furosemide might delay closure in infants with respiratory distress syndrome.[1,2] A systematic review[3] concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

If initial treatment fails to control symptoms after 24 to 48 hours then *indometacin* is generally given to promote closure of the ductus.[1,4-6] The benefits of treatment with indometacin as soon as symptoms become apparent, rather than delaying treatment until signs of congestive failure develop, have been debated.[7,8] Early treatment may significantly reduce the morbidities arising from a persistent patent ductus arteriosus.[7] However, delaying treatment until the end of the first week of life can allow for spontaneous closure and avoid the need of exposing infants to the toxic effects of indometacin.[8]

Indometacin probably leads to closure of the ductus through inhibition of prostaglandin synthesis. It is given as the sodium salt in three intravenous doses at 12- to 24-hour intervals; each dose should be infused over 20 to 30 minutes. Indometacin sodium injection is reconstituted with preservative-free sodium chloride 0.9% for injection or water for injection; glucose solutions should not be used (see Incompatibility, above). The dose of indometacin sodium (expressed as indometacin) depends upon the age of the neonate and the following doses have been suggested based upon the age at the first dose:

- less than 48 hours old: 200 micrograms/kg initially followed by two further doses of 100 micrograms/kg each
- 2 to 7 days old: three doses of 200 micrograms/kg each
- over 7 days old: 200 micrograms/kg initially followed by two further doses of 250 micrograms/kg each

If, 48 hours after this course of therapy the ductus remains open or re-opens, a second course may be used, but if this produces no response (which may be the case in 25% of infants treated[4,9]) surgery may be necessary.

Indometacin has been given orally where the injection is unavailable, but absorption of oral indometacin is poor and incomplete in premature neonates.

A decreased need for surgical closure and reduced recurrences were seen in neonates in whom standard intravenous indometacin therapy was then followed by maintenance therapy (intravenous indometacin 200 micrograms/kg daily for an additional 5 days).[10] Prolonged therapy using high doses of up to 1 mg/kg as a single dose every 12 hours has also been used with some success in a few infants who have not responded to standard regimens.[11] Similar beneficial findings were reported[12] in infants given prolonged low-dose indometacin therapy (100 micrograms/kg daily for 6 days). An additional benefit was a lower incidence of adverse effects; fewer infants had a rise in serum creatinine or urea concentrations. However, a systematic review[13] has suggested that such regimens are no more effective than the shorter standard regimens, and found an increased rather than decreased incidence of adverse effects (including a trend towards increased risk of necrotising enterocolitis[1,6]). Prolonged treatment with indometacin could not be recommended.[13] Prophylactic treatment or treatment of asymptomatic ductus with indometacin has been tried in premature infants, and there is good evidence to suggest that this is effective in reducing the risk of symptomatic patent ductus arteriosus and intraventricular haemorrhage (see above) in such patients;[7,14,15] however, prophylactic treatment has not been shown to significantly reduce the risk of short-term pulmonary complications such as bronchopulmonary dysplasia. Systematic reviews[14,15] have also found no evidence of either benefit or harm in neurological development or other longer term outcomes.

Some other NSAIDs have also been tried in the treatment of patent ductus arteriosus. Ibuprofen appears to be effective in closing a patent ductus arteriosus,[16] and it has been suggested that ibuprofen might be a better choice than indometacin as, unlike indometacin, it does not have adverse effects on renal, mesenteric, and cerebral haemodynamics. However, a recent systematic review[16] found no significant difference in the effectiveness of ibuprofen compared to indometacin and, although the risk of oliguria was reduced with ibuprofen, the risk for chronic lung disease may be increased. Ibuprofen is also effective when used prophylactically; however, there have been reports of pulmonary hypertension with such use and ibuprofen is not recommended.[17]

Oral therapy with ibuprofen has also been tried.[18]

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12. Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991; **66:** 55–8.
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18. Heyman E, *et al.* Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatrics* 2003; **112:** 1170. Full version: http://pediatrics.aappublications.org/cgi/reprint/112/5/e354.pdf (accessed 07/11/07)

Polyhydramnios. Reports[1-3] of the beneficial effects of indometacin in the management of polyhydramnios (an excessive accumulation of amniotic fluid). Polyhydramnios is a feature of the neonatal variant of Bartter's syndrome (see also above).

1. Cabrol D, *et al.* Treatment of symptomatic polyhydramnios with indomethacin. *Eur J Obstet Gynecol Reprod Biol* 1996; **66:** 11–15.
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Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Comparative studies[1,2] have shown that indometacin and ritodrine are equally effective in inhibiting uterine contractions and delaying delivery in patients in preterm labour who have intact membranes and in whom the gestational age is less than or equal to 34 weeks. In one study[2] an initial oral loading dose of indometacin 50 mg was given, followed by 25 to 50 mg orally every 4 hours until contractions stopped and then by a maintenance dose of 25 mg every 4 to 6 hours. In the other comparative study[1] indometacin was given as a 100-mg rectal suppository followed by 25 mg orally every 4 hours for 48 hours; if regular uterine contractions persisted 1 to 2 hours after the initial suppository, an additional 100-mg suppository was given before beginning oral therapy. Terbutaline was given for maintenance therapy.

Unfortunately indometacin can constrict the ductus arteriosus,[3-5] which may lead to pulmonary hypertension,[2] and has also been associated with bronchopulmonary dysplasia,[6] reduced volume of amniotic fluid (oligohydramnios)[2,4] and possible renal damage (see Effects on the Kidneys, above) in the fetus. Another complication is that prenatal indometacin exposure may increase both the incidence and severity of patent ductus arteriosus in premature infants,[7,8] as shown by the increased need for post-natal indometacin therapy and surgical ligation in such infants. However, there is evidence to suggest that there is no significant increase in the risk of neonatal complications in infants exposed to indometacin tocolysis when compared with control groups of infants who received either no treatment or tocolysis with drugs other than indometacin.[9,10]

The evidence for any overall benefit of indometacin in delaying labour is equivocal,[11-13] and it is generally reserved as a second-line tocolytic or for use with an intravenous tocolytic when an additive effect is required.

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7. Norton ME, *et al.* Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993; **329:** 1602–7.
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9. Vermillion ST, Newman RB. Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. *Am J Obstet Gynecol* 1999; **181:** 1083–6.
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Preparations

BP 2008: Indometacin Capsules; Indometacin Suppositories;
USP 31: Indomethacin Capsules; Indomethacin Extended-release Capsules; Indomethacin for Injection; Indomethacin Oral Suspension; Indomethacin Suppositories; Indomethacin Topical Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Agilex; IM 75; Indotex; Klonametacina; ***Austral.:*** Arthrexin; Indocid; Indocid PDA; ***Austria:*** Flexidin; Indo; Indobene; Indocid; Indocollyre; Indohexal; Indomelan; Indoptol; Liometacen; Luiflex; Ralicid; ***Belg.:*** Dolcidium; Indocid; Indocollyre; Luiflex; ***Braz.:*** Agilisin; Indocid; Indocid Colirio†; Metacidil†; ***Canad.:*** Indocid PDA; Indocid†; Indotec†; Novo-Methacin; Nu-Indo; Rhodacine; ***Chile:*** Flexono; Moviflex; ***Cz.:*** Bonidon†; Elmetacin; Indobene; Indocollyre; Vonum Cutan; ***Denm.:*** Confortid; Indocid†; ***Fin.:*** Confortid; Indocid; Indometin; ***Fr.:*** Chrono-Indocid; Indocid; Indocollyre; ***Ger.:*** Confortid; Elmetacin; Indo; Indo Top; Indo-paed; Indo-Phlogont†; Indocolir; Indocontin†; Indomet-ratiopharm; Indomet-ratiopharm m†; Indomet†; Indomisal†; Inflam; Mobilat Akut Indo; Rheubalmin Indo; Sigadoc†; ***Gr.:*** Begincalm†; Dolcispray; Fortathrine; Hastel; Indocid; Indomethol; Itapredin; Reumacid; Reumadolor; ***Hong Kong:*** Indocid; Indocin PDA; Indocollyre; Indogesic†; Indomet†; ***Hung.:*** Elmetacin; Indobene; Indocollyre; ***India:*** Idicin†; Indocap; Indocid; ***Indon.:*** Dialon; ***Irl.:*** Cidomel†; Flexin Continus; Indocid PDA; Indocid†; ***Israel:*** Indocollyre; Indomed; Indoptic†; Indotard; Indovis; ***Ital.:*** Imet†; Indocid; Indocollirio; Indom; Indoxen; Liometacen; Metacen; ***Jpn:*** Catlep; Idomethine; Infree; ***Malaysia:*** Arthrexin†; Domicap†; Indo; Indocid†; Indomen; ***Mex.:*** Antalgin; Artaxol; Biometacin; Draxil; Grindocin†; Indaflex; Indocarsil; Indocid; Indoman; Indotrin; Italon; Labymetacyn†; Malival; Mefazil; Soltacina; Stratasin; ***Neth.:*** Dometin†; Indocid; Indocid PDA; Indocollyre; Indoptol†; ***Norw.:*** Confortid; Indocid; ***NZ:*** Arthrexin; Elmetacin†; Indocid PDA; Rheumacin; ***Philipp.:*** Infree; Vi-Gel; ***Pol.:*** Elmetacin; Indocollyre; Metindol; ***Port.:*** Autritis; Dolovin; Elmetacin; Indocid; Indocollyre; Indogel; Indospray; Reumacide; ***Rus.:*** Indomin (Индомин); Indotard (Индотард)†; Indovis (Индовис)†; Metindol (Метиндол); ***S.Afr.:*** Acuflex; Adco-Indogel; Aflamin; Arthrexin; Betacin; Elmetacin; Flamaret; Flamecid; Indocid; Mediflex†; Methocaps; Nisaid; Restameth-SR†; ***Singapore:*** Indo; Indocollyre; Indomen; ***Spain:*** Aliviosin; Artrinovo; Flogoter; Inacid; Indocaf; Indolgina; Indonilo; Mederreumol†; Neo Decabutin; Reumo†; Reusin; ***Swed.:*** Confortid; Indomee; ***Switz.:*** Bonidon; Elmetacin; Indo-Mepha†; Indocid; Indophtal; ***Thai.:*** Ammi-Indocin; Bucin†; Docin; Elmego; Elmetacin; Idc; Indocid; Indocin; Indocollyre; Indomed; Indono; Inflamate; Inthacine; Liometacen; Metindo; Satogesic; ***Turk.:*** Endol; Endosetin; Indocolir; Inomet; ***UAE:*** Rothacin; ***UK:*** Flexin Continus†; Indocid PDA; Indocid†; Indolar SR; Indomax†; Indomod†; Pardelprin; Rimacid; Slo-Indo; ***USA:*** Indocin; ***Venez.:*** Cevimin; Elmetacin; Indocid; Melior†; Romazulan†.

Multi-ingredient: ***Austria:*** Vonum; ***Fin.:*** Indalgin; ***Fr.:*** Indobiotic; ***Ger.:*** Inflam†; ***Ital.:*** Difmetre; ***Jpn:*** Vantelin; ***Mex.:*** Artridol; Malival Compuesto; Morlan; Reupat; ***Port.:*** Indobiotic; ***Rus.:*** Indovasin (Индовазин); ***Spain:*** Artri; Fiacin; ***Switz.:*** Indobiotic†; Ralur†; ***Turk.:*** Indobiotic.

Infliximab *(BAN, rINN)*

cA2; CenTNF; Infliksimab; Infliksimabi; Infliximabum. Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer.

Инфликсимаб

CAS — 170277-31-3.

ATC — L04AB02.

ATC Vet — QL04AB02.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions during or within 1 to 2 hours of infusion are common with infliximab, and other TNF inhibitors, particularly with the first or second dose. Symptoms include fever, chills, pruritus, urticaria, dyspnoea, chest pain, and hypertension or hypotension. Mild reactions may respond to a reduced rate of infusion or a temporary interruption. If reactions are more severe, therapy should be stopped. Pretreatment with paracetamol, corticosteroids, and antihistamines may be considered. TNF inhibitors should only be given where facilities for resuscitation are available. Delayed reactions have occurred 3 to 12 days after infliximab treatment; symptoms include myalgia, arthralgia, fever, and rash. Similar delayed reactions may also be seen when infliximab has been restarted after an extended period without treatment (see below).

Other, common, adverse effects include nausea and vomiting, abdominal pain, diarrhoea, fatigue, dizziness, headache, and back pain. Antibodies to infliximab (human antichimeric antibodies) may develop, and are associated with an increased incidence of hypersensitivity reactions. Antinuclear antibodies and anti-double-stranded-DNA antibodies have also developed with TNF inhibitor therapy. A lupus-like syndrome has occurred rarely; treatment should be stopped if it develops.

Infections are common in patients treated with infliximab or other drugs that inhibit TNF, and most often affect the upper respiratory tract and the urinary tract. TNF inhibitors have also been associated rarely with the development of serious opportunistic infections, sepsis, pneumonia, and onset or reactivation of tuberculosis (see below), particularly in patients with underlying conditions predisposing them to infections; in some cases death has resulted. TNF inhibitors should not be given to patients with severe infection, including active tuberculosis, abscesses, and opportunistic infections, and should be stopped if these develop. Patients should be evaluated for latent and active tuberculosis before beginning therapy; if evidence of latent tuberculosis is found, the risks and benefits of treatment should be considered carefully and chemoprophylaxis should be started before giving a TNF inhibitor. They should also be used with care in those with chronic infections, a history of recurrent infections, or with underlying conditions that may predispose to infections. Patients with fistulising Crohn's disease with suppurative fistulas should not be given infliximab until possible infection sources such as abscesses have been ruled out. Patients should be instructed to seek medical advice if symptoms suggestive of tuberculosis (such as persistent cough, weight loss, or low grade fever) occur. Patients should be monitored for signs of infection after stopping treatment: for adalimumab and infliximab, which both have long half-lives, monitoring should continue for 5 or 6 months, respectively; because of its relatively shorter half-life, the elimination of etanercept may be quicker.

There have been rare reports of severe hepatic reactions such as acute liver failure, jaundice, hepatitis, and cholestasis with infliximab; some cases have been fatal or required transplantation. Patients with signs or symptoms of hepatotoxicity should be evaluated and infliximab should be stopped in those patients with jaundice or marked elevations in liver enzyme values. Infliximab and other TNF inhibitors have also been associated with the reactivation of hepatitis B in chronic carriers, which has resulted in fatalities in some cases. Patients at risk of hepatitis B infection should be screened before starting treatment; it is recommended that carriers treated with a TNF inhibitor are closely monitored during, and for several months after stopping, treatment.

Blood dyscrasias, including leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia, have been reported rarely with TNF inhibitors; in some cases the outcome was fatal. They should be used with caution in patients with a history of blood dyscrasias.

Rare, and sometimes fatal, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported with TNF inhibitors.

Infliximab and other TNF inhibitors are also associated with an increased incidence of malignancies including lymphoma (see also Carcinogenicity, below), although occurrences are rare. Some groups of patients treated with TNF inhibitors may already have an increased background risk of developing malignancies, regardless of drug treatment. Care has been advocated in patients with a history of malignancy.

Anaphylactic reactions have been reported rarely with TNF inhibitors. Infliximab should be avoided in patients with a history of hypersensitivity to the drug or other murine proteins.

TNF inhibitors have been associated with rare cases with seizures and clinical or radiological worsening of demyelinating disorders such as multiple sclerosis or optic neuritis; care is required in prescribing it to patients with such disorders or symptoms suggestive of their onset.

Worsening and, in some cases, new-onset heart failure has been reported with TNF inhibitors (see Effects on the Heart, below). (NYHA class III or IV). In the UK, infliximab is contra-indicated in patients with moderate to severe heart failure; however, US licensed product information advises that doses up to 5 mg/kg may be used in such patients. It should be used with caution in patients with mild heart failure (NYHA class I or II). All patients with heart failure should be closely monitored and infliximab stopped in those who develop new or worsening symptoms of heart failure. Similar recommendations are given for the TNF inhibitors adalimumab and etanercept, although UK licensed information for etanercept only advises caution in patients with heart failure.

◊ General references.

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Carcinogenicity. Malignancies, especially lymphomas, have been seen in patients treated with TNF inhibitors for rheumatoid arthritis and Crohn's disease;[1] however, the suggestion of a causal relationship is controversial. A meta-analysis[2] in 2006 identified 24 published reports of malignancies in 3493 study patients with rheumatoid arthritis who had received at least one dose of a TNF inhibitor (adalimumab or infliximab) along with 2 cases in 1512 control patients; further, unpublished, cases were also found using FDA data to give 29 malignancies in the treatment groups and 3 in the control groups. Based on these figures, there was a 3.3-fold increase in the risk of malignancy in patients receiving TNF inhibitors when compared with controls. These results have, however, been criticised[3] on a number of points including the difficulty in applying them to current practice because etanercept was not included in the analysis, and, in particular, the unexpectedly low rate of malignancies in the control groups. Other studies in patients with rheumatoid arthritis[4,5] and Crohn's disease[6] have generally concluded that the overall risk of malignancies is not significantly increased in patients taking TNF inhibitors when compared with patients who have not taken these drugs. Some studies[4,7] in patients with rheumatoid arthritis have, however, shown a possible increased risk of lymphoma with TNF inhibitor treatment, but caution in interpreting these results was recommended as they were based on a small number of cases; in addition, the background risk of lymphoma is increased in rheumatoid arthritis regardless of treatment. The risk of malignancies with TNF inhibitors requires further study.

Rare cases of hepatosplenic T-cell lymphoma have been seen in adolescents and young adults given infliximab for the treatment of Crohn's disease. In July 2006, the manufacturer was aware of 6 cases of this type of lymphoma in 5 adolescents aged 12 to 19 years and one 31-year-old adult;[8] 4 of the 6 cases occurred in males. The treatment duration ranged from 1 or 2 infusions to over 4 years of therapy; in all cases, patients were also taking or had taken azathioprine or 6-mercaptopurine. This type of lymphoma is aggressive and 5 of the above patients died. A causal relationship was not clearly established although it could neither be excluded. Further cases have since been reported.[9]

1. Brown SL, *et al.* Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002; **46:** 3151–8.
2. Bongartz T, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295:** 2275–85. Correction. *ibid.*; 2482.
3. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. *Arthritis Res Ther* 2006; **8:** 111.
4. Geborek P, *et al.* Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; **64:** 699–703.
5. Setoguchi S, *et al.* Tumor necrosis factor α antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 2757–64. Correction. *ibid.*; 3134.
6. Biancone L, *et al.* Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006; **55:** 228–33.
7. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; **50:** 1740–51.
8. Schering, Canada. Health Canada endorsed important safety information on Remicade (infliximab) (issued 24th July, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/remicade_3_hpc-cps-eng.pdf (accessed 29/08/08)
9. Mackey AC, *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44:** 265–7.

Delayed reactions. Ten of 37 patients with Crohn's disease retreated with infliximab after a 2 to 4 year period without treatment had delayed hypersensitivity reactions, of which 6 were considered serious. None of the patients had had infusion-related adverse effects with their original infliximab therapy. Adverse reactions developed in 9 of the 23 patients originally treated with a discontinued liquid formulation, and in 1 of the 14 patients who previously received the marketed formulation, leading to speculation that the formulation may have been a contributing factor.

Effects on blood lipids. A 35-year-old man with psoriatic arthritis and psoriasis developed markedly elevated triglyceride levels and a mildly increased total cholesterol level after a single infusion of infliximab;[1] tests prior to therapy had shown a mild hypertriglyceridaemia for which he had received no treatment. No further doses of infliximab were given and his triglyceride levels subsequently improved.

1. Antoniou C, *et al.* Elevated triglyceride and cholesterol levels after intravenous antitumour necrosis factor-α therapy in a patient with psoriatic arthritis and psoriasis vulgaris. *Br J Dermatol* 2007; **156:** 1090–1.

Effects on the CNS. Aseptic meningitis developed in a patient after his fifth injection of infliximab for rheumatoid arthritis.[1] Similar symptoms also occurred after a sixth injection.

Two patients with inflammatory bowel disease developed acute motor neuropathy with multiple conduction blocks following infliximab treatment; both patients improved after infliximab was stopped.[2] Similar adverse effects were reported in 2 further patients:[3] one was taking etanercept for rheumatoid arthritis and the other infliximab for ankylosing spondylitis. Three cases of bilateral optic neuropathy associated with infliximab therapy have also been reported.[4] Other neuropathies have been associated with TNF inhibitor treatment, including Guillain-Barré syndrome.[5]

1. Marotte H, *et al.* Infliximab-induced aseptic meningitis. *Lancet* 2001; **358:** 1784.
2. Singer OC, *et al.* Acute neuropathy with multiple conduction blocks after TNFα monoclonal antibody therapy. *Neurology* 2004; **63:** 1754.
3. Richez C, *et al.* Neuropathy resembling CIDP in patients receiving tumor necrosis factor-α blockers. *Neurology* 2005; **64:** 1468–70.
4. ten Tusscher MPM, *et al.* Bilateral anterior toxic optic neuropathy and the use of infliximab. *BMJ* 2003; **326:** 579.
5. Stübgen J-P. Tumor necrosis factor-α antagonists and neuropathy. *Muscle Nerve* 2008; **37:** 281–92.

Effects on the heart. The FDA has reported[1] on 47 patients who developed heart failure during long-term therapy with TNF antibodies (etanercept and infliximab) for arthritic conditions or Crohn's disease. Of these, 38 developed new-onset heart failure, 19 having documented risk factors for heart failure, and 9 had exacerbation of existing heart failure. The median time to new-onset heart failure was 3.5 months. However, studies[2-4] investigating a possible association between TNF inhibitors and the development of heart failure have been equivocal and further investigation is warranted.

Preliminary investigations on the use of infliximab in the treatment of moderate to severe heart failure failed to show any clinical improvement in patients given infliximab 5 mg/kg or 10 mg/kg when compared with placebo;[5] in addition, those given the higher dose had an increased risk of death or hospitalisation due to worsening heart failure.

1. Kwon HJ, *et al.* Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003; **138:** 807–11.
2. Jacobsson LTH, *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1213–18.
3. Curtis JR, *et al.* Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-α antagonists. *Rheumatology (Oxford)* 2007; **46:** 1688–93.
4. Listing J, *et al.* Does tumor necrosis factor α inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008; **58:** 667–77.
5. Chung ES, *et al.* Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) trial. *Circulation* 2003; **107:** 3133–40.

Effects on the lungs. Infliximab treatment has been associated with a fatal exacerbation of previously asymptomatic fibrosing alveolitis in 3 patients with chronic rheumatoid arthritis;[1] all 3 patients were also taking azathioprine and prednisolone. There was no evidence of infection or other underlying causes for the decline in respiratory function.

1. Ostor AJK, *et al.* Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 2004; **329:** 1266.

Effects on the skin. Patients with rheumatoid arthritis receiving TNF inhibitor therapy are more likely to develop adverse skin reactions than those who are not.[1] Of 289 patients taking TNF inhibitors (infliximab, etanercept, adalimumab, and lenercept), 72 (25%) reported 128 dermatological events including skin infections, eczema, drug-related eruptions, and malignancies such as actinic keratosis; of the 289 patients not taking TNF inhibitors, 37 (13%) reported dermatological events.

In another review,[2] cutaneous adverse effects were seen in 35 out of 150 patients receiving TNF inhibitors (adalimumab, etanercept, or infliximab) for rheumatic disorders; cases included dermatitis herpetiformis and leucocytoclastic vasculitis although eczematous and skin infections were more common or infectious. Perhaps unexpectedly, psoriasis-like lesions were seen in 8 patients, 6 of whom had no history of psoriasis; similar effects have also been noted in other patients with rheumatoid arthritis[3] or Crohn's disease.[4]

Rare cases of serious skin reactions have been associated with TNF inhibitor treatment.[5] Since approval in 1998, the FDA has received 15 cases of erythema multiforme, 5 cases of Stevens-Johnson syndrome, and 1 case of toxic epidermal necrolysis associated with infliximab; cases for etanercept, approved in the same year, included 13 reports of erythema multiforme, and 4 reports each of Stevens-Johnson syndrome and toxic epidermal necrolysis. For adalimumab, which was marketed late in 2002, there have been 4 cases of erythema multiforme and 2 of Stevens-Johnson syndrome.

1. Flendrie M, *et al.* Dermatological conditions during TNF-α-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; **7:** R666–R676.

2. Lee H-H, *et al.* Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-α antagonists. *Br J Dermatol* 2007; **156:** 486–91.
3. Dereure O, *et al.* Psoriatic lesions induced by antitumour necrosis factor-α treatment: two cases. *Br J Dermatol* 2004; **151:** 506–7.
4. Verea MM, *et al.* Psoriasiform eruption induced by infliximab. *Ann Pharmacother* 2004; **38:** 54–7.
5. FDA. Tumor necrosis factor alpha (TNF-α) antagonists: serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 18–20. Available at: http://www.fda.gov/cder/dsn/2008_winter/2008_winter.pdf (accessed 17/06/08)

Infection. There have been spontaneous reports of onset or reactivation of *tuberculosis* in patients treated with infliximab, including cases of miliary tuberculosis and unusual extrapulmonary disease.[1] The UK CSM noted in February 2001 that there had been 28 such reports worldwide. The US manufacturers subsequently reported[2] (in October 2001) that other serious opportunistic infections, including *histoplasmosis*, *listeriosis*, and *pneumocystosis* had occurred, and had led to some deaths; the number of reported cases of tuberculosis had risen to 84. Further opportunistic infections also continued to be reported; FDA data up to August 2002 included reports of *candidiasis*, *coccidioidomycosis*, *nocardiosis*, *aspergillosis*, and infections due to non-tuberculous mycobacteria.[3] Health Canada reported[4] in October 2004 that it had received 188 and 109 reports of infections associated with infliximab and etanercept, respectively, from January 2000 to May 2004. Of these, 10 and 2 reports were of tuberculosis associated with infliximab and etanercept, respectively. The FDA also received 25 reports of tuberculosis associated with etanercept between November 1998 and March 2002.[5] Although the majority of patients also had a history of treatment with immunosuppressants including corticosteroids, the inhibition of TNF may affect normal immune responses and predispose patients to opportunistic infections.

Guidelines[6] have been issued by the British Thoracic Society to quantify the risks of reactivation of tuberculosis with TNF inhibitors and to advise on the treatment of such infection in patients being assessed for TNF inhibitor therapy.

1. CSM/MCA. Infliximab (Remicade) and tuberculosis. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&DocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
2. Schaible TF [Centocor, Inc.]. Important drug warning (issued 5th October, 2001). Available at: http://www.fda.gov/medwatch/safety/2001/remicadeTB_deardoc.pdf (accessed 13/06/08)
3. Wallis RS, *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; **38:** 1261–5. Correction. *ibid.*; **39:** 1254–5.
4. Health Canada. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. *Can Adverse React News* 2004; **14** (4): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 29/08/08)
5. Mohan AK, *et al.* Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004; **39:** 295–9.
6. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment. *Thorax* 2005; **60:** 800–5. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Anti%20TNF%20Treatment/Guidelines/antitnf_treatment.pdf (accessed 13/06/08)

Interactions

Live vaccines should not be given with infliximab or other drugs that inhibit TNF as the effect of such drugs on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with the interleukin-1 receptor antagonist anakinra may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar interaction has been seen with TNF inhibitors and the co-stimulation blocker abatacept.

Abatacept. Use of the TNF inhibitor etanercept with abatacept has resulted in an increase in the incidence of serious adverse effects including serious infections; in addition, there was no increase in clinical benefit.[1] Combinations of abatacept with TNF inhibitors are not recommended by UK licensed product information.

1. Weinblatt M, *et al.* Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007; **66:** 228–34.

Anakinra. The incidence of serious infections, injection site reactions, and neutropenia is increased when anakinra is given with the TNF inhibitor etanercept.[1] In addition, the combination did not provide any further clinical benefit when compared to etanercept alone. Similar findings may be expected if anakinra is given with other TNF inhibitors.

1. Genovese MC, *et al.* Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; **50:** 1412–19.

Pharmacokinetics

Infliximab shows linear pharmacokinetics. It is distributed primarily in the vascular compartment and, after single doses, has a terminal elimination half-life of 8 to 9.5 days. After repeated doses, infliximab has been detected in serum for at least 8 weeks.

◊ References.

1. Klotz U, *et al.* Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; **46:** 645–60.

Uses and Administration

Infliximab is a chimeric monoclonal antibody to tumour necrosis factor α (TNF), a pro-inflammatory mediator. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and Crohn's disease and ulcerative colitis. Elevated TNF levels are also found in psoriatic plaques.

Infliximab is given by intravenous infusion over a usual period of not less than 2 hours; shorter infusion times have been used in some patients with rheumatoid arthritis (see below for further details).

Infliximab is used with methotrexate in the management of moderate to severe, active **rheumatoid arthritis** to reduce the signs and symptoms of the disease, delay structural damage, and improve physical function; in the UK it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs) although, in severe progressive cases, it may be used in patients not previously treated with methotrexate or other DMARDs; in the USA it may be used for treating early rheumatoid arthritis. Infliximab is given in a dose of 3 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. For the first 3 doses infliximab should be infused for at least 2 hours; however, UK licensed product information suggests that subsequent infusion times may be reduced to a minimum period of 1 hour in those who tolerate the initial infusions. A clinical response is usually achieved within 12 weeks of starting treatment. Patients with an inadequate response during this period or who later relapse may benefit by increasing the dose: in the UK, a maximum dose of 7.5 mg/kg every 8 weeks (with increases made in steps of 1.5 mg/kg) is recommended whereas, in the USA, a maximum dose of 10 mg/kg is allowed. Alternatively, a dose of 3 mg/kg may be given as often as every 4 weeks in such patients. Continuing therapy in those who show no response within the first 12 weeks of treatment or after dose adjustment should be carefully reconsidered: in the UK NICE recommends that infliximab be withdrawn if there is no adequate response within 6 months of starting treatment.

Patients with moderate to severe, active **Crohn's disease** unresponsive to conventional treatment may be given a single infliximab dose of 5 mg/kg. This may be followed by a maintenance regimen of additional infusions of 5 mg/kg at 2 and 6 weeks after the initial infusion and then every 8 weeks, or the drug may be readministered when signs and symptoms of the disease recur (but see below). UK licensed product information does not recommend further doses in patients who are unresponsive after the first 2 doses; in the USA, a patient is not considered to be unresponsive until 3 doses have been given. A similar regimen is used in patients with fistulising Crohn's disease although therapy should not be considered ineffective until after the third dose of infliximab. US product information suggests that doses of up to 10 mg/kg may be used in patients who relapse after an initial response. Infliximab is also used in the treatment of moderate to severe, active **ulcerative colitis** in patients unresponsive to conventional therapy; the recommended dose is 5 mg/kg given as a regimen similar to that used for Crohn's disease (see above). Therapy should not be considered ineffective until after the third dose of infliximab.

In the treatment of **ankylosing spondylitis**, UK licensed product information recommends that infliximab should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early treatment, to reduce the signs and symptoms. The initial dose is 5 mg/kg, repeated at 2 and 6 weeks and then every 6 to 8 weeks; if there is no response after 2 doses no further treatment should be given.

Infliximab is also used in the treatment of active and progressive **psoriatic arthritis**; in the UK, its use is limited to patients who have had an inadequate response to standard DMARD but, as before, US licensed product information allows earlier use. In the USA, it may be given with or without methotrexate; however, UK product information only recommends use without methotrexate in those patients who are intolerant of or have contra-indications to such treatment. It is given in a single dose of 5 mg/kg, repeated at 2 and 6 weeks and then every 8 weeks thereafter. Guidance issued by NICE in the UK recommends that treatment with infliximab is stopped after 12 weeks in those who show an inadequate response.

Infliximab is used in the treatment of moderate to severe plaque **psoriasis**. Its use is usually limited to patients in whom other treatments are not suitable. Infliximab is given in a dose of 5 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. Treatment should be stopped after 14 weeks (4 doses) in patients who show no response.

If the signs and symptoms of rheumatoid arthritis or Crohn's disease recur infliximab may be readministered if within 16 weeks of the last infusion. **Readministration** after a drug-free interval of more than 16 weeks may be associated with an increased risk of delayed hypersensitivity (see Delayed Reactions, above) and consequently is not recommended. Recommendations regarding the readministration of infliximab for other indications (other than those detailed above) have not been established. Limited data from readministration with a single dose of infliximab in psoriasis after an interval of 20 weeks suggest reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared with the initial regimen.

For details of infliximab use in children, see below.

Administration in children. Infliximab is licensed for use in moderate to severe, active Crohn's disease in children aged 6 years and over who have not responded to conventional therapy, or who have contraindication for or are intolerant of such treatments; doses are the same as those used in adults (see above). UK licensed product information suggests that the dosage interval may be adjusted to maintain any benefits; however, further treatment is unlikely to be of use in patients not responding within the first 10 weeks.

Although unlicensed for such use in the UK, infliximab has also been used in children with fistulising Crohn's disease; the *BNFC* recommends that those aged 6 to 18 years may be treated with the same dosage regimen that is used for this indication in adults (see above).

Asthma. TNF inhibitors such as infliximab have been investigated in the treatment of refractory asthma (p.1108).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[2]

1. Erin EM, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor-α in asthma. *Am J Respir Crit Care Med* 2006; **174:** 753–62.
2. Brightling C, *et al.* Targeting TNF-alpha: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Inflammatory bowel disease. Infliximab is used in adults for the treatment of Crohn's disease[1-11] and ulcerative colitis[8,12-16] (see Inflammatory Bowel Disease, p.1697); it has also been used in children in the treatment of inflammatory bowel disease,[17-20] particularly Crohn's disease.

In the treatment of Crohn's disease, guidance issued in the UK by NICE recommends that infliximab is used in patients with severe disease when treatment with immunomodulators and corticosteroids has failed or is not tolerated, and when surgery is inappropriate.[21]

In the treatment of ulcerative colitis, guidance issued by NICE recommends against the use of infliximab in subacute manifestations of moderately to severely active disease (defined as that which would normally be managed in an outpatient setting, and does not require hospitalisation or the consideration of urgent surgical intervention).[22] The use of infliximab in acute manifestations of moderately to severely active ulcerative colitis is under review by NICE.

1. Present DH, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340:** 1398–405.
2. Rutgeerts P, *et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117:** 761–9.
3. Hanauer SB, *et al.* ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359:** 1541–9.
4. Rutgeerts P, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126:** 402–13.
5. Sands BE, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350:** 876–85.
6. Panaccione R, *et al.* Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. *Can J Gastroenterol* 2004; **18:** 503–8. Also available at: http://www.cag-acg.org/uploads/guidelines/Infliximab%20guidelines%202004.pdf (accessed 13/06/08)
7. Siddiqui MAA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. *Drugs* 2005; **65:** 2179–2208. Correction. *ibid.* 2006; **66:** 1359.
8. Rutgeerts P, *et al.* Review article: infliximab therapy for inflammatory bowel disease — seven years on. *Aliment Pharmacol Ther* 2006; **23:** 451–63.
9. Rutgeerts P, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63:** 433–42.
10. Lémann M, *et al.* Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130:** 1054–61.
11. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. *Gastroenterol Clin North Am* 2006; **35:** 795–820.
12. Probert CS, *et al.* Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003; **52:** 998–1002.
13. Rutgeerts P, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–76. Correction. *ibid.* 2006; **354:** 2200.
14. Lawson MM, *et al.* Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
15. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35:** 821–36.
16. Gisbert JP, *et al.* Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.
17. Baldassano R, *et al.* Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol* 2003; **98:** 833–8.
18. Hyams J, *et al.* REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; **132:** 863–73.
19. de Ridder L, *et al.* Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45:** 3–14.
20. Veres G, *et al.* Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67:** 1703–23.
21. NICE. Guidance on the use of infliximab for Crohn's disease: Technology Appraisal Guidance 40 (issued April 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/NiceCROHNS40GUIDANCE.pdf (accessed 13/06/08)
22. NICE. Infliximab for subacute manifestations of ulcerative colitis: Technology Appraisal Guidance 140 (issued April 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA140Guidance.pdf (accessed 28/07/08)

Leprosy. Infliximab has been used[1] in the treatment of recurrent type 2 (erythema nodosum leprosum) lepra reactions (see Leprosy, p.176). However, 2 cases of rapidly progressive leprosy developing in patients given infliximab for rheumatoid arthritis have also been described;[2] reversal (type 1) reactions occurred in both when infliximab was stopped.

1. Faber WR, *et al.* Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; **355:** 739.
2. Scollard DM, *et al.* Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis* 2006; **43:** e19–e22.

Psoriasis. Infliximab is used in the treatment of moderate to severe plaque psoriasis (p.1583).[1-8] In the UK, NICE recommends[8] that it be reserved for severe cases, unresponsive to standard therapies (including ciclosporin, methotrexate, and PUVA) or where such therapies cannot be used.

1. Benoit S, *et al.* Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. *Br J Dermatol* 2004; **150:** 1009–12.
2. Gottlieb AB, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51:** 534–42.
3. Reich K, *et al.* EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366:** 1367–74.
4. Reich K, *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154:** 1161–8.
5. Smith CH, *et al.* Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155:** 160–9.
6. Menter A, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2006; **56:** 31.e1–15.
7. Poulalhon N, *et al.* A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156:** 329–36.
8. NICE. Infliximab for the treatment of adults with psoriasis: Technology Appraisal Guidance 134 (issued January 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA134Guidance.pdf (accessed 22/08/08)

Rheumatoid arthritis. TNF inhibitors play an increasingly important role in the management of rheumatoid arthritis; they tend to be reserved for patients who are unresponsive to more conventional disease-modifying drugs, although some favour use earlier in management.

Some references to the use of infliximab in rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10).

1. Maini R, *et al.* ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354:** 1932–9.
2. Lipsky PE, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1594–1602.
3. Maini RN, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; **50:** 1051–65.
4. Quinn MA, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 27–35.
5. Voulgari PV, *et al.* Infliximab therapy in established rheumatoid arthritis: an observational study. *Am J Med* 2005; **118:** 515–20.
6. Ruperto N, *et al.* Paediatric Rheumatology International Trials Organisation. Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3096–3106.
7. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)

Sarcoidosis. For a mention of possible benefit from infliximab in sarcoidosis, see p.1512.

Spondyloarthropathies. References to the use of infliximab in the treatment of ankylosing spondylitis and psoriatic arthritis (p.13). In the UK, NICE considers that TNF inhibitors should be reserved for severe active psoriatic arthritis unresponsive to at least 2 standard disease-modifying drugs; etanercept or adalimumab are preferred to infliximab.

1. Brandt J, *et al.* Infliximab in the treatment of active and severe ankylosing spondylitis. *Clin Exp Rheumatol* 2002; **20** (Suppl 28): S106–S110.
2. Brandt J, *et al.* Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.
3. Collantes-Estévez E, *et al.* Infliximab in refractory spondyloarthropathies: a multicentre 38 week open study. *Ann Rheum Dis* 2003; **62:** 1239–40.
4. Robinson DM, Keating GM. Infliximab: in ankylosing spondylitis. *Drugs* 2005; **65:** 1283–91.
5. NICE. Etanercept and infliximab for the treatment of adults with psoriatic arthritis: Technology Appraisal Guidance 104 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA104guidance.pdf (accessed 13/06/08)
6. Rott S, *et al.* Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157:** 191–2.

Uveitis. Infliximab has been tried with some success in the treatment of uveitis (p.1515) including that associated with Behçet's syndrome (p.1499). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with infliximab may improve ocular symptoms in addition to its effect on the primary disorder.

References.

1. Murphy CC, *et al.* Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology* 2004; **111:** 352–6.
2. Bodaghi B, *et al.* Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors. *Ann Rheum Dis* 2005; **64:** 962–4.
3. Braun J, *et al.* Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.
4. Richards JC, *et al.* Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol* 2005; **33:** 461–8.
5. Lindstedt EW, *et al.* Anti-TNF-α therapy for sight threatening uveitis. *Br J Ophthalmol* 2005; **89:** 533–6.
6. Saurenmann RK, *et al.* Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006; **45:** 982–9.
7. Kahn P, *et al.* Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; **113:** 860–4.e2.
8. Guignard S, *et al.* Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006; **65:** 1631–4.
9. Tynjälä P, *et al.* Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; **66:** 548–50.
10. Ardoin SP, *et al.* Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol* 2007; **144:** 844–849.
11. Pipitone N, *et al.* Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. *Arthritis Rheum* 2008; **59:** 285–90.

Vasculitic syndromes. For a preliminary report on the use of infliximab in Takayasu's arteritis, see p.1514. Infliximab has also been investigated in the management of Kawasaki disease (p.2228) in patients who are unresponsive to standard treatment.[1-3]

1. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
2. Saji T, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006; **149:** 426.
3. O'Connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)* 2007; **46:** 345–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Remicade†; Revellex†; ***Austral.:*** Remicade; ***Belg.:*** Remicade; ***Braz.:*** Remicade; ***Canad.:*** Remicade; ***Chile:*** Remicade; ***Cz.:*** Remicade; ***Denm.:*** Remicade; ***Fin.:*** Remicade; ***Fr.:*** Remicade; ***Ger.:*** Remicade; ***Gr.:*** Remicade; ***Hong Kong:*** Remicade; ***Hung.:*** Remicade; ***Indon.:*** Remicade; ***Irl.:*** Remicade; ***Israel:*** Remicade; ***Ital.:*** Remicade; ***Jpn:*** Remicade; ***Malaysia:*** Remicade; ***Mex.:*** Remicade; ***Neth.:*** Remicade; ***Norw.:*** Remicade; ***NZ:*** Remicade; ***Philipp.:*** Remicade; ***Pol.:*** Remicade; ***Port.:*** Remicade; ***Rus.:*** Remicade (Ремикейд); ***S.Afr.:*** Revellex; ***Singapore:*** Remicade; ***Spain:*** Remicade; ***Swed.:*** Remicade; ***Switz.:*** Remicade; ***Thai.:*** Remicade; ***Turk.:*** Remicade; ***UK:*** Remicade; ***USA:*** Remicade; ***Venez.:*** Remicade.

Isonixin *(rINN)*

Isonixine; Isonixino; Isonixinum. 2-Hydroxy-*N*-(2,6-dimethylphenyl)nicotinamide.

Изониксин

$C_{14}H_{14}N_2O_2 = 242.3.$
CAS — 57021-61-1.

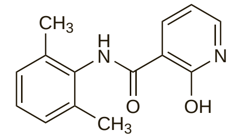

Profile

Isonixin is an NSAID (p.96) that has been used in the management of pain and inflammation associated with musculoskeletal and joint disorders. It has been used in doses of 400 mg two to four times daily by mouth or by rectal suppository. It has also been applied topically as a 2.5% cream.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Nixyn.

Multi-ingredient: ***Spain:*** Nixyn.

Kebuzone *(rINN)*

Kebuzona; Kébuzone; Kebuzonum; Ketophenylbutazone. 4-(3-Oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione.

Кебузон

$C_{19}H_{18}N_2O_3 = 322.4.$
CAS — 853-34-9.
ATC — M01AA06.
ATC Vet — QM01AA06.

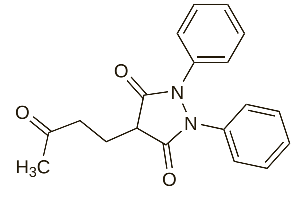

Profile

Kebuzone, a phenylbutazone derivative, is an NSAID (p.96). It has been given for musculoskeletal, joint, and soft-tissue disorders in oral doses of up to 1.5 g daily in divided doses. Kebuzone has also been given as the sodium salt by intramuscular injection in doses equivalent to 1 g of base once or twice daily.

Porphyria. Kebuzone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ketazon†; ***Cz.:*** Ketazon†.
Multi-ingredient: ***Austria:*** Rheumesser; ***Cz.:*** Ketazon Compositum†.

Ketobemidone Hydrochloride *(BANM, rINNM)*

Cétobémidone, chlorhydrate de; Cetobemidone Hydrochloride; Cetobemidoni hydrochloridum; Hidrocloruro de cetobemidona; Ketobemidon-hydrochlorid; Ketobemidonhydroklorid; Ketobemidoni Hydrochloridum; Ketobemidonihydrokloridi; Ketobemidono hidrochloridas. 1-(4-*m*-Hydroxyphenyl-1-methyl-4-piperidyl)propan-1-one hydrochloride.

Кетобемидона Гидрохлорид

$C_{15}H_{21}NO_2$,HCl = 283.8.
CAS — 469-79-4 (ketobemidone); 5965-49-1 (ketobemidone hydrochloride).
ATC — N02AB01.
ATC Vet — QN02AB01.

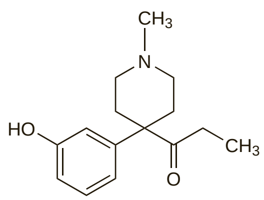

(ketobemidone)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ketobemidone Hydrochloride). White or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 5.5.

Profile

Ketobemidone is an opioid analgesic (p.101). It has been given as the hydrochloride orally, by injection, or rectally, sometimes with an antispasmodic.

◊ References.

1. Al-Shurbaji A, Tokics L. The pharmacokinetics of ketobemidone in critically ill patients. *Br J Clin Pharmacol* 2002 **54:** 583–6.
2. Jylli L, *et al.* Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study. *Acta Anaesthesiol Scand* 2004; **48:** 1256–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Ketodur†; ***Norw.:*** Ketodur†; Ketorax; ***Swed.:*** Ketodur†; Ketogan Novum.
Multi-ingredient: ***Denm.:*** Ketogan; ***Norw.:*** Ketogan; ***Swed.:*** Ketogan.

Ketoprofen *(BAN, USAN, rINN)*

Ketoprofeeni; Ketoprofén; Ketoprofenas; Kétoprofène; Ketoprofeno; Ketoprofenum; RP-19583. (*RS*)-2-(3-Benzoylphenyl)propionic acid.

Кетопрофен

$C_{16}H_{14}O_3$ = 254.3.
CAS — 22071-15-4 (ketoprofen); 57469-78-0 (ketoprofen lysine); 57495-14-4 (ketoprofen sodium).
ATC — M01AE03; M02AA10.
ATC Vet — QM01AE03; QM02AA10.

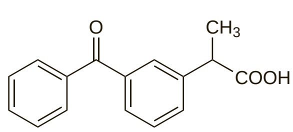

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Ketoprofen). A white or almost white, crystalline powder. M.p. 94° to 97°. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
USP 31 (Ketoprofen). Store in airtight containers.

Dexketoprofen Trometamol *(BANM, rINNM)*

(*S*)-(+)-Dexketoprofen Trometamol; Dexkétoprofène Trométamol; Dexketoprofeno trometamol; Dexketoprofenum Trometamolum.

Декскетопрофен Трометамол

CAS — 22161-81-5 (dexketoprofen).
ATC — M01AE17.
ATC Vet — QM01AE17.

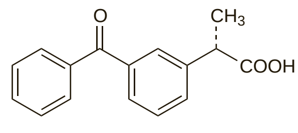

(dexketoprofen)

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

When ketoprofen is given intramuscularly there may be pain at the injection site and occasionally tissue damage. Topical preparations containing ketoprofen may cause application site reactions. Ketoprofen suppositories may cause local irritation; rectal use should be avoided in patients with a history of proctitis or haemorrhoids. Ketoprofen should be used with caution in patients with renal or hepatic impairment; it should not be used in those with severe renal impairment.

Dexketoprofen should be avoided in patients with moderate to severe renal or severe hepatic impairment, and in those with severe heart failure.

Effects on the skin. Contact and photoallergic dermatitis has been seen after topical use of ketoprofen.[1,2] A retrospective study[3] found that of the 139 cases of contact reactions to topical NSAIDs reported to the Spanish Pharmacovigilance System between 1996 and 2001, 84 involved ketoprofen (16 allergy; 68 photoallergy). Totals for other NSAIDs included piroxicam (21), etofenamate (10), piketoprofen (5), salicylates (4), fepradinol (3), diclofenac (3), indometacin (2). phenylbutazone (2), benzydamine (2), aceclofenac (1), naproxen (1), and mabuprofen (1). Analysis indicated that the number of reports for topical ketoprofen was disproportionately high in relation to its usage.

1. Matthieu L, *et al.* Contact and photocontact allergy to ketoprofen: the Belgian experience. *Contact Dermatitis* 2004; **50:** 238–41.
2. Hindsén M, *et al.* Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; **54:** 150–7.
3. Diaz RL, *et al.* Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54:** 239–43.

Hypersensitivity. Life-threatening asthma, urticaria, and angioedema developed in 2 aspirin-sensitive patients after taking ketoprofen 50 mg by mouth.[1] Cardiac and respiratory arrest occurred in an asthmatic patient shortly after taking ketoprofen.[2] Life-threatening asthma has also occurred after topical application of ketoprofen.[3]

There has been a report[4] of delayed skin hypersensitivity in a patient who used a topical gel containing ketoprofen. The reaction recurred on rechallenge to ketoprofen gel but not to a similar gel containing diclofenac. The authors of the report noted that the UK CSM had received 15 reports of skin reactions to ketoprofen gel, including two each of dermatitis and urticaria.

See also Effects on the Skin, above.

1. Frith P, *et al.* Life-threatening asthma, urticaria, and angiœdema after ketoprofen. *Lancet* 1978; **ii:** 847–8.
2. Schreuder G. Ketoprofen: possible idiosyncratic acute bronchospasm. *Med J Aust* 1990; **152:** 332–3.
3. Kashiwabara K, Nakamura H. Analgesic-induced asthma caused by 2.0% ketoprofen adhesive agents, but not by 0.3% agents. *Intern Med* 2001; **40:** 124–6.
4. Oh VMS. Ketoprofen gel and delayed hypersensitivity dermatitis. *BMJ* 1994; **309:** 512.

Myasthenia gravis. There has been a brief report[1] of a cholinergic crisis precipitated by a single oral dose of ketoprofen 50 mg in a patient with well-controlled myasthenia gravis. The patient had previously noted a similar but milder reaction with aspirin, but not with paracetamol.

1. McDowell IFW, McConnell JB. Cholinergic crisis in myasthenia gravis precipitated by ketoprofen. *BMJ* 1985; **291:** 1094.

Pancreatitis. Pancreatitis has been associated with ketoprofen use.[1,2]

1. Cobb TK, Pierce JR. Acute pancreatitis associated with ketoprofen. *South Med J* 1992; **85:** 430–1.
2. Mété D, *et al.* Pancréatite aiguë et kétoprofène. *Gastroenterol Clin Biol* 2001; **25:** 721–2.

Photosensitivity. Ketoprofen causes photosensitivity reactions[1,2] and cross-sensitivity to other drugs, notably the fibrates bezafibrate, ciprofibrate, and fenofibrate, has also been reported. The cross reactions were attributed to the benzoyl ketone structure that the drugs have in common.

See also Effects on the Skin (above).

1. Bagheri H, *et al.* Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. *Drug Safety* 2000; **22:** 339–49.
2. Veyrac G, *et al.* Bilan de l'enquête nationale sur les effets indésirables cutanés du kétoprofène gel enregistrés entre le 01/09/1996 et le 31/08/2000. *Therapie* 2002; **57:** 55–64.

Renal impairment. The elimination half-life and unbound plasma concentrations of dexketoprofen are increased in patients with renal impairment given racemic ketoprofen;[1,2] this appears to be principally attributable to impaired renal clearance of the acyl-glucuronide conjugates in a stereoselective fashion, with subsequent hydrolysis of the unstable conjugate back to the aglycone producing increased plasma-ketoprofen concentrations.[2,3] The authors of one study suggested[3] that dosage adjustments of racemic ketoprofen were indicated only for patients with moderately severe renal failure (creatinine clearance of less than 20 mL/minute).

For advice on the dose of dexketoprofen in patients with renal impairment see under Uses and Administration, below. See also Adverse Effects and Precautions, above.

1. Hayball PJ, *et al.* The influence of renal function on the enantioselective pharmacokinetics and pharmacodynamics of ketoprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1993; **36:** 185–93.
2. Grubb NG, *et al.* Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination. *Br J Clin Pharmacol* 1999; **48:** 494–500.
3. Skeith KJ, *et al.* The influence of renal function on the pharmacokinetics of unchanged and acyl-glucuroconjugated ketoprofen enantiomers after 50 and 100 mg racemic ketoprofen. *Br J Clin Pharmacol* 1996; **42:** 163–9.

Interactions

For interactions associated with NSAIDs, see p.99.

Probenecid delays the excretion of ketoprofen and decreases its extent of protein binding resulting in increased plasma-ketoprofen concentrations. Not unexpectedly, a similar interaction may be seen with dexketoprofen and probenecid.

Pharmacokinetics

Ketoprofen is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 2 hours after an oral dose. When ketoprofen is given with food, the bioavailability is not altered but the rate of absorption is slowed. Ketoprofen is well absorbed from the intramuscular and rectal routes; only a small amount of percutaneous absorption occurs after topical application. Ketoprofen is 99% bound to plasma proteins and substantial concentrations of drug are found in the synovial fluid. The elimination half-life in plasma is about 1.5 to 4 hours. Ketoprofen is metabolised mainly by conjugation with glucuronic acid, and is excreted mainly in the urine.

Ketoprofen possesses a chiral centre. It is usually given as the racemate but its pharmacological actions appear to be due largely to the (*S*)-enantiomer, dexketoprofen. The pharmacokinetics of ketoprofen appear to exhibit little stereoselectivity (but see under Renal Impairment, above).

◊ References.

1. Debruyne D, *et al.* Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. *Clin Pharmacokinet* 1987; **12:** 214–21.
2. Flouvat B, *et al.* Pharmacokinetics of ketoprofen in man after repeated percutaneous administration. *Arzneimittelforschung* 1989; **39:** 812–15.
3. Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. *Clin Pharmacokinet* 1990; **19:** 197–217.
4. Geisslinger G, *et al.* Pharmacokinetics of ketoprofen enantiomers after different doses of the racemate. *Br J Clin Pharmacol* 1995; **40:** 73–5.
5. Barbanoj MJ, *et al.* Pharmacokinetics of dexketoprofen trometamol in healthy volunteers after single and repeated oral doses. *J Clin Pharmacol* 1998; **38:** 33S–40S.
6. Kokki H, *et al.* Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; **40:** 354–9.
7. Barbanoj M-J, *et al.* Clinical pharmacokinetics of dexketoprofen. *Clin Pharmacokinet* 2001; **40:** 245–62.
8. Kokki H, *et al.* Pharmacokinetics of intravenous and rectal ketoprofen in young children. *Clin Pharmacokinet* 2003; **42:** 373–9.
9. Valles J, *et al.* Clinical pharmacokinetics of parenteral dexketoprofen trometamol in healthy subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 7–12.
10. Valles J, *et al.* Single and repeated dose pharmacokinetics of dexketoprofen trometamol in young and elderly subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 13–19.

Uses and Administration

Ketoprofen, a propionic acid derivative, is an NSAID (p.99). Its anti-inflammatory properties may be weaker than those of some other NSAIDs. Ketoprofen is a racemic mixture; in *animal* studies the S-(+) enantiomer, dexketoprofen, has about twice the analgesic activity of ketoprofen by weight.

Ketoprofen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. It is also used in dysmenorrhoea, postoperative pain, in painful and inflammatory conditions such as acute gout or soft-tissue disorders, and to reduce fever. Dexketoprofen is used in the treatment of mild to moderate pain such as musculoskeletal pain, dysmenorrhoea, or dental pain.

In the treatment of rheumatic disorders a usual oral daily dose of ***ketoprofen*** is 100 to 200 mg in 2 to 4 divided doses; modified-release formulations taken once daily may also be used. Some licensed product information suggests initial oral doses of 75 mg three times daily or 50 mg four times daily increased as needed to a maximum of 300 mg daily in divided doses. Ketoprofen may also be given rectally as suppositories in a dose of 100 mg at night or 100 mg twice daily. It is recommended that the total daily combined oral and rectal dose should not exceed 200 mg. The usual oral dose for the treatment of other painful conditions including dysmenorrhoea is 25 to 50 mg every 6 to 8 hours. For details on the use of ketoprofen in patients with hepatic or renal impairment, see below.

Ketoprofen may be given by deep intramuscular injection into the gluteal muscle for acute exacerbations of musculoskeletal, joint, peri-articular and soft-tissue disorders and in the management of pain after orthopaedic surgery. Doses of 50 to 100 mg may be given every 4 hours, up to a maximum dose of 200 mg in 24 hours for up to 3 days. In some countries, ketoprofen has also been given intravenously in similar doses.

Ketoprofen may be applied as a 2.5% gel for local pain relief. Doses vary slightly between preparations: typically, they are applied 2 to 4 times daily for up to 10 days.

Dexketoprofen is given orally as the trometamol salt. Doses are expressed in terms of the base; dexketoprofen trometamol 36.9 mg is equivalent to about 25 mg of dexketoprofen. Usual doses are 12.5 mg every 4 to 6 hours or 25 mg every 8 hours; the total daily dose should not exceed 75 mg. Elderly patients should be started on a total daily dose not exceeding 50 mg. Dose reductions are also necessary in patients with hepatic or renal impairment, see below. It is usually recommended that NSAIDs are taken with or after food to reduce any adverse gastrointestinal effects; however, licensed product information for dexketoprofen states that absorption is delayed if the drug is taken with food and therefore recommends that in acute pain dexketoprofen should be given at least 30 minutes before food.

Ketoprofen has also been used as the lysine and as the sodium salt.

◊ Reviews.

1. Mauleón D, *et al*. Preclinical and clinical development of dexketoprofen. *Drugs* 1996; **52:** 24–46.

Administration in hepatic or renal impairment. No specific dosage recommendations for racemic *ketoprofen* in patients with hepatic or renal impairment are given by UK licensed product information, although the drug is contra-indicated in severe renal impairment and it is advised that the dose be kept as low as possible and renal function be monitored in more moderate renal impairment (but see also Renal Impairment, above). In the USA, however, it has been recommended that patients with hepatic impairment and a serum albumin concentration of less than 3.5 g/dL should be given a maximum initial daily dose of 100 mg orally. Patients with mild renal impairment should be given a maximum daily dose of 150 mg and those with more severe impairment (GFR less than 25 mL/minute per 1.73 m^2 or end-stage renal impairment) should not exceed a maximum daily dose of 100 mg.

UK licensed product information for *dexketoprofen* recommends a reduced initial daily dose of 50 mg orally in patients with mild to moderate hepatic or mild renal impairment. Dexketoprofen should not be used in patients with severe hepatic or moderate to severe renal impairment.

Preparations

BP 2008: Ketoprofen Capsules; Ketoprofen Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Enantyum; Helenil; Orudis†; Profenid†; Salicrem K; ***Austral.:*** Orudis; Oruvail; ***Austria:*** Keprodol†; Profenid; Prontoket; ***Belg.:*** Bi-Rofenid; Fastum; Rofenid; ***Braz.:*** Artrifenil; Artrinid; Artrosil; Bi-Profenid; Ceprofen; Flamador; Ketop†; Profenid; ***Canad.:*** Apo-Keto; Novo-Keto; Orafen†; Orudis†; Rhodis; Rhovail†; ***Chile:*** Bonil; Cirus; Desketo; Dolo-Ketazon; Dolofar; Fastum; Flogofin; Profenid; Relatene; Talflex; ***Cz.:*** Bi-Profenid†; Dexoket; Fastum; Keplat; Ketesse; Ketobene†; Ketonal; Profenid; Prontoflex; Prontoket; Toprec†; ***Denm.:*** Orofen; Orudis; ***Fin.:*** Keto; Ketomex; Ketorin; Orudis; Zon; ***Fr.:*** Bi-Profenid; Ketum; Profenid; Topfena; Toprec; ***Ger.:*** Alrheumun; Effekton mit Ketoprofen; Gabrilen; Ketolist†; Orudis†; Phardol Schmerz; Spondylon; Sympal; Togal Mobil-Gel mit ketoprofen; ***Gr.:*** Drastirel; Farbovil; Ketodur†; Menaril; Nosatel; Oruvail; Profinject†; Totifen; Viaxal; ***Hong Kong:*** Fastum; Mohrus; Orudis; Oruvail; ***Hung.:*** Algoflex; Fastum; Ketodex; Ketospray; Profenid; Prontoket; ***India:*** Rofenid†; ***Indon.:*** Altofen; Fetik; Kaltrofen; Ketesse; Ketros; Lantiflam; Molaflam; Nasaflam; Nazovell; Ovurila; Profecom; Profenid; Profika; Pronalges; Protofen; Remapro; Rematof; Rhetoflam; Suprafenid; ***Irl.:*** Fastum; Keral; Orudis†; Orugesic; Oruvail; ***Israel:*** Ketonal†; Oruvail; Profenid; ***Ital.:*** Alket; Artrosilene; Desketo; Dolgosin; Enantyum; Euketos; Fastum; Flexen; Ibifen; Isofenal; Keplat; Ketartrium; Ketesse; Ketodol; Ketofarm; Ketoplus; Ketoselect; Lasonil CM; Meprofen; Oki; Orudis; Reuprofen; Toprek; Zepelindue†; ***Jpn:*** Mohrus; ***Malaysia:*** Apo-Keto; Fastum; Kenhancer; Ketotop†; Orudis; Oruvail†; Provail†; ***Mex.:*** Arket; Arthril; Bibix; Efiken; K-Profen; Keduril†; Ketoflex; Orudis; Painsik; Profenid; Stadium; ***Neth.:*** Enantyum; Orudis; Oruvail; Oscorel; Rilies; Stadium; ***Norw.:*** Orudis; Zon; ***NZ:*** Orudis; Oruvail; ***Philipp.:*** Ketotop; Orudis; Udzapen; ***Pol.:*** Bi-Profenid; Dexak; Fastum; Febrofen; Ketonal; Ketoprom; Ketopronil; Ketores; Ketospray; Profenid; Ultrafastin; ***Port.:*** Artrofene†; Deflogix†; Enantyum; Fastum; Keplat; Ketesse; Ketofene†; Profenid; Quetral; ***Rus.:*** Artrosilen (Артрозилен); Bystrumgel (Быструмгель); Dexalgin 25 (Дексалгин 25); Fastum (Фастум); Febrofid (Феброфид); Flexen (Флексен); Ketonal (Кетонал); Oki (Оки); ***S.Afr.:*** Fastum; Ketoflam; Myproflam; Orucote†; Oruject†; Oruvail; ***Singapore:*** Apo-Keto; Fastum; Kefentech; Kenhancer; Ketotop†; Oruvail; Provail†; ***Spain:*** Adolquir; Arcental; Badyket†; Enangel; Enantyum; Extraplus; Fastum; Ketesgel; Ketesse; Ketosolan; Orudis; Pyrsal; Quiralam; Quirgel; ***Swed.:*** Orudis; Prodon; Siduro; Zon; ***Switz.:*** Fastum; Ketesse; ***Thai.:*** Fastum; Kaprofen; Lolita; Oruvail; Profenid; Rofepain; Vestam; ***Turk.:*** Fastjel; Keto; Ketofen; Profenid; ***UK:*** Keral; Ketocid; Ketovail; Ketozip†; Larafen; Orudis; Oruvail; Powergel; Tiloket; ***USA:*** Orudis†; Oruvail†; ***Venez.:*** Dolomax; Kelfen; Keto; Keydol; Lindilan; Orofeno; Peindol; Profenid; Profenol†.

Multi-ingredient: *Gr.:* Profenil†; ***Mex.:*** Bifebral; Reumophan.

Ketorolac Trometamol *(BANM, rINNM)*

Ketorolaakkitrometamoli; Kétorolac trométamol; Ketorolac Tromethamine *(USAN)*; Ketorolaco trometamol; Ketorolacum Trometamoli; Ketorolacum trometamolum; Ketorolak Trometamol; Ketorolak z trometamolem; Ketorolaktrometamol; Ketorolak-trometamol; RS-37619-00-31-3. (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1 : 1).

Кеторолак Трометамол

$C_{19}H_{24}N_2O_6$ = 376.4.

CAS — 74103-06-3 (ketorolac); 74103-07-4 (ketorolac trometamol).

ATC — M01AB15; S01BC05.

ATC Vet — QM01AB15; QS01BC05.

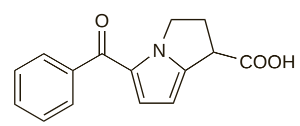

(ketorolac)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ketorolac Trometamol). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 5.7 to 6.7. Protect from light.

USP 31 (Ketorolac Tromethamine). A white to off-white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran; practically insoluble in acetone, in acetonitrile, in butyl alcohol, in dichloromethane, in dioxan, in ethyl acetate, in hexane, and in toluene. pH of a 1% solution in water is between 5.7 and 6.7. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Concern over the high incidence of reported adverse effects with ketorolac trometamol has led to its withdrawal in some countries while in others its permitted dosage and maximum duration of treatment have been reduced.

Adverse effects reported include gastrointestinal disturbances including gastrointestinal bleeding (especially in the elderly), perforation, and peptic ulceration. Hypersensitivity reactions such as anaphylaxis, rash, bronchospasm, laryngeal oedema, and hypotension have also occurred. Other adverse effects reported include drowsiness, dizziness, headache, mental and sensory changes, psychotic reactions, sweating, dry mouth, thirst, fever, convulsions, myalgia, aseptic meningitis, hypertension, dyspnoea, pulmonary oedema, bradycardia, chest pain, palpitations, fluid retention, increases in blood urea and creatinine, acute renal failure, oedema, hyponatraemia, hyperkalaemia, urinary frequency or retention, nephrotic syndrome, flank pain with or without haematuria, purpura, thrombocytopenia, epistaxis, inhibition of platelet aggregation, increased bleeding time, postoperative wound haemorrhage, haematoma, flushing or pallor, and pancreatitis. Severe skin reactions including Stevens-Johnson syndrome and Lyell's syndrome have been reported. Liver function changes may occur; hepatitis and liver failure have been reported. There may be pain at the site of injection.

Ketorolac eye drops may produce transient stinging and other minor symptoms of ocular irritation. As with some other NSAIDs used in the eye, ketorolac has been implicated in reports of corneal toxicity (see p.45).

Incidence of adverse effects. Adverse effects reported with ketorolac are mainly those common to all NSAIDs with gastrointestinal reactions being the most frequent followed by haematological, renal, hypersensitivity, and then neurological reactions. From 1990 to 1993, 97 reactions with a fatal outcome were reported worldwide.[1] The causes of death were: gastrointestinal bleeding or perforation (47 cases); renal impairment or insufficiency (20); anaphylaxis or asthma (7); haemorrhagic reactions (4); and unexplained or miscellaneous causes (19). Concern over the safety of ketorolac has led to adverse reactions being monitored closely and to the implementation of restrictions on dose and duration of treatment (see Uses and Administration, below). A postmarketing surveillance study[2] examined the risks of parenteral ketorolac in 9 900 patients given 10 272 courses of ketorolac. The results indicated a dose-response relationship with average daily ketorolac dose for both gastrointestinal bleeding and operative site bleeding, the expected major risks, and an association between gastrointestinal bleeding and therapy for over 5 days. The risk of serious gastrointestinal bleeding and operative site bleeding was higher for elderly patients [licensed product information recommends that the elderly should not receive daily parenteral doses greater than 60 mg]. Although the overall associations between ketorolac use and both gastrointestinal bleeding and operative site bleeding are small, the risk becomes clinically important as doses increase, in elderly patients, and, for gastrointestinal bleeding only, when used for longer than 5 days.

US product information has consequently emphasised that ketorolac is a potent NSAID and is indicated only for the short-term management of moderate to severe pain and not for minor or chronic painful conditions; its use carries many risks and related adverse effects can be serious especially when used inappropriately. After examining data from the above study the EU Committee for Proprietary Medicinal Products adopted the opinion that ketorolac had a narrow therapeutic margin but that it was indicated for the short-term management of moderate to severe acute postoperative pain.

Further references to ketorolac's adverse effects are given below.[3-12]

1. CSM/MCA. Ketorolac: new restrictions on dose and duration of treatment. *Current Problems* 1993; **19:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 07/11/07)
2. Strom BL, *et al*. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. *JAMA* 1996; **275:** 376–82.
3. Rotenberg FA, Giannini VS. Hyperkalemia associated with ketorolac. *Ann Pharmacother* 1992; **26:** 778–9.
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5. Schoch PH, *et al*. Acute renal failure in an elderly woman following intramuscular ketorolac administration. *Ann Pharmacother* 1992; **26:** 1233–6.
6. Goetz CM, *et al*. Anaphylactoid reaction following ketorolac tromethamine administration. *Ann Pharmacother* 1992; **26:** 1237–8.
7. Randi ML, *et al*. Haemolytic uraemic syndrome during treatment with ketorolac trometamol. *BMJ* 1993; **306:** 186.
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9. Corelli RL, Gericke KR. Renal insufficiency associated with intramuscular administration of ketorolac tromethamine. *Ann Pharmacother* 1993; **27:** 1055–7.
10. Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. *Pediatrics* 1996; **98:** 294–6.
11. Feldman HI, *et al*. Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med* 1997; **126:** 193–9.
12. Reinhart DJ, *et al*. Minimising the adverse effects of ketorolac. *Drug Safety* 2000; **22:** 487–97.

Precautions

As for NSAIDs in general, p.98.

In light of the concern over the toxicity of ketorolac it has been recommended that it should not be used during pregnancy or labour and some recommend that it should not be given to mothers who are breast feeding (but see below).

Ketorolac is contra-indicated in patients with a history of hypersensitivity to aspirin or other NSAIDs, a history of asthma, nasal polyps, bronchospasm, or angioedema, a history of peptic ulceration or gastrointestinal bleeding, in patients with moderate or severe renal impairment, and in those with hypovolaemia or dehydration. Ketorolac should not be given to patients with coagulation or haemorrhagic disorders or those with confirmed or suspected cerebrovascular bleeding. It is contra-indicated as a prophylactic analgesic before surgery and for intraoperative use because of its inhibitory effects on platelets; it should also not be given postoperatively to those who have undergone procedures with a high risk of haemorrhage.

The total daily dose of ketorolac should be reduced in the elderly and in patients weighing less than 50 kg. It is recommended that patients with mild renal impairment should receive a reduced dose of ketorolac and undergo close monitoring of renal function. Ketorolac should be used with caution in heart failure, hepatic impairment and conditions leading to reduction in blood volume or in renal blood flow. Ketorolac should be withdrawn if clinical symptoms of hepatotoxicity develop.

Drowsiness and dizziness may affect the performance of skilled tasks such as driving.

Breast feeding. The concentration of ketorolac distributed into breast milk is very low and a study[1] considered that the amount ingested by the infant would probably be too small to be harmful. The American Academy of Pediatrics[2] also states that there have been no reports of any clinical effect on the infant associated with the use of ketorolac by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. However, the *BNF* and both UK and US licensed product information recommend that ketorolac should be avoided in mothers who are breast feeding.

1. Wischnik A, *et al.* The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *Eur J Clin Pharmacol* 1989; **36:** 521–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

Interactions

For interactions associated with NSAIDs, see p.99.

Ketorolac should not be given to patients already receiving anticoagulants or to those who will require prophylactic anticoagulant therapy, including low-dose heparin. The risk of ketorolac-associated bleeding is also increased by other NSAIDs or aspirin and by pentoxifylline and use together should be avoided. Probenecid increases the half-life and plasma concentrations of ketorolac and the two drugs should not be given together.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Ketorolac trometamol is absorbed after intramuscular or oral doses. At physiological pH ketorolac trometamol dissociates to form an anionic ketorolac molecule which is less hydrophilic than the trometamol salt. The peak plasma concentration of ketorolac is reached within about 30 to 60 minutes; absorption after intramuscular injection may be slower than that after oral doses in some individuals. Ketorolac is over 99% bound to plasma proteins. It does not readily penetrate the blood-brain barrier. Ketorolac crosses the placenta and small amounts of drug are distributed into breast milk. The terminal plasma half-life is about 4 to 6 hours, but is about 6 to 7 hours in the elderly and 9 to 10 hours in patients with renal dysfunction. The major metabolic pathway is glucuronic acid conjugation; there is some *para*-hydroxylation. About 90% of a dose is excreted in urine as unchanged drug and conjugated and hydroxylated metabolites, the remainder is excreted in the faeces.

◊ References.

1. Kauffman RE, *et al.* Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Ther* 1999; **65:** 382–8.
2. Hamunen K, *et al.* Stereoselective pharmacokinetics of ketorolac in children, adolescents and adults. *Acta Anaesthesiol Scand* 1999; **43:** 1041–6.
3. Dsida RM, *et al.* Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002; **94:** 266–70.
4. McAleer SD, *et al.* Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 13–18.

Uses and Administration

Ketorolac, a pyrrolizine carboxylic acid derivative structurally related to indometacin (p.66), is an NSAID (p.99). It is used principally as an analgesic.

Ketorolac is used intramuscularly, intravenously, or orally as the trometamol salt in the short-term management of moderate to severe **postoperative pain**. However, it should be noted that because of concerns over the high incidence of reported adverse effects with ketorolac its dosage and maximum duration of use are restricted. The recommended maximum duration for parenteral therapy is 2 days in the UK, and patients should be transferred to oral therapy as soon as possible; oral use is limited to 7 days. In the USA it is recommended that the maximum combined duration of use of parenteral and oral ketorolac should not exceed 5 days.

- In the UK the recommended initial dose by the *parenteral* route is 10 mg of ketorolac trometamol followed by 10 to 30 mg every 4 to 6 hours as required, although ketorolac may be given as often as every 2 hours in the initial postoperative period if required. The total maximum daily dose is 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg). Intravenous injections should be given over at least 15 seconds. During transfer from parenteral to oral therapy the combined daily dose for all forms of ketorolac trometamol should not exceed 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg) of which no more than 40 mg should be given orally.
- Regimens in use in the USA include a single intramuscular dose of 60 mg or a single intravenous dose of 30 mg, or a multiple-dose regimen comprising 30 mg every 6 hours intramuscularly or intravenously, up to a maximum of 120 mg daily. These doses should be halved in the elderly, those with renal impairment, and those weighing less than 50 kg.
- The recommended *oral* dose in the UK is 10 mg every 4 to 6 hours (every 6 to 8 hours in the elderly) to a maximum of 40 mg daily for a maximum duration of 7 days.
- In the USA the recommended oral dose is 20 mg (10 mg in the elderly, the renally impaired, and those weighing under 50 kg), followed by 10 mg every 4 to 6 hours to a maximum of 40 mg daily.

For doses in children see Administration in Children, below.

Ketorolac trometamol is used as 0.5% eye drops to relieve **ocular itching** associated with seasonal allergic conjunctivitis. Ketorolac trometamol eye drops 0.5% have also been used for the topical treatment of **cystoid macular oedema** and for the prevention and reduction of **inflammation** associated with ocular surgery. In the USA, a 0.4% eye drop is also available for postoperative ocular inflammation.

◊ Reviews.

1. Gillis JC, Brogden RN. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; **53:** 139–88.

Administration in children. In the USA, children aged between 2 to 16 years may be given a single intramuscular dose of 1 mg/kg of ketorolac trometamol up to a maximum of 30 mg or a single intravenous dose of 0.5 mg/kg up to a maximum of 15 mg. In the UK, parenteral ketorolac is only recommended for those aged 16 and over; doses are as for adults (see above).

Oral ketorolac is not licensed for use in children.

Administration in renal impairment. Ketorolac is contra-indicated in patients with moderate to severe renal impairment; for suggested doses in less advanced renal impairment, see Uses and Administration, above.

Preparations

USP 31: Ketorolac Tromethamine Injection; Ketorolac Tromethamine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acular; Dolten; Kelac; Kemanat; Kerarer; Ketopharm; Klenac; Nolarac†; Poenkerat; Sinalgico; Teledol; Tenkdol; Unicalm; ***Austral.:*** Acular; Toradol; ***Austria:*** Acular; ***Belg.:*** Aculare; Taradyl; ***Braz.:*** Acular; Cetrolac; Deocil†; Toradol; Toragesic; ***Canad.:*** Acular; Toradol; ***Chile:*** Acular; Brodifac; Burten; Dilox; Dolgenal; Findedol†; Netaf; Poenkerat; Syndol; ***Denm.:*** Acular; Toradol; ***Fin.:*** Acular; Toradol; ***Fr.:*** Acular; ***Ger.:*** Acular; ***Gr.:*** Acular; ***Hong Kong:*** Acular; Keto; Toradol; ***India:*** Cadolac; Ketanov; Ketlur; Ketodrops; Ketonic†; Torolac; ***Indon.:*** Dolac; Ketopain; Lantipain; Remopain; Rolac; Scelto; Toradol; Toramine; Torasic; Torpain; Trolac; Xevolac; ***Irl.:*** Acular; ***Israel:*** Topadol; ***Ital.:*** Acular; Lixidol; Tora-Dol; ***Malaysia:*** Acular; Ketanov†; Keto; Toradol; ***Mex.:*** Acularen; Ainelac; Aitornet; Alidol; Apotoke; Brunacol; Celfax; Doket; Dolac; Dolcoplaz; Dolikan; Dolotor†; Drometak; Efimerol; Estopein; Exorol; Findol†; Finlac; Geldako; Glicima; Godek; Italker; Kendolit; Koprak; Lacdol; Lacomin; Lenaken; Lorotec; Mavidol; Onemer; Plusindol; Rapix; Rolesen; Rolodiquim; Rometran-K; Sebapain; Supradol; Toloran; Toral; Torkol; Trodorol; Tromedal; Ultilap; Zafidol; ***Neth.:*** Acular; ***Norw.:*** Toradol; ***NZ:*** Acular; ***Philipp.:*** Acular; Ketanov; Ketomed; Kortezor; Toradol; ***Port.:*** Acular; Elipa; Toradol; ***Rus.:*** Adolor (Адолор); Dolac (Долак); Ketalgin (Кеталгин); Ketanov (Кетанов); Ketorol (Кеторол); ***S.Afr.:*** Acular; Tora-Dol; ***Singapore:*** Acular; Keto†; Toradol†; ***Spain:*** Acular; Algikey; Droal; Tonum; Toradol; ***Swed.:*** Toradol; ***Switz.:*** Acular; Tora-Dol; ***Thai.:*** Acular; ***Turk.:*** Acular; ***UK:*** Acular; Toradol; ***USA:*** Acular; Toradol†; ***Venez.:*** Acular†; Dolak; Kelac; Ketorel†; Ketorol†; Notolac; Ocudol; Poenkerat.

Multi-ingredient: ***Mex.:*** Gammadol; Sinergix.

Leflunomide *(BAN, USAN, rINN)*

HWA-486; Leflunomid; Leflunomida; Léflunomide; Leflunomidi; Leflunomidum; RS-34821; SU-101. α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide.

Лефлуномид

$C_{12}H_9F_3N_2O_2$ = 270.2.

CAS — 75706-12-6.

ATC — L04AA13.

ATC Vet — QL04AA13.

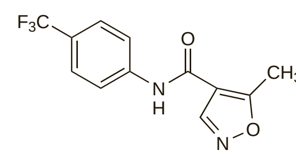

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Leflunomide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Leflunomide). White to almost white powder. Practically insoluble in water; freely soluble in acetone, in acetonitrile, in alcohol, in chloroform, in ethyl acetate, in isopropyl alcohol, and in methyl alcohol. Store at a temperature not exceeding 30°.

Adverse Effects, Treatment and Precautions

Common adverse effects seen with leflunomide are hypertension, gastrointestinal disturbances (particularly diarrhoea), weight loss, headache, dizziness, leucopenia, asthenia, paraesthesia, joint disorders and synovitis, upper respiratory-tract infections, alopecia, eczema, and dry skin. Hypersensitivity reactions may occur and a few cases of Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, or vasculitis have been reported. Hepatotoxicity has occurred. It is usually mild and reversible but rare cases of severe, sometimes fatal, liver disease, including acute hepatic necrosis, have been seen particularly in the first 6 months of therapy. Other adverse effects that have been reported include anxiety, peripheral neuropathy, hypokalaemia, and mild hyperlipidaemia. There have been rare reports of pancytopenia, agranulocytosis, and thrombocytopenia; these effects are more common when leflunomide is given with other myelosuppressive drugs (see Interactions, below). There have been occasional reports of pancreatitis, interstitial lung disease, and severe infections, including fatal sepsis. Renal failure has also been reported.

The active metabolite of leflunomide, A-771726, has a half-life of about 2 weeks. Consequently, the adverse effects of leflunomide may continue even after therapy has been stopped. When severe reactions occur, a drug washout procedure (see below) may be required.

Leflunomide should not be given to immunocompromised patients or to patients with severe infections, hepatic or moderate to severe renal impairment, severe hypoproteinaemia, or bone-marrow dysplasia. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided for the same reason. Blood pressure should be monitored regularly during therapy.

In the UK, liver enzyme values should be checked before beginning therapy and at fortnightly intervals during the first 6 months of treatment; US licensed product information recommends monthly monitoring for the first 6 months. Subsequent monitoring should be carried out at 6- to 8-week intervals. Dosage should be reduced if moderate elevations of liver enzyme values occur (see Administration in Hepatic Impairment, below); for persistent or more severe elevations leflunomide should be stopped and washout procedures begun. Monitoring of liver enzymes should be continued after stopping therapy until they return to within the normal range. Blood counts should also be checked at the same time as liver enzyme values.

Effects on the lungs. Up to December 2006, the Australian Adverse Drug Reactions Advisory Committee had received 142 reports of respiratory symptoms with leflunomide use since its introduction in 2000.[1] Of these, 22 reports mentioned at least one of the following serious reactions: pneumonitis (8), interstitial lung disease (9), lung infiltration (4), or pulmonary fibrosis (3); it was considered that all these were likely to represent interstitial lung disease. Four patients died, but relative causality was difficult to assign as methotrexate was also given in many cases, however, several patients had been on methotrexate long-term without any problems. It was recommended that the pulmonary status of patients should be considered before starting leflunomide and monitored during treatment; if symptoms such as cough or dyspnoea develop or worsen, leflunomide may need to be stopped.

The risk of interstitial lung disease with leflunomide has also been assessed using data from a large cohort study.[2] This study found that, overall, there was a twofold increase in the risk of interstitial lung disease in patients treated with leflunomide compared with those who did not receive leflunomide. However, subgroup analysis showed that this increase was limited to those patients with a history of methotrexate use or interstitial lung disease; in those with no previous methotrexate use or no history of interstitial lung disease, there was no increased risk with leflunomide. See also under Interactions, below.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and interstitial lung disease. *Aust Adverse Drug React Bull* 2006; **25:** 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 13/06/08)
2. Suissa S, *et al.* Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 1435–9.

Effects on the nervous system. Peripheral neuropathy has been associated with leflunomide use.[1-3] Up to October 2006, the Australian Adverse Drug Reactions Advisory Committee had received 659 reports of adverse reactions associated with leflunomide, 30 of which mentioned neuropathy or peripheral neuropathy;[4] leflunomide was the sole suspected drug in 24 of these cases. Recovery was noted after drug withdrawal in 6 patients, of whom 3 underwent washout procedures; however, 15 patients had not recovered at the time of the reports and there was no information on the remaining cases.

1. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther* 2004; **75:** 580–5.
2. Martin K, *et al.* Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005; **64:** 649–50.
3. Metzler C, *et al.* Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide. *Ann Rheum Dis* 2005; **64:** 1798–1800.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and peripheral neuropathy. *Aust Adverse Drug React Bull* 2006; **25:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 13/06/08)

Effects on the skin. A 58-year-old woman developed lupus erythematosus 1 month after starting leflunomide 20 mg daily for treatment of Sjögren's syndrome.[1] The rash resolved within 4 weeks of stopping leflunomide but recurred on 2 separate occasions when she took the drug again.

1. Gensburger D, *et al.* Lupus erythematosus with leflunomide: induction or reactivation? *Ann Rheum Dis* 2005; **64:** 153–5.

Overdose. Unintentional overdoses with leflunomide have been reported in 2 patients. In one case, no adverse effects were seen in a 40-year-old woman who had mistakenly taken both a 100-mg and a 20-mg tablet daily for 28 days;[1] in another case, a 70-year-old man who took 100 mg weekly, in addition to 20 mg daily, for over 2 years was found to have interstitial nephritis which improved after leflunomide was stopped.[2] In both cases, the 100-mg dose was meant to be taken for 2 or 3 days only as a loading dose.

1. Kamali S, *et al.* An unusual overdose of leflunomide in a patient with rheumatoid arthritis. *Ann Pharmacother* 2004; **38:** 1320–1.
2. Haydar AA, *et al.* Chronic overdose of leflunomide inducing interstitial nephritis. *Nephrol Dial Transplant* 2004; **19:** 1334–5.

Pregnancy. Leflunomide is contra-indicated during pregnancy as its active metabolite has been shown to be teratogenic in *animals*. Pregnancy should therefore be excluded before beginning therapy, and licensed product information states that reliable contraception should be used in women of child-bearing potential (UK product information also recommends reliable contraception in men treated with leflunomide). Women wishing to become pregnant should wait for 2 years after stopping therapy, or if this is infeasible, a washout procedure (see below) should be performed and a waiting period of 6 weeks be observed from the time plasma concentrations of the metabolite fall below 20 nanograms/mL before attempting conception. A washout procedure with a waiting period of at least 3 months is recommended in men who wish to father children. Women who become pregnant during therapy should also undergo a washout procedure.

Washout procedure. If serious adverse effects occur during leflunomide therapy, licensed product information recommends that a drug washout procedure is performed. This may also be considered if a patient becomes pregnant while taking leflunomide, or if it is necessary to swap to another disease-modifying antirheumatic drug such as methotrexate.

For the washout procedure, either 8 g of colestyramine is given orally 3 times daily or 50 g of activated charcoal is given orally or via a nasogastric tube 4 times daily. Therapy is normally continued for 11 days, but should be repeated until plasma concentrations of the primary metabolite A-771726 are below 20 nanograms/mL, verified by two separate tests at least 14 days apart.

Interactions

Increased adverse effects may occur if leflunomide is given with other hepatotoxic or myelosuppressive drugs; these effects may also be seen when leflunomide treatment is followed by such drugs without a drug washout procedure (above). The risks of combined use with other disease-modifying antirheumatic drugs, particularly in the long term, have not been studied and such use is not advised in the UK; however, US licensed product information recommends that if long-term combined use is necessary, liver enzyme values and blood counts should be monitored monthly rather than every 6 to 8 weeks (see Adverse Effects, Treatment, and Precautions, above).

See above for precautions about use with live vaccines.

Anticoagulants. For reference to the effect of leflunomide on the activity of *warfarin*, see under Immunosuppressants, p.1431.

Methotrexate. Leflunomide therapy has been rarely associated with pancytopenia. Of the 18 cases (median age 65.5 years) reported in one series, 14 patients were also receiving methotrexate therapy.[1] The pancytopenia was typically severe and required hospitalisation; 5 patients had died, 4 of whom were also taking methotrexate. Time to onset of pancytopenia ranged from 11 days to 4 years. The authors concluded that the risk of pancytopenia during leflunomide treatment appeared to increase when used with methotrexate, and emphasised the importance of ongoing monitoring of blood counts.

Leflunomide therapy has also been rarely associated with interstitial lung disease including interstitial pneumonitis (see above). Up to March 2006, the Centre for Adverse Reactions Monitoring (CARM) in New Zealand[2] had received 7 reports of pneumonitis associated with leflunomide in patients who were also taking methotrexate. Of these, 4 had taken methotrexate (which is also associated with pneumonitis) for more than 1 year. Respiratory symptoms developed 12 to 36 weeks after starting leflunomide therapy; 5 patients recovered, 1 died, and another improved but had some persisting respiratory impairment.

For advice on a drug washout procedure, see above.

1. Chan J, *et al.* Leflunomide-associated pancytopenia with or without methotrexate. *Ann Pharmacother* 2004; **38:** 1206–11.
2. Savage R. Leflunomide and pneumonitis. *Prescriber Update* 2006; **27:** 7–9.

Pharmacokinetics

After oral doses leflunomide undergoes first-pass metabolism in the liver and gut wall to A-771726 (teriflunomide), which is responsible for the majority of the *in vivo* activity. The bioavailability of leflunomide after oral doses ranges from 82 to 95%. Peak plasma concentrations of the active metabolite may occur from 1 to 24 hours after a dose.

A-771726 is more than 99% bound to plasma proteins, mainly albumin. It is some further metabolism. About 43% of a dose is eliminated in the urine, mainly as glucuronides, and 48% is eliminated in the faeces via the bile.

A-771726 has an elimination half-life of about 2 weeks, which is thought to be mainly due to enterohepatic recycling. Colestyramine or activated charcoal are able to interrupt recycling and can therefore accelerate drug elimination.

Studies in *animals* suggest that leflunomide or its metabolites are distributed into breast milk.

◊ References.

1. Rozman B. Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet* 2002; **41:** 421–30.
2. Shi J, *et al.* Population pharmacokinetics of the active metabolite of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis. *J Pharmacokinet Pharmacodyn* 2005; **32:** 419–39.
3. Chan V, *et al.* Population pharmacokinetics and association between A77 1726 plasma concentrations and disease activity measures following administration of leflunomide to people with rheumatoid arthritis. *Br J Clin Pharmacol* 2005; **60:** 257–64.

Uses and Administration

Leflunomide has immunosuppressant and antiproliferative properties. It is used as a disease-modifying antirheumatic drug in the treatment of active rheumatoid arthritis. It is also used in the treatment of active psoriatic arthritis and has been investigated in the management of various solid neoplasms.

Because of the long half-life of the principal metabolite, a loading dose of leflunomide is required to reach steady-state concentrations relatively rapidly. Therapy should start with an oral loading dose of 100 mg once daily for 3 days. However, in practice, the loading dose may be omitted in those patients at an increased risk of adverse effects, particularly haematological or hepatic effects. The maintenance dose is 10 to 20 mg once daily for rheumatoid arthritis and 20 mg once daily for psoriatic arthritis. Dose adjustments may be necessary in patients who develop abnormal liver enzyme values, see below. The therapeutic effect usually starts after 4 to 6 weeks of therapy and further improvements may occur for up to 6 months.

Administration in hepatic impairment. Leflunomide is contra-indicated in patients with hepatic impairment. Patients who develop moderate elevations of liver enzyme values (defined as transaminase levels 2 to 3 times the normal upper limit) while receiving leflunomide treatment should have their dose reduced to 10 mg daily; if necessary, monitoring of liver enzyme values should also be performed at weekly intervals. If moderate elevations persist or if severe elevations occur, leflunomide should be stopped and washout procedures started (see above).

Inflammatory bowel disease. Leflunomide has been tried, with some success, in the management of Crohn's disease (p.1697).

References.

1. Prajapati DN, *et al.* Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. *J Clin Gastroenterol* 2003; **37:** 125–8.

Rheumatoid arthritis. References to the use of leflunomide in rheumatoid arthritis (p.11).

1. Strand V, *et al.* Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; **159:** 2542–50.
2. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. *Drugs* 1999; **58:** 1137–64.
3. Emery P, *et al.* A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39:** 655–65.
4. McCarey DW, *et al.* Leflunomide in treatment of rheumatoid arthritis. *Lancet* 2002; **359:** 1158.
5. Miceli-Richard C, Dougados M. Leflunomide for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2003; **4:** 987–97.

6. Maddison P, *et al.* Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxford)* 2005; **44:** 280–6. Correction. *ibid.*; 569.
7. Silverman E, *et al.* Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2005; **52:** 554–62.
8. Silverman E, *et al.* Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005; **352:** 1655–66.

Spondyloarthropathies. References to the use of leflunomide in ankylosing spondylitis and psoriatic arthritis (see Spondyloarthropathies, p.13).

1. Cuchacovich M, Soto L. Leflunomide decreases joint erosions and induces reparative changes in a patient with psoriatic arthritis. *Ann Rheum Dis* 2002; **61:** 942–3.
2. Kaltwasser JP, *et al.* Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; **50:** 1939–50.
3. Haibel H, *et al.* Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 124–6.
4. van Denderen JC, *et al.* Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 1761–4.
5. Schmitt J, Wozel G. Psoriasis-arthritis—Langzeit-therapie zweier Patienten mit Leflunomid. *J Dtsch Dermatol Ges* 2005; **2:** 763–6.
6. Nash P, *et al.* Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology* 2006; **212:** 238–49.

Preparations

USP 31: Leflunomide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afiancen; Arava; Filartros; Inmunoartro; Lefluar; Molagar†; ***Austral.:*** Arabloc; Arava; ***Austria:*** Arava; ***Belg.:*** Arava; ***Braz.:*** Arava; ***Canad.:*** Arava; ***Chile:*** Arava; Artrimod; ***Cz.:*** Arava; ***Denm.:*** Arava; ***Fin.:*** Arava; ***Fr.:*** Arava; ***Ger.:*** Arava; ***Gr.:*** Arava; ***Hong Kong:*** Arava; ***Hung.:*** Arava; ***India:*** Arava; Lara†; Lefumide; Rumalef; ***Indon.:*** Arava; ***Irl.:*** Arava; ***Israel:*** Arava; ***Ital.:*** Arava; ***Malaysia:*** Arava; ***Mex.:*** Arava; ***Neth.:*** Arava; ***Norw.:*** Arava; ***NZ:*** Arava; ***Philipp.:*** Arava; ***Pol.:*** Arava; ***Port.:*** Arava; ***Rus.:*** Arava (Арава); ***S.Afr.:*** Arava; ***Singapore:*** Arava; ***Spain:*** Arava; ***Swed.:*** Arava; ***Switz.:*** Arava; ***Thai.:*** Arava; ***Turk.:*** Arava; ***UK:*** Arava; ***USA:*** Arava; ***Venez.:*** Arava.

Levacetylmethadol *(rINN)*

l-α-Acetylmethadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); LAM; Levacetilmetadol; Levacetylmetadol; Lévacétylméthadol; Levacetylmethadolum; Levasetyylimetadoli; Levomethadyl Acetate *(USAN)*; *l*-Methadyl Acetate. (−)-4-Dimethylamino-1-ethyl-2,2-diphenylpentyl acetate.

Левацетилметадол

$C_{23}H_{31}NO_2$ = 353.5.
CAS — 1477-40-3 (levomethadyl); 34433-66-4 (levacetylmethadol).
ATC — N07BC03.
ATC Vet — QN07BC03.

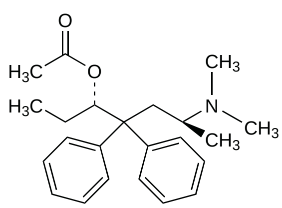

Levacetylmethadol Hydrochloride *(rINNM)*

Hidrocloruro de levacetilmetadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); Lévacétylméthadol, Chlorhydrate de; Levacetylmethadoli Hydrochloridum; Levomethadyl Acetate Hydrochloride *(USAN)*; MK-790. (−)-(3*S*,6*S*)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate hydrochloride.

Левацетилметадола Гидрохлорид

$C_{23}H_{31}NO_2,HCl$ = 390.0.
CAS — 43033-72-3.
ATC — N07BC03.
ATC Vet — QN07BC03.

Profile

Levacetylmethadol, a diphenylheptane derivative, is a long-acting opioid analgesic (p.104); it is a derivative of methadone (p.84). It was used as the hydrochloride in the management of opioid dependence. However, the proarrhythmic effects led to its withdrawal in the EU and the USA.

Preparations

Proprietary Preparations (details are given in Part 3)
Irl.: OrLAAM†; ***Spain:*** OrLAAM†; ***USA:*** OrLAAM†.

Levomethadone Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levometadona; Levometadonhidroklorid; Levometadonhydroklorid; Levometadonihydrokloridi; Levometadono hidrochloridas; Lévométhadone, chlorhydrate de; Levomethadon-hydrochlorid; Levomethadoni hydrochloridum; (−)-Methadone Hydrochloride. (−)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

Левометадона Гидрохлорид

$C_{21}H_{27}NO,HCl$ = 345.9.
CAS — 125-58-6 (levomethadone); 5967-73-7 (levomethadone hydrochloride).

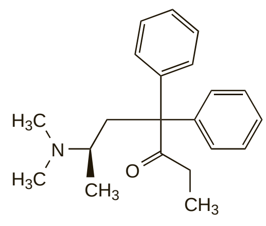

(levomethadone)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Levomethadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

Profile

Levomethadone is an opioid analgesic (p.101). It is the active isomer of racemic methadone (p.82) and is used similarly, as the hydrochloride, in the treatment of severe pain and in the management of opioid dependence.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: L-Polamidon.

Levorphanol Tartrate *(BANM, rINNM)*

Levorphan Tartrate; Levorphanol Bitartrate; Lévorphanol, Tartrate de; Levorphanoli Tartras; Methorphinan Tartrate; Tartrato de levorfanol. (−)-9a-Methylmorphinan-3-ol hydrogen tartrate dihydrate.

Леворфанола Тартрат

$C_{17}H_{23}NO,C_4H_6O_6,2H_2O$ = 443.5.
CAS — 77-07-6 (levorphanol); 125-72-4 (anhydrous levorphanol tartrate); 5985-38-6 (levorphanol tartrate dihydrate).

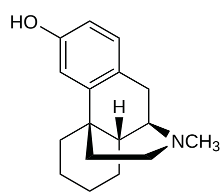

(levorphanol)

Pharmacopoeias. In *US.*
USP 31 (Levorphanol Tartrate). A practically white, odourless, crystalline powder. Soluble 1 in 50 of water and 1 in 120 of alcohol; insoluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Profile

Levorphanol tartrate, a phenanthrene derivative, is a potent opioid analgesic (p.101) used in the management of moderate to severe pain. The analgesic effect usually begins about 10 to 60 minutes after oral doses and lasts up to about 8 hours. A usual initial oral dose of levorphanol tartrate is 2 mg repeated in 6 to 8 hours if necessary; the dose may be increased to 3 mg every 6 to 8 hours, adjusted according to response. The maximum initial daily dose in non-opioid tolerant patients should not exceed 12 mg. Elderly or debilitated patients may require lower doses; initial doses should be reduced by 50% or more.

Levorphanol tartrate has also been given by intramuscular, subcutaneous, or slow intravenous injection for pain relief and for premedication.

Preparations

USP 31: Levorphanol Tartrate Injection; Levorphanol Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Levo-Dromoran†.

Lithium Salicylate

Lithium Salicylicum; Salicilato de litio.

Лития Салицилат

$C_7H_5LiO_3$ = 144.1.
CAS — 552-38-5.

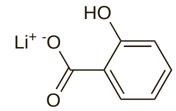

Profile

Lithium salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used in rheumatic disorders, but its use cannot be recommended because of the pharmacological effect of the lithium ion.

Lithium salicylate is used in homoeopathic medicine.

Lonazolac Calcium *(rINNM)*

Calcii Lonazolacum; Lonatsolaakkikalsium; Lonazolac Calcique; Lonazolaco cálcico; Lonazolacum Calcicum; Lonazolakkalcium. Calcium 3-(4-chlorophenyl)-1-phenylpyrazol-4-ylacetate.

Кальций Лоназолак

$C_{34}H_{24}CaCl_2N_4O_4$ = 663.6.
CAS — 53808-88-1 (lonazolac); 75821-71-5 (lonazolac calcium).
ATC — M01AB09.
ATC Vet — QM01AB09.

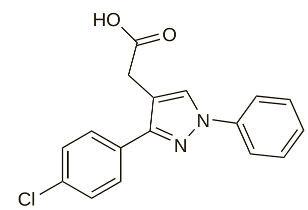

(lonazolac)

Profile

Lonazolac calcium is an NSAID (p.96). It has been given orally and rectally in the treatment of pain, inflammation, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Irritren†; ***Ger.:*** Argun†; arthro akut†; ***Port.:*** Atrilon†.

Lornoxicam *(BAN, USAN, rINN)*

Chlorotenoxicam; Chlortenoxicam; CTX; Lornoksikaami; Lornoksikam; Lornoxicamum; Lornoxicanum; Lornoxikam; Ro-13-9297; TS-110. 6-Chloro-4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-thieno[2,3-e][1,2]-thiazine-3-carboxamide 1,1-dioxide.

Лорноксикам

$C_{13}H_{10}ClN_3O_4S_2$ = 371.8.
CAS — 70374-39-9.
ATC — M01AC05.
ATC Vet — QM01AC05.

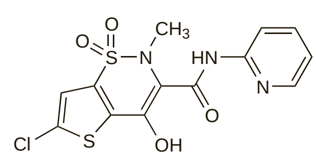

Profile

Lornoxicam, an oxicam derivative, is an NSAID (p.96). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis; it is also used in the treatment of other painful conditions including postoperative pain.

In the treatment of osteoarthritis and rheumatoid arthritis lornoxicam is given in an initial oral daily dose of 12 mg in two or three divided doses; if necessary the daily dose may be increased to a maximum of 16 mg.

Lornoxicam is given in oral doses of 8 to 16 mg daily for the treatment of pain. Similar doses may be given by intravenous or intramuscular injection, although in rare cases the maximum initial daily dose may be increased to 24 mg.

◊ References.

1. Balfour JA, *et al.* Lornoxicam: a review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; **51:** 639–57.
2. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam: a short half-life oxicam. *Clin Pharmacokinet* 1998; **34:** 421–8.
3. Frizziero L, *et al.* Studio a lungo termine su efficacia e sicurezza terapeutica di lornoxicam nell'artrite reumatoide. *Minerva Med* 2002; **93:** 315–20.
4. Thienthong S, *et al.* Treatment of pain after spinal surgery in the recovery room by single dose lornoxicam: a randomized, double blind, placebo-controlled trial. *J Med Assoc Thai* 2004; **87:** 650–5.
5. Zhao H, *et al.* Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin Med Sci J* 2005; **20:** 59–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acabel†; Hypodol; ***Austria:*** Artok; Lornox; Xefo; ***Chile:*** Acabel†; ***Cz.:*** Xefo; ***Denm.:*** Xefo; ***Ger.:*** Telos; ***Gr.:*** Xefo; ***Hung.:*** Xefo; ***Israel:*** Xefo; ***Ital.:*** Noxon; Taigalor; ***Jpn:*** Lorcam; ***Port.:*** Acabel; Bosporon; ***Rus.:*** Xefocam (Ксефокам); ***S.Afr.:*** Xefo; ***Spain:*** Acabel; Bosporon; ***Swed.:*** Xefo; ***Switz.:*** Xefo; ***Thai.:*** Xefo†; ***Turk.:*** Xefo; ***Venez.:*** Acabel.

Loxoprofen Sodium *(rINNM)*

CS-600 (loxoprofen); Loxoprofène Sodique; Loxoprofeno sódico; Natrii Loxoprofenum. Sodium (±)-*p*-[(2-oxocyclopentyl)methyl]hydratropate dihydrate.

Натрий Локсопрофен

$C_{15}H_{17}O_3Na,2H_2O = 304.3.$

CAS — 68767-14-6 (loxoprofen); 80382-23-6 (loxoprofen sodium dihydrate).

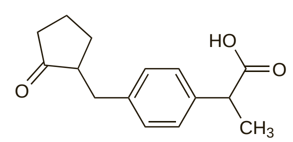

(loxoprofen)

Pharmacopoeias. In *Jpn.*

Profile

Loxoprofen sodium is an NSAID (p.96) given orally for the management of pain and inflammation associated with musculoskeletal and joint disorders or operative procedures. Loxoprofen sodium is given as the dihydrate although doses are expressed in terms of the anhydrous salt. Anhydrous loxoprofen sodium 10 mg is equivalent to about 11.3 mg of loxoprofen sodium dihydrate. A usual oral dose equivalent to 60 mg of the anhydrous form has been given three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Oxeno; ***Braz.:*** Loxonin; ***Jpn:*** Lobu; Loxonin; ***Mex.:*** Loxonin; ***Philipp.:*** Loxonin; ***Thai.:*** Loxonin; ***Venez.:*** Loxonin.

Lumiracoxib *(BAN, USAN, rINN)*

Cox-189; Lumiracoxibum. 2-{[(2-Chloro-6-fluorophenyl)amino]-5-methylphenyl}acetic acid.

Лумиракоксиб

$C_{15}H_{13}ClFNO_2 = 293.7.$

CAS — 220991-20-8.

ATC — M01AH06.

ATC Vet — QM01AH06.

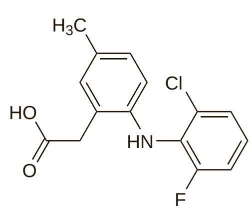

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving lumiracoxib; it should be stopped at the first signs of hypersensitivity.

Lumiracoxib use, particularly at high doses, may cause severe liver toxicity (see Effects on the Liver, below) and its use is contra-indicated in patients with hepatic disease. It should also not be used in those with a history of drug-induced increases in transaminase values greater than 3 times the upper limit of normal (ULN) or in those taking other drugs known to cause clinically significant hepatic toxicity. All patients should have baseline liver function tests before starting lumiracoxib treatment; those in whom transaminases are more than 1.5 times the ULN should not start treatment. Liver function tests should be repeated monthly and lumiracoxib should be stopped in those patients with an increase in transaminases greater than 3 times the ULN; in those with an increase greater than 2 times the ULN, liver function tests should be repeated in 7 days. Patients should be advised to report any symptoms suggestive of liver toxicity such as anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, and jaundice.

Lumiracoxib should not be used in patients with ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.

Lumiracoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and moderate to severe renal impairment associated with a creatinine clearance of less than 50 mL/minute. Caution is recommended when using lumiracoxib in dehydrated patients; it may be advisable to rehydrate patients before giving lumiracoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p.121). The cardiovascular safety of lumiracoxib has been assessed in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[1] which involved over 18 000 patients with osteoarthritis. Lumiracoxib 400 mg daily (2 to 4 times the recommended dose) was compared against either naproxen 1 g daily, or ibuprofen 2.4 g daily; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After a planned treatment duration of 1 year, the incidence of myocardial infarction, stroke, or cardiovascular death with lumiracoxib was found to be similar to that for ibuprofen or naproxen. More events were noted in the lumiracoxib versus naproxen subgroup than in the lumiracoxib versus ibuprofen group; however, this difference was not statistically significant and the authors considered that the higher number of patients with a history of vascular risk in the lumiracoxib versus naproxen subgroup could explain this finding. In addition, it was noted that the incidence of heart failure was less frequent with lumiracoxib although, again, this was not significant; however, blood pressure changes from baseline were significantly less likely with lumiracoxib than with ibuprofen or naproxen.

More recently, a meta-analysis[2] by the manufacturer (which included the above study along with other published and unpublished clinical studies of lumiracoxib in the treatment of osteoarthritis and rheumatoid arthritis) has also found no evidence that the risk of thrombotic events with lumiracoxib is significantly increased when compared to placebo, to naproxen (1 g daily), or to the NSAIDs diclofenac (150 mg daily), ibuprofen (2.4 g daily), celecoxib (up to 400 mg daily), and rofecoxib (25 mg daily) as a group.

For further details on the relative risk of cardiovascular thrombotic events with NSAIDs, see p.97.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p.34.

1. Farkouh ME, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; **364:** 675–84.
2. Matchaba P, *et al.* Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials ≥1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; **27:** 1196–1214.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as lumiracoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information has stated that upper gastrointestinal ulceration and bleeds, in some cases fatal, have occurred with lumiracoxib treatment; consequently it should be used with caution in patients at risk of such events.

Results from controlled studies confirm that NSAIDs selective for COX-2 are associated with a lower incidence of serious gastrointestinal effects. A study[1] in patients with osteoarthritis taking lumiracoxib at supratherapeutic doses (400 mg daily) concluded that there was a lower incidence of definite or probable upper gastrointestinal ulcer complications (bleeding, perforation, or obstruction) after 12 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or naproxen 1 g daily). The incidence of endoscopically-detected ulcers was also less with lumiracoxib than with non-selective NSAIDs. However, the use of low-dose aspirin appeared to nullify any protective gastrointestinal effect of lumiracoxib.

An analysis[2] of pooled data from 15 pre-licensing studies in patients with rheumatoid arthritis or osteoarthritis has also concluded that the risk of upper gastrointestinal ulcers and ulcer complications is less with lumiracoxib than with non-selective NSAIDs (diclofenac, naproxen, and ibuprofen).

1. Schnitzer TJ, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; **364:** 665–74.
2. Hawkey CJ, *et al.* Gastrointestinal tolerability of lumiracoxib in patients with osteoarthritis and rheumatoid arthritis. *Clin Gastroenterol Hepatol* 2006; **4:** 57–66.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as lumiracoxib suggests that these NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Effects on the liver. In August 2007, the regulatory authority in Australia withdrew lumiracoxib from the market after reports of hepatotoxicity.[1,2] In the 6 months since marketing, there had been 8 reports of serious adverse liver reactions resulting in 2 deaths and 2 transplantations. There was some concern that pre-licensing clinical study data seemed to suggest that those patients who developed elevated liver function tests while on lumiracoxib would recover once the drug was stopped; however, in the 8 Australian cases, some patients did not improve because of the severity of the hepatic damage.

In response to the Australian data, the MHRA in the UK reported that it had received 16 reports of suspected adverse reactions to lumiracoxib;[3] of these, one was a case of hepatotoxicity in which the patient recovered after the drug was withdrawn. Worldwide, the MHRA was aware of 11 reports of serious hepatotoxicity including 9 cases of liver failure, 2 deaths, and 3 liver transplants suspected to be at least possibly related to lumiracoxib use. The dose used in most of the cases was higher than the maximum dose of 100 mg daily that is recommended in the UK and other European countries. (Higher maximum daily doses have been licensed in other countries; in Australia, the licensed maximum dose was 400 mg daily for some conditions.) At that time in the UK, new prescribing restrictions on the use of lumiracoxib in osteoarthritis were issued (see Adverse Effects and Precautions, above) while its safety was reviewed by European regulatory authorities. However, lumiracoxib was withdrawn from the Canadian market after Health Canada noted 4 cases of severe hepatotoxicity, including 2 in Canada, associated with the 100-mg dose of lumiracoxib.[4] Following the review of the risks and benefits of lumiracoxib in October 2007, the MHRA reiterated its earlier prescribing restrictions and stated the issue of hepatotoxicity would continue to be monitored. They also advised that, worldwide up until then, there had been 19 cases of severe liver reactions, including 13 of liver failure, 2 deaths, and 3 liver transplants suspected to be possibly related to use of lumiracoxib.[5] However, in November 2007, after a further review of worldwide safety data showed an increased number of serious liver reactions with the 100-mg dose which, in some cases, occurred with short-term use, the MHRA suspended the product licence for lumiracoxib.[6] Subsequently, the EMEA[7] has recommended its withdrawal in the EU.

1. Australian Therapeutic Goods Administration. Urgent advice regarding management of patients taking lumiracoxib (Prexige) (issued 13th August, 2007). Available at: http://www.tga.gov.au/alerts/prexige.htm (accessed 08/11/07)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Withdrawal of lumiracoxib in Australia. *Aust Adverse Drug React Bull* 2008; **27:** 6–7. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0804.pdf (accessed 17/07/08)
3. MHRA. New (interim) restrictions on prescription of lumiracoxib, following concerns over liver safety (issued 24th August, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032098 (accessed 29/08/08)
4. Health Canada. Withdrawal of market authorisation for Prexige. (issued 4th October, 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_141_e.html (accessed 30/10/07)
5. MHRA. Lumiracoxib and liver adverse reactions (issued 16th October, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032831 (accessed 29/08/08)
6. MHRA. Lumiracoxib (Prexige): suspension of marketing authorisations (issued 19th November, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033073 (accessed 29/08/08)
7. EMEA. European Medicines Agency recommends withdrawal of the marketing authorisations for lumiracoxib-containing medicines (issued 13th December, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/PR_Lumiracoxib_57930107en.pdf (accessed 17/07/08)

Interactions

For interactions associated with NSAIDs in general, see p.99. Lumiracoxib may cause liver toxicity and consequently it should not be used with other drugs known to cause clinically significant hepatotoxicity.

There is the possibility that lumiracoxib may decrease the clearance of drugs that are cytochrome P450 CYP2C9 substrates and caution is advised when it is given with CYP2C9 substrates that have a narrow therapeutic index such as phenytoin and warfarin.

Pharmacokinetics

Lumiracoxib is absorbed from the gastrointestinal tract after oral use with peak plasma concentrations reached in about 2 hours.

Protein binding is at least 98%. Lumiracoxib undergoes extensive hepatic metabolism; several enzymes appear to be involved including glucuronosyltransferase and cytochrome P450 isoenzymes. The main oxidative pathway is mediated by the CYP2C9 isoenzyme; however, this does not appear to be the major pathway. Three major metabolites have been identified: 4′-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib, and 4′-hydroxy-5-carboxy-lumiracoxib. The 4′-hydroxy metabolite is active as a cyclo-oxygenase-2 (COX-2) inhibitor although it is less potent than lumiracoxib. The plasma half-life of lumiracoxib is about 4 hours. Slightly more of a dose is excreted in the urine (54%) than in the faeces (about 43%); only about 5% of a dose is excreted unchanged.

◊ References.

1. Scott G, *et al.* Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin Pharmacokinet* 2004; **43:** 467–78.

Uses and Administration

Lumiracoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It has been withdrawn in many countries after reports of hepatotoxicity. In the UK, lumiracoxib was used in the treatment of osteoarthritis of the knee and hip in an oral dose of 100 mg once daily. Higher doses of up to 400 mg daily have been used in some countries but may be associated with an increased risk of hepatotoxicity (see Effects on the Liver, above).

◊ References.

1. Lyseng-Williamson KA, Curran MP. Lumiracoxib. *Drugs* 2004; **64:** 2237–46.
2. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2 selective inhibitor. *Expert Opin Invest Drugs* 2005; **14:** 521–33.
3. Rordorf CM, *et al.* Clinical pharmacology of lumiracoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2005; **44:** 1247–66.
4. Schnitzer TJ, *et al.* Lumiracoxib in the treatment of osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of three dose-response studies. *Curr Med Res Opin* 2005; **21:** 151–61.
5. Berenbaum F, *et al.* Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. *J Int Med Res* 2005; **33:** 21–41.
6. Sheldon E, *et al.* Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; **27:** 64–77.
7. Fleischmann R, *et al.* Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006; **25:** 42–53.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Prexige; ***Austral.:*** Prexige†; ***Braz.:*** Prexige; ***Chile:*** Prexige; ***Hung.:*** Prexige; ***Indon.:*** Prexige; ***NZ:*** Prexige; ***Port.:*** Frexocel†; Hirzia†; ***UK:*** Prexige†.

Lysine Aspirin

Acetilsalicilato de lisina; Aspirin DL-Lysine; Lysiiniasetyylisalisylaatti; Lysinacetylsalicylat; Lysine Acetylsalicylate; DL-Lysine Acetylsalicylate; Lysinum Acetylsalicylicum.

Лизин-Аспирин

$C_{15}H_{22}N_2O_6$ = 326.3.
CAS — 62952-06-1.

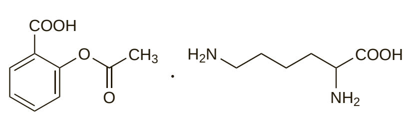

Pharmacopoeias. In *Fr.*

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20. Anaphylactic shock has been reported in patients given lysine aspirin by injection.

Lysine aspirin, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Hypersensitivity. For a suggestion that lysine aspirin might be more suitable than aspirin for the diagnosis of sensitivity to NSAIDs, see under Hypersensitivity on p.21.

Interactions

For interactions associated with aspirin, see p.23.

Uses and Administration

Lysine aspirin has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p.23). When given, lysine aspirin dissociates into lysine and aspirin; aspirin is then hydrolysed to salicylic acid. Lysine aspirin 900 mg is equivalent to about 500 mg of aspirin.

Lysine aspirin is used in the treatment of pain, fever, and rheumatic disorders. It is given in oral doses equivalent to 0.5 to 1 g of aspirin, repeated every 4 hours as needed up to a maximum of 3 g of aspirin daily (2 g daily in the elderly) for pain and fever. The dose for rheumatic disorders is equivalent to 3 to 6 g of aspirin daily in 3 or 4 divided doses. Lysine aspirin is also given intramuscularly or intravenously in similar doses; the maximum daily parenteral dose is equivalent to 4 g of aspirin for very severe pain and to 6 g of aspirin for rheumatic disorders.

Lysine aspirin is also used with metoclopramide in the treatment of migraine.

Lysine aspirin has also been used in the management of thromboembolic disorders.

Headache. Some references to the use of lysine aspirin, often with metoclopramide, in the treatment of migraine.

1. Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–6.
2. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. *Cephalalgia* 1999; **19:** 581–8.
3. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks: comparison with placebo and oral sumatriptan. *Funct Neurol* 2000; **15** (suppl 3): 196–201.

Nasal polyps. Two long-term controlled studies[1] suggested that topical (endonasal) lysine aspirin may be effective in preventing the recurrence of nasal polyps after surgical removal (see p.1508) in both aspirin-tolerant and aspirin-sensitive patients. This effect may be attributed to the non-specific anti-inflammatory properties of lysine aspirin. Although no adverse effects were reported in this study, hypersensitivity reactions have been seen after use of salicylates in the presence of nasal polyps (see Hypersensitivity under Adverse Effects of Aspirin, p.21).

In another study[2] intranasal lysine aspirin did not show significant clinical benefit in preventing the recurrence of nasal polyps when compared with placebo. However, significant improvement at a microscopic level was noted.

1. Nucera E, *et al.* Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax* 2000; **55** (suppl 2): S75–78.
2. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope* 2005; **115:** 1385–90.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aspirina; Corplus†; Decitriol; Yectaspirin; ***Belg.:*** Aspegic; Cardegic; ***Cz.:*** Aspegic†; Dolorosan†; Kardegic; ***Fr.:*** Aspegic; Cardiosolupsan; Kardegic; ***Ger.:*** Aspisol†; ***Gr.:*** Aspicalm; Egicalm; Egicalm Cardio; ***Hung.:*** Aspegic; Kardegic; Kardiren†; ***Israel:*** Lysoprin†; ***Ital.:*** Aspegic; Aspidol†; Cardirene; Flectadol; ***Malaysia:*** Aspegic†; ***Mex.:*** Coraspir; Kardegic; ***Neth.:*** Aspegic; Cardegic; ***Pol.:*** Laspal; ***Port.:*** Aspegic; Inesprin; Intraspir; Kardegic; Lisaspin; Tiplac†; ***Spain:*** ASL; Inyesprin; Lysinotol†; Solusprin†; ***Switz.:*** Alcacyl instantanee; Aspegic; Kardegic; ***Venez.:*** Asalis†.

Multi-ingredient: ***Belg.:*** Migpriv; ***Chile:*** Dolotol 12; ***Cz.:*** Migpriv†; ***Denm.:*** Migpriv†; ***Fin.:*** Migpriv; ***Fr.:*** Aspegic Codeine†; Migpriv; ***Gr.:*** Premig; ***Hung.:*** Migpriv; ***Ital.:*** Migpriv; Migraprim; ***Mex.:*** Antigram; ***Neth.:*** Migrafin; ***Norw.:*** Migpriv†; ***Pol.:*** Migpriv; ***Spain:*** Fluxal†; ***Swed.:*** Migpriv; ***Switz.:*** Migpriv; ***UK:*** Migramax.

Magnesium Salicylate

Salicilato magnésico.

Магния Салицилат

$C_{14}H_{10}MgO_6,4H_2O$ = 370.6.
CAS — 18917-89-0 (anhydrous magnesium salicylate); 18917-95-8 (magnesium salicylate tetrahydrate).

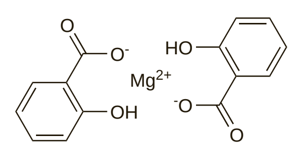

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Magnesium Salicylate). A white, odourless, efflorescent, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20. Magnesium salicylate should also be used with caution in renal impairment because of the risk of hypermagnesaemia.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed drug information extends this precaution to magnesium salicylate.

Interactions

For interactions associated with salicylates, see Aspirin, p.23.

Uses and Administration

Magnesium salicylate has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p.23). Anhydrous magnesium salicylate 1 g is equivalent to about 1.2 g of aspirin. It is used in the treatment of pain and fever and has been used in the management of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and other arthritides. Usual oral doses of magnesium salicylate, expressed in terms of anhydrous magnesium salicylate, are about 300 to 600 mg every 4 hours for pain or fever.

Preparations

USP 31: Magnesium Salicylate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Rati Salil E†; ***Canad.:*** Herbogesic; ***USA:*** Backache Maximum Strength Relief; Bayer Select Maximum Strength Backache; Doans; Magan; Mobidin; Momentum Muscular Backache Formula; MST; Novasal; Nuprin Backache†.

Multi-ingredient: ***Cz.:*** Cholagol; ***Hung.:*** Cholagol; ***Rus.:*** Cholagol (Холагол); ***USA:*** Cafgesic Forte; Combiflex ES; Durabac Forte; Extra Strength Doans PM; Mobigesic; Painaid BRF Back Relief Formula; Tetra-Mag.

Meclofenamic Acid *(BAN, USAN, rINN)*

Acide Méclofénamique; Ácido meclofenámico; Acidum Meclofenamicum; CI-583; INF-4668. *N*-(2,6-Dichloro-*m*-tolyl)anthranilic acid.

Меклофенамовая Кислота

$C_{14}H_{11}Cl_2NO_2$ = 296.1.
CAS — 644-62-2.
ATC — M01AG04; M02AA18.
ATC Vet — QM01AG04; QM02AA18.

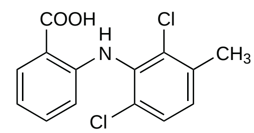

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Meclofenamic Acid). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in ether; soluble in dimethylformamide and in 1M sodium hydroxide.

Meclofenamate Sodium *(BANM, USAN, rINNM)*

Méclofénamate de Sodium; Meclofenamato sódico; Natrii Meclofenamas.

Натрий Меклофенамат

$C_{14}H_{10}Cl_2NNaO_2,H_2O$ = 336.1.
CAS — 6385-02-0.

Pharmacopoeias. In *US.*

USP 31 (Meclofenamate Sodium). A white to creamy white, odourless to almost odourless, crystalline powder. Freely soluble in water, the solution sometimes being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; the solution is clear above pH 15. Slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Incidence of adverse effects. The commonest adverse effect in 2500 patients given meclofenamate sodium was gastrointestinal disturbance.[1] Diarrhoea occurred in 11.2% of patients in double-blind studies and 32.8% of patients in long-term studies (up to 3 years). Ulcers were detected in 22 patients during therapy and skin rashes occurred in 4% of patients. Transient increases in serum aminotransferases and BUN occurred in some patients.

1. Preston SN. Safety of sodium meclofenamate (Meclomen™). *Curr Ther Res* 1978; **23** (suppl 4S): S107–12.

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with meclofenamate therapy.

1. Wishner AJ, Milburn PB. Meclofenamate sodium-induced agranulocytosis and suppression of erythropoiesis. *J Am Acad Dermatol* 1985; **13:** 1052–3.
2. Rodriguez J. Thrombocytopenia associated with meclofenamate. *Drug Intell Clin Pharm* 1981; **15:** 999.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Meclofenamate sodium is readily absorbed when given orally. Peak plasma concentrations occur about 0.5 to 2 hours after ingestion. Meclofenamate is over 99% bound to plasma proteins. The plasma elimination half-life of meclofenamate sodium is about 2 to 4 hours. It is metabolised by oxidation, hydroxylation, dehalogenation, and conjugation with glucuronic acid and excreted in urine mainly as glucuronide conjugates of the metabolites. About 20 to 30% is recovered in the faeces. One of the metabolites, a 3-hydroxymethyl compound, is reported to be active although to a lesser extent than the parent drug.

◊ References.

1. Koup JR, *et al.* A single and multiple dose pharmacokinetic and metabolism study of meclofenamate sodium. *Biopharm Drug Dispos* 1990; **11:** 1–15.

Uses and Administration

Meclofenamic acid, an anthranilic acid derivative similar to mefenamic acid (below), is an NSAID (p.99). It is given orally as the sodium salt in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, in mild to moderate pain, and in dysmenorrhoea and menorrhagia.

Doses of meclofenamate sodium are expressed in terms of the equivalent amount of meclofenamic acid. Meclofenamic acid 100 mg is equivalent to about 113.5 mg of meclofenamate sodium. In arthritic conditions it is given in doses equivalent to 200 to 400 mg daily; daily doses are usually given in 3 or 4 divided doses. For relief of mild to moderate pain doses are 50 to 100 mg every 4 to 6 hours; the daily dose should not exceed 400 mg. The dose in the treatment of dysmenorrhoea and menorrhagia is 100 mg three times daily for up to 6 days during menstruation.

Meclofenamic acid has been given as a rectal suppository and is also used in veterinary medicine.

Preparations

USP 31: Meclofenamate Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Chile: Meclomen; ***Ital.:*** Lenidolor; Meclodol†; Movens; ***Spain:*** Meclomen†.

Mefenamic Acid *(BAN, USAN, rINN)*

Acide méfénamique; Ácido mefenámico; Acidum mefenamicum; CI-473; CN-35355; INF-3355; Kwas mefenamowy; Kyselina mefenamová; Mefenaamihappo; Mefenamik Asit; Mefenaminsav; Mefenamo rūgštis; Mefenamsyra. *N*-(2,3-Xylyl)anthranilic acid.

Мефенамовая Кислота

$C_{15}H_{15}NO_2$ = 241.3.

CAS — 61-68-7.

ATC — M01AG01.

ATC Vet — QM01AG01.

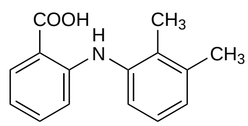

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Mefenamic Acid). A white to almost white, microcrystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; dissolves in dilute solutions of alkali hydroxides.

USP 31 (Mefenamic Acid). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in chloroform; soluble in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Treatment should be stopped if diarrhoea and rashes occur. Other effects reported include drowsiness, and effects on the blood such as thrombocytopenia, occasionally haemolytic anaemia, and rarely aplastic anaemia. Convulsions may occur on overdosage.

Mefenamic acid is contra-indicated in patients with inflammatory bowel disease. Licensed product information recommends that blood counts and liver and renal function should be monitored during long-term therapy. Drowsiness may affect the performance of skilled tasks.

Mefenamic acid may give a false positive in some tests for the presence of bile in the urine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given mefenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of mefenamic acid distributed into breast milk is too small to be harmful to a breast-fed infant. An early study[2] confirms that the distribution of mefenamic acid into breast milk is minimal. However, licensed product information contra-indicates the use of mefenamic acid in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Buchanan RA, *et al.* The breast milk excretion of mefenamic acid. *Curr Ther Res* 1968; **10:** 592–6.

Effects on the blood. References to haematological reactions in patients taking mefenamic acid including haemolytic anaemia,[1] leucopenia,[2] neutropenia,[3] and agranulocytosis.[4]

1. Scott GL, *et al.* Autoimmune haemolytic anaemia and mefenamic acid therapy. *BMJ* 1968; **3:** 534–5.
2. Burns A, Young RE. Mefenamic acid induced leucopenia in the elderly. *Lancet* 1984; **ii:** 46.
3. Handa SI, Freestone S. Mefenamic acid-induced neutropenia and renal failure in elderly females with hypothyroidism. *Postgrad Med J* 1990; **66:** 557–9.
4. Muroi K, *et al.* Treatment of drug-induced agranulocytosis with granulocyte-colony stimulating factor. *Lancet* 1989; **ii:** 55.

Effects on the gastrointestinal tract. Reversible steatorrhoea has occurred[1] with mefenamic acid; it may also provoke colitis in patients without a history of this condition.[2]

1. Marks JS, Gleeson MH. Steatorrhoea complicating therapy with mefenamic acid. *BMJ* 1975; **4:** 442.
2. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.

Effects on the kidneys. Nonoliguric renal failure has occurred in elderly patients who had had diarrhoea and vomiting while taking mefenamic acid and had continued to take the drug. It is normally recommended that mefenamic acid be stopped in the event of diarrhoea and it was suggested that in these patients the gastrointestinal toxicity had led to fluid and electrolyte depletion, thus predisposing these patients to mefenamic acid's nephrotoxicity.[1] There has been a subsequent report[2] of nonoliguric renal failure in elderly patients given mefenamic acid for musculoskeletal pain.

1. Taha A, *et al.* Non-oliguric renal failure during treatment with mefenamic acid in elderly patients: a continuing problem. *BMJ* 1985; **291:** 661–2.
2. Grant DJ, MacConnachie AM. Mefenamic acid is more dangerous than most. *BMJ* 1995; **311:** 392.

Effects on the skin. Bullous pemphigoid, together with haemolytic anaemia and diarrhoea,[1] and fixed drug eruptions[2-4] have been associated with the use of mefenamic acid. Additionally, Stevens-Johnson syndrome, together with cholestatic hepatitis and haemolytic anaemia, in one patient has been attributed to mefenamic acid.[5] It is generally recommended that mefenamic acid should be withdrawn if skin reactions develop.

1. Shepherd AN, *et al.* Mefenamic acid-induced bullous pemphigoid. *Postgrad Med J* 1986; **62:** 67–8.
2. Wilson CL, Otter A. Fixed drug eruption associated with mefenamic acid. *BMJ* 1986; **293:** 1243.
3. Long CC, *et al.* Fixed drug eruption to mefenamic acid: a report of three cases. *Br J Dermatol* 1992; **126:** 409–11.
4. Rallis E. 'Dalmatian dog'-like skin eruption (two cases of multifocal fixed drug eruption induced by mefenamic acid). *J Eur Acad Dermatol Venereol* 2005; **19:** 753–5.
5. Chan JCN, *et al.* A case of Stevens-Johnson syndrome, cholestatic hepatitis and haemolytic anaemia associated with use of mefenamic acid. *Drug Safety* 1991; **6:** 230–4.

Overdosage. Mefenamic acid overdose has been associated with CNS toxicity, especially with convulsions.[1] Coma[2,3] has also been reported.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Gössinger H, *et al.* Coma in mefenamic acid poisoning. *Lancet* 1982; **ii:** 384.
3. Hendrickse MT. Mefenamic acid overdose mimicking brainstem stroke. *Lancet* 1988; **ii:** 1019.

Pancreatitis. A report of pancreatitis associated with mefenamic acid.[1]

1. van Walraven AA, *et al.* Pancreatitis caused by mefenamic acid. *Can Med Assoc J* 1982; **126:** 894.

Porphyria. Mefenamic acid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Mefenamic acid is absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 4 hours after ingestion. The plasma elimination half-life is reported to be about 2 to 4 hours. Mefenamic acid is more than 90% bound to plasma proteins. It is distributed into breast milk. Mefenamic acid is metabolised by the cytochrome P450 isoenzyme CYP2C9 to 3-hydroxymethyl mefenamic acid, which may then be oxidised to 3-carboxymefenamic acid. Over 50% of a dose may be recovered in the urine, as unchanged drug or, mainly, as conjugates of mefenamic acid and its metabolites.

Uses and Administration

Mefenamic acid, an anthranilic acid derivative, is an NSAID (p.99), although its anti-inflammatory properties are considered to be minor.

It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, and dysmenorrhoea, in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and in menorrhagia.

In the UK, the usual oral dose is 500 mg three times daily. US licensed product information recommends an initial dose of 500 mg followed by 250 mg every 6 hours as needed. In addition, in the USA, when mefenamic acid is used in the treatment of mild to moderate pain in adults and adolescents aged 14 years and over, it is also recommended that it should not be given for longer than 7 days at a time.

For doses of mefenamic acid in children, see below.

Administration in children. In the UK, licensed product information states that mefenamic acid may be used in children for the treatment of Still's disease (see Juvenile Idiopathic Arthritis, p.10) and fever; however, the *BNFC* does not recommend mefenamic acid for juvenile idiopathic arthritis, nor for postoperative or mild to moderate pain. A suggested oral dose of mefenamic acid for children over 6 months of age is 25 mg/kg daily in divided doses. Treatment in children should be given for no longer than 7 days unless they are receiving mefenamic acid for juvenile idiopathic arthritis.

Preparations

BP 2008: Mefenamic Acid Capsules; Mefenamic Acid Tablets;
USP 31: Mefenamic Acid Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Ponstil; ***Austral.:*** Mefic; Ponstan; ***Austria:*** Parkemed; ***Braz.:*** Ponstan; Pontin†; ***Canad.:*** Ponstan†; ***Chile:*** Algex; Algifemin; Dolcin†; Flipal; Sicadol; Tanston; Templadol; ***Fin.:*** Ponstan; ***Fr.:*** Ponstyl; ***Ger.:*** Parkemed†; Ponalar†; ***Gr.:*** Acinic; Aidol; Ponstan; Vidan; ***Hong Kong:*** Dyspen†; Hamitan; Hostan; Medicap; Mefa; Mefamic; Mefic; Namic; Napan; Pekaso; Ponstan; Pontacid; Sefmic; ***Hung.:*** Ponmel; ***India:*** Dysmen-500†; Ponstan; ***Indon.:*** Analspec; Asam; Asimat; Benostan; Cetalmic; Corstanal; Datan; Dolfenal; Dolos; Dystan; Femisic; Fensik; Gitaramin; Lapistan; Licostan; Mectan; Mefast; Mefinal; Mefinter; Mefix; Menin; Molasic; Nichostan; Opistan; Ponalar; Poncofen; Pondex; Ponsamic; Ponstan; Ponstelax; Stanalin; Stanza; Stelpon; Topgesic; Tropistan; ***Irl.:*** Mefac; Ponalgic; Ponmel; Ponstan; ***Ital.:*** Lysalgo; ***Malaysia:*** Beafemic; Mefen†; Mefic; Namic; Napan; Pongesic†; Ponstan; Pontalon; ***Mex.:*** Artriden; Namifen; Ponstan; ***NZ:*** Ponstan; ***Philipp.:*** Acidan; Afligec; Analcid; Aprostal; Atmose; Calibral; Dolfenal; Dolmetine; Dolsten; Escandar; Eurostan; Finox; Gardan; Gisfen; Hispen; Inflasic; Istan; Kramon; Laffed; Mecid A; Mefenax; Metaflam; Neostan; Penomor; Ponser; Ponstan; Pontaser; Ralgec; Revalan; Selmac; Senflam; Spegic; Suprazen; Tynostan; Vamgesic; Vandifen; Zanovic; ZapAn; Zestan; ***Pol.:*** Mefacit; ***Port.:*** Ponstan; ***S.Afr.:*** Fenamin; Ponac; Ponstan; Ponstel; ***Singapore:*** Beafemic; Mefacap†; Mefenix; Ponstan†; Pontalon; Pontyl†; ***Spain:*** Coslan; ***Switz.:*** mefe-basan†; Mefenacide; Melur; Mephadolor; Ponstan; Spiralgine; ***Thai.:*** Conamic; Dolfen; Dolfenal†; Dyspen†; Femen; Fenamic; Gandin; Manic; Manomic; Masafen; Mednil; Mefa; Mefen; Mefenan; Namic; Painnox; Panamic; Pefamic†; Pondnadysmen; Ponnesia; Ponstan; Prostan; Pynamic; Sefmic; Vestan; ***Turk.:*** Ponstan; Rolan; ***UK:*** Dysman†; Ponstan; ***USA:*** Ponstel; ***Venez.:*** Ponstan.

Multi-ingredient: ***India:*** Cyclo-Meff; Dysmen; Dysmen Forte; Meftal Forte; Spasmonil Forte; Spasmonil Plus; Tranfib MF; Ze-Spas; ***Thai.:*** Difemic; Mainnox; Med-Anspasmic†.

Meloxicam *(BAN, USAN, rINN)*

Meloksikaami; Meloksikam; Méloxicam; Meloxicamum; Meloxikam; UH-AC-62; UH-AC-62XX. 4-Hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Мелоксикам

$C_{14}H_{13}N_3O_4S_2$ = 351.4.

CAS — 71125-38-7.

ATC — M01AC06.

ATC Vet — QM01AC06.

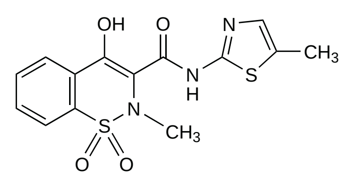

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2008 (Meloxicam). A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

USP 31 (Meloxicam). A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Incidence of adverse effects. Between September 1996, when meloxicam was first marketed in the UK, and mid-June 1998 the UK CSM had received a total of 773 reports of 1339 suspected adverse reactions for meloxicam.[1] Of all the reactions 41% were gastrointestinal and of these 18% involved gastrointestinal perforation, ulceration and/or bleeding; the mean age of the patients involved was 64 years. Although most patients recovered after withdrawal of meloxicam and/or treatment, 5 died. A total of 193 reactions involved the skin, the most common being pruritus, rash, and urticaria. There were also reports of angioedema (25), photosensitivity (12), and bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome (5). No patients died from skin reactions and most recovered after meloxicam was withdrawn. Other frequently reported reactions were neurological (mostly headache), cardiovascular (oedema and palpitations), dizziness, flushing, and fatigue. A prescription event monitoring study has also analysed events reported with meloxicam use.[2] In a cohort of 19 087 patients who had received meloxicam some time between December 1996 and March 1997, 203 patients had had 252 events considered to be suspected adverse reactions. The majority of reactions were not serious or were labelled adverse effects of meloxicam. Rare, serious suspected adverse reactions included 2 reports of thrombocytopenia and 1 each of interstitial nephritis and idiosyncratic liver abnormality. The most frequent gastrointestinal event was dyspepsia; other more serious gastrointestinal events occurring during meloxicam exposure included upper gastrointestinal bleeding (33 reports) and peptic ulcer (19 reports). However it was considered that the incidence of gastrointestinal disturbance was low in the absence of gastrointestinal risk factors. Adverse drug reactions reported during the first year of marketing of meloxicam to the Swedish Medical Products Agency suggested a similar safety profile to other NSAIDs.[3] Of the 15 reports, 6 were for gastrointestinal disturbances and 5 involved skin reactions.

1. CSM/MCA. Meloxicam (Mobic): gastrointestinal and skin reactions. *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Martin RM, *et al.* The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study. *Br J Clin Pharmacol* 2000; **50:** 35–42.
3. Anonymous. Meloxicam safety similar to other NSAIDs. *WHO Drug Information* 1998; **12:** 147.

Effects on the gastrointestinal tract. It is generally accepted that inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of NSAIDs, and that selective inhibition of the other isoform, COX-2, by NSAIDs such as meloxicam may cause less gastrotoxicity than that seen with the non-selective inhibition of traditional NSAIDs. However, there has been little convincing evidence that the risk of severe gastrointestinal events is lower with meloxicam than with other NSAIDs at equi-effective doses.[1] Two large multicentre studies[2,3] have reported a lower incidence of gastrointestinal adverse effects with meloxicam than with non-selective cyclo-oxygenase inhibitors (diclofenac[2] or piroxicam[3]) but in one of these[2] the dose of meloxicam given also appeared to be less effective than the reference drug. A more recent systematic review[4] also found a lower risk of serious gastrointestinal toxicity with meloxicam 7.5 mg daily when compared with diclofenac (100 or 150 mg daily), naproxen (500 mg twice daily), or piroxicam (20 mg daily); however, when given at a dose of 15 mg daily, the risk of toxicity with meloxicam was significantly lower only when compared with piroxicam.

Individual case reports of gastrointestinal toxicity with meloxicam included one of ischaemic colitis associated with high-dose (15 mg daily) meloxicam treatment.[5]

1. Anonymous. Meloxicam—a safer NSAID? *Drug Ther Bull* 1998; **36:** 62–4.
2. Hawkey C, *et al.* Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998; **37:** 937–45.
3. Dequeker J, *et al.* Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998; **37:** 946–51.
4. Singh G, *et al.* Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med* 2004; **117:** 100–106.
5. Garcia B, *et al.* Ischaemic colitis in a patient taking meloxicam. *Lancet* 2001; **357:** 690.

Precautions

As for NSAIDs in general, p.98.

Meloxicam should be avoided in severe hepatic impairment, in bleeding disorders, and in patients with renal failure unless receiving dialysis. Rectal use should be avoided in patients with a history of proctitis, haemorrhoids, or rectal bleeding.

Renal impairment. The pharmacokinetics of meloxicam were not substantially altered in patients with a creatinine clearance (CC) of 41 to 60 mL/minute compared with those with normal renal function.[1] In those with a CC of 20 to 40 mL/minute, total plasma-meloxicam concentrations were lower but meloxicam free fractions were higher. Such free meloxicam concentrations were similar to the other groups. On the basis of these results, it was suggested that it was not necessary to reduce meloxicam doses in patients with a CC greater than 20 mL/minute.

1. Boulton-Jones JM, *et al.* Meloxicam pharmacokinetics in renal impairment. *Br J Clin Pharmacol* 1997; **43:** 35–40.

Interactions

For interactions associated with NSAIDs, see p.99.

Colestyramine increases the clearance and decreases the half-life of meloxicam.

Pharmacokinetics

Meloxicam is well absorbed after oral or rectal doses with peak plasma concentrations reached in up to 6 hours. It is 99% bound to plasma proteins. Meloxicam has a plasma-elimination half-life of about 20 hours. It is extensively metabolised, mainly by oxidation to its major metabolite, 5′-carboxymeloxicam. *In vitro* studies suggest that the cytochrome P450 isoenzyme CYP2C9 plays an important role in the metabolism of meloxicam with CYP3A4 involved to a lesser degree. Meloxicam, in the form of metabolites, is excreted in similar amounts in the urine and in the faeces; less than 5% of a dose is excreted unchanged. The volume of distribution is increased in renal failure.

◊ References.

1. Narjes H, *et al.* Pharmacokinetics and tolerability of meloxicam after i.m. administration. *Br J Clin Pharmacol* 1996; **41:** 135–9.
2. Türck D, *et al.* Clinical pharmacokinetics of meloxicam. *Arzneimittelforschung* 1997; **47:** 253–8.
3. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam: a cyclooxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999; **36:** 115–26.
4. Meineke I, Türck D. Population pharmacokinetic analysis of meloxicam in rheumatoid arthritis patients. *Br J Clin Pharmacol* 2003; **55:** 32–8.
5. Burgos-Vargas R, *et al.* Pharmacokinetics of meloxicam in patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2004; **44:** 866–72.

Renal impairment. For reference to the pharmacokinetics of meloxicam in renal impairment, see under Precautions, above.

Uses and Administration

Meloxicam, an oxicam derivative, is an NSAID (p.99). It is reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). Meloxicam is used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis. It may also be used in the treatment of juvenile idiopathic arthritis.

In the treatment of rheumatoid arthritis and ankylosing spondylitis, meloxicam is given in a usual oral dose of 15 mg daily as a single dose. Those with an increased risk of adverse reactions should be started on 7.5 mg daily. A dose of 7.5 mg daily is recommended for long-term treatment in the elderly. In the treatment of acute exacerbations of osteoarthritis the usual oral daily dose of meloxicam is 7.5 mg, increased if necessary to a maximum of 15 mg daily given as a single dose.

For dosage details in children see below.

Meloxicam may be given by rectal suppository in doses similar to those used orally but use should be limited to the shortest time possible.

For the dose of meloxicam in patients with renal impairment, see below.

Administration in children. In the USA, meloxicam is used in the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral dose is 125 micrograms/kg once daily, up to a maximum of 7.5 mg daily. In the UK, licensed product information states that meloxicam should not be used in children aged under 15 years; however, the *BNFC* has suggested the following oral doses, according to body-weight, in those aged 12 to 18 years who are intolerant of other NSAIDs:

- less than 50 kg: 7.5 mg once daily
- over 50 kg: 15 mg once daily

Administration in renal impairment. Meloxicam is normally contra-indicated in patients with severe renal impairment. However, in dialysed patients, meloxicam may be given in a dose of 7.5 mg daily by mouth or by rectal suppository. No dose reduction is required in those with mild to moderate renal impairment (creatinine clearance of greater than 25 mL/min).

Musculoskeletal and joint disorders. Meloxicam is used in the treatment of osteoarthritis (see p.11), rheumatoid arthritis (see p.11) including juvenile idiopathic arthritis (p.10), and ankylosing spondylitis (see Spondyloarthropathies, p.13). However, in the UK, the use of meloxicam and other selective cyclo-oxygenase-2 (COX-2) inhibitors is limited to those patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p.97).

References.

1. Lemmel EM, *et al.* Efficacy and safety of meloxicam in patients with rheumatoid arthritis. *J Rheumatol* 1997; **24:** 282–90.
2. Yocum D, *et al.* Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000; **160:** 2947–54.
3. Combe B, *et al.* Comparison of intramuscular and oral meloxicam in rheumatoid arthritis patients. *Inflamm Res* 2001; **50** (suppl 1): S10–16.
4. Fleischmann R, *et al.* Meloxicam. *Expert Opin Pharmacother* 2002; **3:** 1501–12.

Veterinary use. For the suggestion that meloxicam should be used as an alternative to diclofenac in cattle in South Asia (to reduce toxicity to vultures who may consume their carcasses), see under Precautions of Diclofenac, p.45

Preparations

BP 2008: Meloxicam Tablets;
USP 31: Meloxicam Oral Suspension; Meloxicam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bronax; Dominadol; Flexidol; Flexium; Loxitenk; Meloxid†; Merapiran†; Mextran; Miogesil†; Miolox; Mobic; Skudal†; Telaroid; Tenaron; ***Austral.:*** Mobic; Movalis; Moxicam; ***Austria:*** Melodyn; Meloxistad; Metosan; Movalis; ***Belg.:*** Docmeloxi; Mobic; ***Braz.:*** Alivian; Artritec†; Bioflac; Diatec†; Dormelox; Flamatec; Inicox; Leutrol; Lonaflam†; Loxam; Loxiflan; Melocox; Melonan†; Melonax†; Melotec; Meloxigran; Meloxil; Mevamox; Movacox†; Movatec; Movoxicam; ***Canad.:*** Mobicox; ***Chile:*** Anposel; Ecax; Hyflex; Isox; Melic; Melodol; Mexan; Mexilal; Mibloc FT; Mobex; Sition; Tenaron; Zix†; ***Cz.:*** Artrilom; Duplicam; Galoxiway; Melobax; Melocox; Melovis; Meloxistad; Movalis; Recoxa; ***Denm.:*** Mobic; ***Fin.:*** Latonid; Mobic; ***Fr.:*** Mobic; ***Ger.:*** Mobec; ***Gr.:*** Arsitec; Arthrox; Auroxicam; Brosiral; Doctinon; Examel; Farmelox; Flumidon; Iamaxicam; Iaten; Iconal; Infomel; Loxitan; Mecalox; Medoxicam; Melice; Melocalm; Melock; Melocox; Melodin; Meloprol; Melorilif; Melotec; Melotop; Meloxil; Meloxitor; Meomel; Movatec; Movaxin; Moxalid; Notpel; Partial; Philipon-S; Rentilox; Reumotec; Reumotherm; Sanetron; Saniflam; Starmelox; Supercad; Transantor; Tropofin; Valoxin; Vexicam; Zametrixal; Zerelin; ***Hong Kong:*** Melflam; Melox; Mobic; ***Hung.:*** Camelox; Melodyn; Melogen; Meloxan; Meloxep; Movalis; Moxicam; Noflamen; ***India:*** Mel-OD; Melflam; Melstar†; ***Indon.:*** Artrilox; Flamoxi; Loxinic; Mecox; Meloxin; Mevilox; Mexpharm; Mobiflex; Movi-Cox; Movix; Moxam; Moxic; Nulox; Ostelox; Velcox; X-Cam; ***Irl.:*** Areloger; Melcam; Mobic; Mobiglan; Movox; ***Ital.:*** Leutrol; Mobic; ***Jpn:*** Mobic; ***Malaysia:*** Mel-OD; Melocam; Melox; Mobic; Rafree; ***Mex.:*** Aflamid; Anflatox†; Anpre; Auricam; Dolocam; Exel; Flexiver; Flexol; Lexpram; Loxam; Loxibach; Loxibest; Masflex†; Mavicam; Maxoflam; Meflen; Melarthryl; Melican; Melosteral; Menflixil; Mobicox; Promotion; Reosan; Retoflam; ***Neth.:*** Movalis; Movicox; ***Norw.:*** Mobic; ***NZ:*** Mobic; ***Philipp.:*** Melora; Mobic; ***Pol.:*** Aglan; Aspicam; Lormed; Meloksam; Melokssia; Meloxic; MeloxiLek; Meloxistad; Movalis; ***Port.:*** Marlex; Melpor; Movalis; Ziloxican†; ***Rus.:*** Lem (Лем); Melokan (Мелокан); Melox (Мелокс); Mirlox (Мирлокс); Movalis (Мовалис); Movasin (Мовасин); ***S.Afr.:*** Coxflam; Flexocam; Loxiflam; Melflam; Mobic; ***Singapore:*** Melox; Mobic; ***Spain:*** Aliviodol; Movalis; Parocin; Uticox; ***Swed.:*** Latonid†; Mobic; ***Switz.:*** Mobicox; Zilutrol†; ***Thai.:*** Melcam; Melobic; Melox; Mobic; ***Turk.:*** Exen; Melox; Mobic; Zeloxim; ***UK:*** Mobic; ***USA:*** Mobic; ***Venez.:*** Biomelox; Calmox†; Mecox†; Melonax; Melovax; Mobic; Mowin†; Taucaron.

Multi-ingredient: ***Arg.:*** Flexidol Relax; Mextran Flex; ***India:*** Melodol; ***Mex.:*** Dolocam Plus; Dolocartigen; Dorsal; Flexamol; Nuro-B; Retoflam F.

Meptazinol Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de meptazinol; IL-22811 (meptazinol); Meptazinol, Chlorhydrate de; Meptazinoli Hydrochloridum; Wy-22811 (meptazinol). 3-(3-Ethyl-1-methylperhydroazepin-3-yl)phenol hydrochloride.

Мептазинола Гидрохлорид

$C_{15}H_{23}NO,HCl = 269.8.$

CAS — 54340-58-8 (meptazinol); 59263-76-2 (meptazinol hydrochloride); 34154-59-1 (±-meptazinol hydrochloride).

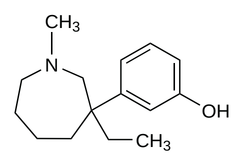

(meptazinol)

Pharmacopoeias. In *Br.*

BP 2008 (Meptazinol Hydrochloride). A white or almost white powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol; very slightly soluble in acetone; dissolves in dilute solutions of alkali hydroxides. Store at a temperature not exceeding 25°.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

◊ In assessing the dependence potential of meptazinol, a WHO expert committee[1] noted in 1989 that abrupt discontinuation of chronic meptazinol use precipitated only slight withdrawal signs in *animals* and that meptazinol did not suppress opioid withdrawal signs and symptoms in humans dependent on morphine. Abuse had not been reported. They considered that the likelihood of abuse was moderate and that international control was not warranted at that time.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Gastrointestinal adverse effects are commonly reported with meptazinol and include abdominal pain, constipation, dyspepsia, diarrhoea, and nausea and vomiting. Meptazinol is claimed to have a low incidence of respiratory depression; nonetheless, UK licensed product information states that it should not be used in patients with acute respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. As meptazinol has both antagonist and agonist properties its effects may be only partially reversed by naloxone, but use of the latter is still recommended in overdosage.

Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Abuse. See under Dependence and Withdrawal, above.

Effects on the respiratory system. Meptazinol is said to have a relatively low potential for respiratory depression and in healthy subjects was reported to produce substantially less respiratory depression than morphine or pentazocine at usual analgesic doses.[1] However, respiratory depression does occur in anaesthetised patients given meptazinol[2] and the effects on respiration may be similar to those of morphine[3,4] or pethidine.[5,6] Compensatory mechanisms may come into play after repeated doses of meptazinol but the intravenous use of meptazinol during anaesthesia should be viewed with as much caution as with any other opioid.[6]

Respiratory arrest occurred after an *overdose* of 50 meptazinol 200-mg tablets and a quarter of a bottle of whisky.[7] Full recovery eventually followed supportive measures although spontaneous respiration was not re-established by naloxone intravenously to a cumulative total dose of 10 mg.

1. Jordan C, *et al.* A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br J Anaesth* 1979; **51:** 497–502.
2. Hardy PAJ. Meptazinol and respiratory depression. *Lancet* 1983; **ii:** 576.
3. Frater RAS, *et al.* Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postoperative period. *Br J Anaesth* 1989; **63:** 260–5.
4. Verborgh C, Camu F. Post-surgical pain relief with zero-order intravenous infusions of meptazinol and morphine: a double-blind placebo-controlled evaluation of their effects on ventilation. *Eur J Clin Pharmacol* 1990; **38:** 437–42.
5. Wilkinson DJ, *et al.* Meptazinol—a cause of respiratory depression in general anaesthesia. *Br J Anaesth* 1985; **57:** 1077–84.
6. Lee A, Drummond GB. Ventilatory effects of meptazinol and pethidine in anaesthetised patients. *Br J Anaesth* 1987; **59:** 1127–33.
7. Davison AG, *et al.* Meptazinol overdose producing near fatal respiratory depression. *Hum Toxicol* 1987; **6:** 331.

Interactions

For interactions associated with opioid analgesics, see p.103.

Plasma concentrations of meptazinol may be increased by ritonavir and use together should be avoided (see also p.103).

Pharmacokinetics

After oral doses of meptazinol peak plasma concentrations have been achieved within 0.5 to 2 hours, but bioavailability is low since it undergoes extensive first-pass metabolism. Systemic availability is improved after rectal doses. Peak plasma concentrations have been achieved 30 minutes after rectal or intramuscular use. Plasma protein binding has averaged only about 27%. Elimination half-lives of about 2 hours have been reported. Meptazinol is extensively metabolised in the liver and is excreted mainly in the urine as the glucuronide conjugate. Less than 10% of a dose has been recovered from the faeces. Meptazinol crosses the placenta.

◊ References.

1. Franklin RA, *et al.* Studies on the metabolism of meptazinol, a new analgesic drug. *Br J Clin Pharmacol* 1976; **3:** 497–502.
2. Franklin RA, *et al.* Studies on the absorption and disposition of meptazinol following rectal administration. *Br J Clin Pharmacol* 1977; **4:** 163–7.
3. Davies G, *et al.* Pharmacokinetics of meptazinol in man following repeated intramuscular administration. *Eur J Clin Pharmacol* 1982; **23:** 535–8.
4. Norbury HM, *et al.* Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. *Eur J Clin Pharmacol* 1983; **25:** 77–80.
5. Murray GR, *et al.* The systemic availability of meptazinol in man after oral and rectal doses. *Eur J Clin Pharmacol* 1989; **36:** 279–82.

The elderly. A lower clearance and longer elimination half-life has been reported for meptazinol in elderly patients, but dosage reduction was not considered warranted on pharmacokinetic grounds. Mean half-lives in elderly and young subjects were 3.39 and 1.94 hours, respectively after single oral doses[1] and 2.93 and 2.06 hours, respectively after intravenous doses.[2]

1. Norbury HM, *et al.* Pharmacokinetics of meptazinol after single and multiple oral administration to elderly patients. *Eur J Clin Pharmacol* 1984; **27:** 223–6.
2. Murray GR, *et al.* Pharmacokinetics of meptazinol after parenteral administration in the elderly. *Eur J Clin Pharmacol* 1987; **31:** 733–6.

Hepatic impairment. Oral bioavailability of meptazinol appeared to be enhanced in patients with liver disease. After a single oral dose of meptazinol mean peak plasma concentrations were 184 nanograms/mL, 131 nanograms/mL, and 53 nanograms/mL in cirrhotic patients, patients with non-cirrhotic liver disease, and patients with normal liver function, respectively, although there was no evidence of accumulation after chronic dosing.[1] There were no significant differences in plasma clearance after an intravenous dose. Reduced oral doses of meptazinol might be advisable in cirrhotic patients.

1. Birnie GG, *et al.* Enhanced oral bioavailability of meptazinol in cirrhosis. *Gut* 1987; **28:** 248–54.

Pregnancy. In women given an intramuscular injection of 100 to 150 mg during labour, meptazinol was found to cross the placenta readily but was rapidly eliminated from the neonate.[1] This contrasted with pethidine which was known to be excreted very slowly from neonates. As in the adult, elimination of meptazinol by the neonate appeared to take place mainly by conjugation with glucuronic acid.[2] A half-life of 3.4 hours, similar to that in adults, has been reported in the neonate,[3] in contrast to 22.7 hours for pethidine in neonates.

Disposition of meptazinol appears not to be significantly affected by pregnancy. Mean half-lives of 1.36 and 1.68 hours were reported in pregnant and non-pregnant women, respectively,[4] compared with 2.06 hours in men.

1. Franklin RA, *et al.* Preliminary studies on the disposition of meptazinol in the neonate. *Br J Clin Pharmacol* 1981; **12:** 88–90.
2. Dowell PS, *et al.* Routes of meptazinol conjugation in the neonate. *Br J Clin Pharmacol* 1982; **14:** 748–9.
3. Jackson MBA, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgrad Med J* 1983; **59** (suppl 1): 47–51.
4. Murray GR, *et al.* The disposition of meptazinol after single and multiple intravenous administration to pregnant and non-pregnant women. *Eur J Clin Pharmacol* 1989; **36:** 273–7.

Uses and Administration

Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the μ_1 opioid receptor (see p.104); it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.

Meptazinol hydrochloride is given orally or by intramuscular or intravenous injection; doses are expressed in terms of the base. Meptazinol hydrochloride 115.6 mg is equivalent to about 100 mg of meptazinol. For the short-term treatment of moderate pain meptazinol is given in an oral dose of 200 mg every 3 to 6 hours, as required. The intramuscular dose is 75 to 100 mg given every 2 to 4 hours, as required; for obstetric pain a dose of 2 mg/kg (100 to 150 mg) may be used. Meptazinol is also given by slow intravenous injection in doses of 50 to 100 mg every 2 to 4 hours, as required.

Administration. *EPIDURAL ROUTE.* Epidural meptazinol 90 mg for postoperative pain was reported to be superior to an intramuscular dose of 90 mg.[1] However, in another study[2] a 30-mg dose was ineffective and associated with an unacceptable incidence of adverse effects. A 60-mg dose was also found to be ineffective because of its short duration of action.[3]

UK licensed product information states that the injectable formulation is not suitable for epidural or intrathecal use.

1. Verborgh C, *et al.* Meptazinol for postoperative pain relief in man: comparison of extradural and im administration. *Br J Anaesth* 1987; **59:** 1134–9.
2. Francis RI, Lockhart AS. Epidural meptazinol. *Anaesthesia* 1986; **41:** 88–9.
3. Birks RJS, Marsh DRG. Epidural meptazinol. *Anaesthesia* 1986; **41:** 883.

Administration in hepatic impairment. See under Pharmacokinetics, above for a suggestion that doses may need to be reduced in patients with cirrhosis.

Preparations

BP 2008: Meptazinol Injection; Meptazinol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Meptidol†; ***Ger.:*** Meptid; ***Irl.:*** Meptid; ***UK:*** Meptid.

Methadone Hydrochloride

(BANM, pINNM) ⊗

Amidine Hydrochloride; Amidone Hydrochloride; Hidrocloruro de amidina; Hidrocloruro de metadona; Metadon Hidroklorür; Metadon-hidroklorid; Metadonhydroklorid; Metadonihydrokloridi; Metadono hidrochloridas; Metadonu chlorowodorek; Methadon hydrochlorid; Méthadone, chlorhydrate de; (±)-Methadone Hydrochloride; Methadoni hydrochloridum; Phenadone. (±)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

Метадона Гидрохлорид

$C_{21}H_{27}NO,HCl = 345.9.$

CAS — 76-99-3 (methadone); 297-88-1 (±methadone); 1095-90-5 (methadone hydrochloride); 125-56-4 (±methadone hydrochloride).

ATC — N07BC02.

ATC Vet — QN07BC02.

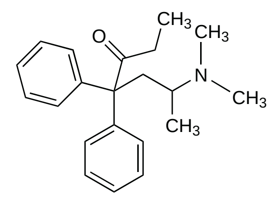

(methadone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methadone:
Amidone; Balloons; Breeze; Burdock; Buzz bomb; Dollies; Dolls; Done; Doses; Fizzies; Juice; Jungle juice; Junk; Meta; Mud; Phy; Phyamps; Tootsie roll.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Methadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Methadone Hydrochloride). Odourless colourless crystals or white crystalline powder. Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerol. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. There appears to be adequate evidence that stable solutions containing methadone hydrochloride and hydroxybenzoate esters can be formulated but the risk of precipitation exists if syrup preserved with hydroxybenzoates is used to extemporaneously prepare a methadone mixture 1 mg/mL to the DTF formula.[1] An oral formulation of methadone hydrochloride 5 mg/mL containing methyl hydroxybenzoate 0.1% as preservative rather than chloroform has been reported stable for at least 4 months at room temperature.[2]

1. *PSGB Lab Report P/80/1* 1980.
2. Ching MS, *et al.* Stability of methadone mixture with methyl hydroxybenzoate as a preservative. *Aust J Hosp Pharm* 1989; **19:** 159–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Methadone withdrawal symptoms are similar to, but more prolonged than, those produced by morphine or diamorphine. They develop more slowly and do not usually appear until 3 to 4 days after the last dose.

Methadone is used for substitution therapy in the management of opioid dependence (see Uses and Administration, below) including neonatal abstinence syndrome (see Administration in Children, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Methadone has a more prolonged effect than morphine and readily accumulates with repeated doses. It may have a relatively greater respiratory depressant effect than morphine and, although reported to be less sedating, repeated doses of methadone may result in marked sedation. QT prolongation and torsade de pointes have been reported rarely with methadone use, particularly at doses above 100 mg daily. After gross overdosage symptoms are similar to those of morphine poisoning. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Methadone causes pain at injection sites; subcutaneous injection causes local tissue irritation and induration.

Effects on the cardiovascular system. Methadone prolongs the QT interval and has rarely been associated with torsade de pointes. In a retrospective case series,[1] 17 patients on high-dose methadone (mean daily dose of 397 mg) developed torsade de pointes; of these, 14 had potential risk factors for arrhythmia and 6 had had their dose increased within the last month. In another study[2] torsade de pointes developed in 5 patients taking methadone (mean daily dose 268 mg); however, they all had other contributing risk factors. Other studies[3,4] did not find instances of torsade de pointes and the increase in QT interval was considered clinically insignificant; in one study,[4] the mean daily dose of methadone was 110 mg and some patients also had risk factors for arrhythmia.

For a report of QT interval prolongation in an infant born to a mother on maintenance methadone therapy for opioid addiction, see Pregnancy, below.

In a small case-controlled study of sudden cardiac deaths,[5] the prevalence of underlying cardiac disease or structural abnormalities was lower in the 22 cases with evidence of therapeutic methadone levels when compared with the 106 cases without evidence of methadone use. The authors considered that the low prevalence of cardiac risk factors in the methadone group suggested a role for methadone itself in the pathogenesis of sudden death in this group.

1. Krantz MJ, *et al.* Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002; **137:** 501–4.
2. Sticherling C, *et al.* Methadone-induced torsade de pointes tachycardias. *Swiss Med Wkly* 2005; **135:** 282–5.
3. Martell BA, *et al.* The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; **139:** 154–5.
4. Cruciani RA, *et al.* Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage* 2005; **29:** 385–91.
5. Chugh SS, *et al.* A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med* 2008; **121:** 66–71.

Effects on the endocrine system. Hypoadrenalism has been found in chronic methadone addicts. Findings consistent with deficient ACTH production and subsequent secondary hypoadrenalism have been reported[1] although there is also evidence[2] of methadone-induced primary adrenal cortical hypofunction.

Hyperprolactinaemia and galactorrhoea have also been reported.[3] See also Effects on Sexual Function, below.

1. Dackis CA, *et al.* Methadone induced hypoadrenalism. *Lancet* 1982; **ii:** 1167.
2. Pullan PT, *et al.* Methadone-induced hypoadrenalism. *Lancet* 1983; **i:** 714.
3. Bennett J, Whale R. Galactorrhoea may be associated with methadone use. *BMJ* 2006; **332:** 1071.

Effects on the nervous system. Choreic movements occurred in a 25-year-old man on long-term methadone maintenance treatment of 45 to 60 mg daily for diamorphine addiction.[1] Similar adverse effects were seen in a 41-year-old woman taking 5 mg methadone four times daily for complex regional pain syndrome.[2] In both cases, symptoms resolved when methadone was stopped.

1. Wasserman S, Yahr MD. Choreic movements induced by the use of methadone. *Arch Neurol* 1980; **37:** 727–8.
2. Clark JD, Elliott J. A case of a methadone-induced movement disorder. *Clin J Pain* 2001; **17:** 375–7.

Effects on the respiratory system. Sleep apnoea has been reported[1,2] in patients on stable methadone maintenance treatment.

1. Teichtahl H, *et al.* Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction* 2001; **96:** 395–403.
2. Wang D, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; **128:** 1348–56.

Effects on sexual function. Sexual performance was impaired in 29 male diamorphine addicts receiving methadone maintenance therapy.[1] The function of secondary sex organs was markedly suppressed when compared with untreated diamorphine addicts or controls and serum-testosterone concentrations were 43% lower in those on methadone. However, in a more recent study[2] in 92 opioid addicts also receiving methadone maintenance, rates of sexual dysfunction (erectile, libido, and orgasm dysfunction) were found to be similar to that of the general population. Rates of dysfunction between patients just started on methadone and those on methadone for at least 60 days were not significantly different although new patients generally had lower rates. Mean plasma levels of testosterone and prolactin were within normal ranges and although 8 individuals had low testosterone levels, only 1 case of dysfunction was reported in this group.

1. Cicero TJ, *et al.* Function of the male sex organs in heroin and methadone users. *N Engl J Med* 1975; **292:** 882–7.
2. Brown R, *et al.* Methadone maintenance and male sexual dysfunction. *J Addict Dis* 2005; **24:** 91–106.

Overdosage. Most cases of methadone poisoning occur in persons not on maintenance,[1-4] particularly children or family members of maintenance patients.[1] Methadone is highly toxic to anyone who is not tolerant to opioids; 50 to 100 mg can be life-threatening in non-tolerant adults and 10 mg can be fatal in a young child.[1] Furthermore, life-threatening toxicity from oral doses as low as 5 mg has been reported in children.[2,4]

Various groups[5,6] have found that the risk of death from methadone toxicity is greatest during the first 2 weeks of maintenance therapy. This has been attributed to the difficulty in determining a safe and effective starting dose of methadone and unreliable accounts of a patient's recent drug use.

1. Harding-Pink D. Opioid toxicity: methadone: one person's maintenance dose is another's poison. *Lancet* 1993; **341:** 665–6.
2. Aronow R, *et al.* Childhood poisoning: an unfortunate consequence of methadone availability. *JAMA* 1972; **219:** 321–4.
3. Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug Alcohol Rev* 2002; **21:** 131–6.
4. Sachdeva DK, Stadnyk JM. Are one or two dangerous? Opioid exposure in toddlers. *J Emerg Med* 2005; **29:** 77–84.
5. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust* 1999; **170:** 104–9.
6. Buster MCA, *et al.* An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002; **97:** 993–1001.

Precautions

As for Opioid Analgesics in general, p.103.

Methadone should be given with caution to patients at risk of developing prolongation of the QT interval including those with cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with a family history of sudden death. It should also be used with caution in patients who are taking other potentially arrhythmogenic drugs, drugs likely to cause electrolyte imbalance, or drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). ECG monitoring is recommended before starting methadone treatment in these patients, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

Administration. Methadone has a long half-life and accumulation may occur with repeated doses, especially in elderly or debilitated patients. An 81-year-old woman given methadone 5 mg three times daily orally for 2 days became deeply unconscious but awoke immediately when given naloxone 400 micrograms intravenously.[1]

Sudden death in 10 diamorphine addicts occurred between 2 and 6 days after starting a methadone maintenance programme.[2] The mean prescribed dose of methadone at the time of death had been about 60 mg. There was evidence of chronic persistent hepatitis in all cases and liver disease could have reduced methadone clearance resulting in higher than expected blood concentrations. Liver function tests and urine testing for the presence of drugs before entry into methadone maintenance programmes, and lower starting doses, might decrease the likelihood of such deaths. Like dextropropoxyphene, methadone has membrane stabilising activity and can block nerve conduction, and it was suggested[3] that the sudden deaths were mainly due to accumulation of methadone over several days resulting in complications such as cardiac arrhythmias or cardiovascular collapse (above). See also Overdosage, above.

For the effects of hepatic and renal impairment on the disposition of methadone, see under Pharmacokinetics, below.

1. Symonds P. Methadone and the elderly. *BMJ* 1977; **i:** 512.
2. Drummer OH, *et al.* Deaths of heroin addicts starting on a methadone maintenance programme. *Lancet* 1990; **335:** 108.
3. Wu C, Henry JA. Deaths of heroin addicts starting on methadone maintenance. *Lancet* 1990; **335:** 424.

Breast feeding. The American Academy of Pediatrics considers that the use of methadone in breast-feeding mothers is usually compatible with breast feeding.[1] The *BNF* also permits breast feeding by mothers on methadone maintenance although the dose should be as low as possible and the infant monitored to avoid sedation. Others have suggested that the amount of methadone in breast milk is unlikely to have any pharmacological effect on the infant.[2-8] However, in the past, there has been a report of the death of a 5-week-old breast-fed infant whose mother was on methadone maintenance.[9]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Blinick G, *et al.* Methadone assays in pregnant women and progeny. *Am J Obstet Gynecol* 1975; **121:** 617–21.
3. Wojnar-Horton RE, *et al.* Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *Br J Clin Pharmacol* 1997; **44:** 543–7.
4. Geraghty B, *et al.* Methadone levels in breast milk. *J Hum Lact* 1997; **13:** 227–30.
5. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lact* 2000; **16:** 115–20.
6. Begg EJ, *et al.* Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. *Br J Clin Pharmacol* 2001; **52:** 681–5.
7. Jansson LM, *et al.* Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* 2008; **121:** 106–14.
8. Jansson LM, *et al.* Methadone maintenance and long-term lactation. *Breastfeed Med* 2008; **3:** 34–7.
9. Smialek JE, *et al.* Methadone deaths in children. *JAMA* 1977; **238:** 2516–17.

Pregnancy. Methadone is not recommended for use in labour because its prolonged duration of action increases the risk of neonatal respiratory depression.

Neonatal abstinence syndrome and low birth-weight are immediate problems in infants born to women receiving methadone for the management of opioid addiction; increased still-birth rates have also been noted.[1-3] In the neonatal period moderate to severe opioid abstinence syndrome occurred in 75% of infants in a study,[2] as well as reduced head circumference and raised systolic blood pressure. At follow-up over 18 months these children had a higher incidence of otitis media, of reduced head circumference, and of abnormal eye findings when compared with drug-free controls. Neurobehavioural abnormalities and lower scores on mental and motor developmental indices were thought to be possible predictors of later learning and behavioural problems. In a later study,[4] the use of methadone alone during pregnancy as part of a maintenance program was claimed to increase the risk of prematurity twofold, of intra-uterine growth retardation fourfold, and of microcephaly threefold when compared with a normal population. In addition, in those mothers who continued to abuse other drugs, as well as receive methadone, the risks of these events were further increased. However, an earlier study[5] has reported that methadone or diamorphine had no specific effect on intra-uterine and postnatal growth.

The relationship between maternal methadone dose and the incidence and severity of neonatal abstinence syndrome is unclear. Although a retrospective study[6] found a correlation in some pregnancies, others[7,8] did not and there was no evidence of an increased incidence of neonatal withdrawal symptoms even with high maternal doses of 100 mg or more daily.[8]

A small retrospective study[9] comparing the use of methadone during pregnancy for the treatment of chronic pain with use in maintenance therapy for opioid addiction found a lower incidence of neonatal abstinence syndrome and better growth parameters in infants born to the former group of mothers; however, a higher rate of slight prematurity was also found in this group of infants. The authors suggested that lower maternal doses and shorter durations of treatment may account for the favourable findings, in addition to better maternal health, nutrition, and socio-economic status.

Clinically significant prolongation of the QT interval has been reported[10] in an infant born to a mother taking methadone 50 mg daily for maintenance therapy; the infant had mild withdrawal symptoms and follow-up at 2 months of age was normal.

1. Blinick G, *et al.* Methadone maintenance, pregnancy, and progeny. *JAMA* 1973; **225:** 477–9.
2. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *J Pediatr* 1982; **101:** 192–6.
3. Kalter H, Warkany J. Congenital malformations. *N Engl J Med* 1983; **308:** 491–7.
4. Arlettaz R, *et al.* Methadone maintenance program in pregnancy in a Swiss perinatal center (II): neonatal outcome and social resources. *Acta Obstet Gynecol Scand* 2005; **84:** 145–50.
5. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; **102:** 686–91.
6. Dashe JS *et al.* Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol* 2002; **100:** 1244–9.
7. Berghella V, *et al.* Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol* 2003; **189:** 312–17.
8. McCarthy JJ, *et al.* High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2005; **193:** 606–10.
9. Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F33–F36.
10. Hussain T, Ewer AK. Maternal methadone may cause arrhythmias in neonates. *Acta Paediatr* 2007; **96:** 768–9.

Interactions

For interactions associated with opioid analgesics, see p.103.

Methadone is metabolised in the liver mainly via the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 are also thought to be involved. Consequently, use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of methadone and, possibly adverse effects. There is a risk of cardiac events in patients receiving methadone who are also taking drugs that affect cardiac conduction or electrolyte balance.

◊ Drugs that *acidify* or *alkalinise* the urine may have an effect on methadone pharmacokinetics since body clearance is increased at acidic pH and decreased at alkaline pH.[1]

1. Nilsson M-I, *et al.* Effect of urinary pH on the disposition of methadone in man. *Eur J Clin Pharmacol* 1982; **22:** 337–42.

Antibacterials. Withdrawal symptoms have been reported in patients maintained on methadone when they were given the enzyme inducer *rifampicin*.[1-3] Conversely, the use of *ciprofloxacin*, which inhibits CYP1A2 and CYP3A4, has resulted in signs of methadone toxicity.[4]

1. Kreek MJ, *et al.* Rifampin-induced methadone withdrawal. *N Engl J Med* 1976; **294:** 1104–6.

2. Bending MR, Skacel PO. Rifampicin and methadone withdrawal. *Lancet* 1977; **i:** 1211.
3. Raistrick D, *et al.* Methadone maintenance and tuberculosis treatment. *BMJ* 1996; **313:** 925–6.
4. Herrlin K, *et al.* Methadone, ciprofloxacin, and adverse drug reactions. *Lancet* 2000; **356:** 2069–70.

Antidepressants. *SSRIs* such as fluoxetine[1] and fluvoxamine[1,2] may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity. *St John's wort* reduced the plasma-methadone concentration to dose ratios by 47% in 4 patients on methadone maintenance therapy for opioid addiction; 2 patients reported symptoms suggestive of a withdrawal syndrome.[3]

1. Eap CB, *et al.* Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *J Clin Psychopharmacol* 1997; **17:** 113–17.
2. Bertschy G, *et al.* Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit* 1994; **16:** 42–5.
3. Eich-Höchli D, *et al.* Methadone maintenance treatment and St. John's Wort: a case report. *Pharmacopsychiatry* 2003; **36:** 35–7.

Antiepileptics. Opioid withdrawal symptoms have been reported in patients maintained on methadone when they were given *carbamazepine*,[1,2] *phenobarbital*,[3] or *phenytoin*.[4,5] Conversely, methadone-induced respiratory depression developed in a patient on carbamazepine, gabapentin, and methadone for neuropathic pain, after carbamazepine was stopped.[6]

1. Bell J, *et al.* The use of serum methadone levels in patients receiving methadone maintenance. *Clin Pharmacol Ther* 1988; **43:** 623–9.
2. Saxon AJ, *et al.* Valproic acid, unlike other anticonvulsants, has no effects on methadone metabolism: two cases. *J Clin Psychiatry* 1989; **50:** 228–9.
3. Liu S-J, Wang RIH. Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. *Am J Psychiatry* 1984; **141:** 1287–8.
4. Finelli PF. Phenytoin and methadone tolerance. *N Engl J Med* 1976; **294:** 227.
5. Tong TG, *et al.* Phenytoin-induced methadone withdrawal. *Ann Intern Med* 1981; **94:** 349–51.
6. Benítez-Rosario MA, *et al.* Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Symptom Manage* 2006; **32:** 99–100.

Antifungals. Use of methadone with *fluconazole* has been reported[1] to increase serum concentrations of methadone although the authors considered that for patients being treated for opioid dependence the interaction was unlikely to require adjustment of the methadone dose. However, respiratory depression has been reported[2] after intravenous doses of fluconazole were given to a 60-year-old man also taking oral methadone for pain relief in advanced gastric cancer. Although a randomised placebo-controlled study[3] found that giving *voriconazole* to patients on methadone maintenance therapy for opioid addiction was generally safe and well tolerated, the authors recommended monitoring and possible dose reduction of methadone when the 2 drugs are used together. Similar recommendations are also given in the licensed product information for voriconazole.

1. Cobb MN, *et al.* The effect of fluconazole on the clinical pharmacokinetics of methadone. *Clin Pharmacol Ther* 1998; **63:** 655–62.
2. Tarumi Y, *et al.* Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage* 2002; **23:** 148–53.
3. Liu P, *et al.* Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. *Antimicrob Agents Chemother* 2007; **51:** 110–18.

Antivirals. The potential for interaction between antiretrovirals and methadone has been reviewed.[1] Available evidence for HIV-protease inhibitors suggests that *atazanavir*, *indinavir*, and, possibly, *saquinavir* alone have no effect on plasma concentrations of methadone; *amprenavir*, *nelfinavir*, *ritonavir*, and *ritonavir-boosted saquinavir* may reduce plasma-methadone concentrations but the effect is unlikely to be clinically significant. *Lopinavir-ritonavir* may also reduce methadone concentrations and, although most studies found the interaction to be insignificant, one study reported opioid withdrawal symptoms in some patients. Unpublished data [also referred to in the licensed product information] on *tipranavir* (boosted with ritonavir) in healthy, opioid-naive subjects suggest that it may decrease plasma-methadone; licensed product information for tipranavir recommends that patients are monitored for symptoms of opioid withdrawal.

The NNRTIs *nevirapine* and *efavirenz* have both been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when they were given to patients receiving methadone. Conversely, *delavirdine* may increase methadone concentrations although the effect is unlikely to be clinically significant. Methadone possibly increases plasma concentrations of the NRTI *zidovudine* (see p.915).

1. Bruce RD, *et al.* Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr* 2006; **41:** 563–72.

Gastrointestinal drugs. Histamine H_2-antagonists such as *cimetidine* (see p.103) may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity.

Grapefruit juice. Grapefruit juice, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, has been shown to modestly increase the bioavailability of methadone;[1] although no symptoms of methadone toxicity were seen in the studied patients, the authors commented that such effects may occur in patients with reduced opioid tolerance, particularly when starting methadone treatment.

1. Benmebarek M, *et al.* Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* 2004; **76:** 55–63.

Pharmacokinetics

Methadone hydrochloride is readily absorbed from the gastrointestinal tract and from subcutaneous or intramuscular injections. It is widely distributed in the tissues, diffuses across the placenta, and is distributed into breast milk. It is extensively protein bound. Methadone is metabolised in the liver, mainly by *N*-demethylation and cyclisation, and the metabolites are excreted in the bile and urine. Metabolism is primarily catalysed by CYP3A4, although other cytochrome P450 isoenzymes also play a role (see Interactions, above). It has a prolonged half-life and is subject to accumulation.

◊ In reviews of the pharmacokinetics of methadone[1-5] particular reference has been made to its long elimination half-life, accumulation after repeated doses, and wide interindividual variations.

Methadone is rapidly absorbed after oral doses and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after a single tablet by mouth. It undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrroline, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine with unchanged methadone. Other metabolites, including methadol and normethadol, have also been described. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver, and released again mainly unchanged. Urinary excretion of methadone is pH-dependent, the lower the pH the greater the clearance.

In addition to marked interindividual variations there are differences in the pharmacokinetics of methadone after single or multiple doses. Elimination half-lives vary considerably (a range of 15 to 60 hours has been quoted) and may be much longer than the 18 hours reported following a single dose. Careful adjustment of dosage is necessary with repeated doses.

Most studies have been in addicts. Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. These variations in kinetics have also been seen in cancer patients.

1. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
3. Eap CB, *et al.* Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002; **41:** 1153–93.
4. Ferrari A, *et al.* Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res* 2004; **50:** 551–9.
5. Lugo RA, *et al.* Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* 2005; **19:** 13–24.

Administration. Methadone is considerably more lipid-soluble than morphine. A study of plasma concentrations and analgesia after intramuscular injection indicated that more rapid and greater relief of pain might be achieved if lipid-soluble opioid analgesics were injected into the deltoid rather than the gluteal muscle; there was no significant difference in absorption of morphine from the two sites.[1]

Other routes investigated in pharmacokinetic studies include continuous intravenous infusion[2] and continuous epidural infusion.[3] Rectal administration[4] has also been studied.

1. Grabinski PY, *et al.* Plasma levels and analgesia following deltoid and gluteal injections of methadone and morphine. *J Clin Pharmacol* 1983; **23:** 48–55.
2. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
3. Shir Y, *et al.* Plasma concentrations of methadone during postoperative patient-controlled extradural analgesia. *Br J Anaesth* 1990; **65:** 204–9.
4. Dale O, *et al.* Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 156–62.

Hepatic impairment. Overall hepatic dysfunction does not seem unduly to disrupt methadone metabolism[1] and it has been suggested[2] that maintenance dosage of methadone need not be changed in stable chronic liver disease, although abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

In a study of patients on methadone maintenance therapy[2] apparent terminal half-life of methadone was prolonged from a mean of 18.8 hours in those with healthy livers to 35.5 hours in patients with severe chronic liver disease. However, plasma concentrations were not increased in such patients.

1. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
2. Novick DM, *et al.* Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981; **30:** 353–62.

Pregnancy. Plasma concentrations of methadone were reduced in methadone-maintained pregnant women, probably due to enhanced metabolism.[1,2] It was suggested that the dose of methadone might need to be increased in such patients.

1. Pond SM, *et al.* Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther* 1985; **233:** 1–6.
2. Wolff K, *et al.* Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 2005; **61:** 763–8.

Renal impairment. The urinary excretion of methadone was reduced in renal failure,[1] but plasma concentrations were within the usual range and faecal excretion accounted for the majority of the dose. Very little methadone was removed by peritoneal dialysis or haemodialysis.

1. Kreek MJ, *et al.* Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980; **5:** 197–205.

Uses and Administration

Methadone hydrochloride, a diphenylheptane derivative, is an opioid analgesic (p.104) that is primarily a μ opioid agonist. Single doses of methadone have a less marked sedative action than single doses of morphine. Methadone is a racemic mixture and levomethadone (p.77) is the active isomer.

Methadone hydrochloride is used in the treatment of moderate to severe pain; it may be of use for those patients who experience excitation or exacerbation of pain with morphine. Methadone is also used in the management of opioid dependence. It has a depressant action on the cough centre and has been used as a cough suppressant in terminal illness, although the *BNF* discourages this use because of the risks of accumulation.

For **pain relief** starting oral doses of methadone hydrochloride may range from 2.5 to 10 mg given every 6 to 8 hours or longer and thereafter adjusted as necessary. Methadone may also be given parenterally. In the UK, the subcutaneous and intramuscular routes are licensed with the intramuscular route being recommended for prolonged use; US licensed product information states that the intravenous, intramuscular, and subcutaneous routes may be used although it gives doses for the intravenous route only. Initial dose ranges for parenteral routes are similar to those used orally; however, if transferring between oral and parenteral methadone, US product information states that the initial conversion dose should be based on the guide that 10 mg of oral methadone is equivalent to about 5 mg of parenteral methadone. The analgesic effect of methadone begins about 10 to 20 minutes after parenteral injection and about 30 to 60 minutes after oral doses, the effect of a single dose usually lasting about 4 hours. As accumulation occurs with repeated doses, the effects become more prolonged. Consequently, to avoid the risk of opioid overdose, it is recommended that in prolonged use methadone should not be given more than twice daily.

Methadone is used as part of the treatment of **opioid dependence**, although prolonged use of methadone itself may result in dependence. Initially, methadone hydrochloride is given in doses sufficient to suppress signs of opioid withdrawal but avoid toxicity; the *BNF* and US licensed product information recommended a starting dose of 10 to 40 mg daily. Subsequent dose adjustments should be made cautiously because of the risks of accumulation; the *BNF* suggests adjusting the dose in steps of 10 mg to a maximum weekly increase of 30 mg. Once the dose has been stabilised, patients may choose to receive prolonged therapy with a carefully selected methadone dose for each individual; most patients in such maintenance programmes are stabilised on once-daily doses of 60 to 120 mg. Alternatively, detoxification may be appropriate with the dose of methadone being gradually decreased until total withdrawal is achieved. Methadone is usually given orally for the treatment of dependence although parenteral routes may be used, particularly when oral therapy is not possible; the doses stated above may be given orally or parenterally. In the UK, oral treatment is commonly given as a mixture containing 1 mg/mL of methadone hydrochloride.

For details of doses in children, see below.

For the control of intractable **cough** associated with terminal lung cancer, methadone hydrochloride is usually given in the form of a linctus in a dose of 1 to 2 mg every 4 to 6 hours, but reduced to twice daily on prolonged use.

Administration. Although duration of action after single doses of methadone is similar to that of morphine, it increases considerably with multiple dosing of methadone because of the long elimination half-life (see under Pharmacokinetics, above). The minimum effective dose of methadone can be difficult to titrate for the individual patient. A fixed 10-mg oral dose with a flexible patient-controlled dosage interval has been used in patients with chronic cancer pain.[1] Dosage not more frequently than every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements, was advised.

A suggested initial dose for patients who need to switch from oral morphine to methadone because of poor pain control is one tenth of the total daily dose of morphine, but not greater than 100 mg, given at intervals determined by the patient, typically every 8 hours.[2]

When switching from oral to parenteral use it was suggested[3] that the dose of methadone should be halved and adjusted thereafter as necessary.

Evidence of the prolonged effect of methadone was demonstrated when a single intravenous bolus dose of 20 mg resulted in postoperative analgesia lasting about 25 hours.[4] An initial 2-hour loading intravenous infusion of methadone 100 to 200 micrograms/kg per hour to provide rapid analgesia followed by infusion at a lower maintenance rate of 10 to 20 micrograms/kg per hour for continuous pain relief has been used in burn patients.[5] Methadone has also been given by continuous subcutaneous infusion for severe cancer pain[6,7] although this route has been associated with local tissue irritation and induration. Epidural methadone has been used successfully in doses of up to 5 mg for analgesia in association with bupivacaine.[8,9] Intermittent and continuous epidural infusion of methadone has also been tried[10] in postoperative analgesia.

A small case series[11] found topical methadone powder to be effective for pain relief of open, exudative wounds.

1. Säwe J, *et al.* Patient-controlled dose regimen of methadone for chronic cancer pain. *BMJ* 1981; **282:** 771–3.
2. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.
3. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11:** 87–106.
4. Gourlay GK, *et al.* Methadone produces prolonged postoperative analgesia. *BMJ* 1982; **284:** 630–1.
5. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30:** 70–5.
6. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. *J Pain Symptom Manage* 1999; **18:** 49–52.
7. Makin MK, Morley JS. Subcutaneous methadone in terminally-ill patients. *J Pain Symptom Manage* 2000; **19:** 237–8.
8. Drenger B, *et al.* Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy. *Br J Anaesth* 1989; **62:** 82–6.
9. Martin CS, *et al.* Extradural methadone and bupivacaine in labour. *Br J Anaesth* 1990; **65:** 330–2.
10. Prieto-Alvarez P, *et al.* Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. *Can J Anaesth* 2002; **49:** 25–31.
11. Gallagher RE, *et al.* Analgesic effects of topical methadone: a report of four cases. *Clin J Pain* 2005; **21:** 190–2.

Administration in children. Methadone is not licensed for use in children. However, it has been tried[1] intravenously in children aged 3 to 7 years to prevent postoperative **pain**; a dose of 200 micrograms/kg was given perioperatively followed postoperatively by 50 micrograms/kg every 10 minutes until the patient was both comfortable and adequately alert. Methadone has also been tried[2] orally for the treatment of severe pain in hospitalised children; daily doses ranged from 200 to 600 micrograms/kg for up to 6 weeks.

Methadone is used for the management of **neonatal abstinence syndrome** (p.102). The *BNFC* suggests an initial oral dose of 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; once stabilised, the total daily dose is given in 2 divided doses for maintenance. When withdrawing methadone, the dose should be reduced over 7 to 10 days.

1. Berde CB, *et al.* Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; **119:** 136–41.
2. Shir Y, *et al.* Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. *Clin J Pain* 1998; **14:** 350–3.

Cancer pain. Methadone is used as an alternative to morphine in the treatment of severe cancer pain (p.5). A better understanding of its pharmacokinetics and of equianalgesic doses may address early concerns about the risk of cumulative toxicity associated with prolonged use. However, its long terminal half-life makes it less suitable for the treatment of breakthrough pain.

Methadone has been given by the oral, rectal, and parenteral routes.

References.

1. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000; **173:** 536–40.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med* 2002; **5:** 127–38.
3. Bruera E, *et al.* Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22:** 185–92.
4. Moryl N, *et al.* Methadone in the treatment of pain and terminal delirum [sic] in advanced cancer patients. *Palliat Support Care* 2005; **3:** 311–17.
5. Mannino R, *et al.* Methadone for cancer-related neuropathic pain: a review of the literature. *J Opioid Manag* 2006; **2:** 269–76.
6. Nicholson AB. Methadone for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 26/06/08).

Opioid dependence. The treatment of opioid dependence is discussed on p.101. In the UK, oral liquid preparations of methadone hydrochloride 1 mg/mL are widely used for this purpose. It is important to note that these preparations are 2.5 times **stronger** than Methadone Linctus (BP 2008), and although some are licensed for analgesia in severe pain, many are licensed for the treatment of opioid dependence only. Methadone Oral Solution (1 mg/mL) (BP 2008) is available as a ready-to-use solution or may be prepared from Methadone Hydrochloride Oral Concentrate. However, most commercially available preparations in the UK still follow an earlier formula formerly listed in the Drug Tariff Formulary (DTF):

Methadone Mixture 1 mg/mL
methadone hydrochloride 10 mg
Green S and Tartrazine Solution (BP 1980) 0.02 mL
Compound Tartrazine Solution (BP 1980) 0.08 mL
syrup, unpreserved 5 mL
chloroform water, double-strength to 10 mL.

Some commercially available forms of DTF Methadone Mixture 1 mg/mL use a preservative system based on hydroxybenzoate esters rather than chloroform; however, syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing (see under Incompatibility, above).

References.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. Wolff K, *et al.* Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clin Pharmacol Ther* 1991; **50:** 199–207.
3. Wilson P, *et al.* Methadone maintenance in general practice: patients, workload, and outcomes. *BMJ* 1994; **309:** 641–4.
4. Farrell M, *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; **309:** 997–1001.
5. Henry JA. Methadone: where are we now? *Hosp Med* 1999; **60:** 161–4.
6. Faggiano F, *et al.* Methadone maintenance at different dosages for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 28/08/08).
7. Mattick RP, *et al.* Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 26/06/08).
8. Amato L, *et al.* Methadone at tapered doses for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).
9. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)

Preparations

BP 2008: Methadone Injection; Methadone Linctus; Methadone Oral Solution (1 mg per mL); Methadone Tablets;
USP 31: Methadone Hydrochloride Injection; Methadone Hydrochloride Oral Concentrate; Methadone Hydrochloride Oral Solution; Methadone Hydrochloride Tablets; Methadone Hydrochloride Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Gobbidona; ***Austral.:*** Biodone†; Physeptone; ***Austria:*** Heptadon; ***Belg.:*** Mephenon; ***Braz.:*** Metadon; Mytedom; ***Canad.:*** Metadol; ***Chile:*** Amidona†; ***Fin.:*** Dolmed; ***Hong Kong:*** Physeptone†; ***Hung.:*** Depridol; Metadon; ***Irl.:*** Phymet DTF; Physeptone†; Pinadone DTF; ***Israel:*** Adolan; ***Ital.:*** Eptadone; ***Malaysia:*** Aseptone; ***Neth.:*** Symoron; ***NZ:*** Biodone; Methatabs; Pallidone; ***S.Afr.:*** Physeptone; ***Singapore:*** Physeptone†; ***Spain:*** Metasedin; ***Switz.:*** Ketalgine; ***UK:*** Eptadone; Martindale Methadone Mixture DTF; Methadose; Physeptone; Synastone; ***USA:*** Diskets; Dolophine; Methadose.

Methyl Butetisalicylate

Butetisalicilato de metilo; Methyl Diethylacetylsalicylate. Methyl *O*-(2-ethylbutyryl)salicylate.
$C_{14}H_{18}O_4$ = 250.3.

Profile

Methyl butetisalicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p.85) as a rubefacient for the relief of musculoskeletal, joint, and soft-tissue pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Doloderm.

Methyl Gentisate

Gentisato de metilo. 2,5-Dihydroxybenzoic acid methyl ester.
$C_8H_8O_4$ = 168.1.
CAS — 2150-46-1.

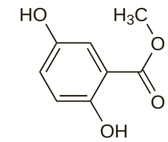

Profile

Methyl gentisate has been used topically for the relief of musculoskeletal and joint pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Reumacort.

Methyl Nicotinate *(USAN)*

Méthyle, nicotinate de; Methyli Nicotinas; Methylis nicotinas; Methyl-nikotinát; Metilo nikotinatas; Metylnikotinat; Metyylinikotinaatti; Nicotinato de metilo. Methyl pyridine-3-carboxylate.
$C_7H_7NO_2$ = 137.1.
CAS — 93-60-7.

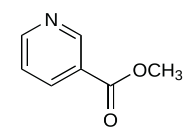

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Methyl Nicotinate). A white or almost white powder. M.p. 40° to 42°. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Methyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Pickles Chilblain Cream.

Multi-ingredient: ***Arg.:*** Infrarub†; Medex Rub; ***Austral.:*** Deep Heat; ***Austria:*** Berggeist; ***Belg.:*** Algipan; Emerxil; Percutalgine; Rado-Spray†; ***Canad.:*** Arthricare for Women Multi-Action†; Arthricare Triple Medicated†; Midalgan†; ***Chile:*** Frixio; Konirub; Mentobalsam; ***Fr.:*** Algipan; Capsic; Cliptol Sport†; Decontractyl; Gel Rubefiant; Percutalgine; Sedartryl†; ***Ger.:*** Doloneuro†; Forapin E†; Kytta-Balsam f; Rheuma Bad; Spondylon; Tetesept Badekonzentrat Rheuma Bad†; ***Gr.:*** Faragel-Forte; ***India:*** Algipan; Flamar; Medicreme; Relaxyl; ***Indon.:*** Remakrim; ***Irl.:*** Algipan; ***Israel:*** Deep Heat Spray; ***Ital.:*** Altadrine; Balsamo Sifcamina; Relaxar; Sedalpan; ***Neth.:*** Cremor capsici comp; Cremor Capsici compositus; Kruidvat Spierbalsem; ***Pol.:*** Deep Heat; ***Port.:*** Midalgan†; ***S.Afr.:*** Deep Heat Spray; Infrarub; Sloan's Heat Rub; ***Singapore:*** Deep Heating Spray†; ***Spain:*** Doctofril Antiinflamat; Doctomitil†; Radio Salil; ***Switz.:*** Kytta Baume; Midalgan; Radalgin; ***Thai.:*** Percutalgine†; ***UK:*** Cremalgin; Deep Heat Spray; Dubam; Fiery Jack; Radian-B Red Oils; Ralgex; Ralgex Heat Spray (low-odour); Red Oil; Transvasin Heat Spray; ***USA:*** Arthricare Odor Free; Arthricare Triple Medicated; Musterole.

Methyl Salicylate

Methyl Sal.; Méthyle, salicylate de; Methyli Salicylas; Methylis salicylas; Methyl-salicylát; Metilsalicilatas; Metilsalisilat; Metil-szalicilát; Metylsalicylat; Metylu salicylan; Metyylisalisylaatti; Salicilato de metilo. Methyl 2-hydroxybenzoate.

Метилсалицилат
$C_8H_8O_3$ = 152.1.
CAS — 119-36-8.

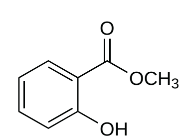

NOTE. Methyl salicylate and methyl salicylate liniment have been known previously as oil of wintergreen, wintergreen, and wintergreen oil. Wintergreen oil has also been known as sweet birch oil.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Methyl Salicylate). A colourless or slightly yellow liquid. Very slightly soluble in water; miscible with alcohol, and with fatty and essential oils. Protect from light.

USNF 26 (Methyl Salicylate). It is produced synthetically or is obtained from the leaves of *Gaultheria procumbens* (Ericaceae) [wintergreen] or from the bark of *Betula lenta* (Betulaceae) [sweet or black birch]. The source of the methyl salicylate must be indicated on the label.

A colourless, yellowish, or reddish liquid having the characteristic odour of wintergreen. Slightly soluble in water; soluble in alcohol and in glacial acetic acid. Store in airtight containers.

Storage. Certain plastic containers, such as those made from polystyrene, are unsuitable for liniments or ointments containing methyl salicylate.

Adverse Effects, Treatment, and Precautions

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate (see Overdosage, below).

Overdosage. Ingestion of methyl salicylate poses the threat of severe, rapid-onset salicylate poisoning because of its liquid concentrated form and lipid solubility.[1] It is readily absorbed from the gastrointestinal tract and most is rapidly hydrolysed to free salicylate. The symptoms, which may appear within 2 hours of ingestion, are similar to those of salicylate poisoning in general (see Adverse Effects of Aspirin, p.20), although methyl salicylate is expected to be more toxic because of its lipid solubility. There have been reports of fatalities after ingestion of as little as 4 mL in a child and 6 mL in an adult, although the adult lethal dose is estimated to be 30 mL.[1] Topical Chinese herbal medicinal preparations may contain methyl salicylate in variable amounts, and salicylate poisoning has been reported in a 40-year-old man after a total body application of such a preparation.[2] Salicylate poisoning has also been reported in a woman who had attempted suicide by ingesting Red Flower Oil, a topical Chinese herbal oil.[3] The authors also noted that some patients took small amounts of this preparation orally in an attempt to enhance its analgesic effects.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Bell AJ, Duggin G. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. *Emerg Med (Fremantle)* 2002; **14:** 188–90.
3. Chan TH, *et al.* Severe salicylate poisoning associated with the intake of Chinese medicinal oil ('Red Flower Oil'). *Aust N Z J Med* 1995; **25:** 57.

Percutaneous absorption. Like other salicylates, methyl salicylate may be absorbed through intact skin.[1] Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Results from a study in healthy subjects showed that a considerable amount of salicylic acid may be absorbed through the skin after topical application of products containing methyl salicylate.[2] Both the rate and extent of absorption increased after repeated application; the bioavailability of the ointment preparation used in the study increased from 15% after the second dose to 22% after the third to eighth dose. The authors recommend that topical analgesic preparations containing methyl salicylate or other salicylates should be used with caution in patients at increased risk of developing salicylate adverse effects (see Precautions of Aspirin, p.22).

Results from another study[3] showing high tissue to plasma ratios after topical application of a methyl salicylate formulation suggest that direct penetration and not recirculation in the blood is responsible for the salicylate concentrations found. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.

However, for a study suggesting limited absorption from a patch preparation containing camphor, menthol, and methyl salicylate, see Menthol, p.2340.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; **15:** 747–50.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topical applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.
3. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.

Interactions

Absorption of methyl salicylate through the skin can occur after excessive topical application (see above), and interactions would be expected to be as for other salicylates (see Interactions of Aspirin, p.23).

Anticoagulants. Potentiation of *warfarin* anticoagulation has been reported[1-3] after topical application of methyl salicylate preparations.

1. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; **263:** 2888.
2. Tam LS, *et al.* Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med* 1995; **25:** 258.
3. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother* 2000; **34:** 729–33.

Uses and Administration

Methyl salicylate is a salicylic acid derivative that is irritant to the skin and is used topically in rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It is also used for minor peripheral vascular disorders such as chilblains and as an ingredient in inhalations for the symptomatic relief of upper respiratory-tract disorders.

Wintergreen oil is also used in aromatherapy.

Preparations

BP 2008: Kaolin Poultice; Methyl Salicylate Liniment; Methyl Salicylate Ointment; Surgical Spirit.

Proprietary Preparations (details are given in Part 3)
Arg.: Aspi-Rub†; Rati Salil Gel; ***Austral.:*** Linsal†; ***Canad.:*** Deep Heating; ***Chile:*** Parche Calorub; ***Ger.:*** Hewedolor N; ***India:*** Dolocide Plus; ***Mex.:*** Balsamo Nordin; Friccion Don Juan; Tolan; ***S.Afr.:*** Thermo-Rub; ***Thai.:*** My-gesal; ***UK:*** Numark Muscle Rub; ***USA:*** Argesic†; Exocaine†; Gordogesic; ***Venez.:*** Novofric†; Ultrafil†.

Multi-ingredient: numerous preparations are listed in Part 3.

Mofebutazone *(rINN)*

Mofebutatsoni; Mofebutazon; Mofebutazona; Mofébutazone; Mofebutazonum; Monobutazone; Monophenylbutazone. 4-Butyl-1-phenylpyrazolidine-3,5-dione.

Мофебутазон

$C_{13}H_{16}N_2O_2$ = 232.3.
CAS — 2210-63-1.
ATC — M01AA02; M02AA02.
ATC Vet — QM01AA02; QM02AA02.

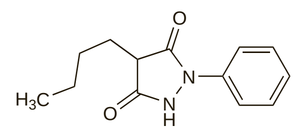

Profile

Mofebutazone, a derivative of phenylbutazone (p.117), is an NSAID (p.96). It has been used in the management of musculoskeletal and joint disorders. The sodium salt has been given by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Mofesal N†.

Mofezolac *(rINN)*

Mofézolac; Mofezolaco; Mofezolacum; N-22. 3,4-Bis(*p*-methoxyphenyl)-5-isoxazoleacetic acid.

Мофезолак

$C_{19}H_{17}NO_5$ = 339.3.
CAS — 78967-07-4.

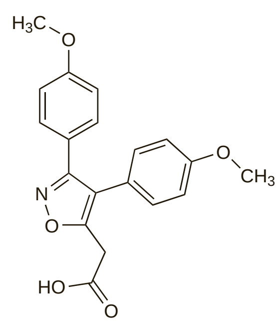

Profile

Mofezolac is an NSAID (p.96) given orally in the management of pain and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Disopain.

Morniflumate *(USAN, rINN)*

Morniflumato; Morniflumatum; UP-164. 2-Morpholinoethyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

Морнифлумат

$C_{19}H_{20}F_3N_3O_3$ = 395.4.
CAS — 65847-85-0.
ATC — M01AX22.
ATC Vet — QM01AX22.

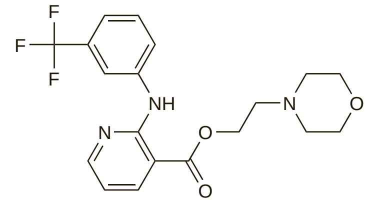

Profile

Morniflumate, the morpholinoethyl ester of niflumic acid (p.95), is an NSAID (p.96). It has been used in inflammatory conditions in doses of 700 mg given twice daily by mouth or rectally as suppositories.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nifluril; ***Ital.:*** Flomax; Flumarin; Morniflu; Niflam; ***Spain:*** Niflactol.

Morphine *(BAN)* ⊗

Morfiini; Morfin; Morfina; Morphinum. 7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol.

Морфин

$C_{17}H_{19}NO_3$ = 285.3.
CAS — 57-27-2 (anhydrous morphine); 6009-81-0 (morphine monohydrate).
ATC — N02AA01.
ATC Vet — QN02AA01.

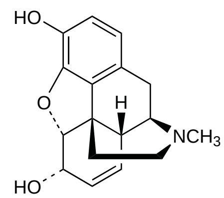

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of morphine:

Adolf; Block; China White; Cube; Dreamer; Drug store dope; Drugstore dope; Emsel; First line; German boy; God's drug; Goma; Hard stuff; Hospital Heroin; Hows; Hydrogen Bomb; M; Miss Emma; Mister blue; Mojo; Monf; Monkey; Morf; Morfs; Morfa; Morphia; Morphina; Morpho; Morphy; Mr. Blue; M.S.; MS; Mud; Murphy; Nasty; Nazi; Sweet Jesus; Sweet Morpheus; Tar; Unkie; White Stuff.

Morphine Hydrochloride *(BANM)* ⊗

Morfiinihydrokloridi; Morfin Hidroklorür; Morfina, hidrocloruro de; Morfin-hidroklorid; Morfin-hydrochlorid trihydrát; Morfinhydroklorid; Morfino hidrochloridas; Morfiny chlorowodorek; Morphine, chlorhydrate de; Morphini hydrochloridum; Morphini Hydrochloridum Trihydricum; Morphinii Chloridum; Morphinum Chloratum.

Морфина Гидрохлорид

$C_{17}H_{19}NO_3,HCl,3H_2O$ = 375.8.
CAS — 52-26-6 (anhydrous morphine hydrochloride); 6055-06-7 (morphine hydrochloride trihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.*

Ph. Eur. 6.2 (Morphine Hydrochloride). Colourless, silky needles, cubical masses or a white or almost white, crystalline powder. It is efflorescent in a dry atmosphere. Soluble in water; slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

Incompatibility. See under Morphine Sulfate, below.

Morphine Sulfate ⊗

Morfiinisulfaatti; Morfin Sülfat; Morfina, sulfato de; Morfino sulfatas; Morfinsulfat; Morfin-sulfát pentahydrát; Morfin-szulfát; Morfiny siarczan; Morphine, sulfate de; Morphine Sulphate *(BANM)*; Morphini sulfas; Morphini Sulfas Pentahydricus.

Морфина Сульфат

$(C_{17}H_{19}NO_3)_2,H_2SO_4,5H_2O$ = 758.8.
CAS — 64-31-3 (anhydrous morphine sulfate); 6211-15-0 (morphine sulfate pentahydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Morphine Sulphate). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

USP 31 (Morphine Sulfate). White, feathery, silky crystals, cubical masses of crystals, or a white crystalline powder. Is odourless and when exposed to air it gradually loses water of hydration. It darkens on prolonged exposure to light. Soluble 1 in 16 of water and 1 in 1 of water at 80°; soluble 1 in 570 of alcohol and 1 in 240 of alcohol at 60°; insoluble in chloroform and in ether. Store in airtight containers at a temperature up to 40° as permitted by the manufacturer. Protect from light.

Incompatibility. Incompatibility data for morphine has been extensively studied[1,2] and may depend on many factors such as the formulation used, and order and ratio of mixing; however, most studies are usually only short term and contain few details on mixing the same drugs in a variety of different situations.

Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities, sometimes attributed to particular formulations, have included:

- Aciclovir sodium—precipitate noted 2 hours after admixture with morphine sulfate solution[3]
- Chlorpromazine hydrochloride injection—precipitation was considered to be due to chlorocresol present in the morphine sulfate injection[4]
- Doxorubicin—addition of morphine sulfate 1 mg/mL to doxorubicin hydrochloride liposomal injection 400 micrograms/mL in dextrose 5% resulted in turbidity changes[5]
- Fluorouracil—immediate precipitate formed after admixture of fluorouracil 1 or 16 mg/mL with morphine sulfate 1 mg/mL in dextrose 5% or sodium chloride 0.9%[6]
- Furosemide—precipitate noted 1 hour after admixture with morphine sulfate solution[3]
- Haloperidol—immediate precipitation seen after admixture of haloperidol and morphine sulfate solution[7]
- Heparin sodium—incompatibility has been reported from straightforward additive studies.[1] Another study[8] indicated that morphine sulfate and heparin sodium were only incompatible at morphine sulfate concentrations greater than 5 mg/mL and that this incompatibility could be prevented by using 0.9% sodium chloride solution as the admixture diluent rather than water
- Pethidine hydrochloride—incompatibility has been noted after admixture with morphine sulfate[1,9]
- Prochlorperazine edisilate—immediate precipitation was attributed to phenol in the morphine sulfate injection formulation[10,11]
- Promethazine hydrochloride—cloudiness was reported to develop when 12.5 mg of promethazine hydrochloride was drawn into a syringe containing morphine sulfate 8 mg.[12] Others[9] have noted no incompatibility
- Ranitidine hydrochloride—crystal needles and/or sticky spots observed in admixtures of morphine hydrochloride and ranitidine hydrochloride in various ratios stored at different temperatures[13]
- Tetracyclines—colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with morphine sulfate in 5% glucose injection[14]

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.
3. Pugh CB, *et al.* Visual compatibility of morphine sulphate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Crapper JB. Mixing chlorpromazine and morphine. *BMJ* 1975; **i:** 33.
5. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
6. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.
7. LeBelle MJ, *et al.* Compatibility of morphine and midazolam or haloperidol in parenteral admixtures. *Can J Hosp Pharm* 1995; **48:** 155–60.
8. Baker DE, *et al.* Compatibility of heparin sodium and morphine sulfate. *Am J Hosp Pharm* 1985; **42:** 1352–5.
9. Parker WA. Physical compatibilities of preanesthetic medications. *Can J Hosp Pharm* 1976; **29:** 91–2.
10. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; **42:** 2651.
11. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
12. Fleischer NM. Promethazine hydrochloride—morphine sulfate incompatibility. *Am J Hosp Pharm* 1973; **30:** 665.
13. Vermeire A, *et al.* A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care. *Palliat Med* 2002; **16:** 417–24.
14. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.

Stability. ***INTRAVENOUS PREPARATIONS.*** Solutions of morphine sulfate for intravenous infusion appear to be relatively stable. In a study[1] solutions containing 40 micrograms/mL and 400 micrograms/mL retained more than 90% of their initial concentration of morphine sulfate when stored at 4° or 23° for 7 days, whether or not they were protected from light. Solutions prepared from commercially available injection or from powder, in 0.9% sodium chloride or 5% glucose, and stored in PVC bags or glass bottles did not differ in stability from one another. In a further study[2] 10 mg/mL or 5 mg/mL solutions of morphine sulfate in glucose or sodium chloride and stored in portable infusion pump cassettes retained more than 95% of their initial concentration when kept at 23° for 30 days. A 0.9% solution of sodium chloride containing morphine sulfate 2 mg/mL was stable for 6 weeks when stored in polypropylene syringes at ambient temperatures in the light or dark but a similar solution which also contained 0.1% sodium metabisulfite lost 15% of its potency during the same period.[3] Stability of such a solution with or without sodium metabisulfite was considered to be unacceptable when stored in glass syringes in the dark.[4]

A more recent review[5] (which included some of the above studies) has concluded that the degradation of morphine solutions is not affected by oxygen, light, diluent type, salt form, or morphine concentration when stored under normal conditions; it was considered that morphine solutions could be stored for at least 3 months without stability problems.

1. Vecchio M, *et al.* The stability of morphine intravenous infusion solutions. *Can J Hosp Pharm* 1988; **41:** 5–9, 43.
2. Walker SE, *et al.* Hydromorphone and morphine stability in portable infusion pump cassettes and minibags. *Can J Hosp Pharm* 1988; **41:** 177–82.
3. Grassby PF. The stability of morphine sulphate in 0.9 per cent sodium chloride stored in plastic syringes. *Pharm J* 1991; **248:** HS24–HS25.
4. Grassby PF, Hutchings L. Factors affecting the physical and chemical stability of morphine sulphate solutions stored in syringes. *Int J Pharm Pract* 1993; **2:** 39–43.
5. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; **187:** 17–51.

ORAL PREPARATIONS. Studies[1,2] have shown that for optimum stability of morphine content, Kaolin and Morphine Mixture (BP) needed to be stored in well-filled glass containers.

1. Helliwell K, Game P. Stability of morphine in kaolin and morphine mixture BP. *Pharm J* 1981; **227:** 128–9.
2. Helliwell K, Jennings P. Kaolin and morphine mixture BP: effects of containers on the stability of morphine. *Pharm J* 1984; **232:** 682.

TOPICAL PREPARATIONS. When mixed with about 8 g of *Intrasite* gel (*Smith & Nephew Healthcare, UK*) morphine sulfate, in a concentration of 1.25 mg/mL, remained chemically stable over a 28-day period stored at 4° or at room temperature, irrespective of light exposure.[1] However, unless prepared under sterile conditions, the mixture should be used within 7 days because of the risk of microbial contamination once the gel has been opened.

1. Zeppetella G, *et al.* Stability of morphine sulphate and diamorphine hydrochloride in Intrasite gel . *Palliat Med* 2005; **19:** 131–6.

Morphine Tartrate *(BANM)* ⊗

Morfina, tartrato de.

Морфина Тартрат

$(C_{17}H_{19}NO_3)_2,C_4H_6O_6,3H_2O = 774.8.$

CAS — 302-31-8 (anhydrous morphine tartrate); 6032-59-3 (morphine tartrate trihydrate).

Incompatibility. See under Morphine Sulfate, above.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than that associated with κ-receptor agonists. With morphine, withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Morphine is used for substitution therapy in the management of neonatal abstinence syndrome (see Administration in Children, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

◊ References.

1. Cherny N, *et al.* Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001; **19:** 2542–54.

Effects on the cardiovascular system. For a reference to the effects of morphine on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on the muscles. Severe rectovaginal spasms that occurred in a patient given intrathecal morphine[1] were successfully controlled with midazolam.

1. Littrell RA, *et al.* Muscle spasms associated with intrathecal morphine therapy: treatment with midazolam. *Clin Pharm* 1992; **11:** 57–9.

Effects on the nervous system. Myoclonus, often associated with hyperalgesia, has been reported in patients with advanced malignant disease treated with morphine.[1-5] It appears to be uncommon with typical oral doses of morphine and is more often associated with high intravenous and spinal doses. Neuroexcitatory metabolites of morphine are often implicated in the development of myoclonus;[2,4,5] however, other possible mechanisms such as drug interactions cannot be ruled out.[4-6]

It has been reported that myoclonus induced by morphine can be successfully controlled using a benzodiazepine such as midazolam.[7] Indeed, some researchers[8] consider benzodiazepines to be the drugs of choice: clonazepam, diazepam, and lorazepam were most frequently used. Dantrolene[5,8] and gabapentin[9] have also been tried.

1. Potter JM, *et al.* Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. *BMJ* 1989; **299:** 150–3.
2. Glare PA, *et al.* Normorphine, a neurotoxic metabolite? *Lancet* 1990; **335:** 725–6.
3. De Conno F, *et al.* Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. *Pain* 1992; **47:** 337–9.
4. Sjøgren P, *et al.* Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine. *Pain* 1993; **55:** 93–7.
5. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998; **74:** 5–9.
6. Quinn N. Myoclonus associated with high doses of morphine. *BMJ* 1989; **299:** 683–4.
7. Holdsworth MT, *et al.* Continuous midazolam infusion for the management of morphine-induced myoclonus. *Ann Pharmacother* 1995; **29:** 25–9.
8. Ferris DJ. Controlling myoclonus after high-dosage morphine infusions. *Am J Health-Syst Pharm* 1999; **56:** 1009–10.
9. Mercadante S, *et al.* Gabapentin for opioid-related myoclonus in cancer patients. *Support Care Cancer* 2001; **9:** 205–6.

Precautions

As for Opioid Analgesics in general, p.103.

Biliary-tract disorders. See under Precautions of Opioid Analgesics, p.103.

Breast feeding. Measurable blood concentrations of morphine have been detected in 2 breast-fed infants whose mothers received oral or intrathecal morphine during and after their pregnancies; however, no adverse effects were reported in either of these infants.[1,2] In a group of 7 women given patient-controlled analgesia with intravenous morphine after caesarean delivery, the concentrations of morphine and its metabolite morphine-6 glucuronide in the colostrum were found to be very small.[3] Although no infants were breast fed during the study, it was considered that the effects of maternal morphine on breast-fed infants would be negligible.[3] The American Academy of Pediatrics[4] also states that the use of morphine is usually compatible with breast feeding.

1. Robieux I, *et al.* Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol* 1990; **28:** 365–70.
2. Oberlander TF, *et al.* Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact* 2000; **16:** 137–42.
3. Baka N-E, *et al.* Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* 2002; **94:** 184–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hepatic impairment. In view of its hepatic metabolism, caution is generally advised when giving morphine to patients with hepatic impairment (but see under Pharmacokinetics, below). The *BNF* advises that use should be avoided or the dose reduced because of the risk of precipitating a coma, although it is also noted that many patients with hepatic impairment tolerate morphine well. Others have considered that severe hepatic impairment may affect morphine metabolism but less severe impairment does not.[1]

The mean elimination half-life of morphine in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine preparation (*MST-Continus; Napp, UK*) and peak serum concentrations were almost three times as high.[2] Patients with cirrhosis had a greater degree of sedation but none developed encephalopathy. It was recommended that the dose for modified-release preparations should be reduced and that it be given less often when patients have cirrhosis.

In a later study[3] 15 patients with liver cancer were given the same oral morphine preparation and compared with 10 healthy subjects from the previous study; the area under the serum concentration-time curve of morphine was increased three- to fourfold in those with cancer. The elimination half-life of morphine was also prolonged in patients with primary cancer when compared with healthy subjects and those with secondary metastatic disease. Adverse effects were more frequent in the primary cancer group and included 2 cases of respiratory depression; the authors commented that altered blood-brain transportation may have been partly responsible for such effects.

1. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 274.

2. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. *Br J Anaesth* 1997; **79:** 804–6.
3. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br J Anaesth* 2005; **94:** 95–9.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma. For further details, see p.103.

Renal impairment. Severe and prolonged respiratory depression has occurred in patients with renal impairment given morphine. Toxicity in 3 such patients was attributed to the accumulation of the active metabolite morphine-6-glucuronide.[1] Plasma concentrations of this metabolite were found[2] to be ten times higher than normal in a 7-year-old girl with haemolytic uraemic syndrome given morphine intravenously although the half-life of morphine was also prolonged. Plasma concentrations of morphine-6-glucuronide were also reported[3] to be persistently increased 19 days after stopping morphine by intravenous infusion in a 17-year-old girl with normal renal function. The authors of the report suggested that alterations in bowel flora after antibacterial therapy or inhibition of morphine-3-glucuronide glucuronidation by lorazepam might be responsible. It has also been reported[4] that accumulation of morphine can occur in renal failure, although to a lesser extent than accumulation of metabolites (see also under Pharmacokinetics, below).

1. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
2. Hasselström J, *et al.* Long lasting respiratory depression induced by morphine-6-glucuronide? *Br J Clin Pharmacol* 1989; **27:** 515–18.
3. Calleja MA, *et al.* Persistently increased morphine-6-glucuronide concentrations. *Br J Anaesth* 1990; **64:** 649.
4. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.

Interactions

For interactions associated with opioid analgesics, see p.103.

US licensed product information for some once-daily modified-release preparations of morphine sulfate states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of rapid release and absorption of a potentially fatal dose of morphine; *in-vitro* studies showed that alcohol accelerated the release of morphine.

◊ For references to myoclonus associated with morphine and the concurrent use of other drugs, see Effects on the Nervous System under Adverse Effects, above.

Antibacterials. There is some evidence[1] that the potent enzyme inducer *rifampicin* can reduce the serum concentration of morphine and decrease its analgesic effect; induction of the enzymes responsible for conversion of morphine to the active glucuronide metabolite did not seem to occur.

1. Fromm MF, *et al.* Loss of analgesic effect of morphine due to coadministration of rifampin. *Pain* 1997; **72:** 261–7.

Benzodiazepines. An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and *midazolam.*[1]

For reference to a suggestion that *lorazepam* may inhibit morphine-3-glucuronide glucuronidation, see Renal Impairment under Precautions, above.

1. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.

Cisapride. Plasma concentrations of morphine have been increased by oral cisapride.[1]

1. Rowbotham DJ, *et al.* Effect of cisapride on morphine absorption after oral administration of sustained-release morphine. *Br J Anaesth* 1991; **67:** 421–5.

Histamine H_2-antagonists. See under Opioid Analgesics, p.103.

Local anaesthetics. Prior use of epidural *chloroprocaine*, when compared with lidocaine, has been reported to reduce the duration[1] and efficacy[2] of epidural morphine analgesia. However, a later study[3] found no such effects; the authors suggested that findings from the previous 2 studies were due to breakthrough pain caused by the early resolution of chloroprocaine anaesthesia occurring before the maximum onset of morphine analgesia.

1. Eisenach JC, *et al.* Effect of prior anesthetic solution on epidural morphine analgesia. *Anesth Analg* 1991; **73:** 119–23.
2. Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. *Acta Anaesthesiol Scand* 1997; **41:** 774–8.
3. Hess PE, *et al.* Chloroprocaine may not affect epidural morphine for postcesarean delivery analgesia. *J Clin Anesth* 2006; **18:** 29–33.

Metoclopramide. Reports on the effects of metoclopramide on morphine have included an increased rate of onset and degree of sedation when oral metoclopramide was given with modified-release morphine[1] and antagonism of the effects of morphine on gastric emptying by intravenous metoclopramide.[2]

1. Manara AR, *et al.* The effect of metoclopramide on the absorption of oral controlled release morphine. *Br J Clin Pharmacol* 1988; **25:** 518–21.
2. McNeill MJ, *et al.* Effect of iv metoclopramide on gastric emptying after opioid premedication. *Br J Anaesth* 1990; **64:** 450–2.

Tricyclic antidepressants. Both *clomipramine* and *amitriptyline* significantly increased the plasma availability of morphine when given to cancer patients taking oral morphine solution.[1] It was noted however that the potentiation of the analgesic effects of morphine by these drugs might not be confined to increased bioavailability of morphine; the dose of tricyclic to use with morphine in the treatment of cancer pain should be decided by clinical evaluation rather than by pharmacokinetic data.

1. Ventafridda V, *et al.* Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* 1987; **i:** 1204.

Pharmacokinetics

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability since they undergo extensive first-pass metabolism in the liver and gut. After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses. Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2.4 to 6.7 hours for morphine-3-glucuronide have been reported.

Up to 10% of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

◊ Much has been published on the metabolism and disposition of morphine and its relevance to the clinical use of morphine, in particular the analgesic effect of repeated oral doses and the relative potency of oral to parenteral doses. There has been uncertainty as to the contributions in man of first-pass metabolism in the liver and gut,[1-4] the possible role of renal metabolism,[2,3,5,6] the analgesic activity and clinical importance of the metabolite morphine-6-glucuronide,[2,7-21] and enterohepatic circulation.[2,9] There has also been interest in the effects of the metabolite morphine-3-glucuronide.[21-24]

1. Hanks GW, Aherne GW. Morphine metabolism: does the renal hypothesis hold water? *Lancet* 1985; **i:** 221–2.
2. Hanks GW, *et al.* Explanation for potency of repeated oral doses of morphine? *Lancet* 1987; **ii:** 723–5.
3. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
5. McQuay H, Moore A. Metabolism of narcotics. *BMJ* 1984; **288:** 237.
6. Moore A, *et al.* Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984; **35:** 641–5.
7. McQuay HJ, *et al.* Potency of oral morphine. *Lancet* 1987; **ii:** 1458–9.
8. Hanks GW, *et al.* Enterohepatic circulation of morphine. *Lancet* 1988; **i:** 469.
9. Osborne R, *et al.* Analgesic activity of morphine-6-glucuronide. *Lancet* 1988; **i:** 828.
10. Hanks GW, Wand PJ. Enterohepatic circulation of opioid drugs: is it clinically relevant in the treatment of cancer patients? *Clin Pharmacokinet* 1989; **17:** 65–8.
11. Paul D, *et al.* Pharmacological characterization of morphine-6β-glucuronide, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; **251:** 477–83.
12. Hanna MH, *et al.* Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine. *Br J Anaesth* 1990; **64:** 547–50.
13. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
14. McQuay HJ, *et al.* Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clin Pharmacol Ther* 1990; **48:** 236–44.
15. Hanna MH, *et al.* Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *Br J Anaesth* 1991; **66:** 103–7.
16. Portenoy RK, *et al.* The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther* 1992; **51:** 422–31.
17. Thompson PI, *et al.* Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995; **40:** 145–52.
18. Lötsch J, Geisslinger G. Morphine-6-glucuronide: an analgesic of the future? *Clin Pharmacokinet* 2001; **40:** 485–99.
19. Wittwer E, Kern SE. Role of morphine's metabolites in analgesia: concepts and controversies. *AAPS J* 2006; **8:** E348–E352.
20. van Dorp ELA, *et al.* Morphine-6-glucuronide: morphine's successor for postoperative pain relief? *Anesth Analg* 2006; **102:** 1789–97.
21. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care Pharmacother* 2003; **16** (4): 5–18.
22. Smith MT, *et al.* Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sci* 1990; **47:** 579–85.
23. Morley JS, *et al.* Paradoxical pain. *Lancet* 1992; **340:** 1045.
24. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342:** 1243.

Administration. There have been many studies on the pharmacokinetics of morphine given by various routes and methods. These include the buccal route (see below), modified-release oral preparations,[1,2] the rectal route,[3,4] the topical route,[5] the pulmonary route,[6,7] continuous subcutaneous compared with intravenous infusion,[8] and the intraspinal route.[9-13]

Slow dural transfer of morphine and its prolonged presence in the CSF appear to correlate with its slow onset and long duration of action by epidural and intrathecal injection.[14] More lipid-soluble opioids, such as diamorphine and pethidine, enter and leave the CSF more rapidly than morphine.

The pharmacokinetics of morphine given by 5 different routes—intravenous bolus injection and oral, sublingual, buccal, and modified-release buccal tablets—were studied[15] with particular reference to morphine-6-glucuronide, the active metabolite. This metabolite occurred in large quantities after intravenous doses and plasma concentrations rapidly exceeded those of morphine. After oral doses morphine-6-glucuronide and morphine-3-glucuronide were present in quantities similar to those seen after intravenous morphine; morphine concentrations in plasma were very low and the mean morphine-6-glucuronide to morphine area under the curve ratio was 9.7 to 1. There was delayed absorption with attenuation and delay of peak morphine and metabolite plasma concentrations after sublingual or buccal dosage.

Compared with oral doses, concentrations of morphine were higher and those of its glucuronides lower when morphine was given rectally,[16] suggesting avoidance of first-pass metabolism.

Morphine was not absorbed systemically when applied topically to ulcers although some absorption may occur when a large surface area is involved.[5]

1. Pinnock CA, *et al.* Absorption of controlled release morphine sulphate in the immediate postoperative period. *Br J Anaesth* 1986; **58:** 868–71.
2. Savarese JJ, *et al.* Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; **11:** 505–10.
3. Moolenaar F, *et al.* Drastic improvement in the rectal absorption profile of morphine in man. *Eur J Clin Pharmacol* 1985; **29:** 119–21.
4. Cole L, *et al.* Further development of a morphine hydrogel suppository. *Br J Clin Pharmacol* 1990; **30:** 781–6.
5. Ribeiro MDC, *et al.* The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004; **27:** 434–9.
6. Ward ME, *et al.* Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clin Pharmacol Ther* 1997; **62:** 596–609.
7. Masood AR, Thomas SHL. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 250–2.
8. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
9. Gustafsson LL, *et al.* Disposition of morphine in cerebrospinal fluid after epidural administration. *Lancet* 1982; **i:** 796.
10. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; **35:** 40–5.
11. Max MB, *et al.* Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clin Pharmacol Ther* 1985; **38:** 631–41.
12. Nordberg G, *et al.* Extradural morphine: influence of adrenaline admixture. *Br J Anaesth* 1986; **58:** 598–604.
13. Ionescu TI, *et al.* The pharmacokinetics of intradural morphine in major abdominal surgery. *Clin Pharmacokinet* 1988; **14:** 178–86.
14. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
15. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; **47:** 12–19.
16. Babul N, Darke AC. Disposition of morphine and its glucuronide metabolites after oral and rectal administration: evidence of route specificity. *Clin Pharmacol Ther* 1993; **54:** 286–92.

BUCCAL ROUTE. Conflicting results from studies on buccal morphine may reflect differences in formulation[1] and hence absorption. Some[2] reported equivalent analgesia with buccal and intramuscular morphine although others[3] found marked interindividual variability with mean peak serum concentrations of morphine some eight times lower after a buccal tablet than after an intramuscular injection and occurring a mean of 4 hours later. Morphine sulfate in aqueous solution has been reported to be moderately well absorbed from the buccal mucosa.[4] Absolute bioavailability for morphine was estimated to be 23.8% after an oral solution, 22.4% after a modified-release oral tablet (*MST Continus; Napp, UK*), and 20.2% after a modified-release buccal tablet, with maximum plasma-morphine concentrations at 45 minutes, 2.5 hours, and 6 hours respectively; mean ratios of area under the plasma concentration-time curve for morphine-6-glucuronide to morphine in plasma were 11:1 after buccal and oral morphine compared with 2:1 for intravenous morphine.[5] There was considerable inter-subject variation in plasma concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide after buccal doses of morphine as a modified-release formulation,[6] and lack of pain relief was subsequently reported with this buccal formulation.[7] Poor absorption of morphine from modified-release buccal tablets when compared with intramuscular injection was also reported;[8] bitterness of the tablets, leading to their premature removal, and poor dissolution may have contributed.

1. Calvey TN, Williams NE. Pharmacokinetics of buccal morphine. *Br J Anaesth* 1990; **64:** 256.
2. Bell MDD, *et al.* Buccal morphine—a new route for analgesia? *Lancet* 1985; **i:** 71–3.
3. Fisher AP, *et al.* Serum morphine concentrations after buccal and intramuscular morphine administration. *Br J Clin Pharmacol* 1987; **24:** 685–7.
4. Al-Sayed-Omar O, *et al.* Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide. *J Pharm Pharmacol* 1987; **39:** 934–5.
5. Hoskin PJ, *et al.* The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 499–505.
6. Manara AR, *et al.* Pharmacokinetics of morphine following administration by the buccal route. *Br J Anaesth* 1989; **62:** 498–502.
7. Manara AR, *et al.* Analgesic efficacy of perioperative buccal morphine. *Br J Anaesth* 1990; **64:** 551–5.
8. Simpson KH, *et al.* An investigation of premedication with morphine given by the buccal or intramuscular route. *Br J Clin Pharmacol* 1989; **27:** 377–80.

Children. The pharmacokinetics of morphine in *children* are generally considered similar to those in adults;[1-3] in both an elimination half-life of about 2 hours has been reported after intravenous administration of morphine. In *neonates*, however, clearance is generally reduced[4-7] and pharmacokinetics are more variable.[8-10] Studies[7,11] have found significantly higher plasma concentrations of morphine and a significantly lower morphine-6-glucuronide to morphine ratio in neonates when compared with older infants and children; however, the morphine-6-glucuronide to morphine-3-glucuronide ratio remains constant irrespective of age.[7] Elimination half-lives of 6.7 and 10 hours have been reported in term and preterm infants, respectively after a single intravenous dose of morphine, with nearly 80% of the dose remaining unbound.[10] The reduced clearance, which is dependent on gestational age and birth weight,[12,13] and higher morphine concentrations are probably due to reduced metabolism in neonates as well as immature renal function: the capacity to conjugate morphine by glucuronidation is reduced in preterm infants,[6,8,9] and some premature neonates may lack the capacity entirely.[9]

1. Dahlström B, *et al.* Morphine kinetics in children. *Clin Pharmacol Ther* 1979; **26:** 354–65.
2. Stanski DR, *et al.* Kinetics of high-dose intravenous morphine in cardiac surgery patients. *Clin Pharmacol Ther* 1976; **19:** 752–6.
3. Olkkola KT, *et al.* Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet* 1995; **5:** 385–404.
4. Koren G, *et al.* Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985; **107:** 963–7.
5. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; **66:** 136–9.
6. Choonara IA, *et al.* Morphine metabolism in children. *Br J Clin Pharmacol* 1989; **28:** 599–604.
7. Bouwmeester NJ, *et al.* Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* 2003; **90:** 642–52.
8. Hartley R, *et al.* Pharmacokinetics of morphine infusion in premature neonates. *Arch Dis Child* 1993; **69:** 55–8.
9. Bhat R, *et al.* Morphine metabolism in acutely ill preterm newborn infants. *J Pediatr* 1992; **120:** 795–9.
10. Bhat R, *et al.* Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. *J Pediatr* 1990; **117:** 477–81.
11. Bouwmeester NJ, *et al.* Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003; **29:** 2009–15.
12. Scott CS, *et al.* Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr* 1999; **135:** 423–9.
13. Saarenmaa E, *et al.* Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000; **68:** 160–6.

The elderly. The pharmacokinetics of morphine were compared[1] in 7 healthy elderly (60 to 69 years) and 13 healthy young (24 to 28 years) subjects, after a single intravenous injection of morphine sulfate 10 mg per 70 kg. Although the terminal rate of drug disappearance from plasma was faster in the elderly group, apparent volume of distribution at steady state was about half that of the young group and plasma clearance was reduced.

1. Owen JA, *et al.* Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; **34:** 364–8.

Hepatic impairment. The liver is a major site of morphine metabolism and therefore hepatic impairment could be expected to affect elimination (see under Precautions, above). There is some evidence that in cirrhosis glucuronidation might be relatively spared compared with other metabolic processes and that some extrahepatic metabolism may occur. Several studies have served to illustrate these points:

- Hepatic extraction of morphine was impaired in cirrhotic patients, but less than expected[1]
- Morphine metabolism was minimal during the anhepatic phase of liver transplantation, but increased markedly when the new liver was reperfused[2]
- Morphine metabolism was virtually complete after liver transplantation with only 4.5% unchanged morphine being excreted in the urine 24 hours after administration[3]
- Morphine elimination was reduced when hepatic blood flow was impaired[4]

1. Crotty B, *et al.* Hepatic extraction of morphine is impaired in cirrhosis. *Eur J Clin Pharmacol* 1989; **36:** 501–6.
2. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 380–4.
3. Shelly MP, *et al.* Pharmacokinetics of morphine in patients following orthotopic liver transplantation. *Br J Anaesth* 1989; **63:** 375–9.
4. Manara AR, *et al.* Morphine elimination and liver blood flow: a study in patients undergoing distal splenorenal shunt. *Br J Hosp Med* 1989; **42:** 148 (abstract).

Renal impairment. Only a small amount of morphine is excreted unchanged in the urine. There are conflicting reports of morphine accumulation in patients with renal impairment; some for,[1,2] others against.[3-5] It does seem clear though that morphine metabolites accumulate in such patients[5-9] including those on peritoneal dialysis;[10] the half-life of the active metabolite morphine-6-glucuronide was reported to be prolonged and its clearance reduced when morphine-6-glucuronide was given to patients with renal impairment.[11] Opioid intoxication[12] and a prolonged opioid effect[13] in patients with renal failure has been associated with morphine-6-glucuronide (see also under Precautions, above).

1. Ball M, *et al.* Renal failure and the use of morphine in intensive care. *Lancet* 1985; **i:** 784–6.
2. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; **54:** 158–67.
3. Säwe J, *et al.* Kinetics of morphine in patients with renal failure. *Lancet* 1985; **ii:** 211.
4. Woolner DF, *et al.* Renal failure does not impair the metabolism of morphine. *Br J Clin Pharmacol* 1986; **22:** 55–9.
5. Chauvin M, *et al.* Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; **66:** 327–31.
6. Säwe J, Odar-Cederlöf I. Kinetics of morphine in patients with renal failure. *Eur J Clin Pharmacol* 1987; **32:** 377–82.
7. Wolff J, *et al.* Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur J Clin Pharmacol* 1988; **34:** 353–7.
8. Sear JW, *et al.* Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *Br J Anaesth* 1989; **62:** 28–32.
9. Peterson GM, *et al.* Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur J Clin Pharmacol* 1990; **38:** 121–4.
10. Pauli-Magnus C, *et al.* Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 1999; **14:** 903–9.
11. Hanna MH, *et al.* Morphine-6-glucuronide disposition in renal impairment. *Br J Anaesth* 1993; **70:** 511–14.
12. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; **292:** 1548–9.
13. Bodd E, *et al.* Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol* 1990; **9:** 317–21.

Uses and Administration

Morphine, a phenanthrene derivative, is the main alkaloid of opium (p.105). It is now commonly obtained from whole opium poppies (*Papaver somniferum*) which are harvested as poppy straw; a concentrate of poppy straw is known as CPS.

Morphine is an opioid analgesic (p.104) with agonist activity mainly at μ opioid receptors and perhaps at κ and δ receptors. It acts mainly on the CNS and smooth muscle. Although morphine is mainly a CNS depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce both physical and psychological dependence (see p.101) and should therefore be used with discrimination. Tolerance may also develop.

Morphine is used for the relief of moderate to severe pain, especially that associated with cancer, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain and it is useful as a hypnotic where sleeplessness is due to pain. It is also used in the management of neonatal abstinence syndrome (see Administration in Children, below).

Morphine reduces intestinal motility but its role, if any, in the symptomatic treatment of diarrhoea is very limited. It also relieves dyspnoea associated with various conditions, including that due to pulmonary oedema resulting from left ventricular failure. It is an effective cough suppressant, but codeine is usually preferred as there is less risk of dependence; morphine may however be necessary to control intractable cough associated with terminal lung cancer. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures such as open-heart surgery.

Morphine is usually **administered** as the sulfate, although the hydrochloride and the tartrate are used in similar doses. Doses are expressed as the salts. Dosage routes include the oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes. Subcutaneous injections are considered unsuitable for oedematous patients. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

Doses should generally be reduced in the elderly or debilitated or in patients with hepatic or renal impairment (see also under Precautions, above).

For **pain**:

- *Oral* doses are usually in the range of 5 to 20 mg every 4 hours and may be given as an aqueous solution of the hydrochloride or sulfate, as modified-release granules or tablets, or as tablets. With modified-release preparations the 24-hour dose is usually given as a single dose or in 2 divided doses; in the USA, a modified-release preparation (*MS Contin, Purdue*) that allows dosing every 8 or 12 hours is also available. With all modified-release preparations, additional doses of a conventional formulation may be needed if breakthrough pain occurs. As with the other routes, high oral doses may be required for effective analgesia in palliative care.
- Morphine is sometimes given *rectally* generally as suppositories in doses of 10 to 30 mg every 4 hours. Oral modified-release preparations have also been used rectally although such use is unlicensed in the UK and is generally not recommended except, possibly, in some emergency situations.
- The usual dose by *subcutaneous* or *intramuscular* injection is 10 mg every 4 hours but may range from 5 to 20 mg.
- Doses of up to 15 mg have been given by slow *intravenous* injection, sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration maintenance doses have generally ranged from 0.8 to 80 mg/hour, although some patients have required and been given much higher doses. Similar doses have been given by continuous subcutaneous infusion.
- For myocardial infarction, the *BNF* recommends that 10 mg may be given by intravenous injection at a rate of 2 mg/minute followed by a further 5 to 10 mg if necessary; half this dose should be used in elderly or debilitated patients.
- Intraspinal doses are in the region of 5 mg for an initial *epidural* injection; if pain relief is unsatisfactory after one hour, further doses of 1 to 2 mg may be given up to a total dose of 10 mg per 24 hours. The recommended initial dose for continuous epidural infusion is 2 to 4 mg per 24 hours increased if necessary by further doses of 1 to 2 mg. A modified-release formulation of liposomal morphine sulfate for lumbar epidural use is also available for the treatment of pain after major surgery; doses range from

10 to 20 mg, depending on the type of surgery, and should be given before the operation, or after clamping of the umbilical cord if used during caesarean section. It is intended for single-use only and no other drugs should be administered into the epidural space for at least the next 48 hours.

- *Intrathecal* use of morphine and its salts has tended to be less common than epidural. Doses of 200 micrograms to 1 mg have been injected intrathecally on a single occasion.

For details of doses in children see below.

In **acute pulmonary oedema** 5 to 10 mg may be given by intravenous injection at a rate of 2 mg/minute.

For the control of intractable **cough** associated with terminal lung cancer, morphine oral solution is given in an initial dose of 5 mg every 4 hours.

Administration. *CONTINUOUS INFUSION.* Both acute and chronic pain have been controlled satisfactorily by continuous intravenous or subcutaneous infusions of morphine sulfate[1-3] but diamorphine hydrochloride or hydromorphone hydrochloride may be preferred for subcutaneous infusion because their greater solubility in water allows a smaller dose volume. Continuous subcutaneous infusions may be preferred to continuous intravenous infusions.[4] Continuous subcutaneous infusion may be less effective than epidural morphine for relief of postoperative pain;[5] however, it was still considered to provide simple and relatively effective analgesia with a low rate of adverse effects.

See also Patient-controlled Analgesia, below.

1. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; **39:** 768–71.
2. Goudie TA, *et al.* Continuous subcutaneous infusion of morphine for postoperative pain relief. *Anaesthesia* 1985; **40:** 1086–92.
3. Stuart GJ, *et al.* Continuous intravenous morphine infusions for terminal pain control: a retrospective review. *Drug Intell Clin Pharm* 1986; **20:** 968–72.
4. Drexel H. Long-term continuous subcutaneous and intravenous opioid infusions. *Lancet* 1991; **337:** 979.
5. Hindsholm KB, *et al.* Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief. *Br J Anaesth* 1993; **71:** 580–2.

INTRA-ARTICULAR ROUTE. Intra-articular injection of morphine into the knee at the end of arthroscopy has been reported to provide some degree of postoperative pain relief;[1,2] such pain relief may be more pronounced than that produced by the same dose given intravenously[1] or intramuscularly.[2] The effect appears to be due to the action of morphine on peripheral opioid receptors[2] although a systemic effect has not been completely excluded.[1]

There have been conflicting results on whether addition of morphine to intra-articular bupivacaine improves analgesia[3,4] and a systematic review[5] concluded that from the few well-controlled studies there was no evidence of an added analgesic effect of morphine compared with saline alone.

Doses of morphine reported to have been injected intra-articularly have ranged from 1 to 10 mg.

1. Gupta A, *et al.* A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* 2001; **93:** 761–70.
2. Raj N, *et al.* Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. *Eur J Anaesthesiol* 2004; **21:** 932–7.
3. Laurent SC, *et al.* Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth* 1994; **72:** 170–3.
4. Heine MF, *et al.* Intra-articular morphine after arthroscopic knee operation. *Br J Anaesth* 1994; **73:** 413–15.
5. Rosseland LA. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* 2005; **30:** 83–98.

INTRANASAL ROUTE. An intranasal formulation of morphine is under investigation for the relief of acute pain.

INTRASPINAL ROUTE. Morphine is given epidurally and intrathecally to relieve both acute and chronic pain. However, reviews on the role of spinal opioids have generally concluded that they should be reserved for pain not controlled by more conventional routes.[1-3] When converting from conventional routes it has been suggested that 1% of the total daily dose could be tried as the daily intrathecal dose and 10% as the epidural dose.[3] Conversion from intrathecal to oral dosage has also been investigated.[4]

Intrathecal morphine may be delivered continuously via an implanted programmable infusion pump for the long-term management of chronic non-malignant and cancer pain.

See also Patient-controlled Analgesia, below.

1. Anonymous. Spinal opiates revisited. *Lancet* 1986; **i:** 655–6.
2. Gustafsson LL, Wiesenfeld-Hallin Z. Spinal opioid analgesia: a critical update. *Drugs* 1988; **35:** 597–603.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; **63:** 213–26.
4. Sylvester RK, *et al.* The conversion challenge: from intrathecal to oral morphine. *Am J Hosp Palliat Care* 2004; **21:** 143–7.

PATIENT-CONTROLLED ANALGESIA. Morphine is one of the most frequently used opioid analgesics for patient-controlled analgesia (see p.4). Most experience has been with the intravenous route, but the intramuscular, subcutaneous, oral, pulmonary, and epidural[1] routes have also been used. Reasonable initial settings recommended for intravenous use have been a demand dose of 1 to 2 mg of morphine sulfate (or its equivalent) and a lockout interval of 5 to 10 minutes.[2]

1. Sjöström S, *et al.* Patient-controlled analgesia with extradural morphine or pethidine. *Br J Anaesth* 1988; **60:** 358–66.
2. Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005; **101** (suppl): S44–S61.

PULMONARY ROUTE. For reference to the use of nebulised morphine see Dyspnoea, below.

TOPICAL ROUTE. Morphine has been applied topically for local analgesia in oral mucositis[1,2] and cutaneous ulceration[3-6] including epidermolysis bullosa.[7]

1. Cerchietti LC, *et al.* Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* 2000; **95:** 2230–6. Correction. *ibid.* 2003; **97:** 1137.
2. Cerchietti L. Morphine mouthwashes for painful mucositis. *Support Care Cancer* 2007; **15:** 115–16.
3. Twillman RK, *et al.* Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999; **17:** 288–92.
4. Krajnik M, *et al.* Potential uses of topical opioids in palliative care–report of 6 cases. *Pain* 1999; **80:** 121–5.
5. Zeppetella G, *et al.* Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003; **25:** 555–8.
6. Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. *J Pain Symptom Manage* 2005; **29:** 118–19.
7. Watterson G, *et al.* Peripheral opioids in inflammatory pain. *Arch Dis Child* 2004; **89:** 679–81.

Administration in children. Opioid analgesics are used in children in the management of moderate to severe **pain** (see p.3); morphine is the most widely used opioid for severe pain in children and is the standard against which other opioids are compared. Morphine may be given to children requiring acute analgesia as a result of surgery or invasive procedures. It may also be given for chronic non-malignant pain and is the opioid of choice for the oral treatment of severe pain in palliative care. Its analgesic and sedative properties are useful in the management of children in intensive care (see p.957); morphine is considered to be a more rational choice than fentanyl in settings where long-term infusions are required. Respiratory depression with morphine treatment is a risk in all children; however, neonates (and particularly those who are breathing spontaneously) may have an enhanced susceptibility because of the pharmacokinetic differences of morphine in this age group (see above).

The following initial doses are recommended by the *BNFC*; doses should thereafter be adjusted according to response:

- By subcutaneous or intramuscular injection, neonates may be given 100 micrograms/kg every 6 hours; those aged 1 to 6 months, 100 to 200 micrograms/kg every 6 hours; 6 months to 2 years, 100 to 200 micrograms/kg every 4 hours; 2 to 12 years, 200 micrograms/kg every 4 hours; 12 to 18 years, 2.5 to 10 mg every 4 hours
- By intravenous injection over at least 5 minutes, neonates may be given 50 micrograms/kg every 6 hours; those aged 1 to 6 months, 100 micrograms/kg every 6 hours; 6 months to 12 years, 100 micrograms/kg every 4 hours; 12 to 18 years, 2.5 mg every 4 hours

  The following doses given by slow intravenous injection are suggested as loading doses for continuous intravenous infusion: neonates may be given 25 to 100 micrograms/kg; those aged 1 to 6 months, 100 to 200 micrograms/kg; 6 months to 12 years, 100 to 200 micrograms/kg; 12 to 18 years, 2.5 to 10 mg. The loading dose may be followed by an infusion given in a dose dependent on the patient's age: neonates, 5 to 40 micrograms/kg per hour; 1 to 6 months, 10 to 30 micrograms/kg per hour; 6 months to 18 years, 20 to 30 micrograms/kg per hour
- By mouth or rectum, infants aged 1 to 12 months may be given 80 to 200 micrograms/kg every 4 hours; those aged 1 to 2 years, 200 to 400 micrograms/kg every 4 hours; 2 to 12 years, 200 to 500 micrograms/kg, to a maximum of 20 mg, every 4 hours; 12 to 18 years, 5 to 20 mg every 4 hours. In *palliative care*, modified-release oral preparations may be used; they are given as a single daily dose or in 2 divided doses
- By continuous subcutaneous infusion, children aged 1 to 3 months may be given 10 micrograms/kg per hour; those aged 3 months to 18 years, 20 micrograms/kg per hour

Intraspinal doses of morphine that have been tried[1] in children are as follows:

- Caudal epidural block, 100 micrograms/kg
- Thoracic or lumbar epidural block, 50 micrograms/kg
- Intrathecal doses of 20 or 30 micrograms/kg have provided satisfactory postoperative pain relief, but respiratory depression occurred in 10 and 25%, respectively

Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intravenous morphine as an alternative to, or after initial treatment with, intranasal diamorphine for *severe pain* such as that associated with large burns, long bone dislocation, appendicitis, or sickle-cell crisis, but it should be used with caution if there is risk of depression of airway, breathing, or circulation.

In the UK, morphine is also used in the management of **neonatal abstinence syndrome** (p.102) under specialist supervision. The *BNFC* recommends an initial oral dose of 40 micrograms/kg (increase dose if necessary) every 4 hours until symptoms are controlled; the dosage frequency should be reduced gradually over 6 to 10 days until a dose of 40 micrograms/kg once daily is achieved after which the drug should be stopped.

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
2. British Association for Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in children (2004). Available at: http://www.emergencymed.org.uk/BAEM/CEC/assets/cec_pain_in_children.pdf (accessed 26/06/08)

Cancer pain. Morphine is the opioid of choice for moderate to severe cancer pain (p.5); guidelines for its use issued by the European Association for Palliative Care[1] include:

- the optimal route for use is by mouth. For best effect, both conventional (for dose titration) and modified-release (for maintenance) dosage forms are required
- the simplest method of dose titration is with conventional morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue dose' may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take into account the amount needed for breakthrough pain
- if pain returns consistently before the next dose is due the regular dose should be increased. Conventional formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain
- if a conventional formulation of morphine is not available and treatment is started with modified-release morphine, changes to the regular dose should not be made more often than every 48 hours, which means that dose titration will be prolonged
- for patients taking conventional morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep
- if patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful
- when converting dosage, the relative potency of oral to subcutaneous morphine is between about 1:2 and 1:3, so 20 to 30 mg of oral morphine is equianalgesic to 10 mg by subcutaneous injection
- in patients who need continuous parenteral morphine the preferred route is by subcutaneous infusion. However, intravenous infusion may be preferred:

  in patients who already have an indwelling intravenous line

  in those with generalised oedema

  if erythema, soreness, or sterile abscess develop during subcutaneous dosage

  in patients with coagulation disorders

  where peripheral circulation is poor
- when converting dosage, the relative potency of oral to intravenous morphine is also between about 1:2 and 1:3
- the buccal, sublingual, and nebulised routes of administration are not recommended in the absence of evidence for clinical advantage over more usual routes
- a small proportion of patients develop intolerable adverse effects with oral morphine (in conjunction with adjuvant non-opioid analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid, or a change in the route should be considered. Although switching between opioids complicates pain management, adequate pain relief for some may depend on the use of alternative drugs, the use of intraspinal routes, or non-drug methods of pain control

Similar recommendations are given in guidelines issued by the US National Comprehensive Cancer Network.[2]

1. Hanks GW, *et al.* Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; **84:** 587–93.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2008). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf (accessed 26/06/08)

Dyspnoea. In the treatment of dyspnoea (p.104), doses of morphine tend to be smaller than those used for pain relief. Morphine hydrochloride or sulfate may be given as an oral solution in carefully titrated doses, starting at a dose of 5 mg every 4 hours; as little as 2.5 mg every 4 hours may be sufficient for opioid-naive patients.[1] In acute pulmonary oedema, 5 to 10 mg may be given by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:[2]

- mild dyspnoea: 25 to 50% of usual analgesic dose
- moderate dyspnoea: 50 to 100% of usual analgesic dose
- severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.[3] Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,[4] several subsequent studies[5-7] have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.[1,8-10] Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
2. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, *et al.* Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; **119:** 906–7.
4. Young IH, *et al.* Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989; **44:** 387–90.
5. Beauford W, *et al.* Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients. *Chest* 1993; **104:** 175–8.
6. Noseda A, *et al.* Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997; **10:** 1079–83.
7. Jankelson D, *et al.* Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10:** 2270–4.
8. Polosa R, *et al.* Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08).
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.

Preparations

BP 2008: Chloroform and Morphine Tincture; Morphine and Atropine Injection; Morphine Sulphate Injection; Morphine Suppositories; Morphine Tablets; Prolonged-release Morphine Tablets;
USP 31: Morphine Sulfate Extended-Release Capsules; Morphine Sulfate Injection; Morphine Sulfate Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Algedol; Amidiaz; Analmorph; Duramorph; GNO; MST Continus; Neocalmans; ***Austral.:*** Anamorph; Kapanol; MS Contin; MS Mono; Ordine; Sevredol; ***Austria:*** Compensan; Kapabloc; Kapanol; M-Dolor; Morapid; Mundidol; Substitol; Vendal; ***Belg.:*** Docmorfine; Kapanol; MS Contin; MS Direct; Oramorph; Stellorphinad; Stellorphine; ***Braz.:*** Dimorf; Dolo Moff; MS-Long†; MST Continus†; ***Canad.:*** Kadian; M-Eslon; Morphitec†; MOS; MS Contin; MSIR; Oramorph†; Statex†; ***Chile:*** M-Eslon; ***Cz.:*** Doltard†; M-Eslon; MST Continus; MST Uno†; Oramorph†; Sevredol; Skenan†; Slovalgin; Vendal; ***Denm.:*** Contalgin; Depolan; Doltard; ***Fin.:*** Depolan; Dolcontin; ***Fr.:*** Actiskenan; Kapanol; Moscontin; Oramorph; Sevredol; Skenan; ***Ger.:*** Capros; Kapanol; M-beta; M-Dolor†; M-long; M-Stada; Mogetic†; Morph; Morphanton; MSI; MSR; MST; Onkomorphin†; Oramorph; Painbreak; Sevredol; ***Hong Kong:*** M-Eslon; MST Continus; ***Hung.:*** M-Eslon; Moretal; MST Continus; Sevredol; ***India:*** Morcontin; ***Indon.:*** MST; ***Irl.:*** Morstel†; MST Continus; MXL; Oramorph; Sevredol; Slo-Morph†; ***Israel:*** Kapanol†; MCR; MIR; Morphex; MSP; ***Ital.:*** MS Contin; Oramorph; Skenan†; Ticinan; Twice; ***Jpn:*** MS Contin; ***Malaysia:*** MST Continus; ***Mex.:*** Analfin; Duralmor†; Graten; ***Neth.:*** Kapanol; MS Contin; Noceptin†; Oramorph; Sevredol; Skenan; ***Norw.:*** Dolcontin; ***NZ:*** Kapanol; LA Morph; M-Eslon; MST Continus†; MST Mono†; RA Morph; Sevredol; ***Philipp.:*** M-Dolor; MST Continus; Relimal; ***Pol.:*** MST Continus; Sevredol; Vendal; ***Port.:*** Ethirfin; MST; MXL†; Oramorph; Sevredol; Skenan; ***S.Afr.:*** MST Continus; SRM-Rhotard; ***Singapore:*** MST Continus; SRM-Rhotard†; Statex; ***Spain:*** MST Continus; MST Unicontinus; Oglos†; Oramorph; Sevredol; Skenan; ***Swed.:*** Depolan; Dolcontin; ***Switz.:*** Kapanol; M-retard; MST Continus; Sevre-Long; Sevredol; ***Turk.:*** M-Eslon; Vendal; ***UK:*** Filnarine; Morcap†; Morphgesic; MST Continus; MXL; Oramorph; Rhotard; Sevredol; Zomorph; ***USA:*** Astramorph; Avinza; DepoDur; Duramorph; Infumorph; Kadian; MS Contin; MSIR; Oramorph; RMS; Roxanol; ***Venez.:*** MS Contin.

Multi-ingredient: ***Austral.:*** Morphalgin†; ***Austria:*** Modiscop; ***Belg.:*** Spasma†; ***Irl.:*** Cyclimorph; ***Ital.:*** Cardiostenol; ***Pol.:*** Doltard; ***S.Afr.:*** Chloropect; Cyclimorph; Enterodyne; Pectrolyte; ***Swed.:*** Spasmofen; ***Switz.:*** Spasmosol; ***UK:*** Collis Browne's; Cyclimorph; Diocalm Dual Action; Opazimes.

Morpholine Salicylate

Morfoliinisalisylaatti; Morfolinsalicylat; Morpholini Salicylas; Salicilato de morfolinio. 2-Hydroxybenzoic acid compounded with morpholine (1 : 1).

Морфолин Салицилат

$C_{11}H_{15}NO_4$ = 225.2.
CAS — 147-90-0.
ATC — N02BA08.
ATC Vet — QN02BA08.

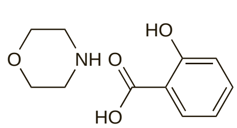

Profile

Morpholine salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used for musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Israel: Dolical.

Nabumetone *(BAN, USAN, rINN)*

BRL-14777; Nabumeton; Nabumetona; Nabumetonas; Nabumétone; Nabumetoni; Nabumetonum. 4-(6-Methoxy-2-naphthyl)butan-2-one.

Набуметон

$C_{15}H_{16}O_2$ = 228.3.
CAS — 42924-53-8.
ATC — M01AX01.
ATC Vet — QM01AX01.

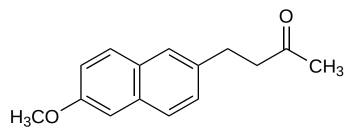

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in acetone; slightly soluble in methyl alcohol. Protect from light.
USP 31 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Nabumetone is contra-indicated in patients with severe hepatic impairment.

Effects on the gastrointestinal tract. Like other NSAIDs nabumetone can produce adverse effects on the gastrointestinal tract, although some studies have produced favourable comparisons with ibuprofen[1] or naproxen.[2] A recent review[3] noted that limited comparative data suggest that nabumetone has a similar gastrointestinal adverse effect profile to that of selective COX-2 inhibitors. It has been suggested[4] that nabumetone may be a preferential inhibitor of cyclo-oxygenase-2 (COX-2) but the significance of this in determining its adverse effects is uncertain.

1. Roth SH, *et al.* A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med* 1993; **153:** 2565–71.
2. Roth SH, *et al.* A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol* 1994; **21:** 1118–23.
3. Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. *Drug Safety* 2008; **31:** 485–503.
4. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Effects on the lungs. Pulmonary fibrosis developed in a 68-year-old woman taking nabumetone 1.5 g; symptoms appeared after 2 weeks of therapy and worsened during the next 6 weeks.[1] There was rapid resolution on stopping nabumetone and treatment with oral corticosteroids.

1. Morice A, *et al.* Pulmonary fibrosis associated with nabumetone. *Postgrad Med J* 1991; **67:** 1021–2.

Effects on the skin. Pseudoporphyria characterised by blistering on the neck and hands developed in a 36-year-old woman taking nabumetone and auranofin for rheumatoid arthritis.[1] Stopping auranofin had no effect on the blistering which only resolved once nabumetone was withdrawn. The authors of the report stated that the UK CSM had received 3 additional reports of pseudoporphyria suspected to be caused by nabumetone.

1. Varma S, Lanigan SW. Pseudoporphyria caused by nabumetone. *Br J Dermatol* 1998; **138:** 549–50. Correction. *ibid.* **139:** 759. [dose]

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Nabumetone is well absorbed from the gastrointestinal tract. Plasma concentrations after oral doses are too small to be measured, as it undergoes rapid and extensive first-pass metabolism in the liver to the principal active compound 6-methoxy-2-naphthylacetic acid (6-MNA) and other inactive metabolites. 6-MNA is more than 99% bound to plasma proteins. It diffuses into synovial fluid, crosses the placenta, and is distributed into breast milk. There is considerable interindividual variation in the plasma elimination half-life of 6-MNA, especially in the elderly; some reported mean values at steady state include 22 to about 27 hours for young adults and about 25 and 34 hours in elderly patients. 6-MNA eventually undergoes further metabolism by *O*-methylation and conjugation. About 80% of a dose is excreted in the urine as inactive or conjugated metabolites and less than 1% as unchanged 6-MNA.

◊ References.

1. Brier ME, *et al.* Population pharmacokinetics of the active metabolite of nabumetone in renal dysfunction. *Clin Pharmacol Ther* 1995; **57:** 622–7.
2. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Uses and Administration

Nabumetone is a non-active prodrug whose major metabolite is an NSAID (p.99) structurally similar to naproxen (p.92). It is used for the relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis in a usual oral dose of 1 g taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

◊ References.

1. Friedel HA, *et al.* Nabumetone: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases. *Drugs* 1993; **45:** 131–56.
2. Proceedings of a symposium: continuing developments with nabumetone: an investigators' update. *Am J Med* 1993; 95 (suppl 2A): 1S–45S.
3. Dahl SL. Nabumetone: a "nonacidic" nonsteroidal antiinflammatory drug. *Ann Pharmacother* 1993; **27:** 456–63.
4. Hedner T, *et al.* Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs* 2004; **64:** 2315–43.

Preparations

BP 2008: Nabumetone Oral Suspension; Nabumetone Tablets;
USP 31: Nabumetone Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Relifex†; ***Canad.:*** Relafen; ***Cz.:*** Relifex; Rodanol S†; ***Denm.:*** Relifex; ***Fin.:*** Relifex; ***Fr.:*** Nabucox; ***Gr.:*** Akratol; Anfer; Ethyfen†; Flogmed; Mevedal; Nabuton; Naditone; Relifex; ***Hong Kong:*** Relifex†; ***Hung.:*** Relifex; Rodanol S†; ***India:*** Nabuflam; ***Indon.:*** Goflex; ***Irl.:*** Relifex; Religer; ***Israel:*** Nabuco; Relifex; ***Ital.:*** Artaxan; Nabuser; ***Jpn:*** Relifen; ***Mex.:*** Naflam; Relifex; ***Neth.:*** Mebutan; ***Norw.:*** Relifex; ***Philipp.:*** Relifex; ***Pol.:*** Coxalgan; Coxeton; Nabuton; Relifex; Rodanol S; ***Port.:*** Balmox; Elitar; ***Rus.:*** Rodanol (Роданол); ***S.Afr.:*** Relifen; Relisan; Relitone; ***Spain:*** Listran; Relif; ***Swed.:*** Relifex; ***Switz.:*** Balmox; ***Thai.:*** Aflex; Anfer†; Bumetone; Nabone; Nabonet; Naflex; Nametone; No-Ton†; Relifex; ***Turk.:*** Relifex; ***UK:*** Relifex; ***USA:*** Relafen†.

Nalbuphine Hydrochloride

(BANM, USAN, rINNM)

EN-2234A; Hidrocloruro de nalbufina; Nalbufine Hydrochloride; Nalbuphine, Chlorhydrate de; Nalbuphini Hydrochloridum. 17-Cyclobutylmethyl-7,8-dihydro-14-hydroxy-17-normorphine hydrochloride; (−)-(5*R*,6*S*,14*S*)-9a-Cyclobutylmethyl-4,5-epoxymorphinan-3,6,14-triol hydrochloride.

Налбуфина Гидрохлорид

$C_{21}H_{27}NO_4$,HCl = 393.9.
CAS — 20594-83-6 (nalbuphine); 23277-43-2 (nalbuphine hydrochloride).
ATC — N02AF02.
ATC Vet — QN02AF02.

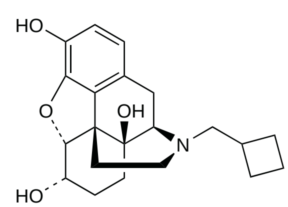

(nalbuphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nalbuphine hydrochloride:
Nubian.

Incompatibility. Incompatibility has been reported between injections of nalbuphine hydrochloride and nafcillin sodium,[1] diazepam,[2] pentobarbital sodium,[2] or thiethylperazine maleate.[2] US licensed product information states that nalbuphine is also physically incompatible with ketorolac.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462–4.
2. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.

The symbol † denotes a preparation no longer actively marketed

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

◊ A WHO expert committee considered in 1989 that the likelihood of nalbuphine abuse was low to moderate and was not great enough to warrant international control.[1] Abuse had been reported infrequently and the withdrawal syndrome produced when naloxone was given after continuous nalbuphine dosage was less severe than that in morphine dependence. Subsequently, there have been occasional reports of abuse[2,3] including misuse among athletes.[4,5]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)
2. Spadari M, *et al.* Pharmacodépendance à la nalbuphine (Nubain): à propos de 2 cas. *Therapie* 2002; **57:** 504–5.
3. Klinzig F, *et al.* Hair analysis by LC-MS as evidence of nalbuphine abuse by a nurse. *J Anal Toxicol* 2007; **31:** 62–5.
4. McBride AJ, *et al.* Three cases of nalbuphine hydrochloride dependence associated with anabolic steroid use. *Br J Sports Med* 1996; **30:** 69–70.
5. Wines JD, *et al.*. Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999; **8:** 161–4.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Headache may occur. Nausea and vomiting occur less than with other opioids. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. As nalbuphine has both antagonist and agonist activity its effects may be only partially reversed by naloxone, but use of the latter is still recommended in nalbuphine overdose.

Effects on the respiratory system. Nalbuphine produces similar respiratory depression to morphine at equianalgesic doses, but there is a ceiling effect with nalbuphine and, unlike morphine, respiratory depression does not increase appreciably with higher doses.[1] In a cumulative-dose study[2] a plateau effect was seen with nalbuphine above a total dose of 30 mg per 70 kg intravenously. Similar ventilatory depression has been noted[3] with single intravenous doses of nalbuphine of 15, 30, or 60 mg per 70 kg; naloxone failed to reverse the depression at the highest dose.

1. Klepper ID, *et al.* Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986; **58:** 625–9.
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; **27:** 478–85.
3. Pugh GC, *et al.* Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers. *Br J Anaesth* 1989; **62:** 601–9.

Precautions

As for Opioid Analgesics in general, p.103.

Nalbuphine may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

The dose of nalbuphine should be reduced in patients with hepatic or renal impairment.

Abuse. See under Dependence and Withdrawal, above.

Pregnancy. When nalbuphine is used for analgesia during labour there is more placental transfer and sedation in mothers and their infants than with pethidine.[1] There have also been reports of bradycardia and respiratory depression in neonates whose mothers received nalbuphine during labour.[2,3] It was considered that nalbuphine should be given with caution during labour, especially by the intravenous route. Some[2] have recommended subcutaneous dosage and advised that nalbuphine should not be given around the expected time of delivery.

Further references on the transplacental transfer of nalbuphine are given under Pharmacokinetics, below.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Guillonneau M, *et al.* Perinatal adverse effects of nalbuphine given during parturition. *Lancet* 1990; **335:** 1588.
3. Sgro C, *et al.* Perinatal adverse effects of nalbuphine given during labour. *Lancet* 1990; **336:** 1070.

Interactions

For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics

There appears to be considerable first-pass metabolism of nalbuphine after oral doses. On intramuscular injection nalbuphine has been reported to produce peak plasma concentrations after 30 minutes. It is metabolised in the liver and is excreted in the urine and faeces as unchanged drug and conjugates. Nalbuphine crosses the placenta and small amounts are distributed into breast milk.

◊ References.

1. Sear JW, *et al.* Disposition of nalbuphine in patients undergoing general anaesthesia. *Br J Anaesth* 1987; **59:** 572–5.
2. Kay B, *et al.* Pharmacokinetics of oral nalbuphine in postoperative patients. *Br J Anaesth* 1987; **59:** 1327P.
3. Aitkenhead AR, *et al.* The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers. *Br J Clin Pharmacol* 1988; **25:** 264–8.
4. Jaillon P, *et al.* Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989; **46:** 226–33.

Pregnancy. References.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Dadabhoy ZP, *et al.* Transplacental transfer of nalbuphine in patients undergoing cesarean section: a pilot study. *Acta Anaesthesiol Ital* 1988; **39:** 227–32.
3. Nicolle E, *et al.* Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol* 1996; **49:** 485–9.

Uses and Administration

Nalbuphine hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.104). It has mixed opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Nalbuphine hydrochloride is reported to act within 15 minutes of subcutaneous or intramuscular injection or within 2 to 3 minutes of intravenous injection and generally to produce analgesia for 3 to 6 hours. It is given subcutaneously, intramuscularly, or intravenously. Intravenous infusion as part of a patient-controlled analgesia system has also been used.

The usual adult dose of nalbuphine hydrochloride for **pain** relief is 10 to 20 mg every 3 to 6 hours as required.

As an adjunct in balanced **anaesthesia** a usual dose is 0.3 to 3 mg/kg given intravenously over 10 to 15 minutes at induction. Maintenance doses of 250 to 500 micrograms/kg may be given as intravenous boluses if required.

Action. Nalbuphine is generally described as a mixed agonist and antagonist acting mainly as an agonist at κ opioid receptors and as an antagonist or partial agonist at μ receptors. It has shown antagonist activity similar to that seen with naloxone in opioid-dependent subjects.[1] Nalbuphine is structurally related to naloxone and oxymorphone. Pharmacologically nalbuphine is qualitatively similar to pentazocine, but nalbuphine is a more potent antagonist at μ opioid receptors, is less likely to produce psychotomimetic effects such as hallucinations, and is reported to produce no significant cardiovascular effects in patients with ischaemic heart disease. It differs from pure μ agonists such as morphine in that its analgesic, sedative, and respiratory depressant actions are subject to a 'ceiling' effect and may not increase proportionately with dose.

1. Preston KL, *et al.* Antagonist effects of nalbuphine in opioid-dependent human volunteers. *J Pharmacol Exp Ther* 1989; **248:** 929–37.

Administration. References to alternative routes or dosage schedules.

1. Krenn H, *et al.* Nalbuphine by PCA-pump for analgesia following hysterectomy: bolus application versus continuous infusion with bolus application. *Eur J Pain* 2001; **5:** 219–26.
2. Woollard M, *et al.* Hitting them where it hurts? Low dose nalbuphine therapy. *Emerg Med J* 2002; **19:** 565–70.
3. Sung KC, *et al.* Transdermal delivery of nalbuphine and its prodrugs by electroporation. *Eur J Pharm Sci* 2003; **18:** 63–70.
4. Gear RW, *et al.* Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003; **351:** 5–8.
5. Liu KS, *et al.* Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br J Anaesth* 2004; **92:** 712–15.
6. Woollard M, *et al.* Less IS less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* 2004; **21:** 362–4.
7. Gordon AT, *et al.* Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med* 2007; **8:** 525–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gobbinal; Naltrox; Nubaina; Nubak†; Onfor; ***Austria:*** Nubain; ***Braz.:*** Nubain; ***Canad.:*** Nubain†; ***Cz.:*** Nubain; ***Fr.:*** Nubain†; ***Ger.:*** Nubain†; ***Gr.:*** Nubain; ***Hong Kong:*** Intapan; Nubain†; ***Hung.:*** Nubain; ***Israel:*** Nubain†; ***Malaysia:*** Nubain†; ***Mex.:*** Bufigen; Bufilem; Nalcryn; Nubain†; ***NZ:*** Nubain†; ***Philipp.:*** Nubain; ***S.Afr.:*** Nubain†; ***Singapore:*** Nubain†; ***Switz.:*** Nubain; ***Thai.:*** Nubain; ***UK:*** Nubain†; ***USA:*** Nubain; ***Venez.:*** Bufidol; Nubain†.

Naproxen *(BAN, USAN, rINN)*

Naprokseeni; Naproksen; Naproksenas; Naproxén; Naproxène; Naproxeno; Naproxenum; RS-3540. (+)-2-(6-Methoxy-2-naphthyl)propionic acid.

Напроксен

$C_{14}H_{14}O_3$ = 230.3.

CAS — 22204-53-1.

ATC — G02CC02; M01AE02; M02AA12.

ATC Vet — QG02CC02; QM01AE02; QM02AA12.

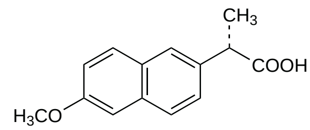

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Naproxen). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Naproxen). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in dehydrated alcohol, and in chloroform; sparingly soluble in ether. Store in airtight containers.

Naproxen Sodium *(BANM, USAN, rINNM)*

Naproksen Sodyum; Naproxène sodique; Naproxeno sódico; Naproxenum natricum; Natrii Naproxenum; RS-3650.

Натрий Напроксен

$C_{14}H_{13}NaO_3$ = 252.2.

CAS — 26159-34-2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Naproxen Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; freely soluble or soluble in methyl alcohol. A 2% solution in water has a pH of 7.0 to 9.8. Store in airtight containers. Protect from light.

USP 31 (Naproxen Sodium). A white to creamy crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol; very slightly soluble in acetone; practically insoluble in chloroform and in toluene. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Suppositories containing naproxen may cause rectal irritation and occasional bleeding.

Naproxen should be used with caution in renal impairment, and use is not recommended in patients whose creatinine clearance is less than 20 mL/min.

◊ Reviews.

1. Bansal V, *et al.* A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol* 2001; **41:** 127–38.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of naproxen by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of naproxen distributed into breast milk is too small to be harmful to a breast-fed infant; however, some licensed product information recommends that breast feeding should be avoided during naproxen therapy.

In a study[2] of a breast-fed infant only 0.26% of the mother's dose was recovered from the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Jamali F, Stevens DRS. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm* 1983; **17:** 910–11.

Effects on the blood. Haematological adverse effects reported in patients given naproxen include haemolytic anaemia,[1,2] aplastic anaemia,[3] agranulocytosis,[4] and immune thrombocytopenia.[5]

1. Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum* 1983; **26:** 1054.
2. Lo TCN, Martin MA. Autoimmune haemolytic anaemia associated with naproxen suppositories. *BMJ* 1986; **292:** 1430.
3. McNeil P, *et al.* Naproxen-associated aplastic anaemia. *Med J Aust* 1986; **145:** 53–4.
4. Nygard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA* 1987; **257:** 1732.
5. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. *Blood* 2001; **97:** 3846–50.

Effects on the cardiovascular system. For a discussion of the possible cardiovascular effects of naproxen, see p.96.

Effects on the CNS. Aseptic meningitis has been associated with naproxen therapy;[1,2] attacks may be recurrent and cross-sensitivity with other NSAIDs has occurred.[2]

There has been a report[3] of a patient with Parkinson's disease whose symptoms had previously been well controlled but who deteriorated when she was given naproxen. She improved on withdrawal of naproxen and the effect was confirmed by rechallenge. It was noted that the UK CSM had recorded a case of parkinsonism associated with a combined preparation of naproxen and misoprostol and 12 other reports of tremor or ataxia precipitated by naproxen.

1. Weksler BB, Lehany AM. Naproxen-induced recurrent aseptic meningitis. *DICP Ann Pharmacother* 1991; **25:** 1183–4.
2. Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs – a reminder. *Postgrad Med J* 1999; **75:** 771–2.
3. Shaunak S, *et al.* Exacerbation of idiopathic Parkinson's disease by naproxen. *BMJ* 1995; **311:** 422.

Effects on the eyes. Keratopathy, characterised by whorl-like corneal opacities, occurred in a woman taking naproxen; complete regression occurred after stopping the drug.[1] There has also been a report of exacerbation of glaucoma in a 65-year-old woman given naproxen.[2]

For reference to effects on the optic nerve associated with naproxen, see p.97.

1. Szmyd L, Perry HD. Keratopathy associated with the use of naproxen. *Am J Ophthalmol* 1985; **99:** 598.
2. Fincham JE. Exacerbation of glaucoma in an elderly female taking naproxen sodium: a case report. *J Geriatr Drug Ther* 1989; **3:** 139–43.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are among the most frequently reported during short- and long-term treatment with naproxen. Acute proctocolitis associated with the use of naproxen has been reported.[1] Oesophageal ulceration reported in 7 patients[2] may have arisen due to incorrect consumption (such as taking the dosage without fluids or lying down after a dose) but other causes could not be dismissed.

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.
2. Kahn LH, *et al.* Over-the-counter naproxen sodium and esophageal injury. *Ann Intern Med* 1997; **126:** 1006.

Effects on the kidneys. Acute renal failure,[1] renal papillary necrosis,[2,3] interstitial nephritis,[4] and hyperkalaemia[1] have been reported in patients receiving naproxen. As with other NSAIDs, renal adverse effects occur more frequently in patients with certain risk factors such as volume depletion, diuretic therapy, heart failure, and pre-existing renal dysfunction.[1]

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Caruana RJ, Semble EL. Renal papillary necrosis due to naproxen. *J Rheumatol* 1984; **11:** 90–1.
3. Kovacevic L, *et al.* Renal papillary necrosis induced by naproxen. *Pediatr Nephrol* 2003; **18:** 826–9.
4. Quigley MR, *et al.* Concurrent naproxen- and penicillamine-induced renal disease in rheumatoid arthritis. *Arthritis Rheum* 1982; **25:** 1016–19.

Effects on the liver. There have been a few reports[1,2] of moderate to severe jaundice attributed to naproxen including one in which the patient also had a similar reaction with fenoprofen.[2]

1. Victorino RMM, *et al.* Jaundice associated with naproxen. *Postgrad Med J* 1980; **56:** 368–70.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the lungs. See Hypersensitivity, below.

Effects on the salivary glands. For reference to salivary gland swelling associated with naproxen therapy, see Hypersensitivity, below.

Effects on the skin. Cutaneous reactions reported in patients receiving naproxen include erythema nodosum,[1] lichen planus,[2] toxic pustular skin eruption,[3] bullous dermatosis,[4] and fixed drug eruption.[5] Photodermatitis, characterised by vesicle formation or increased skin fragility on sun-exposed skin, has been reported in adults[6-8] and children.[9,10]

A relapse of subacute cutaneous lupus erythematosus was reported to be possibly associated with naproxen.[11]

For reference to facial scars of unknown origin developing in children receiving NSAIDs, and in particular naproxen, see under NSAIDs, p.98.

1. Grattan CEH, Kennedy CTC. Naproxen induced erythema nodosum. *BMJ* 1984; **288:** 114.
2. Heymann WR, *et al.* Naproxen-induced lichen planus. *J Am Acad Dermatol* 1984; **10:** 299–301.
3. Page SR, Grattan CEH. Pustular reaction to naproxen with cholestatic jaundice. *BMJ* 1986; **293:** 510.
4. Bouldin MB, *et al.* Naproxen-associated linear IgA bullous dermatosis: case report and review. *Mayo Clin Proc* 2000; **75:** 967–70.
5. Leivo T, Heikkilä H. Naproxen-induced generalized bullous fixed drug eruption. *Br J Dermatol* 2004; **151:** 232.
6. Howard AM, *et al.* Pseudoporphyria due to naproxen. *Lancet* 1985; **i:** 819–20.
7. Rivers JK, Barnetson RS. Naproxen-induced bullous photodermatitis. *Med J Aust* 1989; **151:** 167–8.
8. Levy ML, *et al.* Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *J Pediatr* 1990; **117:** 660–4.
9. Parodi A, *et al.* Possible naproxen-induced relapse of subacute cutaneous lupus erythematosus. *JAMA* 1992; **268:** 51–2.
10. Lang BA, Finlayson LA. Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis. *J Pediatr* 1994; **124:** 639–42.
11. Cox NH, Wilkinson DS. Dermatitis artefacta as the presenting feature of auto-erythrocyte sensitization syndrome and naproxen-induced pseudoporphyria in a single patient. *Br J Dermatol* 1992; **126:** 86–9.

Hypersensitivity. In an early case-report in 11 aspirin-sensitive asthmatic patients, all developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) after taking naproxen in doses of 40 to 80 mg.[1] More recently, angioedema occurred after a single dose of naproxen in a patient known to be aspirin-sensitive.[2] Hypersensitivity to individual NSAIDs is believed to be closely linked to the extent to which these drugs inhibit prostaglandin (see under Aspirin, p.21). There may therefore be a dose threshold below which no detectable symptoms occur. Such an effect has been reported[3] in a patient previously stabilised on naproxen for about one year who had a hypersensitivity reaction after a dosage increase.

A hypersensitivity reaction characterised by pulmonary infiltrates with eosinophilia[4,5] has been reported in patients taking naproxen. There has also been a report of a generalised hypersensitivity reaction with acute eosinophilic colitis in a 57-year-old woman treated with naproxen for osteoarthritis.[6] Bilateral swelling of the major salivary glands, a generalised rash, and eosinophilia suggestive of a hypersensitivity response was reported in another patient after use of naproxen.[7] Leukocytoclastic vasculitis with peripheral neuropathy and nephritis has also been noted in a 62-year-old woman after naproxen treatment.[8]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. Ghislain P-D, Ghislain E. Oedème de Quincke de la nuque induit par l'acide acétylsalicylique, avec réaction croisée pour le naproxène sodique. *Ann Med Interne (Paris)* 2000; **151:** 227–9.
3. Briscoe-Dwyer L, Etzel JV. Dyspnea and periorbital edema following an increase in naproxen dose. *Ann Pharmacother* 1994; **28:** 1110.
4. Nader DA, Schillaci RF. Pulmonary infiltrates with eosinophilia due to naproxen. *Chest* 1983; **83:** 280–2.
5. Buscaglia AJ, *et al.* Pulmonary infiltrates associated with naproxen. *JAMA* 1984; **251:** 65–6.
6. Bridges AJ, *et al.* Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med* 1990; **89:** 526–7.
7. Knulst AC, *et al.* Salivary gland swelling following naproxen therapy. *Br J Dermatol* 1995; **133:** 647–9.
8. Schapira D, *et al.* Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol* 2000; **19:** 242–4.

Parkinsonism. For a report of a patient whose symptoms of Parkinson's disease were exacerbated by naproxen, see Effects on the CNS, above.

Interactions

For interactions associated with NSAIDs, see p.99.

The excretion of naproxen is delayed by probenecid resulting in raised plasma concentrations of naproxen.

Antiepileptics. For the effect of naproxen on the protein binding of *valproic acid*, see p.510.

Pharmacokinetics

Naproxen and naproxen sodium are readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained about 1 to 2 hours after ingestion of naproxen sodium and in about 2 to 4 hours after ingestion of naproxen. Food reduces the rate but not the extent of absorption. Naproxen and naproxen sodium are also well absorbed rectally. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen diffuses into synovial fluid; it crosses the placenta and is distributed into breast milk in small amounts. Naproxen has a plasma elimination half-life of about 12 to 17 hours. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the faeces.

◊ References.

1. Bruno R, *et al.* Naproxen kinetics in synovial fluid of patients with osteoarthritis. *Br J Clin Pharmacol* 1988; **26:** 41–4.
2. Bertin P, *et al.* Sodium naproxen: concentration and effect on inflammatory response mediators in human rheumatoid synovial fluid. *Eur J Clin Pharmacol* 1994; **46:** 3–7.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet* 1997; **32:** 268–93.
4. Bowalgaha K, *et al.* S-Naproxen and desmethylnaproxen glucuronidation by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGT): role of UGT2B7 in the elimination of naproxen. *Br J Clin Pharmacol* 2005; **60:** 423–33.

Uses and Administration

Naproxen, a propionic acid derivative, is an NSAID (p.99).

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. Naproxen is usually given *orally* as the free acid or as the sodium salt. The doses in the licensed product information are expressed in terms of the free acid or the sodium salt as appropriate for an individual preparation; however, the doses given below are expressed in terms of the equivalent amount of free acid only. Each 550 mg of naproxen sodium is equivalent to about 500 mg of naproxen.

In the treatment of **rheumatic disorders**, the usual dose of naproxen or naproxen sodium is the equivalent of 500 mg to 1 g of naproxen daily either as a single dose or in 2 divided doses. US licensed product information states that patients who tolerate lower doses may have their dosage increased to 1.5 g daily for a period of up to 6 months, if required. For dosage in children, see below.

In **other painful conditions** such as dysmenorrhoea and acute musculoskeletal disorders the usual regimen is the equivalent of 500 mg of naproxen initially, followed by 250 mg every 6 to 8 hours, up to a maximum daily dose of 1.25 g on the first day and 1 g thereafter.

In **acute gout** an initial dose equivalent to 750 mg of naproxen followed by 250 mg every 8 hours is used.

For the treatment of **migraine**, the equivalent of 750 mg of naproxen can be given at the first symptom of an impending attack and, if necessary, this may be followed after at least half an hour by further doses of 250 to 500 mg throughout the day to a total maximum daily dose of 1250 mg. See below for a suggested dose for the prophylaxis of migraine.

Naproxen has been given *rectally* in similar doses to those used orally.

Naproxen has also been used as the piperazine, aminobutanol, and lysine salts, and as naproxen cetrimonium. Naproxen is available in a combination pack with misoprostol (p.2013) for patients at risk of NSAID-induced peptic ulceration. Alternatively, packs containing naproxen with lansoprazole capsules are available in some countries for such patients.

◊ Reviews.

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Mason L, *et al.* Single dose oral naproxen and naproxen sodium for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/11/07).
3. Curran MP, Wellington K. Delayed-release lansoprazole plus naproxen. *Drugs* 2004; **64:** 1915–19.

Administration in children. In the treatment of juvenile idiopathic arthritis (p.10), US licensed product information recommends an oral dose of about 10 mg/kg daily of naproxen in 2 divided doses for children aged 2 years and over. In addition, higher doses may also be used: the *BNFC* suggests a dose of 5 to 10 mg/kg twice daily in children aged 1 month to 18 years which may be increased to 10 to 15 mg/kg twice daily (maximum of 1 g daily) for short-term use in severe disease.

Headache. An NSAID such as naproxen is among the drugs tried first for the symptomatic treatment of various types of headache including migraine (p.616) and tension-type headache (p.617). An NSAID given at the onset of symptoms can successfully treat an acute attack of migraine.[1] Co-treatment with a triptan may provide additional benefit and a preparation containing both sumatriptan succinate and naproxen sodium has recently been developed.[2,3]

NSAIDs also appear to be effective for the prophylaxis of migraine, although propranolol is generally preferred. Studies have indicated that naproxen sodium 550 mg [equivalent to 500 mg of naproxen] given twice daily may be useful for reducing the number of attacks suffered.[4-6]

1. Treves TA, *et al.* Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992; **32:** 280–2.

2. Winner P, *et al.* Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* 2007; **82:** 61–8.
3. Brandes JL, *et al.* Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; **297:** 1443–54.
4. Sargent J, *et al.* A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; **25:** 320–4.
5. Welch KMA, *et al.* Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; **35:** 1304–10.
6. Sances G, *et al.* Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; **30:** 705–9.

Malignant neoplasms. Some NSAIDs such as naproxen may be of value both for the differential diagnosis and the management of neoplastic fever[1-4] as they appear to be more effective in reducing this type of fever than against fever associated with infections. However, the reliability of naproxen in the diagnosis of neoplastic fever has been questioned.[5] In a group of 72 patients, naproxen decreased body temperature in 55% of patients with neoplastic disorders and 38% of patients with other conditions. Thus, the sensitivity of the test was calculated as 55% and its specificity as 62%, which the authors considered to be too low to be reliable.

1. Chang JC, Gross HM. Neoplastic fever responds to the treatment of an adequate dose of naproxen. *J Clin Oncol* 1985; **3:** 552–8.
2. Azeemuddin SK, *et al.* The effect of naproxen on fever in children with malignancies. *Cancer* 1987; **59:** 1966–8.
3. Economos K, *et al.* The effect of naproxen on fever in patients with advanced gynecologic malignancies. *Gynecol Oncol* 1995; **56:** 250–4.
4. Cunha BA, *et al.* Fever of unknown origin (FUO) caused by multiple myeloma: the diagnostic value of the Naprosyn test. *Heart Lung* 2006; **35:** 358–62.
5. Vanderschueren S, *et al.* Lack of value of the naproxen test in the differential diagnosis of prolonged febrile illnesses. *Am J Med* 2003; **115:** 572–5.

Preparations

BP 2008: Gastro-resistant Naproxen Tablets; Naproxen Oral Suspension; Naproxen Suppositories; Naproxen Tablets;
USP 31: Naproxen Delayed-Release Tablets; Naproxen Oral Suspension; Naproxen Sodium Tablets; Naproxen Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aleve; Algioprux†; Alidase; Bumaflex N; Causalon Pro†; Congex; Debril; Fabralgina; Fadalivio; Flaxvan; Flogocefal†; Melgar; Monarit; Naprofidex; Naprogen; Naprontag; Naprux; Neuralprona; Sicadentol Plus†; Tundra; Veradol†; Xicane†; ***Austral.:*** Aleve†; Anaprox; Chemists Own Period Pain Tablets; Crysanal; Femme Free; Inza; Naprogesic; Naprosyn; Nurolasts†; Proxen; ***Austria:*** Aleve; Miranax; Naprobene; Nycopren; Proxen; ***Belg.:*** Aleve; Apranax; Naproflam; Naprosyne; ***Braz.:*** Flanax; Napronax; Naprosyn; Naprox; ***Canad.:*** Anaprox; Apo-Napro-Na; Naprosyn; Naxen†; Novo-Naprox; Nu-Naprox; Synflex†; ***Chile:*** Atac; Deucoval; Eurogesic; Inveoxel†; Naprogesic; Reprost†; Triox NF; ***Cz.:*** Aleve; Emoxen; Nalgesin; Naprobene†; Napsyn†; ***Denm.:*** Bonyl; Miranax†; Naprosyn; ***Fin.:*** Alpoxen; Miranax; Naprometin; Napromex; Naprosyn†; Naxopren; Pronaxen; ***Fr.:*** Aleve; Apranax; Naprosyne; ***Ger.:*** Alacetan NNA; Aleve; Dolormin mit Naproxen; Dysmenalgit; prodolor†; Proxen; ***Gr.:*** Anaprox; Naprosyn; Nycopren-E; ***Hong Kong:*** Apo-Napro-Na; Inza; Naprorex; Naprosyn; Napxen; Noflam-N; Proxen†; Soden; Soren†; Synflex†; ***Hung.:*** Aleve; Apranax; Napmel; Naprosyn; ***India:*** Artagen; Easy Dayz; Naprosyn; Xenobid; ***Indon.:*** Naxen; Synflex; ***Irl.:*** Gerinap; Napmel†; Naprex†; Naprosyn; Synflex; ***Israel:*** Naproxi; Narocin; Naxyn; Point; ***Ital.:*** Aleve; Algonapril; Aperdan; Axer†; Floginax; Flogogin†; Floxalin; Gibixen; Gynestrel; Laser; Momendol; Napreben†; Naprius; Naprocet; Naprorex†; Naprosyn; Neo Eblimon; Nitens; Prexan; Proxagol; Synalgo; Synflex; Ticoflex†; Uninapro; Xenar†; ***Malaysia:*** Apo-Napro-Na; Inza†; Roxyn†; Seladin; Sunprox; Synflex; ***Mex.:*** Actiquim; Analgen; Anapsyl; Arsenal; Artron†; Arxen; Atiflan; Bioxan; Bixen; Dafloxen; Deflamox; Diferbest; Dolxen; Donaprox; Edem; Faraxen; Flanax; Flavoxen; Flaxendol; Flexen†; Flogen; Fuxen; Genalgen†; Inflanox; Iqfasol; Kenaprox†; Lixogan†; Lorexen†; Messelxen; Naflapen; Napoxol; Naprodil; Nasocan†; Navixen; Naxen; Naxopaar; Neonaxil; Nixal†; Novaxen; Pactens; Praxedol; Pronat; Pronax-P†; Pronaxil; Pronoxen; Propional†; Proxalin; Proxem†; Salupran†; Sertrixen; Sodixen; Tandax; Tanizona; Unirelaxed; Vantin; Velsay; ***Neth.:*** Aleve; Femex†; Momendol; Naprelan; Naprocoat; Naprovite; Nycopren†; ***Norw.:*** Alpoxen†; Ledox; Napren; Naprosyn; ***NZ:*** Naprogesic; Naprosyn; Naxen; Noflam; Synflex; ***Philipp.:*** Alpron; Flanax; Naprelan; Naprosyn; Sanomed; ***Pol.:*** Aleve; Anapran; Boloxen; Emochol†; Natrax; ***Port.:*** Momendol; Naprocet; Naprosyn; Reuxen; ***Rus.:*** Nalgesin (Налгезин); ***S.Afr.:*** Acusprain; Aleve; Fibroxyn†; Nafasol; Napflam; Naprel†; Naproscript†; Naprosyn†; Synflex; Traumox; ***Singapore:*** Aleve; Apo-Napro-Na; Bipronyl†; Gesiprox†; Inza; Noflam-N†; Nuprafen†; Seladin; Soden; Soproxen; Zynal†; ***Spain:*** Aleve; Aliviomas; Antalgin; Denaxpren; Lundiran; Momen; Naprosyn; Naproval; Tacron; ***Swed.:*** Alpoxen; Naprosyn; Pronaxen; ***Switz.:*** Aleve; Apranax; Naprosyn†; Nycopren; Proxen; ***Thai.:*** Annoxen; Naproflex; Naprosian; Naprosyn; Napsen†; Napxen†; Narzen†; Polyxen; Proxen; Roxen†; Serviproxan; Sonap; Soproxen; Synflex; U-Proxyn; Vinsen; ***Turk.:*** A-Nox; Aleve; Anaprotab; Apraljin; Apranax; Aprol; Apromed; Aprowell; Bonmin; Kapnax; Karoksen; Naponal; Napradol; Napren; Naprodeva; Naprosyn; Naprotab; Opraks; Relokap; Romaksen; Romatim; Rumazolidin; Synax; Syndol; ***UK:*** Arthrosin†; Arthroxen; Feminax Ultra; Napratec; Naprosyn; Nycopren†; Synflex; Timpron†; ***USA:*** Aleve; Anaprox; Naprelan; Naprosyn; Prevacid NapraPAC; ***Venez.:*** Apranax†; Synaprosyn†.

Multi-ingredient: ***Arg.:*** Naprontag Flex; Papasine; ***Ital.:*** Momendol; ***Mex.:*** Acxen†; Analgen Forte; Arsenal Compuesto; Arxen Compositum; Bifardol; Blocacid; Brax; Contraxen; Dafloxen-F; Decosil; Deflamox Plus; Dolotandax; Drunen; Farxen; Febrax; Fiverdol; Flucol; Grifed; Kensedal; Movex; Naprodil Plus; Naxodol; Nedoxal; Neorpan Plus; Onexmol; Pensodil; Polet; Profenlax; Proxalin Plus; Raxenol; Reucortil; Somalgesic; Taxenan; Ulpafie-N; Velsay-S Compuesto; Viplus; ***Rus.:*** Cefecon N (Цефекон Н); Pentalgin-N (Пенталгин-Н).

Nefopam Hydrochloride

(BANM, USAN, rINNM)

Benzoxazocine; Fenazoxine; Hidrocloruro de nefopam; Néfopam, Chlorhydrate de; Nefopami Hydrochloridum; R-738. 3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine hydrochloride.

Нефопама Гидрохлорид

$C_{17}H_{19}NO,HCl = 289.8.$

CAS — 13669-70-0 (nefopam); 23327-57-3 (nefopam hydrochloride).

ATC — N02BG06.

ATC Vet — QN02BG06.

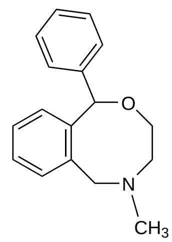

(nefopam)

Pharmacopoeias. In *Chin.*

Adverse Effects and Treatment

Adverse effects occurring with nefopam include gastrointestinal disturbances, such as nausea and vomiting, sweating, drowsiness, insomnia, urinary retention, dizziness, hypotension, tremor, paraesthesia, palpitations, lightheadedness, nervousness, confusion, blurred vision, headache, dry mouth, syncope, angioedema, allergic reactions, and tachycardia. Euphoria, hallucinations, and convulsions have occasionally been reported, as has temporary pink discoloration of the urine. Symptoms of overdosage have included CNS and cardiovascular toxicity.

Effects on the urinary tract. In January 1989, the UK CSM[1] reported that it had received 53 reports in which nefopam was associated with the development of urinary retention or symptoms of hesitancy, poor stream, or dribbling. In one case there was a history of prostatism.

1. CSM. Nefopam hydrochloride (Acupan). *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)

Overdosage. There have been reports of fatal overdoses with nefopam.[1-3] One report[1] also provided details of 9 other patients who recovered with routine supportive treatment.

1. Piercy DM, *et al.* Death due to overdose of nefopam. *BMJ* 1981; **283:** 1508–9.
2. Urwin SC, Smith HS. Fatal nefopam overdose. *Br J Anaesth* 1999; **83:** 501–2.
3. Tracqui A, *et al.* Fatal overdosage with nefopam (Acupan). *J Anal Toxicol* 2002; **26:** 239–43.

Precautions

Nefopam is contra-indicated in patients with a history of convulsive disorders. It should be used with caution in the elderly and in patients with glaucoma, urinary retention, or impaired hepatic or renal function.

Abuse. Abuse of parenteral nefopam has been reported in 3 patients with a history of chronic pain.[1] Psychostimulant-like symptoms such as agitation, impatience, and violence, were noted in 2 of the patients; antimuscarinic effects were also seen. All 3 patients were found to be psychologically dependent; in 2 who attempted to stop nefopam, withdrawal symptoms were noted.

1. Villier C, Mallaret MP. Nefopam abuse. *Ann Pharmacother* 2002; **36:** 1564–6.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving nefopam, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

Studies in 5 healthy nursing mothers given nefopam for post-episiotomy pain indicated that nefopam was present in human milk in an equivalent concentration to that in plasma.[2] It was calculated that on a body-weight basis a breast-fed infant would receive less than 3% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/10/06)
2. Liu DTY, *et al.* Nefopam excretion in human milk. *Br J Clin Pharmacol* 1987; **23:** 99–101.

Interactions

It has been recommended that nefopam should not be given to patients receiving MAOIs and should be used cautiously in those receiving tricyclic antidepressants. The adverse effects of nefopam may be additive to those of other drugs with antimuscarinic or sympathomimetic activity.

Pharmacokinetics

Nefopam is absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1 to 3 hours after a dose by mouth and up to 1 hour after intramuscular injection. About 73% is bound to plasma proteins. Nefopam is distributed into breast milk. It has an elimination half-life of about 4 hours. It is extensively metabolised and excreted mainly in urine, in which less than 5% of a dose is excreted unchanged. About 8% of a dose is excreted via the faeces.

Uses and Administration

Nefopam hydrochloride is a non-opioid analgesic considered to act centrally, although its mechanism of action is unclear. It also has some antimuscarinic and sympathomimetic actions. Nefopam hydrochloride is used for the relief of moderate acute and chronic pain. The usual oral dose range is 30 to 90 mg three times daily; the recommended initial dose is 60 mg (or 30 mg in elderly patients) three times daily. Nefopam hydrochloride may also be given in doses of 20 mg by intramuscular injection, repeated every 6 hours if necessary; it has been recommended that the patient should always be lying down when receiving the injection and should remain so for 15 to 20 minutes afterwards. It has also been given by slow intravenous injection in doses of 20 mg every 4 hours up to a maximum of 120 mg daily.

Hiccup. In two case series[1,2] involving 10 patients in total, hiccups refractory to standard therapy stopped after treatment with intravenous nefopam. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Bilotta F, Rosa G. Nefopam for severe hiccups. *N Engl J Med* 2000; **343:** 1973–4.
2. Bilotta F, *et al.* Nefopam for refractory postoperative hiccups. *Anesth Analg* 2001; **93:** 1358–60.

Shivering. Nefopam is one of several drugs tried in the prevention of postoperative shivering (p.1779).

References.

1. Bilotta F, *et al.* Nefopam and tramadol for the prevention of shivering during neuraxial anesthesia. *Reg Anesth Pain Med* 2002; **27:** 380–4.
2. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.
3. Bilotta F, *et al.* Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; **60:** 124–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Acupan; ***Fr.:*** Acupan; ***Ger.:*** Ajan†; Silentan†; ***Irl.:*** Acupan; ***Ital.:*** Nefam†; Oxadol†; ***NZ:*** Acupan; ***Rus.:*** Oxadol (Оксадол); ***Switz.:*** Acupan†; ***UK:*** Acupan.

Nepafenac *(USAN, rINN)*

AHR-9434; AL-6515; Népafénac; Nepafenaco; Nepafenacum. 2-(2-Amino-3-benzoylphenyl)acetamide.

Непафенак

$C_{15}H_{14}N_2O_2 = 254.3.$

CAS — 78281-72-8.

ATC — S01BC10.

ATC Vet — QS01BC10.

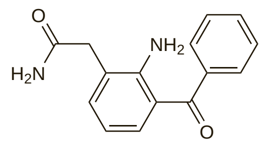

Profile

Nepafenac, an NSAID (p.96), is a prodrug of amfenac. It is used in the treatment of pain and inflammation following cataract surgery. An ophthalmic suspension containing nepafenac 0.1% is instilled 3 times daily starting on the day before surgery and continuing for 2 weeks after surgery.

◊ References.

1. Colin J, Paquette B. Comparison of the analgesic efficacy and safety of nepafenac ophthalmic suspension compared with diclofenac ophthalmic solution for ocular pain and photophobia after excimer laser surgery: a phase II, randomized, double-masked trial. *Clin Ther* 2006; **28:** 527–36.
2. Lane SS. Nepafenac: a unique nonsteroidal prodrug. *Int Ophthalmol Clin* 2006; **46:** 13–20.
3. Lane SS, *et al.* Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg* 2007; **33:** 53–8. Correction. *ibid.*; 564.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nevanac; ***Chile:*** Nevanac; ***Cz.:*** Nevanac; ***Port.:*** Nevanac; ***USA:*** Nevanac.

Nicoboxil *(rINN)*

Butoxyethyl Nicotinate; Nicoboxilo; Nicoboxilum. 2-Butoxyethyl nicotinate.

Никобоксил

$C_{12}H_{17}NO_3 = 223.3.$

CAS — 13912-80-6.

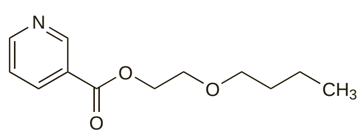

Profile

Nicoboxil is a nicotinate used in topical preparations as a rubefacient. It is also included in some topical preparations used for the treatment of acne vulgaris.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Finalgon; ***Austria:*** Finalgon; ***Canad.:*** Finalgon†; ***Ger.:*** Finalgon; ***Ital.:*** Anti-Acne; ***NZ:*** Finalgon†; ***Port.:*** Finalgon; ***Rus.:*** Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Finalgon (Финалгон); ***Spain:*** Finalgon; ***UK:*** Actinac.

Nicomorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nicomorfina; Nicomorphine, Chlorhydrate de; Nicomorphini Hydrochloridum. 3,6-Di-*O*-nicotinoylmorphine hydrochloride; (−)-(5*R*,6*S*)-4,5-Epoxy-9a-methylmorphin-7-en-3,6-diyl dinicotinate hydrochloride.

Никоморфина Гидрохлорид

$C_{29}H_{25}N_3O_5,HCl = 532.0.$

CAS — 639-48-5 (nicomorphine); 12040-41-4 (nicomorphine hydrochloride); 35055-78-8 (nicomorphine xHCl).

ATC — N02AA04.

ATC Vet — QN02AA04.

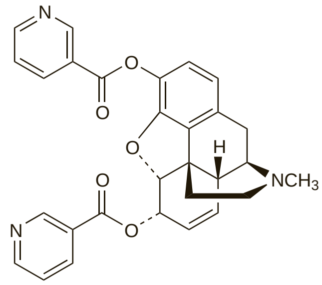

(nicomorphine)

Profile

Nicomorphine hydrochloride is an opioid analgesic (p.101) used in the treatment of moderate to severe pain. It is given in oral doses of 5 to 10 mg daily or by intramuscular, slow intravenous, or subcutaneous injection in doses of 10 to 20 mg; higher doses have also been used. It may also be given rectally in usual doses of 10 to 20 mg daily.

◊ References.

1. Koopman-Kimenai PM, *et al.* Pharmacokinetics of intravenously administered nicomorphine and its metabolites in man. *Eur J Anaesthesiol* 1993; **10:** 125–32.
2. Koopman-Kimenai PM, *et al.* Rectal administration of nicomorphine in patients improves biological availability of morphine and its glucuronide conjugates. *Pharm World Sci* 1994; **16:** 248–53.
3. Koopman-Kimenai PM, *et al.* The bioavailability of intramuscularly administered nicomorphine (Vilan) with its metabolites and their glucuronide conjugates in surgical patients. *Int J Clin Pharmacol Ther* 1995; **33:** 442–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Vilan; ***Denm.:*** Vilan; ***Neth.:*** MorZet; Vilan†; ***Switz.:*** Vilan.

Niflumic Acid *(rINN)*

Acide niflumique; Ácido niflúmico; Acidum niflumicum; UP-83. 2-(ααα-Trifluoro-*m*-toluidino)nicotinic acid.

Нифлумовая Кислота

$C_{13}H_9F_3N_2O_2 = 282.2.$

CAS — 4394-00-7.

ATC — M01AX02; M02AA17.

ATC Vet — QM01AX02; QM02AA17.

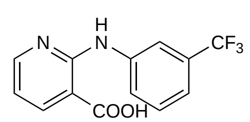

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Niflumic Acid). A pale yellow, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol; freely soluble in acetone.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Fluoride-associated osteosis has been reported with prolonged use. Niflumic acid should be stopped if hypersensitivity skin reactions appear.

Effects on the skin. From a case-control study[1] of children admitted to a hospital emergency department in Italy it was calculated that the odds-ratio of users of niflumic acid, or its derivative morniflumate, developing serious cutaneous reactions was 4.9. Given this figure and the fact that safer drugs were available the authors considered that there was no indication for which niflumic acid was required in children. However, a large cohort study[2] involving 193 727 children aged between 0 and 14 years found that niflumic acid was not associated with a higher risk of mucocutaneous reactions when compared with other NSAIDs or paracetamol. The authors of the later study suggested that the conclusions of the original study may have been confounded because there was no adjustment for age or indication.

1. Menniti-Ippolito F, *et al.* Niflumic acid and cutaneous reactions in children. *Arch Dis Child* 2001; **84:** 430–1.
2. Sturkenboom M, *et al.* Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Abstract: *Pediatrics* 2005; **116:** 212. Full version: http://pediatrics.aappublications.org/cgi/content/full/116/1/e26 (accessed 08/11/07)

Uses and Administration

Niflumic acid, a nicotinic acid derivative, is an NSAID (p.99). It has been used in inflammatory and musculoskeletal and joint disorders in usual oral doses of about 250 mg three or four times daily; up to 1500 mg daily has been used in severe disorders. It has also been used topically as a 3% cream or ointment or 2.5% gel. The morpholinoethyl ester, morniflumate (p.86), has similar uses.

Niflumic acid glycinamide has been used topically in inflammatory mouth disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Flogovital; ***Belg.:*** Niflugel; Nifluril; ***Cz.:*** Niflugel; Nifluril; ***Fr.:*** Flunir†; Niflugel; Nifluril; ***Gr.:*** Niflamol; Novopone†; ***Hung.:*** Donalgin; ***Ital.:*** Niflam; ***Port.:*** Nifluril; ***Rus.:*** Donalgin (Доналгин); ***Spain:*** Niflactol.

Multi-ingredient: ***Arg.:*** Flogodisten.

Nimesulide *(BAN, rINN)*

Nimesulid; Nimesulida; Nimesulidas; Nimésulide; Nimesulidi; Nimesulidinum; Nimesulidum; Nimeszulid; R-805. 4′-Nitro-2′-phenoxymethanesulphonanilide.

Нимесулид

$C_{13}H_{12}N_2O_5S = 308.3.$

CAS — 51803-78-2.

ATC — M01AX17.

ATC Vet — QM01AX17.

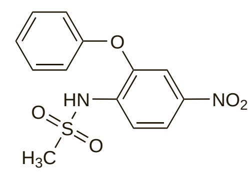

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nimesulide). A yellowish crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in acetone.

Profile

Nimesulide is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It may be given in oral doses of up to 100 mg twice daily for inflammatory conditions, fever, pain, and dysmenorrhoea; use in the EU is limited to a maximum of 15 days due to reports of hepatotoxicity (see Adverse Effects, below). It has also been given rectally in a dose of 200 mg twice daily or applied topically as a 3% gel. Nimesulide betadex (nimesulide betacyclodextrin complex) has been used similarly.

◊ References.

1. Bennett A, *et al.* Nimesulide: a multifactorial therapeutic approach to the inflammatory process? a 7-year clinical experience. *Drugs* 1993; **46:** (suppl 1): 1–283.
2. Senna GE, *et al.* Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996; **14:** 94–103.
3. Vizzardi M, *et al.* Nimesulide beta cyclodextrin (nimesulide-betadex) versus nimesulide in the treatment of pain after arthroscopic surgery. *Curr Ther Res* 1998; **59:** 162–71.
4. Bernareggi A. Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet* 1998; **35:** 247–74.
5. Shah AA, *et al.* Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut* 2001; **48:** 339–46.
6. Nüing RM, *et al.* Pathogenetic role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome: therapeutic use of the cyclooxygenase-2 inhibitor nimesulide. *Clin Pharmacol Ther* 2001; **70:** 384–90.

Adverse effects. Although *thrombocytopenia* is a common feature in patients infected with HIV, a group of workers considered that thrombocytopenia in one of their patients was related to the use of nimesulide.[1]

There have been reports[2-4] of *hepatotoxicity* after treatment with nimesulide. Data from spontaneous reports has also suggested that nimesulide may be associated with a higher risk of hepatotoxicity than other NSAIDs.[4] A cohort study[5] involving about 400 000 users of NSAIDs in one region of Italy between 1997 and 2001 found that those taking nimesulide were 1.3 times more likely to develop hepatotoxicity than users of other NSAIDs and 1.9 times more likely to suffer severe liver injury. In May 2007 the Irish regulatory authority withdrew nimesulide from the Irish market after concerns about hepatotoxicity.[6] Since being licensed in 1995, nimesulide had generated 53 adverse reaction reports involving liver toxicity, including 9 cases of liver failure, 3 of which resulted in death and 6 in liver transplantation; there had also been 1 other liver-related fatality. The EMEA[7] subsequently recommended that treatment with nimesulide should be limited to 15 days.

There have been reports[8,9] of *toxic pustuloderma* (acute generalised exanthematous pustulosis) after receiving oral nimesulide. *Fixed drug eruptions* have also been seen.[10]

An infant developed hypotension and hypothermia after inadvertently taking an *overdose* of 8 times the recommended daily dose of nimesulide.[11] The patient recovered after gastric lavage with activated charcoal and supportive therapy.

1. Pasticci MB, *et al.* Nimesulide, thrombocytopenic purpura, and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1990; **112:** 233–4.

2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; **353:** 40–1.
3. Sbeit W, *et al.* Nimesulide-induced acute hepatitis. *Ann Pharmacother* 2001; **35:** 1049–52.
4. Maciá MA, *et al.* Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. *Clin Pharmacol Ther* 2002; **72:** 596–7.
5. Traversa G, *et al.* Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ* 2003; **327:** 18–22.
6. Irish Medicines Board. Immediate suspension of the marketing of medicines containing nimesulide (issued 15th May, 2007). Available at: http://www.imb.ie/EN/Safety--Quality/Advisory-Warning--Recall-Notices/Human-Medicines/Nimesulide-Suspension.aspx?page=1&noticetypeid=-1&year=2007 (accessed 08/11/07)
7. EMEA. Questions and answers on the CHMP recommendation on nimesulide-containing medicines (issued 21st September, 2007). Available at: http://www.emea.europa.eu/pdfs/human/opinion/43098807en.pdf (accessed 08/11/07)
8. Lateo S, Boffa MJ. Localized toxic pustuloderma associated with nimesulide therapy confirmed by patch testing. *Br J Dermatol* 2002; **147:** 624–5.
9. Teixeira M, *et al.* Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; **12:** 20. Available at: http://dermatology.cdlib.org/126/case_presentations/agep/teixeira.html (accessed 08/11/07)
10. Malheiro D, *et al.* Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; **33:** 285–7.
11. Yapakci E, *et al.* Hypoglycaemia and hypothermia due to nimesulide overdose. *Arch Dis Child* 2007; **85:** 510.

Pregnancy. Irreversible *end-stage renal failure* has been reported in a neonate born to a mother who received nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[1] Others have reported neonatal renal failure associated with nimesulide.[2] *Premature closure of the ductus arteriosus* leading, in some cases, to *persistent pulmonary hypertension* has also been seen in 10 neonates whose mothers self-medicated with nimesulide during the third trimester of pregnancy.[3]

1. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; **354:** 1615. Correction. *ibid.* 2000; **355:** 238.
2. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; **355:** 575.
3. Paladini D, *et al.* Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005; **25:** 357–61.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in patients with a history of preterm delivery (p.2003). Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal.[1] There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 (COX-1) and that a relatively selective COX-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, in a small study short-term effects on the fetus were similar for nimesulide, indometacin, and sulindac.[2]

Adverse effects have been reported in some neonates whose mothers received nimesulide during their pregnancies, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; **350:** 265–6.
2. Sawdy RJ, *et al.* A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; **188:** 1046–51.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aldoron; Aulin†; Doloctaprin†; Flogovital NF; Metaflex†; Virobron; ***Austria:*** Aulin; Mesulid; ***Belg.:*** Mesulid; ***Braz.:*** Antiflogil†; Cimelide; Deflogen; Deltaflan; Fasulide; Flogilid†; Inflalid; Maxsulid; Neosulida; Nimalgex†; Nimedalin†; Nimeflan†; Nimesilam; Nimesubal; Nimesulin; Nimesulix; Nimesulon; Nisalgen†; Nisoflan; Nisuflex; Nisulid; Optaflan†; Scaflam; Scalid; Sintalgin; ***Chile:*** Ainex; Aulin†; Doloc; Nimepast; Nimesyl; Nimex†; Nisulid; Nisural; ***Cz.:*** Aulin; Coxtral; Mesulid; Nimed; Nimesil; ***Fin.:*** Nimed†; ***Fr.:*** Nexen; ***Gr.:*** Aflogen; Alencast; Algosulid; Algover; Amocetin; Aulin; Auromelid; Chemisulide†; Cliovyl; Discorid; Dolostop; Edrigyl; Elinap; Erlecit; Fladalgin; Flogostop; G-Revm; Kartal; Lalide; Lasazin; Lemesil; Lizepat; Londopon†; Lovirem; Melicate; Melimont; Mesulid; Mesupon; Min-A-Pon; Mosuolit; Multiformil; Myxina; Naofid; Niberan; Nimegel; Nimelide; Nimesul; Omnibus; Rhemid; Ristolzit; Ritamine; Rolaket; Scaflam†; Specilid; Sudinet; Tranzicalm; Ventor; Volonten; ***Hong Kong:*** Mesulid; Nidol; Nimm; ***Hung.:*** Mesulid; Nidol; Nimelid; Xilox; ***India:*** Beta Nicip; Mesulid; Nicip; Nilide; Nimcet; Nimfast; Nimica; Nimodol; Nimulid; Nimusyp; Nimutab; Nimvista; Nise; Willgo†; ***Indon.:*** Arnid; Aulin; Nicox; Nimed; Nimost; Sohoflam; Ximede; ***Irl.:*** Aulin†; Mesine†; Mesulid†; ***Israel:*** Mesulid; ***Ital.:*** Algimesil; Algolider; Antalgo; Areuma; Aulin; Biosal†; Delfos; Dimesul; Doleside†; Doloxtren†; Domes; Edemax†; Efridol; Erreflog; Eudolene; Fansidol†; Fansulide; Flolid; Idealid; Isodol; Laidor†; Ledolid†; Ledoren; Lidenix†; Mesulid; Migraless; Nerelid; Nide†; Nimedex; Nimenol; Nimesil; Nimesulene; Nimexan†; Nims; Noalgos; Noxalide; Pantames; Remov; Resulin; Solving; Sulidamor; Sulide; ***Malaysia:*** Nidol†; ***Mex.:*** Apolide; Cargespril; Defam; Degorflan; Dexlin; Eskaflam; Fenoxil; Flamide; Flamozin; Inim; Lesiden; Lusemin; Meliden; Mesulid; Minus†; Nimepis; Nizurin; Quidofril; Redaflam; Severin; Sidel; Sindel; Sulidek; Sundir; Ul-Flam; ***Philipp.:*** Aulin; Flamesul; Mesulid; Nidolid; Sorini; ***Pol.:*** Aulin; Minesulin; Nimesil; ***Port.:*** Aulin; Donulide; Gerilide; Jabasulide; Nimalge; Nimartin; Nimed; Nimesulene; Reumolide; Sulidor; Sulimed; Vitolide; ***Rus.:*** Actasulid (Актасулид); Aponil (Апонил); Coxtral (Кокстрал); Nimesil (Нимесил); Nimica (Нимика); Nise (Найз); ***Singapore:*** Nidol†; Nise†; ***Switz.:*** Aulin; Nisulid; ***Thai.:*** Neptide; Nidol; Nilide; Nimes†; Nimind; Nimulid; ***Turk.:*** Mesulid; Motival; Nimes; Sulidin; ***Venez.:*** Ainex; Aulin; Drexel; Nimecox; Nimelid; Nimepirex†; Niprolide†; Nise†; Normosilen†; Reduben; Scaflan.

Multi-ingredient: *Arg.:* Doloctaprin Plus†; Metaflex Plus†; Mio Aldoron; Mio-Virobron; ***India:*** Cipzen N; Niciflex-T; Nicip Cold; Nicip D; Nicip MR; Nicip Plus; Nicip Super; Nicip T; Nicispas; Nimica Plus; Nimulid MR; Nimulid Nugel; Nimulid SP; Nimvista Plus; Nizer; ***Mex.:*** Amoxiclide; Zithroflam.

Nonivamide *(rINN)*

Nonivamida; Nonivamidum; Noniwamid; Nonylvanillamide; PAVA; Pelargonyl Vanillylamide; Pseudocapsaicin. *N*-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide.

Нониvамид

$C_{17}H_{27}NO_3$ = 293.4.
CAS — 2444-46-4.

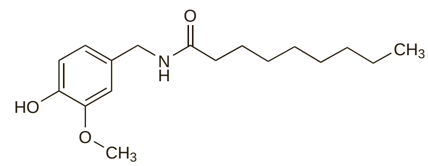

NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is a synthetic analogue of capsaicin (p.32) that is used in topical preparations for the relief of muscular and rheumatic pain.

Nonivamide has also been used as a food flavour and in 'pepper sprays' for law enforcement and self defence.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: ABC Hydrogel-Warmepflaster; ***Ger.:*** ABC Warme-Pflaster Sensitive†; Gothaplast Capsicum-Warmepflaster; Hansaplast ABC Warme-Pflaster Sensitive†.

Multi-ingredient: *Austral.:* Finalgon; ***Austria:*** Finalgon; Rubriment; ***Canad.:*** Finalgon†; ***Cz.:*** Pain Expeller†; ***Ger.:*** Finalgon; Infrotto Ultra†; Lomazell forte N†; Ostochont†; Rheumasalbe†; Rubriment; Vertebralon N†; ***NZ:*** Finalgon†; ***Port.:*** Finalgon; ***Rus.:*** Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Capsicam (Капсикам); Finalgon (Финалгон); ***Spain:*** Finalgon; ***Switz.:*** Forapin†; Histalgane; Radalgin; Thermocutan†; ***Thai.:*** Ammeltz.

Nonsteroidal Anti-inflammatory Drugs

AINE; AINS; Fármacos antiinflamatorios no esteroideos; NSAIDs; NSAİ'ler.

НПВП; НПВС; НСПВП; Нестероидные Противовоспалительные Препараты

Adverse Effects and Treatment

The commonest adverse effects of NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects of NSAIDs, including those selective for COX-2 inhibition, are discussed in detail below.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Incidence of adverse effects. The relative toxicity of NSAIDs is a subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] The toxicity of selective cyclo-oxygenase-2 (COX-2) inhibitors has also been reviewed.[3] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; **10:** 183–95.
2. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
3. Chaiamnuay S, *et al.* Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health-Syst Pharm* 2006; **63:** 1837–51.

Effects on the blood. The UK CSM has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)

Effects on bone. Prostaglandins have been shown to play an important role in the bone-healing process and, consequently, the decrease in prostaglandin levels produced by NSAID use may impair the healing process.[1] Under experimental conditions, many NSAIDs including the cyclo-oxygenase-2 (COX-2) inhibitors have been shown to reduce healing.[1] However, clinical evidence of such an effect is rare.[2] There is also concern that some NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[3,4]

1. Harder AT, An YH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43:** 807–15.
2. Glassman SD. *et al.* The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998; **23:** 834–8.
3. Rashad S, *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii:** 519–22.
4. Huskisson EC, *et al.* Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. *J Rheumatol* 1995; **22:** 1941–6.

Effects on the cardiovascular system. ***BLOOD PRESSURE.*** A meta-analysis[1] of 50 randomised studies of the effects of NSAIDs on blood pressure in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

1. Johnson AG, *et al.* Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; **121:** 289–300.
2. Pope JE, *et al.* A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153:** 477–84.
3. Gurwitz JH, *et al.* Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 1994; **272:** 781–6.

Heart failure. The recent use of NSAIDs has been associated with an increased risk of developing heart failure in elderly patients.[1] A case-control study[2] found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure.

1. Bleumink GS, *et al.* Nonsteroidal anti-inflammatory drugs and heart failure. *Drugs* 2003; **63:** 525–34.
2. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000; **160:** 777–84.

Thrombotic events. After the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors, concerns arose that the risk of thrombotic events such as myocardial infarction and stroke might be increased in patients treated with these selective NSAIDs, and their safety was continuously reviewed by some regulatory bodies. Subsequently, clinical study data confirmed that there was a small increased risk of these events with the COX-2 inhibitors which prompted the general world-wide withdrawal of rofecoxib (see p.121) and valdecoxib (see p.132). For those selective NSAIDs that remained, prescribing restrictions were imposed (for further details, see under Celecoxib, p.34).

Concerns have also been raised that the increased risk of thrombotic events seen with the selective COX-2 inhibitors may also apply to the non-selective NSAIDs. After a review of data available at the time, the FDA[1] reported in April 2005 that the use of non-selective NSAIDs may potentially increase cardiovascular risk. In August 2005, the UK CSM advised that any cardiovascular risk with the non-selective NSAIDs was likely to be small and associated with continuous long-term treatment and higher doses;[2] no changes to current prescribing practices were recommended. This advice was endorsed a few months later by the EMEA in Europe.[3] However, new information has since become available and, in October 2006, the EMEA updated its advice.[4] Based on data which included the MEDAL programme[5] and reviews of several important epidemiological studies[6-8] the following points were made:

- the results from the MEDAL programme suggest that *diclofenac* (150 mg daily) has a risk of thrombotic events similar to that of etoricoxib (60 mg or 90 mg daily); however, further issues need to be considered before this can be considered conclusive
- based on study and epidemiological evidence, diclofenac, particularly at a high dose (150 mg daily), may be associated with an increased risk of thrombotic events
- clinical study data suggest that high-dose *ibuprofen* (2.4 g daily) is associated with an increased risk of thrombotic events; however, overall, epidemiological studies do not support an increased risk with low-dose ibuprofen (1.2 g daily or less)
- *naproxen* (1 g daily) may be associated with a lower risk for thrombotic events than the COX-2 inhibitors, but a small risk cannot be excluded; overall, there is no evidence of a cardioprotective effect
- for all *other non-selective NSAIDs* there are insufficient data to assess the thrombotic risk and consequently an increased risk cannot be excluded; a small increase in absolute risk seems most likely when used in high doses and for long-term treatment

It has been suggested that NSAIDs may reduce the cardioprotective effect of aspirin, but see under Interactions of Aspirin, p.23.

1. FDA. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs) (issued 7th April, 2005). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html (accessed 08/11/07)
2. CSM. Cardiovascular safety of NSAIDs: review of evidence. Message from Professor G Duff, Chairman of CSM (issued August 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con1004303&RevisionSelectionMethod=Latest (accessed 08/11/07)
3. EMEA. European Medicines Agency update on non-selective NSAIDs (issued 17th October, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/29896405en.pdf (accessed 29/08/08)
4. EMEA. Opinion of the Committee for Medicinal Products for Human Use pursuant to article 5(3) of regulation (EC) no 726/2004, for non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 18th October, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/nsaids.pdf (accessed 08/11/07)
5. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368:** 1771–81.
6. Kearney PM, *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; **332:** 1302–8.
7. Hernández-Díaz S, *et al.* Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98:** 266–74.
8. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296:** 1633–44.

Effects on the CNS. A literature review[1] revealed that headache, hearing loss, and tinnitus are the most frequent CNS adverse effects in patients taking NSAIDs. Aseptic meningitis had occurred rarely in patients using NSAIDs such as naproxen, sulindac, or tolmetin, but the most common reports were in patients with SLE who were receiving ibuprofen (see also p.64).

Reports of psychosis appear to be rare[1,2] and have involved indometacin or sulindac, but in some reviewers' experience it was probably under-reported and was typically seen in elderly patients given indometacin.[1]

Adverse CNS effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

The role of NSAIDs in the development of cognitive decline in the elderly is unclear. They have been associated with memory impairment and attention deficits in elderly patients,[1,3] especially when given in high doses;[4] however, some authors have also reported that long-term NSAID use may reduce the rate of cognitive decline[4,5] or the risk of developing Alzheimer's disease[6-8] (see also Dementia, under Uses and Administration, below).

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Onder G, *et al.* NSAID-related psychiatric adverse events: who is at risk? *Drugs* 2004; **64:** 2619–27.
3. Saag KG, *et al.* Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol* 1995; **22:** 2142–7.
4. Karplus TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function - do they have a beneficial or deleterious effect? *Drug Safety* 1998; **19:** 427–33.
5. Rozzini R, *et al.* Protective effect of chronic NSAID use on cognitive decline in older persons. *J Am Geriatr Soc* 1996; **44:** 1025–9.
6. Stewart WF, *et al.* Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; **48:** 626–32.
7. in 't Veld BA, *et al.* Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001; **345:** 1515–21.
8. Vlad SC, *et al.* Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008; **70:** 1672–7.

Effects on electrolytes. See Effects on the Kidneys, below.

Effects on the eyes. Ocular effects such as blurred vision occur rarely in patients taking NSAIDs. Other more serious effects on the eyes associated with NSAIDs also appear to be rare. In the USA the National Registry of Drug-Induced Ocular Side Effects analysed 144 reports they received of possible adverse optic nerve reactions associated with the use of NSAIDs.[1] Of the 24 cases of papilloedema with or without pseudotumor cerebri more than half were associated with propionic acid derivatives, but it was considered that the data indicated that, on rare occasions, most NSAIDs could cause this effect; the number of reports for individual drugs was: 7 for ibuprofen, 5 each for indometacin and naproxen, 3 for meclofenamate, and 1 each for diflunisal, ketoprofen, sulindac, and tolmetin. Almost two-thirds of the 120 cases of optic or retrobulbar neuritis were also associated with propionic acid derivatives; the number of reports for individual drugs was: ibuprofen 43, naproxen 17, indometacin 9, benoxaprofen 8, phenylbutazone 8, piroxicam 8, zomepirac 7, sulindac 6, fenoprofen 5, oxyphenbutazone 3, meclofenamate 2, tolmetin 2, diflunisal 1, and ketoprofen 1.

Ocular adverse effects have also been reported with the selective Cyclo-oxygenase-2 (COX-2) inhibitors.[2]

There have been reports of severe corneal toxicity associated with the use of some topical NSAIDs, such as diclofenac and ketorolac, in the eye (see p.45).

1. Fraunfelder FT, *et al.* Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutan Ocul Toxicol* 1994; **13:** 311–16.
2. Coulter DM, *et al.* Celecoxib, rofecoxib, and acute temporary visual impairment. *BMJ* 2003; **327:** 1214–15.

Effects on fertility. Reversible infertility has been reported in women on long-term NSAIDs.[1-3] Prostaglandins are considered to be involved in the processes of ovulation and it is thought that NSAIDs may compromise ovulation via inhibition of cyclo-oxygenase-2 (COX-2). Women trying to become pregnant may need to avoid treatment with NSAIDs.

1. Mendonça LLF, *et al.* Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology (Oxford)* 2000; **39:** 880–2.
2. Norman RJ. Reproductive consequences of COX-2 inhibition. *Lancet* 2001; **358:** 1287–8.
3. Stone S, *et al.* Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link? *Drug Safety* 2002; **25:** 545–51.

Effects on the gastrointestinal tract. NSAIDs can cause clinically important damage of the gastrointestinal tract, increasing the incidence of bleeding in the upper gastrointestinal tract and of perforation, although serious complications and death are relatively infrequent. They have also been associated with damage to the distal small intestine and colon.[1-3]

The complex **mechanisms** involved are not fully understood, although it is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in gastrointestinal toxicity and that the selective COX-2 inhibitors are less gastrotoxic than the traditional NSAIDs (see below).[4-8] The gastric mucosa is damaged both by local and systemic effects of NSAIDs.[5] The local effect is pH-dependent and varies between individual drugs. The systemic effect is pH-independent, can occur with any route of administration, and is less drug specific; it is this effect that is thought to involve COX-1 inhibition.

Risk factors continue to be studied and so far the most important patient-related factors for upper gastrointestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids.[9] It has also been suggested that risk is increased in children.[10] *Helicobacter pylori* infection exacerbates the risk of ulceration, but patients remain at increased risk even if infection is eradicated.[11] Duration of therapy is not thought to influence the risk for serious events; a cohort study[12] found that the risk of gastrointestinal bleeding or perforation with NSAIDs was constant throughout treatment, and risk quickly declines after NSAID withdrawal.[13]

Several studies[14-17] have been conducted on the **relative toxicity** of oral NSAIDs on the upper gastrointestinal tract and various rankings of these drugs have been discussed.[18-22] The UK CSM[20] examined 10 epidemiological studies for 7 oral non-aspirin NSAIDs and also examined the spontaneous reports they had received of gastrointestinal effects associated with NSAIDs. The CSM concluded that:

- azapropazone was associated with the *highest* risk of gastrointestinal reactions
- ibuprofen carried the *lowest* risk (but this may be related to dose, see below)
- piroxicam, ketoprofen, indometacin, naproxen, and diclofenac had an *intermediate* risk; it was considered that the risk for piroxicam might be higher than for the other NSAIDs with intermediate toxicity

A later update[23] by the CSM confirmed these findings.

The relative gastrointestinal toxicity of NSAIDs has also been reviewed by the EMEA[21] using data from epidemiological studies and spontaneous adverse drug reaction reports. Available evidence suggested that piroxicam and ketoprofen, particularly in high doses, were associated with the greatest risk of gastrointestinal toxicity when compared to diclofenac, etodolac, ibuprofen, indometacin, meloxicam, nabumetone, naproxen, and nimesulide. No firm conclusions were made for the other NSAIDs although there was weak evidence to suggest that the risk of toxicity was slightly higher for indometacin and naproxen than for diclofenac and ibuprofen. As a result of this review the EMEA carried out a full benefit-risk assessment for piroxicam and subsequently placed restrictions on its systemic usage (see p.118).

In a systematic review[24] of controlled epidemiological studies that found a relation between NSAID use and hospital admission for gastric haemorrhage or perforation, the low risk of serious gastric toxicity with ibuprofen appeared to be attributable mainly to the low doses used clinically; higher doses of ibuprofen were associated with a similar risk to indometacin and naproxen. For reference to an association between aspirin and the most severe gastric lesions compared with other NSAIDs, see p.21.

Results from controlled studies have confirmed that the **selective COX-2 inhibitors** are associated with a lower incidence of serious gastrointestinal effects, such as bleeding, perforation, and obstruction, than the traditional NSAIDs[25] (see also Celecoxib, p.35 for further details). However, since the risk of such effects is inherently low in those with no history of peptic ulcer disease, the general prescribing of selective COX-2 inhibitors to all patients requiring an NSAID is questioned, particularly in the light of concerns about their cardiovascular effects (see Thrombotic Events, above). In the UK, the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID. High-risk patients include the elderly, those already receiving gastrotoxic drugs, and those with existing gastrointestinal disorders.

There has been concern that **topical** use of NSAIDs may also be associated with gastrointestinal toxicity but a case-controlled study[26] concluded that this route was not associated with significant upper gastrointestinal bleeding or perforation.

Apart from the selection of an NSAID with a lower risk for gastrointestinal toxicity, other methods used for the **prevention** or **treatment** of NSAID-associated ulceration are discussed under the treatment of peptic ulcer disease on p.1702.

1. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. *Mayo Clin Proc* 1995; **70:** 55–61.
2. Gleeson MH, *et al.* Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347:** 904–5.
3. Evans JMM, *et al.* Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40:** 619–22.
4. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
5. Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996; **101** (suppl 1A): 25S–32S.
6. Soll A. Pathogenesis of nonsteroidal anti-inflammatory drug-related upper gastrointestinal toxicity. *Am J Med* 1998; **105** (suppl 5A): 10S–16S.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353:** 307–14. Correction. *ibid.* 1440. [dose]
8. Wolfe MM, *et al.* Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999; **340:** 1888–99.
9. Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract: indigestion and non-steroidal anti-inflammatory drugs. *BMJ* 2001; **323:** 1236–9.

10. Mulberg AE, *et al.* Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–9.
11. Pounder RE. Helicobacter pylori and NSAIDs—the end of the debate? *Lancet* 2002; **358:** 3–4.
12. MacDonald TM, *et al.* Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315:** 1333–7.
13. Mellemkjaer L, *et al.* Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* 2002; **53:** 173–81.
14. Kaufman DW, *et al.* Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53:** 485–94.
15. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 769–72.
16. Langman MJS, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 1075–8.
17. Lewis SC, *et al.* Dose–response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; **54:** 320–6.
18. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994; **343:** 1051–2.
19. Smith CC, *et al.* NSAIDs and gut toxicity. *Lancet* 1994; **344:** 56–7.
20. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
21. EMEA. Public CHMP assessment report of medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 7th November, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf (accessed 08/11/07)
22. Laporte J-R, *et al.* Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Safety* 2004; **27:** 411–20.
23. CSM/MCA. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and gastrointestinal (GI) safety. *Current Problems* 2002; **28:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
24. Henry D, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312:** 1563–6.
25. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345:** 433–42.
26. Evans JMM, *et al.* Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995; **311:** 22–6.

Effects on the kidneys. NSAIDs can produce renal disorders on systemic or topical use,[1] some of which are due to their inhibition of prostaglandin synthesis.[2,3] In the presence of renal vasoconstriction the vasodilator action of prostaglandins increases renal blood flow and thereby helps to maintain renal function.[4,5] Patients whose renal function is being maintained by prostaglandins are therefore at risk from NSAIDs. Such patients include those with impaired circulation, the elderly, those on diuretics, and those with heart failure or renal vascular disease.[2,4] Other risk factors for renal impairment with NSAIDs include dehydration, cirrhosis, surgery, sepsis,[6] and a history of gout or hyperuricaemia.[6,7] The half-life of an NSAID may be a more important determinant of the risk of developing functional renal impairment than the ingested dose.[7] Evidence of renal toxicity due to cyclo-oxygenase-2 (COX-2) selective inhibitors is less extensive; however, such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs.[8,9]

ACE inhibitors and angiotensin receptor antagonists can also produce renal impairment and combined use with NSAIDs should be undertaken with great care.[10,11] The Australian Adverse Drug Reactions Advisory Committee[10] stated in August 2003 that over 50% of cases of renal failure reported to the committee were associated with use of NSAIDs, ACE inhibitors, or diuretics (alone or together); where all these were taken together the fatality rate for reported cases of renal failure was 10%.

Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or sodium depletion.[4] NSAIDs, therefore, tend to counteract the action of diuretics and antihypertensives.[2,4] There have been isolated reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in patients taking NSAIDs.[12,13]

Potassium homoeostasis is less dependent on prostaglandins and hyperkalaemia occurs infrequently with NSAIDs.[3] It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.[3] Indometacin appears to be the main NSAID implicated.

NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response,[2,3,14] and it may progress to interstitial fibrosis or papillary necrosis.[3,15]

Analgesic abuse or prolonged excessive use can produce nephropathy, a condition characterised by renal papillary necrosis and chronic interstitial nephritis, and, eventually, renal failure.[16] Phenacetin, a para-aminophenol derivative, has long been recognised as being one of the main drugs responsible for analgesic nephropathy,[17,18] but nephropathy has also been associated with the long-term use of NSAIDs and paracetamol without phenacetin.[19]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.
2. Kendall MJ, Horton RC. Clinical pharmacology and therapeutics. *Postgrad Med J* 1990; **66:** 166–85.
3. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991; **31:** 588–98.
4. Harris K. The role of prostaglandins in the control of renal function. *Br J Anaesth* 1992; **69;** 233–5.
5. Kenny GNC. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (suppl 5): 31–7.
6. MacDonald TM. Selected side-effects: 14. non-steroidal anti-inflammatory drugs and renal damage. *Prescribers' J* 1994; **34:** 77–80.
7. Henry D, *et al.* Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol* 1997; **44:** 85–90.
8. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
9. Noroian G, Clive D. Cyclo-oxygenase-2 inhibitors and the kidney: a case for caution. *Drug Safety* 2002; **25:** 165–72.
10. Adverse Drug Reactions Advisory Committee (ADRAC). ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adverse Drug React Bull* 2003; **22:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 08/11/07)
11. Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the 'triple whammy'. *Br J Clin Pharmacol* 2005; **59:** 239–43.
12. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
13. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.
14. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *Br J Clin Pharmacol* 1999; **47:** 203–10.
15. Sandler DP, *et al.* Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991; **115:** 165–72.
16. De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med* 1998; **338:** 446–52.
17. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
18. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
19. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.

Effects on the liver. A retrospective study involving over 220 000 adults who were either using, or had used, NSAIDs identified a small excess risk of serious, acute non-infectious liver injury; in current users there was a twofold increase in risk and there was a predominance of the cholestatic type of liver injury among such patients. Nonetheless, admissions to hospital for liver injury had been rare.[1] In a review[2] of cohort and case-control studies describing an association between NSAIDs and liver disease, the strongest evidence emerged for sulindac. There were also a significant number of reports of hepatotoxicity on rechallenge with diclofenac. Evidence of hepatotoxicity for other NSAIDs was weak, although the risk appeared to be high when they were used with other hepatotoxic drugs. However, the overall incidence of liver disease with NSAIDs was very low.

A later review has also concluded that NSAID-induced hepatotoxicity is an uncommon event.[3] Nevertheless, an increased risk of hepatotoxicity has been associated with the selective cyclo-oxygenase-2 (COX-2) inhibitor lumiracoxib which led to its subsequent withdrawal in many countries (see p.78). For similar reasons, nimesulide has been withdrawn in some countries and its use is limited in others (see p.95).

1. García Rodríguez LA, *et al.* The role of non-steroidal anti-inflammatory drugs in acute liver injury. *BMJ* 1992; **305:** 865–8. Correction. *ibid.*: 920.
2. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. *Drug Safety* 1996; **15:** 64–71.
3. O'Connor N, *et al.* Hepatocellular damage from non-steroidal anti-inflammatory drugs. *Q J Med* 2003; **96:** 787–91.

Effects on the lungs. Adverse pulmonary effects such as pneumonitis, alveolitis, pulmonary infiltrates, and pulmonary fibrosis, often suggestive of an allergic or immune reaction, have been reported with a number of NSAIDs. For references, see under individual monographs.

Effects on the pancreas. A review[1] of drug-induced pancreatitis considered that sulindac was amongst the drugs for which a definite association with pancreatitis had been established. There had been isolated reports of pancreatitis with ketoprofen, mefenamic acid, and piroxicam but any association was considered to be questionable. A more recent population-based, case-controlled study found a substantial variation in the risk of pancreatitis between individual NSAIDs.[2] The increase in risk was highest for diclofenac and ketoprofen (adjusted odds ratios of 5.0 and 4.8, respectively), with indometacin and ibuprofen showing smaller but nonetheless significant increases (odds ratios of 3.6 and 1.5, respectively). Of the other NSAIDs studied (celecoxib, etodolac, naproxen, and rofecoxib), all showed a small but non-significant increase in risk of pancreatitis in current NSAID users.

For further references see under individual monographs.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Sørensen HT, *et al.* Newer cyclo-oxygenase-2 selective inhibitors, other non-steroidal anti-inflammatory drugs and the risk of acute pancreatitis. *Aliment Pharmacol Ther* 2006; **24:** 111–16.

Effects on the skin. The diverse cutaneous reactions to NSAIDs including those selective for cyclo-oxygenase-2 (COX-2) inhibition have been reviewed.[1-3]

Of 250 children attending a rheumatology clinic 34 (13.6%) were found to have 4 or more facial scars of unknown origin.[4] This number of scars was found in 22.2% of the 116 children who had received naproxen and in 9.2% of the 87 who had received other NSAIDs. Children affected were more likely to have light skin and blue or green eyes. It was not known whether this was a form of phototoxic reaction but pseudoporphyria-like eruptions associated with NSAIDs, and naproxen in particular (see p.93), have been reported.[5,6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see p.118).

See also Hypersensitivity, below.

1. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985; **12:** 866–76.
2. La Grenade L, *et al.* Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Safety* 2005; **28:** 917–24.
3. Layton D, *et al.* Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. *Drug Safety* 2006; **29:** 687–96.
4. Wallace CA, *et al.* Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; **125:** 819–22.
5. Checketts SR, *et al.* Nonsteroidal anti-inflammatory-induced pseudoporphyria: is there an alternative drug? *Cutis* 1999; **63:** 223–5.
6. Al-Khenaizan S, *et al.* Pseudoporphyria induced by propionic acid derivatives *J Cutan Med Surg* 1999; **3:** 162–6.

Hypersensitivity. NSAIDs have produced a wide range of hypersensitivity reactions in susceptible individuals; the most common include skin rashes, urticaria, rhinitis, angioedema, bronchoconstriction, and anaphylactic shock. Hypersensitivity to NSAIDs appears to occur more frequently in patients with asthma or allergic disorders but other risk factors have been identified (for further details see under Aspirin, p.21). The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the 'aspirin triad'. There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. For references to hypersensitivity reactions associated with NSAIDs, see under individual monographs. See also Effects on the Skin (p.73) for a report suggesting that ketoprofen is more allergenic than other topical NSAIDs.

Overdosage. In general, symptoms of NSAID poisoning are mild, and usually include nausea and vomiting, headache, drowsiness, blurred vision, and dizziness. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities. Seizures are a particular problem with mefenamic acid overdosage.

Treatment of NSAID overdosage is entirely supportive. Gastric lavage and activated charcoal may be of benefit within 1 hour of ingestion of a potentially toxic amount. Multiple doses of activated charcoal may be useful in enhancing elimination of NSAIDs with long half-lives such as piroxicam and sulindac. Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of benefit for NSAID overdosage, although haemodialysis may be required if oliguric renal failure develops.

Precautions

All NSAIDs are contra-indicated in patients with active peptic ulceration; in addition, the non-selective NSAIDs should be used with caution, if at all, in patients with a history of such disorders. To reduce the risk of gastrointestinal effects, NSAIDs may be taken with or after food or milk. Histamine H_2-antagonists, proton pump inhibitors such as omeprazole, or misoprostol may be used for a similar purpose in high-risk patients taking non-selective NSAIDs (see Peptic Ulcer Disease, p.1702). However, food, milk, and such measures may reduce the rate and extent of drug absorption. The UK CSM recommends that NSAIDs associated with the lowest risk of gastrointestinal toxicity (see Effects on the Gastrointestinal Tract, under Adverse Effects, above) should be tried first in the lowest recommended dose, and not more than one oral NSAID should be used at a time; selective inhibitors of cyclo-oxygenase-2 (COX-2) should be reserved for patients at highest risk of ulcer, perforation, or bleeding, and after assessment of cardiovascular risk. There is no evidence to justify the use of gastroprotective drugs with selective inhibitors of COX-2 to further reduce the risk of gastrointestinal effects.

All NSAIDs are contra-indicated in severe heart failure; furthermore selective COX-2 inhibitors should not be used in patients with moderate heart failure, ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. NSAIDs should be used with caution in patients with hypertension; the selective COX-2 inhibitors should also be used with caution in patients with left ventricular failure, oedema, or a history of cardiac failure, and in patients with risk factors for developing heart disease.

NSAIDs should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked (for the suggestion that they should not be used in children with varicella see below). They should also be used with caution in patients with asthma or allergic disorders. NSAIDs (including topical NSAIDs) are contra-indicated in patients with a history of hypersensitivity reactions to such drugs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

Other general precautions to be observed include use in patients with haemorrhagic disorders or impaired renal or hepatic function. Patients undergoing therapy with some NSAIDs may need to be monitored for the development of blood, kidney, liver, or eye disorders. NSAIDs should be used with caution in the elderly and may need to be given in reduced doses.

Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Further details concerning the precautions of the individual NSAIDs may be found under their respective monographs.

Pregnancy. Most licensed product information recommends avoidance of NSAIDs during pregnancy, unless the proposed benefit outweighs the risks, but in many cases published data on use of the drugs in pregnancy is scanty or absent, making an informed decision difficult. Use of NSAIDs during pregnancy may delay the onset of labour and increase its duration.

Use of NSAIDs during the third trimester of pregnancy may result in the *premature closure of fetal ductus arteriosus*. A recent meta-analysis[1] suggested that the short-term use of NSAIDs was associated with a fifteen fold increase in the risk of premature closure when compared to either placebo or other non-NSAIDs. There was insufficient data to predict the outcome of long-term NSAID treatment in late pregnancy; however, it seemed likely that the risk of premature closure would be even greater with such treatment.

Results from a case-control interview study[2] suggested that prenatal ingestion of aspirin or other NSAIDs might be implicated in *persistent pulmonary hypertension* of the newborn. The authors suggested that these drugs may be responsible for gestational structural or functional alterations of the pulmonary vasculature. However, the primary cause might also have been the underlying disorder for which the NSAIDs or aspirin were ingested. They were unable to pinpoint in which trimester the drugs might have their proposed action. A more recent study[3] has found that persistent pulmonary hypertension of the newborn is significantly associated with *in-utero* NSAID exposure, particularly to aspirin, ibuprofen, and naproxen. Fetal exposure to an NSAID was confirmed by meconium analysis.

The risk of *miscarriage* may be increased with NSAID use;[4,5] however, this observation remains to be confirmed. One study[4] also found no association between NSAID use and congenital abnormalities, low birth weight, or preterm birth.

1. Koren G, *et al.* Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006; **40:** 824–9.
2. Van Marter LJ, *et al.* Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. *Pediatrics* 1996; **97:** 658–63.
3. Alano MA, *et al.* Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001; **107:** 519–23.
4. Nielsen GL, *et al.* Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001; **322:** 266–70.
5. Li D-K, *et al.* Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; **327:** 368–71.

Renal impairment. The *BNF* recommends that NSAIDs in general should be given at the lowest effective dose in patients with mild renal impairment and that renal function should be carefully monitored; they should be avoided if possible in patients with moderate to severe renal impairment.

See also under individual monographs.

Thyroid function tests. References[1,2] to the interference with thyroid function tests by some NSAIDs.

1. Bishnoi A, *et al.* Effect of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. *Am J Med* 1994; **96:** 235–8.
2. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Varicella. The French regulatory authorities noted in July 2004 that after the report of 3 cases of septic shock, 1 fatal, in children treated with NSAIDs for fever and pain, pharmacovigilance studies had discovered a number of other cases of severe complications relating to infection of the skin lesions of chickenpox in NSAID-treated children.[1] Although these, and a few reports in the literature[2,3] could not establish a causal relation, it was considered prudent to avoid the use of NSAIDs in children with chickenpox, and licensed product information for the relevant drugs was to be modified appropriately.[1] More recently, a nested case-control study[4] of nearly 250 000 patients with chickenpox or shingles in the UK General Practice Research Database found an increased risk of severe skin and soft tissue complications associated with the use of NSAIDs, mostly in children with chickenpox.

1. Agence Française de Sécurité Sanitaire des Produits de Santé. L'utilisation d'anti-inflammatoires nonstéroïdiens (AINS), dans le traitement de la fièvre et/ou de la douleur, n'est pas recommandée chez l'enfant atteint de varicelle (issued 15th July, 2004). Available at: http://www.agmed.sante.gouv.fr/htm/10/filltrpsc/lp040701.htm (accessed 08/11/07)
2. Zerr DM, *et al.* A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999; **103:** 783–90.
3. Lesko SM, *et al.* Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. *Pediatrics* 2001; **107:** 1108–15.
4. Mikaeloff Y, *et al.* Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. *Br J Clin Pharmacol* 2008; **65:** 203–9.

Interactions

Interactions involving NSAIDs include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone) and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and some diuretics, including potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. NSAIDs may increase the effects of phenytoin and sulfonylurea antidiabetics.

Use of more than one NSAID together (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, the SSRIs, the SNRI venlafaxine, the antiplatelets clopidogrel and ticlopidine, iloprost, erlotinib, sibutramine, or, possibly, alcohol, bisphosphonates, or pentoxifylline. There may be an increased risk of haematotoxicity if zidovudine is used with NSAIDs. Ritonavir may increase the plasma concentrations of NSAIDs. Licensed product information for mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by NSAIDs or aspirin may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when NSAIDs were given with misoprostol although such combinations have sometimes been used to *decrease* the gastrointestinal toxicity of NSAIDs.

Further details concerning the interactions of the individual NSAIDs may be found under their respective monographs.

◊ References.

1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; **27:** 462–85.

Antihypertensives. For reference to the relative effects of NSAIDs in antagonising different types of antihypertensive drugs, see Effects on the Cardiovascular System and Effects on the Kidneys under Adverse Effects, above.

Aspirin. It has been suggested that NSAIDS such as ibuprofen may reduce the cardioprotective effect of aspirin but see under Interactions of Aspirin, p.23.

Pharmacokinetics

Details of the pharmacokinetics of individual NSAIDs may be found under their respective monographs.

◊ General reviews.

1. Woodhouse KW, Wynne H. The pharmacokinetics of non-steroidal anti-inflammatory drugs in the elderly. *Clin Pharmacokinet* 1987; **12:** 111–22.
2. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. *Clin Pharmacokinet* 1989; **17** (suppl 1): 116–37.
3. Simkin PA, *et al.* Articular pharmacokinetics of protein-bound antirheumatic agents. *Clin Pharmacokinet* 1993; **25:** 342–50.
4. Lapicque F, *et al.* Protein binding and stereoselectivity of nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1993; **25:** 115–25.
5. Day RO, *et al.* Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. *Clin Pharmacokinet* 1999; **36:** 191–210.

Uses and Administration

Given as single doses or in short-term intermittent therapy NSAIDs can relieve mild to moderate pain. However, it may take up to 3 weeks of use before their anti-inflammatory effects become evident. The combined analgesic and anti-inflammatory effects make them particularly useful for the symptomatic relief of painful and/or inflammatory conditions including rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and the spondyloarthropathies, and also in peri-articular disorders, and soft-tissue rheumatism. Some NSAIDs are used in the management of dental or post-operative pain. Some NSAIDs, but not aspirin or other salicylates, are also used to treat acute gouty arthritis.

Generally, it is felt that there are only small differences in anti-inflammatory activity between the various NSAIDs and choice is largely empirical. Responses of individual patients vary widely. Thus, if a patient fails to respond to one NSAID, another drug may be successful. However, it has been recommended that NSAIDs associated with a low risk of gastrointestinal toxicity should generally be preferred and the lowest effective dose used. Treatment with NSAIDs that are selective inhibitors of cyclo-oxygenase-2 (COX-2), such as celecoxib, is limited in the UK to those patients with a history of serious gastrointestinal problems or considered to be at high risk of developing such problems if given a non-selective NSAID (see Effects on the Gastrointestinal Tract, above).

NSAIDs are usually given orally, with or after food, although some such as diclofenac, ketoprofen, ketorolac, parecoxib, piroxicam, and tenoxicam can be given intramuscularly; diclofenac, ketorolac, parecoxib, and tenoxicam can also be given intravenously. Some NSAIDs are applied topically or given rectally as suppositories.

Several NSAIDs are used in ophthalmic preparations for the inhibition of intra-operative miosis, control of postoperative ocular inflammation, and prevention of cystoid macular oedema.

Action. Cyclo-oxygenases play an important role in the biosynthesis of prostaglandins (p.2374). Non-selective NSAIDs inhibit both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2); the idea that inhibition of COX-1 is associated with adverse gastrointestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity,[1-6] led to the development[7] of preferential or selective inhibitors of COX-2. Meloxicam and nimesulide are preferential inhibitors of COX-2, (i.e. they have a higher selectivity for COX-2 than COX-1 but are not exclusive COX-2 inhibitors); etodolac and nabumetone are also claimed to have preference for COX-2 although there is less evidence for this. Drugs with a very high selectivity for COX-2 are also available; celecoxib and parecoxib are two examples. Although the selective inhibition of COX-2 may be associated with reduced gastrointestinal toxicity, adverse effects associated with such inhibition have been noted in other body systems, see Thrombotic Events under Effects on the Cardiovascular System, and Effects on the Kidneys, above.

There is evidence that NSAIDs may also have a central mechanism of action that augments the peripheral mechanism.[6]

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity.[8,9] For example, indometacin, its analogues, and some arylpropionic acids are chiral drugs with the S(+)-enantiomer in most cases showing the dominant pharmacological activity. However, the ratio of S/R activity varies between drugs and between *animal* species. NSAIDs are generally used clinically as the racemate with only a few currently being given as the (S)-enantiomer (for example, dexibuprofen and dexketoprofen). The chirality of a drug may have subtle effects on its toxicity and interactions, and it may be more desirable to use a drug as its active enantiomer.[9]

1. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
2. Bennett A, Tavares IA. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 1105.
3. Vane JR. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 1105–6.
4. Jouzeau J-Y, *et al.* Cyclo-oxygenase isoenzymes: how recent findings affect thinking about nonsteroidal anti-inflammatory drugs. *Drugs* 1997; **53:** 563–82.
5. Richardson C, Emery P. The clinical implications of inhibition of the inducible form of cyclo-oxygenase. *Drug Safety* 1996; **15:** 249–60.
6. Cashman JN. The mechanisms of action of NSAIDs in analgesia. *Drugs* 1996; **52** (suppl 5): 13–23.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353:** 307–14. Correction. *ibid.* 1440. [dose]
8. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; **338:** 1565–8.
9. Hayball PJ. Chirality and nonsteroidal anti-inflammatory drugs. *Drugs* 1996; **52** (suppl 5): 47–58.

Colic pain. Prostaglandins have been implicated in the aetiology of biliary colic (p.5), and some NSAIDs such as diclofenac, indometacin, and ketoprofen have been used to relieve such pain.

Dementia. A systematic review[1] of observational studies suggested that the risk of developing dementia (p.362) is lower in patients who are taking NSAIDs. However, a randomised trial[2] found no benefit from treatment with naproxen or rofecoxib in patients with existing mild to moderate Alzheimer's disease. Another systematic review[3] has suggested that the beneficial effects of NSAIDs seen in some studies are likely to be due to biases such as recall introduced by the study's design; the benefit of NSAIDs in preventing dementia or cognitive impairment was 50% in studies with prevalent (pre-existing) dementia cases, which decreased to 20% in studies of incident dementia cases (those developing during the study period), and was absent in those which used cognitive decline as an end-point. Further studies are needed to determine the role of NSAIDs in dementia.[4,5]

1. Etminan M, *et al.* Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ* 2003; **327:** 128–31.
2. Aisen PS, *et al.* Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003; **289:** 2819–26.
3. de Craen AJM, *et al.* Meta-analysis of nonsteroidal antiinflammatory drug use and risk of dementia. *Am J Epidemiol* 2005; **161:** 114–20.
4. Launer LJ. Nonsteroidal anti-inflammatory drug use and the risk for Alzheimer's disease: dissecting the epidemiological evidence. *Drugs* 2003; **63:** 731–9.
5. Townsend KP, Praticò D. Novel therapeutic opportunities for Alzheimer's disease: focus on nonsteroidal anti-inflammatory drugs. *FASEB J* 2005; **19:** 1592–1601.

Diabetes insipidus. NSAIDs such as indometacin have been used in the treatment of diabetes insipidus; for some references, see p.68.

Ectopic ossification. Ectopic ossification (heterotopic ossification) is a condition in which mature bone develops in non-skeletal tissues, commonly the connective tissue of muscles. It occurs after local trauma, for example after joint dislocation or surgery such as total hip replacement, and also after neurological damage such as severe head or spinal cord injuries.[1,2] Ectopic bone formation usually starts about 2 weeks after the injury, though symptoms, which include localised pain, fever, swelling, erythema, and restriction of movement, may not appear for 8 to 12 weeks.[1,3] Neurogenic ectopic ossification may develop even several years after spinal cord injury.[3] A congenital form of ectopic ossification, myositis ossificans progressiva (fibrodysplasia ossificans progressiva), also occurs but is rare. The principal complications of ectopic ossification are loss of joint mobility and function.[1,2]

Ectopic ossification should be distinguished from the calcification of soft tissue which may occur in connective tissue disorders or in parathyroid disorders as a result of high circulating concentrations of calcium and or phosphate; in these conditions calcification occurs without bone formation.

Surgical resection can improve joint motion[1,3] in patients with ectopic ossification, but may be associated with severe complications and poor outcome, and ossification may recur postoperatively.[3] Delaying surgery as long as possible until bone formation has decreased may lessen the likelihood of these complications,[1] although earlier surgery may prevent fibrous ankylosis and muscle contracture.[3] Although there is no consensus on treatment, early, regular and cautious physiotherapy is recommended to mobilise joints;[1-3] aggressive manipulation may cause further ossification.

Prophylactic measures include radiotherapy or drug therapy. While prophylaxis does not always prevent the development of ectopic ossification, it can decrease its occurrence and severity. Prophylactic measures should be begun as early as possible and with regard to orthopaedic surgery may be started before the operation. Prophylaxis is also required if mature ectopic bone is to be surgically excised in order to minimise the rate of recurrence. Low-dose radiotherapy is as effective as high-dose, and pre-operative irradiation is as effective as postoperative.[4] Studies suggest that NSAID prophylaxis is of similar efficacy to radiotherapy.[4] NSAIDs appear to significantly reduce the incidence of ectopic bone formation,[2-5] possibly by inhibiting inflammation and suppressing mesenchymal cell proliferation.[3] While controversy exists as to duration and doses, indometacin is considered the NSAID of choice by some; naproxen, tenoxicam, and diclofenac may also be of benefit.[4] Ibuprofen has been tried; however, a recent study[6] has found that, although it significantly reduced the rate of ectopic bone formation, there were no clinical benefits 6 to 12 months after surgery. Bisphosphonates that inhibit the mineralisation of the deposited bone, such as etidronate, have also been used but they do not prevent the formation of the osteoid matrix. Also when etidronate is stopped, some mineralisation can occur, resulting in delayed ectopic or rebound ossification, though it is usually less severe. Prolonged treatment may be needed.[2,3] A systematic review,[7] however, found insufficient evidence to recommend the use of etidronate for the treatment of acute ectopic ossification.

1. Shehab D, *et al.* Heterotopic ossification. *J Nucl Med* 2002; **43:** 346–53.
2. Vanden Bossche L, Vanderstraeten G. Heterotopic ossification: a review. *J Rehabil Med* 2005; **37:** 129–36.
3. van Kuijk AA, *et al.* Neurogenic heterotopic ossification in spinal cord injury. *Spinal Cord* 2002; **40:** 313–26.
4. Fijn R, *et al.* Prevention of heterotopic ossification after total hip replacement with NSAIDs. *Pharm World Sci* 2003; **25:** 138–45.
5. Fransen M, Neal B. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 08/11/07).
6. Fransen M, *et al.* Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. *BMJ* 2006; **333:** 519–21.
7. Haran M, *et al.* Pharmacological interventions for treating acute heterotopic ossification. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/11/07).

Eye disorders. Miosis resistant to conventional mydriatics often develops during ocular surgery, possibly due to release of prostaglandins and other substances associated with trauma. NSAIDs, which are prostaglandin synthetase inhibitors, are therefore used prophylactically as eye drops before ocular surgery to ameliorate intra-operative miosis but there has been some doubt that the effect they produce is of clinical significance. Those commonly used include diclofenac, indometacin, and flurbiprofen. These drugs do not possess intrinsic mydriatic properties.

Some NSAIDs are used topically or systemically in inflammatory ocular disorders, including inflammation and cystoid macular oedema following ocular surgery (see below). Topical NSAIDs are also effective analgesics when used in the management of corneal abrasions. However, their role in the treatment of macular oedema associated with uveitis (p.1515) is less clear. NSAIDs are also used in the treatment of scleritis (see p.1512). Diclofenac and ketorolac have also both been used in the management of seasonal allergic conjunctivitis (see p.564).

References.

1. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol* 1992; **36:** 259–84.
2. Koay P. The emerging roles of topical non-steroidal anti-inflammatory agents in ophthalmology. *Br J Ophthalmol* 1996; **80:** 480–5.
3. Schalnus R. Topical nonsteroidal anti-inflammatory therapy in ophthalmology. *Ophthalmologica* 2003; **217:** 89–98.
4. Calder LA, *et al.* Topical nonsteroidal anti-inflammatory drugs for corneal abrasions: meta-analysis of randomized trials. *Acad Emerg Med* 2005; **12:** 467–73.

POSTOPERATIVE INFLAMMATORY OCULAR DISORDERS. Corticosteroids are used topically for the control of **postoperative ocular inflammation** but caution is required as they can delay wound healing and mask postoperative infection. They should only be used for short periods as they can cause glaucoma in susceptible individuals. Topical NSAIDs have also been tried and appear to be as effective as corticosteroids in controlling signs of inflammation after ocular surgery,[1] but there has been some concern about reports of corneal toxicity (see p.45).

Cystoid macular oedema may follow cataract or retinal detachment surgery due to a disturbance of the blood-retinal barrier. A number of NSAIDs,[1-7] including diclofenac, flurbiprofen, indometacin, and ketorolac are used topically with or without corticosteroids to prevent or relieve cystoid macular oedema. NSAIDs such as indometacin are also used systemically in its management. However, a recent systematic review[6,7] has found insufficient evidence for the efficacy of NSAIDs (topical and oral) in acute or chronic cystoid macular oedema after cataract surgery although topical ketorolac may have a positive effect in chronic disease.

1. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. *Drugs* 2007; **67:** 1291–1308.
2. Italian Diclofenac Study Group. Efficacy of diclofenac eyedrops in preventing postoperative inflammation and long-term cystoid macular edema. *J Cataract Refract Surg* 1997; **23:** 1183–9.
3. Jampol LM. Pharmacologic therapy of aphakic and pseudophakic cystoid macular edema. *Ophthalmology* 1985; **92:** 807–10.
4. Flach AJ, *et al.* Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. *Am J Ophthalmol* 1987; **103:** 479–86.
5. Jampol LM, *et al.* Nonsteroidal anti-inflammatory drugs and cataract surgery. *Arch Ophthalmol* 1994; **112:** 891–4.
6. Sivaprasad S, *et al.* Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review. *Br J Ophthalmol* 2005; **89:** 1420–2.
7. Sivaprasad S, *et al.* Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 31/10/07).

Fever. Paracetamol, salicylates, and some other NSAIDs are the main antipyretics used to control fever (p.10). Paracetamol is usually the antipyretic of choice in infants and children but ibuprofen is an effective alternative; alternation of the two may be better than either alone, although this is controversial. Salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects of Aspirin, p.22).

Gout. NSAIDs are the drugs usually used first for the treatment of acute attacks of gout (p.552). Since the drug treatment of chronic gout can lead to the mobilisation of urate crystals from established tophi to produce acute attacks, NSAIDs may also be used for the prophylaxis of acute gout during the first few months of urate-lowering therapy.

Headache. An NSAID is often tried first for the symptomatic treatment of various types of headache including migraine (p.616) and tension-type headache (p.617). NSAIDs may also be effective prophylactic drugs for migraine, although propranolol is generally preferred. Paroxysmal hemicrania, a rare variant of cluster headache (p.616), responds to indometacin.

Kidney disorders. Although NSAIDs can produce adverse effects on the kidney (see above) they may have a role in the management of some types of glomerular kidney disease (p.1504). They may be of use for the control of proteinuria due to nephrotic syndrome except when there is overt renal failure.

Malignant neoplasms. An early study by the American Cancer Society[1] suggested that regular use of aspirin might reduce the risk of developing fatal cancer of the oesophagus, stomach, colon, or rectum. Death rates due to other gastrointestinal cancers did not appear to be affected. Some studies[2-11] appear to support this reduced risk of colorectal cancer (see Prophylaxis, under Malignant Neoplasms of the Gastrointestinal Tract, p.666) in regular users of aspirin or other NSAIDs, particularly in high-risk patients, conclusions that were cautiously endorsed by a systematic review.[12] However, other studies[13,14] have found no evidence of an association between the use of aspirin or NSAIDs and the incidence of colorectal cancer, although the authors suggest that these results may be explained by the short treatment period and the low dose of aspirin used. Although a subsequent review[15] prepared for the US Preventive Services Task Force (USPSTF) indicated that cyclo-oxygenase-2 (COX-2) inhibitors and NSAIDs reduce the incidence of colonic adenomas and that NSAIDs also reduce the incidence of colorectal cancer, the USPSTF issued a statement[16] that, because of the adverse cardiovascular and gastrointestinal effects associated with these agents, their use to prevent colorectal cancer could not be recommended in those at average risk of colorectal cancer.

The potential role that inhibition of COX-2 may play in the management of cancer has been discussed[17,18] and a recent study[19] has found that regular use of aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2 but not those with weak or absent expression of COX-2.

A large case-control study,[20] using data held on the UK general practice research database, has examined information on NSAID use and the development of common cancers. This study also found that the use of NSAIDs (including aspirin) may protect against cancer of the oesophagus, stomach, colon, and rectum. However, the study failed to show any decrease in risk of non-gastrointestinal cancers. More recently, 2 meta-analyses[21,22] have also suggested that aspirin and NSAID use reduce the risk of other gastrointestinal cancers such as oesophageal or stomach cancer. In addition, one analysis[21] considered the effect of NSAID and aspirin use on non-gastrointestinal cancers: aspirin use showed a chemoprotective effect in pancreatic cancer although this was not significant statistically; there was also a slight, but nonetheless significant, reduction in the risk of breast cancer associated with both aspirin and NSAID use. The results for other sites, namely ovary, lung, bladder, and prostate, suggested no effect or possibly a slight reduced risk. The authors considered that it was unclear if any potential benefit in non-gastrointestinal cancers may be offset by the known adverse effects associated with the long-term use of these drugs particularly in those cancers with a low incidence.

Treatment with sulindac (see Gastrointestinal Disorders, p.127) has been found to reduce the number of polyps in patients with familial adenomatous polyposis, a condition which predisposes to development of colorectal cancer. Celecoxib has similar effects (see p.36) and it is now licensed for use in such patients.

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Menstrual disorders. Menorrhagia (p.2126) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p.6). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenamates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p.1530) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (see Choice of Analgesic, p.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p.3), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p.7) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p.4), and are of particular value after day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic after major surgery, but may be used with stronger analgesics and may allow dosage reduction of opioids. The pain of mild sickle-cell crises (p.9) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine; NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p.11) and spondyloarthropathies (p.13), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p.11). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p.13); topical formulations of some NSAIDs are also used.

Scleroderma. NSAIDs should be used with caution in scleroderma (p.1817) because of the risk of exacerbating renal and other problems.

Opioid Analgesics

Analgésicos opioides u opiáceos; Analgésiques Opioïdes; Opioid-analgetika.

Опиоидные Анальгетики

Dependence and Withdrawal

Repeated use of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the use of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine in opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see Uses and Administration, below) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than those associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months after the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below.

◊ Review.

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Diagnosis. Naloxone (p.1455) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of a number of reviews and discussions.[1-10]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* (an opioid agonist) given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily use. Oral *diamorphine* has been used similarly to methadone; reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. The partial opioid agonist *buprenorphine*, given sublingually, is another alternative to methadone in the treatment of opioid dependence, and withdrawal symptoms may possibly resolve more quickly than with methadone.[11] However, it should only be given to patients with moderate dependence; those dependent on high doses of opioids may experience withdrawal symptoms when given buprenorphine. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the management of acute pain or in an intensive care setting for more than 5 to 10 days. Methadone has been used successfully to manage opioid withdrawal in adult intensive care patients.[12] However, some[13] avoid using methadone to manage withdrawal in children because of the stigma of its associations with managing withdrawal in drug addicts. In physically dependent but non-addicted patients, gradual weaning using the same opioid that was used therapeutically is preferred where possible, although in some cases, it may be necessary to change to a different opioid because of ease of use, duration of action, and ability to taper the dose; virtually any opioid can be used.[13]

Other drugs used in the management of opioid withdrawal include alpha$_2$-adrenoceptor agonists such as *clonidine* and opioid antagonists such as *naltrexone* and *naloxone*. Clonidine may help to suppress symptoms of opioid withdrawal, such as anxiety, insomnia, and muscle aches. It appears to be more effective when used in the control of symptoms after abrupt withdrawal than when used during gradual withdrawal of methadone. Hypotension may limit its usefulness in some patients. The clonidine analogue *lofexidine* may produce similar results to those obtained with clonidine and appears to be less sedating and hypotensive.[14]

Naltrexone and naloxone block the euphoriant effects of opioids although their use as monotherapy in detoxification is limited by unacceptable opioid withdrawal effects. Naltrexone may be used with alpha$_2$-adrenoceptor agonists such as clonidine or lofexidine to ameliorate symptoms but there are insufficient data to determine whether such combinations reduce the duration of withdrawal treatment or increase the rate of transfer to maintenance therapy with an opioid antagonist.[15] Naloxone and naltrexone are also being used in the relatively new technique of rapid or ultra rapid opioid detoxification,[16-18] which is achieved while the patient is heavily sedated or under *general anaesthesia* and hence unaware of any unpleasant withdrawal symptoms. However, although detoxification may be achieved within 24 hours and has a high initial success rate, the technique itself is not without risks and it does not obviate the need for maintenance treatment (see below).

Concomitant counselling and other psychosocial services have been shown to be important in the outcome of withdrawal therapy.[19,20] Detoxification alone does not ensure long-term abstinence.

A number of other drugs may be of use as **adjuncts** in the management of withdrawal symptoms. *Diphenoxylate* with atropine or *loperamide* may be used for the control of diarrhoea. *Promethazine* has been used for its antiemetic and sedative actions. Beta blockers such as *propranolol* may be of use for patients with pronounced somatic anxiety symptoms. *Benzodiazepines* or *clomethiazole* can be given to relieve anxiety and associated insomnia but only short courses should be used in order to minimise the risk of dependence and abuse.

Long-term **maintenance** treatment (stabilisation treatment) with an opioid is sometimes used, in conjunction with psychosocial support, to enable the patient to acquire some form of social stability. *Methadone* is most commonly used; the use of *diamorphine* although feasible[21,22] is controversial[23] and is advocated by only a few individual centres. *Buprenorphine* is another possibility.[24] The use of methadone for maintenance has been reviewed.[25-27] *Naltrexone* can be effective in maintaining abstinence in opioid addicts after detoxification, especially after rapid or ultra rapid detoxification. It is considered that naltrexone would probably be of most use in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1,28,29]

The problems associated with the management of the **pregnant** patient with opioid dependence have been discussed.[30] The aim should be to stabilise the patient first using *methadone* since acute withdrawal can result in fetal death. Drug withdrawal is best done slowly during the second trimester. It has been suggested that if patients present during the final trimester and cannot be detoxified, maintenance with *diamorphine* might be preferable to the use of methadone as it might produce less severe withdrawal symptoms in the neonate.[31] The management of neonatal abstinence syndrome is discussed below.

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NEONATAL ABSTINENCE SYNDROME. Infants born to opioid-dependent mothers may suffer withdrawal, with signs including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress, yawning, sneezing, mottling, and fever. Onset of symptoms is partly dependent on the drug and varies from shortly after birth to 2 weeks of age, although most symptoms appear within 72 hours. Some symptoms may persist for 3 months or more.

The American Academy of Pediatrics (AAP)[1] recommended that treatment of the neonate with abstinence syndrome should be primarily supportive and considered that many infants with signs of drug withdrawal could be managed in this way. They advised adoption of abstinence scoring methods to judge the need for drug therapy, although such systems do not appear to have been validated. Drugs that have been used for opioid withdrawal include paregoric (a USP 31 preparation containing opium), diluted tincture of opium, morphine, methadone, diazepam, chlorpromazine, phenobarbital, and clonidine. Naloxone should not routinely be given to infants of opioid-dependent mothers because of the risk of seizures with abrupt opioid withdrawal. The AAP[1] made no definite recommendations but considered that, when appropriate, specific drug therapy should be used for treatment of withdrawal symptoms. Thus for opioid withdrawal, tincture of opium was the preferred drug. Others favour treatment with oral morphine solution.[2] The *BNFC* notes that although morphine is widely used and the dose can be easily adjusted, methadone may provide smoother control of symptoms.

Practice varies widely and evidence for the efficacy of particular drugs in the management of neonatal abstinence syndrome is scanty and difficult to compare.[3,4] It has been suggested that diazepam may be less useful than phenobarbital or paregoric but the use of paregoric (which contains both camphor and alcohol) has been questioned. In the UK, chlorpromazine has also been widely used[5] although a systematic review[6] found insufficient evidence to support such use. The authors[6] also found that phenobarbital may reduce the severity of withdrawal symptoms in those receiving an opioid; there was insufficient evidence to support the use of clonidine.

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Adverse Effects

In usual doses the commonest adverse effects of opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance to these (except constipation) generally develops with long-term use. Micturition may be difficult and there may be ureteric or biliary spasm; the latter may be associated with alterations in liver enzyme values. There is also an antidiuretic effect. Dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis also occur. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain. Raised intracranial pressure occurs in some patients. Muscle rigidity has been reported after high doses. The euphoric activity of opioids has led to their abuse. For a discussion of opioid dependence, see above.

Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur, especially in infants and children. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. Toxic doses of specific opioids vary considerably with the individual and regular users may tolerate large doses. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops. Pulmonary oedema after overdosage is a common cause of fatalities among opioid addicts.

Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Contact dermatitis has been reported and pain and irritation may occur on injection. Anaphylactic reactions after intravenous injection have been reported rarely.

◊ The adverse effects associated with individual opioid analgesics may reflect to some extent their activity at specific opioid receptors (see Uses and Administration, below) or may result from a direct toxic effect.[1,2] Some adverse effects of pure opioid agonists, such as the respiratory depressant effect of morphine, are dose related, whereas agonist-antagonists such as buprenorphine, butorphanol, and nalbuphine exhibit a 'ceiling effect' as the dose increases.

The type and extent of adverse effects experienced in practice may depend on whether or not opioid-sensitive pain is present, whether the opioid analgesic is being given for the control of chronic severe pain or acute pain, and the route used. In a review[3] of the use of opioids in *chronic pain* it was noted that, despite worries to the contrary, respiratory depression and dependence liability are not generally a problem when appropriate doses are used to treat opioid-sensitive pain. In fact the presence of opioid-sensitive pain appears to protect against the respiratory depressant effect, although it may occur if the source of opioid-sensitive pain is removed (e.g. by surgery) without adequate reduction in opioid dosage. The adverse effects of opioid analgesics when used in advanced cancer have also been discussed.[4] Constipation was considered to be the most troublesome adverse effect; significant respiratory depression was rarely seen with recommended regimens, since pain antagonises the central depressant effects of morphine.

In the context of *acute postoperative pain* opioid-induced respiratory depression is of concern but short-term postoperative use is unlikely to cause dependence (although see Treatment of Opioid Dependence, above for references to iatrogenic physical dependence).[5] It was hoped that giving opioids by the *spinal route* would result in fewer adverse effects, especially respiratory depression. In postoperative pain relief with spinal opioids, the incidence of adverse effects is said to be low when patients are properly monitored.[6] However, some[7] have reported pruritus, nausea and vomiting, and urinary retention to be common and respiratory depression to occur; more seriously the appearance of respiratory depression could be considerably delayed. These effects were more common with morphine, but all opioid analgesics had the propensity to produce respiratory depression when given spinally.[7] Delayed respiratory depression has been attributed to the poor lipid solubility of morphine, but does occur after other opioids. Some have considered that despite earlier worries, potentially fatal late respiratory depression was as rare with the spinal route as postoperative respiratory depression with the conventional route.[8,9] Disputes regarding the frequency of respiratory depression associated with even conventional use of opioid analgesics might be due to the methods used for measuring respiratory effects.[10] The incidence of ventilatory depression has been reported to be higher after intrathecal than epidural use of morphine.[11]

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11. Gustafsson LL, *et al.* Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; **54:** 479–85.

Effects on the cardiovascular system. For reference to histamine release and cardiovascular effects following the intravenous administration of some opioids see under Pethidine, p.114.

Effects on the endocrine system. Endogenous opioid peptides may have a role in the regulation of endocrine function. Like endorphin and enkephalins, morphine has been found to stimulate prolactin release[1] and synthetic analogues of morphine are reported to have similar properties; long-term intrathecal opioids (morphine or hydromorphone) have been reported to produce hypogonadotrophic hypogonadism, adrenal insufficiency, and growth hormone deficiency, although tolerance to the effects on prolactin develops with long-term use.[2] Opioids such as morphine are also part of a large group of drugs implicated in causing hyperglycaemia.[3]

1. Hell K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; **3:** 463–98.
2. Abs R, *et al.* Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; **85:** 2215–22.
3. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; **40:** 203–19.

Treatment of Adverse Effects

Activated charcoal may be given orally in conscious patients if a substantial overdose has been ingested within 1 hour provided that the airway can be protected (see below); it should be considered in all patients if a substantial amount of a modified-release preparation has been ingested.

Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used for rapid reversal of the severe respiratory depression and coma produced by excessive doses of opioid analgesics (see p.1454). Since naloxone has a shorter duration of action than many opioids patients who have already responded should be kept under close observation for signs of relapse and repeated injections given according to the respiratory rate and depth of coma. Alternatively, in situations where repeated administration is required, such as where a longer acting opioid is known or suspected to be the cause of symptoms, a continuous intravenous infusion of naloxone, adjusted according to response, may be used. All patients should be observed for at least 6 hours after the last dose of naloxone.

The use of opioid antagonists such as naloxone in persons physically dependent on opioids may induce withdrawal symptoms.

Activated charcoal. The National Poisons Information Service in the UK considers the benefit of gastric decontamination in the management of overdosage with opioid analgesics to be uncertain. However, it is suggested that oral activated charcoal may be considered if given within 1 hour of ingestion and the quantity of opioid analgesic is substantial or, for these specific drugs, exceeds the following amount:

- buprenorphine: 100 micrograms/kg (adult); 100 micrograms/kg (child)
- codeine: 350 mg (adult); 5 mg/kg (child)
- dihydrocodeine: 420 mg (adult); 3 mg/kg (child)
- methadone: any amount in an opioid-naive patient or more than the prescribed daily dose if on methadone therapeutically
- tramadol: 500 mg (adult); 10 mg/kg (child)

See also under individual monographs.

Constipation. For reference to the use of opioid antagonists, particularly naloxone, to relieve opioid-induced constipation without compromising analgesic control in patients receiving long-term therapy with opioids, see Reversal of Opioid Effects under Uses and Administration of Naloxone, p.1454.

References.

1. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003; **63:** 649–71.

Precautions

Opioid analgesics are generally contra-indicated in acute respiratory depression and obstructive airways disease, although opioids such as morphine are used in some forms of dyspnoea (see below). They are also contra-indicated or should be used with great caution in acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised. They should not be given to comatose patients.

Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. Dosage should be reduced in elderly or debilitated patients.

Opioid analgesics should be given with great care to infants, especially neonates. Their use during labour may cause respiratory depression in the neonate. Babies born to opioid-dependent mothers may suffer withdrawal symptoms (see Neonatal Abstinence Syndrome, above).

Therapy with opioid analgesics should be stopped gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see Dependence, above). Opioid analgesics with some antagonist activity, such as buprenorphine, butorphanol, nalbuphine, or pentazocine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine.

Drowsiness may affect the ability to perform skilled tasks; those so affected should not drive or operate machinery.

Asthma. Opioids appear to be safe and may be used with caution in controlled asthma; however, they should be avoided during acute exacerbations.[1]

1. Barnes PJ, Chung KF. Difficult asthma. *BMJ* 1989; **299:** 1031–2.

Biliary-tract disorders. It is usually recommended that opioids such as morphine should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi[1] and may therefore be expected to exacerbate rather than relieve pain in patients with biliary colic (p.5) or other biliary-tract disorders. Biliary-type pain after cholecystectomy has also been associated with codeine[2] and morphine.[3]

Morphine caused a more marked delay in gallbladder emptying than pethidine, pentazocine, or butorphanol in a study[4] in healthy subjects; this was considered confirmation that morphine should be avoided in biliary disorders. In another study[5] fentanyl and sufentanil did not constrict the common bile duct like morphine; they may be suitable for perioperative pain control in patients in whom spasm of the common bile duct is undesirable. The suggestion that pethidine should be preferred to morphine in patients with acute pancreatitis (p.9), because of its lesser effect on the bile duct, has been questioned.[6]

1. Helm JF, *et al.* Effects of morphine on the human sphincter of Oddi. *Gut* 1988; **29:** 1402–7.
2. Druart-Blazy A, *et al.* The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. *Gastroenterol Clin Biol* 2005; **29:** 1220–3.
3. Roberts-Thomson IC, *et al.* Sympathetic activation: a mechanism for morphine induced pain and rises in liver enzymes after cholecystectomy? *Gut* 1990; **31:** 217–21.
4. Hahn M, *et al.* The effect of four narcotics on cholecystokinin octapeptide stimulated gall bladder contraction. *Aliment Pharmacol Ther* 1988; **2:** 129–34.
5. Vieira ZEG, *et al.* Evaluation of fentanyl and sufentanil on the diameter of the common bile duct by ultrasonography in man: a double blind, placebo controlled study. *Int J Clin Pharmacol Ther* 1994; **32:** 274–7.
6. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; **96:** 1266–72.

Children. Children under 6 months of age may be more sensitive to opioids; neonates in particular may be more sensitive to respiratory depression with morphine than adults. Pharmacokinetic differences may contribute to this increased sensitivity. Nonetheless, neonates can be treated with opioids such as morphine (see p.90) if receiving respiratory support.

Older infants and children can be treated effectively with morphine or other opioid analgesics and from the age of 5 or 6 months morphine metabolism follows the course seen in adults.

For a discussion of the choice of analgesic in children see p.3. The use of opioids for sedation and analgesia in neonates in intensive care is mentioned on p.957.

References.

1. Choonara IA. Pain relief. *Arch Dis Child* 1989; **64:** 1101–2.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
3. Bhatt-Mehta V. Current guidelines for the treatment of acute pain in children. *Drugs* 1996; **51:** 760–76.
4. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.

The elderly. Ageing can affect the pharmacokinetics and pharmacodynamics of opioids although the net effects of these changes on opioid analgesia in the elderly remain unclear.[1] Practical recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids.

1. Wilder-Smith OHG. Opioid use in the elderly. *Eur J Pain* 2005; **9:** 137–40.

Hepatic impairment. The pharmacokinetics of opioids may be altered in patients with hepatic dysfunction. A review[1] of opioid use in this patient group considered that opioids such as morphine and hydromorphone that are metabolised by glucuronidation were relatively safe when compared with those metabolised by cytochrome P450 isoenzymes; the half-lives of glucuronidated opioids were found to be maintained until late disease whereas the prolonged half-lives seen with opioids metabolised by P450 isoenzymes were not accurately predicted by disease severity. It was also recommended that oral immediate-release or parenteral, short-acting opioids were preferable to long-acting preparations such as transdermal or modified-release formulations.

1. Davis M. Cholestasis and endogenous opioids: liver disease and exogenous opioid pharmacokinetics. *Clin Pharmacokinet* 2007; **46:** 825–50.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release. Both diamorphine[1] and pethidine[2] have been reported to cause hypertension when given to patients with phaeochromocytoma and histamine-releasing opioids should be avoided in such patients. Alfentanil, like fentanyl, does not release histamine and may be the opioid of choice in the anaesthetic management of patients with phaeochromocytoma.[3]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.
2. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.
3. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

Renal impairment. A literature review[1] concluded that codeine and morphine are best avoided in patients with renal failure and/or on dialysis; hydromorphone may be used with caution and monitoring, and use of fentanyl and methadone appeared to be safe. Similar recommendations have been made for patients with end-stage renal disease who are not undergoing dialysis.[2] See also under the individual monographs.

1. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004; **28:** 497–504.
2. Murtagh FE, *et al.* The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007; **21:** 5–16.

Interactions

As serious and sometimes fatal reactions have followed use of pethidine in patients receiving MAOIs (including moclobemide), pethidine and related drugs are contra-indicated in patients taking MAOIs or within 14 days of stopping such treatment; other opioid analgesics should be avoided or given with extreme caution (for further details, see p.418). Life-threatening reactions have also been reported when selegiline, a selective inhibitor of monoamine oxidase type B, has been given with pethidine. The depressant effects of opioid analgesics are enhanced by other CNS depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics. Cyclizine may counteract the haemodynamic benefits of opioids. Cimetidine inhibits the metabolism of some opioids, especially pethidine.

The actions of opioids may in turn affect the activities of other drugs. For instance, their gastrointestinal effects may delay absorption as with mexiletine or may be counteractive as with cisapride, metoclopramide, or domperidone. Opioid premedicants such as papaveretum have been reported to reduce serum concentrations of ciprofloxacin.

Alcohol. Rapid release or dose-dumping of hydromorphone from a modified-release preparation (*Palladone; Purdue Frederick, USA*) has been associated with the ingestion of alcohol (for further details, see under Interactions of Hydromorphone, p.63). Health Canada[1] has warned that this interaction may occur with all modified-release formulations of opioid analgesics. Licensed product information for some modified-release preparations of morphine sulfate also warns against such use (see Interactions of Morphine, p.88).

1. Health Canada. Potentially fatal interaction between slow-release opioid painkillers and alcohol (issued 3rd August, 2005). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2005/2005_84-eng.php (accessed 26/06/08)

Antivirals. Interactions between opioid analgesics and *HIV-protease inhibitors* or *reverse transcriptase inhibitors* are complex, and the results of the limited number of studies and reports *in vivo* have not always borne out predictions about the nature of potential interactions.

- Substantial **decreases** in the area under the plasma concentration-time curve (AUC) and in the plasma concentration have been reported for pethidine when given with *ritonavir*; however, plasma concentrations of the toxic metabolite norpethidine are greatly **increased**, and licensed product information for ritonavir counsels against such combined use. Ritonavir is predicted to reduce plasma concentrations of morphine. Plasma concentrations of methadone may be reduced if given with HIV-protease inhibitors although the effect may not be clinically significant. The NNRTIs *nevirapine* and *efavirenz* have also been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when given to patients receiving methadone. (For further details on the interactions of methadone with antivirals, see p.84.) In addition, efavirenz has been reported to decrease the AUC of buprenorphine (see p.30).
- In contrast, an **increase** in AUC and in elimination half-life of fentanyl has been reported in subjects also receiving ritonavir (see p.57). Licensed product information for ritonavir also considers that increased plasma concentrations of buprenorphine (p.30), dextropropoxyphene, and tramadol, with an increased likelihood of opioid toxicity, may occur if these drugs are given during ritonavir treatment. Licensed information for meptazinol also states that increased plasma concentrations of meptazinol have been noted when given with ritonavir. The NNRTI *delavirdine* has been reported to increase the plasma concentrations of buprenorphine (see p.30) and methadone (p.84).

Histamine H_2-antagonists. Histamine H_2-antagonists may enhance the effects of some opioid analgesics. *Cimetidine* was reported to alter the clearance and volume of distribution of pethidine[1] whereas *ranitidine* did not.[2] Morphine has been considered less likely to interact with cimetidine than pethidine because of differences in metabolism. In a study[3] cimetidine did not affect the disposition of morphine in healthy subjects. A later study[4] in patients undergoing major surgery suggested that pre- or postoperative intravenous cimetidine did not significantly affect outcomes such as morphine consumption and incidence of adverse effects when compared with placebo. Nevertheless, there have been isolated reports of possible interactions between morphine and H_2-antagonists; apnoea, confusion, and muscle twitching have been associated with cimetidine plus morphine,[5] and confusion associated with ranitidine plus morphine.[6] There has also been a report[7] of a patient receiving regular analgesia with oral methadone and subcutaneous morphine who became unresponsive 6 days after starting cimetidine for prophylaxis of peptic ulcer; treatment with naloxone was required.

1. Guay DRP, *et al.* Cimetidine alters pethidine disposition in man. *Br J Clin Pharmacol* 1984; **18:** 907–14.
2. Guay DRP, *et al.* Ranitidine does not alter pethidine disposition in man. *Br J Clin Pharmacol* 1985; **20:** 55–9.
3. Mojaverian P, *et al.* Cimetidine does not alter morphine disposition in man. *Br J Clin Pharmacol* 1982; **14:** 809–13.
4. Chia Y-Y, *et al.* Randomized, double-blind study comparing postoperative effects of treatment timing with histamine H -receptor antagonist cimetidine. *Acta Anaesthesiol Scand* 2005; **49:** 865–9.
5. Fine A, Churchill DN. Potentially lethal interaction of cimetidine and morphine. *Can Med Assoc J* 1981; **124:** 1434, 1436.
6. Martinez-Abad M, *et al.* Ranitidine-induced confusion with concomitant morphine. *Drug Intell Clin Pharm* 1988; **22:** 914–15.
7. Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. *Drug Intell Clin Pharm* 1983; **17:** 60–1.

Uses and Administration

Opioid analgesics possess some of the properties of naturally occurring or **endogenous opioid peptides**. Endogenous opioid peptides are widely distributed in the CNS and are also found in other parts of the body. They appear to function as neurotransmitters, modulators of neurotransmission, or neurohormones. Their presence in the hypothalamus suggests a role in the regulation of endocrine function. Opioids have been shown to stimulate the release of some pituitary hormones, including prolactin and growth hormone, and to inhibit the release of others, including corticotropin.

Endogenous peptides include the enkephalins, endorphins, and dynorphins; their polypeptide precursors may also be precursors for non-opioid peptides. Proenkephalin is the precursor of met- and leu-enkephalin; pro-opiomelanocortin is the precursor of beta-endorphin, beta-lipotrophin, melanocyte-stimulating hormone, and corticotropin; and prodynorphin is the precursor of dynorphins and neoendorphins.

Pharmacologically the opioid analgesics are broadly similar; qualitative and quantitative differences may be dependent on their interaction with **opioid receptors**. There are several types of opioid receptor and they are distributed in distinct patterns through the central and peripheral nervous systems. The three main types in the CNS were originally designated μ (mu), κ (kappa), and δ (delta) although they have been reclassified as OP_3, OP_2, and OP_1, respectively. Activities attributed to the stimulation of these receptors have been as follows:

- μ—analgesia (mainly at supraspinal sites), respiratory depression, miosis, reduced gastrointestinal motility, and euphoria; μ_1 (supraspinal analgesia) and μ_2 (respiratory depression and gastrointestinal activity) subtypes have been postulated
- κ—analgesia (mainly in the spinal cord); less intense miosis and respiratory depression, dysphoria and psychotomimetic effects
- δ—less certain in man, but probably analgesia; selective for enkephalins
- Other receptors include σ (sigma) and ε (epsilon) receptors. The psychotomimetic effects of agonist-antagonists such as pentazocine that are poorly antagonised by naloxone have been thought by some to be mediated by σ receptors

Opioids act at one or more of these receptors as full or partial agonists, or as antagonists. Morphine and similar opioid agonists (sometimes called μ agonists) are considered to act primarily at μ and perhaps at κ and δ receptors. Opioid agonist-antagonists such as pentazocine appear to act as κ agonists and μ antagonists whereas buprenorphine is a partial agonist at μ receptors with some antagonist activity at κ receptors. The opioid antagonist naloxone acts at μ, κ, and δ receptors.

In addition to differing affinities for particular receptors the degree of activation once bound also differs. The full agonist morphine produces maximum activation at the μ receptor and its effects increase with dose, whereas partial agonists and agonist-antagonists may demonstrate a 'ceiling effect' in that above a certain level their effects do not increase proportionately with dose.

Other differences between opioid analgesics may relate to their lipid solubility and pharmacokinetics; speed of onset and duration of action may influence the choice of analgesic.

Opioid analgesics were traditionally classified as weak or strong opioids; however this classification has largely been replaced by the one used in the WHO three-step analgesic ladder (see Cancer Pain, p.5). In this system opioids are divided into those that are used for **mild to moderate pain** and those that are used for **moderate to severe pain**. Examples of opioids in the first group include codeine, dextropropoxyphene, and dihydrocodeine; such opioids are distinguished by the existence of a ceiling effect and are often used with non-opioid analgesics. The principal opioid for the treatment of moderate to severe pain is morphine. Others include diamorphine, fentanyl, methadone, and pethidine.

In addition to the relief of pain, opioids are used in **anaesthesia** for premedication, induction, or maintenance; however, pre-operative use is generally limited to patients who require control of existing pain. In balanced anaesthesia they are used with an anaesthetic and a neuromuscular blocker. When used with an antipsychotic they can produce a state of mild sedation with analgesia called neuroleptanalgesia.

Some opioids are used for analgesia, sedation, and suppression of respiration in the management of mechanically ventilated patients under **intensive care** (p.957).

Opioids such as codeine, hydrocodone, and hydromorphone are used for the suppression of **cough**; for intractable cough in terminal illness morphine may be used.

Opioids may relieve some forms of **dyspnoea**; morphine and diamorphine are probably the most commonly used in the UK, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried.

Methadone and buprenorphine are used in the treatment of opioid **dependence** (see above).

◊ References.

1. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996; **51:** 713–37.
2. Upton RN, *et al.* Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet* 1997; **33:** 225–44.
3. Walsh D. Advances in opioid therapy and formulations. *Support Care Cancer* 2005; **13:** 138–44.
4. Hanks GW, Reid C. Contribution to variability in response to opioids. *Support Care Cancer* 2005; **13:** 145–52.

Action. Some references to opioid receptors.

1. Pleuvry BJ. Opioid receptors and their ligands: natural and unnatural. *Br J Anaesth* 1991; **66:** 370–80.
2. Pleuvry BJ. Opioid receptors and awareness of the Greek alphabet. *Br J Hosp Med* 1992; **48:** 678–81.
3. Atcheson R, Lambert DG. Update on opioid receptors. *Br J Anaesth* 1994; **73:** 132–4.
4. Dhawan BN, *et al.* International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol Rev* 1996; **48:** 567–86.
5. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002; **18** (4 suppl): S3–S13.
6. Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer* 2005; **13:** 153–9.

Administration in children. See under Precautions, above.

Administration in the elderly. See under Precautions, above.

Anaesthesia. Opioid analgesics have been given intravenously as supplements during general anaesthesia with inhalational or intravenous drugs. They have also been widely used as premedication before surgery to reduce anxiety, for smooth induction of anaesthesia, to reduce overall anaesthetic requirements, and to provide postoperative pain relief. Such use of opioids is now rare and is restricted to patients already in pain or to those who will experience pain before induction of anaesthesia. Very high doses of morphine have been infused intravenously to produce anaesthesia for cardiac surgery, but shorter acting drugs such as fentanyl and related opioids are generally used now; some may prefer agonist-antagonist opioids. Sedation and respiratory depression may be prolonged necessitating assisted ventilation; reversal of these effects can be achieved by opioid antagonists such as naloxone. For a discussion of the various drugs used to achieve and maintain conditions suitable for surgery, including the use of opioids in the induction and maintenance of anaesthesia, see p.1780. Opioid analgesics, most commonly fentanyl, have been used with an antipsychotic to induce a state known as neuroleptanalgesia in which the patient is calm and indifferent to the surroundings yet is responsive to commands. For a brief discussion of neuroleptanalgesia and similar anaesthetic techniques, see p.1780.

POSTOPERATIVE SHIVERING. Pethidine appears to be effective in the treatment of postoperative shivering (see p.1779) but not all opioids are necessarily effective.

Cough. Opioids are used to suppress cough (p.1547). Pholcodine (p.1570) and dextromethorphan (p.1555), which lack classical analgesic activity and have fewer adverse effects, are the most commonly used opioids. Of the analgesic opioids, codeine is the most widely used as a cough suppressant. However, these opioids are seldom sufficiently potent to be effective in severe cough. Morphine and diamorphine are used for the relief of intractable cough in terminal illness, although morphine is now preferred. Methadone has also been used but should be avoided as it has a long duration of action and tends to accumulate.

Cough suppressants containing codeine or similar opioids are generally not recommended for use in children, and should be avoided in those under 2 years of age.

Diarrhoea. Oral rehydration therapy, which is the treatment of choice for acute diarrhoea (p.1694), prevents dehydration, but it does not necessarily shorten the duration of the diarrhoea. Preparations containing codeine, morphine, or other opioids have therefore been used for their antimotility action as adjuncts in the management of acute diarrhoea. However, the WHO considers that such antidiarrhoeal drug therapy is of limited value, and should never be given to children. Furthermore opioids should not be used in conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in diarrhoeal conditions such as severe ulcerative colitis or antibiotic-associated colitis.

Dyspnoea. Dyspnoea (a subjective feeling of abnormally uncomfortable, difficult, or laboured breathing) is associated with diseases that interfere with oxygenation of the blood. It is best relieved by treatment of the underlying disorder (the treatment of dyspnoea associated with asthma and chronic obstructive pulmonary disease is discussed on p.1108 and p.1112, respectively). Where this is impossible or ineffective, symptomatic management is required.

Oxygen may reduce dyspnoea in some patients even if dyspnoea is not related to hypoxia. A flow of air directed across the face by a fan can also be effective. Despite the hazards of using benzodiazepines in patients with any form of respiratory depression or pulmonary insufficiency (see under Precautions of Diazepam, p.989), drugs such as diazepam, lorazepam, or midazolam may be helpful in patients with advanced cancer who have rapid shallow respiration, especially when this is associated with anxiety.[1-3] Levomepromazine is occasionally used as an alternative.

Opioids may relieve some forms of dyspnoea,[2,4,5] such as those due to acute left ventricular failure, pulmonary oedema, and malignant chest disease. Guidelines[6] (based on the findings of systematic reviews[7]) issued for the management of dyspnoea in palliative care recommend that opioids should be considered in patients with severe and unrelieved dyspnoea. The cause of dyspnoea should be established since the use of opioids is generally not advised, or only with extreme caution, in patients with obstructive airways disease whose dyspnoea may be relieved by other means. In the UK, morphine and diamorphine are probably the most commonly used opioids for dyspnoea, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried. It is unclear if all opioids are equally effective.[5]

Nebulised morphine, hydromorphone, or fentanyl have been tried for the management of dyspnoea, and there are anecdotal reports of benefit, especially in palliative care, but evidence from controlled studies to date does not support such use.[2-4,8-11] See also under Morphine, p.90.

In patients with advanced cancer and intractable dyspnoea unresponsive to the above measures, chlorpromazine may be useful to relieve air hunger and sedate dying patients who have unrelieved distress;[1] midazolam may be used as an alternative. Promethazine has also been used. High doses of a corticosteroid such as dexamethasone may help to relieve dyspnoea in patients with airways obstruction due to a tumour by reducing oedema around the tumour.

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.
2. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
3. American Thoracic Society. Dyspnea. Mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med* 1999; **159:** 321–40. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/dyspnea1-20.html (accessed 26/06/08)
4. Jennings AL, *et al.* Opioids for the palliation of breathlessness in terminal illness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 26/06/08).

5. Kvale PA, *et al.* American College of Chest Physicians. Lung cancer: palliative care. *Chest* 2003; **123** (suppl): 284S–311S. Also available at: http://www.chestjournal.org/cgi/reprint/123/1_suppl/284S.pdf (accessed 26/06/08)
6. Qaseem A, *et al.* Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008; **148:** 141–6. Also available at: http://www.annals.org/cgi/reprint/148/2/141.pdf (accessed 28/08/08)
7. Lorenz KA, *et al.* Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med* 2008; **148:** 147–59.
8. Chandler S. Nebulized opioids to treat dyspnea. *Am J Hosp Palliat Care* 1999; **16:** 418–22.
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.
11. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Pain. Opioid analgesics are used for the relief of acute and chronic pain (see Choice of Analgesic, p.2). Not every type of pain responds; neuropathic pain, for example, may not be alleviated by opioid therapy. For further discussion of specific pain states and the role of opioid analgesics in their treatment see p.5 onwards.

There has also been interest in the local analgesic effects of opioids themselves.[1,2]

The use of opioid analgesics in opioid-dependent patients receiving maintenance treatment with an opioid is the subject of much debate; however, some consider such use to be appropriate in the management of acute pain in these patients and recommendations have been issued.[3]

1. Thompson DF, Pierce DR. Local analgesia with opioid drugs. *Ann Pharmacother* 1995; **29:** 189–90.
2. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; **332:** 1685–90.
3. Alford DP, *et al.* Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006; **144:** 127–34.

HEADACHE. Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine (see p.616) or tension-type headache (see p.617), but are best avoided, especially in patients who experience frequent attacks.

Restless legs syndrome. Some opioids may be beneficial in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p.958), although evidence is scanty.

Sedation. In addition to their analgesic action opioids have been used for their sedative properties. Mention of this use of opioids can be found in the discussions of anaesthesia (p.1780), endoscopy (p.956), and intensive care (p.957).

Tetanus. Opioid analgesics can be used to provide analgesia and additional sedation in patients undergoing treatment for tetanus (p.196 and p.1901). Opioids such as fentanyl, morphine, and sufentanil have also been given to control the sympathetic overactivity in such patients.[1-3]

1. Rocke DA, *et al.* Morphine in tetanus—the management of sympathetic nervous system overactivity. *S Afr Med J* 1986; **70:** 666–8.
2. Moughabghab AV, *et al.* Management of autonomic dysfunction in severe tetanus: the use of fentanyl. *Can J Anaesth* 1995; **42:** 955.
3. Bhagwanjee S, *et al.* Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. *Crit Care Med* 1999; **27:** 1721–5.

Opium

Gum Opium; Nyers ópium; Opijus, žaliavinis; Opio; Opium brut; Opium crudum; Opium surové; Raakaoopiumi; Råopium; Raw Opium.

Опиум

ATC — A07DA02; N02AA02.
ATC Vet — QA07DA02; QN02AA02.

NOTE. The following terms have been used as ‘street names’ (see p.vi) or slang names for various forms of opium:
Ah-pen-yen; Aunti; Aunti Emma; Big O; Black; Black pill; Black shit; Black stuff; Black tar opium; Block; Boulette; Chandoo; Chandu; China; Chinese molasses; Chinese tobacco; Chocolate; Cruz; Dopium; Dover’s deck; Dover’s powder; Dream gum; Dream gun; Dream stick; Dreams; Dutch courage; Easing powder; Fi-do-nie; Gee; God’s medicine; Goma; Gondola; Gong; Goric; Great tobacco; Gum; Guma; Hard stuff; Hocus; Hop; Hops; Incense; Indonesian bud; Joy plant; Midnight oil; Mira; Mud; O; O.P.; Ope; O-Rock DC; Pen yan; Pin gon; Pin yen; Pox; Skee; Tar; Toxy; Toys; When-shee; Ze; Zero.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*
Chin., Eur., and *US* include a monograph for prepared or powdered opium. *Eur.* also contains monographs for standardised opium dry extract or standardised opium tincture. *Jpn* includes prepared opium and a diluted opium powder containing 1% of anhydrous morphine.
Ph. Eur. 6.2 (Opium, Raw; Opium BP 2008). The air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It has a characteristic odour and a blackish-brown colour. It should contain not less than 10% of anhydrous morphine, not less than 2% of anhydrous codeine, and not more than 3% of anhydrous thebaine. Protect from light.
Ph. Eur. 6.2 (Opium, Prepared; Opii Pulvis Normatus). Raw opium powdered and dried at a temperature not exceeding 70°. It is a yellowish-brown or dark brown powder and contains 9.8 to 10.2% of morphine and not less than 1.0% of codeine, calculated with reference to the dried drug. The content may be adjusted by adding a suitable excipient or raw opium powder.
USP 31 (Opium). The air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum* (Papaveraceae). Externally it is pale olive-brown or olive-grey; internally it is reddish-brown. It has a very characteristic odour and a very bitter taste. It yields not less than 9.5% of anhydrous morphine.
USP 31 (Powdered Opium). Opium dried at a temperature not exceeding 70°, and reduced to a very fine light brown or moderately yellowish-brown powder that yields not less than 10% and not more than 10.5% of anhydrous morphine. It may contain any of the permitted diluents with the exception of starch.

Profile

Opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* (Papaveraceae). It contains morphine, codeine, and thebaine and a variable mixture of other alkaloids including noscapine and papaverine. The exuded latex is dried and manipulated to form cakes of uniform composition, variously shaped according to the country of origin, and known in commerce as Turkish, Indian, or European opium.

Opium has the properties of opioid analgesics (p.101). Its analgesic and sedative actions are due mainly to its content of morphine (p.89). It acts less rapidly than morphine since opium appears to be more slowly absorbed; the relaxing action of the papaverine and noscapine on intestinal muscle makes it more constipating than morphine.

Opium is intended only as the starting material for the manufacture of galenical preparations and is not dispensed as such. It is used as Prepared Opium (Ph. Eur. 6.2), as Powdered Opium (USP 31), as Opium Tincture (BP 2008 or USP 31), or as Camphorated Opium Tincture (BP 2008) or Paregoric (USP 31) in various oral preparations. These have included Opiate Squill Linctus (BP 2008) (Gee’s linctus) for cough.

Paregoric (USP 31) has been advocated in the USA for the treatment of neonatal abstinence syndrome.

Abuse. Reports of squill-associated cardiac toxicity resulting from the abuse of opiate squill linctus (Gee’s linctus).[1,2]

1. Thurston D, Taylor K. Gee’s linctus. *Pharm J* 1984; **233:** 63.
2. Smith W, *et al.* Wenckebach’s phenomenon induced by cough linctus. *BMJ* 1986; **292:** 868.

Preparations

BP 2008: Camphorated Opium Tincture; Concentrated Camphorated Opium Tincture; Opium Tincture;
Ph. Eur.: Opium Dry Extract, Standardised; Opium Tincture, Standardised;
USP 31: Opium Tincture; Paregoric.

Proprietary Preparations (details are given in Part 3)
Braz.: Elixir Paregorico.

Multi-ingredient: ***Braz.:*** Camomila; Elixir de Marinheiro†; ***Denm.:*** Pectyl; ***Fin.:*** Tannopon; ***Fr.:*** Colchimax; Lamaline; Paregorique; ***Hong Kong:*** Brown Mixture; ***Israel:*** Davilla; Doveri; ***Mex.:*** Reglosedyl†; ***S.Afr.:*** Parogoriese-Elikser; Tandpyndruppels; ***Spain:*** Digestovital†; Tanagel; ***Switz.:*** Bromocod N; Pectocalmine; ***USA:*** B & O Supprettes No. 15A; B & O Supprettes No. 16A; ***Venez.:*** Atrobel.

Hydrochlorides of Mixed Opium Alkaloids

Alkaloidosum Opii Hydrochloridum; Extractum Concentratum Opii; Mezclas de hidrocloruros de alcaloides del opio; Omnoponum; Opialum; Opium Concentratum.

Гидрохлориды Смешанных Алкалоидов Опия

Pharmacopoeias. Preparations of the hydrochlorides of mixed opium alkaloids are included in *Jpn.*

Papaveretum *(BAN)*

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride, and 20 parts of codeine hydrochloride.

Папаверетум

CAS — 8002-76-4.
ATC — N02AA10.
ATC Vet — QN02AA10.

NOTE. Do not confuse papaveretum with papaverine (p.2191).

Pharmacopoeias. In *Br.*
BP 2008 (Papaveretum). It contains 80.0 to 88.4% of anhydrous morphine hydrochloride, 8.3 to 9.2% of papaverine hydrochloride, and 6.6 to 7.4% of anhydrous codeine hydrochloride. A white or almost white crystalline powder. Soluble in water, sparingly soluble in alcohol. A 1.5% solution in water has a pH of 3.7 to 4.7. Protect from light.

Profile

The opium alkaloids are the prototypical opioid analgesics (p.101). Mixtures of opium alkaloids such as papaveretum have the analgesic and sedative properties of morphine (p.89) and are used in the treatment of moderate to severe pain including postoperative and severe chronic pain. They may also be used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum (BP 2008) 15.4 mg contains the equivalent of about 10 mg of the major component, anhydrous morphine.

- In the UK, papaveretum formerly contained the hydrochlorides of morphine, codeine, noscapine, and papaverine. However, because of concern over the potential genotoxicity of noscapine (p.1566) UK preparations containing papaveretum were reformulated to exclude the noscapine component and the name papaveretum was redefined in the BP 1993 to reflect this change of formulation. It is possible that in other countries the term papaveretum is still being used to describe a mixture containing noscapine.

Doses. Papaveretum is generally given by subcutaneous or intramuscular injection in doses of 7.7 to 15.4 mg every 4 hours if necessary. The initial dose in the elderly or debilitated patients should not exceed 7.7 mg.

In the treatment of pain and as an adjunct in anaesthesia, papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose. For pre-operative medication papaveretum is given intramuscularly or subcutaneously sometimes with hyoscine hydrobromide.

For details of doses in children, see below.

Oral preparations containing papaveretum with aspirin have been given for the management of moderate to severe pain.

◊ Papaveretum has been confused with papaverine (p.2191) and in one such case[1] a patient became unconscious after self-injection of papaveretum in mistake for papaverine.

1. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.

Administration in children. Papaveretum may be given to children in the treatment of moderate to severe pain including postoperative and severe chronic pain. It is also used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum is generally given by subcutaneous or intramuscular injection every 4 hours if necessary, according to age as follows:
- neonates: 115 micrograms/kg
- 1 to 12 months: 154 micrograms/kg
- 1 to 6 years: 1.93 to 3.85 mg
- 6 to 12 years: 3.85 to 7.7 mg

Older children may be given the usual adult dose (see above).

In the treatment of pain and as an adjunct to anaesthesia papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose.

Preparations

BP 2008: Papaveretum Injection.

Proprietary Preparations (details are given in Part 3)
S.Afr.: Omnopon.

Multi-ingredient: ***UK:*** Aspav.

Oxaprozin *(BAN, USAN, rINN)*

Oksaprotsiini; Oxaprozina; Oxaprozine; Oxaprozinum; Wy-21743. 3-(4,5-Diphenyloxazol-2-yl)propionic acid.

Оксапрозин

$C_{18}H_{15}NO_3$ = 293.3.
CAS — 21256-18-8.
ATC — M01AE12.
ATC Vet — QM01AE12.

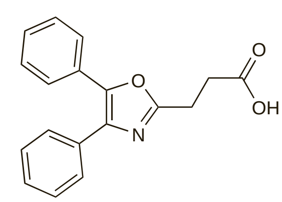

Pharmacopoeias. In *Chin., Jpn.,* and *US.*
USP 31 (Oxaprozin). A white to yellowish-white, crystalline powder. Store in airtight containers at a temperature of 20° to 25°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Diagnosis and testing. False-positive results for testing of benzodiazepines in urine have been reported in patients taking oxaprozin.[1] The manufacturer[2] has commented that the interaction occurs with some immunoassay tests and that thin-layer chromatography can successfully discriminate between benzodiazepines and oxaprozin. False-positive results for a fluorescence polarisation immunoassay for phenytoin have also been reported in patients receiving oxaprozin.[3]

1. Pulini M. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905.
2. Raphan H, Adams MH. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905–6.
3. Patel T, *et al.* Assay interaction between oxaprozin and phenytoin. *Ann Pharmacother* 1997; **31:** 254.

The symbol † denotes a preparation no longer actively marketed

Effects on the liver. Fatal fulminant hepatitis occurred[1] in a 56-year-old woman who had received 600 to 1200 mg of oxaprozin daily for about 6 weeks. In another patient symptomatic hepatitis developing during oxaprozin use resolved on stopping the drug.[2]

1. Purdum PP, *et al.* Oxaprozin-induced fulminant hepatitis. *Ann Pharmacother* 1994; **28:** 1159–61.
2. Kethu SR, *et al.* Oxaprozin-induced symptomatic hepatotoxicity. *Ann Pharmacother* 1999; **33:** 942–4.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Oxaprozin is slowly but extensively absorbed from the gastrointestinal tract; it is 99% bound to plasma proteins, mainly albumin. Peak plasma concentrations are reached after about 2 to 3 hours. At steady state, the biological half-life is about 44 hours. Oxaprozin is metabolised mainly in the liver by microsomal oxidation and conjugation with glucuronic acid to form inactive metabolites which are excreted in the urine (65%) and faeces (35%).

◊ References.

1. Karim A. Inverse nonlinear pharmacokinetics of total and protein unbound drug (oxaprozin): clinical and pharmacokinetic implications. *J Clin Pharmacol* 1996; **36:** 985–97.
2. Karim A, *et al.* Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; **37:** 267–78.
3. Davies NM. Clinical pharmacokinetics of oxaprozin. *Clin Pharmacokinet* 1998; **35:** 425–36.

Uses and Administration

Oxaprozin, a propionic acid derivative, is an NSAID (p.99). It is used in the treatment of osteoarthritis and rheumatoid arthritis in a usual oral dose of 1.2 g given once daily, although in osteoarthritis, patients with low body-weight or mild disease should be given an initial dose of 600 mg once daily. The recommended maximum daily dose is 1.8 g or 26 mg/kg, whichever is the lower.

For doses in patients with renal impairment and in children see below.

◊ References.

1. Miller LG. Oxaprozin: a once-daily nonsteroidal anti-inflammatory drug. *Clin Pharm* 1992; **11:** 591–603.
2. Anonymous. Oxaprozin for arthritis. *Med Lett Drugs Ther* 1993; **35:** 15–16.
3. Dallegri F, *et al.* A review of the emerging profile of the anti-inflammatory drug oxaprozin. *Expert Opin Pharmacother* 2005; **6:** 777–85.

Administration in children. Oxaprozin is given orally in the treatment of juvenile idiopathic arthritis (p.10) in children aged 6 years and over. Doses are expressed in terms of body-weight and may be given once daily:

- 22 to 31 kg: 600 mg
- 32 to 54 kg: 900 mg
- 55 kg and over: 1200 mg

Administration in renal impairment. US licensed product information for oxaprozin recommends that the initial oral dose in patients with severe renal impairment or on dialysis is 600 mg once daily. The dose may be increased to 1.2 g once daily, if necessary.

Preparations

USP 31: Oxaprozin Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Zakoprosin; ***Belg.:*** Duraprox; ***Canad.:*** Daypro; ***Chile:*** Duraprox; Walix; ***Cz.:*** Dayrun; ***Ger.:*** Danoprox†; Dayrun†; ***Gr.:*** Duraprox; Misaf; Nisaid; Oxapron; Trimelot; ***Ital.:*** Walix; ***Jpn:*** Alvo; ***S.Afr.:*** Deflam; ***USA:*** Daypro.

Oxycodone *(BAN, USAN, rINN)* ⊗

Dihydrone; 14-Hydroxydihydrocodeinone; NSC-19043; Oksikodoni; Oxicodona; Oxikodon; Oxycodonum. 6-Deoxy-7,8-dihydro-14-hydroxy-3-*O*-methyl-6-oxomorphine; (−)-(5*R*,6*S*,14*S*)-4,5-Epoxy-14-hydroxy-3-methoxy-9a-methylmorphinan-6-one.

Оксикодон

$C_{18}H_{21}NO_4$ = 315.4.
CAS — 76-42-6.
ATC — N02AA05.
ATC Vet — QN02AA05.

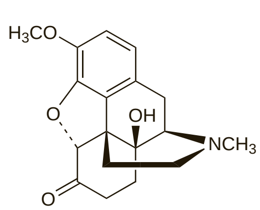

NOTE. Compounded preparations of oxycodone may be represented by the following names:

- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol.

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of oxycodone:
40; 40-bar; 80; Blue; Cotton; Hillbilly heroin; Kicker; OC; Os; Ox; Oxy; Oxy Cotton; Oxycotton; Percs; Perks; Pills; Pink spoons; Rushbo.

Oxycodone Hydrochloride *(BANM, USAN, rINNM)* ⊗

7,8-Dihydro-14-hydroxycodeinone hydrochloride; Dihydrone Hydrochloride; Hidrocloruro de oxicodona; Oksikodonihydrokloridi; Oksikodono hidrochloridas; Oxikodonhydroklorid; Oxycodone, chlorhydrate d'; Oxycodoni hydrochloridum; Oxycone Hydrochloride; Oxykodon-hydrochlorid; Thecodine.

Оксикодона Гидрохлорид

$C_{18}H_{21}NO_4$,HCl = 351.8.
CAS — 124-90-3.
ATC — N02AA05.
ATC Vet — QN02AA05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US. Jpn* includes the trihydrate.

Ph. Eur. 6.2 (Oxycodone Hydrochloride). A white or almost white, hygroscopic, powder. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.

USP 31 (Oxycodone Hydrochloride). A white to off-white, odourless, hygroscopic crystals or powder. Soluble in water; slightly soluble in alcohol. Store in airtight containers.

Oxycodone Terephthalate ⊗

Oxicodona, tereftalato de. 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one 1,4-benzenedicarboxylate (2:1) salt.

Оксикодона Терефталат

$(C_{18}H_{21}NO_4)_2$,$C_8H_6O_4$ = 796.9.
CAS — 64336-55-6.

Pharmacopoeias. In *US.*

USP 31 (Oxycodone Terephthalate). Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics in general, p.101.

Oxycodone has been subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

◊ Takotsubo-like cardiomyopathy developed in a 61-year-old woman when her dose of oxycodone was inadvertently and greatly reduced 7 days after surgery for degenerative osteoarthritis.[1] The patient had a chronic history of opioid dependence and had been treated with oxycodone (80 mg daily) and hydromorphone (4 mg every 3 hours as needed) for several months before surgery; postoperatively, her dose of oxycodone had been increased to 120 mg daily with additional doses for breakthrough pain.

1. Rivera JM, *et al.* "Broken heart syndrome" after separation (from OxyContin). *Mayo Clin Proc* 2006; **81:** 825–8.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

UK licensed product information contra-indicates the use of oxycodone in patients with moderate to severe hepatic impairment or severe renal impairment; however, product information in the USA permits its cautious use in patients with severe hepatic or severe renal impairment although doses may need to be reduced.

Abuse. Oxycodone hydrochloride modified-release tablets have been subject to abuse.[1-3] The crushed tablets have been inhaled or injected by addicts and in some cases this has resulted in fatalities.

1. Wolf BC, *et al.* One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. *J Forensic Sci* 2005; **50:** 192–5.
2. Cicero TJ, *et al.* Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004. *J Pain* 2005; **6:** 662–72.
3. Adlaf EM, *et al.* Use of OxyContin by adolescent students. *Can Med Assoc J* 2006; **174:** 1303.

Effects on the respiratory system. References[1,2] to respiratory depression occurring in children given oxycodone.

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; **38:** 71–6.
2. Kalso E. Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1995; **39:** 214.

Hepatic impairment. The clearance and elimination of oxycodone were prolonged in 6 women with end-stage liver cirrhosis awaiting liver transplantations.[1] Significant ventilatory depression also occurred. Pharmacokinetic values after successful transplantation were similar to those previously reported for healthy adults. It was recommended that, when giving oxycodone to patients with end-stage liver disease, the dosing frequency should be reduced and the dose lowered.

1. Tallgren M, *et al.* Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* 1997; **61:** 655–61.

Porphyria. Oxycodone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For interactions associated with opioid analgesics, see p.103.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of oxycodone and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397.

Pharmacokinetics

Oxycodone is absorbed from the gastrointestinal tract; oral bioavailability is about 60 to 87% due to lower pre-systemic and/or first-pass metabolism compared with other opioids. About 45% is bound to plasma proteins. It is metabolised to noroxycodone, via cytochrome P450 isoenzymes of the CYP3A family, and, to a lesser extent, to oxymorphone (p.107) via CYP2D6. Both metabolites undergo glucuronidation and are excreted with unchanged drug in urine. The elimination half-life of oxycodone is reported to be 2 to 4 hours. Oxycodone crosses the placenta and is distributed into breast milk.

◊ References.

1. Pöyhiä R, *et al.* The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; **32:** 516–18.
2. Leow KP, *et al.* Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. *Clin Pharmacol Ther* 1992; **52:** 487–95.
3. Mandema JW, *et al.* Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol* 1996; **42:** 747–56.
4. Kaiko RF, *et al.* Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther* 1996; **59:** 52–61.
5. Gammaitoni AR, Davis MW. Comparison of the pharmacokinetics of oxycodone administered in three Percocet formulations. *J Clin Pharmacol* 2002; **42:** 192–7.
6. Lalovic B, *et al.* Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* 2006; **79:** 461–79.

Children. The pharmacokinetics of oxycodone in children have been studied[1-4] and are generally considered similar to those in adults.[2,4] However, pharmacokinetics may be more variable in infants aged from 0 to 6 months, particularly those aged 2 months and under.[5]

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; **38:** 71–6.
2. Kokki H, *et al.* Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clin Pharmacokinet* 2004; **43:** 613–22.
3. El-Tahtawy A, *et al.* Population pharmacokinetics of oxycodone in children 6 months to 7 years old. *J Clin Pharmacol* 2006; **46:** 433–42.
4. Kokki H, *et al.* Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. *Clin Pharmacokinet* 2006; **45:** 745–54.
5. Pokela ML, *et al.* Marked variation in oxycodone pharmacokinetics in infants. *Paediatr Anaesth* 2005; **15:** 560–565.

Uses and Administration

Oxycodone, a phenanthrene derivative, is an opioid analgesic (p.104). Oxycodone hydrochloride is given orally or by subcutaneous or intravenous injection for the relief of moderate to severe pain.

A usual oral starting dose for opioid-naive patients in severe pain is 5 mg every 4 to 6 hours increased thereafter as necessary according to response. For patients who have been receiving a strong opioid analgesic the initial dose of oxycodone should be based on the daily opioid requirement; UK licensed product information suggests that 10 mg of oral oxycodone is equivalent to about 20 mg of oral morphine. Most patients do not require more than 400 mg daily. Preparations containing oxycodone hydrochloride and aspirin, ibuprofen, or paracetamol are also used. Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours.

For details of doses in children, see below.

Intravenous doses of oxycodone hydrochloride range from 1 to 10 mg, given over 1 to 2 minutes, and repeated not more often than every 4 hours; a dose of 2 mg/hour is the recommended starting dose as an intravenous infusion. The intravenous route may also be used for patient-controlled analgesia. When given subcutaneously, the starting dose is 5 mg every 4 hours; subcutaneous infusions should be started at 7.5 mg daily in opioid-naive patients. When transferring between oral and parenteral oxycodone, UK licensed product information advises that, as a guide, 2 mg of oral oxycodone is equivalent to about 1 mg of parenteral oxycodone.

Oxycodone has been given rectally as suppositories containing 30 mg of oxycodone (as the pectinate) or 10 or 20 mg of oxycodone hydrochloride; the dose may be repeated every 6 to 8 hours.

For doses in patients with hepatic or renal impairment, see below.

Oxycodone terephthalate is also used orally.

Administration in children. Although oxycodone hydrochloride is not licensed in the UK for use in children under 18 years old, the *BNFC* suggests that it may be given for the treatment of moderate to severe pain in palliative care. Those aged from 1 month to 12 years may be given initial oral doses of 200 micrograms/kg (up to 5 mg) every 4 to 6 hours increased thereafter as necessary according to response; older children may be given the usual adult dose (see above). Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours to those aged 8 years and older.

Administration in hepatic or renal impairment. The plasma concentrations of oxycodone may be increased in patients with hepatic or renal impairment and consequently dosage adjustment may be necessary in such patients. In the UK, licensed product information recommends that the oral starting dose for adult patients with mild hepatic impairment or mild to moderate renal impairment should be 2.5 mg given every 6 hours; it contra-indicates the use of oxycodone in those with moderate to severe hepatic impairment or severe renal impairment. US product information permits the cautious use of oxycodone in adult patients with severe hepatic or severe renal impairment.

Pain. References.

1. Sunshine A, *et al.* Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* 1996; **36:** 595–603.
2. Curtis GB, *et al.* Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. *Eur J Clin Pharmacol* 1999; **55:** 425–9.
3. Gimbel JS, *et al.* Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003; **60:** 927–34.
4. Gammaitoni AR, *et al.* Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg/acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain.*J Clin Pharmacol* 2003; **43:** 296–304.
5. Oldfield V, Perry CM. Oxycodone/ibuprofen combination tablet: a review of its use in the management of acute pain. *Drugs* 2005; **65:** 2337–54.
6. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; **29** (suppl): S47–S56.
7. Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother* 2006; **20:** 33–9.
8. Reid CM, *et al.* Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 837–43. Correction. *ibid.*; 2387.
9. Portenoy RK, *et al.* Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain* 2007; **23:** 287–99.
10. Pan H, *et al.* Efficacy and tolerability of oxycodone hydrochloride controlled-release tablets in moderate to severe cancer pain. *Clin Drug Invest* 2007; **27:** 259–67.

Preparations

USP 31: Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Oxycodone and Aspirin Tablets; Oxycodone Hydrochloride Extended-Release Tablets; Oxycodone Hydrochloride Oral Solution; Oxycodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Oxicalmans; Oxinovag; Oxycontin; ***Austral.:*** Endone; Oxycontin; Oxynorm; Proladone; ***Austria:*** Oxycontin; Oxynorm; ***Belg.:*** Oxycontin; ***Braz.:*** Oxycontin; ***Canad.:*** Oxy IR; Oxycontin; Supeudol; ***Chile:*** Oxycontin; ***Cz.:*** Oxycontin; ***Denm.:*** Oxycontin; Oxynorm; ***Fin.:*** Oxanest; Oxycontin; Oxynorm; ***Fr.:*** Eubine†; Oxycontin; Oxynorm; ***Ger.:*** Oxygesic; ***Hung.:*** Oxycontin; ***Irl.:*** Oxycontin; Oxynorm; ***Israel:*** Oxycod; Oxycontin; ***Ital.:*** Oxycontin; ***Jpn:*** Oxycontin; ***Malaysia:*** Oxycontin; ***Mex.:*** Oxycontin†; ***Neth.:*** Oxycontin; Oxynorm; ***Norw.:*** Oxycontin; Oxynorm; ***NZ:*** Oxycontin; Oxynorm; ***Philipp.:*** Oxycontin; ***Port.:*** Oxycontin; ***Singapore:*** Oxycontin; Oxynorm; ***Spain:*** Oxycontin; Oxynorm; ***Swed.:*** Oxycontin; Oxynorm; ***Switz.:*** Oxycontin; Oxynorm; ***UK:*** Oxycontin; Oxynorm; ***USA:*** Endocodone†; ETH-Oxydose; Oxycontin; Oxyfast; OxyIR; Percolone†; Roxicodone; ***Venez.:*** Oxycontin.

Multi-ingredient: ***Arg.:*** Oxinovag Complex; ***Canad.:*** Endocet; Endodan; Percocet; Percodan; ratio-Oxycocet; ratio-Oxycodan; ***Israel:*** Percocet; Percodan; ***Ital.:*** Depalgos; ***USA:*** Combunox; Endocet; Magnacet; Narvox; Percocet; Percodan; Perloxx; Roxicet; Roxilox; Roxiprin†; Tylox.

Oxymorphone Hydrochloride *(BANM, rINNM)* ⊗

7,8-Dihydro-14-hydroxymorphinone hydrochloride; Hidrocloruro de oximorfona; Oximorfone Hydrochloride; Oxymorphone, Chlorhydrate d'; Oxymorphoni Hydrochloridum. 6-Deoxy-7,8-dihydro-14-hydroxy-6-oxomorphine hydrochloride; (−)-(5R,6S,14S)-4,5-Epoxy-3,14-dihydroxy-9a-methylmorphinan-6-one hydrochloride.

Оксиморфона Гидрохлорид

$C_{17}H_{19}NO_4$,HCl = 337.8.

CAS — 76-41-5 (oxymorphone); 357-07-3 (oxymorphone hydrochloride).

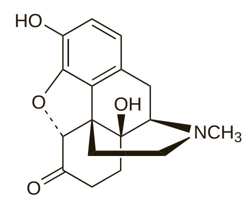

(oxymorphone)

Pharmacopoeias. In *US.*

USP 31 (Oxymorphone Hydrochloride). A white or slightly off-white odourless powder, darkening on exposure to light. Its aqueous solutions are slightly acidic. Soluble 1 in 4 of water, 1 in 100 of alcohol, and 1 in 25 of methyl alcohol; very slightly soluble in chloroform and in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics in general, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

For details on the use of oxymorphone in patients with hepatic or renal impairment see below.

Interactions

For interactions associated with opioid analgesics, see p.103.

Licensed product information for a modified-release preparation of oxymorphone hydrochloride (*Opana ER; Endo, USA*) states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of increased plasma concentrations and a potentially fatal overdose of oxymorphone.

Pharmacokinetics

Oxymorphone hydrochloride is absorbed from the gastrointestinal tract after oral doses, but bioavailability is only about 10% because of first-pass metabolism. Absorption is increased after a high-fat meal. About 10% is bound to plasma proteins. Oxymorphone is extensively metabolised in the liver by glucuronidation and less than 1% of a dose appears in the urine and faeces as unchanged drug. With regard to its major metabolites between 33 and 38% of a dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% as 6-OH-oxymorphone. Oxymorphone crosses the placenta.

◊ References.

1. Adams MP, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: results of a randomized crossover study. *Pharmacotherapy* 2004; **24:** 468–76.
2. Adams MP, Ahdieh H. Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs R D* 2005; **6:** 91–9.

Uses and Administration

Oxymorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.101) with actions and uses similar to those of morphine (p.86), apart from a lack of cough suppressant activity. Oxymorphone is given orally, parenterally, or rectally for the relief of moderate to severe pain, including pain in obstetrics, and is reported to provide analgesia for 3 to 6 hours. It may also be used parenterally for premedication, as an adjunct to anaesthesia, and to relieve dyspnoea due to pulmonary oedema resulting from left ventricular failure.

A usual *oral* starting dose for opioid-naive patients is 10 to 20 mg of oxymorphone hydrochloride every 4 to 6 hours adjusted thereafter as necessary; some patients may be started on lower doses of 5 mg. For patients who have been receiving a strong opioid analgesic the initial dose of oxymorphone should be based on the daily opioid requirement; licensed product information suggests that 10 mg of oral oxymorphone is equivalent to about 30 mg of oral morphine and recommends giving half the calculated equivalent dose of oxymorphone initially. Oxymorphone hydrochloride may also be given orally as a modified-release preparation every 12 hours. Oral preparations of oxymorphone should be taken on an empty stomach.

Oxymorphone hydrochloride is given by *intramuscular* or *subcutaneous injection* in initial doses of 1 to 1.5 mg, repeated every 4 to 6 hours as necessary; 500 micrograms may be given by intravenous injection. The usual dose for analgesia during labour is 0.5 to 1 mg intramuscularly. When transferring between oral and parenteral oxymorphone, licensed product information advises that, as a guide, 10 mg of oral oxymorphone is equivalent to about 1 mg of parenteral oxymorphone.

Oxymorphone hydrochloride is also given *rectally* as a suppository in a dose of 5 mg every 4 to 6 hours.

◊ References.

1. Prommer E. Oxymorphone: a review. *Support Care Cancer* 2006; **14:** 109–15.
2. Chamberlin KW, *et al.* Oral oxymorphone for pain management. *Ann Pharmacother* 2007; **41:** 1144–52.

Administration in hepatic impairment. Advice on the use of oxymorphone in patients with hepatic impairment is conflicting. Licensed product information for one range of preparations (*Opana* and *Opana ER tablets; Endo, USA*) recommends caution in patients with mild hepatic impairment; these patients should be started on the lowest oral dose and titrated slowly thereafter. In addition, it is stated that oxymorphone is contra-indicated in those with moderate or severe impairment. However, licensed information for another oxymorphone preparation (*Numorphan injection and suppositories; Endo, USA*) only recommends caution in hepatic disease although lower doses (unspecified) are advised in those patients with severe impairment.

Administration in renal impairment. In patients with moderate to severe renal impairment, the bioavailability of oxymorphone was found to increase by over 50%; consequently, it is recommended that oxymorphone is given with caution and in reduced doses (unspecified) to those with a creatinine clearance of less than 50 mL/minute.

Preparations

USP 31: Oxymorphone Hydrochloride Injection; Oxymorphone Hydrochloride Suppositories.

Proprietary Preparations (details are given in Part 3)
Canad.: Numorphan†; ***USA:*** Numorphan; Opana.

Oxyphenbutazone *(BAN, rINN)*

G-27202; Hydroxyphenylbutazone; Oksifenbutatsoni; Oxifenbutazon; Oxifenbutazona; Oxyphenbutazonum. 4-Butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione monohydrate.

Оксифенбутазон

$C_{19}H_{20}N_2O_3$,H_2O = 342.4.

CAS — 129-20-4 (anhydrous oxyphenbutazone); 7081-38-1 (oxyphenbutazone monohydrate).

ATC — M01AA03; M02AA04; S01BC02.

ATC Vet — QM01AA03; QM02AA04; QS01BC02.

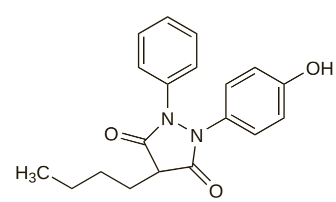

Profile

Oxyphenbutazone, a metabolite of phenylbutazone (p.117), is an NSAID (p.96). It has been applied topically to the eye as an anti-inflammatory ointment in conditions such as episcleritis. Oxyphenbutazone was used systemically in disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis but such use is no longer considered justified because of the risk of severe haematological adverse effects (see also Effects on the Blood, under Phenylbutazone, p.117).

The piperazine salt has also been used.

Porphyria. Oxyphenbutazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Sioril†; ***Mex.:*** Edefen†; Redolet†.

Multi-ingredient: ***Braz.:*** Algi Peralgin†; Algiflamanil; Analtrix†; Febupen; Flamanan; Reumazine†; ***Mex.:*** Dartrizon.

Paracetamol *(BAN, rINN)*

Acetaminofeno; Acetaminophen; *N*-Acetyl-*p*-aminophenol; Asetaminofen; Paracétamol; Paracetamolis; Paracetamolum; Parasetamol; Parasetamoli. 4′-Hydroxyacetanilide; *N*-(4-Hydroxyphenyl)acetamide.

Парацетамол

$C_8H_9NO_2$ = 151.2.

CAS — 103-90-2.

ATC — N02BE01.

ATC Vet — QN02BE01.

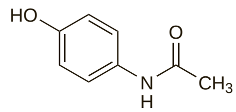

NOTE. Compounded preparations of paracetamol may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—paracetamol and codeine phosphate
- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w)
- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol
- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol, respectively
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol
- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w)
- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 31 (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1*N* sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

Adverse Effects and Treatment

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, below.

◊ References.

1. Graham GG, *et al.* Tolerability of paracetamol. *Drug Safety* 2005; **28:** 227–40.

Effects on the kidneys. For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, p.98.

See also under Overdosage, below.

Effects on the respiratory tract. The results of a case-control study[1] have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, a further study and a review have found an increase in the prevalence of asthma[2,3] and COPD[2] with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, below). However, another review[4] stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdosage. The review concluded that a strong link between paracetamol use and asthma was unlikely.

1. Shaheen SO, *et al.* Frequent paracetamol use and asthma in adults. *Thorax* 2000; **55:** 266–70.
2. McKeever TM, *et al.* The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; **171:** 966–71.
3. Eneli I, *et al.* Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; **127:** 604–12.
4. Nuttall SL, *et al.* Does paracetamol cause asthma? *J Clin Pharm Ther* 2003; **28:** 251–7.

Hypersensitivity. Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults[1-4] and children.[5,6] Angioedema has also been reported.[7] Fixed drug eruptions, confirmed by rechallenge, have been described,[8-11] and toxic epidermal necrolysis has occurred.[12]

1. Stricker BHC, *et al.* Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; **291:** 938–9.
2. Van Diem L, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990; **38:** 389–90.
3. Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hosp Med* 1999; **60:** 66–7.
4. Bachmeyer C, *et al.* Acetaminophen (paracetamol)-induced anaphylactic shock. *South Med J* 2002; **95:** 759–60.
5. Ellis M, *et al.* Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* 1989; **114:** 654–6.
6. Bousetta K, *et al.* Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; **60:** 1174–7.
7. Idoko JA, *et al.* Angioneurotic oedema following ingestion of paracetamol. *Trans R Soc Trop Med Hyg* 1986; **80:** 175.
8. Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; **115:** 357–9.
9. Cohen HA, *et al.* Fixed drug eruption caused by acetaminophen. *Ann Pharmacother* 1992; **26:** 1596–7.
10. Harris A, Burge SM. Vasculitis in a fixed drug eruption due to paracetamol. *Br J Dermatol* 1995; **133:** 790–1.
11. Hern S, *et al.* Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; **139:** 1129–31.
12. Halevi A, *et al.* Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; **34:** 32–4.

Overdosage. Acute ***oral*** overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Ingestion of as little as 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Patients should be considered at risk of severe liver damage if they have ingested more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.[1,2]

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at special risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia or AIDS. It has also been suggested that fasting may predispose to hepatotoxicity.[3]

Early **signs** of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly. However, as both paracetamol[4] and acetylcysteine[5] can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.[6]

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)[2] in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

Treatment of oral paracetamol overdosage. The management of paracetamol overdosage as practised in the UK and US has been the subject of numerous reviews.[3,6-13] Guidelines have also been issued in the UK by the Paracetamol Information Centre.[14] Separate consensus guidelines have also been issued by clinical toxicologists in Australia and New Zealand.[15]

Prompt treatment is essential, even when there are no obvious symptoms, and all patients should be admitted to hospital; full supportive measures should also be instituted.

- Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.
- There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.
- The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 (p.109) and Figure 2 (p.109). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is higher than the appropriate line (but see below).
- Patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or those with malnutrition or a history of alcohol abuse, are considered at high risk, and should receive an antidote even if their plasma-paracetamol concentrations are up to 50% below the standard reference line.
- Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatic toxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.[16-18] Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.[19-21]
- Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.
- Deaths from liver failure have occurred in patients presenting with plasma-paracetamol concentrations below the treatment line: suggested explanations include inadequate patient histories and a need for a lower treatment threshold.[22]
- If there is any doubt about timing or the need to treat, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.[23]
- Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

Choice of antidote. Acetylcysteine (p.1548) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.[6,24] Intravenous use has been associated with anaphylactic reactions but is the preferred route in the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also used, and is clearly effective. The use of methionine (p.1450) by mouth is licensed in the UK, despite the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and may be used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting.

Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,[25] and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.[26,27] Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.[28]

- An initial dose of 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given intravenously over 15 minutes in the UK, or over 60 minutes in the USA. This is followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.

Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.

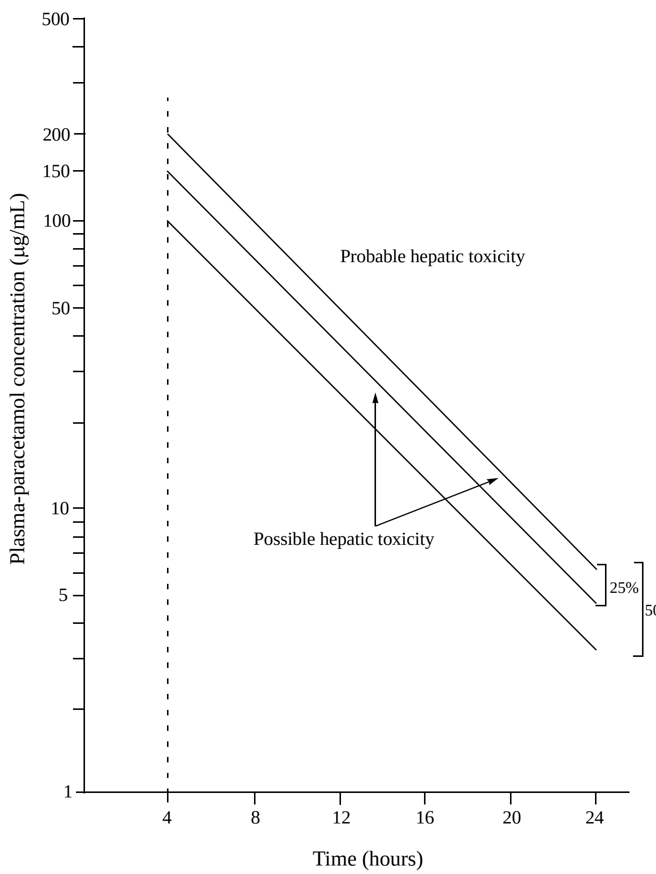

Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55:** 871–6.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. The solid line 25% below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose.
5. The solid line 50% below the standard nomogram is to assess the possible hepatic toxicity in patients receiving enzyme-inducing drugs or with malnutrition or a history of alcohol abuse.
6. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified release preparations of paracetamol.

Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.

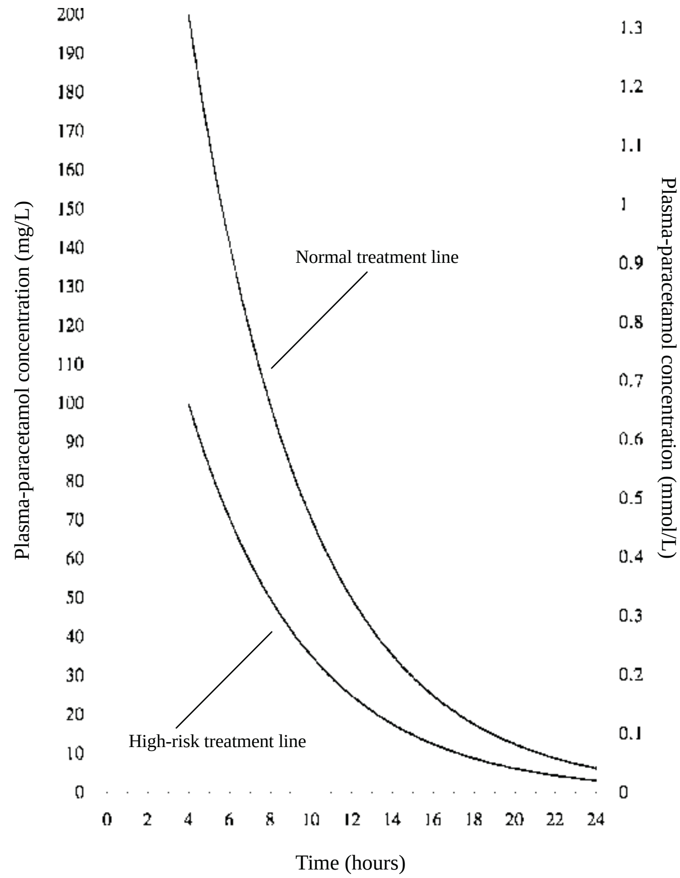

Courtesy of P A Routledge.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. Patients whose plasma-paracetamol concentrations are above the normal treatment line should be treated.
5. Patients on enzyme-inducing drugs or with malnutrition or a history of alcohol abuse should be treated if their plasma-paracetamol concentrations are above the high-risk treatment line.
6. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified release preparations of paracetamol.

- In the USA, acetylcysteine may also be given orally as an alternative to parenteral treatment. It is given as an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Some[29] have suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas others[30] have found that the efficacy of acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol overdosage. However, it is not as effective if treatment is delayed[31-33] and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.

- The usual oral dose of methionine in adults and children over 6 years is 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children under 6 years should be given 1 g every 4 hours for 4 doses. It has also been given intravenously.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the doses quoted above refer to DL-methionine. Preparations containing both methionine and paracetamol (co-methiamol) have been formulated for use in situations where overdosage may occur. However, the issue of whether methionine should be routinely added to paracetamol preparations is contentious for medical and ethical reasons.

Histamine H_2-antagonists. It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.[6,10,11,34]

Liver transplantation may be considered as a last recourse in some patients.

After maternal **overdosage during pregnancy** fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases.[35]

There is little information available on overdosage when paracetamol is given as an ***intravenous infusion***. The standard nomogram may not be appropriate in determining treatment from plasma-paracetamol concentrations after intravenous overdose, as it is based on data from acute paracetamol ingestion rather than intravenous administration. The National Poisons Information Service in the UK recommends that the need for antidote treatment should be based on the total administered dose of paracetamol and/or any resultant hepatic impairment.

1. Miles FK, *et al.* Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; **171:** 472–5.
2. American Academy of Pediatrics Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001; **108:** 1020–4.
3. Whitcomb DC, *et al.* Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* 1994; **272:** 1845–50.
4. Whyte IM, *et al.* Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. *Ther Drug Monit* 2000; **22:** 742–8.
5. Schmidt LE, *et al.* Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. *Lancet* 2002; **360:** 1151–2.
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13. Dart RC, *et al.* Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006; **44:** 1–18.
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33. Tee LGB, *et al.* N-Acetylcysteine for paracetamol overdose. *Lancet* 1986; **i:** 331–2.
34. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.
35. Wilkes JM, *et al.* Acetaminophen overdose in pregnancy. *South Med J* 2005; **98:** 1118–22.

Pancreatitis. Drug-induced pancreatitis associated with paracetamol was reported[1] to be a rare reaction only occurring in patients taking more than recommended doses. In a retrospective study of data from 814 patients who had taken paracetamol overdoses, hyperamylasaemia was detected in 246, and was more common and more severe in patients transferred to a specialist unit because of more severe poisoning.[2] However, acute pancreatitis was diagnosed only in 33 cases.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Schmidt LE, Dalhoff K. Hyperamylasaemia and acute pancreatitis in paracetamol poisoning. *Aliment Pharmacol Ther* 2004; **20:** 173–9.

Precautions

Paracetamol should be given with care to patients with impaired kidney or liver function. It should also be given with care to patients with alcohol dependence.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving paracetamol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant.

Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/mL were achieved in 1 to 2 hours. Plasma concentrations were determined in 2 mothers; a breast milk/plasma ratio of about 1 was reported.[2] Similar findings have been reported from other studies.[3,4]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/10/06)
2. Berlin CM, *et al.* Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatr Pharmacol* 1980; **1:** 135–41.
3. Hurden EL, *et al.* Excretion of paracetamol in human breast milk. *Arch Dis Child* 1980; **55:** 969–72.
4. Bitzén P-O, *et al.* Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 123–5.

Hepatic impairment. A short review[1] concluded that there was evidence that paracetamol could be and had been used safely in patients with liver disease. Studies had also shown that although the half-life of paracetamol was prolonged in such patients, glutathione concentrations in those taking recommended doses were not depleted to the critical levels that would enable accumulation of paracetamol's hepatotoxic metabolite. The *BNF* warns that large doses should be avoided.

1. Benson GD, *et al.* The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* 2005; **12:** 133–41.

Pregnancy. Paracetamol is generally considered to be the analgesic of choice in pregnant patients. However, the frequent use of paracetamol (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant[1] which may persist into childhood[2] (but see also Effects on the Respiratory Tract, above). The authors emphasised that the number of pregnant women taking frequent doses was very small and they recommended that *infrequent* paracetamol should remain the analgesic of choice in pregnancy.

1. Shaheen SO, *et al.* Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; **57:** 958–63.
2. Shaheen SO, *et al.* Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; **35:** 18–25.

Renal impairment. Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.[1-3] It has been suggested that paracetamol itself may be regenerated from these metabolites.[1,2] There are conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.[2,3]

1. Prescott LF, *et al.* Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. *Eur J Clin Pharmacol* 1989; **36:** 291–7.
2. Martin U, *et al.* The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. *Eur J Clin Pharmacol* 1991; **41:** 43–6.
3. Martin U, *et al.* The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. *Eur J Clin Pharmacol* 1993; **45:** 141–5.

Interactions

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

◊ Reviews.

1. Toes MJ, *et al.* Drug interactions with paracetamol. *Am J Ther* 2005; **12:** 56–66.

Antibacterials. The plasma-paracetamol concentrations considered an indication for antidote treatment (see under Overdosage, above) should be halved in patients receiving enzyme-inducing drugs such as *rifampicin*. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving *isoniazid*, alone[1-3] or with other drugs for tuberculosis.[4]

For the effects of paracetamol on *chloramphenicol*, see p.241.

1. Murphy R, *et al.* Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann Intern Med* 1990; **113:** 799–800.
2. Moulding TS, *et al.* Acetaminophen, isoniazid, and hepatic toxicity. *Ann Intern Med* 1991; **114:** 431.
3. Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993; **88:** 590–2.
4. Nolan CM, *et al.* Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. *Chest* 1994; **105:** 408–11.

Anticoagulants. For the effects of paracetamol on oral anticoagulants, see under Warfarin, p.1427.

Antiepileptics. The plasma-paracetamol concentrations considered an indication for antidote treatment (see under Overdosage, above) should be halved in patients receiving enzyme-inducing drugs such as *carbamazepine*, *phenobarbital*, *phenytoin*, or *primidone*.

For the effects of paracetamol on *lamotrigine*, see p.486.

Antivirals. For reports of adverse effects on the liver associated with use of paracetamol with antiviral drugs, see under Interferon Alfa, p.888 and Zidovudine, p.915.

Probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.[1] Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

1. Kamali F. The effect of probenecid on paracetamol metabolism and pharmacokinetics. *Eur J Clin Pharmacol* 1993; **45:** 551–3.

Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

◊ References.

1. van der Marel CD, *et al.* Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol* 2003; **59:** 243–51.

Absorption. The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subjects.[1]

1. Prescott LF, *et al.* Impaired absorption of paracetamol in vegetarians. *Br J Clin Pharmacol* 1993; **36:** 237–40.

Uses and Administration

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain and for fever (p.10). It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer, and children.

The usual **oral** dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may also be given as suppositories in a **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Paracetamol is also given by **intravenous** infusion over 15 minutes; dosage may be calculated by weight as follows:

- patients weighing over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
- from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less)

For doses in children or in renal impairment, see below.

◊ References.

1. Prescott LF. *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996.
2. Bannwarth B, Péhourcq F. Bases pharmacologiques de l'emploi du paracétamol: aspects pharmacocinétiques et pharmacodynamiques. *Drugs* 2003; **63** (suppl 2): 5–13.
3. Prescott LF. Nouvelles perspectives avec le paracétamol. *Drugs* 2003; **63** (suppl 2): 51–6.

Administration in children. In the UK, the licensed **oral** doses in children are:

- 3 months to 1 year: 60 to 120 mg
- 1 to 5 years: 120 to 250 mg
- 6 to 12 years: 250 to 500 mg

These doses may be given every 4 to 6 hours when necessary up to a maximum of 4 doses in 24 hours.

In younger children the *BNFC* suggests the following doses:

- neonates 28 to 32 weeks postmenstrual age (gestational age at birth plus chronological age): 20 mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 20 mg/kg as a single dose then 10 to 15 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher doses for use in children with more ***severe*** symptoms:

- 1 to 3 months: 20 mg/kg as a single dose followed by 15 to 20 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- older children: 20 mg/kg every 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer if necessary followed by 15 mg/kg every 6 hours. Usual adult maximum doses (see above) should not be exceeded

For ***post-immunisation pyrexia***, a dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after six hours; if the pyrexia persists after that dose, medical advice should be sought.

UK licensed **rectal** doses, which may be given to children every 4 to 6 hours, up to 4 times daily are:

- 1 to 5 years: 125 to 250 mg
- 6 to 12 years: 250 to 500 mg

The *BNFC* suggests the following rectal doses in younger children:

- neonates 28 to 32 weeks postmenstrual age: 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours
- 3 to 12 months of age: 60 to 125 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours

The *BNFC* also suggests higher rectal doses for use in children with more ***severe*** symptoms:

- 1 to 3 months: 30 mg/kg as a single dose followed by 20 mg/kg every 8 hours to a maximum of 60 mg/kg daily
- older children: 40 mg/kg as a single dose followed by 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer, if necessary, before reducing to 15 mg/kg every 6 hours. Usual adult maximum doses (see above) should not be exceeded

Doses by **intravenous** infusion in children, given over 15 minutes, are:

- full-term neonates and other children below 10 kg: single doses of 7.5 mg/kg every 4 or more hours, to a maximum of 30 mg/kg daily; intravenous paracetamol has not been studied in premature neonates
- between 10 and 33 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 2 g daily (whichever is less)
- from 33 to 50 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less)
- over 50 kg: usual adult doses (see above)

The intravenous solution may be diluted to a minimum strength of one-tenth of its original concentration in sodium chloride 0.9% or glucose 5%; the diluted solution should be used within 1 hour of preparation.

It has been suggested[1] that the recommended doses of paracetamol for children may result in subtherapeutic blood concentrations, and that an initial loading dose should be given, followed by regular doses up to the recommended maximum daily dose. However, the appropriate maximum daily dose remains controversial, and there is obvious concern given the risks of overdosage.

1. Zacharias M, Watts D. Pain relief in children. *BMJ* 1998; **316:** 1552.

Administration in renal impairment. In patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

Headache. Non-opioid analgesics such as paracetamol, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine (see p.616) and tension-type headache (see p.617). These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

Pain. Paracetamol is used in the management of mild to moderate pain (see Choice of Analgesic, p.2). It is of similar potency to aspirin, but with weak anti-inflammatory activity. Paracetamol may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5). Paracetamol is the preferred choice for pain in children (p.3) because of the association of aspirin with Reye's syndrome in this age group (see p.22). In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of paracetamol. However, it may be of benefit for simple pain control in rheumatoid arthritis (p.11) and ankylosing spondylitis (see under Spondyloarthropathies, p.13), although these patients usually require the additional anti-inflammatory effects provided by NSAIDs. Synovial inflammation is usually only a minor component of osteoarthritis (p.11), and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. Paracetamol is useful for the relief of acute low back pain (p.7).

Dependence and tolerance are not a problem with non-opioid analgesics such as paracetamol, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

Preparations

BP 2008: Co-codamol Capsules; Co-codamol Tablets; Co-dydramol Tablets; Co-proxamol Tablets; Dispersible Paracetamol Tablets; Effervescent Co-codamol Tablets; Paediatric Paracetamol Oral Solution; Paracetamol Capsules; Paracetamol Oral Suspension; Paracetamol Suppositories; Paracetamol Tablets; Soluble Paracetamol Tablets;

USP 31: Acetaminophen and Aspirin Tablets; Acetaminophen and Caffeine Tablets; Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen Capsules; Acetaminophen Extended-Release Tablets; Acetaminophen for Effervescent Oral Solution; Acetaminophen Oral Solution; Acetaminophen Oral Suspension; Acetaminophen Suppositories; Acetaminophen Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Hydrocodone Bitartrate and Acetaminophen Tablets; Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules; Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Napsylate and Acetaminophen Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acetolit; Alikal Dolor; Apracur Antifebril; Bio Grip-T; Causalon; Custodial†; Dirox; Doxidol; Dristancito†; Fiebrol†; Fiebrolito; Flash; Guemusin†; Inmunogrip T Caliente; Invernosan†; Itedal; Mejoral; Multifebrin†; Nodipir; Nodolex†; Novo Asat; Para Z Mol†; Parageniol; Paratral; Parclen; PH 4 Plus†; Plovacal; Predualito†; Qura Plus; Tafirol; Termofren; Tetradox; Tylenol†; Vick Vitapyrena; Viclor; ***Austral.:*** Chemists Own Pain & Fever; Childrens Panadol; Dymadon; Febridol; Lemsip; Ordov Febrigesic†; Panadol; Panamax; Parahexal; Paralgin; Perfalgan; Setamol†; Tylenol†; ***Austria:*** Becetamol; Ben-u-ron; Duaneo; Enelfa; Gewamol; Grippostad; Kratofin simplex; Mexalen; Momentum; OSA; Parakapton; Paraspeed; Peinfort; Perfalgan; ***Belg.:*** Algostase Mono; Curpol; Dafalgan; Dolol-Instant; Dolprone; Lemsip; Panadol; Pe-Tam; Perdolan; Perfusalgan; Sanicopyrine; ***Braz.:*** Acetamil; Acetofen; Anatyl; Cefabrina; Cetafrin†; Cetynol†; Contradol†; Cyfenol; Dorfen; Dorib†; Dorico; Dorsanol; Dorvan†; Emsgrip; Febralgin†; Fervex; Gripeonil†; Gripotermon; Pacemol†; Paracemil†; Paracen; Paralgen; Paratermol†; Piramin; Pyrimel; Sonridor; Termo-Ped†; Termol; Tilekin; Trifen; Tyflen†; Tylalgin†; Tyleflan†; Tylenol; Tylephen; Tylidol; Unigrip; ***Canad.:*** Abenol; Acet; Alsiphene†; Artritol; Atasol; Cephanol; Childrens Feverhalt; Multi-gesic; Novo-Gesic; Pain Aid Free; Panadol; Pediatrix; Robigesic†; Tantaphen; Tempra; Tylenol; ***Chile:*** Acamol; Asafen Nueva Formula†; Cotibin Compuesto; Cryogenine Plus†; Daimeton†; Fibrimol†; Geniol-P; Kitadol; Panadol; Panagesic; Parox Meltab; Rapidol; Supracalm; Tapsin Infantil; Tapsin SC; Winasorb; Xumadol; Zolben; ***Cz.:*** Ben-u-ron; Calpol; Daleron; Effect Comfort; Efferalgan; Gelocatil†; Medipyrin; Mexalen; Panadol; Paralen; Paramax Rapid; Perfalgan; ***Denm.:*** Pamol; Panam; Panodil; Paratabs; Perfalgan; Pinex; ***Fin.:*** Pamol; Panadol; Para-Suppo; Para-Tabs; Paraceon; Paramax Rap; Perfalgan; ***Fr.:*** Claradol; Dafalgan; Doliactic; Doliprane; Dolitabs; Dolko; Dolotec; Efferalgan; Efferalganodis; Expandox; Febrectol†; Geluprane; Panadol; Paralyoc; Perfalgan; ***Ger.:*** Ben-u-ron; Captin; Contac Erkaltungs-Trunk; Doloreduct†; Dorocoff-Paracetamol†; Enelfa; Fensum; Grippostad Heissgetrank†; Mono Praecimed; Paedialgon; Parapaed; PCM; Perfalgan; Pyromed†; RubieMol†; Sinpro N; Togal; ***Gr.:*** Apotel; Calmodor; Cetinject†; Dalminette†; Depon; Depon Maximum; Depon Odis; Dolal; Genspir†; Lonarid Aplo; Panadol; Par; Perfalgan; protAlgon; Tunelzin†; ***Hong Kong:*** Afebrin†; Angenol; Arfen; Ben-u-ron; Biogesic; Calpol†; Children's Tylenol†; Christamol; Cortal for Children; Dhamol; Europain; Fortolin†; Infant's Tylenol†; Junior Strength Tylenol†; Panadol; Parcemol; Parmol; Progesic; Serimol; Setamol; Tiffy; Tylenol†; Uni-Febrin; ***Hung.:*** Ben-u-ron; Efferalgan; Febrilin; Grippostad; Mexalen; Panadol; Paramax Rapid; Perfalgan; Rubophen; ***India:*** Calpol; Crocin; Disprin Paracetamol; Doliprane†; Febridol; Febrinil; Jagcin; Malidens; Pacimol; Paracin; Paracip; Parafizz†; Pyrexon; Pyrigesic; Ultragin; ***Indon.:*** Afebrin; Alphamol; Biogesic; Bodrex Forte; Calapol; Contratemp; Cupanol; Dapyrin; Dumin; Erphamol; Farmadol; Fevrin; Grafadon; Gunaceta; Itamol; Lanamol; Maganol; Naprex; Nasamol; Nufadol; Ottopan; Pamol; Panadol; Paracetol; Praxion; Progesic; Propyretic; Pyrex; Pyrexin; Pyridol; Sanmol; Sumagesic; Tempra; Termorex; Turpan; Xepamol; ***Irl.:*** Anadin Paracetamol; Calpol; Disprol; Hedex; Lemsip Children's Cold Relief; Panadol; Paralief; Paralink; Parapaed; Paratabs; Perfalgan; Tylenol†; ***Israel:*** Abrol; Abrolet; Acamol; Acamoli; Aldolor; Dexamol; Dexamol Kid; Efferalgan†; Panadol; Paramol; Paramolan; Rokamol; Sensamol; Supramol†; Vimoli; ***Ital.:*** Acetamol; Efferalgan; Levadol; Minofen; Normaflu†; Panadol; Perfalgan; Piros; Puernol†; Sanipirina; Tachipirina; ***Malaysia:*** Acet†; Arfen; Biogesic; Dhamol; Dumin†; Hoemal; Naprex†; Panadol; Parafizz; Partamol; Poro; Rapidol; Serimol†; Setromol†; Uphamol; ***Mex.:*** Abatem; Ac-Fast; Acetafen; Acetif; Alpirex; Amolgen; Analphen; Andopan†; Andox; Antidol; Biofer; Bremotel†; Calinofen; Coriver; Datril; Dismifen; Dolgan Flash; Dolotemp†; Doluvital; Dolviran; Farpik; Febran†; Ferridal; Filanc; Frilen; Ginol†; Icetazol; Ifutemp†; Infalgina; Magnidol; Magnidol-Plus; Mejoral Acti-Rapido; Mejoralito; Minofen; Neodol; Neodolito†; Nordinet Infantil; Notem; Panofen; Pharmacen; Piralgina; Piralgina 650; Piralyn; Piremol; Precifen; Prosedal; Quitadol; Resfin; Sedalito; Sinedol; Soltadol; Sons Piral; Sudis; Tafirol; Temperal; Tempire; Tempofin; Tempra; Tempre†; Temprin; Temzzard; Termotrin†; Tylenol; Tylex; Ulpafie; Winasorb; ***Neth.:*** Daro; Democyl; Finimal Junior†; Hedex; Kinder Finimal†; Lagalgin†; Momentum; Panadol; Perfalgan; Sinaspril-Paracetamol; Tylenol; Vicks Paracetamol; ***Norw.:*** Pamol; Panodil; Paracet; Perfalgan; Pinex; ***NZ:*** Disprol†; Lemsip Cold & Flu Original, Cold & Flu Max; Pacimol; Pamol; Panadol; Paracare; Parapaed; Perfalgan; ***Philipp.:*** Acet; Acetadol; Aeknil; Alvedon; Baropyrine; Biogesic; Calpol; Cloxina; Corgic; Crocin; Detramol; Dolexpel; Febrinil; Gendol; Gifaril P; Lexalgin; Medgenol; Naprex; Nektol; Neo-Kiddielets; Opigesic; Para-4-Kids; Parvid; Rexidol; Riber; Saridon; Tempain; Tempra; Tylenol; Ultragesic; Zestagesic; Zydinol; ***Pol.:*** Acenol; Apap; Calpol; Codipar; Efferalgan; Grippostad; Novo-Gesic; Panadol; Perfalgan; Tazamol; ***Port.:*** Anti-Gripe Asclepius; Atralidon; Beluron; Ben-u-ron; Calpol†; Cofedron; Dafalgan; Efferalgan; Fludeten†; Gelocatil; Katagrip; Neogrip; Panadol; Panasorbe; Pantadolor; Paracetol; Paramolan; Parsel; Perdolan Mono†; Perfalgan; Singrips; Supofen; Takiprina; Tylenol; Zaramol†; ***Rus.:*** Calpol (Калпол); Cefecon D (Цефекон Д); Daleron (Далерон); Dolomol (Доломол); Flutabs (Флютабс); Panadol (Панадол); Perfalgan (Перфалган); ***S.Afr.:*** Anadin-3; Antalgic; Brunomol†; Calpol; Dolorol; Empaped; Fevamol; Go-Pain P; Junior Disprin†; Medpramol; Merck-Gesic†; Micro-Gesic; Napamol; Pacimol; Painamol; Panado; Paradco; Paramed; Perfalgan; Prolief; Pyradol; Tylenol; Varipan; Winpain†; ***Singapore:*** Acet; Biogesic; Calpol; Childrens Panadol Drops for Infants; Dhamol; Fibrexin; Milidon†; Napa; Naprex; Pacemol†; Panadol; Panamol; Paximol; Poro; Rapidol; Remedol; Tylenol; ***Spain:*** Acertol; Actron†; Antidol; Apiretal; Bandol†; Bolidol; Calmanticold†; Cupanol; Dafalgan; Dolgesic; Dolostop; Duorol; Efetamol; Efferalgan; Febrectal; Gelocatil; Melabon Infantil; Panadol; Parafludeten; Pediapirin†; Perfalgan; Resakal†; Resolvebohm; Sinmol; Talgo; Temperal†; Termalgin; Termocatil; Tylenol; Xumadol; ***Swed.:*** Alvedon; Curadon; Panodil; Perfalgan; Reliv; ***Switz.:*** Acetalgine; Becetamol; Ben-u-ron; Contre-Douleurs P; Dafalgan; Democyl†; Demogripal†; DoloStop nouvelle formule†; Dolprone; Influbene N; Kafa; Malex; Nina†; Osa Suppositoires contre douleurs et fievre; Panadol; Perfalgan; Pharmacard Family Douleurs & Fievre†; Rivodol†; Seranex N; Siniphen Nouvelle formule; Treupel Dolo Paracetamol; Treuphadol; Tylenol; Zolben; ***Thai.:*** A-Mol; Aceta-P†; Acetasil; Algogen; Biogesic; Calpol; Cemol; Daga; Denamol; Depyret; Detamol†; Fenn; Icolid Plus; Kit; Lotemp; Mypara; Nasa; Nutamol†; Panadol; Para GDEK; Para-G; Paracap; Paracet; Paragin; Paramol; Paramol TP; Paranal-L; Paranal†; Parat; Paratol; Partamol; Pemol; Pyracon; Pyretal†; Ramol; Sara†; Tempra; Tumdi; Tylenol; Tymol; Umeda Para-J; Unicap; Unimol; Uracet; Vemol†; Xebramol; ***Turk.:*** A-Per; Asomal; Babinoks; Berko-Setamol; Calpol; Efferalgan; Efpa; Ekosetol; Geralgine; Gripin; Minafen; Minoset; Noral; Panadol; Para-Nox; Paracet; Parasedol; Parol; Paroma; Pirofen; Polmofen; Sedalon; Setamol; Tamol; Tempo; Termacet; Termalgine; Tylol; Vermidon; Volpan; ***UAE:*** Adol; ***UK:*** Abdine Cold Relief; Alvedon; Anadin Paracetamol; Boots Pain Relief Suspension 6 Years Plus; Calpol; Disprol; Fennings Childrens Cooling Powders; Galpamol; Hedex; Infadrops; Mandanol; Medinol; Miradol; Obimol; Paldesic; Panadol; Panaleve; Paracets; Paraclear; Parapaed; Perfalgan; Salzone; ***USA:*** Acephen; Aceta; Apacet; Apap; Apra; Arthritis Pain Formula Aspirin Free; Aspirin Free Anacin; Aspirin Free Pain Relief; Bromo Seltzer; Childrens Dynafed Jr†; Childrens Mapap; Comtrex Maximum Strength Sore Throat; Dolono; Dynafed EX†; Feverall; Genapap; Genebs; Halenol; Infantaire; Liquiprin; Mapap; Maranox; Meda†; Oraphen-PD; Panadol; Panitone; Redutemp; Ridenol; Silapap; Tapanol†; Tempra; Tylenol; Tylenol Sore Throat Daytime; UN-Aspirin; Uni-Ace; ***Venez.:*** Acetafen; Acetalis; Aceval; Agurin; Alivax; Amifen; Ananty; Apiret; Apyrene; Atamel; Brexin; Cadafen†; Colprin†; Menpirin†; Paracor; Parstelin†; Tachipirin; Tempra; Tylenol; Tylex; Vestax; Winadol†.

Multi-ingredient: numerous preparations are listed in Part 3.

Parecoxib Sodium *(BANM, USAN, rINNM)*

Natrii Parecoxibum; Parecoxib sódico; Parécoxib Sodique; SC-69124A. *N*-{[*p*-(5-Methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl}-propionamide sodium.

Натрий Парекоксиб

$C_{19}H_{17}N_2NaO_4S = 392.4.$

CAS — 198470-84-7 (parecoxib); 197502-82-2 (parecoxib sodium).

ATC — M01AH04.

ATC Vet — QM01AH04.

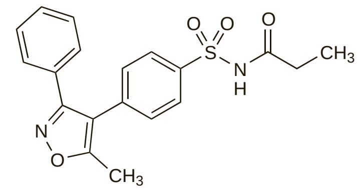

(parecoxib)

Incompatibility. Parecoxib sodium should not be mixed with products other than those recommended in licensed product information (see Uses and Administration, below). In particular, the use of lactated Ringer's solution with or without glucose will cause parecoxib to precipitate. Parecoxib should also not be given in the same syringe as opioids. The use of sterile water for injection is not recommended as the resulting solution is not isotonic.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Hypersensitivity reactions, including anaphylaxis and angioedema and serious skin reactions, have been reported with valdecoxib and may therefore occur with parecoxib, a prodrug of valdecoxib (see also p.132). Parecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions occurred in patients with a history of allergic reactions to sulfonamides and the use of parecoxib is contra-indicated in such patients.

Parecoxib should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more), inflammatory bowel disease, and moderate to severe heart failure (NYHA class II to IV). It should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should also not be used after coronary artery bypass graft surgery as there may be an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, stroke, renal impairment, deep surgical infections, and sternal wound complications. This may apply especially in obese patients or those with a history of cerebrovascular disease. Parecoxib should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Caution is also recommended when using parecoxib in dehydrated patients; rehydration may be advisable before giving parecoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the general worldwide withdrawal of rofecoxib (see p.121). The short-term use of parecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those given intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p.34.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as parecoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information reports that upper gastrointestinal perforation, ulceration, and bleeds have occurred with parecoxib treatment and therefore it should be used with caution in patients with a history of such events.

Effects on the kidneys. Increasing evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as parecoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Up to June 2004, the Australian Adverse Drug Reactions Advisory Committee had received 20 reports of adverse reactions associated with parecoxib.[1] Of these, 13 mentioned renal impairment with raised creatinine levels and/or oliguria; acute renal failure was reported in 4 of the 13 cases and multiple doses of parecoxib had been given in 6 cases. (In Australia, parecoxib was approved for single-dose use only because of safety concerns about multiple doses.)

1. Adverse Drug Reactions Advisory Committee (ADRAC). Parecoxib—one shot only. *Aust Adverse Drug React Bull* 2004; **23:** 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0406.pdf (accessed 08/11/07)

Interactions

For interactions associated with NSAIDs, see p.99.

Parecoxib is rapidly hydrolysed to its active metabolite, valdecoxib; the metabolism of valdecoxib is mainly mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Consequently, caution is recommended when using parecoxib with inhibitors of such isoenzymes. Licensed product information advises that the dose of parecoxib should be reduced if given with fluconazole, a CYP2C9 inhibitor; however, dose adjustment of parecoxib is not generally necessary when giving with ketoconazole, a CYP3A4 inhibitor, despite increased plasma concentrations of valdecoxib. The effects of enzyme inducers such as carbamazepine, dexamethasone, phenytoin, and rifampicin have not been studied; theoretically, the metabolism of valdecoxib may be increased by these drugs.

Valdecoxib has been noted to increase the plasma levels of dextromethorphan, a CYP2D6 substrate, and therefore caution is recommended when giving parecoxib with drugs that are metabolised via CYP2D6 and that have a narrow therapeutic index. Such drugs include flecainide, metoprolol, and propafenone. Valdecoxib may also affect the plasma levels of drugs that are metabolised via CYP2C19: an increase in the plasma levels of omeprazole was seen in patients using valdecoxib.

Pharmacokinetics

On intravenous or intramuscular injection, parecoxib is rapidly hydrolysed in the liver to its active metabolite, valdecoxib, and propionic acid; the plasma half-life of parecoxib is about 22 minutes. Plasma protein binding is about 98%. Valdecoxib is also extensively metabolised in the liver; pathways involved include those via the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and glucuronidation. Another active metabolite has been identified but it is not considered to contribute a significant clinical effect. Excretion is mainly via the urine with about 70% of a dose appearing as inactive metabolites. Less than 5% of a dose appears as unchanged valdecoxib in the urine. No unchanged parecoxib is found in the urine with only trace amounts in the faeces. The elimination half-life of valdecoxib is about 8 hours.

◊ References.

1. Karim A, *et al.* A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects. *J Clin Pharmacol* 2001; **41:** 1111–19.

Uses and Administration

Parecoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is a prodrug of valdecoxib (p.132) and is used for the short-term treatment of postoperative pain in patients aged 18 years and over. Parecoxib is given as the sodium salt although doses are expressed as the base; 42.4 mg of parecoxib sodium is equivalent to about 40 mg of parecoxib. The recommended dose is 40 mg given by intravenous or slow intramuscular injection; this may be followed by 20 or 40 mg every 6 to 12 hours as required. The maximum daily dose is 80 mg. Elderly patients weighing less than 50 kg should begin treatment with half the usual dose, repeated to a maximum of 40 mg daily. Doses may need to be reduced in hepatic impairment, see below.

Parecoxib should be reconstituted with either sodium chloride 0.9%, glucose 5%, or sodium chloride 0.45% with glucose 5%; no other solvents are recommended in licensed product information. In addition the reconstituted solution may only be injected into intravenous lines delivering sodium chloride 0.9%, glucose 5%, sodium chloride 0.45% with glucose 5%, or lactated Ringer's solution. (See above for details on incompatibilities.)

◊ References.

1. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; **61:** 1133–41.
2. Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postsurgical patients. *Ann Pharmacother* 2004; **38:** 882–6.
3. Mehlisch DR, *et al.* The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc* 2004; **135:** 1578–90.
4. Malan TP, *et al.* The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. *Anesth Analg* 2005; **100:** 454–60.
5. Beaussier M, *et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; **100:** 1309–15.
6. Sindhvananda W, *et al.* Parecoxib versus tramadol for post-appendectomy pain. *J Med Assoc Thai* 2005; **88:** 1557–62.
7. Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. *Curr Top Med Chem* 2007; **7:** 235–49.

Administration in hepatic impairment. Licensed product information in the UK states that no dosage adjustment is generally necessary for parecoxib in patients with *mild* hepatic impairment (Child-Pugh score 5 or 6). For those with *moderate* impairment (Child-Pugh score 7 to 9) parecoxib should be given at half the usual dose (see above), repeated to a maximum dose of 40 mg daily. Use in patients with *severe* impairment (Child-Pugh score 10 and over) is not recommended as there is no clinical experience in such patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Dynastat; ***Austria:*** Dynastat; ***Belg.:*** Dynastat; ***Chile:*** Pro-Bextra; ***Cz.:*** Dynastat; ***Denm.:*** Dynastat; ***Fin.:*** Dynastat; ***Fr.:*** Dynastat; ***Ger.:*** Dynastat; ***Gr.:*** Dynastat; ***Hong Kong:*** Dynastat; ***Hung.:*** Dynastat; ***India:*** Bioval-P†; Valcox; Valdixx; Valdone-P; Valus-P†; Vorth-P; ***Indon.:*** Dynastat; ***Irl.:*** Dynastat; ***Ital.:*** Dynastat; ***Mex.:*** Dynastat; ***Neth.:*** Dynastat; ***Norw.:*** Dynastat; ***NZ:*** Dynastat; ***Port.:*** Dynastat; ***Rus.:*** Dynastat (Династат); ***S.Afr.:*** Rayzon; ***Spain:*** Dynastat; ***Swed.:*** Dynastat; ***Switz.:*** Bextra†; ***Thai.:*** Dynastat; ***UK:*** Dynastat; ***Venez.:*** Dynastat†.

Pentazocine *(BAN, USAN, rINN)* ⊗

NIH-7958; NSC-107430; Pentatsosiini; Pentazocin; Pentazocina; Pentazocinas; Pentazocinum; Win-20228. (2*R**,6*R**,11*R**)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol.

Пентазоцин

$C_{19}H_{27}NO$ = 285.4.
CAS — 359-83-1.
ATC — N02AD01.
ATC Vet — QN02AD01.

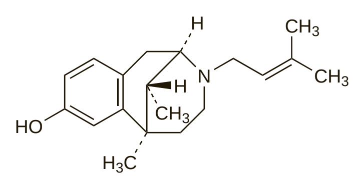

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Pentazocine). A white or almost white powder. It shows polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Pentazocine). A white or very pale, tan-coloured powder. Practically insoluble in water; soluble 1 in 11 of alcohol, 1 in 2 of chloroform, and 1 in 42 of ether; soluble in acetone; sparingly soluble in ethyl acetate and in benzene. Store in airtight containers. Protect from light.

Pentazocine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de pentazocina; Pentatsosiinihydrokloridi; Pentazocine, chlorhydrate de; Pentazocin-hidroklorid; Pentazocin-hydrochlorid; Pentazocinhydroklorid; Pentazocini hydrochloridum; Pentazocino hidrochloridas.

Пентазоцина Гидрохлорид

$C_{19}H_{27}NO,HCl$ = 321.9.
CAS — 2276-52-0; 64024-15-3.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Pentazocine Hydrochloride). A white or almost white powder. It shows polymorphism. Sparingly soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 31 (Pentazocine Hydrochloride). A white crystalline powder. It exhibits polymorphism, one form melting at about 254° and the other at about 218°. Soluble 1 in 30 of water, 1 in 20 of alcohol, and 1 in 4 of chloroform; very slightly soluble in acetone and in ether; practically insoluble in benzene. Store in airtight containers. Protect from light.

Pentazocine Lactate *(BANM, USAN, rINNM)* ⊗

Lactato de pentazocina; Pentatsosiinilaktaatti; Pentazocine, lactate de; Pentazocini lactas; Pentazocinlaktat; Pentazocin-laktát; Pentazocino laktatas.

Пентазоцина Лактат

$C_{19}H_{27}NO,C_3H_6O_3$ = 375.5.
CAS — 17146-95-1.

Pharmacopoeias. In *Eur.* (see p.vii). *US* includes only Pentazocine Lactate Injection.

Ph. Eur. 6.2 (Pentazocine Lactate). A white or almost white powder. Sparingly soluble in water; slightly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5. Protect from light.

BP 2008 (Pentazocine Lactate). A white to pale cream powder. Sparingly soluble in water, in alcohol, and in chloroform; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5.

Incompatibility. Commercial injections of pentazocine lactate are reported to be incompatible with soluble barbiturates and other alkaline substances including sodium bicarbonate. Diazepam and chlordiazepoxide have also been reported to be incompatible, as have glycopyrronium bromide[1] and nafcillin sodium.[2]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36:** 508–10.
2. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Pentazocine is subject to abuse.

◊ Pentazocine does produce physical dependence, but withdrawal symptoms are substantially less severe than with morphine. It does not typically produce drug-seeking behaviour of the same degree or intensity as morphine or other prototypic μ agonists, nor does it substitute for morphine in dependent subjects.[1] Pentazocine injection has been abused,[2] but street abuse, especially in the USA, has more often involved the intravenous use of crushed tablets of pentazocine and tripelennamine ('T's and Blues').[3-5] A decreased incidence of pentazocine abuse in the USA appeared to coincide with the introduction of oral tablets incorporating naloxone,[1] the rationale being that naloxone antagonises the effect of pentazocine if illicitly injected, but has no effect when taken orally. Some continued to abuse the new pentazocine/naloxone formulation;[6] intravenous abuse in one woman, who was unaware of the reformulation, resulted in opioid withdrawal symptoms and severe hypertension.[7] A 1989 report from the WHO committee[1] rated the likelihood of abuse of pentazocine as moderate, based on its pharmacological profile, dependence potential, and actual abuse. The committee considered that it should continue to be scheduled as a psychotropic substance rather than a narcotic drug.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 27/06/08)
2. Hunter R, Ingram IM. Intravenous pentazocine abuse by a nurse. *Lancet* 1983; **ii:** 227.
3. Poklis A, Whyatt PL. Current trends in the abuse of pentazocine and tripelennamine: the metropolitan St. Louis experience. *J Forensic Sci* 1980; **25:** 72–8.
4. Senay EC. Clinical experience with T's and B's. *Drug Alcohol Depend* 1985; **14:** 305–11.
5. Jackson C, *et al.* Fatal intracranial hemorrhage associated with phenylpropanolamine, pentazocine, and tripelennamine overdose. *J Emerg Med* 1985; **3:** 127–32.
6. Reed DA, Schnoll SH. Abuse of pentazocine-naloxone combination. *JAMA* 1986; **256:** 2562–4.
7. Reinhart S, Barrett SM. An acute hypertensive response after intravenous use of a new pentazocine formulation. *Ann Emerg Med* 1985; **14:** 591–3.

Adverse Effects

As for Opioid Analgesics in general, p.102.

Pentazocine may cause hallucinations and other psychotomimetic effects such as nightmares and thought disturbances. High doses may result in hypertension and tachycardia; increased aortic and pulmonary artery pressure with an increase in cardiac work has followed intravenous use in patients with myocardial infarction. Like morphine it causes respiratory depression, but pentazocine is said to have a 'ceiling' effect and the depth of respiratory depression does not increase proportionately with higher doses.

Rare adverse effects with pentazocine have included agranulocytosis and serious skin reactions such as erythema multiforme and toxic epidermal necrolysis.

Pentazocine injections may be painful. Local tissue damage may occur at injection sites particularly after subcutaneous injection or multiple doses; there have been reports of muscle fibrosis associated with intramuscular injections.

Effects on the blood. There have been reports of agranulocytosis associated with pentazocine.[1-3]

1. Marks A, Abramson N. Pentazocine and agranulocytosis. *Ann Intern Med* 1980; **92:** 433.
2. Haibach H, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1984; **130:** 1165–6.
3. Sheehan M, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1985; **132:** 1401.

Effects on the CNS. Oculogyric crisis has been associated with the use of pentazocine.[1]

1. Burstein AH, Fullerton T. Oculogyric crisis possibly related to pentazocine. *Ann Pharmacother* 1993; **27:** 874–6.

Effects on the skin. Toxic epidermal necrolysis in a 62-year-old man was attributed to pentazocine;[1] he had taken 50 to 75 mg every 4 hours for 8 days. His severe uraemia was attributed to fluid loss through the skin.

1. Hunter JAA, Davison AM. Toxic epidermal necrolysis associated with pentazocine therapy and severe reversible renal failure. *Br J Dermatol* 1973; **88:** 287–90.

Treatment of Adverse Effects

As for Opioid Analgesics in general, p.102.

As pentazocine has both opioid agonist and antagonist activity its effects may not be completely reversed by naloxone, but use of the latter is still recommended in pentazocine overdosage.

Precautions

As for Opioid Analgesics in general, p.103.

Pentazocine has weak opioid antagonist actions and may precipitate withdrawal symptoms if given to patients who are physically dependent on opioids. It should generally be avoided after myocardial infarction and in patients with heart failure or arterial or pulmonary hypertension.

When frequent injections are needed, pentazocine should be given intramuscularly rather than subcutaneously and the injection sites should be varied.

Abuse. See under Dependence and Withdrawal, above.

Porphyria. Pentazocine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with opioid analgesics, see p.103.

Tobacco smoking. Smokers metabolised about 40% more pentazocine than non-smokers, although there was large inter-subject variation;[1] tobacco smoking might induce liver enzymes responsible for drug oxidation.

1. Vaughan DP, *et al.* The influence of smoking on the inter-subject variation in pentazocine elimination. *Br J Clin Pharmacol* 1976; **3:** 279–83.

Pharmacokinetics

Pentazocine is well absorbed from the gastrointestinal tract; after an oral dose, peak plasma concentrations occur in 1 to 3 hours and the half-life is reported to be about 2 to 3 hours. After intramuscular injection, peak plasma concentrations are reached in 15 minutes to 1 hour and the half-life is about 2 to 5 hours. About 50 to 75% has been reported to be bound to plasma proteins. Pentazocine undergoes extensive first-pass metabolism in the liver; oral bioavailability is low with only about half of a dose reaching the systemic circulation. Metabolites and a small amount of unchanged drug are excreted in the urine. It crosses the placenta and is distributed into breast milk.

Hepatic impairment. Clearance of pentazocine was significantly reduced and terminal half-life and oral bioavailability increased in cirrhotic patients when compared with healthy subjects.[1]

1. Neal EA, *et al.* Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology* 1979; **77:** 96–102.

Uses and Administration

Pentazocine, a benzomorphan derivative, is an opioid analgesic (p.104) that has mixed opioid agonist and antagonist actions. Agonist activity is thought to be mainly at κ opioid receptors (with possibly some σ receptor activity); it acts as a weak antagonist or partial agonist at μ receptors. Pentazocine is used for the relief of moderate to severe pain including the pain of labour. Combined preparations with paracetamol or aspirin may also be used in the treatment of moderate pain. It may also be used for pre-operative sedation and as an adjunct to anaesthesia. Its analgesic effect declines more rapidly than that of morphine.

Pentazocine is given orally as the hydrochloride; doses may be expressed as either the base or the salt. Pentazocine is also given parenterally and rectally as the lactate; doses are expressed in terms of the base. Pentazocine 100 mg is equivalent to about 112.8 mg of pentazocine hydrochloride or 131.6 mg of pentazocine lactate.

A usual oral dose is the equivalent of 50 to 100 mg of pentazocine or pentazocine hydrochloride every 3 to 4 hours after food, to a maximum of 600 mg daily.

The usual initial dose by subcutaneous, intramuscular, or intravenous injection is the equivalent of pentazocine 30 mg as a single dose. Thereafter, the dose may be adjusted according to response; in some patients 45 to 60 mg by subcutaneous or intramuscular injection may be required. In the USA single intravenous doses of not more than 30 mg are advised. Doses may be repeated every 3 to 4 hours; it should not be necessary to exceed 360 mg daily. Also if frequent injections are needed, the intramuscular route should be used rather than the subcutaneous route, and the injection sites should be varied. In obstetric analgesia 30 mg may be given as a single dose by intramuscular injection during labour; alternatively, 20 mg may be given by intravenous injection as soon as contractions occur at regular intervals and repeated 2 or 3 times at intervals of 2 to 3 hours if necessary.

For details of doses in children, see below.

Pentazocine is given rectally in suppositories usually in a dose equivalent to pentazocine 50 mg up to 4 times daily.

As a deterrent to abuse a combined oral preparation of pentazocine hydrochloride and naloxone hydrochloride is available in some countries.

Administration in children. In the UK, pentazocine is licensed for the relief of moderate to severe pain in children and doses may be repeated every 3 to 4 hours if necessary. Those aged 6 to 12 years may be given a usual oral dose of 25 mg. Children aged 1 to 12 years may be given doses of up to 1 mg/kg by subcutaneous or intramuscular injection or up to 500 micrograms/kg by intravenous injection.

Preparations

BP 2008: Pentazocine Capsules; Pentazocine Injection; Pentazocine Suppositories; Pentazocine Tablets;
USP 31: Pentazocine and Aspirin Tablets; Pentazocine and Naloxone Tablets; Pentazocine Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Fortral†; ***Austria:*** Fortral; ***Belg.:*** Fortal; ***Canad.:*** Talwin; ***Cz.:*** Fortral; ***Denm.:*** Fortral†; ***Fr.:*** Fortal†; ***Ger.:*** Fortral; ***Gr.:*** Fortal; ***India:*** Fortwin; Pentawin; ***Israel:*** Rafazocine†; Talwin NX†; Talwin†; ***Ital.:*** Talwin; ***Jpn:*** Peltazon†; Pentagin†; Sosegon†; ***Neth.:*** Fortral; ***Norw.:*** Fortralin†; ***NZ:*** Fortral†; ***Port.:*** Sosegon†; ***S.Afr.:*** Ospronim; Sosenol; ***Spain:*** Sosegon; ***Switz.:*** Fortalgesic†; ***Thai.:*** Fortwin†; Pangon; Sosegon†; ***UK:*** Fortral; ***USA:*** Talwin; Talwin NX.

Multi-ingredient: ***India:*** Expergesic; Foracet; ***Irl.:*** Fortagesic†; ***USA:*** Emergent-Ez; Talacen; Talwin Compound†.

Pethidine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de petidina; Meperidine Hydrochloride; Péthidine, chlorhydrate de; Pethidin-hydrochlorid; Pethidini hydrochloridum; Petidiinihydrokloridi; Petidin Hidroklorür; Petidin-hidroklorid; Petidinhydroklorid; Petidino hidrochloridas; Petydyny chlorowodorek. Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

Петидина Гидрохлорид

$C_{15}H_{21}NO_2,HCl = 283.8.$

CAS — 57-42-1 (pethidine); 50-13-5 (pethidine hydrochloride).

ATC — N02AB02.

ATC Vet — QN02AB02.

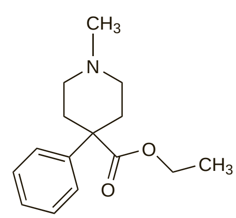

(pethidine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of pethidine:
Bam; Peth.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Pethidine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Meperidine Hydrochloride). A fine white odourless crystalline powder. Very soluble in water; soluble in alcohol; sparingly soluble in ether. pH of a 5% solution in water is about 5. Protect from light.

Incompatibility. Solutions of pethidine hydrochloride are acidic. They are incompatible with barbiturate salts and loss of clarity was also seen in an early additive study[1] with other drugs including aminophylline, heparin sodium, meticillin sodium, morphine sulfate, nitrofurantoin sodium, phenytoin sodium, sodium iodide, sulfadiazine sodium, and sulfafurazole diolamine. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with pethidine hydrochloride in 5% glucose injection.[2] In the same study an immediate precipitate occurred on admixture with cefoperazone sodium or mezlocillin sodium; with nafcillin sodium an immediate cloudy appearance cleared on agitation. Incompatibility has also been seen between pethidine hydrochloride and aciclovir sodium, imipenem, furosemide,[3] liposomal doxorubicin hydrochloride,[4] and idarubicin.[5] Solutions of cefazolin sodium[6] and pethidine hydrochloride mixed in 5% glucose injection turned light yellow after storage for 5 days at 25°; the admixture was stable for at least 20 days at 4°.

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
2. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
3. Pugh CB, *et al.* Visual compatibility of morphine sulfate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 123–5.
4. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
5. Turowski RC, Durthaler JM. Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 2181–4.
6. Lee DKT, *et al.* Stability of cefazolin sodium and meperidine hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 1608–10.

Stability. Pethidine hydrochloride injection 100 mg/mL was stable[1] for at least 24 hours at room temperature when diluted to a concentration of 300 mg/litre in glucose 5% and 4% and in sodium chloride injection (0.9%) and sodium chloride injection (0.9%) diluted 1 in 5.

Accelerated stability studies using elevated temperatures and humidities to simulate tropical conditions classified pethidine hydrochloride as a 'less stable drug substance'.[2] It was suggested that during quality assurance of preparations containing pethidine hydrochloride particular attention should be paid to their stability.

1. Rudd L, Simpson P. Pethidine stability in intravenous solutions. *Med J Aust* 1978; **2:** 34.
2. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 26/06/08)

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Doses of pethidine as large as 3 or 4 g daily have been taken by addicts. As tolerance to the CNS stimulant and antimuscarinic effects is not complete with these very large doses, muscle twitching, tremor, mental confusion, dilated pupils, and sometimes convulsions may be present.

Withdrawal symptoms appear more rapidly than with morphine and are of shorter duration.

For the abuse of pethidine analogues, see under Precautions, below.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

The effects on smooth muscle may be relatively less intense than with morphine and constipation occurs less frequently. Local reactions often follow injection of pethidine; general hypersensitivity reactions occur rarely. Pethidine given intravenously may increase the heart rate. After overdosage, symptoms are generally similar to those of morphine poisoning. However, stimulation of the CNS and convulsions may also occur, especially in tolerant individuals or after toxic oral doses; these have been attributed mainly to the metabolite norpethidine.

Incidence of adverse effects. The incidence of adverse effects in hospitalised patients receiving pethidine was monitored by the Boston Collaborative Drug Surveillance Program.[1] Adverse reactions to oral pethidine were reported in 16 of 366 patients and mainly involved the gastrointestinal tract. After pethidine by injection 102 of 3268 patients had adverse effects, the CNS being involved in 38.

More recently, 20 adverse reactions were identified in a chart review of 141 patients given pethidine and considered to be at high risk of developing toxicity;[2] high-risk patients were defined as those with renal impairment (creatinine clearance 50 mL/minute or less), those receiving patient-controlled analgesia (PCA) with pethidine, and those given intravenous pethidine in doses of over 200 mg daily for several days. The most common adverse reactions were confusion and anxiety; other reported adverse effects included nervousness, seizures, and hallucinations. Patients who developed adverse reactions were significantly older, more likely to be taking a benzodiazepine, and had longer hospital stays than those without adverse effects. Out of the 20 reports, 16 adverse effects were noted in the 123 patients who received pethidine via a PCA pump; cumulative doses for patients using PCA were found to be a significant risk factor in the development of adverse effects.

1. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol* 1978; **18:** 180–9.
2. Seifert CF, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine usage patterns and frequency of adverse drug reactions. *Pharmacotherapy* 2004; **24:** 776–83.

Effects on the cardiovascular system. Histamine release was more frequent after pethidine than after morphine, fentanyl, or sufentanil given intravenously for the induction of anaesthesia.[1] Increased plasma-histamine concentrations occurred in 5 of 16 patients given pethidine in a mean dose of 4.3 mg/kg and were generally accompanied by hypotension, tachycardia, erythema, and increased plasma-adrenaline concentrations. Only 1 of 10 given morphine and none of those receiving fentanyl or sufentanil showed evidence of histamine release. All of the histamine releasers were young women.

1. Flacke JW, *et al.* Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; **66:** 723–30.

Effects on the nervous system. CNS excitatory effects of pethidine such as tremors, muscle twitches, and convulsions have been associated with toxic doses and have been attributed to the metabolite norpethidine. Accumulation of norpethidine may occur if large doses of pethidine are repeated at short intervals (including for patient-controlled analgesia) and is especially likely when renal function is impaired.[1-13]

1. Kaiko RF, *et al.* Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; **13:** 180–5.
2. Lieberman AN, Goldstein M. Reversible parkinsonism related to meperidine. *N Engl J Med* 1985; **312:** 509.
3. Mauro VF, *et al.* Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia. *Clin Pharm* 1986; **5:** 837–9.
4. Morisy L, Platt D. Hazards of high-dose meperidine. *JAMA* 1986; **255:** 467–8.
5. Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg* 1986; **65:** 536–8.
6. Eisendrath SJ, *et al.* Meperidine-induced delirium. *Am J Psychiatry* 1987; **144:** 1062–5.
7. Kyff JV, Rice TL. Meperidine-associated seizures in a child. *Clin Pharm* 1990; **9:** 337–8.
8. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
9. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.
10. Stone PA, *et al.* Norpethidine toxicity and patient controlled analgesia. *Br J Anaesth* 1993; **71:** 738–40.
11. Marinella MA. Meperidine-induced generalized seizures with normal renal function. *South Med J* 1997; **90:** 556–8.
12. McHugh GJ. Norpethidine accumulation and generalized seizure during pethidine patient-controlled analgesia. *Anaesth Intensive Care* 1999; **27:** 289–91.
13. Hubbard GP, Wolfe KR. Meperidine misuse in a patient with sphincter of Oddi dysfunction. *Ann Pharmacother* 2003; **37:** 534–7.

Precautions

As for Opioid Analgesics in general, p.103.

Pethidine should also be given cautiously to patients with a history of convulsive disorders or supraventricular tachycardias.

Abuse. A synthetic analogue of pethidine, MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), manufactured illicitly for recreational use, achieved notoriety when it was accidentally contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) leading to an epidemic of parkinsonism among intravenous drug abusers.[1] WHO has also identified another analogue, PEPAP (1-phenylethyl-4-phenyl-4-acetoxypiperidine) as being liable to abuse.[2]

1. Buchanan JF, Brown CR. 'Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_761.pdf (accessed 26/06/08)

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were given pethidine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

The elderly. Pethidine had a slower elimination rate in elderly compared with young patients and a reduction in total daily dose might be necessary in elderly patients receiving repeated doses of pethidine.[1] Another study concluded that age-related changes in disposition were not sufficient to warrant modification of pethidine dosage regimens.[2]

1. Holmberg L, *et al.* Comparative disposition of pethidine and norpethidine in old and young patients. *Eur J Clin Pharmacol* 1982; **22:** 175–9.
2. Herman RJ, *et al.* Effects of age on meperidine disposition. *Clin Pharmacol Ther* 1985; **37:** 19–24.

Phaeochromocytoma. Pethidine provoked episodes of hypertension in a patient with phaeochromocytoma; the effect was suppressed by labetalol.[1] Like other histamine-releasing opioids, pethidine should be used with caution in such patients.

1. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.

Pregnancy and the neonate. Pethidine has been widely used for analgesia during labour. It rapidly crosses the placenta and like other opioid analgesics may cause respiratory depression in the neonate, although perhaps less so than morphine. Respiratory depression varies according to the timing and size of the maternal dose.

Fetal depression was not apparent when delivery occurred within 1 hour of giving pethidine, but was present in 6 of 24 infants delivered 1 to 3 hours after injection and in all of 5 infants delivered 3 to 6 hours after injection.[1] However, higher blood concentrations of pethidine were seen in infants delivered within 1 hour of an intramuscular dose of pethidine compared with those delivered 1 to 4 hours after injection. The role of pethidine metabolites was uncertain. It has also been reported[2] that depressed neonatal responses persisted for the first 2 days of life; depression was dose-related being greatest with the highest dose of pethidine (75 to 150 mg within 4 hours of delivery). Neonates appear able to metabolise pethidine, although probably more slowly than adults.[3] The amounts of pethidine and norpethidine excreted by the neonate increased significantly with the maternal dose-delivery interval for intervals of up to 5 hours and most of the placentally transferred pethidine should be excreted by the third day. Elimination of pethidine took up to 6 days in the neonates in another study.[4]

Further references on the transplacental transfer of pethidine can be found in Pregnancy under Pharmacokinetics, below.

Neither psychological nor physical effects were found in 5-year-olds born to mothers who had received pethidine during labour.[5] Neonatal behaviour does not appear to have been affected significantly by pethidine, although it has been acknowledged that the relationship between maternal analgesia in labour and subsequent infant behaviour is by no means simple.[6] The results of early studies that suggested an excess of cases of cancer in children whose mothers received pethidine during labour have been refuted by a later and larger study.[7]

1. Morrison JC, *et al.* Metabolites of meperidine related to fetal depression. *Am J Obstet Gynecol* 1973; **115:** 1132–7.
2. Hodgkinson R, *et al.* Double-blind comparison of the neurobehaviour of neonates following the administration of different doses of meperidine to the mother. *Can Anaesth Soc J* 1978; **25:** 405–11.
3. Hogg MIJ, *et al.* Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *Br J Anaesth* 1977; **49:** 891–9.
4. Cooper LV, *et al.* Elimination of pethidine and bupivacaine in the newborn. *Arch Dis Child* 1977; **52:** 638–41.
5. Buck C. Drugs in pregnancy. *Can Med Assoc J* 1975; **112:** 1285.
6. Anonymous. To measure life. *Lancet* 1981; **ii:** 291–2.
7. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.

Renal impairment. Caution is necessary when pethidine is given to patients with renal impairment; UK licensed product information recommends that it should be avoided in those with severe impairment, whereas US product information suggests to use reduced doses. Evidence of CNS excitation, including seizures and twitches, in 2 patients with renal insufficiency given multiple doses of pethidine was attributed to accumulation of the metabolite norpethidine; both patients had high norpethidine : pethidine plasma concentration ratios.[1]

See also under Pharmacokinetics, below.

1. Szeto HH, *et al.* Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med* 1977; **86:** 738–41.

Interactions

For interactions associated with opioid analgesics, see p.103.

Very severe reactions, including coma, severe respiratory depression, cyanosis, and hypotension have occurred in patients receiving MAOIs (including moclobemide and selegiline) and given pethidine. There are also reports of hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Pethidine should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Use of pethidine with phenothiazines has produced severe hypotensive episodes and may prolong the respiratory depression due to pethidine.

Plasma concentrations of norpethidine are increased by ritonavir, with a resultant risk of toxicity; use together should be avoided (see also p.103).

Antibacterials. See MAOIs below for interactions between pethidine and *isoniazid* and *linezolid*.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of pethidine and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397. See also MAOIs, below.

Barbiturates. Opioid analgesics and barbiturates can be expected to have additive CNS depressant effects. Prolonged sedation with pethidine in the presence of *phenobarbital* has also been attributed to induction of *N*-demethylation of pethidine, resulting in the enhanced formation of the potentially neurotoxic metabolite norpethidine.[1,2]

1. Stambaugh JE, *et al.* A potentially toxic drug interaction between pethidine (meperidine) and phenobarbitone. *Lancet* 1977; **i:** 398–9.
2. Stambaugh JE, *et al.* The effect of phenobarbital on the metabolism of meperidine in normal volunteers. *J Clin Pharmacol* 1978; **18:** 482–90.

Histamine H_2-antagonists. See under Opioid Analgesics, p.103.

MAOIs. Some of the most serious interactions involving pethidine have been with non-selective MAOIs and have been manifest as enhanced depressant effects or hyperexcitability (see Interactions, above). However, a life-threatening interaction has also been reported between pethidine and *selegiline*, a selective monoamine oxidase type B inhibitor.[1] Also, symptoms suggestive of a mild serotonin syndrome developed in a 73-year-old woman taking *moclobemide* (a reversible inhibitor of monoamine oxidase type A), nortriptyline, and lithium after she was given pethidine intravenously.[2]

Use of the antibacterial *isoniazid* with pethidine led to a drop in blood pressure and lethargy in a 54-year-old man.[3] Serotonin syndrome developed in a 27-year-old man after the use of pethidine with *linezolid*;[4] symptoms resolved when pethidine was stopped. The authors of both studies attributed the interaction to the inhibitory action of isoniazid and linezolid on monoamine oxidase.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.*; 440.
2. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.
3. Gannon R, *et al.* Isoniazid, meperidine, and hypotension. *Ann Intern Med* 1983; **99:** 415. Correction. *ibid.*; 740.
4. Das PK, *et al.* Serotonin syndrome after concomitant treatment with linezolid and meperidine. *Clin Infect Dis* 2008; **46:** 264–5.

Phenothiazines. *Prochlorperazine* prolonged the respiratory depressant effect of pethidine in healthy subjects.[1] Enhanced CNS depression and hypotension were reported when healthy subjects were given *chlorpromazine* in addition to pethidine; there was evidence of increased *N*-demethylation of pethidine.[2]

1. Steen SN, Yates M. Effects of benzquinamide and prochlorperazine, separately and combined with meperidine, on the human respiratory center. *Clin Pharmacol Ther* 1972; **13:** 153.
2. Stambaugh JE, Wainer IW. Drug interaction: meperidine and chlorpromazine, a toxic combination. *J Clin Pharmacol* 1981; **21:** 140–6.

Phenytoin. The hepatic metabolism of pethidine appears to be enhanced by phenytoin; use together resulted in reduced half-life and bioavailability in healthy subjects; blood concentrations of norpethidine were increased.[1]

1. Pond SM, Kretschzmar KM. Effect of phenytoin on meperidine clearance and normeperidine formation. *Clin Pharmacol Ther* 1981; **30:** 680–6.

Pharmacokinetics

Pethidine hydrochloride is absorbed from the gastrointestinal tract, but only about 50% of the drug reaches the systemic circulation because of first-pass metabolism. Absorption after intramuscular injection is variable. Peak plasma concentrations have been reported 1 to 2 hours after oral doses. It is about 60 to 80% bound to plasma proteins.

Pethidine is metabolised in the liver by hydrolysis to pethidinic acid (meperidinic acid) or demethylation to norpethidine (normeperidine) and hydrolysis to norpethidinic acid (normeperidinic acid), followed by partial conjugation with glucuronic acid. Norpethidine is pharmacologically active and its accumulation may result in toxicity. Pethidine is reported to have a plasma elimination half-life of about 3 to 6 hours in healthy subjects; the metabolite norpethidine is eliminated more slowly, with a half-life reported to be up to about 20 hours. Both pethidine and norpethidine appear in the CSF. At the usual values of urinary pH or if the urine is alkaline, only a small amount of pethidine is excreted unchanged; urinary excretion of pethidine and norpethidine is enhanced by acidification of the urine. Pethidine crosses the placenta and is distributed into breast milk.

◊ Reviews.

1. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Administration. The elimination half-life of pethidine was prolonged and plasma clearance decreased when given perioperatively compared with postoperatively.[1]

During labour the pharmacokinetics of pethidine may depend on how it is given. In a comparison of intramuscular injection at different sites, absorption of pethidine from the gluteus muscle was impaired and the deltoid muscle was preferred.[2]

No statistically significant differences were found in pharmacokinetic parameters for deltoid and gluteal intramuscular injections in elderly postoperative patients.[3] However, substantial interpatient variability was noted for both sites, and the authors suggested that more rapid and predictable routes such as intravenous injection may be more appropriate for postoperative use in the elderly.

1. Tamsen A, *et al.* Patient-controlled analgesic therapy, part 1: pharmacokinetics of pethidine in the per- and postoperative periods. *Clin Pharmacokinet* 1982; **7:** 149–63.
2. Lazebnik N, *et al.* Intravenous, deltoid, or gluteus administration of meperidine during labor? *Am J Obstet Gynecol* 1989; **160:** 1184–9.
3. Erstad BL, *et al.* Site-specific pharmacokinetics and pharmacodynamics of intramuscular meperidine in elderly postoperative patients. *Ann Pharmacother* 1997; **31:** 23–8.

Hepatic impairment. The terminal half-life of pethidine was prolonged to about 7 hours in cirrhotic patients compared with 3 hours in healthy subjects, which was attributed to impairment of the drug-metabolising activity of the liver.[1] Another study concluded that although impaired hepatic metabolism might confer relative protection from norpethidine toxicity in patients with cirrhosis, there might be an increased risk of cumulative toxicity because of slow elimination of the metabolite.[2]

1. Klotz U, *et al.* The effect of cirrhosis on the disposition and elimination of meperidine in man. *Clin Pharmacol Ther* 1974; **16:** 667–75.
2. Pond SM, *et al.* Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. *Clin Pharmacol Ther* 1981; **30:** 183–8.

Pregnancy. Some references to the pharmacokinetics of pethidine during labour are given below.

1. Tomson G, *et al.* Maternal kinetics and transplacental passage of pethidine during labour. *Br J Clin Pharmacol* 1982; **13:** 653–9.
2. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: I mother. *Am J Obstet Gynecol* 1985; **151:** 406–9.
3. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: II fetus and neonate. *Am J Obstet Gynecol* 1985; **151:** 410–15.

Renal impairment. Plasma protein binding of pethidine was reported to be decreased in renal disease and ranged from 58.2% in healthy subjects to 31.8% in anuric patients.[1] The same workers also reported prolonged elimination of pethidine in patients with renal dysfunction.[2]

See also under Precautions, above.

1. Chan K, *et al.* Plasma protein binding of pethidine in patients with renal disease. *J Pharm Pharmacol* 1983; **35:** 94P.
2. Chan K, *et al.* Pharmacokinetics of low-dose intravenous pethidine in patients with renal dysfunction. *J Clin Pharmacol* 1987; **27:** 516–22.

Uses and Administration

Pethidine, a phenylpiperidine derivative, is a synthetic opioid analgesic (p.104) that acts mainly as a μ opioid agonist. Pethidine is used for the relief of most types of moderate to severe acute pain including the pain of labour. It is more lipid soluble than morphine and has a less potent and shorter lasting analgesic effect; analgesia usually lasts for 2 to 4 hours. Its short duration of action and accumulation of its potentially neurotoxic metabolite norpethidine on repeated dosage make it unsuitable for the management of chronic pain. Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis (but see Biliary-tract Disorders, p.103). It is also used for premedication and as an adjunct to anaesthesia. It has been given with phenothiazines such as promethazine to achieve basal narcosis. Pethidine has little effect on cough or on diarrhoea.

For the relief of **pain**, pethidine hydrochloride is given in oral doses of 50 to 150 mg every 4 hours if necessary. It may also be given by intramuscular or subcutaneous injection in doses of 25 to 100 mg and by slow intravenous injection in doses of 25 to 50 mg repeated after 4 hours. For *postoperative* pain, the *BNF* suggests that the subcutaneous or intramuscular doses may be given every 2 to 3 hours if necessary.

In *obstetric analgesia* 50 to 100 mg may be given by intramuscular or subcutaneous injection as soon as contractions occur at regular intervals. This dose may be repeated after 1 to 3 hours if necessary up to a maximum of 400 mg in 24 hours.

For **premedication** 25 to 100 mg may be given intramuscularly about 1 hour before surgery. It may also be given subcutaneously in similar doses. As an **adjunct to anaesthesia** 10 to 25 mg may be given by slow intravenous injection.

For details of doses in children, see below.

Administration. In addition to the conventional routes pethidine has been given epidurally,[1-4] intraperitoneally,[5,6] and intrathecally.[7-9] It has also been given by various routes as a patient-controlled system.[10-13] However, some consider that the use of pethidine should be avoided for patient-controlled analgesia because of the increased risk of norpethidine-induced seizures[14] (see also Incidence of Adverse Effects and Effects on the Nervous System, above).

1. Perriss BW. Epidural pethidine in labour: a study of dose requirements. *Anaesthesia* 1980; **35:** 380–2.
2. Husemeyer RP, *et al.* A study of pethidine kinetics and analgesia in women in labour following intravenous, intramuscular and epidural administration. *Br J Clin Pharmacol* 1982; **13:** 171–6.
3. Perriss BW, *et al.* Analgesia following extradural and im pethidine in post-caesarean section patients. *Br J Anaesth* 1990; **64:** 355–7.
4. Blythe JG, *et al.* Continuous postoperative epidural analgesia for gynecologic oncology patients. *Gynecol Oncol* 1990; **37:** 307–10.
5. Colbert ST, *et al.* An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. *Anesth Analg* 2000; **91:** 667–70.
6. O'Hanlon DM, *et al.* Intraperitoneal pethidine versus intramuscular pethidine for the relief of pain after laparoscopic cholecystectomy: randomized trial. *World J Surg* 2002; **26:** 1432–6.
7. Acalovschi I, *et al.* Saddle block with pethidine for perineal operations. *Br J Anaesth* 1986; **58:** 1012–16.
8. Yu SC, *et al.* Addition of meperidine to bupivacaine for spinal anaesthesia for caesarean section. *Br J Anaesth* 2002; **88:** 379–83.
9. Vranken JH, *et al.* Plasma concentrations of meperidine and normeperidine following continuous intrathecal meperidine in patients with neuropathic cancer pain. *Acta Anaesthesiol Scand* 2005; **49:** 665–70.
10. Striebel HW, *et al.* Patient-controlled intranasal analgesia (PCINA) for the management of postoperative pain: a pilot study. *J Clin Anesth* 1996; **8:** 4–8.
11. Kee N, *et al.* Comparison of patient-controlled epidural analgesia with patient-controlled intravenous analgesia using pethidine or fentanyl. *Anaesth Intensive Care* 1997; **25:** 126–32.
12. Sharma SK, *et al.* Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87:** 487–94.
13. Chen PP, *et al.* Patient-controlled pethidine after major upper abdominal surgery: comparison of the epidural and intravenous routes. *Anaesthesia* 2001; **56:** 1106–12.
14. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; **27:** 29–32.

Administration in children. Pethidine is used for the relief of moderate to severe acute pain and for premedication in children.

For the relief of **pain**, the *BNFC* suggests that children aged 2 months to 12 years may be given pethidine hydrochloride 0.5 to 2 mg/kg orally or by subcutaneous or intramuscular injection every 4 to 6 hours if necessary; older children up to 18 years of age may be given 50 to 100 mg orally, or 25 to 100 mg intramuscularly or subcutaneously, every 4 to 6 hours if necessary. Injection solutions may be given orally if needed, to achieve a suitable dose. Pethidine may also be given by intravenous injection in doses of 0.5 to 1 mg/kg to neonates and children up to 12 years of age, repeated every 10 to 12 hours if necessary in those up to 2 months of age and every 4 to 6 hours if necessary in older children; those aged 12 to 18 years may be given the usual adult intravenous dose (see above) repeated every 4 to 6 hours if necessary. An intravenous injection of 1 mg/kg as a loading dose followed by continuous intravenous infusion of 100 to 400 micrograms/kg per hour adjusted according to response may also be given to those aged 1 month and over.

For **premedication**, UK licensed product information recommends that 1 to 2 mg/kg is given intramuscularly about 1 hour before surgery.

See also Lytic Cocktails, below.

Eclampsia and pre-eclampsia. See Lytic Cocktails under Sedation, below.

Pain. Pethidine produces prompt but short-lasting analgesia, and may be preferred to morphine when rapid control of acute pain is required. It has been widely used in obstetrics to control the pain of labour (although the *BNF* notes that morphine or other opioids are often preferred for obstetric pain), and for postoperative pain relief after caesarean section or other surgical procedures.

In a study of patients with intractable pain the minimum effective analgesic blood concentration ranged from 100 to 820 nanograms/mL (median 250 nanograms/mL) in 15 of 16; the remaining patient failed to obtain analgesia with pethidine. Additional measures were considered necessary[1] if the minimum effective concentration exceeded 400 nanograms/mL.

Pethidine has traditionally been given by intermittent intramuscular injection in the treatment of acute pain, but inconsistent pain relief can be expected because of fluctuating blood-pethidine concentrations;[2] continuous intravenous infusion might be more effective for acute pain. For reference to use by other routes see Administration, above.

1. Mather LE, Glynn CJ. The minimum effective analgesic blood concentration of pethidine in patients with intractable pain. *Br J Clin Pharmacol* 1982; **14:** 385–90.
2. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; **7:** 421–33.

SICKLE-CELL CRISIS. Concern has been expressed over the continued use of pethidine for analgesia in painful crises in sickle-cell disease. Control of pain may be inadequate and doses commonly used to manage crises may lead to accumulation of the neuroexcitatory metabolite of pethidine and precipitate seizures.[1,2] See also Effects on the Nervous System, above.

1. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304:** 1478–9.
2. Harrison JFM, *et al.* Pethidine in sickle cell crisis. *BMJ* 1992; **305:** 182.

Sedation. Some references to the use of pethidine for endoscopy are given below.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; **47:** 319–23.
2. Diab FH, *et al.* Efficacy and safety of combined meperidine and midazolam for EGD sedation compared with midazolam alone. *Am J Gastroenterol* 1996; **91:** 1120–5.
3. Laluna L, *et al.* The comparison of midazolam and topical lidocaine spray versus the combination of midazolam, meperidine, and topical lidocaine spray to sedate patients for upper endoscopy. *Gastrointest Endosc* 2001; **53:** 289–93.

LYTIC COCKTAILS. Lytic cocktails consisting of chlorpromazine, pethidine, and/or promethazine have been given intravenously in some countries for the management of pre-eclampsia and imminent eclampsia. However, the use of phenothiazines is generally not recommended late in pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p.1171); the management of eclampsia, which is the convulsive phase, is discussed on p.470.

Lytic cocktails have also been used for sedation and analgesia in children, by intramuscular or occasionally intravenous injection. However, there is a high rate of therapeutic failure as well as serious adverse effects with such combinations, and the American Academy of Pediatrics[1] had recommended that alternative sedatives and analgesics should be considered. Lytic cocktails are not the most appropriate means of sedation for short procedures since patients must be monitored for about 1 hour before the procedure while the drugs take effect, and for even longer during the recovery period.[2]

1. American Academy of Pediatrics Committee on Drugs. Reappraisal of Lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1995; **95:** 598–602.
2. Barst SM, *et al.* A comparison of propofol and Demerol-Phenergan-Thorazine for brief, minor, painful procedures in a pediatric hematology-oncology clinic. *Int J Pediatr Hematol/Oncol* 1995; **1:** 587–91.

Shivering. For reference to the use of pethidine in the management of shivering associated with anaesthesia, see under Adverse Effects of General Anaesthetics, p.1779. Pethidine has also been used to treat amphotericin B-induced shaking chills.[1]

1. Burks LC, *et al.* Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980; **140:** 483–4.

Preparations

BP 2008: Pethidine Injection; Pethidine Tablets;
USP 31: Meperidine Hydrochloride Injection; Meperidine Hydrochloride Syrup; Meperidine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cluyer; Meperol; ***Austria:*** Alodan; ***Belg.:*** Dolantine; ***Braz.:*** Dolantina; Dolosal; Dornot; ***Canad.:*** Demerol; ***Chile:*** Demerol†; ***Cz.:*** Dolsin; ***Ger.:*** Dolantin; ***Hung.:*** Dolargan; ***Israel:*** Dolestine; ***Philipp.:*** Demerol; ***Pol.:*** Dolargan; Dolcontral; ***Spain:*** Dolantina; ***Turk.:*** Aldolan; ***USA:*** Demerol; ***Venez.:*** Demerol†; Dispadol†.

Multi-ingredient: ***Austral.:*** Marcain with Pethidine†; ***UK:*** Pamergan P100.

Phenacetin *(rINN)*

Aceto-*p*-phenetidide; Acetophenetidin; Acetylphenetidin; Fenacetin; Fenacetina; Fenasetiini; Paracetophenetidin; Phénacétine; Phenacetinum. *p*-Acetophenetidide; 4′-Ethoxyacetanilide; *N*-(4-Ethoxyphenyl)acetamide.

Фенацетин

$C_{10}H_{13}NO_2$ = 179.2.
CAS — 62-44-2.
ATC — N02BE03.
ATC Vet — QN02BE03.

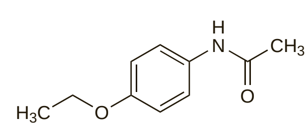

Adverse Effects and Precautions

Phenacetin may cause methaemoglobinaemia, sulfhaemoglobinaemia, and haemolytic anaemia.

Prolonged use of large doses of analgesic mixtures containing phenacetin has been associated with the development of renal papillary necrosis (see Effects on the Kidneys, p.98) and transitional-cell carcinoma of the renal pelvis.

Porphyria. Phenacetin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Uses and Administration

Phenacetin, a para-aminophenol derivative, has analgesic and antipyretic properties. It was usually given with aspirin, caffeine, or codeine but is now little used because of adverse haematological effects and nephrotoxicity.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Cz.:*** Dinyl†; Mironal†; ***Hung.:*** Antineuralgica; Dolor.

Phenazone *(BAN, rINN)*

Analgésine; Antipyrin; Antipyrine; Azophenum; Fenatsoni; Fenazon; Fenazona; Fenazonas; Phénazone; Phenazonum; Phenyldimethylpyrazolone. 1,5-Dimethyl-2-phenyl-4-pyrazolin-3-one.

Феназон

$C_{11}H_{12}N_2O$ = 188.2.
CAS — 60-80-0.
ATC — N02BB01.
ATC Vet — QN02BB01.

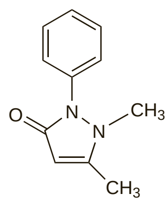

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Phenazone). White or almost white crystalline powder or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Antipyrine). Colourless crystals or white crystalline powder. Is odourless. Very soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether. Solutions are neutral to litmus. Store in airtight containers.

Phenazone and Caffeine Citrate

Antipyrino-Coffeinum Citricum; Fenazona y citrato de cafeína; Migrenin; Phenzone and Caffeine Citrate.

Феназон и Кофеина Цитрат

Description. Phenazone and caffeine citrate is a powder usually containing phenazone 90%, caffeine 9%, and citric acid monohydrate 1%.

Pharmacopoeias. In *Jpn*.

Phenazone Salicylate

Antipyrin Salicylate; Fenatsonisalisylaatti; Fenazona salicilato; Fenazonsalicylat; Phenazoni Salicylas; Salipyrin.

Феназона Салицилат

$C_{11}H_{12}N_2O,C_7H_6O_3$ = 326.3.
CAS — 520-07-0.

Pharmacopoeias. In *Fr.*

Adverse Effects and Precautions

Phenazone is liable to give rise to skin eruptions and in susceptible individuals even small doses may have this effect. Hypersensitivity reactions and nephrotoxicity have been reported. Large oral doses may cause nausea, drowsiness, coma, and convulsions.

Effects on the blood. Phenazone can cause haemolytic anaemia in certain individuals with a deficiency of G6PD.[1] Episodes of agranulocytosis were reported[2] in 6 women using a cream containing phenazone; all recovered on withdrawal.

1. Prankerd TAJ. Hemolytic effects of drugs and chemical agents. *Clin Pharmacol Ther* 1963; **4:** 334–50.
2. Delannoy A, Schmit J-C. Agranulocytosis after cutaneous contact with phenazone. *Eur J Haematol* 1993; **50:** 124.

Effects on the kidneys. Phenazone is considered nephrotoxic but only limited clinical information on phenazone is available because it has been mainly used with phenacetin.[1]

1. Prescott LF. Analgesic nephropathy: a reassessment of the role of phenacetin and other analgesics. *Drugs* 1982; **23:** 75–149.

Effects on the skin. In a summary[1] of 77 cases of fixed drug eruption phenazone derivatives were considered to be the causative agent in 9 of the 14 cases that were severe generalised reactions.

1. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.

Hypersensitivity. Immediate allergic reactions to phenazone have been reported.[1,2] In one patient leucopenia was detected 8 weeks later.[1]

1. Kadar D, Kalow W. Acute and latent leukopenic reaction to antipyrine. *Clin Pharmacol Ther* 1980; **28:** 820–22.
2. McCrea JB, *et al.* Allergic reaction to antipyrine, a marker of hepatic enzyme activity. *DICP Ann Pharmacother* 1989; **23:** 38–40.

Porphyria. Phenazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Phenazone affects the metabolism of some other drugs and its own metabolism is affected by other drugs that increase or reduce the activity of liver enzymes.

Pharmacokinetics

Phenazone is absorbed from the gastrointestinal tract and peak plasma concentrations are obtained within 1 to 2 hours of ingestion. It is distributed throughout the body fluids with concentrations in the saliva and breast milk reaching about the same levels as those in plasma. Less than 10% is bound to plasma proteins and it has an elimination half-life of about 12 hours. Phenazone is metabolised in the liver to 3 major metabolites 3-hydroxymethylphenazone, 4-hydroxyphenazone, and norphenazone. Phenazone, 3-hydroxymethylphenazone, and glucuronidated metabolites are all excreted in the urine. A small portion may be eliminated via the bile.

Uses and Administration

Phenazone is an NSAID (p.99) and has been given orally; phenazone and caffeine citrate and phenazone salicylate have similarly been given orally as analgesics.

Solutions containing about 5% of phenazone have been used topically as ear drops in disorders such as acute otitis media (but see below).

Phenazone is used as a test for the activity of drug-metabolising enzymes in the liver.

Diagnosis and testing. A review[1] of normal plasma-phenazone pharmacokinetics, urinary metabolite disposition, and total body clearances of phenazone in the presence of cirrhosis, fatty liver, hepatitis, and cholestatis.

1. St Peter JV, Awni WM. Quantifying hepatic function in the presence of liver disease with phenazone (antipyrine) and its metabolites. *Clin Pharmacokinet* 1991; **20:** 50–65.

Otitis media. There appears to be no justification[1] for the inclusion of phenazone in topical preparations used in treating acute otitis media (p.182). It is presumably included in such preparations because it is believed to have a local anti-inflammatory and, therefore, analgesic action. It would, however, seem unlikely that phenazone would have any action on the skin of the intact tympanic membrane and, therefore, on the pain which is due primarily to the stretching and distention of the membrane.

1. Carlin WV. Is there any justification for using phenazone in a local application prescribed for the treatment of acute otitis media? *BMJ* 1987; **294:** 1333.

Preparations

USP 31: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Erasol; ***Ger.:*** Aequiton-P†; Migrane-Kranit; Mono Migranin; ***Hong Kong:*** Tropex; ***Irl.:*** Tropex; ***Pol.:*** Antotalgin; ***S.Afr.:*** Aurone; Oto-Phen; ***Venez.:*** Otamina.

Multi-ingredient: ***Arg.:*** Aqua Lent Colirio; Bajumol†; Bideon; Cerosporin GS†; Clarisoft; Coliria; Cristalomicina; Irix; Kalopsis; Leroid†; Otalex G; Otocalmia Biotic; Otocerol; Otocuril; Otonorthia; Sincerum; Usualix; Vislus; ***Austral.:*** Auralgan; ***Austria:*** Asthma Efeum; Coffo Selt; Otalgan; Spalt†; ***Belg.:*** Hemorhinol; Otocalmine; Ouate Hemostatique; Tympalgine†; ***Braz.:*** Anestesiol†; Espasmalgon†; Osmotil†; Otovix†; ***Canad.:*** Auralgan; ***Cz.:*** Otipax; ***Denm.:*** Koffisal; ***Fr.:*** Brulex; HEC; Otipax; ***Ger.:*** Coffeemed N†; Migranin†; Otalgan; ***Hung.:*** Otipax; ***India:*** Tytin; ***Israel:*** Anaesthetic Ear Drops; Otidin; ***Ital.:*** Otalgan; Otomidone; Otopax; ***Neth.:*** Spalt N; ***Norw.:*** Antineuralgica; Fanalgin; ***NZ:*** Auralgan; Degest 2†; ***Philipp.:*** Auralgan; ***Port.:*** Otocalma†; Profrin-A†; ***Rus.:*** Otipax (Отипакс); ***S.Afr.:*** Auralyt; Aurasept; Aurone Forte; Covancaine; Ilvico; Otised; Oto-Phen Forte; Universal Earache Drops; ***Singapore:*** HEC†; Tropex; ***Spain:*** AB FE†; Epistaxol; Otalgan†; Otosedol; Pomada Heridas†; Quimpedor; Tabletas Quimpe; ***Swed.:*** Doleron†; Koffazon; ***Switz.:*** Otalgan; Otipax; Otosan; Otothricinol; Seranex sans codeine†; Spedralgin sans codeine†; ***Thai.:*** Auralgan†; ***USA:*** Allergen; Auralgan; Auroguard Otic; Auroto†; Cy-Gesic; Otocalm†; Tympagesic†; ***Venez.:*** Audocaina†; Otan; Otanol†; Otirilin; Otodon†; Otofrin†.

Phenazopyridine Hydrochloride

(BANM, USAN, rINNM)

Chloridrato de Fenazopiridina; Fenazopiridin Hidroklorür; Fenazopirydyny chlorowodorek; Hidrocloruro de fenazopiridina; NC-150; NSC-1879; Phénazopyridine, Chlorhydrate de; Phenazopyridini Hydrochloridum; W-1655. 3-Phenylazopyridine-2,6-diyldiamine hydrochloride.

Феназопиридина Гидрохлорид

$C_{11}H_{11}N_5$,HCl = 249.7.
CAS — 94-78-0 (phenazopyridine); 136-40-3 (phenazopyridine hydrochloride).
ATC — G04BX06.
ATC Vet — QG04BX06.

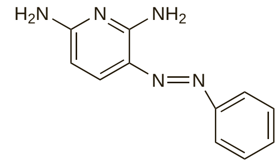

(phenazopyridine)

Pharmacopoeias. In *Pol.* and *US*.

USP 31 (Phenazopyridine Hydrochloride). A light or dark red to dark violet crystalline powder. Is odourless or with a slight odour. Soluble 1 in 300 of cold water, 1 in 20 of boiling water, 1 in 59 of alcohol, 1 in 331 of chloroform, and 1 in 100 of glycerol; very slightly soluble in ether. Store in airtight containers.

Removal of stains. Phenazopyridine stains may be removed from fabric by soaking in a 0.25% solution of sodium dithionite.

Adverse Effects

Phenazopyridine hydrochloride has caused gastrointestinal adverse effects, headache, and rashes. Hepatotoxicity, haemolytic anaemia, methaemoglobinaemia, and acute renal failure have also been reported, generally associated with overdosage or with therapeutic doses in patients with renal impairment. Crystal deposits of phenazopyridine have formed in the urinary tract.

Abnormal coloration of body tissues or fluids may occur. Urine is tinged either orange or red and underclothes are apt to be stained.

Effects on the CNS. A case of aseptic meningitis, with distinct episodes of fever and confusion, was associated with the use of phenazopyridine.[1]

1. Herlihy TE. Phenazopyridine and aseptic meningitis. *Ann Intern Med* 1987; **106:** 172–3.

Overdosage. Report of a 2-year-old child who developed cyanosis and methaemoglobinaemia after ingesting at most three 200-mg tablets of phenazopyridine hydrochloride.[1]

1. Gold NA, Bithoney WG. Methemoglobinemia due to ingestion of at most three pills of pyridium in a 2-year-old: case report and review. *J Emerg Med* 2003; **25:** 143–8.

Precautions

Phenazopyridine hydrochloride is contra-indicated in patients with renal impairment or severe hepatitis and should be used with caution in those with G6PD deficiency. Treatment should be stopped if the skin or sclerae become discoloured; this may indicate accumulation as a result of impaired renal excretion. Phenazopyridine may interfere with urinalysis based on colour reactions or spectrometry.

Staining of contact lenses may occur.

Pharmacokinetics

Phenazopyridine hydrochloride is absorbed from the gastrointestinal tract. It is excreted mainly in the urine; up to 65% may be excreted as unchanged phenazopyridine and 18% as paracetamol.

Uses and Administration

Phenazopyridine is an azo dye that exerts an analgesic effect on the mucosa of the urinary tract and is used to provide symptomatic relief of pain and irritability in conditions such as cystitis and prostatitis (see p.2178 and p.2181, respectively), and urethritis (p.199). Phenazopyridine hydrochloride has been given in usual oral doses of about 200 mg three times daily after food. If given with an antibacterial for the treatment of urinary-tract infections (p.199), treatment should usually not exceed 2 days, although lower doses have been given as part of a combined preparation for at least a week.

Urinary-tract infections. There is currently no well-substantiated role for phenazopyridine in the treatment of urinary-tract infections and its adverse effects are potentially serious.[1]

1. Zelenitsky SA, Zhanel GG. Phenazopyridine in urinary tract infections. *Ann Pharmacother* 1996; **30:** 866–8.

Preparations

USP 31: Phenazopyridine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cistalgina; ***Belg.:*** Uropyrine; ***Braz.:*** Pyridium; Pyrisept; Urologin; Urotril†; ***Canad.:*** Phenazo; Pyridium†; ***Chile:*** Nazamit; Nordox; Pyridium†; ***Hong Kong:*** CP-Pyridine; Phenadine; Pyridium; ***India:*** Pyridium; ***Indon.:*** Pyridium; Urogetix; ***Israel:*** Sedural; ***Mex.:*** Alvena; Azofur; Bioferina; Pirimir; Urezol; ***Philipp.:*** Azomir; ***Pol.:*** Nefrecil; ***S.Afr.:*** Pyridium; ***Singapore:*** Urogesic; ***Thai.:*** Ammilazo; Anazo; Phendiridine; Sumedium; ***USA:*** Azo-Standard; Baridium; Prodium; Pyridiate†; Pyridium; Re-Azo; Urogesic; ***Venez.:*** Pyridium†.

Multi-ingredient: ***Arg.:*** Bacti-Uril; Nor 2; Priper Plus; Uro-Bactrim†; Urotem Dol; ***Braz.:*** Minazol; Uro-Baxapril†; Urobiotic†; Uroctrin; Urofen†; Uropac; Uropielon; ***Chile:*** Uro-Micinovo; ***Ger.:*** Urospasmon†; ***India:*** Nephrogesic; ***Mex.:*** Azo-Uronalin; Azo-Wintomylon; Azogen; Mictasol; Nalixone; Naxilan-Plus; Pirifur; Urovec; Vodelan; ***Spain:*** Micturol Sedante; ***Turk.:*** Azo Gantrisin; Azosilin; Uriseptin; ***USA:*** Phenazopyridine Plus; Pyridium Plus; Trellium Plus; Urelief Plus; Urobiotic-250; ***Venez.:*** Azo-Mandelamine; Bacteval.

Phenylbutazone *(BAN, rINN)*

Butadione; Fenilbutazon; Fenilbutazona; Fenilbutazonas; Fenylbutazon; Fenylobutazon; Fenyylibutatsoni; Phénylbutazone; Phenylbutazonum. 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione.

Фенилбутазон

$C_{19}H_{20}N_2O_2$ = 308.4.
CAS — 50-33-9 (phenylbutazone); 129-18-0 (phenylbutazone sodium); 4985-25-5 (phenylbutazone piperazine).
ATC — M01AA01; M02AA01.
ATC Vet — QM01AA01; QM02AA01.

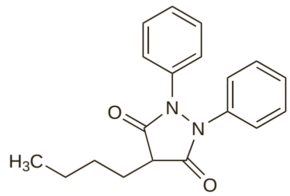

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Phenylbutazone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; it dissolves in alkaline solutions. Protect from light.
USP 31 (Phenylbutazone). A white to off-white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone and in ether. Store in airtight containers.

Profile

Phenylbutazone, a pyrazolone derivative, is an NSAID (p.96). However, because of its toxicity and in particular its adverse haematological reactions (see Effects on the Blood, below), it is not used as a general analgesic or antipyretic. Although phenylbutazone is effective in almost all musculoskeletal and joint disorders including ankylosing spondylitis, acute gout, osteoarthritis, and rheumatoid arthritis, it should only be used in acute conditions where less toxic drugs have failed. Initial oral doses of up to 600 mg daily in divided doses have been used in the treatment of rheumatic disorders although up to 800 mg daily may be required in acute gout. After 1 to 3 days, the dose should be reduced to the minimum effective amount, which may be as little as 200 mg daily; treatment should be given for the shortest period possible, up to a usual maximum of 1 week. Reduced doses are recommended in elderly patients.

In some countries phenylbutazone has also been given as a rectal suppository and applied topically for musculoskeletal pain and in soft-tissue injury. It has also been given intramuscularly as the sodium salt. Other salts of phenylbutazone that have been used in musculoskeletal, joint, and soft-tissue disorders include the calcium, megallate, and piperazine salts.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given phenylbutazone, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, when phenylbutazone had been available in the UK the *BNF* had advised that phenylbutazone should be avoided during breast feeding as small amounts are distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Both phenylbutazone[1-3] and oxyphenbutazone[1,3] are well known for their adverse effects on the blood and especially for fatal agranulocytosis and aplastic anaemia. Leucopenia, pancytopenia, haemolytic anaemia, and thrombocytopenia may also occur. The UK CSM[4] noted that between July 1963 and January 1993 it had received 74 reports of agranulocytosis (39 fatal) associated with phenylbutazone and 40 reports of neutropenia (4 fatal). Up-to-date figures were not provided on oxyphenbutazone, but it is considered to be more toxic to the bone marrow than phenylbutazone.[1]

1. Anonymous. Phenylbutazone and oxyphenbutazone: time to call a halt. *Drug Ther Bull* 1984; **22:** 5–6.
2. Böttiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *BMJ* 1973; **3:** 339–43.
3. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
4. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)

Porphyria. Phenylbutazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Butazolidin; ***Braz.:*** Butazolidina; Butazolon†; Butazona; Butazonil†; Neo Butazol; Peralgin†; ***Fr.:*** Butazolidine†; ***Ger.:*** Ambene; exrheudon OPT; ***Indon.:*** Akrofen; Berlizon; Irgapan; ***Ital.:*** Kadol; ***Mex.:*** Astrofen; Bloken; Bresal; Butalen; Butazolidina; Delbulasa†; Fezona†; Lorfenil†; Meprosona-F; Rudesol†; ***Neth.:*** Butazolidin; ***Pol.:*** Butapirazol; ***Port.:*** Basireuma†; ***Rus.:*** Butadion (Бутадион); ***S.Afr.:*** Inflazone; ***Spain:*** Butazolidina; ***Switz.:*** Butadion; ***Thai.:*** Buta†; Neo-Pyrazol; ***Venez.:*** Promifen†; Ticinil.

Multi-ingredient: ***Austria:*** Ambene; Ambene N; ***Braz.:*** Butazil†; Dorend†; Mioflex; Reumat†; Reumix†; ***Chile:*** Balsamo Analgesico con Fenilbutazona; ***Fr.:*** Dextrarine Phenylbutazone; ***Ger.:*** Ambene Comp†; ***Hung.:*** Rheosolon; ***Indon.:*** Butamidon; Cetapyrin; Enkapyrin; New Skelan; ***Mex.:*** Butayonacol; Butisel; Dexadutil; Dibutasona; Vengesic†; Zolidime†; ***Rus.:*** Ambene (Амбене); ***Spain:*** Artrodesmol Extra; Doctofril Antiinflamat; ***Switz.:*** Butaparin; Hepabuzone; ***Thai.:*** Alaxan; Asialax; Buta Pee Dee†; Butarion; Myophen; Trabit†.

Piketoprofen *(rINN)*

Pikétoprofène; Piketoprofeno; Piketoprofenum. *m*-Benzoyl-*N*-(4-methyl-2-pyridyl)hydratropamide.

Пикетопрофен

$C_{22}H_{20}N_2O_2$ = 344.4.
CAS — 60576-13-8.

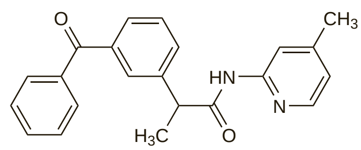

Profile

Piketoprofen is an NSAID (p.96) that has been used topically as the hydrochloride in concentrations of about 2% in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Picalm; Zemalex; ***Spain:*** Calmatel; Triparsean.

Piritramide *(BAN, rINN)*

Pirinitramide; Piritramid; Piritramida; Piritramidi; Piritramidum; R-3365. 1-(3-Cyano-3,3-diphenylpropyl)-4-piperidinopiperidine-4-carboxamide.

Пиритрамид

$C_{27}H_{34}N_4O$ = 430.6.
CAS — 302-41-0.
ATC — N02AC03.
ATC Vet — QN02AC03.

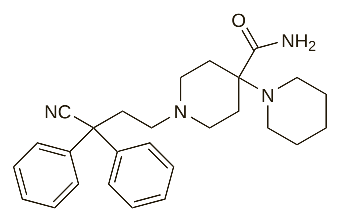

Profile

Piritramide is an opioid analgesic (p.101).

It is used for the management of severe pain including postoperative pain, for premedication, and to provide analgesia during anaesthesia. It is given by intramuscular, subcutaneous, or slow intravenous injection as the tartrate in doses equivalent of up to about 30 mg of the base.

◊ Reviews.

1. Kumar N, Rowbotham DJ. Piritramide. *Br J Anaesth* 1999; **82:** 3–5.

Porphyria. Piritramide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Dipidolor; ***Belg.:*** Dipidolor; ***Cz.:*** Dipidolor; ***Ger.:*** Dipidolor; ***Neth.:*** Dipidolor.

Piroxicam *(BAN, USAN, rINN)*

CP-16171; Piroksikaami; Piroksikam; Piroksikamas; Piroxicamum; Piroxikám; Piroxikam. 4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Пироксикам

$C_{15}H_{13}N_3O_4S$ = 331.3.
CAS — 36322-90-4.
ATC — M01AC01; M02AA07; S01BC06.
ATC Vet — QM01AC01; QM02AA07; QS01BC06.

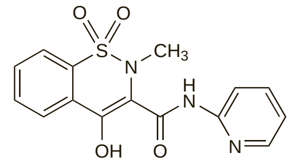

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Piroxicam). A white or slightly yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.
USP 31 (Piroxicam). An off-white to light tan or light yellow, odourless powder. It forms a monohydrate that is yellow. Very slightly soluble in water, in dilute acids, and in most organic solvents; slightly soluble in alcohol and in aqueous alkaline solutions. Store in airtight containers. Protect from light.

Piroxicam Betadex *(USAN, rINNM)*

CHF-1194; Piroxicam Beta Cyclodextrin; Piroxicam Beta Cyclodextrin Complex; Piroxicam Bétadex; Piroxicamum Betadexum.

Пироксикам Бетадекс

$(C_{15}H_{13}N_3O_4S)_2,(C_{42}H_{70}O_{35})_5$ = 6337.6.
CAS — 96684-40-1.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Local irritation and occasionally bleeding may occur with piroxicam suppositories and there may be pain and occasionally tissue damage at the injection site on intramuscular use. Application site reactions have also occurred with topical preparations of piroxicam.

Piroxicam is considered to be associated with an intermediate risk of gastrointestinal effects although there is some suggestion that the risk may be higher than for other intermediate-risk NSAIDs (p.97).

◊ A report[1] of the adverse reactions associated with piroxicam in South Africa during 1981-86 included two reactions, paraesthesia and hair loss, not previously recorded in the literature.

1. Gerber D. Adverse reactions of piroxicam. *Drug Intell Clin Pharm* 1987; **21:** 707–10.

Effects on the blood. Decreases in haemoglobin and haematocrit not associated with obvious gastrointestinal bleeding, have occurred in patients taking piroxicam. Thrombocytopenia, thrombocytopenic purpura,[1] and aplastic anaemia[2] have been described in patients on piroxicam.

1. Bjørnstad H, Vik Ø. Thrombocytopenic purpura associated with piroxicam. *Br J Clin Pract* 1986; **40:** 42.
2. Lee SH, *et al.* Aplastic anaemia associated with piroxicam. *Lancet* 1982; **i:** 1186.

Effects on electrolytes. Reversible hyperkalaemic hyperchloraemic acidosis has been reported[1,2] in patients receiving piroxicam. Severe hyponatraemia and symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion have also been associated with piroxicam.[3]

See also Effects on the Kidneys, below.

1. Grossman LA, Moss S. Piroxicam and hyperkalemic acidosis. *Ann Intern Med* 1983; **99:** 282.
2. Miller KP, *et al.* Severe hyperkalemia during piroxicam therapy. *Arch Intern Med* 1984; **144:** 2414–15.
3. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.

Effects on the kidneys. Acute nephropathy with characteristic features of Henoch-Schönlein purpura,[1] acute renal failure,[2] uraemia with hyperkalaemia, and acute interstitial nephritis[3] have been associated with systemic use of piroxicam. Nephrotic syndrome and interstitial nephritis have followed topical use of piroxicam gel.[4]

1. Goebel KM, Mueller-Brodmann W. Reversible overt nephropathy with Henoch-Schönlein purpura due to piroxicam. *BMJ* 1982; **284:** 311–12.
2. Frais MA, *et al.* Piroxicam-induced renal failure and hyperkalemia. *Ann Intern Med* 1983; **99:** 129–30.
3. Mitnick PD, Klein WJ. Piroxicam-induced renal disease. *Arch Intern Med* 1984; **144:** 63–4.
4. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.

Effects on the liver. Necrosis of the liver, sometimes fatal, has been associated with piroxicam.[1,2]

1. Lee SM, *et al.* Subacute hepatic necrosis induced by piroxicam. *BMJ* 1986; **293:** 540–1.
2. Paterson D, *et al.* Piroxicam induced submassive necrosis of the liver. *Gut* 1992; **33;** 1436–8.

Effects on the skin. As with other NSAIDs, rash has occurred in patients taking piroxicam. Phototoxic reactions have been described.[1] Serious skin reactions attributed to piroxicam therapy include toxic epidermal necrolysis,[2] pemphigus vulgaris,[3] erythema multiforme,[4] and Stevens-Johnson syndrome.[5] Fixed drug eruptions have also been reported.[6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see below).

1. Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; **309:** 186–7.
2. Chosidow O, *et al.* Intestinal involvement in drug-induced toxic epidermal necrolysis. *Lancet* 1991; **337:** 928.
3. Martin RL, *et al.* Fatal pemphigus vulgaris in a patient taking piroxicam. *N Engl J Med* 1983; **309:** 795–6.
4. Prieto A, *et al.* Piroxicam-induced erythema multiforme. *Contact Dermatitis* 2004; **50:** 263.
5. Katoh N, *et al.* Piroxicam induced Stevens-Johnson syndrome. *J Dermatol* 1995; **22:** 677–80.
6. Cuerda Galindo E, *et al.* Fixed drug eruption from piroxicam. *J Eur Acad Dermatol Venereol* 2004; **18:** 586–7.

Overdosage. Details of 16 patients who were considered to have taken an overdosage of piroxicam alone were reported[1] to the National Poisons Information Service of the UK. Thirteen patients (including 5 children) had no symptoms after doses estimated to be up to 300 to 400 mg; 2 patients complained of dizziness and blurred vision after 200 to 300 mg; the last patient, who claimed to have taken 600 mg presented in coma, regained consciousness within one hour, and had recovered fully within 24 hours. Severe multisystem toxicity has been reported in a 2-year-old child after ingestion of 100 mg of piroxicam.[2]

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. MacDougall LG, *et al.* Piroxicam poisoning in a 2-year-old child: a case report. *S Afr Med J* 1984; **66:** 31–3.

Pancreatitis. Pancreatitis has been associated with piroxicam use.[1,2]

1. Haye OL. Piroxicam and pancreatitis. *Ann Intern Med* 1986; **104:** 895.
2. Heluwaert F, *et al.* Pancréatite aiguë au piroxicam. *Gastroenterol Clin Biol* 2006; **30:** 635–6.

Precautions

As for NSAIDs in general, p.98.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given piroxicam, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount excreted into breast milk to be too small to be harmful to a breast-fed infant.

Piroxicam appears in breast milk in concentrations of about 1% of those in the maternal plasma.[2] Similar data are also included in the licensed product information although it does not recommend piroxicam use during breast feeding as clinical safety has not been established.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Østensen M. Piroxicam in human breast milk. *Eur J Clin Pharmacol* 1983; **25:** 829–30.

Porphyria. Piroxicam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with NSAIDs, see p.99.

Use of aspirin with piroxicam results in decreased plasma concentrations of piroxicam to about 80% of normal. The UK licensed product information for ritonavir suggests that use of piroxicam with ritonavir may result in increased plasma concentrations of piroxicam and an increased risk of toxicity; it recommends that use together should be avoided.

Pharmacokinetics

Piroxicam is well absorbed from the gastrointestinal tract; peak plasma concentrations are reached 3 to 5 hours after an oral dose. Piroxicam is more rapidly absorbed after intramuscular use; it is also absorbed to some degree after topical application. Piroxicam is 99% bound to plasma proteins. It has been detected in breast milk. Piroxicam has a long plasma elimination half-life of about 50 hours. Because of this, steady-state concentrations are not reached for 7 to 12 days. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and excreted mainly in the urine with smaller amounts in the faeces. Enterohepatic recycling occurs. Less than 5% of the dose is excreted unchanged in the urine and faeces.

Piroxicam betadex dissociates in the gastrointestinal tract to its components piroxicam and betadex (p.2291). Piroxicam absorption from piroxicam betadex is more rapid than that of unmodified piroxicam; peak plasma concentrations of piroxicam are reached 30 to 60 minutes after an oral dose. Betadex is not absorbed but is metabolised in the colon to various sugars.

◊ References.

1. Richardson CJ, *et al.* Piroxicam and 5′-hydroxypiroxicam kinetics following multiple dose administration of piroxicam. *Eur J Clin Pharmacol* 1987; **32:** 89–91.
2. Mäkelä A-L, *et al.* Steady state pharmacokinetics of piroxicam in children with rheumatic diseases. *Eur J Clin Pharmacol* 1991; **41:** 79–81 (higher clearance and shorter half-life in children).
3. Rudy AC, *et al.* The pharmacokinetics of piroxicam in elderly persons with and without renal impairment. *Br J Clin Pharmacol* 1994; **37:** 1–5.
4. Deroubaix X, *et al.* Oral bioavailability of CHF1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy subjects under single dose and steady-state conditions. *Eur J Clin Pharmacol* 1995; **47:** 531–6.
5. Karim A, *et al.* Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; **37:** 267–78.
6. Wang D, *et al.* Comparative population pharmacokinetic-pharmacodynamic analysis for piroxicam-β-cyclodextrin and piroxicam. *J Clin Pharmacol* 2000; **40:** 1257–66.

Uses and Administration

Piroxicam, an oxicam derivative, and piroxicam betadex are NSAIDs (p.99). Piroxicam betadex may have a more rapid onset of therapeutic effect due to its enhanced solubility (see Pharmacokinetics above). Both have been used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis including juvenile idiopathic arthritis, in soft-tissue disorders, in acute gout, and in postoperative pain but systemic usage in the EU is now restricted (see below) to chronic painful and inflammatory conditions.

In rheumatic disorders a usual initial oral dose of *piroxicam* is 20 mg daily as a single dose. Daily maintenance doses may vary between 10 and 30 mg given in single or divided doses; use of doses in excess of 20 mg daily for more than a few days is associated with an increased risk of gastrointestinal adverse effects. Piroxicam has been given in similar doses as a rectal suppository or on a short-term basis by intramuscular injection.

For dosage in children, see below.

Piroxicam is also used in the local treatment of a variety of painful or inflammatory conditions as a topical gel in a concentration of 0.5% applied three or four times daily; treatment should be reviewed after 4 weeks. A 1% gel is also available. Piroxicam has been used in some countries as a 0.5 or 1% cream and as eye drops in a concentration of 0.5%.

Doses of piroxicam betadex are expressed in terms of the equivalent amount of piroxicam. Piroxicam betadex 191.3 mg is equivalent to about 20 mg of piroxicam. In rheumatic and acute musculoskeletal disorders *piroxicam betadex* is given in an oral dose equivalent to 20 mg of piroxicam daily as a single dose. This dose may be reduced to 10 mg daily in elderly patients.

Other salts or compounds that have also been used include piroxicam cinnamate (cinnoxicam), piroxicam choline, and piroxicam pivalate.

◊ Reviews.

1. Lee CR, Balfour JA. Piroxicam-β-cyclodextrin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in rheumatic diseases and pain states. *Drugs* 1994; **48:** 907–29.
2. Moore A, *et al.* Single dose piroxicam for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 29/08/08).

◊ Following a review[1] of the benefit-risk balance for piroxicam the EMEA placed restrictions on its systemic use and stated that:

- *its use in acute painful and inflammatory conditions should be abandoned*
- *its use should be limited only to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis*
- *it should not be used as a first-line treatment*
- *the dose should be limited to 20 mg daily*
- *treatment should be reviewed within 14 days of starting*
- *it should only be started by doctors experienced in treating chronic painful and inflammatory conditions*
- *use with a gastroprotective drug should be considered*
- *it should not be given to patients at risk of gastrointestinal disorders associated with bleeding or to those who have had skin reactions to other drugs*
- *it should not be used with another NSAID or an anticoagulant*

1. EMEA. Questions and answers on the review of piroxicam (issued 21st June, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/piroxicam_26457807en.pdf (accessed 08/11/07)

Administration in children. In the UK, piroxicam may be used in children aged 6 years or over with juvenile idiopathic arthritis (p.10). The usual oral dose is:

- less than 15 kg: 5 mg once daily
- 16 to 25 kg: 10 mg once daily
- 26 to 45 kg: 15 mg once daily
- 46 kg or over: 20 mg once daily

UK licensed product information states that only the dispersible tablets are recommended for use in children.

Preparations

BP 2008: Piroxicam Capsules; Piroxicam Gel;
USP 31: Piroxicam Capsules; Piroxicam Cream.

Proprietary Preparations (details are given in Part 3)

Arg.: Axis†; Benisan; Brionot; Calmapir†; Fabopxicam; Feldene†; Flogosine; Homocalmefyba; Ketazon†; Maxtol; Micar; Nac; Nalgesic; Osteocalmine; Piroalgin; Pirofix†; Roxicam†; Sindrolen†; Solocalm; Tirovel; Tricifa†; Trixicam; Truxa R†; Truxa†; Vefren†; Velaned†; ***Austral.:*** Candyl†; Feldene; Mobilis; Pirohexal-D; Rosig†; ***Austria:*** Brexidol; Brexin; Felden; Pirocal; Pirocam; Pirorheum; Pirox; Piroxistad; Tonimed; ***Belg.:*** Brexine; Docpiroxi; Feldene; Piromed; Piroxitop; Piroxymed; Polydene; Solicam; ***Braz.:*** Anartrit†; Anflene; Brexin; Cicladol; Farmoxicam†; Feldanax; Feldene; Feldox†; Feldran†; Flamostat; Flogene; Flogoxen†; Floxicam; Inflamene; Inflanan; Inflanox†; Inflax; Lisedema†; Pirogreen; Piroxam†; Piroxene; Piroxifar; Piroxifen†; Piroxiflam†; Piroxil; Piroxin; Piroxinid; Piroxiplus†; Prodoxidil; ***Canad.:*** Brexidol†; Feldene†; Fexicam†; Novo-Pirocam; Nu-Pirox; ***Chile:*** Fabudol; Feldene; Foldox; Notagol†; Pemar; Pricam; Sinartrol†; ***Cz.:*** Arthremin†; Feldene†; Flamexin; Hotemin; Piroflam†; Pirox†; Pro-Roxikam†; Reumador†; ***Denm.:*** Brexidol†; Felden; Pirom; Piroxigea†; ***Fin.:*** Brexidol†; Felden; Piroxal; Piroxin; ***Fr.:*** Brexin; Cycladol; Feldene; Geldene; Inflaced; Proxalyoc; Zofora†; ***Ger.:*** Brexidol; clinit; durapirox†; Felden; Flexase; Jenapirox; Mobilat Akut Piroxicam; Piro; Piro KD; Piro-Phlogont†; Pirobeta; Piroflam; Piroflex†; Pirorheum†; PirorheumA; Pirox; Pra-Brexidol†; ratioMobil†; Rheumitin†; ***Gr.:*** Bleduran; Brexin; Conzila; Feldene; Flodeneu; Neo Axedil; Painrelipt-D; Pedifan; Proponol; Rheumaplus†; Ruvamed; Sinartrol; Valopon†; Zerospasm; Zitumex; ***Hong Kong:*** CP-Pirox; Feldene; Felxicam†; Flamatrol†; Hotemin†; Piroxica; Piroxy†; Sefdene; Sotilen†; Synoxicam; Vidapirocam; ***Hung.:*** Brexin; Erazon†; Feldene; Flamexin; Hotemin; Huma-Pirocam; Pirorheum; ***India:*** Brexic-DT; Dolokam; Dolonex; Mobicam DT; Movon; Pirox; Suganril; ***Indon.:*** Faxiden; Felcam; Feldene; Infeld; Kifadene; Lanareuma; Licofel; Maxicam; Pirocam; Pirodene; Pirofel; Rexicam; Rexil; Rosic; Roxidene; Scandene; Sofden; Tropidene; ***Irl.:*** Feldene; Pericam; ***Israel:*** Exipan; Feldene; ***Ital.:*** Algoxam; Antiflog; Artroxicam; Brexin; Brexivel; Bruxicam; Cicladol; Ciclafast†; Clevian; Dexicam; Errekam; Euroxi; Feldene; Flodol; Ipsoflog; Lampoflex; Oxicam†; Piroftal; Polipirox; Reucam†; Reudene†; Reumagil; Riacen†; Roxene; Roxenil; Roxiden; Sinartrol; Spirox; Zelis; ***Jpn:*** Baxo; ***Malaysia:*** Brexin; Feldene; Felxicam†; Focam†; Rhumagel; Roxitan†; Uphaxicam; ***Mex.:*** Ainek†; Androxicam; Apopiran†; Arlexicam; Artinor†; Artyflam; Asabon; Axtrim; Bapixied; Bioximil; Brexicam; Brexodin; Brucam; Campirex; Citoken T†; Dixonal; Dolzycam; Edecam; Facicam; Farmicam†; Feldene; Flogosan†; Glandicin; Osteral; Oxi-Reul; Oxicanol; Pirodax; Pirox; Piroxan; R-Tyflam; Reucam; Reutricam; Ripox; Serpicam; Tripirol; Vatrem; ***Neth.:*** Brexine; ***Norw.:*** Brexidol; Felden; Pirox; ***NZ:*** Candyl; Piram-D; Pirohexal-D; ***Philipp.:*** Feldene; Flaxine; Macroxam; Neperlan; Parixam; Pirostad; Proximax; Raxicam; ***Pol.:*** Feldene; Flamexin; Hotemin; ***Port.:*** Brexin; Feldene; Flexar; Flogocan; Remisil; Reumoxican; Roxazin; ***Rus.:*** Erazon (Эразон); Finalgel (Финалгель); ***S.Afr.:*** Brexecam; Feldene†; Pixicam; Pyrocaps; Rheugesic; Xycam; ***Singapore:*** Brexin†; Capxidin†; Feldene; Rosiden; Sefdene; Vitaxicam; ***Spain:*** Artragil†; Brexinil; Cycladol; Doblexan; Feldegel; Feldene; Improntal; Salvacam; Sasulen; Vitaxicam; ***Swed.:*** Brexidol; Felden†; ***Switz.:*** Brexidol†; Felden; Pirocam; Pirosol; pirox-basan†; ***Thai.:*** Ammidene; Bicam†; Brexin; Felcam; Feldene; Felrox; Flamic; Ifemed; Manoxicam; Maswin; Moxicam; Neogel; Neotica†; PC-20; Piram; Pirax; Pirox; Piroxam†; Piroxcin; Piroxen; Piroxsil; Polyxicam; Posedene; Pyroxy†; Roccaxin†; Roxifen; Roxium; Roxycam; Rumadene; Rumaxicam; Sotilen; Xicam; ***Turk.:*** Cycladol; Felden; Inflamex; Oksikam; ***UK:*** Brexidol; Feldene; ***USA:*** Feldene; ***Venez.:*** Biopirox†; Ciclofast†; Feldene; Feldenedi; Flamalit; Lepexal†; Maxipiro; Pirocam†; Piromax†; Piroval†; Pixorid.

Multi-ingredient: ***Arg.:*** Algio-Truxa†; Buta Rut B12; Calmapir-P†; Flexicamin; Flexicamin A; Flexicamin B12; Flexicamin Crema†; Flogiatrin; Flogiatrin B12; Ketazon Flex†; Peganix; Rumisedan; Rumisedan Fuerte†; Sindrolen Vitaminado†; Sindrolen†; Solocalm Plus; Solocalm-B; Solocalm-Flex; ***Indon.:*** Counterpain-PXM; ***Thai.:*** Counterpain Plus.

Pranoprofen *(rINN)*

Pranoprofène; Pranoprofeno; Pranoprofenum. α-Methyl-5*H*-[1]-benzopyrano[2,3-*b*]pyridine-7-acetic acid.

Пранопрофен

$C_{15}H_{13}NO_3$ = 255.3.
CAS — 52549-17-4.
ATC — S01BC09.
ATC Vet — QS01BC09.

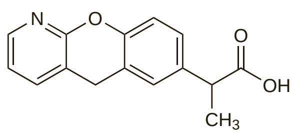

Pharmacopoeias. In *Jpn.*

Profile

Pranoprofen, a propionic acid derivative, is an NSAID (p.96). It is used as eye drops in a concentration of 0.1% for ocular inflammation. Pranoprofen has also been given orally for the treatment of pain, inflammation, and fever.

◊ References.

1. Notivol R, *et al.* Treatment of chronic nonbacterial conjunctivitis with a cyclo-oxygenase inhibitor or a corticosteroid. *Am J Ophthalmol* 1994; **117:** 651–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Pranox; ***Braz.:*** Difen; ***Gr.:*** Pranofen; ***Ital.:*** Oftalar; Pranoflog; ***Jpn:*** Niflan; ***Port.:*** Oftalar; ***Spain:*** Oftalar; ***Turk.:*** Oftalar.

Proglumetacin Maleate *(BANM, rINNM)*

CR-604; Maleato de proglumetacina; Proglumétacine, Maléate de; Proglumetacinum Maleas; Protacine Maleate. 3-{4-[2-(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-ylacetoxy)ethyl]piperazin-1-yl}propyl 4-benzamido-*N*,*N*-dipropylglutaramate dimaleate.

Проглуметацина Малеат

$C_{46}H_{58}ClN_5O_8,2C_4H_4O_4$ = 1076.6.
CAS — 57132-53-3 (proglumetacin); 59209-40-4 (proglumetacin maleate).
ATC — M01AB14.
ATC Vet — QM01AB14.

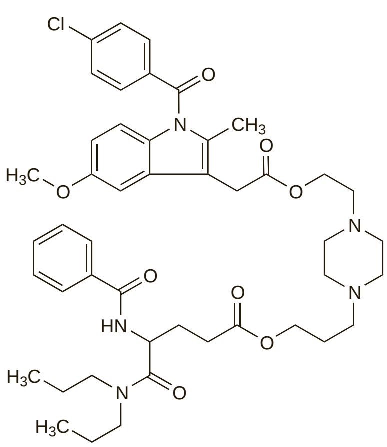

(proglumetacin)

Profile

Proglumetacin maleate, an indoleacetic acid derivative related to indometacin (p.66), is an NSAID (p.96). It has been used in musculoskeletal and joint disorders in oral doses of up to 600 mg daily, in divided doses. Proglumetacin maleate has also been given as rectal suppositories and topically as a 5% cream.

◊ References.

1. Appelboom T, Franchimont P. Proglumetacin versus indometacin in rheumatoid arthritis: a double-blind multicenter study. *Adv Therapy* 1994; **11:** 228–34.
2. Martens M. Double-blind randomized comparison of proglumetacin and naproxen sodium in the treatment of patients with ankle sprains. *Curr Ther Res* 1995; **56:** 639–48.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alaidol†; Bruxel; ***Belg.:*** Tolindol; ***Chile:*** Afloxan†; ***Ger.:*** Protaxon; ***Hong Kong:*** Afloxan; ***Ital.:*** Afloxan; Proxil; ***Jpn:*** Miridacin; ***Philipp.:*** Afloxan; ***Port.:*** Protaxil; ***Spain:*** Prodamox; ***Thai.:*** Afloxan.

Propacetamol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propacetamol; Propacétamol, chlorhydrate de; Propacetamol-hidroklorid; Propacetamol-hydrochlorid; Propacetamolhydroklorid; Propacetamoli hydrochloridum; Propacetamolio hidrochloridas; Propasetamolihydrokloridi. The hydrochloride of *N*,*N*-diethylglycine ester with paracetamol; 4-Acetamidophenyl diethylaminoacetate hydrochloride.

Пропацетамола Гидрохлорид

$C_{14}H_{20}N_2O_3$,HCl = 300.8.
CAS — 66532-85-2 (propacetamol).
ATC — N02BE05.
ATC Vet — QN02BE05.

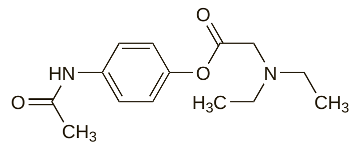

(propacetamol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Propacetamol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. Protect from moisture.

Profile

Propacetamol hydrochloride, a para-aminophenol derivative, is hydrolysed to paracetamol (p.108) in the plasma. It has been given intramuscularly or intravenously in usual doses of 1 to 2 g every 4 hours up to 4 times daily if necessary, to a maximum dose of 8 g daily, for the treatment of pain (see Choice of Analgesic, p.2) and fever (p.10). For doses in children, see below.

Administration in children. In some countries propacetamol is used intravenously in the treatment of pain and fever in neonates and children.[1,2] Doses range from 20 to 30 mg/kg given over 15 minutes up to 4 times daily, not exceeding a maximum daily dose of 120 mg/kg propacetamol (equivalent to a daily dose of 60 mg/kg of paracetamol).

1. Allegaert K, *et al.* Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F25–F28.
2. Walson PD, *et al.* Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28:** 762–9.

Adverse effects. Occupational contact dermatitis has been reported in healthcare professionals after preparing injections of propacetamol.[1-3]

Propacetamol is the hydrochloride of *N*,*N*-diethylglycine ester with paracetamol and the results of a study[4] have suggested that allergic reactions to propacetamol are related to sensitisation to the activated ester rather than to paracetamol itself.

1. Barbaud A, *et al.* Occupational allergy to propacetamol. *Lancet* 1995; **346:** 902.
2. Szczurko C, *et al.* Occupational contact dermatitis from propacetamol. *Contact Dermatitis* 1996; **35:** 299–301.
3. Gielen K, *et al.* Occupational allergic contact dermatitis from drugs in healthcare workers *Contact Dermatitis* 2001; **45:** 273–9.
4. Berl V, *et al.* Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated *N*,*N*-diethylglycine. *Contact Dermatitis* 1998; **38:** 185–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Pro-Dafalgan†; ***Denm.:*** Pro-Dafalgan†; ***Fin.:*** Pro-Dafalgan†; ***Gr.:*** Pro-Dafalgan; Pro-depon†; ***Israel:*** Pro-Dafalgan†; ***Ital.:*** Pro-Efferalgan†; ***Mex.:*** Tempra†; ***Norw.:*** Pro-Dafalgan; ***Port.:*** Pro-Dafalgan†; ***Spain:*** Pro-Efferalgan†; ***Swed.:*** Pro-Dafalgan†; ***Switz.:*** Pro-Dafalgan†.

Propyl Nicotinate

Nicotinato de propilo.

$C_9H_{11}NO_2$ = 165.2.
CAS — 7681-15-4.

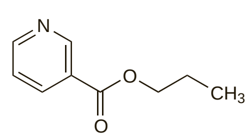

Profile

Propyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Elacur; Nicodan†.

Propyphenazone *(BAN, rINN)*

Isopropylantipyrine; Isopropylantipyrinum; Isopropylphenazone; Propifenazon; Propifenazona; Propifenazonas; Propyfenatsoni; Propyfenazon; Propyphénazone; Propyphenazonum. 4-Isopropyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

Пропифеназон

$C_{14}H_{18}N_2O$ = 230.3.
CAS — 479-92-5.
ATC — N02BB04.
ATC Vet — QN02BB04.

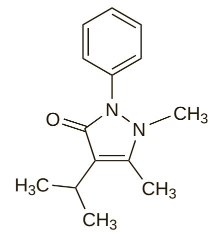

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Propyphenazone). A white or slightly yellowish crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Propyphenazone, a pyrazolone derivative related to phenazone (p.116), has analgesic and antipyretic properties. It has been given orally and as a rectal suppository in the treatment of pain and fever. The usual oral adult dose is 0.5 to 1 g up to four times daily. There have been some reports of severe hypersensitivity reactions in patients receiving propyphenazone.

Porphyria. Propyphenazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Dim-Antos; ***Ger.:*** Demex; Eufibron†; Hewedolor propy†; Isoprochin P†.

Multi-ingredient: ***Arg.:*** Algio-Bladuril; Espasmo Cibalena; Saridon; ***Austria:*** Adolorin; APA; Avamigran; Coldagrippin; Contraforte†; Eu-Med; Gewadal; Melabon; Migradon; Montamed; Nervan; Rapidol; Saridon; Spasmoplus; Tonopan; Toximer; Vivimed; Waldheim Influvidon; Waldheim Schmerztabletten; ***Belg.:*** Kranit Nova†; Optalidon†; Saridon†; Spasmoplus†; ***Braz.:*** Saridon; Tonopan; ***Chile:*** Abalgin; Droxel; Espasmo Cibalgina; Espasmo Cibalgina Compuesta; Feminosan†; Gripasan Compuesto; Immediat†; SAE; ***Cz.:*** Saridon; Spasmoveralgin Neo†; Valetol; ***Denm.:*** Kodamid; ***Ger.:*** Avamigran N†; Cibalgin Compositum N†; Copyrkal N†; Ergo-Kranit†; Eudorlin†; Fomagrippin N†; Ichtho-Bellol compositum S†; Migrane-Kranit Duo†; Migrane-Kranit N†; Migratan S†; Norgesic N†; Optalidon N; Optalidon special NOC†; RubieNex spezial†; Saridon; Schworalgin; Spasmo-Cibalgin S†; Titretta S; ***Hong Kong:*** Epizon†; Saridon; Tonterin†; ***Hung.:*** Saridon; Trinell Pro; ***Indon.:*** Butamidon; Cetapyrin; Enkapyrin; Migran; Paramex; Saridon; ***Ital.:*** Cistalgan; Influrem†; Influvit; Micranet†; Mindol-Merck†; Neo-Optalidon; Odontalgico Dr. Knapp con Vit. B1; Optalidon; Saridon; Sedol; Spasmo-Cibalgina†; Spasmoplus; Uniplus; Veramon; ***Mex.:*** Espasmo Cibalgina; Tonopan; ***Neth.:*** Daro Hoofdpijnpoeders; Kruidvat; Para-don; Sanalgin; Saridon; ***Pol.:*** Analget; Cefalgin; Gardan P; Kropla Zoladkowe; Pabialgin P; Saridon; ***Port.:*** Avamigran†; Optalidon; Saridon N; ***Rus.:*** Caffetin (Каффетин); Coffedon (Коффедон); Gewadal (Гевадал); Kofan (Кофан); Saridon (Саридон); ***S.Afr.:*** Ilvico; ***Spain:*** Abdominol; Calmoplex; Dolodens; Flexagil†; Hubergrip†; Melabon; Meloka; Optalidon; Quimpedor; Saridon; Sedalmerck†; Sulmetin Papaver; Sulmetin Papaverina†; Tabletas Quimpe; Tonopan; ***Switz.:*** Barbamin†; Caposan†; Cerebrol†; Comprimes analgesiques "S"†; Dialgine forte†; Dolopyrine†; Dolostop†; Escalgin sans codeine†; Escogripp sans codeine; Gewodine†; Nicaphlogyl†; Saridon†; Seranex sans codeine†; Sinedal†; Spasmo-Barbamin†; Spasmo-Barbamine compositum†; Spasmo-Cibalgin comp†; Spasmo-Cibalgin†; Spedralgin sans codeine†; Tonopan†; ***Turk.:*** Aljil; Bioptan; Minoset Plus; Panalgine.

Proquazone *(BAN, USAN, rINN)*

43-715; Procuazona; Prokuazon; Prokvatsoni; Prokvazon; Proquazonum; RU-43-715-n. 1-Isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one.

Проквазон

$C_{18}H_{18}N_2O$ = 278.3.
CAS — 22760-18-5.
ATC — M01AX13.
ATC Vet — QM01AX13.

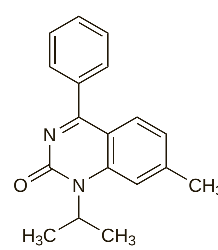

The symbol † denotes a preparation no longer actively marketed

Profile
Proquazone is an NSAID (p.96) that has been used orally and rectally in musculoskeletal and joint disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Hung.: Biarison†; ***Turk.:*** Biarison.

Ramifenazone *(rINN)*

Isopropylaminophenazone; Isopyrin; Ramifenazona; Ramifénazone; Ramifenazonum. 4-Isopropylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

Рамифеназон

$C_{14}H_{19}N_3O = 245.3.$

CAS — 3615-24-5.

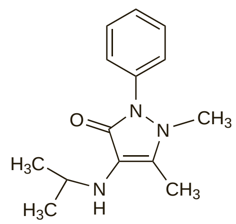

NOTE. The name Isopyrin has also been applied to isoniazid.

Profile
Ramifenazone is an NSAID (p.96) that has been used in preparations for painful and inflammatory conditions; it has also been used in veterinary medicine. Ramifenazone has been given as the hydrochloride and the salicylate.

Remifentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

GI-87084B; Hidrocloruro de remifentanilo; Rémifentanil, Chlorhydrate de; Remifentanili Hydrochloridum. 4-Carboxyl-4-(*N*-phenylpropionamido)-1-piperidine propionic acid dimethyl ester monohydrate.

Ремифентанила Гидрохлорид

$C_{20}H_{28}N_2O_5,HCl = 412.9.$

CAS — 132539-07-2.

ATC — N01AH06.

ATC Vet — QN01AH06.

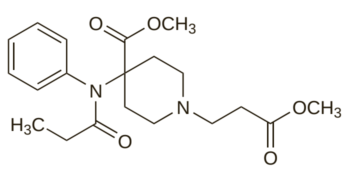

(remifentanil)

Incompatibility. Remifentanil hydrochloride should not be mixed in the same intravenous solution as blood products. UK licensed product information states that it should not be mixed with lactated Ringer's injection with or without 5% glucose; however, in the USA the product literature states that remifentanil hydrochloride is stable for 4 hours at room temperature after reconstitution and dilution to 20 to 250 micrograms/mL with lactated Ringer's injection and for 24 hours if lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanil 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 0.6 mg/mL and remifentanil 250 micrograms/mL (as the hydrochloride) in 5% glucose.[1]

1. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Dependence and Withdrawal
As for Opioid Analgesics, p.101.

Adverse Effects and Treatment
As for Opioid Analgesics in general, p.102 and for Fentanyl, p.56.

Precautions
As for Opioid Analgesics in general, p.103.

Administration. Remifentanil hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

Hepatic impairment. Although the pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment, such patients may be more sensitive to the respiratory depressant effects and should be monitored with doses titrated to individual requirements.

Renal impairment. The pharmacokinetics of remifentanil are not changed in patients with severe renal impairment (a creatinine clearance of less than 10 mL/minute) and licensed product information states that the carboxylic acid metabolite is unlikely to accumulate to clinically active concentrations in such patients after remifentanil infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies[1,2] in intensive care patients with renal impairment given remifentanil infusions at a rate of 100 to 150 nanograms/kg per minute for up to 3 days.

1. Breen D, *et al.* Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; **8:** R21–R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *Br J Anaesth* 2004; **92:** 493–503.

Interactions
For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics
After parenteral doses remifentanil hydrochloride has a rapid onset and short duration of action. Its effective biological half-life is about 3 to 10 minutes and is independent of dose. Remifentanil is about 70% bound to plasma proteins, mainly to α_1-acid glycoprotein. It is hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite. About 95% of a dose of remifentanil is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanil may cross the placenta and is distributed into breast milk.

◊ Licensed product information for remifentanil gives values for a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes.

References.

1. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; **29:** 80–94.
2. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. *Curr Opin Anaesthesiol* 2000; **13:** 449–55.
3. Ross AK, *et al.* Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; **93:** 1393–1401.

Uses and Administration
Remifentanil, an anilidopiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is a short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anaesthesia. It is also used to provide analgesia into the immediate postoperative period, and may be used as the analgesic component of local or regional anaesthesia with or without benzodiazepine sedation. Remifentanil is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care.

Remifentanil is given intravenously as the hydrochloride, usually by infusion. Its onset of action is within 1 minute and the duration of action is 5 to 10 minutes. Doses are expressed in terms of the base; remifentanil hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanil. Initial doses for anaesthesia in elderly patients should be half the recommended adult doses and then titrated to individual requirements. Obese patients may require doses based on their ideal (lean) bodyweight. For details of doses in children, see below.

When used to provide **analgesia** during *induction* of anaesthesia an intravenous infusion is given in doses of 0.5 to 1 micrograms/kg per minute. An additional initial intravenous bolus of 1 microgram/kg may be given over 30 to 60 seconds particularly if the patient is to be intubated less than 8 minutes after the start of the infusion.

For provision of analgesia during *maintenance* of anaesthesia in ventilated patients, usual infusion doses range from 0.05 to 2 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response. Supplemental intravenous boluses of 0.5 to 1 micrograms/kg may be given every 2 to 5 minutes in response to light anaesthesia or intense surgical stress. The infusion dosage in spontaneous respiration is initially 0.04 micrograms/kg per minute adjusted according to response within a usual range of 0.025 to 0.1 micrograms/kg per minute. Bolus doses are not recommended during spontaneous ventilation.

For continuation of analgesia into the immediate *postoperative* period typical doses by intravenous infusion have ranged from 100 to 200 nanograms/kg per minute; supplemental intravenous bolus doses are not recommended during the postoperative period.

To provide **analgesia and sedation** in ventilated patients under intensive care, remifentanil is given as an intravenous infusion at an initial rate of 100 to 150 nanograms/kg per minute. Doses should then be titrated to provide adequate analgesia and sedation; a period of 5 minutes should be allowed between dose adjustments. Additional sedative drugs should be given to those patients inadequately sedated with remifentanil infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanil infusion may be necessary if additional analgesia is required to cover stimulating or painful procedures such as wound dressing. Doses of up to 750 nanograms/kg per minute have been given to some patients. Bolus doses of remifentanil are not recommended in intensive care.

Remifentanil is also used as an analgesic in patients receiving monitored anaesthesia care. In the USA, it may be given intravenously in a single dose of 1 microgram/kg 90 seconds before the local anaesthetic; alternatively, a dose of 100 nanograms/kg per minute may be given as an intravenous infusion, starting 5 minutes before the local anaesthetic, which should be reduced to 50 nanograms/kg per minute after the local anaesthetic. Subsequent adjustments of 25 nanograms/kg per minute at 5-minute intervals may be made to maintain a balanced analgesia.

Remifentanil has a very rapid offset of action and no residual opioid action remains 5 to 10 minutes after stopping an infusion. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

◊ References and reviews.

1. Patel SS, Spencer CM. Remifentanil. *Drugs* 1996; **52:** 417–27.
2. Duthie DJR. Remifentanil and tramadol. *Br J Anaesth* 1998; **81:** 51–7.
3. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. *Clin Pharmacokinet* 2005; **44:** 787–96.
4. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; **65:** 1793–1823. Correction. *ibid.*; 2286.
5. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006; **66:** 365–85.
6. Welzing L, Roth B. Experience with remifentanil in neonates and infants. *Drugs* 2006; **66:** 1339–50.

Administration in children. Remifentanil hydrochloride, given by continuous intravenous infusion, is used for analgesia during maintenance of general anaesthesia in children. Usual infusion doses (expressed as the base) for those aged from 1 to 12 years range from 0.05 to 1.3 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response; supplemental intravenous boluses of 1 microgram/kg may be given over at least 30 seconds. US licensed product information also states that neonates and children aged up to 2 months may be given infusion doses of 0.4 to 1 micrograms/kg per minute with supplemental boluses of 1 microgram/kg. Similar doses are suggested in the *BNFC* for use in neonates although in the UK remifentanil is not licensed for use in children under 1 year of age.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Remicit; Ultiva; ***Austral.:*** Ultiva; ***Austria:*** Ultiva; ***Belg.:*** Ultiva; ***Braz.:*** Ultiva; ***Canad.:*** Ultiva; ***Chile:*** Ultiva; ***Cz.:*** Ultiva; ***Denm.:*** Ultiva; ***Fin.:*** Ultiva; ***Fr.:*** Ultiva; ***Ger.:*** Ultiva; ***Gr.:*** Ultiva; ***Hong Kong:*** Ultiva; ***Hung.:*** Ultiva†; ***Irl.:*** Ultiva†; ***Israel:*** Ultiva; ***Ital.:*** Ultiva; ***Mex.:*** Ultiva; ***Neth.:*** Ultiva; ***Norw.:*** Ultiva; ***NZ:*** Ultiva; ***Pol.:*** Ultiva; ***Port.:*** Ultiva; ***S.Afr.:*** Ultiva; ***Singapore:*** Ultiva; ***Spain:*** Ultiva; ***Swed.:*** Ultiva; ***Switz.:*** Ultiva; ***Turk.:*** Ultiva; ***UK:*** Ultiva; ***USA:*** Ultiva; ***Venez.:*** Ultiva.

Rofecoxib *(BAN, USAN, rINN)*

MK-966; MK-0966; Rofécoxib; Rofecoxibum; Rofekoksibi; Rofekoxib. 4-[*p*-(Methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone.
Рофекоксиб
$C_{17}H_{14}O_4S$ = 314.4.
CAS — 162011-90-7.
ATC — M01AH02.
ATC Vet — QM01AH02.

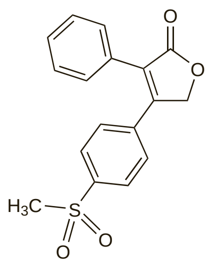

Profile

Rofecoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis, and in the management of acute pain, dysmenorrhoea, and migraine but was generally withdrawn worldwide after reports of cardiovascular adverse effects (see below).

Rofecoxib has been applied topically in some countries.

Effects on the cardiovascular system. As of February 2001, the UK CSM had received a small number of reports of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[1] At that time it noted that COX-2 inhibitors such as rofecoxib did not possess the intrinsic antiplatelet activity associated with aspirin, and consequently did not provide protection against ischaemic cardiac events. Data from a large, randomised study also showed the incidence of myocardial infarction to be greater in patients taking rofecoxib than in those taking naproxen.[2] Postmarketing surveillance of rofecoxib continued to provide further case reports of adverse cardiovascular effects. In addition, results of the then unpublished APPROVe study of rofecoxib for prevention of adenomatous polyposis indicated that the risk of myocardial infarction and stroke was markedly increased in patients receiving the drug compared to those on placebo; however, this difference was only apparent after 18 months of treatment. As a result, the study was stopped early and, in September 2004, the manufacturer generally withdrew rofecoxib worldwide. The cardiovascular findings from the APPROVe study were published in 2005;[3] the results showed a twofold increase in the risk of adverse cardiovascular events in patients receiving rofecoxib 25 mg daily when compared with those on placebo. More recently, 1-year follow-up data for patients in the APPROVe study has been released. In a statement from the manufacturer,[4] it is noted that in the year after rofecoxib was stopped there was no statistically significant difference in the risk of confirmed thrombotic cardiovascular events in those patients who had previously taken rofecoxib compared with those who had been given placebo; however, when data from both the on- and off-treatment periods were considered together, the difference in the risk of cardiovascular events between the rofecoxib and the placebo groups remained significant. Combined data from the on- and off-treatment periods also showed that there was an increased risk of confirmed heart attacks and ischaemic strokes in the rofecoxib group when compared to the placebo group. (The data for ischaemic stroke were later published.[5]) Similar data, suggesting a 1.5-fold increase in risk of thrombotic events with rofecoxib, were reported from a study of adjuvant use for colorectal cancer.[6] A cumulative meta-analysis also indicated an increased risk of myocardial infarction in patients receiving rofecoxib.[7]

Subsequent investigation by US and European regulatory authorities has confirmed that other COX-2 inhibitors are also associated with some increased cardiovascular risk (see under Celecoxib, p.34), as are some non-selective NSAIDs (see Thrombotic Events, p.97).

A review[8] of prospective studies evaluating the effect of selective COX-2 inhibitors on blood pressure was unable to determine if there was any association between the use of these drugs and blood pressure elevations. Of the studies considered, a randomised study in elderly, hypertensive patients with osteoarthritis has suggested that the risk of developing *increased systolic blood pressure* is greater in those patients receiving rofecoxib than in those receiving celecoxib.[9] However, the manufacturers of rofecoxib have pointed out that the trial used doses of rofecoxib greater than those recommended for elderly or hypertensive patients.

1. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Bombardier C, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1520–8.
3. Bresalier RS, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352:** 1092–1102. Correction. *ibid.* 2006; **355:** 221.
4. Merck, USA. Merck announces preliminary analyses of off-drug extension of APPROVe study (issued 11th May, 2006). Available at: http://www.merck.com/newsroom/press_releases/corporate/2006_0511.html (accessed 08/11/07)
5. Afilalo J, *et al.* Long-term risk of ischemic stroke associated with rofecoxib. *Cardiovasc Drugs Ther* 2007; **21:** 117–20.
6. Kerr DJ, *et al.* Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007; **357:** 360–9.
7. Jüni P, *et al.* Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; **364:** 2021–9.
8. Johnson DL, *et al.* Effect of cyclooxygenase-2 inhibitors on blood pressure. *Ann Pharmacother* 2003; **37:** 442–6.
9. Whelton A, *et al.* Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001; **8:** 85–95.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Antidol†; Blokium Cox†; Coxiro†; Foldox†; Toloxane†; Vioxx†; ***Austral.:*** Vioxx†; ***Austria:*** Ceoxx†; Coxxil†; Vioxx†; ***Belg.:*** Vioxx†; ***Braz.:*** Vioxx†; ***Canad.:*** Vioxx†; ***Chile:*** Ceoxx†; ***Cz.:*** Vioxx†; ***Denm.:*** Vioxx†; Vioxxalt†; ***Fin.:*** Vioxx†; ***Fr.:*** Vioxx†; ***Ger.:*** Vioxx†; ***Gr.:*** Peroxx†; Vioxx†; ***Hong Kong:*** Vioxx†; ***Hung.:*** Vioxx†; ***India:*** Alrof†; Dolib†; Rofetab†; Rofib; Rofixx†; Rofiz; Versatil†; ***Irl.:*** Ceoxx†; Vioxx†; ***Israel:*** Vioxx†; ***Ital.:*** Arofexx†; Coxxil†; Dolcoxx†; Dolostop†; Miraxx†; Vioxx†; ***Malaysia:*** Vioxx†; ***Mex.:*** Vioxx†; ***Neth.:*** Vioxx†; ***Norw.:*** Vioxx†; ***NZ:*** Vioxx†; ***Port.:*** Ceoxx†; Coxxil†; Vioxx†; ***S.Afr.:*** Vioxx†; ***Singapore:*** Vioxx†; ***Spain:*** Ceoxx†; Vioxx†; ***Swed.:*** Vioxx†; Vioxxakut†; ***Switz.:*** Vioxx†; ***Thai.:*** Vioxx†; ***UK:*** Vioxx†; ***USA:*** Vioxx†; ***Venez.:*** Vioxx†.

Multi-ingredient: ***India:*** Rofecip Plus†.

Salamidacetic Acid

Carbamoylphenoxyacetic acid; Salamidacético, ácido; Salicylamide *O*-acetic acid. (2-Carbamoylphenoxy)acetic acid.
Натрия Салициламидацетат (sodium salamidacetate)
$C_9H_9NO_4$ = 195.2.
CAS — 25395-22-6 (salamidacetic acid); 3785-32-8 (sodium salamidacetate).

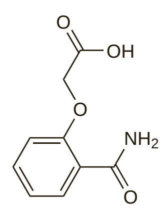

Profile

Salamidacetic acid is a salicylic acid derivative (see Aspirin, p.20) that has also been used as the sodium and diethylamine salts for the treatment of musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Akistin; ***Ger.:*** Clinit N†.

Multi-ingredient: ***Austria:*** Ambene; Rheumesser; ***Ger.:*** Caye Rheuma-Balsam; ***Rus.:*** Ambene (Амбене); ***Thai.:*** Trabit†.

Salicylamide *(BAN, rINN)*

Salicilamida; Salicylamid; Salicylamidum; Salisyyliamidi. 2-Hydroxybenzamide.
Салициламид
$C_7H_7NO_2$ = 137.1.
CAS — 65-45-2.
ATC — N02BA05.
ATC Vet — QN02BA05.

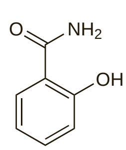

Pharmacopoeias. In *Pol.* and *US.*

USP 31 (Salicylamide). A white practically odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol and in propylene glycol; freely soluble in ether and in solutions of alkalis.

Profile

Salicylamide is a salicylic acid derivative (see Aspirin, p.20) but is not hydrolysed to salicylate; it is almost completely metabolised to inactive metabolites during absorption and on first pass through the liver. It is given in usual oral doses of 325 to 650 mg or more, usually with other analgesics, three or four times daily for pain and fever. Salicylamide has also been applied topically in rubefacient preparations in concentrations of up to about 5% for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Waldheim Rheuma-Creme.

Multi-ingredient: ***Arg.:*** Finagrip†; Funciogrip; Venter; ***Austria:*** Rilfit; Rubriment; Sigmalin B ; Sigmalin B forte; Sigmalin B ohne Coffein; Spalt†; Waldheim Influvidon; Waldheim Sport- und Rheuma-Fluid; ***Belg.:*** Percutalgine; ***Braz.:*** Coristina R; Nogripe; Resprax; Termogripe C†; Vita Grip; ***Denm.:*** Kodamid; Koffisal; ***Fr.:*** Percutalgine; ***Ger.:*** Glutisal†; Salistoperm†; ***Gr.:*** Myalgesic†; ***Hong Kong:*** Antiflu Forte; Antiflu-N-Forte; DF Multi-Symptom; Flu-Zep; Neozep; Qualizep; ***Indon.:*** Cold Cap; Corexin; Neozep; Refagan; ***Ital.:*** Anticorizza†; ***Mex.:*** Artrilan; Butayonacol; ***NZ:*** Calm-U; ***Pol.:*** Reumosol; Scorbolamid; ***Rus.:*** Cefecon N (Цефекон Н); Percutalgine (Перкуталжин)†; ***S.Afr.:*** Colcaps; Flutex Cold and Flu; Histamed Compound; Ilvico; Specific Nerve Pain Remedy; ***Spain:*** Coricidin†; Hubergrip†; Pridio; Rinomicine; Rinomicine Activada; Yendol; ***Switz.:*** Escalgin sans codeine†; Escogripp sans codeine; Grippalgine N†; Osa Gel de dentition; ***Thai.:*** Apracur; Fecol; Percutalgine†; ***UAE:*** Adol Compound; Flukit; ***UK:*** Intralgin†; ***USA:*** Anabar; BC; Be-Flex Plus; By-Ache; Combiflex; Duraxin; Levacet; Lobac; Painaid; Saleto; Stanback Headache; Trim-Elim†; ***Venez.:*** Cotar†; Praxona.

Salix

Corteza de sauce; Écorce de Saule; Fűzfakéreg; Gluosnių žievė; Kora wierzby; Pajunkuori; Sälgbark; Salicis cortex; Saule, écorce de; Vrbová kůra; Weidenbaumrinde; White Willow Bark; Willow Bark.

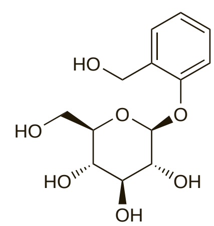

(salicin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Willow Bark). The whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of the genus *Salix*, including *Salix purpurea*, *S. daphnoides*, and *S. fragilis*. It contains not less than 1.5% of total salicylic derivatives, expressed as salicin ($C_{13}H_{18}O_7$ = 286.3), calculated with reference to the dried drug. Protect from light.

Profile

Salix contains variable amounts of tannin and also of salicin, which has antipyretic and analgesic actions similar to those of aspirin. Salix has been used in a variety of herbal remedies for painful and inflammatory conditions and for fever. It was once used as a bitter.

Adverse effects. An *anaphylactic reaction* developed in a 25-year-old woman with asthma and a known allergy to aspirin, within 75 minutes of ingesting a dietary supplement containing willow bark extract.[1] The link between salicylate and willow bark allergy was also reported in a carpenter who experienced a widespread *rash*, similar to that he developed with aspirin, when working with willow wood.[2]

1. Boullata JI, *et al.* Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* 2003; **37:** 832–5.
2. Jennings A. Link between salicylate and willow bark. *Pharm J* 2006; **276:** 417.

Pain. Preparations containing willow bark extract have been tried with some success in the treatment of musculoskeletal disorders such as low back pain[1-3] and osteoarthritis.[4] However, the quality of reporting in trials is generally poor and further studies are needed to establish their place in therapy.

1. Chrubasik S, *et al.* Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000; **109:** 9–14.

2. Chrubasik S, *et al.* Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. *Rheumatology (Oxford)* 2001; **40:** 1388–93.
3. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).
4. Biegert C, *et al.* Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004; **31:** 2121–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Zortrix; ***Ger.:*** Assalix; Assplant; Lintia†; Rheumakaps; Rheumatab Salicis†; ***Pol.:*** Salicortex; ***Switz.:*** Assalix.

Multi-ingredient: ***Austral.:*** Arthritic Pain Herbal Formula 1; Bioglan Arthri Plus; Extralife Migrai-Care; Extralife PMS-Care; Guaiacum Complex†; Lifesystem Herbal Formula 1 Arthritic Aid†; Prost-1†; ***Austria:*** Digestodoron; ***Braz.:*** Calman; Calmiplan; Floriny; Pasalix; Pasic; Passi Catha†; Passiflorine; ***Cz.:*** Antirevmaticky Caj; Erkaltungstee†; Valofyt Neo; ***Fr.:*** Arkophytum†; Mediflor Tisane Circulation du Sang No 12; Phytheol; ***Ger.:*** Digestodoron; Dr Wiemanns Rheumatonikum; ***Ital.:*** Biothymus DS; Bodyguard; Donalg; Influ-Zinc; Nepiros; Nevril; Passiflorine; Reumafort; ***Malaysia:*** Celery Plus†; ***Mex.:*** Ifupasil; ***Pol.:*** Enterosol; Pyrosal; Reumacor; Reumosol; Termasil; ***Port.:*** Neurocardol†; ***S.Afr.:*** Digestodoron; ***Spain:*** Dolosul†; Jaquesor†; Mesatil†; Natusor Harpagosinol†; Natusor Jaquesan†; ***Switz.:*** Dragees antirhumatismales; Strath Gouttes Rhumatisme; Tisane antirhumatismale; ***UK:*** Bio-Strath Willow Formula; Gerard House Reumalex; Herbal Pain Relief; St Johnswort Compound; ***Venez.:*** Passiflorum.

Salol

Benzofenolsalicylaat; Benzophénol Salicylate; Fenylsalicylat; Fenylu salicylan; Fenyylisalisylaatti; Phenyli Salicylas; Phenylis Salicylas; Salicilato de fenilo. Phenyl salicylate.

$C_{13}H_{10}O_3$ = 214.2.
CAS — 118-55-8.
ATC — G04BX12.
ATC Vet — QG04BX12.

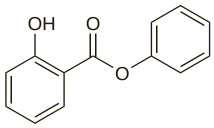

Pharmacopoeias. In *Pol.*

Profile

Salol is a salicylic acid derivative (see Aspirin, p.20). It was formerly used as an intestinal antiseptic, but effective doses were toxic owing to the liberation of phenol. It is used in oral preparations containing methenamine for the treatment of lower urinary-tract infections.

Salol has been used topically as a sunscreen.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Aussie Tan Sunstick.

Multi-ingredient: ***Arg.:*** Dermithan; ***Austria:*** Carl Baders Divinal; ***Belg.:*** Borostyrol; ***Braz.:*** Talco Alivio†; ***Canad.:*** Franzbranns†; ***Chile:*** Galutec†; Polisep†; ***Cz.:*** Parodontal F5†; ***Fr.:*** Borostyrol; Dermophil Indien†; Nisacalm; ***Pol.:*** Salotannal; Urosal; ***Switz.:*** Borostyrol N†; Dermophil Indien; GU Eau†; Penta; ***Turk.:*** Sandolin; ***USA:*** Atrosept; Dolsed†; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X†; UAA; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira.

Salsalate *(BAN, USAN, rINN)*

NSC-49171; Salicyl Salicylate; Salicylosalicylic Acid; Salicylsalicylic Acid; Salsalato; Salsalatum; Salysal; Sasapyrine. *O*-(2-Hydroxybenzoyl)salicylic acid.

Сальсалат

$C_{14}H_{10}O_5$ = 258.2.
CAS — 552-94-3.
ATC — N02BA06.
ATC Vet — QN02BA06.

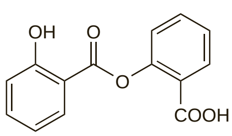

Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Salsalate). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to salsalate.

Effects on the gastrointestinal tract. Salsalate is associated with less faecal blood loss than aspirin and has been reported to cause fewer gastric lesions than piroxicam.[1] However, small-bowel ulcerations were reported in a patient when salsalate was added to a regimen of ranitidine and metoclopramide which had been prescribed for duodenal ulcer.[2]

1. Porro GB, *et al.* Salsalate in the treatment of rheumatoid arthritis: a double-blind clinical and gastroscopic trial versus piroxicam: II—endoscopic evaluation. *J Int Med Res* 1989; **17:** 320–3.
2. Souza Lima MA. Ulcers of the small bowel associated with stomach-bypassing salicylates. *Arch Intern Med* 1985; **145:** 1139.

Effects on the kidneys. A case of minimal-change nephrotic syndrome associated with salsalate use.[1]

1. Vallès M, Tovar JL. Salsalate and minimal-change nephrotic syndrome. *Ann Intern Med* 1987; **107:** 116.

Effects on the mouth. Ulcerated lesions on the tongue of a 77-year-old man were caused by taking salsalate tablets incorrectly.[1] The patient had placed the tablets under his tongue rather than swallowing them whole, resulting in prolonged, direct contact with the tongue.

1. Ruscin JM, Astroth JD. Lingual lesions secondary to prolonged contact with salsalate tablets. *Ann Pharmacother* 1998; **32:** 1248.

Interactions

For interactions associated with salicylates, see Aspirin, p.23.

Pharmacokinetics

Salsalate is insoluble in acidic gastric fluids but is soluble in the small intestine. One molecule of salsalate is hydrolysed to 2 molecules of salicylic acid; hydrolysis occurs both in the small intestine and after absorption of the parent compound. Additional details on the pharmacokinetics of salicylic acid are provided in aspirin (see p.23). Not all of the absorbed salsalate is hydrolysed and about 13% of salsalate is excreted as glucuronide conjugates in the urine; thus, the amount of salicylic acid available from salsalate is less than that from aspirin when the two drugs are given in equimolar equivalents of salicylic acid.

Uses and Administration

Salsalate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p.23). It is used for pain and fever and also in inflammatory disorders such as osteoarthritis and rheumatoid arthritis. A usual oral dose is up to 3 g daily given in divided doses with food.

Preparations

USP 31: Salsalate Capsules; Salsalate Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Amigesic; Argesic-SA; Artha-G; Disalcid; Marthritic; Mono-Gesic†; Salflex; Salsitab.

Sarracenia Purpurea

Pitcher Plant.

Profile

The roots and leaves of *Sarracenia purpurea* (Sarraceniaceae) have been used in the form of an aqueous distillate, given by local injection, for neuromuscular or neuralgic pain.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Sarapin.

Sodium Aurothiomalate *(rINN)*

Aurothiomalate de Sodium; Aurotiomalato de sodio; Gold Sodium Thiomalate; Natrii aurothiomalas; Natrium-aurothiomalát; Natriumaurotiomalaatti; Natriumaurotiomalat; Sodium, aurothiomalate de; Sodium Aurothiosuccinate; Sodu aurotiojabłczan; Sodyum Orotiyomalat.

Натрия Ауротиомалат

CAS — 12244-57-4 (anhydrous xNa); 39377-38-3 (disodium monohydrate).
ATC — M01CB01.
ATC Vet — QM01CB01.

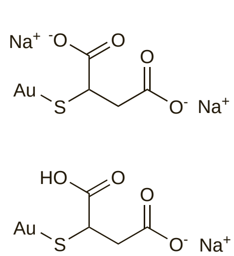

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Sodium Aurothiomalate). A mixture of monosodium and disodium salts of (2*RS*)-2-(aurosulphanyl)butanedioic acid. It contains 44.5 to 46.0% of gold and 10.8 to 11.8% of sodium, calculated with reference to the dried substance. A fine, pale yellow, hygroscopic powder. Very soluble in water; practically insoluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 6.0 to 7.0. Store in airtight containers.

USP 31 (Gold Sodium Thiomalate). A mixture of the mono-sodium and disodium salts of gold thiomalic acid [(aurothio)succinic acid] ($C_4H_4AuNaO_4S$ = 368.1 and $C_4H_3AuNa_2O_4S$ = 390.1) that has a gold content of 44.8 to 49.6%, and 49.0 to 52.5% calculated on the dried alcohol-free and glycerol-free material. pH of a 10% solution in water is between 5.8 and 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Reports show a wide range for the incidence of adverse effects of sodium aurothiomalate. However, some consider that with careful treatment about one-third of patients will experience adverse effects. It is also considered that about 5% of patients will experience severe adverse effects and that some of the effects will be fatal. The most common effects involve the skin and mucous membranes with pruritus (an early sign of intolerance) and stomatitis (often with a metallic taste) being the most prominent. Rashes with pruritus often occur after 2 to 6 months of intramuscular treatment and may require stopping therapy. Other reactions affecting the skin and mucous membranes include erythema, maculopapular eruptions, erythema multiforme, urticaria, eczema, seborrhoeic dermatitis, lichenoid eruptions, alopecia, exfoliative dermatitis, glossitis, pharyngitis, vaginitis, photosensitivity reactions, and irreversible pigmentation (chrysiasis).

Toxic effects on the blood include eosinophilia, thrombocytopenia, leucopenia, agranulocytosis, and aplastic anaemia.

Effects on the kidneys include mild transient proteinuria which may lead to heavy proteinuria, haematuria, and nephrosis.

Other effects reported include pulmonary fibrosis, dyspnoea, toxic hepatitis, cholestatic jaundice, peripheral neuritis, encephalitis, psychoses, fever, and gastrointestinal disorders including enterocolitis. Gold deposits may occur in the eyes. Vasomotor or nitritoid reactions, with weakness, flushing, palpitations, and syncope, may occur after injection of sodium aurothiomalate. Local irritation may also follow injection.

Sometimes there is an initial exacerbation of the arthritic condition.

Some adverse effects of gold have an immunogenic component.

◊ Reviews.

1. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2:** 177–89.
2. van Roon EN, *et al.* Parenteral gold preparations. Efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; **32:** 1026–30.

Effects on the blood. Blood disorders such as eosinophilia, leucopenia, granulocytopenia, and thrombocytopenia have occurred in patients receiving gold therapy. Eosinophilia has been reported to be the most frequent haematological abnormality.[1] It has been estimated that thrombocytopenia develops in 1 to 3% of patients receiving gold salts.[2]

Fatal consumption coagulopathy occurred in 4 children after the second injection of sodium aurothioglucose or sodium aurothiomalate.[3]

1. Foster RT. Eosinophilia—a marker of gold toxicity. *Can J Hosp Pharm* 1985; **85:** 150–1.
2. Coblyn JS, *et al.* Gold-induced thrombocytopenia: a clinical and immunogenetic study of twenty-three patients. *Ann Intern Med* 1981; **95:** 178–81.
3. Jacobs JC, *et al.* Consumption coagulopathy after gold therapy for JRA. *J Pediatr* 1984; **105:** 674–5.

Effects on the cardiovascular system. Vasomotor or nitritoid reactions associated with gold compounds are usually transient and self-limiting and although they may be mild there have been isolated reports of associated complications such as myocardial infarction, stroke, transient ischaemic attack, and transient monocular visual loss.[1] Most reactions have been associated with sodium aurothiomalate (a reported incidence of 4.7%) but they have also occurred with auranofin and sodium aurothioglucose. Tachyphylaxis usually occurs to the reactions and most patients are able to continue treatment but paradoxically in some the severity increases with repeated doses; 2.8% of patients receiving sodium aurothiomalate may require a change of treatment due to recurrent reactions. It is important to distinguish such reactions from true anaphylactic reactions to gold.[1] Patients taking ACE inhibitors may be at increased risk of nitritoid reactions.[2,3] Transfer of the patient to sodium aurothioglucose or reduction of the dose by 50%, injection in the recumbent position, and observation for 20 minutes have been recommended for the next few injections after a reaction.[2]

1. Ho M, Pullar T. Vasomotor reactions with gold. *Br J Rheumatol* 1997; **36:** 154–6.
2. Arthur AB, *et al.* Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001; **28:** 2209–12.
3. Nixon J, Pande I. Gold, nitritoid reactions and angiotensin-converting enzyme inhibitors. *Rheumatology (Oxford)* 2006; **45:** 118–19.

Effects on the gastrointestinal tract. A case report of enterocolitis due to sodium aurothiomalate has been published[1] and 27 other cases associated with gold therapy reviewed. For colitis associated with oral gold see also under Auranofin, p.25.

1. Jackson CW, *et al.* Gold induced enterocolitis. *Gut* 1986; **27:** 452–56.

Effects on the immune system. Details of a patient who developed an immune deficiency syndrome that was attributed to gold therapy with sodium aurothiomalate.[1]

1. Haskard DO, Macfarlane D. Adult acquired combined immune deficiency in a patient with rheumatoid arthritis on gold. *J R Soc Med* 1988; **81:** 548–9.

Effects on the kidneys. Proteinuria developed in 21 patients while receiving a standard regimen of sodium aurothiomalate.[1] The severity of the proteinuria varied greatly and in 11 it increased for 4 months after treatment was stopped. Eight patients were considered to have developed the nephrotic syndrome. The median duration of proteinuria was 11 months, resolving in all 21 patients when treatment was withdrawn; at 24 months 3 patients were still experiencing proteinuria and it was not until 39 months that all were free of the condition. Renal biopsy indicated several types of kidney damage.

See under Auranofin (p.25) for a comparative incidence of proteinuria in patients receiving sodium aurothiomalate or auranofin.

1. Hall CL, *et al.* The natural course of gold nephropathy: long term study of 21 patients. *BMJ* 1987; **295:** 745–8.

Effects on the lungs. 'Gold lung' is the term used to describe symptoms of dyspnoea on exertion, weakness, dry cough, and malaise that are seen rarely in patients on gold treatment.[1] Such symptoms usually develop some weeks or months after starting gold treatment and are associated with cumulative doses of several hundred milligrams although, very rarely, they have been seen with cumulative doses of less than 100 mg.[2] Pulmonary insufficiency may eventually develop and there have been occasional fatalities.[3] The pulmonary lesions usually subside on withdrawal of gold therapy, although persistent symptoms have been reported.

Nonbacterial thrombotic endocarditis associated with gold-induced pulmonary disease has also been reported.[4] This was considered to be a manifestation of gold-induced immune complex deposition.

1. Sinha A, *et al.* Gold-induced pneumonitis: computed tomography findings in a patient with rheumatoid arthritis. *Rheumatology (Oxford)* 2001; **40:** 712–14.
2. Hafejee A, Burke MJ. Acute pneumonitis starting 2 hours after intramuscular gold administration in a patient with rheumatoid arthritis. *Ann Rheum Dis* 2004; **63:** 1525–6.
3. Soler MJ, *et al.* Fatal, gold-induced pneumonitis. *Rheumatol Int* 2003; **23:** 207–10.
4. Kollef MH, *et al.* Nonbacterial thrombotic endocarditis associated with gold induced pulmonary disease. *Ann Intern Med* 1988; **108:** 903–4.

Effects on the nails. A 34-year-old woman with severe rheumatoid arthritis receiving intramuscular gold developed yellow thickened toenails and fingernails after 2 years of treatment.[1] Although there was some improvement in nail growth on stopping treatment, some light yellow discoloration in all 20 nails persisted.

1. Roest MAB, Ratnavel R. Yellow nails associated with gold therapy for rheumatoid arthritis. *Br J Dermatol* 2001; **145:** 855–6.

Effects on the nervous system. Neurological complications with gold salts are infrequent but may include peripheral neuropathy, Guillain-Barré syndrome, myokymia (repeated involuntary contractions of muscle fibre), and encephalopathy. Some reports[1-6] are given below.

1. Dick DJ, Raman D. The Guillain-Barre syndrome following gold therapy. *Scand J Rheumatol* 1982; **11:** 119–20.
2. Schlumpf U, *et al.* Neurologic complications induced by gold treatment. *Arthritis Rheum* 1983; **26:** 825–31.
3. Cerinic MM, *et al.* Gold polyneuropathy in juvenile rheumatoid arthritis. *BMJ* 1985; **290:** 1042.
4. Cohen M, *et al.* Acute disseminated encephalomyelitis as a complication of treatment with gold. *BMJ* 1985; **290:** 1179–80.
5. Dubowitz MN, *et al.* Gold-induced neuroencephalopathy responding to dimercaprol. *Lancet* 1991; **337:** 850–1.
6. Garrido JA, *et al.* Mioquimias inducidas por sales de oro. *Neurologia* 1995; **10:** 235–7.

Effects on the skin. Chrysiasis is a distinctive pigmentation that develops in light-exposed skin of patients receiving parenteral gold salts. In a study[1] of 31 patients with chrysiasis who were receiving intramuscular sodium aurothiomalate for rheumatoid arthritis, it was noted that visible changes developed above a threshold equivalent to 20 mg/kg gold content. The severity of the pigmentation depended upon cumulative dose. Focal aggregates of gold are deposited in the reticular and papillary dermis with no obvious increase in melanin. The pigmentation is permanent but benign, although the cosmetic effects may cause some patients distress. Prevention of chrysiasis is difficult but avoidance of exposure to sunlight may be helpful.

1. Smith RW, *et al.* Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133:** 671–8.

Hypersensitivity. Many adverse effects associated with gold treatment have an immunological basis. Patients with contact allergy to gold may exhibit a flare-up, associated with cytokine release, when given sodium aurothiomalate intramuscularly.[1] Small amounts of nickel have been detected in sodium aurothiomalate injection[2] and in sodium aurothioglucose injection[3] and it has been suggested that gold therapy may also exacerbate or induce hypersensitivity to nickel.[2-4]

Anaphylaxis may occur occasionally[5] but vasomotor or 'nitritoid' reactions (see Effects on the Cardiovascular System, above) may produce similar symptoms.

1. Möller H, *et al.* The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Dermatitis* 1999; **40:** 200–4.
2. Choy EHS, *et al.* Nickel contamination of gold salts: link with gold-induced skin rash. *Br J Rheumatol* 1997; **36:** 1054–8.
3. Wijnands MJH, *et al.* Chrysotherapy provoking exacerbation of contact hypersensitivity to nickel. *Lancet* 1990; **335:** 867–8.
4. Fulton RA, *et al.* Another hazard of gold therapy? *Ann Rheum Dis* 1982; **41:** 100–1.
5. Neustadt DH. Another anaphylactic reaction after gold (aurothiomalate) injection. *J Rheumatol* 1995; **22:** 190.

Pancreatitis. It was suggested that pancreatitis reported in a woman receiving gold injections and in a woman on oral gold therapy may have been due to a hypersensitivity reaction.[1]

1. Eisemann AD, *et al.* Pancreatitis and gold treatment of rheumatoid arthritis. *Ann Intern Med* 1989; **111:** 860–1.

Treatment of Adverse Effects

The treatment of the adverse effects of gold is usually symptomatic and most effects resolve when gold therapy is withdrawn. In severe cases a chelator such as dimercaprol (p.1444) may be used.

Precautions

Gold therapy is contra-indicated in exfoliative dermatitis, SLE, necrotising enterocolitis, and pulmonary fibrosis. It should be used with caution in the elderly and in renal or hepatic impairment; use is contra-indicated if renal or hepatic disorders are severe. Patients with a history of haematological disorders or who have previously shown toxicity to heavy metals should not be given gold salts, nor should any severely debilitated patient.

It is recommended that diabetes mellitus and heart failure should be adequately controlled in any patient before gold is given. Patients with a history of urticaria, eczema, or colitis should be treated with caution. Patients with a poor sulfoxidation status may be more susceptible to adverse effects of sodium aurothiomalate.

Use of gold compounds with other therapy capable of inducing blood disorders should be undertaken with caution, if at all.

Because of the risk of vasomotor reactions, patients should remain recumbent for about 10 minutes after each injection.

Urine should be tested for albumin before each injection and a full blood count carried out. Patients receiving gold compounds either orally or parenterally should be warned to report the appearance of sore throat or tongue, metallic taste, pruritus, rash, buccal ulceration, easy bruising, purpura, epistaxis, bleeding gums, unexplained bleeding, menorrhagia, pyrexia, indigestion, diarrhoea, or unexplained malaise. The development of breathlessness or cough should also be reported. Effects such as eosinophilia, proteinuria, pruritus, and rash arising during gold treatment should be allowed to resolve before therapy is continued.

Licensed product information recommends that annual chest X-rays should be carried out.

Breast feeding. The American Academy of Pediatrics considers that gold compounds are usually compatible with breast feeding.[1]

Gold has been detected in breast milk[2-4] and found bound to the red blood cells of breast-fed babies.[3,4] In a report[2] of a breast-fed infant it was calculated that the weight-adjusted dose of gold received by the infant exceeded that received by the mother although the infant exhibited no ill-effects during 100 days of breast feeding and developed normally thereafter. Nonetheless, because of the relatively high exposure it was recommended that breast-fed infants should be closely monitored.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/11/06)
2. Bennett PN, *et al.* Use of sodium aurothiomalate during lactation. *Br J Clin Pharmacol* 1990; **29:** 777–9.
3. Needs CJ, Brooks PM. Antirheumatic medication during lactation. *Br J Rheumatol* 1985; **24:** 291–7.
4. Blau SP. Metabolism of gold during lactation. *Arthritis Rheum* 1973; **16:** 777–8.

Porphyria. Sodium aurothiomalate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Although healthy neonates have been born after *in utero* exposure to gold compounds,[1,2] *animal* studies and a report[1] of malformation in a child born to a woman treated with sodium aurothiomalate led to a suggestion that gold might possibly have teratogenic effects. Licensed product information advises that sodium aurothiomalate should be avoided during pregnancy.

1. Rogers JG, *et al.* Possible teratogenic effects of gold. *Aust Paediatr J* 1980; **16:** 194–5.
2. Bennett PN, *et al.* Use of sodium aurothiomalate during lactation. *Br J Clin Pharmacol* 1990; **29:** 777–9.

Interactions

There is an increased risk of toxicity when gold compounds are given with other nephrotoxic, hepatotoxic, or myelosuppressive drugs. Use of gold compounds with penicillamine may increase the risk of haematologic or renal adverse reactions.

ACE inhibitors. For a possible increased risk of nitritoid reactions when gold compounds are given to patients taking ACE inhibitors, see Effects on the Cardiovascular System, above.

Penicillamine. For a discussion on the effects of previous therapy with gold salts affecting penicillamine toxicity, see p.1458.

Pharmacokinetics

Sodium aurothiomalate is absorbed readily after intramuscular injection and 85 to 95% becomes bound to plasma proteins. With doses of 50 mg weekly a steady-state serum concentration of gold of about 3 to 5 micrograms/mL is reached in 5 to 8 weeks. It is widely distributed to body tissues and fluids, including synovial fluid, and accumulates in the body.

The serum half-life of gold is about 5 to 6 days but this increases after successive doses and after a course of treatment, gold may be found in the urine for up to 1 year or more owing to its presence in deep body compartments. Sodium aurothiomalate is mainly excreted in the urine, with smaller amounts in the faeces.

Gold has been detected in the fetus when sodium aurothiomalate was given to the mother. Gold is distributed into breast milk.

◊ Reviews.

1. Blocka KLN, *et al.* Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11:** 133–43.
2. Tett SE. Clinical pharmacokinetics of slow-acting antirheumatic drugs. *Clin Pharmacokinet* 1993; **25:** 392–407.

Uses and Administration

Sodium aurothiomalate and other gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. They are generally used as disease-modifying antirheumatic drugs in patients whose symptoms are unresponsive to or inadequately controlled by NSAIDs alone.

Sodium aurothiomalate therapy should only be undertaken where facilities are available to carry out the tests specified under Precautions, above.

Sodium aurothiomalate is given by deep intramuscular injection; the area should be gently massaged and, due to the possibility of vasomotor reactions, the patient should remain recumbent for 10 minutes and kept under close observation for 30 minutes after each injection. In the UK, 10 mg is given in the first week to test the patient's tolerance. If satisfactory, this may be followed by doses of 50 mg at weekly intervals until signs of remission occur; the dosage interval is then increased to 2 weeks until full remission occurs and then increased gradually to every 4 to 6 weeks. Treatment may be continued for up to 5 years after remission.

Improvement may not be seen until a total dose of 300 to 500 mg has been given. If no major improvement has occurred after a total of 1 g has been given (excluding the test dose) therapy should be stopped; alternatively in the absence of toxicity, 100 mg may be given weekly for a further 6 weeks; should there be no response at this dose other forms of therapy should be tried. In patients who relapse while receiving maintenance therapy, the interval between doses should be reduced to one week and should not be increased again until control has been obtained; however, if no response is obtained within 2 months, alternative treatment should be used. It is important to avoid complete relapse since a second course of gold therapy is not usually effective.

For doses in juvenile idiopathic arthritis, see Administration in Children, below.

NSAIDs may be continued when sodium aurothiomalate therapy is begun.

Other gold compounds that have been used include auranofin (p.25), aurothioglucose (p.26), aurotioprol (p.26), gold keratinate (p.62), and sodium aurotiosulfate (below).

Administration in children. For children with progressive juvenile idiopathic arthritis the suggested initial weekly dose of sodium aurothiomalate is 1 mg/kg by deep intramuscular injection to a maximum of 50 mg weekly (one-tenth to one-fifth of the calculated initial weekly dose may be given for 2 to 3 weeks to test the patient's tolerance). Weekly doses should continue until signs of remission occur, at which point the dosage interval may be increased to fortnightly. With full remission, the dosage interval may again be increased gradually to every 4 weeks. If no improvement has occurred after 20 weeks, the dose could be raised slightly or another antirheumatic drug tried. For the view that use of gold compounds is no longer appropriate to treat juvenile idiopathic arthritis see Rheumatic Disorders, below.

Asthma. For comment on the use of parenteral gold compounds in the treatment of asthma, see under Auranofin, p.26.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Intramuscular gold therapy has been used concomitantly to permit a reduction in corticosteroid dosage although evidence for the steroid-sparing effect is lacking;[1,2] it has been suggested that gold therapy should be reserved for patients who cannot tolerate corticosteroids or in whom they are contra-indicated.[1]

1. Bystryn J-C, Steinman NM. The adjuvant therapy of pemphigus: an update. *Arch Dermatol* 1996; **132:** 203–12.
2. Pandya AG, Dyke C. Treatment of pemphigus with gold. *Arch Dermatol* 1998; **134:** 1104–7.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p.11). Although toxicity has now reduced its popularity, intramuscular gold has long been used for the treatment of rheumatoid arthritis[1-4] and is often the standard against which the efficacy of other treatments is measured. Oral gold is less toxic but is also much less effective. It is unclear if there are differences between available intramuscular forms, but a study[5] in 120 patients converted from aurothioglucose to aurothiomalate found that 29 withdrew from the latter drug within 12 months, mostly because of lack of efficacy or the development of adverse effects not seen with the previous drug.

Gold compounds have also been used in the treatment of juvenile idiopathic arthritis (p.10); however, the *BNFC* states that gold is no longer used for this indication.

Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p.13).

1. Epstein WV, *et al.* Effect of parenterally administered gold therapy on the course of adult rheumatoid arthritis. *Ann Intern Med* 1991; **114:** 437–44.
2. Anonymous. Gold therapy in rheumatoid arthritis. *Lancet* 1991; **338:** 19–20.
3. Klinkhoff AV, Teufel A. How low can you go? Use of very low dosage of gold in patients with mucocutaneous reactions. *J Rheumatol* 1995; **22:** 1657–9.
4. Clark P, *et al.* Injectable gold for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1997 (accessed 13/11/06).
5. van Roon, EN, *et al.* Parenteral gold preparations: efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; **32:** 1026–30.

Preparations

BP 2008: Sodium Aurothiomalate Injection;
USP 31: Gold Sodium Thiomalate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Myocrisin; ***Austria:*** Tauredon; ***Canad.:*** Myochrysine; ***Cz.:*** Tauredon; ***Denm.:*** Myocrisin; ***Fin.:*** Myocrisin; ***Ger.:*** Tauredon; ***Gr.:*** Miocrin; Myocrysine†; Tauredon; Tuaredon†; ***Hung.:*** Tauredon†; ***Irl.:*** Myocrisin; ***Neth.:*** Tauredon; ***Norw.:*** Myocrisin; ***NZ:*** Myocrisin; ***Port.:*** Tauredon; ***S.Afr.:*** Myocrisin†; ***Singapore:*** Miocrin; ***Spain:*** Miocrin; ***Swed.:*** Myocrisin; ***Switz.:*** Tauredon; ***Thai.:*** Myocrisin; ***UK:*** Myocrisin; ***USA:*** Aurolate; Myochrysine.

Sodium Aurotiosulfate *(rINN)*

Aurotiosulfate de Sodium; Aurotiosulfato de sodio; Gold Sodium Thiosulphate; Natrii Aurotiosulfas; Natrii Aurotiosulphas; Natriumaurotiosulfaatti; Natriumaurotiosulfat; Sodium Aurothiosulphate; Sodium Dithiosulfatoaurate.

Натрия Ауротиосульфат

$Na_3Au(S_2O_3)_2,2H_2O = 526.2.$
CAS — 10233-88-2 (anhydrous sodium aurotiosulfate); 10210-36-3 (sodium aurotiosulfate dihydrate).
ATC — M01CB02.
ATC Vet — QM01CB02.

Profile

Sodium aurotiosulfate has a gold content of about 37%. It has similar actions and uses to those of sodium aurothiomalate (p.122). It is given by intramuscular injection in a usual dose of 56.1 mg every 5 to 7 days.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Crytion; ***Chile:*** Crytioro; ***Ital.:*** Fosfocrisolo.

Sodium Gentisate *(rINN)*

Gentisate de Sodium; Gentisato de sodio; Gentisato Sodico; Natrii Gentisas. Sodium 2,5-dihydroxybenzoate dihydrate.

Натрия Гентизат

$C_7H_5NaO_4,2H_2O = 212.1.$
CAS — 490-79-9 (gentisic acid); 4955-90-2 (anhydrous sodium gentisate).

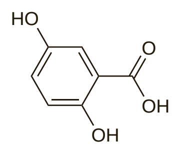

(gentisic acid)

Pharmacopoeias. In *Fr.*

Profile

Sodium gentisate has been used as an analgesic in the treatment of musculoskeletal and joint disorders. It is also used as a preservative.

Sodium Salicylate

Natrii salicylas; Natrio salicilatas; Natriumsalicylat; Natriumsalisylaatti; Nátrium-szalicilát; Salicilato sódico; Salicylan sodný; Sodium, salicylate de; Sodu salicylan; Sodyum Salisilat. Sodium 2-hydroxybenzoate.

Салицилат Натрия

$C_7H_5NaO_3 = 160.1.$
CAS — 54-21-7.
ATC — N02BA04.
ATC Vet — QN02BA04.

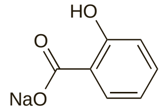

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Sodium Salicylate). Colourless small crystals or shiny flakes, or white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Sodium Salicylate). Amorphous or microcrystalline powder or scales. It is colourless or has not more than a faint pink tinge. It is odourless or has a faint characteristic odour. A freshly made 10% solution in water is neutral or acid to litmus. Freely (and slowly) soluble in water and in glycerol; very soluble in boiling water and in boiling alcohol; slowly soluble in alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

Although sodium salicylate has been used in the treatment of rheumatic fever, its high sodium content may cause problems in patients with cardiac complications.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed drug information extends this precaution to sodium salicylate.

Effects on the eyes. Retinal haemorrhages were reported in a 60-year-old woman taking sodium salicylate 6 g daily by mouth for 2 months and in a 10-year-old girl taking sodium salicylate, 4 g daily by mouth, for 40 days.[1] In both cases the haemorrhages gradually resolved after the treatment was stopped.

1. Mortada A, Abboud I. Retinal haemorrhages after prolonged use of salicylates. *Br J Ophthalmol* 1973; **57:** 199–200.

Interactions

For interactions associated with salicylates, see Aspirin, p.23.

Uses and Administration

Sodium salicylate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p.23). Sodium salicylate 1 g is equivalent to about 1.1 g of aspirin. It is used in the treatment of pain, fever, and in rheumatic disorders such as osteoarthritis and rheumatoid arthritis. The usual oral dose of sodium salicylate for pain or fever is 325 to 650 mg every four hours as required. The oral dose for rheumatic disorders is 3.6 to 5.4 g daily in divided doses. Sodium salicylate has also been used in the symptomatic treatment of rheumatic fever but its high sodium content may cause problems in patients with cardiac complications.

Sodium salicylate has also been given by intravenous infusion and topically.

Preparations

USP 31: Sodium Salicylate Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Dodds†; Saliject; ***NZ:*** Hairscience Shampoo†; ***Turk.:*** Enter-Sal; ***UK:*** Jackson's Pain & Fever.

Multi-ingredient: ***Braz.:*** A Saude da Mulher; Abacateirol†; Pilulas De Witt's†; ***Canad.:*** Plax; Thunas Tab for Menstrual Pain†; ***Chile:*** Eucerin Shampoo Anticaspa; ***Fr.:*** Brulex; ***Ger.:*** Gelonida NA†; ***Hong Kong:*** Gly Thymol; ***S.Afr.:*** Colphen; Doans Backache Pills; Ilvico; TCP; ***UK:*** Antiseptic Mouthwash; Doans Backache Pills; TCP; ***USA:*** Cystex; Scot-Tussin Original 5-Action; Tussirex; ***Venez.:*** Boncilin†; Inquilim†.

Sodium Thiosalicylate

Tiosalicilato sódico. Sodium 2-sulfanylbenzoate.

Тиосалицилат Натрия

$C_7H_5O_2NaS = 176.2.$
CAS — 134-23-6.

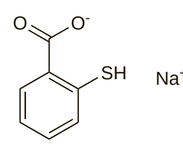

Profile

Sodium thiosalicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used parenterally in the treatment of musculoskeletal disorders, osteoarthritis, rheumatic fever, and acute gout.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Rexolate†.

Sufentanil *(BAN, rINN)* ⊗

R-30730; Sufentaniili; Sufentanilis; Sufentanilo; Sufentanilum; Szufentanil. *N*-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide.

Суфентанил

$C_{22}H_{30}N_2O_2S = 386.6.$
CAS — 56030-54-7.
ATC — N01AH03.
ATC Vet — QN01AH03.

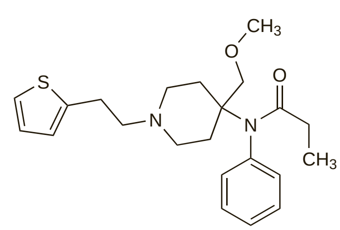

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Sufentanil). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Sufentanil Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de sufentanilo; R-33800; Sufentaniilisitraatti; Sufentanil citrát; Sufentanil, citrate de; Sufentanil Sitrat; Sufentanilcitrat; Sufentanili citras; Sufentanilio citratas; Szufentanil-citrát. *N*-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide citrate.

Суфентанила Цитрат

$C_{22}H_{30}N_2O_2S,C_6H_8O_7$ = 578.7.
CAS — 60561-17-3.
ATC — N01AH03.
ATC Vet — QN01AH03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Sufentanil Citrate). A white or almost white powder. Soluble in water and in alcohol; freely soluble in methyl alcohol. Protect from light.
USP 31 (Sufentanil Citrate). A white powder. Soluble in water; sparingly soluble in alcohol, in acetone, and in chloroform; freely soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Sufentanil (as the citrate) diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.[1]

1. Chapalain-Pargarde S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102 and Fentanyl, p.56.

Breast feeding. Concentrations of sufentanil were similar in colostrum and serum in 7 women given sufentanil by continuous epidural infusion during the first postoperative day after caesarean section. In the light of its poor oral availability such an amount was not considered to be a hazard to the breast-fed infant, and a maternal dose of 5 micrograms/hour epidurally was considered to be safe for such infants.[1]

1. Ausseur A, *et al.* Continuous epidural infusion of sufentanil after caesarean section: concentration in breast milk. *Br J Anaesth* 1994; **72** (suppl 1): 106.

Effects on the cardiovascular system. For a reference to the effects of sufentanil on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on the nervous system. There have been reports of tonic-clonic movements or seizures in a few patients receiving sufentanil.[1] There was no evidence of cortical seizure activity in a patient whose EEG was recorded,[2] suggesting that the observed myoclonus was not a convulsion or seizure.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Bowdle TA. Myoclonus following sufentanil without EEG seizure activity. *Anesthesiology* 1987; **67:** 593–5.

Effects on the respiratory system. Sufentanil, like other opioid agonists, causes dose-related respiratory depression. There have been reports of significant respiratory depression associated with chest wall rigidity in the early postoperative period after anaesthesia with intravenous sufentanil.[1,2] Respiratory depression has also been reported after intrathecal sufentanil for postoperative analgesia[3] and labour pain.[4]. A retrospective chart review[3] of a 6-year period, during which 4870 patients received intrathecal sufentanil for the management of labour pain, found that the case above was the only one of respiratory arrest reported in the group.

1. Goldberg M, *et al.* Postoperative rigidity following sufentanil administration. *Anesthesiology* 1985; **63:** 199–201.
2. Chang J, Fish KJ. Acute respiratory arrest and rigidity after anesthesia with sufentanil: a case report. *Anesthesiology* 1985; **63:** 710–11.
3. Fournier R, *et al.* Respiratory depression after 5 μgrams of intrathecal sufentanil. *Anesth Analg* 1998; **87:** 1377–8.
4. Ferouz F, *et al.* Risk of respiratory arrest after intrathecal sufentanil. *Anesth Analg* 1997; **85:** 1088–90.

The elderly. The pharmacokinetics of sufentanil in elderly patients have been variable in different studies, but a review[1] considered that there had been no evidence overall for differences between the elderly and younger adults. Nevertheless, as with fentanyl, reduced initial doses have been advised in the elderly.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.

Handling. Avoid contact with skin and the inhalation of particles of sufentanil citrate.

Obesity. The elimination half-life and volume of distribution of sufentanil were increased in obese subjects.[1,2] Licensed product information recommends that for obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of the patients' lean body-weight.

1. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in the obese. *Anesthesiology* 1986; **65** (suppl 3A): A562.
2. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in obese patients. *Anesth Analg* 1991; **73:** 790–3.

Interactions

For interactions associated with opioid analgesics, see p.103.

Benzodiazepines. For the effects of using opioids such as sufentanil with benzodiazepines, see Analgesics under Interactions of Diazepam, p.989.

Pharmacokinetics

After parenteral doses sufentanil citrate has a rapid onset and short duration of action. The terminal elimination half-life of sufentanil is about 2.5 hours. It is extensively bound to plasma proteins (about 90%). It is metabolised in the liver and small intestine by *N*-dealkylation and *O*-demethylation and the inactive metabolites are excreted in the urine and faeces. About 80% of a dose is excreted within 24 hours and 2% is eliminated as unchanged drug. Sufentanil crosses the placenta and is distributed into breast milk.

◊ The pharmacokinetics of sufentanil have been reviewed.[1,2] Sufentanil is very lipid-soluble. Like alfentanil it is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. The elimination half-life lies between that of alfentanil and fentanyl. The manufacturers of sufentanil have given values for a three-compartment pharmacokinetic model with a distribution half-life of 1.4 minutes, a redistribution half-life of 17.1 minutes, and an elimination half-life of 164 minutes. Accumulation may be relatively limited when compared with fentanyl. In practice the pharmacokinetics of sufentanil may vary according to the age and condition of the patient and the procedures undertaken. For example, the elimination half-life of sufentanil has been reported to be longer in patients undergoing cardiac surgery (595 minutes),[3] in hyperventilated patients (232 minutes),[4] in those undergoing abdominal aortic surgery (more than 12 hours),[5] and in ventilated intensive care patients under sedation (25.5 hours).[6]

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Howie MB, *et al.* Serum concentrations of sufentanil and fentanyl in the post-operative course in cardiac surgery patients. *Anesthesiology* 1984; **61:** A131.
4. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. *Br J Anaesth* 1989; **63:** 385–8.
5. Hudson RJ, *et al.* Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; **70:** 426–31.
6. Ethuin F, *et al.* Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med* 2003; **29:** 1916–20.

Administration. References to the pharmacokinetics of sufentanil given epidurally,[1,2] intrathecally,[1] or transdermally.[3]

1. Ionescu TI, *et al.* Pharmacokinetic study of extradural and intrathecal sufentanil anaesthesia for major surgery. *Br J Anaesth* 1991; **66:** 458–64.
2. Hansdottir V, *et al.* The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. *Anesth Analg* 1995; **80:** 724–9.
3. Sebel PS, *et al.* Transdermal absorption of fentanyl and sufentanil in man. *Eur J Clin Pharmacol* 1987; **32:** 529–31.

Children. Neonates (up to 1 month old) had a significantly lower plasma clearance rate and greater elimination half-life than infants (1 month to 2 years), children, and adolescents.[1] Others[2] have found that infants and small children (1 month to 3 years) with cardiac disease had higher clearance rates and shorter elimination half-lives than reported for adults. Older children (aged 2 to 8 years) with no history of cardiac, renal, or hepatic disease have also been noted to have shorter elimination half-lives and higher clearance rates than adults.[3]

1. Greeley WJ, *et al.* Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987; **66:** 1067–72.
2. Davis PJ, *et al.* Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. *Anesth Analg* 1987; **66:** 203–8.
3. Guay J, *et al.* Pharmacokinetics of sufentanil in normal children. *Can J Anaesth* 1992; **39:** 14–20.

Hepatic impairment. Because of the efficient hepatic extraction and clearance of sufentanil[1] liver dysfunction might be expected to affect its pharmacokinetics. However, elimination kinetics and plasma protein binding were found to be similar in cirrhotic and non-cirrhotic patients after a single dose of sufentanil.[2]

1. Schedewie H, *et al.* Sufentanil and fentanyl hepatic extraction rate and clearance in obese patients undergoing gastroplasty. *Clin Pharmacol Ther* 1988; **43:** 132.
2. Chauvin M, *et al.* Sufentanil pharmacokinetics in patients with cirrhosis. *Anesth Analg* 1989; **68:** 1–4.

Renal impairment. The pharmacokinetics of sufentanil were reported[1] to be unaffected in patients with chronic renal failure, although elevated plasma concentrations of sufentanil have been noted[2] in one such patient.

1. Sear JW. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *Br J Anaesth* 1989; **63:** 60–7.
2. Wiggum DC, *et al.* Postoperative respiratory depression and elevated sufentanil levels in a patient with chronic renal failure. *Anesthesiology* 1985; **63:** 708–10.

Uses and Administration

Sufentanil, a phenylpiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is highly lipid-soluble and more potent than fentanyl. Sufentanil is used as an analgesic adjunct in anaesthesia and as a primary anaesthetic in procedures requiring assisted ventilation. It has a rapid onset and recovery is considered to be more rapid than with fentanyl. It is also used as an analgesic in the management of postoperative pain and labour pain.

Sufentanil is given as the citrate either intravenously by slow injection or as an infusion, or epidurally. Doses are expressed as the base; sufentanil citrate 15 micrograms is equivalent to about 10 micrograms of sufentanil. Lower initial doses are advised in the elderly and debilitated patients. For obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of the patient's lean body-weight. For details of doses in children, see below. In all patients supplementary maintenance doses should be based on individual response and length of procedure. Doses of up to the equivalent of 8 micrograms/kg of sufentanil produce profound analgesia. Higher doses produce a deep level of anaesthesia but are associated with prolonged respiratory depression and assisted ventilation may be required in the postoperative period.

When used as an analgesic **adjunct to anaesthesia** with nitrous oxide and oxygen for surgical procedures lasting up to 8 hours, the total *intravenous* dosage should not exceed 1 microgram/kg per hour. It is customary to give up to 75% of the dose before intubation followed as necessary during surgery by additional injections of 10 to 50 micrograms or by a suitable continuous or intermittent infusion given so that the total hourly dose is not exceeded. Thus, for an operation lasting 1 to 2 hours the total dose would be 1 to 2 micrograms/kg with 0.75 to 1.5 micrograms/kg being given before intubation.

When used as a **primary anaesthetic** in major surgery *intravenous* doses of 8 to 30 micrograms/kg are given with 100% oxygen; doses of 25 to 30 micrograms/kg block sympathetic response including catecholamine release and are indicated in procedures such as cardiovascular surgery or neurosurgery. Anaesthesia may be maintained by additional injections of 0.5 to 10 micrograms/kg or by a suitable continuous or intermittent infusion given so that the total dosage for the procedure does not exceed 30 micrograms/kg.

In postoperative **pain**, sufentanil is given *epidurally* in an initial dose of 30 to 60 micrograms, which should provide analgesia for 4 to 6 hours. Additional boluses of up to 25 micrograms may be given at intervals of not less than 1 hour if necessary.

Sufentanil is also given *epidurally* for the relief of pain during labour and delivery. Recommended doses are 10 to 15 micrograms given with 10 mL of bupivacaine 0.125% (or its equivalent) with or without adrenaline;

the dose may be repeated twice at not less than one-hour intervals until delivery. The total dose of sufentanil should not exceed 30 micrograms.

◊ General reviews of sufentanil.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36:** 286–313.
2. Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clin Pharm* 1991; **10:** 581–93.

Administration. Sufentanil is usually given intravenously, but the epidural route is also used (see below). Intranasal (see Anaesthesia, Pain, and Sedation, below), intrathecal (see below), and sublingual use (see Pain, below) have also been tried.

EPIDURAL. In a laboratory assessment of epidural sufentanil in healthy subjects,[1] a dose of 50 micrograms produced analgesia for 2 to 3 hours; analgesia was intensified and prolonged, and respiratory and other adverse effects, especially drowsiness, were reduced by the addition of adrenaline. Epidural sufentanil or fentanyl provided effective postoperative analgesia following caesarean section with comparable adverse effect profiles.[2] Sufentanil doses of 20 and 30 micrograms showed equivalent efficacy and provided greater analgesia for a longer duration than a dose of 10 micrograms. Addition of sufentanil to local anaesthetics such as bupivacaine during labour has considerably reduced the local anaesthetic requirements[3] and improved the quality of epidural analgesia.[4] Combination of sufentanil with a local anaesthetic (ropivacaine or bupivacaine) has been used for patient-controlled epidural analgesia (PCEA),[5-9] although an early study suggested that PCEA with sufentanil alone had little advantage over patient-controlled analgesia with intravenous morphine.[10]

Effective analgesia has been achieved in children with epidural sufentanil.[11]

1. Klepper ID, *et al.* Analgesic and respiratory effects of extradural sufentanil in volunteers and the influence of adrenaline as an adjuvant. *Br J Anaesth* 1987; **59:** 1147–56.
2. Grass JA, *et al.* A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
3. Buyse I, *et al.* Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. *Int J Obstet Anesth* 2007; **16:** 22–8.
4. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
5. Gogarten W, *et al.* A multicentre trial comparing different concentrations of ropivacaine plus sufentanil with bupivacaine plus sufentanil for patient-controlled epidural analgesia in labour. *Eur J Anaesthesiol* 2004; **21:** 38–45.
6. Boselli E, *et al.* Background infusion is not beneficial during labor patient-controlled analgesia with 0.1% ropivacaine plus 0.5 microg/ml sufentanil. *Anesthesiology* 2004; **100:** 968–72.
7. Bremerich DH, *et al.* Comparison of continuous background infusion plus demand dose and demand-only parturient-controlled epidural analgesia (PCEA) using ropivacaine combined with sufentanil for labor and delivery. *Int J Obstet Anesth* 2005; **14:** 114–20.
8. Missant C, *et al.* Patient-controlled epidural analgesia following combined spinal-epidural analgesia in labour: the effects of adding a continuous epidural infusion. *Anaesth Intensive Care* 2005; **33:** 452–6.
9. Schenk MR, *et al.* Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. *Anesth Analg* 2006; **103:** 1311–17.
10. Grass JA, *et al.* Patient-controlled analgesia after cesarean delivery: epidural sufentanil versus intravenous morphine. *Reg Anesth* 1994; **19:** 90–7.
11. Benlabed M, *et al.* Analgesia and ventilatory response to CO following epidural sufentanil in children. *Anesthesiology* 1987; **67:** 948–51.

INTRATHECAL. Sufentanil, alone or in combination, has been given intrathecally for labour pain: a combination of sufentanil, bupivacaine, and adrenaline given intrathecally provided excellent analgesia during labour and had a more rapid onset, a longer duration of action, and reduced local anaesthetic requirements compared with epidural administration.[1] Intrathecal sufentanil and bupivacaine provided shorter duration of analgesia when given during the advanced stages of labour compared with early labour.[2] There has been some concern about the effect of intrathecal use on fetal heart rate. An early study[3] found no significant difference in the heart rate when intrathecal sufentanil was compared with epidural bupivacaine; however, a more recent study[4] reported that high-dose intrathecal sufentanil (7.5 micrograms) when given on its own increased the risk of fetal heart rate abnormalities when compared with low-dose intrathecal sufentanil (2.5 micrograms) given with bupivacaine and adrenaline. Nonetheless, there was no evidence of a difference in adverse neonatal outcomes between the groups.

A small study in patients undergoing hip replacement found that intrathecal sufentanil 7.5 micrograms produced better and longer lasting analgesia than the same dose given intravenously.[5]

Intrathecal sufentanil has also been tried in the treatment of chronic pain.[6]

1. Kartawiadi SL, *et al.* Spinal analgesia during labor with low-dose bupivacaine, sufentanil, and epinephrine: a comparison with epidural analgesia. *Reg Anesth* 1996; **21:** 191–6.
2. Viscomi CM, *et al.* Duration of intrathecal labor analgesia: early versus advanced labor. *Anesth Analg* 1997; **84:** 1108–12.
3. Nielsen PE, *et al.* Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. *Anesth Analg* 1996; **83:** 742–6.
4. Van de Velde M, *et al.* Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesth Analg* 2004; **98:** 1153–9.
5. Fournier R, *et al.* Intrathecal sufentanil is more potent than intravenous for postoperative analgesia after total-hip replacement. *Reg Anesth Pain Med* 2005; **30:** 249–54.
6. Waara-Wolleat KL, *et al.* A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med* 2006; **7:** 251–9.

Administration in children. Although experience of paediatric use is limited, sufentanil citrate is licensed for the induction and maintenance of anaesthesia in children under 12 years of age undergoing cardiovascular surgery. Intravenous doses of 10 to 25 micrograms/kg are given with 100% oxygen with maintenance doses of up to 25 to 50 micrograms.

Anaesthesia. Sufentanil, like fentanyl (p.59), appears to produce fewer circulatory changes than morphine, which may offer some advantages in cardiovascular surgery.

Premedication with sufentanil given intranasally has been tried in children[1-3] and in adults.[4]

Sufentanil is one of the opioids that have been used with a neuroleptic to produce *neuroleptanalgesia.*

1. Henderson JM, *et al.* Pre-induction of sufentanil. *Anesthesiology* 1988; **68:** 671–5.
2. Zedie N, *et al.* Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; **59:** 341–8.
3. Bayrak F, *et al.* A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. *J Opioid Manag* 2007; **3:** 74–8.
4. Helmers JHJH, *et al.* Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth* 1989; **36:** 494–7.

Pain. For the epidural or intrathecal use of sufentanil in the management of pain, see above. Intranasal sufentanil has been tried for breakthrough cancer pain[1] and postoperative analgesia.[2] It has also been tried sublingually in the management of breakthrough cancer pain.[3]

1. Jackson K, *et al.* Pilot dose finding study of intranasal sufentanil for breakthrough and incident cancer-associated pain. *J Pain Symptom Manage* 2002; **23:** 450–2.
2. Mathieu N, *et al.* Intranasal sufentanil is effective for postoperative analgesia in adults. *Can J Anesth* 2006; **53:** 60–6.
3. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* 2001; **22:** 627–30.

Sedation. Some references to the use of sufentanil for sedation are given below. See also Anaesthesia, above.

1. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
2. Lefrant JY, *et al.* Sufentanil short duration infusion for postoperative sedation in critically ill patients. *Br J Anaesth* 1995; **74** (suppl 1): 114.
3. Kinirons BP, *et al.* Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerve block. *Anesth Analg* 2000; **90:** 1118–21.

Preparations

USP 31: Sufentanil Citrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Sufenta; ***Austria:*** Sufenta; ***Belg.:*** Sufenta; ***Braz.:*** Fastfen; Sufenta; ***Canad.:*** Sufenta; ***Chile:*** Sufenta; ***Cz.:*** Sufenta; ***Denm.:*** Sufenta; ***Fin.:*** Sufenta; ***Fr.:*** Sufenta; ***Ger.:*** Sufenta; ***Indon.:*** Sufenta; ***Ital.:*** Disufen; Fentatienil; ***Malaysia:*** Sufenta†; ***Neth.:*** Sufenta; ***Norw.:*** Sufenta; ***Port.:*** Sufenta; ***S.Afr.:*** Sufenta; ***Swed.:*** Sufenta; ***Switz.:*** Sufenta; ***Turk.:*** Sufenta; ***USA:*** Sufenta†.

Sulindac *(BAN, USAN, rINN)*

MK-231; Sulindaakki; Sulindaco; Sulindacum; Sulindak; Szulindak.
(*Z*)-[5-Fluoro-2-methyl-1-(4-methylsulphinylbenzylidene)inden-3-yl]acetic acid.

Сулиндак

$C_{20}H_{17}FO_3S = 356.4.$

CAS — 38194-50-2.

ATC — M01AB02.

ATC Vet — QM01AB02.

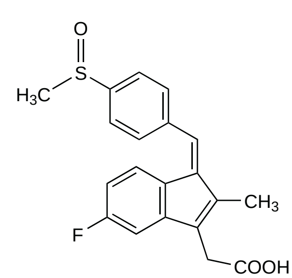

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Sulindac). A yellow, polymorphic, crystalline powder. Very slightly soluble in water and in ether; sparingly soluble in alcohol; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Sulindac). A yellow, odourless or practically odourless, crystalline powder. Practically insoluble in water and in hexane; slightly soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; very slightly soluble in ethyl acetate and in isopropyl alcohol.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Urine discoloration has occasionally been reported with sulindac.

Sulindac metabolites have been reported as major or minor components in renal stones. It should therefore be used with caution in patients with a history of renal stones and such patients should be kept well hydrated while receiving sulindac.

UK licensed product information recommends that patients with hepatic impairment should not be given sulindac; in the USA, however, licensed information states that patients with poor hepatic function may be given a reduced dose of sulindac with close monitoring. The dose of sulindac may also need to be reduced in those with renal impairment. Licensed information recommends that sulindac is not used in patients with advanced renal disease, but this appears to be based on a lack of data in such patients.

Effects on the blood. Agranulocytosis,[1] thrombocytopenia,[2] haemolytic anaemia,[3] and aplastic anaemia[4] have been reported in patients taking sulindac.

1. Romeril KR, *et al.* Sulindac induced agranulocytosis and bone marrow culture. *Lancet* 1981; **ii:** 523.
2. Karachalios GN, Parigorakis JG. Thrombocytopenia and sulindac. *Ann Intern Med* 1986; **104:** 128.
3. Johnson FP, *et al.* Immune hemolytic anemia associated with sulindac. *Arch Intern Med* 1985; **145:** 1515–16.
4. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the CNS. Acute deterioration of parkinsonism occurred in a patient after starting sulindac.[1]

See also Hypersensitivity, below.

1. Sandyk R, Gillman MA. Acute exacerbation of Parkinson's disease with sulindac. *Ann Neurol* 1985; **17:** 104–5.

Effects on the endocrine system. A case of reversible gynaecomastia associated with sulindac therapy has been reported.[1] There has also been a report[2] of reversible hypothyroidism in an elderly patient taking sulindac.

1. Kapoor A. Reversible gynecomastia associated with sulindac therapy. *JAMA* 1983; **250:** 2284–5.
2. Iyer RP, Duckett GK. Reversible secondary hypothyroidism induced by sulindac. *BMJ* 1985; **290:** 1788.

Effects on the gallbladder. A "sludge" composed of crystalline metabolites of sulindac has been found in the common bile duct during surgery for biliary obstruction in patients who had been taking sulindac.[1]

1. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the kidneys. Sulindac-induced renal impairment, interstitial nephritis, and nephrotic syndrome have been reported.[1] It has been suggested that sulindac, as a prodrug, may not inhibit renal prostaglandin synthesis in therapeutic doses. However, this potentially important therapeutic advantage has not been uniformly seen in short-term studies in patients with renal dysfunction.[2-4]

There have been reports of renal stones consisting of between 10 and 90% of sulindac metabolites developing in patients given sulindac.[5]

1. Whelton A, *et al.* Sulindac and renal impairment. *JAMA* 1983; **249:** 2892.
2. Klassen DK, *et al.* Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. *J Clin Pharmacol* 1989; **29:** 1037–42.
3. Eriksson L-O, *et al.* Effects of sulindac and naproxen on prostaglandin excretion in patients with impaired renal function and rheumatoid arthritis. *Am J Med* 1990; **89:** 313–21.
4. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. *Ann Intern Med* 1990; **112:** 568–76.
5. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the liver. Hepatotoxicity reported in patients receiving sulindac includes hepatocellular injury and cholestatic jaundice.[1,2] Symptoms of hypersensitivity including rash, fever, or eosinophilia have been reported in 35 to 55% of patients with sulindac-induced liver damage;[2] in these patients the liver damage occurred usually within 4 to 8 weeks of beginning sulindac therapy. For reference to a report citing the strongest evidence for an association of sulindac with liver disease compared with other NSAIDs, see under NSAIDs, p.98.

See also Effects on the Skin, below.

1. Gallanosa AG, Spyker DA. Sulindac hepatotoxicity: a case report and review. *Clin Toxicol* 1985; **23:** 205–38.
2. Tarazi EM, *et al.* Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104:** 569–74.

Effects on the lungs. For reference to pneumonitis associated with sulindac therapy, see Hypersensitivity, below.

Effects on the skin. Toxic epidermal necrolysis has occurred in patients taking sulindac.[1] In a patient toxic hepatitis and the Stevens-Johnson/toxic epidermal necrolysis syndrome resulted in death.[2]

An unusual pernio-like reaction affecting the toes, which was also confirmed by rechallenge, has been reported.[3]

Sulindac has also been reported to cause photosensitivity reactions.[4]

1. Small RE, Garnett WR. Sulindac-induced toxic epidermal necrolysis. *Clin Pharm* 1988; **7:** 766–71.
2. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol* 1983; **10:** 512–13.
3. Reinertsen JL. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24:** 1215.
4. Anonymous. Drugs that cause photosensitivity. *Med Lett Drugs Ther* 1986; **28:** 51–2.

Hypersensitivity. Hypersensitivity reactions to sulindac include pneumonitis,[1,2] generalised lymphadenopathy,[3] aseptic meningitis,[4] and anaphylactoid reaction.[5]

See also Effects on the Liver and Effects on the Skin, above.

1. Smith FE, Lindberg PJ. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244:** 269–70.
2. Fein M. Sulindac and pneumonitis. *Ann Intern Med* 1981; **95:** 245.
3. Sprung DJ. Sulindac causing a hypersensitivity reaction with peripheral and mediastinal lymphadenopathy. *Ann Intern Med* 1982; **97:** 564.
4. Fordham von Reyn C. Recurrent aseptic meningitis due to sulindac. *Ann Intern Med* 1983; **99:** 343–4.
5. Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151:** 387–8.

Pancreatitis. Reports[1-4] of pancreatitis associated with sulindac therapy.

1. Goldstein J, *et al.* Sulindac associated with pancreatitis. *Ann Intern Med* 1980; **93:** 151.
2. Siefkin AD. Sulindac and pancreatitis. *Ann Intern Med* 1980; **93:** 932–3.
3. Lilly EL. Pancreatitis after administration of sulindac. *JAMA* 1981; **246:** 2680.
4. Memon AN. Pancreatitis and sulindac. *Ann Intern Med* 1982; **97:** 139.

Interactions

For interactions associated with NSAIDs, see p.99.

Dimethyl sulfoxide reduces plasma concentrations of the active metabolite of sulindac and use of the two drugs together has also resulted in peripheral neuropathy. Diflunisal and aspirin are reported to reduce the plasma concentration of the active metabolite of sulindac. Unlike other NSAIDs, sulindac is reported not to reduce the antihypertensive effects of drugs such as thiazide diuretics, but nevertheless licensed product information recommends that blood pressure be closely monitored in patients taking antihypertensives with sulindac.

Pharmacokinetics

Sulindac is absorbed from the gastrointestinal tract. It is metabolised by reversible reduction to the sulfide metabolite, which appears to be the active form, and by irreversible oxidation to the sulfone metabolite. Peak plasma concentrations of the sulfide metabolite are achieved in about 2 hours. The mean elimination half-life of sulindac is about 7.8 hours and of the sulfide metabolite about 16.4 hours. Sulindac and its metabolites are over 90% bound to plasma proteins. About 50% is excreted in the urine mainly as the sulfone metabolite and its glucuronide conjugate, with smaller amounts of sulindac and its glucuronide conjugate; about 25% appears in the faeces, primarily as sulfone and sulfide metabolites. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

◊ References.

1. Davies NM, Watson MS. Clinical pharmacokinetics of sulindac: a dynamic old drug. *Clin Pharmacokinet* 1997; **32:** 437–59.

Uses and Administration

Sulindac is an NSAID (p.99) structurally related to indometacin (p.68); its activity appears to be due to its sulfide metabolite. Sulindac is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and also in the short-term management of acute gout and peri-articular conditions such as bursitis and tendinitis. It has also been used to reduce fever.

A usual initial oral dose of sulindac is 150 or 200 mg twice daily, reduced according to response; the maximum recommended daily dose is 400 mg. Licensed product information recommends that the treatment of peri-articular disorders should be limited to 7 to 14 days; for acute gout, 7 days of therapy is usually adequate.

Sulindac sodium has been given by rectal suppository.

Administration in hepatic or renal impairment. The dose of sulindac may need to be reduced in patients with hepatic or renal impairment but see Adverse Effects and Precautions, above..

Gastrointestinal disorders. In placebo-controlled studies[1,2] sulindac 150 to 200 mg twice daily for 6 to 9 months has reduced the number and size of polyps in patients with familial adenomatous polyposis but the effect may be incomplete and in a study[2] only polyps less than 2 mm in size regressed. In addition, the size and number of polyps has been reported[1] to increase on stopping treatment. The benefit of long-term therapy has therefore been studied. Reduced effectiveness has been seen[3] with long-term use but others[4] have reported management of recurrences by adjustment of maintenance dosage; there seemed to be individual variations in sensitivity to sulindac with respect to prevention of polyp recurrence although an average maintenance dose of 200 mg daily appeared to be needed.[4]

There is evidence[5] that sulindac alters the ratio of apoptosis of surface cells relative to those lying deeper in the crypt of rectal mucosa, thus altering epithelial homoeostasis. Whether sulindac prevents malignant degeneration is unknown but there have been reports[6-8] of patients who developed rectal cancer during or after long-term therapy for adenomatous polyposis. A more recent, placebo-controlled trial[9] has also reported that sulindac did not reduce the development of adenomas in patients with familial adenomatous polyposis. Some[1,9] consider that sulindac is unlikely to replace surgery as primary therapy for familial adenomatous polyposis.

A sulfone metabolite of sulindac, exisulind (p.720) has also been investigated for the treatment of familial adenomatous polyposis.

Sulindac has also been reported to have produced beneficial effects in a patient with duodenal polyps associated with Gardner's syndrome[10] but a placebo-controlled study has suggested that it may not be effective against sporadic type colonic polyps.[11]

For a discussion of evidence suggesting that regular use of NSAIDs may protect against various types of malignant neoplasms of the gastrointestinal tract, see Malignant Neoplasms in NSAIDs, p.100.

1. Giardiello FM, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328:** 1313–16.
2. Debinski HS, *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; **345:** 855–6.
3. Tonelli F, Valanzano R. Sulindac in familial adenomatous polyposis. *Lancet* 1993; **342:** 1120.
4. Labayle D, *et al.* Sulindac in familial adenomatous polyposis. *Lancet* 1994; **343:** 417–18.
5. Keller JJ, *et al.* Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac. *Gut* 1999; **45:** 822–8.
6. Thorson AG, *et al.* Rectal cancer in FAP patient after sulindac. *Lancet* 1994; **343:** 180.
7. Matsuhashi N, *et al.* Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. *Am J Gastroenterol* 1998; **93:** 2261–6.
8. Cruz-Correa M, *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002; **122:** 641–5.
9. Giardiello FM, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002; **346:** 1054–9.
10. Parker AL, *et al.* Disappearance of duodenal polyps in Gardner's syndrome with sulindac therapy. *Am J Gastroenterol* 1993; **88:** 93–4.
11. Ladenheim J, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995; **108:** 1083–7.

Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Sulindac has also been tried[1,2] as an alternative to indometacin as it appears to have little placental transfer and may therefore have fewer fetal adverse effects.[1] However, the authors of a subsequent study suggested that sulindac had many of the same adverse fetal effects as indometacin and its use could only be described as investigational.[3] A study[4] using relatively low doses of sulindac (100 mg twice daily) did not note any significant fetal or maternal adverse effects but also found the drug to be ineffective in extending gestation or improving outcome.

1. Carlan SJ, *et al.* Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. *Obstet Gynecol* 1992; **79:** 223–8.
2. Carlan SJ, *et al.* Outpatient oral sulindac to prevent recurrence of preterm labor. *Obstet Gynecol* 1995; **85:** 769–74.
3. Kramer WB, *et al.* A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999; **180:** 396–401.
4. Humphrey RG, *et al.* Sulindac to prevent recurrent preterm labor: a randomized controlled trial. *Obstet Gynecol* 2001; **98:** 555–62.

Preparations

BP 2008: Sulindac Tablets;
USP 31: Sulindac Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Aclin; Clinoril†; ***Austria:*** Clinoril; ***Belg.:*** Clinoril; ***Canad.:*** Apo-Sulin; Novo-Sundac; ***Cz.:*** Clinoril†; ***Denm.:*** Clinoril†; ***Fr.:*** Arthrocine; ***Hong Kong:*** Aclin; Clinoril; ***Irl.:*** Clinoril; ***Ital.:*** Algocetil; Clinoril; Sulen†; ***Malaysia:*** Aclin†; Apo-Sulin†; Clinoril†; ***Mex.:*** Atriser; Bio-Dac; Clinoril; Clison; Copal; Kenalin; Renidac; Sulifur; Vindacin; ***Norw.:*** Clinoril; ***NZ:*** Clinoril; Daclin; ***Port.:*** Artribid; ***Singapore:*** Apo-Sulin; ***Spain:*** Sulindal; ***Swed.:*** Clinoril; ***Switz.:*** Clinoril†; ***Thai.:*** Cenlidac; Clinoril; ***UK:*** Clinoril; ***USA:*** Clinoril; ***Venez.:*** Clinoril†.

Superoxide Dismutase

SOD; Superóxido dismutasa.

Description. Superoxide dismutase represents a group of water-soluble protein congeners widely distributed in nature which catalyse the conversion of superoxide radicals to peroxide. Several different forms exist, which vary in their metal content; forms containing copper or copper and zinc are common.

Orgotein *(BAN, USAN, rINN)*

Bovine Superoxide Dismutase; Orgoteiini; Orgoteína; Orgotéine; Orgoteinum; Ormetein.

Орготеин

CAS — 9016-01-7.
ATC — M01AX14.
ATC Vet — QM01AX14.

Description. Orgotein is a superoxide dismutase produced from beef liver as Cu-Zn mixed chelate. Mol. wt about 33 000 with a compact conformation maintained by about 4 gram-atoms of chelated divalent metal.

Pegorgotein *(USAN, rINN)*

Pegorgoteína; Pégorgotéine; Pegorgoteinum; PEG-SOD; Win-22118.

Пэгорготеин

CAS — 155773-57-2.

Description. Pegorgotein is a superoxide dismutase conjugated with polyethylene glycol to prolong its duration of action.

Sudismase *(rINN)*

Sudismasa; Sudismasum.

Судизмаза

CAS — 110294-55-8.

Description. Sudismase is a human *N*-acetylsuperoxide dismutase produced by recombinant DNA technology and containing a copper and zinc prosthetic group.

Adverse Effects

Anaphylaxis and other hypersensitivity reactions, sometimes fatal, have been reported with orgotein. Local reactions and pain may occur at the site of injection of orgotein.

Pharmacokinetics

◊ References.

1. Tsao C, *et al.* Pharmacokinetics of recombinant human superoxide dismutase in healthy volunteers. *Clin Pharmacol Ther* 1991; **50:** 713–20.
2. Uematsu T, *et al.* Pharmacokinetics and safety of intravenous recombinant human superoxide dismutase (NK341) in healthy subjects. *Int J Clin Pharmacol Ther* 1994; **32:** 638–41.
3. Jadot G, *et al.* Clinical pharmacokinetics and delivery of bovine superoxide dismutase. *Clin Pharmacokinet* 1995; **28:** 17–25.
4. Rosenfeld WN, *et al.* Safety and pharmacokinetics of recombinant human superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1996; **97:** 811–17.
5. Davis JM, *et al.* Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1997; **100:** 24–30.
6. Schwedhelm E, *et al.* Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. *Clin Pharmacokinet* 2003; **42:** 437–59.

Uses and Administration

Superoxide dismutases have anti-inflammatory properties. Orgotein, a bovine derived superoxide dismutase, has been given by local injection, into the joints for degenerative joint disorders, but hypersensitivity reactions have limited its use. It has also been tried for the amelioration of adverse effects from radiotherapy. Forms of human superoxide dismutase derived by recombinant DNA technology have been developed.

Superoxide dismutases are also under investigation for their free-radical scavenging properties in a variety of conditions including the prevention of bronchopulmonary dysplasia in neonates.

Bronchopulmonary dysplasia. Use of sudismase in premature infants treated for respiratory distress syndrome did not prevent development of bronchopulmonary dysplasia (p.1500) in the first month.[1] However, treated infants subsequently showed a lower incidence of severe respiratory disease and hospitalisations in the first year, suggesting a reduction in chronic lung injury. The antioxidant was given intratracheally in a dose of 5 mg/kg every 48 hours as long as intubation and ventilation were necessary. A systematic review[2] was unable to reach a firm conclusion about the efficacy of superoxide dismutases in preventing chronic lung disease.

1. Davis JM, *et al.* Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; **111:** 469–76.
2. Suresh GK, *et al.* Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/05/05).

Head injury. Pegorgotein was found[1] to be little more effective than placebo in improving neurological outcome or reducing mortality in patients with severe head injury.

1. Young B, *et al.* Effects of pegorgotein on neurologic outcome of patients with severe head injury: a multicenter, randomized controlled trial. *JAMA* 1996; **276:** 538–43.

Motor neurone disease. A small percentage of patients with familial amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) have been shown to have a mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase but there has been no consensus as to whether patients with this mutation should be given superoxide dismutase supplements.[1]

1. Orrell RW, deBelleroche JS. Superoxide dismutase and ALS. *Lancet* 1994; **344:** 1651–2.

Radiotherapy. Although some studies[1,2] indicate that orgotein can ameliorate the adverse effects of radiotherapy for bladder tumours, another study[3] was terminated prematurely because of unacceptable hypersensitivity reactions and apparent inefficacy.

1. Sanchiz F, *et al.* Prevention of radioinduced cystitis by orgotein: a randomized study. *Anticancer Res* 1996; **16:** 2025–8.
2. Valencia J, *et al.* The efficacy of orgotein in the treatment of acute toxicity due to radiotherapy on head and neck tumors. *Tumori* 2002; **88:** 385–9.
3. Nielsen OS, *et al.* Orgotein in radiation treatment of bladder cancer: a report on allergic reactions and lack of radioprotective effect. *Acta Oncol* 1987; **26:** 101–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Ontosein†.

Multi-ingredient: ***Arg.:*** Vitix; ***Indon.:*** Glisodin.

Suprofen *(BAN, USAN, rINN)*

R-25061; Suprofeeni; Suprofène; Suprofeno; Suprofenum; Sutoprofen. 2-[4-(2-Thenoyl)phenyl]propionic acid.

Супрофен

$C_{14}H_{12}O_3S = 260.3.$
CAS — 40828-46-4.
ATC — M01AE07.
ATC Vet — QM01AE07.

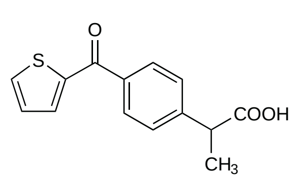

Pharmacopoeias. In *US.*
USP 31 (Suprofen). A white to off-white powder, odourless or having a slight odour. Sparingly soluble in water.

Profile

Suprofen is an NSAID (p.96). Suprofen has been used as 1% eye drops to inhibit the miosis that may occur during ocular surgery.

It was formerly given orally in mild to moderate pain and in osteoarthritis and rheumatoid arthritis but, after reports of adverse renal reactions, marketing of the oral dose form was suspended worldwide.

Preparations

USP 31: Suprofen Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
USA: Profenal†.

Suxibuzone *(BAN, rINN)*

Suksibutsoni; Suksibuzonas; Suxibuzon; Suxibuzona; Suxibuzonum; Szuxibuzon. 4-Butyl-4-hydroxymethyl-1,2-diphenylpyrazolidine-3,5-dione hydrogen succinate (ester).

Суксибузон

$C_{24}H_{26}N_2O_6 = 438.5.$
CAS — 27470-51-5.
ATC — M02AA22.
ATC Vet — QM01AA90; QM02AA22.

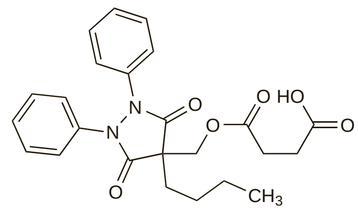

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Suxibuzone). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone; practically insoluble in cyclohexane.

Profile

Suxibuzone, a derivative of phenylbutazone (p.117), is an NSAID (p.96) that has been applied topically at a concentration of about 7% in musculoskeletal and joint disorders. Concern over safety and toxicity after oral use has led to its withdrawal from the market in many countries.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Danilon.

Tenoxicam *(BAN, USAN, rINN)*

Ro-12-0068; Ro-12-0068/000; Tenoksikaami; Tenoksikam; Tenoksikamas; Ténoxicam; Tenoxicamum; Tenoxikám; Tenoxikam. 4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-thieno[2,3-e][1,2]thiazine-3-carboxamide 1,1-dioxide.

Теноксикам

$C_{13}H_{11}N_3O_4S_2 = 337.4.$
CAS — 59804-37-4.
ATC — M01AC02.
ATC Vet — QM01AC02.

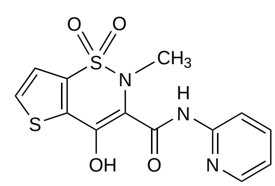

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Tenoxicam). A yellow, polymorphic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in dichloromethane; it dissolves in solutions of acids and alkalis. Protect from light.

Stability. An admixture of tenoxicam 0.02% and ceftazidime 0.5% (as the sodium salt) in glucose injection 5% appeared stable when stored for up to 120 hours at 25° in glass bottles;[1] when stored in PVC bags, the admixture was stable for up to 72 hours at 25° and for up to 144 hours at 4°.

1. Wang D-P, *et al.* Compatibility and stability of ceftazidime sodium and tenoxicam in 5% dextrose injection. *Am J Health-Syst Pharm* 2004; **61:** 1924–7.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Incidence of adverse effects. Adverse effects associated with tenoxicam have been reviewed.[1] The majority of adverse effects relate to the gastrointestinal tract (11.4%), nervous system (2.8%), or skin (2.5%).

Gastrointestinal disturbances including nausea and vomiting (14.7%) and dyspepsia (2.3%), surgical site bleeding (4.3%), wound infection (2.7%), dizziness (5.7%), and headache (10.7%) were the most common adverse effects reported in a placebo-controlled study involving 1001 patients following the perioperative use of oral and intravenous tenoxicam.[2] It was noted, however, that the incidence of dizziness, nausea and vomiting, and headache was greater in the placebo group and that the difference in the incidence of dyspepsia between the 2 groups was not significant.

1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41:** 625–46.
2. Merry AF, *et al.* Clinical tolerability of perioperative tenoxicam in 1001 patients – a prospective, controlled, double-blind, multi-centre study. *Pain* 2004; **111:** 313–22.

Effects on the kidneys. A review[1] of the effects of tenoxicam on renal function concluded that tenoxicam could be given at normal recommended doses to elderly patients or those with mild to moderate renal impairment who were not at high risk of renal failure or receiving potentially nephrotoxic therapy. Data from the manufacturer's database[1] on 67 063 patients, including 17 005 over 65 years of age, who had received tenoxicam indicated that there had been 45 adverse events relating to urinary system function, described as severe in 7. The prevalence of adverse events was similar in elderly and non-elderly patients, the most common effects being dysuria and renal pain.

1. Heintz RCA. Tenoxicam and renal function. *Drug Safety* 1995; **12:** 110–19.

Effects on the liver. A report[1] of acute hepatitis associated with the use of tenoxicam.

1. Sungur C, *et al.* Acute hepatitis caused by tenoxicam. *Ann Pharmacother* 1994; **28:** 1309.

Effects on the skin. A report of 3 cases of toxic epidermal necrolysis (Lyell's syndrome) associated with tenoxicam.[1]

For the general incidence of dermatological effects see above.

1. Chosidow O, *et al.* Toxidermies sévères au ténoxicam (Tilcotil). *Ann Dermatol Venereol* 1991; **118:** 903–4.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Tenoxicam is well absorbed after oral doses; peak plasma concentrations occur within about 2 hours in fasting subjects; this may be delayed to about 6 hours when tenoxicam is given with food but the extent of absorption is not affected. It is also rapidly absorbed when given by intramuscular injection. Tenoxicam is about 99% protein bound and penetrates synovial fluid. The plasma elimination half-life ranges from 42 to 81 hours; with daily dosage, steady-state concentrations are reached within 10 to 15 days. Tenoxicam is completely metabolised to inactive metabolites which are excreted mainly in the urine; there is some biliary excretion of glucuronide conjugates of the metabolites.

◊ References.

1. Nilsen OG. Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet* 1994; **26:** 16–43.
2. Guentert TW, *et al.* Relative bioavailability of oral dosage forms of tenoxicam. *Arzneimittelforschung* 1994; **44:** 1051–4.
3. Nilsen OG, *et al.* Single- and multiple-dose pharmacokinetics, kidney tolerability and plasma protein binding of tenoxicam in renally impaired patients and healthy volunteers. *Pharmacol Toxicol* 2001; **89:** 265–72.

Uses and Administration

Tenoxicam, a piroxicam (p.117) analogue, is an NSAID (p.99). It is used in the symptomatic management of musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and also in the short-term management of soft-tissue injury. Tenoxicam is given as a single oral daily dose usually of 20 mg. In acute musculoskeletal disorders treatment for up to 7 days is usually sufficient but in severe cases it may be given for up to a maximum of 14 days. Doses similar to those given orally have been given by intramuscular or intravenous injection for initial treatment for 1 or 2 days. Tenoxicam has also been given by rectal suppository.

◊ References.

1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41:** 625–46.

Preparations

BP 2008: Tenoxicam Injection; Tenoxicam Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Mefenix†; ***Austria:*** Tilcotil; ***Belg.:*** Tilcotil; ***Braz.:*** Inflagel; Prodoxican; Teflan; Tenobio†; Tenocam†; Tenotec; Tenoxen†; Tilatil; Tilonax; Tiloxican†; Titenil†; ***Chile:*** Avancel†; Bioflam; Mitrotil; Recaflex; Texicam†; Tilcotil; ***Denm.:*** Tilcotil; ***Fin.:*** Tilcotil; ***Fr.:*** Tilcotil; ***Gr.:*** Admiral; Algin-Vek; Amcinafal; Ampirovix; Artroxicam; Artruic†; Aspagin; Biodruff; Docticam†; Dranat; Hobaticam; Indo-bros; Istotosal; Liaderyl; Neo-adlibamin; Neo-antiperstam; Neo-endusix; Octiveran; Oxytel; Ponsolit; Redac; Soral; Tenox†; Tentepanil; Tilcitin; Toscacalm; Velasor; Voir; Zibelant; ***Hong Kong:*** Nadamen†; Seftil†; Tilcotil; ***Hung.:*** Tilcotil; ***India:*** Tobitil; ***Indon.:*** Articom; Meditil; Notritis; Oxaflam; Pilopil; Thenil; Tilcotil; Tilflam; Xotilon; ***Irl.:*** Mobiflex†; ***Ital.:*** Dolmen; Rexalgan; Tilcotil; ***Jpn:*** Tilcotil; ***Malaysia:*** Nadamen†; Seftil; Sinoral†; Tilcotil; ***Mex.:*** Tilcotil; ***Neth.:*** Tilcotil; ***NZ:*** Tilcotil; ***Philipp.:*** Tilcotil; ***Port.:*** Bioreucam†; Calibral†; Doxican; Tenalgin; Tilcotil; ***S.Afr.:*** Tilcotil; Tobitil†; ***Singapore:*** Nadamen†; ***Spain:*** Artriunic; Reutenox; Tilcotil†; ***Swed.:*** Alganex; ***Switz.:*** Tilcotil; ***Thai.:*** Memzotil; Nadamen†; Seftil; Sinoral; Teconam; Tenax; Tenocam; Tenox; Tenoxil; Tenxil; Tilcotil; Tonox; ***Turk.:*** Nobateks; Oksamen; Tenoksan; Tenoktil; Tenox; Tilcotil; Tilko; VienOks; Zikaral; ***UK:*** Mobiflex; ***Venez.:*** Rodix; Tecam†; Tenoxin; Tilcotil†.

Multi-ingredient: ***Arg.:*** Mefenix Relax†.

Tepoxalin *(USAN, rINN)*

ORF-20485; RWJ-20485; Tepoksaliini; Tepoxalina; Tépoxaline; Tepoxalinum. 5-(*p*-Chlorophenyl)-1-(*p*-methoxyphenyl)-*N*-methylpyrazole-3-propionohydroxamic acid.

Тепоксалин

$C_{20}H_{20}ClN_3O_3$ = 385.8.

CAS — 103475-41-8.

ATC Vet — QM01AE92.

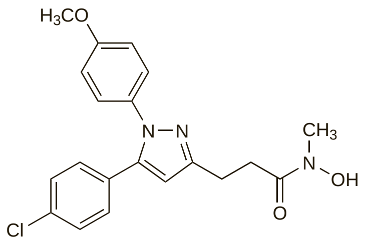

Profile

Tepoxalin, a propionic acid derivative, is an NSAID used in veterinary medicine for the treatment of inflammation and pain in dogs.

Tetridamine *(rINN)*

POLI-67; Tetridamina; Tétridamine; Tetridaminum; Tetrydamine *(USAN)*. 4,5,6,7-Tetrahydro-2-methyl-3-(methylamino)-2*H*-indazole.

Тетридамин

$C_9H_{15}N_3$ = 165.2.

CAS — 17289-49-5.

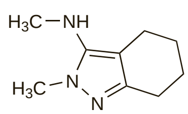

Profile

Tetridamine is an NSAID (p.96) that has been used as the maleate as a douche in the treatment of vaginitis.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Deb; ***Spain:*** Fomene.

Thurfyl Salicylate

Salicilato de turfilo. Tetrahydrofurfuryl salicylate.

$C_{12}H_{14}O_4$ = 222.2.

CAS — 2217-35-8.

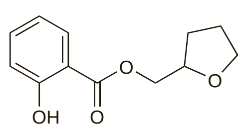

Profile

Thurfyl salicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p.85) in topical rubefacient preparations at concentrations of up to 14% for musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Austral.:* Biosal Arthritis; ***Belg.:*** Transvane; ***Irl.:*** Transvasin; ***UK:*** Transvasin Heat Rub.

Tiaprofenic Acid *(BAN, rINN)*

Acide tiaprofénique; Ácido tiaprofénico; Acidum tiaprofenicum; FC-3001; Kyselina tiaprofenová; RU-15060; Tiaprofeenihappo; Tiaprofenik Asit; Tiaprofeno rūgštis; Tiaprofensyra. 2-(5-Benzoyl-2-thienyl)propionic acid.

Тиапрофеновая Кислота

$C_{14}H_{12}O_3S$ = 260.3.

CAS — 33005-95-7.

ATC — M01AE11.

ATC Vet — QM01AE11.

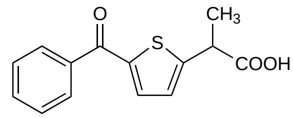

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tiaprofenic Acid). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Tiaprofenic acid may cause cystitis, bladder irritation, and other urinary-tract symptoms (see below). It should not be given to patients with active urinary-tract disorders or prostatic disease or a history of recurrent urinary-tract disorders. It should be stopped immediately if urinary-tract symptoms occur and urinalysis and urine culture performed.

Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment.

Breast feeding. Although tiaprofenic acid is distributed into breast milk, the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. Licensed product information also states that exposure to tiaprofenic acid via breast milk is unlikely to be of pharmacological significance; however, it is recommended that either treatment or breast feeding is stopped as necessary.

Effects on the urinary tract. Cystitis and bladder irritation have been associated with the use of tiaprofenic acid.[1-6] In August 1994 the UK CSM stated[4] that since the introduction of tiaprofenic acid in the UK in 1982 they had received 69 reports of cystitis and 32 other reports of urinary-tract symptoms associated with tiaprofenic acid including frequency, dysuria, and haematuria whereas only 8 cases of cystitis had been reported for all other NSAIDs combined. Analysis of spontaneous reports received by WHO[7] confirmed that cystitis was more commonly associated with tiaprofenic acid than with other NSAIDs. The Australian Adverse Drug Reactions Advisory Committee had received similar reports.[3] Since the 1994 warning, the CSM[8] had received reports of a further 74 cases of cystitis, but the majority of these had occurred before the warning was issued. The duration of treatment in patients affected had varied considerably. Most patients recovered when tiaprofenic acid was withdrawn.

The CSM recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and that it should be stopped in patients who develop urinary-tract symptoms. Patients should be advised that if they develop symptoms such as urinary frequency, nocturia, urgency, or pain on urination, or have blood in their urine they should stop taking tiaprofenic acid and consult their doctor. Older patients may be at increased risk.[9]

1. Ahmed M, Davison OW. Severe cystitis associated with tiaprofenic acid. *BMJ* 1991; **303:** 1376.
2. O'Neill GFA. Tiaprofenic acid as a cause of non-bacterial cystitis. *Med J Aust* 1994; **160:** 123–5.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Update on tiaprofenic acid and urinary symptoms. *Aust Adverse Drug React Bull* 1994; **13:** 6.
4. CSM/MCA. Severe cystitis with tiaprofenic acid (Surgam). *Current Problems* 1994; **20:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
5. Harrison WJ, *et al.* Adverse reactions to tiaprofenic acid mimicking interstitial cystitis. *BMJ* 1994; **309:** 574.
6. Mayall FG, *et al.* Cystitis and ureteric obstruction in patients taking tiaprofenic acid. *BMJ* 1994: **309:** 599.
7. The ADR Signals Analysis Project (ASAP) Team. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacol Toxicol* 1997; **80:** 211–17.
8. Crawford MLA, *et al.* Severe cystitis associated with tiaprofenic acid. *Br J Urol* 1997; **79:** 578–84.
9. Buchbinder R, *et al.* Clinical features of tiaprofenic acid (surgam) associated cystitis and a study of risk factors for its development. *J Clin Epidemiol* 2000; **53:** 1013–19.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Tiaprofenic acid is absorbed from the gastrointestinal tract with peak plasma concentrations being reached within about 1.5 hours after oral doses. It has a short elimination half-life of about 2 hours and is highly bound to plasma proteins (about 98%). Excretion of tiaprofenic acid and its metabolites is mainly in the urine in the form of acyl glucuronides; some is excreted in the bile. Tiaprofenic acid crosses the placenta and is distributed into breast milk.

◊ References.

1. Davies NM. Clinical pharmacokinetics of tiaprofenic acid and its enantiomers. *Clin Pharmacokinet* 1996; **31:** 331–47.

Uses and Administration

Tiaprofenic acid, a propionic acid derivative, is an NSAID (p.99). It is used for the relief of pain and inflammation in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in peri-articular disorders such as fibrositis and capsulitis, and in soft-tissue disorders such as sprains and strains. The usual oral dose is 600 mg daily given in 2 or 3 divided doses; in patients with cardiac, hepatic, or renal impairment, licensed product information suggests that the dose is reduced to 200 mg twice daily. A modified-release preparation may be available for once-daily use. Tiaprofenic acid has also been given rectally. It has been given intramuscularly as the trometamol salt in acute conditions.

◊ References.

1. Plosker GL, Wagstaff AJ. Tiaprofenic acid: a reappraisal of its pharmacological properties and use in the management of rheumatic diseases. *Drugs* 1995; **50:** 1050–75.

Administration in hepatic or renal impairment. Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment; for dosage details in those with more moderate impairment, see Uses and Administration, above.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Surgam; ***Canad.:*** Albert Tiafen†; Surgam; ***Cz.:*** Surgam; Thialgin; ***Denm.:*** Surgamyl; ***Fin.:*** Surgamyl; ***Fr.:*** Flanid; Surgam; ***Ger.:*** Surgam; ***Hung.:*** Surgam; ***Irl.:*** Surgam; ***Ital.:*** Suralgan†; Surgamyl; Tiaprofen†; ***Mex.:*** Surgam; ***Neth.:*** Surgam; ***NZ:*** Surgam; ***Pol.:*** Surgam; ***Port.:*** Surgam; ***S.Afr.:*** Surgam; ***Thai.:*** Fengam; Surgam†; ***Turk.:*** Surgam; ***UK:*** Surgam; ***Venez.:*** Torpas.

Tiaramide Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de tiaramida; NTA-194; Tiaperamide Hydrochloride; Tiaramide, Chlorhydrate de; Tiaramidi Hydrochloridum. 5-Chloro-3-{2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl}benzothiazolin-2-one hydrochloride.

Тиарамида Гидрохлорид

$C_{15}H_{18}ClN_3O_3S,HCl$ = 392.3.

CAS — 32527-55-2 (tiaramide); 35941-71-0 (tiaramide hydrochloride).

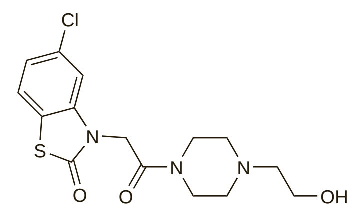

(tiaramide)

Pharmacopoeias. In *Jpn.*

Profile

Tiaramide hydrochloride is an NSAID (p.96) that has been given orally for the relief of pain and inflammation.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Solantal†.

Tilidine Hydrochloride *(USAN, pINNM)*

Gö 1261-C; Hidrocloruro de tilidina; Tilidate Hydrochloride *(BANM)*; Tilidiinihydrokloridihemihydraatti; Tilidine, Chlorhydrate de; Tilidine (chlorhydrate de) hémihydraté; Tilidin-hydrochlorid hemihydrát; Tilidinhydroklorid hemihydrat; Tilidini Hydrochloridum; Tilidini hydrochloridum hemihydricum; Tilidino hidrochloridas hemihidratas; W-5759A. (±)-Ethyl *trans*-2-dimethylamino-1-phenylcyclohex-3-ene-1-carboxylate hydrochloride hemihydrate.

Тилидина Гидрохлорид

$C_{17}H_{23}NO_2,HCl,\frac{1}{2}H_2O$ = 318.8.

CAS — 20380-58-9 (tilidine); 27107-79-5 (anhydrous tilidine hydrochloride); 24357-97-9 (anhydrous +-trans-tilidine hydrochloride).

ATC — N02AX01.

ATC Vet — QN02AX01.

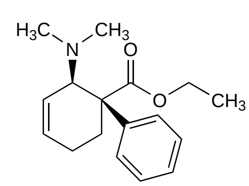

(tilidine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tilidine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. A suitable antoxidant may be added. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics in general, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

Overdosage. Cyanosis, respiratory depression, and seizures developed in a 28-year-old woman after an overdose of a combination preparation of tilidine and naloxone.[1] The authors commented that the amount of naloxone included in the preparation, in order to prevent abuse, was insufficient to prevent respiratory depression after severe overdose.

1. Regenthal R, *et al.* Poisoning with tilidine and naloxone: toxicokinetic and clinical observations. *Hum Exp Toxicol* 1998; **17:** 593–7.

Porphyria. Tilidine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics

Tilidine is absorbed from the gastrointestinal tract. It is metabolised and excreted in the urine mainly as metabolites nortilidine (nortilidate) and bisnortilidine (bisnortilidate). Nortilidine is responsible for the analgesic activity of tilidine.

◊ References.

1. Vollmer K-O, *et al.* Pharmacokinetics of tilidine and metabolites in man. *Arzneimittelforschung* 1989; **39:** 1283–8.
2. Seiler K-U, *et al.* Pharmacokinetics of tilidine in terminal renal failure. *J Clin Pharmacol* 2001; **41:** 79–84.
3. Hajda JP, *et al.* Sequential first-pass metabolism of nortilidine: the active metabolite of the synthetic opioid drug tilidine. *J Clin Pharmacol* 2002; **42:** 1257–61.
4. Brennscheidt U, *et al.* Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; **57:** 106–11.

Uses and Administration

Tilidine hydrochloride is an opioid analgesic (p.104). It is used in the control of moderate to severe pain.

Tilidine hydrochloride may be given in usual oral doses of up to 50 mg four times daily. It has been given as a suppository, or by intravenous, intramuscular, or subcutaneous injection. Tilidine has also been given as the phosphate in modified release tablets. As a deterrent to abuse combined oral preparations of tilidine hydrochloride with naloxone hydrochloride are available in some countries.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Tinalox; Valoron†; Valtran; ***Cz.:*** Valoron†; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura; Tiligetic†; Tilimerck†; Tilnalox; Valoron N; ***S.Afr.:*** Valoron; ***Switz.:*** Valoron.

Tolfenamic Acid *(BAN, rINN)*

Acide Tolfénamique; Ácido tolfenámico; Acidum tolfenamicum; Kyselina tolfenamová; Tolfenaamihappo; Tolfenaminsav; Tolfenamo rūgštis; Tolfenamsyra. *N*-(3-Chloro-*o*-tolyl)anthranilic acid.

Толфенамовая Кислота

$C_{14}H_{12}ClNO_2$ = 261.7.
CAS — 13710-19-5.
ATC — M01AG02.
ATC Vet — QM01AG02.

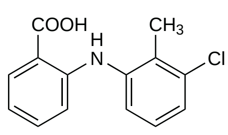

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tolfenamic Acid). A white or slightly yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; soluble in dimethylformamide. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Dysuria, most commonly in males and probably due to local irritation of the urethra by a metabolite, has been reported. Tremor, euphoria, and fatigue have also occurred. Tolfenamic acid is contra-indicated in patients with significant hepatic or renal impairment.

Breast feeding. Although tolfenamic acid is distributed into breast milk, the amount is considered by the *BNF* and licensed product information to be too small to be harmful to a breast-fed infant.

Effects on the lungs. Pulmonary infiltration has been associated with tolfenamic acid treatment in 6 patients.[1]

1. Strömberg C, *et al.* Pulmonary infiltrations induced by tolfenamic acid. *Lancet* 1987; **ii:** 685.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Tolfenamic acid is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached about 60 to 90 minutes after an oral dose. Tolfenamic acid is about 99% bound to plasma proteins. The plasma half-life is about 2 hours. Tolfenamic acid is metabolised in the liver; the metabolites and unchanged drug are conjugated with glucuronic acid. About 90% of an ingested dose is excreted in the urine and the remainder in the faeces. Tolfenamic acid is distributed into breast milk.

Uses and Administration

Tolfenamic acid, an anthranilic acid derivative related to mefenamic acid (p.80), is an NSAID (p.99). In the treatment of acute attacks of migraine tolfenamic acid is given in a usual oral dose of 200 mg when the first symptoms appear; if a satisfactory response is not obtained this dose may be repeated once after 1 to 2 hours. Tolfenamic acid has also been given for the relief of mild to moderate pain in disorders such as dysmenorrhoea, rheumatoid arthritis, or osteoarthritis in doses of 100 to 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Flocur; ***Austria:*** Migea; ***Braz.:*** Fenamic†; ***Cz.:*** Migea; ***Denm.:*** Clotam†; Migea; ***Fin.:*** Clotam; Migea†; ***Gr.:*** Clotam; Gantil; Polmonin; Primactam; Purfalox; Tolfamic; Turbaund; ***Mex.:*** Bifenac†; Flocur†; ***Neth.:*** Clotam; Rociclyn†; ***Norw.:*** Migea†; ***Pol.:*** Migea; ***Swed.:*** Migea†; ***Switz.:*** Clotam†; ***UK:*** Clotam; ***Venez.:*** Clotan†.

Tolmetin Sodium *(BANM, USAN, rINNM)*

McN-2559-21-98; McN-2559 (tolmetin); Natrii Tolmetinum; Tolmetina sódica; Tolmétine Sodique. Sodium (1-methyl-5-*p*-toluoylpyrrol-2-yl)acetate dihydrate.

Натрий Тольметин

$C_{15}H_{14}NNaO_3,2H_2O$ = 315.3.
CAS — 26171-23-3 (tolmetin); 35711-34-3 (anhydrous tolmetin sodium); 64490-92-2 (tolmetin sodium dihydrate).
ATC — M01AB03; M02AA21.
ATC Vet — QM01AB03; QM02AA21.

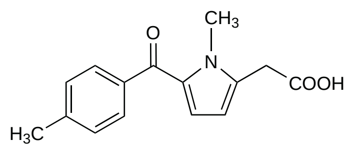

(tolmetin)

Pharmacopoeias. In *US.*

USP 31 (Tolmetin Sodium). A light yellow to light orange crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; very slightly soluble in chloroform.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given tolmetin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, licensed product information recommends that tolmetin should be avoided in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with tolmetin.

1. Sakai J, Joseph MW. Tolmetin and agranulocytosis. *N Engl J Med* 1978; **298:** 1203.
2. Lockhart JM. Tolmetin-induced thrombocytopenia. *Arthritis Rheum* 1982; **25:** 1144–5.

Effects on the CNS. See Hypersensitivity, below.

Effects on the gastrointestinal tract. Erosive oesophagitis has been reported[1] in an 11-year-old child after ingestion of a dose of tolmetin while lying down and without drinking any water.

1. Palop V, *et al.* Tolmetin-induced esophageal ulceration. *Ann Pharmacother* 1997; **31:** 929.

Effects on the kidneys. Interstitial nephritis[1] and nephrotic syndrome[2,3] have been reported in patients given tolmetin.

1. Katz SM, *et al.* Tolmetin: association with reversible renal failure and acute interstitial nephritis. *JAMA* 1981; **246:** 243–5.
2. Chatterjee GP. Nephrotic syndrome induced by tolmetin. *JAMA* 1981; **246:** 1589.
3. Tietjen DP. Recurrence and specificity of nephrotic syndrome due to tolmetin. *Am J Med* 1989; **87:** 354–5.

Hypersensitivity. Anaphylactic shock,[1] urticaria and angioedema,[2] and aseptic meningitis[3] are among the hypersensitivity reactions reported in patients taking tolmetin.

1. Rossi AC, Knapp DE. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; **307:** 499–500.
2. Ponte CD, Wisman R. Tolmetin-induced urticaria/angioedema. *Drug Intell Clin Pharm* 1985; **19:** 479–80.
3. Ruppert GB, Barth WF. Tolmetin-induced aseptic meningitis. *JAMA* 1981; **245:** 67–8.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Tolmetin is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are attained about 30 to 60 minutes after ingestion. It is extensively bound to plasma proteins (over 99%) and has a biphasic plasma half-life of about 1 to 2 hours and 5 hours, respectively. Tolmetin penetrates synovial fluid and very small amounts are distributed into breast milk. It is excreted in the urine as an inactive dicarboxylic acid metabolite and its glucuronide and as tolmetin glucuronide with small amounts of unchanged drug.

Uses and Administration

Tolmetin sodium is an NSAID (p.99). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, including juvenile idiopathic arthritis. It is given orally as the sodium salt although doses are expressed in terms of the base; tolmetin sodium dihydrate 122.5 mg is equivalent to about 100 mg of tolmetin.

For the treatment of rheumatoid arthritis and osteoarthritis, the usual initial oral dose is the equivalent of 400 mg of tolmetin three times daily. Doses should be adjusted after 1 to 2 weeks according to response; maintenance doses of 600 mg to a maximum of 1800 mg daily in divided doses have been used.

For dosage details in children, see below.

Tolmetin as the free acid has been applied as a topical gel.

Administration in children. For the treatment of juvenile idiopathic arthritis in children aged 2 years and over, tolmetin sodium is given in initial oral doses equivalent to 20 mg/kg of tolmetin daily in three or four divided doses; maintenance doses of 15 mg/kg to a maximum of 30 mg/kg daily have been used.

Preparations

USP 31: Tolmetin Sodium Capsules; Tolmetin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Tolectin†; ***Canad.:*** Tolectin†; ***Mex.:*** Tolectin; ***S.Afr.:*** Tolectin; ***Spain:*** Artrocaptin; ***Switz.:*** Tolectin†; ***Turk.:*** Tolectin; ***USA:*** Tolectin.

Tramadol Hydrochloride

(BANM, USAN, rINNM)

CG-315; CG-315E; Hidrocloruro de tramadol; Tramadol, chlorhydrate de; Tramadol Hidroklorür; Tramadol-hidroklorid; Tramadol-hydrochlorid; Tramadolhydroklorid; Tramadoli hydrochloridum; Tramadolihydrokloridi; Tramadolio hidrochloridas; U-26225A. (±)-*trans*-2-Dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride.

Трамадола Гидрохлорид

$C_{16}H_{25}NO_2,HCl$ = 299.8.
CAS — 27203-92-5 (tramadol); 22204-88-2 (tramadol hydrochloride); 36282-47-0 (tramadol hydrochloride).
ATC — N02AX02.
ATC Vet — QN02AX02.

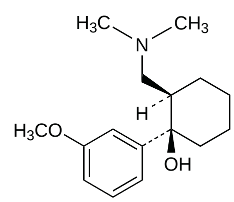

(tramadol)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tramadol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in acetone. Protect from light.

Incompatibility. Some manufacturers state that tramadol hydrochloride injection 50 mg/mL is incompatible with injections of diazepam, diclofenac sodium, flunitrazepam, glyceryl trinitrate, indometacin, midazolam, piroxicam, and phenylbutazone if mixed in the same syringe. A study[1] also found tramadol hydrochloride injection (diluted to 400 micrograms/mL) to be incompatible with aciclovir and clindamycin when mixed together.

1. Abanmy NO, *et al.* Compatibility of tramadol hydrochloride injection with selected drugs and solutions. *Am J Health-Syst Pharm* 2005; **62:** 1299–1302.

Stability. Oral suspensions of tramadol hydrochloride 5 mg/mL, prepared by mixing crushed tablets with a strawberry syrup and *Ora-Plus* (1:1) or with *Ora-Sweet* and *Ora-Plus* (1:1) were found to be stable for at least 90 days when stored either in the refrigerator or at room temperature.[1] Oral suspensions containing tramadol hydrochloride 7.5 mg/mL and paracetamol 65 mg/mL, prepared by mixing the crushed tablets of a combination preparation with the above vehicles, were also found to be stable for at least 90 days when stored under similar conditions.[2]

1. Wagner DS, *et al.* Stability of oral liquid preparations of tramadol in strawberry syrup and a sugar-free vehicle. *Am J Health-Syst Pharm* 2003; **60:** 1268–70.
2. Johnson CE, *et al.* Stability of tramadol hydrochloride–acetaminophen (Ultracet) in strawberry syrup and in a sugar-free vehicle. *Am J Health-Syst Pharm* 2004; **61:** 54–7.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Tramadol may have lower potential for producing dependence than morphine.

◊ A WHO expert committee[1] considered in 2003 that the available information on tramadol was not sufficient to warrant international control. Studies in *animals* indicated that tramadol produced little tolerance, had mild withdrawal symptoms, and a lower abuse potential than codeine and pentazocine. Subsequently, when reviewed in 2006, the committee[2] considered that, despite an increase in its use, tramadol continued to show a low level of abuse and concluded that there was not sufficient evidence to justify a further review.

Nevertheless, there have been reports[3-8] of dependence and abuse, particularly in opioid-dependent persons, and of withdrawal symptoms. In October 1996, the UK CSM[9] commented that since June 1994 they had received reports of drug dependence in 5 patients and withdrawal symptoms associated with tramadol in 28 patients, which corresponded to a reporting rate of about 1 in 6000. Doses in excess of the recommended maximum of 400 mg daily had been taken by 5 of the patients. The duration of treatment before onset of these effects ranged from 10 to 409 days (average 3 months). Withdrawal symptoms reported were typically those of opioid withdrawal in general. A more recent report from the Swedish Medical Products Agency[10] stated that between 1996 to 2005 they had received 71 reports of withdrawal symptoms associated with tramadol; treatment duration ranged from 1 week to over 3 years at daily doses of between 50 mg to 2 g.

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Also available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 26/06/08)
2. WHO. WHO expert committee on drug dependence: thirty-forth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
3. Rodriguez Villamañan JC, *et al.* Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract* 2000; **50:** 406.
4. Yates WR, *et al.* Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001; **158:** 964.
5. Brinker A, *et al.* Abuse, dependence, or withdrawal associated with tramadol. *Am J Psychiatry* 2002; **159:** 881.
6. Skipper GE, *et al.* Tramadol abuse and dependence among physicians. *JAMA* 2004; **292:** 1818–19.
7. Soyka M, *et al.* Tramadol use and dependence in chronic noncancer pain patients. *Pharmacopsychiatry* 2004; **37:** 191–2.
8. Ripamonti C, *et al.* Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry* 2004; **161:** 2326–7.
9. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
10. Läkemedelsverket (Medical Products Agency—Sweden). Utsättningsreaktioner av tramadol—ett större problem än förväntat? (issued 14 November, 2006). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage____5449.aspx (accessed 26/06/08)

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Tramadol may produce fewer typical opioid adverse effects such as respiratory depression and constipation. In addition to hypotension, hypertension has occasionally occurred.

Effects on the CNS. The UK CSM[1] commented in February 1995 that since June 1994 they had received reports of 15 patients who had experienced *confusion* and/or *hallucinations* while taking tramadol. The majority of the reactions developed 1 to 7 days after starting treatment and in most patients resolved rapidly on withdrawal. It was noted that psychiatric reactions comprised about 10% of all reactions reported with tramadol.

In a later comment[2] in October 1996, the CSM noted that 27 reports of *convulsions* and one of worsening epilepsy had been received, which corresponded to a reporting rate of about 1 in 7000. Of the 5 patients receiving intravenous tramadol, 2 had been given doses equivalent to 1.45 and 4 g daily, well in excess of those recommended (see also Overdosage, below). Of the patients receiving oral tramadol, the majority were taking other drugs known to cause convulsions, including tricyclic antidepressants and SSRIs. A similar pattern has been reported in the USA[3] and Australia.[4-6]

A debilitating CNS-mediated reaction to an initial dose of tramadol has been described in a patient.[7] Symptoms, which lasted about 4 hours, included ataxia, dilatation of the pupils, numbness in all limbs, tremulousness, and dysphoria. Although the exact mechanism of the reaction was not known, it was suggested that since the patient was an extensive metaboliser with very high activity of the cytochrome P450 isoenzyme CYP2D6, high concentrations of the active *O*-desmethyl metabolite were the cause. The patient recovered with no sequelae. It is possible that this represents a case of the *serotonin syndrome*, since tramadol is known to be associated with this condition, particularly at high doses or when given with other drugs that raise serotonin concentrations.[4]

1. CSM/MCA. Tramadol (Zydol)—psychiatric reactions. *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
3. Kahn LH, *et al.* Seizures reported with tramadol. *JAMA* 1997; **278:** 1661.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol—four years experience. *Aust Adverse Drug React Bull* 2003; **22**: 1–2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 26/06/08)
5. Labate A, *et al.* Tramadol and new-onset seizures. *Med J Aust* 2005; **182:** 42–3.
6. Boyd IW. Tramadol and seizures. *Med J Aust* 2005; **182:** 595–6.
7. Gleason PP, *et al.* Debilitating reaction following the initial dose of tramadol. *Ann Pharmacother* 1997; **31:** 1150–2.

Effects on the respiratory system. Respiratory depression has been reported after tramadol infusion anaesthesia,[1] although in a postoperative study[2] tramadol had no significant respiratory depressant effect when equianalgesic doses of morphine, pentazocine, pethidine, piritramide, and tramadol were compared.

1. Paravicini D, *et al.* Tramadol-infusionsanaesthesie mit Substitution von Enfluran und differenten Lachgaskonzentrationen. *Anaesthesist* 1985; **34:** 20–7.
2. Fechner R, *et al.* Clinical investigations on the effect of morphine, pentazocine, pethidine, piritramide and tramadol on respiration. *Anasth Intensivmed* 1985; **26:** 126–32.

Overdosage. In a multicentre case series,[1] 126 cases of tramadol toxicity were reported between October 1995 and August 1996; of these, 87 involved exposure to tramadol alone. Common symptoms included lethargy, nausea, tachycardia, and agitation; seizures were also noted. Respiratory depression was seen in only 2 patients. The inhibitory effects of tramadol on monoamine reuptake, rather than its opioid effects, was considered to result in much of its toxicity. A similar pattern of toxicity has also been seen in a more recent report.[2] In 190 tramadol-only exposures reported between January 1999 and July 2001, the main symptoms of overdosage were CNS depression, nausea and vomiting, tachycardia, and seizures. Again, the incidence of respiratory depression was rare, with only 1 case reported.

1. Spiller HA, *et al.* Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 1997; **35:** 361–4.
2. Marquardt KA, *et al.* Tramadol exposures reported to statewide poison control system. *Ann Pharmacother* 2005; **39:** 1039–44.

Precautions

As for Opioid Analgesics in general, p.103.

Tramadol should be used with caution in patients with renal or hepatic impairment and should be avoided if renal impairment is severe. Removal by haemodialysis is reported to be minimal at 7%.

Tramadol should be used with care in patients with a history of epilepsy or those susceptible to seizures. See also Effects on the CNS under Adverse Effects, above.

Abuse. See under Dependence and Withdrawal, above.

Anaesthesia. Licensed product information warns against using tramadol during very light planes of general anaesthesia because of possible intra-operative awareness, although it may be used intra-operatively provided anaesthesia is maintained with a potent volatile or intravenous anaesthetic. Intra-operative awareness was reported in 65% of a group of 20 patients when used to provide analgesia during light general anaesthesia with nitrous oxide and intermittent enflurane.[1] However, in a study[2] of 51 patients given tramadol during stable light continuous isoflurane-nitrous oxide anaesthesia there was no clinically significant lightening of anaesthesia and others have commented that during extensive use of tramadol intra-operatively over several years, there had not been any incidence of recall in any patient treated at their clinic.[3]

1. Lehmann KA, *et al.* Zur Bedeutung von Tramadol als intraoperativem Analgetikum: eine randomisierte Doppelblindstudie im Vergleich zu Placebo. *Der Anaesthetist* 1985; **34:** 11–19.
2. Coetzee JF, *et al.* Effect of tramadol on depth of anaesthesia. *Br J Anaesth* 1996; **76:** 415–18.
3. Budd K. Tramadol. *Br J Anaesth* 1995; **75:** 500.

Interactions

For interactions associated with opioid analgesics, see p.103.

Carbamazepine is reported to diminish the analgesic activity of tramadol by reducing serum concentrations.

The risk of seizures is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold. See also Effects on the CNS under Adverse Effects, above.

Tramadol inhibits reuptake of noradrenaline and serotonin and enhances serotonin release and there is the possibility that it may interact with other drugs that enhance monoaminergic neurotransmission including lithium, tricyclic antidepressants, and SSRIs; it should not be given to patients receiving MAOIs or within 14 days of their discontinuation.

◊ Metabolism of tramadol is mediated by the cytochrome P450 isoenzyme CYP2D6. Use with specific inhibitors of this enzyme, such as *quinidine*, may increase concentrations of tramadol and lower concentrations of its active metabolite but the clinical consequences of this effect are unclear.

Anticoagulants. For reports of the effect of tramadol on oral anticoagulants, see Analgesics under Interactions of Warfarin, p.1427.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of tramadol and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397.

5-HT$_3$-receptor antagonists. The pre-operative use of *ondansetron* has been noted to reduce the postoperative analgesic efficacy of tramadol.[1,2] In one study,[1] the cumulative dose of tramadol was up to 35% greater in those patients who also received ondansetron compared to those who received no antiemetic. In addition there was no difference in the incidence of postoperative nausea and vomiting between the two groups.

1. De Witte JL, *et al.* The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; **92:** 1319–21.
2. Arcioni R, *et al.* Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT spinal receptor involvement in acute pain in humans. *Anesth Analg* 2002; **94:** 1553–7.

Pharmacokinetics

Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite *O*-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine, predominantly as metabolites. Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

Children. References.

1. Murthy BVS, *et al.* Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; **84:** 346–9.
2. Payne KA, *et al.* Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—a pilot study. *Anesth Prog* 2003; **49:** 109–12.
3. Zwaveling J, *et al.* Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* 2004; **93:** 224–7.
4. Garrido MJ, *et al.* Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* 2006; **23:** 2014–23.
5. Saudan S, Habre W. Particularités pharmacologiques du tramadol chez l'enfant. *Ann Fr Anesth Reanim* 2007; **26:** 560–3.

The elderly. Pharmacokinetic parameters in elderly patients were found to be similar to those in younger patients.[1]

1. Likar R, *et al.* Pharmacokinetic and pharmacodynamic properties of tramadol IR and SR in elderly patients: a prospective, age-group—controlled study. *Clin Ther* 2006; **28:** 2022–39.

Metabolism. Production of the active metabolite *O*-desmethyltramadol is dependent on the cytochrome P450 isoenzyme CYP2D6, which exhibits genetic polymorphism.[1,2] For a reference to a debilitating CNS-mediated reaction in a patient who was an extensive metaboliser with high CYP2D6 activity, see Effects on the CNS under Adverse Effects, above.

1. Poulsen L, *et al.* The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60:** 636–44.
2. Pedersen RS, *et al.* Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol* 2006; **62:** 513–21.

Uses and Administration

Tramadol hydrochloride is an opioid analgesic (p.104). It also has noradrenergic and serotonergic properties that may contribute to its analgesic activity. Tramadol is used for moderate to severe pain.

Tramadol hydrochloride is given by mouth, intravenously, or rectally as a suppository. The intramuscular route has also been used. It may also be given by infusion or as part of a patient-controlled analgesia system.

Usual oral doses are 50 to 100 mg every 4 to 6 hours. Tramadol hydrochloride may also be given orally as a modified-release preparation once or twice daily. The total oral daily dosage should not exceed 400 mg. Preparations containing tramadol hydrochloride with other analgesics such as paracetamol are also used.

A dose of 50 to 100 mg may be given every 4 to 6 hours by intramuscular or intravenous injection over 2 to 3 minutes, or by intravenous infusion. For the treatment of postoperative pain, the initial dose is 100 mg followed by 50 mg every 10 to 20 minutes if necessary to a total maximum (including the initial dose) of 250 mg in the first hour. Thereafter, doses are 50 to 100 mg every 4 to 6 hours up to a total daily dose of 600 mg.

Usual rectal doses by suppository are 100 mg up to 4 times daily.

For details of doses in children and in patients with hepatic or renal impairment, see below.

◊ References.

1. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; **60:** 139–76.
2. McClellan K, Scott LJ. Tramadol/paracetamol. *Drugs* 2003; **63:** 1079–86. Correction. *ibid.*; 1636.
3. Bennett RM, *et al.* Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med* 2003; **114:** 537–45.
4. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; **43:** 879–923.
5. Leppert W, Luczak J. The role of tramadol in cancer pain treatment—a review. *Support Care Cancer* 2005; **13:** 5–17.
6. Close BR. Tramadol: does it have a role in emergency medicine? *Emerg Med Australas* 2005; **17:** 73–83.
7. Cepeda MS, *et al.* Tramadol for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
8. Hollingshead J, *et al.* Tramadol for neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
9. Keating GM. Tramadol sustained-release capsules. *Drugs* 2006; **66:** 223–30.
10. Hair PI, *et al.* Tramadol extended-release tablets. *Drugs* 2006; **66:** 2017–27.
11. Lee EY, *et al.* Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1-week, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28:** 2052–60.
12. Freeman R, *et al.* Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin* 2007; **23:** 147–61.

Administration in children. In the UK, tramadol hydrochloride is licensed for the management of moderate to severe pain in children 12 years of age and older; usual adult doses may be given (see above). However, in some other European countries it is licensed in younger children although the age range permitted can vary: for example, in *France*, a usual dose in those aged 3 years and over is 1 to 2 mg/kg orally, which may be repeated 3 or 4 times daily, whereas in *Germany*, similar doses are permitted in children as young as 1 year old. Tramadol has also been given parenterally to children in doses similar to those used orally.

Some references on the use of tramadol in children.

1. Finkel JC, *et al.* An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg* 2002; **94:** 1469–73.
2. Demiraran Y, *et al.* A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. *Br J Anaesth* 2005; **95:** 510–13.
3. Bozkurt P. Use of tramadol in children. *Paediatr Anaesth* 2005; **15:** 1041–7.
4. Chu Y-C, *et al.* Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening and less sedation than morphine in children after cardiac surgery. *Anesth Analg* 2006; **102:** 1668–73.

Administration in hepatic or renal impairment. A dosage interval of 12 hours is recommended for tramadol usage in severe hepatic impairment. The dosage interval should also be increased to 12 hours in patients with a creatinine clearance (CC) less than 30 mL/minute; in the USA licensed product information suggests that the maximum oral dose should not exceed 200 mg daily in these patients. Tramadol should not be given to patients with more severe renal impairment (CC less than 10 mL/minute).

Preparations

BP 2008: Tramadol Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Adamon†; Calmador; Nobligan; Trama-Klosidol; Tramal; Tramalan†; ***Austral.:*** Tramahexal; Tramal; Tramedo; Zydol; ***Austria:*** Adamon; Contramal; Cromatodol; Dolol; Lanalget; Nycodol; Tradolan; Tramabene; Tramadolor; Tramal; Tramamed; Tramastad; Tramundal; Tramundin; ***Belg.:*** Contramal; Doctramado; Dolzam; Tradonal; Tramium; ***Braz.:*** Anangor; Dorless; Sensitram; Sylador; Timasen†; Trabilin; Tramadon; Tramal; Tramal-iv; Zamadol; ***Chile:*** Manol; Minidol; Timarol; Tramal; Zodol; ***Cz.:*** Mabron; Noax Uno; Protradon; Trabar†; Tradef; Tradonal†; Tralgit; Tramabene; Tramagit; Tramal; Tramundin; ***Denm.:*** Dolol; Mandolgin; Nobligan; Tadol; Tradolan; ***Fin.:*** Tradolan; Tramadin; Tramagetic; Tramal; Trambo; ***Fr.:*** Biodalgic; Contramal; Monocrixo; Orozamudol; Takadol; Topalgic; Trasedal†; Zamudol; Zumalgic; ***Ger.:*** Amadol; Jutadol; T-long; Tial; Tradol†; Trama; Trama-Dorsch†; Tramabeta; Tramadoc; Tramadolor; Tramadura; Tramagetic†; Tramagit; Tramal; Tramundin; Travex One; ***Gr.:*** Tramal; ***Hong Kong:*** Acugesic; Mabron; Sefmal; Tradonal†; Tramal; Tramo; ***Hung.:*** Adamon; Contramal; Ralgen; Tramadolor; Tramalgic; ***India:*** Contramal; Tramacip; Tramazac; TRD-Contin; Urgendol; ***Indon.:*** Andalpha; Bellatram; Camigesik; Contram; Dolana; Dolgesik; Dolocap; Forgesic; Kamadol; Katrasic; Nonalges; Nufapotram; Orasic; Pinorec; Radol; Simatral; Tradosik; Tradyl; Tragesik; Tramal; Trasik; Traumasik; Trunal; Tugesal; Zumatram; ***Irl.:*** Biodol; By-Madol; Tradol; Tramake; Tramapine; Tramex; Xymel; Zamadol; Zydol; ***Israel:*** Trabar; Tramadex; Tramal; ***Ital.:*** Adamon; Contramal; Fortradol; Fraxidol; Prontalgin; Tradonal; Traflash; Tralodie; Tramalin; ***Malaysia:*** Acugesic; Analab; Mabron; Pengesic; Sefmal; Tracidol; Tramada; Tramal†; Tramundin; ***Mex.:*** Durodor; Nobligan; Prontofort; Tradol; Tralic; Tramed; Trexol; Veldrol; ***Neth.:*** Doltard; Theradol; Tradonal; Tramagetic; Tramal; Tramelene; ***Norw.:*** Nobligan; Tradolan; Tramagetic; ***NZ:*** Tramal; Tramedo; Zytram; ***Philipp.:*** Dolmal; Dolotral; Dolpaz; Milador; Pengesic; Peptrad; Siverol; TDL; Tolma; Tradonal; Tramal; Tramkor; Tramundin; Unitral; ***Pol.:*** Poltram; Tramahexal; Tramal; Tramcod; Tramundin; ***Port.:*** Dolpar; Gelotralib; Nobligan; Paxilfar; Tramal; Tramy; Travex; Zydol; Zytram; ***Rus.:*** Mabron (Маброн); Sintradon (Синтрадон); Tramal (Трамал); ***S.Afr.:*** Dolotram; Tramahexal; Tramal; Tramazac; ***Singapore:*** Mabron; Pengesic; Sefmal; Tradol†; Tramal; Tramium; ***Spain:*** Adolonta; Ceparidin; Dolodol; Sofrodol; Tioner; Tradonal; Tralgiol; Zytram; ***Swed.:*** Nobligan; Tiparol; Tradolan; ***Switz.:*** Dolotramine; Ecodolor; Tramal; Tramundin; ***Thai.:*** Amanda; Ammitram; Anadol; Analab; Mabron†; Madol; Madola; Millidol; Paindol†; Pharmadol; Rofy; Sefmal; Tamolan; Tracine; Tradolgesic; Tradonal; Tramadil; Tramal; Tramamed; Tramax; Tramoda; Trosic; Volcidol-S; ***Turk.:*** Contramal; Tramadolor; ***UK:*** Dromadol; Larapam; Mabron; Nobligan; Tradorec; Tramake; Tramulief; Zamadol; Zeridame; Zydol; ***USA:*** Ultram; ***Venez.:*** Tramal.

Multi-ingredient: ***Arg.:*** Calmador Plus; Tramacet; ***Austria:*** Zaldiar; ***Belg.:*** Zaldiar; ***Braz.:*** Ultracet; ***Canad.:*** Tramacet; ***Chile:*** Cronus; Minidol Plus; Zafin; Zaldiar; ***Cz.:*** Zaldiar; ***Fr.:*** Ixprim; Zaldiar; ***Ger.:*** Zaldiar; ***Hong Kong:*** Ultracet; ***India:*** Tolydol; Tramacip Plus; Ultrazac; ***Malaysia:*** Ultracet; ***Mex.:*** Gammadol; Sinergix; Tramacet; Zaldiar; ***Neth.:*** Tilalgin; Zaldiar; ***Philipp.:*** Dolcet; ***Pol.:*** Zaldiar; ***Port.:*** Tilalgin; Zaldiar; ***Rus.:*** Zaldiar (Залдиар); ***S.Afr.:*** Tramacet; ***Singapore:*** Ultracet; ***Spain:*** Pazital; Pontalsic; Zaldiar; ***Switz.:*** Zaldiar; ***Thai.:*** Ultracet; ***UK:*** Tramacet; ***USA:*** Ultracet; ***Venez.:*** Ultracet; Zaldiar.

Trimeperidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimeperidina; Promedol (trimeperidine); Promedolum (trimeperidine); Triméperidine, Chlorhydrate de; Trimeperidini Hydrochloridum. 1,2,5-Trimethyl-4-phenyl-4-piperidyl propionate hydrochloride.

Тримеперидина Гидрохлорид

$C_{17}H_{25}NO_2,HCl = 311.8.$

CAS — 64-39-1 (trimeperidine); 125-80-4 (trimeperidine hydrochloride).

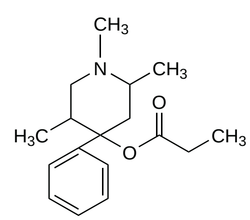

(trimeperidine)

Profile

Trimeperidine hydrochloride is an opioid analgesic (p.101) with actions and uses similar to those of pethidine (p.113).

Trolamine Salicylate *(pINNM)*

Salicilato de trietanolamina; Triethanolamine Salicylate; Trolamine, Salicylate de; Trolamini Salicylas.

Троламина Салисилат

$C_{13}H_{21}NO_6 = 287.3.$

CAS — 2174-16-5.

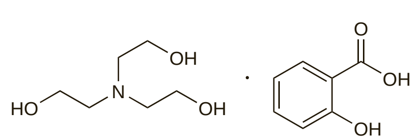

Pharmacopoeias. In *US.*

USP 31 (Trolamine Salicylate). A compounded mixture of trolamine and salicylic acid in propylene glycol. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers in a cool place.

Profile

Trolamine salicylate is a salicylic acid derivative used similarly to methyl salicylate (p.85) in topical rubefacient preparations in a concentration of 10 to 20% for the relief of muscular and rheumatic pain. It has also been used as a sunscreen.

Percutaneous absorption. In contrast to methyl salicylate, which undergoes considerable absorption and produces high subcutaneous and dermal concentrations of salicylic acid after application to intact skin, concentrations of salicylic acid after topical application of trolamine salicylate were substantially lower in tissue[1] and undetectable in serum.[2]

1. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Geniol Flex†; ***Austral.:*** Dencorub Arthritis; Goanna Arthritis Cream; Metsal AR Analgesic; ***Canad.:*** Antiphlogistine Rub A-535 No Odour; Aspercreme; Bengay No Odor; Myoflex; ***Mex.:*** Myoflex; ***Singapore:*** Metsal AR Analgesic; ***Spain:*** Bexidermil; ***USA:*** Analgesia Creme; Aspercreme; Coppertone Tan Magnifier; Flex-Power Performance Sports; Mobisyl; Myoflex; Sportscreme; Tropical Blend Tan Magnifier.

Multi-ingredient: ***Arg.:*** Duo Minoxi†; ***Canad.:*** Myoflex Extra Strength Ice.

Valdecoxib *(BAN, USAN, rINN)*

SC-65872; Valdécoxib; Valdecoxibum; Valdekoksib. *p*-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide.

Вальдекоксиб

$C_{16}H_{14}N_2O_3S = 314.4.$

CAS — 181695-72-7.

ATC — M01AH03.

ATC Vet — QM01AH03.

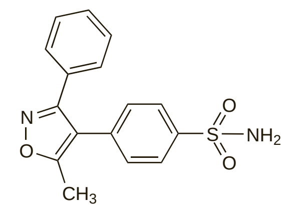

Profile

Valdecoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally in the treatment of osteoarthritis and rheumatoid arthritis, and for the pain of dysmenorrhoea. The risk of serious skin reactions with valdecoxib, in addition to its cardiovascular adverse effects (see below), prompted its general withdrawal worldwide in April 2005.

Effects on the cardiovascular system. The short-term use of parecoxib and valdecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those who had received intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days. Those patients who received oral valdecoxib only for 7 days postoperatively had a non-significant increase in risk for adverse cardiovascular effects.

The adverse cardiovascular effects associated with valdecoxib treatment were one of the reasons the drug was generally withdrawn in April 2005.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the skin. Toxic epidermal necrolysis developed in a patient who took valdecoxib for 8 days, despite stopping the drug at the first signs of a rash and starting treatment with oral prednisolone;[1] the patient had a history of hypersensitivity to sulfonamides. Health Canada[2] noted in January 2004 that it had received 5 reports of serious cutaneous adverse reactions associated with valdecoxib over less than 1 year from marketing of the drug in December 2002. However, none of these were erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis although such reactions had been reported to other regulatory authorities. In December 2004, the EMEA[3] stated that it had received reports of all 3 reactions, as well as exfoliative dermatitis; most of them had occurred within the first 2 weeks of starting treatment and the incidence rate appeared greater for valdecoxib than other selective COX-2 inhibitors. The EMEA also noted that use of parecoxib (a prodrug of valdecoxib, see p.111) had been associated with erythema multiforme.

The increased risk of serious skin reactions with valdecoxib treatment was one of the reasons the drug was generally withdrawn in April 2005.

1. Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfa drugs. *Pharmacotherapy* 2003; **23:** 551–3.

2. Health Canada. Valdecoxib (Bextra): severe cutaneous reactions. *Can Adverse React News* 2004; **14** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 29/08/08)
3. EMEA. EMEA public statement on valdecoxib (Bextra/Valdyn) and parecoxib sodium (Dynastat/Rayzon): cardiovascular risks in coronary artery bypass graft (CABG) surgery and serious adverse skin reactions (issued 15th December, 2004). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/20480204en.pdf (accessed 29/08/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Bextra†; ***Braz.:*** Bextra†; ***Canad.:*** Bextra†; ***Chile:*** Bextra†; ***Cz.:*** Bextra†; ***Fin.:*** Bextra†; ***Fr.:*** Bextra†; ***Ger.:*** Bextra†; ***Gr.:*** Bextra†; ***Hong Kong:*** Bextra†; ***India:*** Bioval†; Valdiff†; Valdixx†; Valdone†; Valus†; Vorth†; ***Indon.:*** Bextra†; ***Irl.:*** Bextra†; ***Malaysia:*** Bextra†; ***Neth.:*** Kudeq†; ***Norw.:*** Bextra†; ***NZ:*** Bextra†; ***Port.:*** Bextra†; ***S.Afr.:*** Bextra†; ***Singapore:*** Bextra†; ***Swed.:*** Bextra†; ***Switz.:*** Bextra†; ***Thai.:*** Bextra†; ***UK:*** Bextra†; ***USA:*** Bextra†; ***Venez.:*** Bextra†.

Multi-ingredient: ***India:*** Valus Insta†; Valus-XT†; Vectra-P†; Vorth Insta†; Vorth-XT†.

Vedaprofen *(BAN, USAN, rINN)*

CERM-10202; PM-150; Vedaprofeeni; Védaprofène; Vedaprofeno; Vedaprofenum. (±)-4-Cyclohexyl-α-methyl-1-naphthaleneacetic acid.

Ведапрофен

$C_{19}H_{22}O_2$ = 282.4.
CAS — 71109-09-6.
ATC Vet — QM01AE90.

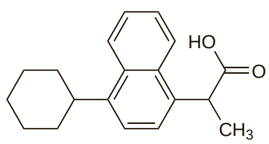

Profile

Vedaprofen, a propionic acid derivative, is an NSAID used in veterinary medicine for the treatment of inflammation and pain.

Viminol Hydroxybenzoate *(rINNM)*

Diviminol Hydroxybenzoate; Hidroxibenzoato de viminol; Viminol, Hydroxybenzoate de; Viminoli Hydroxybenzoas; Z-424 (viminol). 1-[1-(2-Chlorobenzyl)pyrrol-2-yl]-2-(di-sec-butyl)aminoethanol 4-hydroxybenzoate.

Виминола Гидроксибензоат

$C_{21}H_{31}ClN_2O,C_7H_6O_3$ = 501.1.
CAS — 21363-18-8 (viminol); 21466-60-4 (viminol hydroxybenzoate); 23784-10-3 (viminol hydroxybenzoate).
ATC — N02BG05.
ATC Vet — QN02BG05.

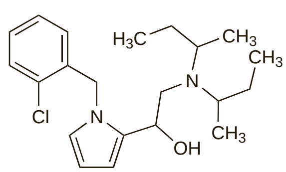

(viminol)

Profile

Viminol hydroxybenzoate has analgesic and antipyretic properties. The equivalent of 400 mg of viminol has been given daily in divided doses by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Dividol; ***Ital.:*** Dividol.

Zaltoprofen *(rINN)*

CN-100; Zaltoprofène; Zaltoprofeno; Zaltoprofenum; ZC-102. (±)-10,11-Dihydro-α-methyl-10-oxodibenzo[*b,f*]thiepin-2-acetic acid.

Зальтопрофен

$C_{17}H_{14}O_3S$ = 298.4.
CAS — 89482-00-8.

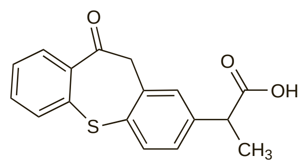

Pharmacopoeias. In *Jpn.*

Profile

Zaltoprofen is an NSAID (p.96) that has been given in an oral dose of 80 mg three times daily for pain and musculoskeletal and joint disorders.

◊ References.

1. Ishizaki T, *et al.* Pharmacokinetic profile of a new nonsteroidal anti-inflammatory agent, CN-100, in humans. *Drug Invest* 1991; **3:** 1–7.
2. Hatori M, Kokubun S. The long-term efficacy and tolerability of the new anti-inflammatory agent zaltoprofen in rheumatoid arthritis. *Curr Med Res Opin* 1998; **14:** 79–87.
3. Hase K, *et al.* The effect of zaltoprofen on physiotherapy for limited shoulder movement in breast cancer patients: a single-blinded before-after trial. *Arch Phys Med Rehabil* 2006; **87:** 1618–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Soleton.

Ziconotide *(USAN, rINN)*

CI-1009; ω-Conotoxin M VIIA; SNX-111; Ziconotida; Ziconotidum. L-Cysteinyl-L-lysylglycyl-L-lysylglycl-L-alanyl-L-lysyl-L-cysteinyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L-α-aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysyl-L-cysteinamide cyclic(1→16),(8→20),(15→25)-tris(disulfide).

Зиконотид

$C_{102}H_{172}N_{36}O_{32}S_7$ = 2639.1.
CAS — 107452-89-1.
ATC — N02BG08.
ATC Vet — QN02BG08.

Ziconotide Acetate *(rINNM)*

Acetato de ziconotida; Ziconotide, Acétate de; Ziconotidi Acetas.

Зиконотида Ацетат

$C_{102}H_{172}N_{36}O_{32}S_7, C_2H_4O_2$ = 2699.2.
ATC — N02BG08.
ATC Vet — QN02BG08.

Adverse Effects and Precautions

The most common adverse effects reported with ziconotide have included dizziness, nausea and vomiting, nystagmus, abnormal gait, blurred vision, headache, elevated creatine kinase levels, and asthenia. Cognitive impairment, particularly confusion and impaired memory, is also very common, and typically develops after several weeks of treatment. Severe CNS symptoms such as hallucinations, paranoid reactions, speech disorders, aphasia, and decreased alertness may occur but convulsions, stroke, delirium, encephalopathy, and coma have been reported less commonly. Creatine kinase may be elevated, and monitoring of blood concentrations is recommended, but clinical myopathy or rhabdomyolysis is uncommon. Ziconotide may cause or exacerbate depression. Patients with a history of psychosis should not be treated with ziconotide.

◊ References.

1. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of ziconotide. *Pain* 2000; **85:** 291–6.

Uses and Administration

Ziconotide is a synthetic form of a peptide derived from the venom of the cone shell *Conus magus* (a sea snail). It is reported to be a neurone-specific calcium-channel blocker. Ziconotide is given as a continuous intrathecal infusion in the management of severe chronic pain in patients who are intolerant of or refractory to more conventional treatments (see Choice of Analgesic, p.2).

Ziconotide is given intrathecally as the acetate; doses may be expressed in terms of the base or the acetate. In the EU, the initial dose (expressed in terms of the base) is 2.4 micrograms daily adjusted according to response, in increments of up to 2.4 micrograms, to a maximum daily dose of 21.6 micrograms. Licensed product information recommends that the interval between dose increases is at least 2 days. In the USA, the initial dose (expressed in terms of the acetate) should be no more than 2.4 micrograms daily, adjusted according to response. Dose increases of up to 2.4 micrograms two or three times a week are permitted, over a period of at least 3 weeks, up to a maximum daily dose of 19.2 micrograms.

Ziconotide has been tried in other conditions such as head trauma.

◊ References.

1. Verweij BH, *et al.* Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). *Neurol Res* 1997; **19:** 334–9.
2. Jain KK. An evaluation of intrathecal ziconotide for the treatment of chronic pain. *Expert Opin Invest Drugs* 2000; **9:** 2403–10.
3. Wermeling D, *et al.* Pharmacokinetics and pharmacodynamics of intrathecal ziconotide in chronic pain patients. *J Clin Pharmacol* 2003; **43:** 624–36.
4. Staats PS, *et al.* Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA* 2004; **291:** 63–70.
5. Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. *Pharmacotherapy* 2005; **25:** 1084–94.
6. Rauck RL, *et al.* A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage* 2006; **31:** 393–406.
7. Lynch SS, *et al.* Intrathecal ziconotide for refractory chronic pain. *Ann Pharmacother* 2006; **40:** 1293–1300.
8. Wermeling DP, Berger JR. Ziconotide infusion for severe chronic pain: case series of patients with neuropathic pain. *Pharmacotherapy* 2006; **26:** 395–402.
9. Lyseng-Williamson KA, Perry C. Ziconotide. *CNS Drugs* 2006; **20:** 331–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Prialt; ***Fr.:*** Prialt; ***Neth.:*** Prialt; ***Port.:*** Prialt; ***UK:*** Prialt; ***USA:*** Prialt.

Anthelmintics

Ancylostomiasis, p.134
Angiostrongyliasis, p.134
Ascariasis, p.134
Capillariasis, p.135
Clonorchiasis, p.135
Cutaneous larva migrans, p.135
Cysticercosis, p.135
Diphyllobothriasis, p.136
Dracunculiasis, p.136
Echinococcosis, p.136
Enterobiasis, p.136
Fascioliasis, p.136
Fasciolopsiasis, p.136
Gnathostomiasis, p.136
Heterophyiasis, p.136
Hookworm infections, p.136
Hymenolepiasis, p.136
Intestinal fluke infections, p.136
Liver fluke infections, p.137
Loiasis, p.137
Lung fluke infections, p.137
Lymphatic filariasis, p.137
Mansonella infections, p.137
Metagonimiasis, p.137
Nanophyetiasis, p.137
Necatoriasis, p.137
Onchocerciasis, p.137
Opisthorchiasis, p.138
Paragonimiasis, p.138
Schistosomiasis, p.138
Strongyloidiasis, p.138
Syngamosis, p.138
Taeniasis, p.139
Toxocariasis, p.139
Trichinosis, p.139
Trichostrongyliasis, p.139
Trichuriasis, p.139

This chapter describes the important helminth or worm infections that occur in man (see Table 1, p.135) and the anthelmintics used to treat them.

Choice of Anthelmintic

Helminth infections are among the most common infections in man, affecting a large proportion of the world's population, mainly in tropical regions. In developing countries they pose a large threat to public health, and contribute to the prevalence of malnutrition, anaemia, eosinophilia, and pneumonia. Helminth infections causing severe morbidity include lymphatic filariasis (a cause of elephantiasis), onchocerciasis (river blindness), and schistosomiasis. These infections can affect the majority of populations in endemic areas with major economic and social consequences. WHO is making strenuous efforts to control a number of these infections in endemic areas. Control of these infections in both individuals and populations depends not only on the use of chemotherapeutic agents but also on preventing transmission by advice on food preparation and hygiene, the provision of adequate sanitation and sewage treatment (especially where sewage is used as fertiliser), the provision of safe potable water supplies, and effective vector control.

The worms that cause infection in man generally fall either into the phylum Nematoda, which includes the nematodes or roundworms, or into the phylum Platyhelminthes, which includes the cestodes or tapeworms and the trematodes or flukes.

The **nematodes** (or roundworms) are a large group of worms, some of which are capable of producing infections in man. In many cases man is the primary (definitive) host but human infections caused by parasites for which animals are the primary hosts also occur. Nematodes do not generally multiply in man; strongyloidiasis is an exception as re-infection can occur without environmental re-exposure. Nematode infections are most common in warm, moist climates, but some species of nematode can tolerate cool or arid conditions and infective forms can persist in the environment for long periods. An understanding of the life cycle of the infective species is necessary for diagnostic tests to be made at appropriate times, usually to coincide with the infective stage of the cycle, and for the choice of appropriate control measures.

The nematode infections can be divided into filarial infections, intestinal infections, and tissue infections.

Filarial nematodes are endemic in large areas of the tropics and produce considerable morbidity. The adult worms may live for several years, releasing large numbers of motile embryos known as microfilariae into the blood or skin, depending on the species. Transmission is usually by biting insects, which form the intermediate host. In some endemic areas multiple infections with filarial nematodes are common.

Filarial nematode infections include:

- loiasis
- lymphatic filariasis
- mansonella infections
- onchocerciasis.

Intestinal nematode infections (roundworms) are very common especially in developing countries in the tropics and subtropics. Children are particularly at risk and these infections contribute to morbidity through malnutrition, vitamin deficiencies, diarrhoea, anaemia, and pneumonia. Poor sanitation and sewage disposal perpetuate infections with soil-borne nematodes. Often several different worm infections are endemic in the same region, resulting in mixed infections. When this occurs, broad-spectrum anthelmintics may be used to reduce the overall infection burden in the population (see under Ascariasis, below).

Intestinal nematode infections include:

- angiostrongyliasis
- ascariasis
- capillariasis
- enterobiasis
- hookworm infections
- strongyloidiasis
- trichostrongyliasis
- trichuriasis.

The *tissue nematodes* represent a miscellaneous group causing a variety of pathological conditions in man. In cutaneous larva migrans and toxocariasis, the nematodes have a primary animal host and the human disease is caused by infection with infective larvae which do not subsequently mature in man. Trichinosis and gnathostomiasis affect a number of carnivorous animals and man is an incidental host. Syngamosis is primarily an infection of domestic fowl and wild birds although infection in man has been reported rarely. In dracunculiasis, man is the primary (definitive) host. Although these diseases are not generally fatal they cause a considerable degree of morbidity and treatment is complicated by the lack of effective, non-toxic systemic anthelmintics.

Tissue nematode infections include:

- angiostrongyliasis
- cutaneous larva migrans
- dracunculiasis
- gnathostomiasis
- syngamosis
- toxocariasis
- trichinosis.

The **cestodes** (flatworms, segmented worms, or tapeworms) cause infection in man in most parts of the world. Man may be the primary host, harbouring the adult worm in the intestine, or an intermediate host carrying the larval form. With the exception of *Hymenolepis nana* the adult worms do not usually multiply within the same host. However, larval forms may be produced and, as with infection or ingestion of these forms, systemic infection may develop.

Cestode infections include:

- cysticercosis
- diphyllobothriasis
- echinococcosis
- hymenolepiasis
- taeniasis.

Trematode (or fluke) infections are caused by parasitic worms of the class Trematoda. There are 4 categories of fluke which are pathogenic in man; the blood flukes *Schistosoma* spp., the intestinal flukes *Fasciolopsis, Heterophyes, Metagonimus,* and *Nanophyetus* spp., the liver flukes *Clonorchis*, *Fasciola*, and *Opisthorchis* spp., and the lung flukes *Paragonimus* spp. Symptoms are usually only seen in heavy infections and commonly include fever, pain, and eosinophilia.

Trematode infections include:

- intestinal fluke infections
- liver fluke infections
- lung fluke infections
- schistosomiasis.

Ancylostomiasis

See under Hookworm Infections, below. Larvae of *Ancylostoma* spp. are also a cause of cutaneous larva migrans (see below).

Angiostrongyliasis

Two forms of angiostrongyliasis are recognised and both are due to accidental infection with species of the animal nematode *Angiostrongylus.*

Infection with the larvae of the rat lungworm *A. cantonensis* causes an eosinophilic meningoencephalitis. Transmission follows ingestion of raw or undercooked snails or crustaceans, or of contaminated vegetables. The disease is generally self-limiting.

Intestinal infection with *A. costaricensis* can cause eosinophilic gastro-enteritis. It most commonly occurs in children after ingestion of vegetables contaminated by infected slugs. Surgical resection of the affected bowel may be necessary. Mebendazole and albendazole have been tried in the management of both these infections. However, anthelmintic drugs have not been shown to be effective and in *A. cantonensis* infection, severe host reaction to the dying larvae may result. Most patients will in fact have a self-limited course and recover completely. Symptomatic treatment with analgesics, corticosteroids, and removal of CSF may relieve pressure in *A. cantonensis* meningitis.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Ascariasis

Ascariasis is an infection caused by *Ascaris lumbricoides*, the common or giant roundworm. The term roundworm is also applied to nematodes in general. It is usually an infection of the small intestine but on rare occasions there may be severe ectopic infections. It is commonly found in the tropics and especially in rural areas. Eggs are excreted in the faeces and can remain viable in moist soil for several years. On ingestion of mature eggs the larvae hatch and penetrate the intestinal wall. They migrate in the bloodstream via the liver to the lungs where they enter the alveoli. The larvae then move up the bronchial tree and are swallowed. The mature adult develops in the intestines, and it has been estimated that a gravid female is produced about 2 months after infection. The life span of the adult worm is 1 to 2 years. Ascariasis may be asymptomatic. When symptoms of intestinal infection do occur they include anorexia, abdominal pain, and diarrhoea; nutritional deficiency may result. The pulmonary stage may cause pneumonitis and bronchospasm often accompanied by eosinophilia. Heavy infections can cause intestinal or biliary obstruction. Migration of the worm from the small intestine can produce ectopic infection of the genito-urinary tract, lungs, liver, or heart. Such infections are rare but serious.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] with both drugs being equally highly effective. Pyrantel embonate[3] and levamisole are alternatives, while the potential of nitazoxanide for the treatment of ascariasis is being investigated.[1] Ivermectin has also been used.[2] Such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Drugs such as tiabendazole

Table 1. Helminths: classification and diseases.

Group	Helminth	Common Name	Clinical infection
Nematodes	*Brugia malayi*		lymphatic filariasis (Malayan, brugian)
(filarial)	*Brugia timori*		lymphatic filariasis (Timorian, brugian)
	Loa loa	eye-worm	loiasis
	Mansonella spp.		Mansonella infections
	Onchocerca volvulus		onchocerciasis (river blindness)
	Wuchereria bancrofti		lymphatic filariasis (bancroftian)
Nematodes	*Ancylostoma duodenale*	Old World hookworm	ancylostomiasis
(intestinal)	*Angiostrongylus costaricensis*		angiostrongyliasis
	*Ascaris lumbricoides**	common roundworm, giant roundworm	ascariasis
	Capillaria philippinensis		capillariasis
	*Enterobius vermicularis**	threadworm, pinworm	enterobiasis
	Necator americanus	New World hookworm	necatoriasis
	Strongyloides stercoralis	sometimes called threadworm in USA	strongyloidiasis
	Trichostrongylus spp.		trichostrongyliasis
	*Trichuris trichiura**	whipworm	trichuriasis
Nematodes	*Ancylostoma* spp.	dog/cat hookworm	cutaneous larva migrans (creeping eruption)
(tissue)	*Angiostrongylus cantonensis*		angiostrongyliasis
	Dracunculus medinensis	guinea-worm	dracunculiasis (dracontiasis)
	Gnathostoma spinigerum		gnathostomiasis
	Syngamus spp.	gapeworm	syngamosis
	Toxocara spp.*		toxocariasis (visceral larva migrans, ocular larva migrans)
	*Trichinella spiralis**		trichinosis (trichinellosis)
Cestodes	*Diphyllobothrium latum*	broad fish tapeworm	diphyllobothriasis
(tapeworms)	*Echinococcus* spp.		echinococcosis (hydatid disease)
	Hymenolepis nana	dwarf tapeworm	hymenolepiasis
	*Taenia saginata**	beef tapeworm	taeniasis
	*Taenia solium**	pork tapeworm	cysticercosis (larval form), taeniasis (adult worm)
Trematodes	*Clonorchis sinensis*	Chinese liver fluke	clonorchiasis
(flukes)	*Fasciola hepatica*	liver fluke	fascioliasis
	Fasciolopsis buski	intestinal fluke	fasciolopsiasis
	Heterophyes heterophyes	intestinal fluke	heterophyiasis
	Metagonimus yokogawi	intestinal fluke	metagonimiasis
	Nanophyetus salmincola	intestinal fluke	nanophyetiasis
	Opisthorchis spp.	liver fluke	opisthorchiasis
	Paragonimus spp.	oriental lung fluke	paragonimiasis
	Schistosoma spp.	blood fluke	schistosomiasis

NOTE: Infections due to worms marked with an asterisk may occur in temperate climates. Infections due to other worms are generally limited to tropical or localised areas, but may occur in travellers who have visited those areas.

with little or no activity against *Ascaris* should be avoided for the initial treatment of mixed infections since they may stimulate the worm to migrate to a different body site. Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease.[1]

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.

Capillariasis

Capillariasis is caused by infection with *Capillaria philippinensis,* a nematode endemic in the Philippines and southern Thailand. Infection in man is through eating raw or undercooked freshwater fish containing infective larvae. The larvae mature in the intestines and the adults produce both eggs and infective larvae so that auto-infection occurs and heavy infections can result. Symptoms are mostly gastrointestinal, with abdominal pain, vomiting, and severe prolonged diarrhoea leading to cachexia and muscle wasting. The infection has a mortality rate of between 20 and 30% if untreated. Prolonged treatment with mebendazole or, alternatively, albendazole, is necessary.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Clonorchiasis

See under Liver Fluke Infections, below.

Cutaneous larva migrans

Cutaneous larva migrans (creeping eruption) occurs when man becomes infected with the larvae of animal hookworms, usually *Ancylostoma braziliense* or *A. caninum*, hookworms of cats and dogs. Other hookworms may also be involved or may cause other infections (see Hookworm Infections, below). The larvae penetrate the skin and then migrate causing characteristic trails in the skin. This migration can persist for several months and can be a source of intense pruritus. Occasionally larvae migrate to the lungs causing eosinophilia and pulmonary symptoms. Albendazole or ivermectin may be given by mouth and may be better tolerated than oral tiabendazole; tiabendazole can also be applied topically but is of limited value for multiple lesions.

Infection with *Gnathostoma spinigerum* or *Strongyloides stercoralis* can also cause cutaneous larva migrans (see Gnathostomiasis and Strongyloidiasis, below). Ocular and visceral larva migrans are features of toxocariasis (see below).

References.

1. Caumes E. Treatment of cutaneous larva migrans. *Clin Infect Dis* 2000; **30:** 811–14.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Cysticercosis

Infection with the pork tapeworm, *Taenia solium* may result in taeniasis (intestinal infection with adult tapeworms—see below) or cysticercosis (tissue infection with larval forms). Cysticercosis may develop after ingestion of *T. solium* eggs in food or water contaminated with infected human faecal material, or as a result of auto-infection in intestinal carriers of adult tapeworms. Ingested eggs release larvae that may penetrate the intestinal wall to be carried via the bloodstream to skeletal muscles, heart, eyes, brain, and spinal cord where they form encapsulated cysts (cysticerci). Human cysticercosis is associated with poverty and endemic in areas where hygiene is poor and sanitation inadequate.

Infection is typically subclinical, but symptoms may develop when the encysted larvae die and elicit an inflammatory reaction. Clinical features depend on the number, size, location, and stage of development of the cysticerci, as well as on the host's immune response. Cysts in the CNS (**neurocysticercosis**) may result in seizures and headaches, and are a common cause of epilepsy in endemic areas. Other symptoms include confusion, attention deficit, and ataxia. Hydrocephalus and intracranial hypertension may result from obstruction of CSF flow. Cysts in the spinal cord, eyes, or heart may also cause serious morbidity.

Treatment of neurocysticercosis consists of managing seizures with antiepileptics. Antiepileptics can usually be discontinued if patients have been seizure-free for more than 2 years.[1]

The use of anthelmintics in the treatment of neurocysticercosis remains controversial.[1-3] Live cysticerci usually do not provoke seizures whereas dead or dying parasites can elicit an inflammatory response, seizures, and transient neurological effects, hence treatment does not necessarily reduce seizure frequency. Patients with viable or degenerating parenchymal cysts and those with extraparenchymal cysts (such as subarachnoid cysts, including giant cysts and racemose forms) may benefit from anthelmintics.[1,3,4] Anthelmintics are of little or no benefit in patients with inactive, calcified lesions, and are contra-indicated in patients with cysticercotic encephalitis as they may exacerbate intracranial hypertension.[1,2] A double-blind, placebo-controlled study in patients with seizures due to viable parenchymal cysts confirmed that albendazole therapy (with dexamethasone) was safe and decreased the burden of parasites and the number of generalised seizures.[5] Albendazole is now considered to be the drug of choice, but praziquantel may also be used.[1,4,6] Adjunctive corticosteroids are recommended for parenchymal infections if there are numerous cysts, or if neurological symptoms or intracranial hypertension develops after starting treatment. Patients with subarachnoid cysticercosis should also be given adjunctive corticosteroids. However, use of corticosteroids with praziquantel may be complicated by a pharmacokinetic interaction— see Corticosteroids, under Interactions of Praziquantel p.154 for further details. If hydrocephalus is present, surgical removal of cysts or ventricular shunting may be indicated.[1] Detailed consensus guidelines for the treatment of neurocysticercosis have been developed.[2]

Prevention of infection with *T. solium* is possible by avoiding ingestion of undercooked pork and food and water contaminated with human faeces. Ideally, prevention measures should include adequate sanitation, sewage treatment, and abattoir inspection. Those already infected with *T.solium* and their close contacts should be treated with anthelmintics in order to interrupt or reduce the cycle of direct person-to-person transmission. Universal or selected treatment of human taeniasis with praziquantel has significantly reduced the prevalence in areas where *T. solium* infection is endemic.[3,7]

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3. García HH, *et al.* Taenia solium cysticercosis. *Lancet* 2003; **362:** 547–56.
4. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis— albendazole and praziquantel. *Ann Intern Med* 2006; **145:** 43–51.
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6. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
7. WHO. *Control of neurocysticercosis*. Geneva: WHO, 2003. Also available at: http://www.who.int/gb/ebwha/pdf_files/WHA56/ea5610.pdf (accessed 09/08/07)

Diphyllobothriasis

Diphyllobothriasis is an intestinal infection with the fish tapeworm *Diphyllobothrium latum* and other *Diphyllobothrium* spp. and is acquired in man through ingestion of raw, infected, freshwater fish. The infection is rarely symptomatic. However, because the adult worm competes for vitamin B_{12}, some patients may develop megaloblastic anaemia with its associated neurological symptoms. Concentrations of other vitamins may also be reduced. Treatment is with a single dose of praziquantel; niclosamide is an alternative.[1] Vitamin supplements should also be given to correct any deficiencies.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Dracunculiasis

Dracunculiasis (dracontiasis, guinea-worm infection) is caused by infection with the nematode *Dracunculus medinensis*. It has been endemic in parts of Africa and Asia but is increasingly coming under control and the hope is that it will soon be eradicated.[1] The disease is transmitted through drinking water containing larvae that develop in freshwater crustaceans. The larvae penetrate the intestinal mucosa and mature in connective tissue. The adult female migrates to the subcutaneous tissues, normally of the legs, after about 1 year. Ulceration of the overlying skin releases larvae which are ingested by the crustacean host to complete the life cycle. The first symptom is the lesion caused by the emerging worm, although a generalised hypersensitivity reaction may also occur. Secondary infection is a common complication.

The most effective method of controlling dracunculiasis is by provision of safe drinking water. The WHO eradication campaign is based on health education, and the provision of safe water by measures including water treatment with pesticides such as temefos and encouraging the use of domestic filters.

There is no effective direct drug therapy against any stage in man. The traditional treatment is removal of the adult worm by gentle traction sometimes over several weeks. Metronidazole or tiabendazole may provide symptomatic benefit in the management of dracunculiasis although they have no direct anthelmintic effect. They are thought to act by weakening the anchorage of the worms within the subcutaneous tissues, thus allowing them to be removed more quickly.

1. WHO. Dracunculiasis eradication. Available at: http://www.who.int/dracunculiasis/en/ (accessed 16/07/08)

Echinococcosis

Echinococcosis, or hydatid disease, in man is infection with the larval stage of the cestode *Echinococcus granulosus* or *E. multilocularis*. These two species cause distinct forms of the disease known as cystic echinococcosis and alveolar echinococcosis respectively. Various animals are involved in the transmission of the disease, man becoming infected through ingestion of eggs from contaminated faeces. The eggs hatch in the intestine and the embryos penetrate the intestinal wall and invade body organs, usually the liver. The embryo develops into a cyst which slowly increases in size and may remain intact for many years. Symptomatic infection usually only occurs when the cyst is large enough to cause obstruction or to compress adjacent structures, or if rupture occurs. Where possible, surgical removal of the intact cyst is the first line of treatment.

In **cystic echinococcosis**, drugs may be given locally or systemically before surgery to kill infective larvae within the cyst and reduce the risk of further infection. They are also given postoperatively if a cyst ruptures during surgery. Local injection of a larvicidal agent such as alcohol, cetrimide, or hypertonic saline has been used. Chemotherapy is also used as an adjunct or when surgery is not possible. The preferred drug for associated systemic treatment is albendazole. Mebendazole may be used, although some have suggested it is not as effective as albendazole. Praziquantel has also been reported to be effective. Albendazole may be a suitable alternative to surgery as initial treatment in uncomplicated cases; use with cimetidine (to inhibit its metabolism) may increase its effectiveness.

A further option when surgery is not possible is the PAIR (puncture/aspiration/injection/re-aspiration) procedure which consists of ultrasound-guided cyst puncture followed by aspiration of the cyst fluid, local injection of alcohol or hypertonic saline into the cyst, and re-aspiration of the cyst contents. Concomitant chemotherapy is recommended.

E. multilocularis infection (**alveolar echinococcosis**) is more invasive and is characterised by a tumour-like infiltrative growth; it usually requires both surgery and long-term treatment with a benzimidazole, such as albendazole, although some patients have improved on albendazole alone.

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1. Kumar A, Chattopadhyay TK. Management of hydatid disease of the liver. *Postgrad Med J* 1992; **68:** 853–6.
2. Wen H, *et al*. Diagnosis and treatment of human hydatidosis. *Br J Clin Pharmacol* 1993; **35:** 565–74.
3. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996; **74:** 231–42.
4. Reuter S, *et al*. Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature. *J Antimicrob Chemother* 2000; **46:** 451–6.
5. Mcmanus DP, *et al*. Echinococcosis. *Lancet* 2003; **362:** 1295–1304.
6. Smego RA, *et al*. Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1073–83.
7. Smego RA, Sebanego P. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 2005; **9:** 69–76.
8. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Enterobiasis

Enterobiasis is an infection with *Enterobius vermicularis* (pinworm, threadworm). It is one of the few intestinal nematodes which is common in temperate climates and is particularly common in young children. Like trichuriasis it is an infection of the large intestine and transmission follows ingestion or inhalation of mature eggs. The larvae mature in the gut in about 2 months. The eggs are not released into the gut contents but the mature female migrates to the anus at night and lays its eggs on the perianal and perineal skin. The eggs become infective within 6 hours. Diagnosis is based on detecting eggs around the anus. The most common symptom is perianal itching but many infections are asymptomatic. Rarely ectopic disease such as appendicitis or salpingitis may occur. The adult worm has a life span of about 6 weeks and, if re-infection can be prevented, the infection is self-limiting. While additional hygiene measures can prevent re-infection, treatment of the whole family with an anthelmintic should remain the main therapeutic response; more than one course may be required.

Treatment is with a benzimidazole carbamate derivative, such as albendazole or mebendazole, or with pyrantel embonate.[1] Such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Other anthelmintics used in enterobiasis include piperazine or pyrvinium embonate.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Fascioliasis

See under Liver Fluke Infections, below.

Fasciolopsiasis

See under Intestinal Fluke Infections, below.

Gnathostomiasis

Gnathostomiasis is an infection with, in most cases, the larval form of the nematode *Gnathostoma spinigerum*, although other *Gnathostoma* spp. have been identified. *G. spinigerum* inhabits the stomach of cats and dogs. Eggs shed in their faeces are ingested by freshwater crustaceans and hatch into larvae which are ingested by fish or other animals; man acquires the infection by consumption of the raw or undercooked flesh of these secondary hosts. Once ingested the larva penetrates the gut wall and migrates via the liver to other tissues including skin, eyes, and CNS. Rarely, dermal infiltration may result in cutaneous larva migrans (above).

The preferred treatment of gnathostomiasis is surgical removal of the gnathostome but this is rarely possible. Albendazole or, alternatively, ivermectin, may be used.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Heterophyiasis

See under Intestinal Fluke Infections, below.

Hookworm infections

Infections with the hookworms *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis) are a major cause of iron-deficiency anaemia in large areas of the tropics and sub-tropics, especially in rural communities. Eggs deposited in warm moist soil hatch into larvae which develop further into the infective form. Infection is normally by penetration through the skin although it may be by ingestion. The larvae migrate to the lungs and are subsequently swallowed and mature to the adult form in the small intestine. Eggs appear in the faeces about 6 to 8 weeks after infection and the adult worm may live for several years. *A. duodenale* larvae are capable of remaining dormant in the tissues, only maturing to the adult when climatic conditions are favourable. Symptoms correspond to the stage of infection. Visitors to endemic areas may develop intense pruritus, erythema, and papulovesicular eruption at the site of infection, known as ground itch. Migration through the lungs during the first infection may cause pneumonitis and bronchospasm with accompanying eosinophilia. The main symptoms of intestinal infection are iron-deficiency anaemia and severe hypoalbuminaemia. In addition, abdominal pain, diarrhoea, and weight loss may occur.

Treatment is usually with a benzimidazole carbamate derivative such as mebendazole or albendazole,[1-3] and such broad-spectrum therapy can also be useful if the patient has a mixed intestinal nematode infection. Albendazole may be more effective than mebendazole.[4] Other anthelmintics used in hookworm infections include levamisole or pyrantel embonate,[2-4] but these may be less effective against *N. americanus* than against *A. duodenale*. Iron-deficiency anaemia caused by hookworm infections responds rapidly to oral iron therapy; folic acid supplements may be necessary in some patients. Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of infection.[2,5]

1. Hotez PJ, *et al*. Hookworm infection. *N Engl J Med* 2004; **351:** 799–807.
2. Bethony J, *et al*. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
4. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.
5. Idris MA, *et al*. Effective control of hookworm infection in school children from Dhofar, Sultanate of Oman: a four-year experience with albendazole mass chemotherapy. *Acta Trop* 2001; **80:** 139–43.

Hymenolepiasis

Hymenolepiasis is an infection of the intestine with *Hymenolepis nana*, or dwarf tapeworm. Infection is acquired through ingestion of eggs in contaminated food or water or on hands and can be passed directly from person to person. It is more common in children. Clinical symptoms occur in heavy infections and include diarrhoea and abdominal pain. Treatment is with a single dose of praziquantel. Nitazoxanide may be used as an alternative.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Intestinal fluke infections

The intestinal fluke infections **fasciolopsiasis**, **heterophyiasis**, **metagonimiasis**, and **nanophyetiasis** are caused by *Fasciolopsis buski*, *Heterophyes heterophyes* and some other *Heterophyes* spp., *Metagonimus yokogawai*, and *Nanophyetus salmincola* respectively. Fasciolopsiasis, heterophyiasis, and metagonimiasis are endemic in the Far East and Southeast Asia, and heterophyiasis is also common in the Middle East. Nanophyetiasis has occurred increasingly in the Pacific Northwest of the USA. Fasciolopsiasis is caused by the ingestion of infected aquatic plants, while undercooked or raw infected fish are the sources of *H. heterophyes*, *M. yokogawai*, and *N. salmincola* infections.

Fasciolopsiasis is usually asymptomatic, but heavy infections can cause diarrhoea, abdominal pain, and, rarely, intestinal obstruction and an allergic oedematous reaction. Metagonimiasis is also generally asymptomatic but may cause mild diarrhoea, while pain and mucous diarrhoea are common in heterophyiasis. Similar gastrointestinal symptoms plus eosinophilia occur in nanophyetiasis. Eggs of *M. yokogawai* and *H. heterophyes* may rarely penetrate the bowel wall and enter the bloodstream to be deposited in various organs, leading to serious complications such as heart failure or fatal embolism in the heart or brain.

Treatment of intestinal fluke infections is with praziquantel.[1,2]

1. WHO. Control of foodborne trematode infections. *WHO Tech Rep Ser 849* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_849_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_849_(part2).pdf (accessed 16/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Liver fluke infections

Fasciola hepatica, *Opisthorchis viverrini*, *O. felineus*, and *Clonorchis sinensis* are liver flukes transmitted by the ingestion of infected aquatic plants, grasses or water (*F. hepatica*), or raw or undercooked fish (*Opisthorchis* spp., *C. sinensis*). **Fascioliasis** is primarily a disease of sheep and cattle and human infections may occur wherever these animals are raised, whereas **clonorchiasis** and **opisthorchiasis** are seen mainly in Southeast Asia and eastern Europe.

Fascioliasis in the acute phase is usually characterised by fever, gastrointestinal symptoms, pain due to liver enlargement, and marked eosinophilia, but these symptoms decline as the worms enter their final habitat in the bile ducts. Acute symptoms occur rarely with clonorchiasis and opisthorchiasis and infections tend to be asymptomatic for many years. Adult flukes live in the bile ducts and symptoms of biliary-tract obstruction appear after repeated or heavy infections with liver flukes. Cholangiocarcinoma (bile-duct cancer) is now generally accepted to be associated with liver fluke infection although its exact pathogenesis is unclear.

Praziquantel is used for the treatment of most liver fluke infections.[1,2] Bithionol is more effective than praziquantel in fascioliasis and has been the preferred treatment, although in the USA the CDC considers triclabendazole to be the treatment of choice; dehydroemetine has also been used, and nitazoxanide[2] may be effective.

Praziquantel remains the treatment of choice for clonorchiasis and opisthorchiasis.[1,2] Albendazole is a suggested alternative for clonorchiasis.[2]

1. WHO. Control of foodborne trematode infections. *WHO Tech Rep Ser 849* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_849_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_849_(part2).pdf (accessed 16/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Loiasis

Loiasis is an infection with the filarial nematode *Loa loa* which occurs in areas of Central and West Africa. It is transmitted by the biting tabanid fly *Chrysops*. The infective larvae mature to adult worms which migrate through subcutaneous tissues and occasionally the subconjunctiva. Symptoms include pruritus, swelling, and pain, with occasional subcutaneous swellings, often on the arms or legs, that are characteristic of the disease. Passage of a worm through the subconjunctiva produces intense conjunctivitis. Eosinophilia may be severe, especially in visitors from non-endemic areas. Other complications include renal disease, endomyocardial fibrosis, encephalopathy, and peripheral neuropathy.

Diethylcarbamazine is used for treatment;[1] it is effective against the microfilariae, larval forms, and a proportion of adult worms. In some cases, treatment has been associated with acute encephalitis, particularly in patients with heavy microfilaraemia. It has been assumed that this is related to blockage of capillaries in the brain and meninges and for this reason small doses of diethylcarbamazine are given initially, with a corticosteroid and antihistamine, gradually increasing to full therapeutic doses over several days. However this does not eliminate the risk of encephalitis entirely and the role of the microfilariae in this syndrome has been questioned. Albendazole may be useful where diethylcarbamazine cannot be used, but repeated courses may be needed.[1] Some consider that ivermectin could be used[1] but, as with diethylcarbamazine, there is concern over its potential neurotoxic effects in patients with heavy microfilaraemia.

Diethylcarbamazine is also used for prophylaxis[1] but it has been suggested that it should be reserved for subjects at high risk of exposure. Vector control is regarded as impractical and methods aimed at reducing contact with the vector such as window screens and protective clothing are recommended.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Lung fluke infections

The lung fluke infection **paragonimiasis** is caused by *Paragonimus* spp., commonly *P. westermani*, and occurs in Asia, Africa, and Central or South America. The disease is transmitted by the ingestion of raw infected freshwater crabs or crayfish, or from drinking infected water.

The flukes mature in the lungs where they cause local necrosis, haemorrhage, inflammation, and fibrosis. Symptoms of paragonimiasis include fever, pain, and chest complaints, but most light to moderate infections are asymptomatic. The worms may also develop at other sites, particularly the brain where they can cause epilepsy, symptoms of cerebral tumours, or cerebral embolism, which may be fatal.

Treatment is with praziquantel or bithionol.[1] Triclabendazole has been studied.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Lymphatic filariasis

Lymphatic filariasis is a parasitic disease caused by filarial nematodes. The three species of filariae that cause lymphatic filariasis are *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, and *B. timori* (brugian filariasis, also known as Malayan and Timorian filariasis respectively). Adult worms produce larvae (microfilariae) which enter the peripheral bloodstream and through mosquito vectors infective larvae may be transmitted from person to person. The larvae migrate from the skin to the lymphatic system where they mature into adult worms that may live for several years. Development of lymphatic filariasis requires multiple bites from infected mosquitoes over a prolonged period of time (months to years); consequently, people living in endemic areas are at greatest risk of developing the disease.

Filarial infection is usually contracted in childhood and most infections are initially asymptomatic, although nearly all those infected will have some degree of subclinical lymphatic and kidney damage. Infection may remain occult or species- and body-site-dependent symptoms may follow. Acute inflammatory reactions to immature and dead or dying adult worms in the lymphatic system are referred to as *adenolymphangitis*, and are characterised by episodic attacks of fever, malaise, and inflammation of the inguinal lymph nodes, testis, and spermatic cord, and focal lymphoedema. These acute episodes usually resolve spontaneously after about a week, but can recur several times a year. *Chronic filariasis* may develop 10 to 15 years after initial symptoms and results from recurrent inflammation with subsequent damage to the lymphatic system, leading to impaired lymph drainage and lymphoedema. Manifestations include mild to massive enlargement of the legs, arms, breasts, or genitals (testicular hydrocele or swelling of the vulva), chyluria, and elephantiasis (grossly swollen limbs with thickened, hard, rough, and fissured skin). Lymphangitis may result from secondary bacterial infections.

Occult filariasis refers to filarial infection in which microfilariae are not detected in the peripheral blood but may be found in other body fluids and tissues. It is rare and is thought to result from a hypersensitivity reaction to filarial antigens. Clinical manifestations include tropical pulmonary eosinophilia, glomerulopathies, endomyocardial fibrosis, filarial arthritis, and filarial granulomas in the breast.

There is no entirely satisfactory **treatment** for individuals with lymphatic filariasis. Current treatments are effective against microfilariae, and thus prevent disease transmission, but have little or no effect on the adult worms and do not halt the progression of symptoms once the disease has developed. Diethylcarbamazine removes circulating microfilariae and is partially effective against the adult worm and is considered the treatment of choice.[1] Treatment may trigger acute lymphangitis, and diethylcarbamazine should not be given during an acute episode as it may cause further worm death and thus exacerbate the inflammatory response. Ivermectin is only active against microfilariae and is mainly used in areas also endemic for onchocerciasis or loiasis. Albendazole plus either of these two drugs is considered to increase their effectiveness and such combinations are recommended for mass treatment programmes.[2] However, systematic reviews of randomised studies[3,4] found insufficient evidence to either confirm or reject the observation that albendazole with diethylcarbamazine or ivermectin is more effective than either drug given alone. Secondary infections with bacteria and fungi occur in poorly vascularised tissues and therefore rigorous hygiene, skin care, physiotherapy, and other measures to promote lymph flow in the affected areas are recommended; in some cases antibiotics are needed. Large hydroceles and scrotal elephantiasis are generally not reversible with drug therapy and usually require surgical intervention after a treatment course with diethylcarbamazine.

Filaria have been shown to contain *Wolbachia* endobacteria which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of filariasis, and oral doxycycline for 8 weeks has resulted in a reduction in adult worms and prolonged reduction in microfilaraemia.[5]

Tropical pulmonary eosinophilia responds to a 3-week course of diethylcarbamazine but patients may relapse and require re-treatment. Filarial arthritis responds rapidly to treatment with diethylcarbamazine.

In communities where lymphatic filariasis is endemic **mass treatment** of the entire community is the basis of the Global Programme to Eliminate Lymphatic Filariasis.[2] The primary goal is to eliminate microfilariae from the blood of infected individuals thereby interrupting transmission. The programme recommends a single dose of 2 drugs (albendazole plus either diethylcarbamazine or ivermectin) given once-yearly for 4 to 6 years.[2,3] Albendazole plus ivermectin is used in areas where onchocerciasis or loiasis are also endemic. An alternative approach is the use of diethylcarbamazine-medicated salt for 6 to 12 months throughout the community at risk.

Ongoing **vector control** should be carried out before or during peak transmission season, in order to consolidate the effects of mass chemotherapy. People living in or visiting endemic areas are advised to sleep under a mosquito net and use mosquito repellent on exposed skin between dusk and dawn.

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Mansonella infections

Infections with the filarial nematodes *Mansonella perstans*, *M. ozzardi*, and *M. streptocerca* are generally asymptomatic but symptoms including malaise, fever, joint pain, and meningeal symptoms have been described. Infection is transmitted by biting midges and flies. Treatment with diethylcarbamazine may be effective depending on the infecting species (although it has no effect in *M. ozzardi* infections[1]). Mebendazole may be effective alone[1] or with levamisole or diethylcarbamazine[2] in *M. perstans*; albendazole is considered the drug of choice in this infection.[1] Ivermectin has been suggested for *M. ozzardi* infections[1] and may be the drug of choice for *M. streptocerca.*

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Bregani ER, *et al.* Comparison of different anthelmintic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; **100:** 458–63.

Metagonimiasis

See under Intestinal Fluke Infections, above.

Nanophyetiasis

See under Intestinal Fluke Infections, above.

Necatoriasis

See under Hookworm Infections, above.

Onchocerciasis

Onchocerciasis (river blindness) is a parasitic disease caused by infection with the filarial nematode *Onchocerca volvulus*. It is endemic in large areas of West and Central Africa, areas of Latin America, and Yemen. It is particularly prevalent near fast flowing rivers, the breeding ground of the blackfly which is the vector of the parasite. After infection, the larvae mature into adult worms in fibrous nodules, usually in the subcutaneous tissue. The adult female worms release large numbers of microfilariae which migrate from the nodules into other tissues, most notably the skin and the eyes. Death of microfilariae in the eyes causes severe inflammation and scarring that may lead to lesions in the eyes and impaired vision. There is some evidence that antigens released from symbiotic *Wolbachia* bacteria within the microfilariae also play a role.[1-3] Repeated infection over several years may result in irreversible blindness. In the skin the dying microfilariae trigger a subcutaneous inflammatory response that causes intense itching. Over time the skin becomes swollen and thickened (lizard skin) and may lose some of its elasticity and pigment (leopard skin).

Onchocerciasis is controlled either by treating the infected patient, thereby reducing the transmission of the infection from the human host to the vector, or by interrupting the transmission from vector to human. The drug of choice for the **treatment** of onchocerciasis is ivermectin.[2-5] A single oral dose of ivermectin rapidly eliminates microfilariae from the skin and more gradually eliminates them from the cornea and anterior chamber of the eye.[4] It has little effect on the adult worms although it suppresses release of microfilariae for several cycles. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Control of the disease in endemic areas relies upon the use of ivermectin every 12 months in Africa (and every 6 months in Central and South America) and this may be combined with vector control (below). Because the adult worms live for about 15 years, treatment will need to be continued for many years. Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in *community-wide mass treatment programmes* in all countries in which onchocerciasis is endemic, where it is given to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg, and those unable to walk or otherwise seriously ill.[6] For further details, see under Ivermectin, p.146. Increasing the frequency of the standard doses of ivermectin to every 3 months appears to increase efficacy compared with annual treatments.[7] Evidence from Ghana suggests that ivermectin-resistant populations of parasites are emerging and that its ability to suppress skin microfilariae repopulation is reduced over time in some communities.[8]

In areas where onchocerciasis and loiasis are co-endemic, care should be taken because ivermectin may cause serious adverse effects, including encephalopathy, in some patients with high *Loa loa* microfilaraemias (see Incidence of Adverse Effects, under Ivermectin, p.145). The Mectizan Expert Committee and the Technical Consultative Committee[9] have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis.

Before the introduction of ivermectin in 1988, diethylcarbamazine was the usual treatment for onchocerciasis, but it is no longer recommended by WHO.[4] The major limitations to its use are the severe allergic reaction (the Mazzotti reaction) associated with its microfilaricidal action, aggravation of existing ocular lesions or precipitation of new ones, and the need to give repeated courses of treatment for continued suppression of the disease.[4] Suramin has also been used in the treatment of onchocerciasis and is effective against adult worms.[4] However, its use is restricted because of its toxicity. Moxidectin is an anthelmintic used in veterinary medicine and is currently being evaluated for human use.[10] Amocarzine has also been evaluated in onchocerciasis.[4]

Recently it has been shown that adult worms contain *Wolbachia* endobacteria, which are essential for adult worm fertility and viability. This symbiotic dependency on *Wolbachia* has provided a new approach in the treatment of onchocerciasis. Treatment with oral doxycycline daily for 6 weeks has been shown to sterilise adult worms for the 4-month study period.[11] When given with a single dose of ivermectin, embryogenesis is interrupted for at least 18 months.[12] The long doxycycline treatment regimen is not suitable for mass treatment programmes, but it may be used with ivermectin for treatment of patients who permanently leave an endemic area.

In non-endemic areas ivermectin may be given every 3 to 6 months depending on the recurrence of symptoms or presence of microfilariae.

Vector control with larvicides, continued for the life span of an adult worm, is used to interrupt the transmission of infection and was the main strategy for onchocerciasis control before the introduction of ivermectin. However, despite initial success fly re-invasion became a problem, as the flight range of the vector was longer than expected.[13]

1. Saint André A, *et al.* The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. *Science* 2002; **295:** 1892–5.
2. Hoerauf A, *et al.* Onchocerciasis. *BMJ* 2003; **326:** 207–10.
3. Udall DN. Recent updates on onchocerciasis: diagnosis and treatment. *Clin Infect Dis* 2007; **44:** 53–60.
4. WHO. Onchocerciasis and its control: report of a WHO expert committee on onchocerciasis control. *WHO Tech Rep Ser 852* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 03/10/07)
5. WHO. Onchocerciasis (river blindness). Available at: http://www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html (accessed 15/06/06)
6. Pond B. Distribution of ivermectin by health workers. *Lancet* 1990; **335:** 1539.
7. Gardon J, *et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; **360:** 203–10.
8. Osei-Atweneboana MY, *et al.* Prevalence and intensity of Onchocerca volvulus infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet* 2007; **369:** 2021–9.
9. The Mectizan Expert Committee and Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: http://www.mectizan.org/library/EnglishMECTCCLoaRecs-June04.pdf (accessed 14/09/07)
10. Cotreau MM, *et al.* The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003; **43:** 1108–15.
11. Hoerauf A, *et al.* Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; **355:** 1242–3.
12. Hoerauf A, *et al.* Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001; **357:** 1415–6.
13. Thylefors B, Alleman M. Towards the elimination of onchocerciasis. *Ann Trop Med Parasitol* 2006; **100:** 733–46.

Opisthorchiasis

See under Liver Fluke Infections, above.

Paragonimiasis

See under Lung Fluke Infections, above.

Schistosomiasis

Schistosomiasis (bilharziasis) is a parasitic infection caused by *Schistosoma* spp., largely *S. mansoni*, *S. japonicum*, and *S. haematobium*, and to a lesser extent *S. intercalatum* and *S. mekongi*. The disease is seen mainly in Africa, Asia, South America, and the Caribbean, where it is a hazard to individuals exposed to fresh water containing the intermediate host, infected freshwater snails.

Free-swimming cercariae are released from the snail and penetrate human skin causing a pruritic papular rash in sensitised individuals (swimmer's itch). Parasites mature in the lungs and liver within about 6 weeks, then migrate to the blood vessels, the bladder, or intestines. Mature female worms produce eggs which are excreted in urine or stools, or become lodged in tissues, and immunological reaction to these eggs results in disease. The acute reaction to egg deposition has been termed Katayama fever, a self-limiting but sometimes fatal illness resembling serum sickness and most frequently seen in *S. japonicum* infection. The chronic phase of infection is often asymptomatic for many years, but usually results in granuloma formation and fibrosis in tissues where eggs are deposited, such as the liver, lungs, intestines, or urinary tract, the site depending on the infecting species.

Praziquantel is used for the treatment of chronic schistosomiasis[1-6] and is effective against all species of schistosomes. Metrifonate and oxamniquine have been used as alternatives against *S. haematobium*[1,2] and *S. mansoni*[1,3-5] respectively. Artemisinin derivatives used alone or in combination with praziquantel are also under investigation for *S. mansoni* infection[6-8] and *S. haematobium*.[9]

Niclosamide is used as a molluscicide for the treatment of water in schistosomiasis control programmes. Copper sulfate or sodium pentachlorophenate have also been used but to a lesser extent.

Schistosomiasis vaccines are in development.

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
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3. Saconato H, Atallah A. Interventions for treating schistosomiasis mansoni. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 16/05/05).
4. WHO. Schistosomiasis. Available at: http://www.who.int/tdr/diseases/schisto/diseaseinfo.htm (accessed 15/06/06)
5. Ross AGP, *et al.* Schistosomiasis. *N Engl J Med* 2002; **346:** 1212–20.
6. Gryseels B, *et al.* Human schistosomiasis. *Lancet* 2006; **368:** 1106–18.
7. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94:** 90–1.
8. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355:** 1320–5.
9. Borrmann S, *et al.* Artesunate and praziquantel for the treatment of Schistosoma haematobium infections: a double-blind, randomized, placebo-controlled study. *J Infect Dis* 2001; **184:** 1363–6.

Strongyloidiasis

Strongyloidiasis[1] is an infection of the small intestine caused by *Strongyloides stercoralis*, known as threadworm in the USA. It generally occurs in the tropics and subtropics and can also occur in some areas of South and East Europe, Japan, and the USA. In contrast with other intestinal nematodes, the eggs of *S. stercoralis* hatch before leaving the gastrointestinal tract, and can cause autoinfection, particularly in immunocompromised patients. Larvae reaching the soil can either mature into free-living adults or remain in an infective larval stage. Infective larvae cause infection by penetrating the skin. The larvae migrate to the lungs, move up the bronchial tree to be swallowed, and finally penetrate the mucosa of the small intestine where they mature. Eggs are deposited about 28 days after initial infection.

Infection may be asymptomatic, but commonly patients have symptoms relating to the stages of infection. Penetration of larvae through the skin causes intense pruritus and an erythematous rash. The rash may follow the course of migration and is one of the causes of cutaneous larva migrans (above). An inflammatory response to migration through the lungs may be seen and may include pneumonitis and bronchospasm. In heavy infections, which are most common in immunocompromised patients as a result of autoinfection, massive pulmonary invasion can occur resulting in fatal alveolar haemorrhage. Abdominal symptoms include colicky pain, diarrhoea, and vomiting, leading to nutritional deficiencies and weight loss. Eosinophilia may also be present. Disseminated disease may occur in immunocompromised patients and produce severe pulmonary and abdominal symptoms, shock, encephalopathy, meningitis, and Gram-negative septicaemia. Since strongyloidiasis is commonly fatal in these patients, vulnerable patients from endemic areas should be screened regularly and treated promptly at the first sign of infection.

Ivermectin is considered to be the treatment of choice.[1,2] Tiabendazole was widely used, and still is in some countries, but albendazole is more effective and better tolerated. Mebendazole has also been suggested but it must be given for longer periods than albendazole since it has only a limited effect on migrating larvae. A combination of ivermectin and albendazole has been suggested in disseminated disease.[2] These broad-spectrum anthelmintics (except tiabendazole) are also useful if the patient is suffering from a mixed intestinal nematode infection.

1. Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. *Ann Pharmacother* 2007; **41:** 1992–2001.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Syngamosis

Syngamosis, or gapeworm infection, is caused by *Syngamus* and *Mammomonogamus* spp. and is mainly an infection of domestic fowl and wild birds and mammals, although infection in man has been reported very rarely.[1-6] Man may become infected by eating foods contaminated with infective larvae which penetrate the intestinal wall and migrate to the lungs, where they mature into adult worms. The major symptom is cough, due to irritation of the bronchi and increased mucus production. The infection may be confused with asthma. Tiabendazole and mebendazole have been used successfully to treat the infection in man.

1. Timmons RF, *et al.* Infection of the respiratory tract with Mammomanogamus (Syngamus) laryngeus: a new case in Largo, Florida, and a summary of previously reported cases. *Am Rev Respir Dis* 1983; **128:** 566–9.

2. Gardiner CH, Schantz PM. Mammomonogamus infection in a human: report of a case. *Am J Trop Med Hyg* 1983; **32:** 995–7.
3. Leers WD, *et al.* Syngamosis, an unusual cause of asthma: the first reported case in Canada. *Can Med Assoc J* 1985; **132:** 269–70.
4. Nosanchuk JS, *et al.* Case report of and description of parasite in Mammomonogamus laryngeus (human syngamosis) infection. *J Clin Microbiol* 1995; **33:** 998–1000.
5. Turner P, *et al.* A case of human syngamosis. *Travel Med Infect Dis* 2003; **1:** 231–3.
6. Castaño JC, *et al.* Reporte del primer caso humano de infección parasitaria por Mammomonogamus laryngeus en Colombia. *Biomedica* 2006; **26:** 337–41.

Taeniasis

Taeniasis is an infection of the intestine with beef tapeworm, *Taenia saginata*, or pork tapeworm, *T. solium*, acquired through ingestion of contaminated raw or undercooked meat. The larval form of *T. solium* can cause the systemic infection cysticercosis (see above).

Infection with the adult worm usually produces symptoms only when the worm reaches a size that can cause obstruction or related problems. Segments of the worm containing eggs may be excreted in the faeces so maintaining the cycle of reproduction. Treatment is with a single dose of praziquantel,[1] which has the advantage of also being active, in higher doses, against the larval form of *T. solium*. Niclosamide is also effective but is only active against adult worms.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Toxocariasis

Toxocariasis[1] is infection with the larval form of *Toxocara canis* or, less commonly, *T. cati*. The adult worms live in the intestines of dogs and cats respectively, and man becomes infected when eggs excreted in animal faeces are ingested. Once ingested the eggs hatch and the larvae migrate from the intestine to other organs, most commonly the liver, lung, and eye. Most infections are asymptomatic but two clinical syndromes, ocular larva migrans and visceral larva migrans, can occur, usually in children.

Ocular larva migrans occurs when larvae invade the eye causing a granuloma which may impair vision and can cause blindness. There is no specific treatment.[2] Anthelmintics such as albendazole or tiabendazole, corticosteroids, ocular surgery, and laser photocoagulation have been used but assessment of their efficacy is difficult because of the variable natural course of the disease.

The clinical symptoms of visceral larva migrans depend upon the organs involved but commonly include cough, wheezing, fever, and hepatomegaly. Encephalitis and seizures may occur and there is usually eosinophilia. Acute infection normally resolves without treatment.[3] However, severe or prolonged infections may be treated with albendazole;[4] mebendazole or tiabendazole have also been used.[1,4]

1. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; **16:** 265–72.
2. Shields JA. Ocular toxocariasis: a review. *Surv Ophthalmol* 1984; **28:** 361–81.
3. Gillespie SH. Human toxocariasis. *Commun Dis Rep* 1993; **3:** R140–R143.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Trichinosis

Trichinosis (trichinellosis) is an infection caused by *Trichinella spiralis.* Man becomes infected through ingestion of raw or undercooked meat, usually pork, containing infective larvae. The larvae mature into adult worms in the small intestine and the mature females deposit larvae which migrate in the blood to skeletal muscle and sometimes to the myocardium. Symptoms usually occur only in heavy infections. Invasion of the intestines by the maturing adult worms can cause diarrhoea, abdominal pain, and vomiting followed about a week later by hypersensitivity reactions to the migrating larvae. These may include eosinophilia, fever, muscle pain, periorbital oedema and, more rarely, encephalitis, myocarditis, or pneumonia which may be fatal.

All patients with confirmed or suspected infection should be treated to prevent the continued production of larvae. Albendazole or mebendazole are considered to be the anthelmintics of choice. A corticosteroid should be given for severe hypersensitivity reactions.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Trichostrongyliasis

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. including *T. colubriformis*. *Trichostrongylus* spp. are normally parasites of herbivores, but infections in man have been found. They have a similar life cycle to *Ancylostoma duodenale* (see Hookworm Infections, above). Pyrantel embonate, albendazole, or mebendazole are recommended for the treatment of trichostrongyliasis.[1] Successful treatment with ivermectin has occurred in areas where widespread use of benzimidazole carbamate derivatives in grazing animals has led to resistance to these drugs.[2]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Ralph A, *et al.* Abdominal pain and eosinophilia in suburban goat keepers. *Med J Aust* 2006; **184:** 467–9. Correction. *ibid.*; **185:** 49. [title]

Trichuriasis

Trichuriasis is an infection of the large intestine with *Trichuris trichiura*, sometimes known as whipworm. Distribution is worldwide, but most infections occur in the tropics and subtropics. Eggs are excreted in the faeces and can remain viable in the soil for extended periods. Under optimum conditions the eggs become infective in about 2 to 4 weeks. After ingestion, larvae are released from the eggs and develop within the wall of the small intestine for about 3 to 10 days, before migrating to the lumen of the large intestine where they remain attached to the mucosal lining. Eggs are detectable in the faeces about 1 to 3 months after infection. Trichuriasis is often asymptomatic, but heavy infection can result in anaemia, diarrhoea, and rectal prolapse.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] and such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Ivermectin[2] and nitazoxanide[4] are alternatives. However, a systematic review[3] considered the treatment of trichuriasis to be unsatisfactory with current drugs.

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; **367:** 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.
4. Juan JO, *et al.* Comparative clinical studies of nitazoxanide, albendazole and praziquantel in the treatment of ascariasis, trichuriasis and hymenolepiasis in children from Peru. *Trans R Soc Trop Med Hyg* 2002; **96:** 193–6.

Abamectin *(USAN, rINN)*

Abamectina; Abamectine; Abamectinum; MK-0936. A mixture of abamectin component B_{1a} and abamectin component B_{1b}.

Абамектин

CAS — 65195-55-3 (component B_{1a}); 65195-56-4 (component B_{1b}).

ATC Vet — QP54AA02.

Profile

Abamectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Albendazole *(BAN, USAN, rINN)*

Albendatsoli; Albendazol; Albendazolas; Albendazolum; SKF-62979. Methyl 5-propylthio-1*H*-benzimidazol-2-ylcarbamate.

Альбендазол

$C_{12}H_{15}N_3O_2S$ = 265.3.

CAS — 54965-21-8.

ATC — P02CA03.

ATC Vet — QP52AC11.

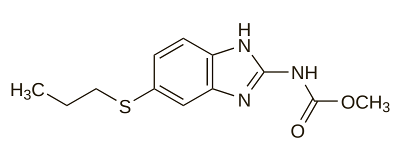

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; freely soluble in anhydrous formic acid. Protect from light.

USP 31 (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in ether and in dichloromethane; freely soluble in anhydrous formic acid. Store in airtight containers.

Adverse Effects and Precautions

As for Mebendazole, p.148.

Incidence of adverse effects. Although generally well-tolerated, the following adverse reactions were reported in the first phase of WHO-coordinated studies[1] involving 30 patients given *high-dose* therapy with albendazole for the treatment of cystic echinococcosis (hydatid disease): raised serum-transaminase levels (2 patients), reduced leucocyte counts (1), gastrointestinal symptoms (1), allergic conditions (1), and loss of hair (1). Treatment was stopped in a further patient with alveolar echinococcosis because of depressed bone-marrow activity. In the second phase of these studies,[2] of 109 patients given albendazole for cystic echinococcosis, 20 had adverse effects; similar findings were reported with mebendazole. The range of effects with albendazole was: elevation of transaminases (5 patients), abdominal pain and other gastrointestinal symptoms (7), severe headache (4), loss of hair (2), leucopenia (2), fever and fatigue (1), thrombocytopenia (1), and urticaria and itching (1). Albendazole had to be withdrawn in 5 patients because of adverse effects, although in 3 the withdrawal was only temporary.

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64:** 383–8.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Effects on growth. A multiple-dose regimen of albendazole in children with asymptomatic trichuriasis has been reported to be associated with impaired growth in those with low levels of infection.[1] However it was considered that this should not prevent the use of single doses in mass treatment programmes.[2]

1. Forrester JE, *et al.* Randomised trial of albendazole and pyrantel in symptomless trichuriasis in children. *Lancet* 1998; **352:** 1103–8.
2. Winstanley P. Albendazole for mass treatment of asymptomatic trichuris infections. *Lancet* 1998; **352:** 1080–1.

Effects on the liver. In a series of 40 patients given albendazole for echinococcosis, 7 developed abnormalities in liver function tests during therapy.[1] Six had a hepatocellular type of abnormality attributable to albendazole; the seventh had cholestatic jaundice which was probably not due to albendazole. See also Incidence of Adverse Effects, above for reports of raised serum-transaminase levels.

Albendazole should only be used in the treatment of echinococcosis if there is constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Morris DL, Smith PG. Albendazole in hydatid disease—hepatocellular toxicity. *Trans R Soc Trop Med Hyg* 1987; **81:** 343–4.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Pregnancy. Albendazole is teratogenic in some *animals* and there are no adequate and well controlled studies in human pregnancy. Albendazole is therefore usually contra-indicated during pregnancy and licensed product information cautions against becoming pregnant while taking albendazole or within one month of completing treatment.

Interactions

Anthelmintics. The plasma concentration of albendazole sulfoxide has been increased by *praziquantel*,[1] although the practical consequences of this were considered uncertain.

1. Homeida M, *et al.* Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* 1994; **88:** 551–9.

Antiepileptics. *Phenytoin*, *carbamazepine*, and *phenobarbital* appear to induce the oxidative metabolism of albendazole via the cytochrome P450 isoenzyme CYP3A by roughly the same extent, resulting in significantly reduced concentrations of albendazole sulfoxide. This interaction is likely to be clinically significant when albendazole is used to treat systemic worm infections, and increased doses of albendazole would be needed.[1] The interaction is probably not clinically significant when albendazole is used for intestinal worm infections.

1. Lanchote VL, *et al.* Pharmacokinetic interaction between albendazole sulfoxide enantiomers and antiepileptic drugs in patients with neurocysticercosis. *Ther Drug Monit* 2002; **24:** 338–45.

Corticosteroids. Plasma concentrations of the active metabolite of albendazole (albendazole sulfoxide) were reported to be raised by about 50% in a study in 8 patients receiving *dexamethasone*.[1]

1. Jung H, *et al.* Dexamethasone increases plasma levels of albendazole. *J Neurol* 1990; **237:** 279–80.

Histamine H_2-antagonists. Concentrations of albendazole sulfoxide have been found to be raised in bile and hydatid cyst fluid when albendazole was given with *cimetidine*, which may increase effectiveness in the treatment of echinococcosis.[1]

1. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88:** 49–52.

Pharmacokinetics

Absorption of albendazole from the gastrointestinal tract is poor but may be enhanced by a fatty meal. Albendazole rapidly undergoes extensive first-pass metabolism. Its principal metabolite albendazole sulfoxide has anthelmintic activity and a plasma half-life of about 8.5 hours. Albendazole sulfoxide is widely distributed throughout the body including into the bile and the CSF. It is about 70% bound to plasma protein. Albendazole sulfoxide is eliminated in the bile; only a small amount appears to be excreted in the urine.

◊ References.

1. Marriner SE, *et al*. Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol* 1986; **30:** 705–8.
2. Morris DL, *et al.* Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987; **28:** 75–80.
3. Steiger U, *et al.* Albendazole treatment of echinococcosis in humans: effects on microsomal metabolism and drug tolerance. *Clin Pharmacol Ther* 1990; **47:** 347–53.
4. Jung H, *et al.* Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol* 1992; **32:** 28–31.
5. Jung H, *et al.* Clinical pharmacokinetics of albendazole in children with neurocysticercosis. *Am J Ther* 1997; **4:** 23–6.

Uses and Administration

Albendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148) and with similar activity. It is used in relatively high doses in the treatment of the cestode infections cysticercosis and echinococcosis (hydatid disease). In some countries albendazole is used in the treatment of single and mixed intestinal nematode infections including ascariasis, enterobiasis, hookworm, strongyloidiasis, and trichuriasis. It may also be used in the treatment of angiostrongyliasis, capillariasis, gnathostomiasis, and trichostrongyliasis. Albendazole may be effective in the treatment of the tissue nematode infections cutaneous larva migrans, toxocariasis, and trichinosis and has been tried in loiasis, and, with other anthelmintics, in mass treatment programmes in areas where lymphatic filariasis is endemic. For discussions of these infections and their treatment, see under Choice of Anthelmintic (p.134), and under the individual headings below.

In the treatment of **echinococcosis**, albendazole is given orally with meals in a dose of 400 mg twice daily for 28 days for patients weighing over 60 kg. A dose of 15 mg/kg daily in two divided doses (to a maximum total daily dose of 800 mg) is used for patients weighing less than 60 kg. For cystic echinococcosis, the 28-day course may be repeated after 14 days without treatment to a total of 3 treatment cycles. For alveolar echinococcosis, cycles of 28 days of treatment followed by 14 days without treatment may need to continue for months or years.

In the treatment of **neurocysticercosis**, US licensed product information recommends doses of albendazole for parenchymal cysts similar to the doses used in echinococcosis (see above); the recommended duration of treatment is 8 to 30 days. Current expert opinion also favours similar doses of 15 mg/kg daily but with a duration of treatment of only 8 days for parenchymal disease and about 1 month for subarachnoid disease. For further information on dosage regimens, see Cysticercosis, below.

Albendazole is given orally, usually as a single dose, in the treatment of single or mixed **intestinal nematode infections**. The usual dose for adults and children aged 2 years or over with ascariasis, enterobiasis, hookworm infections, or trichuriasis is 400 mg as a single dose. In enterobiasis, the dose may be repeated in 1 to 4 weeks. Some consider that children of 1 to 2 years of age may be given 200 mg for enterobiasis. In strongyloidiasis, 400 mg is given once or twice daily for 3 consecutive days; this may be repeated after 3 weeks if necessary.

Albendazole has also been used to treat **giardiasis** (p.824); suggested doses are 400 mg daily by mouth for 5 days.

Ascariasis. Albendazole is used as an alternative to mebendazole in the treatment of ascariasis (p.134). Both drugs are equally highly effective with a cure rate greater than 98% reported for albendazole in one study.[1]

1. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.

Capillariasis. Albendazole in a dose of 400 mg daily for 10 days has been suggested[1] as an alternative to mebendazole for the treatment of capillariasis (p.135).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Cutaneous larva migrans. Albendazole has been reported[1-4] to be effective in the treatment of cutaneous larva migrans (p.135) and is an alternative to tiabendazole or ivermectin. Albendazole, generally in a dose of 400 mg daily for three[1] or five[2] days, has alleviated the discomfort of cutaneous larva migrans; treatment for seven days may be more effective and has not been associated with an increased incidence of adverse effects.[4] A single dose of 400 mg has also been effective.[3] An ointment containing albendazole 10%, applied 3 times a day for 10 days, was reported to be effective in treating cutaneous larva migrans in 2 young children.[5]

1. Jones SK, *et al.* Oral albendazole for the treatment of cutaneous larva migrans. *Br J Dermatol* 1990; **122:** 99–101.
2. Sanguigni S, *et al.* Albendazole in the therapy of cutaneous larva migrans. *Trans R Soc Trop Med Hyg* 1990; **84:** 831.
3. Oriheula AR, Torres JR. Single dose of albendazole in the treatment of cutaneous larva migrans. *Arch Dermatol* 1990; **126:** 398–9.
4. Veraldi S, Rizzitelli G. Effectiveness of a new therapeutic regimen with albendazole in cutaneous larva migrans. *Eur J Dermatol* 1999; **9:** 352–3.
5. Caumes E. Efficacy of albendazole ointment on cutaneous larva migrans in 2 young children. *Clin Infect Dis* 2004; **38:** 1647–8.

Cysticercosis. The use of anthelmintics in the treatment of neurocysticercosis (see Cysticercosis, p.135) remains controversial, but if indicated albendazole is considered to be the drug of choice.[1-3] The dose of albendazole originally used was the same as that used in echinococcosis, typically about 15 mg/kg daily orally for 1 month. There is now some evidence that shorter courses of treatment may be appropriate in some forms of neurocysticercosis. A study[4] confirmed that a 10-day course of albendazole 400 mg twice daily, together with dexamethasone, was safe and decreased the burden of parasites and the number of generalised seizures in patients with viable parenchymal cysts. Albendazole has also been reported to be effective for extraparenchymal infection, such as subarachnoid, ventricular,[2,5,6] and spinal cord cysticercosis,[2] but the longer treatment period of 1 month with a dose of 15 mg/kg daily is usually used. Alternatively, a higher dose of albendazole for a shorter time may be considered. A study[5] of 36 patients with subarachnoid and intraventricular cysticercosis found that 30 mg/kg daily for 8 days was safe and more effective than 15 mg/kg daily for 8 days, both regimens being given with corticosteroids.

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.
2. Takayanagui OM. Therapy for neurocysticercosis. *Expert Rev Neurother* 2004; **4:** 129–39.
3. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel.*Ann Intern Med* 2006; **145:** 43–51.
4. Garcia HH, *et al.* A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004; **350:** 249–58.
5. Góngora-Rivera F, *et al.* Albendazole trial at 15 or 30 mg/kg/day for subarachnoid and intraventricular cysticercosis. *Neurology* 2006; **66:** 436–8.
6. Proaño JV, *et al.* Medical treatment for neurocysticercosis characterized by giant subarachnoid cysts. *N Engl J Med* 2001; **345:** 879–85.

Echinococcosis. Albendazole is used in the treatment of echinococcosis (p.136) as an adjunct to, or instead of, surgery. It is generally preferred to mebendazole.

References.

1. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37:** 1679–84.
2. Gil-Grande LA, *et al.* Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. *Lancet* 1993; **342:** 1269–72.
3. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88:** 49–52.
4. Wen H, *et al.* Albendazole chemotherapy for human cystic and alveolar echinococcosis in north-western China. *Trans R Soc Trop Med Hyg* 1994; **88:** 340–3.
5. Liu Y, *et al.* Continuous long-term albendazole therapy in intraabdominal cystic echinococcosis. *Chin Med J (Engl)* 2000; **113:** 827–32.
6. Keshmiri M, *et al.* Albendazole versus placebo in treatment of echinococcosis. *Trans R Soc Trop Med Hyg* 2001; **95:** 190–4.
7. Falagas ME, Bliziotis IA. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. *Am J Med Sci* 2007; **334:** 171–9.

Gnathostomiasis. Albendazole has been reported to be effective in the treatment of gnathostomiasis (p.136). Doses of 400 mg once or twice daily have been given for 2 or 3 weeks.[1-4]

1. Kraivichian P, *et al.* Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* 1992; **86:** 418–21.
2. Suntharasamai P, *et al.* Albendazole stimulates outward migration of Gnathostoma spinigerum to the dermis in man. *Southeast Asian J Trop Med Public Health* 1992; **23:** 716–22.
3. Nontasut P, *et al.* Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2000; **31:** 374–7.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Hookworm infections. Hookworm infections (p.136) are commonly treated with benzimidazole carbamates such as albendazole. In 77 patients with light necatoriasis (*Necator americanus* infection) albendazole, in a single 400-mg dose, produced an 84% cure rate and an 82% reduction in egg count in those patients not cured.[1] In another study,[2] although the cure rate was only 56.8% after a single 400-mg dose of albendazole this was superior to treatment with mebendazole which had a cure rate of 22.4%. A further study[3] comparing albendazole with mebendazole and pyrantel in the treatment of necatoriasis also found albendazole to be the most effective.

Albendazole is given in mass treatment programmes to reduce the overall burden of infection.[1,4]

1. Nahmias J, *et al.* Evaluation of albendazole, pyrantel, bephenium, pyrantel-praziquantel and pyrantel-bephenium for single-dose mass treatment of necatoriasis. *Ann Trop Med Parasitol* 1989; **83:** 625–9.
2. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.
3. Sacko M, *et al.* Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the southern region of Mali, West Africa. *Trans R Soc Trop Med Hyg* 1999; **93:** 195–203.
4. Idris MA, *et al.* Effective control of hookworm infection in school children from Dhofar, Sultanate of Oman: a four-year experience with albendazole mass chemotherapy. *Acta Trop* 2001; **80:** 139–43.

Loiasis. Albendazole has been investigated[1,2] to reduce microfilariasis in patients infected with *Loa loa* (see Loiasis, p.137) with modest success.

1. Klion AD, *et al.* Albendazole in human loiasis: results of a double-blind, placebo-controlled trial. *J Infect Dis* 1993; **168:** 202–6.
2. Tabi TE, *et al.* Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. *Am J Trop Med Hyg* 2004; **71:** 211–15.

Lymphatic filariasis. Albendazole is used in the management of lymphatic filariasis (p.137). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. The Global Programme to eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single dose of albendazole 400 mg with either a single dose of ivermectin 150 to 200 micrograms/kg (if there is co-endemic loiasis or onchocerciasis) or with a single dose of diethylcarbamazine 6 mg/kg (if there is no co-endemic loiasis or onchocerciasis); these doses are given once each year for at least 5 years.

Microsporidiosis. Albendazole has been tried[1-6] in the treatment of the protozoal infection microsporidiosis (p.826) in patients with AIDS. Albendazole has also been used empirically in the treatment of HIV-associated infections and complications (p.857).

1. Blanshard C, *et al.* Treatment of intestinal microsporidiosis with albendazole in patients with AIDS. *AIDS* 1992; **6:** 311–13.
2. Dieterich DT, *et al.* Treatment with albendazole for intestinal disease due to Enterocytozoon bieneusi in patients with AIDS. *J Infect Dis* 1994; **169:** 178–82.
3. Franzen C, *et al.* Intestinal microsporidiosis with Septata intestinalis in a patient with AIDS—response to albendazole. *J Infect* 1995; **31:** 237–9.
4. Dore GJ, *et al.* Disseminated microsporidiosis due to Septata intestinalis in nine patients infected with the human immunodeficiency virus: response to therapy with albendazole. *Clin Infect Dis* 1995; **21:** 70–6.
5. Molina J-M, *et al.* Albendazole for treatment and prophylaxis of microsporidiosis due Encephalitozoon intestinalis in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis* 1998; **177:** 1373–7.
6. Tremoulet AH, *et al.* Albendazole therapy for Microsporidium diarrhea in immunocompetent Costa Rican children. *Pediatr Infect Dis J* 2004; **23:** 915–18.

Strongyloidiasis. Albendazole is generally preferred to tiabendazole or mebendazole in the treatment of strongyloidiasis (p.138) although ivermectin is now generally considered to be the drug of choice. Both drugs have been used together in disseminated disease.

References.

1. Rossignol JF, Maisonneuve H. Albendazole: placebo-controlled study in 870 patients with intestinal helminthiasis. *Trans R Soc Trop Med Hyg* 1983; **77:** 707–11.
2. Chanthavanich P, *et al.* Repeated doses of albendazole against strongyloidiasis in Thai children. *Southeast Asian J Trop Med Public Health* 1989; **20:** 221–6.
3. Mojon M, Nielsen PB. Treatment of Strongyloides stercoralis with albendazole: a cure rate of 86 per cent. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 1987; **263:** 619–24.

4. Archibald LK, *et al.* Albendazole is effective treatment for chronic strongyloidiasis. *Q J Med* 1993; **86:** 191–5.
5. Pornsuriyasak P, *et al.* Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2004; **35:** 531–4.
6. Singthong S, *et al.* Randomized comparative trial of two high-dose albendazole regimens for uncomplicated human strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2006; **37** (suppl 3): 32–4.

Toxocariasis. Albendazole is one of the drugs that might be used for the treatment of toxocariasis (p.139) and in a small study[1] it produced improvement similar to that achieved with tiabendazole but with fewer problems.

1. Stürchler D, *et al.* Thiabendazole vs albendazole in treatment of toxocariasis: a clinical trial. *Ann Trop Med Parasitol* 1989; **83:** 473–8.

Trichinosis. Albendazole may be effective in the treatment of trichinosis (p.139). A retrospective study in 44 patients with trichinosis comparing albendazole treatment with tiabendazole found that, while the two drugs were of comparable efficacy, albendazole was the better tolerated.[1] Albendazole has been used to treat a patient infected with *Trichinella pseudospiralis*, an organism related to *T. spiralis*, the usual cause of trichinosis.[2]

1. Cabié A, *et al.* Albendazole versus thiabendazole as therapy for trichinosis: a retrospective study. *Clin Infect Dis* 1996; **22:** 1033–5.
2. Andrews JRH, *et al.* Trichinella pseudospiralis in humans: description of a case and its treatment. *Trans R Soc Trop Med Hyg* 1994; **88:** 200–3.

Trichostrongyliasis. Albendazole in a single dose of 400 mg has been suggested[1] as an alternative to pyrantel embonate or mebendazole in the treatment of trichostrongyliasis (p.139).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Trichuriasis. Albendazole is used in the treatment of trichuriasis (p.139). It is normally given in a single dose and is often used in mixed intestinal nematode infections.[1] However, it has been reported[1-3] that in children with mixed intestinal worm infections single doses of albendazole are ineffective in eliminating *Trichuris trichiura* and multiple doses are required to produce worthwhile reductions in egg production. Treatment for 3 days has been used[4] (but for a suggestion that such regimens may be associated with impaired growth in less heavily infected children, see Effects on Growth under Adverse Effects, above). Combined use of albendazole with ivermectin may prove useful.[5]

1. Hall A, Anwar KS. Albendazole and infections with Trichuris trichiura and Giardia intestinalis. *Southeast Asian J Trop Med Public Health* 1991; **22:** 84–7.
2. Hall A, Nahar Q. Albendazole and infections with Ascaris lumbricoides and Trichuris trichiura in children in Bangladesh. *Trans R Soc Trop Med Hyg* 1994; **88:** 110–12.
3. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88:** 585–9.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
5. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of Trichuris trichiura infections in Sri Lanka. *Ann Trop Med Parasitol* 1999; **93:** 501–4.

Preparations

USP 31: Albendazole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Vastus; ***Austral.:*** Eskazole; Zentel; ***Austria:*** Eskazole; ***Braz.:*** Alba-3; Albel; Alben†; Albendrox†; Albendy†; Albenix†; Albentel; Albenzonil; Albezin†; Alib†; Alin; Alzoben†; Bentiamin†; Benzol; Imavermil; Mebenix; Monozol; Neo Bendazol; Parasin; Parazol; Totelmin†; Verdazol†; Vermiclase; Vermital; Zentel; Zolben; Zoldan†; ***Chile:*** Ceprazol; Vermoil; Zentel; ***Cz.:*** Zentel; ***Fr.:*** Zentel; ***Ger.:*** Eskazole; ***Gr.:*** Eskazole; Zentel; ***India:*** Albezole; Bendex; Combantrin-A; Emanthal; Nemozole; Olworm; Zentel; ***Israel:*** Eskazole; ***Ital.:*** Zentel; ***Malaysia:*** Albendol; Champs D-Worms; Thelban†; Vemizol; Zentel; Zoben; ***Mex.:*** Albensil; Aldamin; Alfazol; Bendapar; Bradelmin; Dazocan; Dazolin; Dezabil; Digezanol; Entoplus; Eskazole; Euralben; Flatezol†; Gascop; Helmisons; Kolexan; Loveral; Lurdex; Olbendital; Rivazol; Serbendazol; Synparyn; Tenibex; Veranzol; Vermilan†; Vermin Plus; Vermisen; Zelfin; Zenaxin; Zentel; ***Neth.:*** Eskazole; ***Philipp.:*** Zentel; ***Pol.:*** Zentel; ***Port.:*** Zentel; ***Rus.:*** Nemozole (Немозол); ***S.Afr.:*** Bendex; Zentel; ***Singapore:*** Alzental; Zentel; ***Spain:*** Eskazole; ***Switz.:*** Zentel; ***Thai.:*** Abentel; Albatel; Alben; Albenda; Alda†; Alfuca; Alzol; Anthel†; Gendazel; Labenda; Leo-400; Manoverm; Masaworm†; Mesin; Mycotel; Vermixide; Zeben; Zela; Zentel; Zenzera; ***Turk.:*** Andazol; ***UAE:*** Albenda; ***USA:*** Albenza; ***Venez.:*** Albezol; Albicar; Bevindazol; Helal; Sostril; Taron; Vendazol; Zentel.

Multi-ingredient: ***Mex.:*** Oxal.

Amocarzine *(rINN)*

Amocarzina; Amocarzinum; CGP-6140. 4-Methyl-4′-(*p*-nitroanilino)thio-1-piperazinecarboxanilide.

Амокарзин

$C_{18}H_{21}N_5O_2S = 371.5.$

CAS — 36590-19-9.

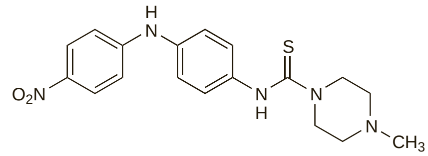

NOTE. Amocarzine has sometimes been referred to as thiocarbamazine.

Profile

Amocarzine is an antifilarial anthelmintic that is active against the adult worms of *Onchocerca volvulus.* It has been studied for the oral treatment of onchocerciasis (p.137).

◊ References.

1. Poltera AA, *et al.* Onchocercacidal effects of amocarzine (CGP 6140) in Latin America. *Lancet* 1991; **337:** 583–4.
2. Cooper PJ, *et al.* Onchocerciasis in Ecuador: evolution of chorioretinopathy after amocarzine treatment. *Br J Ophthalmol* 1996; **80:** 337–42.
3. Awadzi K, *et al.* The safety and efficacy of amocarzine in African onchocerciasis and the influence of ivermectin on the clinical and parasitological response to treatment. *Ann Trop Med Parasitol* 1997; **91:** 281–96.

Trivalent Antimony Compounds

Compuestos de antimonio trivalente.

Antimony Potassium Tartrate

Antim. Pot. Tart.; Antimónico potásico, tartrato; Antymonu potasu winian; Brechweinstein; Kalii Stibyli Tartras; Potassium Antimonyltartrate; Stibii et Kalii Tartras; Tartar Emetic; Tartarus Stibiatus. Dipotassium bis{μ-[2,3-dihydroxybutanedioato(4-)-*O*^{1},*O*^{2}:*O*^{3},*O*^{4}]}-diantimonate(2-) trihydrate; Dipotassium bis[μ-tartrato(4-)]diantimonate(2-) trihydrate.

Антимонил-тартрат Калия

$C_8H_4K_2O_{12}Sb_2,3H_2O = 667.9.$

CAS — 11071-15-1 (anhydrous antimony potassium tartrate); 28300-74-5 (antimony potassium tartrate trihydrate).

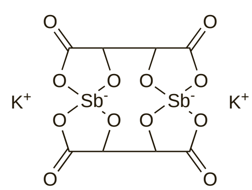

Pharmacopoeias. In *US.*

USP 31 (Antimony Potassium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air and do not readily rehydrate even on exposure to high humidity. Soluble 1 in 12 of water, 1 in 3 of boiling water, and 1 in 15 of glycerol; insoluble in alcohol. Its solutions are acid to litmus.

Antimony Sodium Tartrate

Antim. Sod. Tart.; Antimónico sódico, tartrato; Sodium Antimonyltartrate; Stibium Natrium Tartaricum. Disodium bis{μ-[2,3-dihydroxybutanedioato(4-)-*O*^{1},*O*^{2}:*O*^{3},*O*^{4}]}diantimonate(2-); Disodium bis{μ-[L-(+)-tartrato(4-)]}diantimonate(2-).

Антимонил-тартрат Натрия

$C_8H_4Na_2O_{12}Sb_2 = 581.6.$

CAS — 34521-09-0.

Pharmacopoeias. In *Int.* (as $C_4H_4NaO_7Sb = 308.8$) and *US.*

USP 31 (Antimony Sodium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air. Freely soluble in water; insoluble in alcohol.

Sodium Stibocaptate *(BAN, rINN)*

Antimony Sodium Dimercaptosuccinate; Estibocaptato de sodio; Natrii Stibocaptas; Ro-4-1544/6; Sb-58; Stibocaptate; Stibocaptate de Sodium; TWSb/6. Antimony sodium *meso*-2,3-dimercaptosuccinate. The formula varies from $C_{12}H_{11}NaO_{12}S_6Sb_2 = 806.1$ to $C_{12}H_6Na_6O_{12}S_6Sb_2 = 916.0.$

Натрия Стибокаптат

CAS — 3064-61-7 ($C_{12}H_6Na_6O_{12}S_6Sb_2$).

Stibophen

Estibofeno; Fouadin; Stibophenum. Bis[4,5-dihydroxybenzene-1,3-disulphonato(4−)-*O*^{4},*O*^{5}]antimonate(5−) pentasodium heptahydrate.

Стибофен

$C_{12}H_4Na_5O_{16}S_4Sb,7H_2O = 895.2.$

CAS — 15489-16-4 (stibophen heptahydrate).

ATC — P02BX03.

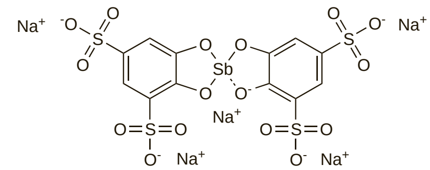

Adverse Effects and Treatment

Trivalent antimony compounds are more toxic than pentavalent antimonials such as sodium stibogluconate, possibly because they are excreted much more slowly. The most serious adverse effects are on the heart and liver. There are invariably ECG changes during treatment, but hypotension, bradycardia, and cardiac arrhythmias are more serious. Sudden death or cardiovascular collapse may occur at any time. Elevated liver enzyme values are common; liver damage with hepatic failure and death is more likely in patients with pre-existing hepatic disease.

Adverse effects immediately after intravenous use of trivalent antimonials, in particular the tartrates, have included coughing, chest pain, pain in the arms, vomiting, abdominal pain, fainting, and collapse, especially after rapid injection. Extravasation during injection is extremely painful because of tissue damage. An anaphylactoid reaction characterised by an urticarial rash, husky voice, and collapse has been reported after the sixth or seventh intravenous injection of a course of treatment.

Numerous less immediate adverse effects have occurred including gastrointestinal disturbances, muscular and joint pains, arthritis, pneumonia, dyspnoea, headache, dizziness, weakness, pruritus, skin rashes, facial oedema, fever, haemolytic anaemia, and kidney damage.

Large oral doses of antimony compounds have an emetic action. Continuous treatment with small doses of antimony may give rise to symptoms of subacute poisoning similar to those of chronic arsenical poisoning.

Treatment of severe poisoning with antimony compounds is similar to that for arsenic poisoning (p.2261); dimercaprol may be of benefit.

◊ References.

1. Stemmer KL. Pharmacology and toxicology of heavy metals: antimony. *Pharmacol Ther* 1976; **1:** 157–60.

Precautions

Trivalent antimony therapy has generally been superseded by less toxic treatment. It is contra-indicated in the presence of lung, heart, liver, or kidney disease. Intravenous injections should be given very slowly and stopped if coughing, vomiting, or substernal pain occurs; extravasation should be avoided.

Some antimony compounds such as the tartrates cause severe pain and tissue necrosis and should not be given by intramuscular or subcutaneous injection.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of antimony by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Glucose-6-phosphate dehydrogenase deficiency. In the event of trivalent antimony compounds being used, patients with G6PD deficiency should be excluded. WHO lists stibophen[1] among the anthelmintics to be avoided in patients with this deficiency.

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67:** 601–11.

Pharmacokinetics

Antimony compounds are poorly absorbed from the gastrointestinal tract. They are slowly excreted, mainly in the urine, after parenteral doses. Antimony accumulates in the body during treatment and persists for several months afterwards. Trivalent antimony has a greater affinity for cell proteins than for plasma proteins.

Uses and Administration

Trivalent antimony compounds were used in the treatment of the protozoal infection leishmaniasis until the advent of the less toxic pentavalent compounds. They continued to be used in the treatment of schistosomiasis, but have now been superseded by less toxic and more easily given drugs such as praziquantel.

The symbol † denotes a preparation no longer actively marketed

Antimony sodium tartrate was formerly used as an emetic. The sodium tartrate and potassium tartrate have also been used as expectorants.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Thai.:*** Brown Mixture.

Ascaridole

Ascaridol. 1-Isopropyl-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-ene.

Аскаридол

$C_{10}H_{16}O_2$ = 168.2.

CAS — 512-85-6.

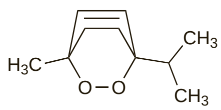

Profile

Ascaridole is the active principle of chenopodium oil (p.142) and has the same actions.

Handling. Ascaridole is an unstable liquid which is liable to explode when heated or when treated with organic acids.

Bephenium Hydroxynaphthoate *(BAN, rINN)*

Bephenii Hydroxynaphthoas; Béphénium, Hydroxynaphtoate de; Hidroxinaftoato de befenio; Naphthammonum. Benzyldimethyl(2-phenoxyethyl)ammonium 3-hydroxy-2-naphthoate.

Бефения Гидроксинафтоат

$C_{28}H_{29}NO_4$ = 443.5.

CAS — 7181-73-9 (bephenium); 3818-50-6 (bephenium hydroxynaphthoate).

ATC — P02CX02.

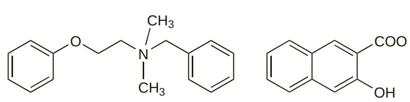

Pharmacopoeias. In *Int.*

Profile

Bephenium hydroxynaphthoate is an anthelmintic formerly used in the treatment of hookworm infections, ascariasis, and trichostrongyliasis.

Betanaphthol

β-Naftol; 2-Naftol; Naphthol. Naphth-2-ol.

Бета-нафтол

$C_{10}H_8O$ = 144.2.

CAS — 135-19-3.

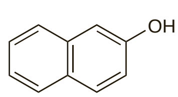

Pharmacopoeias. In *Pol.* and *Swiss.*

Profile

Betanaphthol was formerly used as an anthelmintic in hookworm and tapeworm infections, but it has been superseded by less toxic and more efficient drugs.

Betanaphthol has a potent parasiticidal effect and has been used topically in the treatment of scabies, ringworm, and other skin diseases.

Betanaphthyl benzoate has been used in preparations for the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Hekabetol; ***Austria:*** Salvyl.

Bithionol *(BAN, rINN)*

Bithionololum; Bithionolum; Bitionol; Bitionolol; Bitionololi. 2,2′-Thiobis(4,6-dichlorophenol).

Битионол

$C_{12}H_6Cl_4O_2S$ = 356.1.

CAS — 97-18-7.

ATC — D10AB01; P02BX01.

ATC Vet — QD10AB01; QP52AG07.

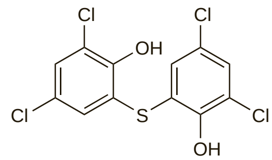

Pharmacopoeias. *Fr.* includes bithionol oxide for veterinary use.

Adverse Effects

Adverse effects in patients taking bithionol by mouth include anorexia, nausea, vomiting, abdominal discomfort, diarrhoea, salivation, dizziness, headache, and skin rashes.

Photosensitivity reactions have occurred in persons using soap containing bithionol. Cross-sensitisation with other halogenated disinfectants has also occurred.

Uses and Administration

Bithionol is a chlorinated bis-phenol with bactericidal and anthelmintic properties. It is active against most trematodes (flukes). Bithionol is used in preference to praziquantel in fascioliasis (see Liver Fluke Infections, p.137) and is also used in paragonimiasis (see Lung Fluke Infections, p.137) as an alternative to praziquantel. It may be given in an oral dose of 30 to 50 mg/kg on alternate days for 10 to 15 doses. Alternatively, for fascioliasis, WHO recommends a regimen of 30 mg/kg daily for 5 days.

Bithionol was formerly used topically as a bactericide but this use has declined because of photosensitivity reactions.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Fonergine.

Bromofenofos *(rINN)*

Bromfenofos; Bromofénofos; Bromofenofós; Bromofenofosum; Bromophenophos; Bromphenphos. 3,3′,5,5′-Tetrabromo-2,2′-biphenyldiolmono(dihydrogen phosphate).

Бромофенофос

$C_{12}H_7Br_4O_5P$ = 581.8.

CAS — 21466-07-9.

ATC Vet — QP52AB02.

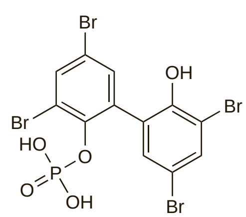

Profile

Bromofenofos is an organophosphorus compound (see Organophosphorus Insecticides, p.2047) used as an anthelmintic in veterinary medicine for the treatment of fluke infections.

Cambendazole *(BAN, USAN, rINN)*

Cambendazol; Cambendazolum; MK-905. Isopropyl 2-(thiazol-4-yl)-1*H*-benzimidazol-5-ylcarbamate.

Камбендазол

$C_{14}H_{14}N_4O_2S$ = 302.4.

CAS — 26097-80-3.

ATC Vet — QP52AC08.

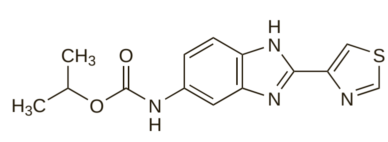

Profile

Cambendazole is a benzimidazole carbamate anthelmintic structurally related to tiabendazole (p.156). It is used in the treatment of strongyloidiasis.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Cambem†.

Multi-ingredient: ***Braz.:*** Exelmin†.

Chenopodium Oil

Aceite de quenopodio; Aetheroleum Chenopodii; Esencia de Quenopodio Vermifuga; Oil of American Wormseed; Wurmsamenöl.

Амброзиевое Масло; Маревое Масло

CAS — 8006-99-3.

Profile

Chenopodium oil is distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum.* It contains ascaridole. It was formerly used as an anthelmintic for the expulsion of roundworms (*Ascaris*) and hookworms. It is toxic and has caused numerous fatalities.

Handling. Chenopodium oil may explode when heated.

Clorsulon *(BAN, USAN, rINN)*

Clorsulón; Clorsulone; Clorsulonum; MK-401. 4-Amino-6-(trichlorovinyl)benzene-1,3-disulphonamide.

Клорсулон

$C_8H_8Cl_3N_3O_4S_2$ = 380.7.

CAS — 60200-06-8.

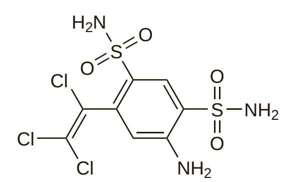

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Clorsulon). A white to off-white powder. Slightly soluble in water; freely soluble in acetonitrile and in methyl alcohol; very slightly soluble in dichloromethane.

Profile

Clorsulon is an anthelmintic used in veterinary medicine for the treatment of liver fluke infections.

Closantel *(BAN, USAN, rINN)*

Closantelum; R-31520. 5′-Chloro-4′-(4-chloro-α-cyanobenzyl)-3,5-di-iodosalicyl-*o*-toluidide.

Клозантел

$C_{22}H_{14}Cl_2I_2N_2O_2$ = 663.1.

CAS — 57808-65-8.

ATC Vet — QP52AG09.

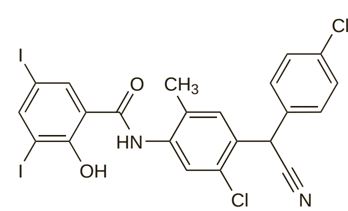

Closantel Sodium *(BANM, rINNM)*

Closantel sódico; Closantel sodique; Closantelum natricum; Klosanteelinatrium; Klosantel sodná sůl; Klosantelnatrium; Natrii Closantelum; R-34828.

Натрий Клозантел

$C_{22}H_{14}Cl_2I_2N_2O_2Na$ = 686.1.

Pharmacopoeias. In *Eur.* (see p.vii) as the dihydrate for veterinary use.

Ph. Eur. 6.2 (Closantel Sodium Dihydrate for Veterinary Use; Closantel Sodium Dihydrate BP(Vet) 2008). A yellow, slightly hygroscopic, powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Closantel is an anthelmintic used in veterinary medicine for the treatment of fluke and nematode infections.

Effects on the eyes. Loss of eyesight was reported in 11 women who received closantel (Flukiver) in mistake for a gynaecological product.[1] Sight was restored after closantel was stopped but incapacitating eye pain remained.

1. 't Hoen E, *et al.* Harmful human use of donated veterinary drug. *Lancet* 1993; **342:** 308–9.

Diamfenetide *(BAN, rINN)*

Diamfenetida; Diamfénétide; Diamfenetidum; Diamphenethide. β,β′-Oxybis(aceto-*p*-phenetidide).

Диамфенетид

$C_{20}H_{24}N_2O_5$ = 372.4.

CAS — 36141-82-9.

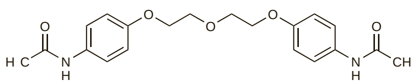

Profile

Diamfenetide is an anthelmintic that has been used in veterinary medicine for the control of fascioliasis in sheep.

Dichlorophen *(BAN, rINN)*

Dichlorophène; Dichlorophenum; Diclorofeno; Di-phenthane-70; G-4. 2,2′-Methylenebis(4-chlorophenol).

Дихлорофен

$C_{13}H_{10}Cl_2O_2$ = 269.1.

CAS — 97-23-4.

ATC — P02DX02.

ATC Vet — QP52AG01.

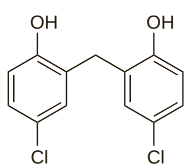

Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Dichlorophen). A white or slightly cream-coloured powder with a not more than slightly phenolic odour. Practically insoluble in water; freely soluble in alcohol; very soluble in ether.

Profile

Dichlorophen is an anthelmintic that was used in the treatment of infection by tapeworms but has been superseded by praziquantel or niclosamide.

Dichlorophen also has antifungal and antibacterial activity and has been used topically in the treatment of fungal infections and as a germicide in soaps and cosmetics.

Preparations

BP 2008: Dichlorophen Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Mycota†; ***UK:*** Mycota.

Diethylcarbamazine Citrate

(BANM, rINNM)

Citrato de dietilcarbamazina; Diethylcarbam. Cit.; Diethylcarbamazine Acid Citrate; Diéthylcarbamazine, citrate de; Diethylcarbamazini citras; Diethylkarbamazin-citrát; Dietilkarbamazin-citrát; Dietilkarbamazino citratas; Dietylkarbamazincitrat; Dietyylikarbamatsiinisitraatti; Ditrazini Citras; RP-3799. *NN*-Diethyl-4-methylpiperazine-1-carboxamide dihydrogen citrate.

Диэтилкарбамазина Цитрат

$C_{10}H_{21}N_3O,C_6H_8O_7$ = 391.4.

CAS — 90-89-1 (diethylcarbamazine); 1642-54-2 (diethylcarbamazine citrate).

ATC — P02CB02.

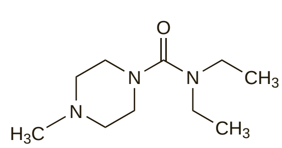

(diethylcarbamazine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Diethylcarbamazine Citrate). A white or almost white, crystalline, slightly hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in acetone. Store in airtight containers.

USP 31 (Diethylcarbamazine Citrate). A white, crystalline, slightly hygroscopic powder, odourless or has a slight odour. Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether. Store in airtight containers.

Adverse Effects

Adverse effects directly attributable to diethylcarbamazine include nausea and vomiting. Headache, dizziness, and drowsiness may occur.

Hypersensitivity reactions arise from the death of the microfilariae. These can be serious, especially in onchocerciasis where there may also be sight-threatening ocular toxicity; fatalities have been reported. Encephalitis may be exacerbated in patients with loiasis and fatalities have occurred.

◊ Reactions occurring during diethylcarbamazine treatment of **lymphatic filariasis** are basically of 2 types: pharmacological dose-dependent responses and a response of the infected host to the destruction and death of parasites.[1]

- Reactions of the first type include weakness, dizziness, lethargy, anorexia, and nausea. They begin within 1 to 2 hours of taking diethylcarbamazine, and persist for a few hours.
- Reactions of the second type are less likely to occur and are less severe in bancroftian than in brugian filariasis. They may be systemic or local, both with or without fever.

  Systemic reactions may occur a few hours after the first oral dose of diethylcarbamazine and generally do not last for more than 3 days. They include headache, aches in other parts of the body, joint pain, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients. Fever and systemic reactions are positively associated with microfilaraemia. Systemic reactions are reduced if diethylcarbamazine is given in spaced doses or in repeated small doses. They eventually cease spontaneously and interruption of treatment is rarely necessary; symptomatic treatment with antipyretics or analgesics may be helpful.

  Local reactions tend to occur later in the course of treatment and last longer; they also disappear spontaneously and interruption of treatment is not necessary. Local reactions include lymphadenitis, abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis may also occur in bancroftian filariasis.

It has been suggested that the release of interleukin-6 may be implicated in diethylcarbamazine's adverse effects in patients with lymphatic filariasis.[2]

In most patients with **onchocerciasis**, the microfilaricidal activity of diethylcarbamazine leads to a series of events with dermal, ocular, and systemic components, known as the *Mazzotti reaction*, within minutes to hours after its use.[3]

- Clinical manifestations can be severe, dangerous, and debilitating. Systemic reactions include increased itching, rash, headache, aching muscles, joint pain, painful swollen and tender lymph nodes, fever, tachycardia and hypotension, and vertigo. Most patients have eye discomfort in the first few hours after diethylcarbamazine treatment. Punctate keratitis can develop as can optic neuritis and visual field loss.

WHO no longer recommends the use of diethylcarbamazine in onchocerciasis as safer alternatives exist.

1. WHO. Lymphatic filariasis: the disease and its control: fifth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 821* 1992.
2. Yazdanbakhsh M, *et al.* Serum interleukin-6 levels and adverse reactions to diethylcarbamazine in lymphatic filariasis. *J Infect Dis* 1992; **166:** 453–4.
3. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987.

Precautions

Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis. Patients with onchocerciasis should be monitored for eye changes. (The use of diethylcarbamazine to treat onchocerciasis is no longer recommended.) In patients with heavy *Loa loa* infection there is a small risk of encephalopathy and diethylcarbamazine should be stopped at the first sign of cerebral involvement.

Infants, pregnant women, the elderly, and the debilitated, especially those with cardiac or renal disease, are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Pregnancy. Pregnant women are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Animal studies[1] suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglandin synthesis; this might explain the mechanism of the abortifacient action previously reported.[2]

1. Joseph CA, Dixon PAF. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol* 1984; **36:** 281–2.
2. Subbu VSV, Biswas AR. Ecbolic effect of diethyl carbamazine. *Indian J Med Res* 1971; **59:** 646–7.

Renal impairment. For a study on the effects of renal impairment on the pharmacokinetics of diethylcarbamazine, see under Pharmacokinetics, below.

Pharmacokinetics

Diethylcarbamazine is readily absorbed from the gastrointestinal tract and also through the skin and conjunctiva. It is widely distributed in tissues and is mainly excreted in the urine unchanged and as the *N*-oxide metabolite. Urinary excretion and hence plasma half-life is dependent on urinary pH. About 5% of a dose is eliminated in the faeces.

Disposition. A pharmacokinetic study in 6 patients with onchocerciasis[1] indicated that diethylcarbamazine is absorbed quickly and almost completely from the gastrointestinal tract, and is eliminated largely as unchanged drug in urine, with relatively small amounts being excreted as the *N*-oxide metabolite. After a single radioactively labelled oral dose of diethylcarbamazine citrate 0.5 mg/kg given as an aqueous solution, peak plasma concentrations of 100 to 150 nanograms/mL were achieved in 1 to 2 hours, followed by a sharp decline, then a marked secondary rise 3 to 6 hours after dosing, followed by a steady decline. The half-life ranged from 9 to 13 hours. Urinary excretion of diethylcarbamazine and diethylcarbamazine *N*-oxide was complete within 96 hours; between 4 and 5% of the dose was recovered in the faeces. Disposition was similar in 5 healthy subjects given a single 50-mg tablet of diethylcarbamazine citrate. Peak plasma concentrations were initially 80 to 200 nanograms/mL, with a secondary rise 3 to 9 hours after dosing, the terminal half-life ranged from 5 to 13 hours, and urinary excretion of unchanged diethylcarbamazine and the *N*-oxide was complete within 48 hours.

When an alkaline urinary pH was maintained, the elimination half-life of diethylcarbamazine and the area under the plasma concentration versus time curve were significantly increased compared with when an acidic urinary pH was maintained.[2]

1. Edwards G, *et al.* Diethylcarbamazine disposition in patients with onchocerciasis. *Clin Pharmacol Ther* 1981; **30:** 551–7.
2. Edwards G, *et al.* The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol* 1981; **12:** 807–12.

Renal impairment. Results in patients with chronic renal impairment and in healthy subjects, given a single 50-mg oral dose of diethylcarbamazine citrate, indicated that the plasma half-life of diethylcarbamazine is prolonged and its 24-hour urinary excretion considerably reduced in those with moderate and severe degrees of renal impairment.[1] Mean plasma half-lives in 7 patients with severe renal impairment (creatinine clearance less than 25 mL/minute), in 5 patients with moderate renal impairment (creatinine clearance between 25 and 60 mL/minute), and in 4 healthy subjects, were 15.1, 7.7, and 2.7 hours, respectively. The patient with the longest plasma half-life of 32 hours did not have the poorest renal function, but it was considered likely that the abnormally slow elimination of diethylcarbamazine was due to the high urinary pH (7) resulting from sodium bicarbonate therapy. A further patient with a half-life longer than expected also had a less acidic urine.

1. Adjepon-Yamoah KK, *et al.* The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol* 1982; **13:** 829–34.

Uses and Administration

Diethylcarbamazine is an anthelmintic used in the treatment of lymphatic filariasis due to *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, or *B. timori* (both known as brugian filariasis and as Malayan and Timorian filariasis respectively). It is also used in loiasis due to *Loa loa*. It was used in onchocerciasis due to *Onchocerca volvulus* before ivermectin became available. Diethylcarbamazine is active against both the microfilariae and adult worms of *W. bancrofti*, *B. malayi*, and *Loa loa*, but only against the microfilariae of *O. volvulus*. It has been tried in *Mansonella* infections and may be most effective against *M. streptocer-*

ca. Diethylcarbamazine is also used in the treatment of toxocariasis (visceral larva migrans). For discussions of these infections and their treatment, see under Choice of Anthelmintic, p.134, and under the individual headings below.

Diethylcarbamazine is usually given orally as the citrate.

In the treatment of **lymphatic filariasis** the recommended dose of diethylcarbamazine citrate is 6 mg/kg daily in 3 divided doses for 3 weeks, given in an initial dosage of 1 mg/kg daily and then gradually increased to 6 mg/kg daily over 3 days to reduce the incidence and severity of hypersensitivity reactions due to the destruction of microfilariae. However, adverse effects of diethylcarbamazine may be reduced, without loss of efficacy, by giving a single dose of 6 mg/kg at weekly or monthly intervals. In areas where lymphatic filariasis is endemic, mass treatment campaigns can reduce the intensity of transmission and incidence of disease. Diethylcarbamazine may also be used in the form of medicated salt to control lymphatic filariasis. For further details, see below.

In the treatment of **loiasis** diethylcarbamazine citrate 6 mg/kg daily in 3 divided doses for 2 to 4 weeks has been given. In heavy infections rapid killing of microfilariae can cause severe adverse effects including encephalitis and treatment should start with very small doses, increasing gradually over 4 days. A corticosteroid has been given concurrently. In the prophylaxis of loiasis, a dose of 300 mg weekly is recommended by WHO.

In the treatment of **toxocariasis** diethylcarbamazine citrate 9 mg/kg daily in 3 divided doses for 21 days has been given. Diethylcarbamazine is considered by some to be the treatment of choice while others do not recommend its use due to higher rates of severe adverse effects.

Administration. Diethylcarbamazine was first used as the chloride, but was subsequently produced as the dihydrogen citrate which contains only half its weight as base. In reporting doses it was therefore important to indicate whether they referred to a specific salt or to the base; unless otherwise stated, it could generally be assumed that the dose referred to the citrate.[1]

1. WHO. Lymphatic filariasis: fourth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 702* 1984. Available at: http://libdoc.who.int/trs/WHO_TRS_702.pdf (accessed 16/07/08)

Loiasis. Diethylcarbamazine is the main drug used in the management of loiasis (p.137).

References.

1. Nutman TB, *et al.* Loa loa infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis* 1986; **154:** 10–18.
2. Nutman TB, *et al.* Diethylcarbamazine prophylaxis for human loiasis: results of a double-blind study. *N Engl J Med* 1988; **319:** 752–6.
3. Nutman TB, Ottesen EA. Diethylcarbamazine and human loiasis. *N Engl J Med* 1989; **320:** 320.
4. Klion AD, *et al.* Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: long-term follow-up. *J Infect Dis* 1994; **169:** 604–10.

Lymphatic filariasis. Diethylcarbamazine is used in the management of lymphatic filariasis (p.137). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is no co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO together with other international agencies, advocates a single dose of diethylcarbamazine citrate 6 mg/kg with a single dose of albendazole 400 mg, given once each year for at least 5 years. If diethylcarbamazine-medicated salt is to be employed then intake of salt needs to be on a daily basis for 6 to 12 months.

Preparations

BP 2008: Diethylcarbamazine Tablets;
USP 31: Diethylcarbamazine Citrate Tablets.

Proprietary Preparations (details are given in Part 3)

Fr.: Notezine; ***Gr.:*** Hetrazan†; Notezine; ***India:*** Banocide; Hetrazan; ***Thai.:*** Diethizine.

Multi-ingredient: ***India:*** Helmazan†; Unicarbazan.

Disophenol

Disofenol. 2,6-Diiodo-4-nitrophenol.

$C_6H_3I_2NO_3$ = 390.9.

CAS — 305-85-1.

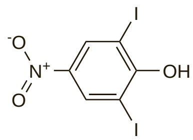

Profile

Disophenol is an anthelmintic used in veterinary medicine.

Doramectin *(BAN, USAN, rINN)*

Doramectina; Doramectine; Doramectinum; Doramektiini; Doramektin; UK-67994.

Дорамектин

CAS — 117704-25-3.

ATC Vet — QP54AA03.

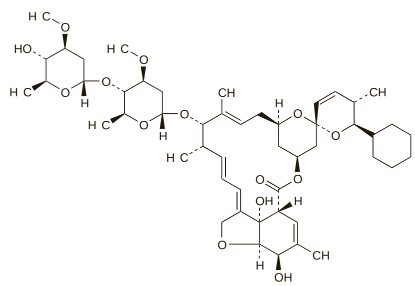

Profile

Doramectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Embelia

Vidang.

Виданга

CAS — 550-24-3 (embelic acid).

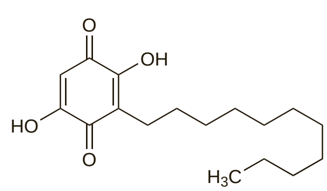

(embelic acid)

Profile

Embelia consists of the dried fruits of *Embelia ribes* and *E. robusta* (= *E. tsjeriamcottam*) (Myrsinaceae), containing about 2.5% of embelic acid (embelin). It has been used in India and other Asian countries for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Happy'tizer.

Eprinomectin *(USAN, rINN)*

Eprinomectina; Éprinomectine; Eprinomectinum; Eprinomektiini; Eprinomektin; MK-397. A mixture of eprinomectin component B_{1a} and eprinomectin component B_{1b}.

Эприномектин

CAS — 159628-36-1 (eprinomectin); 123997-26-2 (eprinomectin); 133305-88-1 (component B_{1a}); 133305-89-2 (component B_{1b}).

ATC Vet — QP54AA04.

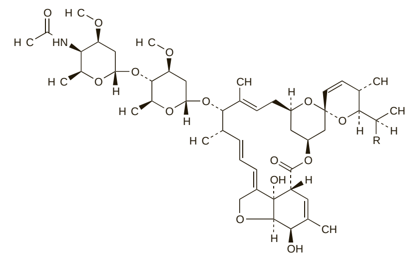

Pharmacopoeias. In *US.*

USP 31 (Eprinomectin). Eprinomectin is a mixture of component B_{1a} ($C_{50}H_{75}NO_{14}$ = 914.1) and component B_{1b} ($C_{49}H_{73}NO_{14}$ = 900.1). It contains not less than 90% of component B_{1a} and not less than 95% of components B_{1a} and B_{1b}, calculated on the anhydrous, solvent-free, and antioxidant-free basis. Antoxidants may be added. A white to off-white powder. Insoluble in cold water. Store in airtight containers at 2° to 8°.

Profile

Eprinomectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Epsiprantel *(BAN, rINN)*

BRL-38705; Epsipranteeli; Epsiprantelum. 2-Cyclohexylcarbonyl-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepin-4-one.

Эпсипрантел

$C_{20}H_{26}N_2O_2$ = 326.4.

CAS — 98123-83-2.

ATC Vet — QP52AA04.

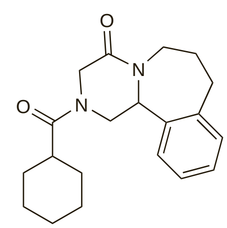

Profile

Epsiprantel is an anthelmintic closely related to praziquantel. It is used in veterinary medicine.

Febantel *(BAN, USAN, rINN)*

Bay-h-5757; Bay-Vh-5757; Febanteeli; Fébantel; Febantelum. 2′-[2,3-Bis(methoxycarbonyl)guanidino]-5′-phenylthio-2-methoxyacetanilide; Dimethyl {2-[2-(2-methoxyacetamido)-4-(phenylthio)phenyl]imidocarbonyl}dicarbamate.

Фебантел

$C_{20}H_{22}N_4O_6S$ = 446.5.

CAS — 58306-30-2.

ATC Vet — QP52AC05.

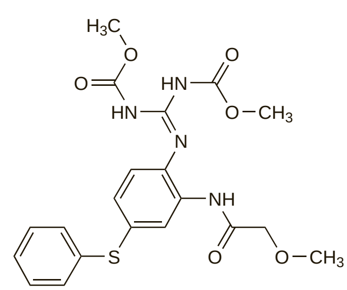

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Febantel for Veterinary Use; Febantel BP(Vet) 2008). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in acetone.

Profile

Febantel is an anthelmintic used in veterinary medicine for the treatment of nematode infections of the gastrointestinal tract and lungs and in tapeworm infections.

Fenbendazole *(BAN, USAN, rINN)*

Fenbendatsoli; Fenbendazol; Fenbendazolum; Hoe-881V. Methyl 5-phenylthio-1*H*-benzimidazol-2-ylcarbamate.

Фенбендазол

$C_{15}H_{13}N_3O_2S$ = 299.3.
CAS — 43210-67-9.
ATC — P02CA06.
ATC Vet — QP52AC13.

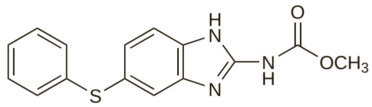

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Fenbendazole for Veterinary Use; Fenbendazole BP(Vet) 2008). A white or almost white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Protect from light.

USP 31 (Fenbendazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Fenbendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Flubendazole *(BAN, USAN, rINN)*

Flubendatsoli; Flubendazol; Flubendazolas; Flubendazolum; Fluorомebendazole; R-17889. Methyl 5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-ylcarbamate.

Флубендазол

$C_{16}H_{12}FN_3O_3$ = 313.3.
CAS — 31430-15-6.
ATC — P02CA05.
ATC Vet — QP52AC12.

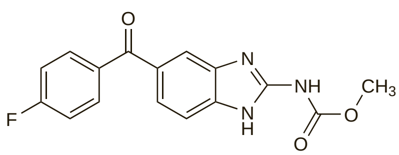

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flubendazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Flubendazole, a benzimidazole carbamate anthelmintic, is an analogue of mebendazole (p.148) and has similar actions and uses.

For the treatment of enterobiasis in adults and children, flubendazole 100 mg is given as a single oral dose, repeated after 2 to 3 weeks. For ascariasis, hookworm infections, and trichuriasis 100 mg is given twice daily for 3 days. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p.134.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Flumoxal; ***Fr.:*** Fluvermal; ***Port.:*** Fluvermal; Teniverme; ***Spain:*** Flicum; ***Venez.:*** Fluvermox.

Haloxon *(BAN, rINN)*

Haloxón; Haloxone; Haloxonum. Bis(2-chloroethyl) 3-chloro-4-methylcoumarin-7-yl phosphate.

Галоксон

$C_{14}H_{14}Cl_3O_6P$ = 415.6.
CAS — 321-55-1.
ATC Vet — QP52AB04.

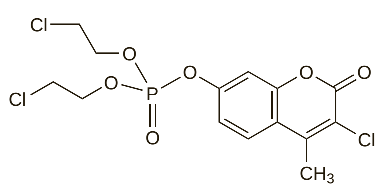

Profile

Haloxon is an organophosphorus compound (see Organophosphorus Insecticides, p.2047) used as an anthelmintic in veterinary medicine.

Hycanthone *(USAN, rINN)*

Hicantona; Hycanthonum; NSC-134434; Win-24933. 1-(2-Diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one.

Гикантон

$C_{20}H_{24}N_2O_2S$ = 356.5.
CAS — 3105-97-3.

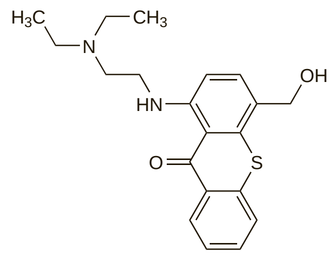

Hycanthone Mesilate *(rINNM)*

Hycanthone, Mésilate d'; Hycanthone Mesylate; Hycanthoni Mesilas; Hydroxylucanthone Methanesulphonate; Mesilato de hicantona.

Гикантона Мезилат

$C_{20}H_{24}N_2O_2S,CH_3SO_3H$ = 452.6.
CAS — 23255-93-8.

Profile

Hycanthone has been used as a schistosomicide in the individual or mass treatment of infection with *Schistosoma haematobium* and *S. mansoni*.

Owing to its toxicity and concern about possible carcinogenicity, mutagenicity, and teratogenicity, hycanthone has been replaced by other drugs such as praziquantel.

Hygromycin B

Higromicina B. *O*-6-Amino-6-deoxy-L-glycero-D-galacto-heptopyranosylidene-(1→2-3)-*O*-β-D-talopyranosyl-(1→5)-2-deoxy-N^3-methyl-D-streptamine.

Гигромицин Б

$C_{20}H_{37}N_3O_{13}$ = 527.5.

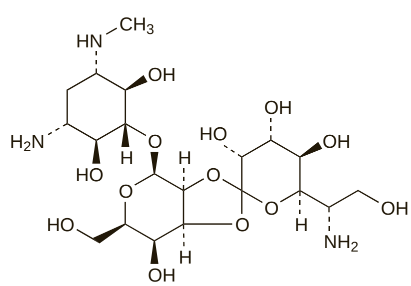

Profile

Hygromycin B is an anthelmintic used in veterinary medicine for nematode infections.

Ivermectin *(BAN, USAN, rINN)*

Ivermectina; Ivermectine; Ivermectinum; Ivermektiini; Ivermektin; Ivermektinas.

Ивермектин

CAS — 70288-86-7 (ivermectin); 70161-11-4 (component B_{1a}); 70209-81-3 (component B_{1b}).
ATC — P02CF01.
ATC Vet — QP54AA01; QS02QA03.

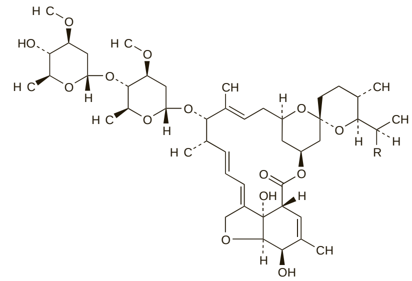

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Ivermectin). A mixture of ivermectin component H_2B_{1a} (5-*O*-demethyl-22,23-dihydroavermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and ivermectin component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1).

A white or yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

USP 31 (Ivermectin). A mixture of component H_2B_{1a} (5-*O*-demethyl-22,23-dihydro-avermectin A_{1a}; $C_{48}H_{74}O_{14}$ = 875.1) and component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-avermectin A_{1a}; $C_{47}H_{72}O_{14}$ = 861.1). It may contain small amounts of suitable antoxidant and chelating agents.

A white to yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in petroleum spirit; soluble in acetone and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature of 2° to 8°. Where the use of an antoxidant is allowed, store at 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

The adverse effects reported with ivermectin in patients with filariasis are generally consistent with a mild Mazzotti reaction arising from its effect on microfilariae. They include fever, pruritus, skin rashes, arthralgia, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, gastrointestinal symptoms, sore throat, cough, and headache. The effects tend to be transient and if treatment is required they respond to analgesics and antihistamines.

Ivermectin may cause mild ocular irritation. Somnolence, transient eosinophilia, and raised liver enzyme values have also been reported.

Ivermectin is not recommended during pregnancy. Mass treatment is generally withheld from pregnant women (see Pregnancy, below), children under 15 kg, and the seriously ill.

Incidence of adverse effects. Some studies have shown quite a high incidence of adverse effects with ivermectin and have associated the effects with the severity of infection.[1-3] However, in none of these studies were the reactions considered to be life-threatening and only symptomatic treatment was required. The severity, incidence, and duration of adverse reactions was reported to be reduced after repeated annual administration.[4] When larger groups of patients were considered in the Onchocerciasis Control Programme (OCP) in West Africa, a much lower incidence of adverse reactions was seen in patients given ivermectin for the first time[5] and when treatment was repeated a year later that incidence was reduced even further. The results from several studies in this programme[6] showed 93 severe reactions in 50 929 patients (1.83%), most of the reactions being orthostatic hypotension or dizziness (53). In a 3-year randomised, double-blind, controlled study of ivermectin for onchocerciasis control in 572 patients,[7] 3-monthly treatment with the standard dose of 150 micrograms/kg was associated with a reduced risk of adverse reactions, especially oedema, pruritus, and back pain, when compared with the same dose given annually. Higher doses of 400 then 800 micrograms/kg, given either 3-monthly or annually, were associated with subjective ocular problems. Another study[8] found 22 severe reactions in 17 877 patients treated for onchocerciasis in an area also endemic for *Loa loa* infection, and demonstrated a relationship to heavy *L. loa* microfilaraemia. The Mectizan® Expert Committee and the Technical Consultative Committee have reported the incidence of encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas to be less than 1 case in 10 000 treatments[9] and have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis to reduce the risk of serious adverse events, especially in areas where the population is ivermectin naive.

Some supervision is considered necessary after doses of ivermectin;[2,6] the OCP recommendation[6] is for resident nurses to monitor patients for a period of 36 hours after treatment, whatever the level of endemicity. However, the incidence of adverse reactions reported after repeated doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.[10]

Neurotoxicity seen in some breeds of *dogs* has not been seen in *cattle* or *horses*[11] and nor was it reported in man in the above studies. Another potential concern was the prolongation of prothrombin times observed in 28 patients given ivermectin,[12] but others have not confirmed this effect[13] or observed any bleeding disorders.[14]

There has been some concern over the use of ivermectin to treat scabies in elderly patients after a report suggesting a possible link to an increased incidence of death among a cohort of 47 patients.[15] It has, however, been argued that no such association has been seen in other populations of elderly patients and that the statistical methods used by the original authors were deficient.[16-18] There was no evidence of an increase in death rate associated with ivermectin in a community-based trial in Papua New Guinea of diethylcarbamazine with or without ivermectin for lymphatic filariasis.[19]

1. Kumaraswami V, *et al.* Ivermectin for the treatment of Wuchereria bancrofti filariasis: efficacy and adverse reactions. *JAMA* 1988; **259:** 3150–3.
2. Rothova A, *et al.* Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; **i:** 1439–41.
3. Zea-Flores R, *et al.* Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Trans R Soc Trop Med Hyg* 1992; **86:** 663–6.
4. Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis: results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; **87:** 313–17.
5. De Sole G, *et al.* Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* 1990; **335:** 1106–7.
6. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67:** 707–19.
7. Kamgno J,*et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98:** 496–504.
8. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
9. The Mectizan Expert Committee and The Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: http://www.mectizan.org/library/EnglishMECTCCLoaRecs-June04.pdf (accessed 20/09/05)
10. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: adverse reactions after the first five treatment rounds. *Trans R Soc Trop Med Hyg* 1991; **85:** 501–5.
11. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_752_(part2).pdf (accessed 16/07/08)
12. Homeida MMA, *et al.* Prolongation of prothrombin time with ivermectin. *Lancet* 1988; **i:** 1346–7.
13. Richards FO, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i;** 1139–40.
14. Pacque MC, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i:** 1140.
15. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; **349:** 1144–5.
16. Diazgranados JA, Costa JL. Deaths after ivermectin treatment. *Lancet* 1997; **349:** 1698.
17. Reintjes R, Hoek C. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215.
18. Coyne PE, Addiss DG. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350:** 215–16.
19. Alexander NDE, *et al.* Absence of ivermectin-associated excess deaths. *Trans R Soc Trop Med Hyg* 1998; **92:** 342.

Breast feeding. Mean ivermectin concentrations in the breast milk of 4 healthy women who had been given a standard dose of ivermectin were 14.13 nanograms/mL.[1] It was felt that in view of this low concentration the precaution of excluding lactating mothers from ivermectin mass treatment programmes should be reconsidered. Some authorities have recommended that ivermectin should not be given to mothers who are breast feeding until the infant is at least one week old. The American Academy of Pediatrics states that, since no adverse effects have been seen in breast-fed infants whose mothers were receiving ivermectin, it may be considered to be usually compatible with breast feeding.[2]

1. Ogbuokiri JE, *et al.* Ivermectin levels in human breast milk. *Eur J Clin Pharmacol* 1994; **46:** 89–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Encephalopathy. For information on encephalopathy following Ivermectin treatment of onchocerciasis in *Loa loa* endemic areas, see Incidence of Adverse Effects, above.

Pregnancy. Ivermectin is teratogenic in *animals* and there are no adequate and well controlled studies in human pregnancy. Ivermectin treatment is therefore usually contra-indicated during pregnancy and pregnant women should be excluded from mass treatment schedules with ivermectin. However, women not yet diagnosed as pregnant or unwilling to admit their pregnancy have been treated. An assessment[1] of 203 pregnancy outcomes to women who had taken ivermectin during pregnancy, mostly during the first 12 weeks, found that the rates of major congenital malformation, miscarriage, and still-birth associated with ivermectin were similar to those in untreated mothers. In another study, 110 women also inadvertently given ivermectin during pregnancy experienced a similar lack of adverse effect on pregnancy outcome;[2] it was considered that the precaution of avoiding the use of ivermectin in women notifying a pregnancy should be adequate.

1. Pacqué M, *et al.* Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; **336:** 1486–9.
2. Chippaux J-P, *et al.* Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg* 1993; **87:** 318.

Pharmacokinetics

Ivermectin is absorbed after oral doses, with peak plasma concentrations being obtained after about 4 hours. Ivermectin is reported to be about 93% bound to plasma proteins and has a plasma elimination half-life of about 12 hours. It undergoes metabolism and is excreted largely as metabolites over a period of about 2 weeks, chiefly in the faeces, with less than 1% appearing in the urine and less than 2% in breast milk (see also Breast Feeding, above).

Uses and Administration

Ivermectin is a semisynthetic derivative of one of the avermectins, a group of macrocyclic lactones produced by *Streptomyces avermitilis*.

It has a microfilaricidal action in onchocerciasis and reduces the microfilarial load without the toxicity seen with diethylcarbamazine. Ivermectin also has a microfilaricidal action in lymphatic filariasis and is used in its management. Ivermectin is active in some other worm infections. It is used in the treatment of strongyloidiasis and has been tried in some *Mansonella* infections. For details of these infections and their treatment, see under Choice of Anthelmintic, p.134, and under the individual headings below.

In the treatment of onchocerciasis, a single oral dose of 3 to 12 mg of ivermectin, based roughly on 150 micrograms/kg for patients weighing more than 15 kg and over 5 years of age, is given annually or every 6 months. This schedule has been adopted for mass treatment in infected areas. No food should be taken for 2 hours before or after the dose.

Ivermectin 200 micrograms/kg as a single dose, or daily on two consecutive days, is used for the treatment of strongyloidiasis.

◊ Reviews.

1. Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother* 1994; **34:** 195–203.
2. Ōmura S. Ivermectin: 25 years and still going strong. *Int J Antimicrob Agents* 2008; **31:** 91–8.

Cutaneous larva migrans. There are some reports[1,2] of ivermectin being effective in the treatment of cutaneous larva migrans (p.135). An oral dose of 200 micrograms/kg daily for 1 to 2 days has been recommended.[3]

1. Caumes E, *et al.* Efficacy of ivermectin in the therapy of cutaneous larva migrans. *Arch Dermatol* 1992; **128:** 994–5.
2. Caumes E, *et al.* A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg* 1993; **49:** 641–4.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Intestinal nematode infections. Ivermectin activity has been seen in man against *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Trichuris trichiura*;[1] although some have failed to detect activity against *Trichuris*,[2] ivermectin given with albendazole has been studied for the treatment of trichuriasis (p.139) and may prove useful. Roundworm expulsion has been reported as a 'side-effect' of ivermectin when used in community-based treatment of onchocerciasis.[3] In a controlled study,[4] single doses of ivermectin 150 or 200 micrograms/kg produced cure rates of 94% in strongyloidiasis (see below) and above 67% in ascariasis, trichuriasis, and enterobiasis. Although some activity has been observed against *Necator americanus*,[1] cure rates for hookworm were considered unsatisfactory.[4]

1. Freedman DO, *et al.* The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989; **159:** 1151–3.
2. Whitworth JAG, *et al.* A field study of the effect of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg* 1991; **85:** 232–4.
3. Whitworth JAG, *et al.* Community-based treatment with ivermectin. *Lancet* 1988; **ii:** 97–8.
4. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; **40:** 304–9.

Loiasis. There is evidence of reduced microfilaraemia after ivermectin treatment[1-5] in patients with loiasis (p.137), but concern exists over its potential for neurotoxicity in patients with a high microfilarial burden.[6,7] Low-dose regimens (about 25 micrograms/kg) have been investigated[8] but did not seem to offer much advantage in reducing neurotoxicity.

1. Martin-Prevel Y, *et al.* Reduction of microfilaraemia with single high-dose of ivermectin in loiasis. *Lancet* 1993; 342: 442.
2. Ranque S, *et al.* Decreased prevalence and intensity of Loa loa infection in a community treated with ivermectin every three months for two years. *Trans R Soc Trop Med Hyg* 1996; **90:** 429–30.
3. Duong TH, *et al.* Reduced Loa loa microfilaria count ten to twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 592–3.
4. Gardon J, *et al.* Marked decrease in Loa loa microfilaraemia six and twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; **91:** 593–4.
5. Chippaux J-P, *et al.* Impact of repeated large scale ivermectin treatments on the transmission of Loa loa. *Trans R Soc Trop Med Hyg* 1998; **92:** 454–8.
6. Anonymous. Encephalitis following treatment of loiasis. *WHO Drug Inf* 1991; **5:** 113–14.
7. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; **350:** 18–22.
8. Kamgno J, *et al.* Randomized, controlled, double-blind trial with ivermectin on Loa loa microfilaraemia: efficacy of a low dose (~25 μg/kg) versus current standard dose (150 μg/kg). *Trans R Soc Trop Med Hyg* 2007; **101:** 777–85.

Lymphatic filariasis. Ivermectin is used in the management of lymphatic filariasis (p.137). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of ivermectin 150 to 200 micrograms/kg with a single oral dose of albendazole 400 mg given once each year for at least 5 years.

Mansonella infections. The response of *Mansonella* infections (p.137) to ivermectin depends on the species. It may be effective against *Mansonella ozzardi*, but studies in *M. perstans* infection have not shown ivermectin to produce a substantial reduction in microfilaraemia.[1,2] A good response to ivermectin has been reported in infections with *M. streptocerca*.[3,4]

1. Van den Enden E, *et al.* Treatment failure of a single high dose of ivermectin for Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 90.
2. Schulz-Key H, *et al.* Efficacy of ivermectin in the treatment of concomitant Mansonella perstans infections in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 1993; **87:** 227–9.
3. Fischer P, *et al.* Treatment of human Mansonella streptocerca infection with ivermectin. *Trop Med Int Health* 1997; **2:** 191–9.
4. Fischer P, *et al.* Long-term suppression of Mansonella streptocerca microfilariae after treatment with ivermectin. *J Infect Dis* 1999; **180:** 1403–5.

Onchocerciasis. Ivermectin has a microfilaricidal action against *Onchocerca volvulus* and is the main drug used in the control of onchocerciasis (p.137). A single oral dose rapidly eliminates microfilariae from the skin, with maximum effect after 1 to 2 months,[1] and gradually eliminates them from the cornea and anterior chamber of the eye.[2] Ivermectin has little effect on the adult worms but does suppress the release of microfilariae from the adult worm for several cycles which accounts for its prolonged activity. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Its action against *O. volvulus* has been attributed to a GABA-agonist effect. Studies have also indicated that ivermectin inhibits the transmission of microfilariae by reducing their uptake from man by the insect vector.[3-6]

Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in community-wide mass treatment programmes in all countries in which onchocerciasis is endemic, where it is given at a standard dose of 150 micrograms/kg once or twice a year to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg, and those unable to walk or otherwise seriously ill.[7] The adult worms live for about 15 years, therefore treatment will need to be continued for many years. Several studies have confirmed the long-term safety and efficacy of such programmes.[8-12] Studies have reported that increasing the frequency of the standard doses of ivermectin to every 3 or 6 months appears to increase efficacy compared with annual treatments[13,14] and that 3-monthly regimens may also reduce risk of adverse effects.[14,15] No additional benefit was noted by increasing the dose of ivermectin to 400 or 800 micrograms/kg given either 3-monthly or annually.

In non-endemic areas, repeated doses may be necessary to reduce recurrence; a study in the UK found that patients given three doses at monthly intervals had fewer relapses at 6 months than patients who received a single dose, but relapses were nevertheless seen in 50% of patients at 12 months.[16]

The ocular microfilarial load can be safely reduced by ivermectin[2,17] and early lesions of the anterior segment of the eye have improved.[17] A reduction in the incidence[18] and progression[19] of optic nerve damage has also been reported, but the effect on posterior segment disease is less certain.[20] A systematic review of 5 placebo-controlled studies, with data from 3810 individuals, found no statistically significant difference between ivermectin and placebo groups for preventing visual acuity loss.[21] Improvements in skin lesions have been reported.[22]

1. Basáñez MG, *et al.* Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 310–22.
2. Newland HS, *et al.* Effect of single-dose ivermectin therapy on human Onchocerca volvulus infection with onchocercal ocular involvement. *Br J Ophthalmol* 1988; **72:** 561–9.
3. Taylor HR, *et al.* Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* 1990; **250:** 116–18.
4. Trpis M, *et al.* Effect of mass treatment of a human population with ivermectin on transmission of Onchocerca volvulus by Simulium yahense in Liberia, West Africa. *Am J Trop Med Hyg* 1990; **42:** 148–56.
5. Chavasse DC, *et al.* Low level ivermectin coverage and the transmission of onchocerciasis. *Trans R Soc Trop Med Hyg* 1995; **89:** 534–7.
6. Boussinesq M, *et al.* Onchocerca volvulus: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments. *Trans R Soc Trop Med Hyg* 1997; **91:** 82–6.
7. Pond B. Distribution of ivermectin by health workers. *Lancet* 1990; **335:** 1539.
8. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67:** 707–19.
9. Pacqué M, *et al.* Safety of and compliance with community-based ivermectin therapy. *Lancet* 1990; **335:** 1377–80.
10. Pacqué M, *et al.* Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. *J Infect Dis* 1991; **163:** 381–5.
11. Steel C, *et al.* Immunologic responses to repeated ivermectin treatment in patients with onchocerciasis. *J Infect Dis* 1991; **164:** 581–7.
12. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly interval. *Trans R Soc Trop Med Hyg* 1992; **86:** 277–80.
13. Greene BM, *et al.* A comparison of 6-, 12-, and 24-monthly dosing with ivermectin for treatment of onchocerciasis. *J Infect Dis* 1991; **163:** 376–80.
14. Gardon J,*et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; **360:** 203–10.
15. Kamgno J, *et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98:** 496–504.
16. Churchill DR, *et al.* A trial of a three-dose regimen of ivermectin for the treatment of patients with onchocerciasis in the UK. *Trans R Soc Trop Med Hyg* 1994; **88:** 242.
17. Dadzie KY, *et al.* Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Trans R Soc Trop Med Hyg* 1991; **85:** 267–71.
18. Abiose A, *et al.* Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993; **341:** 130–4.
19. Cousens SN, *et al.* Impact of annual dosing with ivermectin on progression of onchocercal visual field loss. *Bull WHO* 1997; **75:** 229–36.
20. Whitworth JAG, *et al.* Effects of repeated doses of ivermectin on ocular onchocerciasis: community-based trial in Sierra Lione. *Lancet* 1991; **338:** 1100–1103.
21. Ejere H, *et al.* Ivermectin for onchocercal eye disease (river blindness). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 29/07/07).
22. Pacqué M, *et al.* Improvements in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991; **90:** 590–4.

Scabies and pediculosis. Scabies (p.2035) is usually treated with a topically applied acaricide. However, a single oral dose of ivermectin has been reported to be effective.[1,2] In a study of 11 patients with uncomplicated scabies, a single oral dose of ivermectin 200 micrograms/kg was effective in curing infection after 4 weeks. In a group of 11 patients, also infected with HIV, scabies was cured in 8 after 2 weeks.[1] Two of the remaining 3 patients received a second dose of ivermectin which cured the scabies infection by the fourth week. A single oral dose of ivermectin 150 micrograms/kg was partially effective in an outbreak of scabies in 1153 Tanzanian patients.[3] Crusted (Norwegian) scabies has also been reported to be effectively treated by a single oral dose of 12 mg of ivermectin in addition to topical application of 3% salicylic acid ointment in 2 patients; the treatment was effective in under one week.[2] A single oral dose of ivermectin 200 micrograms/kg was effective for crusted scabies in a 2-year-old infant who had contracted the disease following long-term corticosteroid use.[4]

Ivermectin has also been investigated[5] as a possible treatment for pediculosis (p.2034) although, again, topically applied insecticides are the usual method of control. A study *in vitro* and in *animals* showed that ivermectin killed nymphs and females of the human body louse (*Pediculus humanus humanus*). Ivermectin was known to be effective against other louse species that infect a range of *animals*.[6]

1. Meinking TL, *et al.* The treatment of scabies with ivermectin. *N Engl J Med* 1995; **333:** 26–30.
2. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. *N Engl J Med* 1995; **332:** 612.
3. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; **143:** 520–3.
4. Marlière V, *et al.* Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with ivermectin. *J Pediatr* 1999; **135:** 122–4.
5. Foucault C, *et al.* Oral ivermectin in the treatment of body lice. *J Infect Dis* 2006; **193:** 474–6.
6. Mumcuoglu KY, *et al.* Systemic activity of ivermectin on the human body louse (Anoplura: Pediculidae). *J Med Entomol* 1990; **27:** 72–5.

Strongyloidiasis. Ivermectin is effective in the treatment of strongyloidiasis (p.138) and is considered by some authorities to be the drug of choice.

References.

1. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; **40:** 304–9.
2. Wijesundera M de S, Sanmuganathan PS. Ivermectin therapy in chronic strongyloidiasis. *Trans R Soc Trop Med Hyg* 1992; **86:** 291.
3. Lyagoubi M, *et al.* Chronic persistent strongyloidiasis cured by ivermectin. *Trans R Soc Trop Med Hyg* 1992; **86:** 541.
4. Datry A, *et al.* Treatment of Strongyloides stercoralis infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 1994; **88:** 344–5.
5. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169:** 1076–9.
6. Marti H, *et al.* A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 1996; **55:** 477–81.
7. Igual-Adell R, *et al.* Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother* 2004; **5:** 2615–9.

Trichostrongyliasis. For mention of the use of ivermectin in *Trichostrongylus* infections, see p.139.

Preparations

USP 31: Ivermectin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dermopero; Securo; ***Austral.:*** Stromectol; ***Braz.:*** Ivermec†; Leverctin; Revectina; Vermectil; ***Fr.:*** Mectizan; Stromectol; ***Jpn:*** Stromectol; ***Mex.:*** Ivexterm; ***Neth.:*** Stromectol; ***NZ:*** Stromectol; ***USA:*** Mectizan; Stromectol.

Levamisole *(BAN, rINN)*

Levamisol; Lévamisole; Levamisoli; Levamisolum; Levamizol. (*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*][1,3]thiazole.

Левамизол

$C_{11}H_{12}N_2S$ = 204.3.

CAS — 14769-73-4.

ATC — P02CE01.

ATC Vet — QP52AE01.

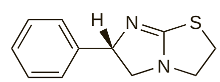

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Levamisole for Veterinary Use; Levamisole BP(Vet) 2008). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Levamisole Hydrochloride *(BANM, USAN, rINNM)*

Cloridrato de Levamizol; Hidrocloruro de levamisol; ICI-59623; Lévamisole, chlorhydrate de; Levamisol-hydrochlorid; Levamisolhydroklorid; Levamisoli hydrochloridum; Levamisolihydrokloridi; Levamizol-hidroklorid; Levamizolio hidrochloridas; Lewamizolu chlorowodorek; NSC-177023; R-12564; RP-20605; *l*-Tetramisole Hydrochloride; *l*-Tetramisole Hydrochloride.

Левамизола Гидрохлорид

$C_{11}H_{12}N_2S,HCl$ = 240.8.

CAS — 16595-80-5.

ATC — P02CE01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Levamisole Hydrochloride). A white to almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. A 5% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 31 (Levamisole Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 4.5. Protect from light.

Adverse Effects

When given in single doses for the treatment of ascariasis or other worm infections, levamisole is generally well tolerated and adverse effects are usually limited to nausea, vomiting, diarrhoea, abdominal pain, dizziness, and headache.

When levamisole is used as an immunostimulant and given for longer periods, adverse effects are more frequent and diverse and, in common with other immunomodulators, may sometimes result from exacerbation of the primary underlying disease. Adverse effects associated especially with the more prolonged use of levamisole have included: hypersensitivity reactions such as fever, a flu-like syndrome, arthralgia, muscle pain, skin rashes, and cutaneous vasculitis; CNS effects including headache, insomnia, dizziness, and convulsions; haematological abnormalities such as agranulocytosis, leucopenia, and thrombocytopenia; and gastrointestinal disturbances, including an abnormal taste in the mouth.

Incidence of adverse effects. In a review[1] (by the manufacturers) of 46 controlled studies in which 2635 cancer patients received adjuvant levamisole treatment, most patients received levamisole on 3 consecutive days every 2 weeks (1102 patients) or on 2 consecutive days every week (1156 patients), usually in a daily dose of 150 mg. Levamisole caused several adverse effects, such as skin rash, nausea, vomiting, and a metallic or bitter taste in the mouth, which although troublesome were relatively trivial and often regressed during therapy or disappeared on cessation of therapy. A total of 38 patients developed agranulocytosis and of these 36 had received weekly treatment. Several contracted possible life-threatening infections and 2 died of septic shock.

1. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; **5:** 1–9.

Effects on the endocrine system. Rechallenge confirmed that levamisole was responsible for inappropriate antidiuretic hormone syndrome in a patient receiving levamisole with fluorouracil.[1]

1. Tweedy CR, *et al.* Levamisole-induced syndrome of inappropriate antidiuretic hormone. *N Engl J Med* 1992; **326:** 1164.

Effects on the liver. Elevated aspartate aminotransferase concentrations in 2 of 11 patients given levamisole for recurrent pyoderma suggested liver toxicity, a very rarely occurring adverse effect.[1] In a later report, liver enzyme concentrations were raised in a 14-year-old boy treated with levamisole for minimal change nephrotic syndrome.[2]

1. Papageorgiou P, *et al.* Levamisole in chronic pyoderma. *J Clin Lab Immunol* 1982; **8:** 121–7.
2. Bulugahapitiya DTD. Liver toxicity in a nephrotic patient treated with levamisole. *Arch Dis Child* 1997; **76:** 289.

Effects on the nervous system. Reports[1,2] of inflammatory leukoencephalopathy were associated with the use of fluorouracil and levamisole in 4 patients being treated for adenocarcinoma of the colon. Active demyelination was demonstrated in 2 patients.[1] Clinical improvement occurred when chemotherapy was stopped; 3 patients were treated with corticosteroids.[1] A similar syndrome has been reported in a patient with a history of hepatitis C given levamisole alone.[3]

1. Hook CC, *et al.* Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992; **31:** 262–7.
2. Kimmel DW, Schutt AJ. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. *Mayo Clin Proc* 1993; **68:** 363–5.
3. Lucia P, *et al.* Multifocal leucoencephalopathy induced by levamisole. *Lancet* 1996; **348:** 1450.

Precautions

The use of levamisole should be avoided in patients with pre-existing blood disorders. Patients given levamisole with fluorouracil should undergo appropriate monitoring of haematological and hepatic function.

Rheumatoid arthritis. The presence of HLA B27 in seropositive rheumatoid arthritis is an important predisposing factor to the development of agranulocytosis with levamisole; it is recommended that the use of levamisole in this group should be avoided.[1]

1. Mielants H, Veys EM. A study of the hematological side effects of levamisole in rheumatoid arthritis with recommendations. *J Rheumatol* 1978; **5** (suppl 4): 77–83.

Sjögren's syndrome. The appearance of adverse effects in 9 of 10 patients with rheumatoid arthritis and Sjögren's syndrome while being treated with levamisole led to abandonment of the study.[1] Levamisole should be given with caution, if at all, to patients with Sjögren's syndrome.

1. Balint G, *et al.* Sjögren's syndrome: a contraindication to levamisole treatment? *BMJ* 1977; **2:** 1386–7.

Interactions

Alcohol. US licensed product information states that levamisole can produce a disulfiram-like reaction with *alcohol.*

Anticoagulants. For an increase in the activity of *warfarin* when given with levamisole and fluorouracil, see Interactions, Levamisole, under Warfarin, p.1431.

Antiepileptics. For increased *phenytoin* concentrations when given with levamisole and fluorouracil, see Interactions, Antineoplastics, under Phenytoin, p.499.

Pharmacokinetics

Levamisole is rapidly absorbed from the gastrointestinal tract. Maximum plasma concentrations are attained within 1.5 to 2 hours. It is extensively metabolised in the liver. The plasma half-life for levamisole is 3 to 4 hours and for the metabolites is 16 hours. It is excreted mainly in the urine as metabolites and a small proportion in the faeces. About 70% of a dose is excreted in the urine over 3 days, with about 5% as unchanged levamisole.

◊ References.

1. Luyckx M, *et al.* Pharmacokinetics of levamisole in healthy subjects and cancer patients. *Eur J Drug Metab Pharmacokinet* 1982; **7:** 247–54.
2. Kouassi E, *et al.* Novel assay and pharmacokinetics of levamisole and p-hydroxylevamisole in human plasma and urine. *Biopharm Drug Dispos* 1986; **7:** 71–89.

Uses and Administration

Levamisole hydrochloride is the active laevo-isomer of tetramisole hydrochloride. It is used as an anthelmintic and as an adjuvant in malignant disease. It has also been tried in several conditions where its stimulant effect on the depressed immune response might be useful.

Levamisole is active against intestinal nematode worms and appears to act by paralysing susceptible worms which are subsequently eliminated from the intestines. In particular, levamisole is effective in the treatment of ascariasis (p.134). It is also used in hookworm infections (p.136).

Doses of levamisole hydrochloride are expressed in terms of the equivalent amount of levamisole. Levamisole hydrochloride 1.18 g is equivalent to about 1 g of levamisole. The usual adult dose in ascariasis is 150 mg of levamisole orally as a single dose; children have been given 3 mg/kg as a single dose. For the hookworm infection ancylostomiasis or for mixed ascariasis-hookworm infections, both adults and children may be given 2.5 mg/kg as a single dose, repeated after 7 days in cases of severe hookworm infection.

Levamisole influences host defences by modulating cell-mediated immune responses; it restores depressed T-cell functions and has been described as an immunostimulant, although stimulation above normal levels does not seem to occur. It has been tried in many disorders, including bacterial and viral infections and rheumatic disorders, although in these conditions results have not been encouraging.

Levamisole has also been used as an adjunct in patients with malignant disease, although it is not clear that any response is due to its action on the immune system. Adjuvant treatment with levamisole and fluorouracil has been given to reduce recurrence after resection of adenocarcinoma of the colon with regional lymph node involvement (but see Malignant Neoplasms, below).

◊ Reviews.

1. Amery WKP, Bruynseels JPJM. Levamisole, the story and the lessons. *Int J Immunopharmacol* 1992; **14:** 481–6.
2. Scheinfeld N, *et al.* Levamisole in dermatology : a review. *Am J Clin Dermatol* 2004; **5:** 97–104.

Malignant neoplasms. Levamisole has been tried in the adjuvant treatment of various malignant neoplasms[1,2] with conflicting results. Based on the results of early adjuvant trials,[3-5] levamisole was used as standard therapy to modulate fluorouracil in patients with colorectal cancer (p.665), particularly in the USA. However, whether levamisole actually added to the beneficial effect of adjuvant fluorouracil was unclear. Adjuvant levamisole alone was no more effective than placebo in 1 study,[6] and more recent trials have indicated that levamisole is no more effective than placebo when added to fluorouracil,[7] or to fluorouracil plus folinic acid.[8]

1. Spreafico F. Use of levamisole in cancer patients. *Drugs* 1980; **20:** 105–16.
2. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; **5:** 1–9.
3. Laurie JA, *et al.* Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil: the North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 1989; **7:** 1447–56.
4. Moertel CG, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322:** 352–8.
5. Moertel CG, *et al.* Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 1995; **122:** 321–6.
6. Chlebowski RT, *et al.* Long-term survival following levamisole or placebo adjuvant treatment of colorectal cancer: a Western Cancer Study Group trial. *Oncology* 1988; **45:** 141–3.
7. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355:** 1588–96.
8. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; **17:** 3553–9.

Mansonella infections. Levamisole is one of the drugs that has been suggested for the treatment of *Mansonella* infections (p.137). There have been reports[1,2] of response when given with mebendazole.

1. Maertens K, Wery M. Effect of mebendazole and levamisole on Onchocerca volvulus and Dipetalonema perstans. *Trans R Soc Trop Med Hyg* 1975; **69:** 359–60.
2. Bernberg HC, *et al.* The combined treatment with levamisole and mebendazole for a perstans-like filarial infection in Rhodesia. *Trans R Soc Trop Med Hyg* 1979; **73:** 233–4.

Mouth ulceration. Levamisole might be beneficial in severe mouth ulceration (p.1700) but is limited by its adverse effects. A review[1] of its use in recurrent aphthous stomatitis indicated that beneficial results have been reported with levamisole in open studies, but results of double-blind studies have been conflicting. Nevertheless, there have been patients with severe recurrent aphthous stomatitis refractory to all other modes of treatment who have responded to levamisole. Dosage has been with 150 mg daily in divided doses given for 3 days at the first sign of ulceration, followed by 11 days without treatment, repeated as necessary.

1. Miller MF. Use of levamisole in recurrent aphthous stomatitis. *Drugs* 1980; **20:** 131–6.

Renal disorders. In a randomised double-blind study, children with frequently relapsing corticosteroid-sensitive and corticosteroid-dependent nephrotic syndrome were given placebo or levamisole 2.5 mg/kg on alternate days and steroid therapy was gradually withdrawn.[1] Of 31 children being treated with levamisole, 14 were still in remission 112 days after the start of the study compared with 4 of 30 receiving placebo. There have been subsequent reports of adjunctive use in children with nephrotic syndrome,[2-6] but its place in therapy remains to be established. For a discussion of the treatment of glomerular kidney disorders, including the nephrotic syndrome, see p.1504.

1. British Association for Paediatric Nephrology. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. *Lancet* 1991; **337:** 1555–7.
2. Donia AF, *et al.* Levamisole: adjunctive therapy in steroid dependent minimal change nephrotic children. *Pediatr Nephrol* 2002; **17:** 355–8.
3. Fu LS, *et al.* Levamisole in steroid-sensitive nephrotic syndrome children with frequent relapses and/or steroid dependency: comparison of daily and every-other-day usage. *Nephron Clin Pract* 2004; **97:** c137–c141.
4. Sümegi V, *et al.* Long-term effects of levamisole treatment in childhood nephrotic syndrome. *Pediatr Nephrol* 2004; **19:** 1354–60.
5. Al-Saran K, *et al.* Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2006; **21:** 201–5.
6. Boyer O, *et al.* Short- and long-term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. *Pediatr Nephrol* 2008; **23:** 575–80.

Vitiligo. In a study[1] involving 36 patients with limited slow-spreading vitiligo, response to levamisole treatment occurred in 34 within 2 to 4 months. Patients received 150 mg of oral levamisole daily on 2 consecutive days each week. Patients who were additionally treated with topical fluocinolone or clobetasol had higher rates of repigmentation. A later controlled study[2] involving 43 patients reported less benefit.

The usual treatment of vitiligo is discussed under Pigmentation Disorders, p.1582.

1. Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. *Int J Dermatol* 1994; **33:** 584–7.
2. Agarwal S, *et al.* A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *Br J Dermatol* 2005; **153:** 163–6.

Preparations

USP 31: Levamisole Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Levam; Meglum; ***Austral.:*** Ergamisol†; ***Belg.:*** Ergamisol†; ***Braz.:*** Ascaridil; ***Canad.:*** Ergamisol†; ***Cz.:*** Decaris†; ***Ger.:*** Ergamisol†; ***Gr.:*** Ergamisol; ***Hong Kong:*** Decaris; ***Hung.:*** Decaris; ***India:*** Levomol; Vermisol; Vizole; ***Indon.:*** Askamex; ***Irl.:*** Ketrax†; ***Israel:*** Ergamisol; ***Mex.:*** Decaris; ***Neth.:*** Ergamisol†; ***Rus.:*** Decaris (Декарис); ***S.Afr.:*** Ergamisol; ***Turk.:*** Paraks; Sitraks; ***UK:*** Ketrax†; ***USA:*** Ergamisol†; ***Venez.:*** Decaris†.

Male Fern

Aspidium; Farnwurzel; Felce Maschio; Feto Macho; Filix Mas; Fougère Mâle; Helecho macho; Rhizoma Filicis Maris.

Щитовник Мужской

Pharmacopoeias. In *Chin.*

Profile

Male fern consists of the rhizome, frond-bases, and apical bud of *Dryopteris filix-mas* agg. (Polypodiaceae), collected late in the autumn, divested of the roots and dead portions and carefully dried, retaining the internal green colour. It contains not less than 1.5% of filicin. During storage the green colour of the interior gradually disappears, often after a lapse of 6 months, and such material is unfit for medicinal use.

Filicin is the mixture of ether-soluble substances obtained from male fern. Its activity is chiefly due to flavaspidic acid, a phloroglucinol derivative.

Male fern has anthelmintic properties and was formerly used as male fern extract (aspidium oleoresin) for the expulsion of tapeworms. However, male fern is highly toxic and has been superseded by other drugs.

Adverse effects include headache, nausea and vomiting, severe abdominal cramp, diarrhoea, dyspnoea, albuminuria, hyperbilirubinaemia, dizziness, tremors, convulsions, visual disturbances including blindness (possibly permanent), stimulation of uterine muscle, coma, respiratory failure, bradycardia, and cardiac failure. Fatalities have occurred.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Digestodoron; ***Ger.:*** Digestodoron; ***S.Afr.:*** Digestodoron.

Mebendazole *(BAN, USAN, rINN)*

Mebendatsoli; Mebendazol; Mebendazolas; Mébendazole; Mebendazolum; R-17635. Methyl 5-benzoyl-1*H*-benzimidazol-2-ylcarbamate.

Мебендазол

$C_{16}H_{13}N_3O_3$ = 295.3.

CAS — 31431-39-7.

ATC — P02CA01.

ATC Vet — QP52AC09.

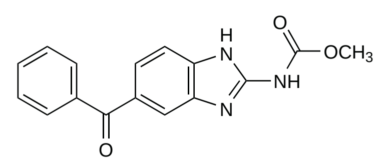

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Mebendazole). A white or almost white powder. It shows polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Mebendazole). A white to slightly yellow, almost odourless, powder. Practically insoluble in water, in alcohol, in chloroform, in ether, and in dilute mineral acids; freely soluble in formic acid.

Adverse Effects

Since mebendazole is poorly absorbed from the gastrointestinal tract at the usual therapeutic doses, adverse effects have generally been restricted to gastrointestinal disturbances, such as transient abdominal pain and diarrhoea, and have tended to occur in patients being treated for heavy intestinal infection. Headache and dizziness have been reported. Adverse effects have been reported more frequently with the high doses tried in echinococcosis and have included allergic reactions, raised liver enzyme values, alopecia, and bone marrow depression.

Incidence of adverse effects. In the first phase[1] of WHO-coordinated multicentre studies on the treatment of echinococcosis (hydatid disease) involving *Echinococcus granulosus* or *E. multilocularis*, the most frequent adverse effects in the 139 patients given *high-dose* mebendazole, generally for 3 months, were reduced leucocyte count (25 patients), gastrointestinal symptoms (22), and raised serum-transaminase values (22). Other adverse effects were allergic conditions such as fever and skin reactions (4), CNS symptoms including headache (6), and loss of hair (7). Seven patients stopped treatment because of adverse effects.

The second phase of studies[2] compared albendazole with mebendazole in more prolonged high-dosage schedules for cystic *E. granulosus* infection. Adverse effects were similar to those reported with the first phase. However, in the first phase the allergic consequences of the 14 ruptured lung cysts and the 4 ruptured liver cysts that occurred with mebendazole were not reported. In the second phase, 2 patients suffered anaphylactic shock as a result of rupture of a lung cyst and a cyst in the abdominal cavity. These 2 patients were withdrawn from mebendazole treatment, as were another 4 patients as a consequence of their adverse reactions, although in 3 the withdrawal was only temporary.

Although albendazole is preferred to mebendazole in the treatment of echinococcosis, if either drug is used there should be constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64:** 383–8.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67:** 503–8.

Overdosage. Respiratory arrest and tachyarrhythmia associated with continuous convulsions were reported[1] in an 8-week-old infant after accidental poisoning with mebendazole. Treatment by exchange transfusion and anticonvulsants was successful.

1. el Kalla S, Menon NS. Mebendazole poisoning in infancy. *Ann Trop Paediatr* 1990; **10:** 313–14.

Precautions

Patients given high doses of mebendazole, such as those with echinococcosis, should be supervised closely with blood counts and liver function being monitored; such high-dose therapy may be inappropriate in those with hepatic impairment (see under Incidence of Adverse Effects, above).

Monitoring drug concentrations. In a retrospective analysis of patients given high doses of mebendazole for echinococcosis,[1] no relationship was found between dose and plasma concentration of mebendazole and considerable intra- and interindividual variation in plasma concentrations was observed, emphasising the need for repeated monitoring. Several patients appeared to have what were considered to be subtherapeutic plasma concentrations.

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31:** 443–8.

Pregnancy. Mebendazole is teratogenic in *rats* and there are no adequate and well controlled studies in human pregnancy. Mebendazole is therefore usually contra-indicated during pregnancy. However, it was noted that in a survey of a limited number of pregnant women who had inadvertently taken mebendazole during the first trimester, the incidence of malformation and spontaneous abortion was no greater than that observed in the general population.

Interactions

Antiepileptics. *Phenytoin* or *carbamazepine* have been reported to lower plasma-mebendazole concentrations in patients receiving high doses for echinococcosis, presumably as a result of enzyme induction; *valproate* had no such effect.[1]

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31:** 443–8.

Histamine H_2-antagonists. Plasma concentrations of mebendazole have been raised when the enzyme inhibitor *cimetidine* was also given, and this has resulted in the resolution of previously unresponsive hepatic hydatid cysts.[1]

1. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations: implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol* 1987; **24:** 390–2.

Pharmacokinetics

Mebendazole is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass elimination, being metabolised in the liver, eliminated in the bile as unchanged drug and metabolites, and excreted in the faeces. Only about 2% of a dose is excreted unchanged or as metabolites in the urine.

Mebendazole is highly protein bound.

Uses and Administration

Mebendazole, a benzimidazole carbamate derivative, is an anthelmintic with activity against most nematodes and some other worms; activity against some larval stages and ova has also been demonstrated. It inhibits or destroys cytoplasmic microtubules in the worm's intestinal or absorptive cells. Inhibition of glucose uptake and depletion of glycogen stores follow as do other inhibitory effects leading to death of the worm within several days.

Mebendazole, being poorly absorbed from the gastrointestinal tract, is used principally in the treatment of the intestinal nematode infections ascariasis (roundworm infection), enterobiasis (pinworm or threadworm infections), hookworm (ancylostomiasis and necatoriasis), and trichuriasis (whipworm infection); it is useful in mixed infections. During treatment with mebendazole, migration of worms with expulsion through the mouth and nose has occurred in some patients heavily infected with *Ascaris*. Mebendazole is also used in the treatment of capillariasis and trichostrongyliasis and has been used in strongyloidiasis. Other nematode infections which may respond to mebendazole are infection with the filarial nematode *Mansonella perstans*, and the tissue infections toxocariasis and trichinosis. Mebendazole has also been tried in high doses in the treatment of echinococcosis (hydatid disease). For discussions of these infections and their treatment, see under Choice of Anthelmintic, p.134, and under the individual headings below.

Mebendazole is given orally. The usual dose for adults and children aged over 2 years with enterobiasis is 100 mg as a single dose, repeated if necessary after 2 to 3 weeks; for ascariasis, hookworm infections, and trichuriasis the usual dose in adults and children over 1 year is 100 mg twice daily for 3 days, although a single dose of 500 mg may be effective.

Angiostrongyliasis. Mebendazole was formerly used for the treatment of angiostrongyliasis (p.134) but current opinion is that there is no convincing evidence to support its use.

Capillariasis. Mebendazole in a dose of 200 mg twice daily for 20 days has been used[1] for the treatment of capillariasis (p.135).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Echinococcosis. Mebendazole has been used[1-9] in echinococcosis (p.136), but albendazole is generally preferred. The usual dose of mebendazole in cystic echinococcosis is 40 to 50 mg/kg daily for at least 3 to 6 months.[8] A similar dose is used as an adjuvant to surgery. For alveolar echinococcosis, the dose is adjusted after 4 weeks to produce a plasma concentration of at least 250 nanomoles/litre (74 nanograms/mL), although adults should not be given more than 6 g daily. Treatment is continued for at least 2 years after radical surgery, or indefinitely in inoperable cases.

1. Ammann RW, *et al.* Recurrence rate after discontinuation of long-term mebendazole therapy in alveolar echinococcosis (preliminary results). *Am J Trop Med Hyg* 1990; **43:** 506–15.
2. Messaritakis J, *et al.* High mebendazole doses in pulmonary and hepatic hydatid disease. *Arch Dis Child* 1991; **66:** 532–3.
3. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37:** 1679–84.
4. Göçmen A, *et al.* Treatment of hydatid disease in childhood with mebendazole. *Eur Respir J* 1993; **6:** 253–7.
5. Ammann RW, *et al.* Effect of chemotherapy on the larval mass and the long-term course of alveolar echinococcosis. *Hepatology* 1994; **19:** 735–42.
6. Erdinçler P, *et al.* The role of mebendazole in the surgical treatment of central nervous system hydatid disease. *Br J Neurosurg* 1997; **11:** 116–20.
7. Vutova K, *et al.* Effect of mebendazole on human cystic echinococcosis: the role of dosage and treatment duration. *Ann Trop Med Parasitol* 1999; **93:** 357–65.
8. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996; **74:** 231–42.
9. Smego RA, *et al.* Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1073–83.

Giardiasis. For mention of the use of mebendazole for the treatment of giardiasis, see p.824.

Mansonella infections. Mebendazole is one of the drugs that has been suggested for the treatment of infections with *Mansonella perstans* (p.137). Some patients have responded to mebendazole with levamisole,[1,2] diethylcarbamazine,[3] or to mebendazole alone.[3,4]

1. Maertens K, Wery M. Effect of mebendazole and levamisole on Onchocerca volvulus and Dipetalonema perstans. *Trans R Soc Trop Med Hyg* 1975; **69:** 359–60.
2. Bernberg HC, *et al.* The combined treatment with levamisole and mebendazole for a perstans-like filarial infection in Rhodesia. *Trans R Soc Trop Med Hyg* 1979; **73:** 233–4.
3. Bregani ER, *et al.* Comparison of different anthelmintic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; **100:** 458–63.
4. Wahlgren M, Frolov I. Treatment of Dipetalonema perstans infections with mebendazole. *Trans R Soc Trop Med Hyg* 1983; **77:** 422–3.

Strongyloidiasis. Mebendazole has been used for the treatment of strongyloidiasis (p.138), but needs to be given for longer periods than albendazole to control auto-infection, so that, of the two, albendazole is preferred.[1-3]

1. Wilson KH, Kauffman CA. Persistent Strongyloides stercoralis in a blind loop of the bowel: successful treatment with mebendazole. *Arch Intern Med* 1983; **143:** 357–8.
2. Mravak S, *et al.* Treatment of strongyloidiasis with mebendazole. *Acta Trop (Basel)* 1983; **40:** 93–4.
3. Pelletier LL, Baker CB. Treatment failures following mebendazole therapy for chronic strongyloidiasis. *J Infect Dis* 1987; **156:** 532–3.

Syngamosis. Mebendazole has been used successfully[1] to treat syngamosis (p.138).

1. Timmons RF, *et al.* Infection of the respiratory tract with Mammomanogamus (Syngamus) laryngeus: a new case in Largo, Florida, and a summary of previously reported cases. *Am Rev Respir Dis* 1983; **128:** 566–9.

Toxocariasis. Mebendazole has been used in the treatment of toxocariasis (p.139). In comparative studies, mebendazole has been reported to produce similar improvements to those obtained with tiabendazole[1] and with diethylcarbamazine,[2] in each case with a lower incidence of adverse effects.

1. Magnaval JF, Charlet JP. Efficacité comparée du thiabendazole et du mébendazole dans le traitement de la toxocarose. *Therapie* 1987; **42:** 541–4.
2. Magnaval J-F. Comparative efficacy of diethylcarbamazine and mebendazole for the treatment of human toxocariasis. *Parasitology* 1995; **110:** 529–33.

Trichinosis. Mebendazole is used for the treatment of trichinosis (p.139) in some countries.

References.

1. Levin ML. Treatment of trichinosis with mebendazole. *Am J Trop Med Hyg* 1983; **32:** 980–3.

Preparations

USP 31: Mebendazole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dazomet; Helmint; Mebutar; Nemasole; Tesical; ***Austral.:*** Chemists Own De Worm; Combantrin-1 with Mebendazole; Vermox; ***Austria:*** Pantelmin; ***Belg.:*** Docmebenda; Vermox; ***Braz.:*** Ascariobel†; Averpan†; Bendrax†; Crisdazol†; Divermil†; Ductelmin; Eraverm†; Feller†; Geophagol; Gran-Verm†; Ibdazol†; Kindelmin; Mebental†; Mebiozol†; Medazol; Menbel; Moben; Multielmin†; Multizol; Necamin; Neo Mebend; Novelmin; Panfugan; Pantelmin; Panverm†; Paraverm†; Pentazole†; Pluriverm; Plurivermil†; Polidazol†; Probendazol; Quintelmin†; Sifbem†; Sirben; Tetrahelmin†; Trotil†; Vermiben; Verminon†; Vermirax†; Vermoplex; Vermoral; Verzol; Zoldaben†; ***Canad.:*** Vermox; ***Chile:*** Diacor; ***Cz.:*** Vermox; ***Denm.:*** Vermox; ***Ger.:*** Surfont; Vermox; ***Gr.:*** Vermox; ***Hong Kong:*** Elmetin†; Vermox; ***Hung.:*** Vermox; ***India:*** Mebex; Wormin; ***Indon.:*** Gavox; Vermox; ***Irl.:*** Vermox; ***Israel:*** Vermox; ***Ital.:*** Vermox; ***Malaysia:*** Quemox; Thelmox; Vermox; ***Mex.:*** Amatol; Bensolmin; Bestelar; Carbatil†; Daben; Diazolen; Exaverm†; Exbenzol; Exteny; Fanciadazol; Hedazol; Helminzole†; L-Ombrix; Lumbicid; M-Bentabs†; Meb-Overoid; Mebelmin; Mebendicin; Mebensole; Mebentiasis; Mebentral; Nemapres; Panvermin; Paranzol†; Prodazol†; Profenzol; Revapol; Soltric†; Vermicol; Vermidil; Vermin-Dazol; Vermox; Vertex†; Vertizole; ***Neth.:*** Anti-Worm; Kruidvat Anti-worm; Madicure; Trekpleister Anti-Worm†; Vermox; ***Norw.:*** Vermox; ***NZ:*** Combantrin-1; Mindol†; Vermox; ***Philipp.:*** Antiox; ***Pol.:*** Vermox; ***Port.:*** Pantelmin; Toloxim; ***Rus.:*** Vermox (Вермокс); Wormin (Вормин); ***S.Afr.:*** Adco-Wormex; Cipex; D-Worm; Rioworm; Rolab-Anthex; Vermox; Wormgo; Wormstop; ***Spain:*** Bantenol†; Lomper; Mebendan; Oxitover†; Sufil; ***Swed.:*** Vermox; ***Switz.:*** Vermox; ***Thai.:*** Benda†; Big-Ben; Drivermide; Fugacar; Masaworm-1; Meba†; Meben; Mebenda-P†; Medazole; Noxworm†; Vagaka†; Warca; ***Turk.:*** Vermazol; Versid; ***UAE:*** Mebzol; ***UK:*** Boots Threadworm Tablets 2 Years Plus; Ovex; Pripsen; Vermox; ***USA:*** Vermox; ***Venez.:*** Bendacor; Bendamen; Eprofil; Flemdazole†; Pantelmin†; Pival†; Tamixan†; Vermalon.

Multi-ingredient: ***Arg.:*** Aduar; Helmint Compuesto; Mebutar Compuesto; Tru Compuesto; ***Braz.:*** Eraverm-T†; Exelmin†; Forverm; Helmi-Ped†; Helmib†; Helmiben; Helmidrax†; Josverm†; Metiaben†; Neovermin; Octelmin†; Poliben†; Profium; Prohelmin†; Vermol†; Zoles†; ***India:*** Mebex Plus; ***Mex.:*** Amibriz†; Amoebriz; Mebeciclol; Vermox-Plus.

Melarsomine *(rINN)*

Melarsomina; Mélarsomine; Melarsominum. Bis(2-aminoethyl) *p*-[(4,6-diamino-*s*-triazin-2-yl)amino]dithiobenzenearsonite.

Меларсомин

$C_{13}H_{21}AsN_8S_2$ = 428.4.
CAS — 128470-15-5.
ATC Vet — QP51AD06.

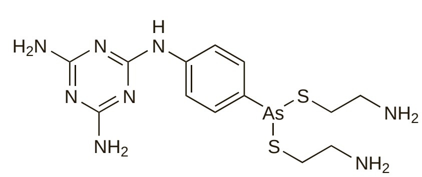

Profile

Melarsomine is a trivalent arsenical derivative used in veterinary practice for the control of canine heartworm (dirofilariasis).

Metrifonate *(BAN, rINN)*

Bayer-L-1359; DETF; Metrifonaatti; Metrifonát; Metrifonat; Metrifonatas; Métrifonate; Metrifonato; Metrifonatum; Metriphonate; Trichlorfon *(USAN)*; Trichlorphon. Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate.

Метрифонат

$C_4H_8Cl_3O_4P$ = 257.4.

CAS — 52-68-6.

ATC — P02BB01.

ATC Vet — QP52AB01; QP53AF02.

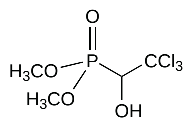

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Metrifonate). A white or almost white, crystalline powder. M.p. is between 76° and 81°. Freely soluble in water, in alcohol, and in acetone; very soluble in dichloromethane. Protect from light.

USP 31 (Metrifonate). A white crystalline powder. M.p. about 78° with decomposition. Freely soluble in water, in alcohol, in acetone, in chloroform, in ether, and in benzene; very soluble in dichloromethane; very slightly soluble in hexane and in pentane. Decomposed by alkali. Store at a temperature not exceeding 25°.

Adverse Effects, Treatment, and Precautions

Metrifonate is generally well tolerated, but may cause nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and weakness.

It is an organophosphorus compound and because of its anticholinesterase properties depresses plasma-cholinesterase concentrations. For a description of the toxic effects of organophosphorus compounds and the treatment of acute poisoning, see Organophosphorus Insecticides, p.2047. Atropine has been used to relieve cholinergic adverse effects without affecting metrifonate's activity against *Schistosoma haematobium*.

Anticholinesterase effects. Metrifonate depresses cholinesterase activity and there has been the occasional report of severe cholinergic adverse effects.[1] However, it does not usually give rise to troublesome effects at doses normally used, even though there may temporarily be almost complete inhibition of plasma cholinesterase and considerable inhibition of erythrocyte cholinesterase[2] (but see also under Alzheimer's Disease, below).

The environmental aspects of metrifonate usage have been considered by WHO.[3]

1. Jamnadas VP, Thomas JEP. Metriphonate and organophosphate poisoning. *Cent Afr J Med* 1979; **25:** 130.
2. Pleština R, *et al.* Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull WHO* 1972; **46:** 747–59.
3. WHO. Trichlorfon. *Environmental Health Criteria 132.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc132.htm (accessed 16/07/08)

Handling. Bulk metrifonate is very toxic when inhaled, swallowed, or spilled on the skin. It can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Pregnancy. WHO reported[1] that metrifonate had not shown embryotoxicity or teratogenicity, but did not recommend the use of metrifonate in pregnant patients unless immediate intervention was essential. There has been a report of an infant born with massive hydrocephalus and a large meningomyelocele whose mother had been treated twice with metrifonate during the second month of pregnancy.[2] A possible link between congenital abnormalities and the use of metrifonate to eradicate fish parasites has also been postulated.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Monson MH, Alexander K. Metrifonate in pregnancy. *Trans R Soc Trop Med Hyg* 1984; **78:** 565.
3. Czeizel AE, *et al.* Environmental trichlorfon and cluster of congenital abnormalities. *Lancet* 1993; **341:** 539–42.

Interactions

Patients treated with metrifonate should not be given depolarising neuromuscular blockers such as suxamethonium for at least 48 hours.The use of metrifonate should be avoided in those recently exposed to insecticides or other agricultural chemicals with anticholinesterase activity.

Pharmacokinetics

Metrifonate is absorbed after oral doses and some is converted to dichlorvos which is considered to be the active moiety. Plasma concentrations of dichlorvos are about 1% of those of metrifonate with peak concentrations of both substances occurring within 2 hours. Excretion is via the kidney, mainly as glucuronides.

◊ References.

1. Nordgren I, *et al.* Plasma levels of metrifonate and dichlorvos during treatment of schistosomiasis with Bilarcil. *Am J Trop Med Hyg* 1980; **29:** 426–30.
2. Nordgren I, *et al.* Levels of metrifonate and dichlorvos in plasma and erythrocytes during treatment of schistosomiasis with Bilarcil. *Acta Pharmacol Toxicol (Copenh)* 1981; **49** (suppl V): 79–86.
3. Pettigrew LC, *et al.* Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. *J Clin Pharmacol* 1998; **38:** 236–45.

Uses and Administration

Metrifonate is an organophosphorus compound and is converted in the body to the active metabolite dichlorvos (p.2040), an anticholinesterase.

Metrifonate has anthelmintic activity against *Schistosoma haematobium* and has been given orally as an alternative to praziquantel in the treatment of schistosomiasis due to *S. haematobium*. It has usually been given in three doses of 7.5 to 10 mg/kg at intervals of 2 weeks.

Metrifonate has also been used as an insecticide and as a parasiticide in fish and domestic animals.

Alzheimer's disease. Metrifonate, like a number of other cholinesterase inhibitors, has been tried in the treatment of Alzheimer's disease (see Dementia, p.362). Clinical studies[1,2] produced modest benefits but research was stopped after reports of muscle weakness, sometimes requiring respiratory support.

1. Becker RE, *et al.* Effects of metrifonate on cognitive decline in Alzheimer disease: a double-blind, placebo-controlled, 6-month study. *Alzheimer Dis Assoc Disord* 1998; **12:** 54–7.
2. Morris JC, *et al.* Metrifonate benefits cognitive, behavioral, and global function in patients with Alzheimer's disease. *Neurology* 1998; **50:** 1222–30.

Schistosomiasis. While praziquantel is now the main treatment for schistosomiasis (p.138), metrifonate is an alternative for infection due to *Schistosoma haematobium*. Cure rates with standard doses in schistosomiasis control programmes range from 40 to more than 80%, with a reduction of more than 80% in egg counts among those not cured, but a comparison with praziquantel has shown praziquantel to be the more effective drug.[1] In addition, metrifonate's dosage schedule of 3 doses at intervals of 2 weeks has caused problems of patient compliance;[2] giving 5 mg/kg three times in one day has produced similar results to a standard dosage schedule.[3]

1. Squires N. Interventions for treating schistosomiasis haematobium. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 16/05/05).
2. Aden Abdi Y, Gustafsson LL. Poor patient compliance reduces the efficacy of metrifonate treatment of Schistosoma haematobium in Somalia. *Eur J Clin Pharmacol* 1989; **36:** 161–4.
3. Aden Abdi Y, Gustafsson LL. Field trial of the efficacy of a simplified and standard metrifonate treatments of Schistosoma haematobium. *Eur J Clin Pharmacol* 1989; **37:** 371–4.

Milbemycin Oxime

CGA-179246; Milbemicina oxima. A mixture of milbemycin A_4 5-oxime and milbemycin A_3 5-oxime.

Мильбемицин Оксим

CAS — 129496-10-2.

ATC Vet — QP54AB01.

Profile

Milbemycin oxime is an anthelmintic used in veterinary medicine.

Morantel Citrate *(BANM, pINNM)*

Citrato de morantel; Morantel, Citrate de; Moranteli Citras. (*E*)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine citrate monohydrate.

Морантела Цитрат

$C_{12}H_{16}N_2S,C_6H_8O_7,H_2O$ = 430.5.

CAS — 20574-50-9 (morantel); 69525-81-1 (morantel citrate).

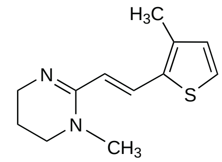

(morantel)

Morantel Tartrate *(BANM, USAN, pINNM)*

CP-12009-18; Moranteelivetytartraatti; Morantel, hydrogénotartrate de; Morantel, Tartrate de; Morantel-hidrogén-tartarát; Morantel-hydrogen-tartarát; Moranteli hydrogenotartras; Moranteli Tartras; Morantelvätetartrat; Tartrato de morantel; UK-2964-18.

Морантела Тартрат

$C_{12}H_{16}N_2S,C_4H_6O_6$ = 370.4.

CAS — 20574-50-9 (morantel); 26155-31-7 (morantel tartrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Morantel Hydrogen Tartrate for Veterinary Use; Morantel Tartrate BP(Vet) 2008). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. A 1% solution in water has a pH of 3.3 to 3.9. Protect from light.

USP 31 (Morantel Tartrate). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. pH of a 1% solution in water is between 2.8 and 3.9. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Morantel is an analogue of pyrantel. The citrate and the tartrate are used as anthelmintics in veterinary medicine for the treatment of gastrointestinal roundworms.

Moxidectin *(BAN, USAN, rINN)*

CL-301423; Moksidektiini; Moxidectina; Moxidectine; Moxidectinum; Moxidektin. (6*R*,15*S*)-5-*O*-Demethyl-28-deoxy-25-[(*E*)-1,3-dimethylbut-1-enyl]-6,28-epoxy-23-oxomilbemycin B (*E*)-23-*O*-methyloxime.

Моксидектин

$C_{37}H_{53}NO_8$ = 639.8.

CAS — 113507-06-5.

ATC Vet — QP54AB02.

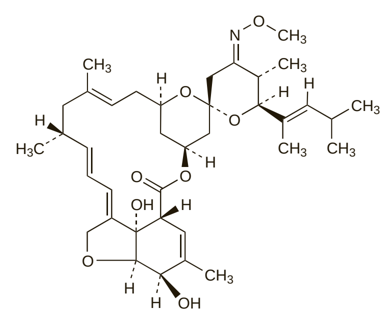

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use.

Ph. Eur. 6.2 (Moxidectin for Veterinary Use). A white or pale yellow, amorphous powder. Practically insoluble in water; very soluble in alcohol; slightly soluble in hexane.

Profile

Moxidectin is an anthelmintic used in veterinary medicine. It is also used as a systemic veterinary ectoparasiticide and is under investigation for the treatment of human onchocerciasis.

◊ References.

1. Cotreau MM, *et al.* The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003; **43:** 1108–15.

Naftalofos *(BAN, USAN, rINN)*

Bay-9002; E-9002; ENT-25567; Naftalofós; Naftalofosum; Naphthalophos; Phthalophos; S-940. Diethyl naphthalimido-oxyphosphonate.

Нафталофос

$C_{16}H_{16}NO_6P$ = 349.3.

CAS — 1491-41-4.

ATC Vet — QP52AB06.

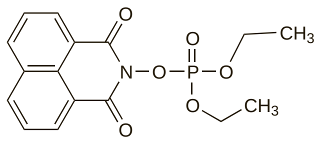

Profile

Naftalofos is an organophosphorus compound (see Organophosphorus Insecticides, p.2047) used as an anthelmintic in veterinary medicine.

Netobimin *(BAN, USAN, rINN)*

Netobimina; Nétobimine; Netobiminum; Sch-32481. 2-{3-Methoxycarbonyl-2-[2-nitro-5-(propylthio)phenyl]guanidino}ethanesulphonic acid.

Нетобимин

$C_{14}H_{20}N_4O_7S_2$ = 420.5.

CAS — 88255-01-0.

ATC Vet — QP52AC06.

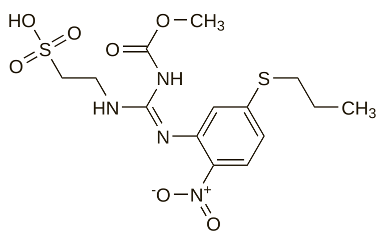

Profile

Netobimin is an anthelmintic used in veterinary medicine.

Niclosamide *(BAN, USAN, rINN)*

Anhydrous Niclosamide; Bay-2353; Niclosamida; Niclosamida Anidra; Niclosamide anhydre; Niclosamidum; Niclosamidum anhydricum; Niklosamid; Niklosamid, vattenfri; Niklosamidi; Niklosamidi, vedetön; Niklozamid; Niklozamid bezwodny; Niklozamidas, bevandenis; Phenasale; Vízmentes niklozamid. 2′,5-Dichloro-4′-nitrosalicylanilide; 5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.

Никлозамид

$C_{13}H_8Cl_2N_2O_4$ = 327.1.

CAS — 50-65-7.

ATC — P02DA01.

ATC Vet — QP52AG03.

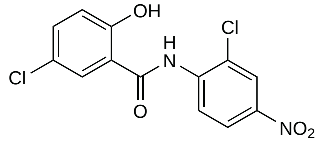

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Int. permits the anhydrous substance or the monohydrate under the title Niclosamide.

Ph. Eur. 6.2 (Niclosamide, Anhydrous). Yellowish-white to yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Store in airtight containers. Protect from light.

Niclosamide Monohydrate *(BANM)*

Niclosamida Mono-hidratada; Niclosamida monohidrato; Niclosamide monohydraté; Niclosamidum monohydricum; Niklosamid monohydrát; Niklosamidimonohydraatti; Niklosamidmonohydrat; Niklozamidas monohidratas; Niklozamid-monohidrát.

Никлозамид Моногидрат

$C_{13}H_8Cl_2N_2O_4,H_2O$ = 345.1.

ATC — P02DA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Int. permits the monohydrate or the anhydrous substance under the title Niclosamide.

Ph. Eur. 6.2 (Niclosamide Monohydrate). Yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Protect from light.

Adverse Effects

Gastrointestinal disturbances may occur occasionally with niclosamide. Lightheadedness and pruritus have been reported less frequently.

Pharmacokinetics

Niclosamide is not significantly absorbed from the gastrointestinal tract.

Uses and Administration

Niclosamide is an anthelmintic which is active against most tapeworms, including the beef tapeworm (*Taenia saginata*), the pork tapeworm (*T. solium*), the fish tapeworm (*Diphyllobothrium latum*) and the dog tapeworm (*Dipylidium caninum*); it has also been given for infections with the dwarf tapeworm, *Hymenolepis nana*. For discussions of the treatment of tapeworm infections, see Diphyllobothriasis, p.136, Hymenolepiasis, p.136, and Taeniasis, p.139. The activity of niclosamide against these worms appears to be due to inhibition of mitochondrial oxidative phosphorylation; anaerobic ATP production is also affected.

Niclosamide is given as tablets, which must be chewed thoroughly before swallowing and washed down with water.

For infections with pork tapeworm a single 2-g dose is given after a light breakfast. Niclosamide is not active against the larval form (cysticerci) and, although the risk of inducing cysticercosis appears to be theoretical, a laxative is given about 2 hours after the dose to expel the killed worms and minimise the possibility of the migration of ova of *T. solium* into the stomach; an antiemetic may also be given before treatment.

For infections with beef or fish tapeworms the 2-g dose of niclosamide may be divided, with 1 g taken after breakfast and 1 g an hour later.

In dwarf-tapeworm infections an initial dose of 2 g has been given on the first day followed by 1 g daily for 6 days.

Children aged 2 to 6 years are given half the above doses and those under 2 years of age are given one-quarter the above doses.

Unless expulsion of the worm is aided by a laxative, portions are voided in a partially digested form after treatment with niclosamide; the scolex is rarely identifiable.

In schistosomiasis (p.138), niclosamide is used as a molluscicide in water-treatment control programmes.

Preparations

BP 2008: Niclosamide Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Yomesan; ***Braz.:*** Atenase†; ***Cz.:*** Yomesan†; ***Denm.:*** Yomesan†; ***Fin.:*** Kontal; ***Fr.:*** Tredemine; ***Ger.:*** Yomesan; ***Gr.:*** Tredemine; Yomesan; ***India:*** Niclosan; ***Israel:*** Yomesan; ***Ital.:*** Yomesan; ***Mex.:*** Overoid; ***Neth.:*** Yomesan; ***S.Afr.:*** Yomesan; ***Swed.:*** Yomesan; ***Thai.:*** Manozide; Niclosan†; Telmitin; Unicide; Yomesan; ***Turk.:*** Yomesan; ***UK:*** Yomesan.

Multi-ingredient: ***Thai.:*** Zenda†.

Nitroscanate *(BAN, USAN, rINN)*

CGA-23654; Nitroscanato; Nitroscanatum; Nitroskanaatti; Nitroskanat. 4-(4-Nitrophenoxy)phenyl isothiocyanate.

Нитросканат

$C_{13}H_8N_2O_3S$ = 272.3.

CAS — 19881-18-6.

ATC Vet — QP52AX01.

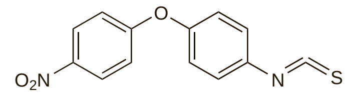

Profile

Nitroscanate is an isothiocyanate anthelmintic used in veterinary medicine.

Nitroxinil *(BAN, rINN)*

Nitroxinilo; Nitroxinilum; Nitroxynil. 4-Hydroxy-3-iodo-5-nitrobenzonitrile.

Нитроксинил

$C_7H_3IN_2O_3$ = 290.0.

CAS — 1689-89-0 (nitroxinil); 27917-82-4 (nitroxinil eglumine).

ATC Vet — QP52AG08.

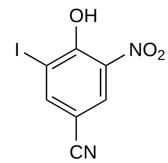

Pharmacopoeias. In *BP(Vet)*. Also in *Fr.* for veterinary use only.

BP(Vet) 2008 (Nitroxinil). A yellow to yellowish brown powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in ether; it dissolves in solutions of alkali hydroxides. Protect from light.

Profile

Nitroxinil is an anthelmintic used in veterinary medicine for the treatment of fascioliasis and some gastrointestinal roundworms in cattle and sheep.

Oxamniquine *(BAN, USAN, rINN)*

Oxamniquina; Oxamniquinum; UK-4271. 1,2,3,4-Tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolylmethanol.

Оксамнихин

$C_{14}H_{21}N_3O_3$ = 279.3.

CAS — 21738-42-1.

ATC — P02BA02.

ATC Vet — QP52AA02.

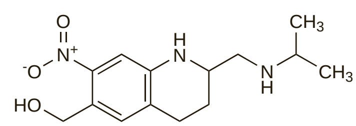

Pharmacopoeias. In *Fr.* and *Int.*

Adverse Effects

Oxamniquine causes severe pain at the injection site when given intramuscularly and is no longer given by this route.

It is generally well tolerated after oral doses, although dizziness with or without drowsiness occurs in at least a third of patients, beginning up to 3 hours after a dose and usually lasting for up to 6 hours. Headache and gastrointestinal effects such as nausea, vomiting, and diarrhoea are also common.

Allergic-type reactions including urticaria, pruritic skin rashes, and fever may occur. Liver enzyme values have been raised transiently in some patients. Epileptiform convulsions have been reported, especially in patients with a history of convulsive disorders. Hallucinations and excitement have occurred rarely.

A reddish discoloration of urine, probably due to a metabolite of oxamniquine, has been reported.

Effects on body temperature. A review[1] in 1987 noted that although a modest post-treatment rise in temperature had been reported occasionally, fever was not a common adverse effect of oxamniquine, except in Egypt where it appeared to be characteristic. The cause was not known. Increased immune complexes and excretion of antigens occurred in only half the cases, there was no evidence that Egyptian patients metabolised the drug differently to produce a pyrogenic metabolite, and the effect had not been seen in other areas where a similar high-dose regimen was used.[1]

1. Foster R. A review of clinical experience with oxamniquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 55–9.

Effects on the nervous system. In 37 patients with *Schistosoma mansoni* infection treated successfully with oxamniquine,[1] dizziness and drowsiness were most common, but the most significant adverse effect was the development of EEG abnormalities in 6 of 34 patients whose pre-treatment EEG was normal. Of the 3 patients with pre-existing EEG abnormalities, 1 suffered a tonic-clonic seizure during therapy as previously reported,[2] 1 did not suffer seizures, and the third received phenytoin prophylaxis during oxamniquine therapy. It was considered prudent to give antiepileptics before starting oxamniquine in patients with a history of seizure disorder. After completion of this study, a patient with no history of seizures suffered a tonic-clonic seizure 2 hours after each of the second and third doses of oxamniquine.

The main neuropsychiatric adverse effects seen in 180 Brazilian patients with *Schistosoma mansoni* infection treated with single oral doses of oxamniquine were: drowsiness (50.6%), dizziness (41.1%), headache (16.1%), temporary amnesia (2.2%), behavioural disturbances (1.7%), chills (1.1%), and seizures (1.1%).[3] An EEG was performed before and after treatment in 20 patients; there were alterations in 3 but they were not associated with neuropsychiatric changes.

1. Krajden S, *et al*. Safety and toxicity of oxamniquine in the treatment of Schistosoma mansoni infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg* 1983; **32:** 1344–6.
2. Keystone JS. Seizures and electroencephalograph changes associated with oxamniquine therapy. *Am J Trop Med Hyg* 1978; **27:** 360–2.
3. de Carvalho SA, *et al*. Neurotoxicidade do oxamniquine no tratamento da infeçáo humana pelo Schistosoma mansoni. *Rev Inst Med Trop Sao Paulo* 1985; **27:** 132–42.

Precautions

Oxamniquine should be used with caution in patients with epilepsy or a history of convulsive disorders. Patients should be warned that oxamniquine can cause dizziness or drowsiness and if affected they should not drive or operate machinery.

Pharmacokinetics

Oxamniquine is readily absorbed after oral doses. Peak plasma concentrations are achieved 1 to 3 hours after a dose and the plasma half-life is 1 to 2.5 hours.

It is extensively metabolised to inactive metabolites, principally the 6-carboxy derivative, which are excreted in the urine. About 70% of a dose of oxamniquine is excreted as the 6-carboxy metabolite within 12 hours of a dose; traces of the 2-carboxy metabolite have also been detected in the urine.

Uses and Administration

Oxamniquine is an anthelmintic used in the treatment of schistosomiasis caused by *Schistosoma mansoni*, but not by other *Schistosoma* spp. It causes worms to shift from the mesenteric veins to the liver where the male worms are retained; the female worms return to the mesentery, but can no longer release eggs. Resistance may occur.

Oxamniquine is given orally, preferably after food. Dosage depends on the geographical origin of the infection and total doses range from 15 mg/kg as a single dose to 60 mg/kg given over 2 to 3 days. A single dose should not exceed 20 mg/kg.

Schistosomiasis. Oxamniquine is an alternative to praziquantel for the treatment of schistosomiasis (p.138) due to *Schistosoma mansoni*, although resistance has occurred, particularly in South America,[1] and it is somewhat less effective than praziquantel.[2]

The dose ranges between a single dose of 15 mg/kg and 60 mg/kg given over 2 or 3 days.[1,3] Doses in the low range have been used effectively in South America, the Caribbean, and West Africa while patients in Egypt, South Africa, and Zimbabwe require doses at the top end of the range; intermediate doses may be effective in other parts of Africa.[3]

After the appropriate therapeutic dose of oxamniquine, cure rates of at least 60%, and often more than 90%, can be expected. Egg excretion in those not cured will be reduced by over 80%, and usually by over 90%, one year after treatment.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Ferrari ML, *et al.* Efficacy of oxamniquine and praziquantel in the treatment of Schistosoma mansoni infection: a controlled trial. *Bull WHO* 2003; **81:** 190–6.
3. WHO. The control of schistosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 728* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_728.pdf (accessed 16/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Mansil; ***Gr.:*** Vansil†.

Oxantel Embonate *(BANM, rINNM)*

CP-14445-16; Embonato de oxantel; Oxantel, Embonate d'; Oxantel Pamoate *(USAN)*; Oxanteli Embonas. (*E*)-3-[2-(1,4,5,6-Tetrahydro-1-methylpyrimidin-2-yl)vinyl]phenol 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Оксантела Эмбонат

$C_{13}H_{16}N_2O,C_{23}H_{16}O_6$ = 604.6.
CAS — 36531-26-7 (oxantel); 68813-55-8 (oxantel embonate); 42408-84-4 (oxantel embonate).
ATC — P02CC02.

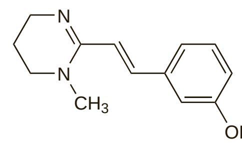

(oxantel)

Profile

Oxantel is an analogue of pyrantel that has been used as the embonate in the treatment of trichuriasis. It is used with pyrantel for various intestinal nematode infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Indon.:*** Quantrel; ***Philipp.:*** Quantrel; ***Venez.:*** Dualid; Quantrel.

Oxfendazole *(BAN, USAN, rINN)*

Oksfendatsoli; Oxfendazol; Oxfendazolum; RS-8858. Methyl 5-phenylsulphinyl-1*H*-benzimidazol-2-ylcarbamate.

Оксфендазол

$C_{15}H_{13}N_3O_3S$ = 315.3.
CAS — 53716-50-0.
ATC Vet — QP52AC02.

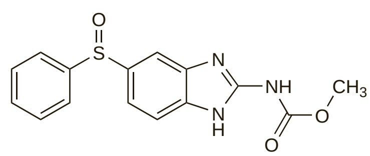

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.

Ph. Eur. 6.2 (Oxfendazole for Veterinary Use; Oxfendazole BP(Vet) 2008). A white or almost white powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Oxfendazole). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Oxfendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Oxibendazole *(BAN, USAN, rINN)*

Oxibendazol; Oxibendazolum; SKF-30310. Methyl 5-propoxy-1*H*-benzimidazol-2-ylcarbamate.

Оксибендазол

$C_{12}H_{15}N_3O_3$ = 249.3.
CAS — 20559-55-1.
ATC Vet — QP52AC07.

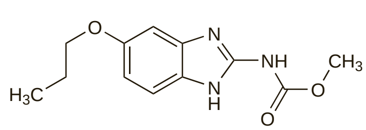

Profile

Oxibendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p.148). It is used in veterinary medicine.

Oxyclozanide *(BAN, rINN)*

ICI-46683; Oxiclozanida; Oxyclozanidum. 3,3′,5,5′,6-Pentachloro-2′-hydroxysalicylanilide.

Оксиклозанид

$C_{13}H_6Cl_5NO_3$ = 401.5.
CAS — 2277-92-1.
ATC Vet — QP52AG06.

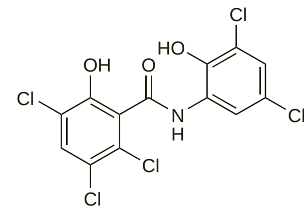

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Oxyclozanide). A pale cream or cream-coloured powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone; slightly soluble in chloroform.

Profile

Oxyclozanide is an anthelmintic used in veterinary medicine for the control of fascioliasis in cattle and sheep.

Piperazine

Piperatsiini; Piperazin; Piperazina; Piperazinum.

Пиперазин

$C_4H_{10}N_2$ = 86.14.
CAS — 110-85-0.
ATC — P02CB01.
ATC Vet — QP52AH01.

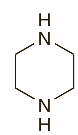

Pharmacopoeias. In *US.*

USP 31 (Piperazine). White to off-white lumps or flakes having an ammoniacal odour. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Piperazine Adipate

Piperatsiiniadipaatti; Piperaz. Adip.; Piperazina, adipato de; Piperazinadipat; Piperazin-adipát; Pipérazine, adipate de; Piperazini adipas; Piperazino adipatas; Piperazinum Adipicum.

Пиперазина Адипат

$C_4H_{10}N_2,C_6H_{10}O_4$ = 232.3.
CAS — 142-88-1.
ATC — P02CB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn,* and *Viet.*

Ph. Eur. 6.2 (Piperazine Adipate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol.

Piperazine Citrate

Hydrous Tripiperazine Dicitrate; Piperatsiinisitraatti; Piperazina, citrato de; Piperazincitrat; Piperazin-citrát; Piperazin-citrát hydrát; Pipérazine, citrate de; Piperazini citras; Piperazini Citras Hydricus; Piperazino citratas.

Пиперазина Цитрат

$(C_4H_{10}N_2)_3,2C_6H_8O_7,xH_2O$ = 642.7 (anhydrous substance).
CAS — 144-29-6 (anhydrous piperazine citrate); 41372-10-5 (piperazine citrate hydrate).
ATC — P02CB01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Piperazine Citrate). A white or almost white granular powder. It contains a variable amount of water. Freely soluble in water; practically insoluble in alcohol.

USP 31 (Piperazine Citrate). A white, crystalline powder having not more than a slight odour. Soluble in water; insoluble in alcohol and in ether. pH of a 10% solution in water is about 5.

Stability. A decrease in the content of piperazine [as citrate] in syrups on storage was attributed to interaction with fructose and glucose formed by hydrolysis of sucrose.[1] A syrup prepared with sorbitol lost no potency when stored at 25° for 14 months.

1. Nielsen A, Reimer P. The stability of piperazine in syrup. *Arch Pharm Chemi (Sci)* 1975; **3:** 73–8.

Piperazine Hydrate

Piperatsiinihydraatti; Piperazin Heksahidrat; Piperazin hexahydrát; Piperazina hexahidrato; Piperazinas hidratas; Pipérazine, hydrate de; Piperazin-hidrát; Piperazinhydrat; Piperazini Hydras; Piperazinium Hexahydricum; Piperazinum hydricum; Piperazyna uwodniona. Piperazine hexahydrate.

Пиперазина Гидрат

$C_4H_{10}N_2,6H_2O$ = 194.2.
CAS — 142-63-2.
ATC — P02CB01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.*
Ph. Eur. 6.2 (Piperazine Hydrate). Colourless deliquescent crystals. M.p. about 43°. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 10.5 to 12.0. Store in airtight containers. Protect from light.

Piperazine Phosphate

Piperazina, fosfato de; Piperazini Phosphas.

Пиперазина Фосфат

$C_4H_{10}N_2,H_3PO_4,H_2O$ = 202.1.
CAS — 14538-56-8 (anhydrous piperazine phosphate); 18534-18-4 (piperazine phosphate monohydrate).
ATC — P02CB01.

Pharmacopoeias. In *Br., Chin., Jpn,* and *Viet.*
BP 2008 (Piperazine Phosphate). A white odourless or almost odourless crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5.

Adverse Effects

Serious adverse effects are rare with piperazine and generally indicate overdosage or impaired excretion. Nausea, vomiting, diarrhoea, abdominal pain, headache, skin rashes, and urticaria occasionally occur. Severe neurotoxicity and EEG abnormalities have been reported with symptoms including somnolence, dizziness, nystagmus, muscular incoordination and weakness, ataxia, paraesthesia, myoclonic contractions, choreiform movements, tremor, convulsions, and loss of reflexes.

Transient visual disturbances such as blurred vision have occurred occasionally and there were reports of cataract formation after treatment with piperazine although they do not appear to have been substantiated.

Hypersensitivity reactions such as bronchospasm, Stevens-Johnson syndrome, and angioedema have occurred in some individuals.

◊ Piperazine has been taken off the market in some European countries because of general concern about its safety.[1] A study carried out in Sweden on 2 healthy subjects had indicated that mononitrosation of piperazine can occur in the stomach to produce the potential carcinogen *N*-mononitrosopiperazine; the more potent *N,N*-dinitrosopiperazine was not found.[2] However, the disease risk to man from such *N*-nitroso compounds has been questioned[3] and certainly reports of tumours associated with the use of piperazine have not been traced. Also, in the UK the CSM concluded that the incidence of serious adverse effects associated with piperazine was low and that, with appropriate pack warnings, piperazine products could remain as medicines available to the public through pharmacies.[1]

1. Anonymous. Data sheet changes for piperazine in pregnancy. *Pharm J* 1988; **240:** 367.
2. Bellander BTD, *et al.* Nitrosation of piperazine in the stomach. *Lancet* 1981; **ii:** 372.
3. Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. *Lancet* 1983; **i:** 629–32.

Abuse. Derivatives of piperazine have been developed and abused as 'designer drugs'—see Benzylpiperazine (p.2152).

Effects on the blood. A 4-year-old African boy with G6PD deficiency developed haemolytic anaemia; no cause for the haemolysis was found except that 2 days previously he had taken *Pripsen* (piperazine and senna).[1] Severe thrombocytopenia with epistaxis and haemoptysis, which developed in a 61-year-old man after piperazine self-medication, was probably the result of sensitisation to piperazine 15 years earlier.[2]

1. Buchanan N, *et al.* G-6-PD deficiency and piperazine. *BMJ* 1971; **2:** 110.
2. Cork MJ, *et al.* Pruritus ani, piperazine, and thrombocytopenia. *BMJ* 1990; **301:** 1398.

Effects on the liver. A reaction resembling viral hepatitis occurred on 2 occasions in a 25-year-old woman after use of piperazine; it appeared to be a hypersensitivity reaction.[1]

1. Hamlyn AN, *et al.* Piperazine hepatitis. *Gastroenterology* 1976; **70:** 1144–7.

Hypersensitivity. A patient experienced a serum-sickness-like illness associated with piperazine,[1] which was followed by a delayed hypersensitivity vasculitis.

See also Effects on the Blood and Effects on the Liver, above.

1. Balzan M, Cacciottolo JM. Hypersensitivity vasculitis associated with piperazine therapy. *Br J Dermatol* 1994; **131:** 133–4.

Precautions

Piperazine is contra-indicated in patients with epilepsy or severe renal impairment and should be given with care to patients with neurological disturbances or mild to moderate renal impairment. It should also be avoided or given with extreme caution in patients with hepatic impairment.

Breast feeding. The UK licensed product information for *Pripsen* (piperazine and senna) states that piperazine is distributed into breast milk. Mothers should be advised to take a dose after breast feeding then not to breast feed for 8 hours during which period milk should be expressed and discarded at the regular feeding times.

Pregnancy. It has been reported that piperazine is teratogenic in *rabbits* and that there have been isolated reports of fetal malformations after clinical use, though no causal relationship has been established. Two infants with malformations have been described briefly:[1] one had bilateral hare lip, cleft palate, and anophthalmia; the other had an abnormality of one foot. Both mothers had taken *Pripsen* (piperazine and senna). UK licensed product information for *Pripsen* advises against use in pregnancy, especially during the first trimester, unless immediate treatment with piperazine is essential.

1. Leach FN. Management of threadworm infestation during pregnancy. *Arch Dis Child* 1990; **65:** 399–400.

Interactions

The anthelmintic effects of piperazine and pyrantel may be antagonised when the two compounds are used together. The possibility that piperazine may enhance the adverse effects of phenothiazines such as chlorpromazine is discussed on p.975.

Pharmacokinetics

Piperazine is readily absorbed from the gastrointestinal tract and is excreted in the urine within 24 hours, partly as metabolites. The rate at which different individuals excrete piperazine has been reported to vary widely. It is distributed into breast milk.

Uses and Administration

Piperazine is an anthelmintic effective against the intestinal nematodes *Ascaris lumbricoides* (roundworm) and *Enterobius vermicularis* (pinworm, threadworm), although other anthelmintics are usually preferred (see the discussions on the treatment of ascariasis and enterobiasis on p.134 and p.136). In roundworms piperazine produces a neuromuscular block leading to a flaccid muscle paralysis in susceptible worms, which are then easily dislodged by the movement of the gut and expelled in the faeces.

Piperazine is usually given as the citrate or phosphate, but the adipate may also be used. The dosage of the salts of piperazine is usually expressed in terms of piperazine hydrate; 100 mg of piperazine hydrate is equivalent to about 44.4 mg of piperazine, 120 mg of piperazine adipate, 125 mg of piperazine citrate (110 mg of anhydrous piperazine citrate), and to 104 mg of piperazine phosphate.

For the treatment of ascariasis, a single dose, repeated once after 14 days, has been used. In adults and children over 12 years of age, a dose equivalent to 4.5 g of piperazine hydrate is given orally. Children aged 9 to 12 years may be given the equivalent of 3.75 g, those aged 6 to 8 years the equivalent of 3 g, those aged 4 to 5 years the equivalent of 2.25 g, and those aged 1 to 3 years the equivalent of 1.5 g. Children under 1 year should receive piperazine on medical advice only; a dose equivalent to 120 mg/kg has been suggested.

For enterobiasis, piperazine has been given for 7 days. A second course after a 7-day interval may be required. Adults and children over 12 years of age are given the equivalent of 2.25 g of the hydrate once daily, children aged 7 to 12 years the equivalent of 1.5 g daily, those aged 4 to 6 years the equivalent of 1.125 g daily, and those aged 1 to 3 years the equivalent of 750 mg daily. Children under 1 year should receive piperazine on medical advice only; a dose equivalent to 45 to 75 mg/kg has been suggested.

Piperazine is also used as a preparation with senna in a single dose of 4 g of the phosphate for adults and children over 6 years of age, repeated after 14 days for enterobiasis, or repeated monthly if necessary for up to 3 months to treat and prevent ascariasis.

Preparations

BP 2008: Piperazine Citrate Elixir; Piperazine Phosphate Tablets;
USP 31: Piperazine Citrate Syrup; Piperazine Citrate Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Ascarinase†; Ortovermim†; Vermifran†; Vermilen†; ***Canad.:*** Entacyl†; ***Fr.:*** Vermifuge†; ***Indon.:*** Combicitrine; Piperacyl; Upixon; ***Ital.:*** Citropiperazina; ***Mex.:*** Desparasil†; Helmifar†; Lu-Peracina; Overpon; Piperawitt DS†; Piperazil; Pipergress; Pipermed†; Pirzinol; Verfid; Vermin; ***Port.:*** Lombrimade†; Pipermel; Pipertox; ***S.Afr.:*** Padax; Pipralen; Piprine; SB Tox Worm; ***Spain:*** Mimedran; Vermi; ***Thai.:*** Vermex; ***Turk.:*** Asepar; Askaripar; Helmicide; Helmipar; Oksiaskaril; Siropar; ***UK:*** Pripsen†; ***Venez.:*** Ciperina; Inquiper†; Jetsan†; Oxine†; Piperato; Piperazil; Piperdin; Piperzan; Verpirol.

Multi-ingredient: ***Braz.:*** Vermilen Composto†; ***India:*** Helmazan†; ***Irl.:*** Pripsen†; ***Port.:*** Biureol; ***UK:*** Pripsen.

Pomegranate Bark

Granado; Granati Cortex; Granatrinde; Granatum; Grenadier; Melograno; Pomegranate; Pomegranate Root Bark; Romeira.

Кора Гранатового Дерева

Profile

Pomegranate bark, the dried bark of the stem and root of *Punica granatum* (Punicaceae) containing about 0.4 to 0.9% of alkaloids,, has been used for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Hexaporine.

Praziquantel *(BAN, USAN, rINN)*

EMBAY-8440; Pratsikvanteli; Prazicuantel; Prazikvantel; Prazikvantelis; Praziquantelum. 2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydropyrazino[2,1-*a*]isoquinolin-4-one.

Празиквантел

$C_{19}H_{24}N_2O_2$ = 312.4.
CAS — 55268-74-1.
ATC — P02BA01.
ATC Vet — QP52AA01.

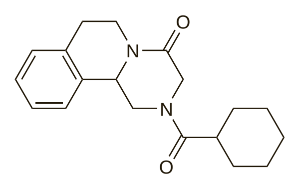

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Praziquantel). White or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Praziquantel). A white or practically white crystalline powder; odourless or with a faint characteristic odour. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Protect from light.

Adverse Effects

Adverse effects with praziquantel may be common but are usually mild and transient. Headache, diarrhoea, dizziness, drowsiness, malaise, abdominal discomfort, nausea, and vomiting have been reported most frequently. Hypersensitivity reactions such as fever, urticaria, pruritic skin rashes, and eosinophilia can occur; they may be due to death of the infecting parasites. Raised liver enzyme values have been reported rarely.

Most patients with neurocysticercosis who are given praziquantel suffer CNS effects, including headache, hyperthermia, seizures, and intracranial hypertension, which are thought to result from an inflammatory response to dead and dying parasites in the CNS. Use with corticosteroids is advised in such patients.

Effects on the gastrointestinal tract. Colicky abdominal pain and bloody diarrhoea occurred in a small community in Zaire shortly after treatment for *Schistosoma mansoni* infection with single oral doses of praziquantel 40 mg/kg.[1] A similar syndrome has been reported in some patients with *Schistosoma japonicum* infection given praziquantel.[2] The abdominal pain occurring in these patients was very different from the mild abdominal discomfort much more commonly reported with praziquantel therapy.

1. Polderman AM, *et al.* Side effects of praziquantel in the treatment of Schistosoma mansoni in Maniema, Zaire. *Trans R Soc Trop Med Hyg* 1984; **78:** 752–4.
2. Watt G, *et al.* Bloody diarrhoea after praziquantel therapy. *Trans R Soc Trop Med Hyg* 1986; **80:** 345–6.

Effects on the nervous system. Adverse nervous system effects are common in patients with neurocysticercosis given praziquantel. Neurological symptoms have also been reported[1] with the much lower doses of praziquantel used in the treatment of taeniasis in a patient with undiagnosed neurocysticercosis.

1. Flisser A, *et al.* Neurological symptoms in occult neurocysticercosis after single taenicidal dose of praziquantel. *Lancet* 1993; **342:** 748.

Precautions

Praziquantel should not be used in patients with ocular cysticercosis because of the risk of severe eye damage resulting from destruction of the parasite.

Patients should be warned that praziquantel may cause dizziness or drowsiness and if affected they should not drive or operate machinery during or for 24 hours after treatment.

Breast feeding. Praziquantel is distributed into breast milk and mothers should not breast feed during treatment or for 72 hours thereafter.

Pregnancy. In a review of 637 women given praziquantel in a mass distribution programme, 88 had had a single oral dose during pregnancy, including 37 in their first trimester. All pregnancies ended in full-term babies and there was no evidence of clinical abnormality. No difference was found in the rates of preterm delivery or abortion compared with a control group.[1]

1. Adam I,*et al.* Is praziquantel therapy safe during pregnancy? *Trans R Soc Trop Med Hyg* 2004; **98:** 540–3.

Interactions

Anthelmintics. For reference to plasma concentrations of the active metabolite of *albendazole* being increased by praziquantel, see p.139.

Antibacterials. A study[1] in healthy subjects found that oral *rifampicin* decreased plasma concentrations after single and multiple doses of oral praziquantel to subtherapeutic levels.

1. Ridtitid W, *et al.* Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. *Clin Pharmacol Ther* 2002; **72:** 505–13.

Antiepileptics. *Carbamazepine* and *phenytoin* have been reported to reduce the bioavailability of praziquantel.[1]

1. Quinn DI, Day RO. Drug interactions of clinical importance: an updated guide. *Drug Safety* 1995; **12:** 393–452.

Antimalarials. *Chloroquine* has been reported to reduce the bioavailability of praziquantel.[1]

1. Masimirembwa CM, *et al.* The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos* 1994; **15:** 33–43.

Corticosteroids. Corticosteroids may be used to reduce the inflammatory reactions that often occur within 2 to 3 days of starting cysticidal therapy. However, use is complicated by the fact that dexamethasone roughly halves the plasma concentration of praziquantel. It has therefore been suggested that when praziquantel is given in the 2-week treatment regimen, corticosteroids should not be given prophylactically but only if an inflammatory reaction develops. Dexamethasone is then given daily for 2 or 3 days and most of the treatment period will be free of pharmacokinetic interaction. When the short course praziquantel regimen is used (3 doses given 2 hours apart), the corticosteroid may be given prophylactically. The first dose of dexamethasone is given 4 hours after the last dose of praziquantel (when the concentration of praziquantel is starting to decrease and the pharmacological action is assumed to have been accomplished) and then daily for 2 to 3 days. No pharmacokinetic interaction would be expected at this point.[1]

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase praziquantel bioavailability.[1,2]

1. Metwally A, *et al.* Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. *Arzneimittelforschung* 1995; **45:** 516–18.
2. Jung H, *et al.* Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. *Antimicrob Agents Chemother* 1997; **41:** 1256–9.

Pharmacokinetics

Praziquantel is rapidly absorbed after oral doses; more than 80% of a dose is reported to be absorbed. Peak plasma concentrations occur 1 to 3 hours after a dose, but there is a pronounced first-pass effect and praziquantel undergoes rapid and extensive metabolism in the liver, being hydroxylated to metabolites that are thought to be inactive. It is distributed into the CSF. The plasma elimination half-life of praziquantel is about 1 to 1.5 hours and that of the metabolites about 4 hours.

It is excreted in the urine, mainly as metabolites, about 80% of the dose being eliminated within 4 days and more than 90% of this in the first 24 hours.

Praziquantel is distributed into breast milk.

◊ References.

1. Leopold G, *et al.* Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes: an example of a complex study covering both tolerance and pharmacokinetics. *Eur J Clin Pharmacol* 1978; **14:** 281–91.
2. Bühring KU, *et al.* Metabolism of praziquantel in man. *Eur J Drug Metab Pharmacokinet* 1978; **3:** 179–90.
3. Patzschke K, *et al.* Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokinet* 1979; **3:** 149–56.
4. Mandour M El M, *et al.* Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. *Trans R Soc Trop Med Hyg* 1990; **84:** 389–93.

Uses and Administration

Praziquantel is an anthelmintic with a broad spectrum of activity against trematodes (flukes) including all species of *Schistosoma* pathogenic to man, and against cestodes (tapeworms). It is used in the treatment of cysticercosis, diphyllobothriasis, hymenolepiasis, schistosomiasis, taeniasis, and intestinal, liver, and lung fluke infections. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p.134, and under the individual headings below.

Praziquantel is given orally with food.

In the treatment of schistosomiasis in adults and children over 4 years it is given on one day as three doses of 20 mg/kg at intervals of 4 to 6 hours or it is given as a single dose of 40 to 60 mg/kg (but see below).

Doses in adults and children over 4 years in the liver fluke infections clonorchiasis and opisthorchiasis are 25 mg/kg three times daily for one or two days or a single dose of 40 mg/kg. Similar doses may be used in intestinal fluke and lung fluke infections (see below).

Single doses of 5 to 25 mg/kg are used in adults and children over 4 years in tapeworm infections.

Praziquantel is used in adults and children over 4 years in the treatment of neurocysticercosis in a dose of 50 mg/kg daily in 3 divided doses for 14 days. An alternative regimen of 3 doses of 25 mg/kg every 2 hours has been proposed.

◊ Reviews.

1. Pearson RD, Guerrant RL. Praziquantel: a major advance in anthelmintic therapy. *Ann Intern Med* 1983; **99:** 195–8. Correction. *ibid.*; 574.
2. King CH, Mahmoud AAF. Drugs five years later: praziquantel. *Ann Intern Med* 1989; **110:** 290–6.
3. Cioli D, Pica-Mattocia L. Praziquantel. *Parasitol Res* 2003; **90** (suppl 1): S3–S9.

Cysticercosis. Praziquantel is used in the treatment of neurocysticercosis (p.135) although albendazole is also considered to be the drug of choice.

References.

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; **34:** 503–15.
2. Del Brutto OH, *et al.* Single-day praziquantel versus 1-week albendazole for neurocysticercosis. *Neurology* 1999; **52:** 1079–81.
3. OH Del Brutto, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med* 2006; **145:** 43–51.

Echinococcosis. Praziquantel may be used as an adjunct to surgery in echinococcosis (p.136). Praziquantel has been reported to possess a scolicidal effect *in vitro* against *Echinococcus granulosus*[1] and there has been a report of the successful treatment of disseminated peritoneal hydatid disease with praziquantel and surgery.[2] In this case praziquantel was effective against the small cysts; 2 large cysts were removed surgically, one before praziquantel was started. However, activity in 9 other patients given praziquantel was disappointing.[3] A combination of praziquantel with albendazole may be effective.[4]

1. Morris DL, *et al.* Protoscolicidal effect of praziquantel— in vitro and electron microscopical studies on Echinococcus granulosus. *J Antimicrob Chemother* 1986; **18:** 687–91.
2. Henriksen T-H, *et al.* Treatment of disseminated peritoneal hydatid disease with praziquantel. *Lancet* 1989; **i:** 272.
3. Piens MA, *et al.* Praziquantel dans l'hydatidose humaine: évaluation par traitement médical pré-opératoire. *Bull Soc Pathol Exot Filiales* 1989; **82:** 503–12.
4. Ayles HM, *et al.* A combined medical and surgical approach to hydatid disease: 12 years' experience at the Hospital for Tropical Diseases, London. *Ann R Coll Surg Engl* 2002; **84:** 100–105.

Intestinal fluke infections. Praziquantel is used in the treatment of intestinal fluke infections (p.136). In the treatment of fasciolopsiasis, heterophyiasis, and metagonimiasis, the usual recommended dose is 25 mg/kg three times daily for one day.[1] However, a single dose of 25 mg/kg has also been recommended.[2] Single doses of 15 mg/kg, 25 mg/kg, or 40 mg/kg all yielded a cure rate of 100% in a study in 72 primary-school children in Thailand who were harbouring *Fasciolopsis buski*, suggesting that a single dose of 15 mg/kg at bedtime might be tried.[3] In another study, 9 patients infected with the trematode *Nanophyetus salmincola* were treated with praziquantel 20 mg/kg three times daily for one day and were negative for eggs in their stools 2 to 12 weeks later,[4] and this has become the usual recommended dose.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. WHO. *WHO model formulary.* Geneva: WHO, 2004.
3. Harinasuta T, *et al.* Efficacy of praziquantel on fasciolopsiasis. *Arzneimittelforschung* 1984; **34:** 1214–15.
4. Fritsche TR, *et al.* Praziquantel for treatment of human Nanophyetus salmincola (Troglotrema salmincola) infection. *J Infect Dis* 1989; **160:** 896–9.

Liver fluke infections. Praziquantel is used in the treatment of clonorchiasis and opisthorchiasis, and has also been used in the treatment of fascioliasis (p.137) although in this latter infection bithionol or triclabendazole are preferred.

Various studies have shown praziquantel to be effective in clonorchiasis[1-4] and opisthorchiasis,[5,6] although one study in opisthorchiasis[7] showed that re-infection was common despite praziquantel therapy, particularly in those with heavy initial infection. A study in Thailand[8] confirmed that mass treatment for opisthorchiasis with a single dose of praziquantel was beneficial, although it was suggested that ideally treatment should be given twice a year.

While praziquantel is not the drug of choice for fascioliasis, there has been a report[9] of successful treatment of a patient with severe infection. Subsequent studies[10-12] have, however, shown praziquantel to be of little benefit.

1. Soh C-J. Clonorchis sinensis: experimental and clinical studies with praziquantel in Korea. *Arzneimittelforschung* 1984; **34:** 1156–9.
2. Chen C-Y, Hsieh W-C. Clonorchis sinensis: epidemiology in Taiwan and clinical experience with praziquantel. *Arzneimittelforschung* 1984; **34:** 1160–2.
3. Kuang Q-H, *et al.* Clonorchiasis: treatment with praziquantel in 50 cases. *Arzneimittelforschung* 1984; **34:** 1162–3.
4. Lee S-H. Large scale treatment of clonorchis sinensis infections with praziquantel under field conditions. *Arzneimittelforschung* 1984; **34:** 1227–8.
5. Bunnag D, *et al.* Opisthorchis viverrini: clinical experience with praziquantel in hospital for tropical diseases. *Arzneimittelforschung* 1984; **34:** 1173–4.
6. Ambroise-Thomas P, *et al.* Therapeutic results in opisthorchiasis with praziquantel in a reinfection-free environment in France. *Arzneimittelforschung* 1984; **34:** 1177–9.
7. Upatham ES, *et al.* Rate of re-infection by Opisthorchis viverrini in an endemic northeast Thai community after chemotherapy. *Int J Parasitol* 1988; **18:** 643–9.
8. Pungpak S, *et al.* Opisthorchis viverrini infection in Thailand: studies on the morbidity of the infection and resolution following praziquantel treatment. *Am J Trop Med Hyg* 1997; **56:** 311–14.
9. Schiappacasse RH, *et al.* Successful treatment of severe infection with Fasciola hepatica with praziquantel. *J Infect Dis* 1985; **152:** 1339–40.
10. Farag HF, *et al.* A short note on praziquantel in human fascioliasis. *J Trop Med Hyg* 1986; **89:** 79–80.
11. Farid Z, *et al.* Unsuccessful use of praziquantel to treat acute fascioliasis in children. *J Infect Dis* 1986; **154:** 920–1.
12. Farid Z, *et al.* Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82:** 299.

Lung fluke infections. Praziquantel is used in the treatment of the lung fluke infection paragonimiasis (p.137).

References.

1. Vanijanonta S, *et al.* Paragonimus heterotremus and other Paragonimus spp. in Thailand: pathogenesis clinic and treatment. *Arzneimittelforschung* 1984; **34:** 1186–8.
2. Pachucki CT, *et al.* American paragonimiasis treated with praziquantel. *N Engl J Med* 1984; **311:** 582–3.
3. De NV, *et al.* Epidemiology, symptoms and treatment of paragonimiasis in Sin Ho district, Lai Chau province, Vietnam. *Southeast Asian J Trop Med Public Health* 2000; **31** (suppl 1): 26–30.

Schistosomiasis. Praziquantel is the main drug[1,2] used in the treatment of schistosomiasis (p.138). It is effective against all species of schistosomes.[1] Doses are either 20 mg/kg given three times in one day or a single dose of 40 mg/kg. WHO considers[1] that in the field such a single-dose treatment will produce a cure rate of 60 to 90% with a reduction in egg count in those not cured of 90 to 95%. Good as such results are, a single dose or one day's sole treatment should not be considered to be all that is required to achieve a permanent cure or prevent re-infection, and any treatment plan should be reassessed after 6 or 12 months.[3,4] Such an approach with annual screening and targeted chemotherapy can provide, at least in some endemic areas, successful protection for children against intense infection and consequent hepatic disease.[4]

Several studies indicate that doses lower than those recommended above might be effective and in some control programmes 20 mg/kg might be enough for *S. haematobium*[5-7] or 30 mg/kg for *S. mansoni.*[5] The extent to which low doses contribute to resistance, as has been suggested with oxamniquine,[8] is unclear, but refractory infections have been reported. A 4-day treatment course was needed to produce a complete cure in a patient who relapsed twice following standard one-day treatment regimens.[9] Hepatic impairment, specifically hepatic fibrosis, is a feature of some schistosomal infections and patients with such liver involvement have benefited from treatment with praziquantel.[4,10]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993.
2. Doenhoff MJ, Pica-Mattoccia L. Praziquantel for the treatment of schistosomiasis: its use for control in areas with endemic disease and prospects for drug resistance. *Expert Rev Anti Infect Ther* 2006; **4:** 199–210.
3. Anonymous. The chemotherapy of schistosomiasis control. *Bull WHO* 1986; **64:** 23–5.
4. Anonymous. Mass treatment of schistosomiasis with praziquantel. *WHO Drug Inf* 1988; **2:** 184–5.
5. Taylor P, *et al.* Efficacy of low doses of praziquantel for Schistosoma mansoni and S. haematobium. *J Trop Med Hyg* 1988; **91:** 13–17.
6. King CH, *et al.* Dose-finding study for praziquantel therapy of Schistosoma haematobium in Coast Province, Kenya. *Am J Trop Med Hyg* 1989; **40:** 507–13.
7. Hatz C, *et al.* Ultrasound scanning for detecting morbidity due to Schistosoma haematobium and its resolution following treatment with different doses of praziquantel. *Trans R Soc Trop Med Hyg* 1990; **84:** 84–8.
8. Coles GC, *et al.* Tolerance of Kenyan Schistosoma mansoni to oxamniquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 782–5.
9. Murray-Smith SQ, *et al.* A case of refractory schistosomiasis. *Med J Aust* 1996; **165:** 458.
10. Zwingenberger K, *et al.* Praziquantel in the treatment of hepatosplenic schistosomiasis: biochemical disease markers indicate deceleration of fibrogenesis and diminution of portal flow obstruction. *Trans R Soc Trop Med Hyg* 1990; **84:** 252–6.

Taeniasis. Praziquantel is used in the treatment of taeniasis (p.139). It has been studied in the mass control of taeniasis when a single dose of 5 mg/kg was used.[1]

Praziquantel is also effective against the larval form of *Taenia solium* and is used to treat neurocysticercosis (see above).

1. Cruz M, *et al.* Operational studies on the control of Taenia solium taeniasis/cysticercosis in Ecuador. *Bull WHO* 1989; **67:** 401–7.

Preparations

USP 31: Praziquantel Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Prazitral; ***Austral.:*** Biltricide; ***Braz.:*** Cestox; Cisticid; ***Canad.:*** Biltricide; ***Chile:*** Cesol; Cisticid; ***Fr.:*** Biltricide; ***Ger.:*** Biltricide; Cesol; Cysticide; ***Gr.:*** Biltricide; ***Hong Kong:*** Biltricide; ***Israel:*** Biltricide; ***Mex.:*** Bio-Cest†; Cesol; Cisticid; Extiser-Q†; Prozitel†; Tecprazin; Teniken; Zifartel; ***Neth.:*** Biltricide; ***Rus.:*** Biltricid (Бильтрицид); ***S.Afr.:*** Biltricide; Cysticide; ***Thai.:*** Mycotricide; Opticide; Praquantel; Prasikon; Prazite; Wormicide; ***USA:*** Biltricide; ***Venez.:*** Cestox; Cisticid†.

Pyrantel Embonate *(BANM, rINNM)*

CP-10423-16; Embonato de pirantel; Pirantel Pamoat; Pirantel Pamoate; Pirantelio embonatas; Pyranteeliembonaatti; Pyrantel, embonate de; Pyrantel Pamoate *(USAN)*; Pyrantelembonat; Pyrantel-embonát; Pyranteli embonas; Pyrantelu embonian. 1,4,5,6-Tetrahydro-1-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Пирантела Эмбонат

$C_{11}H_{14}N_2S,C_{23}H_{16}O_6$ = 594.7.

CAS — 15686-83-6 (pyrantel); 22204-24-6 (pyrantel embonate); 33401-94-4 (pyrantel tartrate).

ATC — P02CC01.

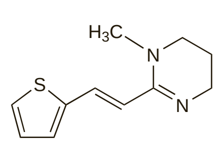

(pyrantel)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Pyrantel Embonate). A pale yellow or yellow powder. Practically insoluble in water and in methyl alcohol; soluble in dimethyl sulfoxide. Protect from light.

USP 31 (Pyrantel Pamoate). A yellow to tan solid. Practically insoluble in water and in methyl alcohol; soluble in dimethyl sulfoxide; slightly soluble in dimethylformamide. Protect from light.

Adverse Effects and Precautions

The adverse effects of pyrantel embonate are generally mild and transient. The most frequent are gastrointestinal effects such as nausea and vomiting, anorexia, abdominal pain, and diarrhoea. Other adverse effects reported include headache, dizziness, drowsiness, insomnia, skin rashes, and raised liver enzyme values.

Pyrantel embonate should be used with caution in patients with hepatic impairment.

Interactions

The anthelmintic effects of both pyrantel and piperazine may be antagonised when the two drugs are used together.

Pharmacokinetics

Only a small proportion of a dose of pyrantel embonate is absorbed from the gastrointestinal tract. Up to about 7% is excreted as unchanged drug and metabolites in the urine but over half of the dose is excreted unchanged in the faeces.

Uses and Administration

Pyrantel embonate is an anthelmintic effective against intestinal nematodes including roundworms (*Ascaris lumbricoides*), threadworms (*Enterobius vermicularis*), and *Trichostrongylus* spp., the tissue nematode *Trichinella spiralis*, and hookworms, although it is possibly less effective against *Necator americanus* hookworms than against *Ancylostoma duodenale*. Pyrantel embonate is one of the anthelmintics that may be used in the treatment of infections with these worms, as discussed under Choice of Anthelmintic, p.134. It appears to act by paralysing susceptible worms which are then dislodged by peristaltic activity.

Pyrantel is given orally as the embonate, but doses are described in terms of the base. Pyrantel embonate 2.9 g is equivalent to about 1 g of pyrantel.

Single or mixed infections due to susceptible worms in adults and children may be treated with the equivalent of pyrantel 10 mg/kg as a single oral dose. Ascariasis occurring alone may only require 5 mg/kg; a single dose of 2.5 mg/kg given three or four times a year has been used in mass treatment programmes. In necatoriasis, 10 mg/kg daily for 3 or 4 days or 20 mg/kg daily for 2 days may be necessary. The response in enterobiasis may be improved by repeating the 10 mg/kg dose after 2 to 4 weeks. In trichinosis, a dose of 10 mg/kg daily for 5 days has been used.

Pyrantel tartrate has been used as a veterinary anthelmintic.

Preparations

USP 31: Pyrantel Pamoate Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Aut†; ***Austral.:*** Anthel; Combantrin; Early Bird; ***Austria:*** Combantrin; ***Braz.:*** Ascarical; ***Canad.:*** Combantrin; Jaa Pyral; ***Chile:*** Combantrin; ***Fr.:*** Combantrin; Helmintox; ***Ger.:*** Helmex; ***Gr.:*** Combantrin†; ***Hong Kong:*** Combantrin; Pyrantin; Pyrantrin†; ***India:*** Nemocid; ***Indon.:*** Combantrin; Konvermex; Medicomtrin; Piraska; Proworm; ***Israel:*** Combantrin†; ***Ital.:*** Combantrin; ***Mex.:*** Combantrin; Pirantrim; ***NZ:*** Combantrin; ***Philipp.:*** Combantrin; Gelminthic; ***Port.:*** Combantrin; Vertel†; ***Rus.:*** Helmintox (Гельминтокс); Nemocid (Немоцид); ***S.Afr.:*** Combantrin; ***Singapore:*** Bearantel; ***Spain:*** Lombriareu; Trilombrin; ***Switz.:*** Cobantril; ***Thai.:*** Bantel†; Pyrapam; ***Turk.:*** Kontil; ***USA:*** Antiminth†; Pin-Rid; Pin-X; Reese's Pinworm; ***Venez.:*** Combantrin; Etimex†; Pamoval†; Pleosan†; Tamoa; Tenecha†.

Multi-ingredient: ***India:*** Mebex Plus; ***Indon.:*** Quantrel; ***Philipp.:*** Quantrel; ***Venez.:*** Dualid; Quantrel.

Pyrvinium Embonate *(rINNM)*

Embonato de pirvinio; Pirvinyum Pamoat; Pyrvinii Embonas; Pyrvinium, Embonate de; Pyrvinium Pamoate *(BAN)*; Viprynium Embonate; Viprynium Pamoate. Bis{6-dimethylamino-2-[2-(2,5-dimethyl-1-phenylpyrrol-3-yl)vinyl]-1-methylquinolinium} 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Пирвиния Эмбонат

$C_{52}H_{56}N_6,C_{23}H_{14}O_6$ = 1151.4.

CAS — 3546-41-6.

ATC — P02CX01.

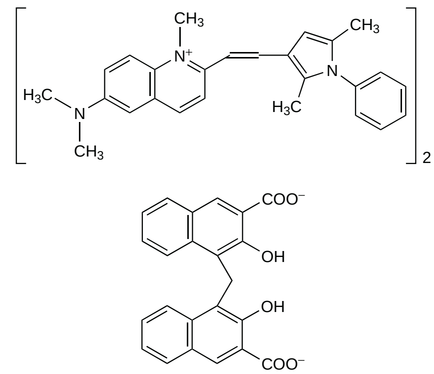

Pharmacopoeias. In *US.*

USP 31 (Pyrvinium Pamoate). A bright orange or orange-red to practically black crystalline powder. Practically insoluble in water and in ether; slightly soluble in chloroform and in methoxyethanol; freely soluble in glacial acetic acid; very slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects

Pyrvinium occasionally causes nausea, vomiting, abdominal pain, and diarrhoea. Hypersensitivity reactions and photosensitivity have been reported. Headache may occur.

Pyrvinium stains the stools bright red and may stain clothing if vomiting occurs.

Pharmacokinetics

Pyrvinium embonate is not significantly absorbed from the gastrointestinal tract.

Uses and Administration

Pyrvinium embonate is an effective anthelmintic in the treatment of enterobiasis (p.136), but has generally been superseded by other drugs.

Pyrvinium is given as the embonate but doses are described in terms of the base. Pyrvinium embonate 7.5 mg is equivalent to about 5 mg of pyrvinium.

It has been given orally in a single dose equivalent to pyrvinium 5 mg/kg, repeated after 2 to 3 weeks.

Preparations

USP 31: Pyrvinium Pamoate Oral Suspension; Pyrvinium Pamoate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Tru; ***Austria:*** Molevac; ***Braz.:*** Enterocid†; Pyr-Pam†; Pyverm; ***Canad.:*** Vanquin†; ***Denm.:*** Vanquin; ***Fin.:*** Pyrvin; ***Fr.:*** Povanyl; ***Ger.:*** Molevac; Pyrcon; ***Norw.:*** Vanquin; ***Spain:*** Pamoxan; ***Swed.:*** Vanquin; ***Turk.:*** Pirok.

Rafoxanide *(BAN, USAN, rINN)*

MK-990; Rafoxanida; Rafoxanidum. 3′-Chloro-4′-(4-chlorophenoxy)-3,5-di-iodosalicylanilide.

Рафоксанид

$C_{19}H_{11}Cl_2I_2NO_3$ = 626.0.

CAS — 22662-39-1.

ATC Vet — QP52AG05.

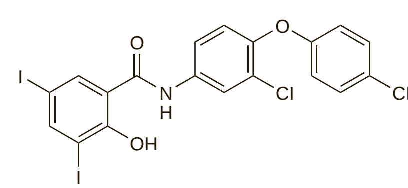

Profile

Rafoxanide is an anthelmintic used in veterinary medicine for the treatment of fascioliasis in cattle and sheep.

Santonin

Santoniini; Santonina; Santoninum. (3*S*,3a*S*,5a*S*,9b*S*)-3a,5,5a,9b-Tetrahydro-3,5a,9-trimethylnaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione.

Сантонин

$C_{15}H_{18}O_3$ = 246.3.
CAS — 481-06-1.

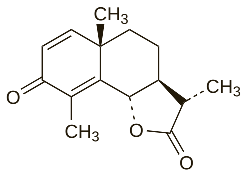

Pharmacopoeias. In *Jpn.*

Profile

Santonin is a crystalline lactone obtained from the dried unexpanded flowerheads of *Artemisia cina* (santonica, wormwood) and other species of *Artemisia* (Compositae). It was formerly used as an anthelmintic in the treatment of roundworm (*Ascaris*) infection, but has been superseded by other less toxic anthelmintics.

It is used as a flavour in food.

Selamectin *(USAN, rINN)*

Selamectina; Sélamectine; Selamectinum; Selamektiini; Selamektin; UK-124114. (2a*E*,4*E*,5′*S*,6*S*,6′*S*,7*S*,8*E*,11*R*,13*R*,15*S*,17a*R*,20a*R*,20b*S*)-6′-Cyclohexyl-7-[(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-3′,4′,5′,6,6′,7,10,11,14,15,20a,20b-dodecahydro-20b-hydroxy-5′,6,8,19-tetramethylspiro(11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*p*,*q*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran)-17,20(17a*H*)-dione 20-oxime.

Селамектин

$C_{43}H_{63}NO_{11}$ = 770.0.
CAS — 165108-07-6.
ATC Vet — QP54AA05.

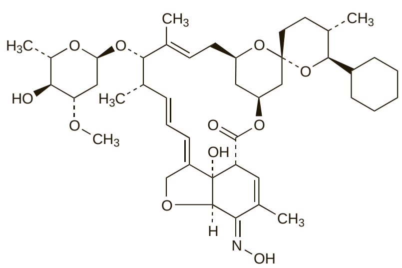

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Selamectin for Veterinary Use). A semi-synthetic product derived from a fermentation product. A white or almost white, hygroscopic powder. Practically insoluble in water; soluble in acetone and in dichloromethane; freely soluble in isopropyl alcohol; sparingly soluble in methyl alcohol. Store in airtight containers.

Profile

Selamectin is an avermectin anthelmintic and ectoparasiticide used in veterinary medicine.

Tetramisole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de tetramisol; ICI-50627; McN-JR-8299-11; R-8299; Tétramisole, Chlorhydrate de; Tetramisoli Hydrochloridum. (±)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride.

Тетрамизола Гидрохлорид

$C_{11}H_{12}N_2S,HCl$ = 240.8.
CAS — 5036-02-2 (tetramisole); 5086-74-8 (tetramisole hydrochloride).

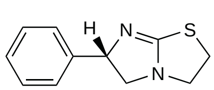

(tetramisole)

Pharmacopoeias. In *Fr.* for veterinary use only.

Profile

Tetramisole hydrochloride is an anthelmintic used in veterinary medicine for the control of nematode infections. It is a racemic mixture and the laevo-isomer, levamisole hydrochloride (p.147), accounts for most of its activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Ascarizole†; Tetramizotil†.
Multi-ingredient: *India:* Jetomisol-P.

Thiacetarsamide *(rINNM)*

Thiacétarsamide; Thiacetarsamidum; Tiacetarsamida. *p*-[Bis(carboxymethylmercapto)arsino]benzamide; 4-Carbamylphenyl bis[carboxymethylthio]arsenite.

Тиацетарсамид

$C_{11}H_{12}AsNO_5S_2$ = 377.3.
CAS — 531-72-6.
ATC Vet — QP52AX08.

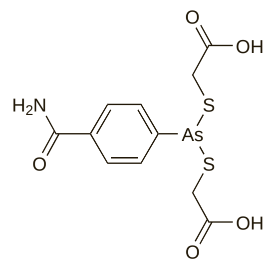

Profile

Thiacetarsamide is an anthelmintic used in veterinary medicine.

Thiophanate *(BAN)*

Tiofanato. 4,4′-*o*-Phenylenebis(ethyl 3-thioallophanate).

$C_{14}H_{18}N_4O_4S_2$ = 370.4.
CAS — 23564-06-9.
ATC Vet — QP52AC04.

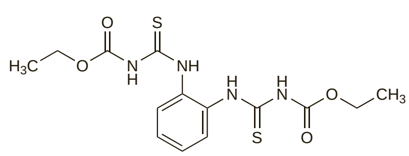

Profile

Thiophanate is an anthelmintic used in veterinary medicine for the control of nematode infections.

Tiabendazole *(BAN, rINN)*

E233; MK-360; Thiabendazole *(USAN)*; Tiabendatsoli; Tiabendazol; Tiabendazolas; Tiabendazolum. 2-(Thiazol-4-yl)-1*H*-benzimidazole.

Тиабендазол

$C_{10}H_7N_3S$ = 201.2.
CAS — 148-79-8.
ATC — D01AC06; P02CA02.
ATC Vet — QD01AC06; QP52AC10.

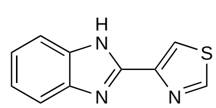

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Tiabendazole). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; it dissolves in dilute mineral acids. Protect from light.

USP 31 (Thiabendazole). A white to practically white, odourless or practically odourless, powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in chloroform and in ether.

Adverse Effects

Dizziness and gastrointestinal disturbances, especially anorexia, nausea and vomiting, diarrhoea, and abdominal pain are common during treatment with tiabendazole. Other adverse effects occurring occasionally include pruritus, skin rashes, headache, fatigue, drowsiness, drying of mucous membranes, hyperglycaemia, disturbance of vision including colour vision, leucopenia, tinnitus, effects on the liver including cholestasis and parenchymal damage (in some cases severe and irreversible), enuresis, crystalluria, and bradycardia and hypotension. There have also been reports of erythema multiforme, fatal Stevens-Johnson syndrome, toxic epidermal necrolysis, convulsions, and effects on mental state.

Fever, chills, angioedema, and lymphadenopathy have been reported, but may represent allergic response to dead parasites rather than to tiabendazole.

The urine of some patients taking tiabendazole may have a characteristic odour similar to that after eating asparagus; it is attributed to the presence of a tiabendazole metabolite.

Effects on the salivary glands. Dry mouth with swollen parotid and salivary glands suggestive of the sicca complex preceded the development of cholestatic jaundice in a 17-year-old boy given tiabendazole.[1]

1. Davidson RN, *et al.* Intrahepatic cholestasis after thiabendazole. *Trans R Soc Trop Med Hyg* 1988; **82:** 620.

Hypersensitivity. Severe erythema multiforme developed in a patient 16 days after a course of tiabendazole.[1] Many of the lesions encircled pre-existing melanocytic naevi.

1. Humphreys F, Cox NH. Thiabendazole-induced erythema multiforme with lesions around melanocytic naevi. *Br J Dermatol* 1988; **118:** 855–6.

Precautions

Tiabendazole should be used with caution in patients with hepatic or renal impairment. Tiabendazole causes drowsiness in some patients and those affected should not drive or operate machinery.

Tiabendazole should not be used in mixed worm infections involving *Ascaris lumbricoides* as it can cause these roundworms to migrate; live roundworms have emerged through the mouth or nose.

Pregnancy. Tiabendazole is teratogenic in *mice* although there are no adequate and well controlled studies in human pregnancy.

Renal impairment. Tiabendazole and its 5-hydroxy metabolite did not accumulate in an anephric patient on haemodialysis and haemoperfusion who was treated for severe strongyloidiasis.[1] However, the potentially toxic conjugated glucuronide and sulfate metabolites did accumulate. The clearance of all 3 metabolites was poor by haemodialysis; haemoperfusion was much more efficient, although for rapid removal the haemoperfusion columns should be changed every hour.

1. Bauer L, *et al.* The pharmacokinetics of thiabendazole and its metabolites in an anephric patient undergoing hemodialysis and hemoperfusion. *J Clin Pharmacol* 1982; **22:** 276–80.

Interactions

Xanthines. For the effect of tiabendazole on serum concentrations of *theophylline*, see p.1145.

Pharmacokinetics

Tiabendazole is readily absorbed from the gastrointestinal tract and reaches peak concentrations in the plasma after 1 to 2 hours. It is metabolised to 5-hydroxythiabendazole and excreted principally in the urine as glucuronide or sulfate conjugates; about 90% is recovered in the urine within 48 hours of ingestion, but only 5% in the faeces. Absorption may occur from preparations applied to the skin or eyes.

◊ References.

1. Tocco DJ, *et al.* Absorption, metabolism, and excretion of thiabendazole in man and laboratory animals. *Toxicol Appl Pharmacol* 1966; **9:** 31–9.

Uses and Administration

Tiabendazole, a benzimidazole derivative, is an anthelmintic with activity against most nematode worms; activity against some larval stages and ova has also been demonstrated. The mode of action is not certain, but tiabendazole may inhibit the fumarate-reductase system of worms thereby interfering with their source of energy.

Tiabendazole is used in the treatment of cutaneous larva migrans, dracunculiasis (guinea worm infection), and toxocariasis. It may also be used in the treatment of strongyloidiasis, and can provide symptomatic relief during the larval invasion stage of trichinosis. Tiabendazole is also active against some intestinal nematodes, but should not be used as primary therapy; the treatment of mixed infections including ascariasis is not recommended since tiabendazole may cause the worms to migrate to other body organs causing serious complications. For discussions of the treatment of the above infections see under Choice of Anthelmintic, p.134, and under the individual headings below.

Tiabendazole is given orally, with meals, usually in a dose of 25 mg/kg twice daily for 2 or more days, the duration depending on the type of infection; the daily dose should not exceed 3 g. For those unable to tolerate 2 doses daily, 25 mg/kg may be given after the largest meal on day 1 and repeated 24 hours later after a similar meal on day 2. For mass treatment, a single dose of 50 mg/kg after the evening meal is suggested although the incidence of adverse effects may be higher than with 2 doses of 25 mg/kg.

In cutaneous larva migrans, 25 mg/kg may be given twice daily for 2 days, repeated after 2 days if necessary; topical treatment with a 10 to 15% suspension intended for oral use has also been advocated as an alternative or adjunct to oral treatment.

In dracunculiasis, 25 to 50 mg/kg may be given twice daily for one day; in massive infection a further 50 mg/kg may be given after 5 to 8 days.

In strongyloidiasis, 25 mg/kg may be given twice daily for 2 or 3 days or 50 mg/kg as a single dose; when the infection is disseminated treatment for at least 5 days may be necessary.

In trichinosis, 25 mg/kg may be given twice daily for 2 to 4 successive days.

In toxocariasis, 25 mg/kg may be given twice daily for 5 to 7 days.

Tiabendazole also has some antifungal activity. It is used as a fungicidal preservative for certain foods.

Dracunculiasis. Tiabendazole[1,2] may be used for symptomatic treatment of dracunculiasis (p.136), although it has no direct anthelmintic effect. It is used to facilitate removal of the worm from subcutaneous tissues.

1. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57:** 683–9.
2. Kale OO, *et al.* Controlled comparative trial of thiabendazole and metronidazole in the treatment of dracontiasis. *Ann Trop Med Parasitol* 1983; **77:** 151–7.

Strongyloidiasis. Tiabendazole may be used in the treatment of strongyloidiasis (p.138), but albendazole or ivermectin are generally preferred.

References.

1. Grove DI. Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness. *Trans R Soc Trop Med Hyg* 1982; **76:** 114–18.
2. Barnish G, Barker J. An intervention study using thiabendazole suspension against strongyloides fuelleborni-like infections in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1987; **81:** 60–3.
3. Boken DJ, *et al.* Treatment of Strongyloides stercoralis hyperinfection syndrome with thiabendazole administered per rectum. *Clin Infect Dis* 1993; **16:** 123–6.
4. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169:** 1076–9.
5. Pitisuttithum P, *et al.* A randomized comparative study of albendazole and thiabendazole in chronic strongyloidiasis. *Southeast Asian J Trop Med Public Health* 1995; **26:** 735–8.
6. Schaffel R, *et al.* Thiabendazole for the treatment of strongyloidiasis in patients with hematologic malignancies. *Clin Infect Dis* 2000; **31:** 821–2.

Syngamosis. Tiabendazole has been used successfully[1,2] to treat syngamosis (p.138) when it has occurred in man.

1. Grell GAC, *et al.* Syngamus in a West Indian. *BMJ* 1978; **2:** 1464.
2. Leers W-D, *et al.* Syngamosis, an unusual case of asthma: the first reported case in Canada. *Can Med Assoc J* 1985; **132:** 269–70.

Preparations

BP 2008: Tiabendazole Tablets;
USP 31: Thiabendazole Oral Suspension; Thiabendazole Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Foldan; ***Austral.:*** Mintezol; ***Braz.:*** Benzol†; Foldan; Thiaben†; Thianax; Tiabenzol†; Tiadol; Tiaplex; ***Chile:*** Soldrin; ***Gr.:*** Mintezol; ***Mex.:*** Eprofil; ***Spain:*** Triasox†; ***USA:*** Mintezol; ***Venez.:*** Drofen†.

Multi-ingredient: ***Braz.:*** Derms; Eraverm-T†; Folderm Pomada; Forverm; Helmi-Ped†; Helmib†; Helmiben; Helmidrax†; Josverm†; Metiaben†; Micoplex; Neovermin; Octelmin†; Poliben†; Profium; Prohelmin†; Thiabena†; Vermilen Composto†; Vermol†; Zoles†.

Triclabendazole *(BAN, rINN)*

Triclabendazol; Triclabendazolum. 5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylthio)benzimidazole.

Триклабендазол

$C_{14}H_9Cl_3N_2OS$ = 359.7.
CAS — 68786-66-3.
ATC — P02BX04.
ATC Vet — QP52AC01.

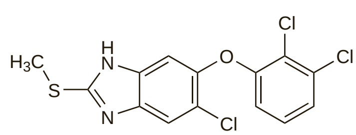

Profile

Triclabendazole is a benzimidazole anthelmintic used in veterinary medicine for the treatment of fascioliasis. It is also increasingly being used in the treatment of human fascioliasis, and is under investigation for the treatment of human paragonimiasis.

Liver fluke infections. Although bithionol or praziquantel are used to treat fascioliasis (p.137), some consider triclabendazole to be the drug of choice.[1] A suggested oral dose is 10 mg/kg, given as a single dose after food; the dose may be repeated once.[1] Several studies[2-7] have demonstrated the efficacy of triclabendazole in fascioliasis.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Apt W, *et al.* Treatment of human chronic fascioliasis with triclabendazole: drug efficacy and serologic response. *Am J Trop Med Hyg* 1995; **52:** 532–5.
3. El-Karaksy H, *et al.* Human fascioliasis in Egyptian children: successful treatment with triclabendazole. *J Trop Pediatr* 1999; **45:** 135–8.
4. Millán JC, *et al.* The efficacy and tolerability of triclabendazole in Cuban patients with latent and chronic Fasciola hepatica infection. *Am J Trop Med Hyg* 2000; **63:** 264–9.
5. Graham CS, *et al.* Imported Fasciola hepatica infection in the United States and treatment with triclabendazole. *Clin Infect Dis* 2001; **33:** 1–5.
6. Talaie H, *et al.* Randomized trial of a single, double and triple dose of 10 mg/kg of a human formulation of triclabendazole in patients with fascioliasis. *Clin Exp Pharmacol Physiol* 2004; **31:** 777–82.
7. Marcos LA, *et al.* Natural history, clinicoradiologic correlates, and response to triclabendazole in acute massive fascioliasis. *Am J Trop Med Hyg* 2008; **78:** 222–7.

Lung fluke infections. Encouraging results were reported from a pilot study of triclabendazole[1] in the treatment of paragonimiasis (p.137). In an open comparative study[2] in 62 patients, a more rapid parasitological response was obtained with triclabendazole in oral doses of 5 mg/kg once daily for 3 days, 10 mg/kg twice on one day, or 10 mg/kg as a single dose, than with praziquantel. Clinical symptoms resolved at a comparable rate in all groups. A later study compared the two one-day regimens in 154 patients.[3] After 3 months, the cure rates (assessed by clearance of eggs from sputum) were 84.4% in those given a single dose of 10 mg/kg, and 90.9% in those given two such doses on the same day. In those who were still infected at 3 months, a second two-dose course resulted in complete parasitological clearance at 1 year.

1. Ripert C, *et al.* Therapeutic effect of triclabendazole in patients with paragonimiasis in Cameroon: a pilot study. *Trans R Soc Trop Med Hyg* 1992; **86:** 417.
2. Calvopiña M, *et al.* Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg* 1998; **92:** 566–9.
3. Calvopiña M, *et al.* Comparison of two single-day regimens of triclabendazole for the treatment of human pulmonary paragonimiasis. *Trans R Soc Trop Med Hyg* 2003; **97:** 451–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Egaten.

Antibacterials

Drug Groups, p.158
Aminoglycosides, p.158
Antimycobacterials, p.159
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Macrolides, p.160
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Gastro-enteritis, p.171
Antibiotic-associated colitis, p.171
Campylobacter enteritis, p.172
Cholera and other vibrio infections, p.172
Escherichia coli enteritis, p.173
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Relapsing fever, p.189
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Staphylococcal infections, p.195
Surgical infection, p.195
Syphilis, p.196
Tetanus, p.196
Tonsillitis, p.196
Toxic shock syndrome, p.196
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Trench fever, p.196
Tuberculosis, p.196
Tularaemia, p.198
Typhoid and paratyphoid fever, p.198
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Urethritis, p.199
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This chapter includes antimicrobial drugs whose main use is the treatment and prophylaxis of bacterial infections. In practice the term 'antibiotics' is often, and in some instances erroneously, used to encompass all of these drugs. In *Martindale* the term antibacterial is preferred for the drugs in this chapter. The groups into which these drugs may be categorised are described below. Antibacterials described elsewhere in *Martindale* include metronidazole (p.837), nitazoxanide (p.842), and tinidazole (p.848), which, as well as being antiprotozoals, are used in the treatment of anaerobic bacterial infections.

Immunological approaches to the treatment and prophylaxis of bacterial infections are discussed under Vaccines Immunoglobulins and Antisera, p.2201.

In addition, disinfectants and preservatives (p.1622) are used to kill or inhibit the growth of micro-organisms.

Drug Groups

Although antibacterials are very diverse compounds they are often classified and discussed in groups. They may be classified according to their mode of action or spectrum of antimicrobial activity, but generally those with similar chemical structures are grouped together.

Aminoglycosides

The aminoglycosides are a closely related group of bactericidal antibacterials derived from bacteria of the order Actinomycetales or, more specifically, the genus *Streptomyces* (framycetin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin) and the genus *Micromonospora* (gentamicin and sisomicin). They are polycationic compounds that contain an aminocyclitol, usually 2-deoxystreptamine, or streptidine in streptomycin and related compounds, with cyclic amino-sugars attached by glycosidic linkages. Therefore, they have also been termed aminoglycosidic aminocyclitols. The sulfate salts are generally used.

The aminoglycosides have broadly similar toxicological features. Ototoxicity is a major limitation to their use; streptomycin and gentamicin are generally considered to be more toxic to the vestibular branch of the eighth cranial nerve and neomycin and kanamycin to be more toxic to the auditory branch. Other adverse effects common to the group include nephrotoxicity, neuromuscular blockade, and allergy, including cross-reactivity.

The pharmacokinetics of the aminoglycosides are very similar. Little is absorbed from the gastrointestinal tract but they are generally well distributed in the body after parenteral dosage although penetration into the CSF is poor. They are excreted unchanged in the urine by glomerular filtration.

The aminoglycosides have a similar antimicrobial spectrum and appear to act by interfering with bacterial protein synthesis, possibly by binding irreversibly to the 30S and to some extent the 50S portions of the bacterial ribosome. The manner in which they bring about cell death is not fully understood. They are most active against Gram-negative rods. *Staphylococcus aureus* is susceptible to the aminoglycosides but otherwise most Gram-positive bacteria, and also anaerobic bacteria, are naturally resistant. Aminoglycosides show enhanced activity with penicillins against some enterococci and streptococci. Bacterial resistance to streptomycin may occur by mutation, whereas with the other aminoglycosides it is usually associated with the plasmid-mediated production of inactivating enzymes which are capable of phosphorylation, acetylation, or adenylation. The aminoglycosides have a postantibiotic effect, that is antibacterial activity persisting after concentrations have dropped below minimum inhibitory concentrations.

Streptomycin was the first aminoglycoside to become available commercially and was isolated from a strain of *Streptomyces griseus* in 1944. Its use is now restricted mainly to the treatment of tuberculosis when it is always given with other antituberculous drugs because of the rapid development of resistance. *Dihydrostreptomycin*, a reduction product of streptomycin, is only rarely used because of its toxicity. The *neomycin* complex of antibacterials were the next to be isolated; neomycin itself is mainly a mixture of the B and C isomers and neomycin B is considered to be identical with *framycetin*. Because of their toxicity they are not given systemically. The related compound *paromomycin* (p.843) also has antiprotozoal and anthelmintic properties and may be used in the treatment of intestinal amoebiasis, cestode infections, cryptosporidiosis, and leishmaniasis. *Kanamycin* is less toxic than neomycin and can be used systemically. Although it has been used in penicillin-resistant gonorrhoea, it is not active against *Pseudomonas aeruginosa* and has generally been replaced by gentamicin and other newer aminoglycosides.

Gentamicin was isolated from *Micromonospora purpurea* in 1963 and, being active against *Ps. aeruginosa* and *Serratia marcescens*, is widely used in the treatment of life-threatening infections. *Tobramycin* is one of several components of the nebramycin complex of aminoglycosides produced by *Streptomyces tenebrarius*. It has an antimicrobial spectrum very similar to that of gentamicin and is reported to be more active against *Ps. aeruginosa*. *Amikacin*, a semisynthetic derivative of kanamycin, has a side-chain rendering it less susceptible to inactivating enzymes. It has a spectrum of activity like that of gentamicin but Gram-negative bacteria resistant to gentamicin, tobramycin, and kanamycin are often sensitive. *Sisomicin* is closely related structurally to gentamicin. *Netilmicin*, the *N*-ethyl derivative of sisomicin, may be active against some gentamicin-resistant strains of bacteria although not to the same extent as amikacin. Other aminoglycosides include *apramycin*, *arbekacin*, *astromicin*, *bekanamycin*, *dibekacin*, *etimicin*, *isepamicin*, and *micronomicin*.

Aminoglycosides should in general only be used for the treatment of serious infections because of their potential toxicity and antimicrobial spectrum. Doses must be carefully regulated to maintain plasma concentrations within the therapeutic range but avoid accumulation, especially in patients with renal impairment. Neomycin and framycetin, which are considered too toxic to be given parenterally, have been given orally to suppress the intestinal flora. The topical use of neomycin and gentamicin has been associated with allergic reactions and the emergence of resistant bacteria. Gentamicin or tobramycin are the drugs of choice in the treatment of life-threatening infections due to aminoglycoside-sensitive organisms and are often used with other antibacterials. With the continuing emergence of resistant strains, amikacin and netilmicin should be reserved for severe infections resistant to gentamicin and the other aminoglycosides.

Described in this chapter are

Amikacin, p.200	Gentamicin, p.282
Apramycin, p.205	Isepamicin, p.288
Arbekacin, p.206	Kanamycin, p.291
Astromicin, p.206	Micronomicin, p.300
Bekanamycin, p.211	Neomycin, p.305
Dibekacin, p.265	Netilmicin, p.306
Dihydrostreptomycin, p.266	Sisomicin, p.332
Etimicin, p.276	Streptomycin, p.333
Framycetin, p.279	Tobramycin, p.354

Antimycobacterials

The antimycobacterials are a miscellaneous group of antibacterials whose spectrum of activity includes *Mycobacterium* spp. and which are used in the treatment of tuberculosis, leprosy, and other mycobacterial infections. They include the rifamycins, also known as ansamycins or rifomycins, a group of antibacterials isolated from a strain of *Amycolatopsis mediterranei* (*Nocardia mediterranei*; *Streptomyces mediterranei*). The main antibacterial in this group, *rifampicin,* is a mainstay of regimens for the treatment of tuberculosis and leprosy, and is increasingly being used for other infections. The related drug *rifabutin* is also used in mycobacterial disease, especially nontuberculous mycobacterial infections due to *Mycobacterium avium* complex (MAC). Other rifamycins described in this chapter include *rifapentine*, *rifaximin* which is poorly absorbed and is mainly used for a local effect on the gastrointestinal tract, and *rifamycin sodium,* a rifamycin rarely used as it has been superseded by more effective drugs.

Another antimycobacterial widely used for tuberculosis is *isoniazid*, a derivative of isonicotinic acid; it is invariably used with other drugs to avoid or delay emergence of resistance. *Pyrazinamide,* a nicotinamide derivative, is also an important component of regimens for tuberculosis, while *ethambutol* and the aminoglycoside *streptomycin* are added when resistance to first-line drugs is likely. The thiosemicarbazone derivative *thioacetazone* is now less widely used in tuberculosis because of its toxicity and because more effective drugs are available, but is sometimes used in developing countries. Other drugs that have been used to treat tuberculosis including *aminosalicylic acid* and its salts, *capreomycin, cycloserine*, *ethionamide, protionamide*, and *kanamycin* are regarded as secondary drugs and are reserved for patients in whom resistance or toxicity to first-line drugs is a problem.

The sulfones have been used since the 1940s in the treatment of leprosy, but the only one widely used now is *dapsone*, an important component of multidrug regimens. Its action is thought to involve inhibition of folate metabolism, similarly to the sulfonamides, and dapsone is also used for the prophylaxis of malaria and for prophylaxis and treatment of pneumocystis pneumonia. Also important in the treatment of leprosy is the phenazine dye *clofazimine*. Additionally, it has a role in the treatment of type 2 lepra reactions and has been used in other mycobacterial infections. The thioamides *ethionamide* and *protionamide* have been used in the treatment of leprosy and tuberculosis, but have generally been replaced by less toxic drugs, for example *clarithromycin*, *ofloxacin*, *minocycline,* or *pefloxacin*, in alternative antileprotic regimens.

Described in this chapter are

Aminosalicylic Acid, p.201	Methaniazide, p.298
Capreomycin, p.215	Morinamide, p.302
Clofazimine, p.254	Protionamide, p.320
Cycloserine, p.260	Pyrazinamide, p.320
Dapsone, p.261	Rifabutin, p.323
Ethambutol, p.274	Rifampicin, p.325
Ethionamide, p.275	Rifamycin, p.329
Ftivazide, p.279	Rifapentine, p.329
Isoniazid, p.288	Rifaximin, p.330
	Thioacetazone, p.351

Cephalosporins and related beta lactams

The cephalosporins or cephem antibacterials are semisynthetic antibacterials derived from cephalosporin C, a natural antibacterial produced by the mould *Cephalosporium acremonium*. The active nucleus, 7-aminocephalosporanic acid, is very closely related to the penicillin nucleus, 6-aminopenicillanic acid, and consists of a beta-lactam ring fused with a 6-membered dihydrothiazine ring and having an acetoxymethyl group at position 3. Cephalosporin C has a side-chain at position 7 derived from D-α-aminoadipic acid. Chemical modification of positions 3 and 7 has resulted in a series of drugs with different characteristics. Substitution at the 7-amino group tends to affect antibacterial action whereas at position 3 it may have more of an effect on pharmacokinetic properties.

The cephalosporins are bactericidal and, like the penicillins, they act by inhibiting synthesis of the bacterial cell wall. The most widely used system of classification of cephalosporins is by generations and is based on the general features of their antibacterial activity, but may depend to some extent on when they were introduced. Succeeding generations generally have increasing activity against Gram-negative bacteria. *Cefalotin* was one of the first cephalosporins to become available and is representative of the **first-generation** cephalosporins. It has good activity against a wide spectrum of Gram-positive bacteria including penicillinase-producing, but not meticillin-resistant, staphylococci; enterococci are, however, resistant. Its activity against Gram-negative bacteria is modest. Cefalotin is not absorbed from the gastrointestinal tract and must be given parenterally although intramuscular dosage is painful. Cefalotin has generally been replaced by *cefazolin* or *cefradine*. *Cefaloridine* is now rarely used because of its nephrotoxicity. Cefradine is absorbed from the gastrointestinal tract and can be given both orally and by injection. *Cefadroxil, cefatrizine*, and *cefalexin* are all given orally. All of these drugs have a very similar spectrum of antimicrobial activity to cefalotin. *Cefaclor* is also given orally. It has similar activity to cefalotin against Gram-positive cocci, but because of its greater activity against Gram-negative bacteria, particularly *Haemophilus influenzae*, it is often classified as a second-generation drug. *Cefprozil* is an oral cephalosporin with a longer half-life than cefaclor.

Cefamandole was the first available **second-generation** cephalosporin. It has similar or slightly less activity than cefalotin against Gram-positive bacteria, but greater stability to hydrolysis by beta lactamases produced by Gram-negative bacteria and enhanced activity against many of the Enterobacteriaceae and *Haemophilus influenzae*. It is given parenterally. *Cefuroxime* has a similar spectrum of activity to cefamandole although it is even more resistant to hydrolysis by beta lactamases. It is given parenterally but, *cefuroxime axetil*, the acetoxyethyl ester of cefuroxime, is given orally. Other drugs classified as second-generation cephalosporins and given parenterally include *cefonicid, ceforanide*, and *cefotiam*; these all have spectra of activity similar to cefamandole. Cephamycins (see below) are also classified with second-generation cephalosporins.

The **third-generation** cephalosporins, sometimes referred to as **extended-spectrum** cephalosporins, are even more stable to hydrolysis by beta lactamases than cefamandole and cefuroxime. Compared with the earlier generations of cephalosporins they have a wider spectrum and greater potency of activity against Gram-negative organisms, including most clinically important Enterobacteriaceae. Their activity against Gram-positive organisms is said to be less than that of the first-generation drugs, but they are very active against streptococci. *Cefotaxime* was the first of this group to become available and it has relatively modest activity against *Pseudomonas aeruginosa*. *Cefmenoxime*, *cefodizime*, *ceftizoxime*, and *ceftriaxone* are all very similar to cefotaxime in their antimicrobial activity. These drugs are all given parenterally and differ mainly in their pharmacokinetic characteristics. *Cefixime* is a third-generation cephalosporin given by mouth; others include *cefdinir*, *cefetamet pivoxil*, *cefpodoxime proxetil*, and *ceftibuten*. *Ceftazidime* is typical of a group of parenteral third-generation cephalosporins with enhanced activity against *Ps. aeruginosa*. *Cefoperazone* is similar in its activity to ceftazidime. *Cefpiramide* is structurally related to cefoperazone and has comparable activity. Although *cefsulodin* is classified as a third-generation cephalosporin its activity against Gram-negative bacteria is confined to *Ps. aeruginosa*. *Latamoxef* is an **oxacephalosporin** which differs from the true cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by an oxygen atom. It differs from cefotaxime mainly in its enhanced activity against *Bacteroides fragilis*.

The newer cephalosporins *cefepime* and *cefpirome* are generally considered to be **fourth-generation** because of their broad spectrum of activity. *Ceftobiprole* is active against meticillin-resistant staphylococci.

The semisynthetic **cephamycins** are chemical modifications of cephamycin C, a beta-lactam antibacterial produced naturally by *Streptomyces* spp. They differ from the cephalosporins by the addition of a 7-α-methoxy group to the 7-aminocephalosporanic acid nucleus. Steric hindrance by this methoxy group is considered to be responsible for their greater stability to beta lactamases. For practical purposes they are generally classified with the second-generation cephalosporins, but are more active against anaerobic bacteria, especially *Bacteroides fragilis*. *Cefoxitin* was one of the first cephamycins available; *cefmetazole* and *cefotetan* have been introduced more recently. Another is *cefminox*. All these cephamycins must be given parenterally.

Imipenem was the first of the **carbapenem** group of antibacterials to become available; it is the *N*-formimidoyl derivative of thienamycin which is produced by *Streptomyces cattleya*. It is bactericidal, and, similarly to the cephalosporins, acts by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of antimicrobial activity including Gram-positive and Gram-negative aerobic and anaerobic organisms; it has good activity against both *Ps. aeruginosa* and *B. fragilis*. Imipenem is given parenterally with cilastatin, a dehydropeptidase I inhibitor that inhibits the renal metabolism of imipenem. Similarly, the carbapenem panipenem is given with the renal protectant betamipron. Two other carbapenems, *ertapenem* and *meropenem*, are relatively stable to renal dehydropeptidase and can be used without such an inhibitor. Ertapenem has a narrower spectrum of activity than other carbapenems, including no activity against *Ps. aeruginosa*. *Doripenem* is a carbapenem claimed to have particular activity against *Ps. aeruginosa*.

The **monobactams** were first identified as monocyclic beta lactams isolated from bacteria; they are now produced synthetically. *Aztreonam* was the first commercially available monobactam. It is bactericidal with a similar action on bacterial cell-wall synthesis to the cephalosporins. Its antimicrobial activity, however, differs from imipenem and the newer cephalosporins in that it is restricted to Gram-negative aerobic organisms. It has good activity against *Ps. aeruginosa*. Aztreonam is given parenterally. Other monobactams include *carumonam*.

Carbacephems are structurally related to the cephalosporins, but the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by a methylene group. *Loracarbef* is an oral carbacephem.

Described in this chapter are

Aztreonam, p.209	Cefotiam, p.230
Betamipron, p.215	Cefovecin, p.230
Biapenem, p.215	Cefoxitin, p.230
Carumonam, p.217	Cefozopran, p.231
Cefaclor, p.217	Cefpiramide, p.231
Cefadroxil, p.218	Cefpirome, p.231
Cefalexin, p.218	Cefpodoxime, p.232
Cefalonium, p.219	Cefprozil, p.232
Cefaloridine, p.219	Cefquinome, p.233
Cefalotin, p.219	Cefradine, p.233
Cefamandole, p.220	Cefsulodin, p.233
Cefapirin, p.221	Ceftazidime, p.234
Cefatrizine, p.221	Cefteram, p.235
Cefazolin, p.222	Ceftezole, p.235
Cefbuperazone, p.222	Ceftibuten, p.235
Cefcapene, p.223	Ceftiofur, p.236
Cefdinir, p.223	Ceftizoxime, p.236
Cefditoren, p.223	Ceftobiprole, p.236
Cefepime, p.223	Ceftriaxone, p.237
Cefetamet, p.224	Cefuroxime, p.238
Cefixime, p.224	Cilastatin, p.243
Cefmenoxime, p.225	Doripenem, p.266
Cefmetazole, p.225	Ertapenem, p.269
Cefminox, p.226	Faropenem, p.276
Cefodizime, p.226	Flomoxef, p.276
Cefonicid, p.226	Imipenem, p.286
Cefoperazone, p.227	Latamoxef, p.292
Ceforanide, p.227	Loracarbef, p.295
Cefoselis, p.228	Meropenem, p.297
Cefotaxime, p.228	Panipenem, p.313
Cefotetan, p.229	

Chloramphenicols

Chloramphenicol is an antibacterial which was first isolated from cultures of *Streptomyces venezuelae* in 1947 but is now produced synthetically. It has a relatively simple structure and is a derivative of dichloroacetic acid with a nitrobenzene moiety. Chloramphenicol was the first broad-spectrum antibacterial to be discovered; it acts by interfering with bacterial protein synthesis and is mainly bacteriostatic. Its range of activity is similar to that of tetracycline and includes Gram-positive and Gram-negative bacteria, Rickettsia spp., and Chlamydiaceae. The sensitivities of *Salmonella typhi, Haemophilus influenzae*, and

Bacteroides fragilis to chloramphenicol have dictated the principal indications for its use.

Shortly after its introduction chloramphenicol was found to have a serious and sometimes fatal depressant effect on the bone marrow. The 'grey syndrome', another potentially fatal adverse effect, was reported later in neonates. As a result of this toxicity the systemic use of chloramphenicol has been restricted in many countries; it should only be given when there is no suitable alternative and never for minor infections.

Chloramphenicol is active when given orally and, unlike most other antibacterials, it diffuses into the CSF even when the meninges are not inflamed. The majority of a dose is inactivated in the liver, only a small proportion appearing unchanged in the urine.

Chloramphenicol is widely used for typhoid fever, although resistance is a problem in some countries. For *Haemophilus influenzae* infections, especially meningitis, the emergence of ampicillin-resistant strains led to a reappraisal of the use of chloramphenicol, and suggestions that ampicillin and chloramphenicol should both be given empirically to patients with meningitis until the sensitivity of the infecting organisms was known, but the newer third-generation cephalosporins are increasingly preferred because of resistance. For proven *H. influenzae* meningitis, chloramphenicol is used as an alternative to the third-generation cephalosporins, which are now regarded as treatment of choice. Chloramphenicol is also effective against many anaerobic bacteria and may be valuable in such conditions as cerebral abscess where anaerobes such as *Bacteroides fragilis* are often involved, although metronidazole may be preferred.

Chloramphenicol sodium succinate is used parenterally and the palmitate is given orally. Ophthalmic and other topical preparations of chloramphenicol are used widely in some countries.

Thiamphenicol is a semisynthetic derivative of chloramphenicol in which the nitro group on the benzene ring has been replaced by a methylsulfonyl group, resulting, in general, in a loss of activity *in vitro*. It has been claimed that thiamphenicol is less toxic than chloramphenicol and there have been fewer reports of aplastic anaemia but reversible bone-marrow depression may occur more frequently. It is also less likely to cause the 'grey syndrome'. Unlike chloramphenicol, thiamphenicol is not metabolised in the liver to any extent and is excreted largely unchanged in the urine. It has been used similarly to chloramphenicol in some countries.

Azidamfenicol is another analogue of chloramphenicol that has been used topically in the treatment of eye infections.

Described in this chapter are

Azidamfenicol, p.206
Chloramphenicol, p.239
Florfenicol, p.277
Thiamphenicol, p.351

Glycopeptides

Vancomycin has a glycopeptide structure; it acts by interfering with bacterial cell wall synthesis and is very active against Gram-positive cocci. Intravenous vancomycin is reserved for the treatment of severe staphylococcal infections and for the treatment and prophylaxis of endocarditis when other antibacterials cannot be used, either because of patient sensitivity or bacterial resistance. It is the treatment of choice for infections caused by meticillin-resistant staphylococci. Vancomycin hydrochloride is poorly absorbed when taken orally; it is used in the treatment of pseudomembranous colitis. *Teicoplanin* is a glycopeptide with similar properties to vancomycin, but a longer duration of action. It can be given intramuscularly as well as intravenously. *Ramoplanin* is under investigation, especially for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for the prevention of infection due to vancomycin-resistant enterococci. Also under investigation are *dalbavancin* and *oritavancin*.

Described in this chapter are

Avoparcin, p.206
Dalbavancin, p.261
Norvancomycin, p.310
Oritavancin, p.311
Ramoplanin, p.323
Teicoplanin, p.344
Vancomycin, p.358

Lincosamides

Lincomycin is an antibacterial produced by a strain of *Streptomyces lincolnensis* and was first described in 1962; *clindamycin* is the 7-chloro-7-deoxy derivative of lincomycin.

Although not related structurally to erythromycin and the other macrolide antibacterials, the lincosamides have similar antimicrobial activity and act at the same site on the bacterial ribosome to suppress protein synthesis.

The lincosamides are bacteriostatic or bactericidal, depending on the concentration, and are active mainly against Gram-positive bacteria, and against *Bacteroides* spp. They also appear to have some antiprotozoal activity. Clindamycin and lincomycin have qualitatively similar activity but clindamycin is more active than lincomycin *in vitro*. Cross-resistance occurs between the lincosamides, macrolides, and streptogramins.

The lincosamides have been used, like erythromycin, as an alternative to penicillin, but reports of severe and sometimes fatal pseudomembranous colitis in association with lincomycin and clindamycin have led to the recommendation that they should only be used when there is no suitable alternative.

Both lincomycin and clindamycin can be given orally and parenterally, but clindamycin is much better absorbed from the gastrointestinal tract and less affected by the presence of food in the stomach. They both penetrate well into bone and have been used successfully in osteomyelitis. They have also been used topically in the treatment of acne vulgaris.

The main indication for the use of lincosamides is now in the treatment of severe anaerobic infections, although metronidazole (p.839) or some beta lactams may be a more suitable choice in such infections. Clindamycin also has a role in the prophylaxis of endocarditis in penicillin-allergic patients and has been used, usually with other antiprotozoals, in babesiosis, chloroquine-resistant malaria, toxoplasmosis, and pneumocystis pneumonia.

Described in this chapter are

Clindamycin, p.251
Lincomycin, p.293
Pirlimycin, p.316

Macrolides

The macrolides are a large group of antibacterials mainly derived from *Streptomyces* spp. and having a common macrocyclic lactone ring to which one or more sugars are attached. They are all weak bases and only slightly soluble in water. Their properties are very similar and in general they have low toxicity and a similar spectrum of antimicrobial activity with cross-resistance between individual members of the group. The macrolides are bacteriostatic or bactericidal, depending on the concentration and the type of micro-organism, and are thought to interfere with bacterial protein synthesis. Their antimicrobial spectrum is similar to that of benzylpenicillin but they are also active against such organisms as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and some rickettsias, chlamydias, and chlamydophilas. Macrolides and related drugs have a postantibiotic effect: that is, antibacterial activity persists after concentrations have dropped below the minimum inhibitory concentration.

Erythromycin was discovered in 1952 and is the macrolide used most widely. It is destroyed by gastric acid and must therefore be given as enteric-coated formulations or as one of its more stable salts or esters such as the stearate or ethyl succinate. Hepatotoxicity has been reported after the use of erythromycin, most commonly as the estolate. Erythromycin lactobionate or gluceptate may be given intravenously. Cardiac arrhythmias have been reported occasionally after intravenous use. Erythromycin is used as an alternative to penicillin in many infections, especially in patients who are allergic to penicillin. It has similar uses to tetracycline in the treatment of infections due to *Mycoplasma pneumoniae* and *Chlamydia trachomatis*, and in acne vulgaris. It is also used in the treatment of infections caused by *Legionella pneumophila*.

More recently developed macrolides include *azithromycin*, *clarithromycin*, *dirithromycin*, and *roxithromycin*. These drugs all appear to have similar properties to erythromycin although they may differ in their pharmacokinetics. Clarithromycin and, to a lesser extent, azithromycin are more active than erythromycin against opportunistic mycobacteria such as *Mycobacterium avium* complex. Clarithromycin is also used in the treatment of leprosy and in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease. Both azithromycin and clarithromycin have activity against protozoa including *Toxoplasma gondii*.

Flurithromycin is another newer macrolide in use.

Other macrolides include *spiramycin*, which has been used extensively in Europe and has also been used in the treatment and prophylaxis of toxoplasmosis. It may be useful in the treatment of cryptosporidiosis.

Oleandomycin has been used orally and parenterally as the phosphate. Its ester, *troleandomycin*, is better absorbed from the gastrointestinal tract but, like erythromycin estolate, has proved hepatotoxic and more effective antibacterials are generally preferred. *Josamycin*, *kitasamycin*, *midecamycin*, and *rokitamycin* have been used in Europe and/or Japan. *Meleumycin* has been used in China.

Tilmicosin, *tulathromycin*, and *tylosin* are used in veterinary practice.

The **streptogramin** group of antibacterials are also derived from *Streptomyces* spp. and include *pristinamycin* and *virginiamycin*. They consist of two components that act synergistically and are therefore also known as synergistins. One of the components is structurally related to the macrolides, and they have a similar spectrum of antimicrobial activity to erythromycin. Semisynthetic derivatives such as *quinupristin/dalfopristin* may be useful in the treatment of infections with multidrug-resistant organisms including meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

Cross-resistance is often observed between the macrolides, lincosamides, and streptogramins. The **ketolide** antibacterials *telithromycin* and *cethromycin* are semisynthetic derivatives of erythromycin A that have been developed to overcome macrolide resistance in respiratory-tract pathogens.

Described in this chapter are

Azithromycin, p.207
Cethromycin, p.239
Clarithromycin, p.248
Dirithromycin, p.266
Erythromycin, p.269
Flurithromycin, p.278
Josamycin, p.291
Kitasamycin, p.292
Meleumycin, p.297
Midecamycin, p.300
Oleandomycin, p.311
Pristinamycin, p.319
Quinupristin/Dalfopristin, p.322
Rokitamycin, p.330
Roxithromycin, p.331
Spiramycin, p.333
Telithromycin, p.345
Tilmicosin, p.354
Troleandomycin, p.357
Tulathromycin, p.357
Tylosin, p.357
Virginiamycin, p.361

Penicillins

Penicillin was the first antibacterial to be used therapeutically and was originally obtained, as a mixture of penicillins known as F, G, X, and K, from the mould *Penicillium notatum*. Better yields were achieved using *P. chrysogenum* and benzylpenicillin (penicillin G) was selectively produced by adding the precursor phenylacetic acid to the fermentation medium. The term 'penicillin' is now used generically for the entire group of natural and semisynthetic penicillins. Penicillins are still widely used; they are generally well tolerated, apart from hypersensitivity reactions, and are usually bactericidal by virtue of their inhibitory action on the synthesis of the bacterial cell wall.

Penicillins all have the same ring structure and are monobasic acids that readily form salts and esters; 6-aminopenicillanic acid, the penicillin nucleus, consists of a fused thiazolidine ring and a beta-lactam ring with an amino group at the 6-position.

The earlier or so-called 'natural' penicillins were produced by adding different side-chain precursors to fermentations of the *Penicillium* mould; *benzylpenicillin*, with a phenylacetamido side-chain at the 6-position, and *phenoxymethylpenicillin* (penicillin V), with a phenoxyacetamido side-chain, were 2 of the first and are still widely used. Benzylpenicillin can be considered the parent compound of the penicillins and is active mainly against Gram-positive bacteria and *Neisseria* spp. It is inactivated by penicillinase-producing bacteria and because of its instability in gastric acid it is usually injected. Long-acting preparations include *procaine benzylpenicillin* and *benzathine benzylpenicillin*, which slowly release benzylpenicillin after injection. Phenoxymethylpenicillin is acid-stable and is therefore given orally but it is also inactivated by penicillinase. It is generally used for relatively mild infections.

When no side-chain precursor is added to the fermentation medium, 6-aminopenicillanic acid itself is obtained. A range of penicillins has been synthesised from 6-aminopenicillanic acid by substitution at the 6-amino position in an effort to improve on the instability of benzylpenicillin to gastric acid and penicillinases, to widen its antimicrobial spectrum, and to reduce its rapid rate of renal excretion. Phenoxypenicillins with an α-phenoxypropionamido (*pheneticillin*) or α-phenoxybutyramido (*propicillin*) side-chain are more stable to acid than benzylpenicillin but offer no advantage over phenoxymethylpenicillin.

Meticillin has a 2,6-dimethoxybenzamido group at the 6-position and was the first penicillin found to be resistant to destruction by staphylococcal penicillinase. However, it is not acid-resistant and has to be injected. The isoxazolyl penicillins, *cloxacillin*, *dicloxacillin*, *flucloxacillin*, and *oxacillin*, are resistant to penicillinase and gastric acid. They have very similar chemical structures and differ mainly in their absorption characteristics. *Nafcillin* is a similar penicillinase-resistant antibacterial but is irregularly absorbed when taken orally.

Ampicillin has a D(−)-α-aminophenylacetamido side-chain and a broader spectrum of activity than benzylpenicillin; although generally less active against Gram-positive bacteria, some Gram-negative organisms including *Escherichia coli*, *Haemophilus influenzae*, and *Salmonella* spp. are sensitive although resistance is being reported increasingly. *Pseudomonas* spp. are not sensitive. Ampicillin is acid-stable and can be given orally but is destroyed by penicillinase. A number of prodrugs including *bacampicillin*, *metampicillin*, and *pivampicillin* are also said to be better absorbed and are hydrolysed to ampicillin *in vivo*. *Amoxicillin*, with a D(−)-α-aminohydroxyphenylacetamido side-chain, only differs from ampicillin by the addition of a hydroxyl group, but is better absorbed from the gastrointestinal tract.

Carbenicillin, with an α-carboxyphenylacetamido side-chain, has marked activity against *Pseudomonas aeruginosa* and some *Proteus* spp. but otherwise is generally less active than ampicillin. It has to be given by injection and large doses are required. *Carfecillin* and *carindacillin* are the phenyl and indanyl esters of carbenicillin respectively and are hydrolysed to carbenicillin *in vivo* when taken orally. *Sulbenicillin* has an α-phenylsulfoacetamido side-chain and *ticarcillin* an α-carboxythienylacetamido side-chain and both have similar activity to carbenicillin; ticarcillin is more active against *Ps. aeruginosa*. The ureidopenicillins *azlocillin* and *mezlocillin*, and the closely related drug *piperacillin* are more active than carbenicillin against *Ps. aeruginosa* and have a wider range of activity against Gram-negative bacteria.

Temocillin, a 6-α-methoxy derivative of ticarcillin, is resistant to many beta lactamases and is active against most Gram-negative aerobic bacteria, but not *Ps. aeruginosa*.

Mecillinam is a penicillanic acid derivative with a substituted amidino group in the 6-position. Unlike the 6-aminopenicillanic acid derivatives it is active mainly against Gram-negative bacteria, although *Ps. aeruginosa*, and *Bacteroides* spp. are considered resistant. Mecillinam itself is not active orally; it is given as *pivmecillinam*, which is hydrolysed to mecillinam on absorption.

The beta-lactamase inhibitors *clavulanic acid*, *sulbactam*, and *tazobactam* are used to extend the antimicrobial range of certain beta-lactam antibacterials.

Described in this chapter are

Amoxicillin, p.202
Ampicillin, p.204
Aspoxicillin, p.206
Azidocillin, p.206
Azlocillin, p.208
Bacampicillin, p.210
Benethamine Penicillin, p.212
Benzathine Benzylpenicillin, p.212
Benzathine Phenoxymethylpenicillin, p.212
Benzylpenicillin, p.213
Carbenicillin, p.216
Carfecillin, p.217
Carindacillin, p.217
Ciclacillin, p.243
Clavulanic Acid, p.250
Clemizole Penicillin, p.251
Clometocillin, p.255
Cloxacillin, p.256
Dicloxacillin, p.265
Flucloxacillin, p.277
Mecillinam, p.297
Metampicillin, p.298
Meticillin, p.299
Mezlocillin, p.299
Nafcillin, p.303
Oxacillin, p.311
Penethamate, p.314
Pheneticillin, p.314
Phenoxymethylpenicillin, p.314
Piperacillin, p.315
Pivampicillin, p.316
Pivmecillinam, p.317
Procaine Benzylpenicillin, p.319
Propicillin, p.319
Sulbactam, p.335
Sulbenicillin, p.335
Sultamicillin, p.344
Tazobactam, p.344
Temocillin, p.346
Ticarcillin, p.352

Quinolones

The quinolonecarboxylic acids, carboxyquinolones, or 4-quinolones are a group of synthetic antibacterials structurally related to nalidixic acid. The term 4-quinolone has been used as a generic name for the common 4-oxo-1,4-dihydroquinoline skeleton. Under this system nalidixic acid, a naphthyridene derivative, is an 8-aza-4-quinolone, cinoxacin, a cinnoline derivative, is a 2-aza-4-quinolone, and pipemidic and piromidic acids, pyrido-pyrimidine derivatives, are 6,8-diaza-4-quinolones.

Nalidixic acid is active against Gram-negative bacteria but has little activity against *Pseudomonas* and Gram-positive organisms. Because bactericidal concentrations can only be achieved in urine its use has generally been limited to the treatment of urinary-tract infections.

Modification of the structure of nalidixic acid has produced related antibacterials such as *oxolinic acid*, *cinoxacin*, and *rosoxacin*. Although some of these have a greater activity *in vitro* against Gram-negative organisms and activity against some Gram-positive organisms, none has been considered to represent a significant clinical advance over nalidixic acid; rosoxacin is only used in the treatment of gonorrhoea. Addition of a piperazinyl radical at position 7, as in *pipemidic acid*, appears to confer some activity against *Pseudomonas*. *Flumequine* was the first fluorinated 4-quinolone to be synthesised, but has no piperazinyl group. Addition of the 7-piperazinyl group and a fluorine atom at position 6 has produced a group of fluorinated piperazinyl quinolones or **fluoroquinolones** with a broader spectrum of activity than nalidixic acid and pharmacokinetic properties more suitable for the treatment of systemic infections. They include *ciprofloxacin*, *enoxacin*, *fleroxacin*, *gatifloxacin*, *gemifloxacin*, *levofloxacin*, *lomefloxacin*, *moxifloxacin*, *nadifloxacin*, *norfloxacin*, *ofloxacin*, *pazufloxacin*, *pefloxacin*, *rufloxacin*, *sparfloxacin*, and *trovafloxacin*. Trovafloxacin and its prodrug, *alatrofloxacin*, have been withdrawn worldwide after reports of unpredictable hepatotoxicity, including some fatalities. Other fluoroquinolones withdrawn because of toxicity include: *clinafloxacin*, *grepafloxacin*, and *temafloxacin*. *Danofloxacin*, *enrofloxacin*, *ibafloxacin*, *marbofloxacin*, *orbifloxacin*, and *sarafloxacin* are used in veterinary practice. Development of *difloxacin* for human use was suspended because of the high incidence of adverse effects, but it is used in veterinary practice.

The fluoroquinolones are very active against aerobic Gram-negative bacilli and cocci including the Enterobacteriaceae, *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* and are also active against *Pseudomonas aeruginosa*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*, although some fluoroquinolones now developed have increased activity against these organisms. They also have activity against mycobacteria, mycoplasmas, and rickettsias. Some, for example ofloxacin, have useful activity against *Chlamydia trachomatis*. Activity against anaerobic bacteria is generally poor. There is concern that the emergence of resistant strains of organisms may limit the usefulness of fluoroquinolones.

One disadvantage of the quinolone antibacterials is that they are generally not recommended for use in children, adolescents, and pregnant or breast-feeding women because of their propensity to cause joint erosions in immature *animals*.

Described in this chapter are

Alatrofloxacin, p.200
Balofloxacin, p.211
Cinoxacin, p.243
Ciprofloxacin, p.243
Danofloxacin, p.261
Difloxacin, p.265
Enoxacin, p.268
Enrofloxacin, p.269
Fleroxacin, p.276
Flumequine, p.278
Garenoxacin, p.281
Gatifloxacin, p.281
Gemifloxacin, p.281
Ibafloxacin, p.286
Levofloxacin, p.292
Lomefloxacin, p.295
Marbofloxacin, p.296
Moxifloxacin, p.302
Nadifloxacin, p.303
Nalidixic Acid, p.303
Norfloxacin, p.309
Ofloxacin, p.310
Orbifloxacin, p.311
Oxolinic Acid, p.312
Pazufloxacin, p.313
Pefloxacin, p.313
Pipemidic Acid, p.315
Piromidic Acid, p.316
Prulifloxacin, p.320
Rosoxacin, p.330
Rufloxacin, p.331
Sarafloxacin, p.331
Sparfloxacin, p.332
Tosufloxacin, p.355
Trovafloxacin, p.357

Sulfonamides and diaminopyrimidines

The sulfonamides are analogues of *p*-aminobenzoic acid. The first sulfonamide of clinical importance was *Prontosil*, an azo dye that is metabolised *in vivo* to *sulfanilamide*. It was synthesised in Germany in 1932. Many sulfonamides have since been synthesised; they differ only slightly in their antimicrobial activity, but vary in their pharmacokinetic properties. The sulfonamides have been classified according to their rate of excretion as short-, medium- or intermediate-, long-, and ultra-long-acting. The **short-acting** sulfonamides are excreted in the urine in high concentrations and have therefore been of particular use in the treatment of urinary-tract infections. The solubility in urine of earlier short-acting sulfonamides, such as *sulfapyridine*, and their acetyl metabolites is low and hence crystalluria has been reported frequently. Of the short-acting sulfonamides most commonly used, *sulfadiazine* also has low solubility in urine whereas *sulfadimidine* and *sulfafurazole* and their acetyl conjugates are very soluble. Three short-acting sulfonamides (triple sulfonamides) have been given together to reduce the risk of crystalluria, as the constituent sulfonamides can co-exist in solution in urine without affecting each other's solubility. Preparations of mixed sulfonamides have, however, generally been replaced by the more soluble sulfonamides. The **medium-acting** sulfonamides such as *sulfamethoxazole*, the **long-acting** sulfonamides such as *sulfadimethoxine*, *sulfamethoxypyridazine*, and *sulfametoxydiazine*, and the **ultra-long-acting** sulfonamides such as *sulfadoxine* and *sulfametopyrazine* do not attain such high concentrations in the urine and rarely cause crystalluria. Sulfonamides that are slowly excreted from the body do appear, however, to have been more commonly implicated in the development of reactions such as the Stevens-Johnson syndrome.

The sulfonamides are usually bacteriostatic, and interfere with folic acid synthesis of susceptible organisms; their broad spectrum of antimicrobial activity has, however, been limited by the development of resistance. The clinical use of sulfonamides has therefore been greatly reduced; in general they are indicated only in the treatment of urinary-tract infections and a few other disorders such as nocardiosis. Sulfonamides such as *sulfaguanidine*, *succinylsulfathiazole*, *phthalysulfacetamide*, and *phthalylsulfathiazole* are poorly absorbed from the gastrointestinal tract and have been used for the treatment of gastrointestinal infections although they are now rarely indicated. *Sulfadiazine silver*, *sulfathiazole silver*, and *mafenide* are applied topically for their antibacterial action in patients with burns. *Sulfasalazine* (p.1773), a conjugate of 5-aminosalicylic acid (mesalazine) and sulfapyridine, is used in the treatment of inflammatory bowel diseases and in rheumatoid arthritis.

Trimethoprim is a diaminopyrimidine that also inhibits folic acid synthesis but at a different stage in the metabolic pathway to that inhibited by the sulfonamides. It has a similar spectrum of antimicrobial activity to sulfonamides and often shows synergy *in vitro* with these drugs. Trimethoprim was initially available only in combination with sulfonamides, most commonly with sulfamethoxazole as co-trimoxazole. It is now used alone particularly in the treatment of infections of the urinary and respiratory tracts. Analogues of trimethoprim include *baquiloprim*, *brodimoprim*, *ormetoprim*, and *tetroxoprim*.

Co-trimoxazole generally replaced use of sulfonamides alone in the treatment of systemic infections, although its use has also been restricted in some countries and trimethoprim may be preferred. Co-trimoxazole is however indicated for pneumocystis pneumonia and nocardiosis and may be useful in protozoal infections such as toxoplasmosis. Other sulfonamides which have been combined with trimethoprim include sulfadiazine (see *co-trimazine*), sulfamethoxypyridazine, sulfametopyrazine, sulfametrole, and sulfamoxole (see *co-trifamole*). Sulfadiazine has been used with tetroxoprim (see *co-tetroxazine*).

Sulfonamides have also been used with pyrimethamine (p.610) in the treatment or prophylaxis of some protozoal infections. Common combinations are sulfadoxine and pyrimethamine for malaria, and sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.

Described in this chapter are

Baquiloprim, p.211
Brodimoprim, p.215
Co-tetroxazine, p.257
Co-trifamole p.257
Co-trimazine, p.258
Co-trimoxazole, p.258
Formosulfathiazole, p.278
Mafenide, p.296
Ormetoprim, p.311
Phthalylsulfacetamide, p.315
Phthalylsulfathiazole, p.315
Succinylsulfathiazole, p.334
Sulfabenzamide, p.335
Sulfacarbamide, p.335
Sulfadimidine, p.338
Sulfadoxine, p.338
Sulfafurazole, p.338
Sulfaguanidine, p.339
Sulfamerazine, p.339
Sulfamethizole, p.339
Sulfamethoxazole, p.340
Sulfamethoxypyridazine, p.342
Sulfamethylthiazole, p.342
Sulfametopyrazine, p.342
Sulfametrole, p.342
Sulfamonomethoxine, p.342
Sulfamoxole, p.342
Sulfanilamide, p.343
Sulfapyridine, p.343

Sulfacetamide, p.335
Sulfachlorpyridazine, p.336
Sulfachrysoidine, p.336
Sulfaclozine, p.336
Sulfadiazine, p.336
Sulfadiazine Silver, p.337
Sulfadicramide, p.337
Sulfadimethoxine, p.337
Sulfaquinoxaline, p.343
Sulfasuccinamide, p.343
Sulfathiazole, p.343
Sulfathiazole Silver, p.343
Sulfatroxazole, p.343
Sulfisomidine, p.344
Tetroxoprim, p.350
Trimethoprim, p.355

Tetracyclines

The tetracyclines are a group of antibacterials, originally derived from certain *Streptomyces* spp., having the same tetracyclic nucleus, naphthacene, and similar properties. Unlike the penicillins and aminoglycosides they are usually bacteriostatic at the concentrations achieved in the body but act similarly to the aminoglycosides by interfering with protein synthesis in susceptible organisms.

Tetracyclines all have a broad spectrum of activity which includes Gram-positive and Gram-negative bacteria, chlamydias and chlamydophilas, rickettsias, mycoplasmas, spirochaetes, some mycobacteria, and some protozoa, but the emergence of resistant strains and the development of other antimicrobials has often reduced their value. Adverse effects have also restricted their usefulness. Gastrointestinal disturbances are common and other important toxic effects include deposition in bones and teeth, precluding their use in pregnancy and young children; antianabolic effects, especially in patients with renal impairment; fatty changes in the liver; and photosensitivity, especially with demeclocycline. Allergic reactions are relatively uncommon. Because of these adverse effects tetracyclines should be avoided in pregnant women, children, and, apart from doxycycline and minocycline, patients with renal impairment.

The first tetracycline to be introduced was *chlortetracycline* in 1948 and, like chloramphenicol which was discovered at about the same time, it was found to have a broad spectrum of activity and to be active orally unlike benzylpenicillin or streptomycin, the only other antibacterials then in use. The discovery of chlortetracycline was followed closely by that of *oxytetracycline* and then *tetracycline*, a reduction product of chlortetracycline which may be produced semisynthetically. All three have very similar properties, although chlortetracycline is less well absorbed and oxytetracycline may cause less staining of teeth. *Demeclocycline*, demethylated chlortetracycline, has a longer half-life than tetracycline but is more often associated with phototoxic reactions. It has been used with some success in patients with the syndrome of inappropriate secretion of antidiuretic hormone.

These four tetracyclines are all natural products that have been isolated from *Streptomyces* spp. The more recent tetracyclines, namely methacycline, doxycycline, and minocycline, are semisynthetic derivatives. *Methacycline*, like demeclocycline, has a longer half-life than tetracycline and has been given twice daily. *Doxycycline* and *minocycline* are both more active *in vitro* than tetracycline against many species. More importantly, minocycline is active against some tetracycline-resistant bacteria, including strains of staphylococci. Both are well absorbed and, unlike the other tetracyclines, absorption is not significantly affected by the presence of food. They can be given in lower doses than the older members of the group and, having long half-lives, doxycycline is usually given once daily and minocycline twice daily. Also, they do not accumulate significantly in patients with renal impairment and can, with care, be given to such patients; however, usual doses of minocycline can lead to higher serum concentrations resulting in possible liver toxicity. Both doxycycline and minocycline are more lipid-soluble than the other tetracyclines and they penetrate well into tissues. The use of minocycline may, however, be limited by its vestibular adverse effects.

Tetracyclines are not generally the antibacterials of choice in Gram-positive or Gram-negative infections because of the emergence of resistant organisms and the discovery of drugs with narrower antimicrobial spectra. However, they have a place in the treatment of chlamydial infections, rickettsial infections such as typhus and the spotted fevers, mycoplasmal infections such as atypical pneumonia, pelvic inflammatory disease, Lyme disease, brucellosis, tularaemia, plague, cholera, periodontal disease, and acne. The tetracyclines have also been useful in the treatment of penicillin-allergic patients suffering from venereal diseases, actinomycosis, bronchitis, and leptospirosis. Minocycline may sometimes be used in multidrug regimens for leprosy. Doxycycline may be used for the treatment and prophylaxis of malaria; it is also used in the management of anthrax.

Described in this chapter are
Chlortetracycline, p.242
Demeclocycline, p.264
Doxycycline, p.267
Lymecycline, p.296
Meclocycline, p.297
Methacycline, p.298
Minocycline, p.300
Oxytetracycline, p.312
Rolitetracycline, p.330
Tetracycline, p.347

Miscellaneous Antibacterials

Spectinomycin is an aminocyclitol antibacterial with some similarities to streptomycin although it is not an aminoglycoside. Spectinomycin is active against a wide range of bacteria but its clinical use is restricted to the treatment of chancroid and gonorrhoea. Trospectomycin, a water-soluble derivative, has been investigated.

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens* with activity against most strains of staphylococci and streptococci and also some Gram-negative bacteria. It is applied topically.

Fosfomycin is a derivative of phosphonic acid; it is active against a range of Gram-positive and Gram-negative bacteria and is given by mouth or parenterally.

The fusidane antibacterial *fusidic acid* is derived from *Fusidium coccineum* and has a narrow spectrum of antibacterial activity, but it is very active against *Staphylococcus aureus* and has been used both topically and systemically in the treatment of staphylococcal infections. Resistance develops readily and it is often used with other antibacterials.

The polymyxins are basic antibacterials produced by the growth of different strains of *Bacillus polymyxa* (*B. aerosporus*). *Polymyxin B* and *colistin* have been used clinically, but their systemic use has been more or less abandoned because of their toxicity, notably to the kidneys and nervous system. They are not absorbed when taken orally and have therefore been given in gastrointestinal infections for their bactericidal activity against Gram-negative bacteria. They continue to be widely used as components of topical preparations.

Bacitracin, gramicidin, gramicidin S, and *tyrothricin* are polypeptide antibacterials also produced by certain strains of *Bacillus* spp. but they are active against Gram-positive bacteria. Like the polymyxins, they are toxic when used systemically and are therefore mainly used topically.

The halogenated hydroxyquinoline *clioquinol* has antibacterial, antifungal, and antiprotozoal activity. It was formerly used in gastrointestinal infections including amoebiasis but is of little value and can produce severe neurotoxicity. It is now mainly used locally for superficial infections of the skin and external ear. *Chlorquinaldol* and *halquinol* are used similarly.

Urinary antimicrobials such as *nitrofurantoin*, and also *methenamine* which has generally been given as the hippurate or mandelate, may be used in the treatment and prophylaxis of infections of the lower urinary tract. They are concentrated in the urine, but do not usually achieve antimicrobial concentrations in the blood.

The oxazolidinone *linezolid* has activity against Gram-positive organisms including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is used in infections of the skin and respiratory tract due to these organisms.

The glycylcycline *tigecycline* has activity against Gram-positive bacteria, including meticillin-resistant *Staph. aureus*, and also against some Gram-negative and some anaerobic bacteria. It is used in the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.

The pleuromutilin antibacterial *retapamulin* is derived from the fungus *Clitopilus passeckerianus*; it has activity against *Staphylococcus aureus* and *Streptococcus pyogenes*. It is applied topically.

Described in this chapter are
Acediasulfone, p.200
Arsanilic Acid, p.206
Avilamycin, p.206
Bacitracin, p.210
Bambermycin, p.211
Broxyquinoline, p.215
Carbadox, p.216
Chlorquinaldol, p.242
Clioquinol, p.254
Clofoctol, p.255
Colistin, p.256
Daptomycin, p.264
Mupirocin, p.302
Nifuroxazide, p.307
Nifurpirinol, p.307
Nifurtoinol, p.307
Nifurzide, p.307
Nisin, p.307
Nitrofurantoin, p.308
Nitrofurazone, p.309
Nitroxoline, p.309
Novobiocin, p.310
Polymyxin B, p.317
Retapamulin, p.323
Fosfomycin, p.278
Furaltadone, p.279
Furazidin, p.279
Fusafungine, p.279
Fusidic Acid, p.279
Gramicidin S, p.286
Gramicidin, p.286
Halquinol, p.286
Linezolid, p.293
Magainins, p.296
Mandelic Acid, p.296
Methenamine, p.298
Spectinomycin, p.332
Sulfamazone, p.339
Taurolidine, p.344
Terizidone, p.347
Thenoic Acid, p.351
Thiostrepton, p.352
Tiamulin, p.352
Tigecycline, p.353
Trospectomycin, p.357
Tyrothricin, p.358
Valnemulin, p.358
Xibornol, p.361

Choice of Antibacterial

Ideally, antibacterial treatment of infections should be chosen after the infecting organisms have been identified and the results of sensitivity tests are known. In practice, empirical treatment is often necessary initially, bearing in mind local patterns of infection and resistance. Other factors such as site of infection and tissue penetration are also important in deciding which antibacterial to give.

The prophylactic use of antibacterials is restricted mainly to patients undergoing some types of surgery. Other groups requiring infection prophylaxis include patients at special risk of developing endocarditis and those who have had rheumatic fever, who are splenectomised, or who are immunocompromised.

Abscess, abdominal

See under Abscess, Liver, below, and under Peritonitis, p.184.

Abscess, brain

Brain abscesses can result from otitis media, sinusitis, trauma, or dental sepsis, or they may be metastatic secondary to, for example, lung abscesses. Opportunistic infections in immunocompromised patients may present as brain abscesses.

Treatment of brain abscesses entails removal of pus or excision and use of high doses of antibacterials. Ideally the choice of antibacterial depends on the infecting organisms and penetration by the antibacterial into brain tissue and abscess pus. Until organisms can be cultured empirical treatment should be given.

There is very little good quality published information on the treatment of brain abscess. For many years, combined treatment with benzylpenicillin and chloramphenicol was the mainstay of empirical therapy, but a report by the British Society for Antimicrobial Chemotherapy,[1] based on published information and the authors' expertise, recommended the following regimens for first-line empirical treatment, according to the site of the abscess and origin of the infection:

- for frontal lobe abscesses originating from infection of the paranasal sinuses or teeth, a combination of metronidazole with one of cefuroxime, cefotaxime, or ceftriaxone
- for temporal lobe or cerebellar abscesses originating from infection of the middle ear or sphenoidal sinuses, ampicillin and metronidazole with either ceftazidime or gentamicin
- for abscesses associated with penetrating trauma, flucloxacillin, cefuroxime, cefotaxime, or ceftriaxone
- for metastatic abscesses, usually in the area supplied by the middle cerebral artery, one of cefuroxime, cefotaxime, or ceftriaxone, with or without metronidazole, or, if associated with endocarditis or cyanotic congenital heart disease, benzylpenicillin

Similar suggestions have been made by a more recent review,[2] which also suggested the use of oxacillin with metronidazole and a third-generation cephalosporin for empirical management of abscesses associated with penetrating trauma, and vancomycin plus a third-generation cephalosporin for abscess occurring postoperatively.

1. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. The rational use of antibiotics in the treatment of brain abscess. *Br J Neurosurg* 2000; **14:** 525–30.
2. Lu C-H, *et al.* Strategies for the management of bacterial brain abscess. *J Clin Neurosci* 2006; **13:** 979–85.

Abscess, liver

Bacteria commonly responsible for pyogenic liver abscesses include Enterobacteriaceae, especially *Escherichia coli* and in some countries[1] *Klebsiella pneumo-*

niae; anaerobes, especially *Bacteroides fragilis*; and *Streptococcus milleri* (these can be microaerophilic). As elsewhere in the abdomen (see under Peritonitis, p.184), infections are often mixed. Treatment involves percutaneous aspiration and drainage of pus and the use of high doses of antibacterials.[2,3] Broad-spectrum empirical therapy should be started immediately; more specific therapy may be possible when the results of cultures following diagnostic percutaneous aspiration of the abscess are known. Gentamicin with clindamycin has been commonly used[4,5] but other antibacterial combinations, involving cefoxitin, chloramphenicol, carboxypenicillins, third-generation cephalosporins, and metronidazole, might be appropriate.[5] A regimen of ampicillin, gentamicin, and metronidazole has become standard in some centres, but may be hazardous in patients with *Klebsiella*-related liver abscess, in whom a combination of an aminoglycoside with either an extended-spectrum beta-lactam such as piperacillin or a second- or third-generation cephalosporin, may be preferred.[1] Antibacterial therapy has been successful without surgical intervention, but may not be consistently so,[6] although this might be due to inadequate treatment against enteric anaerobes, especially *B. fragilis*.[5]

For the treatment of amoebic liver abscess, see under Amoebiasis in Antiprotozoals, p.822.

1. Lederman ER, Crum NF. Pyogenic liver abscess with a focus on Klebsiella pneumoniae as a primary pathogen: an emerging disease with unique clinical characteristics. *Am J Gastroenterol* 2005; **100:** 322–31.
2. Barakate MS, *et al*. Pyogenic liver abscess: a review of 10 years' experience in management. *Aust N Z J Surg* 1999; **69:** 205–9.
3. Alvarez Pérez JA, *et al*. Clinical course, treatment, and multivariate analysis of risk factors for pyogenic liver abscess. *Am J Surg* 2001; **181:** 177–86.
4. Herbert DA, *et al*. Pyogenic liver abscesses: successful non-surgical therapy. *Lancet* 1982; **i:** 134–6.
5. Herbert DA, *et al*. Medical management of pyogenic liver abscesses. *Lancet* 1985; **i:** 1384.
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Abscess, lung

Lung abscesses are often secondary to aspiration pneumonia and are discussed under Pneumonia, p.186. The organisms involved are commonly anaerobic bacteria.

Actinomycosis

Actinomycosis is mainly caused by the oral commensal *Actinomyces israelii*, a Gram-positive anaerobic or microaerophilic bacterium. Other species sometimes responsible include *A. meyeri*, *A. naeslundii*, and *A. viscosus*. One of the commonest forms has been cervicofacial actinomycosis, generally associated with poor oral hygiene and dental procedures.[1] Other forms include abdominal, thoracic,[2] and disseminated actinomycosis; pelvic actinomycosis is associated with the use of intra-uterine contraceptive devices.

The antibacterial of choice is benzylpenicillin given intravenously in high doses for 2 to 6 weeks, followed by an oral penicillin (e.g. phenoxymethylpenicillin or amoxicillin) for 6 to 12 months.[2] There is evidence that actinomycosis can be successfully treated with less prolonged regimens of penicillin; however, short-course treatment regimens are generally not advised for patients with large lesions and/or abdominal disease unless surgical debridement is performed.[2] Tetracycline is an alternative in patients allergic to penicillin; other alternatives include erythromycin or clindamycin. In one patient, actinomycosis resistant to conventional treatment responded to a prolonged course of ciprofloxacin.[3] Other antibacterials used successfully to treat actinomycosis include intravenous imipenem for 6 to 10 weeks and parenteral ceftriaxone for 3 weeks followed by oral ampicillin for 3 months.[2]

1. Anonymous. Essential drugs: systemic mycoses. *WHO Drug Inf* 1991; **5:** 129–36.
2. Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis* 2004; **38:** 444–7.
3. Macfarlane DJ, *et al*. Treatment of recalcitrant actinomycosis with ciprofloxacin. *J Infect* 1993; **27:** 177–80.

Anaerobic bacterial infections

Anaerobic bacteria predominate in the normal microbial flora of man and are a common cause of infections, especially those arising from the gastrointestinal tract, upper respiratory tract, skin, or vagina. Common anaerobic pathogens are *Bacteroides*, *Prevotella* (formerly non-fragilis *Bacteroides*), *Fusobacterium*, *Clostridium*, *Peptostreptococcus*, and *Actinomyces* spp. Apart from single species infections such as tetanus, gas gangrene, pseudomembranous colitis, and actinomycosis, most anaerobic infections are of mixed aetiology. Abscesses are often a feature. Infections include: brain abscess; acute necrotising gingivitis and other periodontal infections; chronic otitis media and chronic sinusitis; aspiration pneumonia and lung abscess; peritonitis and intra-abdominal abscess; bacterial vaginosis and pelvic inflammatory disease; cellulitis, ulcers, bites, and other wound infections.[1]

Sensitivity testing *in vitro* is often impractical and treatment is usually empirical.[1-4] Benzylpenicillin was traditionally considered the antibacterial of choice when *B. fragilis* was unlikely (infections above the diaphragm) although resistance is increasingly a problem. Antibacterials with activity against the *B. fragilis* group and other anaerobic pathogens include metronidazole and other 5-nitroimidazole derivatives, chloramphenicol, clindamycin, cefoxitin, antipseudomonal penicillins, imipenem-cilastatin, and combinations of a beta lactam and a beta-lactamase inhibitor.[2]

Surveys of susceptibility patterns in clinical isolates of anaerobic bacteria have shown increasing resistance of the *B. fragilis* group (including *B. distasonis*, *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*) to clindamycin, continuing penicillin resistance in non-fragilis *Bacteroides* spp. (now reclassified as *Prevotella* spp. and including the type species *P. melaninogenica*), and rare beta-lactamase-mediated resistance of *Fusobacterium* to penicillin. Resistance of some *Clostridium* spp. to penicillin and clindamycin had declined, but no changes were noted for *Cl. perfringens*. The emergence of multi-drug resistant anaerobes has been noted.[5]

The *B. fragilis* group are the most frequently isolated anaerobic bacteria in clinical infections and all members of the group may be pathogenic.[6] Most strains produce beta lactamase and thus are resistant to penicillins and cephalosporins although there is varied susceptibility within the group.[7] In a survey of susceptibility patterns[8] the most active drugs *in vitro* against *B. fragilis* group strains were imipenem, metronidazole, and chloramphenicol; resistance to cefoxitin, clindamycin, and piperacillin was not widespread and combinations of beta-lactamase inhibitors with penicillins or cephalosporins (e.g. ampicillin or cefoperazone with sulbactam; ticarcillin with clavulanate) were also very active. Others have reported similar results.[7] On the basis of activity *in vitro* in another study[9] metronidazole, imipenem, ticarcillin with clavulanate, cefoxitin, and amoxicillin with clavulanate were considered suitable for the treatment of *B. fragilis* group infections. However, a more recent commentary[5] suggested that cefoxitin and clindamycin were no longer drugs of choice due to increasing resistance. A clinical isolate of *B. fragilis*, simultaneously resistant to metronidazole, amoxicillin with clavulanate, and imipenem, was reported in the UK;[10] treatment with clindamycin was successful on this occasion. Tigecycline is considered promising for the management of anaerobic infections; other drugs with potential for oral therapy may include nitazoxanide, ramoplanin, and rifaximin.[5]

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2. Styrt B, Gorbach SL. Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections (second of two parts). *N Engl J Med* 1989; **321:** 298–302.
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7. Cuchural GJ, *et al*. Comparative activities of newer β-lactam agents against members of the Bacteroides fragilis group. *Antimicrob Agents Chemother* 1990; **34:** 479–80.
8. Cornick NA, *et al*. The antimicrobial susceptibility patterns of the Bacteroides fragilis group in the United States, 1987. *J Antimicrob Chemother* 1990; **25:** 1011–19.
9. Jacobs MR, *et al*. β-Lactamase production, β-lactam sensitivity and resistance to synergy with clavulanate of 737 Bacteroides fragilis group organisms from thirty-three US centres. *J Antimicrob Chemother* 1990; **26:** 361–70.
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Anthrax

Anthrax is caused by *Bacillus anthracis*, a spore-forming Gram-positive aerobe found in the soil. It most commonly infects herbivorous mammals. Humans can become infected by contact with infected animals or infected or contaminated animal products, or by inhalation of anthrax spores. Person-to-person transmission has not been reported. Although rare in western countries it remains a problem in many areas, including Africa, Asia, some southern European countries, the Americas, and parts of Australia. Anthrax has also been used as a weapon for biological warfare.

In humans anthrax presents most often in the cutaneous form. Gastrointestinal or inhalation anthrax can also occur and in these types the prognosis is poor without prompt treatment. In *cutaneous* anthrax symptoms may develop within hours, or up to 12 days, after contact and initially involves a painless, pruritic papule, which enlarges to an ulcer. Later (2 to 6 days) a vesicle with a black eschar develops. The incubation period for *inhalation* anthrax is usually about 10 days. Initial symptoms are non-specific and resemble a flu-like illness with fever, non-productive cough, dyspnoea, fatigue, headache, malaise, sweats, weakness, abdominal pain, and vomiting. This initial stage may last from a few hours to days and is followed in some patients by a short period of recovery while others progress directly to respiratory failure. *Gastrointestinal* anthrax has an incubation period of up to 1 week (usually 2 to 5 days) and initial symptoms are fever, abdominal pain, nausea, vomiting, gastric ulcers, haematemesis, and diarrhoea (usually bloody). Systemic disease progresses rapidly and hypotension, shock, and death may occur 2 to 5 days after initial symptoms.

The **treatment** of naturally occurring anthrax has traditionally been with benzylpenicillin with ciprofloxacin or doxycycline (or other tetracycline) as alternatives. Other drugs with *in vitro* activity are aminoglycosides, amoxicillin, chloramphenicol, clindamycin, imipenem, linezolid, the macrolides, meropenem, rifampicin, and vancomycin.[1-3] There are currently no clinical trial data on the optimal treatment for anthrax and treatment recommendations and guidelines[1-3] are based largely on the experience gained during the 1979 incident in Sverdlovsk (accidental release of biological warfare agents), the 2001 attack in the USA (deliberate release), isolated case reports of naturally occurring disease, and *in vitro* data. Because of the risks of engineered drug-resistant strains of *B. anthracis*, inducible beta-lactamases, and *in vitro* resistance to ofloxacin, guidelines[1-3] for the treatment of anthrax (occurring after deliberate release) recommend the use of 2 or more antibacterials which should be started as soon as possible. Corticosteroids may be given as adjunctive therapy. For the treatment of *inhalation* and *gastrointestinal* anthrax intravenous ciprofloxacin or oral doxycycline plus one or two additional antibacterials with *in vitro* activity are recommended until antimicrobial susceptibility is known. Treatment should be given for 60 days. For *cutaneous* anthrax, oral ciprofloxacin or oral doxycycline is generally recommended. A change to amoxicillin, particularly in pregnant women and children, may be considered if the organism is found to be susceptible or first-line drugs cannot be taken. Treatment for 7 to 10 days is usually recommended for cutaneous anthrax, but in the event of a deliberate release or if concurrent inhalation is suspected then treatment should be continued for 60 days. If there are signs of systemic involvement, extensive oedema, or lesions on the head or neck, intravenous, and a multi-drug approach is recommended.

Anthrax can be **prevented** by controlling and eliminating infected animals and vaccinating livestock. In humans, chemoprophylaxis may be given when exposure to anthrax is suspected. US[4] and UK[3] guidelines recommend antibacterial prophylaxis with oral ciprofloxacin or oral doxycycline for 60 days. UK guidelines suggest that amoxicillin may be considered if the organism is found to be susceptible. Anthrax vaccines may be used for active immunisation and are recommended for persons working with potentially infected animals or animal products (including laboratory workers). The vaccine may also be given with antibacterials as part of a postexposure prophylaxis regimen.[2,3,5] In such situations, antibacterial prophylaxis may be reduced to 4 to 6 weeks.[3,5] In the USA, specific guidelines[5,6] for the use of anthrax vaccine, including its use in response to terrorism, have been developed.

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001; **50:** 909–19. Correction. *ibid*.; 962. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm (accessed 22/05/07)
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Antibiotic-associated colitis

See p.171.

Arthritis, bacterial

See under Bone and Joint Infections, p.164.

Bacillary angiomatosis

See under Cat Scratch Disease, p.166.

Bacterial vaginosis

Bacterial vaginosis (anaerobic vaginosis; non-specific vaginitis) results from a reduction of the normal vaginal bacteria (*Lactobacillus* spp.) and an overgrowth of anaerobic bacteria (including *Gardnerella vaginalis*, *Mycoplasma hominis*, or *Mobiluncus* or *Prevotella* spp.). It is a common and often distressing condition that is not thought to be sexually transmitted but is generally associated with sexual activity. Infections may be asymptomatic or result in a fishy-smelling vaginal discharge.

Various antibacterial regimens for the **treatment** of bacterial vaginosis are recommended in guidelines issued in the UK,[1] and in the USA[2] and also by WHO[3] but relapse is common after any regimen.

- **WHO:**
  - oral metronidazole 400 or 500 mg twice daily for 7 days

  alternatives are:
  - a single oral dose of metronidazole 2 g
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 5 days
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days
- **UK:**
  - oral metronidazole 400 or 500 mg twice daily for 5 to 7 days *or* a single oral 2-g dose

  alternatives are:
  - intravaginal metronidazole 0.75% gel once daily for 5 days
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin as a 2% cream once daily for 7 days
  - a single oral dose of tinidazole 2 g
- **USA:**
  - oral metronidazole 500 mg twice daily for 7 days, *or*
  - intravaginal metronidazole 5 g of a 0.75% gel once daily for 5 days, *or*
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 100 mg at bedtime for 3 days

An association has been reported between bacterial vaginosis and adverse ***pregnancy*** outcomes, including miscarriage and premature births of low-weight infants, and some have advised treatment early in the second trimester of pregnancy.[4,5] A systematic review[6] of clinical studies has concluded that there is little evidence that screening and treatment of all pregnant women for bacterial vaginosis would prevent premature birth and its consequences, but there is some suggestion that treatment before 20 weeks of gestation may reduce the risk of preterm birth. In women with a history of a previous premature birth, treatment of bacterial vaginosis may reduce the risk of preterm birth.[2] Symptomatic pregnant women should be treated and the following regimens have been recommended:

- **WHO:**
  - oral metronidazole 200 or 250 mg three times daily for 7 days, after the first trimester, *or*
  - a single oral dose of metronidazole 2 g, if treatment is needed in the first trimester

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days *or*
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 7 days
- **USA:**
  - oral metronidazole 500 mg twice daily *or* 250 mg three times daily for 7 days *or*
  - oral clindamycin 300 mg twice daily for 7 days

Treatment of male sex partners does not prevent the recurrence of bacterial vaginosis.[1-3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[2]

1. Clinical Effectiveness Group (British Association for Sexual Health and HIV). National guideline for the management of bacterial vaginosis (2006). Available at: http://www.bashh.org/documents/62/62.pdf (accessed 15/08/08)
2. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 22/03/07)
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Biliary-tract infections

Infections of the biliary tract are usually associated with obstructive and inflammatory conditions such as cholecystitis and cholangitis. Complications can include gangrene, hepatic or intraperitoneal abscesses, peritonitis, and septicaemia. The organisms involved are typically gut flora, including Gram-negative aerobes such as *Escherichia coli* and *Klebsiella* spp., and anaerobes including *Bacteroides fragilis*.

Treatment of uncomplicated acute cholecystitis is usually conservative. Antibacterials including cephalosporins, tetracyclines, or broad-spectrum penicillins are commonly given, although some have questioned their use.[1] For more severe infections including suppurative cholangitis, prompt treatment with appropriate antibacterial drugs is necessary. Since biliary obstruction prevents adequate concentrations of many antibacterials being achieved in the bile, the main aim of treatment is to control bacteraemia. Antibacterials used, often in combination, include cephalosporins, aminoglycosides, ampicillin (or amoxicillin), piperacillin, fluoroquinolones, metronidazole, clindamycin, and imipenem or its analogues.[2-5] In most cases of obstruction, definitive treatment depends on restoring drainage of bile by surgical or medical treatment of gallstones (p.2409).

Antibacterial prophylaxis is common in biliary surgery (see Surgical Infection, p.195) to prevent acute cholangitis and wound infections. Cephalosporins are often used for this purpose.[2]

Antibacterials may also have a role as maintenance therapy in recurrent cholangitis.

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4. Westphal J-F, Brogard J-M. Biliary tract infections: a guide to drug treatment. *Drugs* 1999; **57:** 81–91.
5. Jain MK, Jain R. Acute bacterial cholangitis. *Curr Treat Options Gastroenterol* 2006; **9:** 113–21.

Bites and stings

Wound infections after cat or dog bites may be due to a mixture of organisms,[1] often including the Gram-negative aerobe *Pasteurella multocida*. The treatment of choice for *P. multocida* is benzylpenicillin[2] and it should be given for infections evident within 24 hours of a bite;[3] alternatives are amoxicillin-clavulanic acid, ampicillin-sulbactam, or a second- or third-generation cephalosporin.[2] A tetracycline such as doxycycline is a further alternative in patients allergic to penicillin.[2] The fluoroquinolone ciprofloxacin has been used successfully to treat *P. multocida* cellulitis associated with a cat bite.[4]

In addition to *P. multocida*, other bacteria involved in cat or dog bite wound infections include *Staphylococcus*, *Streptococcus*, *Bacteroides*, and *Fusobacterium* spp. and their presence will influence the choice of treatment. For example, a penicillinase-resistant penicillin may be necessary if *Staph. aureus* is present. Also, combinations of antibacterials may be necessary in patients allergic to penicillin since tetracycline, the alternative suggested against *P. multocida* infection, has only limited activity against aerobic Gram-positive cocci.

More unusual organisms include *Capnocytophaga canimorsus* (formerly called dysgonic fermenter type 2 or DF-2) which has been associated in particular with dog bites,[5,6] but also with cat bites. It is an opportunistic pathogen especially hazardous to immunocompromised patients including splenectomised patients; the best treatment is benzylpenicillin,[7] amoxicillin-clavulanic acid, or erythromycin.[8] Infection with *C. canimorsus* following dog bites may be severe and has led to fatal septicaemia, disseminated intravascular coagulation, meningitis, or endocarditis,[5] highlighting the importance of early antibacterial treatment and debridement.

See also under Cat Scratch Disease (p.166).

A systematic review[9] has concluded that there is no evidence that the use of prophylactic antibacterials is effective for cat or dog bites, though, if necessary, prophylaxis or treatment for rabies (p.2234) should be instituted. A combined tetanus and diphtheria vaccine (see Tetanus Vaccine, p.2240) should be given to patients whose primary tetanus immunisation is incomplete or unknown, or boosters are not up-to-date.

Among the more unusual infections acquired from animals is seal finger, caused by an as yet unidentified organism and treated with tetracycline.[10] The Gram-negative bacilli *Spirillum minus* (or *minor*) and *Streptobacillus moniliformis* are both causes of rat-bite fever. In each case the treatment of choice is benzylpenicillin;[2] a tetracycline or streptomycin are alternatives.

Envenomation after bites and stings by snakes, scorpions, spiders, and some marine animals is usually treated symptomatically and with specific antivenoms and antisera (see Jellyfish Stings, p.2220, Scorpion Stings, p.2237, Snake Bites, p.2239, Spider Bites, p.2239, and Stone Fish Venom Antisera, p.2239).

1. Talan DA, *et al.* Bacteriologic analysis of infected dog and cat bites. *N Engl J Med* 1999; **340:** 85–92.
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Bone and joint infections

In *bacterial arthritis* (septic arthritis) joints may be infected via the blood with a variety of organisms, including staphylococci, streptococci, enterococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and anaerobes, although the commonest is probably *Staphylococcus aureus*. *Haemophilus influenzae* is a common cause in young children, as is *Neisseria gonorrhoeae* in sexually active young adults. In addition to gonococcal arthritis, other specific types of bacterial arthritis include Lyme disease and meningococcal, salmonellal, and tuberculous arthritis (see under the appropriate disease for further details).

With the exception of *N. gonorrhoeae*, infecting organisms in *osteomyelitis* (infection of bone) are similar to those in bacterial arthritis.[1-3]

In *reactive arthritis* (aseptic arthritis) joint inflammation follows infection elsewhere in the body. It is generally secondary to sexually transmitted, especially chlamydial, infections, or to enteric infections. Reactive arthritis in association with urethritis or cervicitis, or both, is termed Reiter's syndrome.

Empirical treatment regimens for bacterial arthritis or osteomyelitis usually include antistaphylococcal antibacterials such as flucloxacillin, nafcillin, oxacillin, a first-generation cephalosporin,[4] clindamycin, or fusidic acid; vancomycin is used to combat possible meticillin-resistant *Staph aureus*. Linezolid may be used as an alternative in patients unable to take vancomycin.[4] Children under 5 years may be given amoxicillin or cefuroxime because of the likelihood of *H. influenzae* infection. Ceftriaxone may be used for empirical treatment where infection is thought to be caused by *Streptococcus* spp. and *N. gonorrhoeae*.

Empirical antibacterial treatment for infections caused by Gram-negative bacteria includes ceftriaxone, ceftazidime, or ciprofloxacin.[4] Treatment of bone and joint infection is usually started intravenously; if high bone concentrations can be achieved with an appropriate oral antibacterial, patients may be switched to oral therapy. Successful treatment of septic arthritis is generally achieved after 2 to 3 weeks of therapy, while osteomyelitis and prosthetic joint infections may need to be treated for weeks to months.[5]

A systematic review and meta-analysis[6] of antibacterial treatment of bone and joint infections concluded that most studies were methodologically flawed and that there was little high-quality evidence regarding treatment. Rifampicin has also been used, sometimes with other drugs; in one study[7] use of rifampicin with ciprofloxacin improved control of staphylococcal bone infections related to orthopaedic devices in comparison with ciprofloxacin alone.

For reference to infection prophylaxis in orthopaedic patients, see under Surgical Infection, below.

Reactive arthritis is treated with anti-inflammatories; the role of antibacterials is less certain.[8] Results in arthritis associated with chlamydial infections have been more promising than in that triggered by enteric infections.[9] Long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[10]

For mention of the use of tetracyclines, usually minocycline, in the treatment of *rheumatoid arthritis*, see under Musculoskeletal and Joint Disorders, p.350.

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Botulism

For a discussion of botulism and its management, see p.2207.

Bronchitis

Bronchitis may be defined as inflammation of the bronchi and is associated with excessive sputum production and cough. The bronchi of healthy people are said to be nearly always sterile whereas the upper respiratory tract is often colonised with commensal bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Acute bronchitis[1] in previously healthy subjects is commonly associated with viral respiratory infections such as colds and influenza. There may sometimes be secondary bacterial infection that responds to antibacterial therapy as for acute exacerbations of chronic bronchitis (see below). *Acute bronchiolitis* occurs in infants as a result mainly of viral infection and antibacterials are not given routinely (see Respiratory Syncytial Virus Infection, p.860).

Chronic bronchitis and emphysema often occur together and have been termed chronic obstructive pulmonary disease (p.1112). Acute exacerbations of chronic bronchitis may be viral in origin, but bacteria are often present in purulent sputum, the commonest being *Str. pneumoniae* and *H. influenzae*; *Moraxella catarrhalis* (*Branhamella catarrhalis*) is increasingly reported.

The value of antibacterial treatment in both acute bronchitis and acute exacerbation of chronic disease has been controversial and difficult to assess.[1-6] After a comparison of a broad-spectrum antibacterial (amoxicillin, co-trimoxazole, or doxycycline) with placebo,[7] it was considered that antibacterials were justified in exacerbations of chronic obstructive pulmonary disease characterised by increased dyspnoea, sputum production, and sputum purulence. Also, a meta-analysis of randomised studies indicated a small improvement due to therapy in patients with exacerbations of disease.[8] However, a further meta-analysis[9] assessing the use of antibacterials for acute bronchitis concluded that, although there was some benefit to be obtained this did not outweigh the risks of adverse effects and increased resistance and that the use of antibacterials could therefore not be advocated in otherwise healthy patients with no evidence of chronic disease. A systematic review[10] also concluded that the modest benefit associated with antibacterial use in acute disease needed to be considered in the broader context of potential adverse effects, the necessity to treat a self-limiting condition, development of resistance, and cost of treatment. If antibacterials are given it is common practice to give a 7- to 10-day oral course of a broad-spectrum drug such as amoxicillin (alone or with clavulanic acid), ampicillin, an oral cephalosporin such as cefaclor or cefuroxime axetil, co-trimoxazole, erythromycin or a newer macrolide such as azithromycin or clarithromycin, tetracycline, or trimethoprim (preferred to co-trimoxazole in the UK), the choice depending on local patterns of resistance.

Long-term prophylaxis in patients with frequent exacerbations of bronchitis is controversial. A systematic review[11] of the value of antibacterial prophylaxis in chronic bronchitis concluded that it did have a small but significant effect in reducing the number of days of illness, but that it had no place in routine therapy because of concerns over adverse effects and the development of resistance.

Bronchitis associated with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) and responding to tetracycline or erythromycin has also been reported.[12]

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Brucellosis

Brucellosis (also known as undulant or Mediterranean fever) is caused by *Brucella* spp., aerobic Gram-negative bacteria found primarily in livestock and domestic animals. Humans can become infected by direct contact with infected animals or animal material (such as the placenta), indirectly by consuming infected and unpasteurised milk products, or by inhalation of contaminated dust or droplets. Rarely, human infection has been reported from exposure to some live veterinary vaccines.[1,2] The principal *Brucella* spp. affecting humans are *B. melitensis*, from sheep, goats, camels, and sometimes cattle; *B. abortus*, from cattle, buffalo, camels, and yaks; *B. suis*, from pigs; and rarely *B. canis*, from dogs. Although rare or controlled in countries such as the UK brucellosis remains a problem in many areas, including eastern Europe, the Mediterranean region, South and Central America, Mexico, the Caribbean, the Indian subcontinent, parts of Africa and Asia, and the Middle East.

Symptoms usually develop 2 to 8 weeks after infection and resemble a flu-like illness with anorexia, fever, headache, lethargy, malaise, depression, myalgia and back pain, sweating, and weakness. Laboratory findings include anaemia, leucopenia, lymphocytosis, pancytopenia, and thrombocytopenia. Brucellosis may be acute, relapsing, or chronic (disease duration of more than 1 year) and can affect any part of the body, including joints (peripheral arthritis, sacroiliitis, and spondylitis), heart (endocarditis), liver (hepatitis), the CNS (meningitis, encephalitis, meningoencephalitis, meningovascular disease, brain abscesses, and demyelinating syndrome), and the reproductive system (epididymo-orchitis). Relapses occur in about 10% of patients, usually in the first year after infection, and typically cause milder symptoms.[3]

Treatment of brucellosis shortens the duration of illness, and reduces complications and the risk of relapse. Tetracyclines, although highly active against *Brucella* spp., are associated with high relapse rates when given as monotherapy and therefore combination therapy is now used. Common regimens are: doxycycline and rifampicin both orally for at least 6 weeks;[4,5] doxycycline orally for 6 weeks with a parenteral aminoglycoside (streptomycin,[6,7] gentamicin,[5,8,9] or netilmicin[10]) for the first 1 to 2 weeks. Fewer relapses have been reported with doxycycline and streptomycin than with doxycycline and rifampicin, perhaps due to rifampicin reducing plasma concentrations of doxycycline.[11] Higher relapse rates have been reported with netilmicin than with gentamicin.[10] Studies[12,13] have shown that combination treatment with a fluoroquinolone plus either doxycycline or rifampicin is effective although fluoroquinolone monotherapy is not. A review of the literature on fluoroquinolone-based combination treatment did not support their use as first-line treatment,[13] but they can be considered as part of an alternative regimen for patients who experience relapse or toxicity problems with the usual first-line antibacterials. Co-trimoxazole when used is usually given in triple-drug regimens.[3] A systematic review and meta-analysis[14] of 30 randomised controlled studies on the treatment of brucellosis found that a triple drug regimen of doxycycline, gentamicin, and rifampicin was better than doxycycline plus an aminoglycoside. It also found that 6 weeks of treatment was associated with a lower rate of relapse than treatment regimens of 30 days or less.

Tetracyclines should be avoided in young *children* (usually specified as below 8 years of age in the US and below 12 years in the UK). The preferred regimens for these children appear to be co-trimoxazole with rifampicin both orally for at least 6 weeks or co-trimoxazole orally with parenteral gentamicin for the first 2 weeks.[5,6] Alternative regimens include rifampicin orally for at least 6 weeks with either gentamicin or netilmicin for the first 5 days.[6]

For the treatment of brucellosis during *pregnancy*, WHO recommends rifampicin monotherapy for 6 weeks as the drug of choice and that co-trimoxazole or tetracycline should only be given if rifampicin is unavailable; streptomycin is contra-indicated.[4] Co-trimoxazole with rifampicin for 4 weeks has also been tried.[6]

No one antibacterial combination has been found to be superior for the treatment of *spondylitis* although a 3-month course of doxycycline with ciprofloxacin has been proposed based on an evaluation of the literature.[15] In the treatment of *neurobrucellosis*, the length of therapy appears to be of critical importance; relapses may occur after treatment lasting only 2 to 3 weeks and it is recommended that doxycycline be given with 2 or more other drugs (rifampicin, an aminoglycoside, co-trimoxazole, or ceftriaxone) for several months depending on the response. Corticosteroids are often given but their efficacy is unproven. A similar treatment regimen is used in the management of paediatric neurobrucellosis and a 3-drug regimen (doxycycline, rifampicin, and an aminoglycoside) given for 3 months has been shown to be effective. In young children doxycycline should be replaced with co-trimoxazole.[16] Treatment of *endocarditis* in adults generally requires long-term triple or quadruple drug regimens (a tetracycline, an aminoglycoside, rifampicin, and/or co-trimoxazole) usually with surgical valve replacement.[17,18] Treatment should be continued for 3 months or longer and some recommend the addition of ceftriaxone and/or a fluoroquinolone to reduce the need for surgery. Cardiac complications in children are generally less severe than in adults and treatment with tetracycline for 3 weeks with streptomycin for 2 weeks has been found to be effective.[18]

Brucellosis can be **prevented** by controlling and eliminating infected animals, pasteurising milk products, and vaccinating cattle and other livestock. There is no human vaccine currently available for brucellosis, although many have been tested and some have been available from time to time in various countries.[3]

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Campylobacter enteritis

See p.172.

Cat scratch disease

Cat scratch disease usually occurs after a cat scratch or bite. The condition is characterised by regional lymphadenopathy and is often self-limiting, but may be disseminated in immunocompromised patients.

In the 1980s a Gram-negative bacillus presumed to be responsible for cat scratch disease was isolated and subsequently named *Afipia felis.* However, it now appears that *Bartonella henselae* (formerly *Rochalimaea henselae*) is the main cause of cat scratch disease[1] and that *A. felis* causes few, if any, cases, although there is some evidence for a joint role.[2] With uncertainty over aetiology there has been no specific antibacterial therapy and treatment with antibacterials is generally not recommended in patients with mild to moderate infection.[1] There are, however, reports of successful treatment with gentamicin[3] or co-trimoxazole[4] in children and with ciprofloxacin[5] in adults. Azithromycin has also been found to be of benefit in adults[6] and is considered the treatment of choice in both adults and children with extensive lymphadenopathy. Doxycycline with rifampicin may be given as an alternative for these patients and is the recommended treatment for complicated cat scratch disease.[1]

Bacillary angiomatosis, in which both *B. henselae* and *B. quintana*[7] (the causative organism of trench fever) have been implicated, resembles a disseminated form of cat scratch disease but occurs predominantly in HIV-infected patients. Disseminated disease in immunocompromised patients has not responded to ciprofloxacin,[8,9] but has responded to treatment with doxycycline[8-11] or erythromycin[8] or azithromycin. Erythromycin for 3 months is the drug of choice for bacillary angiomatosis; doxycycline may be given as an alternative. Immunocompromised patients with acute, life-threatening infection should be treated with rifampicin plus erythromycin or doxycycline.[1] Care is required in patients with AIDS since the lesions of bacillary angiomatosis closely resemble those of Kaposi's sarcoma, and if the diagnosis is missed, life-saving antibacterial therapy may not be given.[12]

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Cellulitis

See under Skin Infections, p.194.

Cervicitis

Gonorrhoea in women occurs mainly as cervicitis, but mucopurulent cervicitis is frequently caused by sexually transmitted *Chlamydia trachomatis*. The two infections often occur together and should be treated concurrently. Guidelines for treatment are given under Gonorrhoea, p.191, and Chlamydial Infections, below.

Chancroid

See under Sexually Transmitted Diseases, p.191

Chlamydial infections

The chlamydia organism belongs to the family Chlamydiaceae. Species that are pathogenic in man are *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis*; they are generally sensitive to tetracyclines or erythromycin.

C. pneumoniae (formerly classified as a TWAR strain of *C. psittaci*) is a respiratory pathogen. It was first described as a cause of community-acquired pneumonia (see Pneumonia, p.186), but has since been associated with other clinical presentations including pharyngitis (see p.185) and has been implicated in the pathogenesis of ischaemic heart disease (see Atherosclerosis, p.1159).

C. psittaci is transmitted to man from birds and causes psittacosis, which also affects the lungs (see Psittacosis, p.188).

C. trachomatis causes a wide range of diseases. Many are sexually transmitted and the spectrum is similar to that with *Neisseria gonorrhoeae* (see Gonorrhoea, p.191); infections with the two organisms often occur concurrently. In women *C. trachomatis* may cause endometritis, pelvic inflammatory disease, ectopic pregnancy, and infertility. In the USA[1,2] routine screening for *C. trachomatis* infection is recommended in all sexually active women aged 25 years or less, whether or not they are pregnant, and in women aged over 25 years if they are considered to be at increased risk of infection.

Guidelines produced by WHO,[3] by an expert group in the UK,[4] and by the CDC in the USA[2] for the **treatment** of uncomplicated anogenital infection with *C. trachomatis* are as follows:

- **WHO:**
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily
- **UK:**
  - first-line therapy is the same as WHO

  alternatives are:
  - oral erythromycin 500 mg twice daily for 10 to 14 days
  - oral ofloxacin 200 mg twice daily *or* 400 mg once daily for 7 days
- **USA:**
  - first-line therapy is the same as WHO

  alternatives, given for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

Pregnant women infected with *C. trachomatis* may be at risk of premature rupture of membranes and preterm labour (see Premature Labour, p.188). They may also infect their offspring to cause ophthalmia neonatorum (see Neonatal Conjunctivitis, p.180) or pneumonia (p.186). Infected pregnant women should be treated and the following regimens have been recommended:

- **WHO:** treatment for 7 days with:
  - oral erythromycin 500 mg four times daily *or*
  - oral amoxicillin 500 mg three times daily
- **UK:**
  - as for WHO, *or*
  - oral erythromycin 500 mg twice daily for 14 days, *or*
  - a single oral dose of azithromycin 1 g
- **USA:**
  - a single oral dose of azithromycin 1 g *or*
  - oral amoxicillin 500 mg three times daily for 7 days

  alternatives are:
  - erythromycin-containing regimens

Sexual partners of those infected with *C. trachomatis* should be tested and treated.[2-4]

For further reference to sexually transmitted *C. trachomatis* infections, see under Epididymitis (p.170), Pelvic Inflammatory Disease (p.184), and Urethritis (p.199)

Specific serotypes of *C. trachomatis* are responsible for another sexually transmitted disease, lymphogranuloma venereum (p.192).

Reactive arthritis (see Bone and Joint Infections, p.164) may be secondary to chlamydial infections.

Other *C. trachomatis* infections that are not sexually transmitted include trachoma and inclusion conjunctivitis in adults (see Trachoma, p.196).

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Cholera and other vibrio infections

See p.172.

Cystic fibrosis

Cystic fibrosis is a genetic disorder associated with the production of abnormally viscous mucus. The underlying defect is mutation in the gene which codes for cystic fibrosis transmembrane conductance regulator (CFTR), a protein which functions as a chloride channel. Mutations result in defective ion transport with reduced chloride ion secretion and accelerated sodium ion absorption, and related changes in the composition and properties of mucin secreted. Now that patients with cystic fibrosis usually survive into adulthood, it is increasingly seen to be a multisystem disease. However, the main clinical manifestations are still pulmonary disease, with recurrent bacterial infections and the production of copious viscous sputum, and malabsorption due to pancreatic insufficiency. Other complications include male infertility and hepatobiliary disease. There is increased salt loss in sweat.

Pulmonary disease is the major cause of mortality. Cystic fibrosis is an underlying cause of bronchiectasis (chronic dilatation of the bronchi) as a result of excessive secretion of mucus and recurrent infections. Cough and excessive production of sputum are characteristic of cystic fibrosis and the lungs are generally colonised with bacterial pathogens, especially mucoid strains of *Pseudomonas aeruginosa*. Pseudomonal pulmonary infection is the major cause of morbidity and mortality in cystic fibrosis. Monitoring of bacterial pathogens in the sputum, including their sensitivity, is necessary for rational treatment. Apart from *Ps. aeruginosa*, *Staphylococcus aureus* is often present and may be the predominant pathogen in infants. *Burkholderia cepacia* complex (*Pseudomonas cepacia*) has been recognised as a cause of serious lung infection in cystic fibrosis and is readily transmitted by social contact. In a proportion who acquire it, *B. cepacia* has been associated with rapid deterioration and death. Other bacteria isolated include *Haemophilus influenzae* and atypical *Mycobacteria* spp.

Various diagnostic methods are available[1-3] and clinical diagnosis of cystic fibrosis may be confirmed by establishing that chloride concentrations in sweat are raised. This may be done by using the pilocarpine sweat test (see Pilocarpine, p.1885). Identification of gene mutation is possible and may be used for further confirmation of the diagnosis and identification of carrier status.[4] In some areas neonatal screening programs have been instituted, to allow for early intervention.

The reduced morbidity and improved survival in patients with cystic fibrosis are largely due to the management of pulmonary disease with antibacterials and physiotherapy and to nutritional management. Several reviews have discussed both established and experimental therapy.[5-9] Despite the successes, the evidence base for some procedures is scanty,[9] and there may be variations in management between centres. However, the cornerstones of current management are:[8,9]

- mechanical airway clearance, with the use of adjuncts such as dornase alfa and hypertonic saline
- prevention or eradication of pulmonary infections in early disease
- suppression of bacterial load through antibacterial treatment of chronic infection in more advanced disease
- use of ibuprofen or azithromycin to control lung inflammation
- aggressive antibacterial treatment of pulmonary exacerbations
- nutritional support to ensure an adequate intake of calories and salt, with supplementation of pancreatic enzymes and the fat-soluble vitamins A, D, E, and K
- maintaining regular physical activity

Airway clearance by manual chest percussion and mechanical techniques including chest-wall or airway oscillation helps to loosen secretions and aid their removal. Dornase alfa[10] is given by aerosol inhalation and reduces the viscosity of the sputum by breaking down the large quantities of DNA released by degenerating inflammatory cells. The use of dornase alfa has been associated with some improvement in lung function and it might be a useful adjunct to bronchial drainage, although it is unclear whether it prevents the development of progressive lung damage. However, a randomised, multicentre, placebo-controlled study in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a period of 96 weeks.[11] Mucolytics such as acetylcysteine are generally not considered to be effective in cystic fibrosis.[12] Inhalation of hypertonic saline has, however, been shown to be of benefit (see p.1687) and has become part of management in many centres.[8,9] The time required for such therapies and their associated monitoring may prove challenging to patients and their families.[8]

In young patients with early disease, **prevention or eradication of infection** for as long as possible is a reasonable aim, in order to maintain good lung function.[9] Staphylococcal infections commonly develop during the first decade of life, and some clinicians start antistaphylococcal antibacterials on diagnosis of cystic fibrosis. Others wait until the first clinical infection occurs before starting treatment. Once started, antistaphylococcal therapy is continued indefinitely in some centres, while others only treat when symptomatic exacerbations or positive sputum cultures occur. Systematic reviews confirmed that antistaphylococcal treatment is effective and also concluded that prophylaxis is likely to be beneficial in young children with cystic fibrosis.[13,14] In the UK, flucloxacillin or co-amoxiclav are commonly given.[9] It is unclear whether intermittent or continuous therapy produces the best clinical outcome. Other potential disadvantages to prophylaxis are the possible early acquisition of *Ps. aeruginosa* infection[15] (this seems to be a risk mainly if broad spectrum cephalosporins are given) and an increased incidence of drug-resistant staphylococci with continuous therapy.[16]

Management of **chronic infection** is aimed at control of bacterial load,[9] since permanent eradication is impossible. Selection of an antibacterial must be individualised, and will depend on the infecting organisms,[9] and local prescribing policies and availability. Long-term intermittent treatment with inhaled antibacterials, particularly tobramycin, is favoured;[8,9,17,18] other nebulised antibacterials that may be of benefit include aztreonam and colistin.[8,19] A systematic review confirmed that inhaled antipseudomonal antibacterials improved lung function and reduced the frequency of exacerbations.[20] Although there is some evidence of an increase in resistance with such treatment,[20] it is claimed to be less frequent than feared.[8] In contrast, oral antipseudomonal therapy has not been conclusively shown to be of benefit in chronic infection,[21] and is generally avoided because of fears of resistance.[8]

The macrolide azithromycin is, however, used orally in chronic infection, but may be acting as an immunomodulator to **reduce inflammation** rather than specifically as an antibacterial.[8,9,22] A systematic review[23] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear. A small anti-inflammatory benefit has also been reported from treatment with high-dose oral ibuprofen,[24] and this is used in some centres, particularly in the USA.[9] However, there are some concerns about the potential for adverse effects; it has been recommended that if used, such therapy be stopped in patients who require intravenous aminoglycosides, and should be avoided in those with gastrointestinal risk factors.[24] There is no evidence supporting a role for corticosteroid therapy,[25,26] except in the management of patients who develop allergic bronchopulmonary aspergillosis.[9]

Aggressive **management of exacerbations** with appropriate antibacterials is crucial.[8,9,27,28] Treatment should be based on recent culture results, but there appears to be no additional value in combination antibacterial sensitivity testing.[29] In patients with *Ps. aeruginosa* infection a combination of intravenous antibacterials, typically an aminoglycoside such as tobramycin and a beta-lactam with antipseudomonal activity such as ceftazidime, is favoured.[27,28,30] Once-daily dosing with the aminoglycoside is as effective as giving it in divided doses, and may be associated with less nephrotoxicity in children.[31] High doses are necessary because of the poor penetration of these antipseudomonal antibacterials into the site of infection and their increased renal clearance in patients with cystic fibrosis.[32,33] Treatment is generally given for 2 to 3 weeks although there is no good evidence to support a particular length of therapy.[34] Intermittent elective intravenous therapy has become more practical with the development of regimens that enable patients to be treated at home.[30,35]

Infection with *B. cepacia* complex is difficult to treat because the majority of antipseudomonal antibacterials are not effective. Co-trimoxazole has been suggested[36] and can be given orally;[28] meropenem and ceftazidime have some *in-vitro* activity, and temocillin has been tried.[28] Other problems may include meticillin-resistant *Staph. aureus* infections; intravenous teicoplanin has been used, as have oral doxycycline or linezolid where sensitivity patterns permit.[28] The possibility of fungal or viral infections should also be considered.[28]

Nutritional management of cystic fibrosis should ensure adequate calorie intake from a balanced diet in order to counteract malabsorption due to pancreatic insufficiency and the increased metabolic requirements of patients with cystic fibrosis.[37,38] Supplements of the fat-soluble vitamins A, D, and E, and sometimes vitamin K, may be necessary. Investigation of bone mineral density[39] and direct assessment of vitamin status[40] suggest that current supplements may be inadequate. Pancreatic enzymes, as pancreatin or pancrelipase, are taken before or with each meal or snack.[41]

Many **other interventions** have been tried.[42,43]

Bronchodilators including both beta agonists and antimuscarinics may be useful in selected patients although there are few meaningful clinical trial results.[44] A therapeutic trial is often justified in individual patients since it is difficult to predict which patients will respond.[42] While use by nebuliser is regarded as most effective, inhalers may be more practical where compatibility with other nebulised drugs could be a problem.[43] Alpha$_1$-proteinase inhibitor, the main inhibitor of neutrophil elastase in the lung has also been investigated[45] as has pentoxifylline,[46] a drug with anticytokine activity.

Experimental treatment aimed at modifying the pulmonary disease process has also included ion transport therapy. This involves the use of aerosolised drugs that either inhibit sodium ion absorption across airway epithelia (for example the sodium channel blocker amiloride) or induce chloride ion secretion. However, nebulised amiloride was not found to be a useful adjunct in patients on optimal treatment.[47]

In patients with severe lung disease, oxygen therapy may give some relief of symptoms but its effect on mortality and morbidity is uncertain.[48] At present the only available treatment for patients with end stage pulmonary disease is lung transplantation. Although individuals with cystic fibrosis do as well as those referred for transplantation with other lung diseases, the 5-year survival rate after the procedure is reported to be only 50%.[8]

Somatic **gene therapy** represents the nearest approach to a cure for cystic fibrosis.[49] It aims to introduce the normal CFTR gene sequence into cells of affected tissue. Most effort has been directed at gene delivery to the lungs using adenovirus vectors or liposomes, but results have been variable.[50-53] Difficulties encountered include inefficient gene transfer, immunity to viral vectors, and a systemic inflammatory reaction provoked by plasmid DNA.[4] For a discussion of the general principles of gene therapy, see p.2310.

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Diarrhoea, infective

See Gastro-enteritis, p.171.

Diphtheria

Diphtheria is caused by infection, usually of the upper respiratory tract or the skin, with the Gram-positive aerobe *Corynebacterium diphtheriae*. It occurs worldwide and, despite the effectiveness of immunisation (see Diphtheria Vaccines, p.2209), is still common in parts of the world, including the tropics. Although the risk to travellers is said to be low, diphtheria should be considered in patients returning from endemic areas with a sore throat.

The most serious manifestations of infection are due to exotoxin produced by toxigenic strains and thus treatment is primarily with diphtheria antitoxin. Erythromycin or benzylpenicillin are also given to eliminate *C. diphtheriae*, thereby terminating toxin production and preventing the spread of infection to contacts. Close contacts of primary cases of diphtheria may be given a 7-day prophylactic course of erythromycin orally or a single intramuscular dose of benzylpenicillin,[1] in addition to boosters or primary immunisation with diphtheria vaccine. Non-toxigenic *C. diphtheriae* is the most common isolate in clinical cases in the UK[1,2] and generally causes a less severe form of the disease; it does, however, have the potential to cause invasive disease in some patients.[3]

Asymptomatic carriers may harbour non-toxigenic strains of *C. diphtheriae* that can be converted to toxigenic strains. A single intramuscular injection of benzathine benzylpenicillin has been less effective than oral erythromycin, but may be used if compliance is uncertain;[4] clindamycin for 7 days by mouth has also eliminated the carrier state,[4] but erythromycin remains the drug of choice. Bacteriological follow-up should be carried out 2 weeks after completing treatment to be certain *C. diphtheriae* has been eradicated from carriers.[5]

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Ear infections

See Otitis Externa, and Otitis Media, p.182.

Ehrlichiosis

Ehrlichioses are a group of diseases produced by infection with rickettsia-like bacteria of the family Anaplasmataceae, a family that contains the genera *Anaplasma*, *Ehrlichia*, *Neorickettsia*, and *Wolbachia*. At one time such organisms were considered to be only animal pathogens but it is now recognised that humans may also become infected. One of the earliest human forms of ehrlichiosis identified was Sennetsu fever, a disease found in Japan and Malaysia, and which is caused by *N. sennetsu* (*E. sennetsu*). Subsequently *Anaplasma phagocytophilum* (*E. phagocytophila*), *E. chaffeensis*, *E. ewingii*, and possibly *E. canis* have emerged as tick-borne human pathogens.

E. chaffeensis mainly infects mononuclear cells and in humans the resulting disease is commonly called human monocytic (or monocytotropic) ehrlichiosis (HME) whereas *A. phagocytophilum* mainly infects granulocytes and in humans produces human granulocytic (or granulocytotropic) ehrlichiosis (HGE), now also known as human granulocytic anaplasmosis (HGA). *E. ewingii* and *E. canis* mainly infect granulocytes and mononuclear cells respectively.

Some patients with HGA may also be co-infected with *Borrelia burgdorferi*, the cause of Lyme disease, and/or *Babesia microti*, the cause of babesiosis, as they are all transmitted by tick bites from the same *Ixodes* spp. For details on the treatment of patients with HGA co-infected with Lyme disease, see p.177.

Human ehrlichiosis is characterised by fever, headache, myalgia, and malaise. Laboratory findings include leucopenia, thrombocytopenia, and elevated liver enzymes.[1,2] Symptoms more commonly seen in patients with HME are gastrointestinal disturbances, cough, confusion, and skin rash. HME is a relatively severe infection and patients may require hospitalisation for complications such as acute respiratory distress, coagulopathy, hepatitis, hepatic failure, meningoencephalitis, acute renal failure, and shock. Fulminant infections may give rise to other opportunistic infections, particularly in immunocompromised patients. Fatalities have been reported in 2 to 3% of patients with HME. Clinical symptoms of infections with *E. ewingii* or *A. phagocytophilum* are generally similar to those of *E. chaffeensis*[3,4] although usually less severe. Cough, confusion, and skin rash have not been seen with infections caused by *E. ewingii* and most cases have been diagnosed in immunocompromised patients; no deaths have been reported. HGA is generally a mild, self-limiting disease, but may be severe in about 5 to 7% of patients and reported fatalities are less than 1%. Most severe cases have been diagnosed in immunocompromised patients. Skin rash, gastrointestinal and respiratory disturbances, and CNS involvement are less frequent with HGA.[1]

Prompt **treatment** is recommended due to the potential for serious complications. Treatment for all infections is with a tetracycline, preferably doxycycline, given for 7 to 10 days or for at least 3 days after the patient has become afebrile. Chloramphenicol has been used as an alternative for HME, although its efficacy is controversial and it should not be considered as a first-line treatment.[1,5] It is also not effective against *A. phagocytophilum in vitro*. Despite the known adverse effects of doxycycline in children, the American Academy of Pediatrics[6] and the Infectious Diseases Society of America (IDSA)[7] state that a shortened course may be given to those who are less than 8 years of age who are severely ill and not co-infected with Lyme disease; the dose is 4 mg/kg daily in two divided doses and should be given for at least 3 days after the patient has become afebrile (a total of about 5 to 10 days). Successful treatment of HGA with rifampicin has been reported in pregnancy (gestational age of 10 to 36 weeks)[8] and in 2 children with non-life-threatening infection.[9] The IDSA[7] recommends that patients with mild disease who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days; children may be given 10 mg/kg twice daily. Antibacterial susceptibility testing has suggested that rifamycins and fluoroquinolones are promising alternatives in the treatment of HGA.[10]

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Endocarditis

Infective endocarditis is an infection of the endocardium after invasion of the bloodstream by bacteria or fungi, and particularly affects the heart valves. Infection has traditionally been classified as acute or subacute; however, changes in the clinical spectrum of infection have meant that some now prefer to classify it into the categories:[1]

- native-valve endocarditis (often associated with congenital or chronic rheumatic heart disease, and classically due to streptococci although cases due to staphylococcal infection are increasingly frequent)
- prosthetic valve endocarditis (which may occur early, within 60 days of surgery, which is often due to staphylococci, or late, in which case it is often due to streptococci or more exotic organisms such as the HACEK group)
- endocarditis in intravenous drug users (usually associated with infection by skin pathogens, especially *Staphylococcus aureus*)
- nosocomial endocarditis (related to catheter implantation or other invasive medical or surgical procedures; it is usually due to staphylococci or enterococci and has a high mortality rate). An increasing incidence is also seen in patients undergoing haemodialysis

Treatment of infective endocarditis is essential, as infection can result in heart failure, embolisation and infarction of major organs, and death. Diagnosis is often difficult as many of the symptoms (which include fever, malaise, headache, petechiae, and splinter haemorrhages under the nails) are nonspecific. A set of diagnostic criteria known as the Duke criteria have been developed, and some modifications subsequently proposed.[2] The Duke criteria identify endocarditis primarily on the basis of microbiological data (blood culture of the infecting organism) and anatomical lesions of the valves (identified by echocardiography or the development of new valvular regurgitation); minor criteria such as development of fever, or presence of predisposing conditions such as heart defects or intravenous drug use, are also considered.[2]

Virtually any organism can cause endocarditis but streptococci, enterococci, and staphylococci continue to be major culprits.

- Among the commonest causes are the alpha-haemolytic *streptococci* originating mainly from the mouth and throat; they have been called viridans streptococci or even '*Streptococcus viridans*' (although this is not a true species) and include *Str. mitis*, *Str. mutans*, *Str. oralis*, *Str. salivarius*, and *Str. sanguis*. Other streptococci originate in the gut and include *Str. bovis*.
- Also increasingly common is endocarditis due to *staphylococci* such as *Staphylococcus aureus*, a common cause in intravenous drug abusers, but endocarditis may also be caused by coagulase-negative *staphylococci*, particularly *Staph. lugdunensis*. Prosthetic valve infection is often caused by *Staph. epidermidis* or other staphylococci.
- *Enterococci* (faecal streptococci) originate in the gut and include *Enterococcus faecalis* and, to a lesser extent, *E. faecium*. Endocarditis due to any of these bacteria is commonly subacute or insidious.

Less common causes of endocarditis include:[3]

- Gram-negative bacteria such as the Enterobacteriaceae and
- *Pseudomonas* spp.
- the HACEK group of slow-growing organisms (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*)
- the rickettsia *Coxiella burnetii* (the cause of Q fever, p.188)
- *Bartonella* spp. (also formerly classified as rickettsia)
- fungi such as *Candida* and *Aspergillus* (see p.519).

Guidelines for the treatment and prophylaxis of endocarditis have been issued by bodies in many countries. Although some common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice.

Endocarditis treatment.

Treatment of endocarditis relies on prompt identification of the infecting organisms and their sensitivity to antibacterials. Three sets of blood cultures, each from a separate venepuncture, should be taken before antimicrobial treatment is started; MICs for the causative organism should be measured. As already mentioned, guidelines vary,[4-8] but in general:

- a microbicidal antibacterial, or combination of antibacterials, should be used for treatment; many regimens are based on a beta-lactam or glycopeptide plus an aminoglycoside
- treatment should be given at high doses, and by the intravenous route
- except in the most sensitive infections, treatment should be given for at least 4 weeks (or at least 6 weeks if the patient has prosthetic valves or other prosthetic material implanted in the heart)
- ideally, it is preferable to wait for the results of blood culture before starting therapy; however, empirical treatment is given to patients presenting with acute or severe disease
- associated complications such as heart failure should be managed appropriately; management may include referral for early surgical intervention

If *empirical treatment* is to be given until the laboratory results are known, then it is most likely to be with gentamicin plus benzylpenicillin.[4-6] An isoxazolyl penicillin (cloxacillin, dicloxacillin, flucloxacillin, or oxacillin) may be added, or used instead of benzylpenicillin, in more severe or acute presentations. Vancomycin is likely to be the antibacterial of choice in penicillin-allergic patients requiring empirical treatment,[5] and may be used empirically with an aminoglycoside in patients with prosthetic valves or where penicillin resistance is suspected.[4,6] (UK guidelines also add rifampicin in these situations.[6])

Once the causative organism and its antibiotic susceptibility have been identified, appropriate *pathogen-directed* therapy may be begun.

- **Streptococcal endocarditis**. Streptococci vary in their susceptibility to penicillin, and guidelines generally divide regimens according to whether the organism is of low, intermediate, or high penicillin resistance, although at what MIC these categories are defined varies between guidelines.

  For uncomplicated cases of infection with the most *penicillin sensitive streptococci*, benzylpenicillin may be used, with or without gentamicin.[4-8] Typically, if used alone in native-valve infection it would be given for 4 weeks, whereas the combination regimen is given only for 2 weeks.[6-8] Indicative doses would be 1.2 to 2.4 g of benzylpenicillin every 4 hours, and gentamicin 1 mg/kg every 8 hours. Ceftriaxone or vancomycin may be considered as an alternative,[6] although these are more often given to treat less sensitive strains, or in patients unable to tolerate penicillin.

  For *streptococci less sensitive to penicillin* benzylpenicillin may be given as above but for 4 to 6 weeks,[4,6,7] usually with gentamicin for at least the first 2 weeks. Alternatively, 4 weeks of treatment with ceftriaxone or vancomycin may be considered.[6-8] Typical doses are 2 g daily of ceftriaxone as a single injection, or 30 mg/kg of vancomycin daily (up to a usual maximum of 2 g daily), in 2 divided doses.

  For *penicillin resistant streptococci* treatment is similar to that for enterococcal endocarditis.[6,7] A combination of vancomycin and gentamicin may be given for 4 to 6 weeks. Streptomycin is a possible alternative to gentamicin for *gentamicin resistant* isolates.[6]

  For *streptococci in penicillin-allergic patients*, vancomycin for 4 to 6 weeks may be given; UK guidelines advise 4 weeks of treatment combined with gentamicin for the first 2 weeks.[6] Teicoplanin, typically in doses of 6 to 10 mg/kg daily (higher loading doses should be given initially to establish a suitable trough concentration) is a possible alternative to vancomycin.[6] Some patients may tolerate ceftriaxone.[4]

  For patients with *prosthetic valve endocarditis*, a regimen similar to that for less sensitive streptococci (above) has been suggested, given for at least 6 weeks.[6-8]

- **Staphylococcal endocarditis**. The treatment of staphylococcal endocarditis is based on the use of an isoxazolyl penicillin or a glycopeptide. In contrast to streptococcal or enterococcal endocarditis, the benefits of adding an aminoglycoside are uncertain, and guidelines differ in whether they recommend this. Combination therapy is recommended where prosthetic valves or other intracardiac prostheses are present.

  For *meticillin sensitive staphylococci*, typically cloxacillin, dicloxacillin, or flucloxacillin is given in a dose of 2 g every 4 to 6 hours for at least 4 weeks.[4-8] Some guidelines continue to recommend addition of gentamicin for the first 3 to 5 days of therapy.[7,8] Patients with right-sided endocarditis due to intravenous drug abuse may respond to shorter courses of 2 weeks of combination therapy with an isoxazolyl penicillin plus gentamicin.[4,6-8]

  For *staphylococci resistant to meticillin/oxacillin*, vancomycin may be given alone for 6 weeks,[4,7,8] or with rifampicin or perhaps gentamicin or sodium fusidate (depending on sensitivity) for at least 4 weeks.[5-8] Such combinations may also be appropriate in patients with *penicillin allergy*. Teicoplanin should not be used as the reported incidence of treatment failure is unacceptably high.[6]

  For *staphylococcal endocarditis in the presence of intracardiac prostheses* either an isoxazolyl penicillin or vancomycin may be used with rifampicin or gentamicin or both; an indicative regimen might be intravenous doses of 2 g of the penicillin every 4 to 6 hours, or 1 g of vancomycin every 12 hours, plus rifampicin 300 mg by mouth every 8 hours, both given for 6 to 8 weeks, plus gentamicin 1 mg/kg intravenously every 8 hours for the first 2 weeks.[6-8] Gentamicin may be given for the entire period of treatment if the infection is due to more recalcitrant strains of meticillin-resistant *Staph. aureus* or coagulase-negative staphylococci.[6]

- **Enterococcal endocarditis**. Treatment of enterococcal endocarditis is based on combinations of an aminoglycoside with another antibacterial, usually a beta lactam or a glycopeptide, depending on the sensitivity of the isolated organism.

  For *gentamicin sensitive, penicillin sensitive enterococci*: intravenous bolus injections of ampicillin or amoxicillin 2 g (or benzylpenicillin 2.4 g) every 4 hours and gentamicin 1 mg/kg every 8 or 12 hours, both given for at least 4 weeks.[4,6,8]

  If the patient is *allergic to penicillin*, or the isolate is *penicillin resistant but gentamicin sensitive*, then a combination of vancomycin or teicoplanin with gentamicin may be given for at least 4 weeks.[6-8]

  For *enterococci with high level gentamicin resistance*, a penicillin as above may be used with streptomycin 7.5 mg/kg twice daily (intramuscularly or intravenously) for at least 4 weeks.[6,8] If there is also *penicillin resistance*, or the patient is *penicillin allergic*, streptomycin as above may be given with vancomycin or teicoplanin.[6] If streptomycin cannot be used then treatment should be given for at least 8 weeks.[6]

  Endocarditis due to *multiply resistant enterococci* not susceptible to penicillin, gentamicin, or vancomycin, is still infrequent and there seem to be no established regimens; options may include the use of linezolid or quinupristin/dalfopristin where available.[6,8] A combination of ampicillin with ceftriaxone or imipenem-cilastatin, given for at least 8 weeks, has been suggested for multiply resistant *E. faecalis* infection in US guidelines.[8]

- **HACEK endocarditis**. The HACEK organisms are slow and difficult to culture and treatment must often, therefore, be empirical. Traditionally, treatment for this group of organisms was based on ampicillin and gentamicin. However, because of the emergence of beta-lactamase producing strains, empirical treatment is now based on beta-lactamase-stable cephalosporins.

  Preferred treatment for native-valve endocarditis due to HACEK organisms is therefore with intramuscular or intravenous ceftriaxone (usually in a dose of 2 g once daily) for 4 weeks,[4,6-8] although cefotaxime[4] or other third-generation cephalosporin may be used instead. UK guidelines recommend addition of gentamicin for the first 2 weeks of therapy.[6] Alternatively, if the isolate is penicillin sensitive, ampicillin plus 2 weeks of gentamicin,[6] or ampicillin-sulbactam[8] have been suggested. US guidelines consider that a fluoroquinolone such as ciprofloxacin for 4 weeks, by mouth or intravenously, may also be effective.[8]

- **Endocarditis due to other organisms**. Treatment of endocarditis due to other organisms depends greatly on the organism and its susceptibility; early surgery is often required. For endocarditis due to *Pseudomonas* spp. a combination of an antipseudomonal beta-lactam with tobramycin has been suggested.[5,7] Endocarditis associated with the intracellular pathogen *Coxiella burnetii* requires very prolonged therapy with doxycycline,[6,7] in combination with rifampicin[7] or a fluoroquinolone such as ciprofloxacin.[6] Regimens suggested for *Bartonella* endocarditis have included a penicillin or ceftriaxone in combination with gentamicin, or doxycycline plus gentamicin.[6,8] For other potential causes of culture-negative endocarditis, empirical treatment with a penicillin or vancomycin plus gentamicin, sometimes in combination with a third antibiotic such as rifampicin or ciprofloxacin, has been suggested.[4,7,8]

Endocarditis prophylaxis.

Because of the potentially severe consequences of endocarditis, prophylaxis is widely practised in patients considered to be at increased risk when they are exposed to procedures likely to produce bacteraemia, although much of the evidence to support the practice is circumstantial and the benefits and risks therefore hard to calculate. Patients who have been considered to be at risk of developing endocarditis include those with:[4,7,9]

- acquired valvular heart disease
- congenital heart disease, including septal defects, tetralogy of Fallot, or aortic stenosis
- hypertrophic cardiomyopathy
- mitral valve prolapse with valvular regurgitation
- prosthetic valves or shunts
- a history of endocarditis

Traditionally, these groups have been subdivided into those at moderate and high risk, but some guidelines no longer make such a distinction.

As for treatment, guidelines have been periodically issued to guide the selection of antibacterials for prophylaxis before various procedures in patients at risk.[4,7,9-11] Procedures that have been thought likely to produce bacteraemia and therefore to require prophylactic treatment include any dental intervention likely to cause bleeding, other oral or upper-respiratory tract operations such as tonsillectomy, certain gastrointestinal procedures such as sclerotherapy for oesophageal varices or biliary-tract surgery, and some urinary-tract surgery.[4,7,9] Whether prophylaxis is truly needed before dental procedures is a subject of controversy. US guidelines[10] recommend antibacterial prophylaxis only for dental procedures that involve manipulation of gingival tissues or periapical region of teeth, or perforation of oral mucosa in patients considered to be at the highest risk of developing adverse outcomes from endocarditis (such as those with a history of infective endocarditis, cardiac valve replacement surgery, or some patients with congenital heart disease). US guidelines also recommend antibacterial prophylaxis for high-risk patients for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue, but do not recommend prophylaxis for genitourinary or gastrointestinal tract procedures. Similar recommendations were made in the UK by the British Society for Antimicrobial Chemotherapy in 2006[9] but subsequent guidelines issued by NICE[11] and adopted by the *BNF* essentially abolished the requirement for standard antibacterial prophylaxis in any procedure.

Antibacterial prophylaxis is aimed mainly at viridans streptococci and HACEK organisms before dental, oral, respiratory, and oesophageal procedures, and at enterococci, *Strep. bovis*, and the Enterobacteriaceae before gastrointestinal and genito-urinary procedures.[7] Drugs should be given in a regimen that assures adequate blood concentrations throughout the procedure. They are generally given as a single dose before the procedure, sometimes repeated about 6 hours later; the oral route is used if possible.

- A penicillin such as amoxicillin is the basis for prophylactic therapy, typically in a single dose of 2 to 3 g by mouth or 1 to 2 g intravenously.[4,7,9,10] For *dental* procedures it may be replaced, in patients allergic to penicillin or who have received more than a single dose in the previous month, by clindamycin 600 mg orally or 300 to 600 mg intravenously, or by azithromycin 500 mg orally. All oral drugs should be given 1 hour before the procedure.[4,7,9,10]

- For *gastrointestinal* or *genito-urinary* procedures the penicillin is usually combined with a single dose of gentamicin 1.5 or 2 mg/kg intravenously or intramuscularly before the procedure; a second dose of amoxicillin (typically half the initial dose) may be given after 6 hours. In patients allergic to penicillin, or who have received more than a single dose of penicillin in the previous month, amoxicillin may be substituted with an infusion of 1 g of vancomycin over 1 to 2 hours before the procedure, or injection of 400 mg of teicoplanin immediately beforehand.[4,7,9]
- For *nasal packing and intubation* flucloxacillin 1 g intravenously is given; in penicillin allergic patients clindamycin 600 mg intravenously may be used.[9]
- For *infected skin, skin structure, or musculoskeletal tissue* procedures a penicillin such as amoxicillin is usually given in a single oral or intravenous dose of 2 g, or a cephalosporin such as cefalexin is given in a single oral dose of 2 g. Vancomycin or clindamycin may be given to patients allergic to penicillin or who are known or suspected of having an infection caused by a meticillin-resistant strain of staphylococcus.[10]

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Endometritis

Endometritis (or endomyometritis) is a uterine infection that may be a part of pelvic inflammatory disease (p.184) or may be a postoperative complication of caesarean section.

Antibacterial prophylaxis may be given at caesarean section after cord clamping to prevent postpartum endometritis as well as wound infection. While the use of antimicrobial prophylaxis in patients at high risk of infection is well established, prophylaxis in low-risk patients remains controversial. A systematic literature review[1] has shown prophylaxis to be beneficial after both elective and non-elective caesarean section, but USA surgical guidelines do not recommend routine prophylaxis in low-risk patients.[2] A penicillin or first-generation cephalosporin such as cefazolin is often used.[2]

Early postpartum endometritis has a polymicrobial aetiology. In one study the most common organisms isolated included *Gardnerella vaginalis*, *Peptococcus* spp., *Bacteroides* spp., *Staphylococcus epidermidis*, group B streptococci, and *Ureaplasma urealyticum*.[3] *Chlamydia trachomatis* has been implicated more often in late postpartum endometritis, but a wide variety of micro-organisms may also be responsible including genital mycoplasmas and, to a lesser extent, facultative and anaerobic bacteria.[4]

In the USA, standard empirical therapy for postpartum endometritis has been a short course of intravenous antibacterials, often clindamycin with gentamicin, given until the patient has been afebrile and asymptomatic for 24 to 48 hours and sometimes followed by a course of oral treatment, often amoxicillin. A systematic review[5] has confirmed the suitability of clindamycin with gentamicin and indicated that oral therapy is not necessary after successful intravenous therapy. It may, however, be recommended in patients with staphylococcal bacteraemia.[2]

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Enterococcal infections

Enterococcal infections are causing increasing concern, particularly with the emergence of drug-resistant strains.[1-6] Enterococci, principally *Enterococcus faecalis* (formerly *Streptococcus faecalis*) but also *E. faecium* and *E. avium*, can cause infections including those of the biliary tract and urinary tract, endocarditis, and peritonitis. Since they are frequently present in the gut flora they are a common cause of nosocomial infections. Enterococci are resistant to cephalosporins, tetracyclines, macrolides, and chloramphenicol. The emergence of resistance to gentamicin, penicillins, and the glycopeptide antimicrobials vancomycin and teicoplanin has compromised the previously standard treatment for enterococcal infections of a penicillin or glycopeptide with gentamicin. Further therapeutic options have more recently emerged with the development of linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin for the treatment of vancomycin-resistant enterococcal infections,[7] although the latter is active against *E. faecium* but not against *E. faecalis.* There has, however, been a report of enterococcal resistance to linezolid.[8] In general, there can be no recommendations for treatment at present and the choice of antibacterial should be made according to local patterns of resistance and antibacterial sensitivity tests. The lack of effective antibacterials has placed emphasis on measures to prevent the spread of vancomycin-resistant enterococci.[9]

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Epididymitis

Epididymitis is often associated with urethritis, and in young men (less than 35 years) occurs most commonly as a complication of sexually transmitted infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, but may occur in homosexual males as a result of infection with enteric organisms, particularly *Escherichia coli*.

In men over 35 years and in children, epididymitis is not usually sexually transmitted but generally results from bacteriuria secondary to urinary-tract infection with *Pseudomonas aeruginosa* and other Gram-negative bacilli, urinary-tract instrumentation or surgery, systemic disease, or immunosuppression.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of epididymitis are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO:**
  for chlamydial epididymitis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single dose of oral azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p.191).
- **UK:**
  for probable chlamydial infections or infections with other non-gonococcal, non-enteric organisms:
  - oral doxycycline 100 mg twice daily for 10 to 14 days is recommended

  for infections with enteric organisms:
  - oral ofloxacin 200 mg twice daily for 14 days, *or*
  - oral ciprofloxacin 500 mg twice daily for 10 days

  for disease most probably due to gonococcal infection:
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - a single oral dose of ciprofloxacin 500 mg *plus* oral doxycycline 100 mg twice daily for 10 to 14 days

  in patients allergic to cephalosporins and/or tetracyclines infections from all causes may be treated with:
  - oral ofloxacin 200 mg twice daily for 14 days
- **USA:** empirical treatment recommended:
  likely cause gonococcal or chlamydial infection:
  - a single intramuscular dose of ceftriaxone 250 mg *plus* oral doxycycline 100 mg twice daily for 10 days

  likely cause an enteric organism *or* in patients allergic to cephalosporins and/or tetracyclines:
  - oral ofloxacin 300 mg twice daily for 10 days, *or*
  - oral levofloxacin 500 mg once daily for 10 days

Sexual contacts should also be treated if epididymitis is caused by a sexually transmitted pathogen.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

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Epiglottitis

In acute epiglottitis rapid swelling of the epiglottis and surrounding soft tissues results in sudden airway obstruction which can be fatal. It is often due to bacteraemic infection with *Haemophilus influenzae* type b (see p.174) and has occurred mainly in young children, although the incidence has decreased in this age group since the introduction of Haemophilus influenzae vaccine.[1] Acute epiglottitis also occurs in adults.[1]

Treatment and prophylaxis is similar to that for Haemophilus influenzae meningitis (see under Meningitis, p.178). Immediate management includes the maintenance of an adequate airway and the intravenous use of antibacterials active against *H. influenzae* type b. Chloramphenicol has been the drug of choice, but third-generation cephalosporins such as cefotaxime and ceftriaxone are increasingly used.[2,3] Prophylaxis with rifampicin may be given to index cases and contacts.

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Escherichia coli enteritis

See p.173.

Eye infections

Conjunctivitis is a common superficial eye disorder and may be caused by infection with bacteria, viruses, or, less often, fungi. Acute bacterial conjunctivitis is often caused by staphylococci or streptococci in adults, and *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) in children. Other causes of bacterial conjunctivitis include gonococci (see Gonorrhoea, p.191) and *Chlamydia trachomatis* (see Trachoma, p.196). Neonatal chlamydial and gonococcal conjunctivitis are discussed under Neonatal Conjunctivitis, p.180. Uncomplicated bacterial conjunctivitis may be self-limiting but empirical treatment with topical antibacterials is often given. In the UK, topical chloramphenicol remains the treatment of choice despite concerns over the potential risk of aplastic anaemia (see Ocular Use under Precautions of Chloramphenicol, p.240). Alternatives include gentamicin, tobramycin, erythromycin (especially when infection with Gram-positive organisms is suspected), fluoroquinolones including ciprofloxacin and ofloxacin, framycetin, fusidic acid (especially for staphylococcal infections), and polymyxin B in combination with bacitracin, trimethoprim, or neomycin.

Blepharitis is an infection of the lid margins. It usually presents as a chronic condition and may require prolonged treatment, typically involving local hygiene to remove encrustations and topical application of a broad-spectrum antibacterial ointment.

Keratitis may be caused by infection of the cornea by bacteria, fungi, viruses, or protozoa, usually after trauma to the surface of the eye, including that due to contact lens wear (see Contact Lens Care, p.1622). Common bacterial pathogens include staphylococci, streptococci, *Pseudomonas* spp., and Enterobacteriaceae. Bacterial keratitis is potentially sight-threatening and requires prompt aggressive treatment with broad-spectrum antibacterials. It is customary to obtain material for sensitivity testing, but increasingly, empirical treatment is then begun without delay. Frequent or continuous topical application of drops or the use of local drug delivery devices have been used to ensure prolonged elevated drug concentrations. Subconjunctival or systemic therapy may occasionally be necessary. Topical treatment with cefazolin and either gentamicin or tobramycin has traditionally been used when *Pseudomonas* is not suspected. More recently, fluoroquinolones or ceftazidime have been used, and semisynthetic penicillins or vancomycin are other alternatives. For the treatment of Acanthamoeba keratitis, see p.822.

Endophthalmitis is a devastating ocular disease resulting from infection of the ocular cavity, usually after penetrating trauma or surgery. Depending on the route of infection, causative organisms often include staphylococci, streptococci, *H. influenzae*, *Bacillus cereus*, and *Propionibacterium acnes*. Fungal infections occur less commonly. Bacterial endophthalmitis requires immediate aggressive treatment with antibacterials, usually given intravitreally. The value of concurrent parenteral antibacterials is unclear. The choice of antibacterial for intravitreal use depends on the most likely pathogen. Third-generation cephalosporins or vancomycin are used, but aminoglycosides may produce retinal toxicity. Clindamycin may be effective if *B. cereus* is suspected. Adjunctive treatment includes vitrectomy, surgical removal of infected lens structures, and corticosteroids to control inflammatory and immune responses.

For a discussion of fungal infections of the eye, see p.519; for cytomegalovirus retinitis and ocular herpes simplex infections, see under Cytomegalovirus Infections, p.853, and Herpes Simplex Infections, p.854, respectively.

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Gas gangrene

Clostridium spp. are anaerobic Gram-positive bacteria some of which cause gas gangrene with muscle necrosis and systemic toxicity as a result of toxin formation. *Cl. perfringens* is the species most frequently responsible. Gas gangrene is usually associated with traumatic or surgical wounds. The main treatment is surgical debridement of all necrotic muscle and large doses of benzylpenicillin. Alternative antibacterials have included clindamycin, metronidazole, imipenem, a tetracycline, or chloramphenicol. Hyperbaric oxygen is used as an adjunct to surgical debridement. Gas-gangrene antitoxins are rarely used nowadays.

Benzylpenicillin is also recommended as prophylaxis against gas gangrene in patients undergoing high amputations of lower limbs or after major trauma; metronidazole is an alternative in patients allergic to penicillin.

Gastro-enteritis

Diarrhoea is a symptom of simple gastro-enteritis and of most intestinal infections. It is a major problem in developing countries, but is common worldwide. Although viruses are often responsible, the severest forms of infectious diarrhoea are generally those due to bacteria. Common bacterial pathogens include *Campylobacter jejuni*, *Escherichia coli*, *Salmonella enteritidis*, *Shigella* spp., *Vibrio cholerae*, and *Yersinia enterocolitica*. Intestinal protozoa also cause diarrhoea and are important in AIDS-associated diarrhoea. For discussions of viral and protozoal gastro-enteritis and their treatment, see p.850 and p.824, respectively.

In acute diarrhoea (p.1694) of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Acute, watery diarrhoea caused by non-invasive pathogens is usually self-limiting and may be treated conservatively. Inflammatory diarrhoea, predominantly caused by invasive pathogens and affecting the colon, often requires treatment with antibacterials. Guidelines published in the UK[1] recommended that empirical treatment of acute diarrhoea with antibacterials should be reserved for patients with symptoms suggesting infection with invasive pathogens and those at high risk of complications. Similarly antibacterial treatment was considered appropriate in tropical regions for diarrhoea due to invasive but not non-invasive organisms.[2] Nevertheless, some clinicians consider such an approach to be unnecessarily conservative in adults with severe acute diarrhoea in developed countries[3] in whom empirical treatment with fluoroquinolones can relieve symptoms and shorten the illness without significant adverse effects. In the USA, empirical therapy is considered for any patients in whom a bacterial cause is suspected; stool samples should be obtained for identification of the causative organism.[4]

In **infants and children** oral rehydration therapy is universally recognised as appropriate initial treatment of acute diarrhoea, but it has been underutilised in both developed and developing countries.[2,5,6] Nutritional support and management of secondary complications, including systemic infections, is also particularly important in this age group.[2] Antibacterials have little place in management in most cases and their inappropriate use has contributed to a high prevalence of resistance in commensal bacteria.[5] WHO[6,7] has stipulated that antibacterials should only be used in children with acute diarrhoea when there is dysentery or suspected cholera; *Shigella* is the most important cause of dysentery in young children. Giardiasis and amoebiasis should also be treated. WHO emphasised[6] that oral preparations containing streptomycin or dihydrostreptomycin, neomycin, halogenated hydroxyquinolines, or nonabsorbable sulfonamides (sulfaguanidine, succinylsulfathiazole, phthalylsulfathiazole) should not be used.

Persistent or prolonged diarrhoea may not have an infective cause and antibacterial treatment should not be started unless a pathogen can be identified. **Tropical sprue**, a syndrome characterised by malabsorption often presenting as chronic diarrhoea, is believed to have an infective component and may respond to tetracycline, although this may be less effective in indigenous populations than in expatriates.[2]

HIV-associated diarrhoea. Diarrhoea is common in HIV infection and AIDS (p.856) and causative organisms may be bacterial, protozoal, or viral. The most common bacterial cause is the *Mycobacterium avium* complex (see Nontuberculous Mycobacterial Infections, p.181); others include *Campylobacter*, *Salmonella*, and *Shigella* spp. Supportive care and appropriate conventional antibacterial therapy may be adequate, as described under the specific infections, below.

'Food poisoning' is generally a self-limiting form of gastro-enteritis, although serious outbreaks of foodborne illness have been associated with bacteria such as *Salmonella enteritidis*. Other common food-poisoning organisms include *Listeria monocytogenes*, *Campylobacter* spp., *Yersinia enterocolitica*, *Vibrio parahaemolyticus*, and *E. coli*. An enterotoxin is responsible for food poisoning associated with *Staphylococcus aureus*, *Clostridium* spp., and *Bacillus* spp.[8,9]

Travellers' diarrhoea. Acute diarrhoea associated with travel occurs worldwide. The most common bacterial pathogen is enterotoxigenic *E. coli*, although enteroadherent *E. coli* is also sometimes involved. Other bacteria include *Campylobacter jejuni*, *Salmonella* and *Shigella* spp., *Vibrio cholerae*, and non-cholera vibrios such as *V. parahaemolyticus*. Viruses and the protozoa *Giardia intestinalis*, *Entamoeba histolytica*, and *Cryptosporidium* may also be responsible. Recommendations for the management of travellers' diarrhoea are published by national and international bodies including WHO, the Department of Health in the UK, and the Centers for Disease Control in the USA. Clinical features depend on the pathogen responsible and treatment varies according to severity and duration of diarrhoea. Onset of diarrhoea is generally delayed with *Giardia* and *Entamoeba* because of the incubation period. Diarrhoea is often mild and self-limiting and increased fluid intake or oral rehydration therapy is usually all that will be required. Symptomatic treatment with antimotility drugs such as loperamide may be of benefit in mild to moderate diarrhoea. Bismuth salicylate may be used to reduce the frequency of diarrhoea. Although antimicrobial therapy is not indicated in most cases of infective diarrhoea, empirical treatment with a fluoroquinolone has been effective for moderate to severe attacks. Co-trimoxazole has also been used, but its use is restricted by its toxicity and increasingly widespread bacterial resistance is of concern. When the infecting bacteria are known, specific therapy may be necessary, as described below.

The risk of developing travellers' diarrhoea can be reduced by avoiding possibly contaminated foods as embodied in the advice to '***cook it, boil it, peel it, or forget it***'. Prophylactic drug regimens have been suggested, including various antibacterials, usually a fluoroquinolone or co-trimoxazole, in addition to bismuth salicylate. However, routine antimicrobial prophylaxis is not generally recommended because of the danger of drug reactions, superinfections, and increasing bacterial resistance; it should be reserved for those at special risk.[10] Many authorities prefer early treatment, including self-medication, with clear instructions on when medical help should be sought.

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Antibiotic-associated colitis. Although other organisms, including *Candida* spp.,[1] have been implicated in antibiotic-associated diarrhoea, colonisation of the colon with *Clostridium difficile*, a toxin-producing Gram-positive anaerobe, is the most common identifiable cause of antibiotic-associated colitis and pseudomembranous colitis. Restrictive antibacterial policies have decreased the incidence of *Cl. difficile*-associated diarrhoea in some hospitals[2] but it remains a major hazard of antibacterial use. Antibiotic-associated colitis has been associated with the use of most antibacterials, but particularly with clindamycin, lincomycin, ampicillin, amoxicillin, and cephalosporins and, less frequently, with fluoroquinolones, tetracycline, carbapenems, and trimethoprim. The diarrhoea may be mild and self-limiting or debilitating and persistent and can be life-threatening. Although the diarrhoea generally resolves within a few days of stopping the offending drug, together with fluid and electrolyte replacement, early specific antibacterial therapy should be given to patients with severe illness characterised by high fever, marked abdominal pain, and marked leucocytosis and to elderly, toxic, or debilitated patients, or those unresponsive to supportive therapy.[3,4] Antibacterials are probably unnecessary in mild disease.[5] Antidiarrhoeal drugs should be avoided since they may aggravate the condition and may occasionally increase the possibility of toxic megacolon.[3]

Vancomycin or metronidazole are widely used when antibacterial treatment is necessary.[3,4,6,7] Metronidazole tends to be the drug of first choice and vancomycin is reserved for those who do not respond to, or who cannot tolerate, metronidazole, for those who are severely immunocompromised, and for those with severe illness.[3,4,6-8] This view is also endorsed by expert bodies in the USA whose aim is to provide guidelines for preventing the spread of vancomycin resistance.[9] Metronidazole can be given orally or intravenously as appropriate. Vancomycin is only given orally; it should not be given intravenously since it does not give rise to adequate concentrations of the drug in the bowel lumen.[3] The severity of the diarrhoea often decreases within 48 to 72 hours, but may not stop for a week or more. Treatment is usually continued for 10 days.[6] Relapses are quite common,[8] but usually respond to re-treatment with vancomycin or metronidazole.[3,8]

Other drugs that have been investigated in the treatment of antibiotic-associated colitis include teicoplanin,[10-12] fusidic acid,[12,13] and bacitracin,[14] although experience with their use remains limited. A systematic review[5] found that metronidazole, bacitracin, rifaximin, nitazoxanide, or fusidic acid seemed to be as effective as vancomycin in terms of symptomatic cure, and teicoplanin might be slightly more effective. Bacitracin and fusidic acid seemed to be less effective than vancomycin in terms of bacteriological cure and resolution.[5] Ramoplanin and tiacumicin B (OPT-80) have also been investigated.[7]

The anion-exchange resins colestyramine and colestipol hydrochloride have been shown to bind the *Cl. difficile* toxin *in vitro*, and colestyramine has been used to treat pseudomembranous colitis.[15] The use of vancomycin together with colestyramine has been suggested,[16] but the value of the combination is uncertain. In general, the use of colestyramine is not recommended.[6] An experimental toxin-binding polymer, tolevamer has also been investigated.[7]

Oral immunoglobulin A, used with vancomycin, was effective in controlling severe diarrhoea in a child who had not responded to other therapies.[17] Normal immunoglobulin given intravenously was also effective when added to vancomycin and metronidazole therapy in 2 elderly patients unresponsive to antibacterials alone.[18] Vaccines against *C. difficile* have also been investigated.[7]

Treatment and prevention strategies aimed at colonising the gut with non-pathogenic organisms have included use of lactic-acid-producing organisms such as *Lactobacillus*,[4,19] and the yeasts *Saccharomyces boulardii*,[4] and *S. cerevisiae*.[20]

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Campylobacter enteritis. *Campylobacter jejuni* is a major cause of acute diarrhoea. *C. coli* is less common and *C. upsaliensis* has more recently been identified as an enteropathogen.[1,2] Food is a common source of infection.[3,4] In the UK, several sources are responsible[5] including contaminated food and water and one important source is from doorstep deliveries of foil-topped bottled milk that have been pecked by birds.[5-7]

The macrolides erythromycin or azithromycin are of benefit[8] in severely affected patients, but the infection is usually self-limiting and fluid and electrolyte replacement is generally sufficient. A fluoroquinolone, a tetracycline, or gentamicin may be alternative antimicrobials.[8] Treatment with erythromycin can eradicate the organism from the faeces,[9-11] but may not reduce the duration of symptoms unless treatment is started early in the course of the disease.[9-11] Some strains of *Campylobacter* are resistant to erythromycin,[12] and resistance is also an increasing problem with ciprofloxacin.[13,14] Multiple drug resistance has been reported.[15,16]

Severe systemic infections with *C. fetus* require parenteral therapy with a third-generation cephalosporin or gentamicin,[8] depending on susceptibility.

There is some evidence of an association between *C. jejuni* infection and the Guillain-Barré syndrome.[17,18]

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Cholera and other vibrio infections. Cholera results from infection with the enterotoxin-producing Gram-negative bacillus *Vibrio cholerae* which causes acute secretory diarrhoea. It can be associated with two serogroups of *V. cholerae*, O1 and O139. Serogroup O1 can then be divided into two biotypes (classical and El Tor) and each of these has three serotypes (Inaba, Ogawa, and Hikojima). The seventh pandemic[1-6] began in 1961 in South East Asia, and reached South America in January 1991. This pandemic is caused by *V. cholerae* O1 biotype El Tor. In late 1992 and 1993 epidemic cholera caused by *V. cholerae* O139 was reported in India and Bangladesh and subsequently identified in Thailand and other Asian countries. *V. cholerae* O139 became the dominant strain in India in less than 2 months and some workers declared it responsible for the eighth cholera pandemic.[2] However, there was some evidence that by 1994 it was abating and that by 1996 O1 was again the prevalent type in India and Bangladesh. There appears to be no cross-immunity between O1 and the O139 serogroup.

Individuals can reduce the risk of contracting cholera by good personal hygiene, avoiding possibly contaminated foodstuffs, and by boiling or otherwise disinfecting drinking water. Methods of preventing or containing cholera epidemics include ensuring a safe water supply, providing good sanitation, and promoting safe handling and preparation of foods. Mass chemoprophylaxis, vaccination, and travel and trade restrictions are not effective[7] although oral vaccines show more promise.

Most cases of vibrio gastro-enteritis are mild to moderate and generally require no therapy other than fluid and electrolyte replacement with an appropriate oral rehydration solution (see Diarrhoea, p.1694). Patients with severe gastro-enteritis, dehydration, and shock should receive vigorous fluid replacement, preferably intravenously.[8] Antimicrobial therapy has been shown to decrease the duration and volume of diarrhoea in cholera and may also decrease the duration of other vibrio diarrhoeas.[9] WHO recommends a single dose of doxycycline as the treatment of choice for adults except pregnant women. Tetracycline, ciprofloxacin, co-trimoxazole, furazolidone, erythromycin, and chloramphenicol are alternatives, with furazolidone being preferred for pregnant women and erythromycin for children. Recommendations from the USA for adults specify a tetracycline as the first choice with co-trimoxazole or a fluoroquinolone such as ciprofloxacin as alternatives.[10] One study has suggested that single-dose ciprofloxacin might be preferred to doxycycline, particularly in areas of tetracycline resistance,[11] and in Bangladesh, ampicillin has been found to be as effective as either erythromycin or tetracycline[12] and may be a useful alternative in children. Studies[13-15] in Bangladesh and India found single-dose azithromycin to be effective in children and adults. The O139 strain is reported to be sensitive to ciprofloxacin,[16] erythromycin,[16] and tetracyclines,[2] but resistant to co-trimoxazole.[2] There has also been some resistance to furazolidone.[2] Multiple drug resistance may be a problem; differing sensitivity and resistance patterns have been reported for the 2 biotypes classical and El Tor *V. cholerae*.[17] The outbreak strain in Rwandan refugees was resistant to tetracycline, doxycycline, co-trimoxazole, chloramphenicol, and ampicillin.[2]

Mass chemoprophylaxis is not recommended but may be justified for household contacts,[1,18] especially those at high risk because of age or pregnancy.[1] The type of cholera vaccines traditionally available are not very effective although promising results have been reported with the use of oral vaccines in areas where cholera is endemic.

Marine or halophilic *Vibrio* spp. known to cause gastro-enteritis include *V. parahaemolyticus* which is responsible for food poisoning from raw or undercooked seafood, especially in Japan.[19,20] Another halophilic sp., *V. vulnificus*, is increasingly associated with wound infection and septicaemia.[19] On the basis of *in-vitro* sensitivity testing[21] and anecdotal clinical experience, empirical therapy with aminoglycosides, ceftazidime, imipenem, or ciprofloxacin should all be effective.[22]

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Escherichia coli enteritis. *Escherichia coli* is a normal intestinal commensal and member of the Gram-negative family of bacteria the Enterobacteriaceae. Pathogenic strains causing distinct syndromes of diarrhoeal disease and also associated with foodborne illness include: enteropathogenic *E. coli* (EPEC)—an important cause of infantile diarrhoea in many developing countries; enteroinvasive *E. coli* (EIEC)—producing an invasive type of diarrhoea resembling that of *Shigella* dysentery; enterotoxigenic *E. coli* (ETEC)—an important cause of travellers' diarrhoea (see Gastro-enteritis, above); and enterohaemorrhagic *E. coli* (EHEC)—associated with haemorrhagic colitis, haemolytic-uraemic syndrome, and thrombotic thrombocytopenic purpura.[1] Enteroadherent *E. coli* (EAEC) is a cause of chronic diarrhoea in young children.[2]

Although these organisms are generally sensitive to a wide range of antibacterials only special categories of *E. coli* diarrhoea should be treated.[2]

Neonates with severe EPEC diarrhoea have been given oral non-absorbable antibacterials such as neomycin or gentamicin although in older children or adults this diarrhoea may be self-limiting.[2] Evidence for the efficacy of neomycin is largely limited to uncontrolled studies.[3] However, improvement with antibacterials has been noted beyond the neonatal period;[4] EPEC infection has been reported to be a common treatable cause of life-threatening *chronic* diarrhoea in infancy, possibly associated with travel to a developing country.[5] Symptoms could become persistent and life-threatening in previously healthy infants, requiring intravenous rehydration and parenteral antibacterials such as gentamicin and penicillin.[5]

Vero cytotoxin-producing strains of EHEC (VTEC; Shiga toxin producing *E. coli*; STEC), in particular serotype O157, have been associated with bloody diarrhoea, haemorrhagic colitis, and haemolytic-uraemic syndrome.[6,7] Children and the elderly are at greater risk of severe disease,[6] but the illness is usually self-limiting.[7] Cases have generally been linked with the consumption of foods derived from cattle, especially undercooked beef and unpasteurised milk, although there have been outbreaks associated with the consumption of fresh vegetables and unpasteurised juices, probably as a result of faecal contamination. Person-to-person spread is also common, and direct spread from infected animals may occur. *E. coli* O157 has also been reported as a cause of epidemic haemorrhagic colitis in Africa, where it may be difficult to distinguish from shigellosis.[8,9] Treatment is generally supportive, including correcting and maintaining the fluid and electrolyte balance.[7] Antibacterial treatment is controversial and there is uncertainty as to whether it influences the course of enterohaemorrhagic *E. coli* infection and the development of haemolytic-uraemic syndrome[10] or thrombotic thrombocytopenic purpura;[6,7,11] the non-antibacterial treatment of these two latter complications is discussed in Plasma, under Thrombotic Microangiopathies, p.1076. Oral preparations of Vero cytotoxin-binding resins are under investigation.

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Necrotising enterocolitis. Necrotising enterocolitis in the newborn is thought to result from hypoxia or ischaemic injury to the intestinal mucosa with subsequent infection. Bacteria implicated in the disease include *Pseudomonas*, *Escherichia coli*, *Klebsiella*, *Salmonella* spp., and *Clostridium* spp. Treatment involves suspension of oral feeding, intravenous fluid therapy, and surgical excision of the affected gut. References to the use of oral vancomycin for the treatment[1] of neonatal necrotising enterocolitis indicate that it may be of benefit. In a comparison of intravenous regimens to treat the condition it was reported that ampicillin with gentamicin appeared as effective as vancomycin with cefotaxime in neonates over 2.2 kg birth-weight, but in smaller neonates results were better with vancomycin and cefotaxime.[2] A systematic review has concluded that prophylactic oral antibacterials might well reduce the incidence of necrotising enterocolitis in low birth-weight or preterm infants in a high-risk environment,[3] but there are concerns about adverse outcomes, and prophylactic use (particularly of vancomycin) is not generally recommended because of the risk of inducing resistance. It has been suggested[4] that oral immunoglobulins may prevent necrotising enterocolitis in low-birth-weight infants; however, a systematic review[5] concluded that the available evidence did not support this claim. There is, however, some evidence[6] of the value of probiotics in this group. Supplementation with arginine has also been investigated,[7] but there is insufficient evidence to determine its value.

Necrotising enteritis in older children and adults, known as pigbel, has been attributed to toxins produced by *Clostridium perfringens*. Both sporadic and epidemic forms are mainly seen in the highlands of Papua New Guinea, but sporadic cases have been reported elsewhere. Treatment is supportive with surgical intervention where necessary. A vaccine is available for prophylaxis.

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Salmonella enteritis. *Salmonella* spp. are Gram-negative bacteria belonging to the Enterobacteriaceae family. They can be divided into those causing enteric fever, namely *S. typhi* and *S. paratyphi*, where infection is systemic although affecting the gastrointestinal tract (see under Typhoid and Paratyphoid Fever, p.198) and non-typhoid *Salmonella*, including *S. enteritidis* and *S. typhimurium* which cause acute gastro-enteritis, usually through food poisoning. There are numerous *Salmonella* serotypes identified with food poisoning and they have often been named according to the place where they were first isolated. The increase in salmonellosis in Great Britain has been almost entirely due to *S. enteritidis*[1] and this reflects an increase internationally.[2] Non-typhoid *Salmonella* spp. can cause invasive salmonellosis which may present as septicaemia or localised infections such as meningitis or osteomyelitis.

Uncomplicated non-typhoid *Salmonella* enteritis is usually managed by fluid and electrolyte replacement. Antibacterial therapy produces no clinical benefit in uncomplicated *Salmonella* enteritis[3] and may prolong *Salmonella* detection in stools.[3] Attempts to eradicate the carrier state with antibacterial therapy (for example fluoroquinolones) appear to have been unsuccessful so far[4] and routine use is not recommended.[5] Patients with underlying debility or evidence of invasive salmonellosis should be given antibacterial therapy. Amoxicillin, ampicillin, or co-trimoxazole have been suggested[6,7] as have trimethoprim, ceftriaxone,[7] azithromycin,[7] a fluoroquinolone[7] such as ciprofloxacin,[8] or chloramphenicol.[7] However, there is concern over the emergence of resistant strains, particularly to the fluoroquinolones.[9,10] Resistance to cephalosporins has also been recognised.[11,12] Multiresistant R-type strains of *S. typhimurium* DT 104 (another common cause of *Salmonella* enteritis in the UK) have severely limited the treatment options for infections with this organism.[13-16]

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Shigellosis. Shigellosis (bacillary dysentery) is an enteric infection caused by the *Shigella* spp. *S. dysenteriae*, *S. flexneri*, *S. boydii*, or *S. sonnei*. They are Gram-negative bacteria belonging to the Enterobacteriaceae family and are able to invade the colon. Depending on the species involved, the disease ranges from mild self-limiting secretory diarrhoea to severe colitis and dysentery with blood and mucus in the stools. *S. dysenteriae* is the most common in the developing world and causes the most severe disease. In developed countries *S. flexneri* and *S. sonnei* are more common. Some *S. flexneri* can cause severe colitis and toxic dilatation of the colon has been reported in travellers.[1] *S. sonnei* is the least pathogenic of the species.

As with any form of diarrhoea, rehydration is the key to treatment.[2] Antibacterial therapy may be with ampicillin (amoxicillin appears to be less effective), co-trimoxazole (or trimethoprim), nalidixic acid, or fluoroquinolones such as ciprofloxacin, but will depend on the prevailing resistance patterns (see below) and the severity of the disease. Bacterial resistance is common and some consider that antibacterials should be restricted to the most severe cases, particularly those due to *S. dysenteriae*;[3] in the UK, the Public Health Laboratory Services (PHLS) Working Group has concluded that therapy is seldom indicated for *S. sonnei* infections.[4] WHO[5] has advised that children with *Shigella* dysentery should be given antimicrobial therapy and recommended co-trimoxazole as treatment of choice with nalidixic acid or ampicillin as alternatives; it was noted that resistance to ampicillin is frequent.[6]

The rapid development of resistance and the emergence of multiresistant strains of *Shigella*, particularly in developing countries, has led to some changes in treatment recommendations.[6] In 1992, nalidixic acid had become the preferred drug in developing countries unless ampicillin or co-trimoxazole were known to be effective in the region.[7] For *S. dysenteriae* it might be necessary to use pivmecillinam. It was concluded that the fluoroquinolones should continue to be reserved for infections resistant to nalidixic acid or pivmecillinam.[7] Reduced susceptibility to fluoroquinolones of some strains of *S. sonnei* has been reported from Japan,[8] and fluoroquinolone-resistant *S. dysenteriae* has been reported.[2] Fluoroquinolones are generally not used in children, although a study[9] in Bangladesh has used ciprofloxacin in children with shigellosis and found it to be of similar efficacy to pivmecillinam. In studies from Israel, the third-generation cephalosporins ceftriaxone[10] or cefixime[11] were more effective than ampicillin or co-trimoxazole, respectively, in children with shigellosis. Other studies in adults in Bangladesh found cefixime to be ineffective compared with pivmecillinam[12] and azithromycin to be effective, although slightly less so, than ciprofloxacin.[13] Rifaximin has also been investigated.[2]

Vitamin A may be a useful adjunct to treatment, especially in children in developing countries (see Diarrhoea, under Vitamin A, p.1973).

Oral shigella vaccines are being studied for prophylaxis.

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Yersinia enteritis. *Yersinia enterocolitica* is a Gram-negative bacteria of the Enterobacteriaceae family and the species most commonly responsible for yersiniosis. The predominant form of infection is an enteric illness with or without mesenteric adenitis[1] although clinical manifestations can range from self-limited enterocolitis to potentially fatal systemic infection, and post-infection complications can include erythema nodosum and reactive arthritis.[2] *Y. enterocolitica* is a recognised foodborne pathogen[3] and in some temperate countries rivals *Salmonella* and exceeds *Shigella* as a cause of acute gastro-enteritis; pigs are a major reservoir. Increased susceptibility to *Yersinia* infection has occurred in patients with iron overload treated with desferrioxamine (see p.1440).

Isolates of *Y. enterocolitica* are reported to be susceptible to co-trimoxazole, aminoglycosides, chloramphenicol, tetracycline, third-generation cephalosporins, and quinolones *in vitro*.[1,2] As with any form of diarrhoea, rehydration is the key to treatment and most forms of mild uncomplicated enteritis do not require antibacterial treatment. There has been no general consensus concerning the antibacterial of choice when treatment becomes necessary: as with many other enteric infections there is a lack of good clinical evidence. Drugs with good intracellular activity such as trimethoprim, co-trimoxazole, tetracycline, chloramphenicol, or fluoroquinolones may be preferred.[1] Doxycycline or co-trimoxazole have been recommended[2] for complicated gastrointestinal and focal extra-intestinal infections or doxycycline and an aminoglycoside empirically in bacteraemia. Co-trimoxazole as first choice or alternatively a fluoroquinolone, an aminoglycoside, or cefotaxime have also been recommended.[4] A patient with chronic *Yersinia* infection who responded well to tetracycline or co-trimoxazole, but relapsed on withdrawal, was treated successfully with ciprofloxacin.[5]

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Gonorrhoea

See under Sexually Transmitted Diseases, p.191.

Granuloma inguinale

See under Sexually Transmitted Diseases, p.192.

Haemophilus influenzae infections

Haemophilus influenzae is a Gram-negative bacterium that colonises the upper respiratory tract in the majority of healthy people. Most are carriers of non-encapsulated strains, but a small proportion carry *H. influenzae* type b, the commonest encapsulated strain. Serious invasive infections have usually been caused by type b strains and have occurred mainly in young children. They include the bacteraemic diseases meningitis, pneumonia, epiglottitis, cellulitis, and arthritis. Non-encapsulated strains commonly cause otitis media, sinusitis, and conjunctivitis and infect patients with chronic bronchitis. However, they too can cause invasive infections such as pneumonia, septicaemia, and meningitis and, with the introduction of *H. influenzae* type b vaccines, non-encapsulated strains may be responsible for a greater proportion of invasive *H. influenzae* disease.

For further details of these infections and their management, see under the specific disease side-headings.

Ampicillin and chloramphenicol have been the antibacterials of choice against *H. influenzae*, but increasing resistance, especially to ampicillin, should be borne in mind; there have been several reports of multiresistant strains.[1-4] Injectable cephalosporins are popular alternatives for multiresistant type b organisms although there is controversy over their effectiveness against fully sensitive strains when compared with ampicillin or chloramphenicol or both; experience has been favourable with cefotaxime and ceftriaxone, but there have been treatment failures in *H. influenzae* meningitis with cefuroxime and there is argument over its efficacy.[5] Meropenem is a further alternative.[6]

For serious *H. influenzae* infections cefotaxime or ceftriaxone are currently preferred. For upper respiratory infections and bronchitis, co-trimoxazole (or trimethoprim in the UK) is preferred; ampicillin, amoxicillin (with or without clavulanic acid), oral second- or third-generation cephalosporins, a tetracycline, a fluoroquinolone, or the macrolides azithromycin or clarithromycin are suggested alternatives.[6]

In the UK, secondary prophylaxis with rifampicin is given after *H. influenzae* type b meningitis (see p.178). A vaccine against *H. influenzae* type b is available and vaccination is included in the infant immunisation schedules in some countries including the UK and USA.

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Helicobacter pylori infections

Antibacterial therapy is used to eradicate *Helicobacter pylori* infection in peptic ulcer disease (p.1702) and MALT lymphoma of the stomach (p.657). The role of *H. pylori* and the value of its eradication in dyspepsia (p.1695) and gastro-oesophageal reflux disease (p.1696) is less clear.

Infections in immunocompromised patients

Patients with a defective immune system are at increased risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, or splenectomy may all cause neutropenia and impaired humoral and cellular immunity in varying degrees. The risk and severity of infections depends upon the duration of compromised immunity, the degree to which immune function is compromised, whether cellular or humoral functions are affected, and upon breaches in physical barriers, for example due to severe mucositis or prolonged vascular access. Thus patients with profound neutropenia or a history of splenectomy are prone to rapidly progressive and potentially life-threatening infections; those with neutropenia induced by cytotoxic chemotherapy or by preparation for transplantation are particularly vulnerable to acute infections whereas those in whom immunosuppression results from viral infections or congenital defects are at lower risk of acute infections.[1] Patients in whom neutropenia persists for more than 10 days are not only at risk of opportunistic bacterial infections but also susceptible to viral, fungal, and parasitic infections.

Infectious diseases are a major cause of morbidity and mortality in patients with AIDS (see HIV-associated Infections, p.857). Some are due to common pathogens, but others are opportunistic and are caused by normally avirulent commensals. Children with HIV infection appear to be at special risk of serious bacterial infections with common encapsulated bacteria. For further reference to some bacterial infections associated with AIDS, see Gastro-enteritis (p.171), Nontuberculous Mycobacterial Infections (p.181), and Tuberculosis (p.196). Fungal, protozoal, and viral infections which can affect immunocompromised patients are discussed in the relevant chapters under Infections in Immunocompromised Patients, p.520, p.824, and p.859, respectively.

Common causative organisms of unexplained fever in neutropenic patients include the Gram-negative bacteria *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* spp. and Gram-positive organisms particularly staphylococci, streptococci, enterococci, and *Corynebacterium* spp. Gram-negative organisms have historically been responsible for most immediate life-threatening infections, but Gram-positive infections are increasing in importance and now predominate in many areas.[1,2] Factors influencing this change include the wider use of selective gut decontamination and of central venous catheters,[3] and possibly the prophylactic use of quinolones.

TREATMENT. Onset of fever in neutropenic patients is indicative of potentially serious infection which may progress to septicaemia and death. The severity of infections depends on numerous factors (see above) and it is therefore difficult to produce a standard drug regimen; in addition, the choice of empirical therapy must be adapted according to prevailing local antibacterial susceptibility patterns. Guidelines have been produced in many countries, of which those issued by the Infectious Diseases Society of America[4] for both the initial and subsequent management of febrile neutropenic patients are fairly typical:

- the patient's risk of life-threatening infection should first be assessed. If the risk is considered high, empirical intravenous antibacterial therapy should be started immediately
- secondly, consideration should be given to whether the patient requires vancomycin therapy. If so, treatment should begin with vancomycin plus cefepime, ceftazidime, or a carbapenem, with or without an aminoglycoside.
- if vancomycin is not indicated, intravenous monotherapy should be given with
  - either a cephalosporin (cefepime, although concerns have been raised about its safety,[5] or ceftazidime) or a carbapenem (imipenem-cilastatin or meropenem) for uncomplicated cases
  - in more complicated cases, or where resistance is a problem, combined treatment should be given with an aminoglycoside and one of cefepime, ceftazidime, a carbapenem, or an antipseudomonal penicillin such as ticarcillin with clavulanic acid or piperacillin with tazobactam.
- low-risk patients may be treated empirically either orally with ciprofloxacin and amoxicillin with clavulanic acid, or intravenously as for uncomplicated cases above. Initial treatment with oral antibacterials alone is, however, not recommended for children[4]

The initial regimen usually needs to be given for 3 to 5 days in order to determine its efficacy. In *patients in whom fever resolves* and in whom a causative organism is identified, antibacterial treatment should be modified for the specific organisms and broad-spectrum antibacterials continued for at least 7 days or until culture results are negative and the patient has clinically recovered.[4] In afebrile patients in whom no causative organism is found but who were considered at high risk at the onset of treatment, the same antibacterials should be continued intravenously; those considered at low risk initially may be switched to oral therapy with ciprofloxacin plus either amoxicillin-clavulanic acid (adults) or cefixime (children).[4]

Patients in whom fever persists throughout the first 3 to 5 days but for whom no aetiology is determined may have a non-bacterial infection, a bacterial infection that is refractory to treatment, the emergence of a second infection, or drug fever.[4] Such patients should be reassessed and then one of three options followed. If the patient's condition is clinically stable, the same antibacterial treatment may be continued; if there is still no change in the patient's condition, consideration should be given to stopping vancomycin if it has been given. Alternatively, if there is evidence of progressive disease or drug toxicity, the antibacterials given may be changed; if vancomycin has not been given, it may be added to the regimen. The third option is to add an antifungal drug (amphotericin B) with or without a change to the antibacterial regimen if the patient is febrile through days 5 to 7 and resolution of neutropenia is not imminent.[4]

The optimum *duration of therapy* is governed by the clinical situation. The most important determinant of successfully stopping antibacterials is the neutrophil count:[4]

- if no infection is identified after day 3, the neutrophil count exceeds 500 cells/mm^3 for 2 consecutive days, and the patient has been afebrile for at least 48 hours, then antibacterial treatment may be stopped
- if neutropenia persists in the absence of fever, it is reasonable to stop antibacterial treatment after 5 to 7 days in patients who were initially considered at low risk and who are clinically well, though such patients should be closely monitored and intravenous antibacterials reinstigated immediately on recurrence of fever or evidence of infection.[4] In afebrile patients with profound neutropenia (less than 100 cells/mm^3), or in those with mucositis or other risk factors, continuous antibacterial treatment should be considered throughout the entire neutropenic period
- in patients with persistent fever and prolonged neutropenia in whom haematological recovery cannot be anticipated, consideration may be given to stopping antibacterials after 2 weeks if no infection has been identified and careful observation is possible.[4]
- clinically well patients with persistent fever may have their antibacterials stopped after 4 to 5 days if the neutrophil count remains at least 500 cells/mm^3 throughout this period and there is no sign of infection and no response to therapy; such patients should be closely monitored for subsequent infections which are usually easily treatable, and empirical amphotericin B should be considered despite cessation of antibacterials if fever persists for 5 to 7 days after the start of initial therapy[4]
- patients who remain febrile after recovery from neutropenia and despite broad-spectrum antibacterials should be reassessed for undiagnosed infection which may be fungal, mycobacterial, or viral

The routine use of colony-stimulating factors as an adjunct to antibacterial treatment is not generally recommended[4] but may be indicated in febrile neutropenic patients at high risk of serious infections or infection-related complications; examples include some patients with malignant neoplasms[6,7] and those with persistent severe neutropenia and infections that are not responsive to antibacterials alone.[4] A systematic review[8] of the use of colony-stimulating factors in patients with febrile neutropenia due to cancer chemotherapy concluded that their use did not affect overall mortality but did reduce time spent in hospital and the neutrophil recovery time.

PROPHYLAXIS. Most infections in immunocompromised patients are caused by organisms from their own alimentary tract and in cancer patients, for example, may follow chemotherapy-induced mucosal damage to the tract. Although antibacterial prophylaxis may be effective in afebrile patients likely to be neutropenic, the efficacy of empirical treatment means that prophylaxis is less widely used[9] and the Infectious Diseases Society of America[4] discourages routine use; reasons include toxicity of the antibacterial, potential fungal overgrowth, and problems of bacterial resistance (see below). Most experience with prophylaxis has been in patients with leukaemia. Possible prophylactic regimens have included selective decontamination of the alimentary tract using oral nonabsorbable antibacterials (see also under Intensive Care, below). Co-trimoxazole has also been widely used.[9] More recently, prophylaxis with fluoroquinolones has been commonly used although, generally, prophylaxis with these drugs has resulted in reduction in Gram-negative but not in Gram-positive infections in immunocompromised patients,[10] and improved morbidity and mortality has not been observed.[11] Combination prophylaxis with fluoroquinolones and phenoxymethylpenicillin[12] or rifampicin[13] has been tried to improve cover against Gram-positive organisms. Nevertheless, concern about the emergence of resistant organisms has led to the recommendation that routine prophylaxis should be avoided.[4]

Immunocompromised patients may benefit from appropriate immunisation against common infections, although precautions relating to the use of live vaccines in such patients should be observed (p.2202).

The duration and severity of neutropenia can be reduced by the use granulocyte or granulocyte-macrophage colony-stimulating factors, and this may be a useful adjunct in infection control in selected patients.[6] Bone marrow protective agents such as amifostine are also being studied.

For further reference to prophylaxis in high-risk patients, see Intensive Care, below.

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Intensive care

Like immunocompromised patients (above), those in intensive care units are often very susceptible to endogenous infections, especially respiratory and urinary-tract infections, arising from gastrointestinal colonisation by aerobic Gram-negative bacilli acquired in hospital. Selective digestive tract decontamination (SDD), using oral non-absorbable antibacterial regimens, and selective parenteral and enteral antisepsis regimens (SPEAR), incorporating selective decontamination with systemic antibacterial prophylaxis, have been used in an attempt to prevent colonisation and infection in these high-risk patients, although their effectiveness is debated. SDD has generally not been widely adopted in the USA[1] particularly in relation to prevention of nosocomial pneumonia,[2] although benefit of short-term use may be seen in some patient groups.[3] It may be more effective in surgical patients.[4]

Selective decontamination is achieved by elimination of aerobic, potentially pathogenic, organisms from the throat and intestines while preserving the indigenous, mostly anaerobic, flora.[5,6] Regimens commonly include two or three non-absorbable or poorly absorbed antibacterial drugs, for example colistin, neomycin, norfloxacin, or polymyxin, with an antifungal, usually amphotericin B. The drugs are usually applied topically to the oropharyngeal mucosa in addition to oral or intragastric dosage, although local application to the oropharynx alone is also reported to be effective.[7,8] A parenteral third-generation cephalosporin, usually cefotaxime, may be given for a few days until oral medication takes effect.[9,10] Strict adherence to the protocol is reported to be necessary for maximum efficacy[11] and constant monitoring for the emergence of antimicrobial resistance is considered essential[10,11] although this has rarely been seen in practice.[11,12] However, most regimens have little or no activity against potential Gram-positive pathogens such as *Enterococcus* spp., and so their use may increase the risk for colonisation and infection with these organisms.[13] There is particular concern over the emergence of vancomycin-resistant strains.

Despite numerous clinical studies, many of which have shown a reduction in potential Gram-negative pathogens[9,10,14] and in the incidence of respiratory-tract infections,[7,8] it has been difficult to demonstrate that SDD or SPEAR reduces mortality.[15-18] Although meta-analyses[19,20] of randomised controlled trials concluded that a combination of a systemic and topical antibacterial could be beneficial it has been argued that the effect was largely due to the systemic component of the treatment.[21] It has been suggested[22] that equivalent infection control could be achieved more economically by emphasis on high standards of hygiene and avoidance of histamine H_2-receptor antagonists, which could allow overgrowth of potentially pathogenic bacteria as a result of the change in gastric pH. Oral decontamination with chlorhexidine may be useful in preventing ventilator-associated pneumonia.[23]

Another potential source of infection in intensive care is from the use of **intravascular catheters**. The organisms implicated most frequently have been coagulase-negative staphylococci.[24] Prevention and control of infection depend on good aseptic technique and care of the insertion site, and also catheter design;[24-27] guidelines have been produced in the USA for the prevention of infection.[28] Catheters should be removed as soon as possible (often after 48 to 72 hours for peripheral lines) and any infections treated promptly with antibacterials; vancomycin or teicoplanin are appropriate for empirical treatment provided resistance is not a problem.[24] There have been some favourable results with antibacterial prophylaxis, but such use is discouraged because of concern over the emergence of resistant organisms.[29] Topical antiseptics and antibacterials have produced promising results.[24] Antibacterials could also prove useful in reducing or eliminating colonisation of the catheter lumen[30] and catheters coated with antibacterials[31] or heparin[32] are under investigation. Randomised clinical studies have shown that the use of catheters coated with minocycline and rifampicin[33] or with antiseptics (p.1624) can reduce the risk of systemic infections. Some evidence suggests that catheters impregnated with minocycline and rifampicin are more effective in minimising risk of infection than those coated with chlorhexidine or sulfadiazine silver.[34]

The importance of maintaining high standards of infection control, including handwashing, in intensive care units has been reinforced by the increasing incidence of nosocomial infections that are difficult to treat such as those due to vancomycin-resistant enterococci and *Acinetobacter.* In one such outbreak due to *A. baumannii* some strains were resistant to imipenem and all other antibacterials except polymyxin B and sulbactam.[35] Intensive infection control measures and irrigation of all open wounds with polymyxin B solution were used to eliminate infection and colonisation.

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Legionnaires' disease

Legionnaires' disease[1] is a legionella pneumonia caused by the Gram-negative bacterium *Legionella pneumophila*. Serious outbreaks have been associated with infected air-conditioning systems or water supplies. Pontiac fever is a milder, usually self-limiting, flu-like illness also caused by *L. pneumophila* as well as by other *Legionella* spp. Legionellosis has been suggested as a broad term to cover pneumonic and non-pneumonic clinical syndromes caused by any *Legionella* spp., which may include *L. bozemanii, L. micdadei* (Pittsburgh pneumonia agent), and *L. wadsworthii*.

The usual treatment for *Legionella* infections is with a macrolide, with erythromycin now increasingly replaced by azithromycin;[2,3] clarithromycin, roxithromycin, or telithromycin may be further acceptable alternative macrolides.[2,3] Fluoroquinolones are also increasingly recommended as alternatives to the macrolides.[1-3] Doxycycline or co-trimoxazole are further alternatives.[4] Rifampicin has been given in addition to fluoroquinolones or doxycycline, especially in severe or deteriorating illness or in immunocompromised patients, although this may be of little further benefit.[3]

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Leprosy

Leprosy (Hansen's disease) is a chronic disease caused by the bacillus, *Mycobacterium leprae*; it has a prolonged incubation period (years) and slow onset of symptoms. Disease results from bacillary infiltration of the peripheral nervous system, skin, eyes, respiratory mucosa, bones, and testes. It is not highly infectious and transmission requires both prolonged close contact with an infected patient and an inherent immunological susceptibility to the disease in the exposed person. Clinical leprosy may be regarded as a consequence of deficient cell-mediated immunity in susceptible individuals; most individuals are naturally immune, and symptoms are suppressed. The clinical manifestations depend on the bacillary load and the host's immune response to the mycobacterium. Patients with leprosy may be classified as having:

- **Multibacillary** (or lepromatous) leprosy, which occurs when cellular immunity is largely deficient, and includes the sub-groups lepromatous (LL), borderline lepromatous (BL), and midborderline leprosy (BB), as well as any other types giving a positive skin smear for acid-fast bacilli. Generally the lepromin test (p.2333) is negative.
- **Paucibacillary** (or tuberculoid) leprosy, which results when cellular immunity is only partially deficient, and includes the sub-groups borderline tuberculoid (BT), tuberculoid (TT), and indeterminate leprosy (I) when the skin smear is negative. Generally the lepromin test is positive.

For the purpose of treatment, WHO classifies patients with more than 5 skin lesions as having multibacillary leprosy, and those with 1 to 5 skin lesions as having paucibacillary leprosy. The use of this clinical classification avoids the necessity to provide facilities for bacteriological examination of skin smears.

Changes in the hosts immune response to the mycobacteria may result in **lepra reactions** and unless treated these may lead to severe nerve and tissue damage.[1] Most reactions belong to one of two main types:

- **Type 1** lepra reactions, or reversal reactions, are caused by spontaneous increases in T-cell reactivity to mycobacterial antigens (type IV hypersensitivity) and occur in patients with borderline forms of leprosy. These reactions are characterised by erythema and oedema of the skin and tenderness of peripheral nerves. Prompt treatment with corticosteroids is necessary to prevent permanent nerve damage.[2-5] Treatment is usually continued for 3 to 6 months. Adding azathioprine may permit the use of lower cumulative doses of corticosteroid.[6] Methotrexate was found to be effective in treating a patient intolerant to corticosteroids,[7] while ciclosporin is considered to be effective for chronic neuritis.[2,8] Prophylactic use of low-dose corticosteroids during the first 4 months of standard multidrug treatment for leprosy has also been investigated, and found to decrease the number of reactional episodes by 75%; but the protective effect was lost by the end of 12 months.[9]
- **Type 2** lepra reactions, also known as erythema nodosum leprosum (ENL), represent a systemic inflammatory response (type III hypersensitivity) to dead bacteria and are accompanied by high levels of circulating tumour necrosis factor alpha (TNFα). This reaction occurs only in patients with borderline lepromatous or lepromatous leprosy. Mild type 2 reactions may be treated with anti-inflammatories but moderate or severe reactions should be treated with corticosteroids or thalidomide (in males and post menopausal women).[2-4] The incidence and severity of ENL has decreased since the inclusion of clofazimine in multidrug regimens, probably owing to the drug's anti-inflammatory action.[2] Clofazimine does not act as rapidly as either corticosteroids or thalidomide, nor is it as effective.[2,3] Other TNFα inhibiting drugs that have been tried include pentoxifylline[5,10] and infliximab.[11] Chloroquine has also been used with limited effect.[1] Antileprotic drug therapy is generally continued during lepra reactions.

Although measures to manage the consequences of nerve damage and lepra reactions are an important part of the management of leprosy, curative antibacterial therapy is the mainstay of **treatment**. Dapsone monotherapy, long the basis of this, has been replaced since the 1980s with multidrug oral regimens designed to overcome the development of resistance. Dapsone, rifampicin, and clofazimine form the elements of the standard combinations.[5,12] Newer alternatives include clarithromycin, minocycline, and fluoroquinolones such as ofloxacin and pefloxacin. These may be used as second-line therapy for patients unable to tolerate dapsone or clofazimine. Ethionamide or protionamide have been used in light-skinned patients to avoid clofazimine's tendency to pigment the skin, but are no longer recommended because of their risk of hepatotoxicity.

The most widely used multidrug regimens are those recommended by WHO[3] and in these the choice of drugs and length of treatment are based on the clinical classification outlined above.

- MULTIBACILLARY LEPROSY

  The standard regimen recommended by WHO for multibacillary leprosy[3,4] is rifampicin 600 mg and clofazimine 300 mg both given once a month, with clofazimine 50 mg and dapsone 100 mg both daily. Treatment is continued for 12 months.[4]

  A 2-year treatment duration was chosen originally because it is highly effective in the majority of cases and avoids the need to assess response with skin smears. However, such a long treatment duration is an obstacle to implementing treatment programmes in areas where healthcare is inaccessible or the infrastructure is poor. Ongoing clinical studies and experience with patients defaulting from treatment have encouraged WHO to now recommend that treatment for 12 months is adequate.[4] Early hopes that reducing duration of treatment to as little as one month would be possible have not been supported by a study using daily rifampicin and ofloxacin.[13]

  In patients for whom rifampicin is unsuitable because of resistance or intolerance, WHO recommends[3] daily treatment with clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg for the first 6 months; treatment is then continued for at least a further 18 months with clofazimine together with either minocycline or ofloxacin.

  When clofazimine cannot be given ofloxacin 400 mg daily or minocycline 100 mg daily may be substituted in the standard regimen.[14]

  Rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (ROM) given once a month for 24 months was found to be as effective as the WHO standard regimen given for 24 months[15] and has been suggested as an alternative regimen.[3]

- PAUCIBACILLARY LEPROSY

  The WHO recommended regimen[3,4] for paucibacillary leprosy is rifampicin 600 mg monthly and dapsone 100 mg daily. Treatment is continued for 6 months. If there are severe toxic effects with dapsone it should be substituted with clofazimine.[14]

  On the basis of a clinical study[16] showing that a single dose each of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg given in combination is only slightly less effective than standard multidrug treatment, WHO has suggested that this is a suitable alternative for patients with single-lesion paucibacillary leprosy.[3] However, reservations have been expressed about the study, including concerns regarding the short follow-up[17] and poor microbiological rationale.[18]

- RELAPSE

  Relapse after a recommended course of multidrug therapy for multibacillary or paucibacillary leprosy can occur and WHO recommends re-treatment with the initial regimen.[3,4] Although the relapse rate after standard multidrug therapy for multibacillary leprosy is generally low,[3,19] there is insufficient information on the long-term efficacy of shorter treatment courses.[13]

- PREGNANCY

  Standard multidrug therapy is safe during pregnancy.[4,5] Leprosy patients who are pregnant or breast feeding may experience clinical deterioration and, in general, antileprotic therapy is continued in such patients.

• PROPHYLAXIS

Leprosy is spread from person to person through respiratory droplets, so household contacts may become infected. A systematic review and meta-analysis[20] has concluded that prophylaxis, usually with dapsone, in some household contacts may prevent disease in this high-risk group. A large randomised placebo-controlled study[21] found that a single dose of rifampicin given to contacts of new patients with leprosy significantly reduced the incidence of developing leprosy in the first 2 years but no difference was noted beyond 2 years. WHO[3] suggests that contacts of newly diagnosed cases should be examined for evidence of leprosy and then advised how to watch for early signs of the disease; prophylaxis with rifampicin or other antileprotics is not recommended in leprosy control programmes. BCG vaccine appears to be protective. Vaccines specifically against leprosy are under investigation.

• ELIMINATION

The multidrug therapy regimens recommended by WHO have been widely implemented in recent years raising the possibility of eliminating leprosy as a public health problem: that is, reducing the prevalence to less than 1 case per 10 000 population in endemic areas. Considerable progress towards this target has been made, and it was announced in 2001 that the global level of leprosy had decreased by over 90%. Full control of leprosy, however, has still not been attained in several countries and continued efforts are necessary. WHO has since developed a global strategy for the further reduction of the leprosy burden and sustained leprosy control.[22]

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Leptospirosis

Leptospirosis[1] is an infectious disease caused by serovars of the spirochaete *Leptospira interrogans*, the commonest in the UK being *L. hardjo* and *L. icterohaemorrhagiae*.[2] *Leptospira* are widely distributed in wild and domestic animals, including cattle. Rats are a common source of infection in man and transmission is often by contact with water or soil contaminated with infected urine. The main occupational group at risk in the UK has been farmers and agricultural workers, although there have been outbreaks elsewhere among recreational water users such as canoeists.[3] The majority of symptomatic patients have no more than a mild flu-like illness, although a small proportion develop Weil's disease with haemorrhagic complications and severe hepatic and renal impairment.

The use of antibacterials is controversial since many patients recover without treatment. There is insufficient evidence to conclude whether treatment with antibacterials is worthwhile.[4] However, treatment for suspected leptospirosis within 4 to 7 days has been recommended to prevent complications.[5,6] The intravenous use of either benzylpenicillin 900 mg, ampicillin 1 g, or erythromycin 500 mg every 6 hours, or the oral use of amoxicillin 500 mg every 8 hours or doxycycline 100 mg twice daily has been suggested;[6] treatment is continued for 7 days. Benzylpenicillin has been given intravenously in higher doses for severe leptospirosis; 7.2 to 9.6 g daily for 5 days followed by 1.44 g daily for a further 5 days has been advocated.[7] However, intravenous doses of 900 mg every 6 hours for 7 days have proved successful even when given late in the course of illness.[8] Intravenous ceftriaxone 1 g daily,[9] intravenous cefotaxime 1 g every 6 hours (followed by a switch to oral amoxicillin),[10] and intravenous doxycycline given as an initial dose of 200 mg, then 100 mg every 12 hours (followed by a switch to oral doxycycline),[10] each regimen given for a total of 7 days, have also been found to be effective for treatment of severe leptospirosis. In severe infections, supportive therapy with analgesics and antiemetics may be required. Renal function should be monitored and dialysis instigated if necessary, and blood products may be necessary to control haemorrhagic complications.[5]

The incidence of leptospirosis in US soldiers in Panama was reduced when they were given prophylaxis with oral doxycycline 200 mg weekly throughout the period of exposure.[11] Leptospirosis vaccines are available in some countries.

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Listeriosis

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive bacterium widespread in the environment and capable of growing at low temperatures. Increased awareness of *L. monocytogenes* as a human pathogen has followed epidemics of listeriosis associated with the consumption of contaminated food products including soft cheeses, coleslaw, and milk. *L. monocytogenes* has since been detected in many types of food, especially uncooked hot dogs, undercooked chicken, and pâté. It has been acknowledged[1-3] that it is a relatively rare infection and that despite epidemics associated with identified food products it typically occurs sporadically and the source is usually not certain. Infection occurs primarily in pregnant women, neonates, the elderly, and immunocompromised patients. Clinical manifestations vary. Pregnant women may have relatively mild flu-like symptoms, but infection may result in spontaneous abortion, fetal death, or perinatal sepsis or meningitis in the neonate. Non-perinatal listeriosis may cause sepsis but commonly presents as meningitis. Endocarditis has occurred in patients with cardiac lesions. Focal infections after initial bacteraemia occur mainly in immunocompromised patients.

The treatment of choice is generally ampicillin with gentamicin,[1,2,4,5] although some have advocated ampicillin alone;[6] synergy has been reported *in vitro*. Ampicillin or amoxicillin alone may be used in pregnant women.[7] In penicillin-allergic patients co-trimoxazole, vancomycin or teicoplanin, erythromycin, and tetracycline are alternatives,[1,3] but the choice of treatment in these patients is more difficult. Gentamicin with chloramphenicol or with vancomycin has been used[4] as has erythromycin plus gentamicin.[8] According to some,[4] tetracycline should not be used to treat listeriosis in the UK because of bacterial resistance. Others[3] recommend against use of cephalosporins.

Further details specifically concerning neonatal listerial meningitis and its treatment can be found under Meningitis, p.178.

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Lyme disease

Lyme disease is a seasonal infectious disease caused by the spirochaete *Borrelia burgdorferi* and transmitted primarily by *Ixodes* ticks. *I. scapularis*, one of the species of ticks that may cause Lyme disease, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Babesia microti* and therefore the bite from this tick may lead to Lyme disease, human granulocytic anaplasmosis (see Ehrlichiosis, p.168), or babesiosis (p.823) as a single infection or as a co-infection.[1] Lyme disease was first recognised in the 1970s in Lyme, Connecticut, but when the spirochaete responsible was later identified, it was found to occur worldwide with regional variations. Lyme disease is a multisystem disease characterised by inflammatory reactions that principally affects the skin, nervous system, heart, and joints, and can be divided into 3 stages. In the early stage a characteristic skin lesion (erythema migrans) occurs at the site of the tick bite and may be accompanied by flu-like or meningitis-like symptoms. This may be followed weeks or months later by signs of disseminated infection, including neurological and cardiac abnormalities, and even years later by chronic arthritis and the late skin manifestation acrodermatitis chronica atrophicans, both signs of persistent infection.

Appropriate **treatment** should prove curative, especially in the early stages. Recommendations for treatment[1-4] give oral tetracyclines (doxycycline or tetracycline) and the beta-lactam antibacterials (amoxicillin, phenoxymethylpenicillin, or cefuroxime) as the antibacterials of choice for *early* Lyme disease in the absence of neurological symptoms or advanced AV block. Treatment is usually for 14 days (range 10 to 21 days for doxycycline and 14 to 21 days for amoxicillin or cefuroxime). The macrolides (azithromycin, clarithromycin, erythromycin, and roxithromycin) are less effective and should only be used in patients allergic to, or who cannot be given, the first-line agents.[2,3] Young children (usually specified as below 8 years of age in the US and below 12 years in the UK) may be given amoxicillin or cefuroxime.[1,3] Pregnant women should avoid tetracyclines but may be given any of the other oral regimens.[1,3]

Adults and children presenting with *neurological symptoms*, either early or late, should be treated with intravenous ceftriaxone, cefotaxime, or benzylpenicillin for 14 to 28 days. Patients allergic to cephalosporins or penicillins may be given oral doxycycline 200 to 400 mg daily in 2 divided doses.[1,3] Early Lyme disease with *cardiac* complications may be treated with either an oral or intravenous antibacterial for 14 to 21 days. Lyme *arthritis* can generally be effectively treated with one of the oral regimens given for 28 days. Patients with ongoing or recurrent joint pain after the initial treatment course may be re-treated with either another 4-week course of oral antibacterials or with intravenous ceftriaxone for 2 to 4 weeks. *Acrodermatitis chronica atrophicans* may be treated with an oral antibacterial for 21 days.[3]

A small percentage of patients continue to experience non-specific symptoms after appropriate treatment of Lyme disease; there is some controversy over whether prolonged treatment is effective in these patients and studies have suggested otherwise.[5-7] The use of antibacterials in patients with chronic (more than 6 months) subjective symptoms after recommended treatment is hotly debated[8,9] but the Infectious Diseases Society of America (IDSA) does not support such therapy.[3]

Adults and older children *co-infected* with *A. phagocytophilum* should be treated with doxycycline for 10 days. In the US, recommended treatment for severely ill children less than 8 years of age is doxycycline for 4 to 5 days followed by amoxicillin or cefuroxime to complete a 14-day course. Patients with mild illness and who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days plus amoxicillin or cefuroxime.[3]

Preventive measures against Lyme disease include the use of tick repellents, physical protection,[3,10,11] and prompt removal of attached ticks.[3] Most guidelines[3,10] do not support the use of empirical antibacterial therapy or serologic testing after tick bites as generally the risk of infection is low,[12] particularly if the tick is removed promptly. The risk of infection may, however, be greater if the tick has fed to repletion.[13] A study[14] has shown that empirical treatment with a single dose of doxycycline given within 72 hours of a tick bite may be warranted in endemic areas where the probability of infection is high. Although routine antibacterial prophylaxis is not recommended by the IDSA,[3] they recommend that a single dose of doxycycline may be given provided that the tick has been attached for 36 hours or more, prophylaxis can be started within 72 hours of the time of tick removal, and the tick species can be identified as *I. scapularis*. Lyme disease vaccines are available in some countries.

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Lymphogranuloma venereum

See under Sexually Transmitted Diseases, p.192.

Melioidosis

Melioidosis is caused by the Gram-negative aerobic bacterium *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and has been found mainly in south-east Asia and northern Australia.[1] Its true incidence and distribution may be much wider than originally thought;[2] diagnosis is difficult because of the broad spectrum of clinical manifestations. Pulmonary melioidosis is probably the commonest form and has been treated with doxycycline for 3 to 6 months.[3] Chronic or subacute non-bacteraemic melioidosis has also been treated long term with tetracycline or co-trimoxazole.[3]

Septicaemic melioidosis is an important cause of death in Thailand. Because *B. pseudomallei* is intrinsically resistant to many antibacterials, including aminoglycosides and the early beta lactams, it has been unresponsive to many empirical regimens for septicaemia.[2] Treatment was based on anecdotal regimens until, in a study from Thailand,[4] intravenous ceftazidime halved the mortality of severe melioidosis when compared with conventional parenteral treatment with high doses of chloramphenicol intravenously, doxycycline, and co-trimoxazole. As a result ceftazidime came to be considered the treatment of choice for septicaemic melioidosis.[2] A systematic review[5] of treatment of acute melioidosis has also concluded that regimens should contain ceftazidime or imipenem parenterally. Parenteral treatment for a minimum of 7 days is followed by oral maintenance therapy with amoxicillin-clavulanic acid or the conventional regimen (chloramphenicol, doxycycline, and co-trimoxazole);[1,4] amoxicillin-clavulanic acid has shown promise[4] and appears to be a safe alternative to the conventional regimen for the oral treatment of melioidosis.[6] However, resistance to ceftazidime and amoxicillin-clavulanic acid has been reported,[7] emphasising the importance of careful monitoring for the emergence of resistance during treatment. Ceftazidime plus co-trimoxazole, both given intravenously, has been advocated by some for severe melioidosis, especially in patients with septicaemia.[8]

B. pseudomallei has the potential for prolonged latency as demonstrated by a Vietnam war veteran who presented with melioidosis of the bone 18 years after exposure to the organism.[9] He was treated with ceftriaxone intravenously for 8 weeks followed by oral ciprofloxacin.

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Meningitis

Meningitis refers to infection of the subarachnoid space and meninges, which may be caused by viruses, bacteria, protozoa, or fungi. The symptoms and signs of meningitis result from the host inflammatory response to infection. Whereas viruses cause the majority of generally mild cases of infectious meningitis, bacterial meningitis is usually a more serious condition. Meningitis may occasionally be a manifestation of non-infectious (auto-immune or neoplastic) disease. This section discusses bacterial meningitis and its management. For reference to fungal meningitis, see p.520.

The bacteria most often encountered in adult or childhood meningitis are *Neisseria meningitidis* (meningococci) and *Streptococcus pneumoniae* (pneumococci). *N. meningitidis* A, C, and W135 are the main subtypes involved in epidemics in the African meningitis belt, whereas B and C subtypes are responsible for outbreaks in Europe and North America. In neonates, infants, pregnant women, immunocompromised patients, and the elderly, *Listeria monocytogenes* and Gram-negative bacilli may also be encountered, and *Str. agalactiae* may cause meningitis in neonates and infants. *Haemophilus influenzae* meningitis was a common cause of meningitis in infants and young children before the availability of *H. influenzae* type b vaccine, and this pathogen is still encountered in non-vaccinated young children, particularly in resource-poor countries. Meningitis after head trauma, neurosurgery, or in the presence of CSF shunts is not infrequently caused by staphylococci (both *Staphylococcus aureus* and coagulase-negative staphylococci) or Gram-negative bacilli.

The bacteria are transmitted from person to person through droplets of respiratory or throat secretions. Infection is spread by prolonged close contact (such as kissing, sneezing and coughing, living in close quarters or dormitories, and sharing eating or drinking utensils). The average incubation period is 4 days, ranging between 2 and 10 days. The clinical presentation of acute bacterial meningitis is largely dependent on the patient's age. The classic manifestations of meningitis in older children and adults, including fever, headache, neck stiffness, photophobia, confusion, and vomiting, are rarely present in infants. In general, the younger the patient, the more subtle and atypical are the signs and symptoms. Fatality rates can be as low as 2% in infants and children, and as high as 20 to 30% in neonates and adults depending on the causative bacteria and patient's age. Brain damage, transient or permanent deafness, or learning disability may occur in up to one-third of survivors.[1,2] A less common but more severe (often fatal) form of meningococcal disease is meningococcal septicaemia which is characterised by a widespread haemorrhagic rash, acute adrenal insufficiency, and rapid circulatory collapse.[1] (For further information see Meningococcal Infections, below p.179.)

Choice of treatment. Bacterial meningitis is a medical emergency and almost universally requires hospitalisation. Death may occur in a matter of hours if left untreated. Outcome is worse if treatment is delayed and therefore doctors in the UK are advised[3,4] to give emergency treatment with parenteral benzylpenicillin in all suspected cases of meningitis before transfer to hospital. Alternative antibacterials include a third generation cephalosporin or chloramphenicol.[3,5] Patients with suspected or confirmed bacterial meningitis should have blood and/or CSF samples taken for culture and receive *empirical* therapy until the causative organism has been identified and susceptibility patterns have become available.[4,6,7] Empiric antibacterials are given intravenously in relatively high doses, and treatment should be targeted at specific organisms as soon as the results of blood and/or CSF cultures are known. The choice of empirical therapy depends on the bacterial pathogens (and their antibacterial susceptibility patterns) that are most likely to have caused meningitis and varies with age and the presence of predisposing factors such as trauma or neurosurgery. Guidelines have been published for the UK[4,6,8] and the USA,[7] and country specific guidelines should be consulted where available. In most countries, a third generation cephalosporin (high-dose ceftriaxone or cefotaxime) is recommended as empirical treatment for bacterial meningitis in adults and children. These drugs are active against *N. meningitidis*, most *Str. pneumoniae* strains, and *H. influenzae*, and penetrate CSF well. However, in situations where ceftriaxone or cefotaxime are not available or are unaffordable, a combination of ampicillin and chloramphenicol or chloramphenicol alone may be used as an alternative.[9] For those patients allergic to both penicillins and cephalosporins, a combination of vancomycin and chloramphenicol may be given.[4] In patients over 55 years ampicillin should be added to cover *Listeria*.[6] Empirical treatment in neonates may include cefotaxime, ampicillin to cover *Listeria*, and an aminoglycoside to cover Gram-negative organisms.[7,10] In the USA and other areas where penicillin and cephalosporin-resistant pneumococci or meticillin-resistant staphylococci are encountered, vancomycin (with or without rifampicin) should be given with a third-generation cephalosporin to children or adults with bacterial meningitis.[4,6-8] Vancomycin together with ceftazidime (or/cefepime or meropenem) should be given to patients with meningitis complicating neurosurgery, head trauma, or CSF shunts. Because of concern of suboptimal CSF penetration, vancomycin should not be used alone in patients with meningitis due to resistant pneumococci or staphylococci, especially when dexamethasone is given as well. The duration of antibacterial treatment depends on the organism isolated. For *Str. pneumoniae* 10 to 14 days of treatment is recommended and for *H. influenzae* 7 to 14 days. For *N. meningitidis* 7 days, treatment is sufficient. In *L. monocytogenes* and group B streptococcal meningitis, antibacterials should be given for a minimum of 14 to 21 days while Gram-negative bacilli should be treated for a minimum of 3 weeks.[7,11]

Chloramphenicol is effective for the treatment of epidemic meningococcal meningitis and is the drug of choice for patients over 1 year of age in areas with limited health facilities.[1,12] An intramuscular dose of ceftriaxone (100 mg/kg to a maximum of 4 g) was found to be as effective as an intramuscular dose of oily chloramphenicol (100 mg/kg to a maximum of 3 g) for the treatment of meningococcal meningitis during epidemics in resource-poor settings.[13] For children under 2 months, intravenous ampicillin for 7 days is recommended to cover *Listeria*, while for children aged between 2 months and 1 year, intramuscular ceftriaxone for 5 days or intravenous ampicillin for 7 days may be used.[12]

Prophylaxis. Immunisation is the most effective way of preventing bacterial meningitis in children. Vaccination is also recommended for travellers to areas affected by meningococcal outbreaks and is compulsory for pilgrims going to Saudi Arabia. Several vaccines are available to prevent bacterial meningitis. Unconjugated polysaccharide vaccines against *N. meningitidis* subtypes A, C, Y, and/ or W135, in various combinations, have been available for many years and are recommended for children older than 2 years who are at high risk of infection, such as those with asplenia and with terminal complement deficiencies, and students living in dormitories. A newer conjugated tetravalent ACWY meningococcal vaccine protects against A, C, W135 and Y meningococcal subtypes and is now a visa requirement for pilgrims to Saudi Arabia. A monovalent conjugate vaccine against *N. meningitidis* subtype C has recently been licensed in developed countries for use in children and adolescents. This conjugate vaccine produces better protection than unconjugated polysaccharide vaccine, in children under 2 years of age.[1,3] For further information on meningococcal vaccines see, p.2224. The newer conjugate *Haemophilus* vaccines (see p.2213) are similarly more immunogenic than the polysaccharide vaccine, and universal immunisation of infants with these conjugate vaccines has been associated with more than 99% reduction in invasive *H. influenzae* type b diseases in developed countries.[2] In 2000, a conjugate vaccine, directed against the seven most prevalent invasive pneumococcal strains in the USA, was approved for routine childhood immunisation. Three doses of this vaccine, given at 2, 4, and 6 months of age, were associated with a reduction of more than 90% in invasive pneumococcal infections, including sepsis and meningitis.[2] For further information on pneumococcal vaccines see, p.2231.

Close contacts of patients infected with meningococcus A, C, Y, or W135 and aged over 2 years should be offered tetravalent meningococcal vaccine.[2-4,11] Those over 3 months and exposed to serogroup A infection may also be given a tetravalent meningococcal vaccine, while those over 2 months of age and exposed to serogroup C infection who are unimmunised or incompletely immunised may be vaccinated with a meningococcal C vaccine. Those who completed a course more than one year before should be offered a booster.[3] All unimmunised index cases under the age of 25 years should also be offered a meningococcal C vaccine. Cases of confirmed serogroup C disease who have previously been immunised with meningococcal C or tetravalent vaccines should be offered a meningococcal C vaccine before discharge from hospital.[3]

Antibacterial treatment does not eliminate nasopharyngeal carriage of *N. meningitidis* and **chemoprophylaxis** should be given to close contacts of the index case (irrespective of vaccination status) to reduce the risk of invasive disease.[3] A systematic review[14] found that ceftriaxone, ciprofloxacin, and rifampicin were all effective at eradicating carriage for up to 2 weeks although resistance to rifampicin may occur after prophylactic treatment; penicillin was less effective. Oral rifampicin twice daily for 2 days (or a single oral dose of ciprofloxacin or a single dose of intramuscular ceftriaxone) should be started in the close contacts within 24 hours or as soon as possible after diagnosis of the index case. If further cases occur within a group of close contacts within 4 weeks of receiving prophylaxis with rifampicin, then repeat prophylaxis should be with either ciprofloxacin or ceftriaxone. Index cases (except those whose disease was treated with ceftriaxone) should be given antibacterial prophylaxis before discharge from hospital.[3] Chemoprophylaxis is also recommended for health care workers whose mouth or nose is directly exposed to large particle droplets or secretions from the respiratory tract of a probable or confirmed index case of meningococcal disease during acute illness and until 24 hours of systemic antibacterial treatment has been completed.[3] Similarly, treatment of *H. influenzae* meningitis does not eliminate nasopharyngeal carriage of the organism and rifampicin should be given to index cases for 4 days before discharge from hospital. Anyone who has been in direct or prolonged close contact with the infected persons should also be given rifampicin for 4 days. Unvaccinated children should be immunised. Chemoprophylaxis is not normally indicated for close contacts of pneumococcal and other types of bacterial meningitis.[4,11]

The WHO recommendation for outbreak control is mass vaccination of persons residing in districts in the epidemic phase as well as surrounding districts in an alert phase. It is estimated that a mass immunisation campaign, promptly implemented, can avoid 70% of cases.[1]

Adjunctive treatment. Mortality and morbidity, including deafness in children, remain high in meningitis despite effective antibacterial therapy. Endotoxins and other microbial products, released from bacteria after antibacterial treatment, are able to elicit a severe inflammatory response, suggesting that anti-inflammatory drugs may be of benefit. A systematic review[15] of adjunctive corticosteroid therapy concluded that corticosteroids reduce mortality, neurological sequelae, and especially the risk of severe hearing loss in both children and adults. This systematic review concludes that corticosteroids should be given before, or with the first dose of antibacterial in adults; the same recommendations apply to children living in high-income countries. However, results from a study in sub-Saharan Africa[16] did not support the routine use of adjunctive corticosteroids in the treatment of adults with bacterial meningitis in resource-poor countries where *Strep. pneumoniae* is the main pathogen and where a large number of patients are also likely to have advanced HIV disease. Another study[17] of dexamethasone in Vietnamese patients over 14 years of age with suspected bacterial meningitis reported that dexamethasone did not improve survival in all patients; significant benefit was only seen in patients with proven bacterial meningitis, including those given prior treatment with antibacterials. This finding was thought to be due to patients with tuberculosis meningitis in the treatment group.

Careful management of fluid and electrolyte balance may be important in the treatment of meningitis and fluid restriction to prevent cerebral oedema has been widely advocated and used in children.[18,19] This practice was based on reports of hyponatraemia which were attributed to inappropriately increased concentrations of antidiuretic hormone. However, subsequent studies have suggested that the raised concentration of antidiuretic hormone may be an appropriate host response to hypovolaemia, and that more liberal use of parenteral fluids may be beneficial.[2] A systematic review[18] concluded that there is some evidence to support the use of intravenous fluids, in preference to restricted fluid intake, particularly in the first 48 hours in settings with high mortality rates. However, where children present early and mortality rates are lower, there is probably little benefit and insufficient evidence to guide practice; it has been suggested that fluids should not be restricted in children.[11] The British Infection Society working party[4,6] recommends that adult patients with meningitis should not be fluid restricted in an attempt to reduce cerebral oedema.

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Meningococcal infections

Meningococcal disease[1-3] refers to systemic infection with *Neisseria meningitidis* and may present clinically either as meningitis or septicaemia, or both. Less common forms of metastatic meningococcal infection include polyarthritis, pericarditis, pneumonitis, and genito-urinary-tract infections. *N. meningitidis* is a Gram-negative bacterium, occurring worldwide, and is classified into several serotypes. Serotypes A, C, and W135 are responsible for epidemic meningitis in sub-Saharan Africa, while serotypes B and C are the cause of outbreaks in Europe and North America. The number of cases of meningococcal disease due to serotype C has decreased significantly after the introduction of vaccination in developed countries.

Infections are more common in young children under 5 years of age and in adolescents. *N. meningitidis* only infects humans and about 10 to 25% of the population may be carriers of the organism. The bacteria are carried in the pharynx and may sometimes penetrate the mucosa and spread through the bloodstream causing systemic disease that may rapidly progress to shock and death. Patients with meningococcal disease and asymptomatic nasopharyngeal carriers may spread meningococcal infection via respiratory droplets or throat secretions. Close and prolonged contact such as kissing, sneezing and coughing, living in close quarters, and sharing eating or drinking utensils are established risk factors.[1,2,4] Symptoms and signs during the early stage of meningococcal disease are non-specific and include fever, vomiting, malaise, and lethargy. Most patients with meningococcal septicaemia develop a vasculitic rash (petechiae or purpura) which is often scant or absent in patients with meningitis. Purpuric rash, drowsiness or impaired consciousness, and shock are late presentations and associated with high mortality rates, which may be up to 50% in severe forms. Meningococcal meningitis usually presents with headache, neck stiffness, photophobia, and drowsiness. Mortality from meningococcal meningitis is less than in septicaemia and may be below 5% with prompt treatment.[1,2,5]

Guidelines for prevention and control of meningococcal disease have been developed for the UK[6] and the USA.[7,8]

Choice of treatment. Mortality is reduced by early recognition of the disease and prompt treatment with antibacterials. In the UK doctors are advised that if meningococcal disease is suspected, benzylpenicillin should be given parenterally, preferably intravenously, before transfer to hospital.[1,5,6] Alternative antibacterials include a third generation cephalosporin or chloramphenicol.[6] Both initial empiric and later treatment may be with benzylpenicillin, ampicillin, chloramphenicol, or third-generation cephalosporins such as cefotaxime or ceftriaxone. Oily chloramphenicol or ceftriaxone are used during epidemics in Africa and in areas with limited health facilities. Uncomplicated meningococcal disease usually requires 7 days of antibacterial treatment.[4,5,9,10] For further details of the treatment of meningococcal meningitis, including the treatment of close contacts, see Meningitis, above. Immunisation is the most effective way of preventing meningococcal meningitis and several vaccines are available (see Meningococcal Vaccines, p.2224).

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Mouth infections

Infections of the mouth include those of dental origin such as dental caries, abscesses, gingivitis, and periodontal infections, and those without a dental origin. Infections arising in the nasal cavity, middle ear, oropharynx, and paranasal sinuses can also affect the oral cavity. Emphasis has shifted from treatment to prevention of oral diseases.[1] This discussion deals mainly with infections of dental origin.

The organisms most often encountered in oral infections are viridans streptococci, a variety of anaerobes, and facultative streptococci.[2]

Dental caries[3] is caused by the erosion of tooth enamel due to acid produced by bacteria (usually *Streptococcus mutans*) in plaque. Fluoride in various forms is used in dental caries prophylaxis, where it may promote remineralisation or reduce acid production by plaque bacteria.[1] Sugar-free chewing gum can help prevent caries by stimulating the production of saliva.[4] Dental caries vaccines have also been investigated.

The term **periodontal disease**[5] encompasses specific conditions affecting the gingiva and the supporting connective tissue and alveolar bone. **Gingivitis** is thought to be caused by a non-specific bacterial plaque flora that gradually changes from predominantly Gram-positive to more Gram-negative. Gingivitis may or may not develop into periodontitis, but periodontitis is always preceded by gingivitis. **Periodontitis** is associated with a Gram-negative anaerobic microflora. Most gingivitis and periodontitis can be prevented and treated by adequate oral hygiene and plaque removal using mechanical means such as toothbrushing. Mechanical removal of calculus is necessary where the build up is significant. Antiseptics may also help to reduce plaque accumulation and several, but most notably chlorhexidine, have been used.[6,7]

Penicillin has continued to be an effective drug in combating oral pathogens, and erythromycin or metronidazole are alternatives. In the UK, the *BNF* advises against the routine use of clindamycin in oral infections, but notes that it can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or metronidazole. Fusiform bacteria and spirochaetes have been linked with acute necrotising ulcerative gingivitis (also called Vincent's infection or trench mouth);[8] systemic metronidazole is often the treatment of choice. Tinidazole has also been used. Tetracyclines or metronidazole have been used for chronic periodontal disease.[9] Antibacterials and antiseptics delivered locally to the periodontal pocket may be of value.[7]

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Mycetoma

Mycetoma is a localised chronic infection seen especially in the tropics and subtropics and involving subcutaneous tissue, bone, and skin. It has been termed Madura foot when affecting the sole of the foot. Mycetomas caused by fungi (p.520) such as *Madurella mycetomatis* are called eumycetomas and those caused by the filamentous bacteria, actinomycetes, are called actinomycetomas. *Nocardia brasiliensis* is the commonest actinomycete responsible; others include *Actinomadura madurae*, *A. pelletieri*, and *Streptomyces somaliensis*. For details of systemic infections caused by *Nocardia* spp., see under Nocardiosis, p.181.

Various treatment regimens for actinomycetomas have been tried. Combined drug treatment is preferred so as to avoid resistance and eradicate residual infection.[1] The most common regimen is streptomycin and dapsone; co-trimoxazole may replace dapsone in patients who have not responded to initial treatment after a few months and in those who cannot tolerate dapsone. Successful treatment has been reported with amikacin, either as monotherapy or with co-trimoxazole.[1] Rifampicin, pyrimethamine-sulfadoxine, and sulfonamides have also been tried in resistant infections and are considered suitable for second-line therapy.[1] Cures were achieved after treatment for 4 to 24 months. In a study of antibacterial activity *in vitro* against strains of *S. somaliensis* isolated from mycetoma patients, rifampicin was the most effective followed in decreasing order of activity by erythromycin, tobramycin, fusidic acid, and streptomycin; all strains were resistant to trimethoprim.[2] The successful use of hyperbaric oxygen in addition to co-trimoxazole[3] or of amoxicillin-clavulanic acid[4] in the treatment of *N. brasiliensis* actinomycetoma previously resistant to conventional therapy has been described.

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Necrotising enterocolitis

See p.173.

Necrotising fasciitis

Necrotising fasciitis is a severe soft-tissue infection resulting in necrosis of the subcutaneous tissue and adjacent fascia, together with severe systemic illness. It may be caused by a mixture of aerobic and anaerobic organisms, but can be due to group A streptococci or staphylococci alone and may be associated with a toxic shock syndrome (p.196).

Complete debridement of the infected tissue is considered essential for treatment. Antibacterial therapy is given as an adjunct and should be continued until no further debridements are needed.[1] Antibacterial treatment regimens should cover Gram-positive, Gram-negative, and anaerobic organisms. The possibility of infection with group A *Streptococcus* or *Clostridium* species should also be considered. Possible treatment regimens include monotherapy with ertapenem, imipenem, meropenem, piperacillin-tazobactam, or tigecycline; multidrug regimens include high-dose benzylpenicillin and clindamycin plus a fluoroquinolone or an aminoglycoside. Until meticillin-resistant staphylococcal infection has been ruled out, treatment regimens should also include vancomycin, daptomycin, or linezolid.[1] Hyperbaric oxygen therapy has also been beneficial although prospective controlled studies are lacking.[2] Intravenous normal immunoglobulins have also been tried in patients with necrotising fasciitis caused by group A streptococcus.[3]

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Neonatal conjunctivitis

Conjunctivitis of the newborn, also known as ophthalmia neonatorum, is defined as any conjunctivitis with discharge occurring during the first 28 days of life.[1] That due to *Neisseria gonorrhoeae* is the most serious; it usually appears by the third day after birth and can rapidly result in blindness; systemic infections, especially severe septicaemia, may occur. *Chlamydia trachomatis* is another major cause of neonatal conjunctivitis (inclusion conjunctivitis); it characteristically occurs 5 to 14 days after birth and is less threatening to sight than gonococcal infection, but may also infect the nasopharynx and can cause pneumonia. Chlamydial conjunctivitis is more common than gonococcal conjunctivitis in developed countries. Both organisms are sexually transmitted and the infants of mothers with such genital-tract infections are infected during their passage through the birth canal. Other less serious bacterial causes of neonatal conjunctivitis include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus* spp., and *Pseudomonas* spp.; they are often hospital-acquired.[1]

The management of gonococcal and chlamydial neonatal conjunctivitis varies from country to country depending on the prevalence of gonorrhoea and *C. trachomatis* infection and on bacterial resistance.

- PROPHYLAXIS

  The ideal method of prophylaxis is to treat the infected mother during pregnancy, but this is not always possible. Where the risk of *gonococcal infection* is high, ocular prophylaxis at birth is particularly important because of the rapid onset of conjunctivitis and its potential seriousness and is preferable to early diagnosis and treatment of the neonate.[2] Cleansing of the neonate's eyes immediately after birth followed by the topical application of either tetracycline 1% eye ointment,[3,4] erythromycin 0.5% eye ointment,[3] or silver nitrate 1% eye drops is advised[4] and is sometimes required by law.[3] Silver nitrate[1] is active against all strains of *N. gonorrhoeae* regardless of their susceptibility to antibacterials; it is inexpensive and widely available, but may cause chemical conjunctivitis and has been ineffective in preventing chlamydial conjunctivitis (see below). Tetracycline has been reported to be as effective as silver nitrate in protecting against gonococcal conjunctivitis caused by multiresistant strains[5] and WHO now lists both drugs as the drugs of choice.[4]

  The value of prophylaxis against *chlamydial neonatal conjunctivitis* is less certain. Tetracycline ointment has been reported to be less effective in preventing chlamydial infection than gonococcal infection[5] and erythromycin ointment has also been unreliable.[6] Silver nitrate is generally considered ineffective,[1] despite an unexpected reduction in the incidence of chlamydial conjunctivitis in one study.[5] The CDC[3] does not recommend prophylactic antibacterial treatment for infants born to mothers with untreated chlamydial infection. Screening and treatment of pregnant women for *C. trachomatis* infection may be a more effective method of control than ocular prophylaxis.[5,7] This approach also tackles the more serious problem of pneumonia.[8]

  Neonatal conjunctivitis continues to cause blindness, especially in developing countries. Povidone-iodine is less expensive and perhaps more readily available in such countries than silver nitrate or erythromycin. In a study in Kenya involving more than 3000 infants[9] a 2.5% ophthalmic solution of povidone-iodine appeared to be a more effective prophylactic than either a 1% ophthalmic solution of silver nitrate or erythromycin 0.5% eye ointment. In particular, there were fewer cases of chlamydial conjunctivitis with povidone-iodine.

- TREATMENT

  All cases of neonatal conjunctivitis should be treated for both *N. gonorrhoeae* and *C. trachomatis* because of the possibility of mixed infection.[4] *Gonococcal neonatal conjunctivitis* must be treated systemically. WHO[4] recommends ceftriaxone 50 mg/kg by intramuscular injection as a single dose (to a maximum of 125 mg) or, if ceftriaxone is not available, spectinomycin 25 mg/kg (to a maximum of 75 mg) or kanamycin 25 mg/kg (to a maximum of 75 mg) by intramuscular injection as a single dose.

  In the USA, CDC[3] recommends a single intravenous or intramuscular injection of ceftriaxone 25 to 50 mg/kg (up to 125 mg) when there is no evidence of disseminated infection.

  See also under Gonorrhoea (p.191) for the treatment of infants exposed to gonorrhoea at birth or with established gonococcal infection at any site.

  For *nongonococcal neonatal conjunctivitis* WHO[4] and CDC[3] recommend erythromycin 50 mg/kg daily in 4 divided doses orally for 14 days; WHO[4] recommend co-trimoxazole 240 mg twice daily for 14 days as an alternative. There is no indication that topical therapy is of additional benefit.[3,4]

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Nocardiosis

Nocardia spp. are Gram-positive aerobic branching bacteria that cause systemic or localised infection. The principal pathogenic species in man is *N. asteroides*; others include *N. brasiliensis*, *N. pseudobrasiliensis*, and *N. caviae*. Localised chronic infection or actinomycetoma is described under Mycetoma (p.180). Systemic nocardiosis is mainly a lung infection and often involves abscess formation; it occurs especially in immunocompromised patients and may be disseminated with abscesses in the brain and subcutaneous tissues.

The treatment of choice has been a sulfonamide such as sulfadiazine or co-trimoxazole,[1-5] although a study *in vitro* indicated that the fixed ratio of trimethoprim:sulfamethoxazole in co-trimoxazole might contain too little trimethoprim for optimal activity.[6] Sulfafurazole[7] has been used successfully. There have been reports of the effective treatment of nocardiosis with amikacin,[8,9] linezolid,[10] minocycline,[11,12] or ciprofloxacin with doxycycline.[13] Other suggested alternatives include ceftriaxone, imipenem or meropenem.[14] Treatment needs to be prolonged and may continue for 6 to 12 months.

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Nontuberculous mycobacterial infections

Environmental mycobacteria are widespread, and a number of species other than those responsible for leprosy (p.176) and tuberculosis (p.196) are facultative parasites capable of producing disease in man. These organisms, which have been referred to as atypical, nontuberculous (NTM), tuberculoid, opportunistic, or MOTT (mycobacteria other than tuberculous), are rarely, if ever, transmitted from person to person but are acquired from the environment. Symptomatic infections are usually associated with focal or generalised defects in the host's immune system. The diseases produced include localised skin and soft tissue lesions, pulmonary infections, lymphadenitis, and disseminated infections.

Cutaneous disease may follow traumatic inoculation with *Mycobacterium marinum* ('swimming pool' or 'fish-tank' granuloma), *M. ulcerans* (Buruli ulcer), *M. chelonae* (*M. chelonei*), *M. abscessus* (formerly *M. chelonae* subspecies), or *M. fortuitum*. Ulcerated lesions due to *M. haemophilum* have been described mainly in immunocompromised patients.

Pulmonary disease may be clinically indistinguishable from pulmonary tuberculosis, and has most frequently been attributed to the *M. avium* complex (MAC), which includes *M. avium* and *M. avium-intracellulare*, or to *M. kansasii*, and to a lesser extent *M. xenopi*; less common causes include *M. abscessus*, *M. asiaticum*, *M. celatum*, *M. chelonae*, *M. fortuitum*, *M. malmoense*, *M. scrofulaceum*, *M. simiae*, and *M. szulgai*.

Lymphadenitis, which is usually self-limiting and occurs particularly in children under 5 years of age, may be caused by many species but the great majority of cases are due to *M. avium* complex, *M. genavense*, *M. malmoense*, and *M. scrofulaceum* (sometimes collectively known as the MAIS complex).

Dissemination of opportunistic mycobacterial infections may occur rapidly in immunocompromised patients. The majority of cases have been attributed to the *M. avium* complex; other species implicated include *M. abscessus*, *M. celatum*, *M. chelonae*, *M. genavense*, *M. haemophilum*, *M. kansasii*, *M. malmoense*, *M. scrofulaceum*, and *M. simiae*.

The treatment depends on the site and nature of the infection and whether immunodeficiency is present. Both HIV-negative and HIV-positive patients may be affected and the possibility of drug interactions should be borne in mind in patients receiving antiretroviral therapy. For further information on drug interactions with antiretrovirals see Table 1, p.917, and Table 2, p.944, in Antivirals.

- MYCOBACTERIUM AVIUM COMPLEX (MAC).

  US guidelines[1,2] produced by the CDC, National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America recommend that the **treatment** of **HIV-positive patients** with MAC should consist of at least 2 antimycobacterial drugs. Clarithromycin is the preferred first drug (with azithromycin as an alternative) and is given with ethambutol. Rifabutin may be added as a third drug in patients with advanced immunosuppression, high mycobacterial loads, or if the patient is not taking effective HAART. The fluoroquinolones (ciprofloxacin or levofloxacin) or amikacin may be given when rifabutin is contra-indicated or not tolerated. In ***disseminated*** disease, patients who are not taking HAART should start antiretroviral treatment at the same time as starting treatment for MAC or at least 1 to 2 weeks thereafter. Those already on HAART should continue this treatment.

  UK guidelines from the British Thoracic Society (1999)[3] for treatment of HIV-positive patients with MAC broadly concur with the US recommendations. Rifampicin or rifabutin, ethambutol, and clarithromycin or azithromycin are recommended. A fluoroquinolone such as ciprofloxacin, or even amikacin, may be added for patients who are intolerant of first-line drugs or who fail to respond. UK guidelines recommend lifelong treatment; the US considers that treatment may be stopped in selected patients (see Chemoprophylaxis, below). In ***disseminated*** disease, the same treatment should be given and continued indefinitely.

  A prospective, randomised study[4] undertaken to compare 3 regimens (clarithromycin and ethambutol, clarithromycin and rifabutin, and all 3 drugs) for the treatment of disseminated MAC in patients with AIDS found that all regimens appeared to provide effective treatment and the differences were not statistically significant. However, patients taking the 3-drug regimen had greater overall clinical efficacy, a lower relapse rate, and a lower risk of death.

  The British Thoracic Society guidelines (1999)[3] state that treatment for **HIV-negative patients** with MAC pulmonary disease should consist of rifampicin and ethambutol for 24 months, with or without isoniazid. In extrapulmonary disease affecting lymph nodes, surgical excision of the nodes should be undertaken; chemotherapy with rifampicin, ethambutol, and clarithromycin for up to 2 years should be considered if disease recurs or where the excision is incomplete or impossible. In sites other than lymph nodes, chemotherapy should be given for 18 to 24 months.

  Prophylactic treatment is used to reduce the incidence of disseminated MAC disease in patients with HIV infection. There appears to be a tendency to delay starting prophylaxis until later in the disease process; the guidelines[5] from the US Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA) recommend starting prophylaxis at a CD4+ count of less than 50 cells/microlitre with either azithromycin or clarithromycin. If these drugs cannot be tolerated then rifabutin may be given as an alternative. Combination therapy with one of the macrolides and rifabutin is not recommended. The US guidelines state that prophylaxis need not be lifelong in patients responding to HAART; specifically, primary prophylaxis may be stopped in patients whose CD4+ count has increased to more than 100 cells/microlitre for 3 months or more, but should be restarted if the CD4+ count falls to below 50 to 100 cells/microlitre again. Observational data from a large cohort of patients in the USA found no evidence of increased risk of MAC in patients who had stopped primary prophylaxis in accordance with the USPHS/IDSA guidelines.[6]

  The US guidelines[5] also state that it may be possible to stop secondary prophylaxis (chronic maintenance therapy) in HIV-infected patients who have completed at least 12 months of treatment for MAC, who remain asymptomatic with respect to MAC, and who have a sustained response to HAART (CD4+ count greater than 100 cells/microlitre). Secondary prophylaxis should be restarted if CD4+ count falls below 100 cells/microlitre.

  In the UK, however, the British Thoracic Society guidelines note there is no general agreement about when prophylaxis should be used. If prophylaxis is to be given to patients with a CD4+ count below 50 cells/microlitre the first drug of choice would be azithromycin; clarithromycin is an alternative and azithromycin with rifabutin would be a third choice.[3] The UK guidelines, partly based on studies which predate the wide use of HAART, recommend that prophylaxis be continued indefinitely.[3]

- MYCOBACTERIUM KANSASII INFECTION.

  UK guidelines state that infections with *M. kansasii* may be treated with rifampicin (or rifabutin) and ethambutol.[3] Pulmonary disease in HIV-negative patients is usually treated for 9 months whereas HIV-positive patients should receive therapy for 2 years or until the sputum has been negative for 12 months. For disseminated infection in HIV-positive patients, clarithromycin should be added and possibly also isoniazid. The place of macrolides and fluoroquinolones in pulmonary or disseminated *M. kansasii* infection remain to be established. In extrapulmonary disease in HIV-negative patients, chemotherapy with rifampicin and ethambutol may be used before excision of an infected lymph node. In other extrapulmonary disease the guidelines state that the data are insufficient to make recommendations, but consider that rifampicin and ethambutol for 9 months appears sensible with the addition of protionamide and streptomycin and/or a macrolide if the condition is not responding.[3]

- OTHER OPPORTUNISTIC MYCOBACTERIA.

  In *M. malmoense* and *M. xenopi* **pulmonary** disease, the UK guidelines recommend that rifampicin and ethambutol should be given for 2 years in HIV-negative patients. Extrapulmonary *M. malmoense* infections should be treated in the same manner as extrapulmonary MAC or *M. kansasii* infections. *M. malmoense* infection rarely occurs in AIDS patients, but if necessary, treatment with rifampicin, ethambutol, and clarithromycin, and possibly isoniazid should be used. For *M. xenopi* in HIV-positive patients the guidelines state that there is no evidence on which to base recommendations; treatment as for pulmonary or disseminated MAC infection is suggested.[3]

  For pulmonary disease due to rapidly growing bacteria (*M. abcessus*, *M. chelonae*, *M. fortuitum*, and *M. gordonae*) and other species (*M. genavense*, *M. haemophilum*, *M. simiae*, *M. szulgai*, and *M. ulcerans*) surgery should be used if possible. Drug therapy should probably include rifampicin, ethambutol, and clarithromycin. Amikacin, cefoxitin, imipenem, quinolones, and sulfonamides may have a place in treatment. For extrapulmonary disease due to these organisms, there have been several anecdotal reports outlining treatment but there is no evidence from controlled clinical studies.[3] Successful treatment of *M. simiae* infection in patients with AIDS was reported with clarithromycin, ethambutol, and ciprofloxacin.[7] Surgical treatment and intensive antibacterial regimens have been used for *M. scrofulaceum* infections.[8] Symptomatic improvement was achieved in an AIDS patient with *M. celatum* infection with a regimen of isoniazid, rifampicin, and ethambutol.[9]

For **cutaneous** infections due to *M. marinum* (swimming-pool granuloma or fish-tank granuloma) numerous antibacterial regimens have been used,[10] including rifampicin with ethambutol[11] or isoniazid, rifabutin with ciprofloxacin,[12] minocycline with co-trimoxazole,[13] clarithromycin with rifabutin[14] or ciprofloxacin[12] or ethambutol.[12] Monotherapy with clarithromycin, minocycline, doxycycline, or co-trimoxazole[15] have each been tried, mainly in small series of patients.

Buruli ulcer, due to *M. ulcerans*, is difficult to treat and usually requires surgery; responses to antimycobacterial monotherapies have been generally disappointing. However, recent evidence suggests that combination antibacterial therapy may reduce the healing time and recurrence rates of ulcers, and minimise or avoid the need for surgery.[16] Treatment of nodules and plaques of early Buruli ulcers with rifampicin and streptomycin for up to 12 weeks, showed inhibition of growth 4 weeks after starting treatment.[17] Furthermore, no lesions enlarged during the treatment period. WHO therefore recommends the use of rifampicin and streptomycin or amikacin for 8 weeks.[18] Consensus recommendations issued by practitioners in Victoria, Australia[19] consider surgery to be the best treatment for Buruli ulcer, with antibacterial therapy being indicated for more extensive disease. Use of antibacterial may also possibly allow more conservative resection and reduce the risk of relapse. The recommended oral regimens were: at least 3 months of rifampicin given with clarithromycin, ciprofloxacin, or moxifloxacin. For more severe or extensive disease patients may also require intravenous amikacin for 4 to 8 weeks in addition to oral therapy. Reports of other therapies include a beneficial response with topical nitrogen oxides in a small pilot study of 37 patients with Buruli ulcer,[20] and healing after local application of phenytoin.[21]

Cutaneous disease due to *M. haemophilum* infection has been treated with an initial treatment course of rifabutin, ciprofloxacin, and clarithromycin, followed by clarithromycin for 2 years.[22] *M. chelonae* was successfully treated with clarithromycin and linezolid for one month, followed by a further 5 months of treatment with clarithromycin.[23]

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Obstetric disorders

See under: Endometritis (the prophylaxis and treatment of postpartum endometritis), p.170; Premature Labour, p.188; and Urinary-Tract Infections in Pregnancy, p.199. See also Neonatal Conjunctivitis, p.180, and Perinatal Streptococcal Infections, p.184.

Osteomyelitis

See under Bone and Joint Infections, p.164.

Otitis externa

Otitis externa is a general term used to describe inflammation of the skin of the external auditory canal that may be due to infection with bacteria, viruses, or fungi or secondary to skin disorders such as eczema. Otitis externa is associated with high humidity, warmer temperatures, swimming, local trauma, or obstruction of the ear canal. Subtypes include acute localised otitis externa, acute diffuse otitis externa (swimmer's ear), chronic otitis externa, and necrotising (malignant) otitis externa. Acute diffuse disease is characterised by erythema, itching, pain, purulent discharge, oedema, fullness, and deafness. If left untreated or if treated inadequately it may progress to chronic otitis externa. Chronic otitis externa may also result from allergic contact dermatitis or other underlying skin conditions, such as eczema. Malignant otitis externa is rare and occurs mainly in immunocompromised persons and in diabetics and can be life-threatening if temporal bone infections occur.

The **treatment** of both acute and chronic otitis externa includes thorough cleansing and the use of appropriate acidifying and/or antibacterial ear drops, with or without a corticosteroid, even though some have doubted the value of topical antibacterials. Ear drops containing aminoglycosides, such as gentamicin, neomycin, or framycetin, or polymyxins should not be used when the ear drum is perforated because of the risk of ototoxicity.

The management of the various subtypes of otitis externa has been described.[1-4]

Acute localised otitis externa is an infection of the hair follicle (furunculosis), commonly due to *Staphylococcus aureus*. It may cause severe pain, which may be treated with an analgesic such as paracetamol or ibuprofen. If the furuncle is not pointing (ready to rupture spontaneously), local heat application and systemic treatment with a penicillinase-resistant penicillin such as flucloxacillin or a first-generation cephalosporin such as cefalexin may be used.[1] Others have suggested application of topical antibacterials using wicks which are left in the ear canal for 3 to 5 days.[3] Pointed furuncles require incision and drainage followed by a course of topical and/or oral antibacterials.[1,3]

In *acute diffuse otitis externa*, *Staphylococcus aureus*, *S. epidermidis*, and *Pseudomonas* spp. are often present. Treatment includes thorough cleansing of the ear canal and instillation of ear drops including acidifying agents (2% acetic acid) and antibacterials such as aminoglycosides, fluoroquinolones (ciprofloxacin and ofloxacin), chloramphenicol, or polymyxin B, with or without corticosteroids such as dexamethasone.[1,3] Antifungals may sometimes be required. A wick may be used if instillation proves difficult.[1] Systemic antibacterials may be necessary in severe cases of otitis externa.[1,3]

Chronic otitis externa is treated similarly, although the topical antibacterials and corticosteroids used should not be the same as those used previously for the treatment of acute disease.[1]

Necrotising (malignant) otitis externa, due to fulminating infection, especially with *Pseudomonas*, is uncommon but can occur in susceptible patients. Topical antibacterials are not effective and systemic treatment with antipseudomonal drugs such as gentamicin, ceftazidime, a carbapenem, or a fluoroquinolone is needed for about 4 to 8 weeks.[1,3] However, resistance to ciprofloxacin has been reported.[5] Combination treatment with an aminoglycoside and another antipseudomonal drug or a penicillin (such as azlocillin, piperacillin, or ticarcillin) may also be used.[1,3]

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Otitis media

Otitis media is a general term used to describe inflammation of the middle ear that usually results from dysfunction of the Eustachian tube after a viral infection of the nasopharynx. It is one of the most frequent childhood illnesses seen in general practice. Subtypes of otitis media may be classified as follows:

- *acute otitis media (AOM)* is seen especially in young children and is often due to bacterial and/or viral infection and is sometimes associated with upper respiratory-tract infection. It is characterised by rapid onset, ear discomfort, and pain. Common bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*)
- *recurrent acute otitis media* refers to frequent episodes of AOM (3 or more episodes within 6 months or 4 episodes within 12 months) and may be due to relapse or re-infection
- *otitis media with effusion (OME) or serous otitis media*, commonly known as 'glue ear', is defined as the accumulation of fluid in the middle ear without local or systemic illness. It may be associated with recurrent upper respiratory-tract infection and is characterised by deafness although some episodes may be asymptomatic
- *chronic suppurative otitis media (CSOM)* is often preceded by one or more episodes of AOM and is associated with perforation of the ear drum, and continued infection and inflammation in the middle ear causing persistent or recurrent discharge and deafness. The condition has been divided into inactive or active. Inactive disease (tubo-tympanic disease) is typically characterised by perforation of the ear drum, deafness, and a profuse mucoid discharge associated with upper respiratory-tract infection. In active disease (attico-antral disease) there may be cholesteatoma with bone involvement. The commonest infecting organisms are *Pseudomonas aeruginosa* and anaerobes. Other common infecting aerobic organisms are diphtheroids, *Staphylococcus aureus*, and *Klebsiella*.[1]

TREATMENT Treatment of *acute otitis media* aims to relieve symptoms, avoid complications, and prevent relapse, recurrence, and progression to the chronic state. Sometimes an analgesic such as paracetamol may be all that is required as long as frequent inspection is possible. However, it is common practice to prescribe a systemic antibacterial as well as an analgesic,[2] although the need for routine antibacterial treatment is questionable.[3-5] Systemic antibacterial treatment aims to speed resolution and prevent complications. However, meta-analyses and reviews have shown only modest benefits from routine use of antibacterials[6-8] and experience from studies where antibacterials are not given routinely for AOM suggested that there is no consequent increase in complications.[4,8,9] Another meta-analysis[10] to estimate the natural history of AOM found that about 60% of children not initially treated with an antibacterial showed symptomatic improvement within 24 hours, and that symptoms resolved within 3 days in about 80% of these children. Suppurative complications occurred in about 0.12% of children not immediately treated with antibacterials and in 0.24% of those given immediate treatment. A systematic review[9] reported that clinical signs and symptoms resolved within 4 to 7 days in 78% of children not initially treated with an antibacterial. However, some clinicians have argued that although the benefit is modest, it is significant and therefore the routine use of antibacterials is clinically justifiable.[6] A later systematic review[11] concluded that antibacterials do provide a small benefit in very young children and a further meta-analysis[12] reported that most benefit was seen in children under 2 years of age with bilateral AOM, and in children with both AOM and discharge. Another suggested approach has been to delay the start of antibacterials for 72 hours and to then only give them if the patient remains unwell.[8,13,14] No one antibacterial has been found to be superior to another in the treatment of AOM.[9] Adjunctive treatment with topical and systemic decongestants and antihistamines has not been found to be beneficial[15] and there is insufficient information to conclude whether there is any benefit from the use of topical analgesics (including corticosteroids, local anaesthetics, and NSAIDs).[16]

The American Academy of Pediatrics has produced guidelines[17] for the diagnosis and management of uncomplicated AOM in children from 2 months to 12 years of age. They suggest that in a select group of children an observation period may be recommended depending on the patient's age, the diagnostic certainty, and the severity of illness. These children should be given symptomatic treatment and observed for 48 to 72 hours; if the illness worsens during the observation period or there is no improvement then systemic antibacterials should be considered. Pain management is important, and appropriate analgesics should be offered. If antibacterial treatment is given high-dose amoxicillin (80 to 90 mg/kg daily) is recommended for most children. In children with severe illness or those not responding to amoxicillin and thought to be infected with *H. influenzae* or *M. catarrhalis* high-dose amoxicillin with clavulanic acid should be given. Alternatives in penicillin-allergic children include cephalosporins, azithromycin, or clarithromycin. Similar recommendations have been made for the treatment of AOM in the UK.[18]

Duration of therapy for AOM has varied from 5 to 10 or more days. A systematic review[19] of published clinical studies suggests that a 5-day treatment course may be given to children with uncomplicated AOM. The American Academy of Pediatrics recommends treatment with antibacterials for 10 days in younger children (up to 6 years of age) and for children with severe disease; those aged 6 years or older with mild to moderate disease may be given treatment for 5 to 7 days.[17]

Penicillin-resistant strains of *Str. pneumoniae* have been reported in children with otitis media and are reported to be increasingly prevalent.[20] About one-quarter of *Str. pneumoniae* isolates, one third of *H. influenzae* isolates, and nearly all *M. catarrhalis* isolates are resistant to penicillin and amoxicillin.[2] However, resistance rates vary between countries[21] and many penicillin-resistant strains remain sensitive *in vivo* to high-dose amoxicillin.[20,22,23]

Optimal treatment of *otitis media with effusion* is controversial and the majority of cases will resolve spontaneously within 3 months. Guidelines have been developed in the USA[24] for the diagnosis and management of uncomplicated disease in children from 2 months to 12 years of age. They suggest careful assessment and observation for at least 3 months before considering surgery. Those at increased risk of developmental difficulties such as children with cleft palate or Down's syndrome should be referred to a specialist. Similar recommendations have been made for the treatment of OME in the UK.[25] Antihistamines, decongestants, and mucolytics are ineffective.[24-26] Oral or topical intranasal corticosteroids alone or with an antibacterial have only short-term benefit[27] and their use is not recommended as routine treatment.[24,25] A meta-analysis[28] on the use of antibacterials for the treatment of OME failed to find any benefit and their use cannot be justified.[24,25]

Treatment of *chronic suppurative otitis media* aims to stop the discharge, eradicate the infection, heal the ear drum, and to prevent serious complications. Treatment options for uncomplicated cases include aural toilet (thorough cleansing and mopping of the ear), systemic antibacterials, and topical treatments with either an antiseptic or antibacterial, sometimes also with a corticosteroid. Surgery may be needed if complications develop.[1,29] There is controversy over the use of ear drops containing aminoglycosides or polymyxins in the presence of a perforated ear drum, as they are potentially ototoxic. However, it is considered that untreated disease is more likely to result in deafness than a short course of these ear drops. A systematic review[29] found that treatment with topical fluoroquinolone ear drops was more effective at drying the ear than no drug treatment or topical antiseptics; effects of topical non-fluoroquinolone antibacterials when compared with no drug treatment or topical antiseptics were less clear. Another systematic review[30] found that ear drops containing fluoroquinolones were also more effective than systemic antibacterials at drying the ear. Effects of topical non-fluoroquinolone antibacterials or antiseptics were less clear and no additional benefit was noted by adding a systemic antibacterial to topical antibacterial treatment.

PREVENTION Long-term antibacterial prophylaxis has been tried in children at high risk including those with *recurrent acute otitis media*,[31,32] but the evidence for its benefit is inconsistent. A meta-analysis[33] on the use of antibacterials to prevent recurrent AOM concluded that they appeared to have limited benefit and that 9 children would need to be treated to show an improved outcome in one. A later meta-analysis[34] concluded that antibacterials reduced the probability of disease recurring during the treatment period, but that the long-term benefits of treatment were unclear and that 5 children would need to be treated to show an improved outcome in one.

The use of xylitol, which inhibits the growth of *Str. pneumoniae*, as chewing gum[35,36] or as syrup for very young children[36,37] has been reported to reduce the incidence of AOM. Randomised studies[35,36] with xylitol chewing gum reported a 40% reduction in the incidence of AOM in children with recurrent AOM. However, xylitol was found to be ineffective when it was used only during an acute respiratory-tract infection[38] and the need for use 5 times a day may make this treatment impractical.[35,36]

Vaccination against AOM with pneumococcal vaccines has also been tried but unconjugated multivalent polysaccharide vaccines do not prevent AOM in children under 2 years of age[23,39] and their benefit in older children is minimal.[39] A meta-analysis[39] found that starting immunisation with the 7-valent pneumococcal conjugate vaccine by 2 months of age reduces the incidence of recurrent AOM. No benefit was noted in children with recurrent infections who received their first vaccination after 1 year of age. In a later study[40] in children 2 to 8 years of age with recurrent OME, vaccination with the 7-valent conjugated vaccine before, and the 23-valent polysaccharide vaccine after, insertion of a tympanostomy tube did not prevent recurrences.

Vaccination may also have a role in reducing the incidence and in preventing the development of antibacterial resistance[23] but use of conjugated pneumococcal vaccines was found to cause a shift in the pathogens responsible for AOM from vaccine-type pneumococci to nonvaccine-type strains and to *H. influenzae*.[23]

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Pancreatitis

The overall management of pancreatitis is discussed on p.2361. Although there has been some uncertainty about the value of prophylactic antibacterials in acute pancreatitis, a meta-analysis[1] of 8 prospective studies showed a positive benefit in reducing mortality. The advantage was limited to patients with severe pancreatitis given broad-spectrum drugs that achieved therapeutic levels in pancreatic tissue, such as imipenem or a fluoroquinolone. A retrospective study[2] reported a reduction in the incidence, but not in the time of onset, of infection in those given antibacterial prophylaxis in severe disease. However, a systematic review[3] of the value of antibacterial prophylaxis in patients with severe acute necrotising pancreatitis concluded that, despite variations in drugs used (cefuroxime, imipenem, or metronidazole with ciprofloxacin or ofloxacin) and in the quality and methodology of studies conducted, antibacterial prophylaxis appeared to reduce the risk of death in patients with pancreatic necrosis but not, overall, the rate of infected pancreatic necrosis. However, there was some evidence that beta lactams were associated with both a reduction in risk of death, and risk of infected pancreatic necrosis whereas quinolone plus imidazole regimens were not.

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Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is a broad term for infectious disorders of the upper genital tract in women and may include endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. It is generally due to ascending infection through the cervix and uterus to the fallopian tubes, resulting in salpingitis, and from there may extend to the ovaries and peritoneum. Long-term complications include infertility and ectopic pregnancy. The use of intrauterine contraceptive devices might increase the likelihood of PID although the risk may have been overstated;[1] it appears to be greatest during the first 20 days after insertion of the device.[2]

The majority of these infections are probably sexually transmitted and at one time were mainly due to *Neisseria gonorrhoeae*, but *Chlamydia trachomatis* is increasingly responsible and may be the commonest cause of PID in some areas. Other organisms that have been isolated include *Mycoplasma hominis*; *Ureaplasma urealyticum*; anaerobes such as *Bacteroides*, *Peptococcus*, and *Peptostreptococcus* spp.; Gram-negative enteric aerobes such as *Escherichia coli*; and Gram-positive aerobes such as group B streptococci. Some of these organisms occur in the abnormal vaginal flora associated with bacterial vaginosis (p.164). Thus, the aetiology of PID appears to be polymicrobial; some think that primary infection with *N. gonorrhoeae* or *C. trachomatis*, or both, allows opportunistic infection with aerobic and anaerobic bacteria.[1]

Treatment regimens are of necessity broad spectrum and empirical and should include antibacterials active against the major pathogens. Many consider that treatment should be started in hospital so that drugs can be given parenterally. Guidelines produced by WHO,[3] by an expert group in the UK,[4] and by the CDC in the USA[5] are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO**
  - *inpatients*:
    - intramuscular ceftriaxone 250 mg daily, *plus*
      oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times a day), *plus*
      oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily
    - intravenous clindamycin 900 mg every 8 hours, *plus*
      intravenous gentamicin 1.5 mg/kg every 8 hours
    - oral ciprofloxacin 500 mg twice daily or intramuscular spectinomycin 1 g four times daily, *plus*
      oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times a day), *plus*
      oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily

    Therapy should be continued for at least 48 hours after clinical improvement, and *then* followed by doxycycline or tetracycline orally for 14 days.
  - *outpatients*:
    - a single-dose treatment for uncomplicated gonorrhoea such as a single intramuscular dose of ceftriaxone 125 mg is recommended (see Gonorrhoea, p.191) *plus*
      oral metronidazole 400 to 500 mg twice daily *and* oral doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times a day) for 14 days.
- **UK**:
  - *inpatients*:
    with the regimens below intravenous therapy is continued until 24 hours after clinical improvement, and the oral regimen is *then* substituted until therapy has been given for at least 14 days.
    - intravenous cefoxitin 2 g three times daily *plus* intravenous (or oral if tolerated) doxycycline 100 mg twice daily, until clinical improvement, *then*
      oral doxycycline 100 mg twice daily, *plus* oral metronidazole 400 mg twice daily
    - intravenous clindamycin 900 mg three times daily *plus* intravenous gentamicin (2 mg/kg as a loading dose, *then* 1.5 mg/kg three times daily *or* a single daily dose of 7 mg/kg) until clinical improvement, *then*
      oral clindamycin 450 mg four times daily or oral doxycycline 100 mg twice daily *plus* oral metronidazole 400 mg twice daily

    alternative regimens, given for a total of 14 days, are:
    - intravenous ofloxacin 400 mg twice daily *plus*
      intravenous metronidazole 500 mg three times daily
    - intravenous ciprofloxacin 200 mg twice daily *plus*
      intravenous metronidazole 500 mg three times daily, *plus*
      intravenous or oral doxycycline 100 mg twice daily

    Metronidazole may be stopped in women with mild or moderate disease who tolerate it poorly, but the improved coverage of anaerobic infection that it provides is more important in women with severe disease.
  - *outpatients*:
    - a single intramuscular dose of ceftriaxone 250 mg *or* cefoxitin 2 g with oral probenecid 1 g, *then*
      oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days, *or*
    - oral ofloxacin 400 mg plus oral metronidazole 400 mg both twice daily for 14 days
- **USA:**
  - *parenteral* treatment:
    - (regimen A): intravenous cefoxitin 2 g every 6 hours or cefotetan 2 g every 12 hours *plus*
      oral or intravenous doxycycline 100 mg every 12 hours
    - (regimen B): intravenous clindamycin 900 mg every 8 hours *plus*
      parenteral gentamicin 2 mg/kg as a loading dose *then* 1.5 mg/kg every 8 hours

    In each case parenteral treatment is continued for 24 hours after substantial clinical improvement has occurred and *then* followed by oral therapy to complete a total of 14 days of treatment.
    - in regimen A, continuation is usually with oral doxycycline 100 mg twice daily; in patients with tubo-ovarian abscesses oral clindamycin *or* oral metronidazole may be added to doxycycline
    - in regimen B, continuation may be with oral clindamycin 450 mg four times a day *or* doxycycline; oral clindamycin is preferred in patients with tubo-ovarian abscesses

    Another parenteral regimen which has been tried is:
    - ampicillin/sulbactam 3 g every 6 hours *plus*
      oral or intravenous doxycycline 100 mg every 12 hours.
  - *oral* treatment:
    - a single intramuscular dose of cefoxitin 2 g *plus* oral probenecid 1 g, *or* a single intramuscular dose of ceftriaxone 250 mg (*or* equivalent third-generation cephalosporin), *plus*
      oral doxycycline 100 mg twice daily, with or without oral metronidazole 500 mg twice daily, for 14 days

Pregnant women who have suspected PID disease should be hospitalised and treated with a parenteral regimen.[5]

Sexual partners of patients with PID should be tested and treated.[5]

Women co-infected with HIV appear to be more likely to develop tubo-ovarian abscesses but respond similarly to treatment compared to women who are HIV-negative.[5]

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Peptic ulcer disease

The Gram-negative bacterium *Helicobacter pylori* is involved in the aetiology of gastritis and peptic ulceration, and treatment regimens to eradicate the organism are recommended in peptic ulcer disease (p.1702).

Perinatal streptococcal infections

Group B streptococci are a major cause of perinatal infections, often leading to neonatal pneumonia or septicaemia, sometimes with meningitis, although the incidence varies in different parts of the world. Infections are acquired through maternal genital carriage during pregnancy. *Prevention* of group B streptococcal infection in infants may be achieved by giving appropriate antibacterials to the mother during labour.[1] Ideally maternal carriers of group B streptococci would be identified during pregnancy, but this may not be practical. Factors that increase the risk of acquiring neonatal infection include premature labour, prolonged rupture of membranes, maternal fever, a previous child with neonatal group B streptococcal infection, and multiple pregnancy and they will influence the decision of whether or not to give intrapartum antibacterial prophylaxis to the mother. A penicillin is the preferred drug.

Guidelines from the USA[1] recommend prophylaxis based on universal prenatal screening. Where required, they recommend benzylpenicillin or, alternatively, ampicillin, given intravenously during labour. In women allergic to penicillin but who are not considered to be at high risk of anaphylaxis, intravenous cefazolin is recommended as an alternative; those considered to be at high risk of anaphylaxis should be given clindamycin or erythromycin intravenously or, where there is resistance to clindamycin and erythromycin or susceptibility is unknown, intravenous vancomycin.

In other parts of the world, including Europe, the incidence of neonatal streptococcal infections is much lower and the US model for prophylaxis may not be appropriate.[2,3]

Another strategy suggested for areas with a high incidence of neonatal group B streptococcal disease (above 1.5 per 1000 live births) is to give a single dose of penicillin to all neonates at birth.[4]

As mentioned under Premature Labour, p.188, the elimination of bacteria such as group B streptococci in pregnant women might also reduce the risk of premature labour.

Streptococcus group B vaccines are under investigation for use in pregnant women to prevent neonatal infection.

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Peritonitis

Intra-abdominal infections include peritonitis, which may be complicated by intraperitoneal abscesses, and abscesses of the intra-abdominal viscera such as those of the liver (see under Abscess, Liver, p.162), pancreas, and spleen. Infective peritonitis may be primary or secondary or may be a complication of continuous ambulatory peritoneal dialysis (CAPD).

Primary peritonitis. In primary or spontaneous bacterial peritonitis there is no specific focus of infection and it occurs most often as a complication of ascites. Infecting bacteria include *Escherichia coli*, other Enterobacteriaceae, and streptococci. Initial empirical treatment has been with broad-spectrum chemotherapy such as ampicillin plus an aminoglycoside, but third-generation cephalosporins such as cefotaxime are considered by some to be the treatment of choice.[1-3] Other alternatives include other broad-spectrum penicillins, carbapenems, and combinations of penicillins with beta-lactamase inhibitors.[2,3] Oral ofloxacin has been reported to be as effective as intravenous cefotaxime in uncomplicated infections.[4] If infection with anaerobic organisms is suspected, metronidazole or clindamycin may be added to the chosen regimen.[2] In cirrhotic patients with low levels of ascitic fluid protein[5] the use of oral norfloxacin for selective intestinal decontamination appeared to prevent spontaneous bacterial peritonitis and prophylaxis with norfloxacin has been recommended to decrease the recurrence of spontaneous bacterial peritonitis.[1] However, prophylaxis with norfloxacin will not prevent infection by Gram-positive bacteria including *Staphylococcus aureus* or quinolone-resistant Gram-negative bacteria.[2] Co-trimoxazole has also been reported to be an effective prophylactic.[6]

Secondary peritonitis. Secondary peritonitis is associated with perforation of the gastrointestinal tract, conditions such as appendicitis and diverticulitis, and contamination at surgery. Infections are generally mixed and originate from the gastrointestinal tract. Bacteria responsible include *E. coli* and other Enterobacteriaceae, anaerobes (especially *Bacteroides fragilis*), enterococci, and sometimes *Pseudomonas aeruginosa*. Broad-spectrum antibacterial therapy is therefore usually used, at least until the infecting organisms are known, and a combination of two or three drugs is often given. The intravenous route is generally preferred. Nevertheless, it is difficult to assess the relative merits of surgical therapy against medical management that includes antibacterial therapy.[2] An aminoglycoside such as gentamicin or a cephalosporin, plus metronidazole or clindamycin, have often been used, but many other regimens have been tried. Patterns of resistance further complicate the choice of antibacterial: resistance to beta lactams may emerge among some Gram-negative organisms, which are most likely to infect patients with prolonged hospital stays, previous antibacterial treatment, postoperative peritonitis, or recurrent peritonitis. Such patients are best treated with a regimen that includes a carbapenem, cefepime, a fluoroquinolone, or an aminoglycoside.[2] Resistant isolates of *B. fragilis* and *Clostridium difficile* (with associated diarrhoea) are more common after clindamycin than after metronidazole.[2] Microaerophilic Gram-positive cocci are resistant to metronidazole but not to clindamycin,[2] so metronidazole should be used with a beta lactam other than aztreonam.[2]

For reference to the prevention of postoperative infection, see under Surgical Infection, p.195.

CAPD peritonitis. Peritonitis is the main complication of CAPD, a technique widely used in end-stage renal failure. Unlike secondary peritonitis, above, a single infecting organism is often responsible. The most common infections have usually been due to Gram-positive organisms, especially staphylococci, but infections with Gram-negative bacteria (typically Enterobacteriaceae) are becoming more common, and fungi are an increasingly important cause of peritonitis in CAPD.[2] The International Society for Peritoneal Dialysis recommends[7] that the choice of antibacterial for empirical therapy be based on the history of sensitivities of organisms causing peritonitis in the particular hospital or centre involved. In some cases a first-generation cephalosporin (such as cefalotin or cefazolin) for Gram-positive organisms, with a third-generation cephalosporin or an aminoglycoside for Gram-negative coverage, may be suitable; however, many centres have a high rate of meticillin-resistant infections and vancomycin for Gram-positive coverage may be necessary. Quinolones for Gram-negative organisms should only be used if local sensitivity is demonstrated. Aztreonam can be used in patients with cephalosporin hypersensitivity. The antibacterials are given intraperitoneally by mixing with the dialysate. Once-daily dosing regimens for aminoglycosides are considered appropriate for CAPD patients. Once the infecting organism is identified, an appropriate narrow-spectrum antibacterial can be substituted. Treatment is generally continued for 14 days in patients who have a clinical response. Treatment should be extended to 21 days in patients with severe infections (such as *Staph. aureus*, Gram-negative, or enterococcal peritonitis).

Exit-site infections can be treated with an oral penicillinase-resistant penicillin, a first-generation cephalosporin such as cefalexin, or co-trimoxazole for Gram-positive infections. Vancomycin should be avoided for routine use but may be needed if there is meticillin resistance. Rifampicin may be added in severe *Staph. aureus* infections. An oral fluoroquinolone such as ciprofloxacin may be used for Gram-negative infections.[7] Intraperitoneal ceftazidime may be added in cases of pseudomonal infection where resolution of infection is slow or where there is recurrence.

Long-term antibacterial prophylaxis is not generally effective, but *Staph. aureus* nasal carriage is associated with increased risk of exit-site infections and intranasal or exit-site mupirocin (cream, as ointment may damage the catheter) or exit-site gentamicin cream have been used to reduce them.[7] Dramatic reductions in peritonitis rates have been achieved with programmes based on stringent aseptic wound care and on minimising contact of the CAPD system with domestic water.[8]

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Pertussis

Pertussis or whooping cough[1] is caused by infection with the respiratory pathogen *Bordetella pertussis*, a Gram-negative aerobic bacterium. The related species *B. parapertussis* causes a similar but generally milder illness. Pertussis is very infectious and occurs most frequently in children, but may be more common in adults than once thought. The incidence of pertussis has been greatly reduced by the active immunisation of infants (see under Pertussis Vaccines, p.2231) and effective prevention by the adequate uptake of vaccine remains the ultimate objective.

Erythromycin has been the antibacterial of choice, but the newer macrolides, clarithromycin and azithromycin, have similar effectiveness and are also recommended for the **treatment** of pertussis.[1-3] Once infection has occurred antibacterial therapy is thought to render the patient non-infectious by eliminating nasopharyngeal carriage of *B. pertussis*. Such treatment is unlikely to affect the clinical course of pertussis because diagnosis is difficult until the paroxysmal stage, by which time the bacteria have already damaged the respiratory tract and released their toxins. Effective regimens include:[2,3]

- oral azithromycin 500 mg daily on the first day of treatment then 250 mg for 4 days; infants and children may be given oral azithromycin 10 mg/kg daily for 3 to 5 days, or 10 mg/kg daily on the first day of treatment then 5 mg/kg daily for 4 days
- oral clarithromycin 500 mg twice daily for 7 days; infants and children may be given oral clarithromycin 7.5 mg/kg twice daily for 7 days
- oral erythromycin 500 mg four times daily for 14 days; infants and children may be given oral erythromycin 40 to 50 mg/kg daily in 3 to 4 divided doses for 7 to 14 days, or 60 mg/kg daily in 3 divided doses for 14 days

Oral co-trimoxazole for 7 to 14 days may be given as an alternative treatment for patients unable to tolerate macrolides. Oxytetracycline or chloramphenicol are not recommended because of their potential side effects.

Macrolide antibacterials, given in the same doses as for treatment and within 3 weeks of onset of cough in the index patients, may also be given **prophylactically** to close contacts.[2] However, protection is limited and a systematic review[3] concluded there was insufficient evidence to determine the benefit of prophylactic treatment of healthy pertussis contacts.

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Pharyngitis

Pharyngitis and tonsillitis are upper respiratory-tract infections with similar causes and occur especially in children. Acute pharyngitis is an inflammatory syndrome of the oropharynx that may include the tonsils whereas tonsillitis is, strictly speaking, a more localised infection. The commonest causes are viral and a sore throat is often a symptom of the common cold as well as influenza and infectious mononucleosis. For further details of these viral infections, see under Choice of Antiviral, p.850.

The most important bacterial cause of acute pharyngitis and tonsillitis is the group A beta-haemolytic streptococcus, *Streptococcus pyogenes*. An erythrogenic toxin-producing strain causes pharyngitis and tonsillitis in scarlet fever.

In view of the prevalence of a viral cause, opinions have differed over whether and when to treat pharyngitis with antimicrobial drugs. Some have advocated waiting until a definite diagnosis of *Str. pyogenes* infection is made, but others treat immediately if streptococcal pharyngitis is suspected because of the risk of longer term complications such as rheumatic fever and the need to eradicate *Str. pyogenes* from the throat.[1-3] The incidence of rheumatic fever has been low for many years in developed countries, but there was evidence of a resurgence in parts of the USA in the mid-1980s. Thus, in addition to shortening the illness and interrupting transmission, the antibacterial treatment of streptococcal pharyngitis also serves as primary prevention of rheumatic fever (see below). However, in countries in which the incidence of rheumatic fever remains low the routine use of antibacterials for the management of sore throats is discouraged.[4,5]

Penicillin is the standard treatment for streptococcal pharyngitis or tonsillitis,[6-8] generally as phenoxymethylpenicillin by mouth for 10 days; benzylpenicillin may be given by injection initially. A single intramuscular injection of benzathine benzylpenicillin is perhaps the treatment of choice, especially if compliance with a 10-day course of oral penicillin is unlikely, and is advocated by WHO and the American Heart Association for the primary prevention of rheumatic fever (see under Rheumatic Fever, p.189), but the injection may not be available in some countries. Ampicillin should probably be avoided because of the risk of maculopapular rash if the patient proves to have infectious mononucleosis.[9] Erythromycin or another macrolide may be given to penicillin-allergic patients, except where there is evidence of significant resistance, as in some parts of Europe,[6] the USA,[10] Japan,[11] and Finland;[12] it may also be a better choice than penicillin if there is a likelihood of infection with *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*) (see below). Oral cephalosporins are another alternative, and a meta-analysis[13] has shown that the likelihood of treatment failure with oral cephalosporins may be approximately half that with penicillin.

Despite the general effectiveness of penicillin a trend of increasing numbers of relapses and recurrent infections has been noted.[14] Some treatment failures have been attributed to poor patient compliance with a 10-day course of penicillin and attempts to overcome this have included giving fewer daily doses or shortening the length of treatment. Meta-analysis of studies supports the use of twice-daily dosing of phenoxymethylpenicillin which appears to be as effective as doses three or four times daily,[15] but a single daily dose is less effective. Courses of phenoxymethylpenicillin shorter than 10 days have not proved effective.[16,17] There is some evidence that shorter courses may be possible with some alternative antibacterials. Studies have shown that courses of 5 days or less of erythromycin,[18] cefotiam hexetil,[19] azithromycin,[20,21] clarithromycin,[22] or cefuroxime axetil[23,24] may be as effective as a 10-day course of phenoxymethylpenicillin. However, definitive studies have not been done, and the broader spectrum and higher cost of these regimens are drawbacks.[6,7]

Penicillin resistance in *Str. pyogenes* remains rare. In addition to poor compliance, treatment failures with penicillin, leading to recurrent infection, might be explained by the presence of beta-lactamase-producing oropharyngeal bacteria that are able to protect *Str. pyogenes* against penicillin,[25] although this theory was not supported by a study in 462 children.[26] Antibacterials less susceptible to beta lactamase have been effective, sometimes more so than phenoxymethylpenicillin. They include the oral cephalosporins cefaclor,[27] cefuroxime axetil,[28] cefixime,[29] cefprozil,[30] and cefadroxil[31] and the combined preparation amoxicillin with clavulanic acid[32,33] (like ampicillin, amoxicillin should perhaps be avoided because of the risk of maculopapular rash if the patient proves to have infectious mononucleosis). Clindamycin has eradicated *Str. pyogenes* and beta-lactamase-producing bacteria in children of 12 years and under with recurrent tonsillitis, but might be less effective in older patients.[34] It was also effective where penicillin and erythromycin had failed in an outbreak of streptococcal pharyngitis.[35]

Pharyngeal carriage of *Str. pyogenes* is common, especially in primary-school children and thus its presence does not necessarily reflect acute infection. Eradication may be beneficial in selected cases and has been achieved by a single intramuscular injection of benzathine benzylpenicillin together with a 4-day course of oral rifampicin;[36] a 10-day course of oral clindamycin has also been effective.[37] In order to ensure that outbreaks of *Str. pyogenes* are prevented in closely confined populations, some have recommended prophylactic antibacterials for *all* members of these populations, without exception.[38]

Other bacterial causes of pharyngitis include *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*), *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Corynebacterium diphtheriae* (see under Diphtheria, p.168), *Neisseria gonorrhoeae* (see under Gonorrhoea, p.191), group C beta-haemolytic streptococci, and anaerobic bacteria.

A. haemolyticum is thought to be an important cause of pharyngitis in adolescents and young adults; there is often an accompanying scarlatiniform rash. It has been reported to respond to a single injection of benzathine benzylpenicillin or a 10-day course of oral erythromycin, but not to phenoxymethylpenicillin.[7]

Pharyngitis is often associated with *Chlamydophila pneumoniae* infection and tetracycline or erythromycin are effective antibacterials.[39]

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Pinta

See under Syphilis, p.192.

Plague

Plague[1] is caused by the Gram-negative bacillus *Yersinia pestis* (*Yersinia pseudotuberculosis* subsp. *pestis*) and is usually transmitted to man via rodents and their infected fleas. It has occurred as worldwide pandemics, for example, the Black Death in Europe in the Middle Ages. In the 1980s the largest numbers of cases reported were in Tanzania, Vietnam, Brazil, Peru and more recently in Madagascar. Plague may take several forms of which bubonic plague is the most common; others include pneumonic, septicaemic, and meningitic plague. Streptomycin, tetracycline, and chloramphenicol have traditionally been used in the treatment of plague[2] with streptomycin being the treatment of choice, although the possibility of a Jarisch-Herxheimer reaction resulting from the bactericidal effect of streptomycin must be borne in mind; it is also contra-indicated in pregnancy. Success has also been reported with aminoglycosides such as gentamicin and kanamycin. Although there is no clinical experience with fluoroquinolones, *in-vitro* susceptibilities and *animal* studies suggest that they would be effective.[2]

In the UK, the recommended treatment for adults is gentamicin (first choice in pregnancy); ciprofloxacin or doxycycline may be used if aminoglycosides are unsuitable and may also be used for first-line therapy in children, but doxycycline is only suitable for children over 8 years of age. If plague meningitis is suspected chloramphenicol should be used as it crosses the blood-brain barrier.[2] Similar information is provided by WHO,[3] with sulfonamides being mentioned as alternatives. In UK guidelines[2] ciprofloxacin is considered to be the drug of choice for prophylaxis in adults and children considered to be at risk after close contact with cases of pneumonic disease or after a deliberate release of *Y. pestis*; doxycycline may be used as an alternative in those over 12 years of age. Other suggested antibacterials include chloramphenicol and co-trimoxazole.

Commenting on the plague epidemic that occurred in India in 1994, workers from the US CDC[4] also noted that streptomycin continues to be the drug of choice for treating plague, that tetracycline and gentamicin are alternatives, and that chloramphenicol is preferred for plague meningitis. They considered that prophylaxis should be given to those who have had face-to-face contact or who have occupied a closed space with someone who has pneumonic plague. For prophylaxis, tetracycline can be given to adults and older children or sulfonamides to children of 8 years or less; chloramphenicol is also effective.[4]

Infection with a strain of *Y. pestis* resistant to all the drugs usually effective against plague identified in a patient from Madagascar[5] responded to treatment with co-trimoxazole and streptomycin.

A vaccine is available for active immunisation.

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Pneumonia

Pneumonia[1] is a respiratory disease characterised by inflammation of the lung parenchyma with congestion. It is mostly due to bacterial or viral infection, but may be caused by fungi in immunocompromised patients or by the aspiration of chemical irritants. Pneumonia is a common illness occurring in all age groups and throughout the world; it is a major cause of death among the elderly and those who are chronically and/or terminally ill. Symptoms and signs of pneumonia include chills, cough, dyspnoea, fever, headache, myalgia, pleuritic chest pain, and sputum production. Treatment of pneumonia relies on prompt use of antibacterials and identification of the infecting organisms and their sensitivity to antibacterials. Cases of pneumonia are usually classified as community-acquired or hospital-acquired (nosocomial) pneumonia. Cases of community-acquired pneumonia can also be further sub-divided into those who can be treated in an ambulatory (outpatient) setting and those that need hospitalisation. Patients who need hospitalisation are generally infected with unusual pathogens and/or have more severe disease. Pneumonia occurring in long-term-care facilities can be treated as either community-acquired or hospital-acquired pneumonia. Cases of hospital-acquired pneumonia are divided according to whether ventilator assistance is needed. These categories also provide a rough guide as to the likely pathogen and severity of the disease.

Other types of pneumonia include aspiration pneumonia and the various forms of interstitial pneumonia or pneumonitis (see also Aspiration Syndromes, p.1693, and Diffuse Parenchymal Lung Disease, p.1502). Interstitial pneumonitis is a common complication in cancer patients and has also been associated with certain drugs, for example amiodarone, bleomycin, and nitrofurantoin.

Community-acquired pneumonia. In community-acquired pneumonia[2-7] the commonest pathogen in previously healthy subjects is *Streptococcus pneumoniae* (pneumococcus). Other common pathogens include *Haemophilus influenzae* and atypical pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* (see Legionnaires' Disease, p.176).[2,4] Less common causes include *Staphylococcus aureus*, which usually occurs as a secondary bacterial infection after influenza and is associated with high mortality; *Moraxella catarrhalis* (*Branhamella catarrhalis*) occurs especially in patients with chronic lung disease; Gram-negative enteric bacilli; *Pseudomonas aeruginosa*; *Chlamydophila psittaci* (*Chlamydia psittaci*) (see Psittacosis, p.188); and *Coxiella burnetii* (see Q Fever, p.188). Gram-negative bacilli rarely cause pneumonia in the community, especially in previously healthy patients, although the frequency of such infections is increasing.[8] Anaerobic bacteria are associated with aspiration pneumonia. Viruses are the commonest pathogens in young children.

Pneumococcal pneumonia usually develops over a number of days and in elderly patients onset may be insidious. *Str. pneumoniae* has usually been considered to be sensitive to penicillins (benzylpenicillin, amoxicillin, or ampicillin), cephalosporins, erythromycin, or co-trimoxazole, but there is increasing prevalence of global resistance although there are marked geographical differences.[9,10] A survey[10] which, during 1999 to 2000, collected data from 69 centres in 25 countries found 22.1% resistance overall to benzylpenicillin (but 71.5% in South Korea, 46.2% in France, 42.1% in Spain, 32.6% in the USA, 15.3% in Latin America, 5.5% in the UK, 4.4% in Australia, and 0% in the Netherlands); resistance overall to erythromycin was 31.0% (87.6% in South Korea, 57.6% in France, 28.6% in Spain, 30.9% in the USA, 15.3% in Latin America, 13.2% in the UK, 12.3% in Australia, and 7.8% in the Netherlands). Macrolide resistance as high as 35% has been reported in some areas of the USA and Europe; 96% resistance has been reported in Taiwan. Fluoroquinolone resistance was low overall (1%) although 14.3% of isolates were resistant in Hong Kong.[9,10] However, in clinical practice pneumococcal pneumonia frequently responds to high doses of penicillins or cephalosporins and the routine use of penicillin for community-acquired pneumonia may still be reasonable in many countries.

The treatment of community-acquired pneumonia is complicated by the increasing spectrum of causative organisms and prevalence of antibacterial resistance. Furthermore, since the causative pathogen is often unknown, initial antibacterial therapy is usually empirical. Guidelines for the treatment of pneumonia have been issued by bodies in many countries.[8,11-18] Although common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice. These guidelines generally give advice for differences associated with age, the severity of the infection and the presence or absence of underlying or co-existent disorders.

In the UK, guidelines for the management of community-acquired pneumonia have been produced by the British Thoracic Society (BTS).[8] For initial ***empirical treatment in the community*** amoxicillin is usually preferred. Erythromycin is an alternative in penicillin-allergic patients and should also be given during epidemics of mycoplasmal pneumonia and when *Legionella* is suspected; clarithromycin may be given if there is gastrointestinal intolerance to erythromycin.

In those patients ***hospitalised with non-severe community-acquired pneumonia*** there is an increased likelihood of infection with atypical pathogens, or with *Legionella* spp.; consequently, combined empirical treatment orally with amoxicillin plus either erythromycin or clarithromycin is preferred.[8] When oral therapy is inappropriate, intravenous ampicillin or benzylpenicillin is given, together with intravenous erythromycin or, preferably, clarithromycin. For those intolerant of beta-lactams and macrolides or when there are local concerns over *Clostridium difficile*-associated diarrhoea, a fluoroquinolone with enhanced activity against pneumococci may be given as an alternative (levofloxacin orally or intravenously or moxifloxacin orally).[8] In practice, however, many patients with non-severe community-acquired pneumonia are admitted to hospital for non-clinical reasons such as old age, family preference, inadequate home care, or adverse social circumstances, and in these patients it is considered appropriate to treat with monotherapy as for patients treated in the community (see above).[8]

Patients ***hospitalised with severe community-acquired pneumonia*** should receive parenteral empirical treatment regardless of their ability to take oral medication. Since community-acquired pneumonia caused by *Legionella* spp. is more likely to result in severe disease, the initial empirical regimen should include appropriate therapy. Current recommendations[8] are for combined intravenous treatment with a broad-spectrum beta-lactamase-stable antibacterial such as amoxicillin with clavulanic acid or a second- or third-generation cephalosporin such as cefuroxime, cefotaxime, or ceftriaxone, together with a macrolide (clarithromycin or erythromycin). For life-threatening infection where *Legionella* is suspected, the further addition of rifampicin is recommended;[8] although rifampicin may result in reduced serum concentrations of macrolides, this is not known to be of clinical significance when treating community-acquired pneumonia. As in non-severe infection, in patients who are intolerant of beta-lactams and macrolides or when there are local concerns over *C. difficile*-associated diarrhoea, levofloxacin may be given as an alternative, but with the addition of benzylpenicillin for severe infection.[8]

The following treatments are recommended in the UK,[8] in conjunction with local microbiological advice, for the minority of patients with community-acquired pneumonia in whom the ***causative organism*** has been identified, usually in hospital:

- *Str. pneumoniae*: preferred treatment, oral amoxicillin or intravenous benzylpenicillin; alternatives, oral erythromycin or clarithromycin, or intravenous cefuroxime, cefotaxime, or ceftriaxone
- *M. pneumoniae* or *C. pneumoniae*: preferred treatment, oral or intravenous erythromycin or clarithromycin; alternatives, oral tetracycline or oral or intravenous fluoroquinolone
- *C. psittaci* or *C. burnetii*: preferred treatment, oral or intravenous tetracycline; alternatives, oral or intravenous erythromycin or clarithromycin
- *Legionella* spp.: preferred treatment, oral or intravenous clarithromycin with or without oral or intravenous rifampicin; alternative, oral or intravenous fluoroquinolone
- *H. influenzae* (non-beta-lactamase-producing): preferred treatment, oral amoxicillin or intravenous ampicillin; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or oral or intravenous fluoroquinolone
- *H. influenzae* (beta-lactamase-producing): preferred treatment, oral or intravenous amoxicillin with clavulanic acid; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or oral or intravenous fluoroquinolone
- Gram-negative enteric bacilli: preferred treatment, intravenous cefuroxime, cefotaxime, or ceftriaxone; alternatives, intravenous fluoroquinolone, imipenem, or meropenem
- *Ps. aeruginosa*: preferred treatment, intravenous ceftazidime plus either gentamicin or tobramycin; alternatives, intravenous ciprofloxacin or piperacillin plus either gentamicin or tobramycin
- *Staph. aureus* (non-meticillin-resistant): preferred treatment, intravenous flucloxacillin with or without oral or intravenous rifampicin; alternative, intravenous teicoplanin with or without oral or intravenous rifampicin
- *Staph. aureus* (meticillin-resistant): preferred treatment, intravenous vancomycin; alternative, intravenous teicoplanin with or without oral or intravenous rifampicin

In the USA, guidelines for the management of community-acquired pneumonia in adults have been jointly produced by the Infectious Diseases Society of America (IDSA) and by the American Thoracic Society (ATS).[12] For previously healthy ***outpatients*** with no risk factors for drug-resistant *Str. pneumoniae* (DRSP) infection they recommend a macrolide (such as erythromycin, azithromycin, or clarithromycin); doxycycline may be given as an alternative. In those with co-existing cardiopulmonary disease and/or other complicating factors (such as renal disease, diabetes mellitus, alcoholism, malignancies, or asplenia), taking immunosuppressive drugs, those who have received antibacterial therapy within the previous 3 months, or those with other risks for DRSP infection a 'respiratory fluoroquinolone' (gemifloxacin, levofloxacin, or moxifloxacin) is recommended. Alternatively a beta-lactam (high dose amoxicillin with or without clavulanic acid, or ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide (or doxycycline) may be given.

In ***hospitalised*** patients who are not in intensive care the preferred treatment is a beta-lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem) plus a macrolide (or doxycycline). In penicillin-allergic patients a respiratory fluoroquinolone is recommended. In hospitalised patients who are in intensive care the preferred treatment is a beta-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. In penicillin-allergic patients a respiratory fluoroquinolone and aztreonam are recommended. For *Pseudomonas* infection, an antipneumococcal, antipseudomonal beta-lactam (such as piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin are recommended. Alternative regimens include an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin, or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone. In penicillin-allergic patients aztreonam should be used in place of the beta-lactam. For community-acquired meticillin-resistant *Staph. aureus* infection, vancomycin or linezolid should be added.

In **children** pneumonia is caused by a wider spectrum of organisms than in adults. Viruses, especially respiratory syncytial virus, are very common pathogens in infants and children up to 4 years of age and, as in adults, pneumococci are very common bacterial pathogens. Guidelines for the management of community-acquired pneumonia in children have been produced by the BTS.[11] Amoxicillin is considered the antibacterial of first choice for empirical oral therapy in children under 5 years of age because it is effective against the majority of causative organisms. Alternatives are amoxicillin with clavulanic acid, cefaclor, erythromycin, clarithromycin, or azithromycin. Macrolides should be given as first-line empirical therapy in children over 5 years since *M. pneumoniae* pneumonia is more prevalent in older children. Macrolides should also be used in children of any age if either *M. pneumoniae* or *C. pneumoniae* are suspected. Amoxicillin should be used as first-line treatment at any age if *Str. pneumoniae* is thought to be the likely pathogen. If *Staph. aureus* is suspected then a macrolide or a combination of flucloxacillin with amoxicillin is appropriate. Intravenous therapy should be given in severe infection or when the child is unable to absorb oral antibacterials, for example due to vomiting; appropriate intravenous drugs for severe pneumonia include amoxicillin with clavulanic acid, cefuroxime, or cefotaxime. If the causative organism is known to be *Str. pneumoniae* a penicillin may be used alone. *Chlamydia trachomatis* is another common cause in infants up to 3 months of age for which erythromycin may be used or, alternatively, sulfafurazole.

Pneumonia in neonates is usually due to organisms acquired from the mother's genital tract, especially group B streptococci, *Escherichia coli*, and *Klebsiella pneumoniae*; initial treatment with gentamicin and benzylpenicillin or ampicillin has been suggested. For prophylaxis against group B streptococci in neonates, see under Perinatal Streptococcal Infections, p.184.

Similar guidelines for the empirical management of community-acquired pneumonia in children have been developed in South Africa.[15] Additional recommendations have been made to take into account the high prevalence of HIV infection. The drug of choice is amoxicillin; although standard doses of amoxicillin will treat most cases of pneumococcal pneumonia the use of high-dose amoxicillin (30 mg/kg given 3 times daily) is recommended in order to overcome and limit the emergence of resistant pneumococci, and to successfully treat those few children with high-level pneumococcal resistance the following additional factors should be considered:

- children younger than 2 months have more Gram-negative infections and therefore need an intravenous aminoglycoside or an intravenous cephalosporin, while children older than 5 years have more infections caused by *M. pneumoniae* and *C. pneumoniae* and need a macrolide (erythromycin, clarithromycin, or azithromycin)
- HIV-infected children requiring hospitalisation and those with a high risk of being HIV-infected or who have symptomatic HIV disease or who are severely malnourished should be given an aminoglycoside plus their empirical antibacterial regimen; alternatively they may be given a regimen that provides effective treatment against Gram-negative bacteria
- if pneumocystis pneumonia is suspected, co-trimoxazole should be added. All hospitalised HIV-exposed children less than 6 months of age should be treated empirically with co-trimoxazole, unless HIV infection status is negative and the child is not being breast-fed. Empirical treatment with co-trimoxazole plus amoxicillin and an aminoglycoside should also be given to older HIV-infected children with features of AIDS who are not on co-trimoxazole prophylaxis
- when *Staph. aureus*, is suspected, cloxacillin is the drug of choice. In HIV-infected children, about 60% of community-acquired *Staph. aureus* may be resistant to cloxacillin and vancomycin should be given

Hospital-acquired pneumonia. Most reports on hospital-acquired or nosocomial pneumonia have been from the USA. The organisms most commonly responsible for hospital-acquired pneumonia are Gram-negative enteric bacilli, *Staph. aureus*, *Str. pneumoniae*, Enterobacteriaceae, and *H. influenzae*; others that may need to be considered, particularly in the presence of specific risk factors, are *Legionella* spp., *Ps. aeruginosa*, anaerobes and, in severe infection, *Acinetobacter* spp. Hospital-acquired pneumonia occurring 48 hours after mechanical ventilation is termed ventilator-associated pneumonia; cases usually result from aspiration of pathogenic material that commonly colonises the oropharynx. The organisms often responsible for early onset ventilator-associated pneumonia are *Staph. aureus*, *Str. pneumoniae*, and *H. influenzae* while late-onset ventilator-associated pneumonia is often caused by resistant nosocomial pathogens such as *Ps. aeruginosa*, meticillin resistant *Staph. aureus*, *Klebsiella* spp., and *Acinetobacter baumannii*.[19]

Broad spectrum antibacterial therapy is essential for hospital-acquired pneumonia and most initial therapy is empirical. As in the treatment of community-acquired pneumonia selection of antibacterials must be localised. For initial empirical treatment of early-onset hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, and any disease severity, ATS recommends[20] the following drugs: ceftriaxone; levofloxacin, moxifloxacin, or ciprofloxacin; ampicillin/sulbactam; or ertapenem. Where there is late-onset infection or risk factors for multidrug resistance the following are recommended: an antipseudomonal cephalosporin (cefepime or ceftazidime) or an antipseudomonal carbapenem (imipenem or meropenem) or piperacillin-tazobactam together with an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin); if MRSA is likely then linezolid or vancomycin should also be used. Intravenous therapy should be given to all patients initially, and changed to the oral or enteral route as soon as possible. Efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to as little as 7 days provided *Ps. aeruginosa* is absent and that the patient shows a good clinical response.

Nosocomial pneumonia is especially likely in immunocompromised or neutropenic patients. Prophylactic measures in ventilated patients are those mentioned under Intensive Care, p.175.

Immunocompromised patients. Immunosuppressed patients are at increased risk of pneumonia. In addition to the bacteria mentioned above they are susceptible to opportunistic infections with *Mycobacterium tuberculosis* (see under Tuberculosis, p.196); viruses such as *Cytomegalovirus* and fungi, in particular *Pneumocystis jirovecii* (see p.521), are also causes of pneumonia in these patients.

Aspiration pneumonia. Aspiration of organisms present in the upper respiratory tract into the lungs, often as a result of loss of consciousness or difficulty in swallowing, can cause aspiration pneumonia.[21] When community acquired the organisms responsible are predominantly anaerobes, but in hospital-acquired aspiration pneumonia Gram-negative bacilli and *Staph. aureus* are also found. Confusion has arisen over the term 'aspiration pneumonia' because it has also been applied more generally to aspiration, for example, of gastric acid (Mendelson's syndrome), resulting in chemical pneumonitis and not associated with bacterial infection. *Lung abscess* generally characterises late-stage aspiration pneumonia involving anaerobic bacteria. The aetiology is rarely established, but specific anaerobic bacteria involved include *Peptostreptococcus*, *Prevotella melaninogenica* (*Bacteroides melaninogenicus*), and *Fusobacterium nucleatum*. Nearly all patients with anaerobic pulmonary infections are treated empirically. Some[21] have expressed the view that penicillin and clindamycin are inadequate and that antibacterials with activity against Gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones, and piperacillin are usually required even in community-acquired aspiration pneumonia. Most patients with lung abscess receive parenteral therapy until they become afebrile and show clinical improvement; oral therapy may then continue for weeks or months if necessary.

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Pregnancy and the neonate

For infections associated specifically with pregnancy, see under Endometritis (p.170), Perinatal Streptococcal Infections (p.184), and Premature Labour (below).

Premature labour

Preterm birth, with or without rupture of membranes, causes significant perinatal morbidity and mortality. There is evidence that infection appears to have an important role in the cause or as a consequence of ruptured membranes[1,2] and as many as 50% of spontaneous preterm births are due to infection, with *Mycoplasma* spp. being the most commonly isolated organisms from the amniotic cavity.[3] Other bacteria that have been implicated include group B streptococci, *Chlamydia trachomatis*, and those associated with bacterial vaginosis. The role of antibacterial treatment has been evaluated. However, it is possible that maternal antibacterial treatment may suppress the stimulation of labour without effectively treating fetal infection[2] and concerns have been expressed that delaying delivery in the presence of a subclinical infection may not produce the best outcome for the neonate.[4]

A meta-analysis[5] and a systematic review[1] of studies of the routine use of antibacterials as adjuncts in the management of premature labour in women with *intact membranes* have failed to demonstrate an overall improvement in neonatal morbidity; indeed, an increase in neonatal mortality was actually noted.[5]

In women with preterm premature *rupture of membranes*, meta-analyses[6,7] and a systematic review[2] have shown that antibacterials could delay delivery, and reduce both maternal morbidity (chorioamnionitis and postpartum infections) and some aspects of neonatal morbidity (sepsis, pneumonia, and intraventricular haemorrhage). No effects on neonatal mortality or gestational age-related morbidity were noted.[2,7] An increased incidence of neonatal necrotising enterocolitis has been found after maternal use of amoxicillin with clavulanic acid and it is considered best avoided in women at risk of premature delivery; erythromycin may be the antibacterial of choice.[2] A systematic review and meta-analysis[3] evaluated the effect of antibacterials on the rate of preterm births when given in the second trimester of pregnancy to women at risk of preterm births. Giving macrolides or clindamycin was associated with a lower rate of preterm delivery, whereas giving metronidazole alone in the second trimester was associated with a greater risk of preterm delivery in a high-risk population.

Clinical infections of the genito-urinary tract during pregnancy are a cause of significant morbidity in the neonate and antimicrobial treatment is necessary (see Bacterial Vaginosis, p.164, Chlamydial Infections, p.166, and Perinatal Streptococcal Infections, p.184).

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Proctitis

Proctitis is inflammation of the rectum that may be caused by sexually transmitted pathogens, most commonly *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, or herpes simplex virus.

For empirical **treatment** of sexually transmitted proctitis the CDC[1] in the USA recommends a single intramuscular dose of ceftriaxone 125 mg, plus oral doxycycline 100 mg twice daily for 7 days.

The specific treatment of rectal infections caused by *C. trachomatis* and *N. gonorrhoeae* is discussed under Chlamydial Infections (p.166) and Gonorrhoea (p.191) respectively. Patients with herpes proctitis should be treated in the same way as those with genital herpes (p.854).

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Prostatitis

See under Urinary-tract Infections, p.199.

Psittacosis

The causative organism of psittacosis (ornithosis) is *Chlamydophila psittaci* (*Chlamydia psittaci*). It is usually transmitted to humans by direct or indirect contact with infected birds and the primary site of infection is the lung.[1] The clinical presentation of psittacosis can vary widely from a mild 'flu-like' illness to a fulminating toxic state with multiple organ involvement.[1] Most patients will have a cough, although this is not always prominent. Tetracyclines are the treatment of choice[1,2] and early therapy may be life-saving; a 21-day course has been recommended since relapses have occurred after shorter periods.[1] An alternative is chloramphenicol.[2] Erythromycin or a similar macrolide have also been used successfully.[3,4]

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Q fever

Q fever[1,2] (or query fever) is a rickettsial infection (p.190) caused by *Coxiella burnetii*. It is a zoonosis occurring worldwide and is transmitted to humans from domestic animals such as cattle and sheep, mainly by inhalation of infected dust. Q fever is asymptomatic in about 50 to 60% of infected persons. Symptomatic acute infection generally presents as a febrile flu-like illness and many patients may also have hepatitis or pneumonia that can progress to acute respiratory distress syndrome. Endocarditis is the most frequent form of chronic infection and the most serious form of Q fever; infection may be difficult to eradicate and prolonged treatment is generally needed. There is also evidence of long-term sequelae including lethargy and fatigue in patients who have not had cardiac involvement.

Subclinical **acute infections** should be treated if recognised and if possible treatment should be started within 3 days of the onset of symptoms. A tetracycline such as doxycycline for 14 days is the treatment of choice for acute Q fever. The role of macrolides in acute infection is unclear and clinical data on the use of fluoroquinolones are limited.[1,2] Co-trimoxazole is recommended for children younger than 8 years of age.[1] **Q fever endocarditis** is more difficult to treat and surgery may be required in addition to antibacterial treatment.[2] Monotherapy with tetracycline decreases symptoms but fails to eradicate *C. burnetii* and combination antibacterial therapy has been evaluated. Long-term treatment with doxycycline plus rifampicin or with ciprofloxacin alone[3] has been successful in individual patients with endocarditis, whereas pefloxacin alone[4] was not. A retrospective comparison of doxycycline alone or with rifampicin, fluoroquinolones (ofloxacin or pefloxacin), or co-trimoxazole, recommended treatment for at least 3 years with doxycycline plus a fluoroquinolone;[5] doxycycline plus rifampicin also appeared effective, but in most cases rifampicin had been stopped after a few months because of interactions with anticoagulants often prescribed at the same time. Patients given doxycycline plus hydroxychloroquine needed a shorter treatment course and had fewer relapses than those treated with doxycycline plus ofloxacin; mortality rate for both groups was 5%.[6] Successful treatment with doxycycline and chloroquine for 2 years has been reported in a patient with a biological prosthetic aortic valve and aortic homograft.[7] The combination of doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily, both given orally for at least 18 months, is considered to be the treatment of choice for Q fever endocarditis.[1,2] An alternative regimen for patients unable to tolerate hydroxychloroquine is doxycycline plus a fluoroquinolone for at least 3 to 4 years.[2]

Q fever during **pregnancy** may result in obstetric complications, such as spontaneous abortion, intra-uterine growth retardation, intra-uterine fetal death, and premature delivery.[8] Treatment with co-trimoxazole for at least 5 weeks during pregnancy was reported to protect against maternal chronic Q fever, placental infection, and obstetric complications (in particular intra-uterine fetal death).[8]

A vaccine is available in some countries for **prophylaxis** in occupational groups who regularly handle potentially infected animal tissues.

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4. Cacoub P, *et al.* Q-fever endocarditis and treatment with the fluoroquinolones. *Arch Intern Med* 1991; **151:** 816, 818.
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Relapsing fever

Relapsing fever is caused by spirochaetes of the *Borrelia* genus that are transmitted to humans by body lice or *Ornithodoros* ticks. *B. recurrentis* causes louse-borne relapsing fever and can occur widely, but is endemic especially in Ethiopia. Many species of *Borrelia* may cause tick-borne relapsing fever.

The treatment of choice for infection due to *B. recurrentis* is a tetracycline; benzylpenicillin or erythromycin are alternatives.[1] Therapy with single oral doses of tetracycline,[2,3] erythromycin,[2,3] or chloramphenicol[3] has been effective. Antibacterial treatment often causes a Jarisch-Herxheimer reaction characterised by rigor, fever and hypotension, which may be fatal.[2,4] Attempts to prevent this reaction include use of paracetamol and corticosteroids;[2,4] antibodies against tumour necrosis factor α have shown promise.[5]

Tick-borne relapsing fever is milder than the louse-borne variety, but has been treated similarly.

1. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy.* 18th ed. New Rochelle NY: The Medical Letter, 2008: 75.
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Respiratory-tract infections

Principal community-acquired bacterial pathogens in the respiratory tract are *Streptococcus pneumoniae* and *Haemophilus influenzae*, although *Moraxella catarrhalis* (*Branhamella catarrhalis*)[1] is increasingly important in some areas. Other respiratory pathogens include *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Legionella pneumophila*, and *Mycoplasma pneumoniae*. *Streptococcus pyogenes* is the predominant cause of pharyngitis. *Staphylococcus aureus* and aerobic Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Klebsiella* spp. may be responsible for hospital-acquired (nosocomial) infections.

Community-acquired lower respiratory-tract infections are very common and are traditionally considered to be viral in origin, but bacterial pathogens similar to those causing pneumonia are commonly isolated from patients with these milder respiratory infections;[2] even so, about one-quarter of patients fail to respond satisfactorily to empirical antibacterial treatment. For previously healthy adults with non-specific upper respiratory-tract infection, US guidelines[3] recommend that antibacterials are not given.

Broad-spectrum antibacterials such as a penicillin or erythromycin may be necessary in some cases of uncomplicated upper or lower respiratory-tract infection. First line empirical treatment with a fluoroquinolone has been avoided in the past because of poor activity against streptococci,[4,5] although some newer fluoroquinolones have much greater activity against streptococci.[6]

In respiratory-tract infections complicating chronic obstructive pulmonary disease, amoxicillin has been recommended for first-line treatment.[7] If a further course is necessary, drugs with activity against penicillin-resistant *H. influenzae* and *M. catarrhalis* should probably be given, such as amoxicillin with clavulanic acid, a fluoroquinolone (bearing in mind that some are not very active against *Str. pneumoniae*), or a second-generation cephalosporin. Ofloxacin has been reported to be beneficial in patients with chronic obstructive pulmonary disease who require mechanical ventilation.[8]

For details on infections of the upper respiratory tract, see under Epiglottitis (p.170), Pharyngitis (p.185), and Sinusitis (p.193); see also Otitis Media (p.182). For infections of the lower respiratory tract, see under Bronchitis (p.165), Cystic Fibrosis (p.166), and Pneumonia (p.186); those with a specific cause include Legionnaires' Disease (p.176), Nocardiosis (p.181), Pertussis (p.185), and Tuberculosis (p.196).

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Rheumatic fever

Acute rheumatic fever occurs especially in children aged 6 to 15 years as a consequence of upper respiratory-tract infections, such as pharyngitis or tonsillitis, with rheumatogenic strains of the group A beta-haemolytic streptococcus, *Streptococcus pyogenes*. The pathogenesis of rheumatic fever is not known, but an immune mechanism may be involved. There may be a latent period of 1 to 5 weeks after the initial infection, before clinical manifestations of rheumatic fever appear. The major ones are arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Those affecting the heart are the most serious and are a major cause of cardiovascular death in children and young adults in developing countries. Rheumatic fever has been associated with poverty and overcrowding and has declined dramatically in developed countries, but is still a major problem in the developing world. However, in the 1980s there was evidence of a resurgence in the USA with outbreaks of rheumatic fever reported in middle-class children[1] and military recruits.[2] Increased pathogenicity of *Str. pyogenes* serotypes might have contributed to this resurgence.[3] A high incidence is also seen among indigenous populations in Australia and New Zealand.[4]

Guidelines for the management and prevention of rheumatic fever have been published by sources including the American Heart Association (AHA),[5] WHO,[6] and an expert group from Australia and New Zealand.[7] Rheumatic fever can usually be prevented by *primary prophylaxis*, that is, by the prompt treatment of streptococcal upper respiratory-tract infection with eradication of group A streptococci from the throat. Penicillin is the drug of choice, either as a single intramuscular injection of benzathine benzylpenicillin or as a course of phenoxymethylpenicillin by mouth for 10 days. An injection containing benzathine benzylpenicillin and procaine benzylpenicillin has been used in children.[5] Erythromycin may be given to patients allergic to penicillin. Other macrolides or oral cephalosporins may also be used. For further details on the treatment of streptococcal sore throat, see under Pharyngitis, p.185. Treatment failure is more common after oral antibacterials and in the USA most of these patients are streptococcal carriers.[5] Treatment of chronic carriers is not usually necessary, but eradication of pharyngeal carriage has been achieved by an injection of benzathine benzylpenicillin plus rifampicin by mouth for 4 days;[8] a 10-day course of oral clindamycin has also been effective.[9] Broad-based primary prophylaxis in communities rather than individuals is controversial and requires careful planning, but, for example, penicillin prophylaxis did control an epidemic of acute tonsillitis associated with *Str. pyogenes* in a junior detention centre.[10] However, a study in military recruits demonstrated that *Str. pyogenes* infection could not be prevented in closely confined communities unless all individuals in the population received prophylaxis.[11]

If acute rheumatic fever occurs, a full therapeutic course of penicillin should be given initially, as for primary prevention, to eradicate group A streptococci.[5] Treatment then comprises bed rest and anti-inflammatory drugs, usually corticosteroids or salicylates, in an attempt to prevent valvular scarring. However, it is unclear whether anti-inflammatory treatment has any influence on such long-term sequelae.[12] Carbamazepine or valproate may be given for severe and distressing chorea.[7] *Secondary prevention* is then continued with prolonged antibacterial prophylaxis because of the high risk of recurrent attacks of rheumatic fever after subsequent streptococcal upper respiratory-tract infections. Again, penicillin is the preferred antibacterial, the usual recommendation being an intramuscular injection of benzathine benzylpenicillin every 4 weeks, although injections every 3 weeks may be warranted where the risk of recurrence is high.[5-7] This advice has been influenced by reports of high recurrence rates with the monthly regimen in such situations.[13] A 12-year study in Taiwan[14] confirmed that prophylaxis with benzathine benzylpenicillin injections every 3 weeks is more effective than injections every 4 weeks and it was recommended that the 3-week regimen should be used in adults and children with a recent episode of rheumatic fever, especially in developing countries where exposure to streptococci is still intense. In addition, pharmacokinetic studies have indicated relatively low serum concentrations of penicillin in the fourth week after an intramuscular injection of benzathine benzylpenicillin,[15,16] despite the successful use of monthly injections in most patients. However, Australian and New Zealand guidelines consider the 4-week regimen suitable in most patients.[7] Alternatively, oral prophylaxis with phenoxymethylpenicillin or sulfadiazine may be given, although, over the long time scale involved, compliance is likely to be a problem;[4,6,7] erythromycin is suggested for the rare patient who is allergic to penicillin and sulfonamides. Sulfonamides should *not* be used for primary prevention because they do not eradicate the streptococci. The duration of secondary prophylaxis depends on the individual patient, but in those who have not had rheumatic carditis it should generally continue for a minimum of 5 years after the last attack of rheumatic fever,[5,6] and at least until the age of 18 or early 20s. A study from Chile supported this view.[17] Those who have had rheumatic carditis but without residual valvular disease should perhaps receive prophylaxis for 10 years[5] or at least until the age of 25 years.[6] For those with carditis and persistent valvular disease, prophylaxis should continue at least until the age of 40 years, or sometimes for life.[5,6] Fears of serious allergic reactions associated with long-term benzathine benzylpenicillin prophylaxis appear to be unfounded.[18]

Household contacts of rheumatic fever patients who themselves have positive streptococcal cultures should be treated.[5]

Patients with rheumatic valvular heart disease as a result of rheumatic fever are at risk of developing infective endocarditis and may need additional appropriate short-term antibacterial prophylaxis when undergoing dental and some surgical procedures (see Endocarditis, p.168).

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Rickettsial infections

Bacteria of the Rickettsiaceae family that infect man include *Rickettsia* spp. (see under Spotted Fevers, p.194 and Typhus, p.198) and *Coxiella burnetii* (see under Q fever, p.188). *Ehrlichia* spp. (see under Ehrlichiosis, p.168) and *Bartonella quintana* (*Rochalimaea quintana*) (see under Trench Fever, p.196) are no longer classified as a rickettsia. The treatment of choice for rickettsial infections is usually doxycycline; chloramphenicol or a fluoroquinolone are alternatives.[1]

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Salmonella enteritis

See p.173.

Salpingitis

See under Pelvic Inflammatory Disease, p.184.

Septicaemia

Traditionally, transient bacteraemia (the presence of bacteria in the blood) has been regarded as a fairly common condition which does not usually cause complications, whereas uncontrolled bacteraemia leads to septicaemia with serious symptoms such as fever and shock. This distinction has not always been adhered to in published sources and the terms have sometimes been used interchangeably. Added to this, the identification of the cascade of inflammatory mediators involved and the realisation that what had been called 'sepsis' could arise in the absence of infection have prompted reassessment of the terminology used both in the UK and in the USA.[1] In the UK, some authorities[2] considered that the term 'septicaemia' should no longer be used since it does not distinguish between mild and severe disease. The term 'sepsis syndrome' was preferred for patients with a generalised systemic response together with evidence of organ dysfunction and 'septic shock' to describe patients who also have hypotension not due to hypovolaemia or cardiac causes. The American College of Chest Physicians and Society of Critical Care Medicine proposed the following series of definitions to cover the spectrum of syndromes resulting from this inflammatory response:[1,3]

- **systemic inflammatory response syndrome** (SIRS), the systemic inflammatory response to infection or various other severe clinical insults including pancreatitis, ischaemia, trauma, and haemorrhagic shock
- **sepsis**, the SIRS caused specifically by infection
- **severe sepsis**, sepsis associated with organ dysfunction, perfusion abnormalities (such as lactic acidosis, oliguria, or an acute alteration in mental status), or hypotension
- **septic shock**, sepsis with hypotension, despite adequate fluid resuscitation, together with perfusion abnormalities
- **multiple organ dysfunction syndrome** (MODS), the presence of altered organ function in an acutely ill patient such that homoeostasis cannot be maintained without intervention; it may be a cause as well as a consequence of SIRS.

Septicaemia can be caused by many bacteria.[4] **Community-acquired** primary septicaemia is often associated with a specific infectious disease, such as meningococcal septicaemia with meningococcal meningitis (p.178) or streptococcal septicaemia with pneumonia (p.186). *Streptococcus pneumoniae* and *Haemophilus influenzae* are common causes of primary septicaemia in children (although this pattern is changing in countries where immunisation against *H. influenzae* type b is routine); Gram-negative rods and group B streptococci are commonest in neonates. **Hospital-acquired** septicaemia is often iatrogenic and may occur as a complication of surgery or indwelling catheters[5] or may be associated with neutropenia in immunocompromised patients (see under Infections in Immunocompromised Patients, p.174). Gram-positive organisms have been reported to be responsible for most infections.[6] Hospital-acquired septicaemia is often associated with acute respiratory distress syndrome (p.1498).

Whatever the cause, septicaemia requires prompt treatment without waiting for the results of laboratory tests. Choice of antibacterial depends on the probable source of infection. For example, urinary-tract infection is likely to be associated with Gram-negative septicaemia due to *Escherichia coli*; abdominal sepsis with Gram-negative septicaemia due to mixed infection with *E. coli*, enterococci, and anaerobic bacteria; and skin sepsis, bacterial arthritis, acute osteomyelitis, and cardiovascular shunts with Gram-positive septicaemia due to staphylococci. The antibacterials used should also reflect current patterns of bacterial resistance in the community or hospital. International guidelines[7] have recommended starting intravenous antibacterial therapy as early as possible, and within the first hour of recognition of septic shock; the initial choice of therapy should be broad enough to cover all likely pathogens, and it should be reassessed daily to optimise activity and prevent the development of resistance. De-escalation of combination therapy to the most appropriate single therapy should be carried out as soon as susceptibility of the infection is known. The typical duration of therapy will be 7 to 10 days. *Empirical treatment* has often begun with a penicillin and an aminoglycoside, metronidazole being added if anaerobic infection is suspected. In the UK, the *BNF* recommends that initial empirical treatment for community-acquired septicaemia is with either a broad-spectrum antipseudomonal penicillin (such as ticarcillin-clavulanic acid or piperacillin-tazobactam) or a broad-spectrum cephalosporin (such as ceftazidime or cefotaxime); for hospital-acquired septicaemia a broad-spectrum antipseudomonal beta-lactam antibacterial (such as ceftazidime, ticarcillin-clavulanic acid, piperacillin-tazobactam, imipenem-cilastatin, or meropenem) is recommended. In both cases, an aminoglycoside should be added if *Pseudomonas* is suspected or if sepsis is severe, metronidazole if anaerobic organisms are suspected, and vancomycin (or teicoplanin) if meticillin-resistant staphylococci are suspected. US guidelines[8] recommend a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime), or piperacillin-tazobactam, or imipenem-cilastatin, or meropenem, in each case with an aminoglycoside (gentamicin, tobramycin, or amikacin) for the initial treatment of life-threatening sepsis in adults. When there is some information on which to base choice of treatment, but before the infecting organisms are definitely known, the following treatment is suggested:

- suspected bacterial endocarditis—ceftriaxone with vancomycin, possibly with gentamicin as well
- suspected meticillin-resistant staphylococci—vancomycin, alone or with gentamicin and/or rifampicin

Once the infecting organisms have been identified, choice of treatment will again depend on their sensitivity and current patterns of resistance in the community or hospital. For comments on the consequences of emerging multidrug-resistant strains of enterococci and staphylococci, see Enterococcal Infections, p.170, and Staphylococcal Infections, p.195.

In addition to antimicrobial therapy, patients with sepsis or septic shock[9,10] require rigorous supportive measures (p.1183).

Septicaemia is generally most lethal in the very old and the very young.

Neonatal septicaemia may be divided into **early-onset**, which is acquired from the mother's genital tract and manifests itself during the first few days after birth, and **late-onset** which may be nosocomially acquired. Bacteria commonly causing early-onset sepsis include enterococci, *E. coli*, *H. influenzae*, *Listeria monocytogenes*, and streptococci. Some of these organisms may also produce meningitis in the neonate (p.178). Empirical treatment for both early- and late-onset sepsis is based on similar principles to those in other patients, giving consideration to local patterns of infection and resistance and to the suitability of individual antibacterials for this age group. However, early-onset sepsis is usually best controlled by prenatal treatment of the mother or by perinatal prophylaxis. Prophylaxis for group B streptococcal infections is discussed under Perinatal Streptococcal Infections, p.184. While vancomycin has been shown to prevent infections with coagulase-negative staphylococci and to reduce the incidence of neonatal sepsis, widespread prophylactic use of this drug is not recommended.[11] Intravenous normal immunoglobulin (see Neonatal Infection, p.2229) and filgrastim (see Neutropenia, p.1071) have been tried for the prevention of septicaemia in preterm neonates with variable results.

Treatment failure in patients with sepsis or septic shock, occurring despite apparently adequate anti-infective therapy, might be due in part to a continuing **inflammatory process** and attempts to modify this are under investigation.[10,12] Endotoxin, a lipopolysaccharide associated with the cell membrane of Gram-negative bacteria, is an important mediator in the septic syndrome. Endotoxin release may occur spontaneously or during antibacterial therapy.[13] When in the circulation it stimulates the release of endogenous mediators such as interleukin-1, interleukin-6, tumour necrosis factor alpha, and other cytokines.[14] These in turn induce a cascade of secondary inflammatory mediators resulting eventually in endothelial damage and severe haemodynamic and metabolic derangements. It is now understood that a similar inflammatory response also occurs after non-infective insults. However, adjunctive therapy with endotoxin antibodies, anticytokines such as anakinra and tumour necrosis factor antibodies, soluble tumour necrosis factor receptor, bactericidal permeability increasing protein, nitric oxide synthase inhibitors, guanylate cyclase inhibitors such as methylthioninium chloride, and platelet-activating factor antagonists has generally produced disappointing results.[12,15,16] A systematic review[17] of the use of intravenous polyclonal immunoglobulin concluded that it had a promising role as adjuvant therapy in sepsis and septic shock. Specific monoclonal immunoglobulins were not effective.[17] Recent theories suggest that a more complex interplay of pro- and anti-inflammatory responses may be involved in the pathophysiology of SIRS and MODS and this may explain the failure of many of these mainly anti-inflammatory treatment modalities.[18] Reduced mortality has been reported[19] after the treatment of patients with severe sepsis with recombinant activated protein C (drotrecogin alfa) which has antithrombotic, anti-inflammatory, and pro-fibrinolytic properties, but its benefits appear to be limited to those at high risk of death. Studies with other physiological anticoagulants such as antithrombin III[20] and tissue factor pathway inhibitor (tifacogin)[21] have not been successful.

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Sexually transmitted diseases

The sexually transmitted diseases, formerly termed venereal diseases, are defined as a group of communicable diseases that are transferred mainly by sexual contact. Many pathogens are known to be transmitted sexually including:

- bacteria:
  - *Chlamydia trachomatis* (see Lymphogranuloma Venereum, p.192 and Chlamydial Infections, p.166)
  - *Haemophilus ducreyi* (see Chancroid, p.191)
  - *Klebsiella granulomatis* (see Granuloma Inguinale, p.192)
  - *Neisseria gonorrhoeae* (see Gonorrhoea, p.191)
  - *Treponema pallidum* (see Syphilis, p.192)
  - *Ureaplasma urealyticum*
- protozoa:
  - *Trichomonas vaginalis* (see Trichomoniasis, p.827).
- viruses:
  - human immunodeficiency virus (see HIV Infection and AIDS, p.856)
  - hepatitis viruses (see Hepatitis, p.851)
  - herpesviruses (see Herpesvirus Infections, p.853)

Clinical syndromes associated with sexually transmitted diseases, and which are discussed in this section, include urethritis (p.199) and epididymitis (p.170) in men; cervicitis (p.166), pelvic inflammatory disease (p.184), and bacterial vaginosis (p.164) in women; and proctitis (p.188). Perinatal transmission of sexually transmitted pathogens from the mother can result in neonatal conjunctivitis (p.180) or pneumonia (p.186).

General guidelines for the management of sexually transmitted diseases have been published[1-3] although recommendations may need to be localised because of differences in patterns of infection and drug resistance. Early detection and treatment are required to prevent long-term complications, including infertility, still-births and neonatal infections, genital cancers, and an increased risk of acquiring and transmitting HIV.

The suggestion that spermicidal contraceptives may provide some protection against sexually transmitted diseases is discussed under Nonoxinols, p.1917.

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Chancroid. Chancroid is a sexually transmitted disease caused by the Gram-negative bacterium *Haemophilus ducreyi*. It occurs worldwide, but is endemic in parts of Africa and South East Asia, where it is a frequent cause of painful genital ulcers and a risk factor in the transmission of HIV.

Specific **treatment** guidelines have been provided by WHO,[1] by expert groups in the UK,[2] and by the CDC in the USA.[3] Treatment failure may be more common in patients also infected with HIV[1] (see below), but in other patients single-dose treatment regimens might be preferable if compliance is a problem. Guideline regimens are as follows:

- **WHO:**
  - oral ciprofloxacin 500 mg twice daily for 3 days, *or*
  - oral erythromycin 500 mg four times daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  an alternative regimen is:
  - a single intramuscular injection of ceftriaxone 250 mg
- **UK:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days *or* as a single oral dose

  further alternatives are:
  - oral erythromycin 500 mg four times daily for 7 days
  - single oral doses of other fluoroquinolones such as fleroxacin 400 mg *or* norfloxacin 800 mg
  - a single intramuscular injection of spectinomycin 2 g
- **USA:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days

  a further alternative is:
  - oral erythromycin 500 mg three times daily for 7 days

Sexual partners of patients with chancroid should also be tested and treated.[2,3]

Patients co-infected with HIV have ulcers that heal more slowly and may need to be treated for longer to prevent treatment failure;[3] treatment failure is common with single-dose regimens.[1]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases – now British Association for Sexual Health and HIV). 2001 National guideline for the management of chancroid. Available at: http://www.bashh.org/documents/85/85.pdf (accessed 18/08/08)
3. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 23/03/07)

Gonorrhoea. Gonorrhoea is a sexually transmitted disease caused by infection of mucosa with *Neisseria gonorrhoeae* (gonococcus), a Gram-negative bacterium. It occurs mainly in the lower genital tract as urethritis (p.199) in men and cervicitis (p.166) in women, but also as pharyngitis, proctitis (p.188), or conjunctivitis. Infection may sometimes ascend to the upper genital tract to cause complications such as pelvic inflammatory disease (p.184) in women and epididymitis (p.170) in men. In the USA[1] routine screening is recommended for all sexually active women with an increased risk of infection. Disseminated gonococcal infection resulting from gonococcal bacteraemia is rare and may lead to septic arthritis, an arthritis-dermatitis syndrome (not to be confused with Reiter's disease which has been associated with non-gonococcal or nonspecific urethritis), and more rarely to conditions such as endocarditis or meningitis. Gonorrhoea in pregnant women may cause neonatal gonococcal conjunctivitis (ophthalmia neonatorum).

Antibacterial drug resistance is a problem in the management of gonococcal infection. Penicillins were once the treatment of choice for *N. gonorrhoeae* but are no longer recommended. High-level plasmid-mediated and chromosomally mediated resistances have also been reported with tetracycline, and chromosomally mediated resistance to other antibiotics may occur. Gonococcal resistance is now monitored in England and Wales via the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP)[2] and in the USA by the Gonococcal Isolate Surveillance Project (GISP).[3] Of concern are the increasing number of reports worldwide of resistance to fluoroquinolones which has resulted in revision of treatment guidelines. In the UK fluoroquinolones are no longer recommended as first-line drugs, while in the USA they are no longer recommended for gonococcal infections.

Infection with *Chlamydia trachomatis* (see under Chlamydial Infections, p.166) often occurs along with gonorrhoea and should be tested for or treated presumptively.

Guidelines produced by WHO,[4] by an expert group in the UK,[5] and by the CDC in the USA[1] for the **treatment** of gonorrhoea are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- UNCOMPLICATED ANOGENITAL GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO**:
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**
    - a single intramuscular dose of ceftriaxone 250 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g, *or*
    - a single oral dose of cefixime 400 mg

    alternative regimens are:
    - a single oral dose of ciprofloxacin 500 mg
    - a single oral dose of ofloxacin 400 mg
    - a single oral dose of ampicillin 2 or 3 g *plus* probenecid 1 g
    - a single intramuscular dose of cefotaxime 500 mg
    - a single intramuscular dose of cefoxitin 2 g plus oral probenecid 1 g
  - **USA:**
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg

    Other single dose cephalosporins may be substituted. A single intramuscular dose of spectinomycin 2 g is an alternative in patients who cannot tolerate cephalosporins.
- PHARYNGEAL INFECTIONS.
  - **UK:**
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of ofloxacin 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 250 mg
  - **USA:**
    - a single intramuscular dose of ceftriaxone 125 mg
- GONOCOCCAL INFECTIONS IN PREGNANT WOMEN.
  - **WHO:**
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**
    - a single intramuscular dose of ceftriaxone 250 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g, *or*
    - a single oral dose of cefixime 400 mg, *or*
    - a single oral dose of amoxicillin 3 g (*or* ampicillin 2 or 3 g) plus probenecid 1 g
  - **USA:**
    - a cephalosporin or spectinomycin
- GONOCOCCAL EYE INFECTIONS IN ADULTS.
  - **WHO:** frequent irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g, *or*
    - a single oral dose of ciprofloxacin 500 mg

    a further alternative is:
    - a single intramuscular dose of kanamycin 2 g
  - **USA:** irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 1 g
- DISSEMINATED GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO:**
    - parenteral ceftriaxone 1 g once daily for 7 days, *or*
    - intramuscular spectinomycin 2 g twice daily for 7 days

    Another third-generation cephalosporin may be substituted if neither of these drugs is available. Treatment for endocarditis should continue for 28 days.
  - **USA:**
    - parenteral ceftriaxone 1 g every 24 hours

    alternatives are:
    - intravenous ceftizoxime 1 g every 8 hours
    - cefotaxime 1 g every 8 hours
    - intramuscular spectinomycin 2 g every 12 hours

    Once improvement has been established for 24 to 48 hours, oral therapy with cefixime 400 mg twice daily, *or* cefpodoxime 400 mg twice daily may be substituted until at least a 1-week treatment period is complete. Provided antimicrobial susceptibility is documented fluoroquinolones may be given as an alternative treatment.

    For gonococcal meningitis and endocarditis, intravenous ceftriaxone 1 to 2 g every 12 hours is recommended; treatment for meningitis should continue for 10 to 14 days and for endocarditis for at least 4 weeks.

- GONOCOCCAL INFECTIONS IN NEONATES AND CHILDREN.

Neonates born to mothers with gonorrhoea are at high risk of infection and require *prophylaxis*:

- **WHO:**
  - a single intramuscular injection of ceftriaxone 50 mg/kg (maximum 125 mg)

  alternatives are:
  - a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg)
  - a single intramuscular dose of kanamycin 25 mg/kg (maximum 75 mg)
- **USA:**
  - a single parenteral dose of ceftriaxone 25 to 50 mg/kg (maximum 125 mg)

For those neonates with *disseminated gonococcal infection* (sepsis, arthritis, meningitis), US recommendations are:

- parenteral ceftriaxone 25 to 50 mg/kg once daily for 7 days, *or*
- parenteral cefotaxime 25 mg/kg every 12 hours for 7 days

Treatment should be extended to 10 to 14 days if meningitis is present.

Treatment for *children* with uncomplicated gonococcal infections, most commonly due to sexual abuse in preadolescents, is as for adults in those weighing 45 kg or more. For those weighing less than 45 kg a single intramuscular dose of ceftriaxone 125 mg *or* spectinomycin 40 mg/kg (maximum 2 g) is recommended. For disseminated infection in all children an intramuscular or intravenous dose of ceftriaxone 50 mg/kg once daily for 7 days, up to a maximum dose of 1 g in those weighing less than 45 kg is recommended.

The prevention and treatment of neonatal gonococcal conjunctivitis is discussed under Neonatal Conjunctivitis, p.180.

Sexual partners of patients with gonococcal infection should be tested and treated.[1]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[1]

1. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 23/03/07) Updated recommended treatment regimens for gonococcal infections and associated conditions—United States, April 2007. Available at: http://www.cdc.gov/std/treatment/2006/GonUpdateApril2007.pdf (accessed 12/04/07)
2. Health Protection Agency. GRASP The Gonococcal Resistance to Antimicrobials Surveillance Programme: annual report, year 2006. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947393147 (accessed 18/08/08)
3. CDC. Sexually transmitted disease surveillance 2005 supplement: Gonococcal Isolate Surveillance Project (GISP) annual report—2005. Available at: http://www.cdc.gov/std/GISP2005/GISPSurvSupp2005short.pdf (accessed 20/04/07)
4. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 20/06/07)
5. Clinical Effectiveness Group (British Association for Sexual Health and HIV). National guideline on the diagnosis and treatment of gonorrhoea in adults 2005. Available at: http://www.bashh.org/documents/116/116.pdf (accessed 18/08/08)

Granuloma inguinale. Granuloma inguinale or donovanosis is caused by the Gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*) and occurs most commonly in the tropics and subtropics, especially Papua New Guinea and India. It is characterised by genital ulcers and is generally considered to be a sexually transmitted disease.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of granuloma inguinale are as follows:

- **WHO:**
  - oral azithromycin 1 g on the first day then 500 mg once daily, *or*
  - oral doxycycline 100 mg twice daily

  alternatives include:
  - oral erythromycin 500 mg four times daily
  - oral tetracycline 500 mg four times daily
  - oral co-trimoxazole 960 mg twice daily

  Treatment is continued until all lesions have completely resolved. The addition of parenteral gentamicin should be considered for HIV-infected patients. Streptomycin is no longer recommended because of its toxicity and the need to reserve it for tuberculosis.
- **UK:**
  - oral azithromycin 1 g once weekly or 500 mg daily, *or*
  - parenteral ceftriaxone 1 g once daily, *or*
  - oral co-trimoxazole 960 mg twice daily, *or*
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral norfloxacin 400 mg twice daily

  The addition of parenteral gentamicin 1 mg/kg every 8 hours should be considered if lesions do not respond during the first few days of treatment.
- **USA:**
  - oral doxycycline 100 mg twice daily for a minimum of 3 weeks

  alternatives are:
  - oral ciprofloxacin 750 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral azithromycin 1 g once weekly, *or*
  - oral co-trimoxazole 960 mg twice daily

  In each case treatment is for 3 weeks. The addition of an aminoglycoside may be considered if lesions do not respond during the first few days of treatment, in pregnant women, and in those co-infected with HIV.

Sexual partners of patients with granuloma inguinale should be tested and treated.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases – now British Association for Sexual Health and HIV). 2001 National guideline for the management of donovanosis (granuloma inguinale). Available at: http://www.bashh.org/documents/39/39.pdf (accessed 18/08/08)
3. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 23/03/07)

Lymphogranuloma venereum. Lymphogranuloma venereum or chlamydial lymphogranuloma is an invasive, systemic infection caused by certain serotypes of *Chlamydia trachomatis* and is endemic in tropical and subtropical areas, but may also occur in the developed world. It is a sexually transmitted disease and in the early phase may cause genital ulceration although the commonest clinical manifestation is unilateral inguinal and/or femoral lymphadenopathy. There is multisystem involvement and late complications, including those related to fibrosis and abnormal lymphatic drainage, may require surgery.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of lymphogranuloma venereum are as follows:

- **WHO:** treatment for 2 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  an alternative is:
  - oral tetracycline 500 mg four times daily
- **UK** and **USA:** treatment for 3 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral tetracycline 2 g daily, *or*
  - oral minocycline 300 mg as a loading dose *then* 200 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  Sexual partners of patients with lymphogranuloma venereum should be treated with:
  - a single oral dose of azithromycin 1 g *or*
  - oral doxycycline 100 mg twice daily for 7 days

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative, although longer therapy may be required.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2006 National guideline for the management of lymphogranuloma venereum (LGV). Available at: http://www.bashh.org/documents/92/92.pdf (accessed 18/08/08)
3. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 23/03/07)

Syphilis. Syphilis is a sexually transmitted disease caused by the spirochaete *Treponema pallidum* and occurs worldwide. Non-venereal treponematoses include endemic syphilis or bejel, also caused by *T. pallidum*; pinta, caused by *T. carateum*; and yaws, caused by *T. pertenue*.

Syphilis may be **classified** as acquired or congenital and in each case has early and late stages. Syphilis may be described as latent, when serological and CSF tests are positive but the patient is asymptomatic.

- In acquired sexually transmitted disease the *early* stage includes primary and secondary syphilis and early latent infection; early latent infection is defined in the UK[1] and by WHO[2] as of not more than 2 years' duration or of less than 1 year's duration by the CDC in the USA.[3]
- *Late* stage disease includes late latent infection and all late clinical stages. The late clinical stages fall broadly into three types: *neurosyphilis* manifesting as neurological symptoms, commonly including dorsal column loss (tabes dorsalis), dementia, or meningovascular involvement; *cardiovascular* syphilis, characterised by aortitis which may manifest as aortic regurgitation, aortic aneurysm, or angina; and *gummata*, inflammatory fibrous nodules or plaques which may be locally destructive and which commonly affect the bone and skin but may occur in any organ. Some term all these late clinical stages tertiary syphilis whereas others use tertiary for benign gummatous syphilis and quaternary for the more serious complications of cardiovascular syphilis and neurosyphilis. The term neurosyphilis has generally been applied to late-stage symptomatic neurological disease, although it is recognised that CNS invasion by *T. pallidum* is common in early syphilis and that CNS involvement may occur at any stage.
- *Congenital syphilis* may result from transplacental infection at any stage of pregnancy and any stage of maternal syphilis.

The incidence of syphilis fell dramatically after the introduction of penicillin and *T. pallidum* remains sensitive to it. There has, however, been a resurgence of syphilis, linked in part with HIV infection. In HIV-infected patients syphilis appears more virulent and neurosyphilis occurs more quickly. Like other diseases causing genital ulcers, syphilis is a risk factor for HIV infection.

The **treatment** of choice for both early and late syphilis is still penicillin and long-acting injections are generally used. Treatment for late syphilis is less well-established than that for early disease and is usually given for longer. A Jarisch-Herxheimer reaction may occur after the first dose of antibacterial, especially in patients with early syphilis, and corticosteroid cover may be beneficial, especially in patients with cardiovascular or neurological involvement.

Guidelines produced by WHO,[2] by an expert group in the UK,[1] and by the CDC in the USA[3] for the treatment of acquired and congenital syphilis are as follows:

- EARLY SYPHILIS
  - **WHO**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) usually given as 2 injections at separate sites in a single session, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 10 days

    alternatives for non-pregnant penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days, *or*
    - oral tetracycline 500 mg four times daily for 14 days

    Pregnant women allergic to penicillin may be given:
    - oral erythromycin 500 mg four times daily for 14 days (but see Syphilis in Pregnancy, below)
  - **UK**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) as a single dose, *or*
    - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 10 days

    An additional alternative if parenteral therapy is refused is:
    - oral amoxicillin 500 mg *plus* oral probenecid 500 mg, both four times daily for 14 days

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral erythromycin 500 mg four times daily for 14 days
    - oral azithromycin 2 g as a single dose
    - oral azithromycin 500 mg daily for 10 days
    - intramuscular ceftriaxone 500 mg daily for 10 days (in the absence of anaphylaxis to penicillin)
  - **USA**:
    - a single intramuscular dose of benzathine benzylpenicillin 1.8 g (2.4 million units)

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral tetracycline 500 mg four times daily for 14 days

    Preliminary data suggest that azithromycin 2 g orally as a single dose may also be effective, *or* parenteral ceftriaxone 1 g daily for 8 to 10 days may also be considered.

- LATE SYPHILIS
  - **WHO**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for 3 consecutive weeks, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 20 consecutive days

    alternatives for non-pregnant penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 30 days, *or*
    - oral tetracycline 500 mg four times daily for 30 days

    Pregnant women allergic to penicillin may be given:
    - oral erythromycin 500 mg four times daily for 30 days

    For those with *neurosyphilis*:
    - intravenous benzylpenicillin 1.2 to 2.4 g (2 to 4 million units) every 4 hours for 14 days, *or*
    - if outpatient compliance can be ensured, intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily *plus* oral probenecid 500 mg four times daily each for 10 to 14 days

    alternatives for non-pregnant penicillin-allergic patients are:
    - oral doxycycline 200 mg twice daily for 30 days
    - oral tetracycline 500 mg four times daily for 30 days
  - **UK**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 doses, *or*
    - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 17 days

    alternatives for patients allergic to penicillin and those declining parenteral therapy are:
    - oral doxycycline 100 mg twice daily for 28 days, *or*
    - if penicillin can be tolerated, oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days

    For those with *neurosyphilis* recommendations are:
    - intramuscular procaine benzylpenicillin 1.8 to 2.4 g (1.8 to 2.4 million units) once daily *plus* oral probenecid 500 mg four times daily for 17 days, *or*
    - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million units) every 4 hours for 17 days

    alternatives are:
    - oral doxycycline 200 mg twice daily for 28 days
    - oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days
    - intramuscular or intravenous ceftriaxone 2 g daily for 10 to 14 days (in the absence of anaphylaxis to penicillin)
  - **USA**:
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 consecutive weeks

    alternatives in penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 28 days, *or*
    - oral tetracycline 500 mg four times daily for 28 days

    For those with *neurosyphilis*:
    - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million units) every 4 hours for 10 to 14 days (or the total daily dose may be given by continuous infusion), *or*
    - if outpatient compliance can be ensured, then intramuscular procaine benzylpenicillin 2.4 g (2.4 million units) daily *plus* oral probenecid 500 mg four times daily, both for 10 to 14 days

    Since the duration of treatment for neurosyphilis is shorter than that for late syphilis in the absence of neurosyphilis, some clinicians give intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for up to 3 weeks after completion of neurosyphilis treatment to provide a comparable total duration of treatment.
- SYPHILIS IN PREGNANCY

  All guidelines recommend penicillin as under early and late syphilis, together with close surveillance. In the USA, CDC[3] note that some recommend a second dose of benzathine benzylpenicillin a week after the initial dose for patients with early syphilis. In the UK[1] it is recommended that when the first dose is given in the third trimester a second dose should be given one week later. According to CDC,[3] pregnant patients who are allergic to penicillin should be given penicillin, after desensitisation if necessary, since the alternatives, tetracyclines, are contra-indicated during pregnancy and erythromycin cannot be relied upon to cure an infected fetus. WHO,[2] on the other hand, advise against desensitisation in a primary care setting and suggest that erythromycin, although inferior, should be given in these circumstances; consideration should probably be given to use of a third-generation cephalosporin in the absence of anaphylaxis. After treatment, the mother should be re-treated if there is serological evidence of re-infection or relapse, and the infant treated.[2] UK guidelines[1] list alternative antibacterials that may be given as: amoxicillin, ceftriaxone, erythromycin or azithromycin. they also state that desensitisation should be considered in those allergic to penicillin.
- CONGENITAL SYPHILIS
  - **WHO**:

    for early congenital syphilis, infants up to 2 years of age and having abnormal CSF may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    For infants with normal CSF (although some treat all infants as if the CSF were abnormal):
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Children older than 2 years may be given:
    - parenteral benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 to 14 days

    For penicillin-allergic infants aged over 1 month:
    - oral erythromycin 7.5 to 12.5 mg/kg four times daily for 30 days
  - **UK**: recommended doses are as for infants up to 2 years with abnormal CSF in WHO guidelines, above.
  - **USA**:

    Neonates (up to 4 weeks of age) and having proven or probable disease:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    Neonates who have a normal physical and a non-treponemal serum titre the same as or less than 4 times the maternal titre may be given, depending on how successfully the mother was treated during pregnancy:
    - one of the above treatment regimens *or*
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Infants and children may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 days.

    Those who are allergic to penicillin should be desensitised if necessary.

Sexual partners of patients with syphilis in any stage should be examined, tested, and treated.[2,3]

In the UK,[1] it is advised that all cases of syphilis in HIV-infected patients be treated as for the appropriate stage of infection as in HIV-negative patients; some experts recommend treatment as for neurosyphilis but the UK guidelines note that evidence for this policy is lacking. The CDC[3] and WHO[2] consider that standard treatment with a single intramuscular dose of benzathine benzylpenicillin 1.8 g (2.4 million units) is sufficient, but acknowledge that some authorities recommend more intensive treatment regimens.

1. Clinical Effectiveness Group British Association for Sexual Health and HIV. 2008 UK national guidelines on the management of syphilis. http://www.bashh.org/documents/1771 (accessed 18/08/08)
2. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
3. CDC. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55**(RR-11): 1–94. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 23/03/07)

Shigellosis

See p.173.

Sickle-cell disease

For prophylaxis against pneumococcal infection in sickle-cell disease, see under Spleen Disorders, p.194.

Sinusitis

Sinusitis or inflammation of the paranasal sinuses can be caused by viral, bacterial, or fungal infection or may be secondary to other disorders such as allergy. Serious complications include bacterial meningitis and brain abscess.

Acute sinusitis often results from viral upper respiratory-tract infections. As in acute otitis media the most frequent bacterial pathogens are *Streptococcus pneumoniae* and unencapsulated *Haemophilus influenzae*, with *Moraxella catarrhalis* (*Branhamella catarrhalis*) increasingly important in children. Other bacterial causes, especially in adults, include mixed anaerobic bacteria (usually associated with dental disease and more frequent in chronic sinusitis), *Staphylococcus aureus*, *Streptococcus pyogenes*, and Gram-negative bacteria including Enterobacteriaceae and *Pseudomonas aeruginosa* (in nosocomial sinusitis). About 5% of primary sinusitis in young adults has been associated with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*).

Acute sinusitis may resolve spontaneously. In an evidence-based report on the diagnosis and treatment of rhinosinusitis,[1] the Agency for Health Care Policy and Research in the USA has stated that most patients with the acute condition will recover without antibacterial therapy, although they will recover faster if antibacterials are given. However, a systematic review concluded that any treatment effect of antibacterials was small.[2] The Agency also considered[1] that the use of new antibacterials for treating uncomplicated community-acquired acute bacterial rhinosinusitis was not justified and that amoxicillin or folate inhibitors were sufficiently effective. This view was supported by a meta-analysis.[3] US guidelines for the management of sinusitis in adults[4] state that most cases will resolve without antibacterial treatment and recommend that antibacterials should be reserved for those patients with persistent moderate or severe symptoms. However, a later meta-analysis[5] considered that antibacterials could not be justified, even in patients who reported symptoms for longer than 7 to 10 days; the only reason for antibacterial treatment was the presence of signs suggestive of a serious complication (such as high fever, periorbital swelling, erythema, or intense facial pain). Guidelines from the American Academy of Pediatrics for the management of sinusitis in children[6] recommend that antibacterials be given to children clinically diagnosed with persistent or severe acute bacterial sinusitis in order to achieve a more rapid clinical cure.

If antibacterials are considered necessary, treatment should be given for an adequate length of time, usually 2 weeks.[6-8] Topical decongestants may also be used to promote drainage and ventilation.[7,8] The choice of antibacterial is similar to that for acute otitis media (p.182). Effective antibacterials include amoxicillin with or without clavulanic acid, cefuroxime, clarithromycin, clindamycin and azithromycin;[6] the emergence of penicillin-resistant strains of *H. influenzae*, *M. catarrhalis*, and *Str. pneumoniae* is of concern.[9] Co-trimoxazole or erythromycin with sulfafurazole have also been used although pneumococcal resistance has been reported to be substantial.[6] Patients with evidence of severe infections may need initial intravenous therapy with vancomycin and ceftriaxone or cefotaxime.[9] Tetracycline or erythromycin are the most effective antibacterials against *Chlamydophila pneumoniae*.[10]

Failure to treat acute sinusitis that does not resolve spontaneously can result in chronic sinusitis or occasionally in complications such as brain abscess or meningitis. Exacerbations of chronic sinusitis are treated as for acute infection. Management of chronic sinusitis is based on reducing obstruction of the sinus cavity using antihistamines, decongestants, anti-inflammatory drugs (including corticosteroids), and saline washes as appropriate.[7,11,12] The usefulness of antibacterials is more contentious,[11] although some clinicians advocate prolonged courses as part of initial treatment.[7,12] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases including chronic sinusitis but large placebo-controlled studies are needed. Surgical intervention may be necessary if medical treatment fails.

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Skin infections

Bacterial infections of the skin may result from invasion of skin structures by endogenous skin flora or by exogenous pathogenic organisms. They include the primary pyodermas (for example, impetigo, folliculitis, furunculosis, erysipelas, cellulitis, and ecthyma) and secondary infections complicating pre-existing skin lesions, for example diabetic or other chronic superficial skin ulcers, burns, bites and stings (p.164), eczema, or may occur as opportunistic infections after skin trauma in immunocompromised patients.

The pyodermas are commonly caused by *Staphylococcus aureus* or, less commonly, by beta-haemolytic streptococci. Skin ulcers and burns may typically be colonised by *Staph. aureus* or *Pseudomonas aeruginosa*; chronic ulcers and fungating tumours may also be colonised by anaerobes which can cause an offensive odour.

Skin disorders of uncertain or mixed aetiology that are treated with antibacterials include acne (p.1577) and rosacea (p.1583). Systemic infections with cutaneous involvement include anthrax (p.163), diphtheria (p.168), and mycetoma (p.180).

Topical antibacterials and antiseptics may be useful for superficial skin infections, but antibacterials should only be used short term because of the risks of inducing bacterial resistance and contact allergy. Topical use of antibacterials that are of value systemically, such as gentamicin, is best avoided, although fusidic acid is used topically in the UK. Application of topical antibacterials to extensive areas of damaged skin can result in systemic toxicity.

Serious infections are treated systemically. Treatment of skin infections is increasingly based on knowledge of the likely infecting organisms and patterns of resistance; empirical treatment with broad-spectrum antibacterials is now discouraged in an attempt to minimise the emergence of resistant organisms.[1] For burns, however, control of infection is important to reduce the risk of sepsis. Topical application of sulfadiazine silver or mafenide acetate has been used in addition to aggressive systemic antibacterial therapy.

Gram-positive pathogens, especially staphylococci and beta-haemolytic streptococci, are commonly associated with primary pyodermas. *Staphylococcus aureus* is implicated in impetigo, cellulitis, folliculitis, furunculosis, and occasionally erysipelas and necrotising fasciitis (p.180), and may colonise burns. Staphylococcal scalded skin syndrome is a severe manifestation of bullous impetigo caused by infection with strains of *Staph. aureus* producing exfoliative exotoxins. The term toxic epidermal necrolysis is used to cover both this syndrome and a morphologically identical syndrome due to various aetiologies. A syndrome resembling scarlet fever may also occur. Staphylococcal infections are usually treated systemically with a penicillinase-resistant penicillin or a first-generation cephalosporin.[2] Erythromycin is an alternative for patients unable to tolerate penicillin. Multidrug-resistant staphylococci are becoming increasingly common, particularly in hospitals, and treatment alternatives for infections with these organisms are discussed under Staphylococcal Infections, p.195. Less severe infections in folliculitis or furunculosis may respond to the application of moist heat without the need for antibacterials. In patients at risk of recurrent staphylococcal infections, nasal application of chlorhexidine plus neomycin or mupirocin alone is used to eliminate nasal carriage of staphylococci.

Beta-haemolytic streptococci are also implicated in pyodermas including impetigo, erysipelas, and cellulitis. Necrotising fasciitis (p.180) may be caused by group A streptococci. Streptococcal infections continue to respond to phenoxymethylpenicillin or benzylpenicillin. Erythromycin is an alternative in patients unable to tolerate penicillins, but increasing resistance may be a problem;[1] clindamycin may be effective in patients with aggressive infections not responding to penicillin.[3] Topical retapamulin is licensed for the treatment of impetigo due to either *Staph. aureus* or *Str. pyogenes*. For community-acquired mixed infections associated with necrotising fasciitis a combination of ampicillin-sulbactam, clindamycin, and ciprofloxacin has been advocated.[2]

Resistance is also emerging in *Propionibacterium acnes*; strains resistant to erythromycin, clindamycin, and tetracycline are reported to be common in patients after treatment for acne.[1]

Gram-negative bacteria are less frequently implicated in skin infections, but *Pseudomonas aeruginosa* and *Proteus* spp. can cause infections, especially if the skin is subjected to damp conditions. These organisms produce proteolytic enzymes that cause the resulting skin damage. *Ps. aeruginosa* may colonise burns and skin ulcers. Pseudomonal infections are treated with aminoglycosides and the antipseudomonal penicillins.

Anaerobic organisms may colonise wounds, particularly chronic ulcers and fungating tumours. Topical metronidazole has been used to control the offensive odour caused by these infections.

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Spleen disorders

Splenectomised patients and those with hyposplenism associated with, for example, sickle-cell disease have impaired immunity and, like other immunocompromised patients (p.174), are at increased risk of infection. Children are at special risk. *Streptococcus pneumoniae* is the commonest infecting bacterium and may cause severe overwhelming infection that is rapid in onset and sometimes fatal. Hence, prophylaxis with an oral penicillin such as phenoxymethylpenicillin is advocated. Pneumococcal vaccine is also used; the newer ones may be more effective than earlier vaccines. Other organisms implicated include *Neisseria meningitidis*, *Haemophilus influenzae*, and *Escherichia coli* in splenectomised patients and *Salmonella* in children with sickle-cell disease. More unusual organisms include *Capnocytophaga canimorsus* (formerly called DF-2) which may cause opportunistic infections in splenectomised patients after animal bites. There may also be an increased risk of falciparum malaria and babesiosis.

- SPLENECTOMISED PATIENTS

  Guidelines for prophylaxis based on published evidence and expert opinion have been published in a number of countries including the UK.[1] Immunisation with polyvalent pneumococcal vaccine is recommended for all asplenic patients and those with functional hyposplenism. *Haemophilus influenzae* (Hib) vaccine is recommended for all patients who have not previously received this vaccine. Influenza vaccination should be given. Meningococcal group C conjugate vaccine is recommended; however, the vaccine currently available does not protect against the group B strain of *N. meningitidis* causing the majority of infections in the UK. In addition, patients travelling abroad should receive a meningococcal vaccine which protects against group A infections. Lifelong prophylaxis with a suitable antibacterial should be offered. Phenoxymethylpenicillin is usually given, but amoxicillin may be preferred, particularly in adults, as it is better absorbed after oral doses and has a broader spectrum of activity. Erythromycin is a suitable alternative in those unable to tolerate penicillins. On a practical level, compliance with lifelong prophylaxis is difficult, but is particularly important in patients with underlying immunodeficiency, in children up to the age of 16 years, and for the first 2 years after splenectomy. Patients should keep a supply of a suitable antibacterial for immediate use should symptoms of infection occur, and be instructed to seek medical advice urgently.

- SICKLE-CELL DISEASE

  Children with sickle-cell disease are particularly susceptible to severe pneumococcal infection which may present as septicaemia, meningitis, or pneumonia.

  Penicillin prophylaxis is usually combined with early immunisation with a polyvalent pneumococcal vaccine. Phenoxymethylpenicillin 125 mg twice daily is effective in young children but amoxicillin may be preferred in adults since it is better absorbed and has a broader spectrum. There is evidence to suggest that, in children who have received pneumococcal immunisation, there is no benefit in continuing penicillin prophylaxis beyond the age of 5 years,[2] although indefinite prophylaxis has been recommended for those who have had a previous pneumococcal septic event.[3] Fears that prolonged prophylaxis could encourage the emergence of resistant pneumococci have not been substantiated,[4] although the prevalence of beta-lactam-resistant pneumococci continues to increase. Neonatal screening for sickle-cell disease is advocated, but compliance with regular penicillin prophylaxis may be poor and effective follow-up is necessary if the full benefit of such screening is to be achieved.[5,6] Nevertheless, availability of penicillin in the home, even if not taken regularly, means that it can be readily used if febrile illness occurs.[5] If children with sickle-cell disease develop a febrile illness they are generally treated in hospital with intravenous antibacterials, although outpatient management may often be possible.[7]

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Spotted fevers

Rickettsial infections of the spotted fever group are transmitted to man by ticks and have also been called tick typhus. They include Rocky Mountain spotted fever, due to *Rickettsia rickettsii* and occurring especially in the USA; boutonneuse or Mediterranean spotted fever, due to *R. conorii* and occurring in Mediterranean countries including the Middle East, Africa, and India; Queensland tick typhus, due to *R. australis* and occurring in Australia; north Asian tick typhus, due to *R. sibirica* and occurring in Siberia and Mongolia; and oriental spotted fever, due to *R. japonica* and occurring in Japan. Rickettsialpox, due to *R. akari* is transmitted from mice by mites and occurs in the USA, Russia, and Africa.

Spotted fevers are recognised increasingly as a cause of febrile illness associated usually, but not always, with a purpuric rash and are becoming an important cause of imported fevers in non-endemic areas.[1,2] Rocky Mountain spotted fever has been one of the most severe of these fevers, but others are potentially serious. A tetracycline, often doxycycline, or chloramphenicol is the treatment of choice for all the spotted fevers. In Rocky Mountain spotted fever, doxycycline 100 mg every 12 hours or chloramphenicol 500 mg every 6 hours for 5 to 10 days may be used. Because tetracyclines are generally contra-indicated in young children, chloramphenicol has been recommended for children with Rocky Mountain spotted fever under the age of 9, but doxycycline is considered the treatment of choice for this and other potentially life-threatening tick-borne rickettsioses, even in young children.[2] The risk of tooth staining with a single short course of doxycycline is considered negligible,[2] and there is evidence that short courses of tetracycline are effective in some of these diseases.[3] Relapses have occurred in patients with Mediterranean spotted fever treated with chloramphenicol.[4] Other alternatives to tetracycline used in Mediterranean spotted fever have included the macrolides azithromycin,[2,5] clarithromycin,[2,5] and erythromycin,[6] or ciprofloxacin[7] or rifampicin. Erythromycin was effective, but less so than tetracycline, in children with Mediterranean spotted fever.[6] Short 2-day courses of ciprofloxacin or doxycycline were curative in adults whose disease was not severe, although there was a more rapid response to doxycycline.[7] A 5-day course of ciprofloxacin has also been used successfully to treat infection with *R. australis*.[8]

Rickettsialpox can be mistaken for chickenpox. However, it will respond to tetracycline although patients have generally recovered without treatment.[9]

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Staphylococcal infections

Staphylococci are Gram-positive bacteria pathogenic to man. Species may be differentiated by various methods, including the coagulase test. Those species of clinical importance are *Staphylococcus aureus*, which is usually coagulase-positive, and *Staph. epidermidis* and *Staph. saprophyticus*, which are coagulase-negative.

Staph. aureus colonises the skin and mucous membranes naturally and many people, including neonates, may be staphylococcal carriers from time to time. Localised *Staph. aureus* infections may follow surgery or trauma and commonly result in abscess formation. Staphylococcal skin infections include impetigo and furunculosis. Conditions associated with staphylococcal extracellular toxin production include staphylococcal scalded skin syndrome, toxic shock syndrome, and staphylococcal food poisoning. Staphylococcal septicaemia is usually a consequence of local infection and may sometimes be associated with intravascular or intraperitoneal catheters or with intravenous drug abuse. Septicaemia often results in staphylococcal endocarditis. Other possible complications of septicaemia are pneumonia and bone and joint infections, although in these cases aspiration or local trauma, respectively, may be the cause.

Staph. epidermidis is also a natural inhabitant of skin and mucous membranes and an increasingly important nosocomial pathogen. Many infections are hospital-acquired and are often associated with indwelling catheters. There has been an increased incidence of bacteraemia due to *Staph. epidermidis* in neonatal units.

Staph. saprophyticus is a common cause of urinary-tract infections in young women.

Staphylococci were sensitive to benzylpenicillin when it was first introduced, but the majority of strains are now resistant as a result of penicillinase production. Meticillin and other penicillinase-resistant penicillins such as flucloxacillin were developed because of their activity against these resistant staphylococci. However, meticillin-resistant staphylococci soon emerged. Both coagulase-negative staphylococci and *Staph. aureus* resistant to meticillin are generally resistant to all beta lactams and often exhibit multiple resistance to other antibacterials (see Meticillin, Antimicrobial Action, p.299). More studies have been published on meticillin-resistant *Staph. aureus* (MRSA) than meticillin-resistant coagulase-negative staphylococci, but both types are a serious problem in hospitals around the world. Resistant strains may be endemic to a single hospital or may be epidemic causing outbreaks of infection at more than one hospital. Colonisation of hospital staff and patients with meticillin-resistant staphylococci is an important factor in the spread of these infections. Current trends are towards health care at home rather than in hospital and there are reports suggesting that MRSA is becoming more prevalent in the community.[1-5]

Guidelines for the control of MRSA are available in many countries.[6] In the UK, revised guidelines[7] for the control of MRSA in healthcare facilities were produced by a joint working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association in 2006. They advise prompt isolation of infected or colonised patients, screening of patients and staff in contact with such patients, the use of protective clothing, handwashing with an antiseptic detergent, and the use by all patients of an antiseptic detergent for washing and bathing. For eradication of nasal carriage they recommend mupirocin nasal ointment. Eradication at other colonised sites is more difficult: antiseptic detergents may be used for skin and hair washing. A systematic review[8] has concluded that there is insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA.

Although ciprofloxacin may be used the emergence of widespread resistance in meticillin-sensitive and meticillin-resistant *Staph. aureus* limits its usefulness (see p.246). Combination therapy may be helpful. Rifampicin is highly active against MRSA, but it must always be used with another drug to prevent the emergence of resistance. Combinations of rifampicin with gentamicin, vancomycin, co-trimoxazole, fusidic acid, quinolones, or novobiocin have been tried. Newer antibacterials such as daptomycin, linezolid, or quinupristin/dalfopristin may be effective and may assume increasing importance.

Isolated reports from around the world of MRSA with intermediate resistance or reduced susceptibility to vancomycin initially emerged in the late 1990s,[9-11] and in response the CDC produced interim[12] and later[13] guidelines for preventing the spread of vancomycin-intermediate *Staph. aureus* (VISA) and vancomycin-resistant *Staph. aureus* (VRSA).

Staphylococcal vaccines have been used for the prophylaxis and treatment of staphylococcal infections.

For the management of staphylococcal infections in general, see under the specific disease headings.

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Surgical infection

Infection is an important cause of postoperative surgical morbidity and mortality and *antimicrobial prophylaxis* is one of several strategies used to reduce the risk of infection. The value of infection prophylaxis is well established in certain types of surgery, especially abdominal surgery and where prostheses are implanted, although recommendations as to the choice of antibacterial and the route, timing, and duration of treatment may vary. Surgical wounds are classified as following clean, clean-contaminated (potentially contaminated), contaminated, and dirty operations. Clean operations exclude those involving the gastrointestinal, genital, urinary, or respiratory tracts. Clean-contaminated operations include those where the gastrointestinal, genital, urinary, or respiratory tracts are opened, but without unusual contamination. Contaminated operations include those where there is acute inflammation or spillage from a hollow viscus. Dirty operations include those where there is pus, gangrene, or perforated viscera. In addition, surgery to repair compound fractures and lacerations due to animal or human bites is considered dirty. The use of antibacterials for the management of contaminated or dirty surgery is considered to be therapeutic rather than prophylactic[1,2] and should continue for several days postoperatively.[3]

Guidelines for the *treatment* of intra-abdominal infections have been produced in the USA by the Surgical Infection Society[4] and by the Infectious Disease Society of America.[5]

ANTIMICROBIAL PROPHYLAXIS. Strictly speaking the term 'prophylaxis' should be confined to elective procedures with no evidence of sepsis at the time of operation. If possible any pre-existing infections should be treated before admission for surgery. For prophylaxis it is customary to give antibacterials systemically as a single pre-operative dose whereas more prolonged use is necessary when they are given therapeutically. Antimicrobial prophylaxis is used in clean-contaminated operations and in clean operations that involve the insertion of prosthetic materials or when an infection, however unlikely, would be catastrophic.[1]

Contaminating organisms. The choice of prophylactic antibacterial will be influenced by the likely contaminants for a particular surgical procedure. The most frequently isolated pathogens include *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and *Escherichia coli*. Infections with antimicrobial-resistant pathogens including *Candida albicans* and meticillin-resistant *Staph. aureus* (MRSA) are increasing in some hospitals.[1] The most common source of infection is the endogenous flora of the patient's skin, mucous membranes, or viscera. Thus, aerobic Gram-positive organisms (for example staphylococci) are common infecting organisms when the source is the skin and mucous membranes, while infections with enterococci, Gram-negative aerobes (for example *E. coli*), and anaerobic bacteria (for example *Bacteroides fragilis*) can arise from the gastrointestinal tract.

Route of administration. Systemic dosage, usually by the intravenous route, is generally preferred. The chosen antibacterial is usually given as a single dose intravenously just before operation at the induction of anaesthesia. The pharmacokinetic properties should be such that adequate serum concentrations are maintained throughout the surgical procedure.[1] Additional doses may be necessary when surgery is prolonged, when there is massive blood loss, or when an antibacterial with a short half-life is used. More controversial routes have included topical or intra-incisional use and peritoneal lavage. Giving non-absorbable antibacterials orally to suppress the intestinal flora was traditional before large bowel surgery, and neomycin with erythromycin is still given for this purpose in the USA. For reference to selective digestive tract decontamination (SDD), see under Intensive Care, p.175. Other dosage forms include bone cement and chains of beads for implantation, both containing gentamicin and used prophylactically in orthopaedic surgery,[6,7] and topical and sometimes subconjunctival antibacterials for ophthalmic surgery.[3]

Choice of antibacterial. The most commonly used antibacterials are cephalosporins, aminoglycosides, and metronidazole. In the UK, the *BNF* recommends that gentamicin or cefuroxime is given before abdominal surgery; before colorectal surgery or hysterectomy metronidazole is given in addition, or amoxicillin with clavulanic acid may be given alone; before endoscopic retrograde cholangiopancreatography gentamicin or ciprofloxacin may be given; before transrectal prostate biopsy ciprofloxacin or gentamicin is given with metronidazole, although for transurethral resection ciprofloxacin, gentamicin, or cefuroxime may be given alone; and before joint replacements, including the hip and knee, cefuroxime or flucloxacillin is recommended. In the USA, cefazolin is commonly given before surgery, except that involving the lower gastrointestinal tract, for which cefoxitin or cefotetan are used to provide activity against anaerobes.[1,2,8] Alternatively, cefazolin may be given with metronidazole in colorectal surgery.[3] The choice of prophylaxis for patients unable to tolerate cephalosporins is less well established. Aztreonam has been suggested as an alternative to cefazolin with the addition of clindamycin or metronidazole if activity against anaerobes is necessary.[1] However, the use of aztreonam plus metronidazole may provide inadequate activity against Gram-positive cocci.[8] Another suggested alternative to cefazolin is vancomycin,[3] but the routine use of vancomycin should be avoided because of the risk of inducing resistance.[9] Vancomycin may be indicated for high-risk procedures if MRSA infections are prevalent,[9] and combination with aztreonam or an aminoglycoside has been suggested to provide activity against Gram-negative organisms.[8] If vancomycin is used for prophylaxis, no more than two doses should be given.[9] Other alternatives for colorectal procedures include an aminoglycoside with either clindamycin or metronidazole.[8]

The necessity for antibacterial prophylaxis in minimally invasive procedures such as laparoscopy and endoscopy is often not clear.[10] US guidelines[1,8] suggest that standard prophylaxis should be used pending further evidence.

Certain categories of patient continue to be at long-term risk of infection after surgery and include splenectomised patients who have impaired immunity and are at risk of pneumococcal and other infections (see under Spleen Disorders, p.194). Opinion is changing as to whether patients at special risk of endocarditis require prophylaxis before dental and surgical procedures (see Endocarditis, p.168). Some have advocated prophylaxis in patients with joint prostheses undergoing dental treatment,[11] but a working party for the British Society for Antimicrobial Chemotherapy considers such prophylaxis to be unjustified.[12]

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Syphilis

See under Sexually Transmitted Diseases, p.192.

Tetanus

Clostridium tetani is a Gram-positive anaerobic spore-forming bacillus present in soil and faeces. The toxin it produces, tetanospasmin, causes tetanus or lockjaw, with uncontrolled muscle spasm.[1] Tetanus can be prevented by active immunisation with tetanus vaccine or passive immunisation with tetanus immunoglobulin. Nowadays it occurs mostly in developing countries and especially in neonates. In developed countries immunity may be relatively low in the elderly.

In addition to the control of muscle spasm with drugs such as diazepam (see p.1901 for the symptomatic treatment of tetanus), treatment includes the use of tetanus immunoglobulin to neutralise any circulating toxin and the use of antibacterials. Benzylpenicillin has traditionally been used, with a tetracycline or metronidazole as possible alternatives, but some now consider metronidazole to be preferable to benzylpenicillin.[2-4]

In rural developing countries where tetanus is common and active immunisation little practised, pre-operative metronidazole or penicillin might be used for patients undergoing emergency operations who have not been immunised against tetanus; the duration of antibacterial cover depends on the contamination risk.[5]

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Tonsillitis

See under Pharyngitis, p.185.

Toxic shock syndrome

Toxic shock syndrome is an acute febrile illness associated with multisystem failure and caused by a toxin, usually toxic shock syndrome toxin-1 (TSST-1), produced by *Staphylococcus aureus*.[1,2] Bacteraemia has been reported to be absent in most cases.[3] In the early 1980s, toxic shock syndrome was reported predominantly in menstruating women using high-absorbency tampons, but it is now appreciated that foci of staphylococcal infection such as surgical wounds, burns, abscesses, and sinuses are often responsible;[1,2] mortality may be higher in non-menstrual than menstrual cases.[4] Treatment of the acute phase requires prevention of further production or absorption of toxin by local measures such as removal of tampons or packing, wound debridement, or drainage of abscesses; elimination of the toxin-producing bacteria by antistaphylococcal antibacterials given intravenously initially; fluid replacement; and sometimes corticosteroids.[1,2] Drotrecogin alfa has also been tried.[5] Continuing antibacterial treatment for 10 days during the convalescent phase to reduce the risk of recurrence has been recommended.[1] The use of prophylactic antibacterial therapy has been suggested in burns patients,[6] but this is controversial.

Group A beta-haemolytic streptococci (*Streptococcus pyogenes*) have been associated with a similar toxin-related syndrome.[7,8] Benzylpenicillin is the treatment of choice[9] but, since it may be difficult to exclude staphylococcal toxic shock syndrome, an antistaphylococcal drug such as flucloxacillin should also be given.[9] Clinical improvement has been reported with intravenous normal immunoglobulins.[10,11]

Toxic shock syndromes may be associated with necrotising fasciitis (see p.180).

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Trachoma

Trachoma[1] results from chronic eye infection with certain *Chlamydia trachomatis* serotypes and is endemic in parts of Africa, the Middle East, and India where it is an important cause of blindness. It is not a sexually transmitted disease, but is associated with poverty, poor sanitation, and poor personal hygiene. The reservoir is chronic eye infection and transmission may be via fingers, fomites, and flies. Inclusion conjunctivitis in infants (see under Neonatal Conjunctivitis, p.180) and in adults is associated with sexually transmitted genital *C. trachomatis* infection and can progress to trachoma when there is persistent or recurrent eye infection.

Guidelines for trachoma control published by WHO in 1981 outlined topical or oral treatment with a tetracycline or alternatively with erythromycin or a sulfonamide.[2] However, topical chemotherapy for trachoma must be intensive and prolonged, 6 weeks being the minimum recommended duration for continuous intensive treatment with tetracycline 1% ophthalmic ointment. With less frequent applications, the duration of treatment must be prolonged and may need to be extended to months or even years. A single oral dose of azithromycin produces a similar rate of resolution to conventional treatment with topical tetracycline for 6 weeks.[3] Mass treatment of African village communities with oral azithromycin once weekly for 3 weeks has resulted in a lower incidence of trachoma at follow-up after one year than a standard course of topical tetracycline.[4,5] Azithromycin has therefore been recommended[6] as the treatment of choice for trachoma, with combined oral and topical treatment with either a tetracycline or a sulfonamide as an alternative.

The SAFE strategy (surgery, antibacterials, facial cleanliness, and environmental improvements) is the cornerstone of efforts by WHO[7] and the International Trachoma Initiative.[8] The aim is to eliminate trachoma by 2020. Tetracycline is still, however, the antibacterial treatment of choice in those countries that are not yet part of the initiative program and for patients in whom azithromycin is contra-indicated.

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Trench fever

Trench fever is a louse-borne bacterial infection so named because of its prevalence among soldiers in the First World War. It is caused by *Bartonella quintana* (formerly *Rochalimaea quintana*) which was until recently classified as a rickettsia. *B. quintana* and *B. henselae* have also been implicated in bacillary angiomatosis, especially in immunocompromised patients, and *B. henselae* is considered to be a cause of cat scratch disease (p.166).

Reports from France[1,2] and the USA[3] of *B. quintana* bacteraemia, sometimes with endocarditis, in the urban poor prompted the suggestion that trench fever has returned.[4,5] Cases of trench fever in Marseilles have been reported[2] and might herald an increasing incidence as a result of migration from endemic areas, poverty, and louse infestation.

Treatment of trench fever has usually been with a tetracycline such as doxycycline or with a macrolide such as erythromycin. Other antibacterials, for example ceftriaxone, were also used in cases of bacteraemia,[3] but there was limited follow-up and clear recommendations could not be given. A review[6] has suggested that gentamicin plus doxycycline should be used in patients with trench fever or chronic *B. quintana* bacteraemia. Similarly, optimal therapy for *Bartonella* endocarditis has not been identified; however, it has been suggested that the usual treatment for blood culture-negative endocarditis (a penicillin plus an aminoglycoside) should be effective.[7] Again, treatment with gentamicin plus doxycycline has also been suggested.[6]

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Tuberculosis

Tuberculosis[1] refers to disease caused primarily by *Mycobacterium tuberculosis* and occasionally by *M. bovis* or *M. africanum*. Infection results from inhalation of infected droplet nuclei. Primary infection is usually asymptomatic and in more than 95% of immune competent individuals is controlled by acquired (cell mediated) immunity. The immune response, however, is unable to eradicate the tubercle bacilli, and these bacilli may give rise to progressive primary infection (if disease occurs within 2 years of initial infection) or post-primary (reactivated) tuberculosis (if disease occurs years to decades after initial infection). Young children and immunocompromised patients are at increased risk of developing active disease. The most common manifestation of tuberculosis is pulmonary disease, although almost any organ may be affected. Patients usually present with cough, fever, night sweats, and weight loss.

During recent years the incidence of tuberculosis in many countries has increased in association with the increasing prevalence of HIV infection. Supervised rifampicin-based (short-course) therapy, using fixed-dose combination tablets, is recommended by WHO to improve cure rates and reduce the emergence of drug-resistant tuberculosis.[2] WHO applies the term **DOTS** (Directly Observed Therapy – Short Course) to its tuberculosis control strategy, which includes standards for diagnosis, supervised therapy, ensuring secure drug supplies, and regular evaluation of the tuberculosis control programme. The feasibility of implantable dosage forms has also been investigated.

• **First-line treatment.** Multidrug treatment for 6 to 8 months is required to cure tuberculosis, reduce the risk of relapse, and prevent the emergence of drug-resistant disease. Treatment regimens recommend an initial intensive phase of 2 to 3 months that is aimed at achieving rapid sputum conversion followed by a continuation phase of 4 to 6 months to eliminate residual bacilli and prevent relapse. The choice of regimen depends on local patterns of drug resistance and the availability of drugs, and are embodied in national and regional treatment protocols in many countries including those in Europe,[3] the UK,[4] and USA.[5] WHO recommended treatment regimens[6,7] are based on disease severity and history of previous tuberculosis treatment.

- **New cases** of pulmonary or extrapulmonary tuberculosis are treated with an initial phase consisting of rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for 2 months, followed by a continuation phase with rifampicin and isoniazid for 4 months, such a regimen being described as: RHZE2/RH4. Rifampicin may be substituted with ethambutol in the continuation phase to reduce costs, although this regimen needs to be given for a total of 8 months and is associated with an increased risk of relapse (RHZE2/HE6). In tuberculous meningitis ethambutol should be replaced with streptomycin (S) (RHZS2) and a 6- to 10-month continuation phase with rifampicin and isoniazid is often recommended. Ethambutol may be omitted from the intensive phase in patients with less severe forms of extrapulmonary tuberculosis or with limited non-cavitary smear-negative pulmonary tuberculosis if drug resistance has been excluded or the risk of drug resistance is deemed to be low (RHZ2/RH4). Cure rates of greater than 90% are typically achieved in patients infected with drug-susceptible organisms who adhere to therapy.
- In patients **previously treated** for tuberculosis, the initial treatment phase is rifampicin, isoniazid, pyrazinamide, and ethambutol given for 3 months with streptomycin being added for the first 2 months. The continuation phase includes 3 drugs (rifampicin, isoniazid, and ethambutol) and is extended to 5 months (RHZES2/RHZE1/RHE5). Because it is relatively cheap thioacetazone has been used in some countries with limited resources but its use is strongly discouraged because of its weak antimycobacterial activity and associated risk of fatal skin toxicity, particularly in HIV patients. All first-line drugs can be given intermittently (at double doses 3 times each week) as an alternative to daily use. Patients who remain smear-positive at the end of supervised short-course chemotherapy may have drug-resistant tuberculosis and treatment usually requires the introduction of second-line drugs (see below).

First-line drugs such as isoniazid, rifampicin, and particularly pyrazinamide may cause severe and possibly fatal drug-induced hepatitis. Further details covering hepatotoxicity and special precautions for use in patients with liver disorders are given in the respective drug monographs—see, Isoniazid p.289; Rifampicin p.326; and Pyrazinamide p.320. UK[4] and US[5] guidelines recommend stopping all potentially hepatotoxic drugs if serum transaminases rise to more than 5 times the upper limit of normal or 3 times in the presence of symptoms of hepatitis or elevated bilirubin. Cautious sequential re-introduction of the same drugs (with or without pyrazinamide) after resolution of the biochemical abnormalities is often possible.[4-6] Patients in whom therapy is interrupted may be given streptomycin, ethambutol, and/or a fluoroquinolone until hepatotoxicity has resolved.

Management of drug-resistant disease. The incidence of drug resistance amongst *M. tuberculosis* strains has increased over recent years typically in countries with poor tuberculosis control programmes.[8,9] Isoniazid and streptomycin resistance are the most prevalent. Multidrug-resistant tuberculosis (caused by strains resistant to both isoniazid and rifampicin) requires a combination of first- and second-line drugs for at least 18 to 24 months (see below).[4,5,8] Drug-resistant tuberculosis is a reflection of poor tuberculosis management, control, and unreliable drug supply; it is difficult to treat, and not infrequently fatal, particularly in HIV-infected patients. Whereas the WHO DOTS programme may limit the development of multidrug-resistant tuberculosis, different strategies are required in areas where multidrug resistance is already established. These have been formulated by the WHO in the **DOTS-plus** strategy for countries with well functioning tuberculosis control programmes.[10]

Patients with multidrug-resistant tuberculosis and those who relapse after completing the WHO standard treatment regimens should receive a DOTS-plus regimen, which includes second-line antituberculous drugs. Drugs used in the treatment of drug-resistant tuberculosis are generally less effective and more toxic than standard therapy and need to be taken daily. They include the aminoglycosides (amikacin, capreomycin, and kanamycin), aminosalicylates, cycloserine, ethionamide, fluoroquinolones (ciprofloxacin, levofloxacin, and ofloxacin), protionamide, and terizidone. The DOTS-plus regimen should consist of at least 3 or 4 oral drugs plus an injectable aminoglycoside, to which the patient has not been exposed and which do not share cross-resistance with drugs given previously. These drugs should be given under direct observation for at least 6 months, and followed by a continuation phase of 12 to 18 months with at least 3 drugs.[5,8] Cross-resistance between rifampicin and rifabutin is common and rifabutin is therefore not recommended as a second-line drug. Cross-resistance among aminoglycosides is uncommon, while cross-resistance is variable within the fluoroquinolones. Cross-resistance is complete between ethionamide and protionamide, and between cycloserine and terizidone. Where available, *M. tuberculosis* resistance testing should be performed to guide the choice of therapy. Single drugs should never be added to a failing regimen.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis that is resistant to isoniazid and rifampicin and also resistant to fluoroquinolones and at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin).[11] XDR-TB can develop when the second-line drugs are misused or mismanaged and by early 2006 cases were being reported from every region in the world.[12] A report from the KwaZulu-Natal province of South Africa highlighted the risk for rapid death in HIV-infected persons with extensively-drug resistant tuberculosis.[13] In this local case series, all but one of 53 patients died, and where the date of death could be confirmed the median survival was 16 days from the time of diagnosis.

• **Children and infants** can be treated with regimens similar to adults but with appropriate dose adjustments for age or body-weight.[4-7] While ethambutol is not usually given to young children because of the perceived difficulty in detecting ocular toxicity (see p.274), a literature review[14] on its use in children found almost no ocular toxicity at daily doses of 15 to 30 mg/kg and it was considered safe in children of all ages.

• **Pregnancy, breast feeding, and the neonate.** Tuberculosis, and especially drug-resistant tuberculosis, during pregnancy poses a serious risk to the mother, fetus, and neonate if not detected early and treated properly.[15] The WHO recommends that pregnant women with tuberculosis are treated similarly to non-pregnant patients (RHZE2/RH4 or RHZ2/RH4). Fluoroquinolones, aminoglycosides, ethionamide, and protionamide are best avoided. Liver enzymes and symptoms of drug-induced hepatitis should be monitored.[4,5,15] Most antituberculous drugs may be used during breast feeding. Drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. In the UK it is recommended that neonates of mothers with tuberculosis should receive isoniazid for 3 months[16] after which time the infant should be re-evaluated. BCG vaccination is recommended by WHO and in the UK when isoniazid is stopped.[16]

• **Co-infection with HIV** increases the risk of patients developing both pulmonary and extrapulmonary tuberculosis, and mortality is higher than in HIV-negative patients in the absence of antiretroviral therapy. HIV patients (including children) with tuberculosis have a similar response to short-course chemotherapy as HIV-negative tuberculosis patients and most can be treated with the standard 6-month regimen (RHZE2/RH4).[4,17-20] In children and patients whose clinical or bacteriological response is slow, treatment should be extended to a total of 9 months.[18-20] Children with extrapulmonary tuberculosis involving the bones or CNS, or in those with miliary disease, should be given treatment for a minimum of 12 months.[18] Treatment failures in HIV-infected patients have been associated with reduced drug concentrations due to malabsorption of antimycobacterials.[21]

Most clinicians would defer starting antiretroviral therapy in HIV co-infected patients with CD4+ counts greater than 200/microlitre until the tuberculosis treatment has been completed. Patients with more severe immunodeficiency benefit from co-administration of HIV and tuberculosis therapy. In these patients, tuberculosis therapy is started first, and HIV treatment added once the patient tolerates tuberculosis therapy, or after 2 months when tuberculosis therapy is simplified. The use of rifamycin-based regimens to treat tuberculosis is recommended as response rates are better compared to non-rifamycin-based regimens. However, drug interactions between rifamycins and antiretrovirals complicate the co-administration of HIV and tuberculosis treatment,[19,20,22] and certain combinations may require dose adjustment or be contra-indicated (for details of the interactions of rifampicin and antiretrovirals see p.327 and for those with rifabutin see p.324). It is important to note that guideline recommendations are based on pharmacokinetic studies, often performed in healthy subjects, rather than on studies of treatment outcome in patients.

Directly observed therapy improves outcome and is recommended wherever possible. Due to the risk for acquired rifamycin resistance highly intermittent (once or twice weekly) tuberculosis regimens should not be used for co-infected patients with CD4+ cell counts less than 100 cells/microlitre.[18-20,22] All HIV and tuberculosis co-infected patients should receive co-trimoxazole if CD4+ counts are below 200 cells/microlitre.[23] Thioacetazone should not be used in HIV-positive patients because of the potential for severe skin toxicity. Paradoxical worsening of tuberculosis symptoms is common in HIV-infected patients who start antiretroviral therapy[24] and incidences of up to 35% have been noted.[22]

• **Adjunctive therapy.** The inflammatory response to tuberculosis can cause considerable tissue damage and adjunctive steroid therapy may be used to counter this. Corticosteroids are of little benefit in uncomplicated pulmonary tuberculosis. However, a study[25] found adjunctive dexamethasone improved survival, but probably not severe disability, in adolescents and adults with tuberculous meningitis. Systematic reviews of tuberculous pleurisy[26] and pericarditis,[27] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions. WHO[17] suggests that corticosteroids may be useful adjuvants to antituberculous therapy for the management of tuberculous meningitis, pericarditis, pleural effusion, laryngitis, tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuberculosis, and massive lymph node enlargement in both HIV-positive and -negative patients. Corticosteroids may also be useful for hypersensitivity reactions to antituberculosis drugs. For further details on the possible role of corticosteroids as an adjunct to antituberculous therapy, see p.1514.

Studies have suggested that injection of suspensions of killed *Mycobacterium vaccae* improved immune responsiveness in patients with pulmonary tuberculosis, although a systematic review[28] concluded that *M. vaccae* immunotherapy was of no benefit.

• **Prevention.** Studies have found that *BCG vaccine* offers protection against serious forms of tuberculosis in children, such as miliary and meningeal tuberculosis, but has variable efficacy against pulmonary tuberculosis in adults. In high prevalence areas, vaccination is recommended for children at birth, except for children with HIV infection. For further information on BCG vaccine see, p.2205.

Tuberculosis skin testing may identify persons with *latent M. tuberculosis* infection. Treatment of tuberculosis skin test-positive persons (also referred to as preventative therapy or chemoprophylaxis) reduces the risk of developing (reactivation) tuberculosis. Treatment is beneficial in HIV-infected patients, contacts of active cases, persons who have recently become tuberculosis skin test positive, and persons at high risk of disease. Chemoprophylaxis is not recommended routinely in developing countries where the priority is to detect and treat patients with active tuberculosis.[17,29] Latent tuberculosis has been treated with isoniazid or rifampicin given alone, or with rifampicin given with either isoniazid or pyrazinamide. Daily isoniazid for 6 to 12 months reduces the risk of active tuberculosis by 60 to 90%[1,30] and in HIV-infected, tuberculosis skin test-positive persons isoniazid for 6 months has also been shown to provide short-term protection against tuberculosis.[31] However, the combination of rifampicin and pyrazinamide has resulted in severe and fatal liver damage in HIV-negative persons and is no longer recommended for tuberculosis prophylaxis.[30,32,33] The American Thoracic Society and the CDC,[30,32] and NICE[16] have issued detailed recommendations for treatment of latent tuberculosis infection. Briefly, UK recommendations for HIV-negative adults and children over 2 years old are for either isoniazid alone for 6 months or isoniazid with rifampicin for 3 months; isoniazid alone for 6 months should be given to all HIV-positive patients. In the USA either isoniazid alone for 9 months (or 6 months in HIV-negative patients) or rifampicin alone for 4 months is recommended.

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Tularaemia

Tularaemia is caused by the Gram-negative bacillus *Francisella tularensis*, an organism that primarily affects rodents and rabbits but may be transmitted to man, usually by handling infected animals or carcasses, or by the bites of insect vectors. It may take several forms, the most common of which is the ulceroglandular form, characterised by rash and ulceration at the site of inoculation accompanied by fever and lymphadenopathy; other forms include the typhoidal and pneumonic forms, which have a higher mortality rate. There has been some concern about its potential use as a biological weapon.[1,2]

Streptomycin is still considered the antibacterial of choice in severe disease, although gentamicin is an alternative.[1,2] A tetracycline or chloramphenicol may be given orally; clinical relapses are more frequent than with the aminoglycosides,[1,2] although relapsed disease will respond to a further course. Ciprofloxacin has also been used successfully.[1] Some patients have also responded to high-dose intravenous erythromycin.[3]

A tularaemia vaccine is available in some countries for active immunisation against the disease.

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Typhoid and paratyphoid fever

Typhoid and paratyphoid fever are systemic infections caused respectively by *Salmonella typhi* and *S. paratyphi* A, B, or C, Gram-negative bacteria belonging to the Enterobacteriaceae family. They are sometimes termed collectively 'enteric fever' but, although initial infection is intestinal, dissemination in the blood leads to more widespread systemic effects. Typhoid and paratyphoid are endemic in many countries and, in most, typhoid is more common. Most cases occurring in the UK are contracted abroad.

Treatment of typhoid fever has traditionally been with chloramphenicol or alternatively amoxicillin, ampicillin, or co-trimoxazole.[1] However, there has been a spread of strains of *S. typhi* resistant to chloramphenicol, ampicillin, amoxicillin, trimethoprim, and co-trimoxazole,[2,3] especially in the Indian subcontinent, in the Middle East, and in South and South-East Asia. Current recommendations therefore emphasise the use of a fluoroquinolone such as ciprofloxacin or ofloxacin for initial treatment of typhoid fever.[3,4] In strains that remain sensitive, chloramphenicol, amoxicillin, or co-trimoxazole are alternatives, while in multidrug-resistant strains a third-generation cephalosporin such as cefixime, cefotaxime, or ceftriaxone may be given. The latter are also an alternative where fluoroquinolone resistance exists;[3,4] this is an increasing problem, particularly in Asia, but most fluoroquinolone-resistant strains seen in the UK retain their sensitivity to cephalosporins, and to azithromycin, which is another alternative.[5] Combination regimens have been investigated,[4] but a study in patients infected with strains showing both multidrug resistance and reduced susceptibility to fluoroquinolones found that azithromycin alone was preferable to azithromycin plus ofloxacin.[6] Interestingly, there is some evidence that as fluoroquinolone resistance spreads, sensitivity to some of the older drugs used to treat the disease, such as chloramphenicol, may be returning.[7,8]

Although fluoroquinolones are not generally indicated in children because of potential toxicity, WHO considers that their benefits in typhoid fever outweigh any putative risk.[3] Azithromycin may also be given.[3] In pregnancy a beta-lactam such as ampicillin or one of the cephalosporins may be preferable,[3] although there are reports of the successful use of fluoroquinolones. WHO also suggests that although there is no evidence to suggest harm, azithromycin should not be used in pregnant or nursing women if alternatives are available.[3]

Patients who develop mental changes should be evaluated for meningitis; if typhoid meningitis is suspected, high-dose intravenous dexamethasone should be given in addition to antibacterial treatment.[3]

On recovery, typhoid patients may continue to excrete *S. typhi* in the faeces or urine for several weeks. Unlike these convalescent carriers, some 1 to 5% of patients become chronic carriers[3] who may excrete *S. typhi* for years without any symptoms; eradication is difficult and prolonged treatment is necessary. An increased risk of biliary-tract and bile-related cancers has been associated with chronic carriage of *S. typhi*, and the importance of eradication has been emphasised.[9]

Typhoid vaccines are used for the prevention of typhoid fever.

Paratyphoid fever is less common and generally milder than typhoid fever. Treatment is similar.

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2. Rowe B, *et al.* Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clin Infect Dis* 1997; **24** (suppl 1): S106–S109.
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Typhus

Rickettsial infections or fevers of the typhus group are transmitted to man by various insect vectors. Louse-borne or epidemic typhus, due to *Rickettsia prowazekii*, and flea-borne or murine typhus, due to the closely related *R. typhi* (*R. mooseri*), have occurred worldwide. Scrub typhus is due to *Orientia tsutsugamushi* (*R. tsutsugamushi*), transmitted by mites, and occurs mainly in Asia, Australia, and the Pacific Islands.

A tetracycline, often doxycycline, or chloramphenicol is the treatment of choice for these infections although strains of *O. tsutsugamushi* resistant to doxycycline and chloramphenicol have been reported in Thailand.[1,2] Ciprofloxacin may be an effective alternative,[3] and rifampicin has been shown to be more effective against scrub typhus than doxycycline.[4] Azithromycin is also effective.[5] Prophylaxis for scrub typhus with doxycycline has shown promise when started before exposure to infection.[6]

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Urethritis

Urethritis or urethral inflammation can result from infectious or noninfectious conditions. Infectious urethritis is a sexually transmitted disease seen most frequently in men. The most common causes are *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (termed nongonococcal urethritis or non-specific urethritis). Other organisms implicated have included *Mycoplasma genitalium* and *Ureaplasma urealyticum*. Gonococcal and chlamydial infections frequently occur together and if a specific clinical diagnosis cannot be made treatment for both infections should be given together otherwise postgonococcal urethritis due to *C. trachomatis* may follow the cure of gonorrhoea. For the treatment of gonococcal urethritis see Gonorrhoea (p.191). For general management of chlamydial infections see p.166.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of urethritis are as follows:

- **WHO:** for chlamydial urethritis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternative regimens for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p.191)
- **UK:** for nongonococcal urethritis:
  - a single oral dose of azithromycin 1 g, *or*
  - oral doxycycline 100 mg twice daily for 7 days

  alternative regimens are:
  - oral erythromycin 500 mg twice daily for 14 days
  - oral ofloxacin 400 mg daily in one single or two divided doses for 7 days

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - oral azithromycin 500 mg to start then 250 mg daily for 4 days *plus* oral metronidazole 400 mg twice daily for 5 days
  - oral erythromycin 500 mg four times daily for 21 days *plus* oral metronidazole 400 mg twice daily for 5 days
  - oral moxifloxacin 400 mg once daily for 10 days
- **USA:** nongonococcal urethritis:
  - as for the UK

  alternative regimens for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - a single oral dose of either metronidazole 2 g or tinidazole 2 g *plus* oral azithromycin 1 g (if it was not used in the initial treatment regimen)

Sexual partners of patients with urethritis should be tested and treated.[2,3]

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Urinary-tract infections

Infections of the urinary tract are especially common in women. They are frequently due to enteric bacteria, in particular *Escherichia coli*, although a common cause in young women is *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus. Other urinary pathogens include *Staph. epidermidis*, enterococci, and *Pseudomonas* spp. An arbitrary definition of urinary-tract infection has been significant bacteriuria with 10^5 or more colony-forming units/mL of a midstream urine specimen; some also consider lower counts to be indicative of infection. Most urinary-tract infections are isolated uncomplicated infections of the lower urinary tract. Recurrent infections may be due to relapse, or more often, re-infection, and are more serious. Patients with complicated urinary-tract infections associated with urinary-tract abnormalities or diseases such as diabetes mellitus may be at risk of kidney damage.

Infections of the lower urinary tract in *women* generally present as cystitis (inflammation of the bladder) and symptoms include dysuria, frequency, and urgency together with pyuria and significant bacteriuria; the urethral syndrome is similar, but there is no significant bacteriuria. In the upper urinary tract, acute pyelonephritis may occur as a complication of cystitis or, more rarely, may result from septicaemia. Asymptomatic bacteriuria may progress to acute pyelonephritis in *pregnant women* and should therefore be treated.

Urinary-tract infections in *men* are less common and are often associated with abnormalities of the genito-urinary tract such as prostatic hyperplasia. Acute bacterial prostatitis is usually caused by organisms similar to those responsible for cystitis in women. Chronic bacterial prostatitis is difficult to treat; the antibacterials used must be able to penetrate into the prostatic fluid. For other genito-urinary infections in men, see under Epididymitis, p.170, and under Urethritis, above.

In preschool *children*, especially girls, asymptomatic bacteriuria together with vesicoureteric reflux can result in renal scarring and should be treated; the use of prophylactic antibacterials is complex and controversial. Long-term follow-up of girls who have had asymptomatic bacteriuria suggests that new kidney damage does not occur after 4 years of age, but highlights the importance of diagnosis and treatment in younger children.

The significance of asymptomatic bacteriuria in *old age* is disputed, but most consider treatment to be unnecessary.

Infections associated with *indwelling bladder catheters* occur in both men and women and probably account for the majority of hospital-acquired urinary-tract infections.

Treatment. Antibacterials used to treat urinary-tract infections need to be excreted in adequate concentrations in the urine. For *acute uncomplicated infections* oral amoxicillin, ampicillin, co-trimoxazole, nalidixic acid, nitrofurantoin, or trimethoprim (preferred to co-trimoxazole in the UK) have been given, although the choice will depend on local patterns of bacterial resistance; *E. coli* resistant to ampicillin and amoxicillin is widespread. Alternatives when resistance is prevalent include amoxicillin with clavulanic acid, oral cephalosporins, fluoroquinolones, or fosfomycin. In pregnant women, nitrofurantoin or a beta lactam can be used. Standard treatment schedules have been for 5 to 7 days; 3-day or single-dose regimens can also be effective and may be preferred in women. Single-dose treatment may be associated with reduced efficacy compared with 3-day regimens. Urinary alkalinising agents such as potassium citrate and sodium citrate have been given by mouth to relieve the pain of cystitis caused by lower urinary-tract infections. Recurrent infections may require long-term low-dose antibacterial prophylaxis.

Acute pyelonephritis may require broad-spectrum parenteral treatment initially with, for example, aztreonam, ceftazidime, cefuroxime, ciprofloxacin, or gentamicin.

Chronic bacterial prostatitis may require treatment for several weeks with trimethoprim, erythromycin, or a fluoroquinolone.

Catheter-related bladder infections may sometimes respond to localised treatment with bladder washouts containing chlorhexidine.

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Whipple's disease

Whipple's disease is a rare chronic systemic condition associated with infection with *Tropheryma whippelii*.[1-4] It was once considered to be a disease predominantly involving the small intestine and resulting in malabsorption, but may affect virtually all organs. There is probably CNS involvement in all patients with Whipple's disease, although it may only be evident in 10 to 20%. Before the use of antibacterial therapy the disease was invariably fatal. The treatment generally recommended is either benzylpenicillin (sometimes given as procaine benzylpenicillin) and streptomycin, or ceftriaxone, parenterally for two weeks, followed by co-trimoxazole orally for at least one year.[2,3,5,6] Such long-term treatment with co-trimoxazole, a drug that crosses the blood-brain barrier, is advisable because of the relatively high frequency and seriousness of CNS relapse. These relapses respond less well to antibacterial treatment; chloramphenicol has been used in those not responding to the above regimen and a patient with CNS relapse improved on ceftriaxone given intravenously.[7] Further alternatives may be a tetracycline[8] or cefixime.[6] A patient intolerant of co-trimoxazole was given phenoxymethylpenicillin and probenecid after the initial 14-day course of benzylpenicillin and streptomycin.[9] There has also been a report of benefit in a penicillin-allergic patient treated with erythromycin.[10] A combination of doxycycline with hydroxychloroquine may be tried in patients without neurological involvement.[3]

1. Relman DA, *et al.* Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992; **327:** 293–301.
2. Marth T, Raoult D. Whipple's disease. *Lancet* 2003; **361:** 239–46.
3. Fenollar F, *et al.* Whipple's disease. *N Engl J Med* 2007; **356:** 55–66.
4. Schneider T, *et al.* Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis* 2008; **8:** 179–90.
5. Singer R. Diagnosis and treatment of Whipple's disease. *Drugs* 1998; **55:** 699–704.
6. Maiwald M, Relman DA. Whipple's disease and Tropheryma whippelii: secrets slowly revealed. *Clin Infect Dis* 2001; **32:** 457–63.
7. Adler CH, Galetta SL. Oculo-facial-skeletal myorhythmia in Whipple disease: treatment with ceftriaxone. *Ann Intern Med* 1990; **112**: 467–9.
8. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy.* 18th ed. New Rochelle NY: The Medical Letter, 2008: 72.
9. Rickman LS, *et al.* Brief report: uveitis caused by Tropheryma whippelii (Whipple's bacillus). *N Engl J Med* 1995; **332:** 363–6.
10. Bowles KM, *et al.* A 35-year-old with swollen knees who had recurrent fever and pericarditis, then diarrhoea before getting better. *Lancet* 1996; **348:** 1356.

Yaws

See under Syphilis, p.192.

Yersinia enteritis

See p.174.

Acediasulfone Sodium *(rINN)*

Acediasulfona sódica; Acédiasulfone Sodique; Acediasulfonnatrium; Acediasulfonum Natricum; Asediasulfoninatrium; Sodium Diaphenylsulphonacetate. *N-p*-Sulphanilylphenylglycine sodium.

Ацедиасульфон Натрий

$C_{14}H_{13}N_2NaO_4S$ = 328.3.

CAS — 127-60-6.

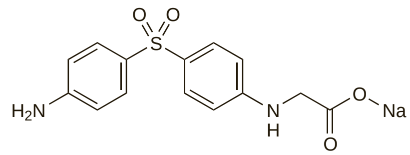

Profile

Acediasulfone sodium is reported to have antibacterial properties and is an ingredient of preparations used topically in the treatment of local infections of the ear.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Ciloprin cum Anaesthetico†; ***Fin.:*** Ciloprin cum Anaesthetico†; ***India:*** Otogesic; ***Switz.:*** Ciloprin ca†.

Alatrofloxacin Mesilate *(rINNM)*

Alatrofloxacin Mesylate *(USAN)*; Alatrofloxacine, Mésilate d'; Alatrofloxacini Mesilas; CP-116517-27; Mesilato de alatrofloxacino. 7-{(1*R*,5*S*,6*s*)-6-[(*S*)-2-((*S*)-2-Aminopropionamido)propionamido]-3-azabicyclo[3.1.0]hex-3-yl}-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulphonate.

Алатрофлоксацина Мезилат

$C_{26}H_{25}F_3N_6O_5,CH_3SO_3H$ = 654.6.

CAS — 157182-32-6 (alatrofloxacin); 157605-25-9 (alatrofloxacin mesilate).

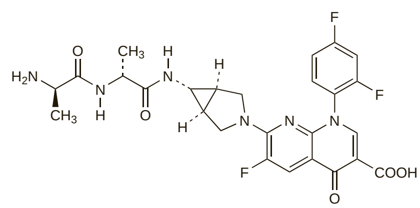

(alatrofloxacin)

Profile

Alatrofloxacin is a prodrug of the fluoroquinolone antibacterial trovafloxacin (p.357) and has been used intravenously as the mesilate in the treatment of susceptible infections.

Alatrofloxacin and trovafloxacin preparations were withdrawn worldwide after reports of unpredictable severe hepatic adverse effects, including some fatalities.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Trovan†; ***USA:*** Trovan†.

Amikacin *(BAN, rINN)*

Amicacina; Amikacina; Amikacinas; Amikacine; Amikacinum; Amikacyna; Amikasiini. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-N^1-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxystreptamine.

Амикацин

$C_{22}H_{43}N_5O_{13}$ = 585.6.

CAS — 37517-28-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

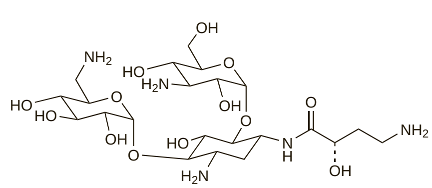

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Amikacin). An antimicrobial substance obtained from kanamycin A. A white or almost white powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 9.5 to 11.5.

USP 31 (Amikacin). A white crystalline powder. Sparingly soluble in water. pH of a 1% solution in water is between 9.5 and 11.5. Store in airtight containers.

Amikacin Sulfate *(USAN, rINNM)*

Amikacin Sulphate *(BANM)*; Amikacin-disulfát; Amikacine, sulfate d'; Amikacini Disulfas; Amikacini sulfas; Amikacino sulfatas; Amikacinsulfat; Amikacin-szulfát; Amikacyny siarczan; Amikasiinisulfaatti; Amikasin Sülfat; BB-K8; Sulfato de amikacina.

Амикацина Сульфат

$C_{22}H_{43}N_5O_{13},2H_2SO_4$ = 781.8.

CAS — 39831-55-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Amikacin Sulphate). A white or almost white powder. It loses not more than 13.0% of its weight on drying. Freely soluble in water; practically insoluble in alcohol and in acetone. The pH of a 1% solution in water is between 2.0 and 4.0. Store in airtight containers.

USP 31 (Amikacin Sulfate). Amikacin sulfate having a molar ratio of amikacin to H_2SO_4 of 1:2 contains the equivalent of not less than 674 micrograms and not more than 786 micrograms of amikacin per mg, calculated on the dried basis. Amikacin sulfate having a molar ratio of amikacin to H_2SO_4 of 1:1.8 contains the equivalent of not less than 691 micrograms and not more than 806 micrograms of amikacin per mg, calculated on the dried basis.

A white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 2.0 and 4.0 (1:2 salt) and 6.0 to 7.3 (1:1.8 salt). Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including amikacin, with beta lactams, see under Gentamicin Sulfate, p.282. Amikacin is also reported to be incompatible with various other drugs. However, reports are contradictory in many cases, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Solutions may darken from colourless to pale yellow but this does not indicate a loss of potency.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Peak plasma concentrations of amikacin greater than 30 to 35 micrograms/mL or trough concentrations greater than 5 to 10 micrograms/mL should be avoided. Amikacin affects auditory (cochlear) function to a greater extent than gentamicin.

Effects on the eyes. A report of retinal damage after intravitreal injection of amikacin.[1]

1. Jackson TL, Williamson TH. Amikacin retinal toxicity. *Br J Ophthalmol* 1999; **83:** 1199–1200.

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. Amikacin is active against a similar range of organisms although it is also reported to have some activity against *Nocardia asteroides*, *Mycobacterium tuberculosis*, and some atypical mycobacterial strains. Amikacin is not degraded by many of the common enzymes often responsible for acquired aminoglycoside resistance. In consequence, cross-resistance with gentamicin and other aminoglycosides is infrequent and amikacin may be effective against strains resistant to other aminoglycosides. However, resistant strains of Gram-negative bacteria and staphylococci have been reported, and it is generally reserved for infections resistant to other aminoglycosides, although reports differ as to the extent and speed of the development of amikacin resistance where it has been widely used.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

On intramuscular injection, peak plasma-amikacin concentrations of about 20 micrograms/mL are achieved 1 hour after a 500-mg dose, reducing to about

2 micrograms/mL 10 hours after injection. A plasma concentration of 38 micrograms/mL has been reported after the intravenous infusion of 500 mg over 30 minutes, reducing to 18 micrograms/mL 1 hour later. Amikacin has been detected in body tissues and fluids after injection; it crosses the placenta but does not readily penetrate into the CSF, although substantial penetration of the blood-brain barrier has been reported in children with meningitis.

A plasma half-life of about 2 to 3 hours has been reported in patients with normal renal function. Most of a dose is excreted by glomerular filtration in the urine within 24 hours.

◊ References.

1. Vanhaeverbeek M, *et al.* Pharmacokinetics of once-daily amikacin in elderly patients. *J Antimicrob Chemother* 1993; **31:** 185–7.
2. Gaillard J-L, *et al.* Cerebrospinal fluid penetration of amikacin in children with community-acquired bacterial meningitis. *Antimicrob Agents Chemother* 1995; **39:** 253–5.
3. Bressolle F, *et al.* Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; **40:** 1682–9.
4. Canis F, *et al.* Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients. *J Antimicrob Chemother* 1997; **39:** 431–3.
5. Tod M, *et al.* Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother* 1998; **42:** 849–56.
6. Tréluyer JM, *et al.* Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother* 2002; **46:** 1381–7.

Uses and Administration

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin and is used similarly to gentamicin (p.284) in the treatment of severe Gram-negative and other infections. It is given as the sulfate, and is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. Amikacin has also been given with antimycobacterials in the treatment of non-tuberculous mycobacterial infections (p.181). As with gentamicin, amikacin may be used with penicillins and with cephalosporins; the injections should be given at separate sites.

Doses of amikacin sulfate are expressed in terms of amikacin base; 1.3 g of amikacin sulfate is equivalent to about 1 g of amikacin. Adults and children may be given 15 mg/kg daily in equally divided doses every 8 or 12 hours by intramuscular injection. In life-threatening infections, the dose may be increased in adults up to a maximum of 500 mg every 8 hours. A dose of 7.5 mg/kg daily in two divided doses (equivalent to 250 mg twice daily in adults) may be given for the treatment of uncomplicated urinary-tract infections. The same doses may be given by slow intravenous injection over 2 to 3 minutes, or by intravenous infusion. In adults, 500 mg in 100 to 200 mL of diluent has been infused over 30 to 60 minutes; proportionately less fluid should be given to children.

Neonates may be given 10 mg/kg as a loading dose, followed by 15 mg/kg daily in two divided doses. If given by intravenous infusion, an infusion period of 1 to 2 hours is recommended. It has been suggested that doses may need to be adjusted in preterm neonates.

Treatment should preferably not continue for longer than 7 to 10 days, and the total dose given to adults should not exceed 15 g. Peak plasma concentrations greater than 30 to 35 micrograms/mL or trough plasma concentrations greater than 5 to 10 micrograms/mL should be avoided. Dosage should be adjusted in all patients according to plasma-amikacin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284. As with some other aminoglycosides, once-daily dosage has been used successfully with amikacin without increasing toxicity, but local guidelines should be consulted (see also Once-daily Dosage, p.285).

A 0.25% solution has been instilled into body cavities in adults.

A liposomal formulation of amikacin is under investigation.

Preparations

BP 2008: Amikacin Injection;
USP 31: Amikacin Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Biklin; Greini; Riklinak; ***Austral.:*** Amikin; ***Austria:*** Biklin; ***Belg.:*** Amukin; ***Braz.:*** Amicacil†; Amicalin†; Amicilon; Aminocina†; Bactomicin†; Klebicil; Novamin; ***Canad.:*** Amikin†; ***Cz.:*** Amikin; Amikozit†; Miacin†; ***Fin.:*** Biklin; ***Fr.:*** Amiklin†; ***Ger.:*** Biklin; ***Gr.:*** Amicagel†; Amicasil; Amikan; Biorisan; Briklin; Cinegel; Durocin; Farcyclin; Flexelite; Fromentyl; Kancin-Gap; Lanomycin; Lifermycin; Likacin; Micalpha; Orlobin; Remikin; Rovericlin; Selaxa; Uzix; ***Hong Kong:*** Amikin; Apalin; Selemycin†; ***Hung.:*** Amikin; Likacin; ***India:*** Amcin; Amicin; Amicip; Mikacin; ***Indon.:*** Alostil; Amikin; Mikasin; ***Irl.:*** Amikin; ***Israel:*** Amikin†; ***Ital.:*** Amicasil; Amik; Amikan; BB-K8; Chemacin; Dramigel; Likacin; Lukadin; Mediamik; Migracin; Mikan; Mikavir; Nekacin; Pierami; ***Malaysia:*** Amikin†; Selemycin†; ***Mex.:*** Agnicin; Akacin; Amicina; Amikafur; Amikalem; Amikasons; Amikavi; Amikayect; Amikin; Amiyec; AMK; Baxi-K†; Beramikin; Biclin; Biokacin; Gamikal; Kafran; Kana; Karmikin; Libamic; Lisobac; Mikazul; Oprad; Plokim; Sermicina; Yectamid; ***Neth.:*** Amukin; ***NZ:*** Amikin; ***Philipp.:*** Amicacide; Amikin; Cidacid; Cinmik; Kamin; Kormakin; Nica; ***Pol.:*** Amikin; Biodacyna; ***Port.:*** Amic; Biclin; Kamina; ***Rus.:*** Amikozit (Амикозит); Selemycin (Селемицин); ***S.Afr.:*** Amikin; Kacinth-A; ***Singapore:*** Amikin; ***Spain:*** Biclin; Kanbine; ***Swed.:*** Biklin; ***Switz.:*** Amikin; ***Thai.:*** Akacin; Akicin; Amikasol†; Amikin; Anbikin; Siamik; Tipkin; Tybikin; ***Turk.:*** Amiketem; Amiklin; Amikozit; Mikasin; ***UAE:*** Mikacin; ***UK:*** Amikin; ***USA:*** Amikin; ***Venez.:*** Amikavax; Amikayect†; Behkacin; Biklin; Likacin.

Aminosalicylic Acid

Acidum Aminosalicylicum; Aminosalicílico, ácido; 4-Aminosalicylic Acid; Aminosalicylsyra; Aminosalisyylihappo; Aminosalylum; Para-aminosalicylic Acid; PAS; Pasalicylum. 4-Amino-2-hydroxybenzoic acid.

Аминосалициловая Кислота

$C_7H_7NO_3$ = 153.1.
CAS — 65-49-6.
ATC — J04AA01.
ATC Vet — QJ04AA01.

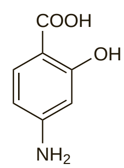

NOTE. Distinguish from 5-aminosalicylic acid (Mesalazine, p.1745).

Pharmacopoeias. In *US.*

USP 31 (Aminosalicylic Acid). A white or practically white, bulky powder that darkens on exposure to light and air; it is odourless or has a slight acetous odour. Slightly soluble in water and in ether; soluble in alcohol; practically insoluble in benzene. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a saturated solution in water is between 3.0 to 3.7. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Calcium Aminosalicylate

Aminosalicilato cálcico; Aminosalicylate calcium; Aminosalylcalcium; Aminosalylkalcium; Aminosalyylikalsium; Calcii Aminosalicylas; Calcii Para-aminosalicylas; Calcium PAS; Kalciumaminosalicylat; Kalsiumaminosalisylaatti. Calcium 4-amino-2-hydroxybenzoate trihydrate.

Аминосалицилат Кальция

$(C_7H_6NO_3)_2Ca,3H_2O$ = 398.4.
CAS — 133-15-3 (anhydrous calcium aminosalicylate).
ATC — J04AA03.
ATC Vet — QJ04AA03.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Sodium Aminosalicylate

Aminosalicilato sódico; Aminosalicylan sodný dihydrát; Aminosalicylate Sodium; Aminosalylnatrium; Monosodium 4-Aminosalicylate Dihydrate; Natrii Aminosalicylas; Natrii aminosalicylas dihydricus; Natrii Paraaminosalicylas; Natrii Para-aminosalicylas; Natrio aminosalicilatas dihidratas; Natriumaminosalicylat; Natriumaminosalicylatdihydrat; Natriumaminosalisylaatti; Natriumaminosalisylaattidihydraatti; Pasalicylum Solubile; Sodium (aminosalicylate de) dihydraté; Sodium Para-aminosalicylate; Sodium PAS; Sodu aminosalicylan. Sodium 4-amino-2-hydroxybenzoate dihydrate.

Аминосалицилат Натрия

$C_7H_6NNaO_3,2H_2O$ = 211.1.
CAS — 133-10-8 (anhydrous sodium aminosalicylate); 6018-19-5 (sodium aminosalicylate dihydrate).
ATC — J04AA02.
ATC Vet — QJ04AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Sodium Aminosalicylate Dihydrate). A slightly hygroscopic, white or almost white, crystalline powder, or white or almost white crystals. Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 31 (Aminosalicylate Sodium). A white to cream-coloured, practically odourless crystalline powder. Soluble 1 in 2 of water; sparingly soluble in alcohol; very slightly soluble in chloroform and in ether. Its solutions decompose slowly and darken in colour. Prepare solutions within 24 hours of use. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a 2% solution in water is between 6.5 and 8.5. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Stability. Aqueous solutions of aminosalicylates are unstable and should be freshly prepared.

Solutions of sodium aminosalicylate in sorbitol or syrup degraded more quickly to *m*-aminophenol than those in glycerol or propylene glycol.[1] Colour developed in all solutions but was not found to be an accurate indicator of decomposition of sodium aminosalicylate as it reflected only oxidation of *m*-aminophenol.

1. Blake MI, *et al.* Effect of vehicle on the stability of sodium aminosalicylate in liquid dosage forms. *Am J Hosp Pharm* 1973; **30:** 441–3.

Adverse Effects and Treatment

Aminosalicylic acid and its salts may cause the adverse effects of salicylates (see Aspirin, p.20).

Gastrointestinal effects are common and include nausea, vomiting, and diarrhoea; they may be reduced by giving doses with food or with an antacid but occasionally may be severe enough that therapy has to be withdrawn. Alteration of gastrointestinal function may lead to malabsorption of vitamin B_{12}, folate, and lipids.

Hypersensitivity reactions have been reported in 5 to 10% of adults, usually during the first few weeks of treatment, and include fever, skin rashes; less commonly, arthralgia, lymphadenopathy, and hepatosplenomegaly may occur and, rarely, a syndrome resembling infectious mononucleosis. Other adverse effects which have been attributed to a hypersensitivity reaction to aminosalicylate include jaundice and encephalitis. Blood disorders reported include haemolytic anaemia in patients with G6PD deficiency, agranulocytosis, eosinophilia, leucopenia, and thrombocytopenia. Psychosis may occasionally occur. Prolonged treatment may induce goitre and hypothyroidism. Crystalluria may occur.

Effects on the liver. Drug-induced hepatitis occurred in 0.32% of 7492 patients receiving antituberculous drugs; aminosalicylic acid was the most common cause.[1]

1. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; **44:** 1–16.

Precautions

Aminosalicylic acid and its salts should be used with great care in patients with hepatic or renal impairment and in patients with gastric ulcer. They should be given with caution to patients with G6PD deficiency. The sodium salt should be used with caution in patients with heart failure.

Aminosalicylates interfere with tests for glycosuria using copper reagents and for urobilinogen using Ehrlich's reagent.

Breast feeding. Small amounts of aminosalicylic acid are present in breast milk. A maximum concentration of 1.1 microgram/mL has been reported in the breast milk of a lactating woman 3 hours after a 4-g dose of aminosalicylic acid.[1]

1. Holdiness MR. Antituberculosis drugs and breast feeding. *Arch Intern Med* 1984; **144:** 1888.

Pregnancy. The use of aminosalicylic acid or its salts is not recommended in pregnant patients due to gastrointestinal intolerance.[1] In addition it has been noted that, a study published in 1964 suggested that first-trimester exposure may be associated with congenital defects although other studies had not found similar effects.[2]

1. Snider D. Pregnancy and tuberculosis. *Chest* 1984; **86:** 10S–13S.
2. Briggs GG, *et al. Drugs in pregnancy and lactation.* 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2005: 59.

Interactions

The adverse effects of aminosalicylates and salicylates may be additive. Probenecid may also increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate. The activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine.

Antimicrobial Action

Aminosalicylic acid is bacteriostatic and is active against *M. tuberculosis*. Other mycobacteria are usually resistant. It has a relatively weak action compared with other antituberculous drugs. Resistance develops quickly if aminosalicylic acid is used alone.

◊ References.

1. Rengarajan J, *et al.* The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. *Mol Microbiol* 2004; **53:** 275–82.

Pharmacokinetics

When given orally, aminosalicylic acid and its salts are readily absorbed, and peak plasma concentrations occur after about 1 to 4 hours.

Aminosalicylate diffuses widely through body tissues and fluids, although diffusion into the CSF occurs only if the meninges are inflamed. About 15% of the sodium salt, and 50 to 70% of the acid, is bound to plasma proteins.

Aminosalicylate is metabolised in the intestine and liver primarily by acetylation. Urinary excretion is rapid, and 80% or more of a dose is excreted within 24 hours; 50% or more of the dose is excreted as the acetylated metabolite. The half-life of aminosalicylic acid is about 1 hour.

Aminosalicylate is distributed into breast milk (see under Precautions, above, for more details).

Uses and Administration

Aminosalicylic acid and its salts are second-line antimycobacterials given orally in the treatment of multidrug-resistant **tuberculosis** (p.196). They should always be given with other antituberculous drugs.

Aminosalicylic acid may be given as the acid or as the sodium salt. Sodium aminosalicylate 1.38 g is equivalent to about 1 g of aminosalicylic acid. However, a usual daily oral dose is 12 g in 3 divided doses and has been recommended for products containing the acid as well as for those containing the sodium salt.

For details of doses in infants, children, and adolescents, see below.

Aminosalicylate sodium is also given rectally in the treatment of **ulcerative colitis** in a usual dose of 2 g once daily.

Attempts have been made in formulation to overcome the bulk and exceedingly unpleasant taste of the aminosalicylates. The salts appear to be better tolerated than the free acid and solutions in iced water prepared immediately before use may be less unpleasant to take.

Administration. A small study suggested that giving aminosalicylic acid in a dose of 4 g twice daily produced adequate serum concentrations (well in excess of 1 microgram/mL, a typical MIC against *Mycobacterium tuberculosis*) for up to 12 hours after each dose.[1] The drug was taken with an acidic beverage such as fruit juice to prevent early release in the stomach. A single 4-g dose was not sufficient to maintain serum concentrations for the full 24-hour dosage interval. The authors had subsequently changed their practice to use a twice-daily regimen for aminosalicylic acid in patients with multidrug-resistant tuberculosis.

1. Peloquin CA, *et al*. Once-daily and twice-daily dosing of p-aminosalicylic acid granules. *Am J Respir Crit Care Med* 1999; **159:** 932–4.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) and WHO suggest an oral dose of para-aminosalicylic acid 200 to 300 mg/kg 2 to 4 times daily, to a maximum dose of 10 g daily.

Administration in renal impairment. It has been recommended that aminosalicylic acid should be avoided in patients with renal impairment.[1] An increase in plasma clearance of aminosalicylic acid (attributed to increased hepatic metabolism) has been noted in patients with renal impairment, hence attempting to give aminosalicylate in reduced doses to such patients may lead to subtherapeutic serum concentrations.[2]

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (first of three parts). *N Engl J Med* 1977; **296:** 663–70.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.

Inflammatory bowel disease. Together with corticosteroids, derivatives of 5-aminosalicylic acid are one of the mainstays of the treatment of inflammatory bowel disease (p.1697). However, aminosalicylic acid (4-aminosalicylic acid) has also been investigated, and beneficial results have been reported with both enemas[1-4] and oral dose forms[5] in ulcerative colitis. Three patients who developed acute pancreatitis while taking mesalazine (5-aminosalicylic acid) for inflammatory bowel disease, later tolerated treatment with 4-aminosalicylic acid enemas.[6]

1. Campieri M, *et al*. 4-Aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) in topical treatment of ulcerative colitis patients. *Gastroenterology* 1984; **86:** 1039.
2. Ginsberg AL, *et al*. Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 195–9.
3. Sharma MP, Duphare HV. 4-Aminosalicylic acid enemas for ulcerative colitis. *Lancet* 1989; **i:** 450.
4. O'Donnell LJD, *et al*. Double blind, controlled trial of 4-aminosalicylic acid and prednisolone enemas in distal ulcerative colitis. *Gut* 1992; **33:** 947–9.
5. Beeken W, *et al*. Controlled trial of 4-ASA in ulcerative colitis. *Dig Dis Sci* 1997; **42:** 354–8.
6. Daniel F, *et al*. Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis* 2004; **10:** 258–60.

Manganese toxicity. Intravenous aminosalicylic acid, given in a course of 6 g daily for 4 days a week, for fifteen courses, produced significant benefit in a patient with parkinsonism induced by chronic occupational manganese exposure.[1] The patient remained well on prolonged follow-up. Other cases of benefit had been reported in the Chinese literature.

1. Jiang Y-M, *et al*. Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006; **48:** 644–9.

Preparations

USP 31: Aminosalicylate Sodium Tablets; Aminosalicylic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Canad.: Nemasol†; ***Chile:*** Aflogol; ***Cz.:*** Quadrasa†; ***Fr.:*** Quadrasa; ***Ger.:*** Pas-Fatol N; ***Ital.:*** Quadrasa†; Salf-Pas; ***Port.:*** Paramino-Corazida; ***Rus.:*** Pask-Akri (Паск-Акри); ***Switz.:*** Perfusion de PAS†; ***Thai.:*** PAS Sodium; ***Turk.:*** PAS; ***USA:*** Paser.

Multi-ingredient: ***India:*** Inapas.

Amoxicillin *(BAN, rINN)*

Amoksisilin; Amoksisilliini; Amoxicilina; Amoxicilline; Amoxicillinum; Amoxycillin. (6*R*)-6-[α-D-(4-Hydroxyphenyl)glycylamino]penicillanic acid.

Амоксициллин

$C_{16}H_{19}N_3O_5S$ = 365.4.

CAS — 26787-78-0.

ATC — J01CA04.

ATC Vet — QG51AX01; QJ01CA04.

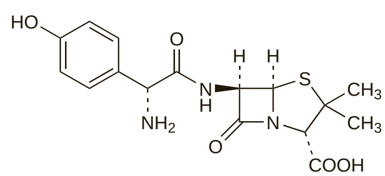

Amoxicillin Sodium *(BANM, USAN, rINNM)*

Amoksicilino natrio druska; Amoksisilin Sodyum; Amoksisilliininatrium; Amoksycylina sodowa; Amoxicilin sodná sůl; Amoxicilina sódica; Amoxicilline sodique; Amoxicillinnatrium; Amoxicillinnátrium; Amoxicillinum natricum; Amoxycillin Sodium; BRL-2333AB-B; Natrii Amoxicillinum.

Натрий Амоксициллин

$C_{16}H_{18}N_3NaO_5S$ = 387.4.

CAS — 34642-77-8.

ATC — J01CA04.

ATC Vet — QJ01CA04.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Amoxicillin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

Amoxicillin Trihydrate *(BANM, rINNM)*

Amoksicilinas trihidratas; Amoksisilin Trihidrat; Amoksisilliinitrihydraatti; Amoksycylina trójwodna; Amoxicilin trihydrát; Amoxicilina trihidrato; Amoxicillin *(USAN)*; Amoxicilline trihydratée; Amoxicillin-trihidrát; Amoxicillintrihydrat; Amoxicillinum trihydricum; Amoxycillin Trihydrate; BRL-2333.

Амоксициллин Тригидрат

$C_{16}H_{19}N_3O_5S,3H_2O$ = 419.4.

CAS — 61336-70-7.

ATC — J01CA04.

ATC Vet — QJ01CA04.

NOTE. Compounded preparations of amoxicillin may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Amoxicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in fatty oils. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 0.2% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Amoxicillin). A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 0.2% solution in water is between 3.5 and 6.0. Store in airtight containers.

Adverse Effects and Precautions

As for Ampicillin, p.204.

The incidence of diarrhoea is less with amoxicillin than ampicillin.

Hepatitis and cholestatic jaundice have been reported with amoxicillin plus clavulanic acid; the clavulanic acid component has been implicated. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Breast feeding. Although amoxicillin is excreted in breast milk in small amounts,[1] the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Kafetzis DA, *et al*. Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/04)

Effects on the liver. Hepatitis and cholestatic jaundice associated with the combination amoxicillin with clavulanic acid (co-amoxiclav) have been reported[1-4] and by 1993 the UK CSM had received 138 reports of hepatobiliary disorders, 3 of which were fatal.[5] It warned that, although usually reversible, the reaction often occurred after stopping therapy with a delay of up to 6 weeks. It appeared that the clavulanic acid was probably responsible. Retrospective analysis of cases reported in Australia[6] and a cohort study in the UK[7] found increasing age and prolonged treatment to be major risk factors for jaundice after co-amoxiclav; male sex is also a risk factor. By 1997 the CSM considered that cholestatic jaundice occurred with a frequency of about 1 in 6000 adult patients and that the risk of acute liver injury was about 6 times greater with co-amoxiclav than with amoxicillin alone. Therefore it recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant strains, and that treatment should not usually exceed 14 days.[8]

1. Stricker BHC, *et al*. Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (Augmentin). *Dig Dis Sci* 1989; **34:** 1576–80.
2. Wong FS, *et al*. Augmentin-induced jaundice. *Med J Aust* 1991; **154:** 698–701.
3. Larrey D, *et al*. Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; **33:** 368–71.
4. Hebbard GS, *et al*. Augmentin-induced jaundice with a fatal outcome. *Med J Aust* 1992; **156:** 285–6.
5. Committee on Safety of Medicines/Medicines Control Agency. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 28/07/08)
6. Thomson JA, *et al*. Risk factors for the development of amoxycillin-clavulanic acid associated jaundice. *Med J Aust* 1995; **162:** 638–40.
7. Rodríguez LAG, *et al*. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996; **156:** 1327–32.
8. Committee on Safety of Medicines/Medicines Control Agency. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Effects on the teeth. A report of tooth discoloration in 3 children associated with the use of amoxicillin with clavulanic acid.[1]

1. Garcia-López M, *et al*. Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics* 2001; **108:** 819–20.

Sodium content. Each g of amoxicillin sodium contains about 2.6 mmol of sodium.

Interactions

As for Ampicillin, p.204.

Antimicrobial Action

As for Ampicillin, p.204.

Amoxicillin has been reported to be more active *in vitro* than ampicillin against *Enterococcus faecalis, Helicobacter pylori,* and *Salmonella* spp., but less active against *Shigella* spp.

Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin. The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor such as clavulanic acid (p.250). As well as reversing resistance to amoxicillin in beta-lactamase-producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included *Bacteroides*, *Legionella*, and *Nocardia* spp., *Haemo-*

philus influenzae, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*). However, *Ps. aeruginosa*, *Serratia marcescens*, and many other Gram-negative bacteria remain resistant. Transferable resistance has been reported in *H. pylori*.

Pharmacokinetics

Amoxicillin is resistant to inactivation by gastric acid. It is more rapidly and more completely absorbed than ampicillin when given orally. Peak plasma-amoxicillin concentrations of about 5 micrograms/mL have been observed 1 to 2 hours after a dose of 250 mg, with detectable amounts present for up to 8 hours. Doubling the dose can double the concentration. The presence of food in the stomach does not appear to diminish the total amount absorbed.

Concentrations of amoxicillin after intramuscular injection are similar to those achieved with oral doses.

About 20% is bound to plasma proteins and plasma half-lives of 1 to 1.5 hours have been reported. The half-life may be prolonged in neonates, the elderly, and patients with renal impairment; in severe renal impairment the half-life may be 7 to 20 hours. Amoxicillin is widely distributed at varying concentrations in body tissues and fluids. It crosses the placenta; small amounts are distributed into breast milk. Little amoxicillin passes into the CSF unless the meninges are inflamed.

Amoxicillin is metabolised to a limited extent to penicilloic acid which is excreted in the urine. About 60% of an oral dose of amoxicillin is excreted unchanged in the urine in 6 hours by glomerular filtration and tubular secretion. Urinary concentrations above 300 micrograms/mL have been reported after a dose of 250 mg. Probenecid reduces renal excretion. Amoxicillin is removed by haemodialysis. High concentrations have been reported in bile; some may be excreted in the faeces.

Amoxicillin with clavulanic acid. The pharmacokinetics of amoxicillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

Uses and Administration

Amoxicillin is the 4-hydroxy analogue of ampicillin (p.205) and is used similarly in susceptible infections. These include actinomycosis, anthrax, biliary-tract infections, bronchitis, endocarditis (particularly for prophylaxis), gastro-enteritis (including salmonella enteritis, but not shigellosis), gonorrhoea, Lyme disease, mouth infections, otitis media, pneumonia, spleen disorders (pneumococcal infection prophylaxis), typhoid and paratyphoid fever, and urinary-tract infections. The beta-lactamase inhibitor clavulanic acid (p.250) widens amoxicillin's antimicrobial spectrum and a combined preparation (co-amoxiclav) can be used when resistance to amoxicillin is prevalent, for example in respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), in the empirical treatment of animal bites, or in melioidosis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Amoxicillin is also given as part of treatment regimens to eradicate *Helicobacter pylori* infection in patients with peptic ulcer disease (p.1702).

Administration and dosage. Amoxicillin is given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of amoxicillin; 1.06 g of amoxicillin sodium and 1.15 g of amoxicillin trihydrate are each equivalent to about 1 g of amoxicillin.

The usual oral dose is 250 to 500 mg every 8 hours, or 500 to 875 mg every 12 hours. Children up to 10 years of age may be given 125 to 250 mg every 8 hours; for those under 40 kg, a dose of 20 to 40 mg/kg daily in divided doses every 8 hours, or 25 to 45 mg/kg daily in divided doses every 12 hours, may be used; in infants less than 3 months old, the maximum dose should be 30 mg/kg daily in divided doses every 12 hours.

Higher oral doses of amoxicillin, either as a single dose or in short courses, are used in some conditions. For example, a dose of 3 g repeated once after 8 hours may be used for dental abscesses. A 3-g dose may be given for uncomplicated acute urinary-tract infections, and repeated once after 10 to 12 hours.

A high-dose regimen of 3 g twice daily may be used in patients with severe or recurrent infections of the respiratory tract. If necessary, children aged 3 to 10 years with otitis media may be given 750 mg twice daily for 2 days. Amoxicillin has also been given as a single dose of 3 g, with probenecid 1 g, in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive.

For the prophylaxis of endocarditis in patients at risk, amoxicillin 2 or 3 g is given about 1 hour before dental procedures.

For the eradication of *H. pylori*, amoxicillin is given with either metronidazole or clarithromycin and a proton pump inhibitor; usual doses of amoxicillin are 0.75 or 1 g twice daily or 500 mg three times daily.

An extended release formulation containing 775 mg of amoxicillin as the trihydrate is available in the USA for the treatment of tonsillitis and pharyngitis due to *Streptococcus pyogenes* in patients aged 12 years or older. It is given orally in a dose of 775 mg daily for 10 days.

Amoxicillin is given by intramuscular or slow intravenous injection in doses of 500 mg every 8 hours. In severe infections, 1 g of amoxicillin may be given every 6 hours by slow intravenous injection over 3 to 4 minutes or by infusion over 30 to 60 minutes. Children up to 10 years of age may be given 50 to 100 mg/kg daily by injection in divided doses.

Doses may need to be reduced in moderate to severe renal impairment (see below).

Amoxicillin with clavulanic acid. Amoxicillin combined with clavulanic acid (co-amoxiclav) is given by mouth in a ratio of amoxicillin (as the trihydrate) 2, 4, 7, or 14 parts to 1 part of clavulanic acid (as the potassium salt), or intravenously in a ratio of 5 parts of amoxicillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses of the combination, calculated on amoxicillin content, are similar to those for amoxicillin used alone.

◊ References.

1. Speller DCE, *et al.*, eds. Clavulanate/β-lactam antibiotics: further experience. *J Antimicrob Chemother* 1989; **24** (suppl B): 1–226.
2. Todd PA, Benfield P. Amoxicillin/clavulanic acid: an update of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1990; **39**: 264–307.
3. Easton J, *et al.* Amoxicillin/clavulanic acid: a review of its use in the management of paediatric patients with acute otitis media. *Drugs* 2003; **63:** 311–40.
4. McCormack PL, Keating GM. Amoxicillin/clavulanic acid 2000mg/125mg extended release (XR): a review of its use in the treatment of respiratory tract infections in adults. *Drugs* 2005; **65:** 121–36.

Administration in renal impairment. Doses of amoxicillin should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: 250 to 500 mg every 12 hours
- CC less than 10 mL/minute: 250 to 500 mg every 24 hours
- haemodialysis patients: 250 to 500 mg every 24 hours and an additional dose both during and after the dialysis session.

Preparations

BP 2008: Amoxicillin Capsules; Amoxicillin Injection; Amoxicillin Oral Suspension; Co-amoxiclav Injection; Co-amoxiclav Tablets;
USP 31: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Amoxicillin Capsules; Amoxicillin for Oral Suspension; Amoxicillin Tablets; Amoxicillin Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Abiotyl†; Almorsan; Amixen; Amox-G; Amoxi; Amoxibiot; Amoxicilina Duo†; Amoxicina; Amoxicler; Amoxidal; Amoxidal Duo; Amoxigrand; Amoxipenil; Amoxipoten; Amoxitenk; Amoxol; Antiamox; Antibiocilina†; Antiobiocilina†; Apracur Biotic†; Ardine†; Atrival†; Biotamoxal; Bioxilina; Clofamox; Darzitil; Dunox; Fabamox; Flemoxon; Fullcilina; Fullcilina Duo†; Grinsil; Grinsil Duo; Mixcilin; Moxitral; Nobactam; Optamox; Oximar; Plamox; Telmox; Trifamox; Trifamox Duo; Xalotina†; ***Austral.:*** Alphamox; Amohexal; Amoxil; Bgramin; Cilamox; Fisamox; Ibiamox; Maxamox; Moxacin; ***Austria:*** Amoxal; Amoxihexal; Amoxilan; Amoxistad; Antibiostad; Clamoxyl; Eramox†; Ospamox; Supramox; ***Belg.:*** Amoxi†; Amoxypen; Bactimed; Clamoxyl; Docamoxici; Flemoxin; Hiconcil; Moxaline†; Moxitop; Novabritine; ***Braz.:*** Amoflux†; Amox; Amoxadene; Amoxi-Ped; Amoxibron; Amoxicap†; Amoxicom†; Amoxidil; Amoxifar; Amoxil; Amoximed; Amoxina†; Amoxipen†; Amoxitan; Amplal†; Amplamox†; Ariproxina†; Bimoxin†; Camoxin†; Duzimicin†; Farmoxil; Flemoxon†; Hiconcil; Hincomox; Ibamoxil†; Licilon; Lifamox†; Moxiplus; Nemoxil†; Neo Moxicilin; Novacil†; Novocilin; Novoxil†; Ocylin; Penvicilin†; Pharmox; Polibac†; Polimoxil; Probenil; Prodoxil; Respicilin†; Trimox; Ultramox†; Uni Amox; Velamox; ***Canad.:*** Apo-Amoxi; Lin-Amox†; Novamoxin; Nu-Amoxi; ***Chile:*** Abiolex; Amobiotic; Amoval; Amoval Duo; Amoxipenil; Moxilanic; Optamox; ***Cz.:*** Amoclen; Amogal†; Amoxihexal; Apo-Amoxi†; Duomox; Gonoform†; Grunamox†; InfectoMox†; Ospamox; ***Denm.:*** Flemoxin; Imacillin; Imadrax; ***Fin.:*** Amorion; Amoxin; Clamox†; Flemoxin†; Penalta†; ***Fr.:*** A-Gram; Amodex; Bactox; Bristamox; Clamoxyl; Flemoxine†; Gramidil†; Hiconcil; ***Ger.:*** Amagesan; Amc-Puren†; Amoxi; Amoxi-Diolan; Amoxi-Hefa; Amoxi-Puren†; Amoxi-Tablinen; Amoxi-Wolff; Amoxibeta; Amoxidoc; Amoxihexal; Amoxillat†; Amoximerck; Amoxypen; Clamoxyl†; espa-moxin†; Flui-Amoxicillin; InfectoMox; Jutamox; Phamoxi†; Sigamopen†; ***Gr.:*** Amospes†; Amoxil; Aproxal; Flemoxin; Ospamox; Paradroxil†; Stevencillin; Triodanin†; ***Hong Kong:*** Amolin; Amoxa†; Amoxapen; Apo-Amoxi; Aroxin; Betamox; Edamox; Hamoxillin; Moxilen; Moxlin; Ospamox; Promox; Ranoxyl; Reichamox; Unimox; ***Hung.:*** Clonamox; Duomox; Humamoxin†; Ospamox; ***India:*** Amoxil; Amoxivan; Aristomox; Biomoxil; Damoxy†; Flemoxin; Genmox; Hipen; Imox; Loxyn; Mokcan; Mox; Moxycarb; Novamox; Ronemox†; Symoxyl; ***Indon.:*** Abdimox; Aclam; Amobiotic; Amosine; Amoxil; Amoxillin; Amoxsan; Arcamox; Bellacid; Bintamox; Bioxyllin; Corsamox; Danoxilin; Dexymox; Erphamoxy; Ethimox; Farmoxyl; Ikamoxyl; Intermoxil; Kalmoxillin; Kimoxil; Lapimox; Leomoxyl; Medimox; Medocyl; Mestamox; Mexylin; Mokbios; Moxlin; Moxtid; Nufamox; Opimox; Ospamox; Penmox; Primoxil; Pritamox; Robamox; Scannoxyl; Silamox; Solpenox; Supramox; Topcillin; Vibramox; Wiamox; Widecillin; Xiltrop; ***Irl.:*** Amoxil; Clonamox; Galenamox†; Geramox; Oramox; Pinamox; ***Israel:*** Amoxi; Hiconcil†; Moxypen; Moxyvit; ***Ital.:*** Alfamox; Amocrin†; Amoflux; Amosol; Amox; Amoxillin; Amoxina; Bradimox; Dodemox†; Erremox†; Genimox†; Hydramox; Ibiamox†; Isimoxin†; Majorpen†; Mopen; Moxiren; Neo-Ampiplus; Neotetranase; Oralmox; Pamocil; Progemox†; Sievert; Simoxil†; Simplamox†; Sintopen; Velamox; Zimox; ***Jpn:*** Pasetocin; ***Malaysia:*** Beamoxy; Moxacil†; Moxilen; Moxipen†; Ospamox; Setmoxil†; ***Mex.:*** Acimox; Acroxil; Ameclina; Amicil; Amobay; Amoxifur; Amoxil; Amoxinovag; Amoxisol; Amoxivet; Ampliron; Amsaxilina; AMX†; Ardine†; Armoxin; Betabiot; Bimoxan; Biovicam; Brenoxil; Dimopen; Doxamil; Examolin; Flemoxon; Gimalxina; Grunicina; Hidramox; Limoxin; Lorexil M; Lumox; Micro Mox; Mocimed; Moxiclina; Moxlin; Penamox; Penticlox; Polymox; Prodomix; Servamox; Servamox-F; Solciclina; Vandix; Xalyn-Or; Xiprocan†; ***Neth.:*** Amoxi; Amoxilag; Clamoxyl; Flemoxin; ***Norw.:*** Amoxillin; Imacillin; ***NZ:*** Alpha-Amoxi; Amoxil; Apo-Amoxi; Flemoxin; Ibiamox; Ospamox; ***Philipp.:*** Amelox; Amoxil; Amusa; Bactigent; Bradoxil; Cartrimox; Cilamox; Cilfam; Clearamox; Daisamox; Eleomox; Essenmox; Gexcil; Globamox; Globapen; Himox; Kramollex; Lewixin; Littmox; Maelenoxyl; Medimoxil; Medvox; Megamox; Montramox; Moxillin; Moxiped; Neomox; Novamox; Pediamox; Penbiosyn; Promox; Roddexil; Sumoxil; Syncloxil; Telsimox; Teramoxyl; Termox; Trexil; Valmox; Vastamox; Vaxman; Westfimox; Yugoxil; Zerrsox; Zymoxyl; ***Pol.:*** Amotaks; Apo-Amoxi; Duomox; Grunamox†; Hiconcil; Novamox; Ospamox; ***Port.:*** Amplamox; Bodisan†; Cipamox; Clamoxyl; Flemoxin; Moxadent; Moxipen†; Oraminax; Ospamox; Penamox†; ***Rus.:*** Amosin (Амосин); Flemoxin (Флемоксин); Hiconcil (Хиконцил); Ospamox (Оспамокс); ***S.Afr.:*** A-Lennon; Acucil; Amocillin; Amoxil; Amoxyfizz; Betamox; C-Mox; Ipcamox; Maxcil; Moxan; Moxypen; Penmox†; Promoxil; Ranmoxy; Spectramox; Xeracil; Zoxil; ***Singapore:*** Amoxa†; Amoxapen; Amoxicap; Amoxigran; Amoxil; Apo-Amoxi; Aroxin; Moxilen; Moxipen; Ospamox; Unimox; ***Spain:*** Actimoxi†; Agerpen; Amitron; Amoflamisan; Amoxaren; Amoxi Gobens; Amoxibacter; Amoximedical†; Apamox; Ardine; Blenox; Bolchipen†; Borbalan; Britamox; Brondix; Clamoxyl; Co Amoxin; Dobriciclin; Edoxil†; Eupen; Flubiotic NF; Hosboral; Inexbron†; Morgenxil†; Reloxyl†; Remisan; Salvapen; Tolodina†; ***Swed.:*** Amimox; Imacillin; ***Switz.:*** amoxi-basan†; Amoxi-Cophar†; Amoxi-Mepha; Amoximex; Antiotic†; Azilline; Clamoxyl; Escamox; Flemoxin†; Penimox†; Spectroxyl; Supramox†; ***Thai.:*** Acticillin†; Amacin; Amox; Amoxa; Amoxcillin; Amoxi; Amoxil; Amoxy; Amoxylin; Asiamox; Coamox†; Ibiamox; Kamoxin; Kenya-Mox†; Manmox; Meixil; Milamox; Moxapen; Moxcil; Moxcin; Moxilcap†; Moxilin; Moximed; Moxipan†; Moxitab; Pondnoxcill; Pulmoxyl; Rancil; Ranoxyl; Samox; Samoxin; Servamox; Sia-Mox; Sil-A-Mox†; TVMox; Unimox; ***Turk.:*** Alfoxil; Amoksilav; Amoksilin; Amoksina; Amosin; Atoksilin; Demoksil; Largopen; Moksilin; Remoxil; Topramoxin; ***UAE:*** Julphamox; ***UK:*** Amix; Amoram; Amoxident; Amoxil; Galenamox; Rimoxallin; ***USA:*** Amoxil; DisperMox; Moxatag; Trimox; ***Venez.:*** Amitrexyl; Amofar; Amoxal; Amoxiduo; Amoxiga; Amoxilan; Amoxipen†; Amoxival; Amylin; Bactamox†; Fibramox†; Flemoxon†; Ofamix†; Ospamox; Sentapen; Strimox; Sumopen; Trimoxal.

Multi-ingredient: ***Arg.:*** Acemuk Biotic; Aclav; Albesine Biotic; Amixen Clavulanico; Amixen Plus; Amoclav; Amox-G Bronquial; Amoxi Plus; Amoxi Respiratorio†; Amoxidal Respiratorio; Amoxidal Respiratorio Duo; Amoxigrand Bronquial; Amoxigrand Compuesto; Amoxipenil Bronquial; Amoxitenk Plus; Amoxitenk Respiratorio†; Aseptobron Respiratorio; Bi Moxal; Bi Moxal Duo; Bioclavid; Bioxilina Plus; Clavulox; Clavulox Duo; Cloximar Duo; Darzitil Plus; Darzitil SB; Desinflam Biotic†; Dibional; Fluimucil Biotic†; Fullcilina Plus†; Glifapen; Grinsil Clavulanico; Grinsil Respiratorio; Heliklar†; Klonalmox; Lertus Biotic†; Muco Dosodos Biotic; No-Tos Biotic; Nobactam Bronquial; Oximar Respiratorio; Rodinac Biotic; Trexirol NF†; Trifamox Bronquial; Trifamox Bronquial Duo; Trifamox IBL; ***Austral.:*** Augmentin; Ausclav†; Clamohexal; Clamoxyl; Clavulin; Curam; Klacid HP 7; Losec Hp 7; Nexium Hp; Pylorid-KA; Somac-MA; ***Austria:*** Amoclan; Amoxicillin comp; AmoxiClavulan; Amoxicomp; Amoxiplus; Amoxistad plus; Augmentin; Benclav; Benomox; Betamoclav; Clavamox; Clavex; Clavolek; Clavoplus; Clavulanex; CombAmox; Curam; Helicocin; Helipac; Lanoclav; Lekamoxiclav; Oxyclav; Xiclav; ***Belg.:*** Amoclane; Augmentin; Clavucid; Co-Amoxi; Co-Amoxilan†; Docamoclaf; ***Braz.:*** Anzopac†; Augmentin; Betaclav; Bronco-Amoxil†; Bronco-Polimoxil; Clav-Air†; Clavoxil†; Clavulin; Erradic; H-Bacter; Helicocid Triplice†; Helicopac; Heliklar; Novamox; Omepramix; Policlavumoxil; Pylorikit; Pyloripac; Pyloritrat; Sigma Clav; Sulbamox; Trifamox; ***Canad.:*** Apo-Amoxi Clav; Clavulin; Hp-Pac; Losec 1-2-3 A; Novo-Clavamoxin; ratio-Aclavulanate; ***Chile:*** Ambilan; Ambilan Bid; Amolex; Augmentin; Augmentin Bid; Clavinex; Clavinex Duo; Clavoxilina Bid; Sulbamox; ***Cz.:*** Amoksiklav; Augmentin; Augmentin-Duo; Betaklav; Curam; Enhancin; Forcid; Klamoxin†; Megamox; ***Denm.:*** Bioclavid; Spektramox; ***Fin.:*** Amoxin Comp; Augmentin; Bioclavid; Clapharin Comp; Clavurion; Clavuxal; Forcid; Helipak A; Helipak K; Losec Helira†; Spektramox†; ***Fr.:*** Augmentin; Ciblor; ***Ger.:*** Abiclav; Amoclav; Amoxclav; Amoxi-Clavulan; Amoxi-saar plus; Amoxicillin comp; Amoxiclav; Amoxidura Plus; Amoxillat-Clav†; Amuclan†; Augmentan; Flanamox; ZacPac; ***Gr.:*** Augmentin; Bioclavid; Forcid; Frolicin; Fugentin; Moxiclav; Tenervan; ***Hong Kong:*** Amoksiklav; Augmentin; Clamovid; Curam; Fleming; Moxiclav; Quali-Mentin; ***Hung.:*** Aktil; Amoclan†; Amoclav; Augmentin; Augmentin-Duo; Augmentin-Extra; Clavumox†; Co-Amoxi; Curam; Enhancin; Forcid; ***India:*** ABClox; Amclo†; Augmentin; Bicidal Plus; Biomoxil-LB; Boostim; Bromolin; Carbomox; Helipac; Hipenox; Imox-Clo; Imox-Clo LB; LMX; Moxycarb-DT†; Novaclav; Novaclox; Novaclox LB; Novamox AX; Novamox LB; Nuclav; Rapiclav†; Respimox; Suprimox; Symbiotik; Symoxyl-LB; ***Indon.:*** Amocomb; Ancla; Augmentin; Auspilic; Bellamox; Betaclav; Biditin; Capsinat; Clabat; Claneksi; Clavamox; Comsikla; Danoclav; Daxet; Dexyclav; Improvox; Lansiclav; Nufaclav; Nuvo-

The symbol † denotes a preparation no longer actively marketed

clav; Prafamoc; Protamox; Surpas; Syneclav; Viaclav; Vulamox; Zumafen; ***Irl.:*** Augmentin; Clavamel; Germentin; Pinaclav; ***Israel:*** Amoxiclav; Augmentin; Clavamox; ***Ital.:*** Abba; Anival; Augmentin; Clavulin; Neoduplamox; Xinamod; ***Malaysia:*** Augmentin; Cavumox; Clamovid; Curam; Enhancin; Klacid HP 7; Moxiclav; Vestaclav†; ***Mex.:*** Acarbixin; Acimox AC; Acimox-Ex; Acroxil-C; Alvi-Tec; Ambrexin; Amobay CL; Amoxibron; Amoxiclav; Amoxiclide; Apoclavox; Augmentin; Avuxilan; Biovicam Ex; Bolbamox†; Bromel; Bromixen; Bromoxil; Broxolim-AM†; Brumax; Cibronal; Clambusil; Clamoxin; Clavant; Clavucyd; Clavulin; Clavuser; Enhancin; Esteclin Bac; Ferlex; Gimabrol; Gramaxin; Hidramox-M; Loexom FC; Loexom FS; Lumoxbron S; Maxint†; Megamox; Moxlin CLV; Mucovibrol Amoxi; Mucoxina; Penamox M; Penbritin Ex; Pentibroxil; Pylopac; Ravotaf; Riclasip; Sekretovit Amoxi; Septacin Amoxi; Sermoxol; Servamox CLV; Sinufin; Solcibrol; Toxol; Trifamox IBL; Valclan; Vanmoxol; ***Neth.:*** Amoclan; Amuclan; Augmentin; Bioclavid; Forcid; PantoPAC; ***Norw.:*** Bremide†; ***NZ:*** Alpha-Amoxyclav; Augmentin; Klacid HP 7†; Losec Hp 7; Synermox; ***Philipp.:*** Amoclav; Augmentin; Augmex; Augurcin; Bactiv; Bactoclav; Bioclavid; Clamovid; Claneksi; Claventin; Clavoxel; Clovimax; Enhancin; Exten; Klavic; Natravox; OAC Hp7; Proxiclav; Sullivan; Suplentin; Valmocel; Xilanic; ***Pol.:*** Amoksiklav; Augmentin; Curam; Forcid; Ramoclav; Taromentin; ***Port.:*** Amoclavam; Amplamox Plus; Augmentin; Betamox; Clavamox; Clavepen; Forcid; Noprilam; Penilan; ***Rus.:*** Amoclan (Амоклан); Amoksiklav (Амоксиклав); Augmentin (Аугментин); Flemoclav (Флемоклав); Medoclav (Медоклав); Panklav (Панклав); Rapiclav (Рапиклав); Trifamox IBL (Трифамокс ИБЛ); ***S.Afr.:*** Adco-Amoclav; Augmaxcil; Augmentin; Bio-Amoksiclav; Clamentin; Clavumox; Co-Amoxyclav; Curam; Forcid; Hiconcil-NS; Losec 20 Triple†; Macropen; Megapen; Moxyclav†; Ranclav; Rolab-Amoclav; Suprapen; ***Singapore:*** Amocla; Augmentin; Augmex†; Clamonex; Clamovid; Curam; Enhancin; Fugentin; Moxiclav; ***Spain:*** Amo Resan†; Amoclave; Amoxi Gobens Mucolitico; Amoxyplus; Ardine Bronquial†; Ardineclav; Augmentine; Bigpen†; Bronco Tonic; Burmicin; Clamoxyl Mucolitico; Clavepen; Clavucid; Clavumox; Duonasa; Edoxil Mucolitico†; Eupeclanic†; Eupen Bronquial; Inmupen†; Kelsopen; Pulmo Borbalan; Reloxyl Mucolitico†; Remisan Mucolitico; Salvapen Mucolitico; ***Swed.:*** Bioclavid; Nexium Hp; Spektramox; ***Switz.:*** Amicosol; Augmentin; Aziclav; Clavamox; clavu-basan†; Co-Amoxi; Co-Amoxicilline; ***Thai.:*** Amocla; Amoksiklav; Augclav; Augmentin; Augpen; Cavumox; Curam; Klamoks; Moxiclav; Moxicle; Pencla; Ranclav; ***Turk.:*** Amoklavin; Augmentin; Bioment; Croxilex; Helipak; Klamoks; Klavunat; Klavupen; ***UAE:*** Julmentin; ***UK:*** Amiclav†; Augmentin; Augmentin-Duo; Heliclear†; ***USA:*** Amoclan; Augmentin; Prevpac; ***Venez.:*** Augmentin; Augmentin Bid†; Clavumox; Curam; Fulgram.

Ampicillin *(BAN, USAN, rINN)*

Aminobenzylpenicillin; Ampicilin; Ampicilina; Ampicilinas, bevandenis; Ampicillin, vattenfritt; Ampicilline; Ampicilline anhydre; Ampicillinum; Ampicillinum anhydricum; Ampicylina bezwodna; Ampisilin; Ampisilliini; Ampicillin, vedetön; Anhydrous Ampicillin; AY-6108; BRL-1341; NSC-528986; P-50; Vízmentes ampicillin. (6*R*)-6-(α-D-Phenylglycylamino)penicillanic acid.

Ампициллин

$C_{16}H_{19}N_3O_4S = 349.4.$

CAS — 69-53-4.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QJ51CA01; QS01AA19.

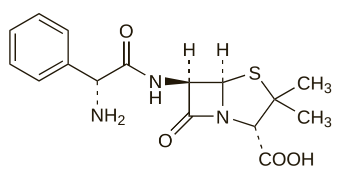

NOTE. Compounded preparations of ampicillin may be represented by the following names:

- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *Viet.*
Int. and *US* permit anhydrous or the trihydrate.

Ph. Eur. 6.2 (Ampicillin, Anhydrous; Ampicillin BP 2008). A white or almost white, crystalline powder. It exhibits polymorphism. Sparingly soluble in water; practically insoluble in alcohol, in acetone, and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30° in airtight containers.

USP 31 (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Ampicillin Sodium *(BANM, USAN, rINNM)*

Aminobenzylpenicillin Sodium; Ampicilin sodná sůl; Ampicilina sódica; Ampicilino natrio druska; Ampicilline sodique; Ampicillinnatrium; Ampicillin-nátrium; Ampicillinum natricum; Ampicylina sodowa; Ampisilliininatrium; Natrii Ampicillinum; Sodyum Ampisilin.

Натрий Ампициллин

$C_{16}H_{18}N_3NaO_4S = 371.4.$

CAS — 69-52-3.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.*

Ph. Eur. 6.2 (Ampicillin Sodium). A white or almost white hygroscopic powder. Freely soluble in water; sparingly soluble in acetone; practically insoluble in liquid paraffin and in fatty oils. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

USP 31 (Ampicillin Sodium). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Very soluble in water and in isotonic sodium chloride and glucose solutions. pH of a solution in water containing the equivalent of ampicillin 1% is between 8.0 and 10.0. Store in airtight containers.

Incompatibility. The incompatibility of ampicillin sodium and aminoglycosides is well established. Incompatibilities have also been reported with a wide range of other drugs, including other antibacterials, and appear to be more pronounced at higher concentrations and in solutions also containing glucose.

Stability. The stability of solutions of ampicillin sodium is dependent on many factors including concentration, pH, temperature, and the nature of the vehicle. Stability decreases in the presence of glucose, fructose, invert sugar, dextrans, hetastarch, sodium bicarbonate, and lactate. It is recommended that reconstituted solutions of ampicillin sodium for injection should be given within 24 hours of preparation, and should be stored at 2° to 8° but should not be frozen. Solutions for infusion are stable for varying periods and details are given in licensed product information.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2**(Mar): 22–39.

Ampicillin Trihydrate *(BANM, rINNM)*

Ampicilin trihydrát; Ampicilina trihidrato; Ampicilinas trihidratas; Ampicillin; Ampicilline trihydratée; Ampicillin-trihidrát; Ampicillintrihydrat; Ampicillinum trihydricum; Ampicylina trójwodna; Ampisilliinitrihydraatti.

Ампициллин Тригидрат

$C_{16}H_{19}N_3O_4S,3H_2O = 403.5.$

CAS — 7177-48-2.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.* In *Chin.* and *Jpn* under the title Ampicillin. *Int.* and *US* permit anhydrous or the trihydrate under the title Ampicillin.

Ph. Eur. 6.2 (Ampicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in alcohol and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Adverse Effects

As for Benzylpenicillin, p.213.

Skin rashes are among the most common adverse effects and are generally either urticarial or maculopapular; the urticarial reactions are typical of penicillin hypersensitivity, while the erythematous maculopapular eruptions are characteristic of ampicillin and amoxicillin and often appear more than 7 days after commencing treatment. Such rashes may be due to hypersensitivity to the beta-lactam moiety or to the amino group in the side-chain, or to a toxic reaction. The occurrence of a maculopapular rash during ampicillin use does not necessarily preclude the subsequent use of other penicillins. However, since it may be difficult in practice to distinguish between hypersensitive and toxic responses, skin testing for hypersensitivity may be advisable before another penicillin is used in patients who have had ampicillin rashes. Most patients with infectious mononucleosis develop a maculopapular rash when treated with ampicillin, and patients with other lymphoid disorders such as lymphatic leukaemia, and possibly those with HIV infection, also appear to be at higher risk. More serious skin reactions may occur and erythema multiforme associated with ampicillin has occasionally been reported.

Gastrointestinal adverse effects, particularly diarrhoea and nausea and vomiting, occur quite often, usually after oral use. Pseudomembranous colitis has also been reported.

Precautions

As for Benzylpenicillin, p.214.

Ampicillin should be stopped if a skin rash occurs. It should preferably not be given to patients with infectious mononucleosis since they are especially susceptible to ampicillin-induced skin rashes; patients with lymphatic leukaemia or possibly HIV infection may also be at increased risk of developing skin rashes.

Myasthenia gravis. The symptoms of a woman with myasthenia gravis were exacerbated when she was given ampicillin.[1]

1. Argov Z, *et al.* Ampicillin may aggravate clinical and experimental myasthenia gravis. *Arch Neurol* 1986; **43**: 255–6.

Sodium content. Each g of ampicillin sodium contains about 2.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Allopurinol. An increased frequency of skin rashes has been reported in patients receiving ampicillin or amoxicillin, with allopurinol, compared with those receiving the antibacterial alone,[1] but this could not be confirmed in a subsequent study.[2]

1. Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. *J Clin Pharmacol* 1981; **21:** 456–8.
2. Hoigné R, *et al.* Occurrence of exanthems in relation to aminopenicillin preparations and allopurinol. *N Engl J Med* 1987; **316**: 1217.

Chloroquine. The absorption of ampicillin has been reduced in healthy subjects taking chloroquine.[1]

1. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. *J Antimicrob Chemother* 1985; **15:** 781–4.

Antimicrobial Action

Ampicillin is a beta-lactam antibiotic. It is bactericidal and has a similar mode of action to that of benzylpenicillin (p.214), but as an aminopenicillin with an amino group side-chain attached to the basic penicillin structure, ampicillin is better able to penetrate the outer membrane of some Gram-negative bacteria and has a broader spectrum of activity.

Spectrum of activity. Ampicillin resembles benzylpenicillin in its action against Gram-positive organisms, including *Streptococcus pneumoniae* and other streptococci, but, with the possible exception of activity against *Enterococcus faecalis*, it is slightly less potent than benzylpenicillin. *Listeria monocytogenes* is highly sensitive. The Gram-negative cocci *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis* are sensitive. Ampicillin is more active than benzylpenicillin against some Gram-negative bacilli, including *Haemophilus influenzae* and Enterobacteriaceae such as *Escherichia coli*, *Proteus mirabilis*, *Salmonella* and *Shigella* spp. It is inactive against *Pseudomonas aeruginosa*. Ampicillin also has activity similar to benzylpenicillin against other organisms including many anaerobes and *Actinomyces* spp.

Activity with other antimicrobials. There is synergy against some beta-lactamase-producing organisms between ampicillin and beta-lactamase inhibitors such as clavulanic acid or sulbactam, and also penicillinase-stable drugs such as cloxacillin or flucloxacillin. Synergy has also been shown between ampicillin and aminoglycosides against a range of organisms, including enterococci. Variable effects ranging from synergy to antagonism have been reported between ampicillin and other beta lactams, bacteriostatic drugs such as chloramphenicol, and rifampicin.

Resistance. Like benzylpenicillin, ampicillin is inactivated by beta lactamases, although other mechanisms may be responsible for resistance in some species. There are geographical variations in the incidence of resistance, but most staphylococci and many strains of *E. coli*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, and *Salmonella* and *Shigella* spp. are resistant.

Pharmacokinetics

Ampicillin is relatively resistant to inactivation by gastric acid and is moderately well absorbed from the gastrointestinal tract after oral doses. Food can interfere with the absorption of ampicillin so doses should preferably be taken at least 30 minutes before meals. Peak concentrations in plasma are attained in about 1 to 2 hours and after a 500-mg oral dose are reported to range from 3 to 6 micrograms/mL.

Peak plasma concentrations of ampicillin after a 500-mg intramuscular dose given as the sodium salt occur within about 1 hour and are reported to range from 7 to 14 micrograms/mL.

Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural, and joint fluids. It crosses the placenta and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. About 20% is bound to plasma proteins and the plasma half-life is about 1 to 1.5 hours, but this may be increased in neonates, the elderly, and patients with renal impairment; in severe renal impairment half-lives of 7 to 20 hours have been reported.

Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion; it is reduced by probenecid. About 20 to 40% of an oral dose may be excreted unchanged in the urine in 6 hours; urinary concentrations have ranged from 0.25 to 1 mg/mL after a dose of 500 mg. After parenteral use about 60 to 80% is excreted in the urine within 6 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in bile; it undergoes enterohepatic recycling and some is excreted in the faeces.

Ampicillin with sulbactam. The pharmacokinetics of ampicillin and sulbactam are broadly similar and neither appears to affect the other to any great extent.

Uses and Administration

Ampicillin is used in the treatment of a variety of infections due to susceptible organisms (see Antimicrobial Action, above). They include biliary-tract infections, bronchitis, endocarditis, gastro-enteritis (including salmonella enteritis and shigellosis), gonorrhoea, listeriosis, meningitis, perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), peritonitis, pneumonia, septicaemia, typhoid and paratyphoid fever, and urinary-tract infections. Resistance to ampicillin is increasingly a problem in some infections, for example, gonorrhoea, pneumococcal infections, respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Salmonella* infections, shigellosis, and infections due to *Escherichia coli*. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. If beta-lactamase-producing organisms are present, ampicillin can be given with a beta-lactamase inhibitor such as sulbactam (see below) or a penicillinase-resistant drug such as cloxacillin, dicloxacillin, or flucloxacillin (known as co-fluampicil). It may also be used with an aminoglycoside to increase the spectrum of organisms covered; it is advisable to give the injections separately.

Administration and dosage. The dosage of ampicillin will depend on the severity of the disease, the age of the patient, and renal function. Ampicillin is usually given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ampicillin; 1.06 g of ampicillin sodium and 1.15 g of ampicillin trihydrate are each equivalent to about 1 g of ampicillin.

The usual adult oral dose is 0.25 to 1 g every 6 hours taken at least 30 minutes before or 2 hours after food. Children may be given half the adult dose. The usual adult dose by injection is 500 mg every 4 to 6 hours intramuscularly or by slow intravenous injection over 3 to 5 minutes or by infusion. Again, children may be given half the adult dose.

For urinary-tract infections, ampicillin 500 mg is given orally every 8 hours.

For typhoid and paratyphoid fever where *Salmonella typhi* strains remain sensitive to ampicillin, an oral dose of 1 to 2 g may be given every 6 hours for 2 weeks for acute infections, and for 4 to 12 weeks in carriers. An intramuscular dose of 10 mg/kg (maximum dose 250 mg) every 6 hours for 4 to 6 weeks has been suggested for children who are chronic carriers.

Ampicillin 2 g given with probenecid 1 g, as a single oral dose, has been used in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive; repeated doses are recommended in females.

In meningitis, higher parenteral doses of 2 to 3 g given intravenously every 4 or 6 hours have been suggested. For infants and children with meningitis, an intravenous dose of 150 mg/kg daily in divided doses may be given; a dose of 50 mg/kg (maximum 3 g) every 4 to 6 hours has also been suggested. Neonates may be given a dose of 50 mg/kg every 12 hours for those under 1 week of age, or every 8 hours for older neonates.

For intrapartum prophylaxis against group B streptococcal infection in the neonate, a maternal dose of 2 g by intravenous injection initially then 1 g every 4 hours until delivery has been suggested.

Ampicillin may also be given by other routes, usually as a supplement to systemic therapy. Intraperitoneal or intrapleural injections are given in a dose of 500 mg daily dissolved in 5 to 10 mL of water. For intra-articular injection, ampicillin 500 mg daily is given dissolved in up to 5 mL of water or a solution of procaine hydrochloride 0.5%.

Ampicillin benzathine has also been given by intramuscular injection.

Ampicillin with sulbactam. The sodium salts of ampicillin and sulbactam (p.335) may be given intramuscularly or intravenously in the treatment of infections due to beta-lactamase-producing organisms. Doses are expressed in terms of the equivalent amounts of ampicillin and sulbactam; available injections contain ampicillin and sulbactam in the ratio 2:1, respectively. The usual dose is ampicillin 1 g with sulbactam 500 mg every 6 hours; doses may be doubled in severe infections.

For oral use sultamicillin (p.344), a mutual prodrug of ampicillin and sulbactam, may be given.

Administration in renal impairment. The dose of ampicillin should be reduced, or the dose interval increased, in severe renal impairment (creatinine clearance less than 10 mL/minute). Patients undergoing dialysis should receive an additional dose after the session.

Preparations

BP 2008: Ampicillin Capsules; Ampicillin Injection; Ampicillin Oral Suspension; Co-fluampicil Capsules; Co-fluampicil Oral Suspension;
USP 31: Ampicillin and Probenecid for Oral Suspension; Ampicillin and Sulbactam for Injection; Ampicillin Capsules; Ampicillin for Injectable Suspension; Ampicillin for Injection; Ampicillin for Oral Suspension; Ampicillin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alpovex; Aminoxidin†; Ampi-Bis; Ampi†; Ampicler; Ampigen; Ampigrand; Ampinox; Ampitenk; Ampixen; Atecilina; Bactilina; Decilina†; Fabopcilina; Galciclina†; Grampenil†; Histopen; Poenbiotico†; Trifacilina; Trimicro; Welticilina; ***Austral.:*** Alphacin; Ampicyn; Austrapen; Ibimicyn; ***Austria:*** Standacillin; ***Belg.:*** Pentrexyl; ***Braz.:*** Ampi; Ampiciflan; Ampiciklyna†; Ampicil; Ampicilab; Ampicilase; Ampicilib†; Ampicilil; Ampicilon; Ampicimax†; Ampicinal†; Ampifar†; Ampigran; Ampilozin; Ampitrat†; Ampival†; Ampixin†; Amplacilina; Amplacin; Amplibac; Amplofen†; Bacterinil†; Binotal; Bipencil†; Cilinon; Cilipen; Emicilin; Expectocilin; Gonol; Gramcilina; Lifacilina†; Notacilin†; Praticilin†; Tandrexin†; ***Canad.:*** Apo-Ampi; Nu-Ampi; ***Cz.:*** Apo-Ampi†; Penstabil†; Standacillin†; ***Denm.:*** Doktacillin†; Pentrexyl; ***Fin.:*** A-Pen; ***Fr.:*** Totapen; ***Ger.:*** Binotal; ***Gr.:*** Copercilex; Isticilline; Pentrexyl; ***Hong Kong:*** Amprexyl; Dhacillin†; Pamecil; Penbritin†; Penodil; Pentrexyl; ***Hung.:*** Penstabil†; Semicillin; Standacillin; ***India:*** Ampilin; Ampipen; Ampisyn; Aristocillin; Biocilin; Campicillin; Ipacillin†; Roscillin; Synthocilin; ***Indon.:*** Ambiopi; Amcillin; Ampi; Arcocillin; Binotal; Biopensyn; Cetacillin; Corsacillin; Kalpicilin; Opicillin; Parpicillin; Penbiotic; Penbritin; Polypen; Primacillin; Sanpicillin; Standacillin; Ultrapen; Viccillin; Xepacillin; ***Irl.:*** Clonamp; Novapen; Penbritin; ***Israel:*** Penibrin; ***Ital.:*** Ampilisa†; Ampilux; Ampiplus Simplex; Amplital; Amplizer; Ibimicyn†; Pentrexyl; ***Malaysia:*** Ampilin; Biocil†; Pamecil; Setcillin†; Standacillin; ***Mex.:*** Acilmed; Alphapen; Alvedrin; Am-An; Ambidrin; Ambiosol; Ampex; Ampi-Quim; Ampi-Tecno; Ampibal†; Ampicidar†; Ampidrat†; Ampigrin; Ampilon†; Ampimex; Ampiset†; Amprexyn; Amsapen; Anglopen; Azpencil; Bestcilina-A; Binotal; Bremecina; Brupen; Deamcilina; Dibacilina; Diferin; Expicin; Flamicina; Gramipen-F; Iqfacilina; Lampicin; Marovilina; Meprizina; Mexapin; Mibiot; Omnipen; Pebiot; Penbritin; Pentiver; Pentrexyl; Procilina; Prodifer; Promecilina; Rayepen†; Sinaplin; Tronex; Yapamicin; Zumorin; ***Neth.:*** Pentrexyl†; ***Norw.:*** Pentrexyl; ***Philipp.:*** Aldribid; Ampicin; Ampinex; Bactimed; Clovillin; Eurocin; Excillin; Gramcil; Obocil; Panacta; Penbritin; Pentrexyl; Picaplin; Polypen; Rotocin; Shinapen; Vatacil; ***Port.:*** Amplifar; Cilin†; Estreptobroncol; Hiperbiotico; Hiperbiotico Retard; ***S.Afr.:*** Ampimax; Ampipen; Be-Ampicil; Penbritin; Penrite; Petercillin; Ranamp; Spectracil; ***Singapore:*** Ampilin; Dhacillin; Pamecil†; Pricillin†; Standacillin; ***Spain:*** Ampiplus; Antibiopen; Britapen; Gobemicina; Nuvapen; ***Swed.:*** Doktacillin; ***Thai.:*** Amcillin†; Amilin; Ampicyn; Ampilin; Ampillin†; Ampra; Amprexyl; Ampro†; Eracillin; Penbritin; Pencotrex; Pentrexyl; Siampicil; Sumapen; Vacillin; Viccillin; ***Turk.:*** Alfasilin; Ampisid; Ampisina; Neosilin; Penbisin; Silina; ***UAE:*** Julphapen; ***UK:*** Magnapen; Penbritin; Rimacillin; ***USA:*** Principen; ***Venez.:*** Alampen; Ampen†; Ampenina; Ampiga†; Ampilan; Arcocilin; Fibrapen†; Intrapen†; Neoampicil†.

Multi-ingredient: ***Arg.:*** Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Amplibenzatin Bronquial; Aseptobron Ampicilina†; Cronopen Balsamico; Grampenil Bronquial†; Meticil; Prixin; Unasyna; Unsayna†; ***Austria:*** Unasyn; ***Braz.:*** Ambezetal; Amplotal; Benzotal; Combactan; Durapen; Optacilin; Parenzyme Ampicilina; Sulbacter†; Unasyn; Urobiotic†; Uropielon; ***Chile:*** Unasyn; ***Cz.:*** Ampiclox†; Unasyn; ***Fr.:*** Unacim; ***Ger.:*** Unacid; ***Gr.:*** Begalin-P; ***Hong Kong:*** Ampiclox†; APT-Ampicloxa; Pamedox; Roscilox; Unasyn; ***Hung.:*** Unasyn; ***India:*** Adilox; Ampilox; Ampilox-LB; Amplus; Ampoxin; Ampoxin-LB; Campicillin Plus; Campilox; Clax; Megaclox; Megaclox LB; Megapen; Sulbacin; ***Irl.:*** Ampiclox†; ***Israel:*** Unasyn; ***Ital.:*** Ampiplus†; Amplium; Bethacil; Diamplicil†; Loricin; Unasyn; ***Jpn:*** Sulperazon†; Unasyn-S†; ***Malaysia:*** Sulbacin; Unasyn; ***Mex.:*** Ampiclox-D; Anglotex; Bisolvon A; Brucilina; Brupen Compuesto; Diamprex; Doxapen; Mucolin A; Panac; Panac K; Pentibrom; Pentidix; Pentrexyl Expec; Unasyna; ***Philipp.:*** Unasyn; ***Pol.:*** Unasyn; ***Rus.:*** Oxamp (Оксамп)†; Sultasin (Сультасин); Unasyn (Уназин); ***S.Afr.:*** Ampiclox; Apen; Cloxam; Megamox; Ranclosil†; ***Singapore:*** Unasyn; ***Spain:*** Ampilevel; Espectral†; Espectrosira†; Gobemicina Retard; Maxicilina; Penisintex Bronquial†; Pulminflamatoria†; Pulmosterin Retard; Retarpen; Retarpen Balsamico†; Retarpen Mucolitico†; Ultrapenil; Unasyn; ***Thai.:*** Ampiclox; Sulam; Unasyn; Viccillin-S; ***Turk.:*** Azosilin; Combicid; Duobak; Duobaktam; Duocid; Nobecid; Sulbaksit; Sulcid; Sultasid; ***UK:*** Magnapen; ***USA:*** Unasyn; ***Venez.:*** Ampibactan; Ampitren†; Fipexiam; Sinif; Unasyn.

Apramycin *(BAN, USAN, rINN)*

47657; Apramicina; Apramycine; Apramycinum; EL-857; EL-857/820; Nebramycin Factor 2. 4-*O*-[(2*R*,3*R*,4a*S*,6*R*,7*S*,8*R*,8a*R*)-3-Amino-6-(4-amino-4-deoxy-α-D-glucopyranosyloxy)-8-hydroxy-7-methylaminoperhydropyrano[3,2-*b*]pyran-2-yl]-2-deoxystreptamine.

Апрамицин

$C_{21}H_{41}N_5O_{11}$ = 539.6.

CAS — 37321-09-8.

ATC Vet — QA07AA92; QJ01GB90; QJ51GB90.

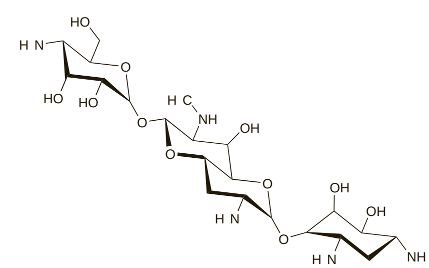

Apramycin Sulfate *(rINNM)*

Apramycin Sulphate *(BANM)*; Apramycine, Sulfate d'; Apramycini Sulfas; Apramycinsulfat; Apramysiinisulfaatti; Sulfato de apramicina.

Апрамицина Сульфат

$C_{21}H_{41}N_5O_{11}.2 \frac{1}{2}H_2SO_4$ = 784.8.

CAS — 41194-16-5.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Apramycin Sulphate). The sulfate of an antibiotic produced by certain strains of *Streptomyces tenebrarius* or by other means. The potency is not less than 430 units per mg, calculated with reference to the anhydrous substance. A light brown hygroscopic powder or granular material. Freely soluble in water; practically insoluble in alcohol, in acetone, in ether, and in methyl alcohol.

Profile

Apramycin is an aminoglycoside antibiotic used as the sulfate in veterinary practice for the treatment of susceptible infections.

The symbol † denotes a preparation no longer actively marketed

Arbekacin Sulfate *(rINNM)*

ABK (arbekacin); AHB-DBK (arbekacin); Arbekacin Sulphate; Arbékacine, Sulfate d'; Arbekacini Sulfas; HABA-Dibekacin (arbekacin); Sulfato de arbekacina. *O*-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1→6)]-*N*′-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxy-L-streptamine sulphate.

Арбекацина Сульфат

$C_{22}H_{44}N_6O_{10},xH_2SO_4$.

CAS — 51025-85-5 (arbekacin).

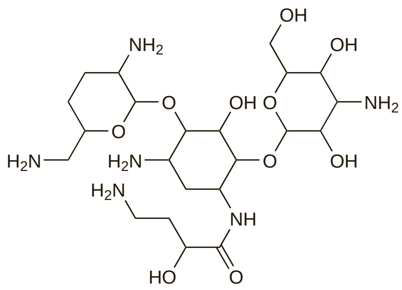

(arbekacin)

Pharmacopoeias. In *Jpn*.

Profile

Arbekacin is an aminoglycoside derived from dibekacin and has general properties similar to those of gentamicin (p.282). It has been used as the sulfate in the treatment of serious infections due to meticillin-resistant *Staphylococcus aureus*.

Arsanilic Acid *(BAN, rINN)*

Acide Arsanilique; Ácido arsanílico; Acidum Arsanilicum; Aminarsonic Acid; AS-101. *p*-Aminobenzenearsonic acid; 4-Aminophenylarsonic acid.

Арсаниловая Кислота

$C_6H_8AsNO_3$ = 217.1.

CAS — 98-50-0.

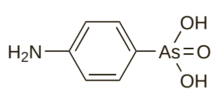

NOTE. The code AS-101 has also been used for an immunomodulator investigated as an antineoplastic and antiviral.

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Arsanilic Acid). A white to off-white crystalline powder. Soluble in hot water, in amyl alcohol, and in solutions of alkali carbonates; slightly soluble in cold water, in alcohol, and in acetic acid; insoluble in acetone, in chloroform, in ether, in benzene, and in dilute mineral acids; sparingly soluble in concentrated mineral acids.

Sodium Arsanilate *(BANM, rINNM)*

Arsanilate de Sodium; Arsanilato sódico; Natrii Arsanilas; Sodium Aminarsonate; Sodium Anilarsonate. Sodium 4-aminophenylarsonate.

Натрий Арсанилат

$C_6H_7AsNNaO_3$ = 239.0.

CAS — 127-85-5.

Pharmacopoeias. *Fr.* includes the anhydrous substance and the trihydrate.

Profile

Arsanilic acid and sodium arsanilate are used in veterinary medicine for the prophylaxis and treatment of enteric infections in pigs and also as growth-promoting agents.

Aspoxicillin *(rINN)*

Aspoxicilina; Aspoxicilline; Aspoxicillinum; TA-058. (2*S*,5*R*,6*R*)-6-{(2*R*)-2-[(2*R*)-2-Amino-3-(methylcarbamoyl)propionamido]-2-(*p*-hydroxyphenyl)acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

Аспоксициллин

$C_{21}H_{27}N_5O_7S$ = 493.5.

CAS — 63358-49-6.

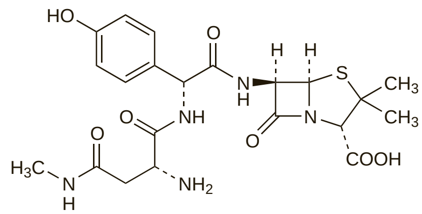

Pharmacopoeias. *Jpn* includes the trihydrate.

Profile

Aspoxicillin is a ureidopenicillin that has been given intravenously in the treatment of susceptible infections.

Astromicin Sulfate *(USAN, pINNM)*

Abbott-44747; Astromicin Sulphate; Astromicine, Sulfate d'; Astromicini Sulfas; Fortimicin A Sulphate; KW-1070; Sulfato de astromicina. 4-Amino-1-(2-amino-*N*-methylacetamido)-1,4-dideoxy-3-*O*-(2,6-diamino-2,3,4,6,7-pentadeoxy-β-L-*lyxo*-heptopyranosyl)-6-*O*-methyl-L-*chiro*-inositol sulphate.

Астромицина Сульфат

$C_{17}H_{35}N_5O_6,2H_2SO_4$ = 601.6.

CAS — 55779-06-1 (astromicin); 72275-67-3 (astromicin sulfate); 66768-12-5 (xH_2SO_4).

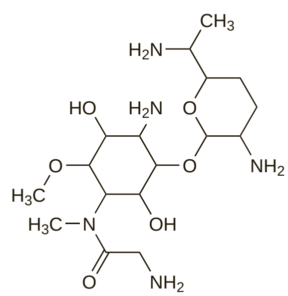

(astromicin)

Pharmacopoeias. In *Jpn*.

Profile

Astromicin is an aminoglycoside antibiotic produced by *Micromonospora* spp. and with actions and uses similar to those of gentamicin (p.282). Astromicin sulfate has been given by intramuscular injection or intravenous infusion. Dosage should be adjusted based on serum-astromicin concentration monitoring.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Fortimicin.

Avilamycin *(BAN, USAN, rINN)*

Avilamicina; Avilamycine; Avilamycinum; LY-048740 (avilamycin or avilamycin A).

Авиламицин

$C_{61}H_{88}Cl_2O_{32}$ (avilamycin A) = 1404.2.

CAS — 11051-71-1 (avilamycin); 69787-79-7 (avilamycin A); 69787-80-0 (avilamycin C).

Profile

Avilamycin is an antibacterial that has been used in veterinary medicine as a growth promotor.

Avoparcin *(BAN, USAN, rINN)*

Avoparcina; Avoparcine; Avoparcinum; Compound 254.

Авопарцин

CAS — 37332-99-3.

Profile

Avoparcin is a glycopeptide antibiotic usually produced by *Amycolatopsis coloradensis* (*Streptomyces candidus*). It has been incorporated into animal feedstuffs to promote growth.

◊ There is evidence of cross-resistance between avoparcin and vancomycin.[1] Suggestions that vancomycin-resistant organisms could enter the human population from the food chain as a result of the use of avoparcin as a growth promotor in animals[2,3] were disputed by the manufacturers of avoparcin.[4,5] After a ban in the EU on the use of avoparcin as a growth promotor in animals there has been some evidence[6] of a decrease in the occurrence of vancomycin-resistant enterococci in poultry meat.

1. Klare I, *et al.* vanA-mediated high-level glycopeptide resistance in Enterococcus faecium from animal husbandry. *FEMS Microbiol Lett* 1995; **125:** 165–72.
2. Howarth F, Poulter D. Vancomycin resistance: time to ban avoparcin? *Lancet* 1996; **347:** 1047.
3. Wise R. Avoparcin and animal feedstuff. *Lancet* 1996; **347:** 1835.
4. Mudd A. Vancomycin resistance and avoparcin. *Lancet* 1996; **347:** 1412.
5. Mudd AJ. Is it time to ban all antibiotics as animal growth-promoting agents? *Lancet* 1996; **348:** 1454–5.
6. Pantosti A, *et al.* Decrease of vancomycin-resistant enterococci in poultry meat after avoparcin ban. *Lancet* 1999; **354:** 741–2.

Azidamfenicol *(BAN, rINN)*

Azidamfénicol; Azidamfenicolum; Azidamphenicol; Azidanfenicol; Azidoamphenicol; Bayer-52910. 2-Azido-*N*-[(α*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

Азидамфеникол

$C_{11}H_{13}N_5O_5$ = 295.3.

CAS — 13838-08-9.

ATC — S01AA25.

ATC Vet — QS01AA25.

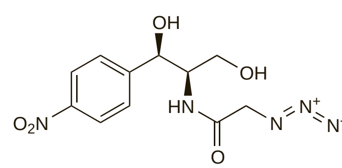

Profile

Azidamfenicol is an antibiotic that is related structurally to chloramphenicol (p.239). It is used as 1% eye drops or eye ointment in the treatment of bacterial eye infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ophthalmo-Azaphenicol†; ***Ger.:*** Berlicetin; Posifenicol; Thilocanfol; ***Gr.:*** Thilocof.

Azidocillin Sodium *(BANM, rINNM)*

Azidobenzylpenicillin Sodium; Azidocilina sódica; Azidocilline Sodique; Natrii Azidocillinum. Sodium (6*R*)-6-(D-2-azido-2-phenylacetamido)penicillanate.

Натрий Азидоциллин

$C_{16}H_{16}N_5NaO_4S$ = 397.4.

CAS — 17243-38-8 (azidocillin); 35334-12-4 (azidocillin sodium).

ATC — J01CE04.

ATC Vet — QJ01CE04.

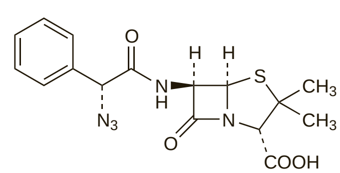

(azidocillin)

Profile

Azidocillin is a semisynthetic penicillin with actions and uses similar to those of phenoxymethylpenicillin (p.314). It is given orally as the sodium salt; doses, expressed in terms of the base, are 750 mg twice daily in the treatment of susceptible infections. The potassium salt has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: InfectoBicillin H.

Azithromycin *(BAN, USAN, rINN)*

Atsitromysiini; Azithromycine; Azithromycinum; Azitromicina; Azitromicinas; Azitromisin; Azitromycin; Azytromycyna; CP-62993; XZ-450. (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-(2,6-Dideoxy-3-*C*-3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)-1-oxa-6-azacyclopentadecan-15-one dihydrate; 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dihydrate.

Азитромицин

$C_{38}H_{72}N_2O_{12},2H_2O = 785.0.$

CAS — 83905-01-5 (anhydrous azithromycin); 117772-70-0 (azithromycin dihydrate).

ATC — J01FA10; S01AA26.

ATC Vet — QJ01FA10; QS01AA26.

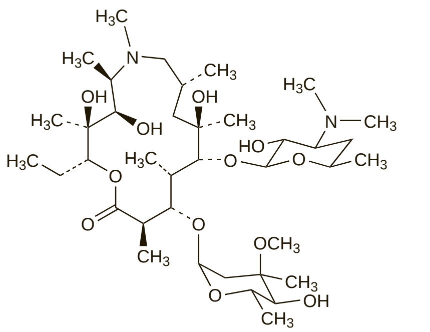

Pharmacopoeias. In *Chin.* and *Jpn.*
Eur. (see p.vii) includes the anhydrous form.
US includes the monohydrate and the dihydrate.

Ph. Eur. 6.2 (Azithromycin). A white or almost white powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. A 0.2% solution in a mixture of methyl alcohol and water (1:1) has a pH of 9.0 to 11.0. Store in airtight containers.

USP 31 (Azithromycin). It is anhydrous or contains one or two molecules of water of hydration. pH of a 0.2% solution in a mixture of methyl alcohol and water (1:1) is between 9.0 and 11.0. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270.

Gastrointestinal disturbances are the most frequent adverse effect of azithromycin but are usually mild and less frequent than with erythromycin. Headache, somnolence, and taste disturbances may occur. Severe hypersensitivity reactions occur rarely but may be prolonged. Thrombocytopenia and mild transient neutropenia have been rarely reported in patients receiving azithromycin. Pain and inflammation may occur at the site of intravenous infusions particularly at high concentrations.

Licensed product information states that azithromycin should be used with caution in patients with hepatic or renal impairment. It should not be given to those with severe hepatic impairment as safety has not been established. Although plasma concentrations may be increased in renal impairment dosage adjustment is not usually required.

Incidence of adverse effects. In patients receiving azithromycin daily long-term for mycobacterial infections,[1] gastrointestinal disorders occurred in 32 of 39 patients (82%), hearing impairment in 10 patients (26%), tinnitus in 18 patients (46%), and poor balance or dizziness in 11 patients (28%). In general, adverse effects were associated with higher serum-azithromycin concentrations.

1. Brown BA, *et al.* Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997; **24:** 958–64.

Effects on the ears. Reversible sensorineural hearing loss was reported in 3 patients given oral azithromycin 500 mg daily with clofazimine and ethambutol for the treatment of disseminated *Mycobacterium avium* complex infection.[1] Irreversible hearing loss has also been reported after low-dose exposure to oral azithromycin.[2,3] A patient who had had 8 days of treatment with intravenous azithromycin 500 mg daily for pneumonia reported complete deafness, which had resolved 20 days after stopping the drug.[4]

See also Incidence of Adverse Effects, above.

1. Wallace MR, *et al.* Ototoxicity with azithromycin. *Lancet* 1994; **343:** 241.
2. Ress BD, Gross EM. Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity: a case report. *Ann Otol Rhinol Laryngol* 2000; **109:** 435–7.
3. Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. *J Otolaryngol* 2007; **36:** 257–63.
4. Bizjak ED, *et al.* Intravenous azithromycin-induced ototoxicity. *Pharmacotherapy* 1999; **19:** 245–8.

Effects on fluid and electrolyte homoeostasis. The syndrome of inappropriate antidiuretic hormone secretion was associated with azithromycin treatment in a patient.[1,2]

1. Cadle RM, *et al.* Symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1997; **31:** 1308–10.
2. Kintzel PE. Correction: symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1998; **32:** 388.

Effects on the kidneys. Acute interstitial nephritis leading to irreversible renal failure has been reported[1] in a patient who received azithromycin for 9 days. A later report[2] described a patient who developed recurrent acute interstitial nephritis after courses of azithromycin. Repeated exposure resulted in persistent renal damage; leucocytosis and eosinophilia were still present 1 year later.

1. Mansoor GA, *et al.* Azithromycin-induced acute interstitial nephritis. *Ann Intern Med* 1993; **119:** 636–7.
2. Soni N, *et al.* Recurrent acute interstitial nephritis induced by azithromycin. *Pediatr Infect Dis J* 2004; **23:** 965–6.

Eosinophilia. A syndrome characterised by eosinophilia, arthralgia, fever, and rash was associated with azithromycin or roxithromycin treatment in a patient on separate occasions.[1] The original authors believed the condition represented the Churg-Strauss syndrome, although this was disputed in correspondence[2] and attributed to the eosinophilia-myalgia syndrome.

1. Hübner C, *et al.* Macrolide-induced Churg-Strauss syndrome in a patient with atopy. *Lancet* 1997; **350:** 563.
2. Kränke B, Aberer W. Macrolide-induced Churg-Strauss syndrome in patient with atopy. *Lancet* 1997; **350:** 1551–2.

Overdosage. Bradycardia with complete heart block was reported[1] in a 9-month-old infant who had been inadvertently given about 50 mg/kg of azithromycin intravenously.

1. Tilelli JA, *et al.* Life-threatening bradyarrhythmia after massive azithromycin overdose. *Pharmacotherapy* 2006; **26:** 147–50.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Giving azithromycin with antacids containing aluminium or magnesium salts can reduce the rate, but not the extent, of its absorption; azithromycin should be given at least 1 hour before or 2 hours after the antacid.

Nelfinavir. Azithromycin serum concentrations are markedly increased when it is given with nelfinavir,[1] but the clinical significance of this is uncertain. US licensed product information for azithromycin states that dosage adjustment is not required although the patient should be closely monitored for adverse effects.

1. Amsden GW, *et al.* A study of the pharmacokinetics of azithromycin and nelfinavir when coadministered in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1522–7.

Antimicrobial Action

As for Erythromycin, p.271. Azithromycin is less active than erythromycin against streptococci and staphylococci, but has greater activity than erythromycin *in vitro* against some Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*), as well as having activity against some of the Enterobacteriaceae such as *Escherichia coli* and *Salmonella* and *Shigella* spp. Azithromycin is also more active than erythromycin against *Chlamydia trachomatis* and *Ureaplasma urealyticum*, and some opportunistic mycobacteria, including *Mycobacterium avium* complex. It has activity against the protozoa *Toxoplasma gondii* and *Plasmodium falciparum*.

Resistance. The pattern of resistance to azithromycin is similar to that seen with clarithromycin (p.249).

Pharmacokinetics

Azithromycin given orally is rapidly absorbed and about 40% bioavailable. Absorption from capsules, but not tablets or suspension, is reduced by food. Peak plasma concentrations occur 2 to 3 hours after an oral dose and 1 to 2 hours after intravenous dosage. However, azithromycin is extensively distributed into the tissues, and tissue concentrations subsequently remain much higher than those in the blood; in contrast to most other antibacterials, plasma concentrations are therefore of little value as a guide to efficacy. High concentrations are taken up into white blood cells. There is little diffusion into the CSF when the meninges are not inflamed. Data from *animal* studies indicate that azithromycin crosses the placenta. Small amounts of azithromycin are demethylated in the liver, and it is excreted in bile mainly as unchanged drug and a number of inactive metabolites have also been detected. About 6% of an oral dose (representing about 20% of the amount in the systemic circulation) is excreted in the urine. The terminal elimination half-life is about 68 hours.

◊ Reviews and references.

1. Lalak NJ, Morris DL. Azithromycin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 370–4.
2. Luke DR, *et al.* Safety, toleration, and pharmacokinetics of intravenous azithromycin. *Antimicrob Agents Chemother* 1996; **40:** 2577–81.
3. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. *Ann Pharmacother* 1998; **32:** 785–93.
4. Chandra R, *et al.* Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. *Clin Pharmacokinet* 2007; **46:** 247–59.

Uses and Administration

Azithromycin is a nitrogen-containing macrolide (azalide) with actions and uses similar to those of erythromycin (p.272). It is given in the treatment of respiratory-tract infections (including otitis media), in skin and soft-tissue infections, and in uncomplicated genital infections. Azithromycin may also be used for the prophylaxis, and as a component of regimens in the treatment, of *Mycobacterium avium* complex (MAC) infections. It is used in some countries for the prophylaxis of endocarditis in at-risk patients unable to take penicillin. It is also used in the management of trachoma and typhoid.

For details of all these infections and their treatment, see under Choice of Antibacterial, p.162.

Azithromycin has been tried in protozoal infections such as babesiosis (below), crytosporidiosis (p.823), and toxoplasmosis (p.826).

It is given orally or by intravenous infusion usually as the dihydrate; doses are expressed in terms of the anhydrous substance. Azithromycin dihydrate 524 mg is equivalent to about 500 mg of anhydrous azithromycin. The capsule formulation should be given at least 1 hour before, or 2 hours after, meals.

The usual oral adult dose of azithromycin is 500 mg as a single dose daily for 3 days. Alternatively, an initial dose of 500 mg may be followed by 250 mg daily for a further 4 days.

For uncomplicated genital infections caused by *Chlamydia trachomatis* and for chancroid, 1 g of azithromycin is given as a single dose. A single dose of 2 g has been given for uncomplicated gonorrhoea. For the treatment of granuloma inguinale, an initial dose of 1 g followed by 500 mg daily may be given, or 1 g may be given once a week for at least 3 weeks, until all lesions have completely healed.

In the USA, a modified-release preparation given as an oral suspension is available. The product delivers a single dose of 2 g and should also be taken on an empty stomach. It is licensed for the treatment of acute bacterial sinusitis or community-acquired pneumonia in adults.

For prophylaxis of disseminated MAC infections, azithromycin 1.2 g may be given once weekly. For treatment or secondary prophylaxis, 500 mg once daily should be given with other antimycobacterials.

For mild or moderate typhoid caused by multidrug-resistant strains, 500 mg once daily may be given for 7 days.

For details of doses in infants and children, see below.

Azithromycin dihydrate may also be given initially by intravenous infusion to adults in doses equivalent to 500 mg of azithromycin as a single daily dose in the treatment of community-acquired pneumonia and pelvic inflammatory disease; treatment should be changed to the oral route after at least 2 days in pneumonia and after 1 or 2 days in pelvic inflammatory disease. It may be given either in a solution containing 1 mg/mL over 3 hours or in a solution containing 2 mg/mL over 1 hour.

In the USA, azithromycin is available as 1% eye drops for the topical treatment of conjunctivitis caused by susceptible strains of bacteria.

◊ Reviews.

1. Peters DH, *et al.* Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1992; **44:** 750–99.
2. Langtry HD, Balfour JA. Azithromycin: a review of its use in paediatric infectious disease. *Drugs* 1998; **56:** 273–97.
3. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; **74:** 613–34.
4. Garey KW, Amsden GW. Intravenous azithromycin. *Ann Pharmacother* 1999; **33:** 218–28.
5. Ioannidis JPA, *et al.* Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. *J Antimicrob Chemother* 2001; **48:** 677–89.
6. Contopoulos-Ioannidis DG, *et al.* Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infections. *J Antimicrob Chemother* 2001; **48:** 691–703.
7. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.
8. Law C, Amsden GW. Single-dose azithromycin for respiratory tract infections. *Ann Pharmacother* 2004; **38:** 433–9.
9. Blumer JL. Evolution of a new drug formulation: the rationale for high-dose, short-course therapy with azithromycin. *Int J Antimicrob Agents* 2005; **26** (suppl 3): S143–S147.
10. Swainston Harrison T, Keam SJ. Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. *Drugs* 2007; **67:** 773–92.
11. Panpanich R, *et al.* Azithromycin for acute lower respiratory tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/06/08).

Administration in children. Azithromycin is licensed for use in infants and children and the usual oral dose in those over 6 months of age is 10 mg/kg once daily for 3 days, or an initial dose of 10 mg/kg may be followed by 5 mg/kg daily for a further 4 days; those who weigh over 45 kg may be given the usual adult dose (see above). A single dose of 30 mg/kg may also be given for acute otitis media. For pharyngitis or tonsillitis in children aged over 2 years, 12 mg/kg once daily for 5 days may be given.

US official guidelines suggest that for prophylaxis of disseminated *Mycobacterium avium* complex infections, azithromycin 20 mg/kg (to a maximum of 1.2 g) once weekly or 5 mg/kg (to a maximum of 250 mg) once daily may be given.[1] For treatment, 10 to 12 mg/kg (to a maximum of 500 mg) once daily should be given with other antimycobacterials.[2]

In the UK, the *BNFC* suggests that azithromycin may be used in penicillin allergic children for the prevention of secondary cases of group A streptococcal infection; those 6 months and older may be given an oral dose of 12 mg/kg (to a maximum of 500 mg) once daily for 5 days.

The *BNFC* also suggests giving azithromycin 10 mg/kg once daily for 7 days in the treatment of mild to moderate typhoid caused by multidrug-resistant strains in those aged 6 months and over.

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf (accessed 01/05/07)
2. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 01/05/07)

Babesiosis. In a prospective, randomised study[1] involving 58 patients with babesiosis (p.823), azithromycin with atovaquone was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Azithromycin 600 mg once daily, or 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, with atovaquone 750 mg twice daily, both orally for 7 to 10 days, has been recommended by some experts[2,3] in the USA for the treatment of *Babesia microti* infections. Immunocompromised patients may be given higher doses of azithromycin (600 to 1000 mg daily). Children may be given azithromycin 12 mg/kg once daily, or 10 mg/kg on day 1 followed by 5 mg/kg once daily thereafter, with atovaquone 20 mg/kg twice daily, both orally for 7 to 10 days. Azithromycin with quinine was reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[4,5]

1. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 12/08/08)
4. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.
5. Shih C-M, Wang C-C. Ability of azithromycin in combination with quinine for the elimination of babesial infection in humans. *Am J Trop Med Hyg* 1998; **59:** 509–12.

Cholera. Azithromycin has been tried[1-3] in the treatment of cholera (p.172). A single dose of 10 or 20 mg/kg was found to be effective in children[1,2] and 1 g in adults.[3]

1. Khan WA, *et al.* Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet* 2002; **360:** 1722–7.
2. Bhattacharya MK, *et al.* Azithromycin in the treatment of cholera in children. *Acta Paediatr* 2003; **92:** 676–8.
3. Saha D, *et al.* Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med* 2006; **354:** 2452–62.

Hyperplasia. For reference to the use of azithromycin to control ciclosporin-induced gingival hyperplasia, see p.1824.

Ischaemic heart disease. Macrolide antibacterials, including azithromycin,[1-4] clarithromycin,[5-9] and roxithromycin,[10-14] have been investigated in the prevention of ischaemic heart disease, based on a suggested link between atherosclerosis and infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) (see p.166). Although preliminary results from some pilot studies were promising, longer-term studies in large numbers of patients were disappointing and none of the three macrolides decreased ischaemic events or provided clinical benefit; indeed, in one study[9] an unexpected increase in cardiovascular mortality was seen in those taking clarithromycin.

1. Anderson JL, *et al.* Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection: the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. *Circulation* 1999; **99:** 1540–7.
2. Cercek B, *et al.* Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet* 2003; **361:** 809–13.
3. O'Connor CM, *et al.* Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA* 2003; **290:** 1459–66.
4. Grayston JT, *et al.* Azithromycin for the secondary prevention of coronary events. *N Engl J Med* 2005; **352:** 1637–45.
5. Sinisalo J, *et al.* Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-Q-wave coronary syndrome. *Circulation* 2002; **105:** 1555–60.
6. Berg HF, *et al.* Effect of clarithromycin on inflammatory markers in patients with atherosclerosis. *Clin Diagn Lab Immunol* 2003; **10:** 525–8.
7. Berg HF, *et al.* Treatment with clarithromycin prior to coronary artery bypass graft surgery does not prevent subsequent cardiac events. *Clin Infect Dis* 2005; **40:** 358–65.
8. Berg HF, *et al.* Effect of clarithromycin treatment on Chlamydia pneumoniae in vascular tissue of patients with coronary artery disease: a randomized, double-blind, placebo-controlled trial. *J Clin Microbiol* 2005; **43:** 1325–9.
9. Jespersen CM, *et al.* Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* 2006; **332:** 22–7. Correction. *ibid.*; 151.
10. Gurfinkel E, *et al.* Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes: the final report of the ROXIS Study. *Eur Heart J* 1999; **20:** 121–7.
11. Wiesli P, *et al.* Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in Chlamydia pneumoniae seropositive men: a randomized, double-blind, placebo-controlled trial. *Circulation* 2002; **105:** 2646–52.
12. Zahn R, *et al.* Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation* 2003; **107:** 1253–9.
13. Sander D, *et al.* Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of Chlamydia pneumoniae seropositivity. *Circulation* 2004; **109:** 1010–15.
14. Kaehler J, *et al.* A randomized trial in patients undergoing percutaneous coronary angioplasty: roxithromycin does not reduce clinical restenosis but angioplasty increases antibody concentrations against Chlamydia pneumoniae. *Am Heart J* 2005; **150:** 987–93.

Malaria. Azithromycin has been studied[1-7] in the management of malaria. Studies[1,4] have shown that an initial loading dose of 750 mg of azithromycin on the first day followed by 250 mg daily thereafter for 20 weeks was effective in the prophylaxis of *Plasmodium vivax* malaria; the drug was well tolerated and the most frequently reported adverse effects were heartburn, paraesthesia, and itching.[3] In the treatment of *P. vivax* malaria, a study[5] found that azithromycin 1 g daily for 3 days resulted in an 88% clinical response rate by day 7, but with a slower onset of action, when compared with chloroquine 600 mg daily for 2 days then 300 mg on day 3 which resulted in a rate of 99%.

Azithromycin in a dose of 0.5 g once daily up to 1.5 g daily in divided doses together with other antimalarials, such as artesunate 200 mg daily[2,7] or quinine 10 mg/kg 3 times daily,[6,7] given for 3 days was found to be effective in the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria.

However, further studies are warranted, especially in children and pregnant women.

1. Taylor WR, *et al.* Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis* 1999; **28:** 74–81.
2. Krudsood S, *et al.* A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated Plasmodium falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2000; **31:** 801–7.
3. Taylor WR, *et al.* Tolerability of azithromycin as malaria prophylaxis in adults in Northeast Papua, Indonesia. *Antimicrob Agents Chemother* 2003; **47:** 2199–2203.
4. Heppner DG, *et al.* Randomized, controlled, double-blind trial of daily oral azithromycin in adults for the prophylaxis of Plasmodium vivax malaria in Western Thailand. *Am J Trop Med Hyg* 2005; **73:** 842–9.
5. Dunne MW, *et al.* A double-blind, randomized study of azithromycin compared to chloroquine for the treatment of Plasmodium vivax malaria in India. *Am J Trop Med Hyg* 2005; **73:** 1108–11.
6. Miller RS, *et al.* Effective treatment of uncomplicated Plasmodium falciparum malaria with azithromycin-quinine combinations: a randomized, dose-ranging study. *Am J Trop Med Hyg* 2006; **74:** 401–6.
7. Noedl H, *et al.* Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated Plasmodium falciparum malaria in adults: a randomized, phase 2 clinical trial in Thailand. *Clin Infect Dis* 2006; **43:** 1264–71.

Respiratory disorders. For reference to the use of azithromycin in the management of respiratory disorders, see under Erythromycin, p.273.

Preparations

USP 31: Azithromycin Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Arzomicin; Azitral; Azitrogal; Azitrolan; Azitrona; Azitrox; Clearsing; Cronopen; Doyle; Fabramicina; Finatres†; Macromax; Misultina; Naxocina; Neblic; Nifostin; Novozitron; Orobiotic; Sitrox; Sumir†; Talcilina; Tanezox; Triamid; Tritab; Vectocilina; Zitromax; ***Austral.:*** Zithromax; ***Austria:*** Zithromax; ***Belg.:*** Zitromax; ***Braz.:*** Astro; Atromicin; Azatill; Azi; Azidromic†; Azimed; Azimix; Azitrax†; Azitrin; Azitrogran; Azitrolab; Azitromicil; Azitromin†; Azitron; Azitronax†; Azitroxil; Biozitrom†; Clindal; Ems-Max; Mac Azi; Mazitrom; Novatrex; Selimax; Selimax Pulso; Siftromin†; Triazi†; Tromix; Trozyman; Zimicina†; Zitril; Zitromax; Zitromil; Zitroneo; ***Canad.:*** Z-Pak; Zithromax; ***Chile:*** Abacten; Asipral†; Atizor; Azitrom; Ricilina; Trex; Zithromax; ***Cz.:*** Azibiot; Azitrox; Sumamed; Zitrocin; ***Denm.:*** Zitromax; ***Fin.:*** Zithromax; ***Fr.:*** Azadose; Zithromax; ***Ger.:*** Ultreon; Zithromax; ***Gr.:*** Azibactron; Azifarm; Azirox; Azirutec; Azithral; Azithrin; Azitrolid; Azivirus; Azytan; Bezanin; Disithrom; Figothrom; Goldamycin; Gramokil; Novozithron; Zinfect; Zithro-Due; Zithromax; Zithropan; Zithrotel; Zithroxyn; Zitrax; ***Hong Kong:*** Zithromax; ***Hung.:*** Azi; Azicid; Sumamed; Zitrocin; ***India:*** Azee; Azibact; Azifast; Azithral; Aziwok; Zithrocin; Zycin; ***Indon.:*** Aztrin; Binozyt; Mezatrin; Zarom; Zibramax; Zicho; Zifin; Zistic; Zithromax; Zycin; ***Irl.:*** Azromax; Zithromax; ***Israel:*** Azenil; Zeto; Zithromax; ***Ital.:*** Azitrocin; Ribotrex; Trozocina; Zitromax; ***Malaysia:*** Zithromax; ***Mex.:*** Amsati; Azibiot; Aziphar; Azitrocin; Azitrohexal; Azo-Max; Koptin; Macrozit; Medatz; Sicalan; Texis; Tromicina; Truxa; Zertalin; Zithran; Zitroken; ***Neth.:*** Azacleus; Azitro; Merckazitro; Nucaza; Zithromax; ***Norw.:*** Azitromax; ***NZ:*** Zithromax; ***Philipp.:*** Zithromax; ZMax; ***Pol.:*** Azibiot; Azimycin; Azitrox; Macromax; Oranex; Sumamed; ***Port.:*** 3Z; Arzomicina†; Azimax; Aziton; Azitrix; Biozitra; Gigatrom; Lazitrom; Neofarmiz; Unizitro; Vascin; Zithromax; Zitrozina; ***Rus.:*** Azithrox (Азитрокс); Azithrus (Азитрус); Azitral (Азитрал); Aziwok (Азивок); Hemomycin (Хемомицин); Sumamed (Сумамед); Zetamax (Зетамакс); ZI-Factor (ЗИ-фактор); Zithrocin (Зитроцин); Zitrolid (Зитролид); ***S.Afr.:*** Zithrogen; Zithromax; ***Singapore:*** Zithromax; ***Spain:*** Altezym; Goxil; Pefloden; Toraseptol; Vinzam; Zentavion; Zitromax; ***Swed.:*** Azitromax; ***Switz.:*** Zithromax; ***Thai.:*** Binozyt; Zithromax; ***Turk.:*** Azacid; Azeltin; Azitro; Azomax; Azro; Tremac; Zitromax; Zitrotek; ***UAE:*** Azomycin; ***UK:*** Zithromax; ***USA:*** AzaSite; Zithromax; Zmax; ***Venez.:*** Amizin; Amovin; Aruzilina; Arzomidol; Atromizin; Azigram; Azimakrol; Azitrom; Azitromin; Binozyt; Saver; Zitromax; Zival.

Multi-ingredient: ***India:*** Orflaz Kit; Safkit; ***Mex.:*** Zithroflam.

Azlocillin *(BAN, USAN, rINN)*

Atslosilliini; Azlocilina; Azlocilline; Azlocillinum. 6-[*N*-(2-Oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

Азлоциллин

$C_{20}H_{23}N_5O_6S$ = 461.5.

CAS — 37091-66-0.

ATC — J01CA09.

ATC Vet — QJ01CA09.

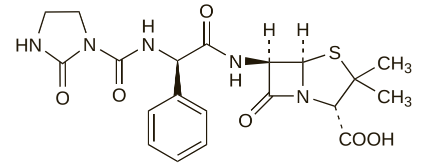

Azlocillin Sodium *(BANM, rINNM)*

Azlocilina sódica; Azlocilline Sodique; Azlocillinum Natricum; Azlocylina sodowa; Bay-e-6905; Natrii Azlocillinum. Sodium (6*R*)-6-[D-2-(2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate.

Натрий Азлоциллин

$C_{20}H_{22}N_5NaO_6S = 483.5.$

CAS — 37091-65-9.

ATC — J01CA09.

ATC Vet — QJ01CA09.

Pharmacopoeias. In *Pol.*

Incompatibility. Azlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Prolongation of bleeding time has been less frequent and less severe with azlocillin than with carbenicillin.

Hypouricaemia. Reports of transient asymptomatic decreases in serum-uric acid concentrations during treatment with azlocillin.[1,2]

1. Faris HM, Potts DW. Azlocillin and serum uric acid. *Ann Intern Med* 1983; **98:** 414.
2. Ernst JA, Sy ER. Effect of azlocillin on uric acid levels in serum. *Antimicrob Agents Chemother* 1983; **24:** 609–10.

Sodium content. Each g of azlocillin sodium contains about 2.1 mmol of sodium. As azlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p.214.

Antibacterials. For the effect of azlocillin on the clearance of *cefotaxime*, and a report of neurotoxicity, see p.228. For reference to azlocillin affecting the disposition of *ciprofloxacin*, see p.246.

Antimicrobial Action

Azlocillin has an antimicrobial action similar to that of piperacillin (p.315). Its activity *in vitro* against Enterobacteriaceae is generally less than that of mezlocillin or piperacillin, but it has comparable activity to piperacillin against *Pseudomonas aeruginosa*.

Pharmacokinetics

Azlocillin is not absorbed from the gastrointestinal tract to any significant extent. It has nonlinear dose-dependent pharmacokinetics. Doubling an intravenous dose results in more than double the plasma concentration. Between 20 and 46% of azlocillin in the circulation is bound to plasma proteins. The plasma half-life is usually about 1 hour, but is longer in neonates; in patients with renal impairment half-lives of 2 to 6 hours have been reported.

Azlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Azlocillin is metabolised to a limited extent. About 50 to 70% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours of a dose, resulting in high urinary concentrations. Azlocillin is partly excreted in the bile where it is also found in high concentrations.

Plasma concentrations are enhanced if probenecid is given.

Azlocillin is removed by haemodialysis.

Uses and Administration

Azlocillin is a ureidopenicillin and, like piperacillin (p.316), is used mainly for the treatment of infections caused by *Pseudomonas aeruginosa*. It has been used particularly for septicaemia, and infections of the respiratory and urinary tracts, and also for peritonitis; for details of these infections, see under Choice of Antibacterial, p.162.

Azlocillin is commonly used with an aminoglycoside; however, they should be given separately as they have been shown to be incompatible (see Incompatibility, above).

Administration and dosage. Azlocillin is given intravenously as the sodium salt. Doses are expressed in terms of the equivalent amount of azlocillin; 1.05 g of azlocillin sodium is equivalent to about 1 g of azlocillin. A 10% solution in a suitable diluent is given by slow injection for doses of 2 g or less; higher doses should be infused over 20 to 30 minutes.

The usual adult dose is 5 g every 8 hours for life-threatening infections, or 2 g every 8 hours for less severe infections and urinary-tract infections.

The following doses may be used for children: premature infants, 50 mg/kg twice daily; neonates less than 7 days old, 100 mg/kg twice daily; infants between 7 days and 1 year, 100 mg/kg three times daily; children up to 14 years, 75 mg/kg three times daily.

Dosage of azlocillin may need to be adjusted in patients with hepatic or renal impairment (see below).

Administration in hepatic or renal impairment. The interval between doses of azlocillin may need to be increased to every 12 hours in moderate to severe renal impairment (creatinine clearance less than 30 mL/minute); additional dosage reductions may be needed in patients with both severe renal and hepatic impairment.

Aztreonam *(BAN, USAN, rINN)*

Atstreonaami; Azthreonam; Aztréonam; Aztreonamum; SQ-26776. (*Z*)-2-{2-Aminothiazol-4-yl-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulphoazetidin-3-ylcarbamoyl]methyleneamino-oxy}-2-methylpropionic acid.

Азтреонам

$C_{13}H_{17}N_5O_8S_2 = 435.4.$

CAS — 78110-38-0.

ATC — J01DF01.

ATC Vet — QJ01DF01.

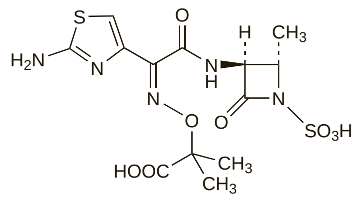

Pharmacopoeias. In *Jpn* and *US*, which allows the anhydrous or hydrated forms.

USP 31 (Aztreonam). A white, odourless crystalline powder. Very slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ethyl acetate, and in toluene; soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers.

Incompatibility and stability. Aztreonam has been reported to be incompatible with cefradine, metronidazole, nafcillin, and vancomycin.

References.

1. Bell RG, *et al.* Stability of intravenous admixtures of aztreonam and cefoxitin, gentamicin, metronidazole, or tobramycin. *Am J Hosp Pharm* 1986; **43:** 1444–53.
2. Riley CM, Lipford LC. Interaction of aztreonam with nafcillin in intravenous admixtures. *Am J Hosp Pharm* 1986; **43:** 2221–4.
3. Belliveau PP, *et al.* Stability of aztreonam and ampicillin sodium-sulbactam sodium in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1994; **51:** 901–4.
4. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 1086–90.
5. Trissel LA, *et al.* Compatibility and stability of aztreonam and vancomycin hydrochloride. *Am J Health-Syst Pharm* 1995; **52:** 2560–4.

Adverse Effects

The adverse effects of aztreonam are similar to those of other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). Hypersensitivity reactions, including skin rashes, urticaria, angioedema, exfoliative dermatitis, eosinophilia, bronchospasm, and rarely anaphylaxis and toxic epidermal necrolysis, may occur in patients receiving aztreonam, although it has been reported to be only weakly immunogenic. Gastrointestinal effects include diarrhoea, nausea, vomiting, mouth ulcer, and an abnormal taste.

Phlebitis or thrombophlebitis has been reported after the intravenous use of aztreonam, and pain or swelling after intramuscular injection.

Use of aztreonam may result in the overgrowth of non-susceptible organisms, including Gram-positive cocci. Pseudomembranous colitis or gastrointestinal bleeding may develop.

Other adverse effects that have been reported with aztreonam include jaundice and hepatitis, increases in liver enzymes, and prolongation of prothrombin and partial thromboplastin times.

Effects on the skin. References.

1. McDonald BJ, *et al.* Toxic epidermal necrolysis possibly linked to aztreonam in bone marrow transplant patients. *Ann Pharmacother* 1992; **26:** 34–5.

Precautions

Aztreonam should not be given to patients who are hypersensitive to it and should be used with caution in those known to be hypersensitive to other beta lactams, although the incidence of cross-sensitivity appears to be low (but see below).

Aztreonam should be used with caution in patients with renal or hepatic impairment.

Breast feeding. In a study in 12 healthy women given aztreonam, peak concentrations in breast milk were found to be less than 1% of those in serum and this was considered suggestive of a low risk of adverse effects in breast-fed infants.[1] The American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers received aztreonam and considers it to be usually compatible with breast feeding,[2] although UK licensed product information recommends that mothers should refrain from breast feeding while receiving aztreonam.

1. Fleiss PM, *et al.* Aztreonam in human serum and breast milk. *Br J Clin Pharmacol* 1985; **19:** 509–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Aztreonam is said to show little cross-reactivity with other beta lactams,[1,2] but there have been isolated reports of immediate hypersensitivity to aztreonam in patients with a history of hypersensitivity to penicillin.[3,4]

1. Saxon A, *et al.* Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. *J Infect Dis* 1984; **149:** 16–22.
2. Adkinson NF. Immunogenicity and cross-allergenicity of aztreonam. *Am J Med* 1990; **88** (suppl 3C): 12S–15S.
3. Alvarez JS, *et al.* Immediate hypersensitivity to aztreonam. *Lancet* 1990; **335:** 1094.
4. Hantson P, *et al.* Immediate hypersensitivity to aztreonam and imipenem. *BMJ* 1991; **302:** 294–5.

Interactions

Caution is recommended in patients receiving aztreonam and oral anticoagulants because of the possibility of increased prothrombin time.

Antimicrobial Action

Aztreonam is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall; it has a high affinity for the penicillin-binding protein 3 (PBP-3) of Gram-negative bacteria. The activity of aztreonam is restricted to Gram-negative aerobic organisms, including beta-lactamase-producing strains, with poor or no activity against Gram-positive aerobes or anaerobic organisms. It is active against most Enterobacteriaceae including *Escherichia coli*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Some strains of *Enterobacter* and *Citrobacter* spp. are resistant. Aztreonam has some activity against *Pseudomonas aeruginosa*, although most strains of other *Pseudomonas* spp. are insensitive. Aztreonam has good activity against *Haemophilus influenzae* and *Neisseria* spp.

Synergy has been reported *in vitro* between aztreonam and aminoglycosides against *Ps. aeruginosa* and some *Enterobacteriaceae.*

Aztreonam is stable to hydrolysis by many beta-lactamases and appears to be a poor inducer of beta-lactamase production. Acquired resistance has occasionally been reported.

Pharmacokinetics

Aztreonam is poorly absorbed from the gastrointestinal tract and is therefore given parenterally. Absorption after intramuscular injection is good; peak plasma concentrations of about 46 micrograms/mL have been achieved within 1 hour of a 1-g dose. Aztreonam has a plasma half-life of about 1.7 hours. The half-life may be prolonged in neonates, in the elderly, in patients with renal impairment, and to some extent in those with hepatic impairment. Aztreonam is about 56% bound to plasma proteins. It is widely distributed in body tissues and fluids, including bile. Diffusion into the CSF is poor unless the meninges are inflamed. It crosses the placenta and enters the fetal circulation; small amounts are distributed into breast milk.

Aztreonam is not extensively metabolised. The principal metabolite, SQ-26992, is inactive and is formed by opening of the beta-lactam ring; it has a much longer half-life than the parent compound. Aztreonam is excreted mainly in the urine, by renal tubular secretion and glomerular filtration; about 60 to 70% of a dose appears within 8 hours as unchanged drug with only small quantities of metabolites. Only small amounts of unchanged drug and metabolites are excreted in the faeces.

Aztreonam is removed by haemodialysis and to a lesser extent by peritoneal dialysis.

◊ Reviews.

1. Mattie H. Clinical pharmacokinetics of aztreonam: an update. *Clin Pharmacokinet* 1994; **26:** 99–106.

Uses and Administration

Aztreonam is a monobactam or monocyclic beta-lactam antibacterial used parenterally as an alternative to aminoglycosides or third-generation cephalosporins for the treatment of infections caused by susceptible Gram-negative aerobic organisms. These have included bone and joint infections, gonorrhoea, intra-abdominal and pelvic infections, lower respiratory-tract infections including pseudomonal infections in patients with cystic fibrosis, meningitis, septicaemia, skin and soft-tissue infections, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. To broaden the spectrum of activity for empirical treatment of infections, aztreonam should be used with other antibacterials. Use with an aminoglycoside may be of benefit in serious *Pseudomonas aeruginosa* infections.

Aztreonam is usually given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. It is given to adults, in usual doses ranging from 1 to 8 g daily, in divided doses every 6 to 12 hours, according to the severity of the infection. Single doses over 1 g should be given by the intravenous route.

UK licensed product information recommends that infants older than one week and children be given aztreonam 30 mg/kg every 6 or 8 hours. For severe infections, children of 2 years or older may be given 50 mg/kg every 6 or 8 hours up to a maximum total daily dose of 8 g. Although not licensed in the UK for neonates less than one week old, the *BNFC* suggests a dose of 30 mg/kg every 12 hours. In the USA the dose for children from 9 months of age is 30 mg/kg every 8 hours for mild to moderate infection, or every 6 to 8 hours in moderate to severe infection up to a maximum total daily dose of 120 mg/kg.

For details of dosage in patients with renal impairment, see below.

A single intramuscular dose of 1 g has been recommended for the treatment of gonorrhoea or cystitis.

Aztreonam lysine is under investigation for inhalational use in respiratory-tract infections.

◊ General references.

1. Brogden RN, Heel RC. Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1986; **31:** 96–130.
2. Neu HC. ed. Aztreonam's role in the treatment of Gram-negative infections. *Am J Med* 1990; **88** (suppl 3C): 1S–43S.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.

Administration. References to the use of aztreonam (as aztreonam lysine) by inhalation in the treatment of airway infections in patients with cystic fibrosis.[1,2]

1. Gibson RL, *et al.* Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006; **41:** 656–65.
2. Retsch-Bogart GZ, *et al.* A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol* 2008; **43:** 47–58.

Administration in renal impairment. Dosage of aztreonam should be reduced in moderate to severe renal impairment. Patients with renal impairment may be given a usual initial dose followed by a maintenance dose adjusted according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: half the initial dose
- CC less than 10 mL/minute: one-quarter of the initial dose
- haemodialysis patients: a supplementary dose of one-eighth of the initial dose may be given after each dialysis session

Preparations

USP 31: Aztreonam for Injection; Aztreonam Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Azactam†; ***Austral.:*** Azactam; ***Austria:*** Azactam; ***Belg.:*** Azactam; ***Braz.:*** Azactam; ***Chile:*** Azactam; ***Cz.:*** Azactam; ***Denm.:*** Azactam; ***Fin.:*** Azactam; ***Fr.:*** Azactam; ***Ger.:*** Azactam; ***Gr.:*** Azactam; Aztreotic†; ***Hong Kong:*** Azactam; ***India:*** Azenam; Trezam†; ***Irl.:*** Azactam; ***Israel:*** Azactam†; ***Ital.:*** Azactam; Primbactam; ***Jpn:*** Azactam; ***Mex.:*** Monobac; ***Norw.:*** Azactam; ***NZ:*** Azactam; ***Philipp.:*** Azactam; ***Pol.:*** Azactam; ***Port.:*** Azactam; ***S.Afr.:*** Azactam; ***Singapore:*** Azactam; ***Spain:*** Azactam; Urobactam†; ***Swed.:*** Azactam; ***Switz.:*** Azactam; ***UK:*** Azactam; ***USA:*** Azactam; ***Venez.:*** Azactam.

Bacampicillin Hydrochloride *(BANM, USAN, rINNM)*

Ampicillin Ethoxycarbonyloxyethyl Hydrochloride; Bacampicilline, chlorhydrate de; Bacampicillini hydrochloridum; Bakampicilin-hydrochlorid; Bakampicilino hidrochloridas; Bakampicillin-hidroklorid; Bakampicillinhydroklorid; Bakampisilin Hidroklorür; Bakampisilliinihydrokloridi; Carampicillin; EPC-272; Hidrocloruro de bacampicilina. 1-(Ethoxycarbonyloxy)ethyl (6*R*)-6-(α-D-phenylglycylamino)penicillanate hydrochloride.

Бакампициллина Гидрохлорид

$C_{21}H_{27}N_3O_7S,HCl = 502.0.$

CAS — 50972-17-3 (bacampicillin); 37661-08-8 (bacampicillin hydrochloride).

ATC — J01CA06.

ATC Vet — QJ01CA06.

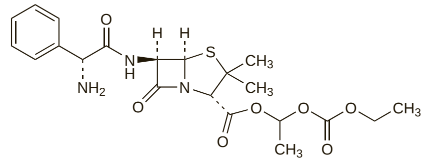

(bacampicillin)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Bacampicillin Hydrochloride). A white or almost white hygroscopic powder or granules. Soluble in water and in dichloromethane; freely soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.5. Store in airtight containers.

USP 31 (Bacampicillin Hydrochloride). A white or practically white, hygroscopic, powder. Soluble in water and in dichloromethane; freely soluble in alcohol and in chloroform; very slightly soluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers.

Adverse Effects and Precautions

As for Ampicillin, p.204. Diarrhoea has been reported to occur less frequently with bacampicillin.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Bacampicillin has the antimicrobial action of ampicillin *in vivo* (p.204). It possesses no intrinsic activity and needs to be hydrolysed to ampicillin.

Pharmacokinetics

Bacampicillin is more rapidly and completely absorbed from the gastrointestinal tract than ampicillin, to which it is hydrolysed in the intestinal wall and plasma. Peak plasma-ampicillin concentrations occur about 30 to 60 minutes after oral doses, and are about 2 to 3 times those after an equivalent dose of ampicillin. The absorption of bacampicillin from tablets does not appear to be affected by the presence of food in the stomach. About 75% of a dose is excreted in the urine as ampicillin within 8 hours.

Uses and Administration

Bacampicillin has actions and uses similar to those of ampicillin (p.205) to which it is rapidly hydrolysed in the body. It is given orally as the hydrochloride in adult doses of 0.8 to 2.4 g daily, in 2 divided doses; children over 5 years of age have been given 25 to 50 mg/kg daily in 2 divided doses.

In uncomplicated gonorrhoea a single dose of bacampicillin hydrochloride 1.6 g with probenecid 1 g may be given in areas where gonococci remain sensitive.

Preparations

USP 31: Bacampicillin Hydrochloride for Oral Suspension; Bacampicillin Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Penglobe; ***Belg.:*** Bacampicin†; ***Canad.:*** Penglobe†; ***Cz.:*** Penglobe†; ***Fr.:*** Bacampicine†; Penglobe†; ***Ger.:*** Ambacamp†; ***Hong Kong:*** Penglobe†; ***Hung.:*** Penglobe†; ***India:*** Penglobe; ***Ital.:*** Ampibac†; Bacacil; Bacagen; Bacasint; Bacattiv†; Bacillin; Bakam; Campixen†; Penglobe; Polibiotic†; Rebacil; Winnipeg; ***Malaysia:*** Penbaccin†; Penglobe†; ***Mex.:*** Penglobe†; ***Philipp.:*** Penglobe; ***Port.:*** Bacampicin†; ***Spain:*** Ambaxino†; Penglobe†; ***Swed.:*** Penglobe†; ***Thai.:*** Penglobe†; ***Turk.:*** Bakamsilin; Penbak.

Bacitracin *(BAN, rINN)*

Bacitracina; Bacitracinas; Bacitracine; Bacitracinum; Bacytracyna; Basitrasiini; Basitrasin.

Бацитрацин

CAS — 1405-87-4.

ATC — D06AX05; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QR02AB04.

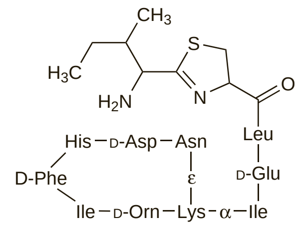

(bacitracin A)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.*

Ph. Eur. 6.2 (Bacitracin). Mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *B. subtilis*. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or almost white hygroscopic powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 6.0 to 7.0. Store at a temperature of 8° to 15° in airtight containers.

USP 31 (Bacitracin). A mixture of polypeptides produced by the growth of an organism of the *licheniformis* group of *Bacillus subtilis* (Bacillaceae). The main components are bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It is a white to pale buff, hygroscopic powder, odourless or having a slight odour. Freely soluble in water; soluble in alcohol, in glacial acetic acid, and in methyl alcohol, the solution in the organic solvents usually showing some insoluble residue; insoluble in acetone, in chloroform, and in ether. Its solutions deteriorate rapidly at room temperature. It is precipitated from its solutions and is inactivated by salts of many of the heavy metals. pH of a solution in water containing 10 000 units/mL is between 5.5 and 7.5. Store in airtight containers at a temperature of 8° to 15°.

Bacitracin Zinc *(BANM, rINNM)*

Bacitracin zinečnatý komplex; Bacitracina zinc; Bacitracin-cink; Bacitracine Zincique; Bacitracine-zinc; Bacitracino cinko kompleksas; Bacitracins Zinc Complex; Bacitracinum Zincicum; Bacitracinum zincum; Bacytracyna cynkowa; Sinkkibasitrasiini; Zinc Bacitracin; Zinci Bacitracinum; Zinkbacitracin.

Цинка Бацитрацин

CAS — 1405-89-6.

ATC — D06AX05; R02AB04.

ATC Vet — QD06AX05; QR02AB04.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Bacitracin Zinc). The zinc complex of bacitracin. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or light-yellowish-grey hygroscopic powder. Slightly soluble in water and in alcohol. The filtrate of a saturated solution has a pH of 6.0 to 7.5. Store in airtight containers.

USP 31 (Bacitracin Zinc). The zinc complex of bacitracin, which consists of a mixture of antimicrobial polypeptides, the main components being bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It contains not less than 4% and not more than 6% of zinc, calculated with reference to the dried substance. A white or pale tan, hygroscopic powder, odourless or having a slight odour. Sparingly soluble in water. pH of a saturated solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 8° to 15°.

Incompatibility. Bacitracin was slowly inactivated in bases containing stearyl alcohol, cholesterol, polyoxyethylene derivatives, and sodium laurilsulfate, and was rapidly inactivated in bases containing water, macrogols, propylene glycol, glycerol, cetylpyridinium chloride, benzalkonium chloride, ichthammol, phenol, and tannic acid.[1]

1. Plaxco JM, Husa WJ. The effect of various substances on the antibacterial activity of bacitracin in ointments. *J Am Pharm Assoc (Sci)* 1956; **45:** 141–5.

Stability. Bacitracin zinc was more stable than bacitracin and could be stored for 18 months at temperatures up to 40° without appreciable loss of activity. Lozenges of bacitracin zinc and ointments and tablets containing bacitracin zinc with neomycin were more stable than the corresponding bacitracin preparations. Bacitracin zinc was less bitter than bacitracin and the taste was more readily disguised.[1]

1. Gross HM, *et al.* Zinc bacitracin in pharmaceutical preparations. *Drug Cosmet Ind* 1954; **75:** 612–13.

Units

The second International Standard Preparation (1964) of bacitracin zinc contains 74 units/mg.

Adverse Effects and Precautions

Systemic bacitracin may produce severe nephrotoxicity, resulting in renal failure due to tubular and glomerular necrosis. Renal function should be determined before, and daily during, therapy. Fluid intake and urinary output should be maintained to avoid kidney toxicity. If renal toxicity occurs, bacitracin should be stopped. Use with other nephrotoxic drugs should be avoided (see Interactions, below).

Nausea and vomiting may occur, as well as pain at the site of injection. Hypersensitivity reactions, including rashes and anaphylaxis, have occurred with both systemic, and more rarely with topical, use.

Interactions

Additive nephrotoxicity would be anticipated if bacitracin were given systemically with other nephrotoxic drugs, particularly colistin, kanamycin, neomycin, polymyxin B, and streptomycin; such use should be avoided.. Bacitracin is reported to enhance the neuromuscular blocking action of certain drugs, such as neuromuscular blockers and anaesthetics, if given during surgery or postoperatively.

Antimicrobial Action

Bacitracin interferes with bacterial cell wall synthesis by blocking the function of the lipid carrier molecule that transfers cell wall subunits across the cell membrane. It is active against many Gram-positive bacteria including staphylococci, streptococci (particularly group A streptococci), corynebacteria, and clostridia. It is also active against *Actinomyces*, *Treponema pallidum*, and some Gram-negative species such as *Neisseria* and *Haemophilus influenzae*, although most Gram-negative organisms are resistant.

Acquired bacterial resistance to bacitracin rarely occurs, but resistant strains of staphylococci have been detected.

Pharmacokinetics

Bacitracin is not appreciably absorbed from the gastrointestinal tract or from intact or denuded skin, wounds, or mucous membranes; however, systemic absorption has been reported after peritoneal lavage. It is rapidly absorbed when given by intramuscular injection. Bacitracin readily diffuses into pleural and ascitic fluids but little passes into the CSF. About 10 to 40% of a single injected dose is excreted slowly by glomerular filtration and appears in the urine within 24 hours.

Uses and Administration

Bacitracin and bacitracin zinc are applied **topically** (as a cream, ointment, dusting powder, or ophthalmic ointment), often with other antibacterials such as neomycin and polymyxin B, and sometimes with corticosteroids, in the treatment of local infections due to susceptible organisms. Typical concentrations of bacitracin or bacitracin zinc in such products are 250 to 500 units/g. Absorption from open wounds and from the bladder or peritoneal cavity may lead to adverse effects, although the dose-limiting toxicity of combined preparations is considered to be due to neomycin.

Parenteral use of bacitracin is usually avoided because of nephrotoxicity but it may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. For details of doses, see below.

Bacitracin has been given **orally** in the treatment of antibiotic-associated colitis due to *Clostridium difficile*.

Administration in children. In the USA, bacitracin may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. Infants weighing less than 2.5 kg may be given a dose of 900 units/kg daily in 2 or 3 divided doses; those weighing more than 2.5 kg may be given 1000 units/kg daily in 2 or 3 divided doses.

Preparations

BP 2008: Polymyxin and Bacitracin Eye Ointment;
USP 31: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin for Injection; Bacitracin Ointment; Bacitracin Ophthalmic Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder.

Proprietary Preparations (details are given in Part 3)

Austria: Rhinocillin B†; ***Canad.:*** Baciguent; Baciject; Bacitin; ***USA:*** Ak-Tracin†; Baci-IM; ***Venez.:*** Baciderm.

Multi-ingredient: *Arg.:* Biotaer an Caramelos; Biotaer Gamma†; Biotaer Nebulizable; Biotaer Ultrason Nebulizable†; Butimerin; Carnot Colutorio; Cicatrex; Nebapol B†; ***Austral.:*** Cicatrin; Nemdyn; Neosporin; ***Austria:*** Baneocin; Cicatrex; Eucillin; Nebacetin; ***Belg.:*** Nebacetine; Neobacitracine; ***Braz.:*** Anaseptil; Antiseptin†; Bacidermina; Bacigen; Bacinantrat†; Bacineo†; Bactoderm; Belcetin†; Cicatrene; Cicatrizan†; Cutiderm; Dermacetin-Ped†; Dermase; Epicitrin; Ferid; Kindcetin; Nebacetin; Nebaciderme; Nebacimed; Nebacitrin†; Nebactrina†; Nebalon†; Neobacina†; Neobacipan†; Neocetrin; Neotop; Neotricin; Polysporin; Pomacetin†; Rinogerol†; Teutomicin; ***Canad.:*** Antibiotique Onguent; Bacimyxin; Band-Aid Antibiotic; Bioderm; Cicatrin; Cortimyxin; Cortisporin; Johnson & Johnson First Aid Ointment†; Neosporin; Neotopic†; Optimyxin; Ozonol Antibiotic Plus; Polycidin†; Polyderm; Polysporin; Polysporin Complete Antibiotic; Polysporin Triple Antibiotic; Polytopic; ***Chile:*** Bacitopic Compuesto; Bacitopic†; Banedif; Banedif Oftalmico; Banedif Oftalmico con Prednisolona; Biodexin†; Dermabiotico; Grifoftal†; Monticina; Nasomin; Oftabiotico; Pensulan; Polvos Antibioticos†; Rinobanedif; Unguento Dermico Antibiotico; ***Cz.:*** Framykoin; Ophthalmo-Framykoin; Ophthalmo-Framykoin Compositum; Pamycon; ***Fin.:*** Bacibact; ***Fr.:*** Bacicoline; Collunovar†; Oropivalone Bacitracine†; ***Ger.:*** Anginomycin†; Bivacyn†; Cicatrex†; Nebacetin; Neobac; Polyspectran; Polyspectran HC; ***Gr.:*** Apobacyn; Lysopaine; Nebacetin; Sopain-Plus; Vioplex-T; ***Hong Kong:*** Bacimycin; Bivacyn; Nebacetin†; Neosporin†; PMS-Baximycin†; Polyfax†; Prednitracin†; ***Hung.:*** Baneocin; Bivacyn; ***India:*** Nebasulf; Neosporin; Neosporin-H; ***Indon.:*** Nebacetin; Netracin; Scanderma Plus; Tracetin; ***Irl.:*** Cicatrin; Polyfax; ***Israel:*** Bamyxin; ***Ital.:*** Bimixin; Cicatrene; Enterostop; Orobicin; ***Malaysia:*** Bacitracin-N; Baneocin; ***Mex.:*** Nebacetina; Neosporin; Polixin; Tribiot; ***Neth.:*** Bacicoline-B; ***Norw.:*** Bacimycin; ***Philipp.:*** BNP Ointment; Terramycin Plus; Trimycin; Trimycin-H; ***Pol.:*** Baneocin; Bivacyn; Multibiotic; Neotopic; Tribiotic; ***Port.:*** Baciderma; Bacitracina Zimaia; Bacitracina-Neo†; Cicatrin; Davimicina†; Dermimade Bacitracina†; Dermobiotico†; Dimicina; Distop; Oralbiotico†; Polisulfade; ***Rus.:*** Baneocin (Банеоцин); ***S.Afr.:*** Cicatrin; Neosporin†; Polysporin; ***Singapore:*** Baneocin; Batramycin; Fast Powder; Polybamycin; ***Spain:*** Bacisporin; Banedif; Dermisone Tri Antibiotic; Dermo Hubber; Edifaringen; Lizipaina; Neo Bacitrin; Oxidermiol Enzima†; Phonal; Pomada Antibiotica; Rinobanedif; Tulgrasum Antibiotico; ***Switz.:*** Bacimycin; Baneopol; Batramycine; Cicatrex; Lysopaine; Nebacetin; Neotracin; Oro-Pivalone; Prednitracin†; ***Thai.:*** Bacal; Banocin; Basina; Biochin†; Genquin; Izac†; Medcin; My-B; Mybacin; Mybacin Dermic; ***Turk.:*** Thiocilline; ***UK:*** Cicatrin†; Polyfax; ***USA:*** Ak-Poly-Bac; Ak-Spore; Betadine First Aid Antibiotics + Moisturizer; Betadine Plus First Aid Antibiotics & Pain Reliever; Cortimycin; Cortisporin†; Lanabiotic†; Mycitracin†; Neocin; Neosporin + Pain Relief; Neosporin†; Neotricin HC; Ocu-Spor-B; Ocutricin; Polycin-B; Polymycin; Polysporin†; Polytracin; Spectrocin Plus†; Tri-Biozene; ***Venez.:*** Dermabiotic.

Balofloxacin *(rINN)*

Balofloxacine; Balofloxacino; Balofloxacinum; Q-35. (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)piperidino]-4-oxo-3-quinolinecarboxylic acid.

Балофлоксацин

$C_{20}H_{24}FN_3O_4$ = 389.4.
CAS — 127294-70-6.

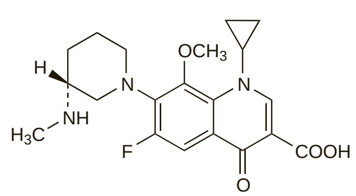

Profile

Balofloxacin is a fluoroquinolone antibacterial used in the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Kor.: Q-Roxin.

Bambermycin *(BAN, pINN)*

Bambermicina; Bambermycine; Bambermycins *(USAN)*; Bambermycinum; Flavophospholipol.

Бамбермицин

$C_{69}H_{108}N_5O_{34}P$ = 1582.6 (moenomycin A).
CAS — 11015-37-5 (bambermycin); 76095-39-1 (moenomycin A).

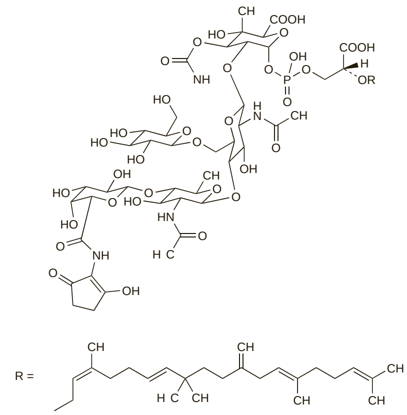

(moenomycin A)

Profile

Bambermycin is an antibacterial complex containing mainly moenomycin A and moenomycin C and which may be obtained from cultures of *Streptomyces bambergiensis* or by other means. It is used as a growth promotor in veterinary practice.

Baquiloprim *(BAN, rINN)*

Bakilopriimi; Bakiloprim; Baquiloprima; Baquiloprime; Baquiloprimum; 138OU. 5-(8-Dimethylamino-7-methyl-5-quinolylmethyl)pyrimidin-2,4-diyldiamine.

Бахилоприм

$C_{17}H_{20}N_6$ = 308.4.
CAS — 102280-35-3.

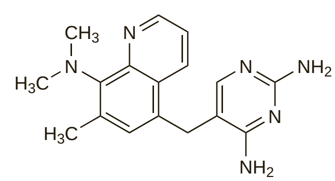

Profile

Baquiloprim is a diaminopyrimidine antibacterial used in veterinary medicine with sulfadimethoxine or sulfadimidine.

Bekanamycin Sulfate *(rINNM)*

Aminodeoxykanamycin Sulphate; Bekanamycin Sulphate; Békanamycine, Sulfate de; Bekanamycini Sulfas; Kanamycin B Sulphate; KDM; NK-1006; Sulfato de bekanamicina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine sulphate.

Беканамицина Сульфат

$C_{18}H_{37}N_5O_{10},2/_{}H_2SO_4$ = 728.7.
CAS — 4696-76-8 (bekanamycin); 70550-99-1 (bekanamycin sulfate).

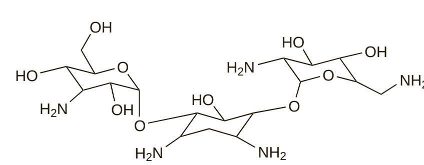

(bekanamycin)

Pharmacopoeias. In *Jpn.*

Profile

Bekanamycin is an aminoglycoside and is a congener of kanamycin. It has properties similar to those of gentamicin (p.282).

It is given topically as the sulfate for the treatment of eye infections. It has also been given intramuscularly and orally. It is reported to be more toxic than kanamycin.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Kanacyl†.
Multi-ingredient: ***Ital.:*** Visucloben Antibiotico; Visumetazone Antibiotico.

Benethamine Penicillin *(BAN, rINN)*

Bénéthamine Pénicilline; Benethaminum Penicillinum; Penicilina-benetamina. Benzyl(phenethyl)ammonium (6*R*)-6-(2-phenylacetamido)penicillanate.

Бенетамин Пенициллин

$C_{15}H_{17}N,C_{16}H_{18}N_2O_4S = 545.7.$

CAS — 751-84-8.

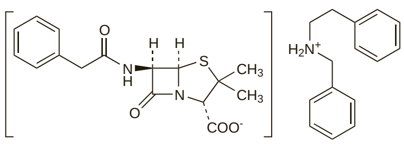

Profile

Benethamine penicillin is a poorly soluble derivative of benzylpenicillin (p.213) with similar actions and uses, although it is not recommended for chronic, severe, or deep-seated infections. After deep intramuscular injection it forms a depot from which it is slowly absorbed and hydrolysed to benzylpenicillin. Benethamine penicillin is usually given with benzylpenicillin sodium and also sometimes procaine benzylpenicillin to produce both an immediate and a prolonged effect; overall, the effect lasts for 2 to 3 days.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Biclinocilline; ***Port.:*** Atralmicina.

Benzathine Benzylpenicillin *(BAN, rINN)*

Bensylpenicillinbensatin; Bensylpenicillinbenzatin; Bentsyylipenisilliinibentsatiini; Benzathin-benzylpenicilin; Benzathine benzylpénicilline; Benzathine Penicillin; Benzathini Benzylpenicillinum; Benzatin Penisilin; Benzatina bencilpenicilina; Benzethacil; Benzilpenicilinas benzatinas; Benzilpenicillina Benzatinica; Benzilpenicillin-benzantin; Benzylopenicylina benzatynowa; Benzylpenicillinum Benzanthinum; Benzylpenicillinum benzathinum; Penicillin G Benzathine; Penisilin G Benzatin; Penzaethinum G. *NN*′-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenylacetamido)penicillanate].

Бензатина Бензилпенициллин

$C_{16}H_{20}N_2(C_{16}H_{18}N_2O_4S)_2 = 909.1.$

CAS — 1538-09-6 (anhydrous benzathine benzylpenicillin); 5928-83-6 (benzathine benzylpenicillin monohydrate); 41372-02-5 (benzathine benzylpenicillin tetrahydrate).

ATC — J01CE08.

ATC Vet — QJ01CE08.

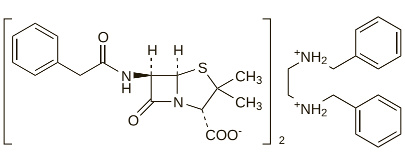

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Int.* *Jpn* and *US* include the tetrahydrate.

Ph. Eur. 6.2 (Benzylpenicillin, Benzathine). It contains a variable quantity of water. A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide and in formamide. Store in airtight containers.

USP 31 (Penicillin G Benzathine). The tetrahydrate is a white, odourless, crystalline powder. Soluble 1 in 5000 of water and 1 in 65 of alcohol. pH in a solution prepared by dissolving 50 mg in 50 mL of dehydrated alcohol, and adding 50 mL of water is between 4.0 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Non-allergic (embolic-toxic) reactions similar to those associated with procaine benzylpenicillin, p.319, have been reported rarely with benzathine benzylpenicillin.

Benzathine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Interactions

As for Benzylpenicillin, p.214.

Pharmacokinetics

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see below).

Distribution into the CSF is reported to be poor.

Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.

Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gastrointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak concentrations are also produced less rapidly, but may persist for longer.

Plasma concentrations. Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks to ensure adequate plasma concentrations of benzylpenicillin. Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study[1] adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study,[2] in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900-mg dose of benzathine benzylpenicillin usually recommended might prolong the duration of protective plasma concentrations of benzylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against rheumatic fever.

1. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; **115:** 146–50.
2. Currie BJ, *et al.* Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrob Agents Chemother* 1994; **38:** 1203–4.

Pregnancy. The pharmacokinetics of benzathine benzylpenicillin appear to be altered in late pregnancy. Of 10 healthy pregnant women given benzathine benzylpenicillin 1.8 g intramuscularly before caesarean section, only 4 achieved adequate serum concentrations of benzylpenicillin (for syphilis, at least 18 nanograms/mL) for 7 days.[1]

1. Nathan L, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; **82:** 338–42.

Uses and Administration

Benzathine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p.214), to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations of benzylpenicillin produced, its use should be restricted to micro-organisms that are highly susceptible to benzylpenicillin. In acute infections, and when bacteraemia is present, the initial treatment should be with benzylpenicillin by injection.

Infections treated with benzathine benzylpenicillin include diphtheria (asymptomatic carriers), pharyngitis (*Streptococcus pyogenes; Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*)), and syphilis (including non-venereal treponematoses). It is also used for primary and secondary prophylaxis of rheumatic fever. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Benzathine benzylpenicillin is given by deep intramuscular injection, sometimes with procaine benzylpenicillin and benzylpenicillin itself. It has been given orally for mild infections, although phenoxymethylpenicillin is usually preferred. Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF. Infants up to 2 years of age may be given a single intramuscular dose of 37.5 mg/kg for the treatment of congenital syphilis, provided there is no evidence of infection in the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given; a dose of 450 mg may be used in children.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg; children under 30 kg may be given 225 to 675 mg. To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4 weeks to adults; a dose of 450 mg has been used for children under 30 kg.

Preparations

USP 31: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Benzathine Injectable Suspension; Penicillin G Benzathine Oral Suspension; Penicillin G Benzathine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Benzetacil; Galtamicina; Pen di Ben; Retarpen; ***Austral.:*** Bicillin L-A; ***Austria:*** Retarpen; ***Belg.:*** Penadur; ***Braz.:*** Bactopen; Benzatron; Benzetacil; Bepeben; Longacilin; Neo Benzil†; Pencil B; ***Cz.:*** Pendepon Compositum; Retarpen; ***Fr.:*** Extencilline; ***Ger.:*** Pendysin; ***Gr.:*** Penadur; ***Hung.:*** Retarpen†; ***India:*** Pencom; Penidure; ***Israel:*** Durabiotic; ***Ital.:*** Diaminocillina; Wycillina; ***Malaysia:*** Retarpen; ***Mex.:*** Benacilina; Bencelin; Benzafur; Benzanil Simple; Benzetacil; Ipenxin; Lentopenil; Unicil 6:3:3; Unicil L-A; ***Neth.:*** Penidural; ***NZ:*** Bicillin L-A; ***Philipp.:*** Penadur; Zalpen; ***Pol.:*** Debecylina; ***Port.:*** Lentocilin S; Penadur†; ***Rus.:*** Bicillin-1 (Бициллин-1); Extencilline (Экстенциллин); ***S.Afr.:*** Bicillin L-A; Penilente LA†; ***Singapore:*** Retarpen; ***Spain:*** Benzetacil; Cepacilina; ***Thai.:*** Penadur†; ***Turk.:*** Benzapen; Benzapen 6.3.3; Deposilin; Deposilin 6.3.3; Penadur; Penadur 6.3.3; ***USA:*** Bicillin L-A; Permapen; ***Venez.:*** Benzetacil L-A; Silcopen†.

Multi-ingredient: ***Austria:*** Retarpen compositum; ***Chile:*** Karbasalin†; ***Ger.:*** Retacillin compositum; Tardocillin; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Pecivax; Pendiben Compuesto; ***Neth.:*** Penidural D/F†; ***Port.:*** Lentocilin; Penadur 6.3.3†; ***Rus.:*** Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Benzetacil Compuesta; Cepacilina 633; Penilevel Retard; ***USA:*** Bicillin C-R; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Benzathine Phenoxymethylpenicillin

Benzatin Fenoksimetil Penisilin; Benzatina fenoximetilpenicilina; Penicillin V Benzathine *(USAN)*; Phenoxymethylpenicillini Dibenzylaethylendiaminum. *N,N*′-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenoxyacetamido)penicillanate].

$(C_{16}H_{18}N_2O_5S)_2,C_{16}H_{20}N_2 = 941.1.$

CAS — 5928-84-7 (anhydrous benzathine phenoxymethylpenicillin); 63690-57-3 (benzathine phenoxymethylpenicillin tetrahydrate).

ATC — J01CE10.

ATC Vet — QJ01CE10.

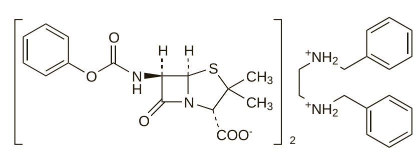

Pharmacopoeias. In *US.*

USP 31 (Penicillin V Benzathine). A practically white powder having a characteristic odour. Soluble 1 in 3200 of water, 1 in 330 of alcohol, 1 in 37 of acetone, 1 in 42 of chloroform, and 1 in 910 of ether. pH of a 3% suspension in water is between 4.0 and 6.5. Store in airtight containers.

Profile

Benzathine phenoxymethylpenicillin has actions and uses similar to those of phenoxymethylpenicillin (p.314) and is given orally in the treatment of susceptible mild to moderate infections. Doses are expressed in terms of phenoxymethylpenicillin.

Preparations

USP 31: Penicillin V Benzathine Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Abbocillin-V; Cilicaine V; ***Austria:*** Ospen; ***Canad.:*** Pen-Vee†; ***Cz.:*** Ospen; ***Fr.:*** Oracilline; ***Ger.:*** InfectoBicillin; ***Gr.:*** Ospen; ***Hung.:*** Ospen; Oxybion†; ***Pol.:*** Ospen; ***Rus.:*** Ospen (Оспен); ***Spain:*** Benoral; ***Switz.:*** Ospen; Phenocillin; ***Turk.:*** Pen-Os; ***Venez.:*** Ospen.

Benzylpenicillin *(BAN, rINN)*

Bencilpenicilina; Bensylpenicillin; Bentsyylipenisilliini; Benzil Penisiliin; Benzylpénicilline; Benzylpenicillinum; Crystalline Penicillin G; Penicillin; Penicillin G; Penisilin G. (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; (6*R*)-6-(2-Phenylacetamido)penicillanic acid.

Бензилпенициллин

$C_{16}H_{18}N_2O_4S$ = 334.4.

CAS — 61-33-6.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QJ51CE01; QS01AA14.

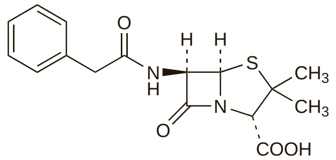

Description. The name benzylpenicillin is commonly used to describe either benzylpenicillin potassium or benzylpenicillin sodium as these are the forms in which benzylpenicillin is used. In *Martindale*, benzylpenicillin means either the potassium or sodium salt.

Benzylpenicillin Potassium *(BANM, rINNM)*

Bencilpenicilina potásica; Bensylpenicillinkalium; Bentsyylipenisilliinikalium; Benzilpenicilino kalio druska; Benzilpenicillin-kálium; Benzylopenicylina potasowa; Benzylpenicilin draselná sůl; Benzylpénicilline potassique; Benzylpenicillinum kalicum; Kalii Benzylpenicillinum; Penicillin G Potassium; Penisilin G Potasyum.

Калия Бензилпенициллин

$C_{16}H_{17}KN_2O_4S$ = 372.5.

CAS — 113-98-4.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Potassium). The potassium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Potassium). Colourless or white crystals, or white crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Very soluble in water, in sodium chloride 0.9%, and in glucose solutions; sparingly soluble in alcohol. Its solutions retain substantially full potency for several days at temperatures below 15°, but are rapidly inactivated by acids, by alkali hydroxides, by glycerol, and by oxidising agents. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility and stability. As for Benzylpenicillin Sodium, below.

Benzylpenicillin Sodium *(BANM, rINNM)*

Bencilpenicilina sódica; Bensylpenicillinnatrium; Bentsyylipenisilliininatrium; Benzilpenicilino natrio druska; Benzilpenicillin-nátrium; Benzylopenicylina sodowa; Benzylpenicilin sodná sůl; Benzylpénicilline sodique; Benzylpenicillinum natricum; Natrii Benzylpenicillinum; Penicillin G Sodium; Sodyum Penisilin G.

Натрий Бензилпенициллин

$C_{16}H_{17}N_2NaO_4S$ = 356.4.

CAS — 69-57-8.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Sodium). The sodium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Sodium). Colourless or white crystals, or white to slightly yellow crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15°. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidising agents, and by penicillinase. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility. Benzylpenicillin has been reported to be incompatible with metal ions and some rubber products. Its stability may be affected by ionic and nonionic surfactants, oxidising and reducing agents, alcohols, glycerol, glycols, macrogols and other hydroxy compounds, some paraffins and bases, some preservatives such as chlorocresol or thiomersal, carbohydrate solutions in an alkaline pH, fat emulsions, blood and blood products, and viscosity modifiers. Benzylpenicillin is incompatible with a wide range of acidic and basic drugs (see Stability, below) and with a number of other antimicrobials, including amphotericin B, some cephalosporins, and vancomycin. Benzylpenicillin and aminoglycosides are mutually incompatible and injections should be given at separate sites.

Stability. Benzylpenicillin is hydrolysed in aqueous solutions by degradation of the beta-lactam ring and hydrolysis is accelerated by increased temperature or alkaline conditions; inactivation also occurs under acid conditions. Degradation products include penillic, penicillenic, and penicilloic acids which lower the pH and cause a progressive increase in the rate of deterioration; *N*-formylpenicillamine and very small amounts of penicillamine have also been detected. Degradation is minimal at about pH 6.8 and deterioration of benzylpenicillin in solution may be retarded by using a citrate buffer. Dilute solutions are more stable than concentrated ones.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2** (Mar): 22–39.
2. Bird AE, *et al.* N-Formylpenicillamine and penicillamine as degradation products of penicillins in solution. *J Pharm Pharmacol* 1986; **38:** 913–17.

Units

The second International Standard Preparation (1952) of benzylpenicillin sodium contained 1670 units of penicillin per mg but was withdrawn in 1968 since penicillin can now be characterised completely by chemical tests. Despite this, doses of benzylpenicillin are still expressed in units in some countries.

Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal.

Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; a sore mouth or tongue or a black hairy tongue have occasionally been reported. Pseudomembranous colitis has been associated with the use of most antibiotics; ampicillin or amoxicillin are the most frequently implicated penicillins (see Antibiotic-associated Colitis, p.171).

Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal dosage and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used.

Hepatitis and cholestatic jaundice have been reported rarely with some penicillins, notably penicillinase-resistant penicillins such as flucloxacillin and oxacillin, and also combinations of amoxicillin or ticarcillin with clavulanic acid.

Nephropathy and interstitial nephritis, which may have some immunological basis, have been especially associated with meticillin, but may be produced by other penicillins.

Some patients with syphilis and other spirochaete infections may experience a Jarisch-Herxheimer reaction shortly after starting treatment with penicillin, which is probably due to the release of endotoxins from the killed treponemes and should not be mistaken for a hypersensitivity reaction. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis, or where there is a serious risk of increased local damage, such as with optic atrophy.

Hypersensitivity. The overall incidence of allergic reactions to penicillin has been reported to vary from about 1 to 10% although some patients may have been incorrectly labelled 'allergic to penicillin'. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking oral penicillin.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia. Reactions are considered to be due mainly to breakdown products produced *in vitro* before use or to metabolites of penicillin, and possibly penicillin itself. These act as haptens which, when combined with proteins and other macromolecules, produce potential antigens. As the hypersensitivity is related to the basic penicillin structure, patients who are genuinely allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other beta-lactam antibiotics.

Tests for hypersensitivity may be used to determine those patients most likely to develop serious allergic reactions to penicillins. Skin tests are used to evaluate the current risk of immediate or accelerated IgE-mediated reactions, the most serious being anaphylaxis. Both the major and minor determinants of penicillin hypersensitivity should be used; the major determinant is available as penicilloyl-polylysine (p.2364) and a minor-determinant mixture consisting of benzylpenicillin and its derivatives, including penicilloic acid and benzylpenicilloylamine, can be used, although if this is not available a solution of benzylpenicillin may be substituted. Adrenaline should be available in case an anaphylactic reaction develops. The results of skin tests are unreliable if a significant time has elapsed before beginning therapy. A number of *in-vitro* tests including the radioallergosorbent test (RAST) have been developed.

Desensitisation may be attempted in patients allergic to penicillin when treatment with penicillin is considered essential. It involves very small doses of penicillin given at relatively short intervals of 15 minutes or more, and gradually increased to therapeutic concentrations. However, desensitisation may be hazardous and should only be carried out if the patient can be monitored continuously and adrenaline and resuscitation equipment are immediately available. Desensitisation should be regarded as temporary, and allergic reactions may recur during the next exposure to penicillin.

Neutropenia. Neutropenia has been widely reported in patients given high doses of beta lactams and an incidence of from 5 to more than 15% has been reported in patients treated for 10 days or more. Warning signs include fever, rash, and eosinophilia. Monitoring of the leucocyte count is recommended during long-term treatment with high doses. Some have proposed a direct toxic effect whereas others have postulated an immune mechanism.

Effects on the blood. References to neutropenia associated with penicillins.

1. Anonymous. Antibiotic-induced neutropenia. *Lancet* 1985; **ii:** 814.
2. Neftel KA, *et al.* Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. *J Infect Dis* 1985; **152:** 90–8.
3. Olaison L, Alestig K. A prospective study of neutropenia induced by high doses of β-lactam antibiotics. *J Antimicrob Chemother* 1990; **25:** 449–53.
4. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.

The symbol † denotes a preparation no longer actively marketed

Effects on the nervous system. References to CNS effects associated with penicillins.

1. Schliamser SE, *et al.* Neurotoxicity of β-lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991; **27:** 405–25.

Hypersensitivity. References to hypersensitivity reactions associated with penicillins.

1. Sullivan TJ, *et al.* Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; **68:** 171–80.
2. Beeley L. Allergy to penicillin. *BMJ* 1984; **288:** 511–12.
3. Holgate ST. Penicillin allergy: how to diagnose and when to treat. *BMJ* 1988; **296:** 1213–14.
4. Anonymous. Penicillin allergy in childhood. *Lancet* 1989; **i:** 420.
5. Surtees SJ, *et al.* Allergy to penicillin: fable or fact? *BMJ* 1991; **302:** 1051–2. Correspondence. *ibid.*: 1462–3.
6. Anonymous. Penicillin allergy. *Drug Ther Bull* 1996; **34:** 87–8.
7. Salkind AR, *et al.* Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285:** 2498–2505.

Precautions

Patients known to be hypersensitive to penicillins should be given an antibacterial of another class. However, sensitised patients may also react to the cephalosporins and other beta lactams. Desensitisation may be attempted if treatment with a penicillin is considered essential (see Adverse Effects, above). Penicillins should be given with caution to patients with a history of allergy, especially to drugs.

Care is necessary if very high doses of penicillins are given, especially if renal function is poor, because of the risk of neurotoxicity. The intrathecal route should be avoided. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Because of the Jarisch-Herxheimer reaction, care is also necessary when treating patients with spirochaete infections, particularly syphilis.

Skin contact with penicillins should be avoided since sensitisation may occur.

Penicillin therapy changes the normal bacterial flora and can lead to superinfection with penicillin-resistant organisms including *Clostridium difficile* or *Candida*, particularly with prolonged use.

Penicillins may interfere with some diagnostic tests such as those for urinary glucose using copper sulfate, direct antiglobulin (Coombs') tests, and some tests for urinary or serum proteins. Penicillins may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Potassium and sodium content. Each g of benzylpenicillin potassium contains about 2.7 mmol of potassium and each g of benzylpenicillin sodium contains about 2.8 mmol of sodium. Care is necessary if large doses of the potassium or sodium salts are given to patients with renal impairment or heart failure. High doses of benzylpenicillin potassium should also be used with caution in patients receiving potassium-containing drugs or potassium-sparing diuretics.

Interactions

Probenecid prolongs the half-life of benzylpenicillin by competing with it for renal tubular secretion and may be used therapeutically for this purpose. Benzylpenicillin may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines (see Antimicrobial Action, below), and may be incompatible *in vitro* with other drugs, including some other antibacterials (see above).

The possibility of a prolonged bleeding time after oral treatment with a broad-spectrum drug like ampicillin should be borne in mind in patients receiving anticoagulants.

Hormonal contraceptives. For the effect of penicillins on oral contraceptives, see p.2068.

Methotrexate. For the effect of penicillins on methotrexate, see p.748.

Antimicrobial Action

Benzylpenicillin is a beta-lactam antibiotic and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

Mechanism of action. It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. However, it is now realised that other earlier stages in cell-wall synthesis can also be inhibited. Other mechanisms involved include bacterial lysis by the inactivation of endogenous inhibitors of bacterial autolysins.

Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Many Gram-negative organisms are intrinsically resistant by virtue of the inability of benzylpenicillin to penetrate their outer membranes. Intrinsic resistance can also be due to structural differences in the target penicillin-binding proteins. See under Resistance, below, for reference to acquired resistance.

Spectrum of activity. The following pathogenic organisms are usually sensitive to benzylpenicillin:

- Gram-positive aerobes and anaerobes including *Bacillus anthracis*, *Clostridium perfringens*, *Cl. tetani*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, *Listeria monocytogenes*, *Peptostreptococcus* spp., non-beta-lactamase-producing staphylococci, and streptococci including *Streptococcus agalactiae* (group B), *Str. pneumoniae* (pneumococci), *Str. pyogenes* (group A), and some viridans streptococci; enterococci are relatively insensitive.
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *Neisseria gonorrhoeae* (gonococci), although beta-lactamase-producing strains are common.
- Gram-negative bacilli including *Pasteurella multocida*, *Streptobacillus moniliformis*, and *Spirillum minus* (or *minor*); most Gram-negative bacilli, including *Pseudomonas* spp. and Enterobacteriaceae, are insensitive although some strains of *Proteus mirabilis* and *Escherichia coli* may be inhibited by high concentrations of benzylpenicillin.
- Gram-negative anaerobes including *Prevotella* (non-fragilis *Bacteroides*) and *Fusobacterium* spp.
- Other organisms including *Actinomyces* and the spirochaetes, *Borrelia*, *Leptospira*, and *Treponema* spp.
- Mycobacteria, fungi, mycoplasmas, and rickettsias are not sensitive.

Activity with other antimicrobials. Benzylpenicillin may exhibit synergy with other antimicrobials, particularly the aminoglycosides, and such combinations have been used against enterococci and other relatively insensitive bacteria. Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been demonstrated for beta-lactam combinations. Antagonism has been reported to occur with some bacteriostatic drugs, such as chloramphenicol or tetracyclines, that interfere with active bacterial growth necessary for benzylpenicillin to achieve its effect.

Resistance. Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. This resistance is usually plasmid-mediated and can be transferred from one bacterium to another. Gram-negative bacteria produce beta-lactamases within their cell membranes which may be chromosomally or plasmid-mediated; all Gram-negative species probably contain small amounts of beta-lactamases. Resistance in Gram-negative species may also be due to changes in their outer membrane resulting in the failure of beta lactams to reach their target penicillin-binding proteins. Changes in the binding characteristics of penicillin-binding proteins may also result in resistance in Gram-positive and Gram-negative bacteria.

Most strains of *Staphylococcus aureus* are now resistant to benzylpenicillin. *Streptococcus pneumoniae* with reduced susceptibility or complete resistance to benzylpenicillin have increasingly been reported. Strains of *Neisseria meningitidis* with reduced sensitivity to benzylpenicillin have been identified. Penicillinase-producing *Neisseria gonorrhoeae* are widespread; reduced sensitivity of gonococci to benzylpenicillin may also result from alterations in penicillin-binding proteins. Most strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are now resistant.

Some organisms, usually Gram-positive cocci such as staphylococci or streptococci, may develop tolerance and are inhibited but not killed by benzylpenicillin; in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration.

Pharmacokinetics

Benzylpenicillin rapidly appears in the blood after intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma concentrations of about 12 micrograms/mL have been reported after single doses of 600 mg.

When given orally, benzylpenicillin is inactivated fairly rapidly by gastric acid and only up to about 30% is absorbed, mainly from the duodenum; maximum plasma-penicillin concentrations usually occur in about 1 hour. In order to attain plasma-penicillin concentrations after oral use similar to those after intramuscular injection, up to 5 times as much benzylpenicillin may be necessary. Absorption varies greatly in different individuals and is better in patients with reduced gastric acid production, including neonates and the elderly. Food decreases the absorption of benzylpenicillin and oral doses are best given at least half an hour before or 2 to 3 hours after a meal.

Benzylpenicillin is widely distributed at varying concentrations in body tissues and fluids. It appears in pleural, pericardial, peritoneal, and synovial fluids, but in the absence of inflammation diffuses only to a small extent into abscess cavities, avascular areas, the eye, the middle ear, and the CSF. Inflamed tissue is, however, more readily penetrated and, for example, in meningitis higher concentrations of benzylpenicillin are achieved in the CSF. Active transport out of the CSF is reduced by probenecid. In patients with uraemia, other organic acids may accumulate in the CSF and compete with benzylpenicillin for active transport; toxic concentrations of benzylpenicillin sufficient to cause convulsions can result.

Benzylpenicillin diffuses across the placenta into the fetal circulation, and small amounts appear in breast milk.

The plasma half-life is about 30 minutes, although it may be longer in neonates and the elderly because of reduced renal function. In renal impairment the half-life may be increased to about 10 hours. Approximately 60% is reported to be bound to plasma protein.

Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivative has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion and about 20% of a dose given by mouth appears unchanged in the urine; about 60 to 90% of a dose of aqueous benzylpenicillin given intramuscularly appears in the urine, mainly within the first hour. Significant concentrations are achieved in bile, but in patients with normal renal function only small amounts are excreted via the bile. Benzylpenicillin is removed by haemodialysis.

Renal tubular secretion is inhibited by probenecid (p.558), which is sometimes given to increase plasma-penicillin concentrations.

Uses and Administration

Benzylpenicillin is used in the treatment of infections due to susceptible organisms (see Antimicrobial Action, above). They include abscess, actinomycosis, anthrax, bites and stings, diphtheria, endocarditis, gas gangrene, leptospirosis, Lyme disease, meningitis, meningococcal infections, necrotising enterocolitis, necrotising fasciitis, neonatal conjunctivitis (if gonococci are sensitive), perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), pharyngitis (or tonsillitis), pneumonia, skin infections, syphilis (neurosyphilis and congenital syphilis), tetanus, toxic shock syndrome, and Whipple's disease. It is also used for surgical infection prophylaxis in first trimester abortion in women at high risk of pelvic infection. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Benzylpenicillin is usually given intramuscularly or intravenously. For some indications benzathine benzylpenicillin (p.212) or procaine benzylpenicillin (p.319), which provide a prolonged effect, are preferred; they are given intramuscularly. Benzylpenicillin is sometimes given orally for infections of moderate severity, but one of the acid-resistant penicillins such as phenoxymethylpenicillin (p.314) is preferable.

Benzylpenicillin is available as the potassium or sodium salt. The dose of benzylpenicillin should be sufficient to achieve an optimum bactericidal concentration in the blood as rapidly as possible; concentrations may be increased by giving it with probenecid (p.559). In some countries, doses are still expressed in units. Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

For some infections, adult doses of 0.6 to 4.8 g of benzylpenicillin daily in 2 to 4 divided doses by intramuscular or slow intravenous injection or intravenous infusion may be adequate, but higher doses given intravenously, often by infusion, are more usual for severe infections. For example, in endocarditis, benzylpenicillin 7.2 g daily (1.2 g every 4 hours) intravenously, usually with an aminoglycoside, is recommended; doses of up to 18 g daily are not unusual for less sensitive streptococci and enterococci. In meningococcal and pneumococcal meningitis, benzylpenicillin 14.4 g daily (2.4 g every 4 hours) intravenously is recommended; up to 18 g daily has been recommended for meningococcal meningitis. High doses should be given slowly to avoid irritation of the CNS and electrolyte imbalance, and a rate of not more than 300 mg/minute is recommended for intravenous doses above 1.2 g. High doses may need to be reduced in patients with renal impairment.

Infants and children from 1 month to 12 years may be given 100 mg/kg daily in 4 divided doses; infants aged 1 to 4 weeks, 75 mg/kg daily in 3 divided doses; and neonates 50 mg/kg daily in 2 divided doses.

As in adults, higher paediatric doses may be necessary in severe infections. A dose of 180 to 300 mg/kg daily given intravenously in 4 to 6 divided doses is recommended for meningococcal meningitis in infants and children from 1 month to 12 years of age; infants aged 1 to 4 weeks may be given 150 mg/kg daily in 3 divided doses; neonates up to 7 days old may be given 100 mg/kg daily in 2 divided doses.

In patients with suspected meningococcal infection, an intravenous or intramuscular injection of benzylpenicillin should be given before transfer to hospital. Doses are: adults and children aged 10 years or more, 1.2 g; children aged 1 to 9 years, 600 mg; children under 1 year, 300 mg.

A dose for intrapartum prophylaxis against group B streptococcal infection is benzylpenicillin 3 g intravenously initially, then 1.5 g every 4 hours until delivery.

Other routes. Benzylpenicillin eye drops and eye ointment are used in the treatment of susceptible eye infections. For subconjunctival injection, 300 or 600 mg of benzylpenicillin has been dissolved in 0.5 to 1.0 mL of water, or another suitable solvent such as lidocaine 2% with or without adrenaline 1 in 200 000 or similar.

Benzylpenicillin has also been given orally on an empty stomach in adult doses of 125 to 312 mg every 4 to 6 hours.

Intrathecal injections are no longer recommended.

Preparations

BP 2008: Benzylpenicillin Injection;
USP 31: Penicillin G Potassium Capsules; Penicillin G Potassium for Injection; Penicillin G Potassium for Oral Solution; Penicillin G Potassium Injection; Penicillin G Potassium Tablets; Penicillin G Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Penilfedrin P; ***Austral.:*** Benpen; ***Braz.:*** Aricilina; Benzecilin; Cristalpen; Megapen†; Pencil P; ***Canad.:*** Crystapen; ***Fin.:*** Geepenil; ***India:*** Pencip; Pentids; ***Irl.:*** Crystapen; ***Mex.:*** Farmabep; Pendiben L-A; Pengesod; Penisol; Procasol; Prosodina; Sodipen; Unicil 3/1; Unicil 6:3:3; Unicil Mega; Xozacil†; ***NZ:*** Benpen; ***Philipp.:*** Pencarv; ***S.Afr.:*** Benzatec; Bio-Pen; Novopen†; ***Spain:*** Coliriocilina†; Penibiot; Penilevel; Peniroger†; Sodiopen; Unicilina; ***Turk.:*** Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Kristapen; Kristasil; Penadur 6.3.3; Pencrist; Penkain-K; Pensilina; Procillin; ***UK:*** Crystapen; ***USA:*** Pfizerpen; ***Venez.:*** Pebencil†; Pronapen; Silcopen†.

Multi-ingredient: ***Austria:*** Fortepen; Ophcillin N; Retarpen compositum; ***Braz.:*** Benapen; Benzapen G; Despacilina; Drenovac†; Expectovac†; Ginurovac†; Linfocilin†; Odontovac†; Ortocilin†; Pencil 400; Penkaron; Wycillin; ***Chile:*** Karbasalin†; Prevepen Forte; ***Fr.:*** Biclinocilline; ***Ger.:*** Bipensaar; Jenacillin A†; Retacillin compositum; ***Hong Kong:*** Penicillin G Procaine Fortified; ***Hung.:*** Promptcillin Forte; ***India:*** Bistrepen; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Aguipental; Anapenil; Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Hidrocilina; Lugaxil; Megapenil Forte; Pecivax; Pendiben Compuesto; Penicil; Penipot; Penisodina; Penprocilina; Procilin; Robencaxil; Suipen; ***Neth.:*** Penidural D/F†; ***Port.:*** Atralcilina; Atralmicina; Lentocilin; Penadur 6.3.3†; Prevecilina; ***Rus.:*** Bicillin-3 (Бициллин-3); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Aquicilina D A; Benzetacil Compuesta; Cepacilina 633; Neopenyl; Penilevel Retard; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Betamipron *(rINN)*

N-Benzoyl-β-alanine; Bétamipron; Betamipronum; CS-443. 3-Benzamidopropionic acid.

Бетамипрон

$C_{10}H_{11}NO_3$ = 193.2.
CAS — 3440-28-6.

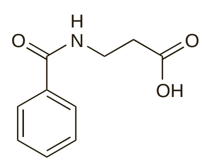

Profile

Betamipron is a renal protectant used with the carbapenem antibacterial panipenem to reduce its adverse renal effects.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Jpn:*** Carbenin.

Biapenem *(USAN, rINN)*

Biapénem; Biapenemum; CL-186815; L-627; LJC-10627. 6-{[(4*R*,5*S*,6*S*)-2-Carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio}-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]-*s*-triazol-4-ium hydroxide, inner salt.

Биапенем

$C_{15}H_{18}N_4O_4S$ = 350.4.
CAS — 120410-24-4.

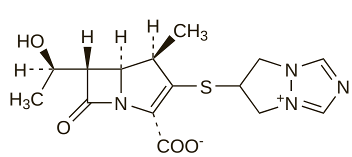

Profile

Biapenem is a carbapenem beta-lactam antibacterial similar to imipenem (p.286), although it is reported to be more stable to renal dehydropeptidase I than imipenem.

◊ Reviews.

1. Perry CM, Ibbotson T. Biapenem. *Drugs* 2002; **62:** 2221–34.

Brodimoprim *(rINN)*

Brodimoprima; Brodimoprime; Brodimoprimum. 2,4-Diamino-5-(4-bromo-3,5-dimethoxybenzyl)pyrimidine.

Бродимоприм

$C_{13}H_{15}BrN_4O_2$ = 339.2.
CAS — 56518-41-3.
ATC — J01EA02.
ATC Vet — QJ01EA02.

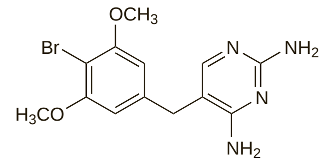

Profile

Brodimoprim is closely related structurally to trimethoprim (p.355) and has been used in the treatment of infections of the respiratory tract and ear.

◊ References.

1. Braunsteiner AR, Finsinger F. Brodimoprim: therapeutic efficacy and safety in the treatment of bacterial infections. *J Chemother* 1993; **5:** 507–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Novatrim†.

Broxyquinoline *(rINN)*

Broksikinoliini; Broxichinolinum; Broxikinolin; Broxiquinolina; Broxyquinolinum. 5,7-Dibromoquinolin-8-ol.

Броксихинолин

$C_9H_5Br_2NO$ = 303.0.
CAS — 521-74-4.
ATC — A07AX01; G01AC06; P01AA01.
ATC Vet — QA07AX01; QG01AC06.

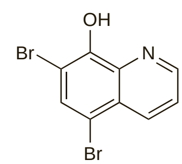

Profile

Broxyquinoline is a halogenated hydroxyquinoline used topically in vaginal infections. It was formerly given by mouth, with broxaldine, in the treatment of intestinal protozoal infections, including amoebiasis, but less toxic drugs are preferred.

Preparations

Proprietary Preparations (details are given in Part 3)
Fin.: Starogyn.
Multi-ingredient: ***Fin.:*** Senikolp†.

Capreomycin Sulfate *(USAN, rINNM)*

34977; Capreomycin Sulphate *(BANM)*; Capréomycine, Sulfate de; Capreomycini Sulfas; Capromycin Sulphate; Sulfato de capreomicina.

Капреомицина Сульфат

CAS — 11003-38-6 (capreomycin); 1405-37-4 (capreomycin sulfate).
ATC — J04AB30.
ATC Vet — QJ04AB30.

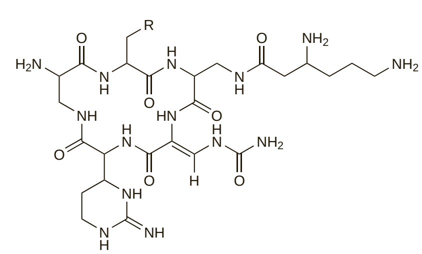

Capreomycin IA R = OH
Capreomycin IB R = H

(capreomycin)

The symbol † denotes a preparation no longer actively marketed

Description. Capreomycin I consists of capreomycin IA ($C_{25}H_{44}N_{14}O_8$ = 668.7) and capreomycin IB ($C_{25}H_{44}N_{14}O_7$ = 652.7), which predominates. Capreomycin II, which makes up about 10% of the mixture, consists of capreomycin IIA and capreomycin IIB.

Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Capreomycin Sulfate). The disulfate of capreomycin, a polypeptide mixture produced by the growth of *Streptomyces capreolus*. It contains not less than 90% of capreomycin I. A white to practically white amorphous powder. Freely soluble in water; practically insoluble in most organic solvents. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers.

Adverse Effects and Treatment

The effects of capreomycin on the kidney and eighth cranial nerve are similar to those of aminoglycosides such as gentamicin (p.282). Nitrogen retention, renal tubular dysfunction, and progressive renal damage may occur. Hypokalaemia and other electrolyte abnormalities have been reported. Vertigo, tinnitus, and hearing loss may also occur and are sometimes irreversible. Abnormalities in liver function have been reported when capreomycin has been used with other antituberculous drugs. Hypersensitivity reactions including urticaria, maculopapular rashes, and sometimes fever have been reported. Leucocytosis and leucopenia have also been observed. Thrombocytopenia has been reported rarely. Eosinophilia commonly occurs with capreomycin. Capreomycin also has a neuromuscular blocking action. There may be pain, induration, and excessive bleeding at the site of intramuscular injection; sterile abscesses may also form.

Teratogenicity has been seen after high doses in *rodents*.

Treatment of overdose is generally supportive. Patients with normal renal function should be hydrated to maintain adequate urine output. Capreomycin may be removed by haemodialysis in patients with significant renal impairment.

Impurities. The manufacturer of a highly-purified capreomycin product (*Capacin; Cheiljedang, Kor.*) has claimed that such purification reduces the toxicity and alters the pharmacokinetics in *animal* studies, suggesting that some of the toxicity of capreomycin is due to such impurities.[1]

1. Lee SH, *et al.* The impurities of capreomycin make a difference in the safety and pharmacokinetic profiles. *Int J Antimicrob Agents* 2003; **22:** 81–3.

Precautions

Capreomycin should be given with care and in reduced dosage to patients with renal impairment. Care is also essential in patients with signs of eighth cranial nerve damage. It is advisable to monitor renal and auditory function and serum-potassium concentrations in patients before and during therapy. Periodic assessment of hepatic function is also recommended.

Interactions

Care should be taken when capreomycin is used with other drugs that have neuromuscular blocking activity. It should not be given with other drugs that are ototoxic or nephrotoxic.

Antimicrobial Action

Capreomycin has activity against various mycobacteria. Resistance develops readily if capreomycin is used alone. It shows cross-resistance with kanamycin and neomycin.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.
2. Maus CE, *et al.* Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2005; **49:** 3192–7.

Pharmacokinetics

Capreomycin is poorly absorbed from the gastrointestinal tract. An intramuscular dose of 1 g has been reported to give a peak serum concentration of about 30 micrograms/mL after 1 or 2 hours. About 50% of a dose is excreted unchanged in the urine by glomerular filtration within 12 hours. Capreomycin is removed by haemodialysis.

Uses and Administration

Capreomycin is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p.196) as part of a multidrug regimen when resistance to primary drugs has developed.

Capreomycin is given as the sulfate by deep intramuscular injection or by intravenous infusion. The usual dose is the equivalent of 1 g of capreomycin base (maximum 20 mg/kg) given daily for 2 to 4 months, then 2 or 3 times weekly for the remainder of therapy.

For details of doses in infants, children, and adolescents, see below.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) suggests an intramuscular dose of capreomycin 15 to 30 mg/kg daily, to a maximum dose of 1 g daily.

Administration in renal impairment. As with aminoglycosides, the dose of capreomycin in patients with renal impairment must be reduced based on creatinine clearance; the desired steady-state serum capreomycin level is 10 micrograms/mL.

Preparations

USP 31: Capreomycin for Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Capastat; ***Austria:*** Capastat; ***Cz.:*** Capastat†; ***Gr.:*** Capastat; ***Rus.:*** Capastat (Капастат); Lykocin (Лайкоцин); ***Spain:*** Capastat; ***UK:*** Capastat; ***USA:*** Capastat.

Carbadox *(BAN, USAN, pINN)*

Carbadoxum; GS-6244. Methyl 3-quinoxalin-2-ylmethylenecarbazate 1,4-dioxide.

Карбадокс

$C_{11}H_{10}N_4O_4$ = 262.2.

CAS — 6804-07-5.

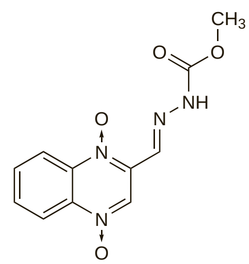

Profile

Carbadox is an antibacterial that has been used in veterinary practice for treating swine dysentery and enteritis and for promoting growth. However, its use has been prohibited in the EU and some other countries after reports of carcinogenicity.

Carbenicillin Sodium *(BANM, rINNM)*

BRL-2064; Carbenicilina sódica; Carbenicillin Disodium *(USAN)*; Carbénicilline sodique; Carbenicillinum natricum; α-Carboxybenzylpenicillin Sodium; CP-15-639-2; GS-3159 (carbenicillin potassium); Karbenicillin-nátrium; Karbenicylina sodowa; Natrii Carbenicillinum; NSC-111071. The disodium salt of (6*R*)-6-(2-carboxy-2-phenylacetamido)penicillanic acid .

Натрий Карбенициллин

$C_{17}H_{16}N_2Na_2O_6S$ = 422.4.

CAS — 4697-36-3 (carbenicillin); 4800-94-6 (carbenicillin disodium); 17230-86-3 (carbenicillin potassium).

ATC — J01CA03.

ATC Vet — QJ01CA03.

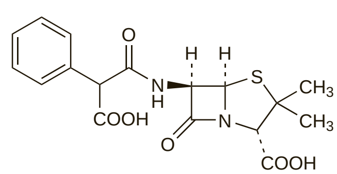

(carbenicillin)

Pharmacopoeias. In *Pol.* and *US.*
USP 31 (Carbenicillin Disodium). A white to off-white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of carbenicillin 1% is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. Carbenicillin sodium has been reported to be incompatible with aminoglycosides, tetracyclines, and a number of other drugs including other antimicrobials and these drugs should therefore be given separately.

Adverse Effects

As for Benzylpenicillin, p.213.

Hypersensitivity reactions have been reported to be less frequent and less severe with carbenicillin than with benzylpenicillin. Pain at the injection site and phlebitis may occur. Electrolyte disturbances, particularly hypokalaemia or hypernatraemia, may follow large doses of carbenicillin sodium.

A dose-dependent coagulation defect has been reported, especially in patients with renal impairment. Carbenicillin appears to interfere with platelet function thereby prolonging bleeding time; purpura and haemorrhage from mucous membranes and elsewhere may result.

Precautions

As for Benzylpenicillin, p.214.

Sodium content. Each g of carbenicillin sodium contains about 4.7 mmol of sodium. Carbenicillin sodium should therefore be given with caution to patients on a restricted sodium diet.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Carbenicillin has a bactericidal mode of action similar to that of benzylpenicillin, but with an extended spectrum of activity against Gram-negative bacteria. The most important feature of carbenicillin is its activity against *Pseudomonas aeruginosa*, although high concentrations are generally necessary. Activity against *Ps. aeruginosa* and some other organisms can be enhanced by gentamicin and other aminoglycosides. Carbenicillin is also active against *Proteus*, including indole-positive spp. such as *Pr. vulgaris*. It is comparable with ampicillin against other Gram-negative bacteria. Sensitive organisms include some Enterobacteriaceae, for example *Escherichia coli* and *Enterobacter* spp.; *Haemophilus influenzae*; and *Neisseria* spp. *Klebsiella* spp. are usually not susceptible. Its activity against Gram-positive bacteria is less than that of benzylpenicillin. Anaerobic organisms are generally susceptible to carbenicillin, but high concentrations are required for *Bacteroides fragilis*.

Resistance. Carbenicillin is inactivated by penicillinases and some other beta-lactamases, although it is more stable to the chromosomally mediated beta-lactamases produced by some Gram-negative organisms, including *Ps. aeruginosa* and some *Proteus* spp. Resistance to carbenicillin may develop in *Ps. aeruginosa* during treatment with carbenicillin or other beta lactams. This resistance may be intrinsic where there are changes in cell wall permeability or penicillin-binding proteins, or it may be due to plasmid-mediated beta-lactamase production that may be transferred to and from certain strains of Enterobacteriaceae.

There may be cross-resistance between carbenicillin and other antipseudomonal penicillins.

Outbreaks of pseudomonal resistance to carbenicillin have been associated with extensive use in, for example, hospital burns units.

Pharmacokinetics

Carbenicillin is not absorbed from the gastrointestinal tract and has therefore been given either intramuscularly or intravenously.

The half-life of carbenicillin is reported to be about 1 to 1.5 hours; it is increased in patients with renal impairment, especially if there is also hepatic impairment, and also in neonates. Half-lives of 10 to 18 hours have been reported in renal impairment. Clearance is enhanced in patients with cystic fibrosis. Carbenicillin is about 50% bound to plasma proteins. Distribution of carbenicillin in the body is similar to that of other penicillins. Small amounts have been detected in breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Relatively high concentrations have been reported in bile, but carbenicillin is excreted principally by renal tubular secretion and glomerular filtration.

Probenecid increases and prolongs plasma concentrations of carbenicillin.

Carbenicillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Uses and Administration

Carbenicillin is a carboxypenicillin that has been given by injection as the disodium salt, often with gentamicin, in the treatment of infections due to *Pseudomonas aeruginosa*; however, other antipseudomonal penicillins such as ticarcillin (p.352) or piperacillin (p.315) are now preferred. It has also been given to treat serious infections due to non-penicillinase-producing strains of *Proteus* spp.

Esters of carbenicillin, such as carfecillin (p.217) and carindacillin (p.217), have been given orally in the treatment of urinary-tract infections.

Preparations

USP 31: Carbenicillin for Injection.

Proprietary Preparations (details are given in Part 3)

Mex.: Carbecin†.

Carfecillin Sodium *(BANM, pINNM)*

BRL-3475; Carbenicillin Phenyl Sodium *(USAN)*; Carfecilina sódica; Carfécilline Sodique; Natrii Carfecillinum. Sodium (6*R*)-6-(2-phenoxycarbonyl-2-phenylacetamido)penicillanate.

Натрий Карфециллин

$C_{23}H_{21}N_2NaO_6S$ = 476.5.

CAS — 27025-49-6 (carfecillin); 21649-57-0 (carfecillin sodium).

ATC — G01AA08.

ATC Vet — QG01AA08.

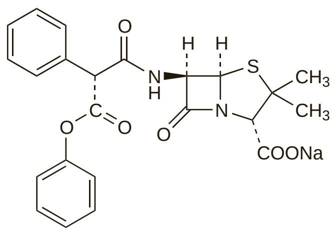

Profile

Carfecillin is the phenyl ester of carbenicillin (p.216) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use has been restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin Sodium *(BANM, pINNM)*

Carbenicillin Indanyl Sodium *(USAN)*; Carindacilina sódica; Carindacilline Sodique; CP-15464-2; Natrii Carindacillinum. Sodium (6*R*)-6-[2-(indan-5-yloxycarbonyl)-2-phenylacetamido]penicillanate.

Натрий Кариндациллин

$C_{26}H_{25}N_2NaO_6S$ = 516.5.

CAS — 35531-88-5 (carindacillin); 26605-69-6 (carindacillin sodium).

ATC — J01CA05.

ATC Vet — QJ01CA05.

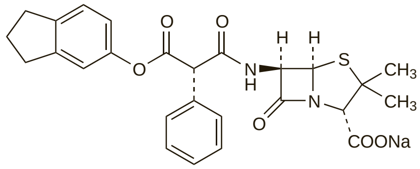

Pharmacopoeias. In *US*.

USP 31 (Carbenicillin Indanyl Sodium). A white to off-white powder. Soluble in water and in alcohol. pH of a 10% solution in water is between 5.0 and 8.0. Store in airtight containers.

Profile

Carindacillin is the indanyl ester of carbenicillin (p.216) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use is restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin is given orally as the sodium salt; 535 mg of carindacillin sodium is equivalent to about 382 mg of carbenicillin. Usual doses, expressed in terms of carbenicillin, are 382 to 764 mg four times daily.

Sodium content. Each g of carindacillin sodium contains about 1.9 mmol of sodium.

Preparations

USP 31: Carbenicillin Indanyl Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Geocillin†.

Carumonam Sodium *(BANM, USAN, rINNM)*

AMA-1080 (carumonam); Carumonam sódico; Carumonam Sodique; Natrii Carumonamum; Ro-17-2301 (carumonam); Ro-17-2301/006 (carumonam sodium). (*Z*)-(2-Aminothiazol-4-yl){[(2*S*,3*S*)-2-carbamoyloxymethyl-4-oxo-1-sulphoazetidin-3-yl]carbamoyl}methyleneamino-oxyacetic acid, disodium salt.

Натрий Карумонам

$C_{12}H_{12}N_6Na_2O_{10}S_2$ = 510.4.

CAS — 87638-04-8 (carumonam); 86832-68-0 (carumonam sodium).

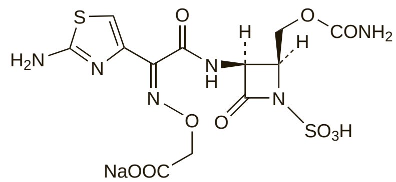

(carumonam)

Pharmacopoeias. In *Jpn*.

Profile

Carumonam is a monobactam antibacterial with a spectrum of antimicrobial action *in vitro* similar to that of aztreonam (p.209). It is given by intramuscular or intravenous injection as the sodium salt and doses are expressed in terms of carumonam; 1.09 g of carumonam sodium is equivalent to about 1 g of carumonam. The usual dose is 1 to 2 g daily in two divided doses.

Sodium content. Each g of carumonam sodium contains about 3.92 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Amasulin.

Cefaclor *(BAN, USAN, pINN)*

Céfaclor; Cefaclorum; Cefaclorum Monohydricum; Cefaklór; Cefaklor; Cefaklor monohydrát; Cefakloras; Compound 99638; Kefakloori; Sefaklor. (7*R*)-3-Chloro-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

Цефаклор

$C_{15}H_{14}ClN_3O_4S,H_2O$ = 385.8.

CAS — 53994-73-3 (anhydrous cefaclor); 70356-03-5 (cefaclor monohydrate).

ATC — J01DC04.

ATC Vet — QJ01DC04.

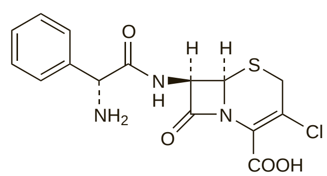

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 6.2 (Cefaclor). A white or slightly yellow powder. Slightly soluble in water; practically insoluble in dichloromethane and in methyl alcohol. A 2.5% suspension in water has a pH of 3.0 to 4.5.

USP 31 (Cefaclor). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in chloroform, in methyl alcohol, and in benzene. pH of a 2.5% suspension in water is between 3.0 and 4.5. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalexin, p.218.

Hypersensitivity. Serum-sickness-like reactions may be more common with cefaclor than several other oral antibacterials[1] especially in young children who have received a number of courses of cefaclor;[2] typical features include skin reactions and arthralgia. A relatively high incidence of anaphylactic reactions has been reported from Japan.[3]

There has been a report of myocarditis that developed as a hypersensitivity reaction to cefaclor in a 12-year-old child.[4]

1. McCue JD. Delayed detection of serum sickness caused by oral antimicrobials. *Adv Therapy* 1990; **7**: 22–7.
2. Vial T, *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; **26:** 910–14.
3. Hama R, Mori K. High incidence of anaphylactic reactions to cefaclor. *Lancet* 1988; **i**: 1331.
4. Beghetti M, *et al.* Hypersensitivity myocarditis caused by an allergic reaction to cefaclor. *J Pediatr* 1998; **132:** 172–3.

Interactions

As for Cefalexin, p.218.

Anticoagulants. UK licensed product information recommends that monitoring of prothrombin time should be considered in patients receiving cefaclor and *warfarin* after rare reports of increased prothrombin times. It is not known whether this interaction is related to the vitamin K-related hypoprothrombinaemia observed with some cephalosporins (see Adverse Effects of Cefamandole, p.221), but cefaclor does not contain the side-chain usually implicated in this reaction.

Antimicrobial Action

Cefaclor is bactericidal and has antimicrobial activity similar to that of cefalexin (p.218) but is reported to be more active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, and *Proteus mirabilis*, and especially against *Haemophilus influenzae*. It is active against some beta-lactamase-producing strains of *H. influenzae*. It may be less resistant to staphylococcal penicillinase than cefalexin or cefradine and a marked inoculum effect has been reported *in vitro*.

Pharmacokinetics

Cefaclor is well absorbed from the gastrointestinal tract. Oral doses of 250 mg, 500 mg, and 1 g produce peak plasma concentrations of about 7, 13, and 23 micrograms/mL respectively after 0.5 to 1 hour. The presence of food may delay the absorption of cefaclor, but the total amount absorbed is unchanged. A plasma half-life of 0.5 to 1 hour has been reported; it may be slightly prolonged in patients with renal impairment. About 25% is bound to plasma proteins.

Cefaclor appears to be widely distributed in the body; it crosses the placenta and low concentrations have been detected in breast milk. It is rapidly excreted by the kidneys; up to 85% of a dose appears unchanged in the urine within 8 hours, the greater part within 2 hours. High concentrations of cefaclor are achieved in the urine within 8 hours of a dose; peak concentrations of 600, 900, and 1900 micrograms/mL have been reported after doses of 0.25, 0.5, and 1 g respectively. Probenecid delays excretion. Some cefaclor is removed by haemodialysis.

◊ References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
2. Sourgens H, *et al.* Pharmacokinetic profile of cefaclor. *Int J Clin Pharmacol Ther* 1997; **35:** 374–80.

Uses and Administration

Cefaclor is a cephalosporin antibacterial given orally similarly to cefalexin in the treatment of susceptible infections including upper and lower respiratory-tract infections, skin infections, and urinary-tract infections. Some classify cefaclor as a second-generation cephalosporin and its greater activity against *Haemophilus influenzae* makes it more suitable than cefalexin for the treatment of infections such as otitis media. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefaclor is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefaclor; 1.05 g of cefaclor monohydrate is equivalent to about 1 g of anhydrous cefaclor. The usual adult dose is 250 to 500 mg every 8 hours; up to 4 g daily has been given. A suggested dose for children over 1 month of age is 20 mg/kg daily in three divided doses, increased if necessary to 40 mg/kg daily, but not exceeding a total daily dose of 1 g. A common dosage regimen is: children over 5 years, 250 mg three times daily; 1 to 5 years, 125 mg three times daily; under 1 year, 62.5 mg three times daily.

Modified-release formulations of cefaclor are available in some countries.

Preparations

BP 2008: Cefaclor Capsules; Cefaclor Oral Suspension; Prolonged-release Cefaclor Tablets;
USP 31: Cefaclor Capsules; Cefaclor Chewable Tablets; Cefaclor Extended-Release Tablets; Cefaclor for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Cec†; Cefaklon†; Cefral†; Kwicap†; ***Austral.:*** Aclor; Ceclor; Cefkor; Karlor; Keflor; Ozcef; ***Austria:*** Cec; Ceclor; Cefastad; Cefax; Lanacef†; ***Belg.:*** Ceclor; Doccefaclo; ***Braz.:*** Ceclor†; Cefacloren; Clorcin-Ped; Faclor†; Plecor†; Reflax†; ***Canad.:*** Ceclor; ***Chile:*** Keflor†; ***Cz.:*** Cec†; Ceclor; Servicior; Vercef; ***Fin.:*** Kefolor; ***Fr.:*** Alfatil; Alphexine†; Haxifal; ***Ger.:*** Cec; Ceclorbeta; Cef-Diolan; Cefa-Wolff†; Cephalodoc†; Hefaclor†; InfectoCef; Panoral; Sigacefal†; ***Gr.:*** Afecton; Camirox; Ceclor; Cefacloril; Fredyren; Hetaclox; Makovan; Panclor; Phacotrex; Ufoxillin†; ***Hong Kong:*** Castal; Ceclor; Cefalor; Medoclor; Qualiceclor; Qualiphor; Soficlor; Vercef; ***Hung.:*** Ceclor; Cecloretta; Vercef; ***India:*** Halocef; Keflor; ***Indon.:*** Capabi-

otic; Ceclor; Cloracef; Especlor; Forifek; Medikoncef; Soclor; ***Irl.:*** Cefager; Distaclor; Keftid; Pinaclor; ***Israel:*** Ceclor†; Cefalor; ***Ital.:*** Altaclor; Bacticef; Bactigram; Cefulton; Citiclor†; Clorad; Clorazer; Dorf; Erreclor†; Eurocefix†; Fuclode†; Geniclor; Kliacef; Lafarclor; Macovan; Necloral; Omaspir; Oralcef; Panacef; Performer; Selanir†; Selviclor; Takecef; Tibifor; Valeclor; ***Malaysia:*** Distaclor†; Sifaclor; Soficlor†; Vercef; ***Mex.:*** Arcefal; Cec; Ceclor; Cefalan; Ceflacid; Fasiclor; Fermed; Ranclor; Serviclor; Teraclox; ***Neth.:*** Ceclor; ***NZ:*** Clorotir; ***Philipp.:*** Aczebri; Brelox; Ceclobid; Ceclor; Clorotir; Ephron; Lorcef; Vefarol; Versef; Verzat; Xelent; Xeztron; ***Pol.:*** Ceclor; Cek; Kloracef†; Panclor; Serviclor; Vercef; ***Port.:*** Ceclor; ***Rus.:*** Ceclor (Цеклор); Vercef (Верцеф); ***S.Afr.:*** Cec; Ceclor†; CloraCEF†; Vercef; ***Singapore:*** Cleancef; Distaclor†; Soficlor; Vercef; ***Spain:*** Ceclor; ***Switz.:*** Ceclor; ***Thai.:*** Celco; Clorotir; Distaclor; Kefaclor†; Sifaclor; Tefaclor†; Vercef; ***Turk.:*** Ceclor; Kefsid; Losefar; ***UAE:*** Recocef; ***UK:*** Bacticlor; Distaclor; Keftid; ***USA:*** Ceclor; Raniclor; ***Venez.:*** Ceclor.

Multi-ingredient: ***Mex.:*** Ceclordox.

Cefadroxil *(BAN, USAN, pINN)*

BL-S578; Cefadroksilis monohidratas; Cefadroksyl jednowodny; Céfadroxil; Cefadroxil monohydrát; Céfadroxil monohydraté; Cefadroxilmonohydrat; Cefadroxilo; Cefadroxilum; Cefadroxilum monohydricum; Cephadroxil; Kefadroksiili; Kefadroksiilimonohydraatti; MJF-11567-3; Sefadroksil. (7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-methyl-3-cephem-4-carboxylic acid monohydrate.

Цефадроксил

$C_{16}H_{17}N_3O_5S,H_2O = 381.4.$

CAS — 50370-12-2 (anhydrous cefadroxil); 119922-85-9 (cefadroxil hemihydrate); 66592-87-8 (cefadroxil monohydrate).

ATC — J01DB05.

ATC Vet — QJ01DB05.

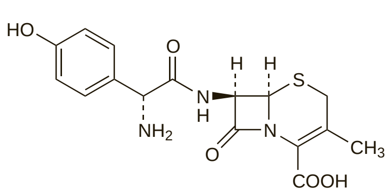

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 6.2 (Cefadroxil Monohydrate). A white or almost white powder. Slightly soluble in water; very slightly soluble in alcohol. A 5% suspension in water has a pH of 4.0 to 6.0. Protect from light.

USP 31 (Cefadroxil). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 4.0 and 6.0. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalexin, p.218.

Breast feeding. Although higher concentrations of cefadroxil were reported in breast milk compared with cefalexin, cefalotin, cefapirin, and cefotaxime,[1] no detectable cefadroxil would be expected in breast-fed infants and no adverse effects have been seen in infants whose mothers were receiving cefadroxil. Accordingly, the American Academy of Pediatrics considers[2] that cefadroxil is usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Interactions

As for Cefalexin, p.218.

Antimicrobial Action

As for Cefalexin, p.218.

Pharmacokinetics

Cefadroxil is almost completely absorbed from the gastrointestinal tract. After oral doses of 500 mg and 1 g, peak plasma concentrations of about 16 and 30 micrograms/mL respectively are obtained after 1.5 to 2 hours. Although peak concentrations are similar to those of cefalexin, plasma concentrations are more sustained. Dosage with food does not appear to affect the absorption of cefadroxil. About 20% of cefadroxil is reported to be bound to plasma proteins. The plasma half-life of cefadroxil is about 1.5 hours and is prolonged in patients with renal impairment.

Cefadroxil is widely distributed to body tissues and fluids. It crosses the placenta and appears in breast milk.

More than 90% of a dose of cefadroxil may be excreted unchanged in the urine within 24 hours by glomerular filtration and tubular secretion; peak urinary concentrations of 1.8 mg/mL have been reported after a dose of 500 mg. Cefadroxil is removed by haemodialysis.

◊ References.

1. Tanrisever B, Santella PJ. Cefadroxil: a review of its antibacterial, pharmacokinetic and therapeutic properties in comparison with cephalexin and cephradine. *Drugs* 1986; **32** (suppl 3): 1–16.
2. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
3. Garrigues TM, *et al.* Dose-dependent absorption and elimination of cefadroxil in man. *Eur J Clin Pharmacol* 1991; **41**: 179–83.

Uses and Administration

Cefadroxil is a first-generation cephalosporin antibacterial that is the para-hydroxy derivative of cefalexin (p.219), and is used similarly in the treatment of mild to moderate susceptible infections. It is given orally, and doses are expressed in terms of the anhydrous substance; 1.04 g of cefadroxil monohydrate is equivalent to about 1 g of anhydrous cefadroxil. The usual adult dose is 1 to 2 g daily as a single dose or in two divided doses. The following doses are used in children weighing less than 40 kg: 500 mg twice daily for those over 6 years of age, 250 mg twice daily for those aged 1 to 6 years, and 25 mg/kg daily in divided doses for infants under 1 year. For details of reduced doses of cefadroxil in patients with renal impairment, see below.

Cefadroxil has also been used as the lysine derivative.

Administration in renal impairment. Following an initial loading dose of 0.5 to 1 g, dosage of cefadroxil should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 26 to 50 mL/minute per 1.73 m^2: 0.5 to 1 g every 12 hours
- CC 11 to 25 mL/minute per 1.73 m^2: 0.5 to 1 g every 24 hours
- CC 10 mL/minute per 1.73 m^2 or less: 0.5 to 1 g every 36 hours.

Preparations

BP 2008: Cefadroxil Capsules; Cefadroxil Oral Suspension;
USP 31: Cefadroxil Capsules; Cefadroxil for Oral Suspension; Cefadroxil Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefabiot†; Cefacar; Cefacilina; Cefadrox; Cefamar; Cefasin; Cefatenk; Droxil; Kandicin; Klonadroxil†; Versatic; ***Austria:*** Biodroxil; Duracef; ***Belg.:*** Duracef; Moxacef†; ***Braz.:*** Cefadroxon; Cefamox; Celoxin†; Drofaxil†; Neo Cefadril; ***Canad.:*** Duricef; ***Chile:*** Adroxef; Biodroxil†; Cefamox; Sedafex; ***Cz.:*** Biodroxil; Cedrox†; Cefadrox†; Duracef; ***Fin.:*** Duracef; ***Fr.:*** Oracefal; ***Ger.:*** Cedrox†; Gruncef; ***Gr.:*** Cefalom†; Kleotrat†; Moxacef; Nefalox†; ***Hong Kong:*** Amben; Androxyl; Biodroxil; Duracef; Qualidrox; Sofidrox†; ***Hung.:*** Biodroxil†; Duracef; ***India:*** Cefadrox; Cefadur; Lactocef; Lydroxil; Odoxil; Pendrox; Vepan; Vistadrox; ***Indon.:*** Alxil; Ancefa; Bidicef; Biodroxil; Cefat; Dexacef; Doxef; Duricef; Erphadrox; Ethicef; Kelfex; Lapicef; Librocef; Longcef; Opicef; Osadrox; Pyricef; Q Cef; Qidrox; Renasistin; Roksicap; Sedrofen; Staforin; Tisacef; Widrox; ***Irl.:*** Ultracef; ***Israel:*** Biodroxil; Duracef†; ***Ital.:*** Cefadril; Ceoxil†; Cephos; Foxil; Oradroxil; ***Malaysia:*** Kefloxin; Sofidrox†; ***Mex.:*** Cefamox; Cepotec; Duracef; Teroxina; ***Philipp.:*** Drolex; Drozid; Lexipad; ***Pol.:*** Biodroxil; Duracef; ***Port.:*** Biofaxil†; Cefacile; Ceforal; Cefra†; ***S.Afr.:*** Cipadur; Dacef; Duracef; ***Singapore:*** Duricef; Sofidrox; ***Spain:*** Duracef; ***Swed.:*** Cefamox; ***Thai.:*** Cefadril†; ***Turk.:*** Cefradur; Duricef; ***UK:*** Baxan; ***USA:*** Duricef†; ***Venez.:*** Bidroxyl; Cedroxim; Cefadril†; Cefaval; Cefonax; Drocef; Droxifan; Grunicef; Sanodril.

Multi-ingredient: ***Arg.:*** Cefacar Mucolitico†; Cefacilina Bronquial; ***Mex.:*** Duracef Expec.

Cefalexin *(BAN, pINN)*

66873; Cefaleksinas monohidratas; Cefaleksyna; Cefalexin monohydrát; Cefalexina; Céfalexine; Céfalexine monohydratée; Cefalexinmonohydrat; Cefalexinum; Cefalexinum monohydricum; Cephalexin *(USAN)*; Kefaleksiini; Kefaleksiinimonohydraatti; Sefaleksin. (7*R*)-3-Methyl-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

Цефалексин

$C_{16}H_{17}N_3O_4S,H_2O = 365.4.$

CAS — 15686-71-2 (anhydrous cefalexin); 23325-78-2 (cefalexin monohydrate).

ATC — J01DB01.

ATC Vet — QJ01DB01; QJ51DA01.

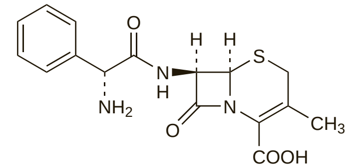

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Cefalexin Monohydrate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 31 (Cephalexin). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Cefalexin Hydrochloride *(BANM, pINNM)*

Céfalexine, Chlorhydrate de; Cefalexini Hydrochloridum; Cephalexin Hydrochloride *(USAN)*; Hidrocloruro de cefalexina; LY-061188.

Цефалексина Гидрохлорид

$C_{16}H_{17}N_3O_4S,HCl,H_2O = 401.9.$

CAS — 105879-42-3.

ATC — J01DB01.

ATC Vet — QJ01DB01.

Pharmacopoeias. In *US.*

USP 31 (Cephalexin Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 100 in water, in acetone, in acetonitrile, in alcohol, in dimethylformamide, and in methyl alcohol; practically insoluble in chloroform, in ether, in ethyl acetate, and in isopropyl alcohol. pH of a 1% solution in water is between 1.5 and 3.0. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

The most common adverse effects of cefalexin and other oral cephalosporins are generally gastrointestinal disturbances and hypersensitivity reactions. Pseudomembranous colitis has been reported.

◊ References.

1. Dave J, *et al.* Cephalexin induced toxic epidermal necrolysis. *J Antimicrob Chemother* 1991; **28**: 477–8.
2. Baran R, Perrin C. Fixed-drug eruption presenting as an acute paronychia. *Br J Dermatol* 1991; **125**: 592–5.
3. Clark RF. Crystalluria following cephalexin overdose. *Pediatrics* 1992; **89**: 672–4.
4. Murray KM, Camp MS. Cephalexin-induced Stevens-Johnson syndrome. *Ann Pharmacother* 1992; **26:** 1230–3.
5. Czechowicz RT, *et al.* Bullous pemphigoid induced by cephalexin. *Australas J Dermatol* 2001; **42:** 132–5.
6. Longstreth KL, *et al.* Cephalexin-induced acute tubular necrosis. *Pharmacotherapy* 2004; **24:** 808–11.
7. Skoog SM, *et al.* Cephalexin-induced cholestatic hepatitis. *J Clin Gastroenterol* 2004; **38:** 833.
8. Penttilä J, *et al.* Delirium in an adolescent patient during treatment with cephalexin. *J Adolesc Health* 2006; **39:** 782–3.

Porphyria. Cefalexin is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

The renal excretion of cefalexin, and many other cephalosporins, is delayed by probenecid.

Hormonal contraceptives. There have been isolated reports of cefalexin decreasing the efficacy of oestrogen-containing oral contraceptives.[1] For a discussion of decreased efficacy of oral contraceptives and the need for additional contraceptive methods in patients taking broad-spectrum antibacterials, see under Hormonal Contraceptives, p.2068.

1. Friedman M, *et al.* Cephalexin and Microgynon-30 do not go well together. *J Obstet Gynaecol* 1982; **2**: 195–6.

Antimicrobial Action

As for Cefalotin Sodium, p.220, although cefalexin is generally less potent. Some strains of Gram-negative bacteria may be inhibited only by the high concentrations achievable in the urinary tract. *Haemophilus influenzae* is moderately resistant to cefalexin.

Pharmacokinetics

Cefalexin is almost completely absorbed from the gastrointestinal tract and produces a peak plasma concentration of about 18 micrograms/mL 1 hour after a 500-mg oral dose. If cefalexin is taken with food, absorption may be delayed, but the total amount absorbed is not appreciably altered. Up to 15% of a dose is bound to plasma proteins. The plasma half-life is about 1 hour; it increases with reduced renal function.

Cefalexin is widely distributed in the body but does not enter the CSF in significant quantities. It crosses the placenta and small quantities are found in breast milk. Cefalexin is not metabolised. About 80% or more of a dose is excreted unchanged in the urine in the first 6 hours by glomerular filtration and tubular secretion; urinary concentrations greater than 1 mg/mL have been achieved after a dose of 500 mg. Probenecid delays urinary excretion. Therapeutically effective concentrations may be found in the bile and some may be excreted by this route.

Cefalexin is removed by haemodialysis and peritoneal dialysis.

◊ References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.

Uses and Administration

Cefalexin is a first-generation cephalosporin antibacterial. It is given orally for the treatment of susceptible infections including those of the respiratory and urinary tracts and of the skin (see under Choice of Antibacterial, p.162). For severe infections, treatment with parenteral cephalosporins is to be preferred.

Cefalexin is usually given as the monohydrate although the hydrochloride is sometimes used. Doses are expressed in terms of the equivalent amount of anhydrous cefalexin; 1.05 g of cefalexin monohydrate and 1.16 g of cefalexin hydrochloride are each equivalent to about 1 g of anhydrous cefalexin.

The usual dose for adults is 1 to 2 g daily given in divided doses at 6-, 8-, or 12-hourly intervals; in severe or deep-seated infections the dose can be increased to up to 6 g daily but when high doses are required the use of a parenteral cephalosporin should be considered. Children may be given 25 to 100 mg/kg daily in divided doses to a maximum of 4 g daily.

For the prophylaxis of recurrent urinary-tract infection, cefalexin may be given in a dose of 125 mg at night.

Cefalexin sodium or cefalexin lysine have been used parenterally.

The dose of cefalexin may need to be reduced in renal impairment, see below.

Administration in renal impairment. Doses of cefalexin may need to be reduced in patients with renal impairment. The *BNF* recommends the following maximum daily doses according to creatinine clearance (CC):

- CC 40 to 50 mL/minute: maximum 3 g daily
- CC 10 to 40 mL/minute: maximum 1.5 g daily
- CC less than 10 mL/minute: maximum 750 mg daily

Preparations

BP 2008: Cefalexin Capsules; Cefalexin Oral Suspension; Cefalexin Tablets; ***USP 31:*** Cephalexin Capsules; Cephalexin for Oral Suspension; Cephalexin Tablets; Cephalexin Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Beliam; Cefalexi†; Cefapoten; Cefarinol; Cefasporina; Cefosporen; Ceporexin; Fabotop; Keforal; Lars; Lexin; Lorbicefax; Novalexin; Pectorina†; Permvastat; Sanibiotic; Septilisin; Trexina; Triblix; Velexina; ***Austral.:*** Cilex; Ialex; Ibilex; Keflex; Rancef; Sporahexal; ***Austria:*** Cepexin; Cephalobene; Keflex; Ospexin; Sanaxin; ***Belg.:*** Ceporex†; Keforal; ***Braz.:*** Betacef†; Cefaben; Cefagel; Cefagon†; Cefagran; Cefalexan†; Cefanal; Cefaxon; Cefexina; Ceflexin†; Celen; Celexin; Celinax†; Ceporexin†; Falexin†; Kefalexin†; Keflaxina†; Keflex; Keforal; Kiflexin†; Lexin; Lifalexin†; Neo Ceflex; Neoceflex; Primacef; Profalexina; Todexin†; Valflex; ***Canad.:*** Apo-Cephalex; Novo-Lexin; Nu-Cephalex; ***Cz.:*** Cefaclen; Oracef†; Ospexin; Sporidex; ***Denm.:*** Keflex; ***Fin.:*** Kefalex; Kefexin; Orakef†; ***Fr.:*** Cefacet; Ceporexine; Keforal; ***Ger.:*** Cephalex; Ceporexin†; Oracef†; ***Hong Kong:*** Anxer; Cefacin-M; Cefacure; Ceporex; Felexin; Keflex†; Medolexin; Ospexin; Sofilex; Solulexin; ***Hung.:*** Keflex†; Pyassan; Servispor†; ***India:*** Alexin†; Betaspore†; Cefmix; Cephadex; Cephaxin; Nufex; Phexin; Rofex†; Sepexin; Sporidex; ***Indon.:*** Cefabiotic; Madlexin; Ospexin; Pralexin; Tepaxin; Theralexin; ***Irl.:*** Ceporex†; Kefexin†; Keflex; ***Israel:*** Cefalin†; Ceforal; Cefovit; Keflex†; ***Ital.:*** Ceporex; Keforal; Lafarin; ***Jpn:*** Larixin; ***Malaysia:*** Cefax†; Celexin; Ceporex†; Felexin; Kefexin†; Medolexin; Ospexin; Refex†; Sofilex†; Sporidex; Uphalexin; ***Mex.:*** Acacin; Arlexen; Cefalver; Ceporex; Facelit; Falexol†; Fleximin; Flextinol; Keflex; Nafacil; Nixelaf-C; Optocef; Paferxin; Quimosporina; Servicef; ***Neth.:*** Keforal; ***Norw.:*** Keflex; ***NZ:*** Keflex†; ***Philipp.:*** Airex; Bacilexin; Bandax; Bloflex; Canelin; Cefalin; Cendalex; Ceporex; Civalex; Eliphorin; Forexine; Halcepin; Infexin; Keflex; Lewimycin; Lexum; Lonarel; Lyceplix; Madexin; Medilexin; Medoxine; Montralex; Nefadon; Neolecsin; Nerfalex; Oneflex; Respinal; Selzef; Servispor; Sorlex; Sporidex; Xinflex; Zepharyl; Zeporin; Zucoflaxin; ***Pol.:*** Keflex; ***Port.:*** Ceflax†; Ceporex; Keflex†; ***S.Afr.:*** Fexin†; Keflex; Lenocef; Ranceph; ***Singapore:*** Celexin; Cephalen; Cephanmycin; Ceporex†; Felexin†; Ospexin; Sofilex; Sporidex; Uphalexin; ***Spain:*** Bioscefal†; Cefalexgobens; Defaxina†; Kefloridina; Lexincef; Sulquipen; Torlasporin; ***Swed.:*** Keflex; ***Thai.:*** Anxer†; Cefexin; Cefxin†; Celex; Celexin; Cephalexyl; Cephin; Ceporex†; Farmalex; Felexin; Ibilex; Keflex; Pondnacef; Sefasin; Sialexin; Sporicef; Sporidex; Toflex; Ulflex; Zeplex; ***Turk.:*** Maksipor; Sef; ***UAE:*** Cefrin; ***UK:*** Ceporex; Keflex; ***USA:*** Biocef†; Cefanex; Keflex; Keftab†; ***Venez.:*** Bidocef; Cefaloga†; Keforal; Stricef.

Multi-ingredient: ***India:*** Caceff; Cephadex LB; ***Mex.:*** Arlexen B; Cefabroxil; Cepobrom; Mucocef; Rombox.

The symbol † denotes a preparation no longer actively marketed

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Cefalonium *(BAN, pINN)*

41071; Carbamoylcefaloridine; Cefalonio; Céfalonium; Cephalonium. (7*R*)-3-(4-Carbamoyl-1-pyridiniomethyl)-7-[2-(2-thienyl)-acetamido]-3-cephem-4-carboxylate.

Цефалоний

$C_{20}H_{18}N_4O_5S_2$ = 458.5.

CAS — 5575-21-3.

ATC Vet — QJ51DA90.

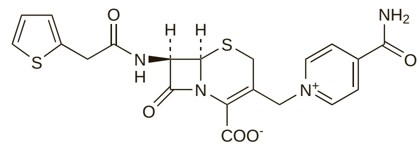

Pharmacopoeias. *BP(Vet)* includes the dihydrate.

BP(Vet) 2008 (Cefalonium). The dihydrate is a white or almost white crystalline powder. Very slightly soluble in water and in methyl alcohol; insoluble in alcohol, in dichloromethane, and in ether; soluble in dimethyl sulfoxide. It dissolves in dilute acids and in alkaline solutions. Store at temperature not exceeding 30°. Protect from light.

Profile

Cefalonium is a cephalosporin antibacterial used in veterinary practice.

Cefaloridine *(BAN, pINN)*

40602; Cefaloridin; Cefaloridina; Céfaloridine; Cefaloridinum; Cephaloridine *(USAN)*; Kefaloridiini. (7*R*)-3-(1-Pyridiniomethyl)-7-[(2-thienyl)acetamido]-3-cephem-4-carboxylate.

Цефалоридин

$C_{19}H_{17}N_3O_4S_2$ = 415.5.

CAS — 50-59-9.

ATC — J01DB02.

ATC Vet — QJ01DB02.

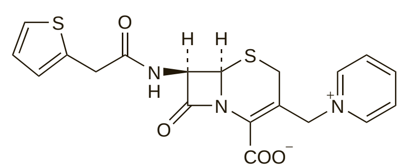

Profile

Cefaloridine was one of the first cephalosporin antibacterials to be available clinically. It has properties similar to those of cefalotin (below), but is more nephrotoxic and is seldom used now.

Cefalotin Sodium *(BANM, pINNM)*

38253; Cefalotin sodná sůl; Cefalotina sódica; Céfalotine sodique; Cefalotinnatrium; Cefalotin-nátrium; Cefalotino natrio druska; Cefalotinum natricum; Cefalotyna sodowa; Cephalothin Sodium *(USAN)*; Kefalotiininatrium; Natrii Cefalotinum; Sodium Cephalothin. Sodium (7*R*)-7-[2-(2-thienyl)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

Натрий Цефалотин

$C_{16}H_{15}N_2NaO_6S_2$ = 418.4.

CAS — 153-61-7 (cefalotin); 58-71-9 (cefalotin sodium).

ATC — J01DB03.

ATC Vet — QJ01DB03.

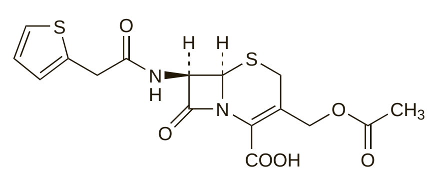

(cefalotin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Cefalotin Sodium). A white or almost white powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 10% solution in water has a pH of 4.5 to 7.0. Protect from light.

USP 31 (Cephalothin Sodium). A white to off-white, practically odourless, crystalline powder. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; insoluble in most organic solvents. pH of a 25% solution in water is between 4.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefalotin sodium has been reported to be incompatible with aminoglycosides and with many other drugs. Precipitation may occur in solutions with a pH of less than 5.

Adverse Effects

The adverse effects associated with cefalotin and other cephalosporins are broadly similar to those described for penicillins (see Benzylpenicillin, p.213). The most common are hypersensitivity reactions, including skin rashes, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis.

There may be a positive response to the Coombs' test although haemolytic anaemia rarely occurs. Neutropenia and thrombocytopenia have occasionally been reported. Agranulocytosis has been associated rarely with some cephalosporins. Bleeding complications related to hypoprothrombinaemia and/or platelet dysfunction have occurred especially with cephalosporins and cephamycins having an *N-methylthiotetrazole* side-chain, including

- cefamandole
- cefbuperazone
- cefmenoxime
- cefmetazole
- cefonicid
- cefoperazone
- ceforanide
- cefotetan
- cefpiramide
- latamoxef.

The presence of a *methylthiadiazolethiol* side-chain, as in cefazolin, or an *N-methylthiotriazine* ring, as in ceftriaxone, might also be associated with such bleeding disorders. Hypoprothrombinaemia which is usually reversible with vitamin K, was once thought to be due to an alteration in intestinal flora but interference with prothrombin synthesis now seems more likely.

Nephrotoxicity has been reported with cefalotin although it is less toxic than cefaloridine. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment, or when used with nephrotoxic drugs such as aminoglycosides. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

Transient increases in liver enzyme values have been reported. Hepatitis and cholestatic jaundice have occurred rarely with some cephalosporins.

Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

Gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea have been reported rarely. Prolonged use may result in overgrowth of non-susceptible organisms and, as with other broad-spectrum antibiotics, pseudomembranous colitis may develop (see also below).

There may be pain at the injection site after intramuscular use, and thrombophlebitis has occurred on intravenous infusion of cephalosporins. Cefalotin appears to be more likely to cause such local reactions than other cephalosporins.

Antibiotic-associated colitis. Pseudomembranous colitis has occurred with many antibacterials, including broad-spectrum cephalosporins.[1-3] In 1991 the UK CSM warned[4] of the dangers of pseudomembranous colitis with the newer, as well as the older, oral cephalosporins. In addition to 33 reports of pseudomembranous colitis associated with cefalexin, cefradine, cefadroxil, and cefaclor, 6 of which proved fatal, they had received 12 reports of probable or confirmed cases with cefuroxime axetil and 15 with cefixime, one of them fatal. In clinical trials of cefuroxime axetil and cefixime, diarrhoea and pseudomembranous colitis appeared to be dose-related and therefore the CSM recommended that higher doses should be reserved for severe infections. In any event they advised that treatment should be stopped if symptoms suggestive of pseudomembranous colitis arose.

For further discussion of the management of this condition, see p.171.

1. de Lalla F, *et al.* Third generation cephalosporins as a risk factor for Clostridium difficile-associated disease: a four-year survey in a general hospital. *J Antimicrob Chemother* 1989; **23:** 623–31.
2. Golledge CL, *et al.* Extended spectrum cephalosporins and Clostridium difficile. *J Antimicrob Chemother* 1989; **23:** 929–31.
3. Freiman JP, *et al.* Pseudomembranous colitis associated with single-dose cephalosporin prophylaxis. *JAMA* 1989; **262:** 902.
4. Committee on Safety of Medicines. Pseudomembranous (antibiotic-associated) colitis and diarrhoea with cephalosporins. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the blood. References.

1. Lipsky JJ. Antibiotic-associated hypoprothrombinaemia. *J Antimicrob Chemother* 1988; **21:** 281–300.
2. Shearer MJ, *et al.* Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status. *J Clin Pharmacol* 1988; **28:** 88–95.
3. Welage LS, *et al.* Comparative evaluation of the pharmacokinetics of N-methylthiotetrazole following administration of cefoperazone, cefotetan, and cefmetazole. *Antimicrob Agents Chemother* 1990; **34:** 2369–74.

Effects on the kidneys. References.

1. Zhanel GG. Cephalosporin-induced nephrotoxicity: does it exist? *DICP Ann Pharmacother* 1990; **24:** 262–5.
2. Tune BM. Nephrotoxicity of beta-lactam antibiotics: mechanisms and strategies for prevention. *Pediatr Nephrol* 1997; **11:** 768–72.

Precautions

Cefalotin should not be given to patients who are hypersensitive to it or to other cephalosporins. Immunological studies have suggested that up to 20% of penicillin-sensitive patients may also be allergic to cephalosporins although clinical studies indicate a lower frequency and the true incidence is uncertain; great care should be taken if cefalotin is to be given to such patients. Care is also necessary in patients with a history of allergy.

Cefalotin should be given with caution to patients with renal impairment; dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy. Cefalotin and some other cephalosporins and cephamycins (ceforanide, cefotetan, cefoxitin, and cefpirome) may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function. Positive results to the direct Coombs' test have been found during treatment with cefalotin and these can interfere with blood cross-matching. The urine of patients being treated with cefalotin may give false-positive reactions for glucose using copper-reduction reactions.

Porphyria. Cephalosporins are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Sodium content. Each g of cefalotin sodium contains about 2.39 mmol of sodium.

Interactions

The use of nephrotoxic drugs such as the aminoglycosides gentamicin and tobramycin may increase the risk of kidney damage with cefalotin. There is also some evidence for enhanced nephrotoxicity with the loop diuretic furosemide, but this is less certain than for furosemide with cefaloridine. As with penicillins, the renal excretion of cefalotin and many other cephalosporins is inhibited by probenecid. There may be antagonism between cefalotin and bacteriostatic antibacterials.

Antimicrobial Action

Cefalotin is a beta-lactam antibacterial. It is bactericidal and acts similarly to benzylpenicillin (p.214) by inhibiting synthesis of the bacterial cell wall. It is most active against Gram-positive cocci, and has moderate activity against some Gram-negative bacilli.

Sensitive Gram-positive cocci include both penicillinase- and non-penicillinase-producing staphylococci, although meticillin-resistant staphylococci are resistant; most streptococci are also sensitive, but not penicillin-resistant *Streptococcus pneumoniae;* enterococci are usually resistant. Some Gram-positive anaerobes are also susceptible. Cefalotin is usually inactive against *Listeria monocytogenes*.

Among Gram-negative bacteria cefalotin has activity against some Enterobacteriaceae including strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella*, and *Shigella* spp., but not against *Enterobacter*, indole-positive *Proteus*, or *Serratia* spp. It is also active against *Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria* spp., though *Haemophilus influenzae* is moderately resistant. *Bacteroides fragilis* and *Pseudomonas aeruginosa* are not sensitive and neither are mycobacteria, mycoplasma, and fungi.

Resistance of bacteria to cefalotin may be due to several mechanisms: the drug may be prevented from reaching its site of action, for example in some Gram-negative organisms the cell wall may be a potential barrier; the target penicillin-binding proteins may be altered so that cefalotin cannot bind with these proteins; or, most importantly, the organism may produce beta-lactamases (cephalosporinases). Cefalotin is relatively resistant to hydrolysis by staphylococcal beta-lactamase, but is inactivated by a variety of beta-lactamases produced by Gram-negative organisms; resistance of Gram-negative organisms often depends on more than one factor. Resistance can be chromosomally or plasmid-mediated and may sometimes be inducible by cephalosporins.

Certain strains of bacteria may be inhibited but not killed by cephalosporins or penicillins and in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration; this is known as tolerance.

As well as with other cephalosporins, some cross-resistance may occur between cefalotin and the penicillinase-resistant penicillins.

Pharmacokinetics

Cefalotin is poorly absorbed from the gastrointestinal tract. After intramuscular injection peak plasma concentrations of about 10 and 20 micrograms/mL are achieved within 30 minutes of doses of 0.5 and 1 g, respectively. A concentration of 30 micrograms/mL has been reported 15 minutes after the intravenous injection of a 1-g dose; a range of 14 to 20 micrograms/mL has been achieved by the continuous intravenous infusion of 500 mg/hour.

Cefalotin is widely distributed in body tissues and fluids except the brain and CSF where the concentrations achieved are low and unpredictable. It crosses the placenta and low concentrations have been detected in breast milk. The plasma half-life varies from about 30 to 50 minutes, but may be longer in patients with renal impairment, especially that of the metabolite. About 70% of cefalotin is bound to plasma proteins.

About 20 to 30% of cefalotin is rapidly deacetylated in the liver and about 60 to 70% of a dose is excreted in the urine by the renal tubules within 6 hours as cefalotin and the less active metabolite, desacetylcefalotin. High urine concentrations of 0.8 and 2.5 mg/mL have been observed after intramuscular doses of 0.5 and 1 g, respectively. Probenecid blocks the renal excretion of cefalotin. A very small amount is excreted in bile.

Uses and Administration

Cefalotin is a first-generation cephalosporin antibacterial that has been used in the treatment of infections due to susceptible bacteria, particularly staphylococci, but has generally been replaced by newer cephalosporins.

Cefalotin is given as the sodium salt by slow intravenous injection over 3 to 5 minutes or by intermittent or continuous infusion. It may be given intramuscularly but this route is painful. Doses are expressed in terms of the equivalent amount of cefalotin; 1.06 g of cefalotin sodium is equivalent to about 1 g of cefalotin. The usual dose is 0.5 to 1 g of cefalotin every 4 to 6 hours; up to 12 g daily has been given in severe infections.

Administration in renal impairment. Reduced doses are recommended if cefalotin is given to patients with renal impairment. After an intravenous loading dose of 1 to 2 g patients may be given the following maximum doses according to their creatinine clearance (CC):

- CC 50 to 80 mL/minute: 2 g every 6 hours
- CC 25 to 50 mL/minute: 1.5 g every 6 hours
- CC 10 to 25 mL/minute: 1 g every 6 hours
- CC 2 to 10 mL/minute: 500 mg every 6 hours
- CC less than 2 mL/minute: 500 mg every 8 hours

Preparations

USP 31: Cephalothin for Injection; Cephalothin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Arecamin; Cefade†; Dasuglor; Keflin; Rupecef†; ***Austral.:*** Keflin Neutral; ***Braz.:*** Cefalin; Cefalot†; Cefalotil; Cefariston; Kefalotin†; Keflin; ***Canad.:*** Ceporacin†; ***Denm.:*** Keflin†; ***Fin.:*** Keflin†; ***Indon.:*** Cephation; Moraxine; ***Israel:*** Keflin†; ***Ital.:*** Keflin†; ***Mex.:*** Cefelen; Ceftina; Falot; Keflin; Liroken I; Loriken†; Lotin; ***Neth.:*** Keflin; ***Norw.:*** Keflin; ***Philipp.:*** Fezef; ***S.Afr.:*** Keflin†; ***Singapore:*** Cefadin; ***Thai.:*** Cefadin†; Keflin†; ***Venez.:*** Cefaciclina†; Ceflen; Keflin†.

Cefamandole *(BAN, USAN, rINN)*

83405; Cefamandol; Céfamandole; Cefamandolum; Cephamandole; Compound 83405; Kefamandoli. (7*R*)-7-D-Mandelamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid; {6*R*-[6α,7β(*R**)]}-7-[(hydroxyphenylacetyl)amino]-3-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Цефамандол

$C_{18}H_{18}N_6O_5S_2$ = 462.5.
CAS — 34444-01-4.
ATC — J01DC03.
ATC Vet — QJ01DC03.

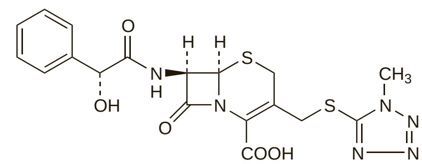

Cefamandole Nafate *(BAN, USAN, rINNM)*

106223; Cefamandole Formate Sodium; Céfamandole, nafate de; Cefamandoli nafas; Cefamandoli Nafatum; Cefamandolio nafatas; Cefamandolnafat; Cefamandol-nafát; Cefamandolu nafan; Cefmandoli Nafas; Cephamandole Nafate; Kefamandolinafaatti; Nafato de cefamandol. Sodium (7*R*)-7-[(2*R*)-2-formyloxy-2-phenylacetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

Цефамандола Нафат

$C_{19}H_{17}N_6NaO_6S_2$ = 512.5.
CAS — 42540-40-9.
ATC — J01DC03.
ATC Vet — QJ01DC03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cefamandole Nafate). A white, or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH, measured after 30 minutes, of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Cefamandole Nafate). A white, odourless, crystalline solid. Soluble in water and in methyl alcohol; practically insoluble in chloroform, in cyclohexane, in ether, and in benzene. pH of a 10% solution in water is between 3.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefamandole nafate has been reported to be incompatible with aminoglycosides and with metronidazole. Formulations of cefamandole nafate available for injection contain sodium carbonate and are incompatible with solutions containing calcium or magnesium salts. When reconstituted with water the sodium carbonate rapidly hydrolyses about 30% of the ester to cefamandole sodium; during storage of the reconstituted solution at room temperature carbon dioxide is produced.

References.

1. Frable RA, *et al.* Stability of cefamandole nafate injection with parenteral solutions and additives. *Am J Hosp Pharm* 1982; **39:** 622–7. Correction. *ibid.*; 1479.

Cefamandole Sodium *(BANM, rINNM)*

Cefamandol sódico; Céfamandole Sodique; Cephamandole Sodium; Natrii Cefamandolum.

Натрий Цефамандол

$C_{18}H_{17}N_6NaO_5S_2$ = 484.5.
CAS — 30034-03-8.
ATC — J01DC03.
ATC Vet — QJ01DC03.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

As mentioned under Cefalotin, cephalosporins with an *N*-methylthiotetrazole side-chain such as cefamandole (and possibly those with methylthiadiazolethiol or *N*-methylthiotriazine side-chains as well) may produce bleeding disorders associated with hypoprothrombinaemia and/or platelet disorders.

Sodium content. 1.05 g of cefamandole sodium and 1.11g of cefamandole nafate each contain about 2.2 mmol of sodium.

Interactions

A disulfiram-like interaction with alcohol may occur and has been attributed to the *N*-methylthiotetrazole side-chain of cefamandole; patients should avoid alcohol during, and for at least several days after, cefamandole treatment. Interactions are also possible with preparations containing significant amounts of alcohol.

Cefamandole, and other cephalosporins with an *N*-methylthiotetrazole side-chain, may enhance the hypoprothrombinaemic response to anticoagulants as discussed under Warfarin (p.1428).

Probenecid reduces the renal clearance of cefamandole and many other cephalosporins.

◊ References.

1. Portier H, *et al.* Interaction between cephalosporins and alcohol. *Lancet* 1980; **ii:** 263.
2. Drummer S, *et al.* Antabuse-like effect of β-lactam antibiotics. *N Engl J Med* 1980; **303:** 1417–18.

Antimicrobial Action

Cefamandole is bactericidal and acts similarly to cefalotin, but has a broader spectrum of activity. It generally has similar or less activity against Gram-positive staphylococci and streptococci, but is resistant to some beta-lactamases produced by Gram-negative bacteria. It is more active than cefalotin against many of the Enterobacteriaceae including some strains of *Enterobacter, Escherichia coli, Klebsiella, Salmonella*, and some *Proteus* spp. However, resistance to cefamandole and other beta lactams has emerged in some species, notably *Enterobacter*, during treatment with cefamandole. Cefamandole is very active *in vitro* against *Haemophilus influenzae* although an inoculum effect has been reported for beta-lactamase-producing strains. Like cefalotin, most strains of *Bacteroides fragilis* are resistant to cefamandole, as are *Pseudomonas* spp.

◊ References.

1. Sabath LD. Reappraisal of the antistaphylococcal activities of first-generation (narrow-spectrum) and second-generation (expanded-spectrum) cephalosporins. *Antimicrob Agents Chemother* 1989; **33:** 407–11.

Pharmacokinetics

Cefamandole is poorly absorbed from the gastrointestinal tract. It is given intramuscularly or intravenously, usually as the nafate which is rapidly hydrolysed to release cefamandole *in vivo*. Peak plasma concentrations for cefamandole of about 13 and 25 micrograms/mL have been achieved 0.5 to 2 hours after intramuscular doses of 0.5 and 1 g respectively; concentrations are very low after 6 hours. About 70% is bound to plasma proteins. The plasma half-life varies from about 0.5 to 1.2 hours depending on the route of injection; it is prolonged in patients with renal impairment.

Cefamandole is widely distributed in body tissues and fluids including bone, joint fluid, and pleural fluid; it diffuses into the CSF when the meninges are inflamed, but concentrations are unpredictable. Cefamandole has also been detected in breast milk. It is rapidly excreted unchanged by glomerular filtration and renal tubular secretion; about 80% of a dose is excreted within 6 hours and high urinary concentrations are achieved. Probenecid competes for renal tubular secretion with cefamandole resulting in higher and prolonged plasma concentrations of cefamandole. Therapeutic concentrations of cefamandole are achieved in bile.

Cefamandole is removed by haemodialysis to some extent.

Uses and Administration

Cefamandole is a second-generation cephalosporin antibacterial used in the treatment of infections due to susceptible bacteria and for surgical infection prophylaxis.

It is given principally as cefamandole nafate (the sodium salt of cefamandole formyl ester). Doses are expressed in terms of the equivalent amount of cefamandole; 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate are each equivalent to about 1 g of cefamandole. It is given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion in doses of 0.5 to 2 g every 4 to 8 hours for adults depending on the severity of the infection. Children over 1 month of age may be given 50 to 100 mg/kg daily in equally divided doses; 150 mg/kg daily may be given in severe infections, but this dose should not be exceeded. For details of reduced doses in patients with renal impairment, see below. If cefamandole is used with an aminoglycoside, the drugs should be given separately.

For surgical infection prophylaxis, a dose of 1 or 2 g intravenously or intramuscularly 30 to 60 minutes before surgical incision, followed by 1 or 2 g every 6 hours for 24 to 48 hours, is recommended. For patients undergoing procedures involving implantation of prosthetic devices, cefamandole should be continued for up to 72 hours. Children over 3 months of age may be treated similarly to adults and given 50 to 100 mg/kg daily in equally divided doses.

Administration in renal impairment. Doses of cefamandole should be reduced for patients with renal impairment. After an initial dose of 1 to 2 g the following maintenance doses have been recommended based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: 0.75 to 2 g every 6 hours
- CC 25 to 50 mL/minute: 0.75 to 2 g every 8 hours
- CC 10 to 25 mL/minute: 0.5 to 1.25 g every 8 hours
- CC 2 to 10 mL/minute: 0.5 to 1 g every 12 hours
- CC less than 2 mL/minute: 0.25 to 0.75 g every 12 hours

Preparations

USP 31: Cefamandole Nafate for Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Mandol; ***Austria:*** Mandokef; ***Belg.:*** Mandol; ***Cz.:*** Mandol†; ***Gr.:*** Acemycin; Cefadin; Mandokef; ***Hong Kong:*** Mandol†; ***Hung.:*** Cefam; Mandokef†; ***Indon.:*** Dardokef; Dofacef; ***Irl.:*** Kefadol†; ***Ital.:*** Cefam; Cemado; Lampomandol; Mancef; Mandokef†; Mandolsan†; Septomandolo†; ***Neth.:*** Mandol; ***NZ:*** Mandol; ***Pol.:*** Tarcefandol; ***Port.:*** Mandokef†; ***Rus.:*** Cefat (Цефат); Mandol (Мандол); ***S.Afr.:*** Kefdole†; Mandokef; ***Switz.:*** Mandokef; ***Thai.:*** Cefadol; Cefmandol; Mandol†.

Cefapirin Sodium *(BANM, pINNM)*

BL-P-1322; Cefapirin sodná sůl; Cefapirina sódica; Céfapirine sodique; Cefapirinnatrium; Cefapirin-nátrium; Cefapirino natrio druska; Cefapirinum natricum; Cephapirin Sodium *(USAN)*; Kefapiriininatrium; Natrii Cefapirinum. Sodium (7*R*)-7-[2-(4-pyridylthio)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(4-pyridylthio)acetamido]-3-cephem-4-carboxylate.

Натрий Цефапирин

$C_{17}H_{16}N_3NaO_6S_2$ = 445.4.
CAS — 21593-23-7 (cefapirin); 24356-60-3 (cefapirin sodium).
ATC — J01DB08.
ATC Vet — QJ01DB08.

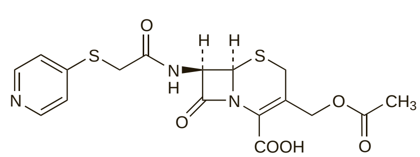

(cefapirin)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
US also includes Cephapirin Benzathine for veterinary use.

Ph. Eur. 6.2 (Cefapirin Sodium). A white or pale yellow powder. Soluble in water; practically insoluble in dichloromethane. A 1% solution in water has a pH of 6.5 to 8.5. Protect from light.

USP 31 (Cephapirin Sodium). A white to off-white crystalline powder, odourless or having a slight odour. Very soluble in water; insoluble in most organic solvents. pH of a solution in water containing the equivalent of cefapirin 1% is between 6.5 and 8.5. Store in airtight containers.

Profile

Cefapirin is a first-generation cephalosporin antibacterial with actions and uses very similar to those of cefalotin (p.219). It is used as the sodium salt but doses are expressed in terms of cefapirin base; 1.05 g of cefapirin sodium is equivalent to about 1 g of cefapirin. The usual dose is the equivalent of 0.5 to 1 g of cefapirin every 4 to 6 hours by intramuscular injection or intravenously. In severe infections up to 12 g daily may be given, preferably intravenously.

Administration in renal impairment. Reduced doses of cefapirin sodium may be necessary in patients with renal impairment. One regimen, based on creatinine clearance (CC), that has been suggested is:

- CC 5 to 20 mL/minute: 1 g every 12 hours
- CC less than 5 mL/minute: 1 g every 24 hours

Patients undergoing haemodialysis may receive 7.5 to 15 mg/kg after each dialysis.

Sodium content. Each g of cefapirin sodium contains about 2.2 mmol of sodium.

Preparations

USP 31: Cephapirin for Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Cefatrexyl†; ***Fr.:*** Cefaloject; ***Gr.:*** Cefatrex†; ***Spain:*** Brisfirina.

Cefatrizine *(BAN, USAN, pINN)*

BL-S640; Cefatrizina; Céfatrizine; Cefatrizinum; SKF-60771; S-640P. (7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефатризин

$C_{18}H_{18}N_6O_5S_2$ = 462.5.
CAS — 51627-14-6.
ATC — J01DB07.
ATC Vet — QJ01DB07.

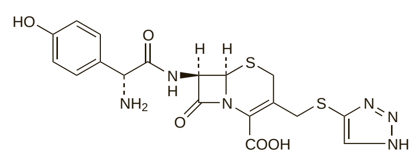

Cefatrizine Propylene Glycol *(BANM, pINNM)*

Cefatrizina propilenglicol; Cefatrizinas propilenglikolis; Céfatrizine propylèneglycol; Cefatrizin-propilénglikol; Cefatrizinpropylenglykol; Cefatrizin-propylenglykol; Cefatrizinum propylen glycolum; Cefatrizinum Propylenglycolum; Kefatritsiinipropyleeniglykoli. (7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylate propylene glycol.

Цефатризин Пропиленгликол

$C_{18}H_{18}N_6O_5S_2$, $(C_3H_8O_2)_n$.
CAS — 64217-62-5.
ATC — J01DB07.
ATC Vet — QJ01DB07.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*.

Ph. Eur. 6.2 (Cefatrizine Propylene Glycol). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane.

Profile

Cefatrizine is a cephalosporin antibacterial with actions and uses similar to those of cefalexin (p.218), although it might be more active *in vitro*. It is given orally as the base or, more often, as a compound with propylene glycol, in usual doses equivalent to 500 mg twice daily of cefatrizine.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cefaperos; ***Fr.:*** Cefaperos†; ***Gr.:*** Anfagladin; Axelorax; Banadroxin†; Ceftazin; Cetrizin; Clomin†; Fica-F; Gertemycin; Izerin; Kentacef; Klevasin; Liamycin; Liferost; Lingopen; Mekan†; Nibocin; Northiron; Phacobiotic†; Relyovix; Specicef-N; Trixilan; ***Ital.:*** Biotrixina†; Cefatrix†; Cetrazil†; Cetrinox†; Faretrizin; Ipatrizina†; Ketrizin; Miracef†; Novacef†; Tamyl†; Tricef†; Trizina; ***Port.:*** Macropen; Supracefa.

Cefazolin *(BAN, pINN)*

Cefazolina; Céfazoline; Cefazolinum; Cephazolin; Kefatsoliini; Sefazolin. 3-[(5-Methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-7-(tetrazol-1-ylacetamido)-3-cephem-4-carboxylic acid.

Цефазолин

$C_{14}H_{14}N_8O_4S_3$ = 454.5.

CAS — 25953-19-9.

ATC — J01DB04.

ATC Vet — QJ01DB04; QJ51DA04.

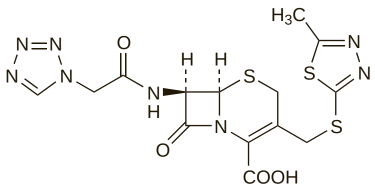

Pharmacopoeias. In *US.*

USP 31 (Cefazolin). A white to slightly off-white, odourless crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in acetone; practically insoluble in chloroform, in dichloromethane, in ether, and in benzene; soluble in dimethylformamide and in pyridine; very slightly soluble in ethyl acetate, in isopropyl alcohol, and in methyl isobutyl ketone. Store in airtight containers.

Cefazolin Sodium *(BANM, USAN, pINNM)*

46083; Cefazolin sodná sůl; Cefazolina sódica; Céfazoline sodique; Cefazolinnatrium; Cefazolin-nátrium; Cefazolino natrio druska; Cefazolinum natricum; Cephazolin Sodium; Kefatsoliininatrium; Natrii Cefazolinum; Sefazolin Sodyum; SKF-41558.

Натрий Цефазолин

$C_{14}H_{13}N_8NaO_4S_3$ = 476.5.

CAS — 27164-46-1.

ATC — J01DB04.

ATC Vet — QJ01DB04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Jpn also includes the pentahydrate.

Ph. Eur. 6.2 (Cefazolin Sodium). A white or almost white, very hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Cefazolin Sodium). A white to off-white, practically odourless, crystalline powder, or a white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of cefazolin 10% is between 4.0 and 6.0. Store in airtight containers.

Incompatibility and stability. Cefazolin sodium has been reported to be incompatible with aminoglycosides and many other drugs. When the pH of a solution exceeds 8.5 there may be hydrolysis and when it is below 4.5 insoluble cefazolin may be precipitated.

References.

1. Nahata MC, Ahalt PA. Stability of cefazolin sodium in peritoneal dialysis solutions. *Am J Hosp Pharm* 1991; **48:** 291–2.
2. Wu C-C, *et al.* Stability of cefazolin in heparinized and nonheparinized peritoneal dialysis solutions. *Am J Health-Syst Pharm* 2002; **59:** 1537–8.
3. Lin Y-F, *et al.* Stability of cefazolin sodium in icodextrin-containing peritoneal dialysis solution. *Am J Health-Syst Pharm* 2002; **59:** 2362, 2364.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219. Stevens-Johnson syndrome has occurred.

Like cephalosporins with an *N*-methylthiotetrazole side-chain, cefazolin has been associated with hypoprothrombinaemia.

Breast feeding. In a study[1] of 20 lactating women receiving cefazolin, the amount of cefazolin in breast milk was found to be extremely small (equivalent to less than 0.075% of the dose). No adverse effects have been seen in breast-fed infants whose mothers were receiving cefazolin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Yoshioka H, *et al.* Transfer of cefazolin into human milk. *J Pediatr* 1979; **94:** 151–2.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the nervous system. References.

1. Manzella JP, *et al.* CNS toxicity associated with intraventricular injection of cefazolin: report of three cases. *J Neurosurg* 1988; **68:** 970–1.
2. Martin ES, *et al.* Seizures after intraventricular cefazolin administration. *Clin Pharm* 1992; **11:** 104–5.

Sodium content. Each g of cefazolin sodium contains about 2.1 mmol of sodium.

Interactions

Cefazolin contains a methylthiadiazolethiol side-chain; like cephalosporins containing the related *N*-methylthiotetrazole side-chain (see Cefamandole, p.221), it may have the potential to cause a disulfiram-like reaction with alcohol, and enhance the effects of warfarin.

The renal excretion of cefazolin and many other cephalosporins is delayed by probenecid.

Antimicrobial Action

As for Cefalotin Sodium, p.220, although cefazolin is more sensitive to staphylococcal beta-lactamase.

Pharmacokinetics

Cefazolin is poorly absorbed from the gastrointestinal tract and is given by the intramuscular or intravenous routes. After a 500-mg dose given intramuscularly, peak plasma concentrations of 30 micrograms or more per mL are obtained after 1 hour. About 85% of cefazolin is bound to plasma proteins. The plasma half-life of cefazolin is about 1.8 hours, and is increased in patients with renal impairment. Cefazolin diffuses into bone and into ascitic, pleural, and synovial fluid but not appreciably into the CSF. It crosses the placenta; only low concentrations are detected in breast milk.

Cefazolin is excreted unchanged in the urine, mainly by glomerular filtration with some renal tubular secretion, at least 80% of a dose given intramuscularly being excreted within 24 hours. Peak urine concentrations of more than 2 and 4 mg/mL have been reported after intramuscular doses of 0.5 and 1 g respectively. Probenecid delays excretion. Cefazolin is removed to some extent by haemodialysis.

High biliary concentrations have been reported, although the amount excreted by this route is small.

Uses and Administration

Cefazolin is a first-generation cephalosporin antibacterial used to treat infections due to susceptible organisms, including biliary-tract infections, endocarditis (staphylococcal), and peritonitis (associated with continuous ambulatory peritoneal dialysis). It is also used for surgical infection prophylaxis, including prophylaxis of endometritis at caesarean section. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefazolin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion. Doses are expressed in terms of the equivalent amount of cefazolin; 1.05 g of cefazolin sodium is equivalent to about 1 g of cefazolin. The usual adult dose is the equivalent of 0.5 to 1 g of cefazolin every 6 to 12 hours. The usual maximum daily dose is 6 g, although up to 12 g has been used in severe life-threatening infections. Children over 1 month of age may be given 25 to 50 mg/kg daily in 3 or 4 divided doses, increased in severe infections to a maximum of 100 mg/kg daily.

For the prophylaxis of infection during surgery, a 1-g dose is given half to one hour before the operation, followed by 0.5 to 1 g during surgery for lengthy procedures. A dose of 0.5 to 1 g is given every 6 to 8 hours postoperatively for 24 hours, or up to 5 days in certain cases.

For details of reduced doses of cefazolin in patients with renal impairment, see below.

Other routes used for cefazolin sodium include intraperitoneal use in peritoneal dialysis solutions, and intra-ocular injection.

In some countries a modified-release intramuscular formulation of cefazolin sodium with the less soluble dibenzylamine salt of cefazolin, in the ratio of 1:4, has been used.

Administration in renal impairment. Dosage of cefazolin should be reduced in patients with renal impairment and various modifications have been recommended. After a loading dose the licensed product information suggests the following doses based on creatinine clearance (CC):

Adults

- CC 55 mL or more per minute: usual doses
- CC 35 to 54 mL/minute: usual doses but at intervals of at least 8 hours
- CC 11 to 34 mL/minute: half the usual dose every 12 hours
- CC 10 mL or less per minute: half the usual dose every 18 to 24 hours

Children

- CC 40 to 70 mL/minute: 60% of the normal daily dose in 2 divided doses
- CC 20 to 40 mL/minute: 25% of the normal daily dose in 2 divided doses
- CC 5 to 20 mL/minute: 10% of the normal daily dose every 24 hours.

One report[1] indicated that, for patients on long-term haemodialysis, a dose of 20 mg/kg given 3 times weekly after dialysis maintained therapeutic cefazolin concentrations.

1. Ahern JW, *et al.* Cefazolin dosing protocol for patients receiving long-term hemodialysis. *Am J Health-Syst Pharm* 2003; **60:** 178–81.

Preparations

BP 2008: Cefazolin Injection;
USP 31: Cefazolin for Injection; Cefazolin Injection; Cefazolin Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Cefalomicina; Cefamezin; ***Austral.:*** Kefzol; ***Austria:*** Kefzol; Servazolin; Zolicef; ***Belg.:*** Cefacidal; Kefzol†; ***Braz.:*** Ceftrat; Cezolin†; Duocef; Fazolon; Kefazol; Zolin†; ***Canad.:*** Kefzol†; ***Chile:*** Kefzol†; ***Cz.:*** Kefzol†; Orizolin†; Vulmizolin; ***Fr.:*** Cefacidal†; ***Ger.:*** Basocef; Elzogram†; ***Gr.:*** Biozolin†; Vifazolin; ***Hong Kong:*** Cefamezin; ***Hung.:*** Totacef†; ***India:*** Azolin; Reflin; Zolfin†; ***Indon.:*** Biozolin; Cefazol; ***Israel:*** Cefamezin; Kefazin; Kefzol†; Totacef†; ***Ital.:*** Acef; Cefabiozim†; Cefamezin; Cefazil; Cromezin; Nefazol; Recef; Sicef; Silzolin†; Totacef; ***Jpn:*** Cefamezin; Otsuka Cez; ***Mex.:*** Cefacidal†; ***Neth.:*** Cefacidal; Cefamezin; Kefzol; Servazolin; ***NZ:*** Kefzol†; Zepilen; ***Philipp.:*** Cifoxim; Cizo; Cloviz; Fazol; Fonvicol; Ilozef; Lupex; Maxcep; Megacef; Oryant; Samarial; Stancef; Zofadep; Zolival; ***Pol.:*** Biofazolin; Tarfazolin; ***Port.:*** Cefamezin; Kurgan; ***Rus.:*** Cefamezin (Цефамезин); Ifizol (Ифизол); Intrazoline (Интразолин); Kefzol (Кефзол); Orizolin (Оризолин); Reflin (Рефлин); ***S.Afr.:*** Cefacidal; Izacef; Kefzol; Ranzol; ***Spain:*** Areuzolin; Brizolina; Camil†; Caricef; Cefa Resan†; Cefacene†; Cefadrex; Dacovo†; Fazoplex; Filoklin†; Gencefal†; Intrazolina; Kefol†; Kurgan; Neofazol†; Tasep; Tecfazolina; Zolival; ***Switz.:*** Kefzol; ***Thai.:*** Cefalin; Cefamezin; Cefazillin; Cefazol; Cefzolin; Fazolin; Zefa; Zepilen†; Zolicef; Zolimed; ***Turk.:*** Cefamezin; Cefozin; Equizolin; Iespor; Maksiporin; Sefamax; Sefazol; ***USA:*** Ancef†; Zolicef†; ***Venez.:*** Cefacidal; Cefarizon; Cellozina; Kefzol†.

Cefbuperazone *(USAN, rINN)*

BMY-25182; Cefbuperazona; Cefbupérazone; Cefbuperazonum; T-1982. 7-[(2*R*,3*S*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-3-hydroxybutyramido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефбуперазон

$C_{22}H_{29}N_9O_9S_2$ = 627.7.

CAS — 76610-84-9.

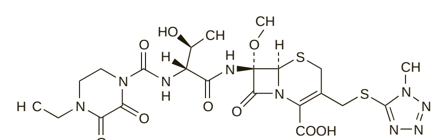

Cefbuperazone Sodium *(rINNM)*

Cefbuperazona de sodio; Cefbupérazone Sodique; Natrii Cefbuperazonum.

Натрий Цефбуперазон

$C_{22}H_{28}N_9NaO_9S_2$ = 649.6.

Pharmacopoeias. In *Jpn.*

Profile

Cefbuperazone is a cephamycin antibiotic similar to cefoxitin (p.230) but with an *N*-methylthiotetrazole side-chain like cefamandole (p.220). It is given by injection as the sodium salt. Its spectrum of activity includes Enterobacteriaceae, but more especially anaerobic bacteria such as *Bacteroides fragilis.* Cefbuperazone does not appear to be active against cefoxitin-resistant strains of *B. fragilis.*

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Tomiporan.

Cefcapene Pivoxil Hydrochloride *(rINNM)*

Cefcapène Pivoxil, Chlorhydrate de; Cefcapeni Pivoxili Hydrochloridum; Hidrocloruro de cefcapeno pivoxilo. Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-pentenamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate monohydrochloride monohydrate.

Цефкапена Пивоксила Гидрохлорид

$C_{23}H_{29}N_5O_8S_2,HCl,H_2O = 622.1.$

CAS — 135889-00-8 (cefcapene); 105889-45-0 (cefcapene pivoxil); 147816-23-7 (anhydrous cefcapene pivoxil hydrochloride); 147816-24-8 (cefcapene pivoxil hydrochloride);.

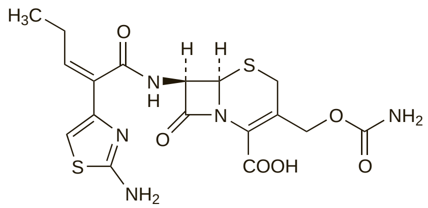

(cefcapene)

Pharmacopoeias. In *Jpn.*

Profile

Cefcapene is an oral cephalosporin antibacterial given orally as the pivaloyloxymethyl ester, cefcapene pivoxil hydrochloride.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p.317.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Flomox.

Cefdinir *(BAN, USAN, rINN)*

Cefdinirum; CI-983; FK-482; Kefdiniiri. (−)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-oxime; 7-{(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-hydroxyimino]acetamido}-3-vinylcephem-4-carboxylic acid.

Цефдинир

$C_{14}H_{13}N_5O_5S_2 = 395.4.$

CAS — 91832-40-5.
ATC — J01DD15.
ATC Vet — QJ01DD15.

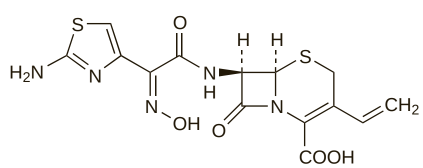

Pharmacopoeias. In *Chin.* and *Jpn.*

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219. There have been reports of reddish stools in patients given cefdinir with iron supplements (see also Interactions, below).

Interactions

Absorption of cefdinir is decreased by antacids or iron supplements and doses should be separated by an interval of at least 2 hours. Probenecid reduces the renal excretion of cefdinir.

Iron. A report[1] of red stools in an infant given cefdinir whilst being fed with an infant formula containing supplemental iron. It was considered important to be aware of the interaction because of the risk that it might be mistaken for a sign of gastrointestinal bleeding.

1. Lancaster J, *et al.* Nonbloody, red stools from coadministration of cefdinir and iron-supplemented infant formulas. *Pharmacotherapy* 2008; **28:** 678–81.

Antimicrobial Action

As for Cefixime, p.224. However, cefdinir is reported to be much more active *in vitro* than cefixime against *Staphylococcus aureus*, but not meticillin-resistant strains, and it is less active against some Enterobacteriaceae.

Pharmacokinetics

Cefdinir is absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring 2 to 4 hours after a dose. Oral bioavailability has been estimated to range from 16 to 25%. It is widely distributed into tissues and is 60 to 70% bound to plasma proteins. Cefdinir is not appreciably metabolised and is excreted in the urine with an elimination half-life of 1.7 hours. Cefdinir is removed by dialysis.

Uses and Administration

Cefdinir is a third-generation oral cephalosporin antibacterial with actions and uses similar to those of cefixime (p.224). It is given orally in a usual adult dose of 600 mg daily as a single dose or in two divided doses. Children may be given 14 mg/kg daily up to a maximum of 600 mg daily. Doses may need to be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Guay DRP. Cefdinir: an expanded-spectrum oral cephalosporin. *Ann Pharmacother* 2000; **34:** 1469–77.
2. Guay DR, *et al.* Cefdinir: an advanced-generation, broad-spectrum oral cephalosporin. *Clin Ther* 2002; **24:** 473–89.
3. Perry CM, Scott LJ. Cefdinir: a review of its use in the management of mild-to-moderate bacterial infections. *Drugs* 2004; **64:** 1433–64.
4. Sader HS, Jones RN. Cefdinir: an oral cephalosporin for the treatment of respiratory tract infections and skin and skin structure infections. *Expert Rev Anti Infect Ther* 2007; **5:** 29–43. Correction. *ibid.*; 754. [dose error]

Administration in renal impairment. Doses of cefdinir should be reduced to 300 mg once daily in patients with renal impairment whose creatinine clearance is less than 30 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Kefnir†; Sefdin; ***Jpn:*** Cefzon; ***Mex.:*** Omnicef; ***Thai.:*** Omnicef; ***USA:*** Omnicef.

Cefditoren Pivoxil *(rINNM)*

Cefditorène, Pivoxil de; Cefditoreni Pivoxil; Cefditoreno pivoxilo; ME-1207; ME-1206 (cefditoren). Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-3-[(*Z*)-2-(4-methyl-5-thiazolyl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 7^2-(*Z*)-(*O*-methyloxime).

Цефдиторена Пивоксил

$C_{25}H_{28}N_6O_7S_3 = 620.7.$

CAS — 104145-95-1 (cefditoren); 117467-28-4 (cefditoren pivoxil).
ATC — J01DD16.
ATC Vet — QJ01DD16.

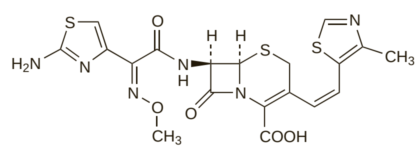

(cefditoren)

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

As for Cefalotin, p.219.

The most frequently reported adverse effects of cefditoren are gastrointestinal disturbances, especially diarrhoea.

For reference to carnitine deficiency with some pivaloyloxymethyl esters, see Pivampicillin, p.317.

Interactions

Absorption of cefditoren after oral doses is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefditoren.

Antimicrobial Action

As for Cefixime, p.224. Cefditoren also has activity against *Staphylococcus aureus.*

Pharmacokinetics

Cefditoren pivoxil is absorbed from the gastrointestinal tract and is hydrolysed to cefditoren by esterases to release active cefditoren in the bloodstream. Peak plasma concentrations average 1.8 micrograms/mL in fasting subjects 1.5 to 3 hours after a 200-mg dose. Bioavailability is about 14% in fasting subjects and is increased when cefditoren pivoxil is given with a high-fat meal. Plasma protein binding is reported to be 88%. The plasma half-life is about 1.6 hours and is prolonged in patients with renal impairment.

Cefditoren is not appreciably metabolised and is excreted mainly in the urine by glomerular filtration and tubular secretion. It is removed by haemodialysis.

Uses and Administration

Cefditoren is a cephalosporin antibacterial with a broad spectrum of activity used in the treatment of susceptible infections, particularly of the respiratory tract and skin. It is given orally as the pivaloyloxymethyl ester, cefditoren pivoxil, but doses are expressed in terms of cefditoren; 245 mg of cefditoren pivoxil is equivalent to about 200 mg of cefditoren. A usual dose is 200 to 400 mg given twice daily.

For details of reduced doses to be used in patients with moderate to severe renal impairment, see below.

◊ Reviews.

1. Wellington K, Curran MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. *Drugs* 2004; **64:** 2597–2618.

Administration in renal impairment. Doses of cefditoren pivoxil should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 30 to 49 mL/minute: the dose should not exceed 200 mg twice daily
- CC less than 30 mL/minute: the dose should be 200 mg once daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Spectracef; ***India:*** Cefditran; ***Indon.:*** Meiact; ***Jpn:*** Meiact; ***Mex.:*** Spectracef; ***Port.:*** Meiact; Spectracef; ***Spain:*** Meiact; Spectracef; Telo; ***Thai.:*** Meiact; ***Turk.:*** Spektracef; ***USA:*** Spectracef.

Cefepime Hydrochloride

(BANM, USAN, rINNM)

BMY-28142 (cefepime); Céfépime, Chlorhydrate de; Céfépime, dichlorhydrate de; Cefepimi dihydrochloridum; Cefepimi Hydrochloridum; Hidrocloruro de cefepima; Sefepim Hidroklorür. {6*R*-[6α,7β(*Z*)]}-1-[(7-{[(2-Amino-4-thiazolyl)-(methoxyimino)acetyl]amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methylpyrrolidinium chloride monohydrochloride monohydrate; 7-{(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-methoxyimino]acetamido}-3-(1-methylpyrrolidiniomethyl)-3-cephem-4-carboxylate hydrochloride.

Цефепима Гидрохлорид

$C_{19}H_{25}ClN_6O_5S_2,HCl,H_2O = 571.5.$

CAS — 88040-23-7 (cefepime); 123171-59-5 (cefepime hydrochloride monohydrate).
ATC — J01DE01.
ATC Vet — QJ01DE01.

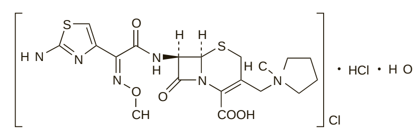

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Cefepime Dihydrochloride Monohydrate). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. Protect from light.

USP 31 (Cefepime Hydrochloride). A white to off-white, nonhygroscopic, crystalline powder. Freely soluble in water. Store in airtight containers. Protect from light.

Incompatibility and stability. References.

1. Stewart JT, *et al.* Stability of cefepime hydrochloride injection in polypropylene syringes at −20°C, 4°C, and 22-24°C. *Am J Health-Syst Pharm* 1999; **56:** 457–9.
2. Stewart JT, *et al.* Stability of cefepime hydrochloride in polypropylene syringes. *Am J Health-Syst Pharm* 1999; **56:** 1134.
3. Williamson JC, *et al.* Stability of cefepime in peritoneal dialysis solution. *Ann Pharmacother* 1999; **33:** 906–9.
4. Baririan N, *et al.* Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units. *J Antimicrob Chemother* 2003; **51:** 651–8.
5. Trissel LA, Xu QA. Stability of cefepime hydrochloride in AutoDose infusion system bags. *Ann Pharmacother* 2003; **37:** 804–7.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

◊ The safety of cefepime has been reviewed.[1-3] A meta-analysis[2] of studies involving cefepime suggested that there might be an increased risk of all-cause mortality compared with other beta-lactams. The FDA subsequently announced that it would review safety data to further evaluate the risk of death associated with cefepime use.[4]

1. Neu HC. Safety of cefepime: a new extended-spectrum parenteral cephalosporin. *Am J Med* 1996; **100** (suppl 6A): 68S–75S.
2. Yahav D, *et al.* Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; **7:** 338–48.
3. Drago L, De Vecchi E. The safety of cefepime in the treatment of infection. *Expert Opin Drug Saf* 2008; **7:** 377–87.
4. FDA. Early communication about an ongoing safety review: cefepime (marketed as Maxipime) (issued 14th November 2007). Available at: http://www.fda.gov/cder/drug/early_comm/cefepime.htm (accessed 04/08/08)

Effects on the nervous system. References to neurotoxicity, sometimes manifesting as nonconvulsive status epilepticus, associated with use of cefepime (particularly but not exclusively in patients with impaired renal function).

1. Chow KM, *et al.* Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; **23:** 369–73.

2. Ferrara N, *et al.* Neurotoxicity induced by cefepime in a very old hemodialysis patient. *Clin Nephrol* 2003; **59:** 388–90.
3. Dakdouki GK, Al-Awar GN. Cefepime-induced encephalopathy. *Int J Infect Dis* 2004; **8:** 59–61.
4. Alpay H, *et al.* Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. *Pediatr Nephrol* 2004; **19:** 445–7.
5. Abanades S, *et al.* Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother* 2004; **38:** 606–8.
6. Capparelli FJ, *et al.* Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology* 2005; **65:** 1840.
7. Maganti R, *et al.* Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav* 2006; **8:** 312–4.
8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy* 2006; **26:** 1169–74.
9. Sonck J, *et al.* The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant* 2008; **23:** 966–70.
10. Garces EO, *et al.* Renal failure is a risk factor for cefepime-induced encephalopathy. *J Nephrol* 2008; **21:** 526–34.

Antimicrobial Action

Cefepime is a fourth-generation cephalosporin and is active against a wide range of Gram-positive and Gram-negative aerobic organisms. Against Gram-positive cocci, its activity is similar to that of cefotaxime (p.228) and includes staphylococci (but not meticillin-resistant *Staphylococcus aureus*) and streptococci. Against Enterobacteriaceae, it has a broader spectrum of activity than other cephalosporins, including activity against organisms producing chromosomally mediated beta-lactamases such as *Enterobacter* spp. and *Proteus vulgaris*. Against *Pseudomonas aeruginosa*, it has similar or slightly less activity than ceftazidime (p.234), although it may be active against some strains resistant to ceftazidime.

Pharmacokinetics

Cefepime is given by injection as the hydrochloride. It is rapidly and almost completely absorbed on intramuscular injection and mean peak plasma concentrations of about 14 and 30 micrograms/mL have been reported about 1.5 hours after doses of 500 mg and 1 g respectively. Within 30 minutes of similar intravenous doses, peak plasma concentrations of about 40 and 80 micrograms/mL are achieved. The plasma half-life of cefepime is about 2 hours and is prolonged in patients with renal impairment. About 20% of cefepime is bound to plasma proteins.

Cefepime is widely distributed in body tissues and fluids. High concentrations are achieved in bile. Low concentrations have been detected in breast milk.

Cefepime is eliminated principally by the kidneys and about 85% of a dose is recovered unchanged in the urine. Cefepime is substantially removed by haemodialysis.

◊ References.

1. Okamoto MP, *et al.* Cefepime clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 88–102.
2. Rybak M. The pharmacokinetic profile of a new generation of parenteral cephalosporin. *Am J Med* 1996; **100** (suppl 6A): 39S–44S.
3. Reed MD, *et al.* Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. *Antimicrob Agents Chemother* 1997; **41:** 1783–7.
4. Allaouchiche B, *et al.* Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 1997; **41:** 2424–7.
5. Blumer JL, *et al.* Review of the pharmacokinetics of cefepime in children. *Pediatr Infect Dis J* 2001; **20:** 337–42.
6. Capparelli E, *et al.* Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005; **49:** 2760–6.

Uses and Administration

Cefepime is a fourth-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms. They include infections of the urinary tract, respiratory tract, and skin. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefepime is given as the hydrochloride by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. Doses are expressed in terms of the equivalent amount of cefepime; 1.19 g of cefepime hydrochloride is equivalent to about 1 g of cefepime. The usual adult dose is 1 to 2 g daily in 2 divided doses for mild to moderate infections, increased to 4 g daily in 2 divided doses in severe infections, although up to 6 g daily in 3 divided doses has been given for febrile neutropenia. Children aged over 2 months and weighing up to 40 kg may be given 50 mg/kg twice daily; this dose may be given 3 times daily for febrile neutropenia.

For details of reduced doses to be used in renal impairment, see below.

◊ Reviews.

1. Various. Cefepime: a β-lactamase-stable extended-spectrum cephalosporin. *J Antimicrob Chemother* 1993; **32** (suppl B): 1–214.
2. Barradell LB, Bryson HM. Cefepime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **47:** 471–505.
3. Okamoto MP, *et al.* Cefepime: a new fourth-generation cephalosporin. *Am J Hosp Pharm* 1994; **51:** 463–77.
4. Wynd MA, Paladino JA. Cefepime: a fourth-generation parenteral cephalosporin. *Ann Pharmacother* 1996; **30:** 1414–24.
5. Wong-Beringer A. Treating serious infections: focus on cefepime. *Pharmacotherapy* 2004; **24:** 216S–23S.
6. Roberts JA, *et al.* Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; **29:** 117–28.

Administration in renal impairment. Dosage of cefepime should be modified in renal impairment. After a normal first dose the maintenance dosage should be adjusted according to the patient's creatinine clearance (CC) and the severity of the infection:

- CC 30 to 60 mL/minute: 0.5 to 2 g every 24 hours (2 g every 12 hours for febrile neutropenia)
- CC 11 to 29 mL/minute: 0.5 to 1 g every 24 hours (2 g every 24 hours for febrile neutropenia)
- CC 10 mL/minute or less: 250 to 500 mg every 24 hours (1 g every 24 hours for febrile neutropenia)

Patients undergoing haemodialysis should be given a dose of 1 g on the first day of treatment, followed by 500 mg daily; the dose should be given after haemodialysis on those days. A dose of 1 g daily should be used for febrile neutropenia. Patients undergoing continuous ambulatory peritoneal dialysis should receive normal recommended doses at intervals of 48 hours. A dose of 2 g every 48 hours is used for febrile neutropenia.

Preparations

USP 31: Cefepime for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Cefimen-K; Maxcef; Rivepime; ***Austral.:*** Maxipime; ***Austria:*** Maxipime; ***Belg.:*** Maxipime; ***Braz.:*** Cefepen†; Cemax†; Clocef; Maxcef; Maxil†; ***Canad.:*** Maxipime; ***Chile:*** Maxipime; ***Cz.:*** Maxipime; ***Denm.:*** Maxipime†; ***Fin.:*** Maxipime; ***Fr.:*** Axepim; ***Ger.:*** Maxipime; ***Gr.:*** Anticepim; Gencef; Maxinject; Maxipime; Verapime; Zefipime; ***Hong Kong:*** Maxipime; ***Hung.:*** Maxipime; ***India:*** Biopime; Ceficad; Forpar; ***Indon.:*** Exepime; Maxicef; Maxipime; Procepim; Sandocef; ***Irl.:*** Maxipime†; ***Israel:*** Maxcef†; ***Ital.:*** Cepim; Cepimex; Maxipime; ***Malaysia:*** Maxipime; ***Mex.:*** Maxipime; ***NZ:*** Maxipime; ***Philipp.:*** Cepimax; ***Pol.:*** Maxipime; ***Port.:*** Maxipime; ***Rus.:*** Maxipime (Максипим); ***S.Afr.:*** Maxipime; ***Singapore:*** Maxipime; ***Spain:*** Maxipime; ***Swed.:*** Maxipime; ***Switz.:*** Maxipime; ***Thai.:*** Maxipime; ***Turk.:*** Maxipime; ***USA:*** Maxipime; ***Venez.:*** Maxipime.

Cefetamet *(USAN, rINN)*

Céfétamet; Cefetametum; LY-097964; Ro-15-8074. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid.

Цефетамет

$C_{14}H_{15}N_5O_5S_2$ = 397.4.
CAS — 65052-63-3 (cefetamet).
ATC — J01DD10.
ATC Vet — QJ01DD10.

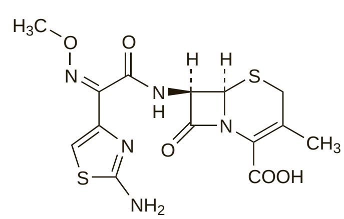

Cefetamet Pivoxil Hydrochloride *(rINNM)*

Céfétamet Pivoxil, Chlorhydrate de; Cefetameti Pivoxili Hydrochloridum; Cefetametpivoxilhydroklorid; Cefetametum Pivoxili Hydrochloridum; Hidrocloruro de cefetamet pivoxilo; Kefetameettipivoksiilihydrokloridi; Ro-15-8075 (cefetamet pivoxil). Cefetamet pivaloyloxymethyl hydrochloride.

Цефетамета Пивоксила Гидрохлорид

$C_{20}H_{25}N_5O_7S_2,HCl$ = 548.0.
CAS — 65243-33-6 (cefetamet pivoxil); 111696-23-2 (cefetamet pivoxil hydrochloride).
ATC — J01DD10.
ATC Vet — QJ01DD10.

Profile

Cefetamet is a third-generation cephalosporin antibacterial similar to cefixime (below). It has been given orally as the hydrochloride of the pivaloyloxymethyl ester, cefetamet pivoxil hydrochloride, which is hydrolysed to cefetamet *in vivo*. The usual dose is 500 mg twice daily.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p.317.

◊ Reviews.

1. Bryson HM, Brogden RN. Cefetamet pivoxil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1993; **45:** 589–621.
2. Blouin RA, Stoeckel K. Cefetamet pivoxil clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 172–88.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Globocef†; ***Ger.:*** Globocef†; ***Hong Kong:*** Globocef†; ***Ital.:*** Globocef†; ***Pol.:*** Tarcevis†; ***Port.:*** Cefec†; Globocef†; ***Switz.:*** Globocef†.

Cefixime *(BAN, USAN, rINN)*

Cefiksimas; Cefixim; Cefixim trihydrát; Cefixima; Céfixime; Cefiximum; Cefiximum Trihydricum; CL-284635; FK-027; FR-17027; Kefiksiimi; Sefiksim. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid trihydrate.

Цефиксим

$C_{16}H_{15}N_5O_7S_2,3H_2O$ = 507.5.
CAS — 79350-37-1.
ATC — J01DD08.
ATC Vet — QJ01DD08.

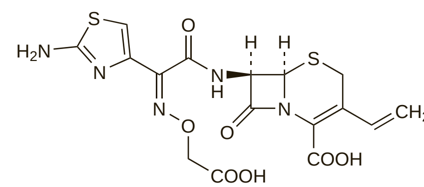

Pharmacopoeias. In *Eur.* (see p.vii) and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 6.2 (Cefixime). A white or almost white, slightly hygroscopic, powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in ethyl acetate; freely soluble in methyl alcohol. A 5% suspension in water has a pH of 2.6 to 4.1. Store in airtight containers. Protect from light.

USP 31 (Cefixime). A white to light yellow crystalline powder. Practically insoluble in water, in ether, in ethyl acetate, and in hexane; slightly soluble in alcohol, in acetone, and in glycerol; soluble in methyl alcohol and in propylene glycol; very slightly soluble in 70% sorbitol and in octanol. pH of a solution in water containing the equivalent of cefixime 0.07% is between 2.6 and 4.1. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

The most frequently reported adverse effects of cefixime are gastrointestinal disturbances, especially diarrhoea. Cefixime should be stopped if diarrhoea is severe.

Although cefixime does not have the *N*-methylthiotetrazole side-chain usually associated with hypoprothrombinaemia increases in prothrombin times have occurred in a few patients.

Antibiotic-associated colitis. For reports of diarrhoea and pseudomembranous colitis associated with cefixime, see Cefalotin, p.219.

Interactions

Care should be exercised in patients receiving anticoagulants and cefixime due to the possibility that cefixime may increase prothrombin times (see above).

Antimicrobial Action

Cefixime is bactericidal and is stable to hydrolysis by many beta-lactamases. It has a mode of action and spectrum of activity similar to those of the third-generation cephalosporin cefotaxime (p.228), but some Enterobacteriaceae are less susceptible to cefixime. *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* are sensitive, including penicillinase-producing strains. Of the Gram-positive bacteria, streptococci are sensitive to cefixime but most strains of staphylococci, enterococci, and *Listeria* spp. are not.

Enterobacter spp., *Pseudomonas aeruginosa*, and *Bacteroides* spp. are resistant to cefixime.

Pharmacokinetics

Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food. Cefixime is better absorbed from oral suspension than from tablets. Absorption is fairly slow; peak plasma concentrations of 2 to 3 micrograms/mL and 3.7 to 4.6 micrograms/mL have been reported between 2 and 6 hours after single doses of 200 and 400 mg, respectively. The plasma half-life is usually about 3 to 4 hours and may be prolonged when there is renal impairment. About 65% of cefixime is bound to plasma proteins.

Information on the distribution of cefixime in body tissues and fluids is limited. It crosses the placenta. Relatively high concentrations may be achieved in bile and urine. About 20% of an oral dose (or 50% of an absorbed dose) is excreted unchanged in the urine within 24 hours. Up to 60% may be eliminated by nonrenal mechanisms; there is no evidence of metabolism but some is probably excreted into the faeces from bile. It is not substantially removed by dialysis.

◊ References.

1. Brittain DC, *et al*. The pharmacokinetic and bactericidal characteristics of oral cefixime. *Clin Pharmacol Ther* 1985; **38:** 590–4.
2. Guay DRP, *et al*. Pharmacokinetics of cefixime (CL-284,635; FK027) in healthy subjects and patients with renal insufficiency. *Antimicrob Agents Chemother* 1986; **30:** 485–90.
3. Faulkner RD, *et al*. Pharmacokinetics of cefixime in the young and elderly. *J Antimicrob Chemother* 1988; **21:** 787–94.
4. Stone JW, *et al*. Cefixime, in-vitro activity, pharmacokinetics and tissue penetration. *J Antimicrob Chemother* 1989; **23:** 221–8.
5. Westphal JF, *et al*. Biliary excretion of cefixime: assessment in patients provided with T-tube drainage. *Antimicrob Agents Chemother* 1993; **37:** 1488–91.
6. Somekh E, *et al*. Penetration and bactericidal activity of cefixime in synovial fluid. *Antimicrob Agents Chemother* 1996; **40:** 1198–1200.

Uses and Administration

Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally in the treatment of susceptible infections including gonorrhoea, otitis media, pharyngitis, lower respiratory-tract infections such as bronchitis, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefixime is available as the trihydrate and doses are expressed in terms of anhydrous cefixime; 1.12 g of cefixime trihydrate is equivalent to about 1 g of anhydrous cefixime. It is given orally in adult doses of 200 to 400 mg daily as a single dose or in two divided doses. Children over 6 months and under 50 kg may be given 8 mg/kg daily as an oral suspension, again as a single dose or in two divided doses. For details of reduced dosage of cefixime in patients with moderate to severe renal impairment, see below.

For uncomplicated gonorrhoea, a single oral dose of 400 mg is given.

◊ General references.

1. Leggett NJ, *et al*. Cefixime. *DICP Ann Pharmacother* 1990; **24:** 489–95.
2. Adam D, Wallace RJ, eds. Symposium on cefixime. *Drugs* 1991; **42** (suppl 4): 1–32.
3. Markham A, Brogden RN. Cefixime: a review of its therapeutic efficacy in lower respiratory tract infections. *Drugs* 1995; **49:** 1007–22.

Administration in renal impairment. Doses of cefixime should be reduced in patients with moderate to severe renal impairment. A dose of 200 mg daily should not be exceeded in patients with a creatinine clearance of less than 20 mL/minute.

Preparations

USP 31: Cefixime for Oral Suspension; Cefixime Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cetaxim†; Novacef; Vixcef; ***Austria:*** Aerocef; Enzine; Exciol; Tricef; Xefotil; Xetinol; ***Braz.:*** Cefnax†; Neo Cefix; Plenax†; ***Canad.:*** Suprax; ***Chile:*** Cefspan†; Tricef; Urotricef; ***Cz.:*** Suprax; ***Fr.:*** Oroken; ***Ger.:*** Cefixdura; Cephoral; InfectoOpticef; Suprax; Uro-Cephoral; ***Gr.:*** Ceftoral; Cov-ocef-N; ***Hung.:*** Suprax; ***India:*** Biotax-O; Cefix; Cefocef-LB; Fixx; Si-Fixim†; Xim; Ziprax; ***Indon.:*** Cefspan; Ceptik; Comsporin; Ethifix; Fixacep; Fixef; Fixiphar; Lanfix; Maxpro; Opixime; Simcef; Sofix; Spancef; Spaxim; Sporetik; Starcef; Tocef; ***Irl.:*** Suprax; ***Israel:*** Supran; ***Ital.:*** Cefixoral; Suprax; Unixime; ***Jpn:*** Cefspan; ***Malaysia:*** Minixime; ***Mex.:*** Denvar; Novacef†; ***Neth.:*** Fixim; ***Philipp.:*** Tergecef; Ultraxime; Zefral; ***Port.:*** Bonocef†; Cefimix; Cefiton; Cefizel; Neocef; Tricef; ***Rus.:*** Suprax (Супракс); ***S.Afr.:*** Fixime; ***Spain:*** Denvar; Necopen; ***Swed.:*** Tricef†; ***Switz.:*** Cephoral; ***Thai.:*** Cefspan; ***Turk.:*** Suprax; Zimaks; ***UK:*** Suprax; ***USA:*** Suprax; ***Venez.:*** Longacef.

Multi-ingredient: ***India:*** Cefix LB.

Cefmenoxime Hydrochloride *(USAN, rINNM)*

Abbott-50192; Cefménoxime, Chlorhydrate de; Cefmenoxime Hemihydrochloride; Cefmenoximi Hydrochloridum; Hidrocloruro de cefmenoxima; SCE-1365 (cefmenoxime). (*Z*)-(7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid hydrochloride.

Цефменоксима Гидрохлорид

$(C_{16}H_{17}N_9O_5S_3)_2$,HCl = 1059.6.

CAS — 65085-01-0 (cefmenoxime); 75738-58-8 (cefmenoxime hydrochloride).

ATC — J01DD05.

ATC Vet — QJ01DD05.

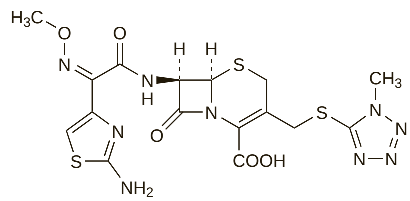

(cefmenoxime)

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Cefmenoxime Hydrochloride). White to light orange-yellow crystals or crystalline powder. Very slightly soluble in water; practically insoluble in dehydrated alcohol and in ether; freely soluble in formamide; slightly soluble in methyl alcohol. Store in airtight containers.

Profile

Cefmenoxime is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefotaxime (p.228). It has been given as the hydrochloride by intramuscular injection, or intravenously by injection or infusion in the treatment of susceptible infections.

Like cefamandole (p.220), cefmenoxime has an *N*-methylthiotetrazole side-chain and coagulopathy and a disulfiram-like interaction with alcohol have been reported rarely.

Cefmenoxime hydrochloride is also given as eye drops for the treatment of eye infections.

◊ Reviews.

1. Campoli-Richards DM, Todd PA. Cefmenoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1987; **34:** 188–221.

Preparations

USP 31: Cefmenoxime for Injection.

Proprietary Preparations (details are given in Part 3)
Gr.: Tacef†; ***Jpn:*** Bestcall; Bestron.

Cefmetazole *(USAN, rINN)*

Cefmetazol; Cefmétazole; Cefmetazolum; U-72791. (6*R*,7*S*)-7-{2-[(Cyanomethyl)thio]acetamido}-7-methoxy-3-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid.

Цефметазол

$C_{15}H_{17}N_7O_5S_3$ = 471.5.

CAS — 56796-20-4.

ATC — J01DC09.

ATC Vet — QJ01DC09.

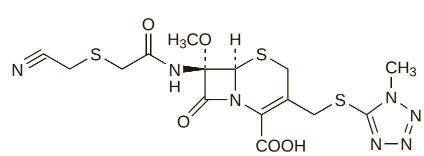

Pharmacopoeias. In *US*.

USP 31 (Cefmetazole). Store in airtight containers.

Cefmetazole Sodium *(USAN, rINNM)*

Cefmetazol sódico; Cefmétazole Sodique; Cefmetazolnatrium; Cefmetazolum Natricum; CS-1170; Kefmetatsolinatrium; Natrii Cefmetazolum; SKF-83088; U-72791A.

Натрий Цефметазол

$C_{15}H_{16}N_7NaO_5S_3$ = 493.5.

CAS — 56796-39-5.

ATC — J01DC09.

ATC Vet — QJ01DC09.

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Cefmetazole Sodium). A white solid. Very soluble in water and in methyl alcohol; soluble in acetone; practically insoluble in chloroform. pH of a 10% solution in water is between 4.2 and 6.2. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefmetazole contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Effects on the blood. References.

1. Breen GA, St Peter WL. Hypoprothrombinemia associated with cefmetazole. *Ann Pharmacother* 1997; **31:** 180–4.

Sodium content. Each g of cefmetazole sodium contains about 2 mmol of sodium.

Interactions

As for Cefamandole, p.221.

Antimicrobial Action

Cefmetazole is a cephamycin antibacterial with a similar spectrum of antibacterial activity to that of cefoxitin (p.230), including the anaerobe *Bacteroides fragilis*.

◊ References.

1. Cornick NA, *et al*. Activity of cefmetazole against anaerobic bacteria. *Antimicrob Agents Chemother* 1987; **31**: 2010–12.

Pharmacokinetics

After cefmetazole sodium 2 g intravenously every 6 hours, peak and trough plasma concentrations of 138 and 6 micrograms/mL have been achieved. Cefmetazole is 65 to 85% bound to plasma proteins, depending on the plasma concentration. A plasma half-life of about 1.1 to 1.5 hours has been reported; it is prolonged in patients with renal impairment. Small amounts have been detected in breast milk. Relatively high concentrations have been achieved in bile.

The majority of a dose is excreted unchanged in the urine resulting in high concentrations; up to 85% of a dose has been recovered within 12 hours. Cefmetazole is partly excreted by renal tubular secretion and probenecid prolongs elimination.

Cefmetazole is removed to some extent by haemodialysis.

Uses and Administration

Cefmetazole is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p.230) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It may also be used in the treatment of gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefmetazole is given intravenously as the sodium salt by infusion over 10 to 60 minutes or by slow injection over 3 to 5 minutes. Cefmetazole sodium is also used intramuscularly in some countries. Doses are expressed in terms of the equivalent amount of cefmetazole; 1.05 g of cefmetazole sodium is equivalent to about 1 g of cefmetazole.

The usual dose is 0.5 to 1 g intramuscularly or intravenously every 12 hours. For severe infections the dose may be increased to 3 to 4 g daily, given in divided doses every 6 to 8 hours.

For details of reduced dosage of cefmetazole in patients with renal impairment, see below.

◊ References.

1. Finch R, *et al*. eds. Cefmetazole: a clinical appraisal. *J Antimicrob Chemother* 1989; **23** (suppl D): 1–142.

Administration in renal impairment. Doses of cefmetazole should be reduced in patients with renal impairment. It has been suggested that the interval between doses should be 12, 16, or 24 hours in patients with mild, moderate, or severe renal impairment, respectively; patients with virtually no renal function might be given cefmetazole every 48 hours, after haemodialysis.

Preparations

USP 31: Cefmetazole for Injection; Cefmetazole Injection.

Proprietary Preparations (details are given in Part 3)
Hong Kong: Cefmetazon†; ***Ital.:*** Metacaf†; Metafar; Metasal†; Metax; Metazol†; ***Jpn:*** Cefmetazon†; ***USA:*** Zefazone†.

Cefminox Sodium *(pINNM)*

Cefminox sódico; Cefminox Sodique; MT-141; Natrii Cefminoxum. Sodium 7-{2-[(*S*)-2-amino-2-carboxyethyl]thioacetamido}-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

Натрий Цефминокс

$C_{16}H_{20}N_7NaO_7S_3$ = 541.6.

CAS — 75481-73-1 (cefminox).

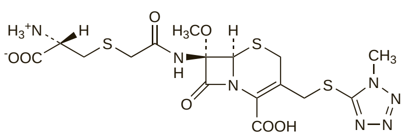

(cefminox)

Pharmacopoeias. *Jpn* includes the heptahydrate.

Profile

Cefminox sodium is a cephamycin antibacterial with properties similar to those of cefoxitin (p.230) but with an *N*-methylthiotetrazole side-chain like cefamandole (p.220). It is given intravenously as the sodium salt but doses are expressed in terms of cefminox; 1.04 g of cefminox sodium is equivalent to about 1 g of cefminox. A usual dose is 2 to 4 g daily given in divided doses.

◊ References.

1. Watanabe S, Omoto S. Pharmacology of cefminox, a new bactericidal cephamycin. *Drugs Exp Clin Res* 1990; **16:** 461–7.
2. Soriano F, *et al.* Comparative susceptibility of cefminox and cefoxitin to β-lactamases of Bacteroides spp. *J Antimicrob Chemother* 1991; **28:** 55–60.
3. Aguilar L, *et al.* Cefminox: correlation between in-vitro susceptibility and pharmacokinetics and serum bactericidal activity in healthy volunteers. *J Antimicrob Chemother* 1994; **33:** 91–101.
4. Mayama T, *et al.* Postmarketing surveillance on side-effects of cefminox sodium (Meicelin). *Int J Clin Pharmacol Ther* 1995; **33:** 149–55.
5. Hoellman DB, *et al.* In vitro activities of cefminox against anaerobic bacteria compared with those of nine other compounds. *Antimicrob Agents Chemother* 1998; **42:** 495–501.
6. Torres AJ, *et al.* Cefminox versus metronidazole plus gentamicin in intra-abdominal infections: a prospective randomized controlled clinical trial. *Infection* 2000; **28:** 318–22.

Sodium content. Each g of cefminox sodium contains about 1.84 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Meicelin; ***Port.:*** Tencef; ***Spain:*** Tencef; ***Thai.:*** Meicelin.

Cefodizime Sodium *(BANM, rINNM)*

Cefodizima sódica; Céfodizime Sodique; HR-221; Natrii Cefodizimum; S-771221B; Sefodizim Disodyum; THR-221; TRH-221. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-carboxymethyl-4-methylthiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

Натрий Цефодизим

$C_{20}H_{18}N_6Na_2O_7S_4$ = 628.6.

CAS — 69739-16-8 (cefodizime); 86329-79-5 (cefodizime sodium).

ATC — J01DD09.

ATC Vet — QJ01DD09.

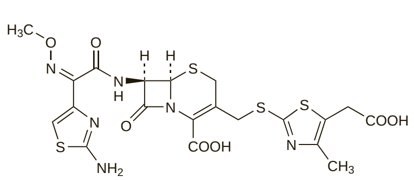

(cefodizime)

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

As for Cefotaxime, p.228.

Sodium content. Each g of cefodizime sodium contains about 3.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefodizime.

Antimicrobial Action

Cefodizime has similar antimicrobial activity to that of cefotaxime (p.228) although cefodizime has no active metabolite. It has variable activity against *Citrobacter* spp., and *Pseudomonas aeruginosa* and *Bacteroides fragilis* are generally resistant.

Pharmacokinetics

Cefodizime is given by injection as the sodium salt. Intramuscular injection of 1 g cefodizime produces peak plasma concentrations of about 60 to 75 micrograms/mL at about 1 to 1.5 hours. Immediately after intravenous doses of 1 or 2 g cefodizime mean peak plasma concentrations of 215 and 394 micrograms/mL, respectively, have been achieved. Cefodizime is about 80% bound to plasma proteins and is widely distributed into body tissues and fluids. It crosses the placenta and small amounts have been detected in breast milk. Plasma elimination is reported to be triphasic with a terminal elimination half-life of about 4 hours. The half-life is prolonged by renal impairment.

The majority of a dose is excreted unchanged in the urine; up to 80% of a dose has been recovered within 24 hours. Cefodizime is mainly excreted by glomerular filtration with some tubular secretion. Probenecid delays excretion. Cefodizime is removed by dialysis.

Uses and Administration

Cefodizime is a third-generation cephalosporin antibacterial with uses similar to those of cefotaxime (p.229).

Cefodizime is given as the disodium salt by intramuscular injection or intravenously by injection or infusion in the treatment of susceptible infections. Doses are expressed in terms of the equivalent amount of cefodizime; 1.08 g of cefodizime sodium is equivalent to about 1 g of cefodizime. Adults are usually given 1 to 2 g every 12 or 24 hours for lower respiratory-tract infections and upper and lower urinary-tract infections. Doses up to 4 g daily may be given in severe infection. In women with uncomplicated lower urinary-tract infections a single dose of 1 to 2 g may be sufficient. For gonorrhoea a single dose of 0.25 to 0.5 g may be given. Doses may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Finch RG, *et al.*, eds. Cefodizime: a third generation cephalosporin with immunomodulating properties. *J Antimicrob Chemother* 1990; **26** (suppl C): 1–134.
2. Barradell LB, Brogden RN. Cefodizime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1992; **44:** 800–834.
3. Thalhammer F, *et al.* Single-dose cefodizime as infection prophylaxis in abdominal surgery: a prospective multicenter study. *Infection* 1998; **26:** 136–8.
4. Matsumoto T, *et al.* Single dose of cefodizime completely eradicated multidrug-resistant strain of Neisseria gonorrhoeae in urethritis and uterine cervicitis. *J Infect Chemother* 2006; **12:** 97–9.
5. Matsumoto T, *et al.* Multiple doses of cefodizime are necessary for the treatment of Neisseria gonorrhoeae pharyngeal infection. *J Infect Chemother* 2006; **12:** 145–7.

Administration in renal impairment. Doses of cefodizime should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: 1 to 2 g daily
- CC less than 10 mL/minute: 0.5 to 1 g daily

In patients undergoing dialysis, 0.5 to 1 g daily is given after dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Timecef; ***Ital.:*** Diezime; Modivid; Timecef; ***Jpn:*** Kenicef; ***Mex.:*** Modivid†; ***NZ:*** Timecef; ***Port.:*** Modivid; ***Turk.:*** Modivid.

Cefonicid Sodium *(BANM, USAN, rINNM)*

Cefonicid sódico; Cefonicide sodique; Céfonicide Sodique; Cefonicidum natricum; Natrii Cefonicidum; SKF-D-75073-Z_2; SKF-D-75073-Z (cefonicid monosodium). 7-[(*R*)-Mandelamido]-3-(1-sulphomethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

Натрий Цефоницид

$C_{18}H_{16}N_6Na_2O_8S_3$ = 586.5.

CAS — 61270-58-4 (cefonicid); 61270-78-8 (cefonicid disodium); 71420-79-6 (cefonicid monosodium).

ATC — J01DC06.

ATC Vet — QJ01DC06.

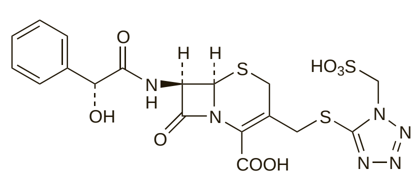

(cefonicid)

Pharmacopoeias. In *US.*

USP 31 (Cefonicid Sodium). A white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose 5%; very slightly soluble in dehydrated alcohol; soluble in methyl alcohol. pH of a 5% solution in water is between 3.5 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefonicid contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia.

Effects on the blood. References.

1. Riancho JA, *et al.* Life-threatening bleeding in a patient treated with cefonicid. *Ann Intern Med* 1995; **123:** 472–3.

Effects on the liver. References.

1. Famularo G, *et al.* Eosinophilic hepatitis associated with cefonicid therapy. *Ann Pharmacother* 2001; **35:** 1669–71.

Sodium content. Each g of cefonicid sodium contains about 3.4 mmol of sodium.

Interactions

As for Cefamandole, p.221.

Antimicrobial Action

Cefonicid sodium has an antimicrobial action and pattern of resistance similar to those of cefamandole (p.221), although it is generally less active against Gram-positive cocci.

Pharmacokinetics

Cefonicid is given parenterally as the sodium salt. Peak plasma concentrations ranging from 67 to 126 micrograms/mL have been achieved 1 to 2 hours after a 1-g intramuscular dose. Cefonicid is more than 90% bound to plasma proteins. It has a plasma half-life of about 4.5 hours, which is prolonged in patients with renal impairment.

Therapeutic concentrations of cefonicid have been reported in a wide range of body tissues and fluids.

Up to 99% of a dose of cefonicid is excreted unchanged in the urine within 24 hours. Probenecid reduces excretion of cefonicid.

Uses and Administration

Cefonicid is a second-generation cephalosporin antibacterial used similarly to cefamandole (p.221) in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the sodium salt by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefonicid; 1.08 g of cefonicid sodium is equivalent to about 1 g of cefonicid. The usual dose is cefonicid 1 g once daily. For uncomplicated urinary-tract infections, a dose of 500 mg once daily is recommended; up to 2 g once daily has been given in severe infections. More than 1 g should not be injected intramuscularly into a single site.

For surgical infection prophylaxis, a single dose of 1 g given 1 hour before surgical incision is usually sufficient, but may be given daily for a further 2 days in prosthetic arthroplasty or open-heart surgery.

◊ References.

1. Saltiel E, Brogden RN. Cefonicid: a review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1986; **32:** 222–59.

Administration in renal impairment. For patients with renal impairment a loading dose equivalent to cefonicid 7.5 mg/kg is recommended, followed by reduced maintenance doses according to the creatinine clearance and the severity of the infection. A dose supplement is not required after dialysis.

Preparations

USP 31: Cefonicid for Injection.

Proprietary Preparations (details are given in Part 3)
Belg.: Monocid†; ***Israel:*** Monocef; ***Ital.:*** Abiocef†; Auricid†; Bacid†; Biocil; Biotici; Cefobacter; Cefodie; Cefoger†; Cefok; Cefoplus; Cefosporin†; Chefir; Clastidin†; Daycef; Delsacid†; Diespor; Emidoxin; Epicef†; Fonexel†; Fonicef†; Fonicid; Fonisal†; Framecef; Ipacid†; Krucef; Lampocef†; Lisa; Maxid; Microcid†; Modicef; Modiem; Monobios; Monobiotic; Monocid†; Necid; Nokid; Pantacid†; Parecid; Praticef; Raikocef; Renbiocid†; Rocid†; Silvercef†; Sintocef; Sofarcid; Unicid†; Valecid; ***Port.:*** Monocid; ***Spain:*** Monocid; Unidie; ***USA:*** Monocid†.

Cefoperazone Sodium

(BANM, USAN, rINNM)

Cefoperazon sodná sůl; Cefoperazon sodowy; Cefoperazona sódica; Céfopérazone sodique; Cefoperazonnatrium; Cefoperazon-nátrium; Cefoperazono natrio druska; Cefoperazonum natricum; CP-52640-2; CP-52640 (anhydrous cefoperazone); CP-52640-3 (cefoperazone dihydrate); Kefoperatsoninatrium; Natrii Cefoperazonum; Sefoperazon Sodyum; T-1551 (cefoperazone or cefoperazone sodium). Sodium (7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-2-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate.

Натрий Цефоперазон

$C_{25}H_{26}N_9NaO_8S_2$ = 667.6.

CAS — 62893-19-0 (cefoperazone); 62893-20-3 (cefoperazone sodium).

ATC — J01DD12.

ATC Vet — QJ01DD12.

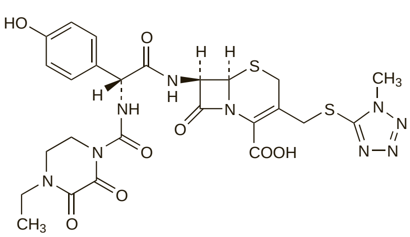

(cefoperazone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Cefoperazone Sodium). A white or slightly yellow, hygroscopic, powder. If crystalline it exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 25% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Cefoperazone Sodium). A white to pale buff crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; insoluble in acetone, in ether, and in ethyl acetate. pH of a 25% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. As with most beta lactams, admixture of cefoperazone sodium with aminoglycosides is not recommended because of the potential for inactivation of either drug.

There have been reports of incompatibility with other drugs including diltiazem,[1] doxorubicin,[2] pentamidine,[3] perphenazine,[4] pethidine,[5] promethazine,[6] and remifentanil.[7]

1. Gayed AA, *et al*. Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52:** 516–20.
2. Trissel LA, *et al*. Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.
3. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.
4. Gasca M, *et al*. Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.
5. Nieves-Cordero AL, *et al*. Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
6. Scott SM. Incompatibility of cefoperazone and promethazine. *Am J Hosp Pharm* 1990; **47:** 519.
7. Trissel LA, *et al*. Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Like cefotaxime (p.228), cefoperazone has the potential for colonisation and superinfection with resistant organisms. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of cefoperazone; diarrhoea may occur more often.

Cefoperazone contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia. Hypoprothrombinaemia has been reported in patients treated with cefoperazone and has rarely been associated with bleeding episodes. Prothrombin time should be monitored in patients at risk of hypoprothrombinaemia and vitamin K used if necessary.

Sodium content. Each g of cefoperazone sodium contains about 1.5 mmol of sodium.

Interactions

As for Cefamandole, p.221.

Unlike many other cephalosporins, probenecid has no effect on the renal clearance of cefoperazone.

Antimicrobial Action

Cefoperazone has antimicrobial activity similar to that of ceftazidime (p.234), although it is slightly less active against some Enterobacteriaceae. It has good activity against *Pseudomonas aeruginosa*, but is less active than ceftazidime.

Cefoperazone is more susceptible than cefotaxime to hydrolysis by certain beta-lactamases.

Activity, particularly against Enterobacteriaceae and *Bacteroides* spp. has been enhanced in the presence of the beta-lactamase inhibitor sulbactam; resistant *Ps. aeruginosa* are not sensitive to the combination.

◊ References.

1. Fass RJ, *et al*. In vitro activities of cefoperazone and sulbactam singly and in combination against cefoperazone-resistant members of the family Enterobacteriaceae and nonfermenters. *Antimicrob Agents Chemother* 1990; **34:** 2256–9.
2. Clark RB, *et al*. Multicentre study on antibiotic susceptibilities of anaerobic bacteria to cefoperazone-sulbactam and other antimicrobial agents. *J Antimicrob Chemother* 1992; **29:** 57–67.

Pharmacokinetics

Cefoperazone is given parenterally as the sodium salt. With intramuscular doses equivalent to cefoperazone 1 or 2 g, peak plasma concentrations of 65 and 97 micrograms/mL have been reported after 1 to 2 hours. The plasma half-life of cefoperazone is about 2 hours, but may be prolonged in neonates and in patients with hepatic or biliary-tract disease. Cefoperazone is 82 to 93% bound to plasma proteins, depending on the concentration.

Cefoperazone is widely distributed in body tissues and fluids, although penetration into the CSF is generally poor. It crosses the placenta, and low concentrations have been detected in breast milk.

Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Urinary excretion is primarily by glomerular filtration. Up to 30% of a dose is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found only rarely *in vivo*.

Uses and Administration

Cefoperazone is a third-generation cephalosporin antibiotic used similarly to ceftazidime (p.235) in the treatment of susceptible infections, especially those due to *Pseudomonas* spp. It is not recommended for the treatment of meningitis because of poor penetration into the CSF.

Cefoperazone is given as the sodium salt by deep intramuscular injection or intravenously by intermittent or continuous infusion. Doses are expressed in terms of the equivalent amount of cefoperazone; 1.03 g of cefoperazone sodium is equivalent to about 1 g of cefoperazone. The usual dose is 2 to 4 g daily in 2 divided doses. In severe infections, up to 12 g daily in 2 to 4 divided doses may be given.

For details of dosage in patients with hepatic and renal impairment, see below.

If cefoperazone is used with an aminoglycoside, the drugs should be given separately.

Cefoperazone has also been given with the beta-lactamase inhibitor sulbactam.

Administration in hepatic and renal impairment. In general, the dose of cefoperazone should not exceed 4 g daily in patients with liver disease or biliary obstruction or 1 to 2 g daily in those with both hepatic and renal impairment; if higher doses are used plasma concentrations of cefoperazone should be monitored.

Preparations

USP 31: Cefoperazone for Injection; Cefoperazone Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefobid†; ***Austria:*** Cefobid; ***Braz.:*** Cefazone†; Neoperazona†; ***Chile:*** Cefobid; ***Cz.:*** Cefobid; ***Hong Kong:*** Cefobid; ***Hung.:*** Cefobid; ***India:*** Cefomycin; Magnamycin; ***Indon.:*** Bifotik; Cefobid; Cefophar; Ceropid; Cerozon; Ferzobat; Logafox; Stabixin; ***Ital.:*** Bioperazone; Cefoneg†; Cefoper; Dardum; Farecef; Ipazone†; Novobiocyl†; Tomabef†; Zoncef†; ***Jpn:*** Cefobid†; Cefoperazin; ***Malaysia:*** Cefobid; Medocef; Shinfomycin; ***Mex.:*** Cefobid; ***Philipp.:*** Bactizon; ***Pol.:*** Biocefazon; Cefobid; Dardum; ***Rus.:*** Cefobid (Цефобид); Medocef (Медоцеф); ***Singapore:*** Cefobid; Cefozone; Dardum; ***Spain:*** Cefobid†; ***Thai.:*** Cefobid; Cefozone†; Medocef; ***Turk.:*** Cefobid; ***USA:*** Cefobid†; ***Venez.:*** Cefobid†; Ortosep†.

Multi-ingredient: ***Arg.:*** Sulperazon†; ***Chile:*** Sulperazon; ***Cz.:*** Sulperazon; ***Hong Kong:*** Sulperazon; ***India:*** Lactagard; Sulbacef; Zosul; ***Indon.:*** Fosular; Stabactam; Sulperazon; ***Malaysia:*** Sulperazon; ***Philipp.:*** Sulperazone; ***Pol.:*** Sulperazon; ***Rus.:*** Sulcef (Сульцеф); Sulperason (Сульперазон); ***Thai.:*** Cebactam; Cefper; Sulcef; Sulperazon; ***Turk.:*** Primasef; Sulperazon; ***Venez.:*** Sulperazon.

Ceforanide *(BAN, USAN, rINN)*

BL-S786; Ceforanida; Céforanide; Ceforanidum. 7-[2-(α-Amino-o-tolyl)acetamido]-3-(1-carboxymethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефоранид

$C_{20}H_{21}N_7O_6S_2$ = 519.6.

CAS — 60925-61-3.

ATC — J01DC11.

ATC Vet — QJ01DC11.

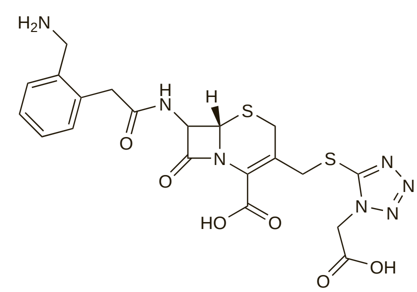

Pharmacopoeias. In *US*.

USP 31 (Ceforanide). A white to off-white powder. Practically insoluble in water, in chloroform, in ether, and in methyl alcohol; very soluble in 1N sodium hydroxide. pH of a 5% suspension in water is between 2.5 and 4.5. Store in airtight containers.

Profile

Ceforanide is a second-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p.220), although it is reported to be less active *in vitro* against some bacteria, including staphylococci and *Haemophilus influenzae.* It is used in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the lysine salt ($C_{26}H_{35}N_9O_8S_2$ = 665.7) but doses are expressed in terms of the equivalent amount of ceforanide; 1.28 g of ceforanide lysine is equivalent to about 1 g of ceforanide. It is given by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion. The usual adult dose is 1 to 2 g every 12 hours. Children may be given 20 mg/kg daily in 2 divided doses. For surgical infection prophylaxis, a dose of 1 to 2 g intravenously 1 hour before surgical incision is used in adults.

Ceforanide contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia and alcohol intolerance. Probenecid does not affect the renal excretion of ceforanide.

◊ References.

1. Campoli-Richards DM, *et al*. Ceforanide: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1987; **34:** 411–37.

Preparations

USP 31: Ceforanide for Injection.

Proprietary Preparations (details are given in Part 3)

Belg.: Precef†; ***Gr.:*** Radacef.

Cefoselis Sulfate *(rINNM)*

Céfosélis, Sulfate de; Cefoselis Sulphate; Cefoselisi Sulfas; FK-037; Sulfato de cefoselís. (−)-5-Amino-2-({(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl}methyl)-1-(2-hydroxyethyl)pyrazolium hydroxide, inner salt, 7^2-(*Z*)-(*O*-methyloxime) sulfate.

Цефозелиса Сульфат

$C_{19}H_{22}N_8O_6S_2,H_2SO_4$ = 620.6.

CAS — 122841-10-5 (cefoselis); 122841-12-7 (cefoselis sulfate).

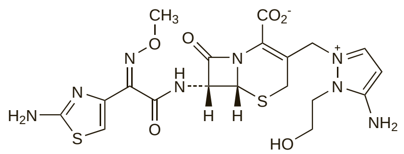

(cefoselis)

Profile

Cefoselis sulfate is a cephalosporin antibacterial that has been used in the treatment of susceptible bacterial infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Wincef†.

Cefotaxime Sodium *(BANM, USAN, rINNM)*

Cefotaksimo natrio druska; Cefotaksym sodowy; Cefotaxim sodná sůl; Cefotaxima sódica; Céfotaxime sodique; Cefotaximnatrium; Cefotaxim-nátrium; Cefotaximum natricum; CTX; HR-756; Kefotaksiiminatrium; Natrii Cefotaximum; RU-24756; Sefotaksim Sodyum. Sodium (7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

Натрий Цефотаксим

$C_{16}H_{16}N_5NaO_7S_2$ = 477.4.

CAS — 63527-52-6 (cefotaxime); 64485-93-4 (cefotaxime sodium).
ATC — J01DD01.
ATC Vet — QJ01DD01.

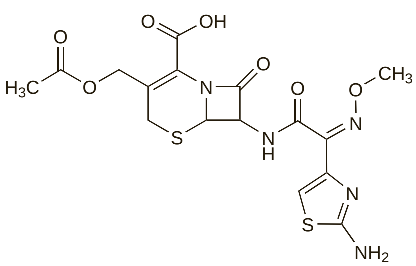

(cefotaxime)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Cefotaxime Sodium). A white or slightly yellow, hygroscopic, powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH of between 4.5 and 6.5. Store in airtight containers. Protect from light.

USP 31 (Cefotaxime Sodium). An off-white to pale yellow crystalline powder. Freely soluble in water; practically insoluble in organic solvents. pH of a 10% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate. Licensed product information recommends that it should be given separately from aminoglycosides.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219. Arrhythmias have been associated with rapid bolus dosage through a central venous catheter in a few cases.

The broad-spectrum third-generation cephalosporins have the potential for colonisation and superinfection with resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Candida*, and enterococci, at various sites in the body, although the incidence has generally been low with cefotaxime. Changes in bowel flora are a predisposing factor and have been more marked with cefoperazone and ceftriaxone, possibly because of their greater biliary excretion. Pseudomembranous colitis, associated with *Clostridium difficile* infection, may occasionally be seen with any of the third-generation cephalosporins.

◊ Reviews on adverse effects associated with third-generation cephalosporins.

1. Neu HC. Third generation cephalosporins: safety profiles after 10 years of clinical use. *J Clin Pharmacol* 1990; **30:** 396–403.
2. Fekety FR. Safety of parenteral third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 38S–44S.

Antibiotic-associated colitis. It has been suggested[1] that cefotaxime is associated with an increased risk of *Clostridium difficile* diarrhoea in elderly patients; however, the manufacturer[2] has disputed this, arguing that cefotaxime compares favourably with alternative third-generation cephalosporins.

1. Impallomeni M, *et al.* Increased risk of diarrhoea caused by Clostridium difficile in elderly patients receiving cefotaxime. *BMJ* 1995; **311:** 1345–6.
2. Rothschild E, *et al.* Risk of diarrhoea due to Clostridium difficile during cefotaxime treatment. *BMJ* 1996; **312:** 778.

Breast feeding. Although cefotaxime is excreted in breast milk in small amounts,[1] no adverse effects have been observed in breast-fed infants whose mothers were receiving cefotaxime, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Sodium content. Each g of cefotaxime sodium contains about 2.09 mmol of sodium.

Interactions

As for many cephalosporins, probenecid reduces the renal clearance of cefotaxime, resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite.

Antibacterials. The total body clearance of cefotaxime has been reduced in patients with normal and reduced renal function by the ureidopenicillins *azlocillin*[1] or *mezlocillin*.[2] Doses of cefotaxime may need to be reduced if either of these penicillins is being given. Encephalopathy with focal motor status and generalised convulsions have been reported in a patient with renal failure given cefotaxime and high doses of azlocillin.[3]

1. Kampf D, *et al.* Kinetic interactions between azlocillin, cefotaxime, and cefotaxime metabolites in normal and impaired renal function. *Clin Pharmacol Ther* 1984; **35:** 214–20.
2. Rodondi LC, *et al.* Influence of coadministration on the pharmacokinetics of mezlocillin and cefotaxime in healthy volunteers and in patients with renal failure. *Clin Pharmacol Ther* 1989; **45:** 527–34.
3. Wroe SJ, *et al.* Focal motor status epilepticus following treatment with azlocillin and cefotaxime. *Med Toxicol* 1987; **2:** 233–4.

Antimicrobial Action

Cefotaxime is a third-generation cephalosporin. It has a bactericidal action similar to cefamandole, but a broader spectrum of activity. It is highly stable to hydrolysis by most beta-lactamases and has greater activity than first- or second-generation cephalosporins against Gram-negative bacteria. Although cefotaxime is generally considered to have slightly less activity than first-generation cephalosporins against Gram-positive bacteria, many streptococci are very sensitive.

Desacetylcefotaxime is an active metabolite of cefotaxime and there may be additive or synergistic effects against some species.

Spectrum of activity. Among Gram-negative bacteria, cefotaxime is active *in vitro* against many Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., both indole-positive and indole-negative *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Other susceptible Gram-negative bacteria, including penicillin-resistant strains, are *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis*. *Brucella melitensis* is also reported to be moderately sensitive. Some strains of *Pseudomonas* spp. are moderately susceptible to cefotaxime, but most are resistant. Desacetylcefotaxime is active against many of these Gram-negative bacteria, but not against *Pseudomonas* spp.

Among Gram-positive bacteria, cefotaxime is active against staphylococci and streptococci. *Staphylococcus aureus*, including penicillinase-producing strains but not meticillin-resistant *Staph. aureus*, is sensitive. *Staph. epidermidis* is also sensitive but penicillinase-producing strains are resistant. *Streptococcus agalactiae* (group B streptococci), *Str. pneumoniae*, and *Str. pyogenes* (group A streptococci) are all very sensitive although truly penicillin-resistant pneumococci are apparently not sensitive. Enterococci and *Listeria monocytogenes* are resistant.

Cefotaxime is active against some anaerobic bacteria. *Bacteroides fragilis* may be moderately sensitive, but many strains are resistant; synergy has been demonstrated with desacetylcefotaxime *in vitro*. *Clostridium perfringens* is sensitive, but most *Cl. difficile* are resistant.

Other organisms sensitive to cefotaxime include the spirochaete *Borrelia burgdorferi* and *Haemophilus ducreyi*.

Activity with other antimicrobials. In addition to possible synergy or additive effects with desacetylcefotaxime, the activity of cefotaxime may be enhanced by aminoglycosides such as gentamicin; synergy has been demonstrated *in vitro* against Gram-negative bacteria including *Pseudomonas aeruginosa*. There have also been reports of enhanced activity *in vitro* with other antibacterials including fosfomycin and ciprofloxacin and variable results with penicillins.

Resistance may develop during treatment with cefotaxime due to derepression of chromosomally mediated beta-lactamases, and has been reported particularly in *Enterobacter* spp., with multiresistant strains emerging during treatment. This type of resistance has also developed in other bacteria including *Citrobacter*, *Serratia*, and *Pseudomonas* spp. Another mechanism of cefotaxime resistance is the development of plasma-mediated, extended-spectrum beta-lactamases, and this has occurred in *Klebsiella* spp. and also other Enterobacteriaceae. Resistance in *Str. pneumoniae* is due to the production of altered penicillin-binding proteins.

◊ References to the antimicrobial activity of cefotaxime and other third-generation cephalosporins, including the problem of bacterial resistance.

1. Neu HC. Pathophysiologic basis for the use of third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 3S–11S.
2. Chow JW, *et al.* Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115:** 585–90.
3. Sanders CC. New β-lactams: new problems for the internist. *Ann Intern Med* 1991; **115:** 650–1.
4. Thomson KS, *et al.* High-level resistance to cefotaxime and ceftazidime in Klebsiella pneumoniae isolates from Cleveland, Ohio. *Antimicrob Agents Chemother* 1991; **35:** 1001–3.
5. Piddock LJV, *et al.* Prevalence and mechanism of resistance to 'third-generation' cephalosporins in clinically relevant isolates of Enterobacteriaceae from 43 hospitals in the UK, 1990-1991. *J Antimicrob Chemother* 1997; **39:** 177–87.
6. Gums JG, *et al.* Differences between ceftriaxone and cefotaxime: microbiological inconsistencies. *Ann Pharmacother* 2008; **42:** 71–9.

Pharmacokinetics

Cefotaxime is given by injection as the sodium salt. It is rapidly absorbed after intramuscular injection and mean peak plasma concentrations of about 12 and 20 micrograms/mL have been reported 30 minutes after doses of 0.5 and 1 g of cefotaxime, respectively. Immediately after intravenous injection of 0.5, 1, or 2 g of cefotaxime, mean peak plasma concentrations of 38, 102, and 215 micrograms/mL, respectively, have been achieved with concentrations ranging from about 1 to 3 micrograms/mL after 4 hours. The plasma half-life of cefotaxime is about 1 hour and that of the active metabolite desacetylcefotaxime about 1.5 hours; half-lives are increased in neonates and in patients with severe renal impairment, especially those of the metabolite, and a reduction in dosage may be necessary. The effects of liver disease on clearance of cefotaxime and its metabolite have been variable, but in general dosage adjustment has not been considered necessary. About 40% of cefotaxime is reported to be bound to plasma proteins.

Cefotaxime and desacetylcefotaxime are widely distributed in body tissues and fluids; therapeutic concentrations are achieved in the CSF particularly when the meninges are inflamed. Cefotaxime crosses the placenta and low concentrations have been detected in breast milk.

After partial metabolism in the liver to desacetylcefotaxime and inactive metabolites, elimination is mainly by the kidneys and about 40 to 60% of a dose has been recovered unchanged in the urine within 24 hours; a further 20% is excreted as the desacetyl metabolite. Relatively high concentrations of cefotaxime and desacetylcefotaxime are achieved in bile and about 20% of a dose has been recovered in the faeces.

Probenecid competes for renal tubular secretion with cefotaxime resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite. Cefotaxime and its metabolites are removed by haemodialysis.

When microbiological assays have been used, reported pharmacokinetic values may relate to cefotaxime plus its active metabolite, desacetylcefotaxime.

Hepatic impairment. References.

1. Höffken G, *et al*. Pharmacokinetics of cefotaxime and desacetylcefotaxime in cirrhosis of the liver. *Chemotherapy* 1984; **30:** 7–17.
2. Graninger W, *et al*. Cefotaxime and desacetyl-cefotaxime blood levels in hepatic dysfunction. *J Antimicrob Chemother* 1984; **14** (suppl B): 143–6.
3. Hary L, *et al*. The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36:** 613–16.
4. Ko RJ, *et al*. Pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with liver disease. *Antimicrob Agents Chemother* 1991; **35:** 1376–80.

Renal impairment. References.

1. Matzke GR, *et al*. Cefotaxime and desacetyl cefotaxime kinetics in renal impairment. *Clin Pharmacol Ther* 1985; **38:** 31–6.
2. Paap CM, *et al*. Pharmacokinetics of cefotaxime and its active metabolite in children with renal dysfunction. *Antimicrob Agents Chemother* 1991; **35:** 1879–83.
3. Paap CM, *et al*. Cefotaxime and metabolite disposition in two pediatric continuous ambulatory peritoneal dialysis patients. *Ann Pharmacother* 1992; **26:** 341–3.
4. Paap CM, Nahata MC. The relation between type of renal disease and renal drug clearance in children. *Eur J Clin Pharmacol* 1993; **44:** 195–7.

Uses and Administration

Cefotaxime is a third-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms, especially serious and life-threatening infections. They include brain abscess, endocarditis, gonorrhoea, intensive care (selective parenteral and enteral antisepsis regimens), Lyme disease, meningitis, peritonitis (primary or spontaneous), pneumonia, septicaemia, and typhoid fever. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefotaxime is given as the sodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion over 20 to 60 minutes. Doses are expressed in terms of the equivalent amount of cefotaxime; 1.05 g of cefotaxime sodium is equivalent to about 1 g of cefotaxime. It is usually given in doses of 2 to 6 g daily in 2 to 4 divided doses to adults. In severe infections up to 12 g may be given daily by the intravenous route in up to 6 divided doses; pseudomonal infections usually require more than 6 g daily, but a cephalosporin with greater antipseudomonal activity, such as ceftazidime, is preferable. Children may be given 100 to 150 mg/kg (50 mg/kg for neonates) daily in 2 to 4 divided doses, increased in severe infections to 200 mg/kg (150 to 200 mg/kg for neonates) daily if necessary.

For details of reduced doses to be used in patients with severe renal impairment, see below.

In the treatment of gonorrhoea, a single dose of 0.5 or 1 g of cefotaxime is given.

For surgical infection prophylaxis, 1 g is given 30 to 90 minutes before surgery. At caesarean section, 1 g is given intravenously to the mother as soon as the umbilical cord is clamped and two further doses intramuscularly or intravenously 6 and 12 hours later.

Cefotaxime may be used with an aminoglycoside as synergy may occur against some Gram-negative organisms, but the drugs should be given separately. It has sometimes been used with another beta lactam to broaden the spectrum of activity. Cefotaxime has also been used with metronidazole in the treatment of mixed aerobic-anaerobic infections.

◊ General references to third-generation cephalosporins.

1. Neu HC, *et al*., eds. Third-generation cephalosporins: a decade of progress in the treatment of severe infections. *Am J Med* 1990; **88** (suppl 4A): 1S–45S.

◊ General references to cefotaxime.

1. Todd PA, Brogden RN. Cefotaxime: an update of its pharmacology and therapeutic use. *Drugs* 1990; **40:** 608–51.
2. Gentry LO. Cefotaxime and prophylaxis: new approaches with a proven agent. *Am J Med* 1990; **88** (suppl 4A): 32S–37S.
3. Davies A, Speller DCE, eds. Cefotaxime—recent clinical investigations. *J Antimicrob Chemother* 1990; **26** (suppl A): 1–83.
4. Brogden RN, Spencer CM. Cefotaxime: a reappraisal of its antibacterial activity and pharmacokinetic properties, and a review of its therapeutic efficacy when administered twice daily for the treatment of mild to moderate infections. *Drugs* 1997; **53:** 483–510.

Administration in renal impairment. Doses of cefotaxime should be reduced in severe renal impairment; after an initial loading dose of 1 g, halving the dose while maintaining the usual frequency of dosing has been suggested.

Preparations

BP 2008: Cefotaxime Injection;
USP 31: Cefotaxime for Injection; Cefotaxime Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefacolin; Terasep; Tizoxim†; ***Austral.:*** Claforan†; ***Austria:*** Claforan; Tirotax; ***Belg.:*** Claforan; ***Braz.:*** Cefacolin†; Ceforan; Claforan; Clafordil; Fotax†; Kefoxin†; Taxima; ***Canad.:*** Claforan; ***Chile:*** Grifotaxima†; ***Cz.:*** Cefantral†; Ceftax; Claforan†; Sefotak; Taxcef; ***Denm.:*** Claforan; ***Fin.:*** Claforan; ***Fr.:*** Claforan; ***Ger.:*** Claforan; ***Gr.:*** Ceramil; Ciltiren; Claforan; Flemycin; Letynol; Molelant; Naspor; Phacocef; Solubilax; Spirosine; Stoparen; ***Hong Kong:*** Cetan†; Claforan; Valoran; ***Hung.:*** Cefalekol; Cefotax†; Claforan; Tirotax; ***India:*** Biotax; Claforan; Lyforan; Novatax; Omnatax; Omnicef; Oritaxim; Talcef†; Zetaxim; ***Indon.:*** Baxima; Biocef; Cefor; Cefovell; Cefoxal; Clacef; Claforan; Clatax; Combicef; Efotax; Ethiclaf; Foxim; Goforan; Kalfoxim; Lancef; Lapixime; Procefa; Rycef; Siclaxim; Soclaf; Starclaf; Taxegram; Taximax; Tirdicef; ***Irl.:*** Claforan; ***Israel:*** Claforan; ***Ital.:*** Aximad; Batixim; Cefomit; Centiax; Claforan; Lirgosin; Refotax; Salocef; Spectrocef; Tafocex; Taxime; Xame; Zariviz; Zimanel; ***Malaysia:*** Cetaxima†; Claforan; Claraxim; ***Mex.:*** Benaxima; Biosint; Cefoclin†; Cefotex; Cefradil; Ceftomax; Claforan; Defradil; Fot-Amsa; Fotexina; Sefoxiram; Sepsilem; Taporin; Tebruxim; Tirotax; Viken; Xendin; ***Neth.:*** Claforan; Tirotax; ***Norw.:*** Claforan; ***NZ:*** Claforan; ***Philipp.:*** Cladex; Clafetam; Claforan; Clafoxim; Clavocef; Clinbaxef; Ofetaxim; Pantaxin; Tafoxam; Zefocent; ***Pol.:*** Biotaksym; Rantaksym; Tarcefoksym; Tirotax; ***Port.:*** Antadar; Cefobetox; Forticeporina†; Ralopar; Resibelacta; Totam; ***Rus.:*** Cefosin (Цефосин); Claforan (Клафоран); Intrataxime (Интратаксим); Oritaxim (Оритаксим); Talcef (Талцеф); Tarcefoksym (Тарцефоксим); ***S.Afr.:*** Claforan; Kefotax; Klafotaxim; Reftax; Totam†; ***Singapore:*** Clacef; Claforan; ***Spain:*** Claforan; ***Swed.:*** Claforan; ***Switz.:*** Claforan; ***Thai.:*** Biotaxime†; Cefomic; Ceforan; Cefotax; Ceftaran†; Ceftaxan; Claforan; Claraxim; Fonax; Fortax†; Fotax; Motaxim; Oritaxime†; Valoran†; ***Turk.:*** Betaksim; Claforan; Deforan; Sefagen; Sefoksim; Sefotak; Taxocef; ***UAE:*** Primocef; ***UK:*** Claforan; ***USA:*** Claforan; ***Venez.:*** Balticina†; Cefam; Cefatox; Cefotas†; Claforan; Novatax; Taxibon†; Tirotax.

Multi-ingredient: ***India:*** Sultax.

Cefotetan *(BAN, USAN, rINN)*

Céfotétan; Cefotetán; Cefotetanum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium). (7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl)carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid.

Цефотетан

$C_{17}H_{17}N_7O_8S_4$ = 575.6.
CAS — 69712-56-7.
ATC — J01DC05.
ATC Vet — QJ01DC05.

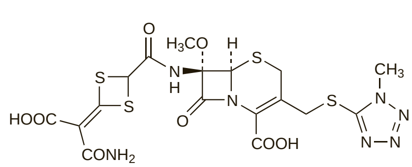

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Cefotetan). Store in airtight containers.

Cefotetan Disodium *(BANM, USAN, rINNM)*

Cefotetán disódico; Céfotétan Disodique; Cefotetanum Dinatricum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium). (7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl)carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt.

Динатрий Цефотетан

$C_{17}H_{15}N_7Na_2O_8S_4$ = 619.6.
CAS — 74356-00-6.
ATC — J01DC05.
ATC Vet — QJ01DC05.

Pharmacopoeias. In *US*.

USP 31 (Cefotetan Disodium). pH of a 10% solution in water is between 4.0 and 6.5. Store in airtight containers.

Incompatibility and stability. There may be incompatibility with aminoglycosides. Precipitation has been reported with promethazine hydrochloride.

References.

1. Das Gupta V, *et al*. Chemical stability of cefotetan disodium in 5% dextrose and 0.9% sodium chloride injections. *J Clin Pharm Ther* 1990; **15:** 109–14.
2. Erickson SH, Ulici D. Incompatibility of cefotetan disodium and promethazine hydrochloride. *Am J Health-Syst Pharm* 1995; **52:** 1347.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefotetan contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Cefotetan, especially at high doses, may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely elevated values; this should be borne in mind when measuring renal function.

Effects on the blood. Reviews[1,2] and a case report[3] of haemolytic anaemia associated with cefotetan.

1. Moes GS, MacPherson BR. Cefotetan-induced hemolytic anemia: a case report and review of the literature. *Arch Pathol Lab Med* 2000; **124:** 1344–6.
2. Viraraghavan R, *et al*. Cefotetan-induced haemolytic anaemia: a review of 85 cases. *Adverse Drug React Toxicol Rev* 2002; **21:** 101–7.
3. Robinson HE, *et al*. Cefotetan-induced life-threatening haemolysis. *Med J Aust* 2006; **184:** 251.

Sodium content. Each g of cefotetan disodium contains about 3.2 mmol of sodium.

Interactions

As for Cefamandole, p.221.

Antimicrobial Action

Cefotetan is a cephamycin antibiotic with a mode of action and spectrum of activity similar to those of cefoxitin (p.230). It is generally much more active *in vitro* than cefoxitin against the Gram-negative Enterobacteriaceae, but has similar activity against *Bacteroides fragilis* and may be less active against some other *Bacteroides* spp.

Pharmacokinetics

On intramuscular injection of cefotetan, peak plasma concentrations of about 70 micrograms/mL at 1 hour and 90 micrograms/mL at 3 hours have been reported after doses of 1 and 2 g, respectively. The plasma half-life of cefotetan is usually in the range of 3.0 to 4.6 hours and is prolonged in patients with renal impairment. About 88% of cefotetan may be bound to plasma proteins, depending on the plasma concentration.

Cefotetan is widely distributed in body tissues and fluids. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations are achieved in bile.

Cefotetan is excreted in the urine, primarily by glomerular filtration, as unchanged drug; 50 to 80% of a dose has been recovered in the urine in 24 hours and high concentrations are achieved. Small amounts of the tautomeric form of cefotetan have been detected in both plasma and urine.

Biliary excretion of cefotetan probably accounts for nonrenal clearance.

Some cefotetan is removed by dialysis.

◊ References.

1. Martin C, *et al*. Clinical pharmacokinetics of cefotetan. *Clin Pharmacokinet* 1994; **26:** 248–58.

Uses and Administration

Cefotetan is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p.230) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections.

It is given as the disodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefotetan; 1.08 g of cefotetan disodium is equivalent to about 1 g of cefotetan. The usual dose is 1 or 2 g every 12 hours. For the treatment of life-threatening infections, 3 g every 12 hours may be given intravenously. Doses of cefotetan should be reduced in patients with moderate to severe renal impairment (see below).

For infection prophylaxis during surgical procedures, an intravenous dose of 1 or 2 g is given 30 to 60 minutes before surgery or, in caesarean section, as soon as the umbilical cord is clamped.

Administration in renal impairment. Dosage of cefotetan should be reduced in patients with moderate to severe renal impairment. US licensed product information gives the following dosing guidelines based on creatinine clearance (CC):

- CC 10 to 30 mL/minute: the usual dose every 24 hours or one-half the usual dose every 12 hours
- CC less than 10 mL/minute: the usual dose every 48 hours or one-quarter the usual dose every 12 hours

In patients undergoing haemodialysis, one-quarter the usual dose may be given every 24 hours on days between dialysis and one-half the usual dose on the day of dialysis.

Preparations

USP 31: Cefotetan for Injection; Cefotetan Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Apatef†; ***Belg.:*** Apacef†; ***Canad.:*** Cefotan†; ***Fr.:*** Apacef†; ***Ital.:*** Apatef†; ***Jpn:*** Yamatetan†; ***NZ:*** Apatef†; ***Port.:*** Apatef†; ***USA:*** Cefotan.

Cefotiam Hydrochloride *(BANM, USAN, rINNM)*

Abbott-48999; Céfotiam, Chlorhydrate de; Cefotiami Hydrochloridum; CGP-14221E (cefotiam or cefotiam hydrochloride); Hidrocloruro de cefotiam; SCE-963. 7-[2-(2-Amino-1,3-thiazol-4-yl)acetamido]-3-[1-(2-dimethylaminoethyl)-1*H*-tetrazol-5-ylthiomethyl]-3-cephem-4-carboxylic acid dihydrochloride.

Цефотиама Гидрохлорид

$C_{18}H_{23}N_9O_4S_3,2HCl = 598.6.$

CAS — 61622-34-2 (cefotiam); 66309-69-1 (cefotiam hydrochloride).

ATC — J01DC07.

ATC Vet — QJ01DC07.

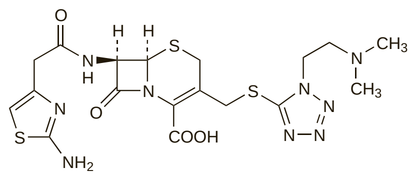

(cefotiam)

Pharmacopoeias. In *Jpn* and *US. Jpn* also includes cefotiam hexetil hydrochloride.

USP 31 (Cefotiam Hydrochloride). Store in airtight containers.

Profile

Cefotiam is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p.220). It is given intravenously or intramuscularly as the hydrochloride but doses are expressed in terms of the base; 1.14 g of cefotiam hydrochloride is equivalent to about 1 g of cefotiam. The usual dose is the equivalent of up to 6 g of cefotiam daily in divided doses, according to the severity of the infection.

Cefotiam hexetil hydrochloride, a prodrug of cefotiam, is given orally in doses equivalent to 200 to 400 mg of cefotiam twice daily.

◊ References.

1. Brogard JM, *et al.* Clinical pharmacokinetics of cefotiam. *Clin Pharmacokinet* 1989; **17:** 163–74.

Preparations

USP 31: Cefotiam for Injection.

Proprietary Preparations (details are given in Part 3)

Austria: Spizef; ***Fr.:*** Taketiam; Texodil; ***Ger.:*** Spizef; ***Indon.:*** Aspil; Cefradol; Ceradolan; Ethidol; Fodiclo; Fotaram; ***Jpn:*** Pansporin; ***Philipp.:*** Ceradolan; ***Singapore:*** Ceradolan; ***Thai.:*** Ceradolan.

Cefovecin Sodium *(USAN, rINNM)*

Cefovecina sódica; Céfovécine Sodique; Natrii Cefovecinum; UK-287074-02. Sodium (6*R*,7*R*)-7-{[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino}-8-oxo-3-[(2*S*)-tetrahydrofuran-2-yl]-5-thia-1-azabicyclo[4.4.0]oct-2-ene-2-carboxylate.

Натрий Цефовецин

$C_{17}H_{18}N_5NaO_6S_2 = 475.5.$

CAS — 234096-34-5 (cefovecin); 141195-77-9 (cefovecin sodium).

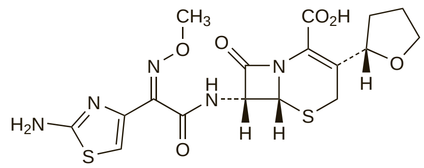

(cefovecin)

Profile

Cefovecin sodium is a third-generation cephalosporin antibacterial used in veterinary medicine.

Cefoxitin Sodium *(BANM, USAN, rINNM)*

Cefoksitino natrio druska; Cefoksytyna sodowa; Cefoxitin sodná sůl; Cefoxitina sódica; Céfoxitine sodique; Cefoxitinnatrium; Cefoxitin-nátrium; Cefoxitinum natricum; Kefoksitiininatrium; L-620388; MK-306; Natrii Cefoxitinum. Sodium 3-carbamoyloxymethyl-7-methoxy-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

Натрий Цефокситин

$C_{16}H_{16}N_3NaO_7S_2 = 449.4.$

CAS — 35607-66-0 (cefoxitin); 33564-30-6 (cefoxitin sodium).

ATC — J01DC01.

ATC Vet — QJ01DC01.

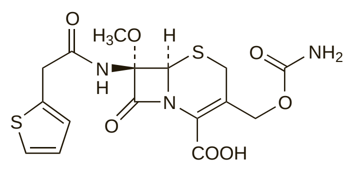

(cefoxitin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cefoxitin Sodium). A white or almost white, very hygroscopic, powder. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH between 4.2 and 7.0. Store in airtight containers.

USP 31 (Cefoxitin Sodium). White to off-white, somewhat hygroscopic, granules or powder, having a slight characteristic odour. Very soluble in water; slightly soluble in acetone; insoluble in chloroform and in ether; sparingly soluble in dimethylformamide; soluble in methyl alcohol. pH of a 10% solution in water is between 4.2 and 7.0. Store in airtight containers at a temperature not exceeding 8°.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefoxitin may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely high values; this should be borne in mind when measuring renal function.

Breast feeding. Cefoxitin is distributed into breast milk but is detectable only in low concentrations. In a study[1] in which cefoxitin was given prophylactically in doses of 2 to 4 g to 18 women undergoing caesarean section, only one sample of breast milk contained measurable concentrations of cefoxitin, 19 hours after the last dose. No adverse effects have been observed in breast-fed infants whose mothers were receiving cefoxitin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Roex AJM, *et al.* Secretion of cefoxitin in breast milk following short-term prophylactic administration in caesarean section. *Eur J Obstet Gynecol Reprod Biol* 1987; **25:** 299–302.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the gastrointestinal tract. Marked changes in anaerobic, facultative, and aerobic faecal flora have been noted with cefoxitin.[1]

1. Mulligan ME, *et al.* Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. *Antimicrob Agents Chemother* 1984; **26:** 343–6.

Sodium content. Each g of cefoxitin sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefoxitin.

Antimicrobial Action

Cefoxitin is a cephamycin antibacterial which, like the other beta lactams, is bactericidal and is considered to act through the inhibition of bacterial cell wall synthesis.

It has a similar spectrum of activity to cefamandole (p.221) but is more active against anaerobic bacteria, especially *Bacteroides fragilis.*

Cefoxitin can induce the production of beta-lactamases by some bacteria, and use of cefoxitin with other beta lactams have been shown to be antagonistic *in vitro.*

Cefoxitin itself is considered to be resistant to a wide range of beta-lactamases, including those produced by *Bacteroides* spp. However, acquired resistance to cefoxitin has been reported in *B. fragilis* (see Anaerobic Bacterial Infections, p.163) and has been attributed to beta-lactamase as well as to alterations in penicillin-binding proteins or to outer membrane proteins; there may be cross-resistance to other antibacterials.

◊ References.

1. Cuchural GJ, *et al.* Transfer of β-lactamase-associated cefoxitin resistance in Bacteroides fragilis. *Antimicrob Agents Chemother* 1986; **29:** 918–20.
2. Piddock LJV, Wise R. Cefoxitin resistance in Bacteroides species: evidence indicating two mechanisms causing decreased susceptibility. *J Antimicrob Chemother* 1987; **19:** 161–70.
3. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
4. Wexler HM, Halebian S. Alterations to the penicillin-binding proteins in the Bacteroides fragilis group: a mechanism for non-β-lactamase mediated cefoxitin resistance. *J Antimicrob Chemother* 1990; **26:** 7–20.
5. Cherubin CE, Appleman MD. Susceptibility of cefoxitin-resistant isolates of bacteroides to other agents including β-lactamase inhibitor/β-lactam combinations. *J Antimicrob Chemother* 1993; **32:** 168–70.

Pharmacokinetics

Cefoxitin is not absorbed from the gastrointestinal tract; it is given parenterally as the sodium salt. After 1 g by intramuscular injection a peak plasma concentration of up to 30 micrograms/mL at 20 to 30 minutes has been reported whereas concentrations of 125, 72, and 25 micrograms/mL have been achieved after intravenous doses of 1 g over 3, 30, and 120 minutes respectively. Cefoxitin is about 70% bound to plasma proteins. It has a plasma half-life of 45 to 60 minutes which is prolonged in renal impairment. Cefoxitin is widely distributed in the body but there is normally little penetration into the CSF, even when the meninges are inflamed. It crosses the placenta and has been detected in breast milk. Relatively high concentrations are achieved in bile.

The majority of a dose is excreted unchanged by the kidneys, up to about 2% being metabolised to descarbamylcefoxitin which is virtually inactive. Cefoxitin is excreted in the urine by glomerular filtration and tubular secretion and about 85% of a dose is recovered within 6 hours; probenecid slows this excretion. After an intramuscular dose of 1 g, peak concentrations in the urine are usually greater than 3 mg/mL.

Cefoxitin is removed to some extent by haemodialysis.

Uses and Administration

Cefoxitin is a cephamycin antibacterial that differs structurally from the cephalosporins by the addition of a 7-α-methoxy group to the 7-β-aminocephalosporanic acid nucleus.

It is generally classified with the second-generation cephalosporins and can be used similarly to cefamandole (p.221) for the treatment of susceptible infections. However, because of its activity against *Bacteroides fragilis* and other anaerobic bacteria, it is used principally in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. Indications include endometritis (prophylaxis at caesarean section), pelvic inflammatory disease, and surgical infection (prophylaxis). It may also be used in the treatment of gonorrhoea and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefoxitin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion.

Doses are expressed in terms of the equivalent amount of cefoxitin; 1.05 g of cefoxitin sodium is equivalent to about 1 g of cefoxitin. The usual adult dose is 1 or 2 g every 8 hours although it may be given more frequently (every 4 or 6 hours). In severe infections up to 12 g daily has been recommended. Children and neonates may be given 20 to 40 mg/kg, every 12 hours for neonates up to 1 week old, every 8 hours for those aged 1 to 4 weeks, and every 6 to 8 hours for older infants and children; in severe infections, up to 200 mg/kg daily may be given, to a maximum of 12 g daily.

For the treatment of uncomplicated urinary-tract infections, cefoxitin 1 g twice daily has been given intramuscularly.

For details of reduced doses of cefoxitin in patients with renal impairment, see below.

For the treatment of uncomplicated gonorrhoea, a single dose of 2 g intramuscularly has been given with probenecid 1 g orally.

For surgical infection prophylaxis, the usual adult dose is cefoxitin 2 g intramuscularly or intravenously 30 to 60 minutes before the procedure and then every 6 hours, not usually for more than 24 hours. Infants and children undergoing surgical procedures can be given doses of 30 to 40 mg/kg, at the same time intervals as adults; neonates may be given 30 to 40 mg/kg, but at intervals of 8 to 12 hours.

At caesarean section a single 2-g dose may be given intravenously to the mother as soon as the umbilical cord is clamped. If necessary, a 3-dose regimen, with further 2-g doses 4 and 8 hours after the initial dose, may be used.

◊ Reviews.

1. DiPiro JT, May JR. Use of cephalosporins with enhanced antianaerobic activity for treatment and prevention of anaerobic and mixed infections. *Clin Pharm* 1988; **7:** 285–302.
2. Goodwin CS. Cefoxitin 20 years on: is it still useful? *Rev Med Microbiol* 1995; **6:** 146–53.

Administration in renal impairment. In renal impairment, dosage of cefoxitin should be reduced according to creatinine clearance (CC). After an initial loading dose of 1 to 2 g, maintenance doses are:

- CC 30 to 50 mL/minute: 1 to 2 g every 8 to 12 hours
- CC 10 to 29 mL/minute: 1 to 2 g every 12 to 24 hours
- CC 5 to 9 mL/minute: 0.5 to 1 g every 12 to 24 hours
- CC below 5 mL/minute: 0.5 to 1 g every 24 to 48 hours

In patients undergoing haemodialysis, the loading dose should be repeated after each dialysis session.

Preparations

BP 2008: Cefoxitin Injection;
USP 31: Cefoxitin for Injection; Cefoxitin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Mefoxin†; Pluricefo†; ***Austral.:*** Mefoxin; ***Austria:*** Mefoxitin; ***Belg.:*** Mefoxin†; ***Braz.:*** Cefoxan; Cefoxin; Cefton; Foxtil†; Gamacef; Mefoxin; Propoten†; ***Canad.:*** Mefoxin†; ***Cz.:*** Mefoxin†; ***Fin.:*** Mefoxin†; ***Fr.:*** Mefoxin†; ***Ger.:*** Mefoxitin; ***Gr.:*** Destrepen†; Mefoxil; Metaptyl; ***Hong Kong:*** Mefoxin; ***Ital.:*** Cefociclin; Mefoxin; Tifox†; ***Neth.:*** Mefoxin†; ***Norw.:*** Mefoxitin†; ***NZ:*** Mefoxin; ***Philipp.:*** Monowel; Panafox; Zepax; ***Port.:*** Atralxitina; Mefoxin†; Niacef; ***S.Afr.:*** Mefoxin; ***Spain:*** Mefoxitin†; ***Swed.:*** Mefoxitin†; ***Switz.:*** Mefoxitin†; ***Thai.:*** Cefoxin; Cefxitin; Maxotin; Zefin; ***UK:*** Mefoxin†; ***USA:*** Mefoxin; ***Venez.:*** Mefoxitin†.

Cefozopran Hydrochloride *(rINNM)*

Céfozopran, Chlorhydrate de; Cefozoprani Hydrochloridum; Hidrocloruro de cefozoprán. (−)-1-{[(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl}-1*H*-imidazo[1,2-*b*]pyridazin-4-ium hydroxide inner salt, 7^2-(*Z*)-(*O*-methyloxime), hydrochloride.

Цефозоприана Гидрохлорид

$C_{19}H_{17}N_9O_5S_2,HCl = 552.0.$

CAS — 113359-04-9 (cefozopran); 113981-44-5 (cefozopran hydrochloride).

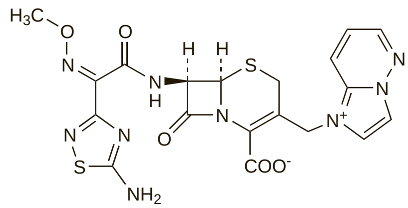

(cefozopran)

Pharmacopoeias. In *Jpn.*

Profile

Cefozopran is a cephalosporin antibacterial used parenterally as the hydrochloride.

◊ References.

1. Iwahi T, *et al.* In vitro and in vivo activities of SCE-2787, a new parenteral cephalosporin with a broad antibacterial spectrum. *Antimicrob Agents Chemother* 1992; **36:** 1358–66.
2. Paulfeuerborn W, *et al.* Comparative pharmacokinetics and serum bactericidal activities of SCE-2787 and ceftazidime. *Antimicrob Agents Chemother* 1993; **37:** 1835–41.
3. Fujii R, *et al.* Pharmacokinetics and clinical effects of cefozopran in pediatric patients. *Jpn J Antibiot* 1996; **49:** 17–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Firstcin.

Cefpiramide *(USAN, rINN)*

Cefpiramida; Cefpiramidum; SM-1652; Wy-44635. (7*R*)-7-[(*R*)-2-(4-Hydroxy-6-methylnicotinamido)-2-(4-hydroxyphenyl)acetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефпирамид

$C_{25}H_{24}N_8O_7S_2 = 612.6.$

CAS — 70797-11-4.

ATC — J01DD11.

ATC Vet — QJ01DD11.

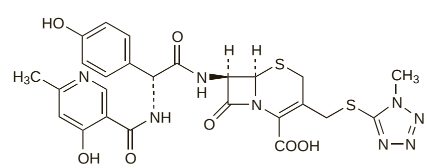

Pharmacopoeias. In *US.*

USP 31 (Cefpiramide). Store in airtight containers. pH of a 0.5% suspension in water is between 3.0 and 5.0.

Cefpiramide Sodium *(USAN, rINNM)*

Cefpiramida sódica; Cefpiramide Sodique; Natrii Cefpiramidum.

Натрий Цефпирамид

$C_{25}H_{23}N_8NaO_7S_2 = 634.6.$

CAS — 74849-93-7.

ATC — J01DD11.

ATC Vet — QJ01DD11.

Pharmacopoeias. In *Jpn.*

Profile

Cefpiramide is a third-generation cephalosporin antibacterial related to cefoperazone (p.227) and with similar activity against *Pseudomonas aeruginosa*, but possibly less active against Enterobacteriaceae. Cefpiramide is also active against staphylococci and streptococci and marginal activity against enterococci *in vitro* has been reported. Like cefamandole (p.220), cefpiramide contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia, alcohol intolerance, and potentiation of anticoagulants.

Cefpiramide is given by intravenous injection or infusion as the sodium salt in the treatment of susceptible infections but doses are expressed in terms of cefpiramide; 1.04 g of cefpiramide sodium is equivalent to about 1 g of cefpiramide. The usual dose is 1 to 2 g daily in 2 divided doses.

◊ References.

1. Wang H, *et al.* In-vitro antibacterial activities of cefpiramide and other broad-spectrum antibiotics against 440 clinical isolates in China. *J Infect Chemother* 2000; **6:** 81–5.

Sodium content. Each g of cefpiramide sodium contains about 1.6 mmol of sodium.

Preparations

USP 31: Cefpiramide for Injection.

Proprietary Preparations (details are given in Part 3)
Jpn: Sepatren.

Cefpirome Sulfate *(USAN, rINNM)*

Cefpirome, sulfate de; Cefpirome Sulphate *(BANM)*; Cefpiromi sulfas; Cefpiromsulfat; HR-810 (cefpirome or cefpirome sulfate); Kefpiromisulfaatti; Sulfato de cefpiroma. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-pyrindiniomethyl)-3-cephem-4-carboxylate sulphate.

Цефпирома Сульфат

$C_{22}H_{22}N_6O_5S_2,H_2SO_4 = 612.7.$

CAS — 84957-29-9 (cefpirome); 98753-19-6 (cefpirome sulfate).

ATC — J01DE02.

ATC Vet — QJ01DE02.

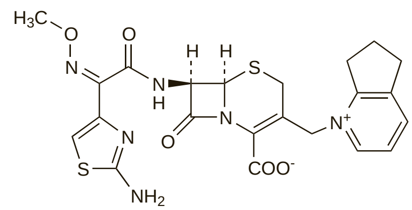

(cefpirome)

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

As for Cefalotin, p.219.

Cefpirome is reported to interfere with the Jaffé method of measuring creatinine concentrations to determine renal function.

◊ References.

1. Rubinstein E, *et al.* A review of the adverse events profile of cefpirome. *Drug Safety* 1993; **9:** 340–5.

Interactions

Probenecid reduces the renal clearance of cefpirome.

Antimicrobial Action

Cefpirome is a fourth-generation cephalosporin that is stable to a wide range of beta-lactamases. It has a spectrum of activity similar to that of the third-generation cephalosporin cefotaxime (p.228), but it appears to be more active *in vitro* against staphylococci, some enterococci, some Enterobacteriaceae, and *Pseudomonas aeruginosa*. Cefpirome may be less active than ceftazidime (p.234) against *Ps. aeruginosa*.

Pharmacokinetics

Cefpirome is given by injection as the sulfate. Mean peak serum concentrations of 80 to 90 micrograms/mL are attained after a single intravenous 1-g dose. The elimination half-life is about 2 hours and is prolonged in patients with renal impairment. Cefpirome is less than 10% bound to plasma proteins.

Cefpirome is widely distributed into body tissues and fluids and appears in breast milk. It is mainly excreted by the kidneys and 80 to 90% of a dose is recovered unchanged in the urine. Significant amounts are removed by haemodialysis.

Uses and Administration

Cefpirome is a fourth-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms. They include infections of the urinary tract, respiratory tract, and skin, and also septicaemia and infections in immunocompromised patients. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefpirome is given by intravenous injection over 3 to 5 minutes or infusion over 20 to 30 minutes as the sulfate, but doses are expressed in terms of the base; 1.19 g of cefpirome sulfate is equivalent to about 1 g of cefpirome. The usual dose is the equivalent of 1 or 2 g of cefpirome every 12 hours. For details of reduced doses to be used in renal impairment, see below.

◊ References.

1. Brown EM, *et al.* eds. Cefpirome: a novel extended spectrum cephalosporin. *J Antimicrob Chemother* 1992; **29** (suppl A): 1–104.
2. Wiseman LR, Lamb HM. Cefpirome: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. *Drugs* 1997; **54:** 117–40.

Administration in renal impairment. Dosage of cefpirome should be modified in renal impairment; after a loading dose of 1 or 2 g depending on the severity of infection, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of infection:

- CC 20 to 50 mL/minute: 0.5 or 1 g twice daily
- CC 5 to 20 mL/minute: 0.5 or 1 g once daily
- CC 5 mL/minute or less (in haemodialysis patients): 0.5 or 1 g once daily plus a half-dose after each dialysis session.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cefrom; ***Austria:*** Cedixen; Cefrom; ***Belg.:*** Cefrom†; ***Cz.:*** Cefrom†; ***Fr.:*** Cefrom; ***Gr.:*** Cefrom†; ***India:*** Bacirom†; Ceforth†; Cefrom; Tafrom; ***Indon.:*** Cefir; Cefnos; Cefrin; Cefrom; Lanpirome; Nufirom; Romicef; Sopirom; Xenoprom; ***Irl.:*** Cefrom†; ***Mex.:*** Cefrom; ***Neth.:*** Cefrom; ***NZ:*** Cefrom†; ***Port.:*** Cefrom†; Cipiram; Farmocefe; ***S.Afr.:*** Cefrom; ***Thai.:*** Cefrom; ***UK:*** Cefrom†.

Cefpodoxime Proxetil

(BANM, USAN, rINNM)

Cefpodoxima proxetilo; Cefpodoxime proxétil; Cefpodoxime, Proxétil de; Cefpodoximi Proxetilum; Cefpodoximum proxetili; CS-807; R-3763 (cefpodoxime); U-76252; U-76253 (cefpodoxime). The 1-[(isopropoxycarbonyl)oxy]ethyl ester of (*Z*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid.

Цефподоксима Проксетил

$C_{21}H_{27}N_5O_9S_2$ = 557.6.

CAS — 80210-62-4 (cefpodoxime); 87239-81-4 (cefpodoxime proxetil).

ATC — J01DD13.

ATC Vet — QJ01DD13.

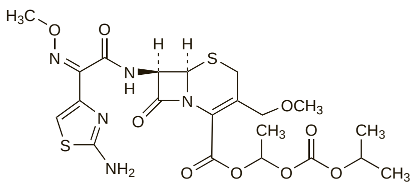

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Cefpodoxime Proxetil). A white to light brownish-white powder, odourless or having a faint odour. Very slightly soluble in water; freely soluble in dehydrated alcohol; soluble in acetonitrile and in methyl alcohol; slightly soluble in ether. Store in airtight containers at a temperature not exceeding 25°.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

The most frequently reported adverse effects of cefpodoxime are gastrointestinal disturbances, especially diarrhoea.

Interactions

Absorption of cefpodoxime is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefpodoxime.

Antimicrobial Action

As for Cefixime, p.224, but cefpodoxime has greater activity against *Staphylococcus aureus*.

◊ References.

1. Valentini S, *et al.* In-vitro evaluation of cefpodoxime. *J Antimicrob Chemother* 1994; **33:** 495–508.

Pharmacokinetics

Cefpodoxime proxetil is de-esterified in the intestinal epithelium after oral doses, to release active cefpodoxime in the bloodstream. Bioavailability is about 50% in fasting subjects and may be increased in the presence of food. Absorption is decreased in conditions of low gastric acidity. Peak plasma concentrations of about 1.5, 2.5, and 4.0 micrograms/mL have been achieved 2 to 3 hours after oral doses of 100, 200, and 400 mg cefpodoxime respectively. About 20 to 30% of cefpodoxime is bound to plasma proteins. The plasma half-life is about 2 to 3 hours and is prolonged in patients with renal impairment.

Cefpodoxime reaches therapeutic concentrations in the respiratory and genito-urinary tracts and bile. It has been detected in low concentrations in breast milk.

Cefpodoxime is excreted unchanged in the urine. Some is removed by dialysis.

Uses and Administration

Cefpodoxime is a third-generation cephalosporin antibiotic used similarly to cefixime (p.225) in the treatment of susceptible infections. It is given orally as the proxetil ester, which is hydrolysed on absorption to cefpodoxime. Doses are expressed in terms of the equivalent amount of cefpodoxime; 130 mg of cefpodoxime proxetil is equivalent to about 100 mg of cefpodoxime. Absorption may be enhanced if cefpodoxime proxetil is given with food. The usual dose for adults is 100 to 200 mg every 12 hours for respiratory-tract and urinary-tract infections. A dose of 200 or 400 mg every 12 hours may be used for skin and soft-tissue infections. In the USA children aged 2 months and older may be given doses of 5 mg/kg every 12 hours, up to a maximum of 200 mg daily for pharyngitis or tonsillitis or 400 mg daily for acute otitis media or maxillary sinusitis. In the UK cefpodoxime may be given to children and infants aged 15 days and older, in a dose of 4 mg/kg every 12 hours, up to a maximum of 200 mg daily, for infections of the respiratory tract, urinary tract, and skin and soft tissues.

The interval between doses of cefpodoxime may need to be extended in patients with renal impairment (see below).

For uncomplicated gonorrhoea, a single dose of 200 mg may be given.

◊ References.

1. Moore EP, *et al.*, eds. Cefpodoxime proxetil: a third-generation oral cephalosporin. *J Antimicrob Chemother* 1990; **26** (suppl E): 1–101.
2. Adam D, *et al.*, eds. Cefpodoxime proxetil: a new third generation oral cephalosporin. *Drugs* 1991; **42** (suppl 3): 1–66.
3. Frampton JE, *et al.* Cefpodoxime proxetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; **44:** 889–917.
4. Chocas EC, *et al.* Cefpodoxime proxetil: a new, broad-spectrum, oral cephalosporin. *Ann Pharmacother* 1993; **27:** 1369–77.
5. Fulton B, Perry CM. Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. *Paediatr Drugs* 2001; **3:** 137–58.

Administration in renal impairment. The interval between doses of cefpodoxime should be extended in patients with renal impairment to every 24 hours in those with creatinine clearance of 10 to 39 mL/minute, and to every 48 hours when the creatinine clearance is less than 10 mL/minute. In patients on haemodialysis the dose should be given after each dialysis session.

Preparations

USP 31: Cefpodoxime Proxetil for Oral Suspension; Cefpodoxime Proxetil Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Biocef; Celiol; Cintalux; Otreon; ***Braz.:*** Orelox; ***Chile:*** Cefirax; ***Cz.:*** Orelox†; ***Fr.:*** Orelox; ***Ger.:*** Orelox; Podomexef; ***Hong Kong:*** Banan; ***India:*** Cefoprox; Cepodem; Kefpod; Monocef-O; Monotax-O; Tambac; ***Indon.:*** Banan; ***Irl.:*** Cefodox; ***Ital.:*** Cefodox; Orelox; Otreon; ***Jpn:*** Banan; ***Mex.:*** Orelox; ***Neth.:*** Orelox; Otreon; ***Philipp.:*** Banan; Zudem; ***Port.:*** Orelox; ***S.Afr.:*** Cepodem; Orelox; ***Spain:*** Gania; Instana; Kelbium; Otreon; ***Swed.:*** Orelox; ***Switz.:*** Orelox; Podomexef; ***Thai.:*** Banan; ***UK:*** Orelox; ***USA:*** Vantin.

Cefprozil *(BAN, USAN, rINN)*

BMY-28100-03-800; BMY-28100 (*cis*-isomer); BMY-28167 (*trans*-isomer); Cefprozilo; Cefprozilum; Kefprotsiili; Sefprozil. (6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-8-oxo-3-(1-propenyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate; 7-(D-4-Hydroxyphenylglycylamino)-3-[(*E*)prop-1-enyl]cephem-4-carboxylic acid monohydrate.

Цефпрозил

$C_{18}H_{19}N_3O_5S,H_2O$ = 407.4.

CAS — 92665-29-7 (anhydrous cefprozil); 121123-17-9 (cefprozil monohydrate).

ATC — J01DC10.

ATC Vet — QJ01DC10.

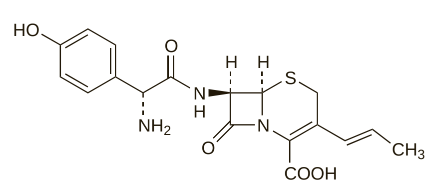

Pharmacopoeias. In *US.*

USP 31 (Cefprozil). pH of a 0.5% solution in water is between 3.5 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalexin, p.218.

Breast feeding. A study[1] in 9 healthy women found that concentrations of cefprozil in breast milk corresponded to no more than 0.3% of a dose and concluded that cefprozil could be given safely during breast feeding. The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of cefprozil in breast-feeding mothers, and that it may be considered to be usually compatible with breast feeding.

1. Shyu WC, *et al.* Excretion of cefprozil into human breast milk. *Antimicrob Agents Chemother* 1992; **36:** 938–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Serum sickness-like reactions were reported in 4 patients, 3 of them children, given cefprozil.[1] Such reactions have been associated with cefaclor (p.217), but whether they represent a class-related hypersensitivity reaction is not clear.

1. Lowery N, *et al.* Serum sickness-like reactions associated with cefprozil therapy. *J Pediatr* 1994; **125:** 325–8.

Interactions

As for Cefalexin, p.218.

Antimicrobial Action

Cefprozil is bactericidal and has a similar but wider range of antimicrobial activity than cefaclor (p.217).

Pharmacokinetics

Cefprozil is well absorbed from the gastrointestinal tract with a reported bioavailability of 90 to 95%. Oral doses of 0.25, 0.5, and 1 g produce peak plasma concentrations of about 6, 10, and 18 micrograms/mL respectively at 1 to 2 hours. The presence of food is reported to have little or no effect on the absorption of cefprozil. A plasma half-life of 1 to 1.4 hours has been reported; it is increased in patients with renal impairment, up to about 6 hours in those with end-stage renal failure. About 35 to 45% of cefprozil is bound to plasma proteins.

Cefprozil is widely distributed in the body tissues. Concentrations of cefprozil in tonsillar and adenoidal tissue are reported to be about 40 to 50% of those in plasma, and less than 0.3% of a 1-g dose has been recovered in breast milk in 24 hours. About 60% of a dose is excreted unchanged in the urine in the first 8 hours by glomerular filtration and tubular secretion. High concentrations of cefprozil are achieved in the urine; concentrations of 700, 1000, and 2900 micrograms/mL have been reported within 4 hours of doses of 0.25, 0.5, and 1 g respectively. Some cefprozil is removed by haemodialysis.

Uses and Administration

Cefprozil is a cephalosporin antibacterial consisting of *cis-* and *trans-* isomers in a ratio of about 90:10. It is used similarly to cefaclor (p.217) in the treatment of susceptible infections, including upper and lower respiratory-tract infections and skin and soft-tissue infections, and should probably be classified as a second-generation cephalosporin.

Cefprozil is given orally as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefprozil; 523 mg of cefprozil monohydrate is equivalent to about 500 mg of anhydrous cefprozil. The usual adult dose is 500 mg daily (as a single dose or in two divided doses), increased to 500 mg twice daily if necessary. Children may be given up to 20 mg/kg once or twice daily (to a maximum of 500 mg once daily, or twice daily if necessary for otitis media).

For details of reduced dosage of cefprozil in patients with renal impairment, see below.

◊ Reviews.

1. Wiseman LR, Benfield P. Cefprozil: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic potential. *Drugs* 1993; **45:** 295–317.
2. Barriere SL. Review of in vitro activity, pharmacokinetic characteristics, safety, and clinical efficacy of cefprozil, a new oral cephalosporin. *Ann Pharmacother* 1993; **27:** 1082–9.

Administration in renal impairment. Doses of cefprozil should be reduced in patients with renal impairment; half the standard dose should be given to patients with a creatinine clearance of less than 30 mL/minute.

Preparations

USP 31: Cefprozil for Oral Suspension; Cefprozil Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ceprof; ***Austria:*** Procef†; ***Braz.:*** Cefzil; ***Canad.:*** Cefzil; ***Chile:*** Procef†; ***Cz.:*** Cefzil; ***Gr.:*** Cefgram; Cefpro; Gramium; Procef; Zamalin; ***Hong Kong:*** Procef; ***Hung.:*** Cefzil; ***India:*** Refzil-O; ***Indon.:*** Cefzil; Lizor; ***Ital.:*** Cronocef; Procef; Rozicel; ***Malaysia:*** Procef†; ***Mex.:*** Procef; ***Philipp.:*** Procef; ***Pol.:*** Cefzil; ***Port.:*** Procef; Radacefe; ***S.Afr.:*** Prozef; ***Singapore:*** Procef†; ***Spain:*** Arzimol; Brisoral; Precef; ***Switz.:*** Procef; ***Thai.:*** Procef; ***Turk.:*** Serozil; ***UK:*** Cefzil†; ***USA:*** Cefzil; ***Venez.:*** Procef.

Cefquinome Sulfate *(USAN, rINNM)*

Cefquinome, Sulfate de; Cefquinome Sulphate *(BANM)*; Cefquinomi Sulfas; HR-111V; Sulfato de cefquinoma. {6*R*-[6α,7β(*Z*)]}-1-[(7-{[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-5,6,7,8,-tetrahydroquinolinium sulfate (1:1).

Цефхинома Сульфат

$C_{23}H_{24}N_6O_5S_2,H_2SO_4 = 626.7.$

CAS — 84957-30-2 (cefquinome); 118443-89-3 (cefquinome sulfate); 123766-80-3 (cefquinome sulfate).

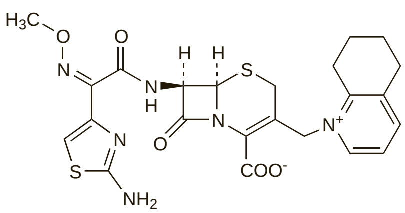

(cefquinome)

Profile

Cefquinome is a fourth-generation cephalosporin antibacterial used as the sulfate in veterinary medicine.

Cefradine *(BAN, rINN)*

Cefradin; Cefradina; Cefradinas; Céfradine; Cefradinum; Cefradyna; Cephradine *(USAN)*; Kefradiini; Sefradin; SKF-D-39304; SQ-11436; SQ-22022 (cefradine dihydrate). (7*R*)-7-(α-D-Cyclohexa-1,4-dienylglycylamino)-3-methyl-3-cephem-4-carboxylic acid.

Цефрадин

$C_{16}H_{19}N_3O_4S = 349.4.$

CAS — 38821-53-3 (anhydrous cefradine); 31828-50-9 (non-stoichiometric cefradine hydrate); 58456-86-3 (cefradine dihydrate).

ATC — J01DB09.

ATC Vet — QJ01DB09.

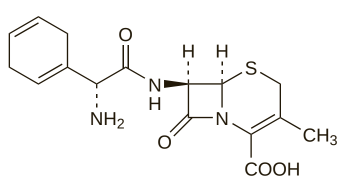

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US* (which allows the anhydrous form, the monohydrate, or the dihydrate).

Ph. Eur. 6.2 (Cefradine). A white or slightly yellow, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol and in *n*-hexane. A 1% solution in water has a pH of 3.5 to 6.0. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Cephradine). A white to off-white crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Incompatibility and stability. Commercially available injections contain sodium carbonate or arginine as neutralisers. Injections containing sodium carbonate are incompatible with solutions such as compound sodium lactate injection that contain calcium salts.

References.

1. Wang Y-C J, Monkhouse DC. Solution stability of cephradine neutralized with arginine or sodium bicarbonate. *Am J Hosp Pharm* 1983; **40:** 432.
2. Mehta AC, *et al.* Chemical stability of cephradine injection solutions. *Intensive Therapy Clin Monit* 1988; **9**: 195–6.

Adverse Effects and Precautions

As for Cefalexin, p.218. Intramuscular injections of cefradine can be painful and thrombophlebitis has occurred on intravenous injection.

Porphyria. Cefradine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

As for Cefalexin, p.218.

Antimicrobial Action

As for Cefalexin, p.218.

Pharmacokinetics

Cefradine is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Doses of 0.25, 0.5, and 1 g given orally have produced peak plasma concentrations of about 9, 17, and 24 micrograms/mL respectively at 1 hour and are similar to those achieved with cefalexin. Absorption is delayed by the presence of food although the total amount absorbed is not appreciably altered. Following intramuscular injection peak plasma concentrations of about 6 and 14 micrograms/mL have been obtained within 1 to 2 hours of doses of 0.5 and 1 g respectively.

Only about 8 to 12% is reported to be bound to plasma proteins. A plasma half-life of about 1 hour has been reported; this is prolonged in patients with renal impairment. Cefradine is widely distributed to body tissues and fluids, but does not enter the CSF in significant quantities. Therapeutic concentrations may be found in the bile. It crosses the placenta into the fetal circulation and is distributed in small amounts into breast milk.

Cefradine is excreted unchanged in the urine by glomerular filtration and tubular secretion, over 90% of an oral dose or 60 to 80% of an intramuscular dose being recovered within 6 hours. Peak urinary concentrations of about 3 mg/mL have been achieved after a 500-mg oral dose. Probenecid delays excretion.

Cefradine is removed by haemodialysis and peritoneal dialysis.

◊ References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
2. Schwinghammer TL, *et al.* Pharmacokinetics of cephradine administered intravenously and orally to young and elderly subjects. *J Clin Pharmacol* 1990; **30:** 893–9.

Uses and Administration

Cefradine is a first-generation cephalosporin antibacterial given orally similarly to cefalexin (p.219) and by the parenteral route similarly to cefazolin (p.222) in the treatment of susceptible infections and in the prophylaxis of infections during surgical procedures.

Cefradine is given orally in doses of 1 to 2 g daily in 2 to 4 divided doses to adults; up to 4 g daily may be given by this route. In severe infections it should be given parenterally, by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion, in doses of 2 to 4 g daily in 4 divided doses; up to 8 g daily may be given parenterally.

In children, the usual daily oral dose is 25 to 50 mg/kg in 2 to 4 divided doses, although 75 to 100 mg/kg daily may be given for otitis media. By injection, 50 to 100 mg/kg daily may be given in 4 divided doses, increasing to 300 mg/kg daily in severe infections.

For surgical infection prophylaxis, 1 to 2 g may be given pre-operatively by intramuscular or intravenous injection; subsequent parenteral or oral doses are given as appropriate.

For details of reduced doses of cefradine in patients with severe renal impairment, see below.

Administration in renal impairment. Doses of cefradine should be reduced in patients with severe renal impairment. The following oral and parenteral doses are recommended in UK licensed product information according to creatinine clearance (CC):

- CC more than 20 mL/minute: 500 mg every 6 hours
- CC 5 to 20 mL/minute: 250 mg every 6 hours
- CC less than 5 mL/minute: 250 mg every 12 hours

Patients undergoing chronic intermittent haemodialysis may be given a 250-mg dose at the start of the session, repeated after 6 to 12 hours, then again 36 to 48 hours after the initial dose, and again at the start of the next haemodialysis if more than 30 hours have elapsed since the previous dose.

Further dosage modification may be required in children with renal impairment.

Preparations

BP 2008: Cefradine Capsules; Cefradine Oral Suspension;
USP 31: Cephradine Capsules; Cephradine for Injection; Cephradine for Oral Suspension; Cephradine Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Velosef; ***Chile:*** Velosef†; ***Fr.:*** Dexef; Kelsef†; Zeefra; ***Gr.:*** Tracilarin†; Vethisel†; ***Hong Kong:*** Qualisef; Velosef; Zeefra; ***Indon.:*** Dynacef; Lovecef; Velosef; ***Irl.:*** Velosef; ***Ital.:*** Cefrabiotic†; Ecosporina; Lisacef; Planocid†; ***Malaysia:*** Sephros†; ***Mex.:*** Veracef; ***Neth.:*** Velosef; ***NZ:*** Velosef†; ***Philipp.:*** Cefralon; Gramcep; Racep; Sedinef; Senadex; Solphride; Tolzep; Vamosef; Velodyne; Yudinef; Zepdril; ***Pol.:*** Tafril; ***Port.:*** Biocefra; Cefalmin; Cefradur; Novacefrex†; Velosef†; ***S.Afr.:*** Bactocef†; Cefril; Ranfradin†; ***Spain:*** Septacef; Velocef; ***UAE:*** Eskacef; Julphacef; ***UK:*** Nicef; Velosef; ***USA:*** Velosef†; ***Venez.:*** Cefracin†; Veracef.

Cefsulodin Sodium *(BANM, USAN, rINNM)*

Abbott-46811; Cefsulodina sódica; Cefsulodine Sodique; Cefsulodinnatrium; Cefsulodinum Natricum; CGP-7174E; Kefsulodiinnatrium; Natrii Cefsulodinum; SCE-129; Sulcephalosporin Sodium. Sodium 3-(4-carbamoylpyridiniomethyl)-7-[(2*R*)-2-phenyl-2-sulphoacetamido]-3-cephem-4-carboxylate.

Натрий Цефсулодин

$C_{22}H_{19}N_4NaO_8S_2 = 554.5.$

CAS — 62587-73-9 (cefsulodin); 52152-93-9 (cefsulodin sodium).

ATC — J01DD03.

ATC Vet — QJ01DD03.

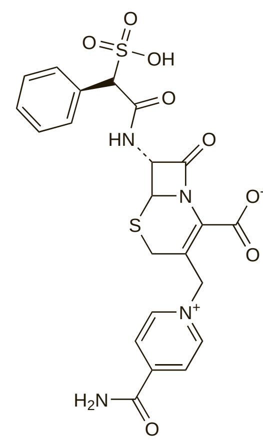

(cefsulodin)

Pharmacopoeias. In *Jpn*.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Sodium content. Each g of cefsulodin sodium contains about 1.8 mmol of sodium.

Antimicrobial Action

Cefsulodin is a bactericidal antibiotic with activity against *Pseudomonas aeruginosa* as great as that of ceftazidime (p.234), but no significant activity against other Gram-negative bacteria. Gram-positive bacteria and anaerobes are not very susceptible. Its activity against *Ps. aeruginosa* may be enhanced by aminoglycosides.

Cefsulodin is stable to hydrolysis by many beta-lactamases, but emergence of resistant *Ps. aeruginosa* has been reported.

Pharmacokinetics

Cefsulodin is given parenterally as the sodium salt. It has a plasma half-life of about 1.6 hours, which is prolonged in renal impairment. Up to 30% of cefsulodin in the circulation is bound to plasma proteins. Therapeutic concentrations have been reported in a wide range of body tissues and fluids. The major route of excretion of cefsulodin is via the urine, mainly by glomerular filtration. Clearance may be enhanced in cystic fibrosis, although there have been conflicting reports.

◊ References.

1. Granneman GR, *et al.* Cefsulodin kinetics in healthy subjects after intramuscular and intravenous injection. *Clin Pharmacol Ther* 1982; **31:** 95–103.
2. Reed MD, *et al.* Single-dose pharmacokinetics of cefsulodin in patients with cystic fibrosis. *Antimicrob Agents Chemother* 1984; **25:** 579–81.
3. Hedman A, *et al.* Increased renal clearance of cefsulodin due to higher glomerular filtration rate in cystic fibrosis. *Clin Pharmacokinet* 1990; **18:** 168–75.

Uses and Administration

Cefsulodin is a third-generation cephalosporin antibiotic with a narrow spectrum of activity that has been used similarly to ceftazidime (p.235) for the treatment of infections caused by susceptible strains of *Pseudomonas aeruginosa*.

It is given as the sodium salt by intravenous injection. Doses are expressed in terms of the equivalent amount of cefsulodin; 1.04 g of cefsulodin sodium is equivalent to about 1 g of cefsulodin. The usual adult dose is 6 g daily in 4 divided doses; in less severe infections daily doses of 3 to 4 g may be given. Children may be given a usual dose of 100 mg/kg daily; 50 mg/kg daily may be given in less severe infections.

◊ References.

1. Smith BR. Cefsulodin and ceftazidime, two antipseudomonal cephalosporins. *Clin Pharm* 1984; **3:** 373–85.
2. Wright DB. Cefsulodin. *Drug Intell Clin Pharm* 1986; **20:** 845–9.

Administration in renal impairment. The dosage of cefsulodin given intravenously should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 20 to 50 mL/minute: a loading dose of 1.5 g then 1 g every 8 hours
- CC 5 to 20 mL/minute: a loading dose of 1.5 g then 1 g every 12 hours
- CC less than 5 mL/minute: a loading dose of 1.5 g then 1 g every 24 hours

In patients undergoing haemodialysis, 1 g is given before and after dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Pyocefal; ***Jpn:*** Takesulin.

Ceftazidime *(BAN, USAN, rINN)*

Ceftazidim; Ceftazidim pentahydrát; Ceftazidima; Ceftazidimas; Ceftazidimum; Ceftazidimum Pentahydricum; Ceftazydym; GR-20263; Keftatsidiimi; LY-139381; Seftazidim. (*Z*)-(7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-(1-pyridiniomethyl)-3-cephem-4-carboxylate pentahydrate.

Цефтазидим

$C_{22}H_{22}N_6O_7S_2,5H_2O = 636.7.$

CAS — 72558-82-8 (anhydrous ceftazidime); 78439-06-2 (ceftazidime pentahydrate).

ATC — J01DD02.

ATC Vet — QJ01DD02.

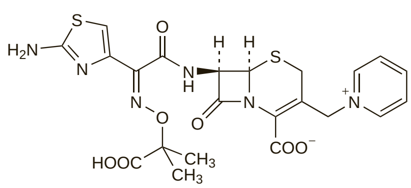

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Ceftazidime). A white or almost white crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol and in acetone; it dissolves in acid and alkali solutions. A 0.5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

USP 31 (Ceftazidime). A white to cream-coloured crystalline powder. Slightly soluble in water, in dimethylformamide, and in methyl alcohol; insoluble in alcohol, in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, and in toluene; soluble in alkali and in dimethyl sulfoxide. pH of a 0.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Formulation. Ceftazidime for injection is available as a dry powder containing ceftazidime with sodium carbonate. When reconstituted ceftazidime sodium is formed with the evolution of carbon dioxide. An alternative formulation, ceftazidime with arginine, appears to overcome the problems associated with effervescence.[1] In some countries a frozen injection containing ceftazidime sodium is also used.

1. Stiles ML, *et al.* Gas production of three brands of ceftazidime. *Am J Hosp Pharm* 1991; **48:** 1727–9.

Incompatibility. It has been reported that ceftazidime does not cause decreased activity when incubated in solution with *gentamicin*[1] or *tobramycin*[2] at 37°, or when mixed with tobramycin in serum.[3] Ceftazidime and tobramycin[4] were also stable for up to 16 hours at room temperature when combined in a glucose-containing dialysis solution, and for a further 8 hours at 37°. However, licensed product information recommends that ceftazidime, like most other beta lactams, should not be mixed with an aminoglycoside in the same giving set or syringe because of the potential for inactivation of either drug.

Ceftazidime is generally considered to be compatible with *metronidazole*, but degradation of ceftazidime has been reported.[5] Precipitation has occurred with *vancomycin*[6] and therefore the product information considers it prudent to flush giving sets and intravenous lines between giving the two drugs. However, in one study[7] ceftazidime and/or vancomycin were stable in a glucose-containing peritoneal dialysis solution when kept for 6 days in a refrigerator or 48 to 72 hours at room temperature, and in a further study[8] the two drugs were stable when combined in similar solutions containing 1.5% or 4.25% glucose for up to 12 hours when stored at 37° and for 24 hours when stored at 4° and 24°. Ceftazidime and *teicoplanin*[9] were stable in combination in a peritoneal dialysis solution at 37° for 8 hours when it had been previously stored at 4°, but not when previously stored at 25°. Ceftazidime was not stable when mixed in solution with *aminophylline*.[10] There was some evidence of possible incompatibility with *pentamidine*.[11]

1. Elliott TSJ, *et al.* Stability of gentamicin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1984; **14:** 668–9.
2. Elliott TSJ, *et al.* Stability of tobramycin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1986; **17:** 680–1.
3. Pennell AT, *et al.* Effect of ceftazidime, cefotaxime, and cefoperazone on serum tobramycin concentrations. *Am J Hosp Pharm* 1991; **48:** 520–2.
4. Mason NA, *et al.* Stability of ceftazidime and tobramycin sulfate in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; **49:** 1139–42.
5. Messerschmidt W. Pharmazeutische kompatibilität von ceftazidim und metronidazol. *Pharm Ztg* 1990; **135:** 36–8.
6. Cairns CJ, Robertson J. Incompatibility of ceftazidime and vancomycin. *Pharm J* 1987; **238:** 577.
7. Vaughan LM, Poon CY. Stability of ceftazidime and vancomycin alone and in combination in heparinized and nonheparinized peritoneal dialysis solution. *Ann Pharmacother* 1994; **28:** 572–6.
8. Stamatakis MK, *et al.* Stability of high-dose vancomycin and ceftazidime in peritoneal dialysis solutions. *Am J Health-Syst Pharm* 1999; **56:** 246–8.
9. Manduru M. *et al.* Stability of ceftazidime sodium and teicoplanin sodium in a peritoneal dialysis solution. *Am J Health-Syst Pharm* 1996; **53:** 2731–4.
10. Pleasants RA, *et al.* Compatibility of ceftazidime and aminophylline admixtures for different methods of intravenous infusion. *Ann Pharmacother* 1992; **26:** 1221–6.
11. Lewis JD. El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1462–3.

Stability. References.

1. Richardson BL, *et al.* The pharmacy of ceftazidime. *J Antimicrob Chemother* 1981; **8** (suppl B): 233–6.
2. Brown AF, *et al.* Freeze thaw stability of ceftazidime. *Br J Parenter Ther* 1985; **6:** 43, 45, 50.
3. Walker SE, Dranitsaris G. Ceftazidime stability in normal saline and dextrose in water. *Can J Hosp Pharm* 1988; **41:** 65–6, 69–71.
4. Wade CS, *et al.* Stability of ceftazidime and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1991; **48:** 1515–19.
5. Stiles ML, *et al.* Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; **49:** 2761–4.
6. Stewart JT, *et al.* Stability of ceftazidime in plastic syringes and glass vials under various storage conditions. *Am J Hosp Pharm* 1992; **49:** 2765–8.
7. Nahata MC, *et al.* Stability of ceftazidime (with arginine) stored in plastic syringes at three temperatures. *Am J Hosp Pharm* 1992; **49:** 2954–6.
8. Bednar DA, *et al.* Stability of ceftazidime (with arginine) in an elastomeric infusion device. *Am J Health-Syst Pharm* 1995; **52:** 1912–14.
9. van Doorne H, *et al.* Ceftazidime degradation rates for predicting stability in a portable infusion-pump reservoir. *Am J Health-Syst Pharm* 1996; **53:** 1302–5.
10. Stendal TL, *et al.* Drug stability and pyridine generation in ceftazidime injection stored in an elastomeric infusion device. *Am J Health-Syst Pharm* 1998; **55:** 683–5.
11. Servais H, Tulkens PM. Stability and compatibility of ceftazidime administered by continuous infusion to intensive care patients. *Antimicrob Agents Chemother* 2001; **45:** 2643–7.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Like cefotaxime (p.228), ceftazidime has the potential for colonisation and superinfection with resistant organisms. The risk of superinfection with, for example, *Staphylococcus aureus* may be higher than with cefotaxime, since ceftazidime is less active against staphylococci.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ceftazidime, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the blood. References.

1. Hui CH, Chan LC. Agranulocytosis associated with cephalosporin. *BMJ* 1993; **307:** 484.

Effects on the nervous system. References.

1. Al-Zahawi MF, *et al.* Hallucinations in association with ceftazidime. *BMJ* 1988; **297:** 858.
2. Jackson GD, Berkovic SF. Ceftazidime encephalopathy: absence status and toxic hallucinations. *J Neurol Neurosurg Psychiatry* 1992; **55:** 333–4.
3. Chow KM, *et al.* Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; **23:** 369–73.

Effects on the skin. References.

1. Vinks SATMM, *et al.* Photosensitivity due to ambulatory intravenous ceftazidime in cystic fibrosis patient. *Lancet* 1993; **341:** 1221–2.

Interactions

Unlike many other cephalosporins, probenecid has little effect on the renal clearance of ceftazidime.

◊ References.

1. Verhagen CA, *et al.* The renal clearance of cefuroxime and ceftazidime and the effect of probenecid on their tubular excretion. *Br J Clin Pharmacol* 1994; **37:** 193–7.

Antimicrobial Action

Ceftazidime has a bactericidal action and broad spectrum of activity similar to that of cefotaxime (p.228), but increased activity against *Pseudomonas* spp.; it is less active against staphylococci and streptococci. Unlike cefotaxime it has no active metabolite.

Ceftazidime is highly stable to hydrolysis by most beta-lactamases. It is active *in vitro* against many Gram-negative bacteria including *Pseudomonas aeruginosa*, *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., both indole-positive and indole-negative *Proteus*, *Providencia*, *Salmonella*, *Serratia*, and *Shigella* spp. and *Yersinia enterocolitica*. Other susceptible Gram-negative bacteria include *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria* spp. Among Gram-positive bacteria it is active against some staphylococci and streptococci, but meticillin-resistant staphylococci, enterococci, and *Listeria monocytogenes* are generally resistant. Ceftazidime is active against some anaerobes, although most strains of *Bacteroides fragilis* and *Clostridium difficile* are resistant.

The activity of ceftazidime against *Ps. aeruginosa* and some Enterobacteriaceae may be enhanced by aminoglycosides. Antagonism has been reported *in vitro* between ceftazidime and chloramphenicol.

Resistance. As with cefotaxime, resistance may develop during treatment due to the derepression of chromosomally mediated beta-lactamases. It has been noted particularly in *Pseudomonas* spp. and in Enterobacteriaceae including *Citrobacter*, *Enterobacter* spp. and *Proteus vulgaris*. Resistance may also occur due to the production of plasmid-mediated extended-spectrum beta-lactamases, particularly in *Klebsiella* spp. and *E. coli*.

Pharmacokinetics

Ceftazidime is given by injection as the sodium salt or in solution with arginine. Mean peak plasma concentrations of 17 and 39 micrograms/mL have been reported about 1 hour after intramuscular doses of 0.5 and 1 g of ceftazidime, respectively. Five minutes after intravenous bolus injections of 0.5, 1, and 2 g of ceftazidime, mean plasma concentrations of 45, 90, and 170 micrograms/mL, respectively, have been reported. The plasma half-life of ceftazidime is about 2 hours, but this is prolonged in patients with renal impairment and in neonates. Clearance may be enhanced in patients with cystic fibrosis. It is about 10% bound to plasma proteins.

Ceftazidime is widely distributed in body tissues and fluids; therapeutic concentrations are achieved in the CSF when the meninges are inflamed. It crosses the placenta and is distributed into breast milk.

Ceftazidime is passively excreted in bile, although only a small proportion is eliminated by this route. It is mainly excreted by the kidneys, almost exclusively by glomerular filtration; probenecid has little effect on the excretion. About 80 to 90% of a dose appears unchanged in the urine within 24 hours. It is removed by haemodialysis and peritoneal dialysis.

Cystic fibrosis. References.

1. Leeder JS, *et al.* Ceftazidime disposition in acute and stable cystic fibrosis. *Clin Pharmacol Ther* 1984; **36:** 355–62.
2. Hedman A, *et al.* Influence of the glomerular filtration rate on renal clearance of ceftazidime in cystic fibrosis. *Clin Pharmacokinet* 1988; **15:** 57–65.
3. Vinks AATMM, *et al.* Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. *J Antimicrob Chemother* 1997; **40:** 125–33.

The elderly. References.

1. LeBel M, *et al.* Pharmacokinetics of ceftazidime in elderly volunteers. *Antimicrob Agents Chemother* 1985; **28:** 713–15.
2. Higbee MD, *et al.* Pharmacokinetics of ceftazidime in elderly patients. *Clin Pharm* 1989; **8:** 59–62.
3. Sirgo MA, Norris S. Ceftazidime in the elderly: appropriateness of twice-daily dosing. *DICP Ann Pharmacother* 1991; **25:** 284–8.

Hepatic impairment. References.

1. El Touny M, *et al.* Pharmacokinetics of ceftazidime in patients with liver cirrhosis and ascites. *J Antimicrob Chemother* 1991; **28:** 95–100.

Neonates. References.

1. van den Anker JN, *et al.* Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 1995; **58:** 650–9.
2. van den Anker JN, *et al.* Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 1995; **40:** 439–43.
3. van den Anker JN, *et al.* Once-daily versus twice-daily administration of ceftazidime in the preterm infant. *Antimicrob Agents Chemother* 1995; **39:** 2048–50.

Renal impairment. References.

1. Welage LS, *et al.* Pharmacokinetics of ceftazidime in patients with renal insufficiency. *Antimicrob Agents Chemother* 1984; **25:** 201–4.
2. Leroy A, *et al.* Pharmacokinetics of ceftazidime in normal and uremic subjects. *Antimicrob Agents Chemother* 1984; **25:** 638–42.
3. Ackerman BH, *et al.* Effect of decreased renal function on the pharmacokinetics of ceftazidime. *Antimicrob Agents Chemother* 1984; **25:** 785–6.
4. Lin N-S, *et al.* Single- and multiple-dose pharmacokinetics of ceftazidime in infected patients with varying degrees of renal function. *J Clin Pharmacol* 1989; **29:** 331–7.
5. Kinowski J-M, *et al.* Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. *Antimicrob Agents Chemother* 1993; **37:** 464–73.
6. Demotes-Mainard F, *et al.* Pharmacokinetics of intravenous and intraperitoneal ceftazidime in chronic ambulatory peritoneal dialysis. *J Clin Pharmacol* 1993; **33:** 475–9.

Uses and Administration

Ceftazidime is a third-generation cephalosporin antibacterial with enhanced activity against *Pseudomonas aeruginosa*. It is used in the treatment of susceptible infections especially those due to *Pseudomonas* spp. They include biliary-tract infections, bone and joint infections, cystic fibrosis (respiratory-tract infections), endophthalmitis, infections in immunocompromised patients (neutropenic patients), melioidosis, meningitis, peritonitis, pneumonia, upper respiratory-tract infections, septicaemia, skin infections (including burns, ecthyma gangrenosum, and ulceration), and urinary-tract infections. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ceftazidime is available as the pentahydrate but it is formulated with sodium carbonate, to form the sodium salt in solution, or with arginine. Doses are expressed in terms of anhydrous ceftazidime; ceftazidime pentahydrate 1.16 g is equivalent to about 1 g of anhydrous ceftazidime. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes. The usual dose for adults ranges from 1 to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised patients. In adults with cystic fibrosis who have pseudomonal lung infections, high doses of 90 to 150 mg/kg daily in 3 divided doses are used; up to 9 g daily has been given to those with normal renal function. Single doses of more than 1 g should be given intravenously.

Children are usually given ceftazidime 30 to 100 mg/kg daily in 2 or 3 divided doses, but in severely ill children up to 150 mg/kg daily to a maximum of 6 g daily (9 g in cystic fibrosis with pseudomonal lung infection) may be given in 3 divided doses. Neonates and infants up to 2 months have been given 25 to 60 mg/kg daily in 2 divided doses.

In the elderly the dose should generally not exceed 3 g daily.

Although not licensed for nebulisation in the UK, the *BNFC* suggests a dose of 1 g inhaled twice daily for the management of chronic *Burkholderia cepacia* (*Pseudomonas cepacia*) infection in patients aged 1 month and older with cystic fibrosis.

For details of reduced doses in patients with renal impairment, see below.

For surgical infection prophylaxis in patients undergoing prostatic surgery, a dose of 1 g may be given at induction of anaesthesia and repeated if necessary when the catheter is removed.

Ceftazidime can be used with an aminoglycoside, another beta lactam such as piperacillin, or vancomycin in patients with severe neutropenia, or, if infection with *Bacteroides fragilis* is suspected, with an antimicrobial such as clindamycin or metronidazole. The drugs should generally be given separately (see also Incompatibility, above).

◊ References.

1. Rains CP, *et al.* Ceftazidime: an update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1995; **49:** 577–617.

Administration in renal impairment. In patients with renal impairment the dosage of ceftazidime may need to be reduced. After a loading dose of 1 g, maintenance doses are based on the creatinine clearance (CC):

- CC 31 to 50 mL/minute: 1 g every 12 hours
- CC 16 to 30 mL/minute: 1 g every 24 hours
- CC 6 to 15 mL/minute: 500 mg every 24 hours
- CC less than 5 mL/minute: 500 mg every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime trough serum concentrations should not exceed 40 micrograms/mL. In patients undergoing peritoneal dialysis a loading dose of 1 g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and then 0.5 to 1 g after each dialysis period.

Preparations

USP 31: Ceftazidime for Injection; Ceftazidime Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Crima; Fortum; Pluseptic; Tinacef; Zidima; ***Austral.:*** Fortum; ***Austria:*** Fortum; Kefazim; ***Belg.:*** Glazidim; Kefadim†; ***Braz.:*** Cefazima†; Ceftanorth†; Ceftazidon; Ceften; Cetaz; Fortaz; Intracef; Kefadim; Roycefax†; ***Canad.:*** Ceptaz†; Fortaz; Tazidime†; ***Chile:*** Fortum; Kefzim†; ***Cz.:*** Fortum; Kefadim†; ***Denm.:*** Fortum; ***Fin.:*** Glazidim; ***Fr.:*** Fortum; Fortumset; ***Ger.:*** Fortum; InfectoZidim; ***Gr.:*** Cefin; Ceftaridem; Ftazidime; Lemoxol; Malocef; Novocral; Septax; Spiel; Solvetan; ***Hong Kong:*** Fortum; ***Hung.:*** Cetazime; Fortum; ***India:*** Cefazid; Ceftaz; Ceftidin; Fortum; Zytaz; ***Indon.:*** Caltum; Ceftum; Cetazum; Extimon; Fortum; Lacedim; Pharodime; Sodime; Thidim; Zefidim; Zibac; Zidifec; ***Irl.:*** Fortum; ***Israel:*** Fortum; ***Ital.:*** Cedizim; Ceftim; Dizatec; Etazim; Fribat; Glazidim; Liotixil; Panzid; Spectrum; Starcef; Tazidif; Tottizim; ***Malaysia:*** Cef-4; Fortum; ***Mex.:*** Fenit; Fortum; Izadima; Lezidim†; Tagal; Taloken; Taxifur; Zadolina; Zidicef; ***Neth.:*** Fortum; Tazalux; ***Norw.:*** Fortum; ***NZ:*** Fortum; ***Philipp.:*** Baxidyme; Dimzef; Fortum; Forzid; Tazicef; Tazidan; Tazidem; Uniranz; Zadim; Zeptrigen; ***Pol.:*** Biotum; Fortum; Mirocef; ***Port.:*** Cefortam; Ceftazim; Zidimox; ***Rus.:*** Bestum (Бестум); Fortum (Фортум); Lorazidime (Лоразидим); ***S.Afr.:*** Fortum; Kefzim†; Taziject; ***Singapore:*** Cefazime; Fortum; ***Spain:*** Fortam; Kefamin; ***Swed.:*** Fortum; ***Switz.:*** Fortam; ***Thai.:*** CEF-4; Cef-Dime; Cefodime; Dimase; Fortadim; Fortum; Forzid; Fournox†; Zeftam; ***Turk.:*** Fortum; Iesetum; ***UAE:*** Negacef; ***UK:*** Fortum; Kefadim; ***USA:*** Ceptaz; Fortaz; Tazicef; Tazidime; ***Venez.:*** Betazidim; Biozidima; Cefgram; Fortum; Kesterina†.

Cefteram Pivoxil *(rINNM)*

Cefteram, Pivoxil de; Cefteram pivoxilo; Cefterami Pivoxil; T-2588. Pivaloyloxymethyl (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-methyl-2*H*-tetrazol-2-ylmethyl)-3-cephem-4-carboxylic acid.

Цефтерама Пивоксил

$C_{22}H_{27}N_9O_7S_2$ = 593.6.

CAS — 82547-58-8 (cefteram); 82547-81-7 (cefteram pivoxil).

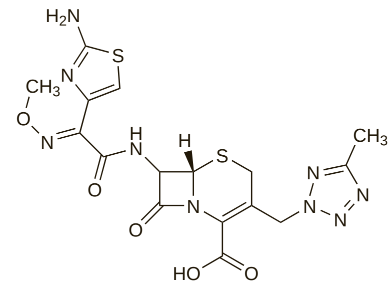

(cefteram)

Pharmacopoeias. In *Jpn.*

Profile

Cefteram is a cephalosporin antibacterial used for the treatment of susceptible infections. It is given orally as the pivaloyloxymethyl ester, cefteram pivoxil, and doses are expressed in terms of cefteram; 186 mg of cefteram pivoxil is equivalent to about 150 mg of cefteram. The usual dose is 150 to 300 mg daily in 3 divided doses after meals. For severe infections, up to 600 mg daily may be given.

For reference to carnitine deficiency occurring after the administration of some pivaloyloxymethyl esters, see Pivampicillin, p.317.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Tomiron.

Ceftezole Sodium *(rINNM)*

Ceftezol sódico; Ceftézole Sodique; Natrii Ceftezolum. Sodium (7*R*)-7-[2-(1*H*-tetrazol-1-yl)acetamido]-3-(1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylate.

Натрий Цефтезол

$C_{13}H_{11}N_8NaO_4S_3$ = 462.5.

CAS — 26973-24-0 (ceftezole); 41136-22-5 (ceftezole sodium).

ATC — J01DB12.

ATC Vet — QJ01DB12.

Pharmacopoeias. In *Chin.*

Profile

Ceftezole is a cephalosporin antibacterial with properties similar to those of cefalotin (p.219). It is given as the sodium salt but doses are expressed in terms of the base; 1.05 g of ceftezole sodium is equivalent to about 1 g of ceftezole. The usual dose is 2 to 4 g daily by intramuscular injection in 2 or 3 divided doses.

Sodium content. Each g of ceftezole sodium contains about 2.16 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Alomen.

Ceftibuten *(BAN, USAN, rINN)*

Ceftibutène; Ceftibuteno; Ceftibutenum; Keftibuteeni; 7432-S; Sch-39720. 7-[2-(2-Amino-1,3-thiazol-4-yl)-4-carboxyisocrotonamide]-3-cephem-4-carboxylic acid.

Цефтибутен

$C_{15}H_{14}N_4O_6S_2$ = 410.4.

CAS — 97519-39-6.

ATC — J01DD14.

ATC Vet — QJ01DD14.

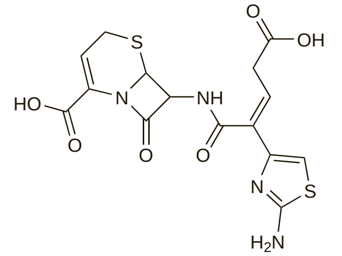

Pharmacopoeias. *Jpn* includes the dihydrate.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

The most frequently reported adverse effects of ceftibuten are gastrointestinal disturbances, especially diarrhoea, and headache.

Antimicrobial Action

As for Cefixime, p.224. It is less active *in vitro* against *Streptococcus pneumoniae*.

◊ References.

1. Shawar R, *et al.* Comparative in vitro activity of ceftibuten (Sch-39720) against bacterial enteropathogens. *Antimicrob Agents Chemother* 1989; **33:** 781–4.
2. Bragman SGL, Casewell MW. The in-vitro activity of ceftibuten against 475 clinical isolates of Gram-negative bacilli, compared with cefuroxime and cefadroxil. *J Antimicrob Chemother* 1990; **25:** 221–6.
3. Wise R, *et al.* Ceftibuten—in-vitro activity against respiratory pathogens, β-lactamase stability and mechanism of action. *J Antimicrob Chemother* 1990; **26:** 209–13.
4. Maioli E, *et al.* In vitro activity of ceftibuten at sub-inhibitory concentrations in comparison with other antibiotics against respiratory and urinary tract pathogens. *J Chemother* 2007; **19:** 152–60.

Pharmacokinetics

Ceftibuten is rapidly absorbed from the gastrointestinal tract, although the rate and extent of absorption are somewhat decreased by the presence of food. Peak plasma concentrations of about 17 micrograms/mL are attained about 2 hours after a 400-mg dose. The plasma half-life of ceftibuten is about 2.0 to 2.3 hours and is prolonged in patients with renal impairment. Ceftibuten is 65 to 77% bound to plasma proteins.

Ceftibuten distributes into middle-ear fluid and bronchial secretions. About 10% of a dose is converted to the *trans*-isomer, which has about one-eighth of the activity of the *cis*-isomer. Ceftibuten is excreted mainly in the urine and also in the faeces. Significant amounts are removed by haemodialysis.

Uses and Administration

Ceftibuten is a third-generation cephalosporin antibacterial used similarly to cefixime (p.225) in the treatment of urinary-tract and respiratory-tract infections. It is given orally as the dihydrate, but doses are expressed in terms of anhydrous ceftibuten; 435 mg of ceftibuten dihydrate is equivalent to about 400 mg of anhydrous ceftibuten. The usual adult dose is 400 mg once daily on an empty stomach. Children over 6 months of age and weighing 45 kg or less may be given 9 mg/kg daily as a single dose. For reduced doses in patients with moderate to severe renal impairment, see below.

◊ Reviews.

1. Wiseman LR, Balfour JA. Ceftibuten: review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1994; **47:** 784–808.
2. Nelson JD, McCracken GH (eds). Ceftibuten: a new orally active cephalosporin for pediatric infections. *Pediatr Infect Dis J* 1995; **14** (suppl): S76–S133.
3. Guay DRP. Ceftibuten: a new expanded-spectrum oral cephalosporin. *Ann Pharmacother* 1997; **31:** 1022–33.
4. Owens RC, *et al.* Ceftibuten: an overview. *Pharmacotherapy* 1997; **17:** 707–20.

Administration in renal impairment. Doses of ceftibuten should be reduced in patients with moderate to severe renal impairment. The following doses based on creatinine clearance (CC) may be used:

- CC 30 to 49 mL/minute: 200 mg once daily
- CC 5 to 29 mL/minute: 100 mg once daily

Patients undergoing haemodialysis 2 or 3 times weekly may be given a dose of 400 mg after each dialysis session.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cedax†; Sepex†; ***Austria:*** Caedax†; ***Cz.:*** Cedax†; ***Ger.:*** Keimax; ***Gr.:*** Caedax†; ***Hong Kong:*** Cedax; ***Hung.:*** Cedax; ***India:*** Procadax; ***Israel:*** Cedax; ***Ital.:*** Cedax; Isocef; ***Jpn:*** Seftem; ***Malaysia:*** Cedax; ***Mex.:*** Cedax; ***Neth.:*** Cedax; ***Philipp.:*** Cedax; ***Pol.:*** Cedax; ***Port.:*** Caedax; ***Rus.:*** Cedax (Цедекс); ***S.Afr.:*** Cedax†; Sepexin†; ***Singapore:*** Cedax; ***Spain:*** Biocef; Cedax; Cepifran†; ***Swed.:*** Cedax; ***Switz.:*** Cedax; ***Thai.:*** Cedax; ***USA:*** Cedax; ***Venez.:*** Cedax; Sepexin†.

Ceftiofur Hydrochloride *(BANM, USAN, rINNM)*

Ceftiofur, Chlorhydrate de; Ceftiofuri Hydrochloridum; Hidrocloruro de ceftiofur; U-64279A. (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-glyoxylamido]-3-mercaptomethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(*Z*)-(*O*-methyloxime), 2-furoate (ester), monohydrochloride.

Цефтиофура Гидрохлорид

$C_{19}H_{17}N_5O_7S_3.HCl = 560.0.$

CAS — 80370-57-6 (ceftiofur); 103980-44-5 (ceftiofur hydrochloride).

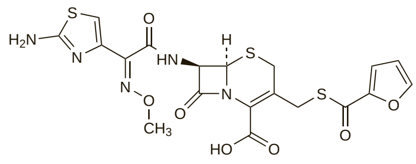

(ceftiofur)

Ceftiofur Sodium *(BANM, USAN, rINNM)*

Ceftiofur sódico; Ceftiofur sodique; Ceftiofurum natricum; CM-31-916; Natrii Ceftiofurum; U-64279E.

Натрий Цефтиофур

$C_{19}H_{16}N_5NaO_7S_3 = 545.5.$

CAS — 104010-37-9.

Profile

Ceftiofur is a cephalosporin antibacterial used as the hydrochloride and sodium salts in veterinary practice.

Ceftizoxime Sodium *(BANM, USAN, rINNM)*

Ceftizoxima sódica; Ceftizoxime Sodique; Ceftizoximnatrium; Ceftizoximum Natricum; FK-749; FR-13749; Keftitsoksiiminatrium; Natrii Ceftizoximum; Seftizoksim Sodyum; SKF-88373-Z. Sodium (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate.

Натрий Цефтизоксим

$C_{13}H_{12}N_5NaO_5S_2 = 405.4.$

CAS — 68401-81-0 (ceftizoxime); 68401-82-1 (ceftizoxime sodium).

ATC — J01DD07.

ATC Vet — QJ01DD07.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Ceftizoxime Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Stability. References.

1. Lesko AB, *et al.* Ceftizoxime stability in iv solutions. *DICP Ann Pharmacother* 1989; **23**: 615–18.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p.228.

Sodium content. Each g of ceftizoxime sodium contains about 2.5 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of ceftizoxime.

Antimicrobial Action

As for Cefotaxime Sodium, p.228, although ceftizoxime has no active metabolite.

Pharmacokinetics

After intramuscular injection of 0.5 and 1 g of ceftizoxime, mean peak plasma concentrations of about 14 and 39 micrograms/mL respectively have been reported after 1 hour. The plasma half-life of ceftizoxime is about 1.7 hours and is prolonged in neonates and in renal impairment. Ceftizoxime is 30% bound to plasma proteins.

Ceftizoxime is widely distributed in body tissues and fluids; therapeutic concentrations are achieved in the CSF when the meninges are inflamed. It crosses the placenta and low concentrations have been detected in breast milk.

Nearly all of a dose is excreted unchanged in the urine within 24 hours of dosage, thus achieving high urinary concentrations. Ceftizoxime is excreted by tubular secretion as well as glomerular filtration and giving it with probenecid results in higher and more prolonged plasma concentrations. Some ceftizoxime is removed by haemodialysis.

Neonates. References.

1. Fujii R. Investigation of half-life and clinical effects of ceftizoxime in premature and newborn infants. *Drug Invest* 1990; **2:** 143–9.
2. Reed MD, *et al.* Ceftizoxime disposition in neonates and infants during the first six months of life. *DICP Ann Pharmacother* 1991; **25:** 344–7.

Uses and Administration

Ceftizoxime is a third-generation cephalosporin antibacterial used similarly to cefotaxime (p.229) for the treatment of susceptible infections.

It is given as the sodium salt by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. If 2 g of ceftizoxime is injected intramuscularly the dose should be divided between sites.

Doses are expressed in terms of the equivalent amount of ceftizoxime; 1.06 g of ceftizoxime sodium is equivalent to about 1 g of ceftizoxime. It is usually given in an adult dose of 1 to 2 g every 8 to 12 hours. In severe infections 2 to 4 g may be given intravenously every 8 hours; doses up to 2 g every 4 hours have been given in life-threatening infections.

Children over 6 months of age may be given 50 mg/kg every 6 to 8 hours.

For the treatment of uncomplicated urinary-tract infections, a dose of 500 mg every 12 hours is used.

For details of reduced doses in patients with renal impairment, see below.

A single intramuscular dose of 1 g has been given in uncomplicated gonorrhoea.

◊ References.

1. Richards DM, Heel RC. Ceftizoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985; **29:** 281–329.

Administration in renal impairment. Doses of ceftizoxime should be modified in renal impairment; after a loading dose of 0.5 to 1 g, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of the infection:

- CC 50 to 79 mL/minute: 0.5 to 1.5 g every 8 hours
- CC 5 to 49 mL/minute: 0.25 to 1 g every 12 hours
- CC less than 5 mL/minute: 250 to 500 mg every 24 hours or 0.5 to 1 g every 48 hours, after dialysis.

Preparations

USP 31: Ceftizoxime for Injection; Ceftizoxime Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Ceftix†; Ceftizon†; ***Canad.:*** Cefizox; ***Cz.:*** Cefizox†; ***Fr.:*** Cefizox†; ***India:*** Cefizox; ***Indon.:*** Cefizox; Tizos; ***Ital.:*** Eposerin; ***Jpn:*** Epocelin†; ***Mex.:*** Cefizox†; ***Neth.:*** Cefizox; ***Philipp.:*** Tergecin; Unizox; ***Port.:*** Cefizox; ***Turk.:*** Cefizox; ***USA:*** Cefizox.

Ceftobiprole Medocaril *(USAN, rINN)*

BAL-5788; BAL-5788-001; BAL-9141 (ceftobiprole); Ceftobiprol Medocarilo; Ceftobiprole Médocaril; Ceftobiprolum Medocarilum; Ro-65-5788; Ro-63-9141 (ceftobiprole). (6*R*,7*R*)-7-[(2*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-3-((*E*){(3′*R*)-1′-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]-2-oxo-(1,3′-bipyrrolidin)-3-ylidene}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Цефтобипрол Медокарил

$C_{26}H_{26}N_8O_{11}S_2 = 690.7.$

CAS — 209467-52-7 (ceftobiprole); 376653-43-9 (ceftobiprole medocaril); 252188-71-9 (ceftobiprole medocaril sodium).

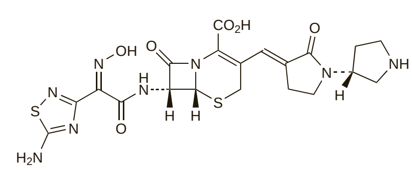

(ceftobiprole)

Profile

Ceftobiprole is a broad-spectrum cephalosporin that is being tried in the treatment of susceptible infections, including meticillin-resistant *Staphylococcus aureus*. It is given as the medocaril derivative.

◊ References.

1. Noel GJ. Clinical profile of ceftobiprole, a novel beta-lactam antibiotic. *Clin Microbiol Infect* 2007; **13** (suppl 2): 25–9.
2. Murthy B, Schmitt-Hoffmann A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. *Clin Pharmacokinet* 2008; **47:** 21–33.
3. Zhanel GG, *et al.* Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008; **9:** 245–54.
4. Deresinski SC. The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials. *Diagn Microbiol Infect Dis* 2008; **61:** 103–9.
5. Anderson SD, Gums JG. Ceftobiprole: an extended-spectrum anti-methicillin-resistant Staphylococcus aureus cephalosporin. *Ann Pharmacother* 2008; **42:** 806–16.

Ceftriaxone Sodium *(BANM, USAN, rINNM)*

Ceftriakson sodowy; Ceftriaksono natrio druska; Ceftriaxon sodná sůl trihemihydrát; Ceftriaxona sódica; Ceftriaxone sodique; Ceftriaxonnatrium; Ceftriaxon-nátrium; Ceftriaxonum natricum; Ceftriaxonum Natricum Trihemihydricum; Keftriaksoninatrium; Natrii Ceftriaxonum; Ro-13-9904; Ro-13-9904/000 (ceftriaxone); Seftriakson Sodyum. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt, sesquaterhydrate.

Натрий Цефтриаксон

$C_{18}H_{16}N_8Na_2O_7S_3,3\frac{1}{2}H_2O = 661.6$.

CAS — 73384-59-5 (ceftriaxone); 74578-69-1 (anhydrous ceftriaxone sodium); 104376-79-6 (ceftriaxone sodium sesquaterhydrate).

ATC — J01DD04.

ATC Vet — QJ01DD04.

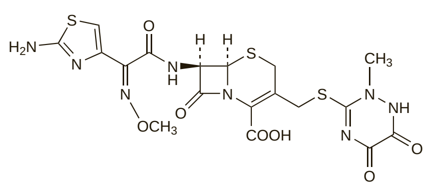

(ceftriaxone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ceftriaxone Sodium). A semi-synthetic product derived from a fermentation product. An almost white to yellowish, slightly hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in methyl alcohol. A 12% solution in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Ceftriaxone Sodium). A white to yellowish-orange crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Incompatibility. UK licensed product information warns of incompatibility if ceftriaxone sodium is mixed with calcium-containing solutions or with aminoglycosides, amsacrine, fluconazole, labetalol, or vancomycin. Published reports of incompatibility have included that between ceftriaxone and vancomycin[1] or pentamidine.[2]

1. Pritts D, Hancock D. Incompatibility of ceftriaxone with vancomycin. *Am J Hosp Pharm* 1991; **48:** 77.
2. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Stability. References.

1. Nahata MC. Stability of ceftriaxone sodium in peritoneal dialysis solutions. *DICP Ann Pharmacother* 1991; **25:** 741–2.
2. Canton E, Esteban MJ. Stability of ceftriaxone solution. *J Antimicrob Chemother* 1992; **30:** 397–8.
3. Bailey LC, *et al.* Stability of ceftriaxone sodium in injectable solutions stored frozen in syringes. *Am J Hosp Pharm* 1994; **51:** 2159–61.
4. Plumridge RJ, *et al.* Stability of ceftriaxone sodium in polypropylene syringes at −20, 4, and 20°C. *Am J Health-Syst Pharm* 1996; **53:** 2320–3.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p.228.

Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of ceftriaxone; diarrhoea may occur more often, especially in children. Biliary sludge or pseudolithiasis due to a precipitate of calcium ceftriaxone has been seen occasionally in patients given ceftriaxone. Similarly, deposition of the calcium salt has occurred rarely in the urine. Isolated cases of death in term or premature neonates have been associated with precipitation of calcium ceftriaxone in lungs and kidneys, and in some of these cases a calcium-containing product has been given by a different route or line, or at a different time. US licensed product information therefore contra-indicates the use of ceftriaxone within 48 hours of products or solutions containing calcium, particularly in neonates. Ceftriaxone is highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates.

Neutropenia has been reported with most cephalosporins; a complex mechanism has been attributed to that associated with ceftriaxone. There have been rare reports of fatal haemolysis associated with ceftriaxone.

Although ceftriaxone has an *N*-methylthiotriazine ring rather than an *N*-methylthiotetrazole side-chain, it might still have the potential to cause hypoprothrombinaemia.

Breast feeding. A study of drug distribution and protein binding between maternal blood and breast milk post partum in a 26-year-old woman given ceftriaxone 2 g daily by intravenous infusion for 10 days found that penetration of ceftriaxone into breast milk increased at these doses as protein binding capacity was saturated, although no adverse effects occurred in the infant.[1] The authors advised caution in breast-feeding mothers given acidic drugs which also have high protein binding such as ceftriaxone[1] although, on the basis that no adverse effects have been observed in breast-fed infants whose mothers were receiving ceftriaxone, the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Bourget P, *et al.* Ceftriaxone distribution and protein binding between maternal blood and milk postpartum. *Ann Pharmacother* 1993; **27:** 294–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the biliary tract. Using abdominal ultrasonography, biliary sludge or pseudolithiasis was found in about 40% of severely ill children being treated with high doses of ceftriaxone[1] and was later reported in adults.[2-4] The sludge has been identified as a calcium salt of ceftriaxone.[5] Patients are often asymptomatic and the sludge usually dissolves once ceftriaxone is stopped. Gallstones with ceftriaxone as a major component have been identified in a patient given long-term high-dose treatment.[6] Similarly, a bile-duct stone composed of ceftriaxone occurred with high-dose ceftriaxone in a child.[7] In another report, intractable hiccups were associated with ceftriaxone-related pseudolithiasis in a 10-year-old boy.[8]

1. Schaad UB, *et al.* Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* 1988; **ii:** 1411–13.
2. Pigrau C, *et al.* Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet* 1989; **ii:** 165.
3. Heim-Duthoy KL, *et al.* Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrob Agents Chemother* 1990; **34:** 1146–9.
4. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 2005; **25:** 1389–95.
5. Park HZ, *et al.* Ceftriaxone-associated gallbladder sludge: identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology* 1991; **100:** 1665–70.
6. Lopez AJ, *et al.* Ceftriaxone-induced cholelithiasis. *Ann Intern Med* 1991; **115:** 712–14.
7. Robertson FM, *et al.* Ceftriaxone choledocholithiasis. *Pediatrics* 1996; **98:** 133–5.
8. Bonioli E, *et al.* Pseudolithiasis and intractable hiccups in a boy receiving ceftriaxone. *N Engl J Med* 1994; **331:** 1532.

Effects on the blood. References.

1. Haubenstock A, *et al.* Hypoprothrombinaemic bleeding associated with ceftriaxone. *Lancet* 1983; **i:** 1215–16.
2. Rey D, *et al.* Ceftriaxone-induced granulopenia related to a peculiar mechanism of granulopoiesis inhibition. *Am J Med* 1989; **87:** 591–2.
3. Bernini JC, *et al.* Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995; **126:** 813–15.
4. Lascari AD, Amyot K. Fatal hemolysis caused by ceftriaxone. *J Pediatr* 1995; **126:** 816–17.
5. Scimeca PG, *et al.* Hemolysis after treatment with ceftriaxone. *J Pediatr* 1996; **128:** 163.
6. Moallem HJ, *et al.* Ceftriaxone-related fatal hemolysis in an adolescent with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1998; **133:** 279–81.
7. Meyer O, *et al.* Fatal immune haemolysis due to a degradation product of ceftriaxone. *Br J Haematol* 1999; **105:** 1084–5.
8. Viner Y, *et al.* Severe hemolysis induced by ceftriaxone in a child with sickle-cell anemia. *Pediatr Infect Dis J* 2000; **19:** 83–5.
9. Seltsam A, Salama A. Ceftriaxone-induced immune haemolysis: two case reports and a concise review of the literature. *Intensive Care Med* 2000; **26:** 1390–4.
10. Citak A, *et al.* Ceftriaxone-induced haemolytic anaemia in a child with no immune deficiency or haematological disease. *J Paediatr Child Health* 2002; **38:** 209–10.

Effects on the pancreas. References.

1. Zimmermann AE, *et al.* Ceftriaxone-induced acute pancreatitis. *Ann Pharmacother* 1993; **27:** 36–7.
2. Maranan MC, *et al.* Gallstone pancreatitis caused by ceftriaxone. *Pediatr Infect Dis J* 1998; **17:** 662–3.

Neonates. References to the displacement of bilirubin by ceftriaxone in neonates.

1. Gulian J-M, *et al.* Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. *J Antimicrob Chemother* 1987; **19:** 823–9.
2. Fink S, *et al.* Ceftriaxone effect on bilirubin-albumin binding. *Pediatrics* 1987; **80:** 873–5.

Sodium content. Each g of ceftriaxone sodium contains about 3.0 mmol of sodium.

Interactions

Ceftriaxone has an *N*-methylthiotriazine side-chain and may have the potential to increase the effects of anticoagulants and to cause a disulfiram-like reaction with alcohol.

Unlike many cephalosporins, probenecid does not affect the renal excretion of ceftriaxone.

Antimicrobial Action

As for Cefotaxime Sodium, p.228, although ceftriaxone has no active metabolite.

◊ References.

1. Goldstein FW, *et al.* Resistance to ceftriaxone and other β-lactams in bacteria isolated in the community. *Antimicrob Agents Chemother* 1995; **39:** 2516–19.

Pharmacokinetics

Ceftriaxone demonstrates nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma proteins depending on the concentration of ceftriaxone.

Mean peak plasma concentrations of about 40 and 80 micrograms/mL have been reported 2 hours after intramuscular injection of 0.5 and 1 g of ceftriaxone respectively. The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it may be prolonged in neonates. The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body tissues and fluids. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations are achieved in bile.

About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the faeces as unchanged drug and microbiologically inactive compounds.

◊ Reviews.

1. Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986; **11:** 76–86.
2. Yuk JH, *et al.* Clinical pharmacokinetics of ceftriaxone. *Clin Pharmacokinet* 1989; **17:** 223–35.
3. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. *Clin Pharmacokinet* 2001; **40:** 685–94.

Hepatic impairment. References.

1. Stoeckel K, *et al.* Single-dose ceftriaxone kinetics in liver insufficiency. *Clin Pharmacol Ther* 1984; **36:** 500–9.
2. Hary L, *et al.* The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36:** 613–16.
3. Toth A, *et al.* Pharmacokinetics of ceftriaxone in liver-transplant recipients. *J Clin Pharmacol* 1991; **31:** 722–8.

Pregnancy. References.

1. Bourget P, *et al.* Pharmacokinetics and protein binding of ceftriaxone during pregnancy. *Antimicrob Agents Chemother* 1993; **37:** 54–9.

Renal impairment. The pharmacokinetics of ceftriaxone are not markedly altered in mild to moderate renal impairment,[1] but the half-life can be prolonged in severe or end-stage renal disease.[1-4] Ceftriaxone is generally not removed by peritoneal dialysis[4] or by haemodialysis[1-3] although a decrease in half-life has been reported during haemodialysis.[5] In many patients no alteration in dosage is necessary, but some individuals have reduced non-renal clearance despite apparently normal hepatic function.[2,3] It is advisable to monitor plasma ceftriaxone in

The symbol † denotes a preparation no longer actively marketed

patients with severe renal impairment and unknown non-renal clearance.

1. Patel IH, *et al.* Ceftriaxone pharmacokinetics in patients with various degrees of renal impairment. *Antimicrob Agents Chemother* 1984; **25:** 438–42.
2. Stoeckel K, *et al.* Single-dose ceftriaxone kinetics in functionally anephric patients. *Clin Pharmacol Ther* 1983; **33:** 633–41.
3. Cohen D, *et al.* Pharmacokinetics of ceftriaxone in patients with renal failure and in those undergoing hemodialysis. *Antimicrob Agents Chemother* 1983; **24:** 529–32.
4. Ti T-Y, *et al.* Kinetic disposition of intravenous ceftriaxone in normal subjects and patients with renal failure on hemodialysis or peritoneal dialysis. *Antimicrob Agents Chemother* 1984; **25:** 83–7.
5. Garcia RL, *et al.* Single-dose pharmacokinetics of ceftriaxone in patients with end-stage renal disease and hemodialysis. *Chemotherapy* 1988; **34:** 261–6.

Uses and Administration

Ceftriaxone is a third-generation cephalosporin antibacterial used similarly to cefotaxime for the treatment of susceptible infections. They include chancroid, endocarditis, gastro-enteritis (invasive salmonellosis; shigellosis), gonorrhoea, Lyme disease, meningitis (including meningococcal meningitis prophylaxis), pneumonia, septicaemia, syphilis, typhoid fever, and Whipple's disease. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ceftriaxone is given as the sodium salt by slow intravenous injection over at least 2 to 4 minutes, by intermittent intravenous infusion over at least 30 minutes, or by deep intramuscular injection. If more than 1 g is to be injected intramuscularly then the dose should be divided between more than one site. Doses are expressed in terms of the equivalent amount of ceftriaxone; 1.19 g of ceftriaxone sodium is equivalent to about 1 g of ceftriaxone. The usual adult dose is 1 to 2 g daily as a single dose or in two divided doses; in severe infections up to 4 g daily may be given. Doses for infants and children (under 50 kg) are 20 to 50 mg/kg once daily; for severe infections up to 80 mg/kg daily may be given. In neonates, the maximum dose should not exceed 50 mg/kg daily; intravenous doses in neonates should be given over 60 minutes. Doses above 50 mg/kg should be given by intravenous infusion only.

A single intramuscular dose of 250 mg is recommended for the treatment of uncomplicated gonorrhoea.

For surgical infection prophylaxis, a single dose of 1 g may be given 0.5 to 2 hours before surgery; a 2-g dose is suggested before colorectal surgery.

For the prevention of secondary cases of meningococcal meningitis, a single intramuscular dose of 250 mg may be used for adults and 125 mg for children.

◊ References.

1. Brogden RN, Ward A. Ceftriaxone: a reappraisal of its antibacterial activity and pharmacokinetic properties, and an update on its therapeutic use with particular reference to once-daily administration. *Drugs* 1988; **35:** 604–45.
2. Lamb HM, *et al.* Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. *Drugs* 2002; **62:** 1041–89.
3. Bijie H, *et al.* In vitro activity, pharmacokinetics, clinical efficacy, safety and pharmacoeconomics of ceftriaxone compared with third and fourth generation cephalosporins: review. *J Chemother* 2005; **17:** 3–24.

Administration in hepatic and renal impairment. A reduction in dosage of ceftriaxone may be necessary in patients with severe renal impairment (creatinine clearance below 10 mL/minute), in whom the daily dose should not exceed 2 g. In patients undergoing dialysis, and in those with both renal and hepatic impairment, plasma concentrations of ceftriaxone should be monitored to determine whether dose adjustment is needed.

Preparations

BP 2008: Ceftriaxone Injection;
USP 31: Ceftriaxone for Injection; Ceftriaxone Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Acantex; Bioteral; Cefomax; Ceftriaz†; Exempla; Rivacefin; Soltrimox; ***Austral.:*** Rocephin; ***Austria:*** Exogran; Rocephin; ***Belg.:*** Rocephine; ***Braz.:*** Amplospec†; Bioteral†; Ceft†; Ceftriax; Glicocef; Mesporan; Neoceftriona; Prodoxin; Rocefin; Rofoxin†; Triaxon; Triaxton; Trioxina; ***Canad.:*** Rocephin; ***Chile:*** Acantex; Grifotriaxona; ***Cz.:*** Cefaxone†; Lendacin; Longaceph†; Megion; Novosef†; Oframax†; Rocephin†; Samixon; ***Denm.:*** Cefotrix; Rocephalin; ***Fin.:*** Rocephalin; ***Fr.:*** Rocephine; ***Ger.:*** Cefotrix; Rocephin; ***Gr.:*** Antibacin; Azatyl; Bresec; Ceftrixon; Farcef; Gladius; Glorixone; Labilex; Medaxone; Rocephin; Rolisporin; Travilan; Ugotrex; Veracol; ***Hong Kong:*** Medaxonum; Mesporin; Rocephin; ***Hung.:*** Cefotrix; Lendacin; Megion; Rocephin; ***India:*** Cefocef; Ciplacef; Lyceft; Monocef; Monotax; Oframax; Powercef; Stericef†; ***Indon.:*** Biotriax; Bioxon; Broadced; Brospec; Cefaxon; Cefriex; Ceftrox; Cefxon; Cephaflox; Criax; Ecotrixon; Elpicef; Erocef; Foricef; Intrix; Rocephin; Socef; Starxon; Terfacef; Termicef; Tricefin; Trijec; Tyason; Zeftrix; ***Irl.:*** Rocephin; ***Israel:*** Keftriaxon; Rocephin; Triax; ***Ital.:*** Axobat; Bixon; Davixon; Daytrix; Deixim; Eftry; Fidato; Frineg; Iliaxone; Kappacef; Kocefan; Monoxar; Nilson; Panatrix; Pantoxon; Ragex; Rocefin; Setriox; Sirtap; Valexime; ***Jpn:*** Rocephin; ***Malaysia:*** Cefaxone; Ceftrex; Eftriax; Mesporin; Rocephin; Trixone; ***Mex.:*** Amcef; Aurofox; Axtar; Benaxona; Cefaxona; Cefraden; Ceftrex; Ceftrilem; Centrifal; Limiprol; Megion; Primotox; Rocephin; Tacex; Terbac; Triaken; Triox; Xonatil; ***Neth.:*** Elfaxone; Exogran; Lopratin; Rocephin; ***Norw.:*** Rocephalin; ***NZ:*** Rocephin; ***Philipp.:*** Acrexon; CEF-3; Cikedrix; Cryaxon; Eurosef; Fenadef; Forgram; Keptrix; Megion; Monocrin; Noxoram; Pantrixon; Retrokor; Rocephin; Roxon; Samjizon; Sergimax; Trixophin; Xtenda; ***Pol.:*** Biotrakson; Lendacin; Rocephin; Tartriakson; ***Port.:*** Betasporina; Ceriax; Kemudin; Mesporin; Rocephin; ***Rus.:*** Azaran (Азаран); Ceftrifin (Цефтрифин); Ificef (Ифицеф); Lendacin (Лендацин); Loraxone (Лораксон); Medaxone (Медаксон); Novosef (Новосеф); Oframax (Офрамакс); Stericef (Стерицеф); Tercef (Терцеф); Torocef (Тороцеф); ***S.Afr.:*** Fraxone†; Oframax; Rocephin; Rociject; ***Singapore:*** Antibacin; Cefaxone; Cefin†; Oframax; Rocephin; Trexofin; Tricefin; ***Spain:*** Rocefalin; ***Swed.:*** Rocephalin; ***Switz.:*** Rocephine; ***Thai.:*** CEF-3; Cef-Zone; Cefine†; Ceftrex; Ceftriphin; Lephin†; Oframax; Rinxofay; Rocephin; Sedalin†; Triacef; Tricephin; Trixone; Zefaxone; ***Turk.:*** Baktisef; Cefaday; Cephaxon; Desefin; Equiceft; Forsef; Iesef; Nevakson; Novosef; Rocephin; Unacefin; ***UAE:*** Triaxone; ***UK:*** Rocephin; ***USA:*** Rocephin; ***Venez.:*** Bioceftrax; Cefin; Cefix; Ceftrialin; Ciplacef; Eftrival; Feliden†; Megion; Rocephin; Strixone; Tricefi.

Multi-ingredient: *India:* Axone; Dibact†; Keftragard.

Cefuroxime *(BAN, USAN, rINN)*

640/359; Cefuroxim; Cefuroxima; Céfuroxime; Cefuroximum; Kefuroksiimi; Sefuroksim. (*Z*)-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid.

Цефуроксим

$C_{16}H_{16}N_4O_8S = 424.4.$

CAS — 55268-75-2.

ATC — J01DC02.

ATC Vet — QJ01DC02; QJ51DA06.

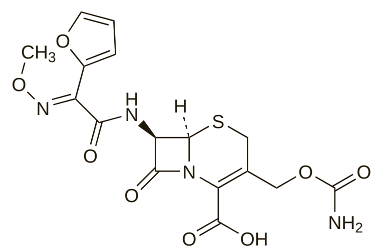

Cefuroxime Axetil *(BANM, USAN, rINNM)*

CCI-15641; Cefuroksimas aksetilas; Cefuroksymu aksetyl; Cefuroxima axetilo; Cefuroximaxetil; Cefuroxim-axetil; Céfuroxime axétil; Céfuroxime, Axétil de; Cefuroximi Axetilum; Cefuroximum axetili; Cefuroximum Axetilum; Kefuroksiimiaksetiili; Sefuroksim Aksetil.

Цефуроксима Аксетил

$C_{20}H_{22}N_4O_{10}S = 510.5.$

CAS — 64544-07-6.

ATC — J01DC02.

ATC Vet — QJ01DC02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Cefuroxime Axetil). A white or almost white powder. Slightly soluble in water and in alcohol; soluble in acetone, in ethyl acetate, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Cefuroxime Axetil). A mixture of the diastereoisomers of cefuroxime axetil. A white or almost white powder. The amorphous form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; soluble in chloroform, in ethyl acetate, and in methyl alcohol. The crystalline form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in chloroform, in ethyl acetate, and in methyl alcohol. Store in airtight containers.

Cefuroxime Sodium *(BANM, rINNM)*

Cefuroksimo natrio druska; Cefuroksym sodowy; Cefuroxim sodná sůl; Cefuroxima sódica; Céfuroxime sodique; Cefuroximnatrium; Cefuroxim-nátrium; Cefuroximum natricum; Kefuroksiiminatrium; Natrii Cefuroximum; Sefuroksim Sodyum.

Натрий Цефуроксим

$C_{16}H_{15}N_4NaO_8S = 446.4.$

CAS — 56238-63-2.

ATC — J01DC02.

ATC Vet — QJ01DC02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Cefuroxime Sodium). A white or almost white slightly hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.5 to 8.5. Store in airtight containers.

USP 31 (Cefuroxime Sodium). A white or faintly yellow powder. Freely soluble in water; very slightly soluble in alcohol, in chloroform, in ether, and in ethyl acetate; soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.5. Store in airtight containers.

Incompatibility and stability. Cefuroxime sodium may be incompatible with aminoglycosides.

References.

1. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
2. Stiles ML, *et al.* Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; **49:** 2761–4.
3. Hebron B, Scott H. Shelf life of cefuroxime eye-drops when dispensed in artificial tear preparations. *Int J Pharm Pract* 1993; **2:** 163–7.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Gastrointestinal disturbances, including diarrhoea, nausea, and vomiting, have occurred in some patients receiving cefuroxime axetil. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Mild to moderate hearing loss has been reported in some children given cefuroxime for the treatment of meningitis.

Antibiotic-associated colitis. For reports of pseudomembranous colitis associated with cefuroxime axetil, see Cefalotin, p.219.

Hypersensitivity. A report[1] of a serum sickness-like reaction to cefuroxime. Similar reactions have occurred with cefaclor (p.217), although it is unclear whether they represent a class effect.

1. Katta R, Anusuri V. Serum sickness-like reaction to cefuroxime: a case report and review of the literature. *J Drugs Dermatol* 2007; **6:** 747–8.

Porphyria. Cefuroxime is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Sodium content. Each g of cefuroxime sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefuroxime.

Antimicrobial Action

Cefuroxime is bactericidal and has a similar spectrum of antimicrobial action and pattern of resistance to those of cefamandole (p.221). It is more resistant to hydrolysis by beta-lactamases than cefamandole, and therefore may be more active against beta-lactamase-producing strains of, for example, *Haemophilus influenzae* and *Neisseria gonorrhoeae*. However, treatment failures have occurred in patients with *H. influenzae* meningitis given cefuroxime and might be associated with a relatively high minimum bactericidal concentration when compared with the minimum inhibitory concentration or with a significant inoculum effect. Reduced affinity of penicillin-binding proteins for cefuroxime has also been reported to be responsible for resistance in a beta-lactamase-negative strain of *H. influenzae*.

◊ References.

1. Arditi M, *et al.* Cefuroxime treatment failure and Haemophilus influenzae meningitis: case report and review of literature. *Pediatrics* 1989; **84:** 132–5.
2. Mendelman PM, *et al.* Cefuroxime treatment failure of nontypable Haemophilus influenzae meningitis associated with alteration of penicillin-binding proteins. *J Infect Dis* 1990; **162:** 1118–23.
3. Brown NM, *et al.* Cefuroxime resistance in Haemophilus influenzae. *Lancet* 1992; **340:** 552.

Pharmacokinetics

Cefuroxime axetil is absorbed from the gastrointestinal tract and is rapidly hydrolysed in the intestinal mucosa and blood to cefuroxime; absorption is enhanced in the presence of food. Peak plasma concentrations are reported about 2 to 3 hours after an oral dose. The sodium salt is given by intramuscular or intravenous injection. Peak plasma concentrations of about 27 micrograms/mL have been achieved 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose. Up to 50% of cefuroxime in the circulation is bound to plasma proteins. The plasma half-life is about 70 minutes and is prolonged in patients with renal impairment and in neonates.

Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. It crosses the placenta and has been detected in breast milk.

Cefuroxime is excreted unchanged, by glomerular filtration and renal tubular secretion, and high concentrations are achieved in the urine. On injection, most of a dose of cefuroxime is excreted within 24 hours, the majority within 6 hours. Probenecid competes for renal tubular secretion with cefuroxime resulting in higher and more prolonged plasma concentrations of cefuroxime. Small amounts of cefuroxime are excreted in bile. Plasma concentrations are reduced by dialysis.

Uses and Administration

Cefuroxime is a second-generation cephalosporin antibacterial used in the treatment of susceptible infections. These have included bone and joint infections, bronchitis (and other lower respiratory-tract infections), gonorrhoea, meningitis (although treatment failures have been reported in *H. influenzae* meningitis), otitis media, peritonitis, pharyngitis, sinusitis, skin infections (including soft-tissue infections), and urinary-tract infections. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefuroxime is given orally as the acetoxyethyl ester, cefuroxime axetil, in the form of tablets or suspension with or after food, or by injection as the sodium salt. Cefuroxime sodium may be given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion. Doses of cefuroxime axetil and cefuroxime sodium are expressed in terms of the equivalent amount of cefuroxime; 1.20 g of cefuroxime axetil and 1.05 g of cefuroxime sodium are each equivalent to about 1 g of cefuroxime.

Usual oral doses for adults are 125 mg twice daily for uncomplicated urinary-tract infections and 250 to 500 mg twice daily for respiratory-tract infections. A dose for children more than 3 months of age is 125 mg twice daily or 10 mg/kg twice daily to a maximum of 250 mg daily. Children over 2 years of age with otitis media may be given 250 mg twice daily or 15 mg/kg twice daily to a maximum of 500 mg daily.

By injection the usual adult dose is 750 mg of cefuroxime every 8 hours but in more severe infections 1.5 g may be given intravenously every 8, or in some cases every 6, hours. Infants and children can be given 30 to 60 mg/kg daily, increased to 100 mg/kg daily if necessary, given in 3 or 4 divided doses. Neonates may be given similar total daily doses but in 2 or 3 divided doses.

Adults with pneumonia or with acute exacerbations of chronic bronchitis may respond to sequential therapy with parenteral cefuroxime 1.5 g twice daily or 750 mg twice daily respectively, followed by oral cefuroxime 500 mg twice daily in each case.

For Lyme disease in adults, an oral dose of 500 mg is given twice daily for 20 days.

For details of reduced dosage of cefuroxime in patients with renal impairment, see below.

For the treatment of meningitis due to sensitive strains of bacteria, cefuroxime is given intravenously in adult doses of 3 g every 8 hours. Infants and children are given 200 to 240 mg/kg daily intravenously in 3 or 4 divided doses, which may be decreased to 100 mg/kg daily after 3 days or when there is clinical improvement. For neonates, a dose of 100 mg/kg daily, decreased to 50 mg/kg daily when indicated, may be used.

In the treatment of gonorrhoea, a single dose of 1.5 g by intramuscular injection, divided between 2 injection sites, has been used. A single 1-g oral dose of cefuroxime has been given for uncomplicated gonorrhoea. In each case an oral dose of probenecid 1 g may be given with cefuroxime.

For surgical infection prophylaxis, the usual dose is 1.5 g of cefuroxime intravenously before the procedure; this may be supplemented by 750 mg intramuscularly every 8 hours for up to 24 to 48 hours depending upon the procedure. For total joint replacement, 1.5 g of cefuroxime powder may be mixed with the methylmethacrylate cement.

◊ Reviews.

1. Perry CM, Brogden RN. Cefuroxime axetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1996; **52:** 125–58.
2. Scott LJ, *et al.* Cefuroxime axetil: an updated review of its use in the management of bacterial infections. *Drugs* 2001; **61:** 1455–1500.

Administration in renal impairment. Parenteral doses of cefuroxime may need to be reduced in renal impairment. Licensed product information suggests the following doses based on creatinine clearance (CC):

- CC 10 to 20 mL/minute: 750 mg twice daily
- CC less than 10 mL/minute: 750 mg once daily

Patients undergoing haemodialysis should receive an additional 750-mg dose following each dialysis; those undergoing continuous peritoneal dialysis may be given 750 mg twice daily.

Preparations

BP 2008: Cefuroxime Axetil Tablets; Cefuroxime Injection;
USP 31: Cefuroxime Axetil for Oral Suspension; Cefuroxime Axetil Tablets; Cefuroxime for Injection; Cefuroxime Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Ceflux†; Cefogram†; Cefurox; Deltrox†; Ligramex†; ***Austral.:*** Zinnat; ***Austria:*** Curocef; Furoxim; Zinnat; ***Belg.:*** Axetine; Cefurim; Doccefuro; Kefurox†; Zinacef; Zinnat; ***Braz.:*** Cefunorth†; Cefuran†; Medcef; Zinacef; Zinnat; ***Canad.:*** Ceftin; Kefurox†; Zinacef; ***Chile:*** Curocef; Zinnat; ***Cz.:*** Axetine; Lifurox†; Xorimax; Zinacef; Zinnat; Zinoxime; ***Denm.:*** Zinacef; Zinnat; ***Fin.:*** Zinacef; Zinnat; ***Fr.:*** Cepazine; Zinnat; ***Ger.:*** Cefu; Cefudura; Cefuhexal; Cefurax; Cefuro-Puren; Cefurox-Wolff; Elobact; Zinacef†; Zinnat; ***Gr.:*** Anaptivan; Cefoprim†; Cefur; Cefuroprol; Cerofene; Ceruxim; Cupax; Ecoline†; Feacef; Foucacillin; Fredyr; Furaxil; Galemin; Genephoxal; Gonif; Interbion; Lyoprovir; Medoxem; Mevecan†; Mosalan; Nelabocin; Nipogalin; Normafenac; Receant; Saxetil; Sedopan; Vekfazolin; Yokel; Zagorine; Zetagal; Zilisten; Zinacef; Zinadol; ***Hong Kong:*** Anikef; Axetine†; Zinacef; Zinnat; ***Hung.:*** Cefurin; Ceroxim; Cexim†; Xorim; Xorimax; Zinacef; Zinnat; ***India:*** Altacef; Cefasyn; Cefogen; Cefoxim; Forcef; Supacef; ***Indon.:*** Anbacim; Cefurox; Celocid; Cethixim; Kalcef; Kenacef; Oxtercid; Roxbi; Sharox; Zinacef; Zinnat; ***Irl.:*** Ceftal; Zinacef; Zinnat; ***Israel:*** Cefurax; Kefurim; Zinacef; Zinnat; ***Ital.:*** Biociclin; Biofurex†; Cefoprim; Cefumax†; Cefur†; Cefurex†; Cefurin; Colifossim†; Curoxim; Deltacef†; Duxima; Ipacef†; Itorex; Kefox†; Kesint; Lafurex; Oraxim; Supero; Tilexim; Zinnat; Zinocep; Zoref; ***Malaysia:*** Ceflour; Efurox; Furoxime; Zinacef; Zinnat; Zocef; ***Mex.:*** Cefagen; Cefuracet; Cetoxil; Froxal; Fucerox; Lemoxin†; Magnaspor; Novador; Ximaken; Xorufec; Zinnat; ***Neth.:*** Cefofix; Zinacef; Zinnat; ***Norw.:*** Zinacef; ***NZ:*** Zinacef; Zinnat; ***Philipp.:*** Aeruginox; Cervin; Clovixime; Fubaxyn; Furocef; Furocem; Furoxy; Infekor; Kefox; Keunzef; Laxinat; Loxatrel; Panaxim; Profurex; Romicef; Ruxim; Sharox; Shincef; Unoximed; Xorimax; Zegen; Zinacef; Zinnat; ***Pol.:*** Biofuroksym; Bioracef; Ceroxim; Novocef; Oframax; Plixym; Tarsime; Xorim; Xorimax; Zamur; Zinacef; Zinnat; ***Port.:*** Antibioxime; Cefaricida†; Cefofix; Cefrix†; Curoxime; Furaxetil†; Lusocef; Pluscef; Zipos; Zoref; ***Rus.:*** Axetine (Аксетин); Kefstar (Кефстар); Ketocef (Кетоцеф); Zinacef (Зинацеф); Zinnat (Зиннат); ***S.Afr.:*** Cefasyn; Cefu-Hexal; Ceroxim; Cipofix†; Intracef; Lifurom†; Medaxime; Zefroxe; Zinacef; Zinnat; ***Singapore:*** Bearcef; Ceftil; Shincef; Zinacef; Zinnat; ***Spain:*** Curoxima; Lifurox†; Nivador; Selan; Zinnat; ***Swed.:*** Zinacef; Zinnat; ***Switz.:*** Cefurim; Zinacef; Zinat; ***Thai.:*** Axetine†; Axurocef; Cefamar; Cefogen†; Cefurim; Farmacef; Furoxime; Magnaspor; Zinacef; Zinnat; Zonef; ***Turk.:*** Aksef; Cefatin; Enfexia; Multisef; Oraceftin; Sefaktil; Sefuroks; Zinnat; ***UAE:*** Cefuzime; ***UK:*** Zinacef; Zinnat; ***USA:*** Ceftin; Zinacef; ***Venez.:*** Xorim; Zencef; Zinacef; Zinnat.

Cethromycin *(USAN, rINN)*

A-195773; Abbott-195773; ABT-773; Céthromycine; Cethromycinum; Cetromicina. (3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-3a,7,9,11,13,15-hexamethyl-11-{[3-(quinolin-3-yl)prop-2-enyl]oxy}-10-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}octahydro-2*H*-oxacyclotetradecino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone.

Цетромицин

$C_{42}H_{59}N_3O_{10}$ = 765.9.

CAS — 205110-48-1.

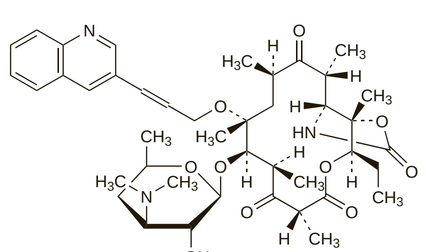

Profile

Cethromycin is a ketolide antibacterial under investigation for the treatment of susceptible respiratory-tract infections.

◊ References.

1. Dougherty TJ, Barrett JF. ABT-773: a new ketolide antibiotic. *Expert Opin Invest Drugs* 2001; **10:** 343–51.
2. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; **62:** 1771–1804.
3. Zhanel GG, *et al.* Ketolides: an emerging treatment for macrolide-resistant respiratory infections, focusing on S. pneumoniae. *Expert Opin Emerg Drugs* 2003; **8:** 297–321.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; **53:** 918–27.
5. Anonymous. Cethromycin: A-195773, A-195773-0, A-1957730, Abbott-195773, ABT 773. *Drugs R D* 2007; **8:** 95–102.
6. Hammerschlag MR, Sharma R. Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. *Expert Opin Invest Drugs* 2008; **17:** 387–400.

Chloramphenicol *(BAN, rINN)*

Chloramfenikol; Chloramfenikolis; Chloramphénicol; Chloramphenicolum; Chloranfenicol; Cloranfenicol; Klóramfenikol; Kloramfenikol; Kloramfenikoli; Laevomycetinum. 2,2-Dichloro-*N*-[(α*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

Хлорамфеникол

$C_{11}H_{12}Cl_2N_2O_5$ = 323.1.

CAS — 56-75-7.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QJ51BA01; QS01AA01; QS02AA01; QS03AA08.

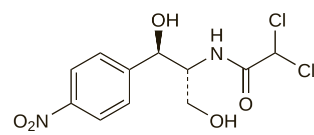

NOTE. CPL is a code approved by the BP 2008 for use on single unit doses of eye drops containing chloramphenicol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Chloramphenicol). A substance produced by the growth of certain strains of *Streptomyces venezuelae*, but now mainly prepared synthetically. A white, greyish-white or yellowish-white, fine crystalline powder or fine crystals, needles, or elongated plates. Slightly soluble in water; freely soluble in alcohol and in propylene glycol. Protect from light.

USP 31 (Chloramphenicol). Fine, white to greyish-white or yellowish-white, needle-like crystals or elongated plates. Soluble 1 in 400 of water; freely soluble in alcohol, in acetone, in ethyl acetate, and in propylene glycol. pH of a 2.5% suspension in water is between 4.5 and 7.5. Its solutions are practically neutral to litmus. It is reasonably stable in neutral or moderately acid solutions. Store in airtight containers.

Chloramphenicol Palmitate *(BANM, rINNM)*

Chloramfenikolio palmitatas; Chloramfenikol-palmitát; Chloramfenikolu palmitynian; Chloramphenicol α-Palmitate; Chloramphénicol, palmitate de; Chloramphenicoli palmitas; Kloramfenikolipalmitaatti; Kloramfenikolpalmitat; Klóramfenikol-palmitát; Palmitato de cloranfenicol; Palmitylchloramphenicol.

Хлорамфеникола Пальмитат

$C_{27}H_{42}Cl_2N_2O_6$ = 561.5.

CAS — 530-43-8.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Chloramphenicol Palmitate). A fine, white or almost white, unctuous, powder. M.p. 87° to 95°. Chloramphenicol palmitate shows polymorphism and the thermodynamically stable form has low bioavailability following oral administration. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone; very slightly soluble in hexane. Protect from light.

USP 31 (Chloramphenicol Palmitate). A fine, white, unctuous, crystalline powder, having a faint odour. M.p. 87° to 95°. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform; soluble in ether; very slightly soluble in hexane. Store in airtight containers.

Chloramphenicol Sodium Succinate

(BANM, rINNM)

Chloramfenikolio natrio sukcinatas; Chloramfenikol-sukcinát sodná sůl; Chloramphenicol α-Sodium Succinate; Chloramphénicol, succinate sodique de; Chloramphenicoli natrii succinas; Kloramfenikol Süksinat Sodyum; Klóramfenikol-hidrogénszukcinát-nátrium; Kloramfenikolinatriumsuksinaatti; Kloramfenikolnatriumsuccinat; Succinato sódico de cloranfenicol.

Хлорамфеникола Натрия Сукцинат

$C_{15}H_{15}Cl_2N_2NaO_8$ = 445.2.

CAS — 982-57-0.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* *Chin.* includes Chloramphenicol Hydrogen Succinate.

Ph. Eur. 6.2 (Chloramphenicol Sodium Succinate). A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in alcohol. A 25% solution in water has a pH of 6.4 to 7.0. Store in airtight containers. Protect from light.

USP 31 (Chloramphenicol Sodium Succinate). A light yellow powder. Freely soluble in water and in alcohol. pH of a solution in water containing the equivalent of chloramphenicol 25% is between 6.4 and 7.0. Store in airtight containers.

Incompatibility. Incompatibility or loss of activity has been reported between chloramphenicol and a wide variety of other substances. Other factors, especially drug concentration, may play a part and many incompatibilities are chiefly seen with concentrated solutions.

Adverse Effects and Treatment

Chloramphenicol may cause serious and sometimes fatal adverse effects. Some of its toxicity is thought to be due to effects on mitochondrial protein synthesis. The most serious adverse effect of chloramphenicol is bone-marrow depression, which can take two different forms. The first is a fairly common dose-related reversible depression occurring usually when plasma-chloramphenicol concentrations exceed 25 micrograms/mL and is characterised by morphological changes in the bone marrow, decreased iron utilisation, reticulocytopenia, anaemia, leucopenia, and thrombocytopenia. This effect may be due to inhibition of protein synthesis in the mitochondria of bone marrow cells.

The second and apparently unrelated form of bone-marrow toxicity is severe irreversible aplastic anaemia. This is fairly rare, with a suggested incidence of about 1:20 000 to 1:50 000, although the incidence varies throughout the world, and is not considered to be dose-related. The aplasia usually develops after a latent period of weeks or even months and has been suggested to be the result of a nitrated benzene radical produced *in vivo*. It is considered that there may be some genetic or biochemical predisposition, but there is no way of identifying susceptible patients. Although the majority of cases were after oral use, aplasia has also occurred after intravenous and topical (eye drops) use of chloramphenicol. Survival is most likely in those with early onset aplasia, but they may subsequently develop acute myeloid leukaemia.

A toxic manifestation—the 'grey syndrome'—characterised by abdominal distension, vomiting, ashen colour, hypothermia, progressive pallid cyanosis, irregular respiration, and circulatory collapse followed by death in a few hours or days, has occurred in premature and other newborn infants given large doses of chloramphenicol. The syndrome is associated with high plasma concentrations of chloramphenicol, due to reduced capacity for glucuronidation and decreased glomerular filtration in children of this age, leading to drug accumulation. Recovery is usually complete if the drug is withdrawn early enough after onset, but up to 40% of infants with the full-blown syndrome may die. The syndrome has also been reported in infants born to mothers given chloramphenicol in late pregnancy. A similar syndrome has been reported in adults and older children given very high doses.

Prolonged oral use of chloramphenicol may induce bleeding, either by bone-marrow depression or by reducing the intestinal flora with consequent inhibition of vitamin K synthesis. Haemolytic anaemia has occurred in some patients with the Mediterranean form of glucose 6-phosphate dehydrogenase deficiency, but is rare in patients with milder forms of the deficiency.

Peripheral as well as optic neuritis has been reported, usually in patients treated over prolonged periods. Although ocular symptoms are often reversible if treatment is withdrawn early, permanent visual impairment or blindness has occurred.

Other neurological symptoms have included encephalopathy with confusion and delirium, mental depression, and headache. Ototoxicity has also occurred, especially after the use of ear drops.

Hypersensitivity reactions including rashes, fever, and angioedema may occur especially after topical use; anaphylaxis has occurred but is rare. Jarisch-Herxheimer reactions may also occur. Gastrointestinal symptoms including nausea, vomiting, and diarrhoea can follow oral use. Disturbances of the oral and intestinal flora may cause stomatitis, glossitis, and rectal irritation. Patients may experience an intensely bitter taste after rapid intravenous use of chloramphenicol sodium succinate.

Aplastic anaemia. A review[1] of the toxicity of chloramphenicol and related drugs, including the potential role of the *p*-nitro group in producing aplastic anaemia, indicated that derivatives such as thiamphenicol, which lack this grouping, are not associated with increased incidence of aplastic anaemia.

1. Yunis AA. Chloramphenicol: relation of structure to activity and toxicity. *Ann Rev Pharmacol Toxicol* 1988; **28:** 83–100.

Overdosage. Charcoal haemoperfusion was found to be far superior to exchange transfusion in the removal of chloramphenicol from blood, although it did not prevent death in a 7-week-old infant with the 'grey syndrome' after a dosage error.[1]

1. Freundlich M, *et al.* Management of chloramphenicol intoxication in infancy by charcoal hemoperfusion. *J Pediatr* 1983; **103:** 485–7.

Precautions

Chloramphenicol is contra-indicated in patients with a history of hypersensitivity or toxic reaction to the drug. It should never be given systemically for minor infections or for prophylaxis. Repeated courses and prolonged treatment should be avoided and it should not be used in patients with pre-existing bone-marrow depression or blood dyscrasias. Routine periodic blood examinations are advisable in all patients, but will not warn of aplastic anaemia.

Use of chloramphenicol with other drugs liable to depress bone-marrow function should be avoided.

Reduced doses should be given to patients with hepatic impairment. Excessive blood concentrations may also occur after usual doses in patients with severe renal impairment and in premature and full-term neonates who have immature metabolic processes. Monitoring of plasma-chloramphenicol concentrations may be desirable in patients with risk factors. A suggested range for peak plasma concentrations is 10 to 25 micrograms/mL and for trough concentrations 5 to 15 micrograms/mL.

Neonates should never be given chloramphenicol systemically, unless it may be life-saving and there is no alternative treatment, because of the risk of the 'grey syndrome'. The use of chloramphenicol is probably best avoided during pregnancy.

Chloramphenicol may interfere with the development of immunity and it should not be given during active immunisation.

Breast feeding. Chloramphenicol is distributed into breast milk[1] and the American Academy of Pediatrics[2] considers that its use by mothers during breast feeding may be of concern, since there have been reports of possible idiosyncratic bone-marrow suppression in the infant.

1. Havelka J, *et al.* Excretion of chloramphenicol in human milk. *Chemotherapy* 1968; **13:** 204–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Ocular use. Ocular chloramphenicol is widely used in the UK for the treatment of superficial eye infections. In view of the potential for serious toxicity, such as aplastic anaemia, after systemic absorption some, particularly in the USA, have advised that its ocular use should be restricted to situations where there is no alternative treatment.[1] However, apart from patients with a personal or family history of blood dyscrasias, the use, particularly of short courses, was defended by several specialists in the UK,[2-4] and the arguments have been the subject of several reviews.[5-7] Prospective case-control studies were considered necessary to clarify the risk.[8] One such study,[9] involving 145 patients with aplastic anaemia and 1226 controls, found that only 3 of the patients had been exposed to ocular chloramphenicol, and calculated that the absolute risk was no more than 0.5 cases per million treatment courses. Similarly, data[10] from 2 other studies revealed that none of 426 patients with aplastic anaemia and 7 of 3118 controls had used chloramphenicol eye drops. In a survey[11] of patients who received prescriptions for chloramphenicol eye drops the risk of serious haematological toxicity was 3 per 442 543 patients or 3 per 674 148 prescriptions.

1. Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995; **310:** 1217–18.
2. Mulla RJ, *et al.* Is it time to stop using chloramphenicol on the eye: fears are based on only six cases. *BMJ* 1995; **311:** 450.
3. Buckley RJK, *et al.* Is it time to stop using chloramphenicol on the eye: safe in patients with no history of blood dyscrasia. *BMJ* 1995; **311:** 450.
4. Hall AV, *et al.* Is it time to stop using chloramphenicol on the eye: risk is low in short courses. *BMJ* 1995; **311:** 450–1.
5. McGhee CNJ, Anastas CN. Widespread ocular use of topical chloramphenicol: is there justifiable concern regarding idiosyncratic aplastic anaemia? *Br J Ophthalmol* 1996; **80:** 182–4.
6. Rayner SA, Buckley RJ. Ocular chloramphenicol and aplastic anaemia: is there a link? *Drug Safety* 1996; **14:** 273–6.
7. Titcomb L. Ophthalmic chloramphenicol and blood dyscrasias: a review. *Pharm J* 1997; **258:** 28–35.
8. Gordon-Smith EC, *et al.* Is it time to stop using chloramphenicol on the eye: prospective study of aplastic anaemia should give definitive answer. *BMJ* 1995; **311:** 451.
9. Laporte J-R, *et al.* Possible association between ocular chloramphenicol and aplastic anaemia—the absolute risk is very low. *Br J Clin Pharmacol* 1998; **46:** 181–4.
10. Wiholm B-E, *et al.* Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ* 1998; **316:** 666.
11. Lancaster T, *et al.* Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ* 1998; **316:** 667.

Porphyria. Chloramphenicol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Sodium content. Each g of chloramphenicol sodium succinate represents about 2.2 mmol of sodium.

Interactions

Chloramphenicol is inactivated in the liver and may, therefore, interact with drugs that are metabolised by hepatic microsomal enzymes. For example, chloramphenicol enhances the effects of coumarin anticoagulants, such as dicoumarol and warfarin, some hypoglycaemics such as chlorpropamide and tolbutamide, and antiepileptics such as phenytoin. Conversely, the metabolism of chloramphenicol may be increased by inducers of hepatic enzymes such as phenobarbital or rifampicin. Some other interactions affecting the activity of chloramphenicol are discussed below.

Chloramphenicol may decrease the effects of iron and vitamin B_{12} in anaemic patients and has occasionally impaired the action of oral contraceptives.

For the effects of chloramphenicol on the activity of other antibacterials, see Antimicrobial Action, below.

Antiepileptics. Serum concentrations of chloramphenicol are usually reduced by the hepatic enzyme induction that occurs with *phenobarbital*,[1,2] and similar reductions have been reported in a case study during *phenytoin* use.[3] Conversely, elevated and potentially toxic serum-chloramphenicol concentrations have resulted during phenytoin use,[2] apparently due to competition for binding sites, although increased metabolism may alternatively lead to decreased serum-chloramphenicol concentrations.

For reference to the effects of chloramphenicol on phenobarbital and phenytoin, see p.493 and p.498, respectively.

1. Bloxham RA, *et al.* Chloramphenicol and phenobarbitone—a drug interaction. *Arch Dis Child* 1979; **54:** 76–7.
2. Krasinski K, *et al.* Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis* 1982; **1:** 232–5.
3. Powell DA, *et al.* Interactions among chloramphenicol, phenytoin, and phenobarbital in a pediatric patient. *J Pediatr* 1981; **98:** 1001–3.

Ciclosporin. For the effect of chloramphenicol on ciclosporin, see p.1825.

Cimetidine. Fatal aplastic anaemia of rapid onset has occurred in 2 patients who received intravenous chloramphenicol and cimetidine.[1,2] As there is usually a latent period of 2 weeks to 12 months before aplastic anaemia develops after chloramphenicol therapy it is plausible that an additive or synergistic effect may have occurred between the 2 drugs to cause bone-marrow toxicity.

1. Farber BF, Brody JP. Rapid development of aplastic anemia after intravenous chloramphenicol and cimetidine therapy. *South Med J* 1981; **74:** 1257–8.
2. West BC, *et al.* Aplastic anemia associated with parenteral chloramphenicol: review of 10 cases, including the second case of possible increased risk with cimetidine. *Rev Infect Dis* 1988; **10:** 1048–51.

Cyclophosphamide. For the effect of chloramphenicol on cyclophosphamide, see p.703.

Oral contraceptives. For the effect of chloramphenicol on oral contraceptives, see Hormonal Contraceptives, p.2068.

Paracetamol. A report of an increase in chloramphenicol half-life from 3.25 to 15 hours when intravenous paracetamol was given to 6 patients in intensive care 2 hours after intravenous chloramphenicol[1] has not been confirmed by subsequent studies in patients receiving oral paracetamol. A study in 5 children found that the half-life of intravenous chloramphenicol was reduced from 3 to 1.2 hours, concomitant with an increase in clearance, when oral paracetamol was given 30 minutes beforehand.[2] Furthermore, a study in 26 children found no evidence of altered disposition when oral paracetamol was given to patients receiving intravenous chloramphenicol,[3] and no significant change in chloramphenicol pharmacokinetics was found in 5 patients given oral chloramphenicol and paracetamol.[4]

1. Buchanan N, Moodley GP. Interaction between chloramphenicol and paracetamol. *BMJ* 1979; **2:** 307–8.
2. Spika JS, *et al.* Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* 1986; **61:** 1121–4.
3. Kearns GL, *et al.* Absence of a pharmacokinetic interaction between chloramphenicol and acetaminophen in children. *J Pediatr* 1985; **107:** 134–9.
4. Stein CM, *et al.* Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol. *Br J Clin Pharmacol* 1989; **27:** 262–4.

Tacrolimus. For the effect of chloramphenicol on tacrolimus, see p.1845.

Antimicrobial Action

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of action against both Gram-positive and Gram-negative bacteria, as well as some other organisms.

Mechanism of action. Chloramphenicol is thought to enter sensitive cells by an active transport process. Within the cell it binds to the 50S subunit of the bacterial ribosome at a site adjacent to the site of action of the macrolides and clindamycin, and inhibits bacterial protein synthesis by preventing attachment of aminoacyl transfer RNA to its acceptor site on the ribosome, thus preventing peptide bond formation by peptidyl transferase. The block in protein synthesis results in a primarily bacteriostatic action, although it may be bactericidal to some organisms, including *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, at higher concentrations.

Spectrum of activity. Chloramphenicol has activity against many types of bacteria, although in most cases there are less toxic alternatives available. The following pathogens are usually susceptible (but see also Resistance, below).

Gram-positive cocci including staphylococci such as *Staph. epidermidis* and some strains of *Staph. aureus*, and streptococci such as *Str., pneumoniae*, *Str. pyogenes*, and the viridans streptococci. Meticillin-resistant staphylococci and *Enterococcus faecalis* are commonly found to be resistant.

Other Gram-positive species including *Bacillus anthracis*, *Corynebacterium diphtheriae*, and anaerobes such as *Peptococcus* and *Peptostreptococcus* spp. are usually susceptible.

Gram-negative cocci such as *Neisseria meningitidis* and *N. gonorrhoeae* are usually highly sensitive, as are *Haemophilus influenzae* and a variety of other Gram-negative bacteria including *Bordetella pertussis*, *Brucella abortus*, *Campylobacter* spp., *Legionella pneumophila*, *Pasteurella*, and *Vibrio* spp. The Enterobacteriaceae vary in their susceptibility, and many strains have shown acquired resistance, but *Escherichia coli*, and strains of *Klebsiella* spp., *Proteus mirabilis*, *Salmonella*, *Shigella*, and *Yersinia* spp. have been reported to be susceptible. Many strains of *Enterobacter*, indole-positive *Proteus*, and *Serratia* spp. are resistant, or at best moderately susceptible. *Pseudomonas aeruginosa* is invariably resistant, although *Burkholderia* (formerly *Pseudomonas*) spp. may be susceptible.

Some Gram-negative anaerobes are susceptible, or moderately so, including *Bacteroides fragilis*, *Veillonella*, and *Fusobacterium* spp.

Other susceptible organisms include *Actinomyces* spp., *Leptospira* spp., spirochaetes such as *Treponema pallidum*, Chlamydiaceae, Mycoplasma spp., and Rickettsia spp. *Nocardia* spp. are resistant. Chloramphenicol is ineffective against fungi, protozoa, and viruses.

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility exists of an antagonistic effect if chloramphenicol is given with a bactericidal drug, and some antagonism has been demonstrated *in vitro* between chloramphenicol and various beta lactams and aminoglycosides, but the clinical significance of most of these interactions is usually held to be doubtful. Chloramphenicol may competitively inhibit the effects of macrolides or lincosamides such as clindamycin because of the adjacency of their binding sites on the ribosome.

Resistance. Acquired resistance has been widely reported, although the prevalence of resistance has tended to decline where use of the drug has become less frequent. The most commonly seen form of resistance has been the production of an acetyltransferase that inactivates the drug. Such resistance is usually plasmid-mediated and may be associated with resistance to other drugs such as the tetracyclines. Other mechanisms that may reduce sensitivity to chloramphenicol include reduced permeability or uptake, and ribosomal mutation.

The actual incidence of resistance varies considerably in different countries and different centres. Epidemics of chloramphenicol-resistant *Salmonella* and *Shigella* spp. have occurred in the past, and although the prevalence of resistance in *Salmonella* spp. has been reported to be negligible except in parts of South or South-east Asia, resistant salmonellal infections acquired in these regions are increasingly being seen elsewhere. Resistance among *Haemophilus* and *Neisseria* spp. occurs, and the latter may be problematic in developing countries, although it does not yet seem to be widespread. However, resistant strains of enterococci and pneumococci are reported to be relatively common in some areas, and over 50% of staphylococcal strains have been reported to show resistance in some hospitals.

Pharmacokinetics

Chloramphenicol is readily absorbed when given by mouth. Blood concentrations of 10 micrograms/mL or more may be reached about 1 or 2 hours after a single oral dose of 1 g, and blood concentrations of about 18.5 micrograms/mL have been reported after multiple 1-g doses. Chloramphenicol palmitate is hydrolysed to chloramphenicol in the gastrointestinal tract prior to absorption, and the sodium succinate, which is given parenterally, is probably hydrolysed to free drug mainly in the liver, lungs, kidneys, and plasma; such hydrolysis may be incomplete in infants and neonates, contributing to the variable pharmacokinetics in this age group. Chloramphenicol sodium succinate is, even in adults, only partially and variably hydrolysed, so that blood concentrations of chloramphenicol obtained after the sodium succinate parenterally are often lower than those obtained after oral chloramphenicol, with up to 30% of a dose excreted unchanged in the urine before hydrolysis can take place (but see under Administration, below).

Chloramphenicol is widely distributed in body tissues and fluids; it enters the CSF, giving concentrations of about 50% of those existing in the blood even in the absence of inflamed meninges; it diffuses across the placenta into the fetal circulation, into breast milk, and into the aqueous and vitreous humours of the eye. It also enters the aqueous humour after topical application. Up to about 60% in the circulation is bound to plasma protein. The half-life of chloramphenicol has been reported to range from 1.5 to 4 hours; the half-life is prolonged in patients with severe hepatic impairment and is also much longer in neonates. Renal impairment has relatively little effect on the half-life of the active drug, due to its extensive metabolism, but may lead to accumulation of the inactive metabolites.

Chloramphenicol is excreted mainly in the urine but only 5 to 10% of an oral dose appears unchanged; the remainder is inactivated in the liver, mostly by conjugation with glucuronic acid. About 3% is excreted in the bile. However, most is reabsorbed and only about 1%, mainly in the inactive form, is excreted in the faeces.

The absorption, metabolism, and excretion of chloramphenicol are subject to considerable interindividual variation, especially in infants and children, making monitoring of plasma concentrations necessary to determine pharmacokinetics in a given patient.

Uses and Administration

The risk of life-threatening adverse effects, particularly bone-marrow aplasia, has severely limited the clinical usefulness of chloramphenicol, although it is still widely used in some countries. It should never be given systemically for minor infections and regular blood counts are usually advisable during treatment. The third-generation cephalosporins replaced chloramphenicol for many of its former indications. There are consequently few unambiguous indications for the use of chloramphenicol. It has been used in severe typhoid and other salmonellal infections, although it does not eliminate the carrier state. Chloramphenicol is an alternative to a third-generation cephalosporin in the treatment of bacterial meningitis, both empirically and against sensitive organisms such as *Haemophilus influenzae*. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. It has been used in the treatment of severe anaerobic infections, particularly in brain abscesses, and in infections below the diaphragm where *Bacteroides fragilis* is often implicated; however, other drugs are usually preferred. Although the tetracyclines remain the treatment of choice in rickettsial infections such as typhus and the spotted fevers, chloramphenicol is also used as an alternative where the tetracyclines cannot be given.

Other bacterial infections in which chloramphenicol may be used as an alternative to other drugs include ehrlichiosis, severe gastro-enteritis (including *Salmonella* enteritis, cholera, and *Yersinia* enteritis), gas gangrene, granuloma inguinale, severe *Haemophilus influenzae* infections (for example in epiglottitis), listeriosis, severe melioidosis, plague (especially if meningitis develops), pneumonia, psittacosis, Q fever, tularaemia (especially when meningitis is suspected), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Chloramphenicol is extensively used in the topical treatment of ear and, in particular, eye infections, despite the fact that many of these are mild and self-limiting. It is also used topically in the treatment of skin infections.

When given orally, chloramphenicol is usually used as capsules or as a suspension of chloramphenicol palmitate. When oral use is not feasible, water-soluble chloramphenicol sodium succinate may be given intravenously, but oral therapy should be substituted as soon as possible; an intravenous dose should be injected over at least 1 minute. Intramuscular injection is controversial because of doubts whether absorption is adequate. In some countries chloramphenicol has been given rectally.

Doses are expressed in terms of chloramphenicol base and are similar whether given orally or intravenously. Chloramphenicol palmitate 1.7 g and chloramphenicol sodium succinate 1.4 g are each equivalent to about 1 g of chloramphenicol base.

For adults and children the usual dose is 50 mg/kg daily in divided doses every 6 hours; up to 100 mg/kg daily may be given in meningitis or severe infections due to moderately resistant organisms, although these higher doses should be reduced as soon as possible. It has been recommended that treatment should be continued after the patient's temperature has returned to normal for a further 4 days in rickettsial diseases, and for 8 to 10 days in typhoid fever, to minimise the risk of relapse.

Where there is no alternative to the use of chloramphenicol, premature and full-term neonates may be given daily doses of 25 mg/kg, in 4 divided doses, and full-term infants over the age of 2 weeks may be given up to 50 mg/kg daily, in 4 divided doses. Monitoring of plasma concentrations is essential to avoid toxicity.

In patients with hepatic impairment or severe renal impairment, the dose of chloramphenicol may need to be reduced because of decreased metabolism or excretion.

In the treatment of eye infections, chloramphenicol is usually applied as a 0.5% solution or as a 1% ointment.

For bacterial infections in otitis externa, chloramphenicol has been given as ear drops in a strength of 5 or 10%.

Chloramphenicol has also been used in the form of other derivatives including the arginine succinate, the cinnamate, the glycinate, the glycinate sulfate, the palmitoylglycolate, the pantothenate, the steaglate, the stearate, and the hydrogen succinate.

Administration. When parenteral use of chloramphenicol is necessary the intravenous route is generally preferred, although the intramuscular route has been advocated. Adequate serum concentrations after intramuscular injection have been reported,[1,2] although this is contrary to the widely held belief that chloramphenicol sodium succinate is poorly absorbed by this route. Pain on injection was also claimed to be minimal.[1] After a study in children with bacterial meningitis,[3] treatment with intramuscular chloramphenicol for 2 or 3 days followed by oral therapy has been suggested, although a later study[2] found that the intramuscular route produced therapeutic concentrations when the oral route did not. However, it has been said[4] that children describe intramuscular chloramphenicol as amongst the worst treatments they ever receive, and certainly much worse than the insertion of intravenous cannulae.

1. Shann F, *et al.* Absorption of chloramphenicol sodium succinate after intramuscular administration in children. *N Engl J Med* 1985; **313:** 410–14.
2. Weber MW, *et al.* Chloramphenicol pharmacokinetics in infants less than three months of age in the Philippines and The Gambia. *Pediatr Infect Dis J* 1999; **18:** 896–901.
3. Shann F, *et al.* Chloramphenicol alone versus chloramphenicol plus penicillin for bacterial meningitis in children. *Lancet* 1985; **ii** 681–3.
4. Coulthard MG, Lamb WH. Antibiotics: intramuscular or intravenous? *Lancet* 1985; **ii:** 1015.

Enterococcal infections. Chloramphenicol has been reported to be effective against vancomycin-resistant *Enterococcus faecium*.[1-3] Although no significant effect of chloramphenicol on mortality was found in one small study,[4] a retrospective analysis[5] of the outcomes of 6 patients with bacteraemia due to vancomycin-resistant *Enterococcus faecium* concluded that chloramphenicol was effective and should be considered as a treatment option.

1. Norris AH, *et al.* Chloramphenicol for the treatment of vancomycin-resistant enterococcal infections. *Clin Infect Dis* 1995; **20:** 1137–44.
2. Papanicolaou GA, *et al.* Nosocomial infections with vancomycin-resistant Enterococcus faecium in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; **23:** 760–6.
3. Mato SP, *et al.* Vancomycin-resistant Enterococcus faecium meningitis successfully treated with chloramphenicol. *Pediatr Infect Dis J* 1999; **18:** 483–4.
4. Lautenbach E, *et al.* The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant Enterococcus. *Clin Infect Dis* 1998; **27:** 1259–65.
5. Ricaurte JC, *et al.* Chloramphenicol treatment for vancomycin-resistant Enterococcus faecium bacteremia. *Clin Microbiol Infect* 2001; **7:** 17–21.

Preparations

BP 2008: Chloramphenicol Capsules; Chloramphenicol Ear Drops; Chloramphenicol Eye Drops; Chloramphenicol Eye Ointment; Chloramphenicol Sodium Succinate Injection;
USP 31: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Prednisolone Ophthalmic Ointment; Chloramphenicol Capsules; Chloramphenicol Cream; Chloramphenicol for Ophthalmic Solution; Chloramphenicol Ophthalmic Ointment; Chloramphenicol Ophthalmic Solution; Chloramphenicol Otic Solution; Chloramphenicol Palmitate Oral Suspension; Chloramphenicol Sodium Succinate for Injection; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: A-Solmicina-C†; Anuar; Bio-Gelin†; Bioticaps; Chloromycetin; Farmicetina; Isopto Fenicol; Klonalfenicol; Pluscloran; Poenfenicol; Quemicetina; Quotal NF†; ***Austral.:*** Chloromycetin; Chlorsig; ***Austria:*** Halomycetin; Kemicetin; Oleomycetin; ***Belg.:*** Isopto Fenicol; Kemicetina†; ***Braz.:*** Amplobiotic†; Arifenicol; Auridonal†; Clorafenil; Cloranfenil†; Farmicetina†; Feniclor†; Fenicloran†; Neo Fenicol; Profenicol; Quemicetina; Sintomicetina; Uni Fenicol; Visalmin; Vixmicina; ***Canad.:*** Chloromycetin; Diochloram†; Pentamycetin; ***Chile:*** Chloromycetin; Clorampast; Gemitin; Quemicetina†; ***Fin.:*** Chloromycetin; Oftan Akvakol; Oftan Chlora; ***Fr.:*** Cebenicol†; ***Ger.:*** Aquamycetin-N†; Chloramsaar N†; Oleomycetin†; Paraxin; Posifenicol C; Thilocanfol C; ***Gr.:*** Chloranic; Ursa-Fenol; ***Hong Kong:*** Aristophen; Chlorment†; Chloroph; Chlorsig; Europhenicol; Kemicetine; Spersanicol†; Vista-Phenicol†; Xepanicol; ***Hung.:*** Chlorocid†; ***India:*** Biophenicol; Chloraxin; Chloromycetin; Kemicetine Otological†; Kemicetine†; Paraxin; Reclor; Vanmycetin; Vitamycetin; ***Indon.:*** Chloramex; Chlorbiotic; Cloramidina; Colain; Colme; Combicetin; Empeecetin; Enkacetyn; Fenicol; Ikamicetin; Isotic Salmicol; Kalmicetine; Kemicetine; Lanacetine; Licoklor; Microtina; Neophenicol; Palmicol; RECO; Ribocine; Spersanicol; Suprachlor; Xepanicol; ***Irl.:*** Chloromycetin; ***Israel:*** Chloroptic; Chlorphenicol; Phenicol; Synthomycine; ***Ital.:*** Chemicetina; Cloramfen†; Mycetin; Sificetina; Vitamfenicolo; ***Malaysia:*** Beaphenicol; Nicol; Spersanicol†; Xepanicol†; ***Mex.:*** Abefen; Alcan†; Biraclor; Brocil; Chloromycetin; Clomicin; Clorafen; Cloramed; Cloramfeni; Clorampler; Cloran; Cloranmicron; Clorazin; Clordil; Clorfenil; Clorofunon; Clorotan; Diarman; Dilclor; Estreptopal; Exacol; Fenicol; Fenisol; Fenizzard; Lebrocetin; Leclor A; Naxo; Oftadil; Omycet; Palcol; Palmiclor; Palmifer; Palmisol; Procloril; Pronicol; Quemicetina; Uniclor; Vixin†; ***Neth.:*** Globenicol†; ***NZ:*** Chloromycetin; Chlorsig; Isopto Fenicol†; ***Philipp.:*** Anphechlor; Aphrenil; Biomycetin; Chloro-S; Chloromycetin; Chlorsig; Clovicol; Esnicol; Fen-Alcon; Forastrol; Genphenil; Gerafen; Kemicetine; Klorfen; Medimycetin; Metrophenicol; Oliphenicol; Optomycin; Pediachlor; Penachlor; ***Pol.:*** Detreomycyna; ***Port.:*** Clorocil; Dermimade Cloranfenicol; Fenoptic†; Micetinoftalmina; ***Rus.:*** Synthomycin (Синтомицин); ***S.Afr.:*** Chloramex; Chlorcol; Chloromycetin; Chloroptic†; Chlorphen; Lennacol; Spersanicol; ***Singapore:*** Beaphenicol†; Isopto Fenicol; Kemicetine; Spersanicol†; Vanafen-S†; ***Spain:*** Chemicetina; Chloromycetin†; Cloranfenic†; Normofenicol†; ***Swed.:*** Chloromycetin; ***Switz.:*** Septicol; Spersanicol†; ***Thai.:*** Antibi-Otic; Archifen; Chloracil; Chloramno; Chloroph; Chlorosin; Cogenate; Cogetine; Fenicol†; Genercin; Kemicetine†; Koro†; Levomycetin; Mycochlorin; Nicolmycetin†; Opsaram†; Pharmacetin; Silmycetin; Synchlolim; Unison Ointment; Vanafen; ***Turk.:*** Armisetin; Kemicetine; Klorasuksinat; ***UK:*** Brochlor; Chloromycetin; Golden Eye; Kemicetine; Optrex Infected Eyes; ***USA:*** Ak-Chlor†; Chloromycetin; Chloroptic†; ***Venez.:*** Chloromycetin†; Cloftal; Cloramfesa†; Quemicetina†.

Multi-ingredient: ***Arg.:*** Acnoxin; Antiflogol; Bioftal; Clorfibrase; Colirio Antibiotico CNH; Esodar; Eubetal Biotic†; Fluoropoen; Iruxol; Klonovan; Neocortizul; Oftal; Oftalmoflogol†; Poenbioptal; Quemicetina con Hidrocortisona; Quemicetina Nasal Compuesta; Vistacloran†; ***Austria:*** Cortison Kemicetin; Oleomycetin-Prednison; ***Belg.:*** De Icol; ***Braz.:*** Dermofibrin C†; Dexaclor†; Dexafenicol; Epitezan; Fenidex; Fibrase; Fibrinase c/Cloranfenicol; Gino-Fibrase; Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; Naxogin Composto; Oto-Biotic†; Otofenicol-D†; Otomicina; Otopen†; Ouvidonal; Procutan†; Regencel; Regenom; Sulnil; ***Canad.:*** Pentamycetin-HC; ***Chile:*** Cortifenol H†; Gemitin con Prednisolona; Naxogin Compositum; Otandrol; Sintoftona; Spersadex Comp†; ***Cz.:*** Betabioptal†; Spersadex Compositum; ***Denm.:*** Spersadex Comp; ***Fin.:*** Iruxol; Oftan C-C; Oftan Dexa-Chlora; ***Fr.:*** Cebedexacol; ***Ger.:*** Aquapred; Berlicetin; Ichthoseptal; Oleomycetin-Prednison†; Spersadex Comp†; Spersadexolin†; ***Gr.:*** Chlorapred; Cortiphenol H; Dexachlor; Dispersadron-C; Geypirina; Nezefib; Spersadexoline†; Sulfachloramphenicol; Sulfanicole; ***Hong Kong:*** Chlomy-P†; Chloram-D; Cortiphenol H; Eurodron; Ginetris†; Neo-Dex (Improved); Sonexa-C; Spersadex Comp; Spersadexoline†; ***Hung.:*** Chlorocid-H†; Spersadex Comp†; ***India:*** Belmycetin-C; Candibiotic; Chlormixin; Chloromycetin Ear Drops; Cortison Kemicetine†; Dexosyn-C; Kemicetine Antiozena; Kemicetine Otological†; Ocupol; Ocupol-D; Otek-AC+; Otek-AC†; Paraxin Ear†; Perfocyn; Pyrimon; ***Indon.:*** Chloramphecort; Chloramphecort-H; Colsancetine; Gynoxa; Indoson; Kemiderm; Kloramixin; Kloramixin D; Klorfeson; Naxogin Complex; Otolin; Particol; Ramicort; Spersadex Comp; ***Israel:*** Phenimixin; Tarocidin; Tarocidin D; Threolone; ***Ital.:*** Antibioptal; Betabioptal; Cloradex; Colbiocin; Cortison Chemicetina; Cosmiciclina; Dexoline; Eubetal Antibiotico; Idracemi; Iruxol; Vasofen; Vitecaf; Xantervit Antibiotico; ***Malaysia:*** De Icol; Spersadex Comp†; Spersadexoline; ***Mex.:*** Cloran Otico; Cloxona-O; Fibrase; Levodexan; Levofenil; Nispil; Ofodex; Otalgan; Otifar; Otolone†; Poral; Pre Clor; Soldrin; Solfranicol; Sulfa Cloran; Trecloran; Ulcoderma; ***Norw.:*** Spersadex med kloramfenikol; ***Philipp.:*** Dexanicol; Spersadex Compound; ***Port.:*** Cloranpectina†; Clorcorticil†; Medrivas Antibiotico; Predniftalmina; ***Rus.:*** Candibiotic (Кандибиотик); Colbiocin (Колбиоцин); Cortomycetin (Кортомицетин); Iruxol (Ируксол); Levomecol (Левомеколь); Levosin (Левосин); ***S.Afr.:*** Covomycin; Covomycin-D; Covotop; Spersacet C†; Spersadex Comp; Spersadexoline; ***Singapore:*** Spersadex Comp†; Spersadexoline†; ***Spain:*** Blefarida; Cloram Zinc; Cloran Hemidex; Cortison Chemicet Topica; Dermisone Epitelizante; Dexam Constric†; Fluo Fenic; Icol; Medrivas Antib; Otosedol Biotico; Predni Azuleno; ***Switz.:*** Spersacet C†; Spersadex Comp; Spersadexoline†; ***Thai.:*** Archifen; Chlorotracin; Dermasol; Levoptin; Spersadexoline; Vagicin; ***UK:*** Actinac; ***Venez.:*** Clorasona; Deicol†; Otandrol†.

Chloroxine *(USAN)*

Cloroxinum; 5,7-Dichlorochinolin-8-ol; 5,7-Dichloroquinolin-8-ol; Kloroxin.

Хлороксин

$C_9H_5Cl_2NO = 214.0.$
CAS — 773-76-2.

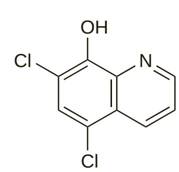

Profile

Chloroxine is a halogenated hydroxyquinoline with antibacterial and antifungal properties similar to those of clioquinol (p.254). It is used topically in the treatment of dandruff and seborrhoeic dermatitis of the scalp. It has also been given orally in preparations for gastrointestinal disorders.

Chloroxine is a component of halquinol (p.286).

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Endiaron; ***USA:*** Capitrol.

Multi-ingredient: ***Cz.:*** Endiform†; Triaderm; Triamcinolon Compositum†; Triamcinolon E; Triamcinolon-Galena†; ***Ital.:*** Beben Clorossina.

Chlorquinaldol *(BAN, rINN)*

Chlorochinaldol; Chlorquinaldolum; Clorquinaldol; Kloorikinaldoli; Klorkinaldol. 5,7-Dichloro-2-methylquinolin-8-ol.

Хлорхинальдол

$C_{10}H_7Cl_2NO = 228.1.$
CAS — 72-80-0.
ATC — D08AH02; G01AC03; P01AA04; R02AA11.
ATC Vet — QD08AH02; QG01AC03; QR02AA11.

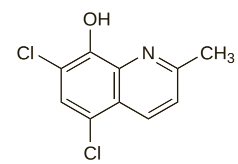

Pharmacopoeias. In *Pol.*

Profile

Chlorquinaldol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p.254). It is mainly applied topically in infected skin conditions and in vaginal infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Chlorosan†; ***Venez.:*** Agel†.

Multi-ingredient: ***Arg.:*** Nerisona C; ***Braz.:*** Bi-Nerisona; ***Chile:*** Bi-Nerisona; ***Cz.:*** Colposeptine†; Proctospre†; ***Denm.:*** Locoidol; ***Fin.:*** Locoidol†; ***Fr.:*** Nerisone C; ***Ger.:*** Nerisona C†; Proctospre†; ***Hong Kong:*** Colposeptine; Nerisone C; ***Indon.:*** Nerisona Combi; ***Irl.:*** Locoid C; ***Israel:*** Multiderm; ***Ital.:*** Impetex; Nerisona C; ***Mex.:*** Bi-Nerisona; ***Norw.:*** Locoidol; ***NZ:*** Locoid C; Nerisone C; ***Philipp.:*** Nerisona Combi; ***Pol.:*** Chlorchinaldin H; Gynalgin; Laticort-CH; ***Port.:*** Locoid C†; Nerisona C; Trophoseptine; ***Rus.:*** Gynalgin (Гиналгин); ***Singapore:*** Nerisone C†; ***Spain:*** Amplidermis; Claral Plus; Quinortar†; ***Switz.:*** Anginazol; ***Turk.:*** Colposeptine; Impetex; Nerisona C; ***UK:*** Locoid C; ***Venez.:*** Binerisona.

Chlortetracycline *(BAN, rINN)*

Chlortétracycline; Chlortetracyclinum; Clortetraciclina; Klooritetrasykliini; Klortetracyklin. (4S,4aS,5aS,6S,12aS)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide; 7-Chlorotetracycline.

Хлортетрациклин

$C_{22}H_{23}ClN_2O_8 = 478.9.$
CAS — 57-62-5.
ATC — A01AB21; D06AA02; J01AA03; S01AA02.
ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QJ51AA03; QS01AA02.

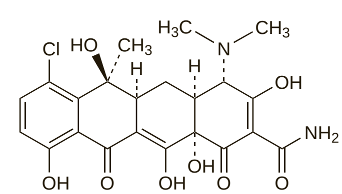

Chlortetracycline Bisulfate *(rINNM)*

Bisulfato de clortetraciclina; Chlortétracycline, Bisulfate de; Chlortetracycline Bisulphate *(BANM)*; Chlortetracyclini Bisulfas.

Хлортетрациклина Бисульфат

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Chlortetracycline Bisulfate). Store in airtight containers. Protect from light.

Chlortetracycline Hydrochloride *(BANM, rINNM)*

Chlorotetracykliny chlorowodorek; Chlortetraciklino hidrochloridas; Chlortétracycline, chlorhydrate de; Chlortetracyclini hydrochloridum; Chlortetracyklin-hydrochlorid; Hidrocloruro de clortetraciclina; Klooritetrasykliinihydrokloridi; Klórtetraciklin-hidroklorid; Klortetracyklinhydroklorid.

Хлортетрациклина Гидрохлорид

$C_{22}H_{23}ClN_2O_8,HCl = 515.3.$
CAS — 64-72-2.
ATC — A01AB21; D06AA02; J01AA03; S01AA02.
ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QS01AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Chlortetracycline Hydrochloride). The hydrochloride of a substance produced by the growth of certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Slightly soluble in water and in alcohol; it dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.3 to 3.3. Protect from light.
USP 31 (Chlortetracycline Hydrochloride). A yellow, odourless crystalline powder. Soluble 1 in 75 of water and 1 in 560 of alcohol; practically insoluble in acetone, in chloroform, in dioxan, and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.3 and 3.3. Store in airtight containers. Protect from light.

Profile

Chlortetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p.347) and is used as the hydrochloride, more often topically than orally. It is used as a 1% ophthalmic ointment and as a 3% ointment for application to the skin. It is poorly absorbed from the gastrointestinal tract compared with other tetracyclines but is sometimes given orally with other tetracycline derivatives.

Preparations

BP 2008: Chlortetracycline Eye Ointment; Chlortetracycline Ointment;
USP 31: Chlortetracycline Hydrochloride Ointment; Chlortetracycline Hydrochloride Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Austria: Aureomycin; ***Belg.:*** Aureomycin; Aureomycine; ***Fr.:*** Aureomycine; ***Ger.:*** Aureomycin; ***Hong Kong:*** Aureomycin†; Chlortralim; ***Ital.:*** Aureomicina; ***Malaysia:*** Chlortralim; ***Norw.:*** Aureomycin†; ***Pol.:*** Chlorocyclinum; ***Port.:*** Aurecil†; Aureodermil†; ***Singapore:*** Chlortralim; ***Spain:*** Aureomicina; Dermosa Aureomicina; ***Thai.:*** Aureomycin; Chlortralim.

Multi-ingredient: *Austria:* Aureocort; ***Braz.:*** Corciclen; ***Ger.:*** Aureodelf†; Aureomycin N†; ***Ital.:*** Aureocort; Aureomix; ***S.Afr.:*** Tritet; ***UK:*** Aureocort; Deteclo†.

Ciclacillin *(BAN, rINN)*

Ciclacilina; Ciclacilline; Ciclacillinum; Ciklacillin; Cyclacillin *(USAN)*; Siklasilliini; Wy-4508. (6*R*)-6-(1-Aminocyclohexanecarboxamido)penicillanic acid.

Циклациллин

$C_{15}H_{23}N_3O_4S = 341.4.$
CAS — 3485-14-1.

Pharmacopoeias. In *Jpn.*

Profile

Ciclacillin is an aminopenicillin with properties similar to those of ampicillin (p.204), although it is generally less active *in vitro*.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Cilinase†.

Cilastatin Sodium *(BANM, USAN, rINNM)*

Cilastatin sodná sůl; Cilastatina sódica; Cilastatine sodique; Cilastatinnatrium; Cilastatino natrio druska; Cilastatinum natricum; Cilasztatin-nátrium; L-642957; MK-791; Natrii Cilastatinas; Natrii Cilastatinum; Natriumsilastatinaatti; Natriumsilastatinat; Silastatininatrium; Silastatin Sodyum. (*Z*)-(*S*)-6-Carboxy-6-[(*S*)-2,2-dimethylcyclopropanecarboxamido]hex-5-enyl-L-cysteine, monosodium salt.

Натрий Циластатин

$C_{16}H_{25}N_2NaO_5S = 380.4.$
CAS — 82009-34-5 (cilastatin); 81129-83-1 (cilastatin sodium).

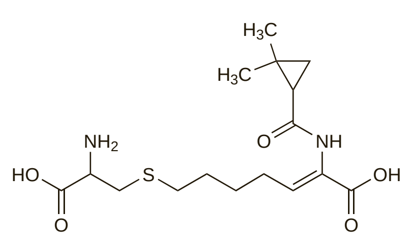

(cilastatin)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Cilastatin Sodium). A white or light yellow, hygroscopic, amorphous powder. Very soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone and in dichloromethane; very slightly soluble in dimethyl sulfoxide. A 1% solution in water has a pH of 6.5 to 7.5. Store at a temperature not exceeding 8° in airtight containers.
USP 31 (Cilastatin Sodium). A white to tan-coloured powder. Soluble in water and in methyl alcohol. pH of a 1% solution in water is between 6.5 and 7.5. Store at a temperature less than 8°.

Profile

Cilastatin is an inhibitor of dehydropeptidase I, an enzyme found in the brush border of the renal tubules. It is given as the sodium salt with the antibacterial imipenem (p.286) to prevent its renal metabolism to microbiologically inactive and potentially nephrotoxic products. This increases the concentrations of imipenem achieved in the urine and protects against any nephrotoxic effects, which were seen with high doses of imipenem given experimentally to *animals*.

Cilastatin has no antibacterial activity itself, and does not affect the antibacterial activity of imipenem.

Preparations

USP 31: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Proprietary Preparations (details are given in Part 3)
Pol.: Tienam.

Multi-ingredient: *Arg.:* Dixabiox; Imipecil; Imistatin; Klonam†; Zienam; ***Austral.:*** Primaxin; ***Austria:*** Zienam; ***Belg.:*** Tienam; ***Braz.:*** Penexil†; Tienam; ***Canad.:*** Primaxin; ***Chile:*** Inem; Tienam; ***Cz.:*** Tienam; ***Denm.:*** Tienam; ***Fin.:*** Tienam; ***Fr.:*** Tienam; ***Ger.:*** Zienam; ***Gr.:*** Primaxin; ***Hong Kong:*** Prepenem; Tienam; ***Hung.:*** Tienam; ***India:*** Cilanem; ***Indon.:*** Pelastin; Tienam; ***Israel:*** Tienam; ***Ital.:*** Imipem; Tenacid; Tienam; ***Malaysia:*** Bacqure; Tienam; ***Mex.:*** Arzomeba; Iminen; Tienam; ***Neth.:*** Tienam; ***Norw.:*** Tienam; ***NZ:*** Primaxin; ***Philipp.:*** Anipen; Tienam; ***Port.:*** Tienam; ***Rus.:*** Tienam (Тиенам); ***S.Afr.:*** Tienam; ***Singapore:*** Tienam; ***Spain:*** Tienam; ***Swed.:*** Tienam; ***Switz.:*** Tienam; ***Thai.:*** Tienam; ***Turk.:*** Tienam; ***UK:*** Primaxin; ***USA:*** Primaxin; ***Venez.:*** Zienam.

Cinoxacin *(BAN, USAN, rINN)*

64716; Azolinic Acid; Cinoxacine; Cinoxacino; Cinoxacinum; Compound 64716; Sinoksasiini. 1-Ethyl-1,4-dihydro-4-oxo-1,3-dioxolo[4,5-g]cinnoline-3-carboxylic acid.

Циноксацин

$C_{12}H_{10}N_2O_5 = 262.2.$
CAS — 28657-80-9.
ATC — J01MB06.
ATC Vet — QJ01MB06.

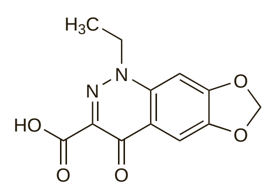

Pharmacopoeias. In *US.*
USP 31 (Cinoxacin). A white to yellowish-white, odourless crystalline solid. Insoluble in water and in most common organic solvents; soluble in alkaline solution. Store in airtight containers.

Adverse Effects and Precautions

As for Nalidixic Acid, p.304.

Cinoxacin should be used in reduced dosage, or not at all, in patients with renal impairment.

◊ References.

1. Stricker BHC, *et al.* Anaphylactic reactions to cinoxacin. *BMJ* 1988; **297:** 1434–5.

Interactions

As for Nalidixic Acid, p.304.

Antimicrobial Action

As for Nalidixic Acid, p.304. Cross-resistance with nalidixic acid has been shown.

Pharmacokinetics

Cinoxacin is rapidly and almost completely absorbed after oral doses. Peak serum concentrations of about 15 micrograms/mL occur 2 to 3 hours after a 500-mg dose. The plasma half-life is about 1 to 2 hours. Cinoxacin is more than 60% bound to plasma proteins.

Cinoxacin appears to be metabolised in the liver and is excreted via the kidney. Over 95% of a dose appears in the urine within 24 hours, over half as unaltered drug and the remainder as inactive metabolites. Mean urinary concentrations of about 300 micrograms/mL have been achieved during the first 4 hours after a 500-mg oral dose. Urinary excretion is reduced by probenecid and in patients with renal impairment.

Uses and Administration

Cinoxacin is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p.304). In the treatment of urinary-tract infections the usual oral dose is 500 mg twice daily; for prophylaxis 500 mg is given at bedtime.
For advice on use in renal impairment, see below.

Administration in renal impairment. Cinoxacin should be used in reduced dosage, or not at all, in patients with renal impairment.

Preparations

USP 31: Cinoxacin Capsules.

Proprietary Preparations (details are given in Part 3)
Gr.: Cinobactin†; ***Ital.:*** Cinobac; Cinocil; Cinoxen; Nossacin; Noxigram†; Uroc; Uronorm†; Uroxacin†; ***Mex.:*** Gugecin†; ***USA:*** Cinobac†.

Ciprofloxacin *(BAN, USAN, rINN)*

Bay-q-3939; Ciprofloksacinas; Ciprofloxacine; Ciprofloxacino; Ciprofloxacinum; Siprofloksasiini; Siprofloksasin; Siprofloxacin. 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

Ципрофлоксацин

$C_{17}H_{18}FN_3O_3 = 331.3.$
CAS — 85721-33-1.
ATC — J01MA02; S01AX13; S02AA15; S03AA07.
ATC Vet — QJ01MA02; QS01AX13; QS02AA15; QS03AA07.

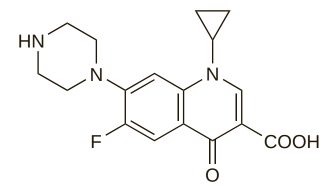

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Ciprofloxacin). An almost white or pale yellow, slightly hygroscopic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.
USP 31 (Ciprofloxacin). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Avoid temperatures above 40°. Protect from light.

Ciprofloxacin Hydrochloride *(BANM, USAN, rINNM)*

Bay-o-9867; Ciprofloksacino hidrochloridas; Ciprofloxacine, chlorhydrate de; Ciprofloxacin-hidroklorid; Ciprofloxacin-hydrochlorid; Ciprofloxacinhydroklorid; Ciprofloxacini hydrochloridum; Cyprofloksacyny chlorowodorek; Hidrocloruro de ciprofloxacino; Siprofloksasiinihydrokloridi; Siprofloksasin Hidroklorür. Ciprofloxacin hydrochloride monohydrate.

Ципрофлоксацина Гидрохлорид

$C_{17}H_{18}FN_3O_3,HCl,H_2O = 385.8.$
CAS — 86483-48-9 (anhydrous ciprofloxacin hydrochloride); 86393-32-0 (ciprofloxacin hydrochloride monohydrate).
ATC — S02AA15.
ATC Vet — QS02AA15.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Ciprofloxacin Hydrochloride). A pale yellow, slightly hygroscopic, crystalline powder. Soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in dichloromethane, and in ethyl acetate; slightly soluble in methyl alcohol. A 2.5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.
USP 31 (Ciprofloxacin Hydrochloride). Faintly yellowish to light yellow crystals. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; slightly soluble in acetic acid and in methyl alcohol; practically insoluble in acetone, in acetonitrile, in dichloromethane, in ethyl acetate, and in hexane. pH of a 2.5% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Ciprofloxacin Lactate *(BANM, rINNM)*

Ciprofloxacine, Lactate de; Ciprofloxacini Lactas; Lactato de ciprofloxacino.

Ципрофлоксацина Лактат

$C_{17}H_{18}FN_3O_3,C_3H_6O_3 = 421.4.$
CAS — 97867-33-9.
ATC — S02AA15.
ATC Vet — QS02AA15.

Incompatibility. Ciprofloxacin infusion is stated in UK licensed product information to have a pH of 3.9 to 4.5 and to be incompatible with injections chemically or physically unstable at this pH range. Incompatibility has been reported between ciprofloxacin and other drugs including some antibacterials.[1-5]

1. Lyall D, Blythe J. Ciprofloxacin lactate infusion. *Pharm J* 1987; **238:** 290.

2. Janknegt R, *et al.* Quinolones and penicillins incompatibility. *DICP Ann Pharmacother* 1989; **23:** 91–2.
3. Goodwin SD, *et al.* Compatibility of ciprofloxacin injection with selected drugs and solutions. *Am J Hosp Pharm* 1991; **48:** 2166–71.
4. Jim LK. Physical and chemical compatibility of intravenous ciprofloxacin with other drugs. *Ann Pharmacother* 1993; **27:** 704–7.
5. Elmore RL, *et al.* Stability and compatibility of admixtures of intravenous ciprofloxacin and selected drugs. *Clin Ther* 1996; **18:** 246–55.

Stability. For mention of loss of activity in ciprofloxacin solutions exposed to ultraviolet light see under Precautions, below.

Adverse Effects

Ciprofloxacin is generally well tolerated. The range of adverse effects associated with ciprofloxacin and the other fluoroquinolones is broadly similar to that of earlier quinolones such as nalidixic acid (p.304). They most often involve the gastrointestinal tract, CNS, or skin.

Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Pseudomembranous colitis, pancreatitis, and dysphagia have been reported rarely.

Headache, dizziness, confusion, insomnia, and restlessness are among the commonest effects on the CNS. Others include tremor, drowsiness, nightmares, visual and other sensory disturbances, hallucinations, psychotic reactions, depression, convulsions, and intracranial hypertension. Paraesthesia and peripheral neuropathy have also been reported.

In addition to rash and pruritus, hypersensitivity-type reactions affecting the skin have included, rarely, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity has occurred, although it may be more frequent with some other fluoroquinolones such as lomefloxacin and sparfloxacin. Anaphylaxis has been associated with ciprofloxacin and some other quinolones. As with other quinolones, reversible arthralgia or myalgia has sometimes occurred and joint erosions have been documented in immature *animals*. Tendon damage has also been reported.

Other adverse effects reported with ciprofloxacin include crystalluria, transient increases in serum creatinine or blood urea nitrogen and, rarely, acute renal failure secondary to interstitial nephritis. Elevated liver enzyme values, jaundice, and hepatitis have occurred, as have haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and, very rarely, pancytopenia, haemolytic anaemia or agranulocytosis. Cardiovascular adverse effects include tachycardia, hypotension, oedema, syncope, hot flushes, and sweating. Some fluoroquinolones may rarely cause prolongation of the QT interval and ventricular arrhythmias, including torsade de pointes (see below).

As with other antibacterials, superinfection with organisms not very susceptible to ciprofloxacin is possible. Such organisms include *Candida*, *Clostridium difficile*, and *Streptococcus pneumoniae*. There is some evidence that fluoroquinolone use may be associated with an increased risk of colonisation by MRSA.

Pain and irritation may occur at the site of infusion accompanied rarely by phlebitis or thrombophlebitis.

Adverse effects reported after ocular use of ciprofloxacin include local burning or discomfort, keratopathy, corneal staining, corneal precipitates or infiltrates, and photophobia.

Local discomfort, pain, or pruritus have occurred after use of ear drops containing ciprofloxacin.

◊ General reviews of the adverse effects of fluoroquinolones[1-7] and ciprofloxacin specifically.[8,9]

1. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; **28:** 352–64.
2. Ball P, *et al.* Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* 1999; **21:** 407–21.
3. Rubinstein E. History of quinolones and their side effects. *Chemotherapy* 2001; **47** (suppl 3): 3–8.
4. Leone R, *et al.* Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Safety* 2003; **26:** 109–20.
5. Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging* 2003; **20:** 289–302.
6. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S144–S157.
7. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007; **41:** 1859–66.
8. Segev S, *et al.* Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. *Clin Infect Dis* 1999; **28:** 299–308.
9. Heyd A, Haverstock D. Retrospective analysis of the safety profile of oral and intravenous ciprofloxacin in a geriatric population. *Clin Ther* 2000; **22:** 1239–50.

Effects on the blood. Haematological disturbances including thrombocytopenia,[1] eosinophilia,[2] leucopenia, and, very rarely, pancytopenia,[3] haemolytic anaemia,[4] or agranulocytosis have been reported with ciprofloxacin and some other fluoroquinolones. There has also been a case report[5] of haemolytic-uraemic syndrome associated with ciprofloxacin therapy; the patient recovered with routine supportive treatment (haemodialysis and plasma exchange) after the drug was stopped. In addition, transient reductions in factor VIII and von Willebrand's factor leading to bleeding in 2 patients receiving ciprofloxacin has been reported.[6] Neutropenia that developed in an elderly patient a few days after starting treatment with intravenous moxifloxacin resolved on stopping the drug.[7]

1. Starr JA, Ragucci KR. Thrombocytopenia associated with intravenous ciprofloxacin. *Pharmacotherapy* 2005; **25:** 1030–4.
2. Mofredj A, *et al.* Norfloxacin-induced eosinophilia in a cirrhotic patient. *Ann Pharmacother* 2002; **36:** 1107–8.
3. Deng JY, Tovar JM. Pancytopenia with levofloxacin therapy for pelvic inflammatory disease in an otherwise healthy young patient. *Ann Pharmacother* 2006; **40:** 1692–3.
4. Oh YR, *et al.* Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother* 2003; **37:** 1010–13.
5. Allan DS, *et al.* Ciprofloxacin-associated hemolytic-uremic syndrome. *Ann Pharmacother* 2002; **36:** 1000–1002.
6. Castaman G, Rodeghiero F. Acquired transitory von Willebrand syndrome with ciprofloxacin. *Lancet* 1994; **343:** 492.
7. Chang C-M, *et al.* Moxifloxacin-associated neutropenia in a cirrhotic elderly woman with lower extremity cellulitis. *Ann Pharmacother* 2008; **42:** 580–3.

Effects on the cardiovascular system. Prolongation of the QT interval,[1,2] sometimes progressing to torsade de pointes,[3-8] has been associated with ciprofloxacin and other fluoroquinolones although a review[9] considered that ciprofloxacin was least likely to produce this effect. Licensed product information recommends that gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin should be avoided in patients with predisposing factors or who are also receiving other drugs that are known to cause this effect and that norfloxacin should be used with caution in such situations.

1. Noel GJ, *et al.* Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003; **73:** 292–303.
2. Nykamp DL, *et al.* QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother* 2005; **39:** 543–6.
3. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001; **21:** 1468–72.
4. Owens RC, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy* 2002; **22:** 663–8.
5. Bertino JS, *et al.* Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002; **34:** 861–3.
6. Amankwa K, *et al.* Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. *Clin Pharmacol Ther* 2004; **75:** 242–7.
7. Dale KM, *et al.* Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007; **41:** 336–40.
8. Knorr JP, *et al.* Ciprofloxacin-induced Q-T interval prolongation. *Am J Health-Syst Pharm* 2008; **65:** 547–51.
9. Owens RC. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; **64:** 1091–1124.

Effects on the gastrointestinal tract. There have been case reports and studies of pseudomembranous colitis or superinfection with *Clostridium difficile* in patients given ciprofloxacin[1-6] and other fluoroquinolones[7-10] although some commentators have questioned this association and pointed out that other circumstances, such as poor infection control, may be significant contributory factors.

1. Cain DB, O'Connor ME. Pseudomembranous colitis associated with ciprofloxacin. *Lancet* 1990; **336:** 946.
2. Bates CJ, *et al.* Ciprofloxacin and Clostridium difficile infection. *Lancet* 1990; **336:** 1193.
3. Low N, Harries A. Ciprofloxacin and pseudomembranous colitis. *Lancet* 1990; **336:** 1510.
4. Hillman RJ, *et al.* Ciprofloxacin as a cause of Clostridium difficile-associated diarrhoea in an HIV antibody-positive patient. *J Infect* 1990; **21:** 205–7.
5. McFarland LV, *et al.* Ciprofloxacin-associated Clostridium difficile disease. *Lancet* 1995; **346:** 977–8.
6. Angel CA, *et al.* Severe ciprofloxacin-associated pseudomembranous colitis in an eight-year-old child. *J Pediatr Surg* 2004; **39:** 1590–2.
7. Dan M, Samra Z. Clostridium difficile colitis associated with ofloxacin therapy. *Am J Med* 1989; **87:** 479.
8. Ortiz-de-Saracho J, *et al.* Moxifloxacin-induced Clostridium difficile diarrhea. *Ann Pharmacother* 2003; **37:** 452–3.
9. Gaynes R, *et al.* Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004; **38:** 640–5.
10. Pépin J, *et al.* Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; **41:** 1254–60.

Effects on glucose metabolism. For the effects of fluoroquinolones, and in particular gatifloxacin, on blood glucose see under Gatifloxacin, p.281.

Effects on the kidneys. A review[1] of case reports of renal toxicity (including interstitial nephritis, acute renal failure, acute tubular necrosis, and crystalluria) associated with ciprofloxacin and other fluoroquinolones indicated that such toxicity, although potentially serious, was rare. It was also noted that nearly all patients developing acute renal failure were over 50 years of age. Another review,[2] confirming that the problem remained rare, noted that risk factors for quinolone-induced nephrotoxicity seemed to include the particular quinolone chosen, with ciprofloxacin the most often involved, as well as the use of high doses, patient age, inadequate hydration, and use of other nephrotoxic drugs or the presence of other processes likely to contribute to renal damage such as diabetes.

1. Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Safety* 2000; **22:** 479–85.
2. Montagnac R, *et al.* Les insuffisances rénales aiguës aux quinolones: revue générale à propos d'une observation avec cristallisation liée à la ciprofloxacine. *Nephrol Ther* 2005; **1:** 44–51.

Effects on the liver. Fluoroquinolones, including ciprofloxacin, may cause elevated liver enzyme values. In most patients this effect is transient and reversible without stopping the drug.

More serious cases of hepatotoxicity, including fatalities, have been reported both with ciprofloxacin[1-5] and with other fluoroquinolones[4,6-14] but they are rare. In many cases the patients were elderly and had co-morbid conditions.

1. Grassmick BK, *et al.* Fulminant hepatic failure possibly related to ciprofloxacin. *Ann Pharmacother* 1992; **26:** 636–9.
2. Sherman O, Beizer JL. Possible ciprofloxacin-induced acute cholestatic jaundice. *Ann Pharmacother* 1994; **28:** 1162–4.
3. Villeneuve J-P, *et al.* Suspected ciprofloxacin-induced hepatotoxicity. *Ann Pharmacother* 1995; **29:** 257–9.
4. Jones SE, Smith RH. Quinolones may induce hepatitis. *BMJ* 1997; **314:** 869.
5. Contreras MÁ, *et al.* Severe ciprofloxacin-induced acute hepatitis. *Eur J Clin Microbiol Infect Dis* 2001; **20:** 434–5.
6. González Carro P, *et al.* Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol* 2000; **95:** 1606.
7. Björnsson E, *et al.* Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. *Am J Gastroenterol* 2000; **95:** 3662–4.
8. Spahr L, *et al.* Acute fatal hepatitis related to levofloxacin. *J Hepatol* 2001; **35:** 308–9.
9. Karim A, *et al.* Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. *Clin Infect Dis* 2001; **33:** 2088–90.
10. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; **97:** 1853–4.
11. Coleman CI, *et al.* Possible gatifloxacin-induced fulminant hepatic failure. *Ann Pharmacother* 2002; **36:** 1162–7.
12. Schwalm J-D, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. *CMAJ* 2003; **168:** 847–8.
13. Cheung O, *et al.* Gatifloxacin-induced hepatotoxicity and acute pancreatitis. *Ann Intern Med* 2004; **140:** 73–4.
14. Çoban Ş, *et al.* Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. *Ann Pharmacother* 2005; **39:** 1737–40.

Effects on the musculoskeletal system. Reversible arthralgia has sometimes occurred with the fluoroquinolones;[1] joint erosions have been documented in immature *animals*. In a report,[2] treatment with pefloxacin may have contributed to the destructive arthropathy that occurred in a 17-year-old youth. For a discussion of the use of fluoroquinolones in children and adolescents, see Administration in Children, under Precautions, below.

There have been reports[3-7] of tendinitis and tendon rupture associated with fluoroquinolones. By July 1995, the UK CSM[5] had received 21 reports of tendon damage, often of the Achilles tendon, associated with these antibacterials—11 with ciprofloxacin and 10 with ofloxacin. In a later case-control study[8] of a cohort of 46 776 users of fluoroquinolones between July 1992 to June 1998, 704 had Achilles tendinitis and 38 had Achilles tendon rupture; the adjusted relative risk of Achilles tendon disorders with current use was 1.9. The risk of tendon damage is increased by use with corticosteroids and is more common with increasing age:[5] the case-control study[8] found that the relative risk for current users rose to 3.2 among those aged 60 and over, and to 6.2 in those in this age group also using corticosteroids. Another case-control study[9] using data from 1988 to 1998 held on a different UK general practice database reported similar findings and concluded that ofloxacin was associated with a higher risk of tendon damage than other fluoroquinolones. A review[10] of the literature between 1966 and 2001 revealed 98 case reports of fluoroquinolone-associated tendon damage. Of these, 36 were associated with pefloxacin therapy and 25 with ciprofloxacin; ofloxacin was associated with 6 cases. Renal disease or impairment was also considered as a risk factor.

Onset may be rapid: rupture has occurred within 48 hours of starting therapy.[11] The CSM[5] warned that at the first sign of pain or inflammation the fluoroquinolone should be withdrawn and the affected limb rested until the tendon symptoms had resolved.

Similar warnings have been issued in other countries, but some cases have continued to be reported.[12] In the USA the FDA has required a warning to be added to prescribing information for the fluoroquinolones stating that there is an increased risk in patients over 60, in kidney, heart, and lung transplant recipients, and with use of concomitant corticosteroid therapy.[13]

There have been reports[14,15] of rhabdomyolysis in patients given fluoroquinolones, including one fatality associated with levofloxacin therapy.[14]

1. Alfaham M, *et al.* Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. *BMJ* 1987; **295:** 699.
2. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; **7:** 310–14.
3. Huston KA. Achilles tendinitis and tendon rupture due to fluoroquinolone antibiotics. *N Engl J Med* 1994; **331:** 748.
4. Szarfman A, *et al.* More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; **332:** 193.
5. Committee on Safety of Medicines/Medicines Control Agency. Tendon damage associated with quinolone antibiotics. *Current Problems* 1995; **21:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
6. Carrasco JM, *et al.* Tendinitis associated with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 120.
7. Mathis AS, *et al.* Levofloxacin-associated Achilles tendon rupture. *Ann Pharmacother* 2003; **37:** 1014–17.
8. van der Linden PD, *et al.* Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ* 2002; **324:** 1306–7.
9. van der Linden PD, *et al.* Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; **163:** 1801–7.
10. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003; **36:** 1404–10.
11. Committee on Safety of Medicines/Medicines Control Agency. Reminder: fluoroquinolone antibiotics and tendon disorders. *Current Problems* 2002; **28:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
12. Adverse Drug Reactions Advisory Committee (ADRAC). Fluoroquinolone antibiotics: remember tendon disorders. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 12/07/06)
13. FDA. Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin and generic ofloxacin)] (issued 8th July, 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm (accessed 12/08/08)
14. Petitjeans F, *et al.* A case of rhabdomyolysis with fatal outcome after a treatment with levofloxacin. *Eur J Clin Pharmacol* 2003; **59:** 779–80.
15. Hsiao S-H, *et al.* Acute rhabdomyolysis associated with ofloxacin/levofloxacin therapy. *Ann Pharmacother* 2005; **39:** 146–9.

Effects on the nervous system. By 1991 the UK CSM[1] had received 26 reports of convulsions associated with ciprofloxacin, 1 with norfloxacin, and 1 with ofloxacin. It was noted that convulsions could occur both in patients with epilepsy and in those with no history of convulsions. Generalised seizures have been reported in patients given gatifloxacin[2] and levofloxacin.[3,4] Seizures have also been associated with the use of ear drops containing ciprofloxacin.[5] All 5 case reports[2-5] involved patients aged 65 years and over; of these, 1 had a history (although unclear) of seizures,[2] 3 had chronic renal impairment,[3-5] and 1 had neither.[3]

Other reports of CNS toxicity associated with ciprofloxacin have included eosinophilic meningitis,[6] delirium,[7] and acute psychoses.[8,9] Peripheral neuropathy,[10] dysaesthesia,[11] catatonia,[12] hemiparesis,[13] and tinnitus[14] have also been reported. Acute psychosis occurred[15] in a patient using ciprofloxacin eye drops. A review[16] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials including ciprofloxacin and ofloxacin.

There have also been reports of sleep disturbances[17] and of a Tourette-like syndrome[18] associated with ofloxacin. Ataxia[19] and hallucinations[20] have been reported with the use of gatifloxacin.

1. Committee on Safety of Medicines. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
2. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. *Ann Pharmacother* 2004; **38:** 235–7.
3. Kushner JM, *et al.* Seizures associated with fluoroquinolones. *Ann Pharmacother* 2001; **35:** 1194–8.
4. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
5. Orr CF, Rowe DB. Eardrop attacks: seizures triggered by ciprofloxacin eardrops. *Med J Aust* 2003; **178:** 343.
6. Asperilla MO, *et al.* Eosinophilic meningitis associated with ciprofloxacin. *Am J Med* 1989; **87:** 589–90.
7. Jay GT, Fitzgerald JM. Ciprofloxacin-induced delirium. *Ann Pharmacother* 1997; **31:** 252.
8. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. *Am J Med* 1991; **90:** 528–9.
9. Reeves RR. Ciprofloxacin-induced psychosis. *Ann Pharmacother* 1992; **26:** 930–1.
10. Aoun M, *et al.* Peripheral neuropathy associated with fluoroquinolones. *Lancet* 1992; **340:** 127.
11. Zehnder D, *et al.* Painful dysaesthesia with ciprofloxacin. *BMJ* 1995; **311:** 1204.
12. Akhtar S, Ahmad H. Ciprofloxacin-induced catatonia. *J Clin Psychiatry* 1993; **54:** 115–16.
13. Rosolen A, *et al.* Acute hemiparesis associated with ciprofloxacin. *BMJ* 1994; **309:** 1411.
14. Paul J, Brown NM. Tinnitus and ciprofloxacin. *BMJ* 1995; **311:** 232.
15. Tripathi A, *et al.* Acute psychosis following the use of topical ciprofloxacin. *Arch Ophthalmol* 2002; **120:** 665–6.
16. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; **22:** 71–81.
17. Upton C. Sleep disturbance in children treated with ofloxacin. *BMJ* 1994; **309:** 1411.
18. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. *Ann Pharmacother* 1996; **30:** 138–41.
19. Mohan N, *et al.* Oral gatifloxacin-induced ataxia. *Am J Health-Syst Pharm* 2002; **59:** 1894.
20. Adams M, Tavakoli H. Gatifloxacin-induced hallucinations in a 19-year-old man. *Psychosomatics* 2006; **47:** 360.

Hypersensitivity. Hypersensitivity and skin reactions have been associated with ciprofloxacin and other fluoroquinolones. Reports have included anaphylaxis (which has sometimes been fatal, and may occur after the first dose),[1-7] serum sickness,[8] Stevens-Johnson syndrome,[9] toxic epidermal necrolysis (sometimes fatal),[10-17] laryngeal oedema,[18] and vasculitis.[19-21] Fatal vasculitis has been reported with ofloxacin.[22]

1. Davis H, *et al.* Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989; **111:** 1041–3.
2. Peters B, Pinching AJ. Fatal anaphylaxis associated with ciprofloxacin in a patient with AIDS related complex. *BMJ* 1989; **298:** 605.
3. Wurtz RM, *et al.* Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989; **i:** 955–6.
4. Assouad M, *et al.* Anaphylactoid reactions to ciprofloxacin. *Ann Intern Med* 1995; **122:** 396–7.
5. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000; **20:** 1520–3.
6. Ho DY, *et al.* Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003; **37:** 1018–23.
7. Sachs B, *et al.* Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Safety* 2006; **29:** 1087–1100.
8. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother* 1990; **34:** 904–5.
9. Hällgren J, *et al.* Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol* 2003; **49** (suppl): S267–S269.
10. Tham TCK, *et al.* Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet* 1991; **338:** 522.
11. Moshfeghi M, Mandler HD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1993; **27:** 1467–9.
12. Yerasi AB, Oertel MD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1996; **30:** 297.
13. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis: a case report. *Dermatology* 1997; **195:** 173–5.
14. Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacother* 2001; **35:** 1388–90.
15. Sahin MT, *et al.* Norfloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 768–70.
16. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
17. Islam AFMS, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 1136–7.
18. Baciewicz AM, *et al.* Laryngeal edema related to ciprofloxacin therapy. *Ann Pharmacother* 1992; **26:** 1456.
19. Choe U, *et al.* Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; **320:** 257–8.
20. Stubbings J, *et al.* Cutaneous vasculitis due to ciprofloxacin. *BMJ* 1992; **305:** 29.
21. Drago F, *et al.* Henoch-Schönlein purpura induced by fluoroquinolones. *Br J Dermatol* 1994; **131:** 448.
22. Pace JL, Gatt P. Fatal vasculitis associated with ofloxacin. *BMJ* 1989; **299:** 658.

Superinfection. Superinfection with *Streptococcus pneumoniae* has been reported in patients receiving ciprofloxacin.[1-3] For references to superinfection with *Clostridium difficile* and associated pseudomembranous colitis, see under Effects on the Gastrointestinal Tract, above.

Fungal otitis externa is also associated with the use of ear drops containing fluoroquinolones.[4]

1. Righter J. Pneumococcal meningitis during intravenous ciprofloxacin therapy. *Am J Med* 1990; **88:** 548.
2. Gordon JJ, Kauffman CA. Superinfection with Streptococcus pneumoniae during therapy with ciprofloxacin. *Am J Med* 1990; **89:** 383–4.
3. Lee BL, *et al.* Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991; **325:** 520–1.
4. Schrader N, Isaacson G. Fungal otitis externa: its association with fluoroquinolone eardrops. *Pediatrics* 2003; **111:** 1123.

Precautions

Ciprofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders. Care is also necessary in those with renal impairment, G6PD deficiency, or myasthenia gravis. An adequate fluid intake should be maintained during treatment with ciprofloxacin and excessive alkalinity of the urine avoided because of the risk of crystalluria.

Since ciprofloxacin and related fluoroquinolones have, like nalidixic acid, been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these drugs should not generally be used in patients aged under 18 years (see also below), pregnant women, or breast-feeding mothers (but see also below) unless the benefits outweigh the risks. Tendon damage may occur rarely with fluoroquinolones (see Effects on the Musculoskeletal System, above) and treatment should be stopped if patients experience tendon pain, inflammation, or rupture; subsequent use of fluoroquinolones is contra-indicated in these patients.

Exposure to strong sunlight or sunlamps should be avoided during treatment with ciprofloxacin. The ability to drive or operate machinery may be impaired, especially when alcohol is also taken.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, above) and should be avoided or used with caution in patients with QT prolongation or relevant risk factors such as uncorrected electrolyte disturbances, bradycardia, or pre-existing cardiac disease. Certain drugs may also increase the risk (see Interactions, below).

Ciprofloxacin and other fluoroquinolones should be avoided in MRSA infections because of the high level of resistance.

Administration in children. Since ciprofloxacin and other fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks.[1-3] For example, ciprofloxacin is licensed in some countries for use in the prophylaxis and treatment of inhalational anthrax and also in the treatment of certain infections in those under 18 years of age (see under Uses and Administration, below).

A comparative cohort study[2] involving about 500 children and adolescents found that the incidence of musculoskeletal adverse effects was higher (10 cases out of 264 patients) in those taking fluoroquinolones (ciprofloxacin, ofloxacin, or pefloxacin) than in those taking other antibacterials (1 out of 237). In the former group of patients, these adverse effects, mainly arthralgias, were reversible and were most frequent with pefloxacin therapy.

1. Burstein GR, *et al.* Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002; **35** (suppl 2): S191–S199.
2. Chalumeau M, *et al.* Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Abstract: *Pediatrics* 2003; **111:** 1427–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/6/e714 (accessed 01/11/06)
3. American Academy of Pediatrics Committee on Infectious Diseases. The use of systemic fluoroquinolones. *Pediatrics* 2006; **118:** 1287–92.

Breast feeding. Ciprofloxacin was found to be undetectable in the serum of a breast-fed infant whose mother took ciprofloxacin 500 mg daily for 10 days.[1] In another study[2] involving 30 women who underwent termination of pregnancy, 10 each were given ciprofloxacin, ofloxacin, or pefloxacin respectively, and all 3 drugs were found to be highly concentrated in breast milk with ratios exceeding 75% of the simultaneous serum concentrations 2 hours after a dose. It was concluded that, because fluoroquinolones had been shown to cause arthropathy in young *animals*, their potential benefits should be weighed against the risk to the infant before they were considered for use in breast-feeding women. The American Academy of Pediatrics[3] considers that the use of ciprofloxacin is usually compatible with breast feeding.

1. Gardner DK, *et al.* Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. *Clin Pharm* 1992; **11:** 352–4.
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Exposure to UV light. Loss of antibacterial activity has been reported after irradiation of ciprofloxacin solutions by UV light.[1] In addition to the possible hazard of photosensitivity reactions, a reduction in both cutaneous and circulating levels of ciprofloxacin was predicted in patients exposed to sunlight through window glass or the longer wavelength UVA radiation from sunbeds.[1]

1. Phillips G, *et al.* The loss of antibiotic activity of ciprofloxacin by photodegradation. *J Antimicrob Chemother* 1990; **26:** 783–9.

Interference with diagnostic tests. Ciprofloxacin did not interfere with determination of urinary-glucose concentrations carried out with *Clinitest*, *Diastix*, or *Tes-Tape*,[1] but pseudoglycosuria, a false-positive reaction for glucose in urine, has been reported with *BM-Test-7* in elderly patients given ciprofloxacin for urinary-tract infections.[2]

1. Tartaglione TA, Flint NB. Effect of imipenem-cilastatin and ciprofloxacin on tests for glycosuria. *Am J Hosp Pharm* 1985; **42:** 602–5.
2. Drysdale L, *et al.* Pseudoglycosuria and ciprofloxacin. *Lancet* 1988; **ii:** 961.

Myasthenia gravis. Caution is advised in patients with myasthenia gravis given fluoroquinolones after reports of the possible exacerbation of symptoms in a patient,[1] and unmasking of subclinical myasthenia gravis in another,[2] by ciprofloxacin. Exacerbation of myasthenia gravis has also been reported with other fluoroquinolones including norfloxacin,[3] ofloxacin,[4] and pefloxacin.[5]

1. Moore B, *et al.* Possible exacerbation of myasthenia gravis by ciprofloxacin. *Lancet* 1988; **i:** 882.
2. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis. *BMJ* 1990; **301:** 818.
3. Rauser EH, *et al.* Exacerbation of myasthenia gravis by norfloxacin. *DICP Ann Pharmacother* 1990; **24:** 207–8.
4. Azevedo E, *et al.* Probable exacerbation of myasthenia gravis by ofloxacin. *J Neurol* 1993; **240:** 508.
5. Vial T, *et al.* Aggravation d'une myasthénie sous péfloxacine. *Rev Neurol (Paris)* 1995; **151:** 286–7.

Interactions

Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as theophylline and tizanidine, that are metabolised by this isoenzyme. Use of ciprofloxacin with tizanidine is contra-indicated, although theophylline may be used providing its dose is reduced and concentrations monitored.

Ciprofloxacin is reported to enhance the effect of oral anticoagulants such as warfarin and the oral antidiabetic glibenclamide. Severe hypoglycaemia, sometimes fatal, has occurred in patients also taking glibenclamide. Renal tubular secretion of methotrexate may be inhibited by ciprofloxacin, potentially increasing its toxicity.

The excretion of ciprofloxacin or related drugs is reduced and plasma concentrations may be increased by probenecid. Cations such as aluminium, calcium, magnesium, or iron reduce the absorption of oral ciprofloxacin or related drugs when given together. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H_2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.

Transient increases in serum creatinine have occurred when ciprofloxacin is given with ciclosporin; monitoring of serum creatinine concentrations is recommended. Altered serum concentrations of phenytoin have been reported in patients also receiving ciprofloxacin.

Further details concerning some of these interactions, and others, are given below.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, above) and should be avoided in patients also receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).

For physical or chemical incompatibilities with ciprofloxacin, see above.

Analgesics. Use of *fenbufen* with fluoroquinolones may increase the incidence of fluoroquinolone CNS adverse effects. Reviews[1,2] have noted cases of convulsions associated with the use of fenbufen and enoxacin reported to the Japanese regulatory authorities. The UK CSM[3] has recognised that convulsions may occur due to an interaction between the fluoroquinolones and *NSAIDs*; by 1991, 3 such interactions had been reported to them. Adverse neurological effects have also been reported in a patient receiving *naproxen* and chloroquine when ciprofloxacin was given, which abated when the antirheumatic drugs were stopped.[4]

Ciprofloxacin also interacts with *opioid analgesics*; peak serum concentrations of ciprofloxacin given by mouth pre-operatively were significantly reduced when intramuscular *papaveretum* was injected.[5] In the UK, licensed product information for ciprofloxacin tablets recommends that opioid premedication should not be used if ciprofloxacin is given for surgical infection prophylaxis.

1. Janknegt R. Drug interactions with quinolones. *J Antimicrob Chemother* 1990; **26** (suppl D): 7–29.
2. Christ W. Central nervous system toxicity of quinolones: human and animal findings. *J Antimicrob Chemother* 1990; **26** (suppl B): 219–25.
3. Committee on Safety of Medicines. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
4. Rollof J, Vinge E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. *Ann Pharmacother* 1993; **27:** 1058–9.
5. Morran C, *et al.* Brief report: pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. *Am J Med* 1989; **87** (suppl 5A): 86S–88S.

Antacids and metal ions. The absorption of ciprofloxacin and other fluoroquinolones is reduced by *antacids* containing *aluminium* or *magnesium* and also by *calcium*, *iron*, and *zinc* salts.[1] *Sucralfate* releases aluminium ions in the stomach and thereby reduces the absorption of ciprofloxacin[2,3] and other fluoroquinolones, including norfloxacin,[4] ofloxacin, and sparfloxacin.[5] In addition, antacids or oral iron preparations might antagonise the antibacterial activity of fluoroquinolones within the gut lumen.[6] *Dairy products* with a high calcium content may also interfere with the absorption of some fluoroquinolones.[7-9] *Enteral feeds*, which contain cations, have also been found to reduce absorption of ciprofloxacin.[10] A reduction in ciprofloxacin bioavailability has also been reported after *chewable tablets* of didanosine which contain aluminium and magnesium ion buffering agents.[11]

It is recommended that oral ciprofloxacin should be given at least 2 hours before or 6 hours after such products; similar advice also applies to other fluoroquinolones.

1. Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones: 1995 update. *Drug Safety* 1995; **12:** 314–33.
2. Garrelts JC, *et al.* Sucralfate significantly reduces ciprofloxacin concentrations in serum. *Antimicrob Agents Chemother* 1990; **34:** 931–3.
3. Van Slooten AD, *et al.* Combined use of ciprofloxacin and sucralfate. *DICP Ann Pharmacother* 1991; **25:** 578–82.
4. Parpia SH, *et al.* Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; **33:** 99–102.
5. Kamberi M, *et al.* The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; **49:** 98–103.
6. Lewin CS, Smith JT. 4-Quinolones and multivalent ions. *J Antimicrob Chemother* 1990; **26:** 149.
7. Neuvonen PJ, *et al.* Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1991; **50:** 498–502.
8. Kivistö KT, *et al.* Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother* 1992; **36:** 489–91.
9. Neuvonen PJ, Kivistö KT. Milk and yoghurt do not impair the absorption of ofloxacin. *Br J Clin Pharmacol* 1992; **33:** 346–8.
10. Healy DP, *et al.* Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother* 1996; **40:** 6–10.
11. Sahai J, *et al.* Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; **53:** 292–7.

Antibacterials. The simultaneous use of parenteral ciprofloxacin and *azlocillin* has resulted in higher and more prolonged serum concentrations of ciprofloxacin.[1] Steady-state plasma concentrations of moxifloxacin are significantly reduced when given with *rifampicin* and *isoniazid* for the treatment of tuberculosis.[2]

1. Barriere SL, *et al.* Alteration in the pharmacokinetic disposition of ciprofloxacin by simultaneous administration of azlocillin. *Antimicrob Agents Chemother* 1990; **34:** 823–6.
2. Nijland HMJ, *et al.* Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; **45:** 1001–7.

Anticoagulants. For reports of ciprofloxacin and other fluoroquinolones enhancing the effect of oral anticoagulants, see under *Warfarin*, p.1428.

Antidiabetics. For reference to elevated *glibenclamide* concentrations in patients who were also given ciprofloxacin, see p.462.

Antiepileptics. For conflicting reports of the effect of ciprofloxacin on serum-*phenytoin* concentrations, see p.498.

Antifungals. Both *fluconazole* and levofloxacin can prolong the QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Antimigraine drugs. For a recommendation to reduce the dosage of *zolmitriptan* when given with ciprofloxacin, see p.628.

Antineoplastics. Absorption of oral ciprofloxacin appears to be reduced after cytotoxic chemotherapy.[1]

For reference to the effect of ciprofloxacin on the pharmacokinetics of *cyclophosphamide*, see p.703.

1. Johnson EJ, *et al.* Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1990; **25:** 837–42.

Antivirals. Both ciprofloxacin and *foscarnet* can cause convulsions and 2 patients developed generalised tonic-clonic seizures while receiving the drugs together.[1]

For reference to reduction of ciprofloxacin bioavailability due to the antacid content of chewable *didanosine* tablets, see under Antacids and Metal Ions, above.

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Anxiolytics. For reference to the effect of ciprofloxacin on the pharmacokinetics of *diazepam*, *midazolam*, and *temazepam*, see under Diazepam, p.989.

Immunosuppressants. For reference to possible interaction between fluoroquinolones and *ciclosporin*, see Quinolones, p.1825. For a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with norfloxacin or norfloxacin plus metronidazole, see p.1837.

Muscle relaxants. For a report of ciprofloxacin increasing the plasma concentrations of *tizanidine*, see p.1898.

Xanthines. Ciprofloxacin and other fluoroquinolones (to a greater or lesser extent) decrease the clearance of *theophylline* (p.1143) and *caffeine* (p.1117) from the body. Seizures have occurred in patients given ciprofloxacin and theophylline and in one such report[1] serum-theophylline concentrations were normal.

1. Bader MB. Role of ciprofloxacin in fatal seizures. *Chest* 1992; **101:** 883–4.

Antimicrobial Action

Ciprofloxacin is bactericidal and acts by inhibiting DNA gyrase and topoisomerase IV, which are essential enzymes in the reproduction of bacterial DNA. It has a broader spectrum of activity and is more potent *in vitro* than the non-fluorinated quinolone nalidixic acid although resistance to many species or strains previously sensitive is emerging. Activity may be reduced in acid media and in the presence of urine but not of serum.

Spectrum of activity. Among Gram-negative aerobic bacteria, ciprofloxacin may be active *in vitro* against Enterobacteriaceae, including *Escherichia coli* and *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. It may also exhibit activity against *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. *H. influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *N. meningitidis* are all sensitive. Other Gram-negative aerobic bacteria reported to be sensitive to ciprofloxacin have included *Gardnerella vaginalis*, *Helicobacter pylori*, *Legionella* spp., *Pasteurella multocida*, and *Vibrio* spp. Variable activity has been reported against *Acinetobacter* spp., *Brucella melitensis*, and *Campylobacter* spp.

Among Gram-positive aerobic bacteria, ciprofloxacin is active against staphylococci, including penicillinase-producing and penicillinase-nonproducing strains, and against some MRSA. Streptococci, in particular *Streptococcus pneumoniae* and enterococci, are less susceptible. Other Gram-positive bacteria sensitive to ciprofloxacin *in vitro* are *Bacillus* spp.; variable activity has been noted for *Corynebacterium* spp.

Most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*, are resistant to ciprofloxacin, although some other *Clostridium* spp. may be susceptible.

Ciprofloxacin has some activity against mycobacteria, mycoplasmas, rickettsias, *Chlamydia trachomatis*, and *Ureaplasma urealyticum*.

Acquired resistance. Resistant strains, particularly of MRSA, *Ps. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *C. jejuni*, *N. gonorrhoeae*, and *Str. pneumoniae* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance geographically. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma-mediated resistance has recently been noted.

Pharmacokinetics

Ciprofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70 to 80% and a peak serum concentration of about 2.4 micrograms/mL occurs 1 to 2 hours after a 500-mg oral dose. Absorption of ciprofloxacin tablets may be delayed by the presence of food, but is not substantially affected overall.

Plasma protein binding ranges from 20 to 40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. It appears in the CSF, but concentrations are only about 10% of those in serum when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed into breast milk. High concentrations are achieved in bile.

The elimination half-life is about 3 to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. However, no dose adjustment is usually necessary in patients with renal impairment unless it is severe; similarly, usual doses can be given to the elderly except in those with severe renal impairment. There is limited information on the effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of the liver. With one or two exceptions, most studies have shown that the pharmacokinetics of ciprofloxacin are not markedly affected by cystic fibrosis.

Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified. Oxociprofloxacin appears to be the major urinary metabolite and sulfociprofloxacin the primary faecal metabolite. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid; it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as metabolites. Up to 70% of a parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 20 to 35% of an oral dose and 15% of an intravenous dose.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

General pharmacokinetics. Reviews of the pharmacokinetics of ciprofloxacin[1] and the fluoroquinolones in general.[2,3]

1. Vance-Bryan K, *et al.* Clinical pharmacokinetics of ciprofloxacin. *Clin Pharmacokinet* 1990; **19:** 434–61.
2. Aminimanizani A, *et al.* Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001; **40:** 169–187.
3. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S127–S135.

Uses and Administration

Ciprofloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid (see Antimicrobial Action, above) and more favourable pharmacokinetics allowing its use in systemic infections. It has been used in the treatment of infections including anthrax, biliary-tract infections, infected bites and stings, bone and joint infections, cat scratch disease, chancroid, exacerbations of cystic fibrosis, ear, nose, and throat infections (including otitis externa, otitis media, and sinusitis), HACEK endocarditis, gastro-enteritis (including travellers' diarrhoea and campylobacter enteritis, cholera, salmonella enteritis, shigellosis, and yersinia enteritis), gonorrhoea, granuloma inguinale, infections in immunocompromised patients (neutropenia), legionnaires' disease, pelvic inflammatory disease, peritonitis, plague, lower respiratory-tract infections (including pseudomonal infections in cystic fibrosis, but excluding infections due to *Streptococcus pneumoniae* such as pneumococcal pneumonia), rickettsial infections (including Q fever, spotted fevers, and typhus), septicaemia, skin infections (including soft-tissue infections), typhoid and paratyphoid fever, and urinary-tract infections including chronic bacterial prostatitis. Ciprofloxacin is used for meningococcal meningitis prophylaxis. It is also used for surgical infection prophylaxis and in the treatment of nontuberculous mycobacterial infections and tuberculosis. Ciprofloxacin is used topically in the treatment of eye and ear infections.

For details of all these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ciprofloxacin is given orally as the hydrochloride or base, by intravenous infusion as the lactate, and in eye drops, eye ointment, or ear drops as the hydrochloride. Doses and strengths are expressed in terms of the base. Ciprofloxacin hydrochloride 291.1 mg is equivalent to about 250 mg of ciprofloxacin. Ciprofloxacin lactate 127 mg is equivalent to about 100 mg of ciprofloxacin.

The usual adult oral dose of ciprofloxacin ranges from 250 to 750 mg twice daily depending on the severity and nature of the infection. Modified-release preparations for once-daily dosage are available in some countries. The usual adult intravenous dose is 200 to 400 mg twice daily, given over 30 to 60 minutes as a solution containing the equivalent of 1 to 2 mg/mL.

Women with acute uncomplicated cystitis may be given an oral dose of 100 to 250 mg twice daily for 3 days or 100 mg twice daily by intravenous infusion. A 28-day course of treatment with an oral dose of 500 mg twice daily or an intravenous dose of 400 mg twice daily should be given for chronic bacterial prostatitis. Bone and joint infections should be treated with an oral dose of 500 to 750 mg twice daily or an intravenous dose of 400 mg two or three times daily for 4 to 6 weeks. Intravenous infusions of 400 mg three times daily have also been recommended in severe or complicated lower respiratory tract or skin infections, nosocomial pneumonia, and with piperacillin for empirical treatment of febrile neutropenic patients.

For treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with initial intravenous doses of 400 mg twice daily followed by oral doses of 500 mg twice daily is recommended; although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of 500 to 750 mg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

Doses should be reduced in patients with severe renal impairment (see below).

Single oral doses of 250 or 500 mg or single intravenous doses of 100 mg are used for the treatment of gonorrhoea, depending upon patterns of resistance. A single oral dose of 750 mg is used for surgical infection prophylaxis, given 60 to 90 minutes before the procedure. Although unlicensed in the UK, the *BNF* suggests a single oral dose of 500 mg for meningococcal meningitis prophylaxis.

For details of doses in children, including infants and adolescents, see below.

For corneal ulcers and superficial ocular infections caused by susceptible strains of bacteria ciprofloxacin is given as the hydrochloride in eye drops and eye ointment containing the equivalent of 0.3% of ciprofloxacin.

Ciprofloxacin is also used topically as the hydrochloride in ear drops containing the equivalent of 0.2 or 0.3% of ciprofloxacin, usually with a corticosteroid such as dexamethasone or hydrocortisone, for the treatment of otitis externa and chronic suppurative otitis media caused by susceptible strains of bacteria.

◊ General references to fluoroquinolones[1-9] including ciprofloxacin specifically.[10-13]

1. von Rosenstiel N, Adam D. Quinolone antibacterials: an update of their pharmacology and therapeutic use. *Drugs* 1994; **47:** 872–901.
2. Balfour JA, Goa KL, eds. Proceedings of the 5th International symposium on new quinolones. *Drugs* 1995; **49** (suppl 2): 1–505.
3. Walker RC. The fluoroquinolones. *Mayo Clin Proc* 1999; **74:** 1030–7.
4. Smith A, *et al.* Fluoroquinolones: place in ocular therapy. *Drugs* 2001; **61:** 747–61.
5. Schaeffer AJ. The expanding role of fluoroquinolones. *Am J Med* 2002; **113** (suppl 1A): 45S–54S.
6. Zhanel GG, *et al.* A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 2002; **62:** 13–59.
7. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. *Drugs* 2004; **64:** 1359–73.
8. Shams WE, Evans ME. Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. *Drugs* 2005; **65:** 949–91.
9. Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis* 2005; **41** (suppl 2): S113–S119.
10. Davis R, *et al.* Ciprofloxacin: an updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; **51:** 1019–74.
11. Campoli-Richards DM, *et al.* Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1998; **35:** 373–447.
12. Gould FK, *et al.*, eds. Ten years of ciprofloxacin: the past, present and future. *J Antimicrob Chemother* 1999; **43** (suppl A): 1–134.
13. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004; **64:** 611–28.

Administration in children. Ciprofloxacin is not recommended for general use in children and adolescents (see under Precautions, above) but, if considered essential, UK licensed product information recommends oral doses of 5 to 15 mg/kg twice daily or intravenous doses of 4 to 8 mg/kg twice daily. The *BNFC* suggests that similar doses may be given to those as young as 1 month of age and that neonates may be given 7.5 mg/kg by mouth twice daily or 5 mg/kg by intravenous infusion twice daily. It is also licensed in different doses for specific indications as outlined below.

Ciprofloxacin is licensed in the UK and the USA for the treatment and postexposure prophylaxis of inhalation ***anthrax*** in children and adolescents. A 60-day course of treatment with initial intravenous doses of 10 mg/kg (to a maximum of 400 mg) twice daily followed by oral doses of 15 mg/kg (to a maximum of 500 mg) twice daily is recommended; the *BNFC* suggests that similar doses may be given to those as young as 1 month of age. Although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of up to 15 mg/kg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

It is also licensed in the UK for acute exacerbations of ***cystic fibrosis*** associated with *Pseudomonas aeruginosa* infection in those aged 5 to 17 years. An oral dose of 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. Although not licensed for younger children, the *BNFC* suggests giving those aged 1 month to 5 years an oral dose of 5 to 15 mg/kg twice daily or an intravenous dose of 4 to 8 mg/kg twice daily.

In the USA, ciprofloxacin is also licensed for complicated ***urinary-tract infections*** or ***pyelonephritis*** caused by *Escherichia coli* in those aged 1 to 17 years. An oral dose of 10 to 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 6 to 10 mg/kg (to a maximum of 400 mg) three times daily is recommended.

Although unlicensed in the UK, the *BNFC* suggests a single oral dose of 125 mg for ***meningococcal meningitis prophylaxis*** in children aged 2 to 5 years; children aged 5 to 12 years may be given a single oral dose of 250 mg, and those aged over 12 years a single oral dose of 500 mg. Single oral doses of 500 mg have also been suggested for the treatment of gonorrhoea in those over 12 years of age.

Administration in renal impairment. The dose of ciprofloxacin should be reduced in ***adult patients*** with renal impairment by either reducing the total daily dose and/or by increasing the dosage interval in accordance with their creatinine clearance (CC); ideally plasma concentrations of ciprofloxacin should be monitored.

In the UK, halving the usual daily oral or intravenous dose in those with a CC of less than 20 mL/minute is recommended.

In the USA, the following doses are recommended:

- CC 30 to 50 mL/minute: up to 500 mg by mouth every 12 hours or the usual dose by intravenous infusion
- CC 5 to 29 mL/minute: up to 500 mg by mouth every 18 hours or up to 400 mg by intravenous infusion every 18 to 24 hours
- haemodialysis or peritoneal dialysis patients: up to 500 mg by mouth every 24 hours after dialysis

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with either venovenous haemofiltration or haemodiafiltration suggested that a dose of ciprofloxacin 400 mg every 24 hours would be suitable in such situations.[1]

There appears to be little guidance on the use of ciprofloxacin in ***paediatric patients*** with renal impairment but the *BNFC* states that half the usual dose should be used for those with a CC of less than 20 mL/minute per 1.73 m^2.

1. Malone RS, *et al.* Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 2001; **45:** 2949–54.

Inflammatory bowel disease. Ciprofloxacin has been given, sometimes with metronidazole, to treat active Crohn's disease[1,2] (see Inflammatory Bowel Disease, p.1697).

1. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91:** 328–32.
2. Ishikawa T, *et al.* Metronidazole plus ciprofloxacin therapy for active Crohn's disease. *Intern Med* 2003; **42:** 318–21.

Tuberculosis. Reviews[1,2] of data obtained from controlled studies, cohorts, and case series, published up to March 2006, evaluating the clinical efficacy of fluoroquinolones for the treatment of tuberculosis (p.196) concluded that substituting or adding fluoroquinolones (in particular the older fluoroquinolones such as ciprofloxacin or ofloxacin) to established first-line treatment regimens did not confer additional benefits, although the newer fluoroquinolones are reported to have good *in-vitro* (levofloxacin, gatifloxacin, moxifloxacin) and *in-vivo* (gatifloxacin and moxifloxacin) bactericidal activity against *Mycobacterium tuberculosis*.[2]

There are very few controlled studies evaluating the use of fluoroquinolones in multi-drug resistant tuberculosis, but 2 retrospective studies support their effectiveness.[2] WHO guidelines[3,4] recommend that patients with multi-drug resistant tuberculosis and those who relapse after completing standard treatment regimens should receive second-line antituberculous drugs as part of a DOTS-plus regimen; such drugs do include ciprofloxacin and ofloxacin, as well as gatifloxacin, levofloxacin, and moxifloxacin. The usual recommended oral doses during the initial phase are as follows:

- ciprofloxacin: 1 to 1.5 g daily
- gatifloxacin: 400 mg daily
- moxifloxacin: 400 mg daily
- levofloxacin: 750 mg daily
- ofloxacin: 400 mg twice daily

1. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/07/08).
2. Moadebi S, *et al.* Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007; **67:** 2077–99.
3. WHO. *Treatment of tuberculosis: guidelines for national programmes.* 3rd ed. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 24/01/07)
4. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis.* Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf (accessed 03/03/08)

Preparations

BP 2008: Ciprofloxacin Intravenous Infusion; Ciprofloxacin Tablets;
USP 31: Ciprofloxacin and Dexamethasone Otic Suspension; Ciprofloxacin Injection; Ciprofloxacin Ophthalmic Ointment; Ciprofloxacin Ophthalmic Solution; Ciprofloxacin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Argeflox; Atibax C; Biotic; Blader†; Ciloxan; Cipro; Cipro-Otico; Ciprotenk; Cirflox-G; Ciriax; Crisacide; Exertial; Floraxina; Gino Ciriax; Golysine; Lorbifloxacina; Medaflox; Microsulf; Neflox; Novidat; Ocefax; Omaflaxina†; Plusgin†; Quisegen; Rexner; Septicide; Ultramicina; ***Austral.:*** C-Flox; Ciloquin; Ciloxan; Ciprol; Ciproxin; Profloxin; Proquin; ***Austria:*** Agyr†; Ciflox; Ciloxan; Cipromed; Ciprostad; Ciproxin; ***Belg.:*** Ciloxan; Ciprobel; Ciproxine; Docciproflo; ***Braz.:*** Bactoflox†; Biamotil; Ciflocina†; Ciflox; Cifloxan†; Cifloxtron; Ciloxan; Cinoflax; Ciprix; Cipro; Ciproant†; Ciprobiot†; Ciprocilin; Ciprocina†; Ciprodine; Ciprofar; Ciproflonax†; Ciproflox†; Ciprofloxil; Cipromizin†; Cipronal†; Cipronom; Ciproxan†; Ciproxen; Ciproxil†; Ductocina; Floxan; Maxiflox; Nixin; Ofoxin; Procin†; Proflox; Proxacin; Quiflox; Quinoflox; Sifloxan†; ***Canad.:*** Ciloxan; Cipro; ***Chile:*** Baycip; Cifloxin; Ciloxacin; Ciproval; Ciproxino; Grifociprox; Oflono; Oftaciprox; ***Cz.:*** Cifloxinal; Cifran; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprobid†; Ciprum; Quintor†; Quipro†; ***Denm.:*** Cifin; Ciloxan; Ciproxin; Sancipro; Sibunar; ***Fin.:*** Cipromed; Ciproxin; Siprion†; ***Fr.:*** Ciflox; Ciloxan; Uniflox; ***Ger.:*** Ciloxan; Cipro; Cipro-Lich†; Cipro-Q; Cipro-saar; Cipro-Wolff; Ciprobay; Ciprobeta; Ciprodoc; Ciprodura; Ciprofat; Ciproflox; Ciproflox-Puren; Ciprogamma; Ciprohexal; Ciprox; Gyracip; Keciflox; Panotile cipro; ***Gr.:*** Afenoxin; Aristin-C; Balepton; Biocipro; Bivorilan; Cidrops†; Ciloxan; Ciprobay†; Ciprofal; Cipromycin; Ciprospes; Ciproxin; Citrovenot; Droll; Flociprin; Forterra; Ginorectol; Glossyfin; Grenis-cipro; Infectina; Labentrol; Ladinin; Limox; Nafloxin; Ravalton; Remena; Revion; Revionorm; Topistin; Ufexil; Urodixin; ***Hong Kong:*** Cifloxin; Ciloxan; Cipide; Ciplox; Ciprol; Ciproxin; Ciproxyl; Cyfloxin; Enoxin; Gonning; Medociprin; Proxacin; Quinocin; Uroxin; Utahzone; ***Hung.:*** Cifloxin; Cifran; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprolen; Cipropharm; Ciprum; Cydonin; ***India:*** Bactoquin†; Biocip; Cifran; Cipgen; Cipro-Cent; Ciprobid; Ciprodac; Ciprowin; Ificipro†; Neocip; Procip†; Quinobact; Strox†; Zoxan; ***Indon.:*** Bactiprox; Baquinor; Bernoflox; Bidiprox; Cetafloxo; Ciflos; Cilox; Ciproxin; Civell; Coroflex; Corsacin; Cylowam; Disfabac; Duflomex; Etacin; Floksid; Floxbio; Floxigra; Girabloc; Interflox; Isotic Renator; Jayacin; Kifarox; Lapiflox; Licoprox; Meflosin; Mensipox; Nilaflox; Poncoflox; Proxcip; Proxitor; Qinox; Quamiprox; Quidex; Quinobiotic; Renator; Scanax; Tequinol; Vidintal; Viflox; Vioquin; Volinol; Wiaflox; Ximex Cylowam; Zumaflox; ***Irl.:*** Biofloxcin; Cifloxager; Ciproxin; Profloxin; Truoxin; ***Israel:*** Ciloxan; Ciplox; Ciprodex; Ciprogis; Ciproxin; Ufexil; ***Ital.:*** Ciproxin; Flociprin; Oftacilox; ***Jpn:*** Ciproxan; ***Malaysia:*** Bactiflox; Cifloxin; Cifran; Ciloxan; Ciprobay; Enoxin; ***Mex.:*** Antimed; Apoflox; Arfloxina; Bacproin; Bioflox; Ci-Sons; Cifran; Ciloxan; Cimogal; Ciprain; Cipro; Ciprobac; Ciprobiotic; Ciproflox; Ciprofur; Ciprohexal; Ciproser; Ciprotec; Ciproxina; Ciqfadin; Dinaflox; Eni; Eufloxin; Floxager; Floxantina; Floxelena; Floxitul; Gibac; Infloxa; Italnik; Kenzoflex; Lemyflox; Liferxina; Maviflox†; Microrgan; Mitroken; Nivoflox†; Novoquin; Oftaquin†; Opthaflox; Patox; Pharcina; Profluxol; Provay; Proxitec†; Quifloxona†; Quinoflox; Rictor; Sinfexina; Sophixin; Spectroflex†; Suiflox; Trigen; Vifloxina; Zipra; ***Neth.:*** Ciloxan; Ciprinol; Ciproxin; ***Norw.:*** Cilox; Ciproxin; ***NZ:*** Cifran; Ciloxan; Cipflox; Ciproxin; DP-Cipro; Topistin; Ufexil; ***Philipp.:*** Baxolyn; Brelcip; Ciclodin; Cidroxal; Ciloxan; Ciprobay; Cipromax; Cipromet; Ciprotor; Cirok; Floroc; Iprolan; Ipromax; Kinoves; Laitun; Nexproxyn; Proxivex; Qinosyn; Quilox; Quinoryl; Quiprime; Rapiqure; Xipro; Zalvos; Zyflox; ***Pol.:*** Cifran; Ciloxan; Ciphin; Ciprinol; Ciprobay; Cipronex; Cipropol; Ciprum; Proxacin; ***Port.:*** Carmicina†; Ciflan; Ciplox; Ciproquinol†; Ciproxina; Colintil; Estecina; Floxacipron†; Giroflox; ISINO; Keefloxin†; Megaflox; Nivoflox; Nixin; Oftacilox; Quinox; Xorpic†; ***Rus.:*** Cifloxinal (Цифлоксинал); Cifran (Цифран); Ciloxan (Цилоксан); Ciprex (Ципрекс); Ciprinol (Ципринол); Ciprobay (Ципробай); Ciprobid (Ципробид); Ciprolet (Ципролет); Ciprolone (Ципролон); Cipromed (Ципромед); Ciprosun (Ципросан); Ificipro (Ифиципро); Medociprin (Медоциприн); Quintor (Квинтор); Sifloks (Сифлокс); ***S.Afr.:*** Adco-Ciprin; Biocip; Cifloc; Cifran; Ciloxan; Ciploxx; Cipro-Hexal; Ciprobay; Ciprogen; Dynafloc; Orpic; Spec-Topistin; ***Singapore:*** Ciloxan; Ciprobay; Ciprolet; Cirok†; Ciroxin†; Cycin; Ginorectol; Neofloxin; Serviflox; Uroxin; ***Spain:*** Aceoto; Baycip; Belmacina; Catex; Ceprimax†; Cetraxal; Cipobacter†; Ciprenit Otico; Ciproctal; Ciproxina Simple; Cunesin; Doriman; Estecina; Felixene; Giroflox; Globuce; Huberdoxina; Numen; Oftacilox; Otociprin; Otosat; Piprol; Plenolyt; Quipro; Rigoran; Sepcen; Septocipro; Tam; Ultramicina; Velmonit†; ***Swed.:*** Ciloxan; Ciproxin; ***Switz.:*** Ciloxan; Cip eco; Ciprine; Cipro-Med; Ciproflox; Ciproxine; Principrox; ***Thai.:*** C-Floxacin; Ciflo; Ciflolan; Cifloxin; Cifran; Cilab; Ciloxan; Cinfloxine; Cipflocin; Cipon; Ciprobay; Ciprobid; Ciprocep; Ciprofin; Ciprogen; Ciproglen†; Ciprolet; Ciprom-H; Ciprosun†; Ciprovid; Ciproxan; Ciproxyl; Cobay; Cyflox; Forexin; Microflox; Poli-Cifloxin; Proflox; Serviflox†; Ultraflox; Uroxin; Vesprocin; ***Turk.:*** Ciflosin; Cifluron; Ciloxan; Ciprasid; Cipro; Ciproktan; Ciproxin; Loxasid; Proxacin; Roflazin; Roxin; Sanset; Sifloks; Siprobel; Siprogut; Siprosan; Sispres; UroCiproxin; ***UAE:*** Sarf; ***UK:*** Ciloxan; Ciproxin; ***USA:*** Ciloxan; Cipro; ***Venez.:*** Bacipro; Baflox; Ciflox; Ciloxan; Ciprivax; Ciproflox; Ciprolet†; Cipronax; Ciproquin; Ciproxina; Cirok; Cypral; Gerxidin†; Iproxin; Klicina†; Lisipin; Oxtin; Quinoftal; Quinotic; Serviflox; Sophixin; Zolina.

Multi-ingredient: *Arg.:* Ciloxadex; Cipro HC; Ciproflox-Otic; Ciriax Otic; Ciriax Otic L; Decadron con Ciprofloxina; Delos Otic; Otex HC; Oto Biotaer; Otobiotic; Otocipro; Otosporin C; Prootocipro; Quidex; Tacines; ***Austral.:*** Ciproxin HC; ***Austria:*** C-Bildz; ***Braz.:*** Biamotil-D; Cilodex; Cipro HC; Cylocort; Maxiflox D; Otociriax; ***Canad.:*** Cipro HC; Ciprodex; ***Chile:*** Cilodex; Ciprodex; Oflono-D; Otex HC; ***Cz.:*** Ciprobay HC Otic; ***Denm.:*** Ciflox; ***Fin.:*** Ciproxin-Hydrocortison; ***Gr.:*** Ciprofloxacin HY†; ***Hong Kong:*** Cipro HC; ***Hung.:*** Ciprobay†; ***India:*** Biocip-TZ; Cipgen TZ; Ciplox; Ciplox D; Ciplox TZ; Ciptini; Citizol; Neocip FC; Neocip M; Ocimix; Tinvista-CF; ***Israel:*** Ciproxin HC; ***Malaysia:*** Cipro HC†; ***Mex.:*** Cilodex; Ciproxina HC; Dinill-D; Oto Eni; Quinoflox Otico; UV IX†; Vodelan; ***NZ:*** Ciproxin HC; ***S.Afr.:*** Ciprobay HC; ***Singapore:*** Ciprobay HC; ***Spain:*** Aceoto Plus; Cetraxal Plus; Cexidal Otico†; Ciproxina; Synalotic; Ultramicina Plus†; ***Switz.:*** Ciproxin HC; ***USA:*** Cipro HC; Ciprodex; ***Venez.:*** Otalex; Quinocort; Quinotic HC.

Clarithromycin *(BAN, USAN, rINN)*

A-56268; Abbott-56268; Clarithromycine; Clarithromycinum; Claritromicina; Klarithromycin; Klaritromicinas; Klaritromisin; Klaritromycin; Klaritromysiini; TE-031.
(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-3-(2,6-Dideoxy-3-*C*,3*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)pentadecan-13-olide; 6-*O*-Methylerythromycin.

Кларитромицин

$C_{38}H_{69}NO_{13}$ = 748.0.
CAS — 81103-11-9.
ATC — J01FA09.
ATC Vet — QJ01FA09.

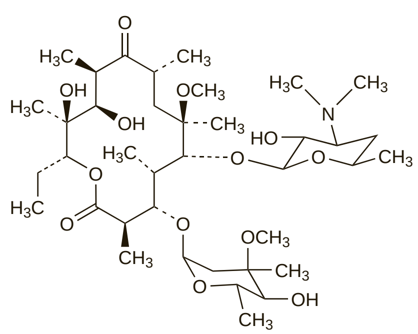

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Clarithromycin). A white or almost white, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; slightly soluble in methyl alcohol.
USP 31 (Clarithromycin). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol, in methyl alcohol, and in acetonitrile; soluble in acetone; slightly soluble in phosphate buffer at pH values of 2 to 5. pH of a 0.2% suspension in a mixture of water and methyl alcohol (19:1) is between 8.0 and 10.0. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270. Gastrointestinal disturbances are the most frequent adverse effect but are usually mild and less frequent with clarithromycin than with erythromycin. Smell and taste disturbances, stomatitis, glossitis, tongue and tooth discoloration, and headache have occurred. There have also been reports of transient CNS effects. Other adverse effects include arthralgia, myalgia, hypoglycaemia, leucopenia, and thrombocytopenia. Interstitial nephritis and renal failure have been reported rarely.

Intravenous doses may cause phlebitis and pain at the injection site.

Caution is required in patients with hepatic or renal impairment and doses should be reduced in those with renal impairment (see under Uses and Administration below). It should not be used during pregnancy if possible as high doses have been associated with embryotoxicity in *animal* studies.

Effects on the blood. Single cases of thrombocytopenia[1] and thrombocytopenic purpura[2,3] associated with clarithromycin have been reported. Cases of agranulocytosis have also been reported.[4] A case of thrombocytopenia accompanied by interstitial nephritis, hepatitis, and elevated serum amylase levels was attributed to an allergic reaction to clarithromycin.[5] Toxic epidermal necrolysis and subsequent death due to aplastic anaemia have been reported in a patient after taking clarithromycin for 3 days.[6]

1. Price TA, Tuazon CU. Clarithromycin-induced thrombocytopenia. *Clin Infect Dis* 1992; **15:** 563–4.
2. Oteo JA, *et al.* Clarithromycin-induced thrombocytopenic purpura. *Clin Infect Dis* 1994; **19:** 1170–1.
3. Alexopoulou A, *et al.* Thrombotic thrombocytopenic purpura in a patient treated with clarithromycin. *Eur J Haematol* 2002; **69:** 191–2.
4. Jacobs P, *et al.* Immune agranulocytosis and clarithromycin. *Hematology* 2004; **9:** 291–6.
5. Baylor P, Williams K. Interstitial nephritis, thrombocytopenia, hepatitis, and elevated serum amylase levels in a patient receiving clarithromycin therapy. *Clin Infect Dis* 1999; **29:** 1350–1.
6. Baz K, *et al.* Fatal aplastic anaemia in a patient with clarithromycin-induced toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2004; **18:** 104–5.

Effects on the cardiovascular system. QT prolongation and torsade de pointes were associated with use of clarithromycin in 2 patients.[1] Renal impairment in 1 of the patients and hepatic impairment and organic heart disease in both could have increased their susceptibility to these effects.

For mention of an unexpected increase in cardiovascular mortality in patients with stable coronary heart disease given clarithromycin, see Ischaemic Heart Disease, in Uses and Administration of Azithromycin, above.

1. Lee KL, *et al.* QT prolongation and torsades de pointes associated with clarithromycin. *Am J Med* 1998; **104:** 395–6.

Effects on the eyes. Corneal opacities, reversible on stopping treatment, were reported in a patient receiving oral clarithromycin as part of a regimen for disseminated *Mycobacterium avium* complex infection.[1] Corneal subepithelial deposits have also been reported in a patient after prolonged use of clarithromycin eye drops for *Mycobacterium avium* complex keratitis. The deposits did not cause any ocular discomfort and resolved on stopping therapy.[2]

1. Dorrell L, *et al.* Toxicity of clarithromycin in the treatment of Mycobacterium avium complex infection in a patient with AIDS. *J Antimicrob Chemother* 1994; **34:** 605–6.
2. Tyagi AK, *et al.* An unreported side effect of topical clarithromycin when used successfully to treat Mycobacterium avium-intracellulare keratitis. *Cornea* 1999; **18:** 606–7.

Effects on the gastrointestinal tract. Pseudomembranous colitis associated with *Clostridium difficile* developed in a child receiving clarithromycin.[1]

1. Braegger CP, Nadal D. Clarithromycin and pseudomembranous enterocolitis. *Lancet* 1994; **343:** 241–2.

Effects on the liver. Progressive cholestatic jaundice, which subsequently proved fatal, developed in a 59-year-old woman after 3 days of clarithromycin therapy for acute maxillary sinusitis.[1] Fulminant hepatic failure in another patient, which developed during clarithromycin therapy, resolved once the drug was withdrawn.[2] Clarithromycin itself was considered responsible although there was the possibility that it had increased concentrations of isradipine, another known hepatotoxic drug that the patient was also receiving.

1. Fox JC, *et al.* Progressive cholestatic liver disease associated with clarithromycin treatment. *J Clin Pharmacol* 2002; **42:** 676–80.
2. Tietz A, *et al.* Fulminant liver failure associated with clarithromycin. *Ann Pharmacother* 2003; **37:** 57–60.

Effects on the lungs. On 2 occasions fever and pulmonary infiltration with eosinophilia occurred in a patient given clarithromycin.[1] Another patient developed eosinophilic pneumonia 3 days after starting clarithromycin; symptoms improved when the drug was stopped.[2]

1. Terzano C, Petroianni A. Clarithromycin and pulmonary infiltration with eosinophilia. *BMJ* 2003; **326:** 1377–8.
2. Ohnishi H, *et al.* Clarithromycin-induced eosinophilic pneumonia. *Intern Med* 2004; **43:** 231–5.

Effects on mental state. Acute psychoses occurred in 2 patients receiving clarithromycin as part of prophylactic treatment for *Helicobacter pylori* infection and were similar to 3 previously reported cases in either AIDS patients or elderly subjects.[1] Delirium[2] has also been associated with clarithromycin monotherapy in an elderly patient, and visual hallucinations have occurred in a 37-year-old woman being treated with ceftriaxone and clarithromycin for suspected pneumonia.[3] A review[4] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials; clarithromycin was found to be the antibacterial most frequently implicated.

1. Gómez-Gil E, *et al.* Clarithromycin-induced acute psychoses in peptic ulcer disease. *Eur J Clin Microbiol Infect Dis* 1999; **18:** 70–1.
2. Özsoylar G, *et al.* Clarithromycin monotherapy-induced delirium. *J Antimicrob Chemother* 2007; **59:** 331.
3. Fernández Arenas O, *et al.* Alucinaciones por administración de una pauta estándar de claritromicina. *Farm Hosp* 2007; **31:** 315–16.
4. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; **22:** 71–81.

Effects on the pancreas. Pancreatitis has been reported in patients receiving clarithromycin.[1-3]

1. Liviu L, *et al.* Pancreatitis induced by clarithromycin. *Ann Intern Med* 1996; **125:** 701.
2. Schouwenberg BJJW, Deinum J. Acute pancreatitis after a course of clarithromycin. *Neth J Med* 2003; **61:** 266–7.
3. González Carro P, *et al.* Acute pancreatitis and modified-release clarithromycin. *Ann Pharmacother* 2004; **38:** 508–509.

Hypersensitivity. In addition to skin rashes and other hypersensitivity reactions which occasionally occur in patients receiving macrolides, leukocytoclastic vasculitis,[1] Henoch-Schönlein purpura,[2] and toxic epidermal necrolysis[3] have been reported in patients receiving clarithromycin.

1. Gavura SR, Nusinowitz S. Leukocytoclastic vasculitis associated with clarithromycin. *Ann Pharmacother* 1998; **32:** 543–5.
2. Borrás-Blasco J, *et al.* Henoch-Schönlein purpura associated with clarithromycin: case report and review of literature. *Int J Clin Pharmacol Ther* 2003; **41:** 213–16. Correction. *ibid.*; 420.
3. Khaldi N, *et al.* Toxic epidermal necrolysis and clarithromycin. *Can J Clin Pharmacol* 2005; **12:** e264–e268.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Antidiabetics. For reference to hypoglycaemia resulting from the addition of clarithromycin to *glibenclamide* or *glipizide*, see Antibacterials, p.462.

Antiretroviral drugs. In studies in healthy subjects,[1,2] the HIV-protease inhibitor *ritonavir* inhibited the metabolism of clarithromycin, increasing plasma concentrations and prolonging half-life. The metabolism of ritonavir was not affected significantly. The two drugs may be given together in usual doses to those with normal renal function but licensed product information for clarithromycin recommends that its dose should be reduced in patients with renal impairment receiving ritonavir and it should be noted that this is an extra reduction over and above that which may be needed for the renal impairment alone. Doses of clarithromycin should be reduced by 50% in patients with a creatinine clearance (CC) of 30 to 60 mL/minute and reduced by 75% in those with a CC below 30 mL/minute; the daily dose should not exceed 1 g. It has been suggested that other HIV-protease inhibitors (see also Table of Interactions of Drugs Used in the Treatment of HIV, p.917) and the NNRTI *delavirdine* may have a similar effect on clarithromycin. Use of *efavirenz* with clarithromycin has decreased plasma concentration of clarithromycin and increased its hydroxy metabolite. The combination has been associated with a high incidence of skin rashes. Decreases in the plasma concentration of clarithromycin have also been noted with *nevirapine*.

Decreased concentrations of *zidovudine* (p.915) have been reported in patients also taking clarithromycin and clarithromycin product information recommends that doses of the two drugs should be separated by 1 to 2 hours.

1. Ouellet D, *et al.* Assessment of the pharmacokinetic interaction between ritonavir and clarithromycin. *Clin Pharmacol Ther* 1996; **59:** 143.
2. Ouellet D, *et al.* Pharmacokinetic interaction between ritonavir and clarithromycin. *Clin Pharmacol Ther* 1998; **64:** 355–62.

Colchicine. For mention of fatal colchicine toxicity associated with concomitant use of clarithromycin, see Macrolides, p.557.

Disulfiram. For a report of an interaction between clarithromycin and disulfiram, see Macrolides, p.2297.

Fluoxetine. For a report of delirium following use of clarithromycin with fluoxetine, see Antibacterials, p.396.

Gastrointestinal drugs. In a study[1] in healthy subjects, concentrations of clarithromycin and its active metabolite were increased in gastric tissue and mucus and, to a lesser extent, in plasma during use of *omeprazole*. In addition, use of clarithromycin with omeprazole resulted in higher and more prolonged plasma concentrations of omeprazole. The investigators suggest that this interaction could account for the synergistic action observed with this combination when used for eradication of *Helicobacter pylori*. However, licensed product information for clarithromycin states that no dosage adjustment to either drug is necessary. Although a study[2] in healthy subjects suggested that some pharmacokinetic parameters of clarithromycin are altered by *cimetidine*, the clinical significance of such changes are unknown.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; **39:** 2078–83.
2. Amsden GW, *et al.* Oral cimetidine prolongs clarithromycin absorption. *Antimicrob Agents Chemother* 1998; **42:** 1578–80.

Antimicrobial Action

As for Erythromycin, p.271.

Clarithromycin is reported to be more active than erythromycin against susceptible streptococci and staphylococci *in vitro*, as well as against some other species including *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Legionella* spp., *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. Clarithromycin is reported to be more active than erythromycin or azithromycin against some mycobacteria, including *Mycobacterium avium* complex and *M. leprae*. It is reported to have some *in-vitro* activity against the protozoan *Toxoplasma gondii*. The major metabolite, 14-hydroxyclarithromycin, is also active, and may enhance the activity of clarithromycin *in vivo*, notably against *Haemophilus influenzae*. The MICs of this metabolite are equal or twofold higher than those of the parent drug; the former is twofold more active than the latter against *H. influenzae*.

Activity with other antimicrobials. Clarithromycin has been reported to enhance the activity of a number of antimycobacterials including ethambutol, isoniazid, pyrazinamide, and rifampicin against *Mycobacterium tuberculosis*.[1,2]

1. Cavalieri SJ, *et al.* Synergistic activities of clarithromycin and antituberculous drugs against multi drug-resistant Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 1995; **39:** 1542–5.
2. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; **41:** 2035–6.

Resistance. Erythromycin-resistant isolates of *Streptococcus pneumoniae* are commonly cross-resistant to clarithromycin.[1] The incidence of resistance to clarithromycin and other macrolides is higher among penicillin-resistant strains than among penicillin-sensitive strains.[2] Clarithromycin-resistant isolates of *Helicobacter pylori* have also emerged.[3-6] Genetic mutations responsible for clarithromycin resistance have been identified in *H. pylori*[7] and in *Mycobacterium* spp.[8,9] Since resistance develops rapidly in *M. avium* during clarithromycin monotherapy, combination therapy is usually recommended. However, resistance to clarithromycin in an AIDS patient with systemic *M. avium* complex infection, despite combined treatment with clofazimine, has been described.[10]

1. Lonks JR, Medeiros AA. High rate of erythromycin and clarithromycin resistance among Streptococcus pneumoniae isolates from blood cultures from Providence, RI. *Antimicrob Agents Chemother* 1993; **37:** 1742–5.
2. Barry AL, *et al.* Macrolide resistance among Streptococcus pneumoniae and Streptococcus pyogenes isolates from out-patients in the USA. *J Antimicrob Chemother* 1997; **40:** 139–40.
3. López-Brea M, *et al.* Evolution of resistance to metronidazole and clarithromycin in Helicobacter pylori clinical isolates from Spain. *J Antimicrob Chemother* 1997; **40:** 279–81.
4. Hultén K, *et al.* Macrolide resistance in Helicobacter pylori: mechanism and stability in strains from clarithromycin-treated patients. *Antimicrob Agents Chemother* 1997; **41:** 2550–3.
5. Kalach N, *et al.* High levels of resistance to metronidazole and clarithromycin in Helicobacter pylori strains in children. *J Clin Microbiol* 2001; **39:** 394–7.
6. Grove DI, Koutsouridis G. Increasing resistance of Helicobacter pylori to clarithromycin: is the horse bolting? *Pathology* 2002; **34:** 71–3.
7. Versalovic J, *et al.* Mutations in 23S rRNA are associated with clarithromycin resistance in Helicobacter pylori. *Antimicrob Agents Chemother* 1996; **40:** 477–80.
8. Nash KA, Inderlied CB. Genetic basis of macrolide resistance in Mycobacterium avium isolated from patients with disseminated disease. *Antimicrob Agents Chemother* 1995; **39:** 2625–30.
9. Wallace RJ, *et al.* Genetic basis for clarithromycin resistance among isolates of Mycobacterium chelonae and Mycobacterium abscessus. *Antimicrob Agents Chemother* 1996; **40:** 1676–81.
10. De Wit S, *et al.* Acquired resistance to clarithromycin as combined therapy in Mycobacterium avium intracellulare infection. *Lancet* 1993; **341:** 53–4.

Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract, and undergoes first-pass metabolism; the bioavailability of the parent drug is about 55%. The extent of absorption is relatively unaffected by the presence of food. Peak plasma concentrations occur 2 to 3 hours after an oral dose. At steady state, peak plasma concentrations of clarithromycin and its principal active metabolite, 14-hydroxyclarithromycin, are about 1 and 0.6 micrograms/mL, respectively, after 250 mg orally every 12 hours as tablets. The same dose given as a suspension to fasting subjects produces steady-state plasma concentrations of about 2 micrograms/mL of clarithromycin and about 0.7 micrograms/mL of 14-hydroxyclarithromycin. Steady-state concentrations are reached within 3 to 4 days.

The pharmacokinetics of clarithromycin are non-linear and dose dependent; high doses may produce disproportionate increases in peak concentrations of the parent drug, due to saturation of the metabolic pathways. However, the non-linearity is slight at the recommended doses of 250 to 500 mg every 8 to 12 hours.

Clarithromycin and 14-hydroxyclarithromycin are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Plasma protein binding has been reported to be about 80%. Clarithromycin has been detected in breast milk. It is extensively metabolised in the liver, and excreted in faeces via the bile; 5 to 10% of the parent drug is recovered from the faeces. At steady state, about 20% and 30% of a 250-mg or 500-mg dose as tablets, respectively, and about 40% of a 250-mg dose as suspension, is excreted in the urine as unchanged drug. 14-Hydroxyclarithromycin as well as other metabolites are also excreted in the urine, accounting for 10 to 15% of the dose. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are about 3 to 4 and 5 to 6 hours, respectively in patients receiving 250 mg every 12 hours, and about 5 to 7 and 7 to 9 hours, respectively, in those receiving 500 mg every 8 to 12 hours. The half-life is prolonged in renal impairment.

◊ Reviews.

1. Rodvold KA. Clinical pharmacokinetics of clarithromycin. *Clin Pharmacokinet* 1999; **37:** 385–98.

Uses and Administration

Clarithromycin is a macrolide derived from erythromycin with similar actions and uses (p.272). It is given in the treatment of respiratory-tract infections (including otitis media) and in skin and soft-tissue infections. Clarithromycin is also used for the prophylaxis and treatment of nontuberculous mycobacterial infections and has been used as a second-line drug in the treatment of leprosy. It is used in some countries as an alternative to penicillins for prophylaxis of endocarditis.

For details of all these infections and their treatment, see under Choice of Antibacterial, p.162.

Clarithromycin may be given to eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease (p.1702). It is used with pyrimethamine as an alternative regimen in the treatment of toxoplasmosis (p.826).

Clarithromycin is given orally or by intravenous infusion. Some clarithromycin preparations are prepared with the aid of lactobionic acid and may be stated to contain clarithromycin lactobionate. Doses are expressed in terms of the equivalent amount of clarithromycin.

Usual oral doses in adults are 250 mg twice daily, increased to 500 mg twice daily if necessary in severe infection. Modified-release tablets allowing once-daily use are available in some countries.

The usual intravenous dose is 500 mg twice daily, given as an infusion over 60 minutes using a solution containing about 0.2% of clarithromycin. Intravenous treatment may continue for 2 to 5 days, but should be changed to oral clarithromycin when possible.

For treatment and prophylaxis of disseminated infection due to *Mycobacterium avium* complex, clarithromycin may be given in an oral dose of 500 mg twice daily; for treatment, it should be given with other antimycobacterials. For leprosy, oral clarithromycin 500 mg daily has been given as part of an alternative multidrug therapy regimen.

For the eradication of *H. pylori* associated with peptic ulcer disease, clarithromycin, usually in an oral dose of 500 mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

For details of doses in infants and children, see below.

Doses may need to be reduced in patients with severe renal impairment (see below).

◊ Reviews.

1. Peters DH, Clissold SP. Clarithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; **44:** 117–64.
2. Barradell LB, *et al.* Clarithromycin: a review of its pharmacological properties and therapeutic use in Mycobacterium avium-intracellulare complex infection in patients with acquired immune deficiency syndrome. *Drugs* 1993; **46:** 289–312.
3. Markham A, McTavish D. Clarithromycin and omeprazole: as Helicobacter pylori eradication therapy in patients with H. pylori-associated gastric disorders. *Drugs* 1996; **51:** 161–78.
4. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; **74:** 613–34.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.

Administration in children. The usual oral dose of clarithromycin for infants and children is 7.5 mg/kg twice daily; those over 12 years of age may be given the usual adult dose (see above).

Although intravenous use is not licensed for children in the UK the *BNFC* suggests a dose of 7.5 mg/kg twice daily for those aged from 1 month to 12 years; older children may be given the adult dose (see above).

For prophylaxis of disseminated infection due to *Mycobacterium avium* complex, clarithromycin may be given in an oral dose of 7.5 mg/kg twice daily; when used for treatment, it should be given with other antimycobacterials and the dose may be increased to 15 mg/kg (to a maximum of 500 mg) twice daily.

For the eradication of *Helicobacter pylori* associated with peptic ulcer disease, the *BNFC* suggests that 7.5 mg/kg twice daily may also be given orally with another antibacterial and a proton pump inhibitor for 7 days to children aged 1 year and over.

Administration in renal impairment. Licensed product information states that in patients with severe renal impairment (creatinine clearance of less than 30 mL/minute) dosage of clarithromycin may need to be halved or the dosing interval doubled.

Ischaemic heart disease. For mention of studies investigating clarithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p.208.

Multiple myeloma. Clarithromycin 500 mg orally twice daily has been added[1] to a regimen of lenalidomide and dexamethasone in treatment-naive patients with multiple myeloma (p.658). The regimen (BiRD) was considered effective and well tolerated, with a higher response rate at lower dexamethasone doses than had been previously reported with lenalidomide and dexamethasone alone. A regimen of clarithromycin, low-dose thalidomide, and dexamethasone (BLT-D) has also been evaluated.[2]

1. Niesvizky R, *et al.* BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood* 2008; **111:** 1101–9.
2. Coleman M, *et al.* BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma* 2002; **43:** 1777–82.

Respiratory disorders. For reference to the use of clarithromycin in the management of respiratory disorders, see under Erythromycin, p.273.

Preparations

USP 31: Clarithromycin Extended-Release Tablets; Clarithromycin for Oral Suspension; Clarithromycin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aeroxina; Centromicina†; Claribiotic; Claricina; Clarimax; Clarimid; Clarovil; Clatromicin†; Corixa; Finasept; Ira; Iset; Kailasa; Klaricid; Klonacid; Macromicina; Orabiot UD†; ***Austral.:*** Clarac; Clarithro; Kalixocin; Klacid; ***Austria:*** Clararcana; Klacid; Maclar; Monocid; ***Belg.:*** Biclar; Heliclar; Maclar; Monaxin†; ***Braz.:*** Clamicin; Claricina†; Clarineo; Claritromax; Claritron†; Clatorin†; Klaricid; Klaritril†; ***Canad.:*** Biaxin; ***Chile:*** Clarimax; Clarosip; Clatic; Euromicina; Infex; Klaricid; Mus†; Pre-Clar; ***Cz.:*** Clarexid; Clarosip; Fromilid; Klabax; Klacid; Lekoklar; Zeclar†; ***Denm.:*** Klacid; ***Fin.:*** Klacid; Zeclar; ***Fr.:*** Mononaxy; Monozeclar; Naxy; Zeclar; ***Ger.:*** Biaxin; Clarithrobeta; Cyllind; Klacid; Mavid; ***Gr.:*** Arecid; Chlamydicin; Claribactron; Clarimex; Claripen; Claromycin; Derizic; Egelif; Eliben; Ezumycin; Geromycin; Glartin; Klaretop; Klaricid; Klarifar; Klarifect; Klarithrin; Klaroxin; Klazidem; Larithro; Laromin; Lyoclar; Macladin; Maxilin; Odycin; Oklaricid†; Pharlemyron; Primocid; Riclemed; Rithroprol; Ritran; Zeclaren; ***Hong Kong:*** Binoclar; Clacin; Cleron; Klacid; Klerimed; Synclar; ***Hung.:*** Cidoclar; Fromilid; Klabax; Klacid; Klamiran†; Klari†; Klarigen; Lekoklar; ***India:*** Bioclar; Clarbact; Claribid; Claricip; Clarimac; Maclar; Synclar; ***Indon.:*** Abbotic; Bicrolid; Binoklar; Clacine; Clapharma; Comtro; Hecobac; ***Irl.:*** Clarosip; Clonocid; Clorom; Klacid; ***Israel:*** Karin; Klacid; Klaridex; ***Ital.:*** Klacid; Macladin; Veclam; ***Jpn:*** Clarith; ***Malaysia:*** Binocular; Crixan; Klacid; Klerimed; Maclar; ***Mex.:*** Adel; Arlecyn-K; Clatrocin; Crolisil; Doycur; Gervaken; Klabet; Klaricid; Klarix; Klarmyn; Klarpharma; Krobicin; Mabicrol; Neo-Clarosip; Quedox; Rolicytin; Torvic; Trimeba; Vikrol; Xuclamin; ***Neth.:*** Clarosip; Klacid; Klaricid; ***Norw.:*** Klacid; ***NZ:*** Clarac; Klacid; ***Philipp.:*** Bysclas; Claranta; Clariget; Klaricid; Klarmyn; Klaz; Larizin; Maxulid; Onexid; ***Pol.:*** Fromilid; Klabax; Klabion; Klacid; Klarmin; Lekoklar; Taclar; ***Port.:*** Ciclinil; Clacina; Clarbac; Clarobiotico; Clarosip; Klacid; Zeclar; ***Rus.:*** Clarbact (Кларбакт); Fromilid (Фромилид); Klabax (Клабакс); Klacid (Клацид); Klaromin (Кларомин); Klerimed (Клеримед); ***S.Afr.:*** Clacee; ClariHexal; Klacid; Klarithran; ***Singapore:*** Clari; Claripen; Cleron; Crixan; Klacid; Klerimed; ***Spain:*** Bremon; Claritur†; Klacid; Kofron; Talicix; ***Swed.:*** Klacid; ***Switz.:*** Claromycine; Klacid; Klaciped; ***Thai.:*** Clarith; Claron; Crixan; Fascar; Klacid; ***Turk.:*** Claricide; Klacid; Klarolid; Klaromin; Klax; Laricid; Macrol; Megacid; Uniklar; ***UAE:*** Clamycin; ***UK:*** Clarosip; Klaricid; ***USA:*** Biaxin; ***Venez.:*** Binoclar; Claranta; Claritic; Claritron; Clarivax; Klaricid.

Multi-ingredient: ***Arg.:*** Heliklar†; ***Austral.:*** Klacid HP 7; Losec Hp 7; Nexium Hp; Pylorid-KA; ***Austria:*** Helipac; ***Braz.:*** Anzopac†; Erradic; H-Bacter; Helicocid Triplice†; Helicopac; Heliklar; Omepramix; Pylorikit; Pyloripac; Pyloritrat; ***Canad.:*** Hp-Pac; Losec 1-2-3 A; Losec 1-2-3 M; ***Fin.:*** Helipak K; ***Ger.:*** ZacPac; ***India:*** OTC HP Kit; Pylokit; ***Malaysia:*** Klacid HP 7; Pylobact Combi; ***Mex.:*** Pylopac; Rezplen; ***Neth.:*** PantoPAC; ***NZ:*** Klacid HP 7†; Losec Hp 7; ***Philipp.:*** OAC Hp7; ***Rus.:*** Pylobact (Пилобакт); ***S.Afr.:*** Losec 20 Triple†; ***Swed.:*** Nexium Hp; ***Turk.:*** Helipak; ***UK:*** Heliclear†; HeliMet†; ***USA:*** Prevpac.

Clavulanic Acid *(BAN, rINN)*

Acide Clavulanique; Ácido clavulánico; Acidum Clavulanicum; BRL-14151; Klavulanik Asit; MM-14151. (*Z*)-(2*R*,5*R*)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Клавулановая Кислота

$C_8H_9NO_5$ = 199.2.

CAS — 58001-44-8 (clavulanic acid); 57943-81-4 (sodium clavulanate).

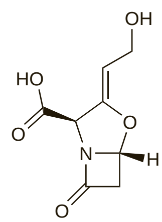

Potassium Clavulanate *(BANM, rINNM)*

BRL-14151K; Clavulanate de Potassium; Clavulanate Potassium *(USAN)*; Clavulanato potásico; Kalii clavulanas; Kalio klavulanatas; Kaliumklavulanaatti; Kaliumklavulanat; Kálium-klavulanát; Kalium-klavulanát; Potassium, clavulanate de; Potasu klawulanian.

Калия Клавуланат

$C_8H_8KNO_5$ = 237.3.

CAS — 61177-45-5.

NOTE. Compounded preparations of potassium clavulanate may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.

Eur. also includes Diluted Potassium Clavulanate.

Ph. Eur. 6.2 (Potassium Clavulanate). The potassium salt of a substance produced by the growth of certain strains of *Streptomyces clavuligerus* or by any other means. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers at a temperature of 2° to 8°.

Ph. Eur. 6.2 (Potassium Clavulanate, Diluted; Kalii Clavulanas Dilutus). A dry mixture of potassium clavulanate and microcrystalline cellulose or anhydrous or hydrated colloidal silicon dioxide. A white or almost white, hygroscopic, powder. A suspension corresponding to 1% of potassium clavulanate in water has a pH of 4.8 to 8.0. Store in airtight containers.

USP 31 (Clavulanate Potassium). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol with decomposition. Stability in aqueous solutions is not good, optimum stability at a pH of 6.0 to 6.3. pH of a 1% solution in water is between 5.5 and 8.0. Store in airtight containers.

Profile

Clavulanic acid is produced by cultures of *Streptomyces clavuligerus*. It has a beta-lactam structure resembling that of the penicillin nucleus, except that the fused thiazolidine ring of the penicillins is replaced by an oxazolidine ring. In general, clavulanic acid has only weak antibacterial activity. It is a potent progressive inhibitor of plasmid-mediated and some chromosomal beta-lactamases produced by Gram-negative bacteria including *Haemophilus ducreyi*, *H. influenzae*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Bacteroides fragilis*, and some Enterobacteriaceae. It is also an inhibitor of the beta-lactamases produced by *Staphylococcus aureus*. Clavulanic acid can permeate bacterial cell walls and can therefore inactivate both extracellular enzymes and those that are bound to the cell. Its mode of action depends on the particular enzyme inhibited, but it generally acts as a competitive, and often irreversible, inhibitor. Clavulanic acid consequently enhances the activity of penicillin and cephalosporin antibacterials against many resistant strains of bacteria. However, it is generally less effective against chromosomally mediated type 1 beta-lactamases; therefore, many *Citrobacter, Enterobacter, Morganella*, and *Serratia* spp., and *Pseudomonas aeruginosa* remain resistant. Some plasmid-mediated extended-spectrum beta-lactamases in *Klebsiella pneumoniae*, some other Enterobacteriaceae, and *Ps. aeruginosa* are also not inhibited by beta-lactamase inhibitors.

Clavulanic acid is given as potassium clavulanate orally and by injection with amoxicillin (co-amoxiclav) (p.202), and by injection with ticarcillin (p.352).

Use of clavulanate with penicillins has been associated with the development of cholestatic jaundice and hepatitis (see under Adverse Effects of Amoxicillin, p.202) and therefore the use of co-amoxiclav has declined (see below).

◊ Because of the risk of cholestatic jaundice co-amoxiclav is not a treatment of choice for common bacterial infections. The UK CSM[1] recommended that it should be reserved for bacterial infections likely to be caused by amoxicillin-resistant beta-lactamase-producing strains and that treatment should not usually exceed 14 days. It may be considered for the following main indications:

- sinusitis, otitis media, recurrent tonsillitis
- acute exacerbations of chronic bronchitis
- bronchopneumonia
- urinary-tract infections, especially when recurrent or complicated, but not prostatitis
- septic abortion, pelvic or puerperal sepsis, and intra-abdominal sepsis
- cellulitis, animal bites, and severe dental abscess with spreading cellulitis.

1. Committee on Safety of Medicines/Medicines Control Agency. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Preparations

BP 2008: Co-amoxiclav Injection; Co-amoxiclav Tablets;
USP 31: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Optamox; ***Indon.:*** Aclam; ***Turk.:*** Amoksilav.

Multi-ingredient: ***Arg.:*** Aclav; Amixen Clavulanico; Amoclav; Amoxi Plus; Amoxigrand Compuesto; Amoxitenk Plus; Bi Moxal; Bi Moxal Duo; Bioclavid; Bioxilina Plus; Clavulox; Clavulox Duo; Cloximar Duo; Darzitil Plus; Dibional; Fullcilina Plus†; Grinsil Clavulanico; Klonalmox; ***Austral.:*** Augmentin; Ausclav†; Clamohexal; Clamoxyl; Clavulin; Curam; Timentin; ***Austria:*** Amoclan; Amoxicillin comp; AmoxiClavulan; Amoxicomp; Amoxiplus; Amoxistad plus; Augmentin; Benclav; Benomox; Betamoclav; Clavamox; Clavex; Clavolek; Clavoplus; Clavulanex; CombAmox; Curam; Lanoclav; Lekamoxiclav; Oxyclav; Xiclav; ***Belg.:*** Amoclane; Augmentin; Clavucid; Co-Amoxi; Co-Amoxilan†; Docamoclaf; Timentin; ***Braz.:*** Augmentin; Betaclav; Clav-Air†; Clavoxil†; Clavulin; Novamox; Policlavumoxil; Sigma Clav; Timentin; ***Canad.:*** Apo-Amoxi Clav; Clavulin; Novo-Clavamoxin; ratio-Aclavulanate; Timentin; ***Chile:*** Ambilan; Ambilan Bid; Amolex; Augmentin; Augmentin Bid; Clavinex; Clavinex Duo; Clavoxilina Bid; ***Cz.:*** Amoksiklav; Augmentin; Augmentin-Duo; Betaklav; Curam; Enhancin; Forcid; Klamoxin†; Megamox; Timentin; ***Denm.:*** Bioclavid; Spektramox; ***Fin.:*** Amoxin Comp; Augmentin; Bioclavid; Clapharin Comp; Clavurion; Clavuxal; Forcid; Spektramox†; ***Fr.:*** Augmentin; Ciblor; Claventin; ***Ger.:*** Abiclav; Amoclav; Amoxclav; Amoxi-Clavulan; Amoxi-saar plus; Amoxicillin comp; Amoxiclav; Amoxidura Plus; Amoxillat-Clav†; Amuclan†; Augmentan; ***Gr.:*** Augmentin; Bioclavid; Forcid; Frolicin; Fugentin; Moxiclav; Tenervan; Timentin; ***Hong Kong:*** Amoksiklav; Augmentin; Clamovid; Curam; Fleming; Moxiclav; Quali-Mentin; Timentin; ***Hung.:*** Aktil; Amoclan†; Amoclav; Augmentin; Augmentin-Duo; Augmentin-Extra; Clavumox†; Co-Amoxi; Curam; Enhancin; Forcid; ***India:*** Augmentin; Boostim; Novaclav; Nuclav; Rapiclav†; Timentin; ***Indon.:*** Amocomb; Ancla; Augmentin; Auspilic; Bellamox; Betaclav; Biditin; Capsinat; Clabat; Claneksi; Clavamox; Comsikla; Danoclav; Daxet; Dexyclav; Improvox; Lansiclav; Nufaclav; Nuvoclav; Prafamoc; Protamox; Surpas; Syneclav; Viaclav; Vulamox; Zumafen; ***Irl.:*** Augmentin; Clavamel; Germentin; Pinaclav; Timentin†; ***Israel:*** Amoxiclav; Augmentin; Clavamox; Timentin; ***Ital.:*** Abba; Anival; Augmentin; Clavucar†; Clavulin; Neoduplamox; Timentin; Xinamod; ***Malaysia:*** Augmentin; Cavumox; Clamovid; Curam; Enhancin; Moxiclav; Vestaclav†; ***Mex.:*** Acarbixin; Acimox AC; Alvi-Tec; Amobay CL; Amoxiclav; Amoxiclide; Apoclavox; Augmentin; Avuxilan; Clambusil; Clamoxin; Clavant; Clavucyd; Clavulin; Clavuser; Enhancin; Gramaxin; Maxint†; Moxlin CLV; Riclasip; Servamox CLV; Sinufin; Timentin; Valclan; ***Neth.:*** Amoclan; Amuclan; Augmentin; Bioclavid; Forcid; Timentin; ***Norw.:*** Bremide†; ***NZ:*** Alpha-Amoxyclav; Augmentin; Synermox; Timentin; ***Philipp.:*** Amoclav; Augmentin; Augmex; Augurcin; Bactiv; Bactoclav; Bioclavid; Clamovid; Claneksi; Claventin; Clavoxel; Clovimax; Enhancin; Exten; Klavic; Natravox; Proxiclav; Sullivan; Suplentin; Timentin; Valmocel; Xilanic; ***Pol.:*** Amoksiklav; Augmentin; Curam; Forcid; Ramoclav; Taromentin; Timentin; ***Port.:*** Amoclavam; Amplamox Plus; Augmentin; Betamox; Clavamox; Clavepen; Forcid; Noprilam; Penilan; ***Rus.:*** Amoclan (Амоклан); Amoksiklav (Амоксиклав); Augmentin (Аугментин); Flemoclav (Флемоклав); Medoclav (Медоклав); Panklav (Панклав); Rapiclav (Рапиклав); Timentin (Тиментин); ***S.Afr.:*** Adco-Amoclav; Augmaxcil; Augmentin; Bio-Amoksiclav; Clamentin; Clavumox; Co-Amoxyclav; Curam; Forcid; Moxyclav†; Ranclav; Rolab-Amoclav; ***Singapore:*** Amocla; Augmentin; Augmex†; Clamonex; Clamovid; Curam; Enhancin; Fugentin; Moxiclav; ***Spain:*** Amoclave; Amoxyplus; Ardineclav; Augmentine; Bigpen†; Burmicin; Clavepen; Clavucid; Clavumox; Duonasa; Eupeclanic†; Inmupen†; Kelsopen; ***Swed.:*** Bioclavid; Spektramox; ***Switz.:*** Amicosol; Augmentin; Aziclav; Clavamox; clavu-basan†; Co-Amoxi; Co-Amoxicilline; Timenten†; ***Thai.:*** Amocla; Amoksiklav; Augclav; Augmentin; Augpen; Cavumox; Curam; Klamoks; Moxiclav; Moxicle; Pencla; Ranclav; ***Turk.:*** Amoklavin; Augmentin; Bioment; Croxilex; Klamoks; Klavunat; Klavupen; ***UAE:*** Julmentin; ***UK:*** Amiclav†; Augmentin; Augmentin-Duo; Timentin; ***USA:*** Amoclan; Augmentin; Timentin; ***Venez.:*** Augmentin; Augmentin Bid†; Clavumox; Curam; Fulgram.

Clemizole Penicillin *(BAN, rINN)*

Clemizol penicilina; Clemizole Benzylpenicillin; Clémizole Pénicilline; Clemizolum Penicillinum; Klemitsolipenisilliini; Klemizolpenicillin; Penicillin G Clemizole. 1-[1-(4-Chlorobenzyl)benzimidazol-2-ylmethyl]pyrrolidinium (6*R*)-6-(2-phenylacetamido)penicillanate.

Клемизол Пенициллин

$C_{16}H_{18}N_2O_4S,C_{19}H_{20}ClN_3$ = 660.2.

CAS — 6011-39-8.

Profile

Clemizole penicillin is a long-acting preparation of benzylpenicillin (p.213) with similar properties and uses.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Prevepen; ***Mex.:*** Megapenil; ***Switz.:*** Megacilline†.

Multi-ingredient: ***Chile:*** Prevepen Forte; ***Mex.:*** Anapenil; Megapenil Forte; ***Port.:*** Prevecilina; ***Spain:*** Neopenyl.

Clindamycin *(BAN, USAN, rINN)*

Clindamicina; Clindamycine; Clindamycinum; Klindamisin; Klindamycin; Klindamysiini; U-21251. Methyl 6-amino-7-chloro-6,7,8-trideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-L-*threo*-D-*galacto*-octopyranoside.

Клиндамицин

$C_{18}H_{33}ClN_2O_5S$ = 425.0.

CAS — 18323-44-9.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

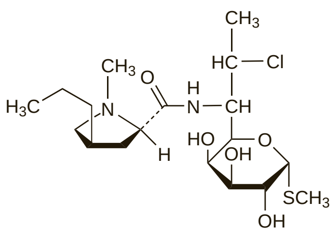

NOTE. The name Clinimycin, which was formerly used for clindamycin, has also been used for a preparation of oxytetracycline.

Clindamycin Hydrochloride *(BANM, rINNM)*

Chlorodeoxylincomycin Hydrochloride; (7*S*)-Chloro-7-deoxylincomycin Hydrochloride; Clindamycine, chlorhydrate de; Clindamycini hydrochloridum; Hidrocloruro de clindamicina; Klindamicin-hidroklorid; Klindamicino hidrochloridas; Klindamisin Hidroklorür; Klindamycin-hydrochlorid; Klindamycinhydroklorid; Klindamycyny chlorowodorek; Klindamysiinihydrokloridi.

Клиндамицина Гидрохлорид

$C_{18}H_{33}ClN_2O_5S,HCl$ = 461.4.

CAS — 21462-39-5 (anhydrous clindamycin hydrochloride); 58207-19-5 (clindamycin hydrochloride monohydrate).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Clindamycin Hydrochloride). A white or almost white, crystalline powder. It contains a variable quantity of water. Very soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 3.0 to 5.0. Store in airtight containers.

USP 31 (Clindamycin Hydrochloride). A white or practically white crystalline powder, odourless or has a faint mercaptan-like odour. Freely soluble in water, in dimethylformamide, and in methyl alcohol; soluble in alcohol; practically insoluble in acetone. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Clindamycin Palmitate Hydrochloride

(BANM, USAN, rINNM)

Clindamycine, Chlorhydrate de Palmitate de; Clindamycini Palmitatis Hydrochloridum; Hidrocloruro del palmitato de clindamicina; U-25179E. Clindamycin 2-palmitate hydrochloride.

Клиндамицина Палмитата Гидрохлорид

$C_{34}H_{63}ClN_2O_6S,HCl$ = 699.9.

CAS — 36688-78-5 (clindamycin palmitate); 25507-04-4 (clindamycin palmitate hydrochloride).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *US.*

USP 31 (Clindamycin Palmitate Hydrochloride). A white to off-white amorphous powder having a characteristic odour. Freely soluble in water, in chloroform, in ether, and in benzene; soluble 1 in 3 of alcohol and 1 in 9 of ethyl acetate; very soluble in dimethylformamide. pH of a 1% solution in water is between 2.8 and 3.8. Store in airtight containers.

Clindamycin Phosphate *(BANM, USAN, rINNM)*

Clindamycine, phosphate de; Clindamycini Dihydrogenophosphas; Clindamycini phosphas; Fosfato de clindamicina; Klindamicin-foszfát; Klindamicino fosfatas; Klindamisin Fosfat; Klindamycin dihydrogen fosfát; Klindamycinfosfat; Klindamysiinifosfaatti; U-28508. Clindamycin 2-(dihydrogen phosphate).

Клиндамицина Фосфат

$C_{18}H_{34}ClN_2O_8PS$ = 505.0.

CAS — 24729-96-2.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn*, and *US.*

Ph. Eur. 6.2 (Clindamycin Phosphate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding 30° in airtight containers.

USP 31 (Clindamycin Phosphate). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Soluble 1 in 2.5 of water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in ether, and in benzene. pH of a 1% solution in water is between 3.5 and 4.5. Store in airtight containers.

Incompatibility. Solutions of clindamycin salts have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution of clindamycin states that incompatibility has been reported between clindamycin and the following drugs: ampicillin, aminophylline, barbiturates, calcium gluconate, ceftriaxone, ciprofloxacin, idarubicin, magnesium sulfate, phenytoin, and ranitidine.

Clindamycin phosphate is incompatible with natural rubber closures.

Adverse Effects and Treatment

Clindamycin is reported to produce diarrhoea in up to 20% of patients after systemic use. In some patients severe antibiotic-associated or pseudomembranous colitis (p.171) may develop during therapy or up to several weeks after it, and has proved fatal. It has been reported to be more frequent in middle-aged and elderly women, particularly after surgery; it may also occur rarely after topical use. Clindamycin should be stopped immediately if significant diarrhoea or colitis occurs. Protein supplementation and use of an antibacterial active against *Clostridium* spp. should be considered for severe antibiotic-associated colitis.

Other gastrointestinal effects include nausea, vomiting, abdominal pain or cramps, and oesophagitis; an unpleasant or metallic taste has occasionally been reported after high intravenous doses.

Skin rashes and urticaria, the most common hypersensitivity reactions, occur in up to 10% of patients usually after 1 to 2 weeks of therapy. Erythema multiforme, Stevens-Johnson syndrome, and exfoliative and vesiculobullous dermatitis have been reported rarely, and a few cases of anaphylaxis have occurred.

Other adverse effects include transient leucopenia or occasionally agranulocytosis, eosinophilia, thrombocytopenia, polyarthritis, and abnormalities of liver function tests; in some cases overt jaundice and hepatic damage have been reported. Renal dysfunction, shown by azotaemia, oliguria, and/or proteinuria has been reported rarely.

Although local irritation is rare, intramuscular injection has led to induration and sterile abscess, and thrombophlebitis may occur after intravenous use. Too rapid intravenous infusion can result in rare instances of cardiopulmonary arrest and hypotension. Some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p.1632).

Topical application may be associated with local irritation and contact dermatitis; sufficient clindamycin may be absorbed to produce systemic effects. Cervicitis, vaginitis, or vulvovaginal irritation has been reported with intravaginal use; a small amount of systemic absorption also occurs.

Effects on the cardiovascular system. Cardiac arrest occurred in a 50-year-old woman after rapid injection of 600 mg of undiluted clindamycin phosphate into a central intravenous line. Further injections were given over 30 minutes without cardiovascular complications.[1] There has also been a case of severely prolonged QT interval attributed to the addition of clindamycin to therapy in an elderly woman;[2] the patient developed AV block and subsequent torsade de pointes, and required resuscitation. When clindamycin was stopped, signs of heart block resolved, and the QT interval returned to normal over several days.

1. Aucoin P, *et al.* Clindamycin-induced cardiac arrest. *South Med J* 1982; **75:** 768.
2. Gabel A, *et al.* Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. *Am J Cardiol* 1999; **83:** 813–15.

Effects on the ears. A 14-year-old boy who was treated with topical clindamycin for acne vulgaris developed unilateral tinnitus during therapy and unilateral sensorineural hearing loss 2 months later;[1] symptoms subsequently recurred upon 2 rechallenges.

1. Scissors B, Shwayder T. Topical clindamycin reproducibly causing tinnitus in a 14-year-old boy. *J Am Acad Dermatol* 2006; **54** (suppl): S243–S244.

Effects on the lymphatic system. A report of lymphadenitis associated with clindamycin.[1]

1. Southern PM. Lymphadenitis associated with the administration of clindamycin. *Am J Med* 1997; **103:** 164–5.

Effects on the skin. There have been reports of toxic epidermal necrolysis[1] and acute generalised exanthematous pustulosis[2,3] associated with clindamycin.

1. Paquet P, *et al.* Toxic epidermal necrolysis following clindamycin treatment. *Br J Dermatol* 1995; **132:** 665–6.
2. Valois M, *et al.* Clindamycin-associated acute generalized exanthematous pustulosis. *Contact Dermatitis* 2003; **48:** 169.
3. Kapoor R, *et al.* Acute generalized exanthematous pustulosis induced by clindamycin. *Arch Dermatol* 2006; **142:** 1080–81.

Precautions

Clindamycin should not be given to patients hypersensitive to it or to the closely related drug lincomycin. It should be used with caution in patients with a history of gastrointestinal disease, particularly colitis, and stopped immediately if significant diarrhoea or colitis occurs. Middle-aged and elderly female patients may be at greater risk of severe diarrhoea or pseudomembranous colitis. Caution has also been advised in atopic patients. Periodic tests of liver and kidney function and blood counts have been recommended in patients receiving prolonged therapy, and in infants. Caution is required during parenteral use in neonates, since some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' (see p.1632).

AIDS. Clindamycin was poorly tolerated by patients with AIDS in a study of its use for *prophylaxis* of toxoplasmic encephalitis.[1] Despite the use of relatively low doses of clindamycin (300 mg twice daily), 23 of 52 patients reported adverse effects that necessitated temporary or permanent withdrawal of the drug, the most frequent adverse reactions being diarrhoea and skin rash. The clindamycin arm of the study had to be terminated prematurely. Nevertheless, clindamycin has been used successfully in patients with AIDS for the *treatment* of both toxoplasmic encephalitis (see Toxoplasmosis, below) and pneumocystis pneumonia (below).

1. Jacobson MA, *et al.* Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 1992; **339:** 333–4.

Breast feeding. US licensed product information states that concentrations of clindamycin in breast milk were 0.7 to 3.8 micrograms/mL after doses of 150 mg orally to 600 mg intravenously. No adverse effects have been seen in breast-fed infants whose mothers were receiving clindamycin, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding. Nevertheless, UK product information states that although it is unlikely that a breast-fed infant could absorb significant amounts, caution should be exercised when clindamycin is given during breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Interactions

Clindamycin has neuromuscular blocking activity in high doses and may enhance the effect of other drugs with this action (see Atracurium, p.1903), leading to a potential danger of respiratory depression. Clindamycin may antagonise the effects of parasympathomimetics. For mention of synergistic and antagonistic antimicrobial activity with other antibacterials, see Antimicrobial Action, below.

Adsorbents. In 16 healthy subjects given clindamycin alone and with a *kaolin-pectin* suspension it was found that the suspension had no effect on the extent of clindamycin absorption but did markedly reduce the absorption rate.[1]

1. Albert KS, *et al*. Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* 1978; **67:** 1579–82.

Antimicrobial Action

Clindamycin is a lincosamide antibacterial with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria.

Mechanism of action. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome, similarly to macrolides such as erythromycin (p.271), and inhibit the early stages of protein synthesis. The action of clindamycin is mainly bacteriostatic, although high concentrations may be slowly bactericidal against sensitive strains.

Spectrum of activity. Clindamycin is active against:

- most aerobic Gram-positive bacteria including streptococci, staphylococci, *Bacillus anthracis*, and *Corynebacterium diphtheriae*
- enterococci are generally resistant
- susceptible Gram-positive anaerobes include *Eubacterium*, *Propionibacterium*, *Peptococcus*, and *Peptostreptococcus* spp., and many strains of *Clostridium perfringens* and *Cl. tetani*
- Gram-negative anaerobes susceptible to clindamycin include *Fusobacterium* spp. (although *F. varium* is usually resistant), *Prevotella* spp., and *Bacteroides* spp., including the *B. fragilis* group
- several *Actinomyces* spp. and *Nocardia asteroides* are reported to be susceptible
- *Mycoplasma* spp. are generally resistant
- most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin; unlike erythromycin, *Neisseria gonorrhoeae*, *N. meningitidis*, and *Haemophilus influenzae* are generally resistant
- fungi, yeasts, and viruses are also resistant; however, clindamycin has been reported to have some antiprotozoal activity against *Toxoplasma gondii* and *Plasmodium* spp.

Activity with other antimicrobials. Synergistic activity has been reported between clindamycin and ceftazidime or metronidazole, and also with ciprofloxacin against some anaerobes. However, there is some evidence that clindamycin inhibits the bactericidal activity of the aminoglycosides, although conflicting reports have suggested variable degrees of synergy against anaerobic organisms. Because of the adjacency of their binding sites on the ribosome, clindamycin may competitively inhibit the effects of macrolides or chloramphenicol. Clindamycin has been reported to diminish the activity of ampicillin *in vitro* against *Staph. aureus*. It is reported to enhance the activity of primaquine against *Pneumocystis jirovecii*. Antagonism between clindamycin and erythromycin has been shown *in vitro*.

Resistance. Most Gram-negative aerobes, such as the Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp., are intrinsically resistant to clindamycin, but acquired resistance also occurs in normally sensitive strains. The **mechanisms** of resistance are the same as those for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein, and, in a few staphylococcal isolates, enzymic inactivation by a plasmid-mediated adenyltransferase. Methylation of the ribosome leads to cross-resistance between the lincosamides and macrolides and streptogramins (the MLS_B phenotype); this type of resistance is usually plasmid-mediated and inducible. Complete cross-resistance exists between clindamycin and lincomycin.

The **incidence** of resistance varies with the organism and the geographical location; it is more frequent in organisms that are also erythromycin-resistant, and some strains of meticillin-resistant *Staph. aureus* are also resistant to clindamycin. In some countries and institutions there is evidence of an increase in resistance amongst the *B. fragilis* group to about 25% of strains or more. Resistance to clindamycin by anaerobes has also been reported in 10 to 20% of *Clostridium* spp. other than *C. perfringens*, 8% of peptostreptococci, 9% of *Fusobacterium* spp., and 11% of *Prevotella* strains.

Action. References suggesting that clindamycin may reduce microbial adherence and enhance phagocytosis by its effects on bacterial slime (glycocalyx)[1-3] and that its antibacterial effects may be independent of plasma concentrations.[4,5]

1. Veringa EM, *et al.* Enhancement of opsonophagocytosis of Bacteroides spp by clindamycin in subinhibitory concentrations. *J Antimicrob Chemother* 1981; **23:** 577–87.
2. Veringa EM, *et al.* The role of glycocalyx in surface phagocytosis of Bacteroides spp, in the presence and absence of clindamycin. *J Antimicrob Chemother* 1989; **23:** 711–20.
3. Khardori N, *et al.* Effect of subinhibitory concentrations of clindamycin and trospectomycin on the adherence of Staphylococcus epidermidis in an in vitro model of vascular catheter colonization. *J Infect Dis* 1991; **164:** 108–13.
4. Xue IB, *et al.* Variation in postantibiotic effect of clindamycin against clinical isolates of Staphylococcus aureus and implications for dosing of patients with osteomyelitis. *Antimicrob Agents Chemother* 1996; **40:** 1403–7.
5. Klepser ME, *et al.* Bactericidal activity of low-dose clindamycin administered at 8- and 12-hour intervals against Staphylococcus aureus, Streptococcus pneumoniae, and Bacteroides fragilis. *Antimicrob Agents Chemother* 1997; **41:** 630–5.

Resistance. Although there is usually cross-resistance between clindamycin and macrolides (above), a resistance pattern has been identified that results in streptococcal resistance to macrolides while retaining susceptibility to clindamycin.[1]

1. Sutcliffe J, *et al.* Streptococcus pneumoniae and Streptococcus pyogenes resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. *Antimicrob Agents Chemother* 1996; **40:** 1817–24.

Pharmacokinetics

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastrointestinal tract; concentrations of 2 to 3 micrograms/mL occur within 1 hour after a 150-mg oral dose, with average concentrations of about 700 nanograms/mL after 6 hours. After doses of 300 and 600 mg, peak plasma concentrations of 4 and 8 micrograms/mL, respectively, have been reported. Absorption is not significantly diminished by food in the stomach but the rate of absorption may be reduced. Clindamycin palmitate hydrochloride is rapidly hydrolysed on oral use to free clindamycin.

After parenteral use, the biologically inactive clindamycin phosphate is also hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 micrograms/mL occurs within 3 hours; 600 mg gives a peak concentration of 9 micrograms/mL. In children, peak concentrations may occur within 1 hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms/mL occur by the end of infusion.

Small amounts of clindamycin may be absorbed after topical application to the skin; bioavailability from topical preparations of the hydrochloride and phosphate (the former in an extemporaneous formulation) has been reported to be about 7.5% and 2% respectively.

About 5% of a dose may be absorbed systemically from an intravaginal cream formulation; absorption from vaginal pessaries is reported to be about 30%.

Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the CSF in significant concentrations. It diffuses across the placenta into the fetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, although this may be prolonged in preterm neonates and in patients with severe renal impairment.

Clindamycin undergoes metabolism, presumably in the liver, to the active *N*-demethyl and sulfoxide metabolites, and also to some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow, and takes place over several days. It is not effectively removed from the blood by dialysis.

AIDS patients. Clindamycin was reported to have higher bioavailability, lower plasma clearance, and a lower volume of distribution in patients with AIDS than in healthy subjects.[1] This may partly be explained by increased binding to plasma proteins.[2]

Although it is generally considered that penetration of clindamycin into the CSF is insignificant, parasiticidal CSF concentrations against *Toxoplasma gondii* were achieved with intravenous clindamycin in patients with AIDS.[3]

1. Gatti G, *et al.* Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. *Antimicrob Agents Chemother* 1993; **37:** 1137–43.
2. Flaherty JF, *et al.* Protein binding of clindamycin in sera of patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1134–8.
3. Gatti G, *et al.* Penetration of clindamycin and its metabolite N-demethylclindamycin into cerebrospinal fluid following intravenous infusion of clindamycin phosphate in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 3014–17.

Uses and Administration

Clindamycin is a lincosamide antibacterial that is a chlorinated derivative of lincomycin. It is a mainly bacteriostatic drug used in the treatment of serious anaerobic infections, notably due to *Bacteroides fragilis.* Clindamycin is also used for some Gram-positive infections due to pneumococci, staphylococci, and streptococci. However, because of its potential for causing pseudomembranous colitis (see Adverse Effects, above) it is usually used only when alternative drugs are unsuitable.

Amongst the conditions that it may be used to treat are liver abscess, actinomycosis, biliary-tract infections, staphylococcal bone and joint infections, the carrier state of diphtheria, endophthalmitis, gas gangrene, various gynaecological infections including bacterial vaginosis, endometritis, and pelvic inflammatory disease (the latter two with an aminoglycoside), intra-abdominal infections including secondary peritonitis, streptococcal pharyngitis (usually to treat the carrier state), serious respiratory-tract infections including empyema and pneumonia (especially lung abscess), septicaemia, and skin and soft-tissue infections involving heavy colonisation with streptococci or anaerobes such as necrotising fasciitis. Clindamycin is also used as part of a multidrug regimen in the treatment of anthrax. It is used in the prophylaxis of endocarditis in penicillin-allergic patients, in the prevention of perinatal streptococcal infections, and with other drugs for the prophylaxis of surgical infection. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax.

For details of these bacterial infections and their treatment, see under Choice of Antibacterial, p.162.

Clindamycin is also applied topically in the treatment of acne (p.1577) and rosacea (below).

Clindamycin has some antiprotozoal actions, and has been used, usually with other antiprotozoals, in various infections (see below) including babesiosis, malaria, and toxoplasmosis. It may also be used with primaquine in the treatment of pneumocystis pneumonia (below).

Clindamycin is given **orally** as capsules containing the hydrochloride or as oral liquid preparations containing the palmitate hydrochloride. The capsules should be taken with a glass of water. Doses are expressed in terms of the base; 1.1 g of clindamycin hydrochloride and 1.6 g of clindamycin palmitate hydrochloride are each equivalent to about 1 g of clindamycin. The usual adult oral dose is 150 to 300 mg every 6 hours; in severe infections the dose may be increased to 450 mg every 6 hours.

Clindamycin is given **parenterally** as the phosphate by intramuscular injection or by intermittent or continuous intravenous infusion over 10 minutes to 1 hour. Doses are again expressed in terms of the base; 1.2 g of clindamycin phosphate is equivalent to about 1 g of clindamycin. For intravenous use, the concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL and the rate of infusion should be not more than 30 mg/minute. Not more than 1.2 g should be given as a single one-hour infusion, and not more than 600 mg should be given as a single intramuscular injection.

The usual parenteral dose is the equivalent of 0.6 to 1.2 g of clindamycin daily in divided doses; in severe infections the dose may be increased to 2.7 g daily and up to 4.8 g daily may be given intravenously in life-threatening situations.

For *prophylaxis* in adult patients at risk of developing endocarditis and who cannot be given a penicillin, an oral dose of clindamycin 600 mg, given 1 hour before procedures such as dental extractions under local or no anaesthesia, has been suggested. For high-risk patients undergoing dental procedures involving general anaesthesia and who cannot be given a penicillin, clindamycin 300 mg given intravenously over at least 10 minutes, at induction or 15 minutes before the procedure, has been suggested. However in the UK the *BNF* and NICE now suggest that such prophylaxis is unnecessary (see p.168).

For details of doses in children, including infants and adolescents, see below.

Topical formulations containing clindamycin phosphate equivalent to 1% of clindamycin are used for the treatment of acne. The hydrochloride may be applied similarly, but systemic absorption may be greater (see Pharmacokinetics, above). Clindamycin phosphate is also available in combination preparations with benzoyl peroxide and tretinoin.

Clindamycin phosphate may be given **intravaginally** as pessaries or as a 2% cream for the treatment of bacterial vaginosis; the equivalent of about 100 mg of clindamycin is given at night for 3 to 7 days.

Administration. A number of studies have suggested that a parenteral regimen of clindamycin 600 mg three times daily is as effective as giving the same dose four times daily,[1] or as giving 900 mg three times daily.[2,3]

1. Buchwald D, *et al.* Effect of hospitalwide change in clindamycin dosing schedule on clinical outcome. *Rev Infect Dis* 1989; **11:** 619–24.
2. Chin A, *et al.* Cost analysis of two clindamycin dosing regimens. *DICP Ann Pharmacother* 1989; **23:** 980–3.
3. Chatwani A, *et al.* Clindamycin dosage scheduling for acute pelvic infection. *Am J Obstet Gynecol* 1990; **163:** 240.

SUBCONJUNCTIVAL ROUTE. It has been suggested, should periocular use of clindamycin be necessary, that the injection solution can be given in doses of 15 to 50 mg by subconjunctival injection.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Administration in children. The usual oral dose for infants and children under 12 years of age is the equivalent of 3 to 6 mg/kg of clindamycin every 6 hours. In the UK, the *BNFC* suggests that neonates aged under 14 days may be given this dose every 8 hours and children aged 1 month and over but weighing less than 10 kg should be given a minimum dose of 37.5 mg every 8 hours; children over 12 years of age may be given the usual adult dose (see above).

The usual parenteral dose for infants and children aged from 1 month to 12 years is the equivalent of 15 to 25 mg/kg of clindamycin daily in 3 or 4 divided doses; in severe infections the dose may be increased to 40 mg/kg daily and a minimum dose of 300 mg daily should be given regardless of body-weight. Children over 12 years of age may be given the usual adult dose (see above). In the USA, it is also licensed for parenteral use in those aged under 1 month and 15 to 20 mg/kg daily may be given in 3 or 4 divided doses. It should be borne in mind that some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p.1632).

For the treatment of staphylococcal lung infection in children aged from 1 month to 18 years with cystic fibrosis, the *BNFC* recommends oral doses of 5 to 7 mg/kg (to a maximum of 600 mg) every 6 hours.

For children's doses in babesiosis, malaria, and toxoplasmosis, see below.

Babesiosis. Clindamycin, given with quinine, both for 7 to 10 days, is recommended by some experts in the USA[1,2] for the treatment of babesiosis (p.823) caused by *Babesia microti*. Dosage regimens include:

- clindamycin 1.2 g intravenously twice daily, with quinine 650 mg three or four times daily by mouth
- clindamycin 300 to 600 mg intravenously every 6 hours, with quinine as above
- clindamycin 600 mg orally three times daily, with quinine as above

Children may be given clindamycin 20 to 40 mg/kg daily intravenously or by mouth in 3 or 4 divided doses with quinine 25 mg/kg daily by mouth in 3 divided doses, both for 7 to 10 days.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Correction. *ibid.* 2007; **45:** 941. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 11/08/08)

Malaria. Quinine sulfate plus follow-on treatment with doxycycline, tetracycline, or clindamycin are recommended regimens for the treatment of chloroquine-resistant falciparum malaria (p.594) in non-endemic malaria areas. Doxycycline is generally preferred because it can be given once daily. However, tetracyclines are contra-indicated in children under 8 years of age and in pregnant women, who may be given clindamycin. Clindamycin is given in the usual *adult* dose of 20 mg/kg daily in 3 divided doses (or 450 mg 3 times daily) for 7 days with quinine sulfate 600 to 650 mg 3 times daily for 3 to 7 days, both orally.[1-5] Parenteral quinine (or quinidine) plus follow-on treatment with a tetracycline or clindamycin may be used for severe falciparum malaria in both endemic and non-endemic malaria areas.[2-5] Patients unable to tolerate oral treatment may begin follow-on therapy intravenously.[2,3]

In the UK[5] public health authorities recommend that *children* be given clindamycin at a dose of 7 to 13 mg/kg 3 times daily for 7 days; US[2] public health authorities recommend giving 20 mg/kg daily in 3 divided doses.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 6th March 2007). Available at: http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf (accessed 28/03/07)
3. British Infection Society. Algorithm for initial assessment and management of malaria in adults (issued February 2007). Available at: http://www.britishinfectionsociety.org/documents/MalariaAlgorithm07.pdf (accessed 20/06/07)
4. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 28/03/07)
5. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54:** 111–21.

Pneumocystis pneumonia. Clindamycin may be used with primaquine as an alternative to co-trimoxazole for the **treatment** of pneumocystis pneumonia (p.521). In the USA, some experts[1,2] recommend giving clindamycin 600 to 900 mg intravenously, or 300 to 450 mg orally, every 6 to 8 hours with primaquine 15 to 30 mg by mouth once daily, both for 21 days. In the UK the *BNF* suggests giving clindamycin 600 mg every 8 hours with primaquine 30 mg daily, both by mouth, for mild to moderate disease (but notes that this combination is associated with considerable toxicity).

A meta-analysis[3] of literature published between January 1975 to August 1999 found that, when compared with other salvage agents (such as atovaquone, co-trimoxazole, eflornithine, pentamidine, and trimetrexate), clindamycin with primaquine was the most effective regimen in patients unresponsive to conventional treatment. The authors also concluded that this latter regimen was effective as primary treatment of mild to moderately severe disease and suggested that it had fewer adverse effects than co-trimoxazole.

Clindamycin with primaquine is not normally recommended for **prophylaxis** although there are reports of it being tried.[4] A retrospective examination[5] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 14/05/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 14/05/07)
3. Smego RA, *et al.* A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med* 2001; **161:** 1529–33.
4. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
5. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Rosacea. Topical clindamycin[1] has improved inflammatory episodes of rosacea (p.1583), although other features of the skin disorder may not respond. A small study[2] showed that once-daily application of clindamycin 1% plus benzoyl peroxide 5% was effective in the treatment of moderate to severe rosacea.

1. Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32:** 65–7.
2. Breneman D, *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol* 2004; **43:** 381–7.

Toxoplasmosis. Clindamycin with pyrimethamine has been used for the treatment and secondary prophylaxis (chronic maintenance) of toxoplasmosis (p.826) instead of the more usual treatment with pyrimethamine plus sulfadiazine, in patients unable to tolerate sulfonamides; folinic acid is also given to counteract the megaloblastic anaemia associated with pyrimethamine. In adult patients with AIDS and toxoplasmic encephalitis, clindamycin 600 mg every 6 hours orally or intravenously for at least 6 weeks, then maintenance therapy with 300 to 450 mg every 6 to 8 hours by mouth, has been recommended in the USA.[1] Children may be given clindamycin 5 to 7.5 mg/kg 4 times daily by mouth or intravenously for at least 6 weeks, followed by chronic maintenance therapy.[2]

Other studies found acute therapy with pyrimethamine and clindamycin, 600 mg 4 times daily by mouth[3] or 1200 mg every 6 hours intravenously,[4] to be as effective as pyrimethamine and sulfadiazine, but oral maintenance therapy with pyrimethamine and clindamycin 300 mg 4 times daily was less effective than pyrimethamine and sulfadiazine at preventing relapses in a population followed for 3 years or more.[3] Clindamycin with fluorouracil produced beneficial responses in a study involving 16 patients.[5]

In contrast, another study, comparing clindamycin alone (in lower oral doses—300 mg twice daily) with pyrimethamine alone for prophylaxis of toxoplasmic encephalitis, reported an unacceptably high incidence of adverse effects with clindamycin, which forced premature termination of the clindamycin arm—see AIDS under Precautions, above.

1. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 14/05/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 14/05/07)
2. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 14/05/07)
3. Katlama C, *et al.* Pyrimethamine-clindamycin vs pyrimethamine-sulphadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996; **22:** 268–75.
4. Dannemann B, *et al.* Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992; **116:** 33–43.
5. Dhiver C, *et al.* 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS* 1993; **7:** 143–4.

Preparations

BP 2008: Clindamycin Capsules; Clindamycin Injection;
USP 31: Clindamycin for Injection; Clindamycin Hydrochloride Capsules; Clindamycin Hydrochloride Oral Solution; Clindamycin Injection; Clindamycin Palmitate Hydrochloride for Oral Solution; Clindamycin Phosphate Gel; Clindamycin Phosphate Topical Solution; Clindamycin Phosphate Topical Suspension; Clindamycin Phosphate Vaginal Cream; Clindamycin Phosphate Vaginal Inserts.

Proprietary Preparations (details are given in Part 3)

Arg.: Acnestop; Clidan; Clindacin; Clindalaf; Clindopax; Clintopic; Dalacin C; Dalacin ST; Dalacin†; Naxoclinda; Torgyn; ***Austral.:*** Cleocin; Clindatech; Dalacin C; Dalacin T; Dalacin V; ***Austria:*** Cleocin; Clidam†; Clindac; Dalacin; Lanacine; ***Belg.:*** Dalacin; Dalacin C; Zindaclin; ***Braz.:*** Anaerocid; Clinagel; Clindacin†; Clindacne; Clindamin C; Clindarix; Dalacin C; Dalacin T; Dalacin V; ***Canad.:*** Clindets; Dalacin C; Dalacin T; Dalacin Vaginal; ***Chile:*** Clidets; Cluvax; Daclin; Dalacin; Dalacin C; Dalacin T; Dalacin V; Dermabel; Divanon; Lexis†; ***Cz.:*** Dalacin; Dalacin C; Dalacin T; Klimicin; Zindaclin; ***Denm.:*** Dalacin; ***Fin.:*** Dalacin; Klindagol; ***Fr.:*** Dalacine; Dalacine T; Zindacline; ***Ger.:*** Aclinda†; Basocin; Clin-Sanorania; Clinda; Clinda-saar; Clindabeta; Clindahexal; Clindastad; Dentomycin; Jutaclin; Sobelin; Turimycin; Zindaclin; ***Gr.:*** Arfarel; Borophen; Botamycin-N; Clidacin; Climycen; Clindagel; Dalacin C; Edason†; Fouch; Lindasol†; Paradis; Sotomycin; Toliken; Upderm; Vagiclin; Veldom; Velkaderm; Ygielle; ***Hong Kong:*** Claribel; Clinac; Clindatech; Dalacin C; Dalacin T; Delta T; Fleminosan†; Qualiclinda; Topicil†; ***Hung.:*** Dalacin; Dalacin C; Dalacin T; Klimicin; ***India:*** Clindac A; Dalacin; Dalcap; ***Indon.:*** Albiotin; Anerocid; Biodasin; Cindala; Climadan; Clinbercin; Clindexcin; Clinidac; Clinika; Clinium; Clinjos; Clinmas; Comdasin; Dacin; Daclin; Dalacin C; Ethidan; Indanox; Lando; Librodan; Lindacyn; Lindan; Mediklin; Niladacin; Nufaclind; Opiclam; Probiotin; Prolic; Zumatic; ***Irl.:*** Dalacin; Dalacin C; Dalacin T; Zindaclin; ***Israel:*** Dalacin C; Dalacin Vaginal; Dalagis T; Zindaclin; ***Ital.:*** Cleocin; Dalacin C; Dalacin T; ***Malaysia:*** C-Mycin†; Clindac; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; ***Mex.:*** Ancine; Apomiclin; Biodaclin; Cigmadil; Clendazaf; Clidets; Clinamsa; Clindazyn; Cutaclin; Dalacin C; Dalacin T; Dalacin V; Dalatina; Dalatina V; Damiclin; Destralina; Feisclin; Galecin; Indamid; Klyndaken; Lindacil; Lisiken; Losertrin; Trexen; Ulmicy; ***Neth.:*** Dalacin C; Dalacin T; ***Norw.:*** Dalacin; ***NZ:*** Clinac†; Dalacin C; Dalacin T†; Topicil; ***Philipp.:*** Anerocin; Clindal; Clindatech; Cliz; Dalacin C; Inprosyn-HP; Lincyn; Myclin; Tidact; Zindal; ***Pol.:*** Clindacin; Clindacne; Clindo; Dalacin C; Dalacin T; Klimicin; Klindacin T; Zindaclin; ***Port.:*** Clincina; Dalacin C; Dalacin T; Dalacin V; Zindaclin; ***Rus.:*** Clindacin (Клиндацин); Dalacin (Далацин); Dalacin C (Далацин Ц)†; Klimicin (Климицин); ***S.Afr.:*** Clindac; Clindahexal; Dalacin C; Dalacin T; Dalacin VC; ***Singapore:*** C-Mycin†; Climadan†; Clindagel; Clindatech; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; ***Spain:*** Clinwas; Dalacin; Zindaclin; ***Swed.:*** Dalacin; ***Switz.:*** Dalacin C; Dalacin T; Dalacin V; ***Thai.:*** Chinacin-T; Clindalin; Clindavid; Clinott; Dacin-F; Dalacin C; Dalacin T; Klimicin; Klindan; Klinna; Lacin; Rosil; ***Turk.:*** Cleocin T; Clin; Klindan; Klindaver; Klinoksin; Klitopsin; Meneklin; ***UK:*** Dalacin; Dalacin C; Dalacin T; Zindaclin; ***USA:*** Cleocin; Cleocin T; Clindagel; ClindaMax; Clindesse; Clindets; Evoclin; ***Venez.:*** Bioclindax; Clindaval; Clindox; Clinfol; Dalacin; Felisep†.

Multi-ingredient: ***Arg.:*** Clindacur; Clindoxyl; CP-Acne; Dermaclean; Duo Clindacin; Ovogin; Perclin; Torgyn Duo; ***Austral.:*** Duac; ***Austria:*** Clindoxyl; ***Braz.:*** Clindoxyl; ***Canad.:*** Benzaclin; Clindoxyl; ***Chile:*** Indoxyl; Klina; ***Cz.:*** Duac; ***Ger.:*** Copal; ***Gr.:*** Indoxyl; ***Hong Kong:*** Duac; ***India:*** Deriva-C; ***Indon.:*** Benzolac Cl; Climadan; Medi-Klin TR; ***Irl.:*** Duac; ***Mex.:*** Benzaclin; Clindapack; Femisan; Gynoclin-V; Indoxyl; Trexen Duo; ***Neth.:*** Duac; ***NZ:*** Duac; ***Pol.:*** Duac; ***Port.:*** Duac; ***Spain:*** Duac; ***Swed.:*** Duac; ***Turk.:*** Cleocin; ***UK:*** Duac Once Daily; ***USA:*** Benzaclin; Duac; Ziana.

Clioquinol *(BAN, rINN)*

Chinoform; Chloroiodoquine; Cliochinolum; Clioquinolum; Iodochlorhydroxyquin; Iodochlorhydroxyquinoline; Kliochinol; Kliokinol; Kliokinoli; Kliokvinolis; PBT-1; Quiniodochlor. 5-Chloro-7-iodoquinolin-8-ol.

Клиохинол

C_9H_5ClINO = 305.5.
CAS — 130-26-7.
ATC — D08AH30; D09AA10; G01AC02; P01AA02; S02AA05.
ATC Vet — QD08AH30; QD09AA10; QG01AC02; QS02AA05.

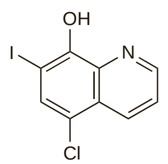

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Clioquinol). An almost white, light yellow, brownish-yellow, or yellowish-grey powder. Practically insoluble in water; very slightly soluble or slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Clioquinol). A voluminous, spongy, yellowish-white to brownish-yellow powder having a slight characteristic odour. It darkens on exposure to light. Practically insoluble in water; soluble 1 in 3500 of alcohol, 1 in 120 of chloroform, and 1 in 4500 of ether; soluble in hot ethyl acetate and in hot glacial acetic acid. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Clioquinol may rarely cause iodism in sensitive patients. Local application of clioquinol in ointments or creams may occasionally cause severe irritation or hypersensitivity and there may be cross-sensitivity with other halogenated hydroxyquinolines.

Clioquinol stains clothing and linen yellow on contact and may stain the skin and discolour fair hair.

Clioquinol given by mouth has been associated with severe neurotoxicity. In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods, and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are principally those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms, such as paraesthesias in the legs progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. A characteristic green pigment, a chelate of clioquinol with iron, is often seen on the tongue and in the urine and faeces. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disablement.

It was suggested that the Japanese epidemic might be due to genetic susceptibility, but a few similar cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, such as broxyquinoline or diiodohydroxyquinoline have been reported from other countries. Oral preparations of clioquinol have now been banned in most countries.

Hypersensitivity. Clioquinol is classified as a contact allergen which can commonly cause sensitisation, especially when applied to eczematous skin; chlorquinaldol can also cause sensitisation, although less frequently.[1] It is important to include clioquinol and chlorquinaldol in routine patch testing since the clinical reaction may be relatively mild and sensitivity easily missed, particularly in the presence of a corticosteroid which suppresses or attenuates the reaction.

1. Anonymous. Skin sensitisers in topical corticosteroids. *Drug Ther Bull* 1986; **24:** 57–9.

Topical application. Absorption of clioquinol through the skin has been noted on topical application.[1,2] The Committee on Drugs of the American Academy of Pediatrics[3] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

1. Fischer T, Hartvig P. Skin absorption of 8-hydroxyquinolines. *Lancet* 1977; **i:** 603.
2. Stohs SJ, *et al.* Percutaneous absorption of iodochlorhydroxyquin in humans. *J Invest Dermatol* 1984; **82:** 195–8.
3. Kauffman RE, *et al.* Clioquinol (iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86:** 797–8.

Uses and Administration

Clioquinol is a halogenated hydroxyquinoline with antibacterial and antifungal activity and is used in creams and ointments, usually containing 3%, in the treatment of skin infections. It is applied with a corticosteroid in inflammatory skin conditions complicated by bacterial or fungal infections. It is also used in ear drops for otitis externa. The treatment of bacterial and of fungal skin infections is described on p.194 and p.521 respectively.

For a discussion of the risks from topical application of clioquinol, see Adverse Effects and Precautions, above.

Clioquinol was formerly given by mouth in the treatment of intestinal amoebiasis. It was also formerly used for the prophylaxis and treatment of traveller's diarrhoea and similar infections but was of doubtful value. Oral preparations have now been withdrawn because of neurotoxicity (see Adverse Effects and Precautions, above). However, clioquinol by mouth has been investigated for its action as a chelator of copper and zinc in the treatment of Alzheimer's disease (see below).

Alzheimer's disease. A systematic review[1] to evaluate the efficacy of metal protein attenuating compounds, such as clioquinol, for the treatment of cognitive impairment due to Alzheimer's disease, evaluated only one small randomised controlled study comparing clioquinol and placebo; no significant differences were found. Further studies with clioquinol have now been stopped, but studies are on-going with a successor compound, PBT2.

1. Sampson E, *et al.* Metal protein attenuating compounds for the treatment of Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 14/05/08).

Preparations

BP 2008: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment;
USP 31: Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone Ointment; Clioquinol Cream; Clioquinol Ointment; Compound Clioquinol Topical Powder.

Proprietary Preparations (details are given in Part 3)

Ger.: Linola-sept; ***Hung.:*** Linola-sept†; ***India:*** Dermoquinol; Entero-Quinol; Entrozyme Plain; ***Mex.:*** Bagton; Bionder-C; Cortifung-C; Lasalar-Y Simple; Luzolona Simple; Nolil; Quindoleina†; Vioformo; ***Port.:*** Quinodermil†.

Multi-ingredient: ***Arg.:*** Betnovate-C; Locorten Vioformo†; Quadriderm†; ***Austral.:*** Hydroform; Locacorten Vioform; Quinaband†; ***Austria:*** Betnovate-C; Locacorten Vioform; ***Belg.:*** Betnelan-VC†; Locacortene Vioforme†; ***Braz.:*** Betnovate-Q; Cremederme; Dreniformio; Hidrocorte; Locorten Vioformio; Permut; Poliderms; Predmicin; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Tetraderm; Vioformio-Hidrocortisona; ***Canad.:*** Locacorten Vioform; Phenoris; Vioform-Hydrocortisone; ***Cz.:*** Lorinden C†; Prednisolon J†; ***Denm.:*** Betnovat med Chinoform; Celeston med Chinoform; Locacorten Vioform; Synalar med Chinoform; ***Fin.:*** Bemetson-K; Betnovat-C; Celestoderm cum Chinoform†; Locacorten Vioform; ***Fr.:*** Diprosept†; Locacortene Vioform; ***Ger.:*** Locacorten Vioform; ***Gr.:*** Betnovate-C; Myco-Synalar; ***Hong Kong:*** Betnovate-C†; Clobeta-G; Dermafacte; Quadriderm; ***Hung.:*** Lorinden C; Prednisolon J; ***India:*** Beclate-C; Betnederm C; Betnovate-C; Cortoquinol; Fourderm; Millicorten-Vioform; Polyderm†; Quiss; ***Indon.:*** Benoson V; Krimbeson; Viohydrocort; Visancort; ***Irl.:*** Betnovate-C; Synalar C†; Vioform-Hydrocortisone; ***Israel:*** Betnovate-C; Topicorten V; ***Ital.:*** Diproform; Locorten; Locorten Vioformio; ***Mex.:*** Bentix; Cetoquina Y; Clio-Betnovate; Clioderm-H; Contefur†; Cortifung-Y; Cortilona Compuesta; Dealan; Diprosone Y; Ditayod; Farmacorti YC; Fluccinol C†; Flunal†; Lasalar-Y; Luzolona Y; Sebryl; Sebryl Plus; Sebstopp; Solfurol; Sultroquin†; Suyodil; Synalar C; Taliviform†; Topsyn-Y; Trilor†; Ultracortin; Vioformo-Cort; Yderm; Yodozona; ***Neth.:*** Locacorten Vioform; ***Norw.:*** Betnovat med Chinoform; Synalar med Chinoform; ***NZ:*** Betnovate-C; Locorten Vioform; ***Philipp.:*** Aplosyn C; Betnovate-C; Dermalin; Diproform; Quadriderm; Quadrotopic; ***Pol.:*** Betnovate-C; Lorinden C; Viosept; ***Port.:*** Betnovate-C; Dexaval V; Locorten Vioformio†; Quinodermil-AS; ***Rus.:*** Dermosolon (Дермозолон); Lorinden C (Лоринден С); ***S.Afr.:*** Betnovate-C; Cortoderm-C; Locacorten Vioform; Quadriderm; Synalar C; ***Singapore:*** Dermanol-C; Hydroderm-C; Quadriderm†; ***Spain:*** Cuatroderm; Menaderm Clio; Menaderm Otologico; Synobel†; ***Swed.:*** Betnovat med Chinoform; Celeston valerat med chinoform; Locacorten Vioform; ***Switz.:*** Betnovate-C; Quadriderm; ***Thai.:*** Banocin; Beta-C; Betnovate-C; Betosone-CE; Chlorotracin; Endothalyl; Genquin; ***Turk.:*** Betnovate-C; Locacortene Vioform; Prednol-A; ***UK:*** Betnovate-C; Locorten Vioform; Quinaband†; Synalar C; Vioform-Hydrocortisone; ***USA:*** I + I-F; Corque; Hysone; ***Venez.:*** Dermosupril C; Diproformo; Locorten Vioformo; Neo-Synalar con Yodoclorohidroxiquina†; Propioformo†; Quadriderm; Tridetarmon; Vio Celestoderm†.

Clofazimine *(BAN, USAN, rINN)*

B-663; Clofazimina; Clofaziminum; G-30320; Klofatsimiini; Klofatzimin; Klofazimin; Klofaziminas; NSC-141046. 3-(4-Chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-phenazin-2-ylideneisopropylamine.

Клофазимин

$C_{27}H_{22}Cl_2N_4$ = 473.4.
CAS — 2030-63-9.
ATC — J04BA01.
ATC Vet — QJ04BA01.

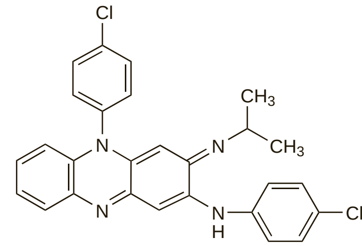

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Clofazimine). A fine reddish-brown powder. It exhibits polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dichloromethane.

USP 31 (Clofazimine). Dark red crystals. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in ethyl acetate; soluble in chloroform and in benzene. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects to clofazimine are dose related, the most common being red to brown discoloration of the skin especially on areas exposed to sunlight; leprotic lesions may become mauve to black. These changes are more noticeable in light-skinned people and may limit its acceptance. The conjunctiva and cornea may also show some signs of red to brown pigmentation. The generalised discoloration may take months to years to disappear after stopping therapy. Discoloration of hair, tears, sweat, sputum, breast milk, urine, and faeces may occur, as may nail discoloration with high doses of 300 mg daily. Severe depression related to skin discoloration has been reported rarely.

Gastrointestinal effects are uncommon for doses of clofazimine less than 100 mg daily and usually are not severe. Symptoms of nausea, vomiting, and abdominal pain experienced shortly after the start of treatment may be due to direct irritation of the gastrointestinal tract and such symptoms usually disappear on dose reduction. Use of doses of 300 mg daily or more for several months sometimes produces abdominal pain, diarrhoea, weight loss, gastrointestinal bleeding, and in severe cases the small bowel may become oedematous and symptoms of bowel obstruction may develop. This may be due to deposition of crystals of clofazimine in the wall of the small bowel and in the mesenteric lymph nodes. Crystal deposition may also occur in other organs including the liver and spleen and there have been rare reports of splenic infarction. Symptoms usually regress on withdrawal of treatment although fatalities have been reported.

Clofazimine may produce a dryness of the skin and ichthyosis as well as decreased sweat production and rashes. Pruritus, acneiform eruptions, and photosensitivity reactions have also been reported.

Eye irritation and decreased tear production may occur.

Headache, drowsiness, dizziness, taste disorders, and elevation of blood glucose levels have been reported rarely.

Incidence of adverse effects. The incidence of adverse effects was reviewed in 65 patients[1] who were receiving, or had received, clofazimine in weekly doses of either 700 mg or less as antimycobacterial therapy, or more than 700 mg as anti-inflammatory therapy. Length of treatment ranged from 1 to 83 months. Adverse effects on the skin included discoloration (20% of patients), pigmentation (64.6%), dry skin (35.4%), and pruritus (5%). Ocular adverse effects were conjunctival pigmentation (49.2%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%). Gastrointestinal adverse effects included abdominal pain (33.8%), nausea (9.2%), diarrhoea (9.2%), and weight loss, vomiting, or loss of appetite (13.8%). The different dose regimens for antimycobacterial therapy or anti-inflammatory effect had similar incidences of adverse effects. Skin pigmentation in 8 patients disappeared on average 8.5 months after stopping therapy with clofazimine, the maximum time required being one year. Adverse effects of clofazimine were considered to be well tolerated.

In another report covering 540 patients receiving clofazimine 100 mg on alternate days or 300 mg daily, the most common adverse effect was skin pigmentation, which occurred in 77.8% of the patients. Ichthyotic changes were reported in 66.7% and pruritus in 20.2%. Gastrointestinal symptoms occurred in 20 patients (about 4%); other effects such as discoloration of sweat, urine, and tears were minor.[2]

1. Moore VJ. A review of side-effects experienced by patients taking clofazimine. *Lepr Rev* 1983; **54:** 327–35.
2. Kumar B, *et al.* More about clofazimine—3 years experience and review of the literature. *Indian J Lepr* 1987; **59:** 63–74.

Effects on the eyes. Accumulation of clofazimine crystals in the eye can lead to pigmentation of the cornea and conjunctiva. Degeneration of the retinal pigment epithelium has also been attributed to clofazimine therapy in a patient.[1] Slight repigmentation was observed after withdrawal of clofazimine.

1. Forster DJ, *et al.* Bull's eye retinopathy and clofazimine. *Ann Intern Med* 1992; **116:** 876–7.

Effects on the gastrointestinal tract. Gastrointestinal effects are uncommon at doses of clofazimine less than 100 mg daily. However, there have been some reports of severe gastrointestinal adverse events, including fatalities, in patients taking clofazimine.[1-4] An 11-year-old child given clofazimine (150 mg daily) for graft-versus-host disease developed severe enteropathy 2 years after starting treatment.[1] Clofazimine was stopped and symptoms resolved after 5 weeks. Enteropathy has also been reported in a 20-year-old patient who had taken 200 mg of clofazimine daily for 4 years.[2] Clofazimine was stopped but his symptoms did not resolve; he developed peripheral oedema and hypoalbuminaemia and died 2 years later due to cerebral thrombosis. In another report,[4] partial intestinal obstruction developed in a patient after 12 months of treatment with clofazimine 100 mg daily for the treatment of multidrug-resistant tuberculosis. The patient recovered 3 weeks after stopping clofazimine. Splenic infarction has been reported after 11 months treatment with high-dose clofazimine for the management of pyoderma gangrenosum.[5] Chronic abdominal pain due to crystal-storing histiocytosis of mesenteric lymph nodes is well recognised, and may mimic the symptoms of gastrointestinal lymphoma or myeloma.[3]

1. Parizhskaya M, *et al.* Clofazimine enteropathy in a pediatric bone marrow transplant recipient. *J Pediatr* 2001; **138:** 574–6.
2. Hameed A, *et al.* A case of clofazimine enteropathy. *Int J Clin Pract* 1998; **52:** 439–40.
3. Sukpanichnant S, *et al.* Clofazimine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. *Am J Surg Pathol* 2000; **24:** 129–35.
4. Üsküdar O, *et al.* Partial intestinal obstruction due to clofazimine in a patient with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; **9:** 703–4.
5. McDougall AC, *et al.* Splenic infarction and tissue accumulation of crystals associated with the use of clofazimine (Lamprene; B663) in the treatment of pyoderma gangrenosum. *Br J Dermatol* 1980; **102:** 227–30.

Effects on the heart. Ventricular tachycardia, thought to be probably torsade de pointes, was reported to be associated with clofazimine.[1]

1. Choudhri SH, *et al.* Clofazimine induced cardiotoxicity—a case report. *Lepr Rev* 1995; **66:** 63–8.

Precautions

Clofazimine should be used with caution in patients with gastrointestinal symptoms such as abdominal pain and diarrhoea. If gastrointestinal symptoms develop during treatment, the dose should be reduced and, if necessary, the interval between doses increased, or the drug should be stopped. Daily doses of more than 100 mg should not be used for more than 3 months because of dose-related adverse effects on the gastrointestinal tract; patients receiving doses greater than 100 mg daily should be under medical supervision.

Patients should be warned that clofazimine may cause a reddish-brown discoloration of breast milk, hair, skin, conjunctiva, tears, sputum, sweat, urine, and faeces. Nails may be discoloured at higher doses.

As clofazimine crosses the placental barrier, neonates of women receiving clofazimine may have skin discoloration at birth.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of clofazimine by mothers during breast feeding may be of concern, since there is the possibility of transfer of a high percentage of the maternal dose and a possible increase in skin pigmentation in the infant. A small study in 8 women calculated that up to 30% of a maternal dose may be ingested by a breast-fed infant.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Venkatesan K, *et al.* Excretion of clofazimine in human milk in leprosy patients. *Lepr Rev* 1997; **68:** 242–6.

Pregnancy. Two successful pregnancies in women who received clofazimine throughout pregnancy have been reported[1] but a literature review revealed 3 neonatal deaths in 13 pregnancies, although the deaths could not be directly attributed to clofazimine. However, WHO[2] states that its recommended multiple drug therapy regimens for leprosy, which may include clofazimine, are safe during pregnancy.

1. Farb H, *et al.* Clofazimine in pregnancy complicated by leprosy. *Obstet Gynecol* 1982; **59:** 122–3.
2. WHO. *Guide to eliminate leprosy as a public health problem.* 1st ed. Geneva: WHO, 2000. Also available at: http://www.who.int/lep/resources/Guide_Int_E.pdf (accessed 28/07/08)

Interactions

Some preliminary data have suggested that the anti-inflammatory action of clofazimine in Type 2 lepra reactions may be reduced by dapsone, although US licensed product information (*Lamprene; Novartis, USA*) states that these findings have not been confirmed; the antimycobacterial effect was not affected.

Elevated plasma and urine concentrations of clofazimine have been detected in patients receiving high doses of clofazimine with isoniazid, although skin concentrations were found to be lower.

For a report of the effect of clofazimine on rifampicin absorption, see p.327.

Antimicrobial Action

Clofazimine is bacteriostatic and weakly bactericidal against *Mycobacterium leprae*. Tissue antimicrobial activity in humans cannot be found until after about 50 days of therapy. Clofazimine is active *in vitro* against various other species of *Mycobacterium*. Resistance has been reported rarely and no cross-resistance occurs with rifampicin or dapsone.

Pharmacokinetics

Clofazimine is absorbed from the gastrointestinal tract in amounts varying from 45 to 70%. Absorption is greatest when clofazimine is given in microcrystalline formulations and when it is taken immediately after food. The time to steady-state plasma concentrations has not been determined but exceeds 42 days.

Average plasma concentrations in leprosy patients receiving 100 or 300 mg daily are reported as 0.7 micrograms/mL and 1.0 microgram/mL, respectively.

Because of its lipophilic nature, clofazimine is mainly distributed to fatty tissue and reticuloendothelial cells, including macrophages. Clofazimine is distributed to most organs and tissues and into breast milk; it crosses the placenta but not the blood-brain barrier.

The tissue half-life after a single dose has been reported to be about 10 days; that after multiple oral doses has been variously estimated to be between 25 and 90 days. Clofazimine accumulates in the body and is largely excreted unchanged in the faeces, both as unabsorbed drug and via biliary excretion. About 1% of the dose is excreted in 24 hours in the urine as unchanged clofazimine and metabolites. A small amount of clofazimine is also excreted through sebaceous and sweat glands, and in sputum.

◊ References.

1. Holdiness MR. Clinical pharmacokinetics of clofazimine: a review. *Clin Pharmacokinet* 1989; **16:** 74–85.

Uses and Administration

Clofazimine is an antimycobacterial and is used as part of multidrug regimens for the treatment of multibacillary leprosy (p.176). It has anti-inflammatory properties and has been given in chronic Type 2 lepra reactions (erythema nodosum leprosum) and in a variety of skin disorders.

Clofazimine is given orally with, or immediately after, food or milk for optimum absorption.

For multibacillary leprosy the most common regimen is that recommended by WHO, in which rifampicin 600 mg and clofazimine 300 mg are both given *once a month*, together with *daily* doses of clofazimine 50 mg and dapsone 100 mg; this treatment continues for 12 months.

For details of doses in children, see below.

Clofazimine 50 mg daily is given with ofloxacin and minocycline in patients unable to take rifampicin.

Clofazimine is not usually given in paucibacillary leprosy. However, it may be used with rifampicin instead of dapsone when the latter has caused severe toxicity.

Clofazimine has been used in the treatment of chronic Type 2 lepra reactions, although the effect may not be evident for 4 to 6 weeks. A dose of up to 300 mg daily has been suggested but it should not be given for longer than 3 months. Corticosteroids may be given with clofazimine, and standard antileprosy treatment should be continued. Clofazimine is not used in Type 1 lepra reactions.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral clofazimine 150 mg plus rifampicin 450 mg and dapsone 50 mg *once a month*, together with dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*. For children less than 10 years of age the dose should be adjusted according to body weight. As for adults, treatment is given for 12 months.

Preparations

BP 2008: Clofazimine Capsules;
USP 31: Clofazimine Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Lamprene; ***Braz.:*** Neozimina; ***Cz.:*** Lamprene; ***Fr.:*** Lamprene; ***Gr.:*** Lamprene; ***Hong Kong:*** Lamprene†; ***India:*** Clofozine; Hansepran; ***Jpn:*** Lampren; ***Malaysia:*** Lamprene†; ***Neth.:*** Lampren; ***NZ:*** Lamprene; ***S.Afr.:*** Lamprene†; ***Spain:*** Lampren; ***Switz.:*** Lamprene†; ***Thai.:*** Lamcoin; ***UK:*** Lamprene†; ***USA:*** Lamprene.

Clofoctol *(rINN)*

Clofoctolum. 2-(2,4-Dichlorobenzyl)-4-(1,1,3,3-tetramethylbutyl)phenol.

Клофоктол

$C_{21}H_{26}Cl_2O = 365.3$.
CAS — 37693-01-9.
ATC — J01XX03.
ATC Vet — QJ01XX03.

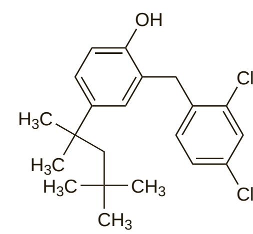

Profile

Clofoctol has bacteriostatic or bactericidal activity against Gram-positive organisms such as staphylococci and streptococci. It is given in doses of 750 mg twice daily rectally in the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Octofene†; ***Ital.:*** Gramplus; Octofene†; ***Port.:*** Octofene†.

Clometocillin Potassium *(rINNM)*

Clometocilina potásica; Clométocilline Potassique; 3,4-Dichloro-α-methoxybenzylpenicillin Potassium; Kalii Clometocillinum; Penicillin 356 (clometocillin). Potassium (6*R*)-6-[2-(3,4-dichlorophenyl)-2-methoxyacetamido]penicillanate.

Калия Клометоциллин

$C_{17}H_{17}Cl_2KN_2O_5S = 471.4$.
CAS — 1926-49-4 (clometocillin); 15433-28-0 (clometocillin potassium).
ATC — J01CE07.
ATC Vet — QJ01CE07.

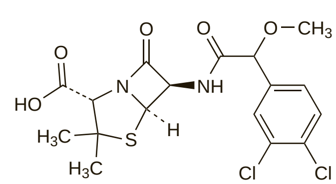

(clometocillin)

Profile

Clometocillin is a penicillin given orally as the potassium salt in the treatment of susceptible bacterial infections. Doses are expressed in terms of the base. The usual adult dose is 500 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Rixapen.

Cloxacillin *(BAN, rINN)*

Cloxacilina; Cloxacilline; Cloxacillinum; Kloksasilliini; Kloxacillin. (6*R*)-6-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

Клоксациллин

$C_{19}H_{18}ClN_3O_5S$ = 435.9.
CAS — 61-72-3.
ATC — J01CF02.
ATC Vet — QJ01CF02; QJ51CF02; QS01AA90.

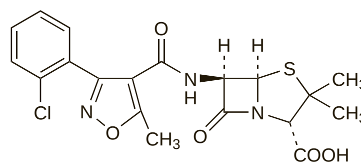

Cloxacillin Benzathine *(BANM)*

Cloxacilina benzatina. The *N,N'*-dibenzylethylenediamine salt of cloxacillin.

$C_{16}H_{20}N_2,(C_{19}H_{18}ClN_3O_5S)_2$ = 1112.1.
CAS — 23736-58-5; 32222-55-2.
ATC — J01CF02.
ATC Vet — QJ01CF02.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.

BP(Vet) 2008 (Cloxacillin Benzathine). A white or almost white powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers.

USP 31 (Cloxacillin Benzathine). White or almost white, almost odourless, crystals or crystalline powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; sparingly soluble in acetone; soluble in chloroform and in methyl alcohol. pH of a 1% suspension in water is between 3.0 and 6.5. Store in airtight containers.

Cloxacillin Sodium *(BANM, USAN, rINNM)*

BRL-1621; Cloxacilina sódica; Cloxacilline sodique; Cloxacillinum natricum; Cloxacillinum Natricum Monohydricum; Kloksacilino natrio druska; Kloksacylina sodowa; Kloksasilliininatrium; Kloxacilin sodná sůl monohydrát; Kloxacillinnatrium; Kloxacillin-nátrium; Natrii Cloxacillinum; P-25.

Натрий Клоксациллин

$C_{19}H_{17}ClN_3NaO_5S,H_2O$ = 475.9.
CAS — 642-78-4 (anhydrous cloxacillin sodium); 7081-44-9 (cloxacillin sodium monohydrate).
ATC — J01CF02.
ATC Vet — QJ01CF02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Cloxacillin Sodium). Semi-synthetic product derived from a fermentation product. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.

USP 31 (Cloxacillin Sodium). A white, odourless, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers at a temperature not exceeding 25°.

Incompatibility. Cloxacillin sodium has been reported to be incompatible with aminoglycosides and a number of other antimicrobials.

Adverse Effects and Precautions

As for Flucloxacillin, p.277.

Effects on the kidneys. References.

1. García-Ortiz R, *et al.* Cloxacillin-induced acute tubulo interstitial nephritis. *Ann Pharmacother* 1992; **26:** 1241–2.

Effects on the liver. References.

1. Enat R, *et al.* Cholestatic jaundice caused by cloxacillin: macrophage inhibition factor test in preventing rechallenge with hepatotoxic drugs. *BMJ* 1980; **280:** 982–3.
2. Konikoff F, *et al.* Cloxacillin-induced cholestatic jaundice. *Am J Gastroenterol* 1986; **81:** 1082–3.
3. Goland S, *et al.* Severe cholestatic hepatitis following cloxacillin treatment. *Postgrad Med J* 1998; **74:** 59–60.

Sodium content. Each g of cloxacillin sodium contains about 2.1 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

As for Flucloxacillin, p.277.

Pharmacokinetics

Cloxacillin is incompletely absorbed from the gastrointestinal tract, and absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 15 micrograms/mL is attained in fasting subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 micrograms/mL have been observed 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentration. About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

Cloxacillin crosses the placenta and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and in bone.

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and up to 10% in the bile. Cloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations in patients with cystic fibrosis have been attributed to both enhanced tubular secretion and enhanced nonrenal clearance of cloxacillin.

Uses and Administration

Cloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Cloxacillin is given orally as the sodium salt and doses are expressed in terms of the equivalent amount of cloxacillin; 1.09 g of cloxacillin sodium is equivalent to about 1 g of cloxacillin. It should be given at least 30 minutes before meals as the presence of food in the stomach reduces absorption.

Usual oral doses are 250 to 500 mg four times daily. Children up to 2 years may be given a quarter of the daily adult dose and those over 2 years half the daily adult dose, in divided doses every 6 hours.

Cloxacillin sodium has also been given by intramuscular or slow intravenous injection or infusion. Other routes have included intra-articular or intrapleural injection, and inhalation.

Cloxacillin may be used with other antibacterials, including ampicillin, to produce a wider spectrum of activity.

Cloxacillin benzathine is used in veterinary medicine.

Preparations

USP 31: Cloxacillin Sodium Capsules; Cloxacillin Sodium for Oral Solution.

Proprietary Preparations (details are given in Part 3)

Belg.: Penstaphon; ***Canad.:*** Apo-Cloxi; Novo-Cloxin; Nu-Cloxi; ***Chile:*** Cloxapen†; ***Fin.:*** Ekvacillin†; Staflocil; ***Fr.:*** Orbenine; ***Gr.:*** Anaclosil; Orbenin; Staphyclox; ***Hong Kong:*** Apo-Cloxi; Cloxil†; Cloxin; Lidoxin; Monoclox; Prostaphlin-A; ***India:*** Bioclox; Iclox†; ***Indon.:*** Meixam; ***Israel:*** Loxavit; Orbenil; ***Malaysia:*** Monoclox; Oxacil†; Proxin†; ***Neth.:*** Orbenin†; ***Norw.:*** Ekvacillin; ***Philipp.:*** Avastoph; Caxin; Ciclox; Cloxigen; Eloxil; Encloxil; Eraclox; Excelox; Jogen; Lewinex; Medix; Orbenin; Oxaclen; Pannox; Patriflex; Prostaphlin-A; Solaze; Vamcloxil; ***Pol.:*** Syntarpen; ***S.Afr.:*** Cloxin; Orbenin; ***Singapore:*** Axocillin†; Cloxacap†; Lidoxin; Monoclox†; ***Spain:*** Anaclosil; Orbenin; ***Swed.:*** Ekvacillin; ***Thai.:*** Cloxa; Cloxalin; Cloxam; Cloxanbin; Cloxapan†; Cloxasian; Cloxgen; Cloxil; Cloxillin†; Corbin; Greater-Gloxa; K-Cil; Lidoxin; Loxzalin; Meiclox; Orbenin; Serviclox†; Socloxin; Syntoclox; Theraclox; Vaclox.

Multi-ingredient: ***Cz.:*** Ampiclox†; ***Hong Kong:*** Ampiclox†; APT-Ampicloxa; Pamedox; Rosciclox; ***India:*** ABClox; Adilox; Amclo†; Ampilox; Ampilox-LB; Amplus; Ampoxin; Ampoxin-LB; Bicidal Plus; Campilox; Clax; Hipenox; Imox-Clo; Imox-Clo LB; Megaclox; Megaclox LB; Megapen; Novaclox; Novaclox LB; Suprimox; Symbiotik; ***Irl.:*** Ampiclox†; ***Ital.:*** Amplium; ***S.Afr.:*** Ampiclox; Apen; Cloxam; Megamox; Ranclosil†; ***Thai.:*** Ampiclox; Viccillin-S.

Colistin Sulfate *(pINNM)*

Colistin Sulphate *(BANM)*; Colistine, sulfate de; Colistini sulfas; Kolistiinisulfaatti; Kolistino sulfatas; Kolistinsulfat; Kolistin-sulfát; Kolistyny siarczan; Kolisztin-szulfát; Polymyxin E Sulphate; Sulfato de colistina.

Колистина Сульфат

CAS — 1066-17-7 (colistin); 1264-72-8 (colistin sulfate).

ATC — A07AA10; J01XB01.

ATC Vet — QA07AA10; QJ01XB01.

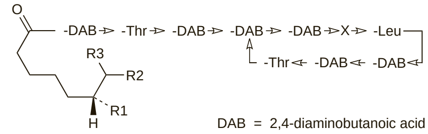

polymyxin	X	R1	R2	R3	Mol. Formula
E1	D-Leu	CH	CH	H	C H N O
E2	D-Leu	CH	H	H	C H N O
E3	D-Leu	H	CH	H	C H N O
E1-I	D-Ile	CH	CH	H	C H N O
E1-7MOA	D-Leu	H	CH	CH	C H N O

(colistin)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Colistin Sulphate). A mixture of the sulfates of polypeptides produced by certain strains of *Bacillus polymyxa* var. *colistinus* or obtained by any other means. It contains a minimum of 77% of the sum of polymyxin E1, polymyxin E2, polymyxin E3, polymyxin E1-I, and polymyxin E1-7MOA. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Colistin Sulfate). The sulfate salt of an antibacterial substance produced by the growth of *Bacillus polymyxa* var. *colistinus*. It has a potency of not less than 500 micrograms of colistin per mg. A white to slightly yellow, odourless, fine powder. Freely soluble in water; insoluble in acetone and in ether; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 7.0. Store in airtight containers.

Stability. Colistin base is precipitated from aqueous solution above pH 7.5.

Colistimethate Sodium *(BANM, USAN, rINN)*

Colistimetato de sodio; Colistimetato de Sódio; Colistimetato sódico; Colistiméthate sodique; Colistimethatum natricum; Colistimethatum Natrium; Colistin Sulphomethate Sodium; Colistineméthanesulfonate Sodique; Kolistimetaattinatrium; Kolistimetatnatrium; Kolistimetato natrio druska; Kolistimethát sodná sůl; Kolistymetat sodowy; Kolisztimetát-nátrium; Pentasodium Colistinmethanesulfonate; Sodium Colistimethate; Sodium Colistinmethanesulphonate; W-1929.

Колистиметат Натрий

CAS — 30387-39-4 (colistimethate); 8068-28-8 (colistimethate sodium).
ATC — A07AA10; J01XB01.
ATC Vet — QA07AA10; QJ01XB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Colistimethate Sodium). It is prepared from colistin by the action of formaldehyde and sodium bisulfite. The potency is not less than 11 500 units/mg, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 31 (Colistimethate Sodium). A white to slightly yellow, odourless, fine powder. It has a potency equivalent to not less than 390 micrograms of colistin per mg. Freely soluble in water; insoluble in acetone and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 6.5 and 8.5.

Stability. After the death of a patient with cystic fibrosis who had been given a liquid solution of colistimethate premixed for inhalation with a nebuliser (see Cystic Fibrosis, under Adverse Effects, below) the US FDA warned[1] that such premixing of colistimethate in an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution and increases the potential for lung toxicity. When colistimethate is mixed with water and buffer it undergoes spontaneous hydrolysis to colistin; polymyxin E1, a component of colistin, has been shown to cause pulmonary inflammation in *animal* studies. Inhalation solutions of colistimethate should therefore be given promptly after preparation.

1. FDA. Colistimethate (marketed as Coly-Mycin M and generic products) (issued 28 June 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/colistimethateHCP.htm (accessed 18/01/08)

Units

The first International Standard Preparation (1968) for colistin contains 20 500 units/mg of colistin sulfate and the first International Reference Preparation (1968) for colistimethate contains 12 700 units/mg of colistimethate.

Adverse Effects, Treatment, and Precautions
As for Polymyxin B Sulfate, p.318.

Colistin sulfate is poorly absorbed from the gastrointestinal tract and adverse effects do not normally occur with usual oral doses. However, gastrointestinal absorption is limited and unpredictable in infants under 6 months of age and systemic adverse effects such as transient sensory disturbances may occur in this patient group.

Cough and bronchospasm may occur during inhalation; cases of sore throat or sore mouth, possibly due to hypersensitivity or superinfection with *Candida* spp., have also been reported. Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery. Pain and local irritation are reported to be less troublesome after intramuscular injection of colistimethate sodium than with colistin sulfate or polymyxin B. Overgrowth of non-susceptible organisms, particularly *Proteus* spp., may occur after prolonged use.

Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/mL) are recommended.

Cystic fibrosis. Intravenous colistin sulfate was reported to be associated with a lower rate of severe nephrotoxicity among 19 patients with cystic fibrosis than has been previously reported in other patient populations.[1] However, fatal acute respiratory distress syndrome (ARDS) has been reported in a cystic fibrosis patient after inhalation of colistimethate sodium 75 mg twice daily.[2] The solution used had been compounded 5 weeks previously, and it was considered that ARDS was caused by the conversion of colistimethate sodium to the active form colistin which may cause airway or alveolar injury. The FDA subsequently warned that inhalation solutions should be used promptly after preparation (see Stability, above).

1. Bosso JA, *et al.* Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991; **25:** 1168–70.
2. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; **357:** 2310–1.

Effects on the cardiovascular system. Significant, but transient, hypotension occurred in a patient after starting aerosolised colistin inhalation.[1] Intravenous colistin, alone or with aerosolised amikacin, had no such effect on blood pressure.

1. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant Pseudomonas aeruginosa. *Ann Pharmacother* 2006; **40:** 1677–80.

Porphyria. Colistin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions
As for Polymyxin B Sulfate, p.318.

Antimicrobial Action
The antimicrobial spectrum and mode of action of colistin is similar to that of polymyxin B (p.318) but colistin sulfate is slightly, and colistimethate significantly, less active.

Pharmacokinetics
Colistin sulfate and colistimethate sodium are poorly absorbed from the gastrointestinal tract of adults and children; however, limited and unpredictable gastrointestinal absorption occurs in infants under 6 months of age. The drugs are not absorbed through mucous membranes, or intact or denuded skin. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistin is reported to be more than 50% but that of colistimethate sodium is low. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate. Some colistimethate sodium may be hydrolysed to colistin *in vivo*. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment; values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute. Half-life may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days.

Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults; it is reduced in patients with renal impairment. Colistin crosses the placenta but diffusion into the CSF is negligible. It is distributed into breast milk.

Cystic fibrosis. References.

1. Reed MD, *et al.* The pharmacokinetics of colistin in patients with cystic fibrosis. *J Clin Pharmacol* 2001; **41:** 645–54.
2. Li J, *et al.* Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. *J Antimicrob Chemother* 2003; **52:** 987–92.
3. Ratjen F, *et al.* Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006; **57:** 306–11.

Uses and Administration
Colistin is a polymyxin antibacterial that has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*, although other drugs are usually preferred. Colistimethate sodium is used by inhalation in the management of respiratory infections, especially in patients with cystic fibrosis (p.166). Colistin has been given orally as the sulfate for the treatment of gastrointestinal infections. Colistin sulfate is also given orally for bowel preparation before abdominal surgery, and with other drugs in regimens for selective digestive tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p.175).

The usual oral dose of colistin sulfate is 1.5 to 3 million units given 3 times daily. For bowel preparation, the same dose is given for 24 hours with the course being completed 12 hours before surgery.

Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units given 3 times daily (maximum dose 6 million units in 24 hours) for patients weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients (see Adverse Effects and Precautions, above).

Colistimethate sodium may also be given by inhalation in respiratory infections as an adjunct to systemic antibacterial therapy. The usual dose is 1 to 2 million units given 2 or 3 times daily. A 3-week course of 2 million units twice daily may be given initially, increased to a maximum of 2 million units given 3 times daily for up to 3 months in frequent recurrent infections; 1 to 2 million units twice daily may be given for long-term therapy. Solutions for inhalation should be freshly prepared (see Stability, above).

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

For details of doses in infants and children, see below.

Colistimethate sodium has also been given by subconjunctival injection and as a bladder instillation. Both colistin sulfate and colistimethate sodium have been applied topically, often with other antibacterials, in the management of ear, eye, and skin infections.

◊ Reviews.

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; **40:** 1333–41. Correction. *ibid.* 2006; **42:** 1819. [dose]
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Li J, *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6:** 589–601.

Administration in children. The following doses of colistin sulfate may be given **orally** to children according to weight:
- up to 15 kg: 0.25 to 0.5 million units 3 times daily
- 15 to 30 kg: 0.75 to 1.5 million units 3 times daily
- over 30 kg: the usual adult dose (see above)

Parenteral doses of colistimethate sodium may vary between countries.

UK according to weight:
- up to 60 kg: 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 60 kg: the usual adult dose (see above)

USA:
- children may be given the usual adult dose, equivalent to colistin base, of 2.5 to 5 mg/kg daily in 2 to 4 divided doses

Monitoring of plasma concentrations is required in some patients (see Adverse Effects, Treatment, and Precautions, above).

For **inhalation** colistimethate sodium may be given in the following doses according to age:
- under 2 years: 0.5 to 1 million units twice daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 2 years: the usual adult dose (see above)

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

Administration in renal impairment. Dosage of parenteral and inhaled colistimethate sodium must be adjusted in renal impairment; both reduction in dose and decreased frequency of dosing may be required.

In the UK, the following **parenteral** doses of colistimethate sodium, based on creatinine clearance (CC), have been suggested for patients weighing more than 60 kg:
- CC 20 to 50 mL/minute: 1 to 2 million units every 8 hours
- CC 10 to 20 mL/minute: 1 million units every 12 to 18 hours
- CC less than 10 mL/minute: 1 million units every 18 to 24 hours

US licensed product information suggests the following modified doses (equivalent to colistin base) for adults with renal impairment in terms of plasma-creatinine concentrations:
- 1.3 to 1.5 mg/100 mL: 150 to 230 mg given daily in two divided doses
- 1.6 to 2.5 mg/100 mL: 133 to 150 mg given daily as a single dose or in 2 divided doses
- 2.6 to 4.0 mg/100 mL: 100 to 150 mg given every 36 hours

The following doses **by inhalation** have been suggested based on creatinine concentrations:
- 106 to 129 micromoles/litre: 1 to 1.5 million units every 12 hours
- 130 to 214 micromoles/litre: 1 million units every 12 or 24 hours
- 215 to 340 micromoles/litre: 1 to 1.5 million units every 36 hours

Preparations
BP 2008: Colistimethate Injection; Colistin Tablets;
USP 31: Colistimethate for Injection; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Colistin Sulfate for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Alfacolin; Alficetin; ***Austral.:*** Coly-Mycin M; ***Belg.:*** Colistineb; ***Canad.:*** Coly-Mycin M; ***Cz.:*** Colimycine†; Colomycin; ***Denm.:*** Colimycin; ***Fr.:*** Colimycine; ***Ger.:*** Diaront mono; ***Gr.:*** Tadim; ***India:*** Walamycin; ***Irl.:*** Colomycin; ***Israel:*** Coliracin; ***Ital.:*** Colimicina; ***Neth.:*** Belcomycine†; Colimycine†; ***Norw.:*** Colimycin; ***NZ:*** Coly-Mycin M†; ***Port.:*** Colixin; ***Spain:*** Colimicina; ***Thai.:*** Colistate; ***UK:*** Colomycin; Promixin; ***USA:*** Coly-Mycin M; ***Venez.:*** Colisil†.

Multi-ingredient: ***Arg.:*** Clarex Compuesto; Eristin; Eubetal Biotic†; ***Fr.:*** Bacicoline; ***Ger.:*** Ecolicin; ***Ital.:*** Colbiocin; Eubetal Antibiotico; ***Mex.:*** Colfur; ***Neth.:*** Bacicoline-B; ***NZ:*** Antibiotic Simplex; ***Philipp.:*** Elicocin; ***Rus.:*** Colbiocin (Колбиоцин); ***USA:*** Coly-Mycin S Otic; Cortisporin-TC.

Co-tetroxazine *(BAN)*
Tetroxoprima y sulfadiazina.
CAS — 73173-12-3.

Profile
Co-tetroxazine, a mixture of tetroxoprim and sulfadiazine in the proportion of 2:5, has properties similar to those of co-trimoxazole (below). It has been given orally, mainly in the treatment of infections of the urinary and respiratory tracts, including pneumocystis pneumonia.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Sterinor†; ***Venez.:*** Esterinor†.

Co-trifamole *(BAN)*
CN-3123; Cotrifamol.
ATC — J01EE04.

Profile
Co-trifamole, a mixture of 5 parts of sulfamoxole and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Supristol†.

Co-trimazine *(BAN)*

Trimetoprima y sulfadiazina.
CAS — 39474-58-3.
ATC — J01EE02.

Profile

Co-trimazine, a mixture of 5 parts of sulfadiazine and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations are available in some countries which contain trimethoprim and sulfadiazine in proportions different to co-trimazine.

Co-trimoxazole *(BAN)*

Cotrimoxazol; Ko-trimoksazol.
CAS — 8064-90-2.
ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Stability. Diluted infusion solutions of co-trimoxazole have a limited stability and eventually form a precipitate: this happens more rapidly at higher concentrations. The manufacturers recommend a dilution of 480 mg in 130 mL, which is usually stable for up to 6 hours, but more concentrated solutions should be used within shorter periods of time, and a dilution of 480 mg in 80 mL should be used within 1 hour. The usual diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, have been stated to be compatible for adequate periods.

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components (see Sulfamethoxazole, p.340, and Trimethoprim, p.355). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, below).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] predominantly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the prescribing of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, below), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and remained predominantly in elderly patients.

1. Committee on Safety of Medicines. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al.* Co-trimoxazole toxicity. *BMJ* 1985; **291:** 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; **291**: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; **ii**: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; **ii**: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; **345:** 1118–19.
8. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Precautions

As for Sulfamethoxazole, p.340 and Trimethoprim, p.355.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of skin rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al.* Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; **25:** 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; **1:** 687–91.

G6PD deficiency. It has been suggested that co-trimoxazole should be avoided by people with G6PD deficiency.[1]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67**: 601–11.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in **patients with AIDS** being treated for *Pneumocystis carinii* pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

The occurrence of high serum concentrations of trimethoprim and sulfamethoxazole in patients has been proposed as a contributing factor to the high incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the **dose** of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] demonstrated no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine **metabolites** of sulfamethoxazole which produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p.340.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92–106.
2. Gordin FM, *et al.* Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
3. Jaffe HS, *et al.* Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; **ii**: 1109–11.
4. Mitsuyasu R, *et al.* Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535.
5. Colebunders R, *et al.* Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **107**: 599–600.
6. Sattler FR, *et al.* Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **109**: 280–7.
7. Stevens RC, *et al.* Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35**: 1884–90.
8. Para MF, *et al.* Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; **24:** 337–43.
9. McLean I, *et al.* Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; **ii**: 857–8.
10. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
11. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
12. Gibbons RB, Lindauer JA. Successful treatment of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in hypersensitive AIDS patients. *JAMA* 1985; **253**: 1259–60.
13. Toma E, Fournier S. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 954.
14. Kreuz W, *et al.* "Treating through" hypersensitivity to co-trimoxazole in children with HIV infection. *Lancet* 1990; **336**: 508–9.
15. Carr A, *et al.* Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7:** 65–71.
16. Absar N, *et al.* Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93:** 1001–5.
17. Cortese LM, *et al.* Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; **30:** 184–6.
18. Caumes E, *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133:** 465–9.
19. Demoly P, *et al.* Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; **102:** 1033–6.
20. Lin D, *et al.* Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/07/08).
21. Woods WG, *et al.* Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia. *J Pediatr* 1984; **105**: 639–44.
22. Drysdale HC, Jones LF. Co-trimoxazole prophylaxis in leukaemia. *Lancet* 1982; **i**: 448.
23. Dib EG, *et al.* Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 2004; **350:** 88–9.

Interference with diagnostic tests. Co-trimoxazole has been reported[1,2] to cause a small reduction in serum-thyroxine and tri-iodothyronine concentrations, probably due to the sulfonamide component.[2] Although co-trimoxazole had not been shown to be a cause of hypothyroidism (since all concentrations remained within the normal range), tests of thyroid function might need to be interpreted with care in patients on such treatment.

1. Cohen HN, *et al.* Effects on human thyroid function of sulphonamide and trimethoprim combination drugs. *BMJ* 1980; **281**: 646–7.
2. Cohen HN, *et al.* Trimethoprim and thyroid function. *Lancet* 1981; **i**: 676–7.

Porphyria. Both sulfonamides and trimethoprim have been associated with acute attacks of porphyria, and are considered unsafe in porphyric patients.

Interactions

Any of the drug interactions reported with sulfamethoxazole (p.341) or trimethoprim (p.356) may occur with co-trimoxazole.

Rifampicin. For reference to potential interaction between co-trimoxazole and rifampicin, see p.327.

Antimicrobial Action

The actions and spectrum of activity of co-trimoxazole are essentially those of its components, sulfamethoxazole (p.341) and trimethoprim (p.356).

Because they act at different points of the folate metabolic pathway a potent synergy exists between its components *in vitro* with an increase of up to about 10-fold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The optimum effect against most organisms is seen at a ratio of 1 part trimethoprim to 20 of sulfamethoxazole; although co-trimoxazole is formulated as a 1 to 5 ratio, differences in the pharmacokinetics of the two drugs mean that the ratio of the peak concentrations is approximately 1:20. However, it is not clear that the optimum ratio is achieved at all sites and, given that both drugs are present in therapeutic concentrations, the contribution of synergy to the effects of co-trimoxazole *in vivo* is uncertain.

Resistance to co-trimoxazole develops more slowly *in vitro* than to either component alone. Resistance has increased, and although initially slow, a more rapid increase was seen in many countries during the 1980s, occurring in both Gram-positive and Gram-negative organisms. Resistance has occurred notably among Enterobacteriaceae. Resistant strains of *Brucella melitensis*, *Haemophilus influenzae*, streptococci, and *Vibrio cholerae* have been reported rarely. Although resistant organisms are usually resistant to both components of the mixture, strains resistant to either the sulfonamide or trimethoprim, and with a reduced sensitivity to co-trimoxazole, have been reported.

◊ References.

1. Martin JN, *et al.* Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis* 1999; **180:** 1809–18.
2. Huovinen P. Resistance to trimethoprim-sulfamethoxazole. *Clin Infect Dis* 2001; **32:** 1608–14.

Pharmacokinetics

As for sulfamethoxazole (p.341) and trimethoprim (p.356). When co-trimoxazole is given orally, plasma concentrations of trimethoprim and sulfamethoxazole are generally around the optimal ratio of 1:20, although they may vary from 1:2 to 1:30 or more. The ratio of the two drugs is usually much lower in the tissues (often around 1:2 to 1:5) since trimethoprim, the more lipophilic drug, penetrates many tissues better than sulfamethoxazole and has a much larger volume of distribution. In urine the ratio may vary from 1:1 to 1:5 depending on the pH.

Uses and Administration

Co-trimoxazole is a mixture of the sulfonamide, sulfamethoxazole, and the diaminopyrimidine, trimethoprim, in the proportion of 5 parts of sulfamethoxazole to 1 part of trimethoprim. It has been used in infections due to susceptible organisms, particularly those of the urinary, respiratory, and gastrointestinal tracts, although the indications for its use are restricted in the UK (see below). Its main uses now are in pneumocystis pneumonia, toxoplasmosis, and nocardiosis.

Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally in combination with other drugs), cat scratch disease, chancroid, *Burkholderia cepacia* (*Pseudomonas cepacia*) infections in cystic fibrosis, some forms of AIDS-associated diarrhoea such as the protozoal infection isosporiasis, gonorrhoea, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients. For details of the bacterial infections listed above and their treatment, see under Choice of Antibacterial, p.162.

Co-trimoxazole is usually given orally in an adult dose of 960 mg (trimethoprim 160 mg and sulfamethoxazole 800 mg) twice daily; in severe infections 2.88 g daily in 2 divided doses has been given. Lower doses are given for long-term treatment and in patients with renal impairment (see Administration in Renal Impairment, below).

Doses of co-trimoxazole to be given twice daily to children are: from 6 weeks to 5 months of age, 120 mg; 6 months to 5 years, 240 mg; 6 to 12 years, 480 mg. Alternatively, children may be given a dose of 24 mg/kg twice daily. Co-trimoxazole should not generally be given to infants below 6 weeks of age because of the risk of kernicterus from the sulfonamide component (see Pregnancy, p.341, under Precautions of Sulfamethoxazole), although it may be used in infants from 4 weeks of age for the treatment or prophylaxis of pneumocystis pneumonia.

Higher doses of co-trimoxazole of up to 120 mg/kg daily given in 2 to 4 divided doses for 14 to 21 days are used in the treatment of pneumocystis pneumonia in adults and children over 4 weeks of age; serum concentrations should be monitored and folate supplementation possibly considered (but see Pneumocystis Pneumonia, below). For prophylaxis in adults with AIDS, the usual dose of co-trimoxazole (960 mg twice daily) may be given, but has been associated with a high incidence of adverse effects (see Immunocompromised Patients, under Precautions, above). Alternatively the following dose regimens may be used: 960 mg daily (7 days each week); 960 mg daily on alternate days (3 days each week); or 960 mg twice daily on alternate days (3 days each week). Children may be given standard doses (see above) for prophylaxis; doses are given on 3 alternate or consecutive days per week or for 7 days per week. Prophylactic doses in children have also been given in terms of body-surface area; the *BNFC* suggests a dose of 450 mg/m² (to a maximum of 960 mg) twice daily for three days of the week, given either consecutively or on alternate days.

For serious infections, if oral use is not possible, co-trimoxazole may begin by intravenous infusion diluted immediately before use in a suitable diluent. The contents of each ampoule containing 480 mg of co-trimoxazole in 5 mL are added to 125 mL of diluent and infused over 60 to 90 minutes, unless fluid restriction is required, in which case only 75 mL of diluent may be used. Dosage is similar to that by mouth.

◊ The place of co-trimoxazole in therapy was reviewed by the UK CSM in 1995 (see also Incidence of Adverse Effects, above).[1] As a result they recommended that its use should be limited to: pneumocystis pneumonia, toxoplasmosis, and nocardiosis; urinary-tract infections and acute exacerbations of chronic bronchitis, but only when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer it to a single antibacterial; and acute otitis media in children, but again only when there is good reason to prefer it.

1. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Administration in renal impairment. Doses of co-trimoxazole, both orally and intravenously, should be reduced in patients with renal impairment. The following recommendations for adults and children over 12 years of age are based on creatinine clearance (CC):

- CC above 30 mL/minute: the standard dose
- CC 15 to 30 mL/minute: half the standard dose
- CC below 15 mL/minute: not recommended.

Blastocystis infection. For a mention of the use of co-trimoxazole in the treatment of *Blastocystis hominis* infection, see p.823.

Cyclosporiasis. Patients with *Cyclospora* infection (p.824) have responded to treatment with co-trimoxazole.[1-3]

1. Pape JW, *et al.* Cyclospora infection in adults infected with HIV: clinical manifestations, treatment and prophylaxis. *Ann Intern Med* 1994; **121:** 654–7.
2. Hoge CW, *et al.* Placebo-controlled trial of co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. *Lancet* 1995; **345:** 691–3. Correction. *ibid.*: 1060.
3. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Granulomatous diseases. Although co-trimoxazole appears to be effective in reducing the incidence of bacterial infection in patients with chronic granulomatous disease,[1-3] a disorder of leucocyte function associated with recurrent life-threatening infection and granuloma formation, its use in systemic vasculitis is much more controversial. There have been a number of reports of benefit from co-trimoxazole in patients with Wegener's granulomatosis (p.1515),[4-7] but even where benefit has been reported relapse appears to be common,[6] and an analysis[8] of the experience of the USA National Institutes of Health in 158 patients, was sceptical of its value: only 1 of 9 patients given 960 mg twice daily by mouth had any prolonged improvement.

Some evidence later emerged that addition of co-trimoxazole to maintenance regimens in patients already in remission reduces the incidence of relapse,[9] although another study suggested that it might actually increase the risk of relapse.[10]

1. Mouy R, *et al.* Incidence, severity, and prevention of infections in chronic granulomatous disease. *J Pediatr* 1989; **114:** 555–60.
2. Margolis DM, *et al.* Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. *J Infect Dis* 1990; **162:** 723–6.
3. Gallin JI, Malech HL. Update on chronic granulomatous diseases of childhood: immunotherapy and potential for gene therapy. *JAMA* 1990; **263:** 1533–7.
4. DeRemee RA, *et al.* Wegener's granulomatosis: observations on treatment with antimicrobial agents. *Mayo Clin Proc* 1985; **60:** 27–32.
5. Bowden FJ, Griffiths H. Co-trimoxazole in the treatment of Wegener's granulomatosis. *Med J Aust* 1989; **151:** 303–4.
6. Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991; **151:** 1649–52.
7. Ohtake T, *et al.* Generalized Wegener's granulomatosis responding to sulfamethoxazole-trimethoprim monotherapy. *Intern Med* 2001; **40:** 666–70.
8. Hoffman GS, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116:** 488–98.
9. Stegeman CA, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335:** 16–20.
10. de Groot K, *et al.* Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; **39:** 2052–61.

Isosporiasis. A regimen of oral co-trimoxazole 960 mg four times daily for 10 days followed by 960 mg twice daily for 3 weeks was reported to be initially effective in patients with AIDS suffering from isosporiasis (p.824), and produced resolution of diarrhoea within 2 days of beginning treatment; it was, however, associated with a high rate of recurrence.[1] A shorter regimen followed by indefinite prophylaxis may be preferable in persons with AIDS; in a small randomised controlled study, co-trimoxazole 960 mg twice daily for 7 days, followed by 10 weeks' prophylaxis, was effective in HIV-infected patients with isosporiasis.[2]

1. DeHovitz JA, *et al.* Clinical manifestations and therapy of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1986; **315:** 87–90.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Nocardiosis. Co-trimoxazole is used in the treatment of nocardiosis (p.181). There is no consensus on the optimum dosage; doses of 2.88 to 3.84 g daily in divided doses for up to 3 months have been used.

Pneumocystis pneumonia. Co-trimoxazole is the preferred drug[1-3] for both the treatment and prophylaxis of pneumocystis pneumonia (p.521). A single dose of 480 mg daily may be effective and better tolerated for prophylaxis than a daily dose of 960 mg.[4] However, some still prefer the latter dose schedule[5] which is also the one preferred by the CDC in the USA[1] and is a licensed dose for prophylaxis in both the UK and USA. Various studies[4-10] have shown intermittent dosing is also effective for the prophylaxis of pneumonia and is better tolerated than daily dosing; the dose has usually been 960 mg three times each week on alternate days[4-9] although 960 mg twice daily three times each week has also been given.[10] The addition of folinic acid has no effect on tolerability and may be associated with a higher rate of therapeutic failure (see HIV Infection and AIDS, p.1944).

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5108.pdf (accessed 18/05/05)
2. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 04/04/05)
3. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 04/04/05) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 13/06/05)
4. Ioannidis JPA, *et al.* A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996; **156:** 177–88.
5. El-Sadr WM, *et al.* A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis* 1999; **29:** 775–83.
6. Wormser GP, *et al.* Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151:** 688–92.
7. Stein DS, *et al.* Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1991; **35:** 1705–9.
8. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337:** 468–71.
9. Bozzette SA, *et al.* The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
10. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.

Toxoplasmosis. There is some evidence that giving co-trimoxazole for prophylaxis of pneumocystis pneumonia produces an additional benefit in acting prophylactically against toxoplasmic encephalitis in persons with HIV infection or AIDS,[1-5] but the evidence (as for other drugs) has been largely anecdotal or from small retrospective studies. In the USA, the CDC recommends[1] that co-trimoxazole 960 mg daily (as for *Pneumocystis carinii* pneumonia prophylaxis, above) be given to HIV-infected patients who are seropositive for *Toxoplasma* and have a CD4+ count below 100 cells/microlitre.

Co-trimoxazole has also produced promising results in preliminary studies for the treatment of toxoplasmic encephalitis in patients with AIDS,[6] and a systematic review[7] considered it an effective treatment, particularly in resource-poor settings where alternatives such as pyrimethamine with sulfadiazine might not be available.

For a discussion of toxoplasmosis and its management, see p.826.

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52.
2. Zangerle R, Allerberger F. Effect of prophylaxis against Pneumocystis carinii on toxoplasma encephalitis. *Lancet* 1991; **337:** 1232.
3. Carr A, *et al.* Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992; **117:** 106–11.
4. Beaman MH, *et al.* Prophylaxis for toxoplasmosis in AIDS. *Ann Intern Med* 1992: **117:** 163–4.
5. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
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7. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).

Preparations

BP 2008: Co-trimoxazole Intravenous Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; ***USP 31:*** Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Adrenol; Bacticel; Bactrim; Cotrizol-G; Danferane; Diocla†; Dosulfin Fuerte; Netocur; Novidrine; Sulfagrand; Tritenk; Urisept NF; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Oecotrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Steroprim†; ***Braz.:*** Assepium; Bac-Sulfitrin; Bacfar; Bacprotin; Bacris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Binoctrin†; Clotrizol†; Dientrin; Duoctrin†; Ectrin; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Septiolan†; Teutrin; Tricban; Trimexazol; Trimezol†; Uropol; ***Canad.:*** Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Septra; ***Chile:*** Bacterol; Bactrimel; Introcin†; Septrin; Trelibec; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Bismoral; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Cotrim; Cotrim-Diolan; CotrimHefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Septrin; ***Hung.:*** Sumetrolim; ***India:*** Bactrim; Ciplin; Colizole; Cotrimol†; Oriprim; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.:*** Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim; Cotrimol; Dumotrim; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim; Meprotrin; Nufaprim; Ottoprim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim; Sultrimmix; Trimezol; Triminex; Trimoxsul; Trixzol; Trizole; Ulfaprim; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.:*** Duobact†; Septrin; ***Israel:*** Diseptyl; Resprim; Septrin; ***Ital.:*** Abacin†; Bactrim; Chemitrim; Eusaprim; Gantrim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Baserin†; Chemix; Cotrim; Resprim; Trimexazole; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Kaltrim; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Sulfotrim; ***Norw.:*** Bactrim; Trimetoprim-Sulfa†; ***NZ:*** Apo-Sulfatrim; Trisul; ***Philipp.:*** Bacidal; Bactille; Bactrim; Bacxal; Baczole; Bantizol; Chromo-Z; Combi-Methoxan; Costazole; Cozole; Drilozole; Fedimed; Forteprim; Globaxol; Ivatrim; Kassemox; Lictora; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Synermed; Triforam; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Septrin; ***Rus.:*** Biseptol (Бисептол); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Purbac; Septran; Spectrim; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; BS†; Chemix; Chemoprim; Dhatrin; Septrin†; Suprim; Trimezole†; ***Spain:*** Broncomega†; Busetal†; Eduprim†; Gobens Trim; Momentol; Septrin; ***Swed.:*** Bactrim; Eusaprim; ***Switz.:*** Agoprim†; Bactrim; Cotrim; Escoprim; Groprim; Lagatrim; Mediprim; Nopil; Sigaprim†; Supracombin†; ***Thai.:*** Actin; Bacin; Bacta†; Bactrim; Baczole; Chemoprim†; Co-Tasian; Co-Trimed; Conprim; Cotamox; Ko-Cap; Ko-Kure; Ladar; Lastrim; Letus; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Septrin; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Septrin; ***USA:*** Bactrim; Cotrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

Multi-ingredient: ***Arg.:*** Bacti-Uril; Bactrim Balsamico; Dosulfin Bronquial; Enterobacticel; Netocur Balsamico; Neumobacticel; Uro-Bactrim†; ***Braz.:*** Assepium Balsamico; Benectrin Balsamico; Diazol; Dispeptrin; Ectrin Balsamico; Metoprin Balsamico; Selectrin Balsamico; Uro-Baxapril†; Uroctrin; ***Chile:*** Entero Micinovo; Uro-Micinovo; ***Hung.:*** Cotripharm; ***Mex.:*** Bactrim Compositum; Brogamax; Guayaprin; Octex; Sadocin; Trimexole Compositum; ***Singapore:*** Co-Trimexazole; Trimaxazole; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Cotrazol; Eduprim Mucolitico; Neumopectolina†; Pulmo Menal†; Pulmosterin Duo.

Cycloserine *(BAN, rINN)*

Cicloserina; D-Cycloserin; Cyclosérine; D-Cycloserine; Cycloserinum; Cykloserin; SC-49088; Sikloserin; Sykloseriini. (+)-(*R*)-4-Aminoisoxazolidin-3-one.

Циклосерин

$C_3H_6N_2O_2$ = 102.1.
CAS — 68-41-7.
ATC — J04AB01.
ATC Vet — QJ04AB01.

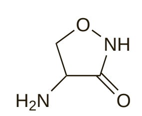

Description. Cycloserine is an antimicrobial substance produced by the growth of certain strains of *Streptomyces orchidaceus* or *S. garyphalus*, or obtained by synthesis.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Cycloserine). A white to pale yellow, crystalline powder, odourless or has a faint odour. It is hygroscopic and deteriorates upon absorbing water. Freely soluble in water. pH of a 10% solution in water is between 5.5 and 6.5. Store in airtight containers.

Adverse Effects and Treatment

The most frequent adverse effects with cycloserine involve the CNS and include anxiety, confusion, disorientation, depression, psychoses possibly with suicidal tendencies, aggression, irritability, and paranoia. Vertigo, headache, drowsiness, speech difficulties, tremor, paresis, hyperreflexia, dysarthria, paraesthesia, coma, and convulsions may also occur. Neurological reactions are dose related and may be reduced by keeping plasma concentrations below 30 micrograms/mL. It has been reported that up to 30% of patients have experienced adverse effects. These reactions usually subside when cycloserine is stopped or the dosage is reduced. Pyridoxine has been used in an attempt to treat or prevent neurological reactions but its value is unproven.

Hypersensitivity reactions including skin reactions and photosensitivity occur rarely. Serum aminotransferase values may be raised, especially in patients with a history of liver disease. Folate and vitamin B_{12} deficiency, megaloblastic anaemia, and sideroblastic anaemia have been reported occasionally when cycloserine has been used with other antituberculous drugs. Heart failure has occurred in patients receiving daily doses of 1 g or more.

Precautions

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cycloserine,[1] and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. Cycloserine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Patients receiving cycloserine and taking alcohol are at increased risk of convulsions; for reference to increased blood-alcohol concentrations in patients receiving cycloserine, see p.1627.

Neurotoxic effects may be potentiated by use of cycloserine with ethionamide, and concurrent use of cycloserine and isoniazid may result in increased CNS toxicity, such as dizziness and drowsiness.

Antimicrobial Action

Cycloserine interferes with bacterial cell wall synthesis by competing with D-alanine for incorporation into the cell wall. It has variable activity against Gram-positive and Gram-negative bacteria including *Escherichia coli* and *Staphylococcus aureus*.

Cycloserine is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistance develops if cycloserine is used alone.

Pharmacokinetics

Cycloserine is readily and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations of 10 micrograms/mL have been obtained 3 to 4 hours after a dose of 250 mg, rising to 20 to 30 micrograms/mL on repeating the dose every 12 hours. The plasma half-life is about 10 hours and is prolonged in patients with renal impairment.

Cycloserine is widely distributed into body tissues and fluids, including the CSF, placenta, and breast milk, producing fetal blood concentrations approaching those in maternal serum.

Cycloserine is excreted largely unchanged by glomerular filtration. About 50% of a single 250-mg dose is excreted unchanged in the urine within 12 hours and about 70% is excreted within 72 hours. As negligible amounts of cycloserine appear in the faeces, it is assumed that the remainder of a dose is metabolised to unidentified metabolites. It is removed by haemodialysis.

Pregnancy and breast feeding. Cycloserine has been shown to pass to the fetus, into amniotic fluid,[1] and into breast milk.[2] Concentrations in breast milk after 250 mg four times daily have been reported to range from 6 to 19 micrograms/mL.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.

Uses and Administration

Cycloserine is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p.196) as part of a multidrug regimen when resistance to primary drugs has developed. It has been used in urinary-tract infections, although less toxic drugs are preferred.

The usual adult oral dose in tuberculosis is 250 mg twice daily for 2 weeks, followed by 0.5 to 1 g daily in divided doses. Dosage in patients with mild to moderate renal impairment should be reduced and doses for all patients should be adjusted by monitoring plasma concentrations (see Precautions, above).

For details of doses in infants, children, and adolescents, see below.

Cycloserine has been tried for the adjunctive treatment of schizophrenia. L-Cycloserine has been investigated for the treatment of Gaucher disease (p.2249).

Administration in children. Use of cycloserine is licensed in both the UK and USA for children, although age ranges are not specified in licensed product information. For the treatment of drug-resistant tuberculosis the American Academy of Pediatrics (AAP) suggests a dose of 5 to 10 mg/kg twice daily, to a maximum dose of 1 g daily.

The *BNFC* suggests the following doses:

- children aged 2 to 12 years; 5 mg/kg twice daily
- children aged 12 to 18 years; 250 mg twice daily for 2 weeks then adjusted to a maximum dose of 1 g daily

Doses are adjusted according to blood concentrations and response.

Preparations

USP 31: Cycloserine Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Closina; ***Gr.:*** D-cycloserin; Seromycin; ***Hong Kong:*** Seromycin; ***India:*** Cyclorine; ***Thai.:*** Proserine; ***Turk.:*** Siklocap; ***UK:*** Cycloserine; ***USA:*** Seromycin.

Dalbavancin *(BAN, USAN, rINN)*

A-A-1; BI-397; Dalbavancina; Dalbavancine; Dalbavancinum; MDL-63397; VER-001. 5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-{2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl}-38-{[3-(dimethylamino)propyl]carbamoyl}-42-*O*-α-D-mannopyranosyl-15-*N*-methyl(ristomycin A aglicone) (main component).

Дальбаванцин

$C_{88}H_{100}Cl_2N_{10}O_{28}$ = 1816.7.

CAS — 171500-79-1.

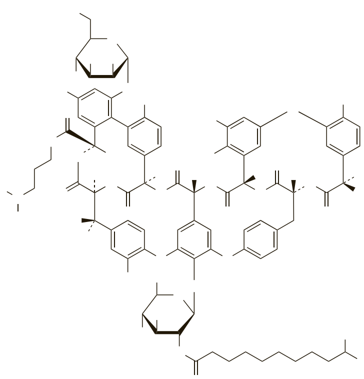

Profile

Dalbavancin is a glycopeptide antibacterial under investigation for the treatment of severe infections due to Gram-positive bacteria, including complicated infections of the skin and soft tissues.

◊ References.

1. Lin S-W, *et al.* Dalbavancin: a new option for the treatment of gram-positive infections. *Ann Pharmacother* 2006; **40:** 449–60.
2. Billeter M, *et al.* Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clin Infect Dis* 2008; **46:** 577–83.
3. Anderson VR, Keating GM. Dalbavancin. *Drugs* 2008; **68:** 639–48.
4. Bailey J, Summers KM. Dalbavancin: a new lipoglycopeptide antibiotic. *Am J Health-Syst Pharm* 2008; **65:** 599–610.

Danofloxacin Mesilate *(BANM, rINNM)*

CP-76136 (danofloxacin); CP-76136-27 (danofloxacin mesilate); Danofloksasiinimesilaatti; Danofloxacin Mesylate *(USAN)*; Danofloxacine, mésilate de; Danofloxacini mesilas; Danofloxacinmesilat; Mesilato de danofloxacino. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-oxo-3-quinolinecarboxylic acid monomethanesulphonate.

Данофлоксацина Мезилат

$C_{19}H_{20}FN_3O_3,CH_4O_3S$ = 453.5.

CAS — 112398-08-0 (danofloxacin); 119478-55-6 (danofloxacin mesilate).

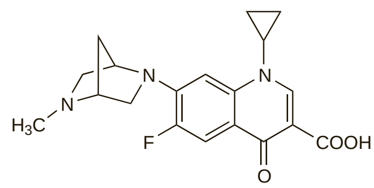

(danofloxacin)

Profile

Danofloxacin is a fluoroquinolone antibacterial used as the mesilate in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Dapsone *(BAN, USAN, rINN)*

DADPS; Dapson; Dapsona; Dapsonas; Dapsoni; Dapsonum; Dapszon; DDS; Diaminodiphenylsulfone; Diaphenylsulfone; Disulone; NSC-6091; 4,4′-Sulfonylbis-benzenamine; Sulphonyldianiline. Bis(4-aminophenyl) sulphone.

Дапсон

$C_{12}H_{12}N_2O_2S$ = 248.3.

CAS — 80-08-0.

ATC — J04BA02.

ATC Vet — QJ04BA02.

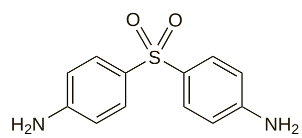

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Dapsone). A white or slightly yellowish-white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves freely in dilute mineral acids. Protect from light.

USP 31 (Dapsone). A white or creamy-white, odourless crystalline powder. Very slightly soluble in water, freely soluble in alcohol; soluble in acetone and in dilute mineral acids. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dapsone prepared from commercially available tablets found them to be stable for 3 months when stored at 4° and at 25°.

1. Nahata MC, *et al.* Stability of dapsone in two oral liquid dosage forms. *Ann Pharmacother* 2000; **34:** 848–50.

Adverse Effects

Varying degrees of dose-related haemolysis and methaemoglobinaemia are the most frequently reported adverse effects of dapsone, and occur in most patients given more than 200 mg daily; doses of up to 100 mg daily do not cause significant haemolysis, but patients with G6PD deficiency are affected by doses above about 50 mg daily.

Although agranulocytosis has been reported rarely with dapsone when used alone, reports have been more common when it has been used with other drugs in the prophylaxis of malaria. Deaths due to agranulocytosis, aplastic anaemia, and other blood dyscrasias have been reported.

Rash and pruritus may develop. Serious cutaneous hypersensitivity reactions occur rarely and include maculopapular rash, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Fixed drug eruptions have occurred.

A 'dapsone syndrome' may occur after 4 to 8 weeks of treatment and resembles mononucleosis in its presentation (see Hypersensitivity Reactions, below).

Peripheral neuropathy with motor loss has been reported in patients on dapsone for dermatological conditions. Peripheral neuropathy may occur as part of leprosy reaction states and is not an indication to stop dapsone.

Other adverse effects occur infrequently and include nausea, vomiting, anorexia, headache, hepatitis, insomnia, psychosis, and tachycardia.

Carcinogenicity. A survey of 1678 leprosy patients admitted for treatment to the National Hansen's Disease Center in the USA between 1939 and 1977 indicated that, although dapsone has been implicated as a carcinogen in *animals*, the use of dapsone did not appear to affect significantly the risk of cancer in these patients.[1] The International Agency for Research on Cancer concluded[2] that there was limited evidence for the carcinogenicity of dapsone in *animals* and insufficient data to be able to classify the carcinogenic risk in humans.

1. Brinton LA, *et al.* Cancer mortality among patients with Hansen's disease. *J Natl Cancer Inst* 1984; **72:** 109–14.
2. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 24* 1980. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol24/volume24.pdf Updated 07/04/88. (accessed 03/10/07)

Effects on the blood. *Haemolysis* is the most frequent serious adverse effect of dapsone and may occur at doses of 200 mg or higher daily.[1] Red blood cells may contain Heinz bodies and there is a reduction in their life span. Well-known risk factors include G6PD deficiency, methaemoglobin reductase deficiency, and haemoglobin M trait; haemoglobin E trait may also increase susceptibility to haemolytic reactions.[2] Haemolytic anaemia has been reported in a neonate after ingestion of dapsone in breast milk.[3]

Methaemoglobinaemia, although common, is rarely symptomatic.[1] However, severe cyanosis was associated with methaemoglobinaemia after an inadvertent overdose with dapsone in an HIV-positive patient with suspected pneumocystis pneumonia.[4] Methaemoglobinaemia has also been reported in an HIV-negative patient with severe renal impairment, who had previously undergone liver and kidney transplantations and who was receiving dapsone for prophylaxis of pneumocystis pneumonia.[5] The metabolite dapsone hydroxylamine is probably responsible for the methaemoglobinaemia and haemolysis associated with dapsone. Studies have shown[6,7] that use of dapsone with cimetidine, which inhibits production of the *N*-hydroxy metabolite, has resulted in a decrease in methaemoglobin levels, at least in the short term.

Agranulocytosis has occurred rarely on use of dapsone in leprosy and skin disease. More cases have been observed when used for malaria prophylaxis[8] (see also under Pyrimethamine, p.610) and dermatitis herpetiformis.[9] The reaction is usually self-limiting once the drug is withdrawn, but fatalities have occurred.[9,10]

Aplastic anaemia has been reported.[11,12] Of 11 fatalities attributed to dapsone reported to the British and Swedish adverse reaction registers[13] between 1968 and 1988, seven were due to white blood cell dyscrasias; none were attributed to red cell dyscrasias, although such reactions formed almost half of all serious reactions reported for dapsone.

Pure red cell aplasia has been reported in an elderly patient taking oral dapsone daily for granuloma annulare.[14]

Thrombocytosis was reported in a patient with AIDS receiving dapsone prophylactically.[15]

See also Hypoalbuminaemia, below.

1. Jopling WH. Side-effects of antileprosy drugs in common use. *Lepr Rev* 1983; **54:** 261–70.
2. Lachant NA, Tanaka KR. Case report: dapsone-associated Heinz body hemolytic anemia in a Cambodian woman with hemoglobin E trait. *Am J Med Sci* 1987; **294:** 364–8.
3. Sanders SW, *et al.* Hemolytic anemia induced by dapsone transmitted through breast milk. *Ann Intern Med* 1982; **96:** 465–6.
4. Seaton RA, *et al.* Blue and breathless. *Hosp Med* 1999; **60:** 530.
5. Ward KE, McCarthy MW. Dapsone-induced methemoglobinemia. *Ann Pharmacother* 1998; **32:** 549–53.
6. Coleman MD, *et al.* The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. *Br J Clin Pharmacol* 1990; **30:** 761–7.
7. Rhodes LE, *et al.* Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* 1995; **132:** 257–62.
8. Firkin FC, Mariani AF. Agranulocytosis due to dapsone. *Med J Aust* 1977; **2:** 247–51.
9. Cockburn EM, *et al.* Dapsone-induced agranulocytosis: spontaneous reporting data. *Br J Dermatol* 1993; **128:** 702–3.
10. Barss P. Fatal dapsone agranulocytosis in a Melanesian. *Lepr Rev* 1986; **57:** 63–6.
11. Foucauld J, *et al.* Dapsone and aplastic anemia. *Ann Intern Med* 1985; **102:** 139.
12. Meyerson MA, Cohen PR. Dapsone-induced aplastic anemia in a woman with bullous systemic lupus erythematosus. *Mayo Clin Proc* 1994; **69:** 1159–62.
13. Björkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bull WHO* 1991; **69:** 297–304.
14. Borrás-Blasco J, *et al.* Pure red cell aplasia associated with dapsone therapy. *Ann Pharmacother* 2005; **39:** 1137–8.
15. Wynn RF, *et al.* Case report of dapsone-related thrombocytosis in an AIDS patient. *Am J Med* 1995; **98:** 602.

Effects on the eyes. There have been rare reports[1-4] of ocular toxicity, usually resulting in permanent loss of visual acuity, after overdoses with dapsone. Toxic effects included blurring of vision,[1,2] optic atrophy,[1] ischaemic retinopathy, ischaemic optic neuropathy,[3] and bilateral macular infarction.[4] These effects were thought to be due to acute hypoxia and obstruction with red cell fragments. A case of anterior ischaemic optic neuropathy[5] has also been reported in a patient taking usual doses of dapsone for dermatitis herpetiformis.

1. Daneshmend TK. The neurotoxicity of dapsone. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 43–58.
2. Alexander TA, *et al.* Presumed DDS ocular toxicity. *Indian J Ophthalmol* 1989; **37:** 150–1.

3. Seo M-S, *et al.* Dapsone maculopathy. *Korean J Ophthalmol* 1997; **11:** 70–3.
4. Chakrabarti M, *et al.* Bilateral macular infarction due to diaminodiphenyl sulfone (4,4′ DDS) toxicity. *Retina* 1999; **19:** 83–4.
5. Chalioulias K, *et al.* Anterior ischaemic optic neuropathy associated with Dapsone. *Eye* 2006; **20:** 943–5.

Effects on the liver. Toxic hepatitis and cholestatic jaundice have been reported by licensed product information to occur early in dapsone therapy. Jaundice may also form part of the dapsone syndrome (see Hypersensitivity Reactions, below). Deterioration in liver function tests during dapsone treatment has been noted in a patient with dermatitis herpetiformis and primary sclerosing cholangitis.[1]

1. Kirby B, *et al.* Abnormal liver function tests induced by dapsone in a patient with dermatitis herpetiformis and primary sclerosing cholangitis. *Br J Dermatol* 1999; **141:** 172–3.

Effects on the lungs. Hypersensitivity reactions to dapsone usually affect the skin, but there have been rare reports of dapsone hypersensitivity presenting with fever, wheezing, and pulmonary eosinophilia.[1-4] Pulmonary eosinophilia occurred in one patient taking dapsone for urticaria[1] and in another taking dapsone as part of the WHO multidrug treatment regimen for leprosy.[2] In both patient symptoms resolved when dapsone was stopped and occurred again on rechallenge. Another patient[3] known to develop fever and wheezing when taking dapsone for leprosy was given a dapsone challenge for 5 days. He became acutely ill and had a high absolute eosinophil count; symptoms resolved 2 weeks after stopping dapsone.

1. Jaffuel D, *et al.* Eosinophilic pneumonia induced by dapsone. *BMJ* 1998; **317:** 181.
2. Kaur J, *et al.* Dapsone-induced eosinophilic pneumonitis in a leprosy patient. *Indian J Lepr* 2005; **77:** 267–71.
3. Arunthathi S, Raju S. Dapsone induced pulmonary eosinophilia without cutaneous allergic manifestations—an unusual encounter—a case report. *Acta Leprol* 1998; **11:** 3–5.
4. Janier M, *et al.* Pulmonary eosinophilia associated with dapsone. *Lancet* 1994; **343:** 860–1.

Effects on mental state. Psychiatric adverse effects have been reported in leprosy patients receiving dapsone, but the role of dapsone in this effect is poorly defined.[1-4] Manic-depressive reactions have been reported in 2 patients[2,3] with skin disorders and psychosis[4] was reported in a patient being treated for leprosy. These reactions appeared to be idiosyncratic reactions to dapsone. In all cases symptoms resolved when dapsone was stopped.

1. Daneshmend T. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **299:** 324.
2. Carmichael AJ, Paul CJ. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **298:** 1524. Correction. *ibid.*; **299:** 56.
3. Gawkrodger D. Manic depression induced by dapsone in patient with dermatitis herpetiformis. *BMJ* 1989; **299:** 860.
4. Balkrishna, Bhatia MS. Dapsone-induced psychosis. *J Indian Med Assoc* 1989; **87:** 120–1.

Effects on the nervous system. A case review[1] of 21 patients who had dapsone-induced neuropathy reported that the median time to onset of symptoms was about 1 year; with a range of 11 days to 18 years. Symptoms occurred in patients taking doses varying from 25 to 800 mg/day and after a total cumulative dose of 4 to 1500 g. Most patients had either pure motor or mixed sensory-motor neuropathies, while pure sensory neuropathy was rarely reported. Patients generally recovered, either partially or completely, within one year of stopping dapsone. Progressive multifocal leukoencephalopathy has been reported in a patient with SLE treated with a dapsone-containing regimen, although it was unclear what role dapsone had played.[2]

1. Méry L, *et al.* Polynévrite sensitive induite par la dapsone (Disulone). *Ann Dermatol Venereol* 2003; **130:** 447–9.
2. Stahl NI. Progressive multifocal leukoencephalopathy in a minimally immunosuppressed patient with systemic lupus erythematosus treated with dapsone. *J Rheumatol* 2008; **35:** 725–7.

Effects on the pancreas. Acute pancreatitis has been associated with the use of dapsone to treat dermatitis herpetiformis in an 87-year-old man.[1] Symptoms resolved on stopping dapsone but recurred upon rechallenge.

1. Jha SH, *et al.* Dapsone-induced acute pancreatitis. *Ann Pharmacother* 2003; **37:** 1438–40.

Effects on taste. A persistent sweet taste and tingling of the face and lips was described in a patient receiving dapsone for ocular cicatricial pemphigoid.[1] The symptoms resolved when dapsone was stopped.

1. Stafanous SN, Morgan SJ. A previously unrecognised side effect of dapsone. *Br J Ophthalmol* 1997; **81:** 1113–14.

Hyperpigmentation. Hyperpigmented macules were reported in 32 of about 800 children given dapsone with pyrimethamine for 3 months or more for malaria prophylaxis.[1] The reaction was attributed to dapsone.

1. David KP, *et al.* Hyperpigmented dermal macules in children following the administration of Maloprim for malaria chemoprophylaxis. *Trans R Soc Trop Med Hyg* 1997; **91:** 204–8.

Hypersensitivity reactions. Dapsone syndrome is a rare idiosyncratic hypersensitivity reaction, although it has been suggested[1-3] that the incidence has increased since the introduction of multidrug therapy for leprosy. It usually occurs in the first 4 to 8 weeks of therapy, is not dose-related, and resolves within 14 days on stopping dapsone. Dapsone syndrome may also occur within 1 to 2 weeks of stopping the drug, due to its long elimination half-life and high protein binding.[4] Common clinical symptoms may include exanthematous skin rash, fever, hepatitis (cholestatic and hepatocellular injuries), eosinophilia, lymphadenopathy, and mononucleosis. The syndrome has occurred in leprosy patients,[5,6] in patients with skin disorders,[7] in patients with AIDS taking dapsone for prophylaxis of pneumocystis pneumonia,[4] and in patients taking weekly dapsone (with pyrimethamine) for malaria prophylaxis.[8] Fatalities have occurred.[9,10] Desensitisation has been successfully carried out in several patients with AIDS who exhibited hypersensitivity to dapsone.[11,12]

1. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev* 1989; **60:** 267–73.
2. Kumar RH, *et al.* Dapsone syndrome—a five year retrospective analysis. *Indian J Lepr* 1998; **70:** 271–6.
3. Rao PN, Lakshmi TSS. Increase in the incidence of dapsone hypersensitivity syndrome—an appraisal. *Lepr Rev* 2001; **72:** 57–62.
4. Lee KB, Nashed TB. Dapsone-induced sulfone syndrome. *Ann Pharmacother* 2003; **37:** 1044–6.
5. Alves-Rodrigues EN, *et al.* Dapsone syndrome with acute renal failure during leprosy treatment: case report. *Braz J Infect Dis* 2005; **9:** 84–6.
6. Bucaretchi F, *et al.* Dapsone hypersensitivity syndrome in an adolescent during treatment during [sic] of leprosy. *Rev Inst Med Trop Sao Paulo* 2004; **46:** 331–4.
7. Sener O, *et al.* Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006; **16:** 268–70.
8. Tee AKH, *et al.* Dapsone hypersensitivity syndrome masquerading as a viral exanthem: three cases and a mini-review. *Ann Acad Med Singapore* 2004; **33:** 375–8.
9. Frey HM, *et al.* Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94:** 777–9.
10. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; **32:** 883–9.
11. Metroka CE, *et al.* Desensitization to dapsone in HIV-positive patients. *JAMA* 1992; **267:** 512.
12. Cook DE, Kossey JL. Successful desensitization to dapsone for Pneumocystis carinii prophylaxis in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1302–5.

Hypoalbuminaemia. Severe and often life-threatening hypoalbuminaemia has been reported rarely in patients taking dapsone for long periods for dermatitis herpetiformis.[1-3] Hypoalbuminaemia usually resolves rapidly once dapsone is withdrawn.

1. Kingham JGC, *et al.* Dapsone and severe hypoalbuminaemia. *Lancet* 1979; **ii:** 662–4 and 1018.
2. Foster PN, Swan CHJ. Dapsone and fatal hypoalbuminaemia. *Lancet* 1981; **ii:** 806–7.
3. Sinclair SA, *et al.* Life threatening hypoalbuminaemia associated with dapsone therapy. *Br J Dermatol* 1996; **135** (suppl 47): 45.

Photosensitivity. Photosensitivity has been reported in 6 patients who had taken dapsone for leprosy[1] and in a patient receiving dapsone for a bullous skin disease;[2] the topic has been reviewed.[3]

1. Dhanapaul S. DDS-induced photosensitivity with reference to six case reports. *Lepr Rev* 1989; **60:** 147–50.
2. Stockel S, *et al.* Dapsone-induced photodermatitis in a patient with linear IgA dermatosis. *Eur J Dermatol* 2001; **11:** 50–3.
3. De D, *et al.* Dapsone induced acute photosensitivity dermatitis; a case report and review of literature. *Lepr Rev* 2007; **78:** 401–4.

Treatment of Adverse Effects

In severe overdosage, repeated oral doses of activated charcoal should be given with the aim of preventing absorption of dapsone but also to aid the elimination of dapsone and its monoacetyl metabolite. Methaemoglobinaemia has been treated with slow intravenous injections of methylthioninium chloride 1 to 2 mg/kg repeated after 1 hour if necessary. Methylthioninium chloride should not be given to patients with G6PD deficiency since it will not be effective. Haemolysis has been treated by infusion of concentrated human red blood cells to replace the damaged cells. Supportive therapy includes giving oxygen and fluids.

Patients who develop dapsone syndrome (see Hypersensitivity Reactions, above) may require several weeks of corticosteroid therapy.

Overdosage. References.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.
2. Endre ZH, *et al.* Successful treatment of acute dapsone intoxication using charcoal hemoperfusion. *Aust N Z J Med* 1983; **13:** 509–12.
3. Hoetelmans RMW, *et al.* Combined dapsone and clofazimine intoxication. *Hum Exp Toxicol* 1996; **15:** 625–8.
4. Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone: a case report and summary of relevant pharmacology and treatment. *Anaesthesia* 1997; **52:** 359–63.
5. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dapsone poisoning; treatment with methylene blue and exchange transfusion. *J R Soc Health* 1999; **119:** 52–5.

Precautions

Dapsone should not be used in patients with severe anaemia. It is recommended that regular blood counts be performed during treatment. Patients deficient in G6PD or methaemoglobin reductase, or with haemoglobin M are more susceptible to the haemolytic effects of dapsone.

Where possible, liver function should be monitored during treatment.

It is now generally considered that the benefits of dapsone in the treatment of leprosy during pregnancy outweigh any potential risks to the pregnant patient or fetus. Some recommend folic acid 5 mg daily for leprosy patients receiving dapsone during pregnancy.

Breast feeding. Dapsone is distributed into breast milk and the American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of dapsone in a breast-feeding mother has resulted in sulfonamide detected in the infant's urine.[2] There has also been a report of haemolytic anaemia in a breast-fed infant (see Effects on the Blood, under Adverse Effects, above). A study in 3 lactating women who were given a single dose of dapsone 100 mg plus pyrimethamine and chloroquine estimated that if their infants were breast fed they would receive 4.6, 10, or 14.3%, respectively, of the maternal dose in the 9-day period after it was given.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Dreisbach JA. Sulphone levels in breast milk of mothers on sulphone therapy. *Lepr Rev* 1952; **23:** 101–6.
3. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.

Porphyria. Dapsone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. References.

1. Brabin BJ, *et al.* Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Safety* 2004; **27:** 633–48.

Interactions

Serum concentrations of dapsone are increased, with a consequent increased risk of adverse effects, when given with probenecid, probably as a result of reduced renal excretion of dapsone. Increased dapsone and trimethoprim concentrations have also been reported in patients receiving both drugs, who may similarly be at greater risk of dapsone toxicity. Rifampicin reduces serum concentrations of dapsone to a level that may compromise efficacy in infections other than leprosy. Rifampicin concentrations are generally unaffected. Dapsone may reduce the anti-inflammatory effects of clofazimine (p.255).

Cimetidine. Cimetidine has been reported to increase the area under the curve for dapsone, but to decrease the area under the curve for the metabolite dapsone hydroxylamine. Haematotoxicity is thought to be related to production of this metabolite (see Effects on the Blood, above).

Pyrimethamine. Although some licensed product information has warned that dapsone-induced haematotoxicity could be potentiated by folic acid antagonists such as pyrimethamine, the tolerability of dapsone plus pyrimethamine was similar to dapsone alone when each treatment was given on a once-weekly basis to patients with HIV infection.[1] Dapsone concentrations were not significantly higher in patients receiving dapsone plus pyrimethamine than in those receiving dapsone alone.

1. Falloon J, *et al.* Pharmacokinetics and safety of weekly dapsone and dapsone plus pyrimethamine for prevention of pneumocystis pneumonia. *Antimicrob Agents Chemother* 1994; **38:** 1580–7.

Trimethoprim. In a study of AIDS patients with pneumocystis pneumonia, the mean peak serum concentrations of dapsone after 7 days were 1.5 micrograms/mL after 100 mg daily and 2.1 micrograms/mL after the same dose with trimethoprim 20 mg/kg daily; concentrations of trimethoprim were also increased.[1] Elevated dapsone concentrations may contribute to the toxicity and the efficacy of this combination.

1. Lee BL, *et al.* Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; **110:** 606–11.

Antimicrobial Action

Dapsone is a sulfone active against a wide range of bacteria and some protozoa, but it is mainly used for its action against *Mycobacterium leprae*. Like the sulfonamides it may inhibit folic acid synthesis in susceptible organisms although this is not considered to be the mechanism of action in *M. leprae*. It is usually considered to be bacteriostatic against *M. leprae*, although it may also possess weak bactericidal activity. It is also active against *Plasmodium* and *Pneumocystis jirovecii*.

As with the sulfonamides, antibacterial activity is inhibited by *p*-aminobenzoic acid.

Secondary (acquired) dapsone resistance of *M. leprae* is mainly associated with dapsone being used on its own. Primary dapsone resistance has also been reported with increasing frequency in areas with secondary resistance. Resistance of *M. leprae* to dapsone should be suspected whenever a patient relapses clinically and bacteriologically.

Drug resistance. Monotherapy with dapsone was the standard of treatment for all forms of leprosy until the 1980's, when concerns about dapsone resistance led WHO to introduce a multidrug treatment (MDT) regimen consisting of dapsone, rifampicin, and clofazimine. Long-term follow-up studies[1,2] designed to evaluate the efficacy of WHO MDT regimen reported relapse rates of 1.1 to 9% after a minimum of 2 years treatment. Drug sensitivity analyses were reported for 15 of these patients; no resistance to clofazimine or rifampicin was reported, while isolates from 3 patients showed dapsone resistance.[1] An evaluation of drug resistance after the introduction of WHO MDT regimen in Nepal[3] concluded that secondary resistance to dapsone does not develop under this regimen. Strains of *Mycobacterium leprae* with multiple resistance to rifampicin, ofloxacin, and dapsone have been isolated from a patient who had previously received dapsone monotherapy followed by treatment with rifampicin plus ofloxacin for 28 days.[4]

1. Cellona RV, *et al.* Long-term efficacy of 2 year WHO multiple drug therapy (MDT) in multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis* 2003; **71:** 308–19.
2. Norman G, *et al.* Relapses in multibacillary patients treated with multi-drug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis* 2004; **72:** 1–7.
3. Roche PW, *et al.* Dapsone drug resistance in the MDT era. *Int J Lepr Other Mycobact Dis* 2000; **68:** 323–5.
4. Cambau E, *et al.* Multidrug-resistance to dapsone, rifampicin, and ofloxacin in Mycobacterium leprae. *Lancet* 1997; **349:** 103–4.

Pharmacokinetics

Dapsone is almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 2 to 8 hours after a dose. Steady-state concentrations are not attained until after at least 8 days of daily dosage; doses of 100 mg daily provide trough concentrations of 500 nanograms/mL, which are well in excess of the MIC for *M. leprae*. About 70 to 90% of dapsone in the circulation is bound to plasma proteins and nearly 100% of its monoacetylated metabolite is bound.

Dapsone undergoes enterohepatic recycling. It is widely distributed; it is present in saliva and breast milk and crosses the placenta. The half-life ranges from 10 to 50 hours; with a mean of 20 to 30 hours.

Dapsone is acetylated to monoacetyldapsone, the major metabolite, and other mono and diacetyl derivatives. Acetylation exhibits genetic polymorphism. Hydroxylation is the other major metabolic pathway resulting in hydroxylamine dapsone, which may be responsible for dapsone-associated methaemoglobinaemia and haemolysis.

Dapsone is mainly excreted in the urine, only 20% of a dose as unchanged drug.

◊ References.

1. Zuidema J, *et al.* Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet* 1986; **11:** 299–315.
2. May DG, *et al.* The disposition of dapsone in cirrhosis. *Clin Pharmacol Ther* 1992; **51:** 689–700.
3. Mirochnick M, *et al.* Pharmacokinetics of dapsone in children. *J Pediatr* 1993; **122:** 806–9.
4. Opravil M, *et al.* Levels of dapsone and pyrimethamine in serum during once-weekly dosing for prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Antimicrob Agents Chemother* 1994; **38:** 1197–9.
5. Gatti G, *et al.* Penetration of dapsone into cerebrospinal fluid of patients with AIDS. *J Antimicrob Chemother* 1997; **40:** 113–15.
6. Mirochnick M, *et al.* Pharmacokinetics of dapsone administered daily and weekly in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1999; **43:** 2586–91.
7. Mirochnick M, *et al.* Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2001; **70:** 24–32.
8. Thiboutot DM, *et al.* Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet* 2007; **46:** 697–712.

Metabolism. Measurement of the relative activity of the two main routes of dapsone metabolism (acetylation and hydroxylation) suggests that the risk of adverse effects is greater in individuals in whom the *N*-hydroxylation route predominates.[1] This is consistent with the hypothesis that the toxicity of dapsone is related to production of an active metabolite. See also Effects on the Blood, above.

1. Bluhm RE, *et al.* Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. *Clin Pharmacol Ther* 1999; **65:** 598–605.

Uses and Administration

Dapsone is used as part of multidrug regimens in the treatment of all forms of leprosy (p.176). It has also been used in the prophylaxis of leprosy and in the management of household contacts of leprosy patients. Dapsone is used as an alternative to co-trimoxazole or pentamidine for the treatment and prophylaxis of pneumocystis pneumonia (below), and has been used with pyrimethamine for the prophylaxis of malaria (see under Pyrimethamine, p.611). It is also used in dermatitis herpetiformis and other dermatoses (see Skin Disorders, below). It has been tried for the prophylaxis of toxoplasmosis (p.826) and for the treatment of cutaneous leishmaniasis (p.824) and actinomycetoma (see Mycetoma, p.180).

Dapsone is usually given orally. There are some reports of it being given by intramuscular injection, but such injections can be painful and cause abscess formation.

The most common regimens for **leprosy** are those recommended by WHO. For multibacillary leprosy, rifampicin 600 mg and clofazimine 300 mg are both given *once a month* with dapsone 100 mg and clofazimine 50 mg both *daily* for 12 months. Adults weighing less than 35 kg receive reduced doses of rifampicin and dapsone, and in such patients the dapsone dose is 50 mg or 1 to 2 mg/kg daily.

The WHO regimen for paucibacillary leprosy consists of rifampicin 600 mg once a month and dapsone 100 mg daily; both are given for 6 months. Doses are reduced in low-weight patients as for multibacillary leprosy.

The doses of dapsone used for the prophylaxis and treatment of **pneumocystis pneumonia** are discussed in more detail under pneumocystis pneumonia, below.

The dose needed to treat **dermatitis herpetiformis** has to be titrated for individual patients, but it is usual to start with an oral dose of 50 mg daily, gradually increased to 300 mg daily or more if required. This dose should be reduced to a minimum as soon as possible. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

In the treatment of **acne**, dapsone is applied topically as a 5% gel twice daily.

For details of doses in infants, children, and adolescents, see below.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral dapsone 50 mg plus rifampicin 450 mg and clofazimine 150 mg *once a month*, together with dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*; both are given for 12 months. For paucibacillary leprosy WHO recommends oral dapsone 50 mg plus rifampicin 450 mg *once a month*, together with dapsone 50 mg *daily*; both are given for 6 months. For children less than 10 years of age the dose should be adjusted according to body weight.

For details of doses for the treatment of pneumocystis pneumonia in infants, children, and adolescents, see below.

Connective tissue disorders. Relapsing polychondritis (p.1510) has responded to dapsone, as has Behçet's syndrome (p.1499) and SLE. Vasculitic syndromes such as hypersensitivity vasculitis (p.1505) have also improved following dapsone.

Idiopathic thrombocytopenic purpura. Dapsone has been reported[1-4] to be of benefit in some patients, including children, with refractory idiopathic thrombocytopenic purpura (p.1505).

1. Radaelli F, *et al.* Adult refractory chronic idiopathic thrombocytopenic purpura: can dapsone be proposed as second-line therapy? *Br J Haematol* 1999; **104:** 641–2.
2. Dutta TK, *et al.* Dapsone in treatment of chronic idiopathic thrombocytopenic purpura in adults. *J Assoc Physicians India* 2001; **49:** 421–5.
3. Meeker ND, *et al.* Dapsone therapy for children with immune thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003; **25:** 173–5.
4. Damodar S, *et al.* Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults—a report on 90 patients. *Eur J Haematol* 2005; **75:** 328–31.

Pneumocystis pneumonia. Dapsone is used alone or with pyrimethamine[1] for *primary and secondary prophylaxis* of pneumocystis pneumonia (p.521) in patients unable to tolerate co-trimoxazole. In adults a dose of dapsone 100 mg daily in one or two doses is commonly used and has been reported to have similar efficacy to co-trimoxazole.[2] Dapsone has also been given with pyrimethamine in various regimens including:

- dapsone 50 mg daily with pyrimethamine 50 mg once weekly[3]
- dapsone 100 mg plus pyrimethamine 50 mg both given twice weekly[4]
- dapsone 200 mg plus pyrimethamine 75 mg both given once weekly[5]

In children from 1 month to 18 years of age the recommended dose of dapsone is 2 mg/kg daily (to a maximum of 100 mg daily) or 4 mg/kg weekly (to a maximum of 200 mg weekly).[1]

For *treatment* of adults and adolescents, dapsone 100 mg once daily with trimethoprim 5 mg/kg three times daily, for 21 days, has been suggested for mild to moderate disease in patients unable to tolerate co-trimoxazole.[6] Infants and children under 13 years of age may be given a dose of dapsone of 2 mg/kg once daily (to a maximum of 100 mg daily) plus trimethoprim 5 mg/kg three times daily.[7]

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5108.pdf (accessed 03/10/07)
2. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
3. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
4. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
5. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20:** 531–41.
6. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 03/10/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5412.pdf (accessed 05/10/07)
7. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 03/10/07)

Skin disorders. Dapsone is used for the suppression of skin lesions in dermatitis herpetiformis (p.1578). The mechanism of action is unknown but is unrelated to its antimicrobial activity. Reports, generally involving small numbers of patients, suggest that dapsone may also be beneficial for bullous or mucous membrane pemphigoid (p.1582), pyoderma gangrenosum (p.1583), recurrent erythema multiforme (p.1580), and urticaria (p.1584). Topical dapsone is available in the USA for the treatment of acne.

Spider bites. As discussed on p.2239, necrotic araneism resulting from the bite of spiders of the genus *Loxosceles* is usually treated conservatively with surgical repair of any persistent defect. A prospective clinical study[1] of 31 patients with brown recluse spider bites indicated that treatment with dapsone 100 mg daily for 14 days followed by delayed surgical intervention if necessary reduced the incidence of wound complications and residual scarring compared with treatment by immediate surgical excision. A dose of 100 mg twice daily has also been given for 14 days.[2] An evaluation[3] of the management of brown recluse spider bites found that common treatments did not reduce healing time or scarring; dapsone was associated with slower healing rate and an increased risk of scarring.

1. Rees RS, *et al.* Brown recluse spider bites: a comparison of early surgical excision versus dapsone and delayed surgical excision. *Ann Surg* 1985; **202:** 659–63.
2. King LE, Rees RS. Dapsone treatment of a brown recluse bite. *JAMA* 1983; **250:** 648.
3. Mold JW, Thompson DM. Management of brown recluse spider bites in primary care. *J Am Board Fam Pract* 2004; **17:** 347–52.

Preparations

BP 2008: Dapsone Tablets;
USP 31: Dapsone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Daps; ***Canad.:*** Aczone; ***Israel:*** Avlosulfon†; ***Mex.:*** Dapsoderm-X; Novasulfon†; ***Philipp.:*** Lepravir; ***Port.:*** Sulfona; ***Spain:*** Sulfona; ***Thai.:*** Dopsan; Servidapsone†; ***USA:*** Aczone.

Multi-ingredient: ***Austral.:*** Maloprim; ***Austria:*** Isoprodian; ***Fr.:*** Disulone; ***Ger.:*** Isoprodian†; ***Irl.:*** Maloprim†; ***S.Afr.:*** Maloprim†; ***Singapore:*** Pyrisone.

Daptomycin *(BAN, USAN, rINN)*

Daptomicina; Daptomycine; Daptomycinum; LY-146032. *N*-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine 1.13-3.4-lactone.

Даптомицин

$C_{72}H_{101}N_{17}O_{26}$ = 1620.7.
CAS — 103060-53-3.
ATC — J01XX09.
ATC Vet — QJ01XX09.

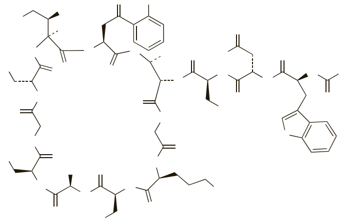

Adverse Effects and Precautions

The most common adverse effects associated with daptomycin are gastrointestinal effects including nausea and vomiting, constipation, diarrhoea, and dyspepsia. Headache, insomnia, dizziness, and fever may occur. Injection site reactions have occurred. Effects on the skin have included rash and pruritus. Abnormal liver function tests and jaundice have been reported. Other reported adverse effects include hypertension or hypotension, renal failure, dyspnoea, and anaemia. There have been rare cases of hypersensitivity, anaphylaxis, and infusion reactions.

Elevated plasma creatine phosphokinase (CPK) concentrations during daptomycin therapy may be associated with muscle pain and/or weakness, myositis, myopathy, and rarely rhabdomyolysis; patients with renal impairment or taking other drugs known to cause myopathy (see Interactions, below) may be at increased risk. All patients should be monitored for the development of muscle pain or weakness, and plasma CPK concentrations measured once weekly. More frequent measurements should be performed in those with an increased risk of myopathy, or with a baseline CPK concentration greater than 5 times the upper limit of normal (ULN), or who develop signs of myopathy. Daptomycin should be stopped in patients with signs of myopathy and CPK concentrations greater than 5 times the ULN, or in those without reported signs of myopathy but with CPK concentrations greater than 10 times the ULN.

Daptomycin should be given with caution and in reduced dosage to patients with renal impairment; clinical response and renal function should be monitored closely.

Consideration should be given to stopping daptomycin therapy in patients who develop signs or symptoms of peripheral neuropathy.

Effects on the lungs. Bronchiolitis obliterans organising pneumonia with eosinophilic infiltration has been reported in an 84-year-old man after 4 weeks of daptomycin therapy;[1] clinical improvement occurred after the drug was stopped. The mechanism of toxicity was unknown and the authors suggested that it might be associated with epithelial injury caused by daptomycin accumulating in the alveolar spaces.

A 60-year-old man receiving daptomycin developed eosinophilic pneumonia resulting in respiratory failure that required mechanical ventilation;[2] he improved after stopping the drug and starting corticosteroid therapy.

1. Cobb E, *et al.* Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother* 2007; **41:** 696–701.
2. Hayes D, *et al.* Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007; **54:** e211–e213.

Pregnancy. Intravenous daptomycin, 4 mg/kg daily for 14 days, was successfully used to treat pyelonephritis associated with vancomycin-resistant enterococci (VRE) in a 27-week pregnant woman; no neonatal abnormalities were reported.[1]

1. Shea K, *et al.* Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. *Ann Pharmacother* 2008; **42:** 722–5.

Interactions

There may be an increased risk of myopathy if daptomycin is given with other drugs also known to have this adverse effect, such as statins, fibrates, and ciclosporin. Licensed product information recommends stopping the latter if possible; otherwise, plasma creatine phosphokinase concentrations should be measured more than once weekly in addition to the usual precautions (see Adverse Effects and Precautions, above).

Daptomycin is mainly excreted by renal filtration and caution is advised if given with drugs that reduce renal filtration, such as NSAIDs and selective inhibitors of cyclo-oxygenase-2, since plasma concentrations of daptomycin may be increased.

Daptomycin has been reported to interact with a particular reagent used in some assays of PT-INR resulting in apparent prolongation of PT and elevation of INR.

Antimicrobial Action

Daptomycin is a lipopeptide antibacterial that is reported to have a spectrum of antibacterial activity similar to that of vancomycin (p.359) and greater potency against most Gram-positive bacterial strains *in vitro*; it is inactive against Gram-negative bacteria. Daptomycin disrupts the bacterial cell membrane potential by binding to the cell membranes in a calcium-dependent process, but without entering the cytoplasm, thus inhibiting the synthesis of protein, DNA, and RNA.

Daptomycin has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci.

It is reported to show antimicrobial synergy *in vitro* with aminoglycosides, beta lactams, and rifampicin against *Staph. aureus* (including meticillin-resistant strains) and enterococci (including vancomycin-resistant strains).

Resistance to daptomycin has been shown in clinical studies but only rarely; the mechanism of resistance has not been identified.

◊ Reviews.

1. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. *Clin Infect Dis* 2007; **45:** 601–8.

Pharmacokinetics

Daptomycin is not absorbed to any significant extent after oral doses. The pharmacokinetics of daptomycin are generally linear at intravenous doses ranging from 4 to 12 mg/kg once daily. Peak plasma concentrations are achieved within 0.5 to 0.8 hours. It is distributed mainly into the extracellular space with a volume of distribution of about 0.1 litres/kg. Daptomycin crosses the blood-brain barrier and the placenta. It is about 90% bound to plasma proteins, mainly serum albumin.

In-vitro studies indicate that daptomycin is not metabolised by, and does not affect, the cytochrome P450 isoenzyme system. Little or no metabolism is thought to take place although 4 minor metabolites have been detected in the urine.

Daptomycin is excreted mainly via renal filtration with about 78% and 6% of a dose recovered in the urine and faeces, respectively. It has an elimination half-life of about 8 hours after an intravenous dose of 4 mg/kg once daily for 7 days and is prolonged in patients with renal impairment; a two- to threefold increase has been reported in those with severe impairment or end-stage renal disease.

Daptomycin is removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Dvorchik B, *et al.* Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2004; **48:** 2799–2807.

Uses and Administration

Daptomycin is given by intravenous infusion over 30 minutes for the treatment of complicated Gram-positive infections of the skin and soft tissues, and *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, caused by meticillin-susceptible and meticillin-resistant strains.

For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

For the treatment of skin and soft-tissue infections, daptomycin is given in a dose of 4 mg/kg once daily for 7 to 14 days. A higher dose of 6 mg/kg once daily is given for 2 to 6 weeks in the treatment of bacteraemia.

For details of dosage modification in patients with renal impairment, see below.

Daptomycin has also been investigated for the treatment of vancomycin-resistant enterococcal infections, complicated urinary-tract infections, and community-acquired pneumonia.

◊ References.

1. Fenton C, *et al.* Daptomycin. *Drugs* 2004; **64:** 445–55.
2. Steenbergen JN, *et al.* Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; **55:** 283–8.
3. Schriever CA, *et al.* Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am J Health-Syst Pharm* 2005; **62:** 1145–58.
4. French GL. Bactericidal agents in the treatment of MRSA infections—the potential role of daptomycin. *J Antimicrob Chemother* 2006; **58:** 1107–17.
5. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 2007; **67:** 1483–1512.
6. Enoch DA, *et al.* Daptomycin. *J Infect* 2007; **55:** 205–13.
7. Weis F, *et al.* Daptomycin, a lipopeptide antibiotic in clinical practice. *Curr Opin Investig Drugs* 2008; **9:** 879–84.
8. Forrest GN, *et al.* Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother* 2008; **42:** 213–17.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, including those receiving dialysis, the intravenous dosage of daptomycin should be modified to 4 mg/kg once every 48 hours in the treatment of skin and soft-tissue infections, and to 6 mg/kg once every 48 hours in the treatment of bacteraemia.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Cubicin; ***Gr.:*** Cubicin; ***Israel:*** Cubicin; ***Port.:*** Cubicin; ***UK:*** Cubicin; ***USA:*** Cubicin.

Demeclocycline *(BAN, rINN)*

Demeclociclina; Déméclocycline; Demeclocyclinum; Demeklocyklin; Demeklosykliini; Demethylchlortetracycline. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyltetracycline.

Демеклоциклин

$C_{21}H_{21}ClN_2O_8$ = 464.9.
CAS — 127-33-3 (demeclocycline); 13215-10-6 (demeclocycline sesquihydrate).
ATC — D06AA01; J01AA01.
ATC Vet — QD06AA01; QJ01AA01.

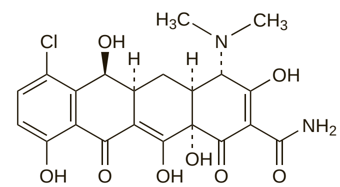

Pharmacopoeias. In *US.*
USP 31 (Demeclocycline). A yellow, odourless crystalline powder. Sparingly soluble in water; soluble 1 in 200 of alcohol and 1 in 40 of methyl alcohol; dissolves readily in 3N hydrochloric acid and in alkaline solutions. pH of a 1% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Demeclocycline Hydrochloride *(BANM, rINNM)*

Déméclocycline, chlorhydrate de; Demeclocyclini hydrochloridum; Demeklociklin-hidroklorid; Demeklociklino hidrochloridas; Demeklocyklin-hydrochlorid; Demeklocyklinhydroklorid; Demeklocykliny chlorowodorek; Demeklosiklin Hidroklorür; Demeklosykliinihydrokloridi; Demethylchlortetracycline Hydrochloride; Hidrocloruro de demeclociclina.

Демеклоциклина Гидрохлорид

$C_{21}H_{21}ClN_2O_8,HCl$ = 501.3.
CAS — 64-73-3.
ATC — D06AA01; J01AA01.
ATC Vet — QD06AA01; QJ01AA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Demeclocycline Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Soluble or sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.
USP 31 (Demeclocycline Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 60 of water and 1 in 50 of methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone and in chloroform; sparingly soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Phototoxic reactions occur more frequently with demeclocycline than with other tetracyclines and patients should avoid direct exposure to sunlight or artificial ultraviolet light.

Reversible nephrogenic diabetes insipidus with polyuria, polydipsia, and weakness may occur in patients treated with demeclocycline, particularly with prolonged treatment and/or high doses. Plasma creatinine should be monitored in patients receiving demeclocycline for long periods for the treatment of inappropriate secretion of antidiuretic hormone, since tetracycline-induced renal impairment may not otherwise be apparent in the absence of oliguria. For a comment that the usefulness of demeclocycline for this indication may be limited by nephrotoxicity in patients with cardiac or hepatic disease, see Syndrome of Inappropriate ADH Secretion under Uses and Administration, below.

Interactions
As for Tetracycline, p.348.

Antimicrobial Action
As for Tetracycline, p.348.

Demeclocycline is stated to be somewhat more active against certain strains of some organisms including *Neisseria gonorrhoeae* and *Haemophilus influenzae*, as well as to being the most active of the tetracyclines *in vitro* against *Brucella* spp.

Pharmacokinetics
For the general pharmacokinetics of the tetracyclines, see Tetracycline, p.349.

About 60 to 80% of a dose of demeclocycline is absorbed from the gastrointestinal tract. Peak plasma concentrations of about 1.5 to 1.7 micrograms/mL have been reported 3 to 4 hours after a single oral dose of 300 mg, but higher plasma concentrations may be achieved with repeated dosage. Its plasma elimination half-life is about 12 hours, although this may be prolonged in patients with renal impairment; values of 42 to 68 hours have been reported in severe impairment. The renal clearance of demeclocycline is about half that of tetracycline.

Uses and Administration
Demeclocycline is a tetracycline derivative with uses similar to those of tetracycline (p.349). It is excreted more slowly and effective blood concentrations are maintained for a longer period.

Demeclocycline is given orally as the hydrochloride; the usual adult dose is 600 mg daily in 2 or 4 divided doses, preferably 1 hour before or 2 hours after meals. For atypical pneumonia, 900 mg daily in 3 divided doses may be given. It is also sometimes given orally with other tetracycline derivatives.

For details of doses in children and adolescents, see below.

Demeclocycline may also be given to adults in the treatment of chronic hyponatraemia associated with the syndrome of inappropriate antidiuretic hormone secretion, when water restriction has proved ineffective. Initially 900 to 1200 mg is given daily in divided doses, reducing to maintenance doses of 600 to 900 mg daily.

For dosage recommendations in patients with hepatic impairment, see below.

The calcium and magnesium salts of demeclocycline have also been used.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential; demeclocycline may be used for the treatment of susceptible infections. In the UK, it is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual doses of 7 to 13 mg/kg daily by mouth in 2 or 4 divided doses.

Administration in hepatic impairment. UK licensed product information states that the dosage of demeclocycline should not exceed 1 g daily in patients with known liver disease.

Syndrome of inappropriate ADH secretion. Demeclocycline may be given in the treatment of the syndrome of inappropriate ADH (antidiuretic hormone) secretion (SIADH—p.2182) to antagonise the effect of ADH on the renal tubules; lithium has been given as an alternative. Both lithium and demeclocycline act by interfering with the cellular action of ADH to produce nephrogenic diabetes insipidus. Demeclocycline was reported to be superior to lithium[1] and became the preferred treatment for chronic SIADH if water restriction was unsuccessful,[2] although fluid restriction is probably still the treatment of choice. However, since nephrotoxicity has been reported in patients with cardiac or hepatic disease, the usefulness of demeclocycline in the treatment of hyponatraemic states might be limited; this view was supported by studies in patients with heart failure[3] and cirrhosis.[4]

1. Forrest JN, *et al.* Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; **298:** 173–7.
2. Schrier RW. Treatment of hyponatremia. *N Engl J Med* 1985; **312:** 1121–2.
3. Zegers de Beyl D, *et al.* Demeclocycline treatment of water retention in congestive heart failure. *BMJ* 1978; **1:** 760.
4. Miller PD, *et al.* Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA* 1980; **243:** 2513–15.

Preparations
BP 2008: Demeclocycline Capsules;
USP 31: Demeclocycline Hydrochloride Capsules; Demeclocycline Hydrochloride Tablets; Demeclocycline Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Ledermycin†; ***Canad.:*** Declomycin; ***Fr.:*** Ledermycine; ***India:*** Ledermycin; ***Neth.:*** Ledermycin; ***UK:*** Ledermycin; ***USA:*** Declomycin.

Multi-ingredient: ***Austria:*** Ledermix; ***Denm.:*** Ledermix†; ***Ger.:*** Ledermix; ***Israel:*** Ledermix; ***Ital.:*** Rubrociclina†; ***S.Afr.:*** Tritet; ***Switz.:*** Ledermix; ***UK:*** Deteclo†; Ledermix.

Dibekacin Sulfate *(rINNM)*

Dibekacin Sulphate *(BANM)*; Dibékacine, Sulfate de; Dibekacini Sulfas; 3′,4′-Dideoxykanamycin B; Sulfato de dibekacina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-streptamine sulphate.

Дибекацина Сульфат

$C_{18}H_{37}N_5O_8,xH_2SO_4$.

CAS — 34493-98-6 (dibekacin); 58580-55-5 (dibekacin sulfate).

ATC — J01GB09.

ATC Vet — QJ01GB09.

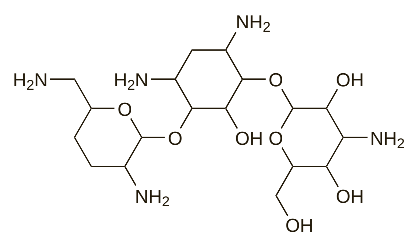

(dibekacin)

Pharmacopoeias. In *Jpn.*

Profile
Dibekacin is an aminoglycoside derived from kanamycin with actions and uses similar to those of gentamicin (p.282). It has been given intramuscularly as the sulfate in doses equivalent to dibekacin 1 to 3 mg/kg daily in divided doses. It has also been given in similar doses by slow intravenous infusion. Dosage should be adjusted based on serum-dibekacin concentration monitoring. It has also been used topically for eye infections.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Dikacine†; ***Jpn:*** Panimycin; ***Venez.:*** Dibekan.

Dicloxacillin *(BAN, USAN, rINN)*

BRL-1702; Dicloxacilina; Dicloxacilline; Dicloxacillinum; Diklok-sasilliini; Dikloxacillin; R-13423. (6*R*)-6-[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

Диклоксациллин

$C_{19}H_{17}Cl_2N_3O_5S$ = 470.3.

CAS — 3116-76-5.

ATC — J01CF01.

ATC Vet — QJ01CF01; QJ51CF01.

Dicloxacillin Sodium *(BANM, USAN, rINNM)*

Dicloxacilina sódica; Dicloxacilline sodique; Dicloxacillinum natricum; Dicloxacillinum Natricum Monohydricum; Dikloksacilino natrio druska; Dikloksasilliininatrium; Dikloxacilin sodná sůl monohydrát; Dikloxacillinnatrium; Dikloxacillin-nátrium; Natrii Dicloxacillinum; P-1011. Sodium dicloxacillin monohydrate.

Натрий Диклоксациллин

$C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$ = 510.3.

CAS — 343-55-5 (anhydrous dicloxacillin sodium); 13412-64-1 (dicloxacillin sodium monohydrate).

ATC — J01CF01.

ATC Vet — QJ01CF01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Dicloxacillin Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.

USP 31 (Dicloxacillin Sodium). A white to off-white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers.

Adverse Effects and Precautions
As for Flucloxacillin, p.277.

Effects on the liver. References.

1. Kleinman MS, Presberg JE. Cholestatic hepatitis after dicloxacillin-sodium therapy. *J Clin Gastroenterol* 1986; **8**: 77–8.

Sodium content. Each g of dicloxacillin sodium contains about 2 mmol of sodium.

Interactions
As for Benzylpenicillin, p.214.

Antimicrobial Action
As for Flucloxacillin, p.277.

Pharmacokinetics
Dicloxacillin is better absorbed from the gastrointestinal tract than cloxacillin but absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, peak plasma concentrations of 10 to 18 micrograms/mL in about 1 hour have been reported in fasting subjects. Doubling the dose can double the plasma concentration. About 97% of dicloxacillin in the circulation is bound to plasma proteins. Dicloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

The distribution of dicloxacillin in body tissues and fluids is similar to that of cloxacillin (p.256).

Dicloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 60% of an oral dose is excreted in the urine. Only small amounts are excreted in the bile. Dicloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations have been reported in patients with cystic fibrosis.

Uses and Administration
Dicloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Dicloxacillin is given intravenously and orally as the sodium salt. All doses are expressed in terms of the equivalent amount of dicloxacillin; 1.09 g of dicloxacillin sodium is equivalent to about 1 g of dicloxacillin. Oral doses should be taken at least 1 hour before, or 2 hours after, meals since the presence of food in the stomach reduces absorption. The usual adult oral dose is 250 mg every 6 hours. Similar doses may be given by slow intravenous injection or, preferably, by intravenous infusion. Doses may be doubled in severe infections.

Preparations
USP 31: Dicloxacillin Sodium Capsules; Dicloxacillin Sodium for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Diclocil; Dicloxsig; Distaph; ***Denm.:*** Dicillin; Diclocil; ***Fin.:*** Diclocil; ***Ger.:*** InfectoStaph; ***Gr.:*** Diclocil; ***Mex.:*** Amifarin; Antiben; Brispen; Butimaxil; Cilpen; Clobioxal; Dicleophen; Diclo-Tecno; Dicloxaquim; Diluxina; Dipxapen†; Ditterolina; Dixen; Doxil; Pardix; Penclox; Posipen; ***Norw.:*** Diclocil; ***NZ:*** Diclocil; ***Port.:*** Diclocil; ***Swed.:*** Diclocil; ***Thai.:*** Amcidil; Cloxydin; Diclex; Diclocil; Diclocillin; Dicloson; Diclox†; Dicloxia; Dicloxin; Dicloxman†; Dicloxno; Diloxin; Ditum†; Dixocillin; Dorox; Servidiclox†; ***Venez.:*** Diclocil; Diclolak†.

Multi-ingredient: ***Ital.:*** Ampiplus†; Diamplicil†; ***Mex.:*** Ampiclox-D; Anglotex; Brucilina; Diamprex; Doxapen; Panac; Panac K; Pentidix.

Difloxacin Hydrochloride *(USAN, rINNM)*

A-56619; Abbott-56619; Difloxacine, chlorhydrate de; Difloxacini hydrochloridum; Hidrocloruro de difloxacino. 6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride.

Дифлоксацина Гидрохлорид

$C_{21}H_{19}F_2N_3O_3$,HCl = 435.9.

CAS — 98106-17-3 (difloxacin); 91296-86-5 (difloxacin hydrochloride).

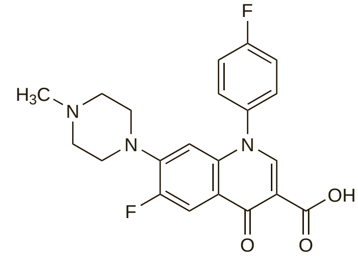

(difloxacin)

Profile

Difloxacin is a fluoroquinolone antibacterial used as the hydrochloride in veterinary medicine for the treatment of susceptible infections in poultry. It was formerly used in humans but was associated with an unacceptable incidence of adverse CNS effects.

Dihydrostreptomycin Sulfate *(rINNM)*

Dihidrosztreptomicin-szulfát; Dihydrostreptomycin sulfát; Dihydrostreptomycin Sulphate *(BANM)*; Dihydrostreptomycine, sulfate de; Dihydrostreptomycini sulfas; Dihydrostreptomycinsulfat; Dihydrostreptomysiinisulfaatti; Sulfato de dihidroestreptomicina. *O*-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-hydroxymethyl-α-L-lyxofuranosyl-(1→4)-N^1,N^3-diamidino-D-streptamine sulphate.

Дигидрострептомицина Сульфат

$(C_{21}H_{41}N_7O_{12})_2,3H_2SO_4$ = 1461.4.

CAS — 128-46-1 (dihydrostreptomycin); 5490-27-7 (dihydrostreptomycin sulfate).

ATC — S01AA15.

ATC Vet — QS01AA15.

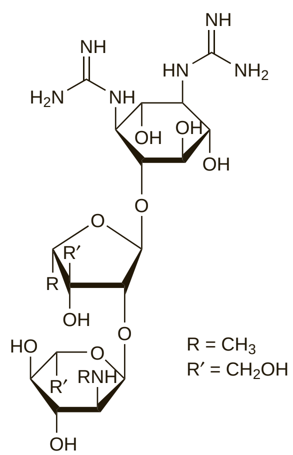

(dihydrostreptomycin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US*, both for veterinary use only.

Ph. Eur. 6.2 (Dihydrostreptomycin Sulphate for Veterinary Use; Dihydrostreptomycin Sulphate BP(Vet) 2008). The sulfate of a substance obtained by catalytic hydrogenation of streptomycin or by any other means. The semi-synthetic product is derived from a fermentation product. Stabilisers may be added. A white or almost white, hygroscopic powder. It contains a maximum of 2.0% streptomycin sulfate calculated with reference to the dried drug. Freely soluble in water; practically insoluble in alcohol, in acetone, and in methyl alcohol. A 25% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 31 (Dihydrostreptomycin Sulfate). A white or almost white amorphous or crystalline powder; the amorphous form is hygroscopic. Freely soluble in water; practically insoluble in acetone, in chloroform, and in methyl alcohol. pH of a solution in water containing the equivalent of dihydrostreptomycin 20% is between 4.5 and 7.0, except that if it is labelled as being solely for oral use, the pH is between 3.0 and 7.0. Store in airtight containers.

Profile

Dihydrostreptomycin is an aminoglycoside antibacterial with actions similar to those of streptomycin (p.333). Since it is more likely than streptomycin to cause partial or complete loss of hearing it is not used parenterally in humans. It is not absorbed after oral doses, and has been given by this route for gastrointestinal infections. It is also used as the sulfate in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Citrocil.

Multi-ingredient: ***Arg.:*** Gemipasmol†; Vagisan; Vagisan Compuesto; ***Mex.:*** Estrefen; ***Spain:*** Cilinafosal Dihidroestreptomicina; Estreptoenterol†; Salitanol Estreptomicina; Sulfintestin Neomicina.

Dirithromycin *(BAN, USAN, rINN)*

ASE-136BS; Dirithromycine; Dirithromycinum; Diritromicin; Diritromicina; Diritromicinas; Diritromisin; Diritromycin; Diritromysiini; LY-237216. (1*R*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-7-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-3-ethyl-2,10-dihydroxy-15-(2-methoxyethoxymethyl)-2,6,8,10,12,17-hexamethyl-9-(3,4,6-trideoxy-3-dimethylamino-β-L-*xylo*-hexopyranosyloxy)-4,16-dioxa-14-azabicyclo[11.3.1]heptadecan-5-one; (9*S*)-9-Deoxo-11-deoxy-9,11-{imino[(1*R*)-2-(2-methoxyethoxy)-ethylidene]oxy}erythromycin.

Диритромицин

$C_{42}H_{78}N_2O_{14}$ = 835.1.

CAS — 62013-04-1.

ATC — J01FA13.

ATC Vet — QJ01FA13.

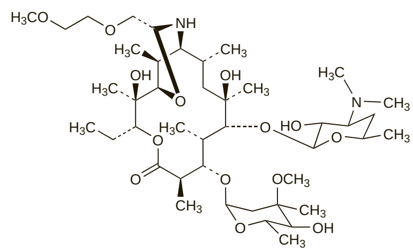

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Dirithromycin). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

USP 31 (Dirithromycin). A white or practically white powder. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

Adverse Effects and Precautions

As for Erythromycin, p.270.

The most frequent adverse effects of dirithromycin are gastrointestinal disturbances; headache has also occurred. Dirithromycin should be used with caution in patients with moderate to severe hepatic impairment since its active metabolite erythromycylamine is primarily eliminated in the bile. It should also be used with caution in those with severe renal impairment.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Dirithromycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The lack of interactions between dirithromycin and theophylline, terfenadine, or warfarin would appear to support this.

Antimicrobial Action

As for Erythromycin, p.271.

Dirithromycin is reported to be generally less active than erythromycin *in vitro*, but may show greater activity *in vivo* than is indicated by *in-vitro* studies and may exert a postantibiotic effect.

Pharmacokinetics

Dirithromycin is readily absorbed after oral doses and undergoes rapid non-enzymatic hydrolysis to its active metabolite erythromycylamine. Absorption is enhanced by food. Bioavailability is about 10%. Daily doses of dirithromycin 500 mg produce peak plasma concentrations of erythromycylamine of about 400 nanograms/mL.

Erythromycylamine is widely distributed and tissue concentrations exceed those in plasma. Protein binding is 15 to 30%. Erythromycylamine is mainly excreted unchanged in the bile with only about 2% in the urine. The mean plasma half-life is about 8 hours and the mean urinary terminal elimination half-life is about 44 hours.

Distribution into milk has been found in studies in *rodents*.

◊ References.

1. Sides GD, *et al.* Pharmacokinetics of dirithromycin. *J Antimicrob Chemother* 1993; **31** (suppl C): 65–75.
2. LaBreque D, *et al.* Pharmacokinetics of dirithromycin in patients with impaired hepatic function. *J Antimicrob Chemother* 1993; **32:** 741–50.
3. Mazzei T, *et al.* Pharmacokinetics of dirithromycin in patients with mild or moderate cirrhosis. *Antimicrob Agents Chemother* 1999; **43:** 1556–9.

Uses and Administration

Dirithromycin is a prodrug of the macrolide antibacterial erythromycylamine, which has similar properties to those of erythromycin (p.269) and is used in respiratory-tract, skin, and soft-tissue infections caused by susceptible organisms.

Dirithromycin is given orally as enteric-coated tablets in a usual dose of 500 mg once daily.

◊ References.

1. Various. Dirithromycin: a new once-daily macrolide. *J Antimicrob Chemother* 1993; **31** (suppl C): 1–185.
2. Brogden RN, Peters DH. Dirithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **48:** 599–616.
3. Wintermeyer SM, *et al.* Dirithromycin: a new macrolide. *Ann Pharmacother* 1996; **30:** 1141–9.
4. McConnell SA, Amsden GW. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. *Pharmacotherapy* 1999; **19:** 404–15.

Preparations

USP 31: Dirithromycin Delayed-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Unibac†; ***Chile:*** Dynabac†; ***Fr.:*** Dynabac; ***Gr.:*** Dynabac†; ***Malaysia:*** Dynabac†; ***Turk.:*** Dynabac; ***USA:*** Dynabac†.

Doripenem *(USAN, rINN)*

Doripénem; Doripenemum; S-4661. (+)-(4*R*5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Дорипенем

$C_{15}H_{24}N_4O_6S_2$ = 420.5.

CAS — 148016-81-3.

Adverse Effects and Precautions

As for Imipenem, p.286.

Doripenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the enzyme, is not required.

Interactions

Probenecid inhibits the renal excretion of doripenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to carbapenem antibacterials, see p.510.

Antimicrobial Action

As for Imipenem, p.287,

Doripenem is claimed to have particular activity against *Pseudomonas aeruginosa*.

Pharmacokinetics

After intravenous infusion of doripenem 500 mg over 1 hour, a mean peak plasma concentration of 23 micrograms/mL is attained, falling to 10 micrograms/mL after 1.5 hours and 1 microgram/mL after 6 hours.

Doripenem is less than 10% bound to plasma proteins and is widely distributed into body tissues and fluids. It is metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite (doripenem-M1). The plasma elimination half-life is about 1 hour in adults; the half-life may be prolonged in patients with renal impairment. Doripenem is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% and 15% of a dose is recovered as unchanged drug and metabolite, respectively, in the urine within 48 hours. Less than 1% is excreted in faeces.

Doripenem is removed by haemodialysis.

Uses and Administration

Doripenem is a carbapenem antibacterial similar to imipenem (p.286). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections such as intra-abdominal infections and complicated urinary-tract infections, including pyelonephritis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

For treatment of susceptible infections doripenem is given by intravenous infusion over 1 hour, in a usual adult dose of 500 mg every 8 hours. For details of reduced doses in renal impairment, see below.

◊ References.

1. Lister PD. Carbapenems in the USA: focus on doripenem. *Expert Rev Anti Infect Ther* 2007; **5:** 793–809.
2. Poulakou G, Giamarellou H. Doripenem: an expected arrival in the treatment of infections caused by multidrug-resistant Gram-negative pathogens. *Expert Opin Invest Drugs* 2008; **17:** 749–71.
3. Chastre J, *et al.* Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008; **36:** 1089–96.
4. Lucasti C, *et al.* Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther* 2008; **30:** 868–83.

Administration in renal impairment. Doses of doripenem given by intravenous infusion should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 50 mL/minute: 250 mg every 8 hours
- CC greater than 10 to less than 30 mL/minute: 250 mg every 12 hours

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Finibax; ***USA:*** Doribax.

Doxycycline *(BAN, USAN, rINN)*

Doksiciklinas monohidratas; Doksisiklin; Doksisykliini; Doksisykliinimonohydraatti; Doksycyklina; Doxiciclina; Doxiciklin; Doxycyclin; Doxycycline Monohydrate; Doxycycline monohydratée; Doxycyclinum; Doxycyclinum monohydricum; Doxycyklin monohydrát; Doxycyklinmonohydrat; GS-3065. (4S,4aR,5S,5aR,6S,12aS)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrate; 6-Deoxy-5β-hydroxytetracycline monohydrate.

Доксициклин

$C_{22}H_{24}N_2O_8,H_2O$ = 462.4.

CAS — 564-25-0 (anhydrous doxycycline); 17086-28-1 (doxycycline monohydrate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

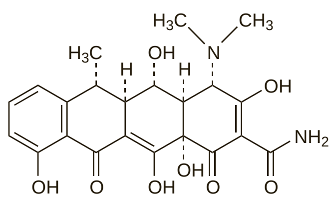

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Doxycycline Monohydrate). A yellow crystalline powder. Very slightly soluble in water and in alcohol. It dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates. A 1% suspension in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Doxycycline). A yellow crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in dilute acid and in alkali hydroxide solutions. pH of a 1% suspension in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Doxycycline Calcium *(BANM, rINNM)*

Calcii Doxycyclinum; Doxiciclina cálcica; Doxycycline Calcique.

Кальций Доксициклин

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

Doxycycline Fosfatex *(BAN, USAN)*

AB-08; DMSC; Doxiciclina fosfatex. 6-Deoxy-5β-hydroxytetracycline—metaphosphoric acid—sodium metaphosphate in the ratio 3:3:1.

$(C_{22}H_{24}N_2O_8)_3(HPO_3)_3NaPO_3$ = 1675.2.

CAS — 83038-87-3.

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

Doxycycline Hyclate *(BANM, rINNM)*

Doksiciklino hiklatas; Doksisykliinihyklaatti; Doksycykliny hyklan; Dossiciclina Iclato; Doxiciklin-hiklát; Doxycycline, hyclate de; Doxycycline Hydrochloride; Doxycyclini hyclas; Doxycyklinhyklat; Doxycyklin-hyklát; Hiclato de doxiciclina. Doxycycline hydrochloride hemiethanolate hemihydrate.

Доксициклина Гиклат

$C_{22}H_{24}N_2O_8,HCl,\frac{1}{2}C_2H_5OH,\frac{1}{2}H_2O$ = 512.9.

CAS — 10592-13-9 (doxycycline hydrochloride); 24390-14-5 (doxycycline hyclate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Doxycycline Hyclate). A yellow hygroscopic crystalline powder. Freely soluble in water and in methyl alcohol; sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides and of carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Store in airtight containers. Protect from light.

USP 31 (Doxycycline Hyclate). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of doxycycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Preparations of doxycycline hyclate have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Gastrointestinal disturbances with doxycycline are reported to be less frequent than with tetracycline and doxycycline may also cause less tooth discoloration.

Oesophageal ulceration may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: doxycycline should be taken with at least half a glass of water, in an upright position, and well before going to bed. Dispersible tablets or liquid formulations should be used in elderly patients, who may be at greater risk of oesophageal injury.

Unlike many tetracyclines, doxycycline does not appear to accumulate in patients with impaired renal function, and aggravation of impairment may be less likely.

Incidence of adverse effects. For the suggestion that doxycycline may cause fewer adverse effects than minocycline, see p.301.

Anosmia. Anosmia or dysosmia (absent or impaired sense of smell) have occasionally been reported in patients receiving doxycycline, although the association has not been definitely established.[1]

1. Bleasel AF, *et al.* Anosmia after doxycycline use. *Med J Aust* 1990; **152:** 440.

Effects on intracranial pressure. Doxycycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p.348.

Porphyria. Doxycycline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Tetracycline, p.348.

Doxycycline has a lower affinity for binding with calcium than many tetracyclines. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc; even intravenous doxycycline may be affected, although less so than when given orally.

The metabolism of doxycycline may be accelerated by drugs that induce hepatic enzymes such as alcohol (chronic use), rifampicin, and antiepileptics including carbamazepine, phenobarbital, phenytoin, and primidone.

It has been suggested that doxycycline could increase ciclosporin concentrations, but evidence for this seems to be scant.

Antimicrobial Action

As for Tetracycline, p.348.

Doxycycline is more active than tetracycline against many bacterial species including *Streptococcus pyogenes*, enterococci, *Nocardia* spp., and various anaerobes. Cross-resistance is common although some tetracycline-resistant *Staphylococcus aureus* respond to doxycycline. Doxycycline is also more active against protozoa, particularly *Plasmodium* spp.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p.349.

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of milk or food in the stomach or duodenum. Mean peak plasma concentrations of 2.6 micrograms/mL have been reported 2 hours after a 200-mg oral dose, falling to 1.45 micrograms/mL at 24 hours. After intravenous infusion of the same dose peak plasma concentrations are briefly somewhat higher, but become very similar to those after oral dosage on equilibration into the tissues.

About 80 to 95% of doxycycline in the circulation is reported to be bound to plasma proteins. Its biological half-life varies from about 12 to 24 hours. Doxycycline is more lipid-soluble than tetracycline. It is widely distributed in body tissues and fluids.

In patients with normal renal function about 40% of a dose is slowly excreted in the urine, although more is excreted by this route if the urine is made alkaline. However, the majority of a dose of doxycycline is excreted in the faeces after chelation in the intestines. Although doxycycline has been reported to undergo partial inactivation in the liver, some sources consider this doubtful; however, the kinetics of doxycycline have been reportedly altered in patients receiving drugs that induce hepatic metabolism.

Doxycycline is stated not to accumulate significantly in patients with renal impairment, although excretion in the urine is reduced; increased amounts of doxycycline are excreted in the faeces in these patients. Nevertheless, there have been reports of some accumulation in renal failure. Removal of doxycycline by haemodialysis is insignificant.

◊ Reviews.

1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15:** 355–66.

Uses and Administration

Doxycycline is a tetracycline derivative with uses similar to those of tetracycline (p.349). It may sometimes be preferred to other tetracyclines in the treatment of susceptible infections because of its fairly reliable absorption and its long half-life that permits less frequent (often once daily) dosing. It also has the advantage that it can be given (with care) to patients with renal impairment. However, relatively high doses may need to be given for urinary-tract infections because of its low renal excretion.

Doxycycline has antiprotozoal actions and may be given in conjunction with quinine in the management of falciparum malaria resistant to chloroquine (p.594).

Solutions of doxycycline are also used for malignant effusions (p.659).

Doxycycline is usually given orally as the base or its various salts, usually the hyclate. Doses are expressed in terms of doxycycline; doxycycline hyclate 115 mg is equivalent to about 100 mg of anhydrous doxycycline. Doxycycline capsules and tablets should be given with plenty of fluid, with the patient in an upright position, and well before going to bed. Doxycycline may be given with food or milk if gastric irritation occurs. Dispersible tablets or liquid formulations are advisable in elderly patients.

In patients in whom oral therapy is not feasible, doxycycline hyclate may be given by slow intravenous infusion of a solution containing 0.1 to 1 mg/mL, in equivalent doses. Infusions should be given over 1 to 4 hours.

The usual adult dose, either orally or intravenously, is 200 mg of doxycycline on the first day (as a single dose or in divided doses), followed by 100 mg daily. In severe infections the initial dosage is maintained throughout the course of treatment.

In patients with uncomplicated gonococcal infections, doxycycline 100 mg twice daily for 7 days is given orally, although it has occasionally been given in a single dose of 300 mg followed by a second similar dose 1 hour later. For syphilis in penicillin-allergic patients, doxycycline 100 to 200 mg twice daily is given orally for at least 14 days; some authorities suggest giving the same dose for 28 to 30 days to patients with late latent disease and those with syphilis for more than a year should be given 100 mg twice daily for 28 days.

For relapsing fever and louse-borne typhus, doxycycline 100 or 200 mg may be given as a single oral dose. For prophylaxis of scrub typhus, 200 mg may be taken as a single oral dose. For the prophylaxis of leptospirosis, 200 mg may be given orally once a week throughout exposure for up to 21 days and 200 mg is also given when leaving the area of infection risk.

Doxycycline is used in non-endemic areas for the treatment of chloroquine-resistant falciparum malaria in an oral dose of 200 mg daily for at least 7 days after treatment with quinine. Doxycycline 100 mg daily may be used for prophylaxis in areas of high risk or where multidrug resistance exists, and can be used prophylactically for up to 2 years.

For treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with oral doses of 100 mg twice daily may be used; one or two other antibacterials should also be given. Although unlicensed, the same regimen is recommended by UK and US public health authorities for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of doxycycline 100 mg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure. If there are signs of systemic involvement, extensive oedema, or lesions on the head and neck, intravenous therapy and a multidrug approach is recommended.

In the treatment of acne, an oral dose of 50 mg daily for 6 to 12 weeks may be adequate, although the *BNF* advocates a dose of 100 mg daily. It is also given in low doses of 40 mg once daily as a modified-release preparation for the treatment of inflammatory lesions associated with rosacea in adults.

Doxycycline may be given orally in low doses of 20 mg twice daily for 3 months as an adjunct to supragingival and subgingival scaling and root planing to adults with periodontitis. For chronic periodontitis, a modified-release subgingival gel containing doxycycline hyclate 10% (released over 7 days) has been inserted into the periodontal pocket.

For details of doses in children and adolescents, see below.

Administration. SUBANTIMICROBIAL DOSES. Doxycycline is given in doses of 20 mg orally twice daily, which are not sufficient to achieve antimicrobial concentrations in the body, as an adjunct in the treatment of periodontal disease. The benefits of treatment are believed to be due to its ability to down-regulate the actions of matrix metalloproteinases, enzymes involved in the breakdown of collagen and which play a key role in the inflammatory and destructive processes of periodontitis.[1] Similar subantimicrobial doses have been investigated, and produced apparent benefit, in patients with acne or rosacea;[2] there was no evidence that even quite prolonged therapy at these doses influenced the development of antibiotic resistance in bacterial flora. A low-dose modified-release preparation containing doxycycline 40 mg is available in some countries for the treatment of inflammatory lesions associated with rosacea.

1. Preshaw PM, *et al.* Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis: a review. *J Clin Periodontol* 2004; **31:** 697–707.
2. Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. *Cutis* 2004; **74:** 118–122.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, doxycycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to children over 8 years old; those weighing 45 kg or less may be given usual oral or intravenous doses of 4.4 mg/kg on the first day (as a single dose or in divided doses), followed by 2.2 mg/kg daily and those weighing over 45 kg may be given the usual adult dose (see above).

In the USA, doxycycline is licensed in children over 8 years old for prophylaxis of chloroquine-resistant falciparum malaria in areas of high risk or where multidrug resistance exists. The recommended oral dose is 2 mg/kg (to a maximum of 100 mg) once daily.

US[1] public health authorities suggest that doxycycline may be given to children under 8 years old for the treatment of inhalation, gastrointestinal, or cutaneous anthrax, and for postexposure prophylaxis of inhalation anthrax. For the treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with initial intravenous doses of 2.2 mg/kg (to a maximum of 100 mg) twice daily followed by the same dose given orally is recommended; the same regimen is also recommended for the treatment of gastrointestinal anthrax. As with the adult regimens, one or two other antibacterials should also be given. In the treatment of cutaneous anthrax, a 7- to 10-day course of treatment with an oral dose of 2.2 mg/kg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure. In the UK[2] public health authorities only recommend doxycycline for those older than 8 years old and weighing over 45 kg who may be given the usual adult dose (see above).

1. CDC. Notice to readers: update: interim recommendations for antimicrobial prophylaxis for children and breastfeeding mothers and treatment of children with anthrax. *MMWR* 2001; **50:** 1014–16. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5045.pdf (accessed 25/04/07)
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: anthrax. Version 5.9, 16 April 2007. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 11/08/08)

Lymphatic filariasis. Filaria have been shown to contain *Wolbachia* endobacteria which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of individuals with lymphatic filariasis (p.137). A double-blind, randomised, placebo-controlled study[1] of 72 patients infected with *Wuchereria bancrofti* found that those given oral doxycycline 200 mg daily for 8 weeks had a significant reduction in the number of adult worms at 14 months; ultrasonography detected adult worms in 22% of those given doxycycline and in 88% of those given placebo. Microfilaraemia was almost completely eliminated at 8 to 14 months follow-up.

See also Onchocerciasis, below.

1. Taylor MJ, *et al.* Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial. *Lancet* 2005; **365:** 2116–21.

Musculoskeletal and joint disorders. For reference to the use of doxycycline in the management of various musculoskeletal and joint disorders, see under Tetracycline, p.350.

Onchocerciasis. As in lymphatic filariasis (above), *Onchocerca volvulus* worms rely on a symbiotic relationship with *Wolbachia* endobacteria, and this has provided a new approach in the treatment of individuals with onchocerciasis (p.137). A 4-month controlled clinical study[1] of 35 patients with onchocerciasis found that those given oral doxycycline 100 mg daily for 6 weeks showed a trend toward more frequent degeneration or death of adult worms and suppressed embryonic development at early stages for the duration of the study period. A subsequent study[2] of 88 patients found that embryogenesis was interrupted for at least 18 months in those given a single standard dose of ivermectin (150 micrograms/kg) plus oral doxycycline 100 mg daily for 6 weeks compared to those given only the standard dose of ivermectin.

1. Hoerauf A, *et al.* Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; **355:** 1242–3.
2. Hoerauf A, *et al.* Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001; **357:** 1415–16.

Preparations

BP 2008: Dispersible Doxycycline Tablets; Doxycycline Capsules;
USP 31: Doxycycline Calcium Oral Suspension; Doxycycline Capsules; Doxycycline for Injection; Doxycycline for Oral Suspension; Doxycycline Hyclate Capsules; Doxycycline Hyclate Delayed-release Capsules; Doxycycline Hyclate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Asolmicina.dox; Atridox; Ciclidoxan; Doxibiot; Granudoxy; Verboril; Vibramicina; ***Austral.:*** Doryx; Doxsig; Doxy; Doxyhexal; Doxylin; Frakas; Vibra-Tabs; Vibramycin; ***Austria:*** Aliudox; Dotur; Doxal; Doxybene; Doxyderm; Doxydyn; Doxyhexal; Doxylan; Doxystad; Supracyclin; Vibramycin; Vibravenos; ***Belg.:*** Docdoxycy; Doxylets; Doxytab; Vibramycine; Vibratab; ***Braz.:*** Ciclisan; Clordox; Doxilina†; Neo Doxicilin; Protectina; Uni Doxiciclin; Vibramicina; ***Canad.:*** Apo-Doxy; Doxycin; Doxytec†; Novo-Doxylin; Vibra-Tabs; ***Chile:*** Doryx; Doxithal; Sigadoxin; Vibramicina; ***Cz.:*** Apo-Doxy†; Deoxymykoin; Doxybene; Doxyhexal; Helvedoclyn†; Unidox†; ***Denm.:*** Atridox†; Vibradox; Vibramycin†; ***Fin.:*** Apodoxin; Atridox†; Dosyklin; Doximed; Doximycin; Doxitin; ***Fr.:*** Doxy; Doxygram; Doxylis; Doxypalu; Granudoxy; Spanor; Tolexine; Vibramycine N; ***Ger.:*** Aknefug Doxy; Antodox; Atridox; Azudoxat†; Clinofug D†; Doxakne; Doxy; Doxy Komb; Doxy M; Doxy-Diolan†; Doxy-HP; Doxy-N-Tablinen; Doxy-Puren†; Doxy-Wolff; Doxyderma; Doxydoc; Doxyhexal; Doxymerck; Doxymono; Jenacyclin†; Mespafin; Neodox†; Sigadoxin†; Supracyclin; Vibramycin†; Vibravenos†; ***Gr.:*** Atridox; Impalamycin; Microvibrate; Novimax; Otosal; Relyomycin; Smilitene; Vibramycin; Vibravenos†; Vibravenosa†; ***Hong Kong:*** Amermycin; Doxitab; Doxy†; Doxymycin; Medomycin; Remycin†; Vibramycin; Wanmycin; Zadorin†; ***Hung.:*** Doxypharm; Doxyprotect; Huma-Doxylin; Tenutan; Vibramycin†; ***India:*** Biodoxi; Doxicip; Doxy; Doxypal-DR; Geeox; Lenteclin; Solomycin; Vibazine†; ***Indon.:*** Dotur; Doxacin; Doxicor; Doxin; Dumoxin; Interdoxin; Siclidon; Viadoxin; Vibramycin; ***Irl.:*** By-Mycin; Periostat; Vibramycin; ***Israel:*** Doxibiotic; Doxy; Doxylin; Doxytrim; Periostat; Vibramycin; ***Ital.:*** Bassado; Miraclin; ***Malaysia:*** Bronmycin†; Doline; Doxacyne†; Doxy†; Doxycillin; Doxymycin; Medomycin; Vibramycin; Wanmycin†; Zadorin†; ***Mex.:*** Apociclina†; Bioximicina; Domiken; Kenciclen; Periosan; Vibramicina; Vivradoxil; ***Neth.:*** Atridox; Doxy; Doxy-Dagra†; Doxymycin†; Periostat; Unidox; Vibra-S†; Vibramycin; ***Norw.:*** Doryx†; Doxylin; Doxysol†; Dumoxin; Vibramycin; ***NZ:*** Atridox†; Doxine; Doxy; ***Philipp.:*** Cytragen; Doxicon; Doxin; Doxylyn; Harvellin; Vibramycin; ***Pol.:*** Dotur; Doxicin; Doxyratio M; Supracyclin; Unidox; ***Port.:*** Actidox; Atridox; Biocin†; Doxytrex; Periostat; Pluridoxina; Sigadoxin; Vibramicina; ***Rus.:*** Apo-Doxy (Апо-докси)†; Doxal (Доксал)†; Medomycin (Медомицин); Unidox (Юнидокс); Vibramycin (Вибрамицин); ***S.Afr.:*** Cyclidox; Doximal; Doxitab; Doxyclin; Doxycyl; Doxyhexal; Doxymycin; Dumoxin; Noritet; Randoclin†; Vibramycin; ***Singapore:*** Apo-Doxy; Bronmycin; Doryx†; Doxilin†; Doxine; Doxycap; Doxyline; Doxymycin; Medomycin; Remycin†; Tetradox; Vibramycin; Wanmycin; ***Spain:*** Docostyl†; Dosil; Doxiclat; Doxicrisol; Doxinate†; Doxiten Bio; Mededoxi; Peledox; Proderma; Retens; Rexilen; Vibracina; Vibravenosa; ***Swed.:*** Atridox; Doryx†; Doxyferm; Vibramycin; ***Switz.:*** Atridox; Diocimex; Doxy-basan†; Doxycline; Doxylag; Doxysol; Periostat; Rudocycline; Sigadoxin†; Supracycline; Tasmacyclin Akne; Vibramycine; Vibraveineuse; Zadorine; ***Thai.:*** Amermycin; Bronmycin; Docline; Docyl; Doxin; Doxy; Doxy-P†; Doxycline; Doxylcap; Doxylin; Dumoxin†; Madoxy; Medomycin; Medoxin; Poli-Cycline; Servidoxyne; Siadocin; Tetradox; Torymycin; Veemycin; Vibramycin; ***Turk.:*** Doksin; Monodoks; Tetradox; ***UAE:*** DuraDox; ***UK:*** Atridox; Demix†; Doxylar; Periostat; Vibramycin; ***USA:*** Adoxa; Alodox; Atridox; Doryx; Monodox; Oracea; Oraxyl; Periostat; Vibra-Tabs; Vibramycin; ***Venez.:*** Doxiclival; Tremesal; Vibrafesa†; Vibramicina C.

Multi-ingredient: ***Cz.:*** Doxycyclin Al Comp; ***Ger.:*** Ambrodoxy; Ambroxol AL comp; Ambroxol comp; Amdox-Puren†; Azudoxat comp†; Doxam; Doximucol; Doxy Comp; Doxy Lindoxyl; Doxy Plus; Doxy-Wolff Mucolyt†; Doxysolvat†; Jenabroxol comp†; Sigamuc†; Terelit†; ***Spain:*** Dosil Enzimatico; Doxiten Enzimatico; Pulmotropic.

Enoxacin *(BAN, USAN, rINN)*

AT-2266; CI-919; Enoksasiini; Enoksasin; Énoxacine; Enoxacino; Enoxacinum; PD-107779. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid.

Эноксацин

$C_{15}H_{17}FN_4O_3 = 320.3.$
CAS — 74011-58-8.
ATC — J01MA04.
ATC Vet — QJ01MA04.

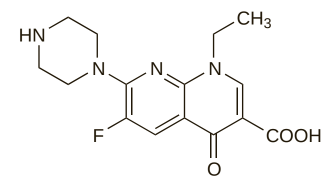

Pharmacopoeias. *Chin.* and *Jpn* include the sesquihydrate.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Reduced dosage may be needed in renal impairment—see Administration in Renal Impairment, under Uses and Administration, below.

Interactions

As for Ciprofloxacin, p.246.

Of the fluoroquinolones, enoxacin has been reported to cause the most marked interaction with theophylline (p.1143) and with caffeine (p.1117).

Antimicrobial Action

As for Ciprofloxacin, p.246, although enoxacin is generally less potent *in vitro.*

Pharmacokinetics

Peak plasma concentrations of 2 to 3 micrograms/mL occur 1 to 2 hours after a 400-mg oral dose of enoxacin. The plasma half-life is about 3 to 6 hours. Plasma protein binding ranges from 18 to 67%. Enoxacin appears to be widely distributed in the body and concentrations higher than those in plasma have been reported in tissues such as lung, kidney, and prostate. High concentrations are achieved in bile, but the extent of biliary excretion is not completely clear.

Enoxacin is eliminated from the body mainly by urinary excretion, but also by metabolism. The major metabolite, 3-oxo-enoxacin, has some antibacterial activity. Urinary excretion of enoxacin is by both tubular secretion and glomerular filtration and may be reduced by probenecid. High concentrations are achieved in the urine since about 60% of an oral dose of enoxacin appears unchanged in the urine within 24 hours; about 10% is recovered as 3-oxo-enoxacin. In renal impairment the half-life of enoxacin may be prolonged and the oxometabolite may accumulate.

Uses and Administration

Enoxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247). It is used mainly in the treatment of urinary-tract infections (p.199) and gonorrhoea (p.191).

For urinary-tract infections, enoxacin is given orally in doses of 200 to 400 mg twice daily.

For details of reduced doses in renal impairment, see below.

A single 400-mg dose is given for uncomplicated gonorrhoea.

◊ References.

1. Patel SS, Spencer CM. Enoxacin: a reappraisal of its clinical efficacy in the treatment of genitourinary tract infections. *Drugs* 1996; **51:** 137–60.

Administration in renal impairment. In renal impairment when the creatinine clearance is 30 mL/minute or less the urinary concentrations achieved may be too low to have a therapeutic effect in urinary-tract infections. In other infections, half the usual dose of enoxacin is recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Enoxor; ***Fr.:*** Enoxor; ***Ger.:*** Enoxor; ***Ital.:*** Bactidan; Enoxen; ***Jpn:*** Flumark; ***Port.:*** Vinone†; ***S.Afr.:*** Bactidron†; ***Turk.:*** Enoksetin; ***USA:*** Penetrex†.

Enrofloxacin *(BAN, USAN, rINN)*

Bay-Vp-2674; Enrofloksasiini; Enrofloxacine; Enrofloxacino; Enrofloxacinum. 1-Cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

Энрофлоксацин

$C_{19}H_{22}FN_3O_3$ = 359.4.

CAS — 93106-60-6.

ATC Vet — QJ01MA90.

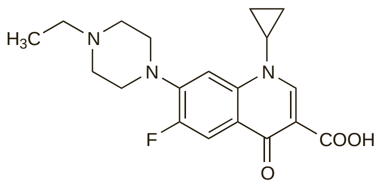

Profile

Enrofloxacin is a fluoroquinolone antibacterial that is used in veterinary practice.

Ertapenem Sodium *(BANM, USAN, rINNM)*

Ertapenem sódico; Ertapénem Sodique; L-749345; MK-826; MK-0826; Natrii Ertapenemum; ZD-4433. Sodium (4R,5S,6S)-3-({(3S,5S)-5-[(*m*-Carboxyphenyl)carbamoyl]-3-pyrrolidinyl}thio)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

Натрий Эртапенем

$C_{22}H_{24}N_3NaO_7S$ = 497.5.

CAS — 153832-46-3 (ertapenem); 153832-38-3 (ertapenem disodium); 153773-82-1 (ertapenem sodium).

ATC — J01DH03.

ATC Vet — QJ01DH03.

Incompatibility and stability. References.

1. McQuade MS, *et al.* Stability and compatibility of reconstituted ertapenem with commonly used iv infusion and coinfusion solutions. *Am J Health-Syst Pharm* 2004; **61:** 38–45.

Adverse Effects and Precautions

As for Imipenem, p.286.

Ertapenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the enzyme, is not required.

Interactions

Probenecid inhibits the renal excretion of ertapenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to ertapenem, see p.510.

Antimicrobial Action

As for Imipenem, p.287,

Ertapenem is reported to be slightly more active *in vitro* than imipenem but has a narrower spectrum of activity and is not active against *Acinetobacter* or *Pseudomonas aeruginosa*.

Pharmacokinetics

After intravenous infusion of ertapenem 1 g over 30 minutes, a mean plasma concentration of 155 micrograms/mL is attained, falling to 9 micrograms/mL after 12 hours and 1 microgram/mL after 24 hours. After the same dose intramuscularly, a plasma concentration of 67 micrograms/mL is achieved after 2 hours. Bioavailability after intramuscular injection is about 90%.

Ertapenem is more than 90% bound to plasma proteins. It is distributed into breast milk. The plasma half-life is about 4 hours in adults and 2.5 hours in infants and in children aged 3 months to 12 years; the half-life may be prolonged in patients with renal impairment.

Ertapenem is partially metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite. About 80% of a dose is excreted in the urine as both unchanged drug and metabolite. About 10% is excreted in faeces.

Ertapenem is removed by haemodialysis.

Uses and Administration

Ertapenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p.287). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections including intra-abdominal infections, acute gynaecological infections, urinary-tract infections, skin and skin structure infections (including diabetic foot infections), and community-acquired pneumonia. It is also used prophylactically in colorectal surgery. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Ertapenem is given as the sodium salt, but doses are expressed in terms of the base; 1.04 g of ertapenem sodium is equivalent to about 1 g of ertapenem. For treatment, it is given by intravenous infusion over 30 minutes or by intramuscular injection, in a usual adult dose of 1 g once daily. For prophylaxis, a single 1- g dose is given intravenously 1 hour before the start of surgery. For details of reduced doses in renal impairment, see below.

For details of doses in infants and children, see below.

◊ Reviews.

1. Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. *Drugs* 2006; **65:** 2151–78.

Administration in children. The dose of ertapenem for children aged 3 months to 12 years is 15 mg/kg twice daily (up to a maximum of 1 g daily) given by intravenous infusion over 30 minutes; if appropriate, the intramuscular route may be used.

Administration in renal impairment. Doses of ertapenem should be reduced in patients with renal impairment according to creatinine clearance (CC) and the following data are based on US prescribing information:

- CC 30 mL or less per minute (including end-stage disease where CC is 10 mL or less per minute): 500 mg daily for adults
- haemodialysis: if the 500-mg dose is given in the 6-hour period before dialysis an additional 150 mg should be given after each session.

The UK product licence, however, states that in advanced renal insufficiency and haemodialysis there are inadequate data to make recommendations and that ertapenem should not be used in these patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Invanz; ***Austral.:*** Invanz; ***Austria:*** Invanz; ***Belg.:*** Invanz†; ***Braz.:*** Invanz; ***Canad.:*** Invanz; ***Chile:*** Invanz; ***Cz.:*** Invanz; ***Denm.:*** Invanz; ***Fin.:*** Invanz; ***Fr.:*** Invanz; ***Ger.:*** Invanz; ***Gr.:*** Invanz; ***Hong Kong:*** Invanz; ***Hung.:*** Invanz; ***Irl.:*** Invanz; ***Israel:*** Invanz; ***Ital.:*** Invanz; ***Malaysia:*** Invanz; ***Neth.:*** Invanz; ***NZ:*** Invanz; ***Philipp.:*** Invanz; ***Pol.:*** Invanz; ***Port.:*** Invanz; ***Rus.:*** Invanz (Инванз); ***S.Afr.:*** Invanz; ***Singapore:*** Invanz; ***Spain:*** Invanz; ***Swed.:*** Invanz; ***Thai.:*** Invanz; ***UK:*** Invanz; ***USA:*** Invanz; ***Venez.:*** Invanz.

Erythromycin *(BAN, rINN)*

Eritromicin; Eritromicina; Eritromicinas; Eritromisin; Érythromycine; Erythromycinum; Erytromycin; Erytromycyna; Erytromysiini. Erythromycin A is (2R,3S,4S,5R,6R,8R,10R,11R,12S,13R)-5-(3-amino-3,4,6-trideoxy-*N*,*N*-dimethyl-β-D-*xylo*-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-13-ethyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethyl-9-oxotridecan-13-olide.

Эритромицин

$C_{37}H_{67}NO_{13}$ = 733.9.

CAS — 114-07-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QJ51FA01; QS01AA17.

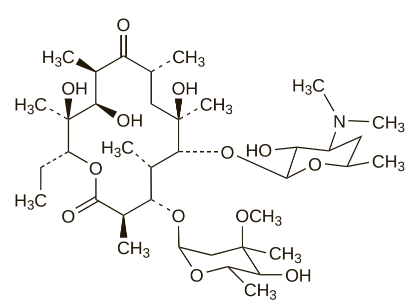

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Erythromycin). It is produced by the growth of a strain of *Streptomyces erythreus* and is a mixture of macrolide antibiotics consisting largely of erythromycin A. It occurs as a white or slightly yellow powder or colourless or slightly yellow crystals; slightly hygroscopic. Slightly soluble in water but less soluble at higher temperatures; freely soluble in alcohol; soluble in methyl alcohol. Protect from light.

USP 31 (Erythromycin). It consists primarily of erythromycin A. A white or slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 1000 of water; soluble in alcohol, in chloroform, and in ether. Store in airtight containers.

Erythromycin Estolate *(BAN, USAN, rINNM)*

Eritromicin-esztolát; Eritromicino estolatas; Erythromycin Propionate Lauryl Sulfate; Erythromycin Propionate Lauryl Sulphate; Érythromycine, estolate d'; Erythromycin-estolát; Erythromycini estolas; Erytromycinestolat; Erytromycyny estolan; Erytromysiiniestolaatti; Estolato de eritromicina; Propionylerythromycin Lauryl Sulphate. Erythromycin 2′-propionate dodecyl sulphate.

Эритромицина Эстолат

$C_{40}H_{71}NO_{14},C_{12}H_{26}O_4S$ = 1056.4.

CAS — 3521-62-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Erythromycin Estolate). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; practically insoluble in dilute hydrochloric acid. Protect from light.

USP 31 (Erythromycin Estolate). A white, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. Practically insoluble in water; soluble 1 in 20 of alcohol, 1 in 15 of acetone, and 1 in 10 of chloroform. Store in airtight containers.

Erythromycin Ethyl Succinate *(BANM)*

Eritromicina, etilsuccinato de; Eritromicin-etilszukcinát; Eritromicino etilsukcinatas; Erythromycin Ethylsuccinate; Érythromycine, éthylsuccinate d'; Erythromycin-ethylsukcinát; Erythromycini ethylsuccinas; Erytromycinetylsuccinat; Erytromycyny etylobursztynian; Erytromysiinietyylisuksinaatti. Erythromycin 2′-(ethylsuccinate).

Эритромицина Этилсукцинат

$C_{43}H_{75}NO_{16}$ = 862.1.

CAS — 41342-53-4.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

NOTE. Compounded preparations of erythromycin ethyl succinate may be represented by the following names:

- Co-erynsulfisox (*PEN*)—erythromycin ethyl succinate and acetyl sulfafurazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Erythromycin Ethylsuccinate; Erythromycin Ethyl Succinate BP 2008). A white or almost white, hygroscopic crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Erythromycin Ethylsuccinate). A white or slightly yellow, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 765 micrograms of erythromycin per mg, calculated on the anhydrous basis. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in macrogol 400. Store in airtight containers.

Erythromycin Gluceptate *(BANM, rINNM)*

Érythromycine, Gluceptate d'; Erythromycini Gluceptas; Gluceptato de eritromicina. Erythromycin glucoheptonate.

Эритромицина Глюцептат

$C_{37}H_{67}NO_{13},C_7H_{14}O_8$ = 960.1.

CAS — 304-63-2; 23067-13-2.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *US.*

USP 31 (Sterile Erythromycin Gluceptate). It is erythromycin gluceptate suitable for parenteral use. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a 2.5% solution in water is between 6.0 and 8.0.

Erythromycin Lactobionate *(BANM, rINNM)*

Eritromicin-laktobionát; Eritromicino laktobionatas; Érythromycine, lactobionate d'; Erythromycini lactobionas; Erythromycin-laktobionát; Erytromycinlaktobionat; Erytromycyny laktobionian; Erytromysiinilaktov; Éthylèneglycol, monostéarate d'; Lactobionato de eritromicina; Lactobionato de eritromicina. Erythromycin mono(4-O-β-D-galactopyranosyl-D-gluconate).

Эритромицина Лактобионат

$C_{37}H_{67}NO_{13},C_{12}H_{22}O_{12}$ = 1092.2.
CAS — 3847-29-8.
ATC — D10AF02; J01FA01; S01AA17.
ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Erythromycin Lactobionate). Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*. White or slightly yellow, hygroscopic powder. Soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very slightly soluble in acetone and in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5. Store in airtight containers.

USP 31 (Sterile Erythromycin Lactobionate). It has a potency equivalent to not less than 525 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a solution in water containing the equivalent of erythromycin 5% is between 6.5 and 7.5.

Erythromycin Propionate *(BANM, USAN, rINNM)*

Erythromycin Propanoate; Érythromycine, Propionate d'; Erythromycini Propionas; Propionato de eritromicina; Propionylerythromycin. Erythromycin 2′-propionate.

Эритромицина Пропионат

$C_{40}H_{71}NO_{14}$ = 790.0.
CAS — 134-36-1.
ATC — D10AF02; J01FA01; S01AA17.
ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *Fr.*

Erythromycin Stearate *(BANM, rINNM)*

Eritromicino stearatas; Eritromicin-sztearát; Eritromisin Stearat; Érythromycine, stéarate d'; Erythromycini stearas; Erythromycin-stearát; Erytromycinstearat; Erytromycyny stearynian; Erytromysiinistearaatti; Estearato de eritromicina. Erythromycin octadecanoate.

Эритромицина Стеарат

$C_{37}H_{67}NO_{13},C_{18}H_{36}O_2$ = 1018.4.
CAS — 643-22-1.
ATC — D10AF02; J01FA01; S01AA17.
ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Erythromycin Stearate). A mixture of the stearates of erythromycin and stearic acid. A white or almost white crystalline powder. Practically insoluble in water; soluble in acetone and in methyl alcohol. Solutions may be opalescent.

USP 31 (Erythromycin Stearate). The stearic acid salt of erythromycin with an excess of stearic acid. White or slightly yellow crystals or powder, odourless or may have a slight, earthy odour. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, and in methyl alcohol. Store in airtight containers.

Incompatibility and stability. The stability of erythromycin derivatives is dependent upon pH, with particularly rapid degradation occurring at a pH greater than 10 or less than 5.5. Incompatibility might reasonably be expected, therefore, when erythromycin preparations are mixed with drugs or preparations that have a highly acidic or alkaline pH. In practice, reports of incompatibility are not always consistent, and other factors such as the temperature and concentration of solutions, and the diluents used, may play a role.

Solutions for infusion. For the preparation of solutions of erythromycin lactobionate for infusion, a primary solution containing not more than 5% of erythromycin should be prepared first; only water for injection should be used in preparing the primary solution. It should be further diluted with sodium chloride 0.9% or other suitable intravenous fluid before use. Acidic solutions, such as glucose, should only be used if neutralised with sodium bicarbonate.

Adverse Effects

Erythromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use, probably because of the stimulant activity of erythromycin on the gut. Gastrointestinal effects are dose related and appear to be more common in young than in older patients. Superinfection with resistant organisms may occur and pseudomembranous colitis has been reported.

Hypersensitivity reactions appear to be uncommon, having been reported in about 0.5% of patients, and include pruritus, urticaria, and skin rash as well as occasional cases of anaphylaxis. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported very rarely. Hypersensitivity or irritation may occur after topical application of erythromycin.

A hypersensitivity reaction is thought to be responsible for the hepatotoxicity sometimes reported in patients receiving erythromycin or its derivatives but this has been disputed by some. Most reports of cholestatic hepatitis have been in patients receiving the estolate, and it has been suggested that the propionyl ester linkage is particularly associated with hepatotoxicity, but symptoms have also been reported in patients given the base and most of the other derivatives, both orally and parenterally. Symptoms indicative of cholestasis, including upper abdominal pain (sometimes very severe), nausea and vomiting, abnormal liver function values, raised serum bilirubin, and usually jaundice, may be accompanied by rash, fever, and eosinophilia. Symptoms usually occur in patients who have been taking the drug for more than 10 days, although they may develop more quickly in patients given the drug previously. Hepatic dysfunction seems to be rare in children under 12 years of age. The effects of erythromycin on the liver are generally reversible on stopping treatment. Erythromycin may interfere with tests for serum aspartate aminotransferase, which might make diagnosis of hepatotoxicity more difficult.

A generally reversible sensorineural deafness, sometimes with tinnitus, has been reported in patients given erythromycin and appears to be related to serum concentration, with an increased likelihood of such effects in patients given doses of 4 g or more daily of base or its equivalent, in those given intravenous therapy, and in those with renal or hepatic impairment.

Other adverse effects that have been reported in patients given erythromycin include agranulocytosis, aggravation of muscular weakness in myasthenia gravis patients, and pancreatitis. Prolongation of the QT interval and other arrhythmias, sometimes fatal, including torsade de pointes have been reported particularly with intravenous use. There have also been isolated reports of transient CNS adverse effects including confusion, hallucinations, seizures, and vertigo.

Parenteral formulations of erythromycin are irritant and intravenous dosage may produce thrombophlebitis, particularly at high doses. Intramuscular injection is generally avoided as it may produce severe pain.

◊ General reviews.

1. Periti P, *et al.* Adverse effects of macrolide antibacterials. *Drug Safety* 1993; **9:** 346–64.
2. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in paediatric patients. *Drug Safety* 1999; **20:** 25–41.
3. Rubinstein E. Comparative safety of the different macrolides. *Int J Antimicrob Agents* 2001; **18** (suppl 1): S71–S76.

Effects on body temperature. A report of hypothermia associated with oral erythromycin in 2 children.[1] Symptoms resolved on stopping the drug. The children were cousins, perhaps indicating a genetic predisposition to the effect. There has also been a similar report of hypothermia in 3 children given azithromycin orally.[2]

1. Hassel B. Hypothermia from erythromycin. *Ann Intern Med* 1991; **115:** 69–70.
2. Kavukçu S, *et al.* Hypothermia from azithromycin. *J Toxicol Clin Toxicol* 1997; **35:** 225 6.

Effects on the cardiovascular system. There have been several reports[1-6] of QT prolongation or torsade de pointes associated with erythromycin, particularly with intravenous use.

A review[7] of reports of torsade de pointes received by the FDA Adverse Event Reporting System between 1987 and December 2000 identified 156 cases associated with use of the macrolides azithromycin, clarithromycin, dirithromycin, or erythromycin. Of these reports, half involved the use of other drugs known to prolong the QT interval; co-morbid diseases and physiological abnormalities, including cardiac abnormalities, were also commonly reported. A retrospective analysis[8] of a cohort of patients who suffered sudden death from cardiac causes found that the rate of sudden cardiac death was twice as high among current users of erythromycin as in those not using antibacterials; there was no such increase among former users, nor among current users of amoxicillin. The greatest increase in risk was seen in patients using erythromycin with inhibitors of the cytochrome P450 isoenzyme subfamily CYP3A; such patients had more than 5 times the risk of sudden cardiac death of patients who took neither.

1. McComb JM, *et al.* Recurrent ventricular tachycardia associated with QT prolongation after mitral valve replacement and its association with intravenous administration of erythromycin. *Am J Cardiol* 1984; **54:** 922–3.
2. Schoenenberger RA, *et al.* Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 1990; **330:** 1375–6.
3. Nattel S, *et al.* Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med* 1990; **89:** 235–8.
4. Gitler B, *et al.* Torsades de pointes induced by erythromycin. *Chest* 1994; **105:** 368–72.
5. Gouyon JB, *et al.* Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994; **13:** 840–1.
6. Drici M-D, *et al.* Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998; **280:** 1774–6.
7. Shaffer D, *et al.* Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* 2002; **35:** 197–200.
8. Ray WA, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; **351:** 1089–96.

Effects on the gastrointestinal tract. Comparison in patients with upper respiratory-tract infections has suggested that erythromycin ethyl succinate may be associated with less abdominal pain than an equivalent dosage of erythromycin base.[1] Another study has indicated that there was no significant difference in gastrointestinal symptoms between plain and enteric-coated formulations of erythromycin base.[2] Severe nausea and vomiting after rapid intravenous infusion of erythromycin lactobionate stopped in 2 patients who transferred to oral erythromycin base or ethyl succinate.[3] However, the adverse effects may have been due to the rate of infusion, since in 2 further patients symptoms resolved when the lactobionate was given more slowly as a more dilute solution.[3]

There have been a number of studies suggesting an association between erythromycin and infantile hypertrophic pyloric stenosis.[4-6] A retrospective cohort study of 469 infants who had received erythromycin found that 43 were diagnosed with the condition including 36 male infants, although erythromycin had been prescribed almost equally for males and females.[5] All the infants in whom stenosis developed were given erythromycin in the first 2 weeks of life. In another study,[6] involving 7138 infants who received erythromycin between 3 and 90 days of life, use of the drug between 3 and 13 days of life was associated with an almost eightfold increased risk of infantile hypertrophic pyloric stenosis. However, it was believed that the evidence did not support a generalisation of this association to the whole class of macrolides[7] although pyloric stenosis has been reported in breast-fed infants associated with the use of erythromycin or several other macrolides in their mothers (see under Precautions, below).

For reference to the stimulant effects of erythromycin on the gastrointestinal tract, see Decreased Gastrointestinal Motility under Uses and Administration, below.

1. Saloranta P, *et al.* Erythromycin ethylsuccinate, base and acistrate in the treatment of upper respiratory tract infection: two comparative studies of tolerability. *J Antimicrob Chemother* 1989; **24:** 455–62.
2. Ellsworth AJ, *et al.* Prospective comparison of patient tolerance to enteric-coated vs non-enteric-coated erythromycin. *J Fam Pract* 1990; **31:** 265–70.
3. Seifert CF, *et al.* Intravenous erythromycin lactobionate-induced severe nausea and vomiting. *DICP Ann Pharmacother* 1989; **23:** 40–4.
4. Honein MA, *et al.* Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet* 1999; **354:** 2101–5. Correction. *ibid.* 2000; **355:** 758.
5. Mahon BE, *et al.* Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001; **139:** 380–4.
6. Cooper WO, *et al.* Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002; **156:** 647–50.
7. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Safety* 2002; **25:** 929–42.

Effects on the neonate. For a suggestion that erythromycin or other macrolides might be associated with an increased risk of infantile hypertrophic pyloric stenosis in neonates, see under Effects on the Gastrointestinal Tract, above.

Effects on the skin. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have rarely been reported with macrolides.[1,2]

1. Lestico MR, Smith AD. Stevens-Johnson syndrome following erythromycin administration. *Am J Health-Syst Pharm* 1995; **52:** 1805–7.
2. Sullivan S, *et al.* Stevens-Johnson syndrome secondary to erythromycin. *Ann Pharmacother* 1999; **33:** 1369.

Overdosage. Acute pancreatitis was reported in a 12-year-old girl after ingestion of about 5 g of erythromycin base.[1] Transient pancreatitis has also been reported in another 15-year-old girl who took 5.328 g of erythromycin base.[2] Erythromycin produces contraction of the sphincter of Oddi resulting in reflux of bile into the pancreas but the resulting pancreatitis is self-limited and remits when sphincter tone returns to normal after the erythromycin is eliminated from the body.

1. Berger TM, *et al.* Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. *Pediatrics* 1992; **90:** 624–6.
2. Tenenbein MS, Tenenbein M. Acute pancreatitis due to erythromycin overdose. *Pediatr Emerg Care* 2005; **21:** 675–6.

Precautions

Erythromycin and its derivatives should be avoided in those known to be hypersensitive to it, or in those who have previously developed jaundice. All forms of erythromycin should be used with care in patients with existing liver disease or hepatic impairment, and the estolate is best avoided in such patients; liver function should be monitored. Repeated courses of the estolate or use for longer than 10 days increases the risk of hepatotoxicity.

The lactobionate should be used with caution in patients with severe renal impairment; dosage reduction may be necessary particularly in those who develop toxicity. A reduced dose of the estolate has also been recommended in severe renal impairment.

Erythromycin may aggravate muscle weakness in patients with myasthenia gravis.

Erythromycin should be used with care in patients with a history of arrhythmias or a predisposition to QT interval prolongation. Certain medications may also increase the risk of arrhythmias (see Interactions, below).

Erythromycin may interfere with some diagnostic tests including measurements of urinary catecholamines and 17-hydroxycorticosteroids. It has also been associated with falsely-elevated serum aspartate aminotransferase values when measured colorimetrically, although genuine elevations of this enzyme, due to hepatotoxicity, also occur, particularly with the estolate.

Erythromycin is irritant; solutions for parenteral use should be suitably diluted and given by intravenous infusion over 20 to 60 minutes to reduce the incidence of thrombophlebitis. Rapid infusion is also more likely to be associated with arrhythmias or hypotension.

Breast feeding. There has been a report[1] of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. A large Danish population-based cohort study[2] later concluded that the use of macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin, or spiramycin) during breast feeding increased the risk of infantile hypertrophic pyloric stenosis. (See also Effects on the Gastrointestinal Tract, above.) A milk-to-plasma ratio of 0.5 has been reported for erythromycin.[3] However, the American Academy of Pediatrics[4] states that, although erythromycin is concentrated in human breast milk, no adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin and it is therefore usually compatible with breast feeding.

1. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. *Minn Med* 1986; **69:** 669–70, 682.
2. Sørensen HT, *et al.* Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J Infect Dis* 2003; **35:** 104–106.
3. Briggs GG, *et al. Drugs in pregnancy and lactation.* 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2005.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/07)

Porphyria. Erythromycin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Of 298 pregnant women who took erythromycin estolate, clindamycin, or placebo for 3 weeks or longer, about 14, 4, and 3% respectively had abnormally high serum aspartate aminotransferase values.[1] Erythromycin estolate should probably not be given to pregnant women.

A study[2] of data from the Swedish Medical Birth Registry of infants born between July 1995 and December 2002 has examined details of infants exposed to erythromycin or phenoxymethylpenicillin during early pregnancy. Of 1844 exposed to erythromycin, 103 (5.6%) had congenital malformations compared with 420 of 9110 (4.7%) for phenoxymethylpenicillin. Of these, 34 (1.8%) and 86 (0.9%) respectively had a cardiovascular malformation, the rate being considered high for erythromycin. This contrasted with a previous study based on a 1980–96 dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities which found no signs of teratogenicity for erythromycin.[3] Although an increased risk for cardiovascular abnormalities was initially apparent when analysing erythromycin usage throughout pregnancy as reported by the mother, this was not confirmed when assessing usage only in the second or third month nor in the entire pregnancy for medically documented intake. The Swedish data also revealed a possible association between infant pyloric stenosis and early prenatal exposure to erythromycin[2] although others had previously failed to confirm such a risk[4] (see also Effects on the Gastrointestinal Tract, above).

1. McCormack WM, *et al*. Hepatotoxicity of erythromycin estolate during pregnancy. *Antimicrob Agents Chemother* 1977; **12:** 630–5.
2. Källén BAJ, *et al.* Is erythromycin therapy teratogenic in humans? *Reprod Toxicol* 2005; **20:** 209–14.
3. Czeizel AE, *et al.* A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. *Reprod Toxicol* 1999; **13:** 531–6.
4. Hussain N, Herson VC. Erythromycin use during pregnancy in relation to pyloric stenosis. *Am J Obstet Gynecol* 2002; **187:** 821–2.

Interactions

Erythromycin and other macrolides have the potential to interact with a large number of drugs through their action on hepatic cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4. Macrolides inhibit drug metabolism by microsomal cytochromes by competitive inhibition and by the formation of inactive complexes. Such interactions can result in severe adverse effects, including ventricular arrhythmias with astemizole, cisapride, and terfenadine. Enzyme inhibition is reported to be particularly pronounced with macrolides such as erythromycin and troleandomycin. Other macrolides such as azithromycin and dirithromycin are reported to have little or no effect on hepatic cytochromes, and consequently may produce fewer interactions (see also Mechanism, below).

Macrolides themselves have been reported rarely to prolong the QT interval and should be used with caution with other drugs known to also have this effect.

Other mechanisms by which macrolides cause interactions include suppression of the gastrointestinal flora responsible for the intraluminal metabolism of digoxin and possibly oral contraceptives, and the stimulant effect of macrolides on gastrointestinal motility which is believed to be responsible for the interaction between spiramycin and levodopa. An alternative mechanism by which macrolides increase serum concentrations of digoxin is thought to be via the inhibition of intestinal or renal P-glycoprotein transport of digoxin.

Few drugs are reported to affect erythromycin but cimetidine may increase and theophylline may decrease erythromycin concentrations (see below).

The effect on antimicrobial action when erythromycin is given with other antimicrobials is discussed under Antimicrobial Action, below.

◊ General references[1-4] to interactions associated with macrolide antibacterials.

1. von Rosenstiel N-A, Adam D. Macrolide antibacterials: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 105–22.
2. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; **50:** 285–95.
3. Pai MP, *et al.* Macrolide drug interactions: an update. *Ann Pharmacother* 2000; **34:** 495–513.
4. Shakeri-Nejad K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother* 2006; **7:** 639–51.

Mechanism

In *rats* and humans, troleandomycin, and erythromycin and some of its derivatives, induce microsomal enzymes; the nitrosoalkane metabolites so formed produce stable inactive complexes with the iron of cytochrome P450. Eventually the oxidative metabolism of other drugs may be decreased. These effects are marked after troleandomycin, moderate after erythromycin, small after oleandomycin, and absent or negligible after josamycin, midecamycin, or spiramycin.[1,2]

1. Pessayre D, *et al*. Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 1985; **16** (suppl A): 181–94.
2. Periti P, *et al.* Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992; **23:** 106–31.

Drugs

For reference to the effects of erythromycin and other macrolides on other drugs, see

- alfentanil (p.17)
- bromocriptine (p.800)
- buspirone (p.966)
- carbamazepine (p.474)
- ciclosporin (p.1825)
- clozapine (p.984)
- colchicine (p.557)
- digoxin (p.1261)
- dihydroergotamine and ergotamine (p.621)
- disopyramide (p.1270)
- levodopa (p.807)
- midazolam and triazolam (p.989)
- phenytoin (p.498)
- pimozide (p.973)
- quetiapine (p.1023)
- quinidine (p.1384)
- repaglinide (p.458)
- rifabutin (p.324)
- sertraline (p.396)
- sildenafil (p.2194)
- simvastatin and other statins (p.1392)
- tacrolimus (p.1845)
- terfenadine (p.591)
- theophylline (p.1143)
- valproate (p.510)
- verapamil (p.1422)
- vinblastine (p.786)
- warfarin (p.1428)
- zopiclone (p.1039)

In the case of astemizole, cisapride, and terfenadine the UK CSM has warned that there is a risk of inducing ventricular arrhythmias if erythromycin, or possibly other macrolides, are also given,[1,2] and that, in particular, cisapride should not be used with macrolides.[3] The Commission on Human Medicines[4] (formerly CSM) later advised that amisulpride, ergotamine, dihydroergotamine, mizolastine, pimozide, simvastatin, and tolterodine should not be given with erythromycin. A warning was also issued that increased erythromycin concentrations may occur when used with other inhibitors of the cytochrome P450 CYP3A isoenzymes such as the azole antifungals, some calcium-channel blockers including diltiazem and verapamil, and HIV-protease inhibitors. For a report of an increased risk of sudden cardiac death associated with such combinations see Effects on the Cardiovascular System, above.

1. Committee on Safety of Medicines. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
2. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid, Alimax): interactions with antifungals and antibiotics can lead to ventricular arrhythmias. *Current Problems* 1996; **22:** 1. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
3. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
4. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Erythromycin and other macrolides: focus on interactions. *Current Problems* 2006; **31:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/01/07)

Cimetidine. Cimetidine may increase plasma concentrations of erythromycin and deafness occurred in a patient taking both drugs.[1]

1. Mogford N, *et al.* Erythromycin deafness and cimetidine treatment. *BMJ* 1994; **309:** 1620.

Theophylline. Intravenous theophylline has been reported[1,2] to decrease serum concentrations of oral erythromycin although other studies[3,4] using intravenous or oral theophylline with intravenous erythromycin did not show any significant pharmacokinetic changes.

For reference to the effects of erythromycin on theophylline, see Macrolides, under Interactions of Theophylline, p.1143.

1. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
2. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
3. Hildebrandt R, *et al.* Influence of theophylline on the renal clearance of erythromycin. *Int J Clin Pharmacol Ther Toxicol* 1987; **25:** 601–4.
4. Pasic J, *et al.* The interaction between chronic oral slow-release theophylline and single-dose intravenous erythromycin. *Xenobiotica* 1987; **17:** 493–7.

Antimicrobial Action

Erythromycin is a macrolide antibacterial with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent some Gram-negative bacteria, as well as other organisms including some *Mycoplasma* spp., Chlamydiaceae, *Rickettsia* spp., and spirochaetes.

Mechanism of action. Erythromycin and other macrolides bind reversibly to the 50S subunit of the ribosome, resulting in blockage of the transpeptidation or translocation reactions, inhibition of protein synthesis, and hence inhibition of cell growth. Its action is mainly bacteriostatic, but high concentrations are slowly bactericidal against the more sensitive strains. Because macrolides penetrate readily into white blood cells and macrophages there has been some interest in their potential synergy with host defence mechanisms *in vivo*. The actions of erythromycin are increased at moderately alkaline pH (up to about 8.5), particularly in Gram-negative species, probably because of the improved cellular penetration of the nonionised form of the drug.

Spectrum of activity. Erythromycin has a broad spectrum of activity. The following pathogenic organisms are usually sensitive to erythromycin (but see also Resistance, below).

Gram-positive cocci, particularly streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* are sensitive. However, resistance has been increasingly reported in both organisms, particularly in penicillin-resistant *Str. pneumoniae*. Most strains of *Staphylococcus aureus* remain susceptible, although resistance can emerge rapidly, and some enterococcal strains are also susceptible.

Many other Gram-positive organisms respond to erythromycin, including *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, and *Listeria monocytogenes*. Anaerobic *Clostridium* spp. are also usually susceptible, as is *Propionibacterium acnes. Nocardia* spp. vary in their susceptibility.

Gram-negative cocci including *Neisseria meningitidis* and *N. gonorrhoeae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are usually sensitive.

Other Gram-negative organisms vary in their susceptibility, but *Bordetella* spp., some *Brucella* strains, and *Flavobacterium* and *Legionella* spp. are usually susceptible. *Haemophilus ducreyi* is reportedly susceptible, but *H. influenzae* is somewhat less so. The Enterobacteriaceae are usually resistant, although some strains may respond at alkaline pH. *Helicobacter pylori* and most strains of *Campylobacter jejuni* are sensitive (about 1% of the latter are reported to be resistant in the USA).

Among the Gram-negative anaerobes most strains of *Bacteroides fragilis* and many *Fusobacterium* strains are resistant.

Other organisms usually sensitive to erythromycin include *Actinomyces*, Chlamydiaceae, rickettsias, spirochaetes such as *Treponema pallidum* and *Borrelia burgdorferi*, some mycoplasmas (notably *Mycoplasma pneumoniae*), and some of the opportunistic mycobacteria: *Mycobacterium scrofulaceum* and *M. kansasii* are usually susceptible, but *M. intracellulare* is often resistant and *M. fortuitum* usually so.

Fungi, yeasts, and viruses are not susceptible to erythromycin.

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility of an antagonistic effect if erythromycin is given with a bactericide exists, and some antagonism has been shown *in vitro* between erythromycin and various penicillins and cephalosporins or gentamicin. However, in practice the results of such concurrent use are complex, and depend on the organism; in some cases synergy has been seen. For example, in the UK, the *BNF* recommends the use of amoxicillin with erythromycin or another macrolide such as azithromycin or clarithromycin for the treatment of uncomplicated community-acquired pneumonia if atypical organisms are suspected. Because of the adjacency of their binding sites on the ribosome, erythromycin may competitively inhibit the effects of chloramphenicol or lincosamides such as clindamycin or lincomycin.

Resistance. Several mechanisms of acquired resistance to erythromycin have been reported of which the most common is a plasmid-mediated ability to methylate ribosomal RNA, resulting in decreased binding of the antimicrobial drug. This can result in cross-resistance between erythromycin, other macrolides, lincosamides, and streptogramin B, because they share a common binding site on the ribosome and this pattern of resistance is referred to as the MLS_B phenotype. It is seen in staphylococci, and to a somewhat lesser extent in streptococci, as well as in a variety of other species including *B. fragilis*, *Clostridium perfringens*, *Corynebacterium diphtheriae*, and *Listeria* and *Legionella* spp.

Decreased binding of antimicrobial to the ribosome may also occur as a result of a chromosomal mutation, resulting in an alteration of the ribosomal proteins in the 50S subunit, which conveys one-step high-level erythromycin resistance. This form of resistance has been found in some strains of *Str. pneumoniae*, *H. pylori*, *M. pneumoniae*, *Escherichia coli*, *Str. pyogenes*, *Staph. aureus, and Campylobacter* spp.

Other forms of erythromycin resistance may be due to the production of a plasmid-determined erythromycin esterase that can inactivate the drug, or to decreased drug penetration. The latter may be partly responsible for the intrinsic resistance of Gram-negative bacteria like the Enterobacteriaceae, but has also been shown to be acquired as a plasmid-mediated determinant in some organisms; production of a protein which increases drug efflux from the cell is thought to explain the M phenotype resistance, in which organisms are resistant to 14-and 15-carbon ring macrolides, but retain sensitivity to 16-carbon ring macrolides, lincosamides, and streptogramins.

The incidence of resistance varies greatly with the area and the organism concerned and, although the emergence of resistance is rarely a problem in the short-term treatment of infection, it is quite common in conditions requiring prolonged treatment such as endocarditis due to *Staph. aureus.* The incidence of resistance in streptococci is generally lower than in *Staph. aureus* but shows geographical variation and may be increasing in some countries, including the UK. In addition, localised outbreaks of resistant strains may occur and produce a much higher incidence of resistance.

Antipseudomonal activity. Although macrolides have limited direct antibacterial activity against *Pseudomonas aeruginosa*, prolonged exposure at sub-MICs has produced antipseudomonal effects *in vitro*[1-3] and synergy has been shown with other antipseudomonals.[4] Erythromycin and clarithromycin appear to have the greatest activity. This action has been partly attributed to the ability of macrolides to reduce the protective biofilm produced by some strains of *P. aeruginosa*.[3,5] Other proposed mechanisms of action include modification of the inflammatory response to infection and direct inhibition of other virulence factors such as twitching motility.[3]

1. Tateda K, *et al.* Effects of sub-MICs of erythromycin and other macrolide antibiotics on serum sensitivity of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1993; **37:** 675–80.
2. Tateda K, *et al.* Direct evidence of antipseudomonal activity of macrolides: exposure-dependent bactericidal activity and inhibition of protein synthesis by erythromycin, clarithromycin, and azithromycin. *Antimicrob Agents Chemother* 1996; **40:** 2271–5.
3. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on Pseudomonas aeruginosa. *Chest* 2004; **125** (suppl 2): 62S–69S.
4. Bui KQ, *et al.* In vitro and in vivo influence of adjunct clarithromycin on the treatment of mucoid Pseudomonas aeruginosa. *J Antimicrob Chemother* 2000; **45:** 57–62.
5. Yasuda H, *et al.* Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. *Antimicrob Agents Chemother* 1993; **37:** 1749–55.

Resistance. A meta-analysis[1] found that reported macrolide resistance in *Streptococcus pneumoniae* varied greatly from country to country. The percentage of erythromycin-resistant *Str. pneumoniae* in the USA (20.7%) was less than that in Europe (32.0%) although this difference was not considered statistically significant, and higher levels of resistance were found in Asia (57.3%). In Europe, *Str. pyogenes* showed greater resistance to erythromycin (36.8%) than *Str. pneumoniae*. However, across all regions, the mean resistance of *Str. pneumoniae* was statistically equivalent (30.4%) and also similar to that of *Str. pyogenes* (30.0%).

1. Halpern MT, *et al.* Meta-analysis of bacterial resistance to macrolides. *J Antimicrob Chemother* 2005; **55:** 748–57.

Pharmacokinetics

Erythromycin base is unstable in gastric acid, and absorption is therefore variable and unreliable. Consequently, the base is usually given in film- or enteric-coated preparations, or one of the more acid-stable salts or esters is used. Food may reduce absorption of the base or the stearate, although this depends to some extent on the formulation; the esters are generally more reliably and quickly absorbed and their absorption is little affected by food, so that the timing of doses in relation to food intake is unimportant.

Peak plasma concentrations generally occur between 1 and 4 hours after a dose and have been reported to range from about 0.3 to 1.0 micrograms/mL after 250 mg of erythromycin base, and from 0.3 to 1.9 micrograms/mL after 500 mg. Similar concentrations have been seen after equivalent doses of the stearate. Somewhat higher peak concentrations may be achieved on repeated use 4 times daily. Higher total concentrations are achieved after oral doses of the estolate or ethyl succinate, but only about 20 to 30% of estolate or 55% of ethyl succinate is present as the active base, the rest being present as the inactive ester (in the case of the estolate as the propionate). Peak concentrations of about 500 nanograms/mL of erythromycin base have been reported after 250 mg of the estolate or 500 mg of the ethyl succinate. A peak of 3 to 4 micrograms/mL can be achieved after 200 mg of gluceptate or lactobionate intravenously.

Erythromycin is widely distributed throughout body tissues and fluids, although it does not cross the blood-brain barrier well and concentrations in CSF are low. Relatively high concentrations are found in the liver and spleen, and some is taken up into polymorphonuclear lymphocytes and macrophages. Around 70 to 75% of the base is protein bound, but after doses as the estolate the propionate ester is stated to be about 95% protein bound. Erythromycin crosses the placenta: fetal plasma concentrations are variously stated to be 5 to 20% of those in the mother. It is distributed into breast milk.

Erythromycin is excreted in high concentrations in the bile and undergoes intestinal reabsorption. About 2 to 5% of an oral dose is excreted unchanged in the urine and as much as 12 to 15% of an intravenous dose may be excreted unchanged by the urinary route. Erythromycin is partly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 via *N*-demethylation to inactive, unidentified metabolites. The half-life of erythromycin is usually reported to be about 1.5 to 2.5 hours, although this may be slightly longer in patients with renal impairment and has been reported to be between 4 to 7 hours in severe impairment.

Erythromycin is not removed by haemodialysis or peritoneal dialysis.

Uses and Administration

Erythromycin is a macrolide antibacterial with a wide spectrum of activity, that has been used in the treatment of a wide range of infections caused by susceptible organisms.

Its uses have included the treatment of severe campylobacter enteritis, chancroid, diphtheria, legionnaires' disease and other *Legionella* infections, neonatal conjunctivitis, pertussis, respiratory-tract infections including bronchitis, pneumonia (mycoplasmal and other atypical pneumonias as well as streptococcal), and sinusitis, and trench fever, and, combined with neomycin, for the prophylaxis of surgical infection in patients undergoing bowel surgery. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. It is also used in the prevention of diphtheria in non-immune patients and of pertussis in non- or partially immune patients.

Erythromycin is used as an alternative to penicillin in penicillin-allergic patients with various conditions including actinomycosis, leptospirosis, listeriosis, mouth infections, otitis media (usually with a sulfonamide such as sulfafurazole), pelvic inflammatory disease caused by *Neisseria gonorrhoeae*, pharyngitis, and staphylococcal and streptococcal skin infections. It has been used in the treatment of penicillin-allergic patients with syphilis, but there are doubts about its efficacy. It is also used in the prevention of perinatal or Group A streptococcal infections, rheumatic fever, and infections in splenectomised patients. In penicillin-allergic patients in the early stages of Lyme disease, erythromycin may be used as an alternative to a tetracycline; this use is generally restricted to pregnant women and young children, since it is less effective than other drugs. It is also used as an alternative to the tetracyclines in patients with cholera, *Chlamydia* or *Chlamydophila* infections (such as epididymitis, lymphogranuloma venereum, nongonococcal urethritis, pneumonia, psittacosis, and trachoma), Q fever, and spotted fevers.

For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Both oral and topical erythromycin may be used in acne (see Skin Disorders, below) and rosacea (p.1583).

Administration and dosage. Erythromycin may be given as the base or its salts or esters; doses are expressed in terms of the base. Each 1 g of erythromycin is equivalent to about the following amounts of each salt or ester:

- erythromycin estolate 1.44 g
- erythromycin ethyl succinate 1.17 g
- erythromycin gluceptate 1.31 g
- erythromycin lactobionate 1.49 g
- erythromycin propionate 1.08 g
- erythromycin stearate 1.39 g

The usual oral adult dose is the equivalent of erythromycin 1 to 2 g daily in 2 to 4 divided doses; for severe infections this may be increased to up to 4 g daily in divided doses. Daily doses higher than 1 g should be given in more than 2 divided doses.

For the prevention of streptococcal infections in patients with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNF* recommends a dose of 500 mg twice daily.

In patients who are unable to take erythromycin orally and in those who are severely ill, in whom it is necessary to attain an immediate high blood concentration, erythromycin may be given intravenously as the lactobionate, in doses equivalent to those given orally. The gluceptate has also been used intravenously. To reduce the risk of venous irritation it should be given only by continuous or intermittent intravenous infusion of a solution containing not more than 0.5% of erythromycin. Intermittent infusions should be given every 6 hours over 20 to 60 minutes.

Doses may need to be limited in patients with renal impairment (see below).

For details of doses in children, including infants and adolescents, see below.

Other routes. Erythromycin was formerly given by intramuscular injection, but such injections are painful and are no longer generally recommended. Erythromycin is used as a 0.5% eye ointment for the treatment of superficial ocular infections, including neonatal conjunctivitis, caused by susceptible strains of bacteria and for the prophylaxis of neonatal conjunctivitis caused by *N. gonorrhoeae* or *C. trachomatis*. It may also be applied topically as a 2 to 4% gel or solution for the treatment of acne vulgaris and is also available in combination preparations with benzoyl peroxide, ichthammol, isotretinoin, tretinoin, and zinc acetate.

Propionyl erythromycin mercaptosuccinate has also been used. Erythromycin thiocyanate and erythromycin phosphate are used in veterinary medicine.

◊ Reviews.

1. Zhanel GG, *et al.* Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 2001; **61:** 443–98.

Administration. A discussion of the significance of different formulations and salts used for oral preparations of erythromycin concluded that there was no clear evidence that any was superior in terms of clinical effect.[1]

1. Anonymous. Giving erythromycin by mouth. *Drug Ther Bull* 1995; **33:** 77–9.

Administration in children. The usual dose for infants and children is the equivalent of about 30 to 50 mg/kg of erythromycin daily in 2 to 4 divided doses although it may be doubled in severe infections. Based on age, the usual dose in children 2 to 8 years old is 1 g daily and in infants and children up to 2 years old 500 mg daily. Those over 8 years of age may be given the usual adult dose (see above).

For the prevention of streptococcal infections in children with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given. The *BNFC* suggests a dose of 125 mg twice daily in those aged 1 month to 2 years. In addition, similar doses have been suggested for prophylaxis against pneumococcal infections.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNFC* recommends a dose of 500 mg twice daily in those over 12 years of age. It also suggests a dose of 250 mg daily in 1 or 2 divided doses for infants with acne.

Although unlicensed in the UK for use in gastrointestinal stasis, the *BNFC* suggests a dose of 3 mg/kg given 4 times daily for infants and children up to 18 years of age (see also below).

Administration in renal impairment. A maximum dose of erythromycin 1.5 g daily has been suggested by the *BNF* for adult patients with severe renal impairment.

Decreased gastrointestinal motility. Erythromycin stimulates gut motility, apparently by acting as a motilin receptor agonist, although it has been suggested that it may have other actions as well.[1] It has been tried, with some success, for its prokinetic action in a small number of patients with decreased gastrointestinal motility (p.1694) including those with functional dyspepsia,[2] gastroparesis,[3] reflux ileus,[4] acute colonic pseudo-obstruction (Ogilvie's syndrome),[4,5] delayed gastric emptying after pancreatic-duodenal surgery,[6] and neonatal postoperative intestinal dysmotility.[7] It has also been used to increase gastrointestinal motility in critically ill, mechanically ventilated patients[8,9] and in preterm very low birth-weight infants.[10,11] However, the prophylactic or routine use of erythromycin in such circumstances has been cautioned against,[9,10] and a systematic review[12] of neonatal use also suggested that erythromycin should be reserved for a very small subset of high-risk preterm neonates with persistent or severe feed intolerance. Adverse effects associated with the long-term use of erythromycin that is necessary in, for example, diabetic gastroparesis, may also be problematic.[13]

For suggested doses in the treatment of children with gastrointestinal stasis, see Administration in Children, above.

1. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut* 1992; **33:** 397–401.
2. Arts J, *et al.* Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54:** 455–60.
3. Maganti K, *et al.* Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003; **98:** 259–63.
4. Armstrong DN, *et al.* Erythromycin for reflux ileus in Ogilvie's syndrome. *Lancet* 1991; **337:** 378.
5. Bonacini M, *et al.* Erythromycin as therapy for acute colonic pseudo-obstruction (Ogilvie's syndrome). *J Clin Gastroenterol* 1991; **13:** 475–6.
6. Yeo CJ, *et al.* Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: a prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; **218:** 229–38.
7. Simkiss DE, *et al.* Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 1994; **71:** F128–9.
8. Chapman MJ, *et al.* Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med* 2000; **28:** 2334–7.
9. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother* 2007; **59:** 347–58.
10. Ng PC, *et al.* Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F177–F182.
11. Nuntnarumit P, *et al.* Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006; **148:** 600–605.
12. Patole S, *et al.* Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F301–F306.
13. Tanis AA, *et al.* Side-effects of oral erythromycin for treatment of diabetic gastroparesis. *Lancet* 1993; **342:** 1431.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that the 14-membered ring macrolides (such as clarithromycin, erythromycin, and roxithromycin) and the 15-membered ring macrolides (such as azithromycin) also have immunomodulatory and anti-inflammatory effects that could be useful in the management of respiratory diseases including asthma (p.1108), chronic obstructive pulmonary disease (p.1112), cystic fibrosis (p.166), diffuse panbronchiolitis, and sinusitis (p.193).[1-3] However, a systematic review[4] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further trials were warranted. A systematic review[5] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear and further studies were needed. A randomised, double-blind, placebo-controlled study[6] to evaluate the use of oral azithromycin given three times a week for 12 months for the treatment of cystic fibrosis in children, reported a significant reduction in the number of pulmonary exacerbations needing treatment with antibacterials, even in the absence of infection with *Pseudomonas aeruginosa*. Azithromycin has also been investigated[7-9] in the management of bronchiolitis obliterans in patients who have undergone lung transplantation (p.1815), although its role has yet to be defined.

1. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. *Chest* 2004; **125** (suppl 2): 52S–61S.
2. Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; **125** (suppl 2): 70S–78S.
3. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; **54:** 21–8.
4. Richeldi L, *et al.* Macrolides for chronic asthma. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/03/07).
5. Southern KW, *et al.* Macrolide antibiotics for cystic fibrosis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 02/03/07).
6. Clement A, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006; **61:** 895–902.
7. Gottlieb J, *et al.* Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2008; **85:** 36–41.
8. Porhownik NR, *et al.* Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. *Can Respir J* 2008; **15:** 199–202.
9. Fietta AM, Meloni F. Lung transplantation: the role of azithromycin in the management of patients with bronchiolitis obliterans syndrome. *Curr Med Chem* 2008; **15:** 716–23.

Skin disorders. *ACNE.* Erythromycin may be used topically or orally in the treatment of acne (p.1577). Topical erythromycin may be used for mild inflammatory acne if benzoyl peroxide is ineffective or poorly tolerated. It is also used as adjunctive treatment in more severe acne. Erythromycin is also available as a complex with zinc acetate that has been reported to be more effective than topical erythromycin alone[1] or oral minocycline.[2] However, development of antibiotic resistance by the skin flora is an increasing problem. Combination therapy with benzoyl peroxide and erythromycin has been reported to be helpful in preventing the selection of antibiotic-resistant mutants[3,4] and to be more effective than topical clindamycin alone.[5] Alternatively, short intervening courses of benzoyl peroxide during antibacterial therapy may help to eliminate any resistant bacteria that have been selected.[6] It has also been recommended that courses of topical antibiotics be continued for no longer than necessary (although treatment should be used for at least 6 months), that the same drug be used if further treatment is required, and that treatment with different oral and topical antibiotics or antibiotic rotation be avoided.[6]

Oral erythromycin may be used as an alternative to a tetracycline in moderate acne. However, resistance to erythromycin is increasing so it may be best reserved for those patients in whom other antibacterials are unsuitable.

1. Habbema L, *et al.* A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. *Br J Dermatol* 1989; **121:** 497–502.
2. Stainforth J, *et al.* A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. *J Dermatol Treat* 1993; **4:** 119–22.
3. Eady EA, *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131:** 331–6.
4. Eady EA, *et al.* The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; **134:** 107–13.
5. Packman AM, *et al.* Treatment of acne vulgaris: combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. *Int J Dermatol* 1996; **35:** 209–11.
6. Eady EA, *et al.* Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *BMJ* 1993; **306:** 555–6.

Preparations

BP 2008: Erythromycin and Zinc Acetate Lotion; Erythromycin Estolate Capsules; Erythromycin Ethyl Succinate Oral Suspension; Erythromycin Ethyl Succinate Tablets; Erythromycin Lactobionate Intravenous Infusion; Erythromycin Stearate Tablets; Gastro-resistant Erythromycin Tablets;

USP 31: Erythromycin and Benzoyl Peroxide Topical Gel; Erythromycin Delayed-release Capsules; Erythromycin Delayed-release Tablets; Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Estolate Capsules; Erythromycin Estolate for Oral Suspension; Erythromycin Estolate Oral Suspension; Erythromycin Estolate Tablets; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Erythromycin Ethylsuccinate for Oral Suspension; Erythromycin Ethylsuccinate Injection; Erythromycin Ethylsuccinate Oral Suspension; Erythromycin Ethylsuccinate Tablets; Erythromycin Lactobionate for Injection; Erythromycin Ointment; Erythromycin Ophthalmic Ointment; Erythromycin Pledgets; Erythromycin Stearate Tablets; Erythromycin Tablets; Erythromycin Topical Gel; Erythromycin Topical Solution; Sterile Erythromycin Ethylsuccinate; Sterile Erythromycin Gluceptate; Sterile Erythromycin Lactobionate.

Proprietary Preparations (details are given in Part 3)

Arg.: Algiderm; Ambamida; Atlamicin; Clarex; Eri; Erigrand; Erisine; Erisol; Erit; Eritroderm; Eritrofarm; Eritromed; Eryacne; Eryfluid; Etisux; Ilosone†; Iloticina†; Ingelets; Kitacne; Lederpax†; Oftalmolets; Pantomicina; Pentoclave; Stiemycin; Toperit; Trixne; Wemid; ***Austral.:*** E-Mycin; EES; Eryacne; Eryc; Eryhexal; Erythrocin; ***Austria:*** Akne Cordes; Aknemycin; Eryaknen; Erybesan; Eryhexal; Erystad; Erythrocin; Meromycin; Stiemycine; ***Belg.:*** Acneryne; Aknemycin; Eryderm†; Erythrocine; Erythroforte; Inderm; Stimycine; ***Braz.:*** Amplobid†; Eribiotic; Eriflogin†; Erimicina†; Eripan†; Eritax†; Eritrax†; Eritrex; Eritril†; Eritrin†; Eritrovit†; Eryacnen; Ilocin†; Ilosone; Kanazima; Lisotran†; Lisotrex†; Ortociclina†; Pantomicina; Rubromicin†; Siftrex†; Stiemycin; Valmicin; ***Canad.:*** Apo-Erythro; Diomycin†; EES; Erybid; Eryc; Erysol; Erythrocin†; Novo-Rythro; PCE; Staticin†; T-Stat†; ***Chile:*** Cinactiv; Eryacnen; Erypark; Gelerit; Labocne; Mercina; Pantomicina; ***Cz.:*** Aknefug-EL; Aknemycin; Emu-V†; Eryfluid; Erythrocin; Erythroskid†; Meromycin†; Monomycin†; ***Denm.:*** Abboticin; Erycin; Escumycin; Hexabotin; ***Fin.:*** Abboticin; Ermysin; ***Fr.:*** Abboticine; Egery; Ery; Eryacne; Eryfluid; Erythrocine; Erythrogel; Erythrogram†; Stimycine; ***Ger.:*** Akne Cordes†; Aknederm Ery; Aknefug-EL; Aknemycin; Ery; Ery-Diolan; Eryaknen; Erybeta; Erycinum; Erydermec; Eryhexal; Erysec; Erythro; Erythro-Hefa†; Erythrocin; Erythrogenat†; Hydrodermed; Inderm; InfectoMycin; Karex†; Monomycin†; Paediathrocin; Sanasepton; Stiemycine; ***Gr.:*** Acne Hermal; Dankit; Eryacne; Erycream†; Erygel; Erythrocin; Erythrogel†; Roug-Mycin†; ***Hong Kong:*** Aknemycin; Apo-Erythro; E-Mycin†; EES; Eryacne†; Erythro; Erythrocin; PCE†; Porphyrocin†; Stiemycin; ***Hung.:*** Aknefug-EL; Aknemycin; Eryc; Erythrotrop; Meromycin; ***India:*** Acnesol; Althrocin; Calthrox; E-Mycin; Eltocin; Erycin; Erycip; Erysafe; Erythrocin; Okamycin; ***Indon.:*** Cetathrocin; Corsatrocin; Duramycin; EES; Erphathrocin; Erycoat; Eryderm; Erymed; Erysanbe; Erythrin; Erythrocin; Jeracin; Opithrocin; Pharothrocin; ***Irl.:*** Erymax; Erythrocin; Erythroped; Primacine; Stiemycin; ***Israel:*** Acnetrim; Eryc†; Eryderm†; Erythro-Teva; Erythrocin; Erythroped†; ***Ital.:*** Eritrocina; Eryacne; Erytrociclin†; Lauromicina; ***Malaysia:*** Aknemycin; EES; Erogran†; Erotab†; Erycin; Eryderm; Eryped; Eryson; Erythrocin; Etrogran†; Etrotab†; Oftalmolosa Cusi; Sethro†; Stiemycin; ***Mex.:*** Apo-Trina; Benitrom; Bestocin; Biotril; Colitromin†; E-Trocima-P†; Eribec; Eriber; Erisuspen; Eritrerba†; Eritrofarmin†; Eritrolat; Eritropharma; Eritroquim†; Eritrosol; Eritrovier; Eritrowel; Eryacnen; Eryderm; Erylar; Examycin†; Iliocin; Ilosin; Ilosone; Iqfamicina; Latotryd; Lauricin; Laurimicina; Lauritran; Lederpax†; Optomicin; Pantomicina; Procephal; Promicin; Quimolauril; Sansacne; Stiemycin; T-Stat; Tropharma; Verytracin†; Witromin; ***Neth.:*** Aknemycin; Eryacne; Eryc†; Eryderm; Erythrocine; Erytrolyve; Inderm; Stiemycin; ***Norw.:*** Abboticin; Ery-Max; ***NZ:*** E-Mycin; EES; Era; Eryacne; Erythrocin; Stiemycin; ***Philipp.:*** Aldricin; Ery-Max; Erycar; Erythrocin; Fildrocin; Ilosone; Romaxin; Sansacne; Stiemycin; Upperzin; ***Pol.:*** Aknemycin; ***Port.:*** Akne-Mycin; Clinac; Eritina†; Eritrazon; Eritrocina; Eryc†; Eryfluid; ESE; ***S.Afr.:*** Acu-Erylate S; Betamycin; Emsyn†; Eromel†; Erycette; Eryderm; Erymycin; Erystat; Erythrocin; Erythroped†; Estomycin; Ilosone; Ilotycin TS; Purmycin; Rubimycin; Spectrasone; Stiemycin; Xeramel; ***Singapore:*** Aknemycin; EES; Ermycin†; Erotab; Eryacne; Eryderm; Eryped; Erysol†; Eryson; Erythrocin†; Ranthrocin; Stiemycin; T-Stat†; ***Spain:*** Bronsema; Deripil; Eridosis; Eritrogobens; Eritroveinte; Euskin; Lagarmicin; Lederpax; Loderm; Neo Iloticina†; Pantodrin†; Pantomicina; ***Swed.:*** Abboticin; Ery-Max; ***Switz.:*** Aknemycin; Aknilox; Erios; Eryaknen; Eryderm; Erythrocine; Inderm†; Karex†; Stiemycine†; ***Thai.:*** Elocin†; Erathrom; Ericin; Erimit; Erimycin; Ery-Tab; Eryacne; Erycin; Erycon; Erymin; Erysil; Eryth-mycin; Erythrocin; Etrola; Etrolate; Ilosone; Malocin; Pocin†; Redrocin; Rythocin; Servitrocin; Stacin; Stiemycin; Tomcin; ***Turk.:*** Aknilox; Erimicin; Eritro; Eritrosif; Eryacne; Erythrocin; ***UAE:*** Eromycin; ***UK:*** Erymax; Erythrocin; Erythroped; Rommix†; Stiemycin; Tiloryth; ***USA:*** Akne-Mycin; ATS; Del-Mycin; E-Base; E-Mycin; EES; Emgel†; Eramycin; Ery-Tab; Eryc†; Erycette; Eryderm; Erygel; Erymax†; Eryped; Erythrocin; Ilosone†; Ilotycin†; PCE; Robimycin Robitabs; Staticin†; T-Stat†; Theramycin Z†; ***Venez.:*** Eritimix†; Eritroped†; Eritrovac†; Eryacne; Ilosone; Iloticina†; Inderm; Laurimicina†; Leda-Rix; Pantomicina; Yisadin.

Multi-ingredient: ***Arg.:*** Acneout; Acnepas E; Benzamycin†; Clarex Compuesto; Ecnagel E; Erimicin; Eristin; Eritrobron; Kitacne AR†; Kitacne PB†; Pantomucol†; Pediazole†; Pentoclave Combi; Peroximicina; Stievamycin; Tratacne; Zineryt; ***Austria:*** Aknemycin compositum; Isotrexin; ***Belg.:*** Benzamycin; Zineryt; ***Braz.:*** Benzac Eritromicina†; Eritrex A; Isotrexin; ***Canad.:*** Benzamycin; Pediazole; Sans-Acne†; Stievamycin; ***Chile:*** Abboderm†; Benzac Plus; Benzamycin†; Bioquin; Dermodan Plus; Erimicin; Erylik; Pediazole†; Stievamycin; ***Cz.:*** Aknemycin Plus; Isotrexin; Zineryt; ***Fr.:*** Antibiotrex; Erylik; Pediazole; ***Ger.:*** Aknemycin; Aknemycin Plus; Clinesfar†; Ecolicin; Isotrexin; Synergomycin†; Zineryt; ***Gr.:*** Benzamycin†; Pediazole; ***Hong Kong:*** Benzamycin; Dermabaz†; Erylik; Pediazole†; ***Hung.:*** Isotrexin; Zineryt; ***Irl.:*** Benzamycin; Isotrexin; Zineryt; ***Israel:*** Aknemycin; Aknemycin Plus; Benzamycin; Pediazole; ***Ital.:*** Isotrexin; Lauromicina; Rubrociclina†; Zineryt; ***Malaysia:*** Aknemycin Plus; ***Mex.:*** Benzac Plus; Benzamycin; Bisolvon E; Eriwest; Pantobron; Pediazole; Quimobrom; Stievamycin; ***Neth.:*** Zineryt; ***NZ:*** Antibiotic Simplex; ***Philipp.:*** Elicocin; ***Pol.:*** Aknemycin Plus; Isotrexin; Zineryt; ***Port.:*** Isotrexin; Zineryt; ***Rus.:*** Zineryt (Зинерит); ***S.Afr.:*** Benzamycine†; Zineryt; ***Singapore:*** Aknemycin Plus; Benzamycin; Isotrexin; ***Spain:*** Bronsema Expectorante; Isotrex Eritromicina; Loderm Retinoico; Tosdiazina†; Zineryt; ***Switz.:*** Aknemycin; ***Thai.:*** Isotrexin; ***Turk.:*** Benzamycin; ***UK:*** Aknemycin Plus; Benzamycin†; Isotrexin; Zineryt; ***USA:*** Benzamycin; Eryzole†; Pediazole; ***Venez.:*** Pediazole†.

Ethambutol Hydrochloride

(BANM, USAN, rINNM)

CL-40881; Etambutol Hidroklorür; Etambutol-hidroklorid; Etambutolhydroklorid; Etambutolihydrokloridi; Etambutolio hidrochloridas; Etambutolu chlorowodorek; Éthambutol, chlorhydrate d'; Ethambutol-dihydrochlorid; Ethambutoli Dihydrochloridum; Ethambutoli hydrochloridum; Hidrocloruro de etambutol. (*S,S*)-*N,N′*-Ethylenebis(2-aminobutan-1-ol) dihydrochloride.

Этамбутола Гидрохлорид

$C_{10}H_{24}N_2O_2,2HCl$ = 277.2.

CAS — 74-55-5 (ethambutol); 1070-11-7 (ethambutol hydrochloride).

ATC — J04AK02.

ATC Vet — QJ04AK02.

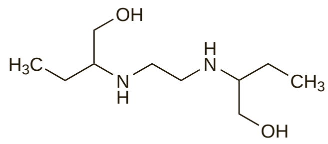

(ethambutol)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Ethambutol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. A 2% solution in water has a pH of 3.7 to 4.0. Store in airtight containers.

USP 31 (Ethambutol Hydrochloride). A white crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol; slightly soluble in chloroform and in ether.

Adverse Effects and Treatment

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness. One or both eyes may be affected. The degree of visual impairment appears to depend on the dose and duration of therapy; toxicity is observed most frequently at daily doses of 25 mg/kg or more and after at least 2 months of therapy. Recovery of vision usually takes place over a period of a few weeks or months, but in rare cases it may take up to a year or more or the effect may be permanent. Retinal haemorrhage has occurred rarely.

Renal clearance of urate may be reduced and acute gout has been precipitated rarely.

Hypersensitivity reactions including skin rashes, pruritus, leucopenia, fever, and joint pains have occurred but appear to be rare with ethambutol. Other adverse effects which have been reported include confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuropathy, thrombocytopenia, pulmonary infiltrates, eosinophilia, and gastrointestinal disturbances such as nausea, vomiting, anorexia, and abdominal pain.

Teratogenicity has been observed in *animals* (but see also Precautions, below).

Blood concentrations of ethambutol after overdosage may be reduced by haemodialysis or peritoneal dialysis.

Effects on the blood. Neutropenia has been reported in a patient on ethambutol, isoniazid, and rifampicin.[1] Each drug induced neutropenia individually on rechallenge. In another patient also receiving mixed antituberculous therapy, eosinophilia and neutropenia were associated with ethambutol; the effects recurred only on rechallenge with this drug.[2] Skin rash, blood eosinophilia, and pulmonary infiltrates occurred in a patient after 8 weeks of multidrug therapy for miliary tuberculosis. Rechallenge again attributed the adverse event to ethambutol.[3] Thrombocytopenia attributable to ethambutol has been reported in 2 patients.[4,5]

1. Jenkins PF, *et al*. Neutropenia with each standard antituberculosis drug in the same patients. *BMJ* 1980; **280:** 1069–70.
2. Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. *Chest* 1994; **106:** 1638–9.
3. Wong PC, *et al.* Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. *Eur Respir J* 1995; **8:** 866–8.
4. Rabinovitz M, *et al.* Ethambutol-induced thrombocytopenia. *Chest* 1982; **81:** 765–6.
5. Prasad R, Mukerji PK. Ethambutol-induced thrombocytopaenia. *Tubercle* 1989; **70:** 211–12.

Effects on the CNS. A 40-year-old man with advanced HIV infection taking oral ethambutol for *Mycobacterium avium* complex infection had rapid cognitive decline, hallucinations, and delusions within 2 weeks of starting ethambutol treatment; symptoms resolved on stopping treatment.[1]

1. Martin SJ, Bowden FJ. Ethambutol toxicity manifesting as acute onset psychosis. *Int J STD AIDS* 2007; **18:** 287–8.

Effects on the eyes. A review[1] on the ocular toxicity of ethambutol reported that when ethambutol is taken for more than 2 months the incidence of retrobulbar neuritis is about 18% in patients receiving a daily dose of more than 35 mg/kg, reducing to 5 to 6% with a daily dose of 25 mg/kg, and less than 1% with a daily dose of 15 mg/kg. An earlier study reported ophthalmic effects in 10 of 2184 patients receiving ethambutol in doses of 25 mg/kg or less daily, although few of the 10 patients complained of symptoms.[2] In 9 of the 10 patients, ocular changes occurred after the second month of treatment. In the 928 patients who only received 2 months of ethambutol therapy, ocular toxicity was not reported. A prospective study[3] of 229 patients taking ethambutol for *Mycobacterium avium* complex lung disease reported that ocular toxicity was more common in patients given daily doses rather than intermittent (3 times a week) therapy.

While short-term use of ethambutol is usually safe, deterioration of vision leading to long-term blindness has been reported after only a few doses of ethambutol;[4] it was suspected that this was an idiosyncratic reaction. Rapid onset reversible ocular toxicity has also occurred.[5]

Visual defects occurring with ethambutol generally resolve when the drug is stopped.

1. Chan RYC, Kwok AKH. Ocular toxicity of ethambutol. *Hong Kong Med J* 2006; **12:** 56–60.
2. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax* 1986; **41:** 737–9.
3. Griffith DE, *et al*. Ethambutol ocular toxicity in treatment regimens for Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2005; **172:** 250–3.
4. Karnik AM, *et al.* A case of ocular toxicity to ethambutol—an idiosyncratic reaction? *Postgrad Med J* 1985; **61:** 811–13.
5. Schild HS, Fox BC. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med* 1991; **90:** 404–6.

Effects on the kidneys. Interstitial nephritis has been reported[1,2] in 5 patients receiving ethambutol and isoniazid; 3 were also receiving additional antimycobacterials. In another patient, acute renal failure occurred secondary to interstitial nephritis which was thought to have been induced by ethambutol.[3]

1. Collier J, *et al*. Two cases of ethambutol nephrotoxicity. *BMJ* 1976; **2:** 1105–6.
2. Stone WJ, *et al.* Acute diffuse interstitial nephritis related to chemotherapy of tuberculosis. *Antimicrob Agents Chemother* 1976; **10:** 164–72.
3. García-Martín F, *et al.* Acute interstitial nephritis induced by ethambutol. *Nephron* 1991; **59:** 679–80.

Effects on the liver. Although transient abnormalities in liver function commonly occur during the early stages of antituberculosis treatment, drugs other than ethambutol are generally considered responsible. Ethambutol has generated fewer reports of hepatotoxicity to the UK CSM than rifampicin, isoniazid, or pyrazinamide,[1] and the use of regimens containing ethambutol has been recommended for patients unable to tolerate standard regimens due to hepatotoxicity.[1-3]

1. Ormerod LP, *et al.* Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51:** 111–13.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005: **53:** 1203. [dose]

Effects on the skin. Toxic epidermal necrolysis[1] and lichenoid[2] and erythema multiforme-type drug eruptions[3] have been associated with the use of ethambutol. Delayed hypersensitivity reactions have also been reported.[4] Licensed product information notes that Stevens-Johnson syndrome and dermatitis have also occurred.

1. Pegram PS, *et al*. Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med* 1981; **141:** 1677–8.
2. Grossman ME, *et al.* Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33:** 675–6.
3. Kurokawa I, *et al.* Erythema multiforme-type drug eruption due to ethambutol with eosinophilia and liver dysfunction. *Int J Antimicrob Agents* 2003; **21:** 596–7.
4. Bakkum RSLA, *et al.* Delayed-type hypersensitivity reaction to ethambutol and isoniazid. *Contact Dermatitis* 2002; **46:** 359.

Hyperuricaemia. In a controlled study of 71 patients receiving ethambutol 20 mg/kg daily orally with other antimycobacterials, serum-uric acid concentrations increased in 66, mainly in the first 2 weeks of treatment.[1] One patient experienced arthralgia and another acute gouty arthritis. Serum-uric acid concentrations did not change in 60 control patients receiving other antimycobacterials.

1. Khanna BK, Gupta VP. Ethambutol-induced hyperuricaemia. *Tubercle* 1984; **65:** 195–9.

Precautions

Ethambutol is generally contra-indicated in patients with optic neuritis. It should be used with great care in patients with visual defects, the elderly, and in children in whom evaluation of changes in visual acuity may be difficult (see also Children, below). Ocular examination is recommended before treatment with ethambutol and some consider that regular examinations are necessary during treatment, especially in children. Patients should be advised to report visual disturbances immediately and to stop ethambutol pending visual evaluation.

Ethambutol should be given in reduced dosage to patients with renal impairment and dosage adjustments may need to be made according to serum concentrations. The *BNF* recommends peak concentrations of 2 to 6 mg/L and trough concentrations of less than 1 mg/L.

Ethambutol may precipitate attacks of gout.

Although ethambutol crosses the placenta and may be teratogenic in *animals*, problems in humans have not been documented. It is generally considered that the benefits of ethambutol in the treatment of tuberculosis outweigh any potential risks in pregnancy.

Breast feeding. Ethambutol distributes into breast milk to produce concentrations similar to those in plasma. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving ethambutol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Children. Due to the possible difficulty of evaluating changes in visual acuity that may be induced in children receiving ethambutol, the *BNFC* advises that it should be used with caution in children under 5 years of age and unable to report visual changes accurately, whereas in the USA licensed product information has advised against use in those under 13 years of age.

The authors of a review of the use of ethambutol in children concluded that no extra precautions were necessary in children aged 5 years or more, and that it could also be used in younger children without undue fear of adverse effects.[1] Another review suggested that visual toxicity is not a particular problem except perhaps when CNS infection is involved.[2] A literature review[3] on the use of ethambutol in children reported almost no ocular toxicity at daily doses of 15 to 30 mg/kg. Ethambutol is therefore considered safe in children of all ages at a daily dose of 20 mg/kg (range 15 to 25 mg/kg) or a three times weekly dose of 30 mg/kg.

1. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tuberc Lung Dis* 1997; **1:** 12–15.
2. Graham SM, *et al.* Ethambutol in tuberculosis: time to reconsider? *Arch Dis Child* 1998; **78:** 274–8.
3. WHO. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf (accessed 03/10/07)

Antimicrobial Action

Ethambutol is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

Pharmacokinetics

About 80% of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Absorption is not significantly impaired by food (but see also Bioavailability, below). After a single dose of 25 mg/kg peak plasma concentrations of up to 5 mg/L appear within 4 hours, and are less than 1 mg/L by 24 hours.

Ethambutol is distributed to most tissues, including the lungs, kidneys, and erythrocytes. About 10 to 50% may diffuse into the CSF when the meninges are inflamed. It has been reported to cross the placenta and is distributed into breast milk. The elimination half-life after oral doses is about 3 to 4 hours.

Ethambutol is partially metabolised in the liver to the aldehyde and dicarboxylic acid derivatives which are inactive and then excreted in the urine. Most of a dose appears in the urine within 24 hours as unchanged drug and 8 to 15% as the inactive metabolites. About 20% of the dose is excreted unchanged in the faeces.

Bioavailability. Although the absorption of ethambutol is not generally regarded as being impaired by food, a study in 14 healthy subjects[1] suggested that giving it with a high-fat meal or an antacid could delay absorption and reduce the maximum plasma concentration.

1. Peloquin CA, *et al.* Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* 1999; **43:** 568–72.

HIV-infected patients. Malabsorption of ethambutol and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see under Rifampicin, p.328.

Pregnancy and breast feeding. Ethambutol crosses the placenta and is present in fetal tissue in amounts of at least 74.5% of the maternal serum concentration.[1] Ethambutol distributes into breast milk to produce concentrations similar to those in plasma.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.

Uses and Administration

Ethambutol is used with other antituberculous drugs in the primary treatment of pulmonary and extrapulmonary tuberculosis (p.196) to suppress emergence of resistance to the other drugs used in the regimens. It is also used as a component of regimens for the treatment of nontuberculous mycobacterial infections (p.181).

In the treatment of tuberculosis, ethambutol is given, as the hydrochloride, usually with isoniazid, rifampicin, and pyrazinamide in the initial 8-week phase and sometimes in the continuation phase. It is given orally in a single daily dose of 15 mg/kg, or 30 mg/kg three times weekly. Initial doses of ethambutol 25 mg/kg daily for 60 days may be given to patients who have previously had antimycobacterial therapy, reduced to 15 mg/kg daily thereafter.

For details of doses in infants, children, and adolescents, see below. If it is used in patients with renal impairment, doses should be adjusted according to serum concentrations (see Precautions, above).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing ethambutol with isoniazid, isoniazid and rifampicin, and isoniazid, rifampicin, and pyrazinamide are available in some countries.

Administration in children. For the treatment of *drug-resistant* tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests a dose of ethambutol 15 to 25 mg/kg daily or 50 mg/kg twice weekly (to a maximum of 2.5 g) by mouth.

For *congenitally acquired* tuberculosis in neonates the *BNFC* suggests a dose of 15 mg/kg once daily. For the treatment of children 1 month and older a dose of 15 mg/kg once daily or 30 mg/kg three times a week for the 2 month initial treatment phase is suggested.

See also Children, under Precautions above

Preparations

BP 2008: Ethambutol Tablets;
USP 31: Ethambutol Hydrochloride Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Myambutol; ***Austria:*** Etibi; Myambutol; ***Belg.:*** Myambutol; ***Canad.:*** Etibi; ***Cz.:*** Sural; ***Denm.:*** Myambutol; ***Fin.:*** Oributol; ***Fr.:*** Myambutol; ***Ger.:*** EMB; Myambutol; ***Gr.:*** Dexambutol; Myambutol; ***Hong Kong:*** EMB; Myambutol†; ***Hung.:*** Sural; ***India:*** Combutol; Myambutol; Mycobact; Mycobutol; Rifacom E-Z; Themibutol; Tibitol; ***Indon.:*** Arsitam; Bacbutol; Cetabutol; Corsabutol; ETH Ciba; Parabutol; Santibi; Tibigon; Tibitol; ***Ital.:*** Etapiam; Miambutol; ***Mex.:*** Apo-Probutol†; Dovalem; Myambutol†; Tambutec; ***Neth.:*** Myambutol; ***NZ:*** Myambutol; ***Philipp.:*** Danbutol; Odetol; ***Port.:*** Turresis; ***Rus.:*** Ebutol (Эбутол); Ethambusin (Этамбусин)†; Upbutol (Апбутол); ***S.Afr.:*** Purderal; ***Singapore:*** E-Butol; ***Spain:*** Myambutol; ***Swed.:*** Myambutol; ***Switz.:*** Myambutol; ***Thai.:*** Conbutol†; Etham; Ethbutol; Lambutol; Myambutol†; Myrin-P; Myrin†; Servambutol; Tobutol; ***Turk.:*** Miambutol; ***USA:*** Myambutol.

Multi-ingredient: ***Austria:*** Myambutol-INH; ***Denm.:*** Rimstar; ***Fin.:*** Rimstar; ***Ger.:*** EMB-INH†; Myambutol-INH; ***India:*** Akt-3; Akt-4; Bicox-E†; Combunex; Coxina-3; Coxina-4; Cx-4; Cx-5; Gocox-4†; Inabutol Forte; Myconex; RHZ-Plus; Rifa E; Wokex-3; Wokex-4; Xeed-3E; Xeed-4; ***Indon.:*** bacbutINH; Erabutol Plus; Meditam-6; Mycothambin-INH; Niazitol; Pulna; Rimstar; Santibi Plus; ***Ital.:*** Etanicozid B6; Miazide B6†; ***Mex.:*** Myambutol-INH†; ***Philipp.:*** 4D; Continukit; Continukit Plus; Econokit; Econokit-MDR; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Myrin; Myrin-P; Quadtab; Rimstar; Sthamizide; SVM-Polypac-A; Tres; Tritab; Viper; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Protiocomb (Протиокомб); Repin B (Репин B); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Myrin†; Rifafour; Rimstar; ***Spain:*** Rimstar; ***Swed.:*** Rimstar; ***Switz.:*** Myambutol-INH†; ***Thai.:*** Rifafour; Rimstar.

Ethionamide *(BAN, USAN, rINN)*

Ethionamid; Éthionamide; Ethionamidum; 2-Ethylthioisonicotinamide; Etionamid; Etionamida; Etionamidas; Etionamide; Etionamidi; 1314-TH. 2-Ethylpyridine-4-carbothioamide.

Этионамид

$C_8H_{10}N_2S = 166.2.$
CAS — 536-33-4.
ATC — J04AD03.
ATC Vet — QJ04AD03.

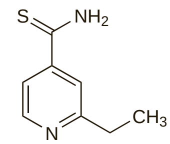

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ethionamide). Small yellow crystals or a yellow crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

USP 31 (Ethionamide). A bright yellow powder having a faint to moderate sulfide-like odour. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol and in propylene glycol; soluble in methyl alcohol. pH of a 1% slurry in water is between 6.0 and 7.0. Store in airtight containers.

Adverse Effects and Treatment

Many patients cannot tolerate therapeutic doses of ethionamide and have to stop treatment. The most common adverse effects are dose-related gastrointestinal disturbances, including nausea, vomiting, diarrhoea, anorexia, excessive salivation, a metallic taste, stomatitis, and abdominal pain. Tolerance may be improved by reducing the dose, adjusting the timing of dosage, or giving an antiemetic.

Mental disturbances including depression, anxiety, and psychosis have been provoked. Dizziness, drowsiness, headache, postural hypotension, and asthenia may also occur occasionally. Peripheral and optic neuropathy, diplopia and blurred vision, and a pellagra-like syndrome have occurred. Pyridoxine or nicotinamide have been suggested for the treatment or prevention of neurotoxic effects. Hepatitis may occur occasionally, with or without jaundice. The incidence of hepatotoxicity is increased when ethionamide is given with rifampicin.

Other adverse effects reported include hypersensitivity reactions, thrombocytopenia and purpura, alopecia, dermatitis (including photodermatitis), endocrine disturbances, hypoglycaemia, and hypothyroidism with or without goitre.

Teratogenic effects have been reported in *animals.*

Effects on the liver. Use of ethionamide or protionamide with rifampicin for the treatment of multibacillary leprosy has been associated with a high incidence of hepatotoxicity. A hepatitis incidence of 4.5 to 5% has been reported for patients on ethionamide or protionamide, rifampicin, and either dapsone or clofazimine.[1,2] In these studies, diagnosis of hepatitis was based on clinical assessment. When laboratory monitoring was used, an incidence of 13% was reported with a regimen of ethionamide or protionamide with rifampicin and dapsone.[3] A regimen of protionamide, dapsone, rifampicin, and clofazimine has been associated with a 22% incidence based on laboratory monitoring.[4] Use of ethionamide with pyrazinamide has also resulted in a high incidence of abnormal liver function tests.[5]

In the above studies rifampicin was given daily during part or all of the regimens. The incidence of hepatotoxicity when ethionamide or protionamide is used with once-monthly rifampicin may be lower; hepatotoxicity was not reported in patients receiving monthly rifampicin and daily protionamide, isoniazid, and dapsone.[6]

1. Pattyn SR, *et al.* Hepatotoxicity of the combination of rifampin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr* 1984; **52:** 1–6.
2. Pattyn SR, *et al.* Combined regimens of one year duration in the treatment of multibacillary leprosy—II: combined regimens with rifampicin administered during 6 months. *Lepr Rev* 1989; **60:** 118–23.
3. Cartel J-L, *et al.* Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin, and a thioamide. *Int J Lepr* 1983; **51:** 461–5.
4. Ji B, *et al.* Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev* 1984; **55:** 283–9.
5. Schless JM, *et al.* The use of ethionamide in combined drug regimens in the re-treatment of isoniazid-resistant pulmonary tuberculosis. *Am Rev Respir Dis* 1965; **91:** 728–37.
6. Ellard GA, *et al.* Long-term prothionamide compliance: a study carried out in India using a combined formulation containing prothionamide, dapsone and isoniazid. *Lepr Rev* 1988; **59:** 163–75.

Precautions

Ethionamide should not be used in severe hepatic impairment. Liver function tests should be carried out before, and regularly during, treatment with ethionamide.

Caution is necessary in patients with depression or other psychiatric illness. Difficulty may be experienced in the management

The symbol † denotes a preparation no longer actively marketed

of diabetes mellitus. Periodic monitoring of blood glucose, thyroid function, and visual function is desirable.

Ethionamide is teratogenic in *animals*.

Porphyria. Ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

The adverse effects of other antimycobacterials may be increased when ethionamide is used (see Effects on the Liver, above, and under Cycloserine, Interactions, p.260).

Alcohol. A psychotic reaction has been reported in a patient receiving ethionamide after excessive intake of alcohol.[1]

1. Lansdown FS, *et al.* Psychotoxic reaction during ethionamide therapy. *Am Rev Respir Dis* 1967; **95:** 1053–5.

Antimicrobial Action

Ethionamide is active only against mycobacteria including *Mycobacterium tuberculosis*, *M. kansasii*, *M. leprae*, and some strains of *M. avium* complex.

Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide. Cross-resistance has been reported *in vitro* with isoniazid or with thioacetazone.

Pharmacokinetics

Ethionamide has been given as a sugar-coated tablet or more recently as a more stable film-coated tablet. Both formulations are readily absorbed from the gastrointestinal tract: after an oral dose of 250 mg, sugar-coated tablets produce a peak plasma concentration of about 1.5 micrograms/mL after 1.5 hours, while film-coated tablets give a peak plasma concentration of 2.16 micrograms/mL after about 1 hour. Distribution of ethionamide from the film-coated tablet into body tissues and fluids has not been studied, but is expected to be similar to that of the sugar-coated tablets. Ethionamide from sugar-coated tablets is widely distributed throughout body tissues and fluids. It crosses the placenta and penetrates the uninflamed meninges, appearing in the CSF in concentrations equivalent to those in serum. It is about 30% bound to plasma proteins. The half-life for the sugar-coated tablet is reported to be 2 to 3 hours and 1.92 hours for the film-coated tablet. Ethionamide is extensively metabolised, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

Distribution. After single oral doses of ethionamide 15 or 20 mg/kg in children with tuberculous meningitis, the peak spinal fluid concentration was reached in 1⁄ to 2⁄ hours.[1] A wide range of concentrations was reported but doses of 20 mg/kg were more likely to produce spinal fluid concentrations above 2.5 micrograms/mL, the concentration considered by the authors to be essential for therapeutic success.

1. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989; **115:** 483–6.

Uses and Administration

Ethionamide is a thioamide derivative considered to be interchangeable with protionamide. It is used with other antituberculous drugs for the treatment of tuberculosis (p.196) when resistance to primary drugs has developed. It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p.176) but less toxic alternatives are now preferred.

In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally. Ethionamide may be given in divided doses with meals, or as a single daily dose after the evening meal, or at bedtime, to minimise gastrointestinal adverse effects. For details of doses in infants, children, and adolescents, see below.

Similar doses were used for the treatment of leprosy.

Ethionamide has also been used as rectal suppositories; the hydrochloride has been given intravenously.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests an oral dose of ethionamide 15 to 20 mg/kg (to a maximum of 1 g) daily, given in 2 to 3 divided doses.

Preparations

USP 31: Ethionamide Tablets.

Proprietary Preparations (details are given in Part 3)

Gr.: Trecator; ***India:*** Ethide; Myobid; ***S.Afr.:*** Ethatyl; ***Thai.:*** Eton; ***Turk.:*** Etyomid; ***USA:*** Trecator.

Etimicin Sulfate

Antibiotic 89-07; E-402. 1-*N*-Ethyl gentamicin C_{1a} sulfate.

$(C_{21}H_{43}N_5O_7)_2,5H_2SO_4$ = 1445.6.

CAS — 59711-96-5 (etimicin); 362045-44-1 (etimicin sulfate).

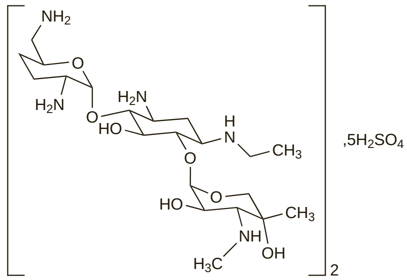

Pharmacopoeias. In *Chin.*

Profile

Etimicin, a derivative of gentamicin C_{1a}, is an aminoglycoside antibacterial with actions similar to those of gentamicin (p.282). It is given intravenously as the sulfate.

◊ References.

1. Zhao C, *et al.* A randomized controlled clinical trial on etimicin, a new aminoglycoside antibiotic, versus netilmicin in the treatment of bacterial infections. *Chin Med J (Engl)* 2000; **113:** 1026–30.

Faropenem Sodium *(rINNM)*

ALP-201; Faropenem sódico; Faropénem Sodique; Fropenem Sodium; Furopenem; Natrii Faropenemum; SUN-5555; SY-5555; Wy-49605; YM-044. Sodium (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

Натрий Фаропенем

$C_{12}H_{14}NaNO_5S$ = 307.3.

CAS — 106560-14-9 (faropenem); 141702-36-5 (faropenem medoxomil); 122547-49-3 (faropenem sodium).

Pharmacopoeias. *Jpn* includes the hemipentahydrate.

Profile

Faropenem is a penem antibacterial that is given orally as the sodium salt for the treatment of susceptible infections.

Faropenem medoxomil (*USAN*) (Bay-56-6854) is being investigated for the treatment of respiratory-tract infections and uncomplicated skin and skin structure infections. NOTE. Faropenem medoxomil has also been referred to as faropenem daloxate although such use of the term daloxate is not in keeping with *INN* nomenclature conventions.

◊ References.

1. Critchley IA, *et al.* Activities of faropenem, an oral β-lactam, against recent US isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. *Antimicrob Agents Chemother* 2002; **46:** 550–5.
2. von Eiff C, *et al.* Comparative in vitro activity of faropenem against staphylococci. *J Antimicrob Chemother* 2002; **50:** 277–80.
3. Milatovic D, *et al.* In vitro activity of faropenem against 5460 clinical bacterial isolates from Europe. *J Antimicrob Chemother* 2002; **50:** 293–9.
4. Wexler HM, *et al.* In vitro activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob Agents Chemother* 2002; **46:** 3669–75.
5. Jones ME, *et al.* Activity of faropenem, a new furanem, against European respiratory pathogens collected during 2000-2001: a comparison with other beta-lactam agents. *J Antimicrob Chemother* 2003; **51:** 196–9.
6. Gettig JP, *et al.* Faropenem medoxomil. *Ann Pharmacother* 2008; **42:** 80–90.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Farom.

Fleroxacin *(BAN, USAN, rINN)*

AM-833; Fleroksasiini; Fléroxacine; Fleroxacino; Fleroxacinum; Ro-23-6240; Ro-23-6240/000. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

Флероксацин

$C_{17}H_{18}F_3N_3O_3$ = 369.3.

CAS — 79660-72-3.

ATC — J01MA08.

ATC Vet — QJ01MA08.

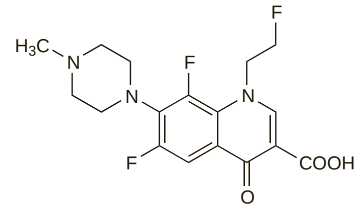

Pharmacopoeias. In *Chin.*

Profile

Fleroxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.243), but is reported to have greater systemic bioavailability and a longer half-life. It is given orally for the treatment of susceptible infections in usual doses of 200 to 300 mg once daily. It has also been given by intravenous infusion.

The incidence of adverse effects associated with fleroxacin has been relatively high.

◊ General references.

1. Balfour JA, *et al.* Fleroxacin: a review of its pharmacology and therapeutic efficacy in various infections. *Drugs* 1995; **49:** 794–850.

Adverse effects. References to adverse effects associated with fleroxacin.

1. Bowie WR, *et al.* Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; **33:** 1778–82.
2. Geddes AM. Safety of fleroxacin in clinical trials. *Am J Med* 1993; **94** (suppl 3A): 201S–203S.
3. Kimura M, *et al.* Photosensitivity induced by fleroxacin. *Clin Exp Dermatol* 1996; **21:** 46–7.

Breast feeding. The American Academy of Pediatrics[1] states that fleroxacin is usually compatible with breast feeding. However, in a study,[2] in which women were given a single 400-mg dose and breast feeding was withheld for 48 hours, it was concluded that although a breast-fed infant would only receive a moderate amount (maximum 10 mg daily), fleroxacin should not be used in breast-feeding mothers due to the potential for adverse effects such as arthropathy in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Dan M, *et al.* Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women. *Antimicrob Agents Chemother* 1993; **37:** 293–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Quinodis†; ***Jpn:*** Megalocin.

Flomoxef Sodium *(rINNM)*

Flomoxef sódico; Flomoxef Sodique; Natrii Flomoxefum; 6315-S. 7*R*-7-[2-(Difluoromethylthio)acetamido]-3-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-ylthiomethyl]-7-methoxy-1-oxa-3-cephem-4-carboxylic acid sodium.

Натрий Фломоксеф

$C_{15}H_{17}F_2N_6NaO_7S_2$ = 518.4.

CAS — 99665-00-6 (flomoxef); 92823-03-5 (flomoxef sodium).

Pharmacopoeias. In *Jpn.*

Profile

Flomoxef is an oxacephalosporin or oxacephem antibacterial with properties similar to latamoxef (p.292). It is given intravenously as the sodium salt and doses are expressed in terms of flomoxef; 1.04 g of flomoxef sodium is equivalent to about 1 g of flomoxef. The usual dose is 1 to 2 g daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Flumarin.

Florfenicol *(BAN, USAN, rINN)*

Florfénicol; Florfenicolum; Florfenikol; Florfenikoli; Sch-25298. 2,2-Dichloro-*N*-[(αS,βR)-α-(fluoromethyl)-β-hydroxy-4-methanesulfonylphenethyl]acetamide.

Флорфеникол

$C_{12}H_{14}Cl_2FNO_4S$ = 358.2.
CAS — 76639-94-6.
ATC Vet — QJ01BA90; QJ51BA90.

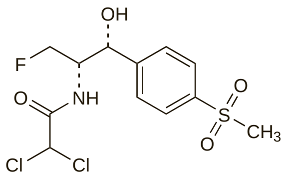

Profile

Florfenicol, a fluorinated analogue of chloramphenicol, is an antibacterial used in veterinary medicine.

Flucloxacillin *(BAN, rINN)*

BRL-2039; Floxacillin *(USAN)*; Flucloxacilina; Flucloxacilline; Flucloxacillinum; Flukloksasilin; Flukloksasilliini; Flukloxacillin. (6*R*)-6-[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

Флуклоксациллин

$C_{19}H_{17}ClFN_3O_5S$ = 453.9.
CAS — 5250-39-5.
ATC — J01CF05.
ATC Vet — QJ01CF05; QJ51CF05.

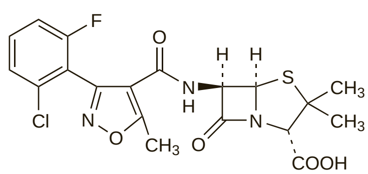

NOTE. Compounded preparations of flucloxacillin may be represented by the following names:

- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Flucloxacillin Magnesium *(BANM, rINNM)*

Flucloxacilina magnésica; Flucloxacilline Magnesique; Flucloxacilline-magnésium; Flucloxacillinum magnesicum; Magnesii Flucloxacillinum.

Магния Флуклоксациллин

$(C_{19}H_{16}ClFN_3O_5S)_2Mg,8H_2O$ = 1074.2.
CAS — 58486-36-5.
ATC — J01CF05.
ATC Vet — QJ01CF05.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flucloxacillin Magnesium Octahydrate). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 6.5.

Flucloxacillin Sodium *(BANM, rINNM)*

Flucloxacilina sódica; Flucloxacilline sodique; Flucloxacillinum natricum; Flucloxacillinum Natricum Monohydricum; Flukloksacilino natrio druska; Flukloksasilin Sodyum; Flukloksasilliininatrium; Flukloxacilin sodná sůl monohydrát; Flukloxacillinnatrium; Flukloxacillin-nátrium; Natrii Flucloxacillinum.

Натрий Флуклоксациллин

$C_{19}H_{16}ClFN_3NaO_5S,H_2O$ = 493.9.
CAS — 1847-24-1.
ATC — J01CF05.
ATC Vet — QJ01CF05.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flucloxacillin Sodium). A white or almost white, crystalline hygroscopic, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.

Incompatibility. As with other penicillins, flucloxacillin sodium is incompatible with aminoglycosides.

Adverse Effects and Precautions

As for Benzylpenicillin p.213.

Hepatitis and cholestatic jaundice have been reported occasionally with flucloxacillin and may be delayed in onset for up to 2 months after treatment has been stopped; older patients and those receiving flucloxacillin for more than 2 weeks are at greater risk. Fatalities have occurred, usually in patients with serious underlying hepatic disease. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis associated with flucloxacillin. Agranulocytosis and neutropenia have been associated rarely with isoxazolyl penicillins such as flucloxacillin. Phlebitis has followed intravenous infusion.

Effects on the liver. In October 2004, the UK CSM issued a reminder[1] that flucloxacillin is associated rarely with an increased risk of hepatitis and cholestatic jaundice. In some patients, almost always those with serious underlying hepatic disease, fatalities have occurred. The onset of hepatic adverse effects may be delayed for up to 2 months after stopping treatment, and is not related to the dose or to the route. Older patients and those receiving flucloxacillin for more than 2 weeks are at increased risk. Flucloxacillin should not be used in patients with a history of hepatic dysfunction related to its use, and should be used only with caution in patients with evidence of other hepatic impairment. Careful enquiry should be made concerning previous hypersensitivity to beta lactams. A cohort study[2] using UK prescription data found that the risk of developing cholestatic liver disease in the 45 days after starting flucloxacillin was 8.5 per 100 000. In contrast to other countries, flucloxacillin continued to be seen as a first-line drug in the UK.

1. Committee on Safety of Medicines. Reminder: flucloxacillin and serious hepatic disorders. *Current Problems* 2004; **30:** 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)
2. Russmann S, *et al.* Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. *Br J Clin Pharmacol* 2005; **60:** 76–82.

Porphyria. Flucloxacillin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Sodium content. Each g of flucloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Flucloxacillin is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to staphylococcal penicillinase. It is active therefore against penicillinase-producing and non-penicillinase-producing staphylococci. Its activity against streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. Flucloxacillin is virtually ineffective against *Enterococcus faecalis.*

Resistance. The resistance of staphylococci to flucloxacillin and other penicillinase-resistant penicillins is described under meticillin (p.299).

Pharmacokinetics

Flucloxacillin is better absorbed from the gastrointestinal tract than cloxacillin, but absorption is reduced by the presence of food in the stomach. After an oral dose of 0.25 to 1 g, in fasting subjects, peak plasma concentrations in about 1 hour are usually in the range of 5 to 15 micrograms/mL. Plasma concentrations after intramuscular injection of flucloxacillin sodium are similar, but peak concentrations are achieved in about 30 minutes. Doubling the dose can double the plasma concentration. About 95% of flucloxacillin in the circulation is bound to plasma proteins. Flucloxacillin has been reported to have a plasma half-life of approximately 1 hour. The half-life is prolonged in neonates.

The distribution of flucloxacillin into body tissues and fluids is similar to that of cloxacillin (p.256).

Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 66% of an oral dose and 76% of a parenteral dose is excreted in the urine within 8 hours. Only small amounts are excreted in the bile. Flucloxacillin is not removed by haemodialysis or peritoneal dialysis.

Plasma concentrations are enhanced by probenecid.

Uses and Administration

Flucloxacillin is an isoxazolyl penicillin used primarily for the treatment of infections due to staphylococci resistant to benzylpenicillin. These include bone and joint infections, endocarditis, pneumonia, skin infections (including soft-tissue infections), and toxic shock syndrome. For discussions of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Flucloxacillin is given parenterally and orally as the sodium or magnesium salt. All doses are expressed as flucloxacillin; 1.18 g of flucloxacillin magnesium and 1.09 g of flucloxacillin sodium are each equivalent to about 1 g of flucloxacillin. Oral doses should be taken at least 30 minutes before meals as the presence of food in the stomach reduces absorption. In severe renal impairment a reduction in dosage may be necessary.

The usual adult dose orally or by intramuscular injection is 250 mg four times daily. It is given intravenously in a dose of 0.25 to 1 g four times daily by slow injection over 3 to 4 minutes or by intravenous infusion. All systemic doses may be doubled in severe infections. Up to 8 g daily in 3 or 4 divided doses may be given for osteomyelitis; in endocarditis a dose of 8 g daily in 4 divided doses may be given to patients weighing up to 85 kg, and 12 g daily in 6 divided doses may be used in those weighing more.

Flucloxacillin has been given by other routes in conjunction with systemic therapy. It has been given in a dose of 250 to 500 mg daily by intra-articular injection, dissolved if necessary in a 0.5% solution of lidocaine hydrochloride, or by intrapleural injection in a dose of 250 mg daily. Using powder for injection, 125 to 250 mg has been dissolved in 3 mL of sterile water and inhaled by nebuliser 4 times daily.

Children up to 2 years of age may be given one-quarter the adult dose and those aged 2 to 10 years one-half the adult dose.

Flucloxacillin may be used with other antibacterials, including ampicillin (known as co-fluampicil), to produce a wider spectrum of activity. If flucloxacillin is given with an aminoglycoside the two drugs should not be mixed.

Preparations

BP 2008: Co-fluampicil Capsules; Co-fluampicil Oral Suspension; Flucloxacillin Capsules; Flucloxacillin Injection; Flucloxacillin Oral Solution; Flucloxacillin Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Austral.: Flopen; Floxapen; Floxsig; Flubiclox; Flucil; Staphylex; ***Austria:*** Floxapen; ***Belg.:*** Floxapen; Staphycid; ***Chile:*** Fluxacina; Vitalpen; ***Denm.:*** Heracillin; ***Ger.:*** Fluclox; Fluclox†; Staphylex; ***Hong Kong:*** Flucloxil; ***India:*** Floxapen†; ***Indon.:*** Floxapen; ***Irl.:*** Floxapen; Flucillin; Flucion; Geriflox; ***Ital.:*** Betabiotic; Cloxillin; Evercid; Faifloc; Fareclox; Flucacid; Flucef; Flucinal; Fluclox; Fluxacil; Fluzerit; Liderclox; Nepenic; Pantaflux; Recaflux; ***Malaysia:*** Staphlex; ***Mex.:*** Floxapen; ***Neth.:*** Floxapen; Stafoxil†; ***NZ:*** Floxapen; Flucloxin; Staphlex; ***Philipp.:*** Stafloxin; ***Port.:*** Floxapen; Floxil†; ***S.Afr.:*** Floxapen; ***Singapore:*** Staphlex; ***Swed.:*** Heracillin; ***Switz.:*** Floxapen; ***Thai.:*** Staphycid; ***Turk.:*** Flix; Floksin; ***UK:*** Floxapen; Fluclomix; Ladropen; ***Venez.:*** Floxapen.

Multi-ingredient: ***Ger.:*** Flanamox; ***S.Afr.:*** Macropen; Megapen; Suprapen; ***UK:*** Magnapen.

Flumequine *(BAN, USAN, rINN)*

Flumechin; Flumekiini; Flumekin; Flumekvinas; Flumequina; Fluméquine; Flumequinum; R-802. 9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid.

Флумехин

$C_{14}H_{12}FNO_3$ = 261.2.
CAS — 42835-25-6.
ATC — J01MB07.
ATC Vet — QJ01MB07.

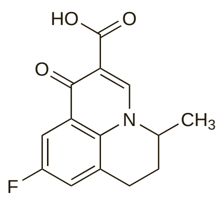

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flumequine). A white or almost white microcrystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol; freely soluble in dilute solutions of alkali hydroxides.

Profile

Flumequine is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p.303). It may be more active *in vitro* against some Enterobacteriaceae. In the treatment of urinary-tract infections doses of 400 mg are given orally 3 times daily.

Porphyria. Flumequine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Apurone.

Flurithromycin Ethyl Succinate *(rINNM)*

Etilsuccinato de fluritromicina; Flurithromycin Ethylsuccinate; Flurithromycine, Éthylsuccinate de; Flurithromycini Ethylsuccinas. (8*S*)-8-Fluoroerythromycin mono(ethyl butanedioate) ester.

Флуритромицина Этилсукцинат

$C_{43}H_{74}FNO_{16}$ = 880.0.
CAS — 82664-20-8 (flurithromycin); 82730-23-2 (flurithromycin ethyl succinate).
ATC — J01FA14.
ATC Vet — QJ01FA14.

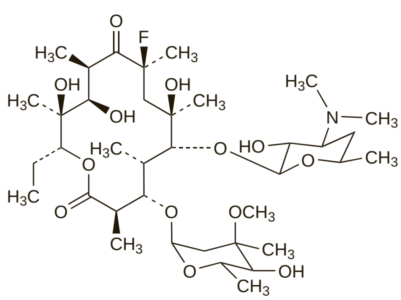

(flurithromycin)

Profile

Flurithromycin is a fluorinated macrolide antibacterial derived from erythromycin (p.269). It is given orally as the ethyl succinate but doses are expressed in terms of the base. The usual dose in the treatment of susceptible infections is the equivalent of 375 mg of flurithromycin twice daily, after meals.

◊ References.

1. Saverino D, *et al.* Antibacterial profile of flurithromycin, a new macrolide. *J Antimicrob Chemother* 1992; **30:** 261–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Flurizic; Mizar; Ritro.

Formosulfathiazole

Formaldehyde-sulphathiazole; Formosulfatiazol; Formosulphathiazole; Methylenesulfathiazole.

CAS — 13968-86-0.
ATC Vet — QA07AB90; QD06BA90.

Profile

Formosulfathiazole, a condensation product of sulfathiazole with formaldehyde, has properties similar to those of sulfamethoxazole (p.340). It is poorly absorbed and has been given for its antibacterial action in the gastrointestinal tract, often with other antibacterials.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Pol.:* Sterovag; ***Spain:*** Sulfintestin Neomicina.

Fosfomycin *(BAN, USAN, rINN)*

Fosfomicina; Fosfomycine; Fosfomycinum; Fosfomysiini; MK-955; Phosphomycin; Phosphonomycin. (1*R*,2*S*)-1,2-Epoxypropylphosphonic acid.

Фосфомицин

$C_3H_7O_4P$ = 138.1.
CAS — 23155-02-4.
ATC — J01XX01.
ATC Vet — QJ01XX01.

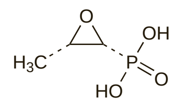

Description. Fosfomycin is an antibacterial isolated from *Streptomyces fradiae* and other *Streptomyces* spp. or produced synthetically.

Fosfomycin Calcium *(BANM, rINNM)*

Calcii Fosfomycinum; Fosfomicina cálcica; Fosfomicino kalcio druska; Fosfomycin vápenatá sůl monohydrát; Fosfomycine calcique; Fosfomycinkalcium; Fosfomycinum calcicum; Fosfomycinum Calcicum Monohydricum; Fosfomysiinikalsium; Foszfomicin-kalcium.

Кальций Фосфомицин

$C_3H_5CaO_4P,H_2O$ = 194.1.
CAS — 26016-98-8.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn*.

Ph. Eur. 6.2 (Fosfomycin Calcium). A white or almost white powder. Slightly soluble in water; practically insoluble in acetone, in dichloromethane, and in methyl alcohol. A 0.1% solution in water has a pH of 8.1 to 9.6. Store in airtight containers. Protect from light.

Fosfomycin Sodium *(BANM, rINNM)*

Fosfomicina sódica; Fosfomicino natrio druska; Fosfomycin disodná sůl; Fosfomycine sodique; Fosfomycinnatrium; Fosfomycinum Dinatricum; Fosfomycinum natricum; Fosfomysiininatrium; Foszfomicin-nátrium; Natrii Fosfomycinum.

Натрий Фосфомицин

$C_3H_5Na_2O_4P$ = 182.0.
CAS — 26016-99-9.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn*.

Ph. Eur. 6.2 (Fosfomycin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; practically insoluble in dehydrated alcohol and in dichloromethane; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 9.0 to 10.5. Store in airtight containers. Protect from light.

Fosfomycin Trometamol *(BANM, rINNM)*

Fosfomicina trometamol; Fosfomicinas trometamolis; Fosfomisin Trometamol; Fosfomycin Tromethamine *(USAN)*; Fosfomycine trométamol; Fosfomycintrometamol; Fosfomycin-trometamol; Fosfomycinum Trometamol; Fosfomycinum Trometamoli; Fosfomycinum trometamolum; Fosfomycyna z trometamolem; Fosfomysiinitrometamoli; Foszfomicin-trometamol; FZ-588; Z-1282.

Фосфомицин Трометамол

$C_3H_7O_4P,C_4H_{11}NO_3$ = 259.2.
CAS — 78964-85-9.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fosfomycin Trometamol). A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

Adverse Effects and Precautions

Gastrointestinal disturbances including nausea and diarrhoea, transient increases in serum concentrations of aminotransferases, headache, visual disturbances, and skin rashes have been reported after use of fosfomycin. Eosinophilia and, rarely, angioedema, aplastic anaemia, exacerbation of asthma, cholestatic jaundice, hepatic necrosis, and toxic megacolon, have also occurred.

Antimicrobial Action

Fosfomycin is a bactericidal antibacterial. After active uptake into the cell it is reported to interfere with the first step in the synthesis of bacterial cell walls. It is active *in vitro* against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, some streptococci, most Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria* spp., and some strains of *Pseudomonas aeruginosa* although some are resistant. *Bacteroides* spp. are not sensitive.

Bacterial resistance to fosfomycin has been reported and can be chromosomal or, in some organisms, transferred by plasmids encoding multiple resistance (for example in *Serratia marcescens*). However, there appears to be little cross-resistance with other antibacterials.

Fosfomycin has been reported to show antimicrobial synergy with a wide range of antibacterials against organisms such as enterococci, meticillin-resistant *Staph. aureus*, and the enterobacteria. Such synergistic effects have been reported particularly with the beta lactams, but also with aminoglycosides, macrolides, tetracyclines, chloramphenicol, rifamycin, and lincomycin. Antimicrobial antagonism with a beta lactam has also been reported.

There is some suggestion that use of fosfomycin with an aminoglycoside may also reduce the nephrotoxicity of the latter *in vivo*.

◊ References.

1. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J Antimicrob Chemother* 1995; **35:** 228–30.

Pharmacokinetics

Fosfomycin or fosfomycin calcium are poorly absorbed from the gastrointestinal tract. Peak plasma concentrations 4 hours after a 1-g dose of fosfomycin calcium are about 7 micrograms/mL, and bioavailability has been calculated at about 30 to 40%. Similar bioavailability has been reported for the trometamol salt, and plasma concentrations of about 22 to 32 micrograms/mL have been reported 2 hours after an oral dose equivalent to 3 g fosfomycin. Fosfomycin disodium is given intramuscularly or intravenously: intravenous infusion of a 4-g dose results in peak plasma concentrations of around 120 micrograms/mL. The plasma half-life is about 2 hours. Fosfomycin does not appear to be bound to plasma proteins. It crosses the placenta and is widely distributed in body fluids including the CSF; small amounts have been found in breast milk and bile. The majority of a parenteral dose is excreted unchanged in the urine, by glomerular filtration, within 24 hours.

Urinary concentrations of up to 3 mg/mL have been reported within 2 to 4 hours of an oral dose of fosfomycin trometamol equivalent to 3 g of fosfomycin; therapeutic concentrations of 200 to 300 micrograms/mL remained in urine after 48 hours.

◊ References.

1. Bergan T, *et al.* Pharmacokinetic profile of fosfomycin trometamol. *Chemotherapy* 1993; **39:** 297–301.

Uses and Administration

Fosfomycin is a phosphonic acid antibacterial given orally as the trometamol or calcium salt and intramuscularly or intravenously as the disodium salt in the treatment of a variety of bacterial infections due to susceptible organisms. Doses are expressed in terms of the base; fosfomycin calcium 1.4 g, fosfomycin sodium 1.3 g, and fosfomycin trometamol 1.9 g are each equivalent to about 1 g of fosfomycin.

In the treatment of acute uncomplicated infections of the urinary tract (p.199), fosfomycin trometamol is given as a single dose equivalent to 3 g of fosfomycin. Fosfomycin trometamol has also been used for the prophylaxis of infection in transurethral surgical procedures. For a discussion of surgical infections and their prophylaxis and treatment, see p.195.

The usual oral dose of fosfomycin calcium is the equivalent of 0.5 to 1 g of fosfomycin every 6 to 8 hours. Higher doses have been given parenterally as the sodium salt, with up to 20 g daily having been given intravenously in severe infection.

Fosfomycin has also been used with beta lactam antibacterials.

◊ References.

1. Reeves DS. Fosfomycin trometamol. *J Antimicrob Chemother* 1994; **34:** 853–8.
2. Patel SS, *et al.* Fosfomycin tromethamine: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; **53:** 637–56.
3. Stein GE. Single-dose treatment of acute cystitis with fosfomycin tromethamine. *Ann Pharmacother* 1998; **32:** 215–19.
4. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 2003; **22** (suppl 2): 79–83.
5. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol: double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005; **55:** 420–7.
6. Sádaba-Díaz de Rada B, *et al.* Fosfomicina trometamol: dosis múltiples como pauta larga en el tratamiento de las infecciones urinarias bajas. *Enferm Infecc Microbiol Clin* 2006; **24:** 546–50.
7. Pullukcu H, *et al.* Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. *Int J Antimicrob Agents* 2007; **29:** 62–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Veramina; ***Austria:*** Monuril; ***Belg.:*** Monuril; ***Braz.:*** Monuril; ***Canad.:*** Monurol; ***Chile:*** Monurol; ***Fin.:*** Monurol†; ***Fr.:*** Fosfocine; Monuril; Uridoz; ***Ger.:*** InfectoFos; Monuril; ***Gr.:*** Monurol†; ***Hong Kong:*** Monurol; ***Hung.:*** Monural; ***Indon.:*** Fosmicin; Fosmidex; Monuril; ***Israel:*** Monurol; ***Ital.:*** Afos†; Faremicin†; Fosfocin; Francital†; Ipamicina†; Monuril; Ultramicina†; ***Jpn:*** Fosmicin-S; ***Malaysia:*** Monurol; ***Mex.:*** Fosfocil; Monurol; ***Neth.:*** Monuril; ***Philipp.:*** Monurol; ***Pol.:*** Monural; ***Port.:*** Monuril; ***Rus.:*** Monural (Монурал); ***S.Afr.:*** Urizone; ***Spain:*** Fosfocina; Monurol; Solufos; ***Swed.:*** Monurol†; ***Switz.:*** Monuril; ***Thai.:*** Fosmicin; ***Turk.:*** Monurol; ***USA:*** Monurol.

Framycetin Sulfate *(rINNM)*

Framicetino sulfatas; Framicetin-szulfát; Framycetin Sulphate *(BANM)*; Framycétine, sulfate de; Framycetini sulfas; Framycetinsulfat; Framycetin-sulfát; Framysetiinisulfaatti; Neomycin B Sulphate; Sulfato de framicetina. 2-Deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]streptamine sulphate.

Фрамицетина Сульфат

$C_{23}H_{46}N_6O_{13},xH_2SO_4$.

CAS — 119-04-0 (framycetin); 4146-30-9 (framycetin sulfate).

ATC — D09AA01; R01AX08; S01AA07.

ATC Vet — QD09AA01; QR01AX08; QS01AA07.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Framycetin Sulphate). A substance produced by growth of selected strains of *Streptomyces fradiae* or *S. decaris* or obtained by any other means. It contains not more than 3% of neomycin C (p.305) and loses not more than 8% of its weight on drying. A white or yellowish-white, hygroscopic powder. The potency is not less than 630 units of neomycin B per mg, calculated with reference to the dried substance. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Framycetin is an aminoglycoside antibiotic which forms the major component of neomycin (p.305) and has similar actions and uses. Framycetin sulfate is used topically in usual concentrations of 1% for the treatment of infections of the skin, and in concentrations of 0.5% for infections of the eye and ear. It is often used with other antibacterials and corticosteroids in topical preparations.

Framycetin sulfate is poorly absorbed from the gastrointestinal tract and has been given orally for the treatment of gastrointestinal infections and pre-operatively for bowel preparation. It has sometimes been given prophylactically as part of regimens for the selective decontamination of the digestive tract in patients in intensive care.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Sofra-Tulle; Soframycin; ***Austria:*** Sofra-Tull; ***Belg.:*** Soframycine; ***Canad.:*** Sofra-Tulle; Soframycin; ***Fin.:*** Sofra-Tulle†; ***Ger.:*** Leukase N; Sofra-Tull†; ***Hong Kong:*** Sofra-Tulle; ***India:*** Sofra-Tulle; Soframycin; ***Indon.:*** Daryant-Tulle; Sofra-Tulle; ***Irl.:*** Soframycin; ***Israel:*** Sofra-Tulle†; ***Malaysia:*** Sofra-Tulle†; ***Norw.:*** Sofra-Tulle†; ***NZ:*** Soframycin; ***Rus.:*** Isofra (Изофра); ***S.Afr.:*** Sofra-Tulle; Soframycin; ***Singapore:*** Sofra-Tulle†; ***Switz.:*** Frakitacine†; Sofra-Tulle†; Soframycin; ***Thai.:*** Sofra-Tulle; ***UK:*** Sofra-Tulle; Soframycin†.

Multi-ingredient: ***Arg.:*** Biotaer Nasal; ***Austral.:*** Otodex; Sofradex; Soframycin; ***Austria:*** Leukase; Leukase-Kegel; ***Belg.:*** Frakidex; Sofraline; Sofrasolone; ***Braz.:*** Fonergin; ***Canad.:*** Opticort; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; Sofracort; Soframycin; ***Cz.:*** Pulpomixine; Septomixine; Sofradex†; ***Denm.:*** Proctosedyl; Sofradex; ***Fin.:*** Proctosedyl; Sofradex; ***Fr.:*** Corticetine; Frakidex; Framyxone; Novomyxine†; Polyfra; ***Ger.:*** Leukase N; ***Hong Kong:*** Frakidex; Frazoline; Proctosedyl†; Sofradex; ***India:*** Proctosedyl; Sofracort; Sofradex; Sofradex-F; ***Indon.:*** Sofradex; ***Irl.:*** Proctosedyl; Sofradex; Soframycin†; ***Malaysia:*** Proctosedyl; Sofradex; ***Neth.:*** Proctosedyl; Sofradex; ***Norw.:*** Proctosedyl; Sofradex; ***NZ:*** Sofradex; Soframycin; ***Philipp.:*** Proctosedyl; ***Pol.:*** Carident; Dexadent; ***Port.:*** Frakidex; ***S.Afr.:*** Proctosedyl; Sofradex; ***Singapore:*** Frakidex†; Proctosedyl; Sofradex; ***Spain:*** Abrasone; Aldo Otico†; Aldoderma; Nesfare; Otomidrin; ***Swed.:*** Proctosedyl†; ***Switz.:*** Corticetine†; Dexalocal-F; Frakidex; Septomixine; Sofradex; ***Thai.:*** Proctosedyl; Sofradex; Topifram; ***UK:*** Sofradex.

Ftivazide *(rINN)*

Ftivazida; Ftivazidum; Phthivazid; Phthivazidum. 2′-Vanillylideneisonicotinohydrazide monohydrate.

Фтивазид

$C_{14}H_{13}N_3O_3,H_2O$ = 289.3.

CAS — 149-17-7 (anhydrous ftivazide).

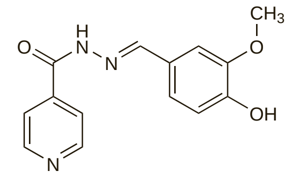

(anhydrous ftivazide)

Pharmacopoeias. In *Chin.* and *Int.*

Profile

Ftivazide is an antimycobacterial given orally in the treatment of tuberculosis. It is a derivative of isoniazid.

Furaltadone Hydrochloride *(BANM, rINNM)*

Furaltadone, Chlorhydrate de; Furaltadoni Hydrochloridum; Hidrocloruro de furaltadona. (±)-5-Morpholinomethyl-3-(5-nitrofurfurylideneamino)oxazolidin-2-one hydrochloride.

Фуральтадона Гидрохлорид

$C_{13}H_{16}N_4O_6,HCl$ = 360.8.

CAS — 139-91-3 (furaltadone); 59302-14-6 (±-furaltadone).

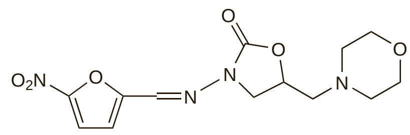

(furaltadone)

Pharmacopoeias. *Fr.* includes Furaltadone for veterinary use.

Profile

Furaltadone was formerly given orally as an antibacterial but was later withdrawn owing to its toxic effects. Furaltadone hydrochloride is still used topically in preparations for ear disorders. Furaltadone has been used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Otozambon; ***Thai.:*** Otosamthong.

Furazidin

Akritoin; Furagin; Furazidine. 1-{[3-(5-Nitro-2-furyl)allylidene]amino}hydantoin.

Фуразидин

$C_{10}H_8N_4O_5$ = 264.2.

CAS — 1672-88-4.

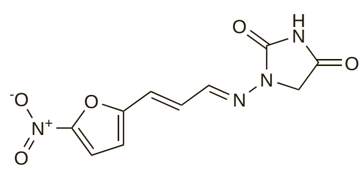

Profile

Furazidin is a nitrofuran antibacterial with properties similar to those of nitrofurantoin. It is used in the treatment of urinary-tract infections. A usual oral dose is 100 mg given four times daily for one day followed by 100 mg given three times daily for 7 to 8 days.

Preparations

Proprietary Preparations (details are given in Part 3)

Pol.: Furaginum.

Fusafungine *(BAN, rINN)*

Fusafungin; Fusafungina; Fusafunginum.

Фузафунгин

CAS — 1393-87-9.

ATC — R02AB03.

ATC Vet — QR02AB03.

Profile

Fusafungine is a depsipeptide antibacterial produced by *Fusarium lateritium* strain 437. It is active against some Gram-positive and Gram-negative organisms, *Candida albicans*, and *Mycoplasma pneumoniae*. It has also been stated to possess anti-inflammatory activity.

It is used in the form of an aerosol spray in the treatment of infections of the upper respiratory tract, inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth. These routes may be used simultaneously if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Locabiosol; ***Belg.:*** Locabiotal; ***Braz.:*** Locabiotal; ***Chile:*** Locabiosol†; ***Cz.:*** Bioparox; ***Ger.:*** Locabiosol; ***Gr.:*** Locabiotal; ***Hong Kong:*** Locabiotal†; ***Hung.:*** Bioparox; ***Irl.:*** Locabiotal; ***Ital.:*** Locabiotal; ***Malaysia:*** Locabiotal; ***Philipp.:*** Locabiotal; ***Pol.:*** Bioparox; ***Port.:*** Locabiosol; ***Rus.:*** Bioparox (Биопарокс); ***S.Afr.:*** Locabiotal; ***Spain:*** Fusaloyos; ***Switz.:*** Locabiotal; ***Turk.:*** Locabiotal; ***UK:*** Locabiotal†.

Fusidic Acid *(BAN, USAN, rINN)*

Acide fusidique; Ácido fusídico; Acidum fusidicum; Acidum Fusidicum Hemihydricum; Fucidinsyra; Fusidiinihappo; Fusidik Asit; Fusidinsyra; Fuzidinsav; Fuzido rūgštis; Kyselina fusidová hemihydrát; SQ-16603. *ent*-16α-Acetoxy-3β-dihydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-(17*Z*)-17(20),24-dien-21-oic acid hemihydrate.

Фузидовая Кислота

$C_{31}H_{48}O_6,\frac{1}{2}H_2O$ = 525.7.

CAS — 6990-06-3 (anhydrous fusidic acid).

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

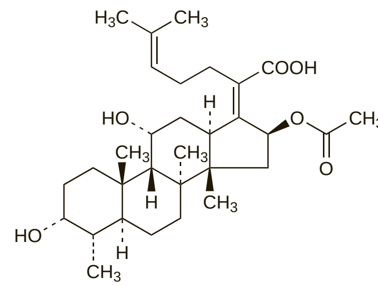

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fusidic Acid). An antimicrobial substance produced by the growth of certain strains of *Fusidium coccineum* or by any other means. A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol. Store at a temperature of 2° to 8°. Protect from light.

Sodium Fusidate *(BANM, rINNM)*

Fusidate de Sodium; Fusidate Sodium *(USAN)*; Fusidato sódico; Natrii fusidas; Natrio fuzidatas; Natriumfusidaatti; Natriumfusidat; Natrium-fusidát; Nátrium-fuzidát; Sodium, fusidate de; Sodyum Fusidat; SQ-16360.

Натрий Фузидат

$C_{31}H_{47}NaO_6$ = 538.7.

CAS — 751-94-0.

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Sodium Fusidate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol. A 1.25% solution in water has a pH of 7.5 to 9.0. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Incompatibility. UK licensed product information states that reconstituted sodium fusidate injection is incompatible with infusion solutions containing glucose 20% or more, lipid infusions, and peritoneal dialysis fluids; precipitation may occur in solutions with a pH of less than 7.4.

Adverse Effects and Precautions

Apart from mild gastrointestinal upsets, fusidic acid or sodium fusidate appear to be well tolerated when given orally. Treatment with fusidates, orally or especially by the intravenous route, has been associated with jaundice and changes in liver function; normal liver function is usually restored when treatment is stopped. Therefore, fusidates should be given with caution to patients with hepatic impairment, and periodic monitoring of hepatic function is recommended in these patients and in those receiving high or prolonged oral doses. Caution is also required in biliary disease or biliary obstruction.

Venospasm, thrombophlebitis, and haemolysis have occurred in patients given fusidates intravenously. To reduce this it is recommended that solutions be buffered and that the solution should be given as a slow infusion into a large vein where there is a good blood flow. Hypocalcaemia has occurred after use of intravenous doses above those recommended, and has been attributed to the phosphate-citrate buffer in the preparation. Intramuscular or subcutaneous use may lead to tissue necrosis and is contra-indicated.

Hypersensitivity reactions in the form of rashes and irritation may occur with topical fusidates; rash is rare after systemic use.

Fusidic acid competes with bilirubin for binding to albumin *in vitro* and caution has been advised if it is given to premature, jaundiced, acidotic, or seriously-ill neonates because of the risk of kernicterus.

Effects on the blood. There have been occasional reports of granulocytopenia[1-3] and thrombocytopenia[3] after the use of fusidic acid systemically. Sideroblastic anaemia has also been reported.[4] UK licensed product information also states that there have been isolated cases of neutropenia, agranulocytosis, and pancytopenia.

1. Revell P, *et al.* Granulocytopenia due to fusidic acid. *Lancet* 1988; **ii:** 454–5.
2. Evans DIK. Granulocytopenia due to fusidic acid. *Lancet* 1988; **ii:** 851.
3. Leibowitz G, *et al.* Leukopenia and thrombocytopenia due to fusidic acid. *Postgrad Med J* 1991; **67:** 591–2.
4. Vial T, *et al.* Sideroblastic anaemia during fusidic acid treatment. *Eur J Haematol* 2004; **72:** 358–60.

Interactions

Although the exact metabolic pathways of fusidic acid are not known, an interaction has been suspected with drugs metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4, and UK licensed product information suggests avoiding their use with fusidic acid.

Antivirals. An HIV-infected patient had fusidic acid toxicity after taking fusidic acid orally for one week with his usual antiretroviral treatment of *ritonavir, saquinavir*, and stavudine.[1] The plasma-fusidic acid concentration was about twice that expected and the ritonavir and saquinavir concentrations were also elevated. Fusidic acid was stopped and the patient initially improved. However, 4 days later he presented with jaundice, nausea, weakness, and further increases in liver function tests and hence all medications were stopped. The fusidic acid concentration, as well as those of ritonavir and saquinavir, were found to be still significantly elevated 6 days after fusidic acid had been stopped. The patient was able to restart his antiretroviral therapy later with no problems. The authors suggested that this interaction may be due to mutual inhibition of metabolism between the HIV-protease inhibitors and fusidic acid, and recommended that use of fusidic acid with either saquinavir or ritonavir should be avoided.

1. Khaliq Y, *et al.* A drug interaction between fusidic acid and a combination of ritonavir and saquinavir. *Br J Clin Pharmacol* 2000; **50:** 82–3.

Statins. For reference to the effect of fusidic acid in patients receiving statins, see p.1392.

Antimicrobial Action

Fusidic acid is a steroidal antibacterial with a bacteriostatic or bactericidal activity, mainly against Gram-positive bacteria.

Fusidic acid inhibits bacterial protein synthesis although, in contrast to drugs such as the macrolides or tetracyclines, it does not bind to the bacterial ribosome, but inhibits a factor necessary for translocation of peptide subunits and elongation of the peptide chain. It is capable of inhibiting protein synthesis in mammalian cells but exerts a selective action against susceptible infecting organisms because of poor penetration into the host cell.

Fusidic acid is very active against staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains). *Nocardia asteroides* and many clostridial strains are also highly susceptible. The streptococci and enterococci are less susceptible.

Most Gram-negative bacteria are intrinsically resistant but fusidic acid is active against *Neisseria* spp. and *Bacteroides fragilis*. It has some activity against strains of *Mycobacterium tuberculosis* and is highly active against *M. leprae*.

Fungi are resistant, but fusidic acid has some activity against a range of protozoa including *Giardia lamblia* and *Plasmodium falciparum*. High concentrations of fusidate are reported to inhibit viral growth *in vitro*, including that of HIV, although it is unclear whether this represents a surfactant effect, a general cytotoxic effect, or a genuine antiviral action.

No synergy has been shown *in vitro* in most studies between fusidic acid and rifampicin or vancomycin, and antagonism of the effects of ciprofloxacin has been reported. Interactions with the penicillins are complex, with either antagonism of the effect of one or both drugs, or no interaction. However, use of an antistaphylococcal penicillin with fusidic acid may prevent the emergence of fusidic acid-resistant staphylococcal mutants, and such combinations may be clinically effective.

Resistance. Resistance may be chromosomally mediated, representing altered protein synthesis, or plasmid-mediated, which appears to be due to reduced penetration of active drug into the cell. For further details on the increase of resistance to fusidic acid, see below.

Resistance. There has been an increase in the number of reports of fusidic acid resistance in *Staphylococcus aureus* particularly in dermatological isolates. The number of clinical isolates of initially resistant staphylococci has historically been low at about 1 to 2% overall.[1-3] However, in the UK the rate of fusidic acid resistance in staphylococcal isolates increased by up to 200% during the 1990s, and over half of all isolates are resistant in some samples.[3] This has been attributed to the widespread topical use of fusidic acid.[1-3]

The rate of resistance to short courses of fusidic acid used in systemic monotherapy is reported to be about 5%. In contrast, when given systemically with other antibacterials, the rate of resistance remains low at 0.8%.[4] Therefore, it has been suggested that systemic fusidic acid should be restricted to use with other antibacterial agents where clinically indicated in order to reduce the rate of resistance.[3,4]

1. Livermore D, *et al.* Fusidic-acid use and resistance. *Lancet* 2002; **360:** 806.
2. Mason BW, *et al.* Fusidic acid resistance in community isolates of methicillin-susceptible Staphylococcus aureus and fusidic acid prescribing. *J Antimicrob Chemother* 2003; **51:** 1033–6.
3. Dobie D, Gray J. Fusidic acid resistance in Staphylococcus aureus. *Arch Dis Child* 2004; **89:** 74–7.
4. Howden BP, Grayson ML. Dumb and dumber—the potential waste of a useful antistaphylococcal agent: emerging fusidic acid resistance in Staphylococcus aureus. *Clin Infect Dis* 2006; **42:** 394–400.

Pharmacokinetics

Sodium fusidate is well absorbed from the gastrointestinal tract, and a single oral 500-mg dose is reported to produce mean plasma concentrations of about 30 micrograms/mL within 2 to 4 hours, although there is considerable interindividual variation. Oral suspensions of fusidic acid are less well absorbed, with a bioavailability reported to be about 70% of that for sodium fusidate. Absorption may be delayed by food and may be more rapid in children than adults. Some accumulation occurs with repeated dosage and plasma concentrations of 100 micrograms/mL or more have been reported after 500 mg of sodium fusidate given three times daily for 4 days.

Fusidate is widely distributed into tissues and body fluids, including bone, pus, and synovial fluid; it penetrates cerebral abscesses but does not enter CSF in appreciable amounts. It has been found in the fetal circulation and in breast milk. About 95% or more of fusidate in the circulation is bound to plasma proteins.

Fusidate has a plasma half-life of about 10 to 15 hours. It is excreted in the bile, almost entirely as metabolites, some of which have weak antimicrobial activity. About 2% appears unchanged in the faeces. Little is excreted in the urine or removed by haemodialysis.

◊ References.

1. Reeves DS. The pharmacokinetics of fusidic acid. *J Antimicrob Chemother* 1987; **20:** 467–76.
2. Peter J-D, *et al.* Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. *Antimicrob Agents Chemother* 1993; **37:** 501–6.
3. Brown NM, *et al.* The pharmacokinetics and protein-binding of fusidic acid in patients with severe renal failure requiring either haemodialysis or continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1997; **39:** 803–9.
4. Turnidge J. Fusidic acid pharmacology, pharmacokinetics and pharmacodynamics. *Int J Antimicrob Agents* 1999; **12** (suppl 2): S23–S34.

Uses and Administration

Fusidic acid and its salts are antibacterials used mainly in the treatment of staphylococcal infections, often with other drugs. They have been used in the treatment of abscess, including brain abscess, in bone and joint infections, in staphylococcal infections in patients with cystic fibrosis, in the treatment of staphylococcal endocarditis, and topically in eye infections and infections of the skin. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

The fusidates are given orally or topically as fusidic acid or sodium fusidate, or intravenously as sodium fusidate. Sodium fusidate 1 g is equivalent to about 0.98 g of fusidic acid. Because of differences in absorption (see Pharmacokinetics, above) 250 mg of fusidic acid is therapeutically equivalent to only 175 mg of the sodium salt, so doses of fusidic acid suspension (commonly used in children) appear relatively higher (see below). The diolamine salt was formerly used intravenously in humans but is still used in topical preparations in veterinary medicine.

Sodium fusidate is given as tablets in a usual oral adult dose of 500 mg every 8 hours, although this dose may be doubled in severe infection. For cutaneous staphylococcal infections, a dose of 250 mg twice daily is suitable. When given orally as the suspension the usual adult dose is 750 mg of fusidic acid three times daily.

In severe infections in adults weighing over 50 kg, sodium fusidate 500 mg is given three times daily by slow intravenous infusion. Each 500-mg dose is usually given as a buffered solution (pH 7.4 to 7.6) diluted to 500 mL with sodium chloride or other suitable intravenous solution. For those weighing less than 50 kg, a dose of 6 to 7 mg/kg three times daily is used. For details of doses in children, see below.

Sodium fusidate as a 2% ointment or medicated dressing, or fusidic acid as a 2% cream or gel, are used in the local treatment of skin infections. Eye drops containing fusidic acid 1% are used in eye infections. Topical use may lead to problems of resistance (see Antimicrobial Action, above).

Administration in children. In the UK, the licensed *oral* doses of **fusidic acid suspension**, given three times daily, are:

- up to 1 year old: about 15 mg/kg
- 1 to 5 years: 250 mg
- 5 to 12 years: 500 mg
- over 12 years: usual adult doses (see above)

Suggested doses of **sodium fusidate** by *intravenous* infusion are:

- 1 month and above: if weighing less than 50 kg, 6 to 7 mg/kg three times daily; heavier children may be given usual adult doses (see above)

The *BNFC* suggests that neonates up to 1 month of age may be given an intravenous dose of 10 mg/kg every 12 hours.

Preparations

BP 2008: Fusidic Acid Cream; Fusidic Acid Eye Drops; Fusidic Acid Oral Suspension; Sodium Fusidate Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Drum; Fucidin; Fucithalmic; Fusimed; Fusitop; Gelbiotic; ***Austral.:*** Fucidin; ***Austria:*** Fucidin; Fucithalmic; ***Belg.:*** Fucidin; Fucithalmic; ***Braz.:*** Verutex; ***Canad.:*** Fucidin; Fucithalmic; ***Chile:*** Fucidin; Fucithalmic; ***Cz.:*** Fucidin; Fucithalmic; ***Denm.:*** Fucidin; Fucithalmic; ***Fin.:*** Fucidin; Fucithalmic; ***Fr.:*** Fucidine; Fucithalmic; ***Ger.:*** Fucidine; Fucithalmic; ***Gr.:*** Flusterix; Fucidin; ***Hong Kong:*** Fucidin; Fucithalmic; Fusidate; Qualifutin; ***Hung.:*** Fucidin; Fucithalmic; ***India:*** Fusibact; Fusiwal; ***Indon.:*** Fucidin; Fucilex; Fucithalmic; Fuladic; Fuson; Fusycom; Futaderm; ***Irl.:*** Fucidin; Fucithalmic; ***Israel:*** Fucidin; Fucithalmic; ***Ital.:*** Dermomycin; Fucidin; Fucithalmic; ***Malaysia:*** Foban; Fucidin; Fucithalmic; Germacid†; ***Mex.:*** Fucidin; Uniderm; ***Neth.:*** Fucidin; Fucithalmic; ***Norw.:*** Fucidin; Fucithalmic; ***NZ:*** Foban; Fucidin; Fucithalmic; ***Philipp.:*** Flexid; Fucidin; Fucithalmic; Hopaq; ***Pol.:*** Fucidin; ***Port.:*** Desdek; Fucidine; Fucithalmic; Fusextrine; Infloc; Nadiclox; ***Rus.:*** Fucidin (Фуцидин); Fucithalmic (Фуциталмик); ***S.Afr.:*** Fucidin; Fucithalmic; ***Singapore:*** Balad†; Duzen; Foban; Forsuderm; Fucidin; Fucithalmic; Fudikin; ***Spain:*** Fucidine; Fucithalmic; ***Swed.:*** Fucidin; Fucithalmic; ***Switz.:*** Fucidin; Fucithalmic; ***Thai.:*** Foban; Fucidin; Fucithalmic; Fusid; ***Turk.:*** Fucidin; Fucithalmic; Stafine; ***UAE:*** Futasole; ***UK:*** Fucidin; Fucithalmic.

Multi-ingredient: ***Arg.:*** Drum B; Fucicort; Fusimed B; Gelbiotic Plus; ***Austria:*** Fucicort; ***Belg.:*** Fucicort; Fucidin Hydrocortisone; ***Braz.:*** Verutex

B; ***Canad.:*** Fucidin H; ***Chile:*** Fucicort; Fucidin H; ***Cz.:*** Fucicort; Fucidin H; ***Denm.:*** Fucicort; Fucidin-Hydrocortison; ***Fin.:*** Fucicort; Fucidin-Hydrocortison; ***Ger.:*** Fucicort; Fucidine plus†; ***Gr.:*** Alpider; Befucil; Betacort; Betafusin; Betasid; Betfu; Fubecot; Fucicort; Fucicream; Fucidin H; Fusibet; Hydrofusin; Roseti; Sensibio; Staficort; ***Hong Kong:*** Fucicort; Fucidin H; ***Hung.:*** Fucicort; Fucidin H; ***Indon.:*** Fucicort; ***Irl.:*** Fucibet; Fucidin H; ***Israel:*** Fucicort; Fucidin H†; ***Ital.:*** Fucicort; Fucidin H; Piodermina; ***Malaysia:*** Axcel Fusi-Corte; Foban-Hydro; Fobancort; Fucicort; Fucidin H; Fusidic B; ***Mex.:*** Fucicort; ***Norw.:*** Fucidin-Hydrocortison; ***NZ:*** Fucicort; ***Philipp.:*** Fucicort; Fucidin H; Hoebedic; ***Port.:*** Fucicort; Fucidine H; ***Rus.:*** Fucicort (Фуцикорт); Fucidin H (Фуцидин Г); ***S.Afr.:*** Fucidin H; ***Singapore:*** Fobancort; Fucicort; Fucidin H; ***Spain:*** Fucibet; Fucidine H; ***Swed.:*** Fucidin-Hydrocortison; ***Switz.:*** Fucicort; Fucidin H; ***Thai.:*** Fucicort; Fucidin H; ***UAE:*** Futasone; ***UK:*** Fucibet; Fucidin H.

Garenoxacin Mesilate *(BANM, rINNM)*

BMS-284756-01; Garenoxacin Mesylate *(USAN)*; Garénoxacine, Mésilate de; Garenoxacini Mesilas; Mesilato de garenoxacino; T-3811ME. 1-Cyclopropyl-8-(difluoromethoxy)-7-[(1*R*)-1-methyl-2,3-dihydro-1*H*-isoindol-5-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulfonate monohydrate.

Гареноксацина Мезилат

$C_{23}H_{20}F_2N_2O_4,CH_4O_3S,H_2O = 540.5.$

CAS — 194804-75-6 (garenoxacin); 223652-82-2 (garenoxacin mesilate); 223652-90-2 (garenoxacin mesilate monohydrate).

ATC — J01MA19.

ATC Vet — QJ01MA19.

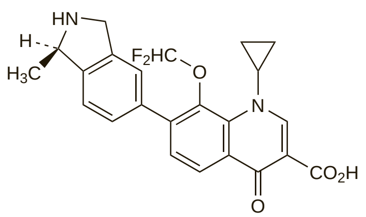

(garenoxacin)

Profile

Garenoxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.247). Garenoxacin is used as the mesilate but doses are given in terms of the base: about 507 mg of the mesilate is equivalent to 400 mg of garenoxacin. It is given orally in the treatment of susceptible infections in usual doses equivalent to 400 mg of garenoxacin daily.

Gatifloxacin *(USAN, rINN)*

AM-1155; BMS-206584-01; CG-5501; Gatifloxacine; Gatifloxacino; Gatifloxacinum. (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

Гатифлоксацин

$C_{19}H_{22}FN_3O_4,1\frac{1}{2}H_2O = 402.4.$

CAS — 160738-57-8 (anhydrous gatifloxacin); 180200-66-2 (gatifloxacin sesquihydrate).

ATC — J01MA16; S01AX21.

ATC Vet — QJ01MA16; QS01AX21.

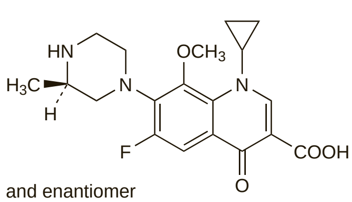

and enantiomer

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported in patients (usually diabetics) taking gatifloxacin. However, hypoglycaemia, and particularly hyperglycaemia, have occurred in non-diabetic patients. Severe life-threatening events, including hyperosmolar nonketotic hyperglycaemic coma, diabetic ketoacidosis, hypoglycaemic coma, convulsions, and mental status changes have been reported very rarely. Although in most cases the blood-glucose disturbance was reversible, fatalities have been reported. Gatifloxacin should not be given to diabetic patients. Other risk factors for developing blood-glucose disturbances include older age (patients 65 years of age or over), renal impairment, or use of other drugs that alter blood-glucose concentrations, particularly hypoglycaemics. Patients with risk factors should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, gatifloxacin should be stopped.

Effects on glucose metabolism. Hypoglycaemia and hyperglycaemia have been associated with gatifloxacin in both diabetic and non-diabetic patients.[1-6] A review[7] of spontaneous adverse effects reported to the FDA in the USA between November 1997 and September 2003 found the rate of blood-glucose disturbances with gatifloxacin to be 10-fold higher when compared with ciprofloxacin, levofloxacin, and moxifloxacin. Subsequent population-based case-control studies[8] in elderly patients given fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, or moxifloxacin), second-generation cephalosporins, or macrolides also found an increased risk of blood-glucose disturbances with gatifloxacin.

While blood-glucose disturbances appear to be mainly associated with gatifloxacin, the possibility that they may also be a class effect of fluoroquinolones cannot be excluded; patients most at risk are the elderly, those with diabetes and/or those taking hypoglycaemic drugs, and patients with impaired renal function.[9] Twenty two case reports of dysglycaemia associated with the use of levofloxacin were received by Health Canada between January 1997 and June 2006; reported cases included 15 diabetic patients.[10] In contrast a review of the effects of moxifloxacin on blood glucose, including data from large postmarketing studies, suggested it had no significant effect.[11]

1. Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. *Ann Pharmacother* 2002; **36:** 1722–6.
2. Donaldson AR, *et al.* Possible gatifloxacin-induced hyperglycemia. *Ann Pharmacother* 2004; **38:** 602–5.
3. Happe MR, *et al.* Gatifloxacin-induced hyperglycemia. *Ann Intern Med* 2004; **141:** 968–9.
4. Khovidhunkit W, Sunthornyothin S. Hypoglycemia, hyperglycemia, and gatifloxacin. *Ann Intern Med* 2004; **141:** 969.
5. Greenberg AL, *et al.* Gatifloxacin therapy associated with hypoglycemia. *Clin Infect Dis* 2005; **40:** 1210–11.
6. Blommel AL, Lutes RA. Severe hyperglycemia during renally adjusted gatifloxacin therapy. *Ann Pharmacother* 2005; **39:** 1349–52.
7. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 2005; **41:** 1269–76.
8. Park-Wyllie LY, *et al.* Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006; **354:** 1352–61.
9. Lewis RJ, Mohr JF. Dysglycaemias and fluoroquinolones. *Drug Safety* 2008; **31:** 283–92.
10. Health Canada. Levofloxacin: dysglycemia and liver disorders. *Can Adverse React News* 2007; **17:** 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ carn-bcei_v17n1-eng.pdf (accessed 17/06/08)
11. Gavin JR, *et al.* Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. *Drug Safety* 2004; **27:** 671–86.

Interactions

As for Ciprofloxacin, p.246.

Use of gatifloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Antidiabetics. Given the adverse effects of gatifloxacin, pharmacodynamic interactions with antidiabetics might reasonably be anticipated. Severe and persistent hypoglycaemia occurred in 3 patients taking oral hypoglycaemics (*repaglinide*, *glibenclamide* and *pioglitazone*, and *glimepiride*) when gatifloxacin was added to their therapy.[1]

1. Menzies DJ, *et al.* Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med* 2002; **113:** 232–4.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Gatifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

◊ References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; **47:** 1308–12.

Pharmacokinetics

Gatifloxacin is readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Peak plasma concentrations occur within 1 to 2 hours of an oral dose. Gatifloxacin is widely distributed into body tissues and is about 20% bound to plasma proteins. It undergoes limited metabolism and has an elimination half-life of 7 to 14 hours. Gatifloxacin is excreted primarily unchanged in the urine with less than 1% as metabolites. About 5% is also excreted unchanged in the faeces. Distribution into milk occurs in *animals*.

Uses and Administration

Gatifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally, or by intravenous infusion as a 2 mg/mL solution over 60 minutes, for the treatment of susceptible infections, including respiratory- and urinary-tract infections and skin infections. The usual adult dose is 400 mg once daily. A single dose of 400 mg or a dose of 200 mg daily for 3 days may be adequate for uncomplicated urinary-tract infections.

For details of reduced doses to be used in renal impairment, see below.

A single dose of 400 mg may also be given for the treatment of uncomplicated gonorrhoea.

Gatifloxacin is also used as 0.3% eye drops for the treatment of bacterial conjunctivitis.

◊ Reviews.

1. Keam SJ, *et al.* Gatifloxacin: a review of its use in the treatment of bacterial infections in the US. *Drugs* 2005; **65:** 695–724.

Administration in renal impairment. Doses of gatifloxacin should be reduced in patients with renal impairment; the usual initial dose of 400 mg should be followed by reduced maintenance doses of 200 mg daily in those with a creatinine clearance of less than 40 mL/minute and in those on haemodialysis or continuous peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gatif; Tequin†; Zymaran; ***Austral.:*** Tequin; ***Braz.:*** Tequin; Zymar; ***Canad.:*** Tequin; Zymar; ***Chile:*** Starox†; Zymar; ***Ger.:*** Bonoq†; ***India:*** Biogat†; Gaticin; Gatiquin; Gatt; Zyquin; ***Indon.:*** Gaticin; Gatimax; ***Jpn:*** Gatiflo; ***Malaysia:*** Tequin†; ***Mex.:*** Tequin; Zymar; ***NZ:*** Tequin; ***Philipp.:*** Tequin; Zymar; ***S.Afr.:*** Tequin; ***Singapore:*** Tequin†; Zymar; ***Thai.:*** Tequin†; Zymar; ***USA:*** Tequin†; Zymar.

Multi-ingredient: ***India:*** Gatiquin Oz Kit.

Gemifloxacin Mesilate *(rINNM)*

Gemifloxacin Mesylate *(USAN)*; Gémifloxacine, Mésilate de; Gemifloxacini Mesilas; LB-20304 (gemifloxacin); LB-20304a; Mesilato de gemifloxacino; SB-265805 (gemifloxacin); SB-265805S. (±)-7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid 7[4]-(*Z*)-(*O*-methyloxime) methanesulfonate.

Гемифлоксацина Мезилат

$C_{18}H_{20}FN_5O_4,CH_4O_3S = 485.5.$

CAS — 204519-64-2 (gemifloxacin); 204519-65-3 (gemifloxacin mesilate).

ATC — J01MA15.

ATC Vet — QJ01MA15.

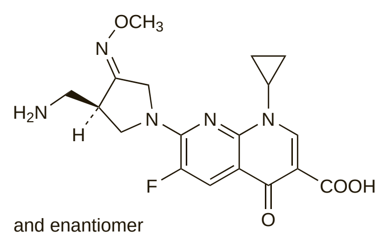

and enantiomer

(gemifloxacin)

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Skin rashes may be more common with gemifloxacin and treatment should be stopped if they occur.

Interactions

As for Ciprofloxacin, p.246.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Gemifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

◊ References.

1. Morrissey I, Tillotson G. Activity of gemifloxacin against Streptococcus pneumoniae and Haemophilus influenzae. *J Antimicrob Chemother* 2004; **53:** 144–8.

Pharmacokinetics

Gemifloxacin is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of about 71%. Peak plasma concentrations occur 0.5 to 2 hours after an oral dose. Gemifloxacin is widely distributed into body tissues including the bronchial mucosa and lungs, and is about 55 to 73% bound to plasma proteins. It undergoes limited hepatic metabolism and has an elimination half-life of about 7 hours. It is excreted as unchanged drug and metabolites in the faeces and urine. Urinary excretion is by active tubular secretion and is reduced by probenecid. Distribution into milk has been found in *rats*.

Uses and Administration

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally, as the mesilate, for the treatment of community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. Doses are expressed in terms of the base; 399 mg of gemifloxacin mesilate is equivalent to about 320 mg of gemifloxacin. The usual dose is 320 mg once daily for 5 days in patients with bronchitis or for 7 days in those with pneumonia.

For details of reduced doses in patients with renal impairment, see below.

◊ Reviews.

1. Lowe MN, Lamb HM. Gemifloxacin. *Drugs* 2000; **59:** 1137–47.
2. Yoo BK, *et al*. Gemifloxacin: a new fluoroquinolone approved for treatment of respiratory infections. *Ann Pharmacother* 2004; **38:** 1226–35.
3. File TM, Tillotson GS. Gemifloxacin: a new, potent fluoroquinolone for the therapy of lower respiratory tract infections. *Expert Rev Anti Infect Ther* 2004; **2:** 831–43.
4. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: in vitro susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2005; **25:** 717–40.
5. Blondeau JM, Tillotson G. Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. *Int J Antimicrob Agents* 2008; **31:** 299–306.
6. Lode HM, *et al.* Gemifloxacin for community-acquired pneumonia. *Expert Opin Invest Drugs* 2008; **17:** 779–86.
7. Tillotson GS. Role of gemifloxacin in community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2008; **6:** 405–18.

Administration in renal impairment. Doses of gemifloxacin should be halved in patients with a creatinine clearance of 40 mL/minute or less, including those receiving haemodialysis or continuous peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Factive; ***Rus.:*** Factiv (Фактив); ***S.Afr.:*** Factive; ***USA:*** Factive.

Gentamicin Sulfate *(USAN, pINNM)*

Gentamicin sulfát; Gentamicin Sulphate *(BANM)*; Gentamicine, sulfate de; Gentamicini sulfas; Gentamicino sulfatas; Gentamicin-sulfát; Gentamicin-szulfát; Gentamisiinisulfaatti; Gentamisin Sülfat; Gentamycyny siarczan; NSC-82261; Sch-9724; Sulfato de gentamicina.

Гентамицина Сульфат

CAS — 1403-66-3 (gentamicin); 1405-41-0 (gentamicin sulfate).

ATC — D06AX07; J01GB03; S01AA11; S02AA14; S03AA06.

ATC Vet — QD06AX07; QJ01GB03; QS01AA11; QS02AA14; QS03AA06.

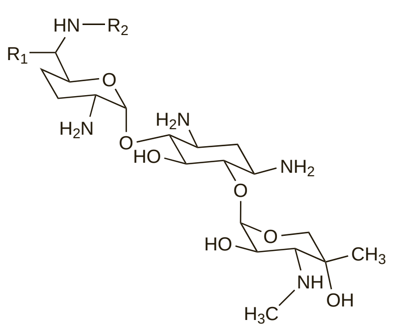

Gentamicin C_1 $R_1 = R_2 = CH_3$
Gentamicin C_2 $R_1 = CH_3$, $R_2 = H$
Gentamicin C_{1a} $R_1 = R_2 = H$

(gentamicin)

NOTE. GNT is a code approved by the BP 2008 for use on single unit doses of eye drops containing gentamicin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Gentamicin Sulphate). A mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a, and C2b. It contains 20 to 40% of gentamicin C1, 10 to 30% of gentamicin C1a; the sum of gentamicins C2, C2a, and C2b is 40 to 60%. The potency is not less than 590 units/mg, calculated with reference to the anhydrous substance. A white or almost white hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Gentamicin Sulfate). The sulfate salt, or a mixture of such salts, of antibiotic substances produced by the growth of *Micromonospora purpurea*. The content of gentamicin C1 is between 25 and 50%, the content of gentamicin C1a is between 10 and 35%, and the sum of the contents of gentamicin C2a and gentamicin C2 is between 25 and 55%. It has a potency equivalent to not less than 590 micrograms of gentamicin per mg, calculated on the dried basis. A white to buff powder. Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 4% solution in water is between 3.5 and 5.5. Store in airtight containers.

Incompatibility. The aminoglycosides are inactivated *in vitro* by various penicillins and cephalosporins via an interaction with the beta-lactam ring, the extent of inactivation depending on temperature, concentration, and duration of contact. The different aminoglycosides vary in their stability, with amikacin apparently the most resistant and tobramycin the most susceptible to inactivation; gentamicin and netilmicin are of intermediate stability. The beta lactams also vary in their ability to produce inactivation, with ampicillin, benzylpenicillin, and antipseudomonal penicillins such as carbenicillin and ticarcillin producing marked inactivation. Inactivation has also been reported with clavulanic acid.

Gentamicin is also incompatible with furosemide, heparin, sodium bicarbonate (the acid pH of gentamicin solutions may liberate carbon dioxide), and some solutions for parenteral nutrition. Interactions with preparations having an alkaline pH (such as sulfadiazine sodium), or drugs unstable at acid pH (for example erythromycin salts), might reasonably be expected.

Given their potential for incompatibility, gentamicin and other aminoglycosides should not generally be mixed with other drugs in syringes or infusion solutions nor given through the same intravenous line. When aminoglycosides are given with a beta lactam, they should generally be given at separate sites.

General references.

1. Henderson JL, *et al.* In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. *Am J Hosp Pharm* 1981; **38:** 1167–70.
2. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; **17:** 906–8.
3. Navarro AS, *et al.* In-vitro interaction between dibekacin and penicillins. *J Antimicrob Chemother* 1986; **17:** 83–9.
4. Courcol RJ, Martin GR. Comparative aminoglycoside inactivation by potassium clavulanate. *J Antimicrob Chemother* 1986; **17:** 682–4.

Stability. There was an average 16% potency loss of gentamicin sulfate from solutions containing 10 and 40 mg/mL when stored at 4° or 25° in plastic disposable syringes for 30 days, and a brown precipitate formed in several. Storage in glass disposable syringes for 30 days produced an average 7% potency loss, which was considered acceptable, but storage for longer resulted in precipitate formation in some cases and was not recommended.[1]

1. Weiner B, *et al*. Stability of gentamicin sulfate injection following unit dose repackaging. *Am J Hosp Pharm* 1976; **33:** 1254–9.

Adverse Effects

The aminoglycosides can produce irreversible, cumulative ototoxicity. This affects both the cochlea (manifest as hearing loss, initially of higher tones, and which, because speech recognition relies greatly on lower frequencies, may not be at first apparent) and the vestibular system (manifest as dizziness or vertigo). The incidence and relative toxicity with different aminoglycosides is a matter of some dispute, but netilmicin is probably less cochleotoxic than gentamicin or tobramycin, and amikacin more so. Netilmicin also exhibits less vestibular toxicity than gentamicin, tobramycin, or amikacin, while streptomycin produces a high incidence of vestibular damage. Vestibular damage is more common than hearing loss in patients receiving gentamicin.

Reversible nephrotoxicity may occur and acute renal failure has been reported, often in association with the use of other nephrotoxic drugs. Renal impairment is usually mild, although acute tubular necrosis and interstitial nephritis have occurred. Decreased glomerular filtration rate is usually seen only after several days, and may even occur after therapy has stopped. Electrolyte disturbances (notably hypomagnesaemia, but also hypocalcaemia and hypokalaemia) have occurred. The nephrotoxicity of gentamicin is reported to be largely due to the gentamicin C_2 component.

Although particularly associated with high plasma concentrations, many risk factors have been suggested for ototoxicity and nephrotoxicity in patients receiving aminoglycosides—see Precautions below.

Aminoglycosides possess a neuromuscular-blocking action and respiratory depression and muscular paralysis have been reported, notably after absorption from serous surfaces. Neomycin has the most potent action and several deaths have been associated with its use.

Hypersensitivity reactions have occurred, especially after local use, and cross-sensitivity between aminoglycosides may occur. Very rarely, anaphylactic reactions to gentamicin have occurred. Some hypersensitivity reactions have been attributed to the presence of sulfites in parenteral formulations, and endotoxic shock has also been reported.

Infrequent effects reported for gentamicin include blood dyscrasias, purpura, nausea and vomiting, stomatitis, and signs of liver dysfunction such as increased serum-aminotransferase values and increased serum-bilirubin concentrations. Neurotoxicity has occurred, with both peripheral neuropathies and central symptoms being reported including encephalopathy, confusion, lethargy, hallucinations, convulsions, and mental depression.

Atrophy or fat necrosis has been reported at injection sites. There have been isolated reports of meningeal irritation, arachnoiditis, polyradiculitis, and ventriculitis after intrathecal, intracisternal, or intraventricular use of aminoglycosides. Subconjunctival injection of gentamicin may lead to pain, hyperaemia, and conjunctival oedema, while severe retinal ischaemia has followed intra-ocular injection.

Effects on the ears. Reviews and references to aminoglycoside-induced ototoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
3. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 797–800.
4. Mattie H, *et al.* Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
5. Schacht J. Aminoglycoside ototoxicity: prevention in sight? *Otolaryngol Head Neck Surg* 1998; **118:** 674–7.
6. Nakashima T, *et al.* Vestibular and cochlear toxicity of aminoglycosides—a review. *Acta Otolaryngol* 2000; **120:** 904–11.
7. Darlington CL, Smith PF. Vestibulotoxicity following aminoglycoside antibiotics and its prevention. *Curr Opin Investig Drugs* 2003; **4:** 841–6.
8. Rizzi MD, Hirose K. Aminoglycoside ototoxicity. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 352–7.

Effects on the kidneys. Reviews and references to aminoglycoside-induced nephrotoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Lietman PS, Smith CR. Aminoglycoside nephrotoxicity in humans. *Rev Infect Dis* 1983; **5** (suppl 2): S284–93.
3. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
4. Kohlhepp SJ, *et al.* Nephrotoxicity of the constituents of the gentamicin complex. *J Infect Dis* 1984; **149:** 605–14.
5. Mattie H, *et al.* Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
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10. Rougier F, *et al.* Aminoglycoside nephrotoxicity. *Curr Drug Targets Infect Disord* 2004; **4:** 153–62.
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Endotoxin reactions. Reports of endotoxin reactions associated with intravenous gentamicin have been received by the CDC and the FDA in the USA.[1] Although endotoxin concentrations in the injections used were within USP limits, giving a single daily dose rather than divided doses was thought to have resulted in toxic serum concentrations of endotoxins.[1,2]

1. CDC. Endotoxin-like reactions associated with intravenous gentamicin—California, 1998. *MMWR* 1998; **47:** 877–80.
2. Krieger JA, Duncan L. Gentamicin contaminated with endotoxin. *N Engl J Med* 1999; **340:** 1122.

Treatment of Adverse Effects

Aminoglycosides may be removed by haemodialysis or to a much lesser extent by peritoneal dialysis. Calcium salts given intravenously have been used to counter neuromuscular blockade; the effectiveness of neostigmine has been variable.

◊ For reference to the potential for calcium-channel blockers to reduce aminoglycoside-related nephrotoxicity, see Kidney Disorders, under Uses of Verapamil, p.1424.

Precautions

Gentamicin is contra-indicated in patients with a known history of hypersensitivity to it, and probably in those hypersensitive to other aminoglycosides. It should be avoided in patients with myasthenia gravis, and great care is required in patients with parkinsonism and other conditions characterised by muscular weakness.

The risk of ototoxicity and nephrotoxicity from aminoglycosides is increased at high plasma concentrations and it is therefore generally desirable to determine dosage requirements by individual monitoring. In patients receiving standard multiple-dose regimens of gentamicin, dosage should be adjusted to avoid peak plasma concentrations above 10 micrograms/mL, or trough concentrations (immediately before next dose) exceeding 2 micrograms/mL. Local guidelines on serum concentration should be consulted where once-daily dosage regimens are used. Monitoring is particularly important in patients receiving high doses or prolonged courses, in infants and the elderly, and in patients with renal impairment, who generally require reduced doses. The *BNF* also considers monitoring to be important in patients with cystic fibrosis or significant obesity; again, altered doses may be required. See Pharmacokinetics below for other patient groups in whom pharmacokinetics may be altered. Impaired hepatic function or auditory function, bacteraemia, fever, and perhaps exposure to loud noises have also been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity. Regular assessment of auditory and renal function is particularly necessary in patients with additional risk factors.

Topical application of gentamicin into the ear is contra-indicated in patients with known or suspected perforation of the ear drum.

Use of aminoglycosides during pregnancy may damage the eighth cranial nerve of the fetus.

Breast feeding. A study[1] involving 10 mothers given gentamicin and their breast-fed infants found measurable gentamicin concentrations in the serum of 5 of the 10 neonates, indicating that appreciable gastrointestinal absorption had occurred. It was, however, considered that these low concentrations would not cause clinical effects and the American Academy of Pediatrics[2] also considers that the use of gentamicin is usually compatible with breast feeding.

1. Celiloglu M, *et al.* Gentamicin excretion and uptake from breast milk by nursing infants. *Obstet Gynecol* 1994; **84:** 263–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interference with assay procedures. The implications of drug interference with assays for aminoglycosides have been reviewed.[1] Other antimicrobials and antineoplastics may alter the results of microbiological assays but this can be overcome by selection of an appropriate assay organism.

Microbiological assays for aminoglycosides in samples also containing *imipenem* could be accomplished by using cysteine hydrochloride to inactivate imipenem, since it is stable to most beta-lactamases and resistant strains are extremely rare.[2] Because aminoglycosides may be inactivated by *penicillins* and *cephalosporins*, it has been recommended that aminoglycoside sampling times should be chosen to coincide with a trough plasma concentration for the beta lactam. Samples should be frozen if there is to be a delay before they are assayed[3] or a penicillinase added. However, one group of workers have reported loss of gentamicin activity after storage at −60° before assay.[4] Furthermore, there have been reports that concentrations of aminoglycosides in patients also receiving beta lactams have been overestimated using a homogeneous enzyme immunoassay, probably because of an inability to differentiate between active drug and inactivated products.[5,6]

The radionuclide *gallium-67* interferes with radio-enzymatic assays, and it has been suggested that an agar diffusion method should be used in patients who have received a gallium scan.[7,8]

Heparin has been shown to produce underestimation of aminoglycoside concentrations when using microbiological, enzymatic, or immunoassays.[9-11] It has been recommended that either serum should be used or that blood samples should not be collected in heparinised tubes or from indwelling catheter lines. Some consider that concentrations of heparin reached in the blood of patients receiving heparin are too low to affect gentamicin.[12]

Falsely low concentrations have also been reported in microbiological assays in the presence of *zinc* salts.[13]

Heat treatment of whole *blood* to inactivate human immunodeficiency virus leads to an increase in the concentration of gentamicin subsequently found on assay.[14]

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
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4. Carlson LG, *et al.* Potential liabilities of gentamicin homogeneous enzyme immunoassay. *Antimicrob Agents Chemother* 1982; **21:** 192–4.
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8. Shannon K, *et al.* Interference with gentamicin assays by gallium-67. *J Antimicrob Chemother* 1980; **6:** 285–300.
9. Nilsson L. Factors affecting gentamicin assay. *Antimicrob Agents Chemother* 1980; **17:** 918–21. Correction. *ibid.*; **18:** 839.
10. Nilsson L, *et al.* Inhibition of aminoglycoside activity by heparin. *Antimicrob Agents Chemother* 1981: **20:** 155–8.
11. O'Connell MB, *et al.* Heparin interference with tobramycin, netilmicin, and gentamicin concentrations determined by Emit. *Drug Intell Clin Pharm* 1984; **18:** 503–4.
12. Regamey C, *et al.* Inhibitory effect of heparin on gentamicin concentrations in blood. *Antimicrob Agents Chemother* 1972; **1:** 329–32.
13. George RH, Healing DE. The effect of zinc on aminoglycoside assay. *J Antimicrob Chemother* 1978; **4:** 186.
14. Eley A, *et al.* Effect of heat on gentamicin assays. *Lancet* 1987; **ii:** 335–6.

Interactions

Use of other nephrotoxic drugs (including other aminoglycosides, vancomycin, some cephalosporins, ciclosporin, cisplatin, and fludarabine), or of potentially ototoxic drugs such as etacrynic acid and perhaps furosemide, may increase the risk of aminoglycoside toxicity. It has been suggested that use of an antiemetic such as dimenhydrinate may mask the early symptoms of vestibular ototoxicity. Care is also required if other drugs with a neuromuscular-blocking action are used (see Atracurium, p.1903). The neuromuscular-blocking properties of aminoglycosides may be sufficient to provoke severe respiratory depression in patients given general anaesthetics or opioids.

There is a theoretical possibility that the antibacterial effects of aminoglycosides could be reduced by bacteriostatic antibacterials, but such combinations have been used successfully in practice.

Since aminoglycosides have been shown to be incompatible with some beta lactams *in vitro* (see Incompatibility, above), these antibacterials should be given separately if both are required; antagonism *in vivo* has been reported only in a few patients with severe renal impairment, in whom aminoglycoside activity was diminished. Aminoglycosides exhibit synergistic activity with a number of beta lactams *in vivo* (see Antimicrobial Action, below).

Renal excretion of zalcitabine may be reduced by aminoglycosides.

For a report of severe hypocalcaemia in a patient treated with aminoglycosides and bisphosphonates, see p.1091.

Gentamicin may inhibit α-galactosidase activity and should not be used with agalsidase alfa or beta.

Antimicrobial Action

Gentamicin is an aminoglycoside antibiotic and has a bactericidal action against many Gram-negative aerobes and against some strains of staphylococci.

Mechanism of action. Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anaerobic, acidic, or hyperosmolar environments. Within the cell they bind to the 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

Spectrum of activity. The following pathogenic organisms are usually sensitive to gentamicin (but see also Resistance, below).

Many strains of Gram-negative bacteria including species of *Brucella*, *Calymmatobacterium*, *Campylobacter*, *Citrobacter*, *Escherichia*, *Enterobacter*, *Francisella*, *Klebsiella*, *Proteus*, *Providencia*, *Pseudomonas*, *Serratia*, *Vibrio*, and *Yersinia*. Some activity has been reported against isolates of *Neisseria*, although aminoglycosides are rarely used clinically in neisserial infections.

Among the Gram-positive organisms many strains of *Staphylococcus aureus* are highly sensitive to gentamicin. *Listeria monocytogenes* and some strains of *Staph. epidermidis* may also be sensitive to gentamicin, but enterococci and streptococci are usually insensitive to gentamicin.

Some actinomycetes and mycoplasmas have been reported to be sensitive to gentamicin, but mycobacteria are insensitive at clinically achievable concentrations; anaerobic organisms, yeasts, and fungi are resistant.

Activity with other antimicrobials. Gentamicin exhibits synergy with beta lactams, probably because the effects of the latter on bacterial cell walls enhance aminoglycoside penetration. Enhanced activity has been demonstrated with a penicillin (such as ampicillin or benzylpenicillin) and gentamicin against the enterococci, and gentamicin has been combined with an antipseudomonal penicillin such as ticarcillin for enhanced activity against *Pseudomonas* spp., and with vancomycin for enhanced activity against staphylococci and streptococci.

Resistance to the aminoglycosides may be acquired by three main mechanisms. The first is by mutation of ribosomal target sites leading to reduced affinity for binding; this type of resistance is generally only relevant for streptomycin and, even then, it appears to be rare in Gram-negative bacteria. Secondly, penetration of aminoglycosides into bacterial cells is by an oxygen-dependent active transport process and resistance may occur because of elimination or reduction of this uptake; when it occurs this generally results in cross-resistance to all aminoglycosides. Thirdly, and by far the most important cause of resistance to the aminoglycosides, is inactivation by enzymatic modification. Three main classes of enzyme conferring resistance have been found, operating by phosphorylation, acetylation, or addition of a nucleotide group, usually adenyl. Enzyme production is usually plasmid-determined and resistance can therefore be transferred between bacteria, even of different species. Resistance to other antibacterials may be transferred at the same time. In *Staph. aureus*, transfer of resistance is more likely when these drugs are used topically. Each type of enzyme produces characteristic patterns of resistance, but their overlapping and variable affinities for their substrates result in a wide range of permutations of cross-resistance to the different aminoglycosides. The different enzymes vary in their distribution and prevalence in different locations, and at different times, presumably with variations in antibacterial usage, but relationships to the use of specific aminoglycosides are difficult to establish. These variations in drug sensitivity require local testing to determine resistance and establish susceptibility of bacteria to the aminoglycoside being used, but such local variations mean that estimates of the incidence of resistance are of limited value. In general, the occurrence of resistant pathogens seems to have been greater in southern than in northern Europe, and perhaps greater in the USA than in Europe. There has been particular concern over the increasing incidence of high-level gentamicin resistance among enterococci (in up to 50% of isolates from some centres), since they already possess inherent or acquired resistance to many drugs, including vancomycin in some cases. A similar problem exists with gentamicin resistance in meticillin-resistant strains of *Staph. aureus*. Such multiply-resistant strains pose a major therapeutic problem in those centres where they occur, since the usual synergistic combinations with other antibacterials are ineffective. However, results from some centres indicate that rational use of a wider range of aminoglycosides (including amikacin which is not affected by most of the aminoglycoside-degrading enzymes) has resulted in a modest decline in overall aminoglycoside resistance.

◊ References.

1. Mingeot-Leclercq M-P, *et al.* Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother* 1999; **43:** 727–37.
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3. Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance for effective dosage regimens. *Drugs* 2001; **61:** 713–21.
4. Magnet S, Blanchard JS. Molecular insights into aminoglycoside action and resistance. *Chem Rev* 2005; **105:** 477–98.

Pharmacokinetics

Gentamicin and other aminoglycosides are poorly absorbed from the gastrointestinal tract but are rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 micrograms/mL have been attained in patients with normal renal function 30 to 60 minutes after an intramuscular dose equivalent to gentamicin 1 mg/kg, which is similar to concentrations achieved after intravenous infusion. There may be considerable individual variation. Several doses are required before plasma equilibrium concentrations occur and this may represent the saturation of binding sites in body tissues such as the kidney. Binding of gentamicin to plasma proteins is usually low.

On parenteral use, gentamicin and other aminoglycosides diffuse mainly into extracellular fluids. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved; diffusion into the eye is also poor. Aminoglycosides diffuse readily into the perilymph of the inner ear. They cross the placenta but only small amounts have been reported in breast milk.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and on instillation into, and irrigation of, wounds, body-cavities (except the urinary bladder), and joints.

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. At steady state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 micrograms/mL may be achieved. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides. Release from these sites is slow and small amounts of aminoglycosides may be detected in the urine for up to 20 days or more after treatment stops. Small amounts of gentamicin appear in the bile.

The pharmacokinetics of the aminoglycosides are affected by many factors, which may become significant because of the relatively small difference between therapeutic and toxic concentrations, reinforcing the need for monitoring.

- Absorption from intramuscular sites may be reduced in critically ill patients, especially in conditions that reduce perfusion such as shock, resulting in **reduced plasma concentrations**. Plasma concentrations may also be reduced in patients with conditions which expand extracellular fluid volume or increase renal clearance including ascites, cirrhosis, heart failure, malnutrition, spinal cord injury, burns, cystic fibrosis, and possibly leukaemia. Clearance is also reportedly increased in intravenous drug abusers, and in patients who are febrile.
- In contrast, renal impairment or reduced renal clearance for any reason (for example in neonates with immature renal function, or in the elderly in whom glomerular function tends to decline with age) can result in markedly **increased plasma concentrations** and/or prolonged half-lives. However, in neonates initial plasma concentrations may actually be reduced, due to a larger volume of distribution. Plasma concentrations may also be higher than expected for a given dose in obese patients (in whom extracellular volume is low relative to weight), and in patients with anaemia.

Renal clearance, and hence plasma concentrations, of aminoglycosides may vary according to a circadian cycle, and it has been suggested that this should be taken into account when determining and comparing plasma aminoglycoside concentrations.

Uses and Administration

Gentamicin is an aminoglycoside antibiotic used, often with other antibacterials, to treat severe systemic infections due to sensitive Gram-negative and other organisms (see Antimicrobial Action, above). Such infections include biliary-tract infections (acute cholecystitis or cholangitis), brucellosis, cat scratch disease, cystic fibrosis, endocarditis (in the treatment and prophylaxis of endocarditis due to streptococci, enterococci, or staphylococci), endometritis, gastroenteritis, granuloma inguinale, listeriosis, meningitis, otitis externa, otitis media, pelvic inflammatory disease, peritonitis, plague, pneumonia, septicaemia, skin infections such as in burns or ulcers (given systemically for pseudomonal and other Gram-negative infections), tularaemia, and urinary-tract infections (acute pyelonephritis), as well as in the prophylaxis of surgical infection and the treatment of immunocompromised patients and those in intensive care. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. Gentamicin is also applied topically for localised infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Gentamicin is often used with other antibacterials to extend its spectrum of activity or increase its efficacy, e.g. with a penicillin for enterococcal and streptococcal infections, or an antipseudomonal beta lactam for pseudomonal infections, or with metronidazole or clindamycin for mixed aerobic-anaerobic infections.

Administration and dosage. Gentamicin is used as the sulfate but doses are expressed in terms of gentamicin base. For many of the infections above it is given intramuscularly every 8 hours to provide a total daily dose of 3 to 5 mg/kg. In the prophylaxis and treatment of streptococcal and enterococcal endocarditis, a dose of 1 mg/kg every 8 hours with a penicillin or vancomycin has been suggested for treatment in the UK; a suggested dose for prophylaxis in high-risk patients is 120 mg before induction of anaesthesia, with a penicillin or vancomycin or teicoplanin. For urinary-tract infections, if renal function is not impaired, 160 mg once daily may be used.

Gentamicin sulfate may also be given intravenously in similar doses to those used intramuscularly, but there is some disagreement as to the appropriate method, since intravenous infusion has been associated with both subtherapeutic and excessive trough concentrations of gentamicin, while bolus intravenous injection may increase the risk of neuromuscular blockade. In the USA, intravenous infusion over 30 minutes to 2 hours is favoured, but sources in the UK differ, with some licensed product information recommending infusion over no more than 20 minutes, in a limited fluid volume, while other products should not be given by slow infusion, recommending bolus injection over at least 2 to 3 minutes, and yet others allow use in a similar way to the USA.

The course of treatment should generally be limited to 7 to 10 days. As gentamicin is poorly distributed into fatty tissue it has been suggested that dosage calculations should be based on an estimate of lean bodyweight.

Doses in infants and children are usually somewhat higher than those in adults but exact dosage recommendations vary. One regimen is gentamicin 3 mg/kg every 12 hours in premature infants and those up to 2 weeks of age, with older neonates and children receiving 2 mg/kg every 8 hours. Alternatively, 2.5 mg/kg every 12 hours in the first week of life, 2.5 mg/kg every 8 hours or 3 mg/kg every 12 hours in infants and neonates, and 1.5 to 2 mg/kg every 8 hours in children has been given.

Dose adjustment and monitoring. Dosage should be adjusted in all patients according to plasma-gentamicin concentrations, and this is discussed in more detail under Administration and Dosage, below.

Once-daily dosage. In many centres, the total daily requirement is increasingly given as a single dose (see Once-daily Dosage, below). In suitable patients this appears to be as safe and effective as conventional regimens, and is more convenient. However, it is not suitable for all patients, especially those with endocarditis, extensive burns, or renal impairment (creatinine clearance less than 20 mL/minute). With once-daily dosage, traditional methods of monitoring peak and trough plasma concentrations may not be applicable and local guidelines on dosage and plasma concentrations should be consulted.

Other routes. Gentamicin has sometimes been given orally for enteric infections and to suppress intestinal flora and has occasionally been given by inhalation in cystic fibrosis. In meningitis it has been given intrathecally or intraventricularly usually in doses of 1 to 5 mg daily with intramuscular therapy. Gentamicin has also been given by subconjunctival injection.

A bone cement impregnated with gentamicin is used in orthopaedic surgery. Acrylic beads containing gentamicin and threaded on to surgical wire are implanted in the management of bone infections.

Gentamicin has also been applied topically for skin infections in concentrations of 0.1%, but such use may lead to the emergence of resistance and is considered inadvisable. Concentrations of 0.3% are used in preparations for topical application to the eyes and ears.

A liposomal formulation of gentamicin is under investigation.

◊ Reviews.

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Administration and dosage. *CONCENTRATION MONITORING.* Measurements of aminoglycoside plasma concentrations are routinely performed to individualise dosage regimens, both in terms of dose given and dosing interval, in order to attain the desired therapeutic range as quickly as possible.[1] This entails measurement of both peak concentrations to monitor efficacy and trough concentrations to avoid accumulation and thereby prevent toxicity. Dosage should be adjusted in all patients according to these concentrations, but this is of particular importance where factors such as age, renal impairment, or high dosage may predispose to toxicity. Although there has been some dispute about the relationship between plasma concentrations and toxicity it is generally recommended that, for multiple daily dosing with gentamicin, trough plasma concentrations (measured just before the next dose) should be less than 2 micrograms/mL, and peak concentrations should reach at least 4 micrograms/mL but not exceed 10 micrograms/mL. In the UK, peak concentrations are generally measured 1 hour after intramuscular and intravenous doses, but practice has varied between centres and countries and this may lead to difficulties when comparing figures.

Methods exist for calculating aminoglycoside dosage requirements, though none has been universally accepted. Simple pharmacokinetic methods involve linear dosage adjustment based on peak or trough concentrations or area under the concentration-time curve, or the use of predictive nomograms.[1] For most patients receiving once-daily dosage (see below), the nomogram is the method of choice, primarily because of its simplicity. However, it has not been validated for children and does not work in patients with either a very high clearance of aminoglycosides or a high volume of distribution, such as those with ascites, burns, or cystic fibrosis, or in other conditions such as pregnancy where the fixed dose assumed in the construction of the nomogram is irrelevant. When a nomogram cannot be applied, a more sophisticated pharmacokinetic method is required, using either Bayesian statistics or non-Bayesian methods such as that of Sawchuk and Zaske.[2,3] Bayesian methods are favoured when the patient population's pharmacokinetic parameters are well known because of their good predictive performance. Otherwise, the Sawchuk and Zaske method is the method of choice because of its robustness and the lack of requirement for prior information about the distribution of parameters within the population.[1]

1. Tod MM, *et al.* Individualising aminoglycoside dosage regimens after therapeutic drug monitoring: simple or complex pharmacokinetic methods? *Clin Pharmacokinet* 2001; **40:** 803–14.
2. Sawchuk RJ, Zaske DE. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm* 1976; **4:** 183–95.
3. Sawchuk RJ, *et al.* Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther* 1977; **21:** 362–9.

In neonates and infants. References.

1. Isemann BT, *et al.* Optimal gentamicin therapy in preterm neonates includes loading doses and early monitoring. *Ther Drug Monit* 1996; **18:** 549–55.
2. Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. *Ann Pharmacother* 1997; **31:** 1514–18.
3. Murphy JE, *et al.* Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. *Am J Health-Syst Pharm* 1998; **55:** 2280–9.
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6. Rastogi A, *et al.* Comparison of two gentamicin dosing schedules in very low birth weight infants. *Pediatr Infect Dis J* 2002; **21:** 234–40.
7. Chattopadhyay B. Newborns and gentamicin—how much and how often? *J Antimicrob Chemother* 2002; **49:** 13–16.
8. Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. *Am J Health-Syst Pharm* 2005; **62:** 823–7.
9. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62:** 1613–16.
10. Khan AM, *et al.* Extended-interval gentamicin administration in malnourished children. *J Trop Pediatr* 2006; **52:** 179–84.

In patients with non-ideal body-weight. References.

1. Traynor AM, *et al.* Aminoglycoside dosing weight correction factors for patients of various body sizes. *Antimicrob Agents Chemother* 1995; **39:** 545–8.

In renal impairment. Although a number of nomograms, schedules, and rules have been devised for the calculation of aminoglycoside dosage in renal impairment, where possible dosage modification should be based on the monitoring of individual pharmacokinetic parameters. Standard dosage calculation methods should not be used for patients undergoing dialysis as they may require supplementary post-dialysis doses.

Individualised regimens based on an initial dose (for moderate to severe infections) of 2 to 2.5 mg/kg, modified in the obese or those with excessive fluid retention, and with subsequent doses after haemodialysis ranging from 1 to 1.8 mg/kg, have been reported to be effective.[1] Serum-aminoglycoside concentrations were not routinely requested unless treatment for more than 4 days was thought likely, and the target concentration was adjusted both for the agressiveness of therapy required and the individual haemodialysis regimen. Typically, about 50% of a dose was eliminated in a haemodialysis session.

1. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. *Ann Pharmacother* 2006; **40:** 9–14.

Once-daily dosage. The concept of giving aminoglycosides once daily rather than in divided doses is attractive on the grounds of convenience and economy. The rationale cited by proponents of single daily doses for preferring high intermittent plasma concentrations includes the prolonged postantibiotic effect of aminoglycosides (persistent antibacterial activity after plasma concentrations have fallen below the MIC), potentially higher antibacterial concentrations at the site of infection, and theoretical reductions in the incidence of adaptive resistance, with no apparent increase in nephrotoxicity. Clinical studies have generally included small numbers of patients with uncomplicated infections and have excluded patients with altered pharmacokinetic profiles, but several meta-analyses have been published which have concluded that once-daily administration appears to be at least as effective as, and no more toxic than, multiple daily dosing in such patient populations.[1-7] Similar results have been seen in children.[8,9] Many centres now use such regimens in suitable patients.

Several methods for calculating doses and monitoring treatment have been proposed.[10-12] There is insufficient information for pregnant or breast-feeding women, or patients with burns or impaired renal or hepatic function.[12-14] However, preliminary reports suggest that once-daily use may be practical in trauma patients,[15] and children with neutropenia,[16] or cystic fibrosis.[17,18] Once daily dosage may, though, be inappropriate for elderly patients[19] (due to an increased incidence of nephrotoxicity), patients in whom the volume of drug distribution or clearance is difficult to predict or markedly abnormal,[20] and in the treatment of enterococcal endocarditis.[12] In the UK, the *BNF* states that a once-daily high dose regimen should be avoided in patients with endocarditis, extensive burns, or creatinine clearance less than 20 mL/minute. For mention of an increase in endotoxin reactions associated with the use of single daily doses see under Adverse Effects, above.

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6. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; **24:** 796–809.
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8. Nestaas E, *et al.* Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F294–F300.
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10. Begg EJ, *et al.* A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmacol* 1995; **39:** 605–9.
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Ménière's disease. Gentamicin and streptomycin have been used for medical ablation in advanced Ménière's disease (p.564). Although gentamicin given systemically is considered to be more ototoxic than streptomycin, evidence from *animal* studies suggests that intratympanic use may be less ototoxic. This, and a higher incidence of adverse effects with streptomycin, has meant that intratympanic gentamicin is now preferred. Intratympanic gentamicin has been reported to control vertigo symptoms in the majority of patients, although some experience a worsening of their hearing loss immediately after treatment.[1-8] However, the ideal regimen for intratympanic gentamicin has yet to be defined.

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Preparations

BP 2008: Gentamicin and Hydrocortisone Acetate Ear Drops; Gentamicin Cream; Gentamicin Ear Drops; Gentamicin Eye Drops; Gentamicin Injection; Gentamicin Ointment;
USP 31: Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Gentamicin Injection; Gentamicin Sulfate Cream; Gentamicin Sulfate Ointment; Gentamicin Sulfate Ophthalmic Ointment; Gentamicin Sulfate Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Gentaderm; Gentamina; Gentapharma; Gentaren; Gentatenk†; Genticol†; Gentoler; Glevomicina; Plurisemina; Provisual; Rupegen†; Sintepul; Ultradermis†; ***Austral.:*** Genoptic; ***Austria:*** Garamycin†; Gentax; Refobacin; Sulmycin; ***Belg.:*** Geomycine; ***Braz.:*** Emisgenta; Garacin; Garamicina; Garamin; Gentac†; Gentagran; Gentamicil; Gentamil; Gentaron; Gentax†; Vitromicin†; ***Canad.:*** Alcomicin; Diogent†; Garamycin; Garatec†; ***Chile:*** Gentalyn; Oftagen; ***Cz.:*** Garamycin; Megental†; Ophtagram†; ***Denm.:*** Garamycin; Gentacoll; Hexamycin; ***Fin.:*** Gensumycin; Gentacoll; ***Fr.:*** Gentalline; ***Ger.:*** Gencin; Gent-Ophtal; Genta; Gentamytrex; Ophtagram†; Refobacin; Sulmycin; Terramycin N; ***Gr.:*** Dabroson; Garamycin; ***Hong Kong:*** Garamycin; Genoptic; Miramycin; Optigen†; ***Hung.:*** Garamycin; ***India:*** Andregen; Biogaracin; G-80†; Garamycin; Gensyn†; Gentacip; Gentasporin; Genticyn; Genticyn Eye/Ear†; ***Indon.:*** Bioderm; Dermabiotik; Dermagen; Ethigent; Garabiotic; Garamycin; Garapon; Garexin; Gentacyl; Gentamerck; Gentamisin; Ikagen; Isotic Timact; Konigen; Licogenta; Nichogencin; Ottogenta; Sagestam; Salgen; Salticin; Timact; Ximex Konigen; ***Irl.:*** Cidomycin; Genticin; ***Israel:*** Cidomycin†; Gentatrim; Lacromycin; Opti-Genta; ***Ital.:*** Ciclozinil; Dergesol; Eutopic; Gentacream; Gentalyn; Gentamen; Gentibioptal†; Genticol; Gentomil; Nemalin; Ribomicin; Tacigen; ***Malaysia:*** Beagenta; Garamycin; Gentamed†; Gentamytrex†; Miramycin; ***Mex.:*** Barmicil†; Beramicina; Fustermicina; G-I; Garacoll; Garakacin; Garalen; Garamicina; Geclicin; Genemicin; Genkova; Genrex; Genser; Genta; Genta-Micron; Gentacin†; Gentamil; Gentanacin†; Gentapat; Gentarim†; Gentazaf Z; Gentazol; Gentialoquin; Geracin; Ikatin; Lifegram; Lisibac†; Progen; Quilagen; Servigenta; Tamigen; Tondex; Tremax; Yectamicina; ***Neth.:*** Garacol; Garamycin; Gentamytrex; ***Norw.:*** Garamycin; Gensumycin; ***NZ:*** Genoptic; ***Philipp.:*** Garamycin; Gentamytrex; Migentax; Minoglen; Obogen; Opthagen; Orimed; Rocygen; Servigenta; Tangyn; Topigen; ***Pol.:*** Garamycin; Gentamytrex†; ***Port.:*** Cronocol; Garalone; Genta Gobens; Gentalin; Gentocil; Ophtagram; Septopal; ***S.Afr.:*** Cidomycin; Garacoll†; Garamycin; Genoptic†; Sabax Gentamix; Sterisol Fermentmycin; ***Singapore:*** Garamycin†; Genoptic; Gentamytrex; Miramycin; ***Spain:*** Coliriocilina Gentam†; Genta Gobens; Gentamedical†; Gentamival; Genticina†; Gevramycin; Gevramycin Topica; Rexgenta; ***Swed.:*** Garamycin; Gensumycin; ***Switz.:*** Garamycin; Ophtagram; ***Thai.:*** Garamycin†; Genta; Genta-Oph; Gentac†; Gentacin; Gental; Grammicin; Grammixin; Miramycin; Skinfect; Versigen; ***Turk.:*** Genmisin; Genta; Gentagut; Gentamed; Genthaver; Gentreks; Getamisin; Getasin; ***UAE:*** Gental; ***UK:*** Cidomycin; Garamycin†; Genticin; ***USA:*** Garamycin; Genoptic; Gentacidin; Gentak; Gentasol; Ocu-Mycin; ***Venez.:*** Catogen†; Gentalyn; Gentamicil†; Gentamilan; Gentisul; Kincinat†; Refobacin†; Solgenta; Yectamicina†.

Multi-ingredient: ***Arg.:*** Adenil; Aeromicrosona C†; Anginotrat; Bacticort; Bacticort Complex; Bactisona; Becortin; Betacort Plus; Blamy; Calmurid; Cevaderm; Cicatrizol; Ciprocort; Cuta Crema; Denvercrem; Dercotex; Dermizol G; Dermizol Trio; Dermoperative; Dermosona; Dermovit†; Dexamytrex; Diprogenta; Factor Dermico; Filoderma; Filoderma Plus; Gentacler; Gentasol; Gentocelina†; Griseocrem; Hifamonil Crema; Lazar-Cort Complex; Linfol Dermico; Lisoderma; Macril; Micozol Compuesto†; Microsona C; Miklogen; Monizol Cort Crema; Novo Bacticort Complex†; Novo Bacticort†; Otalex G; Otonorthia; Pancutan; Provisual Compuesto; Prurisedan Biotic†; Quadriderm; Quiacort G; Quiacort G Plus; Septopal†; Sirotamicin BG; Start NP†; Tribiocort; Tricur; Tridermal; Triefect†; Triliver; Triplex; Vitacortil; ***Austral.:*** Celestone VG†; Palacos E with Garamycin; Palacos R with Garamycin; Septopal; ***Austria:*** Decoderm Compositum; Decoderm trivalent; Dexagenta; Diprogenta; Septopal; Voltamicin; ***Belg.:*** Decoderm Compositum; Dexagenta-POS; Duracoll; Garasone†; Infectoflam; Palacos LV avec Gentamicine†; Palacos R avec Gentamicine†; Septopal; ***Braz.:*** Cauterex; Cremederme; Dexamytrex†; Diprogenta; Emecort†; Garasone; Gentacort; Gino-Cauterex; Microbiogen†; Pan-Emecort†; Permut; Poliderms; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Septopal; Tetraderm; ***Canad.:*** Diprogen†; Garasone; Pentasone; Valisone-G; ***Chile:*** Diprospan G; Gentasone; Labosona G; Mixgen; Oftagen Compuesto; Palacos E con Gentamicina; Palacos R con Gentamicina; Perlas De PMMA con Gentamicina; Pred G†; Vilterm†; ***Cz.:*** Belogent; Clenigen†; Dexa-Gentamicin; Garasone; Infectoflam†; Septopal†; Voltamicin†; ***Denm.:*** Septopal; ***Fin.:*** Celestoderm cum Garamycin; Palacos R cum Gentamicin†; Septopal; ***Fr.:*** Collatamp G†; Indobiotic; Palacos LV avec Gentamicine; Palacos R avec Gentamicine; ***Ger.:*** Betagentam; Cibaflam; CMW mit Gentamicin; Copal; Decoderm Comp; Dexa-Gentamicin; Dexamytrex; Diprogenta; Inflanegent; Palamed G; Refobacin-Palacos R; Septocoll; Septopal; SmartSet GHV; Sulmycin mit Celestan-V; Terracortril N; ***Gr.:*** Celestoderm-V/GA; Dexamytrex; Efemoline; Garamat; Gentadex; Luzin; Palacos R with Gentamycin†; Propiogenta; Septopal†; ***Hong Kong:*** Becogem; Celestoderm-V with Garamycin; Clobeta-G; Conazole; Dermafacte; Diprogenta; Garasone; Lycobeta-G; Quadriderm; Septopal; Triderm; Triditol-G; ***Hung.:*** Garasone; Gentason; Septopal; Vipsogal†; Voltamicin†; ***India:*** Betamil-GM; Betnederm GM; Betnovate-GM; Candiderma†; Cloben-G; Cloderm GM; Clomycin; Cutinorm†; Diclogenta; Ecodax†; Eumosone-G; Fourderm; Fourderm AF; Gentacip D; Genticyn B Eye/Ear†; Genticyn HC†; Lobate-G; Lobate-GM; Quiss; Septopal; Sigmaderm; Tenovate G; Translipo-Triple; ***Indon.:*** Benoson G; Betagentam; Betasin; Biocort; Celestoderm-V with Garamycin; Cinogenta; Digenta; Diprogenta; Diprosta; Garasone; Genolon; Gentacortin; Gentasolon; Isotic Betaracin; Mastroson; Salgen Plus; Sinobiotik; Skilone; Skinal; Sonigen; ***Irl.:*** Gentisone HC; ***Israel:*** Aflumycin; Betacorten-G; Cicloderm-C; Diprogenta; Triderm; ***Ital.:*** Batasalgin; Betacream; Citrizan Antibiotico; Dermabiolene; Egerian; Fidagenbeta; Formomicin; Genalfa; Genatrop; Gentacort; Gentalyn Beta; Kamelyn; Sterozinil; Vasosterone Oto; Voltamicin†; ***Malaysia:*** B-Mycin; Beprogent; Betagen; Betamethasone G; Celestoderm-V with Garamycin†; Dexa-Gentamicin†; Dexamytrex†; Diprogenta; Garasone; Gentadexa; Infectoflam†; Joysun; Septopal†; ***Mex.:*** Barmicil Compuesto; Beclogen; Betrigen; Clotricina; Diprosone G; Garamicina-V; Garasone; Miclobet; Prubagen; Quadriderm NF; Triderm; ***Neth.:*** Dexagenta-POS; Dexamytrex; Septopal; ***Norw.:*** Septopal; ***NZ:*** CMW Gentamicin; Palacos with Garamycin; Vacu-Mix Plus with CMW gentamicin; ***Philipp.:*** Dexamytrex; Diprogenta; Garasone; Infectoflam; Ophtasone; Quadriderm; Quadrotopic; Septopal; Triderm; ***Pol.:*** Bedicort G; Dexamytrex; Diprogenta; Triderm; ***Port.:*** Dexamytrex; Diprogenta; Epione; Gentadexa; Indobiotic; Quadriderme; ***Rus.:*** Akriderm Genta (Акридерм Гента); Akriderm GK (Акридерм ГК); Belogent (Белогент); Betagenot (Бетагенот); Celestoderm-V with Garamycin

The symbol † denotes a preparation no longer actively marketed

(Целестодерм-В с Гарамицином); Dexa-Gentamicin (Декса-Гентамицин); Triderm (Тридерм); ***S.Afr.:*** Celestoderm-V with Garamycin†; Diprogenta; Garasone†; Palacos R with Garamycin; Quadriderm; Septopal; ***Singapore:*** B-Tasone-G; Beprogent; Celestoderm-V with Garamycin†; Combiderm; Conazole; Dexamytrex; Diprogenta; Garasone; Gentriderm; Gentrisone; Infectoflam; Modaderm; Neoderm; Quadriderm†; Refobacin Bone Cement R; Refobacin-Palacos R†; Septopal†; Tri-Micon; Triderm; Voltamicin†; ***Spain:*** Celestoderm Gentamicina; Cuatroderm; Diprogenta; Epitelizante; Flugen; Flutenal Gentamicina; Gentadexa; Interderm; Novoter Gentamicina; ***Swed.:*** Celeston valerat med gentamicin; Septopal†; ***Switz.:*** Diprogenta; Indobiotic†; Infectoflam; Ophtasone; Quadriderm; Septopal; Triderm; Voltamicin; ***Thai.:*** Beprogent; Beprogenta; Dexamytrex; Diprogenta†; Genquin; Gental-F; Infectoflam; Pred Oph; Refobacin-Palacos R; Septopal; ***Turk.:*** Indobiotic; ***UK:*** Collatamp EG; Gentisone HC; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal; Vipsogal; ***USA:*** Pred G; ***Venez.:*** Betaderm con Gentamicina; Celestoderm con Gentalyn; Diprogenta; Garabet; Garasone; Gentidexa; Gentisor†; Propiogenta†; Quadriderm; Triderm; Tridetarmon.

Gramicidin *(BAN, rINN)*

Gramicidin D; Gramicidin (Dubos); Gramicidina; Gramicidinas; Gramicidine; Gramicidinum; Gramisidiini; Gramisidin.

Грамицидин

CAS — 1405-97-6.
ATC — R02AB30.
ATC Vet — QR02AB30.

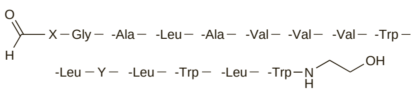

Gramicidin	X	Y	Mol. Formula
A1	-Val	-Trp	C H N O
A2	-Ile	-Trp	C H N O
B1	-Val	-Phe	C H N O
C1	-Val	-Tyr	C H N O
C2	-Ile	-Tyr	C H N O

NOTE. The name gramicidin was formerly applied to tyrothricin.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Gramicidin). It consists of a family of antimicrobial linear polypeptides usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Bacillus brevis*. The main component is gramicidin A1, together with gramicidins A2, B1, C1, and C2 in particular. The potency is not less than 900 units/mg calculated with reference to the dried substance. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Gramicidin). An antibacterial substance produced by the growth of *Bacillus brevis* (Bacillaceae); it may be obtained from tyrothricin. It has a potency of not less than 900 micrograms of gramicidin per mg, calculated on the dried basis. A white or practically white, odourless, crystalline, powder. Insoluble in water; soluble in alcohol. Store in airtight containers.

Profile

Gramicidin has properties similar to those of tyrothricin (p.358) and is too toxic to be given systemically. It is used topically for the local treatment of susceptible infections usually with other antibacterials such as neomycin and polymyxin B, and often with a corticosteroid as well.

Preparations

USP 31: Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Gramicidin Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Antibiocort†; Aseptobron N; Biotaer Nasal; Bucoangin N; Caext; Carnot Colutorio; Desenfriol Caramelos†; Gargaletas; Gramibiotic†; Graneodin; Graneodin N; Kenacomb; Nasomicina; Neo Coltirot; Neo Pelvicillin; Pantometil; Proetztotal; ***Austral.:*** Kenacomb; Neosporin; Otocomb Otic; Otodex; Sofradex; Soframycin; ***Austria:*** Mycostatin V; Topsym polyvalent; Volon A antibiotikahaltig; ***Belg.:*** Mycolog; Polyspectran Gramicidine; ***Braz.:*** Fonergin; Londerm-N; Mud; Neolon-D; Omcilon A M; Onciplus; ***Canad.:*** Antibiotic Cream†; Kenacomb†; Neosporin; Opticort; Optimyxin; Optimyxin Plus; Polycidin†; Polysporin; Polysporin Complete Antibiotic; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polytopic; ratio-Triacomb; Sofracort; Soframycin; Triacomb†; Viaderm-KC; ***Chile:*** Grifoftal†; Oftabiotico; ***Cz.:*** Sofradex†; ***Denm.:*** Kenalog Comp med Mycostatin; Sofradex; ***Fin.:*** Bafucin; Polysporin; Sofradex; ***Ger.:*** Polyspectran; ***Gr.:*** Kenacomb; Neo-Priphen; ***Hong Kong:*** Kenacomb; Neosporin; Polyoph; Sofradex; Triacomb; ***Hung.:*** Polyspor; ***India:*** Kenacomb; Kenalog-S; Neosporin; Sofracort; ***Indon.:*** Blecidex; Isotic Enpigi; Neosyd; Sofradex; ***Irl.:*** Graneodin; Kenacomb; Neosporin†; Sofradex; Soframycin†; ***Israel:*** Dermacombin; Kenacomb†; ***Ital.:*** Eta Biocortilen VC; Vasosterone Antibiotico; ***Malaysia:*** Kenacomb; Pocin G; Sofradex; ***Mex.:*** Biotarson N; Biotarson O; Kenacomb; Neosporin; Nicobio†; Polixin; Poly-Micron; Septilisin; Sulned; ***Neth.:*** Mycolog; Polyspectran G†; Sofradex; ***Norw.:*** Sofradex; ***NZ:*** Kenacomb; Sofradex; Soframycin; Viaderm-KC; ***Philipp.:*** Kenacomb; Lidex NGN; Neosporin; Novasorin; ***Pol.:*** Dicortineff; Triacomb; ***Port.:*** Dropcina; Kenacomb; ***S.Afr.:*** Kenacomb; Neosporin†; Sofradex; ***Singapore:*** Kenacomb†; Sofradex; ***Spain:*** Flodermol; Fludronef; Intradermo Cort Ant Fung†; Midacina; Oftalmowell; Spectrocin†; Tivitis; Trigon Topico; ***Swed.:*** Bafucin; ***Switz.:*** Angidine; Mycolog N; Mycolog†; Neosporin; Sofradex; Topsym polyvalent; Tyrothricine + Gramicidine; ***Thai.:*** Dermacombin; Kenacomb; Neosporin†; Opsacin†; Polyoph; Sofradex; Topifram; Xanalin; ***Turk.:*** Neosporin; ***UAE:*** Panderm; ***UK:*** Graneodin†; Neosporin; Sofradex; Tri-Adcortyl; ***USA:*** Neosporin; Ocu-Spor-G; Ocutricin; Polymycin; ***Venez.:*** Kenacomb.

Gramicidin S *(rINN)*

Gramicidin C; Gramicidina S; Gramicidine S; Gramicidinum S; Soviet Gramicidin.

Грамицидин С

$C_{60}H_{92}N_{12}O_{10}$ = 1141.4.

CAS — 113-73-5.

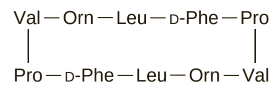

Profile

Gramicidin S is an antibacterial polypeptide, produced by *Bacillus brevis*, and has similar properties to tyrothricin (p.358). It is unsuitable for systemic use and is used topically for the local treatment of susceptible infections and as lozenges for infections of the mouth and throat. The hydrochloride is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Grammidin.

Multi-ingredient: ***Indon.:*** FG Ointment; FG Troches.

Halquinol *(BAN)*

Chlorhydroxyquinoline; Chlorquinol; Halquinols *(USAN)*; SQ-16401. A mixture of the chlorinated products of quinolin-8-ol containing 57 to 74% of 5,7-dichloroquinolin-8-ol (chloroxine, p.242), 23 to 40% of 5-chloroquinolin-8-ol (cloxiquine, p.530), and not more than 4% of 7-chloroquinolin-8-ol.

CAS — 8067-69-4.

Profile

Halquinol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p.254). It is used topically in infected skin conditions.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Valpeda.

Multi-ingredient: ***Denm.:*** Kenacutan; ***Norw.:*** Kenacutan; ***Swed.:*** Kenacutan.

Ibafloxacin *(BAN, USAN, rINN)*

Ibafloksasiini; Ibafloxacine; Ibafloxacino; Ibafloxacinum; R-835; S-25930. 9-Fluoro-6,7-dihydro-5,8-dimethyl-1-oxo- 1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Ибафлоксацин

$C_{15}H_{14}FNO_3$ = 275.3.

CAS — 91618-36-9.
ATC Vet — QJ01MA96.

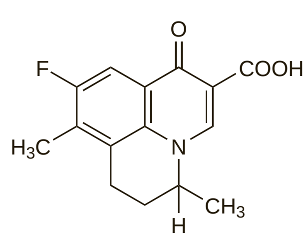

Profile

Ibafloxacin is a fluoroquinolone antibacterial that is used in veterinary medicine for the treatment of susceptible infections in cats and dogs.

Imipenem *(BAN, USAN, rINN)*

N-Formimidoyl Thienamycin; Imipemide; Imipeneemi; Imipénem; Imipenem monohydrát; Imipenemas; Imipenemum; Imipenemum Monohydricum; MK-787; MK-0787. (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-(2-iminomethylaminoethylthio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Имипенем

$C_{12}H_{17}N_3O_4S,H_2O$ = 317.4.

CAS — 64221-86-9 (anhydrous imipenem); 74431-23-5 (imipenem monohydrate).

Description. Imipenem is the *N*-formimidoyl derivative of thienamycin, an antibiotic produced by *Streptomyces cattleya*.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Imipenem). A white, almost white, or pale yellow powder. Sparingly soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 7.0. Store in airtight containers at a temperature of 2° to 8°.

USP 31 (Imipenem). A white to tan-coloured crystalline powder. Sparingly soluble in water; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8°.

Incompatibility and stability. Imipenem is unstable at alkaline or acidic pH and the commercially available injection of imipenem with cilastatin sodium for intravenous use is buffered to provide, when reconstituted, a solution with pH 6.5 to 7.5. Licensed product information advises against mixing with other antibacterials.

References.

1. Bigley FP, *et al.* Compatibility of imipenem-cilastatin sodium with commonly used intravenous solutions. *Am J Hosp Pharm* 1986; **43**: 2803–9.
2. Smith GB, *et al.* Stability and kinetics of degradation of imipenem in aqueous solution. *J Pharm Sci* 1990; **79**: 732–40.

Adverse Effects

Imipenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination.

Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). Hypersensitivity reactions such as skin rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as *Enterococcus faecium*, strains of *Pseudomonas aeruginosa* with acquired resistance, and *Candida* may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive Coombs' test, have been noted.

Local reactions such as pain or thrombophlebitis may occur after injection.

Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses. Mental disturbances and confusion have also been reported.

Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to *animals*. A harmless reddish coloration of urine has been observed in children.

Effects on the nervous system. References.

1. Eng RH, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1989; **149**: 1881–3.
2. Brown RB, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1990; **150**: 1551.
3. Job ML, Dretler RH. Seizure activity with imipenem therapy: incidence and risk factors. *DICP Ann Pharmacother* 1990; **24**: 467–9.
4. Leo RJ, Ballow CH. Seizure activity associated with imipenem use: clinical case reports and review of the literature. *DICP Ann Pharmacother* 1991; **25**: 351–4.
5. Duque A, *et al.* Vertigo caused by imipenem/cilastatin. *DICP Ann Pharmacother* 1991; **25**: 1009.
6. Lucena M, *et al.* Imipenem/cilastatin-associated hiccups. *Ann Pharmacother* 1992; **26**: 1459.
7. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Safety* 1996; **15**: 87–90.

Hypersensitivity. A retrospective analysis[1] involving a total of 211 patients appeared to show that those with a history of reported or documented penicillin allergy had an 11% incidence of hypersensitivity reactions when treated with a carbapenem antibacterial compared with 2.7% for those without such a history of penicillin allergy. There was no difference in the occurrence of allergic-type reactions between imipenem-cilastatin and meropenem.

1. Prescott WA, *et al.* Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004; **38:** 1102–7.

Superinfection. References.

1. Gray JW, *et al.* Enterococcal superinfection in paediatric oncology patients treated with imipenem. *Lancet* 1992; **339**: 1487–8.

Precautions

Imipenem-cilastatin should not be given to patients known to be hypersensitive to it, and should be given with caution to patients known to be hypersensitive to penicillins, cephalosporins, or other beta lactams because of the possibility of cross-sensitivity.

It should be given with caution to patients with renal impairment, and the dose reduced appropriately. Particular care is necessary in patients with CNS disorders such as epilepsy.

Interactions

Seizures have been reported in patients given ganciclovir with imipenem-cilastatin.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to imipenem, see p.510.

Antimicrobial Action

Imipenem is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of activity *in vitro*, including activity against Gram-positive and Gram-negative aerobic and anaerobic organisms, and is stable to hydrolysis by beta-lactamases produced by most bacterial species. Cilastatin, the enzyme inhibitor given with imipenem, appears to have no antibacterial activity.

Most Gram-positive cocci are sensitive to imipenem including most streptococci, and both penicillinase- and non-penicillinase-producing staphylococci, although its activity against meticillin-resistant *Staphylococcus aureus* is variable. Imipenem has good to moderate activity against *Enterococcus faecalis*, but most *E. faecium* are resistant. *Nocardia*, *Rhodococcus*, and *Listeria* spp. are also sensitive.

Among Gram-negative bacteria, imipenem is active against many of the Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Its activity against *Pseudomonas aeruginosa* is similar to that of ceftazidime. Imipenem is also active against *Acinetobacter* spp. and *Campylobacter jejuni*, and also against *Haemophilus influenzae* and *Neisseria* spp., including beta-lactamase-producing strains.

Many anaerobic bacteria, including *Bacteroides* spp., are sensitive to imipenem, but *Clostridium difficile* is only moderately susceptible.

Imipenem is not active against *Chlamydia trachomatis*, *Mycoplasma* spp., fungi, or viruses.

There have been reports of antagonism between imipenem and other beta lactams *in vitro*. Imipenem and aminoglycosides often act synergistically against some isolates of *Ps. aeruginosa*.

Imipenem is a potent inducer of beta-lactamases of some Gram-negative bacteria, but generally remains stable to them. Acquired resistance has been reported in *Ps. aeruginosa* during therapy with imipenem.

Resistance. References.

1. Ballestero S, *et al.* Carbapenem resistance in Pseudomonas aeruginosa from cystic fibrosis patients. *J Antimicrob Chemother* 1996; **38:** 39–45.
2. Rasmussen BA, Bush K. Carbapenem-hydrolyzing β-lactamases. *Antimicrob Agents Chemother* 1997; **41:** 223–32.
3. Livermore DM. Acquired carbapenemases. *J Antimicrob Chemother* 1997; **39:** 673–6.
4. MacKenzie FM, *et al.* Emergence of a carbapenem-resistant Klebsiella pneumoniae. *Lancet* 1997; **350:** 783.
5. Pikis A, *et al.* Decreased susceptibility to imipenem among penicillin-resistant Streptococcus pneumoniae. *J Antimicrob Chemother* 1997; **40:** 105–8.
6. Mainardi J-L, *et al.* Carbapenem resistance in a clinical isolate of Citrobacter freundii. *Antimicrob Agents Chemother* 1997; **41:** 2352–4.
7. Modakkas EM, Sanyal SC. Imipenem resistance in aerobic gram-negative bacteria. *J Chemother* 1998; **10:** 97–101.
8. Tsakris A, *et al.* Outbreak of infections caused by Pseudomonas aeruginosa producing VIM-1 carbapenemase in Greece. *J Clin Microbiol* 2000; **38:** 1290–2.
9. Fierobe L, *et al.* An outbreak of imipenem-resistant Acinetobacter baumannii in critically ill surgical patients. *Infect Control Hosp Epidemiol* 2001; **22:** 35–40.
10. Nagy E, *et al.* Occurrence of metronidazole and imipenem resistance among Bacteroides fragilis group clinical isolates in Hungary. *Acta Biol Hung* 2001; **52:** 271–80.
11. Gulay Z, *et al.* Clonal spread of imipenem-resistant Pseudomonas aeruginosa in the intensive care unit of a Turkish hospital. *J Chemother* 2001; **13:** 546–54.

Pharmacokinetics

Imipenem is not appreciably absorbed from the gastrointestinal tract and is given parenterally.

Imipenem is excreted primarily in the urine by glomerular filtration and tubular secretion and undergoes partial metabolism in the kidneys by dehydropeptidase I, an enzyme in the brush border of the renal tubules, to inactive, nephrotoxic metabolites, with only 5 to 45% of a dose excreted in the urine as unchanged active drug. Imipenem is given with cilastatin sodium (p.243), a dehydropeptidase inhibitor, resulting in increased urinary-imipenem concentrations. Cilastatin does not affect serum concentrations of imipenem.

The pharmacokinetics of imipenem and cilastatin are similar and both have plasma half-lives of about 1 hour; half-lives, especially those of cilastatin, may be prolonged in neonates and in patients with renal impairment. When imipenem with cilastatin is given in doses of 500 or 750 mg intramuscularly, peak plasma-imipenem concentrations of 10 and 12 micrograms/mL respectively are achieved at about 2 hours and prolonged absorption results in plasma-imipenem concentrations of above 2 micrograms/mL for 6 to 8 hours. The bioavailability of imipenem after intramuscular injection is about 75%. Up to 20% of imipenem and 40% of cilastatin is bound to plasma proteins. Imipenem is widely distributed in body tissues and fluids and crosses the placenta. Information on penetration into the CSF is limited, but concentrations appear to be relatively low.

When given with cilastatin about 70% of an intravenous dose of imipenem is recovered unchanged in the urine within 10 hours. A total of 50% of an intramuscular dose is recovered in the urine and urinary concentrations above 10 micrograms/mL are maintained for 12 hours after a dose of 500 or 750 mg. Cilastatin is also excreted mainly in the urine, the majority as unchanged drug and about 12% as *N*-acetyl cilastatin. Both imipenem and cilastatin are removed by haemodialysis.

About 1% of imipenem is excreted via the bile in the faeces.

◊ Reviews.

1. Drusano GL. An overview of the pharmacology of imipenem/cilastatin. *J Antimicrob Chemother* 1986; **18** (suppl E): 79–92.
2. Watson ID, *et al.* Clinical pharmacokinetics of enzyme inhibitors in antimicrobial chemotherapy. *Clin Pharmacokinet* 1988; **15**: 133–64.
3. Mouton JW, *et al.* Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39:** 185–201.

The elderly. References.

1. Finch RG, *et al.* Pharmacokinetic studies of imipenem/cilastatin in elderly patients. *J Antimicrob Chemother* 1986; **18** (suppl E): 103–7.

Hepatic impairment. References.

1. Rolando N, *et al.* The penetration of imipenem/cilastatin into ascitic fluid in patients with chronic liver disease. *J Antimicrob Chemother* 1994; **33:** 163–7.

Pregnancy and the neonate. References.

1. Reed MD, *et al.* Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990; **34:** 1172–7.
2. Heikkilä A, *et al.* Pharmacokinetics and transplacental passage of imipenem during pregnancy. *Antimicrob Agents Chemother* 1992; **36:** 2652–5.

Renal impairment. References.

1. Verbist L, *et al.* Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. *J Antimicrob Chemother* 1986; **18** (suppl E): 115–20.
2. Alarabi AA, *et al.* Pharmacokinetics of intravenous imipenem/cilastatin during intermittent haemofiltration. *J Antimicrob Chemother* 1990; **26:** 91–8.
3. Pietroski NA, *et al.* Steady-state pharmacokinetics of intramuscular imipenem-cilastatin in elderly patients with various degrees of renal function. *Antimicrob Agents Chemother* 1991; **35:** 972–5.
4. Konishi K, *et al.* Removal of imipenem and cilastatin by hemodialysis in patients with end-stage renal failure. *Antimicrob Agents Chemother* 1991; **35:** 1616–20.
5. Chan CY, *et al.* Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1991; **27:** 225–32.
6. Tegeder I, *et al.* Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 1997; **41:** 2640–5.

Uses and Administration

Imipenem is a carbapenem beta-lactam antibacterial, differing from the penicillins in that the 5-membered ring is unsaturated and contains a carbon rather than a sulfur atom. Since imipenem is metabolised in the kidney by the enzyme dehydropeptidase I it is always given with cilastatin (p.243), an inhibitor of the enzyme; this enhances urinary concentrations of active drug and was found to protect against the nephrotoxicity of high doses of imipenem seen in *animal* studies.

Imipenem is used for the treatment of infections caused by susceptible organisms. They include infections in immunocompromised patients (with neutropenia), intra-abdominal infections, bone and joint infections, skin and soft-tissue infections, urinary-tract infections, biliary-tract infections, hospital-acquired pneumonia, and septicaemia. It may also be used for the treatment of gonorrhoea and for surgical infection prophylaxis. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. It is not indicated for CNS infections.

Administration and dosage. Commercial preparations contain imipenem and cilastatin, as the sodium salt, in a ratio of 1 to 1. Doses of the combination are expressed in terms of the amount of anhydrous imipenem. Imipenem is given by intravenous infusion or deep intramuscular injection. When given intravenously, doses of 250 or 500 mg are infused over 20 to 30 minutes, and doses of 750 mg or 1 g over 40 to 60 minutes. The usual intravenous dose in adults and children weighing more than 40 kg is 1 to 2 g daily in divided doses every 6 or 8 hours, depending on the severity of the infection, although up to a maximum daily dose of 4 g or 50 mg/kg has been given in life-threatening infections.

Children of 3 months or more and weighing less than 40 kg may be given 15 to 25 mg/kg every 6 hours by intravenous infusion; the total daily dose should not usually exceed 2 g. Higher doses of up to 4 g daily have been given to children with moderately susceptible *Pseudomonas aeruginosa* infection; up to 90 mg/kg daily has been given to older children with cystic fibrosis. Neonates and infants up to 3 months of age may be given the following doses: 4 weeks to 3 months of age, 25 mg/kg every 6 hours; 1 to 4 weeks of age, 25 mg/kg every 8 hours; up to 1 week of age, 25 mg/kg every 12 hours.

For details of reduced doses in renal impairment, see below.

For surgical infection prophylaxis in adults, imipenem 1 g may be given intravenously on induction of anaesthesia, followed by a further 1 g three hours later, with additional doses of 500 mg at 8 and 16 hours after induction if necessary.

Imipenem may be given intramuscularly in adults with mild to moderate infections in doses of 500 or 750 mg every 12 hours. A single 500-mg intramuscular dose may be given in uncomplicated gonorrhoea.

◊ General reviews.

1. Balfour JA, *et al.* Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996; **51:** 99–136.
2. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.

3. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Safety* 2000; **22:** 191–4.
4. Rodloff AC, *et al.* Two decades of imipenem therapy. *J Antimicrob Chemother* 2006; **58:** 916–29.
5. Zhanel GG, *et al.* Comparative review of the carbapenems. *Drugs* 2007; **67:** 1027–52.

Administration in renal impairment. Doses of imipenem should be reduced in patients with renal impairment; in the UK, the following are the recommended maximum *intravenous* doses based on creatinine clearance (CC):

- CC 31 to 70 mL/minute: 500 mg every 6 to 8 hours
- CC 21 to 30 mL/minute: 500 mg every 8 to 12 hours
- CC 6 to 20 mL/minute: 250 mg (or 3.5 mg/kg, whichever is the lower) every 12 hours or occasionally 500 mg every 12 hours
- CC 5 mL/minute or less: should only be given imipenem if haemodialysis is started within 48 hours

Imipenem and cilastatin are cleared from the body by haemodialysis and doses should be given after a dialysis session and then every 12 hours.

Information is lacking on the safety or effectiveness of the *intramuscular* route in patients with renal impairment.

Preparations

USP 31: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Proprietary Preparations (details are given in Part 3)
Pol.: Tienam.

Multi-ingredient: ***Arg.:*** Dixabiox; Imipecil; Imistatin; Klonam†; Zienam; ***Austral.:*** Primaxin; ***Austria:*** Zienam; ***Belg.:*** Tienam; ***Braz.:*** Penexil†; Tienam; ***Canad.:*** Primaxin; ***Chile:*** Inem; Tienam; ***Cz.:*** Tienam; ***Denm.:*** Tienam; ***Fin.:*** Tienam; ***Fr.:*** Tienam; ***Ger.:*** Zienam; ***Gr.:*** Primaxin; ***Hong Kong:*** Prepenem; Tienam; ***Hung.:*** Tienam; ***India:*** Cilanem; ***Indon.:*** Pelastin; Tienam; ***Israel:*** Tienam; ***Ital.:*** Imipem; Tenacid; Tienam; ***Malaysia:*** Bacqure; Tienam; ***Mex.:*** Arzomeba; Iminen; Tienam; ***Neth.:*** Tienam; ***Norw.:*** Tienam; ***NZ:*** Primaxin; ***Philipp.:*** Anipen; Tienam; ***Port.:*** Tienam; ***Rus.:*** Tienam (Тиенам); ***S.Afr.:*** Tienam; ***Singapore:*** Tienam; ***Spain:*** Tienam; ***Swed.:*** Tienam; ***Switz.:*** Tienam; ***Thai.:*** Tienam; ***Turk.:*** Tienam; ***UK:*** Primaxin; ***USA:*** Primaxin; ***Venez.:*** Zienam.

Isepamicin *(BAN, USAN, rINN)*

HAPA-B; Isepamicina; Isépamicine; Isepamicinum; Sch-21420; Sch-21420. 4-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-(3-amino-L-lactoyl)-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine; 1*N*-(*S*-3-Amino-2-hydroxypropionyl)-gentamicin B.

Изепамицин

$C_{22}H_{43}N_5O_{12}$ = 569.6.
CAS — 58152-03-7; 67479-40-7.
ATC — J01GB11.
ATC Vet — QJ01GB11.

Isepamicin Sulfate *(rINNM)*

Isepamicin Sulphate *(BANM)*; Isépamicine, Sulfate d'; Isepamicini Sulfas; Isepamisin Sülfat; Sulfato de isepamicina.

Изепамицина Сульфат

$C_{22}H_{43}N_5O_{12},2H_2SO_4$ = 765.8.
CAS — 68000-78-2.
ATC — J01GB11.
ATC Vet — QJ01GB11.

Pharmacopoeias. In *Jpn*, which specifies a variable amount of H_2SO_4.

Profile

Isepamicin is a semisynthetic aminoglycoside with actions and uses similar to those of gentamicin (p.282). It is reported not to be degraded by many of the enzymes responsible for aminoglycoside resistance. Isepamicin sulfate is given by intramuscular injection or intravenous infusion in a dose of up to 15 mg/kg daily in 2 divided doses. Once-daily dosage may be possible in selected patients. Dosage should be adjusted based on serum-isepamicin concentration monitoring. In adults, the total daily dose should not exceed 1.5 g.

◊ References.

1. Tod M, *et al.* Clinical pharmacokinetics and pharmacodynamics of isepamicin. *Clin Pharmacokinet* 2000; **38:** 205–23.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Isepacin†; ***Belg.:*** Isepacine†; ***Cz.:*** Isepacin†; ***Fr.:*** Isepalline†; ***Ital.:*** Isepacin†; ***Mex.:*** Isepacin†; ***Turk.:*** Isepacine.

Isoniazid *(BAN, pINN)*

INAH; INH; Isoniatsidi; Isoniazida; Isoniazide; Isoniazidum; Isonicotinic Acid Hydrazide; Isonicotinylhydrazide; Isonicotinylhydrazine; Izoniazid; Izoniazidas; Izoniazyd; Tubazid. Isonicotinohydrazide.

Изониазид

$C_6H_7N_3O$ = 137.1.
CAS — 54-85-3.
ATC — J04AC01.
ATC Vet — QJ04AC01.

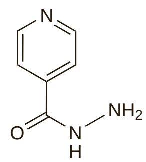

NOTE. The name Isopyrin, which has been applied to isoniazid, has also been applied to ramifenazone.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Isoniazid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.0 to 8.0.

USP 31 (Isoniazid). Colourless, or white, odourless crystals, or white crystalline powder. Soluble 1 in 8 of water and 1 in 50 of alcohol; slightly soluble in chloroform; very slightly soluble in ether. pH of a 10% solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. It has been recommended that sugars such as glucose, fructose, and sucrose should not be used in isoniazid syrup preparations because the absorption of the drug was impaired by the formation of a condensation product.[1] Sorbitol may be a suitable substitute if necessary.

1. Rao KVN, *et al.* Inactivation of isoniazid by condensation in a syrup preparation. *Bull WHO* 1971; **45:** 625–32.

Sterilisation. Solutions of isoniazid should be sterilised by autoclaving.

Adverse Effects

Isoniazid is generally well tolerated at currently recommended doses. However, patients who are slow acetylators of isoniazid and those with advanced HIV disease appear to have a higher incidence of some adverse effects. Also patients whose nutrition is poor are at risk of peripheral neuritis which is one of the commonest adverse effects of isoniazid. Other neurological adverse effects include psychotic reactions and convulsions. Pyridoxine may be given to prevent or treat these adverse effects. Optic neuritis has also been reported.

Transient increases in liver enzymes occur in 10 to 20% of patients during the first few months of treatment and usually return to normal despite continued treatment. Symptomatic hepatitis occurs in about 0.1 to 0.15% of patients given isoniazid as monotherapy, but this can increase with age, regular alcohol consumption, and in those with chronic liver disease. The influence of acetylator status is uncertain. Elevated liver enzymes associated with clinical signs of hepatitis such as nausea and vomiting, or fatigue may indicate hepatic damage; in these circumstances, isoniazid should be stopped pending evaluation and should only be reintroduced cautiously once hepatic function has recovered. Fatalities have occurred due to liver necrosis.

Haematological effects reported on use of isoniazid include various anaemias, agranulocytosis, thrombocytopenia, and eosinophilia.

Hypersensitivity reactions occur infrequently and include skin eruptions (including erythema multiforme), fever, and vasculitis.

Other adverse effects include nausea, vomiting, dry mouth, constipation, pellagra, purpura, hyperglycaemia, lupus-like syndrome, vertigo, hyperreflexia, urinary retention, and gynaecomastia.

Symptoms of overdosage include slurred speech, metabolic acidosis, hallucinations, hyperglycaemia, respiratory distress or tachypnoea, convulsions, and coma; fatalities can occur.

Carcinogenicity. Concern about the carcinogenicity of isoniazid arose in the 1970s when an increased risk of bladder cancer in patients treated with isoniazid was reported.[1-3] However, no evidence to support a carcinogenic effect of isoniazid was found in more than 25 000 patients followed up for 9 to 14 years in studies organised by the USA Public Health Service[4] and in 3842 patients followed up for 16 to 24 years in the UK.[5]

1. Miller CT. Isoniazid and cancer risks. *JAMA* 1974; **230:** 1254.
2. Kerr WK, Chipman ML. The incidence of cancer of bladder and other sites after INH therapy. *Am J Epidemiol* 1976; **104:** 335–6.
3. Miller CT, *et al.* Relative importance of risk factors in bladder carcinogenesis. *J Chron Dis* 1978; **31:** 51–6.
4. Glassroth JL, *et al.* An assessment of the possible association of isoniazid with human cancer deaths. *Am Rev Respir Dis* 1977; **116:** 1065–74.
5. Stott H, *et al.* An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. *Tubercle* 1976; **57:** 1–15.

Effects on the blood. In addition to the effects mentioned above, rare reports of adverse effects of isoniazid on the blood include bleeding associated with acquired inhibition of fibrin stabilisation[1] or of factor XIII,[2] and red cell aplasia.[3-5]

For a reference to neutropenia, see Effects on the Blood, under Ethambutol Hydrochloride, p.274.

1. Otis PT, *et al.* An acquired inhibitor of fibrin stabilization associated with isoniazid therapy: clinical and biochemical observations. *Blood* 1974; **44:** 771–81.
2. Krumdieck R, *et al.* Hemorrhagic disorder due to an isoniazid-associated acquired factor XIII inhibitor in a patient with Waldenström's macroglobulinemia. *Am J Med* 1991; **90:** 639–45.
3. Claiborne RA, Dutt AK. Isoniazid-induced pure red cell aplasia. *Am Rev Respir Dis* 1985; **131:** 947–9.
4. Lewis CR, Manoharan A. Pure red cell hypoplasia secondary to isoniazid. *Postgrad Med J* 1987; **63:** 309–10.
5. Veale KS, *et al.* Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. *J Pediatr* 1992; **120:** 146–8.

Effects on the CNS. In addition to the peripheral neuropathy that is a well-established adverse effect of isoniazid, effects on the CNS have also been reported, including ataxia and cerebellar toxicity,[1,2] psychotic reactions[3-5] (generally characterised by delusions, hallucinations, and confusion), and seizures, particularly after overdosage.[6] Encephalopathy has been reported in dialysis patients.[7,8] Encephalopathy may also be a symptom of pellagra, which may be associated with isoniazid treatment.[9]

1. Blumberg EA, Gil RA. Cerebellar syndrome caused by isoniazid. *DICP Ann Pharmacother* 1990; **24:** 829–31.
2. Lewin PK, McGreal D. Isoniazid toxicity with cerebellar ataxia in a child. *CMAJ* 1993; **148:** 49–50.
3. Pallone KA, *et al.* Isoniazid-associated psychosis: case report and review of the literature. *Ann Pharmacother* 1993; **27:** 167–70.
4. Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother* 1998; **32:** 889–91.
5. Witkowski AE, *et al.* Isoniazid-associated psychosis. *Gen Hosp Psychiatry* 2007; **29:** 85–6.
6. Shah BR, *et al.* Acute isoniazid neurotoxicity in an urban hospital. *Pediatrics* 1995; **95:** 700–4.
7. Cheung WC, *et al.* Isoniazid induced encephalopathy in dialysis patients. *Tuberc Lung Dis* 1993; **74:** 136–9.
8. Wang HY, *et al.* Encephalopathy caused by isoniazid in a patient with end stage renal disease with extrapulmonary tuberculosis. *Ren Fail* 2003; **25:** 135–8.
9. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with isoniazid and other first-line antituberculous drugs, but sometimes hepatotoxicity may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Isoniazid and pyrazinamide are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1] Speculation that fast acetylators of isoniazid could be at increased risk of hepatotoxicity due to production of a hepatotoxic hydrazine metabolite has not been supported;[2] in fact, slow acetylators have generally been found to have a higher risk than fast acetylators.[3,4] This could reflect a reduced rate of subsequent metabolism to non-toxic compounds. In addition, concentrations of hydrazine in the blood have not been found to correlate with acetylator status.[5,6]

A multicentre study[7] considered the incidence of hepatotoxicity from a short-term regimen of daily isoniazid, rifampicin, and pyrazinamide for 8 weeks in the initial phase followed by daily isoniazid and rifampicin for 16 weeks in the continuing phase. Analysis from 617 patients showed an incidence of hepatotoxic reactions of 1.6%; the incidence of elevated aspartate aminotransferase was 23.2%. In the same study, 445 patients on a 9-month regimen of daily isoniazid and rifampicin had a 1.2% incidence of hepatotoxicity and 27.1% incidence of elevated liver enzymes. A similar incidence of hepatitis of 1.4% among 350 patients on a 9-month regimen of rifampicin and isoniazid has also been reported.[8] A retrospective analysis[9] of 430 children on isoniazid and rifampicin revealed hepatotoxic reactions in 3.3%, the highest incidence being in children with severe disease.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[10] for initial measurement of liver function in all patients and regular monitoring in patients with known chronic liver disease. Details are given concerning the response to deteriorating liver function depending on the clinical situation, and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced in the USA.[11,12]

The incidence of hepatotoxicity is lower in patients receiving isoniazid for prophylaxis than in those receiving treatment for active disease. During a 7-year period[13] an incidence of 0.15%

was recorded in 11 141 patients who started prophylactic therapy, whereas it was 1.25% amongst 1427 patients receiving treatment. A similar study[14] in a slightly older patient population reported an incidence of 0.56%. No cases of hepatotoxicity were reported in 556 HIV-infected patients taking a 3-month prophylactic regimen of isoniazid and rifampicin for latent tuberculosis.[15] A meta-analysis[16] concluded that daily isoniazid and rifampicin for 3 months appeared to be as safe as treatment with isoniazid alone for 6 to 12 months.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. Gurumurthy P, *et al.* Lack of relationship between hepatic toxicity and acetylator phenotype in three thousand South Indian patients during treatment with isoniazid for tuberculosis. *Am Rev Respir Dis* 1984; **129:** 58–61.
3. Dickinson DS, *et al.* Risk factors for isoniazid (INH)-induced liver dysfunction. *J Clin Gastroenterol* 1981; **3:** 271–9.
4. Pande JN, *et al.* Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; **51:** 132–6.
5. Gent WL, *et al.* Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients. *Eur J Clin Pharmacol* 1992; **43:** 131–6.
6. Donald PR, *et al.* Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis. *Ann Pharmacother* 1994; **28:** 1340–3.
7. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
8. Dutt AK, *et al.* Short-course chemotherapy for extrapulmonary tuberculosis: nine years' experience. *Ann Intern Med* 1986; **104:** 7–12.
9. O'Brien RJ, *et al.* Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 1983; **72:** 491–9.
10. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
11. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
12. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/sections/publications/statements/resources/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 05/10/07)
13. Nolan CM, *et al.* Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; **281:** 1014–18.
14. Fountain FF, *et al.* Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005; **128:** 116–23.
15. Whalen CC, *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; **337:** 801–8.
16. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; **40:** 670–6.

Effects on the pancreas. Cases of isoniazid-induced pancreatitis have been rarely reported;[1-4] pancreatitis resolved in these patients once treatment with isoniazid was stopped, and recurred on rechallenge. It is recommended if isoniazid-induced pancreatitis is proven that the drug should be permanently avoided.[4] Chronic pancreatic insufficiency, after an acute episode, was reported in a patient given isoniazid, rifampicin, ethambutol, and pyrazinamide and was considered to be a drug hypersensitivity reaction.[5]

1. Chan KL, *et al.* Recurrent acute pancreatitis induced by isoniazid. *Tubercle Lung Dis* 1994; **75:** 383–5.
2. Rabassa AA, *et al.* Isoniazid-induced acute pancreatitis. *Ann Intern Med* 1994; **121:** 433–4.
3. Stephenson I, *et al.* Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. *Am J Gastroenterol* 2001; **96:** 2271–2.
4. Chow KM, *et al.* Recurrent acute pancreatitis after isoniazid. *Neth J Med* 2004; **62:** 172–4.
5. Liu BA, *et al.* Pancreatic insufficiency due to antituberculous therapy. *Ann Pharmacother* 1997; **31:** 724–6.

Effects on the skin and hair. Isoniazid causes cutaneous drug reactions in less than 1% of patients.[1,2] These reactions include urticaria, purpura, acneform syndrome,[3] a lupus erythematosus-like syndrome[4] (see below), and exfoliative dermatitis.[5] Pellagra is also associated with isoniazid.[6] Isoniazid was considered the most likely cause of alopecia in 5 patients receiving antituberculosis regimens which also included rifampicin, ethambutol, and pyrazinamide.[7]

1. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976; **235:** 918–23.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
3. Thorne N. Skin reactions to systemic drug therapy. *Practitioner* 1973; **211:** 606–13.
4. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136:** 508–11.
5. Rosin MA, King LE. Isoniazid-induced exfoliative dermatitis. *South Med J* 1982; **75:** 81.
6. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.
7. FitzGerald JM, *et al.* Alopecia side-effect of antituberculosis drugs. *Lancet* 1996; **347:** 472–3.

Lupus. Antinuclear antibodies have been reported to occur in up to 22% of patients receiving isoniazid; however, patients are usually asymptomatic and overt lupoid syndrome is rare.[1,2] The incidence of antibody induction has been reported to be higher in slow acetylators than in fast acetylators,[3] but the difference was not statistically significant and acetylator phenotype is not considered an important determinant of the risk of isoniazid-induced lupus.[1,4,5] The syndrome appeared to be due to isoniazid itself rather than its metabolite acetylisoniazid.[6]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; **123:** 460–3.
2. Siddiqui MA, Khan IA. Isoniazid-induced lupus erythematosus presenting with cardiac tamponade. *Am J Ther* 2002; **9:** 163–5.
3. Alarcon-Segovia D, *et al.* Isoniazid acetylation rate and development of antinuclear antibodies upon isoniazid treatment. *Arthritis Rheum* 1971; **14:** 748–52.
4. Clark DWJ. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs* 1985; **29:** 342–75.
5. Rychlik-Sych M, *et al.* Acetylation genotype and phenotype in patients with systemic lupus erythematosus. *Pharmacol Rep* 2006; **58:** 22–9.
6. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Pyridoxine hydrochloride 10 mg daily is usually recommended for prophylaxis of peripheral neuritis associated with isoniazid although up to 50 mg daily may be used. A dose of 50 mg three times daily may be given for treatment of peripheral neuritis if it develops.

Nicotinamide has been given, usually with pyridoxine, to patients who develop pellagra.

Isoniazid doses of 1.5 g or more are potentially toxic and doses of 10 to 15 g may be fatal without appropriate treatment. Treatment of overdosage is symptomatic and supportive and consists of activated charcoal, correction of metabolic acidosis, and control of convulsions. Large doses of pyridoxine may be needed intravenously for control of convulsions (see below) and should be given with diazepam. Isoniazid is removed by haemodialysis or peritoneal dialysis.

Overdosage. In adults an initial intravenous dose of pyridoxine hydrochloride equivalent to the estimated amount of isoniazid ingested (or, if the amount ingested is unknown, pyridoxine hydrochloride 5 g) has been recommended by the UK National Poisons Information Service for the management of convulsions; diazepam should also be given. For children the recommended dose of pyridoxine hydrochloride is 70 mg/kg (to a maximum of 5 g). If convulsions continue or recur, this dose may be repeated. Oral activated charcoal (50 g for adults and 10 to 15 g in children) may be considered if this is given within 1 hour of ingestion of isoniazid.

Pyridoxine deficiency. Pyridoxine deficiency associated with isoniazid in doses of 5 mg/kg daily is uncommon. Patients at risk of developing pyridoxine deficiency include those with diabetes, uraemia, alcoholism, HIV infection, and malnutrition.[1,2] Supplementation with pyridoxine should be considered for these at-risk groups as well as for pregnant women and patients with seizure disorders.[1] For the prophylaxis of peripheral neuritis it is common practice to give pyridoxine 10 mg daily, although 6 mg daily might be sufficient.[3] However, in one patient a dose of pyridoxine 10 mg daily failed to prevent psychosis, the symptoms of which only resolved after stopping isoniazid and increasing the pyridoxine dosage to 100 mg daily.[4]

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. Snider DE. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 1980; **61:** 191–6.
4. Chan TYK. Pyridoxine ineffective in isoniazid-induced psychosis. *Ann Pharmacother* 1999; **33:** 1123–4.

Precautions

Isoniazid should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50 mg daily may be used. If symptoms of hepatitis develop, such as malaise, fatigue, anorexia, and nausea, isoniazid should be stopped pending evaluation.

Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and the British Thoracic Society has recommended that isoniazid treatment be suspended if serum aminotransferase concentrations are elevated to more than 5 times the normal upper limit or the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. Careful monitoring should be considered for black and Hispanic women, in whom there may be an increased risk of fatal hepatitis.

When visual symptoms occur during isoniazid treatment periodic eye examinations have been suggested.

Breast feeding. Peak concentrations of isoniazid in breast milk were 6 micrograms/mL after a dose of 5 mg/kg and were 16.6 micrograms/mL after a 300-mg dose.[1] However, drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. Adverse effects on breast-fed infants have not been reported and the American Academy of Pediatrics thus considers isoniazid to be usually compatible with breast feeding,[2] although such infants should be monitored for toxic reactions.

1. Snider D, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. Isoniazid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Pregnancy and the neonate. In a review[1] of antituberculous treatment in pregnant patients it was reported that over 95% of 1480 pregnancies in which isoniazid had been given resulted in a normal term infant. Slightly more than 1% of the infants/fetuses were abnormal and many of these abnormalities were CNS related. Isoniazid is therefore recognised as being suitable for use in regimens for the **treatment** of tuberculosis in pregnant patients.[2,3] Pyridoxine supplementation is recommended[2] (see Treatment of Adverse Effects, above). **Preventive therapy** with isoniazid is generally delayed until after delivery unless other risk factors are present.

1. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122:** 65–79.
2. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)

Interactions

The risk of hepatotoxicity may be increased in patients receiving isoniazid with a rifamycin or other potentially hepatotoxic drugs, including alcohol.

Isoniazid can inhibit the hepatic metabolism of a number of drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine (p.474), ethosuximide (p.480), primidone, and phenytoin (p.498), the benzodiazepines diazepam and triazolam (p.989), chlorzoxazone (p.1895), theophylline (p.1143), and disulfiram. The metabolism of enflurane (see Effects on the Kidneys, p.1782) may be increased in patients receiving isoniazid, resulting in potentially nephrotoxic levels of fluoride. Isoniazid has been associated with increased concentrations and enhanced effects or toxicity of clofazimine (p.255), cycloserine (p.260), and warfarin (p.1428).

For interactions affecting isoniazid, see below.

Alcohol. The metabolism of isoniazid may be increased in chronic alcoholics: this may lead to reduced isoniazid effectiveness.[1] These patients may also be at increased risk of developing isoniazid-induced peripheral neuropathies and hepatic damage (see Precautions, above).

1. Anonymous. Interaction of drugs with alcohol. *Med Lett Drugs Ther* 1981; **23:** 33–4.

Antacids. Oral absorption of isoniazid is reduced by aluminium-containing antacids; isoniazid should be given at least 1 hour before the antacid.[1]

1. Hurwitz A, Schluzman DL. Effects of antacids on gastrointestinal absorption of isoniazid in rat and man. *Am Rev Respir Dis* 1974; **109:** 41–7.

Antifungals. Serum concentrations of isoniazid were below the limits of detection in a patient also receiving rifampicin and *ketoconazole*.[1] For the effect of isoniazid on ketoconazole, see p.539.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109:** 844–5. Correction. *ibid.* 1989; **111:** 96.

Antivirals. The clearance of isoniazid was approximately doubled when *zalcitabine* was given to 12 HIV-positive patients.[1] In addition, care is needed since *stavudine* and zalcitabine may also cause peripheral neuropathy; use of isoniazid with stavudine has been reported to increase its incidence.[2]

1. Lee BL, *et al.* The effect of zalcitabine on the pharmacokinetics of isoniazid in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* 1994; **34:** 3(A4).
2. Breen RAM, *et al.* Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. *AIDS* 2000; **14:** 615.

Corticosteroids. Giving *prednisolone* 20 mg to 13 slow acetylators and 13 fast acetylators receiving isoniazid 10 mg/kg reduced plasma concentrations of isoniazid by 25 and 40% respectively.[1] Renal clearance of isoniazid was also enhanced in both acetylator phenotypes and the rate of acetylation increased in slow acetylators only.[1]

The clinical significance of this effect is not established.

1. Sarma GR, *et al.* Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* 1980; **18:** 661–6.

Food. Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea, and sweating have been reported in patients taking isoniazid after ingestion of *cheese*,[1,2] *red wine*,[1] and some *fish*.[3,4] Accumulation of tyramine[1] or histamine[3] has been proposed as the cause of these food-related reactions, and they could be mistaken for anaphylaxis.[4]

1. Toutoungi M, *et al.* Cheese, wine, and isoniazid. *Lancet* 1985; **ii:** 671.
2. Carvalho ACC, *et al.* Reaction to cheese during TB treatment. *Thorax* 2004; **59:** 635.
3. Kottegoda SR. Cheese, wine and isoniazid. *Lancet* 1985; **ii:** 1074.
4. O'Sullivan TL. Drug-food interaction with isoniazid resembling anaphylaxis. *Ann Pharmacother* 1997; **31:** 928.

Opioid analgesics. For a report of an interaction between isoniazid and *pethidine*, attributed to isoniazid's inhibitory actions on monoamine oxidase, see p.114.

Antimicrobial Action

Isoniazid is highly active against *Mycobacterium tuberculosis* and may have activity against some strains of other mycobacteria including *M. kansasii*.

Although it is rapidly bactericidal against actively dividing *M. tuberculosis*, it is considered to be only bacteriostatic against semi-dormant organisms and has less sterilising activity than rifampicin or pyrazinamide.

Resistance of *M. tuberculosis* to isoniazid develops rapidly if it is used alone in the *treatment* of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of isoniazid with other antimycobacterials which appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when isoniazid is used alone in *prophylaxis*, probably because the bacillary load is low.

Mycobacterium avium complex. Synergistic activity of isoniazid plus streptomycin and, to a lesser degree, isoniazid plus clofazimine, against *Mycobacterium avium* complex (MAC) has been demonstrated *in vitro* and *in vivo*.[1]

1. Reddy MV, *et al.* In vitro and in vivo synergistic effect of isoniazid with streptomycin and clofazimine against Mycobacterium avium complex (MAC). *Tubercle Lung Dis* 1994; **75:** 208–12.

Pharmacokinetics

Isoniazid is readily absorbed from the gastrointestinal tract and after intramuscular injection. Peak concentrations of about 3 to 7 micrograms/mL appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of isoniazid is reduced by food. Isoniazid is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy (see below), and is distributed into breast milk (see under Precautions, above).

The plasma half-life for isoniazid ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by *N*-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised isoniazid is conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly. Ethnic groups differ in their proportions of these genetic phenotypes. When isoniazid is given daily or 2 or 3 times weekly, clinical effectiveness is not influenced by acetylator status.

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the faeces. Isoniazid is removed by haemodialysis.

Distribution. Therapeutic concentrations of isoniazid have been detected in CSF[1,2] and synovial fluid[3] several hours after an oral dose. Diffusion into saliva is good and it has been suggested that salivary concentrations could be used in place of serum concentrations in pharmacokinetic studies.[4]

1. Forgan-Smith R, *et al.* Pyrazinamide and other drugs in tuberculous meningitis. *Lancet* 1973; **ii:** 374.
2. Miceli JN, *et al.* Isoniazid (INH) kinetics in children. *Fedn Proc* 1983; **42:** 1140.
3. Mouries D, *et al.* Passage articulaire de l'isoniazide et de l'éthambutol: deux observations de synovite tuberculeuse du genou. *Nouv Presse Med* 1975; **4:** 2734.
4. Gurumurthy P, *et al.* Salivary levels of isoniazid and rifampicin in tuberculous patients. *Tubercle* 1990; **71:** 29–33.

HIV-infected patients. Malabsorption of isoniazid and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p.328.

Pregnancy. Isoniazid crosses the placenta and average fetal concentrations of 61.5 and 72.8% of maternal serum or plasma concentration have been reported.[1] The half-life of isoniazid may be prolonged in neonates.[1]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.

Uses and Administration

Isoniazid is a hydrazide derivative that is the mainstay of the primary treatment of pulmonary and extrapulmonary tuberculosis (p.196). It is used with other antituberculous drugs usually in regimens including rifampicin, ethambutol, and pyrazinamide. Isoniazid is also used in high-risk subjects for the prophylaxis of tuberculosis.

Isoniazid is given in the initial and continuation phases of short-course tuberculosis regimens. The usual adult dose is 5 mg/kg, to a maximum of 300 mg, daily by mouth on an empty stomach. For intermittent therapy, WHO recommends 10 mg/kg three times a week or 15 mg/kg twice a week, while the recommended dose in the UK is 15 mg/kg three times a week and in the USA 15 mg/kg once weekly or two or three times a week is recommended. Caution is required in patients with hepatic impairment and doses may need to be reduced in those with severe renal impairment.

Similar doses to those used orally may be given by intramuscular injection when isoniazid cannot be taken by mouth; it may also be given by intravenous injection. Isoniazid has also been given intrathecally and intrapleurally.

In the treatment of latent tuberculosis, daily doses of 300 mg for 6 months are recommended by WHO and in the UK, while in the USA the preferred treatment regimen is oral isoniazid 5 mg/kg daily or 15 mg/kg twice weekly for 9 months. As an alternative to such regimens, isoniazid may be given with rifampicin for 3 months.

For details of doses in infants, children, and adolescents, see below.

Isoniazid aminosalicylate (pasiniazid) and isoniazid sodium glucuronate have also been used in the treatment of tuberculosis.

Fixed-dose combination products containing 2, 3, or 4 drugs have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing isoniazid in various combinations with rifampicin, ethambutol, and pyrazinamide are available in some countries.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) suggests an oral dose of isoniazid 10 to 15 mg/kg daily or 20 to 30 mg/kg twice weekly by mouth, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests oral doses of 5 to 10 mg/kg once daily or 15 mg/kg three times a week; WHO recommends 5 mg/kg once daily, or 10 mg/kg three times a week, or 15 mg/kg twice a week.

For the treatment of *latent* tuberculosis the AAP and the American Thoracic society suggest oral doses of 10 to 20 mg/kg daily or 20 to 40 mg/kg twice weekly for 9 months. For children 1 month and older the *BNFC* suggests a dose of 5 mg/kg once daily for 6 months when used alone or for 3 months when given with rifampicin; WHO recommends 5 mg/kg once daily for 6 months.

For daily dosing regimens the maximum oral dose of isoniazid is 300 mg and for intermittent regimens the maximum dose is 900 mg per dose.

Preparations

BP 2008: Isoniazid Injection; Isoniazid Tablets;
USP 31: Isoniazid Injection; Isoniazid Syrup; Isoniazid Tablets; Rifampin and Isoniazid Capsules; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Isoniac; ***Belg.:*** Nicotibine; ***Canad.:*** Isotamine; ***Cz.:*** Nidrazid; ***Fin.:*** Tubilysin; ***Fr.:*** Rimifon; ***Ger.:*** Isozid; Isozid comp N; tebesium; tebesium-s; ***Gr.:*** Cemidon; Dianicotyl; Isozid†; Nicozid; ***Hung.:*** Isonicid; ***India:*** Isokin; Isonex; Rifacom E-Z; ***Indon.:*** INH-Ciba; INHA; Inoxin; Medinh-OD; Niacifort-6; Nufadoxin; Pulmolin; Pyravit; Pyrifort; Suprazid; TB Vit 6; ***Israel:*** Inazid; ***Ital.:*** Nicizina; Nicozid; ***Jpn:*** Hydra; Hydrazide; ***Mex.:*** Erbazid†; Hidrasix; Valifol; ***Philipp.:*** Comprilex; Curazid (Reformulated); Eurocoxin; Isodexid; Isoxin; Nicetal; Odinah; Techxafort; Terozid; Trisofort; Vamsoxid; ***Port.:*** Hidrazida; ***Spain:*** Cemidon; Cemidon B6; ***Swed.:*** Tibinide; ***Switz.:*** Rimifon; ***Thai.:*** Antimic; Myrin-P; Myrin†; ***Turk.:*** INH; Isovit; ***USA:*** Laniazid; Nydrazid.

Multi-ingredient: ***Arg.:*** Bacifim; Rifinah; Risoniac†; ***Austria:*** Isoprodian; Myambutol-INH; Rifater; Rifoldin INH; ***Braz.:*** Isoniaton; ***Canad.:*** Rifater; ***Denm.:*** Rimactazid; Rimstar; ***Fin.:*** Rimactazid; Rimstar; ***Fr.:*** Rifater; Rifinah; ***Ger.:*** EMB-INH†; Iso-Eremfat; Isoprodian†; Myambutol-INH; Rifater; Rifinah; tebesium Duo; tebesium Trio; ***Gr.:*** Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong:*** Rifater; Rifinah; ***Hung.:*** Rifazid; ***India:*** Akt-3; Akt-4; Arzide; Bicox-E†; Combunex; Coxina-3; Coxina-4; Coxinex; Cx-3; Cx-4; Cx-5; Gocox Compound; Gocox-3; Gocox-4†; Inabutol Forte; Inapas; Ipcacin Kid; Ipcazide; Isokin-300; Isokin-T Forte; Isorifam; Myconex; R-Cinex; R-Cinex Z; RHZ; RHZ-Plus; Rifa; Rifa E; Rifacomb Plus†; Rifacomb†; Rimactazid + Z; Rimpazid; Siticox-INH; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed-2; Xeed-3E; Xeed-4; ***Indon.:*** bacbutINH; Erabutol Plus; Meditam-6; Mycothambin-INH; Niazitol; Pulna; Ramicin-ISO; Rimactazid; Rimcure; Rimstar; Santibi Plus; ***Irl.:*** Rifater; Rifinah; Rimactazid; ***Ital.:*** Etanicozid B6; Miazide B6†; Rifater; Rifinah; ***Malaysia:*** Rimactazid; Rimcure; ***Mex.:*** Arpisen; Finater; Finateramida; Isonid†; Myambutol-INH†; Rifater; Rifinah; ***Neth.:*** Rifinah; ***NZ:*** Rifinah; ***Philipp.:*** 4D; Bifix; CombiKids; CombiPack; Continukit; Continukit Plus; Continupack; Econokit; Econokit-MDR; Econopack; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Kidz Kit 2; Kidz Kit 3; Myrin; Myrin-P; Quadtab; Refam Duo; Refam Pedia Kit; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; Sthamizide; SVM-Polypac-A; Tres; Triofix; Tritab; Viper; ***Pol.:*** Rifamazid; ***Port.:*** Rifater; Rifinah; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Phthizopiram (Фтизопирам); Repin B (Репин B); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс); Rimactazid (Римактазид); Rimecure 3-FDC (Римкур 3-ФДС); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Myrin†; Rifafour; Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore:*** Rimactazid; ***Spain:*** Amiopia; Duplicalcio 150†; Duplicalcio B12; Duplicalcio Hidraz†; Rifater; Rifazida†; Rifinah; Rimactazid; Rimcure; Rimstar; Tisobrif; ***Swed.:*** Rimactazid; Rimcure; Rimstar; ***Switz.:*** Myambutol-INH†; Rifater; Rifinah; ***Thai.:*** Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid; Rimcure 3-FDC; Rimstar; ***UK:*** Rifater; Rifinah; Rimactazid†; ***USA:*** IsonaRif; Rifamate; Rifater; ***Venez.:*** Rimactazid; Rimcure.

Josamycin *(BAN, USAN, rINN)*

EN-141; Josamicina; Josamicinas; Josamycine; Josamycinum; Josamysiini; Jozamicin; Leucomycin A_3. A stereoisomer of 7-(formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′-acetate 4″-isovalerate.

Джозамицин

$C_{42}H_{69}NO_{15}$ = 828.0.
CAS — 16846-24-5; 56689-45-3.
ATC — J01FA07.
ATC Vet — QJ01FA07.

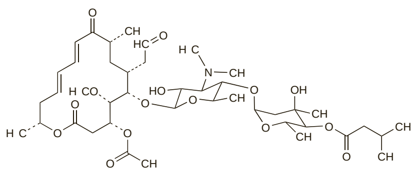

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*.

Ph. Eur. 6.2 (Josamycin). A macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic powder. It contains a minimum of 900 units/mg calculated with reference to the dried substance. Very slightly soluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Josamycin Propionate *(BANM, rINNM)*

Josamicino propionatas; Josamycine, propionate de; Josamycini propionas; Josamycinpropionat; Josamycin-propionát; Josamysiinipropionaatti; Jozamicin-propionát; Propionato de josamicina; YS-20P. Josamycin 10-propionate.

Джозамицина Пропионат

$C_{45}H_{73}NO_{16}$ = 884.1.
CAS — 56111-35-4; 40922-77-8.
ATC — J01FA07.
ATC Vet — QJ01FA07.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*.

Ph. Eur. 6.2 (Josamycin Propionate). It is derived from a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic, crystalline powder. It contains a minimum of 843 units/mg, calculated with reference to the dried substance. Practically insoluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270. Josamycin is reported to produce less gastrointestinal disturbance than erythromycin.

Oedema. A report of josamycin-induced oedema of the foot.[1]

1. Bosch X, *et al.* Josamycin-induced pedal oedema. *BMJ* 1993; **307:** 26.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Josamycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore interact less than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The general absence of an interaction between josamycin and theophylline would appear to support this.

Antimicrobial Action

As for Erythromycin, p.271. Some reports suggest that josamycin may be more active against some strains of anaerobic species such as *Bacteroides fragilis*.

Uses and Administration

Josamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p.272). It is given orally as the base or the propionate but doses are expressed in terms of the base; 1.07 g of josamycin propionate is equivalent to about 1 g of josamycin. Usual doses in the treatment of susceptible infections are the equivalent of 1 to 2 g of josamycin daily in 2 or more divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Josalid; ***Fr.:*** Josacine; ***Ger.:*** Wilprafen†; ***Hung.:*** Wilprafen†; ***Ital.:*** Iosalide; Josaxin†; ***Jpn:*** Josamy; ***Rus.:*** Wilprafen (Вильпрафен); ***Spain:*** Josamina.

Multi-ingredient: ***Ital.:*** Corti-Fluoral.

Kanamycin Acid Sulfate

Kanamicina, sulfato ácido de; Kanamicino rūgštusis sulfatas; Kanamycin Acid Sulphate *(BANM)*; Kanamycin sulfát kyselý; Kanamycine, sulfate acide de; Kanamycini sulfas acidus; Kanamycinsyrasulfat; Kanamysiinihapposulfaatti; Savanyú kanamicin-szulfát.
ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

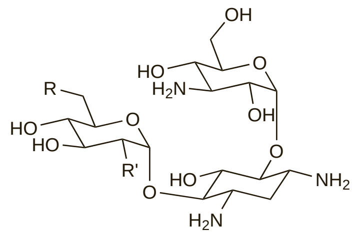

	R	R'
Kanamycin A	NH_2	OH
Kanamycin B	NH_2	NH_2
Kanamycin C	OH	NH_2

(kanamycin)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Kanamycin Acid Sulphate). A form of kanamycin sulfate prepared by adding sulfuric acid to a solution of kanamycin sulfate and drying by a suitable method. A white or almost white, hygroscopic powder containing not less than 670 units/mg and 23 to 26% of sulfate, calculated with reference to the dried material. Soluble 1 in about 1 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 5.5 to 7.5.

Kanamycin Sulfate *(rINNM)*

Kanamicin-monoszulfát; Kanamicino monosulfatas; Kanamycin A Sulphate; Kanamycin monosulfát monohydrát; Kanamycin Monosulphate; Kanamycin Sulphate *(BANM)*; Kanamycine, monosulfate de; Kanamycine, Sulfate de; Kanamycini monosulfas; Kanamycini Monosulfas Monohydricus; Kanamycini Sulfas; Kanamycinmonosulfat; Kanamycyny siarczan; Kanamysiinimonosulfaatti; Sulfato de kanamicina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine sulphate monohydrate.

Канамицина Сульфат

$C_{18}H_{36}N_4O_{11},H_2SO_4,H_2O$ = 600.6.
CAS — 59-01-8 (kanamycin); 25389-94-0 (anhydrous kanamycin sulfate).
ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Jpn includes the anhydrous substance.

Ph. Eur. 6.2 (Kanamycin Monosulphate; Kanamycin Sulphate BP 2008). The sulfate of an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*. A white or almost white, crystalline powder containing not less than 750 units/mg and 15.0 to 17.0% of sulfate, calculated with reference to the dried material. Soluble 1 in about 8 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 6.5 to 8.5.

USP 31 (Kanamycin Sulfate). A white, odourless crystalline powder. It has a potency equivalent to not less than 750 micrograms of kanamycin per mg, calculated on the dried basis. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides such as kanamycin with beta lactams, see under Gentamicin Sulfate, p.282. Kanamycin is also reported to be incompatible with various other drugs including some other antimicrobials as well as with some electrolytes.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282.

For patients given standard regimens, peak plasma concentrations of kanamycin greater than 30 micrograms/mL, and trough concentrations greater than 10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.

Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.

Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin (p.305), have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.

Breast feeding. Although kanamycin is distributed into breast milk[1] the American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers were receiving kanamycin, and therefore considers[2] that its use is usually compatible with breast feeding.

1. Chyo N, *et al.* Clinical studies of kanamycin applied in the field of obstetrics and gynecology. *Asian Med J* 1962; **5:** 265–75.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. It is active against a similar range of organisms although it is not active against *Pseudomonas* spp. Some strains of *Mycobacterium tuberculosis* are sensitive.

Resistance has been reported in strains of many of the organisms normally sensitive to kanamycin, and at one time was widespread, but a decline in the use of kanamycin has meant that resistance has become somewhat less prevalent. Cross-resistance occurs between kanamycin and neomycin, framycetin, and paromomycin, and partial cross-resistance has been reported between kanamycin and streptomycin.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

Less than 1% of an oral dose is absorbed, although this may be significantly increased if the gastrointestinal mucosa is inflamed or ulcerated.

After intramuscular injection peak plasma concentrations of kanamycin of about 20 and 30 micrograms/mL are attained in about 1 hour following doses of 0.5 and 1 g respectively. A plasma half-life of about 3 hours has been reported. Absorption after intraperitoneal instillation is similar to that from intramuscular doses.

Kanamycin is rapidly excreted by glomerular filtration and most of a parenteral dose appears unchanged in the urine within 24 hours. It has been detected in cord blood and in breast milk.

Uses and Administration

Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin (p.284). It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea (p.191) and neonatal gonococcal eye infections (p.180), although its use has declined in many centres because of the development of resistance. As with gentamicin it may be used with penicillins and with cephalosporins; the injections should be given at separate sites. Kanamycin has also been used as a second-line drug in tuberculosis (p.196), but other, safer drugs are usually preferred.

The sulfate or acid sulfate salts are often used: in the USA, preparations containing the bisulfate ($C_{18}H_{36}N_40_{11},2H_2SO_4$), but referred to as the sulfate, are available. Doses are expressed in terms of kanamycin base; 1.2 g of kanamycin sulfate, and 1.34 g of kanamycin acid sulfate, are each equivalent to about 1 g of kanamycin. It is usually given by intramuscular injection, and in acute infections adults may be given 15 mg/kg daily, to a maximum of 1.5 g daily, in 2 to 4 divided doses. The same doses may be given by intravenous infusion of a 0.25 to 0.5% solution over 30 to 60 minutes; in the UK, up to 30 mg/kg daily has been given in 2 or 3 divided doses by this route. Similar doses are used in children. Treatment of acute infections should preferably not continue for longer than 7 to 10 days or exceed a cumulative dose of 10 g kanamycin. A dose of 3 to 4 g weekly, given as 1 g on alternate days or as 1 g twice daily on 2 days each week, has been suggested in the UK for chronic bacterial infections, up to a maximum cumulative dose of 50 g, but prolonged use increases the risk of nephrotoxicity and is not generally recommended.

A single intramuscular dose of 2 g of kanamycin has been used in the treatment of penicillin-resistant gonorrhoea. In the treatment and prophylaxis of neonatal gonococcal infections in infants born to mothers with gonorrhoea, 25 mg/kg, up to a maximum of 75 mg, may be given as a single intramuscular dose.

Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284.

Kanamycin has been used orally similarly to neomycin (p.305), for the suppression of intestinal flora. For pre-operative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.

Kanamycin has also been given in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.

Kanamycin tannate has also been used.

Preparations

USP 31: Kanamycin Injection; Kanamycin Sulfate Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Cristalomicina; ***Ger.:*** Kan-Ophtal; Kana-Stulln; Kanamytrex; ***India:*** Kancin; Kaycin; ***Indon.:*** Kanabiotic; Kanarco; Kanoxin; ***Ital.:*** Keimicina; ***Malaysia:*** Kancin; ***Mex.:*** Cancina; Kanacil†; Kanadrex†; Kanapat; Kantrex; Randikan†; Solkan; Sulmyn; ***Singapore:*** Kancin-L; Kancin†; ***Spain:*** Kantrex†; ***Thai.:*** Anbikan; Kan-Mycin†; Kancin; Kangen; KMH; ***USA:*** Kantrex; ***Venez.:*** Kanacyl†; Kantrex.

Multi-ingredient: ***Arg.:*** Cristalomicina; ***Fr.:*** Sterimycine†; ***Ital.:*** Dermaflogil; ***S.Afr.:*** Kantrexil; ***Spain:*** Kanafosal; Kanafosal Predni; Kanapomada; Naso Pekamin; ***Thai.:*** KA-Cilone; ***Venez.:*** Kanasone†; Monosulpa; Rinomax.

Kitasamycin *(BAN, USAN, rINN)*

Kitasamicina; Kitasamycine; Kitasamycinum; Leucomycin.

Китазамицин

CAS — 1392-21-8 (kitasamycin); 37280-56-1 (kitasamycin tartrate); 178234-32-7 (acetylkitasamycin).

ATC Vet — QJ01FA93.

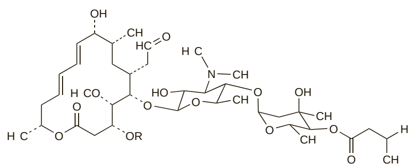

Kitasamycin A : R = H
Kitasamycin A : R = COCH

Pharmacopoeias. In *Chin.* and *Jpn.*
Jpn also includes Acetylkitasamycin and Kitasamycin Tartrate.

Profile

Kitasamycin is a macrolide antibacterial produced by *Streptomyces kitasatoensis*, consisting mainly of kitasamycins A_4 and A_5. It has actions and uses similar to those of erythromycin (p.269) and has been given orally as the base or intravenously as the tartrate in the treatment of susceptible infections. Acetylkitasamycin has also been given orally.

Kitasamycin has been added to animal feeding stuffs as growth promotors for pigs.

Latamoxef Disodium *(BANM, rINNM)*

Latamoksefidinatrium; Latamoxef disódico; Latamoxef Disodique; Latamoxefdinatrium; Latamoxefum Dinatricum; LY-127935; Moxalactam Disodium *(USAN)*; 6059-S. (7*R*)-7-[2-Carboxy-2-(4-hydroxyphenyl)acetamido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-1-oxa-3-cephem-4-carboxylic acid, disodium salt.

Динатрий Латамоксеф

$C_{20}H_{18}N_6Na_2O_9S$ = 564.4.

CAS — 64952-97-2 (latamoxef); 64953-12-4 (latamoxef disodium).

ATC — J01DD06.

ATC Vet — QJ01DD06.

Pharmacopoeias. In *Jpn.*

Profile

Latamoxef is an oxacephalosporin antibacterial that has been given intramuscularly or intravenously as the disodium salt in the treatment of susceptible infections. It differs from the cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by oxygen. Like cefamandole (p.220) it has an *N*-methylthiotetrazole side-chain and may cause hypoprothrombinaemia. Serious bleeding episodes have been reported with latamoxef and prophylaxis with vitamin K and monitoring of bleeding time have been recommended during treatment. In addition to hypoprothrombinaemia, inhibition of platelet function and more rarely immune-mediated thrombocytopenia may be responsible for interference with haemostasis. As with the methylthiotetrazole-containing cephalosporins, a disulfiram-like reaction with alcohol may occur.

Latamoxef has antimicrobial activity similar to that of the third-generation cephalosporin cefotaxime (p.228), although it is generally less active against Gram-positive bacteria and more active against *Bacteroides fragilis*.

Breast feeding. The authors of a pharmacokinetic study[1] in 8 lactating women given latamoxef cautioned that there was a possibility of colonisation of the infant's bowel with Gram-positive bacteria and in consequence a risk of enterocolitis. They therefore advised against breast feeding during maternal use of the drug. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving latamoxef, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Miller RD, *et al.* Human breast milk concentration of moxalactam. *Am J Obstet Gynecol* 1984; **148:** 348–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Shiomarin.

Levofloxacin *(BAN, USAN, rINN)*

DR-3355; HR-355; Levofloksasiini; Levofloksasin; Lévofloxacine; Levofloxacino; Levofloxacinum; *S*-(−)-Ofloxacin; RWJ-25213. (−)-(*S*)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid.

Левофлоксацин

$C_{18}H_{20}FN_3O_4$ = 361.4.

CAS — 100986-85-4 (levofloxacin); 138199-71-0 (levofloxacin hemihydrate).

ATC — J01MA12; S01AX19.

ATC Vet — QJ01MA12; QS01AX19.

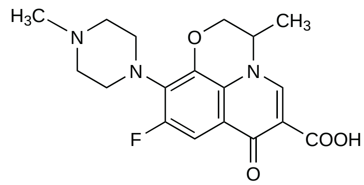

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped.

Effects on glucose metabolism. See also under Gatifloxacin, p.281.

Interactions

As for Ciprofloxacin, p.246.

Use of levofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Levofloxacin does not appear to interact significantly with theophylline or ciclosporin.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Levofloxacin is generally considered to be about twice as active as ofloxacin (p.310), the racemic substance. Levofloxacin has a broad spectrum of activity which includes Gram-positive bacteria.

◊ References.

1. Brown DFJ, *et al.*, eds. Levofloxacin: an extended spectrum 4-quinolone agent. *J Antimicrob Chemother* 1999; **43** (suppl C): 1–90.

Pharmacokinetics

Levofloxacin is rapidly and almost completely absorbed after oral doses with peak plasma concentrations occurring within 1 to 2 hours. It is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor. Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The elimination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, primarily in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 1997; **32:** 101–19.
2. Piscitelli SC, *et al.* Pharmacokinetics and safety of high-dose and extended-interval regimens of levofloxacin in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43:** 2323–7.

Uses and Administration

Levofloxacin is the *S*-(−)-isomer of the fluoroquinolone antibacterial ofloxacin (p.310). It is given orally, or by intravenous infusion as a 5 mg/mL solution over 30 to 90 minutes, to treat susceptible infections including tuberculosis (but see under Uses and Administration of Ciprofloxacin, p.248). Levofloxacin is given as the hemihydrate but doses are expressed in terms of the base; levofloxacin hemihydrate 256 mg is equivalent to about 250 mg of levofloxacin. Usual doses range from 250 to 500 mg once or twice daily for 7 to 14 days depending on the severity and nature of the infection. A dose of 250 mg once daily for 3 days may be given for uncomplicated urinary-tract infections. A 28-day course of treatment with a dose of 500 mg once daily should be given for chronic bacterial prostatitis. In the USA, doses of 750 mg once daily for 7 to 14 days may be used for complicated skin infections and for hospital-acquired pneumonia; a shorter course of 750 mg once daily for 5 days may be given for community-acquired pneumonia, acute bacterial sinusitis, complicated urinary-tract infections, and acute pyelonephritis. A 60-day course of treatment with a dose of 500 mg once daily is also licensed in the USA for treatment and postexposure prophylaxis of inhalation anthrax.

Doses should be reduced in patients with renal impairment (see below).

Levofloxacin is also used topically as the hemihydrate in eye drops. A solution containing the equivalent of 0.5% of levofloxacin is used for the treatment of bacterial conjunctivitis and 1.5% for corneal ulcers caused by susceptible strains of bacteria.

◊ Reviews.

1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; **4:** 677–700.
2. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32:** 320–36.
3. Martin SJ, *et al.* A risk-benefit assessment of levofloxacin in respiratory, skin and skin structure, and urinary tract infections. *Drugs* 2001; **24:** 199–222.
4. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 2003; **63:** 2769–2802.
5. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008; **68:** 535–65.

Administration in children. Since fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks. Although levofloxacin is not licensed for use in this age group in either the UK or USA, a pharmacokinetic study[1] has suggested that the following doses would be needed:

- children 5 years of age and older, 10 mg/kg daily
- infants and children from 6 months to less than 5 years of age, 10 mg/kg every 12 hours

1. Chien S, *et al.* Levofloxacin pharmacokinetics in children. *J Clin Pharmacol* 2005; **45:** 153–60.

Administration in renal impairment. Although initial doses (see above) remain unchanged in patients with renal impairment, subsequent doses of levofloxacin should be adjusted according to creatinine clearance (CC).

In the UK, the following doses are recommended:

- CC 20 to 50 mL/minute: subsequent doses are halved
- CC 10 to 19 mL/minute: subsequent doses are reduced to one-quarter of the usual dose; a regimen of 250 mg daily should be reduced to 125 mg every 48 hours
- CC less than 10 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): usual doses of 250 mg or 500 mg daily are reduced to 125 mg every 48 or 24 hours respectively; a regimen of 500 mg twice daily is reduced to 125 mg every 24 hours

In the USA, the following dose modifications are recommended:

After an initial dose of 750 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 750 mg every 48 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 500 mg every 48 hours

After an initial dose of 500 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 250 mg every 24 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 250 mg every 48 hours

After an initial dose of 250 mg daily,

- CC 10 to 19 mL/minute: subsequent doses are 250 mg every 48 hours

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with either venovenous haemofiltration or haemodiafiltration suggested that a dose of either levofloxacin 250 mg every 24 hours or 500 mg every 48 hours would be suitable in such situations.[1]

1. Malone RS, *et al.* Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 2001; **45:** 2949–54.

Peptic ulcer disease. For mention of the potential use of levofloxacin in eradication regimens for *Helicobacter pylori*, see p.1702.

References.

1. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006; **23:** 35–44.
2. Gisbert JP, *et al.* First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26:** 495–500.
3. Rispo A, *et al.* Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12:** 364–5.
4. Perna F, *et al.* Levofloxacin-based triple therapy for Helicobacter pylori re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007; **39:** 1001–5.
5. Zullo A, *et al.* Helicobacter pylori eradication with either quadruple regimen with lactoferrin or levofloxacin-based triple therapy: a multicentre study. *Dig Liver Dis* 2007; **39:** 806–10.
6. Yee YK, *et al.* Clinical trial: levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy in the treatment of resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2007; **26:** 1063–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Floxlevo; Grepiflox; Leflumax; Levaquin; Septibiotic; Tavanic; Teraquin; Ultraquin; Uniflox; Valiflox; ***Austria:*** Tavanic; ***Belg.:*** Tavanic; ***Braz.:*** Levaquin; Levotac; Levoxin; Tamiram; Tavanic; ***Canad.:*** Levaquin; ***Chile:*** Auxxil; Medibiox; Novacilina; Quinobiot; Recamicina; Tavanic; ***Cz.:*** Oftaquix; Tavanic; ***Denm.:*** Oftaquix; ***Fin.:*** Oftaquix; Tavanic; ***Fr.:*** Tavanic; ***Ger.:*** Oftaquix; Tavanic; ***Gr.:*** Tavanic; ***Hong Kong:*** Cravit; ***Hung.:*** Leflokin; Oftaquix; Tavanic; ***India:*** Glevo†; Leeflox; Levocide; Levoff; Levoflox; Lufi; Tavanic; ***Indon.:*** Armolev; Cravit; Cravox; Difloxin; Farlev; Lefos; Levocin; Levores; Levovid; Levoxal; Lexa; Lovequin; Mosardal; Nislev; Nufalev; Prolecin; Prolevox; Reskuin; Rinvox; Tevox; Volequin; Voxin; ***Irl.:*** Tavanic; ***Israel:*** Levo; Tavanic; ***Ital.:*** Levoxacin; Oftaquix; Prixar; Tavanic; ***Jpn:*** Cravit; ***Malaysia:*** Cravit; Glevo; Loxof; ***Mex.:*** Elequine; Ran-Levo; Tavanic; ***Neth.:*** Oftaquix; Prixar; Tavanic; ***Philipp.:*** Floxel; Levox; Oftaquix; ***Pol.:*** Oftaquix; ***Port.:*** Oftaquix; Tavanic; ***Rus.:*** Lefoxin (Лефоксин); Tavanic (Таваник); ***S.Afr.:*** Tavanic; ***Singapore:*** Cravit; ***Spain:*** Tavanic; ***Swed.:*** Oftaquix; Tavanic; ***Switz.:*** Tavanic; ***Thai.:*** Cravit; Lefloxin; ***Turk.:*** Cravit; Tavanic; ***UAE:*** Jenoquine; ***UK:*** Oftaquix; Tavanic; ***USA:*** Iquix; Levaquin; Quixin; ***Venez.:*** Levaquin; Proxime; Tavanic.

Multi-ingredient: ***India:*** Levoflox Oz Kit.

Lincomycin *(BAN, USAN, rINN)*

Lincomicina; Lincomycine; Lincomycinum; Linkomycin; Linkomysiini; U-10149. Methyl 6-amino-6,8-dideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside.

Линкомицин

$C_{18}H_{34}N_2O_6S = 406.5$.

CAS — 154-21-2.

ATC — J01FF02.

ATC Vet — QJ01FF02.

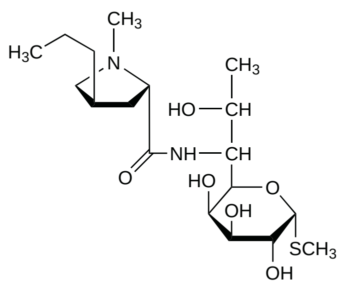

Lincomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lincomicina; Lincomycine, chlorhydrate de; Lincomycini hydrochloridum; Lincomycini Hydrochloridum Monohydricum; Linkomicin-hidroklorid; Linkomicino hidrochloridas; Linkomisin Hidroklorür; Linkomycin hydrochlorid monohydrát; Linkomycinhydroklorid; Linkomycyny chlorowodorek; Linkomysiinihydrokloridi; Lyncomycini Hydrochloridum; NSC-70731. Lincomycin hydrochloride monohydrate.

Линкомицина Гидрохлорид

$C_{18}H_{34}N_2O_6S,HCl,H_2O = 461.0$.

CAS — 859-18-7 (anhydrous lincomycin hydrochloride); 7179-49-9 (lincomycin hydrochloride, monohydrate).

ATC — J01FF02.

ATC Vet — QJ01FF02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Lincomycin Hydrochloride). An antimicrobial substance produced by *Streptomyces lincolnensis* var. *lincolnensis* or by any other means. A white or almost white crystalline powder. It contains not more than 5% of lincomycin B. Very soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30° in airtight containers.

USP 31 (Lincomycin Hydrochloride). A white or practically white crystalline powder, odourless or with a faint odour. Freely soluble in water; very slightly soluble in acetone; soluble in dimethylformamide. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Solutions of lincomycin hydrochloride have an acid pH and incompatibility may be expected with alkaline preparations, or with drugs unstable at low pH.

Adverse Effects, Treatment, and Precautions

As for Clindamycin, p.251.

Hypersensitivity reactions such as skin rashes, urticaria, and angioedema may be less frequent with lincomycin than with clindamycin. Other adverse effects reported rarely with lincomycin include aplastic anaemia, pancytopenia, tinnitus, and vertigo.

Lincomycin should be used with caution in patients with hepatic or renal impairment; consideration should be given to decreasing the dosage frequency and serum concentrations should be monitored during high-dose therapy. Reduced doses may be necessary in those with severe renal impairment (see below).

Interactions

As for Clindamycin, p.251.

Absorption of lincomycin is reduced by adsorbent antidiarrhoeals and cyclamate sweeteners.

Antimicrobial Action

As for Clindamycin, p.252, but it is less potent. There is complete cross-resistance between clindamycin and lincomycin. Some cross-resistance with erythromycin, including a phenomenon known as dissociated cross-resistance or macrolide effect, has been reported.

Pharmacokinetics

About 20 to 30% of an oral dose of lincomycin is rapidly absorbed from the gastrointestinal tract; after a 500-mg dose, peak plasma concentrations of about 2 to 3 micrograms/mL are reached within 2 to 4 hours. Food markedly reduces the rate and extent of absorption. An intramuscular injection of 600 mg produces average peak plasma concentrations of between 11 and 12 micrograms/mL at 60 minutes and a 2-hour intravenous infusion of 600 mg produces an average of about 16 micrograms/mL.

The biological half-life of lincomycin is about 5 hours and may be prolonged in hepatic or renal impairment. Serum half-life may be doubled in patients with hepatic impairment and up to 3 times longer in those with severe renal impairment. Lincomycin is widely distributed in the tissues including bone and body fluids but diffusion into the CSF is poor, although it may be slightly better when the meninges are inflamed. It diffuses across the placenta and is distributed into breast milk.

Lincomycin is partially inactivated in the liver; unchanged drug and metabolites are excreted in the urine, bile, and faeces. Lincomycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

Uses and Administration

Lincomycin is a lincosamide antibacterial with actions and uses similar to those of its chlorinated derivative, clindamycin (p.252). Clindamycin is usually preferred to lincomycin because of its greater activity and better absorption, although the usefulness of both drugs is limited by the risk of pseudomembranous colitis.

Lincomycin is given orally or parenterally as the hydrochloride but doses are expressed in terms of the base; 1.13 g of lincomycin hydrochloride is equivalent to about 1 g of lincomycin. The usual adult oral dose is 500 mg 3 or 4 times daily, taken at least 1 or 2 hours before or after food. It is given parenterally by intramuscular injection in a dose of 600 mg once or twice daily, or by slow intravenous infusion in a dose of 0.6 to 1 g two or three times daily. Higher intravenous doses have been given in very severe infections, up to a total daily dose of about 8 g. For intravenous use, lincomycin 1 g should be diluted in not less than 100 mL of diluent and infused over at least 1 hour.

For details of reduced doses in renal impairment, see below.

For details of doses in infants and children, see below.

Lincomycin hydrochloride may be given by subconjunctival injection in a dose equivalent to 75 mg of lincomycin.

Administration in children. The usual oral dose of lincomycin for infants and children aged 1 month and over is 30 to 60 mg/kg daily in divided doses. It is given parenterally to those over 1 month old in a dose of 10 to 20 mg/kg daily in divided doses by intramuscular injection or intravenous infusion.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. Doses of lincomycin may need to be reduced in patients with severe renal impairment; a reduction down to 25 to 30% of the usual dose (see above) may be appropriate.

Preparations

BP 2008: Lincomycin Capsules; Lincomycin Injection;
USP 31: Lincomycin Hydrochloride Capsules; Lincomycin Hydrochloride Syrup; Lincomycin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Frademicina; ***Austral.:*** Lincocin; ***Belg.:*** Lincocin; ***Braz.:*** Frademicina; Framicin†; Linatron; Lincoflan; Lincomiral; Lincomyn†; Lincoplax†; Lincotax†; Lincovax; Lindemicina; Neo Linco; ***Canad.:*** Lincocin; ***Chile:*** Lincocin; ***Cz.:*** Lincocin†; Neloren; ***Fr.:*** Lincocine; ***Ger.:*** Albiotic†; ***Gr.:*** Lincocin; Pecasolin; ***Hong Kong:*** Lincocin; Medoglycin†; ***India:*** Lynx; ***Indon.:*** Biolincom; Ethilin; Linco; Lincocin; Lincophar; Lincyn; Lintropsin; Nichomycin; Percocyn; Pritalinc; Tamcocin; Tismamisin; Zumalin; ***Ital.:*** Lincocin; ***Malaysia:*** Linco; Lincosa; Medoglycin†; ***Mex.:*** Libiocid; Limidrax; Linbac; Lincocin; Lincopat; Lincover; Lisonin; Princol; Rimsalin; Yectolin; ***Philipp.:*** Adlynx; Lincocin; ***Pol.:*** Lincocin; Neloren; ***Port.:*** Lincocina; ***Rus.:*** Neloren (Нелорен); ***S.Afr.:*** Lincocin; ***Singapore:*** Lincocin; ***Spain:*** Cillimicina; Lincocin; ***Thai.:*** Linco; Lincocilin; Lincocin; Lincogin†; Lincolan; Lincomax; Lincomy†; Lincono; Lingo; Linmycin; Utolincomycin; ***Turk.:*** Lincocin; Lincomed; Linkoles; Linkosol; Linosin; ***USA:*** Lincocin; Lincorex†; ***Venez.:*** Bekalen†; Formicina; Lincocin.

Multi-ingredient: ***Arg.:*** Nicozinc.

Linezolid *(BAN, USAN, rINN)*

Linetsolidi; Linézolide; Linezolidum; PNU-100766; U-100766. *N*-{[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

Линезолид

$C_{16}H_{20}FN_3O_4 = 337.3$.

CAS — 165800-03-3.

ATC — J01XX08.

ATC Vet — QJ01XX08.

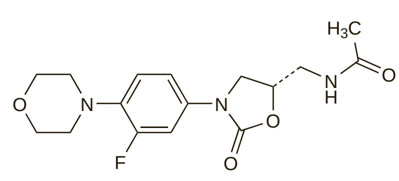

Incompatibility and stability. References.

1. Zhang Y, *et al.* Compatibility and stability of linezolid injection admixed with three quinolone antibiotics. *Ann Pharmacother* 2000; **34:** 996–1001.

Adverse Effects and Precautions

The adverse effects most frequently reported in patients given linezolid include diarrhoea, nausea and vomiting, metallic taste, headache, insomnia, constipation, rashes, dizziness, fever, oral and vaginal candidiasis, and abnormal liver function tests. Lactic acidosis has been reported. Convulsions have also been reported in patients treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. There have been rare reports of bullous skin eruptions including Stevens-Johnson syndrome. Peripheral and optic neuropathy, sometimes progressing to loss of vision, have occurred rarely, mainly in patients given linezolid for more than 28 days. Visual blurring has been reported in some patients given less than 28 days of treatment.

Reversible myelosuppression including anaemia, leucopenia, pancytopenia and, in particular, thrombocytopenia has been reported and blood counts should be monitored weekly in patients receiving linezolid. Patients particularly at risk are those who have received linezolid for more than 10 to 14 days, who are receiving other bone marrow suppressant drugs, or who have pre-existing myelosuppression or severe renal impairment.

Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when linezolid is given as monotherapy (see Increased Mortality, below); linezolid must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients.

◊ References.

1. Rubinstein E, *et al.* Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* 2003; **47:** 1824–31.
2. Bishop E, *et al.* Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; **50:** 1599–1602.

Effects on the blood. Reversible myelosuppression with red cell hypoplasia occurred in 3 patients treated with linezolid.[1] Features of the myelosuppression were considered by some[1,2] to be similar to those associated with chloramphenicol, although this was disputed by the manufacturers.[3]

There have been reports of thrombocytopenia occurring at a higher incidence than that reported by the manufacturers; in one study,[4] 6 of 19 patients who had been treated with linezolid developed thrombocytopenia, while another[5] found that it occurred in 23 of 48 patients given the drug for more than 5 days.

During the initial 8 months of licensed use in the UK 12 reports of haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) were received by the UK CSM.[6]

Studies have shown that the risk of thrombocytopenia and anaemia is increased in patients on prolonged linezolid therapy with pre-existing myelosuppression[7,8] or severe renal impairment.[9]

1. Green SL, *et al.* Linezolid and reversible myelosuppression. *JAMA* 2001; **285:** 1291.
2. Lawyer MC, Lawyer EZ. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1974.
3. Arellano FM. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1973–4.
4. Attassi K, *et al.* Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002; **34:** 695–8.
5. Orrick JJ, *et al.* Thrombocytopenia secondary to linezolid administration: what is the risk? *Clin Infect Dis* 2002; **35:** 348–9.
6. Committee on Safety of Medicines/Medicines Control Agency. Reminder: linezolid (Zyvox) and myelosuppression. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
7. Senneville E, *et al.* Risk factors for anaemia in patients on prolonged linezolid therapy for chronic osteomyelitis: a case-control study. *J Antimicrob Chemother* 2004; **54:** 798–802.
8. Grau S, *et al.* Linezolid: low pre-treatment platelet values could increase the risk of thrombocytopenia. *J Antimicrob Chemother* 2005; **56:** 440–1.
9. Wu V-C, *et al.* High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. *Clin Infect Dis* 2006; **42:** 66–72.

Effects on the eyes. See under Effects on the Nervous System, below.

Effects on mitochondria. Linezolid appears to inhibit mitochondrial protein synthesis when given for prolonged courses. This decreases cellular energy production in tissues that are highly dependent on oxidative phosphorylation, such as the optic nerve, skeletal muscles, liver, and kidneys, leading to adverse effects such as lactic acidosis[1] or hyperlactataemia,[1,2] and optic[3] and/or peripheral neuropathy[1] (see also below). Encephalopathy, lactic acidosis, optic neuropathy, skeletal myopathy, and renal failure were reported[1] in a 63-year-old woman after a 4-month course of linezolid. The symptoms resolved when linezolid was stopped; however, the patient remained blind and disorientated. In contrast, bilateral mitochondrial optic neuropathy seen[3] in a 6-year-old boy after a 1-year course of oral linezolid resolved 3 months after linezolid treatment was stopped. In another study[2] reversible hyperlactataemia was reported in 5 patients given linezolid for 1 to 3 months. Mitochondrial activity and lactic acid levels returned to normal when linezolid therapy was stopped.

1. De Vriese AS, *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006; **42:** 1111–1117.
2. Garrabou G, *et al.* Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother* 2007; **51:** 962–7.
3. Javaheri M, *et al.* Linezolid-induced optic neuropathy: a mitochondrial disorder? *Br J Ophthalmol* 2007; **91:** 111–15. Correction. *ibid.*; 403.

Effects on the nervous system. The Australian Adverse Drug Reactions Advisory Committee[1] stated in February 2003 that it had received 4 reports of peripheral neuropathy in patients who had taken linezolid for 6 to 9 months; none of these cases had resolved at the time of the report. They suggested that the risk of peripheral neuropathy should be considered when treatment was extended beyond 28 days. There have been several published reports of peripheral and optic neuropathy associated with linezolid,[2-9] with some attributing these effects to the inhibition of mitochondrial protein synthesis by linezolid. For further discussion see Effects on Mitochondria, above. The regulatory authority in the UK has warned that patients should be advised to report any symptoms of visual impairment immediately, including changes in visual acuity or colour vision, blurred vision, or visual field defects.[10] Any linezolid-treated patient with new visual symptoms should be evaluated promptly and referred to an ophthalmologist if necessary; regular monitoring is advised in all patients who may require treatment for more than 28 days.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Linezolid and peripheral neuropathy. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.htm (accessed 11/01/08)
2. Corallo CE, Paull AE. Linezolid-induced neuropathy. *Med J Aust* 2002; **177:** 332.
3. Rho JP, *et al.* Linezolid-associated peripheral neuropathy. *Mayo Clin Proc* 2004; **79:** 927–30.
4. Lee E, *et al.* Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; **37:** 1389–91.
5. Bressler AM, *et al.* Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis* 2004; **4:** 528–31.
6. Willcox D. Linezolid (Zyvoxam) and neuropathy *Can Adverse React News* 2005; **15:** 2.
7. Zivkovic SA, Lacomis D. Severe sensory neuropathy associated with long-term linezolid use. *Neurology* 2005; **64:** 926–7.
8. Legout L, *et al.* Linezolid-induced neuropathy. *Clin Infect Dis* 2004; **38:** 767–8.
9. Rucker JC, *et al.* Linezolid-associated toxic optic neuropathy. *Neurology* 2006; **66:** 595–8.
10. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Linezolid (Zyvox): severe optic neuropathy. *Current Problems* 2006; **31:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)

Increased mortality. In March 2007, the FDA[1] issued an alert advising that an open-label, randomised study comparing linezolid to vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections, including catheter-site infections, had found that death rates were significantly higher in patients treated with linezolid (78 of 363) than in the comparator arm (58 of 363), particularly in those with Gram-negative or mixed infections. Mortality did not differ for patients with purely Gram-positive infections.

The FDA[1] and the UK manufacturer[2] therefore advised that linezolid should not be used in infections caused by Gram-negative bacteria and should only be used in mixed Gram-positive and Gram-negative infections when appropriate cover for Gram-negative organisms is given at the same time. Licensed product information now reflects these warnings.

1. FDA. Information for healthcare professionals: linezolid (marketed as Zyvox) (issued 16th March 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/linezolidHCP.pdf (accessed 11/01/08)
2. Pfizer, UK. Important safety information (issued 28th February, 2007). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2030646&RevisionSelectionMethod=Latest (accessed 11/01/08)

Interactions

Linezolid is a reversible, nonselective MAOI and therefore has the potential to interact with adrenergic and serotonergic drugs. Enhanced pressor activity has been reported in patients receiving linezolid with phenylpropanolamine or pseudoephedrine and initial doses of dopamine or adrenaline should be reduced. There have also been cases of serotonin syndrome when linezolid was taken with serotonin reuptake inhibitors, and similar symptoms when it was taken with dextromethorphan. The interactions of conventional MAOIs, both with other drugs and with foods, are described under Phenelzine, p.417.

Antidepressants. Serotonin syndrome has been reported in patients taking linezolid with serotonergic antidepressants such as venlafaxine (see p.429) and SSRIs (though concomitant use may be possible, see p.396).

Opioid analgesics. For a report of an interaction between linezolid and *pethidine*, attributed to linezolid's inhibitory actions on monoamine oxidase, see p.114.

Antimicrobial Action

Linezolid is an oxazolidinone antibacterial with activity against a range of aerobic Gram-positive bacteria including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is less active against Gram-negative bacteria, but has some *in-vitro* activity against *Haemophilus influenzae*, *Legionella* spp., *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *Pasteurella* spp. It is not active against *Acinetobacter* spp., Enterobacteriaceae, or *Pseudomonas* spp.

Oxazolidinone antibacterials are bacteriostatic and act by inhibition of ribosomal protein synthesis. Cross-resistance between oxazolidinones and other classes of antibacterial is considered unlikely.

Resistant strains of enterococci and meticillin-resistant *Staph. aureus* have been reported.

◊ References.

1. Noskin GA, *et al.* In vitro activities of linezolid against important Gram-positive bacterial pathogens including vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 1999; **43:** 2059–62.
2. Cercenado E, *et al.* In vitro activity of linezolid against multiply resistant Gram-positive clinical isolates. *J Antimicrob Chemother* 2001; **47:** 77–81.
3. Gemmell CG. Susceptibility of a variety of clinical isolates to linezolid: a European inter-country comparison. *J Antimicrob Chemother* 2001; **48:** 47–52.
4. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii9–ii16.
5. Jones RN, *et al.* Activity of linezolid against 3,251 strains of uncommonly isolated Gram-positive organisms: report from the SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* 2007; **51:** 1491–3.

Resistance. There have been reports of linezolid resistance in enterococci, involving both *Enterococcus faecium*[1-4] and *E. faecalis*.[2] There is also concern over the emergence of linezolid resistance in staphylococci, such as meticillin-resistant *Staphylococcus aureus*,[5,6] *Staph. auricularis*,[7] and *Staph. epidermidis*.[7,8] A survey[9] of reported resistance to linezolid in the USA found that it was still rare but was no longer limited to enterococci having also occurred in *Staph. epidermidis* and *Streptococcus oralis*.

1. Gonzales RD, *et al.* Infections due to vancomycin-resistant Enterococcus faecium resistant to linezolid. *Lancet* 2001; **357:** 1179.
2. Auckland C, *et al.* Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. *J Antimicrob Chemother* 2002; **50:** 743–6.
3. Herrero IA, *et al.* Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. *N Engl J Med* 2002; **346:** 867–9.
4. Seedat J, *et al.* Rapid emergence of resistance to linezolid during linezolid therapy of an Enterococcus faecium infection. *Antimicrob Agents Chemother* 2006; **50:** 4217–19.
5. Tsiodras S, *et al.* Linezolid resistance in a clinical isolate of Staphylococcus aureus. *Lancet* 2001; **358:** 207–8.
6. Wilson P, *et al.* Linezolid resistance in clinical isolates of Staphylococcus aureus. *J Antimicrob Chemother* 2003; **51:** 186–8.
7. Cieloszyk K, *et al.* Linezolid resistance in three isolates of coagulase-negative staphylococci. *Ann Pharmacother* 2007; **41:** 526–7.
8. Kelly S, *et al.* Linezolid resistance in coagulase-negative staphylococci. *J Antimicrob Chemother* 2006; **58:** 898–9.
9. Mutnick AH, *et al.* Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. *Ann Pharmacother* 2003; **37:** 769–74.

Pharmacokinetics

Linezolid is rapidly and extensively absorbed after oral doses and maximum plasma concentrations are achieved after 1 to 2 hours. It is about 31% bound to plasma proteins. Linezolid is reported to be distributed into bone, fat, lungs, muscle, skin blister fluids, and into the CSF. It is metabolised mainly by oxidation to 2 main inactive metabolites, the hydroxyethyl glycine metabolite (PNU-142586) and the aminoethoxyacetic acid metabolite (PNU-142300); other minor inactive metabolites have also been identified. About 40% of a dose is excreted in the urine as PNU-142586, 30% as linezolid, and 10% as PNU-142300. Small amounts of metabolites are excreted in the faeces. The elimination half-life of linezolid is about 5 to 7 hours.

Children exhibit more rapid clearance of linezolid than adults; half-life is reported to range from about 2 to 4 hours, increasing with age.

◊ References.

1. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii17–ii25.
2. Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clin Pharmacokinet* 2003; **42:** 1129–40.
3. Whitehouse T, *et al.* Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother* 2005; **55:** 333–40.

Uses and Administration

Linezolid is an oxazolidinone antibacterial used for the treatment of Gram-positive infections of the skin and respiratory tract, including those due to vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*.

It is given, orally or by intravenous infusion (over 30 to 120 minutes), in a usual adult dose of 600 mg every 12 hours for 10 to 14 days; treatment for up to 28 days may be necessary if there is vancomycin resistance. In uncomplicated skin and skin structure infections an oral dose of 400 mg every 12 hours for 10 to 14 days is usually sufficient.

For doses in neonates and children, see below.

◊ Reviews.

1. Plouffe JF. Emerging therapies for serious gram-positive bacterial infections: a focus on linezolid. *Clin Infect Dis* 2000; **31**(suppl 4): S144–S149.
2. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious gram-positive infections. *Drugs* 2001; **61:** 525–51.
3. Bain KT, Wittbrodt ET. Linezolid for the treatment of resistant gram-positive cocci. *Ann Pharmacother* 2001; **35:** 566–75.
4. Paladino JA. Linezolid: an oxazolidinone antimicrobial agent. *Am J Health-Syst Pharm* 2002; **59:** 2413–25.
5. Birmingham MC, *et al.* Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; **36:** 159–68.
6. Wilcox MH. Efficacy of linezolid versus comparator therapies in Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii27–ii35.
7. Falagas ME, *et al.* Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother* 2006; **58:** 273–80.
8. Ntziora F, Falagas ME. Linezolid for the treatment of patients with central nervous system infection. *Ann Pharmacother* 2007; **41:** 296–308.
9. Falagas ME, *et al.* Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents* 2007; **29:** 233–9.
10. Manfredi R. Le prospettive terapeutiche di linezolid nelle infezioni da patogeni Gram-positivi multiresistenti. *Recenti Prog Med* 2007; **98:** 143–54.
11. Falagas ME, *et al.* Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis* 2008; **8:** 53–66.

Administration in children. UK licensed product information does not recommend the use of linezolid in children and adolescents below 18 years of age. However, the *BNFC* suggests the following doses of linezolid in the treatment of pneumonia or *complicated* skin and soft-tissue infections, given orally or by intravenous infusion over 30 to 120 minutes:

- neonates up to 7 days old: 10 mg/kg every 12 hours, increasing to every 8 hours if response is poor
- 7 days to 12 years of age: 10 mg/kg (to a maximum of 600 mg) every 8 hours
- 12 to 18 years: usual adult doses (see above).

Similar doses are licensed in the USA. US licensed product information also suggests that in the treatment of *uncomplicated skin* and *skin structure* infections, oral doses given every 12 hours are sufficient in those aged 5 to 11 years.

Further references.

1. Cuzzolin L, Fanos V. Linezolid: a new antibiotic for newborns and children? *J Chemother* 2006; **18:** 573–81.
2. Velissariou IM. Use of linezolid in children: an overview of recent advances. *Expert Rev Anti Infect Ther* 2006; **4:** 947–52.

Administration in renal impairment. Linezolid should be used with caution in patients with renal impairment (creatinine clearance less than 30 mL/minute). Although no dosage adjustment is required, licensed product information states that peak plasma concentrations of linezolid's two major metabolites were about tenfold higher in such patients after several days of treatment. As about 30% of a dose is removed during 3 hours of haemodialysis it is recommended that linezolid should be given after dialysis.

Mycobacterial infections. A systematic review[1] noted that linezolid has been used with some success as an adjunct in the treatment of multidrug-resistant tuberculosis (p.196); it has also been tried in nontuberculous mycobacterial infections (p.181). However, serious adverse effects such as peripheral or optic neuropathy (in 11 of 24 patients), and anaemia (10 of 24) were observed. The review concluded that although there was limited evidence suggesting linezolid may be effective as second-line adjunct therapy for patients with mycobacterial infections, its usefulness is limited by the frequent potentially severe complications of prolonged linezolid use.

1. Ntziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. *Int J Tuberc Lung Dis* 2007; **11:** 606–11. Correction. *ibid.*; 936. (title change)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zyvox; ***Austral.:*** Zyvox; ***Austria:*** Zyvoxid; ***Belg.:*** Zyvoxid; ***Braz.:*** Zyvox; ***Canad.:*** Zyvoxam; ***Chile:*** Zyvox; ***Cz.:*** Zyvoxid; ***Denm.:*** Zyvoxid; ***Fin.:*** Zyvoxid; ***Fr.:*** Zyvoxid; ***Ger.:*** Zyvoxid; ***Gr.:*** Zyvoxid; ***Hong Kong:*** Zyvox; ***Hung.:*** Zyvox†; Zyvoxid†; ***India:*** Linospan; Linox; Lizolid; ***Indon.:*** Zyvox; ***Irl.:*** Zyvox; ***Israel:*** Zyvoxid; ***Ital.:*** Zyvoxid; ***Malaysia:*** Zyvox; ***Mex.:*** Zyvoxam; ***Neth.:*** Zyvoxid; ***Norw.:*** Zyvoxid; ***NZ:*** Zyvox; ***Philipp.:*** Zyvox; ***Pol.:*** Zyvoxid; ***Port.:*** Zyvoxid; ***Rus.:*** Zyvox (Зивокс); ***S.Afr.:*** Zyvoxid; ***Singapore:*** Zyvox; ***Spain:*** Zyvoxid; ***Swed.:*** Zyvoxid; ***Switz.:*** Zyvoxid; ***Thai.:*** Zyvox; ***UK:*** Zyvox; ***USA:*** Zyvox; ***Venez.:*** Zyvox.

Lomefloxacin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lomefloxacino; Lomefloksasiinihydrokloridi; Lomefloksasin Hidroklorür; Loméfloxacine, Chlorhydrate de; Lomefloxacinhydroklorid; Lomefloxacini Hydrochloridum; NY-198; SC-47111; SC-47111A (lomefloxacin). (*RS*)-1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

Ломефлоксацина Гидрохлорид

$C_{17}H_{19}F_2N_3O_3,HCl = 387.8.$

CAS — 98079-51-7 (lomefloxacin); 98079-52-8 (lomefloxacin hydrochloride).

ATC — J01MA07; S01AX17.

ATC Vet — QJ01MA07; QS01AX17.

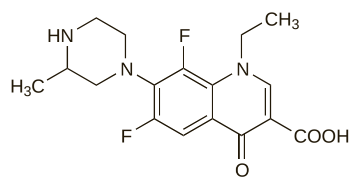

(lomefloxacin)

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

A relatively high incidence of phototoxic reactions has been seen in patients taking lomefloxacin. Patients should be advised to avoid exposure to sunlight during, and for a few days after, lomefloxacin therapy, and to stop the drug immediately if phototoxicity occurs. Risk of phototoxicity may be reduced by taking lomefloxacin in the evening.

Effects on the skin. Lomefloxacin has been associated with a higher incidence of phototoxic reactions, particularly in patients over 60 years of age and/or with a history of fluoroquinolone treatment; the incidence was also high when used for 30 days or longer.[1] Experimental results[2] suggest that use of sunscreens to protect against lomefloxacin-induced phototoxicity may be feasible.

1. Arata J, *et al.* Photosensitivity reactions caused by lomefloxacin hydrochloride: a multicenter survey. *Antimicrob Agents Chemother* 1998; **42:** 3141–5.
2. Reinhardt P, *et al.* Broad-spectrum sunscreens prevent the secretion of proinflammatory cytokines in human keratinocytes exposed to ultraviolet A and phototoxic lomefloxacin. *Can J Physiol Pharmacol* 2006; **84:** 221–6.

Interactions

As for Ciprofloxacin, p.246.

Lomefloxacin does not appear to interact significantly with theophylline or caffeine.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Most streptococci, including *Streptococcus pneumoniae*, are relatively resistant to lomefloxacin.

Pharmacokinetics

Lomefloxacin is rapidly and almost completely absorbed after oral doses with peak plasma concentrations of about 3 micrograms/mL occurring about 1.5 hours after a 400-mg dose. Lomefloxacin is about 10% bound to plasma proteins. It is widely distributed into body tissues including the lungs and prostate.

The elimination half-life of lomefloxacin is about 7 to 8 hours, and is prolonged in patients with renal impairment. Lomefloxacin is excreted in the urine, about 65% as unchanged drug, 9% as the glucuronide, and less than 0.5% as other metabolites. Small amounts (about 10%) are also eliminated unchanged in the faeces. Negligible amounts of lomefloxacin are removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Freeman CD, *et al.* Lomefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 6–19.

Uses and Administration

Lomefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally for the treatment of susceptible infections, including bronchitis due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), and urinary-tract infections. It is also used for surgical infection prophylaxis. Lomefloxacin is given as the hydrochloride but doses are expressed in terms of the base; lomefloxacin hydrochloride 441.5 mg is equivalent to about 400 mg of lomefloxacin. The usual dose is 400 mg once daily for 10 to 14 days. A dose of 400 mg once daily for 3 days is suitable in women with acute uncomplicated cystitis. Dosage in the evening may minimise the risk of phototoxic reactions.

For details of reduced doses in renal impairment, see below.

A single dose of 400 mg is used for surgical infection prophylaxis, given 1 to 6 hours before the procedure.

Lomefloxacin is also used topically as the hydrochloride in eye drops and ear drops containing the equivalent of 0.3% of lomefloxacin for the treatment of bacterial conjunctivitis and for the treatment of otitis externa and otitis media, respectively.

◊ General references.

1. Wadworth AN, Goa KL. Lomefloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1991; **42:** 1018–60.
2. Neu HC, ed. Lomefloxacin: development of a once-a-day quinolone. *Am J Med* 1992; **92** (suppl 4A): 1S–137S.

Administration in renal impairment. Dosage of lomefloxacin should be reduced in patients with renal impairment; the initial dose of 400 mg should be followed by maintenance doses of 200 mg daily in those with a creatinine clearance of 10 to 40 mL/minute per $1.73m^2$ and in those on haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Okacin; ***Austria:*** Okacin; Uniquin; ***Belg.:*** Okacin; ***Braz.:*** Maxaquin; Meflox†; Okacin†; ***Chile:*** Okacin†; ***Cz.:*** Maxaquin†; Okacin; ***Denm.:*** Okacin; ***Fin.:*** Okacin; ***Fr.:*** Decalogiflox; Logiflox; ***Ger.:*** Okacin; ***Gr.:*** Okacin; ***Hong Kong:*** Lomeflox; Maxaquin; Okacin; ***Hung.:*** Okacin; ***India:*** Lomef; Lomflox; Ontop; ***Israel:*** Okacin; ***Ital.:*** Chimono; Lomebact; Maxaquin; Okacin; Uniquin; ***Jpn:*** Lomeflon; ***Malaysia:*** Lomaday†; Okacin†; ***Mex.:*** Lomacin; Maxaquin; ***Philipp.:*** Okacin; ***Pol.:*** Okacin; ***Port.:*** Basab†; Floxaquil†; Loransil; Loxina†; Maxaquin; Monoquin†; Okacin; Uniquin; ***Rus.:*** Ksenakvin (Ксенаквин); Lomflox (Ломфлокс); Maxaquin (Максаквин)†; Okacin (Окацин); ***S.Afr.:*** Maxaquin; Okacyn; Uniquin; ***Singapore:*** Lomflox; Okacin; ***Spain:*** Ocacin; ***Switz.:*** Maxaquin; Okacin; ***Thai.:*** Maxaquin†; Okacin; ***Turk.:*** Okacin; ***UAE:*** Lomax; ***USA:*** Maxaquin; ***Venez.:*** Liexina†; Loflox; Lomaday†; Lomex; Maxaquin; Okacin.

Multi-ingredient: *Rus.:* Lomecomb (Ломекомб); Protiocomb (Протиокомб).

Loracarbef *(BAN, USAN, rINN)*

KT-3777; Loracarbefum; Lorakarbef; Lorakarbefi; LY-163892. (*6R,7S*)-3-Chloro-8-oxo-7-D-phenylglycylamino-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Лоракарбеф

$C_{16}H_{16}ClN_3O_4,H_2O = 367.8.$

CAS — 76470-66-1 (anhydrous loracarbef); 121961-22-6 (loracarbef monohydrate).

ATC — J01DC08.

ATC Vet — QJ01DC08.

Pharmacopoeias. In *US.*

USP 31 (Loracarbef). pH of a 10% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Adverse Effects and Precautions

Adverse effects of loracarbef are generally similar to those of other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). They include gastrointestinal disturbances, particularly diarrhoea, and hypersensitivity reactions such as skin rashes. In-

The symbol † denotes a preparation no longer actively marketed

creases in liver enzymes and abnormalities in haematological parameters have been reported.

Loracarbef should not be given to patients known to be hypersensitive to it or to other beta lactams because of the possibility of cross-sensitivity. It should be given with caution, with appropriate dosage reduction, in patients with renal impairment.

Effects on the kidneys. References.

1. Thieme RE, *et al.* Acute interstitial nephritis associated with loracarbef therapy. *J Pediatr* 1995; **127:** 997–1000.

Interactions

Probenecid decreases the renal excretion of loracarbef thereby increasing its plasma concentrations.

Antimicrobial Action

Loracarbef is bactericidal with antibacterial activity similar to that of cefaclor (p.217).

Pharmacokinetics

Loracarbef is well absorbed from the gastrointestinal tract with a bioavailability of 90%. Peak plasma concentrations after 200- and 400-mg doses as capsules are about 8 and 14 micrograms/mL respectively at 1.2 hours. Peak concentrations are achieved more rapidly after an oral suspension and a paediatric dose of 15 mg/kg produces a concentration of about 19 micrograms/mL within 40 to 60 minutes. Absorption is delayed by the presence of food. A plasma half-life of about 1 hour has been reported which is prolonged in renal impairment. About 25% is bound to plasma proteins.

Loracarbef is excreted largely unchanged in the urine, and therapeutic concentrations are maintained in the urine for up to 12 hours. Probenecid delays excretion. Loracarbef is removed by haemodialysis.

Uses and Administration

Loracarbef is an oral carbacephem antibiotic. The carbacephems are closely related to the cephalosporins, but replacement of the sulfur atom in the 7-aminocephalosporanic acid nucleus by a methylene group is said to enhance stability. It is used similarly to cefaclor in the treatment of susceptible infections of the respiratory and urinary tracts and of skin and soft tissue. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Loracarbef should be given 1 hour before food or on an empty stomach. Loracarbef is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous loracarbef. The usual adult dose is 200 to 400 mg every 12 hours. In uncomplicated urinary-tract infections, a dose of 200 mg daily may be adequate. A dose for children is 7.5 mg/kg every 12 hours for uncomplicated infections or 15 mg/kg every 12 hours for acute otitis media or acute maxillary sinusitis.

For details of reduced doses of loracarbef in patients with renal impairment, see below.

◊ General references.

1. Moellering RC, Jacobs NF. Advances in outpatient antimicrobial therapy: loracarbef. *Am J Med* 1992; **92** (suppl 6A): 1S–103S.
2. Brogden RN, McTavish D. Loracarbef: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 716–36.

Administration in renal impairment. Doses of loracarbef should be reduced in patients with renal impairment; patients with a creatinine clearance of 10 to 49 mL/minute may be given half the usual dose at the usual dosage interval or the full usual dose at twice the usual interval; patients with a creatinine clearance of less than 10 mL/minute may be treated with the usual dose given every 3 to 5 days. Patients on haemodialysis should receive another dose following dialysis.

Preparations

USP 31: Loracarbef Capsules; Loracarbef for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Ger.: Lorafem; ***Gr.:*** Lorbef; ***Mex.:*** Carbac†; Lorabid†; ***S.Afr.:*** Lorabid; ***Swed.:*** Lorabid; ***Turk.:*** Lorabid; ***USA:*** Lorabid†.

Lymecycline *(BAN, rINN)*

Limeciclina; Limesiklin; Lymécycline; Lymecyclinum; Lymecyklin; Lymecyklina; Lymesykliini; Tetracyclinemethylene lysine. (+)-*N*-(5-Amino-5-carboxypentylaminomethyl)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonapthacene-2-carboxamide; N^2-{[(+)-5-Amino-5-carboxypentylamino]methyl}tetracycline.

Лимециклин

$C_{29}H_{38}N_4O_{10}$ = 602.6.
CAS — 992-21-2.
ATC — J01AA04.
ATC Vet — QJ01AA04.

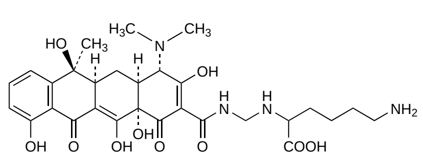

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lymecycline). A reaction product of formaldehyde, lysine, and tetracycline. A yellow, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.8 to 8.2. Store in airtight containers. Protect from light.

Profile

Lymecycline is a tetracycline derivative with general properties similar to those of tetracycline (p.347). Although its absorption is not significantly affected by moderate amounts of milk, it is still affected by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc.

Lymecycline is given orally and doses are expressed in terms of the equivalent amount of tetracycline base. Lymecycline 407 mg is equivalent to about 300 mg of tetracycline and to about 325 mg of tetracycline hydrochloride. The usual adult dose is the equivalent of 300 mg of tetracycline base twice daily. In severe infections total daily doses of up to the equivalent of 1.2 g may be given. In the treatment of acne, the equivalent of 300 mg is given daily for at least 8 weeks.

For details of use in children and adolescents, see below.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, lymecycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given by mouth. However, in some countries, it is licensed for use in those over 8 years old.

Skin disorders. For reference to the use of lymecycline in the treatment of acne, see under Tetracycline, p.350.

Preparations

BP 2008: Lymecycline Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Tetralysal; ***Austria:*** Tetralysal; ***Belg.:*** Tetralysal; ***Braz.:*** Tetralysal; ***Denm.:*** Tetralysal; ***Fin.:*** Tetralysal; ***Fr.:*** Tetralysal; ***Hong Kong:*** Tetralysal; ***Hung.:*** Tetralysal; ***Irl.:*** Tetralysal; ***Ital.:*** Tetralysal; ***Mex.:*** Tetralisal; ***Norw.:*** Tetralysal; ***NZ:*** Tetralysal; ***Philipp.:*** Tetralysal; ***S.Afr.:*** Tetralysal; ***Swed.:*** Tetralysal; ***Switz.:*** Tetralysal; ***UK:*** Tetralysal; ***Venez.:*** Tetralysal.

Mafenide *(BAN, USAN, rINN)*

Mafenid; Mafenida; Maféníde; Mafenidi; Mafenidum; NSC-34632. α-Aminotoluene-*p*-sulphonamide.

Мафенид

CAS — 138-39-6.
ATC — D06BA03.
ATC Vet — QD06BA03.

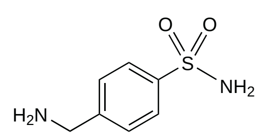

Mafenide Acetate *(BANM, rINNM)*

Acetato de mafenida; Maféníde, Acétate de; Mafenidi Acetas.

Мафенида Ацетат

$C_7H_{10}N_2O_2S,C_2H_4O_2$ = 246.3.
CAS — 13009-99-9.
ATC — D06BA03.
ATC Vet — QD06BA03.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Mafenide Acetate). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.4 and 6.8. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Mafenide is absorbed to some extent after topical application and may produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p.340). Fatal haemolytic anaemia with disseminated intravascular coagulation, related to G6PD deficiency, has been reported.

Mafenide cream may cause pain or a burning sensation on application to the burnt area, with occasional bleeding or excoriation. The separation of the eschar may be delayed and fungal invasion of the wound has been reported. By its action in inhibiting carbonic anhydrase, mafenide may cause metabolic acidosis and hyperventilation; acid–base balance should therefore be monitored, particularly in patients with extensive burns, or with pulmonary or renal impairment. If persistent acidosis occurs, mafenide treatment should be temporarily suspended and fluid therapy continued.

Pharmacokinetics

Mafenide is absorbed from wounds into the circulation and is metabolised to *p*-carboxybenzenesulfonamide, which is excreted in the urine. The metabolite has no antibacterial action but retains the ability to inhibit carbonic anhydrase.

Uses and Administration

Mafenide is a sulfonamide that is not inactivated by *p*-aminobenzoic acid or by pus and serum. The acetate is used as a cream, containing the equivalent of mafenide 8.5%, in conjunction with debridement, for the prevention and treatment of infection, including *Pseudomonas aeruginosa*, in second- and third-degree burns (p.1578). A solution containing mafenide acetate 5% is also available for use under moist dressings in burns. Mafenide hydrochloride and mafenide propionate have also been used.

Preparations

USP 31: Mafenide Acetate Cream; Mafenide Acetate for Topical Solution.

Proprietary Preparations (details are given in Part 3)
USA: Sulfamylon.

Multi-ingredient: ***Indon.:*** FG Ointment; ***Spain:*** Pental Forte†.

Magainins

Magaininas.

Магаинины

Profile

The magainins are a group of antibacterial peptides derived from amphibians. A number of semisynthetic derivatives including pexiganan acetate (MSI-78), MSI-93, and MSI-94 have been investigated as topical anti-infectives.

◊ References.

1. Lamb HM, Wiseman LR. Pexiganan acetate. *Drugs* 1998; **56:** 1047–52.
2. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; **67:** 195–214.

Mandelic Acid

Ácido fenilglicólico; Ácido mandélico racémico; Amygdalic Acid; Mandélico, ácido; Phenylglycolic Acid; Racemic Mandelic Acid. 2-Hydroxy-2-phenylacetic acid.

Миндальная Кислота

$C_8H_8O_3$ = 152.1.
CAS — 90-64-2; 17199-29-0 ((+)-mandelic acid); 611-71-2 ((−)-mandelic acid); 611-72-3 ((±)-mandelic acid).
ATC — B05CA06; J01XX06.
ATC Vet — QB05CA06; QJ01XX06.

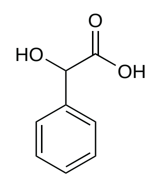

Profile

Mandelic acid has bacteriostatic properties and is used as a 1% flushing solution for the maintenance of indwelling urinary catheters. Mandelic acid and acetyl mandelic acid are used topically in preparations for the treatment of acne. It was formerly given orally in the treatment of urinary-tract infections, usually as the ammonium or calcium salt.

Mandelic acid is a component of methenamine mandelate (p.298).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Rolip†.

Multi-ingredient: ***Chile:*** Neostrata; ***Fr.:*** Sphingogel†; Zeniac LP Fort†; Zeniac LP†; Zeniac†; ***Ital.:*** Neoceuticals Clear Skin; Neoceuticals Spot Treatment; ***Port.:*** Mandelip†.

Marbofloxacin *(BAN, rINN)*

Marbofloksasiini; Marbofloxacine; Marbofloxacino; Marbofloxacinum. 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid.

Марбофлоксацин

$C_{17}H_{19}FN_4O_4$ = 362.4.
CAS — 115550-35-1.
ATC Vet — QJ01MA93.

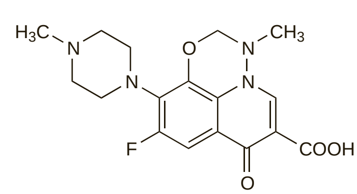

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Marbofloxacin for Veterinary Use). A light yellow, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; sparingly soluble or slightly soluble in dichloromethane. Protect from light.

Profile
Marbofloxacin is a fluoroquinolone antibacterial used in veterinary medicine.

Mecillinam *(BAN, rINN)*

Amdinocillin *(USAN)*; FL-1060; Mecilinam; Mécillinam; Mecillinamum; Mesillinaami; Ro-10-9070. (6*R*)-6-(Perhydroazepin-1-ylmethyleneamino)penicillanic acid.

Мециллинам

$C_{15}H_{23}N_3O_3S = 325.4$.
CAS — 32887-01-7.
ATC — J01CA11.
ATC Vet — QJ01CA11.

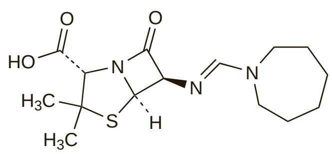

Adverse Effects and Precautions
As for Benzylpenicillin, p.213.

Porphyria. Mecillinam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions
As for Benzylpenicillin, p.214.

Antimicrobial Action
Mecillinam is a derivative of amidinopenicillanic acid. Unlike benzylpenicillin and related antibiotics, it is active against many Gram-negative bacteria, in particular Enterobacteriaceae including *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Salmonella*, and *Shigella* spp. The susceptibility of *Proteus* spp. varies; *Serratia marcescens* is generally resistant. It is less active against *Neisseria* spp. and *Haemophilus influenzae*. *Pseudomonas aeruginosa* and *Bacteroides* spp. are considered to be resistant. It is much less active against Gram-positive bacteria; enterococci including *Enterococcus faecalis* are resistant.

Mecillinam interferes with the synthesis of the bacterial cell wall by binding with a different penicillin-binding protein from benzylpenicillin. This difference in mode of action may explain the synergism against many Gram-negative organisms that has been reported *in vitro* between mecillinam and various penicillins or cephalosporins.

Mecillinam is inactivated by beta-lactamases, but is more stable than ampicillin.

Pharmacokinetics
Mecillinam is poorly absorbed from the gastrointestinal tract. Peak plasma concentrations of about 6 and 12 micrograms/mL have been achieved half an hour after intramuscular doses of 200 and 400 mg, respectively. The usual plasma half-life of about 1 hour has been reported to be prolonged to 3 to 5 hours or more in severe renal impairment. Between 5 and 10% of mecillinam is bound to plasma proteins. Mecillinam is widely distributed into body tissues and fluids; little passes into the CSF unless the meninges are inflamed. It crosses the placenta into the fetal circulation; little appears to be distributed into breast milk.

Mecillinam is metabolised to only a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular filtration and tubular secretion. Renal tubular secretion can be reduced by probenecid. Some mecillinam is excreted in bile where high concentrations are achieved.

Mecillinam is removed by haemodialysis.

Uses and Administration
Mecillinam is a semisynthetic penicillin with a substituted amidino group at the 6-position of the penicillanic acid nucleus. It is given by slow intravenous injection, by intravenous infusion, or intramuscularly, in the treatment of susceptible Gram-negative infections (see under Antimicrobial Action, above).

For urinary-tract infections a dose of 800 mg is given every 6 to 8 hours. A total dose of up to 60 mg/kg daily may be used in very severe infections.

Mecillinam has been used with other beta lactams to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

The pivaloyloxymethyl ester of mecillinam, pivmecillinam, is used orally (see p.317).

Preparations
Proprietary Preparations (details are given in Part 3)
Denm.: Selexid; ***Gr.:*** Selexid; ***Norw.:*** Selexid; ***Swed.:*** Selexid.

Meclocycline *(BAN, USAN, rINN)*

GS-2989; Meclociclina; Méclocycline; Meclocyclinum; Meklocyklin; Meklosykliini; NSC-78502. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

Меклоциклин

$C_{22}H_{21}ClN_2O_8 = 476.9$.
CAS — 2013-58-3.
ATC — D10AF04.
ATC Vet — QD10AF04.

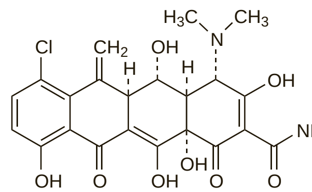

Meclocycline Sulfosalicylate *(USAN)*

Meclociclina, sulfosalicilato de; Meclocycline Sulphosalicylate. Meclocycline 5-sulphosalicylate.

$C_{22}H_{21}ClN_2O_8,C_7H_6O_6S = 695.0$.
CAS — 73816-42-9.
ATC — D10AF04.
ATC Vet — QD10AF04.

Pharmacopoeias. In *US.*

USP 31 (Meclocycline Sulfosalicylate). pH of a 1% solution in water is between 2.5 and 3.5. Store in airtight containers. Protect from light.

Profile
Meclocycline is a tetracycline antibacterial derived from oxytetracycline (p.312). It is applied topically as the sulfosalicylate for the treatment of acne vulgaris and superficial skin infections. Potency is expressed in terms of meclocycline. Preparations containing the equivalent of 1 or 2% are available. Meclocycline sulfosalicylate has also been given as a pessary in the treatment of vulvovaginal infections.

Preparations
USP 31: Meclocycline Sulfosalicylate Cream.

Proprietary Preparations (details are given in Part 3)
Ger.: Meclosorb; ***Ital.:*** Mecloderm; Mecloderm Antiacne; Mecloderm Ovuli; Mecloderm Polvere Aspersoria†; Meclutin Semplice†.

Multi-ingredient: *Ital.:* Anti-Acne; Mecloderm F; Meclutin†.

Meleumycin

Pharmacopoeias. In *Chin.*

Profile
Meleumycin, a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens*, consists of a mixture of midecamycin A_1 and kitasamycin A_6. It has actions and uses similar to those of erythromycin (p.269) and is given orally in the treatment of susceptible infections.

Meropenem *(BAN, USAN, rINN)*

ICI-194660; Meropeneemi; Méropénem; Meropenemum; SM-7338. (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylcarbamoylpyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Меропенем

$C_{17}H_{25}N_3O_5S,3H_2O = 437.5$.
CAS — 96036-03-2 (meropenem); 119478-56-7 (meropenem trihydrate).
ATC — J01DH02.
ATC Vet — QJ01DH02.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*

USP 31 (Meropenem). Colourless to white crystals. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone and in ether; soluble in dimethylformamide and in 5% monobasic potassium phosphate solution. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Adverse Effects and Precautions
As for Imipenem, p.286.

Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem (see also below).

Effects on the nervous system. *Animal* studies have indicated that meropenem induces fewer seizures than imipenem-cilastatin and clinical data from the manufacturer have substantiated this.[1] Comparison of data[2] from 4872 patients with a variety of infections (including meningitis) treated with meropenem with that from 4752 patients who received other antibacterials, principally cephalosporin-based regimens or imipenem-cilastatin, showed that meropenem was not associated with any greater risk of seizures than the other antibacterials and was likely to have less neurotoxic potential than imipenem-cilastatin, making it a suitable drug to use in the treatment of meningitis.

1. Norrby SR, *et al.* Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995; **36** (suppl A): 207–23.
2. Norrby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand J Infect Dis* 1999; **31:** 3–10.

Interactions
Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to meropenem, see p.510.

Antimicrobial Action
As for Imipenem, p.287.

Meropenem is slightly more active than imipenem against Enterobacteriaceae and slightly less active against Gram-positive organisms.

Pharmacokinetics
After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.

Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Meropenem is removed by haemodialysis.

◊ References.

1. Chimata M, *et al.* Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. *Antimicrob Agents Chemother* 1993; **37:** 229–33.
2. Dagan R, *et al.* Penetration of meropenem into the cerebrospinal fluid of patients with inflamed meninges. *J Antimicrob Chemother* 1994; **34:** 175–9.
3. Mouton JW, Van den Anker JN. Meropenem clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 275–86.
4. Blumer JL, *et al.* Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children. *Antimicrob Agents Chemother* 1995; **39:** 1721–5.
5. Novelli A, *et al.* Clinical pharmacokinetics of meropenem after the first and tenth intramuscular administration. *J Antimicrob Chemother* 1996; **37:** 775–81.
6. Thalhammer F, *et al.* Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* 1999; **43:** 523–7.
7. Giles LJ, *et al.* Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. *Crit Care Med* 2000; **28:** 632–7.
8. Thalhammer F, Horl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. *Clin Pharmacokinet* 2000; **39:** 271–9.
9. Ververs TF, *et al.* Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. *Crit Care Med* 2000; **28:** 3412–16.
10. van Enk JG, *et al.* Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23:** 198–201.
11. Goldstein SL, *et al.* Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. *Pediatr Nephrol* 2001; **16:** 1015–18.
12. Ariano RE, *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39:** 32–8.

13. Isla A, *et al.* Meropenem and continuous renal replacement therapy: in vitro permeability of 2 continuous renal replacement therapy membranes and influence of renal replacement therapy on the pharmacokinetics in critically ill patients. *J Clin Pharmacol* 2005; **45:** 1294–1304.
14. Novelli A, *et al.* Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44:** 539–49.
15. Du X, *et al.* Population pharmacokinetics and pharmacodynamics of meropenem in pediatric patients. *J Clin Pharmacol* 2006; **46:** 69–75.

Uses and Administration

Meropenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p.287). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections including intra-abdominal infections, gynaecological infections, meningitis, respiratory-tract infections (including in cystic fibrosis patients), septicaemia, skin and skin structure infections, urinary-tract infections, and infections in immunocompromised patients. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is equivalent to about 1 g of anhydrous meropenem. It is given by slow injection over 3 to 5 minutes or by infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours. A dose of 2 g every 8 hours is given for meningitis; doses of up to 2 g every 8 hours have also been used in cystic fibrosis. For details of reduced doses in renal impairment, see below.

For details of doses in infants and children, see below.

◊ Reviews.

1. Wiseman LR, *et al.* Meropenem: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1995; **50:** 73–101.
2. Finch RG, *et al.* eds. Meropenem: focus on clinical performance. *J Antimicrob Chemother* 1995; **36** (suppl A): 1–223.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.
4. Hurst M, Lamb HM. Meropenem: a review of its use in patients in intensive care. *Drugs* 2000; **59:** 653–80.
5. Lowe MN, Lamb HM. Meropenem: an updated review of its use in the management of intra-abdominal infections. *Drugs* 2000; **60:** 619–46.
6. Edwards SJ, *et al.* Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005; **21:** 785–94.
7. Linden P. Safety profile of meropenem: an updated review of over 6000 patients treated with meropenem. *Drug Safety* 2007; **30:** 657–68.
8. Baldwin CM, *et al.* Meropenem: a review of its use in the treatment of serious bacterial infections. *Drugs* 2008; **68:** 803–38.

Administration in children. Use of meropenem is licensed in both the UK and the USA for infants and children over 3 months of age and weighing less than 50 kg. The usual dose is 10 to 20 mg/kg every 8 hours. A dose of 40 mg/kg is given every 8 hours for meningitis; doses of 25 to 40 mg/kg every 8 hours have been used in children aged 4 to 18 years with cystic fibrosis.

In addition, the *BNFC* suggests the following doses for those under 3 months of age:

- neonates under 7 days of age: 20 mg/kg every 12 hours (or 40 mg/kg every 12 hours in severe infections and in meningitis)
- neonates 7 to 28 days of age: 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in severe infections and in meningitis)
- infants 1 to 3 months of age: 10 mg/kg every 8 hours (or 20 mg/kg every 8 hours in severe infections; 40 mg/kg every 8 hours in meningitis)

Administration in renal impairment. Doses of meropenem should be reduced in patients with renal impairment. The following doses may be given to adults based on creatinine clearance (CC):

- CC 26 to 50 mL/minute: the usual dose given every 12 hours
- CC 10 to 25 mL/minute: one-half the usual dose every 12 hours
- CC less than 10 mL/minute: one-half the usual dose every 24 hours
- haemodialysis patients: the usual dose after the dialysis session

Preparations

USP 31: Meropenem for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Meroefectil; Merotenk; Merozen; Merpem; Zeropenem†; ***Austral.:*** Merrem; ***Austria:*** Optinem; ***Belg.:*** Meronem; ***Braz.:*** Meronem; Meroxil†; ***Canad.:*** Merrem; ***Chile:*** Meronem; ***Cz.:*** Meronem; ***Denm.:*** Meronem; ***Fin.:*** Meronem; ***Ger.:*** Meronem; ***Gr.:*** Meronem; ***Hong Kong:*** Meronem; ***Hung.:*** Meronem; ***India:*** Meronem; ***Indon.:*** Merofen; Meronem; Ronem; Tripenem; ***Irl.:*** Meronem; ***Israel:*** Meronem; ***Ital.:*** Merrem; ***Jpn:*** Meropen; ***Malaysia:*** Meronem; ***Mex.:*** Merrem; ***Neth.:*** Meronem; ***Norw.:*** Meronem; ***NZ:*** Merrem; ***Philipp.:*** Meronem; ***Pol.:*** Meronem; ***Port.:*** Meronem; ***Rus.:*** Meronem (Меронем); ***S.Afr.:*** Meronem; ***Singapore:*** Meronem; ***Spain:*** Meronem; ***Swed.:*** Meronem; ***Switz.:*** Meronem; ***Thai.:*** Meronem; ***Turk.:*** Meronem; ***UK:*** Meronem; ***USA:*** Merrem; ***Venez.:*** Meronem.

Metampicillin Sodium *(rINNM)*

Metampicilina sódica; Métampicilline Sodique; Natrii Metampicillinum. Sodium (6*R*)-6-(D-2-methyleneamino-2-phenylacetamido)penicillanate.

Натрий Метампициллин

$C_{17}H_{18}N_3NaO_4S = 383.4.$
CAS — 6489-97-0 (metampicillin); 6489-61-8 (metampicillin sodium).
ATC — J01CA14.
ATC Vet — QJ01CA14.

Profile

Metampicillin has actions and uses similar to those of ampicillin (p.204).

After oral doses it is almost completely hydrolysed to ampicillin. When given parenterally, however, a proportion of the dose exists in the circulation as unchanged metampicillin which has some antibacterial activity of its own.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Arg.:* Gentocelina†.

Methacycline *(BAN, USAN)*

Metacycline *(pINN)*; GS-2876; Metaciclina; Métacycline; Metacyclinum; Metacyklin; Metasykliini. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

Метациклин

$C_{22}H_{22}N_2O_8 = 442.4.$
CAS — 914-00-1.
ATC — J01AA05.
ATC Vet — QJ01AA05.

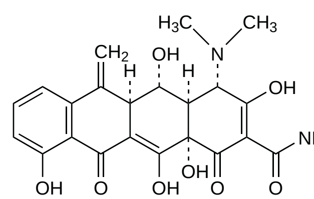

Methacycline Hydrochloride *(BANM)*

Metacycline Hydrochloride *(pINNM)*; Hidrocloruro de metaciclina; Métacycline, Chlorhydrate de; Metacyclini Chloridum; Metacyclini Hydrochloridum; Metacykliny chlorowodorek; Méthylènecycline Chlorhydrate; 6-Methyleneoxytetracycline Hydrochloride.

Метациклина Гидрохлорид

$C_{22}H_{22}N_2O_8,HCl = 478.9.$
CAS — 3963-95-9.
ATC — J01AA05.
ATC Vet — QJ01AA05.

Pharmacopoeias. In *Chin.*, *Pol.*, and *US.*

USP 31 (Methacycline Hydrochloride). A yellow to dark yellow crystalline powder. Soluble 1 in 100 of water, 1 in 300 of alcohol, and 1 in 25 of 0.1N sodium hydroxide; very slightly soluble in chloroform and in ether. pH of a solution in water containing the equivalent of methacycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Profile

Methacycline is a tetracycline derivative with uses similar to those of tetracycline (p.347). Like demeclocycline, it is excreted more slowly than tetracycline and effective blood concentrations are maintained for longer periods; the plasma elimination half-life is about 14 hours.

Methacycline hydrochloride is given orally in a usual adult dose of 600 mg daily in 2 divided doses, preferably 1 hour before or 2 hours after meals.

Preparations

USP 31: Methacycline Hydrochloride Capsules; Methacycline Hydrochloride Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Fr.: Lysocline; Physiomycine; ***Ital.:*** Esarondil; Rotilen; Stafilon.

Methaniazide *(rINN)*

Isoniazid Mesylate; Isoniazid Methanesulfonate; Metaniazida; Méthaniazide; Methaniazidum. 2-Isonicotinoylhydrazinomethanesulphonic acid.

Метаниазид

$C_7H_9N_3O_4S = 231.2.$
CAS — 13447-95-5 (methaniazide); 6059-26-3 (methaniazide calcium); 3804-89-5 (methaniazide sodium).

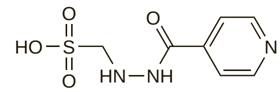

Profile

Methaniazide is a derivative of isoniazid (p.288). It has been used orally and by injection as the calcium and sodium salts respectively in the treatment of tuberculosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Neo-Tizide; ***India:*** Erbazide†.
Multi-ingredient: *India:* Strepto-Erbazide†.

Methenamine *(rINN)*

Aminoform; E239; Esametilentetrammina; Esammina; Formine; Heksamin; Hexamethylenamine; Hexamine; Metenamiini; Meténamin; Metenamin; Metenamina; Metenaminas; Metenammina; Methenamin; Méthénamine; Methenaminum; Urotropine. Hexamethylenetetramine; 1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane.

Метенамин

$C_6H_{12}N_4 = 140.2.$
CAS — 100-97-0.
ATC — J01XX05.
ATC Vet — QJ01XX05.

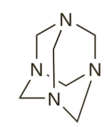

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Methenamine). A white, or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Methenamine). Colourless, practically odourless, lustrous crystals or white crystalline powder. Soluble 1 in 1.5 of water, 1 in 12.5 of alcohol, 1 in 10 of chloroform, and 1 in 320 of ether. Its solutions are alkaline to litmus.

Methenamine Hippurate *(BAN, USAN, rINNM)*

Heksamin Hippurat; Hexamine Hippurate; Hipurato de metenamina; Metenamin Hippurat; Méthénamine, Hippurate de; Methenamini Hippuras. Hexamethylenetetramine hippurate.

Метенамина Гиппурат

$C_6H_{12}N_4,C_9H_9NO_3 = 319.4.$
CAS — 5714-73-8.
ATC — J01XX05.
ATC Vet — QJ01XX05.

Pharmacopoeias. In *US.*

Methenamine Mandelate *(rINNM)*

Heksamin Mandelat; Hexamine Amygdalate; Hexamine Mandelate; Mandelato de metenamina; Metenamin Mandelat; Méthénamine, Mandelate de; Methenamini Mandelas. Hexamethylenetetramine mandelate.

Метенамина Манделат

$C_6H_{12}N_4,C_8H_8O_3 = 292.3.$
CAS — 587-23-5.
ATC — J01XX05.
ATC Vet — QJ01XX05.

Pharmacopoeias. In *US.*

USP 31 (Methenamine Mandelate). A white, practically odourless crystalline powder. Very soluble in water; soluble 1 in 10 of alcohol, 1 in 20 of chloroform, and 1 in 350 of ether. Its solutions have a pH of about 4.

Adverse Effects and Precautions

Methenamine and its salts are generally well tolerated but may cause gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. Skin rashes, pruritus, and occasionally other hypersensitivity reactions, may occur.

Comparatively large amounts of formaldehyde may be formed during prolonged use or when large doses are given. This may produce irritation and inflammation of the urinary tract, especially the bladder, as well as painful and frequent micturition, haematuria, and proteinuria. The effect of the formaldehyde may be reduced by alkalinising drugs, such as sodium bicarbonate, or large quantities of water, but it is then less effective.

Methenamine and its salts are contra-indicated in patients with hepatic impairment because of the liberation of ammonia in the gastrointestinal tract. Although methenamine itself is not contra-indicated in renal impairment, its salts should be avoided in severe impairment because of the risk of mandelate or hippurate crystalluria. They should also be avoided in patients with severe dehydration, metabolic acidosis, or gout.

Interference with laboratory estimations for catecholamines, 17-hydroxycorticosteroids, and oestrogens in the urine has been reported.

Interactions

The use of drugs that alkalinise the urine, including some antacids, potassium citrate, and diuretics such as acetazolamide or the thiazides, should be avoided because the activation of methenamine to formaldehyde may be inhibited (but see above).

Use of methenamine with sulfonamides may increase the risk of crystalluria since methenamine requires low urinary pH for its effect, at which sulfonamides and their metabolites are poorly soluble; methenamine may also form poorly soluble compounds with some sulfonamides.

Antimicrobial Action

Methenamine owes its antibacterial properties to formaldehyde, a non-specific bactericide, which is slowly liberated by hydrolysis at acid pH. Most Gram-positive and Gram-negative organisms and fungi are susceptible. Hippuric and mandelic acids have some antibacterial activity *in vitro*, but their contribution to the antibacterial action of the salts *in vivo*, beyond assisting the maintenance of low urinary pH, is uncertain. Urea-splitting organisms such as *Proteus* and some *Pseudomonas* spp. tend to increase urinary pH and inhibit the release of formaldehyde, thereby decreasing the effectiveness of methenamine. Use with acetohydroxamic acid, a potent inhibitor of bacterial urease, has been suggested for urinary infections due to these organisms. True resistance to formaldehyde does not appear to be a problem in clinical use.

Pharmacokinetics

Methenamine is readily absorbed from the gastrointestinal tract and widely distributed in the body. Under acid conditions methenamine is slowly hydrolysed to formaldehyde and ammonia: about 10 to 30% of an oral dose may be converted in the stomach unless it is given as an enteric-coated preparation. Almost no hydrolysis of methenamine takes place at physiological pH, and it is therefore virtually inactive in the body. The half-life is reported to be about 4 hours. Methenamine is rapidly and almost completely eliminated in the urine, and provided this is acidic (preferably below pH 5.5) bactericidal concentrations of formaldehyde are achieved. Because of the time taken for hydrolysis, however, these are not achieved until the urine reaches the bladder, with peak concentrations occurring up to 2 hours after an oral dose. Absorption, and hence excretion, may be somewhat delayed in patients given enteric-coated formulations.

Methenamine crosses the placenta and small amounts may be distributed into breast milk.

The mandelate and hippurate moieties are also rapidly absorbed and are excreted in urine by tubular secretion as well as glomerular filtration.

Uses and Administration

Methenamine is used, usually as the hippurate or mandelate, in the prophylaxis and treatment of chronic or recurrent, uncomplicated, lower urinary-tract infections and asymptomatic bacteriuria. It has been considered suitable for long-term use because acquired resistance does not appear to develop.

Methenamine and its salts should not be used in upper urinary-tract infections because it is eliminated too rapidly to exert an effect, nor in acute urinary infections. It is only active in acidic urine, when formaldehyde is released, and although hippuric or mandelic acid helps to acidify the urine, ammonium chloride or ascorbic acid may be tried. If urea-splitting bacteria such as *Proteus* or some *Pseudomonas* spp. are present they may produce so much ammonia that the urine cannot be acidified (see also Antimicrobial Action, above).

The usual oral adult dose of methenamine or methenamine mandelate is 1 g given four times daily. Methenamine hippurate is given orally in a usual dose of 1 g twice daily; the dose may be increased to three times daily in catheterised patients.

For details of doses in children, see below.

Methenamine has been used topically in deodorant preparations, since in the presence of acid sweat it liberates formaldehyde. Methenamine calcium thiocyanate has been used in combination preparations for upper respiratory-tract disorders.

◊ Reviews.

1. Schiøtz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand* 2002; **81:** 743–6.
2. Lee BB, *et al.* Methenamine hippurate for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 11/01/08).

Administration in children. In the USA, the usual recommended oral dose of methenamine mandelate in children up to 6 years old is about 18 mg/kg given four times daily; those aged 6 to 12 years may be given methenamine or methenamine mandelate 500 mg four times daily.

In the UK, methenamine hippurate may be given in a usual oral dose of 500 mg twice daily in children aged 6 to 12 years. Doses of up to 1 g twice daily have been given in the USA.

Preparations

USP 31: Methenamine Elixir; Methenamine Hippurate Tablets; Methenamine Mandelate Delayed-release Tablets; Methenamine Mandelate for Oral Solution; Methenamine Mandelate Oral Suspension; Methenamine Mandelate Tablets; Methenamine Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Hiprex; ***Austria:*** Hiprex; ***Belg.:*** Hiprex†; ***Canad.:*** Dehydral; Hiprex; Mandelamine; Urasal†; ***Denm.:*** Geasalol†; Haiprex; ***Fin.:*** Hipeksal; Hiprex; ***Ger.:*** Antihydral; Urotractan; ***Irl.:*** Hiprex†; ***Israel:*** Hiprex; ***Mex.:*** Bioran; ***Neth.:*** Reflux; ***Norw.:*** Hiprex; ***NZ:*** Hiprex; ***Philipp.:*** Hiprex; ***Pol.:*** Stoppot; ***S.Afr.:*** Hippramine†; Mandelamine†; ***Swed.:*** Hiprex; ***Switz.:*** Antihydral; ***Turk.:*** Helpa; Hippurin; Manuprin; Neturone; Purinol; Uron; ***UK:*** Hiprex; ***USA:*** Hiprex; Mandelamine; Urex; ***Venez.:*** Mandelamine.

Multi-ingredient: ***Arg.:*** Calculina†; ***Belg.:*** Carbobel; Mictasol-P; Mictasol†; ***Braz.:*** Abacateirol†; Acridin; Cystex; Sepurin; Urodonal†; ***Chile:*** Uroknop; ***Fr.:*** Mictasol; Pedi-Relax Anti-Transpirant; ***Ger.:*** Antihydral M†; ***Hong Kong:*** Antihydral M†; ***Hung.:*** Bilagit†; ***Mex.:*** Furanton†; ***Pol.:*** Dezorol; Pedipur; Urosal; ***Turk.:*** Helmobleu; ***USA:*** Atrosept; Cystex; Dolsed†; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X†; UAA; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira; ***Venez.:*** Azo-Mandelamine.

Meticillin Sodium *(rINNM)*

BRL-1241; Dimethoxyphenecillin Sodium; Dimethoxyphenyl Penicillin Sodium; Methicillin Sodium *(BANM, USAN)*; Meticilina sódica; Méticilline Sodique; Meticillinum Natricum; Natrii Meticillinum; SQ-16123; X-1497. Sodium (6*R*)-6-(2,6-dimethoxybenzamido)penicillanate monohydrate.

Натрий Метициллин

$C_{17}H_{19}N_2NaO_6S,H_2O = 420.4.$

CAS — 61-32-5 (meticillin); 132-92-3 (anhydrous meticillin sodium); 7246-14-2 (meticillin sodium monohydrate).

ATC — J01CF03.

ATC Vet — QJ01CF03.

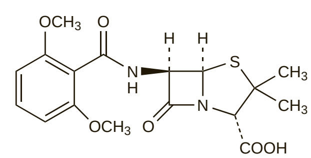

(meticillin)

Incompatibility. Meticillin sodium has been reported to be incompatible with aminoglycosides and a number of other antimicrobials. It has also been reported to be incompatible with acidic and alkaline drugs.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Meticillin is the penicillin most commonly associated with acute interstitial nephritis.

Effects on the kidneys. References.

1. Sanjad SA, *et al.* Nephropathy, an underestimated complication of methicillin therapy. *J Pediatr* 1974; **84:** 873–7.
2. Galpin JE, *et al.* Acute interstitial nephritis due to methicillin. *Am J Med* 1978; **65:** 756–65.

Sodium content. Each g of meticillin sodium contains about 2.4 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Meticillin has a mode of action similar to that of benzylpenicillin (p.214) but it is resistant to staphylococcal penicillinase. There is evidence that meticillin is more stable to staphylococcal penicillinase than the other penicillinase-resistant penicillins.

Meticillin is active against both penicillinase-producing and non-penicillinase-producing staphylococci, and also against *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Str. pneumoniae*, and some viridans streptococci. Its activity against penicillin-sensitive staphylococci and streptococci is less than that of benzylpenicillin. It is virtually ineffective against *Enterococcus faecalis*.

Resistance of staphylococci to meticillin is due to the expression of an altered penicillin-binding protein and is not dependent on penicillinase production. There is cross-resistance with other penicillins, including the penicillinase-resistant penicillins cloxacillin, dicloxacillin, flucloxacillin, nafcillin, and oxacillin, and with the cephalosporins. Meticillin-resistant staphylococci are also frequently resistant to other antibacterials, including aminoglycosides, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, and tetracycline. The incidence of such resistance has varied considerably. However, both endemic (restricted to one hospital) and epidemic (affecting more than one hospital) strains of meticillin-resistant *Staphylococcus aureus* (MRSA) are now recognised and infections are a problem in many hospitals.

There have been fewer studies on coagulase-negative staphylococci, but patterns of meticillin resistance in *Staph. epidermidis* are similar to those for MRSA and the frequency of resistance may be higher.

For further details on meticillin-resistant staphylococci and the management of infections, see under Staphylococcal Infections, p.195.

Resistance. References to meticillin-resistant staphylococci.

1. Hackbarth CJ, Chambers HF. Methicillin-resistant staphylococci: genetics and mechanisms of resistance. *Antimicrob Agents Chemother* 1989; **33:** 991–4.
2. Maple PAC, *et al.* World-wide antibiotic resistance in methicillin-resistant Staphylococcus aureus. *Lancet* 1989; **i:** 537–40.
3. Mouton RP, *et al.* Correlations between consumption of antibiotics and methicillin resistance in coagulase negative staphylococci. *J Antimicrob Chemother* 1990; **26:** 573–83.
4. Marples RR, Reith S. Methicillin-resistant Staphylococcus aureus in England and Wales. *Commun Dis Rep* 1992; **2:** R25–R29.
5. de Lencastre H, *et al.* Molecular aspects of methicillin resistance in Staphylococcus aureus. *J Antimicrob Chemother* 1994; **33:** 7–24.
6. Fluckiger U, Widmer AF. Epidemiology of methicillin-resistant Staphylococcus aureus. *Chemotherapy* 1999; **45:** 121–34.
7. Livermore DM. Antibiotic resistance in staphylococci. *Int J Antimicrob Agents* 2000; **16** (suppl 1): S3–S10.
8. Turnidge JD, Bell JM. Methicillin-resistant Staphylococcal aureus evolution in Australia over 35 years. *Microb Drug Resist* 2000; **6:** 223–9.

Pharmacokinetics

Meticillin is inactivated by gastric acid and must be given by injection. Peak plasma concentrations are attained within 0.5 to 1 hour of an intramuscular injection; concentrations of up to 18 micrograms/mL have been achieved after a dose of 1 g. A half-life of 0.5 to 1 hour has been reported, although this may be increased to 3 to 6 hours in renal impairment. About 40% of the meticillin in the circulation is bound to plasma proteins. It is widely distributed in body fluids and in tissues, but there is little diffusion into the CSF unless the meninges are inflamed. Meticillin also crosses the placenta and appears in breast milk. Relatively high concentrations are achieved in bile compared with plasma, although only small amounts are excreted in bile. The majority is rapidly excreted by tubular secretion and glomerular filtration; up to 80% of an injected dose has been detected unchanged in the urine.

Plasma concentrations are enhanced by probenecid. They may be reduced in patients with cystic fibrosis.

Uses and Administration

Meticillin is a penicillinase-resistant penicillin and has been used similarly to flucloxacillin (p.277) in the treatment of staphylococcal infections resistant to benzylpenicillin. It is not active orally and has been given by injection as the sodium salt.

Mezlocillin *(BAN, USAN, rINN)*

Metslosilliini; Mezlocilina; Mezlocilline; Mezlocillinum. 6-[*N*-(3-Methylsulfonyl-2-oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

Мезлоциллин

$C_{21}H_{25}N_5O_8S_2 = 539.6.$

CAS — 51481-65-3.

ATC — J01CA10.

ATC Vet — QJ01CA10.

Mezlocillin Sodium *(BANM, rINNM)*

Bay-f-1353; Mezlocilina sódica; Mezlocilline Sodique; Natrii Mezlocillinum. Sodium (6*R*)-6-[D-2-(3-mesyl-2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate monohydrate.

Натрий Мезлоциллин

$C_{21}H_{24}N_5NaO_8S_2,H_2O = 579.6.$

CAS — 42057-22-7 (anhydrous mezlocillin sodium); 80495-46-1 (mezlocillin sodium monohydrate).

ATC — J01CA10.

ATC Vet — QJ01CA10.

Pharmacopoeias. In *US.*

USP 31 (Mezlocillin Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 4.5 and 8.0. Store in airtight containers.

Incompatibility. Mezlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Prolongation of bleeding time has been less frequent and less severe with mezlocillin than with carbenicillin.

Sodium content. Each g of mezlocillin sodium contains about 1.7 mmol of sodium. As mezlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p.214.

Cefotaxime. For the effect of mezlocillin on the clearance of cefotaxime, see p.228.

Antimicrobial Action

Mezlocillin has a similar antimicrobial action to piperacillin (p.315). Its activity against *Pseudomonas aeruginosa* is less than that of azlocillin or piperacillin.

Pharmacokinetics

Mezlocillin is not absorbed from the gastrointestinal tract to any significant extent. It is well absorbed after intramuscular injection, with peak plasma concentrations of 15 to 25 micrograms/mL 45 to 90 minutes after a single dose of 1 g. It is reported to have nonlinear dose-dependent pharmacokinetics. Between 16 and 42% of mezlocillin in the circulation is bound to plasma proteins. Mezlocillin is reported to have a plasma half-life of about 1 hour; this is slightly prolonged in neonates, and in patients with renal impairment half-lives of up to about 6 hours have been reported.

Mezlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into CSF except when the meninges are inflamed.

Mezlocillin is reported to be metabolised to a limited extent. About 55% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 6 hours of a dose, hence achieving high urinary concentrations. High concentrations are also found in the bile; up to 30% of a dose has been reported to be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Mezlocillin is removed by haemodialysis, and to some extent by peritoneal dialysis.

Uses and Administration

Mezlocillin is a ureidopenicillin with uses similar to those of piperacillin (p.316). It is commonly used with an aminoglycoside; however they should be given separately as they have been shown to be incompatible.

Administration and dosage. Mezlocillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of mezlocillin; 1.07 g of mezlocillin sodium is equivalent to about 1 g of mezlocillin. Dosage may need to be reduced in renal impairment. It may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 30 minutes, or by deep intramuscular injection. Single intramuscular doses should not exceed 2 g.

For the treatment of serious infections, 200 to 300 mg/kg daily in divided doses may be given intravenously. For life-threatening infections, up to 350 mg/kg daily may be used, but the total daily dose should not normally exceed 24 g. For uncomplicated urinary-tract infections, a dose of 1.5 to 2 g may be given intramuscularly or intravenously every 6 hours.

Uncomplicated gonorrhoea may be treated by a single intramuscular or intravenous dose of mezlocillin 1 to 2 g. Probenecid 1 g orally may be given at the same time or up to 30 minutes before the injection.

For the prophylaxis of infection during surgery, an intravenous pre-operative dose of mezlocillin 4 g, repeated at 6-hourly intervals for 2 further doses, may be given.

Preparations

USP 31: Mezlocillin for Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Baypen; ***Fr.:*** Baypen; ***Ger.:*** Baypen; ***Israel:*** Baypen†; ***Ital.:*** Baypen.
Multi-ingredient: *Ger.:* Optocillin†.

Micronomicin Sulfate *(pINNM)*

Gentamicin C_{2B} Sulphate; KW-1062 (micronomicin); 6′*N*-Methylgentamicin C_{1A} Sulphate; Micronomicin Sulphate; Micronomicine, Sulfate de; Micronomicini Sulfas; Sagamicin Sulphate; Sulfato de micronomicina. *O*-2-Amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-*erythro*-hexopyranosyl-(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)]-2-deoxy-D-streptamine hemipentasulphate.

Микрономицина Сульфат

$(C_{20}H_{41}N_5O_7)_2,5H_2SO_4$ = 1417.5.
CAS — 52093-21-7 (micronomicin).
ATC — S01AA22.
ATC Vet — QS01AA22.

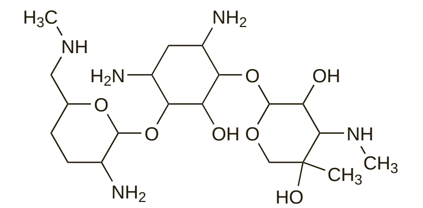

(micronomicin)

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Micronomicin is an aminoglycoside with general properties similar to those of gentamicin (p.282). It is given as the sulfate and doses are expressed in terms of micronomicin; 183 mg of micronomicin sulfate is equivalent to about 120 mg of micronomicin. It is given by intramuscular injection or by intravenous infusion over 30 minutes to 1 hour in doses of 120 to 240 mg daily in 2 or 3 divided doses. Dosage should be adjusted based on serum-micronomicin concentration monitoring. It is also used topically as eye drops or ointment in a concentration of 0.3% for infections of the eye.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Luxomicina; ***Jpn:*** Sagamicin; ***Singapore:*** Sagamicin†.

Midecamycin *(rINN)*

Midecamicina; Midecamycin A_1; Midécamycine; Midecamycinum; Mydecamycin. 7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′,4″-dipropionate.

Мидекамицин

$C_{41}H_{67}NO_{15}$ = 814.0.
CAS — 35457-80-8.
ATC — J01FA03.
ATC Vet — QJ01FA03.

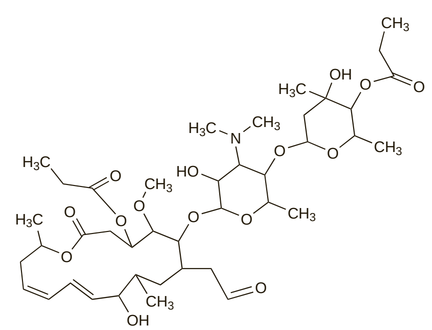

Pharmacopoeias. In *Jpn*.

Midecamycin Acetate *(rINNM)*

Acecamycin; Acetato de midecamicina; Midecamycin Diacetate; Midécamycine, Acétate de; Midecamycini Acetas; Miocamycin; Miokamycin; MOM; Ponsinomycin; 1532-RB. 9,3″-Diacetylmidecamycin; Leucomycin V 3^B, 9-diacetate $3,4^B$-dipropanoate.

Мидекамицина Ацетат

$C_{45}H_{71}NO_{17}$ = 898.0.
CAS — 55881-07-7.
ATC — J01FA11.
ATC Vet — QJ01FA11.

Pharmacopoeias. In *Jpn*.

Profile

Midecamycin is a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens* with actions and uses similar to those of erythromycin (p.269) but it is somewhat less active. It is given orally for the treatment of susceptible infections as the acetate in usual doses of 0.9 to 1.8 g daily in 2 or 3 divided doses. It has also been given as the base.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Myoxam†; ***Belg.:*** Merced; ***Fr.:*** Mosil; ***Gr.:*** Miocacin; Miocamen; ***Hong Kong:*** Medemycin; ***Ital.:*** Macroral; Midecin; Miocamen; Miokacin; ***Jpn:*** Medemycin; Miocamycin; ***Mex.:*** Midecamin†; ***Port.:*** Miocacin; ***Rus.:*** Macropen (Макропен); ***Spain:*** Momicine; Myoxam; Normicina†; ***Thai.:*** Miotin.

Minocycline *(BAN, USAN, rINN)*

Minociclina; Minocyclinum; Minocyklin; Minosiklin; Minosykliini. (4*S*,4a*S*,5a*R*,12a*S*)4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-7-dimethylaminotetracycline.

Миноциклин

$C_{23}H_{27}N_3O_7$ = 457.5.
CAS — 10118-90-8;.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.

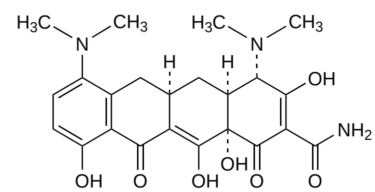

Minocycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de minociclina; Minociklin-hidroklorid; Minociklino hidrochloridas; Minocycline, chlorhydrate de; Minocyclini hydrochloridum; Minocyklin-hydrochlorid; Minocyklinhydroklorid; Minocykliny chlorowodorek; Minosykliinihydrokloridi.

Миноциклина Гидрохлорид

$C_{23}H_{27}N_3O_7,HCl$ = 493.9.
CAS — 13614-98-7.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Minocycline Hydrochloride Dihydrate). A yellow, hygroscopic, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Minocycline Hydrochloride). A yellow crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of minocycline 1% is between 3.5 and 4.5. Store in airtight containers. Protect from light.

Incompatibility. Preparations of minocycline hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Gastrointestinal disturbances with minocycline are reported to be less frequent than with the less well absorbed tetracyclines.

Oesophageal ulceration has occurred and may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: minocycline should be taken with at least half a glass of water, in an upright position, and well before going to bed.

Vestibular adverse effects including dizziness or vertigo may occur with minocycline, particularly in women. Patients should be advised not to drive or operate machinery if affected. Tinnitus and decreased hearing have been reported rarely.

There have also been reports, some fatal, of a hypersensitivity syndrome (comprising eosinophilia, fever, rash, and varying additional symptoms), a lupus-like syndrome, and a serum-sickness-like syndrome (both comprising arthralgia, fever, and joint stiffness or swelling, amongst other symptoms).

Minocycline may also cause hyperpigmentation of the skin (see below).

Although minocycline, unlike many tetracyclines, does not appear to accumulate in patients with renal impairment, usual doses can lead to higher serum concentrations resulting in possible liver toxicity; reduced doses and monitoring of renal function may be necessary, particularly in those with severe impairment.

The *BNF* recommends that if treatment continues for longer than 6 months patients should be monitored every 3 months for hepatotoxicity, pigmentation, and SLE.

Incidence of adverse effects. Severe complications have been reported in patients given minocycline for acne, including serum-sickness-like disease,[1,2] lupus erythematosus,[3] and hepatitis.[3,4] The number of cases reported probably reflects the widespread use of this drug and the true incidence of such adverse effects is difficult to assess.[5] A study of 700 patients receiving minocycline for acne revealed adverse effects in 13.6%, mostly benign.[6] Gastrointestinal disturbances and vestibular disturbances were the most common, each occurring in about 2% of patients, and pigmentation in up to 4% of patients.

Another problem is that of assessing the efficacy of minocycline and the incidence of severe adverse effects relative to other antibacterials commonly used in acne such as tetracycline and erythromycin. A systematic review[7] suggested that the incidence of adverse effects might be greater with minocycline than with doxycycline. A retrospective analysis[8] of a UK population database found that minocycline was associated with an increased risk for drug-induced lupus erythematosus; no increased risk was reported for the other tetracyclines. Other systematic reviews[9,10] concluded that minocycline should not be used as a first-line oral tetracycline in patients with acne since there is no compelling evidence that it is more effective than some other tetracyclines or commonly used treatments; the risk of rare but serious adverse effects also makes it less suitable.[10]

1. Knowles SR, *et al.* Serious adverse reactions induced by minocycline: report of 13 patients and review of the literature. *Arch Dermatol* 1996; **132:** 934–9.
2. Harel L, *et al.* Serum-sickness-like reaction associated with minocycline therapy in adolescents. *Ann Pharmacother* 1996; **30:** 481–3.
3. Gough A, *et al.* Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; **312:** 169–72.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and the liver, the CNS, the skin. *Aust Adverse Drug React Bull* 1996; **15:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 11/08/08)
5. Seukeran DC, *et al.* Benefit-risk assessment of acne therapies. *Lancet* 1997; **349:** 1251–2.
6. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134:** 693–5.
7. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther* 2005; **27:** 1329–42.
8. Margolis DJ, *et al.* Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. *Br J Dermatol* 2007; **157:** 540–6.
9. Garner SE, *et al.* Minocycline for acne vulgaris: efficacy and safety. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/05/05).
10. McManus P, Iheanacho I. Don't use minocycline as first line oral antibiotic in acne. *BMJ* 2007; **334:** 154.

Effects on intracranial pressure. Minocycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p.348.

Effects on the liver. A systematic review[1] considered 65 published case reports of hepatitis or liver damage associated with the use of minocycline for acne, including 4 fatalities, and also data held by WHO concerning 493 reactions involving the liver in 393 patients in whom the indication for the use of minocycline was largely unspecified.

Of the 65 published cases, 38 occurred in females and 61 in patients under 40 years of age. These cases appeared to be of the following types:

- 16 cases appeared to be attributable to a hypersensitivity reaction, with a rapid onset usually within 1 month of starting treatment and sometimes associated with eosinophilia and exfoliative dermatitis
- 29 cases of hepatitis (of which 20 were in females) appeared to be of an auto-immune nature, occurring after 1 year or more of therapy and sometimes associated with lupus-like symptoms
- 20 cases could not be definitively classified into either group

The 393 patients described by the WHO data had 22 different types of hepatic reaction which could be broadly grouped into 4 categories:

- hepatic dysfunction (32% of patients)
- hepatitis (26%)
- abnormal liver function tests (24%)
- hyperbilirubinaemia or jaundice (14%)

There were, in addition, several other reactions, including hepatic damage or necrosis in 11 patients and fatty liver in 7. Gender distribution was almost even. Of the 393 patients, 14 also experienced lupus-like symptoms. The outcome of the hepatic reactions was reported in less than half of the patients, although it was apparent that there had been at least 3 fatalities.

Despite these findings, the reviewers concluded[1] that there was no clear information regarding the absolute or relative risks of hepatitis in patients given minocycline, and that it was inappropriate to comment as to whether monitoring would be worthwhile. A study of the comparative rates of hepatitis in people exposed to minocycline compared with those who were not was required.

1. Lawrenson RA, *et al.* Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Safety* 2000; **23:** 333–49.

Effects on the lungs. Hypersensitivity pneumonitis, characterised by pulmonary infiltrates and eosinophilia, has been reported[1-6] with minocycline. In most cases, the pneumonitis resolved after stopping minocycline but some required corticosteroid therapy; however, residual lung damage can occur. In one case[6] relapsing acute respiratory failure that required mechanical ventilation was reported.

1. Guillon J-M, *et al.* Minocycline-induced cell-mediated hypersensitivity pneumonitis. *Ann Intern Med* 1992; **117:** 476–81.
2. Bridges AJ. Minocycline-induced pneumonia. *Ann Intern Med* 1993; **118:** 749–50.
3. Sigmann P. Minocycline-induced pneumonia. *Ann Intern Med* 1993; **118:** 750.
4. Sitbon O, *et al.* Minocycline pneumonitis and eosinophilia: a report on 8 patients. *Arch Intern Med* 1994; **154:** 1633–40.
5. Dykhuizen RS, *et al.* Minocycline and pulmonary eosinophilia. *BMJ* 1995; **310:** 1520–1.
6. Oddo M, *et al.* Relapsing acute respiratory failure induced by minocycline. *Chest* 2003; **123:** 2146–8.

Hyperpigmentation. Minocycline has been associated with pigmentation of the skin and other tissues.[1-3] Three patterns of skin pigmentation have been described:[1] blue-black macules occurring in areas of inflammation and scarring and possibly due to an iron chelate of minocycline within macrophages; blue-grey macules or hyperpigmentation affecting normal skin and which may be due to a breakdown product of minocycline; or a greyish-brown discoloration occurring particularly in sun-exposed areas of skin ('muddy skin syndrome'), apparently due to melanin deposition. In general, pigmentation results from long-term use of minocycline at cumulative doses greater than 100 g; however, skin or oral mucosal pigmentation may occur regardless of dose or duration of therapy.[2] Indeed, there have been reports[3] of skin pigmentation developing after short-term use ranging from 3 to 28 days. Pigmentation of the skin and oral mucosa usually appears to resolve slowly on stopping the drug although recovery may be incomplete; pigmentation is often permanent when other sites are involved.[2]

1. Basler RSW. Minocycline-related hyperpigmentation. *Arch Dermatol* 1985; **121:** 606–8.
2. Eisen D, Hakim MD. Minocycline-induced pigmentation: incidence, prevention and management. *Drug Safety* 1998; **18:** 431–40.
3. Nakamura S, *et al.* Acute pigmentation due to minocycline therapy in atopic dermatitis. *Br J Dermatol* 2003; **148:** 1073–4.

Interactions

As for Tetracycline, p.348.

Minocycline has a lower affinity for binding with calcium than tetracycline. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc.

Antimicrobial Action

Minocycline has a spectrum of activity and mode of action similar to that of tetracycline (p.348) but it is more active against many species including *Staphylococcus aureus*, streptococci, *Neisseria meningitidis*, various enterobacteria, *Acinetobacter*, *Bacteroides*, *Haemophilus*, *Nocardia*, and some mycobacteria, including *M. leprae*.

Partial cross-resistance exists between minocycline and other tetracyclines but some strains resistant to other drugs of the group remain sensitive to minocycline, perhaps because of better cell-wall penetration.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p.349.

Minocycline is readily absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of food or moderate amounts of milk. Oral doses of 200 mg followed by 100 mg every 12 hours are reported to produce plasma concentrations of about 2 to 4 micrograms/mL. It is more lipid-soluble than doxycycline and the other tetracyclines and is widely distributed in body tissues and fluids with high concentrations being achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva, and sputum. Penetration into the CSF is relatively poor, although a higher ratio of CSF to blood concentrations has been reported with minocycline than with doxycycline. It crosses the placenta and is distributed into breast milk. About 75% of minocycline in the circulation is bound to plasma proteins. It has a low renal clearance: only about 5 to 10% of a dose is excreted in the urine and up to about 34% is excreted in the faeces. However, in contrast to most tetracyclines it appears to undergo some metabolism in the liver, mainly to 9-hydroxyminocycline. Sources differ as to whether the normal plasma half-life of 11 to 26 hours is prolonged in patients with renal impairment, with a consequent risk of accumulation; hepatic impairment does not appear to lead to accumulation. Little minocycline is removed by haemodialysis and peritoneal dialysis.

◊ Reviews.

1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15:** 355–66.

Uses and Administration

Minocycline is a tetracycline derivative with uses similar to those of tetracycline (p.349). It is also a component of multidrug regimens for the treatment of leprosy (p.176) and has been used in the prophylaxis of meningococcal infection to eliminate the carrier state, but the high incidence of vestibular disturbances means that it is not the drug of choice for the latter.

Minocycline is usually given orally as the hydrochloride; doses are expressed in terms of the base. Minocycline hydrochloride 108 mg is equivalent to about 100 mg of minocycline. Minocycline capsules and tablets should be taken with plenty of fluid, with the patient in an upright position, and well before going to bed.

In patients in whom oral therapy is not feasible, minocycline hydrochloride has been given by slow intravenous infusion in doses equivalent to those given orally. In some countries it has also been given by intramuscular injection.

The usual adult oral dose is 200 mg daily in divided doses, usually every 12 hours; an initial loading dose of 200 mg may be given.

An oral dose of 50 mg twice daily or 100 mg once daily is used for the treatment of acne; alternatively, a dose of about 1 mg/kg once daily is also given as a modified-release preparation to patients weighing 45 kg and over. In asymptomatic meningococcal carriers, 100 mg has been given orally twice daily for 5 days, usually followed by a course of rifampicin.

For multibacillary leprosy an oral dose of minocycline 100 mg daily with clofazimine and ofloxacin *or* 100 mg monthly with rifampicin and ofloxacin have been recommended by WHO as alternative multidrug therapy regimens. As an alternative regimen for patients with single-lesion paucibacillary leprosy WHO suggests a single dose of minocycline 100 mg with rifampicin and ofloxacin.

For details of doses in children and adolescents, see below.

For dosage recommendations in patients with renal impairment, see below.

In adults with periodontitis, a modified-release subgingival gel containing minocycline hydrochloride has been inserted into the periodontal pocket as an adjunct to scaling and root planing; each cartridge contains the equivalent of 1 mg of minocycline and the total used depends on the size, shape, and number of pockets being treated. Minocycline has also been applied as a 2% gel for periodontal infections.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, minocycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Administration in renal impairment. US licensed product information states that pharmacokinetics in patients with renal impairment have not been fully characterised and therefore recommends that no more than 200 mg in any 24-hour period should be given to these patients.

Motor neurone disease. Minocycline is being investigated as a potential treatment for amyotrophic lateral sclerosis, a form of motor neurone disease (p.2380), on the basis of its neuroprotective properties.

Movement disorders. Minocycline is under investigation[1,2] for the management of Huntington's chorea (p.953).

1. Huntington Study Group. Minocycline safety and tolerability in Huntington disease. *Neurology* 2004; **63:** 547–9.
2. Bonelli RM, *et al.* Neuroprotection in Huntington's disease: a 2-year study on minocycline. *Int Clin Psychopharmacol* 2004; **19:** 337–42.

Musculoskeletal and joint disorders. For reference to the use of minocycline in the treatment of rheumatoid arthritis, see under Tetracycline, p.350.

Skin disorders. For reference to the use of minocycline in the treatment of various skin disorders, see under Tetracycline, p.350.

Preparations

BP 2008: Minocycline Tablets; Prolonged-release Minocycline Capsules; ***USP 31:*** Minocycline for Injection; Minocycline Hydrochloride Capsules; Minocycline Hydrochloride Oral Suspension; Minocycline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acneclin; Asolmicina†; Clinax; Meibi; Minocin; Pimple; Seboclear; ***Austral.:*** Akamin; Minomycin; ***Austria:*** Auramin; Klinoc†; Minocin†; Minostad; Minotyrol†; Udima; ***Belg.:*** Klinotab; Mino-50; Minocin; Minotab; ***Braz.:*** Minoderm; Minomax†; ***Canad.:*** Enca; Minocin; ***Chile:*** Bagomicina; Minocin†; Pracne; ***Cz.:*** Skid†; ***Fr.:*** Mestacine; Minolis; Mynocine; Parocline; Yelnac†; Zacnan; ***Ger.:*** Akne-Puren†; Aknefug Mino; Aknin-Mino†; Aknosan; Klinomycin; Lederderm†; Minakne; Mino-Wolff†; Minoclir; Minoplus; Skid; Skinocyclin; Udima; ***Gr.:*** Cycline; Minocin; ***Hong Kong:*** Minaxen; Minocin; ***India:*** CNN†; Cynomycin; ***Indon.:*** Minocin; ***Irl.:*** Minocin; Minox; ***Israel:*** Minocin†; Minoclin; ***Ital.:*** Minocin; ***Jpn:*** Periocline; ***Malaysia:*** Borymycin; Minocin†; Minoclin; ***Mex.:*** Banimed; Micromycin; Minocin; Ranmino; ***Neth.:*** Aknemin; Minocin; Minotab; Peritrol; ***NZ:*** Minomycin; Minotabs; ***Philipp.:*** Minocin; ***Port.:*** Arestin; Cipancin; Minocin; Minotrex; ***S.Afr.:*** Cyclimycin; Minotabs; Triomin; ***Singapore:*** Borymycin; Minocin†; ***Spain:*** Minocin; ***Switz.:*** Aknin-N; Aknoral; Minac 50; Minocin; ***Thai.:*** Minocin†; ***UK:*** Aknemin; Blemix†; Dentomycin; Minocin; Sebomin; Sebren; ***USA:*** Arestin; Cleeravue-M; Dynacin; Minocin; Myrac; Solodyn; ***Venez.:*** Minocin†.

Morinamide *(pINN)*

Morinamida; Morinamidum; Morphazinamide. *N*-Morpholinomethylpyrazine-2-carboxamide.

Моринамид

$C_{10}H_{14}N_4O_2$ = 222.2.

CAS — 952-54-5.

ATC — J04AK04.

ATC Vet — QJ04AK04.

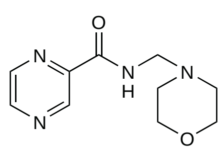

Profile

Morinamide is an antimycobacterial that has been given orally as the hydrochloride in the treatment of tuberculosis.

Preparations

Proprietary Preparations (details are given in Part 3)

Turk.: Morfozid.

Moxifloxacin Hydrochloride *(BANM, USAN, rINNM)*

Bay-12-8039; Hidrocloruro de moxifloxacino; Moxifloxacine, chlorhydrate de; Moxifloxacini hydrochloridum. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid hydrochloride.

Моксифлоксацина Гидрохлорид

$C_{21}H_{24}FN_3O_4$,HCl = 437.9.

CAS — 151096-09-2 (moxifloxacin); 186826-86-8 (moxifloxacin hydrochloride).

ATC — J01MA14; S01AX22.

ATC Vet — QJ01MA14; QS01AX22.

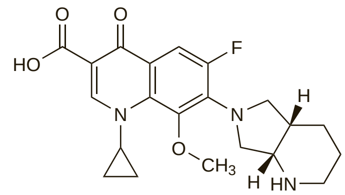

(moxifloxacin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Moxifloxacin Hydrochloride). Produced using a method validated to demonstrate the satisfactory enantiomeric purity of the final product. A light yellow or yellow powder or crystals, slightly hygroscopic. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 0.2% solution in water has a pH of 3.9 to 4.6. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

◊ References.

1. Faich GA, *et al.* Clinical experience with moxifloxacin in patients with respiratory tract infections. *Ann Pharmacother* 2004; **38:** 749–54.
2. Ball P, *et al.* Safety profile of oral and intravenous moxifloxacin: cumulative data from clinical trials and postmarketing studies. *Clin Ther* 2004; **26:** 940–50.
3. Andriole VT, *et al.* Retrospective analysis of the safety profile of oral moxifloxacin in elderly patients enrolled in clinical trials. *Drug Safety* 2005; **28:** 443–52.

Interactions

As for Ciprofloxacin, p.246.

Moxifloxacin does not appear to interact significantly with theophylline or probenecid.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Moxifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

◊ References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; **47:** 1308–12.
2. Pletz MWR, *et al.* Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004; **48:** 780–2.

Pharmacokinetics

Moxifloxacin is readily absorbed from the gastrointestinal tract after oral doses with an absolute bioavailability of about 90%. It is widely distributed throughout the body tissues and is about 30 to 50% bound to plasma proteins. Moxifloxacin has an elimination half-life of about 12 hours, allowing once-daily dosing. It is metabolised mainly via sulfate and glucuronide conjugation, and is excreted in the urine and the faeces as unchanged drug and as metabolites, the sulfate conjugate primarily in the faeces and the glucuronide exclusively in the urine. Distribution into milk has been found in *animals*.

Uses and Administration

Moxifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally, or by intravenous infusion over 60 minutes, for the treatment of susceptible infections including respiratory, skin and skin structure, and intra-abdominal infections. Moxifloxacin is given as the hydrochloride but doses are expressed in terms of the base; moxifloxacin hydrochloride 436.3 mg is equivalent to about 400 mg of moxifloxacin. The usual dose is 400 mg once daily.

Moxifloxacin is also used topically as the hydrochloride in eye drops containing the equivalent of 0.5% of moxifloxacin for the treatment of bacterial conjunctivitis.

◊ Reviews.

1. Keating GM, Scott LJ. Moxifloxacin: a review of its use in the management of bacterial infections. *Drugs* 2004; **64:** 2347–77.
2. Miravitlles M, *et al.* Eficacia clínica del moxifloxacino en el tratamiento de las agudizaciones de la bronquitis crónica: revisión sistemática y metaanálisis. *Arch Bronconeumol* 2007; **43:** 22–8.
3. Miravitlles M. Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD. *Int J Chron Obstruct Pulmon Dis* 2007; **2:** 191–204.
4. O'Brien TP. Evidence-based review of moxifloxacin. *Int Ophthalmol Clin* 2006; **46:** 61–72.

Eye infections. In order to attain therapeutic concentrations most antibacterials used in the treatment of bacterial endophthalmitis need to be given by the intravitreal route but moxifloxacin given systemically may produce adequate concentrations. An oral dose of moxifloxacin 400 mg daily may be given for 10 days.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Avelox; Octegra†; Vigamox; ***Austral.:*** Avelox; ***Austria:*** Actira; Avelox; Octegra; ***Belg.:*** Avelox; Proflox; ***Braz.:*** Avalox; Vigamox; ***Canad.:*** Avelox; Vigamox; ***Chile:*** Avelox; Flovacil; Octegra†; Vigamox; ***Cz.:*** Avelox; ***Denm.:*** Avelox; ***Fin.:*** Avelox; ***Fr.:*** Izilox; ***Ger.:*** Avalox; ***Gr.:*** Avelox; Octegra; Proflox; ***Hong Kong:*** Avelox; Vigamox; ***Hung.:*** Avelox; Octegra; ***India:*** Moxicip; Moxif; ***Indon.:*** Avelox; ***Irl.:*** Avelox; ***Israel:*** Megaxin; Vigamox; ***Ital.:*** Actira; Avalox; Octegra; ***Jpn:*** Avelox; ***Malaysia:*** Avelox; Vigamox; ***Mex.:*** Avelox; Vigamoxi; ***Neth.:*** Actira†; Avelox; Octegra; ***NZ:*** Avelox; ***Philipp.:*** Avelox; Vigamox; ***Pol.:*** Avelox; ***Port.:*** Avelox; Proflox; ***Rus.:*** Avelox (Авелокс); ***S.Afr.:*** Avelon; ***Singapore:*** Avelox; Vigamox; ***Spain:*** Actira; Octegra; Proflox; ***Swed.:*** Avelox; ***Switz.:*** Avalox; ***Thai.:*** Avelox; Vigamox; ***Turk.:*** Avelox; ***UK:*** Avelox; ***USA:*** Avelox; Vigamox; ***Venez.:*** Avelox; Vigamox.

Mupirocin *(BAN, USAN, rINN)*

BRL-4910A; Mupirocina; Mupirocinas; Mupirocine; Mupirocinum; Mupirosiini; Pseudomonic Acid. 9-[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxypyran-2-yl]-3-methylbut-2-enoyloxy]nonanoic acid; (2*S*-{2α(*E*),3β,4β,5α[2*R**,3*R**(1*R**,2*R**)]})-9-{[3-Methyl-1-oxo-4-(tetrahydro-3,4-dihydroxy-5-{[3-(2-hydroxy-1-methyl-propyl)oxiranyl]methyl}-2*H*-pyran-2-yl)-2-butenyl]oxy}nonanoic acid.

Мупироцин

$C_{26}H_{44}O_9$ = 500.6.

CAS — 12650-69-0.

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

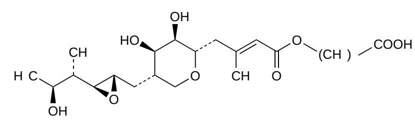

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mupirocin). A white or almost white powder. It shows polymorphism. Slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, and in dichloromethane. The pH of a freshly prepared saturated solution in water is 3.5 to 4.0. Protect from light.

USP 31 (Mupirocin). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ether. pH of a saturated solution in water is between 3.5 and 4.5. Store in airtight containers.

Mupirocin Calcium *(BANM, USAN, rINNM)*

BRL-4910F; Calcii Mupirocinum; Mupirocin vápenatá sůl dihydrát; Mupirocina cálcica; Mupirocine calcique; Mupirocinkalcium; Mupirocin-kalcium; Mupirocino kalcio druska; Mupirocinum calcicum; Mupirocinum Calcicum Dihydricum; Mupirosiinikalsium.

Кальций Мупироцин

$C_{52}H_{86}O_{18}Ca,2H_2O$ = 1075.3.

CAS — 104486-81-9 (anhydrous mupirocin calcium); 115074-43-6 (mupirocin calcium dihydrate).

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Mupirocin Calcium). A white or almost white powder. Very slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane.

USP 31 (Mupirocin Calcium). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

Mupirocin is usually well tolerated but local reactions such as burning, stinging, and itching may occur after the application of mupirocin to the skin.

Some mupirocin products are formulated in a macrogol base: such formulations are not suitable for application to mucous membranes and should be used with caution in patients with extensive burns or wounds because of the possibility of macrogol toxicity. Care is also required in patients with renal impairment.

Antimicrobial Action

Mupirocin is an antibacterial that inhibits bacterial protein synthesis by binding to isoleucyl transfer RNA synthetase. It is mainly bacteriostatic at low concentrations, although it is usually bactericidal in the high concentrations achieved by topical application to the skin. At these concentrations it may have some activity against organisms reported to be relatively resistant to mupirocin *in vitro*.

It is mainly active against Gram-positive aerobes. Most strains of staphylococci (including meticillin-resistant and multiply-resistant *Staph. aureus*) and streptococci are susceptible *in vitro*, although the enterococci are relatively resistant. Mupirocin is also active against *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*. The Gram-negative organisms are generally insensitive, but *Haemophilus influenzae*, *Neisseria* spp. and a few others are sensitive. Anaerobic organisms, both Gram-positive and Gram-negative, are generally resistant, and activity against fungi is low. Mupirocin is more active *in vitro* at acid pH than in alkaline conditions.

Naturally resistant strains of *Staph. aureus* occur rarely but resistance, including high-level plasmid-mediated transferable resistance, has emerged, particularly during long-term use. There has been some concern that inappropriate prescribing of mupirocin has led to this steadily increasing resistance.

Activity against fungi. Activity of mupirocin 2% *in vitro* against *Candida albicans* was comparable to that of other commonly used topical antifungals. Although MICs were considerably in excess of those reported for susceptible bacteria, clinical responses in 10 patients suggested that adequate concentrations of mupirocin were achieved after topical application.[1]

1. Rode H, *et al.* Efficacy of mupirocin in cutaneous candidiasis. *Lancet* 1991; **338:** 578.

Resistance. References.

1. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother* 1998; **41:** 11–18.
2. Schmitz F-J, *et al.* The prevalence of low- and high-level mupirocin resistance in staphylococci from 19 European hospitals. *J Antimicrob Chemother* 1998; **42:** 489–95.
3. Upton A, *et al.* Mupirocin and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother* 2003; **51:** 613–17.
4. Kresken M, *et al.* Prevalence of mupirocin resistance in clinical isolates of Staphylococcus aureus and Staphylococcus epidermidis: results of the Antimicrobial Resistance Surveillance Study of the Paul-Ehrlich-Society for Chemotherapy, 2001. *Int J Antimicrob Agents* 2004; **23:** 577–81.
5. Walker ES, *et al.* A decline in mupirocin resistance in methicillin-resistant Staphylococcus aureus accompanied administrative control of prescriptions. *J Clin Microbiol* 2004; **42:** 2792–5.

Pharmacokinetics

Only very small amounts of topically applied mupirocin are absorbed into the systemic circulation where it is rapidly metabolised to monic acid which is excreted in the urine.

Uses and Administration

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens*. It is applied topically as a 2% ointment in a macrogol base, or as a cream containing mupirocin calcium equivalent to 2% mupirocin, in the treatment of various bacterial skin infections. These preparations should be applied up to 3 times daily for up to 10 days; treatment should be re-evaluated if there is no response after 3 to 5 days. They are not suitable for application to mucous membranes, and therefore a nasal ointment containing mupirocin calcium equivalent to 2% mupirocin in a paraffin basis is used for eradication of the nasal carriage of *Staphylococcus aureus*, particularly epidemic meticillin-resistant strains. The nasal ointment should be applied into each nostril 2 or 3 times daily for a maximum of 7 days.

For further details of skin infections and staphylococcal infections and their treatment, see under Choice of Antibacterial, p.194.

◊ References.

1. Roth VR, *et al.* Should we routinely use mupirocin to prevent staphylococcal infections? *Infect Control Hosp Epidemiol* 2000; **21:** 745–9.
2. Perl TM, *et al.* Mupirocin and the Risk of Staphylococcus Aureus Study Team. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med* 2002; **346:** 1871–7.
3. Takahashi S, *et al.* The preventive effects of mupirocin against nasotracheal intubation-related bacterial carriage. *Anesth Analg* 2003; **97:** 222–5.
4. Laupland KB, Conly JM. Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. *Clin Infect Dis* 2003; **37:** 933–8.
5. Tacconelli E, *et al.* Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. *Clin Infect Dis* 2003; **37:** 1629–38.
6. Wertheim HF, *et al.* Mupirocin prophylaxis against nosocomial Staphylococcus aureus infections in nonsurgical patients: a randomized study. *Ann Intern Med* 2004; **140:** 419–25.
7. Kallen AJ, *et al.* Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005; **26:** 916–22.
8. Unemura Y, *et al.* Impact of prophylactic mupirocin for radical esophagectomy. *J Infect Chemother* 2006; **12:** 257–63.
9. Sit D, *et al.* Prophylactic intranasal mupirocin ointment in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. *Adv Therapy* 2007; **24:** 387–93.

Preparations

BP 2008: Mupirocin Ointment;
USP 31: Mupirocin Cream; Mupirocin Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Bactroban; Mupax; Mupirox; Paldar; Vidox; ***Austral.:*** Bactroban; ***Austria:*** Bactroban; ***Belg.:*** Bactroban; ***Braz.:*** Bacrocin; Bactocin; Bactroban; Bactroneo; ***Canad.:*** Bactroban; ***Chile:*** Bactroban; Bantix; Ultrabiotic; Underan; ***Cz.:*** Bactroban; ***Denm.:*** Bactroban; ***Fin.:*** Bactroban; ***Fr.:*** Bactroban; Mupiderm; ***Ger.:*** InfectoPyoderm; Turixin; ***Gr.:*** Bactroban; Bactrocine; Hevronaz; Micoban; Mupider; Mupiran; Veltion; ***Hong Kong:*** Bactroban; ***Hung.:*** Bactroban; ***India:*** Bactroban; Supirocin; ***Indon.:*** Bactoderm; Bactroban; Pibaksin; ***Irl.:*** Bactroban; ***Israel:*** Bactoderm†; Bactroban; ***Ital.:*** Bactroban; Mupiskin; ***Jpn:*** Bactroban; ***Malaysia:*** Bactroban; Muprin; ***Mex.:*** Bactroban; Sinpebac; ***Neth.:*** Bactroban; ***NZ:*** Bactroban; ***Philipp.:*** Bactifree; Bactroban; Foskina; ***Pol.:*** Bactroban; Mupirox; ***Port.:*** Bactroban; ***Rus.:*** Bactroban (Бактробан); ***S.Afr.:*** Bactroban; ***Singapore:*** Bactroban; Supirocin; ***Spain:*** Bactroban; Plasimine; ***Swed.:*** Bactroban; ***Switz.:*** Bactroban; ***Thai.:*** Bactex; Bactroban; Muporin; ***Turk.:*** Bactroban; ***UK:*** Bactroban; ***USA:*** Bactroban; Centany; ***Venez.:*** Bactroban; Bactrobandos†.

Multi-ingredient: ***India:*** Supirocin-B.

Nadifloxacin *(BAN, rINN)*

Jinofloxacin; Nadifloxacine; Nadifloxacino; Nadifloxacinum; OPC-7251. (±)-9-Fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Надифлоксацин

$C_{19}H_{21}FN_2O_4$ = 360.4.
CAS — 124858-35-1.

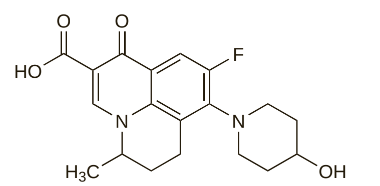

Profile

Nadifloxacin is a fluoroquinolone antibacterial used in topical treatment of acne. It is applied twice daily as a 1% cream or ointment.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Nadixa; ***Gr.:*** Nadixa; ***India:*** Nadiflox; ***Indon.:*** Acuatim; ***Jpn:*** Acuatim; ***Mex.:*** Nadixa†; ***Port.:*** Nadixa.

Nafcillin Sodium *(BANM, USAN, rINNM)*

Nafcilina sódica; Nafcilline Sodique; Nafcillinnatrium; Nafcillinum Natricum; Nafsilliininatrium; Natrii Nafcillinum; Wy-3277. Sodium (6*R*)-6-(2-ethoxy-1-naphthamido)penicillanate monohydrate.

Натрий Нафциллин

$C_{21}H_{21}N_2NaO_5S,H_2O$ = 454.5.
CAS — 147-52-4 (nafcillin); 985-16-0 (anhydrous nafcillin sodium); 7177-50-6 (nafcillin sodium monohydrate).

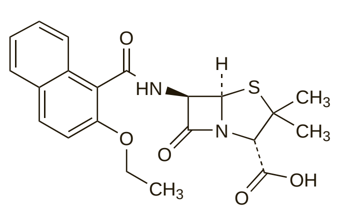

(nafcillin)

Pharmacopoeias. In *US.*

USP 31 (Nafcillin Sodium). A white to yellowish-white powder having not more than a slight characteristic odour. Freely soluble in water and in chloroform; soluble in alcohol. pH of a 3% solution in water is between 5.0 and 7.0. Store in airtight containers.

Incompatibility. Nafcillin sodium has been reported to be incompatible with aminoglycosides and a number of other antibacterials. It has also been reported to be incompatible with acidic and alkaline drugs.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Thrombophlebitis may occur when nafcillin is given by intravenous injection, and tissue damage has been reported on extravasation.

Effects on the kidneys. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26:** 985–90.
2. Guharoy SR, *et al.* Suspected nafcillin-induced interstitial nephritis. *Ann Pharmacother* 1993; **27:** 170–3.
3. Hoppes T, *et al.* Four cases of nafcillin-associated acute interstitial nephritis in one institution. *Nat Clin Pract Nephrol* 2007; **3:** 456–61.

Effects on the liver. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; **26:** 985–90.
2. Presti ME, *et al.* Nafcillin-associated hepatotoxicity: report of a case and review of the literature. *Dig Dis Sci* 1996; **41:** 180–4.

Sodium content. Each g of nafcillin sodium contains about 2.2 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Ciclosporin. For the effect of nafcillin on ciclosporin, see p.1825.

Warfarin. For the effect of nafcillin on warfarin, see p.1428.

Antimicrobial Action

As for Flucloxacillin, p.277.

Pharmacokinetics

Nafcillin is incompletely and irregularly absorbed from the gastrointestinal tract, especially when given after food. After intramuscular injection it is absorbed more reliably, an injection of 0.5 to 1 g producing peak plasma concentrations of 5 to 8 micrograms/mL within about 0.5 to 1 hour. Up to 90% of nafcillin in the circulation is bound to plasma proteins. Nafcillin has been reported to have a plasma half-life of about 0.5 to 1.5 hours. The half-life is prolonged in neonates.

Nafcillin crosses the placenta into the fetal circulation and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Nafcillin is distributed into pleural and synovial fluids and into bone.

Nafcillin differs from most other penicillins in that it is largely inactivated by hepatic metabolism. It is excreted via the bile although some reabsorption takes place in the small intestine. Only about 10% of a dose given orally before food, and about 30% of a dose given intramuscularly, is excreted in the urine.

Plasma concentrations are enhanced by probenecid.

Uses and Administration

Nafcillin is a penicillinase-resistant penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

It is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of nafcillin; 1.1 g of nafcillin sodium is equivalent to about 1 g of nafcillin. Nafcillin sodium may be given intravenously by slow injection over 5 to 10 minutes or by slow infusion over at least 30 to 60 minutes; usual adult doses are 0.5 to 1 g of nafcillin every 4 hours, although it is usually recommended that it be used for not more than 24 to 48 hours because of the risk of thrombophlebitis. It has also been given by intramuscular injection in a dose of 500 mg of nafcillin every 4 to 6 hours.

Nafcillin sodium has also been given orally but other penicillinase-resistant penicillins are preferred.

Preparations

USP 31: Nafcillin for Injection; Nafcillin Injection; Nafcillin Sodium Capsules; Nafcillin Sodium for Oral Solution; Nafcillin Sodium Tablets.

Nalidixic Acid *(BAN, USAN, rINN)*

Acide nalidixique; Ácido nalidíxico; Acidum nalidixicum; Kwas nalidyksowy; Kyselina nalidixová; Nalidiksiinihappo; Nalidiksik Asit; Nalidikso rūgštis; Nalidixinic Acid; Nalidixinsyra; Nalidixsav; NSC-82174; Win-18320. 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

Налидиксовая Кислота

$C_{12}H_{12}N_2O_3$ = 232.2.
CAS — 389-08-2.
ATC — J01MB02.
ATC Vet — QJ01MB02.

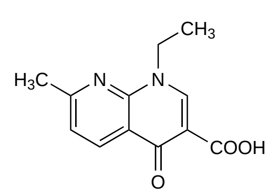

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Nalidixic Acid). An almost white or pale yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 31 (Nalidixic Acid). A white to very pale yellow, odourless crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 910 of alcohol and 1 in 29 of chloroform; slightly soluble in acetone, in methyl alcohol, and in toluene; soluble in dichloromethane and in solutions of fixed alkali hydroxides and carbonates. Store in airtight containers.

Adverse Effects

The most frequent adverse reactions to nalidixic acid involve the gastrointestinal tract, skin, and CNS. Gastrointestinal effects have been reported in about 8% of patients and include nausea, vomiting, diarrhoea, and abdominal pain.

Adverse effects on the skin include photosensitivity reactions with erythema and bullous eruptions, allergic rashes, urticaria, and pruritus. Erythema multiforme and Stevens-Johnson syndrome have been reported rarely. Eosinophilia, fever, angioedema, and, rarely, anaphylactoid reactions have occurred.

Neurological effects include visual disturbances, headache, dizziness or vertigo, drowsiness, and sometimes confusion, depression, excitement, and hallucinations. Toxic psychoses or convulsions have occurred, especially after large doses; convulsions are most likely in patients with predisposing factors such as cerebral arteriosclerosis or epilepsy. There have been reports of intracranial hypertension, especially in infants and young children, and also of metabolic acidosis.

Peripheral neuropathies, muscular weakness, and myalgia are occasional adverse effects. Sixth cranial nerve palsy has been reported rarely.

Arthralgia has been reported (degenerative changes in weight-bearing joints of young *animals* are documented). Tendon damage has occasionally been associated with nalidixic acid and related compounds, the fluoroquinolones (see Effects on the Musculoskeletal System, under Ciprofloxacin, p.244).

Cholestatic jaundice, thrombocytopenia, and leucopenia have occurred rarely, as has haemolytic anaemia in patients who may or may not have G6PD deficiency. There have been isolated reports of fatal auto-immune haemolytic anaemia in elderly patients.

Precautions

Nalidixic acid is contra-indicated in patients with a history of convulsive disorders and in those with severe renal impairment. It should be given with care to patients with hepatic or moderate renal impairment, severe cerebral arteriosclerosis, or G6PD deficiency. Blood counts and renal and hepatic function should be monitored if treatment continues for more than 2 weeks.

It should be avoided in infants less than 3 months old. Since nalidixic acid and related antimicrobials have been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these compounds should not generally be used in patients aged under 18 years, pregnant women, or during breast feeding (but see also below) unless the benefits outweigh the risks. Treatment should be stopped if symptoms of neuropathy or arthralgia occur. Tendon damage may occur rarely and treatment should be stopped if patients experience tendon pain, inflammation, or rupture.

Exposure to strong sunlight or sunlamps should be avoided during treatment with nalidixic acid.

Nalidixic acid may cause false-positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics[1] states that nalidixic acid is usually compatible with breast feeding, although haemolytic anaemia has been reported[2] in a breast-fed infant, with no evidence of G6PD deficiency, whose mother had received nalidixic acid.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Belton EM, Jones RV. Haemolytic anaemia due to nalidixic acid. *Lancet* 1965; **ii:** 691.

Porphyria. Nalidixic acid has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The absorption of nalidixic acid is reduced by sucralfate, and divalent and trivalent cations such as aluminium, calcium, iron, magnesium, and zinc, and therefore use of nalidixic acid with antacids, iron preparations, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. It is recommended that such products should not be given within 2 hours before or after nalidixic acid.

The excretion of nalidixic acid is reduced and plasma concentrations increased by probenecid. Other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline have been shown to antagonise the action of nalidixic acid *in vitro* and should not be used together.

Fatal haemorrhagic enterocolitis has been associated with the use of nalidixic acid and high-dose intravenous melphalan in children; use with other alkylating antineoplastics is also contra-indicated. There is a possible risk of increased nephrotoxicity when nalidixic acid is given with ciclosporin.

Nalidixic acid is reported to enhance the effect of oral anticoagulants such as warfarin (see p.1428); this may be due in part to displacement of anticoagulant from its plasma binding sites. The dose of anticoagulant may need to be reduced.

The effect of some quinolone antibacterials on xanthines is discussed under Caffeine, p.1117, and Theophylline, p.1143.

Convulsions may be precipitated by the use of some quinolones with NSAIDs (see Analgesics, under Interactions of Ciprofloxacin, p.246), although this has not been reported with nalidixic acid.

Antimicrobial Action

Nalidixic acid is considered to act by interfering with the replication of bacterial DNA, probably by inhibiting DNA gyrase (topoisomerase) activity. It is active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Salmonella* spp., and *Shigella* spp., and is usually bactericidal. *Pseudomonas aeruginosa*, Gram-positive bacteria, and anaerobes are not generally susceptible.

Bacterial resistance may develop rapidly, sometimes within a few days of commencing treatment, but it does not appear to be transferable or R-plasmid mediated (see also below). Cross-resistance occurs with oxolinic acid and cinoxacin.

The antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH. Antagonism between nalidixic acid and other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline has been shown *in vitro*.

Resistance. Bacterial plasmid-mediated resistance to quinolones had not been seen by the late 1980s.[1] A report[2] of such resistance to nalidixic acid in *Shigella dysenteriae* responsible for an epidemic of shigellosis in Bangladesh in 1987, was questioned at the time.[3] On reinspection of the data, chromosomal mutation rather than plasmid-mediated resistance was confirmed as the mechanism responsible so far for resistance to quinolones.[1] Subsequent data[4] in an isolate of *Klebsiella pneumoniae* has, however, suggested that plasma-mediated resistance to quinolones may be possible.

1. Courvalin P. Plasmid-mediated 4-quinolone resistance: a real or apparent absence? *Antimicrob Agents Chemother* 1990; **34:** 681–4.
2. Munshi MH, *et al.* Plasmid-mediated resistance to nalidixic acid in Shigella dysenteriae type 1. *Lancet* 1987; **ii:** 419–21.
3. Crumplin GC. Plasmid-mediated resistance to nalidixic acid and new 4-quinolones? *Lancet* 1987; **ii:** 854–5.
4. Martínez-Martínez L, *et al.* Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351:** 797–9.

Pharmacokinetics

Nalidixic acid is rapidly and almost completely absorbed from the gastrointestinal tract, and peak plasma concentrations of 20 to 40 micrograms/mL have been reported 1 to 2 hours after a 1-g oral dose. Plasma half-lives of about 1 to 2.5 hours have been reported (but see below).

Nalidixic acid is partially metabolised to hydroxynalidixic acid, which has antibacterial activity similar to that of nalidixic acid and accounts for about 30% of active drug in the blood. About 93% of nalidixic acid and 63% of hydroxynalidixic acid are bound to plasma proteins. Both nalidixic acid and hydroxynalidixic acid are rapidly metabolised to inactive glucuronide and dicarboxylic acid derivatives; the major inactive metabolite 7-carboxynalidixic acid is usually only detected in urine.

Nalidixic acid and its metabolites are excreted rapidly in the urine, nearly all of a dose being eliminated within 24 hours. More than 80% of the drug excreted in the urine is as inactive metabolites, but peak urinary concentrations of active drug averaging about 150 to 200 micrograms/mL are achieved 3 to 4 hours after a single 1-g dose. Hydroxynalidixic acid accounts for about 80 to 85% of activity in the urine. Urinary excretion is reduced by probenecid. About 4% of a dose is excreted in the faeces.

Traces of nalidixic acid are distributed into breast milk and appear to cross the placenta.

◊ Although a plasma half-life of 1 to 2.5 hours is generally cited for nalidixic acid, values of 6 to 7 hours have been reported for active drug (nalidixic acid and hydroxynalidixic acid) after using more specific and sensitive assay techniques and longer sampling periods than previously.[1]

The elimination rate of nalidixic acid appears to be not markedly altered by renal impairment, but the elimination of hydroxynalidixic acid is significantly reduced. 7-Carboxynalidixic acid has appeared in the plasma of patients with renal impairment.[2] Plasma concentrations of active drug were higher and the half-life prolonged in elderly subjects.[3]

1. Ferry N, *et al.* Nalidixic acid kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1981; **29:** 695–8.
2. Cuisinaud G, *et al.* Nalidixic acid kinetics in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 489–93.
3. Barbeau G, Belanger P-M. Pharmacokinetics of nalidixic acid in old and young volunteers. *J Clin Pharmacol* 1982; **22:** 490–6.

Uses and Administration

Nalidixic acid is a 4-quinolone antibacterial used in the treatment of uncomplicated lower urinary-tract infections due to Gram-negative bacteria other than *Pseudomonas* spp. (p.199). It has also been used to treat shigellosis (bacillary dysentery) (p.173).

The usual dose is about 4 g daily in 4 divided oral doses for 7 to 14 days in acute infections, reducing thereafter to half this dose in chronic infections. Since bacterial resistance may develop rapidly it has been suggested that if treatment with nalidixic acid has not resulted in a negative urine culture within 48 hours another antimicrobial should be used.

For details of reduced doses in renal impairment, see below.

For details of doses in infants and children, see below.

Although the antibacterial activity of nalidixic acid does not appear to be influenced by urinary pH, the use of sodium bicarbonate or sodium citrate does increase the concentration of active drug in the urine. Commercial preparations containing nalidixic acid, sodium bicarbonate, and sodium citrate have been used in some countries.

It is also used with the analgesic phenazopyridine.

Administration in children. Although nalidixic acid is not generally recommended for use in patients under 18 years of age, it is licensed in both the UK and the USA for infants and children over 3 months of age. The usual oral dose is 55 to 60 mg/kg daily in 4 divided doses for at least 7 days, reducing thereafter to about 30 mg/kg daily in 4 divided doses for prolonged treatment (but see Precautions, above).

In addition, the *BNFC* suggests that a dose of 30 mg/kg daily in 2 divided doses may be given for prophylaxis of urinary-tract infections.

Administration in renal impairment. In the UK, some products of nalidixic acid have been licensed for use at half the usual dose in patients with a creatinine clearance below 20 mL/minute (the *BNFC* suggests a similar reduction in children with creatinine clearance 20 mL/minute per 1.73 m^2 or less). However, other licensed product information does not include this information and suggests that nalidixic acid should not be used in patients with severe renal impairment.

Preparations

BP 2008: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets;
USP 31: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Nalidix†; Wintomylon†; ***Braz.:*** Naluril; Wintomylon; ***Canad.:*** NegGram†; ***Chile:*** Wintomylon†; ***Fr.:*** Negram†; ***Gr.:*** Nal-acid†; ***Hong Kong:*** Wintomylon; ***Hung.:*** Nevigramon; ***India:*** Diarlop; Gramoneg; Negadix; ***Indon.:*** Urineg; ***Irl.:*** Negram; ***Israel:*** NegGram†; ***Ital.:*** Betaxina†; Nalidixin†; Naligram†; NegGram†; Uri-Flor; ***Mex.:*** A-N-Dix; Acidix; Fardixon†; Kamilon; Nalix; Pronal Dix; Seltomylon†; Urlix†; Uronalin; Wintomylon; ***Pol.:*** Nevigramon; ***Port.:*** Wintomilon†; ***Rus.:*** Negram (Неграм); ***S.Afr.:*** Puromylon; Winlomylon; ***UK:*** Negram†; Uriben; ***USA:*** NegGram.

Multi-ingredient: ***Irl.:*** Mictral†; ***Mex.:*** Azo-Uronalin; Azo-Wintomylon; Azogen; Nalixone; Naxilan-Plus; Pirifur.

Neomycin *(BAN, rINN)*

Neomicina; Néomycine; Neomycinum; Neomysiini.

Неомицин

CAS — 1404-04-2 (neomycin); 3947-65-7 (neomycin A); 119-04-0 (neomycin B); 66-86-4 (neomycin C).

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

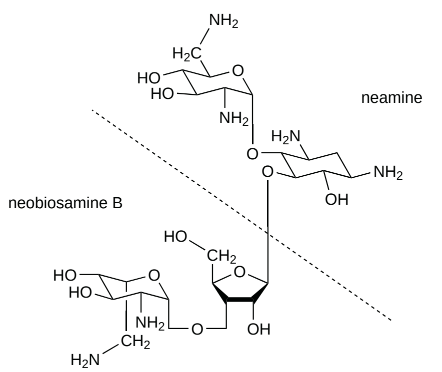

Neomycin B

Description. A mixture of 2 isomers, neomycin B ($C_{23}H_{46}N_6O_{13}$ = 614.6) and neomycin C ($C_{23}H_{46}N_6O_{13}$ = 614.6) with neomycin A (neamine, $C_{12}H_{26}N_4O_6$ = 322.4); neomycins B and C are glycoside esters of neamine and neobiosamines B and C. Framycetin (p.279) consists of neomycin B.

Neomycin Sulfate *(rINNM)*

Fradiomycin Sulfate; Neomicino sulfatas; Neomicin-szulfát; Neomisin Sülfat; Neomycin Sulphate *(BANM)*; Néomycine, sulfate de; Neomycini sulfas; Neomycinsulfat; Neomycin-sulfát; Neomycyny siarczan; Neomysiinisulfaatti; Sulfato de neomicina.

Неомицина Сульфат

CAS — 1405-10-3.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

NOTE. NEO is a code approved by the BP 2008 for use on single unit doses of eye drops containing neomycin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Neomycin Sulphate). A mixture of the sulfates of substances produced by the growth of certain selected strains of *Streptomyces fradiae*, the main component being the sulfate of neomycin B. The potency is not less than 680 units/mg, calculated with reference to the dried substance. A white or yellowish-white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

USP 31 (Neomycin Sulfate). The sulfate salt of a kind of neomycin, an antibacterial substance produced by the growth of *Streptomyces fradiae* (Streptomycetaceae), or a mixture of two or more such salts. It has a potency equivalent to not less than 600 micrograms of neomycin per mg, calculated on the dried basis. A white to slightly yellow powder, or cryodesiccated solid. It is odourless or practically so, and is hygroscopic. Soluble 1 in 1 of water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether. pH of a solution in water containing the equivalent of neomycin 3.3% is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Neomycin Undecenoate *(BANM)*

Neomycin Undecylenate *(USAN, rINNM)*; Néomycine, Undécylénate de; Neomycini Undecylenas; Undecilenato de neomicina. The 10-undecenoate salt of neomycin.

Неомицина Ундециленат

CAS — 1406-04-8.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

Adverse Effects and Treatment

As for Gentamicin Sulfate, p.282.

Neomycin has particularly potent nephrotoxic and ototoxic properties and so is generally no longer given parenterally. However, sufficient may be absorbed after use by other routes (e.g. orally, instillation into cavities or open wounds, or topical application to damaged skin), to produce irreversible partial or total deafness. The effect is dose-related and is enhanced by renal impairment. Nephrotoxic effects may also occur.

When given orally in large doses, neomycin causes nausea, vomiting, and diarrhoea. Prolonged oral use may cause a malabsorption syndrome with steatorrhoea and diarrhoea which can be very severe. Superinfection may occur, especially with prolonged treatment.

Neomycin has a neuromuscular-blocking action similar to, but stronger than, that of other aminoglycosides, and respiratory depression and arrest has followed the intraperitoneal instillation of neomycin. Fatalities have occurred.

Hypersensitivity reactions, such as rashes, pruritus, and sometimes drug fever or even anaphylaxis, during local treatment with neomycin and may be masked by the combined use of a corticosteroid. Cross-sensitivity with other aminoglycosides may occur.

Precautions

As for Gentamicin Sulfate, p.283. Parenteral use of neomycin, or its use for irrigation of wounds or serous cavities such as the peritoneum, is no longer recommended.

Neomycin is contra-indicated for intestinal disinfection when an obstruction is present, in patients with a known history of allergy to aminoglycosides, and in infants under 1 year. It should be used with great care in patients with renal or hepatic impairment, or with neuromuscular disorders, and in those with impaired hearing. The topical use of neomycin in patients with extensive skin damage or perforated tympanic membranes may result in deafness.

Prolonged local use should be avoided as it may lead to skin sensitisation and possible cross-sensitivity to other aminoglycosides.

Hypersensitivity and vaccination. Neomycin was thought to be responsible for a hypersensitivity reaction[1] in a child given measles, mumps, and rubella vaccine containing neomycin 25 micrograms. However, there is also a report of successful vaccination with measles, mumps, and rubella vaccine in a neomycin-sensitive child.[2] Although the vaccine may contain small amounts of neomycin or kanamycin, and sensitivity to either is considered a contra-indication to its use, it is only rarely necessary to withhold it once appropriate expert advice has been taken. There is little logic to intradermal testing since test solutions contain 4 to 40 times as much neomycin as the vaccine.[2]

1. Kwittken PL, *et al*. MMR vaccine and neomycin allergy. *Am J Dis Child* 1993; **147:** 128–9.
2. Elliman D, Dhanraj B. Safe MMR vaccination despite neomycin allergy. *Lancet* 1991; **337:** 365.

Interactions

As for Gentamicin Sulfate, p.283. Absorption after oral or local use may be sufficient to produce interactions with other drugs given systemically.

Neomycin orally has been reported to impair the absorption of other drugs including phenoxymethylpenicillin, digoxin, and methotrexate; the efficacy of oral contraceptives might be reduced. The effects of acarbose may be enhanced by oral neomycin.

Antimicrobial Action

Neomycin has a mode of action and spectrum of activity similar to that of gentamicin (p.283) but it lacks activity against *Pseudomonas aeruginosa.* It is reported to be active against *Mycobacterium tuberculosis.*

Because of its extensive topical use, resistance has been reported to be relatively widespread, notably among staphylococci, and some *Salmonella*, *Shigella*, and *Escherichia coli* strains. Cross-resistance with kanamycin, framycetin, and paromomycin occurs.

Pharmacokinetics

Neomycin is poorly absorbed from the gastrointestinal tract, about 97% of an oral dose being excreted unchanged in the faeces. Doses of 3 g orally produce peak plasma concentrations of up to 4 micrograms/mL and absorption is similar after an enema. Absorption may be increased in conditions which damage or inflame the mucosa. Absorption has also been reported to occur from the peritoneum, respiratory tract, bladder, wounds, and inflamed skin.

Once neomycin is absorbed it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours.

Uses and Administration

Neomycin is an aminoglycoside antibiotic used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms. Most preparations contain the sulfate, but neomycin undecenoate is also used. Neomycin is often used with another antibacterial such as bacitracin, colistin, gramicidin, or polymyxin B. Such combinations have been used topically in the eye before ophthalmic surgery for infection prophylaxis and, with propamidine isetionate, in the treatment of acanthamoeba keratitis (p.822). A cream containing neomycin sulfate and chlorhexidine hydrochloride has been used for application to the nostrils in the treatment of staphylococcal nasal carriers (p.195) but, as with other topical antibacterial preparations, development of resistance may be a problem. Neomycin is often used with topical corticosteroids, but such preparations should be used with caution because of the risk that signs of resistant infection may be suppressed. Care must also be taken where there is skin trauma because of the risk of increased absorption and toxicity (see Adverse Effects, above). For details of bacterial skin infections and their treatment, see p.194.

Because neomycin sulfate is poorly absorbed from the gastrointestinal tract, it has been given orally for bowel preparation before abdominal surgery, often with erythromycin (p.195). Neomycin sulfate is also used with other antibacterials and antifungals in the selective decontamination of the digestive tract in patients in intensive care (p.175).

Neomycin is rarely used in the treatment of existing gastrointestinal infections. Although it has been used in the treatment of diarrhoea due to infection with enteropathogenic *Escherichia coli* (EPEC) (p.173), the use of neomycin in children with acute diarrhoea is generally not recommended.

Neomycin sulfate may be given orally to patients with incipient hepatic encephalopathy (p.1697) to reduce the flora of the gastrointestinal tract.

Neomycin has lipid regulating properties and has occasionally been given orally in the treatment of hyperlipidaemias (see below). It has also been used for the irrigation of wounds and body cavities but such use is no longer recommended because of the risk of toxicity.

Administration and dosage. For pre-operative use, 1 g of neomycin sulfate has been given hourly for 4 hours and then every 4 hours for 2 or 3 days before surgery; suggested doses in children, given every 4 hours, are 1 g in those aged over 12 years and 250 to 500 mg in those aged 6 to 12 years.

As an adjunct in the management of hepatic encephalopathy, 4 to 12 g may be given daily in divided doses, usually for 5 to 7 days; children may be given 50 to 100 mg/kg daily in divided doses. Prolonged use may cause malabsorption.

Topical preparations typically contain the equivalent of 0.35% neomycin base.

Neomycin hydrochloride has also been used.

Hyperlipidaemias. Neomycin has been given in doses of up to 2 g daily by mouth in the treatment of hypercholesterolaemia (p.1169). It is thought to reduce intestinal absorption of cholesterol through its action on microbial flora, resulting in greater catabolism of low-density lipoproteins in the body.[1] However, more effective and safer drugs are preferred.

1. Illingworth DR. Lipid-lowering drugs: an overview of indications and optimum use. *Drugs* 1987, **33:** 259–79.

Preparations

BP 2008: Dexamethasone and Neomycin Ear Spray; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone and Neomycin Cream; Neomycin Eye Drops; Neomycin Eye Ointment; Neomycin Tablets;
USP 31: Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin for Injection; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream; Neomycin Sulfate and Fluorometholone Ointment; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment; Neomycin Sulfate and Gramicidin Ointment; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Neomycin Sulfate and Methylprednisolone Acetate Cream; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Neomycin Sulfate Cream; Neomycin Sulfate Ointment; Neomycin Sulfate Ophthalmic Ointment; Neomycin Sulfate Oral Solution; Neomycin Sulfate Tablets; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Proprietary Preparations (details are given in Part 3)

Arg.: Concatag; Neomas; ***Austral.:*** Neosulf; Siguent Neomycin†; ***Austria:*** Bykomycin; ***Braz.:*** Dermomicin†; Nemicina; Neo POM†; Neocina; Neogecim†; Neom†; Neomed; Neomicon; Neomina†; ***Fr.:*** Bacteomycine†; ***Ger.:*** Bykomycin†; Cysto-Myacyne N; Myacyne; Nebacetin N†; Uro-Nebacetin N; Vagicillin; ***Gr.:*** Nivemycin; ***Hong Kong:*** Neoate; ***Israel:*** Neocin; ***Jpn:*** Francetin; ***Mex.:*** Baycuten; Gemicina†; Neomixen; ***NZ:*** Neosulf†; ***Port.:*** Enteromicina; Oto-Synalar N; ***Thai.:*** Myneocin; ***UK:*** Nivemycin; ***USA:*** Mycifradin†; Neo-fradin.

Multi-ingredient: ***Arg.:*** Adermicina; Antibiocort†; Aseptobron N; Belbar; Betasone-G Compuesto; Betnovate-N; Biocortin†; Bioftal; Biotaer an Caramelos; Biotaer Gamma†; Biotaer Nebulizable; Biotaer Ultrason Nebulizable†; Bucoangin N; Butimerin; Caext; Caramelos Antibioticos Bucoangin†; Cerosporin GS†; Cicatrex; Clevosan; Cloptison-N†; Colirio Antibiotico CNH; Decadron con Neomicina; Delisan; Derivoco†; Dermadex NN; Dexafurazon†; Dexalergin; Diflunazol†; Dotrin; Endomicina†; Factioneye; Farm-X Genicologico; FML Neo; Gargaletas; Ginal Cent; Ginkan; Gramibiotic†; Gramicortil†; Graneodin; Graneodin N; Griseoplus; Hidrocortin†; Irigal; Irix Biotic; Isoptomax; Itro†; Kenacomb; Klonovan; Ledercort con Neomicina†; Lefa Enteril†; Linfol; Linfol Cicatrizante; Mailen; Menaderm N; Min O; Nasojol†; Nasomicina; Naxo TV; Nebapol B†; Neo Coltirot; Neo Kef; Neo Pelvicillin; Neo-Currino; Neo-Mudapenil†; Neobitiol; Neodexa Plus; Neomas L; Neosona; Nesbiler†; Nexadron Compuesto; Nexadron Plus; O-Biol; O-Biol P; Oftal; Opocarbon; Otocalmia Biotic; Otoseptil; Otosporin; Otosporin L; Ovumix; Palan†; Pantometil; Pentol; Plastenan con Neomicina; Poenbioptal; Poenbioptal NF; Polygynax; Polyplex; Proetztotal; Provacsin Nasal; Rezamid†; Rinofilax AG M; Scheriderm; Septigyn; Sincerum; Sincerum Biotic; Sincerum Biotic L; Suavisan N; Tratomax; Tri-Emcortina†; Vagicural; Vagicural Plus; ***Austral.:*** Cicatrin; Kenacomb; Nemdyn; Neo-Medrol; Neosporin; Otocomb Otic; ***Austria:*** Baneocin; Betnesol-N; Betnovate-N; Cicatrex; Dorithricin; Hydoftal; Hydrocortimycin; Locacorten mit Neomycin; Mycostatin V; Nebacetin; Neo-Delphicort; Neocones; Otosporin; Synalar N; Topsym polyvalent; Tropoderm; Tyrothricin comp; Tyrothricin compositum; Ulcurilen; Volon A antibiotikahaltig; ***Belg.:*** De Icin†; Dexa-Polyspectran New; Maxitrol; Mycolog; Nebacetine; Neobacitracine; Otosporin†; Panotile; Polydexa; Polygynax†; Polyspectran Gramicidine; Predmycin P; Rhinovalon Neomycine†; Spitalen†; Statrol; Synalar Bi-Otic; ***Braz.:*** Aftine; Amigdagen; Amigdamicin†; Anaseptil; Anginotricin; Antiseptin†; Bacidermina; Bacigen; Bacinantrat†; Bacineo†; Bactoderm; Belcetin†; Betaderm N; Betazol Cort; Betnovate-N; Bismu-Jet; Celocort; Cetobeta; Cicatrene; Cicatrizan†; Cimecort; Colpagex N; Colpolase; Colutoide; Cutiderm; Decadron Colirio; Decadron Nasal; Dermacetin-Ped†; Dermase; Dermobel†; Dermoxin; Derms; Dexacilin; Dexacort†; Dexanil; Dexavison; Dexazona; Dimicin†; Drenison N; Elotin; Emscort; Epicitrin; Esperson N; Ferid; Flumex N; Fluo-Vaso; Folderm Pomada; Ginec†; Gingilone; Gynax-N; Hidrocin; Hidroneo†; Hipodex; Kindcetin; Larintil†; Locorten†; Londerm-N; Maxitrol; Mentodrin†; Metcort; Micoplex; Mud; Naderm; Nazobel†; Nebacetin; Nebaciderme; Nebacimed; Nebacitrin†; Nebactrina†; Nebalon†; Neobacina†; Neobacipan†; Neocetrin; Neocina†; Neocinolon; Neocortin; Neodex; Neolon-D; Neotop; Neotricin; Nepodex; Novacort; Novaderm; Omcilon A M; Onciplus; Otauril†; Oto Xilodase; Otocort†; Otodol†; Otomixyn; Otosporin; Otosynalar; Panotil; Parenterin; Poliginax; Polipred; Polysporin; Pomacetin†; Rhinosept; Rinogerol†; Rinosite†; Solemil†; Teutomicin; Thiabena†; Tirotrin†; Trivagel N; Trofodermin; Trok-N; Vagitrin-N; Xilodase; ***Canad.:*** Cicatrin; Cortimyxin; Cortisporin; Dioptrol†; Kenacomb†; Maxitrol; Neo-Cortef†; Neo-Medrol Acne; Neo-Medrol Veriderm†; Neosporin; Neotopic†; Optimyxin Plus; ratio-Triacomb; Triacomb†; Viaderm-KC; ***Chile:*** Bacitopic Compuesto; Bacitopic†; Banedif; Banedif Oftalmico; Banedif Oftalmico con Prednisolona; Betnovate-N†; Biodexin†; Celulase Con Neomicina; Escar T-Neomicina; Fluforte N†; Gotalgic; Grifoftal-D; Grifoftal†; Labosona N†; Madecassol Neomicina†; Maxitrol; Monticina; Nasomin; Oftabiotico; Oftasona N; Otazol†; Oticum; Otolisan; Otoseptil; Pensulan; Polvos Antibioticos†; Rinobanedif; Trofodermin Neomicina; Unguento Dermico Antibiotico; ***Cz.:*** Framykoin; Linola-H-compositum N†; Maxitrol; Ophthalmo-Framykoin; Ophthalmo-Framykoin Compositum; Otosporin; Pamycon; Pimafucort; Polygynax; Statrol†; ***Denm.:*** Decadron med Neomycin†; Kenalog Comp med Mycostatin; ***Fin.:*** Bacibact; Maxitrol; Neo-Medrol comp†; Pimafucort; Polysporin; ***Fr.:*** Antibio-Synalar; Antibiotulle Lumiere; Atebemyxine; Betneval-Neomycine†; Cebemyxine; Chibro-Cadron; Cidermex; Corticotulle Lumiere†; Dexagrane; Diprosone Neomycine; Locacortene†; Madecassol Neomycine Hydrocortisone†; Maxidrol; Mycolog†; Panotile; Polydexa; Polygynax; Polygynax Virgo; Pulvo 47 Neomycine†; Tergynan; Trofoseptine†; ***Ger.:*** Antibiotulle Lumiere†; Bivacyn†; Cicatrex†; Corticotulle Lumiere†; Cortidexason comp; Dexa Polyspectran; Dispadex comp; Efflumycin†; Farco-Uromycin†; Halog Tri†; Isopto Max; Jellin polyvalent†; Jellin-Neomycin; Kombi-Stulln N; Linola-H-compositum N†; Lokalison-antimikrobiell Creme N; Nebacetin; Neobac; Polygynax†; Polyspectran; Pulvo Neomycin; Topsym polyvalent; Ulcurilen N†; Volon A antibiotikahaltig N†; ***Gr.:*** Afacort; Antilerg-F†; Apobacyn; Betnovate-N; Dermol; Ekzegamma†; Fluoscin†; FML Neo; Fotocollyre; Genefacort†; Indocort†; Isopto Maxitrol; Kenacomb; Locacorten Neomycin†; Nebacetin; Neo-Priphen; Otocort; Otomize; Precortivit†; Pulvo 47; Saocin-D; Statrol†; Vioplex-T; ***Hong Kong:*** Aplosyn-Otic; Aristobet-N; Bacimycin; Betnovate-N; Bivacyn; Cebemyxine; Chlomy-P†; Corticin†; Derzid-N†; Dexoph; Dextracin; Enterocin Compound; Flunolone; Fluonid-N; Kenacomb; Lozopin; Maxitrol; Nebacetin†; Neo-Medrol Acne; Neosporin; Otosporin; Otozambon; Polydex-N; Polydexa; Polygynax; Polyoph; Prednitracin†; Proctosone†; Synalar N; Synco-CFN; Syneolona; Triacomb; ***Hung.:*** Baneocin; Bivacyn; Dexapolcort N; Flucinar N; Otosporin; Pimafucort; Synalar N†; ***India:*** Beclate-N; Betnederm N; Betnesol-N; Betnesol-N Nasal; Betnor; Betnovate-N; Candiderma +; Candizole-T; Clocip NB; Decdan-N; Dexona Eye/Ear; Dexosyn Plus; Dexosyn-N; Flomex N; Flucort-N; Flucreme NM; Kenacomb; Kenalog-S; Ledercort-N; Lucin-N; Mycidex†; NC-Derm; Nebasulf; Neosporin; Neosporin-H; Stecort-NM; Surfaz-SN; Topicasone with Neomycin; Valbet; Wycort c Neomycin; ***Indon.:*** Apolar-N; Benoson N; Berloson-N; Betason-N; Betnovate-N; Bevalex; Bioplacenton; Blecidex; Centabio; Cinolon-N; Decoderm 3; Denomix; Desolex-N; Fasolon; FG Ointment; FG Troches; Inmatrol; Isotic Enpigi; Isotic Neolyson; Isotic Nepafrin; Kalcinol-N; Kenetrol; Maxitrol; Metaskin-N; Mytaderm; Nebacetin; Nelicort; Neocortic; Neofen; Neosinol; Neosyd; Netracin; Nufacort; Ociderm-N; Oregan; Osatrol; Otopain; Otopraf; Otozambon; Polidemisin; Polifrisin; Proson N; Scanderma Plus; Tracetin; Tuderm-N; Ximex Optixitrol; Zumaderm-N; ***Irl.:*** Audicort†; Betnesol-N; Betnovate-N; Cicatrin; Graneodin; Kenacomb; Maxitrol; Naseptin; Neosporin†; Otomize; Otosporin; Synalar N†; ***Israel:*** Bamyxin; Betnesol-N; Betnovate-N; Dermacombin; Desoren; Dethamycin; Dethaphrine; Dex-Otic; Dexamycin; Dexefrin; Hycocin; Hycomycin; Kenacomb†; Locacorten with Neomycin†; Maxitrol; Neo-Medrol; Nodryl†; Otomize†; Otomycin; Polycutan; Tevacutan; ***Ital.:*** Abiostil; Anauran; Antibioptal; Bimixin; Bio-Delta Cortilen; Cicatrene; Desalfa; Desamix-Neomicina; Doricum; Ecoval con Neomicina; Enterostop; Eta Biocortilen; Eta Biocortilen VC; Halciderm Combi; Idracemi; Idrocet†; Idroneomicil†; Kataval; Localyn; Localyn-Neomicina; Locorten; Menaderm; Mixotone; Nefluan; Neo Cortofen; Neo-Medrol Veriderm†; Nevacort; Orobicin; Otosporin†; Rinojet SF†; Solprene; Streptosil con Neomicina-Fher; Trofodermin; Vasosterone Antibiotico; Vasosterone Collirio; ***Malaysia:*** Bacitracin-N; Baneocin; Beavate N; Besone-N; Betacin; Betamethasone N; Betnesol-N†; Betnosone N; Betnovate-N; Dextracin; Flumicin; Fluonid-N†; Kenacomb; Maxitrol; Neo-Deca; Neo-Hydro†; Neo-Medrol; Pocin G; Pocin H; Proctosone†; Synalar N†; Uniflex-N†; ***Mex.:*** Alin Nasal; Alin Oftalmico; Alosol; Baycuten N; Bexine; Biodexan; Biofrin; Biotarson N; Biotarson O; Cortifung-N; Cortisporin; Decadron con Neomicina; Dermalog-C; Dexamicin; Dexne; Dexsul; Dextone; Fluccinol N; Fluforte N; Flunal-Neo†; Fluo Grin; Gotadex†; Hidromagma†; Hidropolicin; K-Omistron; Kaomycin; Kenacomb; Kodakon†; Maxitrol; Mildex; Nebacetina; Neobacigrin; Neobol; Neoderm-F; Neopecsul; Neosporin; Neoxil; Nicobio†; Ofodex; Otilin; Polideltaxin NF; Polixin; Poly-Micron; Recoveron N; Recoveron NC; Rinadex Compuesto; Rinidyl DN; Scheriderm; Septilisin; Soldrin; Sondex-Of; Sulned; Synalar N; Synalar Neo; Synalar O; Synalar Oftalmico; Tapzol con Neomicina†; Timpacil; Treda; Tribiot; Xyloderm; ***Neth.:*** Maxitrol; Mycolog; Otosporin; Panotile; Pimafucort; Polyspectran G†; Synalar Bi-Otic†; ***Norw.:*** Maxitrol; ***NZ:*** Kenacomb; Maxitrol; Pimafucort; Viaderm-KC; ***Philipp.:*** Aplosyn N; Aplosyn-Otic; Betnovate-N; BNP Ointment; Cortisporin; Dermovate-NN; Hydrospor; Isonep; Isonep H; Kenacomb; Lidex NGN; Maxirap; Maxitrol; Maxoptic; Neo-Synalar; Neosporin; Novasorin; Postop; Postotic; Predmycin-P; Statrol; Synalar Otic; Syntemax; Terramycin Plus; Trimycin; Trimycin-H; ***Pol.:*** Baneocin; Betnovate-N; Bivacyn; Dexapolcort N; Dicortineff; Flucinar N; Lorinden N; Maxitrol; Mecortolon N; Multibiotic; Neotopic; Pimafucort; Proctosone; Triacomb; Tribiotic; ***Port.:*** Baciderma; Bacitracina-Neo†; Betnovate-N; Bienterico; Cicatrin; Conjunctilone; Conjunctilone-S; Davimicina†; Decadron com Neomicina; Dermimade Bacitracina†; Dermobiotico†; Dermovate-NN†; Dexaval N; Dexaval O; Dimicina; Distop; FML Neo; Kenacomb; Leuco Hubber†; Meocil; Neo-Davisolona; Neo-Preocil; Otomize†; Otosporin; Pimafucort; Plastenan Neomicina†; Polydexa; Predniderma†; Synalar N; Zotinar-N; ***Rus.:*** Anauran (Анауран); Baneocin (Банеоцин); Dexona (Дексона); Flucinar N (Флуцинар Н); Maxitrol (Макситрол); Pimafucort (Пимафукорт); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Polygynax (Полижинакс); Terzynan (Тержинан); ***S.Afr.:*** Betanoid N†; Betnesol-N; Betnovate-N; Cicatrin; Covomycin; Covomycin-D; FML Neo; Kenacomb; Maxitrol; Naseptin; Nasomixin†; Neo-Medrol; Neoderm; Neopan; Neosporin†; Otosporin; Synalar N; Trialone; Vibrocil; ***Singapore:*** Baneocin; Batramycin; Besone-N; Celestoderm-V with Neomycin†; Dextracin; Fast Powder; Flunolone; Kenacomb†; Maxitrol; Neo-Hydro; Neo-Medrol; Pivalone Neomycin†; Polybamycin; Polydexa; Polygynax; Predmycin-P†; ***Spain:*** Anasilpiel; Antihemorroidal; Bacisporin; Banedif; Bexicortil; Blastoestimulina; Cilinafosal Hidrocortisona; Cilinafosal Neomicina; Coliriocilina Espectro†; Coliriocilina Prednisona; Creanolona; Decadran Neomicina†; Dermisone Tri Antibiotic; Dermo Hubber; Dermomycose Talco; Edifaringen; Flodermol; Fludronef; Gingilone; Grietalgen Hidrocort†; Intradermo Cort Ant Fung†; Iruxol Neo; Leuco Hubber; Liquipom Dexa Antib; Maxitrol; Menaderm Neomicina; Midacina; Neo Analsona; Neo Bacitrin; Neo Hubber; Neocones; Neodexa; Oftalmowell; Oto Difusor†; Oto Vitna†; Otonina†; Otosporin; Oxidermiol Enzima†; Panotile; Phonal; Plaskine Neomicina; Poly Pred; Pomada Antibiotica; Positon; Prednisona Neomicina; Rino Dexa; Rinobanedif; Rinovel; Spectrocin†; Sulfintestin Neomicina; Synalar Nasal; Synalar Neomicina; Synalar Otico; Tisuderma; Tivitis; Trigon Topico; Tulgrasum Antibiotico; Vinciseptil Otico; ***Swed.:*** Betnovat med Neomycin; Celeston valerat comp†; Decadron cum neomycin†; Isopto Biotic†; ***Switz.:*** Bacimycin; Baneopol; Batramycine; Betnovate-N; Cicatrex; Cortifluid N; Cortimycine; Dermovate-NN; FML Neo; Maxitrol; Mycinopred; Mycolog N; Mycolog†; Nebacetin; Neo-Hydro; Neocones; Neosporin; Neotracin; Otosporin; Otospray†; Panotile; Pivalone compositum; Polydexa; Prednitracin†; Spersapolymyxin; Synalar N; Topsym polyvalent; Tyrocombine; ***Thai.:*** Archidex; Bacal; Banocin; Basina; Besone-N; Beta-Dipo†; Beta-N; Betama-EN†; Betameth-N; Bethasone-N; Betnovate-N; Biochin†; Cadexcin-N†; Clinivate-N; Coccila†; Decadron with Neomycin†; Dermacombin; Derzid-N; Dexacin; Dexasil†; Dexoph; Dexylin; Disento; Eyedex; Farakil; Fluciderm-N†; Flunolone; Fluonid-N; FML Neo†; Izac†; Kenacomb; Maxitrol; Medcin; My-B; Mybacin; Mybacin Dermic; Mysolone-N; Neo-Medrol; Neo-Optal; Neodex; Neopred†; Neosporin†; Neozolone; Opsacin†; Opsardex†; Otosamthong; Otosporin†; Polyoph; Predex†; Predmycin†; Prednisil-N; Prednisil†; Spersapolymyxin; Supracortin 3†; Supralan-N; Synalar N; Topaben-N; Trofodermin†; Unipred; Valbet-N; Vesoph; Xanalin; ***Turk.:*** Cebemyxine; Cormisin; Neosporin; Thiocilline; ***UAE:*** Panderm; ***UK:*** Audicort†; Betnesol-N; Betnovate-N; Cicatrin†; Dermovate-NN; Graneodin†; Gregoderm†; Maxitrol; Naseptin; Neosporin; Otomize; Otosporin; Predsol-N; Synalar N; Tri-Adcortyl; Vista-Methasone N; ***USA:*** Ak-Neo-Dex; Ak-Spore; Ak-Trol†; Coly-Mycin S Otic; Cortatrigen; Cortimycin; Cortisporin; Cortisporin-TC; Cortisporin†; Dexacidin†; Dexacine†; Dexasporin; Ear-Eze; Lanabiotic†; LazerSporin-C; Maxitrol; Mycitracin†; Neo-Dexameth†; Neocin; NeoDecadron†; Neodexasone; Neopolydex; Neosporin; Neosporin + Pain Relief; Neosporin GU; Neosporin†; Neotricin HC; Octicair†; Ocu-Spore-B; Ocu-Spor-G; Ocu-Trol; Ocutricin; Otic-Care; OtiTricin; Otocort; Otomycin-HPN; Otosporin; Pediotic; Poly-Dex; Poly-Pred; Polymycin; Spectrocin Plus†; Tri-Biozene; UAD-Otic; ***Venez.:*** Baycuten N; Bratofil c Neomicina; Clinal†; Decadron†; Decaven; Dermabiotic; Dexaneol†; Flutalon†; Maxicort; Maxitrol; Neo-Synalar con Neomicina; Neo-Synalar†; Neoflu con Neomicina†; Otocort; Poli-Otico.

Netilmicin Sulfate *(USAN, rINNM)*

N[1]-Ethylsissomicin; Netilmicin Sulphate *(BANM)*; Nétilmicine, sulfate de; Netilmicini sulfas; Netilmicino sulfatas; Netilmicinsulfat; Netilmicin-sulfát; Netilmicin-szulfát; Netilmisiinisulfaatti; Netilmisin sülfat; Netylmycyny siarczan; Sch-20569; Sulfato de netilmicina. 4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-1-*N*-ethylstreptamine sulphate.

Нетилмицина Сульфат

$(C_{21}H_{41}N_5O_7)_2,5H_2SO_4 = 1441.6.$

CAS — 56391-56-1 (netilmicin); 56391-57-2 (netilmicin sulfate).

ATC — J01GB07; S01AA23.

ATC Vet — QJ01GB07; QS01AA23.

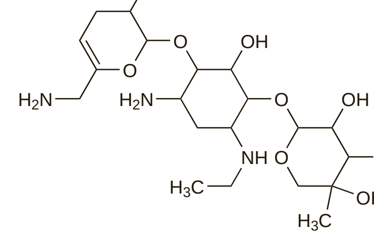

(netilmicin)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Netilmicin Sulphate). A substance obtained by synthesis from sisomicin. The potency is not less than 650 units/mg, calculated with reference to the dried substance. A white or yellowish-white, very hygroscopic, powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Netilmicin Sulfate). The potency is equivalent to not less than 595 micrograms of netilmicin per milligram, calculated on the dried basis. A white to pale yellowish-white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. pH of a solution in water containing the equivalent of netilmicin 4% is between 3.5 and 5.5. Store in airtight containers. Protect from moisture.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including netilmicin, with beta lactams, see under Gentamicin Sulfate, p.282. Netilmicin is also reported to be incompatible with furosemide, heparin, and vitamin B complex.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Some studies suggest that netilmicin is less nephrotoxic and ototoxic than gentamicin or tobramycin, although others have not found any significant differences in their toxicity.

It has been suggested that peak plasma concentrations of netilmicin should not exceed 12 micrograms/mL for prolonged therapy, and troughs should be below 2 micrograms/mL.

Effects on the cardiovascular system. Severe hypotension was associated with netilmicin in a patient undergoing artificial ventilation.[1] Hypotensive episodes were of short duration and coincided with netilmicin injection. They almost disappeared when sedation was stopped.

1. Rygnestad T. Severe hypotension associated with netilmicin treatment. *BMJ* 1997; **315:** 31.

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. It is active against a similar range of organisms although it is also reported to have some activity against *Nocardia*. It may be somewhat less effective against *Pseudomonas aeruginosa*. It is not degraded by all of the enzymes responsible for aminoglycoside resistance, and may be active against some strains resistant to gentamicin or tobramycin, but this is less marked than with amikacin: for example, gentamicin-resistant *Providencia*, *Pseudomonas*, and *Serratia* are usually also netilmicin-resistant. Between about 5 and 20% of Gram-negative isolates are reported to be resistant to netilmicin.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

After intramuscular injection of netilmicin, peak plasma concentrations are achieved within 0.5 to 1 hour, and concentrations of about 7 micrograms/mL have been reported following doses of 2 mg/kg; similar concentrations are obtained after intravenous infusion of the same dose over 1 hour. Peak concentrations after rapid intravenous injection may transiently be 2 or 3 times higher than those following infusion. Standard, once-daily doses may produce transient peak concentrations of 20 to 30 micrograms/mL. In multiple dosing studies, netilmicin in usual doses every 12 hours produced steady-state concentrations on the second day which were less than 20% higher than those seen after the first dose.

The half-life of netilmicin is usually 2.0 to 2.5 hours. About 80% of a dose is excreted in the urine within 24 hours.

Uses and Administration

Netilmicin is a semisynthetic aminoglycoside antibiotic with actions and uses similar to those of gentamicin (p.284). It may be used as an alternative to amikacin (p.201) in the treatment of infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. As with gentamicin, netilmicin may be used with penicillins and with cephalosporins; the injections should be given separately.

Netilmicin is given as the sulfate but doses are expressed in terms of the equivalent amount of base; 1.5 g of netilmicin sulfate is equivalent to about 1 g of netilmicin. It is usually given intramuscularly in doses of 4 to 6 mg/kg daily as a single dose; alternatively, it may be given in equally divided doses every 8 or 12 hours; for the control of life-threatening infections, up to 7.5 mg/kg may be given daily in divided doses every 8 hours for short periods. In the management of urinary-tract infections, a single daily dose of 150 mg for 5 days may be given; for complicated urinary-tract infections, 3 to 4 mg/kg daily in divided doses every 12 hours has been given. A single dose of 300 mg has been licensed for gonorrhoea (p.191).

The same doses may be given by slow intravenous injection over 3 to 5 minutes or infused intravenously over 0.5 to 2 hours in 50 to 200 mL of infusion fluid; proportionately less fluid should be given to children.

Treatment with netilmicin is usually given for 7 to 14 days. Peak plasma concentrations below 12 micrograms/mL and troughs below 2 micrograms/mL have been recommended for divided daily dose regimens.

Dosage recommendations in infants and children vary somewhat. One regimen is 7.5 to 9 mg/kg daily in infants and neonates older than 1 week, and 6 to 7.5 mg/kg daily in older children, both given in divided doses every 8 hours. Premature infants and neonates less than 1 week old may be given 6 mg/kg daily in divided doses every 12 hours. An alternative regimen is 4 to 6.5 mg/kg daily in neonates less than 6 weeks of age, in divided doses every 12 hours, and 5.5 to 8 mg/kg daily in divided doses every 8 or 12 hours in older infants and children.

Dosage should be adjusted in all patients according to plasma-netilmicin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284.

Preparations

USP 31: Netilmicin Sulfate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Netira†; ***Austral.:*** Netromycin†; ***Austria:*** Certomycin; ***Belg.:*** Netromycine†; ***Braz.:*** Netromicina; ***Canad.:*** Netromycin†; ***Cz.:*** Netromycine; Nettacin; ***Denm.:*** Netilyn†; ***Fin.:*** Netilyn; ***Fr.:*** Netromicine; ***Ger.:*** Certomycin; ***Gr.:*** Netromycin; Zaby; ***Hong Kong:*** Netromycin; ***Hung.:*** Netromycine; ***India:*** Netromycin; Netspan; ***Indon.:*** Netromycin; ***Irl.:*** Netillin†; ***Ital.:*** Nettacin; Nettavisc; Zetamicin; ***Malaysia:*** Netromycin; ***Mex.:*** Neticin†; Netromicina; ***Neth.:*** Netromycine; ***Norw.:*** Netilyn; ***NZ:*** Netromycin†; ***Philipp.:*** Keunmixin; Netromycin; ***Pol.:*** Netromycine; ***Port.:*** Netromicina; Tilcin; ***S.Afr.:*** Netromycin; ***Spain:*** Netrocin†; ***Swed.:*** Netilyn; ***Switz.:*** Netromycine; ***Thai.:*** Bactrocin; Nelin; Netil; Netromycin; ***Turk.:*** Netira; Netromycine; ***UK:*** Netillin†; ***Venez.:*** Netromicina.

Multi-ingredient: ***Ital.:*** Netildex.

Nifuroxazide *(rINN)*

Nifuroksatsidi; Nifuroksazid; Nifuroksazidas; Nifuroxazid; Nifuroxazida; Nifuroxazidum. 2′-(5-Nitrofurfurylidene)-4-hydroxybenzohydrazide.

Нифуроксазид

$C_{12}H_9N_3O_5$ = 275.2.

CAS — 965-52-6.

ATC — A07AX03.

ATC Vet — QA07AX03.

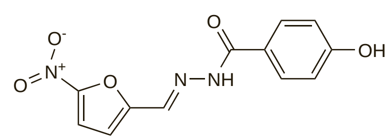

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nifuroxazide). A bright yellow crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Profile

Nifuroxazide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It is given orally in a dose of 800 mg daily in divided doses in the treatment of colitis and diarrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Bacifurane†; Ercefuryl; ***Braz.:*** Passifuril; ***Chile:*** Diarfin†; ***Cz.:*** Ercefuryl; ***Fr.:*** Bacterix; Bifix; Diafuryl; Ediston; Ercefuryl; Erceryl; Lumifurex; Panfurex; Septidiaryl; ***Gr.:*** Ercefuryl; ***Hong Kong:*** Ercefuryl; Panfurex; ***Indon.:*** Fuzide; Nifudiar; Nifural; ***Ital.:*** Diarret†; ***Mex.:*** Akabar; Diarim†; Eskapar; Topron; ***Philipp.:*** Ercefuryl; ***Rus.:*** Enterofuryl (Энтерофурил); ***Singapore:*** Niraben; ***Thai.:*** Debby†; Ercefuryl; Erfuzide; ***Turk.:*** Diafuryl; Durisal; Endosin; Ercefuryl; Erfulyn; Furil; Nifuryl; Nufro.

Multi-ingredient: ***Chile:*** Diaren; Diarfin†; Enterol Con Nifuroxacida; Imecol; Liracol; Nifurat†; Testisan; ***Mex.:*** Dia-Par Compuesto; Eskapar Compuesto.

Nifurpirinol *(USAN, rINN)*

Furpirinol; Nifurpirinolum; P-7138.

Нифурпиринол

$C_{12}H_{10}N_2O_4$ = 246.2.

CAS — 13411-16-0.

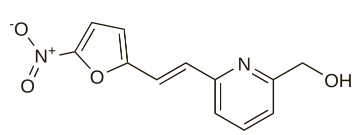

Profile

Nifurpirinol is a nitrofuran antimicrobial used in veterinary medicine for the treatment of bacterial and fungal infections in ornamental fish.

Nifurtoinol *(rINN)*

Hydroxymethylnitrofurantoin; Nifurtoïnol; Nifurtoinolum. 3-Hydroxymethyl-1-(5-nitrofurfurylideneamino)hydantoin.

Нифуртоинол

$C_9H_8N_4O_6$ = 268.2.

CAS — 1088-92-2.

ATC — J01XE02.

ATC Vet — QJ01XE02.

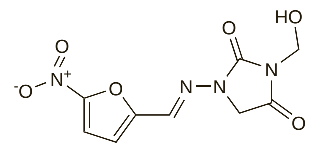

Profile

Nifurtoinol is a nitrofuran antibacterial with properties similar to those of nitrofurantoin (below) and is used in the treatment of urinary-tract infections. It is given orally in doses of up to 300 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Urfadyn PL.

Nifurzide *(rINN)*

Nifurzida; Nifurzidum. 5-Nitro-2-thiophenecarboxylic acid [3-(5-nitro-2-furyl)allylidene]hydrazide.

Нифурзид

$C_{12}H_8N_4O_6S$ = 336.3.

CAS — 39978-42-2.

ATC — A07AX04.

ATC Vet — QA07AX04.

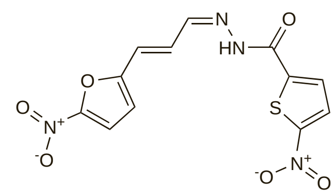

Profile

Nifurzide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It has been given orally in the treatment of diarrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Ricridene†.

Nisin

E234; Nisina.

Низин

CAS — 1414-45-5.

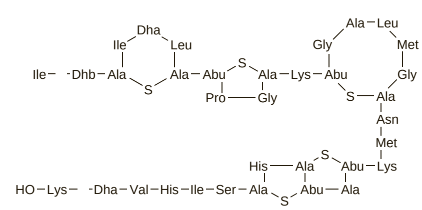

Abu = α-aminobutyric acid
Dha = dehydroalanine
Dhb = dehydrobutyrine

Profile

Nisin is a polypeptide antibacterial produced by *Lactococcus lactis* (*Streptococcus lactis*). It is used as a food preservative.

It has been investigated for the treatment of various infections, including those caused by *Helicobacter pylori* and *Clostridium difficile*.

Nitrofurantoin *(BAN, rINN)*

Furadoninum; Nitrofurantoiini; Nitrofurantoína; Nitrofurantoina; Nitrofurantoinas; Nitrofurantoïne; Nitrofurantoinum. 1-(5-Nitrofurfurylideneamino)hydantoin; 1-(5-Nitrofurfurylideneamino)imidazolidine-2,4-dione.

Нитрофурантоин

$C_8H_6N_4O_5$ = 238.2.

CAS — 67-20-9 (anhydrous nitrofurantoin); 17140-81-7 (nitrofurantoin monohydrate).

ATC — J01XE01.

ATC Vet — QJ01XE01.

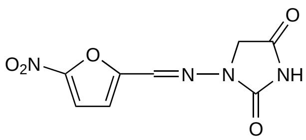

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Int. and *US* specify anhydrous or monohydrate.

Ph. Eur. 6.2 (Nitrofurantoin). A yellow, odourless or almost odourless, crystalline powder or crystals. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store at a temperature not exceeding 25°. Protect from light.

USP 31 (Nitrofurantoin). It is anhydrous or contains one molecule of water of hydration. Lemon-yellow, odourless crystals or fine powder. Nitrofurantoin and its solutions are discoloured by alkalis and by exposure to light, and are decomposed on contact with metals other than stainless steel or aluminium. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store in airtight containers. Protect from light.

Adverse Effects

The estimated incidence of adverse effects with nitrofurantoin has varied enormously, but may be around 10% overall; an incidence of serious reactions of about 0.001% for pulmonary, and 0.0007% for neurological reactions has been suggested. The most common adverse effects of nitrofurantoin involve the gastrointestinal tract. They are dose-related and generally include nausea, vomiting, and anorexia; abdominal pain and diarrhoea occur less frequently. It has been reported that adverse effects on the gastrointestinal tract are less common when nitrofurantoin is given in a macrocrystalline form or with food.

Neurological adverse effects include headache, drowsiness, vertigo, dizziness, nystagmus, and benign intracranial hypertension. Severe and sometimes irreversible peripheral neuropathy has developed, particularly in patients with renal impairment and in those given prolonged therapy.

Hypersensitivity reactions such as skin rashes, urticaria, pruritus, fever, sialadenitis, and angioedema may occur. Anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pancreatitis, a lupus-like syndrome, myalgia, and arthralgia have also been reported. Patients with a history of asthma may experience acute asthmatic attacks.

Acute pulmonary sensitivity reactions characterised by sudden onset of fever, chills, eosinophilia, cough, chest pain, dyspnoea, pulmonary infiltration or consolidation, and pleural effusion may occur within hours to a few days of beginning therapy, but they usually resolve on stopping treatment.

Subacute or chronic pulmonary symptoms including interstitial pneumonitis and pulmonary fibrosis may develop more insidiously in patients on long-term therapy and the latter are not always reversible, particularly if therapy is continued after onset of symptoms.

Hepatotoxicity including cholestatic jaundice, hepatitis, and hepatic necrosis may develop rarely, particularly in women, and may represent a hypersensitivity reaction. Other adverse effects include megaloblastic anaemia, leucopenia, granulocytopenia or agranulocytosis, thrombocytopenia, aplastic anaemia, and haemolytic anaemia in persons with a genetic G6PD deficiency. Transient alopecia has been reported.

Nitrofurantoin may cause a brownish discoloration of the urine.

There is limited evidence from *animal* studies that nitrofurantoin may be carcinogenic, although this has not been shown conclusively in humans.

◊ References.

1. Koch-Weser J, *et al.* Adverse reactions to sulfisoxazole, sulfamethoxazole, and nitrofurantoin: manifestations and specific reaction rates during 2118 courses of therapy. *Arch Intern Med* 1971; **128:** 399–404.
2. Holmberg L, *et al.* Adverse reactions to nitrofurantoin: analysis of 921 reports. *Am J Med* 1980; **69:** 733–8.
3. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. *BMJ* 1982; **284:** 1440–2.
4. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* 1985; **19:** 540–7.
5. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol (Baltimore)* 2004; **172:** 448–53.

Effects on the lungs. References[1,2] to pulmonary toxicity associated with long-term nitrofurantoin treatment.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Pulmonary toxicity with long-term nitrofurantoin. *Aust Adverse Drug React Bull* 2004; **23:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.htm (accessed 11/01/08)
2. Mendez JL, *et al.* Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005; **80:** 1298–1302.

Precautions

Nitrofurantoin should not be given to patients with renal impairment since antibacterial concentrations in the urine may not be attained and toxic concentrations in the plasma can occur. Nitrofurantoin is also contra-indicated in patients known to be hypersensitive to nitrofurans, in those with G6PD deficiency, and in infants (in the UK it is contra-indicated below 3 months of age, though the USA permits use from 1 month old).

Nitrofurantoin should be used with care in the elderly, who may be at increased risk of toxicity, particularly acute pulmonary reactions. All patients undergoing prolonged therapy should be monitored for changes in pulmonary function, and the drug withdrawn at the first signs of pulmonary damage. Care is required in patients with pre-existing pulmonary, hepatic, neurological, or allergic disorders, and in those with conditions (such as anaemia, diabetes mellitus, electrolyte imbalance, debility, or vitamin B deficiency) which may predispose to peripheral neuropathy. Nitrofurantoin should be withdrawn if signs of peripheral neuropathy develop. Although hepatic reactions such as hepatitis, cholestatic jaundice, and hepatic necrosis rarely occur, fatalities have been reported. Patients should be monitored, and the drug stopped immediately if hepatitis occurs.

Nitrofurantoin may cause false positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics considers that, although nitrofurantoin is excreted into breast milk, it is usually compatible with breast feeding, but caution is necessary in breast-fed infants with G6PD deficiency.[1] The *BNFC* suggests that the amount ingested may be enough to produce haemolysis in G6PD-deficient infants; it recommends that nitrofurantoin should be avoided in mothers who are breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 11/01/08)

Porphyria. Nitrofurantoin has been associated with acute attacks of porphyria and is considered to be unsafe in porphyric patients.

Pregnancy. Licensed product information contraindicates the use of nitrofurantoin in pregnant patients at term (38 to 42 weeks' of gestation), or during labour and delivery, because of the possibility of producing haemolytic anaemia in the neonate.

Interactions

Nitrofurantoin and the quinolone antibacterials are antagonistic *in vitro* but the clinical significance is unknown. The antibacterial activity of nitrofurantoin may be decreased in the presence of carbonic anhydrase inhibitors and other drugs that alkalinise the urine.

Probenecid or sulfinpyrazone should not be given with nitrofurantoin as they may reduce its excretion. Magnesium trisilicate may reduce the absorption of nitrofurantoin but it is not clear whether this applies to other antacids.

Antiepileptics. For reference to the effect of nitrofurantoin on *phenytoin*, see p.498.

Antifungals. An elderly patient who had been taking nitrofurantoin daily for 5 years developed combined hepatic and pulmonary toxicity 2 months after also starting *fluconazole* therapy.[1] Although either drug may have caused the hepatic toxicity, possible pharmacokinetic changes induced by an interaction with fluconazole may have precipitated the nitrofurantoin-induced pulmonary toxicity.

1. Linnebur SA, Parnes BL. Pulmonary and hepatic toxicity due to nitrofurantoin and fluconazole treatment. *Ann Pharmacother* 2004; **38:** 612–16.

Hormonal contraceptives. For mention of a possible decrease in contraceptive efficacy when nitrofurantoin was used with oral contraceptives, see under Hormonal Contraceptives, p.2068.

Antimicrobial Action

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens. The mode of action is uncertain but appears to depend on the formation of reactive intermediates by reduction; this process occurs more efficiently in bacterial than in mammalian cells.

It is effective against the enterococci *in vitro*, as well as various other Gram-positive species including staphylococci, streptococci, and corynebacteria, although this is of little clinical significance. Most strains of *Escherichia coli* are particularly sensitive to nitrofurantoin but *Enterobacter* and *Klebsiella* spp. are less susceptible and some may be resistant. *Pseudomonas aeruginosa* is resistant as are most strains of *Proteus* spp.

Nitrofurantoin is most active in acid urine, and if the pH exceeds 8 most of the antibacterial activity is lost. Resistance rarely develops during nitrofurantoin treatment but may occur during prolonged treatment. Plasmid-encoded resistance has been reported in *E. coli*. Resistance may be due to the loss of nitrofuran reductases which generate the active intermediates.

Pharmacokinetics

Nitrofurantoin is readily absorbed from the gastrointestinal tract. The absorption rate is dependent on crystal size. The macrocrystalline form has slower dissolution and absorption rates, produces lower serum concentrations than the microcrystalline form, and takes longer to achieve peak concentrations in the urine. The presence of food in the gastrointestinal tract may increase the bioavailability of nitrofurantoin and prolong the duration of therapeutic urinary concentrations. Preparations of nitrofurantoin from different sources may not be bioequivalent, and care may be necessary if changing from one brand to another.

On absorption, concentrations in blood and body tissues are low because of rapid elimination, and antibacterial concentrations are not achieved. Nitrofurantoin crosses the placenta and the blood-brain barrier and traces have been detected in breast milk. There is some disagreement about the degree of protein binding, and although figures of up to about 60% are quoted by some sources, others suggest that the figure should be as much as 90%. The plasma half-life is reported to range from 0.3 to 1 hour.

Nitrofurantoin is metabolised in the liver and most body tissues while about 30 to 40% of a dose is excreted rapidly in the urine as unchanged nitrofurantoin. Some tubular reabsorption may occur in acid urine. Average doses give a concentration of 50 to 200 micrograms/mL in the urine in patients with normal renal function.

Uses and Administration

Nitrofurantoin is a nitrofuran antibacterial that is used in the treatment of uncomplicated lower urinary-tract infections (p.199), including prophylaxis or long-term suppressive therapy in recurrent infection.

It is given orally, in a usual dose of 50 to 100 mg four times daily, with food or milk. Treatment is usually continued for 7 days. A dual-release formulation, consisting of macrocrystalline nitrofurantoin and nitrofurantoin monohydrate, is available in some countries and is given in a dose of 100 mg twice daily. A usual long-term prophylactic dose is 50 to 100 mg at bedtime.

For details of doses in children, see below.

◊ Reviews.

1. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs* 2001; **61:** 353–64.

Administration in children. In the UK, nitrofurantoin may be given to children aged 3 months to 12 years for the *treatment* of urinary-tract infection in a usual oral dose of 3 mg/kg daily given in 4 divided doses; 1 mg/kg may be given at night for long-term *prophylactic* therapy. However, a systematic review[1] concluded, on the basis of the rather low-grade evidence available, that the adverse effects of nitrofurantoin may outweigh its benefits and render it unacceptable for long-term therapy.

Higher oral doses of 5 to 7 mg/kg daily in 4 divided doses are recommended for the *treatment* of urinary-tract infection in the USA in children aged 1 month and above; for long-term *prophylactic* therapy 1 mg/kg daily given in one or two divided doses is considered adequate.

Older children may be given usual adult doses (see above).

1. Williams GJ, *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/01/08).

Preparations

BP 2008: Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets;
USP 31: Nitrofurantoin Capsules; Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Furadantina; ***Austral.:*** Furadantin; Macrodantin; Ralodantin†; ***Austria:*** Furadantin; ***Belg.:*** Furadantine; ***Braz.:*** Hantina; Macrodantina; Nitrofen; Urogem; ***Canad.:*** Macrobid; Macrodantin†; Novo-Furantoin; ***Chile:*** Macrodantina; Macrosan; Matidan; ***Cz.:*** Furantoin†; Nifurantin†; ***Fin.:*** Nitrofur-C; ***Fr.:*** Furadantine; Furadoine; Microdoine; ***Ger.:*** Furadantin; Nifurantin; Nifuretten; Uro-Tablinen; ***Gr.:*** Furolin; ***India:*** Furadantin; ***Irl.:*** Furadantin; Macrobid; Macrodantin; ***Israel:*** Macrodantin†; Uvamin; ***Ital.:*** Furadantin; Furedan; Furil; Macrodantin; Neo-Furadantin; ***Mex.:*** Biofurin; Furadantina; Furitex; Futroken; Macrodantina; Macrofurin; Promac; Suronit; ***Neth.:*** Furabid; Furadantine MC; ***Norw.:*** Furadantin; ***NZ:*** Furadantin; Nifuran; ***Philipp.:*** Macrodantin; ***Pol.:*** Siraliden; ***Port.:*** Furadantina; ***S.Afr.:*** Furadantin; Macrodantin; ***Spain:*** Furantoina; Furobactina; ***Swed.:*** Furadantin; ***Switz.:*** Furadantine; Urodin; Uvamine retard; ***Turk.:*** Piyeloseptyl; ***UK:*** Furadantin; Macrobid; Macrodantin; ***USA:*** Furadantin; Macrobid; Macrodantin; ***Venez.:*** Furadina†; Macrodantina.

Multi-ingredient: ***Arg.:*** Bagociletas con Anestesia; Bagociletas sin Anestesia†; ***Braz.:*** Urofen†; Uropac; ***Ger.:*** Nifurantin B 6; Urospasmon sine†; Urospasmon†; ***India:*** Nephrogesic; ***Mex.:*** Furanton†; ***Turk.:*** Uriseptin.

Nitrofurazone *(BAN)*

Nitrofural *(pINN)*; Furacilinum; Nitrofuraali; Nitrofurál; Nitrofuralis; Nitrofuralum; Nitrofuratsoni; Nitrofurazon; Nitrofurazonum. 5-Nitro-2-furaldehyde semicarbazone.

Нитрофурал

$C_6H_6N_4O_4$ = 198.1.
CAS — 59-87-0.
ATC — B05CA03; D08AF01; D09AA03; P01CC02; S01AX04; S02AA02.
ATC Vet — QB05CA03; QD08AF01; QD09AA03; QG01AX90; QP51AC02; QS01AX04; QS02AA02.

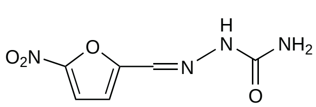

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Nitrofural; Nitrofurazone BP 2008). A yellow or brownish-yellow, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.0. Protect from light.

USP 31 (Nitrofurazone). A lemon-yellow, odourless crystalline powder. It darkens slowly on exposure to light. Soluble 1 in 4200 of water, 1 in 590 of alcohol, and 1 in 350 of propylene glycol; practically insoluble in chloroform and in ether; soluble in dimethylformamide; slightly soluble in polyethylene glycol mixtures. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Sterilisation. Autoclaving gauze dressings impregnated with nitrofurazone, as recommended by the US manufacturer, resulted in a greater than 10% loss of the drug.[1] Since the spectroscopic assay used may not distinguish between nitrofurazone and some of its degradation products, the degree of degradation may have been greater than this.

1. Phillips C, Fisher E. Effect of autoclaving on stability of nitrofurazone soluble dressing. *Am J Health-Syst Pharm* 1996; **53:** 1169–71.

Adverse Effects

Sensitisation and generalised allergic skin reactions may be produced by topical nitrofurazone.

Nitrofurazone is a toxic drug when given orally and serious adverse effects include severe peripheral neuropathy; haemolysis may occur in patients with G6PD deficiency. Nitrofurazone in high oral doses is carcinogenic in *rats.*

Precautions

Nitrofurazone is contra-indicated in patients with known hypersensitivity. Preparations containing macrogols should be used with caution in patients with renal impairment since macrogols can be absorbed and their accumulation in such patients may result in symptoms of further impairment.

Oral nitrofurazone should be used with caution in patients with G6PD deficiency because of the risk of haemolysis.

Antimicrobial Action

Nitrofurazone is a nitrofuran derivative with a broad spectrum of antibacterial activity, but with little activity against *Pseudomonas* spp. It also has antitrypanosomal activity.

Uses and Administration

Nitrofurazone is a nitrofuran derivative that is used topically for wounds, burns, ulcers, and skin infections, and for the preparation of surfaces before skin grafting. It is usually applied in a concentration of 0.2% in a water-soluble or water-miscible basis. A solution of nitrofurazone is used for bladder irrigation.

Urinary catheters impregnated with nitrofurazone, to reduce bacterial colonisation and infection, are available in some countries.

Preparations

USP 31: Nitrofurazone Ointment; Nitrofurazone Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Furacin; Ivoran Pilot†; Nitromed; ***Belg.:*** Furacine; ***Braz.:*** Alivioderm†; Caziderm; Cleanbac†; Furacin; Sensiderme; ***Chile:*** Demodek†; Furacin; ***Ger.:*** Furacin-Sol; ***India:*** Furacin; ***Mex.:*** Furacin; Kufro; Nifurol; Probizal; Vulnizol; ***Neth.:*** Furacine; ***Philipp.:*** Furacin; ***Port.:*** Rayonfur; ***S.Afr.:*** Furacin; Furex; Germex; ***Spain:*** Furacin; ***Thai.:*** Bactacin; Mytrocin; Polycin; ***Turk.:*** Dermikolin; Furacin; Furaderm; Furazol; ***USA:*** Furacin†; ***Venez.:*** Furacin; Furfuril; Fuxal; Polifur†.

Multi-ingredient: ***Arg.:*** Fadanasal; Neo Pelvicillin; O-Biol; Vagicural; Vagisan; Vagisan Compuesto; Vislus; ***Braz.:*** Nitrileno; Nitrolerg†; Otodol†; ***India:*** Furacin-S; ***Ital.:*** Furotricina; ***Mex.:*** Madecassol C; Madecassol N; ***Spain:*** Dertrase; ***Thai.:*** Denson.

Nitroxoline *(BAN, pINN)*

Nitroxolina; Nitroxolinum. 5-Nitroquinolin-8-ol.

Нитроксолин

$C_9H_6N_2O_3$ = 190.2.
CAS — 4008-48-4.
ATC — J01XX07.
ATC Vet — QJ01XX07.

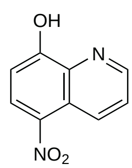

Profile

Nitroxoline has antibacterial and antifungal properties and is used in the treatment of urinary-tract infections in oral doses ranging from 80 to 250 mg three times daily before food. It has also been given with sulfamethizole.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nibiol†; ***Ger.:*** Cysto-Saar; ***Rus.:*** 5-Nitrox (5-Нитрокс); 5-Nok (5-Нок); ***S.Afr.:*** Nicene N.

Multi-ingredient: ***Braz.:*** Minazol.

Norfloxacin *(BAN, USAN, rINN)*

AM-715; *N*-Desmethylpefloxacin; MK-366; Norfloksacinas; Norfloksacyna; Norfloksasiini; Norfloksasin; Norfloxacine; Norfloxacino; Norfloxacinum. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

Норфлоксацин

$C_{16}H_{18}FN_3O_3$ = 319.3.
CAS — 70458-96-7.
ATC — J01MA06; S01AX12.
ATC Vet — QJ01MA06; QS01AX12.

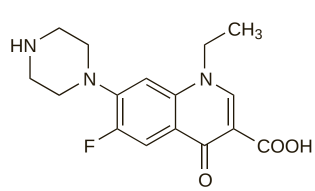

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Norfloxacin). A white or pale yellow, hygroscopic, photosensitive, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone. Store in airtight containers. Protect from light.

USP 31 (Norfloxacin). A white to pale yellow crystalline powder. Slightly soluble in water, in alcohol, and in acetone; freely soluble in acetic acid; sparingly soluble in chloroform; practically insoluble in ether; very slightly soluble in ethyl acetate and in methyl alcohol. Store in airtight containers. Protect from light.

Norfloxacin Pivoxil *(BANM, rINNM)*

Norfloxacine, Pivoxil de; Norfloxacini Pivoxil; Norfloxacino pivoxilo. Pivaloyloxymethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

Норфлоксацина Пивоксил

$C_{22}H_{28}FN_3O_5$ = 433.5.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Interactions

As for Ciprofloxacin, p.246.

Antimicrobial Action

As for Ciprofloxacin, p.246, although norfloxacin is less potent *in vitro.* Norfloxacin is not active against Chlamydiaceae, mycoplasmas, or mycobacteria.

Pharmacokinetics

About 30 to 40% of an oral dose of norfloxacin is absorbed. Peak plasma concentrations of about 1.5 micrograms/mL occur about 1 to 2 hours after a 400-mg oral dose; the presence of food can delay absorption. Norfloxacin is about 14% bound to plasma proteins. It is probably widely distributed, but information is limited. Norfloxacin penetrates well into tissues of the genito-urinary tract. It crosses the placenta. Relatively high concentrations are achieved in bile.

The plasma half-life is 3 to 4 hours and may be prolonged in renal impairment; a value of 6.5 hours or more has been reported when creatinine clearance is below 30 mL/minute per 1.73 m^2. About 30% of a dose is excreted unchanged in the urine within 24 hours, producing high urinary concentrations; norfloxacin is least soluble at a urinary pH of 7.5. Urinary excretion is by tubular secretion and glomerular filtration and is reduced by probenecid, although plasma concentrations of norfloxacin are not generally affected. Some metabolism occurs, possibly in the liver, and several metabolites have been identified in urine, some with antibacterial activity. About 30% of an oral dose is recovered from the faeces.

Uses and Administration

Norfloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243), but it is generally less potent *in vitro.*

Norfloxacin is used mainly in the treatment of urinary-tract infections (p.199) and for the treatment of gonorrhoea (p.191).

Norfloxacin is given orally at least 1 hour before, or 2 hours after, food or milk.

In urinary-tract infections the usual dose is 400 mg twice daily for 3 to 10 days. Treatment may need to be continued for up to 12 weeks in chronic relapsing urinary-tract infections; it may be possible to reduce the dose to 400 mg once daily if there is an adequate response within the first 4 weeks. A 28-day course of treatment with a dose of 400 mg twice daily should be given for acute or chronic bacterial prostatitis.

For details of reduced doses to be used in renal impairment, see below.

A single oral dose of 800 mg is given in the treatment of uncomplicated gonorrhoea.

Eye drops containing 0.3% of norfloxacin are used to treat eye infections.

The pivaloyloxymethyl salt of norfloxacin, norfloxacin pivoxil, is also used in some countries.

Administration in renal impairment. Doses of norfloxacin may need to be reduced in renal impairment; for urinary-tract infections, 400 mg once daily should be given to patients with a creatinine clearance of 30 mL/minute per 1.73 m^2 or less.

Preparations

BP 2008: Norfloxacin Eye Drops; Norfloxacin Tablets;
USP 31: Norfloxacin Ophthalmic Solution; Norfloxacin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bio Tarbun; Chibroxin†; Floxamicin; Floxatral; Memento NF; Norflol; Noroxin; Norsol; Parcetin; Ritromine; Uro-Linfol; Urofos; Uronovag; Uroseptal; Urotem; Uroxacin; Wenflox; Yanurax†; ***Austral.:*** Insensye; Norflohexal; Noroxin; Nufloxib; Roxin; ***Austria:*** Floxacin; Norflostad; Urobacid†; Zoroxin; ***Belg.:*** Chibroxol; Zoroxin; ***Braz.:*** Androfloxin; Chibroxin†; Flox†; Floxacin; Floxanor; Floxatom†; Floxatrat†; Floxilin†; Floxinol; Genitoflox; Neofloxin; Norf; Norflamin†; Norflox; Norfloxasan; Norfloxil; Norfloxmed; Norxacin†; Norxin; Quinoform; Respexil; Uritrat; Uroflox†; Uroplex†; Uroseptal; Uroxazol-N; ***Canad.:*** Apo-Norflox; Noroxin†; ***Chile:*** Chibroxin†; Fulgram; Noroxin†; Urekolin†; ***Cz.:*** Gyrablock; Nolicin; ***Denm.:*** Zoroxin†; ***Fin.:*** Lexinor†; Noroxin†; ***Fr.:*** Chibroxine; Noroxine; ***Ger.:*** Bactracid; Barazan; Chibroxin; Firin; Norflohexal; Norflosal; Norflox; Norflox-Azu†; Norflox-Puren†; Norfloxbeta; Norfluxx; ***Gr.:*** Alenbit; Constilax; Dirunez†; Fluseminal; Grenis; Lemorcan; Lorcamin; Norocin; Ovinol; Pistofil; Setanol; Sinobid; Sofasin; Steinaclox; Urobacid; Urospes-N; Vetamol; ***Hong Kong:*** Floxen; Janacin; Lexiflox; Lexinor†; Mitatonin; Rexacin†; Uroctal; ***Hung.:*** Nolicin; ***India:*** Bacigyl; Biofloxin; Norbactin; Norflox; Normax; ***Indon.:*** Pyrflox; ***Israel:*** Apirol; Chibroxin†; ***Ital.:*** Diperflox; Flossac; Fulgram†; Norflox; Noroxin; Renoxacin; Sebercim; Theanorf; Uticina; Utinor; ***Jpn:*** Baccidal; ***Malaysia:*** Chibroxin†; Floxen†; Janacin; Lexinor†; Norbactin†; Norfloxin; Norfloxinor†; Rexacin; Trizolin; Urinox; Urobacid; ***Mex.:*** Baxamed; Difoxacil; Floxacin; Microxin; Noflorox; Noroxin; Norquinol; Oranor; ***Neth.:*** Chibroxol; Noroxin; ***NZ:*** Noroxin; ***Philipp.:*** Euroflox; Lexinor; Norbactin; Nortram; Septinor; Uritracin; Urobacid; Utiflox; Utinor; Winaflox; ***Pol.:*** Chibroxin; Nolicin; ***Port.:*** Besflox; Chibroxol; Noroxin; Quinoflex†; Taflox†; Uroflox; ***Rus.:*** Gyrablock (Гираблок); Negaflox (Негафлокс); Nolicin (Нолицин); Norbactin (Норбактин); Norfacin (Норфацин); Norilet (Норилет); Normax (Нормакс); ***S.Afr.:*** Floxin; Noroxin; Utin; ***Singapore:*** Bexinor; Chibroxin†; Effectsal; Foxgoria; Gyrablock; Norbactin; Sefnor†; Trizolin†; Urobacid†; ***Spain:*** Amicrobin; Baccidal; Chibroxin; Esclebin; Espeden; Nalion; Norflok; Noroxin; Senro; Uroctal; Xasmun; ***Swed.:*** Lexinor; ***Switz.:*** Chibroxol†; Norflocine; Noroxin; Norsol; Noxufen; ***Thai.:*** BGB Norflox†; Foxin; Foxinon; Gonorcin; Janacin; Lexfor†; Lexinor; Loxone; M-Flox; Manoflox; Myfloxin; Noracin; Norbactin; Norcin; Norfcin; Norflo†; Norflocin; Norfloxin; Norfloxyl; Norsa†; Norxacin; Norxia; Noxine; Noxinor; Proxinor; Rexacin; Sefnor; Snoffocin; Trizolin†; Urinox; Uritracin; Vesxacin; Xacin; ***Turk.:*** Noroxin; ***UAE:*** Uroxin; ***UK:*** Utinor; ***USA:*** Noroxin; ***Venez.:*** Chibroxin†; Danilon; Norflosan†; Norfloval†; Norilet†; Noroxin.

Multi-ingredient: *Arg.:* Nor 2; Urotem Dol; ***India:*** Bacigyl-N†; Bioflox-TZ; NM Powder; Nor T; Norflox TZ; Normax TZ; Parabact; Powergyl; Tinvista-NF; ***Mex.:*** Mictasol.

Norvancomycin Hydrochloride

N-Demethylvancomycin; 56-Demethylvancomycin. (S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(amino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride.

$C_{65}H_{73}Cl_2N_9O_{24}$, HCl = 1471.7.
CAS — 91700-98-0 (norvancomycin).

Pharmacopoeias. In *Chin.*

Profile

Norvancomycin is a glycopeptide antibacterial with properties similar to those of vancomycin (p.358).

Novobiocin *(BAN, rINN)*

Crystallinic Acid; Novobiocina; Novobiocine; Novobiocinum; Novobiosiini; Novobiosin; PA-93; Streptonivicin; U-6591. 4-Hydroxy-3-[4-hydroxy-3-(3-methylbut-2-enyl)benzamido]-8-methylcoumarin-7-yl 3-*O*-carbamoyl-5,5-di-*C*-methyl-α-L-lyxofuranoside.

Новобиоцин

$C_{31}H_{36}N_2O_{11}$ = 612.6.
CAS — 303-81-1.

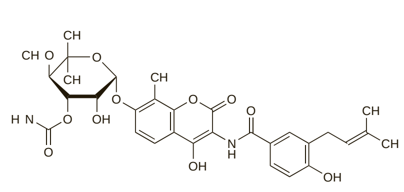

Description. Novobiocin is an antimicrobial substance produced by the growth of *Streptomyces niveus* and *S. spheroides* or related organisms.

Novobiocin Calcium *(BANM, rINNM)*

Calcii Novobiocinum; Calcium Novobiocin; Novobiocina cálcica; Novobiocine Calcique; Novobiocinum Calcium.

Кальций Новобиоцин

$(C_{31}H_{35}N_2O_{11})_2Ca$ = 1263.3.
CAS — 4309-70-0.

Novobiocin Sodium *(BANM, rINNM)*

Natrii Novobiocinum; Novobiocina sódica; Novobiocine Sodique; Novobiocinum Natricum; Sodium Novobiocin.

Натрий Новобиоцин

$C_{31}H_{35}N_2NaO_{11}$ = 634.6.
CAS — 1476-53-5.

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Novobiocin Sodium). A white or yellowish-white, odourless, hygroscopic crystalline powder. Freely soluble in water, in alcohol, in methyl alcohol, in glycerol, and in propylene glycol; practically insoluble in acetone, in chloroform, and in ether; slightly soluble in butyl acetate. pH of a 2.5% solution in water is between 6.5 and 8.5. Store in airtight containers.

Profile

Novobiocin is an antibacterial which is structurally related to coumarin. It is active against Gram-positive bacteria such as *Staphylococcus aureus* (including meticillin-resistant strains) and other staphylococci; *Enterococcus faecalis* is usually resistant but *E. faecium* may be sensitive. Some Gram-negative organisms including *Haemophilus influenzae* and *Neisseria* spp. are also susceptible, as are some strains of *Proteus*, but most of the Enterobacteriaceae are resistant. Its action is primarily bacteriostatic, although it may be bactericidal against more sensitive species at high concentrations. It is an inhibitor of DNA gyrase and is effective in eliminating plasmids, but resistance to novobiocin develops readily *in vitro* and during therapy.

Although novobiocin has been used alone or with other drugs such as rifampicin or sodium fusidate in the treatment of infections due to staphylococci and other susceptible organisms, it has been largely superseded by other drugs because of the problems of resistance and toxicity.

Novobiocin is a potent sensitiser and hypersensitivity reactions are relatively common; they include rashes, fever, and pruritus, and more serious reactions such as Stevens-Johnson syndrome and pneumonitis. Jaundice and liver damage have occurred, although apparent jaundice may be due to a yellow metabolite of the drug rather than hyperbilirubinaemia. Other adverse effects include eosinophilia, leucopenia, thrombocytopenia, agranulocytosis, and haemolytic anaemia; gastrointestinal disturbances are common.

Porphyria. Novobiocin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Ofloxacin *(BAN, USAN, rINN)*

DL-8280; Hoe-280; Ofloksacinas; Ofloksasiini; Ofloksasin; Ofloxacine; Ofloxacino; Ofloxacinum; RU-43280. (±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.

Офлоксацин

$C_{18}H_{20}FN_3O_4$ = 361.4.
CAS — 82419-36-1; 83380-47-6.
ATC — J01MA01; S01AX11.
ATC Vet — QJ01MA01; QS01AX11.

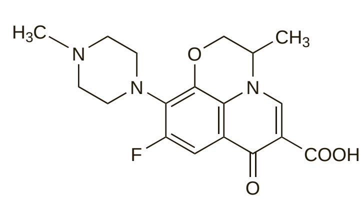

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ofloxacin). A pale yellow or bright yellow crystalline powder. Slightly soluble in water and in methyl alcohol; slightly soluble to soluble in dichloromethane; soluble in glacial acetic acid. Store in airtight containers. Protect from light.

USP 31 (Ofloxacin). Pale yellowish-white to light yellowish-white crystals or crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Ofloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de ofloxacino; Ofloxacine, Chlorhydrate d'; Ofloxacini Hydrochloridum.

Офлоксацина Гидрохлорид

$C_{18}H_{20}FN_3O_4$,HCl = 397.8.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, ofloxacin should be stopped.

A reduction in blood pressure may occur rarely after intravenous infusion. Similarly, sudden reductions in blood pressure may occur when intravenous ofloxacin is given with hypotensive drugs. Cardiovascular function should be monitored in such patients and in those also receiving barbiturate anaesthetics.

Certain medications may also increase these risks (see Interactions, below).

Breast feeding. The American Academy of Pediatrics has stated that no adverse effects have been seen in breast-fed infants whose mothers were receiving ofloxacin and that it is therefore usually compatible with breast feeding.[1] However, in a study[2] of 10 women given ofloxacin after termination of pregnancy, drug concentrations in breast milk were sufficiently high to recommend that the use of ofloxacin in lactating women should be avoided.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.

Interactions

As for Ciprofloxacin, p.246.

Use with drugs that alter blood-glucose concentrations with ofloxacin increases the risk of blood-glucose disturbances.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Ofloxacin is more active than ciprofloxacin against *Chlamydia trachomatis*. It is also active against *Mycobacterium leprae* as well as *M. tuberculosis* and some other *Mycobacterium* spp. Synergistic activity against *M. leprae* has been reported between ofloxacin and rifabutin.

The optically active *S*-(−)-isomer levofloxacin (p.292) has twice the activity of the racemate ofloxacin.

Resistance has been reported in some strains of *Neisseria gonorrhoeae*.

Pharmacokinetics

Ofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is almost 100% and a peak plasma concentration of about 3 to 5 micrograms/mL occurs 1 to 2 hours after an oral dose of 400 mg. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected.

About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.

The elimination of ofloxacin is biphasic; half-lives of about 4 to 5 and 20 to 25 hours have been reported for the 2 phases, respectively. In renal impairment values of 15 to 60 hours have been reported. There is limited metabolism to desmethyl and *N*-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites. From 4 to 8% of a dose may be excreted in the faeces.

Only small amounts of ofloxacin are removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Lamp KC, *et al.* Ofloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **22:** 32–46.

Uses and Administration

Ofloxacin is a fluoroquinolone antibacterial used similarly to ciprofloxacin (p.247). It is also used in *Chlamydia* or *Chlamydophila* infections including nongonococcal urethritis (p.166 and p.199) and in mycobacterial infections such as leprosy (p.176) and tuberculosis (see under Uses and Administration of Ciprofloxacin, p.248).

Ofloxacin is given orally as the base or by intravenous infusion as the hydrochloride. All doses are expressed in terms of the base; ofloxacin hydrochloride 220.2 mg is equivalent to about 200 mg of ofloxacin.

The usual oral or intravenous dose ranges from 200 mg daily to 400 mg twice daily depending on the severity and the nature of the infection. Oral doses of up to 400 mg may be given as a single dose, preferably in the morning. For intravenous use a 0.2% solution is infused over 30 minutes.

An oral dose of 200 mg twice daily for 3 days is suitable in women with acute uncomplicated cystitis. A 6-week course of treatment with an oral dose of 300 mg twice daily should be given for chronic bacterial prostatitis. Oral doses of 400 mg daily with clofazimine and minocycline *or* 400 mg monthly with rifampicin and minocycline have been recommended by WHO as alternative multidrug therapy regimens for multibacillary leprosy. As an alternative regimen for single-lesion paucibacillary leprosy WHO suggests a single dose of ofloxacin 400 mg with rifampicin and minocycline.

A single 400-mg dose of ofloxacin may be given by mouth for uncomplicated gonorrhoea.

Ofloxacin is used topically as 0.3% eye drops for the treatment of conjunctivitis and corneal ulcers caused by susceptible strains of bacteria. It is also used as 0.3% ear drops for the treatment of otitis externa and otitis media.

For details of reduced doses in hepatic or renal impairment, see below.

◊ Reviews.

1. Todd PA, Faulds D. Ofloxacin: a reappraisal of its antimicrobial activity, pharmacology and therapeutic use. *Drugs* 1991; **42:** 825–76.
2. Onrust SV, *et al.* Ofloxacin: a reappraisal of its use in the management of genitourinary tract infections. *Drugs* 1998; **56:** 895–928.
3. Simpson KL, Markham A. Ofloxacin otic solution: a review of its use in the management of ear infections. *Drugs* 1999; **58:** 509–31.
4. Wai TKH, Tong MCF. A benefit-risk assessment of ofloxacin otic solution in ear infection. *Drug Safety* 2003; **26:** 405–20.

Administration in hepatic impairment. The clearance of ofloxacin is reduced in patients with severe hepatic impairment or cirrhosis and lower doses should be used; a maximum dose of 400 mg daily has been recommended.

Administration in renal impairment. Lower doses of ofloxacin may be necessary in patients with renal impairment. After the usual initial dose (see above), subsequent doses are adjusted according to creatinine clearance (CC):

- CC 20 to 50 mL/minute: doses halved to 100 to 200 mg daily or the usual dose is given every 24 hours
- CC less than 20 mL/minute: dose reduced to 100 mg every 24 hours
- patients on haemodialysis or peritoneal dialysis: 100 mg every 24 hours

BCG toxicity. For mention of the possible use of ofloxacin to reduce the incidence of toxicity after BCG intravesicular instillation, see p.2206.

Preparations

USP 31: Ofloxacin Ophthalmic Solution; Ofloxacin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Floxil; Ingeflox; Klonalflox; Newflox; Oflox; Otoflox; Quinomed; Rafocilina; ***Austral.:*** Ocuflox; ***Austria:*** Floxal; Oflox; Tarivid; ***Belg.:*** Docofloxacine; Tarivid; Trafloxal; ***Braz.:*** Floxina; Floxstat; Genoxacin; Nostil; Oflox; Ofloxan†; Ofloxin†; Quinoxan†; ***Canad.:*** Apo-Oflox; Floxin; Ocuflox; ***Chile:*** Ifos†; Oflox; Poenflox; ***Cz.:*** Floxal; Ofloxin; Tarivid; Taroflox; Zanocin; ***Denm.:*** Exocin; Tarivid; ***Fin.:*** Exocin; Tarivid; ***Fr.:*** Exocine; Monoflocet; Oflocet; ***Ger.:*** Floxal; Gyroflox; Oflo; Oflodura; Oflohexal; Oflox; Ofloxbeta; Tarivid; Uro-Tarivid; ***Gr.:*** Ermofan; Exocin; Grenis-Oflo; Hetacloxacin†; Tabrin; Urimax†; ***Hong Kong:*** Flovid; Marfloxacin; Ofus; Puiritol; Quotavil; Tarivid; Viotisone; ***Hung.:*** Floxal; Oflogen; Tarivid; Zanocin; ***India:*** Bactof; Bidoflox†; Bioff; Floxur; Genflox; Ofler; Oflin; Oflox; Olfi; Tariflox; Tarivid; Zanocin; ***Indon.:*** Akilen; Danoflox; Efexin; Ethiflox; Flotavid; Floxan; Floxika; Loxinter; Mefoxa; Nufafloqo; Ostrid; Pharflox; Poncoquin; Qipro; Quinovid; Rilox; Tariflox; Tarivid; Zelavel; Zyflox; ***Irl.:*** Biravid; Exocin; Tarivid; ***Israel:*** Oflodex; Oflox; Tarivid; Uro-Tarivid; ***Ital.:*** Exocin; Flobacin; Oflocin; ***Jpn:*** Tarivid; ***Malaysia:*** Apo-Oflox†; Flovid†; Healox; Inoflox; Medofloxine; Ofcin; Tarivid; Zanocin; ***Mex.:*** Bactocin; Flonacin; Flosep; Floxil; Floxstat; Ocuflox; Oxken; Quiflural; Zanocin; ***Neth.:*** Tarivid; Trafloxal; ***Norw.:*** Tarivid; ***Philipp.:*** Flodemex; Flovid; Gyros; Inoflox; Iquinol; Keftil; Mergexin; Onexacin; Qiflon; Qinolon; Terioxan; Vioson; ***Pol.:*** Floxal; Oflodinex†; Tarivid; ***Port.:*** Bactoflox; Bioquil; Exocin; Floxedol; Megasin; Oflocet; Tarivid; ***Rus.:*** Floxal (Флоксал); Oflo (Офло); Oflocide (Офлоцид); Ofloxin (Офлоксин); Taricin (Тарицин); Tarivid (Таривид); Zanocin (Заноцин); ***S.Afr.:*** Exocin; Octin; Tafloc; Tarivid; Zanocin; ***Singapore:*** Inoflox; Ofcin; Tarivid; ***Spain:*** Exocin; Oflovir; Surnox; ***Swed.:*** Tarivid; ***Switz.:*** Floxal; Tarivid; ***Thai.:*** Floxy; Hyflox; Konovid; O-Flox; Occidal; Oflocee; Oflomet; Ofloxa; Ofloxcin; Orivid; Qinolon; Seracin; Tarivid; Viotisone; ***Turk.:*** Drovid; Exocin; Girasid; Menefloks; Ofkozin; Oflocide; Ofloks; Tarivid; Urosin; ***UK:*** Exocin; Tarivid; ***USA:*** Floxin; Floxin Otic; Ocuflox; ***Venez.:*** Floxstat; Norlamine; Oflox; Poenflox.

Multi-ingredient: ***India:*** Bidoflox-Oz†; Genflox TZ; Ofler-TZ; Oflox D; Oflox TZ; Okaflox M; Olfi TZ; Ornof; Tariflox Plus; ***Mex.:*** Orecil NF.

Oleandomycin Phosphate *(BANM, rINNM)*

Fosfato de oleandomicina; Oléandomycine, Phosphate d'; Oleandomycini Phosphas; PA-105 (oleandomycin). (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*R*,13*R*)-3-(2,6-Dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyloxy)-8,8-epoxymethano-11-hydroxy-2,4,6,10,12,13-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)tridecan-13-olide phosphate.

Олеандомицина Фосфат

$C_{35}H_{61}NO_{12},H_3PO_4$ = 785.9.

CAS — 3922-90-5 (oleandomycin); 7060-74-4 (oleandomycin phosphate).

ATC — J01FA05.

ATC Vet — QJ01FA05.

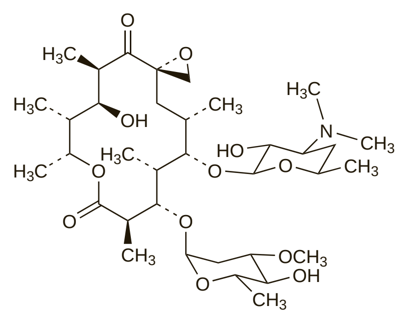

(oleandomycin)

Profile

Oleandomycin is a macrolide antibacterial produced by the growth of certain strains of *Streptomyces antibioticus* with actions and uses similar to those of erythromycin (p.269). It has antimicrobial activity weaker than that of erythromycin. It has been given orally or intravenously as the phosphate in the treatment of susceptible infections.

Troleandomycin (p.357) is the triacetyl ester.

Orbifloxacin *(rINN)*

Orbifloksasiini; Orbifloxacine; Orbifloxacino; Orbifloxacinum. 1-Cyclopropyl-7-(*cis*-3,5-dimethyl-1-piperazinyl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

Орбифлоксацин

$C_{19}H_{20}F_3N_3O_3$ = 395.4.

CAS — 113617-63-3.

ATC Vet — QJ01MA95.

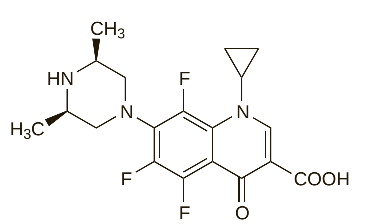

Profile

Orbifloxacin is a fluoroquinolone antibacterial used in veterinary medicine for the treatment of susceptible infections in dogs.

Oritavancin *(rINN)*

LY-333328; Oritavancina; Oritavancine; Oritavancinum. (4″*R*)-22-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-$N^{3''}$-[*p*-(*p*-chlorophenyl)benzyl]vancomycin.

Оритаванцин

$C_{86}H_{97}Cl_3N_{10}O_{26}$ = 1793.1.

CAS — 171099-57-3 (oritavancin); 192564-14-0 (oritavancin phosphate).

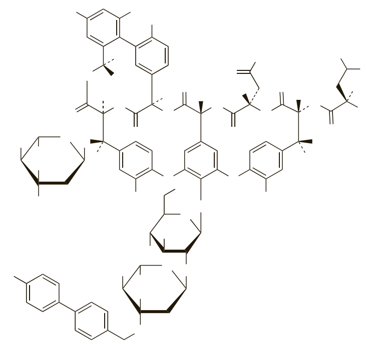

NOTE. Oritavancin phosphate is *USAN*.

Profile

Oritavancin is a glycopeptide antibacterial under investigation for the treatment of complicated infections of the skin and soft tissues due to Gram-positive bacteria.

◊ References.

1. Van Bambeke F, *et al.* Glycopeptide antibiotics: from conventional molecules to new derivatives. *Drugs* 2004; **64:** 913–36.
2. Ward KE, *et al.* Oritavancin—an investigational glycopeptide antibiotic. *Expert Opin Invest Drugs* 2006; **15:** 417–29.
3. Poulakou G, Giamarellou H. Oritavancin: a new promising agent in the treatment of infections due to Gram-positive pathogens. *Expert Opin Invest Drugs* 2008; **17:** 225–43.
4. Crandon J, Nicolau DP. Oritavancin: a potential weapon in the battle against serious Gram-positive pathogens. *Future Microbiol* 2008; **3:** 251–63.

Ormetoprim *(USAN, rINN)*

NSC-95072; Ormetoprima; Ormétoprime; Ormetoprimum; Ro-5-9754. 5-(4,5-Dimethoxy-2-methylphenyl)methyl-2,4-pyrimidinediamine.

Орметоприм

$C_{14}H_{18}N_4O_2$ = 274.3.

CAS — 6981-18-6.

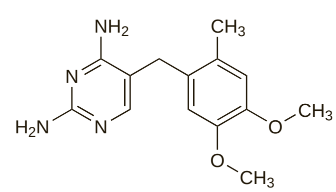

Profile

Ormetoprim is a diaminopyrimidine antibacterial used with sulfadimethoxine in veterinary medicine.

Oxacillin Sodium *(BANM, USAN, rINNM)*

(5-Methyl-3-phenyl-4-isoxazolyl)penicillin Sodium; Natrii Oxacillinum; Oksacylina sodowa jednowodna; Oksasilliininatriummonohydraatti; Oxacilin sodná sůl monohydrát; Oxacilina sódica; Oxacilline Sodique; Oxacilline sodique monohydratée; Oxacillinnatriummonohydrat; Oxacillinum natricum monohydricum; Oxacillinum Natrium; P-12; SQ-16423. Sodium (6*R*)-6-(5-methyl-3-phenylisoxazole-4-carboxamido)penicillanate monohydrate.

Натрий Оксациллин

$C_{19}H_{18}N_3NaO_5S,H_2O$ = 441.4.

CAS — 66-79-5 (oxacillin); 1173-88-2 (anhydrous oxacillin sodium); 7240-38-2 (oxacillin sodium monohydrate).

ATC — J01CF04.

ATC Vet — QJ01CF04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Oxacillin Sodium Monohydrate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 3.0% solution in water has a pH of 4.5 to 7.5.

USP 31 (Oxacillin Sodium). A fine white crystalline powder, odourless or having a slight odour. Freely soluble in water, in dimethyl sulfoxide, and in methyl alcohol; slightly soluble in dehydrated alcohol, in chloroform, in methyl acetate, and in pyridine; insoluble in ether, in ethyl acetate, in ethylene chloride, and in benzene. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers at a mean temperature not exceeding 25°.

Incompatibility. Oxacillin sodium has been reported to be incompatible with aminoglycosides and tetracyclines.

Adverse Effects and Precautions

As for Flucloxacillin, p.277.

Effects on the liver. References.

1. Onorato IM, Axelrod JL. Hepatitis from intravenous high-dose oxacillin therapy: findings in an adult inpatient population. *Ann Intern Med* 1978; **89:** 497–500.
2. Saliba B, Herbert PN. Oxacillin hepatotoxicity in HIV-infected patients. *Ann Intern Med* 1994; **120:** 1048.
3. Maraqa NF, *et al.* Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis* 2002; **34:** 50–4.

Sodium content. Each g of oxacillin sodium contains about 2.3 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

As for Flucloxacillin, p.277.

Resistance. The isolation of pneumococci resistant to oxacillin but sensitive to benzylpenicillin has been reported.[1,2] The resistance was due to acquisition of a low-affinity penicillin-binding protein and conferred cross-resistance to meticillin and cloxacillin, and, to a lesser degree, to cefotaxime.

1. Johnson AP, *et al.* Oxacillin-resistant pneumococci sensitive to penicillin. *Lancet* 1993; **341:** 1222.
2. Dowson CG, *et al.* Genetics of oxacillin resistance in clinical isolates of Streptococcus pneumoniae that are oxacillin resistant and penicillin susceptible. *Antimicrob Agents Chemother* 1994; **38:** 49–53.

Pharmacokinetics

Oxacillin is incompletely absorbed from the gastrointestinal tract. Absorption is reduced by the presence of food in the stomach and is less than with cloxacillin. Peak plasma concentrations of 3 to 6 micrograms/mL have been achieved 1 hour after an oral dose of 500 mg given to fasting subjects. After intramuscular injection of 500 mg, peak plasma concentrations of up to 15 micrograms/mL have been achieved by 30 minutes. Doubling the dose can double the plasma concentration. About 93% of the oxacillin in the circulation is bound to plasma proteins. Oxacillin has been reported to have a plasma half-life of about 0.5 hours. The half-life is prolonged in neonates.

The distribution of oxacillin into body tissues and fluids is similar to that of cloxacillin (p.256).

Oxacillin undergoes some metabolism, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion.

About 20 to 30% of an oral dose, and more than 40% of an intramuscular dose, is rapidly excreted in the urine. Oxacillin is also excreted in the bile.

Plasma concentrations are enhanced by probenecid.

Uses and Administration

Oxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Oxacillin is given orally or by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of oxacillin; 1.1 g of oxacillin sodium is equivalent to about 1 g of oxacillin. Oral doses should preferably be given at least 1 hour before, or 2 hours after, meals. The usual adult oral dose is 1 g of oxacillin twice daily. Oxacillin may be given by intramuscular injection, by slow intravenous injection over about 10 minutes, or by intravenous infusion. Usual parenteral doses for adults are 250 to 500 mg every 4 to 6 hours; doses may be increased to 1 g every 4 to 6 hours for severe infections.

The usual oral dose for children is 500 mg twice daily. The parenteral dose for children weighing less than 40 kg is 50 mg/kg daily in 4 to 6 divided doses; the dose may be increased to 100 mg/kg daily for severe infections.

Preparations

USP 31: Oxacillin for Injection; Oxacillin Injection; Oxacillin Sodium Capsules; Oxacillin Sodium for Oral Solution.

Proprietary Preparations (details are given in Part 3)
Belg.: Penstapho; ***Braz.:*** Oxacil†; Oxanon; Oxapen; Prodoxacilina; Roxacilin†; Staficilin N; Teutocilin†; ***Cz.:*** Prostaphlin; ***Fr.:*** Bristopen; ***Ger.:*** InfectoStaph; ***Ital.:*** Penstapho; ***Philipp.:*** Prostaphlin; Stafcil; Wydox; ***Venez.:*** Biocilina; Oxiclin†; Oxipen; Pebenal†; Prostafilina.

Multi-ingredient: ***Ger.:*** Optocillin†; ***Rus.:*** Oxamp (Оксамп)†.

Oxolinic Acid *(BAN, USAN, rINN)*

Acide oxolinique; Ácido oxolínico; Acidum oxolinicum; Kyselina oxolinová; NSC-110364; Oksoliinihappo; Oksolinik Asit; Oksolino rūgštis; Oxolinsav; Oxolinsyra; W-4565. 5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid.

Оксолиновая Кислота

$C_{13}H_{11}NO_5$ = 261.2.
CAS — 14698-29-4.
ATC — J01MB05.
ATC Vet — QJ01MB05.

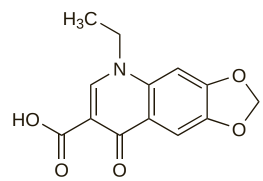

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oxolinic Acid). An almost white or pale yellow crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

Profile

Oxolinic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p.303), although adverse effects on the CNS may be more frequent. It has been given orally in the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Urilin†; ***Cz.:*** Desurol†; ***Port.:*** Cistopax†; ***Spain:*** Oxoinex†.

Oxytetracycline *(BAN, rINN)*

Glomycin; Hydroxytetracycline; Oksitetraciklinas; Oksitetrasiklin; Oksitetrasykliini; Oksytetracyklina; Oxitetraciclina; Oxitetraciklin; Oxitetracyklin; Oxytétracycline; Oxytetracyclinum; Oxytetracyklin; Riomitsin; Terrafungine. 4S,4aR,5S,5aR,6S,12aS-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 5β-Hydroxytetracycline.

Окситетрациклин

$C_{22}H_{24}N_2O_9$ = 460.4.
CAS — 79-57-2 (anhydrous oxytetracycline); 6153-64-6 (oxytetracycline dihydrate).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QG51AA01; QJ01AA06; QJ51AA06; QS01AA04.

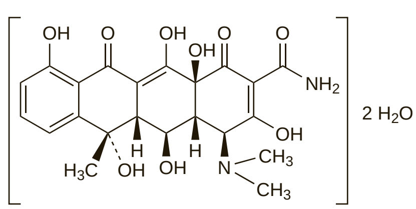

(oxytetracycline dihydrate)

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*, which specify the dihydrate ($C_{22}H_{24}N_2O_9$,$2H_2O$ = 496.5); *US* allows the anhydrous substance or the dihydrate.

Ph. Eur. 6.2 (Oxytetracycline Dihydrate). A substance produced by the growth of certain strains of *Streptomyces rimosus* or obtained by any other means. A yellow, crystalline powder. Very slightly soluble in water; dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 4.5 to 7.5. Store in airtight containers. Protect from light.

USP 31 (Oxytetracycline). A pale yellow to tan, odourless crystalline powder, that darkens on exposure to strong sunlight. Soluble 1 in 4150 of water, 1 in 66 of dehydrated alcohol, and 1 in 6250 of ether; sparingly soluble in alcohol; practically insoluble in chloroform; freely soluble in 3N hydrochloric acid and in alkaline solutions. pH of a 1% suspension in water is between 4.5 and 7.0. It loses potency in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Store in airtight containers. Protect from light.

Oxytetracycline Calcium *(BANM, rINNM)*

Calcii Oxytetracyclinum; Oxitetraciclina cálcica; Oxytétracycline Calcique.

Кальций Окситетрациклин

$C_{44}H_{46}CaN_4O_{18}$ = 958.9.
CAS — 15251-48-6 (xCa).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Oxytetracycline Calcium). A pale yellow to greenish-fawn, crystalline powder. Practically insoluble in water; soluble in dilute acids; dissolves slowly in dilute ammonia solution. A 2.5% suspension in water has a pH of 6.0 to 7.5. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Oxytetracycline Calcium). A yellow to light brown crystalline powder. Insoluble in water; soluble 1 in more than 1000 of alcohol, of chloroform, and of ether, and 1 in 15 of 0.1N sodium hydroxide. pH of a 2.5% suspension in water is between 6.0 and 8.0. Store in airtight containers at a temperature between 8° and 15°. Protect from light.

Oxytetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de oxitetraciclina; Oksitetraciklino hidrochloridas; Oksitetrasiklin Hidroklorür; Oksitetrasykliinihydrokloridi; Oksytetracykliny chlorowodorek; Oxitetraciklin-hidroklorid; Oxitetracyklinhydroklorid; Oxytétracycline, chlorhydrate d'; Oxytetracyclini hydrochloridum; Oxytetracyklin-hydrochlorid.

Окситетрациклина Гидрохлорид

$C_{22}H_{24}N_2O_9$,HCl = 496.9.
CAS — 2058-46-0.
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Oxytetracycline Hydrochloride). A yellow, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Solutions in water become turbid on standing owing to the precipitation of oxytetracycline. A 1% solution in water has a pH of 2.3 to 2.9. Store in airtight containers. Protect from light.

USP 31 (Oxytetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline powder. It decomposes at temperatures exceeding 180°, and exposure to strong sunlight or temperatures exceeding 90° in moist air causes it to darken. Its potency is diminished in solutions having a pH below 2, and it is rapidly destroyed by alkali hydroxide solutions. Freely soluble in water, but crystals of oxytetracycline separate as a result of partial hydrolysis of the hydrochloride; sparingly soluble in alcohol and in methyl alcohol, and even less soluble in dehydrated alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Oxytetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts.

Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Oxytetracycline may produce less tooth discoloration than some other tetracyclines but gastrointestinal symptoms tend to be more severe.

Porphyria. For the suggestion that oxytetracycline might be porphyrinogenic, see under Tetracycline, p.348.

Interactions

As for Tetracycline, p.348.

Antimicrobial Action

As for Tetracycline, p.348.

Oxytetracycline is somewhat less active against many organisms.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p.349.

An oral dose of 500 mg every 6 hours is reported to produce steady-state plasma concentrations of 3 to 4 micrograms/mL. Plasma protein binding is reported to be about 20 to 40% and the half-life to be about 9 hours.

Uses and Administration

Oxytetracycline is a tetracycline derivative with actions and uses similar to those of tetracycline (p.349).

Oxytetracycline dihydrate or hydrochloride are usually used in tablets, capsules, and injections, and the calcium salt in aqueous oral suspensions; all three are also used in topical preparations. Doses have been expressed as anhydrous oxytetracycline, the dihydrate, or the hydrochloride but in practice this appears to make little difference. Oxytetracycline dihydrate and oxytetracycline hydrochloride 269.8 mg, and oxytetracycline calcium 260.3 mg, are each equivalent to about 250 mg of oxytetracycline.

Oxytetracycline is usually given orally in adult doses of 250 to 500 mg four times daily, usually 1 hour before or 2 hours after food. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects.

Doses of oxytetracycline 250 to 500 mg daily have been used in acne, although the *BNF* advocates a dose of 1 g daily.

Oxytetracycline is sometimes given intramuscularly, in doses of 250 mg once daily or 300 mg daily in 2 or 3 divided doses, but this route may be painful and produces lower blood concentrations than recommended oral doses. As intramuscular injections are painful, lidocaine is usually included in the solution. Oxytetracycline has also been given intravenously.

For details of doses in children and adolescents, see below.

Oxytetracycline and its salts have been applied topically, often with other agents, as a variety of eye and ear drops, ointments, creams, and sprays.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, oxytetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 25 to 50 mg/kg daily in 4 divided doses or by intramuscular injection in usual doses of 15 to 25 mg/kg (to a maximum of 250 mg) daily in 2 or 3 divided doses.

Skin disorders. For reference to the use of oxytetracycline in the treatment of various skin disorders, see under Tetracycline, p.350.

Preparations

BP 2008: Oxytetracycline Capsules; Oxytetracycline Tablets;
USP 31: Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Oxytetracycline Calcium Oral Suspension; Oxytetracycline for Injection; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Oxytetracycline Hydrochloride Capsules; Oxytetracycline Injection; Oxytetracycline Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Terramicina; ***Braz.:*** Terramicina; ***Denm.:*** Oxytetral; ***Fr.:*** Posicycline; ***Gr.:*** Terramycin; ***Hong Kong:*** Oxylim; ***Hung.:*** Tetran; ***India:*** Terramycin; ***Indon.:*** Chemotrex; Corsamycin; Terramycin; ***Irl.:*** Clinimycin; ***Malaysia:*** Oxylim; ***Mex.:*** Metrecina; Oxitraklin; Terrados; Terramicina; ***Norw.:*** Oxytetral; ***Philipp.:*** Noxebron; ***Pol.:*** Oxyterracyna†; ***Port.:*** Geomicina†; Terricil; ***S.Afr.:*** Acu-Oxytet; Be-Oxytet; Cotet; O-4 Cycline; Oxymycin; Oxypan; Roxy; Spectratet; Tetracem†; Tetramel†; ***Singapore:*** Oxylim; Terramycin†; ***Spain:*** Terramicina; ***Swed.:*** Oxytetral; ***Thai.:*** Oxycline; Oxylim; ***Turk.:*** Neocol; ***UK:*** Oxymycin; Oxytetramix†; ***USA:*** Terramycin†; ***Venez.:*** Oxifesa†; Terramicina.

Multi-ingredient: ***Arg.:*** Terra-Cortril; Terra-Cortril Nistatina†; Terramicina con Polimixina B†; ***Austria:*** Tetra-Gelomyrtol; ***Belg.:*** Eoline†; Terra-Cortril; Terra-Cortril + Polymyxine B; Terramycine + Polymyxine B; ***Braz.:*** Terra-Cortril; Terramicina c/Polimixina; ***Denm.:*** Hydrocortison med Terramycin; Hydrocortison med Terramycin og Polymyxin-B; Terramycin Polymyxin B; ***Fin.:*** Terra-Cortril; Terra-Cortril P; ***Fr.:*** Auricularum; Primyxine†; Ster-Dex; ***Ger.:*** Corti Biciron N; Farco-Tril†; Oxy Biciron; Terracortril†; Terramycin†; Tetra-Gelomyrtol; ***Gr.:*** Oxacycle-P; Terra-Cortril; Terramycin; ***Hong Kong:*** Terramycin with Polymyxin B; ***Hung.:*** Oxycort; Tetran-Hydrocortison; ***India:*** Terramycin SF; ***Indon.:*** Sancortmycin; Terra-Cortril; Terramycin Poly; ***Israel:*** Auricularum; Terramycin; ***Ital.:*** Cosmiciclina; ***Malaysia:*** Terramycin; ***Mex.:*** Andociclina Balsamica†; Terramicina; ***Neth.:*** Terra-Cortril Gel Steraject met polymyxine-B†; Terra-Cortril met polymyxine-B; ***Norw.:*** Terra-Cortril; Terra-Cortril Polymyxin B; Terramycin Polymyxin B; ***Philipp.:*** Terramycin; ***Pol.:*** Atecortin; Oxycort; ***Port.:*** Corticil T; ***Rus.:*** Gioxyson (Гиоксизон); Oxycort (Оксикорт); ***S.Afr.:*** Terra-Cortril; Terramycin; ***Singapore:*** Terramycin; ***Spain:*** Coliriocilina Espectro†; Terra-Cortril; Terramicina; ***Swed.:*** Terracortril; Terracortril med polymyxin B; Terramycin Polymyxin B; ***Switz.:*** Terracortril†; ***Thai.:*** Terramycin; Terrasil†; ***Turk.:*** Geotril; Heksa; Polimisin; Sekamisin; Terramycin; ***UK:*** Terra-Cortril†; Trimovate; ***USA:*** Terak; Terra-Cortril; Terramycin with Polymyxin B; Urobiotic-250; ***Venez.:*** Ofterra; Terra-Cortril†; Terramicina con Polimixina B.

Panipenem *(rINN)*

Panipénem; Panipenemum. (+)-(5*R*,6*S*)-3{[(*S*)-1-Acetimidoyl-3-pyrrolidinyl]thio}-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Панипенем

$C_{15}H_{21}N_3O_4S$ = 339.4.

CAS — 87726-17-8.

Pharmacopoeias. In *Jpn.*

Profile

Panipenem is a carbapenem beta-lactam antibacterial similar to imipenem (p.286). It has been given with betamipron (p.215), which reduces its adverse renal effects.

◊ References.

1. Goa KL, Noble S. Panipenem/betamipron. *Drugs* 2003; **63:** 913–25.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Jpn:*** Carbenin.

Pazufloxacin Mesilate *(rINNM)*

Mesilato de pazufloxacino; Pazufloxacine, Mésilate de; Pazufloxacini Mesilas; T-3762; T-3761 (pazufloxacin). (−)-(3*S*)-10-(1-Aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid methanesulfonate.

Пазуфлоксацина Мезилат

$C_{16}H_{15}FN_2O_4, CH_3SO_3H$ = 414.4.

CAS — 127045-41-4 (pazufloxacin); 163680-77-1 (pazufloxacin mesilate).

ATC — J01MA18.

ATC Vet — QJ01MA18.

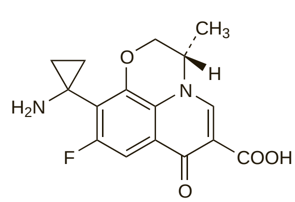

(pazufloxacin)

Profile

Pazufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243). It is given by intravenous infusion as the mesilate in the treatment of susceptible infections in a usual dose equivalent to 1 g of pazufloxacin daily in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Pasil; Pazucross.

Pefloxacin Mesilate *(BANM, rINNM)*

EU-5306 (pefloxacin); Mesilato de pefloxacino; Pefloksacino mesilatas dihidratas; Pefloksacyny mezylan dwuwodny; Pefloksasiinimesilaattidihydraatti; Pefloxacin Mesilate Dihydrate; Pefloxacin mesylát dihydrát; Pefloxacin Mesylate *(USAN)*; Péfloxacine, Mésilate de; Péfloxacine (mésilate de) dihydraté; Pefloxacini Mesilas; Pefloxacini mesilas dihydricus; Pefloxacinmesilatdihydrat; Pefloxacin-mezilát-dihidrát; 1589-RB (pefloxacin); 41982-RP. 1-Ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid methanesulphonate dihydrate.

Пефлоксацина Мезилат

$C_{17}H_{20}FN_3O_3,CH_4O_3S,2H_2O$ = 465.5.

CAS — 70458-92-3 (pefloxacin); 70458-95-6 (pefloxacin mesilate).

ATC — J01MA03.

ATC Vet — QJ01MA03.

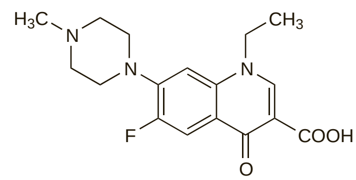

(pefloxacin)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Pefloxacin Mesilate Dihydrate). A fine, white or almost white powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Profile

Pefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.243). It also has bactericidal activity against *Mycobacterium leprae* and has been tried in the treatment of leprosy (p.176).

Pefloxacin has a longer plasma half-life than ciprofloxacin (about 8 to 13 hours) and is also extensively metabolised, the principal metabolite being *N*-desmethylpefloxacin (norfloxacin, p.309).

Pefloxacin is given orally or by intravenous infusion as the mesilate in the treatment of susceptible infections. Doses are expressed in terms of the base; pefloxacin mesilate 558.5 mg is equivalent to about 400 mg of pefloxacin. The usual dose is 400 mg twice daily. A single oral dose of 800 mg may be used in the treatment of gonococcal urethritis in men and acute uncomplicated cystitis in women.

Fluoroquinolones have caused adverse effects on the musculoskeletal system (see under Adverse Effects of Ciprofloxacin, p.244) and in the case of pefloxacin this has led to restrictions in some countries.

Adverse effects. References to adverse effects with pefloxacin.

1. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; **7:** 310–14.
2. Al-Hedaithy MA, Noreddin AM. Hypersensitivity anaphylactoid reaction to pefloxacin in a patient with AIDS. *Ann Pharmacother* 1996; **30:** 612–14.
3. Chang H, *et al.* Pefloxacin-induced arthropathy in an adolescent with brain abscess. *Scand J Infect Dis* 1996; **28:** 641–3.

Pharmacokinetics. References to the pharmacokinetics of pefloxacin.

1. Bressolle F, *et al.* Pefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **27:** 418–46.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Floxinon†; Peflacin; Pefloxidina†; ***Cz.:*** Abaktal; ***Fr.:*** Peflacine; ***Gr.:*** Idrostamin; Labocton; Londoman†; Peflacin†; ***Hung.:*** Abaktal; Peflacine; ***India:*** Ifipef†; Pefbid; Pelox; Qucin; ***Indon.:*** Dexaflox; Noflexin; Peflacine; ***Ital.:*** Peflacin; Peflox; ***Malaysia:*** Peflacine†; Perti†; ***Mex.:*** Nopriken†; Peflacina; ***Philipp.:*** Floxin; ***Pol.:*** Abaktal; Peflacine; ***Port.:*** Peflacine; ***Rus.:*** Abaktal (Абактал); Pelox (Пелокс); Perti (Перти); Unikpef (Юникпеф); ***Spain:*** Azuben†; Peflacine†; ***Thai.:*** Abaktal†; Peflacine†; ***Turk.:*** Peflacine; ***Venez.:*** Peflacina†; Perti†.

The symbol † denotes a preparation no longer actively marketed

Penethamate Hydriodide *(BAN)*

Diethylaminoethyl Penicillin G Hydroiodide; Penetamato, hidroioduro de; Pénéthamate, iodhydrate de; Penethamati hydroiodidum. 2-Diethylaminoethyl (6*R*)-6-(2-phenylacetamido)penicillanate hydriodide.

$C_{22}H_{31}N_3O_4S,HI = 561.5.$

CAS — 3689-73-4 (penethamate); 808-71-9 (penethamate hydriodide).

ATC Vet — QJ01CE90; QJ51CE90.

Profile

Penethamate is a penicillin antibacterial used as the hydriodide in veterinary medicine.

Pheneticillin Potassium *(BANM, rINNM)*

Feneticilina potásica; Kalii Pheneticillinum; Penicillin B; Phenethicillin Potassium; Phénéticilline Potassique; Pheneticillinum Kalicum; Potassium α-Phenoxyethylpenicillin. A mixture of the D(+)- and L(−)-isomers of potassium (6*R*)-6-(2-phenoxypropionamido)penicillanate.

Калия Фенетициллин

$C_{17}H_{19}KN_2O_5S = 402.5.$

CAS — 147-55-7 (pheneticillin); 132-93-4 (pheneticillin potassium).

ATC — J01CE05.

ATC Vet — QJ01CE05.

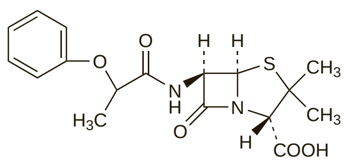

(pheneticillin)

Pharmacopoeias. In *Jpn.*

Profile

Pheneticillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (below). It has been given orally, as the potassium salt, for the treatment of susceptible mild to moderate infections. Pheneticillin sodium has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Neth.: Broxil.

Phenoxymethylpenicillin *(BAN, rINN)*

Fenoksimetilpenicilinas; Fenoksimetyylipenisilliini; Fenoksymetylopenicylina; Fenoximetilpenicilina; Fenoximetilpenicillin; Fenoximetylpenicillin; Fenoxymethylpenicilin; Penicillin, Phenoxymethyl; Penicillin V *(USAN)*; Penisilin V; Phénomycilline; Phenoxymethyl Penicillin; Phénoxyméthylpénicilline; Phenoxymethylpenicillinum. (6*R*)-6-(2-Phenoxyacetamido)penicillanic acid.

Феноксиметилпенициллин

$C_{16}H_{18}N_2O_5S = 350.4.$

CAS — 87-08-1.

ATC — J01CE02.

ATC Vet — QJ01CE02.

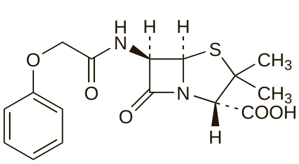

Pharmacopoeias. In *Eur.* (see p.vii), *Int., US*, and *Viet.*
Ph. Eur. 6.2 (Phenoxymethylpenicillin). A substance produced by the growth of certain strains of *Penicillium notatum* or related organisms on a culture medium containing an appropriate precursor, or obtained by any other means. A white or almost white, slightly hygroscopic, crystalline powder. Very slightly soluble in water; soluble in alcohol. A 0.5% suspension in water has a pH of 2.4 to 4.0. Store in airtight containers.
USP 31 (Penicillin V). A white, odourless crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; insoluble in fixed oils. pH of a 3% suspension in water is between 2.5 and 4.0. Store in airtight containers.

Phenoxymethylpenicillin Calcium *(BANM, rINNM)*

Calcii Phenoxymethylpenicillinum; Fenoximetilpenicilina cálcica; Penicillin V Calcium; Phénoxyméthylpénicilline Calcique; Phenoxymethylpenicillinum Calcicum.

Кальций Феноксиметилпенициллин

$(C_{16}H_{17}N_2O_5S)_2Ca,2H_2O = 774.9.$

CAS — 147-48-8 (anhydrous phenoxymethylpenicillin calcium); 73368-74-8 (phenoxymethylpenicillin calcium dihydrate).

ATC — J01CE02.

ATC Vet — QJ01CE02.

Pharmacopoeias. In *Int.*

Phenoxymethylpenicillin Potassium *(BANM, rINNM)*

Fenoksimetil Penisilin Potasyum; Fenoksimetilpenicilino kalio druska; Fenoksimetyylipenisilliinikalium; Fenoksymetylopenicylina potasowa; Fenoximetilpenicilina potásica; Fenoximetilpenicilina Potássica; Fenoximetilpenicillin-kálium; Fenoximetylpenicillin kalium; Fenoxymethylpenicilin draselná sůl; Kalii Phenoxymethylpenicillinum; Penicillin V Potassium *(USAN)*; Phénoxyméthylpénicilline potassique; Phenoxymethylpenicillinum kalicum.

Калия Феноксиметилпенициллин

$C_{16}H_{17}KN_2O_5S = 388.5.$

CAS — 132-98-9.

ATC — J01CE02.

ATC Vet — QJ01CE02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US*, and *Viet.*
Ph. Eur. 6.2 (Phenoxymethylpenicillin Potassium). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.5 to 7.5.
USP 31 (Penicillin V Potassium). A white, odourless crystalline powder. Very soluble in water; soluble 1 in 150 of alcohol; insoluble in acetone. pH of a 3% solution in water is between 4.0 and 7.5. Store in airtight containers.

Units

The first International Standard Preparation (1957) of phenoxymethylpenicillin contained 1695 units/mg but was withdrawn in 1968. Despite this, doses of phenoxymethylpenicillin are still expressed in units in some countries.

Phenoxymethylpenicillin 250 mg is equivalent to about 400 000 units.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Phenoxymethylpenicillin is usually well tolerated but may occasionally cause transient nausea and diarrhoea.

Potassium content. Each g of phenoxymethylpenicillin potassium contains about 2.6 mmol of potassium.

Interactions

As for Benzylpenicillin, p.214.

Antibacterials. Reduced absorption was reported when phenoxymethylpenicillin was given after an oral course of *neomycin*.[1]

1. Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. *N Engl J Med* 1962; **267:** 1296–7.

Beta blockers. Fatal anaphylactic reactions to phenoxymethylpenicillin in 2 patients on *nadolol* and *propranolol* respectively, might have been potentiated by the beta blocker.[1]

1. Berkelman RL, *et al.* Beta-adrenergic antagonists and fatal anaphylactic reactions to oral penicillin. *Ann Intern Med* 1986; **104:** 134.

Antimicrobial Action

Phenoxymethylpenicillin has a range of antimicrobial activity similar to that of benzylpenicillin (p.214) and a similar mode of action. It may be less active against some susceptible organisms, particularly Gram-negative bacteria.

The mechanisms and patterns of resistance to phenoxymethylpenicillin are similar to those of benzylpenicillin.

Pharmacokinetics

Phenoxymethylpenicillin is more resistant to inactivation by gastric acid and is more completely absorbed than benzylpenicillin from the gastrointestinal tract. Absorption is usually rapid, although variable, with about 60% of an oral dose being absorbed. The calcium and potassium salts are better absorbed than the free acid. Peak plasma concentrations of 3 to 5 micrograms/mL have been observed 30 to 60 minutes after a dose of 500 mg. The effect of food on absorption appears to be slight. The plasma half-life of phenoxymethylpenicillin is about 30 to 60 minutes and may be increased to about 4 hours in severe renal impairment. About 80% is reported to be protein bound. The distribution and elimination of phenoxymethylpenicillin is similar to that of benzylpenicillin (p.214). It is metabolised in the liver to a greater extent than benzylpenicillin; several metabolites have been identified including penicilloic acid. The unchanged drug and metabolites are excreted rapidly in the urine. Only small amounts are excreted in the bile.

Uses and Administration

Phenoxymethylpenicillin is used similarly to benzylpenicillin (p.215) in the treatment or prophylaxis of infections caused by susceptible organisms, especially streptococci. It is used only for the treatment of mild to moderate infections, and not for chronic, severe, or deep-seated infections since absorption can be unpredictable. Patients treated initially with parenteral benzylpenicillin may continue treatment with oral phenoxymethylpenicillin once a satisfactory clinical response has been obtained. Specific indications for phenoxymethylpenicillin include anthrax (mild uncomplicated infections), Lyme disease (early stage in pregnant women or young children), pharyngitis or tonsillitis, rheumatic fever (primary and secondary prophylaxis), streptococcal skin infections, and spleen disorders (pneumococcal infection prophylaxis). For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Phenoxymethylpenicillin is given orally, usually as the potassium or calcium salt, preferably at least 30 minutes before, or 2 hours after, food. Benzathine phenoxymethylpenicillin (p.212) is also used.

Doses are expressed in terms of the equivalent amount of phenoxymethylpenicillin; 1.1 g of phenoxymethylpenicillin calcium and 1.1 g of phenoxymethylpenicillin potassium are each equivalent to about 1 g of phenoxymethylpenicillin.

Usual adult doses have been 250 to 500 mg every 6 hours, but the *BNF* recommends up to 1 g every 6 hours in severe infections. Children may be given the following doses every 6 hours: up to 1 year, 62.5 mg; 1 to 5 years, 125 mg; and 6 to 12 years, 250 mg. The *BNFC* recommends that doses be increased to ensure at least 12.5 mg/kg every 6 hours in severe infection. Dosage may need to be modified in severe renal impairment.

To prevent recurrences of rheumatic fever, WHO and the *BNF* recommend 250 mg twice daily.

Preparations

BP 2008: Phenoxymethylpenicillin Oral Solution; Phenoxymethylpenicillin Tablets;
USP 31: Penicillin V for Oral Suspension; Penicillin V Potassium for Oral Solution; Penicillin V Potassium Tablets; Penicillin V Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Pen Oral; Penagrand; Penfantil; Penicina; ***Austral.:*** Abbocillin-VK; Cilicaine VK; Cilopen VK; LPV; Penhexal VK; ***Austria:*** Aliucillin; Cliacil; Megacillin; Ospen; Pen-V; Penbene; Penoral; Penstad; Star-Pen; ***Belg.:*** Peni-Oral; ***Braz.:*** Meracilina; Oracilin; Pen-V-Cil; Pen-Ve-Oral; Pencilin-V; Penicigran; ***Canad.:*** Apo-Pen-VK; Nadopen-V†; Novo-Pen-VK; Nu-Pen-VK; Pen-Vee†; PVFK†; ***Cz.:*** InfectoCillin†; Megacillin†; Ospen; Penbene; Pencid; ***Denm.:*** Calcipen; Pancillin; Primcillin; Rocilin; Vepicombin; ***Fin.:*** Medicillin; Milcopen; V-Pen; ***Fr.:*** Oracilline; Ospen†; ***Ger.:*** Arcasin; durapenicillin†; InfectoCillin; Isocillin; Ispenoral; Jenacillin V†; Megacillin oral; P-Mega-Tablinen; Pen Mega; Pen†; Penbeta; Penhexal; Penicillat†; V-Tablopen†; ***Gr.:*** Ospen; ***Hong Kong:*** Ospen†; ***Hung.:*** Ospen; Vegacillin†; ***Indon.:*** Fenocin; Ospen; ***Irl.:*** Calvepen; Kopen; ***Israel:*** Rafapen Mega; Rafapen V-K; ***Malaysia:*** Beapen; Ospen; Penoxil V†; ***Mex.:*** Anapenil; Kavipen; Megapenil†; Pen-Vi-K; Pota-Vi-Kin; ***Neth.:*** Acipen; Acipen-V; ***Norw.:*** Apocillin; Calcipen†; Kavepenin†; Rocilin†; Weifapenin; ***NZ:*** Cilicaine VK; ***Philipp.:*** Sumapen; ***Pol.:*** Ospen; ***Rus.:*** Ospen (Оспен); ***S.Afr.:*** Betapen; Deltacillin†; Incil; Len V.K.; Novo V-K†; Rolab-Pen-V-K†; Spec-Pen-V-K; ***Singapore:*** Ospen; ***Spain:*** Penilevel; ***Swed.:*** Kavepenin; Peceve; Tikacillin; ***Switz.:*** Brunocillin†; Megacilline†; Ospen; pen-V-basan†; Penisol; Phenocillin; Stabicilline; ***Thai.:*** Pen-V; Pener; Penveno; Servipen-V†; ***Turk.:*** Cilacil; ***USA:*** Pen-Vee K; Veetids; ***Venez.:*** Ospen.

Multi-ingredient: ***Spain:*** Penilevel Retard.

Phthalylsulfacetamide *(BAN)*

Phthalylsulphacetamide; Sulfanilacetamidum Phthalylatum. 4′-(Acetylsulphamoyl)phthalanilic acid.

$C_{16}H_{14}N_2O_6S$ = 362.4.

CAS — 131-69-1.

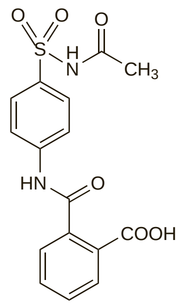

Profile

Phthalylsulfacetamide is a sulfonamide antibacterial. It is poorly absorbed when given orally and has been used for gastrointestinal infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Dimicin†; ***Chile:*** Enterol; Enterol Con Nifuroxacida; Kordinol Compuesto†; ***Mex.:*** Facetin-D.

Phthalylsulfathiazole *(BAN, rINN)*

Ftalilsulfatiazol; Ftalilsulfatiazolas; Ftálilszulfatiazol; Ftalylsulfathiazol; Ftalylsulfatiazol; Ftalyylisulfatiatsoli; Phtalylsulfathiazol; Phthalazolum; Phthalylsulfathiazolum; Phthalylsulphathiazole; Sulfaphtalylthiazol. 4′-(1,3-Thiazol-2-ylsulphamoyl)phthalanilic acid.

Фталилсульфатиазол

$C_{17}H_{13}N_3O_5S_2$ = 403.4.

CAS — 85-73-4.

ATC — A07AB02.

ATC Vet — QA07AB02.

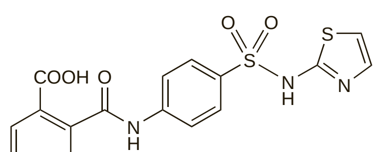

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.*

Ph. Eur. 6.2 (Phthalylsulfathiazole). A white or yellowish-white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; freely soluble in dimethylformamide. Protect from light.

Profile

Phthalylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is poorly absorbed, about 95% remaining in the intestine and only about 5% being slowly hydrolysed to sulfathiazole and absorbed.

It is given, with other antibacterials, for its antibacterial action in the gastrointestinal tract in the treatment of infections and for bowel decontamination before surgery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Antidiar†; Carbon Tabs; Colistop; Colistoral†; Diarrocalmol; Estreptocarbocaftiazol; Gemipasmol†; Lefa Enteril†; Opocarbon; Opocler†; ***Braz.:*** Parenterin; Sanadiar†; ***Chile:*** Imecol; Liracol; Testisan; ***Mex.:*** Bontal; Ditayod; Sultroquin†; ***Port.:*** Cloranpectina†; ***Spain:*** Estreptoenterol†; ***Thai.:*** Chlorotracin; Coccila†; Disento; Endothalyl; Medicocin†.

Pipemidic Acid *(BAN, rINN)*

Acide Pipémidique; Ácido pipemídico; Acidum Pipemidicum; Acidum pipemidicum trihydricum; Kyselina pipemidová trihydrát; Pipemidihappo; Pipemidiinihappotrihydraatti; Pipemidinsav-trihidrát; Pipemidinsyratrihydrat; Pipémidique (acide) trihydraté; Pipemido rūgštis trihidratas; Pipemidsyra; Piperamic Acid; 1489-RB. 8-Ethyl-5,8-dihydro-5-oxo-2-(piperazin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

Пипемидовая Кислота

$C_{14}H_{17}N_5O_3$ = 303.3.

CAS — 51940-44-4 (anhydrous pipemidic acid); 72571-82-5 (pipemidic acid trihydrate).

ATC — J01MB04.

ATC Vet — QJ01MB04.

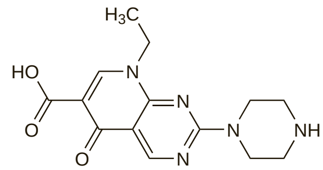

(anhydrous pipemidic acid)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn* (all as the trihydrate).

Ph. Eur. 6.2 (Pipemidic Acid Trihydrate). A pale yellow or yellow crystalline powder. Very slightly soluble in water. It dissolves in dilute solutions of acids and of alkali hydroxides. Protect from light.

Profile

Pipemidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p.303), but is more active *in vitro* against some bacteria, including *Pseudomonas aeruginosa*. It is used (as the trihydrate) in the treatment of urinary-tract infections in oral doses equivalent to 400 mg of the anhydrous substance twice daily.

Interactions. For the effect of pipemidic acid on the clearance of xanthines, see under Caffeine, p.1117, and Theophylline, p.1143.

Porphyria. Pipemidic acid is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Finuret; Memento; Priper; ***Austria:*** Deblaston; ***Braz.:*** Balurol; Elofuran; Pipram; Pipurol; Uroxina; ***Chile:*** Nupra†; Purid; Uropimide; ***Fr.:*** Pipram; ***Ger.:*** Deblaston; ***Hong Kong:*** Urotractin; ***Indon.:*** Impresial; Urinter; Urixin; Urotractin; Utrex; ***Ital.:*** Acipem†; Biosoviran; Cistomid; Diperpen; Faremid; Filtrax†; Pipeacid†; Pipedac; Pipefort; Pipemid; Pipram; Pipurin; Urodene; Uropimid; Urosan; Urosetic; Urotractin; ***Jpn:*** Dolcol; ***Malaysia:*** Urixin†; Urotractin†; ***Mex.:*** Uribac†; Uriken†; Uripiser; Uronovag; Uropipemid; ***Neth.:*** Pipram; ***Philipp.:*** Urixin; ***Pol.:*** Palin; Urolin; ***Rus.:*** Palin (Палин); Pimidel (Пимидель); ***S.Afr.:*** Deblaston; Septidron†; ***Singapore:*** Urotractin; ***Spain:*** Galusan; Nuril; Urisan; Uropipedil; ***Thai.:*** Pipedic†; Urotractin.

Multi-ingredient: ***Arg.:*** Priper Plus.

Piperacillin *(BAN, rINN)*

Piperacilin monohydrát; Piperacilina; Piperacilinas; Pipéracilline; Piperacillinum; Piperacillinum Monohydricum; Piperasilliini. (6*R*)-6-[*R*-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]penicillanic acid monohydrate; 3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate.

Пиперациллин

$C_{23}H_{27}N_5O_7S,H_2O$ = 535.6.

CAS — 61477-96-1 (anhydrous piperacillin); 66258-76-2 (piperacillin monohydrate).

ATC — J01CA12.

ATC Vet — QJ01CA12.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Piperacillin). A white or almost white powder. Slightly soluble in water and in ethyl acetate; freely soluble in methyl alcohol.

USP 31 (Piperacillin). A white to off-white crystalline powder. Very slightly soluble in water; slightly soluble in ethyl acetate; sparingly soluble in isopropyl alcohol; very soluble in methyl alcohol.

Piperacillin Sodium *(BANM, USAN, rINNM)*

CL-227193; Natrii Piperacillinum; Piperacilin sodná sůl; Piperacilina sódica; Piperacilino natrio druska; Pipéracilline sodique; Piperacillin-nátrium; Piperacillinnatrium natricum; Piperacillinum; Piperacillinum natricum; Piperacylina sodowa; Piperasilin Sodyum; Piperasilliininatrium; T-1220.

Натрий Пиперациллин

$C_{23}H_{26}N_5NaO_7S$ = 539.5.

CAS — 59703-84-3.

ATC — J01CA12.

ATC Vet — QJ01CA12.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Piperacillin Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in ethyl acetate. A 10% solution in water has a pH of 5.0 to 7.0. Store in airtight containers.

USP 31 (Piperacillin Sodium). A white to off-white solid. Freely soluble in water and in alcohol. pH of a 40% solution in water is between 5.5 and 7.5. Store in airtight containers.

Incompatibility. Piperacillin sodium has been reported to be incompatible with aminoglycosides and sodium bicarbonate.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35:** 1360–3.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Prolongation of bleeding time has been less frequent and less severe with piperacillin than with carbenicillin.

Effects on the blood. References.

1. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.

Hypersensitivity. In the mid 1980s there were reports of a relatively high incidence of adverse reactions to piperacillin, especially fever, in patients with cystic fibrosis.[1-3] However, the manufacturers[4] considered such patients to be particularly prone to allergy and cited reactions with other semisynthetic penicillins including carbenicillin and azlocillin.

Similar apparent hypersensitivity reactions have been reported in patients taking high doses of piperacillin and other ureidopenicillins, over long periods for other indications,[5] and with other penicillins in patients with cystic fibrosis,[6] although piperacillin does appear to be most frequently implicated.[6]

1. Stead RJ, *et al.* Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; **i:** 857–8.
2. Strandvik B. Adverse reactions to piperacillin in patients with cystic fibrosis. *Lancet* 1984; **i:** 1362.
3. Stead RJ, *et al.* Adverse reactions to piperacillin in adults with cystic fibrosis. *Thorax* 1985; **40:** 184–6.
4. Brock PG, Roach M. Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; **i:** 1070–1.
5. Lang R, *et al.* Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. *Rev Infect Dis* 1991; **13:** 68–72.
6. Pleasants RA, *et al.* Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest* 1994; **106:** 1124–8.

Sodium content. Each g of piperacillin sodium contains about 1.85 mmol of sodium. As piperacillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p.214.

Neuromuscular blockers. Piperacillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p.1903).

Antimicrobial Action

Piperacillin has a similar antimicrobial action to carbenicillin (p.216) and ticarcillin (p.352), but is active against a wider range of Gram-negative organisms, including *Klebsiella pneumoniae*. It is also generally more active *in vitro*, especially against *Pseudomonas aeruginosa* and the Enterobacteriaceae, against Gram-positive *Enterococcus faecalis*, and possibly against *Bacteroides fragilis*. There is, however, an inoculum effect, i.e. minimum inhibitory concentrations of piperacillin increase with the size of the inoculum.

Combinations of piperacillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae. The effect of using piperacillin with other beta lactams has been less predictable. The activity of piperacillin against some organisms, resistant because of the production of beta-lactamases, may be restored by tazobactam, a beta-lactamase inhibitor. Such organisms include beta-lactamase-producing strains of staphylococci, *Escherichia coli*, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of piperacillin against *Ps. aeruginosa* is not enhanced by tazobactam.

Resistance has developed in *Ps. aeruginosa* during treatment with piperacillin, especially when used alone. There may be some cross-resistance with other antipseudomonal penicillins.

◊ References.

1. Higashitani F, *et al.* Inhibition of β-lactamases by tazobactam and in-vitro antibacterial activity of tazobactam combined with piperacillin. *J Antimicrob Chemother* 1990; **25:** 567–74.
2. Mehtar S, *et al.* The in-vitro activity of piperacillin/tazobactam, ciprofloxacin, ceftazidime and imipenem against multiple resistant Gram-negative bacteria. *J Antimicrob Chemother* 1990; **25:** 915–19.
3. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26:** 598–9.

4. Kadima TA, Weiner JH. Mechanism of suppression of piperacillin resistance in enterobacteria by tazobactam. *Antimicrob Agents Chemother* 1997; **41:** 2177–83.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.
6. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. *Clin Microbiol Infect* 2008; **14** (suppl 1): 181–4. Correction. *ibid.*; (suppl 5): 21–4.

Pharmacokinetics

Piperacillin is not absorbed from the gastrointestinal tract. It is well absorbed after intramuscular use, with peak plasma concentrations of 30 to 40 micrograms/mL 30 to 50 minutes after a dose of 2 g. The pharmacokinetics of piperacillin are reported to be nonlinear and dose-dependent. The plasma half-life is about 1 hour, but is prolonged in neonates. In patients with severe renal impairment there may be a threefold increase in half-life; in those with end-stage renal failure half-lives of 4 to 6 hours have been reported, and in those with both renal and hepatic impairment much longer half-lives may result. About 20% of piperacillin in the circulation is bound to plasma proteins.

Piperacillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

About 60 to 80% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours, achieving high concentrations. High concentrations are also found in the bile and up to 20% of a dose may be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Piperacillin is removed by haemodialysis.

Piperacillin with tazobactam. The pharmacokinetics of piperacillin do not appear to be altered by tazobactam, but piperacillin reduces the renal clearance of tazobactam.

◊ References.

1. Heikkilä A, Erkkola R. Pharmacokinetics of piperacillin during pregnancy. *J Antimicrob Chemother* 1991; **28:** 419–23.
2. Wise R, *et al.* Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. *Antimicrob Agents Chemother* 1991; **35:** 1081–4.
3. Johnson CA, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. *Clin Pharmacol Ther* 1992; **51:** 32–41.
4. Dupon M, *et al.* Plasma levels of piperacillin and vancomycin used as prophylaxis in liver transplant patients. *Eur J Clin Pharmacol* 1993; **45:** 529–34.
5. Sörgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother* 1993; **31** (suppl A): 39–60.
6. Reed MD, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother* 1994; **38:** 2817–26.
7. Bourget P, *et al.* Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. *Antimicrob Agents Chemother* 1996; **40:** 139–45.
8. Occhipinti DJ, *et al.* Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. *Antimicrob Agents Chemother* 1997; **41:** 2511–17.

Uses and Administration

Piperacillin is a ureidopenicillin that is used similarly to ticarcillin (p.353) for the treatment of infections caused by *Pseudomonas aeruginosa*, and also infections due to other susceptible bacteria. It has been used particularly in immunocompromised patients (neutropenic patients) and for biliary-tract infections (cholangitis). Other indications have included uncomplicated gonorrhoea due to penicillin-sensitive gonococci, and urinary-tract infections. It has also been used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. For the treatment of serious infections piperacillin is commonly used with an aminoglycoside, but they should be given separately because of possible incompatibility.

Administration and dosage. Piperacillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of piperacillin; 1.04 g of piperacillin sodium is equivalent to about 1 g of piperacillin. Doses should generally be reduced in moderate to severe renal impairment.

Piperacillin may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 20 to 30 minutes, or by deep intramuscular injection. Single doses of more than 2 g for adults or 500 mg for children should not be given by the intramuscular route.

For the treatment of serious or complicated infections, adults may be given piperacillin 200 to 300 mg/kg daily in divided doses intravenously; the usual dose is 3 to 4 g every 4 or 6 hours. In life-threatening infections, particularly those caused by *Pseudomonas* or *Klebsiella* spp., it should be given in a dose of not less than 16 g daily. The usual maximum daily dose is 24 g, although this has been exceeded.

For mild or uncomplicated infections, 100 to 125 mg/kg daily may be given to adults; usual doses are 2 g every 6 or 8 hours, or 4 g every 12 hours, intravenously, or 2 g every 8 or 12 hours intramuscularly.

Uncomplicated gonorrhoea may be treated by a single intramuscular dose of 2 g. Probenecid 1 g may be given orally 30 minutes before the injection.

For the prophylaxis of infection during surgery, 2 g just before the procedure, or when the umbilical cord is clamped in caesarean section, followed by at least 2 doses of 2 g at intervals of 4 or 6 hours within 24 hours of the procedure, may be given.

The intravenous route is preferred for infants and children. Those aged 1 month to 12 years may be given 100 to 300 mg/kg daily in 3 or 4 divided doses. Neonates less than 7 days old or weighing less than 2 kg may be given 150 mg/kg daily in 3 divided doses. Those more than 7 days old and weighing more than 2 kg may be given 300 mg/kg daily in 3 or 4 divided doses.

Piperacillin with tazobactam. Piperacillin has also been used with tazobactam (p.344), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. The combination is given intravenously in a ratio of piperacillin (as the sodium salt) 8 parts to 1 part of tazobactam (as the sodium salt). Doses, calculated on piperacillin content, are similar to those of piperacillin alone.

◊ References.

1. Greenwood D, Finch RG, eds. Piperacillin/tazobactam: a new β-lactam/β-lactamase inhibitor combination. *J Antimicrob Chemother* 1993; **31** (suppl A): 1–124.
2. Schoonover LL, *et al.* Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother* 1995; **29:** 501–14.
3. Perry CM, Markham A. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs* 1999; **57:** 805–43.
4. Kotapati S, *et al.* The clinical and economic benefits of administering piperacillin-tazobactam by continuous infusion. *Intensive Crit Care Nurs* 2005; **21:** 87–93.
5. Gin A, *et al.* Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. *Expert Rev Anti Infect Ther* 2007; **5:** 365–83.

Preparations

BP 2008: Piperacillin Intravenous Infusion;
USP 31: Piperacillin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Algiseptico†; Piperac†; ***Austral.:*** Pipril†; ***Austria:*** Pipril; ***Belg.:*** Pipcil†; ***Canad.:*** Pipracil†; ***Cz.:*** Pipraks†; Pipril†; ***Denm.:*** Ivacin†; ***Ger.:*** Pipera†; Pipril†; ***Gr.:*** Pipril; Zobactam; Zoracilin; ***Hong Kong:*** Pipracil†; ***Hung.:*** Pipril†; ***India:*** Pipracil; ***Irl.:*** Pipril†; ***Israel:*** Picillin†; Pipracin; Pipril†; ***Ital.:*** Avocin†; Biopiper†; Cilpier; Diperil; Ecosette; Eril†; Farecillin; Peracil; Perasint; Picillin; Piperital; Pipersal; Pipertex; Reparcillin; Semipenil; Sintoplus; Viracillina†; ***Jpn:*** Pentcillin; ***Malaysia:*** Pipracil†; ***NZ:*** Pipril†; ***Switz.:*** Pipril†; ***Thai.:*** Peracin; Pipracil†; ***Turk.:*** Pipraks; ***USA:*** Pipracil†.

Multi-ingredient: ***Arg.:*** Pipetexina; Tazonam; ***Austral.:*** Tazocin; ***Austria:*** Tazonam; ***Belg.:*** Tazocin; ***Braz.:*** Tazocin; Tazoxil†; Tazpen†; ***Canad.:*** Tazocin; ***Chile:*** Tazonam; ***Cz.:*** Tazocin; ***Denm.:*** Tazocin; ***Fin.:*** Tazocin; ***Fr.:*** Tazocilline; ***Ger.:*** Tazobac; ***Gr.:*** Bactalin; Gramenox; Oliten; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong:*** Tazocin; ***Hung.:*** Tazocin; ***India:*** Tazact; Tazofast; Tazopen; Zosyn; ***Indon.:*** Tazocin; ***Irl.:*** Tazocin; ***Israel:*** Tazocin; ***Ital.:*** Tazobac; Tazocin; ***Malaysia:*** Tazocin; ***Mex.:*** Tasovak; Tazocin; ***Neth.:*** Tazocin; ***Norw.:*** Tazocin; ***NZ:*** Tazocin; ***Philipp.:*** Tazocin; ***Pol.:*** Tazocin; ***Port.:*** Tazobac; ***S.Afr.:*** Tazobax; Tazocin; ***Singapore:*** Tazocin; ***Spain:*** Tazocel; ***Swed.:*** Tazocin; ***Switz.:*** Tazobac; ***Thai.:*** Tazocin; ***Turk.:*** Tazocin; ***UK:*** Tazocin; ***USA:*** Zosyn; ***Venez.:*** Tazopril; Tazpen.

Pirlimycin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de pirlimicina; Pirlimycine, Chlorhydrate de; Pirlimycinhydroklorid; Pirlimycini Hydrochloridum; Pirlimysiinihydrokloridi; U-57930E. Methyl 7-chloro-6,7,8-trideoxy-6-(*cis*-4-ethyl-L-pipecolamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride monohydrate.

Пирлимицина Гидрохлорид

$C_{17}H_{31}ClN_2O_5S,HCl,H_2O$ = 465.4.

CAS — 79548-73-5 (pirlimycin); 77495-92-2 (pirlimycin hydrochloride).

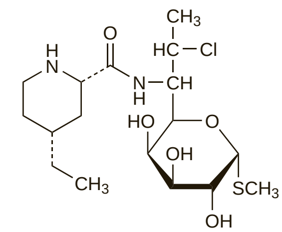

(pirlimycin)

Profile

Pirlimycin is a lincosamide antibacterial used in veterinary medicine.

Piromidic Acid *(rINN)*

Acide Piromidique; Ácido piromídico; Acidum Piromidicum; PD-93; Piromidihappo; Piromidsyra. 8-Ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

Пиромидовая Кислота

$C_{14}H_{16}N_4O_3$ = 288.3.

CAS — 19562-30-2.
ATC — J01MB03.
ATC Vet — QJ01MB03.

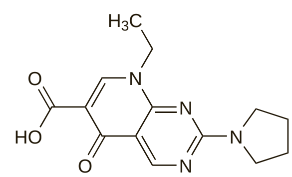

Profile

Piromidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p.303). It has been used in the treatment of susceptible infections. There have been a number of reports of acute renal failure associated with piromidic acid.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Enteromix†.

Pivampicillin *(BAN, rINN)*

MK-191; Pivampicilin; Pivampicilina; Pivampicilinas; Pivampicilline; Pivampicillinum; Pivampisilliini. Pivaloyloxymethyl (6*R*)-6-(α-D-phenylglycylamino)penicillanate.

Пивампициллин

$C_{22}H_{29}N_3O_6S$ = 463.5.

CAS — 33817-20-8.
ATC — J01CA02.
ATC Vet — QJ01CA02.

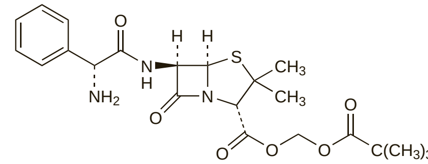

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Pivampicillin). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in methyl alcohol. It dissolves in dilute acids. Store in airtight containers.

Pivampicillin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de pivampicilina; Pivampicilline, Chlorhydrate de; Pivampicillini Hydrochloridum.

Пивампициллина Гидрохлорид

$C_{22}H_{29}N_3O_6S,HCl = 500.0.$

CAS — 26309-95-5.

ATC — J01CA02.

ATC Vet — QJ01CA02.

Adverse Effects and Precautions

As for Ampicillin, p.204. Pivampicillin is reported to cause a lower incidence of diarrhoea than ampicillin. Upper gastrointestinal discomfort may be more frequent when pivampicillin is taken on an empty stomach.

Pivaloyloxymethyl esters such as pivampicillin have been associated with the induction of carnitine deficiency (see below).

Carnitine deficiency. Carnitine deficiency (see p.1933) has been reported after the use of pivampicillin and pivmecillinam.[1] It is thought that the pivalic acid liberated on hydrolysis of these pivaloyloxymethyl esters *in vivo* is excreted as pivaloyl-carnitine with a consequent depletion in plasma and muscle concentrations of carnitine.[2] Low plasma-carnitine concentrations persisted in a patient after stopping pivampicillin, despite 6 weeks of replacement therapy with oral carnitine 1g daily. She had originally presented with skeletal myopathy when given pivampicillin for 3 months. A more intensive carnitine replacement regimen might be necessary in such patients.[3]

1. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; **ii:** 469–73.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631–3.
3. Rose SJ, *et al.* Carnitine deficiency associated with long-term pivampicillin treatment: the effect of a replacement therapy regime. *Postgrad Med J* 1992; **68:** 932–4.

Porphyria. Pivampicillin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Benzylpenicillin, p.214.

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving pivampicillin and valproate.

Antimicrobial Action

Pivampicillin has the antimicrobial activity of ampicillin to which it is hydrolysed *in vivo* (p.204).

Pharmacokinetics

Pivampicillin is acid-stable and is readily absorbed from the gastrointestinal tract. On absorption it is rapidly and almost completely hydrolysed to ampicillin, pivalic acid, and formaldehyde. Plasma-ampicillin concentrations 1 hour after a dose are 2 to 3 times those attained after an equivalent dose of ampicillin. The absorption of pivampicillin is generally not significantly affected by food. About 70% of a dose is excreted in the urine as ampicillin within 6 hours.

Uses and Administration

Pivampicillin is the pivaloyloxymethyl ester of ampicillin (p.205) and has similar uses; 1.3 g of pivampicillin and 1.43 g of pivampicillin hydrochloride are each equivalent to about 1 g of ampicillin.

Pivampicillin is given orally to adults and children over 10 years of age in doses of 500 mg twice daily with food, which may be doubled in severe infections. In children aged 3 months to 1 year a dose of 20 to 30 mg/kg twice daily may be used. Children older than 1 year may be given 12.5 to 17.5 mg/kg twice daily, up to 500 mg twice daily.

In areas where gonococci remain sensitive a single dose of 1.5 g is given for gonorrhoea, with probenecid 1 g.

Pivampicillin hydrochloride has been used in some countries.

Pivampicillin has also been given with pivmecillinam (below).

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Pondocillin; ***Denm.:*** Pondocillin; ***Fr.:*** Proampi; ***Norw.:*** Pondocillin; ***Swed.:*** Pondocillin.

Pivmecillinam *(BAN, rINN)*

Amdinocillin Pivoxil *(USAN)*; FL-1039; Pivamdinocillin; Pivmecilinam; Pivmécillinam; Pivmecillinamum; Pivmesillinaami; Ro-10-9071. Pivaloyloxymethyl (6*R*)-6-(perhydroazepin-1-ylmethyleneamino)penicillanate.

Пивмециллинам

$C_{21}H_{33}N_3O_5S = 439.6.$

CAS — 32886-97-8.

ATC — J01CA08.

ATC Vet — QJ01CA08.

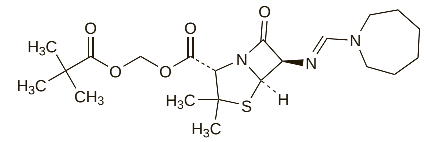

Pivmecillinam Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pivmecilinam; Pivmecillinam-hydrochlorid; Pivmecilinamo hidrochloridas; Pivmécillinam, Chlorhydrate de; Pivmecillinám-hidroklorid; Pivmecillinamhydroklorid; Pivmecillinami hydrochloridum; Pivmesillinaamihydrokloridi.

Пивмециллинама Гидрохлорид

$C_{21}H_{33}N_3O_5S,HCl = 476.0.$

CAS — 32887-03-9.

ATC — J01CA08.

ATC Vet — QJ01CA08.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Pivmecillinam Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 2.8 to 3.8. Store at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Pivaloyloxymethyl esters such as pivmecillinam have been associated with the induction of carnitine deficiency (see Pivampicillin, above).

Administration. Oesophageal injury has been associated rarely with pivmecillinam tablets.[1,2] Patients are advised to take them during a meal, while sitting or standing, and with at least half a glass of water.[3]

1. Committee on Safety of Medicines. Pivmecillinam and oesophageal injury. *Current Problems 19* 1987. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024426&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)
2. Mortimer Ö, Wiholm B-E. Oesophageal injury associated with pivmecillinam tablets. *Eur J Clin Pharmacol* 1989; **37:** 605–7.
3. Anonymous. CSM warning on pivmecillinam. *Pharm J* 1987; **238:** 443.

Porphyria. Pivmecillinam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Pivmecillinam has the antimicrobial activity of mecillinam (p.297) to which it is hydrolysed *in vivo*.

Pharmacokinetics

Pivmecillinam is well absorbed from the gastrointestinal tract and is rapidly hydrolysed to the active drug mecillinam (p.297), pivalic acid, and formaldehyde. The presence of food in the stomach does not appear to have a significant effect on absorption. Peak plasma concentrations of mecillinam of 5 micrograms/mL have been achieved 1 to 2 hours after a 400-mg dose of pivmecillinam.

About 45% of a dose may be excreted in the urine as mecillinam, mainly within the first 6 hours.

◊ References.

1. Heikkilä A, *et al.* The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women. *Br J Clin Pharmacol* 1992; **33**; 629–33.

Uses and Administration

Pivmecillinam is the pivaloyloxymethyl ester of mecillinam (p.297), to which it is hydrolysed after oral dosage. It is used in the treatment of urinary-tract infections (p.199).

Doses of pivmecillinam have often been expressed in a confusing manner since no differentiation has been made between the hydrochloride, used in tablets, and the base, used in suspensions for oral use. Pivmecillinam 1.35 g and pivmecillinam hydrochloride 1.46 g are each equivalent to about 1 g of mecillinam.

Pivmecillinam should preferably be taken with food (see also Administration, under Adverse Effects and Precautions, above).

In acute uncomplicated cystitis, the initial adult dose is 400 mg orally followed by 200 mg three times daily for 8 doses. In chronic or recurrent bacteriuria, 400 mg may be given 3 or 4 times daily. The dose for children (weighing less than 40 kg) with urinary-tract infections is 20 to 40 mg/kg daily in 3 or 4 divided doses.

Pivmecillinam has been given with other beta lactams, particularly pivampicillin (p.316), to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

For parenteral use, mecillinam is given.

◊ References.

1. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; **46** (suppl S1): 35–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Selexid; ***Belg.:*** Selexid†; ***Canad.:*** Selexid†; ***Denm.:*** Selexid; ***Fin.:*** Selexid; ***Fr.:*** Selexid; ***Norw.:*** Selexid; ***NZ:*** Selexid; ***Port.:*** Selecid†; ***Swed.:*** Selexid; ***UK:*** Selexid.

Polymyxin B Sulfate *(rINNM)*

Polimiksin B Sülfat; Polimiksino B sulfatas; Polimixin-B-szulfát; Polimyksyny B siarczan; Polimyxini B sulfas; Polymyksiini-B-sulfaatti; Polymyxin B sulfat; Polymyxin B Sulphate *(BANM)*; Polymyxin-B-sulfát; Polymyxine B, sulfate de; Polymyxini B sulfas; Polymyxinum B Sulfas; Sulfato de polimixina B.

Полимиксина В Сульфат

CAS — 1404-26-8 (polymyxin B); 1405-20-5 (polymyxin B sulfate); 4135-11-9 (polymyxin B1); 34503-87-2 (polymyxin B2); 71140-58-4 (polymyxin B3).

ATC — A07AA05; J01XB02; S01AA18; S02AA11; S03AA03.

ATC Vet — QA07AA05; QJ01XB02; QS01AA18; QS02AA11; QS03AA03.

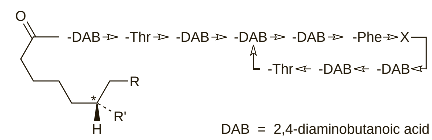

Polymyxin	R	R'	X	Mol. Formula
B1	CH	CH	-Leu	C H N O
B2	H	CH	-Leu	C H N O
B3	CH	H	-Leu	C H N O
B1-I	CH	CH	-Ile	C H N O

(polymyxin B)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Polymyxin B Sulphate). A mixture of the sulfates of polypeptides produced by the growth of certain strains of *Bacillus polymyxa* or obtained by any other means. A white or almost white, hygroscopic powder. Soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 31 (Polymyxin B Sulfate). The sulfate salt of a kind of polymyxin, a substance produced by the growth of *Bacillus polymyxa* (Bacillaceae), or a mixture of two or more such salts. A white to buff-coloured, powder, odourless or has a faint odour. It has a potency of not less than 6000 Polymyxin B units/mg, calculated on the dried substance. Freely soluble in water; slightly soluble in alcohol. pH of a 0.5% solution in water is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported with many other drugs including antibacterials. Polymyxin B sulfate is rapidly inactivated by strong acids and alkalis.

Units

The second International Standard Preparation (1969) of polymyxin B sulfate contains 8403 units/mg.

NOTE. The available forms of polymyxin B sulfate are generally less pure than the International Standard Preparation. Doses have sometimes been stated in terms of pure polymyxin base; 100 mg of pure polymyxin B is considered to be equivalent to 1 million units (1 mega unit).

Adverse Effects, Treatment, and Precautions

When given parenterally, the major adverse effects of the polymyxins are dose-related neurotoxicity and nephrotoxicity. Hypersensitivity reactions are rare, although rashes and fever have been reported, and polymyxins cause histamine release, which may lead to bronchoconstriction and other anaphylactoid symptoms. Polymyxins should be avoided in patients with a history of hypersensitivity to any of the group.

Neurotoxic reactions can occur in up to 7% of patients with normal renal function and include peripheral effects such as circumoral and 'stocking-glove' pattern paraesthesias, visual disturbances, and dizziness, ataxia, confusion, drowsiness, and other CNS effects. The polymyxins are potent neuromuscular blockers, and respiratory paralysis and apnoea may result, especially in overdosage and in patients with renal impairment or pre-existing disorders of neuromuscular transmission such as myasthenia gravis, in whom particular care is needed; certain medications may also increase the risk (see Interactions, below). Neostigmine or calcium salts are usually of little value in reversing neuromuscular blockade and artificial ventilation may be required if it develops.

Nephrotoxicity may occur in up to 20% of patients after parenteral use and may be marked by nitrogen retention, haematuria, proteinuria, and tubular necrosis. Electrolyte disturbances are common. Baseline renal function levels should be established before starting parenteral polymyxin B therapy and renal function and blood concentrations of polymyxins should be monitored frequently during therapy. Patients with pre-existing renal impairment and nitrogen retention are at particular risk and require dosage reduction. Signs of decreasing urine output and increasing nitrogen retention are an indication for stopping the drug in all patients. Although polymyxin B is said to be more nephrotoxic than colistin on a weight-for-weight basis, their effects on the kidney seem to be similar at therapeutically equivalent doses.

Polymyxin B is irritant; pain after intramuscular injection may be severe and thrombophlebitis can occur after intravenous injection. Meningeal irritation, manifest as fever, headache, stiff neck, and increased cell count and protein levels in the CSF, may follow intrathecal doses.

Ear drops containing polymyxins should not be used in patients with perforated ear drums, due to the increased risk of ototoxicity. Topical application to large areas of skin should be avoided because of the risk of systemic absorption resulting in neurotoxicity and nephrotoxicity, particularly in children, the elderly, and patients with renal impairment.

Interactions

Polymyxins may enhance the action of neuromuscular blockers (p.1903) possibly resulting in respiratory depression and apnoea, and concurrent use should be avoided. Additive neurotoxicity and/or nephrotoxicity may occur if polymyxins are given with other potentially neurotoxic and/or nephrotoxic drugs including aminoglycosides and cefaloridine; concurrent use should also be avoided.

Antimicrobial Action

Polymyxin B and the other polymyxin antibacterials act primarily by binding to membrane phospholipids and disrupting the bacterial cytoplasmic membrane. Polymyxin B has a bactericidal action on most Gram-negative bacilli except *Proteus* spp. It is particularly effective against *Pseudomonas aeruginosa*. Of the other Gram-negative organisms, *Acinetobacter* spp., *Escherichia coli*, *Enterobacter* and *Klebsiella* spp., *Haemophilus influenzae, Bordetella pertussis, Salmonella,* and *Shigella* spp. are sensitive. Classical *Vibrio cholerae* 01 is sensitive but the El Tor and O139 biotypes are resistant. *Serratia*, *Burkholderia*, and *Providencia* spp., and *Bacteroides fragilis* are usually resistant. It is not active against *Neisseria* spp., obligate anaerobes, and Gram-positive bacteria. Some fungi such as *Coccidioides immitis* are susceptible but most are resistant.

Antimicrobial synergy has been reported with other drugs, including chloramphenicol, tetracyclines, and the sulfonamides and trimethoprim.

The action of polymyxin B is reduced by divalent cations such as calcium and magnesium, and so activity *in vivo* is less marked than *in vitro*.

Acquired resistance to polymyxin B is uncommon, although adaptive resistance may develop in enterobacteria exposed to sublethal concentrations. There is complete cross-resistance between polymyxin B and colistin.

Pharmacokinetics

Polymyxin B sulfate is not absorbed from the gastrointestinal tract, except in infants who may absorb up to 10% of a dose. It is not absorbed through mucous membranes, or intact or denuded skin.

Peak plasma concentrations after intramuscular injection usually occur within 2 hours, but are variable and polymyxin B sulfate is partially inactivated by serum. It is widely distributed and extensively bound to cell membranes in the tissues; it does not appear to be highly bound to serum proteins. Accumulation may occur after repeated doses. There is no diffusion into the CSF and it does not cross the placenta. Polymyxin B is reported to have a serum half-life of about 6 hours but this is prolonged in renal impairment; values of 2 to 3 days have been reported in patients with a creatinine clearance of less than 10 mL/minute.

Polymyxin B sulfate is excreted mainly by the kidneys by glomerular filtration, about 60% of a dose being recovered unchanged in the urine, but there is a time lag of 12 to 24 hours before polymyxin B is recovered in the urine.

Polymyxin B is not removed to an appreciable extent by peritoneal dialysis or haemodialysis.

Uses and Administration

Polymyxin B sulfate is used topically, often with other drugs, in the treatment of skin, ear, and eye infections due to susceptible organisms. Eye drops containing polymyxin B with neomycin and gramicidin have been used for the prophylaxis of infection in patients undergoing ocular surgery and, with propamidine isetionate, for the treatment of acanthamoeba keratitis (p.822). Polymyxin B has been given orally with other drugs in regimens for selective digestive-tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p.175). Polymyxin B has also been used parenterally for the treatment of infections due to susceptible Gram-negative bacteria, especially *Pseudomonas aeruginosa,* but other drugs are generally preferred. Polymyxin B has been given intrathecally in meningeal infection, and by subconjunctival injection for eye infections.

For topical application polymyxin B is usually available as a 0.1% solution or ointment (10 000 units per mL or per g respectively) combined with other drugs. Intravenous doses range from 15 000 to 25 000 units/kg daily, by infusion and may be given every 12 hours. The intramuscular route has also been used despite the severe pain which may be associated with it; doses range from 25 000 to 30 000 units/kg daily, and may be given every 4 or 6 hours.

Doses should be reduced in patients with renal impairment (see below).

Intrathecal doses of 50 000 units may be given once daily for 3 to 4 days, then on alternate days for at least 2 weeks after the CSF cultures become negative.

For details of doses in children, including infants, see below.

For subconjunctival injection, doses of up to 100 000 units daily may be used for infections of the cornea and conjunctiva.

◊ References.

1. Evans ME, *et al.* Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Ann Pharmacother* 1999; **33:** 960–7.
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Arnold TM, *et al.* Polymyxin antibiotics for gram-negative infections. *Am J Health-Syst Pharm* 2007; **64:** 819–26.
4. Zavascki AP, *et al.* Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. *J Antimicrob Chemother* 2007; **60:** 1206–15.

Administration in children. Up to 40 000 units/kg daily of polymyxin sulfate may be given to infants with normal renal function by intravenous infusion or by intramuscular injection, although the latter is not recommended routinely because of severe pain at injection sites. Doses as high as 45 000 units/kg daily have been tried in premature and full-term neonates. For suggested doses in children with renal impairment see below.

In children under 2 years of age, intrathecal doses of 20 000 units once daily for 3 to 4 days or 25 000 units on alternate days may be given, followed by the latter dose for at least 2 weeks after the CSF cultures become negative.

Older children may be given the usual adult dose (see above).

Administration in renal impairment. Parenteral doses of polymyxin sulfate should be reduced in adults and children with renal impairment; a maximum intravenous dose of 15 000 units/kg daily has been suggested.

Preparations

BP 2008: Polymyxin and Bacitracin Eye Ointment;
USP 31: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Polymyxin B for Injection; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder; Polymyxin B Sulfate and Hydrocortisone Otic Solution; Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Braz.: Polixil B†; ***Philipp.:*** Aerosporin; ***Port.:*** Oto-Synalar N.

Multi-ingredient: ***Arg.:*** Belbar; Ginal Cent; Ginkan; Irix Biotic; Isoptomax; Linfol Cicatrizante; Mailen; Min O; Nebapol B†; Neoftalm; Neoftalm Dexa; Neolag; O-Biol P; Otosporin; Otosporin L; Ovumix; Pantometil; Pentol; Poenbioptal NF; Polygynax; Polyplex; Septigyn; Sincerum Biotic L; Terramicina con Polimixina B†; Trimepol; Trimepol D; Vagicural Plus; ***Austral.:*** Neosporin; ***Austria:*** Neocones; Otosporin; Polytrim; ***Belg.:*** De Icin†; Dexa-Polyspectran New; Maxitrol; Ophtalmotrim†; Otosporin†; Panotile; Polydexa; Polygynax†; Polyspectran Gramicidine; Polytrim; Predmycin P; Statrol; Synalar Bi-Otic; Terra-Cortril + Polymyxine B; Terramycine + Polymyxine B; ***Braz.:*** Anaseptil; Colpolase; Elotin; Ginec†; Lidosporin; Maxitrol; Nepodex; Otauril†; Otocort†; Otomixyn; Otosporin; Otosynalar; Panotil; Poliginax; Polipred; Polysporin; Predmicin; Terramicina c/Polimixina; ***Canad.:*** Antibiotic Cold Sore Ointment; Antibiotic Cream†; Antibiotique Onguent; Bacimyxin; Band-Aid Antibiotic; Bioderm; Cortimyxin; Cortisporin; Dioptrol†; Johnson & Johnson First Aid Ointment†; Lidomyxin; Lidosporin; Maxitrol; Neosporin; Neotopic†; Optimyxin; Optimyxin Plus; Ozonol Antibiotic Plus; PMS-Polytrimethoprim; Polycidin†; Polyderm; Polysporin; Polysporin Complete Antibiotic; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polytopic; Polytrim; ***Chile:*** Dermabiotico; Gotalgic; Grifoftal-D; Grifoftal†; Maxitrol; Oftabiotico; Otazol†; Oticum; Otolisan; Otoseptil; Unguento Dermico Antibiotico†; ***Cz.:*** Maxitrol; Otosporin; Polygynax; Pulpomixine; Statrol†; ***Denm.:*** Hydrocortison med Terramycin og Polymyxin-B; Terramycin Polymyxin B; ***Fin.:*** Maxitrol; Polysporin; Terra-Cortril P; ***Fr.:*** Antibio-Synalar; Antibiotulle Lumiere; Atebemyxine; Auricularum; Cebemyxine; Corticotulle Lumiere†; Framyxone; Maxidrol; Novomyxine†; Panotile; Polydexa; Polyfra; Polygynax; Polygynax Virgo; Primyxine†; Sterimycine†; ***Ger.:*** Antibiotulle Lumiere†; Corticotulle Lumiere†; Dexa Polyspectran; Farco-Tril†; Isopto Max; Kombi-Stulln N; Panotile N†; Polygynax†; Polyspectran; Polyspectran HC; Terracortril†; Terramycin†; ***Gr.:*** Fotocollyre; Isopto Maxitrol; Oxacycle-P; Paroticin; Statrol†; Terramycin; ***Hong Kong:*** Aplosyn-Otic; Cebemyxine; Maxitrol; Neosporin; Otosporin; Otozambon; PMS-Baximycin†; Polydex-N; Polydexa; Polyfax†;

Polygynax; Polyoph; Terramycin with Polymyxin B; ***Hung.:*** Oftalmotrim†; Otosporin; Polyspor; ***India:*** Chlormixin; Dexosyn Plus; Neosporin; Neosporin-H; Ocupol; Ocupol-D; ***Indon.:*** Inmatrol; Isotic Enpigi; Isotic Neolyson; Isotic Nepafrin; Kenetrol; Kloramixin; Kloramixin D; Maxitrol; Nelicort; Neocortic; Neofen; Neosyd; Oregan; Osatrol; Otolin; Otopain; Otopraf; Otozambon; Polidemisin; Polifrisin; Terramycin Poly; Ximex Optixitrol; ***Irl.:*** Maxitrol; Neosporin†; Otosporin; Polyfax; ***Israel:*** Auricularum; Bamyxin; Desoren; Dex-Otic; Maxitrol; Phenimixin; Tarocidin; Tarocidin D; Terramycin; ***Ital.:*** Anauran; Cicatrene; Mixotone; Otosporin†; Rinojet SF†; ***Malaysia:*** Bacitracin-N; Maxitrol; Oftalmotrim; Pocin G; Pocin H; Terramycin; ***Mex.:*** Alosol; Biodexan; Biofrin; Biotriamin; Cortisporin; Dexsul; Hidropolicin; Maxitrol; Neobacigrin; Neosporin; Nicobio†; Polixin; Poly-Micron; Rinadex Compuesto; Septilisin; Sulned; Synalar N; Synalar O; Synalar Oftalmico; Terramicina; Tribiot; ***Neth.:*** Maxitrol; Otosporin; Panotile; Polyspectran G†; Polytrim; Synalar Bi-Otic†; Terra-Cortril Gel Steraject met polymyxine-B†; Terra-Cortril met polymyxine-B; ***Norw.:*** Maxitrol; Terra-Cortril Polymyxin B; Terramycin Polymyxin B; ***NZ:*** Maxitrol; ***Philipp.:*** Aplosyn-Otic; BNP Ointment; Cortisporin; Hydrospor; Isonep; Isonep H; Maxirap; Maxitrol; Maxoptic; Neosporin; Novasorin; Postop; Postotic; Predmycin-P; Statrol; Synalar Otic; Syntemax; Terramycin; Terramycin Plus; Trimycin; Trimycin-H; ***Pol.:*** Atecortin; Dexadent; Maxitrol; Multibiotic; Neotopic; Tribiotic; ***Port.:*** Conjunctilone; Conjunctilone-S; Oftalmotrim; Otosporin; Polisulfade; Polydexa; ***Rus.:*** Anauran (Анауран); Maxitrol (Макситрол); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Polygynax (Полижинакс); ***S.Afr.:*** Maxitrol; Neosporin†; Otosporin; Polysporin; Polytrim†; Terra-Cortril; Terramycin; ***Singapore:*** Maxitrol; Polybamycin; Polydexa; Polygynax; Predmycin-P†; Terramycin; ***Spain:*** Bacisporin; Blastoestimulina; Creanolona; Dermisone Tri Antibiotic; Liquipom Dexa Antib; Maxitrol; Neocones; Oftalmotrim; Oftalmotrim Dexa†; Oftalmowell; Otix; Otosporin; Panotile; Phonal; Poly Pred; Pomada Antibiotica; Synalar Nasal; Synalar Otico; Terra-Cortril; Terramicina; Tivitis; Tulgrasum Antibiotico; Vinciseptil Otico; ***Swed.:*** Isopto Biotic†; Terracortril med polymyxin B; Terramycin Polymyxin B; ***Switz.:*** Baneopol; Maxitrol; Mycinopred; Neosporin; Otosporin; Panotile; Polydexa; Spersapolymyxin; Terracortril†; ***Thai.:*** Banocin; Maxitrol; My-B; Neosporin†; Opsacin†; Otosamthong; Otosporin†; Polyoph; Predmycin†; Primoptic†; Spersapolymyxin; Terramycin; Terrasil†; Xanalin; ***Turk.:*** Cebemyxine; Geotril; Heksa; Neosporin; Oftalmotrim; Polimisin; Polycilline; Polytrim; Sekamisin; Terramycin; ***UK:*** Gregoderm†; Maxitrol; Neosporin; Otosporin; Polyfax; Polytrim†; ***USA:*** Ak-Poly-Bac; Ak-Spore; Ak-Trol†; Betadine First Aid Antibiotics + Moisturizer; Betadine Plus First Aid Antibiotics & Pain Reliever; Cortatrigen; Cortimycin; Cortisporin; Dexacidin†; Dexacine†; Dexasporin; Ear-Eze; Lanabiotic†; LazerSporin-C; Maxitrol; Mycitracin†; Neocin; Neopolydex; Neosporin; Neosporin + Pain Relief; Neosporin GU; Neosporin†; Neotricin HC; Octicair†; Ocu-Spor-B; Ocu-Spor-G; Ocu-Trol; Ocutricin; Otic-Care; OtiTricin; Otobiotic; Otocort; Otomycin-HPN; Otosporin; Pediotic; Poly-Dex; Poly-Pred; Polycin-B; Polymycin; Polysporin†; Polytracin; Polytrim; Spectrocin Plus†; Terak; Terramycin with Polymyxin B; Tri-Biozene; UAD-Otic; ***Venez.:*** Dermabiotic; Maxicort; Maxitrol; Neo-Synalar†; Ofterra; Otocort; Poli-Otico; Terramicina con Polimixina B.

Pristinamycin *(BAN, rINN)*

Pristinamicina; Pristinamycine; Pristinamycinum; RP-7293.

Пристинамицин

CAS — 270076-60-3.
ATC — J01FG01.
ATC Vet — QJ01FG01.

Profile

Pristinamycin is a streptogramin antibacterial produced by the growth of *Streptomyces pristina spiralis*, with actions and uses similar to those of virginiamycin (p.361). It is given orally in the treatment of susceptible infections, particularly staphylococcal infections, in a dose of 2 to 4 g daily in divided doses.

◊ Pristinamycin is a naturally occurring mixture of two synergistic components, pristinamycin I which is a macrolide, and pristinamycin II which is a depsipeptide.[1] It has been available for many years as an oral antistaphylococcal drug, and also acts against streptococci. It is effective against strains showing resistance to erythromycin; resistance to pristinamycin is rare,[2,3] although resistance in staphylococci has been reported in the past.[4,5] It is effective against meticillin-resistant *Staphylococcus aureus* (MRSA)[6,7] but its usefulness in severe infection is limited by its poor solubility, which prevents development of an intravenous formulation. Oral pristinamycin has been shown to be as effective as standard therapy with intravenous then oral penicillin in the treatment of erysipelas.[8]

Mixtures of water-soluble derivatives of pristinamycins I and II, such as quinupristin/dalfopristin (p.322), are in clinical use or under investigation.

1. Hamilton-Miller JMT. From foreign pharmacopoeias: 'new' antibiotics from old? *J Antimicrob Chemother* 1991; **27:** 702–5.
2. Weber P. Streptococcus pneumoniae: absence d'émergence de résistance à la pristinamycine. *Pathol Biol (Paris)* 2001; **49:** 840–5.
3. Leclercq R, *et al.* Activité in vitro de la pristinamycine vis-à-vis des staphylocoques isolés dans les hôpitaux français en 1999-2000. *Pathol Biol (Paris)* 2003; **51:** 400–4.
4. Loncle V, *et al.* Analysis of pristinamycin-resistant Staphylococcus epidermidis isolates responsible for an outbreak in a Parisian hospital. *Antimicrob Agents Chemother* 1993; **37:** 2159–65.
5. Allignet J, *et al.* Distribution of genes encoding resistance to streptogramin A and related compounds among staphylococci resistant to these antibiotics. *Antimicrob Agents Chemother* 1996; **40:** 2523–8.
6. Dancer SJ, *et al.* Oral streptogramins in the management of patients with methicillin-resistant Staphylococcus aureus (MRSA) infections. *J Antimicrob Chemother* 2003; **51:** 731–5.
7. Ng J, Gosbell IB. Successful oral pristinamycin therapy for osteoarticular infections due to methicillin-resistant Staphylococcus aureus (MRSA) and other Staphylococcus spp. *J Antimicrob Chemother* 2005; **55:** 1008–12.
8. Bernard P, *et al.* Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* 2002; **325:** 864–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Pyostacine; ***Israel:*** Pyostacine.

Procaine Benzylpenicillin *(BAN, rINNM)*

Bensylpenicillinprokain; Bentsyylipenisilliiniprokaiini; Benzilpenicilinas prokainas; Benzilpenicillin-prokain; Benzylopenicylina prokainowa; Benzylpenicillin Novocaine; Benzylpénicilline Procaïne; Benzylpenicillinum procainum; Penicillin G Procaine; Procaína bencilpenicilina; Procaïne Benzylpénicilline; Procaine Penicillin G; Procaini Benzylpenicillinum; Procainum Benzylpenicillinum; Prokain Benzilpenisilin; Prokain Penisilin G; Prokain-benzylpenicilin. 2-(4-Aminobenzoyloxy)ethyldiethylammonium (6*R*)-6-(2-phenylacetamido)penicillanate monohydrate.

Прокаин Бензилпенициллин

$C_{13}H_{20}N_2O_2,C_{16}H_{18}N_2O_4S,H_2O$ = 588.7.
CAS — 54-35-3 (anhydrous procaine benzylpenicillin); 6130-64-9 (procaine benzylpenicillin monohydrate).
ATC — J01CE09.
ATC Vet — QJ01CE09; QJ51CE09.

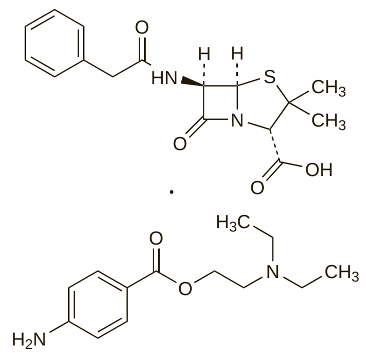

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Benzylpenicillin, Procaine). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol. A 0.33% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Procaine). White crystals or white, very fine, microcrystalline powder, odourless or practically odourless. Slightly soluble in water; soluble in alcohol and in chloroform. It is rapidly inactivated by acids, by alkali hydroxides, and by oxidising agents. pH of a saturated solution in water is between 5.0 and 7.5.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Procaine benzylpenicillin should not be given to patients known to be hypersensitive to either of its components. Procaine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Severe, usually transient, reactions with symptoms of severe anxiety and agitation, confusion, psychotic reactions including visual and auditory hallucinations, seizures, tachycardia and hypertension, cyanosis, and a sensation of impending death have occasionally been reported with procaine benzylpenicillin and may be due to accidental intravascular injection. Since similar reactions have also occurred with other depot penicillin preparations that do not contain procaine, its presence is unlikely to be the major cause of such reactions, but may be a contributory factor, especially after injection of high doses. These reactions have been termed non-allergic, pseudoallergic, pseudoanaphylactic, or Hoigné's syndrome; the term 'embolic-toxic reaction' has also been proposed.

Interactions

As for Benzylpenicillin, p.214.

Pharmacokinetics

When procaine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in 1 to 4 hours, and effective concentrations of benzylpenicillin are usually maintained for 12 to 24 hours. However, plasma concentrations are lower than those after an equivalent dose of benzylpenicillin potassium or sodium.

Distribution into the CSF is reported to be poor.

Uses and Administration

Procaine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p.214) to which it is hydrolysed gradually following deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations produced, its use should be restricted to infections caused by micro-organisms that are highly sensitive to penicillin. Procaine benzylpenicillin should not be used as the sole treatment for severe acute infections, or when bacteraemia is present.

Procaine benzylpenicillin is used mainly in the treatment of syphilis; other indications have included pneumonia (in children in developing countries), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Doses of procaine benzylpenicillin may sometimes be expressed in terms of equivalent units of benzylpenicillin. Procaine benzylpenicillin 600 mg is equivalent to about 360 mg of benzylpenicillin (600 000 units). Procaine benzylpenicillin is given by deep intramuscular injection in usual doses of 0.6 to 1.2 g daily.

Patients with syphilis are given procaine benzylpenicillin 1.2 g daily for 10 to 14 days; infants up to 2 years of age with congenital syphilis may be given 50 mg/kg daily. Treatment may be continued for 3 weeks in patients with late syphilis.

Procaine benzylpenicillin is also used in combined preparations with other penicillins, including benzylpenicillin and benzathine benzylpenicillin.

Preparations

USP 31: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Procaine for Injectable Suspension; Penicillin G Procaine Injectable Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Mudapenil†; Penicil Dermol†; ***Austral.:*** Cilicaine Syringe; ***Cz.:*** Pendepon Compositum; ***Ger.:*** Jenacillin O†; ***Hung.:*** Retardillin; ***Mex.:*** Benzotripen; Farmabep; Promizol; Sodilin; Unicil 3/1; Unicil 6:3:3; ***NZ:*** Cilicaine; ***S.Afr.:*** Bio-Cillin; Novocillin†; Procillin; ***Spain:*** Aqucilina; Farmaproina; ***Turk.:*** Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Penadur 6.3.3; Penkain-K; Procillin; ***USA:*** Crysticillin; ***Venez.:*** Pebencil†; Pronapen; Silcopen†.

Multi-ingredient: ***Austria:*** Fortepen; Retarpen compositum; ***Braz.:*** Benapen; Benzapen G; Despacilina; Drenovac†; Expectovac†; Ginurovac†; Linfocilin†; Odontovac†; Ortocilin†; Pencil 400; Penkaron; Wycillin; ***Chile:*** Karbasalin†; ***Ger.:*** Bipensaar; Jenacillin A†; Retacillin compositum; ***Hong Kong:*** Penicillin G Procaine Fortified; ***Hung.:*** Promptcillin Forte; ***India:*** Bistrepen; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Hidrocilina; Lugaxil; Pecivax; Pendiben Compuesto; Penicil; Penipot; Penisodina; Penprocilina; Procilin; Respicil; Robencaxil; Suipen; ***Neth.:*** Penidural D/F†; ***Port.:*** Atralcilina; Lentocilin; Penadur 6.3.3†; ***Rus.:*** Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Aqucilina D A; Benzetacil Compuesta; Cepacilina 633; ***USA:*** Bicillin C-R; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Propicillin Potassium *(BANM, pINNM)*

Kalii Propicillinum; Potassium α-Phenoxypropylpenicillin; Propicilina potásica; Propicilline Potassique; Propicillinum Kalicum. A mixture of the D(+)- and L(−)-isomers of potassium (6*R*)-6-(2-phenoxybutyramido)penicillanate.

Калия Пропициллин

$C_{18}H_{21}KN_2O_5S$ = 416.5.
CAS — 551-27-9 (propicillin); 1245-44-9 (propicillin potassium).
ATC — J01CE03.
ATC Vet — QJ01CE03.

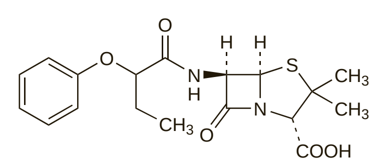

(propicillin)

The symbol † denotes a preparation no longer actively marketed

Profile

Propicillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p.314). Propicillin potassium is given orally for the treatment of susceptible mild to moderate infections in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Baycillin.

Protionamide *(BAN, rINN)*

Prothionamide; Protionamid; Protionamida; Protionamidi; Protionamidum; RP-9778; TH-1321. 2-Propylpyridine-4-carbothioamide.

Протионамид

$C_9H_{12}N_2S$ = 180.3.
CAS — 14222-60-7.
ATC — J04AD01.
ATC Vet — QJ04AD01.

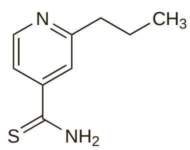

Pharmacopoeias. In *Chin.*, *Int.*, and *Jpn.*

Adverse Effects, Precautions, and Antimicrobial Action

As for Ethionamide, p.275.

Pharmacokinetics

Protionamide is readily absorbed from the gastrointestinal tract and produces peak plasma concentrations about 2 hours after an oral dose. It is widely distributed throughout body tissues and fluids, including the CSF. Protionamide is metabolised to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

Uses and Administration

Protionamide is a thioamide derivative considered to be interchangeable with ethionamide (p.276) and is used as a second-line drug in the treatment of multidrug-resistant tuberculosis (p.196). It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p.176) but less toxic alternatives are now preferred. Complete cross-resistance occurs between the two drugs. Protionamide has been given orally in doses similar to those used for ethionamide. It has also been given as rectal suppositories; protionamide hydrochloride has been given intravenously. Like ethionamide, it has generally been replaced by less toxic antimycobacterials.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: ektebin; Peteha; ***Hong Kong:*** Peteha; ***India:*** Prothicid; ***Turk.:*** Promid; Tionamid.

Multi-ingredient: ***Austria:*** Isoprodian; ***Ger.:*** Isoprodian†; Peteha†; ***Rus.:*** Protiocomb (Протиокомб).

Prulifloxacin *(rINN)*

NM-441; Prulifloxacine; Prulifloxacino; Prulifloxacinum. (±)-7-{4-[(*Z*)-2,3-Dihydroxy-2-butenyl]-1-piperazinyl}-6-fluoro-1-methyl-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid cyclic carbonate.

Прулифлоксацин

$C_{21}H_{20}FN_3O_6S$ = 461.5.
CAS — 123447-62-1.
ATC — J01MA17.
ATC Vet — QJ01MA17.

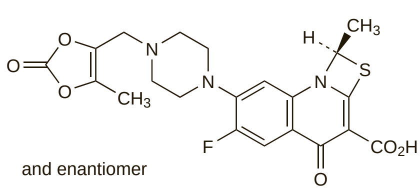

and enantiomer

Profile

Prulifloxacin is the prodrug of ulifloxacin, a fluoroquinolone antibacterial. It is given for the treatment of susceptible infections in a usual oral dose of 600 mg daily.

◊ Reviews.

1. Keam SJ, Perry CM. Prulifloxacin. *Drugs* 2004; **64:** 2221–34.
2. Prats G, *et al.* Prulifloxacin: a new antibacterial fluoroquinolone. *Expert Rev Anti Infect Ther* 2006; **4:** 27–41.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Unidrox; ***Gr.:*** Glimbax; Prixina; ***Ital.:*** Chinoplus; Keraflox; Unidrox; ***Port.:*** Keraflox; Oliflox.

Pyrazinamide *(BAN, rINN)*

Pirazinamid; Pirazinamida; Pirazinamidas; Pirazynamid; Pyratsiiniamidi; Pyrazinamid; Pyrazinamidum; Pyrazinoic Acid Amide. Pyrazine-2-carboxamide.

Пиразинамид

$C_5H_5N_3O$ = 123.1.
CAS — 98-96-4.
ATC — J04AK01.
ATC Vet — QJ04AK01.

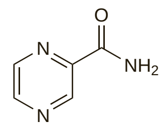

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Pyrazinamide). A white or almost white, crystalline powder. Sparingly soluble in water, slightly soluble in alcohol and in dichloromethane.

USP 31 (Pyrazinamide). A white to practically white, odourless or practically odourless, crystalline powder. Soluble 1 in 67 of water, 1 in 175 of dehydrated alcohol, 1 in 135 of chloroform, 1 in 1000 of ether, and 1 in 72 of methyl alcohol; slightly soluble in alcohol.

Adverse Effects and Treatment

Hepatotoxicity is the most serious adverse effect of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended doses, when given with isoniazid and rifampicin, the incidence of hepatitis has been reported to be less than 3%. Patients may have a transient increase in liver enzyme values; more seriously hepatomegaly, splenomegaly, and jaundice may develop and on rare occasions death has occurred.

Hyperuricaemia commonly occurs and may lead to attacks of gout.

Other adverse effects are anorexia, nausea, vomiting, aggravation of peptic ulcer, arthralgia, malaise, fever, sideroblastic anaemia, thrombocytopenia, and dysuria. Photosensitivity, pellagra, and skin rashes have been reported on rare occasions.

Effects on the cardiovascular system. Acute hypertension was associated with pyrazinamide in a previously normotensive woman.[1]

1. Goldberg J, *et al.* Acute hypertension as an adverse effect of pyrazinamide *JAMA* 1997; **277:** 1356.

Effects on the liver. The risk of hepatitis with antituberculous regimens containing pyrazinamide may be lower than suggested by early studies, in which large doses were used, often for long periods. The incidence of hepatitis in studies[1] of short-course regimens containing pyrazinamide has ranged from 0.2% in Africa, to 0.6% in Hong Kong, to 2.8% in Singapore. These and later studies[2-4] have shown that hepatotoxicity is not increased when pyrazinamide is added to the initial phase of short-term chemotherapy containing rifampicin and isoniazid. Nevertheless, a report[5] of 4 cases of fulminant hepatic failure in patients given triple therapy with the potentially hepatotoxic drugs rifampicin, isoniazid, and pyrazinamide (1 patient also received ethambutol) highlighted the importance of strict liver function monitoring and this was reinforced by others. The Joint Tuberculosis Committee of the British Thoracic Society has produced recommendations[6] for initial measurement of liver function in all patients and regular monitoring in patients with pre-existing liver disease, as well as the response to deteriorating liver function; prompt re-introduction of appropriate antituberculosis therapy is recommended once normal liver function is restored. Similar guidelines have been produced for the USA.[7,8] For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p.288.

The incidence of severe hepatotoxicity was found to be lower in patients receiving isoniazid, rifampicin, and pyrazinamide for initial treatment of active disease, than in those receiving rifampicin and pyrazinamide for 2 months for latent tuberculosis infection. For further information on hepatotoxicity caused by rifampicin and pyrazinamide see Effects on the Liver, under Rifampicin, p.326.

1. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 1984; **65:** 1–4.
2. Parthasarathy R, *et al.* Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1986; **67:** 99–108.
3. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
4. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
5. Mitchell I, *et al.* Anti-tuberculous therapy and acute liver failure. *Lancet* 1995; **345:** 555–6.
6. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
7. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
8. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculous therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/sections/publications/statements/resources/hepatotoxicity-of-antituberculous-therapy.pdf (accessed 05/10/07)

Effects on the nervous system. Convulsions that developed in a 2-year-old child receiving antituberculous therapy appeared to be due to pyrazinamide, given in a dose of 250 mg daily.[1]

1. Herlevsen P, *et al.* Convulsions after treatment with pyrazinamide. *Tubercle* 1987; **68:** 145–6.

Hyperuricaemia. Hyperuricaemia during therapy with pyrazinamide may be due to inhibition of uric acid excretion by pyrazinoic acid, the main metabolite of pyrazinamide.[1]

In a large multicentre study,[2] the incidence of elevated serum concentrations of uric acid for patients receiving rifampicin, isoniazid, and pyrazinamide was 52.2% at 8 weeks while the incidence for patients receiving rifampicin and isoniazid was 5.4%. Arthralgia was reported in 6 of 617 patients receiving rifampicin, isoniazid, and pyrazinamide, but in none of 445 patients receiving rifampicin and isoniazid.

Slight increases in plasma concentrations of uric acid occurred in 9 of 43 children after one month's treatment with rifampicin, isoniazid, ethambutol, and pyrazinamide. Arthralgias and gout did not occur. Uric acid concentrations were normal on completion of treatment with pyrazinamide.[3] Some studies[4] have suggested a relationship between elevated serum uric acid levels and arthralgia, but this has not been confirmed.[5]

1. Ellard GA, Haslam RM. Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. *Tubercle* 1976; **57:** 97–103.
2. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
3. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
4. Hong Kong Tuberculosis Treatment Services/British MRC. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. *Tubercle* 1976; **57:** 81–95.
5. Jenner PJ, *et al.* Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. *Tubercle* 1981; **62:** 175–9.

Pellagra. Pellagra, probably due to pyrazinamide, developed in a 26-year-old woman receiving antituberculous therapy.[1] Symptoms regressed, despite continued therapy, on giving nicotinamide.

1. Jørgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983; **22:** 44–5.

Precautions

Pyrazinamide should be used with caution in patients with liver disorders and is contra-indicated in established chronic or severe liver disease. In patients with liver disorders, liver function should be assessed before and regularly during treatment. The British Thoracic Society has recommended that pyrazinamide treatment should be suspended if serum aminotransferase concentrations are elevated to 5 times the normal upper limit or if the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. WHO recommends that pyrazinamide not be reintroduced if the hepatitis produced a clinical jaundice.

Pyrazinamide should not be given to patients with acute gout or hyperuricaemia and should be used with caution in patients with a history of gout. Caution should also be observed in patients with renal impairment. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Porphyria. Pyrazinamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Although detailed teratogenicity data are not available, WHO,[1] the IUATLD,[2] the British Thoracic Society,[3] and the CDC[4] do not contra-indicate pyrazinamide in pregnant patients.

1. WHO. *Treatment of tuberculosis: guidelines for national programmes*. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 03/10/07)
2. Caminero Luna JA. *A tuberculosis guide for specialist physicians.* Paris: International Union Against Tuberculosis and Lung Disease (IUATLD), 2004. Available at: http://www.tbrieder.org/publications/specialists_en.pdf (accessed 03/10/07)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]

Interactions

Antigout drugs. The complex interactions occurring when pyrazinamide and *probenecid* are given to patients with gout have been studied.[1] Urinary excretion of urate depends on the relative size and timing of doses of the two drugs. Probenecid is known to block the excretion of pyrazinamide. A pharmacokinetic study[2] in 6 healthy subjects found that *allopurinol*, a xanthine oxidase inhibitor, increases concentrations of pyrazinoic acid (the main metabolite of pyrazinamide) thereby worsening pyrazinamide-induced hyperuricaemia. Allopurinol would therefore also appear to be unsuitable for treating pyrazinamide-induced hyperuricaemia.

1. Yü TF, *et al.* The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. *Am J Med* 1977; **63:** 723–8.
2. Lacroix C, *et al.* Interaction between allopurinol and pyrazinamide. *Eur Respir J* 1988; **1:** 807–11.

Zidovudine. Low or undetectable concentrations of pyrazinamide occurred in 4 patients also taking zidovudine.[1] In the same study, 6 of 7 patients with HIV infection taking pyrazinamide without zidovudine had normal serum pyrazinamide concentrations.

1. Peloquin CA, *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30:** 919–25.

Antimicrobial Action

Pyrazinamide has a bactericidal effect on *Mycobacterium tuberculosis* but appears to have no activity against other mycobacteria or micro-organisms *in vitro*. It is almost completely inactive at a neutral pH, but is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages. The initial inflammatory response to chemotherapy increases the number of organisms in the acidic environment. As inflammation subsides and pH increases, the sterilising activity of pyrazinamide decreases. This pH-dependent activity explains the clinical effectiveness of pyrazinamide as part of the initial 8-week phase in short-course treatment regimens.

Resistance to pyrazinamide rapidly develops when it is used alone.

Action. Although the antimicrobial activity of pyrazinamide has been recognised since the 1950s, the mode of action is still unclear. One proposal is that pyrazinoic acid is the active moiety. Pyrazinamidase produced by the tubercle bacilli is known to convert pyrazinamide to pyrazinoic acid. A further proposal[1] is that the pyrazinoic acid formed within the macrophage would be trapped, thereby lowering intracellular pH to levels toxic to tubercle bacilli.

1. Salfinger M, *et al.* Pyrazinamide and pyrazinoic acid activity against tubercle bacilli in cultured human macrophages and in the BACTEC system. *J Infect Dis* 1990; **162:** 201–7.

Activity with other antimicrobials. Pyrazinamide exhibited synergistic activity against *Mycobacterium tuberculosis* with clarithromycin.[1]

1. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; **41:** 2035–6.

Pharmacokinetics

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 hours after an oral dose and have been reported to be about 33 micrograms/mL after 1.5 g, and 59 micrograms/mL after 3 g. Pyrazinamide is widely distributed in body fluids and tissues and diffuses into the CSF. The half-life has been reported to be about 9 to 10 hours. It is metabolised primarily in the liver by hydrolysis to the major active metabolite pyrazinoic acid, which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidneys mainly by glomerular filtration. About 70% of a dose appears in the urine within 24 hours mainly as metabolites and about 4% as unchanged drug. Pyrazinamide is removed by dialysis. Pyrazinamide is distributed into breast milk.

◊ A short distribution phase and an elimination phase of 9.6 hours in healthy subjects after a single oral dose of pyrazinamide 27 mg/kg has been reported;[1] the half-life for the major metabolite pyrazinoic acid was 11.8 hours.

In the major metabolic pathway, pyrazinamide was deaminated to pyrazinoic acid which was hydroxylated to hydroxypyrazinoic acid; in the minor pathway, pyrazinamide was hydroxylated to hydroxypyrazinamide which was then deaminated to hydroxypyrazinoic acid. The limiting step was deamination; oxidation by xanthine oxidase occurred very quickly.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *Eur J Clin Pharmacol* 1989; **36:** 395–400.

Bioavailability. The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[1] However, another report[2] showed slightly reduced peak serum concentrations when pyrazinamide was given with a high-fat meal, and the authors suggested that pyrazinamide should preferably be given on an empty stomach.

1. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; **76:** 109–13.
2. Peloquin CA, *et al.* Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* 1998; **18:** 1205–11.

Breast feeding. The peak concentration of pyrazinamide in breast milk of a 29-year-old woman was 1.5 micrograms/mL 3 hours after a 1-g dose.[1] The peak plasma concentration was 42 micrograms/mL after 2 hours.

1. Holdiness MR. Antituberculosis drugs and breast-feeding. *Arch Intern Med* 1984; **144:** 1888.

Distribution. Pyrazinamide was given to 28 patients with suspected tuberculous meningitis in doses of 34 to 41 mg/kg. The mean concentration of pyrazinamide in the CSF after 2 hours was 38.6 micrograms/mL and represented about 75% of that in serum; concentrations at 5 and 8 hours were 44.5 and 31.0 micrograms/mL respectively and were about 10% higher than those in serum.[1] The use of corticosteroids appeared to have no influence on penetration of pyrazinamide into the CSF of patients with tuberculous meningitis.[2]

1. Ellard GA, *et al.* Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *BMJ* 1987; **294:** 284–5.
2. Woo J, *et al.* Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; **42:** 235–42.

Hepatic impairment. A study[1] of the pharmacokinetics of pyrazinamide was carried out in 10 patients with cirrhosis of the liver. After a dose of 19.3 mg/kg, the elimination phase was about 15 hours for pyrazinamide and 24 hours for the major metabolite pyrazinoic acid.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. *Arzneimittelforschung* 1990; **40:** 76–9.

HIV-infected patients. Malabsorption of pyrazinamide and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p.328.

Uses and Administration

Pyrazinamide is used as part of multidrug regimens for the treatment of tuberculosis (p.196), primarily in the initial 8-week phase of short-course treatment. Pyrazinamide is usually given daily or 2 or 3 times weekly. In the UK, usual recommended oral doses for adults under 50 kg are 1.5 g daily, or 2 g three times weekly, or 3 g twice weekly. The usual dose for those 50 kg or greater is 2 g daily, or 2.5 g three times weekly, or 3.5 g twice weekly. The recommended doses in the USA are 20 to 25 mg/kg daily (maximum 2 g) or 1.5 to 3 g three times weekly or 2 to 4 g twice weekly. WHO recommends 25 mg/kg daily or 35 mg/kg three times weekly.

For details of doses in infants, children, and adolescents, see below.

Pyrazinamide has also been used in the chemoprophylaxis of tuberculosis (see below).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy; thereby decreasing the risk of acquired drug resistance. Combination products containing pyrazinamide with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and ethambutol are available in some countries.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests a dose of pyrazinamide of 20 to 40 mg/kg daily or 50 mg/kg (to a maximum of 2 g) twice weekly by mouth, for the initial treatment phase. For children 1 month and older the *BNFC* suggests a dose of 35 mg/kg (to a maximum of 1.5 g in those under 50 kg and 2 g in those over 50 kg) once daily or 50 mg/kg (to a maximum of 2 g in those under 50 kg and 2.5 g in those over 50 kg) three times a week. WHO recommends 25 mg/kg once daily or 35 mg/kg three times a week.

Administration in hepatic impairment. See Precautions, above.

Administration in renal impairment. Pyrazinamide is mainly metabolised in the liver, but its metabolites are excreted in the urine, therefore the CDC[1] suggests that the dose may need to be reduced in patients with renal impairment. The Joint Tuberculosis Committee of the British Thoracic Society[2] and WHO[3] consider that standard dosage may be used in such patients. Dialysis affects the clearance of pyrazinamide and CDC recommends reducing the dose to 25 to 35 mg/kg three times a week after dialysis.

In a study[4] of 6 patients on haemodialysis, the average amount of pyrazinamide and its metabolites removed during a dialysis session was 926 mg after an oral dose of 1700 mg. It was recommended that the usual pyrazinamide dose be given to patients on dialysis as the risk of accumulation was negligible, and that the dose on dialysis days be given after the procedure.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. WHO. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 03/10/07)
4. Lacroix C, *et al.* Haemodialysis of pyrazinamide in uraemic patients. *Eur J Clin Pharmacol* 1989; **37:** 309–11.

Tuberculosis chemoprophylaxis. In the USA, the American Thoracic Society and the CDC recommended a dose of pyrazinamide 15 to 20 mg/kg daily (maximum 2 g daily) with rifampicin 600 mg daily as an alternative to isoniazid monotherapy for the treatment of latent tuberculosis infection.[1] (In those unable to take rifampicin, it was substituted with rifabutin 300 mg daily.) However, owing to reports of serious and fatal liver damage (see Effects on the Liver, under Adverse Effects, above) the CDC and the American Thoracic Society now recommend that the combination of pyrazinamide with rifampicin should not be offered to persons with latent tuberculosis.[2].

1. American Thoracic Society and CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; **161** (suppl): S221–S247.
2. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52:** 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)

Preparations

BP 2008: Pyrazinamide Tablets;
USP 31: Pyrazinamide Tablets; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Zinamide; ***Austria:*** Pyrafat; ***Belg.:*** Tebrazid; ***Braz.:*** Pirazinon; ***Canad.:*** Tebrazid; ***Cz.:*** Tisamid†; ***Fin.:*** Tisamid; ***Fr.:*** Pirilene; ***Ger.:*** Pyrafat; PZA; ***Hong Kong:*** Pyrafat; ***India:*** Actizid†; P-Zide; Pyzina; PZA-Ciba; Rifacom E-Z; ***Indon.:*** Corsazinamid; Neotibi; Pezeta-Ciba; Prazina; Sanazet; Siramid; TB ZET; ***Irl.:*** Zinamide†; ***Ital.:*** Piraldina; ***Malaysia:*** PZA; ***Mex.:*** Nizamyl; ***NZ:*** Zinamide; ***Philipp.:*** Pyramin; Pyrasol; PZA-Ciba; Zapedia; Zcure; Zinaplex; ***Port.:*** Piraside†; Pramide; ***S.Afr.:*** Pyrazide†; ***Singapore:*** PZA; ***Thai.:*** Myrin-P; Pyramide; Pyratab†; PZA; ***Turk.:*** Pirazinid.

Multi-ingredient: ***Austria:*** Rifater; ***Canad.:*** Rifater; ***Denm.:*** Rimstar; ***Fin.:*** Rimstar; ***Fr.:*** Rifater; ***Ger.:*** Rifater; tebesium Trio; ***Gr.:*** Rifater; ***Hong Kong:*** Rifater; ***India:*** Akt-4; Coxina-4; Cx-5; Gocox-3; R-Cinex Z; RHZ;

The symbol † denotes a preparation no longer actively marketed

RHZ-Plus; Rifacomb Plus†; Rimactazid + Z; Tricox; Wokex-4; Xeed-4; ***Indon.:*** Rimcure; Rimstar; ***Irl.:*** Rifater; ***Ital.:*** Rifater; ***Malaysia:*** Rimcure; ***Mex.:*** Arpisen; Finateramida; Rifater; ***Philipp.:*** 4D; CombiKids; CombiPack; Econokit; Econokit-MDR; Econopack; Fixcom 4; Kidz Kit 3; Myrin-P; Quadtab; Refam Pedia Kit; Rifater; Rimcure; Rimstar; SVM-Polypac-A; Triofix; Viper; ***Port.:*** Rifater; ***Rus.:*** Isocomb (Изоком6); Lomecomb (Ломеком6); Phthizopiram (Фтизопирам); Protiocomb (Протиоком6); Repin B (Репин В); Rifacomb Plus (Рифаком6 Плюс); Rimecure 3-FDC (Римкур 3-ФДС); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Rifafour; Rifater; Rimcure; Rimstar; ***Spain:*** Rifater; Rimcure; Rimstar; ***Swed.:*** Rimcure; Rimstar; ***Switz.:*** Rifater; ***Thai.:*** Rifafour; Rifampyzid; Rifater; Rimcure 3-FDC; Rimstar; ***UK:*** Rifater; ***USA:*** Rifater; ***Venez.:*** Rimcure.

Quinupristin/Dalfopristin

Quinupristin *(BAN, USAN, rINN)*; Dalfopristin *(BAN, USAN, rINN)*; Kinupristiini/dalfopristiini; Kinupristin/dalfopristin; Quinupristina/dalfopristina; Quinupristine/dalfopristine; Quinupristinum/dalfopristinum; RP-59500.

Хинупристин/Дальфопристин

CAS — 126602-89-9 (quinupristin/dalfopristin); 176861-85-1 (quinupristin/dalfopristin).

ATC — J01FG02.

ATC Vet — QJ01FG02.

Dalfopristin Mesilate *(BANM, rINNM)*

Dalfopristin Mesylate; Dalfopristine, Mésilate de; Dalfopristini Mesilas; Mesilato de dalfopristina; RP-54476 (dalfopristin). (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-{[2-(Diethylamino)ethyl]sulfonyl}-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2.1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone methanesulphonate; (26*R*,27*S*)-26-{[2-(Diethylamino)-ethyl]sulfonyl}-26,27-dihydrovirginiamycin M_1 methanesulphonate.

Дальфопристина Мезилат

$C_{34}H_{50}N_4O_9S,CH_4O_3S = 787.0.$

CAS — 112362-50-2 (dalfopristin).

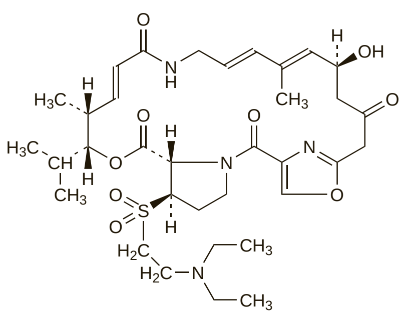

(dalfopristin)

Quinupristin Mesilate *(BANM, rINNM)*

Mesilato de quinupristina; Quinupristin Mesylate; Quinupristine, Mésilate de; Quinupristini Mesilas; RP-57669 (quinupristin). *N*-{(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(Dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-{[(3*S*)-3-quinuclidinylthio]methyl}-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl}-3-hydroxy-picolinamide methanesulphonate; 4-[4-(Dimethylamino)-*N*-methyl-L-phenylalanine]-5-(*cis*-5-{[(*S*)-1-azabicyclo[2.2.2]oct-3-ylthio]methyl}-4-oxo-L-2-piperidinecarboxylic acid)-virginiamycin S_1 methanesulphonate.

Хинупристина Мезилат

$C_{53}H_{67}N_9O_{10}S,CH_4O_3S = 1118.3.$

CAS — 120138-50-3 (quinupristin).

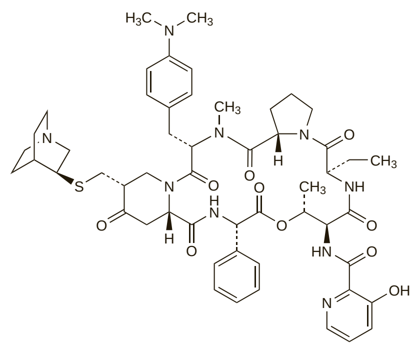

(quinupristin)

Adverse Effects and Treatment

The adverse effects most frequently reported in patients receiving quinupristin/dalfopristin include nausea and vomiting, diarrhoea, skin rash, pruritus, headache, and pain. Myalgia and arthralgia have occurred and may be severe; symptoms may be improved by decreasing the dose frequency. Eosinophilia, anaemia, leucopenia, and neutropenia are also common. Individual cases of severe thrombocytopenia and pancytopenia have been reported. Pseudomembranous colitis has also been reported.

Hyperbilirubinaemia and raised liver enzyme values may occur.

Pain and inflammation at the injection site is common, and thrombophlebitis has occurred.

Quinupristin/dalfopristin is not removed by peritoneal dialysis, and removal by haemodialysis is considered unlikely.

Effects on the musculoskeletal system. References.

1. Olsen KM, *et al.* Arthralgias and myalgias related to quinupristin-dalfopristin administration. Abstract: *Clin Infect Dis* 2001; **32:** 674. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/318702 (accessed 12/08/08)
2. Carver PL, *et al.* Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. *Pharmacotherapy* 2003; **23:** 159–64.
3. Raad I, *et al.* Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. *J Antimicrob Chemother* 2004; **53:** 1105–8.
4. Gupte G, *et al.* Quinupristin-dalfopristin use in children is associated with arthralgias and myalgias. *Pediatr Infect Dis J* 2006; **25:** 281.

Precautions

Quinupristin/dalfopristin should be used with caution in patients with hepatic impairment and avoided in severe impairment, as elevated plasma concentrations of quinupristin and dalfopristin and their metabolites have been found in patients with hepatic dysfunction, and elevated concentrations of quinupristin metabolites have occurred in patients with hyperbilirubinaemia. The combination is contra-indicated in patients who have plasma-bilirubin concentrations greater than 3 times the normal upper limit.

Prolongation of the QT interval has been seen in *animals* given quinupristin/dalfopristin; therefore caution is advised in patients at risk of cardiac arrhythmias.

Interactions

Quinupristin/dalfopristin inhibits the cytochrome P450 isoenzyme CYP3A4 and it may therefore inhibit the metabolism of a number of drugs. In particular, there is a theoretical possibility of serious ventricular arrhythmias when given with drugs that prolong the QT interval, such as astemizole, cisapride, and terfenadine. Quinupristin/dalfopristin has been shown to increase plasma concentrations of ciclosporin, midazolam, nifedipine, and tacrolimus. The use of ergot alkaloids with quinupristin/dalfopristin should be avoided.

Antimicrobial Action

Quinupristin/dalfopristin is a streptogramin antibacterial. Quinupristin and dalfopristin each have bacteriostatic activity and in combination usually act synergistically to produce bactericidal activity. The streptogramins act on the ribosome to block protein synthesis.

Quinupristin/dalfopristin is active against a range of Gram-positive bacteria including meticillin- and multidrug-resistant strains of *Staphylococcus aureus* and *S. epidermidis*, vancomycin-resistant *Enterococcus faecium* (but not *E. faecalis*), and penicillin- and macrolide-resistant *Streptococcus pneumoniae*. It is also active against the anaerobe *Clostridium perfringens*, and Gram-negative bacteria *Legionella pneumophila*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Mycoplasma pneumoniae*, and *Neisseria meningitidis*.

◊ References.

1. Schouten MA, Hoogkamp-Korstanje JAA. Comparative in-vitro activities of quinupristin-dalfopristin against Gram-positive bloodstream isolates. *J Antimicrob Chemother* 1997; **40:** 213–19.
2. Pankuch GA, *et al.* Postantibiotic effect and postantibiotic sub-MIC effect of quinupristin-dalfopristin against Gram-positive and negative organisms. *Antimicrob Agents Chemother* 1998; **42:** 3028–31.
3. Johnson AP, *et al.* Susceptibility to quinupristin/dalfopristin and other antibiotics of vancomycin-resistant enterococci from the UK, 1997 to mid-1999. *J Antimicrob Chemother* 2000; **46:** 125–8.
4. Ling TK, *et al.* In vitro activity and post-antibiotic effect of quinupristin/dalfopristin (Synercid). *Chemotherapy* 2001; **47:** 243–9.
5. Eliopoulos GM, Wennersten CB. Antimicrobial activity of quinupristin-dalfopristin combined with other antibiotics against vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002; **46:** 1319–24.
6. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens. *Lancet Infect Dis* 2005; **5:** 209–18.

Resistance. Although uncommon, isolated reports of *E. faecium* resistant to quinupristin/dalfopristin have emerged,[1-7] and have included a link to the use of the streptogramin virginiamycin as an animal food additive.[3,4]

1. Eliopoulos GM, *et al.* Characterization of vancomycin-resistant Enterococcus faecium isolates from the United States and their susceptibility in vitro to dalfopristin-quinupristin. *Antimicrob Agents Chemother* 1998; **42:** 1088–92.
2. Bozdogan B, *et al.* Plasmid-mediated coresistance to streptogramins and vancomycin in Enterococcus faecium HM1032. *Antimicrob Agents Chemother* 1999; **43:** 2097–8.
3. Werner G, *et al.* Association between quinupristin/dalfopristin resistance in glycopeptide-resistant Enterococcus faecium and the use of additives in animal feed. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 401–2.
4. Hershberger E, *et al.* Quinupristin-dalfopristin resistance in gram-positive bacteria: mechanism of resistance and epidemiology. *Clin Infect Dis* 2004; **38:** 92–8.
5. Oh WS, *et al.* High rate of resistance to quinupristin-dalfopristin in Enterococcus faecium clinical isolates from Korea. *Antimicrob Agents Chemother* 2005; **49:** 5176–8.
6. Donabedian SM, *et al.* Quinupristin-dalfopristin resistance in Enterococcus faecium isolates from humans, farm animals, and grocery store meat in the United States. *J Clin Microbiol* 2006; **44:** 3361–5.
7. Karanika M, *et al.* Reduced susceptibility to quinupristin/dalfopristin in Enterococcus faecium in Greece without prior exposure to the agent. *Int J Antimicrob Agents* 2008; **31:** 55–7.

Pharmacokinetics

After parenteral doses, quinupristin and dalfopristin are rapidly metabolised. At steady state, the half-life of quinupristin and its metabolites is about 3 hours and that of dalfopristin and its metabolites about 1 hour. Elimination half-lives of unchanged quinupristin and dalfopristin are 0.9 and 0.75 hours, respectively. Protein binding ranges from 55 to 78% for quinupristin and 11 to 26% for dalfopristin. The main route of excretion is biliary, with 75 to 77% of a dose detectable in the faeces. Urinary excretion accounts for 15% of the quinupristin and 19% of the dalfopristin dose. Negligible amounts are removed by peritoneal dialysis and probably also by haemodialysis.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet* 2004; **43:** 239–52.

Uses and Administration

Quinupristin/dalfopristin is a streptogramin antibacterial related to pristinamycin. Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin I and pristinamycin IIA respectively, and are used in the ratio 3:7. Quinupristin/dalfopristin is active against a range of Gram-positive and some Gram-negative organisms, but it is reserved for the treatment of serious infections with multidrug-resistant Gram-positive bacteria, specifically MRSA and vancomycin-resistant *Enterococcus faecium*.

Quinupristin/dalfopristin is given as the mesilate salts by intravenous infusion, in glucose 5% over 60 minutes, in a dose of 7.5 mg/kg (equivalent to quinupristin 2.25 mg/kg and dalfopristin 5.25 mg/kg) every 8 or 12 hours for at least 7 days. To minimise venous irritation, the vein should be flushed with glucose 5% after each infusion; alternatively, the infusion may be given through a central venous catheter. The injection should not be diluted with saline solutions since it is incompatible with sodium chloride.

Doses may need to be reduced in patients with hepatic impairment (see below).

◊ References.

1. Bayston R, *et al.*, eds. Quinupristin/dalfopristin—update on the first injectable streptogramin. *J Antimicrob Chemother* 1997; **39** (suppl A): 1–151.
2. Wood MJ (ed). Quinupristin/dalfopristin–a novel approach for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 1999; **44** (suppl A): 1–46.
3. Lamb HM, *et al.* Quinupristin/dalfopristin: a review of its use in the management of serious Gram-positive infections. *Drugs* 1999; **58:** 1061–97.
4. Drew RH, *et al.* Treatment of methicillin-resistant Staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy: for the Synercid Emergency-Use Study Group. *J Antimicrob Chemother* 2000; **46:** 775–84.
5. Allington DR, Rivey MP. Quinupristin/dalfopristin: a therapeutic review. *Clin Ther* 2001; **23:** 24–44.
6. Linden PK, *et al.* Treatment of vancomycin-resistant Enterococcus faecium infections with quinupristin/dalfopristin. *Clin Infect Dis* 2001; **33:** 1816–23.
7. Goff DA, Sierawski SJ. Clinical experience of quinupristin-dalfopristin for the treatment of antimicrobial-resistant gram-positive infections. *Pharmacotherapy* 2002; 748–58.
8. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis* 2003; **36:** 473–81.
9. Brown J, Freeman BB. Combining quinupristin/dalfopristin with other agents for resistant infections. *Ann Pharmacother* 2004; **38:** 677–85.
10. Manfredi R. A re-emerging class of antimicrobial agents: streptogramins (quinupristin/dalfopristin) in the management of multiresistant gram-positive nosocomial cocci in hospital setting. *Mini Rev Med Chem* 2005; **5:** 1075–81.

Administration in hepatic impairment. Licensed product information states that in clinical studies of quinupristin/dalfopristin the incidence of adverse effects in patients with chronic liver impairment or cirrhosis was similar to that in patients with normal liver function. However, pharmacokinetic studies have shown that systemic exposure to quinupristin/dalfopristin and their metabolites may be increased in those with hepatic impairment. In some countries it has therefore been recommended that quinupristin/dalfopristin should be avoided in patients with severe hepatic impairment, and that for those with moderate impairment a dose reduction to 5 mg/kg (equivalent to quinupristin 1.5 mg/kg and dalfopristin 3.5 mg/kg) should be considered if 7.5 mg/kg is not tolerated.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Arg.: Synercid†; ***Austral.:*** Synercid; ***Austria:*** Synercid; ***Braz.:*** Synercid; ***Canad.:*** Synercid; ***Cz.:*** Synercid; ***Fin.:*** Synercid†; ***Fr.:*** Synercid; ***Ger.:*** Synercid†; ***Gr.:*** Synercid; ***Hung.:*** Synercid; ***Irl.:*** Synercid; ***Israel:*** Synercid; ***Ital.:*** Synercid; ***Mex.:*** Synercid†; ***Neth.:*** Synercid; ***NZ:*** Synercid; ***Pol.:*** Synercid; ***Port.:*** Synercid; ***S.Afr.:*** Synercid†; ***Spain:*** Synercid; ***Swed.:*** Synercid†; ***Switz.:*** Synercid†; ***UK:*** Synercid; ***USA:*** Synercid.

Ramoplanin *(USAN, rINN)*

A-16686; MDL-62198; Ramoplanina; Ramoplanine; Ramoplaninum.

Рамопланин

CAS — 76168-82-6.

Profile

Ramoplanin is a glycopeptide antibiotic with a spectrum of activity *in vitro* similar to that of vancomycin (p.359) but considerably more potent. It is also active against *Bacteroides* spp. It is under investigation, notably for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for use in the prevention of systemic infection in patients colonised with vancomycin-resistant enterococci.

◊ Reviews.

1. Farver DK, *et al.* Ramoplanin: a lipoglycodepsipeptide antibiotic. *Ann Pharmacother* 2005; **39:** 863–8.

Retapamulin *(USAN, rINN)*

Retapamulina; Rétapamuline; Retapamulinum; SB-275833. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-Ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propanocyclopenta[8]annulen-8-yl{[(1*R*,3s,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]sulfanyl}acetate.

Ретапамулин

$C_{30}H_{47}NO_4S$ = 517.8.

CAS — 224452-66-8.

ATC — D06AX13.

ATC Vet — QD06AX13.

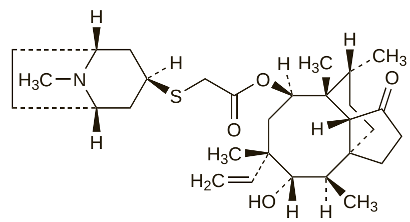

Adverse Effects and Precautions

Retapamulin is usually well tolerated; the most common reported adverse effect is application site irritation. Other local reactions such as erythema, pain, and pruritus occur rarely. Retapamulin ointment contains butylated hydroxytoluene (p.1633), which may cause local adverse effects such as contact dermatitis, or irritation to the eyes and mucous membranes. It should not be applied to abscesses.

Retapamulin has proved ineffective in infections caused by meticillin-resistant *Staphylococcus aureus*, and should not be used in their treatment.

Antimicrobial Action

Retapamulin is an antibacterial that selectively inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It is mainly bacteriostatic against meticillin-susceptible *Staphylococcus aureus*, and streptococci such as *Strep. pyogenes*. Although *in vitro* activity has been shown against meticillin-resistant *Staph. aureus* the *in vivo* efficacy of retapamulin was found to be inadequate in clinical studies.

◊ References.

1. Pankuch GA, *et al.* Activity of retapamulin against Streptococcus pyogenes and Staphylococcus aureus evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. *Antimicrob Agents Chemother* 2006; **50:** 1727–30.
2. Jones RN, *et al.* Activity of retapamulin (SB-275833), a novel pleuromutilin, against selected resistant Gram-positive cocci. *Antimicrob Agents Chemother* 2006; **50:** 2583–6.
3. Rittenhouse S, *et al.* Selection of retapamulin, a novel pleuromutilin for topical use. *Antimicrob Agents Chemother* 2006; **50:** 3882–5.
4. Champney WS, Rodgers WK. Retapamulin inhibition of translation and 50S ribosomal subunit formation in Staphylococcus aureus cells. *Antimicrob Agents Chemother* 2007; **51:** 3385–7.

Pharmacokinetics

Only very small amounts of topically applied retapamulin are absorbed into the systemic circulation. It is about 94% bound to plasma proteins and is shown to be metabolised by mono-oxygenation and N-demethylation *in vitro*.

Uses and Administration

Retapamulin is a pleuromutilin antibacterial isolated from the fungus *Clitopilus passeckerianus*. It is applied topically as a 1% ointment in the treatment of impetigo and other bacterial skin infections due to meticillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. The preparation should be applied twice daily for 5 days; treatment should be re-evaluated if there is no response within about 3 days. It is not suitable for application to mucous membranes.

For further details of skin infections and staphylococcal infections and their treatment, see p.194.

◊ References.

1. Parish LC, *et al.* Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol* 2006; **55:** 1003–1013.
2. Oranje AP, *et al.* Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. *Dermatology* 2007; **215:** 331–40.
3. Yang LPH, Keam SJ. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. *Drugs* 2008; **68:** 855–73.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Altargo; ***UK:*** Altargo; ***USA:*** Altabax.

Rifabutin *(BAN, USAN, rINN)*

Ansamicin; Ansamycin; Ansamycinum; Ansamysiini; LM-427; Rifabutiini; Rifabutina; Rifabutinas; Rifabutine; Rifabutinum. (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo-[2′,3′:7,8]naphth[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate.

Рифабутин

$C_{46}H_{62}N_4O_{11}$ = 847.0.

CAS — 72559-06-9.

ATC — J04AB04.

ATC Vet — QJ04AB04.

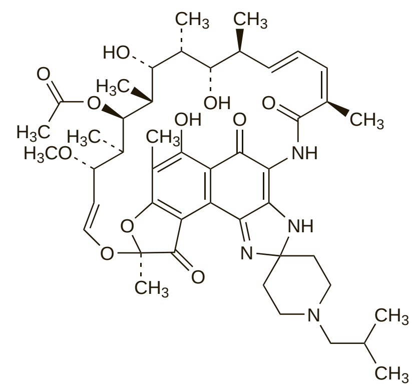

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Rifabutin). A reddish-violet amorphous powder. Slightly soluble in water and in alcohol; soluble in methyl alcohol.

USP 31 (Rifabutin). An amorphous red-violet powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol. Store at a temperature not exceeding 40°. Protect from light.

Stability. Study of the stability of two extemporaneous oral liquid preparations of rifabutin.[1]

1. Haslam JL, *et al.* Stability of rifabutin in two extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1999; **56:** 333–6.

Adverse Effects and Precautions

As for Rifampicin, p.325.

Rifabutin is usually well tolerated. The most common adverse effects include rash, gastrointestinal disturbances, and neutropenia. It produces a syndrome of polyarthralgia-arthritis at doses greater than 1 g daily. Uveitis has been reported, especially in patients also receiving clarithromycin or other macrolides and possibly also with fluconazole. Asymptomatic corneal opacities have been reported after long-term use.

Rifabutin should be used with caution in patients with severe hepatic or renal impairment.

◊ An orange-tan skin pigmentation has been reported to occur in most patients receiving rifabutin.[1] Urine may be discoloured.[2] A flu-like syndrome has been reported in 2 of 12 patients given 300 mg daily for Crohn's disease,[3] in 1 of 16 HIV-infected patients on continuous rifabutin,[1] and in 8 of 15 HIV-infected patients receiving increasing doses of rifabutin.[2]

Other reported adverse effects include hepatitis,[1] leucopenia[2] (including neutropenia[4]), epigastric pain,[3] rash,[3] erythema,[2] and ageusia.[5]

Rash, fever, and vomiting occurred in 1 of 2 children receiving 6.5 mg/kg daily.[6]

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Torseth J, *et al.* Evaluation of the antiviral effect of rifabutin in AIDS-related complex. *J Infect Dis* 1989; **159:** 1115–18.
3. Basilisco G, *et al.* Controlled trial of rifabutin in Crohn's disease. *Curr Ther Res* 1989; **46:** 245–50.
4. Apseloff G, *et al.* Severe neutropenia caused by recommended prophylactic doses of rifabutin. *Lancet* 1996; **348:** 685.
5. Morris JT, Kelly JW. Rifabutin-induced ageusia. *Ann Intern Med* 1993; **119:** 171–2.
6. Levin RH, Bolinger AM. Treatment of nontuberculous mycobacterial infections in pediatric patients. *Clin Pharm* 1988; **7:** 545–51.

Effects on the eyes. Uveitis may occur a few weeks or months after starting rifabutin, and generally necessitates withdrawal of the drug and treatment with topical or systemic corticosteroids and cycloplegics.[1] In 1994, the UK CSM was aware of 48 reports of uveitis in patients taking rifabutin.[2] Most patients were also receiving clarithromycin for treatment of AIDS-related *Mycobacterium avium* complex (MAC) infection and many were also receiving fluconazole (see Interactions, below). A dosage reduction to 300 mg rifabutin daily is now recommended in patients also receiving macrolides or triazole antifungals[2,3] and is reported to produce a satisfactory response in MAC infections.[4] Panuveitis and retinal vasculitis has been reported[5] in 4 patients with active tuberculosis given rifabutin, and was thought to be a result of activation of the immune system by *Mycobacterium tuberculosis* and the very low weight of the patients.

Rifabutin-associated uveitis in children is less commonly reported probably because they may not notice or complain about visual changes, therefore monitoring of their vision while on treatment is advised.[6]

1. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. *Ann Pharmacother* 1995; **29:** 1149–55.
2. Committee on Safety of Medicines. Rifabutin (Mycobutin)—uveitis. *Current Problems* 1994; **20:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
3. Committee on Safety of Medicines. Revised indications and drug interactions of rifabutin. *Current Problems* 1997; **23:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
4. Shafran SD, *et al.* A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS; rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996; **335:** 377–83.
5. Skolik S, *et al.* Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. *Ocul Immunol Inflamm* 2005; **13:** 483–5.
6. Olesen HH, Krag S. Rifabutin-associated uveitis in a child. *Pediatr Infect Dis J* 2005; **24:** 1023–5.

Effects on the joints. A polyarthralgia-arthritis syndrome was reported in an initial dose finding study[1] in 9 of 10 patients receiving rifabutin, as monotherapy, at doses greater than 1 g. The syndrome did not occur in patients receiving less than 1 g daily and disappeared on drug withdrawal. Two patients with polyarthralgia-arthritis symptoms developed uveitis (see also under Effects on the Eyes, above) and aphthous stomatitis at doses of about 1.8 g daily. However, a later study[2] and case reports[3] have reported polyarthralgia-arthritis syndrome when rifabutin was given at doses of 300 to 600 mg daily as part of a multidrug regimen, including a macrolide (azithromycin or clarithromycin), for the treatment of *Mycobacterium avium* complex infection. Concentrations of rifabutin were increased as a result of inhibition of cytochrome P450 isoenzymes by the macrolide and some have suggested a maximum dose of rifabutin of 300 mg daily when used with a macrolide.[2] Higher doses of 450 to 600 mg daily may be considered for patients of large body mass or those who have failed to respond to initial treatment with a lower dose.

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
3. Le Gars L, *et al.* Polyarthralgia-arthritis syndrome induced by low doses of rifabutin. *J Rheumatol* 1999; **26:** 1201–2.

Interactions

As for Rifampicin, p.327.

Rifabutin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme CYP3A4). It is a less potent inducer of cytochrome P450 isoenzymes than rifampicin, but similar interactions should nevertheless be anticipated. Use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of rifabutin, and possibly adverse effects.

Plasma concentrations of rifabutin are increased by clarithromycin (and possibly other macrolides) or fluconazole, resulting in increased rifabutin toxicity, in particular uveitis, (see Effects on the Eyes, above), neutropenia, and polyarthralgia-arthritis syndrome (see Effects on the Joints, above).

Some other interactions affecting the activity of rifabutin are discussed below.

Antiretroviral drugs. Rifabutin may be used as a substitute for rifampicin in the treatment of tuberculosis.[1,2] It has little effect on the serum concentrations of unboosted *HIV-protease inhibitors* (except saquinavir) and ritonavir-boosted HIV-protease inhibitors. However, HIV-protease inhibitors, particularly if boosted with ritonavir, significantly increase serum concentrations and toxicity of rifabutin. The dose of rifabutin is therefore usually substantially decreased when given with HIV-protease inhibitors (see Tuberculosis and HIV infection under Uses, below). Rifabutin should not be given with unboosted saquinavir; but saquinavir may be given with rifabutin if boosted with ritonavir.[2] Increases in the dose of indinavir are also required.[2]

Serum concentrations of rifabutin may be increased or decreased in those taking *NNRTIs*. However, rifabutin may usually be given to patients taking etravirine or nevirapine without the need for any dose modifications. Rifabutin is, however, not recommended in patients taking delavirdine or in those taking etravirine with ritonavir-boosted darunavir or ritonavir-boosted saquinavir. In patients taking efavirenz, the dose of rifabutin should be increased by at least 50% (see Tuberculosis and HIV infection under Uses, below).

No clinically significant interactions are expected with the integrase inhibitor *raltegravir* or the CCR-5 receptor antagonist *maraviroc*.[2] For further information on drug interactions with HIV-protease inhibitors see Table 1, p.917, and with NNRTIs see Table 2, p.944 in Antivirals.

Although rifabutin is reported to reduce the plasma concentrations of *zidovudine*, studies have shown that the effect is not marked (see p.915), and licensed product information for rifabutin suggests that the reduction may not be clinically relevant.

1. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 28/07/08)
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 28/07/08)

Azole antifungals. Rifabutin concentrations are increased by triazole antifungals and patients are at increased risk of rifabutin toxicity, specifically uveitis (see under Effects on the Eyes, above). Rifabutin also markedly reduces the plasma concentrations of *itraconazole*, *posaconazole*, and *voriconazole*, but does not affect the metabolism of *fluconazole*.

The area under the concentration-time curve (AUC) for rifabutin and its active 25-deacetyl metabolite were increased by 82% and 216% respectively when fluconazole was given to 12 HIV-infected patients.[1] Another study[2] in 10 patients with HIV infection, found that fluconazole increased the AUC of rifabutin by 76% and by 152% when the patients were also given clarithromycin. Raised plasma-rifabutin concentrations were reported in a patient who developed uveitis while also receiving itraconazole.[3] The mechanism of the interaction remains uncertain but could involve microsomal cytochrome P450 isoenzyme CYP3A4 (see Metabolism under Pharmacokinetics, below).

1. Trapnell CB, *et al.* Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann Intern Med* 1996; **124:** 573–6.
2. Jordan MK, *et al.* Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob Agents Chemother* 2000; **44:** 2170–2.
3. Lefort A, *et al.* Uveitis associated with rifabutin prophylaxis and itraconazole therapy. *Ann Intern Med* 1996; **125:** 939–40.

Macrolides. As discussed under Effects on the Eyes, above, most patients developing uveitis during rifabutin treatment are also receiving *clarithromycin* and it may also be implicated in the polyarthralgia-arthritis syndrome (see Effects on the Joints, above). In a study[1] of the treatment of *Mycobacterium avium* complex infection in AIDS patients, uveitis or pseudojaundice or both were noted in those receiving rifabutin, ethambutol, and clarithromycin, but not in those receiving rifabutin, ethambutol, ciprofloxacin, and clofazimine. A retrospective study[2] after an outbreak of uveitis in a similar patient population also found clarithromycin to be a risk factor, with a trend towards greater risk at higher rifabutin doses, although patient numbers were small. In 26 patients taking rifabutin with either clarithromycin or *azithromycin*,[3] the incidence and severity of adverse effects in general was similar, although the 2 patients who developed uveitis were both receiving clarithromycin.

Pharmacokinetic studies have found increased rifabutin concentrations when clarithromycin is also used. A study in healthy subjects[4] was terminated prematurely because of the high incidence of adverse effects, including neutropenia, fevers, and myalgia, particularly in subjects receiving rifabutin with azithromycin or clarithromycin. Mean serum concentrations of rifabutin and its 25-*O*-deacetyl metabolite in subjects also receiving clarithromycin were more than 4 times and 37 times those in subjects receiving rifabutin alone. Plasma concentrations were unaffected by azithromycin. Similar effects on rifabutin concentrations were found in HIV-infected subjects receiving clarithromycin[5] and reductions in clarithromycin concentrations were also noted. A study[6] to determine the tolerance and pharmacokinetic interactions of rifabutin and azithromycin in subjects with or without HIV infection found no significant drug interaction; however, the combination was poorly tolerated, mainly because of a high incidence of gastrointestinal symptoms and neutropenia.

1. Shafran SD, *et al.* Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. *N Engl J Med* 1994; **330:** 438–9.
2. Kelleher P, *et al.* Uveitis associated with rifabutin and macrolide therapy for Mycobacterium avium intracellulare infection in AIDS patients. *Genitourin Med* 1996; **72:** 419–21.
3. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
4. Apseloff G, *et al.* Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 830–5.
5. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; **42:** 631–9.
6. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob Agents Chemother* 2001; **45:** 1572–7.

Antimicrobial Action

Rifabutin possesses a spectrum of antibacterial activity similar to that of rifampicin (p.327). However, most investigations have concentrated on its action against mycobacteria. Cross-resistance with rifampicin is common.

Antimycobacterial action. Rifabutin possesses activity against most species of mycobacteria. It may be more active *in vivo* than *in vitro* studies suggest, as a result of its favourable pharmacokinetic profile and prolonged postantibiotic effect.[1]

Rifabutin has been reported to be active in *animal* assays against *Mycobacterium leprae*,[2] including a rifampicin-resistant strain.[3] Synergistic activity against *M. leprae* has been reported[4] *in vitro* for rifabutin with sparfloxacin.

1. Kunin CM. Antimicrobial activity of rifabutin. *Clin Infect Dis* 1996; **22** (suppl 1): S3–S14.
2. Hastings RC, Jacobson RR. Activity of ansamycin against Mycobacterium leprae in mice. *Lancet* 1983; **ii:** 1079–80. Correction. *ibid.*; 1210.
3. Hastings RC, *et al.* Ansamycin activity against rifampicin-resistant Mycobacterium leprae. *Lancet* 1984; **i:** 1130.
4. Dhople AM, Ibanez MA. In-vitro activity of three new fluoroquinolones and synergy with ansamycins against Mycobacterium leprae. *J Antimicrob Chemother* 1993; **32:** 445–51.

Resistance. Rifampicin-resistant strains of *Mycobacterium tuberculosis* have been identified in 2 patients receiving rifabutin alone as prophylaxis against *M. avium* complex.[1,2] It is therefore important to exclude *M. tuberculosis* infection before beginning rifabutin prophylaxis.

Rifampicin-resistant *M. kansasii* has also been reported in a patient receiving rifabutin.[3]

Acquired resistance has been reported in HIV-infected persons receiving highly intermittent regimens (once- or twice-weekly) of rifabutin for the treatment of active tuberculosis,[4,5] and the CDC has advised that such patients receive daily treatment during the intensive phase of therapy and daily or 3 times-weekly treatment during the continuation phase.

1. Weltman AC, *et al.* Rifampicin-resistant Mycobacterium tuberculosis. *Lancet* 1995; **345:** 1513.
2. Bishai WR, *et al.* Brief report: rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *N Engl J Med* 1996; **334:** 1573–6.
3. Meynard JL, *et al.* Rifampin-resistant Mycobacterium kansasii infection in a patient with AIDS who was receiving rifabutin. *Clin Infect Dis* 1997; **24:** 1262–3.
4. CDC. Notice to readers: acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR* 2002; **51:** 214–15.
5. Burman W, *et al.*Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 2006; **173:** 350–6.

Pharmacokinetics

Rifabutin is readily but incompletely absorbed from the gastrointestinal tract and peak plasma concentrations of about 0.25 to 0.6 micrograms/mL have been reported 2 to 4 hours after an oral dose of 300 mg; doubling the dose increases the peak plasma concentration. Food may delay absorption but does not affect the extent of absorption. Rifabutin is about 70% bound to plasma proteins. Rifabutin is lipophilic and therefore is widely distributed in body tissues and fluids.

Rifabutin is rapidly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 mainly to active 25-O-deacetyl and 31-hydroxy metabolites. Rifabutin induces its own metabolism resulting in a lower area under the curve after 4 weeks of continuous treatment than after the first few doses.

About 53% of a dose is found in the urine, mainly as metabolites and about 30% of a dose is excreted in the faeces. The mean half-life for rifabutin is reported to be about 40 hours, with a range of 16 to 69 hours.

◊ References.

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.

HIV-infected patients. Malabsorption of rifabutin and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p.328.

The pharmacokinetics of rifabutin were studied in HIV-infected patients with normal renal and hepatic function.[1] A two-compartment open pharmacokinetic model was proposed. Rifabutin was rapidly but incompletely absorbed from the gastrointestinal tract and bioavailability was poor, being 20% on day 1 of the study and 12% on day 28. Mean peak plasma concentrations occurred 2 to 3 hours after oral doses and were about 350, 500, and 900 nanograms/mL after doses of 300, 600, and 900 mg respectively. The peak and trough concentrations after 600 mg twice daily were about 900 and 200 nanograms/mL respectively. Rifabutin was about 70% bound to plasma proteins. The area under the curve showed a decrease on repeated dosage which might be explained by the induction of drug-metabolising liver enzymes. A large volume of distribution of 8 to 9 litres/kg, indicative of extensive tissue distribution, and a mean terminal half-life of 32 to 38 hours were reported.

This study[1] also showed that the peak plasma concentration of the major metabolite, 25-deacetylrifabutin, was 10% of the parent compound. Only 4% of unchanged rifabutin was excreted in the urine after oral use and between 6 to 14% after intravenous use. Total urinary excretion of rifabutin and metabolite 72 hours after intravenous use was 44%; total faecal excretion was between 30 and 49%.

Peak and trough concentrations at steady state were reported as 900 and 200 nanograms/mL respectively in a patient with tuberculosis given rifabutin 450 mg daily.[2] While these figures were the same as those previously reported with 600 mg twice daily,[1] the earlier study showed that there was considerable interpatient variability.

CSF concentrations in 5 patients with AIDS on rifabutin 450 mg daily ranged from 36 to 70% of serum concentrations.[3]

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.
2. Gillespie SH, *et al.* The serum rifabutin concentrations in a patient successfully treated for multi-resistant mycobacterium tuberculosis infection. *J Antimicrob Chemother* 1990; **25:** 490–1. Correction. *ibid.* 1991; **27:** 877.
3. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.

Metabolism. Five metabolites of rifabutin were identified in an *in-vitro* study[1] using human hepatic and enterocyte microsomes. Cytochrome P450 isoenzyme CYP3A4 was involved in the formation of all metabolites except 25-*O*-deacetylrifabutin. Deacetylation of rifabutin was apparently mediated by microsomal cholinesterase,[1] although another study[2] showed that further metabolism of 25-*O*-deacetylrifabutin is dependent on CYP3A4. The results[1] also suggested that metabolism by intestinal CYP3A4 contributes significantly to presystemic metabolism of rifabutin (and consequently its low bioavailability) and to drug interactions with azole antifungals and with macrolides (see above).

1. Iatsimirskaia E, *et al.* Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems, and drug interactions with macrolides and antifungal agents. *Clin Pharmacol Ther* 1997; **61:** 554–62.
2. Trapnell CB, *et al.* Metabolism of rifabutin and its 25-desacetyl metabolite, LM565, by human liver microsomes and recombinant human cytochrome P-450 3A4: relevance to clinical interaction with fluconazole. *Antimicrob Agents Chemother* 1997; **41:** 924–6.

Uses and Administration

Rifabutin is a rifamycin antibacterial used as an alternative to the macrolides for the prophylaxis of *Mycobacterium avium* complex (MAC) infection in immunocompromised patients. It is also used for the treatment of other nontuberculous mycobacterial infections (including those due to MAC) (p.181) and tuberculosis (p.196). When used for treatment rifabutin, like rifampicin, should be used with other antibacterials to prevent the emergence of resistant organisms.

Rifabutin is given as a single oral daily dose. The dose for the prophylaxis of MAC infection is 300 mg daily. For the treatment of nontuberculous mycobacterial infections the dose is 450 to 600 mg daily in a multidrug regimen for up to 6 months after negative cultures are obtained. For pulmonary tuberculosis the usual dose is 300 mg daily for at least 6 months as part of a multidrug regimen; it can also be given intermittently (usually 3 times each week) as an alternative to daily use.

For details of doses in infants, children, and adolescents, see below.

Doses should be reduced to 300 mg daily in patients also receiving macrolides or azole antifungals (see under Adverse Effects, Effects on the Eyes, above). Dosage alterations may also be necessary in patients receiving HIV-protease inhibitors (see under Tuberculosis, below) and in those with severe renal impairment (see below).

◊ Reviews.

1. Brogden RN, Fitton A. Rifabutin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 983–1009.

Administration in children. For the prophylaxis of MAC in HIV-infected infants and children with low CD4+ counts, the American Academy of Pediatrics (AAP) suggests an oral dose of rifabutin 5 mg/kg daily in those older than 6 years; the *BNFC* suggest the same dose may be given from 1 year of age and those 12 years of age and older may be given the usual adult dose.

For the treatment of nontuberculous mycobacterial disease in children aged 1 month to 12 years the *BNFC* suggests a dose of 5 mg/kg once daily for at least 6 months as part of a multidrug regimen; those 12 years of age and older may be given the usual adult dose.

For the treatment of tuberculosis in those 12 years of age and older the *BNFC* suggests a dose of 150 to 450 mg once daily for at least 6 months as part of a multidrug regimen.

Administration in renal impairment. Dosage of rifabutin should be reduced by 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/minute).

Cryptosporidiosis. Rifabutin may have a potential prophylactic effect against cryptosporidiosis (p.823).

Mycobacterium avium complex infections. Alterations in rifabutin dosage may be necessary in patients receiving antiretrovirals for the management of HIV infection; further details are given under Tuberculosis, below.

Peptic ulcer disease. For mention of the use of rifabutin in eradication regimens for *Helicobacter pylori* see p.1702.

References.

1. Borody TJ, *et al.* Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23:** 481–8. Correction. *ibid.*; **24:** 439.
2. Miehlke S, *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* 2006; **24:** 395–403.
3. González Carro P, *et al.* Efficacy of rifabutin-based triple therapy in Helicobacter pylori infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; **22:** 60–3.
4. Navarro-Jarabo JM, *et al.* Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. *BMC Gastroenterol* 2007; **7:** 31. Available at: http://www.biomedcentral.com/1471-230X/7/31 (accessed 12/11/07).

Toxoplasmosis. A beneficial response to rifabutin used with pyrimethamine was reported in a patient with AIDS-related *Toxoplasma gondii* encephalitis.[1] The patient was allergic to sulfonamides and clindamycin, which are commonly used (see p.826).

1. Schürmann D, *et al.* Rifabutin appears to be a promising agent for combination treatment of AIDS-related toxoplasma encephalitis. *J Infect* 1998; **36:** 352–3.

Tuberculosis and HIV infection. Rifabutin may be used in place of rifampicin in short-course therapy for tuberculosis in patients given antiretroviral drugs for HIV infection and may be preferred for patients unable to take efavirenz.[1,2] However, dose modifications are often necessary; additionally, some combinations, notably rifabutin with delavirdine, or saquinavir alone, should not be used, although rifabutin may be given with saquinavir if ritonavir is also given.

- In patients taking ritonavir-boosted HIV-protease inhibitors the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week
- In patients taking unboosted atazanavir the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week
- In those taking unboosted amprenavir, fosamprenavir, indinavir, or nelfinavir the daily dose of rifabutin should be decreased from 300 mg to 150 mg, and the dose for intermittent therapy should be 300 mg three times weekly. The dose of indinavir may need to be increased
- In patients taking efavirenz, the dose of rifabutin should be increased from 300 mg daily or intermittently to 450 to 600 mg daily or three times each week
- In patients taking nevirapine or etravirine, the usual dose of rifabutin is given (300 mg daily or 300 mg three times each week); rifabutin should not be used in patients taking etravirine plus ritonavir-boosted darunavir or saquinavir

1. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 28/07/08)
2. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 28/07/08)

Preparations

USP 31: Rifabutin Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Mycobutin; ***Austria:*** Mycobutin; ***Belg.:*** Mycobutin; ***Canad.:*** Mycobutin; ***Cz.:*** Mycobutin; ***Fin.:*** Ansatipin; ***Fr.:*** Ansatipine; ***Ger.:*** Alfacid; Mycobutin†; ***Gr.:*** Ansatipin†; Mycobutin; ***Hong Kong:*** Mycobutin; ***Israel:*** Mycobutin; ***Ital.:*** Mycobutin; ***Neth.:*** Mycobutin; ***NZ:*** Mycobutin; ***Port.:*** Mycobutin; ***Rus.:*** Mycobutin (Микобутин); ***S.Afr.:*** Mycobutin; ***Spain:*** Ansatipin; ***Swed.:*** Ansatipin; ***Switz.:*** Mycobutin; ***Turk.:*** Mycobutin; ***UK:*** Mycobutin; ***USA:*** Mycobutin.

Rifampicin *(BAN, rINN)*

Ba-41166/E; L-5103; NSC-113926; Rifaldazine; Rifampicina; Rifampicinas; Rifampicine; Rifampicinum; Rifampin *(USAN)*; Rifampisiini; Rifampisin; Rifamycin AMP; Ryfampicyna. 3-(4-Methylpiperazin-1-yliminomethyl)rifamycin SV; (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-1,2-Dihydro-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-2,7-(epoxypentadeca-[1,11,13]trienimino)naphtho[2,1-*b*]furan-21-yl acetate.

Рифампицин

$C_{43}H_{58}N_4O_{12}$ = 822.9.

CAS — 13292-46-1.

ATC — J04AB02.

ATC Vet — QJ04AB02; QJ54AB02.

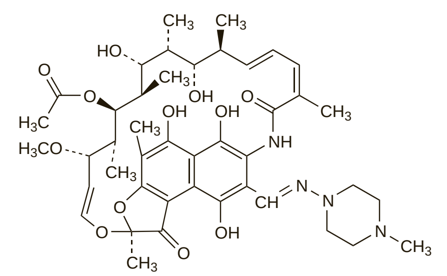

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Rifampicin). A reddish-brown or brownish-red, crystalline powder. Slightly soluble in water, in alcohol, and in acetone; soluble in methyl alcohol. A 1% suspension has a pH of 4.5 to 6.5. Store at a temperature not exceeding 25° in an atmosphere of nitrogen in airtight containers. Protect from light.

USP 31 (Rifampin). A red-brown crystalline powder. Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methyl alcohol. A 1% suspension in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adverse Effects

Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.

Some patients may experience a cutaneous syndrome that presents 2 to 3 hours after a daily or intermittent dose as facial flushing and itching, with or without a rash, or rarely eye irritation and visual disturbances. A flu-like syndrome characterised by episodes of fever, chills, headache, dizziness, bone pain, shortness of breath, and malaise has been associated with intermittent use. It usually occurs after 3 to 6 months of intermittent treatment and has a higher incidence with doses of 25 mg/kg or more given once weekly than with currently recommended regimens. Anaphylaxis or shock has occurred rarely.

Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhoea, and epigastric distress. Taking doses on an empty stomach is recommended for maximal absorption, but dosage after a meal will minimise gastrointestinal intolerance. Pseudomembranous colitis has been reported. Rifampicin produces transient abnormalities in liver function and hepatitis. Fatalities due to hepatotoxicity have been reported occasionally (see Effects on the Liver, below).

Rifampicin can cause thrombocytopenia and purpura, usually when given as an intermittent regimen, and if this occurs further use of rifampicin is contra-indicated. Other haematological adverse effects include eosinophilia, leucopenia, and haemolytic anaemia.

Alterations in kidney function and renal failure have occurred, particularly during intermittent therapy. Menstrual disturbances have been reported.

Nervous system adverse effects include headache, drowsiness, ataxia, dizziness, and numbness.

Oedema, myopathy, and muscular weakness have been reported.

Thrombophlebitis has occurred after prolonged intravenous infusion. Extravasation during intravenous infusion may cause local irritation and inflammation.

Rifampicin causes a harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears, and other body fluids. Soft contact lenses may become permanently stained.

Effects on the blood. Thrombocytopenia may occur in patients taking rifampicin, most commonly as intermittent therapy, and probably has an immunological basis. The platelet count may fall within 3 hours of a dose and return to normal within 36 hours, if additional doses are not given.[1] There may also be a risk of thrombocytopenia when re-introducing rifampicin to patients who have interrupted their treatment.[2] Thrombocytopenia has also been reported in a patient taking rifampicin for the first time for meningococcal prophylaxis.[3] Thrombotic thrombocytopenic purpura has been reported in a patient after two weeks of treatment with oral rifampicin and intravenous vancomycin for a meticillin-resistant *Staphylococcus aureus* infection.[4] Fatalities have occurred when rifampicin was not withdrawn once thrombocytopenic purpura had developed or when treatment with rifampicin was resumed in patients who had experienced purpura.[1] However, there is a report of the successful re-introduction of rifampicin in a patient who developed thrombocytopenia without rifampicin-dependent antibodies.[5]

Bleeding from the oral cavity not associated with thrombocytopenia has been reported in a patient taking rifampicin.[6] Leucopenia,[7,8] haemolysis or haemolytic anaemia,[9] and red cell aplasia[10] have occurred. Disseminated intravascular coagulation has been reported in a patient receiving intermittent rifampicin therapy.[11] The incidence of deep-vein thrombosis increased in one group of hospitalised tuberculosis patients when rifampicin was introduced as standard therapy,[12] but data from others have not supported a causal relationship.[13]

1. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982; **23:** 56–74.
2. Burnette PK, *et al.* Rifampin-associated thrombocytopenia secondary to poor compliance. *Drug Intell Clin Pharm* 1989; **23:** 382–4.
3. Hall AP, *et al.* New hazard of meningococcal chemoprophylaxis. *J Antimicrob Chemother* 1993; **31:** 451.
4. Gupta R, Wargo KA. Rifampin-induced thrombotic thrombocytopenic purpura. *Ann Pharmacother* 2005; **39:** 1761–2.
5. Bhasin DK, *et al.* Can rifampicin be restarted in patients with rifampicin-induced thrombocytopenia? *Tubercle* 1991; **72:** 306–7.
6. Sule RR. An unusual reaction to rifampicin in a once monthly dose. *Lepr Rev* 1996; **67:** 227–33.
7. Van Assendelft AHW. Leucopenia in rifampicin chemotherapy. *J Antimicrob Chemother* 1985; **16:** 407–8.
8. Vijayakumaran P, *et al.* Leucocytopenia after rifampicin and ofloxacin therapy in leprosy. *Lepr Rev* 1997; **68:** 10–15.
9. Lakshminarayan S, *et al.* Massive haemolysis caused by rifampicin. *BMJ* 1973; **2:** 282–3.
10. Mariette X, *et al.* Rifampicin-induced pure red cell aplasia. *Am J Med* 1989; **87:** 459–60.
11. Souza CS, *et al.* Disseminated intravascular coagulopathy as an adverse reaction to intermittent rifampin schedule in the treatment of leprosy. *Int J Lepr* 1997; **65:** 366–71.
12. White NW. Venous thrombosis and rifampicin. *Lancet* 1989; **ii:** 434–5.
13. Cowie RL, *et al.* Deep-vein thrombosis and pulmonary tuberculosis. *Lancet* 1989; **ii:** 1397.

Effects on the gastrointestinal tract. In addition to symptoms of gastrointestinal intolerance, there have been reports of gastrointestinal bleeding and erosive gastritis,[1] ulcerative colitis,[2] and eosinophilic colitis[3] in patients receiving rifampicin.

1. Zargar SA, *et al.* Rifampicin-induced upper gastrointestinal bleeding. *Postgrad Med J* 1990; **66:** 310–11.
2. Tajima A, *et al.* Rifampicin-associated ulcerative colitis. *Ann Intern Med* 1992; **116:** 778–9.
3. Lange P, *et al.* Eosinophilic colitis due to rifampicin. *Lancet* 1994; **344:** 1296–7.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with rifampicin and other first-line antituberculous drugs, but sometimes the hepatotoxicity may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Rifampicin is thought to have a lower potential for hepatotoxicity than isoniazid or pyrazinamide.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1]

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[2] for initial measurement of liver function in all patients and regular monitoring in patients with pre-existing liver disease. Details are given concerning the response to deteriorating liver function and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced for the USA.[3,4]

The incidence of severe hepatotoxicity was found to be lower in patients receiving isoniazid, rifampicin, and pyrazinamide for initial treatment of active disease, than in those receiving rifampicin and pyrazinamide for 2 months for latent tuberculosis infection. Management of latent tuberculosis with the rifampicin plus pyrazinamide regimen was also associated with a higher incidence of severe hepatotoxicity than was isoniazid monotherapy for 6 months.[5] Severe and sometimes fatal hepatotoxicity has been associated with the combined regimen of rifampicin and pyrazinamide for the treatment of latent tuberculosis in a predominantly HIV-negative study population.[5-9] In the USA, the CDC and the American Thoracic Society[10] now recommend that the combination of rifampicin with pyrazinamide should not generally be offered to persons with latent tuberculosis. However, an evaluation of studies[11] for the prevention of tuberculosis, involving HIV-infected patients, reported very little evidence of hepatotoxicity among patients taking rifampicin plus pyrazinamide and among those taking isoniazid.

For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p.288.

Hepatitis and liver dysfunction have also been reported in patients taking rifampicin, in the absence of other hepatotoxic drugs, for the treatment of pruritus associated with primary biliary cirrhosis.[12]

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
4. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/sections/publications/statements/resources/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 05/10/07)
5. van Hest R, *et al.* Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. *Clin Infect Dis* 2004; **39:** 488–96.
6. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. *MMWR* 2001; **50:** 733–5. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf (accessed 05/10/07)
7. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. *MMWR* 2002; **51:** 998–9. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5144.pdf (accessed 05/10/07)
8. Jasmer RM, *et al.* Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002; **137:** 640–7.
9. Ijaz K, *et al.* Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis* 2006; **42:** 346–55.
10. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52:** 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)
11. Gordin FM, *et al.* Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis* 2004; **39:** 561–5.
12. Prince MI, *et al.* Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002; **50:** 436–9.

Effects on the lungs. Pulmonary fibrosis[1] in one elderly man and pneumonitis[2] in another were attributed to rifampicin.

1. Umeki S. Rifampicin and pulmonary fibrosis. *Arch Intern Med* 1988; **148:** 1663, 7.
2. Kunichika N, *et al.* Pneumonitis induced by rifampicin. *Thorax* 2002; **57:** 1000–1001.

Effects on the pancreas. Chronic pancreatic insufficiency has been reported in a patient after use of rifampicin, isoniazid, ethambutol, and pyrazinamide.[1]

1. Liu BA, *et al.* Pancreatic insufficiency due to antituberculosis therapy. *Ann Pharmacother* 1997; **31:** 724–6.

Effects on the skin. Skin reactions to rifampicin are usually mild, irrespective of it being given daily or intermittently.[1] However, there have been a few isolated reports of severe reactions such as toxic epidermal necrolysis,[2] exfoliative dermatitis,[3] fixed drug eruptions,[4,5] and acute generalised exanthematous pustulosis.[6] Contact dermatitis has been seen after handling rifampicin powder.[7]

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; **3:** 115–32.
2. Okano M, *et al.* Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol* 1987; **17:** 303–4.
3. Goldin HM, *et al.* Rifampin and exfoliative dermatitis. *Ann Intern Med* 1987; **107:** 789.
4. Mimouni A, *et al.* Fixed drug eruption following rifampin treatment. *DICP Ann Pharmacother* 1990; **24:** 947–8.
5. John SS. Fixed drug eruption due to rifampin. *Lepr Rev* 1998; **69:** 397–9.
6. Azad A, Connelly N. Case of rifampicin-induced acute generalized exanthematous pustulosis. *Intern Med J* 2006; **36:** 619–20.
7. Anker N, Da Gunha Bang F. Long-term intravenous rifampicin treatment: advantages and disadvantages. *Eur J Respir Dis* 1981; **62:** 84–6.

Hypersensitivity. References.

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; **3:** 115–32.
2. Wurtz RM, *et al.* Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989; **i:** 955–6.
3. Harland RW, *et al.* Anaphylaxis from rifampin. *Am J Med* 1992; **92:** 581–2.
4. Cnudde F, Leynadier F. The diagnosis of allergy to rifampicin confirmed by skin test. *Am J Med* 1994; **97:** 403–4.
5. Sharma VK, *et al.* Rifampicin-induced urticaria in leprosy. *Lepr Rev* 1997; **68:** 331–2.
6. Martínez E, *et al.* Shock and cerebral infarct after rifampin re-exposure in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1998; **27:** 1329–30.

Lupus. Symptoms including malaise, arthralgia, arthritis, and oedema of the extremities, occurring in 4 patients taking rifampicin and 3 taking rifabutin, were considered to be due to drug-induced lupus syndrome.[1] Cutaneous lupus erythematosus was reported in a patient receiving rifampicin with clarithromycin and ethambutol.[2] All patients had positive anti-nuclear antibody titres.[1,2]

1. Berning SE, Iseman MD. Rifamycin-induced lupus syndrome. *Lancet* 1997; **349:** 1521–2.
2. Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol* 2001; **26:** 260–2.

Overdosage. Cases of skin pigmentation induced by rifampicin overdose have been reviewed.[1] Reddish-orange discoloration of the skin appeared within a few hours of taking the drug; urine, mucous membranes, and sclera were also discoloured. Periorbital or facial oedema, pruritus, and gastrointestinal intolerance occurred in most patients. Treatment was supportive and clinical symptoms resolved in most patients over 3 to 4 days, although fatalities occurred with doses over 14 g.

1. Holdiness MR. A review of the redman syndrome and rifampicin overdosage. *Med Toxicol Adverse Drug Exp* 1989; **4:** 444–51.

Precautions

Liver function should be checked before treatment with rifampicin and special care should be taken in alcoholic patients or those with pre-existing liver disease who require regular monitoring during therapy. UK licensed product information states that use is contra-indicated in patients with jaundice. A self-limiting hyperbilirubinaemia may occur in the first 2 or 3 weeks of treatment. Alkaline phosphatase values may be raised moderately due to rifampicin's enzyme-inducing capacity. Isolated results showing hyperbilirubinaemia in the first few weeks and/or moderately elevated transaminase values are not indications to withdraw rifampicin. However, dose adjustment is necessary when there is other evidence of hepatic impairment and treatment should be suspended when there is evidence of more serious liver toxicity.

Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders. Should thrombocytopenia or purpura occur then rifampicin should be withdrawn permanently. UK product information also recommends such withdrawal in patients who develop haemolytic anaemia or renal failure.

Use of rifampicin after interruption of treatment has been associated with increased risk of serious adverse effects.

Patients should be advised that rifampicin may colour faeces, saliva, sputum, sweat, tears, urine, and other body-fluids orange-red. Soft contact lenses may become permanently stained.

Rifampicin should not be given by the intramuscular or subcutaneous route. When given by intravenous infusion care should be taken to avoid extravasation.

Adrenocortical insufficiency. Adrenal insufficiency has been associated with tuberculosis and induction of microsomal enzymes by rifampicin may accelerate the metabolism of cortisol and precipitate an acute adrenal crisis in such patients.[1] Induction of microsomal enzymes may be enough to compromise even patients with mildly impaired cortisol production. Critical hypotension has also developed in non-Addisonian patients within a week to 10 days of starting rifampicin therapy. However, it has not been necessary to suspend the use of rifampicin if patients are treated with corticosteroids.[2] The effectiveness of corticosteroid therapy can be reduced by rifampicin.

1. Elansary EH, Earis JE. Rifampicin and adrenal crisis. *BMJ* 1983; **286:** 1861–2.
2. Boss G. Rifampicin and adrenal crisis. *BMJ* 1983; **287:** 62.

Breast feeding. Rifampicin is excreted into breast milk. No adverse effects have been seen in breast-fed infants whose mothers were taking rifampicin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/10/07)

Porphyria. Rifampicin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Treatment guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] have recommended treatment of pregnant patients with the same rifampicin-containing multidrug regimens as would be used in non-pregnant patients. While use of rifampicin in pregnant patients is generally considered to be safe, the drug does cross into the fetus[4] and malformations and bleeding tendencies have been reported.[5] A literature review[5] revealed 386 normal term infants and 29 elective terminations out of 446 pregnancies in patients who took rifampicin with other antimycobacterial drugs. A variety of malformations were reported; there were 14 abnormal infants or fetuses, 2 premature births, 9 still-births and 7 spontaneous abortions. It was considered that rifampicin did not increase the overall risk of congenital malformations.

Rifampicin treatment can increase the metabolism of vitamin K, resulting in clotting disorders associated with vitamin K deficiency. Bleeding disorders in 2 mothers shortly after delivery, and scalp haemorrhage, anaemia, and shock in one of the infants have been reported.[6] The authors recommended blood coagulation monitoring and giving prophylactic vitamin K to mothers and neonates when the mother has received rifampicin during pregnancy.

1. WHO. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 05/10/07)
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
4. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
5. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122:** 65–79.
6. Chouraqui JP, *et al.* Hémorragie par avitaminose K chez la femme enceinte et le nouveau-né: rôle éventuel de la rifampicine: a propos de 2 observations. *Therapie* 1982; **37:** 447–50.

Interactions

Rifampicin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme CYP3A) or drug transporter proteins (such as p-glycoprotein). Drugs so affected may require an increase in dosage to maintain effectiveness and patients should be monitored closely when starting or stopping concurrent rifampicin treatment. Women taking oral contraceptives should use additional precautions or change to a non-hormonal form of contraception (see Rifamycins, p.2068).

The absorption of rifampicin may be reduced by antacids, but this interaction can be overcome by giving rifampicin 1 hour before any antacids. Similarly, rifampicin and preparations containing bentonite (for example some aminosalicylic acid preparations) should be given 8 hours apart. Isoniazid and halothane may increase the potential for hepatotoxicity when given with rifampicin. Atovaquone may increase the concentration of rifampicin, while rifampicin decreases the concentration of atovaquone. Some other interactions affecting the activity of rifampicin are discussed below.

◊ Reviews.

1. Finch CK, *et al.* Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* 2002; **162:** 985–92.
2. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Safety* 2002; **25:** 111–33.
3. Niemi M, *et al.* Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 2003; **42:** 819–50.

Antiretroviral drugs. Rifamycins can induce the metabolism of *zidovudine*, the NNRTIs delavirdine, efavirenz, and nevirapine, and *HIV-protease inhibitors*, resulting in potentially subtherapeutic plasma concentrations. In addition HIV-protease inhibitors inhibit the metabolism of rifamycins resulting in elevated plasma-rifamycin concentrations and an increased incidence of adverse effects.[1,2]

Guidelines in the UK[3] and the USA[2] recommend that rifampicin should not be used with the *NNRTIs* delavirdine, and etravirine but opinion varies on whether it should be used with nevirapine. Licensed product information for nevirapine contraindicates the use of rifampicin and nevirapine. Rifampicin decreases the serum concentration of efavirenz and it is recommended that the dose of efavirenz be increased in patients weighing more than 60 kg; no dose modification is needed for rifampicin.

It is also recommended that rifampicin should not be used with unboosted or low-dose ritonavir-boosted *HIV-protease inhibitor* regimens. For reference to suitable antiretroviral regimens for use in patients requiring rifampicin-containing treatment for tuberculosis, see p.196.

Rifampicin significantly decreases the serum concentration of the CCR-5 receptor antagonist, *maraviroc*, and it is recommended that the dose of maraviroc be increased; no dose modification is needed for rifampicin. No clinically significant interactions are expected with the integrase inhibitor *raltegravir*,[2] or the HIV fusion inhibitor *enfuvirtide*.[4] For further information on drug interactions with HIV-protease inhibitors see Table 1, p.917 and with NNRTIs see Table 2, p.944. See also p.324 for comment on the interaction of antiretrovirals with rifabutin.

1. Anonymous. Clinical update: impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampin. *MMWR* 1996; **45:** 921–5.
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 28/07/08)
3. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 28/07/08)
4. Boyd MA, *et al.* Lack of enzyme-inducing effect of rifampicin on the pharmacokinetics of enfuvirtide. *J Clin Pharmacol* 2003; **43:** 1382–91.

Clofazimine. Use of clofazimine in leprosy patients receiving rifampicin with or without dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma concentration.[1] In patients receiving clofazimine, rifampicin, and dapsone, the area under the curve for rifampicin was reduced.[1] However, a multiple dose study[2] showed that the pharmacokinetics of rifampicin were similar after 7 days of treatment with rifampicin and dapsone or rifampicin, dapsone, and clofazimine.

1. Mehta J, *et al.* Effect of clofazimine and dapsone on rifampicin (Lositril) pharmacokinetics in multibacillary and paucibacillary leprosy cases. *Lepr Rev* 1986; **57** (suppl 3): 67–76.
2. Venkatesan K, *et al.* The effect of clofazimine on the pharmacokinetics of rifampicin and dapsone in leprosy. *J Antimicrob Chemother* 1986; **18:** 715–18.

Co-trimoxazole. In 15 patients receiving therapy including rifampicin for tuberculosis, a course of co-trimoxazole resulted in increases in maximum plasma concentrations and in the area under the concentration-time curve for rifampicin.[1] No adverse effects were observed and the clinical implications of this observation remain unclear. In another study,[2] significant reductions in the area under the plasma concentration-time curves for trimethoprim and sulfamethoxazole were observed after therapy including rifampicin was given to 10 HIV-infected patients on co-trimoxazole prophylaxis. Again, the clinical significance of this interaction is unclear.

1. Bhatia RS, *et al.* Drug interaction between rifampicin and cotrimoxazole in patients with tuberculosis. *Hum Exp Toxicol* 1991; **10:** 419–21.
2. Ribera E, *et al.* Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2001; **45:** 3238–41.

Isoniazid. There is little significant pharmacokinetic interaction between rifampicin and isoniazid.[1] Although lower blood concentrations of rifampicin have been reported with isoniazid, the effect is not considered clinically significant.[2] Since both drugs are hepatotoxic, there could be an increased incidence of hepatic damage, although the benefits of using this combination are considered to outweigh any potential risks.

1. Acocella G, *et al.* Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease. *Gut* 1972; **13:** 47–53.
2. Mouton RP, *et al.* Blood levels of rifampicin, desacetylrifampicin and isoniazid during combined therapy. *J Antimicrob Chemother* 1979; **5:** 447–54.

Ketoconazole. Giving rifampicin, ketoconazole, and isoniazid together has produced low serum concentrations of each drug resulting in failure of antifungal treatment.[1] Rifampicin serum concentrations are reduced when rifampicin is given with ketoconazole;[2] separation of the doses by 30 minutes[3] to 12 hours[2] may result in similar rifampicin concentrations to those attained when rifampicin is given alone, although serum concentrations of ketoconazole remain depressed regardless of the timing of doses.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109:** 844–5. Correction. *ibid.* 1989; **111:** 96.
2. Engelhard D, *et al.* Interaction of ketoconazole with rifampin and isoniazid. *N Engl J Med* 1984; **311:** 1681–3.
3. Doble N, *et al.* Pharmacokinetic study of the interaction between rifampicin and ketoconazole. *J Antimicrob Chemother* 1988; **21:** 633–5.

Probenecid. Although a study[1] showed that probenecid could increase serum-rifampicin concentrations, another[2] subsequently found that the effect was uncommon and inconsistent and concluded that probenecid had no place as an adjunct to routine rifampicin therapy.

1. Kenwright S, Levi AJ. Impairment of hepatic uptake of rifamycin antibiotics by probenecid and its therapeutic implications. *Lancet* 1973; **ii:** 1401–5.
2. Fallon RJ, *et al.* Probenecid and rifampicin serum levels. *Lancet* 1975; **ii:** 792–4.

Antimicrobial Action

Rifampicin is bactericidal against a wide range of micro-organisms and interferes with their synthesis of nucleic acids by inhibiting DNA-dependent RNA polymerase. It has the ability to kill intracellular organisms. It is active against mycobacteria, including *Mycobacterium tuberculosis*, *M. avium*, and *M. leprae* and, having high sterilising activity against these organisms, it possesses the ability to eliminate semi-dormant or persisting organisms. Rifampicin is also active against Gram-positive bacteria, especially staphylococci, but less active against Gram-negative organisms. The most sensitive Gram-negative bacteria include *Neisseria meningitidis*, *N. gonorrhoeae*, *Haemophilus influenzae*, and *Legionella* spp. Rifampicin also has activity against *Chlamydia trachomatis* and some anaerobic bacteria. At high concentrations it is active against some viruses.

Strains of *M. tuberculosis*, *M. leprae*, and other susceptible bacteria (such as *N. meningitidis*) have shown resistance, both initially and during treatment. Acquired resistance to rifampicin develops rapidly if it is used alone in the treatment of clinical infection, and resistance is thought to be due to a single-step mutation of the DNA-dependent RNA polymerase. Thus in tuberculosis and leprosy treatment regimens, rifampicin is used with other antimycobacterials to delay or prevent the development of rifampicin resistance. Resistance does not appear to be a problem when rifampicin is used alone in the management of latent tuberculosis, probably because the bacillary load is low. Cross-resistance has been shown between rifampicin and other rifamycins. Strains of *M. tuberculosis* resistant to both rifampicin and isoniazid (termed multidrug-resistant tuberculosis) are increasingly being reported; some strains are also resistant to second-line antimycobacterials (termed extensively drug-resistant tuberculosis).

Pharmacokinetics

Rifampicin is readily absorbed from the gastrointestinal tract and peak plasma concentrations varying from 4 to 32 micrograms/mL (average 7 micrograms/mL) have been reported after a dose of 600 mg. Food may reduce and delay absorption. Rifampicin is about 80% bound to plasma proteins. It is widely distributed in body tissues and fluids and diffusion into the CSF is increased when the meninges are inflamed. Rifampicin is distributed into breast milk and crosses the placenta (see Breast Feeding and Pregnancy, under Precautions, above). Half-lives for rifampicin have been reported to range initially from 2 to 5 hours, the longest elimination times occurring after the largest doses. However, as rifampicin induces its own metabolism, elimination time may decrease by up to 40% during the first 2 weeks, resulting in half-lives of about 2 to 3 hours. The half-life is prolonged in patients with severe hepatic impairment.

Rifampicin is rapidly metabolised in the liver mainly to active 25-*O*-deacetylrifampicin and excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases faecal excretion, although significant enterohepatic circulation still takes place. About 60% of a dose eventually appears in the faeces. The amount excreted in the urine increases with increasing doses and up to 30% of a dose may be excreted in the urine, about half of it being unchanged drug. The metabolite formylrifampicin is also excreted in the urine. In patients with renal impairment the half-life of rifampicin is not prolonged at doses of 600 mg or less.

Distribution. Rifampicin is widely distributed in most body tissues and fluids after oral or intravenous use.[1] Rifampicin is also able to penetrate into polymorphonuclear leucocytes to kill intracellular pathogens.[2] Rifampicin does not appear to diffuse well through the uninflamed meninges[3] but therapeutic concentrations have been attained in the CSF after daily doses of 600 and 900 mg when the meninges are inflamed;[4] concentrations in the CSF are about 10 to 20% of simultaneous serum concentrations, and approximately represent the fraction unbound to plasma proteins. Corticosteroids do not appear to influence the penetration of rifampicin into the CSF of patients with tuberculous meningitis.[5]

1. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.
2. Prokesch RC, Hand WL. Antibiotic entry into human polymorphonuclear leukocytes. *Antimicrob Agents Chemother* 1982; **21:** 373–80.
3. Sippel JE, *et al.* Rifampin concentrations in cerebrospinal fluid of patients with tuberculous meningitis. *Am Rev Respir Dis* 1974; **109:** 579–80.
4. D'Oliveira JJG. Cerebrospinal fluid concentrations of rifampin in meningeal tuberculosis. *Am Rev Respir Dis* 1972; **106:** 432–7.
5. Woo J, *et al.* Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; **42:** 235–42.

HIV-infected patients. Malabsorption of rifampicin and other antituberculous drugs has been reported in some patients with HIV infection and tuberculosis,[1-6] and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. It is not clear whether this is related to the HIV infection itself or associated diarrhoea. A pilot study[2] in 26 HIV-positive patients undergoing multidrug antituberculosis treatment found that serum concentrations of isoniazid were generally regarded as adequate; serum concentrations of rifampicin and ethambutol were low. A study[3] in patients with HIV infection but not co-infected with tuberculosis reported reduced absorption for rifampicin and pyrazinamide compared to healthy subjects; isoniazid was generally well absorbed. A pharmacokinetic study[4] reported malabsorption of all first-line antituberculous drugs in patients who had advanced HIV infection with diarrhoea and cryptosporidial infection. A further pharmacokinetic study,[5] in a similar subject population, found a significant degree of malabsorption of rifampicin and isoniazid in HIV-infected patients with or without diarrhoea. Low serum concentrations of rifabutin were reported in HIV-infected patients co-infected with tuberculosis treated with an intermittent (twice-weekly) tuberculosis regimen.[6] However, others found that HIV infection either did not affect[7,8] or uncommonly affected[9] the pharmacokinetics of antituberculous drugs.

Some authorities[10,11] consider that HIV-infected patients (including children) with tuberculosis have a similar response to short-course multidrug therapy as HIV-negative tuberculosis patients, and that most can be treated with the standard 6-month regimen. US[11,12] and UK[13]guidelines recommend that highly intermittent (once or twice weekly) tuberculosis regimens should not be used for co-infected patients with CD4+ cell counts less than 100 cells/microlitre.

1. Patel KB, *et al.* Drug malabsorption and resistant tuberculosis in HIV-infected patients. *N Engl J Med* 1995; **332:** 336–7.
2. Peloquin CA, *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30:** 919–25.
3. Sahai J, *et al.* Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med* 1997; **127:** 289–93.
4. Gurumurthy P, *et al.* Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother* 2004; **48:** 4473–5.
5. Gurumurthy P, *et al.* Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis* 2004; **38:** 280–3.
6. Weiner M, *et al.* Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005; **40:** 1481–91.
7. Choudhri SH, *et al.* Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. *Clin Infect Dis* 1997; **25:** 104–11.
8. Taylor B, Smith PJ. Does AIDS impair the absorption of antituberculosis agents? *Int J Tuberc Lung Dis* 1998; **2:** 670–5.
9. Perlman DC, *et al.* The clinical pharmacokinetics of pyrazinamide in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2004; **38:** 556–64.
10. WHO. *TB/HIV. A clinical manual.* 2nd ed. Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241546344.pdf (accessed 05/10/07)
11. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 05/10/07)
12. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–92. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 05/10/07)
13. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 05/10/07)

Intravenous administration. Mean peak plasma concentrations of 10 micrograms/mL have been reported after rifampicin 600 mg by intravenous infusion over 3 hours. Peak plasma concentrations declined with repeated doses but to a less marked extent than occurs with oral use.[1] Mean peak plasma concentrations of 27 micrograms/mL have been reported in children after doses of 11.5 mg/kg infused over 30 minutes. Mean concentrations of 1.9 micrograms/mL were reported 8 hours after the dose.[2]

1. Acocella G, *et al.* Serum and urine concentrations of rifampicin administered by intravenous infusion in man. *Arzneimittelforschung* 1977; **27:** 1221–6.
2. Koup JR, *et al.* Pharmacokinetics of rifampin in children I. Multiple dose intravenous infusion. *Ther Drug Monit* 1986; **8:** 11–16.

Oral administration. Gastrointestinal absorption of rifampicin is considered good. However, analysis of serum-rifampicin concentrations in children indicated that only 50 ± 22% of a freshly prepared oral suspension was absorbed.[1] Varying oral bioavailability from capsule formulations has also been reported and could result in ineffective therapy[2] or higher than needed serum concentrations.[3]

The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[4] Another report[5] also showed reduced peak serum concentrations when rifampicin was given with a high-fat meal, and it was suggested that rifampicin should preferably be given on an empty stomach.

1. Koup JR, *et al.* Pharmacokinetics of rifampin in children II. Oral bioavailability. *Ther Drug Monit* 1986; **8:** 17–22.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.
3. Ganiswarna SG, *et al.* Bioavailability of rifampicin caplets (600 mg and 450 mg) in healthy Indonesian subjects. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 60–4.
4. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; **76:** 109–13.
5. Peloquin CA, *et al.* Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* 1999; **115:** 12–18. Correction. *ibid.*; 1485.

Uses and Administration

Rifampicin belongs to the rifamycin group of antimycobacterials (p.159) and is used in the treatment of various infections due to mycobacteria and other susceptible organisms (see Antimicrobial Action, above). It is usually given with other antibacterials to prevent the emergence of resistant organisms.

Rifampicin is used, mainly with isoniazid and pyrazinamide, as a component of multidrug regimens for the treatment of tuberculosis, and with dapsone and clofazimine in the treatment of leprosy. For the treatment of nontuberculous mycobacterial infections it is usually used with clarithromycin and ethambutol as part of a multidrug regimen.

Other uses include the treatment of brucellosis, Legionnaires' disease, mycetoma, penicillin-resistant pneumococcal meningitis, Q-fever, and various staphylococcal infections, including endocarditis. Rifampicin is used for the prophylaxis of epiglottitis and meningitis due to *Haemophilus influenzae* and for meningococcal meningitis. It is also used for the eradication of pharyngeal streptococcal carriage in pharyngitis, to reduce staphylococcal carriage, and to eliminate the carrier states for meningococcal and *H. influenzae* meningitis. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. For discussions of all these infections and their treatment, see under Choice of Antibacterial, p.162.

The usual oral adult dose of rifampicin is 8 to 12 mg/kg (to a maximum of 600 mg) daily, preferably on an empty stomach, or the same dose by intravenous infusion as the base or the sodium salt; higher doses are sometimes used (see below).

Rifampicin is given in the initial and continuation phases of short-course **tuberculosis** regimens (p.196) with other antimycobacterials. Rifampicin is given orally on an empty stomach in adult doses of 10 mg/kg (maximum 600 mg) daily or two or three times weekly. (WHO does not recommend twice-weekly regimens as there is an increased risk of treatment failure if one of the doses are missed.) Alternatively, doses may be expressed as follows: with daily use, adults weighing less than 50 kg receive 450 mg and those over 50 kg receive 600 mg; with intermittent use, adults receive 600 to 900 mg three times weekly. The maximum recommended dose is considered to be 900 mg because a greater incidence of adverse effects is associated with doses above 900 mg.

For the treatment of latent tuberculosis oral rifampicin 10 mg/kg (to a maximum dose of 600 mg) may be given once daily with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy may be given daily for 4 to 6 months.

In **leprosy** regimens (p.176), rifampicin is usually given with dapsone for paucibacillary leprosy, and with dapsone and clofazimine for multibacillary leprosy. WHO recommends that rifampicin is given once monthly in a usual oral adult dose of 600 mg. Single-dose treatment with rifampicin, ofloxacin, and minocycline may be an alternative in patients with single-lesion paucibacillary leprosy.

In the treatment of **brucellosis**, **Legionnaires' disease**, and serious **staphylococcal infections** a dose of 600 to 1200 mg daily, orally or by intravenous infusion, in divided doses has been recommended in combination with other antibacterials.

For **prophylaxis** against meningococcal meningitis and the treatment of meningococcal carriers, rifampicin is usually given in an oral dose of 600 mg twice daily for 2 days. For prophylaxis against meningitis due to *Haemophilus influenzae*, an oral dose of 20 mg/kg once daily (to a maximum dose of 600 mg daily) for 4 days is given to adults.

For details of doses in infants, children, and adolescents, see below.

Fixed-dose combination products for antimycobacterial therapy have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing rifampicin with isoniazid, isoniazid and pyrazinamide, isoniazid and ethambutol, and isoniazid, ethambutol, and pyrazinamide are available in some countries.

Doses of rifampicin should be reduced in patients with hepatic impairment (see below).

Administration in children. For the treatment of **tuberculosis** in infants, children, and adolescents the American Academy of Pediatrics (AAP) suggests a dose of rifampicin of 10 to 20 mg/kg (to a maximum of 600 mg) daily or twice weekly by mouth, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests a dose of 10 mg/kg once daily or 15 mg/kg (to a maximum of 900 mg) three times a week by mouth; while WHO recommends 8 to 12 mg/kg (to a maximum of 600 mg) once daily or two or three times a week.

For the treatment of *latent* tuberculosis the *BNFC* suggests that children 1 month and older are given rifampicin 10 mg/kg (to a maximum of 600 mg) once daily by mouth with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy should be given daily for 6 months. The AAP, however, suggest rifampicin 10 to 20 mg/kg daily by mouth for 6 months.

In the treatment of tuberculosis and latent tuberculosis the *BNFC* suggests a maximum dose of rifampicin of 450 mg daily for children weighing less than 50 kg.

In **leprosy** regimens rifampicin is usually given with dapsone for the treatment of paucibacillary leprosy, and with dapsone and clofazimine for the treatment of multibacillary leprosy. WHO recommends that rifampicin is given once monthly in a dose of 450 mg by mouth to children 10 years of age and older.

In the treatment of **brucellosis, Legionnaires' disease**, and serious **staphylococcal infections** doses recommended by the *BNFC* are 5 to 10 mg/kg twice daily in neonates and infants up to 12 months of age, and 10 mg/kg in those older than one year of age. Doses are given by mouth or intravenous infusion and in combination with other antibacterials.

For prophylaxis against meningococcal **meningitis** the AAP recommends infants less then 1 month old are given 5 mg/kg, while infants and children aged 1 month or more are given 10 mg/kg (to a maximum of 600 mg), both twice daily by mouth for 2 days. The *BNFC* recommends doses of 5 mg/kg for neonates and infants up to 12 months of age and 10 mg/kg for children between 1 and 12 years of age, each twice daily by mouth for 2 days.

For prophylaxis against meningitis due to *Haemophilus influenzae* the AAP recommends infants less then 1 month old are given 10 mg/kg once daily by mouth for 4 days, while the *BNFC* suggests that this dose should be given to infants aged 1 to 3 months. For older infants and children both the AAP and the *BNFC* recommend a dose of 20 mg/kg (to a maximum of 600 mg) once daily by mouth for 4 days.

Administration in hepatic impairment. Reduced doses of rifampicin are recommended for patients with hepatic impairment and a maximum of 8 mg/kg daily has been suggested. See also Precautions, above.

Ehrlichiosis. Beneficial responses to rifampicin have been reported[1] in 2 pregnant women with human granulocytic anaplasmosis (see Ehrlichiosis, p.168), in whom the usual treatment with a tetracycline was contra-indicated.

1. Buitrago MI, *et al.* Human granulocytic ehrlichiosis during pregnancy treated successfully with rifampin. *Clin Infect Dis* 1998; **27:** 213–15.

Meningitis prophylaxis. *HAEMOPHILUS INFLUENZAE MENINGITIS PROPHYLAXIS.* Meningeal infection with *Haemophilus influenzae* type b (Hib) in children is associated with substantial morbidity, but the incidence has decreased since the introduction of immunisation with *H. influenzae* type b vaccine. Although a worldwide problem, the disease (p.178) and its prophylaxis has been studied mainly in the USA, where it was shown that children under 4 years of age formed the highest risk group for primary infection while children under 2 years of age formed the highest risk group for secondary infection.[1] The goal of prophylaxis in close contacts is to eliminate carriage of the organism to prevent spread to young children. Risk of infection to young children with recent household contact to the primary case of infection with *H. influenzae* type b is increased 600- to 800-fold,[1,2] but only increased 20-fold[3] from day-care or school contact. The risk may be higher when more than 1 index patient is identified.

Rifampicin in doses of 20 mg/kg once daily for 4 days (maximum dose 600 mg) has been shown to eradicate Hib nasopharyngeal carriage in at least 95% of contacts of the primary case.[4] There is some evidence from a study involving 68 families of patients with Hib infection that rifampicin 20 mg/kg daily for 2 days may be as effective as a 4-day course in eradicating Hib pharyngeal colonisation.[5] Rifampicin prophylaxis appears to be successful in preventing infection in household contacts, but benefit in school settings where there has been a single index case has not been established.[3]

Recommendations have been made for rifampicin prophylaxis.[6,7] The American Academy of Pediatrics (AAP) recommends[6] that all household contacts be given rifampicin prophylaxis where there is at least 1 contact person who is younger than 4 years of age who is not or incompletely immunised against Hib, where there is an unimmunised child younger than 12 months of age, or where there is an immunocompromised child (regardless of vaccine status), in the household. Similar recommendations have been made in the UK.[7] The AAP[6] also recommends rifampicin prophylaxis when 2 or more cases of Hib disease have occurred within 60 days in a day-care or school. In the UK,[7] prophylaxis has been recommended for all room contacts when 2 or more cases of disease have occurred within 120 days. Rifampicin prophylaxis is not recommended for pregnant women.[6]

For recommended *doses* see Uses and Administration and Administration in Children, above.

Rifampicin should also be given to the primary case since treatment of the infection does not eradicate nasopharyngeal carriage.[2,6]

1. Casto DT, Edwards DL. Preventing Haemophilus influenzae type b disease. *Clin Pharm* 1985; **4:** 637–48.
2. Cartwright KAV, *et al.* Chemoprophylaxis for Haemophilus influenzae type b: rifampicin should be given to close contacts. *BMJ* 1991; **302:** 546–7.
3. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on nonsurgical antimicrobial prophylaxis. *Clin Pharm* 1990; **9:** 423–45.
4. Band JD, *et al.* Prevention of Hemophilus influenzae type b disease. *JAMA* 1984; **251:** 2381–6.
5. Green M, *et al.* Duration of rifampin chemoprophylaxis for contacts of patients infected with Haemophilus influenzae type B. *Antimicrob Agents Chemother* 1992; **36:** 545–7.
6. Pickering L, *et al.* eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006.
7. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" Available at: http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Greenbook/DH_4097254 (accessed 05/10/07)

MENINGOCOCCAL MENINGITIS PROPHYLAXIS. *Neisseria meningitidis* is an important cause of bacterial meningitis (p.178); all age groups are at risk during epidemics but children are usually at highest risk during endemic outbreaks. Vaccines are available for meningococci groups A, C, Y, and W135 but not usually for group B, therefore antimicrobial prophylaxis remains important in preventing the spread of the disease. The aim of prophylaxis is to eliminate nasopharyngeal carriage of the organism. Sulfadiazine and minocycline are no longer used because of resistance and adverse effects. The current antibacterial of choice is rifampicin which should be given for 2 days (for doses see Uses and Administration and Administration in Children, above). Alternatives include a single oral dose of ciprofloxacin, ofloxacin, or azithromycin, or a single intramuscular dose of ceftriaxone.[1,2] Antibacterial prophylaxis should be given as soon as possible to close contacts (ideally within 24 hours of diagnosis of the index case). It is also recommended for child care or nursery school contacts in the USA,[2] but is not usually advised for this group in the UK after a single case.[1] The index patient should also receive rifampicin for 2 days before hospital discharge since treatment with penicillin does not eliminate nasopharyngeal carriage.

1. PHLS, Public Health Medicine Environmental Group, Scottish Centre for Infection and Environmental Health. Guidelines for public health management of meningococcal disease in the UK. *Commun Dis Public Health* 2002; **5:** 187–204. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol5/no3/Meningococcal_Guidelines.pdf (accessed 05/10/07)
2. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): prevention and control of meningococcal disease. *MMWR* 2005; **54** (RR-7): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5407.pdf (accessed 05/10/07)

Naegleria infections. For mention of the use of rifampicin in primary amoebic meningoencephalitis, see p.822.

Preparations

BP 2008: Rifampicin Capsules; Rifampicin Oral Suspension;
USP 31: Rifampin and Isoniazid Capsules; Rifampin Capsules; Rifampin for Injection; Rifampin Oral Suspension; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Moxina; Pharmaceutix†; Rifadecina†; Rifadin; ***Austral.:*** Rifadin; Rimycin; ***Austria:*** Eremfat; Rifoldin; Rimactan; ***Belg.:*** Rifadine; ***Braz.:*** Monicil; Rifaldin; Rifamp; ***Canad.:*** Rifadin; Rofact; ***Chile:*** Rifaldin; ***Cz.:*** Arficin; Benemicin; Eremfat; Rifamor†; Tubocin†; ***Denm.:*** Rimactan; ***Fin.:*** Rimapen; ***Fr.:*** Rifadine; Rimactan; ***Ger.:*** Eremfat; Rifa; ***Gr.:*** Rifadin; Rifaldin; ***Hong Kong:*** Ricin; Rifadin; Rifasynt; Rimactane; ***Hung.:*** Rifamed; ***India:*** R-Cin; Rifacilin; Rifacom E-Z; Rifamycin; Rimactane; Siticox; ***Indon.:*** Corifam; Famri; Lanarif; Medirif; Merimac; Prolung; Ramicin; RIF; Rifabiotic; Rifacin; Rifamtibi; Rimactane; ***Irl.:*** Rifadin; Rimactane; ***Israel:*** Rimactan; ***Ital.:*** Rifadin; Rifapiam†; ***Malaysia:*** Ramfin†; Rifasynt; Rimactane; ***Mex.:*** Eurifam; Finamicina; Pestarin; Rifadin; Rimactan; Turifam; ***Neth.:*** Rifadin; Rimactan†; ***Norw.:*** Rimactan; ***NZ:*** Rifadin; ***Philipp.:*** Crisafam; Fampisec; Framacin; Medifam; Natricin; Odifam; Refam; Rexilan; Ricyn; Rifadin; Rifamax; Rimactane; Rimaped; Riprocin; ***Port.:*** Rifadin; Rifex; Rimactan; ***Rus.:*** Benemicin (Бенемицин); ***S.Afr.:*** Rifadin†; Rimactane; ***Singapore:*** Rimactane†; ***Spain:*** Rifagen†; Rifaldin; Rimactan; ***Swed.:*** Rifadin; Rimactan; ***Switz.:*** Rimactan; ***Thai.:*** Manorifcin; Myrin-P; Myrin†; Ramfin†; Rampicin†; Ricin; Rifadin; Rifagen; Rifam; Rifam-P†; Rifamcin; Rifasynt†; Rimactane; Rimecin; ***Turk.:*** Rifadin; Rifcap; Rifex; ***UK:*** Rifadin; Rimactane; ***USA:*** Rifadin; Rimactane; ***Venez.:*** Fampiz†; Rifadin; Rimactan.

Multi-ingredient: ***Arg.:*** Bacifim; Rifaprim; Rifinah; Risoniac†; Ritroprim†; ***Austria:*** Rifater; Rifoldin INH; ***Braz.:*** Isoniaton; ***Canad.:*** Rifater; ***Denm.:*** Rimactazid; Rimstar; ***Fin.:*** Rimactazid; Rimstar; ***Fr.:*** Rifater; Rifinah; ***Ger.:*** Iso-Eremfat; Rifater; Rifinah; tebesium Duo; tebesium Trio; ***Gr.:*** Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong:*** Rifater; Rifinah; ***Hung.:*** Rifazid; ***India:*** Akt-3; Akt-4; Arzide; Bicox-E†; Coxina-3; Coxina-4; Coxinex; Cx-3; Cx-4; Cx-5; Gocox Compound; Gocox-3; Gocox-4†; Ipcacin Kid; Isorifam; R-Cinex; R-Cinex Z; RHZ; RHZ-Plus; Rifa; Rifa E; Rifacomb Plus†; Rifacomb†; Rimactazid + Z; Rimpazid; Siticox-INH; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed-2; Xeed-3E; Xeed-4; ***Indon.:*** Ramicin-ISO; Rimactazid; Rimcure; Rimstar; ***Irl.:*** Rifater; Rifinah; Rimactazid; ***Ital.:*** Rifater; Rifinah; ***Malaysia:*** Rimactazid; Rimcure; ***Mex.:*** Arpisen; Finater; Finateramida; Isonid†; Rifaprim; Rifater; Rifinah; ***Neth.:*** Rifinah; ***NZ:*** Rifinah; ***Philipp.:*** 4D; Bifix; CombiKids; CombiPack; Continukit; Continukit Plus; Continupack; Econokit; Econokit-MDR; Econopack; Fixcom 3; Fixcom 4; Kidz Kit 2; Kidz Kit 3; Myrin; Myrin-P; Quadtab; Refam Duo; Refam Pedia Kit; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; SVM-Polypac-A; Tres; Triofix; Tritab; Viper; ***Pol.:*** Rifamazid; ***Port.:*** Rifater; Rifinah; ***Rus.:*** Isocomb (Изокомб); Repin B (Репин B); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс); Rimactazid (Римактазид); Rimecure 3-FDC (Римкур 3-ФДС); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Myrin†; Rifafour; Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore:*** Rimactazid; ***Spain:*** Rifater; Rifazida†; Rifinah; Rimactazid; Rimcure; Rimstar; Tisobrif; ***Swed.:*** Rimactazid; Rimcure; Rimstar; ***Switz.:*** Rifater; Rifinah; ***Thai.:*** Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid; Rimcure 3-FDC; Rimstar; ***UK:*** Rifater; Rifinah; Rimactazid†; ***USA:*** IsonaRif; Rifamate; Rifater; ***Venez.:*** Rimactazid; Rimcure.

Rifamycin Sodium *(BANM, rINNM)*

M-14 (rifamycin); Natrii Rifamycinum; Rifamicina sódica; Rifamicin-nátrium; Rifamicino natrio druska; Rifamycin sodná sůl; Rifamycin SV Sodium; Rifamycine sodique; Rifamycinnatrium; Rifamycinum natricum; Rifamysiininatrium; Ryfamycinum Natricum; Ryfamycyna sodowa. Sodium (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-21-acetoxy-1,2-dihydro-6,9,17,19-tetrahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,11-dioxo-2,7-(epoxypentadeca-1,11,13-trienimino)-naphtho-[2,1-*b*]furan-5-olate.

Натрий Рифамицин

$C_{37}H_{46}NNaO_{12}$ = 719.8.
CAS — 6998-60-3 (rifamycin); 14897-39-3 (rifamycin sodium); 15105-92-7 (rifamycin sodium).
ATC — J04AB03; S01AA16; S02AA12.
ATC Vet — QJ04AB03; QS01AA16; QS02AA12.

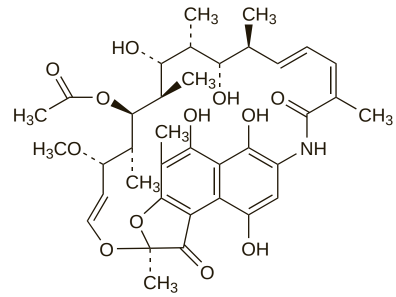

(rifamycin SV)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Rifamycin Sodium). The monosodium salt of rifamycin SV, a substance obtained by chemical transformation of rifamycin B which is produced during growth of certain strains of *Amycolatopsis mediterranei*. Rifamycin SV may also be obtained directly from certain mutants of *A. mediterranei*. The potency is not less than 900 units/mg calculated with reference to the anhydrous substance. A red, fine or slightly granular powder. Soluble in water; freely soluble in dehydrated alcohol. A 5% solution in water has a pH of 6.5 to 8.0. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

Some gastrointestinal adverse effects have occurred after injections of rifamycin. High doses may produce alterations in liver function. Hypersensitivity reactions including rashes, pruritus, and anaphylaxis have occurred rarely, but prolonged use increases the risk of sensitisation. A reddish coloration of the urine and other body fluids has been reported. Rifamycin should be used with care in patients with hepatic dysfunction.

Antimicrobial Action

Rifamycin has similar antimicrobial actions to those of rifampicin (p.327).

Pharmacokinetics

Rifamycin is not effectively absorbed from the gastrointestinal tract. Plasma concentrations of 2 micrograms/mL have been achieved 2 hours after a dose of 250 mg by intramuscular injection; concentrations of about 11 micrograms/mL have been achieved 2 hours after an intravenous dose of 500 mg. Rifamycin is about 80% bound to plasma proteins and has a plasma half-life of about 1 hour.

Rifamycin is excreted mainly in the bile and only small amounts appear in the urine.

Uses and Administration

Rifamycin is a rifamycin antibacterial that has been used in the treatment of infections caused by susceptible organisms including Gram-positive organisms such as staphylococci. It has been given as the sodium salt by intramuscular injection and by slow intravenous infusion and is also given by local instillation and topical application.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Plusderm ATB†; Rifocina; ***Austria:*** Rifocin; ***Belg.:*** Rifocine; ***Braz.:*** Rifan; Rifocina; ***Fr.:*** Otofa; ***Ital.:*** Rifocin; ***Mex.:*** Rifocyna; ***Port.:*** Rifocina; ***Rus.:*** Otofa (Отофа); ***Switz.:*** Otofa; ***Turk.:*** Rif; Rifocin; ***Venez.:*** Rifocina.

Multi-ingredient: ***Braz.:*** Rifocort.

Rifapentine *(BAN, USAN, rINN)*

DL-473; DL-473-IT; L-11473; MDL-473; Rifapentina; Rifapentinum. 3-[*N*-(4-Cyclopentyl-1-piperazinyl)formimidoyl]rifamycin.

Рифапентин

$C_{47}H_{64}N_4O_{12}$ = 877.0.
CAS — 61379-65-5.
ATC — J04AB05.
ATC Vet — QJ04AB05.

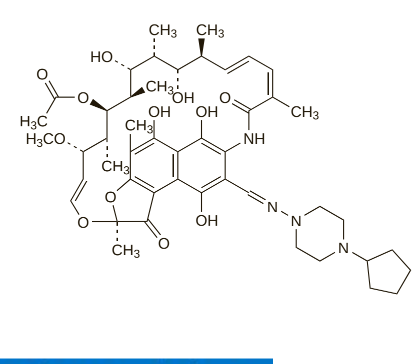

The symbol † denotes a preparation no longer actively marketed

Adverse Effects
As for Rifampicin, p.325.

A higher incidence of hyperuricaemia has been reported with rifapentine than with rifampicin.

Precautions
As for Rifampicin, p.326.

Rifapentine is only licensed for use in once- or twice-weekly regimens, and should not be given to patients with HIV infection because of potential interactions with HIV-protease inhibitors; an increased risk of developing resistance to rifamycins with highly intermittent (once- or twice-weekly) dosing regimens may occur in these patients.

Rifapentine is teratogenic in *animals*.

Interactions
As for Rifampicin, p.327.

Enzyme induction studies have suggested that rifapentine is a more potent inducer of cytochrome P450 isoenzymes than rifabutin, but less potent then rifampicin. It should not be used with HIV-protease inhibitors because of the risk of developing resistance, see Precautions, above.

Antimicrobial Action
As for Rifampicin, p.327.

Cross-resistance is common between rifapentine and rifampicin in *Mycobacterium tuberculosis*.

Antimycobacterial action. References.

1. Mor N, *et al*. Comparison of activities of rifapentine and rifampin against Mycobacterium tuberculosis residing in human macrophages. *Antimicrob Agents Chemother* 1995; **39:** 2073–7.
2. Vernon A, *et al*. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999; **353:** 1843–7.

Pharmacokinetics
Rifapentine is absorbed after oral doses. Absorption is enhanced by about 50% when rifapentine is taken with food. Peak plasma concentrations are achieved 5 to 6 hours after a single dose of 600 mg and steady-state concentrations are achieved by day 10 during daily use. A half-life of about 13 hours has been reported. Rifapentine undergoes nonoxidative metabolism and does not induce its own metabolism. Rifapentine and its active metabolite 25-deacetylrifapentine are 98% and 93% bound to plasma proteins, respectively.

Rifapentine and 25-deacetylrifapentine are excreted mainly in the faeces with a small amount appearing in the urine.

◊ References.

1. Keung ACF, *et al*. Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. *J Clin Pharmacol* 1998; **38:** 517–24.
2. Keung AC-F, *et al*. Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus: a phase I study. *Antimicrob Agents Chemother* 1999; **43:** 1230–3.
3. Conte JE, *et al*. Single-dose intrapulmonary pharmacokinetics of rifapentine in normal subjects. *Antimicrob Agents Chemother* 2000; **44:** 985–90.
4. Weiner M, *et al*. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med* 2004; **169:** 1191–7.
5. Langdon G, *et al*. Population pharmacokinetics of rifapentine and its primary desacetyl metabolite in South African tuberculosis patients. *Antimicrob Agents Chemother* 2005; **49:** 4429–36.

Uses and Administration
Rifapentine is a rifamycin antibacterial (see Rifampicin, p.325) that is used, with other antimycobacterials, for the treatment of tuberculosis (p.196).

For drug-susceptible organisms rifapentine is given orally in a dose of 600 mg twice weekly during the initial intensive phase of short-course tuberculosis regimens, then once weekly during the continuation phase.

◊ Reviews.

1. Jarvis B, Lamb HM. Rifapentine. *Drugs* 1998; **56:** 607–16.
2. Munsiff SS, *et al*. Rifapentine for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 2006; **43:** 1468–75.

Preparations
Proprietary Preparations (details are given in Part 3)
USA: Priftin.

Rifaximin *(USAN, rINN)*

L-105; Rifaxidin; Rifaximina; Rifaximine; Rifaximinum. (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-Pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-*a*]benzimidazole-1,15(2*H*)-dione 25-acetate.

Рифаксимин

$C_{43}H_{51}N_3O_{11}$ = 785.9.
CAS — 80621-81-4.
ATC — A07AA11; D06AX11.
ATC Vet — QA07AA11; QD06AX11; QG51AA06; QJ51XX01.

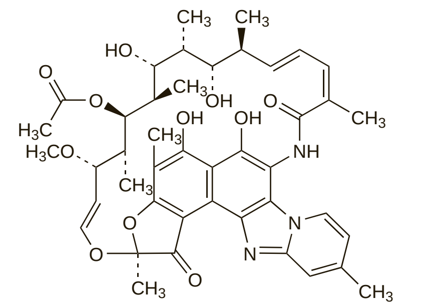

NOTE. The code L-105 has also been applied to the cephalosporin cefuzonam.

Profile
Rifaximin is a rifamycin antibacterial with antimicrobial actions similar to those of rifampicin *in-vitro* (p.327), but which is poorly absorbed from the gastrointestinal tract, having a bioavailability of about only 0.4%. Therefore, it does not have the usual adverse effects or interactions of rifampicin. Hypersensitivity reactions, including exfoliative dermatitis and angioneurotic oedema have been reported. Rifaximin should not be given to patients with travellers' diarrhoea complicated by fever or blood in the stool.

It has been licensed in the USA and some other countries for the treatment of travellers' diarrhoea caused by noninvasive strains of *Escherichia coli*. It has also been tried for other gastrointestinal disorders, including infectious diarrhoea in nontravellers, inflammatory bowel disease, abdominal distension, bloating, and flatulence, small bowel bacterial overgrowth, diverticulitis, Crohn's disease, for surgical infection prophylaxis, and hepatic encephalopathy (p.1697).

For the treatment of travellers' diarrhoea in those 12 years of age and older, the recommended oral dose is 200 mg three times daily for 3 days. Doses given for other indications range from 600 to 1200 mg daily, in 2 to 4 divided doses.

Rifaximin has also been used topically as a 5% ointment.

◊ References.

1. Gillis JC, Brogden RN. Rifaximin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. *Drugs* 1995; **49:** 467–84.
2. DuPont HL, *et al*. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001; **33:** 1807–15.
3. Pakyz AL. Rifaximin: a new treatment for travelers' diarrhea. *Ann Pharmacother* 2005; **39:** 284–9.
4. Robins GW, Wellington K. Rifaximin: a review of its use in the management of traveller's diarrhoea. *Drugs* 2005; **65:** 1697–1713.
5. Ericsson CD. Safety and tolerability of the antibacterial rifaximin in the treatment of travellers' diarrhoea. *Drug Safety* 2006; **29:** 201–7.
6. Adachi JA, DuPont HL. Rifaximin: a novel nonabsorbed rifamycin for gastrointestinal disorders. *Clin Infect Dis* 2006; **42:** 541–7. Correction. *ibid.*; 896. [dose frequency]
7. Pimentel M, *et al*. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006; **145:** 557–63.
8. Fumi AL, Trexler K. Rifaximin treatment for symptoms of irritable bowel syndrome. *Ann Pharmacother* 2008; **42:** 408–12.

Diverticular disease. Rifaximin may be used in the management of diverticular disease (p.1695); for reference to its use in combination with mesalazine see p.1747.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Normix; ***Gr.:*** Lormyx; Rifacol; ***Hung.:*** Normix; ***Ital.:*** Normix; Rifacol; ***Mex.:*** Flonorm; Redactiv†; ***Pol.:*** Xifaxan; ***Port.:*** Flonorm; ***Spain:*** Spiraxin; Zaxine; ***USA:*** Xifaxan.

Rokitamycin *(rINN)*

M-19-Q; 3″-Propionyl-leucomycin A_5; Rikamycin; Rokitamicina; Rokitamycine; Rokitamycinum; TMS-19Q. [(4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-11,13-dien-6-yl]-3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4″-butyrate 3″-propionate.

Рокитамицин

$C_{42}H_{69}NO_{15}$ = 828.0.
CAS — 74014-51-0.
ATC — J01FA12.
ATC Vet — QJ01FA12.

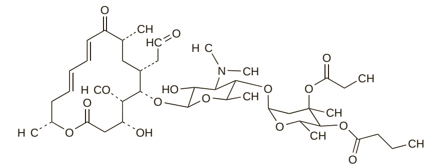

Pharmacopoeias. In *Jpn.*

Profile
Rokitamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p.269). It has been given orally in usual doses of 400 mg twice daily in the treatment of susceptible infections.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Paidocin; Rokital.

Rolitetracycline *(BAN, USAN, rINN)*

PMT; Pyrrolidinomethyltetracycline; Rolitetraciclina; Rolitétracycline; Rolitetracyclinum; Rolitetracyklin; Rolitetrasykliini; SQ-15659. N^2-(Pyrrolidin-1-ylmethyl)tetracycline.

Ролитетрациклин

$C_{27}H_{33}N_3O_8$ = 527.6.
CAS — 751-97-3.
ATC — J01AA09.
ATC Vet — QJ01AA09.

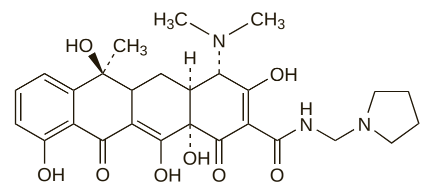

Profile
Rolitetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p.347). It is included in some topical eye preparations used for the treatment of susceptible infections. It has also been given by injection, when it has been associated with shivering and, more rarely, rigor, due to a Jarisch-Herxheimer reaction. Injection has also been followed by a peculiar taste sensation, often similar to ether.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Eubetal Biotic†; ***Ital.:*** Colbiocin; Eubetal Antibiotico; Vitecaf; ***Rus.:*** Colbiocin (Колбиоцин).

Rosoxacin *(BAN, USAN, rINN)*

Acrosoxacin; Rosoksasiini; Rosoxacine; Rosoxacino; Rosoxacinum; Win-35213. 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid.

Розоксацин

$C_{17}H_{14}N_2O_3$ = 294.3.
CAS — 40034-42-2.
ATC — J01MB01.
ATC Vet — QJ01MB01.

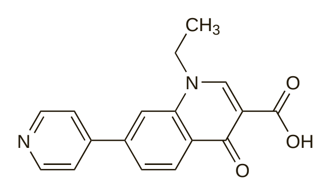

Adverse Effects and Precautions
As for Nalidixic Acid, p.304.

Dizziness, drowsiness, and visual disturbances occur relatively frequently, and patients should be advised not to drive or operate machinery if affected.

Uses and Administration
Rosoxacin is a 4-quinolone antibacterial with actions similar to those of nalidixic acid (p.304). It is active against *Neisseria gonorrhoeae* and has been given as single-dose oral treatment for gonorrhoea. It has also been used in the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Eradacil; ***Mex.:*** Eradacil; ***Port.:*** Eradacil†.

Roxithromycin *(USAN, rINN)*

Roksitromicinas; Roksitromisin; Roksitromysiini; Roxithromycine; Roxithromycinum; Roxitromicin; Roxitromicina; Roxitromycin; RU-965; RU-28965. Erythromycin 9-{*O*-[(2-methoxyethoxy)-methyl]oxime}.

Рокситромицин

$C_{41}H_{76}N_2O_{15}$ = 837.0.

CAS — 80214-83-1.

ATC — J01FA06.

ATC Vet — QJ01FA06.

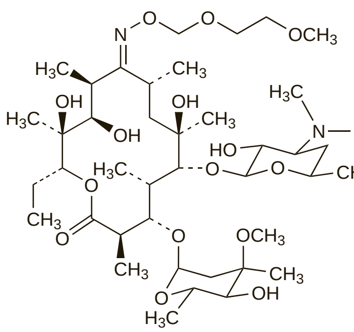

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Roxithromycin). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane; slightly soluble in dilute hydrochloric acid. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270.

Gastrointestinal disturbances are the most frequent adverse effect, but are less frequent than with erythromycin.

The dose of roxithromycin may need to be reduced in patients with hepatic or renal impairment.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in a patient given roxithromycin; renal function improved over several days after the drug was stopped.

1. Akcay A, *et al.* Acute renal failure and hepatotoxicity associated with roxithromycin. *Ann Pharmacother* 2004; **38:** 721–2.

Effects on the lungs. Acute eosinophilic pneumonia was attributed in a patient to the use of roxithromycin.[1] The condition resolved after treatment with methylprednisolone.

1. Pérez-Castrillón JL, *et al.* Roxithromycin-induced eosinophilic pneumonia. *Ann Pharmacother* 2002; **36:** 1808–9.

Effects on the pancreas. Acute pancreatitis, with duodenal inflammation, pain, pancreatic enlargement, and raised serum-amylase developed in a patient within 24 hours of substituting roxithromycin for erythromycin ethyl succinate.[1] Symptoms resolved rapidly once roxithromycin was stopped.

1. Souweine B, *et al.* Acute pancreatitis associated with roxithromycin therapy. *DICP Ann Pharmacother* 1991; **25:** 1137.

Eosinophilia. For a report of an eosinophilic syndrome in a patient after treatment with azithromycin or roxithromycin, see Azithromycin, p.207. See also under Effects on the Lungs, above.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Roxithromycin has a much lower affinity for cytochrome P450 isoenzymes than erythromycin and therefore has fewer interactions. It does not appear to interact with antacids, carbamazepine, oral contraceptives, prednisolone, or ranitidine.

Antimicrobial Action

As for Erythromycin, p.271. It is reported to be as active or slightly less active than erythromycin.

Pharmacokinetics

Roxithromycin is absorbed after oral doses with a bioavailability of about 50%. Peak plasma concentrations of about 6 to 8 micrograms/mL occur around 2 hours after a single dose of 150 mg. The mean peak plasma concentration at steady state after a dose of 150 mg twice daily is 9.3 micrograms/mL. Absorption is reduced when taken after a meal. It is widely distributed into tissues and body fluids; high concentrations are taken up into white blood cells. Small amounts of roxithromycin are distributed into breast milk. It is about 96% bound to plasma proteins (mainly α_1-acid glycoprotein) at trough concentrations, but binding is saturable, and only about 87% is bound at usual peak concentrations. Small amounts of roxithromycin are metabolised in the liver, and the majority of a dose is excreted in the faeces as unchanged drug and metabolites; about 7 to 10% is excreted in urine, and up to 15% via the lungs. The elimination half-life is reported to range from about 8 to 13 hours, but may be more prolonged in patients with hepatic or renal impairment and in children. It has been reported that roxithromycin is not substantially removed by peritoneal dialysis.

◊ References.

1. Puri SK, Lassman HB. Roxithromycin: a pharmacokinetic review of a macrolide. *J Antimicrob Chemother* 1987; **20** (suppl B): 89–100.

Uses and Administration

Roxithromycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p.272). It is given orally to adults in a usual dose of 150 mg twice daily or sometimes 300 mg once daily, at least 15 minutes before meals, for 5 to 10 days in the treatment of susceptible infections.

Dosage may need to be modified in patients with hepatic or renal impairment (see below).

For doses in infants and children, see below.

◊ References.

1. Williams JD, Sefton AM. Comparison of macrolide antibiotics. *J Antimicrob Chemother* 1993; **31** (suppl C): 11–26.
2. Markham A, Faulds D. Roxithromycin: an update of its antimicrobial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **48:** 297–326.
3. Young LS, Lode H, eds. Roxithromycin: first of a new generation of macrolides: update and perspectives. *Infection* 1995; **23** (suppl 1): S1–S52.
4. Lovering AM, *et al.*, eds. Roxithromycin—additional therapeutic potential. *J Antimicrob Chemother* 1998; **41** (suppl B): 1–97.

Administration in children. In children weighing from 6 up to 40 kg a dose of 5 to 8 mg/kg daily of roxithromycin may be used.

Administration in hepatic impairment. The licensed product information for roxithromycin notes that safety in hepatic impairment has not been established and advises halving the usual daily dose (see above) if used.

Administration in renal impairment. The licensed product information for roxithromycin notes that safety in renal impairment has not been established and dosage adjustment details are not specified.

A pharmacokinetic study[1] in 20 subjects (10 with normal renal function and 10 with severely impaired function) suggested that doubling the dosage interval of roxithromycin would be suitable in those with a creatinine clearance of less than 15 mL/minute.

1. Halstenson CE, *et al.* Disposition of roxithromycin in patients with normal and severely impaired renal function. *Antimicrob Agents Chemother* 1990; **34:** 385–9.

Hyperplasia. Gingival hyperplasia is a well recognised adverse effect of ciclosporin treatment; a small study[1] indicated that roxithromycin could reduce overgrowth, possibly by an effect on transforming growth factor-β. For the use of another macrolide, azithromycin, for this indication see Hyperplasia, p.1824.

1. Condé SAP, *et al.* Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2008; **40:** 1435–8.

Ischaemic heart disease. For mention of studies investigating roxithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p.208.

Respiratory disorders. For reference to the use of roxithromycin in the management of respiratory disorders, see under Erythromycin, p.273.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anuar†; Delos; Klomicina; Rulid; Sinurit†; ***Austral.:*** Biaxsig; Roxar; Roximycin; Rulide; ***Austria:*** Roxithrostad; Rulide; ***Belg.:*** Claramid†; Docroxithro; Rulid; ***Braz.:*** Floxid; Rotram; Roxid†; Roxina; Roxitran; Roxitricina†; Roxitrom; Roxitromin†; Rulid; ***Chile:*** Ramivan; ***Cz.:*** Rovenal†; Rulid†; ***Denm.:*** Forilin†; Forimycin; Roximstad; Surlid; ***Fin.:*** Roxibion; Surlid; ***Fr.:*** Claramid; Rulid; Subroxine; ***Ger.:*** Infectoroxit; Romyk†; Roxi; Roxipaed†; Roxi-Puren; Roxi-Q; Roxi-saar; Roxibeta; Roxidura; Roxigamma; Roxigrun; RoxiHefa; RoxiHexal; Roxiklinge†; Roxithro-Lich; Rulid; ***Gr.:*** Acevor; Anti-Bio; Aristomycin; Asmetic; Azuril; Bazuctril; Bicofen; Delitroxin; Erybros; Macrolid-S; Neo-Suxigal; Nirox; Oxetine; Redotrin; Roxibron; Roxicillin; Roximin; Roxitazon; Roxivinol; Roxy-Due; Roxyspes; Rulid; Seide; Siguon; Thriostaxil; Tirabicin; Toscamycin-R; Uramilon; Vaselpin; Vomitoran; ***Hong Kong:*** Roxicin; Rudin; Rulid; Uonin; ***Hung.:*** Renicin; Rulid; ***India:*** Biorox; Roxee; Roxem; Roxeptin; Roxibid; Roxid; Roxivista; Roxyrol; Unorox†; ***Indon.:*** Anbiolid; Biostatik; Ixor; Rolexit; Rulid; Ruxcine; Simacron; Sitro; Uplores; Xorin; ***Israel:*** Roxo; Rulid; ***Ital.:*** Assoral; Overal; Rossitrol; Rulid; ***Malaysia:*** Roxcin; Roxinox; Rulid; Uonin; ***Mex.:*** Crolix; Kensodic; Rulid; Sertrom; ***Neth.:*** Rulide; ***NZ:*** Romicin; ***Philipp.:*** Macrol; Marulide; Rulid; Ruthison; Thromyn; ***Pol.:*** Renicin; Rolicyn; Roxiratio; Roxitron; Rulid; Xitrocin; ***Port.:*** Inferoxin; Odonticina; Roxitron; Rulide; ***Rus.:*** Elrox (Элрокс); Roxeptin (Роксептин); Roxihexal (Роксигексал); Roxylor (Роксилор); Rulid (Рулид); ***S.Afr.:*** Roxulide; Roxxibid; Rulide; Throsyn; ***Singapore:*** Roxid; Rulid†; ***Spain:*** Macrosil; Rotramin; Rulide; ***Swed.:*** Surlid; ***Switz.:*** Rulid; ***Thai.:*** Ammirox; Eroxade; Poliroxin; Rothricin; Roxcin; Roxicin; Roxilan; Roximin; Roxithro; Roxithroxyl; Roxitin; Roxitop; Roxlecon; Roxomycin; Roxthomed; Roxthrin; Roxto; Roxtrocin; Roxy; Roxydin; Rucin; Rulid; Uonin; Utolid; Vesthromycin; ***Turk.:*** Remora; Ritosin; Roksimin; Roksolit; Rulid; ***Venez.:*** Rancolid†; Roxicure; Roxitrol; Rulid.

Multi-ingredient: ***India:*** Roxeptin-ME.

Rufloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de rufloxacino; MF-934 (rufloxacin); Rufloxacine, Chlorhydrate de; Rufloxacini Hydrochloridum. 9-Fluoro-2,3-dihydro-10-[4-methylpiperazin-1-yl]-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid hydrochloride.

Руфлоксацина Гидрохлорид

$C_{17}H_{18}FN_3O_3S,HCl$ = 399.9.

CAS — 101363-10-4 (rufloxacin); 106017-08-7 (rufloxacin hydrochloride).

ATC — J01MA10.

ATC Vet — QJ01MA10.

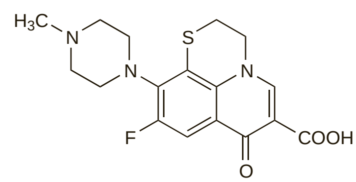

(rufloxacin)

Profile

Rufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243). It is given orally as the hydrochloride in the treatment of susceptible infections in a usual initial dose of 400 mg on the first day followed by 200 mg daily thereafter. A plasma half-life of 30 hours or more has been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Monos; Qari; Tebraxin; ***Mex.:*** Uroflox; ***Philipp.:*** Uroclar; ***Thai.:*** Uroflox.

Sarafloxacin Hydrochloride *(BANM, USAN, rINNM)*

A-57135 (sarafloxacin); A-56620 (sarafloxacin or sarafloxacin hydrochloride); Abbott-56620 (sarafloxacin or sarafloxacin hydrochloride); Hidrocloruro de sarafloxacino; Sarafloxacine, Chlorhydrate de; Sarafloxacini Hydrochloridum.

Сарафлоксацина Гидрохлорид

$C_{20}H_{17}F_2N_3O_3,HCl$ = 421.8.

CAS — 98105-99-8 (sarafloxacin); 91296-87-6 (sarafloxacin hydrochloride).

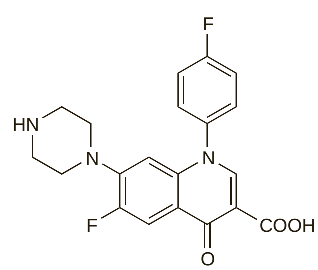

(sarafloxacin)

Profile

Sarafloxacin is a fluoroquinolone antibacterial that has been used as the hydrochloride in veterinary medicine.

The symbol † denotes a preparation no longer actively marketed

Sisomicin Sulfate *(USAN, rINNM)*

Antibiotic 6640 (sisomicin); Rickamicin Sulphate; Sch-13475 (sisomicin); Sisomicin Sulphate *(BANM)*; Sisomicine, Sulfate de; Sisomicini Sulfas; Sissomicin Sulphate; Sulfato de sisomicina. 4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine sulphate; 2-Deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enopyranosyl)streptamine sulphate.

Сизомицина Сульфат

$(C_{19}H_{37}N_5O_7)_2,5H_2SO_4$ = 1385.4.

CAS — 32385-11-8 (sisomicin); 53179-09-2 (sisomicin sulfate).

ATC — J01GB08.

ATC Vet — QJ01GB08.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*

USP 31 (Sisomicin Sulfate). It loses not more than 15% of its weight on drying. 1 mg of sisomicin sulfate has a potency equivalent to not less than 580 micrograms of sisomicin calculated on the dried basis. A 4% solution in water of sisomicin has a pH of 3.5 to 5.5. Store in airtight containers.

Profile

Sisomicin, an antibiotic produced by *Micromonospora inyoensis* and closely related to gentamicin C_{1A}, is an aminoglycoside with general properties similar to those of gentamicin (p.282). It is given as the sulfate but doses are expressed in terms of the base; 1.5 g of sisomicin sulfate is equivalent to about 1 g of sisomicin. The usual dose for adults is 3 mg/kg daily given intramuscularly in 2 or 3 divided doses. It may be given by intravenous infusion if necessary.

Preparations

USP 31: Sisomicin Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
India: Sisoptin; ***Ital.:*** Mensiso†.

Sitafloxacin *(USAN, rINN)*

DU-6859 (anhydrous sitafloxacin); DU-6859a (sitafloxacin sesquihydrate); Sitafloxacine; Sitafloxacino; Sitafloxacinum. (−)-7-[(7*S*)-7-Amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

Ситафлоксацин

$C_{19}H_{18}ClF_2N_3O_3$ = 409.8.

CAS — 127254-12-0 (anhydrous sitafloxacin); 163253-37-0 (sitafloxacin monohydrate); 163253-35-8 (sitafloxacin sesquihydrate).

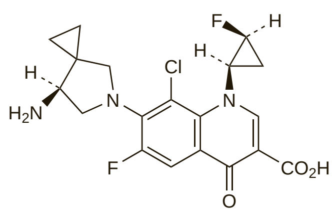

NOTE. Sitafloxacin exists in several hydration states; the name sitafloxacin has been used to refer to both the anhydrous substance and the sesquihydrate ($C_{19}H_{18}ClF_2N_3O_3,1\frac{1}{2}H_2O$ = 436.8); the latter is known in Japan as sitafloxacin hydrate.

Profile

Sitafloxacin is a fluoroquinolone that is given orally in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Gracevit.

Sparfloxacin *(BAN, USAN, rINN)*

AT-4140; CI-978; Esparfloxacino; PD-131501; RP-64206; Sparfloksasiini; Sparfloxacine; Sparfloxacinum. 5-Amino-1-cyclopropyl-7-(*cis*-3,5-dimethylpiperazin-1-yl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

Спарфлоксацин

$C_{19}H_{22}F_2N_4O_3$ = 392.4.

CAS — 110871-86-8.

ATC — J01MA09.

ATC Vet — QJ01MA09.

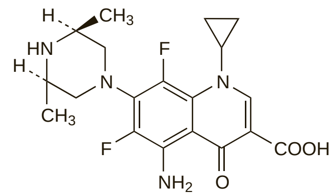

Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Concern over phototoxicity associated with sparfloxacin has led to restriction of its use in some countries; patients should be advised to avoid exposure to sunlight during, and for a few days after, sparfloxacin therapy, and to stop the drug immediately if phototoxicity occurs.

Photosensitivity. In a survey[1] of the reporting rate for phototoxicity associated with sparfloxacin in France, the manufacturer or the French Pharmacovigilance System received 371 reports of severe phototoxic reactions during the first 9 months after marketing of the drug; this approximated to between 4 and 25 times the rate reported for other fluoroquinolones.

1. Pierfitte C, *et al.* The link between sunshine and phototoxicity of sparfloxacin. *Br J Clin Pharmacol* 2000; **49:** 609–12.

Interactions

As for Ciprofloxacin, p.246.

Sparfloxacin does not appear to interact with theophylline or caffeine, nor with warfarin or cimetidine. Probenecid does not alter the pharmacokinetics of sparfloxacin.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Sparfloxacin is reported to be more active *in vitro* than ciprofloxacin against mycobacteria and against Gram-positive bacteria, including *Streptococcus pneumoniae* and other streptococci and staphylococci.

Pharmacokinetics

Sparfloxacin is well absorbed from the gastrointestinal tract with a bioavailability of about 90%. Peak plasma concentrations occur 3 to 6 hours after a dose. Sparfloxacin is widely distributed into body tissues and fluids, including respiratory tissues, but is only about 45% bound to plasma proteins. It is metabolised in the liver by glucuronidation and has an elimination half-life of about 20 hours. It is excreted in equal amounts in the faeces and urine as unchanged drug and as the glucuronide metabolite.

◊ References.

1. Shimada J, *et al.* Clinical pharmacokinetics of sparfloxacin. *Clin Pharmacokinet* 1993; **25:** 358–69.

Uses and Administration

Sparfloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247). It is given orally for the treatment of susceptible infections in a usual dose of 100 to 300 mg in 1 or 2 divided doses daily. It has also been tried in tuberculosis (see under Uses and Administration of Ciprofloxacin, p.248).

◊ General references.

1. Finch RG, *et al.*, eds. Sparfloxacin: focus on clinical performance. *J Antimicrob Chemother* 1996; **37** (suppl A): 1–167.
2. Goa KL, *et al.* Sparfloxacin: a review of its antibacterial activity, pharmacokinetic properties, clinical efficacy and tolerability in lower respiratory tract infections. *Drugs* 1997; **53:** 700–25.
3. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32:** 320–36.
4. Schentag JJ. Sparfloxacin: a review. *Clin Ther* 2000; **22:** 372–87.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Zagam†; ***India:*** Scat; Sparbact; Sparcip; Spardac; Spardrops; Sparquin; Sparvista; Sparx; ***Indon.:*** Newspar; Resflok; Sparos; ***Jpn:*** Spara; ***Rus.:*** Sparflo (Спарфло); ***USA:*** Zagam†.

Spectinomycin *(BAN, rINN)*

Actinospectacin; Espectinomicina; Spectinomycine; Spectinomycinum; Spektinomycin; Spektinomysiini. Perhydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)pyrano[2,3-*b*][1,4]benzodioxin-4-one.

Спектиномицин

$C_{14}H_{24}N_2O_7$ = 332.3.

CAS — 1695-77-8.

ATC — J01XX04.

ATC Vet — QJ01XX04.

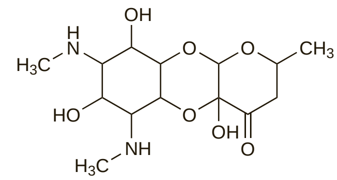

Description. Spectinomycin is an antimicrobial substance produced by the growth of *Streptomyces spectabilis* or by any other means.

Spectinomycin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de espectinomicina; M-141; Spectinomycine, Chlorhydrate de; Spectinomycine (dichlorhydrate de) pentahydraté; Spectinomycini dihydrochloridum pentahydricum; Spectinomycini hydrochloridum; Spektinomicin-hidroklorid; Spektinomicino hidrochloridas; Spektinomycin hydrochlorid; Spektinomycindihydrokloridpentahydrat; Spektinomysiinidihydrokloridipentahydraatti; Spektynomycyny chlorowodorek; Spektynomycyny dichlorowodorek pięciowodny; U-18409AE. Spectinomycin dihydrochloride pentahydrate.

Спектиномицина Гидрохлорид

$C_{14}H_{24}N_2O_7,2HCl,5H_2O$ = 495.3.

CAS — 21736-83-4 (anhydrous spectinomycin hydrochloride); 22189-32-8 (spectinomycin hydrochloride pentahydrate).

ATC — J01XX04.

ATC Vet — QJ01XX04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Spectinomycin Dihydrochloride Pentahydrate). A substance produced by *Streptomyces spectabilis* or by any other means. A white or almost white, slightly hygroscopic, powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

USP 31 (Spectinomycin Hydrochloride). A white to pale buff crystalline powder. 1 mg of monograph substance has a potency equivalent to not less than 603 micrograms of spectinomycin. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

Adverse Effects and Precautions

Nausea, dizziness, fever and chills, insomnia, and urticaria have occasionally occurred with single doses of spectinomycin. Anaphylaxis has occurred rarely. Mild to moderate pain has been reported after intramuscular injections. Alterations in kidney and liver function and a decrease in haemoglobin and haematocrit have occasionally been seen with repeated doses. Although a reduction in urine output has been seen after single and multiple doses, spectinomycin has not been noted to produce functional changes indicative of nephrotoxicity.

Spectinomycin is ineffective in the treatment of syphilis and patients being treated for gonorrhoea should be observed for evidence of syphilis.

Interactions

Lithium. For the effect of spectinomycin on lithium, see Antimicrobials, under Interactions of Lithium, p.404.

Antimicrobial Action

Spectinomycin is an aminocyclitol antibacterial that acts by binding to the 30S subunit of the bacterial ribosome and inhibiting protein synthesis. Its activity is generally modest, particularly against Gram-positive organisms. Anaerobic organisms are mostly resistant. Various Gram-negative organisms are sensitive, including many enterobacteria and also *Haemophilus ducreyi*, and it is particularly effective against *Neisseria gonorrhoeae*. Although generally bacteriostatic, spectinomycin is bactericidal against susceptible gonococci at concentrations not much above the MIC.

Resistance may develop by chromosomal mutation or may be plasmid-mediated in some organisms; resistant gonococci have been reported clinically, notably in the Far East, but in most parts of the world resistant neisserial strains have been uncommon to date.

Pharmacokinetics

Spectinomycin is poorly absorbed orally but is rapidly absorbed after the intramuscular injection of the hydrochloride. A 2-g dose produces peak plasma concentrations of about 100 micrograms/mL at 1 hour while a 4-g dose produces peak concentrations of about 160 micrograms/mL at 2 hours. Therapeutic plasma concentrations are maintained for up to 8 hours. Distribution into saliva is poor (which limits its value in pharyngeal gonorrhoea). It is poorly bound to plasma proteins. Spectinomycin is excreted in an active form in the urine and up to 100% of a dose has been recovered within 48 hours. A half-life of about 1 to 3 hours has been reported; it is prolonged in patients with renal impairment. Spectinomycin is partially removed by dialysis.

Uses and Administration

Spectinomycin is used as an alternative to cephalosporins or fluoroquinolones in the treatment of gonorrhoea (p.191) although poor distribution into saliva limits its usefulness in pharyngeal infections. It has also been used in the treatment of chancroid (p.191).

Spectinomycin is given as the hydrochloride but doses are expressed in terms of the base. Spectinomycin hydrochloride 1.5 g is equivalent to about 1 g of spectinomycin. In the treatment of gonorrhoea it is given by deep intramuscular injection as a single dose equivalent to 2 g of spectinomycin, although a dose of 4 g may sometimes be required, divided between two injection sites. Multiple-dose courses have been used for the treatment of disseminated infections.

Spectinomycin is not effective against syphilis or chlamydial infections and additional therapy for these infections may also be needed.

For details of doses in children, see below.

Administration in children. Parenteral spectinomycin is not recommended in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see p.1632).

For prophylaxis in neonates born to mothers with gonorrhoea WHO recommends a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg) as an alternative to ceftriaxone. The CDC recommends spectinomycin as an alternative to cephalosporins in the treatment of uncomplicated gonorrhoea (p.191) in children beyond the newborn period and weighing under 45 kg; a single intramuscular dose equivalent to 40 mg/kg of spectinomycin may be given.

Preparations

USP 31: Spectinomycin for Injectable Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Togamycin†; ***Austral.:*** Trobicin; ***Austria:*** Trobicin; ***Belg.:*** Trobicin; ***Braz.:*** Trobicin†; ***Fr.:*** Trobicine; ***Ger.:*** Stanilo; ***Hong Kong:*** Kirin; Trobicin; ***India:*** Spectin; Trobicin; ***Israel:*** Togamycin†; ***Ital.:*** Trobicin; ***Malaysia:*** Kirin†; ***Mex.:*** Trobicin; ***Port.:*** Trobicin†; ***Rus.:*** Kirin (Кирин); Trobicin (Тробицин)†; ***S.Afr.:*** Trobicin; ***Singapore:*** Trobicin; ***Spain:*** Kempi; ***Switz.:*** Trobicin; ***Thai.:*** Trobicin; Vabicin; ***Venez.:*** Trobicin†.

Spiramycin *(BAN, USAN, rINN)*

Espiramicina; IL-5902; NSC-55926; NSC-64393 (spiramycin hydrochloride); RP-5337; Spiramicin; Spiramicinas; Spiramisin; Spiramycine; Spiramycinum; Spiramysiini. A mixture comprised principally of (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,16*R*)-(11*E*,13*E*)-6-[(*O*-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-(1→4)-(3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyl)oxy]-7-formylmethyl-4-hydroxy-5-methoxy-9,16-dimethyl-10-[(2,3,4,6-tetradeoxy-4-dimethylamino-D-*erythro*-hexopyranosyl)oxy]oxacyclohexadeca-11,13-dien-2-one (Spiramycin I).

Спирамицин

$C_{43}H_{74}N_2O_{14}$ = 843.1.

CAS — 8025-81-8.

ATC — J01FA02.

ATC Vet — QJ01FA02; QJ51FA02.

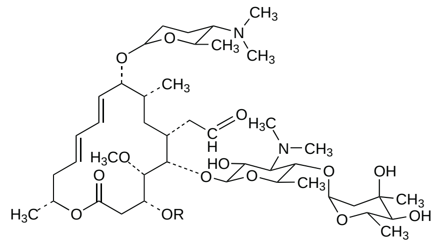

Spiramycin I R = H
Spiramycin II R = $COCH_3$
Spiramycin III R = $COCH_2CH_3$

Pharmacopoeias. In *Eur.* (see p.vii). Also in *BP (Vet)*. *Jpn* includes Acetylspiramycin.

Ph. Eur. 6.2 (Spiramycin). A macrolide antibiotic produced by the growth of certain strains of *Streptomyces ambofaciens* or obtained by any other means. The potency is not less than 4100 units/mg, calculated with reference to the dried substance. A white or slightly yellowish, slightly hygroscopic powder. Slightly soluble in water; freely soluble in alcohol, in acetone, and in methyl alcohol. A 0.5% solution in methyl alcohol and water has a pH of 8.5 to 10.5. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270.

The most frequent adverse effects are gastrointestinal disturbances. Transient paraesthesia has been reported during parenteral use.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Spiramycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The lack of interactions between spiramycin and theophylline and ciclosporin would appear to support this. Nevertheless, a report of torsade de pointes in a patient with a congenital long QT syndrome during treatment with spiramycin and *mequitazine*[1] suggests that caution is still needed.

Reduced plasma concentrations of *levodopa* have been reported when given with spiramycin (see p.807).

1. Verdun F, *et al*. Torsades de pointes sous traitement par spiramycine et méquitazine: à propos d'un cas. *Arch Mal Coeur Vaiss* 1997; **90:** 103–6.

Antimicrobial Action

As for Erythromycin, p.271, although it is somewhat less active *in vitro* against many species. It is active against *Toxoplasma gondii*.

Pharmacokinetics

Spiramycin is incompletely absorbed from the gastrointestinal tract and absorption is reduced by food. It is widely distributed into tissues, although it does not cross the blood-brain barrier. Spiramycin crosses the placenta and is distributed into breast milk. Plasma protein binding ranges from 10 to 25%. An oral dose of 6 million units produces peak blood concentrations of 3.3 micrograms/mL after 1.5 to 3 hours; the half-life is about 5 to 8 hours. High tissue concentrations are achieved and persist long after the plasma concentration has fallen to low levels.

Spiramycin is metabolised in the liver to active metabolites; substantial amounts are excreted in the bile and about 10% in the urine.

Uses and Administration

Spiramycin is a macrolide antibacterial that is used similarly to erythromycin (p.272) in the treatment of susceptible bacterial infections. It has also been used in the protozoal infections cryptosporidiosis (p.823) and toxoplasmosis (p.826).

Spiramycin is given orally as the base or intravenously as the adipate; it has also been given rectally as the adipate. The usual oral adult dose is 6 to 9 million units daily, in 2 or 3 divided doses. Doses of up to 15 million units have been given daily in divided doses for severe infections. A dose of 1.5 million units of spiramycin may be given by slow intravenous infusion every 8 hours; in severe infection the dose may be doubled.

Spiramycin is available in combination preparations with metronidazole in some countries.

Acetylspiramycin is also used.

◊ Reviews.

1. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother* 1998; **42:** 572–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rovamycine; ***Austria:*** Rovamycin; ***Belg.:*** Rovamycine; ***Braz.:*** Rovamicina; ***Canad.:*** Rovamycine†; ***Cz.:*** Rovamycine; ***Fr.:*** Rovamycine; ***Ger.:*** Rovamycine; Selectomycin; ***Gr.:*** Rovamycine; ***Hong Kong:*** Rovamycine; ***Hung.:*** Rovamycine; ***India:*** Rovamycin; ***Indon.:*** Ethirov; Hypermycin; Ismacrol; Medirov; Osmycin; Provamed; Rofacin; Rovadin; Rovamycine; Sorov; Spirabiotic; Spiradan; Spiranter; Spirasin; Varoc; Vipram; ***Israel:*** Rovamycine; ***Ital.:*** Rovamicina; Spiromix; ***Malaysia:*** Rovamycine; ***Mex.:*** Provamicina; ***Neth.:*** Rovamycine; ***Norw.:*** Rovamycin; ***Pol.:*** Rovamycine; ***Port.:*** Rovamycine; ***Rus.:*** Rovamycine (Ровамицин); ***Singapore:*** Rovamycine; ***Spain:*** Dicorvin; Rovamycine; ***Switz.:*** Rovamycine; ***Thai.:*** Rovamycin; Spiracin; ***Turk.:*** Rovamycine; ***Venez.:*** Provamicina.

Multi-ingredient: ***Arg.:*** Estilomicin; ***Braz.:*** Periodontil; ***Cz.:*** Rodogyl†; ***Fr.:*** Birodogyl; Missilor; Rodogyl; ***Malaysia:*** Rodogyl; ***Mex.:*** Rodogyl; ***Spain:*** Rhodogil.

Streptomycin *(BAN, rINN)*

Estreptomicina; Streptomisin; Streptomycine; Streptomycinum; Streptomysiini. *O*-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1→4)-N^3,N^3-diamidino-D-streptamine.

Стрептомицин

$C_{21}H_{39}N_7O_{12}$ = 581.6.

CAS — 57-92-1.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

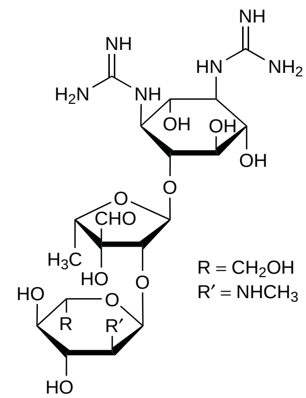

Description. An antimicrobial organic base produced by the growth of certain strains of *Streptomyces griseus*, or by any other means.

Streptomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de estreptomicina; Streptomycine, Chlorhydrate de; Streptomycini Hydrochloridum.

Стрептомицина Гидрохлорид

$C_{21}H_{39}N_7O_{12}$,3HCl = 691.0.

CAS — 6160-32-3.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

Streptomycin Sulfate *(rINNM)*

Streptomicino sulfatas; Streptomycin Sesquisulphate; Streptomycin sulfát; Streptomycin Sulphate *(BANM)*; Streptomycine, sulfate de; Streptomycini sulfas; Streptomycinsulfat; Streptomycyny siarczan; Streptomysiinisulfaatti; Sulfato de estreptomicina; Sztreptomicin-szulfát.

Стрептомицина Сульфат

$(C_{21}H_{39}N_7O_{12})_2$,$3H_2SO_4$ = 1457.4.

CAS — 3810-74-0.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Streptomycin Sulphate). A white or almost white, hygroscopic powder. The potency is not less than 720 units/mg, calculated with reference to the dried substance. Very soluble in water; practically insoluble in dehydrated alcohol. A 25% solution in water has a pH of 4.5 to 7.0. Store in airtight containers.

USP 31 (Streptomycin Sulfate). A white or practically white, hygroscopic powder; odourless or with not more than a faint odour. It has a potency equivalent to not less than 650 micrograms and not more than 850 micrograms of streptomycin per mg. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform. A solution in water containing the equivalent of streptomycin 20% has a pH of 4.5 to 7.0. Store in airtight containers.

Incompatibility. Streptomycin sulfate is incompatible with acids and alkalis.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Like gentamicin the ototoxic effects of streptomycin are mainly vestibular rather than auditory. Ototoxicity has been seen in infants whose mothers had been given streptomycin during pregnancy. However, streptomycin is reported to be somewhat less nephrotoxic than the other aminoglycosides.

Paraesthesia in and around the mouth is not uncommon after intramuscular injection of streptomycin, and other neurological symptoms, including peripheral neuropathies, optic neuritis, and scotoma have occasionally occurred. Intrathecal use has resulted in symptoms of meningeal inflammation including radiculitis, arachnoiditis, nerve root pain, and paraplegia, and some recommend that it be avoided. The risk of neurotoxic reactions is greater in patients with renal impairment or pre-renal azotaemia.

Hypersensitivity skin reactions are reported in about 5% of patients, and eosinophilia may occur. There have been reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, and anaphylaxis. Sensitisation is common among those who handle streptomycin occupationally. Topical and inhalational use of streptomycin should be avoided. If necessary, hypersensitivity can usually be overcome by desensitisation. Aplastic anaemia and agranulocytosis have been reported rarely.

Although sources differ, it is usually suggested that peak plasma concentrations should be between 15 and 40 micrograms/mL, and trough concentrations below 3 to 5 micrograms/mL; in the UK the *BNF* recommends that trough concentrations in excess of 1 microgram/mL should be avoided in those over 50 years of age or those with renal impairment. A total cumulative dose in excess of 100 g may be associated with a higher incidence of adverse effects and should only be exceeded in exceptional circumstances.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving streptomycin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Handling. Streptomycin may cause severe dermatitis in sensitised persons, and pharmacists, nurses, and others who handle the drug frequently should wear masks and rubber gloves.

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

Streptomycin has a mode of action and antimicrobial spectrum similar to that of gentamicin (p.283), although most strains of *Pseudomonas aeruginosa* are resistant. It is effective against *Yersinia pestis, Francisella tularensis,* and *Brucella* spp. Streptomycin has particular activity against *Mycobacterium tuberculosis*.

Resistance to streptomycin has often been reported and may develop in strains which are initially sensitive within a few days or weeks of beginning therapy. The widespread emergence of resistance has largely halted its use in infections due to the common Gram-negative aerobes. Primary resistance in *M. tuberculosis* is relatively uncommon in the UK and USA but may be seen in a third or more of cases in the Far East.

Both low-level and high-level resistance have been reported; the latter is thought to be due to mutation of the ribosomal binding site of the antibiotic and cannot be overcome by the synergistic use of another drug such as a beta lactam, whereas strains with moderate resistance due to decreased uptake or permeability of streptomycin may respond to combined use.

Organisms resistant to framycetin, kanamycin, neomycin, and paromomycin usually show cross-resistance to streptomycin, although streptomycin-resistant strains sometimes respond to one of these drugs.

◊ References.

1. Cooksey RC, *et al.* Characterization of streptomycin resistance mechanisms among Mycobacterium tuberculosis isolates from patients in New York City. *Antimicrob Agents Chemother* 1996; **40:** 1186–8.
2. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284. After intramuscular injection of streptomycin, maximum concentration in the blood is reached in 0.5 to 2 hours but the time taken and the concentration attained, which may be as high as about 50 micrograms/mL after a dose of 1 g, vary considerably. The half-life of streptomycin is about 2.5 hours. About one-third of streptomycin in the circulation is bound to plasma proteins. It is rapidly excreted by glomerular filtration and the concentration of streptomycin in the urine is often very high, with about 30 to 90% of a dose usually being excreted within 24 hours. It is distributed into breast milk.

Uses and Administration

Streptomycin is an aminoglycoside antibacterial mainly used as a first-line drug, with other antimycobacterials, in the treatment of tuberculosis. It is given during the initial phase of treatment unless the risk of drug resistance is small. Streptomycin has been used, with a penicillin, as an alternative to gentamicin in the treatment of bacterial endocarditis. Streptomycin is effective in the treatment of plague, tularaemia, and, with a tetracycline, in brucellosis. It has also been used, with other drugs, in various other infections including mycetoma and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Streptomycin is mostly used as the sulfate but doses are expressed in terms of the base; 1.25 g of streptomycin sulfate is equivalent to about 1 g of streptomycin. It is given by intramuscular injection.

In the treatment of tuberculosis, streptomycin is given during the initial phase of short-course regimens in usual adult doses of 15 mg/kg daily, up to a maximum of 1 g daily. The maximum daily dose should be reduced to 500 to 750 mg in adults aged over 40 years, and in those weighing less than 50 kg. Dosage should also be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. Streptomycin may also be given as part of an intermittent regimen 2 or 3 times weekly. It has been given by the intrathecal route, together with intramuscular dosage, for tuberculous meningitis, but this is no longer recommended.

Children and infants aged 1 month to 18 years with tuberculosis may be given streptomycin 20 to 40 mg/kg daily (to a maximum of 1 g daily).

In the treatment of non-tuberculous infections, streptomycin has been given in usual adult doses of 1 to 2 g daily in divided doses, depending on the susceptibility and severity of infection; children may be given 20 to 40 mg/kg daily (maximum 1 g daily), usually in 2 to 4 divided doses.

In all patients dosage should preferably be adjusted according to plasma-streptomycin concentrations, and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity. The course of treatment (other than in tuberculosis) should usually be limited to 7 to 14 days, and peak plasma concentrations should be between 15 and 40 micrograms/mL and trough concentrations below 3 to 5 micrograms/mL or below 1 microgram/mL in renal impairment or in those over 50 years of age. For discussion of the methods used to calculate aminoglycoside dosage requirements, see under Gentamicin Sulfate, p.284.

Streptomycin has also been used as the hydrochloride, the pantothenate, and as a complex with calcium chloride.

Administration and dosage. A report of the successful use of streptomycin 7 to 15 mg/kg as an intravenous infusion over 30 to 60 minutes in 4 patients with tuberculosis. Despite the view that streptomycin should be given intramuscularly because of the greater risk of toxicity with the intravenous route, this study was considered to indicate that intravenous use was feasible in selected patients unable to tolerate the intramuscular route.[1]

1. Driver AG, Worden JP. Intravenous streptomycin. *DICP Ann Pharmacother* 1990; **24:** 826–8.

Ménière's disease. Streptomycin and gentamicin have been used for medical ablation in advanced Ménière's disease (p.564). Systemic treatment has generally been limited by the development of chronic ataxia and oscillopsia (oscillating vision). However, streptomycin sulfate 1 g twice daily by intramuscular injection on 5 days each week for 2 weeks, repeated as necessary to a total dose of up to 60 g,[1,2] or 1 g twice daily for 5 days, followed if necessary by a further 3 days of treatment in the second week,[3] has produced improvements in vestibular symptoms without hearing loss in patients with Ménière's disease. Local (intratympanic) injections have also been tried,[4] but gentamicin is considered to be less toxic and is now generally preferred.

1. Shea JJ, *et al.* Long-term results of low dose intramuscular streptomycin for Ménière's disease. *Am J Otol* 1994; **15:** 540–4.
2. Balyan FR, *et al.* Titration streptomycin therapy in Meniere's disease: long-term results. *Otolaryngol Head Neck Surg* 1998; **118:** 261–6.
3. Graham MD. Bilateral Meniere's disease: treatment with intramuscular titration streptomycin sulfate. *Otolaryngol Clin North Am* 1997; **30:** 1097–1100.
4. Beck C, Schmidt CL. 10 Years of experience with intratympanally applied streptomycin (gentamycin) in the therapy of Morbus Menière. *Arch Otorhinolaryngol* 1978; **221:** 149–52.

Preparations

BP 2008: Streptomycin Injection;
USP 31: Streptomycin for Injection; Streptomycin Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Strepto-Fatol; ***Ger.:*** Strepto-Fatol; Strepto-Hefa; ***Gr.:*** Pan-Streptomycin†; ***India:*** Ambistryn-S; Cipstryn; ***Mex.:*** Bucomicina; Sulfestrep; ***S.Afr.:*** Bio-Strep; Novostrep†; Solustrep; ***Thai.:*** Strepto.

Multi-ingredient: ***Arg.:*** Estreptocarbocaftiazol; ***Braz.:*** Ortocilin†; ***India:*** Strepto-Erbazide†; ***Mex.:*** Aguipental; ***Port.:*** Bienterico.

Succinylsulfathiazole *(BAN, rINN)*

Succinilsolfatiazolo; Succinilsulfatiazol; Succinylsulfathiazol; Succinylsulfathiazolum; Succinylsulfathiazolum Monohydricum; Succinylsulfatiazol; Succinylsulphathiazole; Sukcinilsulfatiazolas; Sukcinylsulfathiazol monohydrát; Suksinyylisulfatiatsoli; Szukcinilszulfatiazol. 4′-(1,3-Thiazol-2-ylsulphamoyl)succinanilic acid monohydrate.

Сукцинилсульфатиазол

$C_{13}H_{13}N_3O_5S_2,H_2O = 373.4.$
CAS — 116-43-8 (anhydrous succinylsulfathiazole).
ATC — A07AB04.
ATC Vet — QA07AB04.

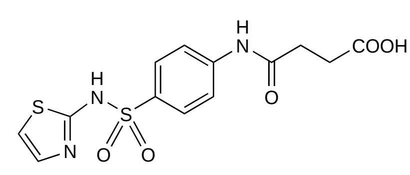

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Succinylsulfathiazole). A white or yellowish-white crystalline powder. Very slightly soluble in water; slightly soluble in acetone and in alcohol; dissolves in solutions of alkali hydroxides and carbonates. Protect from light.

Profile

Succinylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is poorly absorbed and has been given for its antibacterial activity in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Venez.:*** Guanicar.

Sulbactam *(BAN, rINN)*

CP-45899; Sulbactamum; Sulbaktaami; Sulbaktam. Penicillanic acid 1,1-dioxide; (2*S*,5*R*)-3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.

Сульбактам

$C_8H_{11}NO_5S = 233.2.$
CAS — 68373-14-8.
ATC — J01CG01.
ATC Vet — QJ01CG01.

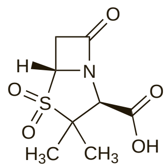

Sulbactam Sodium *(BANM, USAN, rINNM)*

CP-45899-2; Natrii Sulbactamum; Sulbactam sódico; Sulbactam sodique; Sulbactamum natricum; Sulbaktaaminatrium; Sulbaktam sodná sůl; Sulbaktam sodowy; Sulbaktamnatrium.

Натрий Сульбактам

$C_8H_{10}NNaO_5S = 255.2.$
CAS — 69388-84-7.
ATC — J01CG01.
ATC Vet — QJ01CG01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Sulbactam Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in ethyl acetate. It is freely soluble in diluted acids. A 5.0% solution in water has a pH of 4.5 to 7.2; if the substance is sterile: 5.2 to 7.2. Store in airtight containers.

USP 31 (Sulbactam Sodium). A white to off-white crystalline powder. It contains not less than 886 micrograms and not more than 941 microgram of sulbactam per mg, calculated on the anhydrous basis. Freely soluble in water and in dilute acid; sparingly soluble in acetone, in chloroform, and in ethyl acetate. Store in airtight containers.

Pivsulbactam *(BAN)*

CP-47904; Sulbactam Pivoxil *(USAN)*. Pivaloyloxymethyl penicillanate 1,1-dioxide.

Пивсульбактам

$C_{14}H_{21}NO_7S = 347.4.$
CAS — 69388-79-0.

Profile

Sulbactam is a penicillanic acid sulfone with beta-lactamase inhibitory properties. It is active against Neisseriaceae and *Acinetobacter baumanii*, but generally has only weak antibacterial activity against other organisms. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal beta-lactamases and has a similar spectrum of beta-lactamase inhibition to clavulanic acid (p.250), although it is regarded as less potent. Sulbactam can therefore enhance the activity of penicillins and cephalosporins against many resistant strains of bacteria.

It is given with ampicillin (p.204) in the treatment of infections where beta-lactamase production is suspected. Sulbactam is poorly absorbed from the gastrointestinal tract and is given by injection as the sodium salt. The pharmacokinetics of parenteral sulbactam and ampicillin are similar. For oral use the mutual prodrug sultamicillin (p.344) is available in some countries. Sulbactam is also given orally as the pivoxil derivative, pivsulbactam, with amoxicillin. Sulbactam has also been given with cefoperazone.

◊ References.

1. Campoli-Richards DM, Brogden RN. Sulbactam/ampicillin: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. *Drugs* 1987; **33:** 577–609.
2. Payne DJ, *et al.* Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important β-lactamases. *Antimicrob Agents Chemother* 1994; **38:** 767–72.
3. Nicolas-Chanoine MH. Inhibitor-resistant β-lactamases. *J Antimicrob Chemother* 1997; **40:** 1–3.
4. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; **285:** 386–8.
5. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; **18:** 199–209.
6. Kanra G. Experience with ampicillin/sulbactam in severe infections. *J Int Med Res* 2002; **30** (suppl 1): 20A–30A.
7. Rafailidis PI, *et al.* Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; **67:** 1829–49.
8. Akova M. Sulbactam-containing beta-lactamase inhibitor combinations. *Clin Microbiol Infect* 2008; **14** (suppl 1): 185–8.

Breast feeding. Although sulbactam is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Foulds G, *et al.* Sulbactam kinetics and excretion into breast milk in postpartum women. *Clin Pharmacol Ther* 1985; **38:** 692–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Preparations

USP 31: Ampicillin and Sulbactam for Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Combactam; ***Ger.:*** Combactam; ***Turk.:*** Ampisid.

Multi-ingredient: ***Arg.:*** Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Darzitil SB; Prixin; Sulperazon†; Trifamox IBL; Unasyna; Unsayna†; ***Austria:*** Unasyn; ***Braz.:*** Combactan; Sulbacter†; Sulbamox; Trifamox; Unasyn; ***Chile:*** Sulbamox; Sulperazon; Unasyn; ***Cz.:*** Sulperazon; Unasyn; ***Fr.:*** Unacim; ***Ger.:*** Unacid; ***Gr.:*** Begalin-P; ***Hong Kong:*** Sulperazon; Unasyn; ***Hung.:*** Unasyn; ***India:*** Keftragard; Lactagard; Sulbacef; Sulbacin; Sultax; Zosul; ***Indon.:*** Fosular; Stabactam; Sulperazon; ***Israel:*** Unasyn; ***Ital.:*** Bethacil; Loricin; Unasyn; ***Jpn:*** Sulperazon†; Unasyn-S†; ***Malaysia:*** Sulbacin; Sulperazon; Unasyn; ***Mex.:*** Megamox; Trifamox IBL; Unasyna; ***Philipp.:*** Sulperazone; Unasyn; ***Pol.:*** Sulperazon; Unasyn; ***Rus.:*** Sulcef (Сульцеф); Sulperason (Сульперазон); Sultasin (Сультасин); Trifamox IBL (Трифамокс ИБЛ); Unasyn (Уназин); ***Singapore:*** Unasyn; ***Spain:*** Unasyn; ***Thai.:*** Cebactam; Cefper; Sulam; Sulcef; Sulperazon; Unasyn; ***Turk.:*** Combicid; Duobak; Duobaktam; Duocid; Nobecid; Primasef; Sulbaksit; Sulcid; Sulperazon; Sultasid; ***USA:*** Unasyn; ***Venez.:*** Ampibactan; Ampitren†; Fipexiam; Sinif; Sulperazon; Unasyn.

Sulbenicillin Sodium *(rINNM)*

Natrii Sulbenicillinum; Sulbenicilina sódica; Sulbénicilline Sodique; α-Sulfobenzylpenicillin Sodium; Sulfocillin Sodium. The disodium salt of (6*R*)-6-(2-phenyl-2-sulphoacetamido)penicillanic acid.

Натрий Сульбенициллин

$C_{16}H_{16}N_2Na_2O_7S_2 = 458.4.$
CAS — 34779-28-7 (sulbenicillin); 41744-40-5 (sulbenicillin).
ATC — J01CA16.
ATC Vet — QJ01CA16.

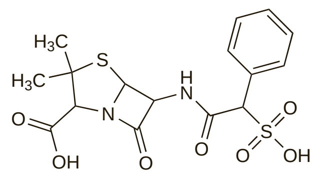

(sulbenicillin)

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Sulbenicillin sodium has actions and uses similar to those of carbenicillin sodium (p.216). It is given by intramuscular or intravenous injection or infusion.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Kedacillin; ***Jpn:*** Lilacillin†; ***Mex.:*** Kedacillin; ***Philipp.:*** Kedacillin.

Sulfabenzamide *(BAN, USAN, rINN)*

Sulfabensamid; Sulfabentsamidi; Sulfabenzamida; Sulfabenzamidum. *N*-Sulphanilylbenzamide.

Сульфабензамид

$C_{13}H_{12}N_2O_3S = 276.3.$
CAS — 127-71-9.

Pharmacopoeias. In *US.*

USP 31 (Sulfabenzamide). A fine, white, practically odourless powder. Insoluble in water and in ether; soluble in alcohol, in acetone, and in sodium hydroxide 4% solution. Protect from light.

Profile

Sulfabenzamide is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is reported to exert an optimal bacteriostatic action at pH 4.6. It is used with sulfacetamide and sulfathiazole in pessaries or a vaginal cream for the treatment of bacterial vaginosis, although its value has been questioned. The vaginal cream has also been used for the prevention of bacterial infection after cervical and vaginal surgery.

Preparations

USP 31: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Sultrin†; ***Braz.:*** Vagi-Sulfa; ***Gr.:*** Sultrin; ***Irl.:*** Sultrin†; ***Philipp.:*** Sultrin; ***Port.:*** Sultrin†; ***S.Afr.:*** Sultrin; ***UK:*** Sultrin†; ***USA:*** Sultrin.

Sulfacarbamide *(BAN, rINN)*

Sulfacarbamida; Sulfacarbamidum; Sulfakarbamid; Sulfanilcarbamide; Sulfaurea; Sulphacarbamide; Sulphanilylurea; Sulphaurea; Urosulphanum. Sulphanilylurea monohydrate.

Сульфакарбамид

$C_7H_9N_3O_3S,H_2O = 233.2.$
CAS — 547-44-4 (anhydrous sulfacarbamide); 6101-35-5 (sulfacarbamide monohydrate).

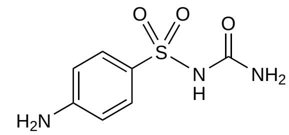

Pharmacopoeias. In *Pol.*

Profile

Sulfacarbamide is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It has been used in the treatment of urinary-tract infections, sometimes with other drugs.

Sulfacetamide *(BAN, rINN)*

Acetosulfaminum; Sulfacetamid; Sulfacetamida; Sulfacétamide; Sulfacetamidum; Sulfatsetamidi; Sulphacetamide. *N*-Sulphanilyacetamide.

Сульфацетамид

$C_8H_{10}N_2O_3S = 214.2.$
CAS — 144-80-9.
ATC — S01AB04.
ATC Vet — QS01AB04.

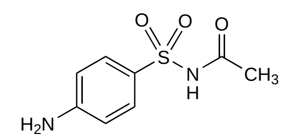

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Sulfacetamide). A white, odourless, crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides; practically insoluble in benzene. Solutions in water are acid to litmus and sensitive to light; they are unstable when acidic or strongly alkaline. Protect from light.

Sulfacetamide Sodium *(BANM, rINNM)*

Natrii Sulfacetamidum; Soluble Sulphacetamide; Sulfacetamid sodná sůl monohydrát; Sulfacetamid sodowy; Sulfacetamida sódica; Sulfacétamide sodique; Sulfacetamidnatrium; Sulfacetamido natrio druska; Sulfacetamidum natricum; Sulfacetamidum Natricum Monohydricum; Sulfacylum; Sülfasetamid Sodyum; Sulfasetamidinatrium; Sulphacetamide Sodium; Sulphacetamidum Sodium; Szulfacetamid-nátrium.

Натрий Сульфацетамид

$C_8H_9N_2NaO_3S,H_2O = 254.2.$
CAS — 127-56-0 (anhydrous sulfacetamide sodium); 6209-17-2 (sulfacetamide sodium monohydrate).
ATC — S01AB04.
ATC Vet — QS01AB04.

NOTE. SULF is a code approved by the BP 2008 for use on single unit doses of eye drops containing sulfacetamide sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Sulfacetamide Sodium). A white or yellowish-white, crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 5% solution in water has a pH of 8.0 to 9.5. Protect from light.

USP 31 (Sulfacetamide Sodium). A white odourless crystalline powder. Soluble 1 in 2.5 of water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 8.0 to 9.5. Store in airtight containers. Protect from light.

Stability. When solutions of sulfacetamide sodium are heated, hydrolysis occurs forming sulfanilamide which may be deposited as crystals, especially from concentrated solutions and under cold storage conditions.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340.

Local application of sulfacetamide sodium to the eye may cause burning or stinging but this is rarely severe enough to require stopping treatment.

The symbol † denotes a preparation no longer actively marketed

Antimicrobial Action

As for Sulfamethoxazole, p.341.

Pharmacokinetics

When sulfacetamide sodium is applied to the eye it penetrates into ocular tissues and fluids; sulfacetamide may be absorbed into the blood when the conjunctiva is inflamed.

Uses and Administration

Sulfacetamide is a sulfonamide antibacterial that is used with sulfabenzamide and sulfathiazole in preparations for vaginal use, and is applied, as the sodium salt, in infections or injuries of the eyes, although it is rarely of much value. Eye drops containing sulfacetamide sodium 10% to 30% and eye ointments containing 10% have been used. The sodium salt is also applied topically in the treatment of skin infections.

Preparations

USP 31: Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension; Sulfacetamide Sodium Ophthalmic Ointment; Sulfacetamide Sodium Ophthalmic Solution; Sulfacetamide Sodium Topical Suspension; Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dermaseb; ***Austral.:*** Acetopt; Bleph-10; Optamide†; ***Austria:*** Beocid Puroptal; Cetazin; ***Belg.:*** Anginamide; Antebor; Sulfa 10; Sulfacollyre†; ***Braz.:*** Queimalive; ***Canad.:*** Ak-Sulf; Cetamide; Diosulf†; Sodium Sulamyd†; ***Fr.:*** Antebor†; ***Ger.:*** Albucid†; ***Hong Kong:*** Bleph-10; Spersacet†; Sulfex; Vista-Cetamide†; ***India:*** Albucid; Locula; Ocu-Sulf; ***Indon.:*** Albucid; Isotic Cetride; ***Israel:*** Klaron; Optisol; Sulfacid; ***Ital.:*** Optamid†; ***Mex.:*** Blef-10; Cetapred; Examida; Sul 10; ***NZ:*** Acetopt; Bleph-10; ***Philipp.:*** Acetopt; Sensocet; ***Rus.:*** Sulfacyl (Сульфацил)†; ***S.Afr.:*** Covosulf†; Spersamide; ***Spain:*** Sulfacetam†; ***Switz.:*** Spersacet†; ***Thai.:*** Bleph-10†; Opsar†; Optal; ***Turk.:*** Optamid; ***USA:*** Ak-Sulf; Bleph-10; Carmol Scalp Treatment; Cetamide; Isopto Cetamide; Klaron; Mexar; Ocusulf; Ovace; Sodium Sulamyd; Sulf-10; Sulfac; Vanocin; ***Venez.:*** Sulfacet.

Multi-ingredient: ***Arg.:*** Blefamide; C-G†; ***Belg.:*** Sultrin†; ***Braz.:*** Isopto Cetapred; Oto-Biotic†; Paraqueimol; Sulnil; Vagi-Sulfa; ***Canad.:*** Blephamide; Dioptimyd†; Sulfacet-R; Vasocidin†; ***Chile:*** Blefamide; Deltamid; ***Cz.:*** Isopto Cetapred†; ***Ger.:*** Blephamide; ***Gr.:*** Blephamide†; Isopto Cetapred; Sulfachloramphenicol; Sulfanicole; Sultrin; ***Hong Kong:*** Blephamide; ***India:*** Cortola-m; Nebasulf; Zinco Sulpha; ***Irl.:*** Sultrin†; ***Israel:*** Blephamide; ***Ital.:*** Antisettico Astringente Sedativo; Aureomix; Brumeton Colloidale S; Cosmiciclina; Visublefarite; ***Malaysia:*** Blephamide†; ***Mex.:*** Blefamide; Blefamide-F; Deltamid; Isopto Cetapred; Locion Axel†; Metimyd†; Premid; Sulfa Cloran; Sulfa Hidro; Sulvi; ***NZ:*** Blephamide; ***Philipp.:*** Cetapred; Isopto Cetapred; Sultrin; ***Port.:*** Meocil; Sultrin†; ***S.Afr.:*** Covancaine; Covosan; Spersacet C†; Sultrin; ***Singapore:*** Blephamide; ***Spain:*** Betamida†; Celestone S; Denticelso; ***Switz.:*** Blephamide; Spersacet C†; ***Turk.:*** Blephamid; Suprenil; ***UK:*** Sultrin†; ***USA:*** Avar; Blephamide; Clenia; FML-S; Metimyd; Nicosyn; Novacet; Plexion; Rosac; Rosanil; Rosula; Rosula NS; Sulfacet-R; Sulfamide; Sultrin; Suphera; Vasocidin; Vasocine; Vasosulf; Zetacet; ***Venez.:*** Sulfacort.

Sulfachlorpyridazine *(BAN, rINN)*

Sulfachlorpyridazinum; Sulfaclorpiridazina; Sulphachlorpyridazine. N^1-(6-Chloropyridazin-3-yl)sulphanilamide.

Сульфахлорпиридазин

$C_{10}H_9ClN_4O_2S$ = 284.7.

CAS — 80-32-0.

ATC Vet — QJ01EQ12.

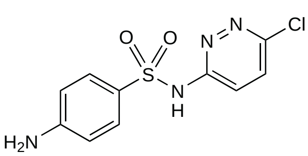

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Sulfachlorpyridazine). Protect from light.

Profile

Sulfachlorpyridazine is a sulfonamide antibacterial.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Mictasol com Sulfa†.

Sulfachrysoidine *(rINN)*

Carboxysulfamidochrysoidine; Sulfachrysoïdine; Sulfachrysoidinum; Sulfacrisoidina. 3,5-Diamino-2-(*p*-sulfamoylphenylazo) benzoic acid.

Сульфахризоидин

$C_{13}H_{13}N_5O_4S$ = 335.3.

CAS — 485-41-6.

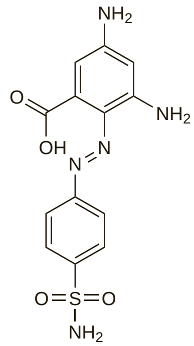

Profile

Sulfachrysoidine is a sulfonamide antibacterial that is used topically as the sodium salt for infections of the oral mucosa.

Sulfaclozine *(rINN)*

Sulfaclozina; Sulfaclozinum; Sulfaklotsiini; Sulfaklozin. N^1-(6-Chloropyrazinyl)sulfanilamide.

Сульфаклозин

$C_{10}H_9ClN_4O_2S$ = 284.7.

CAS — 102-65-8; 27890-59-1.

ATC Vet — QP51AG04.

Profile

Sulfaclozine is a sulfonamide antibacterial that has been used in veterinary medicine.

Sulfadiazine *(BAN, rINN)*

Sulfadiazina; Solfapirimidina; Sulfadiatsiini; Sülfadiazin; Sulfadiazin; Sulfadiazina; Sulfadiazinas; Sulfadiazinum; Sulphadiazine; Szulfadiazin. N^1-(Pyrimidin-2-yl)sulphanilamide.

Сульфадиазин

$C_{10}H_{10}N_4O_2S$ = 250.3.

CAS — 68-35-9.

ATC — J01EC02.

ATC Vet — QJ01EQ10.

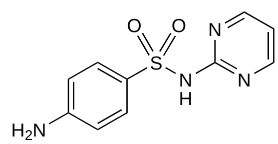

NOTE. Compounded preparations of sulfadiazine may be represented by the following names:

- Co-tetroxazine (*BAN*)—sulfadiazine 5 parts and tetroxoprim 2 parts (see p.257)
- Co-trimazine (*BAN*)—sulfadiazine 5 parts and trimethoprim 1 part (see p.258).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *US,* and *Viet.*

Ph. Eur. 6.2 (Sulfadiazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Practically insoluble in water; very slightly soluble in alcohol; slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 31 (Sulfadiazine). White or slightly yellow, odourless or nearly odourless, powder, slowly darkening on exposure to light. Soluble 1 in 13 000 of water; sparingly soluble in alcohol and in acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides, and ammonia. Protect from light.

Sulfadiazine Sodium *(BANM, rINN)*

Sodium Sulfadiazine; Soluble Sulphadiazine; Sulfadiazina de sodio; Sulfadiazina sódica; Sulfadiazine sodique; Sulfadiazinum Natricum; Sulphadiazine Sodium.

Сульфадиазин Натрий

$C_{10}H_9N_4NaO_2S$ = 272.3.

CAS — 547-32-0.

ATC — J01EC02.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Sulfadiazine Sodium). A white powder. Soluble 1 in 2 of water; slightly soluble in alcohol. On prolonged exposure to humid air it absorbs carbon dioxide with the liberation of sulfadiazine and becomes incompletely soluble in water. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Solutions of sulfadiazine sodium are alkaline, and incompatibility may reasonably be expected with acidic drugs or with preparations unstable at high pH. In the UK, licensed product information states that sulfadiazine sodium injection is incompatible with fructose, iron salts, and salts of heavy metals.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340.

Because of the low solubilities of sulfadiazine and its acetyl derivative in urine, crystalluria is more likely after use of sulfadiazine than after sulfamethoxazole.

Sulfadiazine sodium solution is strongly alkaline and it should therefore be given intravenously in a strength not exceeding 5%, over at least 10 minutes. For the same reason, intramuscular injections are painful and sulfadiazine sodium should not be given by intrathecal or subcutaneous injection.

Carnitine deficiency. Hyperammonaemia and carnitine deficiency developed in an immunocompromised patient given sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.[1]

1. Sekas G, Harbhajan SP. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95:** 112–13.

Effects on the eyes. Numerous white stone-like concretions of sulfadiazine occurred in the conjunctiva of a woman who had used sulfadiazine eye drops for about 1 year.[1]

1. Boettner EA, *et al.* Conjunctival concretions of sulfadiazine. *Arch Ophthalmol* 1974; **92:** 446–8.

Effects on the kidneys. Reports of crystalluria and renal failure associated with the use of sulfadiazine in immunocompromised patients,[1-8] including the suggestion that AIDS patients may be particularly prone to sulfadiazine-induced renal toxicity.[3] Renal failure and leucopenia in a patient treated with sulfadiazine silver for pyoderma gangrenosum were thought to be due to systemic absorption of the silver component.[9]

1. Goadsby PJ, *et al.* Acquired immunodeficiency syndrome (AIDS) and sulfadiazine-associated acute renal failure. *Ann Intern Med* 1987; **107:** 783–4.
2. Ventura MG, *et al.* Sulfadiazine revisited. *J Infect Dis* 1989; **160:** 556–7.
3. Simon DI, *et al.* Sulfadiazine crystalluria revisited: the treatment of Toxoplasma encephalitis in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1990; **150:** 2379–84.
4. Díaz F, *et al.* Sulfadiazine-induced multiple urolithiasis and acute renal failure in a patient with AIDS and Toxoplasma encephalitis. *Ann Pharmacother* 1996; **30:** 41–2.
5. Guitard J, *et al.* Sulfadiazine-related obstructive urinary tract lithiasis: an unusual cause of acute renal failure after kidney transplantation. *Clin Nephrol* 2005; **63:** 405–7.
6. Solano Remírez M, *et al.* Insuficiencia renal por sulfadiazina en paciente VIH con toxoplasmosis cerebral. *An Med Interna* 2005; **22:** 395–6.
7. Hyvernat H, *et al.* Insuffisance rénale aiguë obstructive lors d'un traitement par sulfadiazine. *Presse Med* 2006; **35:** 423–4.
8. de la Prada Alvarez FJ, *et al.* Insuficiencia renal aguda por depósito de cristales de sulfadiacina. *An Med Interna* 2007; **24:** 235–8.
9. Chaby G, *et al.* Insuffisance rénale aiguë après application topique de sulfadiazine argentique. *Ann Dermatol Venereol* 2005; **132:** 891–3.

Effects on the salivary glands. Enlargement of the salivary glands (sialadenitis) has been reported[1] in a patient who received a preparation containing sulfadiazine; complete recovery followed within 3 days of stopping therapy. Rechallenge confirmed that sulfadiazine was the causative agent.

1. Añíbarro B, Fontela JL. Sulfadiazine-induced sialadenitis. *Ann Pharmacother* 1997; **31:** 59–60.

Interactions

As for Sulfamethoxazole, p.341.

Antimicrobial Action

As for Sulfamethoxazole, p.341.

Pharmacokinetics

Sulfadiazine is readily absorbed from the gastrointestinal tract, peak blood concentrations being reached 3 to 6 hours after a single dose; 20 to 55% has been reported to be bound to plasma proteins. It penetrates into the CSF within 4 hours of an oral dose to produce therapeutic concentrations which may be more than half those in the blood. Up to 40% of sulfadiazine in the blood is present as the acetyl derivative. The half-life of sulfadiazine is about 10 hours; it is prolonged in renal impairment.

About 50% of a single dose of sulfadiazine given by mouth is excreted in the urine in 24 hours; 15 to 40% is excreted as the acetyl derivative.

◊ The urinary excretion of sulfadiazine and the acetyl derivative is dependent on pH. About 30% is excreted unchanged in both fast and slow acetylators when the urine is acidic whereas about 75% is excreted unchanged by slow acetylators when the urine is alkaline. The half-life of sulfadiazine ranges from 7 to 12 hours and that of its metabolite from 8 to 12 hours.[1]

1. Vree TB, *et al*. Determination of the acetylator phenotype and pharmacokinetics of some sulphonamides in man. *Clin Pharmacokinet* 1980; **5:** 274–94.

Uses and Administration

Sulfadiazine is a short-acting sulfonamide that has been used similarly to sulfamethoxazole (p.341) in the treatment of infections due to susceptible organisms. It has been used in the treatment of nocardiosis and lymphogranuloma venereum, and has been given for the prophylaxis of rheumatic fever in penicillin-allergic patients. For details of these infections and their treatment, see Choice of Antibacterial, p.162. Sulfadiazine is also given with pyrimethamine for the treatment and prevention of relapse of toxoplasmosis (p.826) and has been tried in disseminated *Acanthamoeba* infection (p.822).

In the treatment of susceptible infections, sulfadiazine may be given orally in usual initial doses of 2 to 4 g, followed by up to 6 g daily in divided doses. A dose in children is 75 mg/kg initially, then 150 mg/kg daily in divided doses to a maximum of 6 g daily. Sulfadiazine is used in infants less than 2 months of age for congenital toxoplasmosis; an oral dose of 50 mg/kg twice daily for 12 months has been suggested by the *BNFC* for use in neonates.

Immunocompromised patients who have toxoplasmosis should be given a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily, which should continue indefinitely. Pyrimethamine should always be given as well.

For the prophylaxis of rheumatic fever, patients weighing less than about 30 kg are given 500 mg once daily, while those over 30 kg may receive 1 g once daily.

Sulfadiazine is also given intravenously as the sodium salt. Sulfadiazine sodium 1.09 g is equivalent to about 1 g of sulfadiazine. The usual dose is the equivalent of sulfadiazine 2 to 3 g initially, then 1 g four times daily for 2 days; subsequent treatment is given orally. Children and infants over 2 months of age may be given the equivalent of 50 mg/kg initially, followed by 25 mg/kg four times daily.

Intravenous doses of sulfadiazine sodium are given by infusion or by slow intravenous injection of a solution containing up to 5% sulfadiazine. It may be diluted with sodium chloride 0.9%. Sulfadiazine sodium has been given by deep intramuscular injection, but great care must be taken to prevent damage to subcutaneous tissues; the intravenous route is preferred.

Sulfadiazine has been used with trimethoprim as co-trimazine (p.258). Sulfadiazine has also been used with other sulfonamides, particularly sulfamerazine and sulfadimidine, to reduce the problems of low solubility in urine.

Preparations

BP 2008: Sulfadiazine Injection;
USP 31: Sulfadiazine Sodium Injection; Sulfadiazine Tablets; Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sulfatral; ***Braz.:*** Neo Sulfazina†; Suladrin; Sulfadiazinac†; ***Fr.:*** Adiazine†; ***Gr.:*** Adiazine; ***Mex.:*** Bioarginol-C; Sularyn; ***Port.:*** Labdiazina.

Multi-ingredient: ***Arg.:*** Afonisan; Anginotrat; Pastillas Lorbi; Sulfatral-Cerio†; ***Austria:*** Ophcillin N; Rhinon; ***Braz.:*** Triglobe; ***Canad.:*** Coptin; ***Fin.:*** Ditrim; Trimetin Duplo; ***Ger.:*** Sterinor†; Urospasmon sine†; Urospasmon†; ***Gr.:*** Geypirina; ***India:*** Aubril; Zad-G; ***Indon.:*** Trisulfa; ***Malaysia:*** Balin; Beaglobe; Triglobe†; Trisulprim†; Trizine; ***Mex.:*** Agin; Estrefen; ***Philipp.:*** Triglobe; Trizine; ***Port.:*** Broncodiazina; ***Singapore:*** Balin; ***Swed.:*** Trimin sulfa†; ***Thai.:*** Sulfatril; ***Turk.:*** Sulfatrim; ***Venez.:*** Esterinor†.

Sulfadiazine Silver *(BANM, rINNM)*

Argenti Sulfadiazinum; Gümüş Sülfadiazin; Hopeasulfadiatsiini; Silver Sulfadiazine *(USAN)*; Silver Sulphadiazine; Silversulfadiazin; Sulfadiazina argéntica; Sulfadiazine Argentique; Sulfadiazinum Argenticum; Sulfadiazinum Argentum; Sulphadiazine Silver.

Сульфадиазин Серебра

$C_{10}H_9AgN_4O_2S$ = 357.1.

CAS — 22199-08-2.

ATC — D06BA01.

ATC Vet — QD06BA01.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.

USP 31 (Silver Sulfadiazine). A white to creamy-white, odourless or almost odourless crystalline powder. It becomes yellow on exposure to light. Practically insoluble in alcohol, in chloroform, and in ether; slightly soluble in acetone; freely soluble in 30% ammonia solution. It decomposes in moderately strong mineral acids. Protect from light.

Adverse Effects, Treatment, and Precautions

Sulfadiazine silver may be absorbed after topical application and produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p.340).

Local pain or irritation are uncommon; the separation of the eschar may be delayed and fungal invasion of the wound may occur.

Transient leucopenia does not usually require withdrawal of sulfadiazine silver, but blood counts should be monitored to ensure they return to normal within a few days. Systemic absorption of silver, resulting in argyria, can occur when sulfadiazine silver is applied to large area wounds or over prolonged periods.

Argyria. A report of argyria, with discoloration of the skin and sensorimotor neuropathy, caused by excessive application of sulfadiazine silver 1% cream to extensive leg ulcers.[1]

1. Payne CMER, *et al.* Argyria from excessive use of topical silver sulphadiazine. *Lancet* 1992; **340**: 126.

Effects on the kidneys. For mention of renal failure and leucopenia associated with the use of sulfadiazine silver see under Sulfadiazine, above.

Interactions

As for Sulfamethoxazole, p.341.

Sulfadiazine silver is not antagonised by *p*-aminobenzoic acid or related compounds. The silver content of sulfadiazine silver may inactivate enzymatic debriding agents.

Antimicrobial Action

Sulfadiazine silver has broad antimicrobial activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, and some yeasts and fungi. Sulfadiazine silver has a bactericidal action; in contrast to sulfadiazine, the silver salt acts primarily on the cell membrane and cell wall and its action is not antagonised by *p*-aminobenzoic acid. Resistance to sulfadiazine silver has been reported and may develop during therapy.

Pharmacokinetics

Sulfadiazine silver slowly releases sulfadiazine when in contact with wound exudates. Up to about 10% of the sulfadiazine may be absorbed; concentrations in blood of 10 to 20 micrograms/mL have been reported, although higher concentrations may be achieved when extensive areas of the body are treated. Some silver may also be absorbed.

Uses and Administration

Sulfadiazine silver is a sulfonamide that is used, in conjunction with debridement, as a 1% cream for the prevention and treatment of infection in severe burns (p.1578).

Sulfadiazine silver has also been used in other skin conditions, such as leg ulcers (p.1585), where infection may prevent healing and for the prophylaxis of infection in skin grafting. It has also been applied to the eyes in the treatment of superficial *Aspergillus* infections.

Catheters impregnated with sulfadiazine silver have been used to reduce catheter colonisation and related bloodstream infection (p.1624).

Preparations

USP 31: Silver Sulfadiazine Cream.

Proprietary Preparations (details are given in Part 3)

Arg.: Silvederma†; ***Austria:*** Flammazine; ***Belg.:*** Flammazine; Sulfasil; ***Braz.:*** Dermazine; Gino Dermazine; Pratazine†; Silglos; Sulfaderm; ***Canad.:*** Dermazin†; Flamazine; SSD†; ***Cz.:*** Dermazin; Flammazine†; ***Denm.:*** Flamazine; ***Fin.:*** Flamazine; ***Fr.:*** Flammazine; Sicazine; ***Ger.:*** Brandiazin; Flammazine; Urgotul S.Ag; ***Gr.:*** Flammazine; ***Hong Kong:*** Aldo-Silverderma; Dermazin; Flamazine; ***Hung.:*** Dermazin; ***India:*** SSZ; ***Indon.:*** Burnazin; ***Irl.:*** Flamazine; ***Israel:*** Silverol; ***Ital.:*** Bacternil; Sofargen; ***Mex.:*** Argemol; Argentafil; Argental; Silvadene; Zitep; ***Neth.:*** Flammazine; ***Norw.:*** Flamazine; ***Philipp.:*** Flammazine; Innoxiderm; Sterizol; ***Pol.:*** Dermazin; ***Port.:*** Flammazine; Sicazine; Silvederma; Silvespray; ***Rus.:*** Dermazin (Дермажин); Silvederma (Сильведерм); Sulphargin (Сульфаргин); ***S.Afr.:*** Argent-Eze; Bactrazine; Flamazine; Silbecor; ***Singapore:*** Flamazine†; ***Spain:*** Flammazine; Silvederma; ***Switz.:*** Flammazine; Silvertone; ***Thai.:*** Dermazin; Flamazine; Silverol†; ***Turk.:*** Silvadene; Silvadiazin; Silvamed; Silverdin; ***UAE:*** Silvadiazin; ***UK:*** Flamazine; ***USA:*** Silvadene; SSD; Thermazene; ***Venez.:*** Menaderm; Protosulfil; Silvederma.

Multi-ingredient: ***Arg.:*** Iuronico Biotic; Platsul A; Sulfadiazina de Plata; Sulfaplat; ***Austral.:*** Silvazine; ***Belg.:*** Flammacerium; ***Braz.:*** Dermacerium; ***Canad.:*** Flamazine C†; ***Chile:*** FCE; Hebermin†; Platsul A; ***Cz.:*** Flammacerium†; Ialugen Plus; ***Fr.:*** Altreet Ag; Flammacerium; Ialuset Plus; Urgotul S.Ag; ***Gr.:*** Flammacerium; ***Hung.:*** Ialugen Plus; ***India:*** Argisept†; Burnheal†; Silverex; ***Ital.:*** Altergen; Connettivina Plus; ***Neth.:*** Flammacerium; ***NZ:*** Silvazine; ***Philipp.:*** Flammacerium; ***Pol.:*** Flammacerium; ***Singapore:*** Silvazine; Silvin; ***Spain:*** Unitul Complex†; ***Switz.:*** Ialugen Plus; ***UK:*** Flammacerium; Physiotulle-Ag.

Sulfadicramide *(rINN)*

Sulfadicramida; Sulfadicramidum; Sulfadikramid; Sulfadikramidi. *N*′-(3,3-Dimethylacroyl)sulphanilamide.

Сульфадикрамид

$C_{11}H_{14}N_2O_3S$ = 254.3.

CAS — 115-68-4.

ATC — S01AB03.

ATC Vet — QS01AB03.

Profile

Sulfadicramide is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is applied as a 15% ointment for superficial infections of the eye.

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Irgamid†; ***Fin.:*** Irgamid†; ***Hung.:*** Irgamid†; ***Switz.:*** Irgamid.

Sulfadimethoxine *(BAN, rINN)*

Solfadimetossina; Solfadimetossipirimidina; Sulfadiméthoxine; Sulfadimethoxinum; Sulfadimetoksiini; Sulfadimetoxin; Sulfadimetoxina; Sulphadimethoxine. N^1-(2,6-Dimethoxypyrimidin-4-yl)-sulphanilamide.

Сульфадиметоксин

$C_{12}H_{14}N_4O_4S$ = 310.3.

CAS — 122-11-2.

ATC — J01ED01.

ATC Vet — QJ01EQ09; QP51AG02.

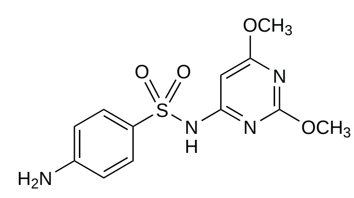

Pharmacopoeias. In *Fr.* and *It.* In *US* for veterinary use only.

USP 31 (Sulfadimethoxine). Practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, in ether, and in hexane; soluble in 2N sodium hydroxide; sparingly soluble in 2N hydrochloric acid. Store in airtight containers. Protect from light.

Profile

Sulfadimethoxine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is used in preparations for the treatment of skin infections and was formerly used for the treatment of urinary-tract infections. It is also used in veterinary medicine, sometimes with baquiloprim or ormetoprim.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Rus.:*** Levosin (Левосин).

Sulfadimidine *(BAN, rINN)*

Solfametazina; Sulfadimerazine; Sulfadimezinum; Sulfadimidiini; Sulfadimidin; Sulfadimidina; Sulfadimidinas; Sulfadimidinum; Sulfamethazine; Sulphadimethylpyrimidine; Sulphadimidine; Sulphamethazine; Szulfadimidin. N^1-(4,6-Dimethylpyrimidin-2-yl)sulphanilamide.

Сульфадимидин

$C_{12}H_{14}N_4O_2S$ = 278.3.

CAS — 57-68-1.

ATC — J01EB03.

ATC Vet — QJ01EQ03; QP51AG01.

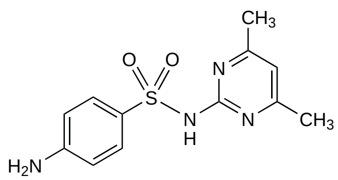

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine (p.344). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet.* Also in *BP (Vet)*.

Ph. Eur. 6.2 (Sulfadimidine). White or almost white powder or crystals. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 31 (Sulfamethazine). White to yellowish-white, practically odourless, powder. It may darken on exposure to light. Very slightly soluble in water and in ether; slightly soluble in alcohol; soluble in acetone. Protect from light.

Sulfadimidine Sodium *(BANM, rINNM)*

Natrii Sulfadimidinum; Soluble Sulphadimidine; Sulfadimidina sódica; Sulfadimidine Sodique; Sulfamethazine Sodium; Sulphadimidine Sodium.

Натрий Сульфадимидин

$C_{12}H_{13}N_4NaO_2S$ = 300.3.

CAS — 1981-58-4.

ATC — J01EB03.

Pharmacopoeias. In *Int.*

Profile

Sulfadimidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340).

It is well absorbed from the gastrointestinal tract and is about 80 to 90% bound to plasma proteins. Reported half-lives have ranged from 1.5 to 4 hours in fast and 5.5 to 8.8 hours in slow acetylators. Because of the relatively high solubility of the drug and its acetyl metabolite, crystalluria may be less likely than with sulfamethoxazole.

In the treatment of susceptible infections, sulfadimidine has been given orally in an initial dose of 2 g, followed by 0.5 to 1.0 g every 6 to 8 hours. It has also been given parenterally as the sodium salt.

Sulfadimidine has also been used with other sulfonamides, particularly sulfamerazine and sulfadiazine. It is also used in veterinary medicine, sometimes with baquiloprim or trimethoprim.

Because its pharmacokinetics differ in fast and slow acetylators, sulfadimidine has been used to determine acetylator status.

Preparations

USP 31: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Proprietary Preparations (details are given in Part 3)
Hung.: Septosyl.

Multi-ingredient: ***Hung.:*** Potesept†; ***Indon.:*** Trisulfa; ***Thai.:*** Sulfatril.

Sulfadoxine *(BAN, USAN, rINN)*

Ro-4-4393; Sulfadoksiini; Sulfadoksinas; Sulfadoxin; Sulfadoxina; Sulfadoxinum; Sulformethoxine; Sulforthomidine; Sulphormethoxine; Sulphorthodimethoxine; Szulfadoxin. N^1-(5,6-Dimethoxypyrimidin-4-yl)sulphanilamide.

Сульфадоксин

$C_{12}H_{14}N_4O_4S$ = 310.3.

CAS — 2447-57-6.

ATC Vet — QJ01EQ13.

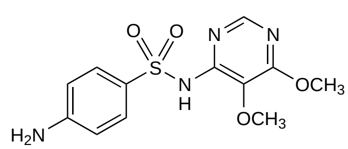

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Sulfadoxine). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 31 (Sulfadoxine). Protect from light.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340. For reference to the adverse effects of a combination of sulfadoxine and pyrimethamine, see Pyrimethamine, p.610.

If adverse effects occur, sulfadoxine has the disadvantage that several days are required for elimination from the body.

Interactions

As for Sulfamethoxazole, p.341.

Antimicrobial Action

As for Sulfamethoxazole, p.341. Synergy exists between sulfadoxine and pyrimethamine, which act against folate metabolism at different points of the metabolic cycle.

Resistance to the combination of sulfadoxine and pyrimethamine in plasmodia, first noted in Thailand in the late 1970s, has become widespread in many malarious areas of the world. For further details of resistance to antimalarial drugs, see p.594.

Pharmacokinetics

Sulfadoxine is readily absorbed from the gastrointestinal tract. High concentrations in the blood are reached in about 4 hours; the half-life in the blood is about 4 to 9 days. About 90 to 95% is reported to be bound to plasma proteins.

Sulfadoxine is widely distributed to body tissues and fluids; it passes into the fetal circulation and has been detected in low concentrations in breast milk. Sulfadoxine is excreted very slowly in urine, primarily unchanged.

Uses and Administration

Sulfadoxine is a long-acting sulfonamide that has been used in the treatment of various infections but is now rarely used alone.

It is given as a fixed-dose combination of 20 parts sulfadoxine with 1 part pyrimethamine (*Fansidar*, *Roche*) in the treatment of falciparum malaria resistant to other therapies (p.594), usually after a course of quinine. Although the combination has been used in the prophylaxis of malaria, the risk of toxicity is now generally considered to outweigh its value.

In the treatment of malaria, the usual oral dose is 1.5 g of sulfadoxine with 75 mg of pyrimethamine as a single dose; this should not be repeated for at least 7 days. Oral doses for children are: 5 to 10 kg bodyweight, 250 mg sulfadoxine with 12.5 mg pyrimethamine; 11 to 20 kg, 500 mg sulfadoxine with 25 mg pyrimethamine; 21 to 30 kg, 750 mg sulfadoxine with 37.5 mg pyrimethamine; 31 to 45 kg, 1 g sulfadoxine with 50 mg pyrimethamine.

Sulfadoxine with pyrimethamine has also been given intramuscularly.

Sulfadoxine with pyrimethamine has also been tried in the treatment of actinomycetomas (see Mycetoma p.180), and for prophylaxis of pneumocystis pneumonia in immunocompromised patients (see p.521 for the more usual prophylactic regimens).

A mixture of 5 parts of sulfadoxine with 1 part trimethoprim is used in veterinary medicine.

Preparations

USP 31: Sulfadoxine and Pyrimethamine Tablets.

Proprietary Preparations (details are given in Part 3)
Malaysia: Fansidar.

Multi-ingredient: ***Austral.:*** Fansidar; ***Belg.:*** Malastop†; ***Braz.:*** Fansidar; ***Canad.:*** Fansidar†; ***Denm.:*** Fansidar†; ***Fr.:*** Fansidar; ***India:*** Artemal†; Laridox; Pyralfin; Rimodar; ***Indon.:*** Fansidar; Suldox; ***Irl.:*** Fansidar; ***Israel:*** Fansidar; ***Malaysia:*** Madomine; ***Philipp.:*** Fansidar; ***S.Afr.:*** Fansidar; ***Singapore:*** Madomine†; ***Switz.:*** Fansidar; Fansimef†; ***Thai.:*** Vivaxine†; ***UK:*** Fansidar; ***USA:*** Fansidar.

Sulfafurazole *(BAN, pINN)*

Sulfafuratsoli; Sulfafurazol; Sulfafurazolas; Sulfafurazolum; Sulfisoxazole; Sülfizoksazol; Sulphafuraz; Sulphafurazole; Szulfafurazol. N^1-(3,4-Dimethylisoxazol-5-yl)sulphanilamide.

Сульфафуразол

$C_{11}H_{13}N_3O_3S$ = 267.3.

CAS — 127-69-5.

ATC — J01EB05; S01AB02.

ATC Vet — QJ01EQ05; QS01AB02.

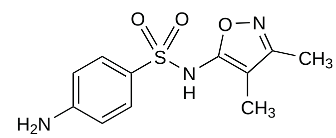

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Sulfafurazole). White or yellowish-white, crystalline powder or crystals. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 31 (Sulfisoxazole). A white to slightly yellowish, odourless crystalline powder. Soluble 1 in 7700 of water and 1 in 10 of boiling alcohol; soluble in 3N hydrochloric acid. Store in airtight containers. Protect from light.

Acetyl Sulfafurazole

Acetilsulfafurazol; Acetyl Sulphafurazole; Sulfisoxazole Acetyl. N^1-Acetyl Sulphafurazole; *N*-(3,4-Dimethylisoxazol-5-yl)-*N*-sulphanilylacetamide.

$C_{13}H_{15}N_3O_4S$ = 309.3.

CAS — 80-74-0.

ATC — J01EB05; S01AB02.

ATC Vet — QS01AB02.

NOTE. Acetyl sulfafurazole is to be distinguished from the N^4-acetyl derivative formed from sulfafurazole by conjugation in the body.

Compounded preparations of acetyl sulfafurazole may be represented by the following name:

- Co-erynsulfisox (*PEN*)—acetyl sulfafurazole and erythromycin ethyl succinate.

Pharmacopoeias. In *US*.

USP 31 (Sulfisoxazole Acetyl). A white or slightly yellow crystalline powder. Practically insoluble in water; soluble 1 in 176 of alcohol, 1 in 35 of chloroform, 1 in 1064 of ether, and 1 in 203 of methyl alcohol. Store in airtight containers. Protect from light.

Sulfafurazole Diolamine *(pINNM)*

NU-445; Sulfafurazol diolamina; Sulfafurazol, Diolamine de; Sulfafurazoli Diolaminum; Sülfisoksazol Dietanolamin; Sulfisoxazole Diolamine *(USAN)*; Sulphafurazole Diethanolamine; Sulphafurazole Diolamine. The 2,2′-iminobisethanol salt of sulphafurazole.

Сульфафуразола Диоламин

$C_{11}H_{13}N_3O_3S,C_4H_{11}NO_2$ = 372.4.

CAS — 4299-60-9.

ATC — J01EB05; S01AB02.

ATC Vet — QS01AB02.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340.

Sulfafurazole and its acetyl derivative are relatively soluble in urine and the risk of crystalluria is generally slight, but nevertheless adequate fluid intake is recommended.

Breast feeding. A study[1] in 6 women who received sulfafurazole concluded that the amount of drug secreted into breast milk poses no risk to the healthy infant beyond the immediate newborn period, but potential risk in breast-fed infants with jaundice or G6PD deficiency, or who are ill, stressed, or premature, was more difficult to evaluate. Based on this evidence, the American Academy of Pediatrics[2] has stated that sulfafurazole is usually compatible with breast feeding, but caution is required in the infants mentioned above.

1. Kauffman RE, *et al.* Sulfisoxazole secretion into human milk. *J Pediatr* 1980; **97:** 839–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Interactions

As for Sulfamethoxazole, p.341.

Sulfafurazole has been reported to increase the anaesthetic effect of thiopental.

Eye preparations of sulfafurazole diolamine should not be applied with preparations of silver salts.

Antimicrobial Action

As for Sulfamethoxazole, p.341.

Pharmacokinetics

Sulfafurazole is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 to 4 hours after an oral dose. Acetyl sulfafurazole (the N^1-acetyl derivative) is broken down to sulfafurazole in the gastrointestinal tract before absorption, resulting in delayed and somewhat lower peak concentrations. After absorption about 85 to 90% is bound to plasma proteins. Sulfafurazole readily diffuses into extracellular fluid, but very little diffuses into cells. Concentrations in the CSF are about one-third of those in the blood. It crosses the placenta into the fetal circulation and is distributed into breast milk. About 30% of sulfafurazole in the blood and in the urine is in the form of the N^4-acetyl derivative.

Sulfafurazole is excreted rapidly in the urine, up to 97% of a single dose being eliminated in 48 hours. The half-life is reported to range from about 5 to 8 hours. Both sulfafurazole and its N^4-acetyl derivative are more soluble than many other sulfonamides in urine.

Uses and Administration

Sulfafurazole is a short-acting sulfonamide that is used similarly to sulfamethoxazole (p.341), notably in the treatment of urinary-tract infections, pneumonia due to *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), nocardiosis, and trachoma. It is also used, usually with erythromycin, in the treatment of otitis media. For details of these infections and their treatment see Choice of Antibacterial, p.162.

Sulfafurazole is usually given orally. In the treatment of susceptible infections, it has been given in an initial dose of 2 to 4 g, followed by 4 to 8 g daily in divided doses every 4 to 6 hours. For children and infants over 2 months of age, the dose has been 75 mg/kg initially, followed by 150 mg/kg daily in divided doses to a maximum of 6 g daily. Dosage modification may be necessary in patients with renal impairment. Acetyl sulfafurazole is tasteless and is used in liquid oral preparations of the drug; doses are expressed in terms of sulfafurazole. 1.16 g of acetyl sulfafurazole is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has been used, as an ophthalmic ointment or solution containing the equivalent of 4% of sulfafurazole, in the topical treatment of susceptible eye infections. Sulfafurazole diolamine 1.39 g is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has also been given parenterally.

Preparations

USP 31: Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Sulfisoxazole Acetyl Oral Suspension; Sulfisoxazole Tablets.

Proprietary Preparations (details are given in Part 3)
Turk.: Gansol; ***USA:*** Gantrisin†; ***Venez.:*** Ganticol; Soxacol†.

Multi-ingredient: ***Arg.:*** Pediazole†; ***Canad.:*** Pediazole; ***Chile:*** Bioquin; Pediazole†; ***Fr.:*** Pediazole; ***Gr.:*** Pediazole; ***Hong Kong:*** Pediazole†; ***Israel:*** Pediazole; ***Mex.:*** Pediazole; Urovec; ***Turk.:*** Azo Gantrisin; ***USA:*** Eryzole†; Pediazole; ***Venez.:*** Pediazole†.

Sulfaguanidine *(BAN, rINN)*

Solfaguanidina; Sulfaguanidiini; Sulfaguanidin; Sulfaguanidina; Sulfaguanidinas; Sulfaguanidinum; Sulfaguanidyna; Sulfamidinum; Sulginum; Sulphaguanidine; Szulfaguanidin. 1-Sulphanilylguanidine; *N'*-Amidinosulphanilamide.

Сульфагуанидин

$C_7H_{10}N_4O_2S = 214.2.$
CAS — 57-67-0 (anhydrous sulfaguanidine); 6190-55-2 (sulfaguanidine monohydrate).
ATC — A07AB03.
ATC Vet — QA07AB03.

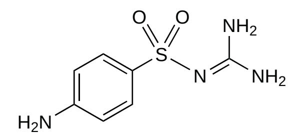

Pharmacopoeias. In *Eur.* (see p.vii).
Viet. includes the monohydrate.
Ph. Eur. 6.2 (Sulfaguanidine). A white or almost white, fine crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in dichloromethane. It dissolves in dilute solutions of mineral acids. Protect from light.

Profile

Sulfaguanidine is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is absorbed to a limited extent from the gastrointestinal tract and may therefore be more likely to cause systemic effects than less well absorbed drugs such as phthalylsulfathiazole and succinylsulfathiazole. It is used, usually with other drugs, in the treatment of gastrointestinal infections, and has also been applied locally to the skin and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Enteropathyl.

Multi-ingredient: ***Braz.:*** Sanadiar†; ***Chile:*** Carbon Sulfaguanidina; ***Mex.:*** Neopecsul; ***Thai.:*** Biodan†.

Sulfamazone Sodium *(rINNM)*

Natrii Sulfamazonum; Sulfamazona sódica; Sulfamazone Sodique; Sulfenazone; Sulphenazone. Sodium α-{*p*-[(6-methoxy-3-pyridazinyl)sulfamoyl]anilino}-2,3-dimethyl-5-oxo-1-phenyl-3-pyrazoline-4-methanesulphonate.

Натрий Сульфамазон

$C_{23}H_{24}N_6O_7S_2Na = 583.6.$
CAS — 65761-24-2 (sulfamazone); 13061-27-3 (sulfamazone sodium).
ATC — J01ED09.

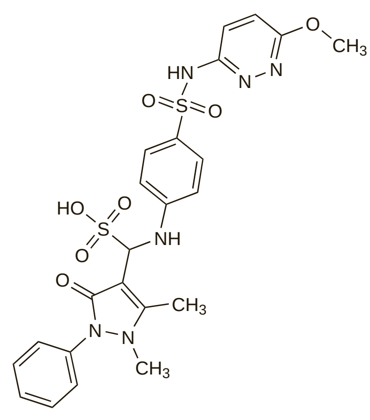

(sulfamazone)

Profile

Sulfamazone is an antibacterial with antipyretic activity that has been given as the sodium salt, orally or rectally, in infections of the upper respiratory tract.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Marespin†.

Sulfamerazine *(BAN, rINN)*

RP-2632; Solfamerazina; Sulfamerasinum; Sulfameratsiini; Sulfamerazin; Sulfamerazina; Sulfamerazinas; Sulfamérazine; Sulfamerazinum; Sulfamethyldiazine; Sulfamethylpyrimidine; Sulphamerazine; Szulfamerazin. N^1-(4-Methylpyrimidin-2-yl)sulphanilamide.

Сульфамеразин

$C_{11}H_{12}N_4O_2S = 264.3.$
CAS — 127-79-7.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.

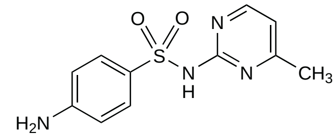

Pharmacopoeias. In *Eur.* (see p.vii). Also in *BP(Vet)*.
Ph. Eur. 6.2 (Sulfamerazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Sulfamerazine Sodium *(BANM, rINN)*

Soluble Sulphamerazine; Sulfamerazina de sodio; Sulfamerazina sódica; Sulfamérazine sodique; Sulfamerazinum Natricum; Sulphamerazine Sodium.

Сульфамеразин Натрий

$C_{11}H_{11}N_4NaO_2S = 286.3.$
CAS — 127-58-2.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.

Profile

Sulfamerazine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). It has usually been given with other sulfonamides, or with trimethoprim.

Preparations

USP 31: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Berlocombin†; ***Indon.:*** Trisulfa; ***Thai.:*** Sulfatril.

Sulfamethizole *(BAN, rINN)*

Sulfaméthizol; Sulfamethizol; Sulfamethizolum; Sulfametitsoli; Sulfametizol; Sulfametizolas; Sulphamethizole; Szulfametizol. N^1-(5-Methyl-1,3,4-thiadiazol-2-yl)sulphanilamide.

Сульфаметизол

$C_9H_{10}N_4O_2S_2 = 270.3.$
CAS — 144-82-1.
ATC — B05CA04; D06BA04; J01EB02; S01AB01.
ATC Vet — QB05CA04; QD06BA04; QJ01EQ02; QS01AB01.

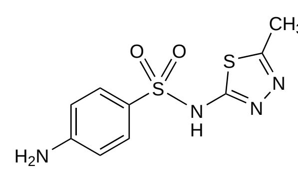

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Sulfamethizole). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.
USP 31 (Sulfamethizole). Practically odourless, white crystals or powder. Soluble 1 in 2000 of water, 1 in 38 of alcohol, 1 in 13 of acetone, and 1 in 1900 of chloroform and of ether; freely soluble in solutions of ammonium, potassium, and sodium hydroxides; soluble in dilute mineral acids; practically insoluble in benzene. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340.

Sulfamethizole and its acetyl derivative are relatively soluble in urine, and the risk of crystalluria is quite low, but an adequate fluid intake should generally be maintained.

Interactions
As for Sulfamethoxazole, p.341.

Antimicrobial Action
As for Sulfamethoxazole, p.341.

Pharmacokinetics
Sulfamethizole is readily absorbed from the gastrointestinal tract; about 90% has been reported to be bound to plasma proteins. Its half-life has been reported to range from about 1.5 to 3 hours. It is only slightly acetylated in the body and is rapidly excreted, about 60% of a dose being eliminated in the urine in 5 hours and around 90% within 10 hours. Sulfamethizole and its acetyl derivative are readily soluble in urine over a wide pH range. Only low concentrations are achieved in blood and tissues because of its rapid excretion.

Uses and Administration
Sulfamethizole is a short-acting sulfonamide that is given orally in the treatment of infections of the urinary tract, sometimes with other antibacterials; it is unsuitable for the treatment of systemic infection since only relatively low concentrations of drug are achieved in the blood and tissues.

It is given in adult doses of 1.5 to 4 g daily in 3 or 4 divided doses. A usual dose for children is 30 to 45 mg/kg daily in 4 divided doses.

Sulfamethizole monoethanolamine has also been used.

Preparations
USP 31: Sulfamethizole Oral Suspension; Sulfamethizole Tablets.

Proprietary Preparations (details are given in Part 3)
Denm.: Lucosil; ***Fr.:*** Rufol; ***Norw.:*** Lucosil†; ***Thai.:*** Luco-Oph†.

Multi-ingredient: ***Spain:*** Micturol Sedante; ***USA:*** Urobiotic-250; ***Venez.:*** Bacteval.

Sulfamethoxazole *(BAN, USAN, rINN)*

Ro-4-2130; Sulfamethoxazol; Sulfaméthoxazole; Sulfamethoxazolum; Sulfametoksatsoli; Sulfametoksazol; Sulfametoksazolas; Sulfametoxazol; Sulfisomezole; Sulphamethoxazole; Szulfametoxazol. N^1-(5-Methylisoxazol-3-yl)sulphanilamide.

Сульфаметоксазол

$C_{10}H_{11}N_3O_3S$ = 253.3.

CAS — 723-46-6.

ATC — J01EC01.

ATC Vet — QJ01EQ11.

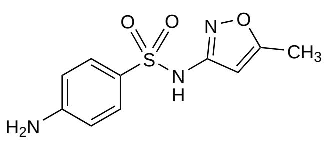

NOTE. Compounded preparations of sulfamethoxazole may be represented by the following names:

- Co-trimoxazole (*BAN*)—sulfamethoxazole 5 parts and trimethoprim 1 part (see p.258)
- Co-trimoxazole (*PEN*)—sulfamethoxazole and trimethoprim.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Sulfamethoxazole). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves in dilute solutions of sodium hydroxide and in dilute acids. Protect from light.

USP 31 (Sulfamethoxazole). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 3400 of water, 1 in 50 of alcohol, and 1 in 1000 of chloroform and of ether; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; freely soluble in acetone and in dilute solutions of sodium hydroxide. Protect from light.

Adverse Effects and Treatment
Nausea, vomiting, anorexia, and diarrhoea are relatively common after use of sulfamethoxazole and other sulfonamides.

Hypersensitivity reactions to sulfonamides have proved a problem. Fever is relatively common, and reactions involving the skin may include rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum. Severe, potentially fatal, skin reactions including toxic epidermal necrolysis and the Stevens-Johnson syndrome have occurred in patients treated with sulfonamides. Dermatitis may also occur from contact of sulfonamides with the skin. SLE, particularly exacerbation of pre-existing disease, has also been reported.

Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in renal failure, have been attributed to hypersensitivity to sulfamethoxazole. Lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine of sulfamethoxazole or its less soluble acetylated metabolite. The risk of crystalluria can be reduced by giving fluids to maintain a high urine output. If necessary, alkalinisation of the urine with sodium bicarbonate may increase solubility and aid the elimination of sulfonamides.

Blood disorders have occasionally occurred during treatment with the sulfonamides including sulfamethoxazole, and include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, hypoprothrombinaemia, and eosinophilia. Many of these effects on the blood may result from hypersensitivity reactions. Sulfonamides may rarely cause cyanosis due to methaemoglobinaemia. Acute haemolytic anaemia is a rare complication which may be associated with G6PD deficiency.

Other adverse effects that may be manifestations of a generalised hypersensitivity reaction to sulfonamides include a syndrome resembling serum sickness, hepatic necrosis, hepatomegaly and jaundice, myocarditis, pulmonary eosinophilia and fibrosing alveolitis, and vasculitis including polyarteritis nodosa. Anaphylaxis has been reported only very rarely.

Other adverse reactions reported after sulfamethoxazole or other sulfonamides include hypoglycaemia, hypothyroidism, neurological reactions including aseptic meningitis, ataxia, benign intracranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache, insomnia, mental depression, peripheral or optic neuropathies, psychoses, tinnitus, vertigo, and pancreatitis.

Sulfonamides may displace serum-bound bilirubin, resulting in kernicterus in premature neonates.

As with other antimicrobials, sulfamethoxazole may cause alterations of the bacterial flora in the gastrointestinal tract. There is, therefore, the possibility, although it appears to be small, that pseudomembranous colitis may occur.

Slow acetylators of sulfamethoxazole may be at greater risk of adverse reactions than fast acetylators.

For further information on the adverse effects of sulfamethoxazole when used with trimethoprim, see Co-trimoxazole, p.258.

Precautions
In patients given sulfamethoxazole, adequate fluid intake is necessary to reduce the risk of crystalluria; the daily urine output should be 1200 mL or more. Compounds that render the urine acidic may increase the risk of crystalluria; the risk may be reduced with alkaline urine.

Treatment with sulfonamides should be stopped immediately a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.

Sulfamethoxazole should be given with care to patients with renal or hepatic impairment and is contra-indicated in patients with severe impairment or with blood disorders. Dosage reduction may be necessary in renal impairment. Complete blood counts and urinalyses with microscopic examination should be carried out particularly during prolonged therapy. Sulfamethoxazole should not be given to patients with a history of hypersensitivity to sulfonamides as cross-sensitivity may occur between drugs of this group. Care is generally advisable in patients with a history of allergy or asthma. Caution is also needed in the elderly, who may be more likely to have other risk factors for reactions. Some consider sulfamethoxazole to be contra-indicated in lupus erythematosus as it may exacerbate the condition. Patients with glucose 6-phosphate dehydrogenase deficiency may be at risk of haemolytic reactions.

Sulfamethoxazole and other sulfonamides are not usually given to infants within 1 to 2 months of birth because of the risk of producing kernicterus; for the same reason, they are generally contra-indicated in women prior to delivery (see below).

Patients with AIDS may be particularly prone to adverse reactions, especially when sulfamethoxazole is given with trimethoprim as co-trimoxazole.

Sulfonamides have been reported to interfere with some diagnostic tests, including those for urea, creatinine, and urinary glucose and urobilinogen.

Breast feeding. Sulfonamides are excreted into breast milk in low concentrations and, although they are generally contra-indicated in the USA in breast-feeding women because of the risk of kernicterus, they are usually thought to pose a negligible risk to healthy neonates. However, sulfonamides should be used with caution in breast-feeding mothers of ill, stressed, or premature infants and of infants with jaundice, hyperbilirubinaemia or G6PD deficiency.

The American Academy of Pediatrics considers sulfamethoxazole, when given with trimethoprim, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Immunocompromised patients. Sulfamethoxazole is mainly conjugated in the liver to the N^4-acetyl derivative, but is also oxidised, to a limited extent, to the hydroxylamine metabolite.[1-5] Although this metabolite was originally implicated[6] in the development of adverse reactions to sulfonamides, recent work[7] has cast some doubt on this hypothesis. The metabolite appears to be produced through cytochrome P450 oxidative metabolism, and it has been suggested that slow acetylators of sulfamethoxazole exhibit increased oxidation compared with other metabolic routes.[1] AIDS patients also exhibit increased oxidation, since they may be depleted of substrates such as acetylcoenzyme A or glutathione necessary for acetylation or detoxification, and this may explain their susceptibility to sulfamethoxazole toxicity.[2,3]

There have been attempts to inhibit the formation of the hydroxylamine metabolite by competitive inhibition of cytochrome P450 enzymes, notably with fluconazole and ketoconazole.[4,5] Encouraging results have been obtained with fluconazole in healthy subjects, but the potential for clinical benefit in AIDS patients requires further study.[5]

However, one successful method of overcoming adverse effects in AIDS patients has been **desensitisation**. Desensitisation by use of initial doses of 4 mg of sulfamethoxazole or 5 mg of sulfadiazine every 6 hours, doubled at 24-hour intervals until the desired dose was reached, was uneventful in 9 of 13 patients with AIDS requiring sulfonamide treatment for opportunistic infections.[8] The remaining 4 had cutaneous reactions with fever, but in 2 of these the reactions were successfully managed with an antihistamine. Although there is a risk of anaphylaxis, patients with AIDS can be successfully treated with sulfonamides after desensitisation.

See also Immunocompromised Patients under Precautions of Co-trimoxazole, p.258.

1. Cribb AE, Spielberg SP. Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 1992; **51:** 522–6.
2. Lee BL, *et al.* The hydroxylamine of sulfamethoxazole and adverse reactions in patients with acquired immunodeficiency syndrome. *Clin Pharmacol Ther* 1994; **56:** 184–9.
3. van der Ven AJA, *et al.* Urinary recovery and kinetics of sulphamethoxazole and its metabolites in HIV-seropositive patients and healthy volunteers after a single oral dose of sulphamethoxazole. *Br J Clin Pharmacol* 1995; **39:** 621–5.
4. Mitra AK, *et al.* Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 332–40.
5. Gill HJ, *et al.* The effect of fluconazole and ketoconazole on the metabolism of sulphamethoxazole. *Br J Clin Pharmacol* 1996; **42:** 347–53.
6. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 431–3.
7. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
8. Torgovnick J, Arsura E. Desensitization to sulfonamides in patients with HIV infection. *Am J Med* 1990; **88:** 548–9.

Porphyria. Sulfonamides have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Pregnancy. Some sulfonamides have been shown to cause fetal abnormalities including cleft palate in *animals*, but fears of teratogenic effects in humans do not appear to be substantiated. Sulfonamides are probably safe in the first trimester of pregnancy, although throughout pregnancy they should be used only in the absence of a suitable alternative drug.[1] Sulfonamides may displace serum-bound bilirubin and they should be avoided close to delivery because of the risk of kernicterus in the neonate. The risk of drug-induced bilirubin displacement has been reviewed.[2] The initial evidence suggesting a kernicterus-promoting effect of drugs in neonates was reported for sulfafurazole, and this drug now serves as a standard displacing agent against which other drugs are evaluated. Although all sulfonamides are highly protein bound, each has a different capacity to displace bilirubin. Sulfadiazine and sulfanilamide have been found to be the least displacing of the sulfonamides and the effects of sulfadiazine on bilirubin may not be clinically significant; an increased incidence of hyperbilirubinaemia and kernicterus has not been shown after use for prophylaxis of rheumatic fever during pregnancy. Sulfasalazine should theoretically cause significant bilirubin displacement, but studies suggest that the drug may be given to patients with Crohn's disease who are pregnant or breast feeding. Metabolites of sulfonamides have also been evaluated for kernicterus-promoting effects; glucuronide metabolites are expected to compete for binding sites less effectively than the parent compound, whereas acetylated metabolites of some sulfonamides appear to be more potent bilirubin displacers.

1. Wise R. Prescribing in pregnancy: antibiotics. *BMJ* 1987; **294:** 42–4.
2. Walker PC. Neonatal bilirubin toxicity: a review of kernicterus and the implications of drug-induced bilirubin displacement. *Clin Pharmacokinet* 1987; **13:** 26–50.

Interactions

The action of sulfonamides may be antagonised by *p*-aminobenzoic acid and its derivatives, particularly potassium aminobenzoate and the procaine group of local anaesthetics.

Sulfamethoxazole and other sulfonamides may potentiate the effects of some drugs, such as oral anticoagulants (p.1428), methotrexate (p.748), and phenytoin (p.498); this may be due to displacement of the drug from plasma protein binding sites or to inhibition of metabolism. However, the clinical significance of these interactions appears to depend on the particular sulfonamide involved. The possibility of interactions with other highly protein-bound drugs, such as NSAIDs, should be considered.

High doses of sulfonamides have been reported to have a hypoglycaemic effect; the antidiabetic effect of the sulfonylurea compounds may be enhanced by sulfonamides (p.462). Some sulfonamides have been associated with a decrease in plasma-ciclosporin concentrations when used together (p.1826). Isolated reports have described possible failures of hormonal contraceptives resulting in pregnancy in patients given sulfonamides (p.2068).

The use of compounds which render the urine acidic may increase the risk of crystalluria.

Antimicrobial Action

Sulfamethoxazole and other sulfonamides have a similar structure to *p*-aminobenzoic acid and interfere with the synthesis of nucleic acids in sensitive micro-organisms by blocking the conversion of *p*-aminobenzoic acid to the coenzyme dihydrofolic acid, a reduced form of folic acid; in man, dihydrofolic acid is obtained from dietary folic acid so sulfonamides do not affect human cells. Their action is primarily bacteriostatic, although they may be bactericidal where concentrations of thymine are low in the surrounding medium. The sulfonamides have a broad spectrum of action, but the development of widespread resistance (see below) has greatly reduced their usefulness, and susceptibility often varies widely even among nominally sensitive pathogens.

Gram-positive cocci, particularly the Group A streptococci and some strains of *Streptococcus pneumoniae*, are usually sensitive and staphylococci also demonstrate sensitivity but to a lesser extent. Enterococci and many of the clostridia are more or less resistant, although strains of *Clostridium perfringens* are moderately susceptible. Among other Gram-positive organisms that have been reported to be sensitive are *Bacillus anthracis* and many strains of Nocardia, especially *N. asteroides*.

The Gram-negative cocci *Neisseria meningitidis* and *N. gonorrhoeae* were formerly extremely susceptible to sulfonamides, but many strains are now resistant. Susceptibility is often seen in *Haemophilus influenzae* although resistance in *H. ducreyi* is increasingly common. Susceptibility varies widely among the Enterobacteriaceae: strains of *Escherichia coli*, *Klebsiella*, *Proteus*, *Salmonella*, and *Serratia* are sometimes sensitive, but few strains of *Shigella* are now susceptible. *Vibrio cholerae* may be sensitive.

Other organisms that have been reported to be sensitive include *Actinomyces* spp., *Brucella*, *Klebsiella granulomatis*, *Legionella*, and *Yersinia pestis*. Chlamydiaceae are sensitive, but not mycoplasmas, rickettsias, or spirochaetes, nor in general the mycobacteria. *Pseudomonas aeruginosa* is resistant, although sulfonamides may be effective against *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*).

Sulfonamides have some activity against the protozoa *Plasmodium falciparum* and *Toxoplasma gondii*. They are also active against *Pneumocystis jirovecii*, but are ineffective against most fungi.

Sulfamethoxazole and other sulfonamides demonstrate synergy with the dihydrofolate reductase inhibitors pyrimethamine and trimethoprim which inhibit a later stage in folic acid synthesis. For reports of the antimicrobial activity of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p.259.

The *in-vitro* antimicrobial activity of sulfamethoxazole is very dependent on both the culture medium and size of inoculum used.

Resistance. Acquired resistance to sulfonamides is common and widespread among formerly susceptible organisms, particularly *Neisseria* spp., *Shigella* and some other enterobacteria, staphylococci, and streptococci.

There appear to be several mechanisms of resistance including alteration of dihydropteroate synthetase, the enzyme inhibited by sulfonamides, to a less sensitive form, or an alteration in folate biosynthesis to an alternative pathway; increased production of *p*-aminobenzoic acid; or decreased uptake or enhanced metabolism of sulfonamides.

Resistance may result from chromosomal alteration, or may be plasmid-mediated and transferable, as in many resistant strains of enterobacteria. High-level resistance is usually permanent and irreversible. There is complete cross-resistance between the different sulfonamides.

Pharmacokinetics

Sulfamethoxazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached after about 2 hours. Following a single 2-g oral dose, blood concentrations of up to 100 micrograms/mL are achieved. About 70% is bound to plasma proteins. The plasma half-life is about 6 to 12 hours; it is prolonged in patients with severe renal impairment.

Sulfamethoxazole, like most sulfonamides, diffuses freely throughout the body tissues and may be detected in the urine, saliva, sweat, and bile, in the cerebrospinal, peritoneal, ocular, and synovial fluids, and in pleural and other effusions. It crosses the placenta into the fetal circulation and low concentrations have been detected in breast milk.

Sulfamethoxazole undergoes conjugation mainly in the liver, chiefly to the inactive N^4-acetyl derivative; this metabolite represents about 15% of the total amount of sulfamethoxazole in the blood. Metabolism is increased in patients with renal impairment and decreased in those with hepatic impairment. Elimination in the urine is dependent on pH. About 80 to 100% of a dose is excreted in the urine, of which about 60% is in the form of the acetyl derivative, with the remainder as unchanged drug and glucuronide.

Sulfamethoxazole is also oxidised to the hydroxylamine, a metabolite that has been implicated in adverse reactions to sulfonamides (see also Immunocompromised Patients, under Precautions, above), although some doubt has been cast upon this hypothesis.

Uses and Administration

The use of sulfamethoxazole and other sulfonamides has been limited by the increasing incidence of resistant organisms. Their main use has been in the treatment of acute, uncomplicated urinary-tract infections, particularly those caused by *Escherichia coli*. They have also been used in nocardiosis, and in some other bacterial infections such as otitis media, *Chlamydia* and *Chlamydophila* infections, and prophylaxis of meningococcal meningitis, but have largely been replaced by other drugs: even where pathogens retain some sensitivity to sulfonamides, a combination such as co-trimoxazole (sulfamethoxazole with trimethoprim) has often been preferred. The usual treatment of these infections is discussed under Choice of Antibacterial, p.162. Sulfonamides are also used, often with pyrimethamine or trimethoprim, in the treatment of protozoal infections, particularly malaria (p.594) and toxoplasmosis (p.826). They are also used similarly in pneumocystis pneumonia (p.521).

Sulfamethoxazole is an intermediate-acting sulfonamide that has been given orally in a usual dose of 2 g initially, followed by 1 g twice daily. In severe infections 1 g three times daily has been given.

Children have been given a dose of 50 to 60 mg/kg initially, followed by 25 to 30 mg/kg twice daily, up to a maximum daily dose of 75 mg/kg.

Reduction of dosage may be required in patients with renal impairment.

For the uses and dosage of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p.259.

Sulfamethoxazole lysine has also been used.

Administration. US licensed product information for a former product of sulfamethoxazole recommended that blood concentrations be measured in patients receiving sulfonamides for serious infections. The following concentrations of free sulfonamide in the blood were considered to be therapeutically effective:

- for most infections, 50 to 150 micrograms/mL
- for serious infections, 120 to 150 micrograms/mL

Concentrations of 200 micrograms/mL should not be exceeded since the incidence of adverse reactions might be increased.

Preparations

BP 2008: Co-trimoxazole Intravenous Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; ***USP 31:*** Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Sulfamethoxazole Oral Suspension; Sulfamethoxazole Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Adrenol; Bacti-Uril; Bacticel; Bactrim; Bactrim Balsamico; Cotrizol-G; Danferane; Diocla†; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Netocur; Netocur Balsamico; Neumobacticel; Novidrine; Sulfagrand; Tritenk; Urisept NF; Uro-Bactrim†; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Oecotrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Steroprim†; ***Braz.:*** Assepium; Assepium Balsamico; Bac-Sulfitrin; Bacfar; Bacprotin; Bacris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Benectrin Balsamico; Binoctrin†; Clotrizol†; Diazol; Dientrin; Dispeptrin; Duoctrin†; Ectrin; Ectrin Balsamico; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Metoprin Balsamico; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Selectrin Balsamico; Septiolan†; Teutrin; Tricban; Trimexazol; Trimezol†; Uro-Baxapril†; Uroctrin; Uropol; ***Canad.:*** Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Septra; ***Chile:*** Bacterol; Bactrimel; Entero Micinovo; Introcin†; Septrin; Trelibec; Uro-Micinovo; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Bismoral; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Cotrim; Cotrim-Diolan; Cotrim-Hefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Septrin; ***Hung.:*** Cotripharm; Sumetrolim; ***India:*** Bactrim; Ciplin; Colizole; Cotrimol†; Oriprim; Pyramet; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.:*** Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim; Cotrimol; Dumotrim; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim; Meprotrin; Nufaprim; Ottoprim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim; Sultrimmix; Trimezol; Triminex; Trimoxsul; Trixzol; Trizole; Ulfaprim; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.:*** Duobact†; Septrin; ***Israel:*** Diseptyl; Resprim; Septrin; ***Ital.:*** Abacin†; Bactrim; Chemitrim; Eusaprim; Gantrim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Baserin†; Chemix; Cotrim; Resprim; Trimexazole; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver;

The symbol † denotes a preparation no longer actively marketed

Bactrim; Bactrim Compositum; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octex; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimexole Compositum; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Sulfotrim; ***Norw.:*** Bactrim; Trimetoprim-Sulfa†; ***NZ:*** Apo-Sulfatrim; Trisul; ***Philipp.:*** Bacidal; Bactille; Bactrim; Bacxal; Baczole; Bantizol; Chromo-Z; Combi-Methoxan; Costazole; Cozole; Drilozole; Fedimed; Forteprim; Globaxol; Ivatrim; Kassemox; Lictora; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Synermed; Triforam; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Septrin; ***Rus.:*** Biseptol (Бисептол); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Purbac; Septran; Spectrim; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; BS†; Chemix; Chemoprim; Co-Trimexazole; Dhatrin; Septrin†; Suprim; Trimaxazole; Trimezole†; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncomega†; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Busetal†; Cotrazol; Eduprim Mucolitico; Eduprim†; Gobens Trim; Momentol; Neumopectolina†; Pulmo Menal†; Pulmosterin Duo; Septrin; Soltrim; ***Swed.:*** Bactrim; Eusaprim; ***Switz.:*** Agoprim†; Bactrim; Cotrim; Escoprim; Groprim; Lagatrim; Mediprim; Nopil; Sigaprim†; Supracombin†; ***Thai.:*** Actin; Bacin; Bacta†; Bactrim; Baczole; Chemoprim†; Co-Tasian; Co-Trimed; Conprim; Cotamox; Ko-Cap; Ko-Kure; Ladar; Lastrim; Letus; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Septrin; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Septrin; ***USA:*** Bactrim; Cotrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

Sulfamethoxypyridazine *(BAN, rINN)*

Solfametossipiridazina; Sulfamethoxypyridazin; Sulfaméthoxypyridazine; Sulfamethoxypyridazinum; Sulfamethoxypyridazinum ad usum veterinarium; Sulfametoksipyridatsiini; Sulfametoxipiridazina; Sulfametoxipyridazin; Sulphamethoxypyridazine; Szulfametoxipiridazin. N^1-(6-Methoxypyridazin-3-yl)sulphanilamide.

Сульфаметоксипиридазин

$C_{11}H_{12}N_4O_3S$ = 280.3.
CAS — 80-35-3.
ATC — J01ED05.
ATC Vet — QJ01EQ15.

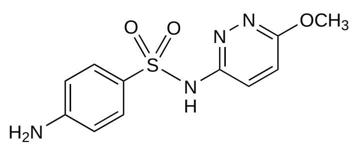

Pharmacopoeias. In *Int.* and *Viet.* In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Sulfamethoxypyridazine for Veterinary Use; Sulfametoxypyridazine BP(Vet) 2008). A white or slightly yellowish crystalline powder which colours slowly on exposure to light. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; very slightly soluble in dichloromethane; dissolves in dilute mineral acids and solutions of alkali hydroxides. Protect from light.

Profile

Sulfamethoxypyridazine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340) and has been used for the treatment of susceptible infections. It is rapidly absorbed from the gastrointestinal tract and excreted slowly in urine, partly as the N^4-acetyl metabolite; it remains detectable for up to 7 days after a dose. It has also been used with trimethoprim similarly to co-trimoxazole.

Acetyl sulfamethoxypyridazine, which is hydrolysed in the gastrointestinal tract forming sulfamethoxypyridazine, and sulfamethoxypyridazine sodium have also been used.

Skin disorders. Reference to the use of sulfamethoxypyridazine in the treatment of pemphigoid.[1] Sulfamethoxypyridazine has also been used in the treatment of dermatitis herpetiformis.[2]

1. Thornhill M, *et al.* An open clinical trial of sulphamethoxypyridazine in the treatment of mucous membrane pemphigoid. *Br J Dermatol* 2000; **143:** 117–26.
2. Fry L. Dermatitis herpetiformis. *Baillieres Clin Gastroenterol* 1995; **9:** 371–93.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Urofen†; Uropac.

Sulfamethylthiazole

Methylsulfathiazole; Sulfametiltiazol. 4-Amino-*N*-(4-methyl-2-thiazolyl)benzenesulfonamide.

$C_{10}H_{11}N_3O_2S_2$ = 269.3.
CAS — 515-59-3.

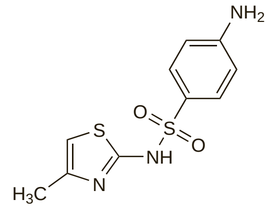

Profile

Sulfamethylthiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is applied topically with tetracycline in the treatment of eye infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Pensulvit.

Sulfametopyrazine *(BAN)*

Sulfalene *(USAN, pINN)*; AS-18908; NSC-110433; Solfametopirazina; Sulfametossipirazina; Sulfaleeni; Sulfalen; Sulfalène; Sulfaleno; Sulfalenum; Sulfamethoxypyrazine; Sulfapirazinmetossina; Sulfapyrazin Methoxyne; Sulphalene. N^1-(3-Methoxypyrazin-2-yl)sulphanilamide.

Сульфален

$C_{11}H_{12}N_4O_3S$ = 280.3.
CAS — 152-47-6.
ATC — J01ED02.

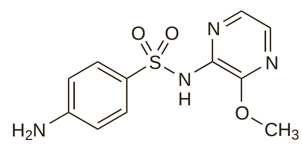

Pharmacopoeias. In *It.*

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p.340.

If adverse effects occur, sulfametopyrazine has the disadvantage that several days are required for its elimination from the body.

Interactions

As for Sulfamethoxazole, p.341.

Antimicrobial Action

As for Sulfamethoxazole, p.341.

Pharmacokinetics

Sulfametopyrazine is readily absorbed from the gastrointestinal tract; 60 to 80% is bound to plasma proteins. Only about 5% of a dose is metabolised to the acetyl derivative. It is slowly excreted in the urine. The biological half-life has been reported to be about 60 to 65 hours.

Uses and Administration

Sulfametopyrazine is a long-acting sulfonamide that has been used orally in the treatment of respiratory- and urinary-tract infections due to sensitive organisms.

Sulfametopyrazine is given with pyrimethamine (p.611) in the treatment of malaria.

It has also been given in the ratio 4 parts of sulfametopyrazine to 5 parts of trimethoprim as a combination with uses similar to those of co-trimoxazole (p.259).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Longum†.

Multi-ingredient: ***Belg.:*** Co-Arinate; Dafrafin; ***Ital.:*** Metakelfin; ***Mex.:*** Kelfiprim†.

Sulfametrole *(BAN, rINN)*

Sulfametrol; Sulfamétrole; Sulfametrolum. N^1-(4-Methoxy-1,2,5-thiadiazol-3-yl)sulphanilamide.

Сульфаметрол

$C_9H_{10}N_4O_3S_2$ = 286.3.
CAS — 32909-92-5.

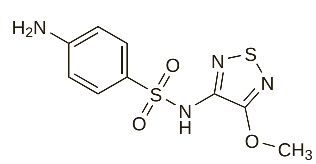

Profile

Sulfametrole is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is given in the ratio of 5 parts of sulfametrole to 1 part of trimethoprim as a combination with uses similar to those of co-trimoxazole (p.259). Usual oral doses are 960 mg (800 mg of sulfametrole and 160 mg of trimethoprim) twice daily. It has also been given as the sodium salt by intravenous infusion.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Lidaprim; ***Gr.:*** Lidaprim; ***Hong Kong:*** Lidaprim; ***Ital.:*** Lidaprim†; ***Neth.:*** Lidatrim; ***Rus.:*** Lidaprim (Лидаприм); ***Thai.:*** Lidaprim†.

Sulfamonomethoxine *(BAN, USAN, rINN)*

DJ-1550; DS-36; ICI-32525; Ro-4-3476; Sulfamonométhoxine; Sulfamonomethoxinum; Sulfamonometoxina. N^1-(6-Methoxypyrimidin-4-yl)sulphanilamide monohydrate.

Сульфамонометоксин

$C_{11}H_{12}N_4O_3S,H_2O$ = 298.3.
CAS — 1220-83-3 (anhydrous sulfamonomethoxine).

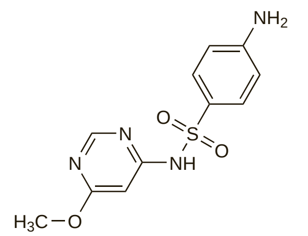

(anhydrous sulfamonomethoxine)

Pharmacopoeias. In *Jpn.*

Profile

Sulfamonomethoxine is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p.340). It is used in veterinary medicine.

Sulfamoxole *(BAN, USAN, rINN)*

Sulfamoksoli; Sulfamoxol; Sulfamoxolum; Sulphadimethyloxazole; Sulphamoxole. N^1-(4,5-Dimethyloxazol-2-yl)sulphanilamide.

Сульфамоксол

$C_{11}H_{13}N_3O_3S$ = 267.3.
CAS — 729-99-7.
ATC — J01EC03.

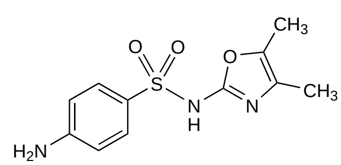

NOTE. Compounded preparations of sulfamoxole may be represented by the following name:

- Co-trifamole (*BAN*)—sulfamoxole 5 parts and trimethoprim 1 part (see p.257).

Pharmacopoeias. In *Fr.*

Profile

Sulfamoxole is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p.340). It has been used with trimethoprim as co-trifamole (p.257).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Supristol†.

Sulfanilamide *(rINN)*

Solfammide; Streptocidum; Sulfaminum; Sulfaniiliamidi; Sulfanilamid; Sulfanilamida; Sulfanilamidas; Sulfanilamidum; Sulphanilamide; Szulfanilamid. 4-Aminobenzenesulphonamide; *p*-Sulphamidoaniline.

Сульфаниламид

$C_6H_8N_2O_2S$ = 172.2.

CAS — 63-74-1.

ATC — D06BA05; J01EB06.

ATC Vet — QD06BA05; QJ01EQ06.

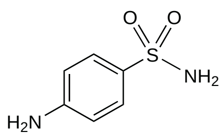

Pharmacopoeias. In *Eur.* (see p.vii). Also in *BP(Vet).*

Ph. Eur. 6.2 (Sulfanilamide). White or yellowish-white crystals or fine powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone; practically insoluble in dichloromethane; dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Sulfanilamide is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). Its antibacterial activity is less than that of sulfamethoxazole. It has been used topically, including vaginally, for the treatment of susceptible infections, often with other drugs. The sodium, sodium mesilate, and camsilate salts have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: AVC†; ***Spain:*** Azol.

Multi-ingredient: ***Arg.:*** Clinal; Iodotiazol†; ***Belg.:*** Polyseptol; Sulfa-Sedemol; ***Braz.:*** Gargotan†; Otovix†; ***Port.:*** Otocalma†; ***S.Afr.:*** Achromide; Daromide; Ung Vernleigh; ***Spain:*** Buco Regis; Cilinafosal; Cilinafosal Dihidroestreptomicina; Cilinafosal Hidrocortisona; Kanafosal; Kanafosal Predni; Nasopomada; Odontocromil c Sulfamida†; Oto Difusor†; Pental Forte†; Polvos Wilfe†; Pomada Heridas†; Pomada Wilfe; Vitavox Pastillas†; ***USA:*** Alasulf; Deltavac; DIT1-2; ***Venez.:*** Otanol†.

Sulfapyridine *(BAN, rINN)*

Sulfapiridina; Sulfapyridiini; Sulfapyridin; Sulfapyridinum; Sulphapyridine. N^1-(2-Pyridyl)sulphanilamide.

Сульфапиридин

$C_{11}H_{11}N_3O_2S$ = 249.3.

CAS — 144-83-2.

ATC — J01EB04.

ATC Vet — QJ01EQ04.

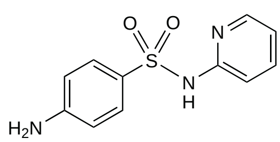

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Sulfapyridine). White or faintly yellowish-white, odourless or practically odourless, crystals, granules, or powder. It slowly darkens on exposure to light. Soluble 1 in 3500 of water, 1 in 440 of alcohol, 1 in 65 of acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides. Protect from light.

Profile

Sulfapyridine is a short- or intermediate-acting sulfonamide, with properties similar to those of sulfamethoxazole (p.340). It is slowly and incompletely absorbed from the gastrointestinal tract and excreted in urine; sulfapyridine and its acetyl metabolite are poorly soluble in urine and the risk of crystalluria is relatively high. Adverse effects are common, and gastrointestinal disturbances may preclude continued therapy. Because of its toxicity, sulfapyridine is now little used except occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment cannot be used; oral doses of up to 1 g four times daily have been given initially, reduced to the minimum effective maintenance dose once improvement occurs.

Breast feeding. The American Academy of Pediatrics[1] states that, although sulfapyridine is usually compatible with breast feeding, caution is required in breast-fed infants with jaundice or G6PD deficiency, or who are ill, stressed, or premature, whose mothers have received the drug.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Pemphigoid. Benefit has been seen with sulfapyridine in ocular cicatricial pemphigoid.[1]

1. Elder MJ, *et al.* Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. *Br J Ophthalmol* 1996; **80:** 549–52.

Preparations

USP 31: Sulfapyridine Tablets.

Sulfaquinoxaline *(BAN, rINN)*

Sulfabenspyrazin; Sulfabentspyratsiini; Sulfabenzpyrazine; Sulfabenzpyrazinium; Sulfabenzpyrazinum; Sulfaquinoxalina; Sulfaquinoxalinum; Sulphaquinoxalina; Sulphaquinoxaline. N^1-(Quinoxalin-2-yl)sulphanilamide.

Сульфахиноксалин

$C_{14}H_{12}N_4O_2S$ = 300.3.

CAS — 59-40-5 (sulfaquinoxaline); 967-80-6 (sulfaquinoxaline sodium).

ATC Vet — QJ01EQ16; QP51AG03.

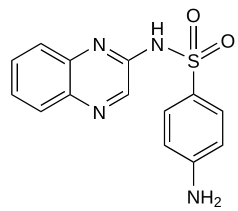

Pharmacopoeias. In *Fr.* Also in *BP(Vet)* and in *US* for veterinary use only.

Fr. also includes Sulfaquinoxaline Sodium, $C_{14}H_{11}N_4NaO_2S$ = 322.3.

BP(Vet) 2008 (Sulfaquinoxaline). A yellow powder. Practically insoluble in water and in ether; very slightly soluble in alcohol. It dissolves in aqueous solutions of alkalis. Protect from light.

USP 31 (Sulfaquinoxaline). Protect from light.

Profile

Sulfaquinoxaline is a sulfonamide antibacterial used in veterinary medicine, sometimes with trimethoprim.

Sulfasuccinamide *(rINN)*

Sulfasuccinamida; Sulfasuccinamidum. 4′-Sulphamoylsuccinanilic acid.

Сульфасукцинамид

$C_{10}H_{12}N_2O_5S$ = 272.3.

CAS — 3563-14-2.

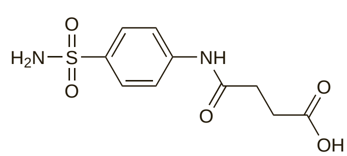

Profile

Sulfasuccinamide is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p.340). It has been applied topically in the treatment of local infections of the ear, nose, and throat. It has also been given as the sodium salt.

Sulfathiazole *(BAN, rINN)*

M&B-760; Norsulfazole; RP-2090; Solfatiazolo; Sulfanilamidothiazolum; Sulfathiazol; Sulfathiazolum; Sulfatiatsoli; Sulfatiazol; Sulfatiazolas; Sulfonazolum; Sulphathiazole; Szulfatiazol. N^1-(1,3-Thiazol-2-yl)sulphanilamide.

Сульфатиазол

$C_9H_9N_3O_2S_2$ = 255.3.

CAS — 72-14-0.

ATC — D06BA02; J01EB07.

ATC Vet — QD06BA02; QJ01EQ07.

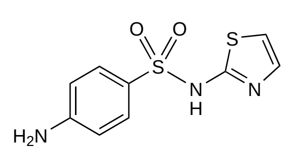

Pharmacopoeias. In *Eur.* (see p.vii), *US,* and *Viet.*

Ph. Eur. 6.2 (Sulfathiazole). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 31 (Sulfathiazole). A white or faintly yellowish-white, practically odourless, fine powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone, in dilute mineral acids, in solutions of alkali hydroxides, and in 6N ammonium hydroxide. Protect from light.

Sulfathiazole Sodium *(BANM, rINNM)*

Natrii Sulfathiazolum; Soluble Sulphathiazole; Sulfathiazol Sodique; Sulfathiazolum Natricum; Sulfatiazol sódico; Sulphathiazole Sodium.

Натрий Сульфатиазол

$C_9H_8N_3NaO_2S_2,5H_2O$ = 367.4.

CAS — 144-74-1 (anhydrous sulfathiazole sodium); 6791-71-5 (sulfathiazole sodium pentahydrate).

ATC — D06BA02; J01EB07.

ATC Vet — QD06BA02.

Pharmacopoeias. In *BP(Vet)* ($1\frac{1}{2}H_2O$ or $5H_2O$).

BP(Vet) 2008 (Sulfathiazole Sodium). A white or yellowish-white crystalline powder or granules. Freely soluble in water; soluble in alcohol. A solution in water containing the equivalent of 1% of the anhydrous substance has a pH of 9.0 to 10.0. Protect from light.

Profile

Sulfathiazole is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is now rarely used systemically due to its toxicity.

Sulfathiazole is used with other sulfonamides, usually sulfabenzamide and sulfacetamide, in preparations for the topical treatment of vaginal infections and is also used with other drugs in the treatment of skin infections.

Sulfathiazole sodium has been applied topically with other drugs in the treatment of eye infections.

Preparations

USP 31: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Blefarosan; Welt-Sulfazol; Yesterday†; ***Port.:*** Stopex†.

Multi-ingredient: ***Arg.:*** Iodotiazol†; Leroid†; Otocuril; Otorinazol†; ***Belg.:*** Sultrin†; ***Braz.:*** Mentozil†; Otobel†; Vagi-Sulfa; ***Chile:*** Gotas Otologicas; Indocalm; Polvos Antibioticos†; Tru; ***Gr.:*** Sultrin; ***Irl.:*** Sultrin†; ***Ital.:*** Streptosil con Neomicina-Fher; ***Mex.:*** Unguento Cruz; Unguento Sulfatiazol Rojtier; ***Philipp.:*** Sultrin; ***Pol.:*** Sulfarinol; ***Port.:*** Sultrin†; ***S.Afr.:*** Sultrin; ***Spain:*** Cremsol; Polvos Wilfe†; Pomada Wilfe; Sabanotropico; Salitanol Estreptomicina; ***UK:*** Sultrin†; ***USA:*** Sultrin; ***Venez.:*** Otanol†.

Sulfathiazole Silver *(BANM, rINNM)*

Argenti Sulfathiazolum; Sulfathiazol Argentique; Sulfatiazol argéntica. 4-Amino-*N*-2-thiazolylbenzenesulfonamide monosilver(1+).

Серебра Сульфатиазол

$C_9H_9N_3O_2S_2Ag$ = 363.2.

CAS — 24342-30-1.

Profile

Sulfathiazole silver is a sulfonamide antibacterial used topically for burns, ulcers, and other infections of the skin.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Argosulfan†; ***Hung.:*** Argosulfan; ***Pol.:*** Argosulfan; ***Rus.:*** Argosulfan (Аргосульфан).

Sulfatroxazole *(BAN, rINN)*

Sulfatroxazol; Sulfatroxazolum. N^1-(4,5-Dimethyl-1,2-oxazol-3-yl)sulfanilamide.

Сульфатроксазол

$C_{11}H_{13}N_3O_3S$ = 267.3.

CAS — 23256-23-7.

ATC Vet — QJ01EQ14.

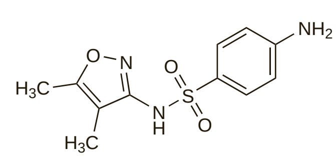

Profile

Sulfatroxazole is a sulfonamide antibacterial used with trimethoprim in veterinary medicine.

Sulfisomidine *(BAN, rINN)*

Sulfa-isodimérazine; Sulfaisodimidiini; Sulfaisodimidin; Sulfaisodimidine; Sulfaisodimidinum; Sulfasomidine; Sulfisomidiini; Sulfisomidin; Sulfisomidina; Sulfisomidinum; Sulfizomidinas; Sulphasomidine; Szulfizomidin. N^1-(2,6-Dimethylpyrimidin-4-yl)sulphanilamide.

Сульфизомидин

$C_{12}H_{14}N_4O_2S$ = 278.3.
CAS — 515-64-0.
ATC — J01EB01.

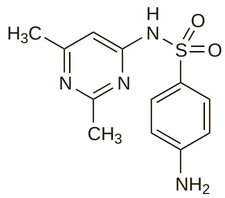

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine, and sulphadimethylpyrimidine is sometimes used as a synonym for sulfadimidine (p.338). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sulfisomidine). White or yellowish-white powder or crystals. Very slightly soluble in water; slightly soluble in alcohol and in acetone; dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Sulfisomidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). It has been used topically for skin or vaginal infections and has also been given orally. The sodium salt has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Thai.: Aristamed†.

Sultamicillin *(BAN, USAN, rINN)*

CP-49952; Sultamicilin; Sultamicilina; Sultamicilline; Sultamicillinum; Sultamisilin; Sultamisilliini; Sultamycylina. Penicillanoyloxymethyl (6*R*)-6-(D-2-phenylglycylamino)penicillanate *S′,S′*-dioxide.

Сультамициллин

$C_{25}H_{30}N_4O_9S_2$ = 594.7.
CAS — 76497-13-7.
ATC — J01CR04.
ATC Vet — QJ01CR04.

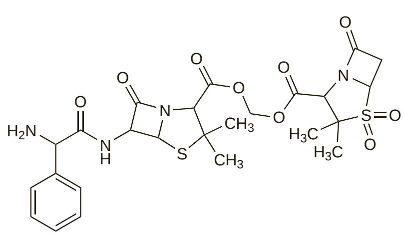

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sultamicillin). A semi-synthetic product derived from a fermentation product. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in methyl alcohol. Store in airtight containers.

Sultamicillin Tosilate *(BANM, rINNM)*

Sultamicilin-tosylát; Sultamicillin Tosylate; Sultamicilline, tosilate de; Sultamicillini tosilas; Sultamicillintosilat; Sultamisilliinitosilaatti; Sultamycyliny tozylan; Tosilato de sultamicilina. Sultamicillin toluene-4-sulphonate.

Сультамициллина Тозилат

$C_{25}H_{30}N_4O_9S_2,C_7H_8O_3S$ = 766.9.
CAS — 83105-70-8.

Pharmacopoeias. In *Chin.*
Eur. (see p.vii) and *Jpn* include the dihydrate.

Ph. Eur. 6.2 (Sultamicillin Tosilate Dihydrate; Sultamicillini Tosilas Dihydricus). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Sultamicillin is a prodrug of ampicillin (p.204) and of the beta-lactamase inhibitor sulbactam (p.335); it consists of the two compounds linked as a double ester. During absorption from the gastrointestinal tract it is hydrolysed, releasing equimolar quantities of ampicillin and sulbactam.

Sultamicillin is given orally as tablets containing sultamicillin tosilate or as oral suspension containing sultamicillin. It is used in the treatment of infections where beta-lactamase-producing organisms might occur, including uncomplicated gonorrhoea, otitis media, and respiratory-tract and urinary-tract infections. The usual dose is 375 to 750 mg of sultamicillin (equivalent to 147 to 294 mg of sulbactam and 220 to 440 mg of ampicillin) twice daily. A single dose of sultamicillin 2.25 g with probenecid 1 g may be used for uncomplicated gonorrhoea.

When parenteral therapy is necessary a combined preparation of ampicillin with sulbactam is given.

◊ References.

1. Friedel HA, *et al.* Sultamicillin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1989; **37**: 491–522.
2. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; **18**: 199–209.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ampigen SB; Unasyna; Unsayna†; ***Austria:*** Unasyn; ***Braz.:*** Unasyn; ***Chile:*** Unasyna; ***Ger.:*** Unacid PD; ***Gr.:*** Begalin; ***Hong Kong:*** Unasyn; ***Hung.:*** Unasyn; ***India:*** Sulbacin; ***Indon.:*** Bactesyn; Cinam; Picyn; Unasyn; Viccillin-SX; ***Ital.:*** Unasyn; ***Malaysia:*** Sulbacin; Unasyn; ***Mex.:*** Pentrexyl-S12-H; Unasyna; ***Philipp.:*** Unasyn; ***Pol.:*** Unasyn; ***Singapore:*** Unasyn; ***Spain:*** Unasyn†; ***Thai.:*** Combicid†; Sulam; Unasyn; ***Turk.:*** Alfasid; Ampisid; Combicid; Duobaktam; Duocid; Nobecid; Sulcid; Sultamat; Sultasid; Sultibac; ***Venez.:*** Fipexiam; Sinif; Sulamp; Sultamicina†; Sultamilan; Unasyn.

Multi-ingredient: ***Cz.:*** Unasyn.

Taurolidine *(BAN, rINN)*

Taurolidina; Taurolidinum. 4,4′-Methylenebis(perhydro-1,2,4-thiadiazine 1,1-dioxide).

Тауролидин

$C_7H_{16}N_4O_4S_2$ = 284.4.
CAS — 19388-87-5.
ATC — B05CA05.
ATC Vet — QB05CA05.

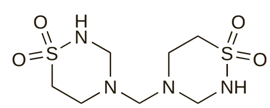

Profile

Taurolidine is a broad-spectrum antibacterial. It is hydrolysed in aqueous solution to its monomeric form taurultam and other metabolites, with the release of what was originally thought to be formaldehyde but is now considered to be activated methylene glycol or methylol groups, from which it is believed to derive its activity. Its antibacterial activity *in vitro* is modest but is reported to be enhanced in the presence of serum or urine; it is active against pathogens including *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Taurolidine is also reported to inactivate bacterial endotoxin.

Taurolidine is used in peritonitis; a solution containing 0.5% is used for irrigation and another containing 2% is available for instillation. It has been given experimentally as an intravenous infusion in the treatment of severe sepsis or endotoxic shock and in pancreatitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Taurolin; ***Ger.:*** Taurolin; ***Neth.:*** Taurolin; ***Switz.:*** Taurolin.

Tazobactam Sodium *(BANM, USAN, rINNM)*

CL-307579; CL-298741 (tazobactam); Natrii Tazobactamum; Tazobactam sódico; Tazobactam sodique; Tazobactamum natricum; Tazobaktam Sodyum; YTR-830; YTR-830H (tazobactam). Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate 4,4-dioxide.

Натрий Тазобактам

$C_{10}H_{11}N_4NaO_5S$ = 322.3.
CAS — 89786-04-9 (tazobactam); 89785-84-2 (tazobactam sodium).
ATC — J01CG02.
ATC Vet — QJ01CG02.

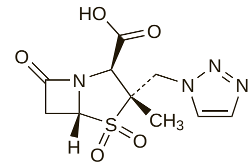

(tazobactam)

Profile

Tazobactam is a penicillanic acid sulfone derivative with beta-lactamase inhibitory properties similar to those of sulbactam (p.335) although it is regarded as more potent. It has the potential to enhance the activity of beta-lactam antibacterials against beta-lactamase-producing bacteria.

Tazobactam sodium is given intravenously with piperacillin sodium (p.315) for the treatment of bacterial infections. The pharmacokinetics of tazobactam and piperacillin are similar.

◊ References.

1. Bush K, *et al.* Kinetic interactions of tazobactam with β-lactamases from all major structural classes. *Antimicrob Agents Chemother* 1993; **37:** 851–8.
2. Payne DJ, *et al.* Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important β-lactamases. *Antimicrob Agents Chemother* 1994; **38:** 767–72.
3. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; **285:** 386–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Zobactam; Zoracilin.

Multi-ingredient: ***Arg.:*** Pipetexina; Tazonam; ***Austral.:*** Tazocin; ***Austria:*** Tazonam; ***Belg.:*** Tazocin; ***Braz.:*** Tazocin; Tazoxil†; Tazpen†; ***Canad.:*** Tazocin; ***Chile:*** Tazonam; ***Cz.:*** Tazocin; ***Denm.:*** Tazocin; ***Fin.:*** Tazocin; ***Fr.:*** Tazocilline; ***Ger.:*** Tazobac; ***Gr.:*** Bactalin; Gramenox; Oliten; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong:*** Tazocin; ***Hung.:*** Tazocin; ***India:*** Dibact†; Tazact; Tazofast; Tazopen; Zosyn; ***Indon.:*** Tazocin; ***Irl.:*** Tazocin; ***Israel:*** Tazocin; ***Ital.:*** Tazobac; Tazocin; ***Malaysia:*** Tazocin; ***Mex.:*** Tasovak; Tazocin; ***Neth.:*** Tazocin; ***Norw.:*** Tazocin; ***NZ:*** Tazocin; ***Philipp.:*** Tazocin; ***Pol.:*** Tazocin; ***Port.:*** Tazobac; ***S.Afr.:*** Tazobax; Tazocin; ***Singapore:*** Tazocin; ***Spain:*** Tazocel; ***Swed.:*** Tazocin; ***Switz.:*** Tazobac; ***Thai.:*** Tazocin; ***Turk.:*** Tazocin; ***UK:*** Tazocin; ***USA:*** Zosyn; ***Venez.:*** Tazopril; Tazpen.

Teicoplanin *(BAN, USAN, rINN)*

A-8327; DL-507-IT; L-12507; MDL-507; Teichomycin A_2; Teicoplanina; Téicoplanine; Teicoplaninum; Teikoplaniini; Teikoplanin.

Тейкопланин

CAS — 61036-62-2 (teichomycin); 61036-64-4 (teichomycin A_2).
ATC — J01XA02.
ATC Vet — QJ01XA02.

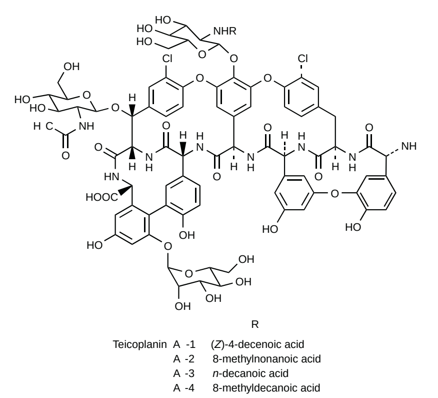

Description. A glycopeptide antibiotic obtained from cultures of *Actinoplanes teichomyceticus* or the same substance obtained by any other means.

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Fever, skin rash and pruritus, and occasional bronchospasm and anaphylaxis have been reported with teicoplanin, but, in comparison with vancomycin (p.359), it appears to be better tolerated when given by rapid intravenous injection and, although erythema and flushing of the upper body have occurred, the 'red-man syndrome' has been reported less often. In addition, unlike vancomycin, teicoplanin does not appear to cause tissue necrosis and can be given by intramuscular injection. Other hypersensitivity reactions have included rigors, angioedema, and, rarely, severe skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Other reported reactions include gastrointestinal disturbances, dizziness, headache, thrombocytopenia (especially at high doses), leucopenia, neutropenia, eosinophilia, disturbances in liver enzyme values, and pain, erythema, and thrombophlebitis or abscess at the injection site. Rare cases of agranulocytosis have occurred. Renal impairment and ototoxicity have been reported but both appear to be less frequent than with vancomycin.

Renal and auditory function should be monitored during prolonged therapy in patients with pre-existing renal impairment, and in those receiving other ototoxic or nephrotoxic drugs, although opinions conflict as to whether increased risk of nephrotoxicity exists with combined therapy with drugs such as the aminoglycosides. In general, periodic blood counts and liver- and renal-function tests are advised during treatment.

No relationship has yet been established between plasma concentration and toxicity, and plasma-concentration monitoring is not generally considered necessary. Dosage adjustment is required in renal impairment.

Hypersensitivity. Although there have been occasional reports of cross-sensitivity to teicoplanin in patients hypersensitive to vancomycin,[1-4] the majority of reports suggest that cross-sensitivity is very rare and teicoplanin can usually be used in patients intolerant of vancomycin.[5-7]

1. McElrath MJ, *et al.* Allergic cross-reactivity of teicoplanin and vancomycin. *Lancet* 1986; **i:** 47.
2. Grek V, *et al.* Allergic cross-reaction of teicoplanin and vancomycin. *J Antimicrob Chemother* 1991; **28:** 476–7.
3. Marshall C, *et al.* Glycopeptide-induced vasculitis—cross-reactivity between vancomycin and teicoplanin. *J Infect* 1998; **37:** 82–3.
4. Kwon HS, *et al.* A case of hypersensitivity syndrome to both vancomycin and teicoplanin. *J Korean Med Sci* 2006; **21:** 1108–10.
5. Schlemmer B, *et al.* Teicoplanin for patients allergic to vancomycin. *N Engl J Med* 1988; **318:** 1127–8.
6. Smith SR, *et al.* Teicoplanin administration in patients experiencing reactions to vancomycin. *J Antimicrob Chemother* 1989; **23:** 810–12.
7. Wood G, Whitby M. Teicoplanin in patients who are allergic to vancomycin. *Med J Aust* 1989; **150:** 668.

Red-man syndrome. Although teicoplanin is believed[1,2] to be less likely than vancomycin to induce the red-man syndrome, symptoms consistent with the syndrome have nevertheless been reported after intravenous use.[3]

1. Sahai J, *et al.* Comparison of vancomycin- and teicoplanin-induced histamine release and "red man syndrome". *Antimicrob Agents Chemother* 1990; **34:** 765–9.
2. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
3. Dubettier S, *et al.* Red man syndrome with teicoplanin. *Rev Infect Dis* 1991; **13:** 770.

Antimicrobial Action

As for Vancomycin Hydrochloride, p.359, although in general teicoplanin is more active against susceptible strains. In particular, it may be more active *in vitro* against enterococci and some anaerobic organisms, including strains of *Clostridium*. However, some coagulase-negative staphylococci are less sensitive to teicoplanin than to vancomycin.

Acquired resistance to teicoplanin has developed in staphylococci during treatment with teicoplanin. Cross-resistance with vancomycin has occurred in staphylococci and enterococci.

Pharmacokinetics

Teicoplanin is poorly absorbed from the gastrointestinal tract. After a 400-mg intravenous dose, peak plasma concentrations 1 hour later are reported to be in the range 20 to 50 micrograms/mL. It is well absorbed on intramuscular injection with a bioavailability of about 90%; after a dose of 3 mg/kg intramuscularly, peak plasma concentrations of 5 to 7 micrograms/mL have been reported after 2 to 4 hours.

The pharmacokinetics of teicoplanin are triphasic, with a biphasic distribution and a prolonged elimination. Penetration into the CSF is poor. It is taken up into white blood cells, and about 90 to 95% of teicoplanin in plasma is protein bound. It is excreted almost entirely by glomerular filtration in the urine, as unchanged drug. The terminal half-life is prolonged, but reported half-lives have ranged from about 30 to 190 hours or longer, depending on the sampling time; an effective clinical half-life of about 60 hours has been suggested for use in calculating dosage regimens. Half-life is increased progressively with increasing degrees of renal impairment. Teicoplanin is not removed by haemodialysis.

Teicoplanin is a mixture of several components, the pharmacokinetics of which have been shown to vary slightly, depending on their lipophilicity.

◊ Reviews.

1. Wilson APR. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet* 2000; **39:** 167–83.

Uses and Administration

Teicoplanin is a glycopeptide antibiotic that may be used as an alternative to vancomycin (p.360) in the treatment of serious Gram-positive infections where other drugs cannot be used, including the treatment and prophylaxis of infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis, and suspected infection in neutropenic or otherwise immunocompromised patients. Teicoplanin, given orally, has been suggested as a possible alternative to vancomycin or metronidazole in antibiotic-associated colitis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Teicoplanin is given intravenously, as a bolus dose or by infusion over 30 minutes, or by intramuscular injection. The usual mean dose is 6 mg/kg intravenously or intramuscularly initially, followed by 3 mg/kg intravenously or intramuscularly on each subsequent day of treatment (in practice this equates to a usual dose of 400 mg initially followed by 200 mg daily, except in patients weighing more than 85 kg in whom it is adapted accordingly). In more severe infections, 6 mg/kg may be given every 12 hours for the first 3 doses, followed by 6 mg/kg daily.

For the prophylaxis of endocarditis in high-risk patients undergoing dental or other procedures who are unable to receive penicillin, teicoplanin may be given in a single dose of 400 mg by intravenous injection, with gentamicin, before the procedure. A similar dose of teicoplanin is given for prophylaxis in orthopaedic surgery at induction of anaesthesia.

In children, a loading dose of 10 mg/kg every 12 hours for 3 doses is followed by 6 to 10 mg/kg daily, depending on the severity of infection. In neonates, a loading dose of 16 mg/kg on the first day is followed by maintenance doses of 8 mg/kg daily, given by intravenous infusion. Although no relationship between plasma concentrations and toxicity has been established, the *BNF* suggests that the former may sometimes be used as a guide to optimise treatment: trough concentrations should be above 10 micrograms/mL (15 to 20 micrograms/mL in patients with endocarditis) but less than 60 micrograms/mL.

Dosage should be adjusted in patients with impaired renal function (see Administration in Renal Impairment, below).

◊ Reviews.

1. Brogden RN, Peters DH. Teicoplanin: a reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 823–54.
2. Murphy S, Pinney RJ. Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J Clin Pharm Ther* 1995; **20:** 5–11.
3. de Lalla F, Tramarin A. A risk-benefit assessment of teicoplanin in the treatment of infections. *Drug Safety* 1995; **13:** 317–28.
4. Periti P, *et al.* Antimicrobial prophylaxis in orthopaedic surgery: the role of teicoplanin. *J Antimicrob Chemother* 1998; **41:** 329–40.
5. Schaison G, *et al.* Teicoplanin in the treatment of serious infection. *J Chemother* 2000; **12** (suppl 5): 26–33.

Administration in renal impairment. Doses of teicoplanin should be adjusted in patients with renal impairment, though reduction is not required until the fourth day of treatment. Teicoplanin should be given in usual doses for the first 3 days of therapy, thereafter the dose is adjusted according to creatinine clearance (CC):

- CC 40 to 60 mL/minute: half initial dose given daily or initial dose given every 2 days
- CC less than 40 mL/minute: one-third initial dose given daily or initial dose given every 3 days

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Targocid; Teicox; Teiklonal; Terbiox; ***Austral.:*** Targocid; ***Austria:*** Targocid; ***Belg.:*** Targocid; ***Braz.:*** Bactomax; Coplaxil†; Kirom; Targocid; Teicon; Teiconin†; Teicozid; ***Chile:*** Targocid; ***Cz.:*** Targocid; ***Denm.:*** Targocid; ***Fin.:*** Targocid; ***Fr.:*** Targocid; ***Ger.:*** Targocid; ***Gr.:*** Targocid; ***Hong Kong:*** Targocid; ***Hung.:*** Targocid; ***India:*** Targocid; Ticocin; ***Indon.:*** Targocid; ***Irl.:*** Targocid; ***Israel:*** Targocid; ***Ital.:*** Targosid; ***Jpn:*** Targocid; ***Malaysia:*** Targocid; ***Mex.:*** Targocid; Teripol; ***Neth.:*** Targocid; ***Norw.:*** Targocid; ***NZ:*** Targocid; ***Pol.:*** Targocid; ***Port.:*** Targosid; ***S.Afr.:*** Targocid; ***Singapore:*** Targocid; ***Spain:*** Targocid; ***Swed.:*** Targocid; ***Switz.:*** Targocid; ***Thai.:*** Targocid; ***Turk.:*** Targocid; ***UK:*** Targocid; ***Venez.:*** Targocid.

Multi-ingredient: ***Ger.:*** Targobone.

Telithromycin *(BAN, USAN, rINN)*

HMR-3647; RU-66647; Télithromycine; Telithromycinum; Telitromicina; Telitromisin. (3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyloctahydro-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-{4-[4-(3-pyridyl)imidazol-1-yl]butyl}-10-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-2*H*-oxacyclotetradecino[4,3-*d*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone.

Телитромицин

$C_{43}H_{65}N_5O_{10}$ = 812.0.

CAS — 173838-31-8; 191114-48-4.

ATC — J01FA15.

ATC Vet — QJ01FA15.

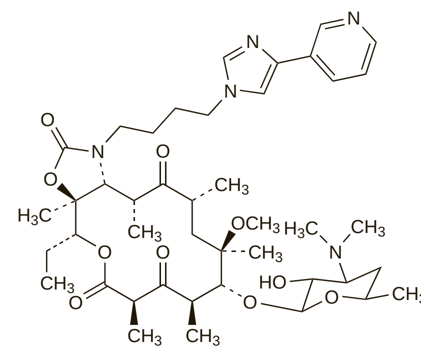

Adverse Effects

Diarrhoea and other gastrointestinal disturbances such as nausea, vomiting, abdominal pain, and flatulence are among the most common adverse reactions after use of telithromycin. Severe, but usually reversible, hepatic dysfunction, including elevation of liver enzymes and hepatitis, with or without jaundice has been reported; however, there have been cases of fatal hepatotoxicity including fulminant hepatitis, hepatic necrosis, and hepatic failure. Effects on the CNS may include dizziness, headache, vertigo, and, occasionally, insomnia or drowsiness. Taste, and very rarely smell, disturbances may occur. Other less commonly reported adverse effects include paraesthesia, eosinophilia, skin rashes, and cardiovascular effects such as arrhythmias, hypotension, and bradycardia. Visual disturbances, particularly affecting accommodation, have occurred. Syncope, usually associated with the vagal syndrome, has been noted. Very rarely reported adverse effects include angioedema and anaphylaxis. There have been isolated cases of erythema multiforme, pseudomembranous colitis, and muscle cramps. Life-threatening acute respiratory failure has been reported in patients with myasthenia gravis (see also Precautions, below).

Effects on the eyes. Visual disturbances, namely blurred vision, difficulty with focusing, and diplopia have been associated with telithromycin. These have been reported to be more common in females under the age of 40 years and to occur in 1.1% of patients compared with 0.28% in those receiving a comparable antibacterial.[1] Licensed product information reports that symptoms are fully reversible, mostly mild to moderate in severity, and typically occur within a few hours of the first or second dose, lasting for several hours and recurring upon subsequent dosing. They have not been associated with any ocular abnormality.

1. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in an 18-year-old man who received telithromycin for 5 days. Complete recovery of renal function occurred 2 weeks after starting symptomatic treatment with methylprednisolone.

1. Tintillier M, *et al.* Telithromycin-induced acute interstitial nephritis: a first case report. *Am J Kidney Dis* 2004; **44:** e25–e27.

Effects on the liver. Hepatotoxicity is an established adverse effect of telithromycin and may be severe. Of 3 case reports of serious liver toxicity in patients with no pre-existing hepatic impairment, after receiving telithromycin at the usual dose,[1] one patient spontaneously recovered, one required a liver transplant, and one died.

1. Clay KD, *et al.* Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann Intern Med* 2006; **144:** 415–20.

Effects on the skin. A 26-year-old woman with a history of rash to penicillin and sulfonamides developed toxic epidermal necrolysis after 13 doses of oral telithromycin for treatment of sinusitis; she was discharged 4 weeks after admission to hospital but had scars on her face and body and had lost her eyelashes.[1]

1. Health Canada. Telithromycin (Ketek): suspected association with toxic epidermal necrolysis. *Can Adverse React News* 2007; **17** (2): 2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 18/06/08)

Precautions

Telithromycin should not be given to patients with known hypersensitivity to it or to the macrolides; similarly, a history of hepatitis and/or jaundice associated with telithromycin or macrolides is a contra-indication.

Telithromycin is contra-indicated in patients with myasthenia gravis because it may exacerbate symptoms of the disease; exacerbations usually occur within 1 to 3 hours of the first dose. Fatalities have been reported.

Patients with a congenital or family history of QT interval prolongation should not receive telithromycin; it should be used with care in those with coronary heart disease, cardiac arrhythmias, and in those with hypokalaemia or hypomagnesaemia, due to its potential to prolong the QT interval. Certain medications may also increase the risk of cardiac arrhythmias and prolong the QT interval (see Interactions, below).

Patients should be informed about signs and symptoms of hepatitis. Should any of these develop during treatment with telithromycin, they should stop taking the drug and consult their doctor. It should be used with caution in patients with hepatic impairment; however, this is based on limited data in such patients. Reduced doses may be necessary in those with severe renal impairment (see below).

Since telithromycin can produce visual disturbances or loss of consciousness caution is advised when driving, operating machinery, or undertaking similar hazardous activities.

Breast feeding. Telithromycin has been shown to be excreted in the milk of lactating *animals* at concentrations about 5 times greater than those in maternal plasma, although corresponding data for humans is not available.

Pregnancy. Reproductive toxicity, but not teratogenicity, has been seen in *animals*; the potential risk for humans is unknown.

Interactions

Telithromycin is an inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Although there have been few clinical reports, drug interactions with telithromycin may be expected to be similar to those seen with erythromycin (see p.271). In particular, caution is required when telithromycin is given with drugs that may prolong the QT interval. Use of telithromycin with cisapride, ergot alkaloid derivatives, pimozide, astemizole, or terfenadine is usually contra-indicated. Caution is usually necessary with benzodiazepines such as alprazolam, midazolam, and triazolam, and with metoprolol. Telithromycin should not be given with drugs that induce the cytochrome P450 isoenzyme CYP3A4, such as rifampicin, phenytoin, carbamazepine, or St John's wort. Telithromycin increases plasma concentrations of some statins and hence the risk of myopathy; it should not be given with atorvastatin, lovastatin, or simvastatin.

Antimicrobial Action

Telithromycin is a ketolide antibacterial with a bactericidal action and is highly active against certain Gram-positive bacteria, including multidrug-resistant strains of *Streptococcus pneumoniae*. Some strains of *Streptococcus pyogenes* and of *Staphylococcus aureus* are also sensitive.

Telithromycin also shows good activity against the Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*). Activity against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) is comparable with macrolides, and it shows greater activity than erythromycin and roxithromycin against *Legionella* spp. *Mycobacterium* spp. are reported to be moderately susceptible.

Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp. are not susceptible.

◊ References.

1. Hammerschlag MR, *et al.* Activity of telithromycin, a new ketolide antibacterial, against atypical and intracellular respiratory tract pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 25–31.
2. Felmingham D, *et al.* Activity of the ketolide antibacterial telithromycin against typical community-acquired respiratory pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 33–42.
3. Felmingham D, *et al.* Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999-2000). *J Infect* 2004; **48:** 39–55.
4. Drago L, *et al.* Selection of resistance of telithromycin against Haemophilus influenzae, Moraxella catarrhalis and streptococci in comparison with macrolides. *J Antimicrob Chemother* 2004; **54:** 542–5.
5. Farrell DJ, Felmingham D. Activities of telithromycin against 13,874 Streptococcus pneumoniae isolates collected between 1999 and 2003. *Antimicrob Agents Chemother* 2004; **48:** 1882–4.

Pharmacokinetics

Telithromycin is rapidly absorbed after an oral dose, with a bioavailability of 57%. Peak plasma concentrations of about 2 micrograms/mL are reached around 1 to 3 hours after a dose of 800 mg. Food does not affect the absorption of telithromycin.

Telithromycin is widely distributed in body fluids and tissues, including those of the respiratory tract, and plasma protein binding is 60 to 70%. Concentrations in target tissues are reported to be higher than plasma concentrations, suggesting the drug may remain active when the plasma concentration has fallen below the MIC.

About two-thirds of a dose is metabolised in the liver to inactive metabolites and the remaining third is eliminated unchanged in the urine and faeces. Metabolism is mediated both by cytochrome P450 isoenzymes (mainly CYP3A4) and non-cytochrome P450 enzymes. The pharmacokinetics of telithromycin are triphasic with a biphasic elimination phase; the elimination half-life is 2 to 3 hours and the terminal half-life about 10 hours.

Distribution into milk has been found in studies in *animals*.

◊ References.

1. Muller-Serieys C, *et al.* Tissue kinetics of telithromycin, the first ketolide antibacterial. *J Antimicrob Chemother* 2004; **53:** 149–57.
2. Shi J, *et al.* Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. *Clin Pharmacokinet* 2005; **44:** 915–34.
3. Ong CT, *et al.* Intrapulmonary concentrations of telithromycin: clinical implications for respiratory tract infections due to Streptococcus pneumoniae. *Chemotherapy* 2005; **51:** 339–46.

Uses and Administration

Telithromycin is a ketolide antibacterial used for the treatment of susceptible respiratory-tract infections in adults including mild to moderate community-acquired pneumonia. In some countries it is also licensed for use in the treatment of acute sinusitis and acute bacterial exacerbations of chronic bronchitis when resistance to beta-lactam and/or macrolide antibacterials is known or suspected; and as an alternative to beta-lactam antibacterials for tonsillitis or pharyngitis caused by Group A *beta streptococci* in patients over 12 years of age. It is given orally in a usual dose of 800 mg once daily.

Doses may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; **62:** 1771–1804.
2. Zhanel GG, Hoban DJ. Ketolides in the treatment of respiratory infections. *Expert Opin Pharmacother* 2002; **3:** 277–97.
3. Ackermann G, Rodloff AC. Drugs of the 21st century: telithromycin (HMR 3647)—the first ketolide. *J Antimicrob Chemother* 2003; **51:** 497–511.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; **53:** 918–27.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18:** 621–49.
6. Wellington K, Noble S. Telithromycin. *Drugs* 2004; **64:** 1683–94.
7. Kasbekar N, Acharya PS. Telithromycin: the first ketolide for the treatment of respiratory infections. *Am J Health-Syst Pharm* 2005; **62:** 905–16.
8. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40:** 1657–64.
9. Nguyen M, Chung EP. Telithromycin: the first ketolide antimicrobial. *Clin Ther* 2005; **27:** 1144–63.
10. Brown SD. Benefit-risk assessment of telithromycin in the treatment of community-acquired pneumonia. *Drug Safety* 2008; **31:** 561–75.

Administration in renal impairment. Doses of telithromycin should be reduced in severe renal impairment (creatinine clearance of less than 30 mL/minute):

- UK licensed product information states that alternating daily doses of 800 mg and 400 mg, starting with 800 mg may be given whether or not hepatic function is also impaired
- US licensed product information recommends a dose of 600 mg once daily if there is no hepatic impairment but a dose of 400 mg once daily if there is co-existing impairment

Doses should be given after dialysis sessions to patients on haemodialysis.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases (see also Respiratory Disorders, under Uses of Erythromycin, p.273). Ketolides also appear to have such effects: a 10-day course of oral telithromycin 800 mg daily, started with standard treatment for acute asthma (p.1108) in adults, was reported to improve asthma symptoms regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[1] The mechanism of this effect is unclear, however, and further studies are needed.

1. Johnston SL, *et al.* The TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; **354:** 1589–1600.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Ketek†; ***Belg.:*** Ketek; ***Braz.:*** Ketek; ***Canad.:*** Ketek; ***Chile:*** Ketek†; ***Cz.:*** Ketek; Levviax†; ***Fin.:*** Ketek; ***Fr.:*** Ketek; ***Ger.:*** Ketek; ***Gr.:*** Ketek; ***Irl.:*** Ketek; ***Ital.:*** Ketek; ***Jpn:*** Ketek; ***Mex.:*** Ketek; ***Neth.:*** Ketek; Levviax†; ***Norw.:*** Ketek; Leviax†; ***Pol.:*** Ketek; ***Port.:*** Ketek; Levviax†; ***S.Afr.:*** Ketek; ***Spain:*** Ketek; Levviax†; ***Swed.:*** Ketek; ***Thai.:*** Ketek; ***Turk.:*** Ketek; ***UK:*** Ketek; ***USA:*** Ketek; ***Venez.:*** Ketek.

Temocillin *(BAN, USAN, rINN)*

Temocilina; Témocilline; Temocillinum. (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.

Темоциллин

$C_{16}H_{18}N_2O_7S_2$ = 414.5.
CAS — 66148-78-5.
ATC — J01CA17.
ATC Vet — QJ01CA17.

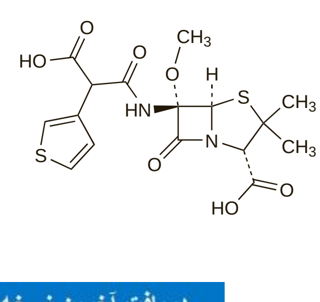

Temocillin Sodium *(BANM, rINNM)*

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Témocilline Sodique. The disodium salt of (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.

Натрий Темоциллин

$C_{16}H_{16}N_2Na_2O_7S_2$ = 458.4.
CAS — 61545-06-0.
ATC — J01CA17.
ATC Vet — QJ01CA17.

Profile

Temocillin is a semisynthetic penicillin that is highly resistant to a wide range of beta-lactamases and is used for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative aerobic bacteria, including those resistant to third-generation cephalosporins.

It is given as the sodium salt and doses are expressed in terms of the base; 1.11 g of temocillin sodium is equivalent to about 1 g of temocillin. It is given by intravenous or intramuscular injection or by intravenous infusion in usual doses of 1 g every 12 hours. A dose of 12.5 mg/kg every 12 hours may be used in children. Intravenous doses may be doubled in severe infections.

In patients with renal impairment the interval between doses may need to be increased.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Negaban; ***Ital.:*** ISF 09338†; ***UK:*** Negaban.

Terizidone *(rINN)*

B-2360; Terizidona; Térizidone; Terizidonum. 4,4′-[*p*-Phenylenebis(methyleneamino)]bis(isoxazolidin-3-one).

Теризидон

$C_{14}H_{14}N_4O_4$ = 302.3.
CAS — 25683-71-0.
ATC — J04AK03.
ATC Vet — QJ04AK03.

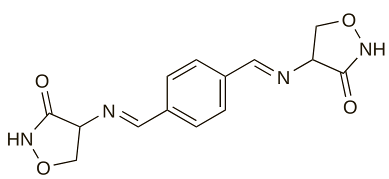

Profile

Terizidone has been used in the treatment of infections of the urinary tract and of pulmonary and extrapulmonary tuberculosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Terivalidin; ***Braz.:*** Terizidex; ***S.Afr.:*** Terivalidin.

Tetracycline *(BAN, rINN)*

Tetraciclina; Tetraciklin; Tetraciklinas; Tétracycline; Tetracyclinum; Tetracyklin; Tetracyklina; Tetrasykliini. A variably hydrated form of (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide.

Тетрациклин

$C_{22}H_{24}N_2O_8$ = 444.4.
CAS — 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate).
ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.
ATC Vet — QA01AB13; QD06AA04; QG01AA90; QG51AA02; QJ01AA07; QJ51AA07; QS01AA09; QS02AA08; QS03AA02.

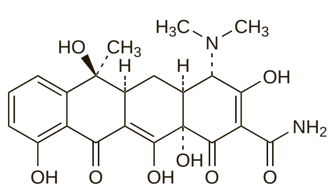

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Tetracycline). A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

USP 31 (Tetracycline). A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Tetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tetraciclina; Tetraciklinhidroklorid; Tetraciklino hidrochloridas; Tétracycline, chlorhydrate de; Tetracyclini hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi.

Тетрациклина Гидрохлорид

$C_{22}H_{24}N_2O_8,HCl$ = 480.9.
CAS — 64-75-5.
ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.
ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

US also includes Epitetracycline Hydrochloride.

Ph. Eur. 6.2 (Tetracycline Hydrochloride). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

USP 31 (Tetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light.

Tetracycline Phosphate Complex *(BAN)*

Tetraciclina, complejo con fosfato.

CAS — 1336-20-5.
ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.
ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

Description. A complex of sodium metaphosphate and tetracycline.

Incompatibility. Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Tetracycline undergoes reversible epimerisation in *solution* to the less active 4-epitetracycline;[1,2] the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.[1] The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.[1] Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose about 8 to 12% of their potency in 24 hours at room temperature.[3] Although epimerisation has been observed to be the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.[4]

In contrast to the case in solution, *suspensions* of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.[2] This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of *solid* dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37° and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.[5] Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.[5] However, although this study, and an accelerated stability study carried out by WHO[6] indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.[7]

1. Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; **52:** 752–6.
2. Grobben-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; **7:** 104–8.
3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; **24:** 434–9.
4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; **6:** 201–14.
5. Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; **59:** 1160–4.
6. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 18/05/07)
7. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–14.

Adverse Effects

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Oesophageal ulceration has been reported with doxycycline, minocycline, and tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime. Other effects that have been reported include glossitis, stomatitis, and dysphagia.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed derivatives such as doxycycline.

Renal dysfunction has been reported with tetracyclines, particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal impairment increase the severity of uraemia with increased excretion of nitrogen and loss of sodium, accompanied by acidosis and hyperphosphataemia, and may lead to excessive systemic accumulation of the tetracycline and possible liver toxicity. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and interstitial nephritis have occurred rarely.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women and in patients with renal impairment or those given high doses. However, hepatotoxicity has also occurred in patients without these predisposing factors but is rarely reported with doxycycline.

Tetracyclines are deposited both in deciduous teeth (milk teeth; primary teeth) and in permanent teeth during their formation, causing permanent discoloration and enamel hypoplasia. The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose given. Doxycycline binds less with calcium compared with other tetracyclines and these changes may occur less frequently. Tetracyclines are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women.

Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances, and papilloedema has been reported. The use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracranial pressure occurs tetracycline treatment should be stopped. Transient myopia in patients taking tetracyclines may be due to changes in refractive power of the lens. Other adverse effects that have occasionally been reported with tetracyclines include increased muscle weakness in patients with myasthenia gravis and exacerbation of SLE.

Hypersensitivity to the tetracyclines is much less common than to the beta lactams, but hypersensitivity reactions, including rashes, fixed drug eruptions, exfoliative dermatitis, toxic epidermal necrolysis, drug fever, pericarditis, angioedema, urticaria, and asthma have been reported; anaphylaxis has occurred very rarely. Photosensitivity, which has been reported with most tetracyclines, occurs most frequently with demeclocycline and other long-acting derivatives, less with chlortetracycline, and very rarely with oxytetracycline and tetracycline; it appears to be phototoxic rather than photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity.

Local pain and irritation can occur when tetracyclines are given parenterally and thrombophlebitis may follow intravenous injections. A Jarisch-Herxheimer reaction occurs commonly in patients with relapsing fever treated with tetracyclines.

Although rare, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Tetracyclines may produce hypoprothrombinaemia. They have also been associated with reductions in serum-vitamin B concentrations, including a case of folate deficiency and concomitant megaloblastic anaemia.

The use of tetracyclines that are out-of-date or which have deteriorated has been associated with the development of a reversible Fanconi-type syndrome characterised by polyuria and polydipsia with nausea, glycosuria, aminoaciduria, hyperphosphaturia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria; these effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline.

Effects on intracranial pressure. Benign intracranial hypertension (pseudotumor cerebri) has been described in patients given tetracyclines.[1] Tetracycline is most commonly implicated, usually in patients being treated for acne; it has also been associated with doxycycline[2,3] and minocycline.[4,5] Presenting symptoms, such as headaches, tinnitus, visual loss, diplopia, nausea, and vomiting, usually develop from within 2 weeks to 1 year or more of starting a tetracycline. Most cases resolved when the drug was stopped although some required symptomatic treatment with diuretics (including acetazolamide), corticosteroids, and/or lumbar puncture. Nevertheless, permanent visual loss has been reported.

1. Digre KB. Not so benign intracranial hypertension. *BMJ* 2003; **326:** 613–14.
2. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ* 2003; **326:** 641–2.
3. Friedman DI, *et al.* Doxycycline and intracranial hypertension. *Neurology* 2004; **62:** 2297–9.
4. Weese-Mayer DE, *et al.* Minocycline and pseudotumor cerebri: the well-known but well-kept secret. *Pediatrics* 2001; **108:** 519–20.
5. Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and not so benign intracranial hypertension. *Aust Adverse Drug React Bull* 2003; **22:** 2–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.pdf (accessed 07/02/07)

Precautions

The tetracyclines are contra-indicated in patients hypersensitive to any of this group of antibacterials, since cross-sensitivity may occur.

Tetracyclines should not be used during pregnancy because of the risk of hepatotoxicity in the mother as well as the effects on the developing fetus. They should also be avoided during breast feeding and in children up to the age of 8, or according to the *BNF*, 12, years. Use in pregnancy, potentially during breast feeding, or in childhood, may result in impaired bone growth and permanent discoloration of the child's teeth.

In general the tetracyclines, with the exception of doxycycline, should be used with caution in those with renal impairment and, if they must be given, doses should be reduced. However, the *BNF* advises avoiding tetracyclines, except doxycycline and minocycline, even in mild impairment. Care should also be taken if tetracyclines are given to patients with hepatic impairment and high doses should be avoided.

Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity. Care is advisable in patients with myasthenia gravis, who may be at risk of neuromuscular blockade. Tetracyclines should be avoided in those with SLE.

Serum monitoring of tetracyclines may be helpful in patients with risk factors given prolonged therapy: it has been suggested that serum concentrations of tetracycline should not exceed 15 micrograms/mL. To avoid the risk of oesophageal ulceration oral tetracyclines (notably doxycycline, see p.267) should be taken with plenty of fluid while sitting or standing, and well before going to bed.

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

Breast feeding. The American Academy of Pediatrics[1] states that, after use of tetracycline by breast-feeding mothers, there is negligible absorption by the infant and that tetracycline is therefore usually compatible with breast feeding. However, licensed product information states that adverse effects including permanent tooth discoloration and enamel hypoplasia may occur in breast-fed infants and that breast feeding is contra-indicated during treatment with tetracyclines.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Porphyria. Tetracyclines are considered to be probably safe in patients with porphyria, although there is conflicting experimental evidence of porphyrinogenicity. Doxycycline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients, and results from *animals* or *in-vitro* systems suggest that oxytetracycline might be porphyrinogenic.

Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore use of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, colestyramine, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralfate are probably of little clinical significance. These interactions can be minimised by giving such products at least 1 to 3 hours apart from tetracyclines. Strontium ranelate should not be given with tetracyclines because of possible complex formation.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together; such use should be avoided. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, halofantrine, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants have also been increased in a few patients. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred after the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the effectiveness of oral contraceptives.

Because of possible antagonism of the action of the penicillins by the mainly bacteriostatic tetracyclines it has been recommended that the two types of drug should not be used together, especially when a rapid bactericidal action is necessary.

Antimicrobial Action

The tetracyclines are mainly bacteriostatic, with a broad spectrum of antimicrobial activity including Chlamydiaceae, *Mycoplasma* spp., *Rickettsia* spp., spirochaetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action. Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis, and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective activity against the infecting organism.

Spectrum of activity. The following pathogenic organisms are usually sensitive to tetracyclines:

Gram-positive cocci including some strains of *Staphylococcus aureus* and coagulase-negative staphylococci, and streptococci including *Str. pneumoniae*, *Str. pyogenes* (group A), and some viridans streptococci. Enterococci are essentially resistant.

Other sensitive Gram-positive bacteria including strains of *Actinomyces israelii*, *Bacillus anthracis*, *Erysipelothrix rhusiopathiae*, *Listeria monocytogenes*, and among the anaerobes some *Clostridium* spp. *Nocardia* spp. are generally much less susceptible although some are sensitive to minocycline. *Propionibacterium acnes* is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations.

Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *N. gonorrhoeae* (gonococci), although some strains are resistant, and *Moraxella catarrhalis* (*Branhamella catarrhalis*). *Acinetobacter* spp. may be resistant to tetracycline, but most strains are susceptible to doxycycline and minocycline.

Other sensitive Gram-negative aerobes including *Bordetella pertussis*, *Brucella* spp., *Klebsiella granulomatis*, *Campylobacter* spp., *Eikenella corrodens*, *Francisella tularensis*, *Haemophilus influenzae* and some strains of *H. ducreyi*, *Legionella* spp., *Pasteurella multocida*, *Streptobacillus moniliformis*, and various members of the Vibrionaceae including *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Vibrio cholerae* and *V. parahaemolyticus*. Although many of the Enterobacteriaceae, including *Salmonella*, *Shigella*, and *Yersinia* spp., are susceptible, resistant strains are common; *Proteus* and *Providencia* spp. are not susceptible. *Pseudomonas aeruginosa* is not susceptible either, although some other species formerly classified as *Pseudomonas* respond, including *Burkholderia mallei*, *B. pseudomallei*, and *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*).

Among the Gram-negative anaerobes *Bacteroides fragilis* may sometimes be susceptible, although wild strains are often resistant, and *Fusobacterium* may also be sensitive.

Other organisms usually sensitive to tetracyclines include *Helicobacter pylori*, Chlamydiaceae, *Rickettsia* and *Coxiella* spp., many spirochaetes including *Borrelia burgdorferi*, *Leptospira* spp., and *Treponema pallidum*, atypical mycobacteria such as *Mycobacterium marinum*, and mycoplasmas including *Mycoplasma pneumoniae* and *Ureaplasma urealyticum*. In addition the tetracyclines are active against some protozoa including *Plasmodium falciparum* and *Entamoeba histolytica*.

Fungi, yeasts, and viruses are generally resistant.

Resistance. Resistance to the tetracyclines is usually plasmid-mediated and transferable. It is often inducible, and appears to be associated with the ability to prevent accumulation of the antibacterial within the bacterial cell, both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries), resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as *Escherichia coli*, *Enterobacter*, *Salmonella*, and *Shigella* spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among group A streptococci, and even more so among group B streptococci; there is also resistance among pneumococci, which often show multiple drug resistance. Emergence of high-level tetracycline-resistant strains of *Neisseria gonorrhoeae* is common in some areas. Frequent resistance is also seen in clostridia, and in *Bacteroides fragilis* (among more than 60% of isolates in some countries), while increasing resistance amongst *Haemophilus ducreyi* has limited the value of tetracyclines in chancroid.

Pharmacokinetics

Most tetracyclines are incompletely absorbed from the gastrointestinal tract, about 60 to 80% of a dose of the drug usually being available. The degree of absorption is reduced by the presence of divalent and trivalent metal ions and also certain drugs, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food (see Interactions above). However, the more lipophilic derivatives doxycycline and minocycline are almost completely absorbed (more than 90%), and they are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline.

Tetracycline 500 mg orally every 6 hours generally produces steady-state plasma concentrations of 4 to 5 micrograms/mL, whereas with doxycycline a dose of 200 mg is sufficient to produce peak concentrations of about 3 micrograms/mL. Peak plasma concentrations occur about 1 to 3 hours after oral use. Higher concentrations can be achieved after intravenous use; concentrations may be higher in women than in men.

In the circulation, tetracyclines are bound to plasma proteins to varying degrees, but reported values differ considerably, ranging from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline, about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and for doxycycline.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed, and small amounts appear in saliva and in the fluids of the eye; higher concentrations are achieved with more lipid-soluble derivatives such as minocycline and doxycycline. Tetracyclines appear in breast milk, where concentrations may be 60% or more of those in the maternal plasma. They diffuse across the placenta and appear in the fetal circulation in concentrations of about 25 to 75% of those in the maternal blood. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines have been classified in terms of their duration of action in the body, although the divisions appear to overlap somewhat. Of the 'short-acting' analogues, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours, and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocycline and methacycline, have reported half-lives of about 12 and 14 hours respectively, although various sources cite values of 7 to 17 hours, and the 'long-acting' minocycline and doxycycline have half-lives of about 16 and 18 hours, with reported values anywhere between 11 to 26 and 12 to 24 hours respectively.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 60% of an intravenous dose of tetracycline, and up to 55% of an oral dose, is eliminated unchanged in the urine; tetracycline concentrations in the urine of up to 300 micrograms/mL may be reached 2 hours after a usual dose is taken and be maintained for up to 12 hours. Usually about 40 to 70% of a dose is excreted in the urine, but for chlortetracycline, doxycycline, and minocycline, rather less is eliminated by this route since chlortetracycline and minocycline undergo metabolism, and doxycycline is excreted mainly in the faeces. Urinary excretion is increased if urine is alkalinised.

The tetracyclines are excreted in the bile, where concentrations 5 to 25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after oral doses and lesser amounts after injection.

Tetracyclines are slowly removed by haemodialysis, except for doxycycline which is not removed; they are not removed by peritoneal dialysis.

Uses and Administration

The tetracyclines are bacteriostatic antibacterials with a wide spectrum of activity and have been used in the treatment of a large number of infections caused by susceptible organisms. With the emergence of bacterial resistance and the development of other antibacterials their use has become more restricted, but they remain drugs of choice in rickettsial infections (including Q fever, spotted fevers, and typhus), ehrlichiosis, trench fever, chlamydial infections (including psittacosis, lymphogranuloma venereum, trachoma, non-gonococcal urethritis, and conjunctivitis), and also pharyngitis, sinusitis, or pneumonia due to *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), and mycoplasmal infections (especially pneumonia caused by *Mycoplasma pneumoniae*). They are widely used as part of regimens for pelvic inflammatory disease. A tetracycline is often used with fluid and electrolyte replacement in the treatment of cholera, and is usually the treatment of choice in relapsing fever and in the early stages of Lyme disease. Tetracyclines may be of benefit in the treatment of melioidosis. They may be used for mouth infections, especially in destructive forms of periodontal disease. Tetracyclines are used, often with streptomycin or rifampicin, in the treatment of brucellosis, and may be given with streptomycin in plague, and as an alternative to streptomycin or gentamicin in the treatment of tularaemia.

Tetracyclines are used as an alternative to other drugs in the treatment of actinomycosis, infected animal bites, anthrax, chronic bronchitis, gas gangrene, gastroenteritis (due to *Campylobacter* or *Yersinia enterocolitica*), granuloma inguinale, leptospirosis, and syphilis. Opinions differ as to their value in listeriosis. There are now relatively few areas where tetracycline-resistant gonococci are uncommon, which limits the value of tetracyclines in gonorrhoea, but they are often given with antigonorrhoeal therapy to treat concomitant chlamydial infections, and they retain some value in the prophylaxis of neonatal gonococcal conjunctivitis by topical application.

For details of all these infections and their treatment, see under Choice of Antibacterial, p.162.

Tetracyclines are also used in the oral treatment of acne and rosacea (see Skin Disorders, below).

Tetracyclines have antiprotozoal actions and tetracycline or doxycycline may be given with quinine in the management of falciparum malaria resistant to chloroquine (below). Tetracyclines are the usual treatment for balantidiasis (p.823) and they have been used with an amoebicide in the treatment of severe amoebic dysentery and in *Dientamoeba fragilis* infections (see Amoebiasis, p.822).

Tetracycline has been used in the management of malabsorption syndromes such as tropical sprue.

Tetracycline has been instilled as a sclerosant solution for pleurodesis and in the management of malignant effusions (p.659).

Administration and dosage. In the treatment of systemic infections the tetracyclines are usually given orally. They should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration. In severe acute infections they have been given by slow intravenous infusion or, rarely, by intramuscular injection; parenteral therapy should be substituted by oral dosage as soon as practicable.

Doses of tetracycline base and tetracycline hydrochloride are expressed in terms of tetracycline hydrochloride. Tetracycline (anhydrous) 231 mg is equivalent to about 250 mg of tetracycline hydrochloride. The usual adult oral dosage of tetracycline hydrochloride is 250 or 500 mg every 6 hours, preferably 1 hour before or 2 hours after meals. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects. It is also sometimes given orally with other tetracycline derivatives.

Tetracycline hydrochloride has been given by slow intravenous infusion or by intramuscular injection in severe infections. As intramuscular injections were painful, procaine hydrochloride was usually included in the solution.

For details of doses in children and adolescents, see below.

Care is required if tetracyclines are given to the elderly. They should be avoided if possible in renal impairment (with the exception of doxycycline and minocycline) and doses reduced if they must be used. For dosage recommendations in patients with hepatic impairment, see below.

Other routes. Although topical application carries the risk of sensitisation and may contribute to the development of resistance, tetracycline hydrochloride has been used as a 3% ointment; a 0.2% solution has been used in acne but systemic treatment appears to produce better results. A 1% eye ointment or eye drops have been used in the treatment of ocular infections due to susceptible organisms. For the treatment of pleural effusions, 500 mg of tetracycline hydrochloride has been dissolved in 30 to 50 mL of sodium chloride 0.9% and instilled into the pleural space. For periodontal disease, fibres that release tetracycline have been inserted into the periodontal pocket.

◊ Reviews.

1. Chopra I, *et al.* Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; **29:** 245–77.
2. Smilack JD. The tetracyclines. *Mayo Clin Proc* 1999; **74:** 727–9.
3. Voils SA, *et al.* Use of macrolides and tetracyclines for chronic inflammatory diseases. *Ann Pharmacother* 2005; **39:** 86–94.
4. Shlaes DM. An update on tetracyclines. *Curr Opin Investig Drugs* 2006; **7:** 167–71.
5. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54:** 258–65.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, tetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see above), to a maximum of 2 g daily, may be given orally. However, in the USA, it may be given to those over 8 years old in usual doses of 25 to 50 mg/kg daily by mouth in 4 divided doses.

Administration in hepatic impairment. Some licensed product information has stated that the dosage of tetracycline should not exceed 1 g daily in patients with known liver disease.

Diabetic complications. The *BNF* notes that diabetic diarrhoea in patients with autonomic neuropathy can often be managed with 2 or 3 doses of oral tetracycline 250 mg.

Malaria. Tetracyclines have been used with quinine to treat falciparum malaria (p.594).[1] They are active against both blood and tissue forms of the parasite, and high cure rates have been obtained with such combinations. The action of tetracyclines is relatively slow and they should never be used alone to treat malaria.

A usual oral regimen is a 3 to 7 day course of quinine given with 7 days of the tetracycline. The total daily dose of tetracycline should be divided, and that usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical in the field. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun; tetracycline should not be used parenterally. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones.

The dose of doxycycline given orally with quinine is 200 mg daily for at least 7 days.

Tetracyclines are not considered suitable for extended prophylactic use, although doxycycline 100 mg daily has been used for short-term prophylaxis in areas of high risk where other drugs are likely to be ineffective.

1. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 6th March 2007). Available at: http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf (accessed 28/03/07)

Mouth ulceration. Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (p.1700) and reportedly reduce ulcer pain and duration,[1] but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (p.1499).

1. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. *Acta Odontol Scand* 1985; **43:** 47–52.

Musculoskeletal and joint disorders. Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (p.11). Studies[1,2] indicate that minocycline can produce modest beneficial effects in patients with advanced disease, but the clinical significance of these improvements has been questioned.[3] Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;[4,5] continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs (DMARDs).[6] A systematic review,[7] which included these and some other studies, reported that the use of tetracyclines (doxycycline, minocycline, or tetracycline) for 3 months or longer was associated with a reduction in disease activity but not in joint damage when compared with placebo or a DMARD (hydroxychloroquine or methotrexate); the authors also noted that patients with early onset disease responded better to tetracyclines. There has been speculation over the role of infection as a cause of rheumatoid arthritis.[3,8] A later study[9] in patients with early seropositive disease found that initial therapy with methotrexate plus doxycycline was superior to methotrexate alone. It was also noted that therapeutic responses to doxycycline 100 mg twice daily and 20 mg twice daily were similar, suggesting that its anti-inflammatory effects were more important; however, further studies are needed.

Although there has been little convincing clinical evidence that any treatment can slow the progression of osteoarthritis (p.11), a placebo-controlled study involving 431 women with unilateral osteoarthritis of the knee found that treatment with doxycycline 100 mg twice daily over 30 months was associated with a reduction in the rate of joint space narrowing.[10] It had no effect on the contralateral knee, and did not reduce pain scores, although these were low at baseline.

The role of antibacterials is also uncertain in reactive arthritis (see Bone and Joint Infections, p.164), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[11] However, another small study[12] found that treatment with a 4-month course of doxycycline 100 mg twice daily was not superior to a 10-day course.

1. Kloppenburg M, *et al.* Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 629–36.
2. Tilley BC, *et al.* Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **122:** 81–9.
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; **345:** 1319–20.
4. O'Dell JR, *et al.* Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; **40:** 842–8.
5. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; **44:** 2235–41.
6. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; **42:** 1691–5.
7. Stone M, *et al.* Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; **30:** 2112–22.
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; **57:** 279–82.
9. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006; **54:** 621–7.
10. Brandt KD, *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; **52:** 2015–25.
11. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; **308:** 1302–3.
12. Putschky N, *et al.* Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006; **65:** 1521–4.

Peptic ulcer disease. Tetracycline has been used as part of triple therapy to eradicate *Helicobacter pylori* in patients with peptic ulcer disease (p.1702). The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.

Periodontal disease. For the use of doxycycline in subantimicrobial doses as an adjunct in the treatment of periodontal disease, see Administration, Subantimicrobial Doses, p.268.

Skin disorders. *ACNE.* Tetracyclines may be used topically or orally in the treatment of acne (p.1577). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium acnes*, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are:

- doxycycline 50 mg daily (the *BNF* advocates 100 mg daily)
- lymecycline equivalent to 300 mg of tetracycline daily
- minocycline 100 mg daily
- oxytetracycline 250 to 500 mg daily (the *BNF* advocates 1 g daily)
- tetracycline 1 g daily

Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 3 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance compared with tetracycline;[1] it has also been reported to be more effective than erythromycin against oxytetracycline-resistant acne.[2] However, a later randomised study[3] found minocycline to be comparable in efficacy to oxytetracycline, topical erythromycin with benzoyl peroxide, and topical benzoyl peroxide alone in the treatment of mild to moderate acne; in another randomised study[4] lymecycline also showed comparable efficacy and safety. Moreover, minocycline can cause skin pigmentation and may be associated rarely with immunologically-mediated reactions.[5] Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.[6]

For the use of doxycycline in subantimicrobial doses in patients with acne, see Administration, Subantimicrobial Doses, p.268.

1. Eady EA, *et al.* Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; **122:** 233–44.
2. Knaggs HE, *et al.* The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatol Treat* 1993; **4:** 53–6.
3. Ozolins M, *et al.* Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004; **364:** 2188–95.
4. Bossuyt L, *et al.* Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; **13:** 130–35.
5. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; **312:** 138.
6. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134:** 693–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (p.1582), although there have been reports[1-8] suggesting that a tetracycline (often minocycline) may be of value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; **132:** 784–9.
3. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
4. Loo WJ, *et al.* Minocycline as a therapeutic option in bullous pemphigoid. *Clin Exp Dermatol* 2001; **26:** 376–9.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Assmann T, *et al.* Therapieresistenter pemphigus vulgaris: Kombinationstherapie mit Methylprednisolon und Doxycyclin. *Hautarzt* 2003; **54:** 979–81.
7. Kakurai M, *et al.* Localized pemphigoid (pretibial type) with IgG antibody to BP180 NC16a domain successfully treated with minocycline and topical corticosteroid. *Clin Exp Dermatol* 2007; **32:** 759–61.
8. Carrozzo M, *et al.* Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* 2008; **18:** 198–200.

ROSACEA. Tetracyclines are commonly used in the treatment of rosacea (p.1583). Long-term treatment is usually necessary.

Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.[1] However, a review[2] of the literature concluded that the treatment effect and optimal dose and duration of these 2 drugs have yet to be established; oxytetracycline was found to be of moderate benefit.

For the use of doxycycline in subantimicrobial doses in patients with rosacea, see p.268.

1. Frucht-Pery J, *et al.* Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; **116:** 88–92.
2. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004; **23:** 106–9.

Preparations

BP 2008: Tetracycline Capsules; Tetracycline Tablets;
USP 31: Tetracycline Hydrochloride and Nystatin Capsules; Tetracycline Hydrochloride Capsules; Tetracycline Hydrochloride for Injection; Tetracycline Hydrochloride for Topical Solution; Tetracycline Hydrochloride Ointment; Tetracycline Hydrochloride Ophthalmic Ointment; Tetracycline Hydrochloride Ophthalmic Suspension; Tetracycline Hydrochloride Oral Suspension; Tetracycline Hydrochloride Tablets; Tetracycline Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Ciclotetryl; Tancilina†; ***Austral.:*** Achromycin V†; Achromycin†; Latycin; Tetrex; ***Austria:*** Achromycin†; Actisite; Latycin; ***Braz.:*** Ambra-Sinto T; Aureciclina; Biotrex†; Cinatrex; Infex; Multigran†; Prociclina; Statinclyne†; Telexin†; Teraciton†; Tetraben; Tetracilil; Tetracina; Tetraclin; Tetragel; Tetramax†; Tetramicin†; Tetraspir†; Tetraxil; Tetrex; Tetrib†; ***Canad.:*** Apo-Tetra; Novo-Tetra†; Nu-Tetra; ***Cz.:*** Tetrachel†; ***Fin.:*** Apocyclin; Oricyclin; ***Ger.:*** Achromycin; Imex; Supramycin†; Tefilin; Tetralution†; ***Gr.:*** Cliten; Hostacyclin; Imex; Muvito; Tetrac; Tracyclin; ***Hong Kong:*** Medocycline; ***India:*** Achromycin; Hostacycline; Resteclin; Subamycin; Tetrabact; ***Indon.:*** Cetacycline-P; Conmycin; Corsatet; Dumocycline; Ikacycline; Indocycline; Licoklin; Sanlin; Spectrocycline; Super Tetra; Tetra; Tetrarco; Tetrin; ***Irl.:*** Topicycline; ***Israel:*** Recycline; Tevacycline; ***Ital.:*** Actisite†; Ambramicina; ***Malaysia:*** Beatacycline; Dhatracin; Latycyn†; Tracyne†; ***Mex.:*** Acromicina; Ambotetra; Berciclina; Biotricina; Cortigrin†; Dibaterr; Educiclina; Forcicline†; Istix†; Laur†; Miciclin; Neoprobal; Ofticlin; Oxi-T; Profalin CPS; Quimocyclar; Senociclin; Solclin; Te-Br; Teclizima; Terrakal; Terranumonyl†; Tetra; Tetra-Zil; Tetrapar; Tetrapres; Tetrerba†; Tetrex; Tetrim; Traplicina†; Triclin†; ***Philipp.:*** Moncycline; ***Port.:*** Ciclobiotico†; Neociclina†; ***Rus.:*** Polcortolon TC (Полькортолон ТС); ***S.Afr.:*** Tetrex; ***Singapore:*** Beatacycline; Biotine; ***Spain:*** Actisite; Quimpe Antibiotico; Tetra Hubber†; ***Switz.:*** Actisite†; ***Thai.:*** Achromycin†; Boramycin; Hydromycin†; Lenocin; Pantocycline; Tetra Central†; Tetralim†; Tetrana; Tetrano; ***Turk.:*** Imex; Tetra; Tetralet; Tetramin; Vitasilin; ***UK:*** Topicycline; ***USA:*** Achromycin V†; Actisite†; Bristacycline; Sumycin; Tetrex; ***Venez.:*** Alfaciclina; Clincor†.

Multi-ingredient: *Arg.:* Dresan Biotic†; Eubetal Biotic†; Febrimicina†; Papasine; Solustres; ***Austria:*** Eftapan Tetra; Fluorex Plus; Mysteclin; ***Braz.:*** Anfoterin†; Gino-Teracin; Monocetin; Novasutin; Parenzyme Tetraciclina; Talsutin; Tericin AT; Tricangine†; Tricocilin B; Trinotrex†; Vagiklin; ***Chile:*** Talseclin†; ***Fin.:*** Helipak T; ***Fr.:*** Amphocycline; ***Ger.:*** Mysteclin; Polcortolon TC; ***Hong Kong:*** Talsutin; ***Hung.:*** Polcortolon TC; ***Indon.:*** Enpicortyn; Talsutin; ***Ital.:*** Alfaflor; Betafloroto; Colbiocin; Eubetal Antibiotico; Flumeciclina; Flumetol Antibiotico†; Mictasone; Pensulvit; Vitecaf; ***Malaysia:*** Talsutin†; ***Mex.:*** Berciclina Enzimatica; Pharbrix; Quimotrip; Solfranicol; Trecloran; Urovec; ***Philipp.:*** Vagimycin; ***Pol.:*** Polcortolon TC; ***Port.:*** Ciclobiotico†; ***Rus.:*** Colbiocin (Колбиоцин); ***S.Afr.:*** Riostatin; Tetrex-F; Tritet; Vagmycin; ***Spain:*** Bristaciclina Dental; Gine Heyden†; Nasopomada; Sanicel; ***UK:*** Deteclo†; ***USA:*** Helidac; Pylera; ***Venez.:*** Talsutin†.

Tetroxoprim *(BAN, USAN, rINN)*

Tetroxoprima; Tétroxoprime; Tetroxoprimum. 5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyldiamine.

Тетроксоприм

$C_{16}H_{22}N_4O_4$ = 334.4.

CAS — 53808-87-0.

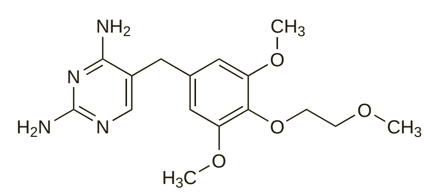

NOTE. Compounded preparations of tetroxoprim may be represented by the following name:

- Co-tetroxazine (*BAN*)—tetroxoprim 2 parts and sulfadiazine 5 parts (see p.257).

Profile

Tetroxoprim is a dihydrofolate reductase inhibitor similar to, but less active than, trimethoprim (p.355). It has been used, with sulfadiazine, as co-tetroxazine (p.257).

Tetroxoprim embonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Ger.:* Sterinor†; ***Venez.:*** Esterinor†.

Thenoic Acid

Tenoic Acid; Tenoico, ácido; 2-Thiophenic Acid. Thiophene-2-carboxylic acid.

Тиофенкарбоновая Кислота

$C_5H_4O_2S$ = 128.1.

CAS — 527-72-0.

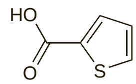

Profile

Thenoic acid has been given orally, rectally, or intranasally as the sodium salt, and orally as the lithium salt, in the treatment of respiratory-tract infections. The monoethanolamine salt has been used sublingually as a mucolytic.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Rhinotrophyl; Soufrane.

Multi-ingredient: ***Fr.:*** Glossithiase; Trophires; Trophires Compose; ***Spain:*** Trophires†.

Thiamphenicol *(BAN, USAN, rINN)*

CB-8053; Dextrosulphenidol; Thiamfenicol; Thiamfenikol; Thiamphénicol; Thiamphenicolum; Thiophenicol; Tiamfenicolo; Tiamfenikol; Tiamfenikoli; Tiamfenikolis; Tianfenicol; Win-5063-2; Win-5063 (racephenicol). (αR,βR)-2,2-Dichloro-N-(β-hydroxy-α-hydroxymethyl-4-methylsulphonylphenethyl)acetamide.

Тиамфеникол

$C_{12}H_{15}Cl_2NO_5S$ = 356.2.

CAS — 15318-45-3 (thiamphenicol); 847-25-6 (racephenicol).

ATC — J01BA02.

ATC Vet — QJ01BA02; QJ51BA02.

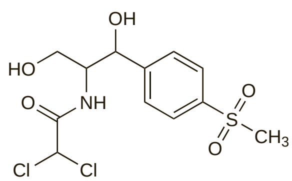

NOTE. Racephenicol, the racemic form of thiamphenicol, is *USAN*.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Thiamphenicol). A fine, white or yellowish-white, crystalline powder or crystals. Slightly soluble in water and in ethyl acetate; sparingly soluble in dehydrated alcohol and in acetone; freely soluble in acetonitrile and in dimethylformamide; very soluble in dimethylacetamide; soluble in methyl alcohol. Protect from light and moisture.

Thiamphenicol Glycinate Hydrochloride

Thiamphenicol Aminoacetate Hydrochloride; Tiamfenicolo Glicinato Cloridrato; Tianfenicol, hidrocloruro del glicinato de.

$C_{14}H_{18}Cl_2N_2O_6S,HCl$ = 449.7.

CAS — 2393-92-2 (thiamphenicol glycinate); 2611-61-2 (thiamphenicol glycinate hydrochloride).

ATC — J01BA02.

ATC Vet — QJ01BA02.

Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for Chloramphenicol, p.240.

Thiamphenicol is probably more liable to cause dose-dependent reversible depression of the bone marrow than chloramphenicol but it is not usually associated with aplastic anaemia. Thiamphenicol also appears to be less likely to cause the 'grey syndrome' in neonates.

Doses of thiamphenicol should be reduced in patients with renal impairment. It is probably not necessary to reduce doses in patients with hepatic impairment.

Interactions

As for Chloramphenicol, p.240.

Although thiamphenicol is not metabolised in the liver and might not be expected to be affected by drugs which induce hepatic enzymes, it is reported to inhibit hepatic microsomal enzymes and may affect the metabolism of other drugs.

Antimicrobial Action

Thiamphenicol has a broad spectrum of activity resembling that of chloramphenicol (p.241). Although in general it is less active than chloramphenicol it is reported to be equally effective, and more actively bactericidal, against *Haemophilus* and *Neisseria* spp.

Cross-resistance occurs between thiamphenicol and chloramphenicol. However, some strains resistant to chloramphenicol may be susceptible to thiamphenicol.

Pharmacokinetics

Thiamphenicol is absorbed from the gastrointestinal tract after oral doses and peak serum concentrations of 3 to 6 micrograms/mL have been achieved about 2 hours after a 500-mg dose.

Thiamphenicol diffuses into the CSF, across the placenta, into breast milk, and penetrates well into the lungs. About 10% is bound to plasma proteins. The half-life of thiamphenicol is around 2 to 3 hours but unlike chloramphenicol the half-life is increased in patients with renal impairment. It is excreted in the urine, about 70% of a dose being excreted in 24 hours as unchanged drug. It undergoes little or no conjugation with glucuronic acid in the liver. A small amount is excreted in the bile and the faeces.

Uses and Administration

Thiamphenicol has been used similarly to chloramphenicol (p.241) in the treatment of susceptible infections, including sexually transmitted diseases. The usual adult oral dose is 1.5 g daily in divided doses; up to 3 g daily has been given initially in severe infections. A daily dose of 30 to 100 mg/kg may be used in children. Equivalent doses, expressed in terms of thiamphenicol base, may be given by intramuscular or intravenous injection as the more water soluble glycinate hydrochloride; 1.26 g of thiamphenicol glycinate hydrochloride is equivalent to about 1 g of thiamphenicol. Doses should be reduced in patients with renal impairment (see below).

For the treatment of gonorrhoea, oral doses of thiamphenicol have ranged from 2.5 g daily for 1 or 2 days through to 2.5 g on the first day followed by 2 g daily on each of 4 subsequent days. The single daily dose may be most appropriate for male patients with uncomplicated gonorrhoea.

Thiamphenicol glycinate hydrochloride may also be given by inhalation, or by endobronchial or intracavitary instillation.

Thiamphenicol has also been used as thiamphenicol glycinate acetylcysteinate, thiamphenicol sodium glycinate isophthalolate, and thiamphenicol palmitate.

Administration in renal impairment. Doses of thiamphenicol should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: 500 mg twice daily
- CC 10 to 30 mL/minute: 500 mg once daily

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Fluimucil Antibiotic; Urfamycine; ***Braz.:*** Glitisol; ***Fr.:*** Thiophenicol; ***Hong Kong:*** Urfamycin; ***Indon.:*** Biothicol; Canicol; Cetathiacol; Comthycol; Conucol; Corsafen; Daiticin; Dexycol; Genicol; Ipibiofen; Kalticol; Lacophen; Lanacol; Nikolam; Nilacol; Nufathiam; Opiphen; Phenobiotic; Promixin; Renamoca; Sendicol; Thiambiotic; Thiamet; Thiamflex; Thiamika; Thiamycin; Thislacol; Troviakol; Urfamycin; Urfekol; Venacol; Zumatab; ***Ital.:*** Fluimucil Antibiotico; Glitisol; ***Mex.:*** Tiofeniclin; ***Rus.:*** Fluimucil Antibiotic (Флуимуцил антибиотик); ***Spain:*** Fluimucil Antibiotico†; Urfamycin†; ***Switz.:*** Urfamycine; ***Thai.:*** Doqua; Thiamcin; Treomycin; Urfamycin; ***Turk.:*** Thiophenicol; Tiofen; Urfamycin.

Multi-ingredient: ***Spain:*** Flumil Antibiotico; ***Thai.:*** Fluimucil Antibiotic.

Thioacetazone *(BAN, rINN)*

Amithiozone; Amitiozon; TBI/698; Tebezonum; Thiacetazone; Thioacétazone; Thioacetazonum; Tiasetazon; Tioacetazona. 4-Acetamidobenzaldehyde thiosemicarbazone.

Тиоацетазон

$C_{10}H_{12}N_4OS$ = 236.3.

CAS — 104-06-3.

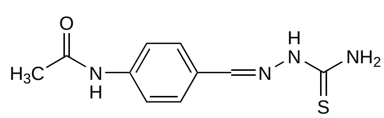

Pharmacopoeias. In *Int.*

Adverse Effects

Gastrointestinal disturbances, hypersensitivity reactions including skin rashes, conjunctivitis, and vertigo are the adverse effects most frequently reported with thioacetazone although the incidence appears to vary between countries. Toxic epidermal necrolysis, exfoliative dermatitis (which has sometimes been fatal), and the Stevens-Johnson syndrome have been reported; the incidence of severe skin reactions is especially high in patients with HIV infection (see below). Thioacetazone may cause bone-marrow depression with leucopenia, agranulocytosis, and thrombocytopenia. Acute haemolytic anaemia may occur and a large percentage of patients will have some minor degree of anaemia. Hepatotoxicity with jaundice may also develop and acute hepatic failure has been reported. Cerebral oedema has been reported. Dose-related ototoxicity may occur rarely.

Incidence of adverse effects. In a 10-year series of 1212 patients with tuberculosis who were treated with a regimen of streptomycin, isoniazid, and thioacetazone, 171 (14%) had adverse reactions associated with thioacetazone. The most common adverse effects were giddiness (10%), occurring mainly when used with streptomycin, and skin rashes (3%) including exfoliation and the Stevens-Johnson syndrome.[1]

1. Pearson CA. Thiacetazone toxicity in the treatment of tuberculosis patients in Nigeria. *J Trop Med Hyg* 1978; **81:** 238–42.

Effects on the nervous system. Acute peripheral neuropathy which occurred in a 50-year-old man on 2 separate occasions within 15 minutes of a dose of thioacetazone may have been due to an allergic reaction.[1]

1. Gupta PK, *et al.* Acute severe peripheral neuropathy due to thiacetazone. *Indian J Tuberc* 1984; **31:** 126–7.

Effects on the skin. A high incidence of severe and sometimes fatal cutaneous hypersensitivity reactions to thioacetazone has been reported in patients with HIV infection being treated for tuberculosis.[1,2] WHO advised that thioacetazone should be avoided in such patients.[3] Unfortunately, thioacetazone has been one of the mainstays of tuberculosis treatment in the developing world because of its relatively low cost.[4] Some have supported a change to rifampicin-based regimens in, for example, parts of Africa with a high incidence of HIV infection.[5] Others have found a lower frequency of fatalities from adverse cutaneous reactions to thioacetazone than reported previously and have suggested that improved management might allow retention of thioacetazone in tuberculosis programmes.[6] This was rejected by other workers who considered that better and more cost-effective regimens were available than those containing thioacetazone.[7] A pragmatic approach may be to adopt a strategy depending upon the prevailing incidence of HIV infection in the population.[8] Thus, where the incidence of HIV infection is high, ethambutol should be substituted for thioacetazone; where the incidence is moderate, routine HIV testing could be used to identify patients at risk; and where the incidence is low, education of patients on the risks of skin reaction would be adequate.

1. Nunn P, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337:** 627–30.
2. Chintu C, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-I. *Arch Dis Child* 1993; **68:** 665–8.
3. Raviglione MC, *et al.* HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment. *Bull WHO* 1992; **70:** 515–26.
4. Nunn P, *et al.* Thiacetazone—avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87:** 578–82.
5. Okwera A, *et al.* Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344:** 1323–8.
6. Ipuge YAI, *et al.* Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346:** 657–60.
7. Elliott AM, *et al.* Treatment of tuberculosis in developing countries. *Lancet* 1995; **346:** 1098–9.
8. van Gorkom J, Kibuga DK. Cost-effectiveness and total costs of three alternative strategies for the prevention and management of severe skin reactions attributable to thiacetazone in the treatment of human immunodeficiency virus positive patients with tuberculosis in Kenya. *Tubercle Lung Dis* 1996; **77:** 30–6.

Hypertrichosis. Hypertrichosis occurred in 2 children receiving thioacetazone.[1]

1. Nair LV, Sugathan P. Thiacetazone induced hypertrichosis. *Indian J Dermatol Venereol* 1982; **48:** 161–3.

Precautions

The efficacy and toxicity of a regimen of treatment which includes thioacetazone should be determined in a community before it is used widely since there appear to be geographical differences.

Thioacetazone should not be given to patients with hepatic impairment. It has also been suggested that, because thioacetazone has a low therapeutic index and is excreted mainly in the urine, it should not be given to patients with renal impairment. Treatment should be stopped if rash or other signs of hypersensitivity occur. It should probably be avoided in HIV-positive patients because they are at increased risk of severe adverse effects (see Effects on the Skin, above).

Interactions

Thioacetazone may enhance the ototoxicity of streptomycin.

Antimicrobial Action

Thioacetazone is bacteriostatic. It is effective against most strains of *Mycobacterium tuberculosis*, although sensitivity varies in different parts of the world.

Thioacetazone is also bacteriostatic against *M. leprae.* Resistance to thioacetazone develops when used alone. Cross-resistance can develop between thioacetazone and ethionamide or protionamide.

Pharmacokinetics

Thioacetazone is absorbed from the gastrointestinal tract and peak plasma concentrations of 1 to 2 micrograms/mL have been obtained about 4 to 5 hours after a 150-mg dose. About 20% of a dose is excreted unchanged in the urine. A half-life of about 12 hours has been reported.

Uses and Administration

Thioacetazone has been used with other antimycobacterials as a first-line drug in the treatment of tuberculosis (p.196). Thioacetazone-containing regimens are less effective than the short-course regimens recommended by WHO but are used in long-term regimens with isoniazid in some developing countries to reduce drug costs. However, thioacetazone is now used as a second-line drug for multidrug-resistant tuberculosis and is not generally recommended for use in HIV-positive patients because of the risk of severe adverse reactions (but see Effects on the Skin, above).

Thioacetazone has been used in the treatment of leprosy (p.176), but WHO now considers that such use is no longer justified.

In the treatment of tuberculosis, thioacetazone has been given orally in doses of 150 mg daily or 2.5 mg/kg daily. Daily use is recommended as the drug is less effective when given intermittently.

Preparations

Proprietary Preparations (details are given in Part 3)
Turk.: Citazon.

Multi-ingredient: ***India:*** Isokin-T Forte.

Thiostrepton

Thiostreptonum; Tiostreptón; Tiostrepton; Tiostreptoni.

Тиострептон

$C_{72}H_{85}N_{19}O_{18}S_5$ = 1664.9.
CAS — 1393-48-2.

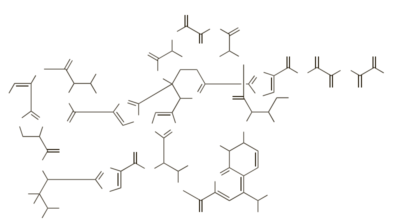

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Thiostrepton). An antibacterial substance produced by the growth of strains of *Streptomyces azureus*. It has a potency of not less than 900 units/mg, calculated on the dried basis. A white to off-white crystalline solid. Practically insoluble in water, in the lower alcohols, in nonpolar organic solvents, and in dilute aqueous acids or alkalis; soluble in glacial acetic acid, in chloroform, in dimethylformamide, in dimethyl sulfoxide, in dioxan, and in pyridine. Store in airtight containers.

Profile

Thiostrepton is an antibacterial produced by strains of *Streptomyces azureus*. It is included in topical antibacterial preparations for veterinary use.

Tiamulin Fumarate *(BANM, USAN, rINNM)*

Fumarato de tiamulina; 81723-hfu; SQ-14055 (tiamulin); SQ-22947 (tiamulin fumarate); Tiamuliinivetyfumaraatti; Tiamuline, Fumarate de; Tiamuline, hydrogénofumarate de; Tiamulin-fumarát; Tiamulini Fumaras; Tiamulini hydrogenofumaras; Tiamulinvätefumarat. 11-Hydroxy-6,7,10,12-tetramethyl-1-oxo-10-vinylperhydro-3a,7-pentanoinden-8-yl (2-diethylaminoethylthio)acetate hydrogen fumarate.

Тиамулина Фумарат

$C_{28}H_{47}NO_4S,C_4H_4O_4$ = 609.8.
CAS — 55297-95-5 (tiamulin); 555297-96-6 (tiamulin fumarate).

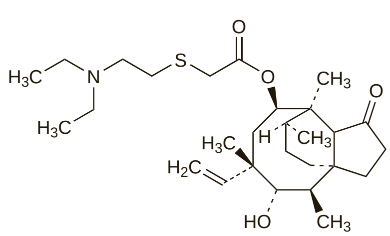

(tiamulin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only. *Eur.* and *US* also include tiamulin for veterinary use only.
Ph. Eur. 6.2 (Tiamulin Hydrogen Fumarate for Veterinary Use; Tiamulin Hydrogen Fumarate BP(Vet) 2008). A white or light yellow, crystalline powder. Soluble in water and in methyl alcohol; freely soluble in dehydrated alcohol. A 1% solution in water has a pH of 3.1 to 4.1. Protect from light.
USP 31 (Tiamulin Fumarate). A 1.0% solution in water has a pH of 3.1 to 4.1. Store in airtight containers. Protect from light.

Profile

Tiamulin fumarate is an antibacterial used in veterinary medicine.

Ticarcillin Monosodium *(BANM, rINNM)*

Ticarcilina monosódica; Ticarcilline Monosodique; Ticarcillinum Mononatricum. Monosodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate monohydrate.

Мононатрий Тикарциллин

$C_{15}H_{15}N_2NaO_6S_2,H_2O$ = 424.4.
CAS — 34787-01-4 (ticarcillin); 3973-04-4 (ticarcillin); 74682-62-5 (ticarcillin monosodium).

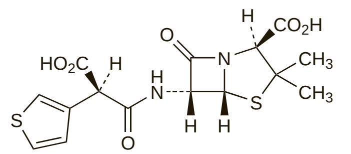

(ticarcillin)

Pharmacopoeias. In *US*.
USP 31 (Ticarcillin Monosodium). Store in airtight containers.

Ticarcillin Sodium *(BANM, rINNM)*

BRL-2288; Natrii Ticarcillinum; Ticarcilina sódica; Ticarcillin Disodium *(USAN)*; Ticarcilline sodique; Ticarcillinum Dinatricum; Ticarcillinum natricum; Tikarcilin disodná sůl; Tikarcilin sodná sůl; Tikarcilino natrio druska; Tikarcillinnatrium; Tikarcillin-nátrium; Tikarsilliininatrium; Tykarcylina sodowa. Disodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate.

Натрий Тикарциллин

$C_{15}H_{14}N_2Na_2O_6S_2$ = 428.4.
CAS — 4697-14-7; 29457-07-6.
ATC — J01CA13.
ATC Vet — QJ01CA13.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Ticarcillin Sodium). A white or slightly yellow, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers at a temperature of 2° to 8°.
USP 31 (Ticarcillin Disodium). A white to pale yellow powder or solid. 1 mg of monograph substance has a potency equivalent to not less than 800 micrograms of ticarcillin, calculated on the anhydrous basis. Freely soluble in water. A 1% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. Ticarcillin sodium has been reported to be incompatible with aminoglycosides.
References.

1. Swenson E, *et al.* Compatibility of ticarcillin disodium clavulanate potassium with commonly used intravenous solutions. *Curr Ther Res* 1990; **48**: 385–94.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35:** 1360–3.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Cholestatic jaundice and hepatitis have been reported when ticarcillin was used with clavulanic acid; the clavulanic acid component has been implicated.

Ticarcillin should be given with caution to patients with renal impairment.

Breast feeding. Although ticarcillin is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. von Kobyletzki D, *et al.* Ticarcillin serum and tissue concentrations in gynecology and obstetrics. *Infection* 1983; **11:** 144–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Effects on the bladder. The Australian Adverse Drug Reactions Advisory Committee had received 15 reports of haemorrhagic cystitis associated with ticarcillin or ticarcillin-clavulanic acid between 1980 and June 2002, mainly in paediatric cystic fibrosis patients.[1] Almost all patients recovered quickly after the withdrawal of ticarcillin.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Haemorrhagic cystitis with ticarcillin in cystic fibrosis patients. *Aust Adverse Drug React Bull* 2002; **21:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 29/07/08)

Effects on the liver. Cholestatic jaundice and hepatitis have been associated with combined preparations of a penicillin and clavulanic acid (see Amoxicillin, p.202) and 2 cases had been reported to the UK CSM with ticarcillin and clavulanic acid.[1] It appeared that the clavulanic acid was probably responsible.

1. Committee on Safety of Medicines/Medicines Control Agency. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)

Sodium content. Each g of ticarcillin sodium contains about 4.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Ticarcillin is bactericidal and has a mode of action and range of activity similar to that of carbenicillin (p.216), but is reported to be 2 to 4 times more active against *Pseudomonas aeruginosa*.

Combinations of ticarcillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae.

The activity of ticarcillin against organisms usually resistant because of the production of certain beta-lactamases is enhanced by clavulanic acid, a beta-lactamase inhibitor. Such organisms have included staphylococci, many Enterobacteriaceae, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of ticarcillin against *Ps. aeruginosa* is not enhanced by clavulanic acid. Resistance to ticarcillin with clavulanic acid has been reported.

There is cross-resistance between carbenicillin and ticarcillin.

◊ References.

1. Pulverer G, *et al.* In-vitro activity of ticarcillin with and without clavulanic acid against clinical isolates of Gram-positive and Gram-negative bacteria. *J Antimicrob Chemother* 1986; **17** (suppl C): 1–5.
2. Masterton RG, *et al.* Timentin resistance. *Lancet* 1987; **ii:** 975–6.
3. Fass RJ, Prior RB. Comparative in vitro activities of piperacillin-tazobactam and ticarcillin-clavulanate. *Antimicrob Agents Chemother* 1989; **33:** 1268–74.
4. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26:** 598–9.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.

Pharmacokinetics

Ticarcillin is not absorbed from the gastrointestinal tract. After intramuscular injection of 1 g peak plasma concentrations in the range of 22 to 35 micrograms/mL are achieved after 0.5 to 1 hour. About 50% of ticarcillin in the circulation is bound to plasma proteins. A plasma half-life of 70 minutes has been reported. A shorter half-life in patients with cystic fibrosis (about 50 minutes in one study) has been attributed to increased renal and non-renal elimination. The half-life is prolonged in neonates and also in patients with renal impairment, especially if hepatic function is also impaired. A half-life of about 15 hours has been reported in severe renal impairment.

Distribution of ticarcillin in the body is similar to that of carbenicillin. Relatively high concentrations have been reported in bile, but ticarcillin is excreted principally by glomerular filtration and tubular secretion. Concentrations of 2 to 4 mg/mL are achieved in the urine after the intramuscular injection of 1 or 2 g. Ticarcillin is metabolised to a limited extent. Up to 90% of a dose is excreted unchanged in the urine, mostly within 6 hours after a dose. Plasma concentrations are enhanced by probenecid.

Ticarcillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Ticarcillin crosses the placenta and small amounts are distributed into breast milk.

Ticarcillin with clavulanic acid. The pharmacokinetics of ticarcillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

◊ References.

1. Staniforth DH, *et al*. Pharmacokinetics of parenteral ticarcillin formulated with clavulanic acid: Timentin. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 123–9.
2. Brogard JM, *et al*. Biliary elimination of ticarcillin plus clavulanic acid (Claventin): experimental and clinical study. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 135–44.
3. de Groot R, *et al*. Pharmacokinetics of ticarcillin in patients with cystic fibrosis: a controlled prospective study. *Clin Pharmacol Ther* 1990; **47:** 73–8.
4. Wang J-P, *et al*. Disposition of drugs in cystic fibrosis IV: mechanisms for enhanced renal clearance of ticarcillin. *Clin Pharmacol Ther* 1993; **54:** 293–302.
5. Burstein AH, *et al*. Ticarcillin-clavulanic acid pharmacokinetics in preterm neonates with presumed sepsis. *Antimicrob Agents Chemother* 1994; **38:** 2024–8.

Uses and Administration

Ticarcillin is a carboxypenicillin used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*. Pseudomonal infections where ticarcillin is used include those in cystic fibrosis (respiratory-tract infections), immunocompromised patients (neutropenia), peritonitis, and septicaemia. Other infections that may be due to *Ps. aeruginosa* include bone and joint infections, meningitis, otitis media (chronic), skin infections (burns, ecthyma gangrenosum, ulceration), and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ticarcillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ticarcillin; 1.1 g of ticarcillin sodium is equivalent to about 1 g of ticarcillin. Doses may need to be reduced in renal impairment (see below).

Ticarcillin is given to adults and children in a dose of 200 to 300 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours.

In adults the use of probenecid 500 mg four times daily by mouth may produce higher and more prolonged plasma concentrations of ticarcillin, but caution is advised in patients with renal impairment.

In the treatment of complicated urinary-tract infections, adults and children may be given a dose of ticarcillin 150 to 200 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours. In uncomplicated urinary-tract infections, the usual adult dose is ticarcillin 1 g every 6 hours intramuscularly or by slow intravenous injection. Children with uncomplicated urinary-tract infections may be given 50 to 100 mg/kg daily in divided doses every 6 or 8 hours. Not more than 2 g of ticarcillin should be injected intramuscularly into one site.

In patients with cystic fibrosis, ticarcillin has been given by nebuliser in the management of respiratory-tract infections.

Ticarcillin is often used with an aminoglycoside but the injections must be given separately because of possible incompatibility.

Ticarcillin with clavulanic acid. Ticarcillin may be used with clavulanic acid (p.250), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. This combination is given by intravenous infusion in a ratio of 15 or 30 parts of ticarcillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses are according to the content of ticarcillin, and usual adult doses range from 9 to 18 g daily in 3 to 6 divided doses.

Administration in renal impairment. Doses of ticarcillin may need to be reduced in patients with renal impairment. After an initial intravenous loading dose of 3 g, the intravenous maintenance dosage should be adjusted according to the patient's creatinine clearance (CC):

- CC 30 to 60 mL/minute: 2 g every 4 hours
- CC 10 to 30 mL/minute: 2 g every 8 hours
- CC less than 10 mL/minute: 2 g every 12 hours (or 1 g intramuscularly every 6 hours)
- CC less than 10 mL/minute in presence of *hepatic impairment*: 2 g intravenously every 24 hours or 1 g intramuscularly every 12 hours
- peritoneal dialysis patients: 3 g every 12 hours
- haemodialysis patients: 2 g every 12 hours plus an additional dose of 3 g after each dialysis session

Preparations

USP 31: Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection; Ticarcillin for Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Ticarpen; ***Neth.:*** Ticarpen; ***Spain:*** Ticarpen; ***USA:*** Ticar.

Multi-ingredient: ***Austral.:*** Timentin; ***Belg.:*** Timentin; ***Braz.:*** Timentin; ***Canad.:*** Timentin; ***Cz.:*** Timentin; ***Fr.:*** Claventin; ***Gr.:*** Timentin; ***Hong Kong:*** Timentin; ***India:*** Timentin; ***Irl.:*** Timentin†; ***Israel:*** Timentin; ***Ital.:*** Clavucar†; Timentin; ***Mex.:*** Timentin; ***Neth.:*** Timentin; ***NZ:*** Timentin; ***Philipp.:*** Timentin; ***Pol.:*** Timentin; ***Rus.:*** Timentin (Тиментин); ***Switz.:*** Timenten†; ***UK:*** Timentin; ***USA:*** Timentin.

Tigecycline *(USAN, rINN)*

GAR-936; TBG-MINO; Tigeciclina; Tigécycline; Tigecyclinum; WAY-GAR-936. (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

Тигециклин

$C_{29}H_{39}N_5O_8$ = 585.6.
CAS — 220620-09-7.
ATC — J01AA12.
ATC Vet — QJ01AA12.

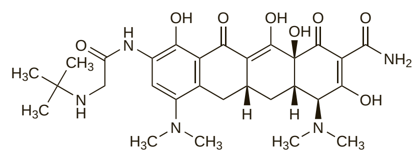

Stability and compatibility. Formulations of tigecycline without excipients should be used immediately after reconstitution; however, a pH-adjusted formulation with lactose monohydrate is available in the USA, and may be stored at room temperature for up to 24 hours after reconstitution (up to 6 hours in the vial and the remaining time in the infusion bag), or up to 45 hours at 2 to 8° after reconstitution and transfer to an infusion bag.

The latter formulation is compatible when given via a Y-site with amikacin, gentamicin, haloperidol, morphine, noradrenaline, piperacillin with tazobactam, propofol, and tobramycin; it is incompatible with diazepam. Both formulations are stated to be compatible with dobutamine, dopamine hydrochloride, lidocaine hydrochloride, potassium chloride, ranitidine hydrochloride, and theophylline, but are incompatible with amphotericin B. The excipient-free formulation should also not be given with chlorpromazine, methylprednisolone, or voriconazole.

Adverse Effects

Tigecycline is a glycylcycline antibacterial with structural similarity to the tetracyclines and adverse effects similar to those of tetracyclines may potentially occur (see p.347). The most common adverse effects associated with tigecycline have been nausea, vomiting, and diarrhoea. Other common adverse effects include abscess, abdominal pain, anorexia, dyspepsia, dizziness, headache, phlebitis, pruritus, and rash. Infection-related serious adverse events, including sepsis or septic shock have been reported; however, a causal relationship could not be established. Raised liver enzymes, bilirubinaemia, increased serum amylase, and increased blood urea nitrogen have also been reported. Local reactions have been reported at the infusion site and thrombocythaemia, anaemia, and leucocytosis may occur. Acute pancreatitis has been reported, usually after at least one week of treatment; symptoms generally resolve on stopping tigecycline. Potentially life-threatening anaphylaxis or anaphylactoid reactions have also been reported.

Precautions

Due to the potential for similar adverse effects, precautions applicable to the tetracyclines (see p.348) should be taken with tigecycline. In particular, tigecycline should not be given in pregnancy as it has caused fetal harm in *animal* studies. Distribution into milk has also been found in *animal* studies. It should also not be given during tooth development (up to 8 years of age) as it may cause permanent tooth discoloration. Caution should be exercised when using tigecycline as monotherapy in patients with complicated intra-abdominal infections secondary to intestinal perforation. Patients taking anticoagulants should be closely monitored as tigecycline may prolong both the prothrombin time and the activated partial thromboplastin time. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (see below).

Antimicrobial Action

Tigecycline is generally bacteriostatic and acts by binding to the 30S subunit of the ribosome and preventing the binding of aminoacyl transfer RNA, similarly to tetracyclines (see p.348). It has activity against a broad range of Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobic organisms. Tigecycline has demonstrated activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci. Gram-negative organisms that have proven susceptible include *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, and some *Klebsiella* spp. Tigecycline also has activity against some anaerobic bacteria including *Bacteroides fragilis* and some other *Bacteroides* spp., *Clostridium perfringens*, and *Peptostreptococcus micros*.

Pharmacokinetics

After intravenous doses tigecycline is widely distributed into the tissues. Binding to plasma proteins has been reported to be 71 to 89% *in vitro*. Tigecycline is not thought to be extensively metabolised, although some trace metabolites have been identified including a glucuronide, an *N*-acetyl metabolite, and a tigecycline epimer. Tigecycline is primarily eliminated (about 60%) via biliary excretion of unchanged drug and some metabolites with a reported half-life of about 42 hours after multiple doses. About 22% is excreted unchanged in the urine.

◊ Reviews.

1. Meagher AK, *et al*. The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; **41** (suppl 5): S333–S340.
2. Rello J. Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. *J Chemother* 2005; **17** (suppl 1): 12–22.
3. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother* 2006; **58:** 256–65.

Uses and Administration

Tigecycline is a glycylcycline antibacterial used in adults for the intravenous treatment of complicated skin and skin structure infections or complicated intra-abdominal infections caused by susceptible organisms. It may also be given empirically. Tigecycline is given by intravenous infusion over 30 to 60 minutes in an initial loading dose of 100 mg followed by 50 mg every 12 hours. For details of reduced dosage to be given in severe hepatic impairment, see below.

◊ Reviews.

1. Zhanel GG, *et al*. The glycylcyclines: a comparative review with the tetracyclines. *Drugs* 2004; **64:** 63–88.
2. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. *Drugs* 2005; **65:** 1317–36.
3. Frampton JE, Curran MP. Tigecycline. *Drugs* 2005; **65:** 2623–35.
4. Kasbekar N. Tigecycline: a new glycylcycline antimicrobial agent. *Am J Health-Syst Pharm* 2006; **63:** 1235–43.
5. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis* 2006; **43:** 518–24.
6. Slover CM, *et al*. Tigecycline: a novel broad-spectrum antimicrobial. *Ann Pharmacother* 2007; **41:** 965–72.
7. Grolman DC. Therapeutic applications of tigecycline in the management of complicated skin and skin structure infections. *Int J Infect Dis* 2007; **11** (suppl 1): S7–S15.
8. Karageorgopoulos DE, *et al*. Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008; **62:** 45–55.
9. Curcio D. Tigecycline for treating bloodstream infections: a critical analysis of the available evidence. *Diagn Microbiol Infect Dis* 2008; **61:** 358–9.
10. Mullangi PK, Pankey GA. Tigecycline in critical care. *Crit Care Clin* 2008; **24:** 365–75.

Administration in hepatic impairment. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (Child-Pugh category C); the initial intravenous loading dose should be 100 mg with reduced maintenance doses of 25 mg every 12 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tygacil; ***Austral.:*** Tygacil; ***Braz.:*** Tygacil; ***Chile:*** Tygacil; ***Cz.:*** Tygacil; ***Gr.:*** Tygacil; ***Hung.:*** Tygacil; ***Indon.:*** Tygacil; ***Malaysia:*** Tygacil; ***Mex.:*** Tygacil; ***Pol.:*** Tygacil; ***Port.:*** Tygacil; ***UK:*** Tygacil; ***USA:*** Tygacil; ***Venez.:*** Tygacil.

Tilmicosin *(BAN, USAN, rINN)*

EL-870; LY-177370; Tilmicosina; Tilmicosine; Tilmicosinum. 4^A-O-De(2,6-dideoxy-3-C-methyl-α-L-*ribo*-hexopyranosyl)-20-deoxo-20-(*cis*-3,5-dimethyl-piperidino)tylosin.

Тильмикозин

$C_{46}H_{80}N_2O_{13}$ = 869.1.
CAS — 108050-54-0.
ATC Vet — QJ01FA91.

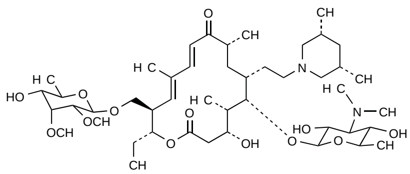

cis-form

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Tilmicosin). White to off-white amorphous solid. Slightly soluble in water and in *n*-hexane. Store at a temperature not exceeding 40°. Protect from light.

Tilmicosin Phosphate *(BANM, USAN, rINNM)*

Fosfato de tilmicosina; Tilmicosine, Phosphate de; Tilmicosini Phosphas.

Тильмикозина Фосфат

$C_{46}H_{80}N_2O_{13},H_3O_4P$ = 967.1.
CAS — 137330-13-3.

Profile

Tilmicosin is a macrolide antibacterial used as the base or the phosphate in veterinary medicine.

Adverse effects. Accidental self-injection of tilmicosin by a farm worker, resulting in asthenia and temporary pulmonary, gastrointestinal, and neuromuscular toxicity has been reported.[1] A review[2] of human exposures to tilmicosin injection reported between March 1992 and March 2005 suggested that the overall risk of serious adverse effects was about 2 cases per million doses. Serious cardiovascular adverse effects, including bradycardia, hypertension, hypotension, tachycardia, and tachypnoea, occurred in 156 of 3168 reported cases and, of these, fatalities occurred in 13.

1. Crown LA, Smith RB. Accidental veterinary antibiotic injection into a farm worker. *Tenn Med* 1999; **92:** 339–40.
2. Veenhuizen MF, *et al.* Analysis of reports of human exposure to Micotil 300 (tilmicosin injection). *J Am Vet Med Assoc* 2006; **229:** 1737–42.

Handling. Contact with tilmicosin should be avoided. It is irritating to the eyes and may cause allergic reactions.

Tobramycin *(BAN, USAN, rINN)*

47663; Nebramycin Factor 6; Tobramicin; Tobramicina; Tobramicinas; Tobramisin; Tobramycine; Tobramycinum; Tobramycyna; Tobramysiini. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)streptamine.

Тобрамицин

$C_{18}H_{37}N_5O_9$ = 467.5.
CAS — 32986-56-4.
ATC — J01GB01; S01AA12.
ATC Vet — QJ01GB01; QS01AA12.

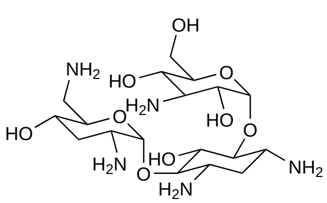

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Tobramycin). A substance produced by *Streptomyces tenebrarius* or obtained by any other means. A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 9.0 to 11.0.

USP 31 (Tobramycin). A white to off-white, hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. Contains not more than 8.0% w/w of water. A 10% solution in water has a pH of 9.0 to 11.0. Store in airtight containers.

Tobramycin Sulfate *(rINNM)*

Sulfato de tobramicina; Tobramycin Sulphate *(BANM)*; Tobramycine, Sulfate de; Tobramycini Sulfas; Tobramycyny siarczan.

Тобрамицина Сульфат

$(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$ = 1425.4.
CAS — 49842-07-1 ($C_{18}H_{37}N_5O_9,xH_2SO_4$); 79645-27-5 ($(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$).
ATC — J01GB01; S01AA12.
ATC Vet — QJ01GB01; QS01AA12.

Pharmacopoeias. In *Pol.* and *US.*

USP 31 (Tobramycin Sulfate). It has a potency of not less than 634 micrograms and not more than 739 micrograms of tobramycin per mg. A 4% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including tobramycin, with beta lactams, see under Gentamicin Sulfate, p.282. Tobramycin is also reported to be incompatible with various other drugs and, as injections have an acid pH, incompatibility with alkaline preparations or with drugs unstable at acid pH may reasonably be expected.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Some studies suggest that tobramycin is slightly less nephrotoxic than gentamicin, but others have not found any significant difference in their effects on the kidneys.

Peak plasma-tobramycin concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) and trough concentrations greater than 2 micrograms/mL should be avoided.

When tobramycin is given by inhalation with other inhaled drugs, they should be given first before the dose of tobramycin. After the first inhaled dose of tobramycin, patients should be monitored for bronchospasm and if it occurs, the test should be repeated using a bronchodilator. Peak flow should be measured before nebulisation and again after it. Caution should be exercised in the presence of severe haemoptysis. Renal function should be monitored before treatment and every six months during use.

Effects on the ear. Reversible vestibular toxicity (ataxia, dizziness, and oscillopsia) occurred in a patient on haemodialysis after about 3 weeks' treatment with inhaled tobramycin for bronchiectasis due to colonisation with *Pseudomonas aeruginosa*.[1]

1. Edson RS, *et al.* Vestibular toxicity due to inhaled tobramycin in a patient with renal insufficiency. *Mayo Clin Proc* 2004; **79:** 1185–91.

Effects on the kidney. Irreversible acute renal failure requiring haemodialysis occurred in a high-risk patient with chronic renal failure after being treated for 4 weeks with inhaled tobramycin for *Pseudomonas aeruginosa* pneumonia.[1]

1. Cannella CA, Wilkinson ST. Acute renal failure associated with inhaled tobramycin. *Am J Health-Syst Pharm* 2006; **63:** 1858–61.

Effects on the liver. A case of possible tobramycin-induced hepatotoxicity was reported in a 20-year-old patient receiving antibacterial treatment for *Pseudomonas aeruginosa* bacteraemia and osteomyelitis. Liver enzyme values started to increase when empirical treatment was changed to intravenous tobramycin and ceftazidime, and markedly increased when the regimen was changed, increasing the dose of tobramycin and replacing ceftazidime with piperacillin/tazobactam and then later aztreonam. Enzyme values began to decrease after all treatment was stopped on day 12.[1]

1. Nisly SA, *et al.* Tobramycin-induced hepatotoxicity. *Ann Pharmacother* 2007; **41:** 2061–5.

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. Tobramycin is reported to be somewhat more active *in vitro* than gentamicin against *Pseudomonas aeruginosa* and less active against *Serratia*, staphylococci, and enterococci; however these differences do not necessarily translate into differences in clinical effectiveness.

Cross-resistance between tobramycin and gentamicin is generally seen, but about 10% of strains resistant to gentamicin are susceptible to tobramycin.

◊ References to activity against *Pseudomonas aeruginosa*.

1. Barclay ML, *et al.* Adaptive resistance to tobramycin in Pseudomonas aeruginosa lung infection in cystic fibrosis. *J Antimicrob Chemother* 1996; **37:** 1155–64.
2. den Hollander JG, *et al.* Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother* 1997; **41:** 95–100.
3. Wu YL, *et al.* Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in Pseudomonas aeruginosa. *J Antimicrob Chemother* 1999; **44:** 389–92.
4. Shawar RM, *et al.* Activities of tobramycin and six other antibiotics against Pseudomonas aeruginosa isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 1999; **43:** 2877–80.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

After intramuscular use of tobramycin, peak plasma concentrations are achieved within 30 to 90 minutes and concentrations of about 4 micrograms/mL have been reported following doses of 1 mg/kg. Usual doses by slow intravenous injection may result in plasma concentrations which briefly exceed 12 micrograms/mL. A plasma half-life of 2 to 3 hours has been reported. Sufficient tobramycin may be absorbed after inhalation to produce systemic adverse effects (see above).

Inhalation. References.

1. Touw DJ, *et al.* Pharmacokinetics of aerosolized tobramycin in adult patients with cystic fibrosis. *Antimicrob Agents Chemother* 1997; **41:** 184–7.
2. Beringer PM, *et al.* Pharmacokinetics of tobramycin in adults with cystic fibrosis: implications for once-daily administration. *Antimicrob Agents Chemother* 2000; **44:** 809–13.

Uses and Administration

Tobramycin is an aminoglycoside antibiotic with actions and uses similar to those of gentamicin (p.284). It is used, usually as the sulfate, particularly in the treatment of pseudomonal infections.

As with gentamicin, tobramycin may be used with penicillins or cephalosporins; the injections should be given separately.

Doses of tobramycin sulfate are expressed in terms of tobramycin base; 1.5 g of tobramycin sulfate is equivalent to about 1 g of tobramycin. Doses are similar to those of gentamicin, with the usual adult dose ranging from 3 to 5 mg/kg daily in 3 or 4 divided doses. In patients with cystic fibrosis, doses of 8 to 10 mg/kg daily in divided doses may be necessary to achieve therapeutic plasma concentrations.

The usual dose for children is 6 to 7.5 mg/kg daily in 3 or 4 divided doses. Premature and full-term neonates may be given 2 mg/kg every 12 hours.

For mild to moderate urinary-tract infections in adults, a dose of 2 to 3 mg/kg once daily may be effective. As with some other aminoglycosides, once-daily dosage has been used successfully in selected patients for the treatment of other infections without increasing toxicity but local guidelines should be consulted for dosage and serum concentrations (see also Once-daily Dosage, under Gentamicin, p.285).

Tobramycin sulfate is given by intramuscular injection, or by intravenous infusion over 20 to 60 minutes in 50 to 100 mL of sodium chloride 0.9% or glucose 5% injection; proportionately less fluid should be given to children. It has also been given slowly by direct intravenous injection.

Treatment should generally be limited to 7 to 10 days, and peak plasma concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) or trough concentrations greater than 2 micrograms/mL should be avoided. In all patients, dosage should be adjusted according to plasma-tobramycin concentrations and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity (see Uses and Administration of Gentamicin Sulfate, p.284).

Tobramycin may be used as a 0.3% eye ointment or eye drops in the treatment of eye infections. It is also given by inhalation in patients with cystic fibrosis to control *Pseudomonas aeruginosa* infections in a dose of 300 mg every 12 hours for 28 days using a suitable nebuliser. Treatment is then stopped for 28 days before being resumed for another treatment period. This cycle may be repeated indefinitely.

◊ Reviews.

1. Cheer SM, *et al.* Inhaled tobramycin (TOBI): a review of its use in the management of pseudomonas aeruginosa infections in patients with cystic fibrosis. *Drugs* 2003; **63:** 2501–20.

Preparations

BP 2008: Tobramycin Injection;
USP 31: Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension; Tobramycin for Injection; Tobramycin Inhalation Solution; Tobramycin Injection; Tobramycin Ophthalmic Ointment; Tobramycin Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Bioptic; Fotex; Gotabiotic; Gotabiotic D; Klonamicin; Oftalbrax†; Radina; Tobi; Tobrabiotic; Tobradosa; Tobragan; Tobranet; Tobrex; Toflamixina; Tuberbut; Xao T; Xibrax; ***Austral.:*** Nebcin; Tobi; Tobrex; ***Austria:*** Brulamycin; Cromycin; Tobi; Tobrasix; Tobrex; ***Belg.:*** Obracin; Tobi; Tobrex; ***Braz.:*** Tobra-M†; Tobracin; Tobragan; Tobramina; Tobranom; Tobrex; Toflamixina†; ***Canad.:*** Nebcin†; Tobi; Tobrex; Tomycine†; ***Chile:*** Tobragan; Tobrex; Tobrin; Xolof; ***Cz.:*** Bramitob; Brulamycin; Tobi; Tobrex; ***Denm.:*** Nebcina; Tobi; Tobrex; ***Fin.:*** Nebcina†; Tobi; Tobrex; Tomycin; ***Fr.:*** Nebcine; Tobi; Tobrex; ***Ger.:*** Brulamycin†; Gernebcin; Tobi; Tobra-cell; Tobramaxin; ***Gr.:*** Colther; Eyebrex; Eyetobrin; Ikobel; Monobracin†; Monotobrin; Nebcin; Thilo-micine; Tobi; Tobrex; ***Hong Kong:*** Nebcin†; Tobrex; Toracin; ***Hung.:*** Brulamycin; Tobi; Tobrex; ***India:*** Ocutob; Tobacin; Tobazon; Tobraneg; ***Indon.:*** Bralifex; Dartobcin; Isotic Tobryne; Tobrex; Tobryne; ***Irl.:*** Nebcin†; Tobi; Tobralex†; ***Israel:*** Nebcin†; Tobi; Tobrex; ***Ital.:*** Bramicil; Bramitob; Nebicina; Tobi; Tobrabact; Tobral; Tobrastill; ***Malaysia:*** Tobrex; ***Mex.:*** Eyebrex; Micitrex; Obry; Tobra†; Tobrex; Trazil; Verbram; ***Neth.:*** Obracin; Tobi; Tobrabact; Tobrex; ***Norw.:*** Nebcina†; Tobi; Tobrex; ***NZ:*** Nebcin; Tobi†; Tobrex; ***Philipp.:*** Ramitop; Tobrex; ***Pol.:*** Tobi; Tobrex; Tobrosopt; ***Port.:*** Bramitob; Distobram†; Tobi; Tobra-Gobens; Tobrex; Tobrexan; Tobridavi; ***Rus.:*** Brulamycin (Бруламицин); Tobrex (Тобрекс); ***S.Afr.:*** Nebcin; Tobrex; ***Singapore:*** Tobrex; ***Spain:*** Tobi; Tobra Gobens; Tobrabact; Tobradistin†; Tobrex; Tobrexan; ***Swed.:*** Nebcina; Tobi; Tobrex; ***Switz.:*** Obracin; Tobi; Tobrex; ***Thai.:*** Tobrex; ***Turk.:*** Thilomaxine; Tobel; Tobrased; Tobrex; Tobsin; ***UK:*** Nebcin†; Tobi; ***USA:*** AkTob; Nebcin†; Tobi; Tobrasol; Tobrex; ***Venez.:*** Poentobral; Tobranax; Tobrasol; Tobrex; Trazil†.

Multi-ingredient: ***Arg.:*** Antibioptal; Bicrinol; Biocort; Bioptic DX; Decadron con Tobramicina; Fotadex; Gotabiotic F; Ingebrax; Klonamicin Compuesto; Larsen; Lotemicin; Polioftal; Radina Dex; Tobrabiotic D; Tobracort; Tobradex; Tobradiclo; Tobragan D; Tobratlas; Toflam; Toflamixina Plus; Xao-Dex†; Xibradex; ***Austria:*** Tobradex; ***Belg.:*** Ocubrax; Tobradex; ***Braz.:*** Tobracin D; Tobracort; Tobradex; ***Canad.:*** Tobradex; ***Chile:*** Poentobral Plus; Tobradex; Tobragan D; Tobrin-D; Todexona; Xolof D; ***Cz.:*** Tobradex; ***Fr.:*** Tobradex; ***Gr.:*** Dexamycin; Eyebrex-Dexa†; Lofoto; O-Biotic; Thilomicine Dex; Tobradex; Tobrafen; ***Hong Kong:*** Tobradex; ***Hung.:*** Ocubrax†; Tobradex; ***India:*** Obrasone; Ocutob-D; Tobazon DM; ***Indon.:*** Bralifex Plus; Isotic Tobrizon; Tobradex; ***Ital.:*** Tobradex; ***Malaysia:*** Tobradex; ***Mex.:*** Obrydex; Obrypre; Tobracort; Tobradex; Trazidex; Trazinac; ***Neth.:*** Tobradex; ***NZ:*** Tobradex; ***Philipp.:*** Tobradex; ***Pol.:*** Tobradex; ***Rus.:*** Tobradex (Тобрадекс); Tobrasone (Тобразон); ***S.Afr.:*** Tobradex; ***Singapore:*** Tobradex; ***Spain:*** Ocubrax; Tobradex; ***Switz.:*** Tobradex; Tobrafen; ***Thai.:*** Tobradex; ***Turk.:*** Ocubrax; ***UK:*** Tobradex; ***USA:*** Tobradex; ***Venez.:*** Poentobral Plus; Tobracort; Tobradex; Tobragan D; Todenac; Todex; Trazidex; Trazinac.

Tosufloxacin *(USAN, rINN)*

A-61827; Abbott-61827; Tosufloxacine; Tosufloxacino; Tosufloxacinum. (±)-7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

Тосуфлоксацин

$C_{19}H_{15}F_3N_4O_3$ = 404.3.

CAS — 100490-36-6 (anhydrous tosufloxacin); 108138-46-1 (anhydrous tosufloxacin); 107097-79-0 (tosufloxacin monohydrate).

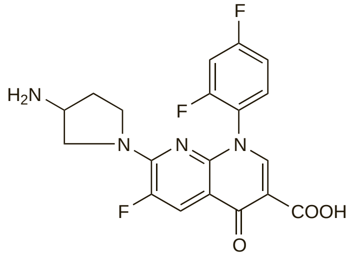

Tosufloxacin Tosilate *(rINNM)*

A-64730; T-3262; Tosilato de tosufloxacino; Tosufloxacin Tosylate; Tosufloxacine, Tosilate de; Tosufloxacini Tosilas. Tosufloxacin toluene-4-sulphonate monohydrate.

Тосуфлоксацина Тозилат

$C_{19}H_{15}F_3N_4O_3,C_7H_8O_3S,H_2O$ = 594.6.
CAS — 115964-29-9; 144742-63-2.

Profile

Tosufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243). It is given orally as the tosilate in the treatment of susceptible infections in usual doses of 300 to 450 mg daily in 2 or 3 divided doses.

For blepharitis, conjunctivitis, corneal ulcers, and other eye infections caused by susceptible strains of bacteria, eye drops containing 0.3% of tosufloxacin tosilate are used.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Ozex.

Trimethoprim *(BAN, USAN, rINN)*

BW-56-72; NSC-106568; Triméthoprime; Trimethoprimum; Trimethoxyprim; Trimetopriimi; Trimetoprim; Trimetoprima; Trimetoprimas. 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine.

Триметоприм

$C_{14}H_{18}N_4O_3$ = 290.3.
CAS — 738-70-5.
ATC — J01EA01.
ATC Vet — QJ01EA01; QJ51EA01.

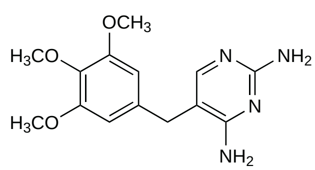

NOTE. Compounded preparations of trimethoprim may be represented by the following names:

- Co-trifamole (*BAN*)—trimethoprim 1 part and sulfamoxole 5 parts (see p.257)
- Co-trimazine (*BAN*)—trimethoprim 1 part and sulfadiazine 5 parts (see p.258)
- Co-trimoxazole (*BAN*)—trimethoprim 1 part and sulfamethoxazole 5 parts (see p.258)
- Co-trimoxazole (*PEN*)—trimethoprim and sulfamethoxazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Trimethoprim). A white or yellowish-white powder. Very slightly soluble in water; slightly soluble in alcohol.

USP 31 (Trimethoprim). White to cream-coloured, odourless crystals or crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone; soluble in benzyl alcohol; practically insoluble in carbon tetrachloride and in ether; sparingly soluble in chloroform and in methyl alcohol. Store in airtight containers. Protect from light.

Trimethoprim Sulfate *(USAN, rINNM)*

BW-72U; Sulfato de trimetoprima; Trimethoprim Sulphate *(BANM)*; Triméthoprime, Sulfate de; Trimethoprimi Sulfas; Trimetoprim Sülfat.

Триметоприма Сульфат

$(C_{14}H_{18}N_4O_3)_2.H_2SO_4$ = 678.7.
CAS — 56585-33-2.

Pharmacopoeias. In *Viet.* and *US.*

USP 31 (Trimethoprim Sulfate). A white to off-white crystalline powder. Soluble in water, in alcohol, in dilute mineral acids, and in fixed alkalis. pH of a 0.05% solution in water is between 7.5 and 8.5. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. UK licensed product information states that trimethoprim injections (containing the lactate) should not be mixed with solutions of sulfonamides because of incompatibility. Although a former such preparation stated that it should not be diluted in chloride-containing infusion solutions, because of the risk of precipitating trimethoprim hydrochloride, others are stated to be compatible with sodium chloride 0.9% and some other chloride-containing solutions including Ringer's solution. Injections are considered compatible with glucose 5% and with sodium lactate.

Adverse Effects and Treatment

Trimethoprim is reasonably well tolerated in general, and the most frequent adverse effects at usual doses are pruritus and skin rash (in about 3 to 7% of patients) and mild gastrointestinal disturbances including nausea, vomiting, and glossitis.

Rarely, more severe effects have been reported. Sulfonamide-like skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Disturbances of liver enzyme values and cholestatic jaundice have been associated with trimethoprim. Rises in serum creatinine and blood-urea nitrogen have been reported although it is unclear whether this represents genuine renal dysfunction or inhibition of tubular secretion of creatinine. Photosensitivity has been reported. Fever is not uncommon but occasionally hypersensitivity reactions may be severe and anaphylaxis and angioedema have been reported. Cases of aseptic meningitis have also occurred.

Trimethoprim may cause a depression of haematopoiesis due to interference of the drug in the metabolism of folic acid, particularly when given over a prolonged period or in high doses. This may manifest as megaloblastic anaemia, or as thrombocytopenia and leucopenia; methaemoglobinaemia has also been seen. Calcium folinate 5 to 15 mg daily by mouth may be given to counter this effect. Trimethoprim is teratogenic in *animals*.

For further information on the adverse effects of trimethoprim when used with sulfamethoxazole, see Co-trimoxazole, p.258.

Effects on the eyes. There have been isolated reports of bilateral anterior uveitis associated with trimethoprim. In 2 such patients,[1,2] the reaction recurred upon rechallenge with trimethoprim. A third patient developed uveitis after co-trimoxazole, and subsequently uveitis with retinal haemorrhage following trimethoprim alone.[3]

1. Gilroy N, *et al.* Trimethoprim-induced aseptic meningitis and uveitis. *Lancet* 1997; **350:** 112.
2. Arola O, *et al.* Arthritis, uveitis, and Stevens-Johnson syndrome induced by trimethoprim. *Lancet* 1998; **351:** 1102.
3. Kristinsson JK, *et al.* Bilateral anterior uveitis and retinal haemorrhages after administration of trimethoprim. *Acta Ophthalmol Scand* 1997; **75:** 314–15.

Hyperkalaemia. Trimethoprim has been reported to induce hyperkalaemia,[1] particularly in HIV-infected patients being treated for pneumocystis pneumonia or in the elderly. The hyperkalaemia may be due to amiloride-like potassium-sparing properties of trimethoprim, and may be potentiated by ACE inhibitors.

1. Perazella MA. Trimethoprim-induced hyperkalaemia: clinical data, mechanism, prevention and management. *Drug Safety* 2000; **22:** 227–36.

Precautions

Trimethoprim should not be given to patients with a history of hypersensitivity to the drug, and it should be stopped if a skin rash appears. Care is necessary in giving trimethoprim to patients with renal impairment to avoid accumulation and toxicity: it should not be given in severe renal impairment unless blood concentrations can be monitored. It should be used with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim.

It is suggested that regular haematological examination should be made during prolonged courses of treatment although the *BNF* considers evidence of their practical value to be unsatisfactory; patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Trimethoprim should not usually be given to patients with serious haematological disorders and particularly not in megaloblastic anaemia secondary to folate depletion. Care should be taken in patients with actual, or possible, folate deficiency and use of folinic acid should be considered. Trimethoprim should be avoided during pregnancy. Elderly patients may be more susceptible to adverse effects and a lower dosage may be advisable.

Trimethoprim may interfere with some diagnostic tests, including serum-methotrexate assay where dihydrofolate reductase is used and the Jaffé reaction for creatinine.

For further information on precautions for trimethoprim given with sulfamethoxazole, see Co-trimoxazole, p.258.

Breast feeding. Trimethoprim appears in breast milk and the US licensed product information has stated that care is required when it is used in breast-feeding mothers.

The American Academy of Pediatrics considers trimethoprim, when given with sulfamethoxazole, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Fragile X syndrome. A warning that trimethoprim and other folate antagonists should be avoided in children with the fragile X chromosome which is associated with mental retardation and is folate sensitive.[1]

1. Hecht F, Glover TW. Antibiotics containing trimethoprim and the fragile X chromosome. *N Engl J Med* 1983; **308:** 285–6.

Porphyria. Trimethoprim has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Trimethoprim may increase serum concentrations and potentiate the effect of a number of drugs, including phenytoin, digoxin, procainamide, rosiglitazone, and repaglinide. The effect may be due to competitive inhibition of renal excretion, decreased metabolism, or both. It has been suggested that trimethoprim may potentiate the effects of warfarin. Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine, and lamivudine. Trimethoprim and dapsone increase each other's serum concentrations, whereas rifampicin may decrease trimethoprim concentrations.

An increased risk of nephrotoxicity has been reported with the use of trimethoprim or co-trimoxazole and ciclosporin. Intravenous use of trimethoprim and sulfonamides may reduce ciclosporin concentrations in blood. Hyponatraemia has been reported in patients given trimethoprim with diuretics. An increased risk of thrombocytopenia has been seen in elderly patients given co-trimoxazole with diuretics, although it is unclear which component of the antibacterial is responsible.

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression, and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Severe hyperkalaemia has been noted in patients given trimethoprim (or co-trimoxazole) together with an ACE inhibitor.

Antimicrobial Action

Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. It acts in the same metabolic pathway as the sulfonamides. It exerts its selective action because of a far greater affinity for the bacterial than the mammalian enzyme. Trimethoprim may be bacteriostatic or bactericidal depending on growth conditions; pus, for example, may inhibit the action of trimethoprim because of the presence of thymine and thymidine.

Spectrum of activity. Trimethoprim is active against many Gram-negative and Gram-positive aerobes, as well as some protozoa. The following species are usually susceptible (but see also Resistance, below).

Many Gram-positive cocci are sensitive, including *Staphylococcus aureus*, streptococci including *Streptococcus pyogenes*, *Str. pneumoniae*, and the viridans streptococci, and to a variable extent enterococci, although their sensitivity is reduced in the presence of folate.

Other sensitive Gram-positive organisms include strains of *Listeria*, *Corynebacterium diphtheriae*, and the Gram-positive bacilli.

Among the Gram-negative organisms, most of the Enterobacteriaceae are susceptible, or moderately so, including *Citrobacter*, *Enterobacter*, *Escherichia coli*, *Hafnia*, *Klebsiella*, *Proteus mirabilis*, *Providencia*, *Salmonella*, some *Serratia*, *Shigella*, and *Yersinia*. *Legionella* and *Vibrio* are also sensitive, and so are *Haemophilus influenzae* and *H. ducreyi*.

Anaerobic species are usually resistant, and so, to varying degrees are *Brucella*, *Neisseria*, and *Nocardia*. *Mycobacterium tuberculosis* is resistant although *M. marinum* may not be. *Pseudomonas aeruginosa* is resistant, and so are the Chlamydiaceae, Mycoplasma spp., and Rickettsia spp., as well as the spirochaetes.

Trimethoprim has some activity against *Pneumocystis jirovecii* and against some protozoa such as *Naegleria*, *Plasmodium*, and *Toxoplasma*.

Activity with other antimicrobials. Because their modes of action are complementary, affecting different stages in folate metabolism, a potent synergistic effect exists between trimethoprim and sulfonamides against many organisms *in vitro*.

Fixed-dose combinations of trimethoprim with various sulfonamides are available, of which co-trimoxazole (trimethoprim with sulfamethoxazole in a 1:5 mixture) is the most widely used. For further details on the antimicrobial action of co-trimoxazole, see p.259.

Synergy has also been reported with rifampicin, and with the polymyxins.

Resistance. Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid-mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants which are intrinsically resistant to trimethoprim because they depend on exogenous thymine and thymidine for growth. Despite fears of a rapid increase in resistance if trimethoprim was used alone there is little evidence that this has been any worse than in areas where it has been used in combination with sulfonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among the Enterobacteriaceae.

◊ References.

1. Huovinen P, *et al.* Trimethoprim and sulfonamide resistance. *Antimicrob Agents Chemother* 1995; **39:** 279–89.

Pharmacokinetics

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation occur about 1 to 4 hours after an oral dose; peak plasma concentrations of about 1 microgram/mL have been reported after a single dose of 100 mg. About 45% is bound to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions; concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in serum. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8 to 10 hours in adults and somewhat less in children, but is prolonged in severe renal impairment and in neonates, whose renal function is immature.

Trimethoprim is excreted primarily by the kidneys through glomerular filtration and tubular secretion. About 10 to 20% of trimethoprim is metabolised in the liver and small amounts are excreted in the faeces via the bile, but most, about 40 to 60% of a dose, is excreted in urine, predominantly as unchanged drug, within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Uses and Administration

Trimethoprim is a diaminopyrimidine antibacterial that is used for the treatment of infections due to sensitive organisms, including gastro-enteritis and respiratory-tract infections, and in particular for the treatment and prophylaxis of urinary-tract infections. For details of these infections and their treatment, see Choice of Antibacterial, p.162.

Trimethoprim is also used with sulfonamides. The most common combination is co-trimoxazole (trimethoprim with sulfamethoxazole) (p.258). Other combinations are co-trimazine (with sulfadiazine) and co-trifamole (with sulfamoxole); trimethoprim has also been used with sulfamerazine, sulfametopyrazine, sulfametrole, and sulfamethoxypyridazine, and, in veterinary practice, with sulfadoxine, sulfaquinoxaline, sulfatroxazole, sulfadimethoxine, sulfadimidine, or sulfafurazole.

Trimethoprim with sulfamethoxazole (co-trimoxazole) or with dapsone is used in the management of pneumocystis pneumonia (p.521).

The usual adult oral dose of trimethoprim in acute infection is 100 or 200 mg twice daily; doses of 200 or 300 mg daily as a single dose are also used. For the dosage of trimethoprim when given with sulfamethoxazole, see under Co-trimoxazole, p.259. Up to 20 mg/kg daily may be given in combination with dapsone for the treatment of pneumocystis pneumonia.

Children may be given 6 to 8 mg/kg daily of trimethoprim in 2 divided doses: regimens for children are, 6 to 12 years, 100 mg twice daily; 6 months to 5 years, 50 mg twice daily; 6 weeks to 5 months, 25 mg twice daily.

For long-term prophylaxis the usual dose is 100 mg at night for adults; children aged 6 to 12 years may be given 50 mg at night and those aged 6 months to 5 years, 25 mg at night. Alternatively, children may be given a dose of 1 to 2 mg/kg at night.

Trimethoprim is also given intravenously by injection or infusion as the lactate although doses are in terms of the base. The usual dose is 200 mg every 12 hours in adults; children may be given 8 mg/kg daily in 2 or 3 divided doses. Initial doses may be higher or given more frequently in severely ill patients.

Care should be taken in patients with moderate to severe renal impairment and doses generally should be reduced (see below).

Trimethoprim with polymyxin B has been used topically in the treatment and prophylaxis of eye infections. Trimethoprim sulfate and trimethoprim hydrochloride are also used.

Administration. *SINGLE-DOSE THERAPY.* Although there are obvious advantages to a single-dose regimen, one study[1] found that there was about a 1 in 4 risk of recurrence of urinary-tract infection within 10 days in 50 children given, according to age, a single dose of 75 to 450 mg of trimethoprim. The problems with a single-dose regimen were confirmed by others[2] in a study involving 344 evaluated cases of cystitis in 306 women. Only 122 of 173 cases treated with trimethoprim 320 mg as a single dose were evaluated as cured after 5 weeks, compared with 149 of 171 given 160 mg twice daily for 1 week (71 versus 87%). Again, these results suggest that about 1 patient in 4 would have to be re-treated.

1. Nolan T, *et al.* Single dose trimethoprim for urinary tract infection. *Arch Dis Child* 1989; **64:** 581–6.
2. Österberg E, *et al.* Efficacy of single-dose versus seven-day trimethoprim treatment of cystitis in women: a randomized double-blind study. *J Infect Dis* 1990; **161:** 942–7.

Administration in renal impairment. Doses of trimethoprim should generally be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 15 to 27 mL/minute: normal dose for 3 days reduced to one-half thereafter
- CC below 15 mL/minute: half the normal dose from the start of treatment

Plasma concentrations should be monitored in patients with severe renal impairment.

Preparations

BP 2008: Co-trimoxazole Intravenous Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; Trimethoprim Oral Suspension; Trimethoprim Tablets;
USP 31: Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution; Sul-

famethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Trimethoprim Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Alprim; Triprim; ***Austria:*** Motrim; Solotrim; Triprim; Wellcoprim; ***Canad.:*** Proloprim†; ***Cz.:*** InfectoTrimet†; Triprim; ***Denm.:*** Monotrim; Trimopan; ***Fin.:*** Trimetin; Trimex; Trimopan; ***Fr.:*** Wellcoprim†; ***Ger.:*** InfectoTrimet; TMP†; ***Irl.:*** Ipral†; Monotrim†; ***Malaysia:*** Alprim; ***Neth.:*** Monotrim; Wellcoprim†; ***NZ:*** TMP; Triprim†; ***Pol.:*** Trimesan; Urotrim; ***S.Afr.:*** Purium; Triprim†; ***Singapore:*** Alprim; ***Spain:*** Tediprima; ***Swed.:*** Idotrim; ***Switz.:*** Monotrim†; ***Thai.:*** Utisept; ***UAE:*** Trimol-A; ***UK:*** Monotrim; Trimopan; ***USA:*** Primsol; Proloprim; Trimpex.

Multi-ingredient: ***Arg.:*** Adrenol; Bacti-Uril; Bacticel; Bactrim; Bactrim Balsamico; Cotrizol-G; Danferane; Diocla†; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Neoftalm; Neoftalm Dexa; Neolag; Netocur; Netocur Balsamico; Neumobacticel; Novidrine; Rifaprim; Ritroprim†; Sulfagrand; Trimepol; Trimepol D; Tritenk; Urisept NF; Uro-Bactrim†; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Lidaprim; Oecotrim; Polytrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Ophtalmotrim†; Polytrim; Steroprim†; ***Braz.:*** Assepium; Assepium Balsamico; Bac-Sulfitrin; Bacfar; Bacprotin; Bacris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Benectrin Balsamico; Binoctrin†; Clotrizol†; Diazol; Dientrin; Dispeptrin; Duoctrin†; Ectrin; Ectrin Balsamico; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Metoprin Balsamico; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Selectrin Balsamico; Septiolan†; Teutrin; Tricban; Triglobe; Trimexazol; Trimezol†; Uro-Baxapril†; Uroctrin; Uropol; ***Canad.:*** Apo-Sulfatrim; Coptin; Novo-Trimel; Nu-Cotrimox; PMS-Polytrimethoprim; Polytrim; Septra; ***Chile:*** Bacterol; Bactrimel; Entero Micinovo; Introcin†; Septrin; Trelibec; Uro-Micinovo; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; Ditrim; Trimetin Duplo; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Berlocombin†; Cotrim; Cotrim-Diolan; CotrimHefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Lidaprim; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Lidaprim; Septrin; ***Hung.:*** Cotripharm; Oftalmotrim†; Potesept†; Sumetrolim; ***India:*** Aubril; Bactrim; Ciplin; Colizole; Cotrimol†; Oriprim; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.:*** Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim; Cotrimol; Dumotrim; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim; Meprotrin; Nufaprim; Ottoprim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim; Sultrimmix; Trimezol; Triminex; Trimoxsul; Trixzol; Trizole; Ulfaprim; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.:*** Duobact†; Septrin; ***Israel:*** Diseptyl; Resprim; Septrin; ***Ital.:*** Abacin†; Bactrim; Chemitrim; Eusaprim; Gantrim†; Lidaprim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Balin; Baserin†; Beaglobe; Chemix; Cotrim; Oftalmotrim; Resprim; Triglobe†; Trimexazole; Trisulprim†; Trizine; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver; Bactrim; Bactrim Compositum; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Kelfiprim†; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octex; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Rifaprim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimexole Compositum; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Lidatrim; Polytrim; Sulfotrim; ***Norw.:*** Bactrim; Trimetoprim-Sulfa†; ***NZ:*** Apo-Sulfatrim; Trisul; ***Philipp.:*** Bacidal; Bactille; Bactrim; Bacxal; Baczole; Bantizol; Chromo-Z; Combi-Methoxan; Costazole; Cozole; Drilozole; Fedimed; Forteprim; Globaxol; Ivatrim; Kassemox; Lictora; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Synermed; Triforam; Triglobe; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizine; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Oftalmotrim; Septrin; ***Rus.:*** Biseptol (Бисептол); Lidaprim (Лидаприм); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Polytrim†; Purbac; Septran; Spectrim; Supristol†; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; Balin; BS†; Chemix; Chemoprim; Co-Trimexazole; Dhatrin; Septrin†; Suprim; Trimaxazole; Trimezole†; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncomega†; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Busetal†; Cotrazol; Eduprim Mucolitico; Eduprim†; Gobens Trim; Momentol; Neumopectolina†; Oftalmotrim; Oftalmotrim Dexa†; Otix; Pulmo Menal†; Pulmosterin Duo; Septrin; Soltrim; ***Swed.:*** Bactrim; Eusaprim; Trimin sulfa†; ***Switz.:*** Agoprim†; Bactrim; Cotrim; Escoprim; Groprim; Lagatrim; Mediprim; Nopil; Sigaprim†; Supracombin†; ***Thai.:*** Actin; Bacin; Bacta†; Bactrim; Baczole; Chemoprim†; Co-Tasian; Co-Trimed; Conprim; Cotamox; Ko-Cap; Ko-Kure; Ladar; Lastrim; Letus; Lidaprim†; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Primoptic†; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Oftalmotrim; Polycilline; Polytrim; Septrin; Sulfatrim; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Polytrim†; Septrin; ***USA:*** Bactrim; Cotrim; Polytrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

Troleandomycin *(BAN, USAN, rINN)*

NSC-108166; Triacetyloleandomycin; Troleandomicina; Troleandomisin; Troléandomycine; Troleandomycinum; Troleandomysiini. The triacetyl ester of oleandomycin .

Тролеандомицин

$C_{41}H_{67}NO_{15}$ = 814.0.

CAS — 2751-09-9.

ATC — J01FA08.

ATC Vet — QJ01FA08.

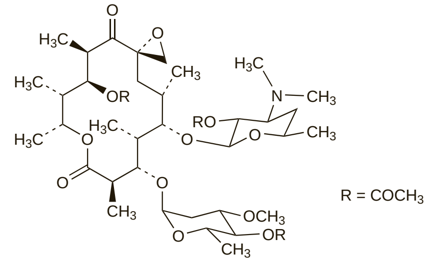

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Troleandomycin). A white, odourless, crystalline powder. It contains the equivalent of not less than 750 micrograms of oleandomycin per mg. Slightly soluble in water and in ether; freely soluble in alcohol; soluble in chloroform. A 10% solution in alcohol and water (1:1) has a pH of 7.0 to 8.5. Store in airtight containers.

Profile

Troleandomycin is a prodrug of the macrolide antibacterial oleandomycin that has actions similar to those of erythromycin (p.269). It has been given orally in the treatment of susceptible infections although more effective antibacterials are generally preferred.

Preparations

USP 31: Troleandomycin Capsules.

Proprietary Preparations (details are given in Part 3)
Ital.: Triocetin†; ***Turk.:*** Tekmisin; ***USA:*** TAO†.

Trospectomycin Sulfate *(USAN, rINNM)*

Sulfato de trospectomicina; Trospectomycin Sulphate *(BANM)*; Trospectomycine, Sulfate de; Trospectomycini Sulfas; U-63366 (trospectomycin); U-63366F. (2*R*,4a*R*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-2-Butyl-4a,7,9-trihydroxy-6,8-bis(methylamino)perhydropyrano[2,3-*b*][1,4]benzodioxin-4-one sulphate pentahydrate.

Тросопектомицина Сульфат

$C_{17}H_{30}N_2O_7,H_2SO_4,5H_2O$ = 562.6.

CAS — 88669-04-9 (trospectomycin); 88851-61-0 (trospectomycin sulfate).

Profile

Trospectomycin is a water-soluble derivative of spectinomycin (p.332) but is more active against Gram-positive organisms, *Haemophilus influenzae*, and *Chlamydia trachomatis* as well as *Neisseria*. It has been investigated in various infections and given as the sulfate intravenously or intramuscularly. Reported adverse effects include perioral paraesthesia, pain at the injection site, nausea, and dizziness.

Trovafloxacin Mesilate *(rINNM)*

CP-99219-27; CP-99219 (trovafloxacin); Mesilato de trovafloxacino; Trovafloxacin Mesylate *(USAN)*; Trovafloxacine, Mésilate de; Trovafloxacini Mesilas. 7-[(1*R*,5*S*,6*S*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulphonate.

Тровафлоксацина Мезилат

$C_{20}H_{15}F_3N_4O_3,CH_4O_3S$ = 512.5.

CAS — 147059-72-1 (trovafloxacin); 147059-75-4 (trovafloxacin mesilate).

ATC — J01MA13.

ATC Vet — QJ01MA13.

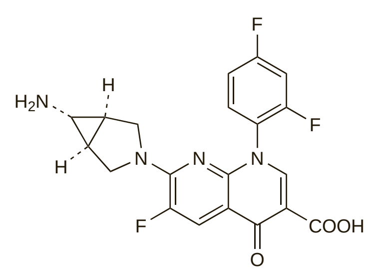

(trovafloxacin)

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Dizziness was the most common adverse effect reported with trovafloxacin.

Trovafloxacin preparations have been withdrawn worldwide after reports of unpredictable severe hepatic adverse effects, including some fatalities. Symptomatic pancreatitis was also reported.

Antimicrobial Action

As for Ciprofloxacin, p.246. It is more active against pneumococci.

Pharmacokinetics

Trovafloxacin is readily absorbed from the gastrointestinal tract after an oral dose, peak plasma concentrations occurring after about 1 to 2 hours. After intravenous use, alatrofloxacin is rapidly converted to trovafloxacin. Oral bioavailability is 88%. Trovafloxacin is widely distributed into body tissues and is about 76% bound to plasma proteins. It appears in breast milk.

The serum half-life of trovafloxacin ranges from about 9 to 12 hours. Trovafloxacin is metabolised by conjugation, 13% of a dose appearing in the urine as the glucuronide and 9% in the faeces as the *N*-acetyl metabolite; other metabolites appear in both the urine and faeces in minor amounts, but about 50% of an oral dose is excreted unchanged, mainly in the faeces but also in the urine.

Uses and Administration

Trovafloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247). It was given orally as the mesilate for the treatment of susceptible infections. The prodrug alatrofloxacin (p.200) was used as the mesilate for intravenous infusion.

Trovafloxacin and alatrofloxacin preparations have been withdrawn worldwide after reports of unpredictable severe hepatic adverse effects, including some fatalities.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Trovan†; ***Gr.:*** Trovan†; ***Mex.:*** Trovan†; ***USA:*** Trovan†.

Tulathromycin *(USAN, rINN)*

CP-472295 (component A); CP-547272 (component B); Tulathromycine; Tulathromycinum; Tulatromicina.

Тулатромицин

$C_{41}H_{79}N_3O_{12}$ = 806.1.

CAS — 217500-96-4 (component A); 280755-12-6 (component B).

ATC Vet — QJ01FA94.

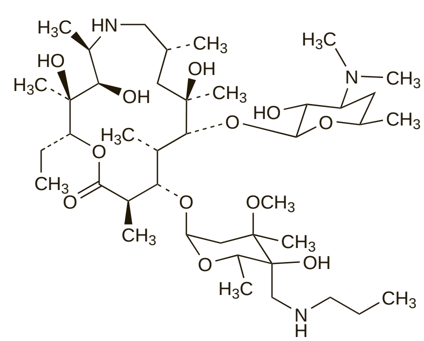

(tulathromycin A)

Profile

Tulathromycin is a macrolide antibacterial used in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Tylosin *(BAN, rINN)*

Tilosina; Tilozin; Tylosiini; Tylosine; Tylosinum; Tylozyna.

Тилозин

$C_{46}H_{77}NO_{17}$ = 916.1.

CAS — 1401-69-0.

ATC Vet — QJ01FA90; QJ51FA90.

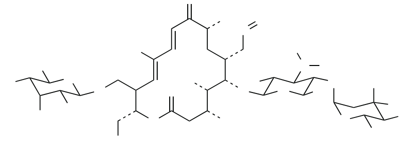

(tylosin A)

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeias. In *Eur.* (see p.vii) and *US*, both for veterinary use.

Ph. Eur. 6.2 (Tylosin for Veterinary Use; Tylosin BP 2008; Tylosin BP(Vet) 2008). A mixture of macrolide antibiotics produced by a strain of *Streptomyces fradiae* or by any other means. The main component of the mixture is tylosin A, but tylosin B (desmycosin), tylosin C (macrocin), and tylosin D (relomycin) may also be present. An almost white or slightly yellow powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane. It dissolves in dilute solutions of mineral acids. A 2.5% suspension in water has a pH of 8.5 to 10.5. Protect from light.

USP 31 (Tylosin). A macrolide antibiotic substance or mixture of such substances produced by the growth of *Streptomyces fradiae* or by any other means. A white to buff-coloured powder. Slightly soluble in water; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; freely soluble in methyl alcohol. It loses not more than 5% of its weight on drying. Protect from light, moisture, and temperatures exceeding 40°.

Tylosin Tartrate *(BANM, rINNM)*

Tartrato de tilosina; Tilozin-tartarát; Tylosiinitartraatti; Tylosin tartarát; Tylosine, tartrate de; Tylosini tartras; Tylosintartrat; Tylozyny winian.

Тилозина Тартрат

$(C_{46}H_{77}NO_{17})_2,C_4H_6O_6$ = 1982.3.

CAS — 1405-54-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use.

Ph. Eur. 6.2 (Tylosin Tartrate for Veterinary Use; Tylosin Tartrate BP 2008; Tylosin Tartrate BP(Vet) 2008). An almost white or slightly yellow hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in dehydrated alcohol. It dissolves in dilute solutions of mineral acids. A 2.5% solution in water has a pH of 5.0 to 7.2. Store in airtight containers. Protect from light.

USP 31 (Tylosin Tartrate). A tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae*, or by any other means. Its potency is not less than 800 micrograms of tylosin per mg, calculated on the dried basis.

An almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids. pH of a 2.5% solution in water is between 5.0 and 7.2. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Tylosin is a macrolide antibacterial with actions similar to those of erythromycin (p.269). Tylosin and its phosphate and tartrate salts are used in veterinary medicine in the prophylaxis and treatment of infections caused by susceptible organisms.

Tylosin and tylosin phosphate have been added to animal feeding stuffs as growth promotors for pigs.

Tylvalosin Tartrate *(USAN, rINNM)*

Acetyl Isovaleryl Tylosin Tartrate; Acetylisovaleryltylosin Tartrate; Tartrato de tilvalosina; Tylvalosine, Tartrate de; Tylvalosini Tartras. (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-Deoxy-2,3-di-*O*-methyl-β-*D*-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Тильвалозина Тартрат

$C_{53}H_{87}NO_{19},xC_4H_6O_6$.

CAS — 63409-12-1 (tylvalosin); 63428-13-7 (tylvalosin tartrate).

ATC Vet — QJ01FA92.

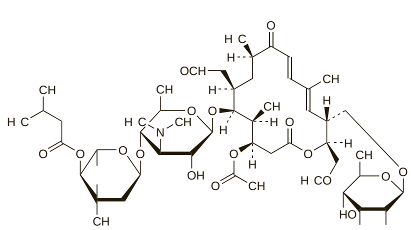

(tylvalosin)

Profile

Tylvalosin is a derivative of tylosin (p.357) and is used similarly as the tartrate in veterinary medicine.

Tyrothricin *(BAN, rINN)*

Tirotricina; Tirotricinas; Tirotrisin; Tyrothricine; Tyrothricinum; Tyrotricin; Tyrotrisiini.

Тиротрицин

CAS — 1404-88-2.

ATC — D06AX08; R02AB02; S01AA05.

ATC Vet — QD06AX08; QR02AB02; QS01AA05.

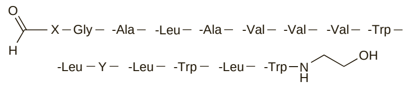

Gramicidin	Mol. Formula	X	Y
A1	C H N O	-Val	-Trp
A2	C H N O	-Ile	-Trp
C1	C H N O	-Val	-Tyr
C2	C H N O	-Ile	-Tyr

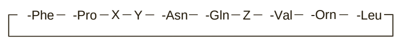

Tyrocidin	Mol. Formula	X	Y	Z
A	C H N O	-Phe	-Phe	-Tyr
B	C H N O	-Trp	-Phe	-Tyr
C	C H N O	-Trp	-Trp	-Tyr
D	C H N O	-Trp	-Trp	-Trp
E	C H N O	-Phe	-Phe	-Phe

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Tyrothricin). A mixture of antimicrobial linear and cyclic polypeptides, isolated from the fermentation broth of *Bacillus brevis*. It consists mainly of gramicidins and tyrocidins; other related compounds may be present in smaller amounts. The potency is 180 to 280 international units/mg, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Tyrothricin). An antibacterial substance produced by the growth of *Bacillus brevis*. It is a mixture consisting chiefly of gramicidin and tyrocidine, the latter being usually present as the hydrochloride. Store in airtight containers.

Adverse Effects and Precautions

Tyrothricin is too toxic to be used systemically; effects that have been reported include hepatic and renal toxicity as well as Stevens-Johnson syndrome. It damages the sensory epithelium of the nose and instances of prolonged loss of smell have occurred after its use as a nasal spray or instillation. Tyrothricin should not be instilled into the nasal cavities or into closed body cavities.

Uses and Administration

Tyrothricin is unsuitable for systemic use. It is active *in vitro* against many Gram-positive bacteria and has been used either alone or with other antibacterials in the local treatment of infections mainly of the skin and mouth.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Codetricine†; ***Ger.:*** Tyrosur; ***Gr.:*** Triciderm; ***Hong Kong:*** Tyrosur†; ***Ital.:*** Faringotricina; Hydrotricine; Rinotricina; ***Port.:*** Hydrotricine; ***Turk.:*** Hydrotricine.

Multi-ingredient: ***Arg.:*** Algiodent; Aseptobron Caramelos; Bagociletas; Biotaer an Caramelos; Biotaer Gamma†; Biotaer Nebulizable; Biotaer Ultrason Nebulizable†; Bucotricin; Caramelos Antibioticos; Caramelos Antibioticos Bucoangin†; Caramelos Antibioticos Lefmar; Collubiazol; Fanaletas; Filotricin A; Fonergine; Gineseptina†; Oralsone C; Pulmosan Caramelos; Solumerin; Suavisan†; Sulfanoral T; Tavinex; Vagicural; Vagisan; Vagisan Compuesto; Vulnofilin Compuesto†; ***Austria:*** Dorithricin; Gingivan; Lemocin; Limexx; Neocones; Tyrothricin comp; Tyrothricin compositum; ***Belg.:*** Lemocin; Pantricine†; Tricidine†; Tyro-Drops; ***Braz.:*** Amidalin†; Amigdagen; Amigdalol; Amigdamicin†; Anginotricin; Auritricin; Colpagex N; Colpolase; Dermosed†; Gargotan†; Gynax-N; Gyrol†; Lacto Vagin†; Larintil†; Malvatricin; Malvatricin Ginecologico; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Mentozil†; Otovix†; Oturga; Passilin†; Tirotrin†; Trivagel N; Vagitrin-N; ***Canad.:*** Antibiotic Cold Sore Ointment; Soropon; ***Cz.:*** Dr Rentschler Halstabletten†; ***Fr.:*** Broncorinol rhinites†; Codetricine vitamine C†; Collunovar†; Ergix†; Veybirol-Tyrothricine†; ***Ger.:*** Anginomycin†; Dorithricin Limone†; Dorithricin Original; Inspirol Halsschmerztabletten†; Lemocin; Nordathricin N†; Trachisan†; Tyrosur; ***Gr.:*** Oulogram; Trachisan; ***Hong Kong:*** Deq; Trachisan†; Tyricine; Tyrocaine; Tyrothricin Co; ***Hung.:*** Dorithricin; Tyrosur; ***India:*** Tytin; ***Indon.:*** Lemocin; ***Irl.:*** Tyrozets; ***Israel:*** Acnex†; Kalgaron; Lemocin; Rafathricin with Benzocaine; ***Ital.:*** Bio-Arscolloid; Deltavagin; Furotricina; Golamixin; Kinogen; Rinocidina; ***Malaysia:*** Deq; Trachisan†; Upha Lozenges; ***Mex.:*** Angenovag; ***Port.:*** Afonina; Mebocaina; Medifon; Mentocaina R; Oralbiotico; ***Singapore:*** Beathricin; Deq; Dorithricin; Trachisan; ***Spain:*** Anginovag; Bucometasana; Cicatral; Cohortan; Denticelso; Diformiltricina; Gradin Del D Andreu†; Hemodren Compuesto†; Miozets; Neocones; Otosedol Biotico; Pastillas Koki Ment Tiro; Piorlis; Roberfarin; Sedofarin; Viberol Tirotricina; ***Switz.:*** Gem; Lemocin; Mebucaine; Mebucasol f; Otothricinol; Rhinothricinol; Sangerol; Solmucaine; Trachisan†; Tyrocombine; Tyroqualine; Tyrothricin; Tyrothricine + Gramicidine; ***Thai.:*** Deq; Iwazin; Sigatricin; Trocacin; Troneo†; ***Turk.:*** Neolet; ***UAE:*** B-Cool; ***UK:*** Tyrozets; ***Venez.:*** Otan.

Valnemulin *(BAN, rINN)*

Valnemuliini; Valnemulina; Valnémuline; Valnemulinum. ({2-[(*R*)-2-Amino-3-methylbutyramido]-1,1-dimethylethyl}thio)acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

Вальнемулин

$C_{31}H_{52}N_2O_5S$ = 564.8.

CAS — 101312-92-9 (valnemulin); 133868-46-9 (valnemulin hydrochloride).

ATC Vet — QJ01XQ02.

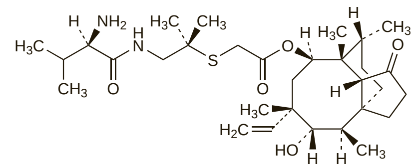

Pharmacopoeias. *Eur.* (see p.vii) includes the hydrochloride for veterinary use.

Profile

Valnemulin is an antibacterial used as the hydrochloride in veterinary medicine.

Vancomycin *(BAN, rINN)*

Vancomicina; Vancomycine; Vancomycinum; Vankomycin; Vankomysiini. (S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid.

Ванкомицин

$C_{66}H_{75}Cl_2N_9O_{24}$ = 1449.3.

CAS — 1404-90-6.

ATC — A07AA09; J01XA01.

ATC Vet — QA07AA09; QJ01XA01.

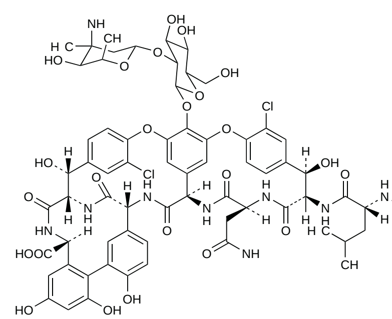

Description. A glycopeptide antimicrobial substance or mixture of glycopeptides produced by the growth of certain strains of *Amycolatopsis orientalis* (*Nocardia orientalis*, *Streptomyces orientalis*), or by any other means.

Pharmacopoeias. In *US*.

USP 31 (Vancomycin). Store in airtight containers.

Vancomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de vancomicina; Vancomycine, chlorhydrate de; Vancomycin-hydrochlorid; Vancomycini hydrochloridum; Vankomicinhidroklorid; Vankomicino hidrochloridas; Vankomisin Hidroklorür; Vankomycinhydroklorid; Vankomysiinihydrokloridi; Wankomycyny chlorowodorek.

Ванкомицина Гидрохлорид

$C_{66}H_{75}Cl_2N_9O_{24},HCl$ = 1485.7.

CAS — 1404-93-9.

ATC — A07AA09; J01XA01.

ATC Vet — QA07AA09; QJ01XA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Vancomycin Hydrochloride). A mixture of related glycopeptides, consisting principally of vancomycin B, a substance produced by certain strains of *Amycolatopsis orientalis* or obtained by any other means. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Vancomycin Hydrochloride). A substance or mixture of substances produced by the growth of *Streptomyces orientalis*. A tan to brown, odourless, free-flowing powder. Freely soluble in water; insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers.

Incompatibility. Solutions of vancomycin hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Reports of incompatibility are not always consistent, and other factors such as the strength of solution, and composition of the vehicles used, may play a part.

Stability. Although licensed product information recommends storage at 2° to 8°, solutions of vancomycin hydrochloride in various diluents (sodium chloride 0.9%, glucose 5%, and peritoneal dialysis solution) have been found to be stable for at least 14 days at room temperature.[1-3]

The stability of vancomycin in ophthalmic solution has also been studied.[4]

1. Das Gupta V, *et al.* Stability of vancomycin hydrochloride in 5% dextrose and 0.9% sodium chloride injections. *Am J Hosp Pharm* 1986; **43:** 1729–31.
2. Walker SE, Birkhans B. Stability of intravenous vancomycin. *Can J Hosp Pharm* 1988; **41:** 233–8.
3. Mauhinuey WM, *et al.* Stability of vancomycin hydrochloride in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; **49:** 137–9.
4. Fuhrman LC, Stroman RT. Stability of vancomycin in an extemporaneously compounded ophthalmic solution. *Am J Health-Syst Pharm* 1998; **55:** 1386–8.

Adverse Effects

The intravenous use of vancomycin may be associated with the so-called 'red-neck' or 'red-man' syndrome, characterised by erythema, flushing, or rash over the face and upper torso, and sometimes by hypotension and shock-like symptoms. The effect appears to be due in part to the release of histamine and is usually related to rapid infusion.

Hypersensitivity reactions may occur in about 5% of patients and include rashes, fever, chills, and rarely, anaphylactoid reactions, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Many reactions have become less frequent with the availability of more highly purified preparations. Reversible neutropenia, eosinophilia, and rarely thrombocytopenia and agranulocytosis have been reported; neutropenia is stated to be more common in patients who have received a total dose of 25 g or more. Nephrotoxicity, including rare cases of interstitial nephritis, may occur, particularly at high doses or in patients with predisposing factors, but has declined in frequency with greater awareness of the problem and appropriate monitoring of plasma concentrations and renal function.

Ototoxicity is also associated with vancomycin, and is more likely in patients with high plasma concentrations, or with renal impairment or pre-existing hearing loss.. It may progress after drug withdrawal, and may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.

Vancomycin is irritant; intravenous use may be associated with thrombophlebitis, although this can be minimised by the slow infusion of dilute solutions, and by using different infusion sites. Extravasation may cause tissue necrosis.

Because of its poor absorption, relatively few adverse effects have been reported after the oral use of vancomycin, although mild gastrointestinal disturbances have occurred.

Effects on the ears. Reviews[1,2] of ototoxicity associated with vancomycin therapy have indicated that the actual number of cases is quite small, and close examination suggests that in most cases where hearing loss occurred patients had also received an aminoglycoside. The degree, and the reversibility, of ototoxicity associated with vancomycin alone is uncertain.

1. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity: a review. *Med Toxicol* 1988; **3:** 376–86.
2. Brummett RE, Fox KE. Vancomycin- and erythromycin-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 791–6.

Effects on the gastrointestinal tract. A 25-year-old woman developed *Clostridium difficile* colitis after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease.[1] The condition resolved after treatment with vancomycin given alone.

1. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; **63:** 993–4.

Effects on the heart. A report[1] of cardiac arrest associated with an inadvertent rapid intravenous dose of vancomycin 150 mg in a neonate.

1. Boussemart T, *et al.* Cardiac arrest associated with vancomycin in a neonate. *Arch Dis Child* 1995; **73:** F123.

Effects on the kidneys. In a study,[1] nephrotoxicity was seen in 14 of 101 patients assigned to vancomycin 1 g before and after vascular surgery for infection prophylaxis compared with 2 of 99 assigned to saline placebo, suggesting that even short regimens of vancomycin can affect renal function. In another study involving 224 patients, nephrotoxicity was seen in 8 of 168 given vancomycin alone, 14 of 63 given vancomycin with an aminoglycoside, and 11 of 103 given an aminoglycoside without vancomycin.[2] This latter study found that use with aminoglycosides, trough serum concentrations of vancomycin greater than 10 micrograms/mL, and prolonged vancomycin therapy (for more than 21 days) were associated with an increased risk of nephrotoxicity. In both studies nephrotoxicity was defined in terms of increased serum creatinine.

1. Gudmundsson GH, Jensen LJ. Vancomycin and nephrotoxicity. *Lancet* 1989; **i:** 625.
2. Rybak MJ, *et al.* Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; **25:** 679–87.

Effects on the liver. A 57-year-old man with multiple medical conditions developed raised liver enzyme values, on 5 different occasions, while being treated with oral vancomycin for episodes of *Clostridium difficile*-associated enterocolitis; liver enzymes returned to normal values each time the vancomycin was stopped.[1]

1. Cadle RM, *et al.* Vancomycin-induced elevation of liver enzyme levels. *Ann Pharmacother* 2006; **40:** 1186–9.

Effects on the nervous system. Reports of encephalopathy[1] (associated with high CSF concentrations after oral doses) and peripheral neuropathy[2] associated with vancomycin.

1. Thompson CM, *et al.* Absorption of oral vancomycin—possible associated toxicity. *Int J Pediatr Nephrol* 1983; **4:** 1–4.
2. Leibowitz G, *et al.* Mononeuritis multiplex associated with prolonged vancomycin treatment. *BMJ* 1990; **300:** 1344.

Effects on the skin. Rashes, erythema, or pruritus are the most common skin reactions associated with vancomycin but there have also been reports of linear IgA dermatosis,[1-4] Stevens-Johnson-like reaction,[5] bullous eruption,[6] local skin necrosis,[7] and exfoliative dermatitis.[6] In an analysis, risk factors for adverse cutaneous reactions were suggested to be age under 40 years and duration of therapy greater than 7 days.[6]

1. Piketty C, *et al.* Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; **130:** 130–1.
2. Nousari HC, *et al.* Vancomycin-associated linear IgA bullous dermatosis. *Ann Intern Med* 1998; **129:** 507–8.
3. Bernstein EF, Schuster M. Linear IgA bullous dermatosis associated with vancomycin. *Ann Intern Med* 1998; **129:** 508–9.
4. Danielsen AG, Thomsen K. Vancomycin-induced linear IgA bullous disease. *Br J Dermatol* 1999; **141:** 756–7.
5. Laurencin CT, *et al.* Stevens-Johnson-like reaction with vancomycin treatment. *Ann Pharmacother* 1992; **26:** 1520–1.
6. Korman TM, *et al.* Risk factors for adverse cutaneous reactions associated with intravenous vancomycin. *J Antimicrob Chemother* 1997; **39:** 371–81.
7. Hoelen DW, *et al.* Severe local vancomycin induced skin necrosis. *Br J Clin Pharmacol* 2007; **64:** 553–4.

Red-man syndrome. References[1-3] to the 'red-man syndrome', and evidence that pretreatment with an antihistamine can provide significant protection against it.[4,5] Similar reactions appear to be much less of a problem with teicoplanin and substitution of teicoplanin for vancomycin may be a viable alternative in patients at risk.[2,3,6] Skin tests are reported[7] to be of little value in predicting the severity of 'red-man syndrome'.

1. Wallace MR, *et al.* Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991; **164:** 1180–5.
2. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. *J Antimicrob Chemother* 1991; **27** (suppl B): 17–29.
3. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
4. Renz CL, *et al.* Oral antihistamines reduce the side effects from rapid vancomycin infusion. *Anesth Analg* 1998; **87:** 681–5.
5. Renz CL, *et al.* Antihistamine prophylaxis permits rapid vancomycin infusion. *Crit Care Med* 1999; **27:** 1732–7.
6. Smith SR. Vancomycin and histamine release. *Lancet* 1990; **335:** 1341.
7. Polk RE, *et al.* Vancomycin skin tests and prediction of "red man syndrome" in healthy volunteers. *Antimicrob Agents Chemother* 1993; **37:** 2139–43.

AFTER ORAL ADMINISTRATION. Reports of rash[1] and 'red-man syndrome'[2,3] after oral vancomycin.

1. McCullough JM, *et al.* Oral vancomycin-induced rash: case report and review of the literature. *DICP Ann Pharmacother* 1991; **25:** 1326–8.
2. Killian AD, *et al.* Red man syndrome after oral vancomycin. *Ann Intern Med* 1991; **115:** 410–11.
3. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother* 1994; **28:** 581–4.

Precautions

Vancomycin should not be given to patients who have experienced a hypersensitivity reaction to it. It should not be given intramuscularly, and care should be taken when it is given intravenously to avoid extravasation, because of the risk of tissue necrosis. The adverse effects of infusion may be minimised by dilution of each 500 mg of vancomycin in at least 100 mL of fluid, and by infusion of doses over not less than 60 minutes.

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. It has been suggested that dosage should be adjusted to avoid peak plasma concentrations above 30 to 40 micrograms/mL and trough concentrations exceeding 10 micrograms/mL, although uncertainty about the optimum methods and sampling times for monitoring, as well as some uncertainty about the degree of risk, means that there is less general agreement than for the aminoglycosides. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment, in neonates (especially if premature), and in the elderly, all of whom may be at increased risk of toxicity. Renal function and blood counts should be monitored regularly in all patients, and monitoring of auditory function is advisable, especially in high-risk patients. Vancomycin should be stopped in patients who develop tinnitus.

Since vancomycin is poorly absorbed, toxicity is much less of a problem after oral use than with the intravenous route, but care is required in patients with inflammatory gastrointestinal disorders, including antibiotic-associated colitis, in whom absorption may be enhanced.

Interactions

Other ototoxic or nephrotoxic drugs, such as aminoglycosides, polymyxins, cisplatin, and loop diuretics, markedly increase the risk of toxicity and should be given with vancomycin only with great caution.

Some of the adverse effects of vancomycin may be enhanced by the use of general anaesthetics; it has been suggested that, where patients require both, vancomycin infusions should be completed before the induction of anaesthesia.

Vancomycin may increase neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

Antimicrobial Action

Vancomycin is a glycopeptide antibiotic with a primarily bactericidal action against a variety of Gram-positive bacteria.

Mechanism of action. Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act primarily to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis.

Spectrum of activity. Staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains), *Streptococcus pneumoniae*, *Str. pyogenes*, and some strains of Group B streptococci are reported to be susceptible to vancomycin. The viridans streptococci, and enterococci such as *Enterococcus faecalis*, are often 'tolerant', i.e. inhibition, but no bactericidal effect, can be achieved at usual plasma concentrations (but see Activity with other Antimicrobials and Resistance, below).

Clostridium difficile is usually highly susceptible as are most other clostridia. *Actinomyces* spp., *Bacillus anthracis*, *Corynebacterium* spp., some lactobacilli, and

Listeria are usually susceptible. Virtually all Gram-negative organisms, as well as mycobacteria and fungi, are intrinsically resistant.

Activity with other antimicrobials. Vancomycin exhibits synergy with the aminoglycosides against enterococci; such combinations are usually bactericidal, even against vancomycin-tolerant strains. The synergistic effect is reported to be greater with gentamicin than with streptomycin. Combinations with an aminoglycoside are also reported to show synergy against *Staph. aureus*; however, variable results, including antimicrobial antagonism, or lack of synergy, have been reported against strains of *Staph. aureus* when vancomycin was combined with rifampicin. Synergy has been reported with the third-generation cephalosporins against *Staph. aureus* and enterococci.

Resistance to vancomycin in normally susceptible organisms has until recently remained relatively uncommon, although high-level intrinsic resistance has been seen in some species of *Lactobacillus, Leuconostoc,* and *Erysipelothrix*. However, there are an increasing number of reports of high-level acquired resistance amongst enterococci, apparently plasmid-mediated and transferable to other Gram-positive organisms, notably *Staph. aureus,* which are causing considerable concern. Organisms exhibiting high-level vancomycin resistance demonstrate cross-resistance to teicoplanin. Low-level resistance has also been reported in enterococci, but these organisms remain sensitive to teicoplanin, and this form of resistance does not appear to be transferable. Low-level vancomycin resistance has also been seen rarely among some staphylococcal strains: in contrast to the enterococci, these are often cross-resistant to teicoplanin. The mechanism of acquired resistance is uncertain, although it appears to be associated with the development of novel cell-membrane proteins.

◊ References to increasing resistance to vancomycin amongst enterococci[1,2] and *Staphylococcus aureus,*[3-9] and guidelines to prevent its spread.[10,11]

1. Murray BE. Vancomycin-resistant enterococci. *Am J Med* 1997; **102:** 284–93.
2. Tacconelli E, Cataldo MA. Vancomycin-resistant enterococci (VRE): transmission and control. *Int J Antimicrob Agents* 2008; **31:** 99–106.
3. Hiramatsu K, *et al.* Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 1997; **40:** 135–6.
4. Johnson AP. Intermediate vancomycin resistance in Staphylococcus aureus: a major threat or a minor inconvenience? *J Antimicrob Chemother* 1998; **42:** 289–91.
5. Ploy MC, *et al.* First clinical isolate of vancomycin-intermediate Staphylococcus aureus in a French hospital. *Lancet* 1998; **351:** 1212.
6. Smith TL, *et al.* Emergence of vancomycin resistance in Staphylococcus aureus. *N Engl J Med* 1999; **340:** 493–501.
7. Sieradzki K, *et al.* The development of vancomycin resistance in a patient with methicillin-resistant Staphylococcus aureus infection. *N Engl J Med* 1999; **340:** 517–23.
8. Hiramatsu K. Vancomycin-resistant Staphylococcus aureus: a new model of antibiotic resistance. *Lancet Infect Dis* 2001; **1:** 147–55.
9. Chang S, *et al.* Infection with vancomycin-resistant Staphylococcus aureus containing the VanA resistance gene. *N Engl J Med* 2003; **348:** 1342–7.
10. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 1995; **16:** 105–13.
11. CDC. Investigation and control of vancomycin-intermediate and resistant Staphylococcus aureus (VISA/VRSA): a guide for health departments and infection control personnel (updated September 2006). Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/visa_vrsa_guide.pdf (accessed 06/07/08)

Pharmacokinetics

Vancomycin is only poorly absorbed from the gastrointestinal tract, although absorption may be somewhat greater when the gastrointestinal tract is inflamed. Infusion of a 1-g dose intravenously over 60 minutes has reportedly been associated with plasma concentrations of up to about 60 micrograms/mL immediately after completion of the infusion, and about 25 micrograms/mL 2 hours later, falling to under 10 micrograms/mL after 11 hours. However, there may be considerable interindividual variation in the pharmacokinetics of vancomycin: a range of half-lives between 3 and 13 hours has been reported, with an average of about 6 hours, in patients with normal renal function. Half-life may be prolonged in patients with renal impairment, to 7 days or more in anephric patients. About 55% is bound to plasma proteins, although large variations have been reported.

Vancomycin diffuses into extracellular fluid, including pleural, pericardial, ascitic, and synovial fluid. Small amounts are found in bile. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved. Vancomycin crosses the peritoneal cavity; about 60% of an intraperitoneal dose is reported to be absorbed in 6 hours. It is reported to cross the placenta. It is also distributed into breast milk.

Little or no metabolism of vancomycin is thought to take place. It is excreted unchanged by the kidneys, mostly by glomerular filtration. Some 80 to 90% of the dose is excreted in urine within 24 hours. There appears to be a small amount of non-renal clearance, although the mechanism for this has not been determined.

The pharmacokinetics of vancomycin may be altered by conditions which affect renal clearance: clearance of vancomycin has been reported to be enhanced in burn patients, whereas in those with renal impairment, or reduced renal function (such as neonates or the elderly), clearance is reduced and plasma-concentrations and half-lives increased. Dosage adjustment is often necessary in patients with reduced or impaired renal function; ideally, this should be based on plasma-concentration monitoring. Although clearance is also altered in hepatic impairment, it has been suggested that dosage adjustment is not necessary in the absence of other factors.

Plasma concentrations of vancomycin are reported to be little affected by conventional haemodialysis, although the use of high-flux membranes may significantly reduce vancomycin concentrations. Peritoneal dialysis, although it may decrease concentrations, is also thought not to do so by significant amounts, but haemoperfusion or haemofiltration effectively removes vancomycin from the blood.

Uses and Administration

Vancomycin is a glycopeptide antibiotic that is used in the treatment of serious staphylococcal or other Gram-positive infections when other drugs such as the penicillins cannot be used because of resistance or patient intolerance. It is used particularly in the treatment of meticillin-resistant staphylococcal infections (p.195), in conditions such as brain abscess, staphylococcal meningitis, peritonitis associated with continuous ambulatory peritoneal dialysis, and septicaemia. It is used alone, or with another drug such as an aminoglycoside, in the treatment and prophylaxis of endocarditis, for the prophylaxis of surgical infection, and in intensive care and the management of immunocompromised patients. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of all these infections and their treatment, see under Choice of Antibacterial, p.162. It is also used (by mouth) in the treatment of antibiotic-associated colitis (p.171).

Vancomycin may be used with other antibacterials to extend the spectrum of efficacy or increase effectiveness, notably with gentamicin or other aminoglycosides, or with rifampicin (but see Antimicrobial Action, above).

Administration and dosage. Vancomycin is given as the hydrochloride but doses are expressed in terms of the base. 1.03 g of vancomycin hydrochloride is equivalent to about 1 g of vancomycin. It is given intravenously, preferably by intermittent infusion, although continuous infusion has been used. For intermittent infusion, a concentrated solution containing the equivalent of 500 mg of vancomycin in 10 mL of water is prepared and then added to glucose 5% or sodium chloride 0.9% to produce a diluted solution containing not more than 5 mg/mL; this diluted solution is then infused over at least 60 minutes for a 500-mg dose or 100 minutes for a 1-g dose. Final concentrations of up to 10 mg/mL may be used for patients requiring fluid restriction, although there is an increased risk of adverse events. For continuous intravenous infusion when intermittent infusion is not feasible, the equivalent of 1 to 2 g is added to a sufficiently large volume of glucose or sodium chloride to permit the daily dose to be given over a period of 24 hours.

The usual adult dose is the equivalent of 500 mg of vancomycin every 6 hours or 1 g every 12 hours. Response is generally seen within 48 to 72 hours in sensitive infections. In patients with staphylococcal endocarditis, treatment for at least 3 weeks has been recommended.

For the prophylaxis of endocarditis in high-risk patients undergoing dental or other procedures who are unable to receive penicillin, vancomycin may be given before the procedure in a single dose of 1 g by intravenous infusion over at least 100 minutes followed by intravenous gentamicin.

Doses in infants and children. UK licensed product information states that children and infants over 1 month of age may be given 10 mg/kg every 6 hours. Neonates and infants up to 1 month old may be given an initial dose of 15 mg/kg; this is followed by 10 mg/kg every 12 hours in the first week of life or by 10 mg/kg every 8 hours in those aged 1 week to 1 month. The *BNFC* recommends the following doses:

- neonates less than 29 weeks postmenstrual age, 15 mg/kg every 24 hours;
- 29 to 35 weeks postmenstrual age, 15 mg/kg every 12 hours
- over 35 weeks postmenstrual age, 15 mg/kg every 8 hours
- infants and children 1 month of age and over, 15 mg/kg every 8 hours (to a maximum daily dose of 2 g)

Dose adjustment and monitoring. It has been recommended that dosage should be adjusted if necessary according to plasma-vancomycin concentrations, and this is particularly important where factors such as age or renal impairment (see also below) may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. There has been some dispute about the relationship between plasma concentrations and toxicity, and this, complicated by differences in the sampling time after the end of infusion and by differences in the regimens and assay method used, has meant that suggested peak and trough concentrations have varied considerably. However, in order to avoid toxic concentrations immediately after the end of infusion the consensus appears to be that concentrations of not more than 30 to 40 micrograms/mL should be aimed for 1 to 2 hours after completion of infusion. It is usually recommended that trough concentrations (measured just before the next dose) should be below 10 micrograms/mL. The *BNF* suggests a trough concentration of 10 to 15 micrograms/mL, or 15 to 20 micrograms/mL to treat less sensitive strains of meticillin-resistant *Staph. aureus*.

Other routes. Vancomycin hydrochloride is given by mouth in the treatment of staphylococcal enterocolitis and antibiotic-associated colitis, including pseudomembranous colitis associated with the overgrowth of *Clostridium difficile*. It is given in a dose of 0.5 to 2 g daily in 3 or 4 divided doses for 7 to 10 days; the lowest dose of 500 mg daily is often considered adequate. A suggested dose for children in licensed product information is 40 mg/kg daily in 3 or 4 divided doses; the *BNFC* suggests a dose of 5 mg/kg 4 times daily for infants and children from 1 month of age up to 5 years of age, 62.5 mg 4 times daily for children aged 5 to 12 years, and 125 mg 4 times daily for children over 12 years of age.

In meningitis or other CNS infections, vancomycin has sometimes been given by the intrathecal or intraventricular route in order to ensure adequate CSF concentrations of antibiotic. Vancomycin has also been applied topically to the eye or given by subconjunctival or intravitreal injection; it has also been given by inhalation.

◊ Reviews.

1. Wilhelm MP, Estes L. Vancomycin. *Mayo Clin Proc* 1999; **74:** 928–35.
2. Stevens DL. The role of vancomycin in the treatment paradigm. *Clin Infect Dis* 2006; **42** (suppl 1): S51–S57.
3. Deresinski S. Vancomycin: does it still have a role as an antistaphylococcal agent? *Expert Rev Anti Infect Ther* 2007; **5:** 393–401.
4. Cunha BA. Vancomycin revisited: a reappraisal of clinical use. *Crit Care Clin* 2008; **24:** 393–420.
5. Levine DP. Vancomycin: understanding its past and preserving its future. *South Med J* 2008; **101:** 284–91.

Administration in renal impairment. Various methods, including predictive nomograms based on creatinine clearance and pharmacokinetic methods such as those using Bayesian statistics, have been suggested for calculating vancomycin dosage requirements in patients with reduced renal function. One suggested approach has been a loading dose of 15 mg/kg followed by a daily dose in mg equivalent to about 15 times the glomerular filtration rate in mL/minute; or in anuric patients a dose of 1 g every 7 to 10 days. However, individualised dosage based on plasma concentrations is generally to be preferred.

Preparations

BP 2008: Vancomycin Intravenous Infusion;
USP 31: Sterile Vancomycin Hydrochloride; Vancomycin Hydrochloride Capsules; Vancomycin Hydrochloride for Injection; Vancomycin Hydrochloride for Oral Solution; Vancomycin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fabomicina; Icoplax; Rivervan; Vancocin†; Vancomax†; Vancotenk; Varedet; ***Austral.:*** Vancocin; ***Belg.:*** Vamysin; Vancocin; ***Braz.:*** Biovancomin†; Vanclomin; Vancoabbott; Vancocid†; Vancocina; Vanconorth†; Vancoplus†; Vancoson; Vancotrat; ***Canad.:*** Vancocin; ***Chile:*** Kovan; Vancocina†; ***Cz.:*** Edicin; Vancocin; Vancoled†; ***Denm.:*** Vancocin†; ***Fin.:*** Orivan†; Vancocin†; ***Fr.:*** Vancocine†; ***Ger.:*** Vanco; Vanco-saar; ***Gr.:*** Vamistol†; Voncon; Vondem; Voxin†; ***Hong Kong:*** Lyphocin; Vancocin; ***Hung.:*** Edicin†; Vancocin; ***India:*** Vancocin; Vancogram; Vanlid; ***Indon.:*** Vancep; ***Irl.:*** Vancocin; ***Israel:*** Vanco-Teva; Vancocin†; Vancoled†; ***Ital.:*** Copovan; Farmaciclin; Levovanox; Maxivanil; Vanco; Vancocina; Vancotex; Zengac; ***Malaysia:*** Vancocin†; Vancotex; ***Mex.:*** Estavam; Ifavac; Vanaurus; Vancam†; Vancocin; Vancox; ***Neth.:*** Vancocin; ***Norw.:*** Vancocin†; ***NZ:*** Vancocin†; ***Philipp.:*** Vancocin; ***Pol.:*** Edicin; Vancocin; ***Port.:*** Glipep; Vancocina†; ***Rus.:*** Edicin (Эдицин); Vancocin (Ванкоцин); ***S.Afr.:*** Vancocin; ***Spain:*** Diatracin†; ***Swed.:*** Vancocin; Vancoscand†; ***Switz.:*** Vancocin; ***Thai.:*** Edicin; Vancocin†; Vancogen; ***Turk.:*** Vancorin; ***UAE:*** Vancolon; ***UK:*** Vancocin; ***USA:*** Lyphocin; Vancocin; Vancoled; ***Venez.:*** Vagran; Vancobehr†.

Virginiamycin *(BAN, USAN, rINN)*

Antibiotic 899; SKF-7988; Virgimycin; Virginiamicina; Virginiamycine; Virginiamycinum.

Виргиниамицин

CAS — 11006-76-1; 21411-53-0 (virginiamycin M_1); 23152-29-6 (virginiamycin S_1).
ATC — D06AX10.
ATC Vet — QD06AX10; QJ01FG90.

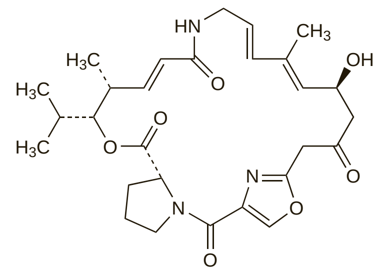

(virginiamycin M_1)

Profile

Virginiamycin is a streptogramin antibacterial mixture consisting principally of 2 antimicrobial substances, virginiamycin M_1, and virginiamycin S_1, produced by the growth of *Streptomyces virginiae*. It has been used for the treatment of infections due to sensitive organisms, particularly Gram-positive cocci. It has been given orally and applied locally. It may cause gastrointestinal disturbances including diarrhoea and vomiting. A few instances of hypersensitivity have been observed.

Virginiamycin has been used in animal feeding stuffs as a growth promotor.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Belg.:* Spitalen†.

Xibornol *(BAN, rINN)*

CP3H; 1HP; 1BX; Xibornolum. 6-(Isoborn-2-yl)-3,4-xylenol; 6-[(1*R*,2*S*,4*S*)-Born-2-yl]-3,4-xylenol.

Ксиборнол

$C_{18}H_{26}O = 258.4.$
CAS — 38237-68-2; 13741-18-9.
ATC — J01XX02.
ATC Vet — QJ01XX02.

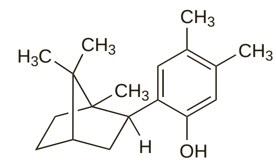

Profile

Xibornol is an antibacterial that is reported to have a bacteriostatic action on Gram-positive organisms such as staphylococci and streptococci, as well as activity against *Haemophilus influenzae*. It has been given orally, as an oral spray, and rectally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bornilene.

Antidementia Drugs

This chapter includes some drugs used or promoted in the management of dementia, including centrally acting anticholinesterases such as donepezil, galantamine, rivastigmine, and tacrine, the *N*-methyl-D-aspartate receptor antagonist memantine, and drugs considered to have nootropic properties, such as piracetam.

Many other drugs have been tried in various forms of dementia (see below) and are discussed elsewhere in *Martindale*.

Dementia

Dementia is a syndrome in which impairment of cortical or subcortical function leads to deterioration of cognitive processes or intellectual abilities including memory, judgement, language, communication, and abstract thinking. Unlike delirium there is no gross clouding of consciousness. There may be changes in personality and behaviour disturbances. Dementia is usually progressive, though not always irreversible, and loss of social and other skills often leads to complete dependence on others.

Although dementia is more prevalent in the elderly it is not an inevitable consequence of ageing. Dementia can result from many conditions[1-4] including:

- *neurodegenerative diseases*: Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Lewy-body disease, multiple sclerosis, progressive supranuclear palsy
- *vascular diseases*: multiple cerebral infarcts, occlusion of carotid artery, cranial arteritis
- *trauma*: subdural haematoma
- *neoplasms*
- *CNS infections*: encephalitis, syphilis, toxoplasmosis, AIDS, Creutzfeldt-Jakob disease
- *endocrine/metabolic disorders*: hypothyroidism, uraemia, hepatic failure, cardiac failure, respiratory failure, hypoxia, hyponatraemia
- *toxic insults*: alcohol, solvents, heavy metals, drug therapy
- *hydrocephalus*
- *nutritional deficiency*: vitamin B_{12}, folic acid, thiamine
- *depression*
- *sleep disorders*: obstructive sleep apnoea, narcolepsy

Alzheimer's disease is the most common cause of dementia and accounts for over half of all patients;[1,2,4-6] about one-third of dementia cases are due to vascular disease.

Treatment of dementia can be broadly divided into control of disturbed behaviour (p.954) and attempts to improve or preserve cognitive function (see below). Although many drugs have been tried in the management of cognitive impairment most have produced little or no benefit.

Alzheimer's disease is a progressive degenerative condition affecting mainly patients over 60 years of age. The rare early-onset form of Alzheimer's disease (familial Alzheimer's disease) is sometimes referred to as pre-senile dementia. Death usually occurs within 10 years of onset.[1] Apart from age other risk factors include Down's syndrome and a family history of Alzheimer's disease.[1,2,4,7] Presence of the ε4 allele of apolipoprotein E is another risk factor; it correlates with prevalence and age of onset in some forms of Alzheimer's disease but use for routine clinical or predictive testing is not recommended.[4,5,8] Elevated levels of plasma homocysteine have been linked with the development of dementia and Alzheimer's disease.[9] Cardiovascular risk factors such as diabetes, hypercholesterolaemia, hypertension, and obesity have also been associated with an increased risk.[4,6] Dialysis dementia, an irreversible condition which has occurred in dialysis patients, has been associated with excess aluminium in the dialysing fluid but the role of aluminium in Alzheimer's disease, if any, is unclear.[5]

Deficiencies in numerous neurotransmitters have been found in patients with Alzheimer's disease but reduced choline acetyltransferase activity leading to reduced synthesis of acetylcholine remains the most consistent defect correlating with the severity of the condition.[10-17] Attempts to increase acetylcholine concentrations in the brain have included use of *acetylcholine precursors*, *cholinesterase inhibitors*, *enhancers of acetylcholine release*, and *cholinergic agonists*. However, none replace lost cholinergic neurones and therefore none affect overall progression of the disease.

Treatments using *precursors of acetylcholine* such as lecithin or choline alone are not generally considered to produce useful improvements,[15-17] although it has been suggested that choline alfoscerate may be of some benefit.

Donepezil, galantamine, rivastigmine, and tacrine are the main *cholinesterase inhibitors*.[6-8,16-23] All have produced modest improvement in cognition and global clinical impression in patients with mild to moderately severe disease. However, there is a lack of long-term studies and little evidence of their effectiveness in advanced disease although donepezil is licensed for the treatment of severe dementia in many countries. Tacrine is often poorly tolerated and may cause serious hepatotoxicity; for these reasons it is rarely used now. Donepezil, galantamine, and rivastigmine may be more acceptable to patients. A systematic review found no evidence of any difference between these 3 drugs with regard to efficacy although there appeared to be fewer adverse effects associated with donepezil compared with rivastigmine.[24] In the UK, NICE[25] recommends that the use of donepezil, galantamine, and rivastigmine is limited to patients with moderate dementia and given under the following conditions:

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that these 3 drugs could no longer be recommended in the treatment of mild dementia because their cost-effectiveness was questionable; however, it was recommended that those currently taking one of these drugs for mild dementia should continue on therapy until it was considered appropriate to stop. Other cholinesterase inhibitors that have been tried in Alzheimer's disease include metrifonate and physostigmine.

Fampridine, which *enhances acetylcholine release from nerve terminals* has also been tried in Alzheimer's disease but there is little evidence of clinical benefit.

Limited improvement has been reported with some *cholinergic agonists* but pilocarpine may exacerbate the dementia. Muscarinic M_1 agonists such as cevimeline and xanomeline have been investigated[17,26] on the basis that muscarinic M_1 receptors appear to be preserved throughout the course of Alzheimer's disease. However, these drugs have not been successful in improving symptoms of the disease. An alternative line of investigation is the *stimulation of nicotinic receptors* using nicotine.[17]

A hypothesis that free radicals may initiate and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease has prompted the investigation of drugs such as vitamin E (e.g. α-tocopherol), ginkgo biloba, idebenone, and selegiline for *antoxidant* therapy but their value remains to be confirmed.[10,15,20,27-29] Although some US guidelines[17] suggested consideration of vitamin E supplementation in an attempt to slow progression of the disease, more recent ones[3] no longer recommend it for the treatment of cognitive symptoms because of limited evidence of efficacy as well as safety concerns. Selegiline has produced mixed results in a large number of controlled studies and US guidelines[3] note that few clinicians actually use the drug in clinical practice. A systematic review[30] has found no convincing evidence that ginkgo biloba is effective in the treatment of dementia or cognitive impairment.

Neurotropic or nootropic drugs such as piracetam are considered to enhance memory and cognition. They have been tried in preventing cognitive deficits associated with Alzheimer's disease and other dementias but there is little convincing evidence of clinical usefulness.[10,13,17]

The *N-methyl-D-aspartate (NMDA) receptor antagonist* memantine has shown some benefit in various dementias[6,7,19,29,31] and is used in the treatment of moderately severe to severe Alzheimer's disease;[21] it is thought to act through modulation of the effects of the neurotransmitter glutamate. However, in the UK, NICE[25] has not recommended memantine in the treatment of patients with moderately severe to severe disease because of insufficient evidence of clinical effectiveness.

Many drugs with *vasodilator activity* were originally tried in dementia when it was believed that the condition was due to 'cerebrovascular insufficiency' (p.1165), but overall there is little convincing evidence of benefit.[32] Ergot derivatives such as codergocrine mesilate and nicergoline have been the most commonly used; however, any effectiveness is now attributed to their action as metabolic enhancers or nootropic drugs and their place in therapy has still to be established.[27]

The *calcium-channel blocker* nimodipine has been of benefit in dementia of various aetiologies but its role in therapy remains unclear.[27,31]

Observations have suggested that *oestrogens* may reduce the risk and delay the onset of Alzheimer's disease in postmenopausal women receiving HRT.[7,8,13,17] However, a large controlled study found that combined HRT increased the risk of substantial decline in global cognitive function, did not prevent the development of mild cognitive impairment, and doubled the risk of dementia. A beneficial effect of oestrogens on cognitive function in postmenopausal women who already have mild or moderate Alzheimer's disease has not been demonstrated in controlled studies (see p.2076).

Some retrospective studies also indicate an inverse association between the use of *anti-inflammatory drugs* such as NSAIDs and the risk of developing Alzheimer's disease.[10,12,17,19] However, there is currently insufficient evidence to support the use of NSAIDs in the treatment of Alzheimer's disease.[6,7,19,33]

The possibility of an association between *statin* therapy and a reduced risk of developing dementia has also been mooted.[34] Evidence has been conflicting and further study is ongoing.[6]

A vaccine for Alzheimer's disease is being investigated.[4,6,19] Methylthioninium chloride, which is thought to dissolve and prevent the aggregation of tau protein filaments in the brain, is also under investigation.

A less marked degree of impaired memory, without dementia, is seen in some patients. Many, but not all, patients with such **mild cognitive impairment** (MCI) go on to develop Alzheimer's disease, and there has been considerable interest in treating them, in the hope of retarding progression to the more severe condition.[35,36] However, appropriate strategies for management are unclear: although treatment with cholinesterase inhibitors, antoxidants, and other drugs used for Alzheimer's disease has been investigated, there has been some concern about a possibly increased risk of death in patients with MCI treated with galantamine (see Effects on the Cardiovascular and Cerebrovascular Systems, p.366). In the UK, NICE[37] does not recommend the use of cholinesterase inhibitors in patients with MCI.

Vascular dementia[31,38-41] is a syndrome produced by ischaemic, hypoxic, or haemorrhagic brain lesions. Vessel occlusion is the most common cause of vascular dementia and produces a variety of cognitive deficits depending on the site of ischaemia. Among the major forms of dementia recognised are those due to multiple infarcts, single strategic infarcts, and subcortical white matter ischaemia (Binswanger's disease). Vascular dementia has a more acute onset than dementia due to Alzheimer's disease and in contrast to the continuous progression of Alzheimer's disease often has a stepwise progression. Risk factors for vascular dementia parallel those for stroke (p.1185) and similar methods for prevention and treatment may be of use but there is a lack of evidence from adequately controlled trials. Cholinergic deficits are well documented in patients with vascular dementia; cholinesterase inhibitors such as *donepezil* and *galantamine* have been found to be well tolerated and effective in these patients. Positive results have also been seen with the NMDA receptor antagonist *memantine*.[31,41] However, in the UK, NICE[37] does not recommend the use of cholinesterase inhibitors or memantine for cognitive decline in vascular dementia.

Lewy-body dementia[32,42-44] is distinguished from other types of dementia by a state of fluctuating cognitive impairment and confusion; hallucinations, paranoid delusions, a tendency to fall for no apparent reason, and transient clouding or loss of consciousness are also characteristic symptoms. In addition, mild extrapyramidal symptoms may be present and there is increased susceptibility to the extrapyramidal adverse effects of antipsychotics (see the Elderly, under Precautions of Chlorpromazine on p.973). Severe cholinergic deficits in patients with Lewy-body dementia have prompted treatment with cholinesterase inhibitors. *Donepezil* and *rivastigmine* have been shown to be well tolerated and effective, but further studies are needed to establish their role.

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Aniracetam *(USAN, rINN)* ⊗

Aniracétam; Aniracetamum; Ro-13-5057. 1-(4-Methoxybenzoyl)-2-pyrrolidinone.

Анирацетам

$C_{12}H_{13}NO_3$ = 219.2.
CAS — 72432-10-1.
ATC — N06BX11.
ATC Vet — QN06BX11.

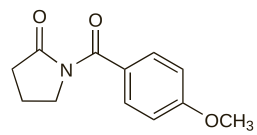

Profile

Aniracetam is a nootropic drug that has been tried in senile dementia (p.362). It is given orally in usual doses of 1.5 g daily.

◊ References.

1. Lee CR, Benfield P. Aniracetam: an overview of its pharmacodynamic and pharmacokinetic properties, and a review of its therapeutic potential in senile cognitive disorders. *Drugs Aging* 1994; **4:** 257–73.
2. Nakamura K. Aniracetam: its novel therapeutic potential in cerebral dysfunctional disorders based on recent pharmacological discoveries. *CNS Drug Rev* 2002; **8:** 70–89.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aniran; Conectol†; Pergamid; ***Gr.:*** Memodrin; Referan; ***Ital.:*** Ampamet; Draganon†.

Bifemelane *(rINN)*

Bifémélane; Bifemelano; Bifemelanum; MCI-2016 (bifemelane hydrochloride). *N*-Methyl-4-[(α-phenyl-*o*-tolyl)oxy]butylamine.

Бифемелан

$C_{18}H_{23}NO$ = 269.4.
CAS — 90293-01-9 (bifemelane); 62232-46-6 (bifemelane hydrochloride).
ATC — N06AX08.
ATC Vet — QN06AX08.

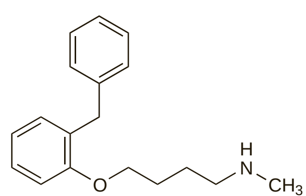

Profile

Bifemelane is a nootropic that has been given orally in a usual dose of 150 mg of the hydrochloride daily in divided doses for the treatment of cerebrovascular disorders including some forms of dementia (p.362).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alemelano†; Cordinal; Neurocine; Neurolea†.

Choline Alfoscerate *(rINN)*

Alfoscerato de colina; Choline, Alfoscérate de; Choline Alphoscerate; Choline Glycerophosphate; Cholini Alfosceras; L-α-Glycerylphosphorylcholine. Choline hydroxide, (*R*)-2,3-dihydroxypropyl hydrogen phosphate, inner salt.

Холина Альфосцерат

$C_8H_{20}NO_6P$ = 257.2.
CAS — 28319-77-9.
ATC — N07AX02.
ATC Vet — QN07AX02.

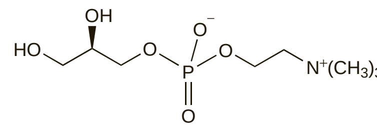

Profile

Choline alfoscerate is a precursor of acetylcholine and has been tried in the treatment of Alzheimer's disease and other dementias (below). The usual oral dose is 0.8 to 1.2 g daily in divided doses; doses of 1 g daily have been given by intramuscular or slow intravenous injection.

Dementia. Treatment with precursors of acetylcholine is not generally thought to be of benefit in dementia (p.362). However, in an analysis[1] of 8 controlled clinical studies the use of choline alfoscerate in patients with dementia of the Alzheimer's type, vascular dementia, or acute cerebrovascular disease was claimed to be of some benefit. Results of a further 3 uncontrolled studies in the same review suggested that it might favour functional recovery in patients with cerebral stroke.

1. Parnetti L, *et al.* Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. *Mech Ageing Dev* 2001; **122:** 2041–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gliatilin†; ***Cz.:*** Gliatilin†; ***Gr.:*** Gliatilin; ***Ital.:*** Brezal; Delecit; Gliatilin; ***Pol.:*** Gliatilin; ***Rus.:*** Cerepro (Церепро); Gliatilin (Глиатилин).

Codergocrine Mesilate *(BAN)*

Codergocrina, mesilato de; Co-dergocrine Mesilate; Codergocrine, mésilate de; Co-dergocrine Mesylate; Co-dergocrine Methanesulphonate; Codergocrini mesilas; Dihydroergotoxine Mesylate; Dihydroergotoxine Methanesulphonate; Dihydrogenated Ergot Alkaloids; Ergoloid Mesylates *(USAN)*; Hydrogenated Ergot Alkaloids; Kodergokriinimesilaatti; Ko-dergokrin Mesilat; Kodergokrinmesilat; Kodergokrin-mesylát; Kodergokrino mesilatas.

CAS — 11032-41-0 (codergocrine); 8067-24-1 (codergocrine mesilate).
ATC — C04AE01.
ATC Vet — QC04AE01.

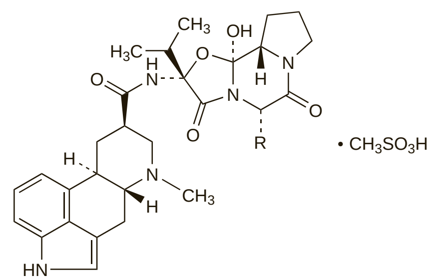

Dihydroergocornine	R = $CH(CH_3)_2$
Dihydroergocristine	R = $CH_2C_6H_5$
Dihydro-α-ergocryptine	R = $CH_2CH(CH_3)_2$
Dihydro-β-ergocryptine	R = $CH(CH_3)CH_2CH_3$

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Codergocrine Mesilate). A mixture of dihydroergocornine mesilate ($C_{31}H_{41}N_5O_5,CH_4O_3S$ = 659.8), dihydroergocristine mesilate, α-dihydroergocryptine mesilate, and β-dihydroergocryptine mesilate (epicriptine mesilate). It contains 30 to 35% of dihydroergocornine, 30 to 35% of dihydroergocristine, 20 to 25% of α-dihydroergocryptine, and 10 to 13% of β-dihydroergocryptine. A white or yellowish powder. Sparingly soluble in water; sparingly soluble to soluble in alcohol; slightly soluble in dichloromethane. A 0.5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 31 (Ergoloid Mesylates). A mixture of the methanesulfonate salts of the three hydrogenated alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergocryptine, in an approximate weight ratio of 1:1:1. Dihydroergocryptine mesylate exists as a mixture of alpha- and beta-isomers. The ratio of alpha- to beta-isomers is not less than 1.5:1.0 and not more than 2.5:1.0. A white to off-white, microcrystalline or amorphous, practically odourless powder. Slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. A 0.5% solution in water has a pH of 4.2 to 5.2. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects occasionally reported with codergocrine mesilate include abdominal cramps, nausea, vomiting, headache, blurred vision, skin rashes, nasal congestion, flushing of the skin, dizziness, bradycardia, and orthostatic hypotension.

Local irritation has occurred after sublingual use.

Effects on the cardiovascular system. Of 8 patients given codergocrine mesilate 1.5 mg three times daily for the treatment of dementia, 3 developed severe sinus bradycardia associated with general deterioration in their condition, necessitating withdrawal of the treatment.[1] However, no sinus bradycardia had been seen in 40 elderly patients in whom the dose was built up to 1.5 mg three times daily over 3 weeks.[2]

1. Cayley ACD, *et al.* Sinus bradycardia following treatment with Hydergine for cerebrovascular insufficiency. *BMJ* 1975; **4:** 384–5.
2. Cohen C. Sinus bradycardia following treatment with Hydergine. *BMJ* 1975; **4:** 581.

Precautions

Codergocrine mesilate should be used with caution in patients with severe bradycardia.

Pharmacokinetics

Codergocrine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached in about 1 to 2 hours after an oral dose. Oral bioavailability is low; this has been attributed to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism. It is 81% bound to plasma proteins. Elimination is biphasic with a short half-life of 1.5 to 2.5 hours (α phase) and a longer half-life of 13 to 15 hours (β phase). Codergocrine is mainly excreted with bile in the faeces, although small amounts are eliminated in the urine as metabolites and unchanged drug.

Uses and Administration

Unlike the natural ergot alkaloids, codergocrine mesilate has only limited vasoconstrictor effects.

A mixture of hydrogenated ergot alkaloids, codergocrine mesilate is used as an adjunct in the symptomatic treatment of mild to moderate dementia in the elderly (see also below). It is given in oral doses of 3 or 4.5 mg daily, preferably before meals. Higher doses have also been used. It is also given sublingually in similar doses. It has been given intramuscularly, subcutaneously, or by intravenous infusion.

In some countries, codergocrine mesilate has been used in the treatment of hypertension, migraine, and in peripheral vascular disease.

Codergocrine esilate has been used similarly to the mesilate.

Dementia. Codergocrine has been used for many years in dementia (p.362) but its value is not established.[1-3] Originally its effects were thought to be mediated through peripheral and cerebral vasodilatation but it is now classified as a metabolic enhancer.

1. Wadworth AN, Chrisp P. Co-dergocrine mesylate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in age-related cognitive decline. *Drugs Aging* 1992; **2:** 153–73.
2. Schneider LS, Olin JT. Overview of clinical trials of Hydergine in dementia. *Arch Neurol* 1994; **51:** 787–98.
3. Olin J, *et al.* Hydergine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 13/02/06).

Erectile dysfunction. For reference to the use of creams containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

Preparations

BP 2008: Codergocrine Tablets;
USP 31: Ergoloid Mesylates Capsules; Ergoloid Mesylates Oral Solution; Ergoloid Mesylates Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: CCK†; Coplexina; Ergoxina†; Hydergina; Somoblon†; Vimotadine; ***Austria:*** Dorehydrin; Ergomed; Hydergin; ***Belg.:*** Hydergine; Ibexone; Stofilan; ***Braz.:*** Hydergine; ***Canad.:*** Hydergine; ***Chile:*** Geroplus†; Hydergina†; ***Cz.:*** Secatoxin Forte; ***Fin.:*** Artergin†; Hydergin; ***Fr.:*** Capergyl; Ergodose†; Hydergine; ***Ger.:*** Circanol†; DCCK; Defluina N†; Ergodesit; ergotox; Hydergin; Hydro-Cebral; Orphol; Sponsin; ***Gr.:*** Engestol-Hyd†; Huperloid†; Hydergine; Santamin†; Zodalin†; ***Hong Kong:*** Hydergine; Perenan†; Stofilan; Trigogine; ***Hung.:*** Redergam†; ***India:*** Cereloid; ***Indon.:*** Cirloid; Ergotika; Exergin; Fontula; Hydergin; Procere; Xepadergin; ***Israel:*** Hydergine; ***Ital.:*** Hydergina; Ischelium†; ***Malaysia:*** Beagocrine†; Headgen; Hydergine; Vasculin†; ***Mex.:*** Hydergina; ***Philipp.:*** Hydergine; ***Port.:*** Hydergine; Redergot†; Secamin†; ***Singapore:*** Headgen; Hydergine; Trigogine; ***Spain:*** Ergodilat†; Hydergina; ***Swed.:*** Hydergin; ***Switz.:*** Ergohydrine; Hydergine; ***Thai.:*** Codergine†; Helcon; Hyceral; Hydergine; Hydrine; Hymed; Naline; Perenan†; Redergin†; Togine; Trigogine; Vasculin; Vasian; ***Turk.:*** Segol; ***UK:*** Hydergine†; ***USA:*** Gerimal; Hydergine; ***Venez.:*** Astergina; Hyderan†; Hydergina†.

Multi-ingredient: ***Arg.:*** CCK Flunarizina†; Difusil; Neuriclor Vascular†; Neuronal Vascular†; Reagin Vascular; ***Austria:*** Pontuc; ***Braz.:*** Vincetron†; ***Port.:*** Euvifor†; ***Spain:*** Clinadil Compositum; Piracetam Complex†.

Dihydroergocristine Mesilate *(BANM)*

Dihidroergocristina, mesilato de; Dihidroergokristino mesilatas; Dihidroergokrisztin-mezilát; Dihydroergocristine, mésilate de; Dihydroergocristine Mesylate; Dihydroergocristine Methanesulphonate; Dihydroergocristini mesilas; Dihydroergokristiinimesilaatti; Dihydroergokristinmesilat; Dihydroergokristin-mesylát. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-isopropyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulphonate.

$C_{35}H_{41}N_5O_5,CH_4O_3S = 707.8$.

CAS — 17479-19-5 (dihydroergocristine); 24730-10-7 (dihydroergocristine mesilate).

ATC — C04AE04.

ATC Vet — QC04AE04.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dihydroergocristine Mesilate). A white or almost white, fine crystalline powder. Slightly soluble in water; soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

Profile

Dihydroergocristine mesilate is a component of codergocrine mesilate (above) and has similar actions. In some countries it has been given orally in doses of 3 to 6 mg daily in divided doses in the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency and in peripheral vascular disease. It has also been given by intramuscular or intravenous injection.

◊ References.

1. Franciosi A, Zavattini G. Dihydroergocristine in the treatment of elderly patients with cognitive deterioration: a double-blind, placebo-controlled, dose-response study. *Curr Ther Res* 1994; **55:** 1391–1401.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nehydrin; ***Braz.:*** Iskemil; Iskevert†; ***Gr.:*** Agiobita; Alfacrist; Beytina; Cristil; Diertina; Ergobel; Ergocrist; Ergofil; Fenitina; Guadal; Memotil; Mentidose†; Normocedon; Thriolan; Tonergon; ***Ital.:*** Defluina†; Diertina†; Difluid†; ***Port.:*** Diertina; ***Spain:*** Diertine; Ergodavur.

Multi-ingredient: ***Arg.:*** Cervilane; Cinacris; Micerfin; ***Austria:*** Brinerdin; Defluina; ***Braz.:*** Isketam; Norogil; Vertizine D; ***Chile:*** Cervilane; ***Cz.:*** Anavenol; Crystepin; Ersilan; Neocrystepin; Trimecryton†; ***Fr.:*** Iskedyl; ***Ital.:*** Brinerdina; ***Mex.:*** Cervilan; ***Pol.:*** Anavenol; Normatens; Venacorn; ***Port.:*** Brinerdine†; Cervilane†; ***Rus.:*** Anavenol (Анавенол); Crystepin (Кристепин); ***S.Afr.:*** Brinerdin; ***Spain:*** Brinerdina†; Clinadil; Diemil; ***Switz.:*** Brinerdine; ***Thai.:*** Bedin; Brinerdin; Hyperdine†.

Dihydroergocryptine Mesilate

Dihidroergocriptina, mesilato de; Dihydroergocryptine Mesylate; Dihydroergocryptine Methanesulphonate; Dihydroergokryptine Mesylate.

$C_{32}H_{43}N_5O_5,CH_4O_3S = 673.8$.

CAS — 25447-66-9 (dihydroergocryptine, α-isomer); 19467-62-0 (dihydroergocryptine, β-isomer); 14271-05-7 (dihydroergocryptine mesilate, α-isomer); 65914-79-6 (dihydroergocryptine mesilate, β-isomer).

ATC — N04BC03.

ATC Vet — QN04BC03.

Profile

Dihydroergocryptine mesilate is a component of codergocrine mesilate (p.363) and has similar actions. It has been given orally in doses of up to 20 mg daily for migraine, and in maintenance doses of up to 60 to 120 mg daily for parkinsonism. It has also been used for age-related dementia and to inhibit lactation. In some countries it has been given with caffeine for cerebrovascular and peripheral vascular disorders.

◊ References.

1. Scarzella L, *et al.* Dihydroergocryptine in the management of senile psycho-organic syndrome. *Int J Clin Pharmacol Res* 1992; **12:** 37–46.
2. Battistin L, *et al.* Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. *Acta Neurol Scand* 1999; **99:** 36–42.
3. Bergamasco B, *et al.* Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. *Acta Neurol Scand* 2000; **101:** 372–80.
4. Micieli G, *et al.* Alpha-dihydroergocryptine and predictive factors in migraine prophylaxis. *Int J Clin Pharmacol Ther* 2001; **39:** 144–51.
5. Tergau F, *et al.* Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Mov Disord* 2001; **16:** 731–5.
6. Albanese A, Colosimo C. Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. *Acta Neurol Scand* 2003; **107:** 349–55.
7. Mailland E, *et al.* Alpha-dihydroergocryptine in the long-term therapy of Parkinson's disease. *Arzneimittelforschung* 2004; **54:** 647–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Almirid; ***Ger.:*** Almirid; Cripar; ***Gr.:*** Daverium; ***Ital.:*** Daverium; ***Mex.:*** Diamin; ***Pol.:*** Almirid; ***Port.:*** Striatal; ***Rus.:*** Vasobral (Вазобрал); ***Switz.:*** Cripar.

Multi-ingredient: ***Fr.:*** Vasobral; ***Hong Kong:*** Vasobral; ***Ital.:*** Vasobral†.

Donepezil Hydrochloride

(BANM, USAN, rINNM)

BNAG; Donépézil, Chlorhydrate de; Donepezil Hidroklorür; Donepezili Hydrochloridum; E-2020; ER-4111 (donepezil); Hidrocloruro de donepezilo. (±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride.

Донепезила Гидрохлорид

$C_{24}H_{29}NO_3,HCl = 416.0$.

CAS — 120014-06-4 (donepezil); 142057-79-2 (donepezil); 120011-70-3 (donepezil hydrochloride); 142057-77-0 (donepezil hydrochloride).

ATC — N06DA02.

ATC Vet — QN06DA02.

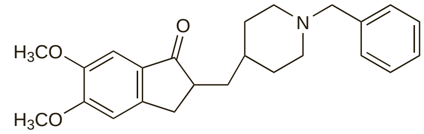

(donepezil)

Adverse Effects and Treatment

Adverse effects of acetylcholinesterase inhibitors such as donepezil notably include nausea, vomiting, anorexia, diarrhoea, fatigue, and dizziness. Other common adverse effects include abdominal pain, dyspepsia, rash, pruritus, headache, somnolence, muscle cramps, insomnia, sweating, tremor, and syncope; upper-respiratory-tract and urinary-tract infections have been noted. Rare cases of angina, sino-atrial and AV blocks, bradycardia, peptic ulcers, gastrointestinal haemorrhage, extrapyramidal symptoms, and seizures have been observed. Psychiatric disturbances, including depression, hallucinations, agitation, aggressive behaviour, and confusion have also been reported. There is a potential for bladder outflow obstruction. Minor increases in serum-creatine kinase have also occurred with donepezil.

Hepatotoxicity has occurred with tacrine, and has limited its use (see Tacrine, Precautions, p.370); individual cases of increased liver transaminases have been noted with other acetylcholinesterase inhibitors.

The use of acetylcholinesterase inhibitors has been associated with weight loss and consequently some licensed product information has recommended that a patient's weight is monitored during treatment. Female patients have been found to be more susceptible to nausea, vomiting, anorexia, and weight loss.

Overdosage with cholinesterase inhibitors may result in 'cholinergic crisis', the details of which are described under Adverse Effects of Neostigmine, p.631.

◊ Reviews of the safety profile of donepezil.

1. Committee on Safety of Medicines/Medicines Control Agency. Donepezil (Aricept). *Current Problems* 1999; **25:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 13/08/07)
2. Jackson S, *et al.* The safety and tolerability of donepezil in patients with Alzheimer's disease. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 1–8.

Effects on the cardiovascular system. The Australian Adverse Drug Reactions Advisory Committee noted in October 2004 that it had received 32 reports of cardiac arrhythmias associated with donepezil (14 of bradycardia, 1 bundle branch block, 5 AV blocks, 10 cases of syncope, and 2 unspecified), as well as 7 cases of myocardial infarction or cardiac arrest.[1] There had been 7 reports of similar cardiovascular effects with rivastigmine and 6 with galantamine; the larger number with donepezil was almost certainly due to wider usage of this drug. Most patients recovered when the drug was stopped or the dose reduced, though many were hospitalised and in 4 cases a pacemaker was required.

One study in vascular dementia reported an increased death rate with donepezil (see Dementia, below) but no increase in vascular events.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cholinesterase inhibitors and cardiac arrhythmias. *Aust Adverse Drug React Bull* 2004; **23:** 19–20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 13/02/06)

Effects on the nervous system. Restless legs, mumbling, and stuttering developed in an elderly patient after increasing the dose of donepezil to 10 mg daily.[1] Symptoms resolved when donepezil was withdrawn and recurred on rechallenge.

1. Amouyal-Barkate K, *et al.* Abnormal movements with donepezil in Alzheimer disease. *Ann Pharmacother* 2000; **34:** 1347.

Effects on the urinary tract. Urinary incontinence is a recognised adverse effect of the older anticholinesterases such as neostigmine; not unexpectedly there have also been cases associated with donepezil.[1]

1. Hashimoto M, *et al.* Urinary incontinence: an unrecognised adverse effect with donepezil. *Lancet* 2000; **356:** 568.

Precautions

Donepezil and other acetylcholinesterase inhibitors should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction; their use is not recommended in patients recovering from bladder or gastrointestinal surgery. Care is also required in patients with a history of asthma, obstructive pulmonary disease, Parkinson's disease, or seizures, and in those, with, or at risk of developing, peptic ulcer disease. Patients with cardiovascular conduction disorders such as sick-sinus syndrome may be susceptible to the vagotonic effects of acetylcholinesterase inhibitors.

Dizziness, somnolence, fatigue, and muscle cramps may occur especially when starting treatment with or increasing the dose of acetylcholinesterase inhibitors; the performance of skilled tasks such as driving may be affected.

Interactions

As for Neostigmine, p.632. Hepatic metabolism of donepezil via the cytochrome P450 system has been demonstrated; plasma concentrations of donepezil may be raised by drugs that inhibit the isoenzyme CYP3A4 such as ketoconazole, itraconazole, and erythromycin, and by those that inhibit the isoenzyme CYP2D6 such as fluoxetine and quinidine. Conversely, plasma-donepezil concentrations may be reduced by enzyme inducers such as rifampicin, phenytoin, carbamazepine, and alcohol.

Antimuscarinics. Although antimuscarinics are expected to antagonise the effects of anticholinesterases, such combinations are sometimes used in patients with dementia who are distressed by symptoms of urge incontinence.[1] There have been, however, a few cases[2] of agitation, anxiety, confusion, aggression, and delusion precipitated by *tolterodine* in patients who had been stable on donepezil or rivastigmine. The interaction appeared to cause a state of cholinergic neurogenic hypersensitivity, similar to sudden withdrawal of the anticholinesterase.

1. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* 2004; **75:** 484–8.
2. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc* 2002; **50:** 1165–6.

Pharmacokinetics

Donepezil hydrochloride is well absorbed from the gastrointestinal tract, maximum plasma concentrations being achieved within 3 to 4 hours after ingestion. It is about 95% bound to plasma proteins, mainly albumin. Donepezil undergoes partial metabolism via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6, to 4 major metabolites. About 11% of a dose is present in plasma as 6-*O*-desmethyldonepezil, which has similar activity to the parent compound. Over 10 days, about 57% of a dose is recovered from the urine as unchanged drug and metabolites, and about 15% from the faeces; 28% remains unrecovered suggesting accumulation. The elimination half-life is about 70 hours. Steady-state concentrations are achieved within 3 weeks of the start of therapy.

◊ References.

1. Tiseo PJ, *et al.* Metabolism and elimination of C-donepezil in healthy volunteers: a single-dose study. *Br J Clin Pharmacol* 1998; **46** (suppl 1): 19–24.
2. Reyes JF, *et al.* Steady-state pharmacokinetics, pharmacodynamics and tolerability of donepezil hydrochloride in hepatically impaired patients. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 9–17.
3. Nagy CF, *et al.* Steady-state pharmacokinetics and safety of donepezil HCl in subjects with moderately impaired renal function. *Br J Clin Pharmacol* 2004; **58** (suppl 1): 18–24.

Uses and Administration

Donepezil hydrochloride, a piperidine derivative, is a reversible and selective inhibitor of acetylcholinesterase with actions similar to those of neostigmine (p.632). It is highly selective for the CNS and is used for the symptomatic treatment of dementia in Alzheimer's disease (below). In the UK, the licensed use of donepezil is limited to those patients with mild to moderately severe dementia; however, in the USA it is also licensed for use in those with severe symptoms.

Regardless of severity, donepezil hydrochloride is given in an initial oral dose of 5 mg once daily increased if necessary after 4 to 6 weeks to a maximum of 10 mg once daily; the dose should be taken just before bedtime. Clinical benefit should be reassessed on a regular basis.

In some countries, donepezil is also licensed for use in patients with vascular dementia (below); doses are similar to those used for the treatment of dementia in Alzheimer's disease.

Dementia. Donepezil hydrochloride is used in the symptomatic treatment of dementia in *Alzheimer's disease* (see Dementia, p.362). In individual studies, it appears to produce modest benefits in some patients with mild to moderately severe dementia.[1-4] These findings are also supported by a systematic review[5] which concluded that, for treatment periods of up to 1 year, donepezil produces modest improvements in cognitive function and global clinical state. Benefit has also been reported in patients with more severe dementia.[5-8] Although there are no comparative studies of donepezil and tacrine it has been suggested[9-11] that donepezil may prove preferable as it appears to be better tolerated and hepatotoxicity has not been reported to be a problem (but see Adverse Effects, above).

In the UK, NICE has recommended that treatment with donepezil should be limited to patients with moderate dementia and given under the following conditions:[12]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that donepezil could no longer be recommended in the treatment of mild dementia because its cost-effectiveness was questionable; however, it was recommended that those currently taking donepezil for mild dementia should continue on therapy until it was considered appropriate to stop.

Donepezil has also been tried in patients with *mild cognitive impairment*.[13,14] Findings from a double-blind study[14] have suggested that although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment when compared with placebo, the rate of progression after 3 years of therapy was not lower than that of the placebo group. The authors of a systematic review[15] of these 2 studies found no evidence to support the use of donepezil in patients with mild cognitive impairment. Any benefits were considered to be minor, short-lived, and associated with significant adverse effects.

Donepezil may be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[16] have shown an improvement in cognition and global function in patients with probable or possible vascular dementia. A systematic review also concluded that donepezil improved mild to moderate vascular cognitive impairment in the short term (treatment for 6 months).[17] The manufacturer has reported[18] that out of a total of 3 studies of donepezil in vascular dementia, one (Study 319) showed an apparently increased mortality compared with placebo: 1.7% and 0%, respectively. In a combined analysis of the other 2 studies, the mortality rate was 1.7% in the donepezil group and 2% in the placebo group. Combined analysis of all 3 studies showed no statistically significant difference in the mortality rates between the donepezil (1.7%) and placebo (1.1%) groups; the risk of vascular events such as stroke and myocardial infarction was also similar for each group. The unexpectedly low mortality rate with placebo in Study 319 was unusual given the age and pathology of the subjects. An increased risk of death has been reported with *galantamine* when used in patients who did not have Alzheimer's disease (see Effects on the Cardiovascular and Cerebrovascular Systems, p.366).

1. Rogers SL, *et al.* A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998; **50:** 136–45.
2. Mohs RC, *et al.* A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001; **57:** 481–8.
3. Winblad B, *et al.* A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57:** 489–95.
4. Holmes C, *et al.* The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004; **63:** 214–19.
5. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 13/02/06).
6. Feldman H, *et al.* A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; **57:** 613–20.
7. Winblad B, *et al.* Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet* 2006; **367:** 1057–65.
8. Black SE, *et al.* Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology* 2007; **69:** 459–69.
9. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
10. Shintani EY, Uchida KM. Donepezil: an anticholinesterase inhibitor for Alzheimer's disease. *Am J Health-Syst Pharm* 1997; **54:** 2805–10.
11. Barner EL, Gray SL. Donepezil use in Alzheimer disease. *Ann Pharmacother* 1998; **32:** 70–7.
12. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)
13. Salloway S, *et al.* Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004; **63:** 651–7.
14. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.
15. Birks J, Flicker L. Donepezil for mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 09/08/07).
16. Black S, *et al.* Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003; **34:** 2323–30.
17. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 13/02/06).
18. Eisai, Jpn. Eisai reports results from latest donepezil study in vascular dementia (issued 16th March, 2006). Available at: http://www.eisai.co.jp/enews/enews200609pdf.pdf (accessed 09/08/07)

Parkinsonism. Although acetylcholinesterase inhibitors such as donepezil hydrochloride may theoretically worsen parkinsonism symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p.954).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alzaimax; Cebrocal; Crialix; Cristaclar; Donepes; Donzeimer; Endoclar; Eranz; Lirpan; Oldinot; Onefin; Valpex; ***Austral.:*** Aricept; ***Austria:*** Aricept; ***Belg.:*** Aricept; ***Braz.:*** Eranz; ***Canad.:*** Aricept; ***Chile:*** Dazolin; Eranz; Evimal; ***Cz.:*** Aricept; Yasnal; ***Denm.:*** Aricept; ***Fin.:*** Aricept; ***Fr.:*** Aricept; ***Ger.:*** Aricept; ***Gr.:*** Aricept; ***Hong Kong:*** Aricept; ***Hung.:*** Aricept; ***India:*** Donaz; Donecept; ***Indon.:*** Alzim; Aricept; Fordesia; ***Irl.:*** Aricept; ***Israel:*** Aricept; Asenta; Memorit; ***Ital.:*** Aricept; Memac; ***Jpn:*** Aricept; ***Malaysia:*** Aricept; ***Mex.:*** Eranz; ***Norw.:*** Aricept; ***NZ:*** Aricept; ***Philipp.:*** Aricept; ***Pol.:*** Aricept; Cogiton; Donepex; Yasnal; ***Port.:*** Aricept; ***Rus.:*** Aricept (Арисепт); ***S.Afr.:*** Aricept; ***Singapore:*** Aricept; ***Spain:*** Aricept; ***Swed.:*** Aricept; ***Switz.:*** Aricept; ***Thai.:*** Aricept; ***Turk.:*** Aricept; ***UK:*** Aricept; ***USA:*** Aricept; ***Venez.:*** Eranz.

Galantamine Hydrobromide

(BANM, USAN, rINNM)

Galantamine, bromhydrate de; Galantamini hydrobromidum; Galanthamine Hydrobromide; Galanthamini Hydrobromidum; Hidrobromuro de galantamina. (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide.

Галантамина Гидробромид

$C_{17}H_{21}NO_3,HBr$ = 368.3.

CAS — 357-70-0 (galantamine); 1953-04-4 (galantamine hydrobromide).

ATC — N06DA04.

ATC Vet — QN06DA04.

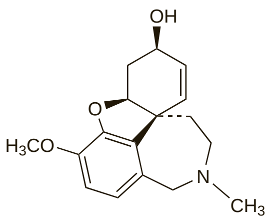

(galantamine)

Description. The hydrobromide of galantamine, an alkaloid which has been obtained from the Caucasian snowdrop (Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae), and related species.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Galantamine Hydrobromide). A white to almost white powder. Sparingly soluble in water; very slightly soluble in alcohol; soluble in 0.1N sodium hydroxide; insoluble in propyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p.364. Hypertension has also been reported with galantamine.

For details regarding dose adjustments in moderate hepatic or renal impairment, see under Uses and Administration, below. There are no data on the use of galantamine in patients with severe hepatic or renal impairment and consequently in the licensed product information it is contra-indicated in such patients; it should also not be given to patients with both significant hepatic and renal impairment.

Effects on the cardiovascular and cerebrovascular systems. Results from 2 studies of the use of galantamine in mild cognitive impairment (an unlicensed indication) have suggested that there may be an increased risk of death in patients given galantamine compared with those on placebo: out of a total of about 2000 patients, 13 died in the galantamine groups with only 1 death reported in the placebo groups.[1,2] About half of the deaths were caused by cardiovascular or cerebrovascular events.

For a suggestion of possibly increased mortality with *donepezil* in patients with vascular dementia, see Dementia, p.365.

1. Janssen-Ortho Inc. Safety information from investigational studies with Reminyl (galantamine hydrobromide) in mild cognitive impairment (MCI) (issued 18th April, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/reminyl_hpc-eng.pdf (accessed 05/08/08)
2. Ortho-McNeil Neurologics, Inc. Important prescribing information: deaths in subjects with mild cognitive impairment (MCI) (issued 31st March, 2005). Available at: http://www.fda.gov/medwatch/SAFETY/2005/reminylDDLmarch.pdf (accessed 14/02/06)

Interactions

As for Neostigmine, p.632. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Consequently its bioavailability may be increased by drugs that inhibit CYP2D6, such as quinidine, fluoxetine, fluvoxamine, and paroxetine, and by those that inhibit CYP3A4, such as ketoconazole and ritonavir. Dose reduction of galantamine may be required when given with such drugs.

Pharmacokinetics

Galantamine is well absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in about 1 hour after ingestion from conventional formulations; with modified-release formulations, peak concentrations occur about 4 to 5 hours after a dose and are somewhat lower. The absolute oral bioavailability of galantamine is about 90%. The presence of food delays the rate of absorption although the extent of absorption is not affected. Protein binding is about 18%. Galantamine is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; a number of active metabolites are formed. The elimination half-life is about 7 to 8 hours. After 7 days, the majority of a single oral dose is recovered in the urine with up to about 6% detected in the faeces; about 20 to 30% of the dose is excreted in the urine as unchanged galantamine. Clearance is reported to be 20% lower in females than in males and 25% lower in poor metabolisers than in extensive metabolisers.

◊ References.

1. Zhao Q, *et al.* Pharmacokinetics and safety of galantamine in subjects with hepatic impairment and healthy volunteers. *J Clin Pharmacol* 2002; **42:** 428–36.
2. Piotrovsky V, *et al.* Galantamine population pharmacokinetics in patients with Alzheimer's disease: modeling and simulations. *J Clin Pharmacol* 2003; **43:** 514–23.
3. Farlow MR. Clinical pharmacokinetics of galantamine. *Clin Pharmacokinet* 2003; **42:** 1383–92.

Uses and Administration

Galantamine hydrobromide is a reversible inhibitor of acetylcholinesterase activity, with actions similar to those of neostigmine (p.632). It also has an intrinsic action on nicotinic receptors. It is used in the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (below).

Galantamine is given as the hydrobromide although doses are expressed in terms of the base; 5.1 mg of galantamine hydrobromide is equivalent to about 4 mg of galantamine. An initial oral dose of 4 mg is given twice daily with food for 4 weeks, then increased to 8 mg twice daily. This dose should be maintained for at least 4 weeks; thereafter, the dose may be further increased to 12 mg twice daily according to response and tolerance. A modified-release preparation is also available for once-daily use. The clinical benefit of galantamine should be reassessed, preferably within the first 3 months, and thereafter on a regular basis. Reductions in dose may be necessary in patients with hepatic or renal impairment (see below) or in those also taking certain cytochrome P450 isoenzyme inhibitors (see Interactions, above).

Galantamine hydrobromide has also been used in various neuromuscular disorders, and to curtail the muscle relaxation produced by competitive neuromuscular blockers.

Administration in hepatic impairment. No dose adjustment is necessary in mild hepatic impairment. Patients with moderate impairment should begin with an oral dose of 4 mg once daily (or 8 mg every other day if using a modified-release preparation), preferably taken in the morning, for at least one week; thereafter the dose may be increased to 4 mg twice daily (or its once-daily equivalent if using a modified-release preparation) for at least 4 weeks, with subsequent increases up to a maximum of 8 mg twice daily (or its once-daily equivalent if using a modified-release preparation). Galantamine is contra-indicated in severe impairment (Child-Pugh Category C) due to lack of data.

Administration in renal impairment. UK licensed product information states that no dose adjustment is necessary in mild or moderate renal impairment. However, US licensed product information recommends that the dose should not exceed 16 mg daily in patients with moderate impairment.

Galantamine is contra-indicated in severe impairment (creatinine clearance less than 9 mL/minute) due to lack of data.

Dementia. Reviews[1-3] suggest that galantamine is of benefit in patients with mild to moderate symptoms of *Alzheimer's disease* (see Dementia, p.362); evidence in more severely impaired subjects is lacking. In the UK, NICE has recommended that the use of galantamine should be limited to patients with moderate dementia and given under the following conditions:[4]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that galantamine could no longer be recommended in the treatment of mild dementia because its cost-effectiveness was questionable; however, it was recommended that those currently taking galantamine for mild dementia should continue on therapy until it was considered appropriate to stop.

Galantamine may also be effective in the treatment of *vascular dementia*. Results from a randomised, controlled study[5] have shown a trend towards improved cognition in patients with probable vascular dementia, although patients numbers were too small for this to be significant. A more recent multicentre study[6] in patients with probable vascular dementia found cognitive improvement with galantamine to be greater than with placebo; however, improvement in daily activities with galantamine was similar to that seen with placebo.

A systematic review[3] concluded that galantamine could not be recommended for treatment in patients with *mild cognitive impairment* because of limited clinical benefit and an unexplained association with an excess death rate (see also Effects on the Cardiovascular and Cerebrovascular Systems, above).

1. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs* 2000; **60:** 1095–1122.
2. Pearson VE. Galantamine: a new Alzheimer drug with a past life. *Ann Pharmacother* 2001; **35:** 1406–13.
3. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/02/06).
4. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)
5. Erkinjuntti T, *et al.* Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002; **359:** 1283–90.
6. Auchus AP, *et al.* Galantamine treatment of vascular dementia: a randomized trial. *Neurology* 2007; **69:** 448–58.

Preparations

USP 31: Galantamine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Intelec; Numencial; Reminyl; ***Austral.:*** Reminyl; ***Austria:*** Reminyl; ***Belg.:*** Reminyl; ***Braz.:*** Reminyl; ***Canad.:*** Reminyl; ***Chile:*** Reminyl; ***Cz.:*** Apo-Galant; Flashemel; Galamed; Kuroment; OxyGal; Reminyl; ZapTron; ***Denm.:*** Reminyl; ***Fin.:*** Reminyl; ***Fr.:*** Reminyl; ***Ger.:*** Reminyl; ***Gr.:*** Reminyl; ***Hong Kong:*** Reminyl; ***Hung.:*** Nivalin†; ***Indon.:*** Reminyl; ***Irl.:*** Reminyl; ***Israel:*** Reminyl; ***Ital.:*** Reminyl; ***Malaysia:*** Reminyl; ***Mex.:*** Reminyl; ***Neth.:*** Reminyl; ***Norw.:*** Reminyl; ***NZ:*** Reminyl; ***Philipp.:*** Reminyl; ***Pol.:*** Nivalin; Reminyl†; ***Port.:*** Reminyl; ***Rus.:*** Nivalin (Нивалин); Reminyl (Реминил); ***S.Afr.:*** Reminyl; ***Singapore:*** Reminyl; ***Spain:*** Reminyl; ***Swed.:*** Reminyl; ***Switz.:*** Reminyl; ***Thai.:*** Reminyl; ***Turk.:*** Reminyl; ***UK:*** Reminyl; ***USA:*** Razadyne; ***Venez.:*** Proneurax.

Idazoxan Hydrochloride *(BANM, pINNM)*

Hidrocloruro de idazoxano; Idazoxan, Chlorhydrate d'; Idazoxani Hydrochloridum; RX-781094. 2-(2,3-Dihydro-1,4-benzodioxin-2-yl)-2-imidazoline hydrochloride.

Идазоксана Гидрохлорид

$C_{11}H_{12}N_2O_2HCl$ = 240.7.

CAS — 79944-58-4 (idazoxan); 79944-56-2 (idazoxan hydrochloride).

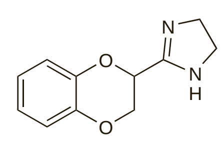

(idazoxan)

Profile

Idazoxan hydrochloride is an $alpha_2$-adrenoceptor antagonist that has been investigated in neurological disorders including depression, dementia, and parkinsonism.

◊ References.

1. Ghika J, *et al.* Idazoxan treatment in progressive supranuclear palsy. *Neurology* 1991; **41:** 986–91.
2. Litman RE, *et al.* Idazoxan, an alpha2 antagonist, augments fluphenazine in schizophrenic patients: a pilot study. *J Clin Psychopharmacol* 1993; **13:** 264–7.
3. Grossman F, *et al.* A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. *J Affect Disord* 1999; **56:** 237–43.
4. Manson AJ, *et al.* Idazoxan is ineffective for levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2000; **15:** 336–7.
5. Rascol O, *et al.* Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease. *Mov Disord* 2001; **16:** 708–13.

Idebenone *(rINN)*

CV-2619; Idebenona; Idébénone; Idebenonum. 2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.

Идебенон

$C_{19}H_{30}O_5$ = 338.4.

CAS — 58186-27-9.

ATC — N06BX13.

ATC Vet — QN06BX13.

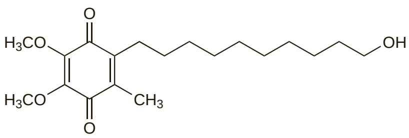

Profile

Idebenone has been used in the treatment of mental impairment associated with cerebrovascular disorders. A dose of 90 mg daily has been given orally in 2 divided doses after food. Idebenone has also been tried in Alzheimer's disease. It has also been investigated for the management of various clinical manifestations of Friedreich's ataxia and is used orally in a dose of 5 mg/kg daily in 3 divided doses for cardiomyopathy in this disease.

Idebenone is also available as a 1% cream for the cosmetic treatment of wrinkles.

Dementia. Idebenone was found to be safe and effective in patients with mild to moderate Alzheimer's disease (p.362) when followed for up to 2 years.[1,2] In a further study,[3] its safety and efficacy were comparable to tacrine. However, another study[4] found no clinically significant slowing of cognitive decline in patients with Alzheimer's disease treated with idebenone.

1. Weyer G, *et al.* Efficacy and safety of idebenone in the long-term treatment of Alzheimer's disease: a double-blind, placebo controlled multicentre study. *Hum Psychopharmacol Clin Exp* 1996; **11:** 53–65.
2. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm* 1998; **54** (suppl): 301–10.
3. Gutzmann H, *et al.* Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry* 2002; **35:** 12–18.
4. Thal LJ, *et al.* Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* 2003; **61:** 1498–1502.

Friedreich's ataxia. Preliminary studies of idebenone in the treatment of Friedreich's ataxia.[1-5]

1. Hausse AO, *et al.* Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 2002; **87:** 346–9.
2. Artuch R, *et al.* Friedreich's ataxia: idebenone treatment in early stage patients. *Neuropediatrics* 2002; **33:** 190–3.
3. Mariotti C, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; **60:** 1676–9.
4. Buyse G, *et al.* Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 2003; **60:** 1679–81.
5. Rustin P, *et al.* Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2004; **62:** 524–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Esanic; Geniceral; Idesole; Nemocebral; Pavertrin; Sicoplus; Ulcouro-na†; ***Ital.:*** Daruma†; Mnesis; ***Mex.:*** Lucebanol; ***Port.:*** Amizal; Cerestabon; Idecortex; ***Rus.:*** Noben (Нобен); ***Switz.:*** Mnesis; ***USA:*** Prevage.

Multi-ingredient: ***Arg.:*** Idesole Plus; Nemocebral Plus.

Memantine Hydrochloride

(BANM, USAN, rINNM)

1-Amino-3,5-dimethyladamantane Hydrochloride; D-145 (memantine); 3,5-Dimethyl-1-adamantanamine hydrochloride; DMAA (memantine); Hidrocloruro de memantina; Memantin Hidroklorür; Mémantine, Chlorhydrate de; Memantini Hydrochloridum. 3,5-Dimethyltricyclo[3.3.1.1.^{3,7}]decan-l-amine hydrochloride.

Мемантина Гидрохлорид

$C_{12}H_{21}N,HCl$ = 215.8.

CAS — 19982-08-2 (memantine); 41100-52-1 (memantine hydrochloride).

ATC — N06DX01.

ATC Vet — QN06DX01.

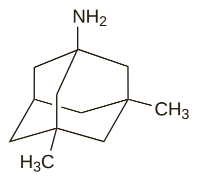

(memantine)

Adverse Effects and Precautions

Common adverse effects with memantine include constipation, dizziness, headache, hypertension, and somnolence. Less common reactions such as anxiety, hallucinations, confusion, fatigue, abnormal gait, hypertonia, vomiting, fungal infections, cystitis, thromboembolism, and increased libido have also occurred. Isolated cases of psychotic reactions and pancreatitis have been reported.

Dosage adjustment may be required in renal impairment, but recommendations vary, (see below).

Only limited clinical data are available for patients with recent myocardial infarction, uncompensated congestive heart failure, and uncontrolled hypertension and use of memantine in these patients should be closely monitored. Seizures have occurred rarely and caution is recommended in patients at risk of convulsions. Conditions that increase urinary pH, such as drastic changes in diet, renal tubular acidosis, or severe infections of the urinary tract, may decrease elimination of memantine resulting in increased plasma levels; patient monitoring is recommended in such cases.

Interactions

Use of other *N*-methyl-D-aspartate antagonists such as amantadine, ketamine, or dextromethorphan with memantine may increase both the incidence and severity of adverse effects and should be avoided. The effects of dopaminergics and antimuscarinics may also be enhanced whereas memantine may reduce the actions of barbiturates and antipsychotics.

Memantine may alter the effects of the antispasmodics baclofen and dantrolene. The clearance of memantine is reduced under alkaline urine conditions and drugs such as carbonic anhydrase inhibitors and sodium bicarbonate should be used with caution.

Pharmacokinetics

Memantine is well absorbed after oral doses. Peak plasma concentrations are achieved in about 3 to 8 hours. Plasma protein binding is about 45%. Memantine undergoes partial hepatic metabolism; the main metabolites include *N*-3,5-dimethyl-gludantan and 1-nitroso-3,5-dimethyl-adamantane. The majority of a dose is excreted unchanged via the kidney; some active renal tubular secretion and reabsorption occurs. The terminal half-life ranges from 60 to 100 hours although under alkaline conditions the rate of elimination is reduced.

◊ References.

1. Periclou A, *et al.* Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clin Pharmacol Ther* 2006; **79:** 134–43.
2. Kornhuber J, *et al.* Memantine pharmacotherapy: a naturalistic study using a population pharmacokinetic approach. *Clin Pharmacokinet* 2007; **46:** 599–612. Correction. *ibid.*; 712.

Uses and Administration

Memantine is a derivative of amantadine (p.792) and is likewise an antagonist of *N*-methyl-D-aspartate receptors. It is given in the treatment of moderate to severe Alzheimer's disease (see Dementia, below). Memantine has also been given in the treatment of parkinsonism and central spasticity, and in other disorders such as brain injury or comatose states. It is given orally as the hydrochloride.

In the treatment of **Alzheimer's disease**, the initial dose of memantine hydrochloride is 5 mg daily in the morning for the first week; this should be increased in weekly increments of 5 mg to a maximum dose of 20 mg daily. Doses of 10 mg daily and over should be taken in 2 divided doses. Dosage adjustment may be required in patients with renal impairment (see below). Clinical benefit should be reassessed on a regular basis.

Memantine hydrochloride has also been given by slow intravenous injection.

Memantine is under investigation in the treatment of glaucoma and peripheral neuropathy.

Administration in renal impairment. UK licensed product information advises that no dose adjustment is needed when memantine hydrochloride is given for Alzheimer's disease in patients with mild renal impairment (creatinine clearance [CC] 50 to 80 mL/minute). However, in those with moderate impairment (CC 30 to 49 mL/minute) a dose of 10 mg daily may be used (after starting at 5 mg daily) and if well tolerated after at least 7 days, it may be increased to 20 mg daily as described above (see above). In those with severe impairment (CC 5 to 29 mL/minute) the maximum daily dose is 10 mg. In the USA, licensed product information states that no dose reduction is required in those with mild or moderate impairment; a target dose of 10 mg daily is recommended in patients with severe impairment (CC 5 to 29 mL/minute).

Dementia. A systematic review[1] of the use of memantine in dementia (p.362) concluded that it did have a small beneficial effect on cognitive and functional decline at 6 months in patients with moderate to severe Alzheimer's disease; the effects were not clinically discernible in those with mild to moderate vascular dementia but were discernible in those with mild to moderate Alzheimer's disease. In the UK, NICE[2] has not recommended memantine in the treatment of patients with moderately severe to severe disease because of insufficient evidence of clinical effectiveness. A general review, including a safety profile, of memantine in Alzheimer's disease has also been published.[3]

1. McShane R, *et al.* Memantine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).
2. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)
3. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. *Drugs* 2006; **66:** 1515–34.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Akatinol; Carrier; Conexine; Ebixa; Fentina; Lucidex; Merital; Neuroplus; Pronervon; ***Austral.:*** Ebixa; ***Austria:*** Axura; Ebixa; ***Belg.:*** Ebixa; ***Braz.:*** Alois; Ebix; ***Canad.:*** Ebixa; ***Chile:*** Ebixa; Eutebrol; Memax; Mimetix; ***Cz.:*** Akatinol†; Axura; Ebixa; ***Denm.:*** Ebixa; ***Fin.:*** Ebixa; ***Fr.:*** Ebixa; ***Ger.:*** Axura; Ebixa; ***Gr.:*** Ebixa; ***Hong Kong:*** Ebixa; ***Hung.:*** Ebixa; ***Irl.:*** Ebixa; ***Israel:*** Ebixa; Memox; ***Ital.:*** Ebixa; ***Mex.:*** Ebixa; Eutebrol; ***Neth.:*** Axura; Ebixa; ***Norw.:*** Ebixa; ***NZ:*** Ebixa; ***Philipp.:*** Abixa; ***Pol.:*** Axura; Ebixa; ***Port.:*** Axura; Ebixa; ***S.Afr.:*** Ebixa; ***Singapore:*** Ebixa; ***Spain:*** Axura; Ebixa; ***Swed.:*** Ebixa; ***Switz.:*** Axura; Ebixa; ***Thai.:*** Ebixa; ***Turk.:*** Ebixa; ***UK:*** Ebixa; ***USA:*** Namenda.

Nefiracetam *(rINN)*

DM-9384; DZL-221; Néfiracétam; Nefiracetamum. 2-Oxo-1-pyrrolidineaceto-2',6'-xylidide.

Нефирацетам

$C_{14}H_{18}N_2O_2$ = 246.3.

CAS — 77191-36-7.

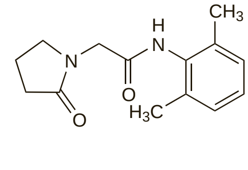

Profile

Nefiracetam acts on the CNS and has been described as a nootropic. It has been investigated in some cerebrovascular disorders and for the treatment of Alzheimer's disease.

Nizofenone *(rINN)*

Nizofenona; Nizofénone; Nizofenonum; Y-9179. 2′-Chloro-2-[2-[(diethylamino)methyl]imidazol-1-yl]-5-nitrobenzophenone.

Низофенон

$C_{21}H_{21}ClN_4O_3$ = 412.9.
CAS — 54533-85-6.
ATC — N06BX10.
ATC Vet — QN06BX10.

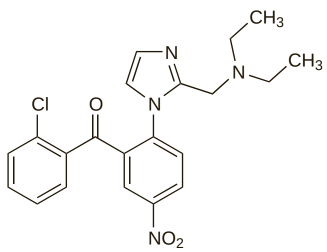

Profile

Nizofenone has been investigated as a nootropic and cerebral vasodilator. It has been used parenterally as the fumarate.

Oxiracetam *(BAN, rINN)*

CGP-21690E; CT-848; ISF-2522; Oksirasetaami; Oxiracétam; Oxiracetamum; Oxracetam. 4-Hydroxy-2-oxo-1-pyrrolidineacetamide.

Оксирацетам

$C_6H_{10}N_2O_3$ = 158.2.
CAS — 62613-82-5.
ATC — N06BX07.
ATC Vet — QN06BX07.

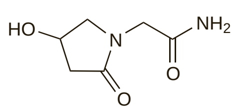

Profile

Oxiracetam has been used as a nootropic in organic brain syndromes and senile dementia.

Dementia. Clinical benefit has been reported in patients with dementia (p.362) given oxiracetam,[1] but in the USA it was withdrawn from phase II clinical studies in patients with Alzheimer's disease due to lack of efficacy.[2]

1. Maina G, *et al.* Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study. *Neuropsychobiology* 1990; **21**: 141–5.
2. Parnetti L. Clinical pharmacokinetics of drugs for Alzheimer's disease. *Clin Pharmacokinet* 1995; **29**: 110–29.

4-Phenylpiracetam ⊗

BRN-5030440; Carphedon; Karfedon. 2-Oxo-4-phenyl-1-pyrrolidineacetamide.

$C_{12}H_{14}N_2O_2$ = 218.3.
CAS — 77472-70-9.

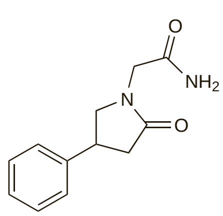

Profile

4-Phenylpiracetam is a nootropic and has been used in the management of various cerebrovascular disorders. It has also been abused in sport.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Phenotropil (Фенотропил).

Piracetam *(BAN, USAN, rINN)*

CI-871; Piracétam; Piracetamas; Piracetamum; Pirasetaami; Pirasetam; Pyrrolidone Acetamide; UCB-6215. 2-(2-Oxopyrrolidin-1-yl)acetamide.

Пирацетам

$C_6H_{10}N_2O_2$ = 142.2.
CAS — 7491-74-9.
ATC — N06BX03.
ATC Vet — QN06BX03.

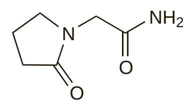

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Piracetam). A white or almost white powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol. Protect from light.

Adverse Effects and Precautions

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, and depression. Other reported adverse effects include gastrointestinal disorders such as abdominal pain, diarrhoea, nausea and vomiting, hypersensitivity reactions, ataxia, vertigo, confusion, hallucinations, angioedema, and rashes. Piracetam should not be given to patients with hepatic impairment or severe renal impairment; dosage reduction is recommended for those with mild to moderate renal impairment. Therapy with piracetam should not be withdrawn abruptly in myoclonic patients due to the risk of inducing seizures. When used to treat cortical myoclonus, piracetam is contra-indicated in patients with cerebral haemorrhage, and should be used with caution after major surgery and in those with haemostatic disorders or severe haemorrhage.

Interactions

Anticoagulants. For reference to the effect of piracetam on *warfarin* therapy, see p.1431.

Pharmacokinetics

Piracetam is rapidly and extensively absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 1.5 hours after oral doses. The plasma half-life is reported to be 5 hours and it crosses the blood-brain barrier. Piracetam is excreted almost completely in the urine. It crosses the placenta and is distributed into breast milk.

Uses and Administration

Piracetam acts on the CNS and has been described as a nootropic; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin, and has also been used in dementia (see also below). Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo, cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

In cortical myoclonus, piracetam is given in oral doses of 7.2 g daily increasing by 4.8 g daily every 3 or 4 days up to a maximum of 20 g daily. It is given in 2 or 3 divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs. For dosage in renal impairment see below.

Piracetam has been given for various other disorders in a usual oral dose of up to 2.4 g daily in 2 or 3 divided doses; higher doses of up to 4.8 g daily have been used in severe cases. In severe disorders it has also been given by intramuscular or intravenous injection.

◊ General references.

1. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. *CNS Drug Rev* 2005; **11**: 169–82.

Administration in renal impairment. Dosage should be reduced in patients with mild to moderate renal impairment according to creatinine clearance (CC):

- CC between 50 and 79 mL/minute: two-thirds of the usual dose, given in 2 or 3 divided doses
- CC between 30 and 49 mL/minute: one-third of the usual dose, given in 2 divided doses
- CC between 20 and 29 mL/minute: one-sixth of the usual dose, given as a single dose
- CC less than 20 mL/minute: contra-indicated

Dementia. Although piracetam is used in some countries in the management of cognitive impairment and dementia (p.362), a systematic review[1] concluded that the evidence from the published literature did not support this use.

1. Flicker L, Grimley Evans J. Piracetam for dementia or cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/02/06).

Myoclonus. A review[1] of 62 case reports, 3 open studies, and 2 double-blind studies concluded that piracetam is beneficial in the treatment of disabling myoclonus (p.470), either as adjunctive treatment or as monotherapy. Similar conclusions were made in another review[2] in which experience of 12 patients with progressive myoclonus epilepsy, 8 of whom benefited from piracetam in doses of up to 45 g daily without significant adverse effects, was described.

1. Van Vleymen B, Van Zandijcke M. Piracetam in the treatment of myoclonus: an overview. *Acta Neurol Belg* 1996; **96**: 270–80.
2. Genton P, *et al.* Piracetam in the treatment of cortical myoclonus. *Pharmacopsychiatry* 1999; **32** (suppl): 49–53.

Stroke. Piracetam did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke in a multicentre, randomised, double-blind study,[1] although post hoc analyses suggested that it might confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate to severe degree. Further analyses of the same data concluded that piracetam did not produce significant adverse effects when given in high doses to patients with acute stroke,[2] and significantly more patients had recovered from aphasia on piracetam than placebo.[3] The results of two further randomised, double-blind, placebo-controlled studies supporting the role of piracetam as an adjunct to intensive speech therapy in improving aphasia following stroke were also reported.[3] In contrast, a systematic review including the first study considered that the trend towards an increased risk of early death in patients allocated to piracetam was of concern, and concluded that the data did not support routine use of piracetam in acute ischaemic stroke.[4]

1. De Deyn PP, *et al.* Treatment of acute and ischemic stroke with piracetam. *Stroke* 1997; **28**: 2347–52.
2. De Reuck J, Van Vleymen B. The clinical safety of high-dose piracetam—its use in the treatment of acute stroke. *Pharmacopsychiatry* 1999; **32** (suppl): 33–7.
3. Huber W. The role of piracetam in the treatment of acute and chronic aphasia. *Pharmacopsychiatry* 1999; **32** (suppl): 38–43.
4. Ricci S, *et al.* Piracetam for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/05/08).

Vertigo. Piracetam has been reported to be of benefit in patients with vertigo (p.565) of both central or peripheral origin.[1]

1. Oosterveld WJ. The effectiveness of piracetam in vertigo. *Pharmacopsychiatry* 1999; **32** (suppl): 54–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Noostan; ***Austria:*** Cerebryl; Nootropil; Novocephal; Pirabene; ***Belg.:*** Braintop; Docpirace; Geratam; Noodis; Nootropil; Piracemed; Piracetop; ***Braz.:*** Cintilan; Nootrofic†; Nootron; Nootropil; ***Chile:*** Nootropyl; ***Cz.:*** Cerebryl†; Geratam; Kalicor; Nootropil; Oikamid; Pirabene; ***Fin.:*** Nootropil; ***Fr.:*** Axonyl†; Gabacet; Geram†; Nootropyl; ***Ger.:*** Avigilen; Cerebroforte†; Cerepar N; Cuxabrain†; Memo-Puren†; Nootrop; Normabrain; Piracebral; Piracetrop; Sinapsan; ***Gr.:*** Aminotrophylle-88; Arterosol†; Cebragil; Latys; Lobelo; Meclivin†; Meditam†; Noforit; Nootrop; Oxynium; Piracem; Stamin; ***Hong Kong:*** Nootropil; Piratin; ***Hung.:*** Cerebryl; Lucetam; Memoril; Nootropil; Pirabene; Pyramen†; ***India:*** Nootropil; Normenta; Pirament; Piratam†; ***Indon.:*** Antikun; Benocetam; Cetoros; Chepamed; Ciclobrain; Encebion; Ethopil; Fepiram; Gotropil; Gracetam; Latropil; Lutrotam; Mersitropil; Neurocet; Neurotam; Noocephal; Nootropil; Nufacetam; Piratrof; Pratropil; Primatam; Procetam; Resibron; Revolan; Scantropil; Sotropil; Tropilex; ***Ital.:*** Cerebropan†; Nootropil; Norzetam†; Psycoton; ***Jpn:*** Myocalm; Nootropil; ***Malaysia:*** Cebrotonin†; Knowful; Nootropil; ***Mex.:*** Dinagen; Nootropil; ***Neth.:*** Nootropil; ***Norw.:*** Nootropil; ***Philipp.:*** Irahex; Nootropil; ***Pol.:*** Lucetam; Memotropil; Nootropil; ***Port.:*** Acetar; Noostan; Nootropil; Oxibran; Stimubral†; ***Rus.:*** Lucetam (Луцетам); Memotropil (Мемотропил); Nootropil (Ноотропил); Phezam (Фезам); Piratropil (Пиратропил); ***S.Afr.:*** Nootropil; ***Singapore:*** Cebrotonin; Cetam†; Nootropil; Piratam; Racetam; ***Spain:*** Ciclofalina; Nootropil; ***Swed.:*** Nootropil; ***Switz.:*** Nootropil; Pirax; ***Thai.:*** Embol; Mempil; Noocetam; Nootropil; Scarda; ***Turk.:*** Nootropil; Norotrop; ***UK:*** Nootropil; ***Venez.:*** Breinox; Nootropil†.

Multi-ingredient: ***Braz.:*** Energiclin; Energivit; Exit; Isketam; Vincetron†; ***Port.:*** Anacervix; Centracetam†; Euvifor†; Stimilfar†; ***Rus.:*** Omaron (Омарон); Piracezine (Пирацезин); Vinpotropile (Винпотропил); ***Spain:*** Anacervix; Devincal; Diemil; Piracetam Complex†; ***Venez.:*** Devincal†.

Posatirelin (rINN)

Posatirelina; Posatiréline; Posatirelinum; RGH-2202. (2S)-N[(1S)-1-[[(2S)-2-Carbamoyl-1-pyrrolidinyl]carbonyl]-3-methylbutyl]-6-oxopipecolamide.

Позатирелин

$C_{17}H_{28}N_4O_4$ = 352.4.
CAS — 78664-73-0.

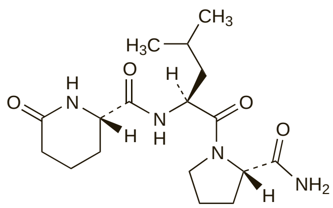

Profile

Posatirelin is an analogue of protirelin (p.2175). It is claimed to have beneficial effects on CNS function, and has been investigated in the management of dementia of various causes.

◊ References.

1. Parnetti L, *et al.* Posatirelin for the treatment of late-onset Alzheimer's disease: a double-blind multicentre study vs citicoline and ascorbic acid. *Acta Neurol Scand* 1995; **92:** 135–40.
2. Parnetti L, *et al.* Posatirelin in the treatment of vascular dementia: a double-blind multicentre study vs placebo. *Acta Neurol Scand* 1996; **93:** 456–63.
3. Reboldi G, *et al.* Pharmacokinetic profile and endocrine effects of posatirelin treatment in healthy elderly subjects. *J Clin Pharmacol* 1996; **36:** 823–31.

Pramiracetam Sulfate (USAN, rINNM)

Amacetam Sulphate; CI-879; Pramiracétam, Sulfate de; Pramiracetam Sulphate; Pramiracetami Sulfas; Sulfato de pramiracetam. N-[2-(Diisopropylamino)ethyl]-2-oxo-1-pyrrolidineacetamide sulphate.

Прамирацетама Сульфат

$C_{14}H_{27}N_3O_2,H_2SO_4$ = 367.5.
CAS — 68497-62-1 (pramiracetam); 72869-16-0 (pramiracetam sulfate).
ATC — N06BX16.
ATC Vet — QN06BX16.

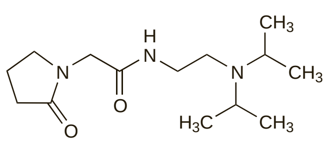

(pramiracetam)

Profile

Pramiracetam sulfate has been used in age-related memory impairment and senile dementia. It has also been tried, without much success, as an adjunct to ECT in severe depression.

◊ References.

1. McLean A, *et al.* Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia. *Brain Inj* 1991; **5:** 375–80.
2. Auteri A, *et al.* Pharmacokinetics of pramiracetam in healthy volunteers after oral administration. *Int J Clin Pharmacol Res* 1992; **12:** 129–32.
3. Scarpazza P, *et al.* Multicenter evaluation of pramiracetam for the treatment of memory impairment of probable vascular origin. *Adv Therapy* 1993; **10:** 217–25.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Neupramir†.

Pyritinol Hydrochloride (BANM, rINNM)

Hidrocloruro de piritinol; Pirytynolu dichlorowodorek; Pyrithioxine Hydrochloride; Pyritinol, Chlorhydrate de; Pyritinoli Dihydrochloridum; Pyritinoli Hydrochloridum. 5,5-Dihydroxy-6,6-dimethyl-3,3-dithiodimethylenebis(4-pyridylmethanol) dihydochloride monohydrate.

Пиритинола Гидрохлорид

$C_{16}H_{20}N_2O_4S_2,2HCl,H_2O$ = 459.4.
CAS — 1098-97-1 (pyritinol); 10049-83-9 (anhydrous pyritinol hydrochloride).
ATC — N06BX02.
ATC Vet — QN06BX02.

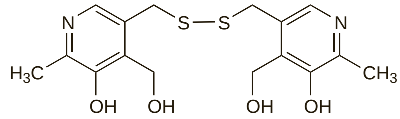

(pyritinol)

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Pyritinol hydrochloride has been described as a nootropic that promotes the uptake of glucose by the brain. It has been used in the treatment of various cerebrovascular and mental function disorders. It has been given in a usual oral dose of 600 mg daily in 3 divided doses. Pyritinol hydrochloride has also been given as an alternative to penicillamine in rheumatoid arthritis. It is also an ingredient of various preparations promoted as tonics.

◊ References.

1. Knezevic S, *et al.* Pyritinol treatment of SDAT patients: evaluation by psychiatric and neurological examination, psychometric testing and rCBF measurements. *Int Clin Psychopharmacol* 1989; **4:** 25–38.
2. Lemmel EM. Comparison of pyritinol and auranofin in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1993; **32:** 375–82.
3. Straumann A, *et al.* Acute pancreatitis due to pyritinol: an immune-mediated phenomenon. *Gastroenterology* 1998; **115:** 452–4.
4. Maria V, *et al.* Severe cholestatic hepatitis induced by pyritinol. *BMJ* 2004; **328:** 572–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Epocan†; ***Austria:*** Encephabol; ***Chile:*** Encefabol; ***Cz.:*** Encephabol; Enerbol; ***Ger.:*** Ardeyceryl P†; Encephabol; ***Hong Kong:*** Encephabol; ***Hung.:*** Enerbol†; ***India:*** Encephabol; ***Indon.:*** Encepan; Encephabol; Enerbol; ***Malaysia:*** Encephabol†; Pyritil; ***Mex.:*** Bonifen†; Encephabol; ***Philipp.:*** Encephabol; ***Port.:*** Bonifen†; Cerbon; ***Rus.:*** Encephabol (Энцефабол); Enerbol (Энербол); ***S.Afr.:*** Encephabol; ***Singapore:*** Encephabol†; ***Thai.:*** Encephabol; Memonol; Pyritil; ***Venez.:*** Acon; Bonifen; Bonitrop; Fitina; Garan†.

Multi-ingredient: ***Arg.:*** Gabimex Plus; ***Spain:*** Refulgin; Viadetres†.

Rivastigmine (BAN, USAN, rINN)

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Rivastigmiini; Rivastigmin; Rivastigmina; Rivastigminum; SDZ-212-713; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate). (−)-m-[(S)-1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate.

Ривастигмин

$C_{14}H_{22}N_2O_2$ = 250.3.
CAS — 123441-03-2.
ATC — N06DA03.
ATC Vet — QN06DA03.

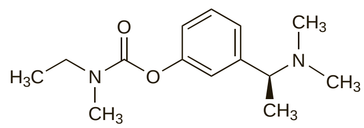

Rivastigmine Hydrogen Tartrate (BANM, rINNM)

ENA-713 (rivastigmine or rivastigmine hydrogen tartrate); Hidrogenotartrato de rivastigmina; Rivastigmine Bitartrate; Rivastigmine, Hydrogénotartrate de; Rivastigmine Tartrate; Rivastigmini Hydrogenotartras; SDZ-ENA-713 (rivastigmine or rivastigmine hydrogen tartrate).

Ривастигмина Гидротартрат

$C_{14}H_{22}N_2O_2.C_4H_6O_6$ = 400.4.
CAS — 129101-54-8.
ATC — N06DA03.
ATC Vet — QN06DA03.

Adverse Effects, Treatment, and Precautions

As for Donepezil, p.364.

Effects on the gastrointestinal tract. A 67-year-old woman experienced severe vomiting after rivastigmine, in an oral dose of 4.5 mg, was mistakenly reintroduced without the recommended titration phase;[1] the vomiting was so severe that the patient also suffered a rupture of the oesophagus that needed corrective surgery. The authors' commented that careful dose titration of rivastigmine is necessary even when restarting treatment.

1. Babic T, *et al.* Spontaneous rupture of oesophagus (Boerhaave's syndrome) related to rivastigmine. *Age Ageing* 2000; **29:** 370–1.

Interactions

As for Neostigmine, p.632. See also Antimuscarinics, under Donepezil, p.365, for mention of an interaction between rivastigmine and tolterodine.

Pharmacokinetics

Rivastigmine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 1 hour after oral doses. Food delays absorption by about 1.5 hours and reduces maximum plasma concentrations. Absorption from transdermal patches is slow and peak plasma concentrations are reached in 10 to 16 hours after applying the first patch; with subsequent patches, peak concentrations are reached in about 8 hours. Exposure to rivastigmine is highest when the patch is applied to the upper back, chest, or upper arm, and about 20 to 30% lower when applied to the abdomen or thigh. Rivastigmine is about 40% bound to plasma proteins and readily crosses the blood-brain barrier; it is widely distributed throughout the body. Rivastigmine is rapidly and extensively metabolised, primarily by cholinesterase-mediated hydrolysis to the weakly active decarbamylated metabolite. The plasma half-life is about 1 hour after oral doses and about 3 hours after patch removal. After oral use, more than 90% of a dose is excreted in the urine within 24 hours; no unchanged rivastigmine is detected in the urine. Less than 1% of a dose appears in the faeces.

◊ References.

1. Hossain M, *et al.* Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. *Clin Pharmacokinet* 2002; **41:** 225–34.
2. Lefèvre G, *et al.* Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of body site application. *J Clin Pharmacol* 2007; **47:** 471–8.
3. Cummings J, *et al.* Pharmacokinetic rationale for the rivastigmine patch. *Neurology* 2007; **69** (suppl 1): S10–S13.
4. Lefèvre G, *et al.* Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients. *Clin Pharmacol Ther* 2008; **83:** 106–14.
5. Lefèvre G, *et al.* Pharmacokinetics and bioavailability of the novel rivastigmine transdermal patch versus rivastigmine oral solution in healthy elderly subjects. *J Clin Pharmacol* 2008; **48:** 246–52.

Uses and Administration

Rivastigmine is a carbamate type reversible acetylcholinesterase inhibitor; it also inhibits butyrylcholinesterase. Rivastigmine is selective for the CNS and is used for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease (below) and idiopathic Parkinson's disease (below). It is given orally as the hydrogen tartrate or in transdermal patches as the base. For both routes doses are expressed in terms of the base; 2.4 mg of rivastigmine hydrogen tartrate is equivalent to about 1.5 mg of rivastigmine.

An initial oral dose is 1.5 mg given twice daily with food. Thereafter, the dose may be increased according to response and tolerance by increments of 1.5 mg twice daily at intervals of at least 2 weeks to a maximum dose of 6 mg twice daily. In the USA, licensed product information recommends dose increments at intervals of at least 4 weeks when treating dementia associated with Parkinson's disease.

Transdermal patches delivering 4.6 or 9.5 mg of rivastigmine over 24 hours are also available for once-daily application. In the USA, rivastigmine patches may be used for the treatment of dementia in Alzheimer's disease or Parkinson's disease; however, in the UK, use is restricted to dementia in Alzheimer's disease. An initial transdermal dose is 4.6 mg daily; after at least 4 weeks and if well tolerated, the dose should be increased to 9.5 mg daily. Patients already taking oral rivastigmine may be changed to the patches as follows:

- those taking 6 mg daily or less of oral rivastigmine may be switched to patches delivering 4.6 mg over 24 hours
- those taking more than 6 mg daily orally may be switched to patches delivering 9.5 mg over 24 hours

The first patch should be applied on the day following the last oral dose. The patch should be applied to intact skin on the upper or lower back, or on the upper arm or chest; it should not be applied to the abdomen or thigh due to decreased bioavailability. Re-application to the same site should be avoided for 14 days.

If treatment with oral or transdermal rivastigmine is interrupted for more than a few days, it should be restarted at the low initial dose, and then increased as described above. Clinical benefit should be reassessed on a regular basis; treatment should be stopped if there is no improvement after 3 months.

Dementia. Studies[1-4] and a systematic review[5] indicate that rivastigmine may be of benefit in the management of patients with mild to moderate dementia in *Alzheimer's disease* (see Dementia, p.362). In the UK, NICE has recommended that its use should be limited to patients with moderate dementia and given under the following conditions:[6]

- treatment should only be started under specialist supervision
- patients who continue on the drug should be reviewed every 6 months
- treatment should only be continued if there was evidence of benefit

In a somewhat controversial decision, NICE considered that rivastigmine could no longer be recommended in the treatment of mild dementia because its cost-effectiveness was questionable; however, it was recommended that those currently taking rivastigmine for mild dementia should continue on therapy until it was considered appropriate to stop.

Rivastigmine given in titrated doses of up to 6 mg twice daily was also found to be well tolerated, and to produce some improvement in behavioural and psychiatric symptoms, in a group of patients with *Lewy-body dementia*.[7] However, a systematic review[8] that included this study noted that rivastigmine did not have significant benefit in cognitive function compared with placebo; the authors considered that the evidence for its use in such patients was weak and that further trials were needed.

Rivastigmine has also been tried in the treatment of *vascular dementia*. A systematic review[9] concluded that although there is some evidence of benefit in these patients, available data are inadequate and further trials were warranted before rivastigmine could be recommended.

For the use of rivastigmine in the treatment of dementia in Parkinson's disease, see below.

1. Anand R, *et al.* Efficacy and safety results of the early phase studies with Exelon (ENA-713) in Alzheimer's disease: an overview. *J Drug Dev Clin Pract* 1996; **8:** 109–116.
2. Agid Y, *et al.* Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. *Curr Ther Res* 1998; **59:** 837–45.
3. Rösler M, *et al.* Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999; **318:** 633–8. Correction. *ibid.* 2001; **322:** 1456.
4. Winblad B, *et al.* IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology* 2007; **69** (suppl 1): S14–S22.
5. Birks J, *et al.* Rivastigmine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 14/02/06).
6. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (issued November 2006; amended September 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA111fullversionamendedSept07.pdf (accessed 05/08/08)
7. McKeith I, *et al.* Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; **356:** 2031–36.
8. Wild R, *et al.* Cholinesterase inhibitors for dementia with Lewy bodies. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 14/02/06).
9. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Parkinsonism. Although acetylcholinesterase inhibitors such as rivastigmine may theoretically worsen parkinsonian symptoms, particularly tremor, it has been tried for use in the treatment of drug-induced psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p.954). In 2 large studies,[1,2] rivastigmine was found to produce some improvement in symptoms of dementia associated with Parkinson's disease when compared with placebo.

1. Emre M, *et al.* Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; **351:** 2509–18.
2. Wesnes KA, *et al.* Benefits of rivastigmine on attention in dementia associated with Parkinson disease. *Neurology* 2005; **65:** 1654–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Exelon; Remizeral; ***Austral.:*** Exelon; ***Austria:*** Exelon; ***Belg.:*** Exelon; ***Braz.:*** Exelon; Prometax; ***Canad.:*** Exelon; ***Chile:*** Exelon; Probrain; ***Cz.:*** Exelon; Prometax; ***Denm.:*** Exelon; ***Fin.:*** Exelon; ***Fr.:*** Exelon; ***Ger.:*** Exelon; ***Gr.:*** Exelon; Prometax; ***Hong Kong:*** Exelon; ***Hung.:*** Exelon; ***India:*** Exelon; ***Indon.:*** Exelon; ***Irl.:*** Exelon; ***Israel:*** Exelon; ***Ital.:*** Exelon; Prometax; ***Malaysia:*** Exelon; ***Mex.:*** Exelon; ***Neth.:*** Exelon; Prometax; ***Norw.:*** Exelon; ***NZ:*** Exelon; ***Philipp.:*** Exelon; ***Pol.:*** Exelon; ***Port.:*** Exelon; Prometax; ***Rus.:*** Exelon (Экселон); ***S.Afr.:*** Exelon; ***Singapore:*** Exelon; ***Spain:*** Exelon; Prometax; ***Swed.:*** Exelon; ***Switz.:*** Exelon; ***Thai.:*** Exelon; ***Turk.:*** Exelon; ***UK:*** Exelon; ***USA:*** Exelon; ***Venez.:*** Exelon.

Sabeluzole *(BAN, USAN, rINN)*

R-58735; Sabeluzol; Sabéluzole; Sabeluzolum. (±)-4-(2-Benzothiazolylmethylamino)-α-[(4-fluorophenoxy)methyl]-1-piperidineethanol.

Сабелузол

$C_{22}H_{26}FN_3O_2S = 415.5.$

CAS — 104153-38-0; 104383-17-7;.

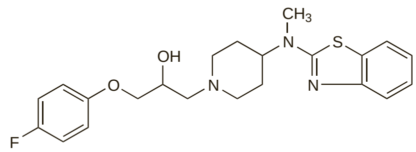

Profile

Sabeluzole is a benzothiazole derivative with anticonvulsant and antihypoxic properties. It has been investigated in the treatment of Alzheimer's disease and of sleep apnoea.

Tacrine Hydrochloride

(BANM, USAN, rINNM)

CI-970; Hidrocloruro de tacrina; Tacrine, chlorhydrate de; Tacrini hydrochloridum; Tetrahydroaminoacridine Hydrochloride; THA. 1,2,3,4-Tetrahydroacridin-9-ylamine hydrochloride.

Такрина Гидрохлорид

$C_{13}H_{14}N_2,HCl = 234.7.$

CAS — 321-64-2 (tacrine); 1684-40-8 (tacrine hydrochloride).

ATC — N06DA01.

ATC Vet — QN06DA01.

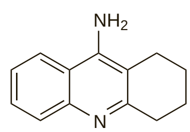

(tacrine)

Pharmacopoeias. In *US* as the monohydrate.

USP 31 (Tacrine Hydrochloride). The monohydrate occurs as a white powder. Freely soluble in water, in alcohol, in dimethyl sulfoxide, in methyl alcohol, in propylene glycol, and in 0.1N hydrochloric acid; sparingly soluble in linoleic acid and in macrogol 400.

Adverse Effects and Treatment

As for Donepezil, p.364. Hepatotoxicity is common, and may be severe.

Effects on the CNS. Tonic or tonic-clonic seizures were reported in 6 of 78 patients given tacrine for mild or moderate dementia of the Alzheimer's type.[1]

1. Lebert F, *et al.* Convulsive effects of tacrine *Lancet* 1996; **347:** 1339–40.

Effects on the liver. Examination of data from 2446 patients who were at least 50 years old and received tacrine for Alzheimer's disease suggested that raised serum-alanine aminotransferase (ALT) concentrations are likely to occur in about 50% of patients.[1] Most cases developed within the first 12 weeks of therapy,[1] but an asymptomatic increase in ALT concentrations has been reported in a patient after more than 80 weeks of therapy.[2] The increase is usually asymptomatic and mild, and resolves upon dosage reduction or stopping treatment. However, a small percentage of patients may develop unpredictable life-threatening hepatotoxicity although frequent monitoring of ALT concentrations during the first 12 weeks of therapy can identify susceptible individuals. No significant correlation has been found between plasma-tacrine concentrations and hepatotoxicity.[3]

For guidelines on the monitoring of ALT concentrations during tacrine therapy, see Precautions, below.

1. Watkins PB, *et al.* Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; **271:** 992–8.
2. Terrell PS, *et al.* Late-onset alanine aminotransferase increase with tacrine. *Ann Pharmacother* 1996; **30:** 301.
3. Ford JM, *et al.* Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. *Clin Pharmacol Ther* 1993; **53:** 691–5.

Precautions

As for Donepezil, p.365. Tacrine should be used with care in patients with impaired liver function or who have a history of such impairment.

Serum-alanine aminotransferase (ALT) concentrations should be monitored in patients receiving continuous treatment with tacrine. Monitoring should be carried out every other week from at least week 4 to week 16 of therapy, and then every 3 months thereafter. Weekly monitoring is recommended in patients with ALT concentrations that are greater than twice the upper limit of the normal range.

If signs of liver involvement worsen, the dose should be reduced or the drug withdrawn. If a three- to five-fold increase of ALT concentrations occurs, a reduction in the dose by 40 mg daily is recommended. For greater increases in ALT, tacrine should be withdrawn. Treatment with tacrine may be restarted once signs of liver dysfunction return to normal; more frequent monitoring of liver enzyme values will be required. Withdrawal is also imperative in patients who develop jaundice, confirmed by elevated total bilirubin levels; such patients should not be treated again with tacrine.

Abruptly stopping tacrine therapy, or a large reduction in the dose, may be associated with behavioural disturbances and a decline in cognitive function.

Interactions

As for Neostigmine, p.632. Since tacrine is metabolised in the liver by the cytochrome P450 enzyme system (principally CYP1A2), drugs that either inhibit or induce the same isoenzymes may raise or lower plasma concentrations of tacrine, respectively. Tacrine may competitively inhibit the metabolism of other drugs that are also metabolised by the cytochrome P450 isoenzyme CYP1A2.

Antidepressants. *Fluvoxamine*, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, has increased plasma concentrations and reduced oral clearance of tacrine.[1]

1. Becquemont L, *et al.* Influence of the CYP1A2 inhibitor fluvoxamine on tacrine pharmacokinetics in humans. *Clin Pharmacol Ther* 1997; **61:** 619–27.

Antiparkinsonian drugs. Tacrine has been reported to exacerbate symptoms of parkinsonism and may therefore appear to reduce the effectiveness of *levodopa* therapy, see Antidementia drugs, p.807.

H_2-antagonists. *Cimetidine*, a non-specific inhibitor of the cytochrome P450 enzyme system, has been shown to inhibit the metabolism of tacrine resulting in reduced oral clearance and an increase in plasma concentrations.[1,2]

1. de Vries TM. Effect of cimetidine and low-dose quinidine on tacrine pharmacokinetics in humans. *Pharm Res* 1993; **10:** S337.
2. Forgue ST, *et al.* Inhibition of tacrine oral clearance by cimetidine. *Clin Pharmacol Ther* 1996; **59:** 444–9.

HRT. HRT with estradiol and levonorgestrel significantly increased tacrine plasma concentrations in all but one person in a study involving 10 healthy female subjects.[1] Metabolism of tacrine via the cytochrome P450 isoenzyme CYP1A2 was said to have been inhibited by the HRT.

1. Laine K, *et al.* Plasma tacrine concentrations are significantly increased by concomitant hormone replacement therapy. *Clin Pharmacol Ther* 1999; **66:** 602–8.

Tobacco smoking. Cigarette smoking can markedly reduce plasma-tacrine concentrations.[1]

1. Welty D, *et al.* The effect of smoking on the pharmacokinetics and metabolism of Cognex in healthy volunteers. *Pharm Res* 1993; **10:** S334.

Xanthines. For the effect of tacrine on the metabolism of *theophylline*, see p.1145.

Pharmacokinetics

Tacrine is rapidly absorbed from the gastrointestinal tract but large interindividual variations in oral bioavailability have been reported; peak plasma concentrations are achieved within 1 to 2 hours. Food reduces the absorption of tacrine by about 30 to 40%. It is about 55% bound to plasma proteins. Tacrine is subject to an extensive first-pass effect in the liver, and is metabolised by the cytochrome P450 system (principally CYP1A2) to several metabolites, the main one of which is the 1-hydroxy metabolite velnacrine. The elimination half-life is about 2 to 4 hours; little unchanged drug is excreted in the urine.

◊ In 3 studies in a total of 21 patients peak plasma concentrations of tacrine hydrochloride were achieved 0.5 to 3 hours after oral doses of 25 or 50 mg and oral bioavailability ranged from less than 5% to up to 36%.[1-3] Mean elimination half-lives were 1.37 and 1.59 hours after the 25 mg dose and 2.14 and 3.2 hours after the 50 mg dose. Tacrine's elimination appears to be mainly by metabolism in the liver and less than 3% of a dose was recovered unchanged in the urine of one patient.[1] Plasma concentrations of tacrine's main metabolite 1-hydroxy-9-aminotetrahydroacridine (velnacrine) rapidly exceed those of the parent compound and elimination half-lives of 43 and 81 minutes were found for this metabolite in 2 patients studied.[2] Tacrine's pharmacokinetics have been reviewed.[4]

1. Forsyth DR, *et al.* Pharmacokinetics of tacrine hydrochloride in Alzheimer's disease. *Clin Pharmacol Ther* 1989; **46:** 634–41.
2. Hartvig P, *et al.* Clinical pharmacokinetics of intravenous and oral 9-amino-1,2,3,4-tetrahydroacridine, tacrine. *Eur J Clin Pharmacol* 1990; **38:** 259–63.
3. Sitar DS, *et al.* Bioavailability and pharmacokinetic disposition of tacrine HCl in elderly patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **57:** 198.
4. Madden S, *et al.* Clinical pharmacokinetics of tacrine. *Clin Pharmacokinet* 1995; **28:** 449–57.

Uses and Administration

Tacrine hydrochloride is a centrally acting reversible inhibitor of acetylcholinesterase activity used in the treatment of mild to moderately severe dementia in Alzheimer's disease (below).

The initial oral dose of tacrine hydrochloride, expressed in terms of the base, is 10 mg four times a day for a minimum of 4 weeks. Dosage should not be increased during this period because the potential exists for a delay in onset of increased liver enzyme concentrations. Serum-alanine aminotransferase concentrations should be monitored regularly (see Precautions, above) and, if there is no significant increase, the daily dose may be increased by 40 mg at four-week intervals according to response and tolerance, to a maximum of 160 mg daily in four divided doses. Tacrine should be taken on an empty stomach to improve absorption, although it can be taken with food if gastrointestinal adverse effects are a problem.

Tacrine has been used intravenously to antagonise competitive neuromuscular blockers and as a postoperative respiratory stimulant.

Dementia. Tacrine is used in the symptomatic management of Alzheimer's disease (see Dementia, p.362). It may delay cognitive decline in some patients with mild or moderate Alzheimer's disease but many cannot tolerate the dosage required and have to stop treatment because of gastrointestinal effects or signs of hepatotoxicity. There have been numerous studies of the use of tacrine in Alzheimer's disease and a meta-analysis[1] found tacrine to have a small beneficial effect on both cognition and global clinical impression, although it was considered that the clinical relevance of these findings was unclear and that there were no data from long-term controlled studies. Some have considered[2-6] that a cautious trial of tacrine may be warranted in patients with mild to moderately severe Alzheimer's disease (although alternative drugs are now available) and various guidelines on its use have been issued.[5,6] The metabolite velnacrine has also been tried but does not appear to be effective, and is also associated with hepatotoxicity.[7]

1. Qizilbash N, *et al.* Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. *JAMA* 1998; **280:** 1777–82.
2. Crimson ML. Tacrine: first drug approved for Alzheimer's disease. *Ann Pharmacother* 1994; **28:** 744–51.
3. Davis KL, Powchik P. Tacrine. *Lancet* 1995; **345:** 625–30.
4. Samuels SC, Davis KL. A risk-benefit assessment of tacrine in the treatment of Alzheimer's disease. *Drug Safety* 1997; **16:** 66–77.
5. Lyketsos CG, *et al.* Guidelines for the use of tacrine in Alzheimer's disease: clinical application and effectiveness. *J Neuropsychiatr Clin Neurosci* 1996; **8:** 67–73.
6. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
7. Birks J, Wilcock GGW. Velnacrine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Preparations

USP 31: Tacrine Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Cognitiv†; ***Austral.:*** THA; ***Braz.:*** Tacrinal†; ***Gr.:*** Cognex†; ***Spain:*** Cognex†; ***USA:*** Cognex.

Xanomeline *(USAN, rINN)*

LY-246708; NNC-11-0232; Xanomelina; Xanoméline; Xanomelinum. 3-[4-(Hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridine.

Ксаномелин

$C_{14}H_{23}N_3OS = 281.4.$

CAS — 131986-45-3.

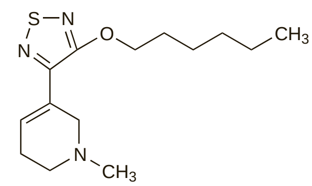

Profile

Xanomeline is a selective muscarinic M_1 agonist. Xanomeline tartrate has been studied in the management of Alzheimer's disease but drugs of this type have not generally produced benefit.

◊ References.

1. Sramek JJ, *et al.* The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol* 1995; **35:** 800–806.
2. Bodick NC, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54:** 465–73.

The symbol † denotes a preparation no longer actively marketed

Antidepressants

Bipolar disorder, p.372
Depression, p.373
Mania, p.375

This chapter describes drugs used principally in the treatment of affective disorders. Affective disorders are disorders of mood that may manifest as ***depression*** or ***mania*** or, in some cases, as ***mixed affective states*** in which depressive and manic or hypomanic episodes may coexist or rapidly alternate.

- The core features of ***depressive disorders*** are low mood, anhedonia (the loss of interest in former pleasures or activities), pessimism, and lethargy. They were formerly classified either as ***endogenous***, in which the symptoms were independent of external factors and considered to be a consequence of factors within the patient, or ***reactive***, in which depressive symptoms were a result of external stressors (i.e. exogenous). It is now recognised that depressive disorders are composed of both endogenous and reactive factors. Similarly, the classification of ***neurotic depression*** is no longer considered useful because it encompasses several different syndromes.

  Depressive episodes generally last for at least 2 weeks and are classified according to severity as mild, moderate, severe, or severe with psychosis. ***Recurrent brief depression*** is defined as depressive episodes of a few days' duration that recur regularly. Depression is often accompanied by characteristic ***somatic*** symptoms, including anorexia, weight loss, insomnia, early morning waking, and psychomotor retardation. Symptoms associated with ***atypical depression*** include overeating and oversleeping. Some classifications distinguish between major depressive episodes and minor (and hence ***major*** or ***minor depression***) based on the number and type of symptoms.
- The main symptoms of ***mania*** are overactivity, mood changes ranging from elation to irritability, expansive ideas, and inflated self-importance. Manic episodes are classified according to severity in a similar manner to depressive disorders: namely, mild, moderate, severe, or severe with psychosis. ***Hypomania*** is differentiated from mania in terms of a reduction in intensity of symptoms and social incapacity.
- Alternating episodes of mania or hypomania and depression are termed ***bipolar disorder (bipolar affective disorder)***. (To differentiate between alternating episodes of depression and mania or depression and hypomania, some classification systems use the terms ***bipolar I disorder*** and ***bipolar II disorder***, respectively.) Since it is very rare for repeated episodes of mania to occur without alternating episodes of depression, it is accepted practice to include mania without depression within the bipolar category. The term ***unipolar disorder*** (***unipolar depression***) is reserved for depressive disorders without mania.
- States of persistent but mild disturbances of mood exist in which the symptoms are not severe enough to meet the criteria for classification as a major depressive or hypomanic disorder, but may nevertheless cause considerable suffering to the patient. ***Dysthymia*** is the term used to describe a chronic milder depressive state whereas ***cyclothymia*** has some similarity to bipolar disorder, the instability characterised by long periods of hypomania and mild depression.
- The term ***seasonal affective disorder*** has been applied to depressive disorders repeatedly occurring seasonally, but not related to seasonal stressful life events; the depressive symptoms usually occur during the autumn and winter months. There have also been reports of patients developing seasonal bipolar disorder with hypomania or mania occurring in the summer months.
- Anxiety is often associated with depressive disorders at all levels of severity and it may be difficult to distinguish between the two conditions, especially in the milder forms. ***Mixed anxiety and depressive disorder*** defines a state in which anxiety and depressive symptoms coexist but neither component is severe enough to merit classification as an anxiety disorder or a depressive disorder.

Classification of antidepressants. Antidepressants are classified into different groups either structurally or depending on which central neurotransmitters they act upon. The older tricyclic (e.g. amitriptyline) and related cyclic antidepressants and the monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine) have now been joined by the selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine), the reversible inhibitors of monoamine oxidase type A (RIMAs) (e.g. moclobemide), and more recently by the serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g. venlafaxine). Other antidepressants that do not fit exactly into these groups include bupropion, the herbal preparation St John's wort, mirtazapine, reboxetine, and trazodone.

Lithium salts provide a source of lithium ions that compete with sodium ions at various sites in the body and thus have an action and adverse effects distinct and separate from those of other antidepressants.

Bipolar disorder

Bipolar disorder (manic depression) is a mixed affective disorder in which the patient has alternating episodes of hypomania or mania and depression. Although isolated episodes of mania may occur, they are more usually part of bipolar disorder; for the purposes of classification, mania without depression is therefore included in the bipolar category. Manic episodes usually start suddenly and last on average for about 4 months. The depressive phase may last longer with an average duration of 6 months. The course of the illness is unpredictable; most patients will suffer a relapse after an initial manic episode, and of these, probably 10 to 20% will experience more than 3 episodes a year with partial or full remission in between, or switch to the alternative phase (rapid cycling). The diagnosis of bipolar disorder can be difficult, particularly if patients are only seen during the depressive phase. The morbidity of the disorder is often substantial especially during the depressive phase. Suicide is a significant risk and up to one-third of patients may attempt to take their own life.

The treatment of bipolar disorder is generally divided into the following phases:

- acute manic or mixed episode
- acute depressive episode
- maintenance and long-term treatment

Guidelines have been issued in the UK[1-4] and USA[5] to facilitate treatment choice in the management of bipolar disorder; international guidelines and expert consensus statements are also available.[6-9] The choice of drug therapy should be guided by severity, the type of episode (including associated symptoms), and patient preference.[5]

In patients with severe **manic** or mixed episodes, initial treatment with an antipsychotic or the mood stabiliser valproate should be considered because of their rapid onset of action; for less severe cases lithium, another mood stabiliser, may also be appropriate.[2,3,6,8] The choice between lithium or valproate as first-line treatment has been a matter of debate: although there is more reliable evidence for the use of lithium, its narrow therapeutic index and monitoring requirements[10-12] (see under Pharmacokinetics of Lithium, p.405) have led to the increased use of valproate in some countries.[10] Lithium must also be given in high doses in acute mania and its antimanic actions may be delayed by at least a week.[11,13] Nonetheless, lithium is still widely used[11] and some guidelines[6,8] prefer it to other mood stabilisers in patients with euphoric mania. However, valproate may be a better first-choice drug in rapid cycling bipolar disorder, for which it is particularly effective, and in mixed or dysphoric states.[3,5,6,8,9] Carbamazepine and its derivative oxcarbazepine are sometimes used as alternatives to lithium or valproate although their efficacy is not as well established and they are considered a second-line choice by most guidelines.[2,5,6,8] Treatment with carbamazepine is also complicated by its numerous drug interactions.[10,12,13]

Patients with mania and co-existing psychotic features usually require treatment with an antipsychotic to produce a rapid tranquillising effect.[5,8] Traditionally, classical antipsychotics such as the phenothiazine chlorpromazine and the butyrophenone haloperidol have been used although most guidelines now recommend the atypical antipsychotics, particularly olanzapine, quetiapine, and risperidone, because of their more favourable adverse effect profile.[2,3,5,6,8] Nevertheless, classical antipsychotics still appear to be widely used in the treatment of mania although high-dose therapy should be avoided because of the risk of extrapyramidal effects.[8] If sedation is required the short-term use of a benzodiazepine such as clonazepam or lorazepam should be considered instead of high-dose antipsychotics;[2,3,5] however, such treatments should be stopped as soon as symptoms subside in order to reduce the risk of dependence.[12]

The initial treatment should be continued at an optimal dose for at least 1 week before making any change to the regimen if the patient is unresponsive; if there is a partial response it may be appropriate to wait at least another week before considering the treatment ineffective. Options for patients who are inadequately controlled on optimised first-line treatment include a trial of lithium or valproate with an antipsychotic.[2,3,5,6,8] (Combination therapy has also been recommended as first-line treatment in patients with particularly severe symptoms.[2,5]) Another option is to try an alternative mood stabiliser or antipsychotic.[6] Clozapine may be considered in more refractory cases[2,5] and ECT is effective in patients who are severely ill or resistant to treatment.[2,3,5,8]

The treatment of the acute **depressive phase** of bipolar disorder depends on the severity of the depression and whether any psychotic symptoms are still present. Less severe cases may be adequately controlled by lithium, which has a modest antidepressant action.[2,7] Alternatively, treatment with lamotrigine or an antidepressant may be considered although most guidelines[2,3,6,7] recommend that antidepressants should be given with a mood stabiliser such as lithium or valproate to reduce the risk of antidepressant-induced switching (see below).

The selection of an antidepressant for bipolar depression generally involves the same considerations as those for unipolar depression (see below) although the risk of switching to mania should also be taken into account. Antidepressants have also been implicated in the induction of rapid cycling;[5,12] they should be tapered and stopped if either switching or rapid cycling occurs.[2,3,6] The SSRIs and possibly bupropion are usually first-choice antidepressants as they have a low risk of switching when compared with other antidepressants.[2,5-7,14] Tricyclic antidepressants should only be used in resistant cases as the risk of switching to mania is higher than with other antidepressant groups.[2,3] Data for the newer antidepressants such as nefazodone and venlafaxine are limited; it has been suggested that the risk of switching with venlafaxine is increased.[6,7] MAOIs may be less likely to induce mania than other antidepressants, but troublesome adverse effects and safety issues have limited their use.

As with the manic phase, treatment should be tried at an optimal dose and for an adequate time before it is considered ineffective.[6] If there is no response, second-line options include adding an antidepressant or lamotrigine in those patients on monotherapy with a mood stabiliser such as lithium, or in those patients already on an antidepressant, an alternative antidepressant may be tried or a second mood stabiliser added.[5-7] Additional treatment with an antipsychotic may be necessary if psychotic symptoms are also present.[2,5,7] However, some atypical antipsychotics have also been shown to be of benefit in non-psychotic bipolar depression when given with an antidepressant[6] and one such combination preparation (olanzapine with fluoxetine) is available in some countries. In the USA, the atypical antipsychotic quetiapine is licensed for use as monotherapy in bipolar depression. ECT is a valuable alternative and should be considered for resistant or severe bipolar depression.[2,3,5,7]

Once the acute phase has been brought under control, drug therapy should be continued until the patient is thought unlikely to suffer a relapse; this might entail **maintaining treatment** for several months.[2,5,15] When full remission has been achieved treatment should be gradually stopped over several weeks unless long-term treatment is planned (see below). Antipsychotics and antidepressants are usually stopped unless residual symptoms persist.

Some guidelines[2,5] recommend that **long-term** treatment should be started after a single episode of mania although others generally wait until a patient has had at least 2 manic episodes.[6] Lithium is often the drug of choice for the long-term treatment of bipolar disorder.[2,3,5] It reduces the risk of relapse, particularly mania,[2] although its prophylactic effects on depression are less obvious.[16] Long-term lithium treatment has also been associated with an anti-suicide effect.[2,15] Other treatment options include valproate, lamotrigine (particularly if bipolar depression is a burden), olanzapine, and possibly carbamazepine or oxcarbazepine.[2,3,5,6,9] Combination therapy may be necessary in those who fail on monotherapy; ECT and clozapine have also been tried in treatment-resistant patients.[2,9] However, it is usual practice for patients to continue with their acute treatment, given at the same doses, if effective.[2,5,6]

There is no consensus on the appropriate duration of long-term treatment and in some patients with severe disorders it may be necessary to continue treatment indefinitely.

1. National Institute for Clinical Excellence. Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder: Technology Appraisal 66 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/66_bipolardisorder_fullguidance.pdf (accessed 14/08/08)
2. Goodwin GM, *et al.* Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2003; **17:** 149–73. Also available at: http://www.bap.org.uk/consensus/FinalBipolarGuidelines.pdf (accessed 24/11/05)
3. Scottish Intercollegiate Guidelines Network. Bipolar affective disorder: a national clinical guideline (issued May 2005). Available at: http://www.sign.ac.uk/pdf/sign82.pdf (accessed 24/11/05)
4. National Collaborating Centre for Mental Health/NICE. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG38niceguideline.pdf (accessed 31/07/08)
5. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002; **159** (suppl): 1–50. Also available at: http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_8.aspx (accessed 14/08/08)
6. Keck PE, *et al.* The expert consensus guideline series: treatment of bipolar disorder 2004. *Postgrad Med* 2004; **Dec** (spec no): 1–120.
7. Grunze H, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, part I: treatment of bipolar depression. *World J Biol Psychiatry* 2002; **3:** 115–24. Also available at: http://www.wfsbp.org/fileadmin/pdf/guides/768BipolarGrunze.pdf (accessed 14/08/08)
8. Grunze H, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part II: treatment of mania. *World J Biol Psychiatry* 2003; **4:** 5–13. Also available at: http://www.wfsbp.org/fileadmin/pdf/guides/769ManiaGrunze.pdf (accessed 14/08/08)
9. Grunze H, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World J Biol Psychiatry* 2004; **5:** 120–35. Also available at: http://www.wfsbp.org/fileadmin/pdf/guides/942ManiaGrunze.pdf (accessed 14/08/08)
10. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; **57:** 179–92.
11. Belmaker RH. Bipolar disorder. *N Engl J Med* 2004; **351:** 476–86.
12. Anonymous. Drug treatments for bipolar disorder: 1 – acute manic or depressive episodes. *Drug Ther Bull* 2005; **43:** 28–32.
13. Müller-Oerlinghausen B, *et al.* Bipolar disorder. *Lancet* 2002; **359:** 241–7.
14. Gijsman HJ, *et al.* Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004; **161:** 1537–47.
15. Anonymous. Drug treatments for bipolar disorder: 2 – maintenance, prevention and special situations. *Drug Ther Bull* 2005; **43:** 33–7.
16. Geddes JR, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; **161:** 217–22.

Depression

Clinical depression (unipolar depression) is a disturbance of mood that is distinguishable from the usual mood fluctuations of everyday life. A depressed mood is usually the major symptom, which may be accompanied by other mental or somatic symptoms representing several depressive syndromes (see p.372). Suicide is a significant risk and up to half of all patients with depression may attempt suicide during their lifetime. Risk factors for developing depression include female gender and a positive family history.

The aetiology of depression is unknown but it may represent an interaction between psychological and biochemical mechanisms rather than any single factor. The symptoms appear to be mediated through alterations in levels of some central neurotransmitters, although it is not certain that this represents a cause of the disorder. However, it is at this level that the antidepressant drugs currently in clinical use exert their action.

Guidelines have been issued nationally in, for example, the UK[1,2] and the USA,[3-5] and internationally,[6,7] which provide evidence-based recommendations for the treatment of depression. The decision to start treatment should be based on the severity of the condition and the risks to the patient.

- Patients with *mild depression* may improve while being monitored without any additional help; in others simple interventions such as problem-solving, counselling, or exercise may be effective.[2] The evidence for the efficacy of antidepressants in mild depression is lacking and initial treatment with antidepressants is not recommended;[1,2,4] however, patients with persistent mild depression or those with a history of depression may benefit from antidepressant treatment.[1,2]
- Patients with *moderate* depression should be treated with an antidepressant;[2] in addition, psychological treatments (particularly cognitive behavioural therapy) are also effective.[2]
- A combination of antidepressants and psychological treatments should be considered in patients with *severe* depression.[2] ECT may also be of value, particularly when a rapid improvement of symptoms is essential (e.g. in patients at high risk of suicide) or in patients with depressive psychosis or psychomotor retardation.[8,9]
- For patients with *psychotic depression*, an antipsychotic may be required in addition to any antidepressant treatment;[2,4] ECT should also be considered.[4]
- Light therapy appears to be effective in patients with *seasonal affective disorder*.[10,11] Exposure to bright artificial light may take place at any time of the day, and the therapy should continue until the natural seasonal remission of the disorder; antidepressant drugs may also be used.

Choice of antidepressant. In more recent years many newer drugs have been licensed and added to the original treatments for depression. The role of these drugs relative to the older drugs is established for some of the newer drug groups, particularly the SSRIs, and evidence suggests that efficacy is comparable. In addition, many new drugs have been promoted on the basis of superior tolerability and this is also supported by clinical studies (see below for further details). The improved choice of treatment options offered by the newer antidepressants has meant that therapy is increasingly tailored to individual patient requirements.

- Tricyclic antidepressants have long been preferred over MAOIs because of the problem of drug interactions and the need for strict dietary precautions with the latter group. Tricyclics with sedative properties may be more suitable for agitated and anxious patients, whereas those with less sedative properties may be preferred for withdrawn and apathetic patients. Unfortunately, the traditional tricyclics such as amitriptyline have antimuscarinic and cardiotoxic adverse effects that can limit their use. Their cardiotoxicity also means that they are associated with a high risk of fatality in patients taking overdoses (see toxicity in overdosage, below).
- Continuing development produced lofepramine and drugs related to the tricyclic group such as mianserin that are less cardiotoxic than the earlier tricyclics.
- The subsequent introduction of SSRIs such as fluoxetine provided a group of drugs with still fewer antimuscarinic and cardiotoxic adverse effects. However, the SSRIs themselves have characteristic adverse effects; gastrointestinal symptoms such as nausea and vomiting may be a problem, and sleep disturbances and anxiety may be exacerbated at the start of treatment. Moreover, those in current clinical use interact to varying degrees with cytochrome P450 isoenzymes, which carries a potential for interaction with a wide range of compounds.
- More recently serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine have been developed, as well as reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide. RIMAs offer a safer alternative to the MAOIs and fewer dietary restrictions are necessary. Nefazodone, mirtazapine, and reboxetine, which have slightly different biochemical profiles from the major groups, are also more recent introductions. Bupropion, another unrelated antidepressant, is also available in some countries. With the exception of nefazodone, which causes hepatotoxicity and venlafaxine, which is cardiotoxic, most of these newer drugs seem to be associated with fewer severe adverse effects; their efficacy is also comparable to that of the tricyclics and SSRIs.[12-14]
- Other drugs used in the treatment of depression include flupentixol, the antidepressant dose of which is lower than that used for the treatment of psychoses. Ademetionine, the active derivative of methionine, has been tried in depressive disorders, and extracts of the plant St John's wort are widely used in some countries for depression. Transdermal patches containing selegiline, an irreversible inhibitor of monoamine oxidase type B, are available in the USA for the treatment of depression. Lithium may be used for the prophylaxis of recurrent unipolar depression as an alternative to standard antidepressants, although it is more commonly used in the management of bipolar disorder (see above); its role in unipolar depression is more usually to augment the effect of standard antidepressants in treatment-resistant disease.

An area of particular concern with regard to initial choice of an antidepressant is the most appropriate drug for patients considered to be a high suicide risk.[15] It is important to remember that suicide is an inherent risk in depression; it is generally accepted that with all antidepressant therapies the risk of suicide may increase in the early stages of recovery (for further details, see Effects on Mental State, under Fluoxetine, p.392). Varying relative risks of **toxicity in overdosage** for different groups of antidepressant have been assessed:[16-19]

- older tricyclics and the tetracyclic maprotiline[20] appear to be more toxic in overdosage than the tetracyclic mianserin[21] and the SSRIs[18,22]
- MAOIs have an intermediate risk[22,23]
- within the tricyclic group, desipramine[16,17,22] has been reported to be associated more frequently with fatal overdosage although some[24] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage; lofepramine[19,22,25] may be one of the safer tricyclics
- toxicity of the SNRI venlafaxine in overdose appears to be greater than other new serotonergic antidepressants and comparable to some of the less toxic tricyclics[22]

Although such analyses cannot determine to what extent the data reflect prescribing patterns and patient selection as opposed to drug toxicity[16,17,25] it is widely accepted that the older tricyclics are more toxic in overdosage, and that the SSRIs[26,27] and the newer tricyclic and related cyclic antidepressants are safer.[27] In practice, it is often difficult to identify patients at high risk for suicide, and it has therefore been suggested that a routine strategy should be to begin antidepressant therapy in all patients with drugs that have low toxicity in overdose.[15,27] However, whichever antidepressant is chosen, all patients should be closely monitored during early therapy until significant improvement in depression has been observed and limited quantities of antidepressants should be prescribed at any one time.

Current guidelines recommend that choice of antidepressant should be based on superior tolerability, safety in overdose, and efficacy at prescribed doses.[1-4,6] Meta-analyses[28-31] comparing the efficacy of SSRIs and tricyclics in general find no difference in efficacy although there is the suggestion of a greater efficacy for some tricyclics when given to inpatients. However, drop-out rates due to adverse effects have generally been higher in patients receiving tricyclics than in those taking SSRIs. Based on these findings, most guidelines recommend that an SSRI[1,2,4,6] should be used as first-line treatment. In addition some consider that lofepramine, nortriptyline, or newer antidepressants such as mirtazapine or reboxetine are suitable alternatives.[1,4,6] Bupropion, which is marketed as an antidepressant in the USA, is considered to be a first-line choice in US guidelines.[4] Older tricyclics may, however, be more appropriate in severely ill, hospitalised patients or in other situations where maximising efficacy is important.[1] The use of an MAOI may be considered in patients with atypical depression[4,6] although, in practice, SSRIs are often tried initially because of their more favourable adverse effects profile.[4]

The sedative properties of some of the antidepressants may adversely affect the performance of potentially hazardous tasks such as driving and the operation of machinery. One of the less sedative antidepressants should be used where appropriate, although care is needed with all psychotropic drugs, especially at the start of treatment.

Regardless of antidepressant choice, certain principles of management apply when **starting antidepressant therapy**.

- A low initial dose will minimise adverse effects; this is then increased until an adequate response is observed.[4] When this is done with the newer antidepressants, including the SSRIs, the dose can generally be increased after a few days; for the tricyclics the increase should be more gradual.[32] Gradual introduction of treatment is of particular importance in the elderly who may be more susceptible to adverse effects.
- Although some adverse effects of antidepressant drugs appear soon after treatment is started, there is a delay of about 2 weeks before any therapeutic benefit is observed, and at least 6 weeks before maximum improvement in depressive symptoms occurs.[33] Claims of a fast onset of action have been made for several antidepressants, but in a review[34] of data relating to onset of action with currently available antidepressants, none have been shown conclusively to work faster than any other. This delay in benefit may relate to a combination of pharmacokinetic and neurochemical factors.
- Patients should not be considered resistant to the chosen drug until they have been maintained at an adequate dose for at least 4 weeks[1,2] (the *BNF* and NICE[2] have recommended 6 weeks in the elderly). Patients with a partial response should continue for a further 2 weeks (6 weeks in the elderly[2]) before being considered resistant.[1,2] Treatment failure is often due to subtherapeutic doses,[1,2] particularly with the older tricyclics whose adverse effects limit maximum tolerable doses in many patients.[35] Where lack of compliance leads to subtherapeutic doses therapeutic drug monitoring may be of value.[6]

In those who show little or no response to an adequate trial of the first-choice antidepressant the following options exist:

- switching to an alternative antidepressant
- adding another drug (augmentation), particularly if there has been a partial response
- introducing psychological treatments such as cognitive behavioural therapy

Guidelines generally consider it preferable to try an alternative single antidepressant before giving combinations of drugs (augmentation).[1-4,6] It has been suggested that for practical purposes a patient should not be considered to have treatment-resistant depression until 2 or more consecutive antidepressants at adequate doses have been tried without response.[2]

If **switching antidepressants** the choice is between a drug from the same pharmacological group or one from a different group.[1-4,6] In the UK, venlafaxine is usually reserved for patients with treatment-resistant depression because of its adverse cardiovascular effects and toxicity in overdose.[2] MAOIs can also be tried in patients who are refractory to or intolerant of treatment with other antidepressants.[1,2,4]

When changing a patient from one type of antidepressant to another an appropriate drug-free interval may be needed. An MAOI (including a RIMA and selegiline) should not be started until at least one week after stopping a tricyclic antidepressant, an SSRI, or any related antidepressant; in the case of bupropion, mirtazapine, and the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine, to 5 weeks because of their longer half-lives. For the tricyclics clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. Conversely, 2 weeks should elapse between stopping MAOI (including selegiline) therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, or any related antidepressant. No treatment-free period is necessary between stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI or another antidepressant.

Drugs that have been used in **augmentation strategies** for resistant depression include lithium,[1,2,4,6] thyroid hormones (liothyronine),[1,4,6,36] and central stimulants[4,36] such as methylphenidate. Pindolol has also been studied as an augmentation agent with several SSRIs and other serotonergic antidepressants.[6,36] Another method is to combine different classes of antidepressants. Although this has been used successfully in the treatment of drug-resistant depression,[2,4,6,36] it may result in enhanced adverse reactions or interactions and the *BNF* considers it hardly ever justified; it should only ever be done under expert supervision. For further details of the interactions between different antidepressants, see under Interactions of Phenelzine, p.418.

If the response to treatment is good, the patient should continue with the same treatment for at least 4 to 6 months,[1-4] and perhaps 12 months in the elderly;[6] symptoms are likely to recur if treatment is stopped too soon.[37-39] In general, the dose should not be reduced for this **continuation phase**.[1-4,7] Continuing therapy beyond this phase[1,2,4,7,40] is a matter of clinical judgement and should take into account the number of prior episodes, any residual symptoms, and the severity of the episode. **Maintenance therapy** should be considered for recurrent depressive disorders,[1,2,4,7,37,39,41] and may be necessary for several years, if not indefinitely, in some cases. Again, full therapeutic doses are recommended for prophylaxis rather than reduced doses.[1,2,4,7,38,41]

Suddenly **stopping antidepressant therapy** after regular use for 8 weeks or more may precipitate withdrawal symptoms.[42-44] Common symptoms seen after antidepressant withdrawal include headache, anorexia, nausea, insomnia, and anxiety; the SSRIs have also been associated with episodes of dizziness and paraesthesia which are rarely seen with the tricyclics.[45] Withdrawal reactions may be more severe with the MAOIs especially tranylcypromine.[45] To minimise symptoms, most guidelines[1,4] and authorities such as the *BNF* recommend reducing the dose over a period of about 4 weeks, although considerably longer periods (6 months) may be required when withdrawing maintenance therapy.

Depressive disorders may arise in **childhood and adolescence**, the prevalence increasing with age.[6] Concerns about a possible increased risk of suicide with antidepressant treatment, have led to considerable uncertainty about appropriate management in young patients.[46-50] In the UK, guidelines state that the mainstay of treatment for this patient group should be psychological therapy;[46] treatment with antidepressants should only be offered alongside psychological therapy. For children and adolescents with mild depression, as for adults, a period of watchful waiting may be appropriate before starting any treatment. If symptoms have not resolved after several weeks, patients should be started on an appropriate course of psychological therapy such as group cognitive behavioural therapy or guided self-help which should be continued for 2 to 3 months. Antidepressants should not be used for the initial treatment of mild depression. Children or adolescents with moderate to severe depression (or those with mild depression unresponsive to the above measures) should be given more specific psychological treatment such as individual cognitive behavioural therapy, interpersonal therapy, or short-term family therapy. Combined treatment with an antidepressant (which, as in adults, appears more effective than either alone[51]) should only be considered if there is a lack of response to psychotherapy alone.[46] The SSRI fluoxetine is considered the first-choice antidepressant in children aged 12 and over because of proven efficacy and low toxicity in overdose;[6,46] although the evidence for its efficacy in younger children has been questioned,[46] a review by the EMEA concluded that studies showed a positive effect and allowed its use throughout the EU in children from 8 years of age.[52] The other SSRIs should not be used in children (but see below) because of a lack of demonstrated efficacy and/or an increased risk of a harmful outcome (see Effects on Mental State under Fluoxetine, p.392 for further details). Similar recommendations have been made for the SNRI venlafaxine (see p.428). Patients who remain unresponsive to combined treatment should be initially tried on an alternative psychological therapy.[46] A change in antidepressant may also be warranted and guidelines issued in the UK have suggested that citalopram and sertraline may be appropriate, provided certain criteria have been met.[46] (Paroxetine and venlafaxine should not be used.[46]) Lithium has also been tried[6] and ECT may be considered for older children with severe, unresponsive depression.[6,46] Tricyclics may have a modest effect in the treatment of depression in adolescents; however, they are not effective in the treatment of younger children.[53] In practice they have often been reserved for refractory cases in adolescents[54] although evidence to support this role is lacking[53] and recent UK guidelines[46] do not recommend their use. There have also been reports of death due to cardiotoxicity in children taking tricyclic antidepressants, in particular desipramine and imipramine.

Following the concerns raised about the possible increased risk of suicide in children and adolescents treated with antidepressants, the FDA undertook a meta-analysis of 372 studies in adults. From 295 studies in psychiatric patients, the overall risk of suicide was not increased, but there was a trend toward increased risk with younger age. Although the effect was not statistically significant, the FDA considered the trend sufficiently convincing to warn that, like children and adolescents, **young adults** (aged 18 to 24 years) treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[55] In the UK, an Expert Working Group of the CSM found no clear evidence that use of SSRIs in young adults increased the risk of self-harm or suicidal thoughts;[56] however, it was noted that such patients have a higher background risk of suicidal behaviour than older adults and consequently should be closely monitored during treatment.

Depression in the **elderly** is not uncommon and may affect up to 4% of this population.[57] Suicide is also more frequent in the elderly than in the general population and depressive symptoms are present in about 80% of patients aged over 74 years who commit suicide.[57] Depression in the elderly is often undertreated and prognosis is poor; treatment is also often complicated by co-existing medical conditions.[4,6,57,58] SSRIs are often the first choice of treatment in the elderly because of their favourable adverse effect profile and low toxicity in overdose.[4,6,57,58] They may be especially appropriate in patients with an existing cardiovascular disease or in those taking other medications that may lower the blood pressure. Tricyclics such as amitriptyline and imipramine are probably best avoided in the elderly as their cardiotoxic, antimuscarinic, and sedative effects may be particularly troublesome. However, the tricyclics desipramine and nortriptyline are considered by some[4,6,57] to be an alternative first-choice as they are less cardiotoxic and have fewer antimuscarinic and sedative actions compared with amitriptyline or imipramine. Other newer antidepressants may also be useful in specific situations; bupropion, which has the advantage of a relative lack of cardiotoxicity and drug interactions, may be an appropriate option.[4] Lower initial doses of antidepressant drugs are often recommended in the elderly to minimise adverse effects but individual differences in metabolism and excretion may mean that some patients are undertreated. The elderly tend to respond more slowly to antidepressants than younger patients[6] and additional psychosocial or psychotherapeutic management is often warranted.[4,57] The treatment of resistant depression in elderly patients should follow the same principles as in younger patients.[6,57] ECT is also safe and effective in the elderly, and should be considered in those at high risk for suicide or who are refractory to or intolerant of antidepressant drugs.[6,57] Depression late in life may require long-term antidepressant treatment beyond the recovery phase, even after first episodes of depression and should be a continuation of the treatment that was successful in the initial acute phase (see above).

Treatment of women with depressive disorders during and after **pregnancy** raises concerns about the risk of teratogenicity, fetal growth retardation, or perinatal problems (see also individual drug monographs); the ratio of risk to the child versus the benefit to the mother must therefore be considered very carefully.[4,6,59] It should also be remembered that untreated depression during pregnancy has been associated with poor neonatal outcomes such as low birthweight.[4] In some cases starting treatment with an antidepressant will be appropriate although psychotherapy and ECT should also be considered as alternatives.[6] Treatment should not be stopped as a matter of routine in early pregnancy in women who become pregnant while taking an antidepressant.[59] Maternal mood disorders in the immediate postpartum period are related to hormonal changes, particularly falling progesterone levels; the symptoms are mild and resolve spontaneously after several days, therefore no treatment is required.[4,6] Of greater concern are major depressive episodes that occur beyond this initial phase, which are clinically identical to depressive disorders in general and call for the same principles of management[59] (although there are few studies to support this[60]). These depressive episodes have been found to be related to the presence of immediate postpartum mood disorders, although no hormonal basis to this association has been identified.[59] Nevertheless, there has been interest in the use of oestrogen as a treatment.

As with use of any medication in **breast-feeding** mothers, the risks to the infant from drugs distributed into breast milk must be considered. The American Academy of Pediatrics[61] considers that all antidepressants are drugs whose effect on nursing infants could be of concern.

Symptoms of **anxiety and depression** often coexist, and although it may be difficult to distinguish which is the predominant disorder, especially in milder forms, patients usually require an antidepressant. Anxiolytics and antipsychotics can be useful adjuncts in agitated depression, but a sedative antidepressant might be preferable. Combination preparations of antidepressants with antipsychotics or anxiolytics should not be used because the dosage of the individual components should be adjusted separately. Also, anxiolytics should only be prescribed on a short-term basis whereas antidepressants are given for longer periods.

The efficacy of antidepressants in **chronic fatigue syndrome** in clinical studies have been equivocal although it has been suggested that antidepressant therapy should be tried in patients with co-existing depression.[62] Cognitive therapy may also be useful.

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60. Hoffbrand S, *et al.* Antidepressant treatment for post-natal depression. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 24/11/05).
61. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
62. The Royal Colleges of Physicians, General Practitioners and Psychiatrists. Chronic fatigue syndrome. *Council Report CR54*; London: Royal Colleges of Physicians, General Practitioners and Psychiatrists, 1997.

Mania

Although isolated episodes of mania (see p.372) may occur, mania is usually followed by depression when it is considered to be part of bipolar disorder. It is accepted practice to include mania without depression within the bipolar category. The treatment and prophylaxis of acute mania are therefore described under Bipolar Disorder, above.

Agomelatine *(rINN)*

Agomelatina; Agomélatine; Agomelatinum; S-20098. *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

Агомелатин

$C_{15}H_{17}NO_2$ = 243.3.
CAS — 138112-76-2.
ATC — N06AX22.
ATC Vet — QN06AX22.

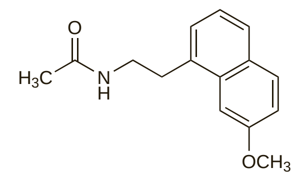

Profile

Agomelatine is an agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptors. It has antidepressant actions and is used orally in the treatment of depression (p.373) in doses of 25 to 50 mg given daily at bedtime.

◊ References.

1. Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 2006; **20:** 981–92.
2. Ghosh A, Hellewell JSE. A review of the efficacy and tolerability of agomelatine in the treatment of major depression. *Expert Opin Invest Drugs* 2007; **16:** 1999–2004.
3. Eser D, *et al.* Evidence of agomelatine's antidepressant efficacy: the key points. *Int Clin Psychopharmacol* 2007; **22** (suppl 2): S15–S19.

Amineptine Hydrochloride *(rINNM)*

Amineptine, Chlorhydrate d'; Amineptini Hydrochloridum; Hidrocloruro de amineptina; S-1694. 7-[(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid hydrochloride.

Аминептина Гидрохлорид

$C_{22}H_{27}NO_2,HCl$ = 373.9.
CAS — 57574-09-1 (amineptine); 30272-08-3 (amineptine hydrochloride).
ATC — N06AA19.
ATC Vet — QN06AA19.

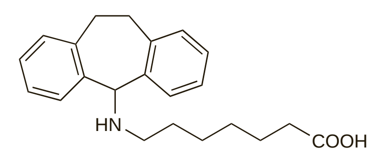

(amineptine)

Profile

Amineptine hydrochloride is a tricyclic antidepressant (see Amitriptyline, below). It has been given orally in the treatment of depression.

Hepatic adverse effects seem to be more common than with most other tricyclic antidepressants (see Effects on the Liver, p.377). Also amineptine has been subject to abuse and withdrawal has been both prolonged and difficult; for these reasons, it is no longer marketed in many countries.

Adverse effects. In 5 patients very severe acne-type lesions were associated with the chronic self-increased use of high doses of amineptine (200 to 1000 mg daily).[1] Unusual lactam metabolites were detected in all patients and in 2 these metabolites were still present, along with the lesions, 3 months after therapy had been withdrawn. In another case, a 48-year-old woman developed acne-like eruptions after long-term treatment with amineptine at a dose of 400 mg daily.[2] There was no clinical improvement 6 months after amineptine withdrawal.

1. Vexiau P, *et al.* Severe acne-like lesions caused by amineptine overdose. *Lancet* 1988; **i:** 585.
2. De Gálvez Aranda MV, *et al.* Acneiform eruption caused by amineptine: a case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15:** 337–9.

Porphyria. Amineptine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Survector†; ***Port.:*** Directim†; Survector†.

Amitriptyline *(BAN, rINN)*

Amitriptilina; Amitriptyliini; Amitriptylin; Amitriptylinum. 3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)propyldimethylamine; 10,11-Dihydro-*N,N*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,}$ -propylamine.

Амитриптилин

$C_{20}H_{23}N$ = 277.4.

CAS — 50-48-6.

ATC — N06AA09.

ATC Vet — QN06AA09.

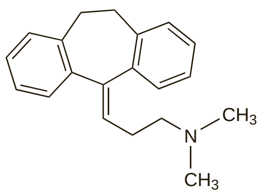

Amitriptyline Embonate *(BANM, rINNM)*

Amitriptyline, Embonate d'; Amitriptylini Embonas; Embonato de amitriptilina.

Амитриптилина Эмбонат

$(C_{20}H_{23}N)_2,C_{23}H_{16}O_6$ = 943.2.

CAS — 17086-03-2.

Pharmacopoeias. In *Br.*

BP 2008 (Amitriptyline Embonate). A pale yellow to brownish-yellow, odourless or almost odourless powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in chloroform. Protect from light.

Amitriptyline Hydrochloride *(BANM, rINNM)*

Amitriptilin Hidroklorür; Amitriptilin-hidroklorid; Amitriptilino hidrochloridas; Amitriptyliinihydrokloridi; Amitriptyline, chlorhydrate d'; Amitriptylin-hydrochlorid; Amitriptylinhydroklorid; Amitriptylini hydrochloridum; Amitryptyliny chlorowodorek; Hidrocloruro de amitriptilina.

Амитриптилина Гидрохлорид

$C_{20}H_{23}N,HCl$ = 313.9.

CAS — 549-18-8.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Amitriptyline Hydrochloride). A white or almost white powder or colourless crystals. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Amitriptyline Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.0.

Stability. Decomposition occurred when solutions of amitriptyline hydrochloride in water or phosphate buffers were autoclaved at 115° to 116° for 30 minutes in the presence of excess oxygen.[1]

The decomposition of amitriptyline as the hydrochloride in buffered aqueous solution stored at 80° in the dark was accelerated by metal ions.[2] Disodium edetate 0.1% significantly reduced the decomposition rate of these amitriptyline solutions but propyl gallate and hydroquinone were less effective. Sodium metabisulfite produced an initial lowering of amitriptyline concentration and subsequently an acceleration of decomposition. The rate of decomposition was also much greater in amber glass ampoules than in clear glass ones (the metal ion content of amber glass is higher than that of clear glass). However, there were considerable variations between different batches of amber glass and, since amitriptyline is photolabile, its solutions are likely to be stored in amber containers.

Solutions of amitriptyline hydrochloride in water are stable for at least 8 weeks at room temperature if protected from light either by storage in a cupboard or in amber containers.[3] Decomposition to ketone and, to a lesser extent, other unidentified products was found to occur on exposure to light.

1. Enever RP, *et al.* Decomposition of amitriptyline hydrochloride in aqueous solution: identification of decomposition products. *J Pharm Sci* 1975; **64:** 1497–9.
2. Enever RP, *et al.* Factors influencing decomposition rate of amitriptyline hydrochloride in aqueous solution. *J Pharm Sci* 1977; **66:** 1087–9.
3. Buckles J, Walters V. The stability of amitriptyline hydrochloride in aqueous solution. *J Clin Pharm* 1976; **1:** 107–12.

Adverse Effects

Many adverse effects of amitriptyline and similar tricyclic antidepressants are caused by their antimuscarinic actions. Antimuscarinic effects are relatively common and occur before an antidepressant effect is obtained. They include dry mouth, constipation occasionally leading to paralytic ileus, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, and hyperthermia. Tolerance is often achieved if treatment is continued and adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Drowsiness may also be common, although a few tricyclic antidepressants possess little or no sedative potential and may produce nervousness and insomnia. Other neurological adverse effects include headache, peripheral neuropathy, tremor, ataxia, epileptiform seizures, tinnitus, and occasional extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include sour or metallic taste, stomatitis, and gastric irritation with nausea and vomiting.

Effects on the cardiovascular system are discussed in more detail below. Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported and, rarely, cholestatic jaundice and blood disorders, including eosinophilia, bone-marrow depression, thrombocytopenia, leucopenia, and agranulocytosis.

Endocrine effects include testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. Sexual dysfunction may also occur. Changes in blood sugar concentrations may also occur, and, very occasionally, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.

Other adverse effects that have been reported are increased appetite with weight gain (or occasionally anorexia with weight loss). Sweating may be a problem.

Symptoms of **overdosage** may include excitement and restlessness with marked antimuscarinic effects, including dryness of the mouth, hot dry skin, dilated pupils, tachycardia, urinary retention, and intestinal stasis. Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypothermia, hypotension, metabolic acidosis, and respiratory and cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery. Delirium, with confusion, agitation and hallucinations, is common during recovery.

Antimuscarinic and antihistaminic properties. Studies *in vitro*[1] showed antidepressant affinities for human muscarinic acetylcholine receptors and therefore the likelihood of antimuscarinic effects to be, in descending order:

- amitriptyline
- protriptyline
- clomipramine
- trimipramine
- doxepin
- imipramine
- nortriptyline
- desipramine
- amoxapine
- maprotiline
- trazodone

The effect of affinities for other receptor sites was less certain, although those antidepressants with high affinity for histamine H_1 receptors might be expected to be more sedating. Affinities for *murine* histamine H_1 receptors in descending order were:

- doxepin
- trimipramine
- amitriptyline
- maprotiline
- amoxapine
- nortriptyline
- imipramine
- clomipramine
- protriptyline
- trazodone
- desipramine

1. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. *Mayo Clin Proc* 1983; **58:** 40–6.

Effects on the blood. After a case report of agranulocytosis linked with imipramine, review of the literature suggested that agranulocytosis associated with tricyclic antidepressant use was a rare idiosyncratic condition, resulting from a direct toxic effect rather than an allergic mechanism, and particularly affected the elderly from 4 to 8 weeks after beginning treatment.[1]

Between 1963 and 1993 the UK CSM received 912 reports of drug-induced agranulocytosis of which 38 were due to tricyclic antidepressants (12 fatal) and 1499 cases of neutropenia of which 46 were due to tricyclics (none fatal).[2] In a report[3] on a patient who developed aplastic anaemia associated with use of remoxipride and dosulepin it was noted that up to May 1993 the CSM had also received 11 reports of aplastic anaemia secondary to use of dosulepin.

Neutropenia reported[4] in a patient after separate exposure to imipramine and nortriptyline, indicated that there might be cross-intolerance between the tricyclic antidepressants and if neutropenia developed with one member of the group the use of others on future occasions should be avoided.

1. Albertini RS, Penders TM. Agranulocytosis associated with tricyclics. *J Clin Psychiatry* 1978; **39:** 483–5.
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
3. Philpott NJ, *et al.* Aplastic anaemia and remoxipride. *Lancet* 1993; **342:** 1244–5.
4. Draper BM, Manoharan A. Neutropenia with cross-intolerance between two tricyclic antidepressant agents. *Med J Aust* 1987; **146:** 452–3.

Effects on the cardiovascular system. The cardiotoxic potential of tricyclic antidepressants after **overdosage** is widely acknowledged; symptoms include arrhythmias, conduction defects, and hypotension. This factor was, in part, responsible for the development of antidepressants with different chemical structures and pharmacological properties that are less cardiotoxic. It also led to some concern over whether tricyclic antidepressants had adverse effects on the heart or cardiovascular system when used in usual therapeutic doses.

Since the introduction of the tricyclic antidepressants, reports, often anecdotal, have been published of adverse cardiovascular effects at **therapeutic doses** and have included malignant hypertension with amitriptyline,[1] and cardiomyopathy in a patient who had received amitriptyline and imipramine.[2] QT prolongation, which in some cases progressed to torsade de pointes, has also been associated with the use of some tricyclics.[3,4] Sudden cardiac death in patients with pre-existing cardiac disease has been linked with amitriptyline[5-7] or imipramine,[6] although the Boston Collaborative Drug Surveillance Program failed to substantiate these findings.[8] In a more recent analysis, it has been suggested that the risk of sudden cardiac death may increase with high doses of tricyclic antidepressants.[9] Using patient medication records, it was found that the rate of sudden cardiac death in patients taking less than 100 mg of amitriptyline or its equivalent, [presumably as a daily dose although this is not specified], did not differ from that among non-users of antidepressants even in those with cardiovascular disease or other conditions considered to increase the risk of sudden death; however, the risk was significantly increased in those patients on doses of 100 mg or greater when compared to non-users, regardless of any predisposing conditions.

There have also been reports of sudden death in children given desipramine[10-12] or imipramine;[12-14] in at least some of these cases plasma concentrations were not elevated and the children had no cardiac abnormality. Again, however, evaluation of much of the evidence for the association suggests it is weak;[15] nonetheless, the American Heart Association recommends baseline ECG monitoring in children who are to be treated with tricyclic antidepressants, and a repeat ECG when steady-state dosage is achieved.[16]

Re-evaluations and reviews of this topic[17,18] concluded that the only significant or serious cardiovascular adverse effects, seen in *patients with no history* of cardiovascular disease given therapeutic doses of tricyclic antidepressants, are orthostatic hypotension and tachycardia, and that these effects may be particularly troublesome in elderly patients. However, a later study[19] also considered that prolongation of the QT interval might occur with therapeutic doses of tricyclics in non-risk patients.

In *patients with overt heart disease* it was considered[17] that increased risk was likely in those with intraventricular conduction abnormalities; in patients with a history of myocardial infarction or angina, but free of conduction defects, the use of tricyclics appeared to be primarily limited by how often they developed orthostatic hypotension and to what degree. In a re-evaluation of the risks and benefits of tricyclics in patients with ischaemic heart disease no consensus was reached.[20] In practice the authors used SSRIs or bupropion as first-choice therapy in patients with ischaemic heart disease who were mildly or moderately depressed; tricyclics were reserved for unresponsive patients and were also used as first-choice therapy for patients with more severe depression despite cardiac risks. More recently an increased risk of myocardial infarction has been found in patients taking tricyclic antidepressants (but not SSRIs) with treatment for heart disease.[21] Results of a later case-control study[22] examining the risk of ischaemic heart disease for different types of antidepressants and individual antidepressants support these findings. After adjustment for confounders and use of other antidepressants the risk of ischaemic heart disease was significantly raised in patients who had ever taken tricyclics but not in those who had received other antidepressants. When the risk was calculated for the tricyclics amitriptyline, dosulepin, and lofepramine, and confounders had been adjusted for, an increased risk of ischaemic heart disease remained only for dosulepin with evidence of a dose-response relationship.

1. Dunn FG. Malignant hypertension associated with use of amitriptyline hydrochloride. *South Med J* 1982; **75:** 1124–5.
2. Howland JS, *et al.* Cardiomyopathy associated with tricyclic antidepressants. *South Med J* 1983; **76:** 1455–6.
3. Baker B, *et al.* Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. *J Clin Psychopharmacol* 1997; **17:** 15–21.
4. Vieweg WVR, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics* 2004; **45:** 371–7.
5. Coull DC, *et al.* Amitriptyline and cardiac disease. *Lancet* 1970; **ii:** 590–1.
6. Moir DC, *et al.* Cardiotoxicity of amitriptyline. *Lancet* 1972; **ii:** 561–4.
7. Moir DC, *et al.* Medicines evaluation and monitoring group: a follow-up study of cardiac patients receiving amitriptyline. *Eur J Clin Pharmacol* 1973; **6:** 98–101.
8. Boston Collaborative Drug Surveillance Program. Adverse reactions to the tricyclic-antidepressant drugs: report from Boston Collaborative Drug Surveillance Program. *Lancet* 1972; **i:** 529–31.
9. Ray WA, *et al.* Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75:** 234–41.
10. Anonymous. Sudden death in children treated with a tricyclic antidepressant. *Med Lett Drugs Ther* 1990; **32:** 53.
11. Riddle MA, *et al.* Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 792–7.
12. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry* 1997; **36:** 390–4.
13. Swanson JR, *et al.* Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy: a review of the literature and possible mechanisms. *J Forensic Sci* 1997; **42:** 335–9.
14. Varley CK. Sudden death of a child treated with imipramine: case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 321–5.
15. Biederman J, *et al.* Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry* 1995; **56:** 87–93.
16. Gutgesell H, *et al.* Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1999; **99:** 979–82. Also available at: http://circ.ahajournals.org/cgi/reprint/99/7/979 (accessed 24/11/05)
17. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med* 1984; **35:** 503–11.
18. Mortensen SA. Cyclic antidepressants and cardiotoxicity. *Practitioner* 1984; **228:** 1180–3.
19. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
20. Glassman AH, *et al.* The safety of tricyclic antidepressants in cardiac patients: risk-benefit reconsidered. *JAMA* 1993; **269:** 2673–5.
21. Cohen HW, *et al.* Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000; **108:** 2–8.
22. Hippisley-Cox J, *et al.* Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care. *BMJ* 2001: **323:** 666–9.

EFFECTS ON THE PERIPHERAL CIRCULATION. Painful vasospastic episodes, characterised by cold and blue hands and feet, occurred in a woman each time she received imipramine 150 mg daily and also with amitriptyline, but only when the dose was increased to 200 mg daily.[1] This suggested that the ability of tricyclic antidepressants to induce vasospasm was not limited to imipramine and that the effect might be partly dose-dependent. Additionally, acrocyanosis of the hands and feet has been reported in a child receiving imipramine for nocturnal enuresis.[2]

1. Appelbaum PS, Kapoor W. Imipramine-induced vasospasm: a case report. *Am J Psychiatry* 1983; **140:** 913–15.
2. Anderson RP, Morris BAP. Acrocyanosis due to imipramine. *Arch Dis Child* 1988; **63:** 204–5.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion with hyponatraemia* has been reported in patients receiving tricyclics and other antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.[1] Case reports of hyponatraemia in 24 patients treated with tricyclics and 20 patients treated with other antidepressants have been summarised.[2]

In a review covering the effects of drugs on *prolactin secretion*[3] it was stated that antidepressants could affect prolactin secretion by disturbing the balance of catecholaminergic inhibition and serotonergic stimulation of prolactin release, although any change is less than with antipsychotic therapy. Clomipramine and nortriptyline had been reported to stimulate prolactin release whereas amitriptyline, desipramine, and imipramine had been reported to be without effect. Such stimulation may account for symptoms of galactorrhoea or amenorrhoea reported with some tricyclics.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
3. Hell K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; **3:** 463–98.

Effects on the gastrointestinal tract. Rare cases of ileus and pseudo-obstruction have apparently resulted from the antimuscarinic effects of tricyclic antidepressants.[1-4] An early report[1] from the UK CSM noted no evidence that any tricyclic was especially liable to cause ileus.

1. CSM. Tricyclic antidepressants and ileus. *Current Problems 3* 1978. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024410&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989; **65:** 948–9.
3. Sood A, Kumar R. Imipramine induced acute colonic pseudo-obstruction (Ogilvie's syndrome): a report of two cases. *Indian J Gastroenterol* 1996; **15:** 70–1.
4. Ross JP, *et al.* Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998; **64:** 242–4.

Effects on the kidneys and urine. Haematuria has been seen in a patient receiving amitriptyline and carbamazepine;[1] carbamazepine had previously been taken alone for a long period without producing this effect.

Amitriptyline may have produced a blue-green colour in urine,[2] although it was considered to be a rare phenomenon.

1. Gillman MA, Sandyk R. Hematuria following tricyclic therapy. *Am J Psychiatry* 1984; **141:** 463–4.
2. Beeley L. *BMJ* 1986; **293:** 750.

Effects on the liver. In a report of 91 cases of hepatitis due to antidepressant therapy, 63 occurred in patients receiving the tricyclic antidepressant amineptine, sometimes with other psychotropic drugs; in about 50% of these amineptine cases, benzodiazepines had also been taken and it was postulated that the benzodiazepines may have increased the oxidation of amineptine to a toxic metabolite.[1] Most patients presented with abdominal pain and mixed liver damage with predominant cholestasis. One died after myocardial infarction, but all the others recovered. The mean amineptine dosage was 200 mg daily. In comparison, only a few cases were attributed to other tricyclic antidepressants—amitriptyline (4), clomipramine (3), and dibenzepin (1). Cross-hepatotoxicity between amineptine and clomipramine has also been reported in a patient.[2]

Hepatotoxicity has also been noted with lofepramine. The UK CSM had by the end of 1987 received 57 reports of abnormal liver function tests associated with lofepramine.[3] They included hepatic failure (1), jaundice (9), and hepatitis (5). All reactions occurred within the first 8 weeks of treatment and all were reversible on stopping the drug.

1. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
2. Larrey D, *et al.* Cross hepatotoxicity between tricyclic antidepressants. *Gut* 1986; **27:** 726–7.
3. CSM. Lofepramine (Gamanil) and abnormal blood tests of liver function. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the mouth. The inhibition of salivation caused by tricyclic antidepressants (in this case clomipramine) has been implicated in dental caries formation.[1]

1. deVries MW, Peeters F. Dental caries with longterm use of antidepressants. *Lancet* 1995; **346:** 1640.

Effects on the nervous system. Effects on the nervous system attributed to tricyclic antidepressants include drowsiness (especially with those with antihistaminic activity), peripheral neuropathy, tremor, ataxia, confusion, and delirium. Of particular concern is a reduction in the seizure threshold (see Epileptogenic Effect, below). Extrapyramidal effects and neuroleptic malignant syndrome (see below) may also occasionally occur.

Effects on sexual function. Loss of libido and impotence are common in depression, often making the role of drugs in producing sexual dysfunction difficult to assess.[1]

Sedation due to tricyclic antidepressants may lead to loss of libido and many of the tricyclics have been reported to cause impotence.[1,2] Amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, and trimipramine have been stated to delay or inhibit ejaculation, and amoxapine, imipramine, and protriptyline, also to cause painful ejaculation. However, some tricyclics have been used for their effect on ejaculation in the management of premature ejaculation (see Clomipramine, p.387).

In women, anorgasmia or delayed orgasm has been reported with amitriptyline, amoxapine, clomipramine, and imipramine,[1-3] although spontaneous orgasm associated with yawning has been reported with clomipramine.[4]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Anonymous. Drugs that cause sexual dysfunction. *Med Lett Drugs Ther* 1987; **29:** 65–70.
3. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.
4. McLean JD, *et al.* Unusual side effects of clomipramine associated with yawning. *Can J Psychiatry* 1983; **28:** 569–70.

Effects on the skin. Hypersensitivity reactions to tricyclic antidepressants are said to be uncommon.[1] Urticaria and angioedema have occurred, the urticaria occasionally clearing without drug withdrawal. Pruritus is also uncommon, but may be associated with transient erythema. Photosensitivity reactions are far less common than with phenothiazines; protriptyline has been the tricyclic most frequently implicated.[2,3] Rarely, exfoliative dermatitis has developed, and purpura, pigmentation, and lichen planus have been noted in isolated reports. In some cases pigmentation changes may be permanent.[4] Toxic epidermal necrolysis has been reported in a patient 2 weeks after starting therapy with amoxapine.[5] Hypersensitivity reactions to tricyclic antidepressants usually occur between 14 and 60 days after the start of treatment.[6]

Amitriptyline and fluoxetine have been implicated in the development of atypical cutaneous lymphoid hyperplasia in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[7] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to lesional resolution.

1. Almeyda J. Drug reactions XIII: cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; **84:** 298–9.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136** (June): 508–11.
3. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.
4. Dean CE, Grund FM. Imipramine-associated hyperpigmentation. *Ann Pharmacother* 2003; **37:** 825–8.
5. Camisa C, Grines C. Amoxapine: a cause of toxic epidermal necrolysis? *Arch Dermatol* 1983; **119:** 709–10.
6. Quitkin F. Cross-tolerance of tricyclic antidepressant drugs. *JAMA* 1979; **241:** 1625.
7. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.

Epileptogenic effect. Seizures have been reported after therapeutic doses of tricyclic antidepressants as well as after overdosage, although the mechanism by which the seizures are induced is unclear.[1] Seizures usually appear within a few days of starting the drug or changing to a higher dose but in patients with no history of epilepsy or no predisposing medical condition the frequency seems[1] to be very low with an incidence of about 1 in 1000. An incidence of 0.4 per 1000 was reported[2] based on 16 cases out of an estimated group of 42 000 patients receiving tricyclics and who had no predisposing factors, but in another review[3] a reasonable estimate of the incidence was considered to be 3 to 6 per 1000. However, it is widely agreed that tricyclics should be used very cautiously in patients with epilepsy or those with a low convulsive threshold.

In a retrospective analysis of 1313 cases[4] of overdosage involving cyclic antidepressants, seizures occurred more commonly with the tricyclics amoxapine (24.5%) and desipramine (17.9%), and the tetracyclic maprotiline (12.2%). In another analysis of 302 consecutive cases of tricyclic overdosage a higher rate of seizures was seen with dosulepin in overdosage (13%) than other tricyclics.[5]

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Jick SS, *et al.* Antidepressants and convulsions. *J Clin Psychopharmacol* 1992; **12:** 241–5.
3. Rosenstein DL, *et al.* Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993; **54:** 289–99.
4. Wedin GP, *et al.* Relative toxicity of cyclic antidepressants. *Ann Emerg Med* 1986; **15:** 797–804.
5. Buckley NA, *et al.* Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 1994: **343:** 159–62.

Extrapyramidal effects. Extrapyramidal effects such as orofacial and choreoathetoid movements, and dyskinesias have been attributed to treatment with tricyclic antidepressants. Dysarthria has also been reported[1] and was said to be not uncommon in those taking higher doses of tricyclic antidepressants, but unusual at lower doses.[2]

Some patients with panic disorder may be sensitive to imipramine, developing symptoms of insomnia, jitteriness, and irritability.[3] Symptoms have also been seen in patients with panic disorder treated with low doses of desipramine although the symptoms usually subsided when the dose of the tricyclic was gradually increased. It has been suggested[4] that these symptoms may be related to akathisia and are more likely to occur with those tricyclics that have a more potent effect on inhibition of noradrenaline reuptake.

Reviews of adverse effects of drugs on the nervous system have also listed acute torsion dystonias and tremors[5] as being caused or exacerbated by tricyclic antidepressants.

1. Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. *BMJ* 1977; **2:** 97.
2. Saunders M. Dysarthria with tricyclic antidepressants. *BMJ* 1977; **2:** 317.
3. Yeragani VK, *et al.* Tricyclic induced jitteriness—a form of akathisia? *BMJ* 1986; **292:** 1529.
4. Cole JO, Bodkin JA. Antidepressant drug side effects. *J Clin Psychiatry* 1990; **51** (suppl): 21–6.
5. Llau M-E, *et al.* Mouvements anormaux d'origine médicamenteuse: l'expérience d'un centre de pharmacovigilance sur cinq ans. *Therapie* 1995; **50:** 425–7.

Hypersensitivity. A hypersensitivity syndrome developed in a 24-year-old woman 3 weeks after starting amitriptyline 50 mg daily for the treatment of depression;[1] symptoms included generalised erythroderma with mild scaling, sinus tachycardia, haematological abnormalities such as eosinophilia, and raised liver enzyme values. The patient recovered after drug withdrawal and treatment with intravenous prednisolone.

See also under Effects on the Skin, above.

1. Milionis HJ, *et al.* Hypersensitivity syndrome caused by amitriptyline administration. *Postgrad Med J* 2000; **76:** 361–3.

Hyponatraemia. See Effects on the Endocrine System, above.

Neuroleptic malignant syndrome. Of 16 cases of neuroleptic malignant syndrome reported to the UK CSM by July 1986, 3 cases occurred in patients receiving a tricyclic antidepressant; amitriptyline with perphenazine had been taken by one patient and dosulepin or clomipramine alone by 2 other patients. The clomipramine case was fatal.[1] Other reports have been associated with amoxapine,[2] clomipramine alone,[3] clomipramine with triazolam,[4] and nortriptyline.[5]

1. CSM. Neuroleptic malignant syndrome—an underdiagnosed condition? *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Madakasira S. Amoxapine-induced neuroleptic malignant syndrome. *DICP Ann Pharmacother* 1989; **23:** 50–1.
3. Haddow AM, *et al.* Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. *BMJ* 2004; **329:** 1333–5.
4. Domingo P, *et al.* Benign type of malignant syndrome. *Lancet* 1989; **i:** 50.
5. June R, *et al.* Neuroleptic malignant syndrome associated with nortriptyline. *Am J Emerg Med* 1999; **17:** 736–7.

Overdosage. In a 1993 report[1] tricyclic antidepressants were associated with a higher risk of fatality after suicide attempts by drug overdose compared with the non-tricyclics available at the time. Some reports[2] have considered desipramine to be associated more frequently than other tricyclic antidepressants with fatal overdosage, although others[3] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage.

Later reviews continue to cite tricyclic antidepressants as one of the most commonly ingested substances in fatal cases of self-poisoning.[3,4]

1. Anonymous. Antidepressant drugs and the risk of suicide. *WHO Drug Inf* 1993; **7:** 18–20.
2. Amitai Y, Frischer H. The toxicity and dose of desipramine hydrochloride. *JAMA* 1994; **272:** 1719–20.
3. Kerr GW, *et al.* Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; **18:** 236–41.
4. Glauser J. Tricyclic antidepressant poisoning. *Cleve Clin J Med* 2000; **67:** 704–19.

Treatment of Adverse Effects

The basis of the management of tricyclic antidepressant poisoning is intensive supportive care and symptomatic therapy.

Since tricyclic antidepressants slow gastrointestinal transit time, absorption may be delayed in overdosage. Activated charcoal may be given by mouth or nasogastric tube if more than 4 mg/kg of a tricyclic antidepressant has been ingested and the patient presents within 1 hour; a second dose may be considered after 2 hours in patients with central features of toxicity. Gastric lavage is rarely used but may be considered in life-threatening overdoses. Multiple doses of charcoal may be appropriate in patients who have ingested modified-release preparations.

The patient should be monitored for cardiac arrhythmias. UK authorities consider that although cardiac arrhythmias are of concern they are best treated by correction of hypoxia and acidosis with intravenous sodium bicarbonate; the use of antiarrhythmic drugs is best avoided. Intravenous sodium bicarbonate should also be given to treat arrhythmias or significant ECG abnormalities even in the absence of acidosis.

Convulsions can be managed by giving diazepam or lorazepam intravenously. Phenytoin should be avoided because it may increase the risk of arrhythmias. Diazepam by mouth is usually adequate to sedate delirious patients, although large doses may be needed.

Peritoneal dialysis, haemodialysis, and measures to increase urine production are not of value in tricyclic antidepressant poisoning, and charcoal haemoperfusion is of doubtful benefit.

Precautions

The antimuscarinic effects of tricyclic antidepressants warrant care in patients with urinary retention, prostatic hyperplasia, or chronic constipation; caution has also been advised in untreated angle-closure glaucoma and in phaeochromocytoma.

The epileptogenic potential of tricyclic antidepressants requires care in patients with a history of epilepsy. In addition, because of their potential cardiotoxicity, tricyclics should be used with caution in patients with cardiovascular disease and avoided in those with heart block, cardiac arrhythmias, or in the immediate recovery period after myocardial infarction. Caution has also been recommended in patients with hyperthyroidism as tricyclics may increase the risk of developing cardiac arrhythmias.

Blood-sugar concentrations may be altered in diabetic patients.

Because tricyclic antidepressants are metabolised and inactivated in the liver they should be used with caution in patients with hepatic impairment and avoided in severe liver disease.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be followed when treating patients with other disorders.

If tricyclic antidepressants are used for the depressive component of bipolar disorder, mania may be precipitated; similarly, psychotic symptoms may be aggravated if tricyclics are used for a depressive component of schizophrenia.

Drowsiness often occurs, particularly at the start of therapy, and patients, if affected, should not drive or operate machinery.

Tricyclic antidepressants may inhibit salivation and regular dental check-ups are recommended for patients on long-term therapy, particularly when taking those with marked antimuscarinic actions.

Elderly patients can be particularly sensitive to the adverse effects of tricyclic antidepressants and a reduced dose, especially initially, should be used.

Tricyclic antidepressants are not recommended for depression in children. If they are used for nocturnal enuresis in children they should be limited to short courses with a full physical examination before subsequent courses.

Tricyclic antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms (see below).

Licensed drug information recommends that, where possible, tricyclic antidepressants should be stopped several days before elective surgery, and that they should be used with caution in patients requiring ECT; however, see also under Anaesthesia, below.

Anaesthesia. Patients receiving tricyclic antidepressants are at an increased risk of developing hypotension or cardiac arrhythmias during anaesthesia. Tricyclics may also dangerously potentiate the cardiovascular effects of vasopressor drugs such as sympathomimetics that may be required during anaesthesia. Although some licensed drug information recommends stopping tricyclics several days before elective surgery where possible, the *BNF* advises that this is unnecessary as long as the anaesthetist is informed.

Commenting on the anaesthetic considerations relevant to ECT,[1] it was considered that therapy with tricyclic antidepressants should not be a contra-indication to anaesthesia for ECT. A major consideration, though, was said to be the interaction of tricyclics with barbiturates resulting in increased sleep time and duration of anaesthesia. This meant that lower doses of barbiturate anaesthetics should be used.

Antidepressants with significant serotonergic effects such as the tricyclic clomipramine may increase the risk of bleeding during surgery; for further details see under Precautions in Fluoxetine, p.396.

1. Gaines GY, Rees DI. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* 1986; **65:** 1345–56.

Breast feeding. In general, only small amounts of tricyclic antidepressants are distributed into breast milk. Nevertheless, the American Academy of Pediatrics[1] considers that all antidepressants, including tricyclics, are drugs whose effect on nursing infants is unknown but may be of concern. In addition, most manufacturers advise that tricyclics should be avoided by the mother during breast feeding.

Case reports indicate that amitriptyline and its metabolite (nortriptyline),[2,3] clomipramine,[4] desipramine and its metabolite (2-hydroxydesipramine),[5] dosulepin and its primary metabolites (nordothiepin, dothiepin-*S*-oxide, and nordothiepin-*S*-oxide),[6] doxepin and its metabolite (*N*-desmethyldoxepin),[7-9] imipramine and its metabolite (desipramine),[10] and maprotiline[11] are all present in breast milk in concentrations similar to those in maternal blood; amoxapine and its metabolite (8-hydroxyamoxapine)[12] have also been detected in breast milk but in concentrations lower than in maternal blood. In all but two of the above cases the infants were breast fed without experiencing adverse effects and tricyclics were undetectable in the infant's blood or present only in minute amounts. In one of the affected infants,[8] adverse effects included sedation and shallow respiration. The infant's mother had received doxepin and, although doxepin was almost undetectable in the infant's serum, the desmethyl metabolite appeared to have accumulated. In the other infant, drowsiness, poor suckling, and difficulty in swallowing were noted.[9] In this case the levels of both doxepin and its desmethyl metabolite were below the lower level of quantification; however, it was considered that the infant may have been at a greater risk for adverse effects because he had also developed hyperbilirubinaemia. There were no data for the effects of amoxapine on breast-fed infants because the case reported[12] involved samples of milk taken from a woman who had galactorrhoea as an adverse effect of tricyclic use. No adverse effects were seen during a 27-month follow-up of 14 breast-fed infants whose mothers had received imipramine 100 to 225 mg daily for 4 to 24 weeks.[13]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1980; **137:** 855–6.
3. Brixen-Rasmussen L, *et al.* Amitriptyline and nortriptyline excretion in human breast milk. *Psychopharmacology (Berl)* 1982; **76:** 94–5.
4. Schimmell MS, *et al.* Toxic neonatal effects following maternal clomipramine therapy. *Clin Toxicol* 1991; **29:** 479–84.
5. Stancer HC, Reed KL. Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1986; **143:** 1597–1600.
6. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.
7. Kemp J, *et al.* Excretion of doxepin and N-desmethyldoxepin in human milk. *Br J Clin Pharmacol* 1985; **20:** 497–9.
8. Matheson I, *et al.* Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 1985; **ii:** 1124.
9. Frey OR, *et al.* Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999; **33:** 690–3.
10. Sovner R, Orsulak PJ. Excretion of imipramine and desipramine in human breast milk. *Am J Psychiatry* 1979; **136:** 451–2.
11. Lloyd AH. Practical considerations in the use of maprotiline (Ludiomil) in general practice. *J Int Med Res* 1977; **5** (suppl 4): 122–38.
12. Gelenberg AJ. Amoxapine, a new antidepressant, appears in human milk. *J Nerv Ment Dis* 1979; **167:** 635–6.
13. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991; **21:** 157–71.

Cardiovascular disease. For comments on the potential cardiotoxicity of tricyclic antidepressants and precautions to be observed in patients with pre-existing cardiovascular disorders, see under Effects on the Cardiovascular System in Adverse Effects, above.

Contact lenses. Based on reports involving amitriptyline[1] and maprotiline[2] it has been considered that the antimuscarinic action of tricyclic antidepressants may decrease tear flow enough to cause corneal drying and staining of contact lenses.[3]

1. Litovitz GL. Amitriptyline and contact lenses. *J Clin Psychiatry* 1984; **45:** 188.
2. Troiano G. Amitriptyline and contact lenses. *J Clin Psychiatry* 1985; **46:** 199.
3. Anonymous. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Diabetes mellitus. The fact that tricyclic antidepressants may cause alterations in blood-glucose concentrations has led to the recommendation that these drugs should be used with caution in diabetic patients. Amitriptyline has also been reported[1] to cause hypoglycaemic unawareness; a patient did not experience the usual adrenergic symptoms that preceded or accompanied her hypoglycaemic episodes.

1. Sherman KE, Bornemann M. Amitriptyline and asymptomatic hypoglycemia. *Ann Intern Med* 1988; **109:** 683–4.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects both of which are more pronounced at the start of treatment; sedative tricyclics, such as amitriptyline and doxepin, are likely to cause greater psychomotor impairment than less sedative tricyclics such as imipramine and nortriptyline.[1] However, an epidemiological study[3] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs. In healthy subjects fluoxetine (an SSRI) and dosulepin appeared to have a similar but apparently small potential for impairing psychomotor and driving performance.[4]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that drugs such as the older tricyclic antidepressants may have pronounced antimuscarinic and antihistaminic effects which may impair driving.[5] In addition, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
4. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

ECT. For comments concerning the precautions to be observed in patients receiving ECT, see under Anaesthesia, above.

Epilepsy. For comments on the epileptogenic effect of tricyclic antidepressants and the need for caution in patients with a history of epilepsy or other risk factors for development of seizures, see under Epileptogenic Effect in Adverse Effects, above.

Food. A high-fibre diet reduced or abolished the effectiveness of tricyclic antidepressant therapy in 3 patients;[1] the tricyclics involved were doxepin in two patients and desipramine in one.

1. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol* 1992; **12:** 438–40.

Gastro-oesophageal reflux disease. The antimuscarinic action of tricyclic antidepressants may cause relaxation of the lower oesophageal sphincter and could aggravate nocturnal symptoms of gastro-oesophageal reflux if given in the late evening.[1]

1. Atkinson M. Use and misuse of drugs in the treatment of gastro-oesophageal reflux. *Prescribers' J* 1982; **22:** 129–36.

Glaucoma. It has been considered by the manufacturers that tricyclic antidepressants, because of their antimuscarinic actions, should be used with caution in patients with angle-closure glaucoma or raised intra-ocular pressure. There have been few reports of glaucoma associated with tricyclics, although acute angle-closure glaucoma was reported in 4 patients with narrow angles while taking imipramine in usual doses,[1] and in another patient taking clomipramine.[2] In the latter case, the presenting sign was amaurosis fugax, caused by the combination of raised intra-ocular pressure and an abnormally large drop in blood pressure on standing.

1. Ritch R, *et al.* Oral imipramine and acute angle closure glaucoma. *Arch Ophthalmol* 1994; **112:** 67–8.
2. Schlingemann RO, *et al.* Amaurosis fugax on standing and angle-closure glaucoma with clomipramine. *Lancet* 1996; **347:** 465.

Phaeochromocytoma. Use of imipramine[1,2] or desipramine[3] has caused adverse effects such as seizures and cardiovascular abnormalities (tachycardia and hypertension or hypotension) in patients with previously undiagnosed phaeochromocytoma. It has been suggested[3] that imipramine and its metabolite, desipramine, may be particularly effective in unmasking phaeochromocytoma and that this may be a reflection of their relative potency in inhibiting the noradrenaline reuptake mechanism.

1. Kaufmann JS. Pheochromocytoma and tricyclic antidepressants. *JAMA* 1974; **229:** 1282.
2. Mok J, Swann I. Diagnosis of phaeochromocytoma after ingestion of imipramine. *Arch Dis Child* 1978; **53:** 676–7.
3. Achong MR, Keane PM. Pheochromocytoma unmasked by desipramine therapy. *Ann Intern Med* 1981; **94:** 358–9.

Porphyria. Amitriptyline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Management of depression during pregnancy can be difficult, and one report[1] on experience in 8 pregnant women being treated with a tricyclic antidepressant suggested that the dose might need to be increased during the second half of pregnancy to achieve a response. There are obvious concerns about such treatment (see also Depression, p.373). However, although there have been isolated reports[2] attributing *congenital malformations* to the use of tricyclic antidepressants during pregnancy, large-scale studies and case-control data[3,4] have failed to substantiate any association.

The effects of tricyclics on *fetal neurodevelopment* were studied[5] in 80 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to tricyclics *in utero* in the first trimester compared with those exposed to fluoxetine or no adverse developmental influences. A subsequent study indicated that exposure to tricyclic antidepressants or fluoxetine throughout gestation did not appear to adversely affect cognition.[6]

Fetal tachyarrhythmia detected at 37 weeks of gestation was attributed to maternal use of dosulepin during pregnancy. When this was stopped, no abnormalities in fetal heart rate were found and an uneventful labour led to a healthy infant being delivered. However, the authors expressed concern that fetal tachycardias might result in *in-utero* cardiac failure and considered that tricyclic antidepressants should be used during pregnancy only if there were compelling reasons.[7]

Withdrawal syndromes manifesting as hypothermia and jitteriness,[8] convulsions,[9,10] or myoclonus[11] have been reported in neonates whose mothers took clomipramine during pregnancy. Management has been with phenobarbital or clomipramine. Licensed product information advises that if it is justifiable to do so, clomipramine should be withdrawn at least 7 weeks before the calculated date of delivery.

1. Wisner KL, *et al.* Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993; **150:** 1541–2.
2. Barson AJ. Malformed infant. *BMJ* 1972; **2:** 45.
3. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; **2:** 853–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
5. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
6. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
7. Prentice A, Brown R. Fetal tachyarrhythmia and maternal antidepressant treatment. *BMJ* 1989; **298:** 190.
8. Musa AB, Smith CS. Neonatal effects of maternal clomipramine therapy. *Arch Dis Child* 1979; **54:** 405.
9. Cowe L, *et al.* Neonatal convulsions caused by withdrawal from maternal clomipramine. *BMJ* 1982; **284:** 1837–8.
10. Bromiker R, Kaplan M. Apparent intrauterine fetal withdrawal from clomipramine hydrochloride. *JAMA* 1994; **272:** 1722–3.
11. Bloem BR, *et al.* Clomipramine withdrawal in newborns. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F77–F79.

Surgery. For comments regarding the precautions to be observed in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms. The symptoms associated with withdrawal of tricyclic antidepressants appear to form four distinct syndromes:[1]

- gastrointestinal disturbances and generalised somatic symptoms such as malaise, chills, headache, and increased perspiration, which may also be accompanied by anxiety and agitation
- sleep disturbances characterised by insomnia followed by excessive and vivid dreams
- parkinsonism or akathisia
- hypomania or mania

Tricyclic withdrawal has also resulted in cardiac arrhythmias in some patients. Withdrawal symptoms seem to be more common and more severe in children.[2]

Many of the symptoms associated with stopping tricyclics may be produced by cholinergic rebound[1] and can be minimised by a gradual reduction in dosage. The *BNF* recommends that any antidepressant, including a tricyclic, that has been given regularly for 8 weeks or more should be stopped gradually over a period of at least 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy. If withdrawal symptoms do occur, they can be managed by restarting at a dose sufficient to eliminate them, and then stopping gradually.[1,2] On the occasions that it may be necessary to stop a tricyclic abruptly, the withdrawal symptoms can be treated with a centrally active antimuscarinic such as atropine or benzatropine,[1] or alternatively, if withdrawal symptoms are just gastrointestinal, an antimuscarinic that does not cross the blood-brain barrier such as propantheline.[1] Awareness of the possibility of withdrawal syndromes helps to avoid misinterpreting new symptoms after withdrawal as evidence of relapse.

Tricyclic antidepressants have been included in some classifications as drugs of dependence because of their potential to produce withdrawal syndromes, but a review[3] of several substance abuse studies challenged this on finding no evidence of abuse or dependence of the barbiturate type developing with the tricyclics.

For reports of withdrawal symptoms in neonates born to mothers who took tricyclic antidepressants during pregnancy, and their management, see under Pregnancy, above.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.
2. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
3. Lichtigfeld FJ, Gillman MA. The possible abuse of and dependence on major tranquillisers and tricyclic antidepressants. *S Afr Med J* 1994; **84:** 5–6.

Interactions

Interactions involving tricyclic antidepressants often result from additive toxicity or from altered metabolism of one drug by the other. Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP2D6 may affect tricyclic metabolism and produce marked alterations in plasma concentrations.

Adverse effects may be enhanced by antimuscarinic drugs or CNS depressants, including alcohol. Barbiturates and other enzyme inducers such as rifampicin and some antiepileptics can increase the metabolism of tricyclic antidepressants and may lower plasma concentrations and reduce antidepressant response. Cimetidine, methylphenidate, antipsychotics, and calcium-channel blockers can reduce the metabolism of the tricyclics, leading to the possibility of increased plasma concentrations and accompanying toxicity.

Patients taking thyroid preparations may show an accelerated response to tricyclic antidepressants and occasionally liothyronine has been used to produce this effect in patients with refractory depression. However, the use of tricyclics with thyroid hormones may precipitate cardiac arrhythmias.

The antihypertensive effects of debrisoquine, guanethidine, and clonidine may be reduced by tricyclic antidepressants. The pressor effects of sympathomimetics, especially those of the direct-acting drugs adrenaline and noradrenaline, can be enhanced by tricyclic antidepressants; however, there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and tricyclic antidepressants. Great care should, however, be taken to avoid inadvertent intravenous injection of the local anaesthetic preparation.

Drugs that prolong the QT interval, including antiarrhythmics such as amiodarone or quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, and thioridazine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants. This may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces tricyclic metabolism.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the serotonin syndrome (see p.416) may occur. For this reason an appropriate drug-free interval should elapse between stopping some types of antidepressant and starting another. Tricyclic antidepressants should not generally be given to patients receiving MAOIs or for at least 2 weeks (3 weeks if starting clomipramine or imipramine) after their withdrawal. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting a tricyclic. At least 1 to 2 weeks (3 weeks in the case of clomipramine or imipramine) should elapse between withdrawing a tricyclic antidepressant and starting any drug liable to provoke a serious reaction (e.g. phenelzine).

Further details concerning some of the above interactions, and others, are given below.

Alcohol. For reference to the effect of alcohol on amitriptyline, see under CNS depressants, below.

Analgesics. Doubling of plasma-doxepin concentrations with associated lethargy has been reported in a patient after the addition of *dextropropoxyphene* to the tricyclic.[1] This was consistent with previous studies indicating that dextropropoxyphene can impair the hepatic metabolism of other drugs.

For general reference to the effect of tricyclic antidepressants, notably amitriptyline and clomipramine, on *opioid analgesics*, see under Morphine, p.88.

1. Abernethy DR, *et al.* Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; **97:** 223–4.

Antiarrhythmics. Antiarrhythmics that prolong the QT interval may increase the likelihood of ventricular arrhythmias when given with tricyclic antidepressants. This includes various class I antiarrhythmics such as *disopyramide*, *flecainide*, *procainamide*, *propafenone*, and *quinidine*, and the class III antiarrhythmic *amiodarone*.

Raised serum-desipramine concentrations and signs of toxicity were noted[1] in a patient taking desipramine after starting treatment with digoxin and propafenone for paroxysmal atrial fibrillation. It was considered that propafenone probably reduced the metabolism and clearance of desipramine.

1. Katz MR. Raised serum levels of desipramine with the antiarrhythmic propafenone. *J Clin Psychiatry* 1991; **52:** 432–3.

Anticoagulants. For the effect of tricyclic antidepressants on anticoagulants, see under Warfarin, p.1428.

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in interactions or enhanced adverse reactions, and should be used only under expert supervision. This practice is considered unsuitable or controversial by some authorities. For further details of the interactions between different antidepressants when used together, see Phenelzine, p.418. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p.416.

Antidiabetics. For the effect of tricyclic antidepressants on *sulfonylureas* and *insulin*, see Interactions, p.461 and p.449, respectively.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

A review[1] of drug interactions with *phenytoin* noted that although there had been reports of interactions between antiepileptics and tricyclic or related antidepressants, most involved enzyme-inducing antiepileptics other than phenytoin or phenytoin with other drugs. In the only report where phenytoin could be identified as the sole antiepileptic used, 2 patients required high doses of desipramine to achieve an antidepressant effect and to maintain plasma-desipramine concentrations in the range usually associated with therapeutic efficacy.

Carbamazepine has been reported to induce the metabolism of a number of tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, and nortriptyline) and to reduce their plasma concentrations. The clinical importance of the interaction is unclear. Use of nortriptyline with carbamazepine in a patient led to a decrease in serum-nortriptyline concentration requiring an increase in nortriptyline dose.[2] In another patient a prolonged QT interval was noted after use of desipramine with carbamazepine;[3] the authors hypothesised that the accelerated metabolism of desipramine had resulted in high levels of a cardiotoxic metabolite.

Valproate has been reported to increase plasma concentrations of amitriptyline,[4] clomipramine,[5] and nortriptyline.[4,6]

For the effect of the cyclic antidepressants desipramine and viloxazine on carbamazepine, see p.474. For the effects of tricyclic antidepressants on phenytoin, see p.498.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.
2. Brøsen K, Kragh-Sørensen P. Concomitant intake of nortriptyline and carbamazepine. *Ther Drug Monit* 1993; **15:** 258–60.
3. Baldessarini RJ, *et al.* Anticonvulsant cotreatment may increase toxic metabolites of antidepressants and other psychotropic drugs. *J Clin Psychopharmacol* 1988; **8:** 381–2.
4. Wong SL, *et al.* Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther* 1996; **60:** 48–53.
5. Fehr C, *et al.* Increase in serum clomipramine concentrations caused by valproate. *J Clin Psychopharmacol* 2000; **20:** 493–4.
6. Fu C, *et al.* Valproate/nortriptyline interaction. *J Clin Psychopharmacol* 1994; **14:** 205–6.

Antifungals. Increased serum concentrations of nortriptyline[1] or amitriptyline[2,3] have occurred in patients also taking *fluconazole*. In some patients the use of amitriptyline with fluconazole has led to syncope[3] or torsade de pointes.[4] Raised serum concentrations of nortriptyline and associated symptoms of intoxication have been reported in 2 patients during treatment with *terbinafine*;[5,6] the interaction was confirmed on rechallenge. In another case, dizziness, dry mouth, and muscle twitching were reported in a patient on long-term imipramine treatment after starting terbinafine;[7] serum imipramine concentrations were found to be elevated and symptoms subsided after the dose of imipramine was reduced. A study in healthy subjects also indicated that terbinafine similarly inhibited the metabolism of desipramine.[8]

1. Gannon RH. Fluconazole-nortriptyline drug interaction. *Ann Pharmacother* 1992; **26:** 1456.
2. Newberry DL, *et al.* A fluconazole/amitriptyline drug interaction in three male adults. *Clin Infect Dis* 1997; **24:** 270–1.
3. Robinson RF, *et al.* Syncope associated with concurrent amitriptyline and fluconazole therapy. *Ann Pharmacother* 2000; **34:** 1406–1409.
4. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* 2000; **18:** 227–9.
5. van der Kuy P-HM, *et al.* Nortriptyline intoxication induced by terbinafine. *BMJ* 1998; **316:** 441.
6. van der Kuy P-HM, *et al.* Pharmacokinetic interaction between nortriptyline and terbinafine. *Ann Pharmacother* 2002; **36:** 1712–14.
7. Teitelbaum ML, Pearson VE. Imipramine toxicity and terbinafine. *Am J Psychiatry* 2001; **158:** 2086.
8. Madani S, *et al.* Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. *J Clin Pharmacol* 2002; **42:** 1211–18.

Antihypertensives. In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but there may be antagonism of the effect of *adrenergic neurone blockers* and of *clonidine*.

Antimigraine drugs. For the effects when some tricyclics are used with *dihydroergotamine*, see p.621.

Antineoplastics. For the effects when tricyclic antidepressants are used with *altretamine*, see p.678.

Antiprotozoals. Toxic psychosis developed in a patient on amitriptyline after starting *furazolidone*, an antiprotozoal with monoamine oxidase inhibiting activity.[1]

1. Aderhold RM, Muniz CE. Acute psychosis with amitriptyline and furazolidone. *JAMA* 1970; **213:** 2080.

Antipsychotics. For a discussion of interactions between antipsychotics and tricyclic antidepressants, see *Chlorpromazine* (p.974). For details of a possible interaction between clomipramine and *clozapine*, see p.984.

Antivirals. HIV-protease inhibitors may increase the plasma concentrations of tricyclic antidepressants whose metabolism is mediated through common cytochrome P450 isoenzymes. *Ritonavir* has produced moderate increases in the plasma concentrations of desipramine and a lower initial dose of desipramine may be appropriate. Licensed product information for ritonavir has warned that a similar increase may occur for other tricyclics; monitoring of therapeutic and adverse effects is recommended when tricyclics are used with ritonavir.

Anxiolytics. For a suggestion that *benzodiazepines* may increase the oxidation of amineptine to a toxic metabolite, see under Effects on the Liver in Adverse Effects, above. For a possible interaction of desipramine and other antidepressants with *zolpidem* see p.1038.

Barbiturates. Antidepressants may antagonise the antiepileptic activity of some barbiturates by lowering the convulsive threshold.

Barbiturates can increase the metabolism of tricyclic antidepressants and thereby produce lower plasma concentrations.

For details of the interaction of tricyclic antidepressants with barbiturate anaesthetics, see under Anaesthesia in Precautions, above.

Beta blockers. Raised imipramine plasma concentrations were noted in two 9-year-old children also given *propranolol*;[1] in both cases, no significant adverse effects were reported. *Labetalol* has also increased the bioavailability of imipramine in healthy subjects and inhibited its metabolism.[2]

The risk of ventricular arrhythmias may be increased when tricyclic antidepressants are taken with *sotalol*.

1. Gillette DW, Tannery LP. Beta blocker inhibits tricyclic metabolism. *J Am Acad Child Adolesc Psychiatry* 1994; **33:** 223–4.
2. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.

Calcium-channel blockers. *Diltiazem* and *verapamil* each increased the bioavailability of imipramine in healthy subjects; second-degree heart block developed in 2 subjects.[1] Diltiazem also increased the bioavailability of nortriptyline in one patient,[2] probably by reducing the first-pass metabolism of nortriptyline. Increased serum concentrations of trimipramine have been reported when taken with diltiazem,[3] although there was no evidence of toxicity.

1. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.
2. Krähenbühl S, *et al.* Pharmacokinetic interaction between diltiazem and nortriptyline. *Eur J Clin Pharmacol* 1996; **49:** 417–19.
3. Cotter PA, *et al.* Asymptomatic tricyclic toxicity associated with diltiazem. *Ir J Psychol Med* 1996; **13:** 168–9.

CNS depressants. Drugs with depressant actions on the CNS may be expected to enhance the drowsiness and related effects produced by the sedating type of tricyclic antidepressants. Such an interaction may occur between *alcohol* and tricyclic antidepressants and a study has shown that alcohol decreases the hepatic first-pass extraction of amitriptyline resulting in increased free plasma-amitriptyline concentrations, especially during the period of drug absorption.[1]

The problems that may be encountered with *barbiturate anaesthetics* are discussed under Anaesthesia in Precautions, above.

1. Dorian P, *et al.* Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. *Eur J Clin Pharmacol* 1983; **25:** 325–31.

Disulfiram. Acute organic brain syndrome has been reported in 2 patients receiving disulfiram after the addition of amitriptyline to their treatment.[1] It was suspected that the syndrome was potentiated by the combined action of the drugs and the synergistic elevation in dopamine concentration.

For a report of the enhancement of the disulfiram-alcohol reaction by amitriptyline, see p.2297.

1. Maany I, *et al.* Possible toxic interaction between disulfiram and amitriptyline. *Arch Gen Psychiatry* 1982; **39:** 743–4.

Dopaminergics. Serious adverse effects have been reported[1] when *selegiline*, an irreversible selective inhibitor of monoamine oxidase type B, was used with tricyclic antidepressants. In some instances effects resembled the potentially fatal serotonin syndromes reported when tricyclics are given with non-selective MAOIs (see under Phenelzine, p.416).

Some manufacturers of selegiline advise that tricyclic antidepressants should not generally be given at the same time, or for at least 2 weeks after it has been discontinued. Similarly, at least one week should elapse between withdrawing a tricyclic antidepressant and starting selegiline.

For reference to the effect of tricyclic antidepressants on *levodopa*, see p.807.

1. Anonymous. Selegiline and antidepressants: risk of serious interactions. *WHO Drug Inf* 1995; **9:** 160–1.

General anaesthetics. For the effect of amitriptyline on *enflurane*, see p.1783. For the effects of using tricyclic antidepressants with *barbiturates* see under Anaesthesia in Precautions, above.

Histamine H_2-antagonists. *Cimetidine* is a known inhibitor of hepatic metabolism of drugs and symptoms of tricyclic toxicity have been reported in patients receiving cimetidine with desipramine,[1] doxepin,[2] and imipramine;[1] there has been a report of psychosis developing in a patient given imipramine and cimetidine.[3] Elevated tricyclic concentrations during combined therapy or reductions in tricyclic concentrations after withdrawal of cimetidine have been reported for imipramine[4] and nortriptyline.[5] Studies in healthy subjects have also indicated increased bioavailability and/or impaired hepatic metabolism of amitriptyline,[6] doxepin,[7,8] and imipramine[9] during cimetidine therapy. Adjustment of tricyclic antidepressant dosage may therefore be required if cimetidine therapy is begun or stopped.

Ranitidine has been reported not to alter the pharmacokinetics of amitriptyline,[10] doxepin,[8] or imipramine.[9]

1. Miller DD, Macklin M. Cimetidine-imipramine interaction: a case report. *Am J Psychiatry* 1983; **140:** 351–2.
2. Brown BA, *et al.* Cimetidine-doxepin interaction. *J Clin Psychopharmacol* 1985; **5:** 245–7.
3. Miller ME, *et al.* Psychosis in association with combined cimetidine and imipramine treatment. *Psychosomatics* 1987; **28:** 217–19.
4. Shapiro PA. Cimetidine-imipramine interaction: case report and comments. *Am J Psychiatry* 1984; **141:** 152.
5. Miller DD, *et al.* Cimetidine's effect on steady-state serum nortriptyline concentrations. *Drug Intell Clin Pharm* 1983; **17:** 904–5.
6. Curry SH, *et al.* Cimetidine interaction with amitriptyline. *Eur J Clin Pharmacol* 1985; **29:** 429–33.
7. Abernethy DR, Todd EL. Doxepin-cimetidine interaction: increased doxepin bioavailability during cimetidine treatment. *J Clin Psychopharmacol* 1986; **6:** 8–12.
8. Sutherland DL, *et al.* The influence of cimetidine versus ranitidine on doxepin pharmacokinetics. *Eur J Clin Pharmacol* 1987; **32:** 159–64.
9. Wells BG, *et al.* The effect of ranitidine and cimetidine on imipramine disposition. *Eur J Clin Pharmacol* 1986; **31:** 285–90.
10. Curry SH, *et al.* Lack of interaction of ranitidine with amitriptyline. *Eur J Clin Pharmacol* 1987; **32:** 317–20.

Muscle relaxants. There has been an isolated report[1] of a patient taking *baclofen* for spasticity who experienced leg weakness and was unable to stand after starting treatment with nortriptyline. Symptoms improved on stopping nortriptyline but recurred when imipramine was given.

1. Silverglat MJ. Baclofen and tricyclic antidepressants: possible interaction. *JAMA* 1981; **246:** 1659.

Sex hormones. There have been anecdotal reports of interactions between tricyclic antidepressants and *oestrogens*[1-3] resulting in a lack of antidepressant response and/or tricyclic toxicity; the significance of these interactions is not, however, established.

1. Prange AJ, *et al.* Estrogen may well affect response to antidepressant. *JAMA* 1972; **219:** 143–4.
2. Khurana RC. Estrogen-imipramine interaction. *JAMA* 1972; **222:** 702–3.
3. Somani SM, Khurana RC. Mechanism of estrogen-imipramine interaction. *JAMA* 1973; **223:** 560.

Smoking. Tobacco smoke has been reported to reduce the plasma levels of tricyclic antidepressants.[1-3] The clinical significance is not, however, fully established as the plasma concentration of unbound drug may not be affected.[3] The mechanism is probably by stimulation of hepatic drug metabolism by components present in cigarette smoke.

1. Perel JM, *et al.* Pharmacodynamics of imipramine in depressed patients. *Psychopharmacol Bull* 1975; **11:** 16–18.
2. John VA, *et al.* Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* 1980; **8** (suppl 3): 88–95.
3. Perry PJ, *et al.* Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* 1986; **8:** 279–84.

Sympathomimetics. The pressor effects of sympathomimetics can be enhanced by tricyclic antidepressants.

For precautions to be observed in patients on tricyclic therapy who may require sympathomimetics during anaesthesia, see under Anaesthesia in Precautions, above.

Thyroid hormones. An increase in receptor sensitivity to catecholamines produced by thyroid hormones has been proposed as the reason for an increase in response to tricyclic antidepressants given with *liothyronine*.[1,2]

1. Banki CM. Cerebrospinal fluid amine metabolites after combined amitriptyline-triiodothyronine treatment of depressed women. *Eur J Clin Pharmacol* 1977; **11:** 311–15.
2. Goodwin FK, *et al.* Potentiation of antidepressant effects by -triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 1982; **139:** 34–8.

Pharmacokinetics

Amitriptyline is readily absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 6 hours after oral doses.

Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and *N*-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

Amitriptyline and nortriptyline cross the placenta and are distributed into breast milk (see Breast Feeding under Precautions, above).

◊ References.

1. Schulz P, *et al.* Discrepancies between pharmacokinetic studies of amitriptyline. *Clin Pharmacokinet* 1985; **10:** 257–68.
2. Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 1989; **36:** 537–47.
3. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.
4. Wood AJJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991; **20**: 350–73.
5. Llerena A, *et al.* Debrisoquin and mephenytoin hydroxylation phenotypes and CYP2D6 genotype in patients treated with neuroleptic and antidepressant agents. *Clin Pharmacol Ther* 1993; **54:** 606–11.
6. Ghahramani P, *et al.* Cytochromes P450 mediating the N-demethylation of amitriptyline. *Br J Clin Pharmacol* 1997; **43:** 137–44.

Uses and Administration

Tricyclic antidepressants such as amitriptyline were developed from phenothiazine compounds related to chlorpromazine and, as the name suggests, possess a 3-ring molecular structure. They inhibit the neuronal reuptake of noradrenaline in the CNS; some, in addition, inhibit the reuptake of serotonin (5-HT). Prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants also possess affinity for muscarinic and histamine H_1 receptors to varying degrees, see under Adverse Effects, above. Amitriptyline is one of the more sedating tricyclics. Antidepressants with one, two, or four rings have also been developed, and these share only some of the properties of the tricyclics.

While the sedative action and other adverse effects of amitriptyline and other tricyclics are soon apparent, it may be several weeks before any antidepressant effect is seen. After a response has been obtained, maintenance therapy should be continued at the optimum dose for at least 4 to 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 5 years and possibly indefinitely. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects.

Amitriptyline, a dibenzocycloheptadiene, is usually given orally as the hydrochloride and doses are expressed in terms of this salt. Amitriptyline hydrochloride is also given by intramuscular or slow intravenous injection; doses may be expressed in terms of the base or the hydrochloride. Amitriptyline hydrochloride 75 mg is equivalent to about 66.3 mg of the base. Amitriptyline has also been given orally as the embonate and as the oxide (amitriptylinoxide).

In the treatment of **depression**, amitriptyline hydrochloride is given initially in a daily dose of 50 to 75 mg orally in divided doses (or as a single dose at night). Thereafter, the dose may be gradually increased, if necessary, to 150 mg daily, the additional doses being given in the late afternoon or evening. Doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

Adolescent and elderly patients often have reduced tolerance to tricyclic antidepressants and UK licensed drug information states that initial doses of amitriptyline hydrochloride as low as 25 mg daily may be used in these groups, given either in divided doses or as a single dose, preferably at bedtime. The *BNF* suggests a minimum initial dose of 30 mg daily. In the UK, the use of amitriptyline in children under 16 years for the treatment of depression is not recommended.

In the initial stages of treatment, if dosage by mouth is impracticable or inadvisable, amitriptyline hydrochloride may be given by intramuscular injection, but the oral route should be substituted as soon as possible. Doses are similar to those usually given orally. The intravenous route has also been used.

Amitriptyline is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for when other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Oral doses of amitriptyline hydrochloride that may be used are:

- 10 to 20 mg for children aged 6 to 10 years
- 25 to 50 mg for children 11 years and over

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Tricyclic antidepressants, including amitriptyline, may be helpful in some **anxiety disorders** such as panic disorder, and in the management of **neuropathic pain** (see below).

Amitriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. For the use of tricyclic antidepressants in anxiety disorders, see under Clomipramine, p.387.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Antidepressants can help to reduce the frequency of overeating and some other symptoms of bulimia but relapse tends to occur when stopped. Many antidepressants have been tried, but the tricyclic desipramine and the SSRI fluoxetine have been the most commonly used and are considered to be well tolerated.

References.

1. Bacaltchuk J, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/11/05).
2. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/11/05).

Ciguatera poisoning. Amitriptyline has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p.1331).

Cocaine dependence. For the use of tricyclic antidepressants in cocaine dependence, see under Desipramine, p.387.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Although less well tolerated than the newer antidepressants, tricyclic antidepressants may still be chosen because of wide experience with their use and familiarity with their pharmacological actions. The more sedating tricyclics such as amitriptyline, clomipramine, dosulepin, doxepin, and trimipramine may be of value in depression with associated agitation or anxiety. The less sedating tricyclics such as amoxapine, desipramine, imipramine, lofepramine, nortriptyline, and protriptyline may be of value for withdrawn or apathetic depressed patients.

Combination therapy with differing classes of antidepressants, including the tricyclics, has been used in the treatment of refractory or drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision; it is considered unsuitable or controversial by some. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

References.

1. Deisenhammer EA, *et al.* Intravenous versus oral administration of amitriptyline in patients with major depression. *J Clin Psychopharmacol* 2000; **20:** 417–22.
2. Guaiana G, *et al.* Amitriptyline for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache and, although they are especially useful when the headache is accompanied by depression, their beneficial effects appear to be independent of their antidepressant action. They are used for the prophylaxis of migraine (p.616) when drugs such as propranolol have proved ineffective. Amitriptyline is the tricyclic usually used but others have been tried. It has also been investigated in children. The *BNF* suggests an adult dosage for amitriptyline in the prophylaxis of migraine of 10 mg at night, increased to a maintenance dose of 50 to 75 mg at night; the need for continuing prophylaxis should be reviewed at intervals of about 6 months. Tricyclics are also used prophylactically in the control of chronic tension-type headache (p.617) although benefit is rarely complete. Improvement is generally seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression.

References.

1. Mathew NT. Prophylaxis of migraine and mixed headache: a randomized controlled study. *Headache* 1981; **21:** 105–9.
2. Pfaffenrath V, *et al.* Combination headache: practical experience with a combination of a β-blocker and an antidepressive. *Cephalalgia* 1986; **6** (suppl 5): 25–32.
3. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.
4. Ziegler DK, *et al.* Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Arch Neurol* 1993; **50:** 825–30.
5. Pfaffenrath V, *et al.* Efficacy and tolerability of amitriptylinoxide in the treatment of chronic tension-type headache: a multi-centre controlled study. *Cephalalgia* 1994; **14:** 149–55.
6. Hershey AD, *et al.* Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000; **40:** 539–49.
7. Holroyd KA, *et al.* Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001; **285:** 2208–15.

Hiccup. Amitriptyline is one of many drugs for which there are anecdotal reports[1] of success in the treatment of intractable hiccup (p.976).

1. Stalnikowicz R, *et al.* Amitriptyline for intractable hiccups. *N Engl J Med* 1986; **315:** 64–5.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p.2148), initial treatment is usually with a central stimulant. Tricyclic antidepressants such as imipramine or desipramine are reserved for patients who fail to respond to or who are intolerant of stimulants. They may also be of use for selected patients with certain co-existing disorders.

Interstitial cystitis. Tricyclic antidepressants have been found to be of benefit in the treatment of interstitial cystitis (p.2179). In a placebo-controlled trial in 48 patients with interstitial cystitis, amitriptyline treatment (in doses ranging from 25 to 100 mg daily) significantly reduced the symptom score and improved pain and urgency when compared to placebo;[1] however, in some patients the antimuscarinic adverse effects of amitriptyline were troublesome. Amitriptyline or imipramine have also been given at night, together with methenamine hippurate during the day, in the treatment of interstitial cystitis.[2]

1. van Ophoven A, *et al.* A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol (Baltimore)* 2004; **172:** 533–6.
2. Cardozo L. Postmenopausal cystitis. *BMJ* 1996; **313:** 129.

Irritable bowel syndrome. A tricyclic antidepressant may be tried in irritable bowel syndrome (p.1699), particularly where diarrhoea and abdominal pain are presenting symptoms.

Micturition disorders. Tricyclic antidepressants are among the drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of **nocturnal enuresis** in children (p.2180) in whom organic pathology has been excluded. However, because of their potentially fatal toxicity in overdosage, there has been concern over the safety of using tricyclics in households with children. Most experience in nocturnal enuresis has been with imipramine, but other tricyclics such as amitriptyline, nortriptyline, and clomipramine have also been used. Their mechanism of action in nocturnal enuresis is unclear. It may be the result of their antimuscarinic and antispasmodic actions as well as their effect on sleep patterns and possible stimulation of antidiuretic hormone secretion. Imipramine appears to be most effective in older children, but many patients develop tolerance and increasingly higher doses are required.

Tricyclic antidepressants are also sometimes used in the management of **urinary incontinence** (p.2180).

References.

1. Glazener CMA, *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 24/11/05).

Narcoleptic syndrome. Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis associated with narcolepsy (p.2148). Imipramine has been widely used for these symptoms although some consider clomipramine more effective. The onset of action is quicker than when used for depression and doses required appear to be lower (typically 10 to 75 mg of imipramine daily) although tolerance may develop. Doses should be titrated to provide maximal protection for the time of day when symptoms usually occur.

Pain. Tricyclic antidepressants, usually amitriptyline, are useful in alleviating some types of pain when given in subantidepressant doses. An initial oral dose of amitriptyline hydrochloride 10 to 25 mg at night increased gradually if necessary to about 75 mg daily has been suggested by the *BNF* for the management of neuropathic pain in adults. Similar doses of amitriptyline hydrochloride are also suggested by the *BNFC* for the treatment of neuropathic pain in palliative care in children aged 12 years and over; in addition, younger children aged 2 years and above may receive an initial dose of 200 to 500 micrograms/kg (to a maximum of 25 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily. See also Choice of Analgesic on p.2. Chronic neuropathic pain as seen in cancer (p.5), central post-stroke pain (p.6), diabetic neuropathy (p.6), phantom limb pain (p.9), and postherpetic neuralgia (p.9) responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic orofacial pain (p.8), and may be of value for patients with complex regional pain syndrome (p.6). Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia (see Soft-tissue Rheumatism, p.13), a condition that responds poorly to analgesics and anti-inflammatory drugs. Patients with migraine or chronic tension-type headache may also benefit from tricyclics (see Headache, above). There is little evidence for an analgesic effect of tricyclics in acute or arthritic pain.

References.

1. Onghena P, Van Houdenhove, B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; **49:** 205–19.
2. McQuay HJ, *et al.* A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68:** 217–27.
3. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
4. McQuay HJ, Moore RA. Antidepressants and chronic pain. *BMJ* 1997; **314:** 763–4.
5. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 996–1000.
6. Arnold LM, *et al.* Antidepressant treatment of fibromyalgia: a meta-analysis and review. *Psychosomatics* 2000; **41:** 104–13.
7. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci* 2001; **26:** 30–6.
8. Reisner L. Antidepressants for chronic neuropathic pain. *Curr Pain Headache Rep* 2003; **7:** 24–33.

Pathological crying or laughing. Pathological crying or laughing can result from lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressants and favourable results have been reported in double-blind studies with amitriptyline[1] and nortriptyline.[2]

1. Schiffer RB, *et al.* Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; **312:** 1480–2.
2. Robinson RG, *et al.* Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993; **150:** 286–93.

Premenstrual syndrome. For reference to the tricyclic antidepressant, clomipramine, in premenstrual syndrome, see p.387.

Schizophrenia. Antidepressants such as the tricyclics are considered worth trying as an adjunct in the treatment of patients with schizophrenia (p.955) who develop depression during the recovery phase after an acute episode of psychosis. There is, however, no clear evidence that they are effective during acute psychotic episodes or for depression during periods of remission in patients with chronic schizophrenia.[1]

1. Anonymous. The drug treatment of patients with schizophrenia. *Drug Ther Bull* 1995; **33:** 81–6.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of tricyclic antidepressants (see Effects on Sexual Function in Adverse Effects, above). Such properties have been studied as a potential form of treatment for men with premature ejaculation (see Clomipramine, p.387).

Skin disorders. See under Doxepin, p.389, for use of tricyclic antidepressants in skin disorders.

Smoking cessation. Tricyclic antidepressants are among the drugs that have been tried with varying degrees of success as alternatives to nicotine replacement therapy (NRT) to alleviate the withdrawal syndrome associated with smoking cessation (p.2354). Nortriptyline is recommended by some as a second-line treatment in those patients who cannot tolerate or relapse after NRT.

References.

1. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Preparations

BP 2008: Amitriptyline Tablets;
USP 31: Amitriptyline Hydrochloride Injection; Amitriptyline Hydrochloride Tablets; Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Perphenazine and Amitriptyline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Tryptanol; Uxen; ***Austral.:*** Endep; Tryptanol; ***Austria:*** Saroten; Tryptizol; ***Belg.:*** Redomex; Tryptizol; ***Braz.:*** Amytril; Neurotrypt; Protanol; Tripsol; Tryptanol; ***Canad.:*** Elavil†; Novo-Triptyn; ***Denm.:*** Saroten; Tryptizol†; ***Fin.:*** Saroten†; Triptyl; ***Fr.:*** Elavil; Laroxyl; ***Ger.:*** Amineurin; Amioxid; Equilibrin; Novoprotect; Saroten; Syneudon; ***Gr.:*** Maxivalet; Saroten; Stelminal; ***Hong Kong:*** Qualitriptine; Tryptanol†; ***Hung.:*** Teperin; ***India:*** Sarotena; Tryptomer; ***Irl.:*** Lentizol†; ***Israel:*** Elatrol; Elatrolet; Tryptal; ***Ital.:*** Adepril; Laroxyl; Triptizol; ***Malaysia:*** Endep†; Tripta; Tryptanol; ***Mex.:*** Anapsique; Tryptanol; ***Neth.:*** Sarotex; Tryptizol; ***Norw.:*** Sarotex; Tryptizol†; ***NZ:*** Amitrip; ***Port.:*** ADT; Tryptizol; ***Rus.:*** Amyzol (Амизол); Eliwel (Эливел); Saroten (Саротен); ***S.Afr.:*** Noriline; Saroten; Trepiline; Tryptanol; ***Singapore:*** Tripta; ***Spain:*** Deprelio; Tryptizol; ***Swed.:*** Saroten; Tryptizol; ***Switz.:*** Saroten; Tryptizol; ***Thai.:*** Polytanol; Tripsyline†; Tripta; Triptyline; Tryptanol; ***Turk.:*** Laroxyl; Triptilin; ***UK:*** Elavil; ***USA:*** Elavil†; ***Venez.:*** Tryptanol.

Multi-ingredient: ***Arg.:*** Mutabon D†; ***Austria:*** Limbitrol; ***Braz.:*** Limbitrol; ***Canad.:*** PMS-Levazine; Triavil†; ***Chile:*** Antalin; Limbatrilin; Morelin; Mutabon D†; Tiperin; ***Fin.:*** Klotriptyl; Limbitrol; Pertriptyl; ***Gr.:*** Minitran; ***India:*** Emotrip; ***Indon.:*** Limbritol; Mutabon-D; Mutabon-M; ***Ital.:*** Diapatol; Limbitryl; Mutabon; Sedans; ***Mex.:*** Adepsique; ***Port.:*** Mutabon; ***Rus.:*** Amixide (Амиксид); ***S.Afr.:*** Etrafon†; Limbitrol; ***Spain:*** Mutabase; Nobritol; ***Switz.:*** Limbitrol; ***Thai.:*** Anxipress-D†; Neuragon; Polybon; ***UK:*** Triptafen; ***USA:*** Etrafon; Limbitrol; Triavil†.

Amoxapine *(BAN, USAN, rINN)*

Amoksapiini; Amoksapin; Amoxapin; Amoxapina; Amoxapinum; CL-67772. 2-Chloro-11-(piperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.

Амоксапин

$C_{17}H_{16}ClN_3O$ = 313.8.
CAS — 14028-44-5.
ATC — N06AA17.
ATC Vet — QN06AA17.

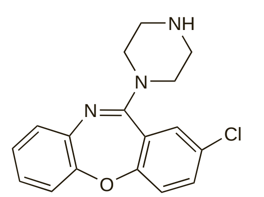

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Amoxapine). A white to yellowish crystalline powder. Practically insoluble in water; slightly soluble in acetone; freely soluble in chloroform; sparingly soluble in methyl alcohol and in toluene; soluble in tetrahydrofuran. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Rare cases of tardive dyskinesias and the neuroleptic malignant syndrome have been reported with amoxapine.

Antidopaminergic effects. Amoxapine is a derivative of the antipsychotic loxapine (p.1005) and possesses some antipsychotic activity. It also has dopamine-receptor blocking properties as do its hydroxylated metabolites. Adverse effects that are symptoms of such blockade have been reported and reviewed[1,2] and include akinesia, akathisia, withdrawal dyskinesia, reversible tardive dyskinesia, persistent dyskinesia, elevated serum concentration of prolactin, and galactorrhoea. Chorea[3] and oculogyric crisis[4] have also been reported.

1. Tao GK, *et al.* Amoxapine-induced tardive dyskinesia. *Drug Intell Clin Pharm* 1985; **19:** 548–9.
2. Devarajan S. Safety of amoxapine. *Lancet* 1989; **ii:** 1455.
3. Patterson JF. Amoxapine-induced chorea. *South Med J* 1983; **76:** 1077.
4. Hunt-Fugate AK, *et al.* Adverse reactions due to dopamine blockade by amoxapine. *Pharmacotherapy* 1984; **4:** 35–9.

Antimuscarinic effects. Amoxapine therapy has been reported to produce adverse effects associated with antimuscarinic activity (such as constipation, blurred vision, and dry mouth), but such reports did not reflect *in-vitro* findings that amoxapine had considerably less affinity for muscarinic binding sites than amitriptyline;[1] this was supported by results in healthy subjects. The adverse effects described as antimuscarinic could possibly be explained by amoxapine affecting noradrenergic mechanisms.

1. Bourne M, *et al.* A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 57–62.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the endocrine system. Reversible nonketotic hyperglycaemia developed in a 49-year-old woman with no history of diabetes mellitus within 5 days of oral therapy with amoxapine 50 mg three times daily.[1] She had previously had nonketotic hyperglycaemic coma after loxapine 150 mg daily. 7-Hydroxyamoxapine, a metabolite common to both amoxapine and loxapine, was implicated.

See also Antidopaminergic Effects, above, for mention of galactorrhoea and hyperprolactinaemia.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Overdosage. In overdosage, amoxapine is reported to cause acute renal failure with rhabdomyolysis,[1,2] coma, and seizures.[3-5] Although there has been some debate as to whether the incidence of seizures and death is higher with overdosage of amoxapine than with other tricyclic antidepressants, some[6] consider that evidence does seem to favour increased neurological consequences.

It has been reported that amoxapine is not cardiotoxic in overdosage[3] but later evidence would suggest that there is cardiotoxic potential.[6,7]

1. Pumariega AJ, *et al.* Acute renal failure secondary to amoxapine overdose. *JAMA* 1982; **248:** 3141–2.
2. Jennings AE, *et al.* Amoxapine-associated acute renal failure. *Arch Intern Med* 1983; **143:** 1525–7.
3. Kulig K, *et al.* Amoxapine overdose: coma and seizures without cardiotoxic effects. *JAMA* 1982; **248:** 1092–4.
4. Litovitz TL, Troutman WG. Amoxapine overdose: seizures and fatalities. *JAMA* 1983; **250:** 1069–71.
5. Jefferson JW. Convulsions associated with amoxapine. *JAMA* 1984; **251:** 603–4.
6. Leonard BE. Safety of amoxapine. *Lancet* 1989; **ii:** 808.
7. Sørensen MR. Acute myocardial failure following amoxapine intoxication. *J Clin Psychopharmacol* 1988; **8:** 75.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Amoxapine is readily absorbed from the gastrointestinal tract. It bears a close chemical relationship to loxapine (p.1005) and is similarly metabolised by hydroxylation. It is excreted in the urine, mainly as its metabolites in conjugated form as glucuronides.

Amoxapine has been reported to have a plasma half-life of 8 hours and its major metabolite, 8-hydroxyamoxapine, has been reported to have a biological half-life of 30 hours; 7-hydroxyamoxapine has been identified as another metabolite. Both metabolites are pharmacologically active. Amoxapine is about 90% bound to plasma proteins.

Amoxapine and its metabolite 8-hydroxyamoxapine are distributed into breast milk.

Uses and Administration

Amoxapine, the *N*-desmethyl derivative of loxapine (p.1005), is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). Amoxapine is one of the less sedating tricyclics and its antimuscarinic effects are mild; it also inhibits the reuptake of dopamine.

In the treatment of depression (p.373) amoxapine is given in oral doses of 50 mg two or three times daily initially, gradually increased up to 100 mg three times daily as necessary. In the USA, higher doses of up to 600 mg daily may also be given, if required, in severely depressed patients in hospital. A suggested dose for the elderly is 25 mg two or three times daily initially, increased after 5 to 7 days to up to 150 mg daily as necessary; in the USA further increases to a maximum of 300 mg daily are permitted, if required.

Once-daily dosage regimens, usually given at night, are suitable for amoxapine up to 300 mg daily; divided-dosage regimens are recommended for doses above 300 mg daily.

It has been claimed that, in the treatment of depression, amoxapine has a more rapid onset of action than amitriptyline or imipramine with a clinical effect possibly appearing 4 to 7 days after starting therapy, although this has been disputed.

Amoxapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Amoxapine has also been investigated for its potential as an antipsychotic.

◊ References.

1. Jue SG, *et al.* Amoxapine: a review of its pharmacology and efficacy in depressed states. *Drugs* 1982; **24:** 1–23.

2. Sa DS, *et al.* Amoxapine shows an antipsychotic effect but worsens motor function in patients with Parkinson's disease and psychosis. *Clin Neuropharmacol* 2001; **24:** 242–4.
3. Apiquian R, *et al.* Amoxapine shows atypical antipsychotic effects in patients with schizophrenia: results from a prospective open-label study. *Schizophr Res* 2003; **59:** 35–9.
4. Fitzgerald PB, *et al.* Amoxapine in schizophrenia: a negative double-blind controlled trial. *J Clin Psychopharmacol* 2004; **24:** 448–50.
5. Apiquian R, *et al.* Amoxapine as an atypical antipsychotic: a comparative study vs risperidone. *Neuropsychopharmacology* 2005; **30:** 2236–44.

Preparations

USP 31: Amoxapine Tablets.

Proprietary Preparations (details are given in Part 3)
Denm.: Demolox†; ***Fr.:*** Defanyl; ***India:*** Demolox; ***Indon.:*** Asendin; ***UK:*** Asendis†; ***USA:*** Asendin†.

Benactyzine Hydrochloride *(BANM, rINNM)*

Amizylum; Bénactyzine, Chlorhydrate de; Benactyzini Hydrochloridum; Hidrocloruro de benacticina. 2-Diethylaminoethyl benzilate hydrochloride.

Бенактизина Гидрохлорид

$C_{20}H_{25}NO_3$,HCl = 363.9.

CAS — 302-40-9 (benactyzine); 57-37-4 (benactyzine hydrochloride).

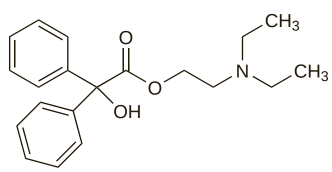

(benactyzine)

Profile

Benactyzine has antidepressant and antimuscarinic activity. It has been used as the hydrochloride in the management of depression and associated anxiety. It is also used as a pharmacological tool. Methylbenactyzium bromide (p.1747), the methobromide of benactyzine, has been used for its antimuscarinic activity in the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Dimaval.

Brofaromine *(rINN)*

Brofaromina; Brofarominum; CGP-11305A (brofaromine hydrochloride). 4-(7-Bromo-5-methoxy-2-benzofuranyl)piperidine.

Брофаромин

$C_{14}H_{16}BrNO_2$ = 310.2.

CAS — 63638-91-5.

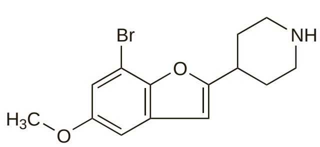

Profile

Brofaromine is a reversible inhibitor of monoamine oxidase type A (RIMA) (see Moclobemide, p.411). It has been studied in the treatment of depression and in anxiety disorders including social anxiety disorder.

Bupropion Hydrochloride

(BANM, USAN, rINNM)

Amfebutamone Hydrochloride; Bupropione, Chlorhydrate de; Bupropionhydroklorid; Bupropioni Hydrochloridum; Bupropionihydrokloridi; BW-323; Hidrocloruro de bupropión. (±)-2-(*tert*-Butylamino)-3′-chloropropiophenone hydrochloride.

Бупропиона Гидрохлорид

$C_{13}H_{18}ClNO$,HCl = 276.2.

CAS — 34911-55-2 (bupropion); 31677-93-7 (bupropion hydrochloride).

ATC — N07BA02.

ATC Vet — QN07BA02.

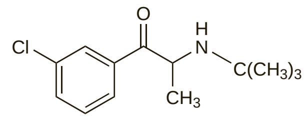

(bupropion)

Pharmacopoeias. In *US.*

USP 31 (Bupropion Hydrochloride). A white powder. Soluble in water, in alcohol, and in 0.1N hydrochloric acid. Protect from light.

Adverse Effects and Treatment

Agitation, anxiety, and insomnia often occur during the initial stages of bupropion therapy. Other relatively common adverse effects reported with bupropion include fever, dry mouth, headache or migraine, dizziness, urinary frequency, nausea and vomiting, constipation, tremor, sweating, and skin rashes. Hypersensitivity reactions, ranging from pruritus and urticaria to, less commonly, angioedema, dyspnoea, and anaphylactoid reactions, have occurred, as have symptoms suggestive of serum sickness. There have been rare reports of Stevens-Johnson syndrome and erythema multiforme. Tachycardia, chest pain, and hypertension (sometimes severe), or occasionally vasodilatation, orthostatic hypotension, palpitations, and syncope have been reported. Psychotic episodes, confusion, nightmares, impaired memory, dysgeusia, anorexia with weight loss, paraesthesia, tinnitus, and visual disturbances have also been reported.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Seizures, which appear to be partially dose-related, may occur with bupropion and have been particularly notable in patients with anorexia nervosa or bulimia nervosa; the risk is also increased in patients with a history of seizure disorders or other predisposing factor. The manufacturers state that the overall incidence of seizure in patients receiving bupropion at recommended doses is about 0.1 to 0.4%.

Symptoms of overdosage include hallucinations, nausea and vomiting, tachycardia, loss of consciousness, and death (following massive overdose); seizures have occurred in about one-third of all bupropion overdose cases. Activated charcoal should be considered in adult patients who have taken more than 450 mg and in all children, if they present within 1 hour of ingestion; gastric lavage may also be used to decrease absorption. Treatment is supportive. Benzodiazepines may be tried for seizures. Diuresis, dialysis, and haemoperfusion are unlikely to be of benefit.

Incidence of adverse effects. Up to 24 July 2002 (the first 25 months of marketing), the UK CSM had received 7630 reports of suspected adverse reactions associated with the use of bupropion.[1] Of these reports, 60 were associated with a fatal outcome although in most cases underlying conditions could have been responsible. Cardiovascular and cerebrovascular disorders such as myocardial infarction and stroke were reported as the cause of death in 70% of cases. The CSM also commented that adverse reactions were mainly recognised ones and listed in the licensed product information.

In January 2005 the German pharmacovigilance network reviewed[2] 273 reports of adverse effects associated with bupropion, received between June 2000 and September 2004. The most frequent adverse effects were: psychiatric disorders (79.3%), including suicide attempts (17.6%), and tachycardia (11.15%), seizures (8.8%), and dyspnoea (8.8%). There were also 4 cases of pancreatitis and one of raised pancreatic enzyme activity three times greater than normal.

1. CSM/MCA. Zyban (bupropion hydrochloride) - safety update (issued 26th July 2002). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019524&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
2. Drug Commission of the German Medical Association. Increased pancreatic enzymes or acute pancreatitis induced by bupropion (Zyban)(from the UAW database). Available at: http://www.akdae.de/en/20/20/Archiv/2005/800_20050110.html (accessed 04/06/06)

Effects on the cardiovascular system. Up to the end of December 2001 the national pharmacovigilance centre in the Netherlands had received 591 adverse reaction reports associated with the use of bupropion for smoking cessation since its marketing 2 years earlier;[1] of these, 45 concerned cardiac complaints such as palpitations (21), arrhythmias (7), myocardial infarction (3), anginal pain (2), and cardiac arrest (1). Twenty-two reports also mentioned chest pain or tightness, although these were considered to be of noncardiac origin. In another report a 43-year-old male suffered an acute myocardial infarction 2 weeks after starting bupropion for smoking cessation;[2] he had experienced central chest and arm pain 3 days before the infarction. The authors of the report said that up to 30 April 2001 the UK CSM had received 238 reports of chest pain and 134 reports of chest tightness associated with bupropion use.

1. de Graaf L, Diemont WL. Chest pain during use of bupropion as an aid in smoking cessation. *Br J Clin Pharmacol* 2003; **56:** 451–2.
2. Patterson RN, Herity NA. Acute myocardial infarction following bupropion (Zyban). *QJM* 2002; **95:** 58–9.

Effects on the cerebrovascular system. A 67-year-old male had paraesthesia, dizziness, tinnitus, confusion, and gait impairment after taking bupropion for smoking cessation.[1] Although a transient ischaemic attack was suspected symptoms resolved on stopping bupropion and recurred on rechallenge.

1. Humma LM, Swims MP. Bupropion mimics a transient ischemic attack. *Ann Pharmacother* 1999; **33:** 305–7.

Effects on the pancreas. See under Incidence of Adverse Effects, above.

Effects on the skin. *Erythema multiforme* developed in a 31-year-old woman several weeks after starting modified-release bupropion for depression.[1] Symptoms resolved on drug withdrawal. In another report, 3 patients with controlled *psoriasis* had an exacerbation of their psoriatic symptoms after starting bupropion for smoking cessation.[2] All 3 patients required hospitalisation to control their symptoms. There have also been several reports of patients developing *generalised acute urticaria*;[3,4] systemic symptoms resembling serum sickness were also reported in 1 case[4] (see also Hypersensitivity, below).

1. Lineberry TW, *et al.* Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; **76:** 664–6.
2. Cox NH, *et al.* Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146:** 1061–3.
3. Fays S, *et al.* Bupropion and generalized acute urticaria: eight cases. *Br J Dermatol* 2003; **148:** 177–8.
4. Loo WJ, *et al.* Bupropion and generalized acute urticaria: a further case. *Br J Dermatol* 2003; **149:** 660.

Extrapyramidal effects. A 44-year-old man had acute head and neck dystonia while taking buspirone and modified-release bupropion.[1] No recurrence was noted on rechallenge with buspirone although symptoms did develop on rechallenge with bupropion when the dose was increased from 150 mg once daily to 150 mg twice daily. In another case, a 42-year-old woman had gross involuntary movements of her torso, arms, and legs (diagnosed as ballism) 8 days after starting bupropion for smoking cessation;[2] the dose had been increased from 150 mg once daily to 150 mg twice daily on the fourth day. She recovered when bupropion was stopped and treatment with haloperidol and oxazepam was given.

1. Detweiler MB, Harpold GJ. Bupropion-induced acute dystonia. *Ann Pharmacother* 2002; **36:** 251–4.
2. de Graaf L, *et al.* Ballism associated with bupropion use. *Ann Pharmacother* 2003; **37:** 302–3.

Hypersensitivity. Eosinophilia has been reported[1] in a patient 12 days after bupropion was added to her existing treatment regimen of glibenclamide and tolmetin. The eosinophil count returned to normal after all medication was stopped. Bupropion appeared to be the causative drug.

Serum sickness or symptoms suggestive of serum sickness has also been associated with bupropion use.[2-5] In one case,[5] although the initial presentation resembled serum sickness, the patient went on to develop multisystem complications that included hepatitis, cholestasis, and myocarditis.

See also Effects on the Skin, above.

1. Malesker MA, *et al.* Eosinophilia associated with bupropion. *Ann Pharmacother* 1995; **29:** 867–8.
2. Yolles JC, *et al.* Serum sickness induced by bupropion. *Ann Pharmacother* 1999; **33:** 931–3.
3. McCollom RA, *et al.* Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; **34:** 471–3.
4. Benson E. Bupropion-induced hypersensitivity reactions. *Med J Aust* 2001; **174:** 650–1.
5. Bagshaw SM, *et al.* Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann Allergy Asthma Immunol* 2003; **90:** 572–5.

Overdosage. Unlike the tricyclic antidepressants, bupropion appears to lack any significant cardiovascular or antimuscarinic adverse effects when taken in overdose. In an early review[1] of 58 overdose cases involving immediate-release bupropion alone, the most common symptoms were sinus tachycardia, lethargy, tremor, and seizures; other effects included confusion, lightheadedness, hallucinations, paraesthesias, and vomiting. Most patients had minor effects or none at all. Similar symptoms have also been noted in reviews of overdose cases involving modified-release bupropion.[2,3] UK licensed prescribing information for bupropion also lists ECG changes such as conduction disturbances, arrhythmias, and tachycardia although a literature review[4] concluded that cardiotoxicity appeared to be rare with bupropion overdosage. Although rare, there have been fatalities after overdose; in some cases other drugs may have been involved.[3,5,6]

More recent case reports and reviews with modified-release preparations have highlighted that seizures are a particular feature of bupropion overdose.[2,3,7,8]

1. Spiller HA, *et al.* Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994; **12:** 43–5.
2. Balit CR, *et al.* Bupropion poisoning: a case series. *Med J Aust* 2003; **178:** 61–3.
3. Shepherd G, *et al.* Intentional bupropion overdoses. *J Emerg Med* 2004; **27:** 147–51.
4. Druteika D, Zed PJ. Cardiotoxicity following bupropion overdose. *Ann Pharmacother* 2002; **36:** 1791–5.
5. Friel PN, *et al.* Three fatal drug overdoses involving bupropion. *J Anal Toxicol* 1993; **17:** 436–8.
6. Harris CR, *et al.* Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; **35:** 321–4.
7. Bhattacharjee C, *et al.* Bupropion overdose: a potential problem with the new 'miracle' anti-smoking drug. *Int J Clin Pract* 2001; **55:** 221–2.
8. Paoloni R, Szekely I. Sustained-release bupropion overdose: a new entity for Australian emergency departments. *Emerg Med (Fremantle)* 2002; **14:** 109–12.

Precautions

Bupropion may induce seizures and consequently its use is contra-indicated in patients with epilepsy. It is also contra-indicated in patients with a history of anorexia nervosa or bulimia nervosa, as a higher incidence of seizures has been noted in such patients treated with bupropion, and in those undergoing abrupt withdrawal from alcohol or benzodiazepines. It should be used with extreme caution, if at all, in patients with a history of seizure disorders or other predisposing factors such as severe hepatic cirrhosis or a CNS tumour. The use of bupropion in patients with other risk factors for seizures (for example, alcohol abuse, a history of head trauma, diabetes, and drugs known to lower the seizure threshold) should only be undertaken when there are compelling clinical reasons.

Bupropion should be used with caution in patients with bipolar disorder or psychoses because of the risk of precipitating mania; use for smoking cessation in such patients may be contra-indicated. It should also be used cautiously in patients with a recent history of myocardial infarction or unstable heart disease, and in hepatic or renal impairment.

When bupropion is used for depression, patients should be closely monitored during early therapy until significant improvement is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other CNS-active drugs, the ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by bupropion, and patients, if affected, should not drive or operate machinery.

Breast feeding. The American Academy of Pediatrics considers[1] that the effect of bupropion on nursing infants is unknown but may be of concern.

There has been a report of accumulation of bupropion in human breast milk in concentrations higher than those in maternal plasma.[2] However, neither bupropion nor its metabolites were detected in the plasma of the infant who was breast fed twice daily by the affected mother, and no adverse effects were noted in the infant. Similar findings have been noted in a more recent study in 2 breast-fed infants whose mothers took bupropion for postpartum depression.[3] However, in another report, a 6-month-old infant had a seizure after being fed breast milk that had been expressed and stored 2 days earlier, after the infant's mother had taken a single dose of bupropion.[4] Before the seizure, the mother had taken 2 doses of bupropion and breast fed the infant several times with no adverse effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Briggs GC, *et al.* Excretion of bupropion in breast milk. *Ann Pharmacother* 1993; **27:** 431–3.
3. Baab SW, *et al.* Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002; **63:** 910–11.
4. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry* 2004; **65:** 881–2.

Children. Bupropion has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age, regardless of indication, is not recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p.392).

Pregnancy. The safety of bupropion in pregnancy has not been established. In a study of 136 women who took bupropion for either depression or smoking cessation in at least the first trimester of pregnancy, there were 105 live births, 20 spontaneous abortions, 10 therapeutic abortions, 1 still-birth, and 1 neonatal death; no major congenital malformations were reported.[1] Compared to a control group not exposed to teratogens, the rate of spontaneous abortions was significantly higher in the bupropion group when both indications were considered; however, there was no difference in the rate when women taking bupropion for depression were compared to this control group and another control group of women taking other antidepressants.

Complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding have been reported with some of the newer antidepressants such as bupropion.[2] Other reported symptoms have included seizures, muscle rigidity, jitteriness, and prolonged crying. It is not known whether such symptoms represent a direct toxicity of bupropion or a possible withdrawal syndrome.

1. Chun-Fai-Chan B, *et al.* Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005; **192:** 932–6.
2. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Bupropion should not be given with or within 14 days of stopping an MAOI; however, no treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting bupropion.

The use of alcohol with bupropion should be minimised or avoided completely because it may alter the seizure threshold. Similarly, extreme caution is needed if other drugs that lower the seizure threshold, such as other antidepressants, antimalarials, antipsychotics, sedating antihistamines, quinolones, tramadol, theophylline, or systemic corticosteroids are used with bupropion. In the UK, where it is licensed as a modified-release product for smoking cessation, a maximum dose of 150 mg daily is recommended if patients are also taking such drugs.

Use of nicotine transdermal patches with bupropion has been associated with hypertension, and patients using both should therefore have their blood pressure monitored.

Caution has been advised in patients receiving either amantadine or levodopa with bupropion because of reports of a higher incidence of adverse effects in patients receiving these combinations.

Animal studies have indicated that bupropion may induce drug-metabolising enzymes and pharmacokinetic interactions with other drugs are therefore a possibility. Bupropion is itself metabolised by hepatic enzyme systems and drugs known to affect such systems may interact with bupropion. For example carbamazepine, phenobarbital, or phenytoin may induce the metabolism of bupropion while other drugs such as cimetidine or valproate may inhibit its metabolism. *In-vitro* studies have shown that bupropion is metabolised by the cytochrome P450 isoenzyme CYP2B6. Consequently interactions may occur between bupropion and drugs that affect this isoenzyme, for example orphenadrine, cyclophosphamide, and ifosfamide.

In-vitro studies have also shown that bupropion is also an inhibitor of the isoenzyme CYP2D6; caution should be exercised when it is given with drugs metabolised by this isoenzyme and they should be started at the lower end of their dose range. Such drugs include some antidepressants, antipsychotics, beta blockers, and type Ic antiarrhythmics.

Antiepileptics. Plasma-bupropion concentrations became undetectable in 2 patients who were also receiving *carbamazepine*; plasma concentrations of hydroxybupropion, an active metabolite of bupropion, were high.[1]

1. Popli AP, *et al.* Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* 1995; **7:** 99–101.

Antivirals. There is some evidence from study *in vitro* that the antivirals *efavirenz, nelfinavir,* and *ritonavir* can inhibit the cytochrome P450 isoenzyme CYP2B6,[1] and licensed product information for ritonavir mentions the possibility of an interaction with bupropion. However, evidence of clinically significant interaction is lacking: a small case series of 10 patients who took bupropion with low-dose ritonavir (100 mg twice daily), or efavirenz or nelfinavir, did not note any episodes of seizures.[2] A study[3] in 7 healthy male subjects also found that 2 days of low-dose ritonavir (200 mg twice daily) had little impact on the pharmacokinetics of a single bupropion dose.

In contrast, the UK licensed product information for bupropion describes a study in healthy subjects in which 20 days of full-dose ritonavir (600 mg twice daily) reduced the area under the concentration-time curve (AUC) and maximum plasma concentration of bupropion, possibly by inducing its metabolism. Plasma concentrations of bupropion's active metabolites were also reduced. In another study[4] in healthy subjects, the plasma concentrations and AUC of bupropion and its active metabolite hydroxybupropion, from a single dose of bupropion, were reduced by about 50% after 14 days of a *lopinavir/ritonavir* combination (400 mg/100 mg twice daily). This effect was attributed to induction of CYP2B6 and UDP-glucuronosyltransferase by the HIV-protease inhibitor combination. In discussing the contrasting results that have been reported, the authors suggested that the higher ritonavir concentrations achieved *in-vitro* had an inhibitory effect, compared with the inducing effect of lower steady-state concentrations achieved *in-vivo*.

1. Hesse LM, *et al.* Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001; **29:** 100–102.
2. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* 2003; **17:** 638–40.
3. Hesse LM, *et al.* Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol* 2006; **46:** 567–76.
4. Hogeland GW, *et al.* Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2007; **81:** 69–75.

Histamine H_2-antagonists. A randomised controlled study in 24 subjects found that *cimetidine* had no effect on the pharmacokinetics of modified-release bupropion or its active metabolite, hydroxybupropion.[1]

1. Kustra R, *et al.* Lack of effect of cimetidine on the pharmacokinetics of sustained-release bupropion. *J Clin Pharmacol* 1999: **39:** 1184–8.

Pharmacokinetics

Bupropion is well absorbed from the gastrointestinal tract but may undergo extensive first-pass metabolism. Several metabolites of bupropion are pharmacologically active and have longer half-lives, and achieve higher plasma concentrations, than the parent compound. Hydroxybupropion is the major metabolite, produced by the metabolism of bupropion by the cytochrome P450 isoenzyme CYP2B6; in *animal* studies hydroxybupropion was one-half as potent as bupropion. Threohydrobupropion and erythrohydrobupropion are produced by reduction and are about one-fifth the potency of the parent compound. Bupropion is 80% or more bound to plasma proteins. The terminal plasma half-life of immediate-release bupropion is about 14 hours; the terminal plasma half-life of modified-release bupropion is about 20 hours. The metabolites of bupropion are excreted primarily in the urine; less than 1% of the parent drug is excreted unchanged. Bupropion and its metabolites cross the placenta and are distributed into breast milk.

◊ References.

1. Sweet RA, *et al.* Pharmacokinetics of single- and multiple-dose bupropion in elderly patients with depression. *J Clin Pharmacol* 1995; **35:** 876–84.

Smoking. No clinically significant differences were seen between the pharmacokinetics of bupropion or its metabolites in cigarette smokers and non-smokers.[1]

1. Hsyu P-H, *et al.* Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 1997; **37:** 737–43.

Uses and Administration

Bupropion is a chlorpropiophenone antidepressant chemically unrelated to other classes of antidepressants but similar in structure to the central stimulant diethylpropion (p.2154). It is a weak blocker of neuronal reuptake of serotonin and noradrenaline compared with tricyclic antidepressants; it also inhibits the neuronal reuptake of dopamine. The antidepressant effect may not be evident until after 4 weeks of therapy. Bupropion is also used as an aid to smoking cessation.

Bupropion is given orally as the hydrochloride. To minimise agitation, anxiety, and insomnia often experienced at the start of therapy, and to reduce the risk of seizures, doses should be increased gradually; the total daily dose should be given in equally divided doses and the maximum recommended single and total daily doses should not be exceeded. Insomnia at the start of therapy may be minimised by avoiding bedtime doses. Patients with hepatic or renal impairment should be given reduced doses and monitored for toxic effects (see below).

In the treatment of **depression** bupropion hydrochloride is given in initial doses of 100 mg twice daily increased, if necessary, after at least 3 days to 100 mg three times daily. In severe cases, if no improvement has been observed after several weeks of therapy, the dose may be increased further to a maximum of 150 mg three times daily. Bupropion hydrochloride is also available as a modified-release preparation given in an initial dose of 150 mg once daily in the morning increased, if necessary, after at least 3 days to 150 mg twice daily; in severe cases, the dose of the modified-release preparation may be increased further after several weeks to 200 mg twice daily. A modified-release preparation that is given once daily is also available; the maximum daily dose for this preparation is 450 mg as a single dose in the morning. A modified-release preparation is also licensed for the prevention of depression in patients with seasonal affective disorder; the maximum dose for this disorder is 300 mg once daily.

Bupropion hydrochloride is given as a modified-release preparation as an aid to **smoking cessation** in an initial dose of 150 mg once daily for 6 days, increasing to 150 mg twice daily on day 7. In the USA, the dose may be increased after 3 days. In the UK, the maximum recommended dose in the elderly, or in patients with predisposing risk factors for seizure (see Precautions, above), is 150 mg daily. Treatment should be started about 1 to 2 weeks before the patient attempts to stop smoking, to allow steady-state blood levels of bupropion to be reached, and normally continues for 7 to 12 weeks; if there is no significant progress towards smoking abstinence by the seventh week, then therapy should be stopped. Use with nicotine transdermal patches may be warranted in some patients, although there is a risk of hypertension with such therapy (see Interactions, above).

Administration in hepatic impairment. When used as an aid to *smoking cessation* in patients with mild to moderate hepatic impairment, bupropion should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily. The use of bupropion in patients with severe hepatic cirrhosis is contra-indicated in the UK although doses of 150 mg every other day are permitted in the USA.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered in patients with mild to moderate impairment. In patients with severe hepatic cirrhosis the dose varies according to the preparation given; for modified-release bupropion the suggested maximum oral dose is 100 mg once daily or 150 mg every other day while the maximum dose of immediate-release bupropion is 75 mg once daily.

Administration in renal impairment. When used as an aid to *smoking cessation* in patients with renal impairment, bupropion should be given at a reduced frequency; UK licensed product information suggests an oral dose of 150 mg once daily.

In the treatment of *depression*, a reduction in the frequency and/or the dose of bupropion should be considered.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Bupropion has a different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, it may be safer in overdosage than the older tricyclics.

References.

1. Kavoussi RJ, *et al.* Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997; **58:** 532–7.
2. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; **35:** 1608–13.
3. Weihs KL, *et al.* Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 2002; **51:** 753–61.
4. Glod CA, *et al.* Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs* 2003; **16:** 123–30.
5. Rush AJ, *et al.* The STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; **354:** 1231–42.
6. Papakostas GI, *et al.* Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. *J Clin Psychiatry* 2007; **68:** 1907–12.
7. Dhillon S, *et al.* Bupropion: a review of its use in the management of major depressive disorder. *Drugs* 2008; **68:** 653–89.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants. Data from open and controlled studies involving small numbers of patients suggest that bupropion is effective in adults and children.[1,2]

1. Cantwell DP. ADHD through the life span: the role of bupropion in treatment. *J Clin Psychiatry* 1998; **59** (suppl 4): 92–4.
2. Wilens TE, *et al.* A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 2001; **158:** 282–8.

Smoking cessation. Bupropion is effective in the management of smoking cessation (p.2354) and may be used as a first-line alternative to nicotine replacement therapy (NRT); its action is said to be independent of its antidepressant activity. Bupropion with NRT has also been used successfully although there is an increased risk of hypertension with this combination (see Interactions, above).

References:

1. Hurt RD, *et al.* A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; **337:** 1195–1202.
2. Jorenby DE, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999; **340:** 685–91.
3. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. *Drugs* 2000; **59:** 1007–1024.
4. Tashkin DP, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; **357:** 1571–5.
5. Gonzales DH, *et al.* Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther* 2001; **69:** 438–44.
6. Hays JT, *et al.* Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. *Ann Intern Med* 2001; **135:** 423–33.
7. NICE. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation: Technology Appraisal 39 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/NiceNRT39GUIDANCE.pdf (accessed 14/08/08)
8. Ahluwalia JS, *et al.* Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. *JAMA* 2002; **288:** 468–74.
9. Fagerström K, *et al.* Smoking cessation treatment with sustained-release bupropion: optimising approaches to management. A seminar-in-print. *Drugs* 2002; **62** (suppl 2): 1–70.
10. Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clin Proc* 2003; **78:** 1020–4.
11. Tonnesen P, *et al.* A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; **254:** 184–92.
12. Simon JA, *et al.* Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 2004; **164:** 1797–1803.
13. Hatsukami DK, *et al.* Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. *Am J Med* 2004; **116:** 151–7.
14. Roddy E. ABC of smoking cessation: bupropion and other non-nicotine pharmacotherapies. *BMJ* 2004; **328:** 509–11.
15. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).
16. Paluck EC, *et al.* Outcomes of bupropion therapy for smoking cessation during routine clinical use. *Ann Pharmacother* 2006; **40:** 185–90.

Preparations

USP 31: Bupropion Hydrochloride Extended-Release Tablets; Bupropion Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Odranal; Wellbutrin; ***Austral.:*** Clorpax; Prexaton; Zyban; ***Austria:*** Quomem; Zyban; ***Belg.:*** Zyban; ***Braz.:*** Bup; Wellbutrin; Zetron; Zyban; ***Canad.:*** Wellbutrin; Zyban; ***Chile:*** Buxon; Dosier†; Mondrian†; Wellbutrin; ***Cz.:*** Elontril; Wellbutrin; Zyban; ***Denm.:*** Zyban; ***Fin.:*** Zyban; ***Fr.:*** Zyban; ***Ger.:*** Zyban; ***Gr.:*** Zyban; ***Hong Kong:*** Wellbutrin; Zyban; ***Hung.:*** Wellbutrin; Zyban†; ***India:*** Nicotex; Zyban; ***Irl.:*** Zyban; ***Israel:*** Zyban; ***Ital.:*** Quomem†; Zyban; ***Malaysia:*** Zyban; ***Mex.:*** Butrew; Wellbutrin; ***Neth.:*** Quomem; Zyban; Zyntabac; ***Norw.:*** Zyban; ***NZ:*** Zyban; ***Pol.:*** Zyban; ***Port.:*** Elontril; Wellbutrin; Zyban; Zyntabac; ***S.Afr.:*** Wellbutrin; Zyban; ***Singapore:*** Wellbutrin; Zyban; ***Spain:*** Quomem; Zyntabac; ***Swed.:*** Zyban; ***Switz.:*** Zyban; ***Thai.:*** Quomem; ***Turk.:*** Zyban; ***UK:*** Zyban; ***USA:*** Budeprion; Wellbutrin; Zyban; ***Venez.:*** Wellbutrin; Zyban†.

Citalopram *(BAN, rINN)*

Citalopramum; Lu-10-171; Sitalopraami. 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

Циталопрам

$C_{20}H_{21}FN_2O$ = 324.4.

CAS — 59729-33-8.

ATC — N06AB04.

ATC Vet — QN06AB04.

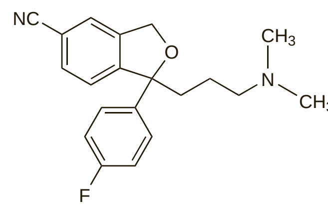

Citalopram Hydrobromide *(BANM, USAN, rINNM)*

Citalopram, bromhydrate de; Citaloprami hydrobromidum; Hidrobromuro de citalopram; Lu-10-171B; Nitalapram Hydrobromide; Sitalopram Hidrobromür.

Циталопрама Гидробромид

$C_{20}H_{21}FN_2O,HBr$ = 405.3.

CAS — 59729-32-7.

Pharmacopoeias. In *US.*

USP 31 (Citalopram Hydrobromide). A white to almost white, crystalline powder. Freely soluble in water, in alcohol, and in chloroform. A 0.5% solution in water has a pH of 5.5 to 6.5.

Citalopram Hydrochloride *(BANM, rINNM)*

Citalopram, chlorhydrate de; Citaloprami hydrochloridum; Hidrocloruro de citalopram.

Циталопрама Гидрохлорид

$C_{20}H_{21}FN_2O,HCl$ = 360.9.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391) although increased appetite and weight gain have also been reported with citalopram. Citalopram may be more cardiotoxic in overdosage than other SSRIs; for further details, see p.394.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Pharmacokinetics

Citalopram is readily absorbed from the gastrointestinal tract and maximum plasma concentrations are reached 2 to 4 hours after oral doses. Citalopram is widely distributed throughout the body; protein binding is less than 80%. Citalopram is metabolised by demethylation, deamination, and oxidation to active and inactive metabolites. The demethylation of citalopram to one of its active metabolites, demethylcitalopram, involves the cytochrome P450 isoenzymes CYP3A4 and CYP2C19; the metabolism of citalopram is also partly dependent on CYP2D6. Didemethylcitalopram has also been identified as a metabolite of citalopram. The elimination half-life of citalopram is reported to be about 36 hours. It is excreted mainly via the liver (85%) with the remainder via the kidneys. About 12% of the daily dose is excreted in the urine as unchanged drug. Citalopram is distributed into breast milk in very low concentrations (see Breast Feeding under Precautions in Fluoxetine, p.394).

Uses and Administration

Citalopram, a phthalane derivative, is an SSRI with actions and uses similar to those of fluoxetine (p.397). Citalopram is given orally as the hydrobromide or hydrochloride, usually as a single daily dose. Doses are expressed in terms of citalopram; citalopram hydrobromide 25.0 mg and citalopram hydrochloride 22.3 mg are each equivalent to about 20.0 mg of citalopram.

In the treatment of **depression**, the initial dose (given as tablets or a liquid) is the equivalent of 20 mg daily by mouth. After at least one week, the dose may be increased to 40 mg daily; a dose of 60 mg daily may be necessary in some patients. In the UK citalopram is also given as the hydrochloride in the form of concentrated oral drops containing the equivalent of 40 mg/mL of citalopram. The bioavailability of the drops is about 25% greater than that of the tablets and consequently daily doses appear to be lower: a 20-mg tablet dose is equivalent to a 16-mg (8 drops) dose of the concentrate. In some countries, citalopram hydrochloride has also been given by intravenous infusion in doses of 20 to 40 mg when the oral route is impracticable.

In the treatment of **panic disorder** with or without agoraphobia, the initial oral dose is 10 mg (or the equivalent as the concentrate) daily increasing to 20 mg daily after one week. The dose may be increased thereafter as required up to a maximum of 60 mg daily. In some countries citalopram is also used in the treatment of **obsessive-compulsive disorder** in doses similar to those used in depression (see above).

A dose of 20 mg daily, up to a maximum of 40 mg (or their equivalents as the concentrate), should be used in elderly patients. For dosage in hepatic and renal impairment see below.

Citalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms.

The *S*-enantiomer of citalopram, escitalopram (p.391) is given for the treatment of depression and some anxiety disorders.

◊ Reviews.

1. Milne RJ, Goa KL. Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. *Drugs* 1991; **41**: 450–77.

Administration in hepatic or renal impairment. Licensed drug information suggests that dosage of citalopram should be restricted to the lower end of the dose range in patients with hepatic impairment. A usual oral dose for depression in this group would be 20 mg daily although the dose may be increased up to 40 mg daily, if necessary.

There is no need for dose adjustment in mild to moderate renal impairment although information is lacking on appropriate dosage in severe impairment.

Anxiety disorders. Citalopram has been given in anxiety disorders (p.952) including panic disorder (p.952), obsessive-compulsive disorder (p.952), post-traumatic stress disorder (p.953), and social anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Bouwer C, Skin DJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord* 1998; **49:** 79–82.
2. Lepola UM, *et al.* A controlled, prospective, 1-year trial of citalopram in the treatment of panic disorder. *J Clin Psychiatry* 1998; **59:** 528–34.
3. Seedat S, *et al.* Open trial of citalopram in adults with post-traumatic stress disorder. *Int J Neuropsychopharmacol* 2000; **3:** 135–40.
4. Montgomery SA, *et al.* Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2001; **16:** 75–86.
5. Perna G, *et al.* A comparison of citalopram and paroxetine in the treatment of panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2001; **34:** 85–90.
6. Marazziti D, *et al.* Citalopram in refractory obsessive-compulsive disorder: an open study. *Int Clin Psychopharmacol* 2001; **16:** 215–19.
7. Atmaca M, *et al.* Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings. *Hum Psychopharmacol* 2002; **17:** 401–5.
8. Varia I, Rauscher F. Treatment of generalized anxiety disorder with citalopram. *Int Clin Psychopharmacol* 2002; **17:** 103–7.
9. Mukaddes NM, *et al.* Citalopram treatment of children and adolescents with obsessive-compulsive disorder: a preliminary report. *Psychiatry Clin Neurosci* 2003; **57:** 405–8.
10. Lenze EJ, *et al.* Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. *Am J Psychiatry* 2005; **162:** 146–50.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as citalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Montgomery SA, *et al.* The optimal dosing regimen for citalopram—a meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol* 1994; **9** (suppl 1): 35–40.
2. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from US trials. *J Clin Psychiatry* 2000; **61:** 896–908.
3. Parker NG, Brown CS. Citalopram in the treatment of depression. *Ann Pharmacother* 2000; **34:** 761–71.
4. Guelfi JD, *et al.* Efficacy of intravenous citalopram compared with oral citalopram for severe depression. Safety and efficacy data from a double-blind, double-dummy trial. *J Affect Disord* 2000; **58:** 201–9.
5. Hochstrasser B, *et al.* Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2001; **178:** 304–10.
6. Klysner R, *et al.* Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. *Br J Psychiatry* 2002; **181:** 29–35.
7. Roose SP, *et al.* Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004; **161:** 2050–9.
8. Trivedi MH, *et al.* The STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006; **163:** 28–40.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Favourable results with citalopram have been reported in a double-blind placebo-controlled study[1] and in case reports.[2,3]

1. Andersen G, *et al.* Citalopram for post-stroke pathological crying. *Lancet* 1993; **342:** 837–9.
2. Andersen G, *et al.* Citalopram treatment of traumatic brain damage in a 6-year-old boy. *J Neurotrauma* 1999; **16:** 341–4.
3. Kaschka WP, *et al.* Treatment of pathological crying with citalopram. *Pharmacopsychiatry* 2001; **34:** 254–8.

Schizophrenia. The treatment of schizophrenia consists mainly of a combination of social therapy and antipsychotic drugs (see p.955). Like other antidepressants, citalopram has been examined for its potential value as an adjuvant in schizophrenia.[1-4] In a preliminary placebo-controlled study[1] in 15 patients with chronic schizophrenia who exhibited signs of impulsive aggression, adding citalopram to existing antipsychotic therapy significantly reduced the frequency, but not the average severity, of aggressive incidents. In a subsequent study involving 90 patients, citalopram appeared to improve subjective well-being but had no clear effect on psychopathological symptoms.[2]

1. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; **91:** 348–51.
2. Salokangas RKR, *et al.* Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 1996; **94:** 175–80.
3. Taiminen TJ, *et al.* Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *Int Clin Psychopharmacol* 1997; **12:** 31–5.
4. Kasckow JW, *et al.* Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. *Int J Geriatr Psychiatry* 2001; **16:** 1163–7.

Sexual dysfunction. SSRIs have been tried in the treatment of premature ejaculation, but results with citalopram have been conflicting, see under Fluoxetine, p.399.

Preparations

USP 31: Citalopram Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Humorap; Psiconor; Seropram; Zentius; ***Austral.:*** Celapram; Ciazil; Cipramil; Talam; Talohexal; ***Austria:*** Apertia†; Cipram†; Citalhexal†; Citalon†; Citalostad; Citarcana; Citor; Eostar; Pram; Sepram†; Seropram; ***Belg.:*** Cipramil; ***Braz.:*** Alcytam; Cipramil; Citta; Denyl; Procimax; ***Canad.:*** Celexa; ***Chile:*** Actipram; Cimal; Cipramil; Cortran; Finap; Pramcil; Prisma; Semax†; Setronil; Temperax; Zebrak; Zentius; ***Cz.:*** Apertia†; Apo-Cital; Cerotor; Cipram; Cita; Citalec; Citalon; Citaratio; Dalsan; Pram; Sepram†; Seropram; Zyloram; ***Denm.:*** Akarin; Cipramil; Citadur; Citaham; ***Fin.:*** Cipramil; Emocal†; Sepram; ***Fr.:*** Seropram; ***Ger.:*** Cilex†; Cipramil; Citadura; CitaLich; Citalo-Q; Citalon; Sepram†; Serital; ***Gr.:*** A-Depress-Therapy; Acelopram; Atinorm; Bibien; Celius; Cilopress; Cinapen; Cipram; Erlicon; Espinal; Goldamit; Lodeprem; Lopracil; Lopraxer; Malicon; Pralotam; Prefucet; Pricital; Ropramin; Selon; Seproc; Seretover; Seropram; Seror; Siloam; Sotovon; Talopram; Talopron; Taprocil; Tasonade; Verus; Vesema; Xadorek; Zanipram; ***Hong Kong:*** Cipram; Cital; ***Hung.:*** Citagen; Citalodep; Citalon; Citalowin; Citapram; Dalsan; Oropram; Seropram; Serotor; Zyloram; ***India:*** Citadep; Citopam; ***Indon.:*** Cipram; ***Irl.:*** Ciprager; Cipramil; Ciprapine; Ciprotan; Citrol; ***Israel:*** Cipramil; Recital; ***Ital.:*** Elopram; Felipram; Feliximir; Frimaind; Kaidor; Lampopram; Marpram; Percital; Pramexyl; Ricap; Seropram; Verisan; ***Malaysia:*** Cipram; ***Mex.:*** Citox; Seropram; Xylorane; ***Neth.:*** Cipramil; Ciprapine; Lontax; ***Norw.:*** Cipramil; Desital†; ***NZ:*** Celapram; Cipramil; ***Philipp.:*** Lupram; ***Pol.:*** Aurex; Cilon; Cipramil; Cital; Citaratio; Citaxin; ***Rus.:*** Cipramil (Ципрамил); Citol (Цитол); Opra (Опра); Pram (Прам); ***S.Afr.:*** Adco-Talomil; Cilift; Cipramil; CitaloHexal; Depramil; Talomil†; ***Singapore:*** Cipram; ***Spain:*** Citalvir; Genprol; Presar; Prisdal; Relapaz; Seropram; Somac; ***Swed.:*** Cipramil; Citavie; ***Switz.:*** Alutan; Claropram; Rudopram; Seropram; ***Thai.:*** Cipram; ***Turk.:*** Cipram; Citara; Citol; Citolap; ***UK:*** Cipramil; ***USA:*** Celexa; ***Venez.:*** Seropram.

Clomipramine Hydrochloride

(BANM, USAN, rINNM)

Chlorimipramine Hydrochloride; Clomipramine, chlorhydrate de; Clomipramini hydrochloridum; G-34586; Hidrocloruro de clomipramina; Klomipramiinihydrokloridi; Klomipramin Hidroklorür; Klomipramin hydrochlorid; Klomipramin-hidroklorid; Klomipraminhydroklorid; Klomipramino hidrochloridas; Monochlorimipramine Hydrochloride. 3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyldimethylamine hydrochloride.

Кломипрамина Гидрохлорид

$C_{19}H_{23}ClN_2,HCl = 351.3.$

CAS — 303-49-1 (clomipramine); 17321-77-6 (clomipramine hydrochloride).

ATC — N06AA04.

ATC Vet — QN06AA04.

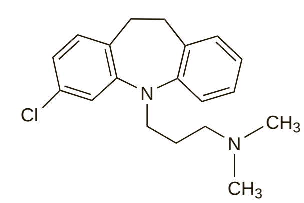

(clomipramine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Clomipramine Hydrochloride). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.0. Protect from light.

USP 31 (Clomipramine Hydrochloride). A white to faintly yellow crystalline powder. Very soluble in water. pH of a 10% solution in water is between 3.5 and 5.0.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Porphyria. Clomipramine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

MAOIs. The combination of clomipramine and *tranylcypromine* is considered particularly hazardous.

The serotonin syndrome (p.416) has occurred in patients receiving clomipramine and *moclobemide* (see under Interactions of Antidepressants in Phenelzine, p.418).

Pharmacokinetics

Clomipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated during first-pass metabolism in the liver to its primary active metabolite, desmethylclomipramine.

Clomipramine and desmethylclomipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Clomipramine has been estimated to have a plasma elimination half-life of about 21 hours, which may be considerably extended in overdosage; that of desmethylclomipramine is longer (about 36 hours).

Paths of metabolism of both clomipramine and desmethylclomipramine include hydroxylation and *N*-oxidation. About two-thirds of a single dose of clomipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; the remainder of the dose is excreted in the faeces. Clomipramine crosses the placenta and is distributed into breast milk.

◊ References.

1. Gex-Fabry M, *et al.* Clomipramine metabolism: model-based analysis of variability factors from drug monitoring data. *Clin Pharmacokinet* 1990; **19:** 241–55.

2. Balant-Gorgia AE, *et al.* Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet* 1991; **20:** 447–62.
3. Nielsen KK, *et al.* Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther* 1994; **55:** 518–27.
4. Herrera D, *et al.* Pharmacokinetics of a sustained-release dosage form of clomipramine. *J Clin Pharmacol* 2000; **40:** 1488–93.

Uses and Administration

Clomipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has antimuscarinic properties and is also a potent serotonin reuptake inhibitor. Clomipramine is one of the more sedating tricyclics. It is used as the hydrochloride.

In the treatment of **depression** in adults, clomipramine hydrochloride is given in oral doses of 10 mg daily initially, increasing gradually to 30 to 150 mg daily if required; up to 250 mg daily or higher may be given in severe cases. A suggested initial dose for the elderly is 10 mg daily increasing gradually over 10 days to 30 to 75 mg daily if required. Clomipramine may be given in divided doses throughout the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

In the treatment of **obsessive-compulsive disorder** and **phobias**, clomipramine hydrochloride may be given in an initial oral dose of 25 mg daily (or 10 mg daily for elderly patients or those sensitive to tricyclics) increased gradually over two weeks to 100 to 150 mg daily. In some countries, maximum doses of 250 mg daily have been used. Similar doses have also been used in the management of **panic disorder**. In some countries clomipramine hydrochloride is also used for the treatment of obsessive-compulsive disorder in children and adolescents aged 10 years and over (see below for doses).

In some countries clomipramine may be given for depression or obsessive-compulsive disorder by the intramuscular or intravenous routes if giving it orally is impracticable or inadvisable. The initial dose of clomipramine hydrochloride by intramuscular injection is 25 to 50 mg daily, increasing to a maximum of 100 to 150 mg daily; oral dosage should be substituted as soon as possible. Clomipramine hydrochloride may also be given by intravenous infusion in doses of 50 to 75 mg daily diluted in 250 to 500 mL of sodium chloride 0.9% or glucose 5% and infused over 1.5 to 3 hours. When a satisfactory response to parenteral doses has been obtained oral therapy should be substituted, initially giving double the parenteral dose by mouth and subsequently adjusting if necessary. Patients must be carefully supervised during intravenous infusion of clomipramine hydrochloride and the blood pressure carefully monitored owing to the risk of hypotension.

In the adjunctive treatment of **cataplexy associated with narcolepsy**, clomipramine hydrochloride is given in an initial oral dose of 10 mg daily and gradually increased until a satisfactory response occurs, usually within the range of 10 to 75 mg daily.

Clomipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in children. In the UK, the use of clomipramine in children under 18 years is not recommended in the treatment of depressive states, phobias, or cataplexy associated with narcolepsy. However, in some countries clomipramine hydrochloride is used for the treatment of *obsessive-compulsive disorder* in children and adolescents aged 10 years and over. Initial oral doses are 25 mg daily, increased gradually during the first 2 weeks to a maximum daily dose of 3 mg/kg or 100 mg, whichever is smaller, and given in divided doses. Further increases are permitted, over several weeks to a maximum daily dose of 3 mg/kg or 200 mg, whichever is smaller. Once titration has been achieved the dose may be given as a single dose at bedtime.

Clomipramine hydrochloride is also licensed for oral use in the management of *nocturnal enuresis* in some countries (for a discussion of tricyclic use in nocturnal enuresis see Micturition Disorders under Amitriptyline, p.381). The age ranges and licensed doses vary somewhat from country to country, however. For example, in *France*, use is licensed in children over 6 years of age, at a daily dose of 10 to 30 mg, or 0.5 to 1 mg/kg, whereas in *Austria* and *Switzerland* the licensed dose is: 6 to 8 years, 20 to 30 mg; 9 to 12 years, 25 to 50 mg; over 12 years, 25 to 75 mg.

Anxiety disorders. Tricyclic antidepressants that inhibit serotonin reuptake, such as clomipramine and imipramine, have been given in the management of anxiety disorders (p.952) including obsessive-compulsive disorder (p.952), panic disorder (p.952), post-traumatic stress disorder (p.953), and trichotillomania.

References.

1. Swedo SE, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989; **321:** 497–501.
2. McTavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs* 1990; **39:** 136–53.
3. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP Ann Pharmacother* 1990; **24:** 739–44.
4. Papp LA, *et al.* Clomipramine treatment of panic disorder: pros and cons. *J Clin Psychiatry* 1997; **58:** 423–5.
5. Fallon BA, *et al.* Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry* 1998; **55:** 918–24.
6. Sasson Y, *et al.* A double-blind crossover comparison of clomipramine and desipramine in the treatment of panic disorder. *Eur Neuropsychopharmacol* 1999; **9:** 191–6.

Autism. Clomipramine reduced adventitious movements when tried in 5 boys with autistic disorder.[1] However, in a small study in 7 children no improvement in symptoms was noted and adverse effects were common and serious.[2] In another study,[3] although clomipramine was found to be as effective as haloperidol in the treatment of some autistic symptoms, patients on clomipramine were significantly less likely to complete the trial for reasons that included the onset of adverse effects.

1. Brasic JR, *et al.* Clomipramine ameliorates adventitious movements and compulsions in prepubertal boys with autistic disorder and severe mental retardation. *Neurology* 1994; **44:** 1309–12.
2. Sanchez LE, *et al.* A pilot study of clomipramine in young autistic children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 537–44.
3. Remington G, *et al.* Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol* 2001; **21:** 440–4.

Micturition disorders. In some countries, clomipramine is used in children for the treatment of nocturnal enuresis; for further details, see Administration in Children, above.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). In a number of countries, clomipramine hydrochloride is licensed for the treatment of chronic pain; oral doses range from 10 to 150 mg daily. Parenteral doses are licensed in some countries.

Premenstrual syndrome. Clomipramine reduced premenstrual irritability and depressed mood when given during the luteal phase;[1] doses of clomipramine ranged from 25 to 75 mg daily. It was postulated that the efficacy of clomipramine in relieving premenstrual symptoms is related to its serotonin reuptake inhibitor activity. For the overall management of premenstrual syndrome, see p.2099.

1. Sundblad C, *et al.* Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* 1993; **9:** 133–45.

Sexual dysfunction. Clomipramine has been used for its inhibitory effect on ejaculation in the management of premature ejaculation[1-5] (p.2181). In some men with very short latencies (less than 1 minute) continuous therapy with a low daily dose of clomipramine, typically 20 or 30 mg, may be more effective than taking 25 mg as required.[5] Any benefits may relate to its effect as a serotonin reuptake inhibitor; other antidepressants with serotonin reuptake inhibiting actions, such as fluoxetine and sertraline, have also been tried in this condition.[4]

1. Hawton K. Erectile dysfunction and premature ejaculation. *Br J Hosp Med* 1988; **40:** 428–36.
2. Althof SE, *et al.* A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry* 1995; **56:** 402–7.
3. Haensel SM, *et al.* Clomipramine and sexual function in men with premature ejaculation and controls. *J Urol (Baltimore)* 1996; **156:** 1310–15.
4. Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol (Baltimore)* 1998; **159:** 425–7.
5. Rowland DL, *et al.* Effective daily treatment with clomipramine in men with premature ejaculation when 25 mg (as required) is ineffective. *BJU Int* 2001; **87:** 357–60.

Stuttering. Clomipramine was of modest success in a controlled study[1] of 17 patients with developmental stuttering (p.1001). It was suggested that its efficacy may be related to its serotonin reuptake inhibitor activity.

1. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.

Preparations

BP 2008: Clomipramine Capsules;
USP 31: Clomipramine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Anafranil; Clomipram†; ***Austral.:*** Anafranil; Clopram; Placil; ***Austria:*** Anafranil; ***Belg.:*** Anafranil; ***Braz.:*** Anafranil; Clo; Clomipran; ***Canad.:*** Anafranil; Novo-Clopamine†; ***Chile:*** Anafranil; Atenual; Ausentron; Deprelin; ***Cz.:*** Anafranil; Hydiphen†; ***Denm.:*** Anafranil; ***Fin.:*** Anafranil; ***Fr.:*** Anafranil; ***Ger.:*** Anafranil; Hydiphen†; ***Gr.:*** Anafranil; ***Hong Kong:*** Anafranil; Zoiral; ***Hung.:*** Anafranil; ***India:*** Anafranil; ***Indon.:*** Anafranil; ***Irl.:*** Anafranil; ***Israel:*** Anafranil; Maronil; ***Ital.:*** Anafranil; ***Malaysia:*** Anafranil; Clopress†; ***Mex.:*** Anafranil; ***Neth.:*** Anafranil; ***Norw.:*** Anafranil; ***NZ:*** Anafranil†; Clopress; ***Philipp.:*** Anafranil; ***Pol.:*** Anafranil; Hydiphen; ***Port.:*** Anafranil; ***Rus.:*** Anafranil (Анафранил); Clofranil (Клофранил); ***S.Afr.:*** Anafranil; Clomidep; Equinorm; ***Singapore:*** Anafranil†; ***Spain:*** Anafranil; ***Swed.:*** Anafranil; ***Switz.:*** Anafranil; ***Thai.:*** Anafranil; Clofranil†; ***Turk.:*** Anafranil; ***UK:*** Anafranil; ***USA:*** Anafranil; ***Venez.:*** Anafranil.

Desipramine Hydrochloride *(BANM, USAN, rINNM)*

Desipramiinihydrokloridi; Désipramine, chlorhydrate de; Desipramin-hydrochlorid; Desipraminhydroklorid; Desipramini hydrochloridum; Desmethylimipramine Hydrochloride; Dezipramin-hidroklorid; Dezipramino hidrochloridas; Dezypraminy chlorowodorek; DMI; EX-4355; G-35020; Hidrocloruro de desipramina; JB-8181; NSC-114901; RMI-9384A. 3-(10,11-Dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl(methyl)amine hydrochloride.

Дезипрамина Гидрохлорид

$C_{18}H_{22}N_2,HCl = 302.8.$

CAS — 50-47-5 (desipramine); 58-28-6 (desipramine hydrochloride).

ATC — N06AA01.

ATC Vet — QN06AA01.

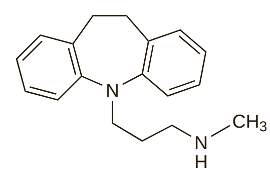

(desipramine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Desipramine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. Protect from light.

USP 31 (Desipramine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 12 of water, 1 in 14 of alcohol, and 1 in 3.5 of chloroform; insoluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Desipramine is the principal active metabolite of imipramine (p.400).

Uses and Administration

Desipramine, the principal active metabolite of imipramine (p.400), is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is one of the less sedating tricyclics and its antimuscarinic effects are mild. Desipramine is used as the hydrochloride.

In the treatment of depression, desipramine hydrochloride is given orally in daily doses of 100 to 200 mg; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. Lower doses should be used in adolescents and the elderly and are usually 25 to 100 mg daily; up to 150 mg daily may be required for severe depression. Initial doses should be low and gradually increased according to tolerance and clinical response. Therapy may initially be given as a single daily dose or in divided doses; maintenance therapy may be given as a single daily dose usually at night.

Desipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Cocaine dependence. Since dopamine depletion may be the cause of the depression often associated with cocaine craving and with relapse, drugs such as desipramine that interact with dopaminergic systems have been tried in managing cocaine

The symbol † denotes a preparation no longer actively marketed

withdrawal symptoms (p.1860). However, a systematic review[1] was unable to find evidence to support the use of antidepressants in the treatment of cocaine dependence although the efficacy of desipramine was suggested in some individual studies.

1. Lima MS, *et al.* Antidepressants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 24/11/05).

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (see p.2148) tricyclic antidepressants such as imipramine or desipramine[1-4] are usually reserved for patients who fail to respond to, or who are intolerant of, stimulants. They may also be of use for selected patients with co-existing disorders such as Tourette's syndrome, anxiety, and enuresis.

1. Rapport MD, *et al.* Methylphenidate and desipramine in hospitalized children: I. separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 333–42.
2. Pataki CS, *et al.* Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1065–72.
3. Singer HS, *et al.* The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995; **95:** 74–81.
4. Spencer T, *et al.* A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2002; **59:** 649–56.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2) when given in subantidepressant doses.

References to the use of desipramine.

1. Kishore-Kumar R, *et al.* Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.
2. Max MB, *et al.* Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326:** 1250–6.
3. Coquoz D, *et al.* Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther* 1993; **54:** 339–44.
4. Gordon NC, *et al.* Temporal factors in the enhancement of morphine analgesia by desipramine. *Pain* 1993; **53:** 273–6.

Preparations

BP 2008: Desipramine Tablets;
USP 31: Desipramine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Nebril†; ***Austria:*** Pertofran; ***Belg.:*** Pertofran†; ***Canad.:*** Norpramin; ***Chile:*** Distonal; ***Fr.:*** Pertofran†; ***Ger.:*** Pertofran†; Petylyl; ***Israel:*** Deprexan; ***Ital.:*** Nortimil; ***Mex.:*** Norpramin†; ***NZ:*** Pertofran†; ***Pol.:*** Petylyl; ***USA:*** Norpramin.

Multi-ingredient: ***Arg.:*** Plafonyl†.

Desvenlafaxine Succinate *(BANM, USAN, rINNM)*

O-Desmethylvenlafaxine succinate; Dèsvenlafaxine, Succinate de; Desvenlafaxini Succinas; DVS-233 (base or succinate); Succinato de desvenlafaxina; Wy-45233. 1-[(1*RS*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate.

Десвенлафаксина Сукcинат

$C_{16}H_{25}NO_2,C_4H_6O_4,H_2O = 399.5.$

CAS — 93413-62-8 (desvenlafaxine); 386750-22-7 (desvenlafaxine succinate).

ATC — N06AX23.

ATC Vet — QN06AX23.

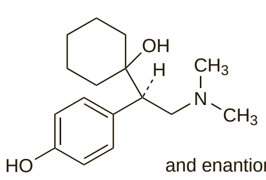

and enantiomer

(desvenlafaxine)

Profile

Desvenlafaxine, the major active metabolite of venlafaxine, is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427). It is given orally as the succinate but doses are expressed in terms of the base; desvenlafaxine succinate 75.8 mg is equivalent to about 50 mg of desvenlafaxine. The succinate is given in the treatment of depression (p.373) as a modified-release preparation providing a dose equivalent to desvenlafaxine 50 mg once daily. Higher doses of up to 400 mg daily have been studied, but provide no additional benefit and are associated with more frequent adverse effects. The dose may need to be reduced in patients with renal impairment (see below).

Desvenlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Desvenlafaxine is under investigation in the management of menopausal vasomotor symptoms, neuropathic pain, and fibromyalgia.

◊ References.

1. DeMartinis NA, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007; **68:** 677–88.
2. Septien-Velez L, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007; **22:** 338–47.
3. Liebowitz MR, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1663–72.

Administration in renal impairment. The usual desvenlafaxine oral dose of 50 mg daily may be given to patients with mild to moderate renal impairment. In severe impairment (creatinine clearance less than 30 mL/minute) a dose of 50 mg may be given on alternate days. Supplemental doses should not be given after dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Pristiq.

Dibenzepin Hydrochloride *(BANM, USAN, rINNM)*

Dibenzépine, Chlorhydrate de; Dibenzepini Hydrochloridum; HF-1927; Hidrocloruro de dibenzepina. 10-(2-Dimethylaminoethyl)-5,10-dihydro-5-methyl-dibenzo[*b*,*e*][1,4]diazepin-11-one hydrochloride.

Дибензепина Гидрохлорид

$C_{18}H_{21}N_3O,HCl = 331.8.$

CAS — 4498-32-2 (dibenzepin); 315-80-0 (dibenzepin hydrochloride).

ATC — N06AA08.

ATC Vet — QN06AA08.

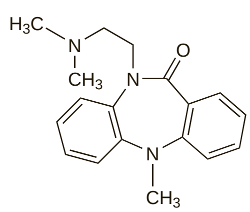

(dibenzepin)

Profile

Dibenzepin hydrochloride is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression dibenzepin hydrochloride is given in oral doses of 480 mg daily; higher doses of up to 720 mg daily may be required in some patients with severe depression. Elderly patients should be given reduced doses of 240 mg daily initially, increased to a maximum of 480 mg daily if required.

Dibenzepin hydrochloride has also been given by intravenous infusion.

In some countries it has also been used for nocturnal enuresis.

Dibenzepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

◊ References.

1. Wirtheim E, Bloch Y. Dibenzepin overdose causing pulmonary edema. *Ann Pharmacother* 1996; **30:** 789–90.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Noveril; ***Cz.:*** Noveril; ***Ger.:*** Noveril†; ***Hung.:*** Noveril; ***Israel:*** Noveril; Victoril†; ***Pol.:*** Noveril; ***Switz.:*** Noveril.

Dosulepin Hydrochloride *(BANM, rINNM)*

Dosulepiinihydrokloridi; Dosulépine, chlorhydrate de; Dosulepin-hydrochlorid; Dosulepinhydroklorid; Dosulepini hydrochloridum; Dosulepino hidrochloridas; Doszulepin-hidroklorid; Dothiepin Hydrochloride *(USAN)*; Hidrocloruro de dosulepina. 3-(Dibenzo[*b*,*e*]thiepin-11-ylidene)propyldimethylamine hydrochloride.

Досулепина Гидрохлорид

$C_{19}H_{21}NS,HCl = 331.9.$

CAS — 113-53-1 (dosulepin); 897-15-4 (dosulepin hydrochloride).

ATC — N06AA16.

ATC Vet — QN06AA16.

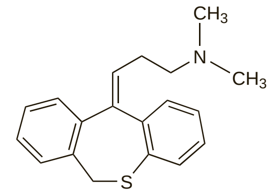

(dosulepin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dosulepin Hydrochloride). A white or faintly yellow crystalline powder. It consists chiefly of the *E*-isomer. Freely soluble in water, in alcohol, and in dichloromethane. A 10% solution in water has a pH of 4.2 to 5.2. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the cardiovascular system. For reference to an increased risk of ischaemic heart disease in patients treated with dosulepin, see under Amitriptyline, p.376.

Overdosage. After an overdose of 1 g of dosulepin, the ECG of a 41-year-old man showed cardiac abnormalities mimicking an acute myocardial infarction.[1] However, as cardiac enzymes did not confirm an ischaemic event, the abnormalities were thought to be due to either the quinidine-like effect of dosulepin or changes in potassium membrane permeability.

1. Steeds RP, Muthusamy R. Abnormal ventricular conduction following dothiepin overdose simulating acute myocardial infarction. *Heart* 2000; **83:** 289.

Porphyria. Dosulepin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Dosulepin hydrochloride is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (also termed northiaden). Paths of metabolism also include *S*-oxidation.

Dosulepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. Elimination half-lives of about 14 to 24 and 23 to 46 hours have been reported for dosulepin and its metabolites, respectively.

Dosulepin is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Maguire KP, *et al.* Clinical pharmacokinetics of dothiepin: single-dose kinetics in patients and prediction of steady-state concentrations. *Clin Pharmacokinet* 1983; **8:** 179–85.
2. Yu DK, *et al.* Pharmacokinetics of dothiepin in humans: a single dose dose-proportionality study. *J Pharm Sci* 1986; **75:** 582–5.
3. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.

Uses and Administration

Dosulepin hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is one of the more sedating tricyclics. In the UK, the MHRA suggests that the use of dosulepin for depression should be limited, because of the small margin of safety between the maximum therapeutic dose and potentially fatal overdose. It advises that treatment should only be started by a specialist-care prescriber, and that the quantity issued per prescription should be limited. In patients with increased risk factors for suicide at the start of treatment, during dose adjustment, and until improvement occurs, the MHRA suggests a maximum supply equivalent to 2 weeks of treatment with 75 mg daily.

In the treatment of depression, dosulepin hydrochloride is given in oral doses of 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary; alternatively a single dose at night may be given. Higher doses of up to 225 mg daily have been given to severely depressed patients in hospital. The recommended initial dose for the elderly is 50 to 75 mg daily.

Dosulepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Dosulepin Capsules; Dosulepin Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Dothep; Prothiaden; ***Belg.:*** Prothiaden; ***Cz.:*** Prothiaden; ***Denm.:*** Prothiaden; ***Fr.:*** Prothiaden; ***Ger.:*** Idom; ***Hong Kong:*** Prothiaden; ***India:*** Prothiaden; ***Irl.:*** Dothep; Prothiaden; ***Ital.:*** Protiaden; ***Malaysia:*** Dothep; Prothiaden; ***Neth.:*** Prothiaden; ***NZ:*** Dopress; Prothiaden; ***Philipp.:*** Prothiaden; ***Port.:*** Protiadene; ***S.Afr.:*** Prothiaden; Thaden; ***Singapore:*** Espin; Prothiaden; ***Spain:*** Prothiaden; ***Switz.:*** Protiaden†; ***Thai.:*** Dopin†; Prothiaden†; ***UK:*** Dothapax†; Prepadine; Prothiaden.

Multi-ingredient: ***Austria:*** Harmomed.

Doxepin Hydrochloride

(BANM, USAN, rINNM)

Doksepiinihydrokloridi; Doksepin Hidroklorür; Doksepino hidrochloridas; Doksepiny chlorowodorek; Doxépine, chlorhydrate de; Doxepin-hidroklorid; Doxepin-hydrochlorid; Doxepinhydroklorid; Doxepini hydrochloridum; Hidrocloruro de doxepina; NSC-108160; P-3693A. (*E*)-3-(Dibenz[*b*,*e*]oxepin-11-ylidene) propyldimethylamine hydrochloride.

Доксепина Гидрохлорид

$C_{19}H_{21}NO,HCl = 315.8.$

CAS — 1668-19-5 (doxepin); 1229-29-4 (doxepin hydrochloride); 4698-39-9 (doxepin hydrochloride, E-isomer); 25127-31-5 (doxepin hydrochloride, Z-isomer).

ATC — N06AA12.

ATC Vet — QN06AA12.

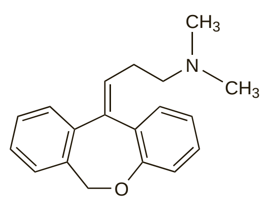

(doxepin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Doxepin Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Doxepin Hydrochloride). It consists of a mixture of *Z*- and *E*-isomers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376). Drowsiness and other systemic effects can also occur after topical application. In addition, local effects, most commonly burning and stinging, have been reported.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the skin. Up to January 2002 the FDA was aware of 26 cases of allergic contact dermatitis associated with the use of doxepin 5% cream;[1] manifestations included eczema, urticaria, purpura, and papulovesicular lesions. Of the 20 cases where details were known, 13 occurred after use for more than the recommended 8 days. Patch testing was positive in the 21 cases where it was performed, supporting an allergic reaction rather than an exacerbation of the original condition.

1. Bonnel RA, *et al.* Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; **48:** 294–6.

Overdosage. An infant became difficult to arouse after the application of doxepin cream 5% to about 50% of her body-surface; an entire 30-g tube of the cream was used in only 2 applications.[1] The cream is not recommended for use in children.

1. Zell-Kanter M, *et al.* Doxepin toxicity in a child following topical application. *Ann Pharmacother* 2000; **34:** 328–9.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Doxepin is readily absorbed from the gastrointestinal tract after oral doses, and is extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desmethyldoxepin. Doxepin is also absorbed through the skin after topical application.

Paths of metabolism of both doxepin and desmethyldoxepin include hydroxylation and *N*-oxidation. Doxepin is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Doxepin and desmethyldoxepin are widely distributed throughout the body; the plasma protein binding of doxepin is about 76%. Doxepin has been estimated to have a plasma elimination half-life ranging from 8 to 24 hours, which may be considerably extended in overdosage; that of desmethyldoxepin is longer.

Doxepin crosses the blood-brain barrier and the placenta. It is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Faulkner RD, *et al*. Multiple-dose doxepin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **34:** 509–15.
2. Joyce PR, Sharman JR. Doxepin plasma concentrations in clinical practice: could there be a pharmacokinetic explanation for low concentrations? *Clin Pharmacokinet* 1985; **10:** 365–70.

Uses and Administration

Doxepin is a dibenzoxepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has moderate antimuscarinic and marked sedative properties and has serotonin reuptake inhibitor activity.

In the treatment of depression doxepin is given orally as the hydrochloride although doses are expressed in terms of the base; doxepin hydrochloride 84.8 mg is equivalent to about 75 mg of doxepin. The initial dose is 75 mg daily, gradually adjusted according to response. Doses of up to 300 mg daily may be required in severely depressed patients; mildly affected patients may respond to as little as 25 to 50 mg daily. Daily doses up to 100 mg may be given in divided doses or as a single dose at bedtime. If the total daily dose exceeds 100 mg, it should be given in 3 divided doses, although the largest portion, up to a maximum of 100 mg, may be given at bedtime. In the USA, the maximum single dose is 150 mg. A suggested starting dose in the elderly is 10 to 50 mg daily.

Doxepin hydrochloride has also been given by intramuscular or intravenous injection.

Doxepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Doxepin has histamine H_1- and H_2-antagonist activity and is used topically in a cream containing 5% of the hydrochloride for the short-term (up to 8 days) relief of moderate pruritus associated with various types of dermatitis (see below).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache—see p.381.

References to the use of doxepin.

1. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.

Insomnia. Doxepin is under investigation in the management of insomnia (p.957). Low oral doses of 1 to 6 mg at night are being studied.[1]

1. Roth T, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007; **30:** 1555–61.

Skin disorders. Tricyclic antidepressants have a wide range of pharmacological activity and some drugs in this group have notable antihistaminic actions. Doxepin in particular has very potent antihistaminic activity. It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria,[1-3] and to be an effective oral treatment for idiopathic cold urticaria.[4,5] In the case of cold urticaria doxepin may act by inhibiting release of a platelet-activating factor-like lipid.[5]

For an overview of the possible treatments for the various urticarias, including mention of the use of doxepin, see p.1584.

Like standard antihistamines (p.565) doxepin has also been used topically for the relief of pruritus (see also p.1582) associated with various types of allergic and inflammatory skin disorders[6,7] although some authorities remain to be convinced of its efficacy.[8,9] Topical application of doxepin can also produce contact dermatitis (see Effects on the Skin, above) and drowsiness and other systemic effects.

1. Greene SL, *et al.* Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985; **12:** 669–75.
2. Harto A, *et al.* Doxepin in the treatment of chronic urticaria. *Dermatologica* 1985; **170:** 90–3.
3. Goldsobel AB, *et al.* Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; **78:** 867–73.
4. Neittaanmäki H, *et al.* Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: usefulness of doxepin. *J Am Acad Dermatol* 1984; **11:** 483–9.
5. Grandel KE, *et al.* Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 1985; **313:** 405–9.
6. Drake LA, *et al.* Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol* 1994; **31:** 613–16.
7. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. *Ann Pharmacother* 1997; **31:** 633–5.
8. Anonymous. Doxepin cream for pruritus. *Med Lett Drugs Ther* 1994; **36:** 99–100.
9. Anonymous. Doxepin cream for eczema? *Drug Ther Bull* 2000; **38:** 31–2.

Preparations

BP 2008: Doxepin Capsules;
USP 31: Doxepin Hydrochloride Capsules; Doxepin Hydrochloride Oral Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Doxederm†; ***Austral.:*** Deptran; Sinequan; ***Austria:*** Sinequan; ***Belg.:*** Sinequan; ***Canad.:*** Sinequan; Zonalon†; ***Denm.:*** Sinequan; ***Fin.:*** Doxal; ***Fr.:*** Quitaxon; ***Ger.:*** Aponal; Doneurin; Doxe; Doxepia; espadox†; Mareen; Sinquan†; ***Gr.:*** Sinequan; ***Hong Kong:*** Qualiquan; Sinequan; ***India:*** Spectra; ***Indon.:*** Sagalon; ***Irl.:*** Sinequan; Xepin†; ***Israel:*** Gilex; ***Mex.:*** Sinequan; ***Neth.:*** Sinequan; ***Norw.:*** Sinequan; ***NZ:*** Anten; ***Pol.:*** Sinequan; ***Spain:*** Sinequan; ***Switz.:*** Sinquane; ***Thai.:*** Sinequan; ***UK:*** Sinepin; Sinequan†; Xepin; ***USA:*** Prudoxin; Sinequan; Zonalon.

Duloxetine Hydrochloride

(BANM, USAN, rINNM)

Duloxétine, Chlorhydrate de; Duloxetini Hydrochloridum; Hidrocloruro de duloxetina; LY-248686 (duloxetine). (+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride.

Дулоксетина Гидрохлорид

$C_{18}H_{19}NOS,HCl = 333.9.$

CAS — 116539-59-4 (duloxetine); 136434-34-9 (duloxetine hydrochloride).

ATC — N06AX21.

ATC Vet — QN06AX21.

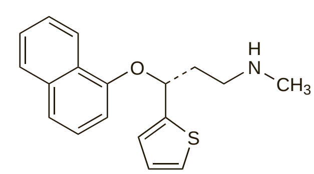

(duloxetine)

Adverse Effects and Treatment

Adverse effects reported most frequently with duloxetine include nausea, headache, insomnia, fatigue, somnolence, dry mouth, dizziness, and constipation. Other common adverse effects include anorexia, diarrhoea, dyspepsia, vomiting, anxiety, visual disturbances, tremor, weight gain or loss, sexual dysfunction, nervousness, lethargy, yawning, hot flushes, increased sweating, and pruritus. Dose-related increases in blood pressure have also been observed in some patients. Reports of reversible increases in liver enzymes, tachycardia, ecchymosis, urinary hesitation, skin rashes, and photosensitivity reactions are less common, and hepatitis, cholestatic jaundice, convulsions and activation of mania or hypomania have occurred rarely. Cases of orthostatic hypotension and syncope, serotonin syndrome, and akathisia have also been reported. Suicidal ideation may occur in some patients.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In the treatment of overdosage oral activated charcoal should be considered if more than 7.5 mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion; this should be followed by symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Precautions

Duloxetine should not be used in patients with hepatic or severe renal impairment and is contra-indicated in patients with uncontrolled narrow-angle glaucoma or hypertension. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Blood pressure should also be monitored because of the risk of hypertension. Increases in fasting blood glucose and in total cholesterol have been reported in diabetic patients. It should be used with caution in patients with a history of seizures, of bleeding disorders, or of hypomania or mania.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, duloxetine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Symptoms reported when duloxetine therapy was stopped abruptly include headache, nausea, vomiting, dizziness, insomnia, anxiety, and paraesthesia. It is therefore recommended that duloxetine should be withdrawn gradually over at least 2 weeks after more than one week of therapy and the patient monitored to minimise the risk of withdrawal reactions.

Children. Duloxetine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not generally recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on the Mental State, under Fluoxetine, p.392).

Interactions

Duloxetine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with duloxetine. At least 5 days should elapse between stopping duloxetine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). The use of duloxetine with other antidepressants including the SSRIs, other serotonin and noradrenaline reuptake inhibitors, and the reversible inhibitors of monoamine oxidase is not recommended. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Caution is advised when using duloxetine with other centrally acting drugs including alcohol and those with sedative properties.

Duloxetine is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6. It should not be given with potent inhibitors of CYP1A2 such as fluvoxamine, ciprofloxacin, and enoxacin as such combinations are likely to result in increased duloxetine concentrations. Similarly, caution is recommended when duloxetine is given with potent CYP2D6 inhibitors such as paroxetine. Duloxetine itself is also a moderate inhibitor of CYP2D6 and, consequently, licensed drug information recommends that it should be used cautiously with drugs that have a narrow therapeutic index and are extensively metabolised by this isoenzyme. In particular, use with thioridazine is contra-indicated because of the risk of serious ventricular arrhythmias and sudden death associated with raised thioridazine concentrations.

Duloxetine is highly protein bound and adverse effects may occur if given with other highly protein-bound drugs.

◊ References.

1. Skinner MH, *et al.* Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* 2003; **73:** 170–7.
2. Lobo ED, *et al.* In vitro and in vivo evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet* 2008; **47:** 191–202.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p.626).

Pharmacokinetics

Duloxetine is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 6 hours after an oral dose. Food delays the time to reach peak concentrations to 10 hours. Protein binding is about 96%, primarily to albumin and $alpha_1$-acid glycoprotein. Duloxetine is extensively metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6; two major, but inactive, metabolites are formed, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. These and other metabolites are principally excreted in the urine; about 20% is excreted in the faeces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine. The elimination half-life of duloxetine is 8 to 17 hours with an average of about 12 hours. Duloxetine is distributed into breast milk.

◊ References.

1. Lantz RJ, *et al.* Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos* 2003; **31**: 1142–50.
2. Skinner MH, *et al.* Effect of age on the pharmacokinetics of duloxetine in women. *Br J Clin Pharmacol* 2004; **57:** 54–61.
3. Lobo ED, *et al.* Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet* 2008; **47:** 103–9.

Uses and Administration

Duloxetine hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427). It is given orally as the hydrochloride although doses are expressed in terms of the base; duloxetine hydrochloride 22.5 mg is equivalent to about 20 mg of duloxetine.

Duloxetine is used in the treatment of **depression** in usual initial doses of 20 or 30 mg twice daily, or 60 mg once daily. A lower starting dose of 30 mg once daily for the first week may be suitable for some patients, to allow them to adjust to the effects of duloxetine before increasing the dose. A dose of 60 mg once daily may be used for maintenance therapy.

Duloxetine is also used in the treatment of **generalised anxiety disorder**, in a usual dose of 60 mg once daily. A lower starting dose of 30 mg daily for the first week may be considered in some patients, before increasing to 60 mg daily.

In the treatment of diabetic **peripheral neuropathic pain** the usual dose is 60 mg once daily. Some patients who respond insufficiently to this dose may benefit from up to 120 mg daily in divided doses. Response to therapy should be evaluated after 2 months and every 3 months thereafter.

Duloxetine is also used in the treatment of moderate to severe **stress urinary incontinence** in women. Usual initial doses are 40 mg twice daily; however, some patients may benefit from an initial dose of 20 mg twice daily for 2 weeks before increasing to 40 mg twice daily.

For dosage in hepatic or renal impairment, see below.

Duloxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, above).

Administration in hepatic or renal impairment. Duloxetine should not be used in patients with hepatic impairment. UK licensed product information for duloxetine states that no dosage adjustment is necessary in mild to moderate renal impairment (creatinine clearance 30 mL/minute or above). However, US information suggests that a lower starting dose and gradual dose increase may be warranted for patients, such as diabetics, with renal impairment. Both UK and US information recommend that duloxetine should not be used in more severe renal impairment (creatinine clearance less than 30 mL/minute).

Anxiety disorders. Duloxetine is used in the treatment of generalised anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Koponen H, *et al.* Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry* 2007; **9:** 100–107.
2. Endicott J, *et al.* Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. *J Clin Psychiatry* 2007; **68:** 518–24. Corrections. *ibid.* 2007; 518, 806.
3. Hartford J, *et al.* Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol* 2007; **22:** 167–74.
4. Allgulander C, *et al.* Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; **23:** 1245–52.
5. Rynn M, *et al.* Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety* 2008; **25:** 182–9.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage. Similar properties may also favour the use of serotonin and noradrenaline reuptake inhibitors such as duloxetine.

References.

1. Goldstein DJ, *et al.* Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; **63:** 225–31.
2. Detke MJ, *et al.* Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; **63:** 308–15.
3. Raskin J, *et al.* Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003; **64:** 1237–44.
4. Goldstein DJ, *et al.* Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 2004; **24:** 389–99.
5. Detke MJ, *et al.* Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 2004; **14:** 457–70.
6. Dugan SE, Fuller MA. Duloxetine: a dual reuptake inhibitor. *Ann Pharmacother* 2004; **38:** 2078–85.

Micturition disorders. Duloxetine is used[1-3] to increase urethral tone in the treatment of women with moderate to severe stress urinary incontinence (p.2180). A systematic review[3] concluded that duloxetine treatment reduced the frequency of incontinence episodes and significantly improved the patient's quality of life; however, it was unclear if these benefits were sustained. In addition, the review showed that adverse effects, particularly nausea, were common with duloxetine and led some patients to stop treatment.

1. McCormack PL, Keating GM. Duloxetine in stress urinary incontinence. *Drugs* 2004; **64:** 2567–73.
2. Ghoniem GM, *et al.* A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol (Baltimore)* 2005; **173:** 1647–53.
3. Mariappan P, *et al.* Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 14/09/06).

Pain. Duloxetine is used[1] in the treatment of diabetic peripheral neuropathic pain (p.6). It has also been tried[2] with some success in fibromyalgia (see Soft-tissue Rheumatism, p.13), a condition that responds poorly to analgesics and anti-inflammatory drugs.

1. Goldstein DJ, *et al.* Duloxetine vs placebo in patients with painful diabetic neuropathy. *Pain* 2005; **116:** 109–18.
2. Arnold LM, *et al.* A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 2004; **50:** 2974–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cymbalta; Duxetin; ***Austral.:*** Cymbalta; ***Belg.:*** Cymbalta; Yentreve; ***Braz.:*** Cymbalta; ***Chile:*** Cymbalta; Yentreve; ***Cz.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Denm.:*** Cymbalta; Yentreve; ***Fin.:*** Cymbalta; Yentreve; ***Fr.:*** Cymbalta; Yentreve; ***Ger.:*** Cymbalta; Yentreve; ***Gr.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Hong Kong:*** Cymbalta; ***Hung.:*** Cymbalta; ***India:*** Delok; ***Indon.:*** Cymbalta; ***Irl.:*** Cymbalta; Yentreve; ***Israel:*** Cymbalta; ***Ital.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Malaysia:*** Cymbalta; ***Mex.:*** Cymbalta; Yentreve; ***Neth.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Norw.:*** Cymbalta; Yentreve; ***Philipp.:*** Cymbalta; ***Port.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Rus.:*** Cymbalta (Симбалта); ***S.Afr.:*** Cymbalta; ***Singapore:*** Cymbalta; ***Spain:*** Cymbalta; Xeristar; ***Swed.:*** Cymbalta; Yentreve; ***UK:*** Cymbalta; Yentreve; ***USA:*** Cymbalta.

Escitalopram Oxalate

(BANM, USAN, rINNM)

S-Citalopram Oxalate; Escitalopram, Oxalate d'; Escitaloprami Oxalas; Lu-26-054/0; Oxalato de escitalopram. (+)-(*S*)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

Эсциталопрама Оксалат

$C_{20}H_{21}FN_2O,C_2H_2O_4$ = 414.4.

CAS — 128196-01-0 (escitalopram); 219861-08-2 (escitalopram oxalate).

ATC — N06AB10.

ATC Vet — QN06AB10.

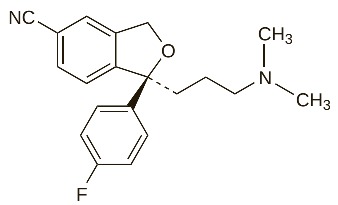

(escitalopram)

Adverse Effects and Precautions

As for Citalopram, p.385.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Pharmacokinetics

Escitalopram has similar pharmacokinetics to those of racemic citalopram (p.385).

◊ References.

1. Søgaard B, *et al.* The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects. *J Clin Pharmacol* 2005; **45:** 1400–6.
2. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007; **46:** 281–90.

Uses and Administration

Escitalopram, the *S*-enantiomer of citalopram (p.385), is an SSRI with actions and uses similar to those of fluoxetine (p.391). It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram.

In the treatment of **depression**, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary.

Escitalopram is also used in the treatment of **panic disorder** with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients.

Doses of escitalopram used in the treatment of **generalised anxiety disorder**, **social anxiety disorder**, and **obsessive-compulsive disorder** are similar to those used in depression.

Initial treatment with half the usual recommended dose and a lower maximum dose should be considered in elderly patients. Patients with hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 may also require lower doses (see below).

Escitalopram should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic impairment. Increases of 51% and 69% in the area under the concentration-time curve occurred in a single-dose study of escitalopram in patients with mild and moderate hepatic impairment (Child-Pugh score 5 or 6, and 7 to 9, respectively).[1] This study also reported that activity of the cytochrome P450 isoenzyme CYP2C19 was a better predictor of escitalopram clearance than the Child-Pugh classification.

UK licensed product information for escitalopram suggests that patients with mild to moderate hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 should receive an initial oral dose of 5 mg daily, increased to 10 mg daily after 2 weeks depending on response; more careful dose titration is advised in those with severe impairment. US licensed product information recommends 10 mg daily as a suitable dose for most patients with hepatic impairment.

1. Areberg J, *et al.* The pharmacokinetics of escitalopram in patients with hepatic impairment. *AAPS J* 2006; **8:** E14–E19.

Anxiety disorders. Escitalopram has been given in anxiety disorders (p.952) including panic disorder (p.952), obsessive-compulsive disorder (p.952), and social anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Stahl SM, *et al.* Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003; **64:** 1322–7.
2. Davidson JR, *et al.* Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004; **19:** 234–40.
3. Lader M, *et al.* Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19:** 241–8.
4. Kasper S, *et al.* Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; **186:** 222–6.
5. Stein DJ, *et al.* Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 2007; **23:** 701–11.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as escitalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Burke WJ, *et al.* Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; **63:** 331–6.
2. Wade A, *et al.* Escitalopram 10mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; **17:** 95–102.
3. Lepola UM, *et al.* Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003; **18:** 211–17.
4. Rapaport MH, *et al.* Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; **65:** 44–9.
5. Montgomery SA, *et al.* A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; **50:** 57–64.
6. Murdoch D, Keam SJ. Escitalopram: a review of its use in the management of major depressive disorder. *Drugs* 2005; **65:** 2379–2404.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aramix; Citalax; Lexapro; Lextor; Meridian; ***Austral.:*** Esipram; Lexapro; ***Austria:*** Cipralex; ***Belg.:*** Sipralexa; ***Braz.:*** Lexapro; ***Canad.:*** Cipralex; ***Chile:*** Celtium; Ectiban; Ipran; Lexapro; Neozentius; Zepaz; ***Cz.:*** Cipralex; ***Denm.:*** Cipralex; ***Fin.:*** Cipralex; ***Fr.:*** Seroplex; ***Ger.:*** Cipralex; ***Gr.:*** Cipralex; Entact; ***Hong Kong:*** Lexapro; ***Hung.:*** Cipralex; ***India:*** Cipralex; Recita; S-Citadep; ***Indon.:*** Cipralex; ***Irl.:*** Lexapro; ***Israel:*** Cipralex; ***Ital.:*** Cipralex; Entact; ***Malaysia:*** Lexapro; ***Mex.:*** Lexapro; ***Neth.:*** Cipralex; Lexapro; ***Norw.:*** Cipralex; ***NZ:*** Lexapro; ***Philipp.:*** Lexapro; ***Pol.:*** Lexapro; ***Port.:*** Cipralex; ***Rus.:*** Cipralex (Ципралекс); ***S.Afr.:*** Cipralex; ***Singapore:*** Lexapro; ***Spain:*** Cipralex; Entact; Esertia; ***Swed.:*** Cipralex; ***Switz.:*** Cipralex; ***Thai.:*** Lexapro; ***Turk.:*** Cipralex; ***UK:*** Cipralex; ***USA:*** Lexapro; ***Venez.:*** Lexapro.

Fluoxetine Hydrochloride

(BANM, USAN, rINNM)

Fluoksetiinihydrokloridi; Fluoksetin Hidroklorür; Fluoksetino hidrochloridas; Fluoksetyny chlorowodorek; Fluoxétine, chlorhydrate de; Fluoxetin-hidroklorid; Fluoxetin-hydrochlorid; Fluoxetinhydroklorid; Fluoxetini hydrochloridum; Hidrocloruro de fluoxetina; Lilly-103472; LY-110140. (±)-*N*-Methyl-3-phenyl-3-(α,α,α-trifluoro-*p*-tolyloxy)propylamine hydrochloride.

Флуоксетина Гидрохлорид

$C_{17}H_{18}F_3NO,HCl$ = 345.8.

CAS — 54910-89-3 (fluoxetine); 59333-67-4 (fluoxetine hydrochloride).

ATC — N06AB03.

ATC Vet — QN06AB03.

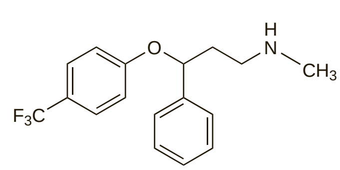

(fluoxetine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fluoxetine:

Distas; Green and whites; Greens; Limes; Pros; Zacs.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluoxetine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.5.

USP 31 (Fluoxetine Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in alcohol and in methyl alcohol; practically insoluble in ether. Store in airtight containers.

Adverse Effects

SSRIs such as fluoxetine are less sedating than tricyclic antidepressants and have fewer antimuscarinic and cardiotoxic effects. Adverse effects reported with SSRIs include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological adverse effects have included either anxiety, restlessness, nervousness, and insomnia, or drowsiness and fatigue; headache, tremor, dizziness, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome (p.416) have also occurred. The concern that SSRIs may be associated with increased suicidal ideation is discussed under Effects on Mental State, below.

Excessive sweating, pruritus, skin rashes, alopecia, photosensitivity, and urticaria have also been reported. Angioedema and anaphylactoid reactions have occurred. In some patients who have developed rashes while taking fluoxetine, systemic hypersensitivity reactions involving the lungs, kidneys, or liver, and possibly related to vasculitis, have developed; it has therefore been advised that fluoxetine therapy should be stopped in any patient who develops a skin rash.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. Hyperprolactinaemia and galactorrhoea have occurred, as have changes in blood sugar, in patients receiving SSRIs.

Arthralgia and myalgia have been reported and there have also been cases of orthostatic hypotension, yawning, urinary retention, and abnormal vision including blurred vision and mydriasis. Abnormal liver function tests have been reported rarely. SSRIs have occasionally been associated with bleeding disorders such as ecchymosis and purpura and other effects on the blood.

In overdosage nausea, vomiting, and excitation of the CNS are considered to be prominent features; death has been reported.

Incidence of adverse effects. In June 1992 the UK CSM had received 1236 reports of adverse effects with fluvoxamine (from about 280 000 prescriptions) compared with 2422 for fluoxetine (from about 480 000 prescriptions).[1] The overall patterns of adverse effects were similar but dermatological reactions were more likely with fluoxetine and gastrointestinal reactions with fluvoxamine. Reports of attempted suicide increased after adverse publicity about SSRIs in 1990, and the number of reports per million prescriptions were similar for the 2 drugs (25 for fluoxetine and 20 for fluvoxamine); at that time such figures were not considered disconcerting given that features of depression, including attempted suicide, can worsen after the introduction of any antidepressant (see also Effects on Mental State, below). A later review[2] by the CSM of the 5 SSRIs available in the UK (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that the SSRIs were broadly similar with respect to their safety profile. A list of adverse reactions common to all SSRIs was provided.

A review[3] of 1861 adverse reactions to citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline reported to the Swedish Adverse Drug Reactions Advisory Committee found that the most commonly reported reactions were neurological (22.4% of all reports), psychiatric (19.5%), and gastrointestinal (18.0%). Compared with other SSRIs, gastrointestinal symptoms were more common with fluvoxamine, psychiatric symptoms with sertraline, and dermatological symptoms with fluoxetine.

A more recent meta-analysis[4] has compared the adverse effect profile of fluoxetine with other antidepressants including the tricyclics and other SSRIs. The overall risk of any adverse effect with fluoxetine was less than that for the tricyclic antidepressants; however, there was no difference in risk when fluoxetine was compared with other SSRIs. When considering individual adverse reactions, fluoxetine was more likely to cause activating effects such as insomnia, agitation, tremor, and anxiety, and gastrointestinal disturbances such as nausea, vomiting, diarrhoea, weight loss, and anorexia than other antidepressants. In contrast, the tricyclics were associated with a greater risk of sedation, antimuscarinic effects (such as dry mouth, dizziness, and blurred vision), constipation, and weight gain, than fluoxetine.

1. CSM. Safety of fluoxetine (Prozac): comparison with fluvoxamine (Faverin). *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 27/11/05)
3. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Safety* 1999; **20:** 277–87.
4. Brambilla P, *et al.* Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry* 2005; **38:** 69–77.

Effects on the blood. Abnormalities in platelet aggregation were associated with fluoxetine given to a severely underweight patient.[1] Platelet activity returned to normal when fluoxetine was stopped. Fluoxetine was also suspected of being the cause of bruising in a patient whose blood clotting parameters were within normal limits.[2] Purpura and bruising have been reported to be the commonest adverse blood effects associated with fluoxetine, paroxetine, or sertraline although cases of thrombocytopenia have been recorded for all three antidepressants.[3] The suggested mechanism was inhibition of uptake of serotonin into platelets, thereby disrupting platelet aggregation; caution was recommended when treating patients with a history of bleeding disorders with SSRIs. However, a subsequent cohort study based on prescription-event monitoring provided only weak evidence of a link between the use of SSRIs and the development of bleeding disorders.[4] A similar study[5] found no evidence of a major increased risk of intracranial haemorrhage with the use of SSRIs, although smaller increases in risk could not be ruled out.

For mention of a possibly increased risk of gastrointestinal bleeding, see Effects on the Gastrointestinal Tract, below.

1. Alderman CP, *et al.* Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; **26:** 1517–19.
2. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; **30:** 786–8.
3. Anonymous. Bruising and bleeding with SSRIs. *Aust Adverse Drug React Bull* 1998; **17:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9808.pdf (accessed 14/08/08)
4. Layton D, *et al.* Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol* 2001; **57:** 167–76.
5. de Abajo FJ, *et al.* Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol* 2000; **50:** 43–7.

Effects on the cardiovascular system. SSRIs are not associated with the same degree of cardiotoxicity as the tricyclic antidepressants (see p.376), although orthostatic hypotension has been reported in some patients. A decrease in heart rate with ECG changes has been noted with fluvoxamine. However, a study[1] on long-term fluvoxamine treatment in 311 patients followed for 1 year revealed no significant effect on ECG findings compared with patients given placebo.

Concern over the use of sertraline in patients with coronary heart disease was raised after a report[2] of a 53-year-old man with a history of coronary heart disease who experienced attacks of sudden precordial chest pain on starting treatment with sertraline. The pain responded to glyceryl trinitrate. The manufacturers[3] pointed out that there had been no ECG changes confirming an ischaemic origin of the disorder in this patient and that in studies sertraline had had no demonstrable clinical effects on intraventricular conduction or ECG intervals. Furthermore, no significant changes in cardiovascular indices had been recorded in patients who had taken overdoses of up to 6 g of sertraline. It was suggested that this might have been an effect on the gastrointestinal tract possibly at the oesophageal level.

1. Hochberg HM, *et al.* Electrocardiographic findings during extended clinical trials of fluvoxamine in depression: one years experience. *Pharmacopsychiatry* 1995; **28:** 253–6.
2. Iruela LM. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1106.
3. Berti CA, Doogan DP. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1510–11.

Effects on the cerebrovascular system. There have been rare reports of cerebral ischaemic events associated with the use of SSRIs. In one case[1] a 57-year-old man receiving long-term treatment for atrial fibrillation and hypercholesterolaemia presented with a facial droop and slurred speech 3 days after starting paroxetine 20 mg twice daily. Symptoms resolved after anticoagulant therapy and stopping paroxetine but recurred when paroxetine was reintroduced at a dose of 10 mg twice daily. Paroxetine was stopped and no further episodes had occurred within 4 months at follow-up.

For a report that there is no major increased risk of intracranial haemorrhage associated with the SSRIs, see Effects on the Blood, above.

1. Manos GH, Wechsler SM. Transient ischemic attack reported with paroxetine use. *Ann Pharmacother* 2004; **38:** 617–20.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion (SIADH)* with *hyponatraemia* has been reported in patients receiving antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant, and usually involved elderly patients.[1] However, the results of a later study[2] have suggested that cases are more likely to occur with serotonergic antidepressants such as the SSRIs, clomipramine, and venlafaxine. Case reports of hyponatraemia in 16 patients treated with SSRIs have been summarised.[3] A further review[4] of reports on 15 patients with hyponatraemia with SIADH induced by fluoxetine (12 cases), fluvoxamine (2 cases), and paroxetine (1 case) showed that the risk was greatest during the early treatment phase. This is borne out by single-case reports[5-12] of hyponatraemia with SIADH in elderly patients receiving either citalopram, paroxetine, or sertraline. A retrospective study[13] of hyponatraemia associated with either fluoxetine or paroxetine use also showed the early onset of the condition and identified low bodyweight as being another risk factor for developing hyponatraemia. Not unexpectedly, replacing one SSRI with another has resulted in a recurrence of hyponatraemia; however, in one report,[14] the symptoms of hyponatraemia did not recur until about 16 months after switching SSRIs.

SSRI-associated *hyperprolactinaemia* has been reported.[15] Lactation and raised prolactin levels occurred in a teenager 3 days after fluoxetine was added to her existing therapy which included pimozide. Stopping fluoxetine had no effect on lactation, which only ceased after withdrawing pimozide. In another report,[16] hyperprolactinaemia and galactorrhoea in an elderly woman receiving fluoxetine resolved on stopping the drug.

Gynaecomastia, unrelated to prolactin concentrations, was associated with the start of fluoxetine therapy in a 49-year-old man. Symptoms subsided 10 months after withdrawing fluoxetine.[17]

Although SSRIs may be favoured for the management of depression in patients with diabetes, there is some evidence that sertraline and fluoxetine can induce *hypoglycaemia*.[18,19] Licensed product information for other SSRIs also warns of similar risks with these products.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Movig KLL, *et al.* Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. *Eur J Clin Pharmacol* 2002; **58:** 143–8.
3. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
4. Canadian Medical Association. Hyponatraemia and selective serotonin reuptake inhibitors. *Can Med Assoc J* 1996; **154:** 63.
5. Bluff DD. SIADH in a patient receiving sertraline. *Ann Intern Med* 1995; **123:** 811.
6. Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. *Med J Aust* 1996; **164:** 562.
7. Kessler J, Samuels SC. Sertraline and hyponatremia. *N Engl J Med* 1996; **335:** 524.
8. Robinson D, *et al.* SIADH—compulsive drinking or SSRI influence? *Ann Pharmacother* 1996; **30:** 885.
9. Monmany J, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by paroxetine. *Arch Intern Med* 1999; **159:** 2089–90.
10. Odeh M, *et al.* Severe life-threatening hyponatremia during paroxetine therapy. *J Clin Pharmacol* 1999; **39:** 1290–1.
11. Barclay TS, Lee AJ. Citalopram-associated SIADH. *Ann Pharmacother* 2002; **36:** 1558–63.
12. Flores G, *et al.* Severe symptomatic hyponatremia during citalopram therapy–a case report. *BMC Nephrol* 2004; **5:** 2.
13. Wilkinson TJ, *et al.* Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 1999; **47:** 211–17.
14. Arinzon ZH, *et al.* Delayed recurrent SIADH associated with SSRIs. *Ann Pharmacother* 2002; **36:** 1175–7.
15. Arya DK, *et al.* Lactation associated with fluoxetine treatment. *Aust N Z J Psychiatry* 1995; **29:** 697.
16. Peterson MC. Reversible galactorrhea and prolactin elevation related to fluoxetine use. *Mayo Clin Proc* 2001; **76:** 215–16.
17. Sahin M, *et al.* A possible case of gynecomastia with fluoxetine. *Ann Pharmacother* 2005; **39:** 1369.
18. Deeg MA, Lipkin EW. Hypoglycemia associated with the use of fluoxetine. *West J Med* 1996; **164:** 262–3.
19. Pollak PT, *et al.* Sertraline-induced hypoglycemia. *Ann Pharmacother* 2001; **35:** 1371–4.

Effects on the eyes. Symptoms of glaucoma that developed in a patient receiving fluoxetine subsided within 2 days of drug withdrawal.[1] Similar symptoms have been reported with citalopram,[2] fluvoxamine,[3] paroxetine,[2,4] and sertraline.[2] In some cases, the SSRI may have aggravated pre-existing glaucoma.[2,3] Intra-ocular pressure after doses of fluoxetine was recorded in 20 patients in a placebo-controlled crossover double-blind study.[5] Significant increases were found in all patients 2 hours after receiving fluoxetine by mouth; some patients still had raised intraocular pressure after 8 hours. A review of case reports documenting SSRI-associated changes in intra-ocular pressure concluded that such changes were difficult to predict;[6] however, it was recommended that those with risk factors for glaucoma, such as elderly patients with a family history, should be considered for ophthalmic consultations before starting an SSRI and regularly throughout treatment.

Anisocoria (uneven pupillary dilatation) has been reported[7] in a patient taking paroxetine and in another taking sertraline. It was noted that the UK CSM had received 21 reports of mydriasis associated with paroxetine but it appeared that noticeably asymmetrical mydriasis as seen in these 2 patients had not previously been reported.

1. Ahmad S. Fluoxetine and glaucoma. *DICP Ann Pharmacother* 1991; **25:** 436.
2. Anonymous. SSRIs and increased intraocular pressure. *Aust Adverse Drug React Bull* 2001; **20:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0102.pdf (accessed 14/08/08)
3. Jiménez-Jiménez FJ, *et al.* Aggravation of glaucoma with fluvoxamine. *Ann Pharmacother* 2001; **35:** 1565–6.
4. Eke T, Carr S. Acute glaucoma, chronic glaucoma, and serotoninergic drugs. *Br J Ophthalmol* 1998; **82:** 976–7.
5. Costagliola C, *et al.* Fluoxetine oral administration increases intraocular pressure. *Br J Ophthalmol* 1996; **80:** 678.
6. Costagliola C, *et al.* SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 2004; **18:** 475–84.
7. Barrett J. Anisocoria associated with selective serotonin reuptake inhibitors. *BMJ* 1994; **309:** 1620.

Effects on the gastrointestinal tract. A case-control study[1] suggested that treatment with SSRIs produced a moderately increased risk of upper gastrointestinal bleeding (adjusted relative risk 3.0). The risk was greatly increased if SSRIs were given with NSAIDs (relative risk 15.6). Treatment with SSRIs did not appear to increase the risk of ulcer perforation. The absolute risk of bleeding was estimated at one case per 8000 prescriptions, a risk similar to that of low-dose ibuprofen. A more recent cohort study[2] found a similar increase in risk. However, others have questioned whether such an association exists.[3]

A retrospective cohort study[4] in *elderly* patients found that there was an increasing risk of upper gastrointestinal bleeding as the extent of inhibition of serotonin reuptake by the antidepressant used increased. The effect was considered to be clinically important for patients with a high risk of such bleeding, namely the very elderly and those with a history of previous upper gastrointestinal bleeding.

Some[5] consider that gastroprotection is unlikely to be justified in those given SSRIs alone and furthermore there are no studies to suggest that gastroprotective drugs reduce the risk of SSRI-associated haemorrhage. However, it has been recommended[5] that such protection should be considered when SSRIs and NSAIDs are used together because of the increased risk.

1. de Abajo FJ, *et al.* Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999; **319:** 1106–9.
2. Dalton SO, *et al.* Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; **163:** 59–64.
3. Dunn NR, *et al.* Association between SSRIs and upper gastrointestinal bleeding. *BMJ* 2000; **320:** 1405–6.
4. van Walraven C, *et al.* Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; **323:** 655–8.
5. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ* 2005; **331:** 529–30.

Effects on the hair. A report[1] on 2 patients who had hair loss associated with the use of fluoxetine noted 4 other published cases and stated that, up to the end of 1991, the US manufacturers had received 498 reports of fluoxetine-associated alopecia.

1. Ogilvie AD. Hair loss during fluoxetine treatment. *Lancet* 1993; **342:** 1423.

Effects on the liver. Acute hepatitis occurred in 2 patients after several months of fluoxetine treatment;[1] it was noted that 5 other cases of acute hepatitis with fluoxetine had been reported.

Abnormal liver function tests were seen in a patient after a suicide attempt with sertraline and cefalexin.[2] The patient was then started on venlafaxine but, again abnormal liver function tests were noted. When these abnormal values had decreased, sertraline was restarted at therapeutic doses, with a subsequent increase in liver function tests. Values returned to normal once all medications were stopped. Auto-immune hepatitis has been reported after therapeutic doses of sertraline;[3] rechallenge in this case was also positive.

Hepatotoxicity has also been rarely associated with citalopram[4] and with paroxetine use.[5]

1. Cai Q, *et al.* Acute hepatitis due to fluoxetine therapy. *Mayo Clin Proc* 1999; **74:** 692–4.
2. Kim KY, *et al.* Acute liver damage possibly related to sertraline and venlafaxine ingestion. *Ann Pharmacother* 1999; **33:** 381–2.
3. Persky S, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. *Dig Dis Sci* 2003; **48:** 939–44.
4. López-Torres E, *et al.* Hepatotoxicity related to citalopram. *Am J Psychiatry* 2004; **161:** 923–4.
5. Azaz-Livshits T, *et al.* Paroxetine associated hepatotoxicity: a report of 3 cases and a review of the literature. *Pharmacopsychiatry* 2002; **35:** 112–15.

Effects on mental state. As early as 1990 there was concern that the SSRIs increased the risk of *suicidal ideation* after the publication of a case series of such events with fluoxetine.[1] Meta-analyses[2,3] performed around that time (criticism of statistical power notwithstanding[4]) did not confirm an increased risk and this was supported by the results of prescription-event monitoring.[5] Nevertheless, reports of suicidal ideation as well as suicide and self-harm have continued to be published for the SSRIs and the issue remains controversial. A subsequent meta-analysis[6] of 702 randomised controlled studies found an increased risk for attempted suicide in those taking SSRIs when compared with placebo but not when compared with tricyclic antidepressants.

Risk analysis of suicidal behaviour with any antidepressant is confounded by the rarity of suicide even in patients with depression, and by the possibility that such behaviour is a manifestation of the underlying depression. Furthermore, the more favourable safety profile of the SSRIs, particularly in overdosage (see Depression, p.373), when compared to the older MAOIs and tricyclic antidepressants may have resulted in the SSRIs being prescribed to those patients at greater risk of suicidal behaviour.

In 2003, the UK CSM established an Expert Working Group to address increasing public concerns regarding the safety of the SSRIs. The serotonergic antidepressants venlafaxine and mirtazapine were also included and the conclusions given below also apply to these drugs. In its final report[7] issued in December 2004, the Working Group concluded that the risk of suicide may increase in the early stages of treatment for depression in **adults** and consequently careful and frequent monitoring is important, particularly if a patient has worsening of symptoms or new symptoms after starting therapy. However, the Working Group noted that increases in the prescribing of SSRIs have not been associated with an increase in suicide rates, although they acknowledged that the interpretation of these findings was difficult. They could not rule out that there might be a modest increase in the risk of suicidal ideation and self-harm with the SSRIs when compared with placebo. However, there was insufficient evidence from clinical trials to determine any differences between the SSRIs as a group, or between the SSRIs and other antidepressants regarding the risk of suicidal behaviour; evidence from the General Practice Research database has suggested that there is no increased risk of such behaviour with the SSRIs when compared with the tricyclic antidepressants. The Working Group also concluded that the evidence for a relationship between suicidal behaviour and a change in dose was not robust; however, patients should be monitored for any new symptoms or worsening of disease around the time of any dose change.

The Expert Working Group of the CSM has also commented[7] on the use of SSRIs in **young adults**. They concluded that although there was no clear evidence of an increased risk of self-harm or suicidal thoughts in young adults of 18 years or over, such patients have a higher background risk of suicidal behaviour than older adults and consequently those treated with SSRIs should be closely monitored. Furthermore, the results of a meta-analysis undertaken by the FDA found that although the overall risk of suicide was not increased in adult patients receiving antidepressants, there was a non-significant trend toward increased risk with younger age. The FDA considered the trend sufficiently convincing to warn that, like children and adolescents, young adults aged between 18 and 24 years treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[8]

In 2003 the CSM recommended (on the basis of their Expert Working Group's finding) that paroxetine should not be used to treat depressive illness in **children under 18 years old**. Data from studies received by CSM in May 2003 failed to show that paroxetine was effective in depressive illness in this age group and indicated that the risk of harmful outcome, including self-harm and potentially suicidal behaviour, was 1.5 to 3.2 times greater in those who received paroxetine when compared with placebo.[9] Following a further review,[10] the CSM extended their recommendation to include the SSRIs citalopram, escitalopram, and sertraline; subsequent analysis had also associated these antidepressants with an unfavourable risk to benefit ratio in the treatment of depression in children under 18. The CSM also included fluvoxamine in their recommendation as its risk to benefit ratio was unassessable. Fluoxetine was not included and the CSM acknowledged that clinical trials had shown a favourable risk to benefit ratio for fluoxetine in the treatment of depression in young patients. The European Medicines Agency (EMEA) has also recommended that serotonergic antidepressants, including the SSRIs, should not be used in children and adolescents except within their approved indications,[11] but considered[12] that studies with fluoxetine in children and adolescents have shown a positive effect that outweighs any potential risks, and recommended that it should be licensed for use where needed, as an adjunct to psychological therapies in children from 8 years of age.

The FDA have not issued advice contra-indicating the use of these antidepressants in those under 18 years old in the USA, although they have stressed that all patients, including adolescents and children, should be closely monitored for worsening depression or suicidal behaviour, especially at the beginning of treatment.[13] They also comment that, apart from fluoxetine, the SSRIs are not licensed in the USA for the treatment of depression in young patients.

The use of SSRIs has been associated with the development of *akathisia*, *restlessness*, and *psychomotor agitation* such as an inability to sit or stand still, particularly in the first few weeks of treatment.[14] In some patients these symptoms have precipitated suicidal behaviour. However, the Expert Working Group of the CSM considered that it was not possible to draw any conclusions on the link between the development of these symptoms and the risk of suicidal behaviour, as such data were not included in the majority of cases.[7]

There have been suggested links between the use of fluoxetine and *irritability, hostility, and aggression*.[15] However, one review[16] noted that an unpublished analysis had indicated that patients taking fluoxetine for a variety of disorders were not more likely to be aggressive than those taking placebo. Prescription-event monitoring has also found no evidence to suggest that fluoxetine increases the frequency of aggression.[5]

Initiation of antidepressant therapy with paroxetine or sertraline has been associated with either worsening or a new onset of *flashback syndrome* in 2 patients with a history of lysergide abuse.[17]

There have been isolated reports of *memory loss* associated with the use of SSRIs.[18]

For further effects on mental function, see also under Withdrawal and under Mania in Precautions, below.

1. Teicher MH, *et al.* Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; **147:** 207–10.
2. Beasley CM, *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991; **303:** 685–92. Correction. *ibid.*; 968.
3. Goldstein DJ, *et al.* Analyses of suicidality in double-blind, placebo-controlled trials of pharmacotherapy for weight reduction. *J Clin Psychiatry* 1993; **54:** 309–16.
4. Li Wan Po A. Fluoxetine and suicide: meta-analysis and Monte-Carlo simulations. *Pharmacoepidemiol Drug Safety* 1993; **2:** 79–84.
5. Nakielny J. Fluoxetine and suicide. *Lancet* 1994; **343:** 1359.
6. Fergusson D, *et al.* Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; **330:**396. Correction. *ibid.*; 653.
7. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
8. Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356:** 2343–6.
9. MHRA. Safety of Seroxat (paroxetine) in children and adolescents under 18 years - contraindication in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th June, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019507.pdf (accessed 14/08/08)
10. MHRA. Selective Serotonin Reuptake Inhibitors - use in children and adolescents with major depressive disorder. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th December, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=2024&noSaveAs=1&Rendition=WEB (accessed 20/09/05)
11. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)
12. Committee for Medicinal Products for Human Use, European Medicines Agency. European Medicines Agency adopts a positive opinion for the use of Prozac in the treatment of children and adolescents suffering from depression (issued 6th June, 2006). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/20255406en.pdf (accessed 14/08/08)
13. The FDA Public Health Advisory. Worsening depression and suicidality in patients being treated with antidepressant medications (issued 22nd March, 2004). Available at: http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm (accessed 24/11/05)
14. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998; **12:** 192–214.
15. Anonymous. Fluoxetine, suicide and aggression. *Drug Ther Bull* 1992; **30**: 5–6.
16. Power AC, Cowen PJ. Fluoxetine and suicidal behaviour; some clinical and theoretical aspects of a controversy. *Br J Psychiatry* 1992; **161:** 735–41.
17. Markel H, *et al.* LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr* 1994; **125:** 817–19.
18. Joss JD, *et al.* Memory loss in a patient treated with fluoxetine. *Ann Pharmacother* 2003; **37:** 1800–3.

Effects on sexual function. Sexual dysfunction is often noted in patients with depression and may be due to their antidepressant medication or to the disease itself. Complaints include a decrease in or loss of libido, delayed ejaculation, erectile difficulty, or anorgasmia in men;[1] loss of libido, delayed orgasm, or anorgasmia have been reported in women.[1,2] Early identification is important since drug-induced sexual dysfunction is a common cause of non-compliance; in addition, it may adversely affect the quality of life of patients and hamper their recovery.[3,4]

It has been considered that sexual dysfunction occurs in up to 1.9% of patients taking fluoxetine, with impotence or ejaculatory problems occurring in less than 1% of patients.[5] However, these figures, which were based on information supplied by the US manufacturer, have been disputed[6,7] and the incidence of sexual dysfunction may be higher than the manufacturer's data suggest. Earlier studies and anecdotal reports quoted rates of 7.8 to 75% for sexual dysfunction with fluoxetine but it appears that only small numbers of men were studied.[8] A later review[9] also estimated the incidence of SSRI-induced sexual dysfunction at between 10 and 75%.

The incidence of sexual dysfunction may differ between types of antidepressants. A large, observational study[3] found the rate of sexual dysfunction to be higher with the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) and the SNRI venlafaxine than with bupropion or nefazodone. However, no significant difference in rate was found among the SSRIs as a group. The study also identified other risk factors for developing sexual dysfunction which included increasing age, the use of high doses, and use with other medications. Gender, race, and length of treatment were not associated with an increased risk.

Suggested[1,4,10] strategies for managing SSRI-induced sexual dysfunction include reducing the dosage of the SSRI or altering the timing of doses, or changing to another antidepressant. In some cases tolerance may develop, particularly if the dysfunction occurred early in treatment. One small study[11] has indicated that spontaneous improvement may occur even up to 6 months after the start of therapy.[11] Evidence of efficacy for drug treatments is mainly anecdotal. Cyproheptadine seems to have been tried most often, but the SSRI may become less effective (see Antihistamines, under Interactions, below) and patients should be monitored for worsening symptoms of depression.

The effects of the SSRIs on sexual function have been studied as a potential form of treatment for men with premature ejaculation (see Sexual Dysfunction in Uses, below).

1. Frye CB, Berger JE. Treatment of sexual dysfunction induced by selective serotonin-reuptake inhibitors. *Am J Health-Syst Pharm* 1998; **55:** 1167–9.
2. Feiger A, *et al.* Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996; **57** (suppl 2): 53–62.
3. Clayton AH, *et al.* Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002; **63:** 357–66.
4. Hirschfeld RMA. Long-term side effects of SSRIs: sexual dysfunction and weight gain. *J Clin Psychiatry* 2003; **64** (suppl 18): 20–4.
5. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1994; **272:** 242.
6. Balon R. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489.
7. Hopkins HS, Gelenberg AJ. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489–90.
8. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1490.
9. Gregorian RS, *et al.* Antidepressant-induced sexual dysfunction. *Ann Pharmacother* 2002; **36:** 1577–89.
10. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother* 1998; **32:** 1209–15.
11. Haberfellner EM, Rittmannsberger H. Spontaneous remission of SSRI-induced orgasm delay. *Pharmacopsychiatry* 2004; **37:** 127–30.

Effects on the skin. *Toxic epidermal necrolysis* developed in a 16-year-old girl 8 days after beginning fluvoxamine therapy.[1] Other drugs, which included metoclopramide, clorazepate, and clomipramine were discounted as possible causes.

Amitriptyline and fluoxetine have been implicated in the development of *atypical cutaneous lymphoid hyperplasia* in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[2] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to the improvement.

Bullous pemphigoid induced by fluoxetine has been reported in a 75-year-old woman.[3] Spontaneous resolution followed within 3 weeks of stopping the drug.

Paroxetine treatment has been associated with the development of *cutaneous vasculitis*, which involved several fingers, in a 20-year-old woman;[4] rechallenge was positive. On both occasions the patient recovered when paroxetine was withdrawn.

A severe *bullous reaction with full-thickness skin necrosis* has been reported in a 48-year-old woman after 6 months of treatment with sertraline.[5] The lesions required extensive skin grafts and recovery was prolonged, with drug-induced scleroderma developing in the affected area.

1. Wolkenstein P, *et al.* Toxic epidermal necrolysis after fluvoxamine. *Lancet* 1993; **342:** 304–5.
2. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.
3. Rault S, *et al.* Bullous pemphigoid induced by fluoxetine. *Br J Dermatol* 1999; **141:** 755–6.
4. Margolese HC, *et al.* Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry* 2001; **158:** 497.
5. Kirkup ME, *et al.* Delayed onset of bullous reaction with severe deep skin necrosis in association with sertraline. *Br J Dermatol* 2004; **150:** 164–6.

Epileptogenic effect. Generalised seizures have been reported in 2 patients with no history of seizures after starting fluoxetine therapy.[1,2] Although convulsions have been noted in patients taking fluvoxamine (see Incidence of Adverse Effects, p.399), a small clinical study involving 35 depressed epileptic patients[3] found no change in the number of seizures or in their nature when fluvoxamine was given in doses of up to 200 mg daily.

1. Weber JJ. Seizure activity associated with fluoxetine therapy. *Clin Pharm* 1989; **8:** 296–8.
2. Ware MR, Stewart RB. Seizures associated with fluoxetine therapy. *DICP Ann Pharmacother* 1989; **23:** 428.
3. Harmant J, *et al.* Fluvoxamine: an antidepressant with low (or no) epileptogenic effect. *Lancet* 1990; **336:** 386.

Extrapyramidal effects. Extrapyramidal effects, such as tics[1] and akathisia,[2,3] have been reported with fluoxetine. By 1993, the

UK CSM had received 39 reports of extrapyramidal reactions with paroxetine including 15 of dystonia of the face and mouth.[4] Although extrapyramidal effects might occur with other SSRIs, orofacial dystonias appeared to be more common with paroxetine. However, evidence from monitoring prescriptions within the UK showed that the overall incidence of extrapyramidal effects was the same for paroxetine as for other SSRIs.[5] Orofacial dystonias (teeth clenching) or dyskinesias (teeth grinding), resulting in severe damage to teeth and gums in many cases, have been reported[6] in 6 patients receiving fluoxetine, fluvoxamine, paroxetine, or sertraline. The authors concluded that these adverse effects were not specific for any particular SSRI. Analysis of spontaneous adverse reaction reports received by the national pharmacovigilance centre in The Netherlands found that there had been 41 reports of extrapyramidal effects associated with the SSRIs over a period of nearly 15 years;[7] parkinsonism and dystonia were the most frequently reported effects. Over the same time period, 14 reports had been received in total for other antidepressants. The authors commented that the results might be biased by the selective reporting of adverse reactions to the SSRIs.

Dyskinesia associated with withdrawal of citalopram and risperidone has been reported in a patient.[8]

The onset of akathisia may be linked to suicidal ideation; for further details, see Effects on Mental State, above.

1. Eisenhauer G, Jermain DM. Fluoxetine and tics in an adolescent. *Ann Pharmacother* 1993; **27:** 725–6.
2. Lipinski JF, *et al.* Fluoxetine-induced akathisia: clinical and theoretical implications. *J Clin Psychiatry* 1989; **50:** 339–42.
3. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry* 1991; **52:** 491–3.
4. CSM/MCA. Dystonia and withdrawal symptoms with paroxetine (Seroxat). *Current Problems* 1993; **19:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Choo V. Paroxetine and extrapyramidal reactions. *Lancet* 1993; **341:** 624.
6. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. *Hum Psychopharmacol Clin Exp* 1995; **10:** 215–19.
7. Schillevoort I, *et al.* Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; **17:** 75–9.
8. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; **34:** 269.

Hypersensitivity. Hypersensitivity reactions to SSRIs are well documented. Interestingly, despite structural dissimilarities, there have been a few reports of cross-sensitivity between SSRIs. A young man who had previously developed a maculopapular rash while taking paroxetine suffered a similar reaction after starting sertraline;[1] both episodes resolved after the SSRI was withdrawn.

1. Warnock CA, Azadian AG. Cross-sensitivity between paroxetine and sertraline. *Ann Pharmacother* 2002; **36:** 631–3.

Hyponatraemia. See Effects on the Endocrine System, above.

Overdosage. SSRIs are generally regarded as being less toxic in overdosage than tricyclic antidepressants or MAOIs. A review[1] of SSRI overdosage, covering the period 1985 to 1997, noted that there had been remarkably few fatal overdoses when taken alone. Moderate overdoses (up to about 30 times the usual daily dose) were generally associated with minor symptoms at most; only at very high doses (more than 75 times the usual daily dose) did more serious effects such as seizures, ECG abnormalities, and decreased consciousness tend to occur. Toxicity was greatly increased, however, when overdoses of SSRIs were taken with alcohol or other drugs. There was no evidence of a difference in the various SSRIs with respect to safety in overdosage. The results of a more recent cohort study[2] have also confirmed the relative safety of the SSRIs in overdosage. However, the study also found that citalopram was potentially more cardiotoxic than other SSRIs in overdose, causing significant prolongation of the QT interval (see below). In addition, serotonin syndrome was noted as being a common feature of SSRI overdosage although in most cases symptoms were not severe or life-threatening.

- Fatal overdose was reported with *citalopram* in 6 patients,[3] although the suggested cause of death as cardiac dysfunction rather than seizures was disputed.[4] Nonetheless, cases[2,5] of cardiac abnormalities (including prolongation of the QT interval) associated with citalopram overdose have continued to be reported, and routine ECG monitoring may be necessary in the management of overdosage. Some authors consider that a metabolite, didemethylcitalopram, rather than citalopram itself, may be responsible for the cardiotoxicity seen with citalopram overdose.[5] At therapeutic doses, concentrations of didemethylcitalopram are much lower than those of citalopram and, in general, significant cardiotoxicity is not seen; however, in overdosage the amount of didemethylcitalopram may be sufficient to induce cardiac conduction abnormalities.
- A report involving 87 cases in which *fluoxetine* was taken in overdosage without other drugs found that the main symptoms were tachycardia, drowsiness, tremor, and nausea and vomiting.[6] These were considered relatively minor, and were of short duration, and supportive care was considered to be the only intervention necessary.
- Of 41 cases of self-poisoning with *fluvoxamine*, only one patient died and even here fluvoxamine was not implicated.[7] Prolonged cerebral depression occurred in a patient after fluvoxamine overdose,[7] but this may have been due to an interaction with temazepam which the patient also took in overdose.
- One hour after taking 2 g of *sertraline* in a suicide attempt a 42-year-old woman was flushed, angry, emotionally labile, and easily distracted but not psychotic.[8] Apart from watery bowel movements recovery was mainly uneventful after treatment with gastric lavage, oral activated charcoal with sorbitol, and intravenous hydration. In another case,[9] symptoms resembling serotonin syndrome developed in a 51-year-old woman after an overdose attempt with sertraline; it was believed that the patient may have taken as much as 8 g of sertraline. She recovered with supportive treatment. Abnormal liver function tests have also been noted after a suicide attempt with sertraline (see Effects on the Liver, above).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

1. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry* 1998; **59** (suppl 15): 42–8.
2. Isbister GK, *et al.* Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; **42:** 277–85.
3. Öström M, *et al.* Fatal overdose with citalopram. *Lancet* 1996; **348:** 339–40.
4. Brion F, *et al.* Fatal overdose with citalopram? *Lancet* 1996; **348:** 1380.
5. Catalano G, *et al.* QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clin Neuropharmacol* 2001; **24:** 158–62.
6. Borys DJ, *et al.* Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 1992; **10:** 115–20.
7. Banerjee AK. Recovery from prolonged cerebral depression after fluvoxamine overdose. *BMJ* 1988; **296:** 1774.
8. Brown DF, Kerr HD. Sertraline overdose. *Ann Pharmacother* 1994; **28:** 1307.
9. Brendel DH, *et al.* Massive sertraline overdose. *Ann Emerg Med* 2000; **36:** 524–6.

Treatment of Adverse Effects

Treatment of overdosage with an SSRI involves appropriate symptomatic and supportive therapy. Activated charcoal may be given by mouth if the amount ingested was large (see below) and treatment is within an hour of ingestion. Dialysis, haemoperfusion, exchange transfusion, and measures to increase urine production are considered unlikely to be of benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with SSRIs to be uncertain. However, it is suggested that oral activated charcoal may be considered if this is given within 1 hour of ingestion and the quantity of SSRI exceeds the following amount:

- citalopram: 5 mg/kg (adult); 5 mg/kg (child)
- escitalopram: 2.5 mg/kg (adult); 2.5 mg/kg (child)
- fluoxetine: 500 mg (adult); 5 mg/kg (child)
- fluvoxamine: 1 g (adult); 100 mg (child)
- paroxetine: 600 mg (adult); 5 mg/kg (child)
- sertraline: 1 g (adult); 10 mg/kg (child)

Precautions

Because of their epileptogenic effect SSRIs should be used with caution in patients with epilepsy or a history of such disorders (and should be avoided if the epilepsy is poorly controlled). Treatment should be stopped if seizures develop or when there is an increase in seizure frequency. Care is advised in patients receiving ECT as prolonged seizures have occurred rarely. SSRIs should also be used with caution in patients with cardiac disease or a history of bleeding disorders. Although SSRIs are preferred to tricyclics for the treatment of depression in patients with diabetes, they may alter glycaemic control and therefore caution is also warranted in diabetic subjects. SSRIs should be used with caution in patients with angle-closure glaucoma.

Fluoxetine should be stopped in patients who develop a rash since systemic effects, possibly related to vasculitis, have occurred in such patients. Fluoxetine undergoes hepatic metabolism and should be used with caution and in reduced doses in patients with impaired hepatic function.

Patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. For a discussion of the concern that SSRIs may increase suicidal ideation, and concerns about their use for depression in children and adolescents, see Effects on Mental State in Adverse Effects, above. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders. If SSRIs are given for the depressive component of bipolar disorder, mania may be precipitated. Symptoms may also worsen during the initial treatment of panic disorder with SSRIs.

SSRIs may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Some licensed product information recommends reduced or less frequent dosage of SSRIs for elderly patients.

SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms although this may be unnecessary for fluoxetine because of its long half-life.

Abuse. There have been occasional reports of individuals abusing fluoxetine.[1,2]

1. Pagliaro LA, Pagliaro AM. Fluoxetine abuse by an intravenous drug user. *Am J Psychiatry* 1993; **150:** 1898.
2. Tinsley JA, *et al.* Fluoxetine abuse. *Mayo Clin Proc* 1994; **69:** 166–8.

Blood disorders. For a reference recommending cautious use of SSRIs in patients with a history of bleeding disorders, see Effects on the Blood in Adverse Effects, above.

Breast feeding. The American Academy of Pediatrics[1] considers that all antidepressants, including SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) are drugs whose effect on nursing infants is unknown but may be of concern. In addition, most licensed drug information advises that SSRIs should be avoided by the mother during breast feeding.

- *Citalopram* and its metabolites have been detected in breast milk; however, in one study, the plasma concentrations in exposed infants were either very low or undetectable and no adverse effects were reported.[2] In another study, 3 out of 31 breast-fed infants whose mothers were taking citalopram had adverse effects, specifically one case each of colic, decreased feeding, and irritability.[3] However, there was no significant increase in the risk of adverse events in this group of infants when compared with either infants of depressed mothers not taking citalopram, or infants of healthy controls.
- Symptoms of colic were reported[4] in a 6-week-old infant whose mother was taking *fluoxetine* 20 mg daily. The concentrations of fluoxetine and its active metabolite norfluoxetine were 69 nanograms/mL and 90 nanograms/mL respectively in breast milk, and 340 nanograms/mL and 208 nanograms/mL respectively in the infant's plasma. The infant's symptoms resolved when he was formula fed. Postnatal weight gain has been reduced in infants exposed to fluoxetine during breast feeding, although in all cases the reduction was less than 2 standard deviations below the norm.[5] In another report,[6] several seizure-like episodes occurred in a breast-fed infant whose mother was taking fluoxetine in addition to carbamazepine and buspirone; however, plasma drug concentrations in the infant were significant only for fluoxetine and norfluoxetine. In a study[7] of 10 women taking fluoxetine while breast feeding 11 infants, breast milk concentrations of fluoxetine ranged from 17.4 to 293 nanograms/mL and of norfluoxetine from 23.4 to 379.1 nanograms/mL. No adverse effects were noted in the infants. Similar levels have occurred in other breast-fed infants without any apparent drug-induced adverse effects.[8-10] Fluoxetine and norfluoxetine were detected in the milk of 14 nursing women.[11] Blood samples were taken from 9 of the infants in the study, and of these, fluoxetine was detected in the plasma of 5 and norfluoxetine in 7. Although it was felt that many infants would tolerate the mean combined dose of fluoxetine and norfluoxetine transmitted via breast milk in this study, there was considerable interpatient variability in estimated infant dose and caution should be exercised; neonates in particular exhibited higher concentrations of norfluoxetine than older infants. Moreover, since both fluoxetine and norfluoxetine have long half-lives, neonates already exposed *in utero* may have an additional risk of adverse effects during breast feeding.
- The excretion of *fluvoxamine* into breast milk was studied[12] in a woman who had been receiving fluvoxamine maleate 100 mg twice daily for 2 weeks. The concentration of fluvoxamine base 4.75 hours after a dose was 310 nanograms/mL in maternal plasma and 90 nanograms/mL in breast milk. It was estimated that an infant would ingest only 0.5% of the daily maternal intake. It was considered that these data supported the notion that the use of fluvoxamine by nursing mothers posed little risk to the infant. A subsequent study[13] found no detectable drug levels in the plasma of breast-fed infants

exposed to fluvoxamine; the authors suggested that fluvoxamine was a reasonable choice for nursing mothers requiring treatment for depression.

- Although *paroxetine* was detected in measurable concentrations in the breast milk of a group of 10 nursing mothers receiving paroxetine no adverse effects were reported in any of their breast-fed infants.[14] Paroxetine could not be detected in the plasma of 7 of the 8 infants from whom samples were obtained and in the other infant, concentrations were not quantifiable. Another study involving 7 women suggested that the dose of paroxetine to suckling infants would be 0.7 to 2.9% of the weight-adjusted maternal dose.[15] A later study[13] also found no detectable drug levels in the plasma of breast-fed infants exposed to paroxetine; the authors suggested that paroxetine was a reasonable choice for nursing mothers requiring treatment for depression. In a prospective cohort study, weight gain at 6 and 12 months of age in infants whose mothers took paroxetine during breast feeding was not adversely affected when compared with the infants of mothers who either did not breast feed or breast fed without taking any drugs during lactation;[16] in addition, there was no difference in reaching the usual developmental milestones between the infants of the 3 groups.
- Plasma concentrations of *sertraline* were undetectable in a breast-fed infant despite the presence of concentrations in the mother's breast milk ranging from 8.8 to 43 nanograms/mL over a 24-hour period.[17] However, the authors pointed out that metabolite levels were not measured and that sertraline may have been present in the infant at a concentration below the level of sensitivity of the assay. Other studies[13,18-21] have detected desmethylsertraline in breast milk, which was also detected in the plasma of some of the infants in a number of the studies[13,18,20,21] but not all.[19] The authors of at least one study[13] suggested that sertraline was a reasonable choice for nursing mothers requiring treatment for depression. In addition, some authors recommend expressing and discarding breast milk 8 to 9 hours after a maternal dose, when levels of desmethylsertraline and sertraline are maximal, in order to significantly reduce infant exposure to sertraline.[21]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Heikkinen T, *et al.* Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 2002; **72:** 184–91.
3. Lee A, *et al.* Frequency of infant adverse events that are associated with citalopram use during breast-feeding. *Am J Obstet Gynecol* 2004; **190:** 218–21.
4. Lester BM, *et al.* Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1253–5.
5. Chambers CD, *et al.* Weight gain in infants breastfed by mothers who take fluoxetine. *Pediatrics* 1999; **104:** 1120–1.
6. Brent NB, Wisner KL. Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. *Clin Pediatr (Phila)* 1998; **37:** 41–4.
7. Taddio A, *et al.* Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996; **36:** 42–7.
8. Isenberg KE. Excretion of fluoxetine in human breast milk. *J Clin Psychiatry* 1990; **51:** 169.
9. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 1992; **89:** 676–7.
10. Yoshida K, *et al.* Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *Br J Psychiatry* 1998; **172:** 175–9.
11. Kristensen JH, *et al.* Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 521–7.
12. Wright S, *et al.* Excretion of fluvoxamine in breast milk. *Br J Clin Pharmacol* 1991; **31:** 209.
13. Hendrick V, *et al.* Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 2001; **179:** 163–6.
14. Begg EJ, *et al.* Paroxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 142–7.
15. Öhman R, *et al.* Excretion of paroxetine into breast milk. *J Clin Psychiatry* 1999; **60:** 519–23.
16. Merlob P, *et al.* Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel. *Eur J Pediatr* 2004; **163:** 135–9.
17. Altshuler LL, *et al.* Breastfeeding and sertraline: a 24-hour analysis. *J Clin Psychiatry* 1995; **56:** 243–5.
18. Stowe ZN, *et al.* Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry* 1997; **154:** 1255–60.
19. Kristensen JH, *et al.* Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998; **45:** 453–7.
20. Epperson N, *et al.* Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am J Psychiatry* 2001; **158:** 1631–7.
21. Stowe ZN, *et al.* The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003; **64:** 73–80.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, above.

Diabetes mellitus. A patient with type 1 diabetes mellitus experienced a loss of hypoglycaemic awareness following the start of treatment with fluoxetine.[1] Awareness returned on tapered withdrawal of fluoxetine. Changes in blood sugar concentrations may occur in patients with diabetes treated for depression with SSRIs (see also Effects on the Endocrine System, above); however, these may represent an improvement in glycaemic control.[2]

1. Sawka AM, *et al.* Loss of hypoglycemia awareness in an adolescent with type 1 diabetes mellitus during treatment with fluoxetine hydrochloride. *J Pediatr* 2000; **136:** 394–6.
2. Lustman PJ, *et al.* Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000; **23:** 618–23.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressants can also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects. These are more pronounced with older antidepressants such as the tricyclic antidepressants than with the SSRIs, but a comparative study[3] of fluoxetine (an SSRI) and dosulepin (a tricyclic) in healthy subjects showed a similar but apparently small potential for impairing psychomotor and driving performance. A later epidemiological study[4] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs.

In the UK, the Driver and Vehicle Licensing Authority[5] considers that drugs such as SSRIs may have fewer adverse effects on drivers than antidepressants with pronounced antimuscarinic or antihistaminic adverse effects, such as tricyclic antidepressants. However, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should also cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
3. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
4. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Gastrointestinal disorders. For the opinion that the SSRIs may produce a clinically important increase in the risk of upper gastrointestinal bleeding in patients with a high risk of such bleeding, see under Effects on the Gastrointestinal Tract, above.

Glaucoma. For reference to SSRIs precipitating or exacerbating symptoms of glaucoma, see Effects on the Eyes, above.

Mania. Hypomania or mania have been reported with the SSRIs; consequently, UK licensed drug information recommends that SSRIs should be withdrawn in any patient entering a manic phase.

Fluvoxamine was associated with manic behaviour in 8 patients who were being treated for major depression;[1] 3 also had obsessive-compulsive disorder. Daily doses of fluvoxamine ranged from 75 to 300 mg and duration of therapy to development of manic behaviour from 2 to 6 weeks. The authors were unable to determine whether fluvoxamine had induced mania or unmasked latent bipolar disorder in these patients. However, they recommended that fluvoxamine-treated patients should be monitored for manic behaviour.

Symptoms of manic behaviour also developed in a 7-year-old girl after taking *sertraline* for about 2 weeks for the treatment of major depression.[2] She recovered within a few weeks of stopping sertraline.

1. Dorevitch A, *et al.* Fluvoxamine-associated manic behavior: a case series. *Ann Pharmacother* 1993; **27:** 1455–7.
2. Ghaziuddin M. Mania induced by sertraline in a prepubertal child. *Am J Psychiatry* 1994; **151:** 944.

Pregnancy. In an early prospective study[1] comparing 128 pregnant women exposed to a mean daily dose of about 26 mg of fluoxetine during their first trimester with control groups receiving tricyclic antidepressants or non-teratogens, the incidence of **neonatal malformations** was similar in all groups and did not exceed that in the general population. However, there was a tendency to a higher incidence of **miscarriages** in the groups receiving fluoxetine or tricyclics. A more recent prospective study[2] comparing 228 pregnant women taking fluoxetine with a control group taking non-teratogens also failed to find a significant increased incidence in major fetal abnormalities in the fluoxetine group; it also did not reveal an increased risk of miscarriage. There was an increase in the incidence of minor fetal abnormalities in infants exposed to fluoxetine during the first trimester. Also, infants exposed to fluoxetine during the third trimester experienced more perinatal complications such as prematurity, low full-term birth-weight and length, and poor neonatal adaptation compared with infants exposed only during the first and second trimesters. However, the design of this study was criticised[3] because of several methodological problems such as unmatched controls and a higher maternal age in the fluoxetine group, which may partly explain the excess of poor perinatal outcomes.

The manufacturer evaluated the outcome of 796 pregnancies in which the mother received fluoxetine during the first trimester and considered that it was unlikely that fluoxetine increased the risk of miscarriage or fetal malformation.[4] A prospective controlled study[5] on pregnancy outcome in women exposed to fluvoxamine, paroxetine, or sertraline also found that, when used in recommended doses, there appeared to be no increase in the risk of major congenital malformations, miscarriages, or still-births when compared with women exposed to non-teratogens. Nonetheless, the results from a more recent meta-analysis which included some of the above studies have suggested that maternal exposure to antidepressant treatment (specifically SSRIs, tricyclics, nefazodone, trazodone, or venlafaxine) may significantly increase the risk of miscarriage in comparison to women not exposed to antidepressants.[6] However, the authors acknowledged that the underlying depression itself might be a contributing factor to the increased risk.

There is some evidence that paroxetine may be more teratogenic than other antidepressants. The manufacturer *GlaxoSmithKline* has reported[7] that overall the data from a retrospective US epidemiological study and a study using the Swedish national birth registry have indicated that there was a twofold increase in cardiovascular malformations, particularly ventricular septal defects, in infants born to mothers who had taken paroxetine during pregnancy compared with the general population. However, whereas the US study also showed an overall risk of major congenital malformations (inclusive of the cardiovascular defects), the Swedish study found no such increase.

Maternal use of SSRIs has been associated with **neonatal complications**. CNS toxicity and an increased heart rate were reported in a neonate whose mother had received 20 mg of fluoxetine daily throughout most of her pregnancy.[8] The neonate's symptoms resolved 96 hours after delivery. In another neonate whose mother took up to 30 mg daily of fluoxetine throughout the third trimester cardiac arrhythmias were noted.[9] In a matched-control study[10] the rate of complications after delivery in 55 infants exposed to paroxetine during the third trimester was higher than in a control group who had been exposed to paroxetine or non-teratogenic agents during the first or second timesters. Complications that occurred in the infants exposed in the third trimester included respiratory distress (9), hypoglycaemia (2), bradycardia (1), jaundice (1), and suckling problems (1). More recently, another matched-control study[11] has suggested that exposure to SSRIs (in this case fluoxetine, paroxetine, and sertraline) after the 20th week of gestation may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Of 377 infants with a confirmed diagnosis of PPHN, the mothers of 14 (3.7%) had taken an SSRI after the 20th week of gestation, compared with only 6 out of 836 infants (0.7%) in the matched-control group. Although these figures represent about a sixfold increase in the risk of PPHN in infants exposed to SSRIs *in utero*, the absolute risk remains relatively low (about 6 to 12 per 1000 women).

A number of reports[2,12-16] have described symptoms such as jitteriness, irritability, sleep disturbances, and altered muscle tone in neonates who had been exposed to SSRIs *in utero*, especially during the third trimester; in the majority of cases the symptoms are mild and self-limiting. Although withdrawal symptoms have been reported with most SSRIs, they have been more commonly reported in those neonates exposed to paroxetine.[17] More recently, some authors have used the term neonatal behavioural syndrome to refer to such symptoms.[15] It is unclear whether the symptoms represent a withdrawal syndrome or direct serotonin toxicity;[14,16,18] however, it has been suggested by some that *in-utero* exposure to SSRIs with a short half-life such as paroxetine may lead to a neonatal withdrawal syndrome whereas exposure to an SSRI with a long half-life, particularly fluoxetine, may manifest as neonatal serotonin toxicity.[15] There have been case reports of intraventricular haemorrhage in neonates whose mothers took SSRIs during late pregnancy but there is currently not enough data to determine whether the frequency of such bleeds in infants exposed to SSRIs is higher than normal.[16]

The effects of fluoxetine on fetal **neurodevelopment** were studied[19] in 55 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to fluoxetine *in utero* during the first trimester compared with those exposed to tricyclic antidepressants or adverse developmental influences. A subsequent study indicated that exposure to fluoxetine or tricyclic antidepressants throughout gestation did not appear to affect cognition adversely.[20] In another follow-up study, subtle differences in motor development and control, in particular tremulousness and inappropriate fine motor movements, were noted in the infants and children of depressed mothers who had taken SSRIs during pregnancy when compared with the infants of depressed mothers who had not taken any medication.[21] However, in other measures of mental development there were no observed differences between the two groups.

1. Pastuszak A, *et al.* Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993; **269:** 2246–8.
2. Chambers CD, *et al.* Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; **335:** 1010–15.
3. Robert E. Treating depression in pregnancy. *N Engl J Med* 1996; **335:** 1056–8.
4. Goldstein DJ, *et al.* Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997; **89:** 713–18.
5. Kulin NA, *et al.* Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998; **279:** 609–10.

6. Hemels MEH, *et al.* Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; **39:** 803–9.
7. GlaxoSmithKline USA. Important prescribing information (issued December 2005). Available at: http://www.fda.gov/medwatch/safety/2005/Paxil_DHCP%20Letter_Dec%202005.pdf (accessed 17/01/06)
8. Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. *Pediatrics* 1993; **92:** 721–2.
9. Abebe-Campino G, *et al.*. Cardiac arrhythmia in a newborn infant associated with fluoxetine use during pregnancy. *Ann Pharmacother* 2002; **36:** 533–4.
10. Costei AM, *et al.* Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002; **156:** 1129–32.
11. Chambers CD, *et al.* Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006; **354:** 579–87.
12. Nijhuis IJM, *et al.* Withdrawal reactions of a premature neonate after maternal use of paroxetine. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F77.
13. Stiskal JA, *et al.* Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F134–F135.
14. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004; **113:** 368–75.
15. Moses-Kolko EL, *et al.* Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; **293:** 2372–83.
16. Nordeng H, Spigset O. Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. *Drug Safety* 2005; **28:** 565–81.
17. Sanz EJ, *et al.* Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet* 2005; **365:** 482–7.
18. Isbister GK, *et al.* Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F147–F148.
19. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
20. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
21. Casper RC, *et al.* Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; **142:** 402–8.

Surgery. In patients undergoing orthopaedic surgery, the risk of perioperative blood loss was significantly increased in those taking serotonergic antidepressants (specifically clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine) when compared with those on non-serotonergic antidepressants.[1] In addition, there was a significant increase in the need for blood transfusion during surgery in those on serotonergic antidepressants compared with those not receiving antidepressant medication.

1. Movig KLL, *et al.* Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; **163:** 2354–8.

Withdrawal. Withdrawal reactions have been reported for all SSRIs and the related antidepressants mirtazapine and venlafaxine on dosage reduction or stopping treatment, although the frequency of such reactions may vary.[1-5] Paroxetine and venlafaxine have been associated with withdrawal reactions more often than other serotonergic antidepressants; in the case of paroxetine this may be due, in part, to its short half-life. Fluvoxamine also has a short half-life and has been shown in some studies to have a high risk of withdrawal reactions. The apparent lower risk of withdrawal reactions with fluoxetine may be due to its long half-life. Other factors that increase the risk of withdrawal reactions include abrupt withdrawal, the use of high doses, and prolonged therapy.[5]

In general, withdrawal reactions tend to occur within 3 days of stopping an SSRI or related antidepressant,[1,4,5] although a delay of up to 2 weeks may be noted with fluoxetine.[5] Common symptoms include dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety, and sleep disorders. In some cases withdrawal symptoms may be severe and disabling. There has also been a report[6] of 2 patients without a history of major psychiatric disorder who developed severe behavioural symptoms when paroxetine was withdrawn. Withdrawal was abrupt in one patient and more gradual, over a 12-day period, in the other. Symptoms were mainly hypomanic over the first few days, followed by a period of escalated ego-dystonic aggression, behavioural dyscontrol, and suicidal ideation.

Antidepressant dose tapering appears to reduce the frequency and severity of withdrawal reactions.[5] The *BNF* recommends that any antidepressant, including an SSRI, that has been taken regularly for 8 weeks or more should be stopped gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The withdrawal syndrome of the SSRIs is not considered to be a consequence of dependence.[4,5]

See also Extrapyramidal Effects under Adverse Effects, above. For debate about whether a withdrawal syndrome exists in neonates whose mothers have received SSRIs see Pregnancy, above.

1. Price JS, *et al.* A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996; **42:** 757–63.
2. Adverse Drug Reactions Advisory Committee (ADRAC). SSRI's and withdrawal syndrome. *Aust Adverse Drug React Bull* 1996; **15:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9602.htm (accessed 14/08/08)
3. Coupland NJ, *et al.* Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol* 1996; **16:** 356–62.
4. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
5. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
6. Bloch M, *et al.* Severe psychiatric symptoms associated with paroxetine withdrawal. *Lancet* 1995; **346:** 57.

Interactions

SSRIs interact with other drugs mainly as a result of their inhibitory activity on hepatic cytochrome P450 isoenzymes. Individual SSRIs do not all exhibit the same degree of inhibition nor do they react with the same isoenzymes. The drugs inhibited by specific SSRIs depends on the isoenzyme affected.

As SSRIs have occasionally been associated with bleeding disorders and other effects on the blood, caution is advised when they are given with drugs known to affect platelet function.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the *serotonin syndrome* (see p.416) may occur. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. SSRIs should not generally be given to patients receiving MAOIs or for at least 2 weeks after their use. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI. At least one week should elapse between withdrawing an SSRI and starting any drug liable to provoke a serious reaction (e.g. phenelzine); in the case of the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine 5 weeks, because of their longer half-lives. (For fluoxetine, the interval may need to be further extended if therapy has been prolonged or if high doses have been given.) Adverse effects such as the serotonin syndrome may also occur when the SSRIs are given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Further details concerning some of these interactions, and others, are given below.

◊ References.

1. Mitchell PB. Drug interactions of clinical significance with selective serotonin reuptake inhibitors. *Drug Safety* 1997; **17:** 390–406.
2. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
3. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; **3:** 13–37.

Antibacterials. Rapid development of delirium was reported[1] in a patient when *clarithromycin* was added to his existing regimen of fluoxetine and nitrazepam. It was suggested that his delirium was a result of increased plasma-fluoxetine concentrations produced by the inhibition of cytochrome P450 enzymes by clarithromycin. Serotonin syndrome developed in a patient given *erythromycin* in addition to sertraline;[2] this was attributed to inhibition of CYP3A4 by the antibacterial, resulting in accumulation of the SSRI. There have also been reports of serotonin syndrome when *linezolid* was given with fluoxetine,[3] sertraline,[4] paroxetine,[5] and citalopram[6]; in the latter case the patient developed complications including metabolic acidosis and ultimately fatal cardiac arrest.[6] Reviews of serotonin syndrome associated with the use of linezolid suggest that SSRIs are the interacting drug most often implicated.[7,8] However, it has been suggested that if warranted, linezolid may be given to patients receiving SSRIs provided the patient is carefully monitored for signs and symptoms of serotonin syndrome.[8]

1. Pollak PT, *et al.* Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 1995; **29:** 486–8.
2. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. *Pharmacotherapy* 1999; **19:** 894–6.
3. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. *Am J Health-Syst Pharm* 2007; **64:** 59–62.
4. Lavery S, *et al.* Linezolid and serotonin syndrome. *Psychosomatics* 2001; **42:** 432–4.
5. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis* 2002; **34:** 1651–2.
6. Bernard L, *et al.* Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis* 2003; **36:** 1197.
7. Lawrence KR, *et al.* Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006; **42:** 1578–83.
8. Taylor JJ, *et al.* Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis* 2006; **43:** 180–7.

Anticoagulants. SSRIs may increase the anticoagulant activity of some anticoagulants including *acenocoumarol* and *warfarin* (see p.1428).

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in enhanced adverse reactions or interactions, and should be used only under expert supervision. This practice is considered unsuitable or controversial by some authorities. For further details of the interactions between different antidepressants when given together, see Phenelzine, p.418. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p.416.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

There has been a report of the serotonin syndrome (see p.416) developing in a patient 14 days after fluoxetine had been added to *carbamazepine* therapy.[1]

Phenobarbital has been reported to reduce serum concentrations of paroxetine.[2] Steady-state serum concentrations of paroxetine were found to be lower in patients taking *phenytoin* than in those taking carbamazepine or valproate.[3]

Low serum concentrations of citalopram have been reported in 2 patients also taking carbamazepine.[4] Serum concentrations increased when carbamazepine was changed to oxcarbazepine.

Some SSRIs have been reported to increase plasma concentrations of carbamazepine (see p.474) and phenytoin (see p.498). For conflicting reports of the effect of fluoxetine on serum-*valproate* concentrations, see p.511.

1. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
2. Greb WH, *et al.* The effect of liver enzyme inhibition by cimetidine and enzyme induction by phenobarbitone on the pharmacokinetics of paroxetine. *Acta Psychiatr Scand* 1989; **80** (suppl 350): 95–8.
3. Andersen BB, *et al.* No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 1991; **10:** 201–4.
4. Leinonen E, *et al.* Substituting carbamazepine with oxcarbazepine increases citalopram levels. A report on two cases. *Pharmacopsychiatry* 1996; **29:** 156–8.

Antihistamines. *Cyproheptadine* given to male and female patients as treatment for sexual dysfunction induced by fluoxetine or paroxetine has produced re-emergence of previously controlled depressive symptoms[1,2] or bulimia nervosa[3] in some patients.

Citalopram, fluoxetine, and fluvoxamine may increase plasma concentrations of *astemizole* or *terfenadine* by inhibition of their hepatic cytochrome P450 metabolism, increasing the risk of ventricular arrhythmias; use together should be avoided.

1. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry* 1991; **52:** 163–4.
2. Christensen RC. Adverse interaction of paroxetine and cyproheptadine. *J Clin Psychiatry* 1995; **56:** 433–4.
3. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry* 1991; **52:** 261–2.

Antimalarials. For mention of the effect of the SSRI fluvoxamine on the metabolism of *proguanil*, see p.609.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of SSRIs with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p.626). Fluvoxamine may inhibit the metabolism of *frovatriptan* and *zolmitriptan* (see p.622 and p.628, respectively). For the effects when some SSRIs are used with *dihydroergotamine*, see p.621.

Antimuscarinics. For the effect of SSRIs on *benzatropine*, see p.797. For the effect of paroxetine on *procyclidine*, see p.815.

Antineoplastics. Paroxetine may inhibit the metabolism of *tamoxifen*; for further details, see p.774.

Antipsychotics. For reports of adverse effects in patients treated with SSRIs and antipsychotics, see under *Chlorpromazine*, p.974. Interactions between SSRIs and atypical antipsychotics are also mentioned under *clozapine*, p.984, *olanzapine*, p.1013, *risperidone*, p.1025, *sertindole*, p.1028, and *zotepine*, p.1040.

Antivirals. Plasma concentrations of fluoxetine and other SSRIs are possibly increased by HIV-protease inhibitors, such as *ritonavir*, which may inhibit metabolism of the SSRI. Unexpectedly, however, total exposure to paroxetine was approximately halved by a *ritonavir-boosted fosamprenavir* combination in a study in healthy subjects.[1] Although the free fraction of paroxetine in plasma was increased, suggesting that it had been displaced from protein binding, the maximum concentration of free paroxetine was reduced.

The serotonin syndrome has been described[2] in a few patients given regimens that included fluoxetine and antiretroviral-dose ritonavir. The reaction also occurred in another patient given fluoxetine and *efavirenz*.

1. van der Lee MJ, *et al.* Interaction study of the combined use of paroxetine and fosamprenavir-ritonavir in healthy subjects. *Antimicrob Agents Chemother* 2007; **51:** 4098–4104.
2. DeSilva KE, *et al.* Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* 2001; **15:** 1281–5.

Anxiolytics. Fluoxetine and fluvoxamine increase plasma concentrations of some *benzodiazepines* (see under Diazepam, p.990). There is a report of hyponatraemia and serotonin syndrome developing in a patient who received high doses of citalopram and *buspirone*.[1]

1. Spigset O, Adielsson G. Combined serotonin syndrome and hyponatraemia caused by a citalopram-buspirone interaction. *Int Clin Psychopharmacol* 1997; **12:** 61–3.

Beta blockers. For the effect of fluoxetine and fluvoxamine on beta blockers, see p.1228.

Ciclosporin. For the effect of fluoxetine and fluvoxamine on ciclosporin, see p.1826.

Cough suppressants. For the effects when using fluoxetine or paroxetine with *dextromethorphan*, see p.1556.

Dopaminergics. *Selegiline* is an irreversible selective inhibitor of monoamine oxidase type B. Serious adverse effects have been reported when selegiline and SSRIs have been used together (see p.817). In some instances, these reactions resemble the potentially fatal serotonin syndromes reported when SSRIs are given with non-selective MAOIs (see p.416).

SSRIs should not generally be given to patients receiving selegiline, or for at least 2 weeks after it has been stopped. Similarly, at least one week should elapse between withdrawing an SSRI and starting selegiline; this interval should be increased to 2 weeks for sertraline, and to 5 weeks for fluoxetine because of their longer half-lives.

Gastrointestinal drugs. Acute dystonia has been noted in a patient given fluvoxamine and *metoclopramide*.[1] Similar reports have been published for other SSRIs (fluoxetine[2] or sertraline[3]) and metoclopramide. Involuntary twitching, tremor, and stiffness of the jaw and tongue occurred on both occasions after the use of intravenous metoclopramide in a patient also taking sertraline.[4] The authors considered the adverse effects to be features of the serotonin syndrome.

For the effect of fluvoxamine on *alosetron*, and a recommendation that the combination be avoided, see p.1706.

For the effect of fluvoxamine on proton pump inhibitors, including *omeprazole*, see p.1755.

1. Palop V, *et al.* Acute dystonia associated with fluvoxamine-metoclopramide. *Ann Pharmacother* 1999; **33:** 382.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 1995; **152:** 122–5.
3. Christensen RC, Byerly MJ. Mandibular dystonia associated with the combination of sertraline and metoclopramide. *J Clin Psychiatry* 1996; **57:** 596.
4. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

General anaesthetics. For a report of a generalised tonic-clonic seizure in a patient receiving paroxetine and *methohexital sodium*, see p.1789.

Hypnotics. For reference to visual hallucinations in patients receiving an SSRI concomitantly with *zolpidem*, see p.1038.

Levothyroxine. For mention of a decreased effect of levothyroxine in patients given sertraline concomitantly, see p.2172.

Local anaesthetics. For the effect of fluvoxamine on *ropivacaine*, see p.1871.

Muscle relaxants. For a report of QT prolongation in a patient taking fluoxetine and *cyclobenzaprine*, see p.1895.

For the effect of fluvoxamine on *tizanidine*, see p.1898.

NSAIDs. For reference to an increased risk of upper gastrointestinal bleeding in patients taking SSRIs and NSAIDs together, see under Effects on the Gastrointestinal Tract, above.

Opioid analgesics. A possible case of serotonin syndrome (p.416) has been reported with *tramadol* and sertraline,[1] and another when sertraline was given with high doses of *oxycodone*.[2] There have also been occasional reports of the syndrome in patients given tramadol with citalopram,[3] fluoxetine,[4] or paroxetine.[5,6] Other reports of serotonin syndrome were associated with use of oxycodone and fluvoxamine,[7] *pethidine* and fluoxetine,[8] and citalopram with *fentanyl*[9] or pethidine.[10] For reference to SSRIs enhancing the effects and toxicity of *methadone*, see p.84.

1. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; **31:** 175–7.
2. Rosebraugh CJ, *et al.* Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. *J Clin Pharmacol* 2001; **41:** 224–7.
3. Mahlberg R, *et al.* Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry* 2004; **161:** 1129.
4. Kesavan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med* 1999; **92:** 474–5.
5. Egberts ACG, *et al.* Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *Int Clin Psychopharmacol* 1997; **12:** 181–2.
6. Lantz MS, *et al.* Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998; **13:** 343–5.
7. Karunatilake H, Buckley NA. Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 2006; **40:** 155–7.
8. Tissot TA. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology* 2003; **98:** 1511–12.
9. Ailawadhi S, *et al.* Serotonin syndrome caused by interaction between citalopram and fentanyl. *J Clin Pharm Ther* 2007; **32:** 199–202.
10. Altman EM, Manos GH. Serotonin syndrome associated with citalopram and meperidine. *Psychosomatics* 2007; **48:** 361–3.

Parasympathomimetics. For the effect of fluvoxamine on *tacrine*, see p.370. For the effect of some SSRIs on *galantamine*, see p.366.

Sibutramine. There is a risk of CNS toxicity due to synergistic serotonergic actions when an SSRI is given with sibutramine.

Smoking. Serum concentrations of fluvoxamine were lower in smokers than non-smokers in a single-dose study.[1] It was proposed that the polycyclic hydrocarbons present in cigarette smoke stimulated hepatic metabolism of fluvoxamine by cytochrome P450 isoenzymes.

1. Spigset O, *et al.* Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; **58:** 399–403.

Stimulants. For the effect of paroxetine on the metabolism of *atomoxetine*, see p.2151.

Theophylline. For the effect of fluvoxamine on theophylline, see p.1143.

Pharmacokinetics

Fluoxetine is readily absorbed from the gastrointestinal tract with peak plasma concentrations appearing about 6 to 8 hours after oral doses. Systemic bioavailability does not appear to be affected by food. Fluoxetine is extensively metabolised, by demethylation, in the liver to its primary active metabolite norfluoxetine. Excretion is mainly via the urine. Protein binding is reported to be about 95%.

Fluoxetine used clinically is a racemic mixture consisting of *R*- and *S*-enantiomers in equal amounts. Both enantiomers are active according to *animal* studies, but *S*-fluoxetine is eliminated more slowly. Metabolism is believed to be mediated by cytochrome P450 isoenzyme CYP2D6 (but see below), and leads to *R*- and *S*-enantiomers of norfluoxetine, with the *S*-enantiomer being considered as active as the parent drug; the *R*-enantiomer is considered to be much less active. This metabolism is subject to genetic polymorphism. While the small proportion of the population known as slow metabolisers do show a different spectrum of parent drug and metabolite, the overall activity does not appear to be altered.

Fluoxetine is widely distributed throughout the body.

Fluoxetine has a relatively long elimination half-life of about 1 to 3 days after acute use and 4 to 6 days after long-term use; that of its metabolite, norfluoxetine, is even longer, being about 4 to 16 days. These long half-lives have clinical implications. Steady-state plasma concentrations will only be attained after several weeks. Additionally, fluoxetine and its metabolites may persist for a considerable time after treatment, and this has led to precautions concerning the subsequent use of other serotonergic drugs (see Interactions, above).

Fluoxetine and norfluoxetine are distributed into breast milk (see Breast Feeding under Precautions, above).

◊ References.

1. Altamura AC, *et al.* Clinical pharmacokinetics of fluoxetine. *Clin Pharmacokinet* 1994; **26:** 201–14.
2. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 1996; **31:** 444–69.
3. Greenblatt DJ, *et al.* Inhibition of human cytochrome P450-3A isoforms by fluoxetine and norfluoxetine: in vitro and in vivo studies. *J Clin Pharmacol* 1996; **36:** 792–8.
4. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
5. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997; **32** (suppl 1): 1–21.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Metabolism. Although fluoxetine is stated by the manufacturers to be metabolised by the cytochrome P450 isoenzyme CYP2D6, which is supported by studies[1] indicating that its disposition is altered in poor metabolisers of debrisoquine (a substrate for this enzyme), others have suggested that CYP2C19, and perhaps CYP2C9, play an important role.[2]

1. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
2. Liu Z-Q, *et al.* Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol* 2001; **52:** 96–9.

Uses and Administration

Prevention of the reuptake of monoamine transmitters such as serotonin, which potentiates their action in the brain, appears to be associated with antidepressant activity. SSRIs such as fluoxetine preferentially inhibit the reuptake of serotonin compared with noradrenaline, and have limited direct action at other neurotransmitter sites, including muscarinic receptors. They therefore cause fewer antimuscarinic or sedative adverse effects than the tricyclic antidepressants and are less cardiotoxic. Citalopram is the most selective of the SSRIs currently available, whereas paroxetine is the most potent.

SSRIs provide an alternative to the tricyclics for the treatment of depression. As with the tricyclics, it may be several weeks before an antidepressant effect is seen. Once depression has then resolved, maintenance therapy should be continued for at least 4 to 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 5 years and possibly indefinitely.

Some SSRIs are also used as part of the management of generalised anxiety disorder, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social phobia, and post-traumatic stress disorder, and as part of the management of bulimia nervosa. Fluoxetine is also used in the treatment of premenstrual dysphoric disorder.

Fluoxetine, a phenylpropylamine derivative, is given orally as the hydrochloride; doses are expressed in terms of the base. Fluoxetine hydrochloride 22.4 mg is equivalent to about 20 mg of fluoxetine.

In the treatment of **depression** the usual initial dose of fluoxetine is 20 mg once daily; US product information recommends giving this dose in the morning. If no clinical response is seen after several weeks, the daily dose may be gradually increased, up to a maximum of 80 mg daily (60 mg in the elderly). Doses above 20 mg daily may be given in 2 divided doses, for example in the morning and at noon, or as a once daily dose. A once-weekly, modified-release preparation equivalent to 90 mg of fluoxetine is available in the USA for use in patients whose depressive symptoms have stabilised, and who require long-term treatment; it is recommended that weekly dosing is started 7 days after the last daily dose of fluoxetine.

Fluoxetine is also used for the treatment of depression in children aged 8 years and over. Initial doses of 10 mg should be increased to 20 mg daily after 1 week (except in low-weight children when such increases should not be made for several weeks, and then only if the clinical response is insufficient). Because of concerns about the use of SSRIs in children (see Effects on Mental State, above) its use is licensed in the European Union only as an adjunct to psychological therapy in children and adolescents with moderate to severe depression who have not responded to psychological therapy alone.

Fluoxetine is used in recommended doses of 60 mg once daily in the management of **bulimia nervosa**.

In the management of **obsessive-compulsive disorder** the initial dose of fluoxetine is 20 mg once daily increased after several weeks if there is no response to up to 60 mg daily. Up to 80 mg daily has been used, sometimes divided into 2 doses. Fluoxetine is also licensed in the USA for use in children aged 7 years and over for obsessive-compulsive disorder. The starting dose is 10 mg daily; in low-weight children this is increased after several weeks to 20 to 30 mg daily, if required. Adolescents and heavier children may be increased to 20 mg daily after 2 weeks; further increases to 60 mg daily may be made after several weeks, as necessary.

Fluoxetine may be used in the treatment of **panic disorder** in initial doses of 10 mg once daily. After a week the dose should be increased to 20 mg daily; further increases to 60 mg daily may be considered after several weeks if no improvement is seen.

A dose of 20 mg daily is used in the treatment of **premenstrual dysphoric disorder**. Intermittent dosing is also permitted: for each new cycle, fluoxetine should be started 14 days before the onset of menstruation and continued until the first full day of menstruation. Treatment may be continued for 6 months; benefit should then be reassessed before continuing further.

A lower or less frequent dosage is recommended in elderly patients. For dosage in hepatic or renal impairment see below.

It should be noted that because fluoxetine and norfluoxetine have prolonged half-lives several weeks of therapy are required before steady-state concentrations are attained; similarly after dosage adjustments a time lag will occur before steady-state concentrations are again achieved. Although SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms, the long half-life may reduce the need for dose tapering with fluoxetine.

Administration in hepatic or renal impairment. Fluoxetine is subject to hepatic metabolism, and, therefore, lower doses, such as alternate-day dosing, have been recommended in patients with significant hepatic impairment.

It is also excreted by the kidneys and licensed information for some UK products recommends a similar dose reduction in patients with mild to moderate renal impairment and that fluoxetine should be avoided in those with severe impairment. However, other UK and US product information states that plasma concentrations of fluoxetine or its metabolite norfluoxetine in patients with severe impairment requiring dialysis did not differ from those in controls with normal renal function when given fluoxetine 20 mg daily for 2 months.

Anorexia nervosa. Counselling and psychotherapy form the major part of treatment of anorexia nervosa and there is little or no role for specific drug therapy. Antidepressants may be indicated when there is co-existing depression or obsessive-compulsive disorder but malnourished anorexic patients may be more susceptible to adverse effects and less responsive than other patients with depression. Fluoxetine has been tried with some success particularly when used to prevent relapse once weight gain has been achieved.

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1. Bergh C, *et al.* Selective serotonin reuptake inhibitors in anorexia. *Lancet* 1996; **348:** 1459–60.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Kaye WH, *et al.* Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001; **49:** 644–52.
4. Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003; **37:** 890–2.

Anxiety disorders. SSRIs have been given in a variety of anxiety disorders but their role in these disorders is most well established in the treatment of *obsessive-compulsive disorder* (p.952). Efficacy in obsessive-compulsive disorder appears to have been best demonstrated for fluvoxamine and fluoxetine but other SSRIs are also effective and patients unresponsive to one SSRI may respond to another. SSRIs are also of use in the treatment of *generalised anxiety disorder* (p.952), *panic disorder* (p.952), and *post-traumatic stress disorder* (p.953). SSRIs are considered to be the first choice for the treatment of *social anxiety disorder* (see under Phobic Disorders, p.953). Fluoxetine is one of the SSRIs that has been tried in the treatment of *trichotillomania.*

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1. Tollefson GD, *et al.* A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1994; **51:** 559–67.
2. Yanchick JK, *et al.* Efficacy of fluoxetine in trichotillomania. *Ann Pharmacother* 1994; **28:** 1245–6.
3. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 1995; **10:** 45–9.
4. Michelson D, *et al.* Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. *Br J Psychiatry* 1999; **174:** 213–18.
5. Connor KM, *et al.* Fluoxetine in post-traumatic stress disorder: randomised, double-blind study. *Br J Psychiatry* 1999; **175:** 17–22.
6. Meltzer-Brody S, *et al.* Symptom-specific effects of fluoxetine in post-traumatic stress disorder. *Int Clin Psychopharmacol* 2000; **15:** 227–31.
7. Geller DA, *et al.* Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 773–9.
8. Romano S, *et al.* Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 2001; **21:** 46–52.
9. Barnett SD, *et al.* Tolerability of fluoxetine in posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 363–7.
10. Liebowitz MR, *et al.* Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1431–8.
11. Birmaher B, *et al.* Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 415–23.
12. Davidson JR, *et al.* Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; **61:** 1005–13.

Bipolar disorder. Treatment of the depressive phase of bipolar disorder (p.372) with antidepressants needs caution since these drugs may precipitate mania or hypomania. SSRIs such as fluoxetine have nonetheless been used in bipolar disorder with some success. In some countries, fluoxetine is also available as a fixed-dose combination with the atypical antipsychotic olanzapine for use in the depressive phase of bipolar disorder.

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1. Amsterdam JD, *et al.* Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 1998; **18:** 435–40.
2. Megna JL, Devitt PJ. Treatment of bipolar depression with twice-weekly fluoxetine: management of antidepressant-induced mania. *Ann Pharmacother* 2001; **35:** 45–7.
3. Tohen M, *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003; **60:** 1079–88. Correction. *ibid.* 2004; **61:** 176.
4. Amsterdam JD, *et al.* Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate. *Bipolar Disord* 2004; **6:** 75–81.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Fluoxetine and the tricyclic desipramine have been suggested as the antidepressants of choice because they have been used extensively and are considered to be well tolerated. Other SSRIs that have been tried include sertraline, fluvoxamine, and paroxetine. Antidepressants in general do not appear to alter the patient's disturbed self-image, although disturbed attitudes might improve during short-term therapy with fluoxetine.

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2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Bacaltchuk J, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/11/05).
4. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/11/05).

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as fluoxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

Combination therapy with differing classes of antidepressants, including the SSRIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and is considered unsuitable or controversial by some workers. For further details see Antidepressants, under Interactions of Phenelzine, p.418.

References to the use of SSRIs in general and to the use of fluoxetine are given below.

1. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995; **310:** 1433–8.
2. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995; **56:** 30–4.
3. Fava M, *et al.* Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. *J Clin Psychiatry* 1995; **56:** 52–5.
4. Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. *Drug Safety* 1998; **18:** 57–82.
5. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; **7** (suppl 1): 11–17.
6. Cheer SM, Goa KL. Fluoxetine: a review of its therapeutic potential in the treatment of depression associated with physical illness. *Drugs* 2001; **61:** 81–110.
7. Sampson SM. Treating depression with selective serotonin reuptake inhibitors: a practical approach. *Mayo Clin Proc* 2001; **76:** 739–44.
8. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001; **61:** 2221–8.
9. Bull SA, *et al.* Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother* 2002 **36:** 578–84.
10. Emslie GJ, *et al.* Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1205–15.
11. March J, *et al.* Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; **292:** 807–20.
12. Devanand DP, *et al.* Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. *Am J Geriatr Psychiatry* 2005; **13:** 59–68.

Disturbed behaviour. SSRIs appear to have been of some benefit in controlling symptoms such as impulsiveness and aggression[1-3] when tried in various disorders for the management of disturbed behaviour (see p.954). There have been several case reports of fluoxetine being used with some success in the control of fantasies associated with various paraphilias.[4]

1. Cornelius JR, *et al.* Fluoxetine trial in borderline personality disorder. *Psychopharmacol Bull* 1990; **26:** 151–4.
2. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; **91:** 348–51.
3. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 1997; **54:** 1081–8.
4. Richer M, Crismon ML. Pharmacotherapy of sexual offenders. *Ann Pharmacother* 1993; **27:** 316–19.

Headache. The results of several studies have suggested that SSRIs may be of benefit in the treatment of chronic tension-type headache (p.617); however, results in the prophylaxis of migraine (p.616) have been conflicting.

References.

1. Sosin D. Clinical efficacy of fluoxetine vs sertraline in a headache clinic population. *Headache* 1993; **33:** 284.
2. Solomon GD, Pearson E. Sertraline in the management of headache. *Clin Pharmacol Ther* 1994; **55:** 130.
3. Jung AC, *et al.* The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; **12:** 384–9.
4. d'Amato CC, *et al.* Fluoxetine for migraine prophylaxis: a double-blind trial. *Headache* 1999; **39:** 716–19.

Hot flushes. HRT with oestrogens is usually the mainstay of acute treatment for symptoms such as hot flushes associated with the menopause (see p.2077); however, HRT has potentially tumour-stimulating effects and may be unsuitable in some patients, particularly those with a history of breast cancer (see Malignant Neoplasms, under Precautions of HRT, p.2075). Preliminary studies have shown that some SSRIs (fluoxetine, paroxetine, and sertraline) have a modest effect on alleviating hot flushes and may be an alternative to HRT in peri- and postmenopausal women and in women with a history of breast cancer.[1-4] However, there is some concern that the SSRI paroxetine may interact with tamoxifen treatment in patients with breast cancer (see Antidepressants under Interactions in Tamoxifen, p.774 for details).

In addition, paroxetine has been tried in the treatment of hot flushes in men receiving anti-androgen therapy for prostate cancer.[5]

The serotonergic antidepressant venlafaxine has also been tried with some success in men and women with hot flushes in whom other treatments were unsuitable.[6]

1. Stearns V, *et al.* Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003; **289:** 2827–34.
2. Kockler DR, McCarthy MW. Antidepressants as a treatment for hot flashes in women. *Am J Health-Syst Pharm* 2004; **61:** 287–92.
3. De Sloover Koch Y, Ernst ME. Selective serotonin-reuptake inhibitors for the treatment of hot flashes. *Ann Pharmacother* 2004; **38:** 1293–6.
4. Stearns V, *et al.* Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005; **23:** 6919–30. Correction. *ibid.*; 8549.
5. Loprinzi CL, *et al.* Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc* 2004; **79:** 1247–51.
6. Schober CE, Ansani NT. Venlafaxine hydrochloride for the treatment of hot flashes. *Ann Pharmacother* 2003; **37:** 1703–7.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (ADHD—p.2148) initial treatment is usually with a central stimulant. SSRIs such as fluoxetine have produced beneficial effects as an adjunct to central stimulants in small numbers of patients with comorbid disorders such as depression or obsessive-compulsive disorder;[1-3] although there is insufficient evidence to assess their efficacy in ADHD alone.

1. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 1–10.
2. Bussing R, Levin GM. Methamphetamine and fluoxetine treatment of a child with attention-deficit hyperactivity disorder and obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 53–8.
3. Finding RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents and adults: a case series. *J Child Adolesc Psychopharmacol* 1996; **6:** 165–75.

Hypochondriasis. SSRIs may be of benefit in patients with hypochondriasis.[1] Fluoxetine in an initial dose of 20 mg daily gradually increased up to 80 mg daily produced some beneficial results in 10 of 14 patients with hypochondriasis (p.954) who completed 12 weeks of treatment.[2] Fluvoxamine[3] and paroxetine[4] have also been tried.

1. Fallon BA, *et al.* The pharmacotherapy of hypochondriasis. *Psychopharmacol Bull* 1996; **32:** 607–11.
2. Fallon BA, *et al.* Fluoxetine for hypochondriacal patients without major depression. *J Clin Psychopharmacol* 1993; **13:** 438–41.
3. Fallon BA, *et al.* An open trial of fluvoxamine for hypochondriasis. *Psychosomatics* 2003; **44:** 298–303.
4. Oosterbaan DB, *et al.* An open study of paroxetine in hypochondriasis. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; **25:** 1023–33.

Hypotension. SSRIs have been used in patients with neurally mediated hypotension refractory to standard treatment (see p.1174), although evidence of benefit is mainly anecdotal. However, a small study[1] found that paroxetine reduced the incidence of both tilt-induced and spontaneous syncope.

See also Orthostatic Hypotension, below.

1. Di Girolamo E, *et al.* Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999; **33:** 1227–30.

Obesity. Fluoxetine has been tried with some success as part of the management of obesity (p.2149). Fluoxetine's mechanism of action in obesity is unknown. Serotonin is believed to be involved in the regulation of satiety[1] but fluoxetine has also been shown to increase resting energy expenditure and raise basal body temperature.[2] A common dose for fluoxetine in the management of obesity has been 60 mg daily; it appears that fluoxetine has a dose-related effect on weight loss.[3] Reviews[1,4,5] agree that fluoxetine can aid weight reduction in the short term but after 16 to 20 weeks some patients have started to regain weight and its long-term efficacy remains to be established. Troublesome adverse effects can occur.[1] Some patients treated with fluoxetine for depression have experienced an increase of appetite and some have gained weight. There has been a report[6] of a patient who lost weight during treatment with fluoxetine for depression despite an increased appetite and food intake.

1. Anonymous. Fluoxetine (Prozac) and other drugs for treatment of obesity. *Med Lett Drugs Ther* 1994; **36:** 107–8.
2. Bross R, Hoffer LJ. Fluoxetine increases resting energy expenditure and basal body temperature in humans. *Am J Clin Nutr* 1995; **61:** 1020–5.
3. Levine LR, *et al.* Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. *Int J Obes* 1989; **13:** 635–45.
4. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann Intern Med* 1993; **119:** 707–13.
5. Mayer LE, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
6. Fichtner CG, Braun BG. Hyperphagia and weight loss during fluoxetine treatment. *Ann Pharmacother* 1994; **28:** 1350–2.

Orthostatic hypotension. Although orthostatic hypotension has been reported in some patients taking SSRIs, there has been a report[1] that fluoxetine 20 mg daily for 6 to 8 weeks produced beneficial effects in 4 of 5 patients with chronic symptomatic orthostatic hypotension (p.1530) refractory to other treatment. Modest benefits have also been seen in patients with orthostatic hypotension associated with parkinsonism.[2]

1. Grubb BP, *et al.* Fluoxetine hydrochloride for the treatment of severe refractory orthostatic hypotension. *Am J Med* 1994; **97:** 366–8.
2. Montastruc JL, *et al.* Fluoxetine in orthostatic hypotension of Parkinson's disease: a clinical and experimental pilot study. *Fundam Clin Pharmacol* 1998; **12:** 398–402.

Pain. SSRIs have been tried in the treatment of painful disorders including fibromyalgia and diabetic neuropathy.

See also Headache, above.

References.

1. Goldenberg D, *et al.* A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; **39:** 1852–9.
2. Jung AC, *et al.* The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; **12:** 384–9.
3. Smith AJ. The analgesic effects of selective serotonin reuptake inhibitors. *J Psychopharmacol* 1998; **12:** 407–13.
4. Anderberg UM, *et al.* Citalopram in patients with fibromyalgia–a randomized, double-blind, placebo-controlled study. *Eur J Pain* 2000; **4:** 27–35.
5. Shimodozono M, *et al.* Reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. *Int J Neurosci* 2002; **112:** 1173–81.
6. Arnold LM, *et al.* A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med* 2002; **112:** 191–7.

Parkinsonism. It has been suggested that fluoxetine might be of use in the management of selected patients with Parkinson's disease (p.791) who have levodopa-induced dyskinesias unresponsive to other measures.[1] However, although fluoxetine has been reported to have produced beneficial results in such patients[2] there has also been a report of increased disability in patients with Parkinson's disease given fluoxetine.[3] Extrapyramidal effects have also been reported in other patients taking fluoxetine (see under Adverse Effects, above). Fluoxetine has been tried in parkinsonism-related orthostatic hypotension (above).

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Durif F, *et al.* Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* 1995; **45:** 1855–8.
3. Steur ENHJ. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993; **43:** 211–3.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Beneficial effects have been claimed for fluoxetine in a number of uncontrolled studies and reports.[1-4]

1. Seliger GM, *et al.* Fluoxetine improves emotional incontinence. *Brain Inj* 1992; **6:** 267–70.
2. Sloan RL, *et al.* Fluoxetine as a treatment for emotional lability after brain injury. *Brain Inj* 1992; **6:** 315–19.
3. Hanger HC. Emotionalism after stroke. *Lancet* 1993; **342:** 1235–6.
4. Tsai WC, *et al.* Treatment of emotionalism with fluoxetine during rehabilitation. *Scand J Rehabil Med* 1998; **30:** 145–9.

Peripheral vascular disease. Anecdotal reports[1,2] and a small pilot study[3] of fluoxetine (in a daily dose of 20 to 60 mg) suggest it may produce favourable therapeutic responses in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188).

1. Bolte MA, Avery D. Case of fluoxetine-induced remission of Raynaud's phenomenon—a case report. *Angiology* 1993; **44:** 161–3.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. *Lancet* 1995; **345:** 1378.
3. Coleiro B, *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; **40:** 1038–43.

Premenstrual syndrome. Fluoxetine is used to control both the psychological and somatic symptoms of women with premenstrual dysphoric syndrome, a severe form of premenstrual syndrome (p.2099). Other SSRIs also appear to be useful, although evidence is so far more limited.

References.

1. Romano S, *et al.* The role of fluoxetine in the treatment of premenstrual dysphoric disorder. *Clin Ther* 1999; **21:** 615–33.
2. Eriksson E. Serotonin reuptake inhibitors for the treatment of premenstrual dysphoria. *Int Clin Psychopharmacol* 1999; **14** (suppl 2): S27–S33.
3. Dimmock PW, *et al.* Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000; **356:** 1131–6.
4. Carr RR, Ensom MHH. Fluoxetine in the treatment of premenstrual dysphoric disorder. *Ann Pharmacother* 2002; **36:** 713–17.
5. Pearlstein T. Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard. *Drugs* 2002; **62:** 1869–85.
6. Wyatt KM, *et al.* Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 24/11/05).
7. Luisi AF, Pawasauskas JE. Treatment of premenstrual dysphoric disorder with selective serotonin reuptake inhibitors. *Pharmacotherapy* 2003; **23:** 1131–40.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs (see Effects on Sexual Function in Adverse Effects, above). Such properties of the SSRIs have been studied as a potential form of treatment for men with premature ejaculation[1-3] (p.2181). The relative effects of the SSRIs on delaying ejaculation have also been studied.[4] Paroxetine was found to cause the strongest delay, followed by fluoxetine and then sertraline; fluvoxamine caused a slight delay although the effect was not significantly different from that seen with placebo. (Citalopram was unavailable at the time of the study; later studies of its effect have been conflicting[3].)

1. Waldinger MD, *et al.* Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994; **151:** 1377–9.
2. Mendels J, *et al.* Sertraline treatment for premature ejaculation. *J Clin Psychopharmacol* 1995; **15:** 341–6.
3. Moreland AJ, Makela EH. Selective serotonin-reuptake inhibitors in the treatment of premature ejaculation. *Ann Pharmacother* 2005; **39:** 1296–1301.
4. Waldinger MD, *et al.* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. *J Clin Psychopharmacol* 1998; **18:** 274–81.

Preparations

BP 2008: Fluoxetine Capsules; Fluoxetine Oral Solution;
USP 31: Fluoxetine Capsules; Fluoxetine Delayed-Release Capsules; Fluoxetine Oral Solution; Fluoxetine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alental; Animex-On; Anzolden; Captaton; Eburnate; Equilibrane; Faboxetina; Felixina; Fibrotina; Fluopiram; Foxetin; Lapsus; Mitilase; Nervosal; Neupax; Neuro Laz; Prozac; Saurat; ***Austral.:*** Auscap; Erocap†; Fluohexal; Fluoxebell; Lovan; Prozac; Zactin; ***Austria:*** Felicium; Fluctine; Fluxenorm; Fluoxibene; Fluoxistad; Fluoxityrol†; Flux; Fluxil; FluxoMed; Mutan; NuFluo; Positivum; ***Belg.:*** Docfluoxetine; Fluox; Fluoxemed; Fluoxone; Fontex; Prosimed; Prozac; ***Braz.:*** Daforin; Deprax; Depress; Eufor; Fluox; Fluxene; Nortec; Prozac; Prozen; Psiquial; Verotina; ***Canad.:*** FXT; Prozac; ***Chile:*** Actan; Alentol; Anisimol; Clinium; Dominium; Pragmaten; Prozac; Sostac; Tremafarm†; ***Cz.:*** Deprenon†; Deprex; Floxet; Flumirex†; Fluocim†; Fluogal†; Fluoxin; Fluval†; Fluxonil†; Fluzak; Framex†; Magrilan; Milezin†; Portal; Prozac; ***Denm.:*** Afeksin; Flutin; Fluxantin†; Folizol; Fondur†; Fonigen†; Fontex; Fonzac; ***Fin.:*** Fluoxal†; Fluxantin†; Fontex†; Seromex; Seronil; ***Fr.:*** Prozac; ***Ger.:*** Fluctin; Fluneurin; Fluox; Fluox-Puren; Fluoxa†; Fluoxe-Q; FluoxeLich; Fluoxemerck†; Fluoxgamma; Fluxet; Fysionorm†; ***Gr.:*** Dagrilan; Dinalexin; Exostrept; Flonital; Fluocalm; Fluxadir; Fokeston; Hapilux; Ladose; Orthon; Sartuzin; Sofelin; Stephadilat-S; Stressless; Thiramil; Zinovat; ***Hong Kong:*** Atd; CP-Fluoxet; Deprexin; Fluxetin; Fluxil; Magrilan†; Nopres; Plazeron†; Provatine†; Prozac; Qualisac; ***Hung.:*** Deprexin; Fefluzin†; Floxet; FluWinox; Portal; Prozac; ***India:*** Depzac; Fludac; Flufran†; Nuzac; Platin; ***Indon.:*** Andep; Ansi; Antiprestin; Courage; Elizac; Kalxetin; Lodep; Nopres; Noxetine; Oxipres; Prozac; ZAC; Zactin; ***Irl.:*** Affex; Biozac; Gerozac; Norzac; Prozac; Prozamel; Prozatan; Prozit; ***Israel:*** Affectine; Flutine; Prizma; Prozac; ***Ital.:*** Azur; Clexiclor; Cloriflox; Deprexen; Diesan; Flotina; Fluoxeren; Fluoxin†; Grinflux†; Ibixetin†; Ipsumor; Prozac; Serezac†; Xeredien; Zafluox†; ***Malaysia:*** Fluran; Fluxetil; Prozac; Salipax; ***Mex.:*** Aponeusak†; Auroken†; Axtin; Deprozin; Farmaxetina; Flocet; Florexal; Fluctine; Fluneurin; Fluoxac; Fluralex; Flutinax; Indozul; Lebensart; Ovisen; Prozac; Quanilene; Regultron; Siquial; Ulmely; Zatin; ***Neth.:*** Fluoxstad; Flustad; Prozac; ***Norw.:*** Fontex; ***NZ:*** Fluox; Plinzene; Prozac; ***Philipp.:*** Adepssir; Deprexone; Deprizac; Prozac; ***Pol.:*** Andepin; Bioxetin; Deprexetin; Salipax; Seronil; ***Port.:*** Digassim; Mizac†; Nodepe†; Prozac; Psipax; Salipax; Selectus; Tuneluz; ***Rus.:*** Apo-Fluoxetine (Апо-Флуоксетин); Fluval (Флувал); Framex (Фрамекс); Portal (Портал); Prodep (Продеп); Proflusak (Профлузак); Prozac (Прозак); ***S.Afr.:*** Deprozan; Lorien; Nuzak; Prohexal; Prozac; Ranflocs; Sanzur†; ***Singapore:*** Deprexin; Fluxetil†; Fluxetin; Fluxil; Foxtin; Magrilan; Prozac; Zactin; ***Spain:*** Adofen; Astrin†; Augort†; Lecimar; Luramon; Nodepe; Prozac; Reneuron; Zaxetina†; ***Swed.:*** Fluxantin†; Fontex; Seroscand†; ***Switz.:*** Fluctine; Fluesco; Fluocim; fluox-basan†; Fluoxifar; Flusol; ***Thai.:*** Actisac†; Anzac; Atd†; Dawnex; Deproxin; Flulox; Flumed; Fluoxine; Flusac; Flutine; Fluxetil; Fluxetin; Fluzac; Hapilux†; Loxetine; Magrilan; Oxetine; Oxsac; Prodep; Prozac; Unprozy; ***Turk.:*** Depreks; Fulsac; Loksetin; Prozac; Seronil; Zedprex; ***UAE:*** Flutin; ***UK:*** Prozac; Prozit; ***USA:*** Prozac; Sarafem; ***Venez.:*** Anoxen; Antipres; Fluxet; Fluzac; Prozac; Psiquial.

Multi-ingredient: *Arg.:* Combined†; Symbyax†; ***Chile:*** Symbyax; ***India:*** Fludep Plus; ***Mex.:*** Symbyax; ***USA:*** Symbyax.

Fluvoxamine Maleate *(BANM, USAN, rINNM)*

DU-23000; Fluvoksamiinimaleaatti; Fluvoksamin Maleat; Fluvoxamine, maléate de; Fluvoxamini maleas; Fluvoxaminmaleat; Maleato de fluvoxamina. (*E*)-5-Methoxy-4′-trifluoromethylvalerophenone *O*-2-aminoethyloxime maleate.

Флувоксамина Малеат

$C_{15}H_{21}F_3N_2O_2,C_4H_4O_4 = 434.4.$

CAS — 54739-18-3 (fluvoxamine); 61718-82-9 (fluvoxamine maleate).

ATC — N06AB08.

ATC Vet — QN06AB08.

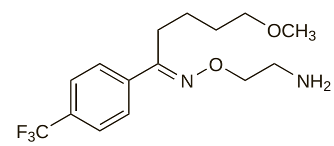

(fluvoxamine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluvoxamine Maleate). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol.

USP 31 (Fluvoxamine Maleate). A white to off-white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in solvent ether. Protect from light.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391).

Bradycardia with ECG changes has been noted with fluvoxamine (but see also Effects on the Cardiovascular System in Adverse Effects of Fluoxetine, p.392).

It is recommended that fluvoxamine should be withdrawn in patients who have increased serum liver enzyme concentrations.

Fluvoxamine may need to be given with caution to patients with hepatic or renal impairment, and to the elderly (see under Uses and Administration, below).

Incidence of adverse effects. The UK CSM has reported[1] that between 25 September 1986 and 23 March 1988 it had received 961 reports of adverse reactions, including 5 deaths, associated with the use of fluvoxamine. The most frequently reported reactions were nausea (183) and vomiting (101). Other reactions included dizziness, somnolence, agitation, headache, tremor, and, during the first few days, worsening of anxiety. There were 13 reports of convulsions. Reports of appetite stimulation and antimuscarinic reactions were unusual. The effects sometimes resolved with time or dose reduction.

The safety profile of fluvoxamine has been reviewed.[2] For a comparison of the adverse reaction profiles of other SSRIs including fluoxetine with that of fluvoxamine, see Incidence of Adverse Effects, under Adverse Effects of Fluoxetine, p.391.

1. CSM. Fluvoxamine (Faverin): adverse reaction profile. *Current Problems 22* 1988. Also available at: http:// www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024429&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Wagner W, *et al.* Fluvoxamine: a review of its safety profile in world-wide studies. *Int Clin Psychopharmacol* 1994; **9:** 223–7.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Fluvoxamine can greatly increase plasma concentrations of theophylline (see p.1143), and they should not be given together, or, if this is unavoidable, the dose of theophylline should be halved and plasma-theophylline concentrations monitored more closely.

◊ References.

1. Wagner W, Vause EW. Fluvoxamine: a review of global drug-drug interaction data. *Clin Pharmacokinet* 1995; **29** (suppl 1): 26–32.

Pharmacokinetics

Fluvoxamine is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 3 to 8 hours after a dose. Systemic bioavailability does not appear to be affected by food. It is extensively metabolised in the liver by oxidative demethylation and deamination, to inactive metabolites. Excretion is mainly in the urine; about 2% of a dose is excreted as unchanged drug. Fluvoxamine is widely distributed throughout the body and protein binding is reported to be about 80%; it has a plasma-elimination half-life of about 15 hours. Fluvoxamine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p.394).

◊ References.

1. Perucca E, *et al.* Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1994; **27:** 175–90.
2. van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 1995; **29** (suppl 1): 1–9.
3. Xu Z-H, *et al.* In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. *Br J Clin Pharmacol* 1996; **42:** 518–21.
4. DeVane CL, Gill HS. Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *J Clin Psychiatry* 1997; **58** (suppl 5): 7–14.
5. Spigset O, *et al.* Non-linear fluvoxamine disposition. *Br J Clin Pharmacol* 1998; **45:** 257–63.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Uses and Administration

Fluvoxamine, an aralkylketone derivative, is an SSRI with actions and uses similar to those of fluoxetine (p.397). It is used as the maleate and doses are expressed in terms of this salt.

In the treatment of **depression** fluvoxamine maleate is given in an initial oral dose of 50 or 100 mg once daily, preferably in the evening; in some patients the dose may need to be gradually increased to a maximum of 300 mg daily. It is recommended that daily dosages exceeding 150 mg should be given in 2 or 3 divided doses.

Fluvoxamine maleate is also used in the management of **obsessive-compulsive disorder**. In the UK, doses are similar to those used in the treatment of depression. The recommended starting dose in the USA is 50 mg once daily; this dose may be increased by increments of 50 mg every 4 to 7 days to a maximum of 300 mg daily. Doses above 100 mg daily should be given in 2 divided doses. In both countries the drug may also be used in children aged 8 years and over with obsessive-compulsive disorder. The recommended starting dose is 25 mg once daily, which may be increased in increments of 25 mg every 4 to 7 days to a maximum daily dose of 200 mg (in the USA adolescents over 11 years may be given a maximum dose of 300 mg daily). Daily doses of more than 50 mg should be given as 2 divided doses. It is recommended that if no improvement occurs within 10 weeks, treatment with fluvoxamine should be re-assessed.

In the USA, a modified-release preparation of fluvoxamine maleate is available for the treatment of obsessive-compulsive disorder and **social anxiety disorder** in adults; the initial dose is 100 mg once daily increased, as necessary, to a maximum of 300 mg once daily.

US licensed product information recommends that dosage modification be considered in elderly patients, in whom clearance may be decreased. For dosage in renal and hepatic impairment, see below.

Fluvoxamine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic or renal impairment. UK licensed drug information recommends that patients with hepatic or renal impairment should begin therapy with a low dose of fluvoxamine maleate and be carefully monitored; US product information only recommends that dosage modification be considered in hepatic impairment, since it considers evidence of accumulation in renal impairment to be lacking.

Anxiety disorders. Fluvoxamine has been given in a variety of anxiety disorders including obsessive-compulsive disorder (p.952), panic disorder (p.952), and social anxiety disorder (see under Phobic Disorders, p.953).

References.

1. van Vliet IM, *et al.* Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. *Psychopharmacology (Berl)* 1994; **115:** 128–34.
2. Freeman CPL, *et al.* Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. *J Clin Psychiatry* 1994; **55:** 301–5.
3. Greist JH, *et al.* Efficacy of fluvoxamine in obsessive-compulsive disorder: results of a multicentre, double blind, placebo-controlled trial. *Eur J Clin Res* 1995; **7:** 195–204.
4. Stein MB, *et al.* Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind placebo-controlled study. *Am J Psychiatry* 1999; **156:** 756–60.
5. Figgitt DP, McClellan KJ. Fluvoxamine: an updated review of its use in the management of adults with anxiety disorders. *Drugs* 2000; **60:** 925–54.
6. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 2001; **344:** 1279–85.
7. Asnis GM, *et al.* Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. *Psychiatry Res* 2001; **103:** 1–14.
8. Hollander E, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 640–7.
9. Stein DJ, *et al.* Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 2003; **6:** 317–23.

Hypochondriasis. For reference to the use of SSRIs, including fluvoxamine, in hypochondriasis, see under Fluoxetine, p.398.

Preparations

BP 2008: Fluvoxamine Tablets;
USP 31: Fluvoxamine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Luvox†; ***Austral.:*** Faverin; Luvox; Movox; Voxam; ***Austria:*** Felixsan; Floxyfral; ***Belg.:*** Dumirox†; Floxyfral; ***Braz.:*** Luvox; ***Canad.:*** Luvox; ***Chile:*** Luvox; ***Cz.:*** Fevarin; ***Denm.:*** Fevarin; ***Fin.:*** Fevarin; Fluvosol†; ***Fr.:*** Floxyfral; ***Ger.:*** Desifluvoxamin†; Fevarin; Fluvohexal; Fluvoxadura; ***Gr.:*** Dumyrox; Myroxine; ***Hong Kong:*** Faverin; ***Hung.:*** Fevarin; ***India:*** Fluvoxin; Sorest; Uvox; ***Indon.:*** Luvox; ***Irl.:*** Faverin; ***Israel:*** Favoxil; ***Ital.:*** Dumirox; Fevarin; Maveral; ***Jpn:*** Luvox; ***Malaysia:*** Luvox; ***Mex.:*** Luvox; Vumix; ***Neth.:*** Fevarin; ***Norw.:*** Fevarin; ***Philipp.:*** Faverin; ***Pol.:*** Fevarin; ***Port.:*** Dumyrox; ***Rus.:*** Fevarin (Феварин); ***S.Afr.:*** Faverin; Luvox; ***Singapore:*** Faverin; ***Spain:*** Dumirox; ***Swed.:*** Fevarin; ***Switz.:*** Flox-ex; Floxyfral; ***Thai.:*** Faverin; Fluvoxin; ***Turk.:*** Faverin; ***UK:*** Faverin; ***USA:*** Luvox; ***Venez.:*** Luvox.

Imipramine *(BAN, rINN)*

Imipramiini; Imipramin; Imipramina; Imipraminum. 3-(10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyldimethylamine.

Имипрамин

$C_{19}H_{24}N_2$ = 280.4.

CAS — 50-49-7.

ATC — N06AA02.

ATC Vet — QN06AA02.

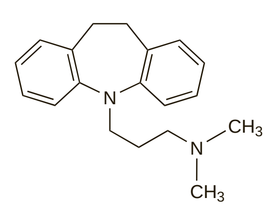

Imipramine Embonate *(BANM, rINNM)*

Embonato de imipramina; Imipramine, Embonate d'; Imipramine Pamoate; Imipramini Embonas.

Имипрамина Эмбонат

$(C_{19}H_{24}N_2)_2,C_{23}H_{16}O_6$ = 949.2.

CAS — 10075-24-8.

Imipramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de imipramina; Imipram. Hydrochlor.; Imipramiinihydrokloridi; Imipramin Hidroklorür; Imipramine, chlorhydrate d'; Imipramin-hidroklorid; Imipramin-hydrochlorid; Imipraminhydroklorid; Imipramini Chloridum; Imipramini hydrochloridum; Imipramino hidrochloridas; Imipraminy chlorowodorek; Imizine.

Имипрамина Гидрохлорид

$C_{19}H_{24}N_2,HCl$ = 316.9.

CAS — 113-52-0.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.*

Ph. Eur. 6.2 (Imipramine Hydrochloride). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 10% solution in water has a pH of 3.6 to 5.0. Protect from light.

USP 31 (Imipramine Hydrochloride). A white to off-white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; insoluble in ether and in benzene. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Porphyria. Imipramine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Imipramine is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desipramine.

Paths of metabolism of both imipramine and desipramine include hydroxylation and *N*-oxidation. Imipramine is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amounts are excreted in the faeces via the bile.

Imipramine and desipramine are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Imipramine has been estimated to have an elimination half-life ranging from 9 to 28 hours, which may be considerably extended in overdosage. Plasma concentrations of imipramine and desipramine vary very widely between individuals but some correlation with therapeutic response has been established.

Imipramine and desipramine cross the blood-brain barrier and placenta and are distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Sallee FR, Pollock BG. Clinical pharmacokinetics of imipramine and desipramine. *Clin Pharmacokinet* 1990; **18:** 346–64.

Uses and Administration

Imipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is usually given orally as the hydrochloride or embonate, with doses expressed in terms of the hydrochloride. Imipramine embonate 149.8 mg and imipramine base 88.5 mg are both equivalent to about 100 mg of imipramine hydrochloride.

In the treatment of **depression**, the usual daily dose of imipramine hydrochloride is up to 75 mg in divided doses initially, gradually increased to 150 to 200 mg daily as necessary; higher doses of up to 300 mg daily may be required in severely depressed patients in hospital. A suggested initial dose for the elderly in the UK is 10 mg daily, gradually increasing to 30 to 50 mg daily. In the USA, daily doses of 25 to 50 mg are recommended for initial therapy in the elderly and adolescents, increasing to a maximum of 100 mg daily as required. Since imipramine has a prolonged half-life, once-daily dosage regimens may also be suitable, usually given at night.

Imipramine, as the hydrochloride, has also been given by intramuscular injection in the treatment of depression.

Imipramine is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Suggested doses of imipramine hydrochloride are:

- 25 mg for children aged 6 to 7 years (20 to 25 kg)
- 25 to 50 mg for children aged 8 to 11 years (25 to 35 kg)
- 50 to 75 mg for children over 11 years (35 to 54 kg)

The dose should be taken just before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Imipramine oxide hydrochloride (imipraminoxide hydrochloride) has also been used as an antidepressant and for nocturnal enuresis.

Imipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. See under Clomipramine, p.387. In some countries, imipramine hydrochloride is licensed for the treatment of panic disorder in an initial oral dose of 10 mg daily; this dose may be increased as necessary to between 75 to 150 mg daily although doses of 200 mg daily may be needed in some patients.

Some references to the use of imipramine in anxiety disorders are given below.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160:** 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8:** 115–18.
3. Rickels K, *et al.* Antidepressants for the treatment of generalised anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 1993; **50:** 884–95.
4. Clark DM, *et al.* A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *Br J Psychiatry* 1994; **164:** 759–69.
5. Barlow DH, *et al.* Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283:** 2529–36. Correction. *ibid.*; **284:** 2597.

Hyperactivity. Although not licensed in the UK for use in children with attention deficit hyperactivity disorder, the *BNFC* has suggested that imipramine hydrochloride may be given to those aged 6 years and over in an oral dose of 10 to 30 mg twice daily.

See also under Desipramine, p.388.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). In some countries, imipramine hydrochloride is also available for the treatment of chronic pain; the usual recommended oral dose is 25 to 75 mg daily, although doses of up to 300 mg daily may be necessary.

Some references to the use of imipramine are given below.

1. Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer. *Proc Am Soc Clin Oncol* 1986; **5:** 237.
2. Sindrup SH, *et al.* Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990; **47:** 509–15.
3. Hummel T, *et al.* A comparison of the antinociceptive effects of imipramine, tramadol and anpirtoline. *Br J Clin Pharmacol* 1994; **37:** 325–33.
4. Cannon RO, *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994; **330:** 1411–17.
5. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
6. Minotti V, *et al.* Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* 1998; **74:** 133–7.

Preparations

BP 2008: Imipramine Tablets;
USP 31: Imipramine Hydrochloride Injection; Imipramine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Elepsin; Tofranil; ***Austral.:*** Melipramine; Tofranil; Tolerade; ***Austria:*** Tofranil; ***Belg.:*** Tofranil; ***Braz.:*** Depramina; Imipra; Praminan; Tofranil; Uni Imiprax; ***Canad.:*** Novo-Pramine; Tofranil; ***Cz.:*** Melipramin; ***Fr.:*** Tofranil; ***Ger.:*** Pryleugan; Tofranil; ***Hong Kong:*** Tofranil†; ***Hung.:*** Melipramin; ***India:*** Antidep; Depsonil; ***Indon.:*** Tofranil; ***Irl.:*** Tofranil; ***Israel:*** Primonil; Tofranil; ***Ital.:*** Tofranil; ***Mex.:*** Fixon; Talpramin; Tofranil; ***NZ:*** Tofranil; ***Philipp.:*** Tofranil; ***Port.:*** Tofranil; ***Rus.:*** Melipramin (Мелипрамин); ***S.Afr.:*** Ethipramine; Mipralin; Tofranil; ***Spain:*** Tofranil; ***Swed.:*** Tofranil†; ***Switz.:*** Tofranil; ***Thai.:*** Celamine; Sermonil; Topramine; ***Turk.:*** Tofranil; ***UK:*** Tofranil†; ***USA:*** Tofranil; ***Venez.:*** Tofranil.

Multi-ingredient: ***India:*** Depsonil-DZ.

Iproniazid Phosphate *(BANM, rINNM)*

Fosfato de iproniazida; Iproniazide, Phosphate d'; Iproniazidi Phosphas. 2′-Isopropylisonicotinohydrazide phosphate.

Ипрониазида Фосфат

$C_9H_{13}N_3O,H_3PO_4$ = 277.2.
CAS — 54-92-2 (iproniazid); 305-33-9 (iproniazid phosphate).
ATC — N06AF05.
ATC Vet — QN06AF05.

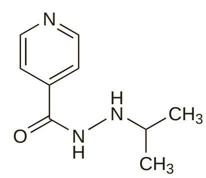

(iproniazid)

Profile

Iproniazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p.419). It has been given orally in the treatment of depression.

Iproniazid is the isopropyl derivative of isoniazid (see p.288) and was developed for use in tuberculosis, but owing to its toxicity is no longer used for this purpose.

Effects on the liver. Of 91 cases of hepatitis due to antidepressant therapy, cytolytic reactions occurred in 11 treated with iproniazid.[1] Five patients died, 3 of them after involuntary rechallenge. High levels of antimitochondrial antibody were found in 5 patients.

1. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.

Porphyria. Iproniazid has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Marsilid†.

Isocarboxazid *(BAN, rINN)*

Isocarboxazida; Isocarboxazide; Isocarboxazidum; Isokarboksatsidi; Isokarboxazid; Ro-50831. 2′-Benzyl-5-methylisoxazole-3-carbohydrazide.

Изокарбоксазид

$C_{12}H_{13}N_3O_2$ = 231.3.
CAS — 59-63-2.
ATC — N06AF01.
ATC Vet — QN06AF01.

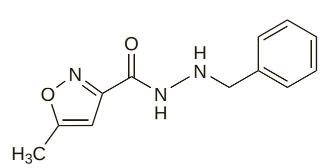

Pharmacopoeias. In *Chin.*

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p.415).

Interactions

For interactions associated with MAOIs, see Phenelzine, p.417.

Pharmacokinetics

Isocarboxazid is readily absorbed from the gastrointestinal tract reaching peak plasma concentrations 3 to 5 hours after ingestion. It is metabolised by the liver, and is excreted in the urine mainly in the form of metabolites.

Uses and Administration

Isocarboxazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p.419).

Isocarboxazid is used in the treatment of depression but because of the risks associated with irreversible non-selective MAOIs (see p.373) usually other antidepressants are preferred. It is given in an initial oral dose of 30 mg daily in single or divided doses. If no improvement occurs after 4 weeks, doses of up to 60 mg daily can be tried for up to 4 to 6 weeks. Once a response has been obtained the dosage may be gradually reduced to a maintenance dose of 10 to 20 mg daily, although doses of up to 40 mg daily may be needed in some patients. Half the normal maintenance dose may be adequate in the elderly.

Isocarboxazid should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Marplan†; ***Denm.:*** Marplan; ***USA:*** Marplan.

Lithium Carbonate *(USAN)*

CP-15467-61; Dilithium Carbonate; Ličio karbonatas; Lithii carbonas; Lithium Carb.; Lithium, carbonate de; Litio, carbonato de; Litiumkarbonaatti; Litiumkarbonat; Lítium-karbonát; Litu węglan; Litu weglan; Lityum Karbonat; NSC-16895; Uhličitan lithný. Carbonic acid, dilithium salt.

Li_2CO_3 = 73.89.
CAS — 554-13-2.
ATC — N05AN01.
ATC Vet — QN05AN01.

NOTE. Commercially available lithium materials have atomic weights ranging from 6.939 to 6.996. The molecular weight of lithium carbonate of 73.89 given above has been calculated using the lowest atomic weight; using the highest figure would give a molecular weight of 74.00. This difference does not affect the figure of 27 mmol of lithium being provided by 1 g of lithium carbonate and is unlikely to contribute noticeably to any variations in serum concentration. Nor should it affect the outcome of assays of serum-lithium concentrations given the limits of error of the assay methods.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Lithium Carbonate). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol.

USP 31 (Lithium Carbonate). A white odourless granular powder. Sparingly soluble in water, very slightly soluble in alcohol; dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate

Citronan lithný tetrahydrát; Ličio citratas; Lithii citras; Lithii Citras Tetrahydricus; Lithium, citrate de; Litio, citrato de; Litiumcitrat; Lítium-citrát; Litiumsitraatti; Lityum Sitrat.

$C_6H_5Li_3O_7,4H_2O$ = 282.0.
CAS — 919-16-4 (anhydrous lithium citrate); 6080-58-6 (lithium citrate tetrahydrate).

NOTE. Commercially available lithium materials have atomic weights ranging from 6.939 to 6.996. The molecular weight of lithium citrate of 282.0 given above has been calculated using the lowest atomic weight; using the highest figure would give a molecular weight of 282.1. This difference does not affect the figure of 10.6 mmol of lithium being provided by 1 g of lithium citrate and is unlikely to contribute noticeably to any variations in serum concentration. Nor should it affect the outcome of assays of serum-lithium concentrations given the limits of error of the assay methods.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
US also includes lithium hydroxide.

Ph. Eur. 6.2 (Lithium Citrate). A white or almost white fine crystalline powder. Freely soluble in water; slightly soluble in alcohol.

USP 31 (Lithium Citrate). A white odourless deliquescent powder or granules. Freely soluble in water; slightly soluble in alcohol. pH of a 5% solution in water is between 7.0 and 10.0. Store in airtight containers.

Adverse Effects

Many of the adverse effects of lithium are dose-related and the margin between the therapeutic and toxic dose is narrow.

Initial adverse effects of lithium therapy include nausea, diarrhoea, vertigo, muscle weakness, and a dazed feeling; these effects often abate with continued therapy. Fine hand tremors, polyuria, and polydipsia may, however, persist. Other adverse effects that may occur at therapeutic serum-lithium concentrations include weight gain and oedema (which should not be treated with diuretics). Hypercalcaemia, hypermagnesaemia, and hyperparathyroidism have been reported. Skin disorders such as acne, psoriasis, and rashes may be exacerbated by lithium therapy. Leucocytosis is a relatively common adverse effect. Long-term adverse effects include hypothyroidism and/or goitre, rarely hyperthyroidism, and mild cognitive and memory impairment. Histological and functional changes in the kidney have been noted after long-term use of therapeutic concentrations of lithium (but see under Effects on the Kidneys, below).

Toxic effects may be expected at serum-lithium concentrations of about 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously.

Signs of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, giddiness with ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyperirritability, choreoathetoid movements, dysarthria, and drowsiness. Symptoms of severe overdosage at serum-lithium concentrations above 2 mmol/litre include hyperreflexia and hyperextension of limbs, syncope, toxic psychosis, seizures, polyuria, renal failure, electrolyte imbalance, dehydration, circulatory failure, coma, and occasionally death.

The hazards of lithium in pregnant patients are discussed under Pregnancy in Precautions, below.

Effects on the blood. A patient developed thrombocytopenia after restarting lithium therapy after a gap of some weeks.[1] Stopping lithium led to an improvement in platelet count, but the count fell when lithium therapy was tried again. Leucocytosis is a recognised effect of lithium which this patient also experienced. Although concerns about leukaemia induction have not been verified, the author noted earlier reports of aplastic and megaloblastic anaemia and a case of fatal haemolytic anaemia reported to the UK CSM.

1. Collings S. Thrombocytopenia associated with lithium carbonate. *BMJ* 1992; **305:** 159.

Effects on the cardiovascular system. Reports of adverse effects on the heart associated with lithium have included bradycardia due to sinus node dysfunction,[1] which has persisted after stopping lithium,[2] premature ventricular contractions,[3] atrioventricular block,[4] and T-wave depression.[5] For the adverse cardiac effects associated with lithium intoxication, see under Overdosage, below.

For mention of myocarditis associated with lithium therapy, see under Effects on the Musculoskeletal System, below.

1. Montalescot G, *et al.* Serious sinus node dysfunction caused by therapeutic doses of lithium. *Int J Cardiol* 1984; **5:** 94–6.
2. Palileo EV, *et al.* Persistent sinus node dysfunction secondary to lithium therapy. *Am Heart J* 1983; **106:** 1443–4.
3. Tangedahl TN, Gau GT. Myocardial irritability associated with lithium carbonate therapy. *N Engl J Med* 1972; **287:** 867–9.
4. Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985; **30:** 114–16.
5. Demers RG, Heninger GR. Electrocardiographic T-wave changes during lithium carbonate treatment. *JAMA* 1971; **218:**381–6.

Effects on the endocrine system. There is a small, but definite, risk that patients taking lithium in therapeutic doses will develop *goitre*, clinical or subclinical *hypothyroidism*, or, rarely, both.[1-3] Published prevalence figures have varied widely although most studies have found an increased risk of hypothyroidism in patients treated with lithium when compared to the general population.[2] Prevalence also appears to be higher in women taking lithium than in men;[2] in addition, the increased risk in women may be greatest during the first 2 years of lithium therapy. Other risk factors identified include a family history of thyroid disorders.[3] However, a long-term, follow-up study[4,5] suggested that the incidence of thyroid abnormalities was no greater in lithium-treated patients than in the general population.

Early goitre and lithium-induced hypothyroidism are both reversible if lithium is withdrawn; if continued treatment with lithium is desirable the patient should be treated with levothyroxine.

There have been rare reports of *hyperthyroidism* in lithium-treated patients[6] and the association may only be one of coincidence, although it is important to realise that hyperthyroidism can precipitate mania and can also be mistaken for an attack of mania.

Increases in serum concentrations of calcium and parathyroid hormone have been described in patients receiving lithium therapy. Although generally considered to be slight, some patients have experienced *parathyroid hyperplasia*.[7,8]

Cases of *diabetes mellitus* developing in patients treated with lithium have been reported but may not be attributable to lithium.[9]

1. Vincent A, *et al.* Lithium-associated hypothyroidism: a practical review. *Lithium* 1994; **5:** 73–4.
2. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism: prevalence and risk factors. *Br J Psychiatry* 1999; **175:** 336–9.
3. Ozpoyraz N, *et al.* Thyroid abnormalities in lithium-treated patients. *Adv Therapy* 2002; **19:** 176–84.
4. Bocchetta A, *et al.* Six-year follow-up of thyroid function during lithium treatment. *Acta Psychiatr Scand* 1996; **94:** 45–8.
5. Bocchetta A, *et al.* Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol* 2001; **21:** 594–8.
6. Yamagishi S-I, Yokoyama-Ohta M. A case of lithium-associated hyperthyroidism. *Postgrad Med J* 1999; **75:** 188–9.
7. Nordenström J, *et al.* Hyperparathyroidism associated with treatment of manic-depressive disorders by lithium. *Eur J Surg* 1992; **158:** 207–11.
8. Taylor JW, Bell AJ. Lithium-induced parathyroid dysfunction: a case report and review of the literature. *Ann Pharmacother* 1993; **27:** 1040–3.
9. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.

Effects on the eyes. Decrease in accommodation has been reported in up to 10% of patients taking lithium; younger patients are most affected.[1] Blurred vision can also occur, most commonly early in therapy, but this may improve with time. Lithium can affect extra-ocular muscles and produce diplopia. A reduction in dosage or withdrawal of therapy may be required. It reduces lachrymal secretions and is excreted in tears in increased concentrations. In rare cases this may result in ocular irritation but this usually causes few problems when artificial tears are used. Photophobia, which occurs rarely with lithium therapy, may also be associated with the excretion of lithium in tears. Lithium can reduce dark adaptation due to a direct neural effect but whether this can progress further to cause irreversible macular or retinal degeneration is not proven. There are some rare but poorly documented reports of deposits in the cornea or conjunctiva. It was considered unlikely that lithium increased the risk of developing senile cataracts.

Lithium can cause nystagmus, many forms of which are reversible on reducing the dose or withdrawal of the drug. However, downbeat nystagmus is a serious adverse effect and is often irreversible. Irreversible oscillopsia can occur rarely secondary to nystagmus. Oculogyric crisis has been associated with lithium therapy and may be exacerbated by haloperidol.

Some ocular effects may be secondary to the effects of lithium on other systems. Exophthalmos and other thyroid-related eye disorders may occur rarely as a secondary effect of lithium on the thyroid. Lithium can also cause pseudotumor cerebri with papilloedema (benign intracranial hypertension). Most cases have occurred a few years after starting therapy but there has been a report of this condition after only 7 months of treatment. Ptosis has been reported, mainly associated with unmasking of myasthenia gravis.

1. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Effects on the kidneys. Polyuria with associated polydipsia, due to drug-induced nephrogenic diabetes insipidus, is the most common result of the effects of lithium on the kidney; an early review[1] stated that the incidence ranged from 4 to 50%. In some patients, irreversible kidney damage, associated with renal histological changes that included tubular atrophy, focal interstitial nephropathy and focal fibrosis, and impairment of glomerular filtration rate, was reported. However, although patients on long-term maintenance lithium therapy did appear to be susceptible to the development of progressive impairment of urinary concentrating ability it was most noticeable in patients with a history of acute lithium toxicity. The risk of renal damage and impaired glomerular filtration rate was thought to be extremely small in patients on stable maintenance lithium therapy with no history of acute lithium intoxication.[1]

A similar review considered that, although it was necessarily an oversimplified view, many, and perhaps all, of the renal adverse effects of lithium were induced by excessive dosage.[2] Others have also defended lithium with respect to its renal toxicity and stated that long-term therapy, if properly controlled, does not necessarily lead to chronic or irreversible renal damage.[3-5]

1. Walker RG, Kincaid-Smith P. Kidneys and the fluid regulatory system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 206–13.
2. George CRP. Renal aspects of lithium toxicity. *Med J Aust* 1989; **150:** 291–2.
3. Schou M. Serum lithium monitoring of prophylactic treatment: critical review and updated recommendations. *Clin Pharmacokinet* 1988; **15:** 283–6.
4. Schou M. Lithium treatment of manic-depressive illness: past, present, and perspectives. *JAMA* 1988; **259:** 1834–6.
5. Gitlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999; **20:** 231–43.

Effects on the musculoskeletal system. The effects of lithium on skeletal muscle are represented mainly by varying degrees of weakness and tremor (for further details see under Effects on the Nervous and Neuromuscular Systems, below). Aggravation of myasthenia gravis has been reported. Acute or subacute painful proximal myopathy causing myalgia, cramps, myokymia, or weakness has also been described. An association with myocarditis has been proposed[1] but it is unclear whether this is causal.

1. Coulter DM, *et al.* Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 2001; **322:** 1207–9.

Effects on the nervous and neuromuscular systems. Neurotoxicity has long been recognised as a potential adverse effect of lithium. Minor effects of lithium on the nervous system can be minimised by reduction of lithium dose during maintenance therapy but severe effects warrant immediate and complete withdrawal of the drug.[1] Minor effects have been considered to include impaired concentration, comprehension, and short-term memory, restlessness and anxiety, depression, fine rapid tremors, and easy fatigue. Serious or severe effects might include declining cognition and mental status, gait disturbances, movement disorders such as choreoathetosis, myoclonus, and parkinsonism, seizures, cerebellar signs, pseudotumor cerebri (although this was rare), neuroleptic malignant syndrome, myopathy, axonal neuropathy, a myasthenic syndrome, and exacerbation of underlying neuromuscular disease. The cognitive effects of lithium such as mental slowing may be subtle.[2]

There are 2 types of lithium-induced tremor.[3] The first is a coarse tremor occurring with impending and actual lithium toxicity and appears to have both cerebellar and parkinsonian components. It is often associated with incoordination, facial spasms, twitching of muscles and limbs, hyperactive reflexes, and more general systemic signs of toxicity. With this type of tremor it was mandatory to stop or decrease the dose of lithium. The second type, which is more common, is a fine tremor, usually occurring within normal therapeutic concentrations, either transiently within a few days of starting treatment or later as a long-standing adverse effect. With this type of fine tremor there was evidence to show that a slight decrease in dose may be beneficial.

In addition to the effects mentioned above, impairment of taste perception (mainly involving butter and celery)[4] and speech disturbances with few other signs of toxicity[5-8] have been reported.

Neurotoxicity persisting for at least 2 months after stopping lithium therapy (SILENT; syndrome of irreversible lithium-effectuated neurotoxicity) has been described.[9] Common presentations included cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia with varying degrees of organic mental syndromes.

For further details of the effects of lithium on the nervous system, see under Effects on the Eyes above, Effects on the Musculoskeletal System, above, and under Epileptogenic Effect, below.

1. Sansone ME, Ziegler DK. Brain and nervous system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 240–5.
2. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. *Psychopharmacology (Berl)* 2003; **170:** 225–34.
3. Johns S, Harris B. Tremor. *BMJ* 1984; **288:** 1309.
4. Himmelhoch JM, Hanin I. Side effects of lithium carbonate. *BMJ* 1974; **4:** 233.
5. Solomon K, Vickers R. Dysarthria resulting from lithium carbonate: a case report. *JAMA* 1975; **231:** 280.
6. Worrall EP, Gillham RA. Lithium-induced constructional dyspraxia. *BMJ* 1983; **286:** 189.
7. McGovern GP. Lithium induced constructional dyspraxia. *BMJ* 1983; **286:** 646.
8. Netski AL, Piasecki M. Lithium-induced exacerbation of stutter. *Ann Pharmacother* 2001; **35:** 961.
9. Adityanjee, *et al.* The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; **28:** 38–49.

Effects on respiration. Lithium is not generally recognised as a respiratory depressant but an episode of reversible respiratory failure about 3 weeks after the start of lithium therapy has been described in a patient with stable chronic airways obstruction.[1] Recovery of consciousness and resolution of hypercapnia occurred within 24 to 36 hours of stopping lithium.

1. Weiner M, *et al.* Effect of lithium on the responses to added respiratory resistances. *N Engl J Med* 1983; **308:** 319–22.

Effects on sexual function and fertility. Lithium does not seem to interfere with sexual function in most patients, but there have been isolated reports of impotence and loss of libido attributed to lithium therapy.[1]

Studies *in vitro* have demonstrated that lithium can inhibit sperm motility in concentrations comparable with those reported to be achieved in semen,[2] but concentrations found in cervico-vaginal mucus were considered unlikely to affect motility.[3]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Raoof NT, *et al.* Lithium inhibits human sperm motility in vitro. *Br J Clin Pharmacol* 1989; **28:** 715–17.
3. Salas IG, *et al.* Lithium carbonate concentration in cervico-vaginal mucus and serum after repeated oral dose administration. *Br J Clin Pharmacol* 1989; **28:** 751P.

Effects on the skin and hair. Patients taking lithium may develop skin disorders, though these are not necessarily serious or severe.[1-3] Male patients may be more susceptible to such effects than female, although early results suggested the reverse.[3] Onset can vary from 2 or 3 weeks to 7 or more years, but many reactions start to appear once optimal serum-lithium concentrations have been attained. Effects reported include psoriasis which may be severe and require lithium withdrawal. Seborrhoeic dermatitis and follicular keratosis also occur and can improve spontaneously or after stopping lithium. Acneform eruptions are found in areas not usually affected by acne vulgaris; in general the face is less affected or not affected at all.

Hair loss, not always severe, is more frequent than cutaneous effects. About 6% of patients may be affected and all forms of alopecias have been found. The onset occurs several weeks or months after the start of lithium therapy. The hair usually regrows despite continuing therapy but in some cases regrowth only occurs after withdrawal of lithium. In a review[4] of the effects on the ocular system, loss of eyebrows and eyelashes was noted as a rare event. Hair loss due to lithium-induced hypothyroidism can be corrected by thyroid replacement therapy.

For references to the association of lithium with lupus, see under Lupus, below.

1. Lambert D, Dalac S. Skin, hair and nails. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 232–4.
2. Gupta AK, *et al.* Lithium therapy associated with hidradenitis suppurativa: case report and a review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; **32:** 382–6.
3. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol* 2004; **5:** 3–8.
4. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Epileptogenic effect. Seizures during lithium therapy usually indicate toxicity or impending toxicity. There have, however, been a few isolated reports describing seizures in patients with serum-lithium concentrations within the normally accepted therapeutic range.[1,2]

1. Demers R, *et al.* Convulsion during lithium therapy. *Lancet* 1970; **ii:** 315–16.
2. Massey EW, Folger WN. Seizures activated by therapeutic levels of lithium carbonate. *South Med J* 1984; **77:** 1173–5.

Lupus. Studies have found that antinuclear antibodies were more common in patients taking lithium carbonate than in controls.[1,2] The absence of anti-DNA antibodies indicated that they did not have true SLE but it was considered that patients ingesting lithium might be at risk. Dermatological manifestations of lupus with the presence of antinuclear antibodies have been reported in a patient taking lithium.[3]

1. Johnstone EC, Whaley K. Antinuclear antibodies in psychiatric illness: their relationship to diagnosis and drug treatment. *BMJ* 1975; **2:** 724–5.
2. Presley AP, *et al.* Antinuclear antibodies in patients on lithium carbonate. *BMJ* 1976; **2:** 280–1.
3. Shukla VR, Borison RL. Lithium and lupuslike syndrome. *JAMA* 1982; **248:** 921–2.

Overdosage. Nausea, vomiting, and diarrhoea are common early features of lithium toxicity, and are followed by coarse tremor, increased muscle tone, cogwheel rigidity, fasciculation, and myoclonus.[1] Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

In **acute overdosage**[2] vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a latency period and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdosage are reported to be mainly related to the gastrointestinal and nervous systems and include abdominal pain, anorexia, nausea, and vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, and depression; renal symptoms have also been noted by some investigators. Efficient detoxification procedures (see Treatment of Adverse Effects, below) should be instituted as rapidly as possible.

Symptoms associated with **chronic intoxication** can be more severe and neurotoxicity may be a particular feature.[3,4] One reviewer considered that the majority of lithium intoxications reported had occurred in patients with renal impairment or in patients who had been given too high a dose.[2] The patient usually experiences a prodromal period of days to a few weeks with minor 'nervous' symptoms which are signs of a manifest slight intoxication. At an unpredictable point renal function starts to deteriorate and within hours or at the most within a few days, the patient will become severely intoxicated. By this point lithium should have been stopped and efficient detoxification measures (see Treatment of Adverse Effects, below) begun if the patient is to make a complete recovery. Other risk factors[3-5] for developing chronic intoxication include use with certain medications (see Interactions, below), older age, and the presence of other conditions such as neurogenic diabetes insipidus and thyroid dysfunction (see also Precautions, below).

In a series of 28 patients with lithium self-poisoning or therapeutic intoxication many of the features and symptoms mentioned above were noted.[6] Other workers[7,8] have also reported cases which illustrate the differences between acute and chronic toxicity encountered clinically.

Serum concentrations of lithium should be measured routinely throughout treatment to ensure that values do not rise to levels associated with toxicity. However, some patients may have concentrations considered to be toxic without showing any symptoms and others may develop signs of toxicity at therapeutic serum concentrations.[9]

Other symptoms that have been noted in case reports of lithium intoxication in individual patients include photophobia,[10] acute polyarthritis involving several large joints,[11] severe hypertension,[12] deep venous thrombophlebitis,[13] reduction of central temperature,[14] and severe leucopenia.[15]

1. Proudfoot AT. Acute poisoning with antidepressants and lithium. *Prescribers' J* 1986; **26:** 97–106.
2. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol* 1988; **3:** 18–32.
3. Oakley PW, *et al.* Lithium toxicity: an iatrogenic problem in susceptible individuals. *Aust N Z J Psychiatry* 2001; **35:** 833–40.
4. Chen K-P, *et al.* Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci* 2004; **58:** 25–9.
5. Montagnon F, *et al.* Lithium: poisonings and suicide prevention. *Eur Psychiatry* 2002; **17:** 92–5.
6. Dyson EH, *et al.* Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 1987; **6:** 325–9.
7. Ananth J, *et al.* Acute and chronic lithium toxicity: case reports and a review. *Lithium* 1992; **3:** 139–45.
8. Bailey B, McGuigan M. Lithium poisoning from a poison control center perspective. *Ther Drug Monit* 2000; **22:** 650–5.
9. Stern R. Lithium in the treatment of mood disorders. *N Engl J Med* 1995; **332:** 127–8.
10. Caplan RP, Fry AH. Photophobia in lithium intoxication. *BMJ* 1982; **285:** 1314–15.
11. Black DW, Waziri R. Arthritis associated with lithium toxicity: case report. *J Clin Psychiatry* 1984; **45:** 135–6.
12. Michaeli J, *et al.* Severe hypertension and lithium intoxication. *JAMA* 1984; **251:** 1680.
13. Lyles MR. Deep venous thrombophlebitis associated with lithium toxicity. *J Natl Med Assoc* 1984; **76:** 633–4.
14. Follézou J-Y, Bleibel J-M. Reduction of temperature and lithium poisoning. *N Engl J Med* 1985; **313:** 1609.
15. Green ST, Dunn FG. Severe leucopenia in fatal lithium poisoning. *BMJ* 1985; **290:** 517.

Treatment of Adverse Effects

In recent acute overdosage with lithium, consideration should be given to emptying the stomach if ingestion has occurred within 1 hour of presentation. However gastric lavage may be of limited value after overdosage with modified-release preparations, which do not disintegrate in the stomach and may be too large to pass through a lavage tube. Activated charcoal is of no value. Whole-bowel irrigation has been suggested although there do not appear to be clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured and any electrolyte imbalance corrected, but forced diuresis or diuretics are contra-indicated. Appropriate supportive care may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

As a result of the narrow margin between therapeutic and toxic serum concentrations, lithium poisoning may also develop during the course of therapy. In some instances temporary withdrawal of lithium therapy and giving generous amounts of sodium and fluid may be all that is required while adverse effects abate. In any serious or severe case of intoxication active measures such as dialysis and supportive measures outlined above may need to be instituted.

◊ References.

1. Smith SW, *et al.* Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 1991; **20:** 536–9.
2. Okusa MD, *et al.* Clinical manifestations and management of acute lithium intoxication. *Am J Med* 1994; **97:** 383–9.
3. Swartz CM, Jones P. Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 1994; **34:** 865–70.
4. Tyrer SP. Lithium intoxication: appropriate treatment. *CNS Drugs* 1996; **6:** 426–39.

Precautions

The margin between the therapeutic and the toxic concentration of lithium is narrow so therapy usually requires specialist advice, and serum concentrations should be monitored regularly under controlled conditions. Patients receiving lithium therapy should be taught to recognise the symptoms of early toxicity (see Adverse Effects, above) and, should these occur, to stop therapy and request medical aid at once. They should be warned not to compensate for an omitted dose by subsequently taking a double dose. Additionally, patients should not be switched between different formulations or preparations of lithium without therapeutic monitoring, as bioavailability may be different.

Lithium should be avoided in patients with cardiac disease or renal impairment; cardiac and renal function should be monitored regularly during treatment. It should also be avoided in Addison's disease or other conditions with a sodium imbalance and in severely debilitated or dehydrated patients.

Patients receiving lithium should be examined periodically for abnormal thyroid function, since goitre and hypothyroidism may develop. Lithium should be avoided in untreated hypothyroidism. Lithium should be used with caution in patients with myasthenia gravis because exacerbation of this disorder has been reported (see Effects on the Musculoskeletal System in Adverse Effects, above).

Lithium should be used with special care in the elderly since this group may be particularly susceptible to toxicity owing to reduced renal function.

Impaired driving performance or machine operating skills may occur in patients receiving lithium (see Driving, below).

It may be necessary to temporarily reduce or stop lithium therapy in patients suffering from vomiting, diarrhoea, intercurrent infection, excessive sweating, or any other condition that causes excessive sodium loss and hence increased serum-lithium concentrations. Conversely, increased sodium levels are likely to reduce serum-lithium concentrations. Patients taking lithium should therefore maintain an adequate fluid intake and should avoid increasing or decreasing sodium intake through dietary changes or ingestion of sodium-containing medicaments. Significant changes in caffeine intake may affect serum-lithium concentrations (see Xanthines under Interactions, below).

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse (see Withdrawal, below).

The risks of using lithium in pregnant patients are described under Pregnancy, below. If lithium is used during pregnancy then dose adjustments will be required to compensate for the altered renal handling.

Lithium should be temporarily stopped 24 hours before major surgery to safeguard the patient from accumulation (see under Anaesthesia, below).

Anaesthesia. The *BNF* states that lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored. Lithium may accumulate because of reduced renal clearance associated with anaesthesia;[1] treatment should be resumed as soon as possible after surgery, when kidney function and fluid-electrolyte balance have become normal. Patients are often not allowed fluids or foods by mouth the night before surgery but patients with lithium-induced polyuria should be given fluids parenterally during the night before the operation, if they vomit copiously, or if they are unconscious for several hours.

There is no clinical evidence of interaction between lithium and anaesthetics, although lithium may prolong the action of neuromuscular blockers.[1]

1. Schou M, Hippus H. Guidelines for patients receiving lithium treatment who require major surgery. *Br J Anaesth* 1987; **59:** 809–10.

Breast feeding. Lithium is distributed into breast milk. Early reports suggested that serum concentrations in breast-fed infants were about one-third to one-half of those measured in mothers.[1] However, advice regarding the decision to breast feed remains equivocal. The American Academy of Pediatrics[2] considers that lithium should be given with caution to breast-feeding women but does not contra-indicate such use, and this is supported by some authors.[3,4] Conversely, most manufacturers in the UK and other authors[5,6] suggest that mothers receiving lithium should bottle feed their infants. It has been recommended[5] that if a mother did want to breast feed this should be done at times to avoid peak blood concentrations of lithium and the infant carefully monitored. Medication should be withheld or breast feeding stopped if the infant developed an infection or dehydration as they would be more susceptible to the adverse effects of lithium.

1. Schou M, Amdisen A. Lithium and pregnancy—III, lithium ingestion by children breast-fed by women on lithium treatment. *BMJ* 1973; **2:** 138.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
3. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
4. Sykes PA, *et al.* Lithium carbonate and breast-feeding. *BMJ* 1976; **2:** 1299.
5. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
6. Llewellyn A, *et al.* The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 1998; **59** (suppl 6): 57–64.

Cystic fibrosis. Reduced renal excretion of lithium was demonstrated in 8 patients with cystic fibrosis compared with healthy subjects.[1] The authors recommended caution when prescribing standard doses of lithium to patients with cystic fibrosis until more definitive data were available.

1. Brager NPD, *et al.* Reduced renal fractional excretion of lithium in cystic fibrosis. *Br J Clin Pharmacol* 1996; **41:** 157–9.

Driving. In the UK, the Driver and Vehicle Licensing Authority considers that patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.[1] Mania or hypomania is particularly dangerous and driving should cease during the acute illness. After an isolated episode, re-licensing can be reconsidered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered.

Treatment with antidepressant drugs, including lithium, may also be hazardous,[2] although patients may be safer drivers with medication than without.[3] Lithium has been reported[2] to adversely affect the choice reaction time (a test to assess the time taken to respond correctly to some signals but not others) to a level considered dangerous for driving. Another study has found that elderly patients taking lithium may be at an increased risk of being involved in an injurious motor vehicle accident while driving when compared to a cohort of elderly, non-lithium users.[4]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)
2. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
3. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
4. Etminan M, *et al.* Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. *BMJ* 2004; **328:** 558–9.

Pregnancy. The decision whether to continue lithium treatment during pregnancy is difficult and should involve careful consideration of the risk-benefit ratio which in some cases may favour treatment. Early case reports of mothers taking lithium during pregnancy pointed to an increased risk of congenital abnormalities with the baby's heart being mainly affected.[1] Support for this increased risk also came from a study[2] of the records of 59 children born to women who had taken lithium during pregnancy. However, another study[3] which prospectively followed 138 pregnant women being treated with lithium did not identify any difference in pregnancy outcome between them and a control group. The authors considered that lithium was not a major teratogen and felt that women with major affective disorders could continue lithium treatment during pregnancy provided that adequate fetal screening tests were carried out. A subsequent review[4] considered that the teratogenic risk was lower than previously thought, but that it would still be wise for women who wished to become pregnant to stop lithium if at all possible, at least during the period of embryogenesis. If lithium is stopped, withdrawal should be slow to prevent a relapse (see below).

There is limited evidence that lithium treatment during pregnancy may increase the risk of fetal macrosomia, premature delivery, and perinatal mortality.[1,5] Polyhydramnios (an excess of amniotic fluid) in the last trimester of pregnancy has been reported and has been attributed to fetal lithium toxicity (polyuria and diabetes insipidus).[6,7]

Monitoring of serum-lithium concentrations is particularly important during pregnancy. The renal clearance of lithium by the mother is not constant during pregnancy; in the second half of the pregnancy clearance rises gradually by 30 to 50% but falls abruptly and significantly after delivery to pre-pregnancy values.[1,8] The increased doses of lithium that may be given during pregnancy to compensate for this increased clearance may result in lithium toxicity.[8] It is generally considered[1,9,10] advisable to stop lithium during the last few days of pregnancy to reduce the risk of maternal lithium toxicity due to accumulation of lithium but it should be started again a few days later after delivery at reduced dosage because of the increased postpartum risk of manic and depressive relapse.[1,10]

Reducing the dosage during the last few days of pregnancy also helps to reduce lithium concentrations in the neonate and avoid associated adverse effects.[1,9] Adverse effects that have been reported in neonates exposed *in utero* to lithium include cyanosis, lethargy, flaccidity, hypotonia, poor gag and sucking reflexes, feeding problems, bradycardia, tachycardia, goitre, hypothyroidism, nephrogenic diabetes, and jaundice;[9-12] withdrawal symptoms have also been observed.

1. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
2. Källén B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 1983; **68:** 134–9.
3. Jacobson SJ, *et al.* Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992; **339:** 530–3.
4. Cohen LS, *et al.* A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994; **271:** 146–50.
5. Troyer WA, *et al.* Association of maternal lithium exposure and premature delivery. *J Perinatol* 1993; **XIII:** 123–7.
6. Krause S, *et al.* Polyhydramnios with maternal lithium treatment. *Obstet Gynecol* 1990; **75:** 504–6.
7. Ang MS, *et al.* Maternal lithium therapy and polyhydramnios. *Obstet Gynecol* 1990; **76:** 517–19.
8. Lemoine J-M. Pregnancy, delivery and lactation. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 139–46.
9. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
10. Pinelli JM, *et al.* Case report and review of the perinatal implications of maternal lithium use. *Am J Obstet Gynecol* 2002; **187:** 245–9.
11. Frassetto F, *et al.* Goiter in a newborn exposed to lithium in utero. *Ann Pharmacother* 2002; **36:** 1745–8.
12. Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: another clinical report and a review of the literature. *Am J Med Genet A* 2005; **132:** 441–4.

Surgery. For comments regarding the precautions to be observed in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Symptoms such as anxiety, tremor, fatigue, nausea, sweating, headache, sleep disturbances, diarrhoea, or blurred vision have developed within days of sudden cessation of treatment with lithium.[1] These symptoms may simply be a recurrence of the mood disorder. Uncontrolled studies of withdrawal symptoms have raised the possibility of a lithium-withdrawal state although controlled studies have been convincingly negative. It is, however, wise to reduce lithium dosage gradually rather than stop high-dosage treatment abruptly.

A frequent worry associated with stopping lithium therapy is that of relapse. Most evidence has supported the view that any relapses occurring in the first weeks after lithium withdrawal are simply part of a pattern of recurrence of bipolar disorder in general and are not indicative of a higher rate of recurrence. Some,[2] however, have found the proportion of patients relapsing on sudden withdrawal of lithium therapy to be 50%, a figure they consider to be too high to be accounted for by the natural history of the disease process. They and others[3] advise that this risk should be considered when prescribing lithium for bipolar disorder. In patients who previously had been stable on lithium for at least 18 months, the risk of early recurrence of bipolar disorder was higher when therapy was withdrawn rapidly in less than 2 weeks than when it was withdrawn gradually over 2 to 4 weeks.[4]

1. Goodnick PJ. Terminating treatment. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 115–17.
2. Mander AJ, Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; **ii:** 15–17.
3. Goodwin GM. Recurrence of mania after lithium withdrawal. *Br J Psychiatry* 1994; **164:** 149–52.
4. Faedda GL, *et al.* Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993; **50:** 448–55.

Interactions

Some diuretics may reduce lithium excretion and result in toxicity (see below for further details). Thiazide diuretics may also show a paradoxical antidiuretic effect. Consequently, diuretics should be avoided or used with caution in those receiving lithium; if used together, a reduction in the lithium dose may be appropriate. Other drugs affecting electrolyte balance may also alter lithium excretion and should be avoided if possible or used with care.

Further interactions reported with lithium are discussed below.

◊ Reviews.

1. Amdisen A. Lithium and drug interactions. *Drugs* 1982; **24:** 133–9.
2. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–2.
3. Harvey NS, Merriman S. Review of clinically important drug interactions with lithium. *Drug Safety* 1994; **10:** 455–63.
4. Finley PR, *et al.* Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995; **29:** 172–91.

ACE inhibitors. Giving lithium with ACE inhibitors has been reported[1-5] to increase serum-lithium concentrations, resulting in some cases in lithium toxicity. ACE inhibitors such as *captopril*,[2] *enalapril*,[1,3,5] and *lisinopril*[4,5] have been implicated, although in a study[6] of enalapril and lithium in healthy subjects, the lithium levels remained unchanged. The mechanism is unclear but it has been suggested[7] that suppression of the renin-angiotensin-aldosterone system by ACE inhibitors may be responsible. Lithium excretion by the kidney is dependent on both glomerular filtration and sodium concentration in the proximal tubule, both of which are reduced by ACE inhibitors. It has also been suggested[5] that inhibition of angiotensin II production may lead to reduced fluid intake through lack of activation of the thirst stimulus and this would enhance the tendency to volume depletion caused by natriuresis. Patients considered[7] to be at risk from this reaction would include those whose renal function is largely dependent on the effect of angiotensin II, those with congestive heart failure, and those with volume depletion.

1. Douste-Blazy P, *et al.* Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet* 1986; **i:** 1448.
2. Pulik M, Lida H. Interaction lithium-inhibiteurs de l'enzyme de conversion. *Presse Med* 1988; **17:** 755.
3. Navis GJ, *et al.* Volume homeostasis, angiotensin converting enzyme inhibition, and lithium therapy. *Am J Med* 1989; **86:** 621.
4. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* 1990; **24:** 946–7.
5. Correa FJ, Eiser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med* 1992; **93:** 108–9.
6. DasGupta K, *et al.* The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* 1992; **53:** 398–400.
7. Mignat C, Unger T. Ace inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Analgesics. See NSAIDs and Opioid Analgesics, below.

Angiotensin II receptor antagonists. There have been case reports of lithium intoxication occurring in patients after the addition of *candesartan*,[1] *losartan*,[2] or *valsartan*[3] to their therapy. The mechanism may be similar to that for ACE inhibitors (above).

1. Zwanzger P, *et al.*. Lithium intoxication after administration of AT blockers. *J Clin Psychiatry* 2001; **62:** 208–9.
2. Blanche P, *et al.* Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* 1997; **52:** 501.
3. Leung M, Remick RA. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* 2000; **20:** 392–3.

Antidepressants. Lithium has been used to augment the effect of other antidepressants in refractory depression. However, there have been reports of adverse reactions with some of these combinations. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Antiepileptics. Severe CNS toxicity despite 'normal' serum-lithium concentrations has been described in a patient also taking *phenytoin* and *phenobarbital*.[1] Symptoms indicative of lithium toxicity have also been reported in a patient taking lithium with phenytoin alone;[2] again concentrations were not abnormal.

For reports of neurotoxicity in patients receiving *carbamazepine* and lithium, see p.474. Carbamazepine-induced renal failure has also resulted in toxic serum-lithium concentrations.[3]

1. Speirs J, Hirsch SR. Severe lithium toxicity with "normal" serum concentrations. *BMJ* 1978; **1:** 815–16.
2. MacCallum WAG. Interaction of lithium and phenytoin. *BMJ* 1980; **280:** 610–11.
3. Mayan H, *et al.* Lithium intoxication due to carbamazepine-induced renal failure. *Ann Pharmacother* 2001; **35:** 560–2.

Antimicrobials. Lithium toxicity has been reported on isolated occasions in patients receiving *doxycycline*,[1] *metronidazole*,[2] *spectinomycin*,[3] and *tetracycline*.[4]

However, it has been noted that lithium and tetracycline have been used together without serious problems in many patients and that additionally tetracycline has been used to treat the acneform skin eruptions induced by lithium.[5] It has also been found[5] that in healthy subjects lithium concentrations were decreased, rather than increased, after the addition of tetracycline but this was probably of no clinical significance.

1. Miller SC. Doxycycline-induced lithium toxicity. *J Clin Psychopharmacol* 1997; **17:** 54–5.
2. Teicher MH, *et al.* Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987; **257:** 3365–6.
3. Anonymous. Possible adverse drug-drug interaction report: lithium intoxication in a spectinomycin-treated patient. *Int Drug Ther Newslett* 1978; **13:** 15.
4. McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* 1978; **1:** 1183.
5. Fankhauser MP, *et al.* Evaluation of lithium-tetracycline interaction. *Clin Pharm* 1988; **7:** 314–17.

Antimigraine drugs. For comment on the suggestion that there may be a risk of increased CNS toxicity when *sumatriptan* and lithium are given together, see p.626.

Antineoplastics. Transient decreases in serum-lithium concentration occurred in a patient given *cisplatin*.[1] The relative contributions of cisplatin itself, or the fluid loading procedure involving intravenous fluids and mannitol, or their combined effects were unclear. The interaction, however, had no apparent clinical significance in this patient although a risk of undertreatment with lithium may occur in other patients.

1. Pietruszka LJ, *et al.* Evaluation of cisplatin-lithium interaction. *Drug Intell Clin Pharm* 1985; **19:** 31–2.

Antipsychotics and anxiolytics. In the control of acute mania lithium is often too slow in onset to be used alone and therefore additional therapy with an antipsychotic may be necessary. It should be noted, however, that such combinations should be used with care as interactions and adverse reactions have occurred.

The renal excretion of lithium is increased by *chlorpromazine* treatment,[1] which means that subsequent withdrawal of chlorpromazine can result in an abrupt rise in serum-lithium concentrations.[2] The serum concentration of chlorpromazine can also be reduced by lithium,[3] and chlorpromazine toxicity may be precipitated by the abrupt withdrawal of lithium in patients previously stabilised on both drugs. Ventricular fibrillation has been described after withdrawal of lithium in a patient also taking chlorpromazine;[4] it was suggested that the chlorpromazine dose should be reduced if lithium is to be stopped.

There have been isolated reports of neurotoxicity or brain damage, characterised by delirium, seizures, encephalopathy, or an increased incidence of extrapyramidal symptoms in patients receiving lithium with *flupentixol decanoate*,[5] *fluphenazine decanoate*,[6] or high-dose *haloperidol*,[7-9] although two earlier retrospective studies of patients taking lithium with antipsychotics had failed to detect such adverse reactions.[10,11] Neurological reactions have also been reported in patients receiving lithium with *thioridazine*,[12,13] *sulpiride*,[14] *clozapine*,[15] and *risperidone*.[16] Although a causal relationship between these events and use of lithium with antipsychotics has not been fully established, patients should be monitored for signs of neurotoxicity if receiving such combinations.

A 1987 review considered that the neurotoxicity induced by lithium and antipsychotics was a rare entity.[17] Whether the combination produced any greater risk than either drug alone, and whether the neurotoxicity was a distinct diagnostic entity or simply represented atypical cases of lithium toxicity or the neuroleptic malignant syndrome, was debatable. The interaction between lithium and haloperidol might represent a form of neuroleptic malignant syndrome and that between lithium and the phenothiazines, especially thioridazine, a form of lithium toxicity. It was concluded that the risk from combination therapy was very small but that the clinician should, nevertheless, be aware of it.

Although lithium has been reported to interact with *diazepam* resulting in hypothermic episodes,[18] this may be an idiosyncratic response rather than a true drug interaction;[17] in general it was considered safe to use lithium with benzodiazepines.

1. Sletten I, *et al.* The effect of chlorpromazine on lithium excretion in psychiatric subjects. *Curr Ther Res* 1966; **8:** 441–6.
2. Pakes GE. Lithium toxicity with phenothiazine withdrawal. *Lancet* 1979; **ii:** 701.
3. Rivera-Calimlim L, *et al.* Effect of lithium on plasma chlorpromazine levels. *Clin Pharmacol Ther* 1978; **23:** 451–5.
4. Stevenson RN, *et al.* Ventricular fibrillation due to lithium withdrawal—an interaction with chlorpromazine? *Postgrad Med J* 1989; **65:** 936–8.
5. West A. Adverse effects of lithium treatment. *BMJ* 1977; **2:** 642.
6. Singh SV. Lithium carbonate/fluphenazine decanoate producing irreversible brain damage. *Lancet* 1982; **ii:** 278.
7. Cohen WJ, Cohen NH. Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 1974; **230:** 1283–7.
8. Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1976; **ii:** 1088.
9. Thomas C, *et al.* Lithium/haloperidol combinations and brain damage. *Lancet* 1982; **i:** 626.
10. Baastrup PC, *et al.* Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 1976; **236:** 2645–6.
11. Prakash R. Lithium-haloperidol combination and brain damage. *Lancet* 1982; **i:** 1468–9.
12. Standish-Barry HMAS, Shelly MA. Toxic neurological reaction to lithium/thioridazine. *Lancet* 1983; **i:** 771.
13. Cantor CH. Encephalopathy with lithium and thioridazine in combination. *Med J Aust* 1986; **144:** 164–5.
14. Dinan TG, O'Keane V. Acute extrapyramidal reactions following lithium and sulpiride co-administration: two case reports. *Hum Psychopharmacol Clin Exp* 1991; **6:** 67–9.
15. Blake LM, *et al.* Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 1992; **12:** 297–9.
16. Swanson CL, *et al.* Effects of concomitant risperidone and lithium treatment. *Am J Psychiatry* 1995; **152:** 1096.
17. Ross DR, Coffey CE. Neuroleptics and anti-anxiety agents. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 167–71.
18. Naylor GJ, McHarg A. Profound hypothermia on combined lithium carbonate and diazepam treatment. *BMJ* 1977; **2:** 22.

Benzodiazepines. See Antipsychotics and Anxiolytics, above.

Calcium-channel blockers. Neurotoxicity has been reported in a patient receiving lithium after the addition of *verapamil*.[1] Serum-lithium concentrations were still inside the accepted therapeutic range and it was considered that the similar actions of lithium and verapamil on neurosecretory processes may have been responsible. Verapamil has also been reported to decrease serum-lithium concentrations.[2] Neurotoxicity has also been reported in a patient receiving lithium and *diltiazem*[3] as well as other drugs. Psychosis, possibly induced by the use of diltiazem and lithium together, has been reported in another patient.[4]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.
3. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.
4. Binder EF, *et al.* Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.

Central stimulants. A woman who had been stabilised on lithium treatment for 15 months developed lithium toxicity within a few days of being given *mazindol*.[1]

There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *sibutramine*.

1. Hendy MS, *et al.* Mazindol-induced lithium toxicity. *BMJ* 1980; **280:** 684–5.

Diuretics. *Thiazide diuretics* produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in serum-lithium concentrations.[1] Patients who are stabilised on lithium therapy and begin taking thiazide diuretics are at significant risk of developing lithium toxicity. Toxic lithium concentrations may be seen within 3 to 5 days of starting a diuretic. *Loop diuretics* (*furosemide*, *bumetanide*, and *etacrynic acid*) seem less likely to cause lithium retention, although caution is warranted, especially in patients whose dietary sodium is restricted.[1] *Amiloride*, and probably other potassium-sparing diuretics, have no effect on lithium excretion, but *acetazolamide* increases lithium excretion. However, the diuretic action of acetazolamide is short-lived and the interaction may therefore be transient.[1]

It has therefore been suggested that if diuretic therapy is necessary in patients stabilised on lithium, the lithium dose should be reduced by 25 to 50%,[1,2] lithium concentrations measured twice weekly until re-stabilisation occurs, and that perhaps loop diuretics such as bumetanide or furosemide would be preferable.

The topic of lithium-diuretic interaction and precautions to be observed has also been discussed.[3]

1. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–3.
2. Ramsay LE. Interactions that matter: diuretics and antihypertensive drugs. *Prescribers' J* 1984; **24:** 60–5.
3. Grau E. Diuretics. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 180–3.

Gastrointestinal drugs. Giving *sodium bicarbonate* with lithium has led to reduced blood-lithium concentrations, attributed to increased renal excretion of the lithium cation in response to the extra load of bicarbonate anion to be excreted.[1] *Antacids* containing combinations of *aluminium and magnesium hydroxides* and *simeticone* had no effect on the dissolution and solubility of lithium carbonate *in vitro*[2] nor on its bioavailability *in vivo*.[3]

There has been a case report describing a possible interaction between lithium and *ispaghula* where low serum concentrations of lithium may have been due to ispaghula inhibiting intestinal absorption of lithium.[4]

There is an increased risk of extrapyramidal effects and the possibility of neurotoxicity when drugs such as *metoclopramide* are given to patients receiving lithium.

Use of *cisapride* with lithium may increase the risk of ventricular arrhythmias.

1. McSwiggan C. A significant drug interaction. *Aust J Pharm* 1978; **59:** 6.
2. Schiessler DM, *et al.* Effect of antacids on lithium carbonate dissolution and solubility in vitro. *Am J Hosp Pharm* 1983; **40:** 825–8.
3. Goode DL, *et al.* Effect of antacid on the bioavailability of lithium carbonate. *Clin Pharm* 1984; **3:** 284–7.
4. Perlman BB. Interaction between lithium salts and ispaghula husk. *Lancet* 1990; **335:** 416.

Ion-exchange resins. The cation-exchange resin *sodium polystyrene sulfonate* may decrease the absorption of lithium salts.

Methyldopa. Lithium toxicity induced by methyldopa has been described on a number of occasions.[1-3] Symptoms of toxicity may occur even though serum-lithium concentrations remain within the therapeutic range.

1. Byrd GJ. Methyldopa and lithium carbonate: suspected interaction. *JAMA* 1975; **233:** 320.
2. O'Regan JB. Adverse interaction of lithium carbonate and methyldopa. *Can Med Assoc J* 1976; **115:** 385–6.
3. Osanloo E, Deglin JH. Interaction of lithium and methyldopa. *Ann Intern Med* 1980; **92:** 433–4.

Muscle relaxants. For reports of hypothermic episodes occurring with lithium and *diazepam*, see under Antipsychotics and Anxiolytics, above.

Severe aggravation of hyperkinetic symptoms occurred in 2 patients with Huntington's chorea when *baclofen* was added to their treatment with lithium and haloperidol.[1]

1. Andén N-E, *et al.* Baclofen and lithium in Huntington's chorea. *Lancet* 1973; **ii:** 93.

Neuromuscular blockers. For reports of prolongation of neuromuscular blockade by lithium see under Atracurium, p.1904. For further comments relating to surgery and anaesthesia, see under Anaesthesia in Precautions, above.

NSAIDs. Decreased clearance and increased serum concentrations of lithium, resulting in toxicity on some occasions, have been reported after use of lithium with *celecoxib*,[1] *diclofenac*,[2] *ibuprofen*,[3,4] *indometacin*,[5,6] *ketorolac*,[7,8] *mefenamic acid*,[9,10] *naproxen*,[11] *piroxicam*,[12,13] *rofecoxib*,[14-16] and *tiaprofenic acid*;[17] secondary sources have also implicated *azapropazone, ketoprofen*,[18] *parecoxib*, and *phenylbutazone*.[18] However, serum-lithium concentration is not increased by *sulindac*.[11,19,20] Although serum-lithium concentrations were increased in a patient receiving *aspirin*[21] this has not been substantiated in others and an interaction is considered unlikely;[6,22] it has also been pointed out that control of sodium balance is necessary in such studies[22] and in the report purporting to demonstrate an interaction the diet had not been controlled.

It has been stated that for mild occasional aches, pains, and fever paracetamol was the preferred analgesic in patients receiving lithium, although occasional doses of aspirin were acceptable.[18] Sulindac appeared to be the safest NSAID for long-term use. Diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, phenylbutazone, and piroxicam should be avoided where possible but if it was necessary to use one of these drugs the maintenance dose of lithium should be reduced. It was also considered that perhaps other NSAIDs, for which no information was available at that time, should be regarded as having the potential to cause a rise in serum-lithium concentrations.

1. Slørdal L, *et al.* A life-threatening interaction between lithium and celecoxib. *Br J Clin Pharmacol* 2003; **55:** 413–14.
2. Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* 1981; **30:** 348–52.
3. Kristoff CA, *et al.* Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* 1986; **5:** 51–5.
4. Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J Clin Psychiatry* 1987; **48:** 161–3.
5. Frölich JC, *et al.* Indomethacin increases plasma lithium. *BMJ* 1979; **1:** 1115–16.
6. Reimann IW, *et al.* Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* 1983; **40:** 283–6.
7. Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. *Can Med Assoc J* 1994; **150:** 1455–6.
8. Iyer V. Ketorolac (Toradol) induced lithium toxicity. *Headache* 1994; **34:** 442–4.
9. Shelley RK. Lithium toxicity and mefenamic acid: a possible interaction and the role of prostaglandin inhibition. *Br J Psychiatry* 1987; **151:** 847–8.
10. MacDonald J, Neale TJ. Toxic interaction of lithium carbonate and mefenamic acid. *BMJ* 1988; **297:** 1339.
11. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* 1986; **6:** 150–4.
12. Kerry RJ, *et al.* Possible toxic interaction between lithium and piroxicam. *Lancet* 1983; **i:** 418–19.
13. Walbridge DG, Bazire SR. An interaction between lithium carbonate and piroxicam presenting as lithium toxicity. *Br J Psychiatry* 1985; **147:** 206–7.
14. Sajbel TA, *et al.* Pharmacokinetic effects of rofecoxib therapy on lithium. *Pharmacotherapy* 2001; **21:** 380.
15. Lundmark J, *et al.* A possible interaction between lithium and rofecoxib. *J Clin Pharmacol* 2002; **53:** 403–4.
16. Rätz Bravo AE, *et al.* Lithium intoxication as a result of an interaction with rofecoxib. *Ann Pharmacother* 2004; **38:** 1189–93.
17. Alderman CP, Lindsay KSW. Increased serum lithium concentration secondary to treatment with tiaprofenic acid and fosinopril. *Ann Pharmacother* 1996; **30:** 1411–3.
18. Furnell MM. Non-steroidal anti-inflammatory drugs. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 183–6.
19. Furnell MM, Davies J. The effect of sulindac on lithium therapy. *Drug Intell Clin Pharm* 1985; **19:** 374–6.
20. Ragheb MA, Powell AL. Failure of sulindac to increase serum lithium levels. *J Clin Psychiatry* 1986; **47:** 33–4.
21. Bendz H, Feinberg M. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 310–11.
22. Reimann I. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 311.

Opioid analgesics. There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *tramadol*.

Parasympathomimetics. For the effect of lithium on parasympathomimetics, see Interactions of Neostigmine, p.632.

Xanthines. It has been reported[1] that *theophylline* enhances the renal clearance of lithium, thus tending to reduce serum-lithium concentrations. Lithium blood concentrations increased by 24% when *caffeine* was eliminated from the diet of 11 patients taking lithium.[2] No toxicity was observed but these patients had been maintained on low baseline lithium concentrations; toxicity might occur in patients maintained at higher concentrations.

1. Cook BL, *et al.* Theophylline-lithium interaction. *J Clin Psychiatry* 1985; **46:** 278–9.
2. Mester R, *et al.* Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* 1995; **37:** 348–50.

Pharmacokinetics

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts. Absorption can be affected by the formulation of the preparation taken. Peak serum concentrations are obtained between 0.5 and 3 hours after ingestion from conventional tablets, capsules, or liquids; with modified-release formulations peak concentrations are delayed and may occur between 2 and 12 hours after a dose. Lithium is distributed throughout the body and distribution is complete within about 6 to 10 hours; higher concentrations occur in the bones, the thyroid gland, and portions of the brain, than in the serum.

Lithium is excreted mainly in the urine; only a small amount can be detected in the faeces, saliva, and sweat. It is not bound to plasma proteins. It crosses the placenta and is distributed into breast milk. The elimination half-life in patients with normal renal function is about 12 to 24 hours, but increases with decreasing renal function; half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not, therefore, be attained until 4 to 7 days after starting treatment.

There is wide intersubject variation in the serum concentrations obtained after a given dose, and also in those required for therapeutic effect. Concentrations also vary considerably according to factors such as the dosage regimen (whether given in single or divided daily doses), renal function, the dietary regimen of the patient, the patient's state of health, the time at which the blood sample is taken, and other medication, such as sodium salts or diuretics, as well as by formulation and bioavailability. Moreover, there is only a narrow margin between the therapeutic and the toxic serum concentration of lithium. Therefore, not only is individual titration of lithium dosage essential to ensure constant appropriate concentrations for the patient, but the conditions under which the blood samples are taken for monitoring must be carefully controlled. In practice, a blood sample drawn 12 hours after the last dose of lithium following a consistent dosing schedule for 4 to 7 days is used for measurement of serum-lithium concentrations. Under these conditions the distribution of the last dose of lithium is complete, and steady-state concentrations will have been attained. The usual maintenance therapeutic serum concentrations of lithium are 0.4 to 1 mmol/litre; toxic effects may be expected at concentrations exceeding 1.5 mmol/litre. For further details regarding monitoring of serum concentrations of lithium, see under Uses and Administration, below. Estimation of lithium concentrations in other body fluids such as saliva has been investigated as a less invasive method of monitoring. However, results have been equivocal and these methods have not replaced serum monitoring in general practice.

◊ References.

1. Ward ME, *et al.* Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994; **34:** 280–5.
2. Reiss RA, *et al.* Lithium pharmacokinetics in the obese. *Clin Pharmacol Ther* 1994; **55:** 392–8.
3. Thomsen K, Schou M. Avoidance of lithium intoxication: advice based on knowledge about the renal lithium clearance under various circumstances. *Pharmacopsychiatry* 1999; **32:** 83–6.
4. Sproule BA, *et al.* Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging* 2000; **16:** 165–77.

Administration. References concerning the pharmacokinetic methods of predicting lithium dosage requirements.

1. Marken PA, *et al.* Preliminary comparison of predictive and empiric lithium dosing: impact on patient outcome. *Ann Pharmacother* 1994; **28:** 1148–52.
2. Taright N, *et al.* Nonparametric estimation of population characteristics of the kinetics of lithium from observational and experimental data: individualization of chronic dosing regimen using a new Bayesian approach. *Ther Drug Monit* 1994 **16:** 258–69.
3. Sproule BA, *et al.* Fuzzy logic pharmacokinetic modeling: application to lithium concentration prediction. *Clin Pharmacol Ther* 1997; **62:** 29–40.
4. Wright R, Crimson ML. Comparison of three a priori methods and one empirical method in predicting lithium dosage requirements. *Am J Health-Syst Pharm* 2000; **57:** 1698–1702.

Cystic fibrosis. For a reference to reduced renal excretion of lithium in patients with cystic fibrosis, see under Precautions, above.

Distribution into breast milk. For references to the distribution of lithium into breast milk, see under Precautions, above.

Pregnancy. For references to changes in renal clearance of lithium during pregnancy, see under Precautions, above.

Uses and Administration

Lithium, given as one of its salts, provides a source of lithium ions, which compete with sodium ions at various sites in the body. It thus has an action and adverse effects distinct and separate from those of other antidepressants. Its mode of action is not understood, but it is effective in the management of **mania**, **bipolar disorder**, and **recurrent unipolar depression**. Since the margin between therapeutic and toxic serum concentrations is narrow the decision to give lithium is usually based on specialist advice; lithium should not be prescribed unless facilities for monitoring serum concentrations are available.

Treatment with lithium needs to be monitored by measurement of serum concentrations, which must be adjusted for each patient to give a clinical response without evidence of toxicity. There is evidence that patients are most likely to respond to concentrations of 0.8 mmol/litre or above, but individual patients may respond to concentrations as low as 0.4 mmol/litre, and it is impossible to identify these patients beforehand. Because toxic effects are associated with concentrations above 1.5 mmol/litre, and may occur with concentrations as low as 1 mmol/litre in susceptible patients such as the elderly, it is therefore recommended that doses are adjusted to provide a serum-lithium concentration of 0.4 to 1 mmol/litre (at the lower end of this range for maintenance therapy and elderly patients). Patients must be taught to recognise the symptoms of early lithium intoxication (see Adverse Effects, above) in order to omit further doses of lithium and seek medical care should it be impending.

The dose of lithium given depends on the preparation chosen since different preparations of lithium salts vary widely in bioavailability. This can be illustrated by the recommended doses for some UK preparations:

- *Camcolit* tablets (*Norgine, UK*) containing lithium carbonate; for treatment, initially 1 to 1.5 g daily; for prophylaxis, initially 300 to 400 mg daily
- *Li-Liquid* syrup (*Rosemont, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.018 to 3.054 g daily in two divided doses (elderly or patients less than 50 kg, 509 mg twice daily)
- *Liskonum* tablets (*GlaxoSmithKline, UK*) containing lithium carbonate; for treatment, initially 450 to 675 mg twice daily (elderly, 225 mg twice daily); for prophylaxis, initially 450 mg twice daily (elderly, 225 mg twice daily)
- *Priadel* tablets (*Sanofi-Aventis, UK*) containing lithium carbonate; for treatment and prophylaxis, initially 400 mg to 1.2 g daily as a single dose or in two divided doses (elderly or patients less than 50 kg, 200 to 400 mg daily)
- *Priadel* syrup (*Sanofi-Aventis, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.04 to 3.12 g daily in two divided doses (elderly or patients less than 50 kg, 520 mg to 1.04 g daily)

Doses of lithium are initially divided throughout the day; however, when serum-lithium concentrations are stabilised once-daily dosage may be preferred.

The initial dose given is adjusted after 4 to 7 days according to the results of serum-lithium estimations obtained under controlled conditions (samples being taken 12 hours after the preceding dose). Serum-lithium concentrations are then checked once a week until the dosage has remained constant for 4 weeks. The frequency of estimations can then be reduced to about once every 3 months. Should the patient's circumstances change such that the lithium pharmacokinetics or requirements might be affected, close control of serum concentrations should be reinstated until the concentrations stabilise once more. Such circumstances could involve a change of lithium preparation, an intercurrent illness (including a urinary-tract infection), a manic or depressive phase, a change in dietary regimen or body temperature, pregnancy, or use of other drugs (in particular, sodium-containing preparations and diuretics). For further details see Precautions and Interactions, above. Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Therefore, long-term treatment should only be undertaken if it is definitely indicated. Patients need to be regularly assessed and treatment should only continue after 3 to 5 years if the benefit persists.

Lithium is also used for the management of **aggressive or self-mutilating behaviour**. The doses are similar to those used in the prophylaxis of recurrent affective disorders described above.

Lithium is not licensed in the UK for use in children; however, the *BNFC* suggests that it may be considered, on the advice of a specialist, in the management of mania, bipolar disorder, recurrent depression, and aggressive or self-mutilating behaviour in those aged 12 years and over. Suggested doses are similar to those given above.

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse. For further details, see Withdrawal under Precautions, above.

Other lithium salts have been used in the treatment of psychiatric disorders and these include the acetate, gluconate, glutamate, and sulfate.

Homoeopathy. Lithium carbonate has been used in homoeopathic medicines under the following names: Lithium carbonicum; Lith. carb.

Lithium citrate has been used in homoeopathic medicines under the following names: Lithium citricum.

Anxiety disorders. Lithium has been tried as augmentation therapy in the treatment of obsessive-compulsive disorder (p.952).

Bipolar disorder. Lithium's main role in the management of bipolar disorder is for prophylaxis (see p.372). It is sometimes used in the control of the acute manic stage, but, because of its slow onset of action, usually with an antipsychotic.

References.

1. Aronson JK, Reynolds DJM. Lithium. *BMJ* 1992; **305:** 1273–6.
2. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994; **331:** 591–8.
3. Jensen HV, *et al.* Lithium prophylaxis of manic-depressive disorder: daily lithium dosing schedule versus every second day. *Acta Psychiatr Scand* 1995; **92:** 69–74.
4. Moncrieff J. Lithium revisited: a re-examination of the placebo-controlled trials of lithium prophylaxis in manic-depressive disorder. *Br J Psychiatry* 1995; **167:** 569–74.
5. Jensen HV, *et al.* Twelve-hour brain lithium concentration in lithium maintenance treatment of manic-depressive disorder: daily versus alternate-day dosing schedule. *Psychopharmacology (Berl)* 1996; **124:** 275–8.
6. Maj M, *et al.* Late non-responders to lithium prophylaxis in bipolar patients: prevalence and predictors. *J Affect Disord* 1996; **39:** 39–42.
7. Anonymous. Using lithium safely. *Drug Ther Bull* 1999; **37:** 22–4.
8. Burgess S, *et al.* Lithium for maintenance treatment of mood disorders. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 24/11/05).
9. Sproule B. Lithium in bipolar disorder: can drug concentrations predict therapeutic effect? *Clin Pharmacokinet* 2002; **41:** 639–60.
10. Geddes JR, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; **161:** 217–22.

Depression. Lithium may be used in the treatment and prophylaxis of recurrent unipolar depression, usually when standard antidepressants have failed (p.373). Lithium is also used to augment the efficacy of other antidepressants in refractory cases.

References.

1. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry* 1998; **59** (suppl 6): 28–33.
2. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 1999; **19:** 427–34. Correction. *ibid.* 2000; **20:** 287.
3. Sackeim HA, *et al.* Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy; a randomized controlled trial. *JAMA* 2001; **285:** 1299–1307.

Disturbed behaviour. For mention of lithium in the management of children with disturbed behaviour see p.954.

Headache. Lithium is one of a number of drugs tried in cluster headache (p.616) to prevent headache attacks during cluster periods when ergotamine is ineffective or has had to be withdrawn. In a double-blind study[1] lithium and verapamil were found to be of similar efficacy for cluster headache prophylaxis although verapamil appeared to produce fewer adverse effects. However, in a later placebo-controlled trial[2] lithium was found to be no more effective than the placebo and the trial was stopped early.

1. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
2. Steiner TJ, *et al.* Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997; **17:** 673–5.

Hyperthyroidism. Lithium has been tried in hyperthyroidism (p.2165), though its practical value is a matter of debate and, rarely, it may even cause hyperthyroidism (see Effects on the Endocrine System in Adverse Effects, above). Pretreatment with lithium has also been reported to prolong the exposure of the thyroid to radioactive iodine in patients with Graves' thyrotoxicosis.[1]

1. Bogazzi F, *et al.* Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with Graves' disease. *J Clin Endocrinol Metab* 2002; **87:** 4490–5.

Schizophrenia. The addition of lithium to antipsychotic treatment has been tried in patients with schizophrenia (p.955) or schizoaffective disorders who fail to respond to an antipsychotic alone. The results of a meta-analysis have suggested that lithium augmentation is of some benefit, particularly in those with schizoaffective disorders, although the evidence is inconsistent.[1] However, significantly more patients with lithium augmentation left the studies early, suggesting adverse effects may be problematic and the danger of an interaction between the drugs should also be borne in mind (see under Interactions, above).

1. Leucht S, *et al*. Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2004; **65:** 177–86.

Skin disorders. Some salts or derivatives of lithium (notably lithium succinate, p.1604, but also lithium gluconate) have been applied topically in preparations for seborrhoeic dermatitis.

References.

1. Dreno B, *et al*. Lithium gluconate 8% vs ketoconazole 2% in the treatment of seborrhoeic dermatitis: a multicentre, randomized study. *Br J Dermatol* 2003; **148:** 1230–6.

Preparations

BP 2008: Lithium Carbonate Tablets; Lithium Citrate Oral Solution; Prolonged-release Lithium Carbonate Tablets;
USP 31: Lithium Carbonate Capsules; Lithium Carbonate Extended-release Tablets; Lithium Carbonate Tablets; Lithium Citrate Syrup.

Proprietary Preparations (details are given in Part 3)
Arg.: Ceglution; Eskalit; Karlit; Lithium; ***Austral.:*** Lithicarb; Quilonum; ***Austria:*** Neurolepsin; Quilonorm; ***Belg.:*** Camcolit; Maniprex; Priadel; ***Braz.:*** Carbolim; Carbolitium; Litiocar†; Neurolithium; ***Canad.:*** Carbolith; Duralith; Lithane; ***Chile:*** Cabalex†; Cade L; Carbolit; Carboron; Psicolit; ***Cz.:*** Contemnol†; ***Denm.:*** Litarex; ***Fin.:*** Lito; ***Fr.:*** Lithioderm; Neurolithium; Teralithe; ***Ger.:*** Hypnorex; leukominerase†; Li 450†; Quilonum; ***Gr.:*** Lithiofor; Milithin; ***Hong Kong:*** Camcolit; Lithicarb; Lithiofor; ***Hung.:*** Liticarb; ***India:*** Licab; Staleth; ***Indon.:*** Frimania; ***Irl.:*** Camcolit; Priadel; ***Israel:*** Licarbium; ***Ital.:*** Carbolithium; ***Jpn:*** Limas; ***Malaysia:*** Priadel†; ***Mex.:*** Carbolit; Litheum; ***Neth.:*** Camcolit; Litarex; Priadel; ***Norw.:*** Lithionit; ***NZ:*** Lithicarb; Priadel; ***Philipp.:*** Quilonium-R; ***Port.:*** Priadel; ***S.Afr.:*** Camcolit; Lentolith; Quilonum; ***Singapore:*** Camcolit; Priadel†; ***Spain:*** Plenur; ***Swed.:*** Lithionit; ***Switz.:*** Litarex; Lithiofor; Neurolithium; Priadel; Quilonorm; ***Thai.:*** Licarb; Limed; Lit-300; Phanate; ***Turk.:*** Kilonum; Lithuril; ***UK:*** Camcolit; Li-Liquid; Liskonum; Lithonate; Priadel; ***USA:*** Eskalith†; Lithobid.

Multi-ingredient: ***Austral.:*** Caprilate; ***Ger.:*** NeyDop N (Revitorgan-Dilutionen N Nr 97)†; Togal Classic; ***Spain:*** Citinoides.

Lofepramine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de lofepramina; Leo-640; Lofépramine, Chlorhydrate de; Lofepramini Hydrochloridum; Lopramine Hydrochloride; WHR-2908A. 5-{3-[*N*-(Chlorophenacyl)-*N*-methylamino]propyl}-10,11-5*H*-dihydrodibenz[*b,f*]azepine hydrochloride.

Лофепрамина Гидрохлорид

$C_{26}H_{27}ClN_2O,HCl = 455.4.$

CAS — 23047-25-8 (lofepramine); 26786-32-3 (lofepramine hydrochloride).

ATC — N06AA07.

ATC Vet — QN06AA07.

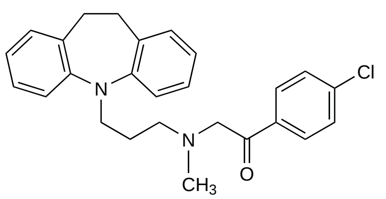

(lofepramine)

Pharmacopoeias. In *Br.*

BP 2008 (Lofepramine Hydrochloride). A fine, yellowish-white to green-yellow powder with a faint characteristic odour. It exhibits polymorphism. Very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376) although it has a lower incidence of antimuscarinic adverse effects. Lofepramine should be avoided in patients with severe hepatic or severe renal impairment.

Effects on the liver. See under Amitriptyline, p.377.

Overdosage. Lofepramine may be less toxic in overdosage than earlier tricyclics.[1] An analysis of data from the Office of National Statistics in England and Wales has also shown that the risk of death after an overdose with lofepramine was not significantly different from that associated with the SSRIs which, as a group, are considered to be safer in overdose than the tricyclics.[2]

1. Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990; **23:** 23–27.
2. Mason J, *et al*. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50:** 366–70.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Lofepramine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 hour of oral doses. Since lofepramine slows gastrointestinal transit time absorption can, however, be delayed, particularly in overdosage. It is extensively demethylated by first-pass metabolism in the liver to its active, primary metabolite, desipramine (p.387). Paths of metabolism also include *N*-oxidation and hydroxylation. The plasma half-life is about 5 hours. Lofepramine is mainly excreted in the urine, chiefly in the form of its metabolites. Up to 99% of lofepramine is bound to plasma proteins. Lofepramine is distributed into breast milk.

Uses and Administration

Lofepramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). One of its metabolites is desipramine (p.387). Lofepramine is one of the less sedating tricyclics.

In the treatment of depression (p.373) lofepramine is given orally as the hydrochloride although doses are expressed in terms of the base. Lofepramine hydrochloride 76.1 mg is equivalent to about 70 mg of lofepramine. The usual dose is the equivalent of 70 mg two or three times daily.

Lofepramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in the elderly. UK licensed drug information suggests that some elderly patients may respond to lower than usual doses of lofepramine, but in a study[1] involving 46 elderly patients with various grades of depression lofepramine 70 mg once daily was no more effective than placebo at the end of 28 days of treatment.

1. Tan RSH, *et al*. The effect of low dose lofepramine in depressed elderly patients in general medical wards. *Br J Clin Pharmacol* 1994; **37:** 321–4.

Preparations

BP 2008: Lofepramine Tablets.

Proprietary Preparations (details are given in Part 3)
Cz.: Tymelyt†; ***Denm.:*** Tymelyt†; ***Ger.:*** Gamonil†; ***Irl.:*** Gamanil; ***Port.:*** Deprimil†; ***S.Afr.:*** Emdalen; ***Spain:*** Deftan†; ***Swed.:*** Tymelyt†; ***Switz.:*** Gamonil†; ***UK:*** Feprapax†; Gamanil†; Lomont.

Maprotiline *(BAN, USAN, rINN)*

Maprotiliini; Maprotilin; Maprotilina; Maprotilinum. 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propyl(methyl)amine; *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propylamine.

Мапротилин

$C_{20}H_{23}N = 277.4.$

CAS — 10262-69-8.

ATC — N06AA21.

ATC Vet — QN06AA21.

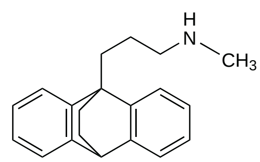

Maprotiline Hydrochloride *(BANM, rINNM)*

Ba-34276; Hidrocloruro de maprotilina; Maprotiliinihydrokloridi; Maprotilin Hidroklorür; Maprotiline, chlorhydrate de; Maprotilin-hidroklorid; Maprotilin-hydrochlorid; Maprotilinhydroklorid; Maprotilini hydrochloridum; Maprotilino hidrochloridas.

Мапротилина Гидрохлорид

$C_{20}H_{23}N,HCl = 313.9.$

CAS — 10347-81-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Maprotiline Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. Slightly soluble in water; soluble in alcohol; very slightly soluble in acetone; sparingly soluble in dichloromethane; freely soluble in methyl alcohol.

USP 31 (Maprotiline Hydrochloride). A fine white to off-white, practically odourless, crystalline powder. Slightly soluble in water; freely soluble in chloroform and in methyl alcohol; practically insoluble in isooctane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Adverse effects with maprotiline, a tetracyclic antidepressant, are broadly similar to those with tricyclic antidepressants (see Amitriptyline, p.376) but antimuscarinic effects are less frequent.

Skin rashes seem more common with maprotiline than with tricyclic antidepressants. Seizures have occurred in patients with no prior history of such disorders as well as in those with a history of epilepsy and the risk is increased if high doses of maprotiline are given. It should not be used in patients with epilepsy or a lowered seizure threshold.

Incidence of adverse effects. By March 1985 the UK CSM[1] had received reports of the following adverse reactions associated with maprotiline from a cumulative total of 2.5 million prescriptions: convulsions (124), hepatic reactions (4), and haematological reactions (8). There had also been 454 reports of skin rashes.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the skin. In addition to many recorded instances of skin rashes with maprotiline (see Incidence of Adverse Effects, above) cutaneous vasculitis, which resolved on stopping therapy, has also been seen.[1]

1. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med* 1985; **15:** 256–7.

Epileptogenic effect. In a retrospective review of 186 psychiatric patients with no history of seizures, 5 of 32 patients taking maprotiline developed generalised tonic-clonic seizures, compared with 1 of 45 receiving a tricyclic antidepressant.[1] There were no seizures in the remaining patients who received other medications, or no drug treatment. Two of the 5 patients having seizures with maprotiline were taking doses of 75 to 150 mg daily, 2 were taking daily doses of 200 to 300 mg, and one patient had partial complex seizures with a daily dose of 150 mg and generalised tonic-clonic seizures after increasing the daily dose to 300 mg.

1. Jabbari B, *et al*. Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 1985; **42:** 480–1.

Overdosage. Apart from seizures being more common with maprotiline, features of overdosage are similar to those experienced with tricyclic antidepressant poisonings (see Adverse Effects of Amitriptyline, p.376).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

References.

1. Crome P, Newman B. Poisoning with maprotiline and mianserin. *BMJ* 1977; **2:** 260.
2. Curtis RA, *et al*. Fatal maprotiline intoxication. *Drug Intell Clin Pharm* 1984; **18:** 716–20.
3. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.
4. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.

Porphyria. Maprotiline hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Interactions associated with maprotiline are similar to those associated with tricyclic antidepressants (see Amitriptyline, p.379).

Pharmacokinetics

Maprotiline is slowly but completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within 8 hours of an oral dose. It is widely distributed throughout the body and plasma protein binding is about 88 to 89%.

Maprotiline is extensively demethylated in the liver to its principal active metabolite, desmethylmaprotiline; paths of metabolism of both maprotiline and desmethylmaprotiline include *N*-oxidation, aliphatic and aromatic hydroxylation, and the formation of aromatic methoxy derivatives. In addition to desmethylmaprotiline, maprotiline-*N*-oxide is also reported to be pharmacologically active. The average elimination half-life of maprotiline is reported to be about 43 hours and that of its active metabolite even longer (range 60 to 90 hours). Maprotiline is excreted in the urine, mainly in the form of its metabolites, either in free or in conjugated form; appreciable amounts are also excreted in the faeces.

Maprotiline is distributed into breast milk (see Breast Feeding under Precautions of Amitriptyline, p.378).

◊ References.

1. Maguire KP, *et al*. An evaluation of maprotiline: intravenous kinetics and comparison of two oral doses. *Eur J Clin Pharmacol* 1980; **18:** 249–54.
2. Alkalay D, *et al*. Bioavailability and kinetics of maprotiline. *Clin Pharmacol Ther* 1980; **27:** 697–703.
3. Firkusny L, Gleiter H. Maprotiline metabolism appears to co-segregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994; **37:** 383–8.

Uses and Administration

Maprotiline is a tetracyclic antidepressant with actions and uses similar to those of tricyclic antidepressants (see Amitriptyline, p.381). It is one of the more sedating antidepressants but antimuscarinic effects are less marked. Like the tricyclics, maprotiline is an inhibitor of the reuptake of noradrenaline; it also has weak affinity for central adrenergic (α_1) receptors.

Maprotiline is usually given orally as the hydrochloride but it has also been given by injection as the mesilate and in oral drops as the resinate.

In the treatment of depression (p.373) maprotiline hydrochloride is given in oral doses of 25 to 75 mg daily in divided doses, gradually increased to 150 mg daily if necessary; up to 225 mg daily may be required in severely depressed patients in hospital. The dosage should be adjusted after 2 weeks according to response. Because of the prolonged half-life of maprotiline the total daily dose may also be given as a single dose. A suggested initial dose for elderly patients is 25 mg daily gradually increased according to response to 50 to 75 mg daily.

Maprotiline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

USP 31: Maprotiline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Ludiomil; ***Belg.:*** Ludiomil; ***Braz.:*** Ludiomil; ***Canad.:*** Ludiomil†; ***Chile:*** Mapromil; ***Cz.:*** Ludiomil; Maprotibene; ***Denm.:*** Ludiomil; Maludil; ***Fr.:*** Ludiomil; ***Ger.:*** Deprilept; Ludiomil; Maprolu; ***Gr.:*** Aprotilin†; Ludiomil; ***Hong Kong:*** Ludiomil†; ***Hung.:*** Ludiomil; Maprolu†; ***Indon.:*** Ludiomil; Ludios; Sandepril; Tilsan; ***Israel:*** Melodil; ***Ital.:*** Ludiomil; ***Malaysia:*** Ludiomil; ***Mex.:*** Ludiomil; ***Neth.:*** Ludiomil; ***NZ:*** Ludiomil; ***Pol.:*** Ludiomil; ***Port.:*** Ludiomil; ***Rus.:*** Ludiomil (Людиомил); ***S.Afr.:*** Ludiomil; ***Singapore:*** Ludiomil†; ***Spain:*** Ludiomil; ***Swed.:*** Ludiomil; ***Switz.:*** Ludiomil; ***Thai.:*** Ludiomil; ***Turk.:*** Ludiomil; Maprotil; ***UK:*** Ludiomil†; ***Venez.:*** Ludiomil.

Melitracen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de melitraceno; Mélitracène, Chlorhydrate de; Melitraceni Hydrochloridum; N-7001; U-24973A. 3-(9,10-Dihydro-10,10-dimethyl-9-anthrylidene)propyldimethylamine hydrochloride.

Мелитрацена Гидрохлорид

$C_{21}H_{25}N,HCl = 327.9.$

CAS — 5118-29-6 (melitracen); 10563-70-9 (melitracen hydrochloride).

ATC — N06AA14.

ATC Vet — QN06AA14.

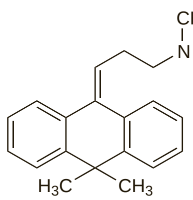

(melitracen)

Profile

Melitracen is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression (p.373) melitracen is given orally as the hydrochloride although doses are expressed in terms of the base; melitracen hydrochloride 28.1 mg is equivalent to about 25 mg of melitracen. The recommended initial dose is the equivalent of 25 mg two or three times daily gradually increased to a total of 225 mg daily if necessary. Elderly patients should generally be given reduced doses of 25 or 30 mg daily initially. Melitracen may also be given in lower doses with flupentixol (p.997) in the management of depression with anxiety. A combination of melitracen 10 mg and flupentixol 500 micrograms is given orally in the morning and at midday. In severe cases the morning dose may be doubled. The total daily dose should not exceed melitracen 40 mg and flupentixol 2 mg. Elderly patients may be given melitracen 10 mg with flupentixol 500 micrograms in the morning; in severe cases this dose may be given in the morning and at midday.

Melitracen should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Dixeran; ***Belg.:*** Dixeran†.

Multi-ingredient: *Austria:* Deanxit; ***Belg.:*** Deanxit; ***Hong Kong:*** Anfree; Deanxit; ***Ital.:*** Deanxit†; ***Singapore:*** Deanxit; ***Spain:*** Deanxit; ***Switz.:*** Deanxit; ***Thai.:*** Deanxit.

Mianserin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de mianserina; Mianseriinihydrokloridi; Mianserin Hidroklorür; Miansérine, chlorhydrate de; Mianserin-hydrochlorid; Mianserinhydroklorid; Mianserini hydrochloridum; Mianserino hidrochloridas; Mianseryny chlorowodorek; Mianszerin-hidroklorid; Org-GB-94. 1,2,3,4,10,14b-Hexahydro-2-methyldibenzo[*c,f*]pyrazino[1,2-*a*]azepine hydrochloride.

Миансерина Гидрохлорид

$C_{18}H_{20}N_2,HCl = 300.8.$

CAS — 24219-97-4 (mianserin); 21535-47-7 (mianserin hydrochloride).

ATC — N06AX03.

ATC Vet — QN06AX03.

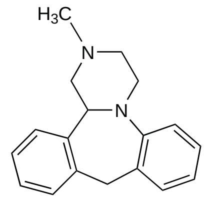

(mianserin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Mianserin Hydrochloride). A white or almost white crystalline powder or crystals. Sparingly soluble in water; slightly soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects

Antimuscarinic and cardiac adverse effects are fewer and milder with mianserin, a tetracyclic antidepressant, than with tricyclic antidepressants but effects are otherwise broadly similar (see Amitriptyline, p.376); mianserin may be associated with a lower risk of cardiotoxicity in overdosage.

The most common adverse effect associated with mianserin is drowsiness. Mianserin also causes bone-marrow depression usually presenting as leucopenia, granulocytopenia, or agranulocytosis; aplastic anaemia has been reported. These adverse haematological reactions generally occur during the first few weeks of therapy and especially in the elderly.

Other adverse effects reported include disturbances of liver function and jaundice, breast disorders (gynaecomastia, nipple tenderness, and non-puerperal lactation), and polyarthropathy.

Effects on the blood. Between 1976 and the end of 1988 the UK CSM had received 239 reports of adverse haematological reactions associated with mianserin use.[1] The reports included 68 of agranulocytosis and 84 of granulocytopenia or leucopenia where mianserin was considered to be the probable or possible cause; there had been 17 fatalities. Allowing for the pattern of prescribing there was a greater number of reports of white blood cell disorders in patients over 65 years of age but there was no sex difference. The data also indicated that the adverse reactions were most likely to develop during the first 3 months of therapy. By the end of 1992 the number of reports of mianserin-induced agranulocytosis or neutropenia received by the CSM[2] had risen to 79 and 105, respectively.

A case of fatal aplastic anaemia associated with mianserin use has also been reported.[3]

Proposed mechanisms of mianserin haematotoxicity have included a direct toxicity[4] and an immunologically-mediated mechanism.[5] There is evidence from studies *in vitro* of a significant correlation between the desmethyl metabolite and cytotoxicity. Mianserin is given as a racemic preparation and the formation of metabolites was greater with the *R*(−)-enantiomer than with the *S*(+)-enantiomer.[6]

1. CSM. Mianserin and white blood cell disorders in the elderly. *Current Problems 25* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024441&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
3. Durrant S, Read D. Fatal aplastic anaemia associated with mianserin. *BMJ* 1982; **285:** 437.
4. O'Donnell JL, *et al.* Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics. *BMJ* 1985; **291:** 1375–6.
5. Stricker BHC, *et al.* Thrombocytopenia and leucopenia with mianserin-dependent antibodies. *Br J Clin Pharmacol* 1985; **19:** 102–4.
6. Riley RJ, *et al.* A stereochemical investigation of the cytotoxicity of mianserin metabolites in vitro. *Br J Clin Pharmacol* 1989; **27:** 823–30.

Effects on the cardiovascular system. Although mianserin is considered to be less cardiotoxic than the tricyclic antidepressants adverse effects have been noted in individual patients. Two elderly patients developed signs of disturbed cardiac function (cardiac failure, atrial and ventricular fibrillation, bradycardia, and frequent ventricular ectopic beats) which resolved after the drug was stopped.[1] One of the patients also developed hypokalaemia which was possibly caused by mianserin. It was suggested that persons most likely to experience problems were the elderly with a history of cardiovascular disorders. Further reports of mianserin-induced cardiac effects include recurrent ventricular fibrillation in a 61-year-old man after an overdose of mianserin[2] and bradycardia in a 50-year-old woman after a therapeutic dose.[3]

1. Whiteford H, *et al.* Disturbed cardiac function possibly associated with mianserin therapy. *Med J Aust* 1984; **140:** 166–7.
2. Haefeli WE, *et al.* Recurrent ventricular fibrillation in mianserin intoxication. *BMJ* 1991; **302:** 415–16.
3. Carcone B, *et al.* Symptomatic bradycardia caused by mianserin at therapeutic doses. *Hum Exp Toxicol* 1991; **10:** 383–4.

Effects on the liver. By March 1985 the UK CSM had received 57 reports of hepatic reactions associated with mianserin use from a total of 5 million prescriptions. Reactions had included jaundice and other abnormalities of liver function, but no fatalities had been reported.[1]

Case reports have also been published concerning jaundice;[2-5] liver function returned to normal after stopping mianserin or lowering the dose.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. Adverse Drug Reactions Advisory Committee. Mianserin: a possible cause of neutropenia and agranulocytosis. *Med J Aust* 1980; **2:** 673–4.
3. Goldstraw PW, *et al.* Mianserin and jaundice. *N Z Med J* 1983; **96:** 985.
4. Zarski J-P, *et al.* Toxicité hépatique des nouveaux anti-dépresseurs: a propos d'une observation. *Gastroenterol Clin Biol* 1983; **7:** 220–1.
5. Otani K, *et al.* Hepatic injury caused by mianserin. *BMJ* 1989; **299:** 519.

Effects on the musculoskeletal system. A patient developed an acute polyarthritis affecting the hands and feet 6 days after starting therapy with mianserin;[1] at that time the UK CSM had received 19 reports of arthritis and arthralgia associated with mianserin. For the suggestion that effects at serotonin receptors may be involved in such adverse effects see under Mirtazapine, p.410.

1. Hughes A, Coote J. Arthropathy associated with treatment with mianserin. *BMJ* 1986; **292:** 1050.

Effects on the skin. Reports of adverse dermatological reactions in individual patients related to mianserin therapy have included toxic epidermal necrolysis[1] and erythema multiforme.[2,3]

1. Randell P. Tolvon and toxic epidermal necrolysis. *Med J Aust* 1979; **2:** 653.
2. Quraishy E. Erythema multiforme during treatment with mianserin—a case report. *Br J Dermatol* 1981; **104:** 481.
3. Cox NH. Erythema multiforme due to mianserin—a case against generic prescribing. *Br J Clin Pract* 1985; **39:** 293–4.

Effects on the tongue. Glossitis associated with mianserin therapy was reported in 2 patients.[1] Additionally, glossitis accompanied by severe facial oedema has been noted in another patient.[2] In all cases symptoms resolved after withdrawal of mianserin.

1. de la Fuente JR, Berlanga C. Glossitis associated with mianserin. *Lancet* 1984; **i:** 233.
2. Leibovitch G, *et al.* Severe facial oedema and glossitis associated with mianserin. *Lancet* 1989; **ii:** 871–2.

Epileptogenic effect. By March 1985 the UK CSM had received 64 reports of convulsions associated with mianserin use from a total of 5 million prescriptions.[1] In a previous review[2] concerning 40 of these cases it was considered that a causal connection could be established only in a minority. It was suggested that mianserin is no more epileptogenic than tricyclic antidepressants, an opinion that was also shared by other reviewers.[3]

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Edwards JG, Glen-Bott M. Mianserin and convulsive seizures. *Br J Clin Pharmacol* 1983; **15:** 299S–311S.
3. Richens A, *et al.* Antidepressant drugs, convulsions and epilepsy. *Br J Clin Pharmacol* 1983; **15:** 295S–298S.

Overdosage. Experience with 100 consecutive cases of intoxication with mianserin[1] revealed that when it was the only drug ingested symptoms were mild and neither deep coma nor convulsions occurred. More serious symptoms and 2 fatalities were seen in patients who had taken multiple drug overdoses. The results suggested that after an acute overdose mianserin is less toxic than the tricyclic antidepressants. This conclusion was also supported by a large follow-up study[2] comparing the outcome of suicide attempts among patients who had taken mianserin in overdose with those who had taken amitriptyline.

1. Chand S, *et al.* One hundred cases of acute intoxication with mianserin hydrochloride. *Pharmakopsychiatrie* 1981; **14:** 15–17.
2. Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; **ii:** 90–2.

Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.378). Although mianserin is less cardiotoxic than the tricyclic antidepressants, it still should be used with caution in patients with cardiovascular disorders, such as heart block, or after recent myocardial infarction. Similarly, patients with angle-closure glaucoma or prostatic hyperplasia should be monitored even though antimuscarinic effects are rare. Mianserin should be used with caution in patients with diabetes mellitus, epilepsy, and hepatic or renal impairment; it should be avoided in severe hepatic disease.

Patients should be carefully monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

A full blood count is recommended every 4 weeks during the first 3 months of treatment with mianserin, because of the risk of bone-marrow depression. Similarly, if a patient receiving mianserin develops fever, sore throat, stomatitis, or other signs of infection, treatment should be stopped and a full blood count obtained. The elderly are considered to be at special risk of blood disorders from mianserin. For further details see Effects on the Blood under Adverse Effects, above.

UK licensed drug information recommends that mianserin should not be given during breast feeding, but the *BNF* considers the amount distributed into breast milk too small to be harmful.

Porphyria. Mianserin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals.*

Interactions

It is recommended that mianserin should not be given to patients receiving MAOIs or for at least 14 days afterwards. At least one week should elapse between withdrawing mianserin and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Unlike the tricyclics (p.379), mianserin does not diminish the effects of the antihypertensives guanethidine, hydralazine, propranolol, or clonidine. However, it is still recommended that blood pressure be monitored when mianserin is prescribed with antihypertensive therapy. Plasma-phenytoin concentrations should be monitored carefully in patients also treated with mianserin; phenytoin has also been reported to reduce concentrations of mianserin (see below). There may be potentiation of effects when mianserin is given with CNS depressants such as alcohol, anxiolytics, or antipsychotics.

Antiepileptics. Reduced plasma concentrations and half-lives of mianserin and desmethylmianserin were seen in 6 patients also receiving antiepileptic therapy consisting of *phenytoin* with either *carbamazepine* or *phenobarbital.*[1] Carbamazepine alone may also reduce the plasma concentration of mianserin.[2,3]

Mianserin may antagonise the action of antiepileptics by lowering the convulsive threshold.

1. Nawishy S, *et al.* Kinetic interaction of mianserin in epileptic patients on anticonvulsant drugs. *Br J Clin Pharmacol* 1982; **13:** 612P–13P.
2. Leinonen E, *et al.* Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 1991; **11:** 313–18.
3. Eap CB, *et al.* Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 1999; **21:** 166–70.

Pharmacokinetics

Mianserin is readily absorbed from the gastrointestinal tract, but its bioavailability is reduced by extensive first-pass metabolism in the liver.

Paths of metabolism of mianserin include aromatic hydroxylation, *N*-oxidation, and *N*-demethylation. Desmethylmianserin and 8-hydroxymianserin are pharmacologically active.

Mianserin is excreted in the urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces.

Mianserin is widely distributed throughout the body and is extensively bound to plasma proteins. It has been found to have a biphasic plasma half-life with the duration of the terminal phase ranging from about 6 to 40 hours. Mianserin crosses the blood-brain barrier and the placenta. It is distributed into breast milk.

◊ References.

1. Hrdina PD, *et al.* Mianserin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **33:** 757–62.
2. Pinder RM, Van Delft AML. The potential therapeutic role of enantiomers and metabolites of mianserin. *Br J Clin Pharmacol* 1983; **15:** 269S–276S.
3. Timmer CJ, *et al.* Absolute bioavailability of mianserin tablets and solution in healthy humans. *Eur J Drug Metab Pharmacokinet* 1985; **10:** 315–23.
4. Begg EJ, *et al.* Variability in the elimination of mianserin in elderly patients. *Br J Clin Pharmacol* 1989; **27:** 445–51.
5. Buist A, *et al.* Mianserin in breast milk. *Br J Clin Pharmacol* 1993; **36:** 133–4.
6. Dahl M-L, *et al.* Stereoselective disposition of mianserin is related to debrisoquin hydroxylation polymorphism. *Clin Pharmacol Ther* 1994; **56:** 176–83.

Uses and Administration

Mianserin is a tetracyclic antidepressant. It does not appear to have significant antimuscarinic properties, but has a marked sedative action. Unlike the tricyclic antidepressants (see Amitriptyline, p.381), mianserin does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic adrenergic (α_2) receptors and increases the turnover of brain noradrenaline. Mianserin is also an antagonist of postsynaptic serotonin receptors in some parts of the brain.

In the treatment of depression (p.373) mianserin hydrochloride is given in initial oral doses of 30 to 40 mg daily increased gradually thereafter as necessary. The effective daily dosage is usually between 30 and 90 mg. The daily dosage may be divided throughout the day or given as a single dose at night. Divided daily dosages of up to 200 mg have been given. The recommended initial daily dose in the elderly is not more than 30 mg, which may be slowly increased if necessary.

Mianserin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Mianserin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Lerivon; ***Austral.:*** Lumin; Tolvon; ***Austria:*** Miabene†; Tolvon; ***Belg.:*** Lerivon; ***Braz.:*** Tolvon; ***Chile:*** Athimil; Prevalina; ***Cz.:*** Lerivon; Miabene; ***Denm.:*** Tolmin; Tolvon; ***Fin.:*** Miaxan; Tolvon; ***Fr.:*** Athymil; ***Ger.:*** Hopacem†; Mianeurin; Prisma†; Tolvin; ***Hong Kong:*** Tolvon; ***Hung.:*** Tolvon; ***India:*** Depnon; ***Irl.:*** Tolvon; ***Israel:*** Bonserin; ***Ital.:*** Lantanon; ***Mex.:*** Tolvon; ***Neth.:*** Tolvon; ***Norw.:*** Tolvon; ***NZ:*** Tolvon; ***Pol.:*** Lerivon; Mianserck; Norserin; ***Port.:*** Tolvon; ***Rus.:*** Lerivon (Леривон); ***S.Afr.:*** Lantanon; ***Spain:*** Lantanon; ***Swed.:*** Tolvon; ***Switz.:*** Amirine; Tolvon; ***Thai.:*** Mealin; Ornate†; Servin; Tolimed; Tolvon; ***Turk.:*** Tolvon; ***Venez.:*** Athimil†.

Milnacipran Hydrochloride *(BANM, rINNM)*

F-2207 (milnacipran); Hidrocloruro de milnaciprán; Midalcipran Hydrochloride; Milnacipran, Chlorhydrate de; Milnaciprani Hydrochloridum. (±)-*cis*-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide hydrochloride.

Мильнаципрана Гидрохлорид

$C_{15}H_{22}N_2O,HCl = 282.8.$

CAS — 92623-85-3 (milnacipran); 101152-94-7 (milnacipran hydrochloride); 175131-61-0 (milnacipran hydrochloride).

ATC — N06AX17.

ATC Vet — QN06AX17.

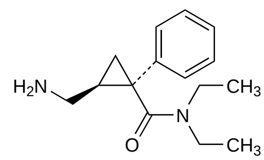

(milnacipran)

Profile

Milnacipran hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427) used for the treatment of depression (p.373). It is given in usual oral doses of 50 mg twice daily. Milnacipran is also being investigated in the treatment of fibromyalgia.

◊ References.

1. Tignol J, *et al.* Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode. *Acta Psychiatr Scand* 1998; **97:** 157–65.
2. Spencer CM, Wilde MI. Milnacipran: a review of its use in depression. *Drugs* 1998; **56:** 405–27.
3. Rouillon F, *et al.* Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. *Int Clin Psychopharmacol* 2000; **15:** 133–40.
4. Clerc G. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int Clin Psychopharmacol* 2001; **16:** 145–51.
5. Fukuchi T, Kanemoto K. Differential effects of milnacipran and fluvoxamine, especially in patients with severe depression and agitated depression: a case-control study. *Int Clin Psychopharmacol* 2002; **17:** 53–8.
6. Vitton O, *et al.* A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol* 2004; **19** (suppl 1): S27–S35.

Interactions. ***ANTIMIGRAINE DRUGS.*** There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin (5-HT_1) agonists such as *sumatriptan* (see p.626).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dalcipran; Ixel; ***Austria:*** Dalcipran; Ixel; ***Braz.:*** Ixel; ***Chile:*** Ixel; ***Cz.:*** Dalcipran; Ixel; ***Fin.:*** Ixel; ***Fr.:*** Ixel; ***Israel:*** Ixel; ***Jpn:*** Toledomin; ***Pol.:*** Ixel; ***Port.:*** Dalcipran; Ixel; ***Rus.:*** Ixel (Иксел); ***Turk.:*** Ixel.

Mirtazapine *(BAN, USAN, rINN)*

6-Azamianserin; Mepirzapin; Mepirzepine; Mirtatsapiini; Mirtazapin; Mirtazapina; Mirtazapinum; Org-3770. (*RS*)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

Миртазапин

$C_{17}H_{19}N_3 = 265.4.$

CAS — 61337-67-5.

ATC — N06AX11.

ATC Vet — QN06AX11.

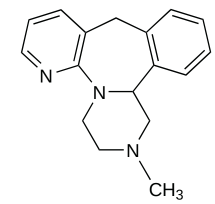

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mirtazapine). A white or almost white powder, slightly hygroscopic to hygroscopic. It exhibits polymorphism. Practically insoluble in water; freely soluble in anhydrous alcohol. Store in airtight containers.

USP 31 (Mirtazapine). It is anhydrous or contains one-half molecule of water of hydration. A white to creamy white, crystalline powder. Practically insoluble in water; soluble in solvent ether; sparingly soluble in *n*-hexane; freely soluble in methyl alcohol and in toluene. Store in airtight containers.

Adverse Effects

Adverse effects commonly reported with mirtazapine are an increase in appetite and weight, and oedema; drowsiness or sedation generally occur during the first few weeks of treatment. Dizziness, headache, and increases in liver enzyme levels have been reported less commonly; jaundice may occur. Other rarely reported adverse effects include orthostatic hypotension, skin rashes, nightmares, agitation, mania, hallucinations, paraesthesia, convulsions, tremor, myoclonus, psychomotor restlessness including akathisia, restless legs syndrome, arthralgia, myalgia, and reversible agranulocytosis, leucopenia, and granulocytopenia.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Incidence of adverse effects. The Australian Adverse Drug Reactions Advisory Committee has reported[1] that, up to October 2003, it had received 253 reports of adverse reactions associated with the use of mirtazapine. The most frequently reported reactions were oedema (33), anxiety or agitation (24), myalgia or arthralgia (24), sedation (23), and skin reactions (20). Other reactions included hyperkinesis, diarrhoea, and nausea and vomiting. There were 16 cases of convulsions, all in patients without a history of epilepsy. Blood dyscrasias were also reported and included 8 cases of neutropenia, 6 of thrombocytopenia, and 1 each of lymphopenia and pancytopenia; in the majority of cases onset was within 2 months of starting mirtazapine.

A prescription-event monitoring study conducted in England identified 13 554 patients who had been prescribed mirtazapine during the first 2 years of marketing in the UK;[2] within this cohort, 807 adverse drug reactions were reported in 573 patients. The most common adverse reactions included drowsiness or sedation (116), malaise (71), dizziness (57), nausea and vomiting (33), weight gain (31), and headache or migraine (21). Facial oedema (5), allergy (3), bone marrow toxicity (2), and myelodysplasia (1) were the more serious suspected adverse reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Convulsions and blood dyscrasias with mirtazapine. *Aust Adverse Drug React Bull* 2003; **22:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0310.pdf (accessed 24/11/05)
2. Biswas PN, *et al.* The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. *J Psychopharmacol* 2003; **17:** 121–6.

Effects on the endocrine system. An elderly woman developed *hyponatraemia* within 4 days of starting mirtazapine at a dose of 15 mg at night.[1] Apart from her age, other risk factors for hyponatraemia included diuretic use and a previous episode while taking venlafaxine.

1. Roxanas MG. Mirtazapine-induced hyponatraemia. *Med J Aust* 2003; **179:** 453–4.

Effects on mental state. An Expert Working Group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs particularly the risk of suicidal behaviour in children; the safety of mirtazapine (another serotonergic antidepressant) was also considered. In its final report[1] in December 2004, the group concluded that data from trials received by the CSM had failed to show that mirtazapine was effective in the treatment of depression in **adolescents and children** under 18 years old, although the risk of suicidal behaviour was not increased. Consequently, it was considered that the balance of risks and benefits of mirtazapine for the treatment of depression in this group was unfavourable. Similar recommendations have also been issued in the EU.[2]

The risk of suicide and suicide-related events with serotonergic antidepressant treatment in **adults**, including young adults, are discussed under Fluoxetine, p.392.

1. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)

Effects on the musculoskeletal system. The Netherlands Pharmacovigilance Centre Lareb received 8 reports of arthralgia associated with the use of mirtazapine between May 1995 and October 2004; the effect usually developed within a short time of starting treatment and resolved once the drug was withdrawn.[1] The authors noted that of 4578 reported reactions to mirtazapine held in the WHO database up to March 2004, 110 concerned the development of arthralgia. Similar reactions have occurred with mianserin and nefazodone, and it was suggested that effects at serotonin 5-HT_1 or 5-HT_2 receptors might be involved.

1. Passier A, van Puijenbroek E. Mirtazapine-induced arthralgia. *Br J Clin Pharmacol* 2005; **60:** 570–2.

Extrapyramidal effects. Akathisia that developed in 2 patients given mirtazapine 30 mg at night[1] resolved in one after being treated with clonazepam and in the other patient after reducing the dose of mirtazapine to 15 mg at night.

1. Girishchandra BG, *et al.* Mirtazapine-induced akathisia. *Med J Aust* 2002; **176:** 242.

Serotonin syndrome. The serotonin syndrome (p.416) is most commonly due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug has caused the syndrome. One such case[1] occurred in an elderly patient given mirtazapine 15 mg daily; he was also taking salbutamol, ipratropium, and nimodipine, although none of these are known to have serotonergic effects.

1. Hernández JL, *et al.* Severe serotonin syndrome induced by mirtazapine monotherapy. *Ann Pharmacother* 2002; **36:** 641–3.

Precautions

Mirtazapine should be used with caution in patients with epilepsy or a history of seizures, and it should be avoided completely if these disorders are unstable. Care is also required in hepatic or renal impairment, and cardiac disorders such as conduction disturbances, angina pectoris, and recent myocardial infarction; caution is further advised in patients with hypotension, diabetes mellitus, psychoses, and in those with a history of bipolar disorder. Treatment should be stopped if jaundice develops. Although mirtazapine has only weak antimuscarinic activity, it should nevertheless be used with care in patients with micturition disturbances, angle-closure glaucoma, and raised intra-ocular pressure.

Because of the risk of bone-marrow depression, patients should be advised to report any of the following symptoms during treatment: fever, sore throat, stomatitis, or other signs of infection; treatment should be stopped and a blood count performed.

Drowsiness is often experienced at the start of therapy and patients, if affected, should not drive or operate machinery.

Patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. Mirtazapine has been detected in breast milk;[1] however, the plasma concentration in a breast-fed infant was very low (0.2 nanograms/mL) and no adverse events were detected.

1. Aichhorn W, *et al.* Mirtazapine and breast-feeding. *Am J Psychiatry* 2004; **161:** 2325.

Children. The use of mirtazapine in adolescents and children with depression is not recommended; for further details, see Effects on Mental State, above.

Pregnancy. A small case series followed the pregnancies of 9 women exposed to mirtazapine during the first trimester;[1] in the majority of cases the women were also exposed to other drugs. Within the group there were 7 healthy deliveries, 1 induced abortion, and 1 spontaneous abortion. In another report healthy male twins were delivered by a mother who was given mirtazapine at 2 periods during her pregnancy for the successful treatment of hyperemesis gravidarum.[2] A follow-up examination of the twins at 6 months was normal.

Health Canada has reported that some newborn infants of mothers who took newer antidepressants such as mirtazapine mainly during the third trimester of pregnancy have experienced complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding.[3] Reported symptoms included seizures, muscle rigidity, jitteriness, and constant crying. It was considered that these symptoms represented either direct toxicity of mirtazapine or a possible withdrawal syndrome.

1. Yaris F, *et al.* Newer antidepressants in pregnancy: prospective outcome of a case series. *Reprod Toxicol* 2004; **19:** 235–8.
2. Rohde A, *et al.* Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. *Arch Gynecol Obstet* 2003; **268:** 219–21.
3. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Mirtazapine should not be used with or within 2 weeks of stopping an MAOI; at least one week should elapse between stopping mirtazapine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Use of mirtazapine with alcohol or benzodiazepines may potentiate sedative effects.

The cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism of mirtazapine and caution is advised when mirtazapine is given with potent inhibitors of this isoenzyme such as HIV-protease inhibitors, azole antifungals including ketoconazole, erythromycin, and nefazodone; raised plasma levels of mirtazapine have been noted after use with ketoconazole. Conversely, carbamazepine and other inducers of CYP3A4 increased the clearance of mirtazapine and the dose of mirtazapine may need to be increased when given with these drugs.

Cimetidine, which inhibits a range of cytochrome P450 isoenzymes, has more than doubled the bioavailability of mirtazapine; the dose of mirtazapine may need to be reduced if given with cimetidine.

Pharmacokinetics

Mirtazapine is well absorbed from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 85%. Mirtazapine is extensively metabolised in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The *N*-desmethyl metabolite is pharmacologically active. Elimination is via urine (75%) and faeces (15%). The mean plasma elimination half-life is 20 to 40 hours. Data from *animal* studies indicate that mirtazapine crosses the placenta. Mirtazapine is distributed into breast milk.

◊ References.

1. Timmer CJ, *et al.* Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinet* 2000; **38:** 461–74.

Uses and Administration

Mirtazapine, a piperazinoazepine, is an analogue of mianserin (p.408); it is a noradrenergic and specific serotonergic antidepressant. It enhances the release of noradrenaline and, indirectly, serotonin through blockade of central presynaptic adrenergic (α_2) receptors. The effects of released serotonin are mediated via 5-HT_1 receptors as mirtazapine blocks both 5-HT_2 and 5-HT_3 receptors. Mirtazapine is given as a racemic mixture: the *S*(+)-enantiomer blocks α_2 and 5-HT_2 receptors whereas the *R*(−)-enantiomer blocks 5-HT_3 receptors. Mirtazapine is also a potent antagonist at histamine (H_1) receptors which gives it sedative properties; it has very little antimuscarinic activity.

In the treatment of depression (p.373), mirtazapine is given in an initial oral daily dose of 15 mg, which may be increased gradually according to response. Changes in dose should be made at intervals of at least 1 to 2 weeks because of the long half-life. The usual effective daily dose lies within the range of 15 to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in 2 equally divided doses. Mirtazapine may also be given by intravenous infusion.

Mirtazapine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. Mirtazapine has been tried with some success in the treatment of anxiety disorders (p.952) including obsessive-compulsive disorder (p.952), panic disorder (p.952), and post-traumatic stress disorder (p.953).

References.

1. Boshuisen ML, *et al.* The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol* 2001; **16:** 363–8.
2. Davidson JR, *et al.* Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry* 2003; **53:** 188–91.
3. Chung MY, *et al.* Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum Psychopharmacol* 2004; **19:** 489–94.
4. Koran LM, *et al.* Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry* 2005; **66:** 515–20.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Mirtazapine is a central presynaptic adrenergic (α_2) receptor antagonist and has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, mirtazapine appears to have fewer unpleasant adverse effects in comparison with the older tricyclics.

References.

1. Kasper S, *et al.* A risk-benefit assessment of mirtazapine in the treatment of depression. *Drug Safety* 1997; **17:** 251–64.
2. Montgomery SA, *et al.* Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 1998; **13:** 63–73.
3. Puzantian T. Mirtazapine, an antidepressant. *Am J Health-Syst Pharm* 1998; **55:** 44–9.
4. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs* 1999; **57:** 607–31.
5. Schatzberg AF, *et al.* Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; **10:** 541–50.
6. Wade A, *et al.* A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int Clin Psychopharmacol* 2003; **18:** 133–41.
7. Versiani M, *et al.* Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs* 2005; **19:** 137–46.

Nausea and vomiting. Mirtazapine has been investigated in the management of severe nausea and vomiting (p.1700). For mention of the successful use of mirtazapine to treat hyperemesis of pregnancy see Pregnancy, under Precautions, above.

Further references.

1. Kast RE. Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. *Support Care Cancer* 2001; **9:** 469–70.
2. Caldis EV, Gair RD. Mirtazapine for treatment of nausea induced by selective serotonin reuptake inhibitors. *Can J Psychiatry* 2004; **49:** 707.
3. Teixeira FV, *et al.* Mirtazapine (Remeron) as treatment for non-mechanical vomiting after gastric bypass. *Obes Surg* 2005; **15:** 707–9.

Preparations

USP 31: Mirtazapine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Comenter; Noxibel; Remeron; ***Austral.:*** Avanza; Axit; Mirtazon; Remeron; ***Austria:*** Lanazapin; Mirtabene; Mirtaron; Mirtel; Remeron; ***Belg.:*** Remergon; ***Braz.:*** Remeron; ***Canad.:*** Remeron; ***Chile:*** Amirel; Ciblex; Divaril; Promyrtil; Zuleptan; ***Cz.:*** Calixta; Esprital; Mirtastad; Mirzaten; Remeron; Valdren; ***Denm.:*** Arintapin; Combar; Mirtazon; Remeron; ***Fin.:*** Mirtaril; Mirtazon; Remeron; ***Fr.:*** Norset; ***Ger.:*** Mirta TAD; MirtaLich; Mirtazelon; Mirtazza; Remergil; ***Gr.:*** Azapin; Depreram; Remeron; ***Hong Kong:*** Remeron; ***Hung.:*** Mirtadepi; Mirtel; Mirzaten; Mizapin; Remeron; ***India:*** Mirtaz; ***Indon.:*** Remeron; ***Irl.:*** Mirap; Tazamel; Zismirt; Zispin; ***Israel:*** Miro; Remeron; ***Ital.:*** Remeron; ***Malaysia:*** Remeron; ***Mex.:*** Comenter; Mirzalux; Remeron; ***Neth.:*** Remeron; ***Norw.:*** Remeron; ***NZ:*** Remeron; ***Philipp.:*** Remeron; ***Pol.:*** Esprital; Mirtastad; Mirzaten; Remeron; ***Port.:*** Mirtazon; Remeron; ***Rus.:*** Mirzaten (Мирзатен); Remeron (Ремерон)†; ***S.Afr.:*** Remeron; ***Singapore:*** Remeron; ***Spain:*** Afloyan; Rexer; Vastat; ***Swed.:*** Remeron; ***Switz.:*** Remeron; ***Thai.:*** Remeron; ***Turk.:*** Remeron; ***UK:*** Zispin; ***USA:*** Remeron; ***Venez.:*** Comenter; Remeron.

Moclobemide *(BAN, USAN, rINN)*

Moclobemida; Moclobémide; Moclobemidum; Moklobemid; Moklobemidi; Ro-11-1163; Ro-11-1163/000. 4-Chloro-*N*-(2-morpholinoethyl)benzamide.

Моклобемид

$C_{13}H_{17}ClN_2O_2$ = 268.7.

CAS — 71320-77-9.

ATC — N06AG02.

ATC Vet — QN06AG02.

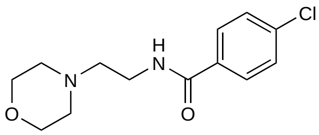

Pharmacopoeias. In *Chin.* and *Swiss.*

Adverse Effects

Adverse effects reported to occur with moclobemide include sleep disturbances, dizziness, agitation, feelings of anxiety, restlessness, irritability, and headache. Gastrointestinal disturbances include dry mouth, diarrhoea, constipation, and nausea and vomiting. Paraesthesia, visual disturbances, and oedema have also been reported, and skin reactions include rash, pruritus, urticaria, and flushing. Confusional states have been observed that disappear rapidly on stopping the drug. Raised liver enzymes and galactorrhoea have been reported rarely.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on the cardiovascular system. Hypertension has been reported[1,2] rarely in patients taking moclobemide, some of whom were also taking other drugs although moclobemide was suspected to be the cause. Blood pressure usually returned to normal after stopping moclobemide.

1. Coulter DM, Pillans PI. Hypertension with moclobemide. *Lancet* 1995; **346:** 1032.
2. Boyd IW. Hypertension with moclobemide. *Lancet* 1995; **346:** 1498.

Effects on the endocrine system. A prescription-event monitoring study found that galactorrhoea is significantly associated with the use of moclobemide.[1]

1. Dunn NR, *et al.* Galactorrhoea with moclobemide. *Lancet* 1998; **351:** 802.

Effects on the liver. An 85-year-old woman developed intrahepatic cholestasis after taking moclobemide for about 1 week;[1] she had previously been taking fluoxetine and was switched to moclobemide without a washout period. She died 12 days after the onset of jaundice despite prompt moclobemide withdrawal.

1. Timmings P, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; **347:** 762–3.

Overdosage. Several case series[1-3] have suggested that moclobemide is relatively safe when taken alone in overdose; symptoms such as gastrointestinal irritation, agitation, aggression, behavioural disturbances, and tachycardia have been noted. However, fatalities have been reported, particularly when taken with other serotonergic drugs.[3,4]

1. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. *Psychopharmacology (Berl)* 1992; **106:** S127–S129.
2. Myrenfors PG, *et al.* Moclobemide overdose. *J Intern Med* 1993; **233:** 113–15.
3. Isbister GK, *et al.* Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; **56:** 441–50.
4. Giroud C, *et al.* Death following acute poisoning by moclobemide. *Forensic Sci Int* 2004; **140:** 101–7.

Precautions

Moclobemide is contra-indicated in patients with acute confusional states and in those with phaeochromocytoma. It should be avoided in excited or agitated patients, unless used with a sedative. Manic episodes may be provoked in patients with bipolar disorder. Care is also required in patients with thyrotoxicosis as moclobemide may theoretically precipitate a hypertensive reaction. Reduced doses should be used in patients with severe hepatic impairment.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Although impairment of mental alertness is generally not expected with moclobemide, caution should be exercised with respect to driving or operating machinery until individual reactions have been assessed.

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. In a study[1] of the distribution of moclobemide into the breast milk of 6 mothers given a single 300-mg dose of moclobemide, a mean of 0.057% of the dose appeared in breast milk as moclobemide and 0.031% as Ro-12-8095, its major metabolite, within 24 hours of a dose. It was considered that this small amount of moclobemide was unlikely to be hazardous to breast-fed infants. UK licensed drug information advises caution and consideration of the benefits of moclobemide therapy to the mother against possible risks to the infant.

1. Pons G, *et al.* Moclobemide excretion in human breast milk. *Br J Clin Pharmacol* 1990; **29:** 27–31.

Children. Moclobemide has not been adequately studied for the treatment of depression in children and its use is not recommended in UK licensed product information. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p.392).

Pregnancy. UK licensed drug information recommends that moclobemide should only be used during pregnancy if the benefits to the mother outweigh any possible risks to the fetus.

A patient who took at least 300 mg daily of moclobemide throughout her pregnancy delivered a healthy, full-term infant after an uncomplicated pregnancy.[1] The infant was monitored from birth, and psychomotor and somatic development for the first 14 months was found to be normal.

1. Rybakowski JK. Moclobemide in pregnancy. *Pharmacopsychiatry* 2001; **34:** 82–3.

Withdrawal. Withdrawal symptoms may occur if an antidepressant such as moclobemide is suddenly stopped after regular use for 8 weeks or more; the *BNF* recommends that the dose should be tapered gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

Despite reducing the dose of moclobemide over 3 days, symptoms such as muscle cramps, shivering, headache, nausea, and hot flushes developed in a 47-year-old woman on the day that moclobemide was completely stopped.[1] The patient had been taking moclobemide for about 15 months.

1. Curtin F, *et al.* Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J Psychopharmacol* 2002; **16:** 271–2.

Interactions

The dietary restrictions that need to be followed with selective reversible inhibitors of monoamine oxidase type A such as moclobemide are less stringent than those for non-selective inhibitors of monoamine oxidase types A and B (see under Interactions of Phenelzine, p.417). However, UK licensed drug information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

Medicines containing *sympathomimetics, dextromethorphan*, or *anorectics* should not be taken with moclobemide. Moclobemide should not be given with *other antidepressants* although, owing to its short duration of action, a treatment-free period is generally considered unnecessary after its cessation. For further details, see Antidepressants under Interactions of Phenelzine, p.418. Therapy with moclobemide should not be started until at least a week after cessation of a tricyclic or related antidepressant or an SSRI or related antidepressant (2 weeks in the case of paroxetine and sertraline; at least 5 weeks in the case of fluoxetine) or for at least a week after stopping treatment with non-selective MAOIs. CNS excitation or depression may occur if moclobemide is taken with *opioid analgesics*, and there is also a risk of CNS toxicity if taken with *serotonin (5-HT$_1$) agonists*. The metabolism of moclobemide is inhibited by *cimetidine*, leading to increased plasma concentrations and a need for reduced dosage (see below).

Antimigraine drugs. For the effects of moclobemide on *serotonin (5-HT$_1$) agonists*, see under Sumatriptan, p.626.

Cimetidine. Cimetidine 1 g daily for 2 weeks increased the mean maximum plasma concentration of moclobemide in 8 healthy subjects from 575 nanograms/mL to 787 nanograms/mL; several other parameters associated with moclobemide absorption and disposition were also affected.[1] It was suggested that a reduction in the dosage of moclobemide might be required. UK licensed drug information for moclobemide recommends reducing its dose by half in patients also receiving cimetidine.

1. Schoerlin M-P, *et al.* Cimetidine alters the disposition kinetics of the monoamine oxidase-A inhibitor moclobemide. *Clin Pharmacol Ther* 1991; **49:** 32–8.

Dopaminergics. Adverse effects including nausea, vomiting, and dizziness were noted in healthy subjects given moclobemide and *levodopa with benserazide*;[1] however, no significant hypertensive reactions were seen.

Caution is also required when *selegiline* and moclobemide are given together.[1] Dietary restrictions with this combination (see under Phenelzine, p.417) are recommended by one manufacturer of selegiline, whereas another advises that this combination should be avoided (as does the manufacturer of moclobemide).

See also under Selegiline, p.817.

1. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* 1993; **7:** 167–80.

Omeprazole. Omeprazole, which is an inhibitor of cytochrome P450 isoenzyme CYP2C19, increased plasma concentrations and elimination half-life of moclobemide in extensive metabolisers of the drug towards values seen in poor metabolisers.[1] It had little effect on pharmacokinetic parameters in poor metabolisers. The clinical effects were uncertain but extra care might be warranted if the 2 drugs are given together.

1. Yu K-S, *et al.* Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **69:** 266–73.

Opioid analgesics. Symptoms suggestive of a mild serotonin syndrome (p.416) developed in a 73-year-old woman taking moclobemide, nortriptyline, and lithium after she was given *pethidine* intravenously.[1] Licensed drug information recommends that moclobemide should not be given with pethidine.

1. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.

Pharmacokinetics

Moclobemide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about 1 hour of ingestion. Absorption is virtually complete but first-pass metabolism reduces bioavailability of the drug. Moclobemide is widely distributed throughout the body and is 50% bound to plasma proteins. It undergoes extensive metabolism in the liver, in part by the cytochrome P450 isoenzymes CYP2C19 and CYP2D6. Metabolites of moclobemide and a small amount of unchanged drug are excreted in the urine. Moclobemide has a plasma elimination half-life of 2 to 4 hours. Moclobemide is distributed into breast milk.

◊ References.

1. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamide oxidase-A inhibitor moclobemide. *Clin Pharmacokinet* 1995; **29:** 292–332.
2. Gram LF, *et al.* Moclobemide: a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin Pharmacol Ther* 1995; **57:** 670–7.

Uses and Administration

Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine oxidase type A (RIMA) (see under Phenelzine, p.419) used for the treatment of depression and of social anxiety disorder.

In the treatment of **depression** the usual initial oral dose of moclobemide is 300 mg daily in divided doses. This may be increased up to 600 mg daily according to response. In some patients, a maintenance dose of 150 mg daily may be sufficient.

In the treatment of **social anxiety disorder**, the initial daily dose of moclobemide is 300 mg increased after 3 days to 600 mg given in 2 divided doses. Treatment should be continued for 8 to 12 weeks to assess efficacy; patients should be periodically re-evaluated thereafter to determine the need for further treatment.

Moclobemide should be taken after food.

Reduced doses should be given in hepatic impairment (see below) and in patients also taking cimetidine (see above).

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

◊ Reviews.

1. Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev* 2003; **9:** 97–140.

Administration in hepatic impairment. UK licensed drug information states that doses of moclobemide in patients with severe hepatic impairment may need to be reduced to half or one-third of the recommended dose (see above).

Anxiety disorders. The use of MAOIs in general in the management of anxiety disorders is discussed under Phenelzine on p.420. For a discussion of the overall treatment of anxiety disorders, see p.952.

References.

1. Noyes R, *et al.* Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol* 1997; **17:** 247–54.
2. Neal LA, *et al.* An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 1997; **12:** 231–7.
3. Schneier FR, *et al.* Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry* 1998; **172:** 70–7.
4. Tiller JW, *et al.* Moclobemide and fluoxetine for panic disorder. *Eur Arch Psychiatry Clin Neurosci* 1999; **249** (suppl 1): S7–S10.
5. Stein DJ, *et al.* Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. *Int Clin Psychopharmacol* 2002; **17:** 161–70.

Depression. As discussed on p.373 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. The traditional MAOIs such as phenelzine are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide offer a safer alternative to the irreversible non-selective MAOIs and fewer dietary restrictions are necessary.

References.

1. Fitton A, *et al.* Moclobemide: a review of its pharmacological properties and therapeutic use in depressive illness. *Drugs* 1992; **43:** 561–96.
2. Angst J, Stabl M. Efficacy of moclobemide in different patient groups: a meta-analysis of studies. *Psychopharmacology (Berl)* 1992; **106** (suppl): S109–S113.
3. Lonnqvist J, *et al.* Moclobemide and fluoxetine in atypical depression: a double-blind trial. *J Affect Disord* 1994; **32:** 169–77.
4. Norman TR, Burrows GD. A risk-benefit assessment of moclobemide in the treatment of depressive disorders. *Drug Safety* 1995; **12:** 46–54.
5. Roth M, *et al.* Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996; **168:** 149–57.
6. Lotufo-Neto F, *et al.* Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* 1999; **20:** 226–47.

Smoking cessation. In a preliminary double-blind, placebo-controlled parallel-group study in 88 smokers, moclobemide facilitated smoking cessation (p.2354) in highly dependent smokers.[1]

1. Berlin I, *et al.* A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clin Pharmacol Ther* 1995; **58:** 444–52.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aurorix†; ***Austral.:*** Amira; Arima; Aurorix; Clobemix; Maosig; Mohexal; ***Austria:*** Aurobemid; Aurorix; ***Belg.:*** Aurorix; ***Braz.:*** Aurorix; ***Canad.:*** Manerix; ***Chile:*** Aurorix; Inpront; ***Cz.:*** Apo-Moclob; Aurorix; ***Denm.:*** Aurorix; Moclostad; ***Fin.:*** Aurorix; ***Fr.:*** Moclamine; ***Ger.:*** Aurorix; Moclix†; Moclobeta; Moclodura; Moclonorm†; ***Gr.:*** Aurorix; ***Hong Kong:*** Aurorix; ***Hung.:*** Aurorix; Maorex; Moclopharm; Mocrim; ***India:*** Rimarex; ***Indon.:*** Aurorix; ***Irl.:*** Manerix; ***Israel:*** Mobemide; ***Malaysia:*** Aurorix; ***Mex.:*** Aurorex; Feraken; ***Neth.:*** Aurorix; ***Norw.:*** Aurorix; ***NZ:*** Aurorix†; ***Philipp.:*** Aurorix; ***Pol.:*** Aurorix; Mobemid; Mocloxil; Moklar; ***Port.:*** Aurorix; ***S.Afr.:*** Aurorix; Clorix; Depnil; ***Singapore:*** Aurorix†; Mobemide; ***Spain:*** Manerix; ***Swed.:*** Aurorix; ***Switz.:*** Aurorix; Moclo A; ***Thai.:*** Aurorix; ***Turk.:*** Aurorix; Lobem; ***UK:*** Manerix.

Nefazodone Hydrochloride *(BANM, USAN, rINNM)*

BMY-13754; Hidrocloruro de nefazodona; MJ-13754-1; Néfazodone, Chlorhydrate de; Nefazodoni Hydrochloridum. 2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-1,2,4-triazol-3-one monohydrochloride.

Нефазодона Гидрохлорид

$C_{25}H_{32}ClN_5O_2,HCl = 506.5.$

CAS — 83366-66-9 (nefazodone); 82752-99-6 (nefazodone hydrochloride).

ATC — N06AX06.

ATC Vet — QN06AX06.

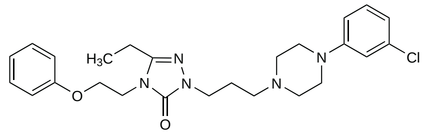

(nefazodone)

Pharmacopoeias. In *US.*

USP 31 (Nefazodone Hydrochloride). A non-hygroscopic white powder. Slightly soluble in water and in macrogols; freely soluble in chloroform; soluble in propylene glycol. Store in airtight containers at a temperature between 15° and 30°.

Adverse Effects and Treatment

The most common adverse effects seen with nefazodone are weakness, dry mouth, nausea, constipation, somnolence, dizziness, insomnia, and lightheadedness. Other effects which have occurred less frequently include chills, fever, orthostatic hypotension, incoordination, vasodilatation, arthralgia, paraesthesia, confusion, memory impairment, abnormal dreams, ataxia, and amblyopia and other visual disturbances. Syncope, priapism, and seizures have occurred rarely and there have been reports of sinus bradycardia. Hepatotoxicity has occurred (see below).

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, the symptoms that have been reported most frequently include hypotension, dizziness, nausea, vomiting, and drowsiness. The value of gastric decontamination in the treatment of overdosage is uncertain. Activated charcoal should be considered if more than 1.5 g (in an adult) or 20 mg/kg (in a child) has been taken and treatment is within 1 hour of ingestion. US licensed product information recommends gastric lavage, although this technique is seldom practicable and should not be attempted unless the airway is protected. Supportive therapy should be given as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

◊ Reviews.

1. Robinson DS, *et al.* The safety profile of nefazodone. *J Clin Psychiatry* 1996; **57** (suppl 2): 31–8.

Effects on the liver. Subfulminant hepatic failure developed in 3 women given nefazodone for depression.[1] Two patients required liver transplantation although this was unsuccessful in one case and the patient died. Hepatitis, positive on rechallenge, has also been reported with nefazodone.[2]

The original US manufacturer (*Bristol-Myers Squibb*) of nefazodone have stated that rare events of raised liver enzymes, hepatitis, hepatic failure and necrosis have been reported since marketing but no causal relationship has been established. In the USA, a reported rate of about 1 case of hepatic failure resulting in death or transplantation per 250 000 to 300 000 patient years of nefazodone treatment has been estimated by the manufacturer; this rate is about 3 to 4 times greater than the background rate of hepatic failure.[3] Onset times for such cases ranged from 2 weeks to 6 months. The Canadian manufacturers have indicated[4] that as of June 2001 there had been 109 reports of serious hepatic adverse events associated with nefazodone from postmarketing surveillance worldwide. These included 23 cases of hepatic failure, of which 16 led to transplantation and/or death. Most cases occurred within 4 months of beginning treatment although a few were after continuous use for up to 2 years. After a review[5] of the data available to December 2002, it was decided to withdraw nefazodone from the Canadian market in November 2003. Subsequently, one manufacturer (*Bristol-Myers Squibb*) withdrew nefazodone worldwide.

1. Aranda-Michel J, *et al.* Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999; **130:** 285–8.
2. Schrader GD, Roberts-Thompson IC. Adverse effect of nefazodone: hepatitis. *Med J Aust* 1999; **170:** 452.
3. Jody DM [Bristol-Myers Squibb]. Important drug warning including black box information. Available at: http://www.fda.gov/medwatch/SAFETY/2002/serzone_deardoc.PDF (accessed 24/11/05)
4. Bristol-Myers Squibb Canada Inc/Linson Pharama Inc. Important safety information on nefazodone HCl: severe and serious hepatic events (issued June 2001). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)
5. Bristol-Myers Squibb Canada. Important safety information regarding the discontinuation of sales of nefazodone in Canada (issued October 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bms-nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)

Overdosage. A 27-year-old woman developed no serious toxicity after taking 3 g of nefazodone in a suicide attempt.[1] Somnolence was the most severe effect noted. In another case, a 31-year-old woman attempted suicide with 16.8 g of nefazodone and an unknown quantity of verapamil.[2] The patient was lethargic, and developed significant bradycardia and hypotension; she recovered after supportive therapy. The authors reported that among the 7 cases of overdose occurring during clinical trials, there were no fatalities or permanent sequelae.

In a review of 1338 cases of nefazodone-only overdoses reported to the American Association of Poison Control Centres over a 2-year period, it was found that the majority of cases were either asymptomatic or mild in nature with symptoms such as nausea, vomiting, dizziness, and drowsiness.[3] More severe symptoms were noted in only 2 patients. In one case, an 11-year-old boy with a history of seizures suffered several seizures after starting nefazodone at a dose of 100 mg twice daily; the other case involved a 47-year-old man who developed premature ventricular contractions, bradycardia, agitation, and hypotension after an intentional overdose of an unknown quantity. No deaths were recorded in any of the cases where the outcome was known.

1. Gaffney PW, *et al.* Nefazodone overdose. *Ann Pharmacother* 1998; **32:** 1249–50.
2. Catalano G, *et al.* Nefazodone overdose: a case report *Clin Neuropharmacol* 1999; **22:** 63–5.
3. Benson BE, *et al.* Toxicities and outcomes associated with nefazodone poisoning: an analysis of 1,338 exposures. *Am J Emerg Med* 2000; **18:** 587–92.

Precautions

Treatment with nefazodone should not generally be started in patients with active hepatic disease or elevated baseline serum transaminases. Patients who develop signs or symptoms of hepatic impairment such as jaundice, anorexia, abdominal pain, elevated transaminase levels, or malaise during treatment should be evaluated for hepatic damage and the drug withdrawn if necessary. Nefazodone is contra-indicated in patients previously withdrawn from the drug because of hepatotoxicity.

Nefazodone should be used with caution in patients with epilepsy, or a history of hypomania or mania. It should also be used with caution in cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (for example recent history of myocardial infarction, unstable heart disease, angina, or ischaemic stroke), and in any condition such as dehydration or hypovolaemia that may predispose patients to hypotension.

Since nefazodone is structurally related to trazodone which is known to have caused priapism (see Effects on Sexual Function, p.425), US licensed product information recommends that any patient developing inappropriate or prolonged penile erections should stop nefazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Nefazodone may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. A study[1] in 2 nursing mothers receiving nefazodone for postpartum depression indicated that nefazodone, but not its major active metabolites, was distributed into breast milk in variable amounts; the quantity present did not seem to be dose-related. The calculated exposure of the two women's offspring was 2.2% and 0.4% of the maternal dose respectively. Another report suggested that even such low exposures might result in clinically significant effects:[2] drowsiness, inability to maintain normal body temperature, and poor feeding were reported in the breast-fed infant of a woman receiving nefazodone. After breast feeding was stopped the symptoms resolved, suggesting an association between the two despite a calculated exposure in the infant of only 0.45% of the maternal dose.

1. Dodd S, *et al.* Nefazodone in the breast milk of nursing mothers: a report of two patients. *J Clin Psychopharmacol* 2000; **20:** 717–18.
2. Yapp P, *et al.* Drowsiness and poor feeding in a breast-fed infant: association with nefazodone and its metabolites. *Ann Pharmacother* 2000; **34:** 1269–72.

Children. US licensed product information considers that the safety and efficacy of nefazodone have not been established for the treatment of depression in adolescents and children. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p.392).

Pregnancy. Licensed drug information states that nefazodone should only be used during pregnancy if the benefits to the mother outweigh the risks to the fetus.

In a multicentre study of 147 women who took either nefazodone or trazodone in at least the first trimester of pregnancy there were 121 live births, 20 spontaneous abortions, 6 therapeutic abortions, and 2 reports of major malformations (Hirschsprung disease and neural tube defect);[1] no still-births were recorded. There were no significant differences in pregnancy outcome in the nefazodone/trazodone group when compared to the 2 control groups (women with depression taking non-teratogenic antidepressants and women taking non-teratogenic drugs). The rate of spontaneous abortions was non-significantly higher in both the antidepressant groups than in the other control group. It was suggested that the rate of major malformations in all 3 groups was not greater than the baseline rate of 1 to 3%.

1. Einarson A, *et al.* A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003; **48:** 106–10.

Interactions

Nefazodone should not be given to patients receiving MAOIs or for at least 14 days after they are stopped; it has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping nefazodone therapy. For further details on the combined use of antidepressants, see Antidepressants under Interactions of Phenelzine, p.418.

Orthostatic hypotension can be a problem with nefazodone, and therefore caution is required for any patient also on antihypertensive therapy.

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 responsible for the metabolism of some benzodiazepines, and consequently it may produce clinically important increases in their plasma concentrations. Use with astemizole, cisapride, pimozide, and terfenadine (which are metabolised by the same isoenzyme) is best avoided because the potential also exists for increased plasma concentrations of these drugs, with the risk of inducing ventricular arrhythmias. Other substrates for this isoenzyme may also interact with nefazodone: atorvastatin, lovastatin, and simvastatin should be used with caution with nefazodone since there have been rare reports of rhabdomyolysis with such combinations. Increased serum concentrations of ciclosporin or tacrolimus, both substrates for CYP3A4, have been reported in patients also receiving nefazodone. Monitoring of serum ciclosporin or tacrolimus levels is recommended when either of these two drugs is given with nefazodone.

Plasma concentrations of digoxin are increased by nefazodone, and because of digoxin's narrow therapeutic index, plasma concentrations of digoxin should be monitored if use with nefazodone is necessary.

Caution should be exercised when haloperidol is given with nefazodone as the clearance of haloperidol may be reduced. Plasma concentrations of carbamazepine are also increased when used with nefazodone. More importantly, carbamazepine may reduce nefazodone plasma concentrations to subtherapeutic levels and therefore use together is not recommended. Giving buspirone with nefazodone significantly increases the serum concentrations of buspirone; the manufacturers of nefazodone recommend that the initial dose of buspirone is reduced if these drugs are given together.

The potential for interaction between nefazodone and general anaesthetics exists and the manufacturer recommends that nefazodone should be stopped before elective surgery for as long as clinically feasible.

Benzodiazepines. For further details of interactions between nefazodone and benzodiazepines, see Diazepam, p.990.

Pharmacokinetics

Nefazodone is readily absorbed from the gastrointestinal tract and peak plasma concentrations have been obtained within about 2 hours after oral doses. Absorption is delayed and reduced by food but this is not considered to be clinically significant. Nefazodone undergoes extensive first-pass metabolism and is more than 99% bound to plasma proteins; it is widely distributed. It is extensively metabolised by *N*-dealkylation and hydroxylation in the liver to several metabolites, two of which, hydroxynefazodone and *m*-chlorophenylpiperazine, are known to be pharmacologically active. Excretion is mainly as metabolites via the urine (about 55%) and the faeces (20 to 30%). The plasma elimination half-life is 2 to 4 hours. Pharmacokinetic parameters are reported to be non-linear with increasing doses. Nefazodone is distributed in small amounts into breast milk (see Breast Feeding, above).

◊ Reviews.

1. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet* 1997; **33:** 260–75.

Uses and Administration

Nefazodone is a phenylpiperazine antidepressant structurally related to trazodone (see p.424). It blocks the reuptake of serotonin at presynaptic neurones and is an antagonist at postsynaptic 5-HT_2 receptors. Unlike trazodone, nefazodone inhibits the reuptake of noradrenaline. It blocks α_1-adrenoceptors but has no apparent effect on dopamine receptors. Nefazodone does not appear to have very significant antimuscarinic properties compared with tricyclic antidepressants.

Nefazodone hydrochloride has been given for the treatment of depression. One manufacturer (*Bristol-Myers Squibb*) has withdrawn nefazodone worldwide (see also Effects on the Liver, above); however, nefazodone remains available in the USA, and possibly some other countries, as a generic preparation. The usual initial oral dose is 100 mg twice daily increased if necessary, in increments of 100 to 200 mg at intervals of at least a week, to a maximum of 300 mg twice daily. Doses are restricted in elderly patients: a recommended initial dose is 50 mg twice daily.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Nefazodone has been tried in anxiety disorders, but other drugs may now be preferred.

Preparations

USP 31: Nefazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Deprefax†; ***Austral.:*** Serzone†; ***Braz.:*** Serzone†; ***Cz.:*** Serzone†; ***Gr.:*** Nefirel†; ***Hong Kong:*** Serzone†; ***Israel:*** Serzonil†; ***Mex.:*** Serzone†; ***NZ:*** Serzone†; ***S.Afr.:*** Serzone†; ***Singapore:*** Serzone†; ***USA:*** Serzone†.

Nortriptyline Hydrochloride

(BANM, USAN, rINNM)

38489; Hidrocloruro de nortriptilina; Nortriptilin-hidroklorid; Nortriptilino hidrochloridas; Nortriptyliinihydrokloridi; Nortriptyline, chlorhydrate de; Nortriptylin-hydrochlorid; Nortriptylinhydroklorid; Nortriptylini hydrochloridum; Nortryptyliny chlorowodorek. 3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene) propyl(methyl)amine hydrochloride.

Нортриптилина Гидрохлорид

$C_{19}H_{21}N,HCl = 299.8.$

CAS — 72-69-5 (nortriptyline); 894-71-3 (nortriptyline hydrochloride).

ATC — N06AA10.

ATC Vet — QN06AA10.

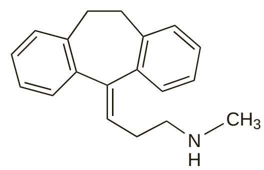

(nortriptyline)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Nortriptyline Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Nortriptyline Hydrochloride). A white to off-white powder having a slight characteristic odour. Soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether, in benzene, and in most other organic solvents. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on ventilation. Severe hyperventilation developed in a 61-year-old man with end-stage renal disease after receiving nortriptyline 125 mg daily;[1] mechanical ventilation was necessary to correct severe respiratory alkalosis.

1. Sunderrajan S, *et al.* Nortriptyline-induced severe hyperventilation. *Arch Intern Med* 1985; **145:** 746–7.

Porphyria. Nortriptyline is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Nortriptyline is the principal active metabolite of amitriptyline (p.381). Nortriptyline has been reported to have a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Metabolism. Individuals with a poor debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline.[1] This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline are mediated by similar enzymatic mechanisms [the cytochrome P450 isoenzyme CYP2D6], with poor oxidisers having higher plasma nortriptyline concentrations.[2,3] A nonlinear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been observed during therapeutic drug monitoring[4] in subjects who were considered to be extensive metabolisers of debrisoquine; nonlinearity did not appear to occur in poor metabolisers. There was no significant correlation between hydroxylation phenotype and amitriptyline concentrations, suggesting that demethylation and hydroxylation of tricyclic antidepressants are mediated by different cytochrome P450 isoenzymes.[5]

The pharmacokinetics and pharmacological actions of 10-hydroxynortriptyline, the major active metabolite of nortriptyline, have been reviewed.[3]

1. Park BK, Kitteringham NR. Adverse reactions and drug metabolism. *Adverse Drug React Bull* 1987; **122:** 456–9.
2. Nordin C, *et al.* Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. *Br J Clin Pharmacol* 1985; **19:** 832–5.
3. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants: emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet* 1995; **28:** 26–40.
4. Jerling M, Alván G. Nonlinear kinetics of nortriptyline in relation to nortriptyline clearance as observed during therapeutic drug monitoring. *Eur J Clin Pharmacol* 1994; **46:** 67–70.
5. Bertilsson L, *et al.* Metabolism of various drugs in subjects with different debrisoquine and sparteine oxidation phenotypes. *Br J Clin Pharmacol* 1982; **14:** 602P.

Therapeutic plasma concentrations. Nortriptyline appears to have an optimum antidepressant effect at plasma concentrations between 50 and 150 nanograms/mL. Outside this range, there is a poor clinical response. Plasma concentration measurements are unequivocally useful in problem patients who do not respond to usual oral doses or in high-risk patients for whom, because of age or medical illness, it is especially important to use the lowest possible effective dose of the drug.[1]

It has been suggested[2] that within this window of total nortriptyline concentrations there is a probability of an antidepressant response of 68% or more with free concentrations of 7 to 10 nanograms/mL.

For reference to dose-dependent kinetics of nortriptyline observed in individuals with an extensive debrisoquine hydroxylation phenotype, see under Metabolism, above.

1. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; **142:** 155–62.
2. Perry PJ, *et al.* The relationship of free nortriptyline levels to antidepressant response. *Drug Intell Clin Pharm* 1984; **18:** 510.

Uses and Administration

Nortriptyline is a dibenzocycloheptadiene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is the principal active metabolite of amitriptyline. Nortriptyline is one of the less sedating tricyclics and its antimuscarinic effects are mild.

Nortriptyline is given orally as the hydrochloride although doses are expressed in terms of the base; nortriptyline hydrochloride 113.8 mg is equivalent to about 100 mg of nortriptyline. In the treatment of **depression** a low starting dose is given gradually increasing to the equivalent of 75 to 100 mg daily in 3 or 4 divided doses. Up to a maximum of 150 mg daily may be required in patients with severe depression. Licensed drug information recommends that plasma concentrations of nortriptyline should be monitored when doses above 100 mg daily are given; however, the *BNF* considers that the evidence of any practical value is uncertain. Adolescents and the elderly may be given 30 to 50 mg daily in divided doses. Since nortriptyline has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

Nortriptyline is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Suggested doses are:

- 10 mg for children aged 6 to 7 years (20 to 25 kg)
- 10 to 20 mg for children aged 8 to 11 years (25 to 35 kg)
- 25 to 35 mg for children aged over 11 years (35 to 54 kg)

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Nortriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). Nortriptyline has also been tried and may produce fewer adverse effects than amitriptyline. An initial oral dose of 10 to 25 mg at night has been suggested by the *BNF* for the management of **neuropathic pain**.

References to the use of nortriptyline.

1. Atkinson JH, *et al.* A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain* 1998; **76:** 287–96.
2. Watson CP, *et al.* Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998; **51:** 1166–71.

Smoking cessation. For reference to the use of nortriptyline in management of smoking cessation, see under Amitriptyline, p.382.

Preparations

BP 2008: Nortriptyline Capsules; Nortriptyline Tablets;
USP 31: Nortriptyline Hydrochloride Capsules; Nortriptyline Hydrochloride Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ateben†; ***Austral.:*** Allegron; ***Austria:*** Nortrilen; ***Belg.:*** Nortrilen; ***Braz.:*** Nortrip; Pamelor; ***Canad.:*** Aventyl; Norventyl†; ***Cz.:*** Nortrilen; ***Denm.:*** Noritren; ***Fin.:*** Noritren; ***Ger.:*** Nortrilen; ***Gr.:*** Nortrilen; ***Hong Kong:*** Nortrilen; ***India:*** Sensival; ***Israel:*** Nortylin; ***Ital.:*** Noritren; ***Neth.:*** Nortrilen; ***Norw.:*** Noritren; ***NZ:*** Norpress; ***Port.:*** Norterol; ***Spain:*** Norfenazin; Paxtibi; ***Swed.:*** Sensaval; ***Switz.:*** Nortrilen; ***Thai.:*** Norline; Nortrilen; Nortyline; Ortrip; ***UK:*** Allegron; ***USA:*** Aventyl; Pamelor.

Multi-ingredient: ***Arg.:*** Karile; ***Chile:*** Motitrel; ***Indon.:*** Motival; ***Irl.:*** Motival; ***Ital.:*** Dominans; ***Mex.:*** Motival; ***S.Afr.:*** Motival; ***Spain:*** Tropargal; ***Thai.:*** Cetavol; ***UK:*** Motival†.

Opipramol Hydrochloride *(BANM, USAN, rINNM)*

G-33040; Hidrocloruro de opipramol; Opipramol, Chlorhydrate d'; Opipramol Hidroklorür; Opipramoli Dihydrochloridum; Opipramoli Hydrochloridum; Opipramolu dichlorowodorek. 2-[4-(3-5*H*-Dibenz[*b,f*]azepin-5-ylpropyl)piperazin-1-yl]ethanol dihydrochloride.

Опипрамола Гидрохлорид

$C_{23}H_{29}N_3O,2HCl$ = 436.4.
CAS — 315-72-0 (opipramol); 909-39-7 (opipramol dihydrochloride).
ATC — N06AA05.
ATC Vet — QN06AA05.

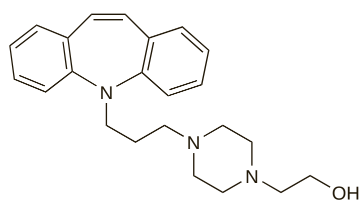

(opipramol)

Pharmacopoeias. In *Pol.*

Profile

Opipramol hydrochloride is a dibenzazepine tricyclic antidepressant (see Amitriptyline, p.376) given in oral doses of 50 to 300 mg daily in the treatment of depression.

It should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Insidon; ***Ger.:*** Insidon; ***Israel:*** Oprimol; ***Pol.:*** Pramolan; ***Switz.:*** Insidon; ***Turk.:*** Deprenil; Insidon; Insomin; Inzeton; Opridon; Oprimol.

Oxitriptan *(rINN)*

5-HTP; L-5-Hydroxytryptophan; Oxitriptán; Oxitriptanum; Ro-0783/B. L-2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

Окситриптан

$C_{11}H_{12}N_2O_3$ = 220.2.
CAS — 4350-09-8 (oxitriptan); 56-69-9 (DL-5-hydroxytryptophan).
ATC — N06AX01.
ATC Vet — QN06AX01.

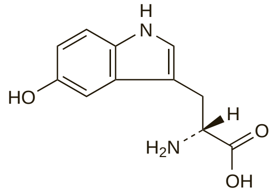

Profile

Oxitriptan is the L form of 5-hydroxytryptophan, a precursor of serotonin. Like tryptophan (p.427) it is used in the treatment of depression; it is given in oral doses of up to 600 mg daily.

Oxitriptan is also used in doses of up to 1 g daily in myoclonic disorders, especially posthypoxic myoclonus (p.470). It has also been used in neurological conditions including migraine, pain syndromes, and sleep disorders, and as an adjunct in epilepsy and parkinsonism.

DL-Oxitriptan has also been used as an antidepressant.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Tript-OH; ***Fr.:*** Levotonine; ***Ger.:*** Levothym†; ***Ital.:*** Tript-OH; ***Port.:*** Cincofarm; ***Spain:*** Cincofarm; ***Switz.:*** Tript-OH.

Multi-ingredient: ***Indon.:*** Deprex; Menose.

Paroxetine *(BAN, USAN, rINN)*

BRL-29060; FG-7051; Paroksetiini; Paroxetin; Paroxetina; Paroxétine; Paroxetinum. (−)-*trans*-5-(4-*p*-Fluorophenyl-3-piperidylmethoxy)-1,3-benzodioxole.

Пароксетин

$C_{19}H_{20}FNO_3$ = 329.4.
CAS — 61869-08-7.
ATC — N06AB05.
ATC Vet — QN06AB05.

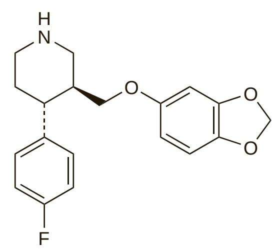

Paroxetine Hydrochloride *(BANM, rINNM)*

BRL-29060A; Hidrocloruro de paroxetina; Paroksetiinihydrokloridihemihydraatti; Paroksetin Hidroklorür; Paroksetino hidrochloridas hemihidratas; Paroksetyny chlorowodorek; Paroxetin hydrochlorid; Paroxétine, chlorhydrate de; Paroxétine (chlorhydrate de) hémihydraté; Paroxetine Hydrochloride Hemihydrate; Paroxetinhydrokloridhemihydrat; Paroxetini hydrochloridum; Paroxetini hydrochloridum hemihydricum.

Пароксетина Гидрохлорид

$C_{19}H_{20}FNO_3,HCl,\frac{1}{2}H_2O$ = 374.8.
CAS — 78246-49-8 (anhydrous paroxetine hydrochloride); 110429-35-1 (paroxetine hydrochloride hemihydrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*, which permit the anhydrous and hemihydrate forms.

Ph. Eur. 6.2 (Paroxetine Hydrochloride, Anhydrous). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers at a temperature not exceeding 25°.

Ph. Eur. 6.2 (Paroxetine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. It exhibits pseudopolymorphism. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Paroxetine Hydrochloride). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white solid. Slightly soluble in water; soluble in alcohol and in methyl alcohol. Store the anhydrous form in airtight containers.

Paroxetine Mesilate *(BANM, rINNM)*

Mesilato de paroxetina; Paroxétine, Mésilate de; Paroxetine Mesylate *(USAN)*; Paroxetini Mesilas.

Пароксетина Мезилат

$C_{19}H_{20}FNO_3,CH_4O_3S$ = 425.5.
CAS — 217797-14-3.
ATC — N06AB05.
ATC Vet — QN06AB05.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391).

Extrapyramidal reactions (including orofacial dystonias) and withdrawal symptoms associated with paroxetine have been reported to the UK CSM more commonly than with other SSRIs. For further details, see Extrapyramidal Effects under Adverse Effects of Fluoxetine, p.393 and Withdrawal under Precautions, p.396.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Pregnancy. For discussion of the risks of SSRIs during pregnancy, and whether paroxetine is associated with a greater teratogenic risk than other SSRIs, see under Fluoxetine, p.395.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Pharmacokinetics

Paroxetine is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about 5 hours of ingestion. It undergoes extensive first-pass metabolism in the liver. The main metabolic pathway is oxidation followed by methylation and formation of glucuronide and sulfate conjugates. The cytochrome P450 isoenzyme CYP2D6 is partly responsible for the metabolism of paroxetine. Paroxetine is widely distributed throughout body tissues and is about 95% bound to plasma proteins. The elimination half-life of paroxetine is reported to be about 21 hours. Excretion is via the urine (about 64%) and the faeces (about 36%), mainly as metabolites in both cases. Paroxetine is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p.394).

◊ References.

1. Dalhoff K, *et al.* Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 1991; **41:** 351–4.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Uses and Administration

Paroxetine, a phenylpiperidine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p.397). It is given orally usually as paroxetine hydrochloride, as a single dose in the morning; it is also given as the mesilate. Doses are expressed in terms of the base; paroxetine hydrochloride 22.8 mg or paroxetine mesilate 25.8 mg are each equivalent to about 20 mg of paroxetine. The doses given below refer to preparations containing paroxetine hydrochloride; similar doses are also used when paroxetine is given as the mesilate.

In the treatment of **depression**, the usual dose of paroxetine is 20 mg daily, increased gradually, if necessary, in weekly increments of 10 mg to a maximum of 50 mg daily (but see Administration, below).

In the treatment of **generalised anxiety disorder**, the initial dose is 20 mg daily; further increases in increments of 10 mg at intervals of at least one week to a maximum of 50 mg have been given (but see Administration, below).

The initial dose in **obsessive-compulsive disorder** is 20 mg daily increased weekly in 10-mg increments to a usual maintenance dose of 40 mg daily; some patients may require up to 60 mg daily (but see Administration, below).

In the treatment of **panic disorder** with or without agoraphobia, the initial dose is 10 mg daily increased weekly in 10-mg increments according to response; the usual recommended maintenance dose is 40 mg daily, although some patients may benefit from 60 mg daily (but see Administration, below).

The recommended starting dose for the treatment of **post-traumatic stress disorder** is 20 mg daily. If necessary this may be increased in increments of 10 mg at intervals of at least one week to a maximum of 50 mg daily (but see Administration, below).

The initial dose for the treatment of **social anxiety disorder** is 20 mg daily increased after several weeks, if necessary, by increments of 10 mg to a maximum of 50 or 60 mg daily (but see Administration, below).

A suggested maximum daily dose in elderly or debilitated patients is 40 mg; US licensed product information also recommends a starting dose of 10 mg daily in such patients. Reduced doses should be given to patients with hepatic or renal impairment, see below.

A modified-release preparation (as the hydrochloride) is also available in the USA for the treatment of depression, panic disorder, and social anxiety disorder; the maximum doses with this preparation may be slightly greater than those recommended with the immediate-release preparation. The modified-release preparation may also be used in the treatment of **premenstrual dysphoric disorder**. The initial dose is 12.5 mg once daily, usually in the morning, which may be increased to 25 mg once daily, if necessary, after an interval of at least one week. Treatment may be given throughout the menstrual cycle or limited to the luteal phase.

Paroxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms. For further details, see Withdrawal under Precautions of Fluoxetine, p.396.

◊ Reviews.

1. Wagstaff AJ, *et al.* Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 2002; **62:** 655–703. Correction. *ibid.*; 1461.

Administration. Although paroxetine is licensed in the UK at higher doses the UK CSM considers that there is a lack of evidence from clinical trials of additional efficacy with paroxetine when given above the following daily doses:

- depression, generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder: 20 mg
- obsessive-compulsive disorder, panic disorder: 40 mg

1. CSM/MCA Paroxetine prescribing advice. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod= LatestReleased (accessed 14/08/08)

Administration in hepatic or renal impairment. In the USA the recommended initial oral dose of paroxetine in patients with severe renal or hepatic impairment is the equivalent of 10 mg daily, increased to a maximum of 40 mg daily as necessary. UK licensed drug information recommends that doses in such patients are limited to the lower end of the range.

Anxiety disorders. Paroxetine is used in anxiety disorders including generalised anxiety disorder (p.952), obsessive-compulsive disorder (p.952), panic disorder (p.952), post-traumatic stress disorder (p.953), and social anxiety disorder (see under Phobic Disorders, p.953). It has also been tried for adult night terrors (see under Sleep-associated Movement Disorders, p.958).

References.

1. Oehrberg S, *et al.* Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1995; **167:** 374–9.
2. Zohar J, *et al.* Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 1996; **169:** 468–74.
3. Lecrubier Y, *et al.* Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand* 1997; **95:** 153–60.
4. Wilson SJ, *et al.* Adult night terrors and paroxetine. *Lancet* 1997; **350:** 185.
5. Stein MB, *et al.* Paroxetine treatment of generalized social phobia (social anxiety disorder). *JAMA* 1998; **280:** 708–13.
6. Baldwin D, *et al.* Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1999; **175:** 120–6.
7. Baldwin DS. Clinical experience with paroxetine in social anxiety disorder. *Int Clin Psychopharmacol* 2000; **15** (suppl): S19–24.
8. Marshall RD, *et al.* Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 2001; **158:** 1982–8.
9. Tucker P, *et al.* Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001; **62:** 860–8.
10. Liebowitz MR, *et al.* A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry* 2002; **63:** 66–74.
11. Stein DJ, *et al.* Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. *Arch Gen Psychiatry* 2002; **59:** 1111–18.
12. Stocchi F, *et al.* Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 2003; **64:** 250–8.
13. Hollander E, *et al.* Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry* 2003; **64:** 1113–21.
14. Lepola U, *et al.* Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 222–9.
15. Sheehan DV, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry* 2005; **66:** 34–40.
16. Rickels K, *et al.* Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry* 2006; **67:** 41–7.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as paroxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Leyman S, *et al.* Paroxetine: post-marketing experience on 4024 depressed patients in Belgium. *Eur J Clin Res* 1995; **7:** 287–96.
2. Rodríguez-Ramos P, *et al.* Effects of paroxetine in depressed adolescents. *Eur J Clin Res* 1996; **8:** 49–61.
3. Franchini L, *et al.* Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J Clin Psychiatry* 1998; **59:** 229–32.
4. Williams JW, *et al.* Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; **284:** 1519–26.
5. Golden RN, *et al.* Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002; **63:** 577–84.
6. Rapaport MH, *et al.* Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry* 2003; **64:** 1065–74.
7. Misri S, *et al.* The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004; **65:** 1236–41.
8. Trivedi MH, *et al.* Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1356–64.
9. Dunner DL, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression: post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. *Clin Ther* 2005; **27:** 1901–11.

Hot flushes. Some SSRIs, including paroxetine, have been tried in the treatment of hot flushes; for further details see under Fluoxetine, p.398.

Hypochondriasis. For mention of the use of SSRIs, including paroxetine, in hypochondriasis, see under Fluoxetine, p.398.

Premenstrual syndrome. Paroxetine (as a modified-release preparation) is used to control both the psychological and somatic symptoms of premenstrual syndrome (p.2099).

References.

1. Cohen LS, *et al.* Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med* 2004; **66:** 707–13.

Pruritus. Paroxetine has produced some benefit in the relief of non-dermatological pruritus.[1]

1. Zylicz Z, *et al.* Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; **26:** 1105–12.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the potential use of these effects in the management of premature ejaculation see Fluoxetine, p.399.

Preparations

BP 2008: Paroxetine Tablets;
USP 31: Paroxetine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afenexil; Aropax; Datevan; Meplar; Neurotrox; Olane; Pamoxet; Paxil; Psicoasten; Sicopax; Sicotral; Sostel; Tiarix; Xilanic; ***Austral.:*** Aropax; Extine; Oxetine; Paxtine; ***Austria:*** Allenopar; Aparo†; Ennos; Glaxopar; Paluxetil†; Parocetan; Paroglax; Paroxat; Seroxat; ***Belg.:*** Aropax; Seroxat; ***Braz.:*** Aropax; Benepax; Cebrilin; Parox; Paxtrat; Pondera; Roxetin; ***Canad.:*** Paxil; ***Chile:*** Aroxat; Bectam; Pamax; Posivyl; Seretran; Traviata; ***Cz.:*** Apo-Parox; Arketis; Parolex; Remood; Seroxat; ***Denm.:*** Oxetine†; Serodur; Seroxat; ***Fin.:*** Optipar; Seroxat; ***Fr.:*** Deroxat; Divarius; ***Ger.:*** Euplix; Oxet†; ParoLich; Paroxat; Paroxedura; Seroxat; Tagonis; ***Gr.:*** Noprilex; Seroxat; Taberil; ***Hong Kong:*** Seroxat; ***Hung.:*** Apodepi; Paretin; Parogen; Paroxat; Rexetin; Seroxat; ***India:*** Pari; Parotin; Xet; ***Indon.:*** Seroxat; ***Irl.:*** Meloxat; Paroser; Parox; Paxt; Seroxat; ***Israel:*** Paxxet; Seroxat; ***Ital.:*** Daparox; Dropaxin; Eutimil; Serestill; Sereupin; Seroxat; Stiliden; ***Jpn:*** Paxil; ***Malaysia:*** Seroxat; ***Mex.:*** Apo-Oxpar; Aropax; Paxil; ***Neth.:*** Seroxat; ***Norw.:*** Seroxat; ***NZ:*** Aropax; Loxamine; ***Philipp.:*** Seroxat; ***Pol.:*** Deprozel; Paromerck; Paxeratio; Paxtin; Rexetin; Seroxat; Xetanor; ***Port.:*** Denerval; Oxepar†; Paxetil; Seroxat; ***Rus.:*** Paxil (Паксил); Rexetin (Рексетин); ***S.Afr.:*** Aropax; Deparoc; Parax; Paxil; Sedarin; Serrapress; Xet; ***Singapore:*** Seroxat; ***Spain:*** Casbol; Frosinor; Motivan; Paratonina; Parotur†; Seroxat; Xetin; ***Swed.:*** Euplix†; Paroxiflex; Seroxat; ***Switz.:*** Deroxat; Dexantol; Parexat; Paronex; Paroxetop; ***Thai.:*** Seroxat; ***Turk.:*** Paxil; Seroxat; ***UK:*** Seroxat; ***USA:*** Paxil; Pexeva; ***Venez.:*** Paxil.

Phenelzine Sulfate *(pINNM)*

Phénelzine, Sulfate de; Phenelzine Sulphate *(BANM)*; Phenelzini Sulfas; Sulfato de fenelzina. Phenethylhydrazine hydrogen sulphate.

Фенельзина Сульфат

$C_8H_{12}N_2,H_2SO_4 = 234.3.$

CAS — 51-71-8 (phenelzine); 156-51-4 (phenelzine sulfate).

ATC — N06AF03.

ATC Vet — QN06AF03.

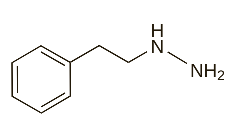

(phenelzine)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Phenelzine Sulphate). A white powder or pearly platelets with a pungent odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Protect from light.

USP 31 (Phenelzine Sulfate). A white to yellowish-white powder having a characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 1% solution in water is between 1.4 and 1.9. Store in airtight containers. Protect from heat and light.

Adverse Effects

Adverse effects commonly associated with phenelzine and other MAOIs include orthostatic hypotension and attacks of dizziness. Other common adverse effects include headache, dry mouth, constipation and other gastrointestinal disturbances (including nausea and vomiting), and oedema. Drowsiness, weakness, and fatigue are reported frequently although CNS stimulation may also occur and symptoms include agitation, nervousness, euphoria, restlessness, insomnia, and convulsions. Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons.

Sweating and muscle tremors, twitching, or hyperreflexia may occur, which in overdosage may present as extreme hyperpyrexia and neuromuscular irritability. Other reported reactions include blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, skin rashes, leucopenia, sexual disturbances, and weight gain with inappropriate appetite. Jaundice has been reported with hydrazine MAOIs and, on rare occasions, fatal progressive hepatocellular necrosis. Peripheral neuropathies associated with the hydrazine derivatives may be caused by pyridoxine deficiency. Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of **overdosage** may be minor at first and progress over the ensuing 24 to 48 hours. After mild overdosage and symptomatic and supportive therapy, recovery may occur in 3 to 4 days, but after massive overdosage symptoms may persist for up to 2 weeks. CNS depression and drowsiness have been observed with overdosage, but CNS stimulation is more common, with irritability, hyperactivity, agitation, hallucinations, or convulsions. Respiratory depression and coma may ultimately occur. Cardiovascular effects include hypertension, sometimes with severe headache, although hypotension is more frequently observed; cardiac arrhythmias and peripheral collapse can also develop. Profuse sweating, hyperpyrexia, and neuromuscular excitation with hyperreflexia are also prominent features of overdosage.

MAOIs have been the most commonly implicated drugs in the serotonin syndrome (see below). A severe hypertensive crisis, sometimes fatal, may occur if an MAOI is taken with some other drugs or certain foods (see Interactions, below). These reactions are characterised by severe headache and a rapid and sometimes prolonged rise in blood pressure followed by intracranial haemorrhage or acute cardiac failure.

For the adverse effects of reversible inhibitors of monoamine oxidase type A (RIMAs), see Moclobemide, p.411.

Incidence of adverse effects. A suspicion that the reported adverse effects of MAOIs were both exaggerated and overemphasised prompted a comparative study in patients receiving phenelzine or imipramine.[1] The report noted that the dosages of phenelzine used were at the upper end of the usual therapeutic range (mean 77 mg daily) while those of imipramine were in the middle of the usual therapeutic range (mean 139 mg daily). A very similar profile of adverse effects in the two groups was observed. With the exception of significantly increased incidence of drowsiness in the phenelzine-treated group, the 2 groups did not differ in the frequency of autonomic, CNS, cardiovascular, or psychological adverse effects. However, a significantly greater number of phenelzine-treated patients had to stop their treatment because of the severity of the adverse effects. Nonetheless it was considered that phenelzine was reasonably well-tolerated when compared with imipramine.

Others have also studied the adverse effect profile of phenelzine and made comparisons with tranylcypromine and imipramine.[2,3] A retrospective review involving 198 patients concluded that although phenelzine was more likely than the other two drugs to induce adverse effects, drug withdrawal because of adverse effects was less likely to occur. This was probably because phenelzine showed clear-cut clinical efficacy resulting in prescribers being reluctant to stop therapy.

1. Evans DL, *et al.* Early and late side effects of phenelzine. *J Clin Psychopharmacol* 1982; **2:** 208–10.
2. Rabkin J, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part I: a comparative study. *J Clin Psychopharmacol* 1984; **4:** 270–8.
3. Rabkin JG, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part II: treatment correlates and clinical management. *J Clin Psychopharmacol* 1985; **5:** 2–9.

Effects on the cardiovascular system. MAOIs are generally considered to be relatively free of adverse cardiovascular effects. The hypertensive reaction that may follow interactions of MAOIs with foods or other drugs is well known (see Interactions, below) but orthostatic hypotension may also occur when these drugs are used on their own.

In a study[1] involving 14 patients it was found that phenelzine produced both a significant decrease in systolic blood pressure while lying down, and significant orthostatic hypotension; in 2 patients these effects on blood pressure meant treatment had to be altered. Differences between the effects of phenelzine and those reported for the tricyclic antidepressants were noted. Tricyclics were not known to affect lying systolic blood pressure and although both tricyclics and phenelzine could cause orthostatic hypotension, with the tricyclics it typically reaches a maximum within the first week of treatment whereas with phenelzine the maximum effect was noted after 4 weeks. Additionally, the study provided some indication that the blood pressure effects of phenelzine may attenuate with time, a phenomenon that is not known to occur with the tricyclics.

1. Kronig MH, *et al.* Blood pressure effects of phenelzine. *J Clin Psychopharmacol* 1983; **3:** 307–10.

Effects on the endocrine system. MAOIs may induce *hyperprolactinaemia*[1] and this has led to galactorrhoea in women.[2] Occasionally, MAOIs may cause *dilutional hyponatraemia* due to a reduction in the renal excretion of free water mediated by both enhanced vasopressin release and increased antidiuretic action on the renal tubule.[3] The UK CSM, commenting on reports[4] it had received of hyponatraemia with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.

1. Slater SL, *et al.* Elevation of plasma-prolactin by monoamine-oxidase inhibitors. *Lancet* 1977; **ii:** 275–6.
2. Segal M, Heys RF. Inappropriate lactation. *BMJ* 1969; **4:** 236.
3. Baylis PH. Drug-induced endocrine disorders. *Adverse Drug React Bull* 1986; No 116: 432–5.
4. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the liver. Published case reports of hepatotoxic reactions to MAOIs have included jaundice in 4 patients[1] and hepatic failure progressing to encephalopathy in 2 patients;[2] this latter reaction was attributed to a hypersensitivity reaction.

Of 91 cases of hepatitis associated with antidepressants reported to French pharmacovigilance centres from 1977 to 1983, an MAOI (iproniazid) was implicated in 11. These 11 cases were associated with cytolytic reactions and 5 patients died.[3]

Two cases of fulminant hepatic failure have been reported[4] after use of phenelzine for 4 months; all other causes of acute liver damage were ruled out. Both patients recovered after emergency liver transplantation.

1. Holdsworth CD, *et al.* Hepatitis caused by the newer amine-oxidase-inhibiting drugs. *Lancet* 1961; **ii:** 621–3.
2. Wilkinson SP, *et al.* Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *BMJ* 1974; **1:** 186–9.
3. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
4. Gómez-Gil E, *et al.* Phenelzine-induced fulminant hepatic failure. *Ann Intern Med* 1996; **124:** 692–3.

Effects on the nervous system. MAOIs produce a variety of effects on the nervous system. Drowsiness is frequently reported but symptoms of CNS stimulation, including agitation, nervousness, and euphoria may also occur; psychotic episodes may be induced in susceptible individuals. Further adverse neurological reactions are described under Epileptogenic Effect and Extrapyramidal Effects, below.

Peripheral neuropathies, sometimes associated with a documented pyridoxine deficiency, have been reported in patients receiving phenelzine.[1,2] In most of the patients the neuropathies developed 6 weeks to 4 months after starting phenelzine,[2] although in one case symptoms did not occur for 11 years.[1] The symptoms also generally disappeared when pyridoxine was given with continued phenelzine therapy.[2] The possibility that the dietary restrictions imposed on persons taking phenelzine might have contributed to a low pyridoxine intake was considered unlikely. The most probable mechanism for the induced pyridoxine deficiency was combination of the hydrazine moiety with the pyridoxal form of the vitamin to form an inactive compound.

Many drugs can inhibit transmission at the myoneural junction under experimental conditions and it has been said that phenelzine may cause postoperative respiratory depression, possibly through a combined action with neuromuscular blockers.[3] For further details, see Anaesthesia under Precautions, below.

1. Heller CA, Friedman PA. Pyridoxine deficiency and peripheral neuropathy associated with long-term phenelzine therapy. *Am J Med* 1983; **75:** 887–8.
2. Stewart JW, *et al.* Phenelzine-induced pyridoxine deficiency. *J Clin Psychopharmacol* 1984; **4:** 225–6.
3. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on sexual function. MAOIs such as phenelzine and tranylcypromine have been implicated in producing both impotence and failure of ejaculation.[1,2] Priapism has been reported with phenelzine.[3] There have also been several reports of female anorgasmia attributed to MAOIs, an effect which appears to be dose-related.[4] Loss of libido and impotence are common symptoms of depression, often making the role of drugs in producing sexual dysfunction difficult to assess.

1. Simpson GM, *et al.* Effects of anti-depressants on genito-urinary function. *Dis Nerv Syst* 1965; **26:** 787–9.
2. Wyatt RJ, *et al.* Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *N Engl J Med* 1971; **285:** 987–91.
3. Yeragani VK, Gershon S. Priapism related to phenelzine therapy. *N Engl J Med* 1987; **317:** 117–18.
4. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.

Epileptogenic effect. Licensed product information indicates that convulsions represent one of the less common adverse effects of MAOIs; they may be a feature of overdosage.

A typical grand-mal seizure with tonic-clonic convulsions has been reported in a patient with no history of epilepsy or predisposing factors shortly after the start of phenelzine therapy.[1] The point was made that phenelzine-induced seizures had rarely been observed.

1. Bhugra DK, Kaye N. Phenelzine induced grand mal seizure. *Br J Clin Pract* 1986; **40:** 173–4.

Extrapyramidal effects. A parkinsonian syndrome developed in a patient about 5 weeks after the start of therapy with phenelzine. Symptoms gradually resolved over 10 days after the withdrawal of phenelzine. The mechanisms by which phenelzine could have induced these effects were discussed.[1]

1. Gillman MA, Sandyk R. Parkinsonism induced by a monoamine oxidase inhibitor. *Postgrad Med J* 1986; **62:** 235–6.

Hyponatraemia. See Effects on the Endocrine System, above.

Lupus. A reversible lupus-like reaction has been reported in a patient who had been taking phenelzine sulfate for 8 months.[1]

1. Swartz C. Lupus-like reaction to phenelzine. *JAMA* 1978; **239:** 2693.

Overdosage. MAOIs in overdose rarely produce severe hypertension; the blood pressure may be high or low, or may alternate between the two. More commonly the patient gradually develops widespread muscle spasms, trismus, and opisthotonus with widely dilated pupils and a hot and sweating skin. About 16 to 24 hours after ingestion potentially fatal hyperthermia may develop; temperatures of 42.1 to 43.8° have been recorded immediately before death. Disseminated intravascular coagulation, rhabdomyolysis, and acute tubular necrosis can also occur.[1]

1. Henry JA. Specific problems of drug intoxication. *Br J Anaesth* 1986; **58:** 223–33.

Serotonin syndrome. The serotonin syndrome is a drug-induced excess in serotonergic activity at central receptors.[1-10] It is characterised by the development of *at least three* of the following clinical features after a recent change in a treatment regimen involving serotonergic drugs:[1]

- agitation
- ataxia
- diaphoresis
- diarrhoea
- fever
- hyperreflexia
- myoclonus
- shivering
- changes in mental status

Strict application of these criteria may not identify early, mild, or subacute cases of serotonin syndrome and a simpler diagnostic approach focusing on neuromuscular features has also been suggested.[10] The syndrome should be distinguished from the hypertensive crises produced by the interaction between MAOIs and tyramine (see Interactions of MAOIs with Foods, below), and from the neuroleptic malignant syndrome (see p.972).[3,8-10]

The onset of the syndrome is often within minutes of altering the regimen,[10] although some cases have occurred as much as several weeks later.[2] The occurrence and severity of the syndrome do not appear to be dose-related,[2] but to depend on the extent and duration of the rise in intrasynaptic serotonin.[5]

The serotonin syndrome is relatively uncommon and symptoms are usually mild. However, severe complications, including disseminated intravascular coagulation, severe hyperthermia, respiratory failure, and seizures have been reported; there have also been fatalities.

The serotonin syndrome may follow exposure to a single serotonergic drug or, more commonly, a combination of such drugs.[2,8-10] In the past, **MAOIs** have been the most commonly implicated drugs in this syndrome, particularly when taken with other antidepressants such as the tricyclics, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs) including venlafaxine, trazodone, lithium, and tryptophan. (The use of combination therapy with serotonergic antidepressant drugs is discussed under Interactions of MAOIs with other Drugs, below.) MAOIs combined with the opioids dextromethorphan and pethidine have also produced the serotonin syndrome. The interaction can occur with both irreversible and reversible MAOIs, and with those selective for monoamine oxidase type A such as moclobemide as well as with non-selective MAOIs.[11] The selective inhibitor of monoamine oxidase type B, selegiline, may also pose problems at high doses as its selectivity starts to diminish.

As usage of the **SSRIs** has increased, so too has the number of reports of adverse reactions when these drugs have been combined with other serotonergic drugs, including the herbal preparation St John's wort.

Other drugs that may potentially cause serotonin syndrome in certain circumstances include antiemetics such as ondansetron, buspirone, carbamazepine, dihydroergotamine, methylenedioxyamfetamine, sibutramine, selective serotonin (5-HT_1) agonists such as sumatriptan, and tramadol.[5,8-10]

Serotonergic potentiation may also occur if one serotonergic drug is used after another without allowing a sufficient **drug-free interval** after stopping the first. This is a particular problem when the first drug is an irreversible MAOI or a drug with a long half-life such as the SSRI fluoxetine.

Most cases of serotonin syndrome resolve within 24 hours after withdrawal of the offending drugs and giving supportive **therapy**,[1-4,8-10] including appropriate management of fever and hyperthermia (p.10). Benzodiazepines may be of value to control agitation, myoclonus, and seizures. The non-specific serotonin antagonist cyproheptadine may be useful in more severe cases although its efficacy has not been established;[8,10] methysergide has also been used with some success.[2,3,6] Other drugs that have been tried include propranolol, chlorpromazine, and dantrolene[2,3,6,8-10] although adverse effects may limit their usefulness.

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; **148:** 705–13.
2. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. *Drug Safety* 1995; **13:** 94–104.
3. Corkeron MA. Serotonin syndrome—a potentially fatal complication of antidepressant therapy. *Med J Aust* 1995; **163:** 481–2.
4. Brown TM, *et al.* Pathophysiology and management of the serotonin syndrome. *Ann Pharmacother* 1996; **30:** 527–33.
5. Gillman PK. Serotonin syndrome: history and risk. *Fundam Clin Pharmacol* 1998; **12:** 482–91.
6. Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol* 1999; **13:** 100–109.
7. Mason PJ, *et al.* Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2000; **79:** 201–9.
8. Birmes P, *et al.* Serotonin syndrome: a brief review. *Can Med Assoc J* 2003; **168:** 1439–42.
9. Bilj D. The serotonin syndrome. *Neth J Med* 2004; **62:** 309–13.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; **352:** 1112–20.
11. Livingston MG. Interactions with selective MAOIs. *Lancet* 1995; **345:** 533–4. Correction. *ibid.* 2007; **356:** 2437.

Treatment of Adverse Effects

In cases of overdosage with MAOIs the benefit of gastric decontamination is uncertain; however, in patients who present within 1 hour activated charcoal may be given by mouth, or, in potentially life-threatening cases, the stomach may be emptied by lavage. Management then largely involves intensive symptomatic and supportive therapy with particular attention being given to CNS effects, raised body temperature (which may develop into malignant hyperthermia), and cardiovascular effects. Delayed effects may develop some time after the overdose even in patients who are initially asymptomatic, and therefore prolonged monitoring is warranted. Other drugs taken with an overdose of MAOIs may complicate the features and result in the need for an even longer period of monitoring. Special care should be observed with any drug therapy used in the management of MAOI overdosage in view of the many known interactions which occur with this class of drugs.

Muscle spasm, agitation, and convulsions should be treated with diazepam. Severe neuromuscular irritability may call for the use of a competitive neuromuscular blocker such as pancuronium and intubation with assisted ventilation. Hyperthermia may be a particular problem; if simple antipyretics such as paracetamol and external cooling measures fail a competitive neuromuscular blocker has often been advocated; dantrolene has also been suggested.

Hypotension, which is a fairly common feature, should be managed by intravenous fluid therapy and volume expansion; vasopressors should be avoided. Conversely, a hypertensive crisis may occasionally occur after an overdose with MAOIs and can be managed with phentolamine given by slow intravenous injection. A short-acting beta blocker such as esmolol or metoprolol has also been advocated for persistent tachycardia and hypertension.

Precautions

Phenelzine and other MAOIs should not be given to patients with liver disease or a history of abnormal liver function tests, or, because of their effects on blood pressure, to patients with congestive heart failure, cerebrovascular disease, or phaeochromocytoma. (Blood pressure should be monitored in all patients.) MAOIs should be avoided or only used with great caution in patients with blood disorders or cardiovascular disease, and in elderly or agitated patients who may be particularly susceptible to their adverse effects. They should be given with caution to epileptic patients. Caution has also been advised in diabetic patients because of conflicting evidence whether glucose metabolism is altered or requirements for hypoglycaemics changed. MAOIs should be used with caution in patients with hyperthyroidism because of increased sensitivity to pressor amines.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Mania may be precipitated if MAOIs are used for the depressive component of bipolar disorder, and they are not usually indicated; similarly psychotic symptoms may be aggravated if they are used for a depressive component of schizophrenia.

MAOIs have a prolonged action so patients should not take any of the foods or drugs known to cause reactions (see Interactions, below) for at least 14 days after stopping treatment. A similar drug-free period has been advised before any patient undergoes surgery since it may involve the use of drugs that can interact with MAOIs, although not all agree that this is necessary; caution has been advised in patients requiring MAOIs with ECT; for further details see under Anaesthesia, below. Patients should carry cards giving details of their MAOI therapy; they and their relatives should be fully conversant with the implications of food and drug interactions and the precautions to be taken.

Patients liable to take charge of vehicles or other machinery should be warned that MAOIs may modify behaviour and state of alertness. Patients affected by drowsiness should not drive or operate machinery.

MAOIs should be withdrawn gradually to reduce the risk of withdrawal symptoms (see below).

For the precautions to be observed with reversible inhibitors of monoamine oxidase A (RIMAs), see Moclobemide, p.411.

Anaesthesia. The considerations given to patients receiving tricyclic antidepressants before receiving anaesthesia for ECT or surgery (see Amitriptyline, p.378) are also generally applicable to patients being treated with MAOIs; licensed drug information for phenelzine also warns that transient respiratory and cardiovascular depression following ECT have been reported. The interactions of other drugs with MAOIs may be more numerous or more severe than those with tricyclics and the interaction with pethidine should not be forgotten.

A review[1] of the potential problems of anaesthesia in patients receiving MAOIs considered that stopping MAOIs about 2 weeks before anaesthesia was unreasonable, as there was a wide range of safe and suitable anaesthetics available, although the dangers of sympathetic overactivity must always be remembered. This view, that it is safe to continue MAOIs throughout the period of anaesthesia, ECT, and surgery, is also held by others[2-4] although some disagree.[5]

Regardless of any decision, the anaesthetist should be informed of all drugs that the patient is or has been taking; this is particularly important when emergency surgery is required in a patient receiving MAOI therapy.

- It has been stated[1] that the interaction between MAOIs and *opioid analgesics* has two distinct forms: an excitatory form [serotonin syndrome—see above]; and a depressive form consisting of respiratory depression, hypotension, and coma as a result of the inhibition of hepatic microsomal enzymes by the MAOI leading to accumulation of free opioid analgesic. *Pethidine* use during anaesthesia has elicited the excitatory response, which has frequently been severe and often fatal. For this reason, pethidine should never be given to patients receiving MAOIs. *Morphine* does not block neuronal serotonin uptake but its narcotic effects may be potentiated in the presence of MAOIs and a single case report of the depressive type of reaction has been described. Thus, morphine is the opioid analgesic of choice but must be given in reduced dosage and the dosage carefully titrated against clinical response. *Papaveretum* would appear to have no advantage over morphine. Although interactions of MAOIs with *pentazocine* have occurred in *animals*, it is not clear if this occurs in man. *Methadone* has been used in a patient without mishap and there is also anecdotal evidence to support the safety of *fentanyl*. A case report[6] described the successful use of *alfentanil* (with propofol and atracurium) mentioning that this was the first report of such use in patients receiving MAOIs. A further case report[7] has also described the safe use of alfentanil (with propofol and suxamethonium) for anaesthesia during ECT in 2 patients taking phenelzine. *Remifentanil* has also been used safely as part of an anaesthetic regimen (with sevoflurane, vecuronium, and isoflurane) in a patient also taking phenelzine.[8] In another case[9] a patient underwent successful anaesthesia with *sufentanil* (with thiopental, lidocaine, and vecuronium) while continuing to take an MAOI (tranylcypromine) as well as a tricyclic antidepressant (imipramine) and lorazepam.
- With regard to induction agents,[1] the use of *ketamine* in patients receiving MAOIs should be avoided on theoretical grounds, although no interactions have been reported. Potentiation of *barbiturates* may be expected.
- With neuromuscular blockers, phenelzine has been shown to decrease plasma cholinesterase concentrations and there have been case reports of a prolonged effect with *suxamethonium*; additionally this prolongation of the effect of suxamethonium may lead to apnoea and modification of the convulsion during ECT. However, a small case series of 4 patients taking tranylcypromine while undergoing ECT treatment (with suxamethonium as the neuromuscular blocker) found no difference in seizure length when compared to previous ECT courses when the patients were not taking an MAOI.[4] There may be a theoretical hazard with *pancuronium* since it releases stored adrenaline (although its use has been advocated in the treatment of symptoms of overdosage with MAOIs, see above), but *alcuronium*, *atracurium*, or *vecuronium* would all appear to be suitable alternatives.[1]
- *Enflurane*, *halothane*, *isoflurane*, and *nitrous oxide* are all safe in the presence of MAOIs, although there is a theoretical possibility of an increased risk of hepatic damage with halothane.
- *Indirect-acting sympathomimetics* pose the risk of a serious and possibly lethal hypertensive interaction but *direct-acting sympathomimetics*, such as *adrenaline*, *isoprenaline*, and *noradrenaline*, are reliable vasopressors in the presence of MAOIs although great care should be taken with their use because of enhanced receptor sensitivity.

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6. Powell H. Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy. *Br J Anaesth* 1990; **64:** 528.
7. Beresford BJ, *et al.* Combination propofol-alfentanil anesthesia for electroconvulsive therapy in patients receiving monoamine oxidase inhibitors. *J ECT* 2004; **20:** 120–2.
8. Ure DS, *et al.* Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* 2000; **84:** 414–16.
9. O'Hara JF, *et al.* Sufentanil-isoflurane-nitrous oxide anesthesia for a patient treated with monoamine oxidase inhibitor and tricyclic antidepressant. *J Clin Anesth* 1995; **7:** 148–50.

Children. Phenelzine is not recommended for the treatment of depression in children and adolescents less than 16 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p.392).

Driving. While affective disorders probably impair driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative properties and some MAOIs can adversely affect psychomotor performance.[1,2]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased;[3] driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances or suicidal thoughts should cease driving pending the outcome of medical enquiry.

1. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
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3. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

ECT. For comments concerning the precautions to be observed in patients receiving ECT, see under Anaesthesia, above.

Porphyria. Phenelzine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Surgery. For comments regarding the precautions to be observed in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more can precipitate withdrawal symptoms which may be very severe.

Symptoms associated with withdrawal of MAOIs[1,2] include gastrointestinal disturbances and generalised somatic symptoms such as nausea and vomiting, anorexia, chills, headache, and giddiness; sleep disturbances characterised by insomnia, severe nightmares, and somnolence; and a range of CNS symptoms including panic, anxiety, restlessness, agitation, cognitive impairment, mood swings, depression and suicidal ideation, hypomania, delusions, and hallucinations. Some of the above may be controlled by restarting the MAOI in low doses, but the best management is considered to be prevention by gradually stopping the drug.[2] The *BNF* recommends reducing the dose over a period of 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The pathophysiology of the MAOI withdrawal syndrome is not fully known, although it has been hypothesised that some of the symptoms represent adrenergic hyperactivity[1] produced by the release of excessive amounts of dopamine and noradrenaline.[2]

With the exception of tranylcypromine, the withdrawal syndrome of MAOIs is not a consequence of drug dependence.[1] Tranylcypromine has been reported to produce dependence and tolerance in patients receiving high doses irrespective of whether or not they had a history of substance abuse. Tranylcypromine is similar in structure to amfetamine, which may be responsible for its addictive properties.[1]

1. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
2. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.

Interactions of MAOIs with Foods

A major disadvantage of MAOIs such as phenelzine is that by inhibiting monoamine oxidase they cause an accumulation of amine neurotransmitters. This means that the pressor effects of *tyramine*, which occurs in a number of common foods and is also metabolised by monoamine oxidase, can be dangerously enhanced. Reactions to foods rich in pressor amines such as tyramine can therefore occur in patients being treated with MAOIs, producing hypertensive crises. Cheese, especially aged or matured cheeses, meat or yeast extracts, pickled herrings, sauerkraut, dry sausage, smoked foods, and broad bean pods have caused such reactions. Patients should be warned not to eat any of these foods while being treated with an MAOI and for at least 14 days after its discontinuation. Some foods will only cause a reaction if large amounts are eaten, and foods may vary in tyramine content depending upon methods of manufacture and storage. Any protein-containing food such as meat, fish, or game subject to hydrolysis, fermentation, pickling, smoking, or spoilage could contain tyramine derived from tyrosine as a result of these processes or of deterioration. Patients taking MAOIs should therefore be advised to eat protein-containing foods only if fresh.

Alcoholic beverages, including wines, beers, and drinks that are de-alcoholised or are low in alcohol, contain variable amounts of tyramine and are best avoided.

The above dietary restrictions that need to be observed with MAOIs may be less stringent for reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (see p.411), although licensed drug information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

◊ MAOIs can, when taken with certain foodstuffs, cause a potentially fatal hypertensive reaction. This effect is accepted and well documented and has led to the publication of many lists of prohibited foods and drinks. Some workers consider that the dangers of the interaction may have been slightly overemphasised or exaggerated and that the published lists may have been overinclusive;[1-3] this may have led to reduced compliance in a number of patients.

A review and discussion[1] of the MAOI interaction with tyramine made the following observations and recommendations:

- the hyperadrenergic state resulting from this interaction consisted of three syndromes although significant overlap between them existed: paroxysmal headache of great severity; cardiovascular symptoms with paroxysmal hypertension; and intracerebral haemorrhage and death
- the most common offending drug reported had been tranylcypromine at doses of 20 to 50 mg daily although a few reports had involved phenelzine
- only 4 foodstuffs clearly warranted total prohibition: aged cheese, pickled herring or fish, concentrated yeast extracts, and broad bean pods
- the ingestion of cheese was said to have been associated with 80% of all case reports and with virtually all fatalities. It was agreed that aged cheese should not be permitted, although cottage and cream cheese required no restriction. There was less agreement concerning dairy products such as yogurt and sour cream and it was suggested that limited amounts were permissible
- pickled herring or smoked fish were to be avoided because of several well-documented cases of hypertensive crisis as well as detection of high levels of tyramine. Any meat may become dangerous unless consumed while fresh as tyramine is formed from bacterial protein degradation
- concentrated yeast extracts have a significant tyramine content and yeast vitamin supplements may also constitute a hazard; baker's yeast was considered to be safe
- broad bean pods contain dopamine although the beans themselves were stated to have little pressor activity and carried no prohibition
- other foods which had been reported to have caused a hypertensive reaction but for which these authors considered that there was insufficient evidence to warrant dietary restriction were chocolate and caffeine-containing beverages, soy sauce, fresh fish, wild game, and fruits although caution was necessary with avocados and bananas.

Other reviews of foods[2,4,5] give broadly similar recommendations.

The consumption of alcoholic beverages, and in particular Chianti wine, has frequently been advised against. However, sources have differed on whether particular types of drink (white wine, red wine, spirits, or beer) are safe or not. A study[6] demonstrated no significant differences in mean free tyramine concentration between white wine, red wine, Chianti, and beer although within each category of wine there could be up to a fiftyfold variation even if from the same grape stock. Mention has also been made[7,8] that alcohol-free or low-alcohol beers are likely to contain similar amounts of tyramine to alcoholic beers. The consumption of alcoholic drinks with MAOIs still appears to be controversial with some advocating total abstinence while others permit a modest intake.

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Interactions of MAOIs with other Drugs

MAOIs inhibit the metabolism of some *amine drugs* (notably indirect-acting sympathomimetics), which can lead to dangerous enhancement of their pressor effects. MAOIs also inhibit other drug-metabolising enzymes and are therefore responsible for a large number of *other drug interactions*. Moreover, they have an additive effect with serotonergic drugs which may result in the *serotonin syndrome* (see under Adverse Effects, above). As in the case of foods, the danger of an interaction persists for at least 14 days after treatment with an MAOI has been stopped.

Severe hypertensive reactions due to enhancement of pressor activity have followed the use of sympathomimetics such as *amfetamines*, *dopamine*, *ephedrine*, *levodopa*, *phenylephrine*, *phenylpropanolamine*, and *pseudoephedrine*. Reactions may also follow the use of anorectics and stimulants with sympathomimetic activity such as *fenfluramine*, *methylphenidate*, *pemoline*, and *phentermine*. There have been case reports of fatalities in patients who took cough preparations containing *dextromethorphan*. There is no clinical evidence of dangerous interactions between *local anaesthetic preparations containing adrenaline* and MAOIs although they could occur if the preparation was accidentally given into a vein. Significant rises in blood pressure have been reported after the use of *buspirone* with MAOIs.

Inhibition of drug-metabolising enzymes by MAOIs may enhance the effects of *barbiturates* and possibly other *hypnotics*, *hypoglycaemics*, and possibly *antimuscarinics*. *Alcohol* metabolism may be altered and its effects enhanced; see also under Interactions of MAOIs with Foods, above. Licensed drug information suggests that the effects of various classes of *antihypertensives* may be enhanced by MAOIs, including *ACE inhibitors*, *beta blockers*, *calcium-channel blockers* and *thiazides*, with the potential for hypotension, although published evidence for most of these seems to be scanty. Some antihypertensives with direct actions on the sympathetic nervous system, such as *guanethidine*, *indoramin*, *methyldopa*, and, historically, *reserpine*, are suggested to be contra-indicated or used with great caution; both hypotensive and hypertensive reactions have been suggested.

Giving *pethidine* and possibly other *opioid analgesics* to patients taking an MAOI has also been associated with very severe and sometimes fatal reactions. When it is considered essential to use an opioid analgesic a test dose of morphine should be given. It has been suggested that the test dose should be one-tenth to one-fifth of the normal dose and if this produces no untoward reaction, the dose of morphine can be gradually and carefully increased over a period of 2 to 3 hours. The use of opioid analgesics and other drugs used during general anaesthesia in patients continuing to take MAOIs is discussed in Anaesthesia under Precautions, above.

Clozapine may enhance the CNS effects of MAOIs.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions may occur. MAOIs should not generally be given to patients receiving *tricyclic antidepressants*, *SSRIs*, *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, *bupropion*, *mirtazapine*, *nefazodone*, *reboxetine*, or *trazodone*. An appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. An MAOI should not be started until at least 1 or 2 weeks after stopping a tricyclic antidepressant. For the tricyclic antidepressants clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. For an SSRI, an SNRI, reboxetine, nefazodone, trazodone, or any related antidepressant the drug-free interval should be at least one week; in the case of bupropion, mirtazapine, and the SSRI sertraline, the interval is extended to 2 weeks, and for fluoxetine, at least 5 weeks because of their longer half-lives. Conversely, 2 weeks should elapse between stopping MAOI therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, an SNRI, bupropion, mirtazapine, reboxetine, or any related antidepressant. For further warnings on the combined use of antidepressants, see below. Interactions can also occur between MAOIs themselves.

For details of the less severe interactions associated with reversible inhibitors of monoamine oxidase A (RIMAs), see Interactions of Moclobemide, p.411.

◊ References.

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Antidepressants. Combination therapy with differing classes of antidepressants may result in interactions or enhanced adverse reactions such as the serotonin syndrome (see under Adverse Effects, above), and is therefore considered unsuitable or controversial by some authorities. Despite these drawbacks certain combinations of drugs have been found to be beneficial in the treatment of drug-resistant depression, although others are considered unsuitable; absence of information documenting unsuitability or hazard does not necessarily imply that the two drugs may be used safely together but may merely reflect an untried combination. Because combination therapy poses increased risks it should be used only under expert supervision.

- MAOIs have been used fairly frequently under expert supervision with tricyclics in refractory depression and it has been stated[1] that the risk of serious problems in combining *tricyclic antidepressant and MAOI* antidepressant therapy is almost exclusively limited to sequential prescribing, in particular the addition of a tricyclic to established treatment with an MAOI. The recommended procedure was said to be to allow a drug-free interval of at least one week and then to start both drugs together at a low dosage. The dosage of both drugs is then gradually increased to around half that normally prescribed for the drugs when given on their own. The dietary restrictions for MAOIs alone apply equally to the combined antidepressant regimen.

  Amitriptyline and trimipramine were considered to be the tricyclics least likely to produce adverse effects with MAOIs, while phenelzine and isocarboxazid were the safest MAOIs. In contrast, clomipramine (a tricyclic with serotonin reuptake inhibiting activity) and imipramine are unsuitable for such use.[2,3] The combination of clomipramine with tranylcypromine is particularly dangerous. Symptoms suggestive of the serotonin syndrome occurred in an elderly patient due to an interaction between clomipramine and moclobemide, a reversible inhibitor of monoamine oxidase type A (RIMA).[4] Two fatalities due to serotonin syndrome have been reported after overdosage with clomipramine and moclobemide.[5] The syndrome has also developed when a patient was switched from clomipramine to moclobemide with no suitable drug-free interval.[6] A 39-year-old woman developed the serotonin syndrome while taking imipramine with moclobemide, although it was suggested that an excessive dose of the tricyclic may have been ingested accidentally.[7]
- The UK CSM has warned[8] that enhanced serotonergic effects may result from using *SSRIs with MAOIs* or other antidepressants. Although such an enhancement may be beneficial in some instances it can produce a life-threatening serotonin syndrome. Such reactions were later reported in patients taking sertraline with MAOIs.[9-11] Three fatalities due to serotonin syndrome have been reported after overdosage with citalopram and moclobemide.[5] A case of serotonin syndrome has been reported after switching from fluoxetine to moclobemide with no suitable drug-free interval.[6] Some authors[12] have reported good efficacy and tolerability with combinations of moclobemide and SSRIs. However, others[13] reported a high rate of adverse events although, as significant improvement in depressive symptoms was observed in some patients, it was suggested that giving moclobemide with SSRIs deserved consideration as an option for the treatment of refractory depression.
- Combination therapy with a *tricyclic antidepressant and an SSRI* has sometimes been used to treat resistant depression. Fluvoxamine[14] and fluoxetine[15] have been reported to increase plasma concentrations of the tricyclic, although to varying degrees. Fluoxetine has been reported to produce three- to fourfold increases in plasma concentrations of desipramine and imipramine. Fluvoxamine has a minimal effect on desipramine plasma levels but produces a three- to fourfold increase in concentrations of imipramine.[16] Plasma-desipramine concentrations are elevated threefold by paroxetine but increases of only 30% are produced by sertraline.[16] However, an inadequate interval of one day between stopping desipramine and starting paroxetine resulted in a case of serotonin syndrome.[6] Serotonin syndrome has also been reported[17] in a patient who received paroxetine and imipramine and in another given sertraline and amitriptyline.[18] A threefold increase in concentrations of trimipramine resulting in sedation and orthostatic hypotension has been reported[19] in 2 patients also given paroxetine. Additionally, norfluoxetine, the active metabolite of fluoxetine, has a long half-life and is responsible for the continuing interaction with tricyclics for

several days or weeks after fluoxetine has been withdrawn. Citalopram was reported to have no effect on plasma-tricyclic concentrations in a patient although antidepressant effects were augmented.[20]

- *Lithium* and *tryptophan* have been used to augment the effect of other antidepressants in refractory depression. Phenelzine has been used successfully with lithium and tryptophan[21] in patients with treatment-resistant chronic depression although such a regimen has probably been used less since the reports of the eosinophilia-myalgia syndrome associated with tryptophan (see p.427). There have, however, been several case reports of reactions similar to the serotonin syndrome in patients receiving MAOIs with tryptophan.[22,23]

  Although lithium is often added to tricyclic antidepressant therapy in patients with refractory depression, epileptic seizures have been reported in a patient receiving amitriptyline when lithium was added.[24] Serotonin syndrome has been reported[25] in a patient given clomipramine and lithium. Severe neurotoxicity has been reported[26,27] in some patients receiving lithium and tricyclic or tetracyclic antidepressants; adverse effects included tremor, memory impairment, disorganised thinking, and auditory hallucinations. One manufacturer of lithium preparations also reports symptoms of nephrogenic diabetes in patients receiving these combinations.

  By 1989 the CSM had received 19 reports of adverse reactions in patients treated with fluvoxamine and lithium; 5 reports concerned convulsions and 1 hyperthermia.[8] Tremor has been reported when lithium was given with paroxetine,[28] and in general the risk of CNS toxicity is increased when lithium is given with fluoxetine, fluvoxamine, paroxetine, or sertraline. There has been a report[29] of a fatality when fluoxetine was replaced by tranylcypromine and tryptophan with no drug-free period; the patient was also receiving other drugs concurrently.
- Use of the serotonin and noradrenaline reuptake inhibitor (SNRI) *venlafaxine with tricyclic antidepressants* has been associated with increased antimuscarinic adverse effects.[30,31] Seizures have also been reported with venlafaxine and trimipramine[32] and serotonin syndrome developed in a patient given amitriptyline, venlafaxine, and pethidine.[33] Similar antimuscarinic adverse effects have occurred in patients given *venlafaxine and the SSRI* fluoxetine;[31] serotonin syndrome has been reported in a patient who received venlafaxine and paroxetine.[6] The use of *venlafaxine with MAOIs* is contra-indicated by the manufacturers of venlafaxine because of the risk of life-threatening adverse reactions. Serious adverse reactions have been reported when venlafaxine was combined with isocarboxazid,[34] moclobemide,[6] phenelzine,[35] or tranylcypromine.[36]
- *Trazodone* is chemically unrelated to other antidepressants but does have serotonergic actions. Serotonin syndrome has been reported when trazodone was combined with the SSRI *paroxetine*.[37]
- Serotonin syndrome has been reported[38] in a patient who took *nefazodone* with *fluoxetine*. There has been a similar report[39] in a patient who received *paroxetine* 2 days after finishing gradual withdrawal from over 6 months of treatment with nefazodone.
- Symptoms resembling serotonin syndrome have occurred in a patient taking the noradrenergic and specific serotonergic antidepressant, *mirtazapine* with *fluvoxamine*;[40] another report[41] suggests that the plasma concentrations of mirtazapine may be increased as much as fourfold by fluvoxamine.
- Raised *nortriptyline* levels were noted in a patient also taking *bupropion*; the effect recurred on rechallenge.[42]
- In a report[43] of an interaction between *St John's wort* and *paroxetine*, a 50-year-old woman was found incoherent, groggy, and slow-moving after self-administering a single dose of paroxetine while taking St John's wort; recovery was uneventful. Use of St John's wort with the SSRIs may potentiate their serotonergic effects and increase the incidence of adverse reactions. The CSM has advised that patients should stop taking St John's wort if treatment with an SSRI is necessary.[44] Symptoms of serotonin syndrome have also been reported when St John's wort and *nefazodone* were taken.[45]

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Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Licensed UK drug product information states that *carbamazepine* should be avoided with or within 2 weeks of a MAOI because of structural similarities with the tricyclic antidepressants; however, published evidence of adverse interactions is lacking. There is also a theoretical possibility of a similar interaction with *oxcarbazepine*.

Antimigraine drugs. For the effect of MAOIs on *serotonin (5-HT_1) agonists*, see under Sumatriptan, p.626.

Antineoplastics. For the effect when MAOIs are used with *altretamine*, see p.678.

Dopaminergics. For the effect of MAOIs with *amantadine*, see p.793, with *levodopa*, see p.807, and with *selegiline*, see p.817.

General anaesthetics. The problems that may occur when patients receiving MAOIs are also given general anaesthetics are discussed under Anaesthesia in Precautions, above.

Ginseng. There have been 2 reports[1,2] of adverse effects, including headaches, insomnia, tremulousness, and irritability when ginseng was taken with phenelzine.

1. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol* 1985; **5:** 65.
2. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *J Clin Psychopharmacol* 1987; **7:** 201–2.

Insulin. For the effect of MAOIs on insulin, see p.449.

Neuromuscular blockers. For the effects of MAOIs on *suxamethonium*, see p.1912. Problems that may be encountered with MAOIs and neuromuscular blockers used during anaesthesia are discussed under Anaesthesia in Precautions, above.

Opioid analgesics. The problems that may occur with MAOIs and opioid analgesics used during anaesthesia are discussed under Anaesthesia in Precautions, above.

Respiratory stimulants. For the effect of MAOIs on *doxapram*, see p.2155.

Pharmacokinetics

Phenelzine is readily absorbed from the gastrointestinal tract reaching peak plasma concentrations 2 to 4 hours after ingestion. It is metabolised in the liver and is excreted in the urine almost entirely in the form of metabolites.

Uses and Administration

Monoamine oxidase inhibitors (MAOIs) inhibit the action of monoamine oxidase, the enzyme responsible for the metabolism of several biogenic amines. Monoamine oxidase exists in two forms, type A and type B. Monoamine oxidase type A preferentially deaminates adrenaline, noradrenaline, and serotonin whereas monoamine oxidase type B preferentially metabolises benzylamine and phenylethylamine; dopamine and tyramine are de-aminated by both forms of the enzyme.

- The traditional MAOIs such as phenelzine, iproniazid, isocarboxazid, and tranylcypromine are inhibitors of both types; apart from tranylcypromine, which produces a less prolonged inhibition of the enzyme than phenelzine, all are hydrazine derivatives and bind irreversibly.
- Selective inhibitors include selegiline (p.817), an irreversible inhibitor of monoamine oxidase type B used in the treatment of Parkinson's disease and depression. Clorgiline, an irreversible selective type A inhibitor, was investigated for use as an antidepressant.
- Reversible inhibitors of monoamine oxidase type A (RIMAs) include brofaromine and moclobemide.

Antidepressant activity appears to reside mainly with inhibition of monoamine oxidase type A although the mode of action of these drugs in depression is not fully understood. Selective inhibitors are claimed to have fewer or less severe adverse effects than non-selective inhibitors. As tyramine is de-aminated by both monoamine oxidase types A and B, inhibiting only one of the enzymes allows for continued, albeit reduced, de-amination. Thus the dietary precautions that need to be observed with non-selective inhibitors are less stringent with the selective inhibitors.

Phenelzine and other antidepressant MAOIs are used in the treatment of atypical depression, particularly where phobic features or associated anxiety are present, or in patients who have not responded to other antidepressants. However, the risks associated with irreversible non-selective MAOIs usually mean that other antidepressants are preferred. Up to a month may elapse before an antidepressant response is obtained with MAOIs. After a response has been obtained maintenance therapy may need to be continued for at least 4 to 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 5 years and possibly indefinitely. Care should be taken in elderly patients because of an increased susceptibility to adverse effects. Moreover, therapy with the non-selective inhibitors is particularly unsuitable for patients considered unable to adhere to the strict dietary requirements necessary for safe usage. (For contra-indication in children, see under Precautions, above).

Phenelzine is given orally as the sulfate although doses are expressed in terms of the base. Phenelzine sulfate 25.8 mg is equivalent to about 15 mg of phenelzine. The usual initial dose is equivalent to phenelzine 15 mg three times daily; if no response has been obtained after 2 weeks the dosage may be increased to 15 mg four times daily; severely depressed patients in hospital may be given up to 30 mg three times daily. Once a response has been obtained the dosage may be gradually reduced for maintenance therapy; some patients may continue to respond to 15 mg on alternate days.

Phenelzine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. MAOIs have been used in the treatment of anxiety disorders. MAOIs appear to be effective in *panic disorder* (p.952). They also appear to be effective in *social anxiety disorder* (see under Phobic Disorders, p.953) and can improve anticipatory anxiety and functional disability. The main treatment for *post-traumatic stress disorder* (p.953) is psychotherapy but MAOIs are one of the alternatives that can help to reduce traumatic recollections and nightmares, and to repress flashbacks.

References.

1. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry* 1987; **48:** 55–9.
2. Frank JB, *et al.* A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry* 1988; **145:** 1289–91.
3. Heimberg RG, *et al.* Cognitive behavioural group therapy vs phenelzine therapy for social phobia: 12 week outcome. *Arch Gen Psychiatry* 1998; **55:** 1133–41.
4. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry* 2003; **57:** 313–15.

Depression. As discussed on p.373 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. MAOIs are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Even in depressed patients with atypical, hypochondriacal, hysterical, or phobic features, for which MAOIs are particularly effective, it is often recommended that another antidepressant type should be tried first. Reversible inhibitors of monoamine oxidase type A (RIMAs) offer an alternative to the MAOIs and less strict dietary restrictions are necessary. They may be effective in a wide range of depressive disorders, although their relative efficacy in atypical depression remains to be established.

Combination therapy with differing classes of antidepressants, including the MAOIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and is considered unsuitable or controversial by some. For further details, see Antidepressants under Interactions, above.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p.2148), initial treatment is usually with a central stimulant. MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use.

Migraine. A number of drugs have been used for the prophylaxis of migraine (p.616), although propranolol is generally preferred. Antidepressants such as the tricyclics can be useful alternatives when these drugs are ineffective or unsuitable. MAOIs are best reserved for severe cases refractory to other forms of prophylactic treatment.

Preparations

BP 2008: Phenelzine Tablets;
USP 31: Phenelzine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Nardil; ***Belg.:*** Nardelzine; ***Canad.:*** Nardil; ***Irl.:*** Nardil; ***NZ:*** Nardil; ***UK:*** Nardil; ***USA:*** Nardil.

Pipofezine Hydrochloride *(rINNM)*

Hidrocloruro de pipofezina; Pipofézine, Chlorhydrate de; Pipofezine Dihydrochloride; Pipofezini Hydrochloridum. 5-Methyl-3-(4-methyl-1-piperazinyl)-5*H*-pyridazino[3,4-*b*][1,4]benzoxazine dihydrochloride.

Пипофезина Гидрохлорид

$C_{16}H_{19}N_5O,2HCl = 370.3.$

CAS — 24886-52-0 (pipofezine); 24853-80-3 (pipofezine hydrochloride).

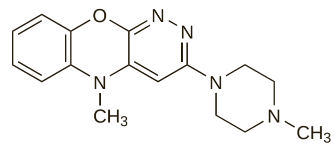

(pipofezine)

Profile

Pipofezine is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression (p.373) pipofezine is usually given orally as the hydrochloride although doses are expressed in terms of the base; pipofezine hydrochloride 31.1 mg is equivalent to about 25 mg of pipofezine. An initial dose is 25 mg given four times daily, increased to an optimum total daily dose of 150 to 200 mg; if necessary up to a maximum of 500 mg may be given daily in divided doses. For maintenance a modified-release preparation providing pipofezine 150 mg may be given once or twice daily.

Pipofezine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Azaphen (Азафен).

Pirlindole *(rINN)*

Pirlindol; Pirlindolum. 2,3,3a,4,5,6-Hexahydro-8-methyl-1*H*-pyrazino[3,2,1-*jk*]carbazole.

Пирлиндол

$C_{15}H_{18}N_2 = 226.3.$

CAS — 60762-57-4.

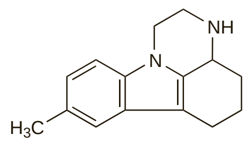

Profile

Pirlindole has been given by mouth in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Implementor; ***Rus.:*** Pyrazidol (Пиразидол).

Protriptyline Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de protriptilina; MK-240; Protriptyline, chlorhydrate de; Protriptylini hydrochloridum. 3-(5*H*-Dibenzo[*a,d*]cyclohept-5-enyl)propyl(methyl)amine hydrochloride.

Протриптилина Гидрохлорид

$C_{19}H_{21}N,HCl = 299.8.$

CAS — 438-60-8 (protriptyline); 1225-55-4 (protriptyline hydrochloride).
ATC — N06AA11.
ATC Vet — QN06AA11.

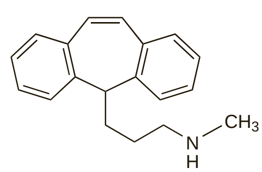

(protriptyline)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Protriptyline Hydrochloride). A white to yellowish-white, odourless or almost odourless, powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.5.

USP 31 (Protriptyline Hydrochloride). A white to yellowish powder. Is odourless or has not more than a slight odour. Soluble 1 in 2 of water, 1 in 3.5 of alcohol, and 1 in 2.5 of chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.5.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Since protriptyline may have some stimulant properties anxiety and agitation can occur more frequently; cardiovascular effects such as tachycardia and orthostatic hypotension may also be more frequent than with other tricyclics. Photosensitivity rashes have been noted more often with protriptyline than with other tricyclic antidepressants and patients taking it should avoid direct sunlight.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Protriptyline is well but slowly absorbed after oral doses: licensed drug information states that peak plasma concentrations are achieved only after 8 to 12 hours.

Paths of metabolism of protriptyline include *N*-oxidation and hydroxylation. Protriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Protriptyline is widely distributed throughout the body and extensively bound to plasma and tissue protein. Protriptyline has been estimated to have a very prolonged elimination half-life ranging from 55 to 198 hours, which may be further prolonged in overdosage.

Uses and Administration

Protriptyline is a dibenzocycloheptatriene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is considerably less sedative than other tricyclics and may have a stimulant effect, thus making it particularly suitable for apathetic and withdrawn patients; its antimuscarinic effects are moderate.

In the treatment of depression, protriptyline hydrochloride is given in oral doses of 5 to 10 mg three or four times daily. It has been suggested that, because of its potential stimulant activity, any dosage increases should be added to the morning dose first and if insomnia occurs the last dose should be given no later than mid-afternoon. Higher doses of up to 60 mg daily may be required in severely depressed patients. A suitable initial dose for adolescents and the elderly is 5 mg three times daily; close monitoring of the cardiovascular system has been recommended if the dose exceeds a total of 20 mg daily in elderly subjects.

Protriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Protriptyline Tablets;
USP 31: Protriptyline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Vivactil.

Reboxetine Mesilate *(BANM, rINNM)*

FCE-20124 (reboxetine or reboxetine mesilate); Mesilato de reboxetina; PNU-155950E; Réboxétine, Mésilate de; Reboxetine Mesylate *(USAN)*; Reboxetini Mesilas. (±)-(2*RS*)-2-[(α*RS*)-α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulphonate.

Ребоксетина Мезилат

$C_{19}H_{23}NO_3,CH_4O_3S = 409.5.$

CAS — 71620-89-8; 98769-81-4 (both reboxetine); 98769-82-5; 98769-84-7 (both reboxetine mesilate).
ATC — N06AX18.
ATC Vet — QN06AX18.

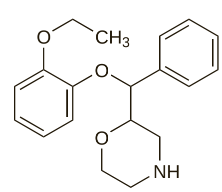

(reboxetine)

Adverse Effects

Adverse effects most commonly seen with reboxetine include insomnia, dry mouth, constipation, and increased sweating. Disturbance of visual accommodation, loss of appetite, vertigo, tachycardia, palpitations, vasodilatation, orthostatic hypotension, urinary hesitancy or retention (mainly in men), and erectile dysfunction including ejaculatory delay are also reported as being common adverse reactions. There have been reports of allergic dermatitis, convulsions, aggressive behaviour, cold extremities, and nausea and vomiting. Reduced plasma-potassium concentrations have been seen in elderly patients after prolonged use.

Hyponatraemia, possibly as a result of inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on the CNS. Episodes of sleepwalking (somnambulism) were seen in an 18-year-old woman several weeks after starting reboxetine (at an initial dose of 2 mg daily gradually increased to 8 mg daily).[1] The patient had a history of childhood somnambulism that had resolved spontaneously; these particular episodes ceased after the dose of reboxetine was reduced to 4 mg daily.

1. Künzel HE, *et al.* Sleepwalking associated with reboxetine in a young female patient with major depression: a case report. *Pharmacopsychiatry* 2004; **37:** 307–8.

Effects on the endocrine system. Hyponatraemia thought to be associated with reboxetine therapy and to be due to the syndrome of inappropriate antidiuretic hormone secretion, has been reported in an elderly patient.[1]

1. Ranieri P, *et al.* Reboxetine and hyponatremia. *N Engl J Med* 2000; **342:** 215–16.

Effects on sexual function. The Australian Adverse Drug Reactions Advisory Committee has received 130 reports of adverse reactions associated with reboxetine use;[1] of these, 22 described male sexual dysfunction including ejaculation disorder (7), erectile dysfunction (4), and testicular pain or swelling (10). In addition there were 2 reports of increased libido in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Effects on the urinary system. The Australian Adverse Drug Reactions Advisory Committee has received 26 reports of urinary symptoms such as hesitancy, reduced urine flow, and retention in patients taking reboxetine.[1] Although the majority of cases occurred in male patients, 6 reports mentioned such symptoms in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Treatment of Adverse Effects

Symptomatic and supportive therapy should be given as required; activated charcoal may be given to adults who have ingested more than 40 mg of reboxetine, and to children, if they present within 1 hour of ingestion. Heart rhythm should be monitored if changes in blood pressure occur.

Genito-urinary disorders. Tamsulosin has been used successfully in the treatment of urinary hesitancy and painful ejaculation associated with reboxetine (see p.2197).

Precautions

Reboxetine should be used with caution in patients with renal or hepatic impairment. It should also be used under close supervision in patients with bipolar disorder, urinary retention, benign prostatic hyperplasia, glaucoma, or a history of epilepsy or cardiac disorders.

Patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by reboxetine and patients, if affected, should not drive or operate machinery.

Children. Reboxetine has not been studied for the treatment of depression in children and consequently its use in such patients is not recommended by UK licensed product information. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in children and adolescents (see Effects on Mental State, under Fluoxetine, p.392).

The elderly. Reboxetine is not recommended by UK licensed product information for use in elderly patients, because of a lack of experience in this patient group. However, reboxetine 2 mg twice daily by mouth was well tolerated in a study in 16 elderly patients (mean age 77.5 years) with post-stroke depression.[1]

1. Rampello L, *et al.* An evaluation of efficacy and safety of reboxetine in elderly patients affected by "retarded" post-stroke depression: a random, placebo-controlled study. *Arch Gerontol Geriatr* 2005; **40:** 275–85.

Interactions

Reboxetine should not be taken with, or within 2 weeks of stopping, an MAOI; at least one week should elapse after stopping reboxetine therapy before starting any drug liable to provoke a serious reaction (e.g. phenelzine). Caution should be exercised when reboxetine is given with other drugs that lower blood pressure because orthostatic hypotension has occurred with reboxetine. However, the use of reboxetine with ergot derivatives may cause an increase in blood pressure. The possibility of hypokalaemia if reboxetine is given with potassium-depleting diuretics should also be considered.

Reboxetine is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4 and potent inhibitors of this isoenzyme may limit the elimination of reboxetine. Consequently, reboxetine should not be given with drugs known to inhibit CYP3A4 such as azole antifungals (e.g. ketoconazole), macrolide antibacterials (e.g. erythromycin) or fluvoxamine. Reboxetine in high concentrations has also been shown *in vitro* to inhibit CYP3A4 and CYP2D6; however studies *in vivo* have suggested that interactions with drugs metabolised by these isoenzymes are unlikely.

Antifungals. Plasma levels of reboxetine were significantly increased when given with *ketoconazole*.[1] The interaction was said to have involved the inhibition of the cytochrome P450 isoenzyme CYP3A4 by ketoconazole.

1. Herman BD, *et al.* Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* 1999; **66:** 374–9.

Pharmacokinetics

Reboxetine is well absorbed from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 97% (92% in elderly subjects). *In-vitro* studies indicate that reboxetine is metabolised by the cytochrome P450 isoenzyme CYP3A4; the main metabolic pathways identified are dealkylation, hydroxylation, and oxidation followed by glucuronide or sulfate conjugation. Elimination is mainly via urine (78%) with 10% excreted as unchanged drug. The plasma elimination half-life is 13 hours. Data from *animal* studies indicate that reboxetine crosses the placenta and is distributed into breast milk.

◊ References.

1. Dostert P, *et al.* Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur Neuropsychopharmacol* 1997; **7** (suppl 1): S23–S35.
2. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* 2000; **39:** 413–27.
3. Coulomb F, *et al.* Pharmacokinetics of single-dose reboxetine in volunteers with renal insufficiency. *J Clin Pharmacol* 2000; **40:** 482–7.
4. Poggesi I, *et al.* Pharmacokinetics of reboxetine in elderly patients with depressive disorders. *Int J Clin Pharmacol Ther* 2000; **38:** 254–9.

Uses and Administration

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Reboxetine has no significant affinity for muscarinic receptors. It is given orally as the mesilate for the treatment of depression with doses expressed as the base. Reboxetine mesilate 5.2 mg is equivalent to about 4 mg of reboxetine. The dose of reboxetine is 4 mg twice daily, which may be increased after 3 to 4 weeks, if necessary, to 10 mg daily; the maximum daily dose should not exceed 12 mg. Reduced doses should be given in hepatic or renal impairment, see below. Reboxetine is not recommended for use in elderly patients (see under Precautions, above).

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic or renal impairment. Lower initial oral doses equivalent to 2 mg of reboxetine twice daily are recommended by UK licensed product information in hepatic or renal impairment; doses may be increased thereafter according to tolerance.

Anxiety disorders. Reboxetine has been tried with some benefit in panic disorder (p.952) although it may be less effective than the SSRIs.

References.

1. Versiani M, *et al.* Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry* 2002; **63:** 31–7.
2. Seedat S, *et al.* Reboxetine and citalopram in panic disorder: a single-blind, cross-over, flexible-dose pilot study. *Int Clin Psychopharmacol* 2003; **18:** 279–84.
3. Bertani A, *et al.* Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2004; **37:** 206–10.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Reboxetine, a selective inhibitor of noradrenaline reuptake, has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, reboxetine appears to have fewer unpleasant adverse effects and to be safer in overdosage in comparison with the older tricyclics.

References.

1. Versiani M, *et al.* Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry* 1999; **60:** 400–406.
2. Holm KJ, Spencer CM. Reboxetine: a review of its use in depression. *CNS Drugs* 1999; **12:** 65–83.
3. Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. *Ann Pharmacother* 2000; **34:** 1302–12.
4. Versiani M, *et al.* Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J Clin Psychopharmacol* 2000; **20:** 28–34.
5. Ferguson JM, *et al.* Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. *Int Clin Psychopharmacol* 2002; **17:** 45–51.
6. Andreoli V, *et al.* Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. *J Clin Psychopharmacol* 2002; **22:** 393–9.
7. Montgomery S, *et al.* The antidepressant efficacy of reboxetine in patients with severe depression. *J Clin Psychopharmacol* 2003; **23:** 45–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Prolift†; ***Austral.:*** Edronax; ***Austria:*** Edronax; ***Belg.:*** Edronax; ***Braz.:*** Prolift; ***Chile:*** Prolift; ***Cz.:*** Edronax†; ***Denm.:*** Edronax; ***Fin.:*** Edronax; ***Ger.:*** Edronax; Solvex; ***Hung.:*** Edronax; ***India:*** Narebox; ***Irl.:*** Edronax; ***Israel:*** Edronax; ***Ital.:*** Davedax; Edronax; ***Mex.:*** Edronax; ***Norw.:*** Edronax; ***NZ:*** Edronax; ***Pol.:*** Edronax; ***Port.:*** Edronax; ***S.Afr.:*** Edronax; ***Spain:*** Irenor; Norebox; ***Swed.:*** Edronax; ***Switz.:*** Edronax; ***Turk.:*** Edronax; ***UK:*** Edronax; ***Venez.:*** Prolift†.

Sertraline Hydrochloride

(BANM, USAN, rINNM)

CP-51974-01; CP-51974-1; Hidrocloruro de sertralina; Sertraline, chlorhydrate de; Sertralini hydrochloridum. (1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl(methyl)amine hydrochloride.

Сертралина Гидрохлорид

$C_{17}H_{17}Cl_2N,HCl = 342.7.$

CAS — 79617-96-2 (sertraline); 79559-97-0 (sertraline hydrochloride).

ATC — N06AB06.

ATC Vet — QN06AB06.

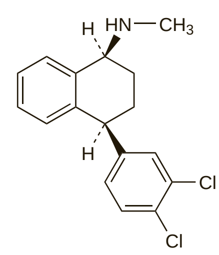

(sertraline)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of sertraline:
Z's; Zloft; Zoomers.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sertraline Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in anhydrous alcohol; slightly soluble in acetone and in isopropyl alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391). Menstrual irregularities and, rarely, erythema multiforme and pancreatitis have also been reported.

Sertraline should be used with caution in patients with hepatic or renal impairment; reduced doses should be considered in patients with hepatic impairment.

Breast feeding. For comments on the use of SSRIs in breast feeding patients, see under Precautions for Fluoxetine, p.394.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Interactions

For interactions associated with SSRIs, see Fluoxetine, p.396.

Pharmacokinetics

Sertraline is slowly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 4.5 to 8.4 hours after ingestion. It undergoes extensive first-pass metabolism in the liver. The main pathway is demethylation to inactive *N*-desmethylsertraline, a process that appears to involve multiple cytochrome P450 isoenzymes; further metabolism and glucuronide conjugation occurs. Sertraline is widely distributed throughout body tissues and is about 98% bound to plasma proteins. The plasma elimination half-life of sertraline is reported to be about 26 hours; steady-state concentrations are achieved after about one week with regular oral doses. Sertraline is excreted in about equal amounts in the urine and faeces, mainly as metabolites. Sertraline is distributed into breast milk (see Breast Feeding under Precautions in Fluoxetine, p.394).

◊ References.

1. Preskorn SH, ed. Sertraline: a pharmacokinetic profile. *Clin Pharmacokinet* 1997; **32** (suppl 1): 1–55.
2. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.
3. Wang J-H, *et al.* Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **70:** 42–7.
4. DeVane CL, *et al.* Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet* 2002; **41:** 1247–66.
5. Obach RS, *et al.* Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. *Drug Metab Dispos* 2005; **33:** 262–70.

Uses and Administration

Sertraline, a naphthaleneamine derivative, is an SSRI with actions and uses similar to those of fluoxetine (p.397). It is given orally as sertraline hydrochloride as a single dose in the morning or evening. Doses are expressed in terms of the base; sertraline hydrochloride 56 mg is equivalent to about 50 mg of sertraline.

In the treatment of **depression**, the usual initial dose of sertraline is 50 mg daily increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

The usual initial dose of sertraline in **obsessive-compulsive disorder** is 50 mg daily. In the treatment of **panic disorder** with or without agoraphobia, **social anxiety disorder**, and **post-traumatic stress disorder**, the usual initial dose is 25 mg daily increased after one week to 50 mg daily. Thereafter, doses in all these disorders may be increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

Sertraline is also given for the treatment of obsessive-compulsive disorder in *children and adolescents* aged 6 years and over. In children aged 6 to 12 years the usual initial dose is 25 mg once daily; adolescents may be started on 50 mg once daily. Increases in doses, if necessary, are similar to those in adults; however, the lower body-weights of children should be considered in order to avoid excessive doses.

In the treatment of **premenstrual dysphoric disorder**, sertraline is given in an initial dose of 50 mg daily either throughout the menstrual cycle or during the luteal phase only, as appropriate. Doses may be increased by 50 mg each menstrual cycle up to a maximum of 150 mg daily for continuous dosing or 100 mg daily when dosing during the luteal phase only. Those patients who require 100 mg daily during luteal phase-only dosing should initially be given 50 mg daily for the first 3 days of each luteal phase dosing period.

Once the optimal therapeutic response is obtained dosage should be reduced to the lowest effective level for maintenance.

Reduced doses are recommended in patients with hepatic impairment, see below.

Sertraline should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in hepatic impairment. The clearance of sertraline was reduced in patients with liver cirrhosis, in a single-dose pharmacokinetic study.[1] US licensed product information states that in a small group of patients with chronic mild impairment (Child-Pugh scores of 5 to 8), given 50 mg daily for 21 days, exposure to sertraline was about 3 times that found in subjects with normal hepatic function. It also states that the effects of sertraline have not been studied in moderate and severe impairment. If sertraline is to be used in patients with hepatic impairment, it suggests that the drug should be used with caution and given at a lower dose or less frequently. UK product information considers sertraline to be contra-indicated in significant hepatic impairment, because of insufficient clinical experience.

1. Démolis J-L, *et al.* Influence of liver cirrhosis on sertraline pharmacokinetics. *Br J Clin Pharmacol* 1996; **42:** 394–7.

Anxiety disorders. Sertraline has been given in a variety of anxiety disorders (p.952) including obsessive-compulsive disorder (p.952), panic disorder (p.952), social anxiety disorder (see under Phobic Disorders, p.953), and post-traumatic stress disorder (p.953).

References.

1. March JS, *et al.* Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA* 1998; **280:** 1752–6.
2. Londborg PD, *et al.* Sertraline in the treatment of panic disorder. A multi-site, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry* 1998; **173:** 54–60.
3. Brady K, *et al.* Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 2000; **283:** 1837–44.
4. Walker JR, *et al.* Prevention of relapse in generalized social phobia: results of a 24-week study in responders to 20 weeks of sertraline treatment. *J Clin Psychopharmacol* 2000; **20:** 636–44.
5. Rynn MA, *et al.* Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry* 2001; **158:** 2008–14.
6. Rapaport MH, *et al.* Sertraline treatment of panic disorder: results of a long-term study. *Acta Psychiatr Scand* 2001; **104:** 289–98.
7. Rapaport MH, *et al.* Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry* 2002; **63:** 59–65.
8. Koran LM, *et al.* Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2002; **159:** 88–95.
9. Zohar J, *et al.* Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 190–5.
10. Liebowitz MR, *et al.* Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. *J Clin Psychiatry* 2003; **64:** 785–92.
11. Allgulander C, *et al.* Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 2004; **161:** 1642–9.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs such as sertraline are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Stowe ZN, *et al.* Sertraline in the treatment of women with postpartum major depression. *Depression* 1995; **3:** 49–55.
2. Keller MB, *et al.* Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* 1998; **280:** 1665–72.
3. Baca E, *et al.* Sertraline is more effective than imipramine in the treatment of non-melancholic depression: results from a multicentre, randomized study. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27:** 493–500.
4. Lepine JP, *et al.* A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. *Am J Psychiatry* 2004; **161:** 836–42.
5. Moscovitch A, *et al.* A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology (Berl)* 2004; **171:** 390–7.

Headache. For reference to the use of SSRIs, including sertraline, in the management of various types of headache, see under Fluoxetine, p.398.

Premenstrual syndrome. Sertraline throughout the menstrual cycle has produced beneficial effects in controlling both the psychological and somatic symptoms of women with premenstrual syndrome (p.2099).[1-3] Giving sertraline solely during the luteal phase was also of benefit.[3-6]

1. Yonkers KA, *et al.* Sertraline in the treatment of premenstrual dysphoric disorder. *Psychopharmacol Bull* 1996; **32:** 41–6.
2. Yonkers KA, *et al.* Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. *JAMA* 1997; **278:** 983–8.
3. Freeman EW, *et al.* Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *Am J Psychiatry* 2004; **161:** 343–51.
4. Young SA, *et al.* Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. *J Clin Psychiatry* 1998; **59:** 76–80.
5. Jermain DM, *et al.* Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. *Arch Fam Med* 1999; **8:** 328–32.
6. Halbreich U, *et al.* Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2002; **100:** 1219–29.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the use of these effects as a potential form of management for premature ejaculation see Fluoxetine, p.399.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Anilar; Atenix; Bicromil; Celonfex; Deprecalm; Insertec; Irradial; Serlina; Servantax; Vunot; Zoloft; ***Austral.:*** Eleva; Setrona; Xydep; Zoloft; ***Austria:*** Gladem; Sertrex; Tresleen; ***Belg.:*** Serlain; ***Braz.:*** Assert; Novativ; Sercerin†; Serenata; Seronip†; Tolrest; Zoloft; ***Canad.:*** Zoloft; ***Chile:*** Altruline; Deprax; Eleval; Emergen; Implicane; Lowfin; Sedoran; Serivo; Seronex; Sertac; Tralinser; ***Cz.:*** Adjuvin; Apo-Sertral; Asentra; Serlift; Setaloft; Stimuloton; Zoloft; ***Denm.:*** Zoloft; ***Fin.:*** Zoloft; ***Fr.:*** Zoloft; ***Ger.:*** Gladem; Sertra; Zoloft; ***Gr.:*** Certorun; Enidap; Neurosedine; Zoloft; Zolotrin; ***Hong Kong:*** Stimuloton; Zoloft; ***Hung.:*** Asentra; Gerotralin; Serlift; Serlosane; Sertadepi; Sertagen; Sertwin; Stimuloton; Zoloft; ***India:*** Inosert; Serdep; Serta; Xsert; ***Indon.:*** Antipres; Deptral; Fatral; Fridep; Nudep; Serlof; Sernade; Zerlin; Zoloft; ***Irl.:*** Depreger; Lusert; Lustral; Serimel; Serlan; Sertraniche; ***Israel:*** Lustral; ***Ital.:*** Tatig; Zoloft; ***Malaysia:*** Serlift; Zoloft; ***Mex.:*** Aleval; Altruline; Aluprex; Deptral; Prosertin; Serolux; Sertex; ***Neth.:*** Asentra; Zoloft; ***Norw.:*** Zoloft; ***NZ:*** Zoloft; ***Philipp.:*** Serenata; Zoloft; ***Pol.:*** Asentra; Luxeta; Sertahexal; Setaloft; Setaratio; Stimuloton; Zoloft; Zotral; ***Port.:*** Zoloft; ***Rus.:*** Asentra (Асентра); Serenata (Серената); Stimuloton (Стимулотон); Torin (Торин); Zoloft (Золофт); ***S.Afr.:*** Serdep; Serlife; Sertzol; Zoloft; ***Singapore:*** Zoloft; ***Spain:*** Altisben; Aremis; Besitran; Depesert; Sealdin†; ***Swed.:*** Zoloft; ***Switz.:*** Gladem; Zoloft; ***Thai.:*** Zoloft; ***Turk.:*** Lustral; Selectra; Seralin; Serdep; ***UK:*** Lustral; ***USA:*** Zoloft; ***Venez.:*** Conexine; Lusedan; Satil; Serline; Serolux; Tialin; Zoloft.

Multi-ingredient: ***India:*** Restyl Forte; Restyl Plus.

Setiptiline *(rINN)*

Setiptilina; Sétiptiline; Setiptilinum; Teciptiline. 2,3,4,9-Tetrahydro-2-methyl-1*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*c*]pyridine.

Сетиптилин

$C_{19}H_{19}N = 261.4.$

CAS — 57262-94-9 (setiptiline); 85650-57-3 (setiptiline maleate).

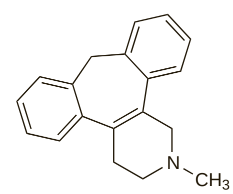

Profile

Setiptiline is an antidepressant that has been used as the maleate in the treatment of depression.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Tecipul.

St John's Wort

Hipérico; Hiperikum; Hyperici herba; Hypericum; Johannesört; Johanniskraut; Jonažolių žolė; Mäkikuisma; Millepertuis; Orbáncfű; Třezalková nať; Ziele dziurawca.

CAS — 548-04-9 (hypericin).

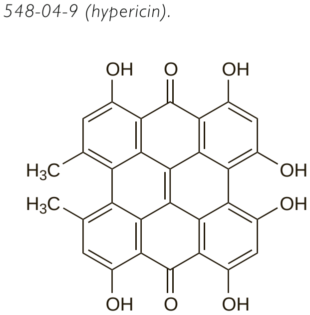

(hypericin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Eur. also includes a form for homoeopathic preparations.

Swiss also includes monographs for hypericum (fresh flowering tops) and hypericum oil.

Ph. Eur. 6.2 (St. John's Wort). The whole or cut, dried flowering tops of *Hypericum perforatum* gathered during flowering. It contains not less than 0.08% of total hypericins, expressed as hypericin ($C_{30}H_{16}O_8$ = 504.4) calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Hypericum for Homoeopathic Preparations; Hypericum Perforatum ad Praeparationes Homoeopathicas). The whole, fresh plant of *Hypericum perforatum*, at the beginning of the flowering period. Protect from light.

USP 31 (St. John's Wort). The dried flowering tops or aerial parts of *Hypericum perforatum* (Hypericaceae), gathered shortly before or during flowering. It contains not less than 0.04% of the combined total of hypericin ($C_{30}H_{16}O_8$ = 504.4) and pseudohypericin ($C_{30}H_{16}O_9$ = 520.4) and not less than 0.6% of hyperforin ($C_{35}H_{52}O_4$ = 536.8). Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse effects reported with St John's wort have included gastrointestinal symptoms, dizziness, headache, confusion, urinary frequency, allergic reactions, and fatigue. Photosensitivity has also been reported; hypericin and pseudohypericin are the constituents of St John's wort thought to be responsible for this reaction.

Effects on the nervous system. Subacute polyneuropathy after sun exposure developed in a woman who had taken St John's wort for mild depression; she improved after drug withdrawal.[1] Seizures and confusion occurred in a 16-year-old girl after an overdose of St John's wort.[2] She had taken large daily doses for 2 weeks and an overdose just before presentation.

1. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. *Lancet* 1998; **352:** 1121–2.
2. Karalapillai DC, Bellomo R. Convulsions associated with an overdose of St John's wort. *Med J Aust* 2007; **186:** 213–14.

Effects on the skin. In addition to photosensitivity reactions associated with St John's wort use,[1] there has been a report of severe erythroderma in a patient who supplemented his regular antidepressant medication (dosulepin) with St John's wort.[2] The reaction was seen on both light-exposed and non-exposed areas, and was thought to be due to the St John's wort although there remained a possibility that it was due to an interaction between the 2 drugs.

1. Lane-Brown MM. Photosensitivity associated with herbal preparations of St John's wort (Hypericum perforatum). *Med J Aust* 2000; **172:** 302.
2. Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; **143:** 1127–8.

Mania. There have been a number of cases of mania or hypomania associated with the use of St John's wort.[1-3]

1. Neirenberg AA, *et al.* Mania associated with St John's wort. *Biol Psychiatry* 1999; **46:** 1707–8.
2. Fahmi M, *et al.* A case of mania induced by hypericum. *World J Biol Psychiatry* 2002; **3:** 58–9.
3. Stevinson C, Ernst E. Can St John's wort trigger psychoses? *Int J Clin Pharmacol Ther* 2004; **42:** 473–80.

Withdrawal. A 58-year-old woman developed symptoms such as nausea, anorexia, dizziness, dry mouth, thirst, chills, and fatigue the day after stopping St John's wort;[1] she had taken the drug for 32 days. The symptoms, which the authors considered suggestive of a withdrawal syndrome, resolved within 8 days.

1. Dean AJ, *et al.* Suspected withdrawal syndrome after cessation of St John's wort. *Ann Pharmacother* 2003; **37:** 150.

Interactions

St John's wort has been shown to induce several drug metabolising enzymes including some cytochrome P450 isoenzymes (in particular CYP3A4) and the transport protein P-glycoprotein. Clinically important interactions resulting in decreased plasma concentrations of the interacting drug have been reported with ciclosporin, digoxin, HIV-protease inhibitors, NNRTIs, oral contraceptives, tacrolimus, theophylline, and warfarin. There is also a possibility of an interaction between St John's wort and antiepileptics. In addition, stopping St John's wort may result in increased, and possibly toxic, concentrations of the interacting drug.

In many countries, including the UK and USA, preparations of St John's wort are not required to be licensed as medicines, and the amount of active ingredient may vary widely between preparations. Changing preparations may therefore alter the degree of enzyme induction.

Use of St John's wort with drugs known to act on serotonergic neurotransmitters may result in synergistic interactions and an increased risk of adverse effects may also occur. Examples include the SSRIs and nefazodone (see Antidepressants, p.418) and the selective serotonin (5-HT_1) agonists (see under Sumatriptan, p.626) used to treat migraine.

◊ References.

1. Roby CA, *et al.* St John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther* 2000; **67:** 451–7.
2. CSM/MCA. Reminder: St John's Wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
3. Dürr D, *et al.* St John's Wort induces intestinal p-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 2000; **68:** 598–604.
4. Wang Z, *et al.* The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001: **70:** 317–26.
5. Hennessy M, *et al.* St John's Wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 2002 **53:** 75–82.
6. Henderson L, *et al.* St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; **54:** 349–56.
7. Mills E, *et al.* Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004; **329:** 27–30.
8. Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. *Drug Safety* 2004; **27:** 773–97.
9. Whitten DL, *et al.* The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol* 2006; **62:** 512–26.

Analgesics. For details of a possible interaction between St John's wort and the opioid analgesic *methadone*, see p.84.

Anticoagulants. For mention of a possible interaction between St John's wort and *warfarin*, see p.1432.

Antiepileptics. There is a possibility of an interaction between St John's wort and antiepileptics such as *carbamazepine* (see p.474), *phenobarbital* (see p.493), and *phenytoin* (see p.498).

Antineoplastics. St John's wort may interact with some antineoplastics; examples include *aminolevulinic acid* (see p.679), *imatinib* (see p.734), and *irinotecan* (see p.737).

Antivirals. For details of a possible interaction between St John's wort and *HIV-protease inhibitors* such as indinavir, see p.883.

Cardiac glycosides. For details of a possible interaction between St John's wort and *digoxin*, see p.1261.

Immunosuppressants. For details of possible interactions between St John's wort and *ciclosporin* or *tacrolimus*, see p.1826 and p.1845, respectively.

Oral contraceptives. For reports of a possible interaction between St John's wort and oral contraceptives, see p.2068.

Verapamil. For details of a possible interaction between St John's wort and verapamil, see p.1423.

Xanthines. For details of a possible interaction between St John's wort and *theophylline*, see p.1143.

Uses and Administration

Herbal preparations containing St John's wort are used, frequently for self-medication, in the treatment of depression. Such preparations are also promoted for the treatment of other nervous disorders such as insomnia and anxiety, particularly if associated with the menopause. St John's wort oil has also been used as an astringent. Hypericin, a major constituent of St John's wort, has been investigated as an antiviral in the treatment of HIV infection and AIDS (but see Antiviral Action, below).

The amount of active constituents can vary between different preparations and doses depend on the preparation being used.

Homoeopathy. St John's wort has been used in homoeopathic medicines under the following names: Hypericum; Hypericum perforatum; Hypericum perforatum ex herba; Hypericum, herba; Hyper.

◊ References.

1. McIntyre M. A review of the benefits, adverse events, drug interactions, and safety of St John's Wort (Hypericum perforatum): the implications with regard to the regulation of herbal medicines. *J Altern Complement Med* 2000; **6:** 115–24.

Antiviral action. A study involving 30 HIV-infected patients suggested that hypericin, given intravenously or by mouth, produced significant phototoxicity and had no effect on virological markers or CD4 cell count.[1]

1. Gulick RM, *et al.* Phase I studies of hypericin, the active compound in St John's Wort, as an antiretroviral agent in HIV-infected adults. *Ann Intern Med* 1999; **130:** 510–14.

Depression. St John's wort extracts are widely used in some countries for the treatment of depression (p.373).

Two systematic reviews[1,2] of randomised controlled studies found St John's wort extracts to be more effective than placebo in the treatment of mild to moderate depressive disorders. However, the results of the more recent review[2] also suggested that St John's wort extracts were only of minor benefit in patients with major depression and probably of no benefit in those with a prolonged history of the condition; in addition, there was no evidence of effectiveness in severe depression. The authors of this review commented that recent placebo-controlled studies tended to show less favourable results for St John's wort than older studies. It was considered that the heterogeneous findings were due partly to overestimation of effects in some smaller, older studies, and partly to the variable efficacy of St John's wort extracts in different patient populations; non-publication of negative studies was not thought to have played a major role.

The efficacy of St John's wort compared with standard antidepressants has also been reviewed and found to be comparable.[2] However, this finding should be interpreted with caution, not least because doses of the standard antidepressants used were at the lower end of the range in some studies.

The mechanism of action of St John's wort extracts in the treatment of depression remains unclear. Extracts contain at least 10 active principles. Hypericin, one of the major constituents of St John's wort, was first thought responsible for the antidepressant effect since it had an inhibitory action on monoamine oxidase *in vitro*. However it was later shown that this action was, at best, weak and it is now generally believed that monoamine oxidase inhibition is not responsible for the antidepressant effect of St John's wort. More recent studies have suggested that hyperforin may be one of the major constituents responsible for the antidepressant effect.[3] Although the evidence is mainly from *in vitro* studies, hyperforin inhibits the reuptake of several major neurotransmitters including serotonin, dopamine, and noradrenaline.[4]

1. Stevinson C, Ernst E. Hypericum for depression: an update of the clinical evidence. *Eur Neuropsychopharmacol* 1999; **9:** 501–5.
2. Linde K, *et al.* St John's wort for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 24/11/05).
3. Laakmann G, *et al.* St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998: **31** (suppl.): 54–9.
4. Chatterjee SS, *et al.* Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci* 1998; **63:** 499–510.

Preparations

Ph. Eur.: St John's Wort Dry Extract, Quantified.

Proprietary Preparations (details are given in Part 3)

Arg.: Amenicil; Felis†; Herbaccion Motivante†; Hipax; Hiperinat; Remotiv†; ***Austral.:*** Bioglan Stress-Relax; Hyperiforte†; Remotiv; ***Austria:*** Esbericum; Felis†; Helarium; Hyperiforce; Jarsin; Johanicum; Johni; Kira; Lunare; Perikan; Psychotonin; Remotiv; Solaguttae; ***Belg.:*** Hyperiplant; Milperinol; Perika; ***Braz.:*** Adprex†; Ciperico; Emotival†; Equilibra†; Fiotan; Fitovital; Hiperex; Hipericin; Hiperico; Hiperifarma†; Hiperil†; Hipersac; Hyperico†; Hyperigreen; Iperisan; Jarsin†; Motiven; Prazen; Remotiv; Triativ; ***Canad.:*** Kira; Movana†; ***Chile:*** Anxium; Ciplazin†; Edual†; Remotiv†; ***Cz.:*** Cesradyston†; Deprim†; Esbericum†; Felisio; Helarium; Hyperikan; Jarsin; Kira†; Laif; Lubovnik†; Nat Trezalky; Psychotonin Forte†; Remotiv; Trezalka v Nalevovych Sacchich; Trezalkova Nat; Trezalkovy Caj; Turineurin†; ***Fr.:*** Bains Romains; Dermum†; Mildac; Procalmil; ***Ger.:*** aar brain N†; Aristo; Aristoforat; Cesradyston; dysto-lux; Esbericum; Felis; Helarium; Herbaneurin†; Hewepsychon uno; Hyperforat; Hypericaps†; Hyperimerck; Hyperpur; Jarsin; Jo-Sabona†; Kira; Kytta-Modal†; Laif; Libertin†; Lomahypericum†; Nervei; Neuroplant; Neurosporal; Neurovegetalin; Psychotonin; Psychotonin M†; Remotiv; Sedovegan†; Syxal†; Texx; Tonizin; Turineurin; Viviplus†; ***Gr.:*** Neukan; ***Hung.:*** Helarium; Hyperikan; Klosterfrau Sedinal; Myrall; Remotiv; ***Indon.:*** Preso; ***Israel:*** Remotiv; ***Ital.:*** Nervaxon; Proserem; Quiens; Remotive; ***Mex.:*** Hiperikan; Nutegen H†; Procalm†; Remotiv; ***Pol.:*** Apatinac; Deprim; Hyperherba; Hyperosedat; Perhip; Remotiv; Silenil; ***Port.:*** Alacre; ***Rus.:*** Deprim (Деприм); Doppelherz Nervotonik (Доппельгерц Нервотоник); Helarium (Гелариум); Negrustin (Негрустин); Novo-Passit (Ново-Пассит); ***S.Afr.:*** Remotiv†; ***Spain:*** Animic; Arkocapsulas Hiperico; Hiperico; Hyneurin; Perika; Quetzal; Vitalium; ***Switz.:*** Hyperforat†; Hypericettes†; Hyperiforce; HyperiMed; Hyperiplant; Hyperval; Jarsin; Libertin†; Lucilium; ReBalance; Remotiv; Solevita; Yakona; ***Turk.:*** Felis; ***UK:*** HyperiCalm; Kira; ***Venez.:*** Hyperikan; Kira†; Qual†.

Multi-ingredient: ***Austral.:*** Bioglan 3B Beer Belly Buster; Cimicifuga Compound; Feminine Herbal Complex; Infant Tonic†; Joint & Muscle Cream; Nappy Rash Relief Cream; Nevaton; Skin Healing Cream†; ***Austria:*** Eryval; Magentee St Severin; Nerventee St Severin; Remifemin plus; Species nervinae; Vulpuran; Wechseltee St Severin; ***Cz.:*** Alvisan Neo; Cajova Smes pri Redukcni Diete†; Cicaderma; Eugastrin†; Fytokliman Planta; Naturident†; Novo-Passit; Species Nervinae Planta; Stomaran; Zaludecni Cajova Smes; ***Fr.:*** Cicaderma; ***Ger.:*** Allya†; anabol-loges; Anisan†; Arthrodynat P†; Befelka-Oel; Cheiranthol†; Dolo-cyl; Gastritol; Gastrol S†; Gutnacht†; Hewepsychon duo†; Hyperesa; Hyperforat-forte†; JuDorm†; JuViton†; Marianon†; Me-Sabona plus†; Neurapas; Oxacant N†; Phytogran†; Presselin Arterien K 5 P†; Presselin Nerven K 1 N†; Psychotonin-sed; Remifemin plus; Rhoival†; Sedariston Konzentrat; Sedariston plus; Venacton†; ***Hung.:*** Remifemin Plus; ***Ital.:*** Controller; Hiperogyn; Mithen; Skab 2; ***Malaysia:*** Gyno-Plus; ***Mex.:*** Nordimenty; ***Pol.:*** Cholesol; Diges-Tonic; Fortestomachicae; Gastrobonisol; Guttae Stomachicae; Herbogastrin; Krople Zoladkowe; Melisal; Melissed; Nervomix; Perfocrat; Prostapol; Psychotonisol; Sedomix; Uroprost; ***Port.:*** Cicaderma; ***Rus.:*** Prostanorm (Простанорм); Sibectan (Сибектан); ***Spain:*** Natusor Gastrolen†; Natusor Somnisedan†; ***Switz.:*** Gel a la consoude; Huile de millepertuis A. Vogel (huile de St. Jean); Hyperiforce comp; Keppur; Kytta Gel†; Malvedrin; Saltrates Rodell†; Saltrates†; The a l'avoine sauvage de Vollmer; Yakona N†; Ziegella; ***UK:*** St Johnswort Compound; Tranquil; ***Venez.:*** Biomicovo†.

Tianeptine Sodium *(rINNM)*

Natrii Tianeptinum; Taneptinum Natricum; Tianeptiininatrium; Tianeptin sodná sůl; Tianeptin Sodyum; Tianeptina sódica; Tianeptine sodique; Tianeptinnatrium; Tianeptin-nátrium; Tianeptino natrio druska; Tianeptinum natricum. The sodium salt of 7-[(3-chloro-6,11-dihydro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11-yl)amino]heptanoic acid *S,S*-dioxide.

Натрий Тианептин

$C_{21}H_{24}ClN_2NaO_4S$ = 458.9.

CAS — 66981-73-5 (tianeptine).

ATC — N06AX14.

ATC Vet — QN06AX14.

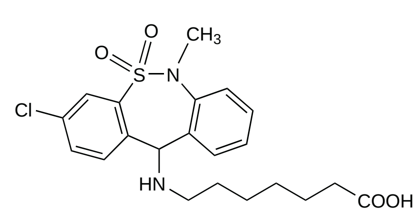

(tianeptine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tianeptine Sodium). A white or yellowish, very hygroscopic, powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. Store in airtight containers.

Profile

Tianeptine sodium is an antidepressant reported to act by increasing (rather than inhibiting) the presynaptic reuptake of serotonin. It is given in oral doses of 12.5 mg three times daily in the treatment of depression (p.373). Doses should be reduced to a total of 25 mg daily in elderly patients; for details of dosage in those with renal impairment, see below.

Isolated cases of hepatitis have been reported during treatment with tianeptine.

Abuse. Reports of misuse of tianeptine.[1,2]

1. Leterme L, *et al.* Usage détourné de tianeptine: à propos de cinq cas de surconsommation. *Ann Med Interne (Paris)* 2003; **154:** 2S58–2S63.
2. Kisa C, *et al.* Is it possible to be dependent to tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31:** 776–8.

Administration in renal impairment. Licensed product information recommends that oral doses of tianeptine sodium should not exceed a total of 25 mg daily in patients with renal impairment.

Asthma. Tianeptine has been reported to improve symptoms in patients with asthma.[1] It was thought that reduction of raised levels of free serotonin found in such patients contributed to the beneficial effect of tianeptine.

1. Lechin F, *et al.* The serotonin uptake-enhancing drug tianeptine suppresses asthmatic symptoms in children: a double-blind, crossover, placebo-controlled study. *J Clin Pharmacol* 1998; **38:** 918–25.

Depression. References to the use of tianeptine in patients with depression (p.373) are given below.

1. Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* 1995; **49:** 411–39.
2. Ginestet D. Efficacy of tianeptine in major depressive disorders with or without melancholia. *Eur Neuropsychopharmacol* 1997; **7** (suppl 3): S341–S345.
3. Wagstaff AJ, *et al.* Tianeptine: a review of its use in depressive disorders. *CNS Drugs* 2001; **15:** 231–59.
4. Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry* 2002; **17** (suppl 3): 331–40.
5. Waintraub L, *et al.* Efficacy and safety of tianeptine in major depression: evidence from a 3-month controlled clinical trial versus paroxetine. *CNS Drugs* 2002; **16:** 65–75.
6. Nickel T, *et al.* Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol* 2003; **23:** 155–68.

Pharmacokinetics. References.

1. Royer RJ, *et al.* Tianeptine and its main metabolite: pharmacokinetics in chronic alcoholism and cirrhosis. *Clin Pharmacokinet* 1989; **16:** 186–91.
2. Carlhant D, *et al.* Pharmacokinetics and bioavailability of tianeptine in the elderly. *Drug Invest* 1990; **2:** 167–72.
3. Demotes-Mainard F, *et al.* Pharmacokinetics of the antidepressant tianeptine at steady state in the elderly. *J Clin Pharmacol* 1991; **31:** 174–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Stablon; ***Austria:*** Stablon; ***Braz.:*** Stablon; ***Cz.:*** Coaxil; ***Fr.:*** Stablon; ***Hung.:*** Coaxil; ***India:*** Stablon; ***Indon.:*** Stablon; ***Malaysia:*** Stablon; ***Mex.:*** Stablon; ***Philipp.:*** Stablon; ***Pol.:*** Coaxil; ***Port.:*** Stablon; ***Rus.:*** Coaxil (Коаксил); ***Singapore:*** Stablon; ***Thai.:*** Stablon; ***Turk.:*** Stablon; ***Venez.:*** Stablon.

Tranylcypromine Sulfate *(rINNM)*

SKF-385; Sulfato de tranilcipromina; Transamine Sulphate; Tranylcypromine, Sulfate de; Tranylcypromine Sulphate *(BANM)*; Tranylcypromini Sulfas. (±)-*trans*-2-Phenylcyclopropylamine sulphate.

Транилципромина Сульфат

$(C_9H_{11}N)_2,H_2SO_4 = 364.5.$

CAS — 155-09-9 (tranylcypromine); 13492-01-8 (tranylcypromine sulfate).

ATC — N06AF04.

ATC Vet — QN06AF04.

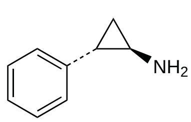

(tranylcypromine)

Pharmacopoeias. In *Br.*

BP 2008 (Tranylcypromine Sulphate). A white or almost white crystalline powder; odourless or with a faint odour of cinnamaldehyde. Soluble in water; very slightly soluble in alcohol and in ether; insoluble in chloroform.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p.415).

Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening.

Hypertensive reactions are more likely to occur with tranylcypromine than with other MAOIs, but severe liver damage occurs less frequently.

Dependence. Dependence on tranylcypromine with tolerance has been reported in patients receiving high doses with or without a history of previous substance abuse. For further details, see Withdrawal under Precautions in Phenelzine, p.417.

Effects on the cardiovascular system. Although orthostatic hypotension is more common, hypertension can occur with MAOIs. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine.[1,2] In the first case it was thought possible that an autointeraction may have occurred between tranylcypromine and amfetamine to which it is partly metabolised. In the second case the provocation of hypertension led to the finding of a previously undiagnosed phaeochromocytoma and it was suggested this may have been a possibility in previous reports of hypertension induced by MAOIs.

1. Gunn J, *et al.* Hypertensive crisis and broad complex bradycardia after a single dose of monoamine oxidase inhibitor. *BMJ* 1989; **298:** 964.
2. Cook RF, Katritsis D. Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma. *BMJ* 1990; **300:** 614.

Porphyria. Tranylcypromine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For interactions associated with MAOIs, see Phenelzine, p.417.

The use of clomipramine with tranylcypromine is particularly hazardous.

Pharmacokinetics

Tranylcypromine is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 3 hours after ingestion. It is excreted in the urine mainly in the form of metabolites. Tranylcypromine has a reported plasma elimination half-life of about 2.5 hours.

◊ In 9 depressed patients, tranylcypromine absorption was rapid after oral dosing.[1] Absorption was biphasic in 7. Elimination was also rapid, with an elimination half-life of 1.54 to 3.15 hours. From 2 to 7 hours after dosing, standing systolic and diastolic blood pressures were lowered, and standing pulse was raised. The onset of the effect on standing systolic blood pressure correlated with the time of peak plasma tranylcypromine concentration. Maximum orthostatic drop of blood pressure and rise in pulse rate occurred 2 hours after dosing. Mean plasma-tranylcypromine concentrations correlated with mean orthostatic drop of systolic blood pressure and rise of pulse rate. Patients experiencing clinically significant hypotensive reactions to tranylcypromine may benefit from changes in their dose regimen aimed at minimising peak concentrations.

1. Mallinger AG, *et al.* Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects. *Clin Pharmacol Ther* 1986; **40:** 444–50.

Uses and Administration

Tranylcypromine, a cyclopropylamine derivative, is an MAOI with actions and uses similar to those of phenelzine (p.419). It produces a less prolonged inhibition of the enzymes than phenelzine.

Tranylcypromine is used in the treatment of depression, but as discussed on p.373 the risks associated with traditional non-selective MAOIs such as tranylcypromine usually mean that other antidepressants are preferred. It is given orally as the sulfate although doses are expressed in terms of the base. Tranylcypromine sulfate 13.7 mg is equivalent to about 10 mg of tranylcypromine.

The usual initial dose is equivalent to tranylcypromine 10 mg in the morning and 10 mg in the afternoon; if the response is inadequate after a week, the afternoon dose may be increased to 20 mg or alternatively, 10 mg may be given additionally at midday. A dosage of 30 mg daily should only be exceeded with caution, although in the USA a maximum dose of 60 mg daily is allowed. Once a satisfactory response has been obtained the dosage may be gradually reduced for maintenance; some patients may continue to respond to 10 mg daily.

Tranylcypromine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Tranylcypromine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Parnate†; ***Austral.:*** Parnate; ***Braz.:*** Parnate; ***Canad.:*** Parnate; ***Cz.:*** Parnate†; ***Ger.:*** Jatrosom N; ***Irl.:*** Parnate; ***NZ:*** Parnate; ***S.Afr.:*** Parnate; ***Spain:*** Parnate; ***USA:*** Parnate.

Multi-ingredient: Arg.: Cuait D; Stelapar; ***Braz.:*** Stelapar†; ***Ital.:*** Parmodalin.

Trazodone Hydrochloride

(BANM, USAN, rINNM)

AF-1161; Hidrocloruro de trazodona; Trazodon Hidroklorür; Trazodone, Chlorhydrate de; Trazodoni Hydrochloridum. 2-[3-(4-*m*-Chlorophenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.

Тразодона Гидрохлорид

$C_{19}H_{22}ClN_5O,HCl = 408.3.$

CAS — 19794-93-5 (trazodone); 25332-39-2 (trazodone hydrochloride).

ATC — N06AX05.

ATC Vet — QN06AX05.

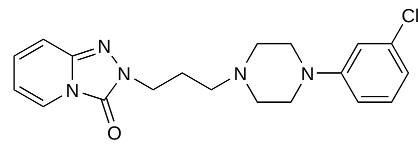

(trazodone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trazodone hydrochloride:

Sleepeasy.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Trazodone Hydrochloride). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 3.9 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Trazodone Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in chloroform. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Trazodone has sedative properties although drowsiness usually disappears on continuing treatment. Other adverse effects occasionally reported include dizziness, headache, nausea and vomiting, weakness, weight loss, tremor, dry mouth, bradycardia or tachycardia, orthostatic hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia, and skin rash. Although some of these effects are typical of antimuscarinic activity it is reported that trazodone has little antimuscarinic activity compared with tricyclic antidepressants. *Animal* studies have also indicated that trazodone is less cardiotoxic than the tricyclics. Priapism has been reported on a number of occasions.

Agranulocytosis, thrombocytopenia, and anaemia have been reported rarely. Adverse effects on hepatic function, including jaundice and hepatocellular damage, which may be severe, have also been reported rarely. There have been occasional reports of serotonin syndrome. Neuroleptic malignant syndrome has occurred rarely.

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of overdosage include drowsiness, dizziness, vomiting, priapism, respiratory arrest, seizures, and ECG changes. The value of gastric decontamination after overdosage is uncertain. However, activated charcoal may be considered in adults who have taken more than 1 g (children more than 150 mg) and present within 1 hour; gastric lavage may also be considered in adults in life-threatening overdoses. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the cardiovascular system. Although trazodone is considered to cause fewer adverse cardiovascular reactions than the tricyclic antidepressants, they have, nevertheless, been reported in individual patients. In therapeutic doses it has been associated with heart block in a patient with pre-existing cardiovascular disease,[1] as well as in a patient with no ECG abnormalities.[2] Similarly, ventricular arrhythmias have been associated with therapeutic doses of trazodone both in patients with a history of cardiac problems,[3,4] and with no history of cardiac abnormalities.[5] Atrial fibrillation has been reported in a patient with ischaemic heart disease.[6]

1. Rausch JL, *et al.* Complete heart block following a single dose of trazodone. *Am J Psychiatry* 1984; **141:** 1472–3.
2. Lippmann S, *et al.* Trazodone cardiotoxicity. *Am J Psychiatry* 1983; **140:** 1383.
3. Janowsky D, *et al.* Ventricular arrhythmias possibly aggravated by trazodone. *Am J Psychiatry* 1983; **140:** 796–7.
4. Vlay SC, Friedling S. Trazodone exacerbation of VT. *Am Heart J* 1983; **106:** 604.
5. Johnson BA. Trazodone toxicity. *Br J Hosp Med* 1985; **33:** 298.
6. White WB, Wong SHY. Rapid atrial fibrillation associated with trazodone hydrochloride. *Arch Gen Psychiatry* 1985; **42:** 424.

Effects on the eyes. A patient receiving clomipramine and trazodone orally noted excessive blinking whenever the dose of trazodone exceeded or equalled that of clomipramine.[1] When trazodone, but not clomipramine, was withdrawn, blinking became normal within 3 weeks.

1. Cooper MA, Dening TR. Excessive blinking associated with combined antidepressants. *BMJ* 1986; **293:** 1243.

Effects on the liver. A mixed hepatocellular-cholestatic liver enzyme pattern has been reported in a patient after about 3 weeks of treatment with trazodone in doses of up to 500 mg daily.[1] The enzyme abnormalities returned to normal 4 weeks after trazodone was stopped but it was suggested that liver enzyme values should be monitored during the first 4 weeks of therapy. A similar case apparently presenting as obstructive jaundice and hepatocellular inflammation, in which the patient had only been receiving 50 mg daily for 2 weeks, has also been described.[2] It was believed that the patient suffered an idiosyncratic drug reaction to trazodone. Further reports of trazodone-induced liver injury include an elderly patient who developed chronic active hepatitis after receiving trazodone 150 mg daily for about 8 months.[3] A case of fatal hepatic necrosis reported in another elderly patient was considered to be due to treatment with trazodone and antipsychotics.[4] The authors of the report[4] noted that up to August 1991 the UK CSM had received 14 reports of adverse effects on the liver associated with trazodone including one episode of fatal hepatic necrosis. In one of 2 later reports of trazodone-induced hepatotoxicity,[5] a female patient with rheumatoid arthritis developed jaundice 18 months after trazodone was added to her existing medications. All drugs were stopped and the patient improved; however, an inadvertent rechallenge with trazodone (without any other medication) led to a recurrence of her symptoms which again resolved following trazodone withdrawal. The second case[6] involved a HIV-positive male who was started on methadone, clonidine, and trazodone as part of a detoxification programme; 4 days later acute hepatitis and cholestasis was noted and trazodone and clonidine were withdrawn with subsequent resolution of symptoms. The authors considered that trazodone was probably the causative agent.

1. Chu AG, *et al.* Trazodone and liver toxicity. *Ann Intern Med* 1983; **99:** 128–9.
2. Sheikh KH, Nies AS. Trazodone and intrahepatic cholestasis. *Ann Intern Med* 1983; **99:** 572.
3. Beck PL, *et al.* Chronic active hepatitis associated with trazodone therapy. *Ann Intern Med* 1993; **118:** 791–2.
4. Hull M, *et al.* Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* 1994; **309:** 378.
5. Fernandes NF, *et al.* Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am J Gastroenterol* 2000; **95:** 532–5.
6. Rettman KS, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother* 2001; **35:** 1559–61.

Effects on mental state. There have been reports of mania,[1,2] and psychosis with hallucinations[3,4] associated with the use of trazodone in depressed patients; delirium[5] in patients with bulimia nervosa and possible psychosis or hypomania[6] in a patient receiving trazodone-tryptophan treatment for aggression have also been reported.

1. Warren M, Bick PA. Two case reports of trazodone-induced mania. *Am J Psychiatry* 1984; **141:** 1103–4.
2. Arana GW, Kaplan GB. Trazodone-induced mania following desipramine-induced mania in major depressive disorders. *Am J Psychiatry* 1985; **142:** 386.
3. Kraft TB. Psychosis following trazodone administration. *Am J Psychiatry* 1983; **140:** 1383–4.
4. Mizoguchi Y, Monji A. Low-dose-trazodone-induced disorganized type psychosis. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 253–4.
5. Damlouji NF, Ferguson JM. Trazodone-induced delirium in bulimic patients. *Am J Psychiatry* 1984; **141:** 434–5.
6. Patterson BD, Srisopark MM. Severe anorexia and possible psychosis or hypomania after trazodone-tryptophan treatment of aggression. *Lancet* 1989; **i:** 1017.

Effects on sexual function. Trazodone is notable for the number of reports of priapism associated with its use.[1,2] In most cases, priapism occurred during treatment with standard doses after 1 to 3 weeks of therapy. Several patients required surgery and recovery was not always complete.[1] A review[3] of priapism induced by psychotropic drugs proposed that the effect was related to blockade of alpha-adrenoceptors in the absence of sufficient antimuscarinic activity, criteria fulfilled by the pharmacological profile of trazodone.

Inhibition of ejaculation,[4] and an increase in libido in women[5] and men[6] have also been reported with trazodone therapy. There have also been reports of trazodone-associated priapism of the clitoris.[7,8]

1. CSM. Priapism and trazodone (Molipaxin). *Current Problems 13* 1984. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024420&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Anonymous. Priapism with trazodone (Desyrel). *Med Lett Drugs Ther* 1984; **26:** 35.
3. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
4. Jones SD. Ejaculatory inhibition with trazodone. *J Clin Psychopharmacol* 1984; **4:** 279–81.
5. Gartrell N. Increased libido in women receiving trazodone. *Am J Psychiatry* 1986; **143:** 781–2.
6. Sullivan G. Increased libido in three men treated with trazodone. *J Clin Psychiatry* 1988; **49:** 202–3.
7. Pescatori ES, *et al.* Priapism of the clitoris: a case report following trazodone use. *J Urol (Baltimore)* 1993; **149:** 1557–9.
8. Medina CA. Clitoral priapism: a rare condition presenting as a cause of vulvar pain. *Obstet Gynecol* 2002; **100:** 1089–91.

Effects on the skin. Individual reports of adverse dermatological reactions to trazodone have included leucocytoclastic vasculitis,[1] erythema multiforme,[2] and exacerbation of psoriasis.[3]

1. Mann SC, *et al.* Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol* 1984; **10:** 699–70.
2. Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy: case report. *J Clin Psychiatry* 1985; **46:** 294–5.
3. Barth JH, Baker H. Generalized pustular psoriasis precipitated by trazodone in the treatment of depression. *Br J Dermatol* 1986; **115:** 629–30.

Epileptogenic effect. Tonic-clonic seizures related to trazodone therapy have been reported in 2 patients[1,2] with no history of seizure disorders.

1. Bowdan ND. Seizure possibly caused by trazodone hydrochloride. *Am J Psychiatry* 1983; **140:** 642.
2. Lefkowitz D, *et al.* Seizures and trazodone therapy. *Arch Gen Psychiatry* 1985; **42:** 523.

Overdosage. Reviews have indicated that the incidence of serious toxicity from trazodone overdose alone was low compared with tricyclic antidepressant overdose.[1-4]

In a review covering 149 overdose cases,[1] only 10 deaths had been reported and in only 1 case was trazodone the sole agent reported to be ingested; in this case autopsy revealed an acute myocardial infarction after the patient was stable. The remaining 9 patients also had histories of ingestion of unknown quantities of alcohol, benzodiazepines, or other sedative-hypnotics that may have contributed to their demise. In the surviving 139 patients, 2 cases of respiratory arrest, 2 cases of right bundle branch block, and one case each of priapism, seizure, atrioventricular block, and T-wave inversion were reported. The remaining patients had minor CNS-depressant effects.

In a second review[2] of 88 cases of overdose, no fatalities occurred in the 39 cases where trazodone alone was ingested. However 9 deaths occurred in the remaining 49 cases where trazodone was ingested with other drugs or alcohol.

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

1. Hassan E, Miller DD. Toxicity and elimination of trazodone after overdose. *Clin Pharm* 1985; **4:** 97–100.
2. Gamble DE, Peterson LG. Trazodone overdose: four years of experience from voluntary reports. *J Clin Psychiatry* 1986; **47:** 544–6.
3. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.
4. Gallant DM. Antidepressant overdose: symptoms and treatment. *Psychopathology* 1987; **20** (suppl 1): 75–81.

Precautions

Trazodone should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease, and its use is not recommended in the immediate recovery phase after myocardial infarction. Similarly, it should be used with caution in patients with epilepsy and severe hepatic or renal impairment. Trazodone should be stopped immediately if patients develop signs of hepatic dysfunction or blood dyscrasias. Patients developing inappropriate or prolonged penile erections should also stop trazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Drowsiness often occurs at the start of trazodone therapy and patients, if affected, should not drive or operate machinery.

As with other antidepressants, trazodone therapy should be withdrawn gradually.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trazodone on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antidepressant drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

A study of 6 women each given a single 50-mg dose of trazodone concluded that the exposure of infants to trazodone via breast milk was very small.[2] However, trazodone has been reported to form an active metabolite and it was not known to what extent this metabolite distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Verbeeck RK, *et al.* Excretion of trazodone in breast milk. *Br J Clin Pharmacol* 1986; **22:** 367–70.

Porphyria. Trazodone hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. UK licensed drug information states that trazodone should be avoided during pregnancy; that for the USA indicates that trazodone should only be used if the benefits to the mother outweigh the risks to the fetus.

For details of outcome in a multicentre study on the use of trazodone during pregnancy, see under Nefazodone, p.412.

Interactions

Trazodone should not be given to patients receiving MAOIs or for at least 14 days afterwards. It has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping trazodone therapy. For further details of combination antidepressant therapy, see Antidepressants under Interactions of Phenelzine, p.418.

It is considered unlikely that trazodone will alter the effects of antihypertensives such as guanethidine; some interaction may, however, occur with clonidine. The dose of other antihypertensives may need to be reduced if used with trazodone.

The sedative effects of trazodone may be enhanced by alcohol or other CNS depressants. The potential for interaction between trazodone and general anaesthetics or muscle relaxants exists and some licensed product information recommends that trazodone should be stopped before elective surgery for as long as clinically feasible.

Trazodone may increase plasma concentrations of digoxin or phenytoin and some product information recommends monitoring their serum concentrations if used with trazodone.

Trazodone is metabolised by the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may limit the elimination of trazodone. Consequently, trazodone may need to be given in reduced doses with drugs known to be potent inhibitors of CYP3A4 such as the azole antifungals itraconazole and ketoconazole, and the HIV-protease inhibitors. CYP3A4 inducers such as carbamazepine may reduce the plasma concentrations of trazodone.

Anticoagulants. For the effect of trazodone on *warfarin*, see p.1428.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Trazodone may increase plasma concentrations of *carbamazepine* (see p.474) and *phenytoin* (see p.498). Some licensed product information recommends monitoring concentrations of phenytoin if used with trazodone.

Antivirals. In a small study in 10 subjects, the use of low-dose *ritonavir* (200 mg twice daily for 2 days) with trazodone (50 mg once daily) more than halved the clearance of trazodone resulting in significant increases in its peak plasma concentrations.[1] Adverse reactions were noted in 3 subjects and included dizziness, nausea, hypotension, and syncope.

1. Greenblatt DJ, *et al.* Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol* 2003; **43:** 414–22.

Ginkgo biloba. Coma, reversible by flumazenil, developed in an 80-year-old woman with Alzheimer's disease 3 days after starting to take a preparation of ginkgo biloba with trazodone.[1]

1. Galluzzi S, *et al.* Coma in a patient with Alzheimer's disease taking low dose trazodone and gingko biloba. *J Neurol Neurosurg Psychiatry* 2000; **68:** 679–80.

Pharmacokinetics

Trazodone is readily absorbed from the gastrointestinal tract although absorption is affected by food. When trazodone is taken shortly after a meal there may be an increase in the amount absorbed, a decrease in the maximum concentration, and a lengthening in the time to maximum concentration compared with the fasting state; peak plasma concentrations occur about one hour after a dose when taken on an empty stomach and after about 2 hours when taken with food. Protein binding is reported to be about 89 to 95%.

Trazodone is extensively metabolised in the liver and paths of metabolism include *N*-oxidation and hydroxylation. It is metabolised to its active metabolite *m*-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4. Trazodone is excreted mainly in the urine almost entirely in the form of its metabolites, either in free or in conjugated form: some is excreted in the faeces via biliary elimination. The elimination of trazodone from the plasma is biphasic, with a terminal elimination half-life of 5 to 9 hours.

Small amounts of trazodone are distributed into breast milk.

◊ References.

1. Bayer AJ, *et al*. Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br J Clin Pharmacol* 1983; **16:** 371–6.
2. Nilsen OG, Dale O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol Toxicol* 1992; **71:** 150–3.
3. Nilsen OG, *et al*. Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* 1993; **72:** 286–9.

Uses and Administration

Trazodone is a triazolopyridine antidepressant chemically unrelated to other classes of antidepressants. It blocks the reuptake of serotonin at presynaptic neurones and has an action at 5-HT_1 receptors. Trazodone is also an antagonist at 5-$HT_{2A/2C}$ receptors. Unlike the tricyclic antidepressants, trazodone does not inhibit the peripheral reuptake of noradrenaline, although it may indirectly facilitate neuronal release. Trazodone blocks central α_1-adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant antimuscarinic properties, but has a marked sedative action.

For the treatment of **depression** trazodone hydrochloride is given in oral doses of 150 mg daily initially; total daily dosage may be increased by 50 mg every 3 or 4 days up to 300 to 400 mg daily if necessary. The daily dosage may be divided throughout the day after food or be given as a single dose at night. Divided daily dosages of up to 600 mg may be given in severe depression in hospitalised patients. A suggested initial dose in elderly and other susceptible patients is 100 mg daily, and total daily doses above 300 mg are unlikely to be needed in these patients.

In the treatment of **anxiety** (p.952), trazodone hydrochloride is given in an initial oral dose of 75 mg daily increasing to 300 mg daily if necessary.

As with other antidepressants, trazodone should be withdrawn gradually.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Trazodone has a different biochemical profile from both the tricyclics and the SSRIs.

References.

1. Weisler RH, *et al*. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994; **14:** 170–9.

Disturbed behaviour. Trazodone has produced beneficial results[1-3] when tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see p.954). Some[4] also consider that, in the management of dementia, trazodone might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant of or unresponsive to antipsychotics. However, the evidence for such use is poor; a systematic review on the use of trazodone in the treatment of behavioural and psychological symptoms of dementia found that the evidence from randomised, placebo-controlled studies was insufficient for any recommendations to be made.[5] The risk of adverse effects such as sedation and orthostatic hypotension, which may be particularly problematic in the elderly, should also be considered.[4]

1. Pasion RC, Kirby SG. Trazodone for screaming. *Lancet* 1993; **341:** 970.
2. Lebert F, *et al*. Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994; **55:** 536–8.
3. Sultzer DL, *et al*. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; **5:** 60–9.
4. Rabins PV, *et al*. APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
5. Martinon-Torres G, *et al*. Trazodone for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 24/11/05).

Sexual dysfunction. Priapism can occur as an adverse effect of trazodone (see Effects on Sexual Function in Adverse Effects, above) and this has led to trials of oral trazodone for the treatment of erectile dysfunction (p.2179). Positive responses have been reported, both with yohimbine[1] and alone.[2] However, there appear to have been few controlled studies and a systematic review[3] considered some of these to be either small, brief, or methodologically weak. Meta-analysis[3] of data from 6 studies did not find trazodone to be superior to placebo but subgroup analysis possibly suggested a better outcome in patients with psychogenic erectile dysfunction and in those given doses of 150 to 200 mg daily.

1. Montorsi F, *et al*. Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 1994; **44:** 732–6.
2. Lance R, *et al*. Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. *Urology* 1995; **46:** 117–20.
3. Fink HA, *et al*. Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU Int* 2003; **92:** 441–6.

Substance dependence. The antidepressant, anxiolytic, and sedative properties of trazodone have been reported to have been useful when tried in patients having withdrawal syndromes from a variety of substances including alcohol (p.1626),[1] cocaine (p.1860),[2] and benzodiazepines (p.987).[3-5]

1. Le Bon O, *et al*. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 2003; **23:** 377–83.
2. Small GW, Purcell JJ. Trazodone and cocaine abuse. *Arch Gen Psychiatry* 1985; **42:** 524.
3. Ansseau M, De Roeck J. Trazodone in benzodiazepine dependence. *J Clin Psychiatry* 1993; **54:** 189–91.
4. Rickels K, *et al*. Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999; **141:** 1–5.
5. Petrovic M, *et al*. A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *Int J Geriatr Psychiatry* 1999; **14:** 754–60.

Preparations

USP 31: Trazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Taxagon; ***Austria:*** Trittico; ***Belg.:*** Nestrolan; Trazolan; ***Braz.:*** Donaren; ***Canad.:*** Desyrel; Trazorel†; ***Chile:*** Diapresan; Trant; Trittico; Tronsalan; ***Cz.:*** Trittico AC; ***Fin.:*** Azona; ***Ger.:*** Thombran; ***Gr.:*** Trittico; ***Hong Kong:*** Trittico; ***Hung.:*** Depsan†; Trittico; ***Irl.:*** Molipaxin; ***Israel:*** Depyrel†; Trazodil; Trittico; ***Ital.:*** Trittico; ***Mex.:*** Sideril; ***Neth.:*** Trazolan; ***Pol.:*** Trittico; ***Port.:*** Trazone; Triticum; ***Rus.:*** Trittico (Триттико); ***S.Afr.:*** Molipaxin; ***Singapore:*** Trittico; ***Spain:*** Deprax; ***Switz.:*** Trittico; ***Thai.:*** Desirel; Trazo; ***Turk.:*** Desyrel; ***UK:*** Molipaxin; ***USA:*** Desyrel†; ***Venez.:*** Trittico.

Trimipramine *(BAN, USAN, rINN)*

IL-6001; 7162-RP; Trimeprimine; Trimipramiini; Trimipramin; Trimipramina; Trimipraminum. Dimethyl{3-(10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl-2-methyl)propyl}amine.

Тримипрамин

$C_{20}H_{26}N_2$ = 294.4.

CAS — 739-71-9.

ATC — N06AA06.

ATC Vet — QN06AA06.

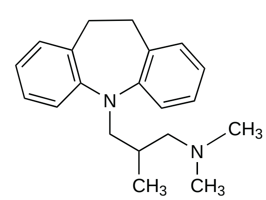

Trimipramine Maleate *(BANM, USAN, rINNM)*

Maleato de trimipramina; Trimipramiinimaleaatti; Trimipramin maleinát; Trimipramine Hydrogen Maleate; Trimipramine, maléate de; Trimipramini maleas; Trimipraminmaleat; Trimipramin-maleát; Trimipramino maleatas.

Тримипрамина Малеат

$C_{20}H_{26}N_2,C_4H_4O_4$ = 410.5.

CAS — 521-78-8.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Trimipramine Maleate). A white or almost white crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

USP 31 (Trimipramine Maleate). A white to almost white crystalline powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Porphyria. Trimipramine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Trimipramine is readily absorbed after oral doses, peak plasma concentrations being obtained in 2 hours. It is metabolised in the liver to its major metabolite desmethyltrimipramine, which is active. Trimipramine is excreted in the urine mainly in the form of its metabolites. It is about 95% bound to plasma proteins. The plasma elimination half-life is reported to be about 23 hours.

◊ References.

1. Maurer H. Metabolism of trimipramine in man. *Arzneimittelforschung* 1989; **39:** 101–3.
2. Musa MN. Nonlinear kinetics of trimipramine in depressed patients. *J Clin Pharmacol* 1989; **29:** 746–7.

Uses and Administration

Trimipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has marked antimuscarinic and sedative properties.

Trimipramine is given orally as the maleate although doses are expressed in terms of the base. Trimipramine maleate 34.9 mg is equivalent to about 25 mg of trimipramine. In the treatment of depression, the usual initial dose is the equivalent of trimipramine 50 to 75 mg daily, gradually increased as necessary to 150 to 300 mg daily. The recommended initial dose for the elderly in the UK is 30 to 75 mg daily, gradually increased as necessary. In the USA, the elderly and adolescents may be given 50 mg daily initially followed by gradual increments as necessary up to a maximum of 100 mg daily. Trimipramine may be given in divided doses during the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable and usually given at night.

Trimipramine has also been given orally as the hydrochloride and the mesilate; the mesilate has also been given intramuscularly.

Trimipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Preparations

BP 2008: Trimipramine Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Surmontil; ***Canad.:*** Apo-Trimip; Novo-Tripramine†; Rhotrimine; Surmontil†; ***Denm.:*** Surmontil; ***Fin.:*** Surmontil; ***Fr.:*** Surmontil; ***Ger.:*** Eldoral†; Herphonal; Stangyl; Trimidura; Trimineurin; ***Hong Kong:*** Surmontil; ***Hung.:*** Sapilent; ***India:*** Surmontil†; ***Irl.:*** Surmontil; ***Israel:*** Surmontil; ***Ital.:*** Surmontil; ***Neth.:*** Surmontil†; ***Norw.:*** Surmontil; ***NZ:*** Surmontil; Tripress; ***Philipp.:*** Surmontil; ***Port.:*** Surmontil; ***S.Afr.:*** Surmontil; Tydamine; ***Spain:*** Surmontil; ***Swed.:*** Surmontil; ***Switz.:*** Surmontil; Trimine; ***UK:*** Surmontil; ***USA:*** Surmontil; ***Venez.:*** Surmontil†.

Tryptophan *(USAN, rINN)*

Triptofán; Triptofanas; Triptófano; Tryptofaani; Tryptofan; L-Tryptophan; Tryptophane; Tryptophanum; W. L-2-Amino-3-(indol-3-yl)propionic acid.

Триптофан

$C_{11}H_{12}N_2O_2$ = 204.2.
CAS — 73-22-3.
ATC — N06AX02.
ATC Vet — QN06AX02.

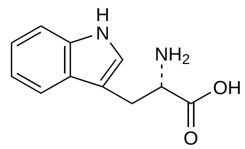

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Tryptophan). A white or almost white crystalline or amorphous powder. Sparingly soluble in water; slightly soluble in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Tryptophan). White to slightly yellowish-white crystals or crystalline powder. Soluble in hot alcohol and in dilute hydrochloric acid. pH of a 1% solution in water is between 5.5 and 7.0.

Adverse Effects

Tryptophan-containing products have been associated with the eosinophilia-myalgia syndrome; for further details, see below.

Other adverse effects that have been reported include nausea, headache, lightheadedness, and drowsiness.

An increased incidence of bladder tumours has been reported in *mice* given L-tryptophan orally as well as in cholesterol pellets embedded in the bladder lumen. However, there was no increase in tumour incidence when only high-dose, oral tryptophan was given.

Eosinophilia-myalgia syndrome. In late 1989 the first notification linking the eosinophilia-myalgia syndrome with the use of tryptophan-containing products was made in the USA.[1] There followed a number of similar published case reports from the USA, Europe, and Japan. Reviews of tryptophan-associated eosinophilia-myalgia syndrome have noted that by early 1990 over 1500 cases were known in the USA.[2,3]

In early 1990 the CDC in the USA summarised the features and known reports concerning the syndrome.[4] As the name implies the characteristic features are an intense eosinophilia together with disabling fatigue and muscle pain, although multisystem organ involvement and inflammatory disorders affecting the joints, skin, connective tissue, lungs, heart, and liver have also been recorded. Symptoms have generally developed over several weeks and the syndrome has occurred in patients who had been receiving tryptophan for many years previously with no untoward effect. In most patients slow and gradual improvement in the degree of eosinophilia and other clinical manifestations has followed the withdrawal of tryptophan, but in some patients the disease has progressed despite withdrawal and there have been fatalities.[5-7] The inflammatory condition has necessitated the use of corticosteroids in some patients.

The eosinophilia-myalgia syndrome has been reported in patients taking both tryptophan-containing prescription products for depression and non-prescription dietary supplements for a number of disorders including insomnia, the premenstrual syndrome, and stress; it does not appear to have occurred in patients receiving amino-acid preparations containing tryptophan as part of total parenteral nutrition regimens. The recognition of this syndrome led to the withdrawal of tryptophan-containing products or severe restrictions being imposed upon their use in many countries during 1990.

Various theories were proposed as to the reason for the association of tryptophan with this syndrome. Confusion existed because the reports implicated a very wide range of products from different manufacturers. However, later evidence appeared to have confirmed that contaminated tryptophan had originated from a single manufacturer in Japan.[8-10] Bulk tryptophan was imported from Japan for manufacture into finished pharmaceutical dosage forms and it was noted in one of these reports[9] that a single product was often found to contain two or more lots of powdered tryptophan that were blended together during the production of tablets or capsules. Many trace contaminants have been found in batches of tryptophan associated with the syndrome.[11] One contaminant has been identified as 1,1′-ethylidenebis(tryptophan).[12] Its inclusion in bulk tryptophan powder appeared to coincide with alterations in the manufacturing conditions that involved a change in the strain of *Bacillus amyloliquefaciens* used in the fermentation process and a reduction in the amount of charcoal used for purification.[9] Other investigations indicated the presence of bacitracin-like peptides in batches of the contaminated tryptophan.[13] However, further work[14] has provided only weak support for an association between the syndrome and any one particular contaminant and the causative agent remains to be confirmed. Nonetheless, since the syndrome only appeared to be associated with tryptophan from one manufacturer, tryptophan preparations were reintroduced in the UK in 1994 for restricted use under carefully monitored conditions.[15] In January 2005, the UK requirement for patient registration and monitoring was removed.

1. Anonymous. Eosinophilia-myalgia syndrome—New Mexico. *MMWR* 1989; **38:** 765–7.
2. Troy JL. Eosinophilia-myalgia syndrome. *Mayo Clin Proc* 1991; **66:** 535–8.
3. Milburn DS, Myers CW. Tryptophan toxicity: a pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP Ann Pharmacother* 1991; **25:** 1259–62.
4. Kilbourne EM, *et al.* Interim guidance on the eosinophilia-myalgia syndrome. *Ann Intern Med* 1990; **112:** 85–6.
5. Anonymous. Eosinophilia-myalgia syndrome associated with ingestion of -tryptophan—United States, through August 24, 1990. *JAMA* 1990; **264:** 1655.
6. Kaufman LD, *et al.* Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. *Lancet* 1991; **337:** 1071–4.
7. Hertzman PA, *et al.* The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. *Ann Intern Med* 1995; **122:** 851–5.
8. Slutsker L, *et al.* Eosinophilia-myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; **264:** 213–17.
9. Belongia EA, *et al.* An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990; **323:** 357–65.
10. Varga J, *et al.* The cause and pathogenesis of the eosinophilia-myalgia syndrome. *Ann Intern Med* 1992; **116**: 140–7.
11. Hill RH, *et al.* Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch Environ Contam Toxicol* 1993; **25:** 134–42.
12. Mayeno AN, *et al.* Characterization of "peak E", a novel amino acid associated with eosinophilia-myalgia syndrome. *Science* 1990; **250:** 1707–8.
13. Barnhart ER, *et al.* Bacitracin-associated peptides and contaminated -tryptophan. *Lancet* 1990; **336:** 742.
14. Philen RM, *et al.* Tryptophan contaminants associated with eosinophilia-myalgia syndrome. *Am J Epidemiol* 1993; **138:** 154–9.
15. CSM/MCA. L-Tryptophan (Optimax): limited availability for resistant depression. *Current Problems* 1994; **20:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Precautions

Tryptophan has been associated with eosinophilia-myalgia syndrome (see above); caution is advised in patients receiving the drug who develop some, but not all, of the symptoms of this syndrome. It should not be used in those with a history of eosinophilia-myalgia syndrome associated with tryptophan treatment.

Patients taking tryptophan may experience drowsiness and, if affected, they should not drive or operate machinery. For further details of the effects of antidepressant therapy on driving see under Amitriptyline, p.379.

Abnormal metabolism of tryptophan may occur in patients with pyridoxine deficiency and tryptophan is thus sometimes given with pyridoxine supplements.

Interactions

Although tryptophan has been given to patients receiving MAOIs in the belief that clinical efficacy may be improved, it should be noted that the adverse effects may also be potentiated. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Use of tryptophan with drugs that inhibit the reuptake of serotonin may exacerbate the adverse effects of the latter and precipitate the serotonin syndrome (p.416).

There have been occasional reports of sexual disinhibition in patients taking tryptophan with phenothiazines or benzodiazepines.

For a report of tryptophan reducing blood concentrations of levodopa, see Nutritional Agents under Interactions of Levodopa, p.808.

Pharmacokinetics

Tryptophan is readily absorbed from the gastrointestinal tract. Tryptophan is extensively bound to plasma albumin. It is metabolised in the liver by tryptophan pyrrolase and tryptophan hydroxylase. Metabolites include hydroxytryptophan, which is then converted to serotonin, and kynurenine derivatives. Some tryptophan is converted to nicotinic acid and nicotinamide. Pyridoxine and ascorbic acid are cofactors in the decarboxylation and hydroxylation, respectively, of tryptophan; pyridoxine apparently prevents the accumulation of the kynurenine metabolites.

◊ References.

1. Green AR, *et al.* The pharmacokinetics of -tryptophan following its intravenous and oral administration. *Br J Clin Pharmacol* 1985; **20:** 317–21.

Uses and Administration

Tryptophan is an amino acid that is an essential constituent of the diet. Tryptophan and DL-tryptophan have been used as dietary supplements.

Tryptophan is a precursor of serotonin. Because CNS depletion of serotonin is considered to be involved in depression, tryptophan has been used in its treatment. Although it has been given alone, evidence of effectiveness is scant and tryptophan has generally been used as adjunctive therapy in depression. It has sometimes been given with pyridoxine and ascorbic acid, which are involved in its metabolism to serotonin (see Pharmacokinetics, above).

In many countries preparations containing tryptophan have either been withdrawn from the market or their availability severely restricted or limited because of its association with the eosinophilia-myalgia syndrome. In the UK, tryptophan is restricted to use as an adjunct to other antidepressant medication or in patients who have failed to respond to an adequate trial of standard antidepressant drug treatment. Therapy should be started by hospital specialists; thereafter tryptophan may be prescribed in the community.

In the treatment of depression the usual oral dose of tryptophan is 1 g given three times daily, but some patients may require up to 6 g daily in divided doses. Lower doses may be required in the elderly especially those with renal or hepatic impairment.

Depression. Evidence of benefit for tryptophan when given alone for depression (p.373) is lacking, though there is some suggestion of a weak antidepressant effect.[1] It has therefore mainly been used with other antidepressants in the belief that it would potentiate their effects. Although beneficial effects have been reported in some patients given tryptophan with SSRIs, tricyclic antidepressants, or MAOIs, either alone or with lithium, evidence of efficacy is mainly limited to case reports and small controlled studies.[2-4]

After the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, above) preparations containing tryptophan for depression were withdrawn from the market or their use restricted. For details of UK restrictions see Uses and Administration, above.

1. Shaw K, *et al.* Tryptophan and 5-hydroxytryptophan for depression. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/11/05).
2. Barker WA, *et al.* The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol* 1987; **2:** 261–72.
3. Smith S. Tryptophan in the treatment of resistant depression—a review. *Pharm J* 1998; **261:** 819–21.
4. Levitan RD, *et al.* Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J Psychiatry Neurosci* 2000; **25:** 337–46.

Dietary supplementation. The use of tryptophan as a dietary supplement has been reviewed.[1] However, because of its association with the eosinophilia-myalgia syndrome (see under Adverse Effects, above), the addition of tryptophan to food intended for human consumption is prohibited in some countries.

1. Li Wan Po A, Maguire T. Tryptophan: useful dietary supplement or a health hazard? *Pharm J* 1990; **244:** 484–5.

Insomnia. Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity for the treatment of insomnia (p.957). However, in comparison with other hypnotics such as the benzodiazepines, the effects of tryptophan have been difficult to substantiate, and enthusiasm for tryptophan has waned considerably amongst sleep researchers.[1] It should also be noted that since the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, above) preparations indicated for insomnia have been withdrawn from the market in many countries.

1. Lahmeyer HW. Tryptophan for insomnia. *JAMA* 1989; **262:** 2748.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Kalma; ***Canad.:*** Tryptan; ***Ger.:*** Ardeydorm; Ardeytropin; Kalma; ***UK:*** Optimax.

Multi-ingredient: ***Fr.:*** Vita-Dermacide; ***Ital.:*** Brioplus; Fisioreve; ***USA:*** PDP Liquid Protein.

Venlafaxine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de venlafaxina; Venlafaxine, chlorhydrate de; Venlafaxin-hydrochlorid; Venlafaxini hydrochloridum; Venlafaxinum hydrochloridum; Wenlafaksyny chlorowodorek; Wy-45030. (*RS*)-1-(2-Dimethylamino-1-*p*-methoxyphenylethyl)cyclohexanol hydrochloride.

Венлафаксина Гидрохлорид

$C_{17}H_{27}NO_2$,HCl = 313.9.
CAS — 93413-69-5 (venlafaxine); 99300-78-4 (venlafaxine hydrochloride).
ATC — N06AX16.
ATC Vet — QN06AX16.

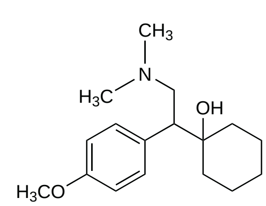

(venlafaxine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Venlafaxine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; slightly soluble or practically insoluble in acetone.

Adverse Effects and Treatment

Adverse effects that have been reported most frequently with venlafaxine include nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, sexual dysfunction, asthenia, sweating, and nervousness. Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain, anxiety, urinary frequency, visual disturbances, mydriasis, vasodilatation, vomiting, tremor, paraesthesia, hypertonia, chills or fever, palpitations, weight gain or loss, increased serum-cholesterol, agitation, abnormal dreams, confusion, arthralgia, myalgia, tinnitus, pruritus, dyspnoea, yawning, and skin rashes. Dose-related increases in blood pressure have also been observed in some patients.

Less common effects have included reversible increases in liver enzymes, orthostatic hypotension, syncope, arrhythmias, tachycardia, mucous membrane bleeding, ecchymosis, hallucinations, bruxism, muscle spasm, myoclonus, alopecia, altered taste, urinary retention, menorrhagia, angioedema, and photosensitivity reactions.

Convulsions, galactorrhoea, haemorrhage including gastrointestinal bleeding, anaphylaxis, hepatitis, erythema multiforme, Stevens-Johnson syndrome, ataxia, dysarthria, extrapyramidal disorders including psychomotor restlessness and akathisia, and activation of mania or hypomania have been reported rarely. Other rare adverse effects include blood dyscrasias such as agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, and thrombocytopenia, prolongation of the QT interval and torsade de pointes, ventricular tachycardia or fibrillation, rhabdomyolysis, delirium, pancreatitis, and pulmonary eosinophilia.

Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. Suicidal ideation has been reported, particularly in children (see under Effects on Mental State, below).

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, symptoms such as sweating, dizziness, somnolence, ECG changes, cardiac arrhythmias, and seizures may be noted. Treatment of overdosage includes consideration of the use of activated charcoal if more than 12.5 mg/kg has been ingested and the patient presents within 1 hour; this should be followed by symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Effects on the endocrine system. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatraemia may be more likely to occur with serotonergic antidepressants such as venlafaxine than with other antidepressants; for further details, see under Fluoxetine p.392.

Effects on the eyes. Acute angle-closure glaucoma developed in a 45-year-old woman 3 days after starting venlafaxine;[1] she recovered after iridotomy. In another case, a 35-year-old man presented with bilateral acute angle-closure glaucoma 10 days after starting venlafaxine.[2] The patient had also experienced visual disturbances while on mirtazapine and sertraline.

1. Ng B, *et al.* Venlafaxine and bilateral acute angle closure glaucoma. *Med J Aust* 2002; **176:** 241.
2. de Guzman MHP, *et al.* Bilateral acute angle closure caused by supraciliary effusions associated with venlafaxine intake. *Med J Aust* 2005; **182:** 121–2.

Effects on the hair. Hair loss has been described in 3 women given venlafaxine. The effect was noticed by the patients within a few weeks[1] to 5 months[2] after starting treatment. One patient who noticed hair loss within 1 week of starting venlafaxine had experienced the same problem during previous fluoxetine treatment.[3] In all 3 cases, hair loss abated soon after stopping venlafaxine. In 2 cases hair regrowth was reported within a few weeks,[2,3] but the third report was unclear as to whether regrowth occurred.[1]

1. Pitchot W, Ansseau M. Venlafaxine-induced hair loss. *Am J Psychiatry* 2001; **158:** 1159–60.
2. Pereira CE, Goldman-Levine JD. Extended-release venlafaxine-induced alopecia. *Ann Pharmacother* 2007; **41:** 1084.
3. O'Bryan EC, Albanese RP. A case report of fluoxetine- and venlafaxine-induced hair loss. *Prim Care Companion J Clin Psychiatry* 2004; **6:** 181.

Effects on the liver. Acute hepatitis developed in a 44-year-old woman about 6 months after starting venlafaxine;[1] she recovered once venlafaxine was withdrawn. In another report,[2] acute hepatitis developed in a 78-year-old man about a month after venlafaxine was added to therapy. Again, symptoms resolved when the drug was stopped. Hepatitis was noted in a 60-year-old woman about a month after starting low-dose venlafaxine (75 mg daily); symptoms resolved when the drug was stopped and recurred on rechallenge.[3] Hepatitis has also been attributed to low-dose venlafaxine (37.5 mg daily) in a patient with chronic hepatitis B; other causes of hepatitis and relapse of viral hepatitis were excluded.[4]

For a report of hepatotoxicity in patients taking venlafaxine subsequent to an attempted overdose with sertraline, see p.392.

1. Horsmans Y, *et al.* Venlaxafine-associated [sic] hepatitis. *Ann Intern Med* 1999; **130:** 944.
2. Cardona X, *et al.* Venlafaxine-associated hepatitis. *Ann Intern Med* 2000; **132:** 417.
3. Phillips BB, *et al.* Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. *Ann Pharmacother* 2006; **40:** 323–7.
4. Sencan I, *et al.* Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. *Ann Pharmacother* 2004; **38:** 352–3.

Effects on mental state. An expert working group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs and, in particular, the risk of suicidal behaviour in children; the safety of venlafaxine (another serotonergic antidepressant) was also considered. An interim report issued in September 2003 concluded that data from trials received by the CSM failed to show that venlafaxine was effective in the treatment of depressive illness in **children under 18 years old** and indicated that the risk of harmful outcome including self-harm and suicidal ideation was increased in those receiving venlafaxine when compared with placebo.[1] The CSM recommended that venlafaxine should not be used to treat depressive illness in children under 18 years old. Similar warnings have also been issued in Canada,[2] the EU,[3] and the USA. (The final report[4] of the CSM's expert working group was published in December 2004.)

The risk of suicide and suicide-related events with antidepressant treatment in **adults** including young adults is discussed under Fluoxetine, p.392.

1. MHRA. Safety of venlafaxine in children and adolescents under 18 years in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 19th September, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019501.pdf (accessed 14/08/08)
2. Wyeth Canada. Important safety information regarding the use of Effexor (venlafaxine HCl) tablets and Effexor XR (venlafaxine HCl) capsules in children and adolescents (issued 10th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/effexor_hpc-cps-eng.pdf (accessed 14/08/08)
3. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)
4. Weller IVD. *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Effects on the skin. Stevens-Johnson syndrome developed in a patient 12 days after beginning treatment with venlafaxine for recurrent depression.[1] She had also been taking several other drugs for at least 6 months. Symptoms resolved on withdrawal of all medication and treatment with an intravenous corticosteroid.

1. Weiss NT, *et al.* A possible case of venlafaxine-induced Stevens-Johnson syndrome. *J Clin Psychiatry* 2004; **65:** 1431–3.

Overdosage. Rare serious events including seizures and ECG changes[1-3] have occurred after venlafaxine overdoses; in some cases, death has ensued.[4,5] Symptoms suggestive of serotonin toxicity may also develop.[6,7]

Venlafaxine may not be as safe in overdose as some other serotonergic antidepressants. A review[8] of UK data recording the number of deaths due to acute poisoning by a single drug, with or without alcohol, found the number of fatalities per million prescriptions (the fatal toxicity index) was higher for venlafaxine than for other serotonergic antidepressants, and was similar to that for some of the less toxic tricyclic antidepressants.

1. White CM, *et al.* Seizure resulting from a venlafaxine overdose. *Ann Pharmacother* 1997; **31:** 178–80.
2. Coorey AN, Wenck DJ. Venlafaxine overdose. *Med J Aust* 1998; **168:** 523.
3. Blythe D, Hackett LP. Cardiovascular and neurological toxicity of venlafaxine. *Hum Exp Toxicol* 1999; **18:** 309–13.
4. Banham NDG. Fatal venlafaxine overdose. *Med J Aust* 1998; **169:** 445, 448.
5. Mazur JE, *et al.* Fatality related to a 30-g venlafaxine overdose. *Pharmacotherapy* 2003; **23:** 1668–72.
6. Oliver JJ, *et al.* Venlafaxine poisoning complicated by a late rise in creatine kinase: two case reports. *Hum Exp Toxicol* 2002; **21:** 463–6.
7. Whyte IM, *et al.* Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 2003; **96:** 369–74.
8. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002; **325:** 1332–3.

Serotonin syndrome. The serotonin syndrome (p.416) is most often due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug may cause the syndrome. One such case[1] was reported to have occurred in a 29-year-old woman who developed symptoms suggestive of serotonin syndrome 3 days after starting low-dose venlafaxine. However, this patient had been switched to venlafaxine the day after stopping imipramine treatment; it is usually recommended that at least 3 weeks should elapse after stopping imipramine before starting another drug with serotonergic properties.

1. Pan J-J, Shen WW. Serotonin syndrome induced by low-dose venlafaxine. *Ann Pharmacother* 2003; **37:** 209–11.

Precautions

Venlafaxine should not be used in patients with an identified very high risk of a serious ventricular arrhythmia or uncontrolled hypertension. Caution is advised in those with a recent history of myocardial infarction or whose condition might be exacerbated by an increase in heart rate. Due to the risk of dose-related increases in blood pressure, blood pressure measurement should be performed regularly during therapy. Measurement of serum-cholesterol levels should also be considered with long-term treatment.

Venlafaxine should be used with caution in patients with moderate to severe hepatic or renal impairment and dosage adjustment may be necessary. It should also be used with caution in patients with a history of epilepsy and avoided in those with unstable disease; it should be stopped in any patient developing a seizure or if there is an increase in seizure frequency. Caution is also advised in patients with a history of bleeding disorders or of hypomania or mania. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Patients who develop a rash, urticaria, or related allergic reaction with venlafaxine should be advised to contact their doctor.

Patients should be closely monitored during early antidepressant therapy until a significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, venlafaxine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery. Patients, especially the elderly, should be warned of the risk of dizziness or unsteadiness due to orthostatic hypotension.

Symptoms reported on abrupt withdrawal or dose reduction of venlafaxine include fatigue, somnolence, headache, nausea, vomiting, anorexia, palpitations, dizziness, dry mouth, diarrhoea, insomnia, agitation, anxiety, nervousness, confusion, hypomania, paraesthesia, sweating, and vertigo. It is therefore recommended that venlafaxine should be withdrawn gradually over at least one week after more than one week's therapy; patients receiving high-dose venlafaxine for longer than 6 weeks should be tapered over at least 2 weeks. All patients should also be monitored to minimise the risk of withdrawal reactions.

Abuse. A patient had an amfetamine-like "high" after taking crushed modified-release tablets of venlafaxine in doses of up to 3600 mg daily.[1] He continued to ingest increasing amounts of venlafaxine until a 4050-mg dose produced chest pain. On evaluation he had a raised pulse and blood pressure but these returned to normal within a few days.

1. Sattar SP, *et al.* A case of venlafaxine abuse. *N Engl J Med* 2003; **348:** 764–5.

Breast feeding. Licensed product information recommends that venlafaxine should not be used in women who are breast feeding.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine were both detected in breast milk in significant quantities in 3 women;[1] there were also measurable concentrations of desmethylvenlafaxine in the infants' plasma. In another study[2] by the same group the mean milk-to-plasma ratio in 6 breast-feeding women was calculated to be 2.5 for venlafaxine and 2.74 for *O*-desmethylvenlafaxine. Detectable plasma concentrations of venlafaxine were found only in 1 of 7 breast-fed infants while 4 had detectable *O*-desmethylvenlafaxine levels; no adverse effects were reported in the infants. Nonetheless, the authors recommended caution when giving venlafaxine to breast-feeding women particularly for those feeding premature or very young neonates. The distribution of venlafaxine into breast milk and the presence of *O*-desmethylvenlafaxine in the serum of a further 5 breast-fed infants has also been reported.[3,4] There were no detectable adverse effects in the infants, and the authors of 1 report[4] suggested that women being treated for postpartum depression should not be generally discouraged from breast feeding. It has been suggested that venlafaxine in breast milk might alleviate a withdrawal syndrome in the neonate (see Pregnancy, below).

1. Ilett KF, *et al.* Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998; **45:** 459–62.
2. Ilett KF, *et al.* Distribution of venlafaxine and its *O*-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 2002; **53:** 17–22.
3. Hendrick V, *et al.* Venlafaxine and breast-feeding. *Am J Psychiatry* 2001; **158:** 2089–90.
4. Berle JØ, *et al.* Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes. *J Clin Psychiatry* 2004; **65:** 1228–34.

Children. Venlafaxine is associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, above.

US licensed product information also refers to studies that suggest that venlafaxine may adversely affect weight and height changes in children. In particular, the difference between the observed and the expected growth rate was larger for those children under 12 years of age than for older children.

Pregnancy. Licensed product information recommends that venlafaxine should not be used during pregnancy unless clearly necessary.

In a study of 150 women who took venlafaxine in the first trimester of pregnancy there were 125 live births, 18 spontaneous abortions, 7 therapeutic abortions, and 2 reports of major malformations (hypospadias and neural tube defect with club foot).[1] Although the rate of spontaneous abortions was non-significantly higher in the venlafaxine group than in historical controls, the rate of major malformations was not greater than the baseline rate of 1 to 3%.

A neonatal withdrawal syndrome developed in the infant of a mother who had taken venlafaxine throughout her pregnancy;[2] symptoms included restlessness, hypertonia, irritability, and poor feeding. The infant recovered within 8 days. Seizures have been described in 2 neonates whose mothers were taking venlafaxine.[3] Lip smacking and extensor limb posturing began at 30 minutes of age in 1 case, and multifocal myoclonic seizures occurred at 24 hours of age in the other; both recovered and were well at 1 year of age. Serum-venlafaxine concentrations had not been measured and the authors were unsure whether the adverse effects in the neonates were due to withdrawal or toxicity. In a retrospective study[4] of women who had taken SSRIs or venlafaxine during the third trimester (9 had taken venlafaxine), there were reports of adverse effects on the CNS and respiratory tract in the neonates, such as abnormal movements, tonus abnormalities, irritability, insomnia, indrawing, apnoea/bradycardia, and tachypnoea. The signs usually appeared on the first day of life and lasted for about 3 days in full-term neonates and about 5 days in those born prematurely.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine are distributed into breast milk (see Breast Feeding, above), and it has been suggested that breast feeding might have helped to alleviate symptoms of a withdrawal syndrome in a neonate whose mother took venlafaxine throughout her pregnancy.[5]

1. Einarson A, *et al.* Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001; **158:** 1728–30.
2. de Moor RA, *et al.* Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy. *Ned Tijdschr Geneeskd* 2003; **147:** 1370–2.
3. Pakalapati RK, *et al.* Neonatal seizures from in utero venlafaxine exposure. *J Paediatr Child Health* 2006; **42:** 737–8.
4. Ferreira E, *et al.* Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007; **119:** 52–9.
5. Koren G, *et al.* Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome? *J Obstet Gynaecol Can* 2006; **28:** 299–301.

Renal impairment. The mean terminal disposition half-life of venlafaxine was prolonged from a mean of 3.8 hours in 18 healthy subjects to 5.8 hours in 12 patients with mild to moderate renal impairment (creatinine clearance 10 to 70 mL/minute) and 10.6 hours in patients requiring haemodialysis;[1] corresponding values for *O*-desmethylvenlafaxine, the active major metabolite of venlafaxine, were 11.8, 16.8, and 28.5 hours, respectively. Because of the large intersubject variability, the change in disposition for venlafaxine and its active metabolite was evident only in patients with a creatinine clearance of less than 30 mL/minute; drug clearance in these patients was reduced by about 55% and half-life more than doubled. It was calculated that for these patients half the usual daily dose could be given once daily.

Similar recommendations are made in licensed drug information, see under Uses and Administration, below.

1. Troy SM, *et al.* The effect of renal disease on the disposition of venlafaxine. *Clin Pharmacol Ther* 1994; **56:** 14–21.

Surgery. Serotonergic antidepressants such as venlafaxine may be associated with an increased risk of blood loss during surgery; for further details, see under Fluoxetine, p.396.

Withdrawal. Withdrawal reactions may be more common with venlafaxine than with some other serotonergic antidepressants; for further details, see under Fluoxetine, p.396. Withdrawal reactions may also be seen in neonates after maternal venlafaxine use, see under Pregnancy above.

Some cases[1,2] of withdrawal reactions to venlafaxine have been reported.

1. Anonymous. Venlafaxine withdrawal reactions. *Med J Aust* 1998; **169:** 91–2.
2. Johnson H, *et al.* Withdrawal reaction associated with venlafaxine. *BMJ* 1998; **317:** 787.

Interactions

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the *serotonin syndrome* (see p.416) may occur. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. Venlafaxine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with venlafaxine. At least 7 days should elapse between stopping venlafaxine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). For further details, see Antidepressants under Interactions of Phenelzine, p.418. Adverse effects such as the serotonin syndrome may also occur when venlafaxine is given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Venlafaxine has occasionally been associated with bleeding disorders and other effects on the blood; caution is advised when giving venlafaxine with other drugs known to affect platelet function.

Although cimetidine inhibits the first-pass hepatic metabolism of venlafaxine, it has no effect on the active metabolite *O*-desmethylvenlafaxine, which is present in the plasma in much greater concentrations. Licensed product information therefore considers that when cimetidine and venlafaxine are used together, clinical monitoring may only be necessary in elderly patients and in those with hepatic impairment or pre-existing hypertension.

◊ Conversion of venlafaxine to its equally active metabolite *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore the potential exists for drugs that inhibit or act as a substrate for this enzyme to affect plasma concentrations of venlafaxine and its active metabolite. However, the US product information indicates that, as the total amount of active compounds is unaffected, no dosage adjustment is usually necessary for venlafaxine. Venlafaxine is also metabolised by CYP3A4 to the less active metabolite *N*-desmethylvenlafaxine. This is a relatively minor pathway and the potential for clinically significant interactions between venlafaxine and CYP3A4 inhibitors is considered to be small. However, potent inhibitors of CYP3A4 or drugs that inhibit both CYP2D6 and CYP3A4 could significantly increase venlafaxine concentrations in patients who are poor CYP2D6 metabolisers; such combinations should therefore be used with caution.

Venlafaxine itself is considered to be a relatively weak inhibitor of CYP2D6.

Antiarrhythmics. Psychosis with raised serum concentrations of venlafaxine and its metabolite *O*-desmethylvenlafaxine developed when *propafenone* therapy was started in a 67-year-old woman. There was improvement when venlafaxine was stopped and restarted at a reduced dose; 50 mg daily was sufficient to maintain therapeutic serum concentrations.[1]

1. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* 2001; **31:** 427–32.

Antibacterials. Tingling in the tip of the tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhoea, cold sweats, and uncontrolled shivering and tremor occurred when *co-amoxiclav* was started in a man taking venlafaxine.[1] The reaction lasted for about 6 hours. It occurred again 2 months later after a single dose of co-amoxiclav. The patient reported that he had taken co-amoxiclav in the past without any reaction at a time when he was not taking venlafaxine. The mechanism for an interaction between venlafaxine and co-amoxiclav causing this serotonin syndrome is unknown. The author also suggested that many patients must have taken this combination without adverse effect, and found no other reports.

Serotonin syndrome has been reported in an elderly patient taking venlafaxine, after 20 days of antibacterial treatment including *linezolid*.[2] In another report, serotonin syndrome developed 8 days after starting treatment with intravenous linezolid in a patient taking venlafaxine.[3]

1. Connor H. Serotonin syndrome after single doses of co-amoxiclav during treatment with venlafaxine. *J R Soc Med* 2003; **96:** 233–4.
2. Jones SL, *et al.* Serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* 2004; **54:** 289–90.
3. Bergeron L, *et al.* Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* 2005; **39:** 956–61.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p.626).

Antipsychotics. For mention of neuroleptic malignant syndrome developing in patients who received venlafaxine with antipsychotics see under Interactions in Chlorpromazine, p.974.

Gastrointestinal drugs. Signs suggestive of the serotonin syndrome that occurred after intravenous *metoclopramide* were attributed to an interaction with venlafaxine.[1] The 32-year-old woman experienced confusion, agitation, generalised shaking, myoclonus, facial twitching, diaphoresis, horizontal nystagmus, and dilated pupils, that resolved within 2 days after stopping both drugs and treatment with diazepam.

1. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

Selegiline. Although it is generally recommended that venlafaxine should not be started for at least 14 days after stopping an MAOI, there is a report[1] of serotonin syndrome developing when a patient began venlafaxine treatment 15 days after stopping selegiline, an MAO type B inhibitor.

1. Gitlin MJ. Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J Clin Psychopharmacol* 1997; **17:** 66–7.

Pharmacokinetics

Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first-pass metabolism in the liver mainly to the active metabolite *O*-desmethylvenlafaxine; formation of *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. The isoenzyme CYP3A4 is also involved in the metabolism of venlafaxine. Other metabolites include *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine. Peak plasma concentrations of venlafaxine and *O*-desmethylvenlafaxine appear about 2 and 4 hours after a dose, respectively. Venlafaxine is 27% and *O*-desmethylvenlafaxine 30% bound to plasma proteins. The mean elimination half-life of venlafaxine and *O*-desmethylvenlafaxine is about 5 and 11 hours, respectively. Venlafaxine is excreted mainly in the urine, mainly in the form of its metabolites, either free or in conjugated form; about 2% is excreted in the faeces. Venlafaxine and *O*-desmethylvenlafaxine have been detected in amniotic fluid and umbilical cord blood, and are distributed into breast milk.

◊ References.

1. Troy SM, *et al.* The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995; **35:** 404–9.
2. Troy SM, *et al.* Pharmacokinetics and effect of food on the bioavailability of orally administered venlafaxine. *J Clin Pharmacol* 1997; **37:** 954–61.
3. Ball SE, *et al.* Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol* 1997; **43:** 619–26.

Pregnancy. Venlafaxine and its metabolite, *O*-desmethylvenlafaxine, have been detected in amniotic fluid[1,2] and umbilical cord blood.[1,3] For adverse effects that have occurred in neonates of women who were taking venlafaxine during the third trimester, see Pregnancy, under Precautions, above.

1. Hostetter A, *et al.* Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry* 2000; **48:** 1032–4.

2. Loughhead AM, *et al.* Antidepressants in amniotic fluid: another route of fetal exposure. *Am J Psychiatry* 2006; **163:** 145–7.
3. Rampono J, *et al.* A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol* 2004; **7:** 329–34.

Uses and Administration

Venlafaxine, a phenylethylamine derivative, is a serotonin and noradrenaline reuptake inhibitor (SNRI); it also weakly inhibits dopamine reuptake. It is reported to have little affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Venlafaxine is given orally as the hydrochloride although doses are expressed in terms of the base; venlafaxine hydrochloride 28.3 mg is equivalent to about 25 mg of venlafaxine.

Venlafaxine is used in the treatment of **depression**. The initial daily dose is equivalent to venlafaxine 75 mg in two or three divided doses with food. In the USA, it is suggested that some patients may be best started on 37.5 mg daily for the first 4 to 7 days before increasing the dose to 75 mg daily. The dose may be increased, if necessary, after several weeks to 150 mg daily. Further increases, to a maximum daily dose of 375 mg, may be made in increments of up to 75 mg at intervals of at least 2 to 4 days. Such doses may be required in severely depressed or hospitalised patients and should be gradually reduced to the minimum effective dose. Modified-release preparations are available for once-daily dosing.

Venlafaxine is also used, as a modified-release preparation, in the treatment of **generalised anxiety disorder**. The recommended initial dose is 75 mg once daily. In the USA it is suggested that some patients may be best begun with 37.5 mg daily for 4 to 7 days initially; dosage may subsequently be adjusted in increments of up to 75 mg, at intervals of at least 4 days, to a maximum of 225 mg daily. Venlafaxine should be withdrawn gradually if there is no response after 8 weeks.

In the USA, modified-release venlafaxine is licensed for the treatment of **social anxiety disorder** in doses similar to those used for generalised anxiety disorder. It is also licensed in the USA for **panic disorder** with or without agoraphobia in doses of 37.5 mg once daily for the first 7 days, then increasing to 75 mg daily. Subsequent increases in increments of up to 75 mg may be made at intervals of at least 7 days, to a maximum dose of 225 mg daily.

Reduced doses may need to be given in hepatic or renal impairment, see below.

Venlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, above).

Administration in hepatic impairment. UK licensed product information considers that patients with mild hepatic impairment do not require a change in dose of venlafaxine. For those with moderate impairment, the dose should be reduced by half and given once daily. There are insufficient data to make any recommendations for patients with severe impairment.

Administration in renal impairment. The UK licensed product information states that, based on glomerular filtration rate (GFR), patients with mild renal impairment (GFR above 30 mL/minute) do not require a change in dose of venlafaxine. For those with moderate impairment (GFR 10 to 30 mL/minute), the dose should be reduced by 50% and once-daily dosage may be appropriate. There are insufficient data to make any recommendations for patients with severe impairment (GFR less than 10 mL/minute).

In the USA, it is recommended that patients with a GFR of 10 to 70 mL/minute reduce the dose of immediate-release venlafaxine by 25% and of modified-release venlafaxine by 25 to 50%; regardless of preparation, in those undergoing haemodialysis, the dose should be reduced by 50% and withheld until the dialysis is completed.

Anxiety disorders. Venlafaxine is used in the treatment of generalised anxiety disorder and social anxiety disorder (see under Phobic Disorders, p.953); it may also be of use in a variety of other types of anxiety disorders (p.952) including the treatment of obsessive-compulsive disorder (p.952), panic disorder (p.952), and post-traumatic stress disorder (p.953).

References.

1. Altamura AC, *et al.* Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol* 1999; **14:** 239–45.
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14. Davidson J, *et al.* Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 2006; **63:** 1158–65.
15. Ferguson JM, *et al.* Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 2007; **68:** 58–68.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. In December 2004 the UK CSM recommended that, because of the risk of adverse cardiovascular effects and toxicity in overdosage (see above), venlafaxine treatment should be begun and maintained under specialist supervision only. After an assessment of further safety evidence, these restrictions were revised in May 2006 and specialist supervision was considered only necessary when starting venlafaxine treatment in severely depressed or hospitalised patients who require doses of 300 mg daily or above. However, it was also advised that venlafaxine should be considered a second-line treatment, after the SSRIs.

The *O*-desmethyl metabolite of venlafaxine, desvenlafaxine (p.388), is also used in depression.

References.

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4. Cohen LS, *et al.* Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry* 2001; **62:** 592–6.
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Hot flushes. For the reference to the use of venlafaxine in the treatment of hot flushes, see under Fluoxetine, p.398.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants; in open studies venlafaxine has been reported to be effective in both adults[1-3] and children[4,5] although in one study[4] some patients experienced a worsening of symptoms.

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4. Olvera RL, *et al.* An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol* 1996; **6:** 241–50.
5. Motavalli Mukaddes N, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci* 2004; **58:** 92–5.

Migraine. Retrospective analysis[1] in patients with tension-type headache (p.617) or migraine (p.616) indicated that venlafaxine, as a modified-release preparation, had potential for headache prophylaxis. A more recent randomised placebo-controlled study[2] also supports the use of modified-release venlafaxine in the prophylaxis of migraine.

1. Adelman LC, *et al.* Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. *Headache* 2000; **40:** 572–80.
2. Ozyalcin SN, *et al.* The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; **45:** 144–52.

Pain. Venlafaxine may be of benefit in the treatment of neuropathic pain syndromes (p.8)[1,2] including painful diabetic neuropathy (p.6).[3-5] It has also shown some promise in the treatment of fibromyalgia (see Soft-tissue Rheumatism, p.13).[6]

1. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. *Ann Pharmacother* 2001; **35:** 557–9.
2. Grothe DR, *et al.* Treatment of pain syndromes with venlafaxine. *Pharmacotherapy* 2004; **24:** 621–9.
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4. Kiayias JA, *et al.* Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. *Diabetes Care* 2000; **23:** 699.
5. Rowbotham MC, *et al.* Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004; **110:** 697–706. Correction. *ibid.* 2005; **113:** 248.
6. Sayar K, *et al.* Venlafaxine treatment of fibromyalgia. *Ann Pharmacother* 2003; **37:** 1561–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Efexor; Elafax; Ganavax; Mezine; Quilarex; Sesaren; ***Austral.:*** Efexor; ***Austria:*** Efectin; ***Belg.:*** Efexor; ***Braz.:*** Efexor; Venlaxin; Venlift; ***Canad.:*** Effexor; ***Chile:*** Depurol; Efexor; Nervix; Norpilen; Senexon; Sentidol; Sesaren; Subelan; Venlax; ***Cz.:*** Argofan; Convalemin; Efectin; Elify; Faxiprol; Lafaxon; Mollome; Olvexya; Velaxin; ***Denm.:*** Efexor; ***Fin.:*** Efexor; ***Fr.:*** Effexor; ***Ger.:*** Trevilor; ***Gr.:*** Arvifax; Efexor; ***Hong Kong:*** Efexor; ***Hung.:*** Efectin; Olwexya; Velaxin; ***India:*** Flavix; Venlor; Vexor; ***Indon.:*** Efexor; ***Irl.:*** Efexor; ***Israel:*** Efexor; Venla; Viepax; ***Ital.:*** Efexor; Faxine; ***Malaysia:*** Efexor; ***Mex.:*** Efexor; Odven SBK; ***Neth.:*** Efexor; ***Norw.:*** Efexor; ***NZ:*** Efexor; ***Philipp.:*** Efexor; ***Pol.:*** Efectin; Velafax; Velaxin; ***Port.:*** Desinax; Efexor; Genexin; Venxin; Xapnev; Zarelix; ***Rus.:*** Efevelone (Эфевелон); Velafax (Велафакс); Velaxin (Велаксин); ***S.Afr.:*** Efexor; Venlor; ***Singapore:*** Efexor; ***Spain:*** Dobupal; Vandral; ***Swed.:*** Efexor; ***Switz.:*** Efexor; ***Thai.:*** Efexor; ***Turk.:*** Efexor; ***UK:*** Efexor; ***USA:*** Effexor; ***Venez.:*** Efexor; Idoxen; Sesaren.

Viloxazine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de viloxazina; ICI-58834; Viloxazine, Chlorhydrate de; Viloxazini Hydrochloridum. 2-(2-Ethoxyphenoxymethyl)morpholine hydrochloride.

Вилоксазина Гидрохлорид

$C_{13}H_{19}NO_3,HCl = 273.8.$

CAS — 46817-91-8 (viloxazine); 35604-67-2 (viloxazine hydrochloride).

ATC — N06AX09.

ATC Vet — QN06AX09.

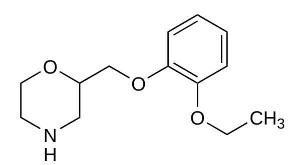

(viloxazine)

Profile

Viloxazine is a bicyclic antidepressant. Like the tricyclic antidepressants (see Amitriptyline, p.376), viloxazine is an inhibitor of the reuptake of noradrenaline; it may also enhance the release of serotonin from neuronal stores. However, it does not have marked antimuscarinic, cardiotoxic, or sedative properties.

Viloxazine is given for the treatment of depression (p.373) as the hydrochloride although doses are expressed in terms of viloxazine; viloxazine hydrochloride 57.7 mg is equivalent to about 50 mg of viloxazine. The usual oral dose is equivalent to viloxazine 200 to 300 mg daily in 2 or 3 divided doses. This may be increased, if necessary, to 600 mg daily as tolerated. The initial dose for the elderly or patients with hepatic or renal impairment is 100 mg daily cautiously increased if necessary. A modified-release preparation is also available for once daily use. Viloxazine hydrochloride has also been given by intravenous infusion.

Viloxazine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Porphyria. Viloxazine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Vivalan†; ***Cz.:*** Vivalan†; ***Fr.:*** Vivalan†; ***Ger.:*** Vivalan†; ***Port.:*** Vivalan†.

Antidiabetics

This chapter describes diabetes mellitus and its management with antidiabetics. The oral drugs included in this chapter are classified in Table 1, below. Insulin, which is given parenterally, is discussed on p.443 and classified in Table 2, p.444. The adjunct pramlintide given subcutaneously, is described on p.457, and the incretin mimetic, exenatide, on p.439.

Table 1. Classification of oral antidiabetics.

Aldose Reductase Inhibitors	*Sulfonylureas*
Epalrestat	Acetohexamide
Alpha-glucosidase Inhibitors	Carbutamide
Acarbose	Chlorpropamide
Miglitol	Glibenclamide
Voglibose	Glibornuride
	Gliclazide
Biguanides	Glimepiride
Buformin	Glipizide
Metformin	Gliquidone
Phenformin	Glisentide
Dipeptidylpeptidase-4 inhibitors	Glisolamide
Sitagliptin	Glisoxepide
Vildagliptin	Glycyclamide
Meglitinides	Tolazamide
Nateglinide	Tolbutamide
Repaglinide	*Thiazolidinediones*
Miscellaneous	Pioglitazone
Glybuzole	Rosiglitazone
Guar Gum	Troglitazone

Diabetes mellitus

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity, or a combination of both factors. It is characterised by hyperglycaemia. As the disease progresses tissue or vascular damage ensues leading to severe complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and foot ulceration.

Diabetes mellitus may be categorised into several types but the two major types are type 1 (insulin-dependent diabetes mellitus; IDDM) and type 2 (non-insulin-dependent diabetes mellitus; NIDDM). The term juvenile-onset diabetes has sometimes been used for type 1 and maturity-onset diabetes for type 2. Malnutrition-related diabetes is no longer considered a separate entity (see Effects of Cassava, under Adverse Effects of Starch, p.1968).

Type 1 diabetes mellitus is present in patients who have little or no endogenous insulin secretory capacity and who therefore require exogenous insulin therapy for survival. This form of the disease has an auto-immune basis in most cases, and usually develops before adulthood. The associated hypoinsulinaemia and hyperglucagonaemia put such patients at risk of ketosis and ketoacidosis.

In **type 2 diabetes mellitus** the disease typically develops in later life. Insulin secretion may appear normal or even excessive (and type 2 patients are thus less prone to ketosis) but it is insufficient to compensate for insulin resistance (p.449). Obesity is present in the majority of type 2 patients; non-obese patients tend to have low insulin secretory capacity (although not as low as in type 1 diabetes) rather than appreciable insulin resistance. It is closely associated with cardiovascular disease, and the 2 may arise from a common antecedent described as the metabolic syndrome.

Diagnosis of diabetes mellitus. Diagnosis is based upon blood-glucose concentrations exceeding set values under specified conditions.[1-4] Diagnostic values for measurements in venous whole blood are greater than or equal to 6.1 mmol/litre for the fasting state and 10.0 mmol/litre after a glucose load. The corresponding values for capillary whole blood are 6.1 and 11.1 mmol/litre, and for venous plasma 7.0 and 11.1 mmol/litre.[1] If there are accompanying symptoms of increased thirst and urine volume, recurrent infections and weight loss, then a plasma-glucose concentration in excess of 11.1 mmol/litre in a single random sample is considered diagnostic. If symptoms are absent, a fasting plasma-glucose of 7.0 mmol/litre or more, repeated on a subsequent day, can be used to confirm the diagnosis. Alternatively, diagnosis can be confirmed with the **oral glucose tolerance test** (OGTT). This test consists of an overnight fast followed by measurement of the fasting blood-glucose concentration, then the administration of a 75-g oral glucose load (in children 1.75 g/kg up to a maximum of 75 g), and further measurement of the blood-glucose concentration two hours later. There has been some confusion at an international level as to whether the glucose load should be 75 g of the anhydrous form or the monohydrate. Sources at WHO have therefore suggested that the form should be standardised as 75 g of anhydrous glucose (anhydrous dextrose), which would be equivalent to 82.5 g of the monohydrate (Glucose BP; dextrose monohydrate). The threshold for the diagnosis of diabetes was lowered in the late 1990s from an earlier fasting plasma glucose concentration of 7.8 mmol/litre,[5] to reflect an increased risk of microvascular disease in patients with concentrations of 7.0 mmol/litre or more. Patients with abnormal blood sugar who do not reach the defined threshold for overt diabetes may be considered to have impaired fasting glucose or impaired glucose tolerance.[6]

Measurement of glycosylated haemoglobin (HbA_{1c}) is not recommended for routine diagnosis.[6] Similarly, other indicators, such as measurement of autoantibodies (to insulin or islet cells, for example) are not routinely used for diagnosis.

Once the presence of diabetes has been confirmed the distinction between type 1 and type 2 is made on clinical grounds.

Management of diabetes mellitus.

- *DIETARY MODIFICATION.* Dietary control is important in both type 1 and type 2 diabetes.[6-10] The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease (see Diabetic Complications, below). Correction of obesity is desirable in all patients, and weight loss in patients with type 2 diabetes can decrease insulin resistance, improve glycaemic and lipid measures, and reduce blood pressure. Anorectic drugs are not appropriate in these patients,[11] although orlistat, a gastric and pancreatic lipase inhibitor, can be used as an adjunctive treatment to reduce weight and improve blood glucose control in overweight patients with type 2 diabetes.[12-14] A high fibre intake may also lower blood-glucose concentrations and additional fibre is sometimes taken in the form of guar gum (see p.443). The influence of diet on diabetes is such that all diabetic patients need to be aware of the composition of foods and to be able to make adjustments to their diet, especially to counteract treatment-induced hypoglycaemia. However, neither protein restriction nor very low calorie diets are recommended.
- *EXERCISE.* All diabetic patients should be encouraged to exercise, according to their age and physical capability.[5,6,8,10] Exercise improves carbohydrate metabolism, insulin sensitivity,[15,16] and cardiovascular function.[17] It is also a useful component of any weight reduction programme although diet may be more effective in promoting weight loss and metabolic control.[11]
- *ORAL ANTIDIABETICS.* If patients with type 2 diabetes have not achieved suitable control after about 3 months of dietary modification and increased physical activity, then oral antidiabetics (oral hypoglycaemics) may be tried. The two major classes are the *sulfonylureas* and the *biguanides.* Sulfonylureas act mainly by increasing endogenous insulin secretion, while biguanides act chiefly by decreasing hepatic gluconeogenesis and increasing peripheral utilisation of glucose. Both types function only in the presence of some endogenous insulin production. More recently developed classes of oral antidiabetics include the *alpha-glucosidase inhibitors,* the *meglitinides,* and the *thiazolidinediones* (see Table 1, above). Alpha-glucosidase inhibitors act by delaying the absorption of glucose from the gastrointestinal tract; meglitinides increase endogenous insulin secretion; and thiazolidinediones appear to increase insulin sensitivity.

  Most patients with type 2 diabetes are overweight, and are preferably treated with the biguanide metformin rather than with a sulfonylurea (which can cause weight gain). Results from the UK Prospective Diabetes Study (UKPDS) have suggested that the use of metformin to provide intensive blood-glucose control in overweight diabetic patients substantially reduced the risk of diabetes-related end-points such as myocardial infarction, stroke, amputation, renal failure, blindness, and death.[18] Metformin is as effective as the sulfonylureas in terms of blood-glucose control and is less likely to cause hypoglycaemia,[18] but has a rare tendency to cause lactic acidosis in patients with renal impairment, in whom it should not be used.

  Oral treatment of type 2 diabetes in patients who are not overweight may be begun with a sulfonylurea. Chlorpropamide and glibenclamide have long half-lives and hence an increased tendency to cause hypoglycaemia, although a large study[19] reported that hypoglycaemic episodes were less frequent with chlorpropamide than glibenclamide. These 2 drugs are best avoided in the elderly; a sulfonylurea with a short half-life, such as gliclazide or tolbutamide, should be used instead.

  There is evidence that the use of low-dose sulfonylurea therapy in patients with diagnosed type 2 diabetes but near-normoglycaemia due to early remission (the so-called honeymoon period) can delay the onset of hyperglycaemia.[20]

  Drug treatment may also involve an alpha-glucosidase inhibitor such as acarbose or miglitol.[21] These have a small but significant effect in lowering blood glucose and do not cause hypoglycaemia when used alone, but they can cause intolerable gastrointestinal effects. Meglitinides such as repaglinide and nateglinide are a new chemical class of antidiabetics which act similarly to sulfonylureas; repaglinide has a rapid onset and short duration of action and is given with meals. The thiazolidinediones, such as pioglitazone or rosiglitazone, appear to increase insulin sensitivity and have been the subject of much interest for type 2 diabetes and insulin resistance.

  Should treatment with one of the oral antidiabetics fail then a different type or in some instances combinations of different types may produce improvement. Alarming evidence[18] of an increased risk of death in UKPDS patients given intensive therapy with metformin plus a sulfonylurea was not borne out by further analysis, and this combination is widely used. In patients in whom such combinations fail or are contra-indicated, pioglitazone or rosiglitazone may be combined with metformin or a sulfonylurea as an alternative to progressing to insulin. Triple therapy, combining a sulfonylurea, metformin, and either rosiglitazone[22] or pioglitazone[23] has also been shown to be effective. Biguanides may also be added to meglitinide therapy. Alpha-glucosidase inhibitors may improve diabetes control when used as an adjunct to sulfonylureas or biguanides. Guar gum may also be used as an adjunct to any of the oral hypoglycaemics to enhance the improvement in blood-glucose control.

  Patients with type 2 diabetes who cannot be controlled adequately by oral therapy and diet need insulin either in addition to or in place of oral therapy. Type 2 diabetes is a progressive disease, and about 30% of those on sulfonylureas will be transferred to insulin treatment within 4 years, a change which now tends to be made earlier owing to increasingly strict criteria for glycaemic control (tight control of blood glucose has now been shown to decrease the risk of complications, see Diabetic Complications, below). However, as insulin therapy is associated with more hypoglycaemic episodes and a greater tendency to weight gain it remains reasonable to begin with oral therapy in type 2 diabetes before proceeding to insulin.[24] Combination of a single insulin injection at bedtime (morning injection is less effective) with oral hypoglycaemics (either a sulfonylurea, metformin, or both) is as effective as insulin alone, and if metformin is used, is associated with less weight gain.[25] In general, as the disease progresses, the majority of patients need multiple therapies to achieve glycaemic control.[26] Biguanides and alpha-glucosidase inhibitors may also be combined with insulin. There is increasing interest in the use of metformin and other oral hypoglycaemics as potential adjuncts to insulin therapy in patients with type 1 diabetes.[27]

Insulin is also substituted for oral treatment to provide cover during periods of severe stress, as in severe infection, trauma, or major surgery. Type 2 patients who become pregnant should also be switched from oral therapy to insulin (see Pregnancy, below).

- ***INSULIN THERAPY.*** While insulin may not be a necessary part of the treatment of type 2 diabetes, it is essential in the treatment of patients with type 1, since they have little or no endogenous insulin secretory capacity.[8,28]

  The aim of insulin therapy is to achieve the best possible control of blood-glucose concentrations without the risk of the hypoglycaemia that can occur if too fine a degree of control is attempted. Tight control of blood-glucose concentrations can reduce the long-term complications of diabetes such as retinopathy, nephropathy, and neuropathy (see Diabetic Complications, below) but in some patients (such as the elderly, or those who lack motivation) it may be better merely to alleviate symptoms rather than attempt tight control. Exercise and dietary discipline are necessary to maintain normal sensitivity to insulin.

  Insulin may be of beef or pork origin, or it may be human insulin produced by gene technology or by modification of porcine insulin. Human and porcine insulin are less immunogenic than bovine insulin and where possible most newly diagnosed type 1 patients are now given human insulin. Modified insulin analogues such as insulin lispro, insulin aspart, insulin detemir, and insulin glargine are now available.

  Insulin is available in preparations offering a short, intermediate, or long action. It may be given intramuscularly but the subcutaneous route is usually preferred. Soluble insulin can also be given intravenously. More recently, products delivering insulin for absorption through the buccal mucosa or lungs have been developed. Details of insulin routes are given on p.450. Insulin dosage schedules make use of the varying durations of action, for example by incorporating a short-acting and intermediate-acting insulin into a daily schedule. Most patients with type 1 diabetes require two or three injections of insulin daily, or with intensive regimens even more. A once-daily regimen can be used if the patient is simply to be kept asymptomatic; this may also be successful in patients with type 2 diabetes not satisfactorily controlled by oral antidiabetics.

- ***IMMUNOSUPPRESSION.*** Many patients with type 1 diabetes have a temporary improvement in pancreatic beta-cell function soon after initial treatment with insulin. This produces a period of partial remission known as the honeymoon period, during which a small dose of insulin (0.5 units/kg or less daily) is sufficient to maintain good control. Attempts to prolong the honeymoon period have included tight control immediately following diagnosis and also, given the probable auto-immune nature of the condition, use of an immunosuppressant.[8] However, results have been at best ambiguous.

- ***PANCREATIC TRANSPLANTATION.*** Transplantation of the whole pancreas in patients with type 1 diabetes poorly controlled by insulin therapy has led to insulin independence, and has usually been carried out with kidney transplantation (see also Pancreatic Transplantation, p.1816).[29] Transplantation of pancreatic islet cells has been investigated as an alternative. Since the introduction of the so-called 'Edmonton Protocol' and related regimens for immunosuppression, and improvements in techniques for harvesting and preparing islet cells, more experienced centres are now reporting some success in achieving insulin independence,[29,30] and development of new immunosuppressive regimens continues.[31,32] However, at present successful patients exchange life-long insulin therapy for life-long immunosuppression. The induction of tolerance, less toxic immunosuppression, and enhanced islet engraftment remain the focus of investigation.[30] Results in *animals* have suggested that a reasonable degree of glycaemic control may be achievable long term without immunosuppression, using a vascularised 'artificial pancreas' containing allogeneic or even xenogeneic islet cells.[33] The use of stem cells as potential sources of islet cells is also under investigation.[34]

- ***OTHER DRUG TREATMENTS.*** Other drugs have been tried for diabetes mellitus, particularly when conventional therapy has proved unsuccessful. Addition of the amylin analogue *pramlintide* to insulin therapy has improved glycaemic control in patients with type 1 and type 2 diabetes.[35,36] Other approaches under investigation include inhibition of fatty acid oxidation or the use of β_3-adrenoceptor agonists (selective agonists of β-receptors thought to be associated with lipolysis and thermogenesis) to stimulate energy expenditure.[37]

  Mecasermin (insulin-like growth factor I; IGF-I) has been shown to improve metabolic control in patients with type 1 diabetes and insulin resistance (and in some type 2 patients).[38,39] The incretin hormone *glucagon-like peptide 1* (GLP-1; insulinotropin) plays a role in glucose homoeostasis, and when given therapeutically improves glycaemic control in type 2 patients.[40,41] Incretin mimics such as *exenatide* (synthetic exendin-4) and *liraglutide*,[42-44] and inhibitors of the incretin-degrading enzyme dipeptidylpeptidase-4 (such as *sitagliptin* and *vildagliptin*),[43,44] are also under investigation or have been licensed for use in type 2 diabetes. Improvements in insulin sensitivity have also been seen in insulin-resistant type 2 patients treated with a haemodialysate of calf blood,[45] while in other studies improved insulin sensitivity was seen after treatment with the *vanadium* salt, vanadyl sulfate.[46,47] Adjunctive *chromium* supplementation may reduce serum-glucose in type 2 diabetes, but high doses may be required and long-term safety and efficacy have not been established.[48]

- ***PROPHYLAXIS.*** Because overt diabetes is the culmination of a prolonged process, methods to delay or prevent its development are being investigated, either by modifying risk factors in populations or groups, or by targeting individuals thought to be at high risk. Strategies under consideration for the prevention of type 1 diabetes include avoidance of cows' milk proteins (thought to be a possible environmental trigger) during infancy;[49] giving free radical scavengers such as nicotinamide;[50] prophylactic insulin[51-53] (or possibly oral antidiabetics) to allow 'beta cell rest'; encouraging the development of antigen tolerance, for example by taking oral antigens such as insulin, glutamic acid decarboxylase, or heat shock protein[52,54,55] (a similar approach using subcutaneous antigen has apparently extended the honeymoon period in *animal* studies[56]); or by immunosuppression (see above) or immunomodulation with agents such as BCG vaccine,[57] although some have found the latter ineffective.[58] Preventive strategies for insulin resistance and type 2 diabetes have tended to focus on weight loss, dietary modification, and exercise. However, prophylactic drug therapy may be possible. A systematic review concluded that there was good evidence for a reduced incidence of diabetes in patients treated with metformin, acarbose, orlistat, and troglitazone, although the attrition rates were high with the latter 2 drugs; evidence of benefit from statins, oestrogen, and various antihypertensive drugs (including ACE inhibitors) was more equivocal. It was considered likely that some of the benefits were indirect, due to drug-induced weight loss, and in no case was the benefit definitive enough that the drug could be recommended for diabetes prevention.[59] Studies are ongoing with drugs including ramipril, telmisartan, valsartan, nateglinide, rosiglitazone, and insulin glargine.[59-61] Guidelines[62] for the prevention of type 2 diabetes recommend that individuals with pre-diabetes (impaired fasting glucose or impaired glucose tolerance) should be counselled on weight loss and exercise, and that drug therapy should not be routinely used until more information becomes available. Screening for diabetes has been encouraged, particularly for those patients with risk factors.[63]

Monitoring of therapy. Monitoring of therapy is an integral part of the management of the diabetic patient.[64] Detection of urinary glucose has generally been superseded by the monitoring of blood glucose (see Glucose Tests, p.2314). For adequate diabetic control, the aim is to reduce fasting blood-glucose concentrations to within the range 3.3 to 5.6 mmol/litre of venous whole blood, and postprandial concentrations to below 10 mmol/litre.[5] Many patients monitor their blood-glucose concentrations regularly at home and this is essential for intensified insulin regimens when tight control is required. Although the value of self-monitoring of blood-glucose concentrations in type 2 patients is less clear, the results of a large cohort study[65] suggest that such monitoring can improve glycaemic control in these patients. Detection of urinary ketones is useful in diabetics prone to ketosis; this is usually done in clinics. Diabetic clinics also measure the degree of haemoglobin glycosylation (HbA_1 or HbA_{1c}) as an indicator of longer term blood-glucose control and hence the risk of complications (see Diabetic Complications, below). UK guidelines[9] recommend that a general target of 6.5 to 7.5% should be set for HbA_{1c} in individuals with type 2 diabetes. In the USA,[6] a target of HbA_{1c} below 7.0% has been recommended for diabetes patients in general. The advanced glycation end-product (AGE) of haemoglobin has also been found to be a useful indicator of long-term blood glucose control.[66] Measurement of glycated serum proteins, particularly albumin, is also used to give an indication of glucose control, but for a shorter period than haemoglobin. Other techniques that have been developed for monitoring blood-glucose concentrations include continuous monitoring by a subcutaneous system, and a minimally invasive device that uses reverse iontophoresis through the skin.

Pregnancy. Adverse pregnancy outcomes, including spontaneous abortion and congenital malformation, are more common in diabetic than in nondiabetic women. Improved management of the pregnant diabetic patient, particularly in early pregnancy, lessens the incidence of such events,[67,68] but an increased risk still exists.[69] Diabetic women are advised to plan their pregnancies so that glycaemic control can be improved before conception.[70] Some may need to avoid pregnancy (most commonly because of renal disease),[71] but management has improved sufficiently for this to be rare.[68]

Insulin is the preferred treatment in pregnancy,[72] even in women with type 2 diabetes; patients taking oral antidiabetics should therefore be switched to insulin. However, there is increasing evidence to suggest that metformin might be used safely during pregnancy, and NICE[73] has suggested that it may be used either as an adjunct or alternative to insulin if the likely benefits from improved glycaemic control outweigh the potential for harm. Insulin regimens are similar to those in nonpregnant patients, the dose being adjusted according to regular blood-glucose measurements. Insulin requirements may decrease during the first trimester but they increase during the latter two, reaching about twice pre-pregnancy requirements at term; they then fall once labour has begun and fall again after delivery.[72]

Pregnant diabetic patients are at risk of nocturnal hypoglycaemia owing to continued fetal glucose consumption while the mother is in a relatively fasting state. They are also prone to diabetic ketoacidosis which must be treated with great urgency because of the high risk of fetal loss.

Gestational diabetes mellitus is defined as glucose intolerance with onset or first recognition during pregnancy.[74-76] Many women with gestational diabetes can be managed by diet alone or, if necessary, also with insulin. Some suggest giving prophylactic insulin even to women who could be managed by diet alone, in view of the metabolic effects of insulin.[77] Insulin analogues such as insulin lispro and insulin aspart have been investigated.[76] Dietary management of gestational diabetes can improve maternal and fetal outcomes, and insulin therapy reduces fetal macrosomia and perinatal morbidity.[75] NICE[73] also considers that metformin or glibenclamide may be considered as an adjunct or alternative to insulin. There has been much debate about the benefits of screening for gestational diabetes, and both universal[74] and selective screening based on risk factors[75] have been promoted.

Surgery. Insulin-dependent diabetics who require surgery may be managed with a continuous intravenous insulin infusion.[78] Insulin is given as normal the night before operation, and switched to either a variable rate infusion via a syringe pump, with a 5 or 10% glucose drip (with potassium chloride, provided the patient is not hyperkalaemic), or to a combined insulin-glucose infusion, on the day of operation. (Many anaesthetists prefer insulin and a sodium chloride infusion if blood glucose is already high.[79]) Subsequent conversion back to subcutaneous insulin should be undertaken before breakfast, giving the first subcutaneous dose 30 minutes before stopping continuous infusion. Non-insulin-dependent patients should have any oral treatment omitted on the day of operation, and may be given insulin by a similar regimen if control is poor or deteriorates as can happen with major surgery.

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Diabetic complications

Much of the increased mortality and morbidity seen in diabetic patients is the result of complications that develop with increasing duration of disease, particularly when glycaemic control is poor. Such complications may originate from increased glycation of proteins and other biological macromolecules in the hyperglycaemic environment, pathological activation of protein kinase C, or from increased accumulation of sorbitol and other polyols via the aldose reductase pathway,[1] but other factors play an important role in determining susceptibility. At the *macrovascular* level, diabetics are prone to hypertension and ischaemic heart disease, and heart disease is a major cause of death; control of blood pressure is now seen as being as important as glycaemic control in patients with type 2 diabetes. *Microvascular* tissue damage is an important factor in the development of diabetic nephropathy and retinopathy; it may also contribute to the other major complication, diabetic neuropathy. Collagen abnormalities are also seen. Diabetics with poor glycaemic control also have an increased liability to severe bacterial or fungal infection. Sometimes several factors may interact; thus neuropathy, infection, and impaired blood flow due to macro- or microvascular disease may all play a role in the development of diabetic foot disease, a complication which can ultimately lead to amputation.

Prevention of diabetic complications. Much attention has been focused on whether strict or tight glycaemic control can modify the development or progression of diabetic complications. In general, the longer-term studies have provided more encouraging results than initial results indicated, and meta-analysis of such studies[2] has suggested that intensive regimens may prevent microvascular complications.

The Diabetes Control and Complications Trial (DCCT)[3] confirmed this view in type 1 diabetes. It compared in selected patients the effects of conventional insulin therapy with those of continuous subcutaneous insulin infusion or multiple-injection regimens, on the development and progression of complications. The intensive treatment was aimed at keeping preprandial blood-glucose concentrations between 3.9 and 6.7 mmol/litre, postprandial concentrations at less than 10 mmol/litre, a weekly 3 a.m. measurement at greater than 3.6 mmol/litre, and the monthly glycosylated haemoglobin measurement at less than 6.05%. Intensive insulin therapy reduced the development and progression of retinopathy; it also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. The major disadvantage of intensive insulin therapy was a threefold greater risk of hypoglycaemia; weight gain was also significantly greater.

While it is accepted that some patients will benefit from intensive insulin regimens, this approach requires caution in patients at risk of hypoglycaemia. Also such intensive treatment may not always be necessary, for example in patients known to maintain good control by conventional dosage schedules, or where improvement can be obtained by setting achievable targets and improving patient education.[4] However, intensive therapy can help sustain endogenous insulin secretion in type 1 diabetes, which is associated with improved metabolic control;[5] this would favour starting intensive insulin therapy at an early stage. After the DCCT finished the patients returned to their own health care providers for diabetes care, but were followed in a cohort study for a further 11 years.[6] Although more than 90% of all patients went on to use intensive therapy, and glycosylated haemoglobin values became very similar for both groups during this time, there were fewer cardiovascular events and less microalbuminuria and albuminuria in the group that had received intensive treatment during the original DCCT, showing that the beneficial effects of intensive therapy were maintained long term.

The reports of the UK Prospective Diabetes Study (UKPDS) have provided similar evidence in patients with type 2 diabetes. This study has examined the benefits of intensive therapy, using a variety of drugs with diet and exercise. Intensive therapy, which aimed at producing fasting plasma-glucose concentrations of below 6 mmol/litre, substantially decreased the risk of microvascular complications (particularly retinopathy). There was no difference in benefit between intensive therapy with sulfonylureas and with insulin.[7] Metformin also produced benefit in the overweight patients who received it.[8] The UKPDS did not provide unequivocal evidence of a reduction in macrovascular disease with improved glycaemic control, although there was some suggestion of a reduction in risk of myocardial infarction (in line with a small earlier Japanese study[9]). However, it did show that vigorous control of blood pressure, using captopril or atenolol as the first-line drugs, reduced the risk of both macrovascular and microvascular complications,[10,11] suggesting that this should have a high priority in the treatment of type 2 diabetes. A subsequent study has confirmed the importance of a multifactorial approach in reducing cardiovascular events.[12] It has been suggested that thiazolidinediones may have beneficial effects in addition to their hypoglycaemic effect, and a study[13] in patients with type 2 diabetes and extensive macrovascular disease found that pioglitazone improved cardiovascular outcome and reduced the need to add insulin. There has, however, been some concern about possible adverse cardiovascular effects of rosiglitazone (see p.459).

Diabetic eye disease. Diabetic patients are prone to potentially blinding eye disease, usually in the form of cataract or diabetic retinopathy. Cataract generally requires surgical extraction, particular care being taken to avoid infection. Diabetic retinopathy may take a 'background', nonproliferative form, or become a more serious proliferative retinopathy associated with neovascularisation, vitreous haemorrhage and retinal detachment. Macular oedema, characterised by retinal thickening from leaky blood vessels, can develop at any stage.[14,15]

Aggressive glycaemic and blood pressure control are the main methods of prevention.[15,16] However, once proliferative retinopathy has developed, glycaemic control is not adequate to prevent worsening.[17] Moreover, transient early worsening may occur in patients transferred to more intensive glycaemic regimens.[18]

Once severe nonproliferative or proliferative retinopathy has developed, photocoagulation using an argon laser or a xenon arc is effective in limiting progression, while vitrectomy may be helpful for vitreous haemorrhage and retinal detachment.[19]

Numerous drugs have been tried for the prevention or retardation of diabetic eye disease, mostly with indifferent results.[15,16] Aldose reductase inhibitors such as sorbinil, aspirin, statins, oxygen (and conversely, the antoxidant vitamin E), ACE inhibitors, angiotensin II receptor antagonists such as losartan, interferon alfa-2a, and the matrix metalloproteinase inhibitor prinomastat, have all produced either minor benefit or no benefit at all, while the non-specific kinase inhibitor PKC-412 has produced some benefit but accompanied by significant adverse effects.[16] Other drugs for which benefit has been claimed include ticlopidine,[20] epoetin,[21] and danaparoid sodium.[22] Ongoing studies include those with the somatostatin analogue octreotide, the specific protein kinase C inhibitor ruboxistaurin mesilate, and the growth factor antagonist pegaptanib.[16] Intravitreal injection of the corticosteroid triamcinolone acetonide may be useful for diabetic macular oedema.[23]

Diabetic nephropathy. Nephropathic changes associated with microvascular disease develop in up to 30% of patients with type 1 diabetes and up to 40% of those with type 2 disease; diabetic nephropathy, of which the first clinical sign is albuminuria, is one of the major causes of end-stage renal disease (see Chronic Renal Failure, p.1672).

Results from the DCCT indicate that strict glycaemic control reduces the incidence of microalbuminuria in type 1 diabetes,[3] (with long-term renal benefits[24]) and a smaller reduction was seen in the UKPDS in patients with type 2 diabetes.[7] However, while good control may prevent development of the initial lesion, it is not clear whether it can prevent progression in patients who are already microalbuminuric. Some studies, including the DCCT, have suggested that this is the case;[3,9] others have failed to confirm it.[25]

Dietary protein restriction (see Renal Failure, p.1923), which appears from a number of small studies to have a beneficial, although small, effect on disease progression,[26,27] has been recommended in patients with overt nephropathy.[28]

The most important approach to slowing the progression of diabetic nephropathy is aggressive antihypertensive control.[10,28-30] Although most patients will require combination therapy, first-line use of ACE inhibitors has been particularly recommended,[28,30] as they have been suggested to reduce proteinuria to a greater extent than other antihypertensives. However, results from the UKPDS showed no difference between the effects of an ACE inhibitor and a beta blocker in reducing microalbuminuria in type 2 diabetics with hypertension,[11] and a systematic review[31] found limited evidence to support a specific renoprotective action in diabetics, independent of their effect on blood pressure. Another systematic review[32] found ACE inhibitors to be effective for the primary prevention of developing microalbuminuria. The authors noted that although data were limited this effect appeared independent of baseline blood pressure, renal function, and type of diabetes. Beneficial effects have also been reported when ACE inhibitors are given to patients with microalbuminuria but without hypertension,[33-35] and it has been recommended that such patients receive ACE inhibitors, initially in small doses, to slow the progression of renal disease.[36] Some consider that small decreases in blood pressure associated with such therapy may be responsible for the benefit.[11] ACE inhibition also had a modest renal protective effect in normotensive diabetics with normal urinary albumin excretion,[37] and such use requires further study.

Angiotensin II receptor antagonists have also been shown to reduce the progression of renal disease in type 2 patients with both microalbuminuria and macroalbuminuria, and US recommendations consider them an equal first choice with ACE inhibitors;[28] UK guidelines suggest they may be used in those unable to tolerate ACE inhibitors.[30] Although a systematic review failed to find evidence that the two classes were equivalent in their effects on survival,[38] their effects on progression of nephropathy appear equivalent.[38,39]

The aldose reductase inhibitors have been investigated for their effects on nephropathy, but results have been, at best, ambiguous; a study in microalbuminuric patients given tolrestat (now withdrawn worldwide) did show a decrease in urinary albumin excretion but there was also a decrease in the (initially raised) glomerular filtration rate.[40] Pimagedine, which inhibits the formation of glycosylated end products, is also under investigation.

Diabetic neuropathy. Peripheral neuropathies are common complications of diabetes mellitus. The intensity and extent of neurological abnormalities are proportional to the degree and duration of hyperglycaemia. Neuropathic symptoms include symmetrical sensory loss, particularly in the feet and lower limbs; features of autonomic neuropathy such as gastroparesis, orthostatic hypotension, erectile dysfunction, and gustatory sweating; pain and cranial nerve palsy associated with mononeuropathies; and acute, painful, sensory neuropathy.[41,42]

Results from the DCCT indicated that strict glycaemic control could substantially reduce the occurrence of clinical neuropathy in patients with type 1 diabetes,[3,43] a result which was not duplicated in the UKPDS in patients with type 2 diabetes.[7]

Although some studies have suggested that aldose reductase inhibitors such as epalrestat[44] can reduce the severity of diabetic neuropathy, larger scale analysis has apparently failed to show any benefit. However, studies with some newer members of the class such as fidarestat are still ongoing.[42] Interesting preliminary results have suggested that ACE inhibitors may also have benefits in diabetic neuropathy.[45] An analysis[46] of 4 studies using the antoxidant thioctic acid found variable results, but an overall benefit, in symptomatic diabetic polyneuropathy. Results from another study[47] have suggested some improvement in cardiac autonomic neuropathy. Inhibition of protein kinase C with ruboxistaurin is also under investigation.[42]

Other management of diabetic neuropathy is essentially symptomatic.[41,42] The pain, which can be severe, may be managed with tricyclic antidepressants; duloxetine, mexiletine, antiepileptics including carbamazepine, and topical capsaicin or lidocaine may also be tried, as discussed on p.6.

Diabetic gastroparesis may respond to prokinetic drugs such as metoclopramide, cisapride, domperidone, or erythromycin,[41,42,48] but their effects can be variable and long-term use may be limited by adverse effects. Endoscopic or surgical interventions may be needed when symptoms cannot be controlled. Diarrhoea may respond to tetracycline (see below), while orthostatic hypotension should be managed conventionally (see under Fludrocortisone, p.1530) although care may be required in the use of elastic stockings in patients with impaired blood flow to the feet. For the management of erectile dysfunction, see p.2179.

Diarrhoea. Diabetic patients may develop intermittent bouts of watery diarrhoea, sometimes alternating with constipation; autonomic neuropathy and abnormalities of digestion and bowel flora may play a role.[49] Clonidine has been suggested for severe cases,[41] and octreotide has been tried,[50,51] but conventional management with antidiarrhoeal drugs (p.1694) is otherwise used; a broad spectrum antibacterial (especially tetracycline) may also be effective. The mechanism of action of tetracycline in diabetic diarrhoea is uncertain, but it has been suggested that one or two doses of tetracycline should be the first line of treatment.[52]

Foot disease. Peripheral arterial disease, neuropathy, collagen changes, and increased susceptibility to infection may contribute to the foot lesions to which diabetics are prone. Ulceration and tissue necrosis at pressure-points may be followed by infection, gangrene, and sepsis. Management involves drainage and debridement of dead and infected tissue, and the use of antibacterials if necessary:[53] broad spectrum cover should be given intravenously if there is severe infection, and adapted once the results of bacteriological culture are available.[54] Local antiseptic therapy may be helpful, especially for infections with *Pseudomonas* or *Proteus* spp. Neuropathic skin ulcers of the lower extremities have responded to a platelet-derived growth factor, becaplermin.[55] Granulocyte colony-stimulating factors have been used as adjunctive therapy with antibacterials in severe foot infections.[56] Strict control of blood glucose is important and insulin should be given as required. Effective pain relief and bed rest may be needed, and surgical reconstruction to improve blood supply may be helpful in some cases. Ultimately, some patients require amputation of all or part of the foot. Preventive care, with regular visits to a chiropodist, is therefore particularly important.

Heart disease. Cardiovascular disease (heart failure, ischaemic heart disease, and stroke) is a major cause of morbidity and death in patients with diabetes, who are at greatly increased risk of such disorders, often have a worse prognosis when they occur, and who may be undertreated for cardiovascular complications.[57-59] Conventional risk factors such as obesity, hypertension, and hyperlipidaemias tend to be common in diabetic patients, but other factors, including hyperglycaemia itself (and particularly postprandial hyperglycaemia[60]), may play a role.

Management of cardiovascular disease in diabetic patients should be essentially the same as in other patients; there have been concerns about the use of individual drug classes—beta blockers, aspirin (which may need to be given in higher than usual doses[61]), and calcium-channel blockers[62]—but in general the benefits of intensive treatment are seen to outweigh the risks.[57-59] Treatment should also include strict glycaemic control: it has been shown that insulin-glucose infusion after myocardial infarction, followed by subcutaneous insulin for at least 3 months, improves long-term survival in patients with both type 1 and type 2 diabetes.[63]

Primary prevention of cardiovascular disease with lipid-lowering drugs (see also Hyperlipidaemias, below) is an increasingly important part of management in high-risk patients.[64,65] It has proved hard to demonstrate that good glycaemic control also plays a role in reducing cardiovascular risk (see Prevention of Complications, above); however, there is evidence from a study in patients with impaired glucose tolerance but not diabetes that decreasing postprandial hyperglycaemia with acarbose reduced the risk of hypertension and cardiovascular events such as myocardial infarction.[66]

Diabetics may also develop a form of restrictive cardiomyopathy in the absence of ischaemic heart disease. Again, the condition is managed similarly to cardiomyopathy in non-diabetic patients (see p.1163).

Cardiac autonomic neuropathy has been reported to be improved by thioctic acid (see Diabetic Neuropathy, above).

Hyperlipidaemias. Insulin plays an important role in lipid metabolism and deficient insulin action means that diabetics are prone to hypertriglyceridaemia and have a blood-lipid profile associated with an increased risk of atherosclerosis, and hence of macrovascular complications (see also Cardiovascular Risk Reduction, p.1164 and Hyperlipidaemias, p.1169). The American Diabetes Association recommends that LDL cholesterol concentrations should be below 2.6 mmol/litre, HDL cholesterol concentrations more than 1.15 mmol/litre, and triglyceride concentrations less than 1.7 mmol/litre.[67]

Where drug therapy is needed, statins, in at least moderate doses, are the lipid-lowering drugs of choice for both secondary and primary prevention of cardiovascular events in type 2 diabetes; studies have shown benefit with atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin, and there is no clear evidence to favour one statin over another in these patients.[68] Fibrates such as gemfibrozil may be an alternative,[67] particularly for secondary prevention in patients with low levels of both LDL and HDL cholesterol.[68] Nicotinic acid has been used to raise HDL cholesterol concentrations,[69] but high doses can have an adverse effect on glycaemic control.[67]

Hypertension. Hypertension is twice as common in the diabetic as in the non-diabetic population, and is associated with both macrovascular complications and microvascular disease (especially diabetic nephropathy). Management of hypertension in diabetics follows the same principles as in the general population, but it should be treated aggressively with a view to retarding development of complications,[10,30,70,71] and the threshold for drug treatment and the treatment goal are lower than in non-diabetic patients (see Hypertension, p.1171). All of the main groups of antihypertensive drugs may be used although an ACE inhibitor,[72,73] such as ramipril,[74] an angiotensin II receptor antagonist,[73] or a beta blocker may be effective in reducing complications.[10,11] Low-dose diuretic therapy has also been shown to be beneficial.[75] Results with calcium-channel blockers have been variable, and there has even been a suggestion that they may increase cardiovascular adverse effects (see Diabetes Mellitus under Precautions of Nifedipine, p.1352). However, a review of randomised studies concluded that they were safe and effective in this population, although possibly less so than other antihypertensive drugs.[62] In the UK, guidelines recommend that long-acting calcium-channel blockers may be used as second-line treatment or as part of combination therapy.[30]

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Diabetic emergencies

Hypoglycaemia. The most frequent complication of insulin therapy is hypoglycaemia and patients taking insulin need to be educated about its cause, symptoms, and treatment. Most patients can recognise the early warning signs of hypoglycaemia and by taking sugar immediately can prevent more serious symptoms developing. Comatose patients need to be given intravenous glucose or, if this is not practicable, subcutaneous, intramuscular, or intravenous glucagon (although glucose is still required if there is no response within 10 minutes). Hypoglycaemia can also develop in patients taking oral antidiabetics, notably the sulfonylureas.

Some patients report loss of the warning signs of hypoglycaemia after transferring from animal to human insulin and these patients, if appropriate, may need to be transferred back to animal insulin. However, the most significant factor in loss of hypoglycaemic warning signs may be exposure to hypoglycaemia itself; a study found that total avoidance of hypoglycaemic episodes for 3 weeks while maintaining glycaemic control restored awareness.[1] Loss of hypoglycaemic awareness, which appears to be due to an adaptive conservation of glucose uptake in the brain,[2] is liable to be a particular problem in patients receiving intensive therapy. There is limited data to suggest that caffeine can improve awareness of hypoglycaemia.[3,4]

For further details on the treatment of insulin-induced hypoglycaemia, see p.447.

Diabetic ketoacidosis is caused by an absolute or relative lack of insulin and commonly occurs after noncompliance or failure to adjust insulin dosage in the presence of factors such as infection that increase insulin requirements (see Precautions for Insulin, p.447). Failure of an insulin pump can be a cause.[5] Also pregnant diabetic women are more prone to development of diabetic ketoacidosis.

Diabetic ketoacidosis is characterised by hyperglycaemia, hyperketonaemia, and acidaemia, with subsequent dehydration and electrolyte abnormalities. Onset may be rapid, or insidious over many days. Initial presenting symptoms such as thirst, polyuria, fatigue, and weight loss are those of any newly presenting type 1 diabetic; they then progress to nausea, vomiting, abdominal pain, and impaired consciousness or coma, and, if untreated, death.[5,6]

Diabetic ketoacidosis is a medical emergency and should be treated immediately with fluid replacement and insulin.[5-8] Fluid requirements depend on the needs of the individual; overvigorous fluid replacement without severe dehydration carries the risk of precipitating cerebral oedema.[6-8]

Soluble insulin should also be given immediately. Large doses were formerly thought necessary, but lower dose regimens accompanied by adequate hydration have since been shown to be preferable.[5] Insulin resistance in diabetic ketoacidosis is generally exacerbated by hyperosmolarity and other confounding factors, and insulin therapy is therefore most effective when preceded or accompanied by adequate fluid and electrolyte replacement.[5] In the UK, the *BNF* considers that insulin should preferably be given by intravenous infusion, with the intramuscular route used if facilities for intravenous infusion are not available. However, in the USA some consider that an intravenous bolus followed by subcutaneous injection may be appropriate in certain patients.[5] Intramuscular or subcutaneous injection are not appropriate in patients with hypovolaemic shock, due to poor tissue perfusion.[5] Where the response to insulin is inadequate the intravenous route is generally required[5] and the rate of infusion may be doubled on an hourly basis until an appropriate response is seen. A case report has suggested that mecasermin may be useful if there is insulin resistance.[9]

When the blood-glucose concentration has fallen to about 12.5 mmol/litre the dose of insulin may be reduced by about half and glucose given intravenously,[5] usually in a strength of 5% with saline although in rare cases a glucose strength of 10% may be necessary.[5] The use of glucose enables insulin to be continued in order to clear ketone bodies without inducing hypoglycaemia. Once glucose concentrations have been controlled and acidosis has completely cleared, subcutaneous injections of insulin can begin;[6] but intravenous insulin should not be stopped until subcutaneous dosage has begun.

Total body stores of potassium are depleted in patients with diabetic ketoacidosis. Insulin deficiency appears to be the main initiating factor for hyperkalaemia in diabetic ketoacidosis.[10] Although patients may present with raised, normal, or decreased serum-potassium concentrations, the concentrations will start to fall with the correction of acidosis. Potassium is added to the infusion fluid after initial fluid expansion and once insulin therapy has begun.[5] In hyperkalaemic patients, potassium is given once serum concentrations have fallen to within normal limits.[5,6] In the rare patient presenting with hypokalaemia potassium replacement should be begun before insulin therapy and the latter withheld until potassium concentrations have risen to normal values.[5]

Intravenous bicarbonate is now generally reserved for patients with severe acidaemia; a common practice[5,6] is to give isotonic bicarbonate to those with a pH of less than 7.0 with the aim of raising the pH to 7.1.

Phosphate concentrations are affected in a similar manner to potassium concentrations in the ketoacidotic state, but there is less agreement on the need for routine doses of phosphate. Phosphate concentrations should be monitored and phosphate given if clinically significant hypophosphataemia occurs.[5,6]

The precipitating cause of diabetic ketoacidosis should also be identified and managed appropriately.

Hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma (HONK) occurs mainly in elderly patients with type 2 diabetes and though much less common than diabetic ketoacidosis it carries a higher mortality. Patients may present in coma with severe hyperglycaemia but with minimal ketosis; dehydration and renal impairment are common.[5] Treatment is similar to that of diabetic ketoacidosis (see above), although potassium requirements are lower and large amounts of fluid and less insulin may be required; some suggest the use of hypotonic fluid if necessary.[11] There is an increased likelihood of thrombotic events, so prophylactic anticoagulation should be considered.

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8. Johnston C. Fluid replacement in diabetic ketoacidosis. *BMJ* 1992; **305:** 522.
9. Usala A-L, *et al.* Brief report: treatment of insulin-resistant diabetic ketoacidosis with insulin-like growth factor I in an adolescent with insulin-dependent diabetes. *N Engl J Med* 1992; **327:** 853–7.
10. Anonymous. Hyperkalaemia in diabetic ketoacidosis. *Lancet* 1986; **ii:** 845–6.
11. Wright AD. Diabetic emergencies in adults. *Prescribers' J* 1989; **29:** 147–54.

Acarbose *(BAN, USAN, rINN)*

Acarbosa; Acarbosum; Akarboosi; Akarbos; Akarbosa; Akarboz; Akarbozė; Bay-g-5421. *O*-{4-Amino-4,6-dideoxy-*N*-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl]-α-D-glucopyranosyl}-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

Акарбоза

$C_{25}H_{43}NO_{18}$ = 645.6.

CAS — 56180-94-0.

ATC — A10BF01.

ATC Vet — QA10BF01.

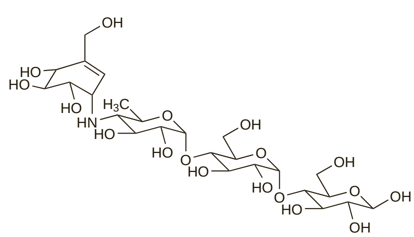

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Acarbose). A white or yellowish, amorphous, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Acarbose). Produced by certain strains of *Actinoplanes utahensis*. Store in airtight containers.

Adverse Effects

Acarbose often causes gastrointestinal disturbances, particularly flatulence due to bacterial action on nonabsorbed carbohydrate in the colon. Abdominal distension, diarrhoea, and pain may occur. Ileus has been rarely reported. A decrease in dosage and improved dietary habits may reduce these adverse effects. Hepatotoxicity may occur and may necessitate a reduction in dosage or withdrawal of the drug. Skin reactions have occurred rarely. Very rarely oedema has been reported.

Incidence of adverse effects. The manufacturers reported that adverse effects of acarbose were rarer in a postmarketing surveillance study than in previous clinical trials;[1] this was held to represent better tailoring of individual doses to patient tolerability.

1. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; **18:** 325–31.

Effects on the liver. Hepatocellular liver damage, with jaundice and elevated serum aminotransferases, have been reported in patients receiving acarbose.[1-3] Symptoms resolved on stopping the drug.

1. Andrade RJ, *et al.* Hepatic injury caused by acarbose. *Ann Intern Med* 1996; **124:** 931.
2. Carrascosa M, *et al.* Acarbose-induced acute severe hepatotoxicity. *Lancet* 1997; **349:** 698–9.
3. Fujimoto Y, *et al.* Acarbose-induced hepatic injury. *Lancet* 1998; **351:** 340.

Effects on the skin. Generalised erythema multiforme and eosinophilia occurred in a male diabetic patient 13 days after starting acarbose.[1] The hypersensitivity reaction was confirmed by rechallenge.

1. Kono T, *et al.* Acarbose-induced generalised erythema multiforme. *Lancet* 1999; **354:** 396–7.

Precautions

Acarbose is contra-indicated in inflammatory bowel disease, particularly where there is associated ulceration, and in gastrointestinal obstruction or patients predisposed to it. It should be avoided in patients with chronic intestinal diseases that significantly affect digestion or absorption, and in conditions which may deteriorate as a result of increased gas formation, such as hernia.

Acarbose is also contra-indicated in patients with hepatic impairment and liver enzyme values should be monitored, particularly at high doses.

If hypoglycaemia should develop in a patient receiving acarbose it needs to be treated with glucose, since the action of acarbose inhibits the hydrolysis of disaccharides.

Breast feeding. In the absence of evidence, licensed product information recommends that acarbose should be avoided during breast feeding.

Interactions

Acarbose may enhance the effects of other antidiabetics, including insulin, and a reduction in their dosage may be needed. Use with gastrointestinal adsorbents and digestive enzyme preparations can diminish the effects of acarbose and should be avoided. Neomycin and colestyramine may enhance the effects of acarbose and a reduction in its dosage may be required. Acarbose may inhibit the absorption of digoxin (see Antidiabetics, under Interactions of Digoxin, p.1261).

Pharmacokinetics

After ingestion of acarbose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity and is metabolised by intestinal enzymes and by the microbial flora. Ultimately about 35% of a dose is absorbed in the form of metabolites. Acarbose is excreted in the urine and faeces.

Uses and Administration

Acarbose is an inhibitor of alpha glucosidases, especially sucrase. This slows the digestion and absorption of carbohydrates in the small intestine and hence reduces the increase in blood-glucose concentrations after a carbohydrate load. It is given in the treatment of type 2 diabetes mellitus (p.431) either alone or with a sulfonylurea, biguanide, or insulin. Acarbose treatment may be started with a low oral dose of 25 or 50 mg daily to minimise gastrointestinal disturbance. It is then gradually increased to a usual dose of 25 or 50 mg three times daily, immediately before food. Doses up to 100 to 200 mg three times daily may be given if necessary. Some benefit has also been found when acarbose is used to supplement insulin therapy in type 1 diabetes mellitus.

Acarbose has also been studied for the treatment of reactive hypoglycaemia, the dumping syndrome, and certain types of hyperlipoproteinaemia.

◊ References.

1. Chiasson J-L, *et al.* The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med* 1994; **121:** 928–35.

2. Coniff RF, *et al.* Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *Am J Med* 1995; **98:** 443–51.
3. Spengler M, Cagatay M. The use of acarbose in the primary-care setting: evaluation of efficacy and tolerability of acarbose by postmarketing surveillance study. *Clin Invest Med* 1995; **18:** 325–31.
4. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet* 1996; **30:** 94–106.
5. Anonymous. Acarbose for diabetes mellitus. *Med Lett Drugs Ther* 1996; **38:** 9–10.
6. Hoffman J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II study. *Am J Med* 1997; **103:** 483–90.
7. Hollander P, *et al.* Acarbose in the treatment of type I diabetes. *Diabetes Care* 1997; **20:** 248–53.
8. Buse J, *et al.* The PROTECT study: final results of a large multicenter postmarketing study in patients with type 2 diabetes. *Clin Ther* 1998; **20:** 257–69.
9. Holman RR, *et al.* A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). *Diabetes Care* 1999; **22:** 960–4.
10. Riccardi G, *et al.* Efficacy and safety of acarbose in the treatment of type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study. *Diabet Med* 1999; **16:** 228–32.
11. Chiasson J-L, *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359:** 2072–7.

Impaired glucose tolerance. A prospective study of patients with impaired glucose tolerance concluded that acarbose significantly reduced the incidence of cardiovascular disease and hypertension.[1]

1. Chiasson J-L, *et al.* Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003; **290:** 486–94.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Glucobay; ***Austral.:*** Glucobay; ***Austria:*** Glucobay; ***Belg.:*** Glucobay; ***Braz.:*** Aglucose; Glucobay; ***Canad.:*** Prandase; ***Chile:*** Glucobay; ***Cz.:*** Glucobay; ***Denm.:*** Glucobay; ***Fr.:*** Glucor; ***Ger.:*** Glucobay; ***Gr.:*** Glucobay; ***Hong Kong:*** Glucobay; ***Hung.:*** Glucobay; ***India:*** Acarbay; Asucrose; Glubose; Glucar; Glucobay; ***Indon.:*** Glucobay; ***Irl.:*** Glucobay; ***Israel:*** Prandase; ***Ital.:*** Glicobase; Glucobay; ***Malaysia:*** Dibose; Glucar; Glucobay; Precose; ***Mex.:*** Glucobay; Incardel; Sincrosa; ***Neth.:*** Glucobay; ***Norw.:*** Glucobay; ***NZ:*** Glucobay; ***Philipp.:*** Glucobay; Gluconase; ***Pol.:*** Glucobay; ***Port.:*** Glucobay; ***Rus.:*** Glucobay (Глюкобай); ***S.Afr.:*** Glucobay; ***Singapore:*** Glucobay; ***Spain:*** Glucobay; Glumida; ***Swed.:*** Glucobay; ***Switz.:*** Glucobay; ***Thai.:*** Glucobay; ***Turk.:*** Glucobay; Glynose; ***UK:*** Glucobay; ***USA:*** Precose; ***Venez.:*** Glucobay.

Acetohexamide *(BAN, USAN, rINN)*

Acetohexamid; Acetohexamida; Acétohexamide; Acetohexamidum; Asetoheksamidi; Compound 33006. 1-(4-Acetylbenzenesulphonyl)-3-cyclohexylurea.

Ацетогексамид

$C_{15}H_{20}N_2O_4S$ = 324.4.

CAS — 968-81-0.

ATC — A10BB31.

ATC Vet — QA10BB31.

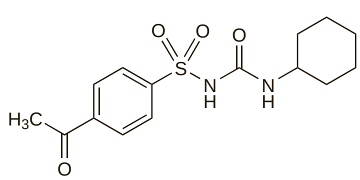

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Acetohexamide). A white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 230 of alcohol and 1 in 210 of chloroform; soluble in pyridine and in dilute solutions of alkali hydroxides.

Profile

Acetohexamide is a sulfonylurea antidiabetic (p.460). Its duration of action is 12 hours or more. It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in a usual initial dose of 250 mg daily before breakfast. The daily dose may then be increased by 250 to 500 mg at intervals of 5 to 7 days, to a maintenance dose of up to 1.5 g daily; increasing the dose above 1.5 g does not usually lead to further benefit. Doses in excess of 1 g daily may be taken in 2 divided doses, before the morning and evening meals.

Preparations

USP 31: Acetohexamide Tablets.

Proprietary Preparations (details are given in Part 3)

USA: Dymelor†.

Biguanide Antidiabetics

Antidiabéticos biguanídicos.

Adverse Effects

Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides; patients may experience taste disturbance and there may be weight loss. Absorption of various substances including vitamin B_{12} may be impaired. Skin reactions have been reported rarely.

Hypoglycaemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.

Lactic acidosis, sometimes fatal, has occurred with biguanides, primarily with phenformin. When it has occurred with metformin most cases have been in patients whose condition contra-indicated the use of the drug, particularly those with renal impairment.

Phenformin has been implicated in the controversial reports of excessive cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

◊ Reviews.

1. Paterson KR, *et al*. Undesired effects of biguanide therapy. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 173–82.
2. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; **20:** 489–503.

Effects on the blood. Megaloblastic anaemia has occurred with biguanide therapy (see Malabsorption, under Effects on the Gastrointestinal Tract, below). A few cases of metformin-induced haemolysis resulting in hyperbilirubinaemia and jaundice have also been described.[1,2]

1. Lin K-D, *et al.* Metformin-induced hemolysis with jaundice. *N Engl J Med* 1998; **339:** 1860–1.
2. Meir A, *et al.* Metformin-induced hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency. *Diabetes Care* 2003; **26:** 956–7.

Effects on the gastrointestinal tract. *DIARRHOEA.* In a retrospective survey,[1] 30 of 265 diabetic patients reported diarrhoea or alternating diarrhoea and constipation, comprising: 11 of 54 taking metformin; 9 of 45 taking metformin with a sulfonylurea; 3 of 53 taking a sulfonylurea only; 5 of 78 on insulin therapy; 2 of 35 on diet alone. Among 150 nondiabetic controls 12 reported diarrhoea. Chronic diarrhoea described as watery, often explosive, and frequently causing faecal incontinence, has been reported as an adverse effect of late onset in patients receiving metformin. Some patients had been on stable metformin therapy for several years before the onset of diarrhoea. Symptoms ceased upon withdrawal of metformin, and recurred in cases of rechallenge.[2,3]

1. Dandona P, *et al*. Diarrhea and metformin in a diabetic clinic. *Diabetes Care* 1983; **6:** 472–4.
2. Raju B, *et al.* Metformin and late gastrointestinal complications. *Am J Med* 2000; **109:** 260–1.
3. Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001; **21:** 1422–4.

MALABSORPTION. Megaloblastic anaemia due to vitamin B_{12} malabsorption in a 58-year-old woman was associated with long-term treatment with metformin.[1]

In a survey of diabetic patients receiving biguanide therapy,[2] malabsorption of vitamin B_{12} was observed in 14 of 46 diabetics taking metformin or phenformin; metformin was more commonly to blame. Withdrawal of the drug resulted in normal absorption in only 7 of the 14. In a series of 10 patients[3] with vitamin B_{12} deficiency associated with metformin, vitamin B_{12} concentrations and blood count abnormalities were reported to have been corrected within 3 months of starting treatment with intramuscular or oral cyanocobalamin; 2 patients were transferred to treatment with other antidiabetic agents.

1. Callaghan TS, *et al*. Megaloblastic anaemia due to vitamin B malabsorption associated with long-term metformin treatment. *BMJ* 1980; **280:** 1214–15.
2. Adams JF, *et al.* Malabsorption of vitamin B and intrinsic factor secretion during biguanide therapy. *Diabetologia* 1983; **24:** 16–18.
3. Andrès E, *et al.* Metformin-associated vitamin B deficiency. *Arch Intern Med* 2002; **162:** 2251–2.

Effects on the liver. Severe cholestatic hepatitis attributed to metformin has been reported.[1]

1. Babich MM, *et al*. Metformin-induced acute hepatitis. *Am J Med* 1998; **104:** 490–2.

Effects on the pancreas. Acute pancreatitis is more commonly associated with phenformin.[1,2] However, there have also been a few cases of pancreatitis associated with metformin, in which renal failure may have precipitated metformin toxicity.[3,4]

1. Wilde H. Pancreatitis and phenformin. *Ann Intern Med* 1972; **77:** 324.
2. Chase HS, Mogan GR. Phenformin-associated pancreatitis. *Ann Intern Med* 1977; **87:** 314–15.
3. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. *Postgrad Med J* 2004; **80:** 239–40.
4. Fimognari FL, *et al.* Metformin-induced pancreatitis: a possible adverse drug effect during acute renal failure. *Diabetes Care* 2006; **29:** 1183.

Hypersensitivity. Vasculitis and pneumonitis in a 59-year-old woman was associated with use of metformin.[1] Symptoms improved on withdrawal of metformin, but reappeared on its reintroduction. Cutaneous vasculitis in a 33-year-old woman also resolved on withdrawal of metformin and recurred with its reintroduction.[2]

1. Klapholz L, *et al.* Leucocytoclastic vasculitis and pneumonitis induced by metformin. *BMJ* 1986; **293:** 483.
2. Salem CB, *et al.* Rare case of metformin-induced leukocytoclastic vasculitis. *Ann Pharmacother* 2006; **40:** 1685–7.

Hypoglycaemia. UK licensed product information for metformin states that hypoglycaemia does not occur with metformin alone, even in overdosage, although it may occur if given with alcohol or other hypoglycaemics. Interim results from the UK Prospective Diabetes Study,[1] however, indicate that metformin therapy was associated with fewer hypoglycaemic episodes than sulfonylurea or insulin treatment, but more than with diet alone. One or more hypoglycaemic episodes were reported in 6% of the patients receiving the biguanide in this study, although only 1 patient had a severe episode.

1. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for 3 years. *BMJ* 1995; **310:** 83–8.

Lactic acidosis. There is a small but definite risk of lactic acidosis associated with use of biguanide antidiabetics. Most early reports involved phenformin, which was consequently removed from the market in many countries although cases of phenformin-associated lactic acidosis still occur.[1-3] There has therefore been concern about the risks of lactic acidosis with metformin, which is still in wide use. However, lactic acidosis with metformin appears to be much less common: a review suggested that the incidence was of the order of 3 cases per 100 000 patient years, which was 20 times less frequent than with phenformin.[4] This concurs with the findings of the FDA after the introduction of metformin to the US market: in the year after the marketing of metformin in the USA, the FDA had received reports of metformin-associated lactic acidosis in 66 patients,[5] the diagnosis being confirmed in 47. This represented a rate of about 5 cases per 100 000. Most patients who do develop lactic acidosis with metformin have one or more precipitating risk factors such as renal impairment, congestive heart failure, or other conditions predisposing to hypoxaemia or acute renal failure, including septicaemia, acute hepatic decompensation, alcohol abuse, acute myocardial infarction, and shock.[4] A systematic review,[6] which considered results comprising nearly 48 000 patient years of treatment with metformin, concluded that provided metformin was prescribed taking into account the proper contra-indications, there was no evidence of an increased risk of lactic acidosis. Nonetheless, there have been a few reports of lactic acidosis developing in metformin-treated patients without apparent risk factors.[4]

1. Rosand J, *et al.* Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997; **127:** 170.
2. Enia G, *et al.* Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997; **315:** 1466–7.
3. Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998; **16:** 881–6.
4. Chan NN, *et al.* Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med* 1999; **16:** 273–81.
5. Misbin RI, *et al.* Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; **338:** 265–6.
6. Salpeter S, *et al.* Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/05/06).

Treatment of Adverse Effects

Acute poisoning with biguanides may lead to the development of lactic acidosis (see Metabolic Acidosis, p.1667) and calls for intensive supportive therapy. Glucose or glucagon may be required for hypoglycaemia, the general management of which is outlined in Insulin, p.447.

Precautions

Biguanides are inappropriate for patients with diabetic coma and ketoacidosis, or for those with severe infection, trauma, or other severe conditions where the biguanide is unlikely to control the hyperglycaemia; insulin should be used in such situations. Biguanides should not be given to patients with even mild renal impairment, as it may predispose patients to lactic acidosis, and renal function should be monitored throughout therapy. Dehydration may contribute to renal impairment. Conditions associated with hypoxia, such as

The symbol † denotes a preparation no longer actively marketed

acute heart failure, recent myocardial infarction, or shock, may increase the risk of lactic acidosis. Other conditions that may also predispose to lactic acidosis in a patient taking a biguanide include excessive alcohol intake and hepatic impairment. Biguanides should be temporarily stopped for examinations using contrast media (see under Interactions, below).

Insulin is preferred for the treatment of diabetes in pregnancy.

Owing to the possibility of decreased vitamin B_{12} absorption, annual monitoring of vitamin B_{12} concentrations is advisable during long-term treatment.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.

References.

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Interactions

Use of a biguanide with other drugs that lower blood-glucose concentrations increases the risk of hypoglycaemia, while drugs that increase blood glucose may reduce the effect of biguanide therapy.

In general fewer drug interactions have been reported with biguanides than with sulfonylureas. Alcohol may increase the risk of lactic acidosis as well as of hypoglycaemia. Care should be taken if biguanides are given with drugs that may impair renal function.

Anticoagulants. For the effect of metformin on *phenprocoumon* activity, see Antidiabetics, p.1428.

Antivirals. Fatal lactic acidosis has been reported[1] in a patient given metformin with *didanosine*, *stavudine*, and *tenofovir*.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Cimetidine. Cimetidine increased plasma-metformin concentrations in 7 healthy subjects.[1] The renal clearance of metformin was reduced; competition for proximal tubular secretion was considered responsible. A reduction in metformin dosage may be required in patients taking metformin and cimetidine, in order to reduce the risk of lactic acidosis.

1. Somogyi A, *et al.* Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; **23:** 545–51.

Contrast media. Biguanides should be temporarily stopped for examinations using iodinated contrast media and withheld after the examination until normal renal function is confirmed, because of the risk of contrast media-induced renal impairment leading to biguanide toxicity and associated lactic acidosis. Licensed product information for some contrast media preparations warns that biguanides should be temporarily stopped 48 hours before the examination, and withheld for at least 48 hours after and until normal renal function is confirmed.

A number of guidelines on the use of iodinated contrast media give advice for the management of patients taking metformin. Some suggest that, in general, metformin can be stopped at the time of the examination.[1,2] Others are more detailed, suggesting that if serum-creatinine is normal metformin may be stopped at the time of the examination, but that if it is raised metformin should be stopped 48 hours before giving the contrast medium.[3,4] They all agree that metformin should be withheld for 48 hours after the examination and until normal renal function is confirmed, although one suggests that no special precaution is needed for patients with normal serum-creatinine who are to be given a low volume of iodinated contrast medium (up to 100 mL).[3]

1. Committee on Drugs and Contrast Media, Commission on General and Pediatric Radiology of the American College of Radiology. Manual on contrast media, 5th ed. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx (accessed 26/06/07)
2. Benko A, *et al.* Canadian Association of Radiologists: consensus guidelines for the prevention of contrast-induced nephropathy. *Can Assoc Radiol J* 2007; **58:** 79–87. Correction available at: http://www.car.ca/Files%5CNephropathy.pdf (accessed 20/08/08) [correct version]
3. Board of the Faculty of Clinical Radiology; The Royal College of Radiologists. Standards for iodinated intravascular contrast agent administration to adult patients (issued November 2005). Available at: http://www.rcr.ac.uk/docs/radiology/pdf/IVcontrastPrintFinal.pdf (accessed 26/06/07)
4. European Society of Urogenital Radiology. ESUR guidelines on contrast media (version 6.0, issued February 2007). Available at: http://www.esur.org/fileadmin/Guidelines/ESUR_2007_Guideline_6_Kern_Ubersicht.pdf (accessed 26/06/07)

Ketotifen. Platelet counts in 10 diabetic patients receiving biguanides fell (markedly in 3 patients) when they were also given ketotifen.[1] Counts returned to normal a few days after the end of ketotifen therapy. However, the investigators did not consider the effect clinically significant.

1. Doleček R. Ketotifen in the treatment of diabetics with various allergic conditions. *Pharmatherapeutica* 1981; **2:** 568–74.

Sulfonylureas. For reference to an apparent increase in mortality with an intensive regimen of metformin plus a sulfonylurea, see p.462.

Uses and Administration

The biguanide antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p.431). They are given to supplement treatment by diet modification when such modification has not proved effective on its own. In addition, because biguanides are not associated with weight gain they are preferred in obese patients. Although sulfonylureas (p.460) may be preferred in non-obese patients, a biguanide is often added or given instead to patients who are not responding to a sulfonylurea.

The mode of action of biguanides is not clear. They do not stimulate insulin release but require that some insulin be present in order to exert their antidiabetic effect. Possible mechanisms of action include delay in the absorption of glucose from the gastrointestinal tract, an increase in insulin sensitivity and glucose uptake into cells, and inhibition of hepatic gluconeogenesis. Biguanides do not usually lower blood-glucose concentrations in non-diabetic subjects.

Hyperlipidaemias. The effect of biguanides on lipid metabolism is unclear, although some studies have shown a beneficial effect on serum-lipid profiles in both obese and lean patients with type 2 diabetes, hypertension, and/or hyperlipidaemia.[1] Reductions in concentrations of total cholesterol, low-density and very low-density-lipoprotein cholesterol have been reported, as well as modest increases in high-density-lipoprotein cholesterol. Some studies have also reported a reduction in serum-triglyceride levels. Such effects may be beneficial in the long-term treatment of type 2 diabetes mellitus with concomitant lipid disorders.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.

Polycystic ovary syndrome. For discussion of the potential of metformin in polycystic ovary syndrome, see p.454.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Azucaps†.

Multi-ingredient: *Mex.:* Glinorboral.

Buformin *(USAN, pINN)*

Buformina; Buformine; Buforminum; DBV; W-37. 1-Butylbiguanide.

Буформин

$C_6H_{15}N_5$ = 157.2.
CAS — 692-13-7 (buformin); 1190-53-0 (buformin hydrochloride).
ATC — A10BA03.
ATC Vet — QA10BA03.

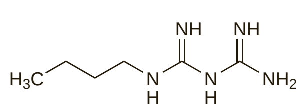

Profile

Buformin is a biguanide antidiabetic (p.437). It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in doses of up to 300 mg daily. Buformin is also used as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Adebit†; Silubin†; ***Hung.:*** Adebit; ***Spain:*** Silubin†; ***Switz.:*** Silubin†.

Carbutamide *(BAN, rINN)*

BZ-55; Ca-1022; Carbutamida; Carbutamidum; Glybutamide; Karbutamid; Karbutamidi; U-6987. 1-Butyl-3-sulphanilylurea.

Карбутамид

$C_{11}H_{17}N_3O_3S$ = 271.3.
CAS — 339-43-5.
ATC — A10BB06.
ATC Vet — QA10BB06.

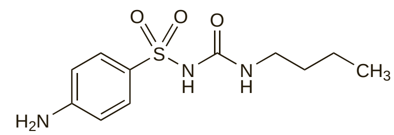

Profile

Carbutamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) in single daily doses of 0.5 to 1 g, but is more toxic than chlorpropamide.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Glucidoral.

Chlorpropamide *(BAN, rINN)*

Chloropropamid; Chlorpropamid; Chlorpropamidas; Chlorpropamidum; Clorpropamida; Klooripropamidi; Klórpropamid; Klorpropamid. 1-(4-Chlorobenzenesulphonyl)-3-propylurea.

Хлорпропамид

$C_{10}H_{13}ClN_2O_3S$ = 276.7.
CAS — 94-20-2.
ATC — A10BB02.
ATC Vet — QA10BB02.

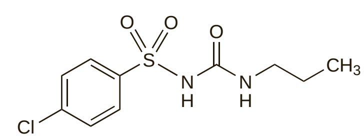

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Chlorpropamide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Chlorpropamide). A white crystalline powder having a slight odour. Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Adverse Effects and Treatment

As for sulfonylureas in general, p.460.

Chlorpropamide may be more likely than other sulfonylureas to induce a syndrome of inappropriate secretion of antidiuretic hormone characterised by water retention, hyponatraemia, and CNS effects. Patients receiving chlorpropamide may develop facial flushing after drinking alcohol.

Precautions

As for sulfonylureas in general, p.461.

Chlorpropamide should be avoided in the elderly and in renal or hepatic impairment because its long half-life increases the risk of hypoglycaemia. The antidiuretic effect of chlorpropamide may cause problems in patients with conditions associated with fluid retention.

Fasting. For the view that although some sulfonylurea antidiabetics may be able to be used with caution in fasting Muslim patients during Ramadan, chlorpropamide is contra-indicated, see under Precautions of Insulin, p.448.

Porphyria. Chlorpropamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Thyroid disorders. Some manufacturers recommend that chlorpropamide should not be used in patients with impaired thyroid function, but see under Sulfonylureas, p.461.

Interactions

As for sulfonylureas in general, p.461.

Chlorpropamide may produce profound facial flushing associated with alcohol ingestion.

Pharmacokinetics

Chlorpropamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. The half-life is about 35 hours. About 80% of a dose is metabolised in the liver; metabolites and unchanged drug are excreted in the urine. Chlorpropamide crosses the placenta and has been detected in breast milk.

Uses and Administration

Chlorpropamide is a sulfonylurea antidiabetic (p.460). It has a duration of action of at least 24 hours, and is given orally in the treatment of type 2 **diabetes mellitus** (p.431) in an initial daily dose of 250 mg as a single dose with breakfast. After 5 to 7 days the dose may be adjusted, in steps of 50 to 125 mg at intervals of 3 to 5 days, to achieve an optimum maintenance dose which is usually in the range 100 to 500 mg daily. Increasing the dose above 500 mg daily is unlikely to produce further benefit, and doses above 750 mg daily should be avoided. Although a reduced dose range has been proposed for the elderly, use of chlorpropamide is inadvisable in this group.

Chlorpropamide, though not the other sulfonylureas, is also sometimes used in cranial **diabetes insipidus** (p.2179). It has been reported to act by sensitising the renal tubules to antidiuretic hormone. The dose has to be carefully adjusted to minimise the risk of hypoglycaemia. An initial dose of 100 mg daily, adjusted if necessary to a maximum of 350 mg daily has been recommended, although doses of up to 500 mg daily have been used.

Diabetes mellitus. Patients with type 2 diabetes whose blood glucose is adequately controlled at first by sulfonylureas often eventually have treatment failure and loss of diabetic control. Results from the UK Prospective Diabetes Study[1] have suggested that the 6-year failure rate was higher in patients treated with glibenclamide (48%) than in those given chlorpropamide (40%). This difference was equivalent to delaying the requirement for additional therapy for a year in chlorpropamide-treated patients.

1. Matthews DR, *et al.* UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabet Med* 1998; **15:** 297–303.

Preparations

BP 2008: Chlorpropamide Tablets;
USP 31: Chlorpropamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diabinese; Idle†; Trane; ***Belg.:*** Diabinese†; ***Braz.:*** Clorpromini†; Clorzin†; Diabecontrol; Diabinese; Glicoben; Glicorp; Pramidalin; ***Canad.:*** Novo-Propamide; ***Chile:*** Diabinese; ***Gr.:*** Diabinese; ***Hong Kong:*** Diabinese; ***India:*** Copamide†; ***Indon.:*** Diabinese; ***Israel:*** Diabinese†; Diabitex; ***Ital.:*** Diabemide; ***Malaysia:*** Anti-D†; Diabinese†; Propamide; ***Mex.:*** Apoprod; Diabiclor; Diabinese; Insogen; ***Philipp.:*** Diabinese; ***S.Afr.:*** Diabinese; Hypomide; ***Singapore:*** Anti-D; Chlomide†; Diabinese†; Propamide; ***Spain:*** Diabinese; ***Thai.:*** Diabeedol; Diabinese; Dibecon; Glycemin; Propamide; ***Turk.:*** Diabinese; ***USA:*** Diabinese; ***Venez.:*** Diabinese.

Multi-ingredient: ***India:*** Chlorformin†; ***Ital.:*** Bidiabe; Pleiamide; ***Mex.:*** Insogen Plus; Mellitron; Obinese; ***Switz.:*** Diabiformine.

Epalrestat *(rINN)*

Épalrestat; Epalrestatum; ONO-2235. 5-[(*Z*,*E*)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid.

Эпалрестат

$C_{15}H_{13}NO_3S_2$ = 319.4.
CAS — 82159-09-9.

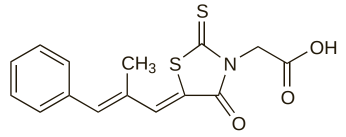

Profile

Epalrestat inhibits the enzyme aldose reductase which catalyses the conversion of glucose to sorbitol. It has been suggested that accumulation of sorbitol in certain cells, occurring only in conditions of hyperglycaemia and resulting in a hyperosmotic effect, may be involved in the pathogenesis of some diabetic complications. Aldose reductase inhibitors have no influence on blood-glucose concentrations. Epalrestat is given orally for the treatment of diabetic complications including neuropathy (p.433), in a usual dose of 50 mg three times daily before meals.

◊ References.

1. Goto Y, *et al.* A placebo-controlled double-blind study of epalrestat (ONO-2235) in patients with diabetic neuropathy. *Diabet Med* 1993; **10** (suppl 2): 39S–43S.
2. Uchida K, *et al.* Effect of 24 weeks of treatment with epalrestat, an aldose reductase inhibitor, on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 1995; **17:** 460–6.
3. Hotta N, *et al.* Clinical investigation of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy in Japan: multicenter study. *J Diabetes Complications* 1996; **10:** 168–72.
4. Ikeda T, *et al.* Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; **43:** 193–8.
5. Iso K, *et al.* Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in type 2 diabetic patients. *J Diabetes Complications* 2001; **15:** 241–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Kinedak.

Exenatide *(BAN, USAN, rINN)*

AC-2993; AC-002993; AC-2993A; Exenatida; Exénatide; Exenatidum; LY-2148568; Synthetic Exendin-4.

Эксенатид

$C_{184}H_{282}N_{50}O_{60}S$ = 4186.6.
CAS — 141758-74-9 (exenatide); 141732-76-5 (exendin-4).
ATC — A10BX04.
ATC Vet — QA10BX04.

H–His–Gly–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Leu– (10)
Ser–Lys–Gln–Met–Glu–Glu–Glu–Ala–Val–Arg– (20)
Leu–Phe–Ile–Glu–Trp–Leu–Lys–Asn–Gly–Gly– (30)
Pro–Ser–Ser–Gly–Ala–Pro–Pro–Pro–Ser–NH_2 (39)

Adverse Effects and Precautions

Hypoglycaemia can occur in patients given exenatide, particularly when given with a sulfonylurea (see also Interactions, below). Exenatide commonly causes mild to moderate nausea, which is dose-dependent and tends to decrease with continued therapy in most patients. Other adverse effects include vomiting, diarrhoea, nervousness, dizziness, headache, and dyspepsia. Less frequent reports include asthenia, decreased appetite, gastro-oesophageal reflux, and hyperhidrosis. Rashes and hypersensitivity reactions have occurred rarely. Acute pancreatitis has been reported, and in such cases exenatide should be stopped permanently.

Exenatide should not be used in type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use is not recommended in patients with severe renal impairment, in whom clearance is reduced and adverse gastrointestinal effects have been reported.

Effects on the pancreas. A 69-year-old man developed pancreatitis within a few days of starting exenatide therapy. Serum-lipase concentrations returned to normal and abdominal pain resolved rapidly when exenatide was stopped.[1] The FDA has also reviewed 30 reports of acute pancreatitis in patients treated with exenatide.[2] In 27 cases there was at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. Improvement after stopping exenatide was confirmed in 22 reports, and in 3 cases of rechallenge there was a return of symptoms of acute pancreatitis. The FDA subsequently reported[3] in August 2008 that they had received reports of 6 cases of haemorrhagic or necrotising pancreatitis associated with exenatide; all patients required hospitalisation and 2 died. It was recommended that exenatide therapy should be stopped if signs or symptoms of pancreatitis develop and should not be restarted if pancreatitis is confirmed. Other antidiabetic drugs should be considered for those with a history of pancreatitis.

1. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care* 2006; **29:** 471.
2. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued October 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatideHCP.htm (accessed 17/10/07)
3. FDA. Information for healthcare professionals: exenatide (marketed as Byetta) (issued August 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm (accessed 20/08/08)

Interactions

A reduction in the sulfonylurea dose may be required when exenatide is added to therapy, because of an increased risk of hypoglycaemia with this combination. No increase in hypoglycaemia occurs when exenatide is used with metformin or a thiazolidinedione. The extent and rate of absorption of oral drugs may be reduced by exenatide. Where such an interaction would be undesirable, the oral medication should be given at least 1 hour before exenatide. If the oral medication is to be taken with food, where possible, it should be with a meal or snack when exenatide is not used.

Pharmacokinetics

After subcutaneous injection, peak plasma concentrations of exenatide are reached in about 2 hours. It is eliminated through the kidneys by glomerular filtration followed by proteolytic degradation, with a terminal half-life of about 2.4 hours. Clearance is reduced in patients receiving dialysis for end-stage renal disease.

◊ References.

1. Kolterman OG, *et al.* Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health-Syst Pharm* 2005; **62:** 173–81.
2. Linnebjerg H, *et al.* Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol* 2007; **64:** 317–27.

Uses and Administration

Exenatide is a synthetic form of exendin-4, a 39-amino acid peptide isolated from the venom of the Gila monster lizard (*Heloderma suspectum*, Helodermatidae). The drug is an incretin mimic that acts as an agonist at the glucagon-like peptide 1 receptor to enhance insulin secretion in the presence of raised glucose concentrations; it also suppresses inappropriate glucagon secretion and slows gastric emptying. Exenatide is used as adjunctive therapy in type 2 diabetes mellitus (p.431) in patients who do not have adequate glycaemic control with metformin, a sulfonylurea, a thiazolidinedione, or dual therapy with metformin plus a sulfonylurea or thiazolidinedione. It is given by subcutaneous injection in an initial dose of 5 micrograms twice daily within 60 minutes before the morning and evening meals. The dose of exenatide may be increased after 1 month to 10 micrograms twice daily if required.

◊ References.

1. Fineman MS, *et al.* Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes Metab Res Rev* 2004; **20:** 411–17.
2. Buse JB, *et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 2628–35.
3. Kendall DM, *et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; **28:** 1083–91.
4. DeFronzo RA, *et al.* Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 1092–1100.
5. Heine RJ, *et al.* Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; **143:** 559–69.
6. Yoo BK, *et al.* Exenatide: a new option for the treatment of type 2 diabetes. *Ann Pharmacother* 2006; **40:** 1777–84.
7. Ratner RE, *et al.* Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2006; **8:** 419–28.
8. Nauck MA, *et al.* A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007; **50:** 259–67.
9. Zinman B, *et al.* The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; **146:** 477–85. Correction. *ibid.*; 896.
10. Cvetković RS, Plosker GL. Exenatide: a review of its use in patients with type 2 diabetes mellitus (as an adjunct to metformin and/or a sulfonylurea). *Drugs* 2007; **67:** 935–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Byetta; ***Austral.:*** Byetta; ***Braz.:*** Byetta; ***Cz.:*** Byetta; ***Port.:*** Byetta; ***UK:*** Byetta; ***USA:*** Byetta.

Glibenclamide *(BAN, rINN)*

Glibenclamida; Glibenclamidum; Glibenklamid; Glibenklamidas; Glibenklamidi; Glybenclamide; Glybenzcyclamide; Glyburide *(USAN)*; HB-419; U-26452. 1-{4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulphonyl}-3-cyclohexylurea.

Глибенкламид

$C_{23}H_{28}ClN_3O_5S = 494.0$.

CAS — 10238-21-8.

ATC — A10BB01.

ATC Vet — QA10BB01.

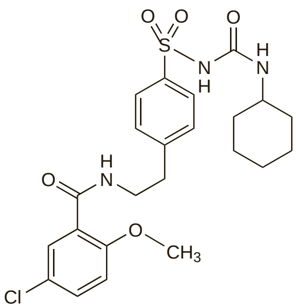

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Glibenclamide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in dichloromethane.

USP 31 (Glyburide). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460.

◊ For a suggestion that the failure rate in type 2 diabetics treated with glibenclamide may be higher than that for those treated with chlorpropamide, see Diabetes Mellitus under Uses and Administration of Chlorpropamide, p.439.

Effects on the blood. References.

1. Nataas OB, Nesthus I. Immune haemolytic anaemia induced by glibenclamide in selective IgA deficiency. *BMJ* 1987; **295:** 366–7.
2. Israeli A, *et al.* Glibenclamide causing thrombocytopenia and bleeding tendency: case reports and a review of the literature. *Klin Wochenschr* 1988; **66:** 223–4.
3. Meloni G, Meloni T. Glyburide-induced acute haemolysis in a G6PD-deficient patient with NIDDM. *Br J Haematol* 1996; **92:** 159–60.
4. Noto H, *et al.* Glyburide-induced hemolysis in myelodysplastic syndrome. *Diabetes Care* 2000; **23:** 129.

Hypoglycaemia. Severe hypoglycaemia may occur in any patient given any sulfonylurea (see p.461); glibenclamide which has a relatively prolonged duration of action, may cause severe hypoglycaemia more often than shorter-acting sulfonylureas.

In a 1983 review[1] of 57 instances of hypoglycaemia associated with glibenclamide the median age of patients affected was 70 years; only one was less than 60 years old. Median daily dosage was 10 mg. Coma or disturbed consciousness was seen in 46 patients. Ten of these remained comatose despite alleviation of their hypoglycaemia and died up to 20 days after presentation. The authors noted that, including their series of 57 cases, there had been published reports on 101 cases of severe hypoglycaemia with glibenclamide, 14 with a fatal outcome.

There has been a report[2] of hypoglycaemic coma associated with the inhalation of glibenclamide by a worker at a pharmaceutical plant.

1. Asplund K, *et al.* Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia* 1983; **24:** 412–17.
2. Albert F, *et al.* Hypoglycaemia by inhalation. *Lancet* 1993; **342:** 47–8.

Porphyria. Glibenclamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Glibenclamide is readily absorbed from the gastrointestinal tract, peak plasma concentrations usually occurring within 2 to 4 hours, and is extensively bound to plasma proteins. Absorption may be slower in hyperglycaemic patients and may differ according to the particle size of the preparation used. It is metabolised, almost completely, in the liver, the principal metabolite being only very weakly active. About 50% of a dose is excreted in the urine and 50% via the bile into the faeces.

◊ References.

1. Coppack SW, *et al.* Pharmacokinetic and pharmacodynamic studies of glibenclamide in non-insulin dependent diabetes mellitus. *Br J Clin Pharmacol* 1990; **29:** 673–84.
2. Jaber LA, *et al.* The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. *Eur J Clin Pharmacol* 1993; **45:** 459–63.
3. Hoffman A, *et al.* The effect of hyperglycaemia on the absorption of glibenclamide in patients with non-insulin-dependent diabetes mellitus. *Eur J Clin Pharmacol* 1994; **47:** 53–5.
4. Rydberg T, *et al.* Concentration-effect relations of glibenclamide and its active metabolites in man: modelling of pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1997; **43:** 373–81.

Uses and Administration

Glibenclamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of up to 24 hours.

The usual initial dose of conventional formulations in type 2 diabetes mellitus is 2.5 to 5 mg daily with breakfast, adjusted every 7 days in steps of 2.5 or 5 mg daily up to 15 mg daily. Although increasing the dose above 15 mg is unlikely to produce further benefit, doses of up to 20 mg daily have been given. Doses greater than 10 mg daily may be given in 2 divided doses. Because of the relatively long duration of action of glibenclamide, it is best avoided in the elderly.

In some countries micronised preparations of glibenclamide are available, in which the drug is formulated with a smaller particle size, and which have enhanced bioavailability. The usual initial dose of one such preparation (*Glynase PresTab; Pharmacia Upjohn, USA*) is 1.5 to 3 mg daily, adjusted every 7 days in steps of 1.5 mg, up to a usual maximum of 12 mg daily. Doses greater than 6 mg daily may be given in 2 divided doses.

Action. Proceedings of a symposium on the mechanism of action of glibenclamide.[1]

1. Gavin JR, ed. Glyburide: new insights into its effects on the beta cell and beyond. *Am J Med* 1990; **89** (suppl 2A): 1–53S.

EFFECTS ON THE HEART. A reduced incidence of ventricular fibrillation has been reported in diabetics treated with glibenclamide who develop myocardial infarction, compared with those receiving other treatments or with nondiabetic patients with myocardial infarction.[1] However, some evidence has also suggested that sulfonylureas may impair the adaptive responses of the heart to ischaemia—see p.461.

1. Lomuscio A, *et al.* Effects of glibenclamide on ventricular fibrillation in non-insulin-dependent diabetes with acute myocardial infarction. *Coron Artery Dis* 1994; **5:** 767–71.

Preparations

BP 2008: Glibenclamide Tablets;
USP 31: Glyburide and Metformin Hydrochloride Tablets; Glyburide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Agobilina; Benclamid; Daonil; Diabe Pass; Diabemin; Euglucon; Gardoton; Glentor; Glibediab†; Glibemida; Glidanil; Gliptid; Glitral; GON; Pira; Siruc; ***Austral.:*** Daonil; Glimel; Semi-Daonil; ***Austria:*** Daonil; Dia-Eptal; Euglucon; Gilemal; Glucobene; Glucostad; Normoglucon; Semi-Euglucon; ***Belg.:*** Bevoren; Daonil; Euglucon; ***Braz.:*** Aglucil; Benclamin; Clamiben; Daonil; Diaben; Diabetty's†; Diabexil; Euglucon; Gliben†; Glibenclamon; Glibendiab; Glibexil†; Glicamin; Glionil; Lisaglucon; Uni Gliben†; ***Canad.:*** DiaBeta; Euglucon; Gen-Glybe; ***Chile:*** Daonil; Euglusid; Mezalit; ***Cz.:*** Betanase†; Glibenhexal†; Glucobene; Humedia†; Maninil; ***Denm.:*** Daonil; Hexaglucon; Regulin†; ***Fin.:*** Daonil†; Euglamin; Euglucon; Origlucon; Semi-Euglucon; ***Fr.:*** Daonil; Euglucan; Hemi-Daonil; Miglucan; ***Ger.:*** Azuglucon†; Bastiverit†; duraglucon N; Euglucon N; Glib; Glib-ratiopharm; Gliben; Gliben-Azu†; Gliben-Puren N†; Glibenbeta; Glibendoc; Glibenhexal; Glimidstada†; Glucoremed†; Glukoreduct†; Glukovital; glycolande N†; Humedia; Jutaglucon†; Maninil; Praeciglucon†; Semi-Euglucon N; ***Gr.:*** Daonil; Deroctyl; Diabefar†; ***Hong Kong:*** Calabren†; Clamide; Daonil; Euglucon; Gliben; Gliboral; Glimel; Glitisol; Marglucon; Semi-Daonil†; Semi-Euglucon; Xeltic; ***Hung.:*** Gilemal; Glucobene; Maninil; ***India:*** Daonil; Euglucon; Glinil; Glybovin; Semi-Daonil; Semi-Euglucon; ***Indon.:*** Condiabet; Daonil; Glidanil; Glimel; Gluconic; Glulo; Glyamid; Libronil; Prodiabet; Prodiamel; Renabetic; Semi-Daonil; Tiabet; Trodeb; ***Irl.:*** Daonil; Semi-Daonil; ***Israel:*** Daonil†; Glibetic; Gluben; ***Ital.:*** Daonil; Euglucon; Gliben; Gliboral; ***Jpn:*** Euglucon; ***Malaysia:*** Claben†; Daonil; Debtan†; Dibelet; Gliben; Glibesyn; Glimide; ***Mex.:*** Abuglib; Apogly; Biostin; Daonil; Dibetid; Diglexol; Euglucon; Gadinor; Glemicid; Glibenil; Glibenval; Glicavin; Glicoxem; Glifarcal; Glihexal; Glikeyer†; Glipar; Glucal; Glucoven; Insusym; Mibeclag; Nadib†; Norboral; Ocrix; Reglusan; ***Neth.:*** Daonil; Hemi-Daonil†; ***Norw.:*** Daonil†; ***NZ:*** Gliben; ***Philipp.:*** Amecladin; Daonil; Diabitor; Euglucon; Eundin; Gluban; Glymod; Insol; Lodulce; Orabetic; Semi-Euglucon; Sentionyl; Sucron; ***Pol.:*** Euclamin; ***Port.:*** Daonil; Euglucon; Semi-Daonil; Semi-Euglucon†; ***Rus.:*** Betanase (Бетаназ); Glibamide (Глибамид)†; Glibex (Глибекс); Glidanil (Гliданил); Maninil (Манинил); ***S.Afr.:*** Daonil; Diacare; Euglucon†; Glycomin; ***Singapore:*** Clamide; Daonil; Dibelet; GBN†; Glibemid†; Glibesyn; Glimel; Glimide; ***Spain:*** Daonil; Euglucon; Glucolon; Norglicem; ***Swed.:*** Daonil; Euglucon; ***Switz.:*** Daonil; Euglucon; gli-basan; Glibenorme; Glibesifar; Melix; Semi-Daonil; Semi-Euglucon†; ***Thai.:*** Benclamin; BNIL; Cytagon†; Daonil; Daono; Debtan; Diabenol; Dibelet; Diclanil; Euglucon; Glencamide†; Gliben†; Glibetic; Glibic; Gluconil; Gluzo; Locose; Manoglucon; Med-Glionil†; Semi-Euglucon†; Sugril; Unil; Xeltic; ***Turk.:*** Dianorm; Diyaben; Gliben; ***UAE:*** Glynase; Mini-Glynase; ***UK:*** Daonil; Diabetamide†; Euglucon†; Semi-Daonil†; ***USA:*** DiaBeta; Glynase; Micronase; ***Venez.:*** Daonil; Euglucon; Gliciron.

Multi-ingredient: *Arg.:* DBI Duo; Glucovance; Isloglib; Medobis G; Metformin Duo; ***Austral.:*** Glucovance; ***Belg.:*** Glucovance; ***Braz.:*** Glucovance; ***Chile:*** Bi-Euglucon M; Diaglitab Plus; Glifortex-G; Glimet; Glucovance; Glukaut; Hipoglucin DA; ***Cz.:*** Glibomet; Glucovance; ***Fr.:*** Glucovance; ***Gr.:*** Daopar†; Normell; ***Hong Kong:*** Glucovance; ***India:*** Diaforte; Glinil M; ***Indon.:*** Glucovance; ***Ital.:*** Bi-Euglucon M; Bi-Euglucon†; Gliben F; Glibomet; Gliconorm; Glicorest; Gliformin; Glucomide; Suguan M; Suguan†; ***Malaysia:*** Glucovance; ***Mex.:*** Apometglu; Bi-Dizalon; Bi-Euglucon M; Bi-Pradia; Duo-Anglucid; Glinorboral; Glucotec; Glucovance; Imalet; Insusym-Forte; Maviglin; Midapharma; Mifelar-C; Nadib-M; Norfaben M; Sibet-C; Sil-Norboral; Wadil; ***Neth.:*** Glucovance; ***Philipp.:*** Euglo Plus; Glucovance; ***Port.:*** Glucovance; ***Rus.:*** Glibomet (Глибомет); Glucovance (Глюкован); ***S.Afr.:*** Glucovance; ***Singapore:*** Glucovance; ***Switz.:*** Glucovance; ***USA:*** Diofen; Glucovance; Glybofen; ***Venez.:*** Bi-Euglucon; Diaformina Plus; Glucovance.

Glibornuride *(BAN, USAN, rINN)*

Glibornurid; Glibornurida; Glibornuridi; Glibornuridum; Ro-6-4563. 1-[(2*S*,3*R*)-2-Hydroxybornyl-3-yl]-3-tosylurea; 1-[(2*S*,3*R*)-2-Hydroxyborn-3-yl]-3-*p*-tolylsulphonylurea.

Глиборнурид

$C_{18}H_{26}N_2O_4S = 366.5$.

CAS — 26944-48-9.

ATC — A10BB04.

ATC Vet — QA10BB04.

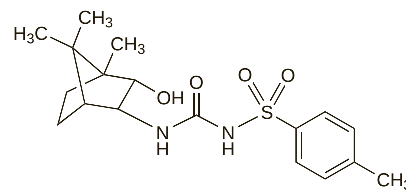

NOTE. The name glibornuride has frequently but erroneously been applied to glibenclamide.

Profile

Glibornuride is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) in doses of 12.5 to 75 mg daily. Daily doses of 50 mg or more are given in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Glutril; ***Fr.:*** Glutril; ***Ger.:*** Glubori d†; Glutril†; ***Switz.:*** Gluborid†; Glutril; ***Turk.:*** Glutril.

Gliclazide *(BAN, rINN)*

Gliclazida; Gliclazidum; Gliklatsidi; Gliklazid; Gliklazidas; Glyclazide; SE-1702. 1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-tosylurea; 1-(3-Azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea.

Гликлазид

$C_{15}H_{21}N_3O_3S = 323.4$.

CAS — 21187-98-4.

ATC — A10BB09.

ATC Vet — QA10BB09.

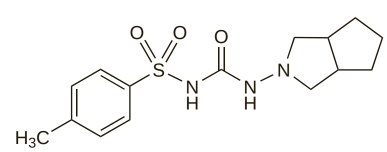

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Gliclazide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460.

The *BNF* suggests that gliclazide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Gliclazide is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins. The half-life is about 10 to 12 hours. Gliclazide is extensively metabolised in the liver to metabolites that have no significant hypoglycaemic activity. Metabolites and a small amount of unchanged drug are excreted in the urine.

◊ References.

1. Kobayashi K, *et al*. Pharmacokinetics of gliclazide in healthy and diabetic subjects. *J Pharm Sci* 1984; **73:** 1684–7.

Uses and Administration

Gliclazide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of 12 to 24 hours. Because its effects are less prolonged than those of chlorpropamide or glibenclamide it may be more suitable for elderly patients, who are prone to hypoglycaemia with longer-acting sulfonylureas. The usual initial dose is 40 to 80 mg daily, gradually increased, if necessary, up to 320 mg daily. Doses of more than 160 mg daily are given in 2 divided doses. A modified-release tablet is also available: the usual initial dose is 30 mg once daily, increased if necessary up to a maximum of 120 mg daily.

◊ References.

1. Palmer KJ, Brogden RN. Gliclazide: an update of its pharmacological properties and therapeutic efficacy in non-insulin-dependent diabetes mellitus. *Drugs* 1993; **46:** 92–125.
2. Mailhot J. Efficacy and safety of gliclazide in the treatment of non-insulin-dependent diabetes mellitus: a Canadian multicenter study. *Clin Ther* 1993; **15:** 1060–8.
3. Ziegler O, Drouin P. Hemobiological properties of gliclazide. *J Diabetes Complications* 1994; **8:** 235–9.
4. Jennings PE. Vascular benefits of gliclazide beyond glycemic control. *Metabolism* 2000; **49** (suppl 2): 17–20.
5. Crepaldi G, Fioretto P. Gliclazide modified release: its place in the therapeutic armamentarium. *Metabolism* 2000; **49** (suppl 2): 21–5.
6. McGavin JK, *et al*. Gliclazide modified release. *Drugs* 2002; **62:** 1357–64.

Preparations

BP 2008: Gliclazide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aglucide; Diamicron; Unava; ***Austral.:*** Diamicron; Glyade; Nidem; Oziclide; ***Austria:*** Diamicron; ***Belg.:*** Diamicron; Uni Diamicron; ***Braz.:*** Azukon; Diamicron; Glicaron; ***Canad.:*** Diamicron; ***Chile:*** Dianormax; ***Cz.:*** Diabrezide†; Diaprel; ***Denm.:*** Diamicron; ***Fr.:*** Diamicron; ***Ger.:*** Diamicron; ***Gr.:*** Diamicron; ***Hong Kong:*** CP-Gliz; Diamicron; Diamitex; Dianorm; Glimicron; Glucozide; Glupozide; Glyzyl; Licla; Marclazide; Nidem; Qualizide; Suclear; Sun-Glizide; ***Hung.:*** Diaprel; Gluctam; ***India:*** Diamicron; Gliza; Glizid; Glycigon; Glycinorm; Glygard; Lycazid; Semi-Glycigon; ***Indon.:*** Diamicron; Fredam; Glicab; Glidabet; Glucodex; Glucored; Glukolos; Glycafor; Linodiab; Meltika; Nufamicron; Pedab; Tiaglib; Xepabet; Zumadiac; ***Irl.:*** Diabrezide; Diaclide; Diamicron; ***Ital.:*** Cronemet; Diabrezide; Diamicron; Dramion; Galtes; Glucobloc; ***Malaysia:*** Diacron†; Diamicron; Dianid; Glimicron; Glucozide; Glyade; Medoclazide; Melicron†; Opglucon; Reclide; Sun-Glizide; ***Mex.:*** Diamicron; ***Neth.:*** Diamicron; ***NZ:*** Diamicron; Glizon; ***Philipp.:*** Clibite; Clizid; Diaclid; Diamicron; Dianorm; Glubitor; Gluconil; Glucoprime; ***Pol.:*** Diabezidum; Diabrezide; Diaprel; Diazidan; Glazide; Glinormax; Norsulin; ***Port.:*** Diamicron; ***Rus.:*** Diabest (Диабест); Diabeton (Диабетон); Diabinax (Диабинакс); Diatica (Диатика); Glucostabil (Глюкостабил); Glydiab (Глидиаб); Reclide (Реклид); ***S.Afr.:*** Diaglucide; Diamicron; Glucomed; Glycron; Glygard; Ziclin; ***Singapore:*** Diamicron; Dianorm; Glimicron; Glizide; Glucozide; Medoclazide; Melicron†; ***Spain:*** Diamicron; Uni Diamicron; ***Switz.:*** Diamicron; ***Thai.:*** Cadicon; Diabeside; Diaclaron†; Diamaze†; Diamexon; Diamicron; Dianid; Glicron; Glucocron; Glucozide; Glycon; Medoclazide; Serviclazide; ***Turk.:*** Betanorm; Diamicron; Glazid; Glumikron; Oramikron; ***UAE:*** Glyzide; ***UK:*** Diaglyk; Diamicron; ***Venez.:*** Diamicron; Glidan; Reclide†.

Multi-ingredient: ***India:*** Exermet GZ; Gliclamet; Glizid-M; Glycigon-M; Glycinorm M; Glygard M; Glyroz.

Glimepiride *(BAN, USAN, rINN)*

Glimepirid; Glimepirida; Glimépiride; Glimepiridi; Glimepiridum; Glimepiryd; Hoe-490. 1-({*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl}sulfonyl)-3-(*trans*-4-methylcyclohexyl)urea.

Глимепирид

$C_{24}H_{34}N_4O_5S$ = 490.6.

CAS — 93479-97-1.

ATC — A10BB12.

ATC Vet — QA10BB12.

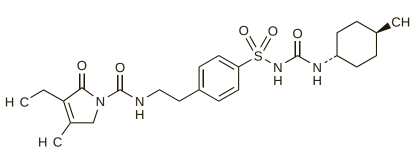

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Glimepiride). A white to almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dichloromethane; soluble in dimethylformamide; very slightly soluble in methyl alcohol.

USP 31 (Glimepiride). A white to almost white powder. Practically insoluble in water; sparingly soluble in dichloromethane; soluble in dimethylformamide; slightly soluble in methyl alcohol. It dissolves in dilute alkali hydroxides and in dilute acids. Store at a temperature not exceeding 25°.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460. In some countries hepatic and haematological monitoring is recommended in patients receiving glimepiride; in the UK the *BNF* considers the practical value of such monitoring unproven.

Fasting. Glimepiride, given in unchanged doses but with the time of the single daily dose switched from morning to just before breaking fast after sunset, was used in Muslim patients during Ramadan without causing an increased incidence of hypoglycaemic episodes.[1]

For further advice on the management of diabetes mellitus in fasting Muslim patients during Ramadan see under Precautions of Insulin, p.448.

1. The Glimepiride in Ramadan (GLIRA) Study Group. The efficacy and safety of glimepiride in the management of type 2 diabetes in Muslim patients during Ramadan. *Diabetes Care* 2005; **28:** 421–2.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Glimepiride is completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 2 to 3 hours, and it is highly protein bound. The drug is extensively metabolised to two main metabolites, a hydroxy derivative and a carboxy derivative. The half-life after multiple doses is about 9 hours. About 60% of a dose is eliminated in the urine and 40% in the faeces.

Uses and Administration

Glimepiride is a sulfonylurea antidiabetic (p.460). It is given orally for the treatment of type 2 diabetes mellitus (p.431). Initial doses of 1 to 2 mg daily may be increased if necessary to 4 mg daily for maintenance. The maximum recommended dose is 6 mg in the UK and 8 mg in the USA.

◊ References.

1. Langtry HD, Balfour JA. Glimepiride: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 1998; **55:** 563–84.
2. Campbell RK. Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. *Ann Pharmacother* 1998; **32:** 1044–52.
3. McCall AL. Clinical review of glimepiride. *Expert Opin Pharmacother* 2001; **2:** 699–713.
4. Massi-Benedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. *Clin Ther* 2003; **25:** 799–816.
5. Weitgasser R, *et al*. Effects of glimepiride on HbA(1c) and body weight in type 2 diabetes: results of a 1.5-year follow-up study. *Diabetes Res Clin Pract* 2003; **61:** 13–19.
6. Feinbock C, *et al*. Prospective multicentre trial comparing the efficacy of, and compliance with, glimepiride or acarbose treatment in patients with type 2 diabetes not controlled with diet alone. *Diabetes Nutr Metab* 2003; **16:** 214–21.

Preparations

USP 31: Glimepiride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Adiuvan; Amaryl; Endial; Glemaz; Gluceride; Glucopirida; Islopir; Lomet; Next Step; ***Austral.:*** Amaryl; Aylide; Diapride; Dimirel; ***Austria:*** Amaryl; ***Belg.:*** Amarylle; ***Braz.:*** Amaryl; Azulix; Bioglic; Diamellitis; Glimepibal; Glimepil; Glimeprid†; Glimeran; Glimesec†; Hipomeril; ***Canad.:*** Amaryl; ***Chile:*** Amaryl; Glemaz; Glucomet; ***Cz.:*** Amarwin; Amaryl; Amyx; Apo-Glimep; Eglymad; Glemid; GlimTek; Glymexan; Melyd; Metis; Oltar; ***Denm.:*** Amaryl; ***Fin.:*** Amaryl; ***Fr.:*** Amarel; ***Ger.:*** Amaryl; Glimegamma; Glimerid; ***Gr.:*** Dialosa; Glimepiron; Glimespes; Glimexin; Gliperin; Mepirid; Penoza; Pharlecon; Saccharofar; Solosa; Sucryl; Tipo II; Toremol; ***Hong Kong:*** Amaryl; Diapride; ***Hung.:*** Amaryl; Dialosa; Glempid; GlimeWin; Glindia; Gliprex; Limeral; Meglimid; Melyd; Sintecal; ***India:*** Amaryl; Betaglim†; Diaglim; Euglim; Glimcip; Glimiprex; Glimitab; Glimulin; Glyree; Glyree M; Karmelitos; ***Indon.:*** Amadiab; Amaryl; Anpiride; Glamarol; Glimexal; Gluvas; Mapryl; Metrix; Relide; ***Irl.:*** Amaryl; ***Israel:*** Amaryl; ***Ital.:*** Amaryl; Solosa; ***Malaysia:*** Amaryl; Diapride; Glimaryl; Glimin; Glimulin; Miaryl; ***Mex.:*** Amaryl; Glupropan; Zukedib; ***Neth.:*** Amaryl; ***Norw.:*** Amaryl; ***NZ:*** Amaryl; ***Philipp.:*** Imerid; Norizec; Solosa; ***Pol.:*** Amaryl; Amyx; Avaron; Betaglid; Diaril; Glemid; Glibetic; Glibezid; Glidiamid; Glimehexal; Glimesan; Glipid; Limeral; Melyd; Oltar; Pemidal; Symglic; ***Port.:*** Amaryl; Diapiride; Glimial; Gludon; ***Rus.:*** Amaryl (Амарил); Glemaz (Глемаз); ***S.Afr.:*** Amaryl; Glamaryl; ***Singapore:*** Amaryl; Diapride; ***Spain:*** Amaryl; Roname; ***Swed.:*** Amaryl; ***Switz.:*** Amaryl; ***Thai.:*** Amaryl; ***Turk.:*** Amaryl; Diameprid; Glimax; ***UK:*** Amaryl; Niddaryl; ***USA:*** Amaryl; ***Venez.:*** Amaryl; Dimavyl; Glimerid.

Multi-ingredient: ***Cz.:*** Avaglim; Tandemact; ***Fr.:*** Avaglim; Tandemact; ***Gr.:*** Avaglim; ***Hung.:*** Avaglim; ***India:*** Betaglim M†; Exermet GM; Glimiprex MF; Glimulin-MF†; ***Indon.:*** Avandaryl; ***Mex.:*** Glimetal; ***Port.:*** Avaglim; Tandemact; ***USA:*** Avandaryl; Duetact.

Glipizide *(BAN, USAN, pINN)*

CP-28720; Glipitsidi; Glipizid; Glipizida; Glipizidas; Glipizidum; Glipizyd; Glydiazinamide; K-4024. 1-Cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzenesulphonyl}urea.

Глипизид

$C_{21}H_{27}N_5O_4S$ = 445.5.

CAS — 29094-61-9.

ATC — A10BB07.

ATC Vet — QA10BB07.

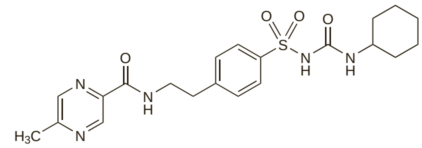

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Glipizide). A white or almost white crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Glipizide). Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460.

Porphyria. Glipizide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Antacids. *Magnesium hydroxide* and *sodium bicarbonate* have been reported to increase the rate of absorption, although not the total amount absorbed, of a dose of glipizide in healthy subjects.[1,2] No such effect was seen with *aluminium hydroxide*.[2]

1. Kivisto KT, Neuvonen PJ. Enhancement of absorption and effect of glipizide by magnesium hydroxide. *Clin Pharmacol Ther* 1991; **49:** 39–43.
2. Kivisto KT, Neuvonen PJ. Differential effects of sodium bicarbonate and aluminium hydroxide on the absorption and activity of glipizide. *Eur J Clin Pharmacol* 1991; **40:** 383–6.

Pharmacokinetics

Glipizide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 to 3 hours after a single dose. It is extensively bound to plasma proteins and has a half-life of about 2 to 4 hours. It is metabolised mainly in the liver and excreted chiefly in the urine, largely as inactive metabolites.

Uses and Administration

Glipizide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of up to 24 hours. The usual initial dose is 2.5 to 5 mg daily given as a single dose about 30 minutes before breakfast. Dosage may be adjusted at intervals of several days by amounts of 2.5 to 5 mg daily, to a maximum of 20 mg daily. Doses up to 40 mg daily have been used, but see below. Doses larger than 15 mg daily are given in two divided doses before meals. Modified-release formulations of glipizide are available in some countries; one such preparation (*Glucotrol XL; Pfizer, USA*) is given in doses of 5 to 10 mg daily as a single dose with breakfast.

Administration. Although glipizide may be given in doses up to a maximum of 40 mg daily, evidence for the benefits of high doses is scanty. A small study in patients with type 2 diabetes mellitus found that not only did increases in glipizide doses to more than 10 mg daily produce little or no benefit, but that the higher doses were associated with reduced rises in plasma-insulin concentrations and a lesser reduction in plasma-glucose concentrations.[1] There is, however, some evidence that glycaemic control and insulin sensitivity can be improved by the use of a modified-release rather than a conventional formulation of glipizide.[2,3]

1. Stenman S, *et al*. What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med* 1993; **118:** 169–72.
2. Berelowitz M, *et al*. Comparative efficacy of once-daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM. *Diabetes Care* 1994; **17:** 1460–4.
3. Leaf E, King JO. Patient outcomes after formulary conversion from immediate-release to extended-release glipizide tablets. *Am J Health-Syst Pharm* 1999; **56:** 454–6.

Preparations

BP 2008: Glipizide Tablets;
USP 31: Glipizide and Metformin Hydrochloride Tablets; Glipizide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Minodiab; ***Austral.:*** Melizide; Minidiab; ***Austria:*** Glibenese; Minidiab; ***Belg.:*** Glibenese; Minidiab; ***Braz.:*** Glipgen†; Minidiab; ***Chile:*** Minidiab; Xiprine; ***Cz.:*** Antidiab†; Glucotrol†; Mediab†; Minidiab; ***Denm.:*** Glibenese; Mindiab; ***Fin.:*** Apamid†; Glibenese; Melizid; Mindiab; ***Fr.:*** Glibenese; Minidiab; Ozidia; ***Gr.:*** Glibenese; Minodiab†; ***Hong Kong:*** Diasef; Glucotrol; Minidiab; Sunglucon; ***Hung.:*** Minidiab; ***India:*** Diaglip; Glez; Glide; Glipicontin†; Glucolip; Glynase; Glyzip; ***Indon.:*** Aldiab; Glucotrol; Glyzid; ***Irl.:*** Glibenese; ***Israel:*** Gluco-Rite; ***Ital.:*** Minidiab; ***Malaysia:*** Dibizide†; Dipazide; Glix; Melizide; Minidiab; ***Mex.:*** Glupitel†; Luditec; Minodiab; Pigloss; Singloben; ***Neth.:*** Glibenese†; ***Norw.:*** Apamid; Mindiab; ***NZ:*** Glipid†; Minidiab; ***Philipp.:*** Glix; Minidiab; ***Pol.:*** Antidiab; Glibenese; ***Port.:*** Minidiab; ***Rus.:*** Glibenese (Глибенез); Minidiab (Минидиаб)†; ***S.Afr.:*** Minidiab; ***Singapore:*** Beapizide; Diactin; Diasef; Melizide; Minidiab; ***Spain:*** Glibenese†; Minodiab; ***Swed.:*** Apamid†; Glipiscand†; Mindiab; ***Switz.:*** Glibenese; ***Thai.:*** Apamid†; Depizide; Diasef; Dipazide; Gipzide; Glipimed; Glizide; Glucodiab; Glygen; GP-Zide; Melizide; Minibit; Minidiab; Namedia; Pezide; ***Turk.:*** Glucotrol; Minidiab; ***UK:*** Glibenese; Minodiab; ***USA:*** Glucotrol; ***Venez.:*** Minidiab.

Multi-ingredient: ***India:*** Diaglip M; Metaglez; ***USA:*** Metaglip.

Gliquidone *(BAN, rINN)*

ARDF-26; Glikidon; Glikidoni; Gliquidona; Gliquidonum. 1-Cyclohexyl-3-{4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1*H*)-isoquinolyl)ethyl]benzenesulphonyl}urea.

Гликвидон

$C_{27}H_{33}N_3O_6S$ = 527.6.
CAS — 33342-05-1.
ATC — A10BB08.
ATC Vet — QA10BB08.

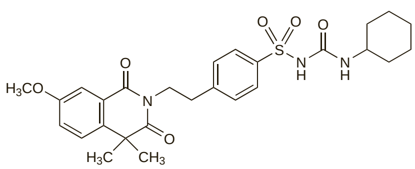

Pharmacopoeias. In *Br.* and *Chin.*
BP 2008 (Gliquidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dimethylformamide.

Adverse Effects, Treatment, and Precautions
As for sulfonylureas in general, p.460.

Interactions
As for sulfonylureas in general, p.461.

Pharmacokinetics
Gliquidone is readily absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins and has a half-life of about 1.5 hours. It is extensively metabolised in the liver, the metabolites having no significant hypoglycaemic effect, and is eliminated chiefly in the faeces via the bile; only about 5% of a dose is excreted in the urine.

Uses and Administration
Gliquidone is a sulfonylurea antidiabetic (p.460). It has been given orally in the treatment of type 2 diabetes mellitus (p.431) in a usual initial dosage of 15 mg daily given as a single dose up to 30 minutes before breakfast. Dosage may be adjusted by increments of 15 mg to a usual dose of 45 to 60 mg daily in 2 or 3 unequally divided doses, the largest dose being taken in the morning with breakfast. Single doses above 60 mg and daily doses above 180 mg are not recommended.

Preparations

BP 2008: Gliquidone Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Glurenorm; ***Belg.:*** Glurenorm; ***Cz.:*** Glurenorm; ***Ger.:*** Glurenorm; ***Gr.:*** Devotan; ***Hung.:*** Glurenorm; ***Indon.:*** Glurenorm; ***Ital.:*** Glurenor; ***Pol.:*** Glurenorm; ***Port.:*** Glurenor†; ***Rus.:*** Glurenorm (Глюренорм); ***Spain:*** Glurenor; ***Thai.:*** Glurenor; ***Turk.:*** Glurenorm; ***UK:*** Glurenorm†.

Glisentide *(rINN)*

Glipentide; Glisentida; Glisentidum. 1-Cyclopentyl-3-[*p*-(2-*o*-anisamidoethyl)benzenesulphonyl]urea.

Глизентид

$C_{22}H_{27}N_3O_5S$ = 445.5.
CAS — 32797-92-5.

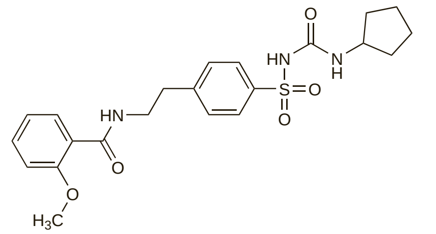

Profile
Glisentide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) in doses of 2.5 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Staticum.

Glisolamide *(rINN)*

Glisolamida; Glisolamidum. 1-Cyclohexyl-3-{*p*-[2-(5-methylisoxazole-3-carboxamido)ethyl]benzenesulphonyl}urea.

Глизоламид

$C_{20}H_{26}N_4O_5S$ = 434.5.
CAS — 24477-37-0.

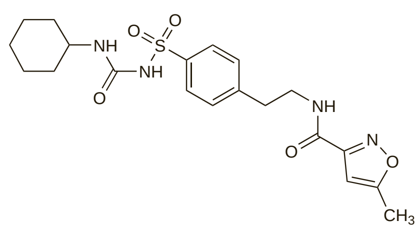

Profile
Glisolamide is a sulfonylurea antidiabetic (p.460). It has been given in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Diabenor†.

Glisoxepide *(BAN, rINN)*

Bay-b-4231; FBB-4231; Glisoxepid; Glisoxepida; Glisoxépide; Glisoxepidum; RP-22410. 1-(Perhydroazepin-1-yl)-3-{4-[2-(5-methylisoxazole-3-carboxamido)ethyl]benzenesulphonyl}urea.

Глизоксепид

$C_{20}H_{27}N_5O_5S$ = 449.5.
CAS — 25046-79-1.
ATC — A10BB11.
ATC Vet — QA10BB11.

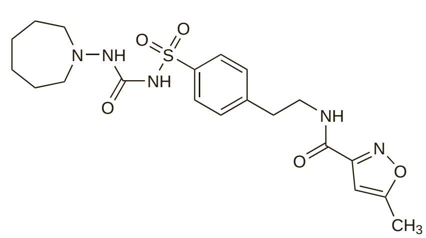

Profile
Glisoxepide is a sulfonylurea antidiabetic (p.460). It has been given in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Pro-Diaban†.

Glybuzole *(rINN)*

AN-1324; Désaglybuzole; Glibuzol; Glybuzolum; RP-7891. *N*-(5-*tert*-Butyl-1,3,4-thiadiazol-2-yl)benzenesulphonamide.

Глибузол

$C_{12}H_{15}N_3O_2S_2$ = 297.4.
CAS — 1492-02-0.

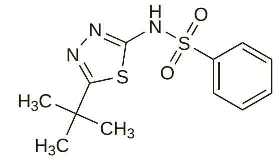

Profile
Glybuzole is an oral antidiabetic with a structure distinct from that of the sulfonylureas, biguanides, or sulfonamidopyrimidines.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Gludiase.

Glycyclamide *(rINN)*

Gliciclamida; Gliciclamide; Glycyclamidum; K-38; K-386; Tolcyclamide. 1-Cyclohexyl-3-tosylurea; 1-Cyclohexyl-3-*p*-tolylsulphonylurea.

Глицикламид

$C_{14}H_{20}N_2O_3S$ = 296.4.
CAS — 664-95-9.

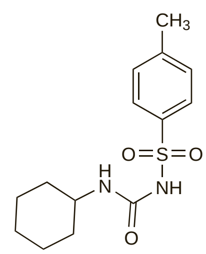

Profile
Glycyclamide is a sulfonylurea antidiabetic (p.460). It is given by mouth in the treatment of type 2 diabetes mellitus.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Diaborale.

Guar Gum

Cyamopsidis seminis pulvis; E412; Goma guar; Guar; Guar Flour; Guar Galactomannan; Guar, galactomannane du; Guar galactomannanum; Guar galaktomanan; Guar galaktomannan; Guaras; Guárbab galaktomannán; Guárbabmag-por; Guargalaktomannaani; Guargalaktomannan; Guaro galaktomananas; Jaguar Gum.
CAS — 9000-30-0.
ATC — A10BX01.
ATC Vet — QA10BX01.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Guar). Guar is obtained by grinding the endosperms of the seeds of *Cyamopsis tetragonolobus*. It consists mainly of guar galactomannan. Guar is a white or almost white powder, yielding a mucilage of variable viscosity when dissolved in water. Practically insoluble in alcohol.
Ph. Eur. 6.2 (Guar Galactomannan). A yellowish-white powder. It is soluble in cold and hot water; practically insoluble in organic solvents. Its main components are polysaccharides composed of D-galactose and D-mannose at molecular ratios of 1:1.4 to 1:2. The molecules consist of a linear main chain of β-(1→4)-glycosidically linked mannopyranoses and single α-(1→6)-glycosidically linked galactopyranoses.
USNF 26 (Guar Gum). A gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, a galactomannan, composed of galactan and mannan units combined through glycosidic linkages. It is a white to yellowish-white, practically odourless, powder. Dispersible in hot or cold water forming a colloidal solution.

Adverse Effects and Precautions

Guar gum can cause gastrointestinal disturbance with flatulence, diarrhoea, or nausea, particularly at the start of treatment.

Because guar gum swells on contact with liquid it should always be washed down carefully with water and should not be taken immediately before going to bed. It should not be used in patients with dysphagia, oesophageal disease, or intestinal obstruction.

Interactions

Guar gum may retard the absorption of other drugs; where this is likely to pose a problem the other drug should be taken at least an hour before guar gum.

Uses and Administration

Guar gum is used in diabetes mellitus (p.431) as an adjunct to treatment with diet, insulin, or oral antidiabetics since it results in some reduction in both postprandial and fasting blood-glucose concentrations. It is given with or immediately before meals in doses of 5 g usually 3 times daily. Adverse gastrointestinal effects may be reduced by using a lower initial dose of 5 g once daily before breakfast for 1 week, then increasing to 5 g twice daily, then 3 times daily, as required. Each dose of guar gum granules should be taken stirred in about 200 mL of a cold drink. Alternatively it can be sprinkled over or mixed with food which must be taken with about 200 mL of fluid.

Guar gum is also used to slow gastric emptying in some patients with the dumping syndrome (p.1695). It is also used as an adjunct in the treatment of hyperlipidaemias.

Guar gum is also used as a thickening and suspending agent, and as a tablet binder. It has been incorporated into processed foods.

◊ Guar gum is an example of a soluble fibre.[1] On contact with water it forms a highly viscous gel, the viscosity of which varies with such factors as its plant source or the form in which it is given.[2]

Fibres such as guar gum reduce postprandial and fasting blood-glucose concentrations as well as plasma-insulin concentrations in healthy subjects and diabetic patients.[1,3,4] Such reductions in blood-glucose concentrations and in glycosylated haemoglobin have been demonstrated in both type 1 and type 2 **diabetes,** but they have generally been small.[3] Possible mechanisms for these effects of guar gum include a delay in gastric emptying,[1,3-5] decreased small-bowel motility,[1,4] decreased glucose absorption resulting from increased viscosity of the contents of the gastrointestinal tract,[1,3] or inhibition of gastrointestinal hormones.[3]

Guar gum also lowers serum total cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations; high-density-lipoprotein (HDL) cholesterol and triglyceride concentrations appear to be unaffected.[4] The most likely mechanism is binding of bile acids, reducing their enterohepatic circulation in a similar way to bile-acid sequestrants.[3,4] When used alone in patients with **hypercholesterolaemia** guar gum has generally produced a modest reduction in plasma-cholesterol and LDL-cholesterol concentrations although some studies have been unable to demonstrate an effect. A few studies have suggested that the cholesterol-lowering effect is attenuated after 8 to 12 weeks of treatment but a long-term study observed a 17% decrease in total serum cholesterol that was maintained for 24 months.[6] Some studies have shown further reductions in cholesterol and LDL-cholesterol concentrations on addition of guar gum to therapy with other lipid regulating drugs.[4] The usual treatment of hyperlipidaemias is discussed on p.1169.

There have been suggestions that guar gum reduces appetite by promoting a feeling of fullness, but a meta-analysis has indicated that it is not effective for reducing body-weight.[7] Products containing guar gum have, however, been promoted as **slimming aids**. Their use cannot be advocated because of the risk of tablets swelling before reaching the stomach and causing oesophageal obstruction.

1. Hockaday TDR. Fibre in the management of diabetes 1: natural fibre useful as part of total dietary prescription. *BMJ* 1990; **300:** 1334–6.
2. Ellis PR, *et al.* Guar gum: the importance of reporting data on its physico-chemical properties. *Diabet Med* 1986; **3:** 490–1.
3. Anonymous. Guar gum: of help to diabetics? *Drug Ther Bull* 1987; **25:** 65–7.
4. Todd PA, *et al.* Guar gum: a review of its pharmacological properties, and use as a dietary adjunct in hypercholesterolaemia. *Drugs* 1990; **39:** 917–28.
5. Tattersall R, Mansell P. Fibre in the management of diabetes 2: benefits of fibre itself are uncertain. *BMJ* 1990; **300:** 1336–7.
6. Salenius J-P, *et al.* Long term effects of guar gum on lipid metabolism after carotid endarterectomy. *BMJ* 1995; **310:** 95–6.
7. Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. *Am J Med* 2001; **110:** 724–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Regudig†; ***Austral.:*** Benefiber†; ***Braz.:*** Benefiber†; Biofibe†; ***Fin.:*** Guarem; ***Ger.:*** Figur-Verlan; Guar Verlan; ***Hong Kong:*** Guarem†; ***Irl.:*** Guarem†; ***Ital.:*** Novafibra; ***NZ:*** Guarcol; ***Spain:*** Fibraguar; Plantaguar; ***Switz.:*** Leiguar; ***UK:*** Resource Benefiber; ***USA:*** Benefiber.

Multi-ingredient: ***Fr.:*** Carres Parapsyllium; Moxydar; Mucipulgite; Mulkine; Seroxydar; ***Ital.:*** Cruscasohn; Resource Gelificata; ***Switz.:*** Mucipulgite†.

Insulin ⊗

Insuliini; Insülin; Insulina; Insuline; Insulinin; Insulinum.

CAS — 9004-10-8 (insulin; neutral insulin); 11070-73-8 (bovine insulin); 12584-58-6 (porcine insulin); 11061-68-0 (human insulin); 8063-29-4 (biphasic insulin); 9004-21-1 (globin zinc insulin); 68859-20-1 (insulin argine); 8049-62-5 (insulin zinc suspensions); 53027-39-7 (isophane insulin); 9004-17-5 (protamine zinc insulin); 116094-23-6 (insulin aspart); 9004-12-0 (dalanated insulin); 51798-72-2 (bovine insulin defalan); 11091-62-6 (porcine insulin defalan); 160337-95-1 (insulin glargine); 133107-64-9 (insulin lispro).

ATC — A10AB01 (human); A10AB02 (beef); A10AB03 (pork); A10AB04 (lispro); A10AB05 (aspart); A10AB06 (glulisine); A10AC01 (human); A10AC02 (beef); A10AC03 (pork); A10AC04 (lispro); A10AE01 (human); A10AE02 (beef); A10AE03 (pork); A10AE04 (glargine); A10AE05 (detemir).

ATC Vet — QA10AB01 (human); QA10AB02 (beef); QA10AB03 (pork); QA10AB04 (lispro); QA10AB05 (aspart); QA10AB06 (glulisine); QA10AC01 (human); QA10AC02 (beef); QA10AC03 (pork); QA10AC04 (lispro); QA10AD01 (human); QA10AD02 (beef); QA10AD03 (pork); QA10AD04 (lispro); QA10AD05 (aspart); QA10AE01 (human); QA10AE02 (beef); QA10AE03 (pork); QA10AE04 (glargine); QA10AE05 (detemir); QA10AF01 (human).

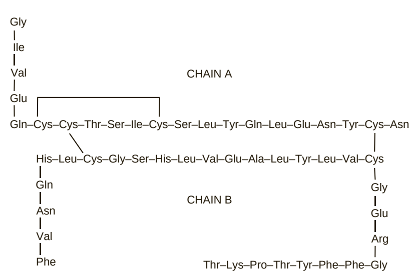

(human)

Pharmacopoeias. Most pharmacopoeias have monographs for insulin and a variety of insulin preparations.

Ph. Eur. 6.2 (Insulin, Bovine). The natural antidiabetic principle obtained from beef pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at −20° until released by the manufacturer. When thawed, insulin may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin, Porcine). The natural antidiabetic principle obtained from pork pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at −20° until released by the manufacturer. When thawed, insulin may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin, Human). A protein having the structure of the antidiabetic hormone produced by the human pancreas. It is produced either by enzymatic modification and suitable purification of insulin obtained from the pancreas of the pig or by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below −18° or below until released by the manufacturer. When thawed, insulin is stored at 2° to 8° and used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin Aspart; Insulinum Aspartum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, except that it has aspartic acid instead of proline at position 28 of the B-chain. As in human insulin, insulin aspart contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in aqueous solutions with a pH around 5.1. In aqueous solutions below pH 3.5 or above pH 6.5, the solubility is greater than or equal to 25 mg/mL. Store in airtight containers. Protect from light. It should be stored at or below −18° until released by the manufacturer. When thawed, insulin aspart may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

Ph. Eur. 6.2 (Insulin Lispro; Insulinum Lisprum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B-chain. Human insulin is Pro(B28), Lys(B29), whereas insulin lispro is Lys(B28), Pro(B29). As in human insulin, insulin lispro contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below −18°. When thawed, insulin lispro is used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

USP 31 (Insulin). A protein that affects the metabolism of glucose obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at −10° to −25°.

USP 31 (Insulin Human). A protein corresponding to the active principle elaborated in the human pancreas that affects the metabolism of carbohydrate (particularly glucose), fat, and protein. It is derived by enzymatic modification of insulin from pork pancreas in order to change its amino acid sequence appropriately, or produced by microbial synthesis via a recombinant DNA process. Store in airtight containers. Protect from light. It should be stored at −10° to −25°.

USP 31 (Insulin Lispro). Insulin Lispro is identical in structure to Insulin Human, except that it has lysine and proline at positions 28 and 29, respectively, of chain B, whereas this sequence is reversed in Insulin Human. It is produced by microbial synthesis via a recombinant DNA process. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at −10° to −25°.

Definitions and Terminology

Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas and consists of 2 chains of amino acids, the A and B chains, connected by 2 disulfide bridges. Insulin produced by different species conforms to the same basic structure but has different sequences of amino acids in the chains. **Porcine insulin** ($C_{256}H_{381}N_{65}O_{76}S_6$ = 5777.5) differs from **human insulin** ($C_{257}H_{383}N_{65}O_{77}S_6$ = 5807.6) in only one amino acid in the B chain, whereas **bovine insulin** ($C_{254}H_{377}N_{65}O_{75}S_6$ = 5733.5) differs from human insulin not only in this same amino acid in the B chain but also in 2 amino acids in the A chain.

The precursor of insulin in the pancreas is proinsulin which is a single polypeptide chain incorporating both the A and B chains of insulin connected by a peptide termed the C-peptide (or connecting-peptide). Although the insulins of various species may be similar in composition the proinsulins are not, in that the sequence and number of amino acids in the C-peptide may vary considerably.

Early commercial insulins were obtained by extraction from bovine or porcine or mixed bovine and porcine pancreases and were purified by recrystallisation only.

Table 2. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Soluble insulins (also known as regular or unmodified insulin)	Soluble Insulin Injection (Ph. Eur. 6.2)	Neutral Insulin Neutral Insulin Injection Soluble Insulin Insulin Injection	Solution of bovine, porcine, or human insulin	6.9 to 7.8				
	Insulin Injection (USP 31)		Solution of bovine or porcine, or a mixture of bovine and porcine, insulin	7.0 to 7.8	Short-acting	30 minutes to 1 hour	2 to 5 hours	6 to 8 hours
	Insulin Human Injection (USP 31)		Solution of human insulin	7.0 to 7.8				
Insulin analogues, rapid	Insulin Aspart Injection (BP 2008)		Solution of insulin aspart	6.9 to 7.8				
	Insulin Lispro Injection (BP 2008)		Solution of insulin lispro	6.9 to 7.8	Short-acting	5 to 20 minutes	1 to 3 hours	2 to 5 hours
	Insulin Lispro Injection (USP 31)		Solution of insulin lispro	7.0 to 7.8				
Biphasic insulins	Biphasic Insulin Injection (Ph. Eur. 6.2)	Biphasic Insulin	Suspension of crystals containing bovine insulin in a solution of porcine insulin	6.6 to 7.2				
	Biphasic Isophane Insulin Injection (Ph. Eur. 6.2)	Biphasic Isophane Insulin	Buffered suspension of porcine insulin or human insulin complexed with protamine sulfate or other suitable protamine, in a solution of porcine insulin or human insulin respectively.	6.9 to 7.8				
	Human Insulin Isophane Suspension and Human Insulin Injection (USP 31)		Buffered suspension of human insulin complexed with protamine sulfate, in a solution of human insulin	7.0 to 7.8				
Insulin suspensions	Isophane Insulin Injection (Ph. Eur. 6.2)	Isophane Insulin Isophane Insulin (NPH) Isophane Protamine Insulin Injection	Suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine. Contains 300 to 600 micrograms of protamine sulfate per 100 units of insulin	6.9 to 7.8				
	Isophane Insulin Suspension (USP 31)		Buffered aqueous suspension of zinc-insulin (bovine or porcine) crystals and protamine sulfate, combined in a manner such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc	7.0 to 7.8	Intermediate-acting	Within 2 hours	4 to 12 hours	Up to 24 hours
	Isophane Insulin Human Suspension (USP 31)		Buffered aqueous suspension of zinc-insulin human crystals and protamine sulfate, combined in such a manner that the solid phase of the suspension consists of crystals composed of insulin human, protamine, and zinc	7.0 to 7.5				
	Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 6.2)	Amorph. I.Z.S. Insulin Semilente Insulin Zinc Suspension (Amorphous)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				

Table 2. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration: Onset	Time to peak	Duration
Insulin suspensions *cont*	Prompt Insulin Zinc Suspension (USP 31)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is amorphous	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Ph. Eur. 6.2)	Insulin Lente I.Z.S. I.Z.S. (Mixed) Insulin Zinc Suspension (Mixed) Insulin Zinc Suspension	Suspension of bovine or porcine, or a mixture of bovine and porcine, or human insulin with a suitable zinc salt; the insulin is in a form practically insoluble in water. It may be produced by mixing Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 6.2) and Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 6.2) in a ratio of 3 to 7	6.9 to 7.8				
	Insulin Zinc Suspension (USP 31)	Insulin Zinc	Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8	Intermediate or long-acting	2 to 3 hours	6 to 15 hours	Up to 30 hours
	Insulin Human Zinc Suspension (USP 31)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 6.2)	Cryst. I.Z.S. Insulin Ultralente Insulin Zinc Suspension (Crystalline)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				
	Protamine Zinc Insulin Injection (BP 2008)	Protamine Zinc Insulin	Buffered suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine and zinc chloride or another suitable zinc salt	6.9 to 7.8				
	Extended Insulin Zinc Suspension (USP 31)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is predominantly crystalline	7.0 to 7.8	Long-acting	4 hours	10 to 20 hours	Up to 36 hours
	Extended Insulin Human Zinc Suspension (USP 31)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension is predominantly crystalline	7.0 to 7.8				

Insulins obtained by such methods were often termed '**conventional insulins**' to distinguish them from insulins which have undergone further purification processes. An extract which has been recrystallised only once can be separated into 3 components or fractions termed the 'a', 'b', and 'c' components. The 'a' component consists of high molecular weight substances and is only usually found in very impure preparations since repeated recrystallisation will remove most of it. The 'b' component consists largely of proinsulin and insulin dimers, and the 'c' component consists of insulin, insulin esters, arginine insulin, and desamidoinsulin. Other pancreatic peptides such as glucagon, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptide are also usually found in products which have not undergone further purification. Gel filtration will substantially reduce the content of proinsulin but will not significantly reduce the content of insulin derivatives or pancreatic peptides; products purified by gel filtration are often termed '**single-peak insulins**'. Addition of ion-exchange chromatography to the purification methods will further reduce the proinsulin content and also reduce the contamination by insulin derivatives and pancreatic peptides. In the UK '**highly purified insulins**' and '**monocomponent insulins**' are terms sometimes applied to insulins which have undergone both gel filtration and ion-exchange chromatography. In the USA the FDA has designated the term '**purified insulins**' for preparations similarly prepared and containing less than 10 ppm of proinsulin.

Much of the insulin now produced has an amino-acid sequence identical to that of human insulin. **Human insulin (emp)** is produced by the enzymatic modification of insulin obtained from the porcine pancreas; it is also sometimes called **semisynthetic human insulin**. The term **human insulin (crb)** is used for insulin produced by the chemical combination of A and B chains which have been obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (prb)** is produced from proinsulin obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (pyr)** is insulin produced from a precursor obtained from a yeast genetically modified by recombinant DNA technology. Human insulin obtained by recombinant DNA technology is sometimes termed **biosynthetic human insulin**.

Insulin or human insulin is supplied in a variety of forms in solution or suspension for injection (see Table 2, p.444). Crystalline insulin may be prepared for therapeutic use merely by making a solution, either of acidic or neutral pH. **Soluble insulin** or '**neutral insulin**' is a short-acting preparation that can be given intravenously if necessary to cover emergencies. Soluble formulations are sometimes referred to as '**regular insulin**' or '**unmodified insulin**'; these names reflect the fact that the preparation has not been formulated in order to prolong the duration of action of the insulin.

In order to prolong the duration of action of insulin, preparations may be formulated as suspensions in 2 general ways. The first involves complexing insulin with a protein from which it is slowly released; examples are **protamine zinc insulin**, which contains an excess of protamine, and **isophane insulin** (NPH insulin), which contains equimolecular amounts of insulin and protamine. The second method of prolonging the action of insulin is to modify the particle size and the various **insulin zinc suspensions** are in this category.

Biphasic insulins are mixtures providing for both immediate and prolonged action.

Chemical modification of the insulin molecule has resulted in insulins such as **dalanated insulin** (prepared by the removal of the C-terminal alanine from the B chain of insulin), **insulin defalan** (prepared by the removal of the terminal phenylalanine), and **sulfated insulin**, but these insulins have not been widely used.

More recently, recombinant DNA technology has enabled production of *insulin analogues* with altered pharmacokinetic profiles. **Insulin lispro** is one such analogue, in which the B28 and B29 amino acid residues of human insulin are replaced with lysine and proline. It is available as a rapidly acting alternative to soluble insulin and as an intermediate-acting complex with protamine. **Insulin aspart** and **insulin glulisine** are other rapidly acting analogues. **Insulin glargine** is a long-acting form for once-daily use, and **insulin detemir** is used once or twice daily. Further information on these can be found under the heading Insulin Analogues and Proinsulin, in Uses, below.

Stability and Storage

Both the Ph. Eur. 6.2 and the USP 31 recommend that insulin preparations be stored in a refrigerator at 2° to 8° and not be allowed to freeze. The Ph. Eur. 6.2 directs that insulin preparations should be protected from light, and the USP 31 that they should be protected from sunlight. It is recognised that patients may not follow such stringent storage guidelines and most manufacturers of commercial insulin preparations consider that storage by the patient at a temperature of up to 25° would be acceptable for up to one month. Patients should still be advised not to expose their vials or cartridges to excessive heat or sunlight.

It is advisable to shake suspensions gently before a dose is withdrawn.

Insulin in powder form should be stored in airtight containers and protected from light. Storage at a low temperature is also recommended. The Ph. Eur. 6.2 advises storage at a temperature of −20° for bovine and porcine insulin and at −18° or below for Human Insulin, and for Insulin Aspart and Insulin Lispro; the USP 31 requires storage at −10° to −25° for all types of insulin. It is stressed that this temperature is for the powder and not for the preparations; preparations should not be subjected to storage conditions that lead to freezing.

Adsorption. The adsorption of insulin onto glass and plastics used in giving sets has been decreased by the addition of albumin or polygeline to insulin solutions but it has been stated[1,2] that in practice this was unnecessary since insulin adsorption was not a major problem. However, in studies of insulin infusions used in neonatal hyperglycaemia, various methods have been investigated and found to reduce the amount of insulin lost by adsorption to the giving set. These included flushing[3] or priming[4] the system with the insulin infusion, or using a concentrated insulin solution to prime the tubing.[5] A study[6] that compared different methods found wide variation in insulin delivery depending on solution concentration, flow rate, addition of albumin, catheter type, and priming or flushing of the system.

1. Alberti KGMM. Diabetic emergencies. *Br Med Bull* 1989; **45:** 242–63.
2. Sanson TH, Levine SN. Management of diabetic ketoacidosis. *Drugs* 1989; **38:** 289–300.
3. Simeon PS, *et al.* Continuous insulin infusions in neonates: pharmacologic availability of insulin in intravenous solutions. *J Pediatr* 1994; **124:** 818–20.
4. Avent M, Whitfield J. Insulin infusions in extremely low birth weight infants. *Pediatrics* 2000; **105:** 915.
5. Fuloria M, *et al.* Effect of flow rate and insulin priming on the recovery of insulin from microbore infusion tubing. *Pediatrics* 1998; **102:** 1401–6.
6. Hewson MP, *et al.* Insulin infusions in the neonatal unit: delivery variation due to adsorption. *J Paediatr Child Health* 2000; **36:** 216–20.

Aggregation. For discussion of the problems of insulin aggregation, see Intensive Administration Regimens under Uses, below.

Units

One unit of *bovine insulin* is contained in 0.03891 mg of the first International Standard (1986). One unit of *porcine insulin* is contained in 0.03846 mg of the first International Standard (1986). One unit of *human insulin* is contained in 0.03846 mg of the first International Standard (1986).

Adverse Effects

The most frequent complication of insulin therapy is hypoglycaemia, the speed of onset and duration of which may vary according to the type of preparation and the route used. It is usually associated with an excessive dosage of insulin, the omission of a meal by the patient, or increased physical activity. Patients, especially the elderly or those with tightly controlled diabetes or diabetes of long standing, may not experience the typical early warning symptoms of a hypoglycaemic attack. There have been reports of hypoglycaemia, sometimes with decreased warning symptoms, in patients changing from animal (especially bovine) to human insulin (see under Hypoglycaemia, below). Symptoms of hypoglycaemia resulting from increased sympathetic activity include hunger, pallor, sweating, palpitations, anxiety, and tremulousness. Other symptoms include headache, visual disturbances such as blurred or double vision, slurred speech, paraesthesia of the mouth and fingers, alterations in behaviour, and impaired mental or intellectual ability. If untreated, hypoglycaemia may lead to convulsions and coma which should not be confused with hyperglycaemic coma.

Insulin, given subcutaneously, may cause either lipoatrophy or lipohypertrophy. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins; if it has occurred, it may be reversed by the injection of a purer animal insulin or human insulin into and around the atrophied site. Lipohypertrophy is usually associated with repeated injections at the same site and may usually be overcome by rotating the site of injection, although absorption of insulin may vary from different anatomical areas. Prolonged insulin therapy may result in weight gain.

Insulin occasionally causes local or systemic hypersensitivity reactions. Local reactions, characterised by erythema and pruritus at the injection site, usually disappear with continued use. Generalised hypersensitivity may produce urticaria, angioedema, and very rarely anaphylactic reactions; if continued therapy with insulin is essential hyposensitisation may be needed. Again, hypersensitivity reactions occur less frequently with purified than with conventional insulins and porcine insulin is less immunogenic than bovine insulin. Although hypersensitivity reactions have been reported in patients transferred from animal to human insulins, there are only isolated reports of such reactions in patients treated exclusively with human insulin.

Many patients treated with insulin, either animal or human insulin, develop antibodies but the clinical significance of this is not entirely clear.

◊ Of patients who received intensive insulin therapy for type 1 diabetes as part of the Diabetes Control and Complications Trial, those who experienced the greatest weight gain also had increased blood concentrations of triglycerides and low-density-lipoprotein cholesterol, and lowered high-density-lipoprotein cholesterol.[1] These lipid changes, with higher blood pressure, increased waist-to-hip ratio, and greater insulin requirements, were held to be similar to the symptoms of insulin resistance and to indicate a possible increased risk of macrovascular disease. Results from the UK Prospective Diabetes Study indicated that type 2 diabetic patients treated with insulin had greater weight gain than those managed with other therapies,[2] but demonstrated no evidence of harmful cardiovascular effects.

For discussion of some of the specific problems associated with continuous infusion of insulin, see Intensive Administration Regimens under Uses, below.

1. Purnell JQ, *et al.* Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *JAMA* 1998; **280:** 140–6. Correction. *ibid.*; 1484.
2. UK Prospective Diabetics Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.

Carcinogenicity. Primary lung malignancies have been found in a few patients receiving inhaled insulin; for further details, see Administration Routes, p.450.

Effects on the liver. For a report of hepatomegaly occurring after insulin overdosage, see under Abuse, in Precautions, below.

Effects on the skin. Delayed pressure urticaria, in the form of large wheals occurring 4 to 6 hours after prolonged pressure, and lasting for up to 24 hours, was seen in a patient with type 1 diabetes within 6 months of changing from animal to human insulin.[1] The condition improved after a switch back to insulin of animal origin, and grew worse again after a second attempt to switch to human insulin. Intermittent urticaria simultaneously affecting previous injection sites was reported in a child receiving human insulin, who had never received animal insulin.[2]

1. Payne CMER, *et al.* True delayed pressure urticaria induced by human Monotard insulin. *Br J Dermatol* 1996; **134:** 184.
2. Sackey AH. Recurrent generalised urticaria at insulin injection sites. *BMJ* 2000; **321:** 1449.

Hypersensitivity. Hypersensitivity reactions to insulin preparations may be caused not only by the insulin itself, but also by other components of the formulation such as zinc[1-3] or protamine.[4-9] Hypersensitivity reactions and lipoatrophy (which is also thought to have an immune basis) have become rare since the introduction of highly purified and human insulins.[10] Although insulin analogues have been used successfully in patients with a history of hypersensitivity to human insulin,[11,12] there are also reports of both local and generalised reactions to insulin analogues.[13-15]

See also Adverse Effects, above and under Precautions, below.

1. Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979; **i:** 122–4.
2. Bruni B, *et al.* Case of generalized allergy due to zinc and protamine in insulin preparation. *Diabetes Care* 1986; **9:** 552.
3. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. *Diabetes Care* 1987; **10:** 789–90.
4. Sánchez MB, *et al.* Protamine as a cause of generalised allergic reactions to NPH insulin. *Lancet* 1982; **i:** 1243.
5. Hulshof MM, *et al.* Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; **127:** 286–8.
6. Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; **65:** 17–23.
7. Dykewicz MS, *et al.* Immunologic analysis of anaphylaxis to protamine component in neutral protamine Hagedorn human insulin. *J Allergy Clin Immunol* 1994; **93:** 117–25.
8. Blanco C, *et al.* Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996; **51:** 421–4.
9. Bollinger ME, *et al.* Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999; **104:** 462–5.
10. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; **16** (suppl 3): 155–65.
11. Airaghi L, *et al.* The insulin analog aspart: a safe alternative in insulin allergy. *Diabetes Care* 2001; **24:** 2000.
12. Yasuda H, *et al.* Human insulin analog insulin aspart does not cause insulin allergy. *Diabetes Care* 2001; **24:** 2008–9.
13. Takata H, *et al.* The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003; **26:** 253–4.
14. Durand-Gonzalez K-N, *et al.* Glargine insulin is not an alternative in insulin allergy. *Diabetes Care* 2003; **26:** 2216.
15. JiXiong X, *et al.* The human insulin analog aspart can induce insulin allergy. *Diabetes Care* 2004; **27:** 2084–5.

HYPOSENSITISATION. After failure of standard hyposensitisation measures in a patient with cutaneous hypersensitivity to insulin, hyposensitisation was attempted by giving insulin by mouth.[1] Aspirin 1.3 g three times daily by mouth was also given to antagonise vascular mediators of the reaction. After one week subsequent hyposensitisation using insulin by injection was successful. When the patient stopped taking aspirin after 6 months the original hypersensitivity reactions recurred; aspirin was then given permanently in a dose of 1.3 g twice daily.

1. Holdaway IM, Wilson JD. Cutaneous insulin allergy responsive to oral desensitisation and aspirin. *BMJ* 1984; **289:** 1565–6.

Hypoglycaemia. Hypoglycaemia is the major adverse effect of insulin treatment, with severe hypoglycaemic episodes occurring in up to a third of all insulin-treated patients at some point in their lives. Moves towards more intensive insulin therapy, in order to reduce the development of diabetic complications, increase the risk of hypoglycaemic episodes.[1,2] Patients maintaining strict glycaemic control are prone to 'hypoglycaemia unawareness' in which the normal adrenergic counter-response to hypoglycaemia (characterised by symptoms such as pallor, sweating, and tremor) is reduced or lost,[3] so that hypoglycaemia can develop without warning. Such a loss of awareness of impending hypoglycaemia also seems to develop as duration of diabetes increases.[4] One of the main reasons for reduced awareness of hypoglycaemia is that repeated hypoglycaemic episodes seem to trigger an adaptive conservation of glucose concentrations in the brain, resulting in higher central than peripheral blood glucose values;[5] avoidance of hypoglycaemia helps restore awareness.

When recombinant human insulin became generally available in the late 1980s a number of patients complained of a loss of awareness of impending hypoglycaemia after transfer to human insulin,[6,7] and there were reports of severe or even fatal hypoglycaemia occurring in patients who had been well stabilised on animal insulins.[6-8]

This was, and remains, a somewhat controversial area. Despite some small studies suggesting a problem, others failed to find evidence of a difference between animal and human insulins, and a systematic review[9] concluded that the available evidence did not support the suggestion that human insulin increased the frequency or severity of hypoglycaemia, or affected the symptoms of hypoglycaemia, compared with animal insulins. However, most commentators appear to consider that patients should continue to have access to animal insulins if desired, and that those well maintained on animal insulin should not be transferred to human insulin without appropriate clinical grounds,[4,8,10-12] and then only with careful monitoring.

There has also been concern about possible long-term sequelae of hypoglycaemic episodes on the CNS. However, a report on patients participating in the Diabetes Control and Complications Trial (DCCT) suggested that the increased risk of hypoglycaemia seen with intensive therapy was not associated with neuropsychological impairment.[13]

For the treatment of insulin-induced hypoglycaemia, see below.

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.
2. Egger M, *et al.* Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; **14:** 919–28.
3. Widom B, Simonson DC. Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. *Ann Intern Med* 1990; **112:** 904–12.
4. Everett J, Kerr D. Changing from porcine to human insulin. *Drugs* 1994; **47:** 286–96.
5. Cranston I, *et al.* Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 1994; **344:** 283–7.
6. Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 1987; **ii:** 382–5.
7. Pickup J. Human insulin: problems with hypoglycaemia in a few patients. *BMJ* 1989; **299:** 991–3.
8. Gale EAM. Hypoglycaemia and human insulin. *Lancet* 1989; **ii:** 1264–6.
9. Airey CM, *et al.* Hypoglycaemia induced by exogenous insulin - 'human' and animal insulin compared. *Diabet Med* 2000; **17:** 416–32.
10. Gerich JE. Unawareness of hypoglycaemia and human insulin. *BMJ* 1992; **305:** 324–5.
11. Williams G, Patrick AW. Human insulin and hypoglycaemia: burning issue or hot air? *BMJ* 1992; **305:** 355–7.
12. Teuscher A, Kiln MR. Patient-empowerment and free insulin market. *Lancet* 1994; **344:** 1299–1300.
13. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 1996; **124:** 379–88.

Oedema. Severe, acute oedema is a rare adverse effect of insulin treatment, occurring most often when starting therapy.[1-4] It should be distinguished from chronic and subacute forms of oedema which may be complications of the diabetic disease process.[2,3] Possible mechanisms of acute oedema are sodium retention resulting from a direct action of insulin on the renal tubule or an effect of insulin on vascular permeability.[1,3] The oedema is usually self-limiting,[2,4] but does respond to a decrease in insulin dosage, or diuretic therapy.[1,3]

1. Bleach NR, *et al.* Insulin oedema. *BMJ* 1979; **2:** 177–8.
2. Lawrence JR, Dunnigan MG. Diabetic (insulin) oedema. *BMJ* 1979; **2:** 445.
3. Evans DJ, *et al.* Insulin oedema. *Postgrad Med J* 1986; **62:** 665–8.
4. Hirshberg B, *et al.* Natural course of insulin edema. *J Endocrinol Invest* 2000; **23:** 187–8.

Treatment of Insulin-induced Hypoglycaemia

In the conscious and cooperative patient hypoglycaemia is treated by eating a readily absorbable form of carbohydrate, such as sugar lumps or a glucose-based drink; all diabetics should always carry a suitable sugar source by way of precaution.

If the patient is drowsy or unconscious, then glucose must be given parenterally. Doses of 50 mL of a 20% solution of glucose or 25 to 50 mL of glucose 50% can be given intravenously; the higher concentration is more viscous and irritant to the veins. Lower concentrations are equally effective, and carry less risk of irritant effects, but larger volumes are required, e.g. up to 500 mL of glucose 5%, or 250 mL of 10%, titrated to patient response. Smaller quantities (e.g. 5 to 10 mL/kg of a 10% solution) are required in children. Bolus doses may need to be repeated, or a maintenance infusion started, to prevent persistent hypoglycaemia. If the patient has not regained consciousness within a few minutes after a bolus dose of glucose, the possibility of cerebral oedema should be considered.

In situations where giving intravenous glucose is impractical or not feasible, glucagon 1 mg for adults and children above 25 kg or 0.5 mg for children below 25 kg by subcutaneous, intramuscular, or intravenous injection may arouse the patient sufficiently to allow oral glucose to be given. If the patient fails to respond to glucagon within about 10 to 15 minutes, then glucose has to be given intravenously despite any impracticalities.

After a return to consciousness, oral carbohydrates may need to be given until the action of insulin has ceased, which for preparations with a relatively long duration of action such as isophane insulin, some insulin zinc suspensions, and protamine zinc insulin, may be several hours.

Carbohydrate. A comparative study[1] of 7 different preparations of oral carbohydrate for the treatment of hypoglycaemia in the conscious patient found no significant difference in effectiveness between glucose or sucrose in solution or tablet form; a hydrolysed polysaccharide solution containing glucose, maltose, and various more complex saccharides (*Glucidex 19*) was also roughly comparable. However, a glucose gel and orange juice were each less effective than the other formulations in treating hypoglycaemia.

1. Slama G, *et al.* The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990: **150:** 589–93.

Glucagon. A discussion of the relative merits of parenteral glucose and glucagon in unconscious hypoglycaemic patients[1] suggested that glucagon should be encouraged as first-line treatment, although in practice (see above) parenteral glucose is usually preferred. The effect of glucagon relies upon the patient having adequate liver glycogen stores, which may not always be the case.

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306:** 600–601.

Overdose. The requirements for glucose are greater and more prolonged when hypoglycaemia is caused by insulin overdosage rather than therapeutic doses.[1] Correction of insulin-induced hypokalaemia may also be required. Surgical excision of tissue at the site of injection has been used for massive overdose of a long-acting insulin.[2,3]

1. Roberge RJ, *et al.* Intentional massive insulin overdosage: recognition and management. *Ann Emerg Med* 1993; **22:** 228–34.
2. Campbell IW, Ratcliffe JG. Suicidal insulin overdose managed by excision of insulin injection site. *BMJ* 1982; **285:** 408–9.
3. Levine DF, Bulstrode C. Managing suicidal insulin overdose. *BMJ* 1982; **285:** 974–5.

Precautions

Dosage requirements of insulin may be altered by many factors. Increased doses are usually necessary during infection, emotional stress, accidental or surgical trauma, puberty, and the latter two trimesters of pregnancy. Decreased doses are usually necessary in patients with impaired renal or hepatic function or during the first trimester of pregnancy. On first stabilising therapy in newly diagnosed diabetic patients, a temporary decrease in requirements may also occur (the so-called honeymoon period).

Because of the possibility of differing responses to insulins from different species, inadvertent change from insulin of one species to another should be avoided. Reduction in insulin dosage may be required on transfer from animal (especially bovine) to human insulin. Hypoglycaemic problems associated with a change to human insulin are discussed under Adverse Effects, above. Care is also necessary during excessive exercise; hypoglycaemia caused by metabolic effects and increased insulin absorption is the usual response, but hyperglycaemia may sometimes occur.

The use of insulin requires monitoring of therapy, such as testing blood or urine for glucose concentrations and the urine for ketones, by the patient.

Drugs which have an effect on blood-glucose concentrations may alter glycaemic control with consequent need for a change in insulin dose (see Interactions, below).

CAUTION. *Biphasic insulin, insulin zinc suspensions, isophane insulin, protamine zinc insulin, insulin detemir, and insulin glargine should never be given intravenously and they are not suitable for the emergency treatment of diabetic ketoacidosis.*

Abuse. Transient recurrent hepatomegaly associated with hypoglycaemia was associated with the surreptitious injection of additional insulin doses in an insulin-dependent diabetic. Increased storage of glycogen in the liver resulting from insulin excess was considered responsible for the hepatomegaly.[1]

Decreased plasma C-peptide concentrations or the presence of anti-insulin antibodies may be used to confirm insulin abuse as a cause of hypoglycaemia in patients who have never been treated with insulin medically.[2] Insulin has been abused by bodybuilders and other sportspersons;[3,4] severe brain damage after prolonged neuroglycopenia has resulted.[3] There are rare reports of the misuse of insulin to induce mind-altering effects of hypoglycaemia.[5]

1. Asherov J, *et al.* Hepatomegaly due to self-induced hyperinsulinism. *Arch Dis Child* 1979; **54:** 148–9.
2. Grunberger G, *et al.* Factitious hypoglycemia due to surreptitious administration of insulin: diagnosis, treatment, and long-term follow-up. *Ann Intern Med* 1988; **108:** 252–7.
3. Elkin SL, *et al.* Bodybuilders find it easy to obtain insulin to help them in training. *BMJ* 1997; **314:** 1280.
4. Honour JW. Misuse of natural hormones in sport. *Lancet* 1997; **349:** 1786.
5. Cassidy EM, *et al.* Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ* 1999; **319:** 1417–18.

Accelerated absorption. Factors such as a hot bath, sauna, or use of a sunbed have been reported to accelerate the absorption of subcutaneous injection, presumably by an increase in skin blood flow.[1-4] There may, therefore, be a risk of hypoglycaemia.[4]

1. Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *BMJ* 1980; **280:** 1411–13.
2. Cüppers HJ, *et al.* Sauna-induced acceleration in insulin absorption? *BMJ* 1980; **281:** 307.
3. Koivisto VA. Sauna-induced acceleration in insulin absorption. *BMJ* 1980; **281:** 621–2.
4. Husband DJ, Gill GV. "Sunbed seizures": a hypoglycaemic hazard for insulin-dependent diabetics. *Lancet* 1984; **ii:** 1477.

Adrenocortical insufficiency. Recurrent severe hypoglycaemia, which occurred in 2 patients with type 1 diabetes, persisted despite a reduction in insulin doses and proved to be due to Addison's disease.[1] Insulin requirements rose again in both patients after replacement therapy with fludrocortisone and hydrocortisone.

1. Armstrong L, Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetics. *BMJ* 1996; **312:** 1601–2.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.[1,2]

Regulations in other countries differ widely.[3]

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)
3. DiaMond Project Group on Social Issues. Global regulations on diabetics treated with insulin and their operation of commercial motor vehicles. *BMJ* 1993; **307:** 250–3.

Exercise. Discussions[1,2] of the metabolic effects of exercise and the precautions to be taken by the exercising type 1 diabetic.

1. Greenhalgh PM. Competitive sport and the insulin-dependent diabetic patient. *Postgrad Med J* 1990; **66:** 803–6.
2. American Diabetes Association. Physical activity/exercise and diabetes. *Diabetes Care* 2004; **27** (suppl 1): S58–S62. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s58.pdf (accessed 08/07/04)

Fasting. Reduction in food intake or alteration in the pattern of meal times may affect insulin requirements and predispose to the development of hypoglycaemia (above). Muslim patients who are receiving antidiabetic therapy and who fast during Ramadan have been shown to be at increased risk of severe hypoglycaemic episodes during this month.[1] A study in 17 fasting patients with type 1 diabetes recommended reduction of the total insulin dose to 85% of that before the fasting period, and supplying 70% as long-acting ultralente insulin and 30% as a rapidly acting soluble insulin; the daily dose was divided into 2 equal portions given before sunrise and after sunset.[2] Others have made similar recommendations: 2 daily injections of an intermediate- or long-acting insulin, given before the predawn and sunset meals, together with a short-acting insulin at the meal itself; or possibly a single daily injection of insulin glargine, or twice-daily insulin detemir, plus a rapidly acting analogue just before the meal.[3]

Patients with type 2 diabetes maintained on insulin may be managed similarly, by judicious use of intermediate or long-acting insulin plus a short-acting insulin given before meals. A single injection of a long-acting analogue such as insulin glargine, or two injections of isophane or lente insulin or insulin detemir before the sunset and predawn meals, may provide adequate coverage provided the dosage is appropriately individualised. However, most patients will still require a short-acting insulin to be added at the sunset meal to cover the large caloric load. Many will also require an additional dose of short-acting insulin at predawn.[3] Studies have suggested that insulin lispro may produce good blood sugar control in fasting patients with type 2 diabetes during Ramadan.[4,5]

Care is also required in patients with type 2 diabetes being treated with oral antidiabetic drugs. Patients being treated with metformin or insulin sensitisers such as the glitazones have a low risk of hypoglycaemia, although it has been suggested that the timing of metformin doses be altered so that two-thirds of the daily dose is taken just before the sunset meal and the other third before the predawn meal. Short-acting secretagogues such as repaglinide or nateglinide can also be taken twice daily before the sunset and predawn meals. However, sulfonylureas should be used with caution, and the use of chlorpropamide may be contra-indicated because of the high risk of prolonged and unpredictable hypoglycaemia.[3]

1. Salti I, *et al.* A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; **27:** 2306–11.
2. Kassem HS, *et al.* Insulin therapy during Ramadan fast for type 1 diabetes patients. *J Endocrinol Invest* 2005; **28:** 802–5.
3. Al-Arouj M, *et al.* Recommendations for management of diabetes during Ramadan. *Diabetes Care* 2005; **28:** 2305–11.
4. Akram J, De Verga V. Ramadan Study Group. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; **16:** 867–74.
5. Mattoo V, *et al.* A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; **59:** 137–43.

Hypersensitivity to protamine. Retrospective surveys have indicated that patients receiving isophane insulin, which contains protamine, have an increased risk of severe anaphylactoid reactions when protamine is used to reverse systemic heparinisation after cardiac catheterisation or cardiac surgery. The degree of increase in risk is unclear, however, as it has been reported as both large[1] and small.[2,3] A review of the literature suggested that surgical patients may be at greater risk because of a higher rate of prior sensitisation to protamine and the larger doses used.[3] A mechanism involving IgE and IgG antibodies to protamine has been proposed.[4]

See also Hypersensitivity under Adverse Effects, above.

1. Stewart WJ, *et al.* Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; **70:** 788–92.
2. Levy JH, *et al.* Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; **98:** 200–204.
3. Vincent GM, *et al.* Protamine allergy reactions during cardiac catheterization and cardiac surgery: risk in patients taking protamine-insulin preparations. *Cathet Cardiovasc Diagn* 1991; **23:** 164–8.
4. Weiss ME, *et al.* Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med* 1989; **320:** 886–92.

Infections. Decreased requirements of insulin, added to the dialysate, occurred in 6 diabetic patients undergoing continuous ambulatory peritoneal dialysis for chronic renal failure during episodes of severe bacterial peritonitis.[1] This was contrary to the increased insulin requirements of most diabetic patients during severe infections and probably resulted from increased absorption of insulin due to mesothelial damage.

1. Henderson IS, *et al.* Decreased intraperitoneal insulin requirements during peritonitis on continuous ambulatory peritoneal dialysis. *BMJ* 1985; **290:** 1474.

Menstruation. Changes in glycaemic control associated with the menstrual cycle have been recorded in women with type 1 diabetes mellitus. In a retrospective review of 124 women,[1] 61% reported perimenstrual changes in glucose concentrations and 36% made adjustments to their insulin dose, usually a small increase in the premenstrual insulin dose followed by a small decrease at the onset of menstruation. Based on mean glycosylated haemoglobin measurements, there was no evidence of improved glycaemic control in women adjusting their insulin dose compared with those leaving it unchanged despite changes in capillary glucose measurements. Changes in appetite and food consumption associated with the menstrual cycle may affect variations in glucose concentrations and insulin requirements.

1. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Morning hyperglycaemia. Morning hyperglycaemia may be the result of mere waning of subcutaneously injected insulin. It may also be rebound hyperglycaemia (posthypoglycaemic hyperglycaemia or the Somogyi phenomenon) occurring after an episode of nocturnal hypoglycaemia. Morning hyperglycaemia has also been observed without antecedent hypoglycaemia even during constant intravenous infusion of insulin, when the waning of previously injected insulin would not be a factor and this is commonly referred to as the dawn phenomenon. Clinically, it is important to distinguish between the dawn phenomenon, simple waning of previously injected insulin, and rebound hyperglycaemia as a cause of early-morning hyperglycaemia because their treatment differs. Management of the dawn phenomenon and insulin waning generally consists of adjusting the evening dose of insulin to provide additional coverage between 4 a.m. and 7 a.m. Management of rebound hyperglycaemia consists of reducing insulin doses or providing additional late-evening carbohydrate, or both, to avoid nocturnal hypoglycaemia. Mistaking rebound hyperglycaemia for the dawn phenomenon or mere waning of injected insulin could result in more serious nocturnal hypoglycaemia, if evening doses of insulin were increased.[1]

1. Cryer PE, Gerich JE. Glucose counterregulation, hypoglycemia, and intensive insulin therapy in diabetes mellitus. *N Engl J Med* 1985; **313:** 232–41.

Pregnancy. For discussion of the precautions necessary in the management of diabetes mellitus during pregnancy, see p.431.

There has been a report of 2 cases of fetal malformation in the offspring of well-controlled diabetic women who received *insulin lispro*.[1] However, the incidence of fetal malformation is increased in infants of women with diabetes. At that time the manufacturers were aware of 19 live births among women treated with insulin lispro, 1 of which exhibited a congenital abnormality.[2] Since then, a number of retrospective studies[3-7] have looked at the rates of fetal malformations in the offspring of women treated with insulin lispro, for either pre-existing diabetes mellitus or gestational diabetes. These have included groups ranging in size from 62 to 496 women, and none have found any evidence of an increase in the incidence of abnormalities with insulin lispro compared with rates published for women treated with other insulins.

There is less information available about the use of other insulin analogues, but a few cases and studies of *insulin glargine* use during pregnancy have been described. It was started in one woman[8] during the fourteenth week of gestation, and continued until delivery with no apparent adverse effect on the baby. In another report,[9] insulin glargine was inadvertently continued by 5 women during the first 6 to 12 weeks of unplanned pregnancies. In these cases, therapy was changed from insulin glargine to isophane insulin, and no fetal malformations were detected. The use of insulin glargine during the entire pregnancy, without adverse effect, has also been described,[10] and successful pregnancies were reported in 4 women given insulin glargine for gestational diabetes.[11] Furthermore, a small case-control study[12] found no significant difference in neonatal outcomes for insulin glargine and human insulin in women with type 1 or gestational diabetes, and another study[13] found no unexpected adverse effects in the babies of 115 women given insulin glargine. A single-dose study has reported[14] that *insulin aspart* was effective in reducing postprandial glucose concentration in gestational diabetes. Randomised studies in women with type 1 diabetes[15] or gestational diabetes[16] have also found no indication of an increase in congenital malformations with insulin aspart compared with human insulin.

1. Diamond T, Kormas N. Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1009.
2. Anderson JH, *et al.* Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1010.
3. Bhattacharyya A, *et al.* Insulin lispro and regular insulin in pregnancy. *Q J Med* 2001; **94:** 255–60.
4. Garg SK, *et al.* Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003; **9:** 187–93.
5. Masson EA, *et al.* Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 2003; **20:** 46–50.
6. Wyatt JW, *et al.* Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 2005; **22:** 803–7.
7. Lapolla A, *et al.* Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetol* 2008; **45:** 61–6.
8. Devlin JT, *et al.* Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 2002; **25:** 1095–6.
9. Di Cianni G, *et al.* Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 2005; **28:** 982–3.
10. Caronna S, *et al.* Pregnancy and the long-acting insulin analogue: a case study. *Acta Biomed* 2006; **77:** 24–6.
11. Graves DE, *et al.* The use of insulin glargine with gestational diabetes mellitus. *Diabetes Care* 2006; **29:** 471–2.
12. Price N, *et al.* Use of insulin glargine during pregnancy: a case-control pilot study. *BJOG* 2007; **114:** 453–7.
13. Gallen IW, *et al.* Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med* 2008; **25:** 165–9.
14. Pettitt DJ, *et al.* Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003; **26:** 183–6.
15. Hod M, *et al.* Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; **198:** 186.e1–186.e7.
16. Pettitt DJ, *et al.* Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med* 2007; **24:** 1129–35.

Prion disease transmission. Studies of cattle with proven bovine spongiform encephalopathy (BSE) have not detected infectivity in the pancreas, from which bovine insulin is derived.[1]

1. Wickham EA. Potential transmission of BSE via medicinal products. *BMJ* 1996; **312:** 988–9.

Renal impairment. See under Infections, above.

Smoking. Smoking has been reported to decrease the absorption of insulin and dosage adjustment may be necessary, although glycaemic control does not seem to be significantly affected.[1]

1. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.

Surgery. For a discussion of the management of diabetes mellitus during surgery, see p.431.

Travelling. Advice for the diabetic patient when travelling, including adjustment of insulin dosage when crossing time zones.[1-3] Since insulin solution or suspension must not be frozen, it should not be carried in the luggage hold of an aircraft.

1. Barry M, Bia F. Advice for the traveling diabetic. *JAMA* 1989; **261:** 1799.
2. Sane T, *et al.* Adjustment of insulin doses of diabetic patients during long distance flights. *BMJ* 1990; **301:** 421–2.
3. Dewey CM, Riley WJ. Have diabetes, will travel. *Postgrad Med* 1999; **105:** 111–13, 117–18, 124–6.

Interactions

Many drugs have an effect on blood-glucose concentrations and may alter insulin requirements. Drugs with hypoglycaemic activity or which may decrease insulin requirements include ACE inhibitors, alcohol, anabolic steroids, aspirin, beta blockers (which may also mask the warning signs of hypoglycaemia), disopyramide, fenfluramine, guanethidine, some MAOIs, mebendazole, octreotide, some tetracyclines, and the tricyclic antidepressant amitriptyline.

On the other hand, increased requirements of insulin may possibly be seen with chlordiazepoxide, chlorpromazine, some calcium-channel blockers such as diltiazem or nifedipine, corticosteroids, diazoxide, lithium, thiazide diuretics, and thyroid hormones.

Both increased and decreased requirements may occur with cyclophosphamide, isoniazid, and oral contraceptives.

ACE inhibitors. Although ACE inhibitors are favoured for use in diabetic patients with hypertension or evidence of incipient nephropathy or both, they may increase insulin sensitivity and thus decrease insulin requirements.[1,2] A study[3] of hospital admissions found that ACE inhibitors increased the risk of severe hypoglycaemia in patients receiving insulin. However, an analysis of pharmacovigilance data[4] and a case-control study[5] have both found no such increase in risk.

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
3. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
4. Moore N, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; **44:** 513–8.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.

Alcohol. Severe hypoglycaemic episodes have been reported in type 1 diabetics after heavy drinking episodes.[1,2] Alcohol inhibits gluconeogenesis, and its effects are therefore likely to be greatest if taken without food; however, it seems to be generally agreed that diabetics need not abstain from a moderate alcohol intake with meals.

1. Arky RA, *et al.* Irreversible hypoglycemia. *JAMA* 1968; **206:** 575–8.
2. Potter J, *et al.* Insulin induced hypoglycaemia in an accident and emergency department: the tip of an iceberg. *BMJ* 1982; **285:** 1180–2.

Aspirin. Aspirin produces a modest decrease in blood-glucose concentrations but a significant interaction at conventional analgesic doses appears to be unlikely. One study in children with type 1 diabetes found an average 15% decrease in blood glucose values following treatment with aspirin 1.2 to 2.4 g daily for 3 days, but there were no significant changes in insulin requirements.[1] However, high doses of aspirin can reduce or even replace the insulin dose required.[2] Other salicylates might be expected to have similar properties.

1. Kaye R, *et al.* Antipyretics in patients with juvenile diabetes mellitus. *Am J Dis Child* 1966; **112:** 52–5.
2. Reid J, Lightbody TD. The insulin equivalence of salicylate. *BMJ* 1959; **1:** 897.

Beta blockers. There are a few reports of severe hypoglycaemia in patients, including insulin-treated diabetics, who were given *propranolol* or *pindolol*;[1-3] there is also a report of an interaction with *timolol* given as eye drops.[4] Some evidence exists of an interaction with *metoprolol*,[5] but little evidence for some of the more selective beta blockers. Because of the effects of beta blockers on the sympathetic nervous system the usual premonitory signs of hypoglycaemia may not occur, allowing a severe episode to develop before the patient is aware and able to counter it.

1. Kotler MN, *et al.* Hypoglycaemia precipitated by propranolol. *Lancet* 1966; **ii:** 1389–90.
2. McMurtry RJ. Propranolol, hypoglycemia, and hypertensive crisis. *Ann Intern Med* 1974; **80:** 669–70.
3. Samii K, *et al.* Severe hypoglycaemia due to beta-blocking drugs in haemodialysis patients. *Lancet* 1976; **i:** 545–6.
4. Angelo-Nielsen K. Timolol topically and diabetes mellitus. *JAMA* 1980; **244:** 2263.
5. Newman RJ. Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia. *BMJ* 1976; **2:** 447–9.

Calcium-channel blockers. Diabetes worsened in an insulin-treated diabetic when given *diltiazem*.[1] The resultant intractable hyperglycaemia improved when the drug was withdrawn, and recurred, although at a more manageable level, when diltiazem was restarted at a lower dose. There are also reports of a diabetogenic effect of *nifedipine*.[2,3] However, reports of significant disturbances of metabolic control appear to be uncommon.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
3. Heyman SN, *et al.* Diabetogenic effect of nifedipine. *DICP Ann Pharmacother* 1989; **23:** 236–7.

Interferons. Markedly increased insulin requirements developed in a previously well controlled diabetic after treatment with *interferon alfa 2a*.[1] Insulin requirements rapidly fell once interferon therapy was stopped.

1. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.

Oral contraceptives. Both increases and decreases (mainly the former) in insulin requirements have been reported in insulin-dependent diabetics given various oral contraceptives.[1] However, it appears that in most cases the effects of a hormonal contraceptive on diabetic control are modest or insignificant: limited data suggest that progestogen-only and combined oral contraceptives in general have little effect.[2,3]

1. Zeller WJ, *et al.* Verträglichkeit von hormonalen Ovulationskemmern bei Diabetikerinnen. *Arzneimittelforschung* 1974; **24:** 351–7.
2. Rådberg T, *et al.* Oral contraception in diabetic women: diabetes control, serum and high density lipoprotein lipids during low-dose progestogen, combined oestrogen/progestogen and non-hormonal contraception. *Acta Endocrinol (Copenh)* 1981; **98:** 246–51.
3. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Pharmacokinetics

Insulin has no hypoglycaemic effect when given by mouth since it is inactivated in the gastrointestinal tract.

It is fairly rapidly absorbed from subcutaneous tissue on injection and although the half-life of unmodified insulin in blood is very short (being only a matter of minutes), the duration of action of most preparations is considerably longer because of their formulation (for further details see Uses and Administration, below). The rate of absorption from different anatomical sites depends on local blood flow, with absorption from the abdomen being faster than that from the arm, and that from the arm faster than from buttock or thigh. Absorption may also be increased by exercise. The absorption of insulin after intramuscular injection is more rapid than that after subcutaneous doses. Human insulin may be absorbed slightly faster from subcutaneous tissue than porcine or bovine insulin.

Insulin is rapidly metabolised, mainly in the liver but also in the kidneys and muscle tissue. In the kidneys it is reabsorbed in the proximal tubule and either returned to venous blood or metabolised, with only a small amount excreted unchanged in the urine.

◊ For discussion of factors which may affect the absorption of insulin, see under Precautions, Accelerated Absorption, above, and Uses, Administration Routes, below.

Resistance to Insulin

The term insulin resistance has traditionally been used to describe a state in which diabetic patients exhibit considerably increased insulin requirements. It is now used in a much wider sense, and is for instance also applied to patients in whom a subnormal biological response to insulin can be demonstrated, although many of these patients do not apparently present difficulties in their clinical management. Insulin resistance is found particularly in obese patients; resistance to endogenous insulin is thought to be linked to the development of type 2 diabetes in such patients. Insulin resistance is frequently associated with lipid disorders, hypertension, and ischaemic heart disease, a complex sometimes described as the metabolic syndrome. In women, it may also be linked to polycystic ovary syndrome.

Insulin resistance of the type manifested by greatly increased insulin requirements may be due to factors including antibody formation and inadequate absorption of insulin from subcutaneous sites. A few patients with severe insulin resistance have responded to insulin lispro (see Insulin Analogues and Proinsulin under Uses, below).

Mecasermin (insulin-like growth factor I) has been observed to improve insulin sensitivity in insulin resistance (see p.1808).

◊ References.

1. Moller DE, Flier JS. Insulin resistance—mechanisms, syndromes, and implications. *N Engl J Med* 1991; **325:** 938–48.
2. Eckel RH. Insulin resistance: an adaptation for weight maintenance. *Lancet* 1992; **340:** 1452–3.
3. Clausen JO, *et al.* Insulin resistance: interactions between obesity and a common variant of insulin receptor substrate-1. *Lancet* 1995; **346:** 397–402.
4. Davidson MB. Clinical implications of insulin resistance syndromes. *Am J Med* 1995; **99:** 420–6.
5. Krentz AJ. Insulin resistance. *BMJ* 1996; **313:** 1385–9. Correction. *ibid.* 1997; **314:** 134.
6. Cochran E, *et al.* The use of U-500 in patients with extreme insulin resistance. *Diabetes Care* 2005; **28:** 1240–4. Correction. *ibid.* 2007; **30:** 1035.
7. Kurtz TW. New treatment strategies for patients with hypertension and insulin resistance. *Am J Med* 2006; **119** (suppl 1): S24–S30.
8. Ballani P, *et al.* Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. *Diabetes Care* 2006; **29:** 2504–5. Correction. *ibid.* 2007; **30:** 455.

Uses and Administration

Insulin is a hormone that plays a key role in regulating carbohydrate, protein, and fat metabolism. The main stimulus for its secretion is glucose, although many other factors including amino acids, catecholamines, glucagon, and somatostatin, are involved in its regulation. The secretion of insulin is not constant and peaks occur in response to the intake of food.

The major effects of insulin on carbohydrate homoeostasis follow its binding to specific cell-surface receptors on insulin-sensitive tissues, notably the liver, muscles, and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood-glucose concentration. It also inhibits lipolysis thereby preventing the formation of ketone bodies.

Therapy with insulin is essential for the long-term survival of all patients with type 1 diabetes mellitus. It may also be necessary in some patients with type 2 disease. The management of diabetes mellitus and the role of insulin in type 1 and type 2 disease is discussed on p.431. Insulin is generally the treatment chosen for all types of diabetes mellitus during pregnancy.

Choice of insulin. The different types of insulin and their formulations are described under Definitions, above. In some countries including the UK the commercially available preparations have been standardised to a single **strength** containing 100 units/mL; a strength of 40 units/mL is still available in some other countries, and in others concentrated injections (500 units/mL) are available to enable high doses to be given subcutaneously in a small volume. All formulations can be given by subcutaneous injection, most by intramuscular injection, but only soluble insulins can be given by the intravenous **route**. The long-term management of diabetic patients usually involves the subcutaneous route. Syringes and needles for subcutaneous injection are preferably disposable. Pen-injector devices which hold the insulin in cartridge form and meter the required dose are becoming increasingly popular. Soluble insulin is often given by the intraperitoneal route to patients on continuous ambulatory peritoneal dialysis. More recently, products supplying short-acting insulin by inhalation have been developed.

The various formulations of insulin are classified, according to their **duration of action** after subcutaneous injection, as short-, intermediate-, or long-acting. The exact duration of action for any particular preparation, however, is variable and may depend upon factors such as interindividual variation, the patient's antibody status, whether the insulin is of human or animal origin, the dose, and the site of injection. *Short-acting* insulins are the soluble insulins, which have an onset after about 30 minutes to 1 hour, a peak activity at about 2 to 5 hours, and a duration of about 6 to 8 hours. Some analogues, such as insulins lispro and aspart, are also short-acting, with a faster onset and shorter duration of action than soluble insulin and are sometimes known as rapid-acting insulins. *Intermediate-acting* insulins include biphasic insulins, isophane insulins, and amorphous insulin zinc suspensions. In general these have an onset within about 2 hours, peak activity after about 4 to 12 hours, and a duration of up to 24 hours. Commercially available mixtures of soluble insulins and isophane insulins have activities which would normally place them within the intermediate-acting category. Mixed insulin zinc suspensions may be classified as either *intermediate- or long-acting* as the duration of action may be up to 30 hours; the onset of action is generally 2 to 3 hours and the time to peak activity 6 to 15 hours. *Long-acting* insulins include crystalline insulin zinc suspensions and protamine zinc insulins. These generally have an onset after about 4 hours, a peak activity at about 10 to 20 hours, and a duration of up to 36 hours. The insulin analogues insulin glargine and insulin detemir are also long-acting. After intramuscular injection, the onset of action of all insulins is generally more rapid and the duration of action shorter.

The type of formulation, its dose, and the frequency of administration are chosen to suit the needs of the individual patient. Whatever the formulation, human insulin is generally used for all newly diagnosed diabetics.

Control. The **dosage** of insulin must be determined for each patient and although a precise dose range cannot be given a total dose in excess of about 80 units daily would be unusual and may indicate the presence of a form of insulin resistance. The dose should be adjusted as necessary according to the results of regular monitoring of blood concentrations (or occasionally urine concentrations) of glucose by the patient.

The WHO has recommended that the glucose concentration of venous whole blood under fasting conditions should be kept within the range of 3.3 to 5.6 mmol/litre (60 to 100 mg per 100 mL) and after meals should not be allowed to exceed 10 mmol/litre (180 mg per 100 mL); blood-glucose concentrations should not be allowed to fall below 3 mmol/litre (55 mg per 100 mL). In practice it seems to be generally acceptable for patients to aim for blood-glucose concentrations between 4 and 10 mmol/litre, with the understanding that occasional variations outside this range may occur. It should be remembered that the glucose concentrations in venous plasma, venous whole blood, and capillary whole blood may be slightly different. Control may also be determined by monitoring of glycosylated haemoglobin concentrations; ideally the aim is an HbA_{1c} level of less than 7% or an HbA_1 of less than 8.8%, compared with normal ranges of 4 to 6% and 5 to 7.5% respectively. Insulin requirements may be altered by various factors (see Precautions, above). The aim of any regimen should be to achieve the best possible control of blood glucose by attempting to mimic as closely as possible the pattern of optimum endogenous insulin secretion. Many **regimens** involve the use of a short-acting soluble insulin with an intermediate-acting insulin, such as isophane insulin or mixed insulin zinc suspension, often given twice daily. It may sometimes be necessary, though, to give 3 or 4 injections daily to achieve good control and this typically involves giving a soluble insulin before meals and an intermediate- or long-acting insulin in the evening. A once-daily injection of an intermediate- or long-acting insulin is now generally considered to be acceptable only for those patients with type 2 diabetes mellitus who still retain some endogenous insulin secretion but nevertheless require insulin therapy, or for those patients with type 1 disease unable to cope satisfactorily with more intensive regimens. If a more intensive regimen is desired, **continuous subcutaneous infusion** may be employed using soluble insulin in an infusion pump. This delivers a constant basal infusion of insulin supplying about half of the total daily requirements, the remainder being provided by patient-activated bolus doses before each meal. The technique has a limited place in the management of diabetes; patients using it need to be well-motivated, reliable, and able to monitor their own blood glucose, and must have access to expert advice at all times. Formulations in which the insulin is in suspension are not suitable for continuous subcutaneous infusion and some brands of soluble insulin are unsuitable for this purpose because of the risk of precipitation in the pump catheter.

Ketoacidosis. Insulin is also an essential part of the emergency management of diabetic ketoacidosis. Only short-acting soluble insulins should be used. Treatment includes adequate fluid replacement, usually by infusing sodium chloride 0.9% initially, and the use of potassium salts to prevent or correct hypokalaemia. Insulin should be given by continuous intravenous infusion if possible, although other routes have also been used—for details of regimens see Diabetic Emergencies, under Diabetes Mellitus, below. Since insulin normally corrects hyperglycaemia before ketosis it is usually necessary to continue giving insulin once normoglycaemia has been achieved but to change the rehydration fluid to glucose-saline so that the additional glucose prevents the development of hypoglycaemia.

◊ General reviews of insulin and its use.[1-5] It has been suggested that the plethora of insulin preparations available might sensibly be reduced,[2] although others dispute this.[6]

1. MacPherson JN, Feely J. Insulin. *BMJ* 1990; **300:** 731–6.
2. Anonymous. Insulin preparations—time to rationalise. *Drug Ther Bull* 1996; **34:** 11–14.
3. American Diabetes Association. Insulin administration. *Diabetes Care* 2004; **27** (suppl 1): S106–S109. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106.pdf (accessed 08/07/04)
4. Mooradian AD, *et al.* Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 2006; **145:** 125–34.
5. Bell DSH. Insulin therapy in diabetes mellitus: how can the currently available injectable insulins be most prudently and efficaciously utilised? *Drugs* 2007; **67:** 1813–27.
6. von Kriegstein E, *et al.* Need for many types of insulin. *Lancet* 1996; **347:** 1045.

Administration. ADMINISTRATION ROUTES. The long-term management of diabetic patients usually involves injection by the **subcutaneous** route. The advice to diabetics has been to inject their insulin using a full-depth perpendicular injection.[1] In many non-obese patients, however, such a technique can result in inadvertent intramuscular injection.[1,2] Since insulin is absorbed more rapidly after intramuscular than subcutaneous injection, this may lead to greater day-to-day variability in blood-glucose control. In particular, overnight control may be inadequate if intermediate-acting preparations such as isophane insulin are used.[1] Some therefore consider that extended-action insulins should be injected at an angle into a raised skin fold. Although injection of soluble insulin into muscle may produce a more physiological action profile, until more data are available a technique that ensures subcutaneous injection may be prudent with soluble insulins as well.[1]

The anatomic *site* of subcutaneous insulin injection is usually rotated in an attempt to decrease local adverse effects (see Adverse Effects, above). However, the rate of absorption varies between sites and such a practice may also contribute to day-to-day variability in blood-glucose concentrations.[3] For example, large variations in blood-glucose concentrations have been reported on subcutaneous injection into the thigh.[4] Some have suggested rotation of injection sites within an anatomic region, or possibly use of the same anatomic region for injections given at a specific time of day.[3]

Jet injectors deliver insulin at high pressure across the skin into the subcutaneous tissue without use of a needle.[5,6] The greater dispersion obtained gives more rapid absorption of short- and intermediate-acting insulins and consequently reduces the total duration of action.[5] Mild pain, bruising, and bleeding may be a problem.[5-7] Despite having been available for some years, there is little information about their benefits and risks and they are not widely used.[6] However, results in a small study in women with gestational diabetes have suggested that jet injection may be associated with less variation in postprandial blood-glucose concentration and a lower incidence of insulin antibodies.[8]

Insulin preparations may also be given by **intramuscular** injection. Absorption is more rapid than from a subcutaneous injection. However, exercise may produce considerable variations in insulin absorption after intramuscular injection.[1] Soluble insulins may be given **intravenously**; this route is used in diabetic ketoacidosis, and also in surgery and labour.[9] Intermittent pulsed intravenous insulin therapy added to a conventional subcutaneous regimen has been reported to improve symptoms of orthostatic hypotension[10] and hypertension.[11]

The subcutaneous and intravenous routes, and, rarely, the intramuscular route have all been used for the continuous administration of insulin (see Intensive Administration Regimens, below).

Formulations of insulin for **intranasal** use are under investigation.[7,12,13] They have been tried in both type 1 and type 2 diabetes, but bioavailability is low and variable. Absorption enhancers have been used to facilitate uptake of insulin from the nasal mucosa and local adverse effects are dependent, in part, on their irritancy. Similarly, **buccal** formulations are under investigation,[7] and have become available in some countries.

Devices for delivering insulin to the lungs via oral **inhalation** have been developed.[7,14,15] Inhaled insulin is effective in maintaining glycaemic control in both type 1 and type 2 diabetes,[16-19] although there is some evidence from longer-term studies that it is slightly less effective than subcutaneous injection; however, patient acceptability is higher.[16] It is given before meals as a short-acting insulin in patients also receiving intermediate or long-acting subcutaneous insulins or oral antidiabetics; in type 2 diabetes it has also been used alone. UK recommendations from NICE are that it should be reserved for patients who are unable to start or intensify subcutaneous insulin therapy because of a marked, persistent fear of injections or severe difficulties with injection sites (for example, due to lipoatrophy).[17] Data regarding the long-term safety of inhaled insulin also need to be collected, given reports of pulmonary effects and higher levels of insulin antibodies in people with type 1 diabetes. A few cases of primary lung malignancies have occurred in clinical trials of inhaled insulin, at a higher incidence than in comparator-treated patients. However, the number of cases was too small to determine whether these events were related to inhaled insulin, and all affected patients had a history of cigarette smoking.

Endogenous insulin is delivered into the portal venous system, and then passes immediately to the liver where a large fraction of the insulin is extracted. The above routes of administration all deliver insulin into the peripheral circulation, with the risk of peripheral hyperinsulinaemia which has been considered a risk factor for atherosclerotic complications.[20] Giving insulin via the **intraperitoneal** or **oral** routes may overcome this problem to some extent. Peritoneal insulin is used routinely in diabetics undergoing chronic ambulatory peritoneal dialysis, but has also been used for continuous administration (see Intensive Administration Regimens, below). Various formulations of insulin for oral delivery are also under investigation.[7,13,21] **Rectal**[13] or **transdermal**[7] insulin has also been tried.

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13. Hoffman A, Ziv E. Pharmacokinetic considerations of new insulin formulations and routes of administration. *Clin Pharmacokinet* 1997; **33:** 285–301.
14. Patton JS, *et al.* Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. *Clin Pharmacokinet* 2004; **43:** 781–801.
15. Odegard PS, Capoccia KL. Inhaled insulin: Exubera. *Ann Pharmacother* 2005; **39:** 843–53.
16. Ceglia L, *et al.* Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann Intern Med* 2006; **145:** 665–75.
17. NICE. Inhaled insulin for the treatment of diabetes (types 1 and 2): Technology Appraisal 113 (issued December 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA113guidance.pdf (accessed 20/08/08)
18. Dunn C, Curran MP. Inhaled human insulin (Exubera): a review of its use in adult patients with diabetes mellitus. *Drugs* 2006; **66:** 1013–32.
19. Pham DQ, *et al.* Inhaled human [rDNA origin] insulin, a novel formulation for diabetes mellitus. *J Clin Pharmacol* 2007; **47:** 890–903.
20. Zinman B. The physiologic replacement of insulin: an elusive goal. *N Engl J Med* 1989; **321:** 363–70.
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INSULIN ANALOGUES AND PROINSULIN. Recombinant-DNA technology has enabled the production of insulin analogues with altered pharmacokinetic profiles.[1,2] Most of the insulin in pharmaceutical preparations is in the form of hexamers, which require time to dissociate before absorption from a subcutaneous site. Substitution of amino-acid residues at the monomer-monomer interface has produced monomeric insulin analogues that retain the biological activity of insulin.

Good results have been reported with an analogue, **insulin lispro**, in which the B28 and B29 residues are replaced with lysine and proline. This analogue is commercially available and has been widely reviewed.[3-7] In comparative studies of insulin lispro versus soluble insulin given before meals to patients also receiving a long-acting insulin, insulin lispro was reported to result in good glycaemic control, and could be given immediately before meals (5 to 15 minutes) rather than 20 to 40 minutes before as with soluble insulin. There is a suggestion that it may result in fewer severe hypoglycaemic episodes in such regimens.[8] However, an analysis of 10 clinical trials did not find any difference between insulin lispro and neutral insulin (Humulin R) with respect to overall adverse effects or development of long-term diabetic complications.[9] (See also insulin aspart, below.) A few cases of response to insulin lispro in patients with severe insulin resistance have been reported.[10,11] Insulin lispro has been complexed with protamine to produce an intermediate-acting form, which is available as a biphasic preparation.

Insulin aspart is another short-acting insulin analogue, with aspartic acid substituted for proline at position B28.[12-15] It is also used immediately before meals and controls postprandial blood glucose concentrations at least as well as regular human insulin, and may cause fewer hypoglycaemic episodes. A meta-analysis involving 42 studies of insulin lispro or insulin aspart versus regular insulin found that there was evidence of a minor benefit of the analogues in improving HbA_{1c} values in adult patients with type 1 diabetes; no superiority could be shown in patients with type 2 diabetes.[16]

Insulin glulisine is another insulin analogue, with asparagine at position B3 replaced by lysine, and lysine at B29 replaced by glutamic acid. It also has a rapid onset and short duration of action.[17,18]

Recombinant-DNA technology has also been used to produce a long-acting basal insulin analogue, **insulin glargine**, suitable for once-daily use.[19-23] It is available as a solution at pH 4; on subcutaneous injection and neutralisation by tissue buffering processes, microprecipitates are formed that slowly release insulin glargine over 24 hours with no pronounced peak in concentration or in metabolic activity. Controlled studies have reported insulin glargine to be more effective than human isophane insulin in producing glycaemic control as part of a basal-bolus regimen, and to be associated with fewer hypoglycaemic episodes.

Insulin detemir is another long-acting insulin analogue that may have some benefit over isophane insulin. It is a neutral soluble human insulin analogue in which the terminal amino acid at B30 has been replaced by a 14-carbon fatty acid chain. This allows insulin detemir to bind reversibly to albumin, producing slow absorption and a prolonged and consistent metabolic effect for up to 24 hours. It appears to be at least as effective as isophane insulin in maintaining overall glycaemic control but with less intrapatient variability, a similar or lower risk of hypoglycaemia, and less body-weight gain.[24]

Proinsulin (the natural precursor of insulin) appears to be more active than insulin in suppressing the hepatic production rather than the peripheral uptake of glucose.[25,26] It has therefore been studied particularly in patients with type 2 diabetes mellitus. However, development by some manufacturers has been suspended because of a higher rate of adverse cardiac effects in patients treated with proinsulin than in controls.[25]

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3. Anonymous. Lispro, a rapid-onset insulin. *Med Lett Drugs Ther* 1996; **38:** 97–8.
4. Campbell RK, *et al.* Insulin lispro: its role in the treatment of diabetes mellitus. *Ann Pharmacother* 1996; **30:** 1263–71.
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6. Anonymous. Humalog—a new insulin analogue. *Drug Ther Bull* 1997; **35:** 57–8.
7. Wilde MI, McTavish D. Insulin Lispro: a review of its pharmacological properties and therapeutic use in the management of diabetes mellitus. *Drugs* 1997; **54:** 597–614.
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9. Glazer NB, *et al.* Safety of insulin lispro: pooled data from clinical trials. *Am J Health-Syst Pharm* 1999; **56:** 542–7.
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11. Lahtela JT, *et al.* Severe antibody-mediated human insulin resistance: successful treatment with the insulin analog lispro. *Diabetes Care* 1997; **20:** 71–3.
12. Setter SM, *et al.* Insulin aspart: a new rapid-acting insulin analog. *Ann Pharmacother* 2000; **34:** 1423–31.
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19. Anonymous. Insulin glargine (Lantus), a new long-acting insulin. *Med Lett Drugs Ther* 2001; **43:** 65–6.
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INTENSIVE ADMINISTRATION REGIMENS. Intensive insulin regimens aim to mimic more closely the physiological insulin pattern in which a basal insulin concentration is supplemented by a preprandial boost of insulin. Such intensive regimens are used to provide tight control in an attempt to avoid long-term complications (see p.433).

Intensified insulin regimens have the advantage of improving the patient's lifestyle and allowing flexibility in timing of meals. However, careful dietary control must still be maintained and regular monitoring of blood-glucose concentrations is an important component of such regimens. Therefore patients must be well-motivated, reliable, and able to monitor their own blood glucose, and must have access to expert 24-hour help. Although there are reports of success with intensive regimens in brittle (labile) diabetics,[1] these patients are generally unlikely to benefit from such regimens.

In **multiple-injection regimens**, the basal insulin is provided by an injection of intermediate- or long-acting insulin given usually at night, and soluble insulin is given before each main meal. Systems for **continuous administration** may be designed on an open-loop or closed-loop delivery system. *Open-loop systems* comprise an infusion pump with the infusion rate programmed or controlled manually according to manual blood-glucose monitoring. *Closed-loop systems* (the 'artificial pancreas') consist of an insulin pump, a glucose sensor, and a computer for analysis of blood-glucose data. Systems for continuous administration have most commonly used the subcutaneous route, but intraperitoneal, intravenous, or intramuscular infusion have also been used.

The most extensively used **open-loop** system is *continuous subcutaneous insulin infusion* (CSII) using an external pump. A battery-powered pump infuses soluble insulin via a subcutaneous catheter which is resited every 2 to 3 days. A background infusion is given at a predetermined rate, and preprandial bolus doses given using an override switch or manual drive.[2] CSII provides better glycaemic control than conventional injection therapy, but may be only slightly more effective than optimised multiple daily injection therapy.[3] Complications include erythema, abscess, or cellulitis at the injection site and, rarely, contact dermatitis to components of the giving set, pump malfunction, or precipitation of insulin and catheter obstruction.[2] Pump therapy increases the risk of ketoacidosis and intensive regimens are associated with decreased hypoglycaemic awareness and more severe hypoglycaemic episodes compared with conventional therapy,[4] although there is some suggestion that CSII might reduce the risk of severe hypoglycaemia compared with multiple daily injection therapy.[2] If the pump fails or there is an acute increase in insulin requirements, the onset of ketoacidosis may be more rapid and more likely to be associated with dangerous hyperkalaemia than with conventional regimens because there is no depot of insulin.[2,5]

Further development of open-loop delivery systems has been in the design of *implantable insulin pumps.* The first pumps delivered insulin at a constant basal rate, but variable rate models are now available. Studies[6,7] have shown that intravenous or intraperitoneal delivery of insulin from an implantable pump can produce excellent glycaemic control, and fewer episodes of severe hypoglycaemia than are associated with intensive subcutaneous multiple-injection regimens. The main problems associated with such therapy are pump slow-down or catheter obstruction due to aggregation of insulin within the device; these can normally be corrected by procedures to flush the pump and catheter,[7,8] although alternative insulin formulations (e.g. with poloxamer) have been investigated. Other problems may include fibrinous obstruction of the catheter or local intolerance of the pump.[8]

Closed-loop continuous infusion systems are generally confined to research and experimental work because glucose sensors suitable for implantation are still being developed.[8] However, results in *animals* have suggested that an alternative to such systems may be a vascularised artificial pancreas containing islet cells.[9]

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8. Selam JL. Implantable insulin pumps. *Lancet* 1999; **354:** 178–9.
9. Maki T, *et al.* Novel delivery of pancreatic islet cells to treat insulin-dependent diabetes mellitus. *Clin Pharmacokinet* 1995; **28:** 471–82.

MIXING OF INSULINS. Mixtures of insulin with differing durations of action may be used in order to produce a more normal pattern of blood glucose variation than can be achieved with a single insulin. However, physicochemical changes in the mixture may occur, either immediately on mixing or over time, and the physiological response to the mixture may therefore be different than if the components were given separately. An early review[1] suggested that insulins from different manufacturers should not be mixed, since formulation differences might render them incompatible. It is important that a consistent routine is followed in preparing and using such mixtures, and manufacturers advise that the shorter-acting insulin should be drawn into the syringe first, to avoid contamination of the vial with the longer-acting component. Prepared mixtures are available from many manufacturers and may be preferable provided that the proportions are suited to the patient's needs.

The American Diabetes Association has issued guidelines[2] for mixing of insulins, including:

- patients well controlled on a particular mixed regimen should maintain their standard procedure for preparing doses
- no other medication or diluent should be mixed with insulin unless approved by the prescriber
- insulin glargine should not be mixed with other forms of insulin because of the low pH of its diluent
- currently available isophane and short-acting insulin formulations when mixed may be used immediately or stored for future use
- rapid-acting insulins (insulin aspart, insulin lispro) can be mixed with isophane, lente, and ultralente insulins. Ultralente insulins do not affect the onset of action of the rapid-acting component; a slight decrease in absorption rate but not bioavailability is seen if rapid-acting insulins are mixed with isophane insulin but postprandial blood-glucose response is similar to that seen with mixtures of rapid-acting and ultralente insulin
- mixtures of rapid-acting insulin with an intermediate- or long-acting insulin should be injected within 15 minutes before a meal
- mixing of short-acting (soluble) and lente or ultralente insulin is not recommended, as zinc ions present in the lente insulin may bind with the short-acting insulin and delay its effects. The degree and rate of binding vary with the insulins used, and may not reach equilibrium for 24 hours; if such mixtures are used the patient should standardise the interval between mixing and injection
- phosphate-buffered insulins (e.g. isophane insulin) should not be mixed with zinc-containing (lente or ultralente) insulins, as zinc phosphate may be precipitated, and the longer acting insulin may be partially and unpredictably converted to a short-acting form

Insulin formulations may change and the manufacturers should be consulted if their recommendations differ from those in the guidelines.

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2. American Diabetes Association. Insulin administration. *Diabetes Care* 2004; **27** (suppl 1): S106–S109. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106.pdf (accessed 08/07/04)

Diabetes mellitus. Insulin is the mainstay of the treatment of **type 1 diabetes mellitus**. For a discussion of the treatment of diabetes mellitus, including the contexts in which insulin is used, see p.431. The possible role of tight glycaemic control with insulin to prevent the development of microvascular and macrovascular complications in patients with type 1 diabetes is discussed on p.433, while further discussion of specific regimens and approaches to insulin therapy is given under Administration, above.

DIABETIC EMERGENCIES. As discussed on p.435, **diabetic ketoacidosis** and hyperosmolar hyperglycaemic state are medical emergencies and should be treated immediately with fluid replacement and insulin. Potassium, and possibly phosphate, replacement may also be required, but bicarbonate should not be given unless acidaemia is very severe. In the *UK* the *BNF* recommends that insulin be given by intravenous infusion for diabetic ketoacidosis, as a solution of soluble insulin 1 unit/mL via an infusion pump. An infusion rate of 6 units/hour in adults and 0.1 units/kg per hour in children is recommended initially, with the rate doubled or quadrupled if the blood glucose concentration fails to decrease by about 5 mmol/litre per hour. When blood glucose concentrations have fallen to 10 mmol/litre the infusion rate can be reduced to 3 units/hour in adults or about 0.05 units/kg per hour in children, and continued, with glucose 5% to prevent hypoglycaemia, until the patient is ready to take food by mouth. The insulin infusion should not be stopped before subcutaneous insulin has been started. Potassium chloride is included in the infusion as appropriate to prevent insulin-induced hypokalaemia. If facilities for intravenous infusion are not available the insulin is given by intramuscular injection: in adults an initial loading dose of 20 units intramuscularly is followed by 6 units intramuscularly every hour until the blood glucose concentration falls to 10 mmol/litre, when the dose is given every 2 hours. Late hypoglycaemia due to insulin accumulation should be watched for and managed appropriately.

In the *USA* the intramuscular or the subcutaneous route have been used as alternatives to intravenous insulin, with other appropriate management. One successful set of protocols for insulin dosage in diabetic ketoacidosis is as follows:[1] an initial intravenous bolus of 0.15 units/kg is followed by infusion of 0.1 units/kg per hour; if blood glucose does not fall by about 2.5 to 3.5 mmol/litre in the first hour the infusion rate is doubled every hour until this rate of decline is achieved. (A similar insulin regimen has proved effective in patients with hyperosmolar hyperglycaemic state.[1]) When given by the intramuscular or subcutaneous routes an initial bolus of 0.4 units/kg is divided and given half by the intravenous route and half either intramuscularly or subcutaneously as appropriate. This is followed by 0.1 units/kg every hour intramuscularly or subcutaneously; if response is inadequate it is replaced by an intravenous bolus of 10 units until blood glucose falls by 2.5 to 3.5 mmol/litre. In children intravenous infusion of 0.1 units/kg per hour is recommended, or if intravenous infusion is impractical an initial intramuscular bolus of 0.1 units/kg followed by 0.1 units/kg per hour either intramuscularly or subcutaneously. Treatment is continued at this rate until a serum-glucose concentration of about 12.5 mmol/litre is reached (or about 15 mmol/litre for hyperosmolar hyperglycaemic state), when the rate is decreased to 0.05 to 0.1 units/kg per hour until acidosis is controlled and subcutaneous insulin replacement treatment can be started.

1. American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S94–S102. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s94.pdf (accessed 26/05/04)

TYPE 2 DIABETES MELLITUS. Traditionally the use of insulin in patients with type 2 diabetes has tended to be reserved for those who cannot be controlled by diet and oral antidiabetics alone.[1,2] Given the possible association between circulating insulin and atherosclerotic cardiovascular symptoms[3] there has been some concern about the use of exogenous insulin in insulin-resistant patients who are already hyperinsulinaemic. Furthermore, patients switched to insulin tend to gain weight[2] which is undesirable in a frequently obese patient group.

Insulin is nonetheless being used more frequently in type 2 patients. This is largely because of a trend toward more intensive regimens designed to produce tighter glycaemic control, on the hypothesis that, as in patients with type 1 disease, this will reduce the development and progression of diabetic complications. Results from the UK Prospective Diabetes Study,[4-6] show that insulin is an effective option in type 2 diabetes, and confirm both the value of intensive therapy in retarding microvascular complications,[6] and that oral therapy should be used before insulin in patients with primary diet failure.[7]

In order to minimise the dose of insulin required, and any risks it may entail, it has been suggested that insulin therapy in type 2 diabetes should be combined with other measures including oral hypoglycaemic drugs.[8] There has long been debate about the value of combined therapy, but a meta-analysis indicated that glycaemic control was better, and insulin requirements lower, in type 2 diabetics who received insulin with a sulfonylurea.[9] For evidence that the insulin analogues insulin lispro and insulin aspart have no advantage over regular insulin in type 2 patients see Insulin Analogues, above.

For further discussion of the management of type 2 diabetes mellitus see p.431.

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2. Taylor R. Insulin for the non-insulin dependent? *BMJ* 1988; **296:** 1015–16.
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4. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. *BMJ* 1995; **310:** 83–8.
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8. Henry RR. Glucose control and insulin resistance in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; **124** (suppl): 97–103.
9. Johnson JL, *et al.* Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomized placebo-controlled trials. *Arch Intern Med* 1996; **156:** 259–64.

Diagnosis and testing. ***PITUITARY FUNCTION.*** Insulin-induced hypoglycaemia has been used to provide a stressful stimulus in order to assess hypothalamic-pituitary function. The insulin stress or insulin-tolerance test has been used as a standard test for assessment of growth hormone or corticotropin deficiency. However, it is unpleasant, expensive, and not without risk, and is contra-indicated in patients with angina, heart failure, cerebrovascular disease, or epilepsy; some recommend its use only when results of alternative tests are equivocal,[1-3] and it should only be performed in specialist units under strict surveillance.[4]

1. Clayton RN. Diagnosis of adrenal insufficiency. *BMJ* 1989; **298:** 271–2.
2. Stewart PM, *et al.* A rational approach for assessing the hypothalamic-pituitary-adrenal axis. *Lancet* 1988; **1:** 1208–10.
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4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.

Hyperkalaemia. Insulin promotes the intracellular uptake of potassium. It is therefore used in the management of moderate to severe hyperkalaemia, when it is given with glucose (see p.1669).

Liver disorders. There have been reports[1,2] of benefit from the use of insulin and glucagon in the treatment of liver disorders, based on their reported hepatotrophic effect. However, randomised studies have found no benefit from insulin and glucagon infusions in fulminant hepatic failure[3] and acute alcoholic hepatitis.[4]

1. Baker AL, *et al.* A randomized clinical trial of insulin and glucagon infusion for treatment of alcoholic hepatitis: progress report in 50 patients. *Gastroenterology* 1981; **80:** 1410–14.
2. Jaspan JB, *et al.* Insulin and glucagon infusion in the treatment of liver failure. *Arch Intern Med* 1984; **144:** 2075–8.
3. Harrison PM, *et al.* Failure of insulin and glucagon infusion to stimulate liver regeneration in fulminant hepatic failure. *J Hepatol* 1990; **10:** 332–6.
4. Bird G, *et al.* Insulin and glucagon infusion in acute alcoholic hepatitis: a prospective randomized controlled trial. *Hepatology* 1991; **14:** 1097–1101.

Myocardial infarction. Discussions on the effects of insulin with glucose and potassium in the ischaemic heart, including its effect in reducing blood free fatty acids, have emphasised its potential benefits in left ventricular failure and cardiogenic shock.[1,2] A meta-analysis[3] of randomised controlled studies performed before the widespread use of thrombolytics found a reduction in mortality in recipients of glucose-insulin-potassium solutions. However, although a pilot study[4] that included patients undergoing reperfusion (thrombolysis or percutaneous coronary intervention) reported benefit, this was not confirmed in larger randomised studies using standard glucose-insulin-potassium infusions.[5,6] A further study[7] found that routine use of such infusions in patients undergoing reperfusion had no effect on myocardial salvage, although some improvement was reported in diabetics.

Intensive glucose control, with insulin-glucose infusion followed by multiple daily subcutaneous insulin injections has been reported to reduce mortality in diabetics who suffered a myocardial infarction.[8,9] A similar study[10] of treatment after myocardial infarction included only patients with type 2 diabetes mellitus who were treated with routine care, or insulin-glucose infusion followed by either long-term subcutaneous insulin or standard glucose control. The study was stopped early due to slow patient recruitment, but results did suggest that although glucose concentration was a strong independent predictor of long-term mortality, the use of long-term insulin treatment did not improve survival compared with conventional treatment at similar levels of glucose control. An observational study[11] in non-diabetics with hyperglycaemia suggested that intensive glucose control also improved outcomes in this population, but another study[12] found no benefit. However, the glucose control achieved in this study was similar in both the intensive and the conventional treatment groups and an analysis based on blood glucose concentrations suggested that strict glucose control was beneficial.[12]

For the conventional management of myocardial infarction, see p.1175.

1. Opie LH. Glucose and the metabolism of ischaemic myocardium. *Lancet* 1995; **345:** 1520–1.
2. Taegtmeyer H, *et al.* Metabolic support for the postischaemic heart. *Lancet* 1995; **345:** 1552–5.
3. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997; **96:** 1152–6.
4. Díaz R, *et al.* Metabolic modulation of acute myocardial infarction: the ECLA Glucose-Insulin-Potassium Pilot Trial. *Circulation* 1998; **98:** 2227–34.
5. Mehta SR, *et al.* Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005; **293:** 437–46.
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7. Pache J, *et al.* A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 2004; **148:** e3.
8. Malmberg K, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; **26:** 57–65.
9. Malmberg K, *et al.* Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997; **314:** 1512–15.
10. Malmberg K, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; **26:** 650–61.
11. Weston C, *et al.* Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart* 2007; **93:** 1542–6.
12. Cheung NW, *et al.* The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 2006; **29:** 765–70.

Neonatal hyperglycaemia. Hyperglycaemia is common in very immature neonates because of delayed or reduced insulin production. It can be treated by glucose restriction until glucose tolerance improves. However, this may not provide enough glucose to meet basal metabolic needs, and the use of an insulin infusion can allow sufficient glucose to be given. It has been suggested that insulin is best given intravenously in a separate, easily titratable solution because of the frequent fluctuations of requirement in these infants.[1]

1. Ditzenberger GR, *et al.* Continuous insulin intravenous infusion therapy for VLBW infants. *J Perinat Neonatal Nurs* 1999; **13:** 70–82.

Overdosage with calcium-channel blockers. High-dose insulin, with glucose and potassium as required to maintain normal plasma concentrations of these, has been reported to be of value in the treatment of overdosage with calcium-channel blockers that has not been adequately managed with conventional therapy (which is described under Treatment of Adverse Effects under Nifedipine, p.1352). A review[1] of 13 reported cases found that various dosage regimens had been tried. These included bolus doses of insulin 10 to 20 units, and continuous infusions of 0.1 to 1 unit/kg per hour. The authors of one report[2] have proposed a regimen that includes an initial intravenous bolus dose of insulin 1 unit/kg, followed by a continuous infusion of 0.5 units/kg per hour; this may be increased to 1 unit/kg per hour if necessary.

1. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
2. Boyer EW, *et al.* Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. *Pediatr Emerg Care* 2002; **18:** 36–7.

Preparations

BP 2008: Insulin Aspart Injection; Insulin Lispro Injection; Protamine Zinc Insulin Injection;
Ph. Eur.: Biphasic Insulin Injection; Biphasic Isophane Insulin Injection; Insulin Zinc Injectable Suspension; Insulin Zinc Injectable Suspension (Amorphous); Insulin Zinc Injectable Suspension (Crystalline); Isophane Insulin Injection; Soluble Insulin Injection;
USP 31: Extended Insulin Human Zinc Suspension; Extended Insulin Zinc Suspension; Human Insulin Isophane Suspension and Human Insulin Injection; Insulin Human Injection; Insulin Human Zinc Suspension; Insulin Injection; Insulin Lispro Injection; Insulin Zinc Suspension; Isophane Insulin Human Suspension; Isophane Insulin Suspension; Prompt Insulin Zinc Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Actrapid HM; Actrapid MC†; Apidra; Biohulin C; Biohulin N; Densulin; Humalog; Humalog Mix 25; Humulin 70/30; Humulin L†; Humulin NPH; Humulin R; Humulin U†; Insulatard HM; Insulatard MC†; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; Monotard MC†; NovoMix 30; NovoRapid; ***Austral.:*** Actrapid; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin NPH; Humulin R; Humulin UL†; Hypurin Isophane; Hypurin Neutral; Lantus; Levemir; Mixtard 20/80, 30/70, 50/50; Monotard†; NovoMix 30; NovoRapid; Protaphane; Ultratard†; ***Austria:*** Actrapid HM; Humalog; Humalog Mix 25 and 50; Huminsulin Basal; Huminsulin Long; Huminsulin Normal; Huminsulin Profil II and III; Huminsulin Ultralong; Insulatard HM; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Mixtard HM 10/90, 20/80, 30/70, 40/60, and 50/50; Monotard HM; Ultratard HM; ***Belg.:*** Actrapid HM; Humaject 30/70†; Humaject NPH†; Humaject Regular†; Humalog; Humalog Mix 25 and 50; Humuline 30/70, 50/50; Humuline Long†; Humuline NPH; Humuline Regular; Humuline Ultralong†; Insulatard; Lantus; Levemir; Mixtard 10, 20, 30, 40, 50; Monotard HM†; NovoMix 30; NovoRapid; Ultratard†; Velosulin; ***Braz.:*** Actrapid MC†; Biohulin 70/30, 80/20, and 90/10†; Biohulin Lenta†; Biohulin NPH; Biohulin Regular; Biohulin Ultralenta†; Exubera; Humalog; Humalog Mix 25; Humulin 70/30; Humulin Lenta; Humulin NPH; Humulin Regular; Insuman Comb 85N/15R and 75N/25R; Insuman N; Insuman R; Lantus; Levemir; Monotard MC†; Novolin 70/30; Novolin L†; Novolin N; Novolin R; Novolin U†; NovoRapid; Protaphane MC†; ***Canad.:*** Humalog; Humalog Mix 25; Humulin 20/80, 30/70; Humulin L; Humulin N; Humulin R; Humulin U; Hypurin NPH; Hypurin Regular; Iletin II Pork Lente; Iletin II Pork NPH; Iletin II Pork Regular; Lantus; Novolin 10/90, 20/80, 30/70, 40/60, 50/50; Novolin Lente†; Novolin NPH; Novolin Toronto; Novolin Ultralente†; NovoRapid; ***Chile:*** Actrapid HM; Actrapid†; Humalog; Humalog Mix 25; Humulin 70/30†; Humulin L†; Humulin N†; Humulin R†; Insulatard HM; Insulatard†; Insuman N; Insuman R; Lantus; Lenta†; Mixtard 30 HM; Monotard HM†; NovoMix 30; NovoRapid; Wosulin 30/70; Wosulin-N; Wosulin-R; ***Cz.:*** Actraphane; Actrapid; Exubera; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humulin L†; Humulin M3; Humulin N; Humulin R; Humulin U†; Hypurin Bovine Isophane†; Hypurin Bovine Protamin Zink Sulfat†; Hypurin Porcin Neutral†; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman

Rapid; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10, 20, 30, 40, and 50; Monotard HM†; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Ultratard HM†; Velosulin; ***Denm.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin Mix 30/70; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Velosulin; ***Fin.:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humulin NPH; Humulin Regular; Humutard†; Insulin Lyhyt†; Insulin Pitka†; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, and 50; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard†; Velosulin†; ***Fr.:*** Actrapid; Apidra; Exubera; Humalog; Humalog Mix 25 and 50; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Insuplant; Lantus; Levemir; Lillypen Rapide†; Mixtard 10, 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; Umuline NPH; Umuline Profil 30; Umuline Rapide; Umuline Zinc Compose†; Umuline Zinc†; Velosulin†; ***Ger.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; B-Insulin†; Berlinsulin H 30/70; Berlinsulin H Basal; Berlinsulin H Normal; Depot-Insulin S†; Depot-Insulin†; H-Tronin†; Humalog; Humalog Mix 25 and 50; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulatard Human†; Insulin Basal; Insulin Comb 30/70; Insulin Monotard HM†; Insulin Novo Semilente MC; Insulin Rapid; Insulin S†; Insulin SNC†; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Komb-Insulin S†; Komb-Insulin†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 30/70†; Monotard; NovoMix 30; NovoRapid; Protaphane; Semilente†; Ultratard; Velosulin; ***Gr.:*** Actraphane HM†; Actrapid; Apidra; Exubera; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humulin Lente; Humulin M2, M3; Humulin NPH; Humulin Regular; Humulin Utralente; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; PenMix 10, 20, 30, 40, or 50†; Protaphane; Ultratard; ***Hong Kong:*** Actrapid HM; Actrapid MC†; Humalog; Humulin 70/30; Humulin L; Humulin N; Humulin R; Insulatard MC†; Lantus; Mixtard 30 HM; Monotard HM; Monotard MC†; NovoMix 30; NovoRapid; Protaphane HM; Ultratard HM; ***Hung.:*** Actrapid; Apidra; Humalog; Humalog Mix25 and Mix50; Humulin L†; Humulin M3; Humulin N; Humulin R; Humulin U†; Insulatard; Insulin Monotard†; Insulin Semilente†; Insulin Ultratard†; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard MC†; NovoMix 30; NovoRapid; ***India:*** Actrapid; Human Actrapid; Human Insultard; Human Mixtard 30 and 50; Human Monotard; Insuman Rapid; Insuman 25/75 and 50/50; Lantus; Lentard; Mixulin; Rapidica; Rapimix; Wosulin Biphasic 30/70 and 50/50; Wosulin-N; Wosulin-R; Zinulin; ***Indon.:*** Actrapid HM; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin N; Humulin R; Insulatard HM; Lantus; Mixtard 30 HM; Monotard HM; ***Irl.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin I; Humulin Lente†; Humulin M3; Humulin S; Humulin Zn†; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 10 , 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; ***Israel:*** Humalog; Humalog Mix 25; Humulin 70/30; Humulin N; Humulin R; Humulin U†; Lantus; Levemir; NovoMix 30; NovoRapid; ***Ital.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Bio-Insulin 30/70 and 50/50†; Bio-Insulin I†; Bio-Insulin L†; Bio-Insulin R†; Bio-Insulin U†; Humalog; Humalog Mix 25 and 50; Humulin 30/70 and 50/50; Humulin I; Humulin L†; Humulin R; Humulin U†; Lantus; Levemir; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard; ***Jpn:*** Humacart 3/7; InnoLet 10R, 20R, 30R, 40R, and 50R; InnoLet N; InnoLet R; Monotard†; NovoLet 10R,20R, 30R, 40R, 50R†; NovoLet N†; NovoLet R†; Novolin 10R, 20R, 30R, 40R, and 50R; Novolin N; Novolin R; Novolin U†; NovoRapid; NovoRapid 30 Mix chu; Penfill N; Penfill R; Penfill 10R, 20R, 30R, 40R, 50R; Velosulin; ***Malaysia:*** Actrapid HM; Humalog; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; NovoMix; NovoRapid; Ultratard HM†; ***Mex.:*** Glinux 70/30; Glinux-N; Humalog; Humalog Mix 25; Humanilusin; Humulin 70/30, 80/20; Humulin L; Humulin N; Humulin R; Insulex; Insuman 100N; Insuman 15R/85N, 25R/75N, and 50R/50N; Insuman R; Lantus; Levemir; Novolin 30/70; Novolin L†; Novolin N; Novolin R; NovoMix 30; NovoRapid; Prodiabin-N; ***Neth.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humuline; Humuline 30/70; Humuline NPH; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Isuhuman Infusat†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Protaphane; Ultratard; Velosulin; ***Norw.:*** Actrapid; Humalog; Humalog Mix 25; Humulin NPH; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; Velosulin†; ***NZ:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humulin 70/30; Humulin L†; Humulin NPH; Humulin R; Humulin U†; Insulatard MC; Lantus; Levemir; Mixtard 30 or 50; Monotard; NovoRapid; PenMix 10, 20, 30, 40, or 50; Protaphane; Ultratard; Velosulin HM; Velosulin MC; ***Philipp.:*** Actrapid HM; Biosulidd L; Humalog; Humulin 70/30; Humulin N (NPH); Humulin R (Regular); Insulatard HM; Lantus; Mixtard 30 HM; NovoMix 30; SciLin M30; SciLin N; SciLin R; ***Pol.:*** Actrapid; Apidra; Gensulin N; Gensulin R; Gensulin M10, M20, M30, M40, or M50; Humaject M3 (30/70)†; Humaject R†; Humalog; Humalog Mix 25 and 50; Humulin M3 (30/70); Humulin N; Humulin R; Insulatard; Insulinum Lente; Insulinum Maxirapid; Insulinum Semilente; Insulinum Ultralente; Insuman Basal; Insuman Comb 25; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; Polhumin Mix-3; Polhumin N; Polhumin R; Ultratard HM; ***Port.:*** Actrapid; Apidra; Exubera; Humalog; Humulin Lenta†; Humulin M3; Humulin NPH; Humulin Regular; Humulin Ultralenta†; Insulatard; Isuhuman Basal†; Isuhuman Comb 25†; Isuhuman Rapid†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10 , 20, 30, 40, and 50 HM; Monotard†; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Protaphane; Ultratard†; Velosulin; ***Rus.:*** Actrapid HM (Актрапид НМ); Actrapid MC (Актрапид МС); Biosulin N (Биосулин Н); Biosulin R (Биосулин Р); Humalog (Хумалог); Humalog Mix 25 (Хумалог Микс 25); Humulin M3 (Хумулин М3); Humulin NPH (Хумулин НПХ); Humulin Regular (Хумулин Регуляр); Insulidd L (Инсулидд Л); Insulidd N (Инсулидд Н)†; Insulidd R (Инсулидд Р)†; Insulin Lt (Инсулин Лт); Insulin Maxirapid (Инсулин Максирапид); Insuman Basal (Инсуман Базал); Insuman Comb 25 (Инсуман Комб 25); Insuman Rapid (Инсуман Рапид); Lantus (Лантус); Levemir (Левемир); Levulin L (Левулин Л); Levulin N (Левулин Н)†; Levulin R (Левулин Р)†; Mixtard 30 HM (Микстард 30 НМ); Monotard MC (Монотард Нм); NovoMix 30 (НовоМикс 30); NovoRapid (Новорапид); Protaphane HM (Протафан НМ); ***S.Afr.:*** Actraphane HM; Actrapid HM; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Lantus; Levemir; Mixtard 20/80†; Monotard HM†; NovoMix 30; NovoRapid; Protaphane HM; Ultratard HM†; ***Singapore:*** Actrapid HM; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Insulatard HM; Lantus; Levemir; Mixtard 30 or 50; Monotard HM†; NovoMix 30; NovoRapid; Ultratard HM†; ***Spain:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humaplus 30/70†; Humaplus NPH†; Humaplus Regular†; Humulina 30:70; Humulina Lenta†; Humulina NPH; Humulina Regular; Humulina Ultralenta†; Insulatard; Insulatard NPH†; Lantus; Levemir; Mixtard 30; Mixtard 30/70†; Monotard†; NovoMix 30; NovoRapid; Ultratard†; ***Swed.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin Mix 30/70; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Ultratard; Velosulin†; ***Switz.:*** Actrapid HM; Actrapid MC; Apidra; Humalog; Huminsulin Basal (NPH); Huminsulin Long; Huminsulin Normal; Huminsulin Profil III; Huminsulin Ultralong; Hypurin 30/70 Mix; Hypurin Isophane; Hypurin Neutral; Insulatard HM; Insulatard MC; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Lente MC†; Levemir; Mixtard 30 MC; Mixtard HM 10, 20, 30, 40, 50; Monotard HM; NovoMix 30; NovoRapid; Semilente MC; Ultratard HM; Velosulin HM†; ***Thai.:*** Actrapid HM; Humalog; Humalog Mix 25; Humulin 70/30; Humulin N; Humulin R; Insulatard; Lantus; Mixtard HM; Monotard HM†; NovoMix 30; NovoRapid; ***Turk.:*** Humalog; Humalog Mix 25 and 50; Humulin M 70/30 and 80/20; Humulin N; Humulin R; Insulatard; Lantus; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; Orgasulin Mix 30/70; ***UAE:*** Jusline 70/30; Jusline N; Jusline R; ***UK:*** Actrapid; Apidra; Exubera†; Humaject S†; Humalog; Humalog Mix 25 and 50; Humulin I; Humulin Lente†; Humulin M3; Humulin S; Humulin Zn†; Hypurin 30/70; Hypurin Isophane; Hypurin Lente; Hypurin Neutral; Hypurin Protamine Zinc; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 30; Monotard†; NovoMix 30; NovoRapid; Pork Actrapid†; Pork Insulatard†; Pork Mixtard 30†; Ultratard†; Velosulin†; ***USA:*** Apidra; Exubera; Humalog; Humalog Mix 75/25 and 50/50; Humulin 70/30, 50/50; Humulin L†; Humulin N; Humulin R; Humulin U Ultralente†; Lantus; Lente; Lente Iletin II; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoLog; NovoLog Mix 70/30; NPH Iletin II†; Regular Iletin II; Ultralente; Velosulin Human BR†; ***Venez.:*** Humalog; Humalog Mix 25; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Insuman N; Insuman R; Lantus; Novolin 70/30†; Novolin L†; Novolin N†; Novolin R†.

Metformin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metformina; LA-6023 (metformin or metformin hydrochloride); Metformiinihydrokloridi; Metformin Hidroklorür; Metformin hydrochlorid; Metformine, chlorhydrate de; Metformin-hidroklorid; Metforminhydroklorid; Metformini hydrochloridum; Metformino hidrochloridas. 1,1-Dimethylbiguanide hydrochloride.

Метформина Гидрохлорид

$C_4H_{11}N_5,HCl = 165.6.$

CAS — 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride).

ATC — A10BA02.

ATC Vet — QA10BA02.

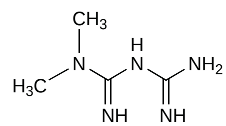

(metformin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Metformin Hydrochloride). White or almost white crystals. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

USP 31 (Metformin Hydrochloride). A white crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for biguanides in general, p.437.

Breast feeding. Based on *animal* studies the UK and US licensed product information warns that metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breast feed while receiving the drug. However, a study in 7 breast-feeding women receiving metformin at a median dose of 1.5 g daily found the concentrations in milk to be about a third of those in maternal plasma, resulting in a mean calculated dose to the infants of 40 micrograms/kg daily. Blood samples were taken from 4 of the infants: metformin concentrations were undetectable in 2, and were very low (10 to 15% of maternal values) in the others. Given these results the authors considered that women receiving metformin need not be discouraged from breast feeding.[1] Similar results from 3 other studies[2,3] that included 13 women have provided further evidence that metformin is distributed into breast milk, that concentrations in milk are less than those in maternal plasma, and that breast-fed infants would be exposed to a very small percentage of the maternal dose. Six infants were breast-fed with no adverse effects that could be attributed to metformin. A prospective study[4] of weight, height, and motor-social development over 6 months, in infants of women taking metformin (1.5 to 2.55 g daily) for polycystic ovary syndrome, found no difference between 61 infants who were breast-fed and 50 who were formula-fed.

1. Hale TW, *et al.* Transfer of metformin into human milk. *Diabetologia* 2002; **45:** 1509–14.
2. Gardiner SJ, *et al.* Transfer of metformin into human milk. *Clin Pharmacol Ther* 2003; **73:** 71–7.
3. Briggs GG, *et al.* Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005; **105:** 1437–41.
4. Glueck CJ, *et al.* Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr* 2006; **148:** 628–32.

Fasting. For the view that metformin could be used with little risk of hypoglycaemia in fasting Muslim patients during Ramadan, and suggestions for modifying the timing of doses, see under Precautions of Insulin, p.448.

Pregnancy. Insulin is generally preferred for treatment of diabetes during pregnancy. However, there are limited data to suggest that metformin does not increase the risk of congenital abnormalities[1,2] and does not adversely affect pregnancy outcome in diabetic women.[2] A controlled study comparing insulin with metformin in gestational diabetes is underway.[3]

The use of metformin to improve ovulation in polycystic ovary syndrome (PCOS) is increasing. There is growing evidence to suggest that metformin used before and during pregnancy in these women does not increase the risk of congenital abnormalities,[1,4-6] and may reduce first trimester spontaneous abortion,[4,6] which is common in women with PCOS.

1. Gilbert C, *et al.* Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006; **86:** 658–63.
2. Hughes RCE, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 2006; **23:** 318–22.
3. Brown FM, *et al.* Metformin in pregnancy: its time has not yet come. *Diabetes Care* 2006; **29:** 485–6.
4. Glueck CJ, *et al.* Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17:** 2858–64.
5. Glueck CJ, *et al.* Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Hum Reprod* 2004; **19:** 1323–30.
6. Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril* 2006; **85:** 1002–9.

Interactions

As for biguanides in general, p.438.

Pharmacokinetics

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

◊ References.

1. Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 1996; **30:** 359–71.
2. Sambol NC, *et al.* Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *J Clin Pharmacol* 1996; **36:** 1012–21.
3. Charles B, *et al.* Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006; **28:** 67–72.

Uses and Administration

Metformin hydrochloride is a biguanide antidiabetic (p.437). It is given orally in the treatment of type 2 diabetes mellitus (p.431), and is the drug of first choice in overweight patients. Initial dosage is 500 mg two or three times daily or 850 mg once or twice daily with or after meals, gradually increased if necessary, at intervals of at least 1 week, to 2 to 3 g daily; doses of 3 g daily are associated with an increased incidence of gastrointestinal adverse effects. Gastrointestinal effects are also common on beginning therapy, and the *BNF* recommends starting therapy more gradually with 500 mg at breakfast for at least 1 week, then increasing to 500 mg twice daily for at least 1 week, with further increases as required, up to a usual maximum of 2 g daily in 3 divided doses with meals. A modified-release preparation is also available, which is given in an initial dose of 500 mg once daily and may be increased in increments of 500 mg, at intervals of at least 1 week, to a maximum of 2 g once daily with the evening meal. If glycaemic control is not adequate the dose may be divided to give 1 g twice daily with meals. If doses above 2 g daily are required, they should be given as the standard preparation. For doses used in children and adolescents, see below.

Metformin is also used as the chlorophenoxyacetate and as the embonate.

◊ General references.

1. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995; **49:** 721–49.
2. Anonymous. Metformin for non-insulin-dependent diabetes mellitus. *Med Lett Drugs Ther* 1995; **37:** 41–2.
3. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; **334:** 574–9.
4. Melchior WR, Jaber LA. Metformin: an antihyperglycemic agent for treatment of type II diabetes. *Ann Pharmacother* 1996; **30:** 158–64.
5. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997; **102:** 99–110.
6. Klepser TB, Kelly MW. Metformin hydrochloride: an antihyperglycemic agent. *Am J Health-Syst Pharm* 1997; **54:** 893–903. Correction. *ibid.*; 1335.
7. Kirpichnikov D, *et al.* Metformin: an update. *Ann Intern Med* 2002; **137:** 25–33.
8. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003; **63:** 1879–94.

Action. A review of the action of metformin[1] considered that although a number of possible mechanisms have been suggested (see Uses and Administration of Biguanide Antidiabetics, p.438), the major action of metformin lay in increasing glucose transport across the cell membrane in skeletal muscle. There is also some evidence *in vitro* that it can inhibit the formation of advanced glycosylation end-products.[2]

1. Klip A, Leiter LA. Cellular mechanism of action of metformin. *Diabetes Care* 1990; **13:** 696–704.
2. Tanaka Y, *et al.* Inhibitory effect of metformin on formation of advanced glycation end products. *Curr Ther Res* 1997; **58:** 693–7.

Administration in children. In children aged 10 years and older with type 2 diabetes mellitus, oral metformin hydrochloride may be used in a starting dose of 500 mg or 850 mg once daily, or 500 mg twice daily, given with or after a meal. It may be gradually increased if needed, at intervals of at least 1 week, to a maximum of 2 g daily given in 2 or 3 divided doses. Modified-release preparations are generally not licensed for use in children.

Although rare, the incidence of type 2 diabetes is increasing in children and adolescents, related in part to the increase in obesity occurring particularly in westernised countries. A small placebo-controlled study[1] of patients aged 10 to 17 years with type 2 diabetes found that metformin improved glycaemic control and that adverse effects were similar to those in adults. In obese children and adolescents with hyperinsulinaemia, who are at risk of developing type 2 diabetes, small studies[2,3] of metformin use have reported improvements in body composition and fasting insulin concentrations. There has also been some interest in the use of metformin as an adjunct to insulin in adolescents with type 1 diabetes; improvements in glycaemic control[4,5] and reductions in insulin doses[4] have been reported.

1. Jones KL, *et al.* Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2002; **25:** 89–94.
2. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Abstract: *Pediatrics* 2001; **107:** 763–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e55 (accessed 25/06/07)
3. Srinivasan S, *et al.* Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *J Clin Endocrinol Metab* 2006; **91:** 2074–80.
4. Hamilton J, *et al.* Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 2003; **26:** 138–43.
5. Särnblad S, *et al.* Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity. *Eur J Endocrinol* 2003; **149:** 323–9.

Diabetes mellitus. Results of the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control with metformin reduces the risk of diabetic complications and death in overweight patients with type 2 diabetes.[1] The study also generated some concern regarding intensive therapy with metformin plus a sulfonylurea (see under Interactions, p.462) but this was not borne out on further analysis and such combinations are widely used. Metformin is also used with the thiazolidinediones,[2-5] or with insulin[6] in patients requiring combined or more intensive therapy. Metformin has also been investigated for the prevention of type 2 diabetes in patients at high risk. Although metformin treatment for an average 2.8 years reduced the incidence of type 2 diabetes by 31% in a study[7] of patients with impaired glucose tolerance, intensive lifestyle modification was actually more effective (58% reduction). Lifestyle modification was also more effective than metformin in reducing cardiovascular risk factors[8] and the development of the metabolic syndrome.[9] The durability of these effects is unknown but follow-up of this study is ongoing.

There is some interest in using oral hypoglycaemics as adjuncts to insulin therapy in patients with type 1 diabetes. Short-term results from small studies have suggested that metformin may be beneficial, in this context, in adolescents with pubertal insulin resistance (see also Administration in Children, above) and perhaps in adults who are overweight or otherwise at risk of reduced insulin sensitivity.[10]

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65.
2. Fonseca V, *et al.* Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000; **283:** 1695–1702. Correction. *ibid.*; **284:** 1384.
3. Einhorn D, *et al.* Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 2000; **22:** 1395–1409.
4. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; **65:** 1581–92.
5. Deeks ED, Scott LJ. Pioglitazone/metformin. *Drugs* 2006; **66:** 1863–77.
6. Avilés-Santa L, *et al.* Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **131:** 182–88.
7. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.
8. The Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005; **28:** 888–94.
9. Orchard TJ, *et al.* The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005; **142:** 611–19.
10. Jefferies CA, *et al.* Potential adjunctive therapies in adolescents with type 1 diabetes mellitus. *Treat Endocrinol* 2004; **3:** 337–43.

Polycystic ovary syndrome. It has been suggested that hyperinsulinism may play a pathogenetic role in stimulating the abnormal androgen production from the ovary seen in women with polycystic ovary syndrome (PCOS, p.2080). Most early studies of metformin in PCOS were small, observational, and of short duration, with mixed results. Although there were reports of reduced insulin levels, increased insulin sensitivity, and improved androgen concentrations, other studies failed to confirm these effects.[1] Later randomised studies were also small, but some were of longer duration. These reported weight reductions of obese patients,[2] reductions in insulin levels[2-4] and increased sensitivity,[5] improved androgen and other hormonal measures,[2,3,5] improved menstrual patterns,[2,4,5] and reduced hirsutism,[2] but again, not consistently. Metformin has also been reported to increase the rate of spontaneous ovulation,[6,7] and may improve the outcome of IVF procedures.[8] Combination of metformin with clomifene appeared to improve ovulatory response, compared with clomifene alone, in studies of women with PCOS,[6,9] though there is also a report of no apparent benefit.[10] Furthermore, 2 large, placebo-controlled studies have found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[11,12]

Some consider that current evidence supports a trial of metformin in patients with anovulation, androgen excess, and vascular risk factors, but because of the lack of data on long-term safety such use should be supervised by an endocrinologist or a physician with suitable expertise.[1]

1. Norman RJ, *et al.* Metformin and intervention in polycystic ovary syndrome. *Med J Aust* 2001; **174:** 580–3.
2. Pasquali R, *et al.* Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85:** 2767–74.
3. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996; **335:** 617–23.
4. Morin-Papunen LC, *et al.* Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2000; **85:** 3161–8.
5. Moghetti P, *et al.* Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000; **85:** 139–46.
6. Nestler JE, *et al.* Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998; **338:** 1876–80.
7. Fleming R, *et al.* Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002; **87:** 569–74.
8. Stadtmauer LA, *et al.* Metformin treatment of patients with polycystic ovary syndrome undergoing in vitro fertilization improves outcomes and is associated with modulation of the insulin-like growth factors. *Fertil Steril* 2001; **75:** 505–9.
9. Kocak M, *et al.* Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002; **77:** 101–6.
10. Sturrock NDC, *et al.* Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice. *Br J Clin Pharmacol* 2002; **53:** 469–73.
11. Moll E, *et al.* Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. Abridged version: *BMJ* 2006; **332:** 1485–8. Full version: http://www.bmj.com/cgi/reprint/332/7556/1485 (accessed 17/06/08) Correction available at: http://www.bmj.com/cgi/content/full/336/7643/0-b (accessed 17/06/08)
12. Legro RS, *et al.* Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007; **356:** 551–66.

Preparations

BP 2008: Metformin Tablets;
USP 31: Glipizide and Metformin Hydrochloride Tablets; Glyburide and Metformin Hydrochloride Tablets; Metformin Hydrochloride Extended-Release Tablets; Metformin Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baligluc; DBI AP; Diab Dos; Glucaminol; Glucogood; Glucophage; Islotin; Mectin; Medobis; Metforal; Metfori†; Oxemet; Redugluc; ***Austral.:*** Diabex; Diaformin; Glucohexal; Glucomet; Glucophage; Novomet; ***Austria:*** Clonarol; Desugar; Diabetex; Glucomin; Glucophage; Meglucon; Orabet†; ***Belg.:*** Glucophage; Metformax; ***Braz.:*** Diaformin; Dimefor; Formet†; Formyn; Glicefor; Glifage; Glucoformin; Metfordin†; Metformed; Teutoformin; ***Canad.:*** Glucophage; Glumetza; Glycon†; ***Chile:*** Diaglitab; Fintaxim; Glafornil; Glicenex; Glidanil; Glifortex; Glucophage; Hipoglucin; Menarini-Metforal†; ***Cz.:*** Adimet; Diaphage; Glucomerck; Glucophage; Gluformin; Glumetsan; Langerin; Metfirex; Metfogamma; Siofor; Stadamet; ***Denm.:*** Glucophage; Orabet; ***Fin.:*** Diformin; Glucophage; Metforem; Oramet; ***Fr.:*** Diabamyl†; Glucophage; Stagid; ***Ger.:*** Biocos; Diabesin; Diabetase†; espaformin†; Glucobon; Glucophage; Juformin; Mediabet; Meglucon; Mescorit; Met; Metfodoc; Metfogamma; Metfor†; Metform†; MetSurrir; Siofor; Thiabet; ***Gr.:*** Glucofree; Glucophage; Metforil; Sukontrol; ***Hong Kong:*** CP-Metform; Diabetmin; Diaformin; Glucomet; Glucophage; Glumet; Guamet; Melbin; ***Hung.:*** Adimet; Gluformin; Maformin†; Meforal; Meglucon; Merckformin; Metfogamma; Metrivin†; Stadamet; ***India:*** Bigomet†; Emfor; Emnorm; Exermet; Formin†; Glumet; Glyciphage; Glyree M; Insumet; Metlong; Walaphage; X-Met; ***Indon.:*** Benofomin; Diabex; Eraphage; Forbetes; Formell; Gliformin; Glucofor; Glucophage; Glucotika; Gludepatic; Glufor; Glumin; Gradiab; Methormyl; Methpica; Metphar; Reglus; Tudiab; Zumamet; ***Irl.:*** Glucophage; ***Israel:*** Apophage; Glucomin; Glucophage; Glufor; ***Ital.:*** Glucophage; Metbay; Metfonorm; Metforal; Metiguanide; ***Jpn:*** Glycoran; Melbin; ***Malaysia:*** Diabemet†; Diabetmin; Glucomet; Glucophage; Glumet; Riomet; Xmet; ***Mex.:*** Aglumet; Anglucid; Apozemia; Dabex; Debeone; Dimefor; Dinamel; Ficonax; Forlucyl; Glucophage; Glunovag; Harbamind; Ifor; Meglubet; Melbexa; Mifelar; Pharmafet; Pre-Dial; ***Neth.:*** Diabex; Dianorm†; Finormet†; Glucophage; Glumeff; Niformina; ***Norw.:*** Glucophage; ***NZ:*** Glucomet; Glucophage†; Metomin; ***Philipp.:*** Diafat; Diazen; Euform; Fornidd; Glucare; Glucoform; Glucomed; Glucophage; Glumet; Glyformin; Horsulin; Humamet; I-Max; Insunex; Neoform; Nidcor; Sucranorm; Vimetrol; Xmet; ***Pol.:*** Glucophage†; Gluformin; Metfogamma; Metformax; Metifor; Siofor; ***Port.:*** Diabex; Glucophage; Mekoll; Risidon; Stagid; ***Rus.:*** Bagomet (Багомет); Formin (Формин Плив); Gliformin (Глиформин); Glucophage (Глюкофаж); Metfogamma (Метфогамма); Siofor (Сиофор); ***S.Afr.:*** Glucophage; Metforal; ***Singapore:*** Diabetmin; Diamin†; Glucophage; Glycomet; Glycoran†; Metforal; ***Spain:*** Dianben; ***Swed.:*** Glucophage; ***Switz.:*** Gluconormine; Glucophage; Metfin; ***Thai.:*** Ammiformin; Deson; Diamet; Formin; Gluco; Glucoles-500; Glucolyte; Glucomet†; Glucono; Glucophage; Gluformin; Glustress†; Glutabloc; Gluzolyte; Macromin†; Maformin; ME-F†; Meformed; Metfor; Metfron; Miformin; Pocophage; Poli-Formin; Prophage; Serformin; Siamformet; ***Turk.:*** Glifor; Glucophage; Gluformin; Glukofen; ***UAE:*** Dialon; ***UK:*** Glucophage; Metsol; ***USA:*** Fortamet; Glucophage; Glumetza; Riomet; ***Venez.:*** Diaformina; Dimefor†; Glafornil; Glucaminol; Glucofage.

Multi-ingredient: ***Arg.:*** Avandamet; DBI Duo; Glucovance; Gludex Plus; Isloglib; Medobis G; Metformin Duo; Rosiglit-Met; ***Austral.:*** Avandamet; Glucovance; ***Belg.:*** Avandamet; Glucovance; ***Braz.:*** Glucovance; Starform; ***Canad.:*** Avandamet; ***Chile:*** Avandamet; Bi-Euglucon M; Diaglitab Plus; Glifortex-G; Glimet; Glucovance; Glukaut; Hipoglucin DA; ***Cz.:*** Avandamet; Competact; Eucreas; Glibomet; Glubrava; Glucovance; ***Denm.:*** Avandamet; ***Fin.:*** Avandamet; ***Fr.:*** Avandamet; Competact; Eucreas; Glucovance; ***Ger.:*** Avandamet; ***Gr.:*** Avandamet; Normell; ***Hong Kong:*** Avandamet; Glucovance; ***Hung.:*** Avandamet; ***India:*** Betaglim M†; Diaforte; Diaglip M; Exermet GM; Exermet GZ; Exermet P; Gliclamet; Glimiprex MF; Glimulin-MF†; Glinil M; Glizid-M; Glycigon-M; Glycinorm M; Glygard M; Metaglez; P-Glitz M; Piomed M; Piosafe MF; Roglin-M; Rosicon MF; ***Indon.:*** Avandamet; Glucovance; ***Irl.:*** Avandamet; ***Israel:*** Avandamet; ***Ital.:*** Avandamet; Bi-Euglucon M; Glibomet; Gliconorm; Glicorest; Glucomide; Pleiamide; Suguan M; ***Malaysia:*** Avandamet; Glucovance; ***Mex.:*** Apometglu; Avandamet; Bi-Dizalon; Bi-Euglucon M; Bi-Pradia; Duo-Anglucid; Glimetal; Glucotec; Glucovance; Imalet; Insogen Plus; Insusym-Forte; Maviglin; Mellitron; Midapharma; Mifelar-C; Nadib-M; Norfaben M; Obinese; Sibet-C; Sil-Norboral; Wadil; ***Neth.:*** Avandamet; Glucovance; ***Norw.:*** Avandamet; ***Philipp.:*** Avandamet; Euglo Plus; Glucovance; ***Pol.:*** Avandamet; ***Port.:*** Avandamet; Competact; Glucovance; ***Rus.:*** Glibomet (Глибомет); Glucovance (Глюкован); ***S.Afr.:*** Glucovance; ***Singapore:*** Avandamet; Glucovance; ***Spain:*** Avandamet; ***Swed.:*** Avandamet; ***Switz.:*** Avandamet; Diabiformine; Glucovance; ***Thai.:*** Avandamet; ***UK:*** Avandamet; Competact; Eucreas; ***USA:*** Actoplus Met; Avandamet; Diofen; Glucovance; Glybofen; Janumet; Metaglip; ***Venez.:*** Avandamet; Bi-Euglucon; Diaformina Plus; Glucovance; Starform.

Miglitol *(BAN, USAN, pINN)*

Bay-m-1099; Miglitoli; Miglitolum. (2*R*,3*R*,4*R*,5*S*)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)piperidine-3,4,5-triol.

Миглитол

$C_8H_{17}NO_5$ = 207.2.
CAS — 72432-03-2.
ATC — A10BF02.
ATC Vet — QA10BF02.

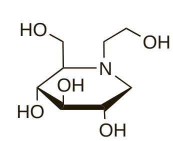

Adverse Effects and Precautions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Skin rash may occur. Miglitol should be used with caution in patients with renal impairment.

Interactions
As for alpha-glucosidase inhibitors in general (see Acarbose, p.436). Miglitol may reduce the bioavailability of propranolol and ranitidine.

Pharmacokinetics
Miglitol is completely absorbed at a dose of 25 mg, but only 50 to 70% is absorbed at a dose of 100 mg. It is not metabolised, and is excreted unchanged in the urine with a plasma elimination half-life of about 2 hours.

Uses and Administration
Miglitol is an alpha-glucosidase inhibitor similar in action to acarbose (p.436). It is given orally in the management of type 2 diabetes mellitus (p.431), alone or with a sulfonylurea. Usual initial doses are 25 mg three times daily with meals, increased if necessary to a maximum of 100 mg three times daily.

◊ References.

1. Campbell LK, *et al.* Miglitol: assessment of its role in the treatment of patients with diabetes mellitus. *Ann Pharmacother* 2000; **34:** 1291–1301.
2. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. *Drugs* 2000; **59:** 521–49.
3. Standl E, *et al.* Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pract* 2001; **51:** 205–13.
4. Chiasson JL, *et al.* The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care* 2001; **24:** 989–94.
5. Van Gaal L, *et al.* Miglitol combined with metformin improves glycaemic control in type 2 diabetes. *Diabetes Obes Metab* 2001; **3:** 326–31.
6. Drent ML, *et al.* Dose-dependent efficacy of miglitol, an alpha-glucosidase inhibitor, in type 2 diabetic patients on diet alone: results of a 24-week double-blind placebo-controlled study. *Diabetes Nutr Metab* 2002; **15:** 152–9.

Preparations
Proprietary Preparations (details are given in Part 3)

Austria: Diastabol; ***Cz.:*** Diastabol; ***Fr.:*** Diastabol; ***Ger.:*** Diastabol; ***Hung.:*** Diastabol; ***India:*** Diamig; Mignar†; ***Mex.:*** Diastabol; ***Neth.:*** Diastabol; ***Pol.:*** Diastabol; ***Port.:*** Diastabol; Limarcan; ***Spain:*** Diastabol; Plumarol; ***Swed.:*** Diastabol†; ***Switz.:*** Diastabol; ***USA:*** Glyset.

Mitiglinide *(rINN)*

Mitiglinida; Mitiglinidum. (−)-(2*S*,3a,7a-*cis*)-α-Benzylhexahydro-γ-oxo-2-isoindolinebutyric acid.

Митиглинид

$C_{19}H_{25}NO_3 = 315.4.$

CAS — 145375-43-5 (mitiglinide); 145525-41-3 (anhydrous mitiglinide calcium); 207844-01-7 (mitiglinide calcium dihydrate).

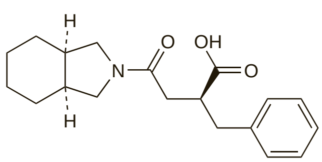

Profile
Mitiglinide is a meglitinide antidiabetic that is under investigation in the treatment of type 2 diabetes mellitus.

◊ References.

1. Yoshihara T, *et al.* Therapeutic efficacy of mitiglinide combined with once daily insulin glargine after switching from multiple daily insulin regimen of aspart insulin and glargine in patients with type 2 diabetes mellitus. *Endocr J* 2006; **53:** 67–72.

Muraglitazar *(USAN, rINN)*

BMS-298585; Muraglitazarum. {[(4-Methoxyphenoxy)carbonyl]{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}amino}acetic acid.

Мураглитазар

$C_{29}H_{28}N_2O_7 = 516.5.$

CAS — 331741-94-7.

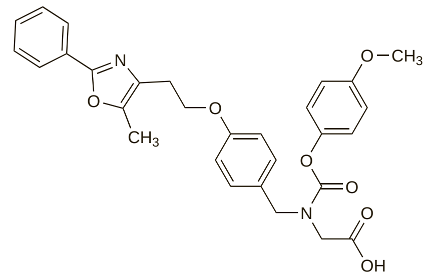

Profile
Muraglitazar is a dual alfa/gamma peroxisome proliferator-activated receptor (PPAR) activator. It has been investigated in the treatment of type 2 diabetes mellitus.

Adverse effects. A review of data from 5 studies suggested that muraglitazar may be associated with an increased risk of adverse cardiovascular events and heart failure.[1]

1. Nissen SE, *et al.* Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; **294:** 2581–6.

Nateglinide *(USAN, rINN)*

A-4166; AY-4166; DJN-608; Nateglinid; Nateglinida; Natéglinide; Nateglinidi; Nateglinidum; SDZ-DJN-608; Senaglinide; YM-026. (−)-*N*-[(*trans*-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine.

Натеглинид

$C_{19}H_{27}NO_3 = 317.4.$

CAS — 105816-04-4.

ATC — A10BX03.

ATC Vet — QA10BX03.

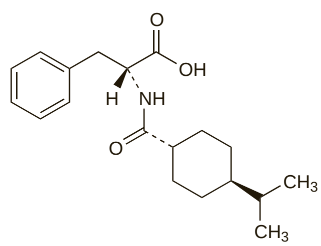

Adverse Effects and Precautions
As for Repaglinide, p.457.

Overdosage. A blood-glucose concentration of 2.0 mmol/litre was measured 1 hour after ingestion of nateglinide 3.42 g in a 30-year-old woman.[1] She was able to walk unaided, but seemed drowsy. The hypoglycaemic effect of nateglinide lasted for 6 hours and was treated with intravenous glucose (total dose 100 g).

1. Nakayama S, *et al.* Hypoglycemia following a nateglinide overdose in a suicide attempt. *Diabetes Care* 2005; **28:** 227–8.

Renal impairment. A single-dose pharmacokinetic study[1] found that moderate to severe renal impairment (creatinine clearance 15 to 50 mL/minute per 1.73 m^2) and haemodialysis did not significantly affect the pharmacokinetics of nateglinide. However, the metabolite M1 has been found to accumulate in patients with renal impairment requiring haemodialysis after repeated doses of nateglinide, but it may be removed by haemodialysis.[2] M1 is a major metabolite that has modest hypoglycaemic activity compared with nateglinide. An analysis[3] of pooled study data found that efficacy and tolerability of nateglinide in elderly diabetic patients were not significantly affected by renal impairment (mean creatinine clearance 50.9 mL/minute per 1.73 m^2). Nevertheless, a 56-year-old diabetic woman whose renal failure was managed with haemodialysis experienced severe hypoglycaemia with nateglinide; the reaction was attributed to the accumulation of M1.[4] Licensed product information in the UK and USA suggest that no dosage adjustment is necessary in renal impairment, although UK information suggests that dose adjustment might be required in patients on haemodialysis.

1. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
2. Inoue T, *et al.* Pharmacokinetics of nateglinide and its metabolites in subjects with type 2 diabetes mellitus and renal failure. *Clin Nephrol* 2003; **60:** 90–5.
3. Del Prato S, *et al.* Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 2003; **26:** 2075–80.
4. Nagai T, *et al.* Hypoglycemia due to nateglinide administration in diabetic patient with chronic renal failure. *Diabetes Res Clin Pract* 2003; **59:** 191–4.

Interactions
As with other oral antidiabetics, the efficacy of nateglinide may be affected by drugs independently increasing or decreasing blood glucose concentrations (see Sulfonylureas, p.461).

◊ Reviews.

1. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. In a study[1] of healthy subjects, *rifampicin* reduced the plasma concentrations and half-life of nateglinide, probably by induction of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but there was a marked interindividual variation in the pharmacokinetic changes, and the authors suggested that some diabetic patients could be affected.

1. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 427–32.

Antifungals. In a study[1] of healthy subjects, *fluconazole* raised the plasma concentrations and prolonged the half-life of nateglinide, probably by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9. The glucose-lowering effect of nateglinide was not affected, but a low dose of nateglinide had been used and the authors suggested that in diabetic patients fluconazole may enhance and prolong the effects of nateglinide.

1. Niemi M, *et al.* Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. *Clin Pharmacol Ther* 2003; **74:** 25–31.

Lipid regulating drugs. A study[1] investigating the effects of the *gemfibrozil* and *itraconazole* combination on the pharmacokinetics of nateglinide showed only a limited interaction. Nateglinide plasma concentrations were raised moderately and the blood glucose response to nateglinide was not significantly changed. This is in contrast to the substantial interaction of gemfibrozil with repaglinide (p.458).

1. Niemi M, *et al.* Coadministration of gemfibrozil and itraconazole has only a minor effect on the pharmacokinetics of the CYP2C9 and CYP3A4 substrate nateglinide. *Br J Clin Pharmacol* 2005; **60:** 208–17.

Pharmacokinetics
Nateglinide is rapidly absorbed after oral doses, with peak plasma concentrations occurring within one hour and an absolute bioavailability of 73%. Nateglinide is 98% bound to plasma proteins. It is mainly metabolised by cytochrome P450 isoenzyme CYP2C9, and to a lesser extent by CYP3A4. Major metabolites include M1 which is less potent than nateglinide. The parent drug and metabolites are mainly excreted in the urine but about 10% is eliminated in the faeces. The elimination half-life is about 1.5 hours.

◊ References.

1. Choudhury S, *et al.* Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 2000; **40:** 634–40.
2. Devineni D, *et al.* Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; **43:** 163–70.
3. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. *Clin Pharmacokinet* 2004; **43:** 97–120.

Uses and Administration
Nateglinide, like repaglinide (p.458), is a meglitinide antidiabetic used in the treatment of type 2 diabetes mellitus (p.431). It is given within the 30 minutes before meals in oral doses of 60 or 120 mg three times daily. This may be increased to 180 mg three times daily if necessary. Nateglinide is also given in similar doses with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by these drugs alone.

Although dose adjustment is not generally required in renal impairment, hypoglycaemia has been attributed to accumulation of the metabolite M1 (see above).

◊ References.

1. Dunn CJ, Faulds D. Nateglinide. *Drugs* 2000; **60:** 607–15.
2. Hanefeld M, *et al.* Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 2000; **23:** 202–7.
3. Horton ES, *et al.* Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; **23:** 1660–5.

4. Levien TL, *et al.* Nateglinide therapy for type 2 diabetes mellitus. *Ann Pharmacother* 2001; **35:** 1426–34.
5. Fonseca V. *et al.* Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improves overall glycemic control. *Diabetes Care* 2003; **26:** 1685–90.
6. Campbell IW. Nateglinide—current and future role in the treatment of patients with type 2 diabetes mellitus. *Int J Clin Pract* 2005; **59:** 1218–28.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nateglin; Starlix; ***Braz.:*** Starlix; ***Canad.:*** Starlix; ***Chile:*** Gluconol; Starlix; ***Cz.:*** Starlix; Trazec; ***Denm.:*** Starlix†; ***Fin.:*** Starlix; ***Ger.:*** Starlix; ***Gr.:*** Starlix; ***Hong Kong:*** Starlix†; ***Hung.:*** Starlix; ***India:*** Glinate; ***Indon.:*** Starlix; ***Irl.:*** Starlix; ***Jpn:*** Starsis; ***Malaysia:*** Starlix; ***Mex.:*** Starlix; ***Neth.:*** Starlix; Trazec; ***Norw.:*** Starlix; ***NZ:*** Starlix†; ***Philipp.:*** Starlix; ***Port.:*** Starlix; Trazec; ***Rus.:*** Starlix (Старликс); ***S.Afr.:*** Starlix; ***Singapore:*** Starlix; ***Spain:*** Starlix; ***Swed.:*** Starlix; ***Switz.:*** Starlix; ***Turk.:*** Starlix; ***UK:*** Starlix; ***USA:*** Starlix; ***Venez.:*** Starlix.

Multi-ingredient: ***Braz.:*** Starform; ***Venez.:*** Starform.

Phenformin Hydrochloride *(BANM, pINNM)*

Fenformina Cloridrato; Hidrocloruro de fenformina; Phenformine, Chlorhydrate de; Phenformini Hydrochloridum. 1-Phenethylbiguanide hydrochloride.

Фенформина Гидрохлорид

$C_{10}H_{15}N_5,HCl = 241.7.$

CAS — 114-86-3 (phenformin); 834-28-6 (phenformin hydrochloride).

ATC — A10BA01.

ATC Vet — QA10BA01.

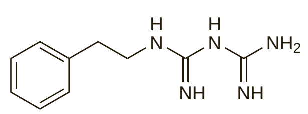

(phenformin)

Pharmacopoeias. In *Chin.*

Profile

Phenformin hydrochloride is a biguanide antidiabetic (p.437). Although it is generally considered to be associated with an unacceptably high incidence of lactic acidosis, often fatal, it is still available in some countries for the treatment of type 2 diabetes mellitus.

Phenformin was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Informin; ***India:*** DBI†; ***Port.:*** Debeina†.

Multi-ingredient: ***Gr.:*** Daopar†; ***India:*** Chlorformin†; ***Ital.:*** Bi-Euglucon†; Bidiabe; Gliben F; Gliformin; Suguan†.

Pimagedine *(rINN)*

Pimagedina; Pimagédine; Pimagedinum. Aminoguanidine.

Пимагедин

$CH_6N_4 = 74.09.$

CAS — 79-17-4.

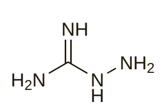

Pimagedine Hydrochloride *(USAN, rINNM)*

GER-11; Hidrocloruro de pimagedina; Pimagédine, Chlorhydrate de; Pimagedini Hydrochloridum. Aminoguanidine monohydrochloride.

Пимагедина Гидрохлорид

$CH_6N_4,HCl = 110.5.$

CAS — 1937-19-5.

Profile

Pimagedine reportedly inhibits the formation of glycosylated proteins (advanced glycosylation end-products) and has other actions including inhibition of aldose reductase. It has been investigated for the prevention of diabetic complications (p.433).

◊ References.

1. Corbett JA, *et al.* Aminoguanidine, a novel inhibitor of nitric oxide formation, prevents diabetic vascular dysfunction. *Diabetes* 1992; **41:** 552–6.
2. Wolffenbuttel BHR, Huijberts MSP. Aminoguanidine, a potential drug for the treatment of diabetic complications. *Neth J Med* 1993; **42:** 205–8.
3. Abdel-Rahman E, Bolton WK. Pimagedine: a novel therapy for diabetic nephropathy. *Expert Opin Invest Drugs* 2002; **11:** 565–74.
4. Thornalley PJ. Use of aminoguanidine (pimagedine) to prevent the formation of advanced glycation endproducts. *Arch Biochem Biophys* 2003; **419:** 31–40.

Pioglitazone Hydrochloride

(BANM, USAN, rINNM)

AD-4833 (pioglitazone); Hidrocloruro de pioglitazona; Pioglitazone, Chlorhydrate de; Pioglitazoni Hydrochloridum; U-72107A; U-72107E (pioglitazone). (±)-5-{*p*-[2-(5-Ethyl-2-pyridyl)-ethoxy]benzyl}-2,4-thiazolidinedione hydrochloride.

Пиоглитазона Гидрохлорид

$C_{19}H_{20}N_2O_3S,HCl = 392.9.$

CAS — 111025-46-8 (pioglitazone); 112529-15-4 (pioglitazone hydrochloride).

ATC — A10BG03.

ATC Vet — QA10BG03.

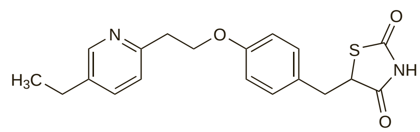

(pioglitazone)

Adverse Effects and Precautions

As for Rosiglitazone Maleate, p.458. The effects of pioglitazone on serum lipid concentrations appear to differ from those of rosiglitazone, see below. Other adverse effects reported include upper respiratory-tract infections, haematuria, and visual disturbances. Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see below).

An increased incidence of bladder cancer has been seen in *rats* but not in *mice* treated with pioglitazone.

Use is contra-indicated in patients with diabetic ketoacidosis. For precautions and contra-indications to the use of thiazolidinediones in heart failure see Effects on the Heart, under Rosiglitazone Maleate, p.459.

Effects on lipids. Thiazolidinediones are reported to affect serum concentrations of lipids. Compared with placebo,[1,2] pioglitazone has been found to reduce triglycerides, increase high-density lipoprotein (HDL)-cholesterol, and have little or no effect on low-density lipoprotein (LDL)- and total cholesterol. In a study[3] of patients being transferred from troglitazone to either pioglitazone or rosiglitazone, there were decreases in concentrations of triglycerides, LDL- and total cholesterol, and an increase in HDL-cholesterol in those patients on pioglitazone, whereas the opposite occurred for rosiglitazone. Whether these effects of pioglitazone reduce cardiovascular risk in patients with type 2 diabetes is yet to be fully established, but the large prospective PROactive study did suggest that it could reduce the risk of macrovascular events in patients with evidence of macrovascular disease, although the risk of heart failure appears to be *increased* (see Diabetic Complications, below, and Effects on the Heart, under Rosiglitazone Maleate, p.459).

1. Kipnes MS, *et al.* Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med* 2001; **111:** 10–17.
2. Rosenblatt S, *et al.* The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis* 2001; **12:** 413–23.
3. Gegick CG, Altheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 2001; **7:** 162–9.

Effects on the liver. There have been isolated reports of hepatocellular injury in patients receiving pioglitazone.[1-5]

The UK and US licensed product information recommends that liver enzymes should be checked before starting therapy with pioglitazone; patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given pioglitazone. ALT concentrations should then be monitored periodically during treatment. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with pioglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. *Ann Intern Med* 2001; **135:** 306.
2. May LD, *et al.* Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **136:** 449–52.
3. Pinto AG, *et al.* Severe but reversible cholestatic liver injury after pioglitazone therapy. *Ann Intern Med* 2002; **137:** 857.
4. Chase MP, Yarze JC. Pioglitazone-associated fulminant hepatic failure. *Am J Gastroenterol* 2002; **97:** 502–3.
5. Farley-Hills E, *et al.* Fatal liver failure associated with pioglitazone. *BMJ* 2004; **329:** 429.

Interactions

When pioglitazone was given with gemfibrozil, an inhibitor of the cytochrome P450 isoenzyme CYP2C8, there was a threefold increase in the area under the concentration-time curve (AUC) of pioglitazone, and a decrease in pioglitazone dose may be needed if it is given with gemfibrozil or similar CYP2C8 inhibitors. Equally, rifampicin, a potent inducer of cytochrome P450, halves the AUC of pioglitazone when both are given, and pioglitazone dose may need to be increased.

Antibacterials. For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving oral hypoglycaemics such as pioglitazone, see p.281.

Pharmacokinetics

Pioglitazone is rapidly absorbed after oral doses. Peak plasma concentrations occur within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolised, primarily by the cytochrome P450 isoenzyme CYP2C8 to both active and inactive metabolites. It is excreted in urine and faeces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Uses and Administration

Pioglitazone is a thiazolidinedione oral antidiabetic similar to rosiglitazone (p.458). It is used in the management of type 2 diabetes mellitus (p.431). It is given as pioglitazone hydrochloride but doses are expressed in terms of the base; pioglitazone hydrochloride 1.1 mg is equivalent to about 1 mg of pioglitazone. It is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. Pioglitazone may also be added to metformin or a sulfonylurea or both, or to insulin, when single-agent therapy is inadequate (but see Administration, below). The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary. Pioglitazone may be taken with or without food.

◊ References.

1. Gillies PS, Dunn CJ. Pioglitazone. *Drugs* 2000; **60:** 333–43.
2. Anonymous. Pioglitazone and rosiglitazone for diabetes. *Drug Ther Bull* 2001; **39:** 65–8.
3. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.
4. O'Moore-Sullivan TM, Prins JB. Thiazolidinediones and type 2 diabetes: new drugs for an old disease. *Med J Aust* 2002; **176:** 381–6. Correction. *ibid.*; **177:** 396.
5. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 2003; **63:** 1373–1405.
6. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.
7. Waugh J, *et al.* Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs* 2006; **66:** 85–109. Correction. *ibid.*; 340–1.
8. Richter B, *et al.* Pioglitazone for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/03/07).

Administration. Although pioglitazone is licensed for use with other antidiabetic drugs, the specifics of licensing and use may vary from country to country. In the UK, use of pioglitazone with insulin was originally considered to be contra-indicated, because of an increased risk of heart failure, although this was subsequently amended to permit dual therapy in patients who could not be given insulin plus metformin. Furthermore, although pioglitazone is licensed for use with metformin or a sulfonylurea (or both if necessary) in patients who do not respond to these drugs, NICE recommends this only in patients unsuited to combination therapy with metformin plus a sulfonylurea.[1] However, in the USA, pioglitazone has always been licensed for use with insulin (with appropriate monitoring), metformin, or a sulfonylurea in any patient in whom single agent therapy is inadequate.

1. NICE. Guidance on the use of glitazones for the treatment of type 2 diabetes (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA63_Glitazones_Review_Guidance.pdf (accessed 20/08/08)

Diabetic complications. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications (p.433). Studies[1,2] in patients with type 2 diabetes mellitus have shown that pioglitazone may slow the progression of carotid intima-media thickness, an indicator for cardiovascular risk. A study[3] of secondary prevention found that, compared with placebo (in addition to usual medications for glucose control), pioglitazone reduced death from any cause, myocardial infarction, and stroke. There was also a reduced need to add insulin for glucose control. However, there was no significant difference between the groups when the end-point was broader and also included acute coronary syndrome, leg amputation, and coronary or leg revascularisation. Subgroup analysis[4] also found that pioglitazone reduced the risk of fatal and non-fatal myocardial infarction and acute coronary syndrome in patients with a history of myocardial infarction. A meta-analysis[5] that included the results of this study with cardiovascular outcome data from studies of glycaemic control found that pioglitazone significantly reduced the risk of death, myocardial infarction, and stroke in a diverse population of patients with type 2 diabetes. However, the risk of serious heart failure was increased (see also Effects on the Heart, p.459).

It is unclear whether other thiazolidinediones might have similar effects and whether patients at lower risk might benefit.[6] Rosiglitazone and pioglitazone are known to have different effects on lipids (above) and there is some evidence that rosiglitazone may have adverse cardiovascular effects (p.459).

1. Langenfeld MR, *et al.* Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation* 2005; **111:** 2525–31.
2. Mazzone T, *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296:** 2572–81.
3. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366:** 1279–89.
4. Erdmann E, *et al.* The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; **49:** 1772–80.
5. Lincoff AM, *et al.* Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298:** 1180–8.
6. Rizza R, *et al.* Commentary on the results and clinical implications of the PROactive study. *Diabetes Care* 2005; **28:** 2965–7.

Hepatitis. A small proof-of-concept study has suggested that pioglitazone 45 mg daily with a hypocaloric diet for 6 months produces greater metabolic and histological improvement in patients with nonalcoholic steatohepatitis than diet alone.[1]

1. Belfort R, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; **355:** 2297–2307.

Malignant neoplasms. For references to the experimental use of pioglitazone with rofecoxib and trofosfamide as anti-angiogenic therapy for malignant neoplasms see Trofosfamide, p.783.

Psoriasis. It has been suggested that by binding to peroxisome proliferator-activated receptor gamma, pioglitazone may have an anti-inflammatory effect in conditions such as chronic plaque psoriasis (p.1583) and psoriatic arthritis (see Spondyloarthropathies, p.13). In a small open-label study,[1] oral doses of 30 mg daily were reported to improve moderate chronic plaque psoriasis in 4 of 5 patients, with definite improvement seen 1 to 3 months after starting therapy. Treatment was stopped in 1 other patient because of fluid retention. In a double-blind study,[2] 70 patients with moderate to severe disease were treated for 10 weeks with daily doses of pioglitazone 15 mg, 30 mg, or placebo. Greater improvements were reported with pioglitazone than with placebo, and the dose of 30 mg appeared to be slightly more effective than 15 mg. There has also been a report[3] of improvements in tender and swollen joints in a small group of patients with psoriatic arthritis who were given a high dose of pioglitazone (30 mg twice daily) for 12 weeks. Fluid retention was also reported.

1. Robertshaw H, Friedmann PS. Pioglitazone: a promising therapy for psoriasis. *Br J Dermatol* 2005; **152:** 189–91.
2. Shafiq N, *et al.* Pilot trial: pioglitazone versus placebo in patients with plaque psoriasis (the P6). *Int J Dermatol* 2005; **44:** 328–33.
3. Bongartz T, *et al.* Treatment of active psoriatic arthritis with the PPARγ ligand pioglitazone: an open-label pilot study. *Rheumatology (Oxford)* 2005; **44:** 126–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Actos; Cereluc; Higlucem; Pioglit; Piotamax; ***Austral.:*** Actos; ***Austria:*** Actos; ***Belg.:*** Actos; ***Braz.:*** Actos; ***Canad.:*** Actos; ***Chile:*** Actos†; Diabestat†; Tiazac; ***Cz.:*** Actos; Glustin; ***Denm.:*** Actos; ***Fin.:*** Actos; ***Fr.:*** Actos; ***Ger.:*** Actos; ***Gr.:*** Actos; ***Hong Kong:*** Actos; ***India:*** Diaglit; G-Tase; Glita; Glizone; Opam; P-Glitz; Pepar; Piomed; Piosafe; Piozulin; ***Indon.:*** Actos; Deculin; ***Ital.:*** Actos; ***Jpn:*** Actos; ***Malaysia:*** Actos; ***Mex.:*** Zactos; ***Neth.:*** Actos; Glustin; ***Norw.:*** Actos; ***NZ:*** Actos; ***Philipp.:*** Actos; Prialta; Zypi; ***Port.:*** Actos; Glustin; ***Rus.:*** Actos (Актос); ***S.Afr.:*** Actos; ***Spain:*** Actos; ***Swed.:*** Actos; ***Switz.:*** Actos; ***Thai.:*** Actos; ***UK:*** Actos; ***USA:*** Actos; ***Venez.:*** Actos.

Multi-ingredient: ***Cz.:*** Competact; Glubrava; Tandemact; ***Fr.:*** Competact; Tandemact; ***India:*** Exermet P; P-Glitz M; Piomed M; Piosafe MF; ***Port.:*** Competact; Tandemact; ***UK:*** Competact; ***USA:*** Actoplus Met; Duetact.

Pramlintide *(BAN, USAN, rINN)*

AC-137; AC-0137 (pramlintide or pramlintide acetate); Pramlintida; Pramlintidum; Tripro-amylin.

Прамлинтид

$C_{171}H_{267}N_{51}O_{53}S_2 = 3949.4.$

CAS — 151126-32-8.

Pramlintide Acetate *(BANM, USAN, rINNM)*

AC-0137 (pramlintide or pramlintide acetate); Acetato de pramlintida; Pramlintide, Acétate de; Pramlintidi Acetas. 25-L-Proline-28-L-proline-29-L-prolineamylin (human) acetate hydrate.

Прамлинтида Ацетат

$C_{171}H_{267}N_{51}O_{53}S_2, xC_2H_4O_2, yH_2O.$

CAS — 196078-30-5.

Incompatibility. Pramlintide should not be mixed in the same syringe with insulin because of reported changes in the pharmacokinetic parameters of pramlintide.

Adverse Effects and Precautions

Pramlintide alone does not cause hypoglycaemia, but increases the risk associated with insulin use, particularly in type 1 diabetes mellitus; severe hypoglycaemia may occur within 3 hours of pramlintide injection. Blood-glucose concentrations must be closely monitored, both before and after meals, and the dose of insulin should be halved when pramlintide therapy is started (see Uses and Administration, below).

Other adverse effects of pramlintide include nausea, vomiting, anorexia, headache, reactions at the injection site, and hypersensitivity. Nausea commonly occurs at the beginning of therapy and decreases with time; incidence and severity are reduced if pramlintide is gradually titrated to the maintenance dose. Pramlintide is contra-indicated in patients with gastroparesis.

Interactions

Pramlintide has the potential to delay the absorption of oral medication; in cases where the rapid onset of action from an oral drug is critical, it should be given at least 1 hour before or 2 hours after pramlintide. Also, pramlintide may interfere with drugs given to alter gastrointestinal motility or absorption.

Pramlintide increases the risk of insulin-induced hypoglycaemia (see Adverse Effects and Precautions, above).

Pharmacokinetics

The bioavailability of pramlintide is about 30 to 40% from a subcutaneous injection. It is metabolised by the kidneys and has a half-life of about 48 minutes in healthy subjects.

Uses and Administration

Pramlintide is a synthetic analogue of amylin, a pancreatic peptide hormone thought to play a role in the regulation of glucose homoeostasis. It differs from amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine). Pramlintide slows the rate of gastric emptying, prevents the postprandial rise in glucagon concentrations, and reduces appetite. It is used in the management of diabetes mellitus (p.431) that is not adequately controlled by mealtime insulin therapy. Pramlintide is given as the acetate, but doses are expressed in terms of the base.

In patients with type 1 diabetes mellitus, an initial dose of pramlintide 15 micrograms is given subcutaneously immediately before major meals. The dose of any rapid-acting or short-acting insulins given before meals should be halved. The pramlintide dose may be increased in increments of 15 micrograms to a maintenance dose of 30 or 60 micrograms when no clinically significant nausea has occurred for at least 3 days. Once the maintenance dose of pramlintide has been achieved, the dose of insulin should be further adjusted for optimum glycaemic control.

In patients with type 2 diabetes mellitus who are using insulin, the initial dose of pramlintide is 60 micrograms, subcutaneously, immediately before major meals. The dose may be increased to 120 micrograms when no nausea has occurred for 3 to 7 days. The dose of insulin therapy should be adjusted as described for patients with type 1 diabetes mellitus (above).

◊ References.

1. Thompson RG, *et al.* Pramlintide, a synthetic analog of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. *Diabetes Care* 1998; **21:** 987–93.
2. Whitehouse F, *et al.* A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 2002; **25:** 724–30.
3. Ratner RE, *et al.* Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther* 2002; **4:** 51–61.
4. Hollander PA, *et al.* Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003; **26:** 784–90.
5. Kleppinger EL, Vivian EM. Pramlintide for the treatment of diabetes mellitus. *Ann Pharmacother* 2003; **37:** 1082–9.
6. Kruger DF, Gloster MA. Pramlintide for the treatment of insulin-requiring diabetes mellitus: rationale and review of clinical data. *Drugs* 2004; **64:** 1419–32.
7. Ratner RE, *et al.* Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004; **21:** 1204–12.
8. Ryan GJ, *et al.* Pramlintide in the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther* 2005; **27:** 1500–12.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Symlin.

Repaglinide *(BAN, USAN, rINN)*

AG-EE-6232W; AG-EE-623-ZW; Repaglinid; Repaglinida; Repaglinidas; Répaglinide; Repaglinidi; Repaglinidum. (+)-2-Ethoxy-α-{[(S)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl}-*p*-toluic acid; (*S*)-2-Ethoxy-4-{[1-(*o*-piperidinophenyl)-3-methylbutyl]carbamoyl-methyl}benzoic acid.

Репаглинид

$C_{27}H_{36}N_2O_4 = 452.6.$

CAS — 135062-02-1.

ATC — A10BX02.

ATC Vet — QA10BX02.

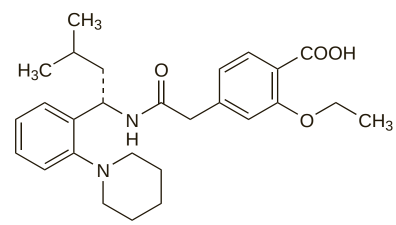

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Repaglinide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 31 (Repaglinide). A white to off-white solid. Soluble in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

Repaglinide may cause gastrointestinal adverse effects including abdominal pain, diarrhoea, constipation, nausea, and vomiting. Hypoglycaemia (usually mild), back and joint pain, hypersensitivity reactions including pruritus, rashes and urticaria, and elevated liver enzyme values may occur. There have been rare cases of transient visual disturbances attributed to changes in blood glucose concentrations associated with starting repaglinide treatment. There have also been rare reports of myocardial infarction in patients who were treated with repaglinide and isophane insulin; the combination is not recommended.

Precautions are similar to those which apply with the shorter-acting sulfonylurea hypoglycaemics (p.461). Repaglinide should be given with caution to patients with hepatic impairment (consideration should be given to extending the interval between doses), and possibly avoided in severe impairment.

Effects on the liver. Hepatotoxic reactions have been reported for repaglinide[1,2] including cholestatic hepatitis and jaundice with pruritus.

1. Nan DN, *et al.* Acute hepatotoxicity caused by repaglinide. *Ann Intern Med* 2004; **141:** 823.
2. López-García F, *et al.* Cholestatic hepatitis associated with repaglinide. *Diabetes Care* 2005; **28:** 752–3.

Fasting. For mention that nateglinide or repaglinide can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p.448.

Hypoglycaemia. Mild hypoglycaemia has been reported in patients receiving repaglinide,[1] although in a study comparing flexible repaglinide dosing with fixed glibenclamide dosing, all hypoglycaemic events recorded were in the glibenclamide group.[2] Other studies have found rates of hypoglycaemia in patients receiving repaglinide to be less than, or similar to, sulfonylureas.[3] The risk of hypoglycaemia may be reduced as patients can omit a dose of repaglinide if a meal is missed.

1. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; **24:** 11–15.

2. Damsbo P, *et al.* A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; **22:** 789–94.
3. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.

Pregnancy. Insulin is generally preferred to oral antidiabetics in the treatment of diabetes mellitus during pregnancy. Repaglinide has been used in 3 women during the first 6 to 7 weeks of gestation;[1,2] treatment was then changed to insulin for the rest of the pregnancy. Their babies were delivered at term, with adequate weight for birth age and no congenital malformations.

1. Napoli A, *et al.* Use of repaglinide during the first weeks of pregnancy in two type 2 diabetic women. *Diabetes Care* 2006; **29:** 2326–7.
2. Mollar-Puchades MA, *et al.* Use of repaglinide on a pregnant woman during embryogenesis. *Diabetes Obes Metab* 2007; **9:** 146–7.

Interactions

As with other oral antidiabetics, the efficacy of repaglinide may be affected by drugs independently increasing or decreasing blood glucose concentrations (see Sulfonylureas, p.461).

Drugs that affect the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 may alter the metabolism of repaglinide. Use of repaglinide with the CYP2C8 inhibitor gemfibrozil has resulted in marked reduction in repaglinide clearance, and severe hypoglycaemia; UK licensed product information contra-indicates concomitant use.

◊ References.

1. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* 2000; **40:** 184–92.
2. Hatorp V, *et al.* Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003; **43:** 649–60.
3. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet* 2007; **46:** 93–108.

Antibacterials. A study[1] in healthy subjects found that the plasma concentration of a single dose of repaglinide was reduced, and its half-life shortened, when it was given 12.5 hours after the last dose of a 5-day course of *rifampicin*. This effect was attributed to the induction of the cytochrome P450 isoenzyme CYP3A4 by rifampicin. In another study[2] repaglinide was given either with the last dose of a 7-day course of rifampicin or 24 hours later, and the effects on repaglinide were found to be greater on day 8 than day 7. The authors suggested that rifampicin acted as both an inducer and an inhibitor of CYP3A4 and possibly CYP2C8, and that after rifampicin was stopped its inductive effect lasted longer, thereby having a greater effect 24 hours later.

A study[3] in healthy subjects reported that *clarithromycin* can increase the plasma concentrations and prolong the elimination half-life of repaglinide, probably by inhibition of CYP3A4. *Telithromycin*, another inhibitor of CYP3A4, also increased plasma concentrations of repaglinide in a study of healthy subjects, although the elimination half-life of repaglinide was not significantly affected.[4] *Trimethoprim*[5] can have a similar effect by the inhibition of CYP2C8.

For a report of hypoglycaemia when *gatifloxacin* was given to a patient already receiving repaglinide, see p.281.

1. Niemi M, *et al.* Rifampin decreases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2000; **68:** 495–500.
2. Bidstrup TB, *et al.* Rifampicin seems to act as both an inducer and an inhibitor of the metabolism of repaglinide. *Eur J Clin Pharmacol* 2004; **60:** 109–14.
3. Niemi M, *et al.* The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; **70:** 58–65.
4. Kajosaari LI, *et al.* Telithromycin, but not montelukast, increases the plasma concentrations and effects of the cytochrome P450 3A4 and 2C8 substrate repaglinide. *Clin Pharmacol Ther* 2006; **79:** 231–42.
5. Niemi M, *et al.* The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 441–7.

Ciclosporin. Ciclosporin markedly increased plasma concentrations of repaglinide in healthy subjects;[1] there is a possibly increased risk of hypoglycaemia if these 2 drugs are taken together.

1. Kajosaari LI, *et al.* Cyclosporine markedly raises the plasma concentrations of repaglinide. *Clin Pharmacol Ther* 2005; **78:** 388–99.

Grapefruit juice. Grapefruit juice increased the bioavailability of repaglinide in a study of healthy subjects.[1] The half-life of repaglinide was not affected, suggesting that grapefruit juice inhibited its presystemic metabolism by the cytochrome P450 isoenzyme CYP3A4 in the gut wall. Blood-glucose concentrations were not affected.

1. Bidstrup TB, *et al.* The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* 2006; **61:** 49–57.

Lipid regulating drugs. A study[1] in healthy subjects found that *gemfibrozil* significantly increased the plasma concentrations of repaglinide and enhanced and prolonged its glucose-lowering effect. Use of this combination should be avoided. Another study[2] in healthy subjects found, however, that repaglinide was not affected by *bezafibrate* or *fenofibrate*.

1. Niemi M, *et al.* Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003; **46:** 347–51.
2. Kajosaari LI, *et al.* Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. *Br J Clin Pharmacol* 2004; **58:** 390–6.

Pharmacokinetics

Repaglinide is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 hour. The mean bioavailability is about 60%. Repaglinide is highly bound to plasma proteins, and has a plasma elimination half-life of about 1 hour. It undergoes almost complete hepatic metabolism involving the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. The metabolites, which are inactive, are excreted in the bile. Higher plasma concentrations and prolonged half-life of repaglinide may occur in patients with renal impairment (creatinine clearance less than 40 mL/minute) or chronic liver disease.

◊ References.

1. Hatorp V, *et al.* Single-dose pharmacokinetics of repaglinide in subjects with chronic liver disease. *J Clin Pharmacol* 2000; **40:** 142–52.
2. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. *Clin Pharmacokinet* 2002; **41:** 471–83.
3. Bidstrup TB, *et al.* CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. *Br J Clin Pharmacol* 2003; **56:** 305–14.

Uses and Administration

Repaglinide is a meglitinide antidiabetic used for the treatment of type 2 diabetes mellitus (p.431). It has a chemical structure different from that of the sulfonylureas, but appears to have a similar mode of action.

Repaglinide is given up to 30 minutes before meals, in usual initial oral doses of 0.5 mg; initial doses of 1 or 2 mg are usually given to patients who have had previous hypoglycaemic treatment. The dose may be adjusted, at intervals of 1 to 2 weeks, up to a maximum of 4 mg before meals; a total of 16 mg daily should not be exceeded. Repaglinide is also given with metformin or a thiazolidinedione in type 2 diabetes not adequately controlled by monotherapy.

◊ References.

1. Anonymous. Repaglinide for type 2 diabetes mellitus. *Med Lett Drugs Ther* 1998; **40:** 55–6.
2. Moses R, *et al.* Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 1999; **22:** 119–24.
3. Wolffenbuttel BH, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 1999; **22:** 463–7.
4. Moses RG, *et al.* Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes Care* 2001; **24:** 11–15.
5. Dornhorst A. Insulinotropic meglitinide analogues. *Lancet* 2001; **358:** 1709–16.
6. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs* 2001; **61:** 1625–60.
7. Moses R. Repaglinide in combination therapy. *Diabetes Nutr Metab* 2002; **15** (suppl): 33–8.
8. Derosa G, *et al.* Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther* 2003; **25:** 472–84.
9. Raskin P, *et al.* Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. *Diabet Med* 2004; **21:** 329–35.

Administration in renal impairment. Although repaglinide is cleared mainly by hepatic metabolism, small pharmacokinetic studies have reported that exposure to repaglinide may be increased in patients with renal impairment.[1,2] A larger open-label study[3] that included 151 patients with normal renal function and 130 patients with varying degrees of renal impairment found that the incidence of adverse effects was not influenced by renal function. However, at the end of the 3-month maintenance treatment period, there was a trend towards lower effective doses of repaglinide with increasing degree of renal impairment.

1. Marbury TC, *et al.* Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin Pharmacol Ther* 2000; **67:** 7–15.
2. Schumacher S, *et al.* Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur J Clin Pharmacol* 2001; **57:** 147–52.
3. Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. *Diabetes Care* 2003; **26:** 886–91.

Preparations

USP 31: Repaglinide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Glukenil; NovoNorm; Sestrine; ***Austral.:*** NovoNorm; ***Austria:*** NovoNorm; ***Belg.:*** NovoNorm; ***Braz.:*** Gluconorm; NovoNorm; Prandin; ***Canad.:*** Gluconorm; ***Chile:*** Hipover; NovoNorm; ***Cz.:*** NovoNorm; Prandin; ***Denm.:*** NovoNorm; ***Fin.:*** NovoNorm; ***Fr.:*** NovoNorm; ***Ger.:*** NovoNorm; ***Gr.:*** NovoNorm; ***Hong Kong:*** NovoNorm; ***Hung.:*** NovoNorm; ***India:*** Rapilin; ***Irl.:*** NovoNorm; ***Israel:*** NovoNorm; ***Ital.:*** NovoNorm; ***Malaysia:*** NovoNorm; ***Mex.:*** NovoNorm; ***Neth.:*** NovoNorm; Prandin; ***Norw.:*** NovoNorm; ***NZ:*** NovoNorm; ***Philipp.:*** NovoNorm; ***Pol.:*** NovoNorm; ***Port.:*** NovoNorm; Prandin; ***Rus.:*** NovoNorm (НовоНорм); ***S.Afr.:*** NovoNorm; ***Singapore:*** NovoNorm; ***Spain:*** NovoNorm; Prandin; ***Swed.:*** NovoNorm; ***Switz.:*** NovoNorm; ***Thai.:*** NovoNorm; ***Turk.:*** NovoNorm; ***UK:*** Prandin; ***USA:*** Prandin.

Rosiglitazone Maleate

(BANM, USAN, rINNM)

BRL-49653-C; Maleato de rosiglitazona; Rosiglitazone, Maléate de; Rosiglitazoni Maleas; Roziglitazon Maleat. (±)-5-{*p*-[2-(Methyl-2-pyridylamino)ethoxy]benzyl}-2,4-thiazolidinedione maleate (1:1).

Розиглитазона Малеат

$C_{18}H_{19}N_3O_3S,C_4H_4O_4 = 473.5.$

CAS — 122320-73-4 (rosiglitazone); 155141-29-0 (rosiglitazone maleate); 316371-84-3 (rosiglitazone potassium).

ATC — A10BG02.

ATC Vet — QA10BG02.

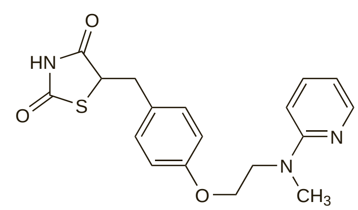

(rosiglitazone)

Adverse Effects and Precautions

Rosiglitazone may cause hypoglycaemia, headache, weight gain, and anaemia. It may also cause dizziness, gastrointestinal disturbances, muscle cramps and myalgia, dyspnoea, paraesthesia, pruritus, and hypercholesterolaemia. Very rarely angioedema and urticaria have been reported. Rosiglitazone can also increase the risk of bone fracture in women.

Rosiglitazone can cause oedema, which may worsen or precipitate heart failure. It should therefore be used with caution in patients with oedema, and should not be used in those with a history of heart failure (see also below). Renal impairment may increase the risk of fluid retention and heart failure. There have been very rare reports of new onset and worsening diabetic macular oedema with decreased visual acuity (see Effects on the Eyes, below). There is some evidence to suggest that rosiglitazone might increase the risk of myocardial ischaemia; until further data become available, UK licensed product information advises that rosiglitazone is not recommended in patients with ischaemic heart disease or peripheral arterial disease (see also below). Liver function should be monitored periodically as there have been isolated reports of liver dysfunction, and the drug should be used with caution in patients with hepatic impairment (see Effects on the Liver, below).

In women who are anovulatory because of insulin resistance, rosiglitazone therapy may result in a resumption of ovulation.

Effects on the bones. Use of thiazolidinediones such as pioglitazone or rosiglitazone has been associated with decreases in bone mineral density and increased risk of fractures in female patients. Analysis of data from a comparative study[1] of glycaemic control with rosiglitazone, metformin, or glibenclamide involving 4360 randomised patients found that the risk of fracture in female patients in these 3 groups was 9.3%, 5.1%, and 3.5% respectively;[2] the risk in male patients was not significantly different in the 3 groups at around 3.4 to 3.95%. Analysis of data from another large ongoing study was also consistent with an increased fracture risk with rosiglitazone,[2] and data from the manufacturer of pioglitazone involving over 8100 treated patients also revealed an increased risk of fracture in women given the drug;[3] the excess risk was calculated to be 0.8 per 100 patient years of use. The pattern of fractures seems to differ from that associated with postmenopausal osteoporosis, being mainly in the upper arm, hand, or foot, rather than hip or spine, but an observational study has suggested that thiazolidinedione use is associated with ongoing loss of whole-body bone mineral density.[4]

1. Kahn SE, *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355:** 2427–43. Correction. *ibid.* 2007; **356:** 1387–8.
2. GSK, Canada. Increased incidence of fractures in female patients who received long-term treatment with Avandia (rosiglitazone maleate) tablets for type 2 diabetes mellitus (23rd February 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avandia_hpc-cps_3-eng.pdf (accessed 20/08/08)
3. Takeda, USA. Re observation of an increased incidence of fractures in female patients who received long-term treatment with Actos (pioglitazone HCl) tablets for type 2 diabetes mellitus (March 2007). Available at: http://www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf (accessed 21/03/07)
4. Schwartz AV, *et al.* Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 2006; **91:** 3349–54.

Effects on the cardiovascular system. It has been suggested that, in addition to their hypoglycaemic effect, thiazolidinediones may have beneficial effects in the prevention of macrovascular diabetic complications, and there is some evidence that pioglitazone may improve some cardiovascular outcomes (see Diabetic Complications, p.457). However, a meta-analysis[1] of 42 studies found that, compared with either placebo or other antidiabetic drugs, rosiglitazone was associated with a significant increase in the risk of myocardial infarction, and an increase of borderline significance in death from cardiovascular causes. There were limitations to this analysis as the studies were not primarily intended to examine cardiovascular outcomes, and many were small and short-term. Another meta-analysis[2] that was restricted to 4 long-term studies (at least 12 months of treatment) that had specified an intention to evaluate cardiovascular adverse effects also found an increased risk of myocardial infarction with rosiglitazone use, without a significant increase in the risk of cardiovascular mortality.

Studies with no recorded cardiovascular events were excluded from the larger meta-analysis,[1] and this has been questioned. An alternative analysis[3] that incorporated these excluded studies, with appropriate analysis adjustment, found odds ratios for myocardial infarction and cardiovascular death that were not statistically significant, and concluded that neither increased nor decreased risk could be established.

In response to concerns raised by the initial meta-analysis, an unplanned interim analysis of an ongoing open-label study designed to assess cardiovascular outcomes has been published (rosiglitazone added to either metformin or a sulfonylurea compared with metformin plus a sulfonylurea).[4] The data, however, were insufficient to determine whether there was an increased risk of myocardial infarction, and the findings were inconclusive regarding any effect on overall risks of hospitalisation or death from cardiovascular causes.

For the risks of heart failure associated with thiazolidinediones, see Effects on the Heart, below.

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356:** 2457–71. Correction. *ibid.*; **357:** 100.
2. Singh S, *et al.* Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298:** 1189–95.
3. Diamond GA, *et al.* Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med* 2007; **147:** 578–81.
4. Home PD, *et al.* RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007; **357:** 28–38.

Effects on the eyes. The manufacturers in the USA and Canada (*GSK*) have received postmarketing reports of the development or worsening of diabetic macular oedema in patients treated with rosiglitazone-containing products; in most cases the patients also reported peripheral oedema or fluid retention.[1,2] In some cases visual impairment improved or resolved after stopping the drug. Rosiglitazone should be used with caution in patients with pre-existing diabetic retinopathy or macular oedema, and should be stopped, and ophthalmological consultation sought, if visual impairment develops while using the drug.[2]

1. GSK, USA. Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin HCl): letter to healthcare professionals (issued December 2005). Available at: http://www.fda.gov/medwaTCH/safety/2006/Avandia_DHCPletter.pdf (accessed 03/05/06)
2. GSK, Canada. Association of Avandia and Avandamet with new onset and/or worsening of macular edema (issued 19th December, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avandia_avandamet_hpc-cps-eng.pdf (accessed 20/08/08)

Effects on the heart. Both pioglitazone and rosiglitazone can cause peripheral and pulmonary oedema, which can worsen or precipitate heart failure; a number of cases have been described.[1-6] A large retrospective cohort study[7] also found that the use of thiazolidinediones increased the risk of heart failure. The incidence of peripheral oedema with monotherapy has been reported[8] to range from 3 to 5%, and this increases slightly when a thiazolidinedione is used with another oral antidiabetic. The incidence is about 15% when a thiazolidinedione is used with insulin. The incidence of heart failure is generally lower, but has been reported to be 2 to 3% when a thiazolidinedione is used with insulin; however, a large prospective study,[9] which was intended to examine the cardiovascular benefits of pioglitazone in preventing secondary macrovascular events in diabetic patients with pre-existing macrovascular disease, reported a 6% incidence of heart failure, compared with 4% in the placebo group. Mortality rates from heart failure did not differ between groups. These figures were confirmed on re-analysis.[10]

The American Heart Association and American Diabetes Association have recommended[8] that patients with risk factors for heart disease or a depressed ejection fraction but without symptoms, and patients with NYHA class I or II heart failure, should start with a low dose of a thiazolidinedione that is only increased gradually as necessary and with careful monitoring. Patients with more severe heart failure (class III and IV) should not receive these drugs. These recommendations are reflected in US licensed product information. UK licensed product information contra-indicates the use of pioglitazone or rosiglitazone in patients with heart failure or any history of heart failure, even of class I or II.

For restrictions on combination therapy see Administration, below.

1. Page RL, *et al.* Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy* 2003; **23:** 945–54.
2. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 2003; **78:** 1088–91.
3. Bell DSH. Unilateral edema due to a thiazolidinedione. *Diabetes Care* 2003; **26:** 2700.
4. Shah M, *et al.* Pioglitazone-induced heart failure despite normal left ventricular function. *Am J Med* 2004; **117:** 973–4.
5. CSM/MHRA. Reminder: thiazolidinediones (glitazones) contraindications. *Current Problems* 2004; **30:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
6. Cheng AYY, Fantus IG. Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother* 2004; **38:** 817–20.
7. Delea TE, *et al.* Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2003; **26:** 2983–9.
8. Nesto RW, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108:** 2941–8. Also available at: http://circ.ahajournals.org/cgi/reprint/108/23/2941.pdf (accessed 26/03/07) Also published in *Diabetes Care* 2004; **27:** 256–63. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/1/256 (accessed 26/03/07)
9. Dormandy JA, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366:** 1279–89.
10. Rydén L, *et al.* Adjudication of serious heart failure in patients from PROactive. *Lancet* 2007; **369:** 189–90.

Effects on lipids. Rosiglitazone and pioglitazone have different effects on serum lipids—see p.456.

Effects on the liver. Several cases of hepatotoxicity have been described[1-5] in patients receiving rosiglitazone. Most of these occurred within a few weeks or months of starting rosiglitazone therapy. However, the causality of some of these cases has been debated[6,7] because of coexisting disease and concomitant medication.

Licensed product information recommends that liver enzymes should be checked before starting therapy with rosiglitazone; patients with aminotransferase (ALT) concentrations more than 2.5 times the upper limit of normal should not be given rosiglitazone. ALT concentrations should then be monitored periodically. If ALT concentrations rise to more than 3 times the upper limit of normal and remain so after retesting then treatment with rosiglitazone should be stopped; treatment should also be stopped if jaundice develops.

1. Forman LM, *et al.* Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med* 2000; **132:** 118–21.
2. Al-Salman J, *et al.* Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med* 2000; **132:** 121–4.
3. Ravinuthala RS, Nori U. Rosiglitazone toxicity. *Ann Intern Med* 2000; **133:** 658.
4. Hachey DM, *et al.* Isolated elevation of alkaline phosphatase level associated with rosiglitazone. *Ann Intern Med* 2000; **133:** 752.
5. Gouda HE, *et al.* Liver failure in a patient treated with long-term rosiglitazone therapy. *Am J Med* 2001; **111:** 584–5.
6. Freid J, *et al.* Rosiglitazone and hepatic failure. *Ann Intern Med* 2000; **132:** 164.
7. Isley WL, Oki JC. Rosiglitazone and liver failure. *Ann Intern Med* 2000; **133:** 393.

Fasting. For mention that glitazones can probably be used with low risk of hypoglycaemia in fasting Muslim patients during Ramadan see under Precautions of Insulin, p.448.

Interactions

Gemfibrozil, ketoconazole, and trimethoprim, can increase plasma concentrations of rosiglitazone. Conversely, rifampicin can reduce rosiglitazone concentrations. These drugs should be given with caution to patients taking rosiglitazone, and glycaemic control should be monitored.

Use of NSAIDs or insulin with rosiglitazone may increase the risk of oedema and heart failure (see also Effects on the Heart, above, and Administration, below).

Antibacterials. *Rifampicin* significantly reduced the plasma concentration and elimination half-life of rosiglitazone in studies[1,2] of healthy subjects, probably by induction of the cytochrome P450 isoenzyme CYP2C8. Conversely, *trimethoprim* can inhibit CYP2C8, and was found to increase the concentration and half-life of rosiglitazone modestly.[2,3]

1. Park J-Y, *et al.* Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004; **75:** 157–62.
2. Niemi M, *et al.* Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. *Clin Pharmacol Ther* 2004; **76:** 239–49.
3. Hruska MW, *et al.* The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 70–9.

Antifungals. In a study[1] of healthy subjects, *ketoconazole* increased the plasma concentration and elimination half-life of rosiglitazone, probably by inhibition of the cytochrome P450 isoenzyme CYP2C8 and to a lesser extent CYP2C9.

1. Park J-Y, *et al.* Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; **58:** 397–402.

Lipid regulating drugs. *Gemfibrozil* increased the plasma concentration and about doubled the half-life of rosiglitazone in a study[1] of healthy subjects, probably by inhibiting its metabolism. The authors suggested that these drugs should not be used together, or that the dose of rosiglitazone should be at least halved if gemfibrozil treatment is started.

1. Niemi M, *et al.* Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. *Diabetologia* 2003; **46:** 1319–23.

Pharmacokinetics

Rosiglitazone is well absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentrations occur within 1 hour and the bioavailability is 99%. It is 99.8% bound to plasma proteins. Rosiglitazone is extensively metabolised, almost exclusively by the cytochrome P450 isoenzyme CYP2C8. It is excreted in the urine and faeces, and has a half-life of 3 to 4 hours.

◊ References.

1. Baldwin SJ, *et al.* Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. *Br J Clin Pharmacol* 1999; **48:** 424–32.
2. Chapelsky MC, *et al.* Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J Clin Pharmacol* 2003; **43:** 252–9.

Uses and Administration

Rosiglitazone is a thiazolidinedione oral antidiabetic that improves insulin sensitivity and is used for the treatment of type 2 diabetes mellitus (p.431). It is usually given as rosiglitazone maleate but doses are expressed in terms of the base; rosiglitazone maleate 1.32 mg is equivalent to about 1 mg of rosiglitazone. The potassium salt is used in some countries. Rosiglitazone is given orally as monotherapy, particularly in patients who are overweight and for whom metformin is contra-indicated or not tolerated. It may also be added to metformin, a sulfonylurea (or a combination of the two), or to insulin, when such therapy is inadequate (but see Administration, below). The usual initial dose is 4 mg daily, given in a single dose or two divided doses. The dose may be increased to a maximum of 8 mg daily if necessary after 8 to 12 weeks in patients receiving monotherapy or combination oral therapy. Rosiglitazone may be taken with or without food.

◊ References.

1. Nolan JJ, *et al.* Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med* 2000; **17:** 287–94.
2. Fonseca V, *et al.* Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000; **283:** 1695–1702. Correction. *ibid.*; **284:** 1384.
3. Lebovitz HE, *et al.* Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2001; **86:** 280–8.
4. Anonymous. Pioglitazone and rosiglitazone for diabetes. *Drug Ther Bull* 2001; **39:** 65–8.
5. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.
6. Raskin P, *et al.* A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 2001; **24:** 1226–32.
7. O'Moore-Sullivan TM, Prins JB. Thiazolidinediones and type 2 diabetes: new drugs for an old disease. *Med J Aust* 2002; **176:** 381–6. Correction. *ibid.*; **177:** 396.

8. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2002; **62:** 1805–37.
9. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 2003; **63:** 1373–1405.
10. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.
11. Dailey GE, *et al.* Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. *Am J Med* 2004; **116:** 223–9.
12. Czoski-Murray C, *et al.* Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2004; **8:** 1–91.
13. Wellington K. Rosiglitazone/metformin. *Drugs* 2005; **65:** 1581–92.
14. Deeks ED, Keam SJ. Rosiglitazone : a review of its use in type 2 diabetes mellitus. *Drugs* 2007; **67:** 2747–79.

Administration. Although rosiglitazone is licensed for use with other antidiabetic drugs the specifics of licensing and use may vary from country to country. In both the UK and USA, rosiglitazone (*Avandia; GSK*) is licensed for use with metformin or a sulfonylurea, or both if necessary, in patients in whom single or dual agent therapy is inadequate. In the UK, however, NICE recommends dual therapy only in patients who cannot be given combination therapy with metformin plus a sulfonylurea.[1]

The combination of rosiglitazone with insulin is now generally avoided because of an increased risk of heart failure and other cardiac adverse events (see also Effects on the Heart, above), although licensed product information may not necessarily contraindicate the combination. In the UK, licensed product information for rosiglitazone warns that insulin should only be added to established rosiglitazone therapy in exceptional cases and under close supervision. In the USA, the combination of rosiglitazone and insulin is not recommended.

1. NICE. Guidance on the use of glitazones for the treatment of type 2 diabetes (issued August 2003). Available at: http://www.nice.org.uk/pdf/TA63_Glitazones_Review_Guidance.pdf (accessed 17/03/05)

Inflammatory bowel disease. There is some evidence[1] to suggest that drugs such as rosiglitazone that act as ligands to peroxisome proliferator-activated receptor γ (PPARγ) may offer a novel therapeutic approach to management of inflammatory bowel disease (p.1697).

1. Lewis JD, *et al.* Rosiglitazone for Ulcerative Colitis Study Group. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology* 2008; **134:** 688–95.

Polycystic ovary syndrome. Insulin resistance is a feature of polycystic ovary syndrome (p.2080) and the use of rosiglitazone is under investigation.[1-3]

1. Baillargeon J-P, *et al.* Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. *Fertil Steril* 2004; **82:** 893–902.
2. Dereli D, *et al.* Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. *Endocr J* 2005; **52:** 299–308.
3. Yilmaz M, *et al.* The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecol Endocrinol* 2005; **21:** 154–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avandia; Diaben; Gaudil; Glimide; Gliximina; Gludex; Rosiglit; ***Austral.:*** Avandia; ***Belg.:*** Avandia; ***Braz.:*** Avandia; ***Canad.:*** Avandia; ***Chile:*** Avandia; ***Cz.:*** Avandia; ***Denm.:*** Avandia; ***Fin.:*** Avandia; ***Fr.:*** Avandia; ***Ger.:*** Avandia; ***Gr.:*** Avandia; ***Hong Kong:*** Avandia; ***Hung.:*** Avandia; ***India:*** Rezult†; Roglin; Rosicon; ***Indon.:*** Avandia; ***Irl.:*** Avandia; ***Israel:*** Avandia; ***Ital.:*** Avandia; ***Malaysia:*** Avandia; ***Mex.:*** Avandia; ***Neth.:*** Avandia; ***Norw.:*** Avandia; ***NZ:*** Avandia; ***Philipp.:*** Avandia; ***Pol.:*** Avandia; ***Port.:*** Avandia; ***Rus.:*** Avandia (Авандия); Roglit (Роглит); ***S.Afr.:*** Avandia; ***Singapore:*** Avandia; ***Spain:*** Avandia; ***Swed.:*** Avandia; ***Switz.:*** Avandia; ***Thai.:*** Avandia; ***Turk.:*** Avandia; ***UK:*** Avandia; ***USA:*** Avandia; ***Venez.:*** Avandia.

Multi-ingredient: ***Arg.:*** Avandamet; Gludex Plus; Rosiglit-Met; ***Austral.:*** Avandamet; ***Belg.:*** Avandamet; ***Canad.:*** Avandamet; ***Chile:*** Avandamet; ***Cz.:*** Avaglim; Avandamet; ***Denm.:*** Avandamet; ***Fin.:*** Avandamet; ***Fr.:*** Avaglim; Avandamet; ***Ger.:*** Avandamet; ***Gr.:*** Avaglim; Avandamet; ***Hong Kong:*** Avandamet; ***Hung.:*** Avaglim; Avandamet; ***India:*** Glyroz; Roglin-M; Rosicon MF; ***Indon.:*** Avandamet; Avandaryl; ***Irl.:*** Avandamet; ***Israel:*** Avandamet; ***Ital.:*** Avandamet; ***Malaysia:*** Avandamet; ***Mex.:*** Avandamet; ***Neth.:*** Avandamet; ***Norw.:*** Avandamet; ***Philipp.:*** Avandamet; ***Pol.:*** Avandamet; ***Port.:*** Avaglim; Avandamet; ***Singapore:*** Avandamet; ***Spain:*** Avandamet; ***Swed.:*** Avandamet; ***Switz.:*** Avandamet; ***Thai.:*** Avandamet; ***UK:*** Avandamet; ***USA:*** Avandamet; Avandaryl; ***Venez.:*** Avandamet.

Ruboxistaurin *(rINN)*

LY-333531; LY-341684 (ruboxistaurin mesilate); Ruboxistaurina; Ruboxistaurine; Ruboxistaurinum. (9*S*)-9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-9*H*,19*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-18,20-dione.

Рубоксистаурин

$C_{28}H_{28}N_4O_3$ = 468.5.

CAS — 169939-94-0 (ruboxistaurin); 169939-93-9 (ruboxistaurin hydrochloride); 202260-21-7 (ruboxistaurin mesilate).

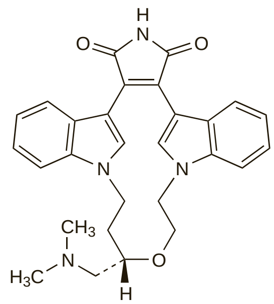

Profile

Ruboxistaurin is an oral inhibitor of the β-isoform of the enzyme protein kinase C, which is thought to play a role in the development of diabetic microvascular complications (p.433). It is under investigation as an adjunct in the treatment of diabetic retinopathy.

◊ References.

1. Joy SV, *et al.* Ruboxistaurin, a protein kinase C β inhibitor, as an emerging treatment for diabetes microvascular complications. *Ann Pharmacother* 2005; **39:** 1693–9.
2. Vinik A. The protein kinase C-β inhibitor, ruboxistaurin, for the treatment of diabetic microvascular complications. *Expert Opin Invest Drugs* 2005; **14:** 1547–59.
3. The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C β Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial. *Diabetes* 2005; **54:** 2188–97.

Sitagliptin Phosphate *(USAN, rINNM)*

Fosfato de sitagliptina; MK-431; MK-0431; Ono-5435; Sitagliptine, Phosphate de; Sitagliptini Phosphas. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazinemonophosphate monohydrate.

Ситаглиптина Фосфат

$C_{16}H_{15}F_6N_5O,H_3O_4P,H_2O$ = 523.3.

CAS — 486460-32-6 (sitagliptin); 654671-78-0 (sitagliptin phosphate); 654671-77-9 (sitagliptin phosphate monohydrate).

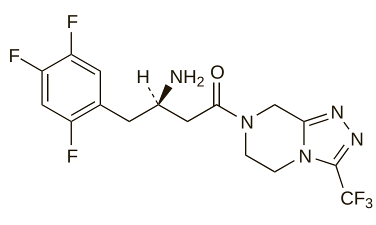

(sitagliptin)

Profile

Like vildagliptin (p.464), sitagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4, an enzyme responsible, among other roles, for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1; insulinotropin), which plays a role in regulating insulin secretion. It is used in the treatment of type 2 diabetes mellitus (p.431), as monotherapy or as dual therapy with metformin, a sulfonylurea, or a thiazolidinedione. Triple therapy using sitagliptin with metformin and a sulfonylurea may be given if dual therapy is inadequate. Sitagliptin is given as the phosphate, but doses are in terms of the base; 128.5 mg of sitagliptin phosphate is equivalent to about 100 mg of sitagliptin. The usual oral dose is the equivalent of 100 mg of sitagliptin once daily, as monotherapy or in combination. When given with metformin in a combination preparation, sitagliptin may be given in 2 divided doses. The dose of sulfonylurea may need to be lowered when used with sitagliptin. Sitagliptin may be taken with or without food. Dosage should be adjusted in patients with renal impairment (see below).

Adverse effects reported with sitagliptin include upper respiratory-tract infections, headache, and nasopharyngitis. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, rash, and Stevens-Johnson syndrome have also been reported.

◊ References.

1. Herman GA,*et al.* Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. *Clin Pharmacol Ther* 2005; **78:** 675–88.
2. Bergman AJ, *et al.* Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. *Clin Ther* 2006; **28:** 55–72.
3. Aschner P, *et al.* Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; **29:** 2632–7.
4. Charbonnel B, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29:** 2638–43.
5. Rosenstock J, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2006; **28:** 1556–68.
6. Brazg R, *et al.* Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab* 2007; **9:** 186–93.
7. Nauck MA, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; **9:** 194–205.
8. Scott R, *et al.* Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract* 2007; **61:** 171–80.
9. Deacon CF. Dipeptidyl peptidase 4 inhibition with sitagliptin: a new therapy for type 2 diabetes. *Expert Opin Invest Drugs* 2007; **16:** 533–545.
10. Lyseng-Williamson KA. Sitagliptin. *Drugs* 2007; **67:** 587–97.

Administration in renal impairment. US licensed product information suggests the following oral doses of sitagliptin in patients with renal impairment, based on creatinine clearance (CC):
- mild impairment (CC 50 mL/minute or more): no adjustment necessary, 100 mg daily
- moderate impairment (CC 30 to less than 50 mL/minute): 50 mg daily
- severe impairment (CC less than 30 mL/minute): 25 mg daily. It may be given without regard to the timing of haemodialysis

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Januvia; ***Braz.:*** Januvia; ***Cz.:*** Januvia; Tesavel; Xelevia; ***Fr.:*** Januvia; ***Gr.:*** Januvia; Xelevia; ***Malaysia:*** Januvia; ***Mex.:*** Januvia; ***Port.:*** Januvia; Tesavel; Xelevia; ***UK:*** Januvia; ***USA:*** Januvia.

Multi-ingredient: ***USA:*** Janumet.

Sulfonylurea Antidiabetics

Antidiabéticos sulfonilureas; Sulphonylurea Antidiabetics.

Adverse Effects

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea, and a metallic taste may occur with sulfonylureas and are usually mild and dose-dependent; increased appetite and weight gain may occur. Skin rashes and pruritus may occur and photosensitivity has been reported. Rashes are usually hypersensitivity reactions and may progress to more serious disorders (see below). Facial flushing may develop in patients receiving sulfonylureas, particularly chlorpropamide, when alcohol is consumed (see under Interactions, below).

Mild hypoglycaemia may occur; severe hypoglycaemia is usually an indication of overdosage and is relatively uncommon. Hypoglycaemia is more likely with long-acting sulfonylureas such as chlorpropamide and glibenclamide, which have been associated with severe, prolonged, and sometimes fatal hypoglycaemia.

Other severe effects may be manifestations of a hypersensitivity reaction. They include altered liver enzyme values, hepatitis and cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema multiforme or the Stevens-Johnson syndrome, exfoliative dermatitis, and erythema nodosum.

The sulfonylureas, particularly chlorpropamide, occasionally induce a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) characterised by water retention, hyponatraemia, and CNS effects. However, some sulfonylureas, such as glibenclamide, glipizide, and tolazamide are also stated to have mild diuretic actions.

Work on tolbutamide has suggested that the sulfonylureas might be associated with an increase in cardiovascular mortality; this has been the subject of considerable debate (see Effects on the Cardiovascular System, below).

◊ Reviews.

1. Paice BJ, *et al*. Undesired effects of the sulphonylurea drugs. *Adverse Drug React Acute Poisoning Rev* 1985; **4:** 23–36.
2. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Safety* 2000; **22:** 313–20.

Effects on the cardiovascular system. A multicentre study carried out under the University Group Diabetes Program (UGDP) reported an increased incidence in mortality from cardiovascular complications in diabetic patients given tolbutamide as compared with those treated with diet alone or insulin;[1] a similar increase was also noted in patients given phenformin.[2] The reports from the UGDP aroused prolonged controversy which was not entirely settled by detailed reassessment of relevant studies.[3] Eventually in 1984 the FDA made it a requirement that sulfonylurea oral antidiabetics be labelled with a specific warning about the possibility of increased cardiovascular mortality associated with the use of these drugs.[4] Subsequently the cardiovascular effects of the sulfonylureas were reviewed.[5] It has been hypothesised that the action of the sulfonylureas in preventing the opening of ATP-sensitive potassium channels in the myocardium may abolish adaptive changes (ischaemic preconditioning) that protect the heart against ischaemic insult.[6] A recent retrospective cohort study has also found that, among patients newly treated for type 2 diabetes, sulfonylurea monotherapy was associated with an increased mortality compared with metformin therapy.[7] However, results from the UK Prospective Diabetes Study did not demonstrate any adverse cardiovascular effects associated with sulfonylurea therapy.[8]

1. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes III: clinical implications of UGDP results. *JAMA* 1971; **218:** 1400–10.
2. University Group Diabetes Program. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes IV: a preliminary report on phenformin results. *JAMA* 1971; **217:** 777–84.
3. Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. *JAMA* 1975; **231:** 583–600.
4. FDA. Class labeling for oral hypoglycemics. *FDA Drug Bull* 1984; **14:** 16–17.
5. Huupponen R. Adverse cardiovascular effects of sulphonylurea drugs: clinical significance. *Med Toxicol* 1987; **2:** 190–209.
6. Yellon DM, *et al.* Angina reassessed: pain or protector? *Lancet* 1996; **347:** 1159–62.
7. Simpson SH, *et al.* Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *Can Med Assoc J* 2006; **174:** 169–74.
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.

Effects on the eyes. When a diabetic patient who had experienced bilateral visual loss for several months and who had been taking chlorpropamide for one year stopped treatment, visual acuity improved and colour vision rapidly returned.[1] A 5-day challenge with chlorpropamide resulted in a mild decrease in acuity followed by return to baseline values when treatment was again stopped. Drug-induced optic neuropathy was considered to have occurred. There is also a report of a patient with type 2 diabetes mellitus who developed myopia two days after starting treatment with glibenclamide 10 mg daily.[2] Visual difficulties resolved a few days after stopping glibenclamide.

1. Wymore J, Carter JE. Chlorpropamide-induced optic neuropathy. *Arch Intern Med* 1982; **142:** 381.
2. Teller J, *et al.* Accommodation insufficiency induced by glybenclamide. *Ann Ophthalmol* 1989; **21:** 275–6.

Effects on the kidneys. The nephrotic syndrome has been reported in a patient treated with chlorpropamide.[1] Serological testing and renal biopsy showed that the glomerular lesions were of an immune-complex nature. Both the nephrotic syndrome and the glomerulonephritis resolved after treatment was stopped. The patient also developed a skin eruption, hepatitis, and eosinophilia.

1. Appel GB, *et al.* Nephrotic syndrome and immune complex glomerulonephritis associated with chlorpropamide therapy. *Am J Med* 1983; **74:** 337–42.

Effects on the liver. Chlorpropamide was implicated[1] in 8 of 53 cases of drug-induced acute liver disease admitted to a hospital in Jamaica over the years 1973 to 1988. Hepatocanalicular cholestasis occurred in 5 cases and diffuse necrosis in 3. One patient with massive hepatic necrosis died. Intrahepatic cholestasis,[2-4] an acute hepatitis-like syndrome,[5] and a combination of both[6] have been described in patients receiving glibenclamide.

1. Lee MG, *et al.* Drug-induced acute liver disease. *Postgrad Med J* 1989; **65:** 367–70.
2. Wongpaitoon V, *et al.* Intrahepatic cholestasis and cutaneous bullae associated with glibenclamide therapy. *Postgrad Med J* 1981; **57:** 244–6.
3. Krivoy N, *et al.* Fatal toxic intrahepatic cholestasis secondary to glibenclamide. *Diabetes Care* 1996; **19:** 385–6.
4. Tholakanahalli VN, *et al.* Glibenclamide-induced cholestasis. *West J Med* 1998; **168:** 274–7.
5. Goodman RC, *et al.* Glyburide-induced hepatitis. *Ann Intern Med* 1987; **106:** 837–9.
6. Petrogiannopoulos C, Zacharof A. Glibenclamide and liver disease. *Diabetes Care* 1997; **20:** 1215.

Effects on the thyroid. See under Precautions, below.

Hypoglycaemia. Severe hypoglycaemia may occur in any patient treated with any sulfonylurea; this potentially life-threatening complication requires prolonged and energetic treatment.[1] Sulfonylureas with a prolonged duration of action such as chlorpropamide and glibenclamide appear to cause severe hypoglycaemia more often than shorter-acting drugs such as tolbutamide. Experience with newer drugs is limited.

A review of 1418 cases of drug-induced hypoglycaemia reported since 1940 showed that sulfonylureas (especially chlorpropamide and glibenclamide), either alone or with a second antidiabetic or potentiating agent, accounted for 63% of all cases.[2] A study of sulfonylurea use in nearly 14,000 patients aged 65 years or older confirmed that chlorpropamide and glibenclamide were associated with hypoglycaemia. However, glipizide caused significantly fewer cases than glibenclamide.[3]

An analysis,[4] of 185 children reported to 10 regional poison centres in the USA after ingesting sulfonylureas found that hypoglycaemia developed only in 56. A lack of hypoglycaemia during the first 8 hours after ingestion was predictive of a benign outcome, and it was recommended that suspected cases be observed for 8 hours with frequent blood glucose monitoring. Children who developed signs of hypoglycaemia, or in whom blood glucose fell below 3.3 mmol/litre could be given intravenous glucose if necessary.

See also under Abuse, below.

1. Ferner RE, Neil HAW. Sulphonylureas and hypoglycaemia. *BMJ* 1988; **296:** 949–50.
2. Seltzer HS. Drug-induced hypoglycemia. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
3. Shorr RI, *et al.* Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996; **44:** 751–5.
4. Spiller HA, *et al.* Prospective multicenter study of sulfonylurea ingestion in children. *J Pediatr* 1997; **131:** 141–6.

Treatment of Adverse Effects

In acute poisoning with sulfonylureas, if the patient is conscious and presents within 1 hour of ingestion, the stomach should be emptied and/or activated charcoal given. Hypoglycaemia should be treated with urgency; the general management of hypoglycaemia is described under insulin (see p.447). The patient should be observed over several days in case hypoglycaemia recurs. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia.

◊ References.

1. Spiller HA. Management of antidiabetic medication in overdose. *Drug Safety* 1998; **19:** 411–24.
2. McLaughlin SA, *et al.* Octreotide: an antidote for sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2000; **36:** 133–8.
3. Carr R, Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. *Ann Pharmacother* 2002; **36:** 1727–32.

Precautions

Sulfonylureas should not be used in type 1 diabetes mellitus. Use in type 2 diabetes mellitus is contra-indicated in patients with ketoacidosis and in those with severe infection, trauma, or other severe conditions where the sulfonylurea is unlikely to control the hyperglycaemia; insulin should be used in such situations.

Insulin is also preferred for therapy during pregnancy.

Sulfonylureas with a long half-life such as chlorpropamide or glibenclamide are associated with an increased risk of hypoglycaemia. They should therefore be avoided in patients with impairment of renal or hepatic function, and a similar precaution would tend to apply in other groups with an increased susceptibility to this effect, such as the elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency. Irregular mealtimes, missed meals, changes in diet, or prolonged exercise may also provoke hypoglycaemia. Where a sulfonylurea needs to be used in patients at increased risk of hypoglycaemia, a short-acting drug such as tolbutamide or gliclazide may be preferred; these 2 sulfonylureas, being principally inactivated in the liver, are perhaps particularly suitable in renal impairment, although careful monitoring of blood-glucose concentration is essential.

Abuse. Severe hypoglycaemia, at first thought to be due to insulinoma but later found to be due to nesidioblastosis [proliferation of the islet cells], was reported in a woman covertly taking chlorpropamide.[1]

1. Rayman G, *et al.* Hyperinsulinaemic hypoglycaemia due to chlorpropamide-induced nesidioblastosis. *J Clin Pathol* 1984; **37:** 651–4.

Administration. It has been suggested that continuously high plasma concentrations of sulfonylureas may lead to the development of tolerance, and that therefore the maximum recommended doses should be reduced.[1]

1. Melander A, *et al.* Is there a concentration-effect relationship for sulphonylureas? *Clin Pharmacokinet* 1998; **34:** 181–8.

Breast feeding. Some sulfonylureas are distributed into breast milk and the class of drugs should be avoided during breast feeding.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.

References.

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Fasting. For the suggestion that sulfonylureas should be used with caution in fasting Muslim patients during Ramadan, and that chlorpropamide is contra-indicated in this group, see under Precautions of Insulin, p.448.

Porphyria. Sulfonylureas have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Thyroid disorders. There are conflicting reports concerning the effects of sulfonylureas on thyroid function, with some studies suggesting an increased incidence of thyroid dysfunction in patients treated with tolbutamide or chlorpropamide,[1] while other suggest no antithyroid action.[2,3] Some licensed product information consequently recommends that chlorpropamide should be avoided in patients with impaired thyroid function. Changes in thyroid function may conversely affect glycaemic control—for mention of the possible effects of thyroid hormones on antidiabetic drug requirements see under Interactions, below.

1. Hunton RB, *et al.* Hypothyroidism in diabetics treated with sulphonylurea. *Lancet* 1965; **ii:** 449–51.
2. Burke G, *et al.* Effect of long-term sulfonylurea therapy on thyroid function in man. *Metabolism* 1967; **16:** 651–7.
3. Feely J, *et al.* Antithyroid effect of chlorpropamide? *Hum Toxicol* 1983; **2:** 149–53.

Interactions

Many interactions have been reported with the sulfonylureas, largely representing either pharmacokinetic interactions (due to the displacement of the antidiabetic from plasma proteins or alteration in its metabolism or excretion) or pharmacological interactions with drugs having an independent effect on blood glucose. In the former class most reports concern older sulfonylureas such as chlorpropamide and tolbutamide, although the possibility of such reactions with newer drugs should be borne in mind.

A diminished hypoglycaemic effect, possibly requiring an increased dose of sulfonylurea, has been seen or might be expected on theoretical grounds with adrenaline, aminoglutethimide, chlorpromazine, corticosteroids, diazoxide, oral contraceptives, rifamycins, thiazide diuretics, and thyroid hormones.

An increased hypoglycaemic effect has occurred or might be expected with ACE inhibitors, alcohol, allopurinol, some analgesics (notably azapropazone, phenylbutazone, and the salicylates), azole antifungals (fluconazole, ketoconazole, and miconazole), chloramphenicol, cimetidine, clofibrate and related compounds, coumarin anticoagulants, fluoroquinolones, heparin, MAOIs, octreotide (although this may also produce hyperglycaemia), ranitidine, sulfinpyrazone, sulfonamides (including co-trimoxazole), tetracyclines, and tricyclic antidepressants.

Beta blockers have been reported both to increase hypoglycaemia and to mask the typical sympathetic warning signs. There are sporadic and conflicting reports of a possible interaction with calcium-channel blockers, but overall any effect seems to be of little clinical significance.

In addition to producing hypoglycaemia alcohol can interact with chlorpropamide to produce an unpleasant flushing reaction. Such an effect is rare with other sulfonylureas and alcohol.

◊ General references.

1. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; **40:** 6–18.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; **40:** 203–19.
3. Girardin E, *et al.* Hypoglycémies induites par les sulfamides hypoglycémiants. *Ann Med Interne (Paris)* 1992; **143:** 11–17.

ACE inhibitors. There are sporadic reports of marked hypoglycaemia developing in patients taking a sulfonylurea who are given an ACE inhibitor (mainly *captopril* or *enalapril*),[1-3] and 2 case-control studies have indicated that the combination is associated with an increased risk of developing severe hypoglycaemia.[4,5] However, other studies have failed to find much evidence of a problem.[6-9]

1. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
2. Rett K, *et al.* Hypoglycemia in hypertensive diabetic patients treated with sulfonylureas, biguanides, and captopril. *N Engl J Med* 1988; **319:** 1609.
3. Arauz-Pacheco C, *et al.* Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. *Am J Med* 1990; **89:** 811–13.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
7. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
8. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; **ii:** 461.
9. Shorr RI, *et al.* Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 1997; **278:** 40–3.

Alcohol. Sulfonylurea-induced alcohol intolerance is seen mainly but not exclusively with chlorpropamide; this is similar to the disulfiram-alcohol interaction, although it is not clear whether the mechanism is the same. Since the main symptom of the reaction (facial flushing) appears to occur more commonly in diabetic than non-diabetic subjects, it has been proposed that this symptom could be used as a diagnostic test for a certain subset of patients with type 2 diabetes mellitus.[1,2] However, some have not considered the test to be sufficiently specific[3-6] and despite a great deal having been published on the chlorpropamide-alcohol flushing test (CPAF), its value remains poorly defined. Alcohol, as well as provoking a flushing reaction with chlorpropamide, has been reported both to increase and to decrease the half-life of tolbutamide depending on whether the alcohol administration was acute or chronic.[7] Alcohol may also have a variable effect of its own on blood-glucose concentrations; there is a general tendency to increased hypoglycaemia when alcohol and sulfonylureas are taken concurrently.[6]

1. Leslie RDG, Pyke DA. Chlorpropamide-alcohol flushing: a dominantly inherited trait associated with diabetes. *BMJ* 1978; **2:** 1519–21.
2. Pyke DA, Leslie RDG. Chlorpropamide-alcohol flushing: a definition of its relation to non-insulin-dependent diabetes. *BMJ* 1978; **2:** 1521–2.
3. de Silva NE, *et al.* Low incidence of chlorpropamide-alcohol flushing in diet-treated, non-insulin-dependent diabetes. *Lancet* 1981; **i:** 128–31.
4. Fui SNT, *et al.* Epidemiological study of prevalence of chlorpropamide alcohol flushing in insulin dependent diabetes, non-insulin dependent diabetics, and non-diabetics. *BMJ* 1983; **287:** 1509–12.
5. Fui SNT, *et al.* Test for chlorpropamide-alcohol flush becomes positive after prolonged chlorpropamide treatment in insulin-dependent and non-insulin-dependent diabetics. *N Engl J Med* 1983; **309:** 93–6.
6. Lao B, *et al.* Alcohol tolerance in patients with non-insulin-dependent (type 2) diabetes treated with sulphonylurea derivatives. *Arzneimittelforschung* 1994; **44:** 727–34.
7. Sellers EM, Holloway MR. Drug kinetics and alcohol ingestion. *Clin Pharmacokinet* 1978; **3:** 440–52.

Analgesics. *Phenylbutazone*[1,2] and related drugs such as *azapropazone*[3] have been associated with acute hypoglycaemic episodes when given to patients receiving sulfonylureas (in most reports, tolbutamide). Other analgesics may enhance the hypoglycaemic effect of sulfonylureas, including *indobufen*,[4] *fenclofenac*,[5] and the *salicylates*.[6,7] Although a study in healthy subjects found no interaction,[7] there has been a report of hypoglycaemia with *ibuprofen* in a diabetic patient who had been stabilised on glibenclamide.[8]

1. Tannenbaum H, *et al.* Phenylbutazone-tolbutamide drug interaction. *N Engl J Med* 1974; **290:** 344.
2. Dent LA, Jue SG. Tolbutamide-phenylbutazone interaction. *Drug Intell Clin Pharm* 1976; **10:** 711.
3. Andreasen PB, *et al.* Hypoglycaemia induced by azapropazone-tolbutamide interaction. *Br J Clin Pharmacol* 1981; **12:** 581–3.
4. Elvander-Ståhl E, *et al.* Indobufen interacts with the sulphonylurea, glipizide, but not with the β-adrenergic receptor antagonists, propranolol and atenolol. *Br J Clin Pharmacol* 1984; **18:** 773–8.
5. Allen PA, Taylor RT. Fenclofenac and thyroid function tests. *BMJ* 1980; **281:** 1642.
6. Richardson T, *et al.* Enhancement by sodium salicylate of the blood glucose lowering effect of chlorpropamide—drug interaction or summation of similar effects? *Br J Clin Pharmacol* 1986; **22:** 43–8.
7. Kubacka RT, *et al.* Effects of aspirin and ibuprofen on the pharmacokinetics and pharmacodynamics of glyburide in healthy subjects. *Ann Pharmacother* 1996; **30:** 20–6.
8. Sone H, *et al.* Ibuprofen-related hypoglycemia in a patient receiving sulfonylurea. *Ann Intern Med* 2001; **134:** 344.

Antibacterials. *Chloramphenicol* markedly inhibits the metabolism of tolbutamide and increases its half-life,[1] which can result in hypoglycaemia. Sulfonamides,[2] including *co-trimoxazole*,[3-5] may also enhance the hypoglycaemic effects of the sulfonylureas. There have been rare reports of elevated glibenclamide concentrations and hypoglycaemia when *ciprofloxacin* was given to patients who were on stable glibenclamide therapy.[6] For reports of hypoglycaemia when *gatifloxacin* was given to patients already receiving a sulfonylurea (glimepiride in one case, and glibenclamide plus pioglitazone in another), see p.281. There have also been a few cases of severe hypoglycaemia when *clarithromycin* was added to glibenclamide or glipizide; renal impairment may have played a role in these cases.[7] *Rifampicin* (and probably other rifamycins) can enhance the metabolism and decrease the effect of tolbutamide, chlorpropamide,[8,9] and glibenclamide[10] and dosage of the hypoglycaemic drug may need to be increased. The effects on glipizide[10] and glimepiride[11] appear to be less pronounced.

1. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
2. Soeldner JS, Steinke J. Hypoglycemia in tolbutamide-treated diabetes: report of two cases with measurement of serum insulin. *JAMA* 1965; **193:** 148–9.
3. Wing LMH, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; **20:** 482–5.
4. Johnson JF, Dobmeier ME. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. *DICP Ann Pharmacother* 1990; **24:** 250–1.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Roberge RJ, *et al.* Glyburide-ciprofloxacin interaction with resistant hypoglycemia. *Ann Emerg Med* 2000; **36:** 160–3.
7. Bussing R, Gende A. Severe hypoglycemia from clarithromycin-sulfonylurea drug interaction. *Diabetes Care* 2002; **25:** 1659–61.
8. Syvälahti EKG, *et al.* Rifampicin and drug metabolism. *Lancet* 1974; **ii:** 232–3.
9. Self TH, Morris T. Interaction of rifampin and chlorpropamide. *Chest* 1980; **77:** 800–1.
10. Niemi M, *et al.* Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clin Pharmacol Ther* 2001; **69:** 400–406.
11. Niemi M, *et al.* Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. *Br J Clin Pharmacol* 2000; **50:** 591–5.

Anticoagulants. *Dicoumarol* increases serum concentrations and therefore the hypoglycaemic effects of tolbutamide, and possibly chlorpropamide. In addition, sulfonylureas may affect anticoagulant function (p.1428).

Antiepileptics. For references to *phenytoin* toxicity when tolbutamide or tolazamide was given, see under Phenytoin p.498.

Antifungals. Increased plasma concentrations of tolbutamide have been reported when *fluconazole* was given,[1] but there was no evidence of hypoglycaemia, and no hypoglycaemic symptoms were seen in 29 women receiving gliclazide or glibenclamide who were given fluconazole or *clotrimazole* for vulvovaginitis.[2] A study in healthy subjects found that fluconazole increased plasma concentrations of glimepiride, but again there was no significant effect on glucose concentrations.[3] However, there are reports of hypoglycaemia in a patient who took fluconazole with glipizide,[4] and another who took fluconazole and co-trimoxazole with gliclazide.[5] Similar interactions have been reported for *ketoconazole* (with tolbutamide, in healthy subjects)[6] and *miconazole* (with tolbutamide, in a diabetic),[7] suggesting that such combinations should be regarded with caution.

1. Lazar JD, Wilner DK. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
2. Rowe BR, *et al.* Safety of fluconazole in women taking oral hypoglycaemic agents. *Lancet* 1992; **339:** 255–6.
3. Niemi M, *et al.* Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 2001; **69:** 194–200.
4. Fournier JP, *et al.* Coma hypoglycémique chez une patiente traitée par glipizide et fluconazole: une possible interaction? *Therapie* 1992; **47:** 446–7.
5. Abad S, *et al.* Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52:** 456–7.
6. Krishnaiah YSR, *et al.* Interaction between tolbutamide and ketoconazole in healthy subjects. *Br J Clin Pharmacol* 1994; **37:** 205–7.
7. Meurice JC, *et al.* Interaction miconazole et sulfamides hypoglycémiants. *Presse Med* 1983; **12:** 1670.

Ciclosporin. For the effect of glibenclamide on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p.1828.

Metformin. Results apparently suggesting increased mortality in patients who received intensive drug therapy with metformin and a sulfonylurea were reported by the UK Prospective Diabetes Study.[1] This was considered to be artefactual, since it was not confirmed by epidemiological analysis, and such combinations are widely used in practice, but some concern remains and further study is needed.

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65. Correction. *ibid.*; 1558.

Thyroid hormones. It has been suggested that starting thyroid replacement therapy may increase the requirement for insulin or oral antidiabetic drugs in diabetic patients, which would not seem unreasonable given the stimulant effects of thyroid hormones on metabolic function. For a discussion of the mooted effects of sulfonylureas on thyroid function, see under Precautions, above.

Pharmacokinetics

◊ Reviews.

1. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents: an update. *Clin Pharmacokinet* 1989; **16:** 100–28.
2. Marchetti P, *et al.* Pharmacokinetic optimisation of oral hypoglycaemic therapy. *Clin Pharmacokinet* 1991; **21:** 308–17.
3. Harrower AD. Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. *Clin Pharmacokinet* 1996; **31:** 111–19.

Uses and Administration

The sulfonylurea antidiabetics are a class of oral antidiabetic drugs used in the treatment of type 2 diabetes mellitus (p.431). They are given to supplement treatment by diet modification when such modification has not proved effective on its own, although metformin is preferred in patients who are obese.

Sulfonylureas appear to have several modes of action, apparently mediated by inhibition of ATP-sensitive potassium channels. Initially, secretion of insulin by functioning islet beta cells is increased. However, insulin secretion subsequently falls again but the hypoglycaemic effect persists and may be due to inhibition of hepatic glucose production and increased sensitivity to any available insulin; this may explain the observed clinical improvement in glycaemic control. The duration of action of sulfonylureas is variable; drugs such as tolbutamide are relatively short-acting (about 6 to 12 hours) while chlorpropamide has a prolonged action (over 24 hours).

Sulfonylurea therapy may be combined with metformin or other oral hypoglycaemics in patients who fail to respond to a single type of drug; such combination therapy is usually tried (in the absence of contra-indications) before considering the addition of, or transfer to, insulin therapy.

◊ Reviews.

1. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004; **64:** 1339–58.

Tolazamide *(BAN, USAN, rINN)*

NSC-70762; Tolatsamidi; Tolazamid; Tolazamida; Tolazamidum; U-17835. 1-(Perhydroazepin-1-yl)-3-tosylurea; 1-(Perhydroazepin-1-yl)-3-*p*-tolylsulphonylurea.

Толазамид

$C_{14}H_{21}N_3O_3S$ = 311.4.
CAS — 1156-19-0.
ATC — A10BB05.
ATC Vet — QA10BB05.

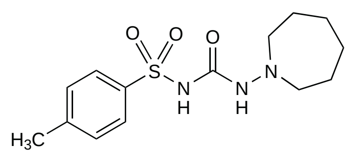

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Tolazamide). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

USP 31 (Tolazamide). A white or off-white crystalline powder, odourless or having a slight odour. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460.

Porphyria. Tolazamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Tolazamide is slowly absorbed from the gastrointestinal tract, peak plasma concentrations occurring 4 to 8 hours after a dose by mouth, and is extensively bound to plasma proteins. It has a half-life of about 7 hours. It is metabolised in the liver to metabolites with some hypoglycaemic activity. About 85% of an oral dose is excreted in the urine, chiefly as metabolites.

Uses and Administration

Tolazamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of at least 10 hours and sometimes up to 20 hours. The usual initial dose is 100 to 250 mg daily given as a single dose with breakfast. Dosage may be increased if necessary at weekly intervals by 100 to 250 mg, usually to a maximum of 1 g daily; no further benefit is likely to be gained with higher doses. Doses of more than 500 mg daily may be given in divided doses.

Preparations

BP 2008: Tolazamide Tablets;
USP 31: Tolazamide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Tolinase†.

Tolbutamide *(BAN, rINN)*

Butamidum; Tolbutamid; Tolbutamida; Tolbutamidas; Tolbutamidi; Tolbutamidum; Tolglybutamide. 1-Butyl-3-tosylurea; 1-Butyl-3-*p*-tolylsulphonylurea.

Тольбутамид

$C_{12}H_{18}N_2O_3S$ = 270.3.
CAS — 64-77-7 (tolbutamide); 473-41-6 (tolbutamide sodium).
ATC — A10BB03; V04CA01.
ATC Vet — QA10BB03; QV04CA01.

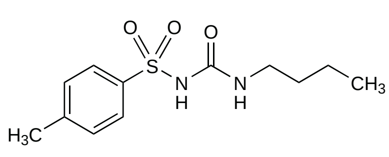

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Tolbutamide). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Tolbutamide). A white or practically white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol and in chloroform.

Adverse Effects, Treatment, and Precautions

As for sulfonylureas in general, p.460. Tolbutamide was implicated in the controversial reports of excess cardiovascular mortality associated with oral hypoglycaemic therapy (see under Sulfonylureas, Effects on the Cardiovascular System, p.461).

Thrombophlebitis with thrombosis has occurred after the intravenous injection of tolbutamide sodium, but this is usually painless and the vein gradually recovers. Rapid injection may cause a transient mild pain or sensation of heat in the vein.

The *BNF* has suggested that tolbutamide may be suitable for use in patients with renal impairment, but that careful monitoring of blood-glucose concentration is essential. UK licensed product information recommends that it should not be used in patients with severe renal impairment.

Breast feeding. Tolbutamide is distributed into breast milk in relatively low quantities.[1] The American Academy of Pediatrics[2] states that, although usually compatible with breast feeding, use of tolbutamide by breast-feeding mothers may possibly result in jaundice in the infant.

1. Moiel RH, Ryan JR. Tolbutamide orinase in human breast milk. *Clin Pediatr (Phila)* 1967; **6:** 480.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Porphyria. Tolbutamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for sulfonylureas in general, p.461.

Pharmacokinetics

Tolbutamide is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins; the half-life is generally within the range of 4 to 7 hours but may be considerably longer. Tolbutamide is metabolised in the liver by hydroxylation mediated by the cytochrome P450 isoenzyme CYP2C9. It is excreted in the urine chiefly as metabolites with little hypoglycaemic activity. Tolbutamide has been detected in breast milk.

Uses and Administration

Tolbutamide is a sulfonylurea antidiabetic (p.460). It is given orally in the treatment of type 2 diabetes mellitus (p.431) and has a duration of action of about 10 hours.

The usual initial dose in type 2 diabetes mellitus may range from 1 to 2 g daily, given either as a single dose with breakfast or, more usually, in divided doses. Maintenance doses usually range from 0.25 to 2 g daily. Although it is unlikely that the response will be improved by increasing the dose further, daily doses of 3 g have been given.

Tolbutamide sodium ($C_{12}H_{17}N_2NaO_3S$ = 292.3) has sometimes been used in the diagnosis of insulinoma as well as other pancreatic disorders including diabetes mellitus. The equivalent of 1 g of tolbutamide is given by intravenous injection as a 5% solution usually over 2 to 3 minutes. Tolbutamide sodium 1.08 g is equivalent to about 1 g of tolbutamide.

Diagnosis and testing. References.

1. McMahon MM, *et al.* Diagnostic interpretation of the intravenous tolbutamide test for insulinoma. *Mayo Clin Proc* 1989; **64:** 1481–8.
2. Marks V. Diagnosis and differential diagnosis of hypoglycemia. *Mayo Clin Proc* 1989; **64:** 1558–61.

Preparations

BP 2008: Tolbutamide Tablets;
USP 31: Tolbutamide for Injection; Tolbutamide Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Rastinon; ***Cz.:*** Dirastan; ***Denm.:*** Arcosal; ***Ger.:*** Orabet; ***Hong Kong:*** Diatol; ***Israel:*** Orsinon; ***Mex.:*** Artosin; Bioglusil†; Dabetil; Diatelan; Diaval; Flusan; Ifumelus†; Rastinon; ***NZ:*** Diatol; ***Pol.:*** Diabetol; ***S.Afr.:*** Tydadex; ***Singapore:*** Tolmide; ***USA:*** Orinase; Orinase Diagnostic.

Troglitazone *(BAN, USAN, rINN)*

CI-991; CS-045; GR-92132X; Troglitazona; Troglitazonum. (±)-*all-rac*-5-{*p*-[(6-Hydroxy-2,5,7,8-tetramethyl-2-chromanyl)methoxy]benzyl}-2,4-thiazolidinedione.

Троглитазон

$C_{24}H_{27}NO_5S$ = 441.5.
CAS — 97322-87-7.
ATC — A10BG01.
ATC Vet — QA10BG01.

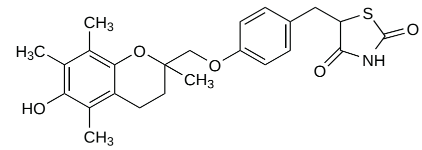

Adverse Effects and Precautions

Troglitazone has been associated with severe hepatic reactions, sometimes fatal, which has led to its withdrawal in most countries. Regular monitoring of liver function during therapy, and withdrawal of the drug in any patient who develops jaundice or signs of liver dysfunction, is required. It should not be given to patients with pre-existing moderate or severe elevations of liver enzyme values, or active liver disease. Increased plasma volume has been reported in healthy subjects given troglitazone: it should be used with caution in patients with heart failure. Other adverse effects reported in patients receiving troglitazone include dizziness, headache, fatigue, musculoskeletal pain, and nausea and vomiting. There is no evidence of hypoglycaemia associated with the use of troglitazone alone.

Effects on the liver. The UK CSM[1] was aware of over 130 cases of hepatic reactions to troglitazone worldwide as of December 1997, although only 1 had been in the UK. There had been 6 deaths. The average time to the onset of the reaction was 3 months, but the frequency of these reactions, and the existence of risk factors predisposing to them, were unclear. The manufacturers had voluntarily withdrawn the drug in the UK.

The US manufacturer and the FDA recommended[2] a schedule for routine monitoring of liver function in November 1997 and revised this again in December 1997. It was estimated that 2% of patients treated with troglitazone would have elevated liver enzyme values necessitating discontinuation of the drug. The FDA[3] had received 560 reports of troglitazone-associated hepatotoxicity by June 1998. There were 24 cases of hepatic failure which were likely to have been caused by the drug; 21 patients died and 3 patients received transplants. More intensive liver function monitoring recommendations were made by the US manufacturer again in July 1998 and in June 1999. Subsequently the manufacturer withdrew the drug in Australia, Japan, and the USA in March 2000. The clinical details of 94 cases of liver failure associated with troglitazone, which were reported to the FDA, have been reviewed.[4]

1. CSM/MCA. Troglitazone (Romozin) withdrawn. *Current Problems* 1997; **23:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 02/06/06)
2. Anonymous. Troglitazone and liver injury. *WHO Drug Inf* 1998; **12:** 13.
3. Misbin RI. Troglitazone-associated hepatic failure. *Ann Intern Med* 1999; **130:** 330.
4. Graham DJ, *et al.* Troglitazone-induced liver failure: a case study. *Am J Med* 2003; **114:** 299–306.

Interactions

Troglitazone may enhance the hypoglycaemic effects of sulfonylureas; dosage adjustment may be necessary. There is a possibility that troglitazone may enhance the metabolism of drugs metabolised by cytochrome P450 isoenzyme CYP3A4, including some oral contraceptives and terfenadine.

Ciclosporin. For the effect of troglitazone on blood concentrations of ciclosporin see Hypoglycaemic Drugs, p.1828.

Colestyramine. Colestyramine markedly impaired the absorption of troglitazone.[1]

1. Young MA, *et al.* Concomitant administration of cholestyramine influences the absorption of troglitazone. *Br J Clin Pharmacol* 1998; **45:** 37–40.

Pharmacokinetics

Troglitazone is rapidly absorbed after oral doses, with peak plasma concentrations 1 to 3 hours after a dose. Bioavailability is about 53%; absorption is markedly increased in the presence of food. In the body, troglitazone is more than 99% bound to plasma albumin. It is extensively metabolised in the liver and excreted largely in faeces as metabolites; small amounts of metabolites are excreted in urine. Plasma elimination half-life ranges from 10 to 39 hours.

◊ Reviews.

1. Loi C-M, *et al.* Clinical pharmacokinetics of troglitazone. *Clin Pharmacokinet* 1999; **37:** 91–104.

Uses and Administration

Troglitazone is a thiazolidinedione oral antidiabetic (see Rosiglitazone Maleate, p.458). It has been given orally for the treatment of type 2 diabetes mellitus (p.431) although as mentioned above it has been withdrawn in most countries owing to hepatotoxicity.

◊ Reviews.

1. Plosker GL, Faulds D. Troglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 1999; **57:** 409–38.
2. Parulkar AA, *et al.* Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134:** 61–71.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Rezulin†.

Vildagliptin *(rINN)*

LAF-237; NVP-LAF-237; Vildagliptina; Vildagliptine; Vildagliptinum. (2*S*)-{[(3-Hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile.

Вильдаглиптин

$C_{17}H_{25}N_3O_2$ = 303.4.
CAS — 274901-16-5.
ATC — A10BH02.
ATC Vet — QA10BH02.

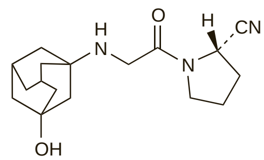

Profile

Vildagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4, an enzyme responsible, among other roles, for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1; insulinotropin), which plays a role in regulating insulin secretion. Vildagliptin is used in the treatment of type 2 diabetes mellitus (p.431); it may be added to metformin, a sulfonylurea, or a thiazolidinedione, when monotherapy with these is insufficient. It is given orally in a dose of 50 mg twice daily when given with metformin or a thiazolidinedione, and in a dose of 50 mg once daily in the morning when given with a sulfonylurea. A total daily dose of more than 100 mg of vildagliptin is not recommended, and in patients taking a combination of vildagliptin with a sulfonylurea, a dose of vildagliptin 100 mg daily is no more effective than vildagliptin 50 mg daily. Vildagliptin may be given with or without food.

Adverse effects of vildagliptin may include dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory-tract infection, and arthralgia. Rare cases of hepatic dysfunction, including hepatitis, have been reported. Vildagliptin should not be used in patients with hepatic impairment; liver function should be tested before starting the drug, and monitored during therapy (every 3 months in the first year and periodically thereafter). Vildagliptin should be stopped if there is a persistent increase of 3 or more times the upper limit of normal in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or if the patient develops jaundice or other signs of liver dysfunction; in such cases, it should not be restarted.

◊ Reviews.

1. Kleppinger EL, Helms K. The role of vildagliptin in the management of type 2 diabetes mellitus. *Ann Pharmacother* 2007; **41:** 824–32.
2. Henness S, Keam SJ. Vildagliptin. *Drugs* 2006; **66:** 1989–2001.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Galvus; ***Fr.:*** Galvus; ***Port.:*** Galvus; ***UK:*** Galvus.

Multi-ingredient: ***Cz.:*** Eucreas; ***Fr.:*** Eucreas; ***UK:*** Eucreas.

Voglibose *(USAN, rINN)*

A-71100; AO-128; Voglibosa; Voglibosum. 3,4-Dideoxy-4-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-2-*C*-(hydroxymethyl)-*D*-epi-inositol.

Воглибоза

$C_{10}H_{21}NO_7$ = 267.3.
CAS — 83480-29-9.
ATC — A10BF03.
ATC Vet — QA10BF03.

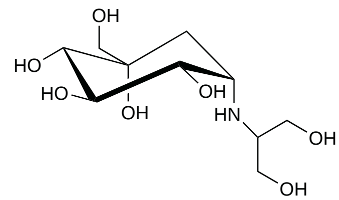

Pharmacopoeias. In *Jpn.*

Profile

Voglibose is an alpha-glucosidase inhibitor with general properties similar to those of acarbose (p.436). It is used in the treatment of diabetes mellitus (p.431) in oral doses of 200 to 300 micrograms three times daily before meals.

Hepatic encephalopathy. Voglibose has been investigated[1] in the management of hepatic encephalopathy (p.1697).

1. Uribe M, *et al.* Beneficial effect of carbohydrate maldigestion induced by a disaccharidase inhibitor (AO-128) in the treatment of chronic portal systemic encephalopathy: a double-blind, randomized controlled trial. *Scand J Gastroenterol* 1998; **33:** 1099–1106.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Basen; ***Philipp.:*** Basen; ***Thai.:*** Basen.

Antiepileptics

Epilepsy, p.465
Epilepsy and breast feeding, p.467
Epilepsy, cognition, and mood, p.468
Epilepsy and driving, p.468
Epilepsy and pregnancy, p.468
Status epilepticus, p.469
Other convulsive disorders, p.470
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Febrile convulsions, p.470
Myoclonus, p.470
Neonatal seizures, p.471
Porphyria, p.471

This chapter describes drugs whose chief use is in the management of epilepsy, status epilepticus, and other convulsive disorders.

Epilepsy

Epilepsy is a common neurological disorder. An individual's lifetime risk of developing epilepsy is between 3 and 5%; neonates, children, and the elderly are at the highest risk of developing the disorder.

Definitions and classification. An epileptic seizure has been defined as a paroxysmal discharge of cerebral neurones accompanied by clinical phenomena apparent to the patient or to an observer. The phenomena can be motor, sensory, or autonomic and there may also be impairment or complete loss of consciousness. Motor disturbances may include convulsions—which are involuntary, violent, and spasmodic—or prolonged contraction of skeletal muscles. The word 'fit' is often used colloquially to describe an epileptic seizure. Epilepsy is defined as a condition characterised by a recurrence of such seizures. A patient should not be described as having epilepsy until a second non-febrile seizure occurs.

The following is a broad account of the classification of seizures, epilepsies, and epileptic syndromes based on the views of the International League Against Epilepsy (ILAE) in 1981[1] and 1989.[2] A later proposed revision of the classification[3] does not yet seem to have been widely adopted.

- **Partial seizures** or **focal seizures** (localisation-related seizures) are epileptic seizures in which the initial neuronal discharges are localised in one area of the brain. The phenomena associated with such a seizure depend on the site of origin of the discharge. If there is no loss of consciousness, the seizure has been known as a *simple partial seizure* and includes Jacksonian epilepsy, which may be associated with motor or sensory disturbances. If there is impaired consciousness the seizure has been referred to as a *complex partial seizure*. Partial seizures were formerly referred to as psychomotor epilepsy or temporal lobe epilepsy, but the terms are not synonymous and should be avoided. Partial seizures may become *secondarily generalised seizures* if the neuronal discharge spreads to involve the entire brain
- **Generalised seizures** are characterised by neuronal discharges involving both cerebral hemispheres simultaneously from the outset. Subclassifications are based on the presence or absence of different types of convulsions.

  Absences (petit mal) are generalised seizures, usually occurring in children, characterised by a sudden loss of consciousness lasting for a few seconds. There is usually accompanying motor activity which may vary in degree from eyelid blinking to more extensive clonic body movements. *Atypical absence seizures* are those with a slower onset and longer duration.

  Myoclonic seizures are epileptic seizures in which the motor manifestation is myoclonus (see below).

  Clonic seizures are characterised by loss of consciousness, autonomic symptoms, and rhythmic clonic contractions of all muscles.

  Tonic seizures are also associated with loss of consciousness and autonomic symptoms accompanied by tonic contractions of the limbs. *Tonic-clonic seizures* (grand mal) are characterised by disordered contraction of muscles. During the tonic phase, all the muscles go into spasm followed up to a minute later by rhythmic clonic contractions. Finally, the patient enters a deep stupor followed by a period of confusion as consciousness is regained.

  Atonic seizures are characterised by loss of postural tone; the head sags or the patient falls down.

Within the categories of partial and generalised epilepsies, seizures have also been classified as **idiopathic, symptomatic** (in which the seizures are associated with diagnosable underlying disorders), or **cryptogenic** or **probably symptomatic** (in which the epilepsies are known or suspected to be symptomatic but the cause is not clear).

Partial **syndromes** include Rolandic and occipital epilepsies (both idiopathic), while generalised idiopathic syndromes include childhood absence epilepsies, juvenile myoclonic epilepsy, and the cryptogenic or symptomatic generalised syndromes include infantile spasms (as for example in West's syndrome), Lennox-Gastaut syndrome, and epilepsy with myoclonic absences. A third unclassified category covers undetermined epilepsies and epileptic syndromes. **Special syndromes** include conditions such as febrile convulsions (see below) in which seizures are related to specific situations.

It has been suggested that classification based on seizure type is the most useful in choice of antiepileptic drug whereas the syndrome classification has more benefits in deciding an overall therapeutic strategy and assessing long-term prognosis.

Status epilepticus has previously been defined as a seizure lasting more than 30 minutes or several distinct episodes without restoration of consciousness in between (but see below).

Other convulsive disorders include alcohol withdrawal syndrome, eclampsia and pre-eclampsia, myoclonus, neonatal seizures, and porphyria, and are discussed below.

Starting antiepileptic therapy. A single seizure does not constitute epilepsy and therefore does not necessarily warrant immediate treatment with antiepileptics. The decision to start antiepileptic therapy should be based on whether the risks of further seizures outweigh the risks of treatment.

- Starting antiepileptic therapy *too early* means that the patient may be unnecessarily exposed to the adverse effects of the drugs used, and may have social implications if erroneously diagnosed, such as the loss of a patient's driving licence
- However, the implications of *delaying* treatment must also be considered. Although there has long been concern that seizures may damage the brain and intellectual capabilities, or even cause death, there are insufficient data to support these claims. Status epilepticus, rather than individual or frequent seizures, may be the factor associated with brain injury or death, but the risks of a newly diagnosed epileptic patient developing status epilepticus are unknown. The most compelling reasons for treatment are risk of personal injury or causing injury to others during a seizure, and the psychosocial consequences of untreated epilepsy such as low self-esteem, anxiety, and domestic and employment difficulties

There has been a long-held belief that seizures beget seizures. This is not necessarily borne out by epidemiological studies,[4] and there is evidence in children[5] and adults[6] that the risk of recurrence after a first unprovoked seizure may be 50% or less. Furthermore, a decelerating disease process with successively longer intervals between seizures has been shown[7] in untreated children with newly diagnosed tonic-clonic seizures followed up for 2 years. Results from another study[8] suggested that seizure control or the prospects for and success of eventual withdrawal of therapy is little influenced by the number of pretreatment seizures up to 10 seizures; above this number there was a reduced chance of completely controlling seizures. Similarly, although patients treated immediately after a first seizure have a lower 2-year risk of recurrence than patients whose treatment is deferred, immediate treatment does not affect the probability of achieving longer-term seizure control.[6,9,10]

However, epilepsy is a heterogeneous disorder and there is some experimental evidence[11] that certain seizure types can have a detrimental effect on prognosis. Differences in reported risks in seizure recurrence may be attributable to differences in methodology as well as different important risk factors in the populations studied; also, few studies have followed up patients for more than 2 to 4 years.

Whether antiepileptic therapy should be started early to improve prognosis or delayed or avoided altogether therefore remains contentious.[12-14] Some neurologists do not advise treatment of a first seizure but prefer to wait for evidence of recurrence unless clinical features such as more than one seizure type or a neurological deficit predispose to poor seizure control. However, a first non-convulsive seizure may go undetected.[14] Furthermore, as single partial seizures appear to occur less frequently than single generalised tonic-clonic seizures, many neurologists assume that the first detected attack of a non-convulsive seizure is in fact one of multiple seizures and begin treatment. UK guidelines[15,16] suggest that antiepileptic therapy should be offered to patients after a first tonic-clonic seizure if a previous myoclonic, absence, or partial seizure has occurred, if the EEG shows unequivocal epileptic discharges, if congenital neurological deficits are present, or if the risk of recurrence is unacceptable to the patient.

Choice of antiepileptic. Once a decision to treat has been made, the choice of antiepileptic is determined mainly by its effectiveness against the type of seizures experienced and its potential adverse effects.[15-28]

In recent years many newer drugs have been licensed and added to the classical treatments for epilepsy. The role of these drugs relative to the classical agents is only slowly becoming established, and evidence of relative efficacy on which to base a choice is limited. Many new drugs have been promoted on the basis of superior tolerance and quality of life for epileptic patients, but even this is not always well established, and will, in any case, vary from patient to patient, as individuals will differ in the symptoms they find intolerable. In consequence, guidelines have often reserved their use for situations in which the older drugs are less suitable.

Certain principles of management are, however, well established.

- monotherapy is preferable to a multiple-drug regimen and treatment is therefore begun with a single drug, increasing the dose gradually until seizures are brought under control or adverse effects become unacceptable
- if treatment with the first drug fails, it is preferable to try alternative single first-line antiepileptics before giving combinations of drugs. It has been suggested that for practical purposes a patient should be considered to have refractory epilepsy if seizure control is not obtained with consecutive trials of 2 well tolerated antiepileptics[26]
- the change-over from one antiepileptic to another should be made cautiously, withdrawing the first drug only when the new regimen has been largely established
- if combinations are necessary in intractable cases, regimens should avoid the inclusion, where possible, of sedating drugs such as the barbiturates or benzodiazepines
- drugs with different modes of action should be selected for combined therapy, to reduce the risk that adverse effects will be additive
- many antiepileptics interact with each other through complex mechanisms and dosage adjustments may be necessary to maintain plasma concentrations within the therapeutic range; plasma monitoring may be advisable with combination therapy. (UK guidelines[16] recommend regular monitoring of antiepileptic drug concentrations only when clinically indicated, e.g. to manage pharmacokinetic interactions, or in cases of suspected toxicity or non-adherence)
- if trials of combination therapy do not produce worthwhile benefits, treatment should revert to the regimen (monotherapy or combination) that has provided the most acceptable balance of seizure control and adverse effects

Around 60% of patients with newly diagnosed epilepsy will respond to monotherapy with the first- or second-choice antiepileptic without developing intolerable adverse effects. The remaining 30 to 40% will have epilepsy that is difficult to control from the start, although some of these patients will respond to combination therapy.[26] Patients who fail to respond to adequate medical treatment may be considered for resective surgery; vagus nerve stimulation by means of an implanted device has also proved effective in those with severe intractable epilepsy who experience an aura before the onset of a seizure.[17,18] UK guidelines recommend consideration of the adjunctive use of vagus nerve stimulation in patients refractory to drug therapy but unsuitable for resective surgery.[15,16]

Partial seizures with or without **secondary generalisation** may be treated with *carbamazepine* or *valproate*, or with the newer drugs *lamotrigine* or *oxcarbazepine*.[15,16,29] *Topiramate* is also used, as monotherapy or as an adjunct to other treatments (in the UK, it is considered a first-line option in some circumstances[16,22]). Other second-line drugs are *phenytoin*, *clobazam*, or the newer antiepileptics *gabapentin*, *levetiracetam*, *tiagabine*, or *zonisamide*,[16,23,29] but whether these are recommended for monotherapy or adjunctive treatment may vary from country to country. Other drugs that have been used[16] include *acetazolamide*, *clonazepam*, and the barbiturates *phenobarbital* or *primidone*, although the latter in particular are little used now because of the problems of sedation. *Vigabatrin* is licensed in the UK for adjunctive use in patients in whom all other combinations have failed.

The response rate is somewhat lower for partial seizures than for tonic-clonic seizures associated with primary generalised epilepsy (see below). There is some evidence in favour of carbamazepine rather than valproate in the treatment of partial seizures.[30] More recently, some evidence was found in favour of lamotrigine rather than carbamazepine,[31,32] and of oxcarbazepine rather than phenytoin,[33] in terms of tolerability and time to treatment failure. However, there is no evidence of any significant difference between phenytoin and carbamazepine[34] or valproate[35] in partial seizures.

Calcium-channel blockers such as *flunarizine* have been studied with equivocal results in patients with refractory epilepsy, particularly those with partial seizures.[36]

The drugs used most often to treat **generalised** tonic-clonic seizures are *carbamazepine*, *lamotrigine*, or *valproate*. For tonic-clonic seizures as part of the syndrome of primary generalised epilepsy, valproate is the drug of choice, although systematic reviews were unable to establish evidence for this.[30,35] *Topiramate* is also considered a first choice in patients in whom the other older drugs are unsuitable or ineffective.[16,22] More recently, valproate was found to be better tolerated than topiramate and more effective than lamotrigine in generalised and unclassified epilepsy.[37] Second-line drugs in UK guidelines are *clobazam*, *levetiracetam*, and *oxcarbazepine*, while other drugs that may be considered include *acetazolamide*, *clonazepam*, *phenobarbital*, *phenytoin*, or *primidone*.[16] *Tiagabine* or *vigabatrin* should be avoided as they may worsen the seizures.[16]

The drugs of choice for **absence seizures** are *ethosuximide*, *valproate*, or, where these are unsuitable, *lamotrigine*,[16,23,38] although the evidence base to support this use is weak.[39] Second-choice drugs include *clobazam*, *clonazepam*, and *topiramate*, but *carbamazepine*, *gabapentin*, *oxcarbazepine*, *phenytoin*, *tiagabine*, and *vigabatrin* should be avoided as they may worsen seizures.[16,38] Since absence seizures occur primarily in children the precautions concerning valproate hepatotoxicity apply. However, where absence seizures are associated with tonic-clonic seizures valproate is the drug of choice since it is effective in both conditions; valproate is also preferred for atypical absence seizures. *Levetiracetam* may be used as an alternative for the syndrome of juvenile absence epilepsy.[16]

Valproate is normally the drug of choice for **myoclonic seizures**, including those associated with juvenile myoclonic epilepsy.[40,41] *Lamotrigine* may also be used in juvenile myoclonic epilepsy,[16,41] although some forms of myoclonus may be exacerbated;[16,40] *topiramate* may be considered, particularly for severe myoclonic epilepsy of infancy (in which *stiripentol* may also be effective), and second-line drugs also include *clobazam* and *clonazepam*, and adjunctive *levetiracetam* or *piracetam*.[16] *Zonisamide*[41] has also been used, as has *ethosuximide*.

The classical antiepileptics may not be particularly effective for **atonic** or **tonic** seizures, which are often associated with specific epileptic syndromes or with cerebral damage or mental retardation. UK guidelines suggest *valproate* or *lamotrigine* as first-line drugs; *clobazam*, *clonazepam*, *levetiracetam*, or *topiramate* are possible second-line drugs, and others that have been tried include *acetazolamide* and the barbiturates such as *phenobarbital*, while *phenytoin* may be considered for tonic seizures.[16]

In **catamenial epilepsy** (epilepsy associated with menstruation) seizures can be predicted and intermittent therapy with *clobazam* may be useful. Hormonal manipulation has also been tried using *progestogens*, *gonadorelin analogues*, and *clomifene*.[42]

The **Lennox-Gastaut syndrome** begins in early childhood and is particularly difficult to treat because multiple seizure types co-exist; seizures rarely remit entirely. *Valproate* is most frequently used[43] because of its broad spectrum of activity; UK guidelines consider *lamotrigine* or *topiramate* as alternative first-line drugs if valproate is unsuitable; second-line choices include *clobazam*, *clonazepam*, *ethosuximide*, or *levetiracetam*.[16] *Felbamate* has also been used. The optimum treatment remains uncertain, but monotherapy with any drug has not been shown to be particularly effective.[44]

The classical antiepileptics are often ineffective in **infantile spasms** (as for example in **West's syndrome**).[45] UK guidelines recommend treatment with *corticotropin* or a *corticosteroid*, or else with *vigabatrin*;[16] in the USA, however, the American Academy of Neurology considers that the evidence does not support the use of corticosteroids, although corticotropin or vigabatrin appear to be of benefit.[46] *Vigabatrin* is effective either as adjunctive treatment or monotherapy. Many consider that, despite the risk of visual field defects,[47] it should replace corticotropin or corticosteroids as the treatment of choice,[48-54] although others disagree.[55,56] However, vigabatrin may offer the best first option in the treatment of infantile spasms due to tuberous sclerosis.[54,57,58] In some countries, *valproate*, alone or with *clonazepam* and/or *pyridoxine*, has been tried for initial management of infantile spasms.[59] Other second-line drugs include *clobazam* and *topiramate*;[16] *nitrazepam*,[16,48] *felbamate*,[45,60] and *lamotrigine*[45,60] have also been used. It is unclear to what extent treatment improves long-term outcome.[38,46,58]

Choice of antiepileptics in children. The use of antiepileptics in general in children has been reviewed.[38,60-67] Again, appropriate treatment depends on seizure type, but there is a lack of evidence to support many therapeutic choices,[62,67-69] in part because of the difficulties in undertaking studies in this population. In addition, children may be particularly susceptible to some adverse effects, including effects on behaviour, cognition, and development; behavioural problems have been associated particularly with phenobarbital.[67,70] Nonetheless the principles of pharmacological management are similar to those in adults (above) although UK guidelines recommend that treatment should only be begun by a specialist.[16] Dietary modification (the ketogenic diet) may also be tried.[67,71-74]

Withdrawal of antiepileptic therapy. Concern over the potential adverse effects of antiepileptic therapy clearly makes withdrawal attractive in patients who achieve prolonged seizure-free periods; however, the practical and social consequences of seizure recurrence may be considerable (for example, loss of driving licence and restricted employment prospects). The incidence of relapse after withdrawal has been variously estimated to range from 12% to over 60%.[75,76] Many studies have been carried out in children; data in adults is more scanty and given the differences between the populations, extrapolation of results in children to adults may be invalid.[75] A meta-analysis[77] that included 25 studies and 5354 patients (children and adults) found the overall rate of relapse in seizure-free patients after stopping antiepileptic therapy was 25% at 1 year and 29% at 2 years. There was a higher risk for relapse in adolescent- and adult-onset epilepsy compared with childhood-onset epilepsy. A more recent longitudinal population-based study[78] following 148 patients long-term from the onset of epilepsy in childhood found that of 90 patients in whom antiepileptic therapy was stopped, 33 relapsed and although in most cases relapse took place within 3 years, in one case it occurred 28 years after withdrawal.

Although these findings indicate that it is often possible to withdraw therapy successfully, it is more difficult to offer an individual *prognosis*. It has been suggested that adult patients whose livelihood or lifestyle depends on being seizure-free would be generally ill advised to contemplate drug withdrawal.[79] Several strategies for predicting the likely outcome after withdrawal of antiepileptic therapy in individuals have been published.[80-82] Recognising that epilepsy is a heterogeneous disorder, scoring systems to allow for various risk factors have been devised.[80,81]

Prognostic risk factors (some of which are likely to be surrogate measures for the underlying condition) may include:

- the *aetiology* of the condition.[75,83] Patients classified as having symptomatic or cryptogenic epilepsy generally fare less well than those with idiopathic epilepsy with regard to seizure control, and withdrawal is less likely to be successful
- the *seizure type* and *syndrome*.[75,76,83] A number of studies have identified an increased risk of relapse in patients with particular seizure types; in particular, patients with partial, generalised tonic-clonic, and mixed seizure types seem to be at increased risk. However, it has been pointed out that increased risk has been associated with almost all seizure types other than generalised absence seizures, which seem to have a favourable prognosis; the context in which the seizure arises, such as the associated epilepsy syndrome and the aetiology, is more important than the type alone when considering withdrawal.[75] Examples of syndromes associated with a favourable outcome for withdrawal include benign childhood epilepsy with centrotemporal spikes, childhood absence epilepsy, and benign neonatal convulsions. However, withdrawal is inappropriate in juvenile myoclonic epilepsy, despite its good response to treatment, as relapse occurs in over 90% of patients
- the presence of accompanying *neurological* or *mental deficits*.[75] Some studies have suggested that mental retardation or other neurological deficits are associated with a poorer prognosis on withdrawal; these are probably surrogate markers for symptomatic epilepsy. However, mental retardation is not a contra-indication to withdrawal, and these patients may benefit from the elimination of any sedative effects if other risk factors are absent[75]
- the *age at onset*.[75,76,83] Several studies have identified a markedly increased risk of relapse on withdrawal in patients with seizure onset in adolescence or adulthood, whereas those with onset before 10 to 12 years of age have a generally more favourable prognosis. This is probably a surrogate marker for particular epileptic syndromes or aetiologies
- the *duration of remission*.[75,76,83,84] There is evidence in children that waiting for at least 2 seizure-free years before attempting withdrawal is associated with less risk of relapse than doing so earlier. However, the 2-year period was chosen arbitrarily, and the true optimum timing is unknown.[84] There is little evidence to guide the timing of withdrawal in adults.[84] However, in practice most support a requirement of at least 2 years free from seizures before drug withdrawal[75,76,83]
- the *response to therapy*.[75] Refractory epilepsy, as indicated by the occurrence of seizures once therapy has been begun, or the need for adjunctive or combination therapy to control seizures, is a poor prognostic sign for withdrawal. Patients with a history of multiple seizures before beginning therapy are also at increased risk on withdrawal

There is less agreement about the prognostic significance of some other factors:

- it is unclear whether the *type of drug* used to control seizures affects the risk of recurrence on withdrawal. It has been suggested that patients taking phenobarbital or benzodiazepines may be at increased risk of relapse, but there is little supportive evidence.[75] A poorer prognosis for patients taking valproate has also been reported;[85] a study in patients given combination therapy noted an increased risk when the carbamazepine component of the regimen was withdrawn.[86] It should be borne in mind that withdrawal of an enzyme-inducing antiepileptic may alter the serum concentrations of other drugs in the regimen[87]
- there is also controversy about the prognostic value of the *EEG* for the success of withdrawal.[75-77,83] Although an abnormal EEG before withdrawal was a negative prognostic factor in many studies, EEG abnormalities are not present in all epileptic patients, and some antiepileptic drugs suppress EEG abnormalities and can lead to false-negative results[75]

When a decision to withdraw is made, it is agreed that the *withdrawal regimen* should be gradual to reduce the risk of provoking withdrawal seizures. Drugs should be withdrawn one at a time but there is no agreement on the order or the optimum rate of withdrawal for individual drugs. It has been suggested that tapering therapy over less than 6 months increases the relapse rate.[75] However, one study in children indicated no significant difference in seizure recurrence rate when various antiepileptics, including barbiturates, were withdrawn over 6 weeks or 9 months.[88] Nonetheless, it has been pointed out that relapses tended to occur earlier in the group tapered more rapidly, and in practice it is rarely necessary to withdraw medication more rapidly than over a 6-month period.[75] It may be possible to withdraw phenytoin or valproate quickly (over a few days in hospital) if necessary.

If seizures recur on withdrawal it is almost always possible to restore good control by *re-instituting therapy*, and morbidity, mortality, and incidence of status epilepticus are reported to be low in the setting of prescribed antiepileptic drug withdrawal.[75] However, in a very small number of patients intractable seizures may develop.[89]

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Epilepsy and breast feeding. Antiepileptics are generally distributed into breast milk (although this information is not always known for the newer ones), but for most of the older established drugs, the concentrations are lower than in maternal plasma, and breast feeding is considered to be safe for these antiepileptics when given in usual doses.[1-9] The American Academy of Pediatrics[10] also considers that most of the older antiepileptics, specifically *carbamazepine*, *ethosuximide*, *phenytoin*, and *valproate*, are usually compatible with breast feeding; however, they also recommend that *phenobarbital* and *primidone* should be used with caution as significant adverse effects have occurred in nursing infants. Problems of neonatal sedation may occur with the *benzodiazepines* and *barbiturates* (including primidone).[1] Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. There is little data for the new antiepileptics regarding breast feeding (the manufacturers and the UK Drugs in Lactation Advisory Service[11] generally recommend that breast feeding should be avoided). *Lamotrigine* may accumulate in breast-fed infants, as the metabolic pathway for lamotrigine may not be fully developed in newborns;[5,12] the American Academy of Pediatrics[10] considers that the use of lamotrigine during breast feeding may be of concern. *Gabapentin*,[13] *levetiracetam*,[14] and *topiramate*[15] are transferred into breast milk in significant amounts, but serum concentrations in breast-fed infants are very low.

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Epilepsy, cognition, and mood. Patients with epilepsy are at increased risk of **cognitive** and **behavioural** deficits. These are often multifactorial in origin: the disease itself and its underlying pathology, psychosocial and environmental factors, and the effects of antiepileptic treatment may all play a role.[1-8] Children are particularly vulnerable: recurrent seizures in the immature brain appear to have an adverse effect on the development of brain structure and function;[8] furthermore, behavioural and cognitive deficits may not be detected for a long time, while imposing detrimental effects on development and learning.[4,6] Because of the multifactorial nature of the problem, and the difficulties of assessing often subtle changes in cognition, it has proved difficult to study appropriately, and evidence is often scanty. Many studies have been small, and have had methodological flaws.[4,6] In addition, there is a need for studies in patient populations at greater risk, such as children.[5,6]

There is particular interest in assessing the risks associated with antiepileptic treatment, since it is perhaps the most readily modifiable factor. Strategies such as avoiding unnecessary polytherapy, using the lowest effective dose of an antiepileptic, keeping drug concentrations in therapeutic ranges, and slow titration when doses are increased, have been associated with fewer cognitive adverse effects. However, it should also be borne in mind that appropriate treatment and good seizure control may offset the negative cognitive effects.[4] (There is an interesting suggestion that suppression of interictal discharges in the EEG with lamotrigine may be associated with an improvement in behaviour in children with epilepsy and behavioural problems.[9])

The most common cognitive effects seem to be sedation, somnolence, distractibility, memory impairment, insomnia, and dizziness; adult patients often experience depression (below), whereas in children hyperactivity and aggression may occur.[5] More subtle effects on cognitive function and neuropsychological variables also occur. It has proved difficult, for the reasons mentioned above, to establish the comparative severity of cognitive effects between different antiepileptics. However, it seems to be generally agreed that barbiturate antiepileptics such as *phenobarbital*, and (particularly in the elderly) benzodiazepines such as *clobazam* and *clonazepam*, have the worst profiles, including decreased arousal and deterioration in most areas of cognitive performance;[4] in children, phenobarbital may decrease IQ and impair academic achievement.[5-7] Other standard antiepileptics such as *phenytoin*, *carbamazepine*, and *valproate* seem to have more modest, and broadly comparable, effects.[2,4-6] Most of the newer antiepileptics appear to be better tolerated; however, *topiramate*, and to some extent *zonisamide*, do produce impairment. There is also limited evidence that *gabapentin*, *lamotrigine*, and *vigabatrin* may enhance cognitive function. However, further data are required for the newer antiepileptics before a definitive assessment can be made.[1-7]

In view of the potential effect of antiepileptics on cognition, the recommendations of the Committee on Drugs of the American Academy of Pediatrics[10] include:

- the relative influence of each antiepileptic on cognitive and behavioural function should be considered along with all other potential adverse effects
- the child's behaviour and academic progress should be monitored through routine questioning of parents and teachers as well as by the physician's own observations of cognitive function, mood, and behaviour
- should behavioural or cognitive changes occur in relation to starting antiepileptic therapy, the need for medication and/or possible alteration of medication must be reassessed

For comment on the potential effects of maternal antiepileptic therapy on fetal neurodevelopment, see Epilepsy and Pregnancy, below.

Epilepsy is also associated with a greater prevalence of mood disorders, particularly **depression**, than is seen in the general population.[11-14] There have been concerns that antiepileptic drugs may play a significant role in exacerbating these. A review[15] has suggested that the commoner antiepileptics could be classified by the risk of associated depression as follows:

- highest risk (about 10% of patients):
  - barbiturate antiepileptics such as phenobarbital
  - topiramate
  - vigabatrin
  - zonisamide (associated with mood disorders in about 7% of those taking high doses)
- intermediate risk (4% or less):
  - felbamate
  - levetiracetam
  - tiagabine
- lower risk (less than 1%; some might actually have positive effects on mood):
  - carbamazepine
  - ethosuximide
  - gabapentin
  - lamotrigine
  - oxcarbazepine
  - phenytoin
  - pregabalin
  - valproate

In January 2008, the FDA issued an alert[16] after analysis of 199 placebo-controlled studies of antiepileptic drugs in the management of not only epilepsy but also psychiatric disorders (including bipolar disorder and depression) and other conditions such as migraine and neuropathic pain. This analysis, which involved 27 863 drug-treated patients and 16 029 controls, found that the risk of suicidal ideation or behaviour was about twice as great in the drug treatment groups (0.43%) as in those given placebo (0.22%). The relative risk was greater in patients with epilepsy than in those with other disorders. Drugs implicated by this analysis were carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. However, the FDA considered that the increased risk was a class effect that would be shared by *all* antiepileptics. It was recommended that prescribers and patients and their families should be aware of the risk, and should be alert for behavioural changes and other warning signs that might signal suicidal ideation. Similar advice has been issued in the EU.[17]

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Epilepsy and driving. Driving by patients with epilepsy is generally regulated[1,2] and restricted to those whose seizures are adequately controlled. Also, antiepileptic drugs may produce CNS-related adverse effects, including dizziness and drowsiness, that could impair a patient's ability to drive a vehicle or operate machinery, particularly during the initial stages of therapy.

In the UK,[3] patients suffering from epilepsy may drive a motor vehicle (but not a heavy goods or public service vehicle) provided that they have had a seizure-free period of 1 year, or, if subject to attacks only while asleep, have established a 3-year period without awake attacks. It is recommended that patients should not drive during withdrawal of antiepileptic drugs, or for 6 months afterwards.

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Epilepsy and pregnancy. The management of epilepsy during pregnancy may present problems for both the mother and the fetus.[1-9]

The outcome of pregnancy in women with epilepsy is generally recognised to be poorer than that in the general population. Still-births and neonatal loss are increased, and maternal deaths are more common;[5,7] there is also an increased incidence of preterm delivery and low birth-weight at term.[6] In addition, there is a clearly increased risk of fetal malformation. The factors responsible for this poorer outcome are complex, and may include the disease itself, seizure frequency during pregnancy, and socio-economic factors, as well as the effects of antiepileptic drugs.[1-3,5-7,10-12]

A single generalised seizure does not usually pose clinical problems for the fetus, but both mother and fetus are at risk of serious trauma from maternal falls, and intra-uterine deaths have been reported. It is widely considered that status epilepticus is associated with significant mortality in mother and fetus.

The frequency of seizures may increase during pregnancy in some women; this might be related to hormonal or other factors such as lack of sleep, but one of the main reasons is likely to be decreased plasma-antiepileptic concentrations due to changes in drug clearance and binding as pregnancy progresses (and some[13,14] have recommended therapeutic drug monitoring in at-risk patients). However, analysis[15] of 1956 pregnancies of 1882 epileptic women recorded in an international antiepileptic drugs and pregnancy registry (EURAP) found that 58.3% were seizure-free throughout pregnancy. Seizures occurred during delivery in 3.5%, most commonly in those who had seizures earlier during pregnancy, and status epilepticus occurred in 1.8%, with one case of still-birth and none of miscarriage or maternal mortality. The authors noted that publication bias favoured the reporting of adverse outcomes in pregnancy.

As with many other aspects of epilepsy, it is difficult to disentangle the potential adverse effects of therapy from those of the disease. However, although the risk of **major malformations** such as congenital heart defects, neural tube defects, urogenital defects, and orofacial clefts is somewhat increased in offspring of all women with epilepsy,[3,7] there is clear evidence that in children of women treated with antiepileptic drugs it is 2 to 3 times that in the general population, and the risk is higher in women taking multiple drugs or in those who take antiepileptics during the first trimester.[7]

Despite this, evidence linking specific drugs with particular patterns of malformation is limited and often unclear. There appears to be strong evidence for a dose-related increased risk of major malformation with *valproate*,[7,10-12,16-20] and increased risk has been reported for *carbamazepine*, *phenobarbital*, and *primidone*.[7,10,11] The rate of major abnormality with *phenytoin* does not seem to be higher than in the general population.[7] However, a well established **fetal antiepileptic syndrome** (FAS) has been reported with phenytoin, as with other antiepileptic drugs,[6] including some older drugs such as *trimethadione*. Although early reports associated syndromes with specific drugs, such as fetal hydantoin syndrome (phenytoin), or fetal valproate syndrome, there is considerable overlap in the reported effects and recent reviews consider these as manifestations of a single condition, FAS.[6,11] The dysmorphic facial changes characteristic of FAS can be quite subtle, and may become less apparent as the child grows.[7]

Evidence for any effect of the newer antiepileptics on the fetus is particularly scanty. It is unclear if *oxcarbazepine* is associated with an increased risk in major malformation,[7] and limited data have not so far suggested a significant increase in risk with *lamotrigine*[11,19,21] and *levetiracetam*.[22] There are reports suggestive of an increased risk with *topiramate*[7] and licensed product information for this drug, and also *pregabalin* and *zonisamide* advises against use in pregnancy on the basis of animal studies and lack of human data. Caution is also advised with *tiagabine* and *vigabatrin*. There appears to be little evidence of teratogenic potential for *felbamate* or *gabapentin* in *animal* studies to date, although cases of malformation have been seen in pregnancies exposed to gabapentin.[7]

In a study[23] of the UK Epilepsy and Pregnancy Register, which examined the outcome of 3607 pregnancies in mothers with epilepsy, the overall rate of major congenital malformations was 3.5% in those untreated with antiepileptics and 4.2% in those given antiepileptics during pregnancy, with rates of 3.7% and 6.0% in those given monotherapy or polytherapy respectively. For monotherapy the malformation rates for individual drugs were topiramate (7.1%), valproate (6.2%), phenytoin (3.7%), gabapentin (3.2%), lamotrigine (3.2%), and carbamazepine (2.2%). For polytherapy, those regimens containing valproate had a significantly higher risk of major congenital malformations than valproate-free combinations. For monotherapy a relationship between malformations and dose was seen for lamotrigine and although the trend with valproate dosage did not reach statistical significance infants exposed to more than 1000 mg valproate daily had the highest rate of malformations for any monotherapy. The authors also noted that for lamotrigine the risk with doses more than 200 mg daily was no different to that associated with 1000 mg or less of valproate daily.

There is evidence that antiepileptic therapy is associated with lower birth-weight at term, presumably due to drug-induced **intra-uterine growth retardation**; the effect may be seen largely in women taking multiple antiepileptic drugs.[7]

Additional problems that may occur in the immediate post-partum period include the potential for neonatal **sedation** and **dependence** with drugs such as phenobarbital or *benzodiazepines*, if given close to term. Evidence of withdrawal symptoms has also been reported in infants exposed to sodium valproate or phenytoin. Some antiepileptics induce hepatic enzymes and may also increase the risk of vitamin K deficiency and **neonatal bleeding**.[6,7]

There is also increasing concern about the possibility of long-term **impairment of neurodevelopment** in children exposed to antiepileptic drugs *in utero*.[5,7,10,11,24,25] A population-based cohort study[26] in young men with epileptic mothers found lower IQ scores and shorter adult heights than in those born to mothers without epilepsy, although information on fetal exposure to individual antiepileptic drugs was unavailable. Again, most evidence implicates valproate;[7,10,11] some consider that there is also evidence for phenytoin and carbamazepine,[7,10,11] and perhaps phenobarbital,[10] although a systematic review could not find evidence to implicate any individual antiepileptic,[24] and a study involving 182 children exposed to carbamazepine monotherapy could not find evidence of a reduction in verbal and nonverbal IQ scores.[27]

Patients with epilepsy should be offered **pre-conception advice** and treatment should be individualised.[1,3,4,6,7] Women should be advised to plan their pregnancies, and informed of the potential risks of seizures to mother and baby as well as the risks of antiepileptics;[7] fatalities have been associated with the mother stopping her antiepileptic regimen inappropriately.[5] It should be borne in mind that some antiepileptics may reduce the effectiveness of oral contraception and increase the risk of unplanned pregnancy.[6,11] Equally, there is some evidence that a degree of sexual dysfunction and impaired fertility may occur in both women[6,11] and men[28,29] with epilepsy.

In women with epilepsy who intend to become pregnant, certain guidelines and principles are widely followed.

- Withdrawal of antiepileptic therapy may be an option if the patient has been seizure-free for at least 2 years (for further details of drug withdrawal, see above); resumption of therapy may be considered after the end of the first trimester.
- If antiepileptics are to be continued throughout pregnancy, monotherapy is preferred using the lowest possible effective dose, although doses may have to be increased in response to changes in drug disposition during pregnancy, with the necessary readjustments being made after delivery.
- High daily doses of valproate (more than 1 g daily) should be avoided if possible, and peak plasma concentrations may be reduced by dividing the daily dose into 3 or 4 parts or by giving a modified-release preparation.
- Since there is a risk of fetal malformations with all the established antiepileptics, and a lack of data for the newer ones, it is generally considered that as long as there is good seizure control there is little to be gained from changing a pregnant patient's antiepileptic.

For those patients who first present when **already pregnant** there is probably little to be gained in altering potentially teratogenic antiepileptics as the time for intervention has almost certainly passed.[3,4,7] If a patient becomes pregnant while taking carbamazepine, phenytoin, or valproate she should be counselled regarding the risk of neural tube and other defects and should be offered antenatal screening. Adequate supplementation of folic acid is advised before pregnancy and during the first trimester to counteract the risk of neural tube defects; it has been suggested that women taking antiepileptics should be given folic acid in similar doses to those used in women who have previously given birth to an infant with neural tube defects (for further details, see Neural Tube Defects under Folic Acid, p.1942). Although folic acid can reduce serum-phenytoin concentrations this does not appear to be a problem in practice (see Vitamins, p.500).

To counteract the risk of neonatal bleeding associated with enzyme-inducing antiepileptics it is particularly important that the neonate be given vitamin K after delivery[6-8] (for further details, see under Vitamin K deficiency bleeding, p.1997). Some have advocated oral doses for the mother in the last 4 weeks of pregnancy,[6] but the justification of prophylactic maternal dosage has been challenged[30] in the face of available evidence.

Patients with epilepsy have also a higher risk of preterm delivery and antenatal corticosteroid therapy may, therefore, be warranted. High doses of corticosteroid may be required in those women receiving enzyme-inducing antiepileptics.[3]

Status epilepticus during pregnancy should be treated in the same way as for the general population (see below). First seizures occurring during the second half of pregnancy may be part of eclampsia (see below) and should be differentiated from epilepsy.

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Status epilepticus

Although status epilepticus has been defined as continuous or repeated seizure activity lasting 30 minutes or more without any regaining of normal consciousness, current definitions generally consider it to be any continuous seizure of more than 5 minutes, or 2 or more seizures without regaining normal consciousness.[1-8] Although status may occur with any seizure type, generalised convulsive status is the most common clinical presentation,[4] with an estimated mortality rate of about 20%; it is most frequent in young children and the elderly.[2,3,9] It is a medical emergency, and the longer seizures continue, the more difficult they are to control and the higher the morbidity and mortality; permanent neuronal damage can occur after 30 minutes of seizure activity.[7]

Management of status epilepticus varies slightly between centres and countries, but the general principles seem to be fairly well established.[1-11]

- In **initial management**, it is important to secure the airway and give oxygen as required, assess cardiac and respiratory function, and establish intravenous access. Blood glucose should be assessed and any hypoglycaemia corrected with glucose; intravenous thiamine should be given if there is any suggestion of alcohol abuse or inadequate nutrition.[3-6,8,11]
- Initial antiepileptic treatment is usually with a benzodiazepine. Although *diazepam* has been widely used in the past, intravenous *lorazepam* is now preferred for first-line treatment in most protocols,[1-6,8-12] as it appears to be more effective and has a longer duration of antiepileptic action.[6,8,12] Rectal diazepam or buccal *midazolam* may be used in the home setting or where intravenous access is not available.[4,5,13] (Rectal diazepam may also have a role in this setting to treat acute repetitive seizures,[14] which may evolve into status epilepticus.) Both midazolam[15,16] and lorazepam[17] have also been given intranasally
- For sustained control in patients with established epilepsy their usual antiepileptic regimen may be given orally or by nasogastric tube once immediate control is established, or if necessary, for those drugs with an intravenous formulation, parenterally.[4,5]
- In other patients, or in patients with **established status** not abolished by the benzodiazepine, additional treatment with one of several first-line antiepileptics is normally required. The choice is usually between intravenous *phenytoin*, *fosphenytoin*, or *phenobarbital*,[3-5,7,8] all of which are effective. Repeat doses may need to be given. Although there is some evidence that phenobarbital is more effective than phenytoin in abolishing seizures,[18] many favour the use of the barbiturate only in patients who do not respond to phenytoin or fosphenytoin,[1-3,9,10] because of the risk of severe respiratory depression. ECG monitoring is required in patients given intravenous phenytoin or fosphenytoin.[4]
- Other antiepileptics have been used for established status. Some have found intravenous *valproate* to be useful in this situation,[7,19-21] and have incorporated it into local protocols. Other alternatives have included *paraldehyde* rectally or by deep intramuscular injection, and intravenous *clomethiazole edisilate* was formerly available. The *BNF* notes that rectal paraldehyde causes little

respiratory depression and may therefore be useful where facilities for resuscitation are poor. Another option is to give *lidocaine* intravenously.[3] *Pyridoxine* may be tried in children under 3 years of age with established convulsive status epilepticus, in case the seizures are pyridoxine dependent or responsive.[1]

- Once seizures have continued for 60 to 90 minutes despite treatment with a benzodiazepine and one of the first-line antiepileptics, the patient is considered to have **refractory status epilepticus**.[3,5] At this point general anaesthesia should be instituted. The usual choice is between treatment with *propofol, midazolam*, or a short-acting barbiturate anaesthetic such as *pentobarbital* or *thiopental*.[3-10,22] The anaesthetic should be continued for 12 to 24 hours after the last clinical or electrographic seizure and the dose then gradually reduced.[5] Some consider that all patients unresponsive to first-line therapy with a benzodiazepine should be considered refractory and proceed to treatment with propofol or midazolam.[6]
- Other drugs tried in refractory status include the inhalational anaesthetics *desflurane* and *isoflurane*.[23] *Tiagabine* and *ketamine* have also been suggested,[6] as has *valproate*,[7,22] and there are a few reports of responses to *levetiracetam*[24] and *topiramate*.[25-27]

Evidence to support the management of **nonconvulsive** forms of status epilepticus (NCSE) is scanty. The *BNF* recommends that usual oral antiepileptics should initially be continued or restarted in patients with incomplete loss of awareness. Otherwise, it has been suggested that management should be as for convulsive status,[6] albeit less aggressive,[28] with intravenous benzodiazepines the first choice for initial management.[4-6,11,28] Subsequent management will probably be influenced by the drugs known to be effective in the given seizure type. The prognosis depends on the aetiology and level of consciousness: comatose patients with refractory NCSE have a poorer prognosis and general anaesthesia may be appropriate.[6] Conscious patients generally have a more favourable outcome and termination of status is considered less urgent; general anaesthetics should thus be used more cautiously.[11,28]

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Other convulsive disorders

Disorders that feature convulsions or epileptic seizures but are not considered to be forms of epilepsy are described below.

Alcohol withdrawal syndrome. For a discussion of the management of seizures associated with alcohol withdrawal syndrome, see p.1626.

Eclampsia and pre-eclampsia. Pre-eclampsia is a hypertensive disorder occurring in pregnancy that entails increased blood pressure together with proteinuria, and sometimes abnormal coagulation, liver dysfunction, and oedema; rarely the disorder may progress to eclampsia, which is a convulsive phase. It is difficult to identify those patients who will have eclamptic seizures. The treatment of pre-eclampsia and eclampsia is primarily aimed at reducing hypertension (see Hypertension in Pregnancy, under Hypertension, p.1171) and treating or preventing resultant seizures. However, the treatment of the hypertension alone may not be sufficient to prevent the progression of pre-eclampsia to eclampsia.

Eclampsia in the UK was traditionally **treated** with *diazepam, clomethiazole*, or *phenytoin*. *'Lytic cocktails'* consisting of chlorpromazine, pethidine, and/or promethazine have also been used in some countries in the management of pre-eclampsia and imminent eclampsia but they result in heavy sedation and the use of phenothiazines is generally not recommended late in pregnancy. *Magnesium sulfate* is now the drug of choice for the treatment of eclampsia;[1-3] it has been the preferred treatment of eclampsia in the USA for many years, on the grounds that it is more effective and causes fewer adverse effects than other antiepileptics. A meta-analysis[4] of 9 randomised studies involving 2390 patients with pre-eclampsia and 1743 patients with eclampsia concluded that magnesium sulfate was more effective than phenytoin or no therapy in prevention of seizures in pre-eclamptic patients. In eclamptic patients, magnesium sulfate was superior to phenytoin, diazepam, or a lytic cocktail in terms of seizure recurrence, a result that was confirmed in subsequent systematic reviews.[5-7]

Until recently there has been insufficient evidence to establish the benefits and hazards of antiepileptics in the **prevention** of eclampsia in pre-eclamptic patients although it was considered that magnesium sulfate was the best choice if an antiepileptic was needed.[8,9] Some commentators suggested,[10] in the light of evidence of possible neonatal toxicity, that magnesium sulfate should be restricted to use in more severe pre-eclampsia or eclampsia. However, the significant benefits of magnesium sulfate in the prevention of eclampsia were confirmed in a large, international trial,[11] and follow-up studies found that magnesium sulfate was not associated with an increased risk of death or disability in the children at 18 months[12] and in the mothers at 2 years.[13]

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11. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; **359:** 1877–90.
12. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for children at 18 months. *BJOG* 2007; **114:** 289–99.
13. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for women at 2 years. *BJOG* 2007; **114:** 300–9.

Febrile convulsions. Febrile convulsions have been defined[1] as epileptic seizures occurring between the ages of 6 months to 5 years and associated with a fever arising from an infectious illness outside the CNS. They usually occur during the rising phase of fever early in the course of the infection and are not considered to be a form of epilepsy.[2,3]

Febrile convulsions are considered to be benign if limited to a single tonic or tonic-clonic seizure lasting less than 15 minutes without any focal characteristics.[2] About one-third of children who have a benign febrile convulsion will have a recurrence.[1,2,4] Risk factors for recurrence include a young onset age, a history of epilepsy or febrile seizures in a first-degree relative, subsequent episodes of fever, and a first complex febrile seizure.[4] The risk of developing epilepsy is low, but nevertheless it is 2 to 3 times greater than the risk in the population as a whole.[2] Unless they are recurrent, benign febrile convulsions need only simple treatment to lower body temperature[1,2] such as that described under Fever and Hyperthermia, p.10.

Prolonged febrile convulsions lasting longer than 15 minutes and associated with some focal characteristics are not considered to be benign and further increase the risk of developing epilepsy.[2,3] When they are prolonged or recurrent they are treated with *diazepam* intravenously, or as a rectal solution, to prevent possible brain damage resulting from continued seizure activity, although any such effect appears to be rare.[5]

The prophylactic use of *antiepileptics* in children thought to be at risk of recurrence of febrile convulsions remains controversial. Many consider that even if recurrences can be prevented there is no evidence that the risk of developing epilepsy is reduced.[1,2,4] A working group of the Royal College of Physicians and the British Paediatric Association considered that pooled analyses of studies of the prophylactic use of *phenobarbital* or *sodium valproate* showed that long-term prophylaxis was rarely indicated.[1] Although some have found that intermittent prophylaxis with phenobarbital or diazepam[6] given at the onset of and during fever could prevent recurrence of febrile convulsions, the working group did not recommend their routine use in this way.[1] Other workers have found that giving paracetamol as an antipyretic and diazepam for intermittent prophylaxis failed to prevent recurrences of febrile convulsions.[7] A later meta-analysis[8] concluded that neither continuous nor intermittent prophylaxis could be recommended as the benefits did not outweigh the potential adverse effects, a view endorsed by the American Academy of Pediatrics.[9]

1. Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association. Guidelines for the management of convulsions with fever. *BMJ* 1991; **303:** 634–6. Also available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1671115&blobtype=pdf (accessed 09/06/08)
2. Smith MC. Febrile seizures: recognition and management. *Drugs* 1994; **47:** 933–44.
3. Sadleir LG, Scheffer IE. Febrile seizures. *BMJ* 2007; **334:** 307–11.
4. Knudsen FU. Febrile seizures: treatment and prognosis. *Epilepsia* 2000; **41:** 2–9.
5. Verity CM. Do seizures damage the brain? The epidemiological evidence. *Arch Dis Child* 1998; **78:** 78–84.
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7. Uhari M, *et al.* Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126:** 991–5.
8. Rantala H, *et al.* A meta-analytic review of the preventative treatment of recurrences of febrile seizures. *J Pediatr* 1997; **131:** 922–5.
9. American Academy of Pediatrics. Practice parameter: long-term treatment of the child with simple febrile seizures. *Pediatrics* 1999; **103:** 1307–9. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;103/6/1307.pdf (accessed 09/06/08)

Myoclonus. Myoclonus consists of brief, involuntary, jerky movements of sudden onset which may be focal, segmental, or generalised, and are caused by muscular contractions (positive myoclonus) or inhibitions/pauses (negative myoclonus). The term 'myoclonus' is non-specific and classification is important in order to decide on treatment:[1-4]

- physiological (in normal subjects)
- essential (no known cause)
- epileptic (seizures dominate)
- symptomatic (encephalopathy dominates—causes include storage diseases, neurodegenerative syndromes, toxic and drug-induced syndromes, and hypoxia)

In epileptic myoclonus, epileptic seizures (myoclonic seizures in which the motor manifestation is myoclonus) dominate. Their treatment is discussed under Epilepsy, above. Essential myoclonus may benefit from *clonazepam*. *Botulinum toxin* has been used successfully for spasmodic movements in some forms of myoclonus.

Myoclonus may also be subdivided into cortical, reticular, or spinal forms. Cortical myoclonus is considered to be a subset of epilepsy and responds best to antiepileptics, usually *valproate* and/or clonazepam; *piracetam* or *levetiracetam* are also used, usually as adjunctive therapy. Reticular myoclonus is usually caused by anoxia or acute encephalopathy and may be treated with clonazepam; *serotonin* or serotonergic agonists have also been tried. Posthypoxic myoclonus occurring after hypoxic coma may respond to *oxitriptan* or serotonin combined with *carbidopa*; antiepileptics may help.

1. Caviness JN. Myoclonus. *Mayo Clin Proc.* 1996; **71:** 679–88.
2. Blindauer K. Myoclonus and its disorders. *Neurol Clin North Am* 2001; **19:** 723–34.
3. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol* 2003; **16:** 515–21.
4. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; **3:** 598–607.

Neonatal seizures. Neonatal seizures differ from epilepsy, and the definitions in the 1989 international classification of epilepsy and epileptic syndromes (see above) may be of little value; (a study[1] has suggested that the proposed 2001 classification may be more helpful). They are frequently subtle and difficult to recognise.[2] Causes include asphyxia, glucose or electrolyte imbalance, infection, CNS or cerebrovascular lesions, inborn errors of metabolism, and drug withdrawal or intoxication.[3-5]

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential.[3-7] Infusion of glucose or electrolytes may be of benefit.[4,5] Current practice involves giving antiepileptic drugs to control seizures, although there is no consensus on, nor good evidence for, their use.[2,7] *Phenobarbital* and *phenytoin* are the most widely used.[3-6] Traditionally, phenobarbital has been considered to be the mainstay of treatment for all types of seizures in neonates; however response rates are variable.[6-8] If seizures persist, phenytoin may be added to therapy.[8] Other drugs that have been tried include *carbamazepine*, *levetiracetam*,[9] *benzodiazepines*,[3-5,8,10,11] *lidocaine*,[3,8,10] and *primidone*.[4,5] Pyridoxine-dependent seizures can be abolished by regular large doses of the vitamin[4,5] (see p.1979).

1. Mastrangelo M, *et al.* Epileptic seizures, epilepsy and epileptic syndromes in newborns: a nosological approach to 94 new cases by the 2001 proposed diagnostic scheme for people with epileptic seizures and with epilepsy. *Seizure* 2005; **14:** 304–11.
2. Rennie J, Boylan G. Treatment of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F148–F150.
3. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F70–F75.
4. Hill A. Neonatal seizures. *Pediatr Rev* 2000; **21:** 117–21.
5. Painter MJ, Alvin J. Neonatal seizures. *Curr Treat Options Neurol* 2001; **3:** 237–48.
6. Painter MJ, *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999; **341:** 485–9.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 09/06/08).
8. Boylan GB, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004; **62:** 486–8.
9. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.
10. Shany E, *et al.* Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007; **22:** 255–9.
11. Castro Conde JR, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005; **64:** 876–9.

Porphyria. Convulsions may occur at the peak of an attack of acute porphyria (p.1448) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease. However, some patients continue to have convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.[1,2] Barbiturates (*phenobarbital*, *primidone*), hydantoins *(phenytoin, ethotoin)*, and *carbamazepine* are considered unsafe, as is *sultiame*. There is limited evidence that the *benzodiazepines*, *sodium valproate*, and probably *valpromide* are porphyrinogenic but status epilepticus has been treated successfully with intravenous *diazepam*. Seizure prophylaxis may be undertaken as a calculated risk using valproate or *clonazepam* if considered essential. *Magnesium sulfate* is safe. *Clomethiazole* is also probably safe. *Gabapentin* and *vigabatrin* have each been tried in a few patients without ill-effect, although there has been a report of a bullous skin eruption in a patient with porphyria cutanea tarda given vigabatrin.[3] Of the other newer antiepileptics, *oxcarbazepine* was used successfully in one patient whilst *lamotrigine* was associated with an acute porphyric attack in another; *tiagabine* and *topiramate* have been found to increase hepatic and urinary porphobilinogen concentrations.[2] Other antiepileptics such as the succinimides *(ethosuximide, mesuximide, phensuximide)* and oxazolidinediones *(trimethadione)* are considered to be unsafe.

1. Gorchein A. Drug treatment in acute porphyria. *Br J Clin Pharmacol* 1997; **44:** 427–34.
2. Solinas C, Vajda FJ. Epilepsy and porphyria: new perspectives. *J Clin Neurosci* 2004; **11:** 356–61.
3. Hommel L, *et al.* Acute bullous skin eruption after treatment with vigabatrine. *Dermatology* 1995; **191:** 181.

4-Amino-3-hydroxybutyric Acid

Ácido 4-amino-3-hidroxibutírico; γ-Amino-β-hydroxybutyric acid; Buxamin; Gabob; Gamma-amino-beta-hydroxybutyric acid.

4-Амино-3-оксимасляная Кислота

$C_4H_9NO_3$ = 119.1.
CAS — 352-21-6.

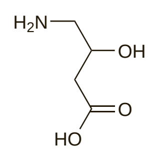

Profile

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including use as an adjunct in the treatment of epilepsy. It has also been promoted as a dietary supplement for its supposed beneficial effects on the CNS and growth hormone. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (GOBAB), which is reported to possess anti-inflammatory and antifungal activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gabimex; ***Braz.:*** Gamibetal†; ***Ital.:*** Gamibetal; ***Mex.:*** Gamibetal; ***Port.:*** Gabomade; Gamibetal†.

Multi-ingredient: ***Arg.:*** Gabimex Plus; ***Braz.:*** Gamibetal Complex†; ***Ital.:*** Gamibetal Complex; Gamibetal Plus; Parvisedil; ***Mex.:*** Gamibetal Complex; ***Port.:*** Gabisedil†; Gamibetal Compositum†; ***Spain:*** Cefabol; Dorken; Gamalate B6; Redutona.

Barbexaclone *(rINN)*

Barbeksaklon; Barbexaclona; Barbexaclonum. Compound of (−)-*N*,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid .

Барбексаклон

$C_{12}H_{12}N_2O_3,C_{10}H_{21}N$ = 387.5.
CAS — 4388-82-3.
ATC — N03AA04.
ATC Vet — QN03AA04.

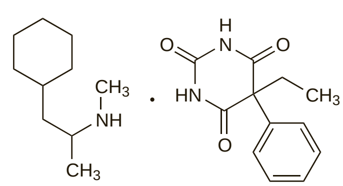

Profile

Barbexaclone is a compound of levopropylhexedrine (see under Propylhexedrine, p.2163) with phenobarbital (p.492). It is used in the treatment of various types of epilepsy (p.465). Usual adult doses are 200 to 400 mg daily given by mouth in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Maliasin; ***Braz.:*** Maliasin; ***Gr.:*** Maliasin; ***Ital.:*** Maliasin; ***Switz.:*** Maliasin; ***Turk.:*** Maliasin.

Benzobarbital *(rINN)*

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum. 1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

Бензобарбитал

$C_{19}H_{16}N_2O_4$ = 336.3.
CAS — 744-80-9.

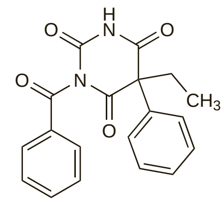

NOTE. The name benzonal has also been used as a proprietary name for benzonatate (p.1552).

Pharmacopoeias. In *Int.*

Profile

Benzobarbital is a barbiturate used in the treatment of epilepsy.

Brivaracetam *(USAN, rINN)*

Brivaracétam; Brivaracetamum; UCB-34714. (2*S*)-2-[(4*R*)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

Бриварацетам

$C_{11}H_{20}N_2O_2$ = 212.3.
CAS — 357336-20-0.

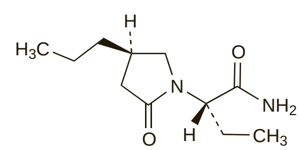

Profile

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

◊ References.

1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63:** 680–8.
2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66:** 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17:** 361–9.

Carbamazepine *(BAN, USAN, rINN)*

Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum. 5*H*-Dibenz[*b*,*f*]azepine-5-carboxamide.

Карбамазепин

$C_{15}H_{12}N_2O$ = 236.3.
CAS — 298-46-4.
ATC — N03AF01.
ATC Vet — QN03AF01.

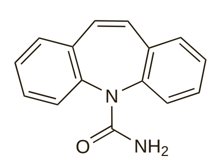

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.

USP 31 (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.[1]

The FDA have received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (*Tegretol*; *Novartis, USA*) followed immediately by chlorpromazine solution (*Thorazine*; *GSK, USA*). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (*Mellaril*; *Novartis, USA*) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, *et al.* Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; **47:** 2034–7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their effectiveness if stored in humid conditions.[1] This appears to be due to formation of a dihydrate form which leads to hardening of the tablet and poor dissolution and absorption.[2,3] As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.[2]

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; **47:** 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; **48:** 2130–1.
3. Wang JT, *et al.* Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; **82:** 1002–5.

Adverse Effects

Fairly common adverse effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. Gastrointestinal disturbances, such as nausea and vomiting, and mild skin reactions are also common. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear spontaneously with continued treatment or at reduced or divided dosage.

Although rare, generalised erythematous rashes can be severe and treatment may have to be withdrawn. Photosensitivity reactions, urticaria, alopecia, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome, and SLE (but see below) have also been reported.

Transient leucopenia is common and usually resolves with continued therapy; however, rarer blood disorders reported include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of liver and kidney function, hepatitis, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Gastrointestinal symptoms reported to be less common include dry mouth, abdominal pain, anorexia, and diarrhoea or constipation. Hyponatraemia, and sometimes oedema, have occurred. Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal use has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the CNS, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, below.

Congenital malformations have been reported in infants born to women given carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of such reactions these recommendations were questioned and the manufacturers subsequently modified their guidelines (see Precautions, below).

Case reports and studies of carbamazepine's haematological effects have been reviewed.[1] The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incidental disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers[1] suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts were at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fell further the dose should be reduced or treatment stopped. It should be noted that the *BNF* doubts the practical value of routine monitoring: in particular, aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, below).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see Folic Acid Deficiency, under Phenytoin, p.495.

1. Sobotka JL, *et al.* A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990; **24:** 1214–19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on electrolytes. There have been reports of *hyponatraemia* or *water intoxication* in patients receiving carbamazepine.[1-7] One review[8] states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from the central and gastrointestinal effects of the drug.[2] The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,[3,4,6] others indicate the reverse,[5,9] and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline[5] is cited as evidence for an effect on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Risk factors for developing carbamazepine-induced hyponatraemia include age of over 40 years, use of sodium-depleting drugs, and low pre-treatment plasma-sodium concentrations; it is unclear whether this adverse effect is dose-related.[7]

1. Henry DA, *et al.* Hyponatraemia during carbamazepine treatment. *BMJ* 1977; **1:** 83–4.
2. Stephens WP, *et al.* Water intoxication due to carbamazepine. *BMJ* 1977; **1:** 754–5.
3. Ashton MG, *et al.* Water intoxication associated with carbamazepine treatment. *BMJ* 1977; **1:** 1134–5.
4. Smith NJ, *et al.* Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *BMJ* 1977; **2:** 804.
5. Ballardie FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; **17:** 763–5.
6. Sørensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; **26:** 719–22.
7. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 2005; **39:** 1943–6.
8. Mucklow J. Selected side-effects 2: carbamazepine and hyponatraemia. *Prescribers' J* 1991; **31:** 61–4.
9. Stephens WP, *et al.* Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *BMJ* 1978; **1:** 1445–7.

Effects on the endocrine system. Carbamazepine may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.[1] Retinotoxicity associated with long-term carbamazepine use has been reported[2] in 2 patients. After stopping the drug visual function and retinal morphological changes improved. A review[3] of the effect of antiepileptics on the eyes noted that despite reports of colour vision disturbances and impaired contrast sensitivity associated with carbamazepine therapy, studies in healthy subjects had shown conflicting results.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; **18:** 63–4.
2. Nielsen NV, Syversen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; **64:** 287–90.
3. Hilton EJR, *et al.* The effect of antiepileptic drugs on visual performance. *Seizure* 2004; **13:** 113–28.

Effects on the heart. A review[1] of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia after carbamazepine overdosage while the other group was composed of older female patients with potentially life-threatening bradycardia or AV block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.[2] Carbamazepine should be avoided in patients who develop conduction abnormalities, or who have conditions such as myotonic dystrophy in which conduction abnormalities are likely.[1]

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.[3]

For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, below.

1. Kasarkis EJ, *et al.* Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; **152:** 186–91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1986; **49:** 1460–1.
3. Ambrosi P, *et al.* Carbamazepine and pacing threshold. *Lancet* 1993; **342:** 365.

Effects on the immune system. There have been reports of hypogammaglobulinaemia associated with carbamazepine.[1-4] The authors of one report[2] stated that this was a recognised but rare adverse effect of carbamazepine and noted that the UK CSM had 9 reports on file of hypogammaglobulinaemia or gammaglobulin abnormalities related to the use of carbamazepine.

1. Moschione Castro APB, *et al.* Secondary hypogammaglobilinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo* 2001; **56:** 189–92.
2. Hayman G, Bansal A. Antibody deficiency associated with carbamazepine. *BMJ* 2002; **325:** 1213.
3. Rice CM, *et al.* Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1011–12.
4. Tamada T, *et al.* Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. *Thorax* 2007; **62:** 100.

Effects on the liver. A report in 1990 commented that of 499 reports of unwanted effects of carbamazepine on the liver about half comprised only abnormal results from liver function tests;[1] however, deaths have occurred from liver failure[1,2] or hepatic necrosis.[3] Reversible vanishing bile duct syndrome has been associated with long-term use of carbamazepine.[4]

Hepatotoxicity may form part of the antiepileptic hypersensitivity syndrome reported with carbamazepine (see below).

1. Hadžić N, *et al.* Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; **65:** 315–17.
2. Zucker P, *et al.* Fatal carbamazepine hepatitis. *J Pediatr* 1977; **91:** 667–8.
3. Smith DW, *et al.* Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; **18:** 575–81.
4. Ramos AMO, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002; **14:** 1019–22.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms[1-3] and with phobias[2] and mood disturbances, including mania[4] and melancholia.[5] One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.[3] For nonconvulsive status epilepticus associated with carbamazepine presenting as psychiatric disorders, see under Effects on the Nervous System, below. The problems of antiepileptic therapy adversely affecting cognition and the risk of mood disorders, including suicidal ideation, are discussed on p.468.

1. Berger H. An unusual manifestation of Tegretol (carbamazepine) toxicity. *Ann Intern Med* 1971; **74:** 449–50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; **296:** 1071.
3. McKee RJW, *et al.* Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; **i:** 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; **45:** 272–4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; **6:** 236–9.

Effects on the nervous system. *ASEPTIC MENINGITIS.* Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge.[1] Aseptic meningitis has also been associated with carbamazepine in patients without Sjögren's syndrome.[2-4]

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; **159:** 363–4.
2. Simon LT, *et al.* Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; **112:** 627–8.
3. Hemet C, *et al.* Aseptic meningitis secondary to carbamazepine treatment of manic-depressive illness. *Am J Psychiatry* 1994; **151:** 1393.
4. Dang CT, Riley DK. Aseptic meningitis secondary to carbamazepine therapy. *Clin Infect Dis* 1996; **22:** 729–30.

ENCEPHALOPATHY. Carbamazepine-induced encephalopathy with symptoms resembling Creutzfeldt-Jakob disease was reported in a 71-year-old man; the cognitive decline, bradykinesia, tremor, and abnormal EEG improved on stopping carbamazepine.[1]

1. Horvath J, *et al.* Carbamazepine encephalopathy masquerading as Creutzfeldt-Jakob disease. *Neurology* 2005; **65:** 650–1.

EXTRAPYRAMIDAL EFFECTS. Although carbamazepine has been associated with extrapyramidal adverse effects,[1-4] it has also been tried in the treatment of movement disorders—see under Uses and Administration, below.

1. Schwartzman MJ, Leppik IE. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleve Clin J Med* 1990; **57:** 367–72.
2. Soman P, *et al.* Dystonia—a rare manifestation of carbamazepine toxicity. *Postgrad Med J* 1994; **70:** 54–5.
3. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. *N Z Med J* 1994; **107:** 360–1.
4. Stryjer R, *et al.* Segmental dystonia as the sole manifestation of carbamazepine toxicity. *Gen Hosp Psychiatry* 2002; **24:** 114–15.

STATUS EPILEPTICUS. Nonconvulsive status epilepticus, misdiagnosed as behavioural and psychiatric disorders, was reported[1] to have been precipitated by carbamazepine in 2 patients; seizure control and behaviour improved when carbamazepine was stopped and replaced with valproate.

1. Marini C, *et al.* Nonconvulsive status epilepticus precipitated by carbamazepine presenting as dissociative and affective disorders in adolescents. *J Child Neurol* 2005; **20:** 693–6.

Effects on the skin. Rashes occurring with carbamazepine may form part of an antiepileptic hypersensitivity syndrome (see below). In a report,[1] erythema multiforme occurred when a generic formulation was given instead of a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. In another report, a 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.[2] Carbamazepine was stopped and the patient eventually made a full recovery; valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p.509). Fatal toxic epidermal necrolysis has been seen when carbamazepine was given to a patient who had previously had Stevens-Johnson syndrome during carbamazepine treatment.[3] Pseudo mycosis fungoides with lymphoid cell infiltration of the dermis and raised liver enzymes has been reported[4] in a 54-year-old man who was taking carbamazepine for seizures; symptoms resolved within about 2 weeks of stopping therapy.

For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, below. For the relative incidence of skin reactions to different antiepileptics, see under Phenytoin, p.496.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug nonequivalency. *N Engl J Med* 1989; **321:** 692–3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; **29:** 538–9.
3. Huang L-Y, *et al.* Fatal toxic epidermal necrolysis induced by carbamazepine treatment in a patient who previously had carbamazepine-induced Stevens-Johnson syndrome. *J Formos Med Assoc* 2007; **106:** 1032–7.
4. Gül Ü, *et al.* Carbamazepine-induced pseudo mycosis fungoides. *Ann Pharmacother* 2003; **37:** 1441–3.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia, has been associated with some antiepileptic drugs including carbamazepine.[1-3] Although a literature search[1] was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[2,3] but the true incidence is uncertain due to variations in presentation and reporting. Most reactions occurred within 30 days of the start of carbamazepine treatment,[1] although symptoms may occur anywhere between 1 and 8 weeks after exposure.[2] In previously sensitised individuals the reactions may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is approximately 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2]

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.[4] Hypersensitivity to carbamazepine with multisystem effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine;[5] all symptoms resolved on stopping carbamazepine and giving prednisone. There have been other cases[6-8] of an infectious mononucleosis syndrome associated with hypersensitivity to carbamazepine, leading the authors to suggest that reactivation of human herpesvirus 6 or 7 infection is a cofactor and an early manifestation of carbamazepine hypersensitivity syndrome; however, further studies are warranted.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.[9] A 21-year-old woman developed fatal fulminant hepatic failure after taking carbamazepine for about 2 months; she had presented with initial symptoms of fever, breathlessness, bloody diarrhoea, and a spreading rash.[10]

Generalised erythroderma with renal, hepatic, and bone-marrow failure (characterised by hypercellularity and dyserythropoiesis) has been reported[11] in an 81-year-old man 50 days after starting carbamazepine therapy. Symptoms recurred following an inadvertent rechallenge. The presence of underlying lymphoproliferative disease may have potentiated the severe drug-induced reaction.

If the antiepileptic hypersensitivity syndrome develops, immediate withdrawal of carbamazepine is recommended. In most cases this is all that is required and does not seem to precipitate an increase in seizures, compared with gradual withdrawal.[12]

Successful desensitisation to carbamazepine was reported[13] in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin. Starting with a low dose of carbamazepine 100 micrograms daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitise 7 patients, all of whom developed dramatic skin rashes when first exposed to carbamazepine.[14] Carbamazepine therapy in full doses was achieved without problem in about 6 weeks. Some[2] consider that desensitisation is not to be recommended in patients with full-blown antiepileptic hypersensitivity syndrome.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; **5:** 11.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Hosoda N, *et al.* Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; **66:** 722–3.
5. Merino N, *et al.* Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; **28:** 402–3.
6. Zeller A, *et al.* Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review. *Infection* 2003; **31:** 254–6.
7. Aihara Y, *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149:** 165–9.
8. Oskay T, *et al.* Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. *Epilepsy Res* 2006; **70:** 27–40.
9. Salzman MB, *et al.* Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; **336:** 878–9.
10. Syn W-K, *et al.* Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract* 2005; **59:** 988–91. Correction. *ibid.*; 1371.
11. Lombardi SM, *et al.* Severe multisystemic hypersensitivity reaction to carbamazepine including dyserythropoietic anemia. *Ann Pharmacother* 1999; **33:** 571–5.
12. Pirmohamed M, *et al.* Hypersensitivity to carbamazepine and lamotrigine: clinical considerations. *Br J Clin Pharmacol* 2000; **49:** 519P–520P.
13. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; **i:** 753.
14. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; **i:** 509–10.

Sudden unexplained death in epilepsy. Sudden unexplained death in epilepsy (SUDEP), a common cause of seizure-related mortality in patients with chronic epilepsy, has been reviewed.[1,2] Risk factors may include early onset of epilepsy, frequent generalised tonic-clonic seizures, intractability, frequent medication changes, and polytherapy. *Carbamazepine* use has also been implicated but the evidence was considered to be tenuous although frequent dose change resulting in plasma-carbamazepine levels outside the therapeutic range was found to be an independent risk factor. Although the FDA in the USA had required data about the specific risk of SUDEP to be included in the prescribing information for the newer antiepileptic drugs *gabapentin, lamotrigine, tiagabine, topiramate,* and *zonisamide*, some commentators[3] consider that none of these antiepileptics have shown an associated change in the risk of SUDEP. It has been suggested[2,3] that the incidence of SUDEP is related to the disease rather than a specific drug effect.

1. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? *Drug Safety* 2003; **26:** 673–83.
2. Nashef L, *et al.* Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; **48:** 859–71.
3. Lathers CM, Schraeder PL. Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol* 2002; **42:** 123–36.

Systemic lupus erythematosus. A review[1] of 80 cases of SLE-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. There have been subsequent reports[2-4] of late-onset SLE occurring after up to 8 years of carbamazepine therapy without previous adverse effects. The symptoms due to carbamazepine usually resolved on stopping treatment.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; **6:** 350–60.
2. Toepfer M, *et al.* Drug-induced systemic lupus erythematosus after 8 years of treatment with carbamazepine. *Eur J Clin Pharmacol* 1998; **54:** 193–4.
3. Pelizza L, *et al.* Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine. *Acta Biomed* 2006; **77:** 17–19.
4. Amerio P, *et al.* Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; **16:** 281–3.

Treatment of Adverse Effects

In the treatment of carbamazepine overdosage repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice, with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning. If there is doubt about the diagnosis, or if multiple-dose oral activated charcoal is being considered, then monitoring plasma-carbamazepine concentration can be useful; it may also help determine when carbamazepine therapy should be restarted. See also Overdosage, below.

Hypersensitivity reactions. For reference to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity under Adverse Effects, above.

Overdosage. Carbamazepine poisoning and its management has been reviewed.[1] Management is primarily supportive, with prompt attention to airway management and seizure control. Activated charcoal should be given; although multiple-dose activated charcoal has been recommended for carbamazepine overdosage, care must be taken to protect the airway since carbamazepine inhibits intestinal motility and there is a significant risk of aspiration. In patients with seizures unresponsive to benzodiazepines phenobarbital should be used; phenytoin is not a drug of choice in this situation. Hypotension is rare, and should be managed with fluid and vasopressor support; hypotension with refractory seizures should be treated aggressively as it has led to permanent neurological disability and death.

Haemodialysis or haemoperfusion may be warranted in patients with unstable cardiac status or status epilepticus complicated by bowel hypomotility and unresponsive to more conventional therapy. However, a report[2] of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended. As carbamazepine is highly protein-bound, albumin-enhanced continuous venovenous haemodialysis was tried and found to be effective in the treatment of a 10-year-old child after ingestion of 1.4 g of carbamazepine.[3]

For a further review of the features and management of poisoning with some antiepileptics, including carbamazepine, see under Phenytoin, p.497.

1. Spiller HA. Management of carbamazepine overdose. *Pediatr Emerg Care* 2001; **17:** 452–6.
2. Kale PB, *et al.* Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; **27:** 866–70.
3. Askenazi DJ, *et al.* Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. *Pediatrics* 2004; **113:** 406–9.

Precautions

Carbamazepine should be avoided in patients with AV conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if severe, progressive, or symptomatic leucopenia develops, or if symptoms suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis occur. Licensed product information recommends blood counts and hepatic and renal-function tests before starting carbamazepine therapy and periodically during treatment, but the *BNF* considers the evidence of practical value unsatisfactory. Clinical monitoring is of primary importance throughout treatment. Some patients of Asian ancestry may be at increased risk of severe skin reactions; for recommendations that such patients' genotype should be tested before beginning carbamazepine see Skin Reactions, below.

Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase in generalised seizures if given carbamazepine. Carbamazepine may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also Uses and Administration, below.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdosage requiring hospital admission has been reported after abuse of carbamazepine.[1]

1. Crawford PJ, Fisher BM. Recreational overdosage of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; **42:** 44–5.

Breast feeding. The American Academy of Pediatrics considers[1] that carbamazepine is usually compatible with breast feeding, although there have been reports[2] of transient cholestatic hepatitis in breast-fed infants.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Frey B, *et al.* Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; **36:** 644–7.

Driving. For comment on antiepileptic drugs and driving, see p.468.

Multiple sclerosis. Exacerbation of symptoms of multiple sclerosis has been reported[1] in 5 patients on starting carbamazepine therapy for paroxysmal neurological symptoms and pain. There was a close temporal association between starting carbamazepine and worsening of symptoms, followed by resolution when it was stopped. A 3-year follow-up observational study[2] found that out of 36 multiple sclerosis patients who received carbamazepine therapy, 12 developed neurological adverse effects that mimicked a relapse. The authors concluded that carbamazepine was associated with higher rates of adverse effects and stopping therapy than gabapentin or lamotrigine.

1. Ramsaransing G, *et al.* Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000; **320:** 1113.
2. Solaro C, *et al.* Antiepileptic medications in multiple sclerosis: adverse effects in a three-year follow-up study. *Neurol Sci* 2005; **25:** 307–10.

Porphyria. Carbamazepine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have also been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.[1] A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described;[2] such syndromes are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324:** 674–7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; **75:** 517–20.

Skin reactions. The FDA has issued a warning[1] that severe and potentially fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the HLA allele HLA-B*1502, which occurs almost exclusively in persons of Asian ancestry. They recommend that patients with such ancestry should be screened for the presence of this allele before beginning therapy with carbamazepine, and if present the risks and benefits of therapy should be considered with particular care; those who have already taken carbamazepine for more than a few months without developing skin reactions are, however, at low risk of them ever developing, regardless of genotype. Similar recommendations have since been issued in the UK by the MHRA.[2]

1. FDA. Information for healthcare professionals: carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). Issued 12th December, 2007. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm (accessed 09/06/08)
2. MHRA/CHM. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Safety Update* 2008: **1** (9): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 09/06/08)

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism by the cytochrome P450 isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity. Conversely, drugs that induce CYP3A4 may increase the metabolism of carbamazepine, leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. Licensed product information advises that, in such situations, the dose of carbamazepine should be adjusted accordingly and/or the plasma concentrations monitored.

Carbamazepine is itself a hepatic enzyme inducer, and induces its own metabolism as well as that of a number of other drugs including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably, oral contraceptives). Carbamazepine and phenytoin may also mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbital.

◊ General references.

1. Spina E, *et al.* Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; **31:** 198–214.

Alcohol. Alcohol may exacerbate the CNS adverse effects of carbamazepine and vice versa.

Analgesics. *Dextropropoxyphene* has been reported to cause substantial elevation of serum-carbamazepine concentrations[1] and carbamazepine toxicity,[1,2] probably due to inhibition of carbamazepine metabolism.[1]

Use of enzyme-inducing antiepileptics such as carbamazepine affects the threshold for use of antidote in the treatment of *paracetamol* poisoning, see p.110.

For the effect of carbamazepine on *tramadol*, see p.131.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; **ii:** 509.
2. Yu YL, *et al.* Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; **62:** 231–3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p.149 and p.154, respectively.

Antibacterials. The antimycobacterial *isoniazid*[1,2] and macrolides[3] such as *clarithromycin*, *erythromycin*, and *troleandomycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity. Clarithromycin has also been reported to have caused hyponatraemia when added to carbamazepine therapy in a 30-year-old epileptic woman.[4] *Rifampicin* and isoniazid decreased the serum concentrations of carbamazepine in a 44-year-old woman being treated for bipolar disorder and suspected tuberculosis, resulting in hypomania.[5]

Use of carbamazepine with isoniazid may increase the risk of isoniazid-induced hepatotoxicity.

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *BMJ* 1982; **285:** 261–2.
2. Wright JM, *et al.* Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307:** 1325–7.
3. Pauwels O. Factors contributing to carbamazepine-macrolide interactions. *Pharmacol Res* 2002; **45:** 291–8.
4. Kanbay M, *et al.* Hyponatremia due to an additive effect of carbamazepine and clarithromycin. *South Med J* 2007; **100:** 222.
5. Zolezzi M. Antituberculosis agents and carbamazepine. *Am J Psychiatry* 2002; **159:** 874.

Anticoagulants. For the effect of carbamazepine on *warfarin*, see p.1429.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *desipramine*,[1] *fluoxetine*,[2] *fluvoxamine*,[3] *nefazodone*[4] (and perhaps *trazodone*[5]), and *viloxazine*[6] increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome (see p.416) has been reported in a patient who received fluoxetine with carbamazepine.[7] Severe neurotoxicity reported during therapy with *lithium* and carbamazepine[8,9] may be due to a synergistic effect as reports indicate that either drug was tolerated when not given with the other and measured plasma concentrations did not indicate overdosage.[9] However, toxic serum concentrations of lithium have also been reported, due to carbamazepine-induced acute renal failure (see p.404).

Because of the structural similarity to tricyclic antidepressants licensed product information suggests that carbamazepine should not be given to patients taking an *MAOI* or within 14 days of stopping such treatment.

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and consequently it has been suggested that it might reduce the blood concentrations of carbamazepine leading to an increased risk of seizure.[10] However, a multiple-dose study[11] in healthy subjects reported that St John's wort had no significant effect on the pharmacokinetics of carbamazepine or its active epoxide metabolite.

For the effect of carbamazepine on antidepressants, see Bupropion (p.384), Fluoxetine (p.396), Mianserin (p.409), Nefazodone (p.413), and Amitriptyline (p.380).

1. Lesser I. Carbamazepine and desipramine: a toxic reaction. *J Clin Psychiatry* 1984; **45:** 360.
2. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51:** 126.
3. Fritze J, *et al.* Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84:** 583–4.
4. Ashton AK, Wolin RE. Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 1996; **153:** 733.
5. Sánchez Romero A, *et al.* Interaction between trazodone and carbamazepine. *Ann Pharmacother* 1999; **33:** 1370.
6. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *BMJ* 1987; **294:** 1355.
7. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
8. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45:** 525.
9. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44:** 30–1.
10. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
11. Burstein AH, *et al.* Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000; **68:** 605–12.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbital*, but without loss of seizure control;[1,2] this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum-carbamazepine concentrations, presumably due to induction of metabolism by phenytoin;[1-3] in return carbamazepine has been reported both to lower and increase serum phenytoin—see p.498. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing phenytoin from 2 patients who had been receiving carbamazepine and phenytoin resulted in a dramatic increase in plasma-carbamazepine concentrations;[4] one patient exhibited neurotoxic symptoms. The authors recommended that plasma-carbamazepine monitoring should be carried out whenever phenytoin is withdrawn in patients taking these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase, although an additional proposed mechanism[5] is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound to which the epoxide is converted under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide*, the amide derivative, is a much more powerful inhibitor of epoxide hydrolase than valproic acid,[6-8] and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.[7] Switching from sodium valproate to valpromide has resulted in toxicity in patients also receiving carbamazepine.[7] Neither valproic acid nor valpromide have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide*, an isomer of valpromide, appears to be at least as potent as valpromide in inhibiting the elimination of the epoxide metabolite of carbamazepine.[9] Valnoctamide has been used as an anxiolytic, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, above. For the effects of carbamazepine on valproate, see p.511.

Of the other antiepileptics *stiripentol*[10,11] has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma-carbamazepine concentrations which may require an increase in the dose of carbamazepine.[12] However, another study[13] has shown a significant increase in plasma-concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been seen after use of carbamazepine with *lamotrigine*.[14] The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely and effectively.[15] Toxic epidermal necrolysis occurred[16] when lamotrigine was added to carbamazepine therapy in a patient who had been taking carbamazepine for 3 years; symptoms resolved progressively when both drugs were stopped. Symptoms of carbamazepine toxicity have been reported[17] when *levetiracetam* was added to carbamazepine therapy; this interaction appeared to be due to a pharmacodynamic mechanism as blood levels of carbamazepine and its epoxide metabolite were not altered. There have also been reports[18] of carbamazepine toxicity when *topiramate* was added to carbamazepine therapy; symptoms resolved when the dose of carbamazepine was reduced. Fulminant liver failure has been reported[19] after an increase in adjunctive topiramate dose in a patient maintained on carbamazepine for 2 years without any signs of hepatotoxicity. The GABA agonist *progabide* has increased plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.[20] *Vigabatrin* is reported[21] to increase the clearance of carbamazepine by about 35%.

For the effects of carbamazepine on *ethosuximide*, see p.480, on *lamotrigine*, see p.486, on *oxcarbazepine*, see p.491, on *primidone*, see p.503, on *tiagabine*, see p.505, and on *topiramate*, see p.506. For interactions with benzodiazepines, see below.

1. Cereghino JJ, *et al.* The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18:** 733–41.
2. Rane A, *et al.* Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19:** 276–83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49:** 543–6.
4. Chapron DJ, *et al.* Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27:** 708–11.
5. Bernus I, *et al.* The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44:** 21–7.
6. Levy RH, *et al.* Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27:** 592.
7. Meijer JWA, *et al.* Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i:** 802.
8. Pisani F, *et al.* Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25:** 611–13.
9. Pisani F, *et al.* Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34:** 85–7.
10. Levy RH, *et al.* Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26:** 544–5.
11. Cazali N, *et al.* Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* 2003; **56:** 526–36.
12. Albani F, *et al.* Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32:** 130–2.
13. Wagner ML, *et al.* Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53:** 536–43.
14. Warner T, *et al.* Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsy Res* 1992; **11:** 147–50.
15. Stolarek I, *et al.* Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 921–4.
16. Mansouri P, *et al.* Toxic epidermal necrolysis associated with concomitant use of lamotrigine and carbamazepine: a case report. *Arch Dermatol* 2005; **141:** 788–9.
17. Sisodiya SM, *et al.* Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. *Epilepsy Res* 2002; **48:** 217–19.
18. Mack CJ, *et al.* Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. *Seizure* 2002; **11:** 464–7.
19. Bjøro K, *et al.* Topiramate and fulminant liver failure. *Lancet* 1998; **352:** 1119.
20. Kroetz DL, *et al.* In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54:** 485–97.
21. Sánchez-Alcaraz A, *et al.* Effect of vigabatrin on the pharmacokinetics of carbamazepine. *J Clin Pharm Ther* 2002; **27:** 427–30.

Antifungals. Malaise, myoclonus, and trembling were reported[1] to have developed in a patient receiving carbamazepine after the addition of *miconazole* to therapy. *Ketoconazole* was associated with a significant increase in plasma-carbamazepine concentrations in 8 epileptic patients stabilised on carbamazepine;[2] plasma concentrations of the epoxide metabolite were unchanged. A threefold increase in serum-carbamazepine concentrations, reported[3] in a patient after addition of *fluconazole* to carbamazepine therapy, was asymptomatic; however, carbamazepine toxicity has been reported[4,5] in 2 patients stabilised on carbamazepine who were given fluconazole. *Terbinafine* has also been reported[6] to cause possible carbamazepine toxicity.

For the effect of carbamazepine on *itraconazole*, see p.537.

1. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
2. Spina E, *et al.* Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* 1997; **19:** 535–8.
3. Finch CK, *et al.* Fluconazole-carbamazepine interaction. *South Med J* 2002; **95:** 1099–1100.
4. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* 1999; **33:** 790–2.
5. Ulivelli M, *et al.* Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* 2004; **251:** 622–3.
6. Baath NS, *et al.* Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* 2006; **13:** e228–e231.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic experienced symptoms of neurotoxicity shortly after starting treatment with terfenadine for rhinitis.[1] The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on stopping terfenadine.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118:** 907–8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotozoals. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea 4 days after the addition of *metronidazole* for diverticulitis.[1]

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28:** 1303–4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Increased plasma concentrations of carbamazepine epoxide have been reported to occur during therapy with carbamazepine and *loxapine*[1] or *quetiapine*,[2] possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide. Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.[3]

For the effect of carbamazepine on antipsychotics, see under Chlorpromazine, p.974.

1. Collins DM, *et al.* Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27:** 1180–3.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* 2002; **22:** 1500–3.
3. Iwahashi K, *et al.* The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18:** 233–6.

Antivirals. *Ritonavir* inhibits several microsomal liver enzymes and therefore may potentially increase plasma concentrations of carbamazepine. Licensed product information for ritonavir advises that such combinations may require monitoring. Carbamazepine toxicity has been reported[1,2] after interaction with ritonavir. In one report,[2] the patient was also taking *nelfinavir* and *lopinavir*, both of which are substrates and inhibitors of CYP450 isoenzymes.

For the effect of carbamazepine on HIV-protease inhibitors, see p.883.

1. Mateu-de Antonio J, Grau S. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* 2001; **35:** 125–6.
2. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. *Ann Pharmacother* 2006; **40:** 1190–5.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic valpromide, see Antiepileptics, above.

See also Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced by induction of hepatic drug-metabolising enzymes in patients who have received long-term therapy with carbamazepine; benzodiazepine plasma concentrations are reduced, half-life is shorter, and clearance is increased[1,2] (see also Antiepileptics, under Interactions of Diazepam, p.990).

Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of *clobazam* to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.[3] In a later study[4] it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Lai AA, *et al.* Time-course of interaction between carbamazepine and clonazepam in normal man. *Clin Pharmacol Ther* 1978; **24:** 316–23.
3. Franceschi M, *et al.* Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; **20:** 119–25.
4. Muñoz JJ, *et al.* The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; **29:** 763–5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations had symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the first dose of *verapamil*.[1] In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was seen. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report[2] of a patient in whom *diltiazem*, but not *nifedipine*, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p.1353.

1. Macphee GJA, *et al.* Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; **i:** 700–703.
2. Brodie MJ, Macphee GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *BMJ* 1986; **292:** 1170–1.

Ciclosporin. For the effect of carbamazepine on ciclosporin, see p.1826.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p.1494.

Danazol. Use of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,[1] resulting in increases in plasma-carbamazepine concentrations of up to 100%[1,2] and resultant toxicity in a number of patients.[2]

1. Krämer G, *et al.* Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; **8:** 387–92.
2. Zielinski JJ, *et al.* Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; **9:** 24–7.

Dermatological drugs. Addition of *isotretinoin* to regular carbamazepine therapy appeared to reduce plasma concentrations of the latter and its active epoxide metabolite.[1] However, no adverse events were noted during a 6-week period of treatment with isotretinoin. Nonetheless, licensed product information for carbamazepine recommends that the levels of carbamazepine are monitored if both are used together.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; **119:** 403–4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with use of carbamazepine and a diuretic (*hydrochlorothiazide* or *furosemide*—see under Interactions of Furosemide, p.1293). Carbamazepine serum concentrations are increased by *acetazolamide*.[1]

1. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1984; **16:** 393.

Gastrointestinal drugs. *Cimetidine* is reported to produce a transient increase in plasma-carbamazepine concentrations, with a return to pre-cimetidine values within about a week;[1] some increase in adverse effects was seen. *Ranitidine* does not appear to affect plasma-carbamazepine concentrations.[2] Neurotoxicity has been seen in a patient receiving carbamazepine and *metoclopramide*.[3]

1. Dalton MJ, *et al.* Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; **27:** 553–8.
2. Dalton MJ, *et al.* Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; **19:** 941–4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *BMJ* 1984; **288:** 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported[1] to be increased by grapefruit juice.

1. Garg SK, *et al.* Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; **64:** 286–8.

Levothyroxine. For the effect of carbamazepine on levothyroxine, see p.2172.

Neuromuscular blockers. For the effect of carbamazepine on *suxamethonium*, see p.1911 and on *competitive neuromuscular blockers*, see under Atracurium, p.1904.

Sex hormones. For the effect of carbamazepine on *oral contraceptives*, see p.2068 and for the possible effect on *tibolone*, see p.2134.

See also Danazol, above

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported[1] in an epileptic patient given theophylline. The patient experienced seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p.1143.

1. Mitchell EA, *et al.* Interaction between carbamazepine and theophylline. *N Z Med J* 1986; **99:** 69–70.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given *nicotinamide*.[1]

For the effect of antiepileptics, including carbamazepine, on *vitamin D* concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p.496.

1. Bourgeois BFD, *et al.* Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; **32:** 1122–6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastrointestinal tract and has a bioavailability of 85 to 100%. It is extensively metabolised in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10,11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosage. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults.

Moreover, the metabolism of carbamazepine is readily induced by drugs that induce hepatic microsomal enzymes (see Interactions, above).

Monitoring of plasma concentrations may be performed when clinically indicated and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 micrograms/mL (17 to 50 micromoles/litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and concentrations in saliva or tears, which contain only free carbamazepine, have also been measured.

Carbamazepine crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of carbamazepine are affected by use with other antiepileptics (see under Interactions, above).

◊ References.

1. Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; **34:** 1252–5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; **11:** 177–98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DICP Ann Pharmacother* 1991; **25:** 1109–12.
4. Kodama Y, *et al.* In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; **44:** 291–3.
5. Bernus I, *et al.* Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; **47:** 355–60.
6. Caraco Y, *et al.* Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; **29:** 843–7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; **45:** 241–6.
8. Cohen H, *et al.* Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; **55:** 1134–40.
9. Bondareva IB, *et al.* Population pharmacokinetic modelling of carbamazepine in epileptic elderly patients: implications for dosage. *J Clin Pharm Ther* 2006; **31:** 211–21.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures, and in some primary generalised seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the management of bipolar disorder unresponsive to lithium.

In the treatment of **epilepsy**, the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary. For details of doses in children, see below.

Oral carbamazepine is usually given in divided doses 2 to 4 times daily. A twice-daily regimen may be associated with improved compliance but can produce widely fluctuating plasma-carbamazepine concentrations that lead to intermittent adverse effects. Twice-daily dosage may nonetheless be suitable for patients receiving carbamazepine monotherapy; modified-release formulations can minimise fluctuations in plasma concentration and may also allow effective twice-daily use. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

The treatment of **trigeminal neuralgia** is typically begun with low oral doses, such as 100 mg of carbamazepine twice daily (although up to 200 mg twice daily has been suggested in the UK), and increased gradually as needed to maintain freedom from pain. This is usually at maintenance doses of 400 to 800 mg in divided doses; up to 1.2 g daily is considered standard maintenance in the USA, while UK licensed product information considers that up to 1.6 g daily may be needed in some patients. When pain relief has been obtained attempts should be made to reduce, and if possible stop, therapy, until another attack occurs.

For the management of **bipolar disorder**, carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine can reduce fluctuations in carbamazepine concentrations,[1] and tolerability and seizure control in patients with epilepsy may be improved.[2,3] Such formulations should be considered in patients receiving high doses who suffer intermittent adverse effects, and might also permit a reduction to twice- or even, in some patients, once-daily dosage.[2,4] However, bioavailability appears to be slightly less than conventional preparations and dosage adjustments may be required when changing between formulations.[1]

1. McKee PJW, *et al.* Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 99–104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; **ii:** 595–7.
3. Ryan SW, *et al.* Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; **65:** 930–5.
4. McKee PJW, *et al.* Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; **36:** 257–61.

Administration in children. In the UK, the usual recommended oral dose of carbamazepine for generalised tonic-clonic and partial seizures in children is 10 to 20 mg/kg daily in divided doses. Alternatively the daily dose may be given according to age as follows:

- up to 1 year: 100 to 200 mg
- 1 to 5 years: 200 to 400 mg
- 5 to 10 years: 400 to 600 mg
- 10 to 15 years: 0.6 to 1 g

As with adults, children should be started on a low initial dose of carbamazepine to minimise adverse effects; the *BNFC* suggests that those aged 1 month to 12 years may initially be given 5 mg/kg at night or 2.5 mg/kg twice daily, increasing by 2.5 to 5 mg/kg every 3 to 7 days as necessary to a usual maintenance dose of 5 mg/kg 2 or 3 times daily. Older children may be given the usual adult dose (see above) although a maximum of 1.8 g daily has been suggested.

The *BNFC* also states that these doses may be used for the treatment of neuropathic pain and some movement disorders, and for mood stabilisation.

Carbamazepine may be given rectally to children in whom oral treatment is temporarily not possible; the *BNFC* suggests this route may be used from 1 month of age. Doses should be about 25% greater than the corresponding oral dose, to a maximum of 250 mg, and given up to 4 times daily.

Bipolar disorder. Carbamazepine may be given as an alternative to lithium or valproate in patients with bipolar disorder (p.372). Studies of its efficacy have been conflicting; although clearly effective in some patients, at least one early study suggested that short-term benefit was not sustained in the longer term.[1] More recent results[2,3] have suggested that lithium or valproate are generally more effective, but that carbamazepine may conceivably have a role in patients with nonclassical features. Carbamazepine has also been used with lithium, particularly in patients unresponsive to either drug alone; although there are suggestions that the combination may be more effective than monotherapy, particularly in patients with a history of rapid cycling,[4] it is associated with a potential risk of serious neurotoxicity—see Antidepressants, under Interactions, above. While some commentators have suggested that carbamazepine is falling out of favour with specialists prescribing for bipolar disorder,[5] a more recent literature review[6] concluded that it was still a feasible treatment option.

1. Frankenburg FR, *et al.* Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; **8:** 130–2.
2. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; **42** (suppl 1): 2–10.
3. Vasudev K, *et al.* Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology (Berl)* 2000; **150:** 15–23.
4. Denicoff KD, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997; **58:** 470–8.
5. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; **57:** 179–92.
6. Stoner SC, *et al.* Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy* 2007; **27:** 68–88.

Depression. Carbamazepine has been tried[1-3] for the augmentation of antidepressant therapy in the treatment of resistant depression (p.373). However, such combined therapy may lead to interactions—see also Antidepressants under Interactions, above.

1. De la Fuente JM, Mendlewicz J. Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 1992; **32:** 369–74.
2. Otani K, *et al.* Carbamazepine augmentation therapy in three patients with trazodone-resistant depression. *Int Clin Psychopharmacol* 1996; **11:** 55–7.
3. Ciusani E, *et al.* Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J Psychopharmacol* 2004; **18:** 559–66.

Diabetes insipidus. Cranial diabetes insipidus is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin (see p.2179). Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.[1,2] Doses of 200 to 400 mg daily by mouth have been given. See also Effects on Electrolytes under Adverse Effects, above.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *BMJ* 1989; **298:** 2–3.
2. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; **157:** 1293–1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation (see p.465). It has been used for generalised tonic-clonic seizures (although valproate is the drug of choice where these occur in primary generalised epilepsy), but it may exacerbate absence and myoclonic seizures.

Hemifacial spasm. Carbamazepine has been reported to have been of help in the treatment of hemifacial spasm (p.1892).

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.[1] Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,[2] a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; **29:** 797–801.
2. Vantrappen G, *et al.* High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; **339:** 265–7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant but meta-analysis of a small number of trials has provided evidence that carbamazepine may be effective.[1]

1. Silva RR, *et al.* Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 352–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p.976) has been reported to improve in those given antiepileptics such as carbamazepine.[1]

1. Roach ES, *et al.* Carbamazepine trial for Lesch-Nyhan self-mutilation. *J Child Neurol* 1996; **11:** 476–8.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of *chorea* (p.953); there have been anecdotal reports of benefit in both non-hereditary[1,2] and hereditary choreas.[3] Carbamazepine is also among the drugs that have been tried in the treatment of *dystonias* that have not responded to levodopa or antimuscarinics (p.809). Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.[4] Carbamazepine therapy has also been associated with movement disorders—see Effects on the Nervous System: Extrapyramidal Effects under Adverse Effects, above.

Carbamazepine has also been used in resistant cases of *tardive dyskinesia* (see under Extrapyramidal Disorders, p.971).

Although not licensed in the UK for movement disorders in children, the *BNFC* suggests that carbamazepine may be tried in disorders such as *paroxysmal kinesigenic choreoathetosis* in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

1. Roig M, *et al.* Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; **82:** 492–5.
2. García González MM, *et al.* Corea de Sydenham: presentación de un caso tratado con carbamazepina con excelente respuesta clínica. *An Pediatr (Barc)* 2007; **66:** 80–3.
3. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; **83:** 1077.
4. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; **26:** 33–6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p.471).

Neuropathic pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neuropathic pain including that associated with diabetic neuropathy (p.6). A systematic review[1] concluded that about two-fifths of patients who take carbamazepine for neuropathic pain will achieve moderate pain relief, but this was based on small studies. The authors found no evidence that carbamazepine was effective for acute pain.

Carbamazepine has also been tried in an attempt to prevent the painful sensory neuropathy associated with oxaliplatin treatment (p.758); results of preliminary studies have been conflicting.[2,3]

Although not licensed in the UK for neuropathic pain in children, the *BNFC* suggests that carbamazepine may be tried in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

1. Wiffen PJ, *et al.* Carbamazepine for acute and chronic pain. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Eckel F, *et al.* Prophylaxe der Oxaliplatin-induzierten Neuropathie mit Carbamazepin: eine Pilotstudie. *Dtsch Med Wochenschr* 2002; **127:** 78–82.
3. Wilson RH, *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; **20:** 1767–74.

Nocturnal enuresis. Carbamazepine has been reported to be of benefit in the treatment of primary nocturnal enuresis; a dose of 200 mg at night for 15 nights markedly decreased the frequency of bed-wetting episodes in 8 children.[1]

For the conventional management of nocturnal enuresis see p.2180.

1. Al-Waili NS, *et al.* Effect of carbamazepine on urinary volume and osmolality, water clearance, and serum osmolality in patients with primary enuresis. *Eur Urol* 2006; **50:** 844–9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with *bipolar disorder* (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage[1-4] (see Disturbed Behaviour, p.954). It may produce modest benefit when used as an adjunct to antipsychotics in the management of refractory *schizophrenia* (p.955) but any improvement appears to be related to its mood stabilising effect.[5] However, a more recent systematic review,[6] albeit based on small studies, found carbamazepine to have no significant benefit either as monotherapy or as an adjunct to antipsychotics; the authors considered that further randomised studies may be warranted. Carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions for Chlorpromazine, p.974). Carbamazepine has also been tried[7] in *post-traumatic stress disorder* (p.953).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; **2:** 159–64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; **51:** 115–18.
3. Tariot PN, *et al.* Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; **155:** 54–61.
4. Cueva JE, *et al.* Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 480–90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; **1:** 269–84.
6. Leucht S, *et al.* Carbamazepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/06/08).
7. Wolf ME, *et al.* Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings; possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; **23:** 642–4.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.[1] Oxcarbazepine has been reported[2] to be of benefit in restless legs syndrome induced by paroxetine.

1. Telstad W, *et al.* Treatment of the restless legs syndrome with carbamazepine: a double blind study. *BMJ* 1984; **288:** 444–6.
2. Öztürk Ö, *et al.* Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. *Gen Hosp Psychiatry* 2006; **28:** 264–5.

Tinnitus. Treatment of tinnitus (p.1866) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of the acute stages of trigeminal neuralgia (p.9). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and adverse effects can be troublesome.

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Reduction in *cocaine use* associated with carbamazepine treatment was found in one short-term controlled study,[1] although a systematic review[2] of data from later studies concluded that there was no evidence to support the use of carbamazepine in the treatment of cocaine dependence (p.1860). It has been reported[3,4] to be of benefit in some patients during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p.987). Carbamazepine has been shown[5,6] to be effective in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1626) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine has also been studied[7] as an aid in the treatment of alcohol dependence.

1. Halikas JA, *et al.* Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; **50:** 81–95.
2. Lima Reisser A, *et al.* Carbamazepine for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 01/09/08).
3. Schweizer E, *et al.* Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; **48:** 448–52.
4. Klein E, *et al.* Alprazolam withdrawal in patients with panic disorder and generalized anxiety disorder: vulnerability and effect of carbamazepine. *Am J Psychiatry* 1994; **151:** 1760–6.
5. Malcolm R, *et al.* Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 1989; **146:** 617–21.
6. Stuppaeck CH, *et al.* Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. *Alcohol Alcohol* 1992; **27:** 153–8.
7. Mueller TI, *et al.* A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997; **21:** 86–92.

Preparations

BP 2008: Carbamazepine Tablets;
USP 31: Carbamazepine Extended-Release Tablets; Carbamazepine Oral Suspension; Carbamazepine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Actinerval; Carbagramon; Carbamat; CMP†; Conformal; Elebe; Tegretol; ***Austral.:*** Tegretol; Teril; ***Austria:*** Deleptin; Neurotop; Sirtal; Tegretol; ***Belg.:*** Tegretol; ***Braz.:*** Carmazin; Convulsan; Tegretard; Tegretol; Tegrex; Tegrezin; Uni Carbamaz; ***Canad.:*** Novo-Carbamaz; Tegretol; ***Chile:*** Carbactol Retard†; Eposal; Tegretal; ***Cz.:*** Biston; Neurotop; Tegretol; Timonil; ***Denm.:*** Nordotol†; Tegretol; Trimonil; ***Fin.:*** Neurotol; Tegretol; ***Fr.:*** Tegretol; ***Ger.:*** Carba; Carbabeta; Carbadura; Carbaflux; Carbagamma; Carbium†; espa-lepsin; Finlepsin; Fokalepsin; Sirtal; Tegretal; Timonil; ***Gr.:*** Tegretol; ***Hong Kong:*** Carzepin; CP-Carba; Tegretol; Teril; ***Hung.:*** Azepal†; Finlepsin†; Neurotop; Stazepine; Tegretol; Timonil; ***India:*** Carbacontin; Cizetol; Mazetol; Tegrital; ***Indon.:*** Bamgetol; Tegretol; Teril; ***Irl.:*** Gericarb; Tegretol; Temporol†; ***Israel:*** Carbi; Tegretol; Teril; Timonil; ***Ital.:*** Tegretol; ***Malaysia:*** Taver; Tegretol; ***Mex.:*** Adepril†; Apobace†; Bioneuril; Biorеunil†; Carbalan; Carbasal; Carbaval; Carbazep; Carbazina; Carpin; Clostedal; Dateril; Neugeron; Neurolep; Sepibest; Tegretol; Trepina; Ultrepyl; Volutol†; Zepiken; ***Neth.:*** Tegretol; ***Norw.:*** Tegretol; Trimonil; ***NZ:*** Tegretol; Teril; ***Philipp.:*** Carbilepp; Epazin; Epikor; Tegretol; ***Pol.:*** Amizepin; Finlepsin; Neurotop; Tegretol; Timonil; ***Port.:*** Tegretol; ***Rus.:*** Carbalepsin (Карбалепсин); Carbapin (Карбапин); Finlepsin (Финлепсин); Tegretol (Тегретол); Zeptol (Зептол); ***S.Afr.:*** Degranol; Tegretol; ***Singapore:*** Carbatol; Neurotop; Tegretol; ***Spain:*** Tegretol; ***Swed.:*** Hermolepsin; Tegretol; Trimonil; ***Switz.:*** Carsol; Neurotop; Tegretol; Timonil; ***Thai.:*** Antafit; Carbatol†; Carbazene; Carmapine; Carpine; Carzepine; Mapezine; Panitol; Taver; Tegretol; Zeptol; ***Turk.:*** Karazepin; Karbalex; Karbasif; Karberol; Kazepin; Tegretol; ***UAE:*** Fitzecalm; ***UK:*** Arbil; Carbagen; Epimaz; Tegretol; Teril†; Timonil†; ***USA:*** Atretol†; Carbatrol; Epitol; Equetro; Tegretol; Teril; ***Venez.:*** Convulex; Gabox†; Tanfedin; Tegretol.

Clobazam *(BAN, USAN, rINN)*

Clobazamum; H-4723; HR-376; Klobatsaami; Klobazam; Klobazamas; LM-2717. 7-Chloro-1,5-dihydro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4(3*H*)-dione.

Клобазам

$C_{16}H_{13}ClN_2O_2$ = 300.7.

CAS — 22316-47-8.

ATC — N05BA09.

ATC Vet — QN05BA09.

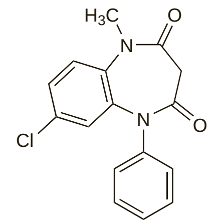

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clobazam). A white or almost white crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Breast feeding. Benzodiazepines, such as clobazam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on menstruation. Occasionally the use of clobazam before menstruation for catamenial epilepsy appeared to delay the period.[1]

1. Feely M. Prescribing anticonvulsant drugs 3: clonazepam and clobazam. *Prescribers' J* 1989; **29:** 111–15.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clobazam, on *cognition* and *mood*, including risk of suicidal ideation, see p.468.

Effects on the skin. Report[1] of toxic epidermal necrolysis that developed in light-exposed areas in a patient being treated with clobazam.

1. Redondo P, *et al.* Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996; **135:** 999–1002.

Porphyria. Clobazam is considered to be unsafe in patients with porphyria although there is conflicting evidence of porphyrinogenicity.

For comments on the use of benzodiazepines in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

As for Diazepam, p.989.

Antiepileptics. For reference to the interactions of clobazam with *felbamate* and *stiripentol*, see under Diazepam, p.990.

Pharmacokinetics

Clobazam is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1 to 4 hours after oral doses. It is about 85% bound to plasma proteins. Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. It is metabolised in the liver by demethylation and hydroxylation but unlike the 1,4-benzodiazepines such as diazepam, clobazam, a 1,5-benzodiazepine, is hydroxylated at the 4-position rather than the 3-position (see also Metabolism under Diazepam, p.992). Clobazam is excreted unchanged and as metabolites mainly in the urine. Mean half-lives of 18 hours and 42 hours have been reported for clobazam and its main active metabolite *N*-desmethylclobazam, respectively.

◊ References.

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.
2. Ochs HR, *et al.* Single and multiple dose kinetics of clobazam, and clinical effects during multiple dosage. *Eur J Clin Pharmacol* 1984; **26:** 499–503.

Uses and Administration

Clobazam is a long-acting 1,5-benzodiazepine with uses similar to those of diazepam (a 1,4-benzodiazepine; see p.992). It may be used as an adjunct in the treatment of epilepsy with other antiepileptics, although its use may be limited by the development of tolerance or sedation (but see below). It is also used in the short-term treatment of acute anxiety.

As an adjunct in **epilepsy** usual oral doses in the UK are 20 to 30 mg daily, increased if necessary to a maximum of 60 mg daily.

For doses in children, see below.

As with other antiepileptics, withdrawal of clobazam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465 and under Clonazepam, below.

For the short-term management of acute **anxiety** usual oral doses of 10 to 30 mg daily may be taken in divided doses or as a single dose at night; up to 80 mg daily has been used in hospitalised patients with severe anxiety states. Low initial doses and cautious increments to a usual daily dose of 10 to 20 mg are recommended in elderly or debilitated patients.

Administration in children. In the UK, clobazam is licensed for use as an adjunct in epilepsy in children over 3 years of age; no more than half the adult dose (see above) should be given. Alternatively, the *BNFC* suggests the following oral doses according to age:

- 1 month to 12 years: initially 125 micrograms/kg twice daily, increased every 5 days to a usual maintenance dose of 250 micrograms/kg twice daily. The maximum dose is 500 micrograms/kg twice daily and should not exceed 15 mg twice daily
- 12 to 18 years: initially 10 mg twice daily, increased every 5 days to a usual maintenance dose of 10 to 15 mg twice daily. The dose should not exceed 30 mg twice daily

The *BNFC* also suggests that clobazam may be given for cluster seizures and as monotherapy under specialist supervision for catamenial seizures (usually for 7 to 10 days each month just before and during menstruation).

Epilepsy. Benzodiazepines are sometimes used in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects.

Clobazam, a 1,5-benzodiazepine, is considered to be somewhat better tolerated than conventional benzodiazepines, and has been widely used for adjunctive oral therapy in patients with epilepsy.[1,2] Clobazam is active against partial and generalised seizures in epilepsy of widely differing aetiology in patients of all ages and has also been used for short-term cover in patients with intermittent seizures, including in women with catamenial epilepsy (seizures associated with menstruation) or patients whose epileptic attacks occur in clusters. Clobazam has also been tried with some success in children, including those with refractory epilepsy[3-5] and epileptic encephalopathy.[6] However, a recent systematic review[7] concluded that although clobazam may reduce seizure frequency and may be most effective in partial onset seizures, it was not clear who would best benefit from its use and over what time-frame.

1. Trimble MR. On the use of tranquillisers in epilepsy. *Epilepsia* 2002; **43** (suppl 2): 25–7.
2. Ng Y-T, Collins SD. Clobazam. *Neurotherapeutics* 2007; **4:** 138–44.
3. Munn R, Farrell K. Open study of clobazam in refractory epilepsy. *Pediatr Neurol* 1993; **9:** 465–9.
4. Sheth RD, *et al.* Clobazam for intractable pediatric epilepsy. *J Child Neurol* 1995; **10:** 205–8.
5. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. *Epilepsia* 1998; **39:** 952–9.
6. Silva RC, *et al.* Clobazam as add-on therapy in children with epileptic encephalopathy. *Can J Neurol Sci* 2006; **33:** 209–13.
7. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 16/06/08).

Neuropathic pain. There has been a mention[1] of the complete relief of *phantom limb pain* (p.9) refractory to other therapy in an elderly patient given clobazam 10 mg three times daily.

1. Rice-Oxley CP. The limited list: clobazam for phantom limb pain. *BMJ* 1986; **293:** 1309.

Preparations

BP 2008: Clobazam Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Karidium; ***Austral.:*** Frisium; ***Austria:*** Frisium; ***Belg.:*** Frisium; ***Braz.:*** Frisium; Urbanil; ***Canad.:*** Frisium; ***Chile:*** Frisin†; Grifoclobam; ***Cz.:*** Frisium; ***Denm.:*** Frisium; ***Fin.:*** Frisium; ***Fr.:*** Urbanyl; ***Ger.:*** Frisium; ***Gr.:*** Frisium; ***Hong Kong:*** Frisium; ***Hung.:*** Frisium; ***India:*** Frisium; ***Indon.:*** Asabium; Clobium; Frisium; Proclozam; ***Irl.:*** Frisium; ***Israel:*** Frisium; ***Ital.:*** Frisium; ***Malaysia:*** Frisium; ***Mex.:*** Frisium; ***Neth.:*** Frisium; ***NZ:*** Frisium; ***Pol.:*** Frisium; ***Port.:*** Castilium; Urbanil†; ***S.Afr.:*** Urbanol; ***Singapore:*** Frisium†; ***Spain:*** Noiafren; ***Switz.:*** Urbanyl; ***Thai.:*** Frisium; ***UK:*** Frisium; ***Venez.:*** Frisium.

Clonazepam *(BAN, USAN, rINN)*

Clonazépam; Clonazepamum; Klonatsepaami; Klonazepám; Klonazepam; Klonazepamas; Ro-5-4023. 5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one.

Клоназепам

$C_{15}H_{10}ClN_3O_3$ = 315.7.

CAS — 1622-61-3.

ATC — N03AE01.

ATC Vet — QN03AE01.

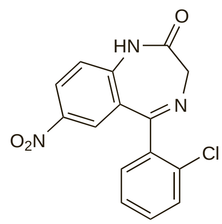

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of clonazepam:

K-Pins; Klondike Bars; Klonnies; Klons; La Roche; Pins; R2; R-2; Roaches; Roachies; Roche.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Clonazepam). A slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Clonazepam). A light yellow powder having a faint odour. Insoluble in water; slightly soluble in alcohol and in ether; sparingly soluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Sorption. Significant loss of clonazepam (up to 50% over 24 hours) has been reported[1] from solutions infused through PVC tubing; the effect was concentration dependent. The authors recommended that non-PVC tubing should always be used.

1. Schneider JJ, *et al.* Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion. *J Pain Symptom Manage* 2006; **31:** 563–7.

Dependence and Withdrawal

As for Diazepam, p.987.

Withdrawal. A study[1] of the withdrawal of clonazepam therapy in 40 epileptic children found that 19 had withdrawal symptoms of increased seizure frequency, either alone or with other symptoms but that this effect was transient. Withdrawal seizures and status might become an obstacle to the removal of useless or even deleterious therapy with clonazepam because the transient nature of these effects was not always recognised. Clonazepam should not be used for more than 3 to 6 months and should be stopped if clear and lasting therapeutic benefit could not be shown.

See also Uses and Administration, below.

1. Specht U, *et al.* Discontinuation of clonazepam after long-term treatment. *Epilepsia* 1989; **30:** 458–63.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

The principal adverse effect of clonazepam is drowsiness, which occurs in about 50% of all patients when starting therapy. Salivary or bronchial hypersecretion may cause respiratory problems in children. Thrombophlebitis has been associated with intravenous use and may be avoided by injection into a large vein at a rate not exceeding 500 micrograms/minute. Respiration and blood pressure should also be monitored.

Care is required when withdrawing clonazepam therapy—see above.

Breast feeding. Benzodiazepines, such as clonazepam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on the endocrine system. Precocious development of secondary sexual characteristics occurred in a 15-month-old girl 2 months after starting treatment with clonazepam 500 micrograms twice daily for convulsions.[1] Symptoms regressed upon withdrawal of clonazepam.

1. Choonara IA, *et al.* Clonazepam and sexual precocity. *N Engl J Med* 1985; **312:** 185.

Effects on mental function. For a review of the effects of antiepileptic therapy, including clonazepam, on *cognition* and mood, including the risk of suicidal ideation, see p.468.

Effects on the mouth. A 52-year-old woman developed burning mouth syndrome after starting clonazepam;[1] some improvement was noted when the dose was reduced but symptoms were still intolerable and clonazepam was withdrawn. Subsequently, symptoms resolved within 3 weeks.

1. Culhane NS, Hodle AD. Burning mouth syndrome after taking clonazepam. *Ann Pharmacother* 2001; **35:** 874–6.

Effects on sexual function. Sexual dysfunction was reported[1] in 18 of 42 male patients receiving clonazepam for the treatment of post-traumatic stress disorder; symptoms resolved when therapy was changed to diazepam in 17 patients and lorazepam in the remaining patient.

1. Fossey MD, Hamner MB. Clonazepam-related sexual dysfunction in male veterans with PTSD. *Anxiety* 1994-95; **1:** 233–6.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of benzodiazepines including clonazepam, see Effects on the Nervous System in Diazepam, p.988. However, clonazepam is also used in the treatment of some extrapyramidal disorders as discussed under Uses and Administration, below.

Porphyria. Clonazepam is considered to be unsafe in patients with porphyria although there is conflicting evidence of porphyrinogenicity.

For comments on the use of benzodiazepines in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

As for Diazepam, p.989.

Antiepileptics. For reference to possible interactions between clonazepam and other antiepileptics, see under Diazepam, p.990 and Benzodiazepines under Interactions of Phenytoin, p.499.

Pharmacokinetics

Clonazepam is quickly absorbed after oral doses with a bioavailability of about 90%; peak plasma concentrations are reached between 1 and 4 hours after ingestion. It is extensively metabolised in the liver, its principal metabolite being 7-aminoclonazepam, which has no antiepileptic activity; minor metabolites are the 7-acetamido- and 3-hydroxy-derivatives. It is excreted mainly in the urine almost entirely as its metabolites in free or conjugated form. It is about 85% bound to plasma proteins and estimations of its elimination half-life range from about 20 to 40 hours, and occasionally more.

A therapeutic range of plasma concentrations has not been established.

Clonazepam crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of clonazepam may be affected by use with other antiepileptics (see under Interactions, above).

◊ A single-dose pharmacokinetic study[1] in healthy subjects found that absorption of clonazepam was slower and intersubject variability was greater after intramuscular injection than after an oral dose. The pharmacokinetics of a modified-release subcutaneous injection have also been studied in healthy subjects;[2] plasma-clonazepam concentrations were sustained and elimination occurred slowly over 13 days.

1. Crevoisier C, *et al.* Comparative single-dose pharmacokinetics of clonazepam following intravenous, intramuscular and oral administration to healthy volunteers. *Eur Neurol* 2003; **49:** 173–7.
2. Greenblatt DJ, *et al.* Clonazepam pharmacokinetics: comparison of subcutaneous microsphere injection with multiple-dose oral administration. *J Clin Pharmacol* 2005; **45:** 1288–93.

Bioavailability. It has been suggested, on the basis of anecdotal evidence,[1] that there may be differences in bioavailability, and hence in clinical effect, between formulations of clonazepam tablets.

1. Rapaport MH. Clinical differences between the generic and non-generic forms of clonazepam. *J Clin Psychopharmacol* 1997; **17:** 424.

Uses and Administration

Clonazepam is a benzodiazepine derivative similar to diazepam (p.992), with marked antiepileptic properties.

It may be used in the treatment of all types of epilepsy and seizures (p.465), including status epilepticus (p.469), but its usefulness in chronic treatment is sometimes limited by the development of tolerance and by sedation, and other antiepileptics are often preferred. It may also be used in myoclonus (p.470) and associated abnormal movements, and for the treatment of panic disorder (see Psychiatric Disorders, below).

For **epilepsy** and **myoclonus** treatment is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses may initially be taken in 3 or 4 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. In the UK the initial oral dose is 1 mg (500 micrograms in the elderly) at night for 4 nights gradually increased over 2 to 4 weeks to a usual maintenance dose of 4 to 8 mg daily; it is recommended that the total dose should not exceed 20 mg daily. Dosage recommendations in the USA are generally similar although initial doses of up to 1.5 mg daily are permitted and dosage increments of 0.5 to 1 mg every 3 days are recommended. There is little value in routinely monitoring plasma-clonazepam concentrations.

Clonazepam may be an alternative to other benzodiazepines in the emergency management of **status epilepticus**. The usual dose is 1 mg given by slow intravenous injection over at least 2 minutes or by intravenous infusion, repeated if necessary to a maximum total dose of 20 mg.

For doses in children, see below.

As with other antiepileptics, withdrawal of clonazepam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465 and above.

In the treatment of **panic disorder**, clonazepam is given in an initial oral dose of 250 micrograms twice daily. This may be increased after 3 days to a total of 1 mg daily; a few patients may benefit from further increases, up to a maximum of 4 mg daily. In order to minimise drowsiness, clonazepam may be taken as a single dose at bedtime. Withdrawal should again be gradual.

Administration. Serum concentrations of clonazepam after buccal, intranasal, or intravenous dosage were measured in a crossover study[1] in 7 healthy males. The results showed that intranasal clonazepam may offer an alternative to buccal use in patients with serial seizures but the initial concentrations were too low to recommend its use as an alternative to intravenous clonazepam in the management of status epilepticus. The nasal formulation used in this study contained dimethyl-β-cyclodextrin as a solubiliser and absorption enhancer.

1. Schols-Hendriks MWG, *et al.* Absorption of clonazepam after intranasal and buccal administration. *Br J Clin Pharmacol* 1995; **39:** 449–51.

Administration in children. For **epilepsy** and **myoclonus** treatment with clonazepam is started with small doses that are progressively increased to an optimum dose according to response. Total daily doses are taken in 3 divided doses; however, once the maintenance dose has been reached, the daily amount may be given as a single dose at night. Alternatively, the *BNFC* suggests giving the initial dose at night for 4 nights and gradually increasing it over 2 to 4 weeks. In the UK, the recommended initial oral daily dose is up to 250 micrograms for infants and children aged up to 5 years, or up to 500 micrograms for older children. The following usual maintenance doses are given according to age:

- neonate to 1 year (although the BNFC recommends a minimum age of 1 month): 0.5 to 1 mg daily
- 1 to 5 years: 1 to 3 mg daily
- 5 to 12 years: 3 to 6 mg daily

Older children may be given the usual adult dose (see above).

If control of childhood epilepsy ceases to be adequate with clonazepam, the dose may be increased, or treatment interrupted for 2 or 3 weeks. The *BNFC* states that the UK injection formulation (*Rivotril; Roche, UK*) can be given orally if necessary; this may not apply to other injection formulations available elsewhere.

In the USA, doses may be given according to body weight. Infants and children aged up to 10 years or weighing up to 30 kg may be given an initial daily dose of 10 to 30 micrograms/kg (maximum 50 micrograms/kg) in 2 or 3 divided doses. This may be increased by a total of 250 to 500 micrograms every 3 days to a maintenance dose of 100 to 200 micrograms/kg daily given in 3 divided doses.

In the emergency management of **status epilepticus**, clonazepam is used as an alternative to other benzodiazepines. The usual dose in children is 500 micrograms given by slow intravenous injection or by intravenous infusion. Alternatively, the *BNFC* suggests giving the following doses by slow intravenous injection over at least 2 minutes according to age:

- neonates: 100 micrograms/kg, repeated if necessary after 24 hours
- 1 month to 12 years: 50 micrograms/kg (maximum 1 mg), repeated if necessary

Older children may be given the usual adult dose.

In children aged over 1 month, these doses by injection may be followed by an intravenous infusion of 10 micrograms/kg per hour, adjusted according to response to a maximum of 60 micrograms/kg per hour.

Extrapyramidal disorders. Clonazepam may be of benefit in some extrapyramidal disorders. It has been tried in the management of patients with *tic disorders* such as *Tourette's syndrome* (p.954) but evidence of efficacy from controlled studies is limited.[1] Some use clonazepam in preference to haloperidol[2] since it does not carry the risk of tardive dyskinesia associated with such antipsychotics and a case report[3] described the successful use of clonazepam for haloperidol-induced tardive Tourette's syndrome in an adult patient. There is also limited evidence of benefit with clonazepam in antipsychotic-induced *akathisia*[4,5] and *tardive dyskinesia*[6,7] (see under Extrapyramidal Disorders, p.971), and of improvement in *dysarthria* in a study in patients with parkinsonism.[8]

1. Goetz CG. Clonidine and clonazepam in Tourette syndrome. *Adv Neurol* 1992; **58:** 245–51.
2. Truong DD, *et al.* Clonazepam, haloperidol, and clonidine in tic disorders. *South Med J* 1988; **81:** 1103–5.
3. Reid SD. Neuroleptic-induced tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004; **27:** 101–4.
4. Kutcher S, *et al.* Successful clonazepam treatment of neuroleptic-induced akathisia in older adolescents and young adults: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1989; **9:** 403–6.
5. Pujalte D, *et al.* A double-blind comparison of clonazepam and placebo in the treatment of neuroleptic-induced akathisia. *Clin Neuropharmacol* 1994; **17:** 236–42.
6. Thaker GK, *et al.* Clonazepam treatment of tardive dyskinesia: a practical GABAmimetic strategy. *Am J Psychiatry* 1990: **147:** 445–51.
7. Shapleske J, *et al.* Successful treatment of tardive dystonia with clozapine and clonazepam. *Br J Psychiatry* 1996; **168:** 516–18.
8. Biary N, *et al.* A double-blind trial of clonazepam in the treatment of parkinsonian dysarthria. *Neurology* 1988; **38:** 255–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Clonazepam may also be of value, especially in neurogenic hiccups.

Neuropathic pain. The management of *phantom limb pain* (p.9) can be difficult, and tricyclic antidepressants and antiepileptics are used for the neuropathic components of the pain. Rapid and marked pain relief was achieved in 2 patients with lancinating phantom limb pain after treatment with clonazepam with or without amitriptyline.[1]

Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), clonazepam may be used in carbamazepine-intolerant patients.

1. Bartusch SL, *et al.* Clonazepam for the treatment of lancinating phantom limb pain. *Clin J Pain* 1996; **12:** 59–62.

Psychiatric disorders. Although the risk of dependence with benzodiazepines may outweigh their benefits in panic disorder (p.952), clonazepam has been used for the treatment of panic disorder with or without agoraphobia, and reported benefit in such patients[1] suggests a similar action to alprazolam. A literature review[2] evaluated the use of clonazepam in a range of psychiatric disorders and found that it may also be effective in the treatment of social anxiety disorder (see Phobic Disorders, p.953) although further studies are warranted. There was evidence to suggest that clonazepam may be useful in acute mania (p.372) and for the augmentation of antidepressant therapy with SSRIs in depression (p.373). A study[3] found that augmentation was significantly more effective with a daily dose of 3 mg of clonazepam than with lower doses.

1. Davidson JRT, Moroz G. Pivotal studies of clonazepam in panic disorder. *Psychopharmacol Bull* 1998; **34:** 169–74.
2. Nardi AE, Perna G. Clonazepam in the treatment of psychiatric disorders: an update. *Int Clin Psychopharmacol* 2006; **21:** 131–42.
3. Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. *J Affect Disord* 1999; **53:** 275–8.

Sleep-associated movement disorders. Treatment of sleep-associated movement disorders (p.958) including sleep behaviour disorder, restless legs syndrome, and periodic limb movements in sleep is largely empirical, but benzodiazepines such as clonazepam are often used.[1] Small studies have provided some evidence for benefit with clonazepam therapy in these disorders,[2-4] including bruxism.[5]

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.
2. Montagna P, *et al.* Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand* 1984; **69:** 428–30.
3. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987; **50:** 1679–81.
4. Saletu M, *et al.* Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol* 2001; **11:** 153–61.
5. Saletu A, *et al.* On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam. *Neuropsychobiology* 2005; **51:** 214–25.

Stiff-man syndrome. Clonazepam has been used as an alternative to diazepam in the management of stiff-man syndrome (see under Muscle Spasm, p.993) and is reported[1] to be effective for familial startle disease, a rare congenital form of stiff-man syndrome.

1. Ryan SG, *et al.* Startle disease, or hyperekplexia: response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. *Ann Neurol* 1992; **31:** 663–8.

Tinnitus. Clonazepam is one of many drugs that have been tried in tinnitus (p.1866), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

References.

1. Ganança MM, *et al.* Clonazepam in the pharmacological treatment of vertigo and tinnitus. *Int Tinnitus J* 2002; **8:** 50–3.
2. Albertino S, *et al.* Pulsatile tinnitus: treatment with clonazepam and propranolol. *Rev Bras Otorrinolaringol (Engl Ed)* 2005; **71:** 111–13.

Preparations

BP 2008: Clonazepam Injection;
USP 31: Clonazepam Oral Suspension; Clonazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alerion; Ciclox; Clonabay; Clonagin; Clonax; Clonazen 2; Cloner; Diocam; Edictum; Felanor; Flozepan; Induzepam; Leptic; Miozepam; Neuryl; Olimer; Placidiax; Riuclonaz; Rivotril; Sedovanon; Sensaton; Solfidin; ***Austral.:*** Paxam; Rivotril; ***Austria:*** Rivotril; ***Belg.:*** Rivotril; ***Braz.:*** Clonotril; Clopan; Epileptil; Navotrax; Rivotril; Uni Clonazepax; ***Canad.:*** Clonapam†; Rivotril; ***Chile:*** Acepran; Clonapam; Clonex; Clozanil; Crismol; Neuryl; Ravotril; Ropsil; Valpax; ***Cz.:*** Antelepsin†; Rivotril; ***Denm.:*** Rivotril; ***Fin.:*** Rivatril; ***Fr.:*** Rivotril; ***Ger.:*** Antelepsin; Rivotril; ***Gr.:*** Rivotril; ***Hong Kong:*** Rivotril; ***Hung.:*** Clonapam; Clonogal†; Rivotril; ***India:*** Epitril; Epizam; Ozepam; ***Indon.:*** Rivotril; ***Irl.:*** Rivotril; ***Israel:*** Clonex; Rivotril; ***Ital.:*** Rivotril; ***Malaysia:*** Rivotril; ***Mex.:*** Kenoket; Kriadex; Rivotril; Zymanta; ***Neth.:*** Rivotril; ***Norw.:*** Rivotril; ***NZ:*** Paxam; Rivotril; ***Philipp.:*** Rivotril; ***Pol.:*** Rivotril; ***Port.:*** Rivotril; ***S.Afr.:*** Rivotril; ***Spain:*** Rivotril; ***Swed.:*** Iktorivil; ***Switz.:*** Rivotril; ***Thai.:*** Povanil; Rivotril; ***Turk.:*** Rivotril; ***UK:*** Rivotril; ***USA:*** Klonopin; ***Venez.:*** Rivotril.

Ethadione

Etadiona. 3-Ethyl-5,5-dimethyl-2,4-oxazolidinedione.

Этадион

$C_7H_{11}NO_3$ = 157.2.
CAS — 520-77-4.
ATC — N03AC03.
ATC Vet — QN03AC03.

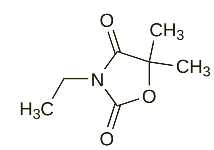

Profile

Ethadione is an oxazolidinedione antiepileptic that has been given orally to treat epilepsy in patients with absence seizures resistant to other therapy.

Preparations

Ethosuximide *(BAN, USAN, rINN)*

CI-366; CN-10395; Ethosuximid; Éthosuximide; Ethosuximidum; Etosüksimid; Etosuksimidas; Etosuksimidi; Etosuksymid; Etosuximid; Etosuximida; Etoszuximid; NSC-64013; PM-671. 2-Ethyl-2-methylsuccinimide.

Этосуксимид

$C_7H_{11}NO_2$ = 141.2.
CAS — 77-67-8.
ATC — N03AD01.
ATC Vet — QN03AD01.

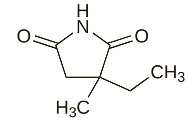

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ethosuximide). A white or almost white powder or waxy solid. It exhibits polymorphism. Freely soluble in water;

The symbol † denotes a preparation no longer actively marketed

very soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Ethosuximide). A white to off-white crystalline powder or waxy solid, having a characteristic odour. Freely soluble in water and in chloroform; very soluble in alcohol and in ether; very slightly soluble in petroleum spirit. Store in airtight containers.

Adverse Effects and Treatment

Gastrointestinal adverse effects including nausea, vomiting, diarrhoea, anorexia, gastric upset, and abdominal pain occur quite often with ethosuximide. Other effects that may occur include headache, fatigue, lethargy, drowsiness, dizziness, ataxia, hiccup, and mild euphoria.

More rarely dyskinesias, personality changes, depression, psychosis, sleep disturbances including night terrors, skin rashes, erythema multiforme or Stevens-Johnson syndrome, SLE, photophobia, gum hypertrophy, tongue swelling, myopia, increased libido, and vaginal bleeding have been reported. There are a few reports of blood disorders including eosinophilia, leucopenia, agranulocytosis, thrombocytopenia, pancytopenia, and aplastic anaemia; fatalities have occurred.

Abnormal renal and liver function values have been recorded.

Effects on mental function. For the effects of antiepileptic therapy on cognition and mood, including the risk of suicidal ideation, see p.468.

Precautions

Ethosuximide should be used with caution in patients with impaired hepatic or renal function. Licensed product information recommends regular hepatic and renal-function tests (and some suggest blood counts) during treatment with ethosuximide, although the practical value of such monitoring has been questioned. Patients or their carers should be told how to recognise signs of blood toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Care is required when withdrawing ethosuximide therapy—see also Uses and Administration, below.

Breast feeding. Ethosuximide is distributed in significant amounts into breast milk; hyperexcitability and poor suckling have been reported in the infant. Although licensed product information recommends that breast feeding should be avoided, the American Academy of Pediatrics[1] considers that ethosuximide is usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Porphyria. Ethosuximide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antibacterials. *Isoniazid* raises the plasma concentration of ethosuximide and increases the risk of toxicity. Psychotic behaviour has been reported[1] in a patient stabilised on ethosuximide and sodium valproate, after the introduction of isoniazid. Serum-ethosuximide concentrations rose substantially until both ethosuximide and isoniazid were stopped.

1. van Wieringen A, Vrijlandt CM. Ethosuximide intoxication caused by interaction with isoniazid. *Neurology* 1983; **33:** 1227–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Antiepileptics. Since ethosuximide has a limited spectrum of antiepileptic action, patients with mixed seizure syndromes may require addition of other antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* have all been shown[1] to increase the clearance of ethosuximide and thus reduce plasma concentrations. This interaction is likely to be clinically relevant and higher ethosuximide dosages may be necessary to achieve therapeutic drug levels. The effect of *valproic acid* on ethosuximide concentrations is unclear. One study[2] showed a marked increase in serum ethosuximide concentrations once valproate was added to combination therapies; increases in ethosuximide concentrations have also been noted in healthy subjects when taken with valproic acid.[3] Conversely, other studies have reported reductions[4] or no significant changes in serum ethosuximide concentrations[5,6] with valproic acid. For the effect of ethosuximide on valproic acid, see p.511.

1. Giaccone M, *et al.* Effect of enzyme inducing anticonvulsants on ethosuximide pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1996; **41:** 575–9.
2. Mattson RH, Cramer JA. Valproic acid and ethosuximide interaction. *Ann Neurol* 1980; **7:** 583–4.
3. Pisani F, *et al.* Valproic acid-ethosuximide interaction: a pharmacokinetic study. *Epilepsia* 1984; **25:** 229–33.
4. Battino D, *et al.* Ethosuximide plasma concentrations: influence of age and associated concomitant therapy. *Clin Pharmacokinet* 1982; **7:** 176–80.
5. Fowler GW. Effect of dipropylacetate on serum levels of anticonvulsants in children. *Proc West Pharmacol Soc* 1978; **21:** 37–40.
6. Bauer LA, *et al.* Ethosuximide kinetics: possible interaction with valproic acid. *Clin Pharmacol Ther* 1982; **31:** 741–5.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of ethosuximide by lowering the convulsive threshold.

Pharmacokinetics

Ethosuximide is readily absorbed from the gastrointestinal tract and extensively hydroxylated in the liver to its principal metabolite which is reported to be inactive. Ethosuximide is excreted in the urine mainly in the form of its metabolites, either free or conjugated, but about 12 to 20% is also excreted unchanged.

Ethosuximide is widely distributed throughout the body, but is not significantly bound to plasma proteins. A half-life of about 40 to 60 hours has been reported for adults with a shorter half-life of about 30 hours in children.

Monitoring of plasma concentrations has been suggested as an aid in assessing control and the therapeutic range of ethosuximide is usually quoted as being 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre); concentrations in saliva and tears have also been measured.

Ethosuximide crosses the placental barrier, and is distributed into breast milk.

The pharmacokinetics of ethosuximide are affected by use with other antiepileptics (see under Interactions, above).

Uses and Administration

Ethosuximide is a succinimide antiepileptic used in the treatment of absence seizures (below). It may also be used for myoclonic seizures. Ethosuximide is ineffective against tonic-clonic seizures and may unmask them if given alone in mixed seizure types.

A plasma-ethosuximide concentration of 40 to 100 micrograms/mL (about 300 to 700 micromoles/litre) appears to be generally necessary. The initial dose is 500 mg daily by mouth. The dosage is then adjusted in steps of 250 mg every 4 to 7 days, according to response. Control of seizures is usually produced with a daily dose of 1 to 1.5 g, although some patients may require doses of up to 2 g; strict supervision is necessary when the dose exceeds 1.5 g. Daily doses at the higher end of the range should be given in 2 divided doses.

For doses in children, see below.

As with other antiepileptics, withdrawal of ethosuximide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Administration in children. Ethosuximide may be used in the treatment of absence (petit mal) seizures and for myoclonic seizures in infants and children. In the UK, the following recommended oral doses are given according to age:

- up to 6 years of age: an initial dose of 250 mg daily, increased gradually in small steps every few days to a usual dose of 20 mg/kg daily; licensed information for one product (*Emeside; Chemidex, UK*) recommends that the dose should not exceed 1 g. (Similar dosages are recommended in the USA for children aged between 3 to 6 years). The *BNFC* suggests giving the daily dose as 2, or if necessary 3, divided doses
- aged 6 years and above: usual adult doses (see above)

Epilepsy. Ethosuximide is a drug of choice in the treatment of absence seizures; it may also be used for myoclonic, atonic, and tonic seizures but is ineffective in other forms of epilepsy (p.465). Ethosuximide may be given with other antiepileptics in the treatment of mixed-seizure syndromes that include absences. It has been suggested that ethosuximide may provoke tonic-clonic seizures, but there is not a great deal of evidence for this. One early report indicated that 22 of 85 patients receiving a regimen of ethosuximide, mesuximide, and trimethadione for absence seizures developed tonic-clonic seizures[1] and another of similar vintage reported exacerbation of mixed-seizure types in 7 patients receiving ethosuximide.[2] However, it is recognised that patients with absence seizures have a high incidence of generalised tonic-clonic seizures[3] and it would presumably be difficult to distinguish such attacks from any putative effect of ethosuximide. Furthermore, ethosuximide is not effective against tonic-clonic seizures, and in patients with mixed-seizure types it might be expected to unmask the non-absence components of the disease.

Ethosuximide has also been tried in the management of absence status epilepticus (p.469).

1. Friedel B, Lempp R. Grand-mal-Provokation bei der Behandlung kindlicher petit-mal mit Oxazolidinen oder Succinimiden und ihre therapeutischen Konsequenzen. *Z Kinderheilk* 1962; **87:** 42–51.
2. de Haas AML, Kuilman M. Ethosuximide (α-ethyl-α-methylsuccinimide) and grand mal. *Epilepsia* 1964; **5:** 90–6.
3. Glauser TA. Succinimides: Adverse Effects. In: Levy RG, *et al.*, eds. *Antiepileptic drugs* 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 658–64.

Preparations

BP 2008: Ethosuximide Capsules; Ethosuximide Oral Solution;
USP 31: Ethosuximide Capsules; Ethosuximide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Zarontin; ***Austral.:*** Zarontin; ***Austria:*** Petinimid; Suxinutin; ***Belg.:*** Zarontin; ***Canad.:*** Zarontin; ***Chile:*** Suxinutin; ***Cz.:*** Petinimid; Suxilep†; ***Denm.:*** Zarondan; ***Fin.:*** Suxinutin; ***Fr.:*** Zarontin; ***Ger.:*** Petnidan; Suxilep; Suxinutin†; ***Gr.:*** Zarontin; ***Hung.:*** Petnidan; Suxinutin†; ***Irl.:*** Zarontin; ***Israel:*** Zarontin†; ***Ital.:*** Zarontin; ***Mex.:*** Fluozoid; ***Neth.:*** Ethymal; Zarontin†; ***NZ:*** Zarontin; ***Pol.:*** Petinimid; ***Rus.:*** Suxilep (Суксилеп); ***S.Afr.:*** Zarontin; ***Spain:*** Zarontin†; ***Swed.:*** Suxinutin; ***Switz.:*** Petinimid; Suxinutin†; ***UK:*** Emeside; Zarontin; ***USA:*** Zarontin.

Ethotoin *(BAN, rINN)*

Éthotoïne; Ethotoinum; Etotoiini; Etotoin; Etotoína. 3-Ethyl-5-phenylhydantoin.

Этотоин

$C_{11}H_{12}N_2O_2$ = 204.2.
CAS — 86-35-1.
ATC — N03AB01.
ATC Vet — QN03AB01.

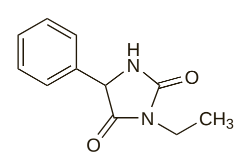

Pharmacopoeias. In *US.*

USP 31 (Ethotoin). A white crystalline powder. Insoluble in water; freely soluble in dehydrated alcohol and in chloroform; soluble in ether. Store in airtight containers.

Profile

Ethotoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p.495), but it is reported to be both less toxic and less effective and is not commonly used in epilepsy (p.465).

Ethotoin is given orally for tonic-clonic and complex partial seizures in initial doses of up to 1 g daily, increased gradually at intervals of several days to 2 to 3 g daily, given in 4 to 6 divided doses after meals.

Administration. A study[1] of the pharmacokinetics of ethotoin given at more convenient intervals of every 8 hours.

1. Browne TR, Szabo GK. A pharmacokinetic rationale for three times daily administration of ethotoin (Peganone). *J Clin Pharmacol* 1989; **29:** 270–1.

Porphyria. Ethotoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Ethotoin Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Peganone.

Felbamate (*USAN, rINN*)

AD-03055; Felbamato; Felbamatum; W-554. 2-Phenyl-1,3-propanediol dicarbamate.

Фелбамат

$C_{11}H_{14}N_2O_4$ = 238.2.

CAS — 25451-15-4.

ATC — N03AX10.

ATC Vet — QN03AX10.

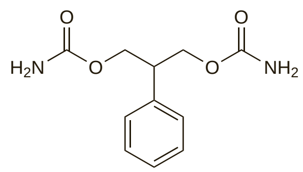

Adverse Effects

The most frequently reported adverse effects with felbamate are anorexia, weight loss, nausea and vomiting, rash, insomnia, headache, dizziness, somnolence, and diplopia. Aplastic anaemia or acute liver failure, sometimes fatal, have occurred rarely, and there have been reports of Stevens-Johnson syndrome.

Effects on the kidneys. A 15-year-old boy receiving up to 3 g of felbamate daily developed urethral obstruction due to formation of urethral stones composed of felbamate.[1] Records revealed that unidentified urinary crystals had been found in the patient's urine 2 years before presentation with acute urolithiasis.

For reports of crystalluria associated with felbamate overdosage, see below.

1. Sparagana SP, *et al.* Felbamate urolithiasis. *Epilepsia* 2001; **42:** 682–5.

Effects on mental function. For the effects of antiepileptic therapy on cognition and mood, including the risk of suicidal ideation, see p.468

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a patient 16 days after she started monotherapy with felbamate for partial complex seizures.

1. Travaglini MT, *et al.* Toxic epidermal necrolysis after initiation of felbamate therapy. *Pharmacotherapy* 1995; **15:** 260–4.

Overdosage. A 20-year-old woman presented with slurred speech and nausea 4 hours after ingesting 18 g of felbamate and 12 to 25 g of sodium valproate.[1] Over the next 4 to 5 hours she became combative, uncooperative, and progressively obtunded and eventually required endotracheal intubation and assisted ventilation. Peak plasma concentrations of 200 micrograms/mL for felbamate and 470 micrograms/mL for sodium valproate occurred 12 and 14 hours respectively after ingestion. Large quantities of macroscopic crystals, identified as containing felbamate, were noted in the urine 18 hours after ingestion and the patient developed renal failure. The crystalluria and renal failure responded to parenteral hydration. In another case report,[2] a 3-year-old child ingested 232 mg/kg of felbamate resulting in ataxia, vomiting, crystalluria, haematuria, and mild tachycardia. The plasma concentration of felbamate 15 hours after ingestion was 138 micrograms/mL. She was successfully treated with an infusion of sodium chloride 0.9% and intravenous metoclopramide; no renal impairment was seen.

1. Rengstorff DS, *et al.* Felbamate overdose complicated by massive crystalluria and acute renal failure. *J Toxicol Clin Toxicol* 2000; **38:** 667–9.
2. Meier KH, *et al.* Acute felbamate overdose with crystalluria. *Clin Toxicol* 2005; **43:** 189–92.

Precautions

Felbamate is contra-indicated in patients with a history of blood disorders or hepatic impairment. It should be used only in the treatment of severe epilepsy refractory to other antiepileptics because of the risk of fatal aplastic anaemia or acute liver failure. Patients or their carers should be advised of the symptoms of aplastic anaemia and be told to report immediately should any such symptoms develop. Complete blood counts should be carried out before the patient starts treatment and regularly during treatment (but see Epilepsy, under Uses and Administration, below). Aplastic anaemia may occur after felbamate has been stopped so patients should continue to be monitored for some time. Liver function tests are also recommended before starting and regularly (at 1- to 2-week intervals) during treatment. Felbamate should be stopped if there is any evidence of bone marrow depression or liver abnormalities.

Felbamate should be used with caution in patients with renal impairment. Felbamate may cause photosensitivity reactions and patients should be advised to take protective measures against exposure to UV radiation.

Care is required when withdrawing felbamate therapy—see also Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

The elderly. Felbamate may need to be given with care in elderly patients (see Administration in the Elderly, below).

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of felbamate is enhanced by enzyme inducers such as phenytoin, phenobarbital, or carbamazepine. In contrast, the half-life of felbamate may be prolonged by gabapentin. Felbamate inhibits or enhances the metabolism of several other antiepileptics and care is required when it is added to therapy.

Anticoagulants. For the effect of felbamate on *warfarin*, see p.1429.

Antiepileptics. For some references to the effect of felbamate on other antiepileptics, see under *Carbamazepine*, p.474, *Phenobarbital*, p.493, *Phenytoin*, p.498, and *Valproate* p.511.

Sex hormones. For the effect of felbamate on *oral contraceptives* see p.2068 and also under Gestodene, p.2105.

Pharmacokinetics

Felbamate is well absorbed from the gastrointestinal tract and peak plasma concentrations have been reported 1 to 6 hours after oral doses. Protein binding is reported to be about 22 to 25%. It is partly metabolised in the liver by hydroxylation and conjugation to inactive metabolites. Felbamate is excreted mainly in the urine as metabolites and unchanged drug (40 to 50%); less than 5% appears in the faeces. The terminal half-life is reported to be between 16 and 23 hours. Felbamate is distributed into breast milk.

The pharmacokinetics of felbamate are reported to be linear at the doses used clinically. Therapeutic plasma concentrations have been reported to be between 30 and 80 micrograms/mL.

The pharmacokinetics of felbamate are affected by use with other antiepileptics (see Interactions, above).

◊ See under Uses and Administration (below) for mention of pharmacokinetic studies of felbamate in the elderly and in patients with renal impairment.

Uses and Administration

Felbamate is a carbamate structurally related to meprobamate (p.1006). It is used in the treatment of epilepsy (see below); however, because of its toxicity, it should only be used in severe cases unresponsive to other drugs.

Felbamate is given orally as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation. It is used in children as adjunctive therapy in controlling the seizures associated with the Lennox-Gastaut syndrome (see below).

The initial dose of felbamate when given as *monotherapy* is 1.2 g daily in 3 or 4 divided doses. The daily dose should be increased gradually under close supervision; increments of 600 mg every 2 weeks are given according to response, up to 2.4 g daily. Thereafter doses may be further increased to a maximum of 3.6 g daily if necessary.

Similar initial doses are given as *adjunctive* therapy, but the doses of the other antiepileptics should be decreased as necessary. This adjunctive dose may be increased by 1.2 g at weekly intervals, up to a maximum of 3.6 g.

As with other antiepileptics, withdrawal of felbamate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

◊ References.

1. Pellock JM, *et al.* Felbamate: consensus of current clinical experience. *Epilepsy Res* 2006; **71:** 89–101.

Administration in children. As an adjunct in Lennox-Gastaut syndrome, the initial oral dose of felbamate in children aged 2 to 14 years is 15 mg/kg daily in 3 to 4 divided doses. This may be increased gradually in increments of 15 mg/kg at weekly intervals to a maximum of 45 mg/kg daily; the doses of other antiepileptics should be decreased as necessary.

Those aged 14 years and over may be given the usual adult dose (see above) as monotherapy or adjunctive therapy for refractory partial seizures with or without secondary generalisation.

Administration in the elderly. The elderly may require lower initial doses of felbamate and slower dose titration. After single doses of felbamate, plasma concentrations and half-lives were greater and mean clearance lower in elderly than in young subjects, whereas pharmacokinetic parameters after multiple dosing schedules were similar.[1]

1. Richens A, *et al.* Single and multiple dose pharmacokinetics of felbamate in the elderly. *Br J Clin Pharmacol* 1997; **44:** 129–34.

Administration in renal impairment. A single-dose pharmacokinetic study[1] indicated that in patients with renal impairment the initial dose of felbamate may need to be lower and increases made more cautiously than in patients with normal renal function (licensed product information suggests halving initial and maintenance doses).

1. Glue P, *et al.* Single-dose pharmacokinetics of felbamate in patients with renal dysfunction. *Br J Clin Pharmacol* 1997; **44:** 91–3.

Epilepsy. Although felbamate was well tolerated in clinical studies, rare but serious adverse effects were noted during early postmarketing use.[1,2] Aplastic anaemia and serious hepatotoxic reactions, sometimes with fatal outcomes, developed in some patients. Patients taking felbamate should have frequent blood counts and monitoring of liver enzymes. However there is no evidence that such monitoring will prevent adverse outcomes; in addition, the risk of aplastic anaemia is thought to decrease after the first year of therapy, and the need for ongoing blood counts is still less clear.[3] Even if detected early, aplastic anaemia and hepatic impairment may not be reversible.[1] Usage in the USA is restricted to patients with refractory partial seizures with or without secondary generalisation or for adjunctive therapy for children with Lennox-Gastaut syndrome. Guidelines on appropriate use have been issued.[3]

The overall management of epilepsy is discussed on p.465.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. *N Engl J Med* 1996; **334:** 1583–90.
2. Appleton RE. The new antiepileptic drugs. *Arch Dis Child* 1996; **75:** 256–62.
3. French J, *et al.* The use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 1999; **40:** 803–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119061174/PDFSTART (accessed 01/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Felbamyl; ***Austria:*** Taloxa; ***Belg.:*** Taloxa; ***Cz.:*** Taloxa†; ***Fr.:*** Taloxa; ***Ger.:*** Taloxa; ***Hung.:*** Taloxa; ***Ital.:*** Taloxa; ***Neth.:*** Taloxa; ***Norw.:*** Taloxa; ***Port.:*** Taloxa; ***Swed.:*** Taloxa; ***Switz.:*** Taloxa; ***USA:*** Felbatol.

Fosphenytoin Sodium (*BANM, USAN, rINNM*)

ACC-9653; ACC-9653-010; CI-982 (fosphenytoin or fosphenytoin sodium); Fosfenitoin Sodyum; Fosfenitoína sódica; Fosphénytoïne Sodique; Natrii Fosphenytoinum; PD-135711-15B. 5,5-Diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium; 3-(Hydroxymethyl)-5,5-diphenylhydantoin disodium phosphate; 2,5-Dioxo-4,4-diphenylimidazolidin-1-ylmethyl phosphate disodium.

Натрий Фосфенитоин

$C_{16}H_{13}N_2Na_2O_6P$ = 406.2.

CAS — 93390-81-9 (fosphenytoin); 92134-98-0 (fosphenytoin sodium).

ATC — N03AB05.

ATC Vet — QN03AB05.

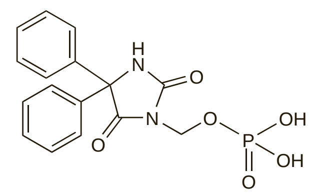

(fosphenytoin)

Pharmacopoeias. In *US.*

USP 31 (Fosphenytoin Sodium). A white to pale yellow solid. Freely soluble in water. pH of a 7.5% solution in water is between 8.5 and 9.5. Store in airtight containers.

Stability. References.

1. Fischer JH, *et al.* Stability of fosphenytoin sodium with intravenous solutions in glass bottles, polyvinyl chloride bags, and polypropylene syringes. *Ann Pharmacother* 1997; **31**: 553–9.

Adverse Effects and Precautions

As for Phenytoin, p.495.

Severe cardiovascular reactions, sometimes fatal, have been reported after intravenous doses of fosphenytoin. Therefore, continuous monitoring of ECG, blood pressure, and respiratory function is recommended during the infusion, and the patient should be kept under observation for at least 30 minutes after the end of the infusion. Hypotension may occur with recommended doses and rates of infusion; a reduction in the infusion rate or stopping therapy may be necessary. Fosphenytoin is contra-indicated in patients with sinus bradycardia, sino-atrial block, second- or third-degree AV block, or Stokes-Adams syndrome.

Burning, itching, and paraesthesia, particularly in the groin area, have also been reported after intravenous fosphenytoin; reducing the rate of, or temporarily stopping, the infusion may relieve the discomfort.

Caution should be exercised when giving fosphenytoin to patients in whom phosphate restriction is necessary. The rate of metabolism of fosphenytoin to phenytoin may be increased in patients with hepatic or renal disease, or in those with hypoalbuminaemia, and consequently there is an increased risk of adverse effects in such patients.

Effects on the cardiovascular system. The UK CSM[1] stated in May 2000 that worldwide there had been reports of 21 cases of asystole, ventricular fibrillation, or cardiac arrest associated with intravenous use of fosphenytoin. Of these, 5 cases had received doses or infusion rates greater than recommended. There had also been 34 reports of hypotension, 15 of bradycardia, and 10 of varying degrees of heart block. Most reactions had occurred within 30 minutes of the infusion. A review[2] of adverse events associated with fosphenytoin infusion received by the FDA Adverse Event Reporting System between 1997 and 2002 identified 29 of adverse cardiac events, including 10 fatalities. Of these reports, 5 were of sinus arrest, 4 of AV block, and 8 of asystole. The authors acknowledged that the majority of patients had serious confounders including renal failure, stroke, acute cardiac ischaemia or failure, overdose, or infection.

ECG changes consistent with hypocalcaemia have occurred in a patient who received 1500 mg-equivalents of phenytoin over 85 minutes as an intravenous infusion of fosphenytoin.[3] The patient had initially been normocalcaemic and it was suggested that the effect may have been due to acute inorganic phosphate toxicity.

1. Committee on Safety of Medicines/Medicines Control Agency. Fosphenytoin sodium (Pro-Epanutin): serious arrhythmias and hypotension. *Current Problems* 2000; **26:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
2. Adams BD, *et al.* Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med* 2006; **30:** 75–9.
3. Keegan MT, *et al.* Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. *Mayo Clin Proc* 2002; **77:** 584–6.

Porphyria. Phenytoin is considered unsafe in porphyric patients; it would be prudent to assume that this consideration also applied to its prodrug, fosphenytoin.

Interactions

As for Phenytoin, p.497.

Pharmacokinetics

Plasma concentrations of fosphenytoin are maximal at the end of intravenous infusion and about 30 minutes after intramuscular injection. Protein binding of fosphenytoin is high (95 to 99%), mainly to albumin, and is saturable. Fosphenytoin displaces phenytoin from protein binding sites which increases the fraction of unbound phenytoin to up to 30% for about half to one hour post-infusion. Fosphenytoin is rapidly and completely hydrolysed to phenytoin with a conversion half-life of about 15 minutes; one mmol of fosphenytoin yields one mmol of phenytoin, and the same of phosphate and formate. Metabolites of phenytoin are excreted in the urine. For the pharmacokinetics of phenytoin, see p.500.

◊ References.

1. Fischer JH, *et al.* Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet* 2003; **42:** 33–58.

Uses and Administration

Fosphenytoin is a prodrug of phenytoin (p.495) used similarly as part of the emergency treatment of status epilepticus (p.469). It is also used for the prevention and treatment of post-traumatic seizures (p.501) associated with neurosurgery or head trauma and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy (p.465).

Fosphenytoin is given as the sodium salt and doses of fosphenytoin sodium are expressed as phenytoin sodium equivalents (PSE); therefore no adjustment in dosage is necessary when substituting fosphenytoin for phenytoin or vice versa. Fosphenytoin may be given by intramuscular injection or intravenous infusion; only the intravenous route is recommended in children.

The maximum rate of intravenous infusion in PSE is 150 mg/minute and should not be exceeded. Continuous monitoring of ECG, blood pressure, and respiratory function is recommended during intravenous infusion. Patients should also be observed for at least 30 minutes after the end of infusion.

In the treatment of tonic-clonic status epilepticus a benzodiazepine such as diazepam or lorazepam is usually given initially intravenously or rectally followed by fosphenytoin. In the UK, the loading dose in PSE is 15 mg/kg given as a single dose by intravenous infusion at a rate of 100 to 150 mg/minute. The intramuscular route is not appropriate for the management of status epilepticus because peak phenytoin concentrations will not be reached quickly enough. The loading dose for seizures other than in status epilepticus is 10 to 15 mg/kg given as a single dose by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Initial maintenance doses for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 or 2 divided doses by intramuscular injection or by intravenous infusion at a rate of 50 to 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given intramuscularly or by intravenous infusion at a rate of 50 to 100 mg/minute may be substituted for oral phenytoin at the same equivalent total daily dose for up to 5 days.

In the USA, loading doses in PSE of up to 20 mg/kg are permitted, and initial maintenance doses are 4 to 6 mg/kg daily.

For doses in children, see below.

A lower loading dose and/or infusion rate, and lower or less frequent maintenance dosing may be necessary for elderly patients; UK licensed product information suggests a reduction in dose or rate of 10 to 25%. Similar reductions are suggested for patients with renal or hepatic impairment (see also below) or in those with hypoalbuminaemia, except in the treatment of status epilepticus.

◊ References.

1. Wilder BJ, *et al.* Safety and tolerance of multiple doses of intramuscular fosphenytoin substituted for oral phenytoin in epilepsy or neurosurgery. *Arch Neurol* 1996; **53:** 764–8.
2. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999; **159:** 2639–44.
3. Heafield MTE. Managing status epilepticus: new drug offers real advantages. *BMJ* 2000: **320:** 953–4.
4. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Safety* 2000; **22:** 459–66.

Administration in children. In the UK, fosphenytoin sodium may be given to children over 5 years of age for the emergency treatment of status epilepticus, the prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma, and as a short-term parenteral substitute for oral phenytoin in the management of epilepsy. It is given by intravenous infusion and doses are expressed as phenytoin sodium equivalents (PSE).

In the treatment of tonic-clonic status epilepticus, the loading dose in PSE is 15 mg/kg given as a single dose at a rate of 2 to 3 mg/kg per minute; however, the *BNFC* allows up to 20 mg/kg. In the treatment or prophylaxis of seizures other than in status epilepticus, the loading dose in PSE is 10 to 15 mg/kg given as a single dose at a rate of 1 to 2 mg/kg per minute. The maximum rate of infusion of loading doses is 3 mg/kg per minute or 150 mg/minute and should not be exceeded. Initial maintenance doses in PSE for status epilepticus and other seizures are 4 to 5 mg/kg daily given in 1 to 4 divided doses at a rate of 1 to 2 mg/kg per minute, not exceeding 100 mg/minute. Subsequent doses are dependent on patient response and trough plasma-phenytoin concentrations.

Fosphenytoin given at a rate of 1 to 2 mg/kg per minute, not exceeding 50 to 100 mg/minute, may be substituted for oral phenytoin at equivalent total daily doses for up to 5 days.

Similar precautions to those in adults apply to the monitoring of clinical parameters and plasma-phenytoin concentrations in children (see above).

Administration in hepatic or renal impairment. The rate and extent of conversion of fosphenytoin to phenytoin in patients with hepatic cirrhosis or renal impairment requiring dialysis was not found to be significantly different from those for healthy controls.[1] However, there was a trend towards an increase in fosphenytoin clearance and a decrease in the time to peak phenytoin concentrations in those with hepatic or renal impairment. Consequently, the authors recommended that fosphenytoin may need to be given at lower doses or infused more slowly (see above for the licensed product recommendations).

1. Aweeka FT, *et al.* Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia* 1999; **40:** 777–82.

Preparations

USP 31: Fosphenytoin Sodium Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Pro-Epanutin†; ***Austria:*** Pro-Epanutin; ***Canad.:*** Cerebyx; ***Denm.:*** Pro-Epanutin; ***Fin.:*** Pro-Epanutin; ***Fr.:*** Prodilantin; ***Gr.:*** Pro-Epanutin; ***Irl.:*** Pro-Epanutin; ***Neth.:*** Pro-Epanutin†; ***Norw.:*** Pro-Epanutin; ***Spain:*** Cereneu; ***Swed.:*** Pro-Epanutin; ***UK:*** Pro-Epanutin; ***USA:*** Cerebyx.

Gabapentin *(BAN, USAN, rINN)*

CI-945; Gabapentiini; Gabapentina; Gabapentine; Gabapentinum; GOE-3450. 1-(Aminomethyl)cyclohexaneacetic acid.

Габапентин

$C_9H_{17}NO_2$ = 171.2.

CAS — 60142-96-3.

ATC — N03AX12.

ATC Vet — QN03AX12.

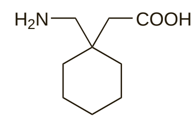

Pharmacopoeias. In *US.*

USP 31 (Gabapentin). A white to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, myalgia, headache, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus.

Gabapentin should be used with caution in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin.

Care is required when withdrawing gabapentin therapy—see also Uses and Administration, below.

Incidence of adverse effects. A postmarketing surveillance study[1] of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. In the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.

1. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002; **43:** 983–92.

Breast feeding. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comment on antiepileptic therapy and breast feeding, see p.467.

Carcinogenicity. It had been reported[1] that studies on gabapentin had been temporarily stopped in 1990 when pancreatic tumours were seen in *rodent* studies. However, the tumours were benign, occurred only with large doses, and were not thought to relate to humans.

1. Ramsay RE. Clinical efficacy and safety of gabapentin. *Neurology* 1994; **44** (suppl 5): S23–S30.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on bone. For the effects of antiepileptics on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on the liver. A report[1] of a patient who developed cholestatic jaundice 2 weeks after starting therapy with gabapentin 300 mg three times daily for diabetic neuropathy. Clinical symptoms and liver function tests improved on withdrawal of gabapentin.

1. Richardson CE, *et al.* Gabapentin induced cholestasis. *BMJ* 2002; **325:** 635.

Effects on mental function. For a review of the effects of antiepileptic therapy including gabapentin on *cognition*, and on *mood* (including the risk of suicidal ideation), see p.468.

Effects on the skin. For a suggestion that skin reactions are less common with gabapentin than with some other antiepileptics see under Phenytoin, p.496.

Overdosage. A 16-year-old girl complained of dizziness 6 hours after ingesting 48.9 g of gabapentin and was lethargic but arousable 2 hours later.[1] Her gabapentin plasma concentration was 62 micrograms/mL 8.5 hours after ingestion. By 18 hours she was alert and had no further complaints of lethargy or dizziness. In another report[2] a patient with renal failure inadvertently received inappropriately high doses of gabapentin for 3 weeks and had a serum gabapentin concentration of 85 micrograms/mL without serious adverse effects. However, a patient with end-stage renal disease who twice took extra doses of gabapentin between haemodialysis sessions developed marked somnolence and hypoxia severe enough to require intubation on both occasions; haemodialysis produced rapid improvement.[3] A prospective observational study[4] of gabapentin exposures reported to 3 poison centers has described a case series of 20 patients who took from 50 mg to 35 g of gabapentin alone. Of these, 12 experienced clinical symptoms including drowsiness, dizziness, gastrointestinal disturbance, hypotension, and mild tachycardia. These effects developed in under 5 hours and lasted for less than 24 hours; toxicity was generally mild and there were no fatalities.

1. Fischer JH, *et al.* Lack of serious toxicity following gabapentin overdose. *Neurology* 1994; **44:** 982–3.
2. Verma A, *et al.* A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit* 1999; **21:** 615–17.
3. Jones H, *et al.* Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Ann Intern Med* 2002; **137:** 74.
4. Klein-Schwartz W, *et al.* Characterization of gabapentin overdose using a poison center case series. *J Toxicol Clin Toxicol* 2003; **41:** 11–15.

Pregnancy. For mention of the pharmacokinetics of gabapentin during pregnancy and breast feeding, see under Pharmacokinetics, below.

For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

The absorption of gabapentin from the gastrointestinal tract is reduced by antacids containing aluminium with magnesium; it is recommended that gabapentin is taken at least 2 hours after any such antacid. Morphine has been reported to reduce the clearance of gabapentin; patients receiving both drugs should be monitored for signs of CNS depression and doses should be reduced accordingly. Cimetidine has also been reported to reduce the renal clearance of gabapentin but licensed product information does not consider this to be of clinical importance. For references to possible interactions with other antiepileptics, see under Phenytoin, p.498 and under Felbamate, p.481.

Pharmacokinetics

Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing peak plasma concentrations are usually achieved within 2 to 3 hours of a dose and steady state achieved within 1 to 2 days. Gabapentin is not appreciably metabolised and most of a dose is excreted unchanged in the urine with the remainder appearing in the faeces. Gabapentin is widely distributed throughout the body but binding to plasma proteins is minimal. The elimination half-life has been reported to be about 5 to 7 hours. Gabapentin is distributed into breast milk.

◊ References.

1. Blum RA, *et al.* Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* 1994; **56:** 154–9.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Berry DJ, *et al.* The absorption of gabapentin following high dose escalation. *Seizure* 2003; **12:** 28–36.

Children. A study[1] of the pharmacokinetics of single doses of gabapentin in healthy children aged 1 month to 12 years found that peak plasma concentrations occurred 2 to 3 hours after the dose in all age groups but that the mean value was higher in those older than 5 years than in younger children, and the exposure was calculated to be about 30% less in the younger age group. As a result it was suggested that the initial dose of gabapentin in studies of safety and efficacy should be 40 mg/kg daily in children aged from 1 month up to 5 years, and 30 mg/kg daily in children aged 5 to 12 years. (For licensed doses, see Administration in children, below.) A pharmacokinetics study[2] in children with uncontrolled seizures (aged from 3 to about 15 years) also found a markedly higher mean oral clearance of gabapentin when compared with adults.

1. Haig GM, *et al.* Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. *J Clin Pharmacol* 2001; **41:** 507–14.
2. Tallian KB, *et al.* Pharmacokinetics of gabapentin in paediatric patients with uncontrolled seizures. *J Clin Pharm Ther* 2004; **29:** 511–15.

Pregnancy and breast feeding. The pharmacokinetics of gabapentin were studied[1] in 6 women, and in their offspring, during pregnancy, delivery, and breast feeding. Findings suggested that gabapentin is actively transported across the placenta and accumulates in the fetus although its effect was unclear. All the deliveries, including one preterm, were uneventful and all of the infants were healthy, apart from one who became cyanosed and mildly hypotonic 8 hours after birth.

The distribution of gabapentin into breast milk was extensive and neonates were found to have a lower capacity to eliminate gabapentin than adults, with an elimination half-life of about 14 hours. However, the plasma concentrations in the breast-fed infants appeared to be low and the relative infant dose was estimated to be 1.3 to 3.8% of the mothers' weight-adjusted dose at 0.2 to 1.3 mg/kg daily. No adverse effects were reported in the infants, and the authors considered that gabapentin was generally safe during breast feeding.

1. Öhman I, *et al.* Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia* 2005; **46:** 1621–4.

Uses and Administration

Gabapentin is an antiepileptic used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. It is not generally considered effective for absence seizures. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor antagonist and its mechanism of action is unknown. Gabapentin is also used in the treatment of neuropathic pain.

In the UK, the initial oral dose of gabapentin for the treatment of **epilepsy** is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg three times daily on the third day; thereafter the dose may be increased in increments of 300 mg every 2 to 3 days until effective antiepileptic control is achieved, which is usually within the range of 0.9 to 3.6 g daily. Higher doses up to a maximum of 4.8 g daily have been reported to be well tolerated. Similar doses are used in the USA. The total daily dose should be taken in three equally divided doses and the maximum dosage interval should not exceed 12 hours.

For details of doses in children, see below.

In the treatment of **neuropathic pain**, doses should be titrated to a usual maximum of 1.8 g daily in three divided doses, in a similar manner to that recommended above for the treatment of epilepsy. Higher doses have sometimes been given.

As with other antiepileptics, withdrawal of gabapentin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose gradually over at least 7 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Dosage of gabapentin should be reduced in patients with renal impairment (see below).

Gabapentin enacarbil (XP-13512) has been investigated as a prodrug of gabapentin.

Administration in children. In the UK, for the treatment of partial seizures with or without secondary generalisation, gabapentin is licensed for use as adjunctive therapy in children aged 6 years and over and as monotherapy in those aged 12 years and over. As *adjunctive therapy,* gabapentin may be given in an initial oral dose of 10 to 15 mg/kg daily, titrated over a period of about 3 days until effective antiepileptic control is achieved, which is usually within the range 25 to 35 mg/kg daily. Higher doses up to a maximum of 50 mg/kg daily have been reported to be well tolerated. Although not licensed for use in younger children, the *BNFC* suggests that similar initial doses may be used in those aged 2 to 12 years; maintenance doses of 10 to 20 mg/kg 3 times daily (up to 900 mg daily for children weighing 36 kg or under, or 1.2 g daily for those over 36 kg) are also recommended. Older children may be given the usual adult dosage regimen (see above) titrated to a maximum of 2.4 g daily. When used as *monotherapy,* the usual adult dosage regimen is given.

In the USA, gabapentin is licensed for *adjunctive* use in children aged 3 years and over. Initial doses are as for the UK; the maintenance dose for children aged 3 to 4 years is 40 mg/kg daily, and for those aged 5 years and over is 25 to 35 mg/kg daily. Children aged 12 years and over may be given the usual adult dosage regimen (see above).

The total daily dose should be taken in 3 equally divided doses and the maximum dosage interval should not exceed 12 hours.

For a pharmacokinetic study suggesting that initial doses in younger children should be proportionately higher than in older ones, see above.

Administration in renal impairment. Reduced doses of gabapentin are recommended for patients with renal impairment or those undergoing haemodialysis. Licensed UK product information recommends the following maintenance doses based on creatinine clearance (CC) and given as 3 divided doses:

- CC 50 to 79 mL/minute: 600 to 1800 mg daily
- CC 30 to 49 mL/minute: 300 to 900 mg daily
- CC 15 to 29 mL/minute: 300 mg on alternate days to 600 mg daily
- CC less than 15 mL/minute: 300 mg on alternate days to 300 mg daily

For those undergoing haemodialysis who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hours of haemodialysis. On dialysis-free days no doses of gabapentin should be given (see also Overdosage, above).

Ciguatera poisoning. Gabapentin has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p.1331).

Epilepsy. Gabapentin is used in epilepsy (p.465) as adjunctive therapy for partial seizures with or without secondary generalisation in patients refractory to standard antiepileptics. In double-blind placebo-controlled studies[1-4] in such patients seizure frequency was reduced when gabapentin was added to treatment. Long-term efficacy has been encouraging,[5-7] and its lack of potential for interactions with other antiepileptics is considered to make it particularly suitable for adjunctive treatment. Dosage is adjusted against clinical response rather than by monitoring blood concentrations. Gabapentin is also used as monotherapy in partial epilepsy;[8-10] its efficacy as adjunctive treatment in generalised seizures remains to be determined.

Gabapentin has been found to be effective as adjunctive therapy in children with refractory partial seizures.[11]

1. UK Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990; **335:** 1114–17.
2. Sivenius J, *et al.* Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991; **32:** 539–42.
3. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993; **43:** 2292–8.
4. Anhut H, *et al.* International Gabapentin Study Group. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. *Epilepsia* 1994; **35:** 795–801.
5. US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994; **18:** 67–73.
6. Sivenius J, *et al.* Long-term study with gabapentin in patients with drug-resistant epileptic seizures. *Arch Neurol* 1994; **51:** 1047–50.
7. Anhut H, *et al.* Long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995; **8:** 44–50.
8. Ojemann LM, *et al.* Long-term treatment with gabapentin for partial epilepsy. *Epilepsy Res* 1992; **13:** 159–65.

9. Beydoun A, *et al.* Gabapentin monotherapy II: a 26-week, double-blind, dose-controlled multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997; **49:** 746–52.
10. Chadwick DW, *et al.* A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998; **51:** 1282–8.
11. Appleton R, *et al.* Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. *Epilepsia* 1999; **40:** 1147–54.

Headache. Benefit has been reported[1] from the use of gabapentin in the prophylaxis of *migraine* (p.616). Gabapentin may also be effective[2,3] in the management of *cluster headache* (p.616), and has been tried[4] in the prophylaxis of *chronic daily headache*.

1. Mathew NT, *et al.* Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; **41:** 119–128.
2. Leandri M, *et al.* Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia* 2001; **21:** 744–6.
3. Schuh-Hofer S, *et al.* The use of gabapentin in chronic cluster headache patients refractory to first-line therapy. *Eur J Neurol* 2007; **14:** 694–6.
4. Spira PJ, Beran RG. Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003; **61:** 1753–9.

Hiccup. Gabapentin has been tried[1,2] in the treatment of hiccups (p.976).

1. Hernández JL, *et al.* Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.
2. Alonso-Navarro H, *et al.* Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol* 2007; **30:** 186–7.

Hot flushes. Gabapentin appears to be of benefit in the management of hot flushes associated with treatment of breast cancer (p.661); a study involving 420 women with breast cancer experiencing hot flushes (excluding women on active chemotherapy, but most of whom were receiving adjuvant endocrine therapy), found that a dose of 900 mg daily in three divided doses for 8 weeks was effective, although a dose of 300 mg daily was not.[1]

There is also evidence of benefit[2,3] from gabapentin in the same dose (900 mg daily) in women experiencing hot flushes as a symptom of the menopause (p.2077). Another randomised placebo-controlled study[4] found gabapentin 2.4 g daily to be as effective as conjugated oestrogens 625 micrograms daily in the treatment of hot flushes in postmenopausal women.

1. Pandya KJ, *et al.* Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005; **366:** 818–24.
2. Guttuso T, *et al.* Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003; **101:** 337–45.
3. Loprinzi CL, *et al.* Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *J Clin Oncol* 2007; **25:** 308–12.
4. Reddy SY, *et al.* Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol* 2006; **108:** 41–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p.976) has been reported to improve in those given antiepileptics such as gabapentin.[1]

1. McManaman J, Tam DA. Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome. *Pediatr Neurol* 1999; **20:** 381–2.

Motor neurone disease. Interest has been shown in gabapentin as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) because it may inhibit glutamate formation. Results from an early study[1] demonstrated a trend towards a beneficial effect; however, a randomised trial[2] failed to confirm any benefit from gabapentin on disease progression or symptoms.

1. Miller RG, *et al.* Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 1996; **47:** 1383–8.
2. Miller RG, *et al.* Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. *Neurology* 2001; **56:** 843–8.

Multiple sclerosis. Gabapentin has been found to control pain, spasm, and spasticity in patients with multiple sclerosis (p.892).[1-6] It may also be of benefit in acquired nystagmus secondary to multiple sclerosis.[7]

1. Mueller ME, *et al.* Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; **78:** 521–4.
2. Samkoff LM, *et al.* Amelioration of refractory dysesthetic limb pain in multiple sclerosis by gabapentin. *Neurology* 1997; **49:** 304–5.
3. Solaro C, *et al.* An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998; **51:** 609–11.
4. Dunevsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *Am J Phys Med Rehabil* 1998; **77:** 451–4.
5. Cutter NC, *et al.* Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Arch Phys Med Rehabil* 2000; **81:** 164–9.
6. Solaro C, *et al.* Gabapentin is effective in treating nocturnal painful spasms in multiple sclerosis. *Multiple Sclerosis* 2000; **6:** 192–3.
7. Shery T, *et al.* The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol* 2006; **90:** 839–43.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p.2). Although carbamazepine appears to be the usual choice, gabapentin is also given in the treatment of neuropathic pain,[1-3] including central pain[4] (see p.6), complex regional pain syndrome (see p.6), postherpetic neuralgia[5-7] (see p.9), trigeminal neuralgia (see p.9), and painful diabetic neuropathy[8,9] (see p.6).

1. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002; **57:** 451–62.
2. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003; **25:** 81–104.
3. Wiffen PJ, *et al.* Gabapentin for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
4. Schachter SC, Sauter MK. Treatment of central pain with gabapentin: case reports. *J Epilepsy* 1996; **9:** 223–5.
5. Rowbotham M, *et al.* Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998; **280:** 1837–42.
6. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001; **94:** 215–24.
7. Singh D, Kennedy DH. The use of gabapentin for the treatment of postherpetic neuralgia. *Clin Ther* 2003; **25:** 852–89.
8. Backonja M, *et al.* Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998; **280:** 1831–6.
9. Morello CM, *et al.* Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999; **159:** 1931–7.

Parkinsonism. While some overall ratings of Parkinson's disease (p.791) appeared to be improved by gabapentin in a double-blind study involving 19 patients with advanced parkinsonism, improvements in individual signs and symptoms were not significant.[1] It was also reported that 5 of 6 other patients with progressive supranuclear palsy had experienced worsening of their disease when given gabapentin. Another study[2] in 15 patients with motor complications failed to find any clinically significant benefit from gabapentin therapy.

1. Olson WL, *et al.* Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 1997; **102:** 60–6.
2. Van Blercom N, *et al.* Effects of gabapentin on the motor response to levodopa: a double-blind, placebo-controlled, crossover study in patients with complicated Parkinson disease. *Clin Neuropharmacol* 2004; **27:** 124–8.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as gabapentin to modulate opioid dosage and efficacy for postoperative pain (see p.4).[1] A systematic review considered that evidence of benefit for gabapentin in acute pain was lacking, and noted that more effective analgesics for this indication were available.[2] However, a later systematic review found that perioperative use of gabapentin effectively reduced opioid consumption and postoperative pain; further studies were considered warranted.[3] It has been suggested that perioperative use of gabapentin may have other benefits, including pre-operative anxiolysis, attenuation of the haemodynamic response to intubation, and reduction in postoperative nausea and vomiting.[4]

1. Dahl JB, *et al.* 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Wiffen PJ, *et al.* Gabapentin for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
3. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.
4. Kong VKF, Irwin MG. Gabapentin: a multimodal perioperative drug? *Br J Anaesth* 2007; **99:** 775–86.

Psychiatric disorders. Gabapentin has psychotropic properties and has been tried in the management of several psychiatric disorders, including as an adjunct in the treatment of resistant *depression*[1] (p.373) and in the treatment of *post-traumatic stress disorder*[2] (p.953). Although early open studies[3] found that gabapentin may be of benefit in patients with *bipolar disorder* (p.372) randomised controlled trials have so far failed to confirm this effect.[4-6] Gabapentin is under investigation for the treatment of *social anxiety disorder* (see under Phobic Disorders, p.953).

1. Yasmin S, *et al.* Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. *J Affect Disord* 2001; **63:** 243–7.
2. Malek-Ahmadi P. Gabapentin and posttraumatic stress disorder. *Ann Pharmacother* 2003; **37:** 664–6.
3. Maidment ID. Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 2001; **35:** 1264–9.
4. Pande AC, *et al.* Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord* 2000; **2:** 249–55.
5. Frye MA, *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; **20:** 607–14.
6. Vieta E, *et al.* A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; **67:** 473–7.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has been largely empirical. Two small randomised double-blind crossover studies[1,2] found 6 weeks of treatment with gabapentin to produce improvement in symptoms; in patients undergoing haemodialysis the effects were seen with a dose of 300 mg after each of the 3 dialysis sessions per week,[1] although in patients with idiopathic disease the mean effective dose was 1.855 g daily.[2]

A prodrug of gabapentin, gabapentin enacarbil, is reported to be under investigation for the treatment of restless legs syndrome.

1. Thorp ML, *et al.* A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis* 2001; **38:** 104–8.
2. Garcia-Borreguero D, *et al.* Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology* 2002; **59:** 1573–9.

Soft-tissue rheumatism. Gabapentin may be of benefit in some patients with fibromyalgia (p.13). In a randomised controlled study treatment with oral gabapentin 1.2 to 2.4 g daily in 75 patients produced a greater improvement in mean pain score over 12 weeks than placebo in 75 controls.[1] Sleep problems were also improved, but there was no difference between the groups in a depression rating scale. The drug was generally well tolerated.

1. Arnold LM, *et al.* Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007; **56:** 1336–44.

Stiff-man syndrome. Gabapentin may improve the symptoms of stiff-man syndrome (see under Muscle Spasm in Uses of Diazepam, p.993) in patients unable to tolerate benzodiazepine therapy.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, gabapentin has also been tried with some success.[1-3]

1. Gironell A, *et al.* A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol* 1999; **56:** 475–80.
2. Ondo W, *et al.* Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial. *Mov Disord* 2000; **15:** 678–82.
3. Faulkner MA, *et al.* Gabapentin for the treatment of tremor. *Ann Pharmacother* 2003; **37:** 282–6.

Preparations

USP 31: Gabapentin Capsules; Gabapentin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Abaglin; Alidial; Logistic; Neurontin; Ultraneural; ***Austral.:*** Gabaran; Gantin; Neurontin; Nupentin; Pendine; ***Austria:*** Gabarex; Gabatal; Neurontin; ***Belg.:*** Neurontin; ***Braz.:*** Gabaneurin; Neurontin; Progresse; ***Canad.:*** Neurontin; ***Chile:*** Dineurin; Gabex; Gabictal; Neugabin; Normatol; Ritmenal; ***Cz.:*** Apo-Gab; Gabagamma; Gabalept; Gabanox; Gabator; Gabenta; Neurontin; Nurabax; ***Denm.:*** Neuril; ***Fin.:*** Gabrion; Geabatan†; Neuril; Neurontin; ***Fr.:*** Neurontin; ***Ger.:*** Gabagamma; GabaLich; Gabax; Neurontin; ***Gr.:*** Gabantin; Gabental; Neurontin; Pentin; ***Hong Kong:*** Neurontin; ***Hung.:*** Gordius; Neurontin; ***India:*** Neurontin; ***Indon.:*** Epiven; Gabexal; Ganin; Nepatic; Neurontin; ***Irl.:*** Gabture; Neurontin; Neurostil; ***Israel:*** Neurontin; ***Ital.:*** Neurontin; ***Malaysia:*** Neurontin; ***Mex.:*** Bapex; Gabantin; Gapridol; Neurontin; Nopatic; ***Neth.:*** Neurontin; ***Norw.:*** Neurontin; ***NZ:*** Neurontin; Nupentin; ***Philipp.:*** Neurontin; ***Pol.:*** Gabax; Neurontin; ***Port.:*** Gabamox; Neurontin; ***Rus.:*** Gapentek (Гапентек); Neurontin (Нейронтин); Tebantin (Тебантин); ***S.Afr.:*** Epleptin; Neurontin; ***Singapore:*** Neurontin; ***Spain:*** Equipax†; Gabamerck; Gabatur; Neurontin; Oxaquin; ***Swed.:*** Neurontin; ***Switz.:*** Neurontin; ***Thai.:*** Neurontin; ***Turk.:*** Neurontin; ***UK:*** Neurontin; ***USA:*** Gabarone; Neurontin; ***Venez.:*** Neurontin.

Lacosamide *(USAN, rINN)*

ADD-234037; Erlosamida; Erlosamide; Erlosamidum; Harkoseride; Lacosamida; Lacosamidum; SPM-927. (2*R*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide.

Эрлозамид

$C_{13}H_{18}N_2O_3$ = 250.3.

CAS — 175481-36-4.

ATC — N03AX18.

ATC Vet — QN03AX18.

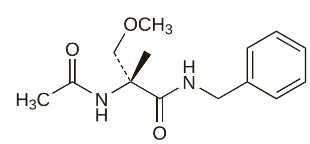

Profile

Lacosamide is an antiepileptic drug that is under investigation for adjunctive therapy in partial seizures. It is also being studied for use in diabetic neuropathic pain, fibromyalgia, osteoarthritis, and migraine.

◊ References.

1. Doty P, *et al.* Lacosamide. *Neurotherapeutics* 2007; **4:** 145–8.
2. Rauck RL, *et al.* Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. *Clin J Pain* 2007; **23:** 150–8.

3. Ben-Menachem E, *et al.* Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; **48:** 1308–17.
4. Biton V, *et al.* Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. *Epilepsia* 2008; **49:** 418–24.
5. Ben-Menachem E. Lacosamide: an investigational drug for adjunctive treatment of partial-onset seizures. *Drugs Today* 2008; **44:** 35–40.

Lamotrigine *(BAN, USAN, rINN)*

BW-430C; Lamotrigiini; Lamotrigin; Lamotrigina; Lamotriginum; Lamotrijin. 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diyldiamine.

Ламотригин

$C_9H_7Cl_2N_5$ = 256.1.

CAS — 84057-84-1.

ATC — N03AX09.

ATC Vet — QN03AX09.

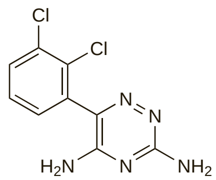

Adverse Effects and Treatment

Skin rashes may occur during therapy with lamotrigine; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine (see Effects on the Skin, below). Symptoms such as fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, facial oedema and, rarely, hepatic dysfunction have been reported. Blood dyscrasias such as leucopenia, neutropenia, and thrombocytopenia have also been reported, sometimes with rashes as part of a hypersensitivity syndrome.

Movement disorders such as tics, ataxia, nystagmus, and tremor have occurred; lamotrigine may worsen symptoms in patients with pre-existing Parkinson's disease. Other adverse effects include angioedema, photosensitivity, diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, insomnia, headache, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion. Very rarely, lupus-like reactions and increases in seizure frequency have been reported.

◊ Licensed product information states that there have been rare instances of death after a rapidly progressive illness involving status epilepticus, multi-organ dysfunction, and disseminated intravascular coagulation in patients taking multiple antiepileptics including lamotrigine, although the role of lamotrigine remains to be established. It has been suggested[1] that multi-organ failure and disseminated intravascular coagulation, with associated rhabdomyolysis, are complications of severe convulsive seizures rather than of lamotrigine therapy. However, there has been a report[2] of a patient with no history of generalised seizures who developed a syndrome of disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, and ataxia 14 days after lamotrigine was added to her antiepileptic regimen. Two cases of disseminated intravascular coagulation were found in a cohort of 11 316 patients involved in prescription-event monitoring of lamotrigine therapy in general practice.[3]

1. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizures. *Lancet* 1992; **340:** 618.
2. Schaub JEM, *et al.* Multisystem adverse reaction to lamotrigine. *Lancet* 1994; **344:** 481.
3. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.

Effects on the blood. Septic shock secondary to leucopenia occurred in a patient when lamotrigine was added to therapy with sodium valproate.[1] There has also been a report of agranulocytosis in a child started on high-dose lamotrigine monotherapy.[2] The fall in the blood count was noted several days after lamotrigine had been stopped due to skin rash. The UK CSM subsequently reported[3] that 7 cases of aplastic anaemia, 12 of bone-marrow depression, and 20 of pancytopenia associated with lamotrigine had been received worldwide. Given the extensive usage of lamotrigine the CSM considered the risk of aplastic anaemia to be small and routine blood monitoring was not recommended. However, prescribers were warned to be alert for symptoms and signs suggestive of bone-marrow depression.

1. Nicholson RJ, *et al.* Leucopenia associated with lamotrigine. *BMJ* 1995; **310:** 504.
2. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999; **318:** 1179.
3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): rare blood dyscrasias. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Effects on bone. For the effects of antiepileptics including lamotrigine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on the liver. Fatal fulminant hepatic failure has been reported[1] in a patient after addition of lamotrigine to antiepileptic therapy with sodium valproate and carbamazepine. Another fatal case was reported[2] in a patient who was given lamotrigine for bipolar disorder; she was also taking other drugs for pain and insomnia. Reversible eosinophilic hepatitis occurred[3] as part of a hypersensitivity syndrome in a patient given lamotrigine for seizures.

1. Makin AJ, *et al.* Fulminant hepatic failure induced by lamotrigine. *BMJ* 1995; **311:** 292.
2. Overstreet K, *et al.* Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. *Dig Dis Sci* 2002; **47:** 1921–5.
3. Fix OK, *et al.* Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol* 2006; **4:** xxvi.

Effects on the lungs. Interstitial pneumonitis with pulmonary infiltrates occurred when lamotrigine was added to antiepileptic therapy in a 57-year-old woman; the condition resolved when lamotrigine was stopped.[1]

1. Saravanan N, *et al.* Interstitial pneumonitis during lamotrigine therapy. *Br J Clin Pharmacol* 2005; **60:** 666–7.

Effects on mental function. Acute *psychosis* was reported[1] in 6 out of about 1400 patients when lamotrigine was added to antiepileptic therapy and/or when the dose of lamotrigine was increased. Symptoms resolved when lamotrigine was stopped, and recurred in 1 case of rechallenge.

For a review of the effects of antiepileptic therapy including lamotrigine on *cognition,* and on *mood* (including the risk of suicidal ideation), see p.468.

1. Brandt C, *et al.* Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and review of the literature. *Epilepsy Behav* 2007; **11:** 133–9.

Effects on the nervous system. Of 93 patients with idiopathic generalised epilepsy who were treated with lamotrigine, 5 adults experienced *de novo* or exacerbated myoclonic jerks.[1] In each case, symptoms resolved when the dose of lamotrigine was reduced by 25 to 50% or stopped altogether. In another report, a 17-year-old girl with idiopathic Rolandic epilepsy experienced a sudden increase in seizure frequency when lamotrigine was added to therapy with sodium valproate; other adverse effects included emotional lability, headaches, and drowsiness.[2] Again symptoms resolved when lamotrigine was stopped.[2]

Overdose of lamotrigine has been known to cause seizures (see below).

1. Crespel A, *et al.* Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005; **65:** 762–4.
2. Cerminara C, *et al.* Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. *Neurology* 2004; **63:** 373–5.

Effects on the skin. Rashes account for withdrawal from therapy in about 2% of those given lamotrigine,[1,2] and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis occur in about 1 in 1000 adult patients.[3,4] The majority of rashes resolve once lamotrigine has been stopped; however, some patients have developed permanent scarring and there have been rare reports of fatalities. The main risk factors appear to be use with valproate, exceeding the recommended initial dose of lamotrigine or the recommended rate of dose escalation, and a history of antiepileptic-induced rash. The risk appears to be greater in children[1,4-6] and has been estimated to be between 1 in 300 and 1 in 50. These skin reactions usually occur within 8 weeks of starting therapy with lamotrigine, but onset as early as the first day and as late as 2 years has been noted.[7] After continuing reports of serious skin reactions in children, UK recommended dosage regimens for children have been revised to further reduce the risk of such reactions.[8] For the relative incidence of rash with different antiepileptics see under Phenytoin, p.496.

1. Mackay FJ, *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38:** 881–6.
2. Messenheimer J, *et al.* Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; **18:** 281–96.
3. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal) and serious skin reactions. *Current Problems* 1996; **22:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015622&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
4. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): increased risk of serious skin reactions in children. *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Mitchell P. Paediatric lamotrigine use hit by rash reports. *Lancet* 1997; **349:** 1080.
6. Hirsch LJ, *et al.* Predictors of lamotrigine-associated rash. *Epilepsia* 2006; **47:** 318–22.
7. Adverse Drug Reactions Advisory Committee (ADRAC). Lamotrigine and severe skin reactions. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr9702.htm (accessed 09/06/08)
8. Committee on Safety of Medicines/Medicines Control Agency. Lamotrigine (Lamictal): revised doses for children. *Current Problems* 2000; **26:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Overdosage. An evaluation[1] of 493 cases of lamotrigine-only overdoses reported to the American Association of Poison Control Centers over a 2-year period found that 52.1% of patients had no toxic effects. The most commonly reported adverse effects were drowsiness, nausea, vomiting, and ataxia. Serious effects such as seizures, coma, and respiratory depression were reported in 0.6 to 1.2% of cases; no deaths were reported.

No serious toxicity was seen in a patient who deliberately took an overdose of 1.35 g of lamotrigine and was subsequently treated with gastric lavage and activated charcoal.[2] Symptoms at presentation one hour after ingestion had included nystagmus and muscle hypertonicity. ECG monitoring had revealed widening of the QRS interval. Low-grade fever, erythema, and periorbital oedema suggestive of a hypersensitivity syndrome developed in another patient who inadvertently received lamotrigine 2.7 g daily for 4 days.[3] The patient recovered after corticosteroid treatment and stopping lamotrigine. Generalised tonic-clonic seizures, tremor, muscle weakness, ataxia, and hypertonia were reported[4] in a 2-year-old child after ingestion of 800 mg of lamotrigine. Symptoms resolved within 24 hours after treatment with gastric lavage and activated charcoal, midazolam, and fluids. Plasma-lamotrigine concentrations were in the high adult therapeutic range (3.8 micrograms/mL) with a slow elimination rate. Generalised seizures also occurred[5] after an unknown quantity of lamotrigine was ingested by a 19-month-old child who had no history of seizures; other presenting symptoms included tachycardia and vomiting. The serum-lamotrigine concentration measured 1 hour post ingestion was 20.3 mg/L. Symptoms resolved within 24 hours after treatment with trimethobenzamide and activated charcoal.

For a further review of the features and management of poisoning with some antiepileptics, including lamotrigine, see under Phenytoin, p.497.

1. Lofton AL, Klein-Schwartz W. Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 2004; **38:** 1811–15.
2. Buckley NA, *et al.* Self-poisoning with lamotrigine. *Lancet* 1993; **342:** 1552–3.
3. Mylonakis E, *et al.* Lamotrigine overdose presenting as anticonvulsant hypersensitivity syndrome. *Ann Pharmacother* 1999; **33:** 557–9.
4. Briassoulis G, *et al.* Lamotrigine childhood overdose. *Pediatr Neurol* 1998; **19:** 239–42.
5. Thundiyil JG, *et al.* Lamotrigine-induced seizures in a child: case report and literature review. *Clin Toxicol* 2007; **45:** 169–72.

Precautions

Lamotrigine should be given with caution to patients with hepatic or renal impairment. All patients should be warned to see their doctor immediately if rashes or symptoms associated with hypersensitivity develop. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Particular care is needed in patients also receiving valproate—see Interactions, below.

Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Care is required when withdrawing lamotrigine therapy—see also under Uses and Administration, below. Abrupt withdrawal should be avoided unless serious skin reactions have occurred. Lamotrigine should not be restarted in patients with previous hypersensitivity.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of lamotrigine by mothers during breast feeding may be of concern, since there is the potential for therapeutic serum concentrations to occur in the infant. A report in 4 breast-fed infants whose mothers were taking lamotrigine found that although serum concentrations of the drug 10 days after birth were about 30% of maternal concentrations in 3 infants, no short-term adverse effects were seen; the drug was undetectable in the fourth.[2] A study[3] in 6 mothers taking lamotrigine found that the relative dose in their breast-fed infants was 7.6% (mean absolute dose: 450 micrograms/kg daily) and infant plasma concentrations were 18% of maternal concentrations; no adverse effects were reported. The authors also noted that no adverse effects were reported in 12 previous cases.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)
2. Liporace J, *et al.* Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav* 2004; **5:** 102–5.
3. Page-Sharp M, *et al.* Transfer of lamotrigine into breast milk. *Ann Pharmacother* 2006; **40:** 1470–1.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Hepatic impairment. The pharmacokinetics of lamotrigine were not significantly altered in patients with moderate cirrhosis;[1] however, those with severe cirrhosis showed significantly lower oral clearance and longer elimination half-lives than those in healthy subjects.

The recommended licensed doses in patients with hepatic impairment are given under Uses and Administration, below.

1. Marcellin P, *et al.* Influence of cirrhosis on lamotrigine pharmacokinetics. *Br J Clin Pharmacol* 2001; **51:** 410–14.

Intellectual impairment. Aggressive behaviour has been reported in intellectually impaired patients given lamotrigine.[1] Of 19 such patients given lamotrigine, aggressive behaviour developed in 9; the drug was stopped in 5, and stopped but reintroduced in a further 2, together with psychiatric management. One patient responded to a reduction in lamotrigine dosage.

1. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998; **39:** 280–2.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468. For reference to alteration of lamotrigine pharmacokinetics in pregnancy, see under Pharmacokinetics, below.

There is a theoretical risk of teratogenicity with lamotrigine because, like valproate, it is a folate antagonist. In 2002 the manufacturer of lamotrigine, *GlaxoSmithKline*, reported[1] that it had follow-up information on 395 outcomes of pregnancies exposed to lamotrigine between September 1992 and September 2001 from the International Lamotrigine Pregnancy Registry. Major birth defects were found in 13 infants but no distinctive pattern of abnormalities suggestive of a common cause could be identified. Of the 168 who had been exposed to lamotrigine monotherapy during the first trimester, birth defects were reported in 3 (1.8%). The frequency of major birth defects in pregnancies exposed to polytherapy containing lamotrigine with valproate was 10% compared with 4.3% in lamotrigine polytherapy without valproate. Although it was considered that the sample sizes were too small to rule out a small increase in the frequency of major birth defects, it was noted that the frequency of malformations after lamotrigine monotherapy did not differ from that reported in the literature for women with epilepsy receiving antiepileptic monotherapy. Updated results from 785 pregnancies up to March 2004 included 414 first-trimester exposures to lamotrigine monotherapy, of which 12 were associated with a major abnormality.[2] As of March 2006, the registry had recorded 802 first-trimester exposures to lamotrigine monotherapy with major abnormalities occurring in 22; there was no evidence to suggest a dose-response relationship with daily doses of up to 400 mg.[3]

In August 2006, the manufacturer[4] reported that data from the North American Antiepileptic Drug Pregnancy Registry suggested an association between lamotrigine and an increased risk of oral clefts. Of 564 first-trimester exposures to lamotrigine monotherapy, 5 cases of oral clefts were reported giving an incidence rate of 8.9 per 1000 compared with 0.37 per 1000 in the reference population. Again, however, no increase in the overall risk of major malformations was found. Analysis of data from other pregnancy registries found 4 additional cases of oral clefts in about 2200 first-trimester exposures to lamotrigine monotherapy.

1. Tennis P, Eldridge RR. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia* 2002; **43:** 1161–7.
2. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005; **64:** 955–60.
3. Cunnington M, *et al.* International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007; **48:** 1207–10.
4. GlaxoSmithKline, Canada. Association of Lamictal® (lamotrigine) with an increased risk of non-syndromic oral clefts (issued 1st August, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_2_hpc-cps-eng.pdf (accessed 01/09/08)

Renal impairment. Results from a pharmacokinetic study[1] indicated that impaired renal function was likely to have little effect on plasma concentrations of lamotrigine. The drug is mainly cleared by metabolism and although the glucuronide metabolite accumulates it is inactive. Nevertheless, there is limited clinical experience with lamotrigine in such patients and caution was recommended.

1. Wootton R, *et al.* Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. *Br J Clin Pharmacol* 1997; **43:** 23–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The metabolism of lamotrigine is enhanced by the enzyme inducers carbamazepine, phenytoin, phenobarbital, and primidone, and inhibited by valproate (see below).

Analgesics. *Paracetamol* affects the metabolic disposition of lamotrigine but the clinical significance of this interaction remains to be determined.[1] Paracetamol reduced the area under the plasma concentration-time curve for lamotrigine, reduced lamotrigine's half-life, and increased the percentage of lamotrigine recovered in the urine.

1. Depot M, *et al.* Kinetic effects of multiple oral doses of acetaminophen on a single oral dose of lamotrigine. *Clin Pharmacol Ther* 1990; **48:** 346–55.

Antibacterials. Use with *rifampicin* significantly increased the clearance of lamotrigine.[1] The total urinary excretion of lamotrigine and the amount excreted as glucuronide were significantly higher compared with placebo.

1. Ebert U, *et al.* Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* 2000; **56:** 299–304.

Antidepressants. An epileptic patient maintained on lamotrigine 200 mg daily complained[1] of increasing confusion and cognitive impairment after starting *sertraline* 25 mg daily for post-traumatic disorder; after 6 weeks her lamotrigine blood concentrations had risen from 2.5 to 5.1 micrograms/mL during this period. The adverse effects cleared and blood concentrations of lamotrigine fell to 3.1 micrograms/mL within 3 weeks of changing the daily dosage to lamotrigine 100 mg and sertraline 50 mg. A patient, with poorly controlled epilepsy, who initially had been taking lamotrigine 450 mg and sertraline 75 mg together daily for 6 weeks without adverse effects had marked sedation, fatigue, and decreased cognition 6 weeks after the daily dosage of lamotrigine was increased to 600 mg. Her lamotrigine blood concentration was 19.3 micrograms/mL. The patient was subsequently stabilised on lamotrigine 800 mg and sertraline 50 mg daily and had less sedation and fatigue and clearer cognition; blood concentrations of lamotrigine fell to 9.8 micrograms/mL.

1. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure* 1998; **7:** 163–5.

Antiepileptics. *Valproate* can inhibit the metabolism of lamotrigine resulting in increased concentrations of lamotrigine. This effect can be beneficial in the control of certain seizures, although careful monitoring is required as toxicity may occur. Disabling tremor occurred in 3 patients taking such a combination which resolved when the dose of lamotrigine or valproate was reduced.[1] Other reports of toxicity, resolving on reduction of the lamotrigine dose, were marked by sedation, ataxia, and fatigue,[2] or delirium.[3] Symptoms of neurotoxicity were reported in 3 patients on lamotrigine therapy who were given valproate, intravenously then orally, for absence status epilepticus. Serum concentrations of lamotrigine in these patients were raised about three- to sevenfold.[4] Reversible encephalopathy has been reported[5] when sodium valproate was substituted for phenytoin in a patient also taking lamotrigine, although her clinical condition had been satisfactory on this new regimen for several months. Symptoms improved when the doses of both valproate and lamotrigine were reduced. Pharmacokinetic studies[6,7] in healthy adults have attempted to elucidate the mechanism of the interaction between lamotrigine and valproate. The clearance of lamotrigine was found to be reduced, and exposure and elimination half-life increased when valproate was also given. Renal elimination was not affected and the investigators[6] suggested that there was hepatic competition for glucuronidation between valproate and lamotrigine. However, there was no substantial alteration in the linear kinetics of lamotrigine in the presence of therapeutic plasma concentrations of valproate.[7] Similar observations were made when lamotrigine was added to existing antiepileptic regimens in children,[8] although the clinical relevance of the influence of age on the pharmacokinetics remains to be determined. Both young age and use with valproate are risk factors for lamotrigine-induced dermatological toxicity—see Effects on the Skin, above.

For details of dosage reductions required for lamotrigine used with valproate, see Uses and Administration, below.

Other antiepileptics also affect plasma concentrations of lamotrigine. In contrast to valproate, *carbamazepine*, *phenytoin*, or *phenobarbital* all markedly induced the elimination of lamotrigine.[9] Others have confirmed a reduction in plasma-lamotrigine concentrations when given with phenytoin and other enzyme-inducing antiepileptics,[10] but analysis of results from another study[11] suggested that the increase in lamotrigine clearance by phenytoin and carbamazepine was of minimal clinical significance. *Oxcarbazepine* has also been reported[12] to decrease serum-lamotrigine concentrations (although to a lesser extent than carbamazepine). However, a study[13] in healthy subjects found that oxcarbazepine did not affect the pharmacokinetics of lamotrigine, although adverse effects occurred more frequently when they were used together (for a report of severe toxicity associated with such use see p.491). *Mesuximide* was found[12,14] to have a marked inducing effect on the metabolism of lamotrigine. In one study,[14] plasma-lamotrigine concentrations were significantly reduced when given together.

For reports of an interaction between lamotrigine and carbamazepine, see p.474. For the effect of lamotrigine on clonazepam concentrations, see p.990.

1. Reutens DC, *et al.* Disabling tremor after lamotrigine with sodium valproate. *Lancet* 1993; **342:** 185–6.
2. Pisani F, *et al.* Interaction of lamotrigine with sodium valproate. *Lancet* 1993; **341:** 1224.
3. Mueller TH, Beeber AR. Delirium from valproic acid with lamotrigine. *Am J Psychiatry* 2004; **161:** 1128–9.
4. Burneo JG, *et al.* Neurotoxicity following addition of intravenous valproate to lamotrigine therapy. *Neurology* 2003; **60:** 1991–2.
5. Hennessy MJ, Wiles CM. Lamotrigine encephalopathy. *Lancet* 1996; **347:** 974–5.
6. Yuen AWC, *et al.* Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol* 1992; **33:** 511–13.
7. Anderson GD, *et al.* Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 1996; **60:** 145–56.
8. Vauzelle-Kervroëdan F, *et al.* Influence of concurrent antiepileptic medication on the pharmacokinetics of lamotrigine as add-on therapy in epileptic children. *Br J Clin Pharmacol* 1996; **41:** 325–30.
9. May TW, *et al.* Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* 1996; **18:** 523–31.
10. Battino D, *et al.* Lamotrigine plasma concentrations in children and adults: influence of age and associated therapy. *Ther Drug Monit* 1997; **19:** 620–7.
11. Grasela TH, *et al.* Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. *J Clin Pharmacol* 1999; **39:** 373–84.
12. May TW, *et al.* Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* 1999; **21:** 175–81.
13. Theis JGW, *et al.* Lack of pharmacokinetic interaction between oxcarbazepine and lamotrigine. *Neuropsychopharmacology* 2005; **30:** 2269–74.
14. Besag FM, *et al.* Methsuximide lowers lamotrigine blood levels: a pharmacokinetic antiepileptic drug interaction. *Epilepsia* 2000; **41:** 624–7.

Antipsychotics. An apparent interaction between lamotrigine and *aripiprazole*, resulting in Stevens-Johnson syndrome, has been reported[1] in 2 patients with schizophrenia after the introduction of lamotrigine; both patients recovered with supportive treatment.

1. Shen Y-C, *et al.* Concomitant use of lamotrigine and aripiprazole increases risk of Stevens-Johnson syndrome? *Int Clin Psychopharmacol* 2007; **22:** 247–8.

Antivirals. A study[1] in healthy subjects found that ritonavir-boosted lopinavir decreased the steady-state minimum plasma concentration of lamotrigine by about 55%; doubling the dose of lamotrigine achieved concentrations similar to those with lamotrigine alone.

1. van der Lee MJ, *et al.* Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2006; **80:** 159–68.

Sex hormones. Studies in patients taking lamotrigine have indicated that *combined oral contraceptives*[1,2] may halve plasma concentrations of the antiepileptic. Other studies[3,4] have also found a significant increase in lamotrigine-plasma concentrations within one week of stopping contraceptive therapy; however, wide interpatient variability was noted in one study.[3] Significant adjustments in maintenance doses of lamotrigine may be needed if combined contraceptives are started or stopped (see below), and patients should be warned not to make changes in their contraceptive therapy without consulting their physician.[5] However, in a study,[6] progestogen-only contraceptives did not appear to affect lamotrigine concentrations. Licensed drug information recommends that, when starting treatment with combined oral contraceptives, the dose of lamotrigine may need to be increased by as much as twofold in those women not taking drugs known to induce cytochrome P450-mediated metabolism of lamotrigine; conversely, the dose of lamotrigine may need to be halved when stopping contraceptive therapy in women not taking enzyme inducers. Dosage adjustment may not be necessary when starting or stopping combined oral contraceptive therapy in women taking lamotrigine with known enzyme inducers.

Adjustments may also be needed if other hormonal preparations are taken with lamotrigine.

Some reduction in plasma concentrations of levonorgestrel, and to a lesser extent ethinylestradiol, may also occur with lamotrigine, and there have been reports of breakthrough bleeding and unexpected pregnancies.[5]

1. Sabers A, *et al.* Oral contraceptives reduce lamotrigine plasma levels. *Neurology* 2003; **61:** 570–1.
2. Sidhu J, *et al.* The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006; **61:** 191–9.

3. Contin M, *et al.* Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia* 2006; **47:** 1573–5.
4. Christensen J, *et al.* Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial *Epilepsia* 2007; **48:** 484–9.
5. GlaxoSmithKline, Canada. Important new safety information concerning the antiepileptic, Lamictal (lamotrigine) (issued September 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/lamictal_hpc-cps-eng.pdf (accessed 01/09/08)
6. Reimers A, *et al.* Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005; **46:** 1414–17.

Pharmacokinetics

Lamotrigine is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of 98%. Peak plasma concentrations occur about 2.5 hours after oral doses. It is widely distributed in the body and is reported to be about 55% bound to plasma proteins. It is extensively metabolised in the liver and excreted almost entirely in urine, principally as an inactive glucuronide conjugate. It slightly induces its own metabolism and the mean elimination half-life is reported to be 24 to 35 hours. Clearance is reported to be higher in children aged up to 12 years than in adults, with the highest values occurring in those under 5 years of age. Lamotrigine is distributed into breast milk.

The pharmacokinetics of lamotrigine are affected by other antiepileptics (see Interactions, above).

◊ General references.

1. Rambeck B, Wolf P. Lamotrigine clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 433–43.
2. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
3. Reimers A, *et al.* Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. *Eur J Clin Pharmacol* 2007; **63:** 687–92.
4. Punyawudho B, *et al.* Population pharmacokinetics of lamotrigine in elderly patients. *J Clin Pharmacol* 2008; **48:** 455–63.

Hepatic impairment. See under Precautions, above.

Pregnancy. Decreased plasma-lamotrigine concentrations have occurred during pregnancy, with deterioration of seizure control and a need for dosage adjustment in some patients.

References

1. Pennell PB, *et al.* The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004; **62:** 292–5.
2. de Haan G-J, *et al.* Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004; **63:** 571–3.
3. Petrenaite V, *et al.* Individual changes in lamotrigine plasma concentrations during pregnancy. *Epilepsy Res* 2005; **65:** 185–8.

Renal impairment. See under Precautions, above.

Therapeutic drug monitoring. A literature review[1] concluded that a clear relationship between lamotrigine concentrations and toxicity or antiepileptic efficacy has not been demonstrated. Routine therapeutic drug monitoring was therefore not recommended and clinical end-points rather than plasma concentrations remained the best guide for dosage adjustment of lamotrigine.

1. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. *Ann Pharmacother* 2002; **36:** 917–20.

Uses and Administration

Lamotrigine, a phenyltriazine compound, is an antiepileptic used mainly for monotherapy or adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures. It may be used for seizures associated with the Lennox-Gastaut syndrome and for the maintenance treatment of bipolar disorder.

The doses given below for the use of lamotrigine in **epilepsy** are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- The initial oral dose for use as *monotherapy* is 25 mg once daily for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily
- The initial oral dose of lamotrigine for use as an *adjunct* to therapy with enzyme-inducing antiepileptics (but *not with valproate*) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily
- In those *taking valproate* the initial oral dose of lamotrigine is 25 mg every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses
- In those *taking oxcarbazepine* but no enzyme-inducing or -inhibiting antiepileptics the dosage regimen of adjunctive lamotrigine is as for monotherapy

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate. For comment on the need to modify maintenance doses when starting or stopping oral contraceptives see Sex Hormones, under Interactions, above.

For doses in children, see below.

In the management of **bipolar disorder**, the target dose of lamotrigine is 200 mg daily as *monotherapy*; for patients *taking valproate* the target dose is 100 mg daily and in those taking enzyme-inducing drugs (but *not with valproate*) the target dose is 400 mg daily. Lamotrigine should be started at a reduced dose and increased gradually to the target dose in a regimen similar to that used in the treatment of epilepsy (see above).

Doses should be reduced in patients with hepatic impairment regardless of indication (see below).

As with other antiepileptics, withdrawal of lamotrigine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. Licensed drug information recommends that regardless of indication the withdrawal of lamotrigine should be tapered over at least 2 weeks.

Administration in children. Lamotrigine is used as an adjunct in the treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures in children aged 2 years and over; it is used as monotherapy in those over 12 years of age. Lamotrigine may also be used for seizures associated with the Lennox-Gastaut syndrome.

The doses given below are those licensed in the UK; similar doses are given in the USA although the use of lamotrigine is more limited than in the UK.

- In those taking enzyme-inducing antiepileptics (but *not with valproate*) the initial oral dose of lamotrigine is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily given in 2 divided doses
- In those *taking valproate* the initial oral dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg daily, given as a single dose or in 2 divided doses
- In those taking *oxcarbazepine* but no enzyme-inducing or -inhibiting antiepileptics the initial oral dose of lamotrigine, given as a single dose or in 2 divided doses, is 300 micrograms/kg daily for 2 weeks, followed by 600 micrograms/kg daily for 2 weeks; thereafter the dose is increased by a maximum of 600 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 10 mg/kg daily, to a maximum of 200 mg daily.

If the calculated daily dose of lamotrigine lies between 1 and 2 mg, then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be given if the calculated daily dose is less than 1 mg.

Children over 12 years of age may be given the adult dosage regimen for monotherapy and adjunctive therapy (see above).

Administration in hepatic impairment. UK licensed product information for lamotrigine recommends that doses should be reduced by about 50% in patients with moderate hepatic impairment (Child-Pugh category B), and by about 75% in severe impairment (Child-Pugh category C). US licensed product information recommends that doses should be reduced by about 25% in patients with moderate to severe hepatic impairment without ascites, and by about 50% in those with severe hepatic impairment with ascites.

Anxiety disorders. Small studies have suggested that lamotrigine may relieve some of the symptoms of post-traumatic stress disorder (p.953).

References.

1. Hertzberg MA, *et al.* A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999; **45:** 1226–9.
2. Hageman I, *et al.* Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. *Acta Psychiatr Scand* 2001; **104:** 411–22.

Bipolar disorder. In a multicentre placebo-controlled study involving 195 patients, lamotrigine 50 or 200 mg daily by mouth produced dose-related improvement in patients with bipolar disorder (p.372) experiencing a major depressive episode.[1] Further data from randomised controlled studies[2-8] have confirmed benefit for depressive symptoms (although not for mania), and reviews[9-13] have generally favoured its use, although some have queried the strength of the evidence.[14] Guidelines for the treatment of bipolar disorder now recommend lamotrigine as a first-line option for bipolar depression, and it is licensed for such use in a number of countries (see also Uses and Administration, above).

1. Calabrese JR, *et al.* A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry* 1999; **60:** 79–88.
2. Bowden CL, *et al.* Lamotrigine in the treatment of bipolar depression. *Eur Neuropsychopharmacol* 1999; **9** (suppl 4): S113–S117.
3. Calabrese JR, *et al.* A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. *J Clin Psychiatry* 2000; **61:** 841–50.
4. Ichim L, *et al.* Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry* 2000; **12:** 5–10.
5. Obrocea GV, *et al.* Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002; **51:** 253–60.
6. Bowden CL, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; **60:** 392–400. Correction. *ibid.* 2004; **61:** 680.
7. Calabrese JR, *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; **64:** 1013–24.
8. Nierenberg AA, *et al.* Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006; **163:** 210–16.
9. Engle PM, Heck AM. Lamotrigine for the treatment of bipolar disorder. *Ann Pharmacother* 2000; **34:** 258–62.
10. Hurley SC. Lamotrigine update and its use in mood disorders. *Ann Pharmacother* 2002; **36:** 860–73.
11. Goldsmith DR, *et al.* Lamotrigine: a review of its use in bipolar disorder. *Drugs* 2003; **63:** 2029–50.
12. Muzina DJ, *et al.* Lamotrigine and antiepileptic drugs as mood stabilizers in bipolar disorder. *Acta Psychiatr Scand Suppl* 2005; 21–8.
13. Smith LA, *et al.* Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007; **9:** 394–412.
14. van der Loos MLM, *et al.* Lamotrigine bij de behandeling van bipolaire stoornissen: een overzicht. *Tijdschr Psychiatr* 2007; **49:** 95–103.

Epilepsy. Lamotrigine is used in the treatment of epilepsy (p.465). It is used in partial seizures with or without secondary generalisation, and in generalised tonic-clonic seizures, although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. It is also recommended in absence seizures, although the evidence base is not particularly strong, and may be used in juvenile myoclonic epilepsy and tried in tonic or atonic seizures.

As monotherapy for partial seizures with or without secondary generalisation, lamotrigine was found to be better than carbamazepine (the established first-line drug) in terms of time to treatment failure and tolerability.[1] In patients with newly-diagnosed partial seizures with or without secondary generalisation, lamotrigine had a similar efficacy to carbamazepine, but again was better tolerated.[2] A systematic review[3] of randomised, placebo-controlled studies concluded that lamotrigine is also effective in reducing the seizure frequency when added to current antiepileptic regimens in patients with refractory partial seizures.

As monotherapy for primary generalised and unclassifiable seizures lamotrigine was found[4] to be significantly inferior to valproate (the established first-line drug) in terms of seizure control, with almost twice the failure rate; valproate was also significantly more effective for achieving 12-month remission and prolonging the time to first seizure. Benefit was seen with adjunctive lamotrigine when compared with placebo in children[5] and adults[6] for treatment-resistant primary generalised seizures; it was also suggested[6] that lamotrigine therapy may be appropriate when determination of the type of epilepsy in these patients is not possible.

Lamotrigine appears to be an effective adjunctive treatment in children with the Lennox-Gastaut syndrome.[7,8]

It has also been found to be effective and well tolerated as adjunctive therapy in paediatric patients with refractory epilepsy including those with developmental impairment;[9] it was particularly effective in absence and atypical seizures in this open-label study. (Evidence for the use of lamotrigine to treat absence seizures, as for the other common alternatives ethosuximide and valproate, is, however, generally poor.[10])

1. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1000–15.
2. Brodie MJ, *et al.* UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; **345:** 476–9.
3. Ramaratnam S, *et al.* Lamotrigine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).
4. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.
5. Trevathan E, *et al.* Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Abstract: *Pediatrics* 2006; **118:** 777–8. Full version: http://www.pediatrics.org/cgi/content/full/118/2/e371 (accessed 09/06/08)
6. Biton V, *et al.* Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. *Neurology* 2005; **65:** 1737–43.
7. Donaldson JA, *et al.* Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut Syndrome). *Epilepsia* 1997; **38:** 68–73.
8. Motte J, *et al.* Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997; **337:** 1807–12. Correction. *ibid.* 1998; **339:** 851–2.
9. Besag FMC, *et al.* Lamotrigine for the treatment of epilepsy in childhood. *J Pediatr* 1995; **127:** 991–7.
10. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).

Migraine. Case reports[1] and open studies[2,3] have suggested that lamotrigine may be of benefit in the prophylaxis of migraine aura.

1. d'Onofrio F, *et al.* Basilar-type migraine responsive to lamotrigine: three case reports. *Neurol Sci* 2007; **28:** S239–S241.
2. Pascual J, *et al.* Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; **44:** 1024–8.
3. Lampl C, *et al.* Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 2005; **76:** 1730–2.

Motor neurone disease. Lamotrigine has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but with disappointing results.[1]

1. Ryberg H, *et al.* A double-blind randomized clinical trial in amyotrophic lateral sclerosis using lamotrigine: effects on CSF glutamate, aspartate, branched-chain amino acid levels and clinical parameters. *Acta Neurol Scand* 2003; **108:** 1–8.

Movement disorders. Symptomatic improvement and a trend towards decreased chorea was reported[1] with lamotrigine in a double-blind, placebo-controlled study of 64 patients with Huntington's chorea (p.953) with motor signs of less than 5 years' duration. There was, however, no clear evidence that lamotrigine retarded the progression of early Huntington disease over a period of 30 months.

1. Kremer B, *et al.* Influence of lamotrigine on progress of early Huntington disease: a randomized clinical trial. *Neurology* 1999; **53:** 1000–11.

Neuropathic pain. There is growing evidence that lamotrigine is of use in the management of neuropathic pain.[1] It was effective when used with carbamazepine or phenytoin in the treatment of refractory *trigeminal neuralgia*[2] (p.9), and has also shown promise in the treatment of pain associated with *HIV-related distal sensory neuropathy*[3] (p.857). Some benefit has been found[4] in the treatment of *diabetic neuropathy* (see p.6). Case reports[5] and a placebo-controlled trial[6] have also indicated that lamotrigine may be effective in *central post-stroke pain* (p.6). More recently, the use of lamotrigine in neuropathic pain has been reviewed.[7,8] Based on the same studies, one review[7] concluded that lamotrigine is an effective treatment for various types of neuropathic pain and that further studies are warranted while another[8] concluded that it is unlikely to be of benefit and that further studies are probably not justified.

1. McCleane GJ. Lamotrigine in the management of neuropathic pain: a review of the literature. *Clin J Pain* 2000; **16:** 321–6.
2. Zakrewska JM, *et al.* Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover study. *Pain* 1997; **73:** 223–30.
3. Simpson DM, *et al.* Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003; **60:** 1508–14.
4. Eisenberg E, *et al.* Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001; **57:** 505–9.
5. Canavero S, Bonicalzi V. Lamotrigine control of central pain. *Pain* 1996; **68:** 179–81.
6. Vestergaard K, *et al.* Lamotrigine for central post-stroke pain: a randomized controlled trial. *Neurology* 2001; **56:** 184–90.
7. Eisenberg E, *et al.* Lamotrigine for neuropathic pain. *Expert Rev Neurother* 2005; **5:** 729–35.
8. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).

Schizophrenia. Lamotrigine has been tried as adjunctive therapy in treatment-resistant schizophrenic patients[1] and a benefit has been reported in few studies,[2-4] although patient numbers have been small. However, a systematic review[5] of the use of lamotrigine in schizophrenia concluded that the evidence for its use was poor, although it was suggestive of a positive effect on symptoms.

1. Large CH, *et al.* The potential role of lamotrigine in schizophrenia. *Psychopharmacology (Berl)* 2005; **181:** 415–36.
2. Tiihonen J, *et al.* Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003; **54:** 1241–8.
3. Kremer I, *et al.* Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004; **56:** 441–6.
4. Zoccali R, *et al.* The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res* 2007; **93:** 109–16.
5. Premkumar TS, Pick J. Lamotrigine for schizophrenia. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 09/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dafex; Epilepax; Lagotran; Lamictal; Lamirax; Lamotril; Latrigin; ***Austral.:*** Elmendos; Lamictal; Lamidus; Lamitrin; Lamogine; Seaze; ***Austria:*** Bipolam; Gerolamic; Lamictal; Lamotriglax; ***Belg.:*** Lambipol; Lamictal; ***Braz.:*** Lamictal; Lamitor; Neural; Neurium; ***Canad.:*** Lamictal; ***Chile:*** Daksol; Lafigin; Lamictal; Lomarin; Meganox; Tradox; Trizol; ***Cz.:*** Danoptin; Epimil; Epiral; Lameton; Lamictal; Lamiger; Lamogine; Lamolep; Lamotax; Lamotri; Lamotrix; Latrigil; Plexxo; Rubimar; Triginet; ***Denm.:*** Lamictal; ***Fin.:*** Lamictal; ***Fr.:*** Lamicstart; Lamictal; ***Ger.:*** Elmendos; Lamictal; Lamo; Lamotriax; Lamotrig; ***Gr.:*** Lamictal; Lamotrix; ***Hong Kong:*** Lamictal; ***Hung.:*** Epitrigine; Lamictal; Lamitrin; Lamolep; Plexxo; ***India:*** Lamepil; Lametec; ***Indon.:*** Lamictal; ***Irl.:*** Lamictal; Larig; ***Israel:*** Lamictal; Lamodex; Lamogine; ***Ital.:*** Lamictal; ***Malaysia:*** Lamictal; Lamotrix; ***Mex.:*** Lamdra; Lamictal; Limatic; Protalgine; ***Neth.:*** Lamictal; Lamitor; Lamochem†; Lamomont; Lamotifi; Plexxo†; Symla; ***Norw.:*** Lamictal; ***NZ:*** Lamictal; Mogine; ***Philipp.:*** Lamictal; ***Pol.:*** Danoptin; Epilactal; Lamia; Lamilept; Lamitrin; Lamotrihexal; Lamotrix; Plexxo; Triginet; ***Port.:*** Lamictal; ***Rus.:*** Convulsan (Конвульсан); Lamictal (Ламиктал); Lamitor (Ламитор); Lamolep (Ламолеп); ***S.Afr.:*** Epitec; Lamictin; Lamitor; ***Singapore:*** Lamictal; ***Spain:*** Crisomet; Labileno; Lamictal; ***Swed.:*** Lamictal; ***Switz.:*** Lamictal; ***Thai.:*** Lamictal; ***Turk.:*** Lamictal; ***UK:*** Lamictal; ***USA:*** Epitrogine; Lamictal; ***Venez.:*** Epifon†; Lamictal.

Levetiracetam *(BAN, USAN, rINN)*

S-Etiracetam; Lévétiracétam; Levetiracetamum; Levetirasetam; SIB-S1; UCB-22059; UCB-L059. (*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide.

Леветирацетам

$C_8H_{14}N_2O_2$ = 170.2.

CAS — 102767-28-2.

ATC — N03AX14.

ATC Vet — QN03AX14.

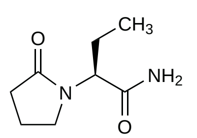

Adverse Effects and Precautions

The most commonly reported adverse effects associated with levetiracetam are somnolence, weakness, and dizziness. Anorexia, diarrhoea, dyspepsia, nausea, weight gain or loss, myalgia, ataxia, headache, amnesia, depression, emotional lability, insomnia, nervousness, tremor, vertigo, diplopia, and rash may occur less frequently. Other adverse effects include paraesthesia, pancreatitis, hepatic failure, and hepatitis. A raised incidence of mild infections, such as the common cold and upper respiratory-tract infections, has been reported. Alopecia may also develop; in some cases, stopping levetiracetam has resulted in regrowth of hair.

Other adverse effects reported include abnormal behaviour, aggression, anger, anxiety, confusion, hallucinations, irritability, and psychotic disorders; these adverse effects may be more common in children than in adults. Blood dyscrasias such as neutropenia, pancytopenia, and thrombocytopenia may develop.

Levetiracetam should be used with caution in patients with renal impairment, and/or severe hepatic impairment.

Care is required when withdrawing levetiracetam therapy—see also Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on the endocrine system. Hyponatraemia developed[1] in a patient given levetiracetam in whom carbamazepine had previously caused the syndrome of inappropriate antidiuretic hormone secretion; symptoms resolved on stopping levetiracetam and recurred on rechallenge.

1. Nasrallah K, Silver B. Hyponatremia associated with repeated use of levetiracetam. *Epilepsia* 2005; **46:** 972–3.

Effects on the lungs. Diffuse interstitial lung disease developed[1] after a dose increase of levetiracetam in a 9-year-old girl who had been taking the drug for 2 years. The condition resolved when levetiracetam was stopped and treatment with corticosteroids was given.

1. Newsome SD, *et al.* Levetiracetam-induced diffuse interstitial lung disease. *J Child Neurol* 2007; **22:** 628–30.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of levetiracetam on *mood* (including the risk of suicidal ideation), see p.468.

Effects on the skin. For a suggestion that skin reactions are less common with levetiracetam than with some other antiepileptics see under Phenytoin, p.496.

Movement disorders. Levetiracetam has been associated with symptoms of parkinsonism including resting tremor, bradykinesia, and rigidity when used to treat Huntington's chorea in a 58-year-old man;[1] symptoms resolved within 7 days of stopping levetiracetam. The patient was also taking a number of other drugs at the time and the authors suggested that these symptoms might have been caused by a drug interaction. However, levetiracetam has been tried in the treatment of some movement disorders as discussed under Uses and Administration, below.

1. Zesiewicz TA, *et al.* Levetiracetam-induced parkinsonism in a Huntington disease patient. *Clin Neuropharmacol* 2005; **28:** 188–90.

Overdosage. A 38-year-old woman who ingested 30 g of levetiracetam vomited 4 hours later and presented with hypoxia, hypotension, and respiratory depression 6 hours after ingestion; peak plasma-levetiracetam concentration was 400 micrograms/mL.[1] The patient recovered without sequelae over 48 hours with symptomatic treatment.

1. Barrueto F, *et al.* A case of levetiracetam (Keppra) poisoning with clinical and toxicokinetic data. *J Toxicol Clin Toxicol* 2002; **40:** 881–4.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

The UK Epilepsy and Pregnancy Register[1] provided data as of July 2005 from 117 first-trimester exposures to levetiracetam with 39 to monotherapy and 78 to adjunctive therapy. In the former group, 4 infants had a low birth-weight and 4 were born at 37 weeks of gestation or less. In the latter, 10 had a low birth-weight, 18 were born at 37 weeks of gestation or less, and 3 had major congenital malformations.

1. Hunt S, *et al.* Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; **67:** 1876–9.

Interactions

Evidence of significant interactions between levetiracetam and other antiepileptics is mostly lacking. However, for the effects of levetiracetam on carbamazepine, see p.474.

Pharmacokinetics

Levetiracetam is readily absorbed from the gastrointestinal tract with a bioavailability of almost 100%; peak plasma concentrations are usually achieved within 1.3 hours of oral doses and steady state achieved after 2 days. Plasma protein binding is minimal at less than 10%. Levetiracetam is not extensively metabolised; about 25% of a dose is metabolised by hydroxylation to inactive metabolites. Around 95% of a dose is excreted as unchanged drug and metabolites in the urine. The plasma elimination half-life has been reported to be about 7 hours in adults and children aged 12 years and over; the half-life may be shorter in younger children. Levetiracetam is distributed into breast milk.

◊ References.

1. Radtke RA. Pharmacokinetics of levetiracetam. *Epilepsia* 2001; **42** (suppl 4): 24–7.
2. Pellock JM, *et al.* Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001; **42:** 1574–9.
3. Coupez R, *et al.* Levetiracetam: relative bioavailability and bioequivalence of a 10% oral solution (750 mg) and 750-mg tablets. *J Clin Pharmacol* 2003; **43:** 1370–6.
4. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet* 2004; **43:** 707 24.
5. Brockmöller J, *et al.* Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther* 2005; **77:** 529–41.

6. Glauser TA, *et al.* Pharmacokinetics of levetiracetam in infants and young children with epilepsy. *Epilepsia* 2007; **48:** 1117–22.
7. Tomson T, *et al.* Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; **48:** 1111–16.
8. Hirsch LJ, *et al.* Effect of age and comedication on levetiracetam pharmacokinetics and tolerability. *Epilepsia* 2007; **48:** 1351–9.

Uses and Administration

Levetiracetam is an analogue of piracetam (p.368). It is used as an adjunct in the treatment of partial seizures with or without secondary generalisations in adults and children aged 4 years and over; in the UK, adults and adolescents aged 16 years and over may also be given levetiracetam as monotherapy for this indication. In addition, levetiracetam is licensed for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy. It is also licensed for use as an adjunct in the treatment of primary generalised tonic-clonic seizures in adults and children with idiopathic generalised epilepsy; for this indication, in the UK, licensed use is restricted to children aged 12 years and over, whereas in the USA, it is licensed from 6 years of age.

The daily oral dose of levetiracetam is given in two divided doses.

- The initial adult dose when used *as an adjunct* is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily.

  The initial dose in children weighing less than 50 kg is 20 mg/kg daily which may be increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily.

  Children and adolescents weighing 50 kg or more should be given the usual adult dose (see above).

  When used as *monotherapy*, the initial dose of levetiracetam is 500 mg daily, increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily.

When oral use is not feasible, levetiracetam may be given by intravenous infusion over 15 minutes in doses similar to those used orally; as with the oral formulation, details of licensed uses and ages may vary from country to country. UK licensed product information states that there has been no experience with the use of intravenous levetiracetam for more than 4 days.

Reduced doses are recommended in renal and severe hepatic impairment (see below).

As with other antiepileptics, withdrawal of levetiracetam therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose in adults by 1 g every 2 to 4 weeks; in children, the dose reduction should not exceed 20 mg/kg every 2 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

◊ References.

1. De Smedt T, *et al.* Levetiracetam: the profile of a novel anticonvulsant drug—part I: preclinical data. *CNS Drug Rev* 2007; **13:** 43–56.
2. De Smedt T, *et al.* Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. *CNS Drug Rev* 2007; **13:** 57–78.

Administration in children. Licensed indications and doses of levetiracetam in children vary from country to country, see Uses and Administration, above. It is mainly used for partial and myoclonic seizures, and in idiopathic generalised epilepsy, often as an adjunct. A retrospective review[1] of 122 children aged from 1 month to 2 years given levetiracetam either as monotherapy (48 patients) or adjunctive therapy (74 patients) found that 70 achieved seizure remission. Of these, a longer duration of remission was seen in those receiving less than 30 mg/kg daily of levetiracetam. A case series[2] of 3 infants aged from 2 days to 3 months reported that levetiracetam 30 mg/kg daily was effective in the treatment of refractory neonatal seizures.

1. Perry MS, Benatar M. Efficacy and tolerability of levetiracetam in children younger than 4 years: a retrospective review. *Epilepsia* 2007; **48:** 1123–7.
2. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007; **22:** 95–8.

Administration in hepatic impairment. No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, creatinine clearance (CC) may underestimate concomitant renal impairment, and UK licensed product information recommends that the usual adult maintenance dose (see above) should be reduced by 50% in those with a CC of less than 70 mL/minute.

Administration in renal impairment. Reduced doses of levetiracetam are recommended for patients with renal impairment. Suitable daily doses according to UK and US licensed product information, based on creatinine clearance (CC) and given in 2 divided doses, are:

- CC 50 to 79 mL/minute: 1 to 2 g
- CC 30 to 49 mL/minute: 500 mg to 1.5 g
- CC less than 30 mL/minute: 500 mg to 1 g

Patients receiving dialysis may be given a loading dose of 750 mg when starting levetiracetam followed by doses of 500 mg to 1 g once daily; a supplemental dose of 250 to 500 mg is recommended after dialysis.

Doses may be given orally or intravenously, as necessary.

See also above for dosage recommendations in those patients with severe hepatic impairment and concomitant renal impairment.

Epilepsy. Levetiracetam is used in epilepsy (p.465) as an adjunct or monotherapy in the management of partial seizures with or without secondary generalisation.[1-6] It is also used as an adjunct in myoclonic seizures[7-9] and for generalised tonic-clonic seizures,[10] although valproate is the drug of choice in the latter where these are associated with the syndrome of primary generalised epilepsy. Levetiracetam may be considered as second-line drug for atonic or tonic seizures, and has been tried in Lennox-Gastaut syndrome and in juvenile absence epilepsy.[11] In children, levetiracetam has also been tried as adjunctive therapy for nonconvulsive status epilepticus,[12] in infantile spasms,[13] and in severe myoclonic epilepsy of infancy,[14] and as monotherapy in partial and generalised epilepsy.[15]

1. Dooley M, Plosker GL. Levetiracetam: a review of its adjunctive use in the management of partial onset seizures. *Drugs* 2000; **60:** 871–93.
2. Chaisewikul R, *et al.* Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Welty TE, *et al.* Levetiracetam: a different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother* 2002; **36:** 296–304.
4. Leach JP. Levetiracetam in the management of epilepsy. *Hosp Med* 2004; **65:** 740–4.
5. Abou-Khalil B. Benefit-risk assessment of levetiracetam in the treatment of partial seizures. *Drug Safety* 2005; **28:** 871–90.
6. Steinhoff BJ, *et al.* The SKATE study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. *Epilepsy Res* 2007; **76:** 6–14.
7. Crest C, *et al.* Levetiracetam in progressive myoclonic epilepsy: an exploratory study in 9 patients. *Neurology* 2004; **62:** 640–3.
8. Specchio LM, *et al.* Open label, long-term, pragmatic study on levetiracetam in the treatment of juvenile myoclonic epilepsy. *Epilepsy Res* 2006; **71:** 32–9.
9. Noachtar S, *et al.* Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 2008; **70:** 607–16.
10. Berkovic SF, *et al.* Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. *Neurology* 2007; **69:** 1751–60.
11. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020fullguideline.pdf (accessed 09/06/08)
12. Trabacca A, *et al.* Levetiracetam in nonconvulsive status epilepticus in childhood: a case report. *J Child Neurol* 2007; **22:** 639–41.
13. Mikati MA, *et al.* Response of infantile spasms to levetiracetam. *Neurology* 2008; **70:** 574–5.
14. Striano P, *et al.* An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007; **69:** 250–4.
15. Khurana DS, *et al.* Levetiracetam monotherapy in children with epilepsy. *Pediatr Neurol* 2007; **36:** 227–30.

Movement disorders. Levetiracetam may be of benefit in some movement disorders. It has been tried in antipsychotic-induced *tardive dyskinesia*[1-3] and with equivocal benefit in levodopa-induced tardive dyskinesia[4,5] (see under Extrapyramidal Disorders on p.971). There is also limited evidence of benefit with levetiracetam for the treatment of *chorea* (p.953) in Huntington's disease[6,7] and in *paroxysmal kinesigenic choreoathetosis*.[8]

1. Konitsiotis S, *et al.* Levetiracetam in tardive dyskinesia: an open label study. *Mov Disord* 2006; **21:** 1219–21.
2. Meco G, *et al.* Levetiracetam in tardive dyskinesia. *Clin Neuropharmacol* 2006; **29:** 265–8.
3. Woods SW, *et al.* Effects of levetiracetam on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2008; **69:** 546–54.
4. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2005; **20:** 1205–9.
5. Lyons KE, Pahwa R. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. *Clin Neuropharmacol* 2006; **29:** 148–53.
6. Zesiewicz TA, *et al.* Open-label pilot study of levetiracetam (Keppra) for the treatment of chorea in Huntington's disease. *Mov Disord* 2006; **21:** 1998–2001.
7. de Tommaso M, *et al.* Efficacy of levetiracetam in Huntington disease. *Clin Neuropharmacol* 2005; **28:** 280–4.
8. Chatterjee A, *et al.* Levetiracetam in the treatment of paroxysmal kinesiogenic choreoathetosis. *Mov Disord* 2002; **17:** 614–15.

Muscle spasm. Levetiracetam has been tried with some success in *Meige's syndrome*,[1] and *hemifacial spasm*.[2] For use in *stiff-man syndrome* see below.

1. Yardimci N, *et al.* Levetiracetam in Meige's syndrome. *Acta Neurol Scand* 2006; **114:** 63–6.
2. Deleu D. Levetiracetam in the treatment of idiopathic hemifacial spasm. *Neurology* 2004; **62:** 2134–5.

Psychiatric disorders. Levetiracetam has psychotropic properties and has been tried in the management of *anxiety disorders*[1] (p.952) including *social anxiety disorder*[2] (see Phobic Disorders, p.953), *post-traumatic stress disorder*[3] (p.953), and *panic disorder*[4] (p.952). There is also limited evidence[5] from case reports and small open-label studies that levetiracetam may be of benefit in the treatment of *bipolar disorder* (p.372).

1. Kinrys G, *et al.* Levetiracetam as adjunctive therapy for refractory anxiety disorders. *J Clin Psychiatry* 2007; **68:** 1010–13.
2. Simon NM, *et al.* An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 1219–22.
3. Kinrys G, *et al.* Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry* 2006; **67:** 211–14.
4. Papp LA. Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study. *J Clin Psychiatry* 2006; **67:** 1573–6.
5. Muralidharan A, Bhagwagar Z. Potential of levetiracetam in mood disorders: a preliminary review. *CNS Drugs* 2006; **20:** 969–79.

Restless legs syndrome. Levetiracetam has been reported to be of benefit in the treatment of refractory restless legs syndrome (see Sleep-associated Movement Disorders, p.958).[1]

1. Della Marca G, *et al.* Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases. *J Neurol Neurosurg Psychiatry* 2006; **77:** 566–7.

Status epilepticus. Levetiracetam has been tried, with some success, in the management of nonconvulsive status epilepticus[1] and refractory status epilepticus.[2] For the conventional management of status epilepticus see p.469.

1. Rupprecht S, *et al.* Levetiracetam as a treatment option in nonconvulsive status epilepticus. *Epilepsy Res* 2007; **73:** 238–44.
2. Patel NC, *et al.* The use of levetiracetam in refractory status epilepticus. *Seizure* 2006; **15:** 137–41.

Stiff-man syndrome. In a report[1] of a patient with stiff-man syndrome, substitution of levetiracetam for previous valproate therapy (because of suspected valproate-induced parkinsonism) resulted in complete suppression of paroxysmal spasms; benefit was sustained with continued therapy over 2 years of follow-up.

1. Rüegg SJ, *et al.* Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome. *Neurology* 2004; **62:** 338.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, levetiracetam has also been tried with some success.[1] Benefit was also reported[2] with levetiracetam in the treatment of tremor secondary to multiple sclerosis.

1. Bushara KO, *et al.* The effect of levetiracetam on essential tremor. *Neurology* 2005; **64:** 1078–80.
2. Striano P, *et al.* Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol* 2006; **253:** 762–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Keppra; Levron; ***Austral.:*** Keppra; ***Belg.:*** Keppra; ***Canad.:*** Keppra; ***Chile:*** Kopodex; ***Cz.:*** Keppra; ***Denm.:*** Keppra; ***Fin.:*** Keppra; ***Fr.:*** Keppra; ***Ger.:*** Keppra; ***Gr.:*** Keppra; ***Hong Kong:*** Keppra; ***Hung.:*** Keppra; ***India:*** Levroxa; ***Indon.:*** Keppra; ***Irl.:*** Keppra; ***Israel:*** Keppra; ***Ital.:*** Keppra; ***Malaysia:*** Keppra; ***Mex.:*** Keppra; ***Neth.:*** Keppra; ***Norw.:*** Keppra; ***NZ:*** Keppra; ***Philipp.:*** Keppra; ***Pol.:*** Keppra; ***Port.:*** Keppra; ***Rus.:*** Keppra (Кеппра); ***S.Afr.:*** Keppra; ***Singapore:*** Keppra; ***Spain:*** Keppra; ***Swed.:*** Keppra; ***Switz.:*** Keppra; ***Thai.:*** Keppra; ***Turk.:*** Keppra; ***UK:*** Keppra; ***USA:*** Keppra.

Losigamone *(rINN)*

AO-33; Losigamona; Losigamonum. (5*R**)-5-[(α*S**)-*o*-Chloro-α-hydroxybenzyl]-4-methoxy-2(5*H*)-furanone.

Лозигамон

$C_{12}H_{11}ClO_4$ = 254.7.

CAS — 112856-44-7.

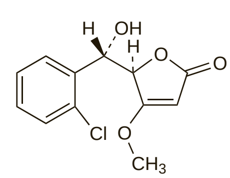

Profile

Losigamone is an antiepileptic that has been investigated as adjunctive therapy in the treatment of partial seizures.

◊ References

1. Bauer J, *et al*. Losigamone add-on therapy in partial epilepsy: a placebo-controlled study. *Acta Neurol Scand* 2001; **103:** 226–30.
2. Baulac M, Klement S. Losigamone Study Group. Efficacy and safety of losigamone in partial seizures: a randomized double-blind study. *Epilepsy Res* 2003; **55:** 177–89.

Mephenytoin *(BAN, USAN, rINN)*

Mefenitoína; Mefenytoiini; Mefenytoin; Mephenetoin; Méphénytoïne; Mephenytoinum; Methantoin; Methoin; NSC-34652; Phenantoin. 5-Ethyl-3-methyl-5-phenylhydantoin.

Мефенитоин

$C_{12}H_{14}N_2O_2$ = 218.3.

CAS — 50-12-4.

ATC — N03AB04.

ATC Vet — QN03AB04.

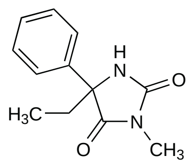

Pharmacopoeias. In *US.*

USP 31 (Mephenytoin). Store in airtight containers.

Profile

Mephenytoin is a hydantoin antiepileptic with actions similar to those of phenytoin (p.495), but it is more toxic. Because of its potential toxicity it is not one of the main drugs used in the treatment of epilepsy (p.465) and is given only to patients unresponsive to other treatment. Some of the adverse effects of mephenytoin may be due to the metabolite, 5-ethyl-5-phenylhydantoin (also termed nirvanol). Like phenytoin the rate of metabolism of mephenytoin is subject to genetic polymorphism.

Mephenytoin is given in an initial oral daily dose of 50 to 100 mg for 1 week; thereafter the daily dose is increased by 50 to 100 mg at weekly intervals until the optimum dose is reached, which is usually between 200 and 600 mg daily for an adult and 100 and 400 mg daily for a child; daily maintenance doses are usually taken in 3 divided doses.

Porphyria. Mephenytoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Mephenytoin Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Epilan; ***Cz.:*** Epilan†.

Mesuximide *(BAN, rINN)*

Mesuksimidi; Mesuximid; Mesuximida; Mésuximide; Mesuximidum; Methsuximide; PM-396. *N*,2-Dimethyl-2-phenylsuccinimide.

Мезуксимид

$C_{12}H_{13}NO_2$ = 203.2.

CAS — 77-41-8.

ATC — N03AD03.

ATC Vet — QN03AD03.

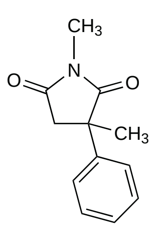

Pharmacopoeias. In *US.*

USP 31 (Methsuximide). A white to greyish-white crystalline powder. Is odourless or has a slight odour. Soluble 1 in 350 of water, 1 in 3 of alcohol, 1 in less than 1 of chloroform, and 1 in 2 of ether. Store in airtight containers.

Profile

Mesuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p.479) that is used in the treatment of absence seizures; although it also has some activity in complex partial seizures it is reported to be less well tolerated than ethosuximide, and is usually only given to patients unresponsive to other antiepileptic treatment. It is thought to owe its activity to its major metabolite *N*-desmethylmesuximide.

The usual initial oral dosage is a single dose of 300 mg daily for the first week, and this is increased by 300 mg at weekly intervals to an optimum dosage, according to response. The suggested maximum daily dose is 1.2 g in divided doses.

Epilepsy. Mesuximide is used for absence seizures that are refractory to less toxic antiepileptics such as ethosuximide or valproate, which are the usual first-line drugs (see p.465). Mesuximide has also been tried in complex partial seizures and myoclonic seizures.

References.

1. Tennison MB, *et al*. Methsuximide for intractable childhood seizures. *Pediatrics* 1991; **87:** 186–9.
2. Sigler M, *et al*. Effective and safe but forgotten: methsuximide in intractable epilepsies in childhood. *Seizure* 2001; **10:** 120–4.

Interactions. For the effect of mesuximide on lamotrigine and valproate, see p.486 and p.511 respectively.

Porphyria. Mesuximide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Methsuximide Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Petinutin; ***Canad.:*** Celontin; ***Ger.:*** Petinutin; ***Israel:*** Celontin†; ***Neth.:*** Celontin; ***Switz.:*** Petinutin; ***USA:*** Celontin.

Methylphenobarbital *(BAN, rINN)*

Enphenemalum; Mephobarbital; Methylfenobarbital; Méthylphénobarbital; Methylphenobarbitalum; Methylphenobarbitone; Metilfenobarbitál; Metilfenobarbital; Metilfenobarbitalis; Metylfenobarbital; Metyylifenobarbitaali; Phemitone. 5-Ethyl-1-methyl-5-phenylbarbituric acid.

Метилфенобарбитал

$C_{13}H_{14}N_2O_3$ = 246.3.

CAS — 115-38-8.

ATC — N03AA01.

ATC Vet — QN03AA01.

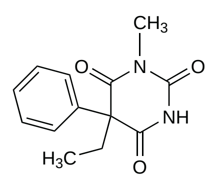

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Methylphenobarbital). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; very slightly soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 31 (Mephobarbital). A white, odourless, crystalline powder. Slightly soluble in water, in alcohol, and in ether; soluble in chloroform and in solutions of fixed alkali hydroxides and carbonates. Its saturated solution in water is acid to litmus.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Phenobarbital, p.492.

Interactions

As for Phenobarbital, p.493.

Pharmacokinetics

Methylphenobarbital is incompletely absorbed from the gastrointestinal tract. It is demethylated to phenobarbital (p.494) in the liver.

Uses and Administration

Methylphenobarbital is used similarly to phenobarbital (p.494) in the treatment of epilepsy (p.465). It is given in oral doses of up to 600 mg daily. It has also been used as a sedative in a usual dose of 50 mg 3 or 4 times daily.

Preparations

BP 2008: Methylphenobarbital Tablets;
USP 31: Mephobarbital Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Prominal†; ***USA:*** Mebaral.

Multi-ingredient: *Arg.:* Cumatil L; ***Ital.:*** Dintoinale; Metinal-Idantoina; Metinal-Idantoina L.

Oxcarbazepine *(BAN, USAN, rINN)*

GP-47680; KIN-493; Okskarbatsepiini; Okskarbazepin; Oxcarbazepin; Oxcarbazepina; Oxcarbazépine; Oxcarbazepinum. 10,11-Dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine-5-carboxamide.

Окскарбазепин

$C_{15}H_{12}N_2O_2$ = 252.3.

CAS — 28721-07-5.

ATC — N03AF02.

ATC Vet — QN03AF02.

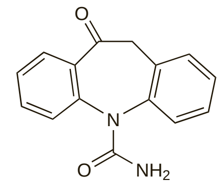

Adverse Effects, Treatment, and Precautions

As for Carbamazepine, p.472.

Hypersensitivity reactions such as skin rashes (see also under Carbamazepine, p.473) occur less frequently with oxcarbazepine than with carbamazepine. However, cross-sensitivity does occur and about 25 to 30% of patients hypersensitive to carbamazepine may experience such reactions with oxcarbazepine. Reductions in plasma-sodium levels have also been observed with oxcarbazepine (see Hyponatraemia, below). Patients with cardiac insufficiency and secondary heart failure should be weighed regularly to detect fluid retention. Oxcarbazepine may, very rarely, impair cardiac conduction and patients with pre-existing conduction disorders should be carefully monitored. Very rarely, oxcarbazepine treatment has been associated with pancreatitis.

Dosage reductions are recommended in renal impairment.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on the blood. Although it would appear that oxcarbazepine is less likely than carbamazepine to cause blood dyscrasias such as leucopenia, individual cases have been reported. In one such case leucopenia and hyponatraemia developed in a 57-year-old woman while taking oxcarbazepine;[1] she recovered after treatment with filgrastim. It was noted that the patient had experienced a similar reaction when taking carbamazepine. Oxcarbazepine has also been associated with reversible pancytopenia[2] in a 40-year-old woman, and reversible thrombocytopenia[3] in a 63-year-old woman.

1. Ryan M, *et al*. Hyponatremia and leukopenia associated with oxcarbazepine following carbamazepine therapy. *Am J Health-Syst Pharm* 2001; **58:** 1637–9.
2. Calamaras MR, *et al*. Pancytopenia associated with the introduction of oxcarbazepine. *J Clin Psychopharmacol* 2007; **27:** 217–18.
3. Mahmud J, *et al*. Oxcarbazepine-induced thrombocytopenia. *Psychosomatics* 2006; **47:** 73–4.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of oxcarbazepine on *mood* (including the risk of suicidal ideation), see p.468.

Effects on sexual function. For mention of the effects of antiepileptics including oxcarbazepine on sexual function in male epileptic patients, see Effects on the Endocrine System, under Phenytoin, p.496.

Hyponatraemia. Hyponatraemia appears to be more pronounced at clinical doses of oxcarbazepine than with carbamazepine. Hyponatraemia was reported[1] in 12 of 15 patients in whom oxcarbazepine was substituted for carbamazepine therapy. The fall in plasma-sodium concentrations appeared to be related to the dose of oxcarbazepine. In another report[2] hyponatraemia occurred in 23% of 350 patients whose serum-sodium concentrations were monitored. The manufacturers state that in 14 controlled studies sodium levels of less than 125 mmol/litre occurred in 2.5% of 1524 patients treated with oxcarbazepine compared to no such patients in the control groups. Most patients remain asymptomatic but some may experience drowsiness, increase in seizure frequency, and impaired consciousness.[3] In a later study[4] in 97 patients taking oxcarbazepine and 451 taking carbamazepine, hyponatraemia occurred in 29 (12 severe) of the former and in 61 (13 severe) of the latter. The authors failed to find a correlation between high doses of oxcarbazepine and the occurrence of hyponatraemia.

It has been suggested that serum-sodium concentrations should be measured before the start of therapy but routine monitoring, may be indicated only in elderly patients or if a high dosage is used.[5] Licensed product information recommends that monitoring be considered in those with pre-existing conditions associated with low sodium levels and in those taking other medications known to interfere with sodium levels, for example NSAIDs and diuretics.

Severe hyponatraemia has been reported[6] in a 12-year-old child during treatment with oxcarbazepine. A review of 48 other children who had received oxcarbazepine in the same centre, found that 9 had hyponatraemia, and the authors suggested that sodium levels should be monitored in paediatric patients. In another case,[7] a 7-year old boy developed a reversible coma caused by oxcarbazepine-induced hyponatraemia.

1. Pendlebury SC, *et al.* Hyponatraemia during oxcarbazepine therapy. *Hum Toxicol* 1989; **8:** 337–44.
2. Friis ML, *et al.* Therapeutic experiences with 947 epileptic outpatients in oxcarbazepine treatment. *Acta Neurol Scand* 1993; **87:** 224–7.
3. Steinhoff BJ, *et al.* Hyponatraemic coma under oxcarbazepine therapy. *Epilepsy Res* 1992; **11;** 67–70.
4. Dong X, *et al.* Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005; **65:** 1976–8.
5. Kälviäinen R, *et al.* Place of newer antiepileptic drugs in the treatment of epilepsy. *Drugs* 1993; **46:** 1009–24.
6. Borusiak P, *et al.* Hyponatremia induced by oxcarbazepine in children. *Epilepsy Res* 1998; **30:** 241–6.
7. Paliwal V, *et al.* Oxcarbazepine induced hyponatremic coma. *Neurol India* 2006; **54:** 214–15.

Overdosage. A 36-year-old man[1] who ingested 30.6 g of oxcarbazepine showed no serious signs of toxicity. Serum concentrations of oxcarbazepine were 31.6 mg/litre 2 hours after ingestion; corresponding serum concentrations of the active monohydroxy metabolite were 37.2 mg/litre, which later peaked at 59.0 mg/litre 7 hours after ingestion. The patient remained conscious, though somnolent, and had fully recovered within 2 days.

1. van Opstal JM, *et al.* Severe overdosage with the antiepileptic drug oxcarbazepine. *Br J Clin Pharmacol* 2004; **58:** 329–31.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Plasma concentrations of the active monohydroxy metabolite of oxcarbazepine may be reduced by strong inducers of cytochrome P450 isoenzymes, such as carbamazepine, phenytoin, or phenobarbital. Oxcarbazepine appears to induce hepatic enzymes to a lesser extent than carbamazepine. However, oxcarbazepine and its active metabolite do inhibit the cytochrome P450 isoenzyme CYP2C19, and in high doses may raise plasma concentrations of phenobarbital or phenytoin. Oxcarbazepine and its metabolite also have the capacity to induce CYP3A4 and CYP3A5 with the possibility of reducing plasma concentrations of drugs such as carbamazepine (but see below), dihydropyridine calcium-channel blockers, and oral contraceptives.

◊ References.

1. Sallas WM, *et al.* Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther* 2003; **74:** 138–49.

Antiepileptics. In a study[1] of epileptic patients the area under the concentration-time curve (AUC) seen with monotherapy of *carbamazepine, phenytoin,* or *valproate* was unchanged when oxcarbazepine was added to treatment; only carbamazepine affected the pharmacokinetics of oxcarbazepine, producing a reduction in the AUC for the active metabolite hydroxycarbazepine. It was considered that there was unlikely to be any clinically relevant pharmacokinetic interaction if oxcarbazepine was used with any of these antiepileptics, including carbamazepine. However, increases in plasma-phenytoin concentration have been reported after use with oxcarbazepine (see p.498).

There is a case-report of severe toxicity occurring with concomitant use of oxcarbazepine and *lamotrigine.*[2] For the effect of oxcarbazepine on lamotrigine concentrations, see p.486.

1. McKee PJW, *et al.* A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. *Br J Clin Pharmacol* 1994; **37:** 27–32.
2. Alving J. Case of severe acute intoxication with oxcarbazepine combined with lamotrigine. *Epilepsia* 1994; **35** (suppl 7): 72.

Pharmacokinetics

Oxcarbazepine is completely absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver to the principal metabolite 10,11-dihydro-10-hydroxy-carbamazepine, often referred to as MHD, which also possesses antiepileptic activity. The monohydroxy metabolite is widely distributed in the body and is about 40% bound to plasma proteins, mainly albumin. The plasma half-life has been reported to be about 2 hours for oxcarbazepine, and about 9 hours for the monohydroxy metabolite; consequently the latter provides most of the antiepileptic activity. Clearance of the monohydroxy metabolite is reported to be about 40% higher in children aged 4 to 12 years, and about 80% higher in those aged 2 to 4 years, than in adults. Oxcarbazepine is excreted in the urine mainly as metabolites; less than 1% is excreted as unchanged drug.

Oxcarbazepine and its monohydroxy metabolite cross the placental barrier and are distributed into breast milk.

The pharmacokinetics of oxcarbazepine and its monohydroxy metabolite are affected by use with other antiepileptics (see Interactions, above).

◊ References.

1. Dickinson RG, *et al.* First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. *Eur J Clin Pharmacol* 1989; **37:** 69–74.
2. Patsalos PN, *et al.* Protein binding of oxcarbazepine and its primary active metabolite, 10-hydroxycarbazepine, in patients with trigeminal neuralgia. *Eur J Clin Pharmacol* 1990; **39:** 413–15.
3. Kumps A, Wurth C. Oxcarbazepine disposition: preliminary observations in patients. *Biopharm Drug Dispos* 1990; **11:** 365–70.
4. van Heiningen PNM, *et al.* The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. *Clin Pharmacol Ther* 1991; **50:** 410–19.
5. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
6. May TW, *et al.* Clinical pharmacokinetics of oxcarbazepine. *Clin Pharmacokinet* 2003; **42:** 1023–42.
7. Rey E, *et al.* Oxcarbazepine pharmacokinetics and tolerability in children with inadequately controlled epilepsy. *J Clin Pharmacol* 2004; **44:** 1290–1300.
8. Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. *Clin Drug Investig* 2004; **24:** 185–203.

Pregnancy. Clearance of the active monohydroxy metabolite of oxcarbazepine was reported to increase[1,2] during pregnancy and to decrease[2] after delivery; one study[1] reported a reduction in plasma concentrations of about 36% during the third trimester. However, sample sizes in both studies were small.

1. Christensen J, *et al.* Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. *Neurology* 2006; **67:** 1497–9.
2. Mazzucchelli I, *et al.* Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006; **47:** 504–9.

Uses and Administration

Oxcarbazepine is a derivative of carbamazepine (p.476) with similar actions. It is used as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. The initial oral dose for monotherapy and adjunctive therapy is 600 mg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 600 mg at approximately weekly intervals until the desired clinical response has been achieved. Maintenance doses are usually in the range of 600 mg to 1.2 g daily or up to 2.4 g daily if given as adjunctive therapy or in refractory patients switched from other antiepileptics.

For doses in children, see below.

Reduced initial doses are recommended in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of oxcarbazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Administration in children. Oxcarbazepine is used in children as monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalisation. In the UK, the recommended initial oral dose for monotherapy and adjunctive therapy in those aged 6 years and over is 8 to 10 mg/kg daily, given in 2 divided doses. The daily dose may be increased thereafter, if necessary, in maximum increments of 10 mg/kg at approximately weekly intervals to a maximum dose of 46 mg/kg daily; usual maintenance doses in adjunctive therapy are around 30 mg/kg daily. In the USA, similar doses are recommended for adjunctive therapy in children aged 2 years and over (the initial dose may be doubled in those weighing under 20 kg), and for monotherapy in those aged 4 years and over; a maximum daily dose of 60 mg/kg is permitted for adjunctive therapy.

Administration in renal impairment. Initial doses of oxcarbazepine for adult patients with a creatinine clearance of less than 30 mL/minute should be 300 mg daily (half the usual starting dose, above), increased at weekly intervals or longer.

Bipolar disorder. Like the related drug carbamazepine (p.476), oxcarbazepine has antimanic properties and has been tried in the management of patients with bipolar disorder (p.372). Reviews[1,2] have suggested that it may be useful in treating acute mania and in patients with refractory disease; however, the evidence base is weak[3] and further studies are needed.

1. Pratoomsri W, *et al.* Oxcarbazepine in the treatment of bipolar disorder: a review. *Can J Psychiatry* 2006; **51:** 540–5.
2. Popova E, *et al.* Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Expert Rev Neurother* 2007; **7:** 617–26.
3. Vasudev A, *et al.* Oxcarbazepine in the maintenance treatment of bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Epilepsy. Oxcarbazepine is used in the treatment of epilepsy (p.465) and may be a useful alternative in patients unable to tolerate carbamazepine.

In a double-blind study[1] involving newly diagnosed adult patients, oxcarbazepine was of similar efficacy and tolerability to valproate for partial or generalised tonic-clonic seizures. Oxcarbazepine was of similar efficacy to phenytoin, but was better tolerated in adults and children with newly diagnosed partial or generalised tonic-clonic seizures.[2,3] Further randomised controlled studies and 2 small systematic reviews[4,5] have also confirmed the efficacy and tolerability of oxcarbazepine as adjunctive therapy[4,6] or monotherapy[5,7-9] in refractory partial seizures in children and adults.

1. Christe W, *et al.* A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997; **26:** 451–60.
2. Bill PA, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997; **27:** 195–204.
3. Guerreiro MM, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997; **27:** 205–13.
4. Castillo S, *et al.* Oxcarbazepine add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 09/06/08).
5. Muller M, *et al.* Oxcarbazepine versus phenytoin monotherapy for epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/06/08).
6. Glauser TA, *et al.* Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000; **54:** 2237–44.
7. Beydoun A, *et al.* Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 2000; **54:** 2245–51.
8. Sachdeo R, *et al.* Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001; **57:** 864–71.
9. Herranz Fernández JL, *et al.* Oxcarbacepina en monoterapia en 324 pacientes con crisis parciales (estudio TRINOVA). *Rev Neurol* 2004; **39:** 601–6.

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p.2). Carbamazepine appears to be the antiepileptic most frequently used, but oxcarbazepine has also been tried in various neuropathic pain syndromes[1] including painful diabetic neuropathy[2-4] (see p.6), postherpetic neuralgia[5,6] (p.9), complex regional pain syndrome[7] (p.6), glossopharyngeal neuralgia,[8] oxaliplatin-induced neuropathy[9] (see p.758), and trigeminal neuralgia (p.9).

1. Magenta P, *et al.* Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. *Neurol Sci* 2005; **26:** 218–26.
2. Dogra S, *et al.* Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. *Eur J Pain* 2005; **9:** 543–54.
3. Grosskopf J, *et al.* A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2006; **114:** 177–80.
4. Beydoun S, *et al.* Long-term safety and tolerability of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2007; **115:** 284–8.
5. Criscuolo S, *et al.* Oxcarbazepine (Trileptal) monotherapy dramatically improves quality of life in two patients with postherpetic neuralgia refractory to carbamazepine and gabapentin. *J Pain Symptom Manage* 2004; **28:** 535–6.
6. Criscuolo S, *et al.* Oxcarbazepine monotherapy in postherpetic neuralgia unresponsive to carbamazepine and gabapentin. *Acta Neurol Scand* 2005; **111:** 229–32.
7. Lalwani K, *et al.* Use of oxcarbazepine to treat a pediatric patient with resistant complex regional pain syndrome. *J Pain* 2005; **6:** 704–6.
8. Luef G, Poewe W. Oxcarbazepine in glossopharyngeal neuralgia: clinical response and effect on serum lipids. *Neurology* 2004; **63:** 2447–8.
9. Argyriou AA, *et al.* Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. *Neurology* 2006; **67:** 2253–5.

Psychiatric disorders. Case reports[1,2] in children and adolescents and a randomised, placebo-controlled study[3] in adults have indicated some benefit from oxcarbazepine in the treatment of *aggression* and *disturbed behaviour*(p.954). A retrospective review[4] of 14 children and adolescents with various psychiatric and behavioural disorders found moderate symptomatic improvement in 50% after the addition of oxcarbazepine. Oxcarbazepine has also been tried in the treatment of *schizophrenia*[5] (p.955) and *post-traumatic stress disorder*[6] (p.953). For use in *bipolar disorder* see above.

1. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry* 2007; **164:** 832–3.
2. Gaudino MP, *et al.* Use of oxcarbazepine for treatment-resistant aggression. *Psychiatr Serv* 2003; **54:** 1166–7.
3. Mattes JA. Oxcarbazepine in patients with impulsive aggression: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2005; **25:** 575–9.
4. Staller JA, *et al.* Oxcarbazepine in the treatment of child psychiatric disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 2005; **15:** 964–9.
5. Leweke FM, *et al.* Oxcarbazepine as an adjunct for schizophrenia. *Am J Psychiatry* 2004; **161:** 1130–1.
6. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother* 2004; **38:** 1852–4.

Withdrawal syndromes and abstinence. Oxcarbazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Although it was not found[1] to be superior to placebo in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1626), oxcarbazepine has been reported[2-4] to be of benefit in relapse prevention; further studies are considered warranted. It has also been tried[5] during *benzodiazepine withdrawal* but such adjunct therapy is not usually indicated (see p.987).

1. Koethe D, *et al.* Oxcarbazepine—efficacy and tolerability during treatment of alcohol withdrawal: a double-blind, randomized, placebo-controlled multicenter pilot study. *Alcohol Clin Exp Res* 2007; **31:** 1188–94.
2. Croissant B, *et al.* Oxcarbazepine in alcohol relapse prevention: a case series. *Pharmacopsychiatry* 2004; **37:** 306–7.
3. Croissant B, *et al.* A pilot study of oxcarbazepine versus acamprosate in alcohol-dependent patients. *Alcohol Clin Exp Res* 2006; **30:** 630–5.
4. Martinotti G, *et al.* High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. *Hum Psychopharmacol* 2007; **22:** 149–56.
5. Croissant B, *et al.* Scheme-based benzodiazepine detoxification with oxcarbazepine: a case report. *Pharmacopsychiatry* 2005; **38:** 222–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Atoxecar†; Aurene; Oxca; Oxcazen†; Rupox; Trileptal; ***Austral.:*** Trileptal; ***Austria:*** Trileptal; ***Belg.:*** Trileptal; ***Braz.:*** Auram; Oleptal; Oxcarb; Trileptal; ***Canad.:*** Trileptal; ***Chile:*** Alox†; Oxicodal; Trileptal; ***Cz.:*** Trileptal; ***Denm.:*** Apydan; Trileptal; ***Fin.:*** Apydan; Trileptal; ***Fr.:*** Trileptal; ***Ger.:*** Timox; Trileptal; ***Gr.:*** Trileptal; ***Hong Kong:*** Trileptal; ***Hung.:*** Apydan; Trileptal; ***India:*** Oxcarb; Oxrate; ***Indon.:*** Barzepin; Prolepsi; Trileptal; ***Irl.:*** Trileptal; ***Israel:*** Trileptin; ***Ital.:*** Tolep; ***Malaysia:*** Trileptal; ***Mex.:*** Actinium; Deprectal; Oxetol; Trileptal; ***Neth.:*** Trileptal; ***Norw.:*** Trileptal; ***NZ:*** Trileptal; ***Philipp.:*** Trileptal; ***Pol.:*** Apydan; Trileptal; ***Port.:*** Epilfarmo; Proaxen; Zigabal; ***Rus.:*** Trileptal (Трилептал); ***S.Afr.:*** Trileptal; ***Spain:*** Trileptal; ***Swed.:*** Trileptal; ***Switz.:*** Trileptal; ***Thai.:*** Trileptal; ***Turk.:*** Trileptal; ***UK:*** Trileptal; ***USA:*** Trileptal; ***Venez.:*** Trileptal.

Pheneturide *(BAN, rINN)*

Ethylphenacemide; Feneturida; Phénéturide; Pheneturidum; S-46. (2-Phenylbutyryl)urea.

Фенетурид

$C_{11}H_{14}N_2O_2$ = 206.2.

CAS — 90-49-3.

ATC — N03AX13.

ATC Vet — QN03AX13.

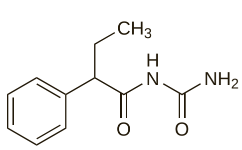

Profile

Pheneturide is an acetylurea antiepileptic used in the treatment of complex partial seizures with or without secondary generalisation (p.465). It is given in usual oral daily doses of 300 to 600 mg in 2 or 3 divided doses, up to a maximum of 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Laburide.

Phenobarbital *(BAN, rINN)*

Ácido feniletilbarbitúrico; Fenobarbitaali; Fenobarbitál; Fenobarbital; Fenobarbitalis; Fenobarbitona; Phenemalum; Phénobarbital; Phenobarbitalum; Phenobarbitone; Phenylethylbarbituric Acid; Phenylethylmalonylurea. 5-Ethyl-5-phenylbarbituric acid.

Фенобарбитал

$C_{12}H_{12}N_2O_3$ = 232.2.

CAS — 50-06-6.

ATC — N03AA02.

ATC Vet — QN03AA02.

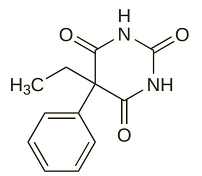

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phenobarbital: Feenies; Phennies; Phenos.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Phenobarbital). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 31 (Phenobarbital). White, odourless, glistening, small crystals or a white crystalline powder. It may exhibit polymorphism. Soluble 1 in 1000 of water and 1 in 10 of alcohol; sparingly soluble in chloroform; soluble in ether and in solutions of fixed alkali hydroxides and carbonates. A saturated solution in water has a pH of about 5.

Phenobarbital Sodium *(BANM, rINN)*

Fenobarbitaalinatrium; Fenobarbital sódico; Fenobarbital sodná sůl; Fenobarbital sodowy; Fenobarbitalio natrio druska; Fenobarbitalnatrium; Fenobarbitál-nátrium; Natrii Phenobarbitalum; Phenemalnatrium; Phénobarbital sodique; Phenobarbitalum natricum; Phenobarbitone Sodium; Sodium Phenylethylbarbiturate; Soluble Phenobarbitone. Sodium 5-ethyl-5-phenylbarbiturate.

Натрий Фенобарбитал

$C_{12}H_{11}N_2NaO_3$ = 254.2.

CAS — 57-30-7.

ATC — N03AA02.

ATC Vet — QN03AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Phenobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in carbon dioxide-free water (a small amount may be insoluble); soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH not greater than 10.2. Store in airtight containers.

USP 31 (Phenobarbital Sodium). Flaky crystals, or white crystalline granules, or a white powder. It is odourless and hygroscopic. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 10% solution in water is between 9.2 and 10.2. Solutions decompose on standing. Store in airtight containers.

Incompatibility. Phenobarbital sodium is incompatible with many other drugs and phenobarbital may be precipitated from mixtures containing phenobarbital sodium. This precipitation is dependent upon the concentration and the pH, and also on the presence of other solvents.

Stability. Extemporaneous oral preparations of phenobarbital 10 mg/mL in a 1:1 mixture of *Ora-Plus* and either *Ora-Sweet* or *Ora-Sweet SF* (*Paddock, USA*) were found[1] to be stable for at least 115 days in amber plastic bottles stored at room temperature.

1. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007; **64:** 644–6.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p.962).

Adverse Effects

The most frequent adverse effect associated with phenobarbital is sedation, but this often becomes less marked with continued use. Like some of the other antiepileptics, phenobarbital may produce subtle mood changes and impairment of cognition and memory that may not be apparent without testing. Depression may occur.

Prolonged use can occasionally result in folate deficiency; rarely, megaloblastic anaemia has been reported. There is some evidence that phenobarbital interferes with vitamin D metabolism.

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) reportedly occur in about 6% of patients with barbiturate overdose.

Sodium salts of barbiturates have a very high pH in solution, and necrosis has followed subcutaneous injection or extravasation. Intravenous injections can be hazardous and cause hypotension, shock, laryngospasm, and apnoea, especially if given too rapidly.

Hypersensitivity reactions occur in a small proportion of patients; skin reactions are reported in 1 to 3% of patients taking phenobarbital, and are most commonly maculopapular, morbilliform, or scarlatiniform rashes. More severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are extremely rare. Hepatitis and disturbances of liver function have been reported.

Paradoxical excitement, restlessness, and confusion may sometimes occur in the elderly, and irritability and hyperactivity may occur in children.

Neonatal drug dependence and symptoms resembling vitamin K deficiency have been reported in infants born to mothers who received phenobarbital during pregnancy. Congenital malformations have been reported in children of women who received phenobarbital during pregnancy but the causal role of the drug is a matter of some debate.

Effects on the blood. For the effects of antiepileptics including phenobarbital on serum folate, see under Phenytoin, p.495.

Effects on bone. For the effects of antiepileptics including phenobarbital on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on connective tissue. The use of phenobarbital and primidone has been associated with the development of Dupuytren's contracture, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain.[1]

1. Mattson RH, *et al.* Barbiturate-related connective tissue disorders. *Arch Intern Med* 1989; **149:** 911–14.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Barbiturates may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

Effects on the liver. For mention of the effects of phenobarbital on the liver, see under Phenytoin, p.496.

Effects on mental function. For a review of the effects of antiepileptics, including phenobarbital, on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

DEPRESSION. Follow-up of 28 patients aged 6 to 16 who had received phenobarbital or carbamazepine for epilepsy indicated that the rate of major depression was significantly higher in those receiving phenobarbital.[1] It was recommended that treatment with phenobarbital should be avoided particularly in patients with a personal or family history of an affective disorder; patients who do receive it should be monitored for symptoms of depression.

1. Brent DA, *et al.* Phenobarbital treatment and major depressive disorder in children with epilepsy: a naturalistic follow-up. *Pediatrics* 1990; **85:** 1086–91.

DISTURBED BEHAVIOUR. Disturbed behaviour is a recognised adverse effect of phenobarbital, especially in children and the elderly; however, no excess in behavioural adverse effects was seen[1] on follow-up for up to 12 months in 40 children who took phenobarbital when compared with 45 who took carbamazepine.

1. Banu SH, *et al.* Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. Abridged version: *BMJ* 2007; **334:** 1207–10. Full version: http://www.bmj.com/cgi/reprint/334/7605/1207 (accessed 09/06/08)

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptics including phenobarbital.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,[1,2] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[1]

1. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
2. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.

Treatment of Adverse Effects

In the treatment of phenobarbital overdosage repeated oral doses of activated charcoal may be helpful after recent ingestion of doses above 10 mg/kg; the aim is not only to prevent absorption but also aid elimination. Care should be taken to protect the airway. The prime objectives of management are then intensive symptomatic and supportive therapy with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions and to the maintenance of electrolyte balance.

Charcoal haemoperfusion may be considered for patients with severe refractory poisoning; other methods aimed at the active removal of phenobarbital include haemodialysis and urine alkalinisation, although the latter appears to be less effective than multiple doses of activated charcoal.

Precautions

Phenobarbital and other barbiturates should be used with care in children and in elderly or debilitated patients, in those in acute pain, and in those with depressive disorders. Phenobarbital should be used with caution in patients with impaired hepatic, renal, or respiratory function; its use is contra-indicated in those with severe respiratory depression.

Breast feeding. The American Academy of Pediatrics[1] considers that phenobarbital should be given with caution to breast-feeding mothers, since there have been significant adverse effects including sedation and methaemoglobinaemia in nursing infants. The *BNF* recommends that phenobarbital should be avoided where possible during breast feeding. Both authorities make similar recommendations for primidone.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Neonates. Care should be taken when giving phenobarbital orally as the elixir to neonates because regular dosing could result in alcohol toxicity [the BP 2008 formulation contains 38% v/v alcohol].[1] Aqueous preparations are more readily made using the sodium salt than the acid.[2]

1. Colquhoun-Flannery W, Wheeler R. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.
2. Leach F. Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol. *Arch Dis Child* 1992; **67:** 152.

Porphyria. Phenobarbital has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Congenital craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described with antiepileptics including phenobarbital. *In utero* exposure to phenobarbital might result in neonatal sedation and drug dependence and also in neonatal bleeding due to vitamin K deficiency.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Valproate and phenytoin have been reported to cause rises in phenobarbital (and primidone) concentrations in plasma.

The effects of phenobarbital and other barbiturates are enhanced by other CNS depressants including alcohol.

Phenobarbital and other barbiturates may reduce the activity of many drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes.

Analgesics. *Dextropropoxyphene* 65 mg given three times daily to 4 epileptic patients stabilised on phenobarbital therapy increased serum-phenobarbital concentration by 8 to 29% but this was not considered of major importance in the light of the normally accepted therapeutic range for phenobarbital.[1]

For the effect of phenobarbital on *fenoprofen*, *methadone*, and *pethidine*, see p.55, p.84, and p.114, respectively. Enzyme-inducing antiepileptics such as phenobarbital also affect the threshold for the use of antidote in the treatment of *paracetamol* poisoning, see p.110.

1. Hansen BS, *et al.* Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* 1980; **61:** 357–67.

Antiarrhythmics. For the effect of phenobarbital on *disopyramide*, *lidocaine*, and *quinidine*, see p.1270, p.1863, and p.1384, respectively.

Antibacterials. Serum concentrations of phenytoin and phenobarbital in a previously stabilised patient were increased when he took *chloramphenicol*.[1] Subsequent monitoring revealed a similar effect when chloramphenicol was taken with phenobarbital alone. In turn, phenobarbital may affect serum concentrations of chloramphenicol (see p.240).

Barbiturates such as phenobarbital and primidone may enhance the metabolism of *doxycycline*.[2]

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.

Anticoagulants. For the effect of barbiturates such as phenobarbital and primidone on *warfarin* and other coumarins, see p.1429.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and so might reduce the blood concentrations of phenobarbital, and increase the seizure risk.[1]

For the effect of phenobarbital on antidepressants, see under the monographs for *amitriptyline* (under Barbiturates, p.380), *bupropion* (p.384), *fluoxetine* (p.396), *lithium* (p.404), and *mianserin* (p.409).

Inhibition of drug-metabolising enzymes by *MAOIs* may enhance the effects of barbiturates.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antiepileptics. Interactions may occur if phenobarbital is given with other antiepileptics, of which probably the most significant is the interaction with *valproate*. Valproate increases plasma-phenobarbital concentration by a reported 17 to 48%,[1] and it may be necessary to reduce the dose of phenobarbital in some patients.[1,2] The mechanism for the increase appears to be inhibition of the metabolism of phenobarbital, resulting in reduced clearance;[2,3] valproate appears to inhibit both the direct *N*-glucosidation of phenobarbital and the *O*-glucuronidation of *p*-hydroxyphenobarbital.[4] However, phenobarbital reciprocally increases the clearance of valproate, and the valproate dose may also need to be adjusted.[5]

A similarly complex interaction exists between phenobarbital and *phenytoin.* Phenytoin can increase plasma concentrations of phenobarbital in some patients[6] since the two drugs compete for metabolism by the same enzyme system, but other evidence suggests that where this occurs it is rarely of significant magnitude.[7] Similarly, although phenobarbital induces the metabolism of phenytoin it is also, as stated, a competitive inhibitor and in practice the two effects appear to balance out, with rarely any need for dose adjustment.[7-9] However, dosage adjustment of phenobarbital may be crucial for some patients.[10] Measurement of serum concentrations of phenytoin and phenobarbital in one patient[10] showed that, in her case, large increases in serum-phenobarbital concentrations resulted from use with phenytoin; the increases were concentration-dependent.

The GABA-agonist, *progabide* has also been reported to cause a significant increase in phenobarbital concentrations when the two were given together to healthy subjects.[11]

Neurotoxicity, attributed to an increase in plasma concentrations of phenobarbital, has been seen[12] in one patient taking phenobarbital and sodium valproate when *felbamate* was added to treatment. The dosage of phenobarbital had already been reduced before treatment with felbamate was started. Data from a pharmacokinetic study[13] indicated that the interaction may result from the inhibition of phenobarbital hydroxylation by felbamate.

Vigabatrin has been reported to lower plasma concentrations of phenobarbital in some patients,[14] although dosage changes were not necessary in these patients.

High dose of *oxcarbazepine* may increase the plasma concentrations of phenobarbital but this was thought unlikely to be clinically significant;[15] conversely phenobarbital may reduce the plasma concentrations of the active metabolite of oxcarbazepine (p.491).

For the effect of phenobarbital on the metabolism of other antiepileptics, see under *Carbamazepine*, p.474, *Diazepam*, p.990, *Ethosuximide*, p.480, *Lamotrigine*, p.486, *Tiagabine*, p.505, and *Zonisamide*, p.515.

1. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* 1975; **4:** 255–6.
2. Patel IH, *et al.* Phenobarbital-valproic acid interaction. *Clin Pharmacol Ther* 1980; **27:** 515–21.
3. Kapetanović IM, *et al.* Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin Pharmacol Ther* 1981; **29:** 480–6.
4. Bernus I, *et al.* Inhibition of phenobarbitone N-glucosidation by valproate. *Br J Clin Pharmacol* 1994; **38:** 411–16.
5. Perucca E, *et al.* Disposition of sodium valproate in epileptic patients. *Br J Clin Pharmacol* 1978; **5:** 495–9.
6. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
7. Eadie MJ, *et al.* Factors influencing plasma phenobarbitone levels in epileptic patients. *Br J Clin Pharmacol* 1977; **4:** 541–7.
8. Cucinell SA, *et al.* Drug interactions in man: lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
9. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
10. Kuranari M, *et al.* Effect of phenytoin on phenobarbital pharmacokinetics in a patient with epilepsy. *Ann Pharmacother* 1995; **29:** 83–4.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.
12. Gidal BE, Zupanc ML. Potential pharmacokinetic interaction between felbamate and phenobarbital. *Ann Pharmacother* 1994; **28:** 455–8.
13. Reidenberg P, *et al.* Effects of felbamate on the pharmacokinetics of phenobarbital. *Clin Pharmacol Ther* 1995; **58:** 279–87.
14. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl): 95S–100S.
15. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.

Antifungals. For the effect of phenobarbital on *griseofulvin*, see p.536, and on *itraconazole*, see p.537.

Antineoplastics. For the effect of phenobarbital on *teniposide*, see p.778.

Antiprotozoals. For the effect of phenobarbital on *metronidazole*, see p.838.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold.

For the effect of phenobarbital on antipsychotics, see under Chlorpromazine, p.974.

Antivirals. A patient stabilised on phenobarbital 100 mg daily had an episode of seizures 4 weeks after starting HAART therapy with abacavir, didanosine, ritonavir-boosted tipranavir, and enfuvirtide.[1] The patient's phenobarbital plasma concentrations had fallen from 16 to 8 micrograms/mL and an increase in the phenobarbital dosage to 150 mg daily was required to restore concentrations. The tipranavir/ritonavir component of HAART therapy was considered to be responsible.

For the possible effect of phenobarbital on *HIV-protease inhibitors*, see p.883.

1. Bonora S, *et al.* Clinically significant drug interaction between tipranavir-ritonavir and phenobarbital in an HIV-infected subject. *Clin Infect Dis* 2007; **45:** 1654–5.

Beta blockers. For the effect of barbiturates on beta blockers, see Anxiolytics and Antipsychotics under Interactions of Beta Blockers, p.1228.

Calcium-channel blockers. For the effect of phenobarbital on *dihydropyridine calcium-channel blockers*, see under Nifedipine, p.1353, and on *verapamil*, see p.1422.

Cardiac glycosides. Phenobarbital may greatly accelerate the metabolism of *digitoxin* (p.1259).

Ciclosporin. For the effect of phenobarbital on ciclosporin, see p.1826.

Corticosteroids. For the effect of phenobarbital on corticosteroids, see p.1494.

Diuretics. Serum-phenobarbital concentrations were raised in 8 of 10 epileptic patients taking phenobarbital and additional antiepileptics when given *furosemide* 40 mg three times daily for 4 weeks.[1] This might have been the cause of drowsiness in 5 of 14 patients, 3 of whom had to stop furosemide.

1. Ahmad S, *et al.* Controlled trial of frusemide as an antiepileptic drug in focal epilepsy. *Br J Clin Pharmacol* 1976; **3:** 621–5.

Levothyroxine. For the effects of barbiturates on levothyroxine, see p.2172.

Montelukast. For the effect of phenobarbital on montelukast, see p.1126.

Sex hormones. For the effect of phenobarbital on sex hormones in *oral contraceptives*, see p.2068.

Theophylline. For the effect of phenobarbital on theophylline, see p.1143.

Vaccines. *Influenza vaccination* can cause prolonged rises in serum-phenobarbital concentrations in some patients.[1]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.

Vitamins. *Pyridoxine* reduced serum-phenobarbital concentrations in 5 patients.[1] Plasma concentrations of phenobarbital and primidone are possibly reduced by *folic acid* and *folinic acid*. For the effect of antiepileptics, including phenobarbital, on *vitamin D* concentrations, see Effects on Bone under Adverse Effects of Phenytoin, p.496.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.

Pharmacokinetics

Like other barbiturates phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid-insoluble; peak concentrations are reached in about 2 hours after oral doses and within 4 hours of intramuscular doses.

Phenobarbital is about 45 to 60% bound to plasma proteins and is only partly metabolised in the liver. About 25% of a dose is excreted in the urine unchanged at normal urinary pH. The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. There is considerable interindividual variation in phenobarbital kinetics.

Monitoring of plasma concentrations has been performed as an aid in assessing control and the therapeutic range of plasma-phenobarbital has been quoted as 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre.

Phenobarbital crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of phenobarbital are affected if given with other antiepileptics (see under Interactions, above).

Uses and Administration

Phenobarbital is a barbiturate that may be used as an antiepileptic to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency management of acute seizures including status epilepticus.

The dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires plasma concentrations of 15 to 40 micrograms/mL or around 60 to 180 micromoles/litre. In the UK, the usual oral dose is 60 to 180 mg daily, taken at night. In the USA, total daily doses of up to 300 mg have been given.

Phenobarbital sodium may be given parenterally as part of the emergency management of acute seizures including status epilepticus. Doses of 200 mg have been given by intramuscular injection, repeated after 6 hours if necessary. Doubts have been expressed about the efficacy of the intramuscular route owing to the delay in achieving adequate blood concentrations, and the subcutaneous route may cause tissue necrosis. In the UK, for the control of status epilepticus, doses of 10 mg/kg to a maximum of 1 g may be given intravenously. The *BNF* recommends that an intravenous injection solution containing 200 mg/mL should be diluted 1 in 10 and given at a rate not exceeding 100 mg/minute.

For doses in children, see below.

As with other antiepileptics, withdrawal of phenobarbital therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Phenobarbital has also been used as a hypnotic and sedative but drugs such as the benzodiazepines are preferred.

Phenobarbital stimulates the enzymes in hepatic microsomes responsible for the metabolism of some drugs and normal body constituents including bilirubin, and for this reason it has been used to reduce hyperbilirubinaemia in neonatal jaundice.

Phenobarbital magnesium and phenobarbital diethylamine have also been used.

Tetrabamate is a complex of phenobarbital, difebarbamate, and febarbamate but its use has been associated with the development of hepatitis.

Administration in children. Phenobarbital may be used in children as an antiepileptic to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency management of status epilepticus. The doses given below for all indications are those recommended by the *BNFC* in the UK.

For treatment of epilepsy, the following doses are given orally, unless stated otherwise, according to age:

- neonates: an initial dose of 20 mg/kg by slow intravenous injection, then 2.5 to 5 mg/kg once daily by slow intravenous injection or orally, adjusted according to response
- 1 month to 12 years: an initial dose of 1 to 1.5 mg/kg twice daily, increased by 2 mg/kg daily if necessary to a usual maintenance dose of 2.5 to 4 mg/kg once or twice daily
- 12 to 18 years: 60 to 180 mg daily

For status epilepticus, an intravenous injection solution containing 200 mg/mL should be diluted 1 in 10 and given by intravenous injection over 20 minutes, at a rate not exceeding 1 mg/kg per minute, in the following doses according to age:

- neonate to 12 years: an initial dose of 20 mg/kg, followed by 2.5 to 5 mg/kg once or twice daily
- 12 to 18 years: an initial dose of 20 mg/kg (to a maximum of 1 g), followed by 300 mg twice daily

Alcohol withdrawal syndrome. Phenobarbital is used in some centres for the management of alcohol withdrawal syndrome (p.1626), but has a lower safety profile than benzodiazepines (the treatment of choice) and creates the potential for multiple drug interactions. Additionally, a lack of well-defined studies make its role difficult to assess.[1]

1. Rodgers JE, Crouch MA. Phenobarbital for alcohol withdrawal syndrome. *Am J Health-Syst Pharm* 1999; **56:** 175–8.

Cerebral malaria. Phenobarbital has been used to prevent convulsions in patients with cerebral malaria (p.594) but a systematic review[1] concluded that, although it was an effective anticonvulsant, it should not be given routinely to patients with cerebral malaria as it might increase mortality. The optimal dose, particularly in children, has yet to be confirmed. In an early study[2] a single intramuscular injection of phenobarbital sodium 3.5 mg/kg, or 200 mg in patients over 60 kg was effective. A dose of 10 to 15 mg/kg was later suggested.[3] Although a single intramuscular dose of phenobarbital 20 mg/kg markedly reduced seizure frequency in young children with cerebral malaria, it was also associated with a doubling of mortality.[4] The frequency of respiratory arrest was higher in the phenobarbital group than in controls given placebo, and mortality was greatly increased in those given phenobarbital who required 3 or more doses of diazepam. Intravenous use has also been tried, and a study[5] suggested giving a loading dose of phenobarbital 15 mg/kg by intravenous infusion followed by 2.5 mg/kg 24 and 48 hours later. WHO recommends[6] that a dose of 20 mg/kg should not be given without respiratory support but states that it is unknown whether ventilation would prevent the increase in mortality; it is also unknown whether lower doses are effective and safer.

1. Meremikwu M, Marson AG. Routine anticonvulsants for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 09/06/08).
2. White NJ, *et al.* Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988; **ii:** 64–6.
3. Gilles HM. *Management of severe and complicated malaria.* Geneva: WHO, 1991.
4. Crawley J, *et al.* Effect of phenobarbitone on seizure frequency and mortality in childhood cerebral malaria: a randomized, controlled intervention study. *Lancet* 2000; **355:** 701–6.
5. Kokwaro GO, *et al.* Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2003; **56:** 453–7.
6. WHO. *Guidelines for the treatment of malaria.* Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 09/06/08)

Epilepsy. Phenobarbital is used in the treatment of epilepsy (p.465) for partial seizures with or without secondary generalisation and for primary generalised tonic-clonic seizures. It may also be tried for atypical absence, atonic, and tonic seizures but is not effective in absence seizures. However, the usefulness of phenobarbital is limited by problems of sedation in adults and paradoxical excitement in children. There is also concern about its effects on behaviour and cognition in children. Phenobarbital is therefore usually reserved for use in cases unresponsive to other antiepileptics, although some have suggested that its low cost and broad efficacy make it a suitable first-line drug in developing countries.

References.

1. Pal DK, *et al.* Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet* 1998; **351:** 19–23.
2. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia* 2004; **45:** 1141–9.
3. Wilmshurst JM, van Toorn R. Use of phenobarbitone for treating childhood epilepsy in resource-poor countries. *S Afr Med J* 2005; **95:** 392, 394, 396.
4. Wang WZ, *et al.* Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol* 2006; **5:** 46–52.

Febrile convulsions. Phenobarbital has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p.470), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.
2. Farwell JR, *et al.* Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; **322:** 364–9. Correction. *ibid.* 1992; **326:** 144.

Neonatal abstinence syndrome. For reference to the use of phenobarbital for the treatment of neonates with opioid abstinence syndrome, see p.102.

Neonatal intraventricular haemorrhage. Phenobarbital is one of several drugs that has been tried to prevent the development of neonatal intraventricular haemorrhage (p.1050). Initial studies[1-3] of antenatal use in the mother were promising, but a larger randomised study[4] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants that could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[5] A systematic review[6] of these and other studies concluded that giving phenobarbital before preterm birth cannot be recommended for routine clinical practice; strategies for future studies were suggested to improve methodology. Studies of use in neonates have also shown inconsistent results. A systematic review[7] of studies of phenobarbital for prophylaxis of intraventricular haemorrhage in preterm neonates concluded that postnatal use cannot be recommended either, and is associated with an increased need for mechanical ventilation.

1. Kaempf JW, *et al.* Antenatal phenobarbital for the prevention of periventricular and intraventricular hemorrhage: a double-blind, randomized, placebo-controlled, multihospital trial. *J Pediatr* 1990; **117:** 933–8.
2. Barnes ER, Thompson DF. Antenatal phenobarbital to prevent or minimize intraventricular hemorrhage in the low-birthweight neonate. *Ann Pharmacother* 1993; **27:** 49–52.
3. Thorp JA, *et al.* Antepartum vitamin K and phenobarbital for preventing intraventricular hemorrhage in the premature newborn: a randomized, double-blind, placebo-controlled trial. *Obstet Gynecol* 1994; **83:** 70–6.
4. Shankaran S, *et al.* The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med* 1997; **337:** 466–71.
5. Shankaran S, *et al.* Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. *Am J Obstet Gynecol* 2002; **187:** 171–7.
6. Crowther CA, Henderson-Smart DJ. Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/06/08).
7. Whitelaw A, Odd D. Postnatal phenobarbital for the prevention of intraventricular hemorrhage in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/06/08).

Neonatal seizures. Some consider phenobarbital to be the mainstay of treatment for all types of neonatal seizures (p.471). In a study[1] in 120 neonates with clinical seizure activity of varying aetiology, 48 were controlled by an initial intravenous loading dose of phenobarbital 15 to 20 mg/kg over 10 to 15 minutes, and a further 37 were controlled by sequential bolus doses of phenobarbital 5 to 10 mg/kg every 20 to 30 minutes up to a serum concentration of 40 micrograms/mL. Of the remaining 35 neonates only 7 responded when the serum-phenobarbital concentration was increased to 100 micrograms/mL, 13 required addition of a second antiepileptic (phenytoin or lorazepam) and 4 were controlled by addition of a third drug. Phenobarbital alone can effectively control seizures in the majority of neonates with recurrent seizure activity.

Phenobarbital given prophylactically as a single dose of about 40 mg/kg intravenously over one hour has also been shown to be effective in reducing the incidence of seizures in 15 infants with severe perinatal asphyxia compared with a control group who only received phenobarbital if there was clinical evidence of seizures.[2] Subsequent follow-up over 3 years suggested that prophylactic phenobarbital might also improve later neurological outcome.[2] However, a later retrospective cohort study[3] found no significant difference in the rate of seizure recurrence and developmental outcome between infants who were discharged with prophylactic phenobarbital (33 patients) and those who were discharged without any antiepileptics (99).

1. Gilman JT, *et al.* Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989; **83:** 674–8.

2. Hall RT, *et al.* High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up. *J Pediatr* 1998; **132:** 345–8.
3. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. *J Child Neurol* 2007; **22:** 389–95.

Status epilepticus. Phenobarbital given intravenously is an alternative to intravenous phenytoin in the management of status epilepticus (p.469). It should not be used in patients who have recently received oral phenobarbital or primidone.

Although one study[1] suggested that phenobarbital might be at least as effective, safe, and practical as diazepam with phenytoin for the initial treatment of convulsive status epilepticus, it tends to be reserved for patients who do not respond to benzodiazepines or phenytoin.

1. Shaner DM, *et al.* Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988; **38:** 202–7.

Preparations

BP 2008: Paediatric Phenobarbital Oral Solution; Phenobarbital Elixir; Phenobarbital Injection; Phenobarbital Sodium Tablets; Phenobarbital Tablets; ***USP 31:*** Phenobarbital Elixir; Phenobarbital Sodium for Injection; Phenobarbital Sodium Injection; Phenobarbital Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alepsal; Gardenal; Luminal; Luminaletas; Neurogabaf; ***Belg.:*** Gardenal; ***Braz.:*** Barbitron; Carbital; Edhanol; Fenocris; Garbital; Gardenal; Unifenobarb; ***Cz.:*** Gardenal†; Luminal; Phenaemal; Phenaemaletten; ***Denm.:*** Fenemal; ***Fr.:*** Aparoxal; Gardenal; Kaneuron; ***Ger.:*** Luminal; Luminaletten; ***Gr.:*** Gardenal; Kaneuron; Lumidrops†; ***Hung.:*** Sevenal; Sevenaletta; ***India:*** Gardenal; Luminal; Luminalettes†; Phenetone; ***Indon.:*** Sibital; ***Israel:*** Luminal†; ***Ital.:*** Comizial†; Gardenale; Luminale; Luminalette; Neurobiol†; ***Mex.:*** Alepsal; Fenabbott; Sevenal†; ***Norw.:*** Fenemal; ***NZ:*** Gardenal†; ***Philipp.:*** Luminal; ***Pol.:*** Luminalum; ***Port.:*** Bialminal; Luminal; Luminaletas; ***S.Afr.:*** Gardenal†; Lethyl; ***Spain:*** Gardenal; Gratusminal; Luminal; Luminaletas; ***Swed.:*** Fenemal; ***Switz.:*** Aphenylbarbit; Luminal; ***Thai.:*** Gardenal; Menobarb; Phenobarb†; Phenotal; ***Turk.:*** Luminal; Luminaletten; ***UK:*** Gardenal†; ***USA:*** Luminal; ***Venez.:*** Gardenal.

Multi-ingredient: ***Arg.:*** Cumatil L; Lotoquis; Trixol†; ***Belg.:*** Epipropane; Vethoine; ***Braz.:*** Espasmalgon†; Gamibetal Complex†; Vagostesyl; ***Canad.:*** Bellergal; ***Chile:*** Abalgin; Baldmin; Bellergal Retardado†; Belupan†; Bufacyl; Dispasmol†; Ergobelan; Immediat†; Sinpasmon; Valpin; ***Cz.:*** Alnagon; Bellaspon†; Contraspan†; Sanepil; Spasmoveralgin Neo†; ***Fr.:*** Alepsal; ***Gr.:*** Diphenal; ***Hung.:*** Atrium†; Germicid-C; Meristin; Radipon; Troparinum; ***India:*** Alergin; Asmapax; Asthmino†; Broncofol†; Cadiphylate; Dilantin with Phenobarbital; Epilan; Garoin; ***Indon.:*** Bellapheen; Ditalin; Piptal; ***Israel:*** Pacetal; Philinal; Philinet; ***Ital.:*** Gamibetal Complex; Metinal-Idantoina L; ***Jpn:*** Trancolon P†; ***Mex.:*** Alepsal Compuesto; Gamibetal Complex; Paliatil; ***Pol.:*** Bellergot; Milocardin; ***Port.:*** Anti-Asmatico; Cosmaxil†; Hidantina Composta†; Prelus†; ***Rus.:*** Pentalgin-N (Пенталгин-Н); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); ***S.Afr.:*** Adco-Phenobarbitone Vitalet; Analgen-SA†; Donnatal; Millerspas; Natrophylline Compound; Propain Forte; ***Spain:*** Epilantin†; Equidan†; Redutona; ***Thai.:*** Bellergal†; Benera; Donnatal†; Neuramizone; ***Turk.:*** Bellergal; Para-Nox; Pedimat; ***UAE:*** Alinal†; ***USA:*** Alkabel; Antispasmodic Elixir; Barbidonna†; Bel-Phen-Ergot S; Bellacane; Bellamine; Bellatal; Bellergal-S; Donnatal; Folergot-DF; Hyosophen; Lufyllin-EPG†; Phenerbel-S; Quadrinal; Susano; Tedrigen; Theodrine; ***Venez.:*** Ervostal; Fedratal†; Fenopol†; Frevag†; Metilfedrin†; Teofedril†; Traveget; Tropifen†.

Phensuximide *(BAN, rINN)*

Fensuksimidi; Fensuximid; Fensuximida; Phensuximidum. *N*-Methyl-2-phenylsuccinimide.

Фенсуксимид

$C_{11}H_{11}NO_2$ = 189.2.
CAS — 86-34-0.
ATC — N03AD02.
ATC Vet — QN03AD02.

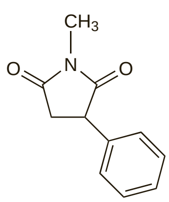

Pharmacopoeias. In *US.*

USP 31 (Phensuximide). A white to off-white crystalline powder. Is odourless or has not more than a slight odour. Slightly soluble in water; soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Phensuximide is a succinimide antiepileptic with actions similar to those of ethosuximide (p.479), but it is reported to be less effective.

Porphyria. Phensuximide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Phensuximide Capsules.

Phenytoin *(BAN, USAN, rINN)*

Difenilhidantoína; Diphenylhydantoin; Fanantina; Fenantoína; Fenitoin; Fenitoína; Fenitoinas; Fenytoiini; Fenytoin; Fenytoina; Phenantoinum; Phénytoïne; Phenytoinum. 5,5-Diphenylhydantoin; 5,5-Diphenylimidazolidine-2,4-dione.

Фенитоин

$C_{15}H_{12}N_2O_2$ = 252.3.
CAS — 57-41-0.
ATC — N03AB02.
ATC Vet — QN03AB02.

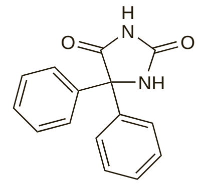

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Phenytoin). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Phenytoin). A white, odourless powder. Practically insoluble in water; soluble in hot alcohol; slightly soluble in cold alcohol, in chloroform, and in ether. Store in airtight containers.

Phenytoin Sodium *(BANM, rINNM)*

Diphenin; Fenitoin Sodyum; Fenitoína sódica; Fenitoin-nátrium; Fenitoino natrio druska; Fenytoiininatrium; Fenytoin sodná sůl; Fenytoina sodowa; Fenytoinnatrium; Natrii Phenytoinum; Phénytoïne sodique; Phenytoinum natricum; Soluble Phenytoin.

Натрий Фенитоин

$C_{15}H_{11}N_2NaO_2$ = 274.2.
CAS — 630-93-3.
ATC — N03AB02.
ATC Vet — QN03AB02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Phenytoin Sodium). A white or almost white, slightly hygroscopic, crystalline powder. Soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 31 (Phenytoin Sodium). A white, odourless powder. Is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide. Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Phenytoin sodium only remains in solution when the pH is considerably alkaline (about 10 to 12) and there have been reports of loss of clarity or precipitation of phenytoin crystals when solutions of phenytoin sodium for injection have been mixed with other drugs[1-6] or added to intravenous infusion fluids,[7-10] while binding has been reported after addition to enteral nutrition solutions.[11] A phenytoin precipitate has blocked implanted central venous access devices after the inadvertent admixture of phenytoin sodium with glucose 5% or glucose in sodium chloride (pH 4);[12,13] the blockage can be successfully cleared by the local instillation of sodium bicarbonate 8.4% to increase the pH of the medium.

1. Misgen R. Compatibilities and incompatibilities of some intravenous solution admixtures. *Am J Hosp Pharm* 1965; **22:** 92–4.
2. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; **23:** 409–11.
3. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
4. Hasegawa GR, Eder JF. Visual compatibility of dobutamine hydrochloride with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 949–51.
5. Gayed AA, *et al.* Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52**: 516–20.
6. Trissel LA, *et al.* Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1287–92.
7. Bauman JL, *et al.* Phenytoin crystallization in intravenous fluids. *Drug Intell Clin Pharm* 1977; **11:** 646–9.
8. Bauman JL, Siepler JK. Intravenous phenytoin (concluded). *N Engl J Med* 1977; **296:** 111.
9. Cloyd JC, *et al.* Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids. *Am J Hosp Pharm* 1978; **35:** 45–8.
10. Giacona N, *et al.* Crystallization of three phenytoin preparations in intravenous solutions. *Am J Hosp Pharm* 1982; **39:** 630–4.
11. Miller SW, Strom JG. Stability of phenytoin in three enteral nutrient formulas. *Am J Hosp Pharm* 1988; **45:** 2529–32.
12. Akinwande KI, Keehn DM. Dissolution of phenytoin precipitate with sodium bicarbonate in an occluded central various access device. *Ann Pharmacother* 1995; **29:** 707–9.
13. Tse CST, Abdullah R. Dissolving phenytoin precipitate in central venous access device. *Ann Intern Med* 1998; **128:** 1049.

Adverse Effects

Adverse effects are fairly frequent in patients receiving phenytoin, but some remit with dose reduction or continued use. Often reported are CNS-related effects (such as headache, dizziness, tremor, transient nervousness, and insomnia), and gastrointestinal disturbances including nausea, vomiting, and constipation. Tenderness and hyperplasia of the gums often occur, particularly in younger patients. Acne, hirsutism, and coarsening of the facial features may be associated with phenytoin therapy, and may be particularly undesirable in adolescents and women.

Phenytoin toxicity may be manifested as a syndrome of cerebellar, vestibular, and ocular effects, notably nystagmus, diplopia, slurred speech, and ataxia. Mental confusion, sometimes severe, may occur, and dyskinesias and exacerbations of seizure frequency have been noted. Hyperglycaemia has been associated with toxic concentrations.

Overdosage may result in hypotension, coma, and respiratory depression. Hypotension and CNS depression may also follow intravenous dosage, if too rapid, as may cardiac arrhythmias and impaired cardiac conduction. Solutions for injection are very alkaline and may result in irritation at the injection site or phlebitis. A syndrome of distal limb oedema, discoloration, and pain ('purple glove syndrome') has been reported occasionally.

Prolonged therapy may produce subtle effects on mental function and cognition, especially in children. In addition there is some evidence that phenytoin interferes with vitamin D and folate metabolism. Rickets and osteomalacia have occurred in a few patients not exposed to adequate sunlight, although the causal role of phenytoin is debatable. A proportion of patients develop peripheral neuropathies, usually mild, and occasional cases of megaloblastic anaemia have been seen.

Mild hypersensitivity reactions are common, with skin rashes, often morbilliform, sometimes accompanied by fever. Bullous, exfoliative, or purpuric rashes may be symptoms of rare but severe reactions such as lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Eosinophilia, lymphadenopathy, hepatitis, polyarteritis nodosa, and blood disorders such as aplastic anaemia, leucopenia, thrombocytopenia, and agranulocytosis, have occurred rarely; some of these conditions may also represent hypersensitivity reactions.

Hypoprothrombinaemia of the newborn after use of phenytoin during pregnancy has been reported. Congenital malformations have been seen in the offspring of mothers receiving phenytoin during pregnancy (see under Precautions, below).

Effects on the blood. ***AGRANULOCYTOSIS.*** Fatal agranulocytosis has been reported[1] in a patient 17 years after starting therapy with phenytoin and primidone. In the report it was stated that since 1963 the UK CSM had received reports of 3 previous cases of fatal agranulocytosis associated with phenytoin and none associated with primidone. The most likely cause was considered to be a direct toxic effect of phenytoin although other possible mechanisms included the ability of both drugs to produce folate deficiency. For a discussion of the effect of antiepileptics on serum folate, see below.

1. Laurenson IF, *et al.* Delayed fatal agranulocytosis in an epileptic taking primidone and phenytoin. *Lancet* 1994, **344:** 332–3.

FOLIC ACID DEFICIENCY. Antiepileptic therapy has long been associated with folate deficiency: early studies suggested that more than half of all patients on long-term therapy with drugs such as phenytoin, phenobarbital, and primidone had subnormal serum-folate concentrations.[1,2] Megaloblastic haematopoiesis is often present,[3] but clinical megaloblastic anaemia appears to be rare.

The relative importance of individual antiepileptics in causing folate deficiency and macrocytosis has been difficult to establish, because of the tendency to use combination regimens; with greater emphasis on single drug therapy there is evidence that monotherapy may produce less significant changes.[4,5] Despite suggestions that carbamazepine has relatively little effect on folic acid concentrations, its effects have been found to be comparable with those of phenytoin;[5] however, valproate had little or no effect on red cell folate concentrations.

The mechanism by which phenytoin and similar antiepileptics reduce serum folate is uncertain; there is good evidence for a reduction in absorption of glutamate both *in vitro*[6] and *in vivo*,[7] but the drugs associated with subnormal serum folate are all enzyme inducers and it has been suggested that enzyme induction and enhanced folate metabolism may also play a role.[2,5,8] Adverse blood changes also result from hypersensitivity (see below).

1. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i:** 563–5.
2. Maxwell JD, *et al.* Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? *BMJ* 1972; **1:** 297–9.
3. Wickramasinghe SN, *et al.* Megaloblastic erythropoiesis and macrocytosis in patients on anticonvulsants. *BMJ* 1975; **4:** 136–7.
4. Dellaportas DI, *et al.* Chronic toxicity in epileptic patients receiving single-drug treatment. *BMJ* 1982; **285:** 409–10.
5. Goggin T, *et al.* A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. *Q J Med* 1987; **NS65** (247): 911–9.
6. Hoffbrand AV, Necheles TF. Mechanism of folate deficiency in patients receiving phenytoin. *Lancet* 1968; **ii:** 528–30.
7. Rosenberg IH, *et al.* Impairment of intestinal deconjugation of dietary folate. *Lancet* 1968; **ii:** 530–2.
8. Kishi T, *et al.* Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. *J Neurol Sci* 1997; **145:** 109–12.

Effects on bone. The effects of phenytoin and other antiepileptics on the skeletal system are a matter of some debate. There are numerous reports indicating effects on bone and on calcium and vitamin D metabolism. Therapy with *carbamazepine*, *phenobarbital*, or *phenytoin* has been associated with reduction in serum-calcium concentration to hypocalcaemic values, significant reduction in 25-hydroxycholecalciferol concentrations, and elevated alkaline phosphatase.[1] In this study, involving 226 outpatients with epilepsy, the association was not seen with *valproate*. The effects were significantly greater in the group of patients receiving polytherapy, and there was limited evidence that these biochemical changes were exacerbated by reduced exposure to sunlight. In contrast, measurements of bone mineral density (BMD) found that children treated for epilepsy have reduced BMD during the first 1 to 5 years of therapy and that this progressively deteriorates thereafter.[2] Studies[3-5] of children receiving antiepileptic monotherapy revealed a reduction in density in those taking *valproate*; no reduction was found with *carbamazepine*.[3,4] The authors of one study[5] concluded that longer duration of therapy and higher doses resulted in lower BMD, and that this effect appeared to be more prominent in children under 5 years of age. A study[6] in 54 male patients followed for 12 to 29 months revealed that treatment with antiepileptics was associated with bone loss at the hip in the absence of vitamin D deficiency. There was no evidence that any particular drug produced more bone loss than another. Risk factors appear to include treatment duration of more than 2 years, age of over 40 years, and use of enzyme-inducing antiepileptics; the greatest rate of bone loss occurred in those with a combination of risk factors.[7] In a large cohort study[8] of women aged 65 years and older, continuous use of antiepileptics, particularly *phenytoin*, almost doubled the rate of bone loss.

A review[9] stated that there have been no significant reports of altered bone metabolism associated with the newer antiepileptics (*gabapentin*, *lamotrigine*, *topiramate*, and *vigabatrin*). However, short stature, low BMD, and reduced bone formation have been reported with long-term *lamotrigine* treatment, particularly when used with *valproate*;[10] further study is needed. *Oxcarbazepine* was found to have[11] similar effects on bone and vitamin D metabolism to *carbamazepine*; both drugs were associated with a reduction in 25-hydroxycholecalciferol serum concentrations and an increased bone turnover.

A more recent literature review[12] considered that most studies to date have been limited by factors such as small sample size, possible selection bias, lack of appropriate controls, and not adjusting for potential confounders. Nevertheless, long-term antiepileptic therapy was found to have an adverse effect on BMD and to increase fracture risk in some patients; there was little information regarding the relative risk with different types of antiepileptics. The authors suggested monitoring indices of bone health, optimising lifestyle factors, maintaining vitamin D and calcium status, and preventing falls in patients on long-term therapy.

Despite these alterations in bone metabolism reports of clinical osteomalacia associated with antiepileptics are rare.[13] A study in 20 epileptic outpatients who had received antiepileptic therapy for a mean of 14⁄ years failed to show any clinical evidence of osteomalacia although there was some evidence of altered calcium metabolism.[14] Similarly osteomalacia was seen in only 1 of 19 elderly inpatients in another study,[15] a rate similar to that previously seen in elderly patients with acute illness not receiving antiepileptic therapy.

1. Gough H, *et al.* A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *Q J Med* 1986; **NS59** (230): 569–77.
2. Sheth RD, *et al.* Progressive bone deficit in epilepsy. *Neurology* 2008; **70:** 170–6.
3. Sheth RD, *et al.* Effect of carbamazepine and valproate on bone mineral density. *J Pediatr* 1995; **127:** 256–62.
4. Kafalı G, *et al.* Effect of antiepileptic drugs on bone mineral density in children between ages 6 and 12 years. *Clin Pediatr (Phila)* 1999; **38:** 93–8.
5. Öner N, *et al.* Bone mineral metabolism changes in epileptic children receiving valproic acid. *J Paediatr Child Health* 2004; **40:** 470–3.
6. Andress DL, *et al.* Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol* 2002; **59:** 781–6.
7. Petty SJ, *et al.* Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005; **65:** 1358–63.
8. Ensrud KE, *et al.* Antiepileptic drug use increases rates of bone loss in older women: a prospective study. *Neurology* 2004; **62:** 2051–7.
9. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic indications. *CNS Drugs* 2001; **15:** 633–42.
10. Guo C-Y, *et al.* Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. *Epilepsia* 2001; **42:** 1141–7.
11. Mintzer S, *et al.* Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. *Epilepsia* 2006; **47:** 510–15.
12. Petty SJ, *et al.* Anti-epileptic medication and bone health. *Osteoporos Int* 2007; **18:** 129–42.
13. Beghi E, *et al.* Adverse effects of anticonvulsant drugs: a critical review. *Adverse Drug React Acute Poisoning Rev* 1986; **2:** 63–86.
14. Fogelman I, *et al.* Do anticonvulsant drugs commonly induce osteomalacia? *Scott Med J* 1982; **27:** 136–42.
15. Harrington MG, Hodkinson HM. Anticonvulsant drugs and bone disease in the elderly. *J R Soc Med* 1987; **80:** 425–7.

Effects on the endocrine system and metabolism. Although it may be difficult to separate from the effects of the disease itself, there is some evidence that antiepileptics can diminish *sexual potency* and *fertility* in male epileptics. Phenytoin is excreted in human semen in small quantities and might affect sperm morphology and motility. Reduced plasma concentrations of free testosterone have been detected in male epileptic patients receiving one or more of the following: carbamazepine, phenytoin, primidone, and sodium valproate.[1] There is, however, some evidence[2] that some of the changes in sex hormone concentrations induced by antiepileptics in men and women are reversible. A higher frequency of sperm abnormalities has been found[3] in men given carbamazepine, oxcarbazepine, or valproate monotherapy when compared with healthy controls; those on valproate also had reduced testicular volume. Women may also have altered reproductive function and impaired fertility associated with antiepileptic therapy, particularly with the enzyme-inducing antiepileptics and valproate.[4]

Gynaecomastia has been reported[5] in 5 men receiving long-term antiepileptic treatment; one also complained of impotence but libido was stated to be normal in all 5. Phenytoin was a component of therapy in all patients and was the sole drug used in one.

Phenytoin may cause reversible *hyperglycaemia* at toxic doses but it does not appear to produce long-term effects on glucose tolerance when used in therapeutic doses.[6] Paradoxically, phenytoin has also been reported to improve insulin resistance in some patients. There has been a case report[7] of severe *hypoglycaemia* in a patient who was given intravenous phenytoin for the treatment of status epilepticus; symptoms resolved when glucose 5% was infused and no further episodes of hypoglycaemia occurred after phenytoin infusion was stopped.

Phenytoin may reduce serum concentrations of *thyroid* hormones through enzyme induction—see under Interactions of Levothyroxine, p.2172.

1. Dana-Haeri J, *et al.* Reduction of free testosterone by antiepileptic drugs. *BMJ* 1982; **284:** 85–6.
2. Lossius MI, *et al.* Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women with epilepsy—a prospective randomized double-blind withdrawal study. *Epilepsia* 2007; **48:** 1875–82.
3. Isojärvi JI, *et al.* Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology* 2004; **62:** 247–53.
4. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.
5. Monson JP, Scott DF. Gynaecomastia induced by phenytoin in men with epilepsy. *BMJ* 1987; **294:** 612.
6. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; **174:** 659–62.
7. Di Gennaro G, *et al.* Hypoglycaemia induced by phenytoin treatment for partial status epilepticus. *J Neurol Neurosurg Psychiatry* 2002; **73:** 349–50.

Effects on the liver. There have been occasional reports of liver damage, probably due to hypersensitivity, associated with phenobarbital and phenytoin; the authors of an early study suggested that such drugs need not be withdrawn if there were merely transient elevations in transaminase values,[1] but care is needed to distinguish such effects from the early symptoms of the antiepileptic hypersensitivity syndrome (see below).

1. Aiges HW, *et al.* The effects of phenobarbital and diphenylhydantoin on liver function and morphology. *J Pediatr* 1980; **97:** 22–6.

Effects on the lungs. Pulmonary eosinophilia and acute respiratory failure requiring mechanical ventilation have been reported[1] in a patient receiving phenytoin; other pulmonary symptoms associated with phenytoin were reviewed.

1. Mahatma M, *et al.* Phenytoin-induced acute respiratory failure with pulmonary eosinophilia. *Am J Med* 1989; **87:** 93–4.

Effects on mental function. For a review of the effects of antiepileptic therapy including phenytoin on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

Effects on the skin. A retrospective analysis involving 1890 outpatients taking antiepileptics found that rates of skin reactions associated with treatment varied with different drugs, the risk being greatest with carbamazepine, lamotrigine, and phenytoin, and lowest with gabapentin, levetiracetam, and valproate.[1] Overall, the rate of skin reactions in this study was 2.8%, but as also mentioned in Hypersensitivity, below (where more details on phenytoin-associated skin reactions are given), there appeared to be cross-sensitivity; risk in this study was increased to 8.8% in those who had previously experienced rash with another antiepileptic drug.

Rare, but severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred.

For reference to cutaneous manifestations of zinc deficiency, possibly due to chelation with phenytoin, see under Valproate, p.509.

1. Arif H, *et al.* Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007; **68:** 1701–9.

Gingival hyperplasia. Gingival hyperplasia, characterised by inflammation and a marked fibrotic response, may affect up to 50% of patients receiving phenytoin. It usually becomes apparent within the first few months of therapy and occurs more frequently in children; there is no increase in alveolar bone loss. The mechanism underlying its development is unknown, although the main metabolite of phenytoin, 5-(4-hydroxyphenyl)-5-phenylhydantoin, has been implicated.[1-3]

1. Ball DE, *et al.* Plasma and saliva concentrations of phenytoin and 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) in relation to gingival overgrowth in epileptic patients. *Br J Clin Pharmacol* 1995; **39:** 539P–588P.
2. Ieiri I, *et al.* Effect of 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) enantiomers, major metabolites of phenytoin, on the occurrence of chronic-gingival hyperplasia: in vivo and in vitro study. *Eur J Clin Pharmacol* 1995; **49:** 51–6.
3. Zhou LX, *et al.* Metabolism of phenytoin by the gingiva of normal humans: the possible role of reactive metabolites of phenytoin in the initiation of gingival hyperplasia. *Clin Pharmacol Ther* 1996; **60:** 191–8.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some antiepileptic drugs including phenytoin.[1-3] Clinical manifestations may include interstitial nephritis, anaemia, interstitial pulmonary infiltrates, thrombocytopenia, eosinophilia, myopathy, and diffuse intravascular coagulation.[1,2] Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic antiepileptics,[2,3] but the true incidence is unknown due to variations in presentation and reporting. The syndrome occurs most frequently on first exposure to the drug, with initial symptoms starting anywhere between 1 and 8 weeks after exposure. The mean interval to onset is 17 to 21 days with phenytoin. In previously sensitised individuals the reaction may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is approximately 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.[2] An early review[1] of the syndrome in patients taking phenytoin commented that it occurred mainly in black male patients and should not be confused with more common mild general hypersensitivity reactions. More recent evidence does not suggest that ethnic origin predicts differences in risk.[2]

Most cases resolve spontaneously on withdrawal of the drug and symptomatic management. The use of corticosteroids in the management of severe cases remains controversial in the absence of controlled studies of their effectiveness.[1,2]

Phenytoin-induced pseudolymphoma mimicking cutaneous T-cell lymphoma has also been reported.[2,4] In most cases, symptoms resolve within 7 to 14 days of stopping the drug, and the condition is not considered premalignant.[2] However, in one report[4] the cutaneous eruption and lymphadenopathy persisted after withdrawal of phenytoin for one year when the patient eventually became asymptomatic.

In a prospective study[5] of 306 patients given phenytoin there was an overall incidence of 8.5% of morbilliform rash, but there was a marked seasonal incidence with most reactions occurring during the summer months. The results did not appear to be due to photosensitivity and might represent seasonal alterations in the immune system.

1. Flowers FP, *et al.* Phenytoin hypersensitivity syndrome. *J Emerg Med* 1987; **5:** 103–8.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; **21:** 489–501.
3. Bessmertny O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; **35:** 533–8.
4. Harris DWS, *et al.* Phenytoin-induced pseudolymphoma: a report of a case and review of the literature. *Br J Dermatol* 1992; **127:** 403–6.
5. Leppik IE, *et al.* Seasonal incidence of phenytoin allergy unrelated to plasma levels. *Arch Neurol* 1985; **42:** 120–2.

Peripheral neuropathies. Electrophysiological abnormalities after prolonged phenytoin treatment are common, but clinically significant peripheral neuropathy is rare.[1] The neuropathy usually involves sensory nerves and lesions are generally mild and asymptomatic.[2] Much of the reported clinical neuropathy has been associated with multiple drug therapy of epilepsy and with exposure to toxic concentrations of phenytoin.[1,3] Although an association with folate deficiency has been suggested, a study in 52 patients on long-term antiepileptic therapy failed to find any convincing evidence of a relationship between serum-folate concentration and peripheral neuropathy.[4]

1. Bruni J. Phenytoin and other hydantoins: adverse effects. In: Levy RH, *et al.*, eds. *Antiepileptic drugs*. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2002; 605–10.
2. Argov Z, Mastaglia FL. Drug-induced peripheral neuropathies. *BMJ* 1979; **1:** 663–6.
3. Toth C, Kotecha SA. Prolonged and excessive phenytoin therapy leading to a severe and partially reversible polyneuropathy. *J Peripher Nerv Syst* 2004; **9:** 198–9.
4. Horwitz SJ, *et al.* Relation of abnormal folate metabolism to neuropathy developing during anticonvulsant drug therapy. *Lancet* 1968; **i:** 563–5.

Treatment of Adverse Effects

Treatment of poisoning with phenytoin tends to be supportive. Repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if a very large amount has been taken within 1 hour.

◊ Multiple oral doses of activated charcoal may reduce the absorption of phenytoin[1,2] but the degree of clinical benefit is unclear.[3] The value of charcoal haemoperfusion in the management of phenytoin overdosage is debatable. A review of haemoperfusion included data from 2 patients who ingested phenytoin[4] but, although it was suggested that haemoperfusion should contribute significantly to drug removal, results are difficult to evaluate in these patients who had also ingested phenobarbital. An evaluation in a patient who had also taken primidone[5] suggested that, although initial clearance of phenytoin was promising, the system rapidly became saturated and there was little overall benefit. A review[3] of the features and management of phenytoin poisoning concluded that supportive care is the mainstay of treatment. Gastric lavage and multiple-dose activated charcoal should not be used routinely, although they might be considered for life-threatening ingestion. They were most effective when used within 1 hour of ingestion; the airway should be secured first. Extracorporeal methods of elimination (e.g. haemodialysis, haemoperfusion, peritoneal dialysis, or plasmapheresis) had not been shown to be of benefit;[3] however, some such procedures may be beneficial in patients with renal failure[3] or hypoalbuminaemia[6] in whom free phenytoin concentrations are raised.

1. Weidle PJ, *et al.* Multiple-dose activated charcoal as adjunct therapy after chronic phenytoin intoxication. *Clin Pharm* 1991; **10:** 711–14.
2. Dolgin JG, *et al.* Pharmacokinetic simulation of the effect of multiple-dose activated charcoal in phenytoin poisoning—report of two pediatric cases. *DICP Ann Pharmacother* 1991; **25:** 646–9.
3. Craig S. Phenytoin poisoning. *Neurocrit Care* 2005; **3:** 161–70.
4. Pond S, *et al.* Pharmacokinetics of haemoperfusion for drug overdose. *Clin Pharmacokinet* 1979; **4:** 329–54.
5. Baehler RW, *et al.* Charcoal hemoperfusion in the therapy for methsuximide and phenytoin overdose. *Arch Intern Med* 1980; **140:** 1466–8.
6. De Schoenmakere G, *et al.* Phenytoin intoxication in critically ill patients. *Am J Kidney Dis* 2005; **45:** 189–92.

Precautions

Phenytoin is metabolised in the liver and should be given with care to patients with impaired liver function. Caution is also advocated in diabetic patients because of the potential effects of phenytoin on blood sugar.

Protein binding may be reduced in certain disease states such as uraemia, and in certain patient populations such as neonates, pregnant women, and the elderly. Although phenytoin is extensively protein bound this may be of little clinical significance in itself, provided that hepatic function is not impaired, because the concentration of free (pharmacologically active) drug in the plasma often remains more or less unchanged, due to distribution, metabolism, and excretion. Thus, an alteration in protein binding would not necessarily require a change in dosage of phenytoin to be made although, when plasma concentrations are being monitored, relatively lower total plasma-phenytoin concentrations will be found to be effective since there is less bound (pharmacologically inactive) phenytoin available for measurement.

Intravenous phenytoin must be given slowly and extravasation and intra-arterial injection must be avoided. Phenytoin should not be given intravenously to patients with sinus bradycardia, heart block, or Stokes-Adams syndrome, and should be used with caution in patients with hypotension, heart failure, or myocardial infarction; monitoring of blood pressure and the ECG is recommended during intravenous use.

Patients or their carers should be told how to recognise signs of blood or skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Phenytoin should be stopped, if necessary under cover of a suitable alternative antiepileptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. It should also be stopped if a skin rash develops; in the case of mild rashes phenytoin may be reintroduced cautiously, but should be stopped immediately and permanently if the rash recurs.

Care is required when withdrawing phenytoin therapy—see also Uses and Administration, below.

Phenytoin may interfere with some tests of thyroid function as it can reduce free and circulating concentrations of levothyroxine, mainly by enhanced conversion to tri-iodothyronine, and it may also produce lower than normal values for dexamethasone and metyrapone suppression tests.

Breast feeding. The American Academy of Pediatrics[1] considers that phenytoin is usually compatible with breast feeding, although there had been an early case report of methaemoglobinaemia in a breast-fed infant.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For comment on antiepileptic drugs and driving, see p.468.

Infections. A 52-year-old woman previously well-controlled on phenytoin 400 mg daily suffered phenytoin toxicity after a viral infection;[1] her plasma-phenytoin concentration had increased from 16 to 51 micrograms/mL. Six weeks later she had recovered and was re-stabilised on phenytoin 400 mg daily.

1. Levine M, Jones MW. Toxic reaction to phenytoin following a viral infection. *Can Med Assoc J* 1983; **128:** 1270–1.

AIDS. Renal abnormalities or hypoalbuminaemia associated with AIDS may increase the risk of elevated free phenytoin concentrations and subsequent toxicity. Altered protein binding resulted in marked phenytoin toxicity, with lethargy and seizure-like activity, in an HIV-positive patient with profound hypoalbuminaemia and moderate renal insufficiency.[1] Therapeutic drug monitoring in 21 patients with AIDS indicated that although total serum concentrations of phenytoin were lower than in a reference population, the fraction of unbound drug was higher.[2] These changes might be attributed to hypoalbuminaemia and it was suggested that free rather than total phenytoin concentrations should be measured in HIV-infected patients with hypoalbuminaemia.

Phenytoin itself was associated with reversible hypogammaglobulinaemia in an HIV-positive patient who previously had borderline hypergammaglobulinaemia.[3]

1. Toler SM, *et al.* Severe phenytoin intoxication as a result of altered protein binding in AIDS. *DICP Ann Pharmacother* 1990; **24:** 698–700.
2. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
3. Britigan BE. Diphenylhydantoin-induced hypogammaglobulinemia in a patient infected with human immunodeficiency virus. *Am J Med* 1991; **90:** 524–7.

Porphyria. Phenytoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including phenytoin, and a variety of syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described. Specific syndromes such as the 'fetal hydantoin syndrome' with phenytoin have been linked to individual antiepileptics. However, there is overlap between the effects seen with different antiepileptics and these are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding with phenytoin.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Since phenytoin is extensively bound to plasma proteins it can be displaced by drugs competing for protein-binding sites, thus liberating more free (pharmacologically active) phenytoin into the plasma. However, elevation of free phenytoin is reported to be of little clinical significance provided hepatic function is not impaired (see Precautions, above). A potentially more serious type of interaction may occur because phenytoin metabolism is saturable: toxic concentrations of phenytoin can develop in patients given drugs that inhibit phenytoin metabolism even to quite a minor degree. Phenytoin itself is also a potent enzyme inducer, and induces the metabolism of a number of drugs, including some antibacterials, anticoagulants, corticosteroids, quinidine, and sex hormones (notably, oral contraceptives).

The hypotensive properties of dopamine and the cardiac depressant properties of drugs such as lidocaine may be dangerously enhanced by intravenous phenytoin.

◊ General references.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin. *Clin Pharmacokinet* 1990; **18:** 37–60 and 131–150.

Anaesthetics. A 10-year-old girl with epilepsy who had been treated with phenytoin 100 mg three times daily for 5 years and who had lateral nystagmus developed symptoms of phenytoin intoxication after anaesthesia with *halothane*.[1] The plasma concentration of phenytoin 72 hours after anaesthesia was 41 microgram/mL. It was suggested that temporary liver dysfunction was responsible for impaired metabolism of phenytoin.

1. Karlin JM, Kutt H. Acute diphenylhydantoin intoxication following halothane anesthesia. *J Pediatr* 1970; **76:** 941–4.

Analgesics. *Aspirin* is reported to displace phenytoin from plasma binding[1,2] but there is no evidence of any effect on metabolism and effects are unlikely to be clinically significant.[3,4] *Paracetamol* is reported to have no significant effect on serum-phenytoin concentrations.[4] (However, enzyme-inducing antiepileptics such as phenytoin affect the threshold for use of antidote in the treatment of paracetamol poisoning, see p.110.) Alterations of the pharmacokinetics of phenytoin have been reported with *bromfenac*, but it was thought unlikely that a change in phenytoin dose would be necessary.[5]

Other analgesic and anti-inflammatory drugs may have clinically significant effects. *Phenylbutazone* has been reported to cause an initial decrease in serum phenytoin, followed by an increase;[4] in addition to effects on protein binding it inhibits phenytoin metabolism[6] and severe phenytoin toxicity may result.[7] *Azapropazone* appears to be a competitive inhibitor of phenytoin metabolism and has also been implicated in interactions resulting in toxicity.[8,9] Substantial increases in serum phenytoin have been found in healthy subjects given the analgesic and muscle relaxant *fenyramidol*,[10] indicating a potential for toxicity. There is a single report of toxicity in a patient receiving *ibuprofen* with phenytoin[11] but in a study in 9 healthy subjects, ibuprofen had no effect on the pharmacokinetics of phenytoin.[12] In another report, phenytoin toxicity developed[13] in a patient who was also taking *celecoxib*.

The opioid analgesic *dextropropoxyphene* has also been reported to affect phenytoin metabolism, with the resultant development of toxic blood-phenytoin concentrations;[14] however, the patient in this case was taking relatively high doses of dextropropoxyphene (650 mg daily). For the effect of phenytoin on *methadone* and *pethidine*, see p.84 and p.114, respectively.

1. Fraser DG, *et al.* Displacement of phenytoin from plasma binding sites by salicylate. *Clin Pharmacol Ther* 1980; **27:** 165–9.
2. Paxton JW. Effects of aspirin on salivary and serum phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1980; **27:** 170–8.
3. Leonard RF, *et al.* Phenytoin-salicylate interaction. *Clin Pharmacol Ther* 1981; **29:** 56–60.
4. Neuvonen PJ, *et al.* Antipyretic analgesics in patients on antiepileptic drug therapy. *Eur J Clin Pharmacol* 1979; **15:** 263–8.
5. Gumbhir-Shah K, *et al.* Evaluation of pharmacokinetic interaction between bromfenac and phenytoin in healthy males. *J Clin Pharmacol* 1997; **37:** 160–8.
6. Andreasen PB, *et al.* Diphenylhydantoin half-life in man and its inhibition by phenylbutazone: the role of genetic factors. *Acta Med Scand* 1973; **193:** 561–4.
7. Kristensen MB. Drug interactions and clinical pharmacokinetics. *Clin Pharmacokinet* 1976; **1:** 351–72.
8. Roberts CJC, *et al.* Anticonvulsant intoxication precipitated by azapropazone. *Postgrad Med J* 1981; **57:** 191–2.
9. Geaney DP, *et al.* Interaction of azapropazone with phenytoin. *BMJ* 1982; **284:** 1373.
10. Solomon HM, Schrogie JJ. The effect of phenyramidol on the metabolism of diphenylhydantoin. *Clin Pharmacol Ther* 1967; **8:** 554–6.
11. Sandyk R. Phenytoin toxicity induced by interaction with ibuprofen. *S Afr Med J* 1982; **62:** 592.
12. Townsend RJ, *et al.* The effects of ibuprofen on phenytoin pharmacokinetics. *Drug Intell Clin Pharm* 1985; **19:** 447–8.
13. Keeling KL, *et al.* Prolonged elimination half-life of phenytoin in an elderly patient also on celecoxib. *Clin Chem* 2002; **48** (suppl): A52–A53.
14. Kutt H. Interactions between anticonvulsants and other commonly prescribed drugs. *Epilepsia* 1984; **25** (suppl 2): S118–S131.

Anthelmintics. For report of an interaction between phenytoin and *levamisole* with fluorouracil, see Antineoplastics, below. For the effect of phenytoin on *mebendazole* and *praziquantel*, see p.149 and p.154, respectively.

Antiarrhythmics. There have been reports of phenytoin toxicity associated with substantial rises in serum-phenytoin concentrations after addition of *amiodarone* to the therapeutic regimen.[1,2] For the effect of phenytoin on amiodarone, see p.1212.

For the effect of phenytoin on other antiarrhythmics, see p.1270 (disopyramide), p.1340 (mexiletine), p.1384 (quinidine), and p.1863 (lidocaine).

1. Gore JM, *et al.* Interaction of amiodarone and diphenylhydantoin. *Am J Cardiol* 1984; **54:** 1145.
2. McGovern B, *et al.* Possible interaction between amiodarone and phenytoin. *Ann Intern Med* 1984; **101:** 650.

Antibacterials. Interactions, some clinically significant, may occur between phenytoin and various antibacterials. Giving *chloramphenicol* with phenytoin has resulted in moderate[1] to marked[2] elevation of serum-phenytoin concentrations due to inhibition of phenytoin metabolism;[2] toxicity has resulted.[3,4] In turn, phenytoin may affect serum concentrations of chloramphenicol (see p.240).

Phenytoin may enhance the metabolism of *doxycycline*.[5]

There is limited evidence that *erythromycin* decreases phenytoin clearance[6] but this was subject to considerable interindividual variation and is of unknown clinical significance. Results from another study[7] suggested that *clarithromycin* might also raise phenytoin levels.

The interaction with *isoniazid* is well documented and potentially significant in slow acetylators of isoniazid who may develop raised phenytoin concentrations and signs of toxicity;[8,9] in at least one case, death has resulted.[10] Plasma-isoniazid concentrations may become sufficiently raised in slow acetylators of isoniazid to produce marked inhibition of the hepatic microsomal enzymes responsible for the metabolism of phenytoin.

There have been conflicting reports of the effect of *ciprofloxacin* on serum concentrations of phenytoin. While some report no effect[11] others have reported reduced[12-16] or increased[17,18] concentrations of phenytoin in patients given ciprofloxacin. A fall in serum-phenytoin concentrations, and resultant loss of seizure control has been reported in a patient in whom *nitrofurantoin* was added to therapy.[19] The mechanism of this interaction is unknown although a combination of impaired absorption and increased metabolism of the phenytoin was suggested. Something similar was reported in a patient given *oxacillin* in whom plasma-phenytoin concentrations dropped markedly and status epilepticus developed.[20] This effect was thought to be due to impaired phenytoin absorption.

Rifampicin can also reduce plasma-phenytoin concentrations and markedly increase its clearance;[21,22] this is in marked contrast to the effects of isoniazid, and when given together it overrides the effects of isoniazid on phenytoin, even in slow acetylators.[22]

Various sulfonamides are reported to interact with phenytoin, reducing clearance and prolonging half-life: *sulfaphenazole* is reportedly the strongest inhibitor of phenytoin metabolism but *sulfamethizole* also inhibits phenytoin metabolism and the latter has been implicated in producing phenytoin toxicity.[23] *Co-trimoxazole* reportedly inhibits phenytoin metabolism to a modest degree; a case of phenytoin toxicity in a child given co-trimoxazole has been reported[24] but the role of the co-trimoxazole is uncertain since the patient was also receiving sultiame. Fatal acute fulminant hepatic failure in a 60-year-old patient was suggested[25] to be due to phenytoin-induced hepatitis exacerbated by addition of co-trimoxazole to her drug regimen.

See also Antiprotozoals, below.

1. Koup JR, *et al.* Interaction of chloramphenicol with phenytoin and phenobarbital. *Clin Pharmacol Ther* 1978; **24:** 571–5.
2. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; **ii:** 1397–9.
3. Ballek RE, *et al.* Inhibition of diphenylhydantoin metabolism by chloramphenicol. *Lancet* 1973; **i:** 150.
4. Rose JQ, *et al.* Intoxication caused by interaction of chloramphenicol and phenytoin. *JAMA* 1977; **237:** 2630–1.
5. Neuvonen PJ, *et al.* Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9:** 147–54.
6. Bachmann K, *et al.* Single dose phenytoin clearance during erythromycin treatment. *Res Commun Chem Pathol Pharmacol* 1984; **46:** 207–17.
7. Burger DM, *et al.* Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* 1994; **16:** 616–20.
8. Brennan RW, *et al.* Diphenylhydantoin intoxication attendant to slow inactivation of isoniazid. *Neurology* 1970; **20:** 687–93.
9. Kutt H, *et al.* Diphenylhydantoin intoxication: a complication of isoniazid therapy. *Am Rev Respir Dis* 1970; **101:** 377–84.
10. Johnson J, Freeman HL. Death due to isoniazid (INH) and phenytoin. *Br J Psychiatry* 1976; **129:** 511.
11. Slavich IL, *et al.* Grand mal epileptic seizures during ciprofloxacin therapy. *JAMA* 1989; **261:** 558–9.
12. Dillard ML, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1992; **26:** 263.
13. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 61–4.
14. Brouwers PJ, *et al.* Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* 1997; **31:** 498.
15. McLeod R, Trinkle R. Unexpectedly low phenytoin concentration in a patient receiving ciprofloxacin. *Ann Pharmacother* 1998; **32:** 1110–11.
16. Otero M-J, *et al.* Interaction between phenytoin and ciprofloxacin. *Ann Pharmacother* 1999; **33:** 251–2.
17. Schroeder D, *et al.* Effect of ciprofloxacin on serum phenytoin concentrations in epileptic patients. *Pharmacotherapy* 1991; **11:** 276.
18. Hull RL. Possible phenytoin-ciprofloxacin interaction. *Ann Pharmacother* 1993; **27:** 1283.
19. Heipertz R, Pilz H. Interaction of nitrofurantoin with diphenylhydantoin. *J Neurol* 1978; **218:** 297–301.
20. Fincham RW, *et al.* Use of phenytoin serum levels in a case of status epilepticus. *Neurology* 1976; **26:** 879–81.
21. Wagner JC, Slama TG. Rifampin-phenytoin drug interaction. *Drug Intell Clin Pharm* 1984; **18:** 497.
22. Kay L, *et al.* Influence of rifampicin and isoniazid on the kinetics of phenytoin. *Br J Clin Pharmacol* 1985; **20:** 323–6.
23. Siersbaek-Nielsen K, *et al.* Sulfamethizole-induced inhibition of diphenylhydantoin and tolbutamide metabolism in man. *Clin Pharmacol Ther* 1973; **14:** 148.
24. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* 1985; **102:** 559.
25. Ilario MJ-M, *et al.* Acute fulminant hepatic failure in a woman treated with phenytoin and trimethoprim-sulfamethoxazole. *Arch Pathol Lab Med* 2000; **124:** 1800–3.

Anticoagulants. Serum-phenytoin concentrations have been reported to be markedly elevated by *dicoumarol*[1,2] and elevated to a lesser extent by *phenprocoumon*;[2] however, although *warfarin* has been implicated in a report of phenytoin toxicity,[3] other evidence suggests that it has no effect on serum-phenytoin concentrations in most patients.[2]

For the effect of phenytoin on anticoagulants such as dicoumarol and warfarin, see p.1429.

1. Hansen JM, *et al.* Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 265–6.
2. Skovsted L, *et al.* The effect of different oral anticoagulants on diphenylhydantoin and tolbutamide metabolism. *Acta Med Scand* 1976; **199:** 513–5.
3. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* 1966; **ii:** 640.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Plasma-phenytoin concentrations rose in 2 epileptic patients also receiving *imipramine* 75 mg daily for about 3 months for depression.[1] In one patient the concentration gradually increased over several weeks to more than twice the pretreatment figure and he showed mild signs of phenytoin intoxication, which remitted after imipramine was stopped. Increased serum-phenytoin concentration and phenytoin toxicity possibly precipitated by addition of *trazodone* has been described;[2] licensed product information for trazodone recommends monitoring serum-phenytoin concentrations in patients receiving these two drugs. Elevated plasma-phenytoin concentrations, in some cases accompanied by signs and symptoms of phenytoin toxicity, have also been reported with *fluoxetine*,[3] *fluvoxamine*,[4,5] *sertraline*,[6] and *viloxazine*.[7] Product information for *mianserin* also recommends that plasma concentrations of phenytoin should be monitored carefully when both are given.

St John's wort has been shown to induce several drug metabolising enzymes (see p.423) and consequently it might reduce the blood concentrations of phenytoin leading to an increased risk of seizure.[8] Some licensed product information for phenytoin in the UK therefore recommends that phenytoin should not be used with St John's wort and warns that the effects of St John's wort may persist for at least 2 weeks after it was last used.

For the effects of phenytoin on antidepressants, see under Amitriptyline (p.380), Fluoxetine (p.396), and Lithium (p.404).

1. Perucca E, Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* 1977; **4:** 485–6.
2. Dorn JM. A case of phenytoin toxicity possibly precipitated by trazodone. *J Clin Psychiatry* 1986; **47:** 89–90.
3. Nightingale SL. Fluoxetine labeling revised to identify phenytoin interaction and to recommend against use in nursing mothers. *JAMA* 1994; **271:** 1067.
4. Feldman D, *et al.* Cas clinique d'interaction médicamenteuse entre phénytoïne et fluvoxamine. *J Pharm Clin* 1995; **14:** 296–7.
5. Mamiya K, *et al.* Phenytoin intoxication induced by fluvoxamine. *Ther Drug Monit* 2001; **23:** 75–7.
6. Haselberger MB, *et al.* Elevated serum phenytoin concentrations associated with coadministration of sertraline. *J Clin Psychopharmacol* 1997; **17:** 107–9.
7. Pisani F, *et al.* Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant interaction. *J Neurol Neurosurg Psychiatry* 1992; **55:** 126–7.
8. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)

Antidiabetics. Transient rises in the amount of non-protein-bound phenytoin were observed in 17 patients when *tolbutamide* was given in addition to phenytoin, but none developed signs of intoxication.[1] Toxic symptoms were reported in another patient given phenytoin with tolbutamide, although she had tolerated this combination on a previous occasion.[2]

Symptoms of phenytoin toxicity are known to have occurred[1] in one patient receiving *tolazamide* and phenytoin.

1. Wesseling H, Mols-Thürkow I. Interaction of diphenylhydantoin (DPH) and tolbutamide in man. *Eur J Clin Pharmacol* 1975; **8:** 75–8.
2. Beech E, *et al.* Phenytoin toxicity produced by tolbutamide. *BMJ* 1988; **297:** 1613–14.

Antiepileptics. Interactions may occur when phenytoin is used with other antiepileptics, but these are often variable in their effect and difficult to predict.

For a discussion of the effect of *benzodiazepines* on plasma concentrations of phenytoin, see Benzodiazepines, below.

Carbamazepine has been generally reported to lower serum-phenytoin concentrations,[1,2] although reports exist of elevated serum-phenytoin concentrations when the two were given concurrently.[3] It should be noted that phenytoin also reduces serum-carbamazepine values—see p.474. These studies have not indicated any loss of seizure control due to this interaction.

For the effects of phenytoin on *ethosuximide*, see p.480.

Felbamate has caused increases in serum-phenytoin concentrations, and in some cases toxicity requiring a reduction in phenytoin dose.[4,5]

Increased plasma concentrations of phenytoin with symptoms of toxicity have been reported in a patient receiving phenytoin, carbamazepine, and clobazam after *gabapentin* was added to treatment.[6]

Phenytoin reduces plasma concentrations of *lamotrigine* as described on p.486.

Phenytoin plasma concentrations may be increased by high doses of *oxcarbazepine*;[7] licensed product information for oxcarbazepine suggests that doses of phenytoin may need to be reduced when high doses of oxcarbazepine are given.

Phenobarbital both induces the metabolism of phenytoin and competes with it for metabolism by the same enzyme system; in practice there is rarely sufficient alteration for a change in phenytoin dosage to be necessary.[8-10] For the effect of phenytoin on phenobarbital, see p.493. Phenytoin has also been reported to enhance the metabolism of *primidone* to phenobarbital, see p.503.

The GABA agonist *progabide* increased blood-phenytoin concentrations[11] and *stiripentol* appears to produce a dose-dependent reduction in phenytoin clearance.[12]

Sultiame causes substantial increases in plasma-phenytoin concentrations, in some cases resulting in phenytoin toxicity;[13] the dose of phenytoin may therefore require adjustment if these drugs are given together.

Modest increases in plasma-phenytoin concentrations have been observed in some patients when *topiramate* was added to therapy, but it was considered that dosage adjustments were unlikely to be necessary.[14] For the effect of phenytoin on topiramate, see p.506.

The interaction between phenytoin and *valproate* is complex. Valproate displaces phenytoin from serum binding sites and may inhibit its metabolism;[15] the former effect increases the concentration of free drug but reduces total serum phenytoin.[16,17] Most studies seem to suggest that the dose of phenytoin need only rarely be adjusted, but the possibility of loss of seizure control, or phenytoin toxicity, does exist.[15] Interestingly there is some evidence that the interactions may be affected by circadian variations in valproate concentrations.[18] Total plasma-phenytoin concentrations rose significantly in 9 of 11 patients, 2 of whom developed toxic symptoms, when the formulation of sodium valproate that they were taking with phenytoin was changed from a standard tablet to a slow-release form.[19] The authors hypothesised that reduced diurnal fluctuations in plasma-valproate concentrations due to the use of slow-release tablets reduced the displacement interaction between phenytoin and valproate, thereby increasing total plasma-phenytoin concentrations. Phenytoin may also cause a fall in serum concentrations of valproate—see p.511.

Gradual or delayed reductions in plasma-phenytoin concentrations have been seen in several studies in patients given *vigabatrin*;[20] a review[20] states that concentrations have been reduced by 20 to 30%. The manufacturer of vigabatrin considers that this is unlikely to be of clinical significance although in a study the reduction was considered to compromise seizure control.[21]

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Windorfer A, Sauer W. Drug interactions during anticonvulsant therapy in childhood: diphenylhydantoin, primidone, phenobarbitone, clonazepam, nitrazepam, carbamazepin, and dipropylacetate. *Neuropadiatrie* 1977; **8:** 29–41.
3. Zielinski JJ, *et al.* Carbamazepine-phenytoin interaction: elevation of plasma phenytoin concentrations due to carbamazepine comedication. *Ther Drug Monit* 1985; **7:** 51–3.
4. Sheridan PH, *et al.* Open pilot study of felbamate (ADD03055) in partial seizures. *Epilepsia* 1986; **27:** 649.
5. Wilensky AJ, *et al.* Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. *Epilepsia* 1985; **26:** 602–6.
6. Tyndel F. Interaction of gabapentin with other antiepileptics. *Lancet* 1994; **343:** 1363–4.
7. Hossain M, *et al.* Drug-drug interaction profile of oxcarbazepine in children and adults. *Neurology* 1999; **52** (suppl 2): A525.
8. Morselli PL, *et al.* Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. *Ann N Y Acad Sci* 1971; **179:** 88–107.
9. Cucinell SA, *et al.* Drug interactions in man: 1. lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin). *Clin Pharmacol Ther* 1965; **6:** 420–9.
10. Booker HE, *et al.* Concurrent administration of phenobarbital and diphenylhydantoin: lack of an interference effect. *Neurology* 1971; **21:** 383–5.
11. Bianchetti G, *et al.* Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* 1987; **28:** 68–73.

12. Levy RH, *et al.* Stiripentol kinetics in epileptic patients: nonlinearity and interactions. *Epilepsia* 1984; **25:** 657.
13. Hansen JM, *et al.* Sulthiame (Ospolot) as inhibitor of diphenylhydantoin metabolism. *Epilepsia* 1968; **9:** 17–22.
14. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37** (suppl 2): S14–S17.
15. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
16. Monks A, Richens A. Effect of single doses of sodium valproate on serum phenytoin levels and protein binding in epileptic patients. *Clin Pharmacol Ther* 1980; **27:** 89–95.
17. Perucca E, *et al.* Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin Pharmacol Ther* 1980; **28:** 779–89.
18. Riva R, *et al.* Time-dependent interaction between phenytoin and valproic acid. *Neurology* 1985; **35:** 510–15.
19. Suzuki Y, *et al.* Interaction between valproate formulation and phenytoin concentrations. *Eur J Clin Pharmacol* 1995; **48:** 61–3.
20. Grant SM, Heel RC. Vigabatrin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991; **41:** 889–926.
21. Browne TR, *et al.* Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. *Neurology* 1987; **37:** 184–9.

Antifungals. There have been several reports of interactions, sometimes resulting in phenytoin toxicity, between imidazole antifungals and phenytoin. The drug most frequently implicated is *miconazole*.[1-3] The related triazole antifungals *fluconazole*[4-6] and *voriconazole*[7] are also reported to interact with phenytoin,[4-6] possibly due to dose-related inhibition of cytochrome P450 isoenzymes by these antifungals.[4,7]

Phenytoin can decrease plasma concentrations of azole antifungals such as *ketoconazole*, voriconazole, and *itraconazole*.

1. Bourgoin B, *et al.* Interaction pharmacocinétique possible phénytoïne-miconazole. *Therapie* 1981; **36:** 347–9.
2. Loupi E, *et al.* Interactions médicamenteuses et miconazole. *Therapie* 1982; **37:** 437–41.
3. Rolan PE, *et al.* Phenytoin intoxication during treatment with parenteral miconazole. *BMJ* 1983; **287:** 1760.
4. Mitchell AS, Holland JT. Fluconazole and phenytoin: a predictable interaction. *BMJ* 1989; **298:** 1315.
5. Howitt KM, Oziemski MA. Phenytoin toxicity induced by fluconazole. *Med J Aust* 1989; **151:** 603–4.
6. Cadle RM, *et al.* Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; **28**: 191–5.
7. Purkins L, *et al.* Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 37–44.

Antigout drugs. Licensed product information for *sulfinpyrazone* states that it displaces phenytoin from its protein-binding sites, and also inhibits microsomal liver enzymes. The net result is an increase in plasma-phenytoin concentrations and a prolonged half-life, which is potentially hazardous.

Reduced doses of phenytoin were necessary to avoid toxicity when *allopurinol* was added to the therapy of a child with the Lesch-Nyhan syndrome.[1] Although the authors thought caution was advisable in using these two drugs together, they did emphasise that overgeneralisation may be dangerous since the child also received other antiepileptics and the role his disease may have played was unknown.

1. Yokochi K, *et al.* Phenytoin-allopurinol interaction: Michaelis-Menten kinetic parameters of phenytoin with and without allopurinol in a child with Lesch-Nyhan syndrome. *Ther Drug Monit* 1982; **4:** 353–7.

Antihistamines. A young woman developed drowsiness, ataxia, diplopia, tinnitus, and episodes of occipital headaches associated with vomiting after taking phenytoin sodium and *chlorphenamine*.[1] Chlorphenamine might have delayed the hepatic metabolism of phenytoin thereby increasing the plasma concentrations.

1. Pugh RNH, *et al.* Interaction of phenytoin with chlorphenamine. *Br J Clin Pharmacol* 1975; **2:** 173–5.

Antihypertensives. In 2 patients with hypoglycaemia associated with hyperinsulinism, therapeutic serum-phenytoin concentrations could not be achieved while they were also receiving *diazoxide*.[1] It was suggested that an increased rate of metabolism, and possibly a decreased binding, of phenytoin induced by diazoxide might have been responsible.

1. Roe TF, *et al*. Drug interaction: diazoxide and diphenylhydantoin. *J Pediatr* 1975; **87:** 480–4.

Antimalarials. Antimalarials may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold.

Antineoplastics. There have been reports of decreased plasma-phenytoin concentrations associated with cancer chemotherapy,[1-4] resulting in some cases in loss of seizure control.[2-4] The effect appears to be due to impaired absorption of phenytoin arising from antineoplastic damage to the gastrointestinal mucosa. In a patient a mean of 32% of an oral dose of phenytoin was absorbed after therapy with *cisplatin*, *vinblastine*, and *bleomycin*; this compared with a reported oral bioavailability of 80% or more.[3] *Trabectedin* may also reduce phenytoin absorption leading to an exacerbation of seizures.

Licensed product information for *levamisole* reports that increased plasma-phenytoin concentrations have been seen in patients taking phenytoin with levamisole given as an adjuvant to *fluorouracil* therapy. Treatment with fluorouracil (alone or with folinic acid) has also led to phenytoin toxicity in patients on long-term antiepileptic therapy.[5-7] Similar interactions have occurred with *doxifluridine*[8] and *capecitabine*[7] (both prodrugs of fluorouracil), and a combination preparation containing *tegafur* (a prodrug of fluorouracil) with *uracil* . However, a decrease in phenytoin serum concentrations has been seen when such a preparation was given with folinic acid to a patient receiving the antiepileptic.[9] For the effect of phenytoin on *busulfan* see Effects on the Nervous System under Adverse Effects of Busulfan, p.690. For the effect of phenytoin on the use of *streptozocin* and on *teniposide* see p.771 and p.778, respectively.

1. Fincham RW, Schottelius DD. Decreased phenytoin levels in antineoplastic therapy. *Ther Drug Monit* 1979; **1:** 277–83.
2. Bollini P, *et al.* Decreased phenytoin level during antineoplastic therapy: a case report. *Epilepsia* 1983; **24:** 75–8.
3. Sylvester RK, *et al.* Impaired phenytoin bioavailability secondary to cisplatinum, vinblastine, and bleomycin. *Ther Drug Monit* 1984; **6:** 302–5.
4. Grossman SA, *et al.* Decreased phenytoin levels in patients receiving chemotherapy. *Am J Med* 1989; **87:** 505–10.
5. Gilbar PJ, Brodribb TR. Phenytoin and fluorouracil interaction. *Ann Pharmacother* 2001; **35:** 1367–70.
6. Rosemergy I, Findlay M. Phenytoin toxicity as a result of 5-fluorouracil administration. *N Z Med J* 2002; **115:** U124.
7. Brickell K, *et al.* Phenytoin toxicity due to fluoropyrimidines (5FU/capecitabine): three case reports. *Br J Cancer* 2003; **89:** 615–16.
8. Konishi H, *et al.* Probable metabolic interaction of doxifluridine with phenytoin. *Ann Pharmacother* 2002; **36:** 831–4.
9. Veldhorst-Janssen NML, *et al.* Oral tegafur/folinic acid chemotherapy decreases phenytoin efficacy. *Br J Cancer* 2004; **90:** 745.

Antiprotozoals. Conflicting results have been reported with *metronidazole*: while one study has suggested only minimal effects on phenytoin concentrations and metabolism,[1] another has indicated inhibition of the metabolism of phenytoin.[2] For the effect of phenytoin on metronidazole, see p.838.

1. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* 1985; **37:** 407–10.
2. Blyden GT, *et al.* Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *Clin Pharmacol Ther* 1986; **39:** 181.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of phenytoin by lowering the convulsive threshold. Two cases of phenytoin toxicity and elevated plasma-phenytoin concentrations associated with the phenothiazine *thioridazine* have been reported;[1] but another study indicated that *thioridazine*, *chlorpromazine*, or *mesoridazine* reduced serum-phenytoin concentrations.[2]

The non-phenothiazine antipsychotic *loxapine* has also been implicated as producing a fall in serum-phenytoin concentration.[3]

For the effect of phenytoin on antipsychotics in general, see under Chlorpromazine, p.974. For the effect of phenytoin on *clozapine*, see p.984.

1. Vincent FM. Phenothiazine-induced phenytoin intoxication. *Ann Intern Med* 1980; **93:** 56–7.
2. Haidukewych D, Rodin EA. Effect of phenothiazines on serum antiepileptic drug concentrations in psychiatric patients with seizure disorder. *Ther Drug Monit* 1985; **7:** 401–4.
3. Ryan GM, Matthews PA. Phenytoin metabolism stimulated by loxapine. *Drug Intell Clin Pharm* 1977; **11:** 428–9.

Antivirals. *Zidovudine* may possibly reduce or increase plasma concentrations of phenytoin. There has been a report[1] of markedly decreased serum-phenytoin concentrations resulting in a recurrence of seizure activity in an epileptic patient after starting *nelfinavir* as part of antiretroviral therapy. Serum concentrations of phenytoin and valproate decreased[2,3] in 2 reports in children after the addition of *aciclovir. Ritonavir-boosted lopinavir* was reported[4] to increase the clearance of phenytoin in healthy subjects, probably due to hepatic enzyme induction; phenytoin similarly increased the clearance of the protease inhibitor. A case report[5] described the inhibition of phenytoin clearance by *efavirenz* resulting in elevated phenytoin plasma concentrations, and subtherapeutic levels of efavirenz resulting from hepatic enzyme induction by phenytoin.

For the possible effect of phenytoin on HIV-protease inhibitors, see p.883.

1. Honda M, *et al.* A generalized seizure following initiation of nelfinavir in a patient with human immunodeficiency virus type 1 infection, suspected due to interaction between nelfinavir and phenytoin. *Intern Med* 1999; **38:** 302–3.
2. Parmeggiani A, *et al.* Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit* 1995; **17:** 312–15.
3. Iglesias Iglesias A-A, *et al.* Disminución de la concentración sérica de antiepilépticos durante el tratamiento con aciclovir. *Med Clin (Barc)* 2005; **124:** 355–6.
4. Lim ML, *et al.* Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. *J Acquir Immune Defic Syndr* 2004; **36:** 1034–40.
5. Robertson SM, *et al.* A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* 2005; **41:** e15–e18.

Anxiolytics. See Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced as a result of induction of hepatic drug-metabolising enzymes after long-term use of phenytoin. In comparison with healthy subjects, half-lives have been shorter and clearance increased.[1,2]

There are sporadic reports of interactions between phenytoin and benzodiazepines, but the evidence is conflicting. Elevated plasma concentrations of phenytoin have been reported in patients given *diazepam*[3,4] or *chlordiazepoxide*[3] but, in contrast, another study suggested that these drugs produced a significant fall in serum-phenytoin concentrations.[5] It has been suggested that phenytoin intoxication could result from the impaired metabolism associated with the combination[3,4,6] but in practice this seems to be uncommon. There are similar conflicting reports for *clonazepam*.[7-9]

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; **12:** 841–4.
2. Scott AK, *et al.* Oxazepam pharmacokinetics in patients with epilepsy treated long-term with phenytoin alone or in combination with phenobarbitone. *Br J Clin Pharmacol* 1983; **16:** 441–4.
3. Vajda FJE, *et al.* Interaction between phenytoin and the benzodiazepines. *BMJ* 1971; **1:** 346.
4. Murphy A, Wilbur K. Phenytoin-diazepam interaction. *Ann Pharmacother* 2003; **37:** 659–63.
5. Houghton GW, Richens A. The effect of benzodiazepines and pheneturide on phenytoin metabolism in man. *Br J Clin Pharmacol* 1974; **1:** 344P–345P.
6. Kutt H, McDowell F. Management of epilepsy with diphenylhydantoin sodium: dosage regulation for problem patients. *JAMA* 1968; **203:** 969–72.
7. Eeg-Oloffson O. Experiences with Rivotril® in treatment of epilepsy—particularly minor motor epilepsy—in mentally retarded children. *Acta Neurol Scand* 1973; **49** (suppl 53): 29–31.
8. Johannessen SI, *et al.* Lack of effect of clonazepam on serum levels of diphenylhydantoin, phenobarbital and carbamazepine. *Acta Neurol Scand* 1977; **55:** 506–12.
9. Saavedra IN, *et al.* Phenytoin/clonazepam interaction. *Ther Drug Monit* 1985; **7:** 481–4.

Calcium-channel blockers. Raised serum-phenytoin concentration with phenytoin toxicity developed in a patient who had been taking *nifedipine* in addition to phenytoin for 3 weeks;[1] symptoms resolved completely after nifedipine withdrawal. The mechanism of interaction appeared to be complex. Similar effects have been reported with *diltiazem*[2] and *isradipine*.[3]

For the effect of phenytoin on dihydropyridine calcium-channel blockers, see under Nifedipine, p.1353, and on verapamil, see p.1422.

1. Ahmad S. Nifedipine-phenytoin interaction. *J Am Coll Cardiol* 1984; **3:** 1582.
2. Bahls FH, *et al.* Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. *Neurology* 1991; **41:** 740–2.
3. Cachat F, Tufro A. Phenytoin/isradipine interaction causing severe neurologic toxicity. *Ann Pharmacother* 2002; **36:** 1399–1402.

Cardiac glycosides. For the effect of phenytoin on cardiac glycosides, see under Digoxin, p.1261.

Corticosteroids. Serum concentrations of phenytoin have been elevated[1] or reduced[2-4] by *dexamethasone* and adjustment of phenytoin dosage may be required.[2-4] For the effect of phenytoin on corticosteroids, see p.1494.

1. Lawson LA, *et al.* Phenytoin-dexamethasone interaction: a previously unreported observation. *Surg Neurol* 1981; **16:** 23–4.
2. Wong DD, *et al.* Phenytoin-dexamethasone: a possible drug-drug interaction. *JAMA* 1985; **254:** 2062–3.
3. Recuenco I, *et al.* Effect of dexamethasone on the decrease of serum phenytoin concentrations. *Ann Pharmacother* 1995; **29:** 935.
4. Lackner TE. Interaction of dexamethasone with phenytoin. *Pharmacotherapy* 1991; **11:** 344–7.

Dermatological drugs. For the effect of phenytoin on *methoxsalen*, see p.1606.

Disulfiram. A well-documented interaction exists between phenytoin and disulfiram, which may result in clinical phenytoin toxicity.[1,2] The effect appears to be due to non-competitive inhibition of the metabolism of phenytoin by disulfiram,[2] which results in a substantial increase in phenytoin half-life and a decrease in its clearance.[3]

1. Dry J, Pradalier A. Intoxication par la phénytoïne au cours d'une association thérapeutique avec le disulfirame. *Therapie* 1973; **28:** 799–802.
2. Taylor JW, *et al.* Mathematical analysis of a phenytoin-disulfiram interaction. *Am J Hosp Pharm* 1981; **38:** 93–5.
3. Svendsen TL, *et al.* The influence of disulfiram on the half-life and metabolic clearance rate of diphenylhydantoin and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **9:** 439–41.

Diuretics. Severe osteomalacia in 2 previously active young women taking *acetazolamide* with phenytoin or primidone and phenobarbital has been reported.[1]

For the effect of antiepileptics such as phenytoin on *furosemide*, see p.1293.

1. Mallette LE. Anticonvulsants, acetazolamide and osteomalacia. *N Engl J Med* 1975; **293:** 668.

Dopaminergics. For the effect of phenytoin on *levodopa*, see p.807.

Enteral and parenteral nutrition. Therapeutic plasma concentrations of phenytoin may be difficult to achieve in patients receiving enteral or total parenteral nutrition.[1,2] Incompatibility studies indicate that phenytoin probably binds to components of the feed (see Incompatibility, above), which might explain this interaction when both are given together nasogastrically, but the same effect has also been reported when they were given separately by the intravenous route.[2] A review[3] of case reports and studies concluded that the exact role of enteral feeding in this interaction still remained unclear because of a lack of prospective, randomised, controlled studies performed in patients, rather than in healthy subjects. However, because of the amount of literature describing such a phenomenon, it was considered unlikely to occur just by chance. Monitoring of serum-phenytoin concentrations to guide therapy was recommended, and measures such as staggering phenytoin and enteral feeding might be considered to minimise the occurrence of this reaction.

1. Summers VM, Grant R. Nasogastric feeding and phenytoin interaction. *Pharm J* 1989; **243:** 181.
2. Messahel FM, *et al.* Does total parenteral nutrition lower serum phenytoin levels? *Curr Ther Res* 1990; **47:** 1017–20.
3. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000 **34:** 896–905.

Gastrointestinal drugs. Evidence for an interaction between phenytoin and *antacids* is conflicting. Some studies have shown a decrease in the bioavailability of phenytoin given with various antacid mixtures[1,2] but others have failed to find any evidence of reduced absorption.[3] Furthermore even those studies that recorded decreased absorption varied in their results with regard to particular drugs, suggesting for example that calcium carbonate both does[1] and does not[2] reduce phenytoin bioavailability. The clinical significance of this data is uncertain but it has been suggested that if antacids and phenytoin are both needed, doses should be spaced several hours apart.[4,5] *Sucralfate* is also reported to reduce phenytoin absorption.[6]

A well documented interaction exists between phenytoin and *cimetidine*, which produces a dose-dependent reduction in phenytoin clearance[7] and a significant elevation of serum-phenytoin concentration.[8] There are reports of phenytoin toxicity when cimetidine was given to epileptic patients[9,10] including a report of severe granulocytopenia.[11] Although some studies have found that neither *ranitidine*[12] nor *famotidine*[13] appear to affect the pharmacokinetics of phenytoin significantly, there have been isolated reports of raised plasma concentrations of phenytoin associated with use of ranitidine[14-16] or famotidine.[17]

Omeprazole 40 mg daily can decrease the plasma clearance of phenytoin[18] and increase the area under the serum-phenytoin concentration-time curve,[19] but one study[20] suggests that the dosage of 20 mg daily usually used for peptic ulcer disease is unlikely to produce a clinically significant effect on the steady-state plasma concentrations of phenytoin in patients with epilepsy.

1. Garnett WR, *et al.* Bioavailability of phenytoin administered with antacids. *Ther Drug Monit* 1979; **1:** 435–6.
2. Kulshrestha VK, *et al.* Interaction between phenytoin and antacids. *Br J Clin Pharmacol* 1978; **6:** 177–9.
3. O'Brien LS, *et al.* Failure of antacids to alter the pharmacokinetics of phenytoin. *Br J Clin Pharmacol* 1978; **6:** 176–7.
4. Cacek AT. Review of alterations in oral phenytoin bioavailability associated with formulation, antacids, and food. *Ther Drug Monit* 1986; **8:** 166–71.
5. D'Arcy PF, McElnay JC. Drug-antacid interactions: assessment of clinical importance. *Drug Intell Clin Pharm* 1987; **21:** 607–17.
6. Smart HL, *et al.* The effects of sucralfate upon phenytoin absorption in man. *Br J Clin Pharmacol* 1985; **20:** 238–40.
7. Bartle WR, *et al.* Dose-dependent effect of cimetidine on phenytoin kinetics. *Clin Pharmacol Ther* 1983; **33:** 649–55.
8. Iteogu MO, *et al.* Effect of cimetidine on single-dose phenytoin kinetics. *Clin Pharm* 1983; **2:** 302–4.
9. Phillips P, Hansky J. Phenytoin toxicity secondary to cimetidine administration. *Med J Aust* 1984; **141:** 602.
10. Hetzel DJ, *et al.* Cimetidine interaction with phenytoin. *BMJ* 1981; **282:** 1512.
11. Sazie E, Jaffe JP. Severe granulocytopenia with cimetidine and phenytoin. *Ann Intern Med* 1980; **93:** 151–2.
12. Watts RW, *et al.* Lack of interaction between ranitidine and phenytoin. *Br J Clin Pharmacol* 1983; **15:** 499–500.
13. Sambol NC, *et al.* A comparison of the influence of famotidine and cimetidine on phenytoin elimination and hepatic blood flow. *Br J Clin Pharmacol* 1989; **27:** 83–7.
14. Bramhall D, Levine M. Possible interaction of ranitidine with phenytoin. *Drug Intell Clin Pharm* 1988; **22:** 979–80.
15. Tse CST, *et al.* Phenytoin concentration elevation subsequent to ranitidine administration. *Ann Pharmacother* 1993; **27:** 1448–51.
16. Tse CST, Iagmin P. Phenytoin and ranitidine interaction. *Ann Intern Med* 1994; **120:** 892–3.
17. Shinn AF. Unrecognized drug interactions with famotidine and nizatidine. *Arch Intern Med* 1991; **151:** 814.
18. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. *Gastroenterology* 1985; **89:** 1235–41.
19. Prichard PJ, *et al.* Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987; **24:** 543–5.
20. Andersson T, *et al.* A study of the interaction between omeprazole and phenytoin in epileptic patients. *Ther Drug Monit* 1990; **12:** 329–33.

Ginkgo biloba. A fatal breakthrough seizure occurred[1] in a 55-year-old man who was taking phenytoin and valproate semisodium for a seizure disorder; he was also taking numerous non-prescription supplements, such as vitamin preparations and herbal medicines including ginkgo biloba extract, without the knowledge of his physician. Autopsy revealed subtherapeutic plasma concentrations of both antiepileptics. Although the exact cause was unclear, the authors postulated that hepatic enzyme induction by ginkgo biloba might have increased the clearance of phenytoin and valproate semisodium.

1. Kupiec T, Raj V. Fatal seizures due to potential herb-drug interactions with ginkgo biloba. *J Anal Toxicol* 2005; **29:** 755–8.

Immunosuppressants. Increased plasma-phenytoin concentrations were reported[1] in one patient when *tacrolimus* was added to existing therapy. Phenytoin was stopped until values were within the therapeutic range and then restarted at a lower dose, tacrolimus therapy continuing throughout; phenytoin levels remained stable thereafter.

For the effect of phenytoin on *ciclosporin*, see p.1826.

1. Thompson PA, Mosley CA. Tacrolimus-phenytoin interaction. *Ann Pharmacother* 1996; **30:** 544.

Levothyroxine. For the effects of phenytoin on levothyroxine, see p.2172.

Muscle relaxants. An increase in serum concentrations of phenytoin has been reported[1] in a patient when *tizanidine* was added to therapy.

1. Ueno K, *et al.* Phenytoin-tizanidine interaction. *DICP Ann Pharmacother* 1991; **25:** 1273.

Neuromuscular blockers. For the effect of phenytoin on *suxamethonium*, see p.1911 and on *competitive neuromuscular blockers*, see under Atracurium, p.1904.

Sex hormones. For the effect of phenytoin on *oral contraceptives*, see p.2068. Similar effects may also be noted in patients receiving *HRT*, see p.2076.

Stimulants and anorectics. Although there has been a report of elevated phenytoin and primidone serum concentrations in a 5-year-old after addition of *methylphenidate* to therapy[1] there was no similar elevation in 2 other children receiving phenobarbital and phenytoin in the same report, nor in 11 patients of varying ages given methylphenidate with antiepileptic therapy as part of a controlled study.[2] The likelihood of an interaction seems small in the majority of patients.

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. *JAMA* 1969; **207:** 2053–6.
2. Kupferberg HJ, *et al.* Effect of methylphenidate on plasma anticonvulsant levels. *Clin Pharmacol Ther* 1972; **13:** 201–4.

Theophylline. Although most reports of an interaction between phenytoin and theophylline concern effects on theophylline concentrations, one study in 14 healthy subjects suggested that treatment with both could lower serum-phenytoin concentrations, with a subsequent rise in concentration on stopping theophylline.[1] The mechanism was suggested to be enzyme induction by the xanthine resulting in increased phenytoin metabolism.

For the effect of phenytoin on theophylline, see p.1143.

1. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.

Ticlopidine. Acute phenytoin toxicity has been reported in a well-stabilised 44-year-old patient on introduction of ticlopidine to prevent restenosis after placement of a coronary stent.[1] The patient also took metoprolol, aspirin, and for a short period lovastatin, but inhibition of the cytochrome P450 isoenzyme CYP2C19 by ticlopidine was considered the most likely cause of the patient's elevated serum phenytoin. A later report[2] by the same authors found that ticlopidine inhibited the clearance of phenytoin in 6 patients on phenytoin monotherapy; the involvement of CYP2C19 was also supported. The authors recommended that dosage adjustment of phenytoin should be considered if ticlopidine is also given.

A similar interaction occurred in a 72-year-old patient,[3] and the authors postulated that, since steady-state plasma concentrations of ticlopidine are almost twofold higher in elderly patients than those in younger patients, the higher ticlopidine concentrations may have played a role in this drug interaction.

1. Donahue SR, *et al.* Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 1997; **62:** 572–7.
2. Donahue S,*et al.* Ticlopidine inhibits phenytoin clearance. *Clin Pharmacol Ther* 1999; **66:** 563–8.
3. Klaassen SL. Ticlopidine-induced phenytoin toxicity. *Ann Pharmacother* 1998; **32:** 1295–8.

Vaccines. Contradictory results have been reported for the effects of *influenza vaccine* on serum-phenytoin concentrations. A significant elevation in total phenytoin concentration has been reported[1] after vaccination, and was suggested to be due to interferon induction and inhibition of the cytochrome P450 enzyme system. In contrast, other reports have suggested that any increase in serum-phenytoin concentration was temporary and not significant overall[2] or even that there was a slight fall in serum-phenytoin concentration.[3] One study reported a significant increase in total phenytoin concentration two days after vaccination, followed by a return to previous values but this was accompanied by evidence of a gradual and prolonged fall in free phenytoin concentrations.[4] The possibility of either phenytoin toxicity or loss of seizure control may exist in some epileptic patients given influenza vaccine during phenytoin therapy.[5]

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* 1986; **5:** 817–20.
2. Levine M, *et al.* Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* 1984; **3:** 505–9.
3. Sawchuk RJ, *et al.* Effect of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monit* 1979; **1:** 285–8.
4. Smith CD, *et al.* Effect of influenza vaccine on serum concentrations of total and free phenytoin. *Clin Pharm* 1988; **7:** 828–32.
5. Grabenstein JD. Drug interactions involving immunologic agents, part 1. vaccine-vaccine, vaccine-immunoglobulin, and vaccine-drug interactions. *DICP Ann Pharmacother* 1990; **24:** 67–81.

Vitamins. *Pyridoxine* given in large doses produced a reduction in serum-phenytoin concentrations in 7 patients,[1] perhaps reflecting increased activity by pyridoxal phosphate-dependent enzymes involved in phenytoin metabolism.

Correction of antiepileptic-associated folate deficiency with *folic acid* has been reported to result in a decrease in serum-phenytoin concentrations and an increase in seizure frequency.[2-4] The effect has been reported to be most marked in subjects with high initial serum-phenytoin concentrations[5] and is associated with an increased phenytoin metabolism.[4,6] However, in the majority of patients the effect is unlikely to assume clinical significance,[2,5] and there is some evidence that very low doses of folic acid may be used to maintain normal serum-folate values without an increase in seizure frequency.[3] Information regarding the dual and interdependent interaction between phenytoin and folic acid has been reviewed.[7] Although limited numbers of patients and healthy subjects were involved, evaluation of the data suggested that starting phenytoin and folic acid at the same time prevents decreased folate levels and steady-state concentrations of phenytoin are reached sooner. Plasma concentrations of phenytoin are also possibly reduced by *folinic acid* (see also Antineoplastics, above).

For the effect of antiepileptics, including phenytoin, on *vitamin D* concentrations, see Effects on Bone under Adverse Effects, above.

1. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* 1976; **i:** 256.
2. Baylis EM, *et al.* Influence of folic acid on blood-phenytoin levels. *Lancet* 1971; **i:** 62–4.
3. Inoue F. Clinical implications of anticonvulsant-induced folate deficiency. *Clin Pharm* 1982; **1:** 372–3.
4. Steinweg DL, Bentley ML. Seizures following reduction in phenytoin level after orally administered folic acid. *Neurology* 2005; **64:** 1982.
5. Furlanut M, *et al.* Effects of folic acid on phenytoin kinetics in healthy subjects. *Clin Pharmacol Ther* 1978; **24:** 294–7.
6. Berg MJ, *et al.* Phenytoin and folic acid interaction: a preliminary report. *Ther Drug Monit* 1983; **5:** 389–94.
7. Lewis DP, *et al.* Phenytoin-folic acid interaction. *Ann Pharmacother* 1995; **29:** 726–35.

Pharmacokinetics

Phenytoin is slowly but almost completely absorbed from the gastrointestinal tract. It is largely insoluble at the acid pH of the stomach, most being absorbed from the upper intestine; the rate of absorption is variable and is reported to be affected by the presence of food. Absorption after intramuscular injection is slower than that from the gastrointestinal tract.

Phenytoin is extensively metabolised in the liver to inactive metabolites, chiefly 5-(4-hydroxyphenyl)-5-phenylhydantoin. The rate of metabolism appears to be subject to genetic polymorphism and may also be influenced by racial characteristics; it is reported to be increased during pregnancy and menstruation and to decrease with age. Phenytoin hydroxylation is saturable and is therefore readily inhibited by drugs that compete for its metabolic pathways; this is also the reason why small increments in dose may produce large rises in plasma concentration. Phenytoin undergoes enterohepatic recycling and is excreted in the urine, mainly as its hydroxylated metabolite, in either free or conjugated form.

Phenytoin is widely distributed throughout the body. It is about 90% bound to plasma proteins, although this may be reduced in certain disease states and in certain patient populations (see Precautions, above). It has a very variable, dose-dependent half-life, but the mean plasma half-life appears to be about 22 hours at steady state; because phenytoin inhibits its own metabolism it may sometimes be several weeks before a steady-state plasma-phenytoin concentration is attained.

Monitoring of plasma concentrations may be performed as an aid in assessing control, and the therapeutic range of total plasma-phenytoin concentrations is usually quoted as 10 to 20 micrograms/mL (40 to 80 micromoles/litre); some patients, however, achieve control at concentrations outside this range. It has been suggested that, because of differences in protein binding, measurement of free phenytoin concentrations in plasma may prove more reliable; measurement of concentrations in saliva, which contains only free phenytoin, has also been performed.

Phenytoin crosses the placental barrier and small amounts are distributed into breast milk.

The pharmacokinetics of phenytoin are affected by other antiepileptics (see Interactions, above).

Uses and Administration

Phenytoin is a hydantoin antiepileptic used to control partial and generalised tonic-clonic seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head. Phenytoin has also been used in the treatment of trigeminal neuralgia. It is a class Ib antiarrhythmic and has been used to treat cardiac arrhythmias.

Doses may be expressed in terms of phenytoin or phenytoin sodium; although phenytoin 92 mg is equivalent to about 100 mg of phenytoin sodium these molecular equivalents are not necessarily biologically equivalent. In the UK an oral suspension of phenytoin 90 mg in 15 mL may be considered about equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg. In the USA a suspension containing phenytoin 125 mg in 5 mL is available.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; in many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range. A suggested initial oral dose of phenytoin or phenytoin sodium given as a single dose or in divided doses is 3 to 4 mg/kg daily or 150 to 300 mg daily progressively increased with care to 600 mg daily if necessary; the suggested minimum interval between increments has ranged from about 7 to 10 days. Particular care is needed at higher doses, where saturation of metabolism may mean that a small increment produces a large rise in plasma concentrations. A usual maintenance dose is 200 to 500 mg daily.

The practice of starting phenytoin therapy with initial small doses means that more than a week may be required before therapeutic plasma concentrations are attained; it has been reported that it may even be several weeks before a steady-state concentration is established. An initial loading dose may therefore be given, with the usual maintenance dosage being instituted 24 hours after the loading dose. Once the patient is stabilised the long half-life of phenytoin may permit the total daily dose to be given in two daily divisions or as a single dose, usually at night.

Although clinical evidence is lacking, different brands of phenytoin, as well as different formulations from the same manufacturer, may vary in their bioavailability and patients may need to be restabilised in the event of a change.

In order to lessen gastric irritation, phenytoin should be taken with or after food. The time and manner of taking phenytoin should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

As with other antiepileptics, withdrawal of phenytoin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Treatment of tonic-clonic **status epilepticus** is usually begun with a benzodiazepine such as diazepam or lorazepam given intravenously or rectally, and followed by phenytoin sodium intravenously. A suggested dose of phenytoin sodium is 10 to 15 mg/kg given by slow intravenous injection or by intermittent infusion at a uniform rate of not more than 50 mg/minute. Thereafter maintenance doses of 100 mg orally or intravenously are given every 6 to 8 hours; the rate and dose should be reduced according to body-weight. For doses in children, see below.

Deaths have been caused by the over-rapid intravenous injection of phenytoin sodium and continuous monitoring of the ECG and blood pressure is recommended whenever phenytoin sodium is given intravenously.

Phenytoin sodium is absorbed slowly and erratically from the intramuscular site and therefore intramuscular injections are not appropriate for the emergency arrest of status epilepticus. They may, however, be used in certain situations to maintain or establish therapeutic plasma concentrations of phenytoin in patients who are unconscious or otherwise unable to take phenytoin orally. Owing to the slower absorption of phenytoin from intramuscular sites, patients stabilised on the oral route require an increase in the intramuscular dose of about 50%; it is recommended that, if possible, intramuscular injections of phenytoin sodium should not be continued for longer than one week. On transfer back to the oral route the patient should receive 50% of the original oral dose for the same period of time as intramuscular injections were given, to allow for continued absorption of the residual phenytoin in the intramuscular sites. For the **prevention and treatment of seizures associated with neurosurgery** in patients who have not previously taken phenytoin sodium, a suggested intramuscular dose is 100 to 200 mg given at 4-hourly intervals during surgery and continued postoperatively for 48 to 72 hours. Thereafter, the dose should be reduced to a maintenance dose of 300 mg and adjusted according to plasma-phenytoin concentrations.

Administration in children. Phenytoin may be given to children for the control of partial and generalised tonic-clonic seizures. It is also used as part of the emergency treatment of status epilepticus and has been used for the prevention and treatment of seizures associated with neurosurgery or severe traumatic injury to the head.

For **epilepsy** the dose of phenytoin should be adjusted to the needs of the individual patient to achieve adequate control of seizures, preferably with monitoring of plasma concentrations; young children may require a higher dose per kg body-weight than adults due to more rapid metabolism. In many patients control requires total plasma-phenytoin concentrations of 10 to 20 micrograms/mL (40 to 80 micromoles/litre), but some are controlled at concentrations outside this range; the *BNFC* suggests concentrations of 6 to 15 micrograms/mL (25 to 60 micromoles/litre) in neonates and those aged up to 3 months. The recommended initial oral dose for children is 5 mg/kg daily in 2 or 3 divided doses up to a maximum of 300 mg daily; the usual maintenance dose is 4 to 8 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests the following doses given according to age:

- neonates: an initial loading dose of 18 mg/kg by slow intravenous injection, over 20 to 30 minutes, followed by oral doses of 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily
- 1 month to 12 years: an initial oral dose of 1.5 to 2.5 mg/kg twice daily followed by 2.5 to 5 mg/kg twice daily adjusted as necessary to a usual maximum of 7.5 mg/kg twice daily or 300 mg daily
- 12 years and older: usual adult doses (see above)

For **status epilepticus** and for the **prevention and treatment of seizures associated with neurosurgery or trauma** an initial loading dose of 15 to 20 mg/kg given by slow intravenous injection may be followed by usual adult doses (see above). Alternatively, the *BNFC* suggests the following doses given by slow intravenous injection or infusion according to age:

- neonates and children up to 12 years: a loading dose of 18 mg/kg followed by 2.5 to 5 mg/kg twice daily
- 12 to 18 years: a loading dose of 18 mg/kg followed by up to 100 mg 3 or 4 times daily

Intravenous injections and infusions of phenytoin should be given at a rate not exceeding 1 mg/kg per minute (a maximum of 50 mg per minute).

A comparison of methods[1] for the prediction of required phenytoin dosage in paediatric patients indicated that all methods produced a sizeable number of predictions with an error of more than 10% and that close monitoring of serum concentrations and clinical status was recommended regardless of the method chosen to adjust dosage. Similar conclusions have been made regarding the need to monitor plasma concentrations of phenytoin in the newborn and young infants.[2]

1. Yuen GJ, *et al.* Phenytoin dosage predictions in paediatric patients. *Clin Pharmacokinet* 1989; **16:** 254–60.
2. Loughnan PM, *et al.* Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977; **52:** 302–9.

Administration in the elderly. Pharmacokinetic studies in elderly patients have shown reduced binding to plasma proteins which was not itself an indication for dosage change,[1] but a study showing a decreased metabolism[2] did indicate that elderly patients may need lower doses of phenytoin than younger adults to maintain similar serum concentrations.

1. Patterson M, *et al.* Plasma protein binding of phenytoin in the aged: in vivo studies. *Br J Clin Pharmacol* 1982; **13:** 423–5.
2. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982; **31:** 301–4.

Cardiac arrhythmias. Phenytoin has been given intravenously in the treatment of ventricular arrhythmias (p.1160), especially those caused by overdosage with cardiac glycosides. Although this use now appears to be obsolete, in the UK the licensed dose of phenytoin sodium is 3.5 to 5 mg/kg given by slow intravenous injection at a uniform rate of not more than 50 mg/minute, repeated once if necessary.

Eclampsia and pre-eclampsia. Phenytoin has been used for eclampsia but now treatment with magnesium sulfate is preferred, see p.470.

Epidermolysis bullosa. There have been reports[1-3] of a favourable but variable clinical response to phenytoin in patients with some variants of epidermolysis bullosa (p.1579), a condition for the severe forms of which there is no truly effective treatment. However, a double-blind placebo-controlled study[4] concluded that phenytoin was not an effective treatment for the recessive dystrophic variant, and offered no overall benefit when compared with placebo.

1. Bauer EA, *et al.* Phenytoin therapy of recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1980; **303:** 776–81.
2. Cooper TW, Bauer EA. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis. *Arch Dermatol* 1984; **120:** 490–5.
3. Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. *Dermatol Online J* 2003; **9:** 6.
4. Caldwell-Brown D, *et al.* Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1992; **327:** 163–7.

Epilepsy. Phenytoin has long been used in the treatment of partial seizures with or without secondary generalisation and in primarily generalised tonic-clonic seizures, although other drugs may be better tolerated and easier to use (see p.465). It is also effective in other forms of epilepsy with the exception of absence and myoclonic seizures.

Hiccup. Phenytoin may be of value for the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Petroski D, Patel AN. Diphenylhydantoin for intractable hiccups. *Lancet* 1974; **i:** 739.

Myotonia. A review[1] of myotonia congenita, a hereditary muscular disorder characterised by symptoms of muscle stiffness especially after rest and on starting to move. Where treatment is necessary it is usually with phenytoin or procainamide, the former being preferred as being better tolerated.

1. Gutmann L, *et al.* Myotonia congenita. *Semin Neurol* 1991; **11:** 244–8.

Neonatal seizures. Phenytoin is one of the antiepileptics that may be used in the management of neonatal seizures (p.471).

Neuropathic pain. Phenytoin is used alone or added to treatment in trigeminal neuralgia (p.9) in patients unresponsive to or intolerant of carbamazepine. It has also been used in the treatment of painful diabetic neuropathy (p.6).

Post-traumatic seizures. About 12% of patients with severe traumatic brain injury develop seizures and the rate may be more than 50% for those with penetrating missile injuries.[1] The use of antiepileptics to treat such seizures is standard but there has been some debate about prophylactic use. Evidence suggests that prophylaxis with phenytoin (and perhaps carbamazepine) is effective in preventing early seizures (arbitrarily defined as those occurring up to 7 days after trauma), but prophylaxis with these or other antiepileptics such as phenobarbital valproate, has not been shown to be effective for preventing late seizures, disability, or death.[1-6] Guidelines and recommendations for such use have been issued.[1,7,8] Children with severe, acute neurotrauma were found to have markedly altered protein binding and phenytoin metabolism, and therefore may require increased doses.[9]

1. Chang BS, Lowenstein DH. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; **60:** 10–16. Also available at: http://www.neurology.org/cgi/reprint/60/1/10.pdf (accessed 09/06/08)
2. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/06/08).
3. Chadwick D. Seizures and epilepsy after traumatic brain injury. *Lancet* 2000; **355:** 334–5.
4. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia* 2001; **42:** 515–24.
5. Agrawal A, *et al.* Post-traumatic epilepsy: an overview. *Clin Neurol Neurosurg* 2006; **108:** 433–9.
6. Beghi E. Overview of studies to prevent posttraumatic epilepsy. *Epilepsia* 2003; **44** (suppl 10): 21–6.
7. Meek PD, *et al.* Guidelines for nonemergency use of parenteral phenytoin products. *Arch Intern Med* 1999; **159:** 2639–44.

8. Bratton SL, *et al.* Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Joint Section on Neuotrauma and Critical Care, AANS/CNS. Guidelines for the management of severe traumatic brain injury—XIII: antiseizure prophylaxis. *J Neurotrauma* 2007; **24** (suppl 1): S-83–S-86. Also available at: http://www.braintrauma.org/site/DocServer/Management_3rd_Edition.pdf?docID=222 (accessed 01/09/08)
9. Stowe CD, *et al.* Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. *J Clin Pharmacol* 2000; **40:** 1452–61.

Status epilepticus. A benzodiazepine is the usual choice to abort an attack of status epilepticus (p.469). If this fails to control the seizures or the seizures recur, then intravenous phenytoin may be given.

Once seizures have been brought under control, maintenance antiepileptic therapy may be started.

Syndrome of inappropriate ADH secretion. Phenytoin has been used occasionally to inhibit pituitary antidiuretic hormone (ADH) secretion in patients with the syndrome of inappropriate ADH secretion (SIADH), the management of which is discussed on p.2182.

Tinnitus. Phenytoin is one of many drugs that have been tried in tinnitus (p.1866), but although it has been reported to be effective in some patients it is rarely used because of problems with adverse effects.

Withdrawal syndromes. Phenytoin has little place in the management of seizures associated with the *alcohol withdrawal syndrome* (p.1626). Prophylaxis with phenytoin has been shown[1,2] to be ineffective for prevention of recurrent alcohol-related seizures and therefore drugs such as the benzodiazepines or clomethiazole, which are effective both for the treatment and prophylaxis of such seizures, are preferred.

Results from a double-blind study[3] indicated that phenytoin was associated with a reduction in *cocaine abuse* compared with placebo. The abuse of cocaine is discussed on p.1858 and treatment of cocaine withdrawal on p.1860.

1. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. *Ann Emerg Med* 1991; **20:** 520–2.
2. Rathlev NK, *et al.* The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; **23:** 513–8.
3. Crosby RD, *et al.* Phenytoin in the treatment of cocaine abuse: a double-blind study. *Clin Pharmacol Ther* 1996; **59:** 458–68.

Wounds and ulcers. Phenytoin has been used to promote wound healing (p.1585). Topical application of phenytoin has produced encouraging results in the healing of various types of ulcers[1-7] and large abscess cavities.[8] It has been suggested that phenytoin may reduce bacterial colonisation by changing the pH or by a direct antibacterial effect.[2] The enhanced wound healing may also be due to increased fibroblast proliferation and increased collagen content.[2] Limited absorption from the wound site may occur[9,10] and patients may need to be monitored for signs of toxicity. A systematic review,[11] which included some of these studies, found evidence to support the use of phenytoin in the treatment of leg ulcers, leprosy wounds, chronic wounds, and diabetic foot ulcers despite the poor methodological quality in the majority of studies.

1. Muthukumarasamy MG, *et al.* Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14:** 909–11.
2. Pendse AK, *et al.* Topical phenytoin in wound healing. *Int J Dermatol* 1993; **32:** 214–17.
3. Anstead GM, *et al.* Phenytoin in wound healing. *Ann Pharmacother* 1996; **30:** 768–75.
4. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92:** 108–9.
5. Rhodes RS, *et al.* Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; **35:** 675–81.
6. Bhatia A, *et al.* Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. *J Dermatolog Treat* 2004; **15:** 321–7.
7. Younes N, *et al.* Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 2006; **12:** 5. Available at: http://dermatology.cdlib.org/126/pearls/phenytoin/younes.html (accessed 09/06/08)
8. Lodha SC, *et al.* Role of phenytoin in healing of large abscess cavities. *Br J Surg* 1991; **78:** 105–8.
9. Gore R, *et al.* Topical phenytoin. *Pharm J* 1991; **247:** 620.
10. Lewis WG, Rhodes RS. Systemic absorption of topical phenytoin sodium. *Ann Pharmacother* 1994; **28:** 961.
11. Shaw J, *et al.* The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol* 2007; **157:** 997–1004.

Preparations

BP 2008: Phenytoin Capsules; Phenytoin Injection; Phenytoin Oral Suspension; Phenytoin Tablets;
USP 31: Extended Phenytoin Sodium Capsules; Phenytoin Oral Suspension; Phenytoin Sodium Injection; Phenytoin Tablets; Prompt Phenytoin Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Epamin; Etoina; Fenigramon; Fenitenk; Lotoquis Simple; Opliphon; ***Austral.:*** Dilantin; ***Austria:*** Epanutin; Epilan-D; Phenhydan; ***Belg.:*** Diphantoine; Epanutin; ***Braz.:*** Dantalin; Epelin; Fenital; Feniton; Hidantal; Unifenitoin; ***Canad.:*** Dilantin; ***Chile:*** Epamin; ***Cz.:*** Epanutin; Epilan-D; Phenhydan†; Sodanton†; ***Fin.:*** Hydantin; ***Fr.:*** Di-Hydan; Dilantin; ***Ger.:*** Epanutin†; Phenhydan; ***Gr.:*** Epanutin; ***Hong Kong:*** Dilantin; Ditoin; ***Hung.:*** Diphedan; Epanutin; ***India:*** Dilantin; Epsolin; Eptoin; ***Indon.:*** Dilantin; Ikaphen; Kutoin; Movileps; Phenilep; ***Irl.:*** Epanutin; ***Israel:*** Dilantin; Epanutin; ***Ital.:*** Aurantin; Dintoina; ***Malaysia:*** Dilantin; Ditoin; ***Mex.:*** Biodan; Comvufen; Epamin; Fenidantoin S; Feniffler; Fenitron; Hidantoina; Nuctane†; ***Neth.:*** Diphantoine; Epanutin; ***Norw.:*** Epinat; ***NZ:*** Dilantin; ***Philipp.:*** Dilantin; Epilantin; ***Pol.:*** Epanutin; ***Port.:*** Fenitan; Hidantina; ***S.Afr.:*** Epanutin; ***Singapore:*** Dilantin; ***Spain:*** Epanutin; Neosidantoina; Sinergina; ***Swed.:*** Epanutin; Fenantoin; Lehydan; ***Switz.:*** Epanutin†; Epilantine†; Phenhydan; ***Thai.:*** Dilantin; Ditoin; Ditomed; Pepsytoin; Utoin; ***Turk.:*** Epanutin; Epdantoin; Hidantin; Phenydan; ***UK:*** Epanutin; ***USA:*** Dilantin; Phenytek; ***Venez.:*** Dantoinal; Dilantin; Epamin; Fentoinal.

Multi-ingredient: ***Arg.:*** Cumatil L; Lotoquis; ***Belg.:*** Vethoine; ***Braz.:*** Dialudon; Gamibetal Complex†; Taludon†; ***Cz.:*** Sanepil; ***Gr.:*** Diphenal; ***India:*** Dilantin with Phenobarbital; Epilan; Garoin; ***Indon.:*** Ditalin; ***Ital.:*** Dintoinale; Gamibetal Complex; Metinal-Idantoina; Metinal-Idantoina L; ***Mex.:*** Alepsal Compuesto; Gamibetal Complex; ***Port.:*** Hidantina Composta†; ***Spain:*** Epilantin†; Equidan†; Redutona.

Pregabalin *(BAN, USAN, rINN)*

CI-1008; PD-144723; Pregabalina; Prégabaline; Pregabalinum.
(*S*)-3-(Aminomethyl)-5-methylhexanoic acid.
Прегабалин
$C_8H_{17}NO_2$ = 159.2.
CAS — 148553-50-8.
ATC — N03AX16.
ATC Vet — QN03AX16.

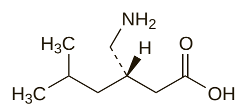

Adverse Effects and Precautions

The most common adverse effects reported during therapy with pregabalin are dizziness and somnolence. Other common adverse effects include blurred vision, diplopia, increased appetite and weight gain, dry mouth, constipation, vomiting, flatulence, euphoria, confusion, reduced libido, erectile dysfunction, irritability, vertigo, ataxia, tremor, dysarthria, paraesthesia, fatigue, and oedema. Disturbances of attention, memory, coordination, and gait also occur frequently. Syncope and congestive heart failure have been reported less frequently. Reversible renal failure, elevation of creatine kinase concentration, and rhabdomyolysis have been reported rarely. Hypersensitivity reactions have occurred shortly after starting pregabalin therapy; symptoms include rash, blisters, urticaria, dyspnoea, and wheezing. Stevens-Johnson syndrome has also been reported. An increased incidence of haemangiosarcoma was observed in *mice* that had been given high doses of pregabalin.

Licensed product information states that care is required when withdrawing pregabalin therapy, regardless of the indication—see also Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of pregabalin on *mood* (including the risk of suicidal ideation), see p.468.

Hypersensitivity reactions. The Australian Adverse Drug Reactions Advisory Committee[1] stated in December 2007 that 13% of all pregabalin adverse reaction reports in its database were hypersensitivity reactions. Presenting symptoms included anaphylaxis, skin rash, and angioedema. Of the 22 reports received, 6 women developed symptoms within hours of their first dose and pregabalin was the sole suspected drug in 14.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Reports of hypersensitivity reactions to pregabalin. *Aust Adverse Drug React Bull* 2007; **26:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0712.pdf (accessed 09/06/08)

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Pharmacokinetics

Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations are achieved within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Steady state is achieved after 1 to 2 days. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by haemodialysis.

Distribution into milk has been found in studies in *rats*.

Renal impairment. References.

1. Randinitis EJ, *et al.* Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003; **43:** 277–83.

Uses and Administration

Pregabalin is an antiepileptic used as an adjunct in the treatment of partial seizures with or without secondary generalisation. It is also used in the treatment of generalised anxiety disorder, neuropathic pain, and fibromyalgia.

Pregabalin is given orally in 2 or 3 divided doses daily.

The initial dose in the treatment of **epilepsy** is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 600 mg daily after another week.

In the treatment of **generalised anxiety disorder**, the initial dose is 150 mg daily; this may be increased at weekly intervals in steps of 150 mg, to a maximum of 600 mg daily.

For **neuropathic pain** the initial dose in the UK is 150 mg daily increased after 3 to 7 days according to response to 300 mg daily and then to 600 mg daily after another 7 days. Similar doses are licensed in the USA for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia, although a maximum daily dose of 300 mg is recommended in diabetic neuropathy.

For **fibromyalgia** the initial dose is 150 mg daily increased after 1 week according to response to 300 mg daily and then to 450 mg daily if necessary.

Dosage of pregabalin should be reduced in patients with renal impairment (see below).

As with other antiepileptics, withdrawal of pregabalin therapy in epilepsy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. Licensed drug information states that if pregabalin therapy has to be stopped, this should be done gradually over a minimum of 1 week, regardless of indication.

◊ References.

1. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother* 2005; **39:** 2029–37.
2. Tassone DM, *et al.* Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* 2007; **29:** 26–48.

Administration in renal impairment. The dose of pregabalin for patients with renal impairment should be reduced according to creatinine clearance (CC):

- CC 30 to less than 60 mL/minute: starting daily dose: 75 mg; maximum daily dose: 300 mg; daily dose given in 2 or 3 divided doses
- CC 15 to less than 30 mL/minute: starting daily dose: 25 to 50 mg; maximum daily dose: 150 mg; daily dose given in 2 divided doses or once daily
- CC less than 15 mL/minute: starting daily dose: 25 mg; maximum daily dose: 75 mg; daily dose given as one dose
- haemodialysis patients should receive in addition to the daily dose a supplementary dose of 25 to 100 mg immediately after each 4-hour haemodialysis session

Anxiety disorders. Pregabalin is used for the treatment of generalised anxiety disorder (p.952); it has also been tried in social anxiety disorder (see Phobic Disorders, p.953).

References.

1. Pande AC, *et al.* Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; **160:** 533–40.
2. Feltner DE, *et al.* A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2003; **23:** 240–9.
3. Pande AC, *et al.* Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2004; **24:** 141–9.
4. Rickels K, *et al.* Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. *Arch Gen Psychiatry* 2005; **62:** 1022–30.
5. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in generalized anxiety. *Drugs Today* 2007; **43:** 601–10.

Epilepsy. Pregabalin is one of the newer drugs used as adjunctive therapy in patients with partial seizures with or without secondary generalisation (p.465). It appears to be reasonably well tolerated.

References.

1. Miller R, *et al.* Exposure-response analysis of pregabalin add-on treatment of patients with refractory partial seizures. *Clin Pharmacol Ther* 2003; **73:** 491–505.
2. Arroyo S, *et al.* Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. *Epilepsia* 2004; **45:** 20–7.
3. Elger CE, *et al.* Pregabalin add-on treatment in patients with partial seizures: a novel evaluation of flexible-dose and fixed-dose treatment in a double-blind, placebo-controlled study. *Epilepsia* 2005; **46:** 1926–36.
4. Hamandi K, Sander JW. Pregabalin: a new antiepileptic drug for refractory epilepsy. *Seizure* 2006; **15:** 73–8.
5. Lozsadi D, *et al.* Pregabalin add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/06/08).

Neuropathic pain. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics (see Choice of Analgesic, p.2). Although carbamazepine appears to be the antiepileptic most frequently used, pregabalin is also given in the treatment of peripheral neuropathic pain[1] including postherpetic neuralgia[2,3] (p.9) and painful diabetic neuropathy[4,5] (p.6). Pregabalin may also be used in central neuropathic pain[6,7] (p.6).

1. Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health-Syst Pharm* 2007; **64:** 1475–82.
2. Sabatowski R, *et al.* Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; **109:** 26–35.
3. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs* 2005; **65:** 111–18.
4. Rosenstock J, *et al.* Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain* 2004; **110:** 628–38.
5. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. *Drugs* 2004; **64:** 2813–20.
6. Siddall PJ, *et al.* Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006; **67:** 1792–800.
7. Vranken JH, *et al.* Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008; **136:** 150–7.

Postoperative pain. There is growing interest in the use of analgesic adjuvants including antiepileptics such as pregabalin to modulate opioid dosage and efficacy for postoperative pain (see p.4).

References.

1. Dahl JB, *et al.* 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; **48:** 1130–6.
2. Tiippana EM, *et al.* Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* 2007; **104:** 1545–56.

Soft-tissue rheumatism. Three large, multicentre controlled studies[1-3] have shown that pregabalin in oral doses of between 300 and 600 mg daily is effective in reducing pain and other core symptoms of fibromyalgia (see Soft-tissue Rheumatism, p.13) such as sleep disturbance and fatigue. The drug was reported to be generally well tolerated, dizziness and somnolence being the most common adverse effects. Pain relief appears to be largely independent of reduction in anxiety or depression scores.[4]

1. Crofford LJ, *et al.* Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 1264–73.
2. Mease PJ, *et al.* A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008; **35:** 502–14.
3. Crofford LJ, *et al.* Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008; **136:** 419–31.
4. Arnold LM, *et al.* The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med* 2007; **8:** 633–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lyrica; ***Austral.:*** Lyrica; ***Belg.:*** Lyrica; ***Canad.:*** Lyrica; ***Chile:*** Lyrica; Pregobin; ***Cz.:*** Lyrica; ***Denm.:*** Lyrica; ***Fin.:*** Lyrica; ***Fr.:*** Lyrica; ***Ger.:*** Lyrica; ***Gr.:*** Lyrica; ***Hong Kong:*** Lyrica; ***Hung.:*** Lyrica; ***India:*** Pregab; ***Indon.:*** Lyrica; ***Irl.:*** Lyrica; ***Ital.:*** Lyrica; ***Mex.:*** Lyrica; ***Neth.:*** Lyrica; ***Norw.:*** Lyrica; ***NZ:*** Lyrica; ***Philipp.:*** Lyrica; ***Pol.:*** Lyrica; ***Port.:*** Lyrica; ***Rus.:*** Lyrica (Лирика); ***Singapore:*** Lyrica; ***Spain:*** Lyrica; ***Swed.:*** Lyrica; ***Switz.:*** Lyrica; ***UK:*** Lyrica; ***USA:*** Lyrica; ***Venez.:*** Lyrica.

Primidone *(BAN, rINN)*

Desoxifenobarbitona; Hexamidinum; Primaclona; Primaclone; Primidon; Primidona; Primidonas; Primidoni; Primidonum; Prymidon. 5-Ethyl-5-phenylperhydropyrimidine-4,6-dione.

Примидон

$C_{12}H_{14}N_2O_2$ = 218.3.

CAS — 125-33-7.

ATC — N03AA03.

ATC Vet — QN03AA03.

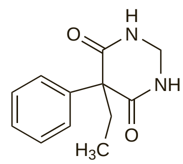

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Primidone). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in alkaline solutions.

USP 31 (Primidone). A white, odourless, crystalline powder. Soluble 1 in 2000 of water and 1 in 200 of alcohol; very slightly soluble in most organic solvents.

Adverse Effects, Treatment, and Precautions

As for Phenobarbital, p.492.

Adverse effects may be more frequent than with phenobarbital. Most patients rapidly develop tolerance to the adverse effects of primidone, including ataxia, dizziness, drowsiness, headache, nausea and vomiting, nystagmus, skin rashes, and visual disturbances.

Care is required when withdrawing primidone therapy—see also Uses and Administration, below.

Effects on the blood. For a report of delayed agranulocytosis in a patient treated with phenytoin and primidone, see p.495.

Effects on the endocrine system. For mention of the effects of antiepileptics on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

Overdosage. Crystalluria has been reported[1] after acute overdosage of primidone and 7 other reported cases were also reviewed. Based on these few reports, crystalluria appears to be associated with serum-primidone concentrations in excess of 80 micrograms/mL. There is evidence from 2 reports of renal damage associated with crystal formation *in vivo*. Vigorous hydration is recommended in patients at risk, in order to lessen the potential for renal toxicity and improve elimination.

1. Lehmann DF. Primidone crystalluria following overdose: a report of a case and an analysis of the literature. *Med Toxicol* 1987; **2:** 383–7.

Porphyria. Primidone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Tremor. It was noted that patients receiving primidone for essential tremor have a high incidence of acute adverse reactions after small initial doses.[1] This could be due to the absence of induced hepatic enzymes in these patients previously not exposed to antiepileptics.

1. Findley LJ, *et al.* Primidone in essential tremor of the hands and head: a double blind controlled clinical study. *J Neurol Neurosurg Psychiatry* 1985; **48:** 911–15.

Interactions

Primidone is metabolised in the body in part to phenobarbital, and interactions recorded for phenobarbital (p.493) might potentially occur in patients receiving primidone. In addition, enzyme-inducing drugs enhance this metabolism and have the potential to produce elevated phenobarbital concentrations.

Antiepileptics. Both *phenytoin*[1] and *carbamazepine*[2] have been reported to enhance the metabolism of primidone to phenobarbital and when primidone was combined with phenytoin there have been instances of phenobarbital toxicity.[3] *Vigabatrin* has been reported[4] to lower plasma concentrations of primidone in some patients, although it is unlikely that dosage changes would be necessary. *Valproate* may increase plasma concentrations of primidone and phenobarbital, but patient response seems to be inconsistent.[5-7]

1. Reynolds EH, *et al.* Interaction of phenytoin and primidone. *BMJ* 1975; **2:** 594–5.
2. Baciewicz AM. Carbamazepine drug interactions. *Ther Drug Monit* 1986; **8:** 305–17.
3. Galdames D, *et al.* Interacción fenitoína-primidona: intoxicación por fenobarbital, en un adulto tratado con ambas drogas. *Rev Med Chil* 1980; **108:** 716–20.
4. Browne TR, *et al.* A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* 1989; **27** (suppl 1): 95S–100S.
5. Windorfer A, *et al.* Elevation of diphenylhydantoin and primidone serum concentration by addition of dipropylacetate, a new anticonvulsant drug. *Acta Paediatr Scand* 1975; **64:** 771–2.
6. Bruni J. Valproic acid and plasma levels of primidone and derived phenobarbital. *Can J Neurol Sci* 1981; **8:** 91–2.
7. Yukawa E, *et al.* The effect of concurrent administration of sodium valproate on serum levels of primidone and its metabolite phenobarbital. *J Clin Pharm Ther* 1989; **14:** 387–92.

Pharmacokinetics

Primidone is readily absorbed from the gastrointestinal tract and is reported to have a plasma half-life ranging from 10 to 15 hours, which is shorter than those of its principal metabolites phenylethylmalonamide and phenobarbital, both of which are active. Therapeutic plasma concentrations of primidone have been suggested to be between 5 and 12 micrograms/mL. It is excreted in urine as unchanged drug (40%) and metabolites.

Primidone is widely distributed but is only partially bound to plasma proteins; it has been suggested that it exhibits variable binding of up to about 20%. It crosses the placenta and is distributed into breast milk.

The pharmacokinetics of primidone may be affected by use with other antiepileptics (see under Interactions, above).

Uses and Administration

Primidone is an antiepileptic that is partially metabolised to phenobarbital (p.494), but is also considered to have some antiepileptic activity in its own right. It may be given to control partial and generalised tonic-clonic seizures. Primidone is also used in the management of essential tremor.

In the treatment of **epilepsy** the dose of primidone should be adjusted according to response; a limited correlation with plasma concentrations has suggested that concentrations of 5 to 12 micrograms/mL (23 to 55 micromoles/litre) are usually necessary, but the *BNF* recommends monitoring of phenobarbital concentrations instead.

Recommended initial oral doses in the UK are 125 mg at bedtime increased, if necessary, by 125 mg every 3 days to a total of 500 mg daily given in 2 divided doses. If necessary, the daily dose may be increased further every 3 days by 250 mg up to a maximum of 1.5 g daily given in divided doses. Usual maintenance doses are 0.75 to 1.5 g daily; maintenance doses are usually given as 2 divided doses. Dosage recommendations in the USA are generally similar although a maximum daily dose of 2 g is permitted.

For doses in children, see below.

As with other antiepileptics, withdrawal of primidone or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

For **essential tremor** primidone is usually started at daily oral doses of 50 mg as the syrup or 62.5 mg as the tablet, increased gradually over 2 to 3 weeks if necessary, to a maximum of 750 mg daily.

Administration in children. Children may be given primidone to control partial and generalised tonic-clonic seizures. Recommended initial oral doses in the UK are 125 mg at bedtime, increased if necessary, by 125 mg every 3 days to the following usual maintenance daily doses (given in 2 divided doses) according to age:

- up to 2 years: 250 to 500 mg
- 2 to 5 years: 500 to 750 mg
- 6 to 9 years: 750 to 1000 mg

Children aged over 9 years may be given the usual adult dose (see above).

In the USA, a lower initial oral dose of 50 mg daily is recommended. This is doubled every 3 days, to reach a maintenance dose of 125 to 250 mg 3 times daily (10 to 25 mg/kg daily in divided doses) after 10 or more days. Children over 8 years of age may be given the usual adult dose as above.

Epilepsy. Primidone, like its metabolite phenobarbital, is used in the treatment of epilepsy (p.465) for partial seizures with or

The symbol † denotes a preparation no longer actively marketed

without secondary generalisation and for primary generalised tonic-clonic seizures. However, because of problems of sedation, it is usually reserved for use in cases unresponsive to other antiepileptics. It has been suggested that it may be suitable for use in patients with QT-interval prolongation.[1]

1. Christidis D, *et al.* Is primidone the drug of choice for epileptic patients with QT-prolongation? A comprehensive analysis of literature. *Seizure* 2006; **15:** 64–6.

Neonatal apnoea. Results from a preliminary study suggested that adjunctive treatment with primidone[1] might be of value in neonatal apnoea resistant to first-line therapy with xanthines alone, but subsequent confirmatory studies seem to be lacking.

1. Miller CA, *et al.* The use of primidone in neonates with theophylline-resistant apnea. *Am J Dis Child* 1993; **147:** 183–6.

Neonatal seizures. Primidone has been tried in the management of neonatal seizures (p.471).

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231) but primidone[1] may also be tried. A high incidence of acute adverse reactions has been reported after initial doses (see Tremor, under Adverse Effects, above). There has been concern that long-term use may produce tolerance to primidone's effects, although a small study has found a reduced response in only a few patients.[2] A later study[3] found a dose of 250 mg daily to be as or more effective than 750 mg daily without there being evidence of loss of efficacy during a 12-month follow-up.

1. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
2. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13:** 67–76.
3. Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor: double-blind comparative study with one-year follow-up. *Parkinsonism Relat Disord* 2003; **10:** 29–33.

Preparations

BP 2008: Primidone Oral Suspension; Primidone Tablets;
USP 31: Primidone Oral Suspension; Primidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Mysoline; ***Austral.:*** Mysoline; ***Austria:*** Cyral; Mysoline; ***Belg.:*** Mysoline†; ***Braz.:*** Epidona†; Mysoline; ***Canad.:*** Mysoline†; ***Chile:*** Mysoline†; ***Cz.:*** Liskantin; ***Denm.:*** Mysoline†; ***Fin.:*** Mysoline†; ***Fr.:*** Mysoline†; ***Ger.:*** Liskantin; Mylepsinum; Resimatil; ***Gr.:*** Mysoline; ***Hung.:*** Sertan; ***India:*** Mysoline†; ***Irl.:*** Mysoline; ***Israel:*** Prysoline; ***Ital.:*** Mysoline; ***Mex.:*** Mysoline; ***Neth.:*** Mysoline; ***Norw.:*** Mysoline†; ***Pol.:*** Mizodin; ***Port.:*** Mysoline; ***Rus.:*** Hexamidin (Гексамидин); ***S.Afr.:*** Mysoline; ***Spain:*** Mysoline; ***Swed.:*** Mysoline†; ***Switz.:*** Mysoline; ***Turk.:*** Mysoline; ***UK:*** Mysoline; ***USA:*** Mysoline; ***Venez.:*** Mutigan†.

Multi-ingredient: ***Cz.:*** Mysoline†.

Rufinamide *(BAN, USAN, rINN)*

60231/4; CGP-33101; E-2080; RUF-331; Rufinamida; Rufinamidum. 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.

Руфинамид

$C_{10}H_8F_2N_4O$ = 238.2.
CAS — 106308-44-5.
ATC — N03AF03.
ATC Vet — QN03AF03.

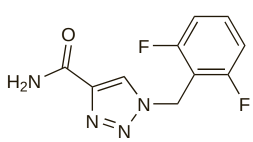

Adverse Effects and Precautions

The most common adverse effects with rufinamide include headache, dizziness, fatigue, somnolence, nausea, and vomiting. Other reported adverse effects include anorexia, weight loss, anxiety, insomnia, vertigo, nystagmus, tremor, dyspepsia, constipation, and diarrhoea. Convulsions, including status epilepticus, have occurred. Lymphadenopathy, abnormal liver function tests, and haematuria, as well as fever and rash, have been reported as part of a hypersensitivity syndrome.

Rufinamide can reduce the QT interval and should be used with caution in those with a shortening of their QT interval or with a family history of congenital short QT syndrome.

Care is required when withdrawing rufinamide therapy—see Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Rufinamide plasma concentrations are reportedly decreased by carbamazepine, phenobarbital, phenytoin, vigabatrin, or primidone. In contrast, significant increases in rufinamide plasma concentrations can occur with valproate and dosage adjustments may be necessary (see Uses and Administration, below).

Rufinamide induces the cytochrome P450 isoenzyme CYP3A4 and may be expected to decrease plasma concentrations of drugs metabolised by this route, such as oral contraceptives. Rufinamide reportedly increases steady-state plasma concentrations of phenytoin.

Pharmacokinetics

Rufinamide is well absorbed after oral doses; peak plasma concentrations are reached after about 6 hours. Food increases the bioavailability of rufinamide by about 34 to 40%. It is 34% bound to serum proteins, mainly to albumin.

Rufinamide is hydrolysed to an inactive metabolite and has a plasma elimination half-life of about 6 to 10 hours, although clearance in children is reported to be slower. It is mainly excreted in urine as the inactive metabolite.

◊ References

1. Cardot JM, *et al.* The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. *Biopharm Drug Dispos* 1998; **19:** 259–62.

Uses and Administration

Rufinamide is an antiepileptic used as an adjunct in the treatment of seizures associated with the Lennox-Gastaut syndrome (p.465) in patients aged 4 years and over. Rufinamide is given orally in 2 divided doses daily with food. The initial daily dose in patients weighing less than 30 kg is 200 mg, increased according to response in increments of 200 mg every 2 days to a usual maximum of 1 g daily; the recommended maximum dose in those taking *valproate* is 600 mg daily. In patients weighing more than 30 kg, the initial daily dose is 400 mg, increased according to response in increments of 400 mg every 2 days to a maximum daily dose of 1.8 g in those weighing up to 50 kg, 2.4 g in those weighing up to 70 kg, and 3.2 g in those over 70 kg.

As with other antiepileptics, withdrawal of rufinamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose by about 25% every 2 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Rufinamide has also been investigated as adjunctive therapy in the treatment of partial and primary generalised tonic-clonic seizures.

◊ References.

1. Jain KK. An assessment of rufinamide as an anti-epileptic in comparison with other drugs in clinical development. *Expert Opin Invest Drugs* 2000; **9:** 829–40.
2. Pålhagen S, *et al.* Rufinamide: a double-blind, placebo-controlled proof of principle trial in patients with epilepsy. *Epilepsy Res* 2001; **43:** 115–24.
3. Deeks ED, *et al.* Rufinamide. *CNS Drugs* 2006; **20:** 751–60.
4. Cheng-Hakimian A, *et al.* Rufinamide: pharmacology, clinical trials, and role in clinical practice. *Int J Clin Pract* 2006; **60:** 1497–501.
5. Glauser T, *et al.* Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; **70:** 1950–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Inovelon; ***Port.:*** Inovelon; ***UK:*** Inovelon.

Stiripentol *(USAN, rINN)*

BCX-2600; Estiripentol; Stiripentolum. 4,4-Dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol.

Стирипентол

$C_{14}H_{18}O_3$ = 234.3.
CAS — 49763-96-4.
ATC — N03AX17.
ATC Vet — QN03AX17.

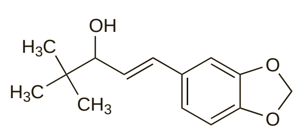

Adverse Effects and Precautions

The most common adverse effects of stiripentol include anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia, and dystonia. Other common adverse effects include nausea, vomiting, and aggressiveness, and other mood or behavioural disorders. Neutropenia is also reported to be common; persistent severe neutropenia usually resolves spontaneously when stiripentol is stopped. Photosensitivity, rash, and urticaria have occurred. Patients may exhibit altered liver enzyme values.

Growth rates, blood counts, and hepatic function should be monitored periodically in patients given stiripentol.

Interactions

Stiripentol is a potent inhibitor of several cytochrome P450 isoenzymes, including CYP1A2, CYP2C19, and CYP3A4, and may markedly reduce clearance of drugs metabolised by these enzymes. The possibility of an effect on stiripentol metabolism by other inhibitors or inducers of these enzymes should also be borne in mind.

For interactions of stiripentol with other antiepileptics, see under Carbamazepine, p.474, Diazepam, p.990, and Phenytoin, p.498.

Uses and Administration

Stiripentol is used with clobazam and valproate as adjunctive therapy in the treatment of refractory generalised tonic-clonic seizures in severe myoclonic epilepsy in infancy. It is thought to be less potent than some conventional antiepileptics, but may reduce their adverse effects when used adjunctively.

Stiripentol is given orally and should be started at a low dose, gradually increased over 3 days, to the recommended dose of 50 mg/kg daily given in 2 or 3 divided doses with food (but not with dairy products, carbonated drinks, fruit juice, or food and drinks that contain caffeine or theophylline). After starting adjunctive stiripentol therapy, the daily dose of clobazam may be reduced by 25% every week if there are signs of adverse effects or overdosage with clobazam. The daily dose of valproate is not usually adjusted, however, it may be reduced by 30% every week if there are signs of gastrointestinal adverse effects.

Epilepsy. A 24-week study[1] in 10 children found that stiripentol might be effective as adjunctive therapy for the treatment of atypical absence seizures (p.465). Further studies suggested benefit from adjunctive use in children with partial epilepsy[2] and severe myoclonic epilepsy.[2-4]

1. Farwell JR, *et al.* Stiripentol in atypical absence seizures in children: an open trial. *Epilepsia* 1993; **34:** 305–11.
2. Perez J, *et al.* Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; **40:** 1618–26.
3. Chiron C, *et al.* Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet* 2000; **356:** 1638–42.
4. Chiron C. Stiripentol. *Expert Opin Invest Drugs* 2005; **14:** 905–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Diacomit; ***Fr.:*** Diacomit; ***Port.:*** Diacomit.

Sultiame *(BAN, rINN)*

Riker-594; Sulthiame *(USAN)*; Sultiaami; Sultiam; Sultiamo; Sultiamum. 4-(Tetrahydro-2*H*-1,2-thiazin-2-yl)benzenesulphonamide *S,S*-dioxide.

Сультиам

$C_{10}H_{14}N_2O_4S_2$ = 290.4.
CAS — 61-56-3.
ATC — N03AX03.
ATC Vet — QN03AX03.

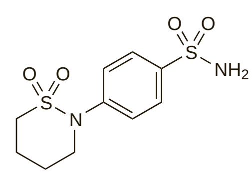

Pharmacopoeias. In *Jpn.*

Profile

Sultiame is a carbonic anhydrase inhibitor that has been used as an antiepileptic in most forms of epilepsy (p.465) except absence seizures. It has usually been given with other antiepileptics and it is believed that much of its activity is due to the inhibition of metabolism of the other drugs.

Sultiame has been given orally in initial doses of 100 mg twice daily or 50 mg three times daily gradually increased according to response to 200 mg three times daily. A dose of 5 to 10 mg/kg daily, adjusted according to response, has been recommended in Rolandic epilepsy.

Interactions. For the effect of sultiame on *phenytoin*, see p.498.

Porphyria. Sultiame has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ospolot; ***Austral.:*** Ospolot; ***Austria:*** Ospolot; ***Cz.:*** Ospolot; ***Ger.:*** Ospolot; ***Gr.:*** Ospolot; ***Hung.:*** Ospolot; ***Israel:*** Ospolot; ***Switz.:*** Ospolot.

Tiagabine Hydrochloride

(BANM, USAN, rINNM)

Abbott-70569.1; ABT-569; Hidrocloruro de tiagabina; NNC-05-0328; NO-05-0328; Tiagabine, Chlorhydrate de; Tiagabini Hydrochloridum. (–)-(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-nipecotic acid hydrochloride.

Тиагабина Гидрохлорид

$C_{20}H_{25}NO_2S_2,HCl = 412.0.$

CAS — 115103-54-3 (tiagabine); 145821-59-6 (tiagabine hydrochloride).

ATC — N03AG06.

ATC Vet — QN03AG06.

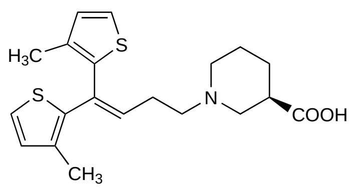

(tiagabine)

Pharmacopoeias. In *US.*

USP 31 (Tiagabine Hydrochloride). A white to off-white powder. Sparingly soluble in water; freely soluble in alcohol and methyl alcohol; soluble in isopropyl alcohol; very slightly soluble in chloroform; practically insoluble in *n*-heptane. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Stability. An extemporaneously prepared suspension containing tiagabine hydrochloride 1 mg/mL in a mixture of simple syrup and 1% methylcellulose was found,[1] when stored in plastic amber bottles, to be stable for 6 weeks at 25° or 13 weeks at 4°. When prepared in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*), the suspension was stable for 10 weeks at 25° or 13 weeks at 4°.

1. Nahata MC, Morosco RS. Stability of tiagabine in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 75–7.

Adverse Effects

The most common adverse effects include dizziness, nervousness, tiredness, somnolence, and tremor. Other reported adverse effects include irritability, confusion, depression, psychosis, difficulties in concentration, diarrhoea, abdominal pain, nausea, ataxia, emotional lability, and nystagmus. Bruising, rashes, speech difficulties, and a flu-like syndrome of chills, fever, myalgia, and headache have also been reported. Visual field defects have been reported rarely and decreased white blood cell counts have been noted at routine screenings.

Incidence of adverse effects. A systematic review[1] considered 5 double-blind studies involving about 1000 patients of whom 675 were receiving tiagabine as adjunctive therapy for refractory partial seizures. Withdrawal due to adverse effects was infrequent and occurred in 15% of patients receiving tiagabine compared with 5% receiving placebo. Adverse effects were usually associated with dose titration, and were generally mild to moderate in severity, and transient. Another review[2] by the same author on data from all clinical studies (52 studies involving nearly 3100 patients) reported that in 21% of patients receiving tiagabine had the drug stopped for adverse effects, mostly during the first 6 months of therapy. Sub-analysis showed that figures for placebo-controlled, adjunctive studies were similar to those of the earlier review.

1. Leppik IE. Tiagabine: the safety landscape. *Epilepsia* 1995; **36** (suppl 6): S10–S13.
2. Leppik IE, *et al.* Safety of tiagabine: summary of 53 trials. *Epilepsy Res* 1999; **33:** 235–46.

Effects on the eyes. Unlike vigabatrin, which is associated with visual field defects (see p.513), studies of visual function in patients taking tiagabine, another GABAergic antiepileptic, have been generally reassuring. However, in a case report[1] a 39-year-old patient was noted to have visual field defects while receiving long-term tiagabine therapy for bipolar disorder. The defects reversed after tiagabine was withdrawn.

1. Kaufman KR, *et al.* Visual fields and tiagabine: a quandary. *Seizure* 2001; **10:** 525–9.

Effects on mental function. For a review of the effects of antiepileptic therapy on *cognition*, and the effects of tiagabine on *mood* (including the risk of suicidal ideation) see p.468.

Effects on the nervous system. Acute dystonic reactions occurred in 3 patients when tiagabine was added to their existing carbamazepine treatment;[1] the reactions were associated with an increase in the dose of tiagabine to 20 mg or more. In all cases the dystonias disappeared despite continuing tiagabine therapy at the same dose, although in one patient carbamazepine was withdrawn.

There have been case reports of nonconvulsive status epilepticus,[2-4] associated with tiagabine. The authors of one such report[2] noted that, in placebo-controlled studies, the incidence of such an event was no higher in the tiagabine group than in the placebo group. However, a retrospective analysis[5] of inpatients with refractory localised epilepsy found that non convulsive status epilepticus occurred more frequently in patients treated with tiagabine (6.7%) than in those who were not (1.1%).

The FDA has warned of the risk of seizures with tiagabine when used in *non-epileptic patients* for unlicensed indications;[6] it had received over 30 reports of new-onset seizures or status epilepticus in such patients. Predisposing factors may include the use of other drugs known to lower the seizure threshold, and probably the dose. Although some cases were noted after doses as low as 4 mg daily, licensed doses in patients with epilepsy take into account the customary use of other enzyme-inducing antiepileptics which can roughly halve the plasma levels of tiagabine by inducing its metabolism. For reports of status epilepticus occurring in non-epileptic patients after tiagabine overdosage, see below.

1. Wolańczyk T, Grabowska-Grzyb A. Transient dystonias in three patients treated with tiagabine. *Epilepsia* 2001; **42:** 944–6.
2. Fitzek S, *et al.* Drug-induced nonconvulsive status epilepticus with low dose of tiagabine. *Epileptic Disord* 2001; **3:** 147–50.
3. Skardoutsou A, *et al.* Non-convulsive status epilepticus associated with tiagabine therapy in children. *Seizure* 2003; **12:** 599–601.
4. Vinton A, *et al.* Tiagabine-induced generalised non convulsive status epilepticus in patients with lesional focal epilepsy. *J Clin Neurosci* 2005; **12:** 128–33.
5. Koepp MJ, *et al.* Status epilepticus and tiagabine therapy revisited. *Epilepsia* 2005; **46:** 1625–32.
6. Food and Drug Administration. Tiagabine hydrochloride (marketed as Gabitril): seizures in patients without epilepsy (issued 18/02/05). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/TiagabineHCP.pdf (accessed 09/06/08)

Overdosage. A 30-year-old man who took 320 mg of tiagabine in overdose together with 400 mg of phenytoin showed no serious signs of toxicity other than significantly depressed levels of consciousness from which he quickly recovered.[1] Plasma concentrations of tiagabine measured 4 hours after ingestion were 30 times higher than those seen with therapeutic doses; phenytoin concentrations just exceeded the therapeutic range. A 46-year-old woman[2] who ingested about 72 mg of tiagabine exhibited facial grimacing, rigid flexure posturing of the upper extremities, and dilated pupils. She was uncommunicative and unresponsive to commands. Treatment with benzodiazepines was given, and symptoms resolved within 12 hours of admission.

Seizures, including status epilepticus, are a recognised adverse effect of tiagabine (see above); there have been reports of status epilepticus occurring in non-epileptic patients after overdosage, including non convulsive status epilepticus[3] in a 14-year-old girl who took about 180 mg of tiagabine, and myoclonic status epilepticus[4] in an 18-year-old man who took 120 mg of tiagabine with 400 mg of lamotrigine.

A retrospective review[5] of 57 overdoses with tiagabine reported to several poison centres in the USA found that the most common adverse effects were lethargy (in 56%), seizures (37%, including status epilepticus in 5%), agitation (32%), confusion (30%), and coma (28%). Other adverse effects included tachycardia, respiratory depression, tremor, and hallucinations; no deaths were reported. The mean onset and duration of symptoms were 1.3 and 9.1 hours, respectively. The lowest dose associated with seizures was 96 mg.

1. Leach JP, *et al.* Deliberate overdose with the novel anticonvulsant tiagabine. *Seizure* 1995; **4:** 155–7.
2. Cantrell FL, *et al.* Intentional overdose with tiagabine: an unusual clinical presentation. *J Emerg Med* 2004; **27:** 271–2.
3. Jette N, *et al.* Tiagabine-induced nonconvulsive status epilepticus in an adolescent without epilepsy. *Neurology* 2006; **67:** 1514–15.
4. Vollmar C, Noachtar S. Tiagabine-induced myoclonic status epilepticus in a nonepileptic patient. *Neurology* 2007; **68:** 310.
5. Spiller HA, *et al.* Retrospective evaluation of tiagabine overdose. *Clin Toxicol* 2005; **43:** 855–9.

Precautions

Hepatic metabolism of tiagabine is reduced in patients with hepatic impairment, and dosage should therefore be reduced and/or the intervals between doses increased. It should not be used in patients with severely impaired hepatic function.

Use of tiagabine in non-epileptic patients may be associated with an increased risk of seizures— see Effects on the Nervous System, above.

Care is required when withdrawing tiagabine therapy—see Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For comment on antiepileptic drugs and driving, see p.468.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. The hepatic metabolism of tiagabine is accelerated by antiepileptics that induce enzymes of the cytochrome P450 system such as carbamazepine, phenobarbital, phenytoin, or primidone. Plasma concentrations of tiagabine may be reduced up to threefold by use with these drugs.

Pharmacokinetics

Tiagabine is readily absorbed after oral doses, with a bioavailability of 89%. Food reduces the rate but not the extent of absorption. The absorption and elimination pharmacokinetics of tiagabine are linear within the therapeutic dosage range.

Tiagabine is widely distributed throughout the body and plasma protein binding is 96%.

Tiagabine is extensively metabolised in the liver and excreted as metabolites in the faeces or, to a lesser extent, in the urine; less than 2% of a dose is eliminated as unchanged drug. The plasma-elimination half-life is 7 to 9 hours, although this may be reduced to 2 to 3 hours by liver enzyme-inducing drugs (see also Interactions, above).

◊ References.

1. Gustavson LE, Mengel HB. Pharmacokinetics of tiagabine, a γ-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiples doses. *Epilepsia* 1995; **36:** 605–11.
2. So EL, *et al.* Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. *Epilepsy Res* 1995; **22:** 221–6.
3. Snel S, *et al.* The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. *J Clin Pharmacol* 1997; **37:** 1015–20.
4. Cato A, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of tiagabine. *Epilepsia* 1998; **39:** 43–7.
5. Samara EE, *et al.* Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. *Epilepsia* 1998; **39:** 868–73.

Uses and Administration

Tiagabine is a nipecotic acid derivative used in the treatment of epilepsy (p.465) as adjunctive therapy for refractory partial seizures with or without secondary generalisation. It inhibits the uptake of GABA into neuronal and glial cells, and therefore increases the availability of GABA at receptor sites.

UK licensing information states that tiagabine hydrochloride is given as the monohydrate, but doses are described in terms of tiagabine; dose forms providing the equivalent of 5, 10, and 15 mg of tiagabine are available. In the USA, however, the licensed product is stated to contain anhydrous tiagabine hydrochloride, and doses are described in terms of this substance; dose forms providing 2, 4, 12, and 16 mg are available. As a result, the doses in the UK and US literature may not be directly comparable.

In the UK, the initial oral daily dose as adjunctive therapy in adults and children over 12 years of age is the equivalent of tiagabine 5 to 10 mg as a single dose or in 2 divided doses, increased weekly as necessary by increments of 5 to 10 mg. The usual maintenance dose is 30 to 45 mg daily, in 2 or 3 divided doses, in patients receiving enzyme-inducing antiepileptics; in patients *not* taking enzyme-inducing drugs an initial maintenance dosage of 15 to 30 mg daily is suggested. Lower initial doses of the hydrochloride are recommended in the USA. Doses should be taken with food to avoid rapid rises in plasma concentrations, thereby reducing the incidence of adverse effects. Reduced doses should be given in hepatic impairment—see below.

As with other antiepileptics, withdrawal of tiagabine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends gradual withdrawal over a period of 2 to 3 weeks. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Administration in hepatic impairment. The initial daily maintenance dosage of tiagabine in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9) should be reduced to 5 to 10 mg given as a single dose or in 2 divided doses. Tiagabine should not be given to patients with severe hepatic impairment.

Epilepsy. Tiagabine is one of a number of drugs that may be used as adjunctive therapy in patients with partial seizures (with or without secondary generalisation) refractory to standard treatment (p.465). It appears to be reasonably well tolerated. For the suggestion that it might be tried in refractory status epilepticus, see p.469.

References.

1. Leach JP, Brodie MJ. Tiagabine. *Lancet* 1998; **351:** 203–7.
2. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. *Drugs* 1998; **55:** 437–60.
3. Luer MS, Rhoney DH. Tiagabine: a novel antiepileptic drug. *Ann Pharmacother* 1998; **32:** 1173–80.
4. Loiseau P. Review of controlled trials of gabitril (tiagabine): a clinician's viewpoint. *Epilepsia* 1999; **40** (suppl 9): S14–S19.
5. Anonymous. Tiagabine: add-on treatment for partial seizures. *Drug Ther Bull* 2000; **38:** 47–8.
6. Dodrill CB, *et al.* Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000; **42:** 123–32.
7. Crawford P, *et al.* Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001; **42:** 531–8.
8. Biraben A, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001; **3:** 91–100.
9. Pereira J, *et al.* Tiagabine add-on for drug-resistant partial epilepsy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 09/06/08).
10. Arroyo S, *et al.* A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy. *Seizure* 2005; **14:** 81–4.

Pain. Antiepileptics are among the drugs used to manage pain (see Choice of Analgesic, p.2); tiagabine has been tried in chronic pain[1] and was found to be effective.

1. Todorov AA, *et al.* Tiagabine and gabapentin for the management of chronic pain. *Clin J Pain* 2005; **21:** 358–61.

Psychiatric disorders. Tiagabine has been tried for the treatment of *generalised anxiety disorder*[1,2] (p.952) and *major depressive disorder* with anxiety[3] (p.373), with variable results. It has also been tried in *post-traumatic stress disorder* (p.953) with some success in a case series[4] and a small open-label study[5] although a later multicentre placebo-controlled study[6] found no significant difference between tiagabine and placebo; further studies are considered warranted. A preliminary study[7] suggested that tiagabine may be effective and generally well tolerated as augmentation therapy in patients with anxiety disorders.

References.

1. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003; **64:** 1245–9.
2. Pollack MH, *et al.* The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 1401–8.
3. Carpenter LL, *et al.* Open-label tiagabine monotherapy for major depressive disorder with anxiety. *J Clin Psychiatry* 2006; **67:** 66–71.
4. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry* 2003; **64:** 1421–5.
5. Connor KM, *et al.* Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006; **184:** 21–5.
6. Davidson JRT, *et al.* The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007; **27:** 85–8.
7. Schwartz TL, *et al.* An open-label study of tiagabine as augmentation therapy for anxiety. *Ann Clin Psychiatry* 2005; **17:** 167–72.

Stiff-man syndrome. There have been anecdotal reports[1] of improvement of stiff-man syndrome (see under Muscle Spasm in Uses of Diazepam, p.993) with tiagabine in patients unable to tolerate benzodiazepine therapy.

1. Murinson BB, Rizzo M. Improvement of stiff-person syndrome with tiagabine. *Neurology* 2001; **57:** 366.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Gabitril; ***Austria:*** Gabitril; ***Belg.:*** Gabitril; ***Cz.:*** Gabitril; ***Denm.:*** Gabitril; ***Fin.:*** Gabitril†; ***Fr.:*** Gabitril; ***Ger.:*** Gabitril; ***Gr.:*** Gabitril; ***Hung.:*** Gabitril; ***Irl.:*** Gabitril; ***Ital.:*** Gabitril; ***Mex.:*** Gabatril†; ***Pol.:*** Gabitril; ***Port.:*** Gabitril; ***Spain:*** Gabitril; ***Switz.:*** Gabitril; ***UK:*** Gabitril; ***USA:*** Gabitril.

Topiramate *(BAN, USAN, rINN)*

KW-6485; McN-4853; RWJ-17021; Topiramaatti; Topiramat; Topiramato; Topiramatum. 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulphamate.

Топирамат

$C_{12}H_{21}NO_8S = 339.4.$

CAS — 97240-79-4.

ATC — N03AX11.

ATC Vet — QN03AX11.

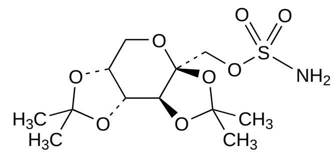

Pharmacopoeias. In *US.*

USP 31 (Topiramate). A white to off-white powder. Freely soluble in dichloromethane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

Effects on bone. For the effects of antiepileptics, including topiramate, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on electrolytes. Metabolic acidosis has been associated with topiramate treatment. Data from clinical trials estimate that the incidence of persistently decreased serum bicarbonate concentrations ranges from 23 to 67% with topiramate compared with 1 to 10% with placebo;[1] children, in particular, may be at a greater risk than adults.[1,2] A retrospective cohort study also found that 48% of adult patients developed decreased serum bicarbonate concentrations while receiving topiramate.[3] Generally, the decreases in serum bicarbonate are mild to moderate and occur soon after starting topiramate. Clinical signs such as hyperventilation may develop.

Some sources such as the US licensed product information recommend that baseline and periodic serum bicarbonate levels should be monitored during topiramate treatment. If metabolic acidosis develops or persists, it may be necessary to reduce the dose or stop topiramate although, in some cases, correcting the acidosis with alkali therapy may be more appropriate.

1. Janssen-Ortho Canada. Important drug safety information: Topamax (topiramate) use is associated with metabolic acidosis (issued 12/01/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/topamax_3_hpc-cps-eng.pdf (accessed 01/09/08)
2. Philippi H, *et al.* Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia* 2002; **43:** 744–7.
3. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. *Ann Pharmacother* 2005; **39:** 424–6.

Effects on the eyes. There have been rare reports of acute myopia with or without secondary angle-closure glaucoma in adults and children receiving topiramate:[1-3] as of April 2002 the UK CSM was aware of 23 cases worldwide occurring with secondary angle-closure glaucoma.[4] Symptoms include decreased visual acuity and ocular pain which generally appear within one month of starting treatment; hyperaemia and raised intra-ocular pressure may be present with or without mydriasis. Choroidal effusions resulting in anterior displacement of lens and iris have been reported. Appropriate measures to reduce intra-ocular pressure should be taken, and topiramate stopped as rapidly as is clinically feasible.[4] A later review[5] of 115 reports of ocular adverse effects associated with topiramate described 83 cases of bilateral and 3 cases of unilateral acute angle-closure glaucoma; of these, 7 sustained permanent loss of vision. Onset of glaucoma was between 1 and 49 days after starting topiramate therapy, with 85% of cases occurring within the first 2 weeks. Also reported were cases of acute bilateral myopia (17 patients), suprachoroidal effusions (9), scleritis (4), blepharospasm (2), oculogyric crisis (2), and myokymia (1). Diplopia and nystagmus were reported with daily doses of at least 200 to 400 mg topiramate.

1. Gubbay SS. The occurrence of drug-induced myopia as a transient side effect of topiramate. *Epilepsia* 1998; **39:** 451.
2. Sen HA, *et al.* Topiramate-induced acute myopia and retinal striae. *Arch Ophthalmol* 2001; **119:** 775–7.
3. Rhee DJ, *et al.* Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001; **119:** 1721–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Topiramate (Topamax): acute myopia and raised intraocular pressure. *Current Problems* 2002; **28:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
5. Fraunfelder FW, *et al.* Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; **111:** 109–11.

Effects on the liver. For reports of hepatotoxicity associated with the addition of topiramate to therapy with carbamazepine or valproate see Interactions, Antiepileptics, on p.474 and p.511 respectively.

Effects on mental function. For a review of the effects of antiepileptic therapy including topiramate on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

Effects on the nervous system. Hyperthermia was reported in 10.5% of patients taking topiramate compared with 0.15% of patients taking other antiepileptic drugs in one centre.[1] Children under the age of 6 years, patients on daily doses of 6 mg/kg or more, and those exposed to high ambient temperatures were most at risk. Licensed product information recommends that children should be monitored closely for decreased sweating and hyperthermia, especially during warm or hot weather. Caution is also advised when giving topiramate with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.

Hemiparesis that resolved on withdrawal of topiramate has been reported[2] in 2 patients, although both already had compromised neurological function.

1. Ziad EK, *et al.* Age, dose, and environmental temperature are risk factors for topiramate-related hyperthermia. *Neurology* 2005; **65:** 1139–40.
2. Stephen LJ, *et al.* Transient hemiparesis with topiramate. *BMJ* 1999; **318:** 845.

Effects on sexual function. Topiramate has been associated with sexual dysfunction[1,2] in male and female patients; in all cases symptoms resolved with dosage reduction or withdrawal of the drug.

1. Holtkamp M, *et al.* Erectile dysfunction with topiramate. *Epilepsia* 2005; **46:** 166–7.
2. Sun C, *et al.* Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. *Headache* 2006; **46:** 1450–3.

Precautions

Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients.

Care is required when withdrawing topiramate therapy—see also Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

◊ References.

1. Bialer M, *et al.* Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* 2004; **43:** 763–80.

Antiepileptics. In pharmacokinetic studies hepatic enzyme inducers such as *carbamazepine*,[1-3] *phenobarbital*,[2] and *phenytoin*[1,2] were reported to decrease the plasma concentration of topiramate.

For the effect of topiramate on phenytoin and carbamazepine, see p.498 and p.474, respectively. For reports of an increased risk of hepatic impairment in patients taking topiramate with valproate, see p.511.

1. Bourgeois BFD. Drug interaction profile of topiramate. *Epilepsia* 1996; **37:** (suppl 2): S14–S17.
2. Contin M, *et al.* Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; **24:** 332–7.
3. Mimrod D, *et al.* A comparative study of the effect of carbamazepine and valproic acid on the pharmacokinetics and metabolic profile of topiramate at steady state in patients with epilepsy. *Epilepsia* 2005; **46:** 1046–54.

Cardiac glycosides. For the effect of topiramate on *digoxin*, see p.1261.

Sex hormones. For the effects of antiepileptics including topiramate on *oral contraceptives*, see p.2068.

Pharmacokinetics

Topiramate is readily absorbed after oral doses, with peak plasma concentrations achieved after about 2 hours. Bioavailability is not affected by the presence of food. Protein binding is about 9 to 17%. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk.

In healthy subjects topiramate is not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme-inducing drugs. It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations are achieved after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not be achieved for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults.

The pharmacokinetics of topiramate may be affected by use with other antiepileptics (see under Interactions, above).

◊ References.

1. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide, and tiagabine. *Clin Pharmacokinet* 1996; **31:** 29–46.
2. Glauser TA, *et al.* Topiramate pharmacokinetics in infants. *Epilepsia* 1999; **40:** 788–91.
3. Öhman I, *et al.* Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. *Epilepsia* 2002; **43:** 1157–60.
4. Ferrari AR, *et al.* Influence of dosage, age, and co-medication on plasma topiramate concentrations in children and adults with severe epilepsy and preliminary observations on correlations with clinical response. *Ther Drug Monit* 2003; **25:** 700–8.
5. Battino D, *et al.* Topiramate pharmacokinetics in children and adults with epilepsy: a case-matched comparison based on therapeutic drug monitoring data. *Clin Pharmacokinet* 2005; **44:** 407–16.

Uses and Administration

Topiramate, a sulfamate-substituted monosaccharide, is an antiepileptic used as adjunctive therapy in refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in patients with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures. Topiramate is also used for the prophylaxis of migraine.

In the UK, for both adjunctive and monotherapy of **epilepsy**, the initial oral dose of topiramate is 25 mg at night for 1 week increased thereafter by increments of 25 or 50 mg at intervals of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for *adjunctive therapy* is 200 to 400 mg although some patients may require up to 800 mg daily. When used as *monotherapy*, usual doses range from 100 mg daily to a maximum of 400 mg daily. Similar target doses are also used in the USA for both adjunctive and monotherapy although higher initial doses of 50 mg daily with weekly increases thereafter are recommended in the licensed product information.

For doses in children, see below.

As with other antiepileptics, withdrawal of topiramate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. The UK product information suggests decreasing the daily dose by 50 to 100 mg at weekly intervals.

In the prophylaxis of **migraine**, topiramate is given orally in initial doses of 25 mg at night for 1 week, increased by 25-mg increments every week, to a usual dose of 50 mg twice daily. UK product information suggests decreasing the daily dose by 25 to 50 mg at weekly intervals when withdrawing topiramate therapy.

Smaller increments or longer intervals between increments may be necessary if patients cannot tolerate the above regimens; US product information suggests that doses should be halved in patients with moderate to severe renal impairment regardless of indication (see also below).

Administration in children. Topiramate is used as adjunctive therapy in children for refractory partial seizures with or without secondary generalisation, seizures associated with the Lennox-Gastaut syndrome, and primary generalised tonic-clonic seizures. It may also be used as monotherapy in those with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures.

In the UK, the initial oral dose for *adjunctive* therapy in children from 2 years of age is 25 mg. This is given as a single dose at night for 1 week, then increased by 1 to 3 mg/kg every 1 to 2 weeks until the effective dose is reached; these higher daily doses are divided and given twice daily. About 5 to 9 mg/kg daily is usually required, although up to 30 mg/kg has been given.

For *monotherapy*, in children from 6 years of age, the initial daily oral dose is 0.5 to 1 mg/kg at night for the first week, increased thereafter by 0.5 to 1 mg/kg every 1 or 2 weeks, to a usual dose of 3 to 6 mg/kg daily in 2 divided doses; up to 16 mg/kg daily has been used.

The adult dose (above) is recommended in those over 16 years of age.

In the USA, licensed doses for adjunctive therapy are similar to those in the UK; however, monotherapy, which is limited to those 10 years of age and over, is given at usual adult doses.

Administration in renal impairment. Patients with moderate to severe renal impairment take longer to reach steady-state plasma concentrations of topiramate than patients with normal renal function (see Pharmacokinetics, above) and the dosage regimen may need adjusting; US licensed product information recommends that usual adult doses (see above) be halved in such patients.

In patients undergoing haemodialysis a supplemental dose equal to about one-half of the daily dose should be given in divided doses (at the start and finish of the procedure).

Alcohol withdrawal and abstinence. Topiramate may be of use as an adjunct in achieving and maintaining abstinence in patients with alcohol dependence[1,2] (p.1626).

1. Johnson BA, *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; **361:** 1677–85.
2. Johnson BA, *et al.* Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; **298:** 1641–51.

Bipolar disorder. Mood-stabilising antiepileptics such as carbamazepine and valproate are alternatives to lithium in the management of bipolar disorder (p.372). Topiramate has also been investigated after favourable case reports,[1,2] but randomised controlled studies[3,4] have produced disappointing results and a systematic review[5] found insufficient evidence for its use as monotherapy or adjunctive therapy.

1. Teter CJ, *et al.* Treatment of affective disorder and obesity with topiramate. *Ann Pharmacother* 2000; **34:** 1262–5.
2. Erfurth A, Kuhn G. Topiramate monotherapy in the maintenance treatment of bipolar I disorder: effects on mood, weight and serum lipids. *Neuropsychobiology* 2000; **42** (suppl 1): 50–1.
3. Kushner SF, *et al.* Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord* 2006; **8:** 15–27.
4. Chengappa KNR, *et al.* Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2006; **67:** 1698–1706.
5. Vasudev K, *et al.* Topiramate for acute affective episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 09/06/08).

Epilepsy. Topiramate is used[1-5] in epilepsy (p.465) for refractory partial seizures, for primary generalised tonic-clonic seizures,[6] and in patients with the Lennox-Gastaut syndrome;[7] in the UK, it may be a first-line option in some circumstances. Starting topiramate therapy gradually improves tolerability without delaying therapeutic response.[8]

Topiramate has also been investigated in children with infantile spasms (as for example in West's syndrome),[9] severe myoclonic epilepsy,[10] and juvenile myoclonic epilepsy;[11] it has been tried as a second-line drug in absence seizures and for tonic or atonic seizures. A retrospective review[12] and later studies[13,14] of the use of topiramate in such drug-resistant childhood epilepsies have concluded that it is efficacious and well tolerated.

Topiramate has also been investigated as an alternative antiepileptic in the management of refractory status epilepticus (p.469).[15,16]

1. Lyseng-Williamson KA, Yang LPH. Topiramate: a review of its use in the treatment of epilepsy. *Drugs* 2007; **67:** 2231–56.
2. Sachdeo RC, *et al.* Topiramate: clinical profile in epilepsy. *Clin Pharmacokinet* 1998; **34:** 335–46.
3. Garnett WR. Clinical pharmacology of topiramate: a review. *Epilepsia* 2000; **41** (suppl 1); S61–S65.
4. Glauser TA, *et al.* Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol* 2007; **22:** 693–9.
5. Jette NJ, *et al.* Topiramate add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 27/08/08).
6. Biton V. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999; **52:** 1330–7.
7. Sachdeo RC, *et al.* A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology* 1999; **52:** 1882–7.
8. Biton V, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001; **35:** 173–9.
9. Glauser TA, *et al.* Long-term response to topiramate in patients with West syndrome. *Epilepsia* 2000; **41** (suppl 1): S91–S94.
10. Nieto-Barrera M, *et al.* Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 2000; **9:** 590–4.
11. Biton V, Bourgeois BFD. Topiramate in patients with juvenile myoclonic epilepsy. *Arch Neurol* 2005; **62:** 1705–8.
12. Yeung S, *et al.* Topiramate for drug-resistant epilepsies. *Eur J Paediatr Neurol* 2000; **4:** 31–3.
13. Al Ajlouni S, *et al.* The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial. *Seizure* 2005; **14:** 459–63.
14. Grosso S, *et al.* Efficacy and safety of topiramate in refractory epilepsy of childhood: long-term follow-up study. *J Child Neurol* 2005; **20:** 893–7.
15. Towne AR, *et al.* The use of topiramate in refractory status epilepticus. *Neurology* 2003; **60:** 332–4.
16. Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. *Epilepsy Behav* 2003; **4:** 757–60.

Headache. Topiramate is used for the prophylaxis of *migraine* (p.616). Results from placebo-controlled studies[1-5] have shown a significant reduction in frequency of migraines in those patients receiving prophylactic topiramate.

Topiramate has been tried for prophylaxis of *cluster headache* attacks[6] (p.616) and chronic *tension-type headache*[7] (p.617). It has also been used to control headache due to *raised intracranial pressure* (see p.1181).

1. Storey JR, *et al.* Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001; **41:** 968–75.
2. Brandes JL, *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291:** 965–73.
3. Silberstein SD, *et al.* Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; **61:** 490–5.
4. Silberstein SD, *et al.* Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; **47:** 170–80.
5. Diener H-C, *et al.* Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; **27:** 814–23.
6. Láinez MJA, *et al.* Topiramate in the prophylactic treatment of cluster headache. *Headache* 2003; **43:** 784–9.
7. Lampl C, *et al.* A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. *Cephalalgia* 2006; **26:** 1203–8.

Hyperhidrosis. Reduced sweating has been associated with topiramate therapy (see Effects on the Nervous System under Adverse Effects, above). There have been 2 case reports[1,2] of the use of topiramate in the treatment of hyperhidrosis.

1. Owen DB, Meffert JJ. The suppression of primary palmar-plantar hyperhidrosis by topiramate. *Br J Dermatol* 2003; **148:** 826–7.
2. Hoehn-Saric R. Facial hyperhidrosis-induced social fear alleviated with topiramate. *J Clin Psychiatry* 2006; **67:** 1157.

Motor neurone disease. Topiramate has been tried as a potential therapy for amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but with disappointing results.[1]

1. Cudkowicz ME, *et al.* A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis. *Neurology* 2003; **61:** 456–64.

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), topiramate has also been tried successfully.[1] It has also been tried[2,3] in the treatment of *diabetic neuropathy* (p.6) and of *phantom limb pain*[4] (p.9).

1. Zvartau-Hind M, *et al.* Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000; **55:** 1587–8.
2. Raskin P, *et al.* Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004; **63:** 865–73.
3. Donofrio PD, *et al.* Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. *Clin Ther* 2005; **27:** 1420–31.
4. Harden RN, *et al.* Topiramate for phantom limb pain: a time-series analysis. *Pain Med* 2005; **6:** 375–8.

Obesity. Weight loss has been associated with topiramate therapy (see Adverse Effects, above) and it has been tried as an adjunct in the treatment of obesity (p.2149) and in overweight patients; topiramate appears to be reasonably well tolerated. It has also been tried in binge eating (see below).

References.

1. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 2004; **12** (suppl): 167S–173S.

2. Kirov G, Tredget J. Add-on topiramate reduces weight in overweight patients with affective disorders: a clinical case series. *BMC Psychiatry* 2005; **5:** 19. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-5-19.pdf (accessed 09/06/08)
3. Khazaal Y, *et al.* Long-term topiramate treatment of psychotropic drug-induced weight gain: a retrospective chart review. *Gen Hosp Psychiatry* 2007; **29:** 446–9.
4. Eliasson B, *et al.* Weight loss and metabolic effects of topiramate in overweight and obese type 2 diabetic patients: randomized double-blind placebo-controlled trial. *Int J Obes* 2007; **31:** 1140–7.

Psychiatric disorders. Topiramate has been tried in several psychiatric disorders, including *schizophrenia*[1] (p.955), *disturbed behaviour*[2] (p.954), *post-traumatic stress disorder*[3] (p.953), and *social anxiety disorder*[4] (see Phobic Disorders, p.953). It has also been tried in *binge eating*.[5-7] For its use in *bipolar disorder* see above.

1. Tiihonen J, *et al.* Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry* 2005; **66:** 1012–15.
2. Nickel MK, *et al.* Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 1515–19.
3. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry* 2004; **4:** 24. Available at: http://www.biomedcentral.com/content/pdf/1471-244X-4-24.pdf (accessed 09/06/08)
4. Van Ameringen M, *et al.* An open trial of topiramate in the treatment of generalized social phobia. *J Clin Psychiatry* 2004; **65:** 1674–8.
5. Nickel C, *et al.* Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 2005; **38:** 295–300.
6. Tata AL, Kockler DR. Topiramate for binge-eating disorder associated with obesity. *Ann Pharmacother* 2006; **40:** 1993–7.
7. Claudino AM, *et al.* Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; **68:** 1324–32.

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231); however, topiramate[1,2] has also been tried.

1. Galvez-Jimenez N, Hargreave M. Topiramate and essential tremor. *Ann Neurol* 2000; **47:** 837–8.
2. Ondo WG, *et al.* Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology* 2006; **66:** 672–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Neutop; Topamac; Topictal; Topirex; ***Austral.:*** Topamax; ***Austria:*** Topamax; ***Belg.:*** Topamax; ***Braz.:*** Topamax; ***Canad.:*** Topamax; ***Chile:*** Topamax; Toprel; ***Cz.:*** Topamax; Topiragis; ***Denm.:*** Epitomax; Topimax; ***Fin.:*** Topimax; ***Fr.:*** Epitomax; ***Ger.:*** Topamax; ***Gr.:*** Topamac; ***Hong Kong:*** Topamax; ***Hung.:*** Topamax; ***India:*** Topamac; Topamate; ***Indon.:*** Topamax; ***Irl.:*** Topamax; ***Israel:*** Topamax; ***Ital.:*** Topamax; ***Malaysia:*** Topamax; ***Mex.:*** Topamax; ***Neth.:*** Epitomax; Topamax; ***Norw.:*** Topimax; ***NZ:*** Topamax; ***Philipp.:*** Topamax; ***Pol.:*** Topamax; ***Port.:*** Topamax; Toptrix; ***Rus.:*** Topamax (Топамакс); ***S.Afr.:*** Topamax; ***Singapore:*** Topamax; ***Spain:*** Bipomax; Topamax; ***Swed.:*** Topimax; ***Switz.:*** Topamax; ***Thai.:*** Topamax; ***Turk.:*** Topamax; ***UK:*** Topamax; ***USA:*** Topamax; ***Venez.:*** Topamax.

Trimethadione *(BAN, rINN)*

Trimetadion; Trimetadiona; Trimetadionas; Trimetadioni; Trimethadion; Triméthadione; Trimethadionum; Trimethinum; Troxidone. 3,5,5-Trimethyl-1,3-oxazolidine-2,4-dione.

Триметадион

$C_6H_9NO_3$ = 143.1.
CAS — 127-48-0.
ATC — N03AC02.
ATC Vet — QN03AC02.

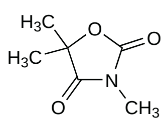

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.*
Ph. Eur. 6.2 (Trimethadione). Colourless or almost colourless crystals. Soluble in water; very soluble in alcohol. Protect from light.

Profile

Trimethadione is an oxazolidinedione antiepileptic that has been given in the treatment of absence seizures refractory to other antiepileptics. However, because of its potential toxicity, other antiepileptics are preferred (see under Epilepsy, p.465).

Porphyria. Trimethadione has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Characteristic congenital malformations, termed the fetal trimethadione syndrome, have been associated with the use of trimethadione in pregnancy.

For comments on the management of epilepsy during pregnancy, see p.468.

Preparations

Valproate

Valproato.
Вальпроат

NOTE. Valproate is a generic term applied to valproic acid and its salts and esters.

Valproic Acid *(BAN, USAN, rINN)*

Abbott-44089; Acide valproïque; Ácido dipropilacético; Ácido valproico; Acidum valproicum; Kyselina valproová; Valproiinihappo; Valproik Asit; Valproinė rūgštis; Valproinsav; Valproinsyra. 2-Propylvaleric acid; 2-Propylpentanoic acid.

Вальпроевая Кислота

$C_8H_{16}O_2$ = 144.2.
CAS — 99-66-1.
ATC — N03AG01.
ATC Vet — QN03AG01.

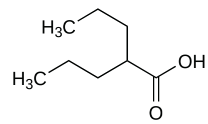

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Valproic Acid). A colourless or very slightly yellow, slightly viscous, clear liquid. Very slightly soluble in water; miscible with alcohol and with dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.
USP 31 (Valproic Acid). A colourless to pale yellow, slightly viscous, clear liquid having a characteristic odour. Slightly soluble in water; freely soluble in alcohol, in acetone, in chloroform, in ether, in methyl alcohol, in benzene, in *n*-heptane, and in 1N sodium hydroxide; slightly soluble in 0.1N hydrochloric acid. Store in airtight glass, stainless steel, or polyethylene containers.

Sodium Valproate *(BANM, rINNM)*

Abbott-44090; Natrii valproas; Natrio valproatas; Natriumvalproaatti; Natriumvalproat; Nátrium-valproát; Natrium-valproát; NIK-240; Sodium, valproate de; Sodyum Valproat; Valproate de Sodium; Valproate Sodium *(USAN)*; Valproato sódico. Sodium 2-propylvalerate; Sodium 2-propylpentanoate.

Натрий Вальпроат

$C_8H_{15}NaO_2$ = 166.2.
CAS — 1069-66-5.
ATC — N03AG01.
ATC Vet — QN03AG01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, and *US.*
Ph. Eur. 6.2 (Sodium Valproate). A white or almost white, hygroscopic, crystalline powder. Very soluble in water; slightly to freely soluble in alcohol. Store in airtight containers.
USP 31 (Divalproex Sodium). A white to off-white powder. Soluble in acetone; practically insoluble in acetonitrile; very soluble in chloroform; freely soluble in ethyl ether and in methyl alcohol. Store in airtight containers.

Valproate Pivoxil *(rINN)*

CHF-1504; Valproato de pivoxilo; Valproate pivoxilo; Valproatum Pivoxilum. Hydroxymethyl 2-propylvalerate pivalate.

Вальпроат Пивоксил

$C_{14}H_{26}O_4$ = 258.4.
CAS — 77372-61-3.
ATC — N03AG01.
ATC Vet — QN03AG01.

Valproate Semisodium *(rINN)*

Abbott-50711; Divalproex Sodium *(USAN)*; Semisodium Valproate *(BAN)*; Valproate Semisodique; Valproato semisódico; Valproatum Seminatricum. 2-Propylvaleric acid—Sodium 2-propylvalerate (1:1); Sodium hydrogen bis(2-propylvalerate) oligomer.

Вальпроат Семинатрий

$C_{16}H_{31}NaO_4$ = 310.4.
CAS — 76584-70-8.
ATC — N03AG01.
ATC Vet — QN03AG01.

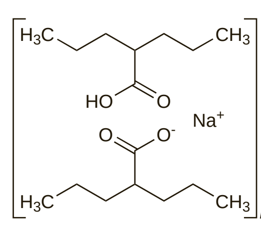

Valpromide *(rINN)*

Dipropilacetamida; Dipropylacetamide; Valpromida; Valpromidum. 2-Propylvaleramide.

Вальпромид

$C_8H_{17}NO$ = 143.2.
CAS — 2430-27-5.
ATC — N03AG02.
ATC Vet — QN03AG02.

Adverse Effects

The most frequently reported adverse effects associated with valproate therapy are gastrointestinal disturbances, particularly at the start of therapy; enteric-coated formulations, taking doses with meals, and starting with low doses may minimise symptoms. There may be increased appetite, and weight gain is common.

Less common adverse effects include oedema, headache, reversible prolongation of bleeding time, and thrombocytopenia. Leucopenia and bone marrow depression have been reported. Neurological adverse effects including ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have occasionally been reported, although these are often associated with too high a starting dose, increasing doses too rapidly, or use with other antiepileptics. Very rare cases of extrapyramidal symptoms or reversible dementia associated with cerebral atrophy have been reported. Increased alertness may occur, which is generally considered beneficial, but occasionally aggression, hyperactivity, and behavioural disturbances have been reported. Hearing loss has been noted. There may occasionally be rashes, and, rarely, hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multiforme. Transient hair loss, sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhoea, and gynaecomastia have been reported rarely.

Liver dysfunction including hepatic failure has occasionally been reported, usually in the first few months of treatment, and requires valproate withdrawal; there have been fatalities. Elevation of liver enzyme values is common but normally transient and dose-related. Hyperammonaemia has occurred, even in the absence of overt hepatic failure, and is sometimes associated with neurological symptoms; hyperglycinaemia has also been reported. Pancreatitis has also been reported rarely, and fatalities have occurred; plasma amylase should be measured if there is acute abdominal pain, although the value of serum amylase as a diagnostic tool has been questioned—see Effects on the Pancreas, below. In a few patients there have been reports of reversible defects in renal tubular function (Fanconi's syndrome).

Congenital malformations have been reported in infants born to women who had received antiepileptics including valproate during pregnancy.

Inflammatory reactions and pain have been reported at the injection site after intravenous doses.

Incidence of adverse effects. Adverse effects were present in 71 of 88 children receiving sodium valproate monotherapy[1] and, although average doses in these patients were significantly higher than in the 17 with no adverse effects, no difference in the plasma concentrations was observed between the 2 groups.

- Behavioural alterations seen in 56 included irritability, longer and deeper sleep, superficial sleep, hyperactivity, being more alert, lassitude, drowsiness, being more sociable, calmness, being happier, absent mindedness, being sadder, aggressiveness, being more skillful, and docility; it was emphasised that stimulatory reactions were as frequent as depressant effects
- Digestive disorders occurred in 43 children with anorexia, abdominal pain, and nausea and vomiting being the most frequent; diarrhoea, constipation, an increase in appetite, and a gain in weight also occurred. With the exception of a temporary increase in plasma transaminase concentrations in 2 patients, hepatic or pancreatic dysfunction was not seen
- Neurological changes in the form of tremor, paraesthesia, or ataxia, occurring in only 4 patients, were less frequent than either behavioural or digestive reactions
- Miscellaneous reactions including polydipsia, polyuria, diaphoresis, enuresis, hair loss, change in hair colour or texture, and rash were seen in 23 children

- Of the 71 children experiencing reactions, therapy continued unchanged in 56, was changed in 3 either by altering the pharmaceutical formulation (syrup, tablets, granules), by changing the frequency of dosing, or by reducing the dose in 6, and in the remaining 9 children valproate therapy was stopped

1. Herranz JL, *et al*. Side effects of sodium valproate in monotherapy controlled by plasma levels: a study in 88 pediatric patients. *Epilepsia* 1982; **23:** 203–14.

Carnitine deficiency. Carnitine deficiency may occasionally arise during long-term use of valproate; although it is unclear whether carnitine supplementation (p.1933) of value in children receiving valproate, some neurologists consider it justified in selected cases, including those with, or at risk of, valproate-induced hepatotoxicity.[1,2]

1. De Vivo DC, *et al*. -Carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; **39:** 1216–25.
2. Lheureux PER, *et al*. Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; **9:** 431–40.

Effects on the blood. A number of reports have implicated valproate as a cause of occasional neutropenia,[1-3] leucopenia,[4] and thrombocytopenia.[2] A 1-year prospective study involving 45 patients found that absolute neutropenia developed in 12 and thrombocytopenia in 15, but that the disorders were transient and self-limiting.[2] However, neutropenia has occasionally been sufficiently severe to warrant withdrawal of valproate.[5] Red cell aplasia has also been associated with valproate therapy.[6,7] A study[8] involving 30 children indicated that valproate might produce symptoms similar to those of von Willebrand's disease; 19 of the 30 had a history of minor haemorrhage during therapy, and 7 had abnormal bleeding times. Factor VIII therapy might need to be given in patients receiving valproate who underwent surgery or in whom bleeding was severe.

For a discussion of the effects of antiepileptics, including valproate, on serum folate, see under Phenytoin, p.495.

1. Jaeken J, *et al*. Neutropenia during sodium valproate treatment. *Arch Dis Child* 1979; **54:** 986–7.
2. Barr RD, *et al*. Valproic acid and immune thrombocytopenia. *Arch Dis Child* 1982; **57:** 681–4.
3. Vesta KS, Medina PJ. Valproic acid-induced neutropenia. *Ann Pharmacother* 2003; **37:** 819–21.
4. Coulter DL, *et al*. Valproic acid therapy in childhood epilepsy. *JAMA* 1980; **244:** 785–8.
5. Symon DNK, Russell G. Sodium valproate and neutropenia. *Arch Dis Child* 1983; **58:** 235.
6. MacDougall LG. Pure red cell aplasia associated with sodium valproate therapy. *JAMA* 1982; **247:** 53–4.
7. Watts RG, *et al*. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr* 1990; **117:** 495–9.
8. Kreuz W, *et al*. Induction of von Willebrand disease type I by valproic acid. *Lancet* 1990; **335:** 1350–1.

Effects on bone. For the effects of antiepileptics including valproate on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on the endocrine system. An early study[1] reported that menstrual disturbances were associated more often with valproate than with other antiepileptics among 238 women with epilepsy; 80% of those treated with valproate before 20 years of age had polycystic ovaries or hyperandrogenism. A later study[2] found that the occurrence of polycystic ovaries in 105 epileptic women taking carbamazepine or valproate was no greater than that in the general population, although valproate appeared to increase glucose-stimulated pancreatic insulin secretion. Subsequent studies[3-5] and reviews[6-9] support the association between valproate therapy and reproductive endocrine disorders and metabolic disturbances in female patients with epilepsy. However, a causal link could not be established since epilepsy itself affects the endocrine system. Symptoms such as hyperandrogenism, menstrual disturbances, polycystic ovaries, weight gain, and insulin resistance have been attributed to the development of polycystic ovary syndrome (p.2080) in some patients. Other adverse effects of valproate on the endocrine system include dyslipidaemia, hypocalcaemia, and hypothyroidism.

For mention of the effects of antiepileptics, including valproate, on *sexual function* in male epileptic patients, see under Phenytoin, p.496.

1. Isojärvi JIT, *et al*. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993; **329:** 1383–8.
2. Luef G, *et al*. Polycystic ovaries, obesity and insulin resistance in women with epilepsy: a comparative study of carbamazepine and valproic acid in 105 women. *J Neurol* 2002; **249:** 835–41.
3. Betts T, *et al*. A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. *Seizure* 2003; **12:** 323–9.
4. Mikkonen K, *et al*. Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 2004; **62:** 445–50.
5. Tan H, *et al*. Valproate-induced insulin resistance in prepubertal girls with epilepsy. *J Pediatr Endocrinol Metab* 2005; **18:** 985–9. Correction. *ibid.*; 1134.
6. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia* 2003; **44** (suppl 4): 11–20.
7. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 2004; **24:** 322–34.
8. Verrotti A, *et al*. Endocrine and metabolic changes in epileptic patients receiving valproic acid. *J Pediatr Endocrinol Metab* 2005; **18:** 423–30.
9. Isojärvi J. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure* 2008; **17:** 111–19.

Effects on the liver. An early review[1] of the hepatotoxicity of valproate included an analysis of 42 cases with fatal hepatitis, 3 cases with a Reye's-like syndrome, and 22 instances of hyperammonaemia:

- In 19 studies the incidence of *abnormal serum aminotransferase* activity ranged from 0 to 44% with an overall incidence of 11% in the 1197 patients monitored; in the non-fatal cases activity was usually between one and three times the upper limit of normal and was not usually, except in the most severe cases, accompanied by rises in serum bilirubin or alkaline phosphatase
- In the 42 cases of *hepatitis* with a fatal outcome the age at presentation ranged from 2.5 months to 34 years with 69% aged 10 years or less. Below the age of 15 years the proportion of males was 62.5% but above this age it was 30%; the disproportionate vulnerability of young individuals, particularly boys, did not appear to be a reflection of prescribing habits in that age group. In more than two-thirds of these patients with a fatal outcome, prodromal symptoms comprised anorexia and vomiting, loss of epilepsy control, impaired consciousness, and ataxia; in about one-third there were signs of liver damage with fever, jaundice, ascites, peripheral oedema, and easy bruising. In all of the patients hepatic coma developed. In 36 patients on whom data were available the onset of hepatic illness in one-third occurred between 1 and 2 months and in only 2 patients did the onset occur after more than 5 months. Of these 42 patients with fatal hepatotoxicity 36 were also given other drugs, mostly antiepileptics
- The 3 children with a *Reye's-like syndrome* all died within 3 weeks of the first occurrence of symptoms as a result of cerebral oedema (2) or aspiration pneumonia (1)
- In the 22 patients with symptomatic *hyperammonaemia*, characterised usually by impaired consciousness and ataxia, but without overt liver disease, withdrawal of valproate resulted in all becoming asymptomatic and biochemical abnormalities returned to normal. Hyperammonaemia has also been reported in asymptomatic patients

Hyperammonaemia and encephalopathy may also be precipitated when valproate is used with certain drugs (see under Antibacterials, p.510 and Antiepileptics, p.511, in Interactions).

Various hypotheses for the cause of valproate hepatotoxicity have been discussed in detail.[2]

Analysis of deaths in the USA attributed to valproate liver toxicity identified a decline in the incidence of fatalities as use in young children and use with other antiepileptics declined.[3] However, occasional reports still occur in some countries.[4]

1. Powell-Jackson PR, *et al*. Hepatotoxicity to sodium valproate: a review. *Gut* 1984; **25:** 673–81.
2. Eadie MJ, *et al*. Valproate-associated hepatotoxicity and its biochemical mechanisms. *Med Toxicol* 1988; **3:** 85–106.
3. Dreifuss FE, *et al*. Valproic acid hepatic fatalities: II US experience since 1984. *Neurology* 1989; **39:** 201–7.
4. Koenig SA, *et al*. Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. *Epilepsia* 2006; **47:** 2027–31.

Effects on mental function. For a review of the effects of antiepileptic therapy including valproate on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

Effects on the nervous system. An *extrapyramidal* syndrome of tremor and rigidity, unresponsive to benzatropine or trihexyphenidyl, developed in a 52-year-old man with schizophrenia given a therapeutic trial of sodium valproate 1 to 2 g daily.[1] Giving sodium valproate to a man with dystonic movements of the neck and spine produced a severe subjective and objective deterioration in his symptoms, which returned to their previous severity on withdrawal of the drug.[2] There have also been reports[3,4] of *parkinsonism* associated with valproate antiepileptic therapy; onset was usually insidious and progressive, occurring after several years of good tolerability. A case series[4] also reported *cognitive impairment* in 6 of 10 patients who developed parkinsonism. In most cases symptoms improved on stopping valproate.

Spasmodic dysphonia associated with valproate has been reported;[5] symptoms resolved when the dose of valproate was reduced.

A *stuporous state* associated with EEG abnormalities has been described[6,7] during valproate therapy for complex partial or mixed seizure types and it was suggested that in certain forms of epilepsy valproate may exhibit a paradoxical epileptogenic effect. Other findings[8] have argued against an epileptic origin for valproate-induced stupor.

1. Lautin A, *et al*. Extrapyramidal syndrome with sodium valproate. *BMJ* 1979; **2:** 1035–6.
2. Dick DJ, Saunders M. Extrapyramidal syndrome with sodium valproate. *BMJ* 1980; **280:** 189.
3. Easterford K, *et al*. Reversible parkinsonism with normal β-CIT-SPECT in patients exposed to sodium valproate. *Neurology* 2004; **62:** 1435–7.
4. Masmoudi K, *et al*. Parkinsonism and/or cognitive impairment with valproic acid therapy: a report of ten cases. *Pharmacopsychiatry* 2006; **39:** 9–12.
5. Oh J, *et al*. Spasmodic dysphonia induced by valproic acid. *Epilepsia* 2004; **45:** 880–1.
6. Marescaux C, *et al*. Stuporous episodes during treatment with sodium valproate: report of seven cases. *Epilepsia* 1982; **23:** 297–305.
7. Stecker MM, Kita M. Paradoxical response to valproic acid in a patient with a hypothalamic hamartoma. *Ann Pharmacother* 1998; **32:** 1168–72.
8. Aguglia U, *et al*. Negative myoclonus during valproate-related stupor: neurophysiological evidence of a cortical non-epileptic origin. *Electroencephalogr Clin Neurophysiol* 1995; **94:** 103–8.

Effects on the pancreas. An early report of 4 cases of pancreatitis associated with valproic acid therapy also reviewed 10 previously published cases.[1] None of the 14 patients, 2 of whom died, suffered other symptoms of a toxic reaction to valproic acid. Pancreatitis was not dose-related and had developed as early as one week and as late as 4.5 years after the introduction of therapy. Symptoms recurred on rechallenge in 6 of 7 patients. However, routine monitoring of serum-amylase concentrations in asymptomatic patients did not seem necessary. In February 1994 the UK CSM commented[2] in a review of drug-induced pancreatitis that they had received 29 reports of pancreatitis, including 2 fatalities, associated with sodium valproate. A later review[3] of 22 children who developed pancreatitis while taking valproate (2 of whom died) found that duration of therapy, dose, serum concentrations, and polytherapy were not risk factors. The authors advised against rechallenge as the rate of relapse is high. Serum amylase concentrations were found to be nondiagnostic in 39% of these patients, and the authors considered that serum lipase concentrations were far more likely to be elevated.

1. Wyllie E, *et al*. Pancreatitis associated with valproic acid therapy. *Am J Dis Child* 1984; **138:** 912–14.
2. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 01/09/08)
3. Werlin SL, Fish DL. The spectrum of valproic acid-associated pancreatitis. *Pediatrics* 2006; **118:** 1660–3.

Effects on the skin, hair, and nails. Five of 250 patients developed curly hair during treatment with sodium valproate 1 g daily;[1] in 3 patients this effect followed temporary alopecia. Another report of hair curling in a patient who received sodium valproate in doses up to 3 g daily for 30 months commented that her hair started to revert to the former straight style 9 months after stopping the drug.[2]

Valproate-induced nicotinic-acid deficiency with an associated pellagra-like syndrome has been reported in a young boy;[3] the condition responded dramatically to treatment with nicotinamide.

Reduced serum-zinc concentrations and cutaneous manifestations of zinc deficiency were found in 2 patients receiving antiepileptic drugs.[4] It was thought that deficiency resulted from chelation by sodium valproate, and possibly phenytoin, in association with malabsorption and that, in one case, malabsorption was triggered by valproate.

Cutaneous vasculitis has been reported[5] in 2 patients taking sodium valproate. The reaction recurred on rechallenge.

Very rarely, skin rashes occurring with valproate may form part of an antiepileptic hypersensitivity syndrome (see below). Valproate might share the same order of risk as other antiepileptics for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis,[6] although it had previously been regarded as safer in this respect. For a suggestion that skin reactions are less common with valproate than with some other antiepileptics see under Phenytoin, p.496.

Reversible yellow nail pigmentation has been reported[7] in a woman who was taking valproate semisodium.

1. Jeavons PM, *et al*. Valproate and curly hair. *Lancet* 1977; **i:** 359.
2. Gupta AK. 'Perming' effects associated with chronic valproate therapy. *Br J Clin Pract* 1988; **42:** 75–7.
3. Gillman MA, Sandyk R. Nicotinic acid deficiency induced by sodium valproate. *S Afr Med J* 1984; **65:** 986.
4. Lewis-Jones MS, *et al*. Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants. *BMJ* 1985; **290:** 603–4.
5. Kamper AM, *et al*. Cutaneous vasculitis induced by sodium valproate. *Lancet* 1991; **337:** 497–8.
6. Anonymous. Drugs as risk factors in severe cutaneous diseases. *WHO Drug Inf* 1996; **10:** 33–5.
7. Buka R, *et al*. Yellow nail pigmentation following Depakote therapy. *J Drugs Dermatol* 2003; **2:** 545–7.

Enuresis. Nocturnal enuresis associated with sodium valproate therapy has been reported[1] in 2 children. Remission of the enuresis was achieved either by reducing or redistributing the doses. Several studies have recorded enuresis as an adverse effect of valproate in children,[2] the frequency being between 1 and 7%. The most likely explanations are that either it is secondary to a central effect on the thirst centre resulting in polydipsia or it is a consequence of the increased depth of sleep associated with valproate.

1. Panayiotopoulos CP. Nocturnal enuresis associated with sodium valproate. *Lancet* 1985; **i:** 980–1.
2. Choonara IA. Sodium valproate and enuresis. *Lancet* 1985; **i:** 1276.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly lymphocytosis, and liver and other organ involvement, has been associated with some aromatic antiepileptic drugs; however, there have also been case reports[1-3] associated with valproate, a non-aromatic compound. In one case[1] a patient developed these symptoms with carbamazepine but they resolved when the drug was stopped; however, when valproate was started 2 weeks later the symptoms reappeared. Another report[2] described a fatal case occurring in a 2-year-old girl who developed fulminant hepatitis.

1. Arévalo-Lorido JC, *et al.* Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. *Br J Clin Pharmacol* 2003; **55:** 415–16.
2. Huang Y-L, *et al.* Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. *J Am Acad Dermatol* 2003; **49:** 316–19.
3. Roepke S, *et al.* Valproic acid and hypersensitivity syndrome. *Am J Psychiatry* 2004; **161:** 579.

Overdosage. A cohort study[1] of valproate poisonings reported to a regional toxicology centre between January 1991 and November 2001 reported 79 cases. Of these, valproate was the only drug taken in 15 cases with a median dose of 15 g; symptoms were mild and included drowsiness (2 patients), vomiting (4), and tachycardia (5). The authors concluded that overdoses of more than 400 mg/kg could cause severe, potentially life-threatening toxicity, but these were uncommon. Symptoms of severe toxicity include significant CNS depression, respiratory insufficiency, and multi-organ failure; fatalities have been reported.[2] Children younger than 2 years of age are considered to be at significant risk for developing fatal valproate-induced hepatotoxicity in overdose; there has been a report of a 26-day-old neonate who died 42 hours after receiving a dose of 75 mg/kg.[3]

1. Isbister GK, *et al.* Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol* 2003; **55:** 398–404.
2. Eyer F, *et al.* Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 2005; **25:** 376–80.
3. Unal E, *et al.* Fatal valproate overdose in a newborn baby. *Hum Exp Toxicol* 2007; **26:** 453–6.

Treatment of Adverse Effects

The value of gastric decontamination for overdose is uncertain since valproic acid and its salts are rapidly absorbed. Activated charcoal may be given orally to adults and children who present within 1 hour of ingesting more than 100 mg/kg; alternatively gastric lavage may be considered in adults within 1 hour of a potentially life-threatening overdose. Supportive therapy alone may then suffice although haemodialysis should be considered in very severe poisoning.

◊ A variety of active treatments including forced diuresis, whole bowel irrigation, naloxone, and haemodialysis or haemoperfusion have been advocated for valproate overdose;[1,2] however, supportive measures provided sufficient treatment for a patient who had taken 25 g of sodium valproate.[1] For a further review of the features and management of poisoning with some antiepileptics such as valproate, see under Phenytoin, p.497.

1. Lakhani M, McMurdo MET. Survival after severe self poisoning with sodium valproate. *Postgrad Med J* 1986; **62:** 409–10.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. *J Toxicol Clin Toxicol* 2002; **40:** 789–801. Correction. *ibid.* 2003; **41:**215.

Precautions

Valproate is contra-indicated in patients with pre-existing liver disease or a family history of severe hepatic dysfunction. Children under 3 years of age and those with congenital metabolic or degenerative disorders, organic brain disease, or severe seizure disorders associated with mental retardation may be at particular risk of hepatotoxicity and the drug should be used with particular caution in these groups. Use with other antiepileptics, which may also increase the risks of liver damage, should be avoided if possible. Liver function tests should be carried out, particularly in those most at risk, before and during the first 6 months of therapy. Raised liver enzymes are not uncommon during treatment and are usually transient or respond to reduction in dosage, but patients should be reassessed clinically and liver function, including prothrombin time, monitored until they return to normal. An abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities, requires treatment to be stopped. If given with salicylates, these should also be stopped. Treatment should also be stopped if pancreatitis is diagnosed.

Patients or their carers should be told how to recognise signs of blood and liver toxicity or pancreatitis, and they should be advised to seek immediate medical attention if symptoms develop.

Patients should be monitored for potential bleeding complications before major elective surgery; some licensed product information suggests regular monitoring before and during therapy.

Valproate should be used with caution if the patient is at risk of SLE.

Patients should be warned of the risk of weight gain and appropriate strategies adopted to minimise the effect.

Care is required when withdrawing valproate therapy—see also Uses and Administration, below.

The protein binding of valproate is saturable and thus shows concentration dependency; significant increases in free drug occur at high total plasma concentrations.

Because valproate is partly excreted in the form of ketone bodies, it may cause false positives in urine tests for diabetes mellitus.

Dosage adjustments may be necessary in severe renal impairment in accordance with free serum valproate levels.

Breast feeding. Thrombocytopenic purpura and anaemia occurred in a breast-fed infant whose mother was being treated with valproic acid.[1] The baby recovered when breast feeding was stopped. Low serum-valproate levels were detected[2] in 6 breast-fed infants whose mothers had been taking valproate semisodium post partum; no adverse effects were seen in the infants. Similar results have previously been obtained for patients taking sodium valproate[3] or valproic acid.[4] The American Academy of Pediatrics considers[5] that valproate is, therefore, usually compatible with breast feeding.

For further comment on antiepileptic therapy and breast feeding, see p.467.

1. Stahl MMS, *et al.* Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. *J Pediatr* 1997; **130:** 1001–3.
2. Piontek CM, *et al.* Serum valproate levels in 6 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2000; **61:** 170–2.
3. Alexander FW. Sodium valproate and pregnancy. *Arch Dis Child* 1979; **54:** 240.
4. von Unruh GE, *et al.* Valproic acid in breast milk: how much is really there? *Ther Drug Monit* 1984; **6:** 272–6.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/06/08)

Driving. For a comment on antiepileptic drugs and driving, see p.468.

HIV infection and AIDS. Limited data from several small *in-vitro* studies have found that valproic acid may induce viral replication of HIV;[1] some clinicians have therefore suggested increased monitoring of viral load in HIV-positive patients treated with valproic acid. For the use of this effect to reduce latent viral load see under Uses and Administration, below.

1. Jennings HR, Romanelli F. The use of valproic acid in HIV-positive patients. *Ann Pharmacother* 1999; **33:** 1113–16.

Porphyria. Valproate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems. There is conflicting evidence of the porphyrinogenicity of valpromide, although it has also been shown to be porphyrinogenic in *in-vitro* systems.

For comments on the use of valproate in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy during pregnancy see p.468.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including valproate and craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described, which may form part of a fetal antiepileptic syndrome.[1] In an unselected series[2] of 17 infants whose epileptic mothers had received valproate during pregnancy, 9 had minor abnormalities and of these 5 also had major abnormalities, including congenital heart defect in 4. In another series,[3] involving 149 women whose offspring were exposed to valproate monotherapy in the first trimester, 16 infants with major malformations were identified (a relative risk calculated at about 7 times that in the population at large). The abnormalities reported included craniosynostosis, spina bifida, and pulmonary atresia. A population-based study[4] of 2350 births to epileptic women between 1991 and 2000 found that the offspring of mothers who were given valproate, as mono- or polytherapy, in the first trimester had a fourfold increase in risk for congenital malformations compared with untreated mothers; the risk was tenfold in those who were given daily doses of more than 1.5 g. The risk of malformations was not increased in the offspring of mothers taking carbamazepine, oxcarbazepine, or phenytoin as mono- or polytherapy without valproate.

Neonatal bleeding, attributed to fibrinogen depletion and sometimes fatal, has been reported after exposure *in utero* to valproate.[5,6] Hypoglycaemia was recorded[7] in 13 of 22 neonates whose mothers had taken valproate during pregnancy. Valproate-withdrawal symptoms, including irritability, jitteriness, hypertonia, seizures, and feeding problems were also noted.

1. Genton P, *et al.* Valproic acid in epilepsy: pregnancy-related issues. *Drug Safety* 2006; **29:** 1–21.
2. Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993; **69:** 288–91.
3. Wyszynski DF, *et al.* Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; **64:** 961–5.
4. Artama M, *et al.* Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005; **64:** 1874–8.
5. Majer RV, Green PJ. Neonatal afibrinogenaemia due to sodium valproate. *Lancet* 1987; **ii:** 740–1.
6. Bavoux F, *et al.* Neonatal fibrinogen depletion caused by sodium valproate. *Ann Pharmacother* 1994; **28:** 1307.
7. Ebbesen F, *et al.* Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** F124–F129.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Caution is recommended when giving valproate with other drugs liable to interfere with blood coagulation, such as aspirin or warfarin. Use with other hepatotoxic drugs should be avoided. Use of highly protein bound drugs with valproate may increase free valproate plasma concentrations.

◊ General references.

1. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.

Analgesics. The free fraction of valproate was increased eightfold in a 76-year-old man[1] who was also given *aspirin* 325 mg daily, resulting in signs of clinical toxicity. Aspirin displaces valproate from plasma protein binding sites, as well as inhibiting its metabolism by inhibition of beta-oxidation. Similarly, the valproic acid free fraction was reported to be increased, as was the half-life, when aspirin was given in a study in 6 epileptic children.[2] Furthermore, salicylates have been associated with an increased risk of Reye's syndrome (p.22) in children, and combination with another hepatotoxic drug such as valproate is clearly undesirable. In addition, both aspirin and valproate affect blood coagulation and platelet function.

Naproxen has also been reported to produce a slight displacement of protein-bound valproic acid but the effect is probably not sufficiently marked for it to have a clinical effect.[3]

1. Sandson NB, *et al.* An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. *Am J Psychiatry* 2006; **163:** 1891–6.
2. Orr JM, *et al.* Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. *Clin Pharmacol Ther* 1982; **31:** 642–9.
3. Grimaldi R, *et al.* In vivo plasma protein binding interaction between valproic acid and naproxen. *Eur J Drug Metab Pharmacokinet* 1984; **9:** 359–63.

Antibacterials. Raised valproate blood concentrations and symptoms consistent with valproate toxicity have been reported in a patient also given *erythromycin*.[1]

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving *pivampicillin* and valproate. Hyperammonaemic encephalopathy developed in a 72-year-old woman who had been taking valproate for 10 months when she was given *pivmecillinam* for a urinary-tract infection. It was suggested that valproate's propensity to produce hyperammonaemia had been exacerbated by a secondary hyperammonaemia induced by both drugs reducing carnitine concentrations.[2]

Decreases in plasma concentrations of valproate to subtherapeutic levels (and sometimes with loss of seizure control) have been noted in patients during therapy with antibacterial treatment containing *ertapenem*,[3] *imipenem*,[4] or *meropenem*.[4-8] Marked reductions in valproate concentrations have also been reported in 3 children given *panipenem* (with betamipron).[9]

Increased serum-valproate concentrations resulting in signs of valproate toxicity occurred in a child after beginning therapy with *isoniazid*;[10] the child was a slow acetylator of isoniazid and valproate dosage had to be reduced by about 60% to maintain satisfactory concentrations. When isoniazid was subsequently stopped, valproate dosage had to be increased to its previous value in order to maintain a therapeutic effect.

1. Redington K, *et al.* Erythromycin and valproate interaction. *Ann Intern Med* 1992; **116:** 877–8.
2. Lokrantz C-M, *et al.* Hyperammonemic encephalopathy induced by a combination of valproate and pivmecillinam. *Acta Neurol Scand* 2004; **109:** 297–301.
3. Lunde JL, *et al.* Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. *Pharmacotherapy* 2007; **27:** 1202–5.

4. Llinares Tello F, *et al.* Interacción farmacocinética entre ácido valproico y antibióticos carbapenémicos: descripción de tres casos. *Farm Hosp* 2003; **27:** 258–63.
5. De Turck BJG, *et al.* Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother* 1998; **42:** 563–4.
6. Coves-Orts FJ, *et al.* Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother* 2005; **39:** 533–7.
7. Fudio S, *et al.* Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther* 2006; **31:** 393–6.
8. Spriet I, *et al.* Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother* 2007; **41:** 1130–6.
9. Nagai K, *et al.* Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother* 1997; **39:** 295–6.
10. Jonville AP, *et al.* Interaction between isoniazid and valproate: a case of valproate overdosage. *Eur J Clin Pharmacol* 1991; **40:** 197–8.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

There have been conflicting reports of the effect of *fluoxetine* on serum concentrations of valproate. While some reported an increase,[1-3] others have reported a decrease[4] in valproate-serum concentrations when the 2 drugs were used together.

For the effect of valproate on *amitriptyline*, see p.380.

1. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. *J Clin Psychopharmacol* 1991; **11:** 389.
2. Lucena MI, *et al.* Interaction of fluoxetine and valproic acid. *Am J Psychiatry* 1998; **155:** 575.
3. Cruz-Flores S, *et al.* Valproic toxicity with fluoxetine therapy. *Mo Med* 1995; **92:** 296–7.
4. Droulers A, *et al.* Decrease of valproic acid concentration in the blood when coprescribed with fluoxetine. *J Clin Psychopharmacol* 1997; **17:** 139–40.

Antiepileptics. The barbiturate antiepileptic *phenobarbital* is reported to decrease serum-valproate concentrations when given together,[1] apparently by induction of valproate metabolism.[2] This effect is overshadowed, however, by the marked increase in serum-phenobarbital concentrations caused by valproate inhibition of phenobarbital metabolism—see p.493. It has been suggested that phenobarbital may also increase the risk of valproate-induced hyperammonaemic encephalopathy.[3]

Carbamazepine and *phenytoin* are also enzyme-inducing drugs and, as might be expected, are reported to increase the metabolism and decrease the serum concentration of valproate.[4-6] The effect may be clinically significant.[7] The reciprocal effects of valproate on both drugs are complex, with conflicting effects on metabolism and protein binding, and the clinical outcome is difficult to predict. For more details see under Carbamazepine, p.474 and Phenytoin, p.498.

Serum concentrations of valproic acid were reduced, with considerable interpatient variability, when *ethosuximide*[8] or *mesuximide*[9] was added to the antiepileptic therapy of some patients.

Raised serum concentrations of valproic acid have been reported in patients given *felbamate*.[10]

Reversible hepatic impairment has been reported[11,12] when *topiramate* was added to valproate therapy in patients who had previously tolerated valproate well. Use of valproate with topiramate has also been associated with hyperammonaemia and encephalopathy.[13]

Valproate inhibits the metabolism of *lamotrigine* which may result in serious toxic reactions—see p.486. There is limited evidence that valproic acid may affect the metabolism of *ethosuximide* in some patients—see p.480. Valproate reduces the half-life of *zonisamide*—see p.515.

For interactions with benzodiazepines, see under Diazepam, p.990.

1. Perucca E. Pharmacokinetic interactions with antiepileptic drugs. *Clin Pharmacokinet* 1982; **7:** 57–84.
2. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
3. Segura-Bruna N, *et al.* Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006; **114:** 1–7.
4. Panesar SK, *et al.* The effect of carbamazepine on valproic acid disposition in adult volunteers. *Br J Clin Pharmacol* 1989; **27:** 323–8.
5. Reunanen MI, *et al.* Low serum valproic acid concentrations in epileptic patients on combination therapy. *Curr Ther Res* 1980; **28:** 456–62.
6. Cramer JA, *et al.* Variable free and total valproic acid concentrations in sole- and multi-drug therapy. *Ther Drug Monit* 1986; **8:** 411–15.
7. Jann MW, *et al.* Increased valproate serum concentrations upon carbamazepine cessation. *Epilepsia* 1988; **29:** 578–81.
8. Sälke-Kellermann RA, *et al.* Influence of ethosuximide on valproic acid serum concentrations. *Epilepsy Res* 1997; **26:** 345–9.
9. Besag FMC, *et al.* Methsuximide reduces valproic acid serum levels. *Ther Drug Monit* 2001; **23:** 694–7.
10. Wagner ML, *et al.* The effect of felbamate on valproic acid disposition. *Clin Pharmacol Ther* 1994; **56:** 494–502.
11. Longin E, *et al.* Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002; **43:** 451–4.
12. Bumb A, *et al.* Adding topiramate to valproate therapy may cause reversible hepatic failure. *Epileptic Disord* 2003; **5:** 157–9.
13. Latour P, *et al.* Drug induced encephalopathy in six epileptic patients: topiramate? valproate? or both? *Hum Psychopharmacol* 2004; **19:** 193–203.

Antimalarials. Low serum concentrations of valproate have been reported[1] in patients taking *mefloquine.* Also, mefloquine and *chloroquine* may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold.

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antineoplastics. A marked reduction in serum-valproate concentration occurred in a 6-year-old child after a high-dose 24-hour infusion of *methotrexate*.[1]

1. Schrøder H, Østergaard JR. Interference of high-dose methotrexate in the metabolism of valproate? *Pediatr Hematol Oncol* 1994; **11:** 445–9.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of valproate by lowering the convulsive threshold. Although a study[1] found that *risperidone* had no significant effect on the pharmacokinetics of valproate, 2 earlier case reports showed conflicting results; one[2] described increased serum-valproate concentrations, and the other[3] decreased concentrations, when risperidone was added to valproate therapy. For the effect of valproate on *clozapine*, see p.984.

1. Ravindran A, *et al.* Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet* 2004; **43:** 733–40.
2. van Wattum PJ. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 866–7.
3. Bertoldo M. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 632.

Antivirals. There have been 2 reports that describe a reduction in plasma-valproate concentrations in HIV-positive patients who were taking valproate for bipolar disorder and were given *efavirenz* in one case[1] and *ritonavir-boosted lopinavir* in another,[2] resulting in mania. However, an earlier study[3] in a small number of HIV-positive patients did not find any clinically significant interactions between these drugs and valproic acid. For the effect of *aciclovir* on valproate, see under Interactions of Phenytoin, p.499.

For the effect of valproate on *zidovudine*, see p.915.

1. Saraga M, *et al.* Reduced valproate plasma levels possible after introduction of efavirenz in a bipolar patient. *Bipolar Disord* 2006; **8:** 415–17.
2. Sheehan NL, *et al.* Possible interaction between lopinavir/ritonavir and valproic acid exacerbates bipolar disorder. *Ann Pharmacother* 2006; **40:** 147–50.
3. DiCenzo R, *et al.* Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; **48:** 4328–31.

Anxiolytics. For interactions between valproate and *benzodiazepines*, see under Diazepam, p.990. For an interaction between valproate and *zolpidem*, see p.1038.

Calcium-channel blockers. For the effect of sodium valproate on *nimodipine*, see under Nifedipine, p.1353.

Colestyramine. Colestyramine may decrease the absorption of valproate.

Gastrointestinal drugs. Use with an *antacid* (aluminium and magnesium hydroxides) significantly increased the bioavailability of a valproic acid preparation in healthy subjects;[1] other antacids in this study (calcium carbonate and an aluminium magnesium trisilicate mixture) had a lesser, insignificant effect.

Cimetidine significantly increased the half-life and decreased the clearance of sodium valproate in another study;[2] *ranitidine* had no effect on valproate pharmacokinetics.[2]

These interactions have not been reported to be of clinical significance, although the possibility must exist, particularly in patients on high-dose therapy.

1. May CA, *et al.* Effects of three antacids on the bioavailability of valproic acid. *Clin Pharm* 1982; **1:** 244–7.
2. Webster LK, *et al.* Effect of cimetidine and ranitidine on carbamazepine and sodium valproate pharmacokinetics. *Eur J Clin Pharmacol* 1984; **27:** 341–3.

Ginkgo biloba. For a report of a fatal breakthrough seizure occurring when phenytoin and valproate semisodium were used with ginkgo biloba, see under Phenytoin, p.500.

Sex hormones. A 26-year-old woman who was taking valproate for epilepsy and a combined *oral contraceptive* had lower serum-valproate concentrations and an increase in seizure frequency during the active pill phase when compared with the inactive pill phase.[1] A subsequent study[2] in 9 epileptic women who were taking valproate and a combined oral contraceptive found that the apparent oral clearance of total and unbound valproic acid increased during contraceptive intake compared with the pill-free interval; the authors suggested that this effect was due to the induction of glucuronidation of valproate by ethinylestradiol.

1. Herzog AG, *et al.* Serum valproate levels with oral contraceptive use. *Epilepsia* 2005; **46:** 970–1.
2. Galimberti CA, *et al.* Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia* 2006; **47:** 1569–72.

Pharmacokinetics

Valproic acid and its salts are rapidly and completely absorbed from the gastrointestinal tract; the rate, but not the extent, of absorption is delayed if given with or after food.

Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other drugs that induce hepatic microsomal enzymes. It is excreted in the urine almost entirely in the form of its metabolites; small amounts are excreted in faeces and expired air.

Valproic acid is extensively bound to plasma proteins. The extent of protein binding is concentration dependent and is stated to be about 90 to 95% at total concentrations of 50 micrograms/mL, falling to about 80 to 85% at 100 micrograms/mL. Reported half-lives for valproic acid have ranged from about 5 to 20 hours; the shorter half-lives have generally been recorded in epileptic patients receiving multiple drug therapy. Clearance is usually higher in children than in adults.

The 'target' range of total plasma-valproic acid is usually quoted as being 40 to 100 micrograms/mL (280 to 700 micromoles/litre) but routine monitoring of plasma concentrations is not generally considered to be of use as an aid to assessing control.

Valproic acid crosses the placental barrier and small amounts are distributed into breast milk.

Valpromide is an amide derivative of valproic acid and its absorption is slower and its bioavailability somewhat less than that of valproic acid. Valpromide is rapidly and almost completely metabolised in the liver to valproic acid.

The pharmacokinetics of valproate are affected by other antiepileptics (see under Interactions, above).

◊ References.

1. Zaccara G, *et al.* Clinical pharmacokinetics of valproic acid—1988. *Clin Pharmacokinet* 1988; **15:** 367–89.
2. Bialer M. Clinical pharmacology of valpromide. *Clin Pharmacokinet* 1991; **20:** 114–22.
3. Cloyd JC, *et al.* Valproic acid pharmacokinetics in children IV: effects of age and antiepileptic drugs on protein binding and intrinsic clearance. *Clin Pharmacol Ther* 1993; **53:** 22–9.
4. Yukawa E, *et al.* Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug-drug interaction and patient characteristics. *J Clin Pharmacol* 1997; **37:** 1160–7.
5. Dutta S, *et al.* Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 737–42.
6. Dutta S, *et al.* Comparative absorption profiles of divalproex sodium delayed-release versus extended-release tablets: clinical implications. *Ann Pharmacother* 2006; **40:** 619–25.
7. Reed RC, *et al.* Every-12-hour administration of extended-release divalproex in patients with epilepsy: impact on plasma valproic acid concentrations. *Epilepsy Behav* 2006; **8:** 391–6.
8. Dutta S, *et al.* Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther* 2007; **32:** 365–71.

Uses and Administration

Valproate is an antiepileptic used particularly in the treatment of primary generalised seizures, has notable benefit in absence and myoclonic seizures, and is also used for partial seizures. Its actions are complex and its mode of action in epilepsy is not fully understood. Valproate is also used to treat the acute manic phase of bipolar disorder and for the prophylaxis of migraine.

Forms used include the sodium salts (valproate semisodium and sodium valproate), the amide derivative (valpromide), and valproic acid. Magnesium valproate has also been tried as has calcium valproate. Valproate should preferably be taken with or after food.

In the treatment of **epilepsy** the dose should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Plasma concentrations of valproate (see Pharmacokinetics, above) are not considered to be a useful index of efficacy and thus their routine monitoring is generally not helpful.

- A suggested initial *oral* daily dose of ***sodium valproate*** is 600 mg given in 2 divided doses. The daily dose may be increased by 200 mg every 3 days to a usual range of 1 to 2 g daily (20 to 30 mg/kg daily); up to a maximum of 2.5 g daily may be necessary if adequate control has not been achieved.

  When oral dosage is not possible, sodium valproate may be given *intravenously* to start therapy or to continue therapy previously given orally. A suggested dose to *begin* therapy is up to 10 mg/kg by intravenous injection over 3 to 5 minutes followed by intravenous infusion, as necessary, up to a maximum of 2.5 g daily. To *continue* therapy intravenously, doses are the same as the patient's previous oral dose. In the USA, intravenous sodium valproate is given in doses equivalent to those used orally for valproic acid (see below).

- A suggested initial oral dose of ***valproic acid*** is 10 to 15 mg/kg daily increased at one-week intervals by 5 to 10 mg/kg. The maximum recommended dose of valproic acid in the UK is 30 mg/kg daily whereas in the USA it is 60 mg/kg daily. Valproic acid may be given in 2 to 4 divided doses.
- ***Valproate semisodium*** is given orally in doses equivalent to those used for oral valproic acid (see above).
- The amide derivative of valproic acid, ***valpromide***, is also used in some countries. Usual oral doses have ranged from 600 mg to 1.8 g daily, in divided doses.

For details of valproate doses in children, see below.

As with other antiepileptics, withdrawal of valproate or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

In the treatment of acute manic episodes of **bipolar disorder**, the initial oral dose of ***valproate semisodium*** is the equivalent of valproic acid 750 mg daily in 2 to 3 divided doses. Thereafter, the dose is increased as rapidly as possible to achieve the optimal response, up to a maximum of 60 mg/kg daily. Patients receiving doses higher than 45 mg/kg daily should be carefully monitored. ***Valpromide*** has also been used in some countries for bipolar disorder in doses similar to those for epilepsy (see above).

In the prophylaxis of **migraine** valproate semisodium is given orally in a dose equivalent to valproic acid 250 mg twice daily; up to 1 g daily may be necessary in some patients.

Action. The actions of valproate are complex and not well understood. As well as enhancing central GABAergic neurotransmission and inhibiting neuronal sodium channels, it affects cellular signalling systems such as the Wnt/β-catenin and extracellular signal-regulated kinase (ERK) pathways, and has actions on inositol and arachidonate metabolism. In addition it has potent effects on transcription of a number of genes, mediated at least in part by its action as a direct histone deacetylase inhibitor. It is probable that its clinical effects in different disorders depend on a combination of such properties.[1]

1. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? *Cell Mol Life Sci* 2007; **64:** 2090–2103.

Administration in children. Valproate is used as an antiepileptic in children in the treatment of primary generalised seizures, notably for absence and myoclonic seizures, and also for partial seizures. Available forms include the sodium salts (valproate semisodium and sodium valproate) or as valproic acid. The *BNFC* suggests that sodium valproate may also be used for infantile spasms.

A suggested initial *oral* dose of ***sodium valproate*** for children weighing over 20 kg is 400 mg daily (irrespective of weight) in 2 divided doses. This may be gradually increased to a usual dose of 20 to 30 mg/kg daily; up to a maximum of 35 mg/kg daily may be necessary if adequate control has not been achieved. Children weighing under 20 kg may be given 20 mg/kg daily in 2 divided doses, which may be increased to 40 mg/kg daily or more if necessary (but see below). Alternatively the *BNFC* suggests the following *oral* or *rectal* doses, given according to age:

- neonates: initially 20 mg/kg once daily followed by a usual maintenance dose of 10 mg/kg twice daily
- 1 month to 12 years: initially 5 to 7.5 mg/kg twice daily followed by a usual maintenance dose of 12.5 to 15 mg/kg twice daily; up to 30 mg/kg twice daily may be given for infantile spasms (but see below)
- over 12 years: usual adult doses (see above)

When used rectally, the *BNFC* recommends that sodium valproate oral solution may be used and retained for 15 minutes; dilution with water may be required, if necessary.

When oral dosage is not possible, sodium valproate is licensed for use *intravenously* to start therapy or to continue therapy previously given orally. The usual dose is in the range of 20 to 30 mg/kg daily by intravenous injection over 3 to 5 minutes or by infusion; up to 40 mg/kg daily or more may be necessary if adequate control is not achieved (but see below). When switching from oral to intravenous therapy, the intravenous dose should be the same as the established oral dose.

Alternatively, the *BNFC* suggests giving neonates, children, and adolescents up to 18 years of age 10 mg/kg twice daily by intravenous injection; those aged from 1 month to 12 years may also be given 10 mg/kg initially by intravenous injection, followed by continuous infusion of 20 to 40 mg/kg daily, and older children may be given the usual adult doses (see above).

When a dose over 20 mg/kg daily is given, regardless of route, it is recommended that plasma-valproate concentrations should be monitored. If the dose exceeds 40 mg/kg daily, the patient's clinical chemistry and haematological parameters should also be monitored.

The *BNFC* states that children of all ages may be given ***valproic acid*** in doses as for sodium valproate (see above). In the USA, valproic acid is only licensed for children aged 10 years and older, who may be given the adult dose.

In the USA, ***valproate semisodium*** may also be given to children aged 10 years and over in the usual adult doses (see above) for the treatment of epilepsy.

Bipolar disorder. Valproate, usually as valproate semisodium, is increasingly being used as an alternative to lithium in patients with bipolar disorder (p.372).[1-9] Most guidelines consider it to be a first-line alternative to lithium particularly in those who have rapid cycling disease with 4 or more affective episodes a year or in those with mixed or dysphoric states. However, a study[9] failed to show particular benefit in rapid cycling disease, and systematic reviews considered that any shift in prescribing practice in favour of valproate was not based on reliable evidence of efficacy,[10] although it was effective in acute mania.[8]

1. Pope HG, *et al.* Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991; **48:** 62–8.
2. Joffe RT. Valproate in bipolar disorder: the Canadian perspective. *Can J Psychiatry* 1993; **38** (suppl 2): S46–S50.
3. Schaff MR, *et al.* Divalproex sodium in the treatment of refractory affective disorders. *J Clin Psychiatry* 1993; **54:** 380–4.
4. Bowden CL, *et al.* Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 1994; **271:** 918–24. Correction. *ibid.*; 1830.
5. Stoll AL, *et al.* Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* 1994; **14:** 311–13.
6. Swann AC, *et al.* Depression during mania: treatment response to lithium or divalproex. *Arch Gen Psychiatry* 1997; **54:** 37–42.
7. Müller-Oerlinghausen B, *et al.* Valproate as adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Psychopharmacol* 2000; **20:** 195–203.
8. Macritchie K, *et al.* Valproate for acute mood episodes in bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/06/08).
9. Calabrese JR, *et al.* A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 2005; **162:** 2152–61.
10. Macritchie KA, *et al.* Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Available in The Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 09/06/08).

Cushing's syndrome. Sodium valproate has been used in the management of Cushing's syndrome (p.2344).

Epilepsy. Valproate is one of the drugs of choice in partial seizures, primary generalised tonic-clonic seizures, absence seizures, and myoclonic seizures (see p.465), although evidence for some of these is lacking. It is also the drug of choice in epileptic syndromes such as the Lennox-Gastaut syndrome because of its wide therapeutic spectrum, and it may be useful in tonic or atonic seizures and infantile spasms.

References.

1. Mattson RH, *et al.* A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med* 1992; **327:** 765–71.
2. Richens A, *et al.* A multicentre trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57:** 682–7.
3. Verity CM, *et al.* A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol* 1995; **37:** 97–108.
4. Beydoun A, *et al.* and the Depakote Monotherapy for Partial Seizures Study Group. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. *Neurology* 1997; **48:** 182–8.
5. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; **34:** 199–205.
6. Posner EB, *et al.* Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
7. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. *Paediatr Drugs* 2006; **8:** 113–29.
8. Aldenkamp A, *et al.* Role of valproate across the ages: treatment of epilepsy in children. *Acta Neurol Scand* 2006; **184** (Suppl): 1–13.
9. Ben-Menachem E, *et al.* Role of valproate across the ages: treatment of epilepsy in adults. *Acta Neurol Scand* 2006; **184** (Suppl): 14–27.
10. Perucca E, *et al.* Role of valproate across the ages: treatment of epilepsy in the elderly. *Acta Neurol Scand* 2006; **184** (Suppl): 28–37.
11. Marson AG, *et al.* SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007; **369:** 1016–26.

Extrapyramidal disorders. Valproate is one of several drugs with GABAergic action that has been tried in the management of tardive dyskinesia (see under Extrapyramidal Disorders on p.971).

Febrile convulsions. Sodium valproate has been used prophylactically in children thought to be at risk of recurrence of febrile convulsions (p.470), but routine use of antiepileptics is no longer recommended.

References.

1. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988; **63:** 1189–91.

Headache. Valproate, as valproate semisodium, may be used for the prophylaxis of *migraine* (p.616) in patients refractory to drugs such as propranolol.[1-7] Valproate has also been shown to be effective and well-tolerated for the prophylaxis of migraine in children aged between 7 and 16 years.[8,9] Intravenous valproate has been tried in the treatment of acute migraine but a review[10] concluded that its use could not be recommended. To date, published studies had mostly been small, open-label, and non-placebo controlled and had used variable doses. Valproate had not been shown to be superior to other antimigraine drugs and had been inferior to prochlorperazine in one study.

Valproate has also been tried in the prophylaxis of persistent chronic daily headache including *tension-type headache* (p.617) unresponsive to other drugs.[11]

It has also been tried for prevention of *cluster headache* (p.616).

1. Sørensen KV. Valproate: a new drug in migraine prophylaxis. *Acta Neurol Scand* 1988; **78:** 346–8.
2. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia* 1992; **12:** 81–4.
3. Coria F, *et al.* Low-dose sodium valproate in the prophylaxis of migraine. *Clin Neuropharmacol* 1994; **17:** 569–73.
4. Mathew NT, *et al.* Migraine prophylaxis with divalproex. *Arch Neurol* 1995; **52:** 281–6.
5. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; **54:** 1141–5.
6. Erdemoglu AK, Ozbakir S. Valproic acid in prophylaxis of refractory migraine. *Acta Neurol Scand* 2000; **102:** 354–8.
7. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull* 2003; **37** (suppl 2): 98–115.
8. Caruso JM, *et al.* The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache* 2000; **40:** 672–6.
9. Ashrafi MR, *et al.* Sodium valproate versus propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol* 2005; **9:** 333–8.
10. Frazee LA, Foraker KC. Use of intravenous valproic acid for acute migraine. *Ann Pharmacother* 2008; **42:** 403–7.
11. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache: an open label study. *Headache* 1991; **31:** 71–4.

Hiccup. Valproic acid may be of value in the treatment of intractable hiccups,[1] especially those of neurogenic origin. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Jacobson PL, *et al.* Treatment of intractable hiccups with valproic acid. *Neurology* 1981; **31:** 1458–60.

HIV infection and AIDS. As mentioned under Precautions, above, valproate appears to induce replication of HIV, and this effect has been used to reduce latent, and therefore treatment-resistant, HIV-infection in resting CD4+ T-cells. In a preliminary study,[1] 4 HIV-positive patients on HAART were started on the fusion inhibitor enfuvirtide to intensify their HIV treatment and prevent viral spread due to valproate; oral valproic acid (500 to 750 mg twice daily) was then introduced a few weeks later and continued for 3 months. In 3 of these patients, the frequency of latent infection in resting T-cells significantly declined after enfuvirtide and valproate treatment when compared with pretreatment values. However, a later study[2] found the levels of latently infected T-cells in 9 HIV-positive patients receiving HAART and oral valproic acid for at least 3 months to be similar to those of patients receiving HAART alone. A case report[3] also described rapid rebound viraemia occurring in a 54-year-old man when HAART and sodium valproate were stopped after more than 2 years of therapy, suggesting little benefit in eradicating latent infection.

1. Lehrman G, *et al.* Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005; **366:** 549–55.
2. Siliciano JD, *et al.* Stability of the latent reservoir for HIV-1 in patients receiving valproic acid. *J Infect Dis* 2007; **195:** 833–6.
3. Steel A, *et al.* No change to HIV-1 latency with valproate therapy. *AIDS* 2006; **20:** 1681–2.

Malignant neoplasms. Valproate appears to have anti-tumour activity, thought to be mediated through the inhibition of cellular histone deacetylase. It has been tried[1-6] usually as an adjunct to other antineoplastics in the treatment of various malignancies, with some reported benefit.

1. Bug G, *et al.* Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia. *Cancer* 2005; **104:** 2717–25.
2. Raffoux E, *et al.* Treatment of elderly acute myeloid leukemia with valproic acid and all-trans retinoic acid. *Haematologica* 2005; **90:** 986–8.
3. Pilatrino C, *et al.* Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid. *Cancer* 2005; **104:** 101–9.
4. Chavez-Blanco A, *et al.* Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer: a phase I study. *Mol Cancer* 2005; **4:** 22. Full version: http://www.molecular-cancer.com/content/pdf/1476-4598-4-22.pdf (accessed 09/06/08)
5. Münster P, *et al.* Phase I trial of histone deacetylase inhibition by valproic acid followed by the topoisomerase II inhibitor epirubicin in advanced solid tumors: a clinical and translational study. *J Clin Oncol* 2007; **25:** 1979–85.
6. Blum W, *et al.* Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; **25:** 3884–91.

Migraine. See under Headache, above.

Muscle spasm. The mainstay of management of *spasticity* is physiotherapy and an antispastic drug (see p.1887). Valproate has been tried for its GABAergic activity and case reports[1] of 4 patients with spastic conditions of various aetiologies indicated that the addition of valproate to the existing regimen of antispastic drugs might produce improvements in spasticity and pain; further studies are warranted.

Valproate has also been tried[2] in the management of *stiff-man syndrome* (see under Muscle Spasm, p.993) unresponsive to diazepam.

1. Zachariah SB, *et al.* Positive response to oral divalproex sodium (Depakote) in patients with spasticity and pain. *Am J Med Sci* 1994; **308:** 38–40.
2. Spehlmann R, *et al.* Improvement of stiff-man syndrome with sodium valproate. *Neurology* 1981; **31:** 1162–3.

Myoclonus. Valproate is used alone or in combination with clonazepam for cortical myoclonus (see p.470).

Neuropathic pain. Although carbamazepine is the drug of choice in the treatment of *trigeminal neuralgia* (p.9), sodium valproate is an alternative antiepileptic that may be used in carbamazepine-intolerant patients. Valproate has also been tried, with some success, in painful *diabetic neuropathy*[1] (p.6), *postherpetic neuralgia*[2] (p.9), and neuropathic *cancer pain*[3] (p.5). However, a placebo-controlled study[4] did not find any benefit with valproate therapy in the treatment of pain in diabetic and nondiabetic polyneuropathy.

1. Kochar DK, *et al.* Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. *QJM* 2004; **97:** 33–8.
2. Kochar DK, *et al.* Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *QJM* 2005; **98:** 29–34.
3. Hardy JR, *et al.* A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2001; **21:** 204–9.
4. Otto M, *et al.* Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. *Neurology* 2004; **62:** 285–8.

Psychiatric disorders. Valproate has psychotropic properties and has been used in the management of bipolar disorder (see above) and in some countries as a mood stabiliser for augmentation of antidepressant therapy in the treatment of resistant depression (p.373). Valproate has also been tried in various disorders for the control of symptoms such as agitation, aggression, and rage[1,2] (see Disturbed Behaviour, p.954). However, a systematic review of the use of valproate for agitation in dementia found no convincing evidence of efficacy at low doses, and adverse effects may be unacceptable at higher doses.[3] Valproate has also been reported[4,5] to be efficacious as adjunctive therapy to antipsychotics, but again, systematic review[6] has thrown doubt upon its effectiveness. It has also been tried in anxiety disorders such as panic disorder[7-9] (p.952), and post-traumatic stress disorder[10,11] (p.953).

1. Geracioti TD. Valproic acid treatment of episodic explosiveness related to brain injury. *J Clin Psychiatry* 1994; **55:** 416–17.
2. Narayan M, *et al.* Treatment of dementia with behavioral disturbances using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997; **58:** 351–4.
3. Lonergan ET, Luxenberg J. Valproate preparations for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 09/06/08).
4. Wassef AA, *et al.* Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* 2000; **20:** 357–61.
5. Grove VE, *et al.* Improvement of Huntington's disease with olanzapine and valproate. *N Engl J Med* 2000; **343:** 973–4.
6. Basan A, *et al.* Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophr Res* 2004; **70:** 33–7.
7. Primeau F, *et al.* Valproic acid and panic disorder. *Can J Psychiatry* 1990; **35:** 248–50.
8. Keck PE, *et al.* Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993; **33:** 542–6.
9. Woodman CL, Noyes R. Panic disorder: treatment with valproate. *J Clin Psychiatry* 1994; **55:** 134–6.
10. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991; **52:** 361–4.
11. Petty F, *et al.* Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 100–101.

Status epilepticus. Valproate has been used in *absence* status epilepticus once the initial attack has been brought under control with intravenous benzodiazepines[1] and has been considered to be the drug of choice to prevent its recurrence.[2] Its place in the management of *convulsive* status epilepticus (p.469) is less clear, but it has been tried, mainly as a second- or third-line drug in benzodiazepine-refractory patients,[3-12] and some centres have included it in management protocols.[5]

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Berkovic SF, *et al.* Valproate prevents the recurrence of absence status. *Neurology* 1989; **39:** 1294–7.
3. Giroud M, *et al.* Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993; **5:** 154–9.
4. Hovinga CA, *et al.* Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. *Ann Pharmacother* 1999; **33:** 579–84.
5. Campistol J, *et al.* Estado de mal convulsivo en el niño: experiencia con valproato endovenoso, actualización del protocolo de tratamiento. *Rev Neurol* 1999; **29:** 359–65.
6. Peters CNA, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; **14:** 164–9.
7. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
8. Limdi NA, *et al.* Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005; **64:** 353–5.
9. Misra UK, *et al.* Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006; **67:** 340–2.
10. Olsen KB, *et al.* Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand* 2007; **187** (Suppl): 51–4.
11. Agarwal P, *et al.* Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; **16:** 527–32.
12. Mehta V, *et al.* Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007; **22:** 1191–7.

Preparations

BP 2008: Gastro-resistant Sodium Valproate Tablets; Sodium Valproate Oral Solution; Sodium Valproate Tablets;
USP 31: Divalproex Sodium Delayed-Release Tablets; Valproate Sodium Injection; Valproic Acid Capsules; Valproic Acid Syrup.

Proprietary Preparations (details are given in Part 3)
Arg.: Depakene; Exibral; Logical; Tekaval†; Valcote; Valnar; ***Austral.:*** Epilim; Valpro; ***Austria:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Epival†; ***Belg.:*** Convulex; Depakine; ***Braz.:*** Depakene; Depakote; Epilenil; Torval; Valpakine; Valprene; ***Canad.:*** Depakene; Epiject; Epival; ***Chile:*** Atemperator; Depakene; DI VP; Leptilan†; Neuractin; Valcote; ***Cz.:*** Absenor; Convulex; Convulsofin†; Depakine; Depakine Chrono; Everiden; Orfiril; ***Denm.:*** Delepsine; Deprakine; Orfiril; ***Fin.:*** Absenor; Deprakine; Deprakine Depot; Orfiril; ***Fr.:*** Depakine; Depakine Chrono; Depakote; Depamide; Micropakine; ***Ger.:*** Convulex; Convulsofin; Ergenyl; Ergenyl Chrono; Espa-Valept†; Leptilan; Orfiril; Valpro; Valpro Beta; Valprodura; Valproflux†; Valprolept†; ValproNa†; ***Gr.:*** Depakine; Depakine Chrono; ***Hong Kong:*** Epilim; Valpro; ***Hung.:*** Convulex; Depakine; Depakine Chrono; Everiden†; Orfiril; ***India:*** Diproex; Epilex; Valcontin; Valparin; Valrate CR; Valtec; ***Indon.:*** Depakene; Depakote; ***Irl.:*** Epilim; Epilim Chrono; ***Israel:*** Depalept; Depalept Chrono; Orfiril; Valporal; ***Ital.:*** Depakin; Depakin Chrono; Depamag; Depamide; ***Jpn:*** Depakene; ***Malaysia:*** Epilim; Orfiril; ***Mex.:*** Atemperator; Criam; Depakene; Edorame; Epival; Leptilan; Pimiken; Provetal†; Trankitec; Valprosid†; ***Neth.:*** Convulex†; Depakine; Depakine Chrono; Orfiril; Propymal; ***Norw.:*** Deprakine; Orfiril; ***NZ:*** Epilim; ***Philipp.:*** Depakene; Depakote; Epival; ***Pol.:*** Convulex; Depakine; Depakine Chrono; Depakine Chronosphere; Depamide; Dipromal; Orfiril; ***Port.:*** Depakine; Depakine Chrono; Depakine Chronosphere; Diplexil; Diplexil-R; Valprolim; ***Rus.:*** Apilepsin (Апилепсин); Convulex (Конвулекс); Convulsofin (Конвульсофин); Depakine (Депакин); Depakine Chrono (Депакин Хроно); Encorate (Энкорат); Encorate Chrono (Энкорат Хроно); Valparin XR (Вальпарин ХР); ***S.Afr.:*** Convulex; Epilim; ***Singapore:*** Convulex; Epilim; Orfiril†; Valparin; ***Spain:*** Depakine; Depakine Crono; Depamide; Milzone; ***Swed.:*** Absenor; Ergenyl; Orfiril; ***Switz.:*** Convulex; Depakine; Depakine Chrono; Orfiril; ***Thai.:*** Depakine; Desorate; Encorate; Valparin; ***Turk.:*** Convulex; Depakin; ***UAE:*** Valopin; ***UK:*** Convulex; Depakote; Epilim; Epilim Chrono; Episenta; Orlept; ***USA:*** Depacon; Depakene; Depakote; Mendatrex; ***Venez.:*** Depakine; Valcote; Valpron.

Vigabatrin *(BAN, USAN, rINN)*

4-Amino-5-hexenoic Acid; MDL-71754; RMI-71754; Vigabatriini; Vigabatrina; Vigabatrine; Vigabatrinum; γ-Vinyl Aminobutyric Acid; γ-Vinyl-GABA. 4-Aminohex-5-enoic acid.

Вигабатрин

$C_6H_{11}NO_2$ = 129.2.

CAS — 60643-86-9.

ATC — N03AG04.

ATC Vet — QN03AG04.

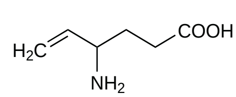

Pharmacopoeias. In *Br.*

BP 2008 (Vigabatrin). A white to almost white powder. Very soluble in water.

Adverse Effects, Treatment, and Precautions

About half of all patients experience adverse effects with vigabatrin. The most common are drowsiness and fatigue, although in children excitation and agitation occur more frequently. The incidence of these effects is generally higher at the start of therapy and decreases over time. Other CNS-related adverse effects include dizziness, headache, ataxia, paraesthesia, tremor, impaired concentration, confusion, and memory disturbances. Other reported adverse effects include weight gain, gastrointestinal disturbances, oedema, alopecia, angioedema, urticaria, and skin rash. Haemoglobin and liver enzyme values may be decreased. Rarely marked sedation, stupor and confusion, together with other symptoms suggestive of encephalopathy, have occurred.

About one-third of all patients receiving vigabatrin have developed irreversible visual field defects, ranging from mild to severe and usually occurring after months or years of therapy. Blurred vision, diplopia, or nystagmus are somewhat less common. Retinal disorders such as peripheral retinal atrophy, or very rarely optic neuritis or atrophy have also been reported (see also below). Visual field function should be assessed before beginning treatment and during routine follow-up (ideally at 6-month intervals), and patients should be warned to report any new visual symptoms that develop during therapy. Vigabatrin should not be used in patients with pre-existing visual field defects.

Psychiatric reactions such as agitation, aggression, irritability, nervousness, depression, and paranoid reactions have occurred in patients with or without a psychiatric history; psychosis, hypomania, or mania have been reported rarely. Patients receiving vigabatrin should be observed carefully for any signs of adverse effects on neurological function. Caution is warranted in patients with a history of psychosis, depression, or behavioural problems.

Vigabatrin may exacerbate myoclonic or absence seizures.

Vigabatrin should be given with caution to the elderly and patients with renal impairment.

Care is required when withdrawing vigabatrin therapy—see also Uses and Administration, below.

Breast feeding. Licensed product information states that breast feeding is not recommended in women receiving vigabatrin. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Particular care should be taken in view of the possible effects of vigabatrin on visual acuity.

Effects on bone. For the effects of antiepileptics, including vigabatrin, on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.496.

Effects on the eyes. A report of 3 patients who developed bilateral severely constricted visual fields 2 to 3 years after vigabatrin was added to their antiepileptic regimens[1] prompted publication of similar anecdotal reports.[2-5] Peripheral retinal atrophy rather than optic nerve damage appeared to be the cause. Symptoms showed no improvement on stopping the drug, although there was no further deterioration. At that time (1997) the manufacturers replied[6] stating that it was a rare occurrence (less than 0.1%) and was being monitored in further clinical studies. The UK CSM subsequently stated[7] (in March 1998) that it had received 41 reports of visual field defects since December 1989, which persisted in most cases despite stopping treatment. The evidence suggested that the onset of symptoms varied from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite stopping vigabatrin.[8,9] Interim results of a Prescription Event Monitoring Study[10] in the UK stated that vigabatrin was considered to be probably or possibly associated with objective evidence of a visual field defect in 0.2% of patients. However, subsequent evidence appears to have confirmed that the incidence of visual field defects is much higher;[11-14] revised product literature issued in late 1999 indicated that visual field defects occurred in about one-third of all patients receiving vigabatrin. Male patients appear to be at an increased risk of developing defects.[15,16] Whether cumulative dose may be considered a risk factor remains unclear.[16,17]

The CSM considered[14] that vigabatrin should only be prescribed by a specialist, and only where all other combination therapies have failed. Ophthalmological consultation and visual field assessment should be undertaken before starting vigabatrin and visual field screening repeated at 6-monthly intervals during treatment. Conventional perimetry is unsuitable in patients under 9 years of age, in whom alternative methods should be employed. Opinion amongst some paediatricians[18] was that the risk of developing visual field defects had to be weighed against the potential benefit of seizure control. In very young patients, in whom monitoring of vision was impossible, the benefits of vigabatrin in the treatment of infantile spasms were felt by some to outweigh this risk.[19]

Vigabatrin should not be used in patients with pre-existing visual field defects.[14,18]

1. Eke T, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 180–1.
2. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693.
3. Wong ICK, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1693–4.
4. Blackwell N, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
5. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694.
6. Backstrom JT, *et al.* Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997; **314:** 1694–5.
7. Committee of Safety of Medicines/Medicines Control Agency. Vigabatrin (Sabril) and visual field defects. *Current Problems* 1998; **24:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
8. Hardus P, *et al.* Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. *Br J Ophthalmol* 2000; **84:** 788–90.
9. Johnson MA, *et al.* Visual function loss from vigabatrin: effect of stopping the drug. *Neurology* 2000; **55:** 40–5.
10. Wilton LV, *et al.* Interim report on the incidence of visual field defects in patients on long term vigabatrin therapy. *Pharmacoepidemiol Drug Safety* 1999; **8** (suppl): S9–S14.
11. Wilton LV, *et al.* Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999; **319:** 1165–6.
12. Kälviäinen R, *et al.* Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual defects. *Neurology* 1999; **53:** 922–6.
13. Lawden MC, *et al.* Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999; **67:** 716–22.
14. Committee on Safety of Medicines/Medicines Control Agency. Vigabatrin (Sabril): visual field defects. *Current Problems* 1999; **25:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 09/06/08)
15. Kälviäinen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001; **15:** 217–30.
16. Wild JM, *et al.* Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007; **48:** 1318–27.
17. Kinirons P, *et al.* Vigabatrin retinopathy in an Irish cohort: lack of correlation with dose. *Epilepsia* 2006; **47:** 311–17.
18. Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998; **317:** 1322.
19. Harding GFA. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1998; **316:** 232–3.

Effects on the liver. Vigabatrin has demonstrated *in-vivo* and *in-vitro* inhibition of plasma-alanine transaminase activity, which may mask signs of early underlying hepatic disease if only transaminase levels are evaluated.[1]

1. Richens A, *et al.* Evidence for both in vivo and in vitro interaction between vigabatrin and alanine transaminase. *Br J Clin Pharmacol* 1997; **43:** 163–8.

Effects on mental function. *Behavioural disturbances* ranging from irritability and confusion to psychotic reactions have been reported in patients receiving vigabatrin.[1-7] An analysis[8] of adverse effect reports from double-blind controlled studies found that the incidence of psychotic reactions was about 2.5% in vigabatrin-treated patients; however, the most common psychiatric reaction was depression, which occurred in 8 to 12% of patients. Symptoms of psychiatric disturbance were often relatively mild. Psychiatric reactions are generally reversible when doses are reduced or gradually stopped. In 2 patients[9,10] psychosis developed after sudden withdrawal of vigabatrin; mental state improved when the drug was reinstated. It is not clear whether patients with a history of previous psychiatric disturbances are at greater risk when given vigabatrin.[8,11] Also, using low doses of vigabatrin to start therapy did not reduce the incidence of disturbances.[11]

The problems of antiepileptic therapy adversely affecting *cognition* and *mood* (including the risk of suicidal ideation) are discussed on p.468.

1. Sander JWAS, Hart YM. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 57.
2. Dam M. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605.
3. Betts T, Thomas L. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 605–6.
4. Johnston SJ. Vigabatrin and behaviour disturbances. *Lancet* 1990; **335:** 606.
5. Robinson MK, *et al.* Vigabatrin and behaviour disturbances. *Lancet* 1990; **336:** 504.
6. Martínez AC, *et al.* Vigabatrin-associated reversible acute psychosis in a child. *Ann Pharmacother* 1995; **29:** 1115–17.
7. Naumann M, *et al.* Bipolar affective psychosis after vigabatrin. *Lancet* 1994; **343:** 606–7.
8. Levinson DF, Devinsky O. Psychiatric adverse events during vigabatrin therapy. *Neurology* 1999; **53:** 1503–11.
9. Ring HA, Reynolds EH. Vigabatrin and behaviour disturbance. *Lancet* 1990; **335:** 970.
10. Brodie MJ, McKee PJW. Vigabatrin and psychosis. *Lancet* 1990; **335:** 1279.
11. Wong ICK. Retrospective study of vigabatrin and psychiatric behavioural disturbances. *Epilepsy Res* 1995; **21:** 227–30.

Effects on the nervous system. Two patients developed disturbances of motor behaviour associated with the addition of vigabatrin to therapy for intractable seizures.[1]

Acute encephalopathy was reported[2] in two patients after starting vigabatrin in addition to carbamazepine; symptoms of stupor, dysphoria, and irritability were present in both and their EEG background activity was slowed. Clinical symptoms could not be related to intoxication with carbamazepine or its epoxide but it was not known whether an interaction between carbamazepine and vigabatrin had caused the acute encephalopathy. Acute encephalopathy was also reported[3] when vigabatrin was given to a 6-month-old girl who was also receiving phenobarbital. Symptoms resolved when vigabatrin was stopped. In another report[4] vigabatrin was associated with the development of encephalopathy in 3 patients already receiving a variety of antiepileptic drugs other than carbamazepine; withdrawal of vigabatrin led to full recovery. The authors suggested that acute encephalopathy after vigabatrin may be related to a pre-existing cerebral abnormality. Other predisposing factors suggested by licensed product information include higher than recommended initial doses, faster dose increases at greater increments than those recommended, and renal failure.

1. Jongsma MJ, *et al.* Reversible motor disturbances induced by vigabatrin. *Lancet* 1991; **338:** 893.
2. Sälke-Kellermann A, Baier H. Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 185.
3. Haas-Lude K, *et al.* Acute encephalopathy associated with vigabatrin in a six-month-old girl. *Epilepsia* 2000; **41:** 628–30.
4. Sharief MK, *et al.* Acute encephalopathy with vigabatrin. *Lancet* 1993; **342:** 619.

Interference with diagnostic tests. Vigabatrin can cause changes in the urinary excretion of amino acids which could be potentially misleading in patients undergoing investigation for metabolic disorders.[1,2]

1. Bonham JR, *et al.* Pyroglutamicaciduria from vigabatrin. *Lancet* 1989; **i:** 1452–3.
2. Shih VE, Tenanbaum A. Aminoaciduria due to vinyl-gaba administration. *N Engl J Med* 1990; **323:** 1353.

Overdosage. For a review of the features and management of poisoning with some antiepileptics such as vigabatrin, see under Phenytoin, p.497.

Porphyria. For comment on the use of vigabatrin in porphyria, see p.471.

Pregnancy. For comments on the management of epilepsy in pregnancy, see p.468.

Little is known of the effects of newer antiepileptics such as vigabatrin on the fetus, although congenital anomalies have been reported in the offspring of some mothers using vigabatrin during pregnancy.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Antiepileptics. For the effect of vigabatrin on plasma concentrations of other antiepileptics, see *Carbamazepine*, p.474; *Phenobarbital*, p.493; *Phenytoin*, p.498; and *Primidone*, p.503.

Pharmacokinetics

Vigabatrin is well absorbed after oral doses of the racemate; the inactive *R*(–)-enantiomer is reported to be present at much higher plasma concentrations than the active *S*(+)-enantiomer, perhaps indicating a difference in bioavailability. About 60 to 80% of an oral dose is excreted in urine as unchanged drug. The elimination half-life is reported to be 5 to 8 hours. Vigabatrin is not significantly bound to plasma proteins.

There does not appear to be any correlation between plasma concentrations of vigabatrin and its efficacy or toxicity. Children exhibit a lower area under the concentration-time curve than adults and may need higher doses to achieve therapeutic plasma concentrations.

Vigabatrin crosses the placenta and is distributed into breast milk.

◊ References.

1. Rey E, *et al.* Vigabatrin: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 267–78.
2. Hoke JF, *et al.* Pharmacokinetics of vigabatrin following single and multiple oral doses in normal volunteers. *J Clin Pharmacol* 1993; **33:** 458–62.
3. Elwes RDC, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin and oxcarbazepine. *Clin Pharmacokinet* 1996; **30:** 403–15.
4. Vauzelle-Kervroëdan F, *et al.* Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. *Br J Clin Pharmacol* 1996; **42:** 779–81.
5. Jacqz-Aigrain E, *et al.* Pharmacokinetics of the S(+) and R(–) enantiomers of vigabatrin during chronic dosing in a patient with renal failure. *Br J Clin Pharmacol* 1997; **44:** 183–5.
6. Armijo JA, *et al.* Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. *Ther Drug Monit* 1997; **19:** 491–8.
7. Tran A, *et al.* Vigabatrin: placental transfer in vivo and excretion into breast milk of the enantiomers. *Br J Clin Pharmacol* 1998; **45:** 409–11.

Uses and Administration

Vigabatrin is an analogue of gamma-aminobutyric acid (GABA) that acts as an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the catabolism of GABA. It is used as an adjunctive antiepileptic in patients with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as adjunctive therapy is 1 g daily, increased, according to response and tolerability, in increments of 500 mg at weekly intervals to a maximum of 3 g daily.

Doses may be divided and given twice daily or taken as a single daily dose. Dosage reductions may be required in the elderly and in patients with renal impairment, particularly those with a creatinine clearance of less than 60 mL/minute.

For details of doses in children, see below.

As with other antiepileptics, withdrawal of vigabatrin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465. Licensed product information recommends that the dose of vigabatrin should be gradually reduced over 2 to 4 weeks.

◊ References.

1. Wheless JW, *et al.* Vigabatrin. *Neurotherapeutics* 2007; **4:** 163–72.

Administration in children. Vigabatrin is used as an adjunctive antiepileptic in children with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. It is also used as monotherapy for infantile spasms (as for example in West's syndrome).

The recommended initial oral dose of vigabatrin as *adjunctive therapy* is 40 mg/kg daily, as a single dose or in 2 divided doses. Maintenance doses are given according to body-weight as follows:

- 10 to 15 kg: 0.5 to 1 g daily
- 15 to 30 kg: 1 to 1.5 g daily
- 30 to 50 kg: 1.5 to 3 g daily
- over 50 kg: 2 to 3 g daily

Alternatively, the *BNFC* suggests giving the following oral doses according to age:

- neonates to 12 years: initially 15 to 20 mg/kg twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 30 to 40 mg/kg twice daily; maximum 150 mg/kg daily
- 12 to 18 years: initially 1 g twice daily, increased over 2 to 3 weeks to a usual maintenance dose of 1 to 1.5 g twice daily

Vigabatrin has been given rectally; in the UK, the *BNFC* has suggested that children over 1 month old may be given the same rectal doses, calculated by age, as those used orally (see above). The commercially available oral powder should be dissolved in a small amount of water before use.

For *monotherapy* in infantile spasms, the recommended initial oral dose of vigabatrin is 50 mg/kg daily, adjusted according to response. Up to 150 mg/kg daily has been used. The *BNFC* suggests starting with 15 to 25 mg/kg twice daily, adjusted according to response over 7 days; the usual maintenance dose is 40 to 50 mg/kg twice daily (maximum of 75 mg/kg twice daily) for neonates and children up to 2 years of age.

Epilepsy. Vigabatrin is used in the treatment of epilepsy (p.465) as adjunctive therapy for refractory seizures. Reviews[1-3] of vigabatrin have considered it to be most effective in the treatment of complex partial seizures with or without secondary generalisation; it may, however, exacerbate myoclonic or absence seizures. Efficacy as adjunctive therapy in refractory partial seizures was shown by 2 multicentre studies[4,5] involving 228 patients (including 46 children) and a study[6] involving 52 patients being assessed for epilepsy surgery. However, in a follow-up study[7] of 120 patients who had participated in an open-label study of vigabatrin as adjunctive therapy for refractory epilepsy 6 to 8 years earlier, it was considered that vigabatrin had had only marginal benefit on the long-term prognosis of severe refractory epilepsy, despite favourable results from the original trial.

Vigabatrin is also of value in infantile spasms (as for example in West's syndrome). In an assessment of vigabatrin as monotherapy in 192 infants with infantile spasms who were followed up for an average of 7.6 months,[8] there was complete cessation of spasms in 131 patients, a decrease in cluster frequency in 37, and no improvement in 24 (including deterioration in 1 infant). A crossover study comparing vigabatrin with corticotropin in 42 infants found that both drugs produced some benefit;[9] a larger multicentre comparison of treatment with prednisolone and tetracosactide versus vigabatrin found that the former produced better initial control, but that the treatments were equivalent after more prolonged follow-up to 12 to 14 months of age.[10] A review of the literature suggested that vigabatrin was particularly effective in infantile spasms associated with tuberous sclerosis;[11] the authors considered that its efficacy might be less in other forms of infantile spasm.[11] A later guideline[12] also tentatively concluded that vigabatrin was effective in the short-term treatment of infantile spasms including those associated with tuberous sclerosis.

1. French JA. Vigabatrin. *Epilepsia* 1999; **40** (suppl 5): S11–S16.
2. Gidal BE, *et al.* Vigabatrin: a novel therapy for seizure disorders. *Ann Pharmacother* 1999; **33:** 1277–86.
3. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001 **43:** 833–5.
4. Dalla Bernadina B, *et al.* Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* 1995; **36:** 687–91.
5. French JA, *et al.* A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996; **46:** 54–61.
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7. Walker MC, *et al.* Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996; **313:** 1184–5.
8. Aicardi J, *et al.* Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37:** 638–42.
9. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997; **38:** 1270–4.
10. Lux AL, *et al.* The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005; **4:** 712–17.
11. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis. *J Child Neurol* 1999; **14:** 71–4.
12. Mackay MT, *et al.* Practice parameter: medical treatment of infantile spasms—report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; **62:** 1668–81.

Metabolic disorders. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been tried in GABA metabolic disorders, with or without concurrent epilepsy,[1-5] with ambivalent results. Data from 23 case reports of patients with succinic semialdehyde dehydrogenase deficiency indicated that vigabatrin was clinically beneficial in only about one-third of patients.[4]

1. Jaeken J, *et al.* Vigabatrin in GABA metabolism disorders. *Lancet* 1989; **i**: 1074.
2. Gibson KM, *et al.* Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet* 1989; **ii:** 1105–6.
3. Stephenson JBP. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. *Lancet* 1992; **340:** 430–1.
4. Gibson KM, *et al.* The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997; **99:** 567–74.
5. Leuzzi V, *et al.* Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2007; **68:** 1320–1.

Stiff-man syndrome. There have been anecdotal reports[1-3] of improvement of stiff-man syndrome (see under Muscle Spasm, p.993) with vigabatrin in patients unable to tolerate benzodiazepine therapy.

1. Vermeij FH, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Lancet* 1996; **348:** 612.
2. Prevett MC, *et al.* Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1997; **48:** 1133–4.
3. Sharoqi IA. Improvement of stiff-man syndrome with vigabatrin. *Neurology* 1998; **50:** 833–4.

Preparations

BP 2008: Vigabatrin Oral Powder; Vigabatrin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sabril; ***Austral.:*** Sabril; ***Austria:*** Sabril; ***Belg.:*** Sabril; ***Braz.:*** Sabril; ***Canad.:*** Sabril; ***Chile:*** Sabril; ***Cz.:*** Sabril; ***Denm.:*** Sabrilex; ***Fin.:*** Sabrilex; ***Fr.:*** Sabril; ***Ger.:*** Sabril; ***Gr.:*** Sabril; ***Hong Kong:*** Sabril; ***Hung.:*** Sabril; ***Irl.:*** Sabril; ***Israel:*** Sabrilan; ***Ital.:*** Sabril; ***Mex.:*** Sabril; ***Neth.:*** Sabril; Sabrilex; ***Norw.:*** Sabrilex; ***NZ:*** Sabril; ***Pol.:*** Sabril; ***Port.:*** Sabril; ***S.Afr.:*** Sabril; ***Singapore:*** Sabril; ***Spain:*** Sabrilex; ***Swed.:*** Sabrilex; ***Switz.:*** Sabril; ***Turk.:*** Sabril; ***UK:*** Sabril.

Zonisamide *(BAN, USAN, rINN)*

AD-810; CI-912; PD-110843; Zonisamida; Zonisamidum. 1-(1,2-Benzoxazol-3-yl)methanesulphonamide.

Зонизамид

$C_8H_8N_2O_3S = 212.2.$

CAS — 68291-97-4.

ATC — N03AX15.

ATC Vet — QN03AX15.

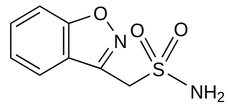

Adverse Effects

The most common adverse effects with zonisamide have included anorexia, gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea, somnolence, dizziness, headache, ataxia, depression, and agitation or irritability. Severe, sometimes fatal, skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. There have been isolated reports of aplastic anaemia, agranulocytosis, thrombocytopenia, leucopenia, pancytopenia, and leucocytosis.

Other adverse effects have included renal calculi (see below), renal impairment, pancreatitis, rhabdomyolysis, abnormal liver function tests, psychosis, psychomotor slowing, reduced concentration, speech or language difficulties, paraesthesia, nystagmus, diplopia, weight loss, and fatigue. Reduced sweating with hyperthermia has occurred in children (see below).

Effects on mental function. For a review of the effects of antiepileptic therapy including zonisamide on *cognition* and *mood* (including the risk of suicidal ideation), see p.468.

Hyperthermia. Decreased sweating and hyperthermia have been reported in patients given zonisamide. By the end of December 2001 the manufacturers in the USA were aware of 40 such cases; of these, 38 had occurred in the first 11 years of marketing in Japan and 2 in the first year of marketing in the USA. Many cases were reported after exposure to high ambient temperatures and some progressed to heat stroke, but none had led to death.

The manufacturer noted that children appeared to be at an increased risk of developing these adverse reactions and should be monitored closely for such effects especially during warm or hot weather. Caution was also advised when zonisamide was given with other drugs known to cause similar effects, for example, carbonic anhydrase inhibitors and antimuscarinics.[1]

1. O'Brien C [Elan Pharmaceuticals]. Important drug warning. Available at: http://www.fda.gov/medwatch/SAFETY/2002/Zonegran_deardoc.pdf (accessed 14/05/04)

Renal calculi. Patients treated with zonisamide in the USA and Europe may have had a higher incidence of renal calculi than those treated in Japan. In one US study,[1] 4 of 113 patients (3.5%) receiving long-term treatment with zonisamide developed renal calculi, but a familial relationship was found for 2. In pooled data[2] from earlier studies, renal calculi had been reported in 13 of 700 patients (1.9%) treated in the USA and Europe compared with 2 of 1008 patients (0.2%) in Japan. Another review,[3] involving information from more than 750 patients, considered the risk of renal calculi in zonisamide-treated patients to be 5 to 9 times greater than that in the general population. However, a later study[4] that evaluated all safety data available at the time (from the US and European clinical trial programme and the manufacturer's postmarketing surveillance database) found the prevalence of symptomatic renal calculi to be low. There has been a report[5] of 3 patients who developed renal calculi associated with zonisamide but were able to continue therapy with hydration and/or citrate supplementation.

1. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
2. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
3. Bennett WM. Risk of kidney stones in patients treated with zonisamide. *Neurology* 2002; **58** (suppl 3): A298–A299.
4. Wroe S. Zonisamide and renal calculi in patients with epilepsy: how big an issue? *Curr Med Res Opin* 2007; **23:** 1765–73.
5. Richards KC, *et al.* Continued use of zonisamide following development of renal calculi. *Neurology* 2005; **64:** 763–4.

Precautions

Zonisamide is a sulfonamide derivative and is therefore contra-indicated in patients with a history of hypersensitivity to sulfonamides.

It should be used with care in patients with renal impairment; there is no data on safety in those with hepatic impairment. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis; adequate hydration is recommended to increase urine output, to try to reduce the risk of developing renal calculi, especially in predisposed patients.

Pancreatic lipase and amylase levels should be monitored in patients who develop pancreatitis and consideration should be given to withdrawing zonisamide. Patients who develop severe muscle pain or weakness, with or without fever, should have their serum creatine phosphokinase and aldolase levels assessed; if these are elevated, zonisamide may need to be withdrawn. A dietary supplement or increased food intake may be appropriate in patients who are losing weight or are underweight with zonisamide; withdrawing zonisamide may be warranted in those with substantial undesirable weight loss. Consideration should be given to withdrawing zonisamide in patients who develop unexplained rash.

Care is required when withdrawing zonisamide therapy—see also Uses and Administration below.

Breast feeding. Zonisamide is distributed into breast milk;[1] in view of the potential for serious adverse effects in infants from zonisamide, licensed product information recommends that it should only be used in nursing mothers if the benefits outweigh the risks. It is also recommended that breast feeding must not be resumed until 1 month after stopping zonisamide therapy. For comment on antiepileptic therapy and breast feeding, see p.467.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Pregnancy. Zonisamide crosses the placenta.[1] For comments on the management of epilepsy during pregnancy, see p.468.

1. Kawada K, *et al.* Pharmacokinetics of zonisamide in perinatal period. *Brain Dev* 2002; **24:** 95–7.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Use with drugs that induce or inhibit the cytochrome P450 isoenzyme CYP3A4 may alter plasma concentrations of zonisamide. Carbamazepine, phenytoin, or phenobarbital reduce the half-life of zonisamide; reductions have also been noted with valproate but to a lesser degree.

The use of zonisamide with other drugs that cause nephrolithiasis should be avoided because of the increased risk of developing renal calculi (see under Adverse Effects, above). Caution is advised when zonisamide is used with other drugs known to cause heat-related disorders because of the increased risk of developing hyperthermia (see Adverse Effects, above).

◊ References.

1. Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007; **48:** 435–41.

Pharmacokinetics

Zonisamide is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 2 to 6 hours of oral doses. Bioavailability is essentially complete; the presence of food does not affect the bioavailability of zonisamide but the time to reach peak plasma concentrations is delayed. Steady-state concentrations are achieved within 14 days. It is widely distributed into body tissues. Plasma protein binding is low (40 to 50%) but zonisamide is extensively bound to erythrocytes. The plasma elimination half-life is about 63 hours.

Zonisamide undergoes acetylation to *N*-acetylzonisamide and reduction mediated by the cytochrome P450 isoenzyme CYP3A4 to 2-sulfamoylacetylphenol (SMAP); both metabolites are inactive. Excretion is mainly in the urine; about 15 to 30% appearing as

The symbol † denotes a preparation no longer actively marketed

unchanged drug, 15% as *N*-acetylzonisamide, and 50% as the glucuronide of SMAP.

Zonisamide crosses the placenta and is distributed into breast milk.

The pharmacokinetics of zonisamide are affected by use with other antiepileptics (see under Interactions, above).

◊ References.

1. Kochak GM, *et al.* Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. *J Clin Pharmacol* 1998; **38:** 166–71.
2. Mimaki T. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther Drug Monit* 1998; **20:** 593–7.
3. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure* 2004; **13** (suppl 1): S5–S9.

Uses and Administration

Zonisamide, a benzisoxazole derivative, is used as an adjunctive antiepileptic in the treatment of partial seizures, with or without secondary generalisation.

In the UK, the usual initial oral dose in adults over 18 years of age is 50 mg daily in 2 divided doses, increased after 1 week to 100 mg daily. Thereafter, the dose may be further increased at weekly intervals by increments of up to 100 mg, to a usual dose of 300 to 500 mg daily, although some patients may respond to lower doses. Dose increments at intervals of 2 weeks should be considered in patients with hepatic or renal impairment and in patients who are not receiving CYP3A4 inducers (see also Interactions, above). Zonisamide may be given as a single dose or in 2 divided doses after the titration phase.

In the USA, the usual initial oral dose in patients over 16 years of age is 100 mg daily, increased after at least 2 weeks to 200 mg daily, given as a single dose or in 2 divided doses. Thereafter, if necessary, the dose may be further increased at intervals of at least 2 weeks by increments of 100 mg, to a dose of 400 mg daily. Doses up to 600 mg daily have been used, but there is no current evidence of an increase in response above 400 mg daily; many of the adverse effects of zonisamide are reported to be more frequent at doses of 300 mg daily and above.

As with other antiepileptics, withdrawal of zonisamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures; UK licensed product information has suggested that the dose may be decreased in steps of 100 mg at weekly intervals. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Bipolar disorder. Zonisamide may have psychotropic properties, and has been tried in the management of bipolar disorder (p.372).

References.

1. Baldassano CF, *et al.* Acute treatment of bipolar depression with adjunctive zonisamide: a retrospective chart review. *Bipolar Disord* 2004; **6:** 432–4.
2. Anand A, *et al.* A preliminary open-label study of zonisamide treatment for bipolar depression in 10 patients. *J Clin Psychiatry* 2005; **66:** 195–8.
3. McElroy SL, *et al.* Open-label adjunctive zonisamide in the treatment of bipolar disorders: a prospective trial. *J Clin Psychiatry* 2005; **66:** 617–24.
4. Ghaemi SN, *et al.* An open prospective study of zonisamide in acute bipolar depression. *J Clin Psychopharmacol* 2006; **26:** 385–8.
5. Wilson MS, Findling RL. Zonisamide for bipolar depression. *Expert Opin Pharmacother* 2007; **8:** 111–13.

Epilepsy. Zonisamide is used in the treatment of refractory epilepsy (p.465). Many studies have been conducted in Japan where clinical experience demonstrated its efficacy mainly in the treatment of partial seizures with or without secondary generalisation.[1,2] Data from studies[3-6] conducted outside Japan have confirmed the efficacy of zonisamide as an adjunct in the treatment of partial epilepsies. Efficacy in primary generalised and mixed-seizure epilepsies appears to be more variable, although it may be of value in refractory myoclonic seizures[7] and absence seizures.[8] Retrospective cohort studies[9,10] have also found that zonisamide may have efficacy as monotherapy. Zonisamide might also be of use in the treatment of epileptic syndromes such as Lennox-Gastaut syndrome,[11] and infantile spasms (as for example in West's syndrome), although only a small number of patients with the latter condition have been studied.[12,13]

1. Peters DH, Sorkin EM. Zonisamide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993; **45:** 760–87.
2. Patsalos PN, Sander JWAS. Newer antiepileptic drugs: towards an improved risk-benefit ratio. *Drug Safety* 1994; **11:** 37–67.
3. Leppik IE, *et al.* Efficacy and safety of zonisamide: results of a multicenter study. *Epilepsy Res* 1993; **14:** 165–73.
4. Schmidt D, *et al.* Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. *Epilepsy Res* 1993; **15:** 67–73.
5. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/08).
6. Brodie MJ, *et al.* Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; **46:** 31–41.
7. Kyllerman M, Ben-Menachen E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. *Epilepsy Res* 1998; **29:** 109–14.
8. Wilfong A, Schultz R. Zonisamide for absence seizures. *Epilepsy Res* 2005; **64:** 31–4.
9. Tosches WA, Tisdell J. Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide. *Epilepsy Behav* 2006; **8:** 522–6.
10. Kothare SV, *et al.* Efficacy and safety of zonisamide monotherapy in a cohort of children with epilepsy. *Pediatr Neurol* 2006; **34:** 351–4.
11. You SJ, *et al.* Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. *Brain Dev* 2008; **30:** 287–90.
12. Yanai S, *et al.* Treatment of infantile spasms with zonisamide. *Brain Dev* 1999; **21:** 157–61.
13. Lotze TE, Wilfong AA. Zonisamide treatment for symptomatic infantile spasms. *Neurology* 2004; **62:** 296–8.

Obesity. Anorexia and weight loss have been associated with zonisamide therapy (see Adverse Effects, above) and it has been tried, with some success, as an adjunct in the treatment of obesity[1,2] (p.2149); it has also been tried in binge-eating disorder associated with obesity.[3] Combination with bupropion (p.383) is under investigation.[2]

1. Gadde KM, *et al.* Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA* 2003; **289:** 1820–5.
2. Gadde KM, *et al.* Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry* 2007; **68:** 1226–9.
3. McElroy SL, *et al.* Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry* 2006; **67:** 1897–1906. Correction. *ibid.* 2007; **68:** 172.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Zonegran; ***Fr.:*** Zonegran; ***Ger.:*** Zonegran; ***Hung.:*** Zonegran; ***Irl.:*** Zonegran; ***Jpn:*** Excegran; ***Neth.:*** Zonegran; ***Port.:*** Zonegran; ***Spain:*** Zonegran; ***Swed.:*** Zonegran; ***UK:*** Zonegran; ***USA:*** Zonegran.

Antifungals

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Blastomycosis, p.518
Candidiasis, p.518
Chromoblastomycosis, p.518
Coccidioidomycosis, p.518
Cryptococcosis, p.519
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Meningitis, p.520
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Mycetoma, p.520
Nail infections, p.520
Paracoccidioidomycosis, p.520
Peritonitis, p.521
Pityriasis versicolor, p.521
Pneumocystis pneumonia, p.521
Protothecosis, p.521
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Sporotrichosis, p.522
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This chapter describes the drugs that are used mainly in the treatment and prophylaxis of fungal infections (mycoses). They include:

- the azole derivatives, including:
  - imidazoles (such as ketoconazole)
  - triazoles (such as fluconazole, itraconazole, posaconazole, and voriconazole)
- the allylamines (naftifine and terbinafine)
- the echinocandins (such as caspofungin and micafungin)
- several polyene antibiotics (including amphotericin B and nystatin)
- other antifungal antibiotics (for example griseofulvin)
- other compounds such as amorolfine, ciclopirox olamine, flucytosine, haloprogin, tolnaftate, and undecenoic acid and its salts.

Choice of Antifungal

Fungi may be classified as yeasts or moulds according to their appearance and means of growth. Examples of yeasts are *Candida* and *Cryptococcus* spp., while moulds include *Aspergillus* spp., the dermatophytes, and the Mucorales fungi. Some fungi are termed dimorphic as they appear to be yeast-like in the host, but grow as moulds *in vitro*. Blastomycosis, chromoblastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis are examples of diseases caused by dimorphic fungi.

Most fungi that are pathogenic in humans are saprophytic in nature, but cause infection when airborne spores reach the lungs or paranasal sinuses or are inoculated accidentally into the skin or cornea. Most fungal infections are therefore not transmissible between patients, with the exception of ringworm of the scalp. Endemic mycoses such as blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis are true pathogens and can cause disease in otherwise healthy persons. Other fungi, such as *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis jirovecii* are of low pathogenicity and require an alteration in the normal defence mechanisms for disease to occur; such disease is called opportunistic. Fungal diseases are classified into 3 groups: the superficial, subcutaneous, and deep or systemic mycoses. **Superficial** infections are confined to the skin, hair, nails, or mucous membranes. **Subcutaneous** infections are largely limited to the subcutaneous tissue but may spread to surrounding bone and skin. **Deep or systemic** infections may involve organs such as the lung, spleen, or brain, or may affect the body as a whole, and tend to occur more frequently in immunocompromised patients. Fungal infections may also be described as **local** when they are restricted to one body area, as **invasive** when there is spread into the tissues, or as **disseminated** when the infection has spread from the primary site to other organs throughout the body.

Ideally antifungal treatment should be chosen after the infecting organism has been identified, but it is often necessary to start empirical treatment before the pathogen can be cultured and identified, especially in immunocompromised patients in whom infections are often rapidly progressive.

The choice of treatment for the important fungal diseases is described below.

Aspergillosis

Aspergillosis is an infection caused by fungi of the genus *Aspergillus*, usually *A. fumigatus*, although *A. flavus*, *A. nidulans*, *A. niger*, and *A. terreus* may occasionally be encountered. Aspergillosis is usually acquired by inhalation and most commonly causes non-invasive disease of the respiratory tract. Other sites of infection include the eye after trauma or cataract surgery. Tissue invasion adjacent to the site of infection and dissemination to distant organs may occur, predominantly in immunocompromised patients. In severely immunocompromised patients aspergillosis usually presents as a severe acute rapidly progressive lung disease. Other organs affected may include the heart (particularly damaged or prosthetic valves), kidneys, bone, brain, liver, and skin.

In general the response of **invasive** aspergillosis to treatment is poor and starting treatment early is essential. Surgical excision may be necessary. High intravenous doses of amphotericin B have traditionally been the antifungal of choice.[1] However, the overall response rate to conventional amphotericin B is reported to be only 30 to 35%; this may be improved by the use of liposomal amphotericin B.[2,3] Studies have shown voriconazole to be superior[4-6] to amphotericin B for the treatment of invasive aspergillosis and comparable[7] as empirical therapy for patients with persistent fever and neutropenia. Favourable responses with caspofungin have been reported in those with invasive disease[8] as well as in patients with persistent fever and neutropenia.[9] Intravenous or oral voriconazole is now the recommended treatment for invasive pulmonary aspergillosis.[1,10,11] Drugs that may be used for salvage therapy include itraconazole, posaconazole, caspofungin, micafungin, and lipid formulations of amphotericin B. Salvage therapy may also include combination therapy with the initial antifungal drug or combination therapy with antifungal drugs from classes other than that used in the initial treatment regimen.[11] A retrospective review of patients given salvage therapy with voriconazole plus caspofungin or voriconazole alone reported that 3-month survival was greater for the combination than for voriconazole alone.[12] Successful treatment for invasive aspergillosis was also described in 2 patients who received a combination of caspofungin and itraconazole.[13] Treatment for invasive pulmonary aspergillosis should be given for a minimum of 6 to 12 weeks; in immunosuppressed patients, it should be continued throughout the period of immunosuppression and until the lesions have cleared.[11]

In neutropenic patients with prolonged fever despite broad-spectrum antibacterial therapy, empirical treatment with amphotericin B or its lipid formulations, itraconazole, voriconazole, or caspofungin is recommended.[11]

Antifungal prophylaxis with posaconazole is recommended for haematopoietic stem cell transplant recipients with graft-versus-host disease and in patients with acute myeloid leukaemia or myelodysplastic syndromes who are at high risk for invasive aspergillosis. Itraconazole may be useful, but it is not well tolerated.[1,11,14]

Non-invasive forms of aspergillosis include allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to *Aspergillus* usually occurring in asthmatic patients, and aspergilloma, a fungal mass or ball developing within a pre-existing pulmonary cavity or paranasal sinus. **Allergic bronchopulmonary aspergillosis** is usually treated with corticosteroids and oral itraconazole.[11,15] A systematic review[16] has concluded that itraconazole modifies the immunological activation associated with allergic bronchopulmonary aspergillosis in asthmatic patients and improves clinical outcome in the first 4 months of treatment. The treatment of **aspergilloma** depends on the severity of symptoms, and includes conservative management, antifungal therapy, or surgical resection. Treatment with itraconazole, voriconazole, and possibly also posaconazole are considered to have some benefit. Surgical resection and direct intracavitary instillation of antifungals may also be useful in selected patients with a single aspergilloma.[11]

Chronic necrotising pulmonary aspergillosis (CNPA or subacute invasive pulmonary aspergillosis)[17] is a subacute infection seen in patients with an underlying lung disease or systemic risk factors for immunosuppression. Various antifungals have been tried in the treatment of CNPA. Case reports have shown amphotericin B to be successful in about 50% of the patients and clinical benefit has also been achieved with intracavitary amphotericin B. Flucytosine has been used with or without amphotericin B. Itraconazole has a reported success rate of 70 to 90%. Treatment needs to be prolonged, so oral antifungals are preferred to parenteral antifungal therapy. Current evidence supports the use of itraconazole, with voriconazole and possibly also posaconazole as alternatives, for the treatment of CNPA.[11]

Aspergillosis of the **eye**, like other fungal eye infections, is difficult to treat; antifungals are generally not well absorbed after topical application and infections extending into the vitreous or anterior chamber require subconjunctival, intra-ocular, and/or systemic treatment. Systemic treatment is necessary for ocular manifestations of disseminated disease. Intravenous and intravitreal amphotericin B are recommended for the treatment of *Aspergillus* endophthalmitis; intravitreal or systemic voriconazole may be given as an alternative. For the management of *Aspergillus* keratitis topical antifungal therapy plus systemic antifungal therapy with either amphotericin B, voriconazole, or itraconazole is recommended.[11] For superficial eye infections a number of drugs including natamycin, amphotericin B, azoles, and sulfadiazine silver have been applied topically alone or as an adjunct to systemic therapy. Surgical excision of infected tissue may be necessary in severe infections.

1. Krishnan-Natesan S, Chandrasekar PH. Current and future therapeutic options in the management of invasive aspergillosis. *Drugs* 2008; **68:** 265–82.
2. White MH, *et al.* Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis. *Clin Infect Dis* 1997; **24:** 635–42.
3. Leenders ACAP, *et al.* Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *Br J Haematol* 1998; **103:** 205–12.
4. Denning DW, *et al.* Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; **34:** 563–71.
5. Herbrecht R, *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347:** 408–15.
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Blastomycosis

Blastomycosis (not to be confused with South American blastomycosis, see Paracoccidioidomycosis, below) is an infection caused by the fungus *Blastomyces dermatitidis*, which is endemic to much of North America. Inhalation of spores results in pulmonary infection which may be followed in 25 to 40% of patients by dissemination; the skin, skeleton, and genito-urinary system may become infected. While blastomycosis may affect anyone living in an endemic area, disseminated disease (including CNS involvement) is more common in immunocompromised patients.

Acute pulmonary infection may be mild and self-limiting in immunocompetent patients, but treatment should be considered in patients presenting with clinical symptoms. All patients with moderate to severe pneumonia or disseminated disease, and all immunocompromised patients require treatment.[1]

In immunocompetent patients, mild to moderate disease is treated with oral itraconazole; the duration of treatment is at least 6 months for pulmonary disease and 12 months for bone disease. Ketoconazole or fluconazole are less effective alternatives (and ketoconazole is more toxic); the role of voriconazole or posaconazole is not clear, although they may be effective. Patients unable to tolerate azoles or in whom disease progresses should be switched to amphotericin B. Life-threatening disease (either pulmonary or extrapulmonary) should be treated intravenously with a lipid or conventional formulation of amphotericin B; patients are usually switched to oral itraconazole once stabilised. All patients with CNS disease should be given a lipid formulation of amphotericin B intravenously for 4 to 6 weeks, followed by an oral azole; the options for the latter include fluconazole, itraconazole, or voriconazole. Oral treatment should be continued for at least 12 months and until resolution of abnormalities in the CSF.

In patients who are immunosuppressed, the recommended initial treatment is a lipid formulation of amphotericin B given intravenously for 1 to 2 weeks, or until improvement is noted. Once the patient has responded to this initial treatment they may be switched to oral itraconazole, which is continued until at least 12 months of therapy has been given. Life-long itraconazole treatment may be needed in patients in whom immunosuppression cannot be reversed, or in those who relapse despite appropriate therapy (a well-documented phenomenon in immunosuppressed patients).

In pregnant patients presenting with blastomycosis a lipid formulation of amphotericin B is recommended; azoles should be avoided because of possible teratogenicity. If the neonate shows signs of infection, treatment with a conventional (deoxycholate) formulation of amphotericin B is recommended. Children may be treated with amphotericin B or oral itraconazole, depending on the severity of infection; in general, they tolerate conventional amphotericin B better than adults, and lipid formulations may not be needed.

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Candidiasis

Candida spp. are commensal fungi commonly found in the gastrointestinal tract, mouth, and vagina; they may become pathogenic when natural defence mechanisms are impaired. *C. albicans* is the species most commonly associated with infection although infections with other *Candida* spp., notably *C. glabrata* (*Torulopsis glabrata*), *C. krusei*, *C. lusitaniae*, *C. parapsilosis*, and *C. tropicalis*, also occur and together are commonly referred to as non-*albicans* species. Predisposing factors for candidiasis include antibacterial therapy, skin or mucosal breach, abdominal surgery, debility, diabetes mellitus, pregnancy, and neutropenia and T-cell immunodeficiency; candidiasis often occurs in patients with HIV infection.

Candidiasis (or candidosis) may be classified as mucocutaneous or superficial, invasive (deep-organ), or disseminated. **Mucocutaneous** candidiasis includes infections of the oropharynx, genital organs, and skin. Oropharyngeal and vulvovaginal candidiasis are commonly termed thrush. Most superficial infections may be effectively treated with topical antifungals, although the rare chronic mucocutaneous candidiasis syndrome usually requires systemic treatment. The choice of antifungal should be guided by the availability of an appropriate formulation for the site of infection, toxicity, and the duration of treatment.

Oropharyngeal candidiasis may be treated with topical clotrimazole, miconazole, or nystatin, or oral fluconazole. Alternatives are oral itraconazole or amphotericin B. Topical therapy may not be adequate in severely immunocompromised patients and oral azole therapy should be considered in these patients.[1-3] Intravenous amphotericin B or caspofungin are usually effective but only indicated in patients with refractory disease.[1-3] Oral posaconazole was found to be as effective as oral fluconazole in the treatment of oropharyngeal candidiasis in HIV-infected persons, but more effective than fluconazole is sustaining clinical benefit after treatment was stopped.[4]

Oesophageal infections are not normally accessible to topical therapy and oral or intravenous fluconazole or itraconazole are considered to be the drugs of choice. Severe or refractory disease may be treated with voriconazole, either intravenously or orally, or intravenous caspofungin or amphotericin B.[1-3,5]

Genital candidiasis responds well to topical antifungal treatment with creams or pessaries. Uncomplicated vaginitis responds to short-course topical therapy with azoles such as butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, terconazole, or tioconazole, to topical nystatin, or to oral therapy with fluconazole or itraconazole.[6,7] Complicated disease, which occurs in up to 10% of cases, requires at least 7 to 14 days of treatment with topical antifungals or an oral dose of fluconazole repeated 72 hours later.[1,6] Vulvovaginal candidiasis with non-*albicans* species may not respond to topical azoles, in which case topical boric acid or topical flucytosine are often effective.[1] In pregnancy, topical azoles are recommended[6,7] and appear to be more effective than nystatin;[8] treatment is given for 7 days. Recurrent vaginal candidiasis should be treated for at least 6 months.[6,7] In the USA,[6] initial treatment with a topical or oral azole is recommended. Some suggest that the duration of therapy be increased to 7 to 14 days for the topical products and that the oral dose of fluconazole may be repeated every 72 hours for a total of 3 doses. Recommended maintenance therapy is with oral fluconazole once weekly; alternative regimens are topical clotrimazole 200 mg twice weekly or 500 mg once weekly, or other topical treatments used intermittently. UK guidelines[7] recommend initial treatment with fluconazole 150 mg every 72 hours for 3 doses followed by maintenance treatment of 150 mg once weekly. Alternatively initial treatment may be with a topical azole product for 10 to 14 days, followed by maintenance with topical clotrimazole 500 mg once weekly, oral fluconazole 100 mg once weekly, or daily oral itraconazole or ketoconazole. Yogurt preparations containing *Lactobacillus* spp. have been used in the treatment and prevention of vaginal candidiasis in an attempt to restore the natural vaginal flora but evidence to support their use is limited.

Infection involving the **nails** and surrounding tissue is difficult to treat. Chronic paronychia (infection affecting the tissue around the nails) is often resistant to treatment but may respond to prolonged application of topical imidazoles or nystatin. Onychomycosis (infection affecting the nail itself) usually only responds to systemic antifungals. Treatment with oral itraconazole appears to be the most appropriate, although oral terbinafine has also been used.[1]

Primary *prophylaxis* against mucocutaneous candidiasis is not recommended for patients with advanced HIV infection since this may select for resistant *Candida* spp.[9] Due to similar concerns, secondary prophylaxis in immunocompromised patients with mucocutaneous candidiasis is largely restricted to those with frequent or severe recurrences, or those at risk of developing invasive disease, in which case oral fluconazole or itraconazole may be considered.[1,9]

Invasive and **disseminated** candidiasis require systemic antifungal treatment. Intravenous amphotericin B, with or without flucytosine, has traditionally been regarded as the standard initial treatment in most infections but flucytosine is now infrequently used because of concerns over its bone-marrow toxicity in AIDS patients. Fluconazole, caspofungin, and a combination of amphotericin B (for 5 to 6 days) and fluconazole have been shown to be effective and now offer alternatives for initial antifungal therapy. Fluconazole may be used as first-line for clinically stable patients with uncomplicated candidaemia who have not recently received treatment with an azole and is preferred for infections with *C. lusitaniae*. Amphotericin B is used for other non-*albicans* infections, although there is some evidence of resistance developing in *C. krusei* and *C. glabrata*. However, these species are susceptible to voriconazole and caspofungin and voriconazole may also be used as an alternative for fluconazole-resistant invasive *Candida* infections.[1] Neonates with disseminated candidiasis are usually best treated with amphotericin B, although fluconazole may also be effective.[1,10]

Empirical antifungal therapy may be appropriate for neutropenic patients. Drugs that may be considered include amphotericin B, itraconazole, or voriconazole. Fluconazole is unsuitable because of its restricted antifungal spectrum. The role of caspofungin is uncertain.[1] Treatment should generally be continued until signs and symptoms have resolved and the patient is no longer neutropenic. For empirical antifungal treatment in non-neutropenic patients, amphotericin B or fluconazole may be considered.[1]

Although antifungal *prophylaxis* is generally not routinely recommended for non-neutropenic patients, some would consider it appropriate in patients who are at high risk of infection such as patients who are critically ill, neutropenic, or receiving solid organ or bone marrow transplants.[1,11]

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Chromoblastomycosis

Chromoblastomycosis (chromomycosis) is a chronic fungal infection that affects skin and subcutaneous tissue. It occurs worldwide but is more common in tropical and subtropical climates. Chromoblastomycosis may result from traumatic inoculation of a number of fungal species including *Fonsecaea compacta* (*Phialophora compacta*), *F. pedrosoi* (*P. pedrosoi*), *Exophiala spinifera*, *E. jeanselmei*, *Phialophora verrucosa*, *Cladosporium carrionii*, and *Rhinocladiella aquaspersa*. In its early stages, when lesions are small, surgical excision or cryotherapy are the treatments of choice, although there is some risk of dissemination during surgery. Many antifungals have been tried but itraconazole and terbinafine, often in high doses and for prolonged periods, have been the most successful. However, recurrence and drug resistance has been a problem with monotherapy. Itraconazole and terbinafine (given daily on alternate weeks or daily concomitantly for up to 9 months) have been shown to be effective in selected cases of chromoblastomycosis that were unresponsive to monotherapy. Local heat treatment aids healing and may be a useful adjunct.

Coccidioidomycosis

Coccidioidomycosis is an infection caused by inhalation of the spores of *Coccidioides immitis*, a fungus found in the soil in arid and semi-desert areas mainly of North, Central, and South America. Common names for the infection include valley fever, desert fever, and desert rheumatism. In endemic areas, coccidioidomycosis is a common opportunistic infection in immunocompromised patients.

Patients with coccidioidomycosis may experience acute or chronic lung infections, meningitis, and disseminated disease although many infections are subclinical. In immunocompetent individuals, acute pulmonary disease is usually mild and self-limiting and in 60% of cases resolves without specific chemotherapy. In some patients the infection progresses to chronic pulmonary coccidioidomycosis with granulomatous lesions, fibrosis, and cavitation. Less than 1% of patients develop acute progressive pneumonia (which is commonly fatal if untreated) or disseminated disease (usually involving the skin, bone, meninges, and joints). Severe pulmonary and disseminated infections are more likely in pregnant women, males, certain ethnic groups, diabetics, and immunocompromised patients.

Treatment is usually reserved for severe, progressive, or disseminated infections or for patients with concurrent risk factors, especially immunosuppression.[1,2] If antifungal therapy is given, it is preferably with an oral azole as initial therapy or with intravenous amphotericin B;[1,3] itraconazole and fluconazole are used most often, while voriconazole has been reported to be effective in some patients who have not responded to fluconazole.[4] Amphotericin B is generally used for rapidly progressive disease while azoles are generally preferred for chronic disease.[1,2] Although combination therapy with an azole and amphotericin B has been used, there is no evidence that it is superior to a single antifungal drug.[1] Diffuse pneumonia is most often seen in immunocompromised patients and treatment is initially with an azole or amphotericin B followed by maintenance treatment with an azole for a year or more. In immunocompromised patients it is advisable to continue treatment indefinitely.[4] Fluconazole is effective in meningeal infections and is the most frequently recommended antifungal for this indication,[1,2,4] although itraconazole has also produced beneficial responses; intrathecal amphotericin B may also be used, especially in aggressive infections.[1,2,5] Due to the high incidence of relapse, indefinite suppressive therapy with fluconazole or itraconazole is recommended for patients with coccidioidal meningitis or diffuse pulmonary coccidioidomycosis.[1] Patients with HIV infection and solid organ transplant recipients who have completed induction therapy should subsequently receive lifelong suppressive fluconazole or itraconazole.[2,6,7] It may, however, be possible to stop therapy in patients with CD4+ lymphocyte counts above 250 cells/microlitre (except in those with meningitis) if there is clinical evidence that the coccidioidal infection is controlled.[1] Primary prophylaxis for HIV-infected patients living in coccidioidomycosis-endemic areas is not routinely recommended.[1,6] However, primary prophylaxis may be considered for solid organ transplant recipients who are at risk of coccidioidal infection.[1,7]

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Cryptococcosis

Cryptococcosis is an infection caused by inhalation of the fungus *Cryptococcus neoformans*. It is rare in immunocompetent individuals, but is an important life-threatening disease in immunocompromised patients, especially those with AIDS, in whom it occurs principally as cryptococcal meningitis.

Mild infections in immunocompetent patients may resolve without treatment, but oral fluconazole is usually effective if treatment is necessary.[1] Itraconazole is a suitable alternative in patients unable to take fluconazole. In either case, treatment should continue for several months. For more severe disease, amphotericin B may be given alone, or, if there is CNS involvement, with flucytosine. Patients may be switched to oral fluconazole after 2 weeks of induction therapy with amphotericin B and flucytosine or may continue on amphotericin B and flucytosine for 6 to 10 weeks.[1]

Cryptococcosis in immunocompromised patients other than those with HIV infection should be treated as for CNS infections in immunocompetent patients.[1]

HIV-infected patients who develop cryptococcosis always require treatment. Those with isolated pulmonary or urinary-tract disease may be treated with oral fluconazole or, if fluconazole is not an option, itraconazole.[1] A further alternative is combined treatment with fluconazole and flucytosine for 10 weeks followed by maintenance with fluconazole, although the toxicity of this regimen limits its usefulness. Those with more severe disease may be given intravenous amphotericin B until symptoms are controlled and then switched to oral fluconazole.[1-3] Patients with HIV infection who develop cryptococcal meningitis should receive induction therapy with intravenous amphotericin B and intravenous flucytosine.[1-3] Amphotericin B may be given alone in patients unable to tolerate flucytosine. In refractory cases, amphotericin B may be given intrathecally or intraventricularly. Oral fluconazole and intravenous flucytosine is an alternative to the use of amphotericin B but carries a high risk of toxicity. After induction, oral fluconazole should be given as consolidation therapy; if fluconazole cannot be given, itraconazole is a suitable though less effective alternative.[1-3]

Immunocompetent patients with CNS disease and immunocompromised patients (without HIV infection) may require 6 to 12 months of suppressive therapy with oral fluconazole after a primary course of antifungal therapy.[1] HIV-infected patients should generally receive lifelong maintenance therapy,[1-4] although it may be possible to stop secondary prophylaxis in patients who exhibit a sustained response to highly active antiretroviral therapy and who remain asymptomatic with regard to cryptococcosis. US guidelines[4] recommend restarting secondary prophylaxis if the CD4+ T lymphocyte count falls below 100 to 200 cells/microlitre.

Primary prophylaxis in patients with HIV infection is not generally recommended since it has not been shown to be more beneficial than treating cryptococcal infections when they occur and may increase the risk of resistance.[4]

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Dermatophytoses

See under Skin Infections, below.

Endocarditis

Infective endocarditis caused by fungi such as *Aspergillus* or *Candida* is much less common than that caused by bacteria (p.168).

Mortality due to fungal endocarditis is high. Patients should be treated with antifungal therapy and in many cases surgical removal of an infected heart valve. Amphotericin B was most commonly used, usually alone but in some cases combined with flucytosine.[1-4] Alternatives for endocarditis caused by *Candida* spp. are fluconazole or caspofungin. Voriconazole may now be the drug of choice for endocarditis caused by *Aspergillus* spp.[4] Since relapse rates of up to 40% have been reported after stopping therapy, secondary prophylaxis is recommended with fluconazole, itraconazole, posaconazole, or voriconazole (depending on the susceptibilities of the infecting organism) for a minimum of 2 years and in some cases for life. Lifelong suppressive therapy is also given to patients who are not suitable candidates for valve replacement.[1-3,5]

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Eye infections

Fungal infections of the eye are less common than infections with bacteria or viruses, but are usually severe and may lead to loss of vision. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with antibacterials. Patients with impaired host resistance such as diabetics or immunocompromised patients are particularly at risk. The most common fungi causing eye infections are *Aspergillus, Candida,* and *Fusarium*; others include *Blastomyces*, *Cryptococcus*, and *Sporothrix*. Corneal infection (keratitis) occurs most frequently, but the orbit, eyelids, lachrymal sacs, conjunctiva, sclera, and intraocular structures may also become infected. Infections of the orbit rarely occur spontaneously but are more common with systemic fungal infection or may spread from the adjacent paranasal sinus tissue, as seen in mucormycosis or aspergillosis.[1,2] Ocular fungal infections are difficult to treat. Diagnosis may be delayed due to a gradual onset of symptoms and empirical treatment with topical antibacterials or corticosteroids. Topical natamycin is generally considered the drug of choice for fungal keratitis due to filamentous fungi, while topical amphotericin B is an alternative. Topical amphotericin B with or without topical flucytosine, is preferred for yeast infections. Azoles exhibit a wide spectrum of activity and clotrimazole, fluconazole, itraconazole, ketoconazole, and miconazole are all used topically. Topical antifungals are not well absorbed and infections extending into the eye require subconjunctival, intra-ocular, or systemic therapy. Systemic treatment may also be indicated when there is a poor response to topical agents, for fungal endophthalmitis, or for ocular manifestations of disseminated fungal disease. When systemic treatment is indicated intravenous amphotericin B is usually given. Azoles may be given for less severe infections or as adjunctive therapy in severe infections. Oral fluconazole and ketoconazole have better penetration into the cornea, aqueous humour, and vitreous humour than itraconazole. Intravitreal injections may be required in infections unresponsive to systemic antifungals.[3,4] Surgical debridement or excision may be necessary if the infection progresses despite appropriate antifungal therapy.[1,2]

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Histoplasmosis

Histoplasmosis is a systemic infection caused by *Histoplasma capsulatum*, a fungus found in the soil in endemic areas, particularly at sites with heavy accumulations of bird or bat excrement. Infection is by inhalation of spores. Two types of histoplasmosis occur:

- American histoplasmosis, due to infection with *H. capsulatum* var. *capsulatum*
- African histoplasmosis, due to infection with *H. capsulatum* var. *duboisii*

H. capsulatum var. *capsulatum* is endemic in the central USA where 50 to 90% of the population is infected. Mild infections are generally asymptomatic. However, acute pulmonary infection can occur. Massive infection can be fatal. Chronic pulmonary histoplasmosis can result in lung fibrosis and cavitation. Acute or chronic disseminated infection involving widespread infiltration of the reticuloendothelial system, is mainly seen in immunodeficient or immunocompromised patients.

Histoplasma capsulatum var. *duboisii* is found in Africa and may cause a chronic disseminated form of histoplasmosis with focal lesions predominantly in skin and bone.

Antifungal therapy for histoplasmosis is necessary in patients with severe acute pulmonary infections, chronic pulmonary disease, or disseminated infection. Infections which are not life-threatening but not resolving spontaneously may be treated with an oral azole in both immunocompetent and immunocompromised patients.[1,2] Itraconazole is the preferred drug.[1,2] Ketoconazole is moderately effective but more toxic. Fluconazole is less effective than either itraconazole or ketoconazole.[2-4] Patients with chronic cavitary pulmonary histoplasmosis should be treated with oral itraconazole for a minimum of 1 year.[1] Patients with moderately severe to severe acute pulmonary histoplasmosis may be treated with intravenous liposomal amphotericin B for 1 to 2 weeks followed by oral itraconazole for a total of 12 weeks. Conventional intravenous amphotericin B may be given as an alternative. The same treatment regimen is recommended for those with progressive disseminated disease; oral itraconazole in these patients should be continued for 12 months.[1] Immunocompromised patients, including those with HIV infection, may need to continue maintenance therapy indefinitely, with itraconazole daily or amphotericin B weekly,[1-3,5] if immunosuppression cannot be reversed.[1] Patients with CNS histoplasmosis should be given intravenous liposomal amphotericin B for 4 to 6 weeks, followed by oral itraconazole for a minimum of 1 year.[1] Primary prophylaxis with itraconazole is not recommended routinely but may be considered for patients with advanced AIDS at especially high risk of infection due to occupational exposure or residence in a hyperendemic area.[5]

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Infections in immunocompromised patients

Immunocompromised patients are at increased risk of infections, including those caused by fungi. Fungi most commonly affecting AIDS patients include *Cryptococcus neoformans*, *Pneumocystis jirovecii* and *Candida albicans* while those associated with immunosuppressive therapy and cancer are mainly *Aspergillus* and *Candida* spp. Immunocompromised patients are also at increased risk of endemic mycoses, such as coccidioidomycosis, histoplasmosis, and *Penicillium marneffei* as well as a growing number of uncommon fungi reported to cause invasive infections, including *Fusarium*, *Scedosporium*, and *Trichosporon* species.

Fungal infections in immunocompromised patients are often invasive or disseminated and treatment should start as early as possible. A fungal cause of infection should be considered in patients with persistent febrile neutropenia who have not responded to broad spectrum antibacterials. If the infection has not been identified, empirical treatment should be started. Conventional intravenous amphotericin B has been considered first-line empirical therapy and is no less effective than lipid formulations. Fluconazole, itraconazole, voriconazole, and caspofungin appear at least as effective as amphotericin B. For patients with renal impairment lipid formulation of amphotericin B or voriconazole may be given. For patients not responding to an amphotericin B formulation voriconazole, itraconazole, or caspofungin are alternatives. Fluconazole may be considered for low risk patients infected with susceptible *Candida* species.

The benefit and role of primary prophylaxis in the management of fungal infections associated with HIV, cancer, and organ transplants is controversial as this may select for resistant isolates and species not susceptible to the antifungals used. This is of particular concern with fluconazole (see Resistance, p.533), one of the drugs most widely used for this purpose. Fluconazole has been shown to be effective as primary prophylaxis against invasive candidiasis but not aspergillosis. Itraconazole or voriconazole are preferred for patients at risk of invasive aspergillosis, such as patients being treated for graft-versus-host disease or cytomegalovirus disease.

Long term suppressive therapy has been recommended for immunocompromised patients with proven or probable invasive aspergillosis or candidiasis. Secondary prophylaxis may be stopped when patients are no longer profoundly neutropenic.

Antifungals are also used in selective digestive tract decontamination (see Intensive Care, p.175).

Treatment and prophylaxis of specific fungal infections in immunocompromised patients is discussed under the appropriate headings—see Aspergillosis, Candidiasis, Coccidioidomycosis, Cryptococcosis, and Histoplasmosis (above), and Pneumocystis Pneumonia (below).

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Meningitis

Fungal diseases associated with meningitis include aspergillosis, candidiasis, coccidioidomycosis, cryptococcosis, and histoplasmosis (see above), although many disseminated fungal infections can involve the CNS, especially in immunocompromised patients. The treatment of each infection is discussed under the appropriate heading, but in general the initial drug of choice in fungal meningitis is intravenous amphotericin B, sometimes with flucytosine.

Mucormycosis

Mucormycosis,[1-5] a rare but invasive and rapidly progressive infection caused by Mucorales fungi, is a form of zygomycosis, a term that is sometimes used synonymously. Mucormycosis usually acquired by inhalation of spores, although trauma and ingestion may also be routes of infection. It usually occurs in poorly controlled diabetic patients or in immunocompromised patients. Patients given desferrioxamine may also be at increased risk of infection (see p.1440). Infections of the mucosa of the respiratory tract or gastrointestinal tract, or of abraded skin, usually with *Rhizopus* or *Rhizomucor* spp., can result in local invasion of deeper tissues including bone and the CNS, with extensive tissue destruction. Disseminated disease may also occur.

The treatment of mucormycosis includes a combination of antifungal therapy, surgical debridement when possible, and management of the underlying disease. The standard antifungal therapy is relatively high doses of intravenous amphotericin B or lipid formulations of amphotericin B. Fluconazole, itraconazole, ketoconazole, voriconazole, or the echinocandins are not considered to have a role in the treatment of mucormycosis, although the newer triazoles, posaconazole and ravuconazole, have reported *in-vitro* activity against zygomycetes and posaconazole has been tried in patients with refractory disease. Invasive or disseminated disease is difficult to treat and is usually fatal.

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Mycetoma

Mycetoma[1-4] has a worldwide distribution, but is most commonly encountered in the tropics and subtropics. It may affect subcutaneous tissue, bone, and skin. The foot is most often affected (70 to 80% of cases), less often hand (12%), legs, and knee joints. The term Madura foot is used for mycetoma affecting the foot. Infection mainly results from trauma to the skin, and may spread locally through the lymphatic system to surrounding tissues, progressively destroying connective tissue and bone. Mycetomas caused by fungi such as *Madurella mycetomatis*, *M. grisea*, or *Pseudallescheria boydii* are called eumycetomas. Those caused by the filamentous bacteria, actinomycetes, are called actinomycetomas and are discussed on p.180. Eumycetomas do not heal spontaneously and are poorly responsive to treatment. They often require both surgical excision and antifungal therapy. Itraconazole or ketoconazole are recommended as first-line antifungals for eumycetomas and the duration of treatment depends on the severity of the infection and ranges from a few months to years. Itraconazole has resulted in good clinical responses and low recurrence rates. Treatment with antifungals before surgery results in lesions that are localised and encapsulated and easier to excise during surgery.[1,2]

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Nail infections

See under Skin Infections, below.

Paracoccidioidomycosis

Paracoccidioidomycosis (South American blastomycosis) is caused by an infection with the fungus *Paracoccidioides brasiliensis*. The disease occurs mainly in inhabitants of Central and South America. Infection is thought to be by inhalation and may remain dormant for long periods. While most primary infections are subclinical, some may be progressive and severe, particularly in immunocompromised patients. Paracoccidioidomycosis usually presents as a chronic infection affecting the lungs. Disseminated disease may affect the skin, mucous membranes, gastrointestinal tract, reticuloendothelial system, and adrenals, and may be acute or chronic. Relatively mild cases may be treated with oral ketoconazole or itraconazole for 6 to 12 months or longer. Itraconazole allows shorter treatment courses and lower doses than ketoconazole; relapse rates are also lower. A small open-label study reported that oral voriconazole was as effective as oral itraconazole for long-term treatment of paracoccidioidomycosis.[1] More severe infections or those not responding to azoles are treated with intravenous amphotericin B followed by maintenance azole therapy.[2] Sulfonamides are now rarely used since more effective drugs are available. Terbinafine has been used successfully when access to azoles was not possible.[3]

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Peritonitis

Fungal peritonitis may be a complication of continuous ambulatory peritoneal dialysis, abdominal surgery, or trauma. It is usually caused by yeasts such as *Candida* and rarely moulds such as *Aspergillus*. Amphotericin B is often used to treat fungal peritonitis;[1-3] intravenous dosage has been preferred to intraperitoneal use since the latter route is painful,[4] but intravenous use may lead to poor penetration into the peritoneum.[3] There is some evidence that early removal of the peritoneal catheter reduces the risk of death.[3] Fluconazole, voriconazole, caspofungin, or flucytosine may also be effective.[3,5] Oral continuation therapy with flucytosine and fluconazole has been given after removal of the catheter.[3] However, fungal peritonitis may be difficult to treat and causes substantial morbidity and mortality.[4]

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Pityriasis versicolor

See under Skin Infections, below.

Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is caused by the organism *Pneumocystis jirovecii* (previously named *Pneumocystis carinii* f. sp. *hominis* and at one time considered to be a protozoan). It is an opportunistic pathogen and infection is acquired by inhalation. In persons with normally functioning immune systems infection rarely produces disease, but in immunocompromised patients it may produce interstitial pneumonia which, if untreated, is almost always fatal. In patients with AIDS (p.856), Pneumocystis pneumonia is a common occurrence.

The **treatment** of choice for PCP is:

- intravenous or oral co-trimoxazole[1-4]

Alternative regimens are:[1-4]

- intravenous pentamidine
- oral clindamycin and primaquine
- oral atovaquone
- oral trimethoprim and dapsone
- nebulised pentamidine is occasionally suggested for mild to moderate infection but is now generally reserved for prophylaxis.
- intravenous trimetrexate plus folinic acid may be a further option to intravenous co-trimoxazole or pentamidine in patients with moderate to severe disease.

Adjunctive folinic acid with co-trimoxazole has been associated with an increased risk of therapeutic failure and death in AIDS patients.[5] Combination therapy with co-trimoxazole and pentamidine is not more effective and is potentially more toxic than either drug alone.[6]

Adjunctive treatment with glucocorticosteroids should be given to patients with severe infection[1,2] if they are hypoxic, and treatment should be started as soon as antimicrobial treatment is begun.

Primary **prophylaxis** is indicated for all HIV-positive adolescents and adults (including pregnant women and patients on highly active antiretroviral therapy) with CD4+ T lymphocyte counts lower than 200 cells/microlitre, or a history of oropharyngeal candidiasis.[2,7] Infants are at increased risk to PCP during their first year of life and, in infants and young children, PCP may occur at higher CD4+ T lymphocyte counts compared with adults. The WHO/UNAIDS/UNICEF[8] and US guidelines[7] recommend that infants under 18 months born to HIV-positive mothers should be given prophylaxis beginning at 4 to 6 weeks of age. Therapy should continue until breast feeding is stopped and the infant is confirmed to be HIV-negative, or for at least 1 year initially. Infants subsequently confirmed to be HIV-positive should remain on prophylactic therapy. In Europe, some clinicians have tended to have a less aggressive approach and only offer prophylaxis once HIV infection is confirmed or opportunistic infections occur.[9] Recommendations for primary prophylaxis in patients without HIV infection suggest that prophylaxis should be considered for patients with primary immune deficiency, severe protein malnutrition, organ or stem cell transplants, persistent CD4+ T lymphocyte counts lower than 200 cells/microlitre, or patients receiving cytotoxic or immunosuppressive therapy.[2,10,11] Secondary prophylaxis is given to all patients following successful treatment of PCP.[2]

For both primary and secondary prophylaxis[1,4,7] the drug of choice is:

- co-trimoxazole

Alternative prophylactic regimens[1,2,4,7] for patients not able to receive co-trimoxazole are:

- dapsone (alone or with pyrimethamine)
- aerosolised pentamidine
- atovaquone

Other prophylactic regimens include intermittent parenteral administration of pentamidine, pyrimethamine with sulfadoxine, clindamycin with primaquine, and trimetrexate, but are not recommended unless the more usual drugs cannot be used.[7] Co-trimoxazole has the added advantage of also protecting against bacterial infections and toxoplasmosis, a common opportunistic infection in AIDS patients.[7]

In HIV-infected patients, primary and secondary prophylaxis may be discontinued in those who attain a CD4+ T lymphocyte count above 200 cells/microlitre on antiretroviral therapy. Primary and secondary prophylaxis should be restarted in patients whose CD4+ T lymphocyte count falls to below 200 cells/microlitre, and in those in whom PCP recurs at a count of greater than 200 cells/microlitre.[7,12] A study of solid organ transplant recipients[13] suggested that lung transplant recipients are at continued risk of developing PCP and prophylaxis should be continued indefinitely in this group.

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Protothecosis

Protothecosis is an infection with algae of the *Prototheca* spp., usually *P. wickerhamii.* Infection occurs rarely in humans but may follow minor trauma or surgery, leading to a chronic skin lesion and occasionally dissemination. Amphotericin B appears to be the most effective antifungal,[1,2] and has been combined with an oral tetracycline.[2] There are also case reports of itraconazole[3,4] being used successfully and fluconazole has been of benefit in a case unresponsive to itraconazole,[5] but azole therapy has also been associated with treatment failure in a number of cases.[2] Azole antifungals and surgery may be considered for patients with more localised disease.[1]

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Respiratory-tract infections

Pathogenic fungi may enter the body by inhalation and colonise the respiratory tract. Fungal infections of the respiratory tract include aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and paracoccidioidomycosis (see above). *Pneumocystis jirovecii* is an important cause of pneumonia in HIV-infected patients (see above). Other fungi reported to produce respiratory-tract infections mainly in immunocompromised patients include *Candida* spp., *Fusarium* spp., *Penicillium marneffei*, *Pseudoallescheria boydii*, and Zygomycetes such as *Rhizopus arrhizus.* Acute pulmonary fungal infections in immunocompetent individuals are mostly self-limiting conditions that resolve without treatment. Severe, persistent, or progressive infections, or infections in immunocompromised patients, require treatment. Intravenous amphotericin B is usually the drug of choice but mild to moderate infection can be treated with an oral azole such as fluconazole, itraconazole, or ketoconazole. Pulmonary granulomas may require surgical removal. Chronic suppressive treatment is recommended for patients with ongoing immunosuppression due to HIV infection.

Skin infections

The most common fungal skin infections are the dermatophytoses, pityriasis versicolor, and candidiasis. The first two are described here; for candidiasis, see above. Other fungal skin infections are discussed under the appropriate headings: blastomycosis, chromoblastomycosis, mycetoma, mucormycosis, protothecosis, and sporotrichosis. Fungal infections that may involve the skin by dissemination include aspergillosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and paracoccidioidomycosis. Less common fungi causing skin infections include *Penicillium marneffei.* Sometimes a fungal infection may affect mucous membranes, nails, or subcutaneous tissue, and there can be spread to deeper tissue and dissemination especially in immunosuppressed patients. The term superficial fungal infections includes those involving the skin, nails, and mucous membranes. Antifungal treatment may be topical or systemic.[1,2]

Dermatophytoses (ringworm, tinea) are infections by dermatophytes, a group of fungi which includes soil-dwelling organisms and human and animal pathogens from 3 genera — *Epidermophyton, Microsporum,* and *Trichophyton.* Dermatophytoses are encouraged by hot and humid conditions and poor hygiene and occur throughout tropical and temperate regions of the world.

Dermatophytoses are classified according to the body site affected. They include

- tinea barbae (beard)
- tinea capitis (scalp)
- tinea corporis (body)
- tinea cruris (groin)
- tinea manuum (hand)
- tinea pedis (athlete's foot)
- tinea unguium (nail)

A chronic infection most commonly seen in the tropics is known as favus (tinea favosa) and a variant of tinea corporis known as tinea imbricata (tokelau) is caused by *T. concentricum* and is endemic in parts of the Far East and Central and South America. A severe form of dermatophytosis caused by animal pathogens with deep, suppurant, inflammatory lesions is known as kerion.

Deep infections may occur rarely in immunocompromised patients; they can spread to involve lymph nodes, liver, and brain, and may be fatal.

Mild localised superficial dermatophytoses of hairless skin sites will often respond to *topical* therapy.[3-5] Non-specific agents with a long history of topical use include benzoic acid, methylrosanilinium chloride, selenium sulfide, and salicylic acid. Many of these agents are effective, and while some older preparations such as Compound Benzoic Acid Ointment may be less cosmetically acceptable than modern products, they still have a role in the treatment of minor infections, particularly in the tropics.[6] However, the use of methylrosanilinium chloride is restricted due to fears over possible carcinogenicity (see p.1653). There are a number of specific topical antifungals that are active against dermatophytes. The azoles used topically include clotrimazole, econazole, ketoconazole, and miconazole. Ciclopirox olamine[7] and the allylamine antifungals naftifine and terbinafine[5] are also active, and a systematic review[5] considered that allylamines such as terbinafine were slightly more effective than azoles in the treatment of fungal infections of the foot. Chlorphenesin, tolnaftate, and undecenoic acid salts are all effective in uncomplicated dermatophytoses, but there are few comparative studies of their relative efficacy. Amorolfine has also been shown to be effective in skin infections, although its major application is in nail infections (see below).

Infections of some body sites respond poorly to topical therapy, as do extensive infections or those in heavily keratinised areas.[4,8] *Systemic* therapy may be appropriate in these cases as well as in disseminated disease. Griseofulvin, ketoconazole, and itraconazole have been the drugs most widely used, although terbinafine has been reported to be more effective than itraconazole in some forms of tinea[9,10] and also requires only short-duration therapy.[11,12] However, efficacy of terbinafine is reported to depend on the infecting organism.[13] Griseofulvin has proved to have few major toxic effects during long-term therapy and is useful for tinea capitis, extensive or disseminated infections, and nail infections in selected patients. However, since it has a narrow spectrum of activity largely confined to the dermatophytes, accurate diagnosis is essential, particularly before embarking on a prolonged treatment course when no immediate response is anticipated. Ketoconazole has a broader spectrum of activity, but severe adverse effects can occur on prolonged use. Itraconazole appears to produce a rapid response and thus requires shorter treatment periods.[4] Other azoles such as fluconazole may also be effective.[14] Selenium sulfide and povidone-iodine shampoos may be useful adjuncts to oral therapy for tinea capitis to improve efficacy and limit the spread of infection.[15,16] A suitable topical antifungal is used in individuals suspected of carrying infection.[17]

Infections of the **nails (onychomycoses)** are notoriously difficult to treat.[18] Infections of the fingernails take up to 6 months to respond to oral griseofulvin and those of the toenails, a year or longer, but about 60% of nail infections fail to respond or relapse after the initial treatment course. The oral antifungals terbinafine, itraconazole, and fluconazole produce persistent antifungal concentrations in the nail more rapidly than griseofulvin.[18,19] Terbinafine and itraconazole have been most widely studied. Both are reported to produce clinical and mycological cures in a high proportion of patients more quickly than griseofulvin, generally after 12 weeks of treatment or less. Long-term follow-up has shown that the response to terbinafine is maintained.[20-22] Terbinafine has been reported to be more effective than itraconazole,[23-26] although neither is effective in all patients. Although topical treatments have generally been ineffective in nail infections, ciclopirox nail lacquer has been reported to be effective,[27] but a systematic review[5] noted that cure rates were poor. Amorolfine as a 5% lacquer has also shown benefit,[28] and may be more effective than ciclopirox although evidence is scanty.[5] It has also been applied in combination with oral itraconazole[29] or terbinafine[30] with some success. Topical butenafine may also be of benefit.[5] Another approach has been the dissolution of the nail plate with 40% urea paste, usually in combination with bifonazole.[31] Guidelines for the treatment of onychomycosis have been published in the UK.[32]

Pityriasis versicolor (tinea versicolor) is a superficial infection caused by the commensal yeast *Malassezia furfur (Pityrosporum orbiculare).* It is more common in tropical than in temperate latitudes and sun exposure may trigger the infection. Pityriasis versicolor will often respond to topical treatment with an azole antifungal or with selenium sulfide. Topical terbinafine (but not oral) or ciclopirox are alternatives.[33] Immunocompromised patients, including those receiving corticosteroids, may develop extensive infections. In addition, these fungi have caused septicaemia in patients receiving parenteral nutrition.[34] Severe infections require oral treatment with an azole.[35] Griseofulvin is not effective.

Other infections in which *Malassezia* yeasts are implicated include seborrhoeic dermatitis (p.1584) and pityrosporum folliculitis, both of which may present in a more severe form in patients with AIDS. Topical or systemic azole antifungals are effective in these conditions and are the main drugs used. However, relapses are common.[36]

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Sporotrichosis

Sporotrichosis is a disease caused by *Sporothrix schenckii*, a fungus found in soil and vegetation. The infection occurs in the Americas and Africa, and may give rise to cutaneous or extracutaneous disease. The cutaneous form is the more common. It probably follows entry of the organism through skin abrasions and usually presents as a single skin lesion, although infection may spread along lymphatic channels causing a series of skin lesions. Extracutaneous sporotrichosis usually presents as osteoarticular infection. Pulmonary infections are occasionally seen and, rarely, CNS and ocular infections.

Infections rarely heal spontaneously and most patients require treatment. Oral potassium iodide has traditionally been used for cutaneous and lymphocutaneous infections although the mode of action is unclear since potassium iodide does not demonstrate antifungal activity *in vitro*. Oral itraconazole 200 mg daily for 3 to 6 months is also effective[1-3] and is regarded by some[3,4] as the treatment of choice. The dose of itraconazole may be increased to 200 mg twice daily in non-responders; alternatively patients may be given oral terbinafine or a saturated potassium iodide solution taken orally. Oral fluconazole should only be used in patients who cannot tolerate any of the preferred drugs.[4]

For patients with osteoarticular infections, oral itraconazole 200 mg twice daily for at least 12 months is recommended, with either liposomal or conventional amphotericin B given intravenously as alternatives. Oral itraconazole 200 mg twice daily may be given as maintenance therapy once the patient has responded to the amphotericin B treatment.[4]

Patients with life-threatening pulmonary, disseminated, or meningeal disease should receive treatment for at least 12 months. The drug of choice is intravenous liposomal amphotericin B with conventional amphotericin B given intravenously as an alternative. Oral itraconazole 200 mg twice daily may be given as maintenance therapy. Oral itraconazole may be given in non-life-threatening pulmonary infections and for patients who cannot tolerate amphotericin B.[4]

Lifelong maintenance therapy with oral itraconazole 200 mg daily may be beneficial after initial treatment for meningeal or disseminated sporotrichosis in immunocompromised patients, including those with AIDS, if immunosuppression cannot be reversed.[4]

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2. Restrepo A, *et al.* Itraconazole therapy in lymphangitic and cutaneous sporotrichosis. *Arch Dermatol* 1986; **122:** 413–17.
3. Anonymous. Antifungal drugs. *Treat Guidel Med Lett* 2005; **3:** 7–14.
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Tinea

See under Skin Infections, above.

Amorolfine *(BAN, USAN, rINN)*

Amorolfiini; Amorolfin; Amorolfina; Amorolfinum; Ro-14-4767/000. (±)-*cis*-2,6-Dimethyl-4-[2-methyl-3-(*p-tert*-pentylphenyl)propyl]morpholine.

Аморольфин

$C_{21}H_{35}NO = 317.5.$

CAS — 78613-35-1.

ATC — D01AE16.

ATC Vet — QD01AE16.

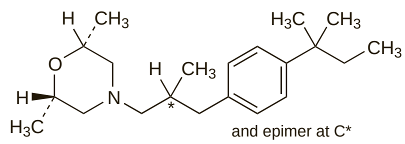

Amorolfine Hydrochloride *(BANM, rINNM)*

Amorolfine, Chlorhydrate d'; Amorolfini Hydrochloridum; Hidrocloruro de amorolfina; Ro-14-4767/002.

Аморольфина Гидрохлорид

$C_{21}H_{35}NO,HCl = 354.0.$

CAS — 78613-38-4.

ATC — D01AE16.

ATC Vet — QD01AE16.

Adverse Effects

Skin irritation, presenting as erythema, pruritus, or a burning sensation, and, rarely, more severe skin reactions have been reported after topical application of amorolfine.

Antimicrobial Action

Amorolfine is a morpholine derivative with antifungal activity. It appears to act by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes.

Amorolfine is active *in vitro* against a wide variety of pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida* spp., *Histoplasma capsulatum*, and *Sporothrix schenckii*. It also has variable activity against *Aspergillus* spp. However, despite its *in vitro* activity, amorolfine is inactive when given systemically and this limits its use to topical application for superficial infections.

Uses and Administration

Amorolfine is a morpholine derivative applied topically as the hydrochloride in the treatment of fungal nail and skin infections (p.521). After topical application, systemic absorption of amorolfine is negligible.

For the treatment of nail infections caused by dermatophytes, yeasts, and moulds a lacquer containing the equivalent of 5% amorolfine is painted onto the affected nail once or sometimes twice weekly until the nail has regenerated. Treatment generally needs to be continued for 6 to 12 months.

For skin infections, including dermatophyte infections, a cream containing the equivalent of 0.25% amorolfine is applied once daily for at least 2 to 3 weeks (up to 6 weeks for foot infections) and continued for 3 to 5 days after clinical cure is achieved.

◊ Reviews.

1. Haria M, Bryson HM. Amorolfine: a review of its pharmacological properties and therapeutic potential in the treatment of onychomycosis and other superficial fungal infections. *Drugs* 1995; **49:** 103–20.
2. Flagothier C, *et al.* New insights into the effect of amorolfine nail lacquer. *Mycoses* 2005; **48:** 91–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Loceryl; Locetar†; Micocide A; ***Austral.:*** Loceryl; ***Austria:*** Loceryl; ***Belg.:*** Loceryl; ***Braz.:*** Loceryl; ***Chile:*** Loceryl; ***Cz.:*** Loceryl; ***Denm.:*** Loceryl; ***Fin.:*** Loceryl; ***Fr.:*** Loceryl; ***Ger.:*** Loceryl; ***Gr.:*** Loceryl; ***Hong Kong:*** Loceryl; ***Hung.:*** Loceryl; ***Irl.:*** Loceryl; ***Ital.:*** Locetar; ***Jpn:*** Pekiron; ***Malaysia:*** Loceryl; ***Mex.:*** Loceryl; ***Norw.:*** Loceryl; ***NZ:*** Loceryl; ***Philipp.:*** Locetar; ***Pol.:*** Loceryl; ***Port.:*** Locetar; ***Rus.:*** Loceryl (Лоцерил); ***S.Afr.:*** Loceryl; ***Singapore:*** Loceryl; ***Spain:*** Locetar; Odenil; ***Swed.:*** Loceryl; ***Switz.:*** Loceryl; ***UK:*** Curanail; Loceryl; ***Venez.:*** Loceryl.

The symbol † denotes a preparation no longer actively marketed

Amphotericin B *(BANM, rINN)*

Amfotericin; Amfotericin B; Amfotericina B; Amfotericinas B; Amfoterisiini; Amfoterisiini B; Amfoterisin; Amfoterisin B; Amfoterycyna b; Amphotericin; Amphotéricine B; Amphotericinum; Amphotericinum B; Anfotericina B.

Амфотерицин В

$C_{47}H_{73}NO_{17} = 924.1.$

CAS — 1397-89-3.

ATC — A01AB04; A07AA07; G01AA03; J02AA01.

ATC Vet — QA01AB04; QA07AA07; QG01AA03; QJ02AA01.

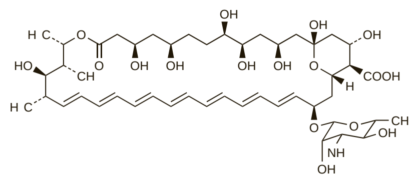

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Amphotericin B; Amphotericin BP 2008). A mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or by any other means. It consists largely of amphotericin B. It occurs as a yellow or orange powder. The potency is not less than 750 units per mg with reference to the dried substance. It contains not more than 10% of tetraenes, or not more than 5% if intended for use in parenteral dosage forms. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide and in propylene glycol; slightly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Amphotericin B is inactivated at low pH values. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Amphotericin B). A yellow to orange, odourless or practically odourless, powder. It contains not less than 750 micrograms of $C_{47}H_{73}NO_{17}$ per mg, and, for material intended for oral or topical use, not more than 15% of amphotericin A, both calculated on the dried substance. Insoluble in water, in dehydrated alcohol, in ether, in benzene, and in toluene; soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8° in airtight containers. Protect from light.

◊ References.

1. Kintzel PE, Smith GH. Practical guidelines for preparing and administering amphotericin B. *Am J Hosp Pharm* 1992; **49:** 1156–64.

Formulation. Conventional formulations of amphotericin B injection are typically a complex of amphotericin B and deoxycholate with suitable buffers which form a colloidal dispersion when reconstituted. Nonconventional '**lipid**' formulations of amphotericin B for injection include liposomal amphotericin B, a colloidal dispersion of an amphotericin B and sodium cholesteryl sulfate complex, and a phospholipid complex.

Incompatibility. Because of the wide range of incompatibilities reported with conventional and lipid formulations of amphotericin B, it is generally advisable not to mix them with any other drug. Most incompatibilities are caused by precipitation of amphotericin B due to a change in pH or by the disruption of the colloidal suspension. Precipitation can occur if amphotericin B is added to sodium chloride 0.9% or to electrolyte solutions.

Although heparin is generally reported to be compatible with conventional amphotericin B injection, care should be taken if heparin flush solutions, which are diluted with sodium chloride solution, are used to maintain the patency of intravenous lines in patients receiving amphotericin B. Flushing the intravenous line with 5% glucose solution has been suggested.

Mixtures of conventional amphotericin B in commercial lipid emulsions have been reported to be unstable,[1-3] although others have reported satisfactory stability.[4-6] In one study,[6] vigorous agitation of the mixtures enhanced their stability when compared with gentle mixing.

1. Ericsson O, *et al.* Amphotericin B is incompatible with lipid emulsions. *Ann Pharmacother* 1996; **30:** 298.
2. Ranchère JY, *et al.* Amphotericin B intralipid formulation: stability and particle size. *J Antimicrob Chemother* 1996; **37:** 1165–9.
3. Heide PE. Precipitation of amphotericin B from iv fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 1449.
4. Lopez RM, *et al.* Stability of amphotericin B in an extemporaneously prepared iv fat emulsion. *Am J Health-Syst Pharm* 1996; **53:** 2724–7.
5. Owens D, *et al.* Stability of amphotericin B 0.05 and 0.5 mg/mL in 20% fat emulsion. *Am J Health-Syst Pharm* 1997; **54:** 683–6.
6. Shadkhan Y, *et al.* The use of commercially available lipid emulsions for the preparation of amphotericin B-lipid admixtures. *J Antimicrob Chemother* 1997; **39:** 655–8. Correction. *ibid.* 1998; **42:** 413.

Preparation of solutions for injection. Recommendations from the manufacturers for preparation of amphotericin solutions are:

- *conventional amphotericin B* formulations for injection are prepared by reconstitution of amphotericin B with sterile water for injection without preservatives, then dilution with glucose injection 5% with a pH above 4.2 to the desired final concentration.
- *liposomal amphotericin B*: injections are prepared by reconstitution with sterile water for injection without a preservative; the required reconstituted amount is then withdrawn and injected via a sterile filter into the desired volume of glucose 5%.
- *amphotericin B-sodium cholesteryl sulfate complex*: injections are prepared by rapidly adding the required amount of water for injection, then further diluting with glucose 5% until the desired final concentration is reached.
- *amphotericin B-phospholipid complex*: before infusion the suspension concentrate must be diluted to the required final concentration with glucose 5%. The required amount of concentrate is injected via a sterile filter into the glucose 5%.

CAUTION: Mixture with sodium chloride injection 0.9% would precipitate amphotericin B.

Stability of oral suspensions. An oral suspension of amphotericin B 100 mg/mL, prepared from powder and a cherry-flavoured vehicle and maintained at pH 5.3, was found to be stable at 22 to 25° for 93 days.[1]

1. Dentinger PJ, *et al.* Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health-Syst Pharm* 2001; **58:** 1021–4.

Adverse Effects

Amphotericin B for intravenous use was originally only available in a conventional colloidal form; lipid formulations have been developed to reduce toxicity. The following adverse effects apply to the **conventional** form. Common adverse effects which occur during or after intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally.

Some degree of nephrotoxicity occurs in almost all patients given amphotericin B intravenously. Both tubular and glomerular damage occur; there may be improvement on cessation of therapy, but there is a risk of permanent renal impairment, particularly in patients given large cumulative doses (over 5 g). Renal tubular acidosis without systemic acidosis may develop. Use of amphotericin B is associated with increased urinary excretion of potassium and magnesium resulting in hypokalaemia and hypomagnesaemia respectively. Uric acid excretion is increased and nephrocalcinosis can occur. Limited data indicate that renal toxicity may be associated with sodium depletion; for strategies to improve sodium load see Nephrotoxicity, under Treatment of Adverse Effects, below.

A reversible, normocytic, normochromic anaemia develops in most patients given amphotericin B, possibly due to a direct suppressive effect on erythropoietin production. There are rare reports of thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, and coagulation defects.

Leukoencephalopathy has been reported rarely in patients also receiving total body irradiation.

Amphotericin B solutions irritate the venous endothelium and may cause pain and thrombophlebitis at the injection site. Extravasation may cause tissue damage.

After intrathecal injection amphotericin B may also cause irritation of the meninges, neuropathy with pain, impaired vision, and retention of urine.

In general, adverse effects of **lipid** formulations have been similar to those of conventional amphotericin B, but are less frequent and less severe. Brief reversible episodes of renal impairment have been observed but these formulations have been considered to be safe enough to use in patients with renal impairment who could not be given conventional amphotericin B. Anaphylaxis has been reported rarely.

Amphotericin applied **topically** may produce local irritation, pruritus, and skin rash.

Effects on the cardiovascular system. Ventricular arrhythmias in 2 patients, resulting in fatal sudden cardiac arrest in 1, were associated with both conventional and liposomal formulations of amphotericin B at conventional doses and infusion rates,[1] but cardiac toxicity is more common with high doses or rapid infusion rates (see Infusion Rate, under Administration, below). Cardiac arrests in 5 infants and children, fatal in 4 cases, were associated[2] with overdoses of conventional amphotericin B of between 3.8 and 40.8 mg/kg. Fatal cardiac toxicity has also been reported in an adult who inadvertently received an overdose (5 mg/kg) of conventional amphotericin B on 2 consecutive days.[3] A case of reversible dilated cardiomyopathy and congestive heart failure has been reported in a 20-year-old male patient after about 2 months of treatment, initially with conventional amphotericin B for 30 days and then with amphotericin B phospholipid complex. Symptoms resolved within 6 weeks of stopping treatment.[4] An increased risk of arrhythmia and cardiac arrest has been reported in patients with evidence of antimony-induced myocardial damage who were switched to amphotericin B treatment for visceral leishmaniasis.[5] A rest period of at least 10 days was advised before beginning amphotericin B in such patients.

Severe hypertension was associated with infusion of phospholipid-amphotericin B complex in 1 patient.[6]

1. Aguado JM, *et al.* Ventricular arrhythmias with conventional and liposomal amphotericin. *Lancet* 1993; **342:** 1239.
2. Cleary JD, *et al.* Amphotericin B overdose in pediatric patients with associated cardiac arrest. *Ann Pharmacother* 1993; **27:** 715–19.
3. Burke D, *et al.* Acute amphotericin B overdose. *Ann Pharmacother* 2006; **40:** 2254–9.
4. Danaher PJ, *et al.* Reversible dilated cardiomyopathy related to amphotericin B therapy. *J Antimicrob Chemother* 2004; **53:** 115–17.
5. Thakur CP. Sodium antimony gluconate, amphotericin, and myocardial damage. *Lancet* 1998; **351:** 1928–9.
6. Rowles DM, Fraser SL. Amphotericin B lipid complex (ABLC)-associated hypertension: case report and review. *Clin Infect Dis* 1999; **29:** 1564–5.

Effects on the eyes. Rapid loss of vision resulting in permanent bilateral blindness occurred in a patient with lupus erythematosus and cryptococcal meningitis after a 1-mg test dose of amphotericin B.[1] Amphotericin B was considered to be the cause as visual disturbances associated with cryptococcal meningitis are usually progressive in nature and acute blindness with normal funduscopic appearance had not previously been reported.

1. Li PKT, Lai KN. Amphotericin B induced ocular toxicity in cryptococcal meningitis. *Br J Ophthalmol* 1989; **73:** 397–8.

Effects on the liver. Amphotericin B has only rarely been associated with adverse effects on the liver. Fatal hepatic failure was reported in a patient after a total dose of 4.82 g given intermittently over 1 year.[1] The patient had been given a potentially incompatible intravenous admixture of amphotericin B and diphenhydramine.

There have been a few reports of abnormal liver-function tests during amphotericin B therapy;[2,3] in such cases amphotericin B should be stopped. Hyperbilirubinaemia associated with amphotericin B has also been reported.[4] An episode of reversible hepatic and renal toxicity has been reported in a child with cystic fibrosis after a cumulative dose of 84 mg of conventional amphotericin B and 168 mg of liposomal amphotericin B.[5]

1. Carnecchia BM, Kurtzke JF. Fatal toxic reaction to amphotericin B in cryptococcal meningo-encephalitis. *Ann Intern Med* 1960; **53:** 1027–36.
2. Miller MA. Reversible hepatotoxicity related to amphotericin B. *Can Med Assoc J* 1984; **131:** 1245–7.
3. Abajo FJ, Carcas AJ. Amphotericin B hepatotoxicity. *BMJ* 1986; **293:** 1243.
4. Olin JL, Spooner LM. Amphotericin B-associated hyperbilirubinemia: case report and review of the literature. *Pharmacotherapy* 2006; **26:** 1011–7.
5. Mohan UR, Bush A. Amphotericin B-induced hepatorenal failure in cystic fibrosis. *Pediatr Pulmonol* 2002; **33:** 497–500.

Effects on the lungs. Reports implicating use of leucocytes[1] or other blood products[2] in the development of pulmonary reactions in patients receiving amphotericin B have been refuted,[3,4] and a report has indicated that amphotericin B can produce pulmonary toxicity in the absence of blood products.[5] An increased incidence of pulmonary symptoms was noted in patients given amphotericin B in lipid emulsion,[6] including acute respiratory distress after starting the infusion. Chest discomfort, including tightness, pain, dyspnoea, and acute hypoxia, has been reported in 3 patients during one-hour infusions of liposomal amphotericin B. The reactions occurred within 5 to 10 minutes of starting the infusion and resolved on stopping the infusion. A slower rate of infusion was subsequently tolerated in 2 patients.[7]

1. Wright DG, *et al.* Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **304:** 1185–9.
2. Haber RH, *et al.* Acute pulmonary decompensation due to amphotericin B in the absence of granulocyte transfusions. *N Engl J Med* 1986; **315:** 836.
3. Forman SJ, *et al.* Pulmonary reactions associated with amphotericin B and leukocyte transfusions. *N Engl J Med* 1981; **305:** 584–5.
4. Bow EJ, *et al.* Pulmonary complications in patients receiving granulocyte transfusions and amphotericin B. *Can Med Assoc J* 1984; **130:** 593–7.
5. Roncoroni AJ, *et al.* Bronchiolis obliterans possibly associated with amphotericin B. *J Infect Dis* 1990; **161:** 589.
6. Schöffski P, *et al.* Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ* 1998; **317:** 379–84.
7. Johnson MD, *et al.* Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. *Pharmacotherapy* 1998; **18:** 1053–61.

Effects on potassium homoeostasis. In addition to the hypokalaemia known to be associated with amphotericin B and due to increased urinary excretion of potassium, hyperkalaemia has been reported in a patient with severe renal impairment who received a rapid infusion of amphotericin B (see Infusion Rate, under Administration, below). Hyperkalaemia also occurred in a 2-year-old child with chronic renal failure after a two-hour infusion of conventional amphotericin B. Hyperkalaemia and fatal cardiac arrest were also reported in a 4-year-old child after 3 infusions of amphotericin B lipid complex.[1]

1. Barcia JP. Hyperkalemia associated with rapid infusion of conventional and lipid complex formulations of amphotericin B. *Pharmacotherapy* 1998; **18:** 874–6.

Hypersensitivity. Anaphylactoid reactions have occurred with conventional amphotericin B, but have also been associated with liposomal amphotericin B,[1-3] including reports of patients who subsequently tolerated conventional formulations.[1,3]

1. Laing RBS, *et al.* Anaphylactic reactions to liposomal amphotericin. *Lancet* 1994; **344:** 682.
2. Torre I, *et al.* Anaphylactic reaction to liposomal amphotericin B in children. *Ann Pharmacother* 1996; **30:** 1036–7.
3. Vaidya SJ, *et al.* Anaphylactic reaction to liposomal amphotericin B. *Ann Pharmacother* 2002; **36:** 1480–1.

Red man syndrome. Red man syndrome (see Vancomycin, p.359) occurred in a patient on 2 occasions after a 1-mg test dose of amphotericin B.[1]

1. Ellis ME, Tharpe W. Red man syndrome associated with amphotericin B. *BMJ* 1990; **300:** 1468.

Treatment of Adverse Effects

To reduce febrile reactions antipyretics and antihistamines may be given before the intravenous infusion of conventional amphotericin B. Hydrocortisone given intravenously before or during amphotericin B infusion may also reduce febrile reactions. However, corticosteroids should not be given indiscriminately to patients given amphotericin B (see Interactions, below) and dosage should be kept to a minimum. In the UK the advice is to give antipyretics or hydrocortisone prophylactically, but only to patients who have previously had acute adverse reactions and in whom continued treatment with intravenous amphotericin B is essential (see Prophylaxis, below). Pethidine has been given intravenously to treat amphotericin B-induced shaking chills. Antiemetics may also be required. Amphotericin B is not removed by haemodialysis. Hypokalaemia and hypomagnesaemia should be corrected, and adequate hydration and sodium supplements may reduce the severity of renal impairment. Lipid formulations of amphotericin B can be substituted for conventional amphotericin B if the latter cannot be tolerated.

Heparin has been added to conventional amphotericin B infusions to reduce the incidence of thrombophlebitis.

Anaemia. Amphotericin B appears to produce a normochromic, normocytic anaemia by suppression of erythropoietin production.[1,2] Stopping amphotericin B reverses the suppression but if the anaemia is severe, or treatment with amphotericin B cannot be stopped, blood transfusions may be required. Recombinant erythropoietin may prove an alternative to blood transfusions in patients who need to continue treatment with amphotericin B.

1. MacGregor RR, *et al.* Erythropoietin concentrations in amphotericin B-induced anemia. *Antimicrob Agents Chemother* 1978; **14:** 270–3.
2. Lin AC, *et al.* Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis* 1990; **161:** 348–51.

Electrolyte disturbances. It has been suggested[1] that amiloride could ameliorate the hypokalaemia and hypomagnesaemia associated with amphotericin B. However, since amiloride may produce sodium depletion and its own associated renal toxicity this strategy is potentially hazardous. Another report[2] has suggested that spironolactone may be a safe and effective method of preventing hypokalaemia.

1. Wazny LD, Brophy DF. Amiloride for the prevention of amphotericin B-induced hypokalemia and hypomagnesemia. *Ann Pharmacother* 2000; **34:** 94–7.
2. Ural AU. Comment: spironolactone prevents amphotericin B-induced hypokalemia in neutropenic patients. *Ann Pharmacother* 2000; **34:** 1488.

Nephrotoxicity. A review of strategies for limiting the toxicity of amphotericin B concluded that sodium balance should be monitored and sodium replacement implemented if necessary and that, where possible, salt restriction and drugs that potentiate sodium loss or nephrotoxicity should be avoided.[1] Correction of sodium depletion may reverse amphotericin B-induced nephrotoxicity.[2] However, assessment of sodium status and correction of deficiency should precede use of amphotericin B.[3,4] While supplementation with 150 mmol sodium has been recommended for suitable patients,[4] routine prophylactic use of sodium is not advised.[5] However, a randomised study in a small number of patients has suggested that prophylactic sodium supplementation could be beneficial, but that it enhances potassium loss.[6] Diuretics in general should be avoided[7] although there have been suggestions that potassium-sparing diuretics such as amiloride or spironolactone may be useful in preventing hypokalaemia (see Electrolyte Disturbances, above). Use of mannitol as a protective agent is controversial and is not recommended.[3,4,8] Amphotericin B is often given on alternate days although this has never been proven to reduce nephrotoxicity.[3,4]

More recently, lipid formulations have been reported to overcome most problems of chronic nephrotoxicity, even in patients with renal impairment after previous treatment with conventional amphotericin B (see Lipid Formulations, under Administration, below).

1. Khoo SH, *et al.* Administering amphotericin B—a practical approach. *J Antimicrob Chemother* 1994; **33:** 203–13.
2. Heidemann HT, *et al.* Amphotericin B nephrotoxicity in humans decreased by salt repletion. *Am J Med* 1983; **75:** 476–81.
3. Warda J, Barriere SL. Amphotericin B nephrotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 25–6.
4. Sabra R, Branch RA. Amphotericin B nephrotoxicity. *Drug Safety* 1990; **5:** 94–108.
5. Gardner ML, *et al.* Sodium loading treatment for amphotericin B-induced nephrotoxicity. *DICP Ann Pharmacother* 1990; **24:** 940–6.
6. Llanos A, *et al.* Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney Int* 1991; **40:** 302–8.
7. Fisher MA, *et al.* Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med* 1989; **87:** 547–52.
8. Bullock WE, *et al.* Can mannitol reduce amphotericin B nephrotoxicity? Double-blind study and description of a new vascular lesion in kidneys. *Antimicrob Agents Chemother* 1976; **10:** 555–63.

Prophylaxis. The value of prophylaxis against generalised reactions to amphotericin B infusion was questioned after a retrospective study in 397 patients.[1] The most commonly used drugs were diphenhydramine, corticosteroids, paracetamol, and heparin. It was concluded that patients who had had an adverse reaction after amphotericin B should be given appropriate premedication before subsequent amphotericin B infusions, but that routine premedication was not justified.

1. Goodwin SD, *et al.* Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995; **20:** 755–61.

Precautions

Although anaphylaxis is rare after intravenous amphotericin B, it is advisable to give a test dose and then to observe the patient carefully for about 30 minutes before starting treatment. Patients experiencing acute toxic reactions in whom treatment is essential may be given prophylactic treatment, as mentioned in Treatment of Adverse Effects, above, to ameliorate the reactions. To reduce the risk of vein irritation and infusion-related adverse effects, the rate of intravenous infusion of conventional amphotericin B should be slow (see Infusion Rate, under Administration, below). Patients given any parenteral form of amphotericin B should be monitored for changes in renal function, liver function, serum electrolytes, and haematological status. If the BUN or creatinine concentrations increase to clinically significant levels amphotericin B therapy should be interrupted or the dose reduced until renal function improves. Alternatively, a lipid amphotericin B preparation may be substituted. Treatment should be stopped if liver function tests are abnormal. Acute pulmonary reactions have been noted in patients given amphotericin B during or shortly after leucocyte transfusions. Although the association is contested (see Effects on the Lungs, above), manufacturers of some amphotericin B products consider it advisable to separate the two and to monitor pulmonary function in these patients.

Care should be taken not to confuse the dosage regimens for individual preparations, and in particular those of conventional and lipid formulations.

Pregnancy. There are case reports of conventional amphotericin B having been used successfully to treat fungal infections in pregnant women without any adverse effects on the infant.[1-3] A review[4] of the use of antifungal drugs in pregnancy concluded that parenteral amphotericin B was the drug of first choice in the treatment of serious fungal infections in pregnancy. The safety of the lipid amphotericin formulations in pregnancy is not yet clear, although there has been a report of a series of 5 pregnant women with visceral leishmaniasis who were treated in the first or second trimester with a short course of liposomal amphotericin B without adverse effects on the infant.[5]

1. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; **126:** 350–3.
2. Peterson CM, *et al.* Coccidiodal meningitis and pregnancy: a case report. *Obstet Gynecol* 1989; **73:** 835–6.
3. Dean JL, *et al.* Use of amphotericin B during pregnancy: case report and review. *Clin Infect Dis* 1994; **18:** 364–8.
4. Sobel JD. Use of antifungal drugs in pregnancy: a focus on safety. *Drug Safety* 2000; **23:** 77–85.
5. Pagliano P, *et al.* Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother* 2005; **55:** 229–33.

Interactions

Most interactions involving amphotericin B have been observed during treatment with conventional formulations. Since lipid formulations appear to be less toxic, it may be anticipated that they will produce fewer serious interactions.

Use of nephrotoxic antibacterials, ciclosporin or other nephrotoxic immunosuppressants, or parenteral pentamidine may lead to an increased risk of nephrotoxicity. If possible, amphotericin B should not be given to patients receiving antineoplastics. Diuretics should generally be avoided in patients taking amphotericin B. If a diuretic has to be given then volume and electrolyte depletion should be monitored carefully. The potassium-depleting effect of amphotericin B may enhance the effects of neuromuscular blocking drugs and may increase the toxicity of digitalis glycosides; corticosteroids may enhance the depletion of potassium and their immunosuppressive effects may be detrimental in patients with severe fungal infections.

Amphotericin B may increase the toxicity of flucytosine, but the combination is nonetheless used in severe infections for its synergistic activity. For information on synergistic and antagonistic effects with other antimicrobials, see under Antimicrobial Action, below. Renal excretion of zalcitabine may be reduced by amphotericin B.

For an increased risk of cardiac arrhythmias and arrest when amphotericin B was given to patients with myocardial damage induced by an antimony compound, see Effects on the Cardiovascular System, under Adverse Effects, above.

Antimicrobial Action

Amphotericin B is a polyene antifungal antibiotic which appears to act mainly by interfering with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. It is reported to be fungistatic at concentrations achieved clinically. It is active against *Absidia* spp., *Aspergillus* spp., *Basidiobolus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Conidiobolus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mucor* spp., *Paracoccidioides brasiliensis*, *Rhizopus* spp., *Rhodotorula* spp., and *Sporothrix schenckii*. Other organisms that have been reported to be sensitive to amphotericin B include the algal *Prototheca* spp. and the protozoa *Leishmania* and *Naegleria* spp. It is inactive against bacteria (including rickettsia) and viruses.

Some resistant strains of *Candida* have been isolated from immunocompromised patients given prolonged treatment with amphotericin B.

Microbiological interactions. *Azoles.* Although there have been occasional reports of synergy between amphotericin B and the azole antifungals, greater emphasis has been placed on possible antagonism. Studies *in vitro* have supported theoretical concerns that the action of amphotericin B (which depends on binding to ergosterol in the fungal cell membrane) would be antagonised by azoles (which inhibit ergosterol synthesis).[1,2] *Animal* studies appear to have confirmed antagonism between amphotericin B and the imidazole ketoconazole, but not between amphotericin B and the triazoles fluconazole or itraconazole. Available clinical evidence seems to indicate that azoles given with, or as continuation therapy after, induction therapy with amphotericin B, are effective in severe infections, although reduced plasma concentrations of itraconazole have been reported in some patients while being given amphotericin B.[3] However, strains of *Candida albicans* resistant to both amphotericin B and fluconazole have emerged in patients who have received repeated or prolonged courses of fluconazole.[4,5]

1. Martin E, *et al.* Antagonistic effects of fluconazole and 5-fluorocytosine on candidacidal action of amphotericin B in human serum. *Antimicrob Agents Chemother* 1994; **38:** 1331–8.
2. Sud IJ, Feingold DS. Effect of ketoconazole on the fungicidal action of amphotericin B in Candida albicans. *Antimicrob Agents Chemother* 1983; **23:** 185–7.
3. Pennick GJ, *et al.* Concomitant therapy with amphotericin B and itraconazole: does this combination affect the serum concentration of itraconazole? *Intersci Conf Antimicrob Agents Chemother* 1994; **34:** 39 (A34).
4. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; **348:** 1523–4.
5. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; **44:** 196–9.

Pharmacokinetics

There is little or no absorption of amphotericin B from the gastrointestinal tract. When given intravenously in the *conventional colloidal form* and in the usual increasing dosage regimens, peak plasma concentrations of 0.5 to 4 micrograms/mL have been reported; the average plasma concentration with maintenance doses of 400 to 600 micrograms/kg daily tends to be 500 nanograms/mL. Amphotericin B is highly bound to plasma proteins and is widely distributed, but passes into the CSF only in small quantities. The plasma half-life is about 24 hours; with long-term use the terminal half-life increases to 15 days.

Unchanged amphotericin B is excreted in small amounts slowly in the urine. Traces are present in the serum and urine several weeks after completion of treatment. Amphotericin B is not removed by haemodialysis.

The pharmacokinetics of the lipid formulations differ considerably from the conventional formulation and from each other:

- at clinical doses of 1 to 7.5 mg/kg, *liposomal amphotericin B* produces peak plasma concentrations of around 8 to 80 micrograms/mL, around 20 times those with conventional formulations
- after doses of 0.5 to 8 mg/kg, *amphotericin B-sodium cholesteryl sulfate complex* produces peak plasma concentrations of about 0.7 to 6.2 micrograms/mL
- at a dose of 5 mg/kg daily, *amphotericin B phospholipid complex* produces maximum plasma concentrations of about 1.7 micrograms/mL

Studies in *animals* have shown that concentrations in the kidney are several times lower after lipid formulations than with conventional ones.

Children and neonates. Serum-amphotericin B concentrations ranged from 0.78 to 10.02 micrograms/mL in 12 children (many with leukaemia) aged 4 months to 14 years after the intravenous infusion of *conventional amphotericin B* 0.25 to 1.5 mg/kg daily. Serum concentrations did not correlate with dose. The elimination half-life was 18.1 ± 6.65 hours. There was an inverse relationship between age and total clearance, suggesting that children older than 9 years may require lower doses.[1]

The pharmacokinetics of amphotericin B have also been studied in a group of 13 neonates with systemic fungal infections.[2] *Conventional amphotericin B* was infused over 4 to 6 hours every 24 hours. Ten of the infants started treatment with 100 micrograms/kg increased over 4 to 6 days to 500 micrograms/kg. Three infants were started on a dose of 800 to 1000 micrograms/kg reduced to 500 micrograms/kg daily. All infants were maintained on 500 micrograms/kg daily; total doses ranged from 17.3 to 28.6 mg/kg. Serum-amphotericin B concentrations were measured after the first dose in 3 infants in the first group and 2 in the second; no serum-amphotericin B could be detected in the 3 infants who had received 100 micrograms/kg. After 5 days of treatment peak serum-amphotericin B concentrations ranged from 0.5 to 4.0 micrograms/mL and this was considered to be the range that could be achieved with the daily maintenance dose of 500 micrograms/kg. The elimination half-life was 14.8 hours. Drug elimination between doses was not detected in 4 of the infants; one was in oliguric renal failure and the other 3 had developed increases in serum-creatinine concentrations. CSF-amphotericin B concentrations in 5 of the neonates ranged from 40 to 90% of simultaneous serum concentrations. It was considered that an initial dose of 500 micrograms/kg was well tolerated and could produce therapeutic serum concentrations more quickly than a regimen which consisted of 100 micrograms/kg on day one increased over 4 to 6 days to 500 micrograms/kg daily.

A comparative study[3] of plasma concentrations of *liposomal amphotericin B* in adults, children, and neonates after a dose of 1 mg/kg daily for 28 days, reported peak concentrations in children and neonates that were significantly lower than in adults. Increases in the mean peak plasma concentrations over days 1 to 28 were: adults, 1.02 to 1.66 micrograms/mL; children aged 1 to 12 years, 0.63 to 1.10 micrograms/mL; and neonates, 0.54 to 0.73 micrograms/mL. This was thought to be due to the greater volume of distribution in the neonates and greater clearance in older children.

The pharmacokinetics of *amphotericin B lipid complex* was studied in a cohort of 6 paediatric cancer patients with hepatosplenic candidiasis receiving a dose of 2.5 mg/kg daily for 6 weeks, to a total dosage of 105 mg/kg.[4] It was noted that the mean plasma concentrations over the dosing interval and area under the curve increased between the first and seventh doses but were similar between doses 7 and 42, suggesting that a steady state was achieved within 1 week of therapy. After the final dose of amphotericin B lipid complex, the mean plasma-amphotericin concentration was noted to be 0.50 micrograms/mL and the maximum concentration in whole blood was 1.69 micrograms/mL.

1. Benson JM, Nahata MC. Pharmacokinetics of amphotericin B in children. *Antimicrob Agents Chemother* 1989; **33:** 1989–93.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.
3. Kotwani RN, *et al.* A comparative study of plasma concentrations of liposomal amphotericin B (L-AMP-LRC-1) in adults, children and neonates. *Int J Pharm* 2002; **238:** 11–15.
4. Walsh TJ, *et al.* Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother* 1997; **41:** 1944–8.

Distribution. Amphotericin B concentrations in various organs and tissues were determined in 13 cancer patients who had received conventional amphotericin B before death.[1] Concentrations were determined by high-pressure liquid chromatography (HPLC) and bioassay. Mean recovery by HPLC reported as a percentage of total dose given was liver 27.5%, spleen 5.2%, lungs 3.2%, kidney 1.5%, heart 0.4%, brain 0.3%, and pancreas 0.2%; each organ had a specific accumulation pattern. The mean total recovery was 38.8%. Reported median bile concentration was 7.3 micrograms/mL. The drug concentrations obtained by bioassay were much lower than those measured by HPLC. As the HPLC-determined concentrations of amphotericin B were higher than the MICs for the pathogens in patients with candidiasis or aspergillosis, the poor clinical outcome in these patients suggested that amphotericin B in the tissue lacked antifungal activity.

In another study,[2] amphotericin B was not detected in the CSF of 4 AIDS patients with cryptococcal meningitis on intravenous maintenance conventional doses of 350 to 1890 micrograms/kg given 1 to 7 times weekly. The clinical success of amphotericin B for this indication could not be explained by measurable CSF drug concentrations.

Concentrations of amphotericin B have been measured in fetal-cord serum in an infant and were 37.5% of maternal serum concentration.[3]

1. Collette N, *et al.* Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. *Antimicrob Agents Chemother* 1989; **33:** 362–8.
2. Dugoni BM, *et al.* Amphotericin B concentrations in cerebrospinal fluid of patients with AIDS and cryptococcal meningitis. *Clin Pharm* 1989; **8:** 220–1.
3. Ismail MA, Lerner SA. Disseminated blastomycosis in a pregnant woman. *Am Rev Respir Dis* 1982; **126:** 350–3.

Half-life. The terminal half-life for amphotericin B was 15 days in 2 patients on completion of conventional amphotericin B infusion therapy for disseminated histoplasmosis.[1] In another study,[2] the half-life was 21.5 hours (based on the exponential phase of disappearance from the blood) in a 65-year-old patient on a maintenance conventional dose of 500 micrograms/kg infused over 1 hour every other day. Serum concentrations appeared to plateau at about 600 nanograms/mL 36 to 48 hours after each dose. This suggested that alternate-day dosage might be effective.

1. Atkinson AJ, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978; **13:** 271–6.
2. Hoeprich PD. Elimination half-life of amphotericin B. *J Infect* 1990; **20:** 173–5.

Lipid formulations. References.

1. Janknegt R, *et al.* Liposomal and lipid formulations of amphotericin B: clinical pharmacokinetics. *Clin Pharmacokinet* 1992; **23:** 279–91.
2. Adedoyin A, *et al.* Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother* 1997; **41:** 2201–8.
3. Adedoyin A, *et al.* A pharmacokinetic study of amphotericin B lipid complex injection (Abelcet) in patients with definite or probable systemic fungal infections. *Antimicrob Agents Chemother* 2000; **44:** 2900–2.
4. Bekersky I, *et al.* Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. *Antimicrob Agents Chemother* 2002; **46:** 828–33.

Uses and Administration

Amphotericin B is a polyene antifungal antibiotic. It is reported to be fungistatic at concentrations achieved clinically. Amphotericin B is given by intravenous infusion in the treatment of severe *systemic* fungal infections including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, paracoccidioidomycosis, and sporotrichosis, and is the usual treatment of choice in fungal endocarditis, meningitis, peritonitis, or severe respiratory-tract infections. Many of these infections are most likely to occur in immunocompromised patients. Amphotericin may be given with flucytosine (p.534) in severe infections.

Amphotericin B is also used for the *local* treatment of superficial candidiasis. It is taken orally for intestinal candidiasis, sometimes as part of regimens for selective decontamination of the digestive tract in patients at special risk of infection, such as those in intensive care (see p.175).

The role of amphotericin B in the treatment of the above systemic and local infections is discussed under Choice of Antifungal, p.517.

Amphotericin B also has antiprotozoal activity. It is used for primary amoebic meningoencephalitis caused by *Naegleria* spp. and for the treatment of visceral and mucocutaneous leishmaniasis.

Administration and dosage. Amphotericin B is given by *intravenous* infusion conventionally as a colloidal complex with sodium deoxycholate. There is also a liposomal form and other complexes of amphotericin B available for use by infusion when conventional amphotericin B is contra-indicated because of toxicity, especially nephrotoxicity. Before starting therapy with any form of intravenous amphotericin B a test dose is usually advised and the patient observed carefully for about 30 minutes.

Details of intravenous administration and dosage vary according to the formulation being used. Therapy has sometimes continued for several months depending on the infection. Doses are expressed in terms of amphotericin B.

- ***Conventional amphotericin B*** (*Fungizone, UK*). After an initial test dose (1 mg infused over 20 to 30 minutes) treatment usually starts with a daily dose of 250 micrograms/kg, increased gradually to a maximum of 1 mg/kg daily; in seriously ill patients up to 1.5 mg/kg daily or on alternate days may be necessary. If treatment is stopped for longer than 7 days, it should be resumed at a dose of 250 micrograms/kg daily and increased gradually. The daily dose is infused over 2 to 4 hours at a concentration of 100 micrograms/mL in glucose 5%. Slower infusion, over up to 6 hours, may be necessary to reduce the incidence of acute toxic effects.
- ***Liposomal amphotericin B*** (*AmBisome, UK*). After an initial test dose (1 mg infused over 10 minutes), the usual dose is 1 mg/kg daily, increased gradually to 3 mg/kg if necessary. The daily dose is infused over 30 to 60 minutes at a concentration of 200 to 2000 micrograms/mL in glucose 5%.
- ***Amphotericin B-sodium cholesteryl sulfate complex*** (*Amphocil, UK*). After an initial test dose (2 mg infused over 10 minutes) the usual dose is 1 mg/kg daily, increased gradually to 3 to 4 mg/kg daily if necessary; doses of up to 6 mg/kg daily have been given. The daily dose is infused at a rate of 1 to 2 mg/kg per hour at a concentration of 625 micrograms/mL in glucose 5%.
- ***Amphotericin B-phospholipid complex*** (*Abelcet, UK*). After an initial test dose (1 mg infused over 15 minutes) the usual dose is 5 mg/kg daily. The daily dose is infused at a rate of 2.5 mg/kg per hour as a diluted suspension containing 1 mg/mL in glucose 5%.

Conventional amphotericin B may be given by *intrathecal* injection to patients with severe meningitis especially when intravenous therapy has been ineffective. Starting with 25 micrograms, the dose is gradually increased to the maximum that can be tolerated without excessive discomfort. The usual dosage is 0.25 to 1 mg given two to four times each week.

Conventional amphotericin B is also used *orally* as 10-mg lozenges or as a suspension containing 100 mg/mL for oral or perioral candidiasis. The suspension is given in a dose of 1 mL four times daily; it should be retained in the mouth for as long as possible before swallowing. The lozenges are intended to be dissolved in the mouth and are given four times daily, increased to 8 lozenges daily if necessary. Doses of 100 to 200 mg are given four times daily as tablets or suspension to suppress intestinal *Candida*.

Conventional amphotericin B has been given for candiduria as a *continuous bladder irrigation* daily at a suggested concentration of 50 mg in 1000 mL of sterile water. Intermittent irrigation has also been tried.

Conventional amphotericin B has also been given into the lung by nebulised solution, into the eye topically or by subconjunctival or intravitreal injection, to the skin by topical application, into body cavities by instillation, and into joint spaces by intra-articular injection.

Administration. *LIPID FORMULATIONS.* A number of lipid formulations of amphotericin B have been developed in an attempt to minimise renal toxicity and acute toxic reactions. Three lipid-based formulations of amphotericin B available commercially in some countries are:

- liposomes (e.g. *AmBisome*)[1]
- a lipid complex with L-α-dimyristoylphosphatidylcholine and L-α-dimyristoylphosphatidylglycerol (e.g. *Abelcet*)
- a colloidal dispersion with sodium cholesteryl sulfate (e.g. *Amphocil*)

The aim of reducing renal toxicity has largely been achieved, and in some cases patients unable to tolerate conventional amphotericin B have subsequently been successfully treated with one of the lipid-based formulations. Experience with these formulations suggests that they also produce fewer acute toxic reactions. Review articles[2-9] on lipid formulations of amphotericin B indicate that clinical studies have generally been encouraging, and that although they differ in their pharmacodynamics, pharmacokinetics, and dosage, they appear to be clinically at least as effective as amphotericin B.[5,6]

1. Barnes RA, *et al.*, eds. AmBisome: an international workshop. *J Antimicrob Chemother* 2002; **49** (suppl S1): 1–86.
2. Coukell AJ, Brogden RN. Liposomal amphotericin B: therapeutic use in the management of fungal infections and visceral leishmaniasis. *Drugs* 1998; **55:** 585–612.
3. Brogden RN, *et al.* Amphotericin-B colloidal dispersion: a review of its use against systemic fungal infections and visceral leishmaniasis. *Drugs* 1998; **56:** 365–83.
4. Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 21/06/05).
5. Dupont B. Overview of the lipid formulations of amphotericin B. *J Antimicrob Chemother* 2002; **49** (Suppl 1): 31–6.
6. Barrett JP, *et al.* A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. *Clin Ther* 2003; **25:** 1295–320.
7. Herbrecht R, *et al.* The lipid formulations of amphotericin B. *Expert Opin Pharmacother* 2003; **4:** 1277–87.
8. Fohrer C, *et al.* Apports des derives lipidiques de l'amphotéricine B dans la prise en charge des infections fongiques. *Therapie* 2006; **61:** 235–42.
9. Adler-Moore JP, Proffitt RT. Amphotericin B lipid preparations: what are the differences? *Clin Microbiol Infect* 2008; **14** (suppl 4): 25–36.

INFUSION RATE. Conventional amphotericin B is licensed for use by intravenous infusion over at least 2 hours. A long infusion time is inconvenient for outpatients and often impractical in patients receiving other intravenous medications. This may be overcome by using one of the lipid formulations that can be infused over 30 to 120 minutes. Shorter infusion times have been tried with conventional amphotericin B but although 2 studies[1,2] in small numbers of patients without pre-existing renal impairment found rapid infusion over 1 hour was generally no more toxic than infusion over 4 hours, another[3] found infusion over 45 minutes to be more toxic than a 4-hour infusion during the first 5 to 7 days of treatment. Cardiac toxicity reported in patients receiving rapid infusions includes atrial fibrillation in a patient with pre-existing cardiac disease,[2] ventricular fibrillation associated with hyperkalaemia in a patient with severe renal impairment,[4] and bradycardia[5] and dilated cardiomyopathy[6] in patients without apparent risk factors. Ventricular dysrhythmias were not observed in 27 patients with adequate renal function.[7]

Conversely, continuous infusion of amphotericin B over 24 hours has resulted in fewer adverse effects and a significant reduction in nephrotoxicity compared with infusion over 4 hours.[8] Furthermore, an observational study of 33 patients concluded that a continuous infusion of amphotericin B deoxycholate, started at 1 mg/kg daily and gradually escalated to 2 mg/kg daily was safe and well tolerated by most patients.[9]

1. Oldfield EC, *et al.* Randomized, double-blind trial of 1- versus 4-hour amphotericin B infusion durations. *Antimicrob Agents Chemother* 1990; **34:** 1402–6.
2. Cruz JM, *et al.* Rapid intravenous infusion of amphotericin B: a pilot study. *Am J Med* 1992; **93:** 123–30.
3. Ellis ME, *et al.* Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrob Agents Chemother* 1992; **36:** 172–9.
4. Craven PC, Gremillion DH. Risk factors of ventricular fibrillation during rapid amphotericin B infusion. *Antimicrob Agents Chemother* 1985; **27:** 868–71.
5. Soler JA, *et al.* Bradycardia after rapid intravenous infusion of amphotericin B. *Lancet* 1993; **341:** 372–3.
6. Arswa EL, *et al.* Amphotericin B-induced dilated cardiomyopathy. *Am J Med* 1994; **97:** 560–2.
7. Bowler WA, *et al.* Risk of ventricular dysrhythmias during 1-hour infusions of amphotericin B in patients with preserved renal function. *Antimicrob Agents Chemother* 1992; **36:** 2542–3.
8. Eriksson U, *et al.* Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ* 2001; **322:** 579–82.
9. Imhof A, *et al.* Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. *Clin Infect Dis* 2003; **36:** 943–51.

Administration in children and neonates. Intravenous doses for conventional and lipid formulations of amphotericin B similar to those in adults have been found to be safe and effective in children and neonates with candidiasis. For neonates with severe disease, dose increments of conventional amphotericin B every 12 hours have been given and daily doses up to 1.5 mg/kg tolerated. For prophylaxis of neonatal intestinal candidiasis conventional amphotericin B solution 100 mg is given orally once daily. Although the most appropriate dose of lipid formulations of amphotericin B for low-birth-weight preterm infants has yet to be firmly established reports suggest that they may be safe and effective at doses similar to those used in adults, relative to body-weight.[1-3]

For information on the pharmacokinetics and doses in children and neonates, see, above.

1. Scarcella A, *et al.* Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998; **17:** 146–8.
2. Weitkamp J-H, *et al.* Candida infection in very low birth-weight infants: outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome). *Infection* 1998; **26:** 11–15.
3. Walsh TJ, *et al.* Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999; **18:** 702–8.

Leishmaniasis. The treatment of visceral and mucocutaneous leishmaniasis including the use of amphotericin B is described on p.824.

VISCERAL LEISHMANIASIS. Evidence of declining responsiveness to pentavalent antimonials has led to the evaluation of intravenous amphotericin B as an alternative for first-line therapy. WHO has included liposomal amphotericin B 3 mg/kg daily on each of 5 consecutive days and a sixth dose 6 days later among the regimens suggested for first-line therapy of Mediterranean visceral leishmaniasis in immunocompetent patients.[1] Similar doses are recommended by licensed product information for one product (*AmBisome; Gilead, USA*), which recommends 3 mg/kg daily for 5 days with further doses on days 14 and 21. Experience with a short course of 10 mg/kg daily for 2 days was also shown to be effective in 41 immunocompetent children under 14 years, although 1 subsequently relapsed after 5 weeks.[2] Responses to liposomal amphotericin B have been reported to be slower in immunocompromised patients; relapses occurred in 8 of 11 patients despite treatment with liposomal amphotericin B 1.38 to 1.85 mg/kg daily for 21 days.[3] Increasing the dose to 4 mg/kg daily given on 10 days over a 38-day period did not improve the long-term outcome, although initial responses were good[4] and this regimen is now that recommended by the licensed product information above. Due to frequent relapse in these patients secondary prophylaxis with intermittent amphotericin B has been considered. An open-label, multicentre study with amphotericin B lipid complex in doses of 3 mg/kg every 21 days for 12 months[5] was effective in 50% of HIV-infected patients. Another cohort study[6] reported that 80% of HIV-infected patients were relapse free at 12 months after receiving an initial treatment course of liposomal amphotericin B in doses of 4 mg/kg daily for 5 consecutive days and then once weekly for 5 weeks, followed by secondary prophylaxis in doses of 5 mg/kg every 3 weeks. However, at 24 months about 45% of the patients had experienced relapses.

Amphotericin B is also being evaluated in other parts of the world. In India, conventional amphotericin B in modest doses (500 micrograms/kg on alternate days) produced good responses both in patients unresponsive to antimonials[7,8] and as first-line therapy.[9] Experience with a higher dose of 1 mg/kg daily for 20 days achieved a 99% cure rate in 938 patients[10] and a lower dose regimen of 0.75 mg/kg daily for 15 days was also found to be effective.[11] Liposomal amphotericin B 2 mg/kg daily on 3, 5 or 7 days over a 10-day period all produced clinical cures and minimal toxicity,[12] as did single infusions of 7.5 mg/kg or 5 mg/kg, or once-daily infusion of 1 mg/kg for 5 days.[13,14] Amphotericin B lipid complex 1, 2, or 3 mg/kg daily for 5 days,[15] or 5 mg/kg given once or twice (5 days apart),[16] has been used successfully although relapses occurred in some patients taking the lower doses in these latter studies. In Brazil, colloidal amphotericin B with sodium cholesteryl sulfate in a dose of 2 mg/kg daily for 5 days produced cures in 10 patients although 1 subsequently relapsed.[17] A study by WHO[18] suggested that more intensive courses of treatment may be needed in Brazil compared with India and Kenya.

MUCOCUTANEOUS LEISHMANIASIS. Amphotericin B is used in mucocutaneous leishmaniasis unresponsive to antimonials. Successful treatment with liposomal amphotericin B has been reported in immunocompetent[19] and immunocompromised[20] patients.

1. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73:** 191–7.
2. Syriopoulou V, *et al.* Two doses of a lipid formulation of amphotericin B for the treatment of Mediterranean visceral leishmaniasis. *Clin Infect Dis* 2003; **36:** 560–6.
3. Davidson RN, *et al.* Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med* 1994; **87:** 75–81.
4. Russo R, *et al.* Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect* 1996; **32:** 133–7.
5. López-Vélez R, *et al.* Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2004; **53:** 540–3.
6. Molina I, *et al.* Efficacy of liposomal amphotericin B for secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother* 2007; **60:** 837–42.
7. Giri OP. Amphotericin B therapy in kala-azar. *J Indian Med Assoc* 1993; **91:** 91–3.
8. Mishra M, *et al.* Amphotericin versus pentamidine in antimony-unresponsive kala-azar. *Lancet* 1992; **340:** 1256–7.
9. Mishra M, *et al.* Amphotericin versus sodium stibogluconate in first-line treatment of Indian kala-azar. *Lancet* 1994; **344:** 1599–1600.
10. Thakur CP, *et al.* Amphotericin B deoxycholate treatment of visceral leishmaniasis with newer modes of administration and precautions: a study of 938 cases. *Trans R Soc Trop Med Hyg* 1999; **93:** 319–23.
11. Sundar S, *et al.* Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions. *Clin Infect Dis* 2007; **45:** 556–61.
12. Thakur CP, *et al.* Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study. *Trans R Soc Trop Med Hyg* 1996; **90:** 319–22.
13. Sundar S, *et al.* Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. *BMJ* 2001; **323:** 419–22.
14. Sundar S, *et al.* Single-dose liposomal amphotericin B in the treatment of visceral leishmaniasis in India: a multicenter study. *Clin Infect Dis* 2003; **37:** 800–4.
15. Sundar S, *et al.* Short-course, low-dose amphotericin B lipid complex therapy for visceral leishmaniasis unresponsive to antimony. *Ann Intern Med* 1997; **127:** 133–7.
16. Sundar S, *et al.* Treatment of antimony-unresponsive Indian visceral leishmaniasis with ultra-short courses of amphotericin-B-lipid complex. *Ann Trop Med Parasitol* 1998; **92:** 755–64.
17. Dietze R, *et al.* Treatment of kala-azar in Brazil with Amphocil (amphotericin B cholesterol dispersion) for 5 days. *Trans R Soc Trop Med Hyg* 1995; **89:** 309–11.
18. Berman JD, *et al.* Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries. *Bull WHO* 1998; **76:** 25–32.
19. Sampaio RNR, Marsden PD. Mucosal leishmaniasis unresponsive to glucantime therapy successfully treated with AmBisome. *Trans R Soc Trop Med Hyg* 1997; **91:** 77.
20. Amato VS, *et al.* Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). *J Antimicrob Chemother* 2000; **46:** 341–2.

Primary amoebic meningoencephalitis. Amphotericin B is active *in vitro* against *Naegleria fowleri* and has been recommended for the treatment of primary amoebic meningoencephalitis (see Naegleria Infections, p.822) caused by this amoeba. There have been some case reports[1-7] of survival after the use of intravenous and intrathecal amphotericin B. In all cases amphotericin B was combined with other antimicrobials, notably oral rifampicin.

1. Anderson K, Jamieson A. Primary amoebic meningoencephalitis. *Lancet* 1972; **i:** 902–3.
2. Seidel JS, *et al.* Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982; **306:** 346–8.
3. Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991; **151:** 1201–2.
4. Poungvarin N, Jariya P. The fifth nonlethal case of primary amoebic meningoencephalitis. *J Med Assoc Thai* 1991; **74:** 112–15.
5. Loschiavo F, *et al.* Acute primary meningoencephalitis from entamoeba Naegleria fowleri: report of a clinical case with a favourable outcome. *Acta Neurol (Napoli)* 1993; **15:** 333–40.
6. Wang A, *et al.* Successful treatment of amoebic meningoencephalitis in a Chinese living in Hong Kong. *Clin Neurol Neurosurg* 1993; **95:** 249–52.
7. Jain R, *et al.* Naegleria meningitis: a rare survival. *Neurol India* 2002; **50:** 470–2.

Preparations

BP 2008: Amphotericin Lozenges; Amphotericin Oral Suspension;
USP 31: Amphotericin B Cream; Amphotericin B for Injection; Amphotericin B Lotion; Amphotericin B Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Abelcet; AmBisome; Amfostat†; Amphotec; Anfogen; ***Austral.:*** Abelcet; AmBisome; Amphocil; Fungilin; Fungizone; ***Austria:*** Abelcet; AmBisome; Ampho-Moronal; Amphocil; ***Belg.:*** Abelcet; AmBisome; Fungizone; ***Braz.:*** Abelcet; AmBisome†; Amphocil; Anforicin B; Fungi B; Fungizon; ***Canad.:*** Abelcet; AmBisome; Amphotec†; Fungizone; ***Chile:*** Fungizon; ***Cz.:*** Abelcet; Amphocil; ***Denm.:*** Abelcet; AmBisome; Fungilin†; Fungizone; ***Fin.:*** Abelcet; AmBisome; Fungizone; ***Fr.:*** Abelcet; AmBisome; Fungizone; ***Ger.:*** Abelcet; AmBisome; Ampho-Moronal; ***Gr.:*** Abelcet; AmBisome; Amphiprol; Amphocil; Fungizone; ***Hong Kong:*** Abelcet; AmBisome; Amphocil†; Fungizone; ***Hung.:*** Abelcet; AmBisome; Amphocil; Fungizone; ***India:*** Fungizone; ***Indon.:*** Fungizone; ***Irl.:*** Abelcet; AmBisome; Amphocil; Fungizone; ***Israel:*** AmBisome; Amphocil; Fungilin†; Fungizone†; ***Ital.:*** Abelcet; AmBisome; Fungilin; Fungizone; ***Jpn:*** AmBisome; ***Malaysia:*** Abelcet†; Amphocil; Fungizone; ***Mex.:*** Amfostat; Amphocil; Candipres; ***Neth.:*** Abelcet; AmBisome; Amphocil; Fungizone; ***Norw.:*** Abelcet; AmBisome; Fungizone; ***NZ:*** Abelcet; AmBisome; Fungilin; Fungizone; ***Philipp.:*** Fungizone; ***Pol.:*** AmBisome; Amphocil; ***Port.:*** Abelcet; AmBisome; Amphocil; Fungizone; ***Rus.:*** AmBisome (АмБизом); Amphoglucamin (Амфоглюкамин); ***S.Afr.:*** AmBisome; Fungizone; ***Singapore:*** Abelcet; AmBisome; Amphocil†; Fungizone; ***Spain:*** Abelcet; AmBisome; Amphocil; Funganiline†; Fungizona; ***Swed.:*** Abelcet†; AmBisome; Fungizone; ***Switz.:*** Abelcet†; AmBisome; Ampho-Moronal; Fungizone; ***Thai.:*** AmBisome†; Amphocil; Fungizone; ***Turk.:*** Abelcet; AmBisome; Fungizone; ***UK:*** Abelcet; AmBisome; Amphocil; Fungilin; Fungizone; ***USA:*** Abelcet; AmBisome; Amphotec; Fungizone†; ***Venez.:*** Amphotec; Fungizone.

Multi-ingredient: ***Austria:*** Mysteclin; ***Braz.:*** Anfoterin†; Gino-Teracin; Novasutin; Talsutin; Tericin AT; Tricocilin B; Vagiklin; ***Chile:*** Talseclin†; ***Fr.:*** Amphocycline; ***Ger.:*** Mysteclin; ***Hong Kong:*** Talsutin; ***Indon.:*** Talsutin; ***Ital.:*** Anfocort; ***Malaysia:*** Talsutin†; ***Philipp.:*** Vagimycin; ***S.Afr.:*** Vagmycin; ***Spain:*** Gine Heyden†; Sanicel; Trigon Topico; ***Venez.:*** Talsutin†.

Anidulafungin *(USAN, rINN)*

Anidulafungina; Anidulafungine; Anidulafunginum; LY-303366; V-Echinocandin. (4*R*,5*R*)-4,5-Dihydroxy-*N*[2]-{[4″-(pentyloxy)-*p*-terphenyl-4-yl]carbonyl}-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide; 1-((4*R*,5*R*)-4,5-Dihydroxy-*N*[2]-{[4″-(pentyloxy)(1,1′:4′,1″-terphenyl)-4-yl]carbonyl}-L-ornithine)-echinocandin B.

Анидулафунгин

$C_{58}H_{73}N_7O_{17}$ = 1140.2.
CAS — 166663-25-8.
ATC — J02AX06.
ATC Vet — QJ02AX06.

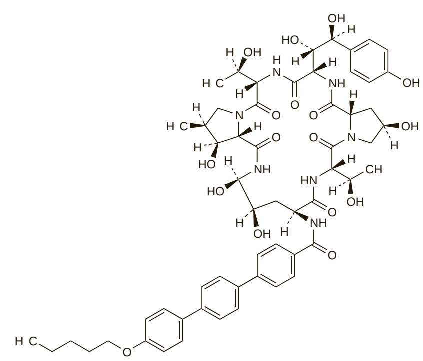

Adverse Effects and Precautions

As for Caspofungin, see p.528.

Dose adjustments are not required in patients with hepatic or renal impairment.

Interactions

Few drug interactions are expected with anidulafungin, as it is not metabolised by the hepatic cytochrome P450 system and almost no renal clearance occurs.

Antimicrobial Action

As for Caspofungin, see p.528.

Pharmacokinetics

Steady state plasma concentrations of anidulafungin are achieved after the first loading dose; systemic clearance is about 1 litre/hour and the terminal elimination half-life is 40 to 50 hours. Anidulafungin is 84% bound to plasma proteins and the volume of distribution is 30 to 50 litres. It is not metabolised, but undergoes slow chemical degradation to inactive peptide degradants. Less than 10% of the intact drug is eliminated in the faeces and less than 1% is excreted in the urine.

◊ References.

1. Dowell JA, *et al.* Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; **44:** 590–8.
2. Benjamin DK, *et al.* Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; **50:** 632–8.

Uses and Administration

Anidulafungin is an echinocandin antifungal active against *Aspergillus* and *Candida* spp. It is used in the treatment of candidaemia, oesophageal candidiasis, and other forms of invasive candidiasis.

Anidulafungin is given by intravenous infusion, the rate of which should not exceed 1.1 mg/minute. For candidaemia and other invasive candidiasis a loading dose of 200 mg is given on the first day followed by 100 mg daily thereafter. For oesophageal candidiasis the loading dose is 100 mg followed by 50 mg daily.

◊ Reviews.

1. Murdoch D, Plosker GL. Anidulafungin. *Drugs* 2004; **64:** 2249–58.
2. Vazquez JA, Sobel JD. Anidulafungin: a novel echinocandin. *Clin Infect Dis* 2006; **43:** 215–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ecalta; ***Port.:*** Ecalta; ***UK:*** Ecalta; ***USA:*** Eraxis.

Bifonazole *(BAN, USAN, rINN)*

Bay-h-4502; Bifonatsoli; Bifonazol; Bifonazolas; Bifonazolum. 1-(α-Biphenyl-4-ylbenzyl)imidazole.

Бифоназол

$C_{22}H_{18}N_2$ = 310.4.
CAS — 60628-96-8.
ATC — D01AC10.
ATC Vet — QD01AC10.

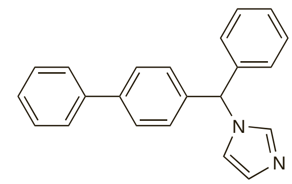

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Bifonazole). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

Profile

Bifonazole is an imidazole antifungal with a broad spectrum of activity; sensitive fungi include dermatophytes, *Malassezia furfur*, and *Candida* spp. It also has some antibacterial activity.

Bifonazole is mainly used by topical application in the treatment of fungal skin and nail infections (p.521). It is applied once daily as a 1% cream, powder, solution, or gel. Treatment is usually continued for 2 to 4 weeks. More prolonged treatment is necessary for nail infections and bifonazole may be applied initially with a 40% urea paste to soften the nail.

Local reactions including burning and itching have been reported.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

◊ Reviews.

1. Lackner TE, Clissold SP. Bifonazole: a review of its antimicrobial activity and therapeutic use in superficial mycoses. *Drugs* 1989; **38:** 204–25.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Bifonal†; Bimicot; Micosol; Mycospor†; Sinamida Plus; ***Austral.:*** Canesten Once Daily; Mycospor; ***Austria:*** Canesten Bifonazol; Fungiderm†; ***Belg.:*** Canestene Derm Bifonazole; Mycospor†; ***Braz.:*** Mycospor; ***Chile:*** Biocitronil†; Micotopic†; Multifung; Mycosporan; ***Cz.:*** Mycospor; ***Fr.:*** Amycor; ***Ger.:*** Bifomyk; Bifon; Canesten Extra; Mycospor; ***Gr.:*** Aeroderma†; Bifized; Bifon; Compaser†; Fungiderm; Gloryskin; Helpovion†; Kavaderm; Myco-flusemidon; Mycospor; Rye; ***Hong Kong:*** Mycospor; ***Hung.:*** Mycospor; ***Indon.:*** Mycospor; ***Israel:*** Agispor; ***Ital.:*** Azolmen; Bifazol; ***Mex.:*** Mycospor; ***Neth.:*** Mycospor; ***Pol.:*** Mycospor; ***Port.:*** Mycospor; Topical; ***Rus.:*** Bifosin (Бифосин); Mycospor (Микоспор); ***S.Afr.:*** Mycospor; ***Spain:*** Bifokey; Levelina; Moldina†; Mycospor; ***Swed.:*** Mycosporan; ***Turk.:*** Mycospor; ***UK:*** Canesten AF Once Daily†; ***Venez.:*** Mycospor.

Multi-ingredient: ***Arg.:*** Empecid Pie; Micatex†; Piecidex NF; Prurisedan Antimicotico†; ***Austria:*** Canesten Bifonazol comp; Fungiderm comp†; ***Chile:*** Mycosporan Onycoset†; ***Cz.:*** Mycospor Sada na Nehty; ***Fr.:*** Amycor Onychoset; ***Ger.:*** Canesten Extra Nagelset; Mycospor Nagelset†; ***Israel:*** Agispor Onychoset; Comagis; Keratospor; ***Mex.:*** Mycospor Onicoset; ***Pol.:*** Mycospor Onychoset; ***Port.:*** Mycospor†; ***Rus.:*** Mycospor (Микоспор); ***S.Afr.:*** Mycospor Onycho-set; ***Spain:*** Mycospor Onicoset; ***Turk.:*** Mycospor; ***Venez.:*** Mycospor Onicoset.

Bromochlorosalicylanilide

Bromchlorsalicylanilidum; Bromisalisyylikloorianilidi; Bromoclorosalicilanilida; Bromsalicylkloranilid. 5-Bromo-4′-chlorosalicylanilide; 5-Bromo-*N*-(4-chlorophenyl)-2-hydroxybenzamide.

Бромохлоросалициланилин

$C_{13}H_9BrClNO_2$ = 326.6.
CAS — 3679-64-9.
ATC — D01AE01.
ATC Vet — QD01AE01.

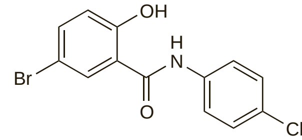

Profile

Bromochlorosalicylanilide is a bromsalan antifungal that has been applied topically. Photosensitivity may occur. See also Bromsalans, p.1632.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***India:*** Multifungin H†; Multifungin†.

Butenafine Hydrochloride *(BANM, USAN, rINNM)*

Butenafiinihydrokloridi; Buténafine, Chlorhydrate de; Butenafinhydroklorid; Butenafini Hydrochloridum; Hidrocloruro de butenafina; KP-363. *N*-(*p*-*tert*-Butylbenzyl)-*N*-methyl-1-naphthalenemethylamine hydrochloride; 4-*tert*-Butylbenzyl(methyl)(1-naphthalenemethyl)amine hydrochloride.

Бутенафина Гидрохлорид

$C_{23}H_{27}N,HCl = 353.9.$
CAS — 101828-21-1 (butenafine); 101827-46-7 (butenafine hydrochloride).
ATC — D01AE23.
ATC Vet — QD01AE23.

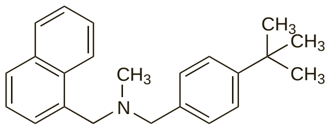

(butenafine)

Profile

Butenafine is a benzylamine antifungal with actions similar to those of the allylamine antifungal terbinafine (p.546). The hydrochloride is used topically as a 1% cream for the treatment of superficial dermatophyte infections (see Skin Infections, p.521).

◊ Reviews.

1. McNeely W, Spencer CM. Butenafine. *Drugs* 1998; **55:** 405–12.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Buticrem†; Ingebut; ***Austria:*** Zaxem; ***Canad.:*** Scholl Athlete's Foot†; ***Chile:*** Dermacom; ***India:*** Butop†; Fintop; ***Israel:*** Mentax; ***Jpn:*** Mentax; ***Philipp.:*** Funcid; ***USA:*** Lotrimin Ultra; Mentax.

Butoconazole Nitrate *(BANM, USAN, rINNM)*

Butoconazole, Nitrate de; Butoconazoli Nitras; Nitrato de butoconazol; RS-35887; RS-35887-00-10-3. 1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)butyl]imidazole mononitrate.

Бутоконазола Нитрат

$C_{19}H_{17}Cl_3N_2S,HNO_3 = 474.8.$
CAS — 64872-76-0 (butoconazole); 64872-77-1 (butoconazole nitrate).
ATC — G01AF15.
ATC Vet — QG01AF15.

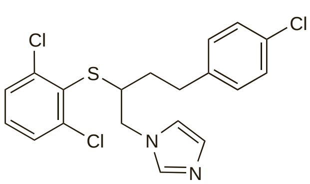

(butoconazole)

Pharmacopoeias. In *US.*

USP 31 (Butoconazole Nitrate). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in acetone, in acetonitrile, in dichloromethane, and in tetrahydrofuran; very slightly soluble in ethyl acetate; sparingly soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Local reactions including burning and irritation and pelvic or abdominal pain or cramping may occur when butoconazole is applied vaginally.

Intravaginal preparations of butoconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Effects on the blood. Severe reversible thrombocytopenia was associated with treatment with intravaginal butoconazole.[1] The patient had previously had a drop in white cell count after treatment with intravaginal clotrimazole, suggestive of an idiosyncratic reaction to imidazoles.

1. Maloley PA, *et al.* Severe reversible thrombocytopenia resulting from butoconazole cream. *DICP Ann Pharmacother* 1990; **24:** 143–4.

Antimicrobial Action

Butoconazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p.539) including activity against *Candida* spp.

Pharmacokinetics

About 5% of a dose of butoconazole is absorbed after vaginal use. The plasma half-life is 21 to 24 hours.

Uses and Administration

Butoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p.518). It is given intravaginally as a 100-mg pessary or as 5 g of a 2% cream for 3 consecutive nights; a single application of the cream has also been used.

Preparations

USP 31: Butoconazole Nitrate Vaginal Cream.

Proprietary Preparations (details are given in Part 3)
Austral.: Gynazole; ***Belg.:*** Gynomyk; ***Braz.:*** Gynazole; ***Canad.:*** Gynazole; ***Fr.:*** Gynomyk; ***Hung.:*** Gynazol; ***Malaysia:*** Gynofort; ***Mex.:*** Gynafem; ***Neth.:*** Gynomyk; ***Pol.:*** Gynazol; ***Rus.:*** Gynofort (Гинофорт); ***Singapore:*** Gynofort; ***USA:*** Gynazole; Mycelex-3.

Candicidin *(BAN, USAN, rINN)*

Candicidina; Candicidine; Candicidinum; Kandicidin; Kandisidiini; NSC-94219.

Кандицидин

CAS — 1403-17-4.
ATC — G01AA04.
ATC Vet — QG01AA04.

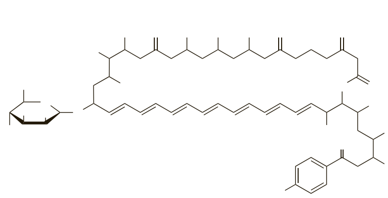

(candicidin D)

Profile

Candicidin is a mixture of antifungal heptaenes produced by *Streptomyces griseus*. It has been used in the treatment of vaginal candidiasis.

Caspofungin Acetate *(BANM, USAN, rINNM)*

Acetato de caspofungina; Caspofungine, Acétate de; Caspofungini Acetas; Kaspofungiiniasetaatti; Kaspofunginacetat; L-743873; MK-0991. (4*R*,5*S*)-5-[(2-Aminoethyl)amino]-*N*²-(10,12-dimethyltetradecanoyl)-4-hydroxy-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-L-threonyl-*threo*-3-hydroxy-L-ornithyl-*trans*-3-hydroxy-L-proline cyclic (6→1)-peptide diacetate.

Каспофунгина Ацетат

$C_{52}H_{88}N_{10}O_{15},2C_2H_4O_2 = 1213.4.$
CAS — 179463-17-3.
ATC — J02AX04.
ATC Vet — QJ02AX04.

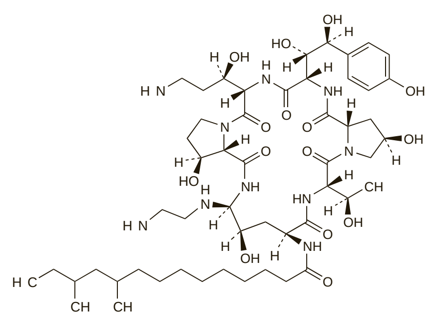

(caspofungin)

Adverse Effects and Precautions

Adverse experiences reported with caspofungin have included anaemia, diarrhoea, nausea and vomiting, flushing, headache, fever, tachycardia, and venous complications around the infusion site. Possible histamine-mediated symptoms have been rash, facial swelling, pruritus, sensation of warmth, or bronchospasm. Anaphylaxis has occurred.

Isolated cases of hepatotoxicity have occurred and patients who develop abnormal liver function tests should be monitored for deterioration in hepatic function. Caspofungin may need to be given in reduced doses to patients with hepatic impairment (see below).

Breast feeding. Caspofungin is excreted in the breast milk of lactating *animals*, but the risk to breast-fed infants is suggested to be low. Recommendations in licensed product information vary: in the UK it recommends against use in women who are breast feeding, while in the USA caution is advised.

Pregnancy. Caspofungin has been shown to cross the placenta in *animal* studies and was shown to be embryotoxic in *rats* and *rabbits*; it was noted that there were no adequate and well-controlled studies in human pregnancy. Caspofungin is generally only recommended in pregnancy if the benefits to the mother are considered to outweigh the risks to the fetus.

Interactions

Although caspofungin is not metabolised by the hepatic cytochrome P450 system, drugs that induce hepatic enzymes may increase its clearance. Such effects have been noted with carbamazepine, dexamethasone, efavirenz, nevirapine, phenytoin, and rifampicin, and an increase in the dose of caspofungin should be considered in patients who are also taking these drugs and who are not clinically responding (see Uses and Administration, below).

When caspofungin has been given with ciclosporin, an increase in the area under the concentration-time curve for caspofungin, as well as increases in hepatic enzymes, were observed and use of the two drugs together is not recommended.

Caspofungin has resulted in decreased blood concentrations of tacrolimus and therapeutic drug monitoring and appropriate dosage adjustments to tacrolimus are recommended.

Antimicrobial Action

Caspofungin inhibits the synthesis of β-1,3-D-glucan, an essential component of the cell wall of many fungi. Caspofungin exhibits *in-vitro* activity against many *Aspergillus* spp. and is fungicidal against *Candida* spp. including non-albicans strains.

Pharmacokinetics

Plasma concentrations of caspofungin decline in a polyphasic manner after intravenous infusion. The initial short α-phase occurs immediately post-infusion and is followed by a β-phase with a half-life of 9 to 11 hours; an additional longer γ-phase also occurs with a half-life of 40 to 50 hours. Plasma clearance is dependent on distribution rather than on biotransformation or excretion. Caspofungin is highly bound to plasma protein. There is slow metabolism of caspofungin by hydrolysis and *N*-acetylation and excretion in faeces and urine.

Uses and Administration

Caspofungin is an echinocandin antifungal used in the treatment of invasive aspergillosis (p.517) in patients who are refractory to, or intolerant of, other therapy. It is also used in the treatment of invasive candidiasis and as empirical therapy for presumed fungal infections in febrile, neutropenic patients.

Caspofungin is used as the acetate but doses are expressed in terms of the base; caspofungin acetate 77.7 mg is equivalent to about 70 mg of caspofungin. It is given by slow intravenous infusion over about 1 hour. A loading dose of 70 mg is given on the first day and is followed by 50 mg daily; in adult patients weighing more than 80 kg, and in patients taking hepatic-enzyme inducing drugs who fail to respond, a daily dose of 70 mg is recommended. Doses may need to be reduced in patients with hepatic impairment (see below).

◊ Reviews.

1. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *J Antimicrob Chemother* 2003; **51:** 513–21.
2. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis* 2003; **36:** 1445–57.
3. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **362:** 1142–51.
4. McCormack PL, Perry CM. Caspofungin: a review of its use in the treatment of fungal infections. *Drugs* 2005; **65:** 2049–68.
5. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. *Am J Health-Syst Pharm* 2006; **63:** 1693–1703.
6. Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 2. *Am J Health-Syst Pharm* 2006; **63:** 1813–20.
7. Falagas ME, *et al.* Caspofungin for the treatment of fungal infections: a systematic review of randomized controlled trials. *Int J Antimicrob Agents* 2007; **29:** 136–43.
8. Hope WW, *et al.* The pharmacology and clinical use of caspofungin. *Expert Opin Drug Metab Toxicol* 2007; **3:** 263–74.
9. Waters L, Nelson M. The use of caspofungin in HIV-infected individuals. *Expert Opin Invest Drugs* 2007; **16:** 899–908.

Administration in children. Caspofungin is not licensed for use in paediatric patients, but has been prescribed.[1] A retrospective study[2] of 25 immunocompromised children with a median age of 9.8 years, given at least one dose of caspofungin, found that it appeared to be safe and well tolerated. Patients weighing less than 50 kg had a dose of 0.8 to 1.6 mg/kg daily, while those over 50 kg were given 50 to 75 mg daily. Another retrospective review[3] of 64 immunocompromised children with a median age of 11.5 years, reported a success rate of 67.7% with caspofungin at a median daily maintenance dose of 1.07 mg/kg, either as monotherapy or with another antifungal. A case series[4] of 10 neonates (9 preterm) with invasive candidiasis not responsive to amphotericin B and/or fluconazole reported that *Candida* spp. were cleared from the blood in all patients in a mean of 4.3 days after starting caspofungin therapy. Nine neonates were given an initial dose of 1 mg/kg daily for the first 2 days followed by 2 mg/kg daily for 15 to 21 days; the other was given a lower dose.

1. Lehrnbecher T, Groll AH. Experiences with the use of caspofungin in paediatric patients. *Mycoses* 2008; **51** (suppl 1): 58–64.
2. Franklin JA, *et al.* Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J* 2003; **22:** 747–9.
3. Groll AH, *et al.* Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother* 2006; **57:** 527–35.
4. Odio CM, *et al.* Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004; **23:** 1093–7.

Administration in hepatic impairment. Patients with mild hepatic impairment do not require dosage adjustment. In patients with moderate hepatic impairment, a daily dose of caspofungin 35 mg should be used after the initial dose of 70 mg; appropriate doses for patients with severe hepatic impairment have not been established.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cancidas; ***Austral.:*** Cancidas; ***Belg.:*** Cancidas; ***Braz.:*** Cancidas; ***Canad.:*** Cancidas; ***Chile:*** Cancidas; ***Cz.:*** Cancidas; ***Denm.:*** Cancidas; ***Fin.:*** Cancidas; ***Fr.:*** Cancidas; ***Ger.:*** Cancidas; ***Gr.:*** Cancidas; ***Hong Kong:*** Cancidas; ***Hung.:*** Cancidas; ***Irl.:*** Cancidas; ***Israel:*** Cancidas; ***Ital.:*** Cancidas; ***Malaysia:*** Cancidas; ***Neth.:*** Cancidas; ***Norw.:*** Cancidas; ***NZ:*** Cancidas; ***Philipp.:*** Cancidas; ***Pol.:*** Cancidas; ***Port.:*** Cancidas; ***Rus.:*** Cancidas (Кансидас); ***Singapore:*** Cancidas; ***Spain:*** Cancidas; ***Swed.:*** Cancidas; ***Switz.:*** Cancidas; ***Thai.:*** Cancidas; ***Turk.:*** Cancidas; ***UK:*** Cancidas; ***USA:*** Cancidas; ***Venez.:*** Cancidas.

Chlormidazole Hydrochloride *(BANM, rINNM)*

Chlormidazole, Chlorhydrate de; Chlormidazoli Hydrochloridum; Clomidazole Hydrochloride; Hidrocloruro de clormidazol. 1-(4-Chlorobenzyl)-2-methylbenzimidazole hydrochloride.

Хлормидазола Гидрохлорид

$C_{15}H_{13}ClN_2,HCl = 293.2.$

CAS — 3689-76-7 (chlormidazole); 54118-67-1 (chlormidazole hydrochloride).

ATC — D01AC04.

ATC Vet — QD01AC04.

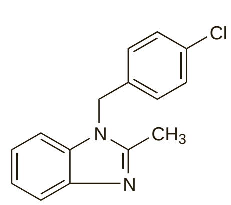

(chlormidazole)

Profile

Chlormidazole hydrochloride is an imidazole antifungal used topically as the hydrochloride in the treatment of fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Unifungicid.

Multi-ingredient: ***Austria:*** Myco-Synalar; ***Pol.:*** Polfungicid; ***Switz.:*** Myco-Synalar†.

Chlorphenesin *(BAN, pINN)*

Chlorphénésine; Chlorphenesinum; Clorfenesina; Kloorifenesiini; Klorfenesin. 3-(4-Chlorophenoxy)propane-1,2-diol.

Хлорфенезин

$C_9H_{11}ClO_3 = 202.6.$

CAS — 104-29-0.

ATC — D01AE07.

ATC Vet — QD01AE07.

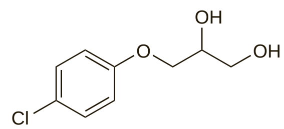

Profile

Chlorphenesin has antifungal and antibacterial properties. It has been applied locally in mild uncomplicated dermatophyte and other cutaneous infections and in vaginal infections.

Chlorphenesin carbamate (p.1894) is used as a skeletal muscle relaxant.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Mycil†; ***Ger.:*** Soorphenesin†; ***India:*** Dermicil†.

Multi-ingredient: ***Austral.:*** ZSC; ***Austria:*** Aleot; ***Braz.:*** Oto Betnovate.

Ciclopirox *(BAN, USAN, rINN)*

Ciclopiroxum; Ciklopiroksas; Ciklopirox; Hoe-296b; Siklopiroksi. 6-Cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

Циклопирокс

$C_{12}H_{17}NO_2 = 207.3.$

CAS — 29342-05-0.

ATC — D01AE14; G01AX12.

ATC Vet — QD01AE14; QG01AX12.

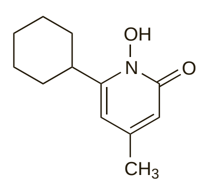

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ciclopirox). A white or yellowish-white, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Ciclopirox). A white to slightly yellowish white, crystalline powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane; soluble in ether. Store at a temperature of 15° to 30°. Protect from light.

Ciclopirox Olamine *(BANM, USAN, rINNM)*

Ciclopirox olamina; Ciclopirox olaminum; Ciclopiroxi Olaminum; Ciclopiroxolamine; Ciclopiroxum Olaminum; Ciklopiroksas olaminas; Ciklopirox olamin; Ciklopiroxolamin; Ciklopiroxolamin; Hoe-296; Siklopiroksiolamiini; Sikloproks Olamin. The 2-aminoethanol salt of 6-Cyclohexyl-1-hydroxy-4-methyl-2-pyridone.

Циклопирокс Оламин

$C_{12}H_{17}NO_2,C_2H_7NO = 268.4.$

CAS — 41621-49-2.

ATC — D01AE14; G01AX12.

ATC Vet — QD01AE14; QG01AX12.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Ciclopirox Olamine). A white or pale yellow crystalline powder. It exhibits polymorphism. Slightly soluble in water; very soluble in alcohol and in dichloromethane; slightly soluble in ethyl acetate; practically insoluble in cyclohexane. A 1% solution in water has a pH of 8.0 to 9.0. Protect from light.

USP 31 (Ciclopirox Olamine). A white to slightly yellowish-white, crystalline powder. Slightly soluble in water; very soluble in alcohol and in dichloromethane; practically insoluble in cyclohexane. pH of a 1% solution in water is between 8.0 and 9.0. Store in airtight containers at a temperature of 5° to 25°. Protect from light.

Adverse Effects

Irritation and pruritus have been reported after topical application of ciclopirox.

Antimicrobial Action

Ciclopirox has a wide spectrum of antifungal activity. It inhibits most *Candida*, *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. and is also active against *Malassezia furfur.* It has some antibacterial activity.

Uses and Administration

Ciclopirox is an antifungal that is applied topically in the treatment of fungal skin and nail infections, including cutaneous candidiasis (p.518), dermatophytosis, pityriasis versicolor (see Skin Infections, p.521), and seborrhoeic dermatitis (p.1584). It has also been used in the treatment of vaginal candidiasis.

It is applied twice daily for skin infections, as a cream, gel, suspension, solution, or powder; both the base and the olamine salt have been used, with products containing the equivalent of 0.77% ciclopirox base.

A lacquer containing 8% ciclopirox base is applied once daily for nail infections.

A shampoo containing 1% ciclopirox base is used twice weekly for the treatment of seborrhoeic dermatitis.

◊ References.

1. Gupta AK, Skinner AR. Ciclopirox for the treatment of superficial fungal infections: a review. *Int J Dermatol* 2003; **42** (suppl 1): 3–9.
2. Gupta AK, Nicol KA. Ciclopirox 1% shampoo for the treatment of seborrheic dermatitis. *Int J Dermatol* 2006; **45:** 66–9.

Preparations

USP 31: Ciclopirox Olamine Cream; Ciclopirox Olamine Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Dermaflor†; Loprox; Micopirox; Stieprox; ***Austral.:*** Stieprox; ***Austria:*** Batrafen; Stieprox; ***Braz.:*** Fungirox†; Gino Loprox; Loprox; Micolamina; Micoliv†; Stiprox; ***Canad.:*** Loprox; Penlac; Stieprox; ***Chile:*** Batrafen; Fungopirox; Mikium†; Stiprox; ***Cz.:*** Batrafen; Dafnegin; Stieprox; ***Denm.:*** Mycofen; Stieprox; ***Fin.:*** Stieprox; ***Fr.:*** Mycosquam; Mycoster; Sebiprox; Stiprox; ***Ger.:*** Batrafen; Ciclopoli; Inimur Myko; Nagel Batrafen; Sebiprox; ***Gr.:*** Candimyc; Dafnegin†; Myclopir; Mycomycen; Neo-botacreme; Neo-mycodermol; Rozolam; Stieprox; ***Hong Kong:*** Batrafen; Stieprox; ***Hung.:*** Batrafen; ***India:*** Olamin; Onylac; ***Indon.:*** Batrafen; Loprox; ***Irl.:*** Batrafen†; Oilatum Scalp Treatment; Stieprox; ***Israel:*** Batrafen; Cicloderm; ***Ital.:*** Batrafen; Biroxol†; Brumixol; Dafnegin; Miclast; Micomicen; Micoxolamina; Sebiprox; Stiprox; ***Malaysia:*** Stieprox; ***Mex.:*** Loprox; Stiprox; ***Neth.:*** Loprox; Sebiprox; ***Norw.:*** Stieprox; ***NZ:*** Batrafen; Stieprox; ***Philipp.:*** Stieprox; ***Pol.:*** Batrafen; Dafnegin; Hascofungin; Pirolam; Stieprox; ***Port.:*** Batrafen; Mycoster; Sebiprox; ***Rus.:*** Batrafen (Батрафен); ***Singapore:*** Stieprox; ***Spain:*** Batrafen; Ciclochem; Fungowas; Rimafungol†; Sebiprox; ***Switz.:*** Batrafen; Dafnegil Neo; ***Thai.:*** Cicloderm†; Loprox; Stieprox; ***Turk.:*** Canolen; Nibulen; ***UK:*** Oilatum Scalp Treatment; ***USA:*** Loprox; Penlac; ***Venez.:*** Batrafen.

Multi-ingredient: ***Arg.:*** Derm's Shampoo; Stieproxal; ***Fr.:*** Novophane; Novophane S; Stiproxal; ***India:*** Flucort-C; ***Israel:*** Cicloderm-C; ***UK:*** Oilatum Scalp Intensive.

Climbazole *(BAN, rINN)*

Bay-e-6975; Climbazol; Climbazolum; MEB-6401. 1-(*p*-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone.

Климбазол

$C_{15}H_{17}ClN_2O_2 = 292.8.$

CAS — 38083-17-9.

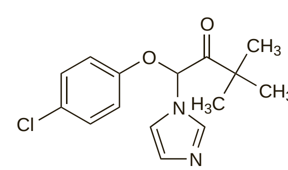

Profile

Climbazole is an azole antifungal included in preparations for the topical treatment of seborrhoeic dermatitis.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Mencogrin; Micocert; Micodual; ***Chile:*** Eucerin Shampoo Anticaspa; Node DS; Shampoo Anticaspa; ***Fr.:*** Item Alphazole; Node DS; Node P; Sebosquam; Squaphane; Squaphane E; Squaphane Masque-Creme; Squaphane P; Squaphane S; ***Ital.:*** Derman-Shampoo AF†; Pitiren; ***Port.:*** Alphazole†; Efluvium Anti-caspa; ***Venez.:*** Node DS; Sensibio DS.

Clotrimazole *(BAN, USAN, rINN)*

Bay-5097; Clotrimazol; Clotrimazolum; FB-5097; Klotrimatsoli; Klotrimazol; Klotrimazolas; Klotrymazol. 1-(α-2-Chlorotrityl)imidazole.

Клотримазол

$C_{22}H_{17}ClN_2$ = 344.8.

CAS — 23593-75-1.

ATC — A01AB18; D01AC01; G01AF02.

ATC Vet — QA01AB18; QD01AC01; QG01AF02; QJ02AB90.

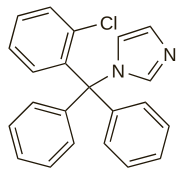

NOTE. Compounded preparations of clotrimazole may be represented by the following names:

- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Clotrimazole). A white or pale yellow crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Clotrimazole). A white to pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, in chloroform, and in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

Nausea, vomiting, unpleasant mouth sensations, and pruritus have been reported after the use of oral clotrimazole lozenges. Raised liver enzyme values have also occurred. Local reactions including irritation and a burning sensation may occur in patients treated topically; contact allergic dermatitis has been reported.

Intravaginal preparations of clotrimazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Gastrointestinal disturbance, elevation of liver enzymes, dysuria, and mental depression have been reported after oral clotrimazole (although this route is no longer used). For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Antimicrobial Action

Clotrimazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p.539).

Pharmacokinetics

When applied topically clotrimazole penetrates the epidermis but there is little if any systemic absorption. Absorption of 3 to 10% of a dose has been reported after vaginal use. Clotrimazole is metabolised in the liver to inactive compounds and excreted in the faeces and urine.

Uses and Administration

Clotrimazole is an imidazole antifungal used topically in superficial candidiasis (p.518), and in the skin infections pityriasis versicolor and dermatophytosis (see Skin Infections, p.521). Clotrimazole may also be used occasionally for symptomatic relief of the protozoal infection trichomoniasis when other drugs are contra-indicated (see p.827).

Clotrimazole is applied topically two or three times daily for 2 to 4 weeks as a 1% cream, lotion, spray, or solution in the treatment of fungal skin infections; a 1% powder may be used with the cream or solution and has been applied to prevent re-infection. The 1% solution is also used topically for fungal otitis externa. Clotrimazole is given as pessaries in dosage regimens of 100 mg for 6 days, 200 mg for 3 days, or a single dose of 500 mg in the treatment of vulvovaginal candidiasis; similar doses are given as a 1, 2, or 10% vaginal cream. It may be necessary to treat balanitis in male partners concurrently.

For the treatment of oropharyngeal candidiasis one 10-mg lozenge of clotrimazole is dissolved in the mouth five times daily for 14 days. For the prophylaxis of oropharyngeal candidiasis in patients receiving immunosuppressant therapy the dose is one 10-mg lozenge three times daily for the duration of the immunosuppressant treatment. Clotrimazole has also been given orally but has now been largely superseded by other azole drugs.

Sickle-cell disease. Oral clotrimazole has been investigated for the treatment of sickle-cell disease (p.1044).[1]

1. Brugnara C, *et al.* Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J Clin Invest* 1996; **97:** 1227–34.

Preparations

BP 2008: Clotrimazole Cream; Clotrimazole Pessaries;
USP 31: Clotrimazole and Betamethasone Dipropionate Cream; Clotrimazole Cream; Clotrimazole Lotion; Clotrimazole Lozenges; Clotrimazole Topical Solution; Clotrimazole Vaginal Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aflorix; Clotri-Q; Clotrix; Empecid; Eximius; Ikolan†; Klomazole; Livomonil; Medifungol; Micoclin; Micomax; Micomazol; Micomazol Deo; Micosep; Micosep B; Micotrim; Mycanden; Panmicol; Sinfung; Trimazol; ***Austral.:*** Canesten; Chemists Own Clozole; Clofeme; Clonea; Clotreme†; Femizol; Gyne-Lotrimin†; Tinaderm Extra; Topizol; ***Austria:*** Candibene; Canesten; Myko Cordes; Pedikurol; ***Belg.:*** Canestene; Gyno-Canestene†; ***Braz.:*** Antimicotico Martel; Canesten; Clomazen; Clomazol; Clotigen; Clotren; Clotriderm; Clotrimix†; Clotrizan; Dermobene; Gino-Canesten; Gino-Clotrimix; Kinasten; Miclonazol; Micosten†; Micotrat; Micotrizol†; Neo Clotrimazyl; ***Canad.:*** Canesten; Clotrimaderm; ***Chile:*** Arnela; Axasol; Canesten; Cestop†; Clotrimin; Cotrisan; Creminem; Funzal; Gynocanesten; Konifungil; Laboterol†; Novacetol; Telugren; ***Cz.:*** Aknecolor; Baycuten; Candibene; Canesten; Canifug; Imazol; Jenamazol; Plimycol†; ***Denm.:*** Canesten; ***Fin.:*** Canesten; ***Ger.:*** Antifungol; Aru C†; Azutrimazol†; Benzoderm Myco†; Candazol†; Canesten; Canifug; Cloderm; Clotrigalen; cutistad†; durafungol; Fungiderm; Fungizid; Gilt; Gyno-Canesten†; Holfungin†; Jenamazol†; KadeFungin; Mycofug; Myko Cordes; Mykofungin; Mykohaug; Ovis Neu†; SD-Hermal; Uromykol; ***Gr.:*** Canesten; Factodin; ***Hong Kong:*** Aristen; Canesten; Clocreme; Clotri-Denk; Clozole; Cotren; Fungizid†; Gyne-Lotremin; Kamicin; Lotremin; Mycoril; Tricloderm; Warimazol†; ***Hung.:*** Candibene; Canesten; Canifug; ***India:*** Candid; Clocip; Clozol; Imidil; Mycocid; Mycoderm-C; Surfaz; ***Indon.:*** Bernesten; Canesten; Clonitia; Fungiderm; Gyne-Lotremin; Kranos; Lotremin; Medisten; Trimadan; ***Irl.:*** Canesten; ***Israel:*** Agisten; Baby Agisten; Clotrimaderm; Myco-Hermal; Oralten Troche; ***Ital.:*** Antimicotico; Canesten; Gyno-Canesten; ***Malaysia:*** Candazole; Candid; Canesten; Clomazole; Cotren†; Fungicip; Gyne-Lotremin; Gynostatum†; Loriderm†; Lotremin; Micoter†; Trimazol†; ***Mex.:*** Altenal; Baycuten; Candimon; Candiphen; Canesten; Cinabel†; Clocan; Clomacin; Dermasten; Euroderm; Liferzol; Lomecan V; Lonestin†; Lotrimin; Tenescan; ***Neth.:*** Canesten; Parvemaxol; ***Norw.:*** Canesten; ***NZ:*** Canesten; Clocreme; Clomazol; Clotrihexal; Clotrimaderm; ***Philipp.:*** Candid V6; Canesten; Cloxy; Gixaderm; Gynesol; Vaff; ***Pol.:*** Canesten; ***Port.:*** Candid†; Canesten; Diomicete; Gino-Canesten; Gino-Lotremine; Lotremine; Micolysin; Nalbix; Pan-Fungex; ***Rus.:*** Amyclon (Амиклон)†; Antifungol (Антифунгол); Candibene (Кандибене); Candid (Кандид); Candid V6 (Кандид В6); Canesten (Канестен); ***S.Afr.:*** A-Por; Canalba; Candaspor; Candizole; Canesten; Canex; Closcript; Covospor; Fungispor; Gyno-Trimaze†; Medaspor; Micomisan; Mycoban†; Mycohexal; Normospor; Stiemazol; Trimaze; Xeraspor; ***Singapore:*** Candazole; Canesten; Cotren; Cristan; Gyne-Lotremin†; Lotremin†; Myco-Hermal; Mycoril; Sastid Anti-Fungal; Vanesten†; ***Spain:*** Canesten; Fungidermo; Gine Canesten; ***Swed.:*** Canesten; ***Switz.:*** Acnecolor; Canestene; Corisol; Eurosan†; Fungotox; Gromazol; Gyno-Canestene; Imazol; Undex; ***Thai.:*** Caginal; Canadine†; Canazol; Candazole; Candid; Candinox; Canesten; Chingazol; Clotri†; Clotricin; Comat; Cotren; CST; Defungo; Dermaten; Fango Cream; Fungicon; Fungiderm; Gynebo; Kanezin; Klamacin; Manomazole; Mycoderm-C; Mycozole; Nestic; Taraten; Vamazole; Vanesten; Zema; ***Turk.:*** Canesten; Clozol; Fungosten; Gyno-Canesten; ***UK:*** Abtrim†; Candiden†; Canesten; Canesten Combi; Fungederm; Privacom†; ***USA:*** Gyne-Lotrimin; Lotrimin; Lotrimin AF; Mycelex; Mycelex-7; ***Venez.:*** Canesten; Clortilen; Clotrizol; Fugolin; Ginolotricomb; Gyno Canesten; Imazol; Ipalat; Lecibis†; Micozol; Oxisol†; Polik.

Multi-ingredient: ***Arg.:*** Becortin; Calmurid; Cortispec; Dermovit†; Empecid Cort; Hongal; Lotricomb; Micomazol B; Quadriderm; Quiacort G Plus; Vagarne†; Vagisan Compuesto; Vitacortil; ***Austral.:*** Canesoral Duo; Hydrozole; ***Austria:*** Myko Cordes; ***Belg.:*** Lotriderm; ***Braz.:*** Baycuten; ***Canad.:*** Lotriderm; ***Chile:*** B-Laboterol; Baycuten; Cestop B†; Clotrimin-B; Creminem-B; Cutanil; Donomix; Locrim; Lotriderm; Novadrel; Novarnela; Telugren Plus; Tribesona; ***Cz.:*** Imacort; Imazol Plus; Lotriderm†; ***Denm.:*** Clotrason; ***Fr.:*** Triazol†; ***Ger.:*** Antifungol; Baycuten HC; Baycuten†; Canesten HC†; Fungidexan; Imazol; Imazol comp; Lotricomb; Myko Cordes Plus; ***Hong Kong:*** Becogem; Canesten HC; Clobeta-G; Clotrinolon; Derzid-C; Lozopin; Synco-CFN; Triderm; ***India:*** Candibiotic; Candid B; Candid Ear Drops; Candid-TV; Candiderma +; Candiderma†; Cloben-G; Clocip B; Clocip NB; Clomycin; Cutinorm†; Fourderm AF; NC-Derm; Neocip FC; Otek-AC+; Sigmaderm; Sofradex-F; Surfaz; Surfaz-SN; Translipo-Triple; ***Indon.:*** Baycuten-N; Heltiskin; Lotriderm; ***Irl.:*** Canesten HC; Lotriderm; ***Israel:*** Agisten with Aloe Vera; Clotrisone; Hydroagisten; Polycutan; Tevacutan; Triderm; ***Ital.:*** Desamix Effe; Meclon; ***Malaysia:*** Baycuten N; Betamethasone Clo; Candacort; Triderm-C; ***Mex.:*** Barmicil Compuesto; Baycuten N; Beclogen; Betrigen; Clotricina; Gelmicin; Miclobet; Prubagen; Quadriderm NF; Triderm; Xyloderm; ***NZ:*** Lotricomb†; ***Philipp.:*** Baycuten; Candibec; Clotrasone; Triderm; ***Pol.:*** Lotriderm; Triderm; ***Port.:*** Baycuten; Beta-Micoter; Flotiran; Quadriderme; ***Rus.:*** Akriderm GK (Акридерм ГК); Candibiotic (Кандибиотик); Candid B (Кандид Б); Metrogyl Plus (Метрогил Плюс); Triderm (Тридерм); ***S.Afr.:*** Lotriderm; ***Singapore:*** Candacort; Canesten HC; Clotrasone†; Combiderm; Gentriderm; Gentrisone; Modaderm; Neoderm; Triderm; ***Spain:*** Beta Micoter; Clotrasone; ***Switz.:*** Imacort; Imazol; Triderm; ***Thai.:*** Bacda-B; Canasone†; Canazol-BE; Candacort; Clotrasone†; Derzid-C; Fango-B; Fungicon; Fungiderm-B; Gynesten-B; Gynestin; Myda-B; Myrazole-B; Twina; ***Turk.:*** Imazol; ***UK:*** Canesten HC; ***USA:*** Lotrisone; ***Venez.:*** Baycuten N; Lotricomb; Lotrisone; Triderm.

Cloxiquine *(rINN)*

5-Chloro-8-hydroxyquinoline; Cloxiquina; Cloxiquinum; Cloxyquin *(USAN)*. 5-Chloroquinolin-8-ol.

Клоксихин

C_9H_6ClNO = 179.6.

CAS — 130-16-5.

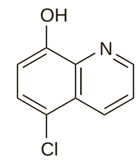

Profile

Cloxiquine has been included in preparations used topically for the treatment of fungal and bacterial skin infections. It is a component of halquinol, p.286.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Decoderm trivalent; ***Indon.:*** Decoderm 3; ***Thai.:*** Supracortin 3†.

Croconazole Hydrochloride *(rINNM)*

Cloconazole Hydrochloride; Croconazol, Chlorhydrate de; Croconazoli Hydrochloridum; Hidrocloruro de croconazol; 710674-S (croconazole). 1-(1-{*o*-[(*m*-Chlorobenzyl)oxy]phenyl}vinyl)imidazole hydrochloride.

Кроконазола Гидрохлорид

$C_{18}H_{15}ClN_2O,HCl$ = 347.2.

CAS — 77175-51-0 (croconazole).

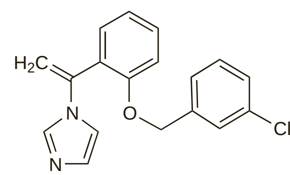

(croconazole)

Pharmacopoeias. In *Jpn.*

Profile

Croconazole is an imidazole antifungal used topically in the treatment of superficial cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. It is applied as a 1% cream or gel containing the hydrochloride.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Pilzcin; ***Ger.:*** Pilzcin; ***Jpn:*** Pilzcin.

Eberconazole Nitrate *(rINNM)*

Éberconazole, Nitrate de; Eberconazoli Nitras; Nitrato de eberconazol. (±)-1-(2,4-Dichloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)imidazole nitrate.

Эберконазола Нитрат

$C_{18}H_{14}Cl_2N_2,NO_3$ = 391.2.

CAS — 128326-82-9 (eberconazole).

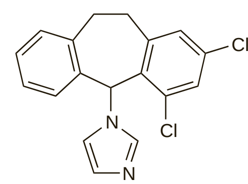

(eberconazole)

Profile

Eberconazole nitrate is an imidazole antifungal used topically as a 1% cream in the treatment of superficial fungal infections of the skin.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

◊ References.

1. del Palacio A, *et al.* A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections. *Mycoses* 2001; **44:** 173–80.
2. Repiso Montero T, *et al.* Eberconazole 1% cream is an effective and safe alternative for dermatophytosis treatment: multicenter, randomized, double-blind, comparative trial with miconazole 2% cream. *Int J Dermatol* 2006; **45:** 600–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Ebernet; Ebertop; Ebesupol.

Econazole *(BAN, USAN, rINN)*

Econazol; Éconazole; Econazolum; Ekonatsoli; Ekonazol; Ekonazolas. 1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole.

Эконазол

$C_{18}H_{15}Cl_3N_2O$ = 381.7.
CAS — 27220-47-9.
ATC — D01AC03; G01AF05.
ATC Vet — QD01AC03; QG01AF05.

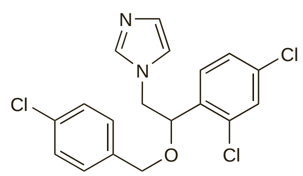

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Econazole). A white or almost white powder. M.p. 88° to 92°. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Protect from light.

Econazole Nitrate *(BANM, USAN, rINNM)*

C-C2470; Éconazole, nitrate d'; Econazoli nitras; Ekonatsolinitraatti; Ekonazolnitrat; Ekonazol-nitrát; Ekonazolo nitratas; Nitrato de econazol; R-14827; SQ-13050. (±)-1-[2,4-Dichloro-β-(4-chlorobenzyloxy)phenethyl]imidazole nitrate.

Эконазола Нитрат

$C_{18}H_{15}Cl_3N_2O,HNO_3$ = 444.7.
CAS — 24169-02-6 (econazole nitrate); 68797-31-9 ((±)-econazole nitrate).
ATC — D01AC03; G01AF05.
ATC Vet — QD01AC03; QG01AF05.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Econazole Nitrate). A white or almost white crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.
USP 31 (Econazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Very slightly soluble in water and in ether; slightly soluble in alcohol; sparingly soluble in chloroform; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Local reactions including burning and irritation may occur when econazole nitrate is applied topically. Contact dermatitis has been reported rarely.

Intravaginal preparations of econazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Porphyria. Econazole nitrate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Antimicrobial Action

Econazole is an imidazole antifungal with antimicrobial activity similar to that of ketoconazole (p.539).

Pharmacokinetics

Absorption is not significant when econazole nitrate is applied to the skin or vagina.

Uses and Administration

Econazole is an imidazole antifungal used topically in the treatment of superficial candidiasis (see p.518) and in dermatophytosis and pityriasis versicolor (see Skin Infections, p.521).

Econazole nitrate is applied topically up to 3 times daily as a 1% cream, lotion, powder, or solution in the treatment of fungal skin infections. Treatment is continued for 2 to 4 weeks. It is also used in the treatment of vaginal candidiasis as pessaries of 150 mg once daily at bedtime for 3 consecutive nights; a single dose of 150 mg in a long-acting formulation has also been used. Intravaginal use of 5 g of a 1% cream once daily at night has been given for 2 weeks. A 1% cream may be used concurrently for the treatment of vulval infections or for the treatment of balanitis in a male partner.

In the treatment of fungal infections of the nails, a 1% cream or lotion is applied once daily and covered with an occlusive dressing.

Econazole nitrate has also been used as eye or ear drops.

Econazole sulfosalicylate has also been used.

Preparations

BP 2008: Econazole Cream; Econazole Pessaries.

Proprietary Preparations (details are given in Part 3)
Arg.: Dermocitran; Micocide; Micofitex†; Micolis; Micotex; Novo Paramicon; Sinamida Econazol; ***Austral.:*** Dermazole; Pevaryl; ***Austria:*** Gyno-Pevaryl; Pevaryl; ***Belg.:*** Gyno-Pevaryl; Pevaryl; ***Braz.:*** Dermazol; Micostyl; ***Canad.:*** Ecostatin; ***Chile:*** Micolis; ***Cz.:*** Gyno-Pevaryl; Pevaryl; ***Denm.:*** Pevaryl; ***Fin.:*** Pevaryl; ***Fr.:*** Dermazol; Fongeryl; Gyno-Pevaryl; Mycoapaisyl; Pevaryl; ***Ger.:*** Epi-Pevaryl; Epi-Pevaryl Pv; Gyno-Pevaryl; ***Gr.:*** Bismultin; Mycobacter; Nectarmicin†; Penicomb; Pevaryl; Unifungin; ***Hong Kong:*** Dermazole†; Econite; Ecosone; Gyno-Pevaryl†; Heads Shampoo; Pevaryl†; ***Hung.:*** Gyno-Pevaryl; Pevaryl; ***India:*** Ecanol; ***Irl.:*** Ecostatin; Gyno-Pevaryl; Pevaryl†; ***Israel:*** Gyno-Pevaryl; Pevaryl; ***Ital.:*** Chemionazolo†; Dermazol†; Eccelium†; Eco Mi; Ecodergin; Ecorex; Ecosteril; Ganazolo; Ifenec; Micos; Pevaryl; Polinazolo; ***Malaysia:*** Ecoderm†; Gyno-Pevaryl; Pevaryl†; Zoliderm†; ***Mex.:*** Micostyl; Pevaryl; ***Neth.:*** Pevaryl; ***Norw.:*** Pevaryl; ***NZ:*** Dermazole†; Ecreme; Gyno-Pevaryl†; Pevaryl; ***Philipp.:*** Pevaryl; ***Pol.:*** Gyno-Pevaryl; Pevaryl; Pevazol; ***Port.:*** Gyno-Pevaryl; Pevaryl; ***Rus.:*** Ecalin (Экалин); Ecodax (Экодакс); Ecomikole (Экомикол)†; Gyno-Pevaryl (Гино-Певарил); Ifenec (Ифенек); ***S.Afr.:*** Ecoderm; Econal-C; Gyno-Pevaryl; Pevaryl; ***Singapore:*** Dermazole†; Gyno-Pevaryl; Pevaryl†; ***Spain:*** Ecotam; Gyno-Pevaryl; Micoespec; Pevaryl; ***Swed.:*** Pevaryl; ***Switz.:*** Gyno-Pevaryl; Pevaryl; Sebolith; ***Thai.:*** Econ; ***UK:*** Ecostatin; Gyno-Pevaryl; Pevaryl; ***USA:*** Spectazole; ***Venez.:*** Gyno-Pevaryl; Gynomiconax†; Miconax; Mizol†; Pevaryl.

Multi-ingredient: ***Arg.:*** Diflunazol†; Filoderma Plus; Griseocrem; Griseoplus; Novo Bacticort Complex†; ***Austria:*** Pevaryl; Pevisone; ***Belg.:*** Pevisone; ***Denm.:*** Pevisone; ***Fin.:*** Pevisone; ***Fr.:*** Pevisone; ***Ger.:*** Epi-Pevaryl Heilpaste†; Epipevisone; ***Gr.:*** Pevison; ***Hong Kong:*** Pevisone; Triconazole; ***India:*** Cobederm-H; Ecodax†; ***Israel:*** Pevisone; ***Ital.:*** Pevisone; ***Malaysia:*** Ecocort; Econazine; Pevisone†; ***Norw.:*** Pevisone; ***Philipp.:*** Nizolex; Pevaryl HP; Pevisone; ***Pol.:*** Pevisone; ***Port.:*** Pevisone; ***S.Afr.:*** Pevisone; ***Singapore:*** Ecocort; Econazine; Pevisone†; ***Swed.:*** Pevisone; ***Switz.:*** Pevaryl; Pevisone; ***Thai.:*** Ecocort; Ecoderm; Pevisone†; Tricozole; ***UK:*** Econacort.

Enilconazole *(BAN, USAN, rINN)*

Enilconazol; Énilconazole; Enilconazolum; Enilkonatsoli; Enilkonazol; R-23979. (±)-1-(β-Allyloxy-2,4-dichlorophenethyl)imidazole.

Энилконазол

$C_{14}H_{14}Cl_2N_2O$ = 297.2.
CAS — 35554-44-0.
ATC Vet — QD01AC90.

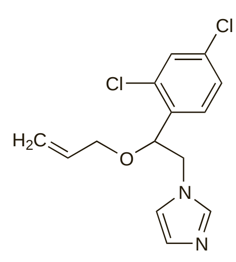

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Enilconazole for Veterinary Use; Enilconazole BP(Vet) 2008). A clear, yellowish, oily liquid or solid mass. Very slightly soluble in water; freely soluble in alcohol, in methyl alcohol, and in toluene. Store in airtight containers. Protect from light.

Profile

Enilconazole is an imidazole antifungal used topically in veterinary medicine for the treatment of fungal skin infections in cattle, horses, and dogs. It is also used by inhalation for the treatment of aspergillosis in ostriches.

Fenticlor *(BAN, USAN, rINN)*

D-25; Fenticloro; Fenticlorum; HL-1050; NSC-4112; Ph-549; S-7. 2,2′-Thiobis(4-chlorophenol).

Фентиклор

$C_{12}H_8Cl_2O_2S$ = 287.2.
CAS — 97-24-5.

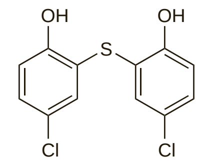

Profile

Fenticlor is an antifungal that has been applied topically in the treatment of dermatophyte infections.

Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Dermisdin†.

Fenticonazole Nitrate *(BANM, USAN, rINNM)*

Fenticonazole, nitrate de; Fenticonazoli nitras; Fentikonatsolinitraatti; Fentikonazolnitrat; Fentikonazol-nitrát; Fentikonazolo nitratas; Nitrato de fenticonazol; Rec-15/1476. (±)-1-[2,4-Dichloro-β-{[*p*-(phenylthio)benzyl]oxy}phenethyl]imidazole mononitrate.

Фентиконазола Нитрат

$C_{24}H_{20}Cl_2N_2OS,HNO_3$ = 518.4.
CAS — 72479-26-6 (fenticonazole); 73151-29-8 (fenticonazole nitrate).
ATC — D01AC12; G01AF12.
ATC Vet — QD01AC12; QG01AF12.

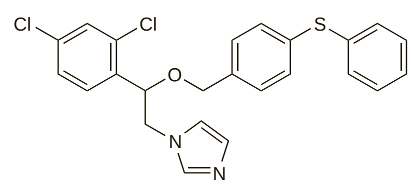

(fenticonazole)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fenticonazole Nitrate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dimethylformamide and in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Burning and itching have been reported after the application of fenticonazole nitrate.

Intravaginal preparations of fenticonazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Antimicrobial Action

Fenticonazole is an imidazole antifungal active against a range of organisms including dermatophyte pathogens, *Malassezia furfur,* and *Candida albicans.*

Uses and Administration

Fenticonazole is an imidazole antifungal used locally as the nitrate in the treatment of vulvovaginal candidiasis (p.518). A 200-mg pessary is inserted into the vagina at bedtime for 3 nights or a 600-mg pessary is inserted once only at bedtime. Fenticonazole nitrate is also applied topically as a 2% cream or solution for the treatment of fungal skin infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lomexin†; ***Austria:*** Lomexin; ***Braz.:*** Fentizol; Lomexin; ***Cz.:*** Lomexin; ***Fr.:*** Lomexin; Terlomexin; ***Ger.:*** Fenizolan; Lomexin; ***Gr.:*** Lomexin; ***Hung.:*** Gynoxin; ***Ital.:*** Falvin; Fentiderm†; Fentigyn†; Lomexin; ***Mex.:*** Lomexin; ***Neth.:*** Gynoxin; ***Pol.:*** Gynoxin; ***Port.:*** Lomexin; ***S.Afr.:*** Lomexin†; ***Singapore:*** Lomexin†; ***Spain:*** Laurimic; Lomexin; Micofulvin; ***Switz.:*** Mycodermil; ***Turk.:*** Gyno-Lomexin; ***UK:*** Lomexin†; ***Venez.:*** Mycofentin.

Fluconazole *(BAN, USAN, rINN)*

Fluconazol; Fluconazolum; Flukonatsoli; Flukonazol; UK-49858. 2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

Флуконазол

$C_{13}H_{12}F_2N_6O$ = 306.3.

CAS — 86386-73-4.

ATC — D01AC15; J02AC01.

ATC Vet — QD01AC15; QJ02AC01.

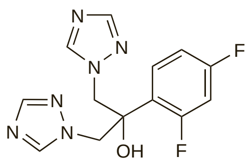

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Fluconazole). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in methyl alcohol; soluble in acetone. Store in airtight containers.

USP 31 (Fluconazole). A white or almost white, crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone; sparingly soluble in chloroform and in isopropyl alcohol; freely soluble in methyl alcohol; very slightly soluble in toluene. Store in airtight containers at a temperature below 30°.

Incompatibility and stability. References.

1. Lor E, *et al.* Visual compatibility of fluconazole with commonly used injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1991; **48:** 744–6.
2. Couch P, *et al.* Stability of fluconazole and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1992; **49:** 1459–62.
3. Hunt-Fugate AK, *et al.* Stability of fluconazole in injectable solutions. *Am J Hosp Pharm* 1993; **50:** 1186–7.
4. Ishisaka DY. Visual compatibility of fluconazole with drugs given by continuous infusion. *Am J Hosp Pharm* 1994; **51:** 2290 and 2292.

Adverse Effects

Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance. Other adverse effects include headache, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy. Anaphylaxis and angioedema have been reported rarely.

Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred, more commonly in patients with AIDS.

Alopecia. Alopecia has occasionally been reported in patients receiving fluconazole, especially during prolonged use.[1,2]

1. Weinroth SE, Tuazon CU. Alopecia associated with fluconazole treatment. *Ann Intern Med* 1993; **119:** 637.
2. Pappas PG, *et al.* Alopecia associated with fluconazole therapy. *Ann Intern Med* 1995; **123:** 354–7.

Effect on electrolyte balance. Hypokalaemia was associated with fluconazole in 3 patients with acute myeloid leukaemia.[1]

1. Kidd D, *et al.* Hypokalaemia in patients with acute myeloid leukaemia after treatment with fluconazole. *Lancet* 1989; **i:** 1017.

Effects on the heart. Prolonged QT interval and torsade de pointes have been reported rarely in patients receiving fluconazole.[1-5]

1. Wassmann S, *et al.* Long QT syndrome and torsade de pointes in a patient receiving fluconazole. *Ann Intern Med* 1999; **131:** 797.
2. Tholakanahalli VN, *et al.* Fluconazole-induced torsade de pointes. *Ann Pharmacother* 2001; **35:** 432–4.
3. Khazan M, Mathis AS. Probable case of torsades de pointes induced by fluconazole. *Pharmacotherapy* 2002; **22:** 1632–7.
4. Pham CP, *et al.* Long QTc interval and torsade de pointes caused by fluconazole. *Ann Pharmacother* 2006; **40:** 1456–61.
5. McMahon JH, Grayson ML. Torsades de pointes in a patient receiving fluconazole for cerebral cryptococcosis. *Am J Health-Syst Pharm* 2008; **65:** 619–23.

Effects on the liver. Although severe hepatic reactions to fluconazole are rare they have been reported, especially in patients with severe underlying diseases or hepatic dysfunction.[1,2] Elevated liver enzymes are commonly found and there have been reports of jaundice.[3,4] Hepatic necrosis has been seen rarely post mortem in patients with severe underlying disease who had received fluconazole. In one such patient, hepatotoxicity was concluded to be dose-dependent.[5]

1. Wells C, Lever AML. Dose-dependent fluconazole hepatotoxicity proven on biopsy and rechallenge. *J Infect* 1992; **24:** 111–12.
2. Jacobson MA, *et al.* Fatal acute hepatic necrosis due to fluconazole. *Am J Med* 1994; **96:** 188–90.
3. Holmes J, Clements D. Jaundice in HIV positive haemophiliac. *Lancet* 1989; **i:** 1027.
4. Franklin IM, *et al.* Fluconazole-induced jaundice. *Lancet* 1990; **336:** 565.
5. Bronstein J-A, *et al.* Fatal acute hepatic necrosis due to dose-dependent fluconazole hepatotoxicity. *Clin Infect Dis* 1997; **25:** 1266–7.

Hypersensitivity. Desensitisation has been successfully carried out in a patient with AIDS who exhibited hypersensitivity to both fluconazole and itraconazole.[1] Gradually increasing oral doses of fluconazole (starting at 5 mg daily) were given over 7 days; thereafter dosage was maintained at 400 mg daily. No adverse reactions were noted during the desensitisation period or in the 3 months up to the publication of the report.

1. Takahashi T, *et al.* Desensitization to fluconazole in an AIDS patient. *Ann Pharmacother* 2001; **35:** 642–3.

Precautions

Fluconazole should be used with caution in patients with impaired hepatic or renal function. Abnormalities in haematological, hepatic, and renal-function tests have been observed in patients with serious underlying diseases such as AIDS or malignancy. Cases of torsade de pointes and QT prolongation have been reported rarely and caution is advised when giving fluconazole to patients with proarrhythmic conditions.

Teratogenicity has occurred in *animals* given high doses of fluconazole and its use is not recommended in pregnancy (see under Pregnancy, below).

Breast feeding. Fluconazole is distributed into breast milk, achieving concentrations similar to those found in maternal plasma,[1] and its use in women who are breast feeding is not recommended by licensed product information.

In one report,[2] no untoward effects, other than a slight increase in lactase dehydrogenase level, were seen in an infant who was exposed to fluconazole in breast milk for 6 weeks.

The American Academy of Pediatrics considers that the use of fluconazole is usually compatible with breast feeding.[3]

1. Force RW. Fluconazole concentrations in breast milk. *Pediatr Infect Dis J* 1995; **14:** 235–6.
2. Bodley V, Powers D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study. *J Hum Lact* 1997; **13:** 307–11.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/06/05)

Pregnancy. High (toxic) doses of *fluconazole*, *itraconazole*, and *ketoconazole* have been reported to be teratogenic in *rodents.* Although there is little information about the use of these drugs in human pregnancy, there is a report of a woman who took fluconazole 400 mg daily throughout pregnancy and who gave birth to an infant with severe craniofacial and limb abnormalities.[1] The abnormalities resembled those associated with the Antley-Bixler syndrome, a genetic disorder, but a teratogenic effect could not be excluded. Although prescription-event-monitoring studies of fluconazole did not reveal adverse effects on the fetus,[2-4] congenital abnormalities have occurred in infants whose mothers were given high doses of fluconazole for 3 months or more. Data collected by the manufacturer,[5] relating to 198 women exposed to itraconazole during the first trimester of pregnancy, indicated that the malformation rate for both exposed women and matched controls was within the expected baseline risk for the general population. Nevertheless, the manufacturers recommend that fluconazole, itraconazole, and ketoconazole should be avoided during pregnancy.

Licensed product information states that doses of *voriconazole* equivalent to those used therapeutically have been shown to be teratogenic and embryotoxic in *rodents*. It therefore recommends that voriconazole should be avoided during pregnancy and that women of child bearing potential should use effective contraception during treatment. Similar recommendations have been made for *posaconazole.*

Other azole antifungals including butoconazole, clotrimazole, econazole, miconazole, sulconazole, terconazole, and tioconazole are reported to be embryotoxic but not teratogenic in *rodents* given high doses. Many of these drugs are used topically or intravaginally and the systemic absorption from these routes of administration varies. While these drugs may not necessarily be contra-indicated in pregnancy, consideration should be given to these potential risks when choosing antifungal therapy for such patients.

1. Lee BE, *et al.* Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992; **11:** 1062–4.
2. Rubin PC, *et al.* Fluconazole and pregnancy: results of a prescription event-monitoring study. *Int J Gynecol Obstet* 1992; **37** (suppl): 25–7.
3. Inman W, *et al.* Safety of fluconazole in the treatment of vaginal candidiasis: a prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994; **46:** 115–18.
4. Sørensen HT, *et al.* Risk of malformations and other outcomes in children exposed to fluconazole in utero. *Br J Clin Pharmacol* 1999; **48:** 234–8.
5. Bar-Oz B, *et al.* Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000; **183:** 617–20.

Renal impairment. For dose adjustments in renal impairment, see Administration in Renal Impairment, under Uses and Administration, below.

Interactions

In general, fewer interactions are considered to occur with fluconazole than with either itraconazole or ketoconazole.

Use of rifampicin with fluconazole results in reduced plasma concentrations of fluconazole. Use of hydrochlorothiazide and fluconazole has resulted in clinically insignificant increases in plasma-fluconazole concentrations.

Fluconazole may interfere with the metabolism of some other drugs, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. This may account for the reported increases in plasma concentrations of bosentan, ciclosporin, midazolam, nevirapine, amitriptyline, nortriptyline, phenytoin, rifabutin, sulfonylurea hypoglycaemics and nateglinide, selective cyclo-oxygenase-2-inhibitors such as celecoxib and parecoxib, tacrolimus, triazolam, warfarin, and zidovudine; fluconazole may inhibit the formation of a toxic metabolite of sulfamethoxazole.

Increases in terfenadine concentrations following high doses of fluconazole have been associated with ECG abnormalities. A similar effect may be anticipated with astemizole. Use of fluconazole with cisapride could result in increased cisapride concentrations and associated toxicity. The use of fluconazole with astemizole, cisapride, or terfenadine should therefore be avoided because of the risk of cardiac arrhythmias. Syncope attributed to increased amitriptyline concentrations has occurred when amitriptyline was given with fluconazole.

Fluconazole may also reduce the clearance of theophylline. The concentration of contraceptive steroids has been reported to be both increased and decreased in patients receiving fluconazole and the efficacy of oral contraceptives may be affected.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

Antineoplastics. For the effect of azole antifungals on *cyclophosphamide* metabolism, see p.703.

Fluoroquinolones. Both *levofloxacin* and fluconazole can cause a prolonged QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Nitrofurans. For a report of pulmonary and hepatic toxicity due to a possible interaction between *nitrofurantoin* and fluconazole, see p.308.

Antimicrobial Action

Fluconazole is a triazole antifungal drug which in sensitive fungi inhibits cytochrome P450-dependent enzymes, resulting in impairment of ergosterol synthesis in fungal cell membranes. It is active against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Microsporum* spp., and *Trichophyton* spp.

Resistance has developed in some *Candida* spp. following long-term prophylaxis with fluconazole, and cross-resistance with other azoles has been reported.

Microbiological interactions. A synergistic antifungal effect was seen *in vitro* with terbinafine and fluconazole against strains of *Candida albicans*.[1] For effects on the antifungal activity of fluconazole when given with amphotericin B, see p.525.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.

Resistance. The emergence of strains of *Candida* spp. resistant to fluconazole has become increasingly important, particularly in immunocompromised patients receiving long-term prophylaxis with fluconazole.[1,2] In addition to resistance in *C. albicans*,[3-5] infections with *C. dubliniensis*,[5] *C. glabrata*, and *C. krusei*, all of which may be less sensitive to fluconazole than *C. albicans*, have been noted in these patients,[6,7] and secondary resistance of *C. glabrata* has been reported during fluconazole therapy.[8,9] Resistance to fluconazole has been reported to occur more frequently than resistance to either ketoconazole or itraconazole and may be related to the widespread use of this drug.[4,7] Cross-resistance with other azoles[10,11] and with amphotericin B[12,13] has been reported.

Fluconazole resistance has also been reported in *Cryptococcus neoformans*[14] and *Histoplasma capsulatum*.[15] Histoplasmosis developed during treatment with fluconazole in a patient with HIV infection.[16] Fluconazole-resistant *C. neoformans* has been isolated from an immunocompetent patient who had not been exposed to azole antifungals previously.[17]

1. Rex JH, *et al.* Resistance of Candida species to fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 1–8.
2. Brion LP, *et al.* Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; **54:** 521–9.
3. Sandven P, *et al.* Susceptibilities of Norwegian Candida albicans strains to fluconazole: emergence of resistance. *Antimicrob Agents Chemother* 1993; **37:** 2443–8.
4. Johnson EM, *et al.* Emergence of azole drug resistance in Candida species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother* 1995; **35:** 103–14.
5. Ruhnke M, *et al.* Development of simultaneous resistance to fluconazole in Candida albicans and Candida dubliniensis in a patient with AIDS. *J Antimicrob Chemother* 2000; **46:** 291–5.
6. Price MF, *et al.* Fluconazole susceptibilities of Candida species and distribution of species recovered from blood cultures over a 5-year period. *Antimicrob Agents Chemother* 1994; **38:** 1422–4.
7. Odds FC. Resistance of yeasts to azole-derivative antifungals. *J Antimicrob Chemother* 1993; **31:** 463–71.
8. Hitchcock CA, *et al.* Fluconazole resistance in Candida glabrata. *Antimicrob Agents Chemother* 1993; **37:** 1962–5.
9. Miyazaki H, *et al.* Fluconazole resistance associated with drug efflux and increased transcription of a drug transporter gene, PDH1, in Candida glabrata. *Antimicrob Agents Chemother* 1998; **42:** 1695–1701.
10. Martinez-Suarez JV, Rodriguez-Tudela JL. Patterns of in vitro activity of itraconazole and imidazole antifungal agents against Candida albicans with decreased susceptibility to fluconazole from Spain. *Antimicrob Agents Chemother* 1995; **39:** 1512–16.
11. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; **44:** 1585–7.
12. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; **348:** 1523–4.
13. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; **41:** 196–9.
14. Venkateswarlu K, *et al.* Fluconazole tolerance in clinical isolates of Cryptococcus neoformans. *Antimicrob Agents Chemother* 1997; **41:** 748–51.
15. Wheat J, *et al.* Hypothesis on the mechanism of resistance to fluconazole in Histoplasma capsulatum. *Antimicrob Agents Chemother* 1997; **41:** 410–14.
16. Pottage JC, Sha BE. Development of histoplasmosis via human immunodeficiency virus infected patient receiving fluconazole. *J Infect Dis* 1991; **164:** 622–3.
17. Omi-Wasserlauf R, *et al.* Fluconazole-resistant Cryptococcus neoformans isolated from an immunocompetent patient without prior exposure to fluconazole. *Clin Infect Dis* 1999; **29:** 1592–3.

Pharmacokinetics

Fluconazole is well absorbed after oral doses, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72 micrograms/mL have been reported in healthy subjects after a 400-mg oral dose. Peak concentrations are reached within 1 to 2 hours of oral doses. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Multiple dosing leads to increases in peak plasma concentrations; steady-state concentrations are reached in 5 to 10 days but may be attained on day 2 if a loading dose is given.

Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma. Concentrations in the CSF range from 50 to 90% of plasma concentrations, even in the absence of meningeal inflammation. Protein binding is only about 12%.

About 80% of a dose is excreted unchanged in the urine and about 11% as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with renal impairment. Fluconazole is removed by dialysis.

◊ Reviews.

1. Debruyne D, Ryckelynek J-P. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet* 1993; **24:** 10–27.
2. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clin Pharmacokinet* 1997; **33:** 52–77.
3. Pittrow L, Penk A. Special pharmacokinetics of fluconazole in septic, obese and burn patients. *Mycoses* 1999; **42** (suppl 2): 87–90.
4. Silling G. Fluconazole: optimized antifungal therapy based on pharmacokinetics. *Mycoses* 2002; **45** (suppl 3): 39–41.

Burns. The mean half-life of fluconazole was decreased to 24.4 hours in 9 patients with burns.[1] Fluconazole clearance was 27.5 mL/minute, which was 30% higher than that reported in healthy subjects.

1. Boucher BA, *et al.* Fluconazole pharmacokinetics in burn patients. *Antimicrob Agents Chemother* 1998; **42:** 930–3.

Children and neonates. References.

1. Saxén H, *et al.* Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993; **54:** 269–77.
2. Nahata MC, Brady MT. Pharmacokinetics of fluconazole after oral administration in children with human immunodeficiency virus infection. *Eur J Clin Pharmacol* 1995; **48:** 291–3.

Distribution. Salivary concentrations of fluconazole after oral doses should be adequate for the treatment of oropharyngeal and oesophageal candidiasis[1,2] even in patients with AIDS who may have decreased salivation.[3] Treatment failures are more likely to be due to inadequate dosage or resistant organisms than to decreased salivary secretion.[3]

Pharmacologically active concentrations of fluconazole have been detected in scalp hair[4] and nails[5] after oral treatment with conventional daily doses and with once-weekly dosage.

1. Force RW, Nahata MC. Salivary concentrations of ketoconazole and fluconazole: implications for drug efficacy in oropharyngeal and esophageal candidiasis. *Ann Pharmacother* 1995; **29:** 10–15.
2. Koks CHW, *et al.* Pharmacokinetics of fluconazole in saliva and plasma after administration of an oral suspension and capsules. *Antimicrob Agents Chemother* 1996; **40:** 1935–7.
3. Garcia-Hermoso D, *et al.* Fluconazole concentrations in saliva from AIDS patients with oropharyngeal candidosis refractory to treatment with fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 656–60.
4. Yeates R, *et al.* Accumulation of fluconazole in scalp hair. *J Clin Pharmacol* 1998; **38:** 138–43.
5. Faergemann J. Pharmacokinetics of fluconazole in skin and nails. *J Am Acad Dermatol* 1999; **40** (suppl): S14–S20.

HIV-infected patients. Plasma clearance of fluconazole may be lower in patients with HIV infection than in immunocompetent patients, and the half-life may be prolonged.[1,2]

1. Tett S, *et al.* Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection. *Antimicrob Agents Chemother* 1995; **39:** 1835–41.
2. McLachlan AJ, Tett SE. Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. *Br J Clin Pharmacol* 1996; **41:** 291–8.

Uses and Administration

Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, histoplasmosis, and sporotrichosis. The place of fluconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

Fluconazole is given by mouth or intravenous infusion in similar doses. For intravenous infusion it is given as a solution containing 2 mg/mL at a rate of 5 to 10 mL/minute (300 to 600 mL/hour). In the USA, a maximum infusion rate of 100 mL/hour is recommended.

For **superficial mucosal candidiasis** (other than genital candidiasis), the usual dose of fluconazole in the UK is 50 mg daily by mouth, although 100 mg daily may be given if necessary. Treatment usually continues for 7 to 14 days in *oropharyngeal* candidiasis (except in severely immunocompromised patients), for 14 days in *atrophic oral candidiasis* associated with dentures, and for 14 to 30 days in other mucosal candidal infections including *oesophagitis*.

Higher doses are recommended in the USA where an initial dose of fluconazole 200 mg is followed by 100 mg daily and where the minimum treatment period is 14 days for oropharyngeal infection, or a minimum of 21 days and at least 14 days after resolution of symptoms for oesophageal infections; doses of up to 400 mg daily may be used for oesophageal candidiasis if necessary.

Fluconazole 150 mg as a single oral dose may be used for **genital candidiasis** (vaginal candidiasis or candidal balanitis).

Dermatophytosis, pityriasis versicolor, and *Candida* **infections of the skin** may be treated with fluconazole 50 mg daily by mouth for up to 6 weeks.

Systemic candidiasis, **cryptococcal meningitis**, and other **cryptococcal infections** may be treated with fluconazole orally or by intravenous infusion; the initial dose is 400 mg followed by 200 to 400 mg daily. Duration of therapy is based on clinical and mycological response, but is usually at least 6 to 8 weeks in cryptococcal meningitis; in the USA, treatment for 10 to 12 weeks after the CSF cultures become negative is recommended. Fluconazole may also be used in daily doses of 100 to 200 mg orally or intravenously to prevent relapse after a primary course of antifungal treatment for acute cryptococcal meningitis in patients with AIDS.

In *immunocompromised patients* at risk of fungal infections, fluconazole may be given **prophylactically** in a dose of 50 to 400 mg daily orally or by intravenous infusion, although long-term prophylaxis has been associated with the emergence of resistant organisms (see under Intermittent Doses, below).

Doses for **children** over 4 weeks of age are 3 mg/kg daily for superficial infections (a loading dose of 6 mg/kg may be used on the first day if necessary), and 6 to 12 mg/kg daily for systemic infections. For prophylaxis in immunocompromised children, a dose of 3 to 12 mg/kg daily may be given. For infants under 2 weeks of age, all these doses should be given once every 72 hours; for those aged between 2 and 4 weeks, the doses should be given every 48 hours. A maximum dose of 400 mg daily should not be exceeded in children, or 12 mg/kg at appropriate intervals in infants.

Dosage may need to be reduced in patients with **renal impairment** (see below).

◊ Reviews.

1. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; **39:** 877–916. Correction. *ibid.* **40:** 862.
2. Kowalsky SF, Dixon DM. Fluconazole: a new antifungal agent. *Clin Pharm* 1991; **10:** 179–94.
3. Goa KL, Barradell LB. Fluconazole: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* 1995; **50:** 658–90.
4. Charlier C, *et al.* Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? *J Antimicrob Chemother* 2006; **57:** 384–410.

Administration. *HIGH DOSES.* Doses higher than those recommended by licensed product information for fluconazole have been tried in patients with life-threatening infections caused by *Candida* spp., *Cryptococcus neoformans*, and *Coccidioides immitis*. Dose finding studies have found daily doses of 800 to 1000 mg of fluconazole to be effective and well tolerated.[1-3] In a study of 11 HIV-infected patients who received fluconazole 800 to 1000 mg daily intravenously for 3 weeks then orally until the CSF culture became negative, 6 patients had responded at 10 weeks and another 2 improved clinically.[1] Daily doses of up to 800 mg have been used in blastomycosis[2] and coccidioidomycosis,[3] and doses of 10 mg/kg daily have been tried in disseminated candidiasis.[4]

1. Menichetti F, *et al.* High-dose fluconazole therapy for cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* 1996; **22:** 838–40.
2. Pappas PG, *et al.* Treatment of blastomycosis with higher doses of fluconazole. *Clin Infect Dis* 1997; **25:** 200–5.
3. Galgiani JN, *et al.* Infectious Diseases Society of America. Practice guidelines for the treatment of coccidioidomycosis. *Clin Infect Dis* 2000; **30:** 658–61. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/313747 (accessed 18/07/08)
4. Graninger W, *et al.* Treatment of Candida albicans fungaemia with fluconazole. *J Infect* 1993; **26:** 133–46.

INTERMITTENT DOSES. Concern has been expressed about the increasingly widespread use of fluconazole[1] and, in particular, about the impact of continuous fluconazole therapy in immunocompromised patients on the development of resistance (see under Antimicrobial Action, above). Nevertheless, fluconazole remains popular for primary and secondary prophylaxis.

Some investigators have suggested the use of intermittent doses[2,3] although this could further increase the risk of infections with resistant organisms.

Once-weekly treatment with fluconazole has been tried in onychomycosis[4] and tinea capitis.[5]

1. Mangino JE, *et al.* When to use fluconazole. *Lancet* 1995; **345:** 6–7.
2. Singh N, *et al.* Low-dose fluconazole as primary prophylaxis for cryptococcal infection in AIDS patients with CD4 cell counts of ≤ 100/mm : demonstration of efficacy in a prospective, multicenter trial. *Clin Infect Dis* 1996; **23:** 1282–6.
3. Schuman P, *et al.* Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 689–96.
4. Scher RK, *et al.* Once-weekly fluconazole (150 mg, 300 mg, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38:** S77–S86.
5. Gupta AK, *et al.* Once weekly fluconazole is effective in children in the treatment of tinea capitis: a prospective, multicentre study. *Br J Dermatol* 2000; **142:** 965–8.

Administration in renal impairment. Patients with renal impairment may require dosage reduction. Normal loading or initial doses of fluconazole should be given on the first day of treatment and subsequent doses should be adjusted according to creatinine clearance (CC):

- CC more than 50 mL/minute: 100% of the standard recommended dose
- CC less than 50 mL/minute and not receiving dialysis: 50% of the standard recommended dose
- patients on regular haemodialysis: 100% of the standard recommended dose after each dialysis session

No dosage adjustment is needed in patients with renal impairment given single-dose therapy.

Leishmaniasis. Fluconazole has been tried in the treatment of cutaneous leishmaniasis (p.824) caused by *Leishmania major.* In a randomised, double-blind, placebo-controlled study,[1] 80 patients received a six-week course of oral fluconazole 200 mg daily, of whom 63 had complete healing of lesions after 3 months, compared with 22 of 65 patients who received placebo. However, others[2] have reported a response rate not significantly different from placebo.

1. Alrajhi AA, *et al.* Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. *N Engl J Med* 2002; **346:** 891–5.
2. Morizot G, *et al.* Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? *Am J Trop Med Hyg* 2007; **76:** 48–52. Correction. *ibid.*; 791.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Candimicol; Damicol; Femixol; Fluconovag; Fluzol; Fungocina; Fungototal; Honguil Plus; Klonazol; Micolis Novo; Mutum; Naxo C; Nifurtox; Niofen; Periplum; Ponaris; Proseda F; Triflucan; ***Austral.:*** Diflucan; Dizole; Fluzole; Ozole; ***Austria:*** Diflucan; Diflucohexal; Difluzol; Fluconabene; Flucosept; Flucozal; Fungata; ***Belg.:*** Diflucan; Fungimed; ***Braz.:*** Candix; Candizol; Celozol†; Farmazol†; Floltec; Flucanil; Flucanol†; Flucazol; Flucodan; Flucoltrix†; Flucomed; Fluconal; Fluconax†; Fluconeo; Flucozen; Flucozix†; Flunal†; Flunazol†; Flutec†; Fungnon; Glyflucan; Helmicin; Monipax†; Pantec; Pronazol†; Riconazol; Triazol; Unizol; Zelix; Zolanix; Zolmic; Zolstatin†; Zoltec; Zoltren; ***Canad.:*** Diflucan; ***Chile:*** Diflucan; Felsol; Flucoxan; Fluctin; Fungimax; Ibarin; Micofin†; Microvaccin; Plusgin; Tavor; ***Cz.:*** Diflazon; Diflucan; Fluco; Forcan; Mycomax; Mycosyst; Mykohexal; ***Denm.:*** Conasol; Diflucan; Fungal†; ***Fin.:*** Diflucan; ***Fr.:*** Beagyne; Triflucan; ***Ger.:*** Canex; Diflucan; Fluc†; Flucobeta; Flucoderm; FlucoLich; Flunazul; Fungata; ***Gr.:*** Azoflu; Farviron; Figalol; Flucocaps; Flucodrug; Fluconapen; Flusenil; Funadel; Fungo; Fungustatin; Fungusteril; Fuxilidin; Gynosant; Hadlinol; Medoflucon; Mycazole; Rifagen; Stabilanol; Tierlite; Varmec; Zidonil; ***Hong Kong:*** Diflucan; Flucoric; Flucozal; Fludicon; Forcan; Lucon; Nofung; Stalene; ***Hung.:*** Dermyc; Diflazon†; Diflucan; Flucohexal; Flucoric; Mycosyst; Nofung; ***India:*** Flumyc†; Fluzon; Forcan; Logican; Nipcan; Syscan; ***Indon.:*** Cancid; Candizol; Cryptal; Diflucan; Flucess; Flucoral; Govazol; Zemyc; ***Irl.:*** Diflazole; Diflucan; Flucandid; Flucol; ***Israel:*** Diflucan; Flucanol; Trican; Triflucan; ***Ital.:*** Biozolene†; Diflucan; Elazor; ***Jpn:*** Diflucan†; ***Malaysia:*** Biozole; Diflucan; Flucoric; Flugal; Fukole; Medoflucon; Stalene; Zolstan; ***Mex.:*** Afungil; Bioxel; Candizol; Diflucan; Difusel; Fectrin; Flucoxan; Fludisol; Fluhexal; Flukezol; Fluxes; Fluxicap; Fluzor; Funser; Lanfluzol; Neofomiral; Ongicil; Oxifungol; Solarisol; Terplex; Zoldicam; ***Neth.:*** Diflucan; ***Norw.:*** Diflucan; ***NZ:*** Canesten Fluconazole; Diflucan; Flucazole; ***Philipp.:*** Diflucan; Funzela; Syscan; ***Pol.:*** Diflucan; Flucofast; Flumycon; Mycomax; Mycosyst; ***Port.:*** Azoflune; Diflucan; Fludocel; Maxflin; Reforce; Supremase; ***Rus.:*** Diflazon (Дифлазон); Diflucan (Дифлюкан); Flucostat (Флюкостат); Flucozan (Флукозан)†; Flumicon (Флюмикон); Fungolon (Фунголон); Funzole (Фунзол); Medoflucon (Медофлюкон); Mycoflucan (Микофлюкан); Mycomax (Микомакс); Mycosyst (Микосист); Syscan (Цискан); ***S.Afr.:*** Diflucan; Difluzole; Flucoric; Fluzol; ***Singapore:*** Diflucan; Medoflucon; Mycorest; Omastin; Stalene; ***Spain:*** Diflucan; Lavisa; Loitin; Solacap†; ***Swed.:*** Diflucan; ***Switz.:*** Diflucan; Flucazol; Fluconax; Flunizol; Mykantol; ***Thai.:*** Biozole; Diflucan; Flucozole; Fludizol; Flunco; Funa; Kyrin; Stalene; ***Turk.:*** Biocanol; Candidin; Flucan; Fluzole; Fungan; Kandizol; Lumen; Triflucan; Trizol; Zolax; ***UK:*** Canesten Oral; Diflucan; ***USA:*** Diflucan; ***Venez.:*** Aflumicort; Albesin; Diflucan; Flucess; Flucon; Flunal; Fluval; Fugin; Fungomax; Funizol; Micoflux; Mutum; Zolstan†.

Multi-ingredient: ***Arg.:*** Gynerium UD; ***Austral.:*** Canesoral Duo; ***India:*** Forcan TZ; Orflaz Kit; Safkit; ***Mex.:*** Afumix.

Flucytosine *(BAN, USAN, rINN)*

5-FC; Flucitosina; Flucitozin; Flucitozinas; Flucytosin; Flucytosinum; Flucytozyna; Flusitozin; Flusytosiini; Ro-2-9915. 5-Fluorocytosine; 4-Amino-5-fluoropyrimidin-2(1*H*)-one.

Флуцитозин

$C_4H_4FN_3O$ = 129.1.

CAS — 2022-85-7.

ATC — D01AE21; J02AX01.

ATC Vet — QD01AE21; QJ02AX01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Flucytosine). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in dehydrated alcohol. Protect from light.

USP 31 (Flucytosine). A white to off-white crystalline powder, odourless or with a slight odour. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. A solution of flucytosine for intravenous infusion should be stored between 18° and 25°. Precipitation may occur at lower temperatures and decomposition, with the formation of fluorouracil, at higher temperatures.

Adverse Effects

Adverse effects of flucytosine include nausea, vomiting, diarrhoea, and skin rashes. Less frequently reported adverse effects include confusion, hallucinations, convulsions, headache, sedation, and vertigo, and also allergic reactions, toxic epidermal necrolysis, and cardiotoxicity. Alterations in liver function tests are generally dose-related and reversible; hepatotoxicity may also occur. Hypokalaemia may occur. There have been a few reports of peripheral neuropathy.

Bone-marrow depression, especially leucopenia and thrombocytopenia, is associated with blood concentrations of flucytosine greater than 100 micrograms/mL, with concurrent use of amphotericin B, and with renal impairment. Fatal agranulocytosis and aplastic anaemia have been reported.

Effects on the blood. Bone marrow toxicity associated with flucytosine has been attributed to its conversion to fluorouracil, possibly by intestinal flora.[1] A pilot study[2] of 6 patients given intravenous flucytosine found that the amounts of fluorouracil in serum samples were undetectable, whereas flucytosine could be detected in the samples. This might be because intravenous dosage did not allow the conversion of flucytosine to fluorouracil by intestinal microflora. However, one patient still developed thrombocytopenia and another leucocytopenia and the authors hypothesised that toxicity might be due to flucytosine and not the metabolite.

1. Pirmohamed M, *et al.* The role of active metabolites in drug toxicity. *Drug Safety* 1994; **11:** 114–44.
2. Vermes A, *et al.* 5-fluorocytosine-related bone-marrow depression and conversion to fluorouracil: a pilot study. *Fundam Clin Pharmacol* 2002; **16:** 39–47.

Precautions

Flucytosine should be given with great care to patients with renal impairment, or with blood disorders or bone marrow depression. Renal and hepatic function and blood counts should be monitored during therapy (at least weekly in patients with renal impairment or blood disorders). In patients with renal impairment, doses should be reduced and trough blood concentrations of flucytosine should be checked regularly from blood samples taken just before an injection of flucytosine (see under Uses, below). Care should be taken in patients given radiation therapy or other drugs which depress bone marrow.

Flucytosine is teratogenic in *rats.*

AIDS. Frequent bone marrow toxicity has been reported in patients with AIDS during flucytosine therapy.[1] However, in a study in 381 patients, no additional haematotoxicity was reported in patients given amphotericin B plus flucytosine compared with those given amphotericin B alone.[2] The toxicity could be minimised by monitoring serum concentrations[3] and the British Society for Antimicrobial Chemotherapy has suggested that these should be maintained within 25 to 50 micrograms/mL in patients with AIDS.[4]

1. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **321:** 794–9.
2. van der Horst CM, *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997; **337:** 15–21.
3. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
4. British Society for Antimicrobial Chemotherapy Working Party. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. *Lancet* 1992; **340:** 648–51.

Pregnancy. Teratogenicity has been reported in some *animal* models and licensed product information recommends that flucytosine should only be used if the benefit justifies that possible risk to the fetus. The congenital defects are thought to be as a result of the conversion of flucytosine to fluorouracil by the intestinal microflora. However, there are some case reports of pregnant patients receiving flucytosine (with or without amphotericin B) in the second[1-4] and third[5] trimesters with no reports of abnormalities in the infants.

1. Philpot CR, Lo D. Cryptococcal meningitis in pregnancy. *Med J Aust* 1972; **2:** 1005–7.
2. Schönebeck J, Segerbrand E. Candida albicans septicaemia during first half of pregnancy successfully treated with 5-fluorocytosine. *BMJ* 1973; **4:** 337–8.
3. Curole DN. Cryptococcal meningitis in pregnancy. *J Reprod Med* 1981; **26:** 317–19.
4. Chotmongkol V, Siricharoensang S. Cryptococcal meningitis in pregnancy: a case report. *J Med Assoc Thai* 1991; **74:** 421–2.
5. Chen C-P, Wang K-G. Cryptococcal meningitis in pregnancy. *Am J Perinatol* 1996; **13:** 35–6.

Interactions

Flucytosine is commonly used with amphotericin B. Amphotericin B can cause a deterioration in renal function, which can result in raised flucytosine blood concentrations and increased toxicity. However, the two drugs are generally regarded as having synergistic antifungal activity. Cytarabine has been claimed to reduce blood concentrations of flucytosine and to antagonise its antifungal activity, although the evidence is limited.

Antimicrobial Action

Flucytosine is a fluorinated pyrimidine antifungal. In susceptible fungi it is converted by cytosine deaminase to fluorouracil which is then incorporated in place of uracil into fungal RNA and disrupts protein synthesis. The activity of thymidilate synthetase is also inhibited and this effect interferes with fungal DNA synthesis.

Flucytosine is active against *Candida* spp., *Cryptococcus neoformans*, *Cladosporium* spp., and *Fonsecaea* spp. Some *Aspergillus* spp. have also been reported to be sensitive. There is synergy between flucytosine and amphotericin B against *Candida* spp. and *Cryptococcus neoformans.*

There is a high incidence of primary resistance to flucytosine among isolates of *Candida* spp. and *Cryptococcus neoformans.* Resistance also develops during treatment with flucytosine and has been reported rarely from combination therapy with flucytosine and amphotericin B.

Pharmacokinetics

Flucytosine is absorbed rapidly and almost completely from the gastrointestinal tract. Bioavailability is 78 to 89%. After oral doses of 37.5 mg/kg every 6 hours, peak plasma concentrations of 70 to 80 micrograms/mL have been achieved within 2 hours; similar concentrations have been achieved but more rapidly, after an intravenous dose. The plasma-flucytosine concentration for optimum response is 25 to 50 micrograms/mL. Flucytosine is widely distributed through the body tissues and fluids; concentrations in the CSF are 65 to 90% of those in serum. About 2 to 4% of flucytosine is protein bound.

About 90% of a dose is excreted unchanged by glomerular filtration; a small amount of flucytosine may be metabolised to fluorouracil. The small amount of an oral dose of flucytosine not absorbed from the gastrointestinal tract is eliminated unchanged in the faeces. The elimination half-life is 2.5 to 6 hours in patients with normal renal function but increases with decreasing renal function. Flucytosine is removed by haemodialysis or peritoneal dialysis.

◊ References[1-3] to the pharmacokinetics of flucytosine. A study[3] reviewing flucytosine concentrations in serum, blood, or plasma from 233 patients, including 33 neonates, found that they were within the therapeutic range in only about 20% of cases; of the remainder, 40% were low (5% undetectable) and 40% were excessive (potentially toxic in about 10% of the samples). The results emphasised the importance of therapeutic drug monitoring.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal agents. *Clin Pharmacokinet* 1983; **8:** 17–42.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.
3. Pasqualotto AC, *et al.* Flucytosine therapeutic monitoring: 15 years experience from the UK. *J Antimicrob Chemother* 2007; **59:** 791–3.

Uses and Administration

Flucytosine is a fluorinated pyrimidine antifungal used in the treatment of systemic fungal infections, the treatments for which are discussed under Choice of Antifungal, p.517. It is mainly used with amphotericin B or fluconazole in the treatment of severe systemic candidiasis and cryptococcal meningitis. It has also been tried in other infections due to susceptible fungi including chromoblastomycosis.

Flucytosine is given by *intravenous infusion* as a 1% solution over 20 to 40 minutes. The usual dose is 200 mg/kg daily in 4 divided doses; a dose of 100 to 150 mg/kg daily may be sufficient in some patients. Dosage should be adjusted to produce trough plasma concentrations of 25 to 50 micrograms/mL. This is particularly important in patients with AIDS who are at increased risk of bone marrow toxicity. Parenteral treatment is rarely given for more than 7 days, except for cryptococcal meningitis when it is continued for at least 4 months. For intravenous doses to be used in patients with renal impairment, see below.

Flucytosine is given *orally* in usual doses of 50 to 150 mg/kg daily in 4 divided doses. Again, blood concentrations should be monitored and dosage adjusted in patients with renal impairment to avoid accumulation of the drug (see below).

Flucytosine has been used *topically* for azole-refractory vaginitis caused by *Candida* spp., but such use may increase problems of resistance.

◊ Reviews.

1. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
2. Summers KK, *et al.* Therapeutic drug monitoring of systemic antifungal therapy. *J Antimicrob Chemother* 1997; **40:** 753–64.
3. Vermes A, *et al.* Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46:** 171–9.

Administration in renal impairment. Flucytosine is mainly excreted by the kidneys and the dose must be adjusted in patients with renal impairment.

Dose intervals for intravenous flucytosine should be adjusted according to creatinine clearance (CC):

For intravenous use,

- CC 20 to 40 mL/minute: 50 mg/kg every 12 hours
- CC 10 to 20 mL/minute: 50 mg/kg every 24 hours
- CC less than 10 mL/minute: 50 mg/kg then further doses should be based on plasma concentrations which should not exceed 80 micrograms/mL

Initial oral doses should be at the lower end of the recommended range (see above) and dosage should be adjusted subsequently to avoid accumulation.

Preparations

BP 2008: Flucytosine Tablets;
USP 31: Flucytosine Capsules; Flucytosine Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Ancotil; ***Austral.:*** Ancotil; ***Austria:*** Ancotil; ***Denm.:*** Ancotil; ***Fr.:*** Ancotil; ***Ger.:*** Ancotil; ***Gr.:*** Ancotil; ***Hong Kong:*** Ancotil; ***Irl.:*** Ancotil; ***Ital.:*** Ancotil; ***Malaysia:*** Ancotil†; ***Neth.:*** Ancotil; ***NZ:*** Alcobon†; Ancotil; ***Pol.:*** Ancotil; ***Rus.:*** Ancotyl (Анкотил); ***Singapore:*** Ancotil†; ***Swed.:*** Ancotil; ***Switz.:*** Ancotil; ***UK:*** Ancotil; ***USA:*** Ancobon.

Flutrimazole *(BAN, rINN)*

Flutrimatsoli; Flutrimazol; Flutrimazolas; Flutrimazolum; UR-4056. 1-[*o*-Fluoro-α-(*p*-fluorophenyl)-α-phenylbenzyl]imidazole; (*RS*)-1-(2,4′-Difluorotrityl)imidazole.

Флутримазол

$C_{22}H_{16}F_2N_2$ = 346.4.
CAS — 119006-77-8.
ATC — D01AC16; G01AF18.
ATC Vet — QD01AC16; QG01AF18.

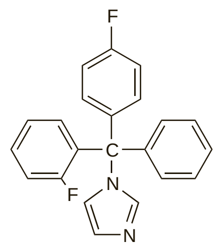

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flutrimazole). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in tetrahydrofuran. Protect from light.

Profile

Flutrimazole is an imidazole antifungal used topically as a 1% cream, gel, powder, or solution in the treatment of superficial fungal infections.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Flusporan†; ***Austria:*** Micetal; ***Braz.:*** Micetal; ***Chile:*** Micetal; ***Cz.:*** Micetal; ***Gr.:*** Topiderm; ***Hung.:*** Micetal; ***Ital.:*** Micetal; ***Mex.:*** Micetal; ***Pol.:*** Micetal; ***Port.:*** Flutrim; ***Spain:*** Flusporan; Funcenal; Micetal.

Fosfluconazole *(BAN, rINN)*

Fosfluconazol; Fosfluconazolum; UK-292663. 1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-[(1*H*-1,2,4-triazol-1-yl)methyl]ethyl dihydrogen phosphate.

Фосфлуконазол

$C_{13}H_{13}F_2N_6O_4P$ = 386.3.
CAS — 194798-83-9.

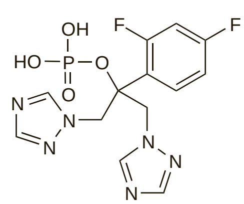

Profile

Fosfluconazole is a phosphate prodrug of fluconazole that is used for the treatment of systemic fungal infections, including oral candidiasis and recurrent cryptococcal meningitis in AIDS patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Prodif.

Griseofulvin *(BAN, rINN)*

Curling Factor; Griseofulviini; Griseofulvina; Griséofulvine; Griseofulvinum; Grizeofulvin; Grizeofulvinas; Gryzeofulwina. (2*S*,4′*R*)-7-Chloro-2′,4,6-trimethoxy-4′-methylspiro[benzofuran-2(3*H*),3′-cyclohexene]-3,6′-dione.

Гризеофульвин

$C_{17}H_{17}ClO_6$ = 352.8.
CAS — 126-07-8.
ATC — D01AA08; D01BA01.
ATC Vet — QD01AA08; QD01BA01.

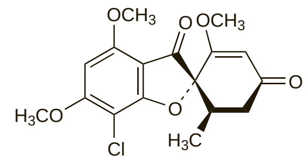

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Griseofulvin). An antifungal substance produced by the growth of certain strains of *Penicillium griseofulvum*, or by any other means. It is a white or yellowish-white powder. The particles of the powder are generally up to 5 micrometres in maximum dimension, though larger particles, which may occasionally exceed 30 micrometres, may be present. It contains 97 to 102% of $C_{17}H_{17}ClO_6$, calculated on the dried substance. Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in dimethylformamide and in tetrachloroethane.

USP 31 (Griseofulvin). A white to creamy-white, odourless powder, in which particles of the order of 4 micrometres in diameter predominate. It has a potency of not less than 900 micrograms of $C_{17}H_{17}ClO_6$ per mg. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, and in dimethylformamide. Store in airtight containers.

Adverse Effects

Adverse effects are usually mild and transient and consist of headache, skin rashes and urticaria, dry mouth, an altered sensation of taste, and gastrointestinal disturbances. Angioedema, erythema multiforme, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, oral candidiasis, peripheral neuropathy, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, impaired coordination, insomnia, and fatigue have also been reported. Griseofulvin may precipitate or aggravate systemic lupus erythematosus.

There have been a few reports of hepatotoxicity attributed to griseofulvin.

Effects on the skin. Fatal toxic epidermal necrolysis in a 19-year-old woman[1] was attributed to griseofulvin that she had taken for 6 days; she had also taken metronidazole for 1 day. There are also reports[2,3] of erythema multiforme in 4 patients occurring within 10 days of starting griseofulvin. The precipitation or aggravation of systemic lupus erythematosus is a known complication of griseofulvin. Most cases are said to be characterised by prominent skin manifestations and absence of renal disease although the nephrotic syndrome has been described[4] in a 16-year-old male after 2 single doses of griseofulvin taken 3 weeks apart.

1. Mion G, *et al.* Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii:** 1331.
2. Rustin MHA, *et al.* Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120:** 455–8.
3. Thami GP, *et al.* Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203:** 84–5.
4. Bonilla-Felix M, *et al.* Nephrotic syndrome related to systemic lupus erythematosus after griseofulvin therapy. *Pediatr Nephrol* 1995; **9:** 478–9.

Hypersensitivity. A serum sickness-like reaction has been reported in a 5-year-old child being treated for tinea capitis with griseofulvin.[1] About 3 weeks after starting treatment the child developed fever, rash on his legs and back, swelling of his toes and fingers, and leg pain. Symptoms resolved after griseofulvin was stopped.

1. Colton RL, *et al.* Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother* 2004; **38:** 609–11.

Precautions

Griseofulvin is contra-indicated in patients with severe liver disease or systemic lupus erythematosus.

Griseofulvin is embryotoxic and teratogenic in *rats* and there have been isolated cases of conjoined twins after its use during the first trimester of pregnancy. It is therefore contra-indicated in pregnancy and women should not become pregnant during, or within 1 month of stopping therapy. Griseofulvin may reduce the effectiveness of oral contraceptives and additional contraceptive precautions should be used during treatment. Data from *in-vitro* and *in-vivo* studies using mammalian cells, which showed aneuploidy, have led to the warning that men taking griseofulvin should not father children within 6 months of treatment.

The symbol † denotes a preparation no longer actively marketed

Griseofulvin may impair the ability to drive or operate machinery, and has been reported to enhance the effects of alcohol.

Porphyria. Griseofulvin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Phenobarbital has been reported to decrease the gastrointestinal absorption of griseofulvin. Plasma concentrations of griseofulvin have also been reported to be reduced by drugs that induce metabolising enzymes.

Griseofulvin may increase the rate of metabolism and diminish the effects of some drugs such as coumarin anticoagulants and oral contraceptives.

Griseofulvin may enhance the effects of alcohol.

Alcohol. In addition to reports of griseofulvin enhancing the effects of alcohol, a severe disulfiram-like reaction to alcohol has been reported in a patient taking griseofulvin.[1]

1. Fett DL, Vukov LF. An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; **24:** 95–7.

Bromocriptine. For a report that griseofulvin can block the response to bromocriptine, see p.800.

Salicylates. Griseofulvin has been reported to reduce plasma concentrations of salicylate in a patient taking aspirin, see p.23.

Antimicrobial Action

Griseofulvin is a fungistatic antibiotic that inhibits fungal cell division by disruption of the mitotic spindle structure. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton*, *Microsporum*, or *Trichophyton*.

Pharmacokinetics

Absorption of griseofulvin from the gastrointestinal tract is variable and incomplete, but is enhanced by reducing the particle size or when given with a fatty meal. Peak plasma concentrations are reached within 4 hours and are maintained for 10 to 20 hours.

Griseofulvin is about 84% bound to plasma proteins. It is deposited in keratin precursor cells and is concentrated in the stratum corneum of the skin and in the nails and hair, thus preventing fungal invasion of newly formed cells. Concentrations of 12 to 25 micrograms/g are maintained in skin during long-term use, while plasma concentrations remain at about 1 to 2 micrograms/mL. Griseofulvin has an elimination half-life of 9 to 24 hours, and is metabolised by the liver mainly to 6-demethylgriseofulvin and its glucuronide conjugate which are excreted in the urine. A large amount of a dose of griseofulvin of reduced particle size appears unchanged in the faeces; less than 1% is excreted unchanged in the urine; some is excreted in the sweat.

Uses and Administration

Griseofulvin is an antifungal used orally in the treatment of dermatophyte infections. It is generally given when such infections involve the scalp, hair, nails, and skin and do not respond to topical treatment (see Skin Infections, p.521); infections of the soles of the feet, the palms of the hands, and the nails respond slowly.

The usual dose of griseofulvin has been 0.5 to 1 g daily in single or divided doses; children have been given 10 mg/kg daily. These doses are for preparations of griseofulvin of reduced particle size, sometimes known as microcrystalline or microsize griseofulvin. Doses have been reduced by about one-quarter when preparations, available in some countries, containing ultramicrocrystalline or ultramicrosize griseofulvin are used. Griseofulvin should be given with or after meals.

The duration of treatment depends on the thickness of the keratin layer: 2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails.

Griseofulvin is also used as a 1% topical spray in tinea pedis.

◊ Reviews.

1. Fleece D, *et al.* Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114:** 1312–15.
2. Gupta AK, *et al.* Meta-analysis: griseofulvin efficacy in the treatment of tinea capitis. *J Drugs Dermatol* 2008; **7:** 369–72.

Non-infective skin disorders. Lichen planus is usually treated with corticosteroids or retinoids (see p.1580) but griseofulvin has been suggested as an alternative to topical corticosteroids in erosive disease.[1] However, some researchers have found it to be of no value.[2]

Dramatic responses of pigmented purpuric dermatoses to griseofulvin 500 to 750 mg daily have been reported in 5 patients.[3]

1. Lamey P-J, Lewis MAO. Oral medicine in practice: white patches. *Br Dent J* 1990; **168:** 147–52.
2. Bagan JV, *et al.* Treatment of lichen planus with griseofulvin. *Oral Surg Oral Med Oral Pathol* 1985; **60:** 608–10.
3. Tamaki K, *et al.* Successful treatment of pigmented purpuric dermatosis with griseofulvin. *Br J Dermatol* 1995; **132:** 159–60.

Preparations

BP 2008: Griseofulvin Tablets;
USP 31: Griseofulvin Capsules; Griseofulvin Oral Suspension; Griseofulvin Tablets; Ultramicrosize Griseofulvin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Grisovin; ***Austral.:*** Griseostatin†; Grisovin; ***Austria:*** Griseomed†; Grisovin; ***Braz.:*** Fulcin; Sporostatin; ***Canad.:*** Fulvicin†; ***Chile:*** Fulvistatin P/G†; ***Fr.:*** Grisefuline; ***Ger.:*** Fulcin S†; Gricin; Griseo; Likuden M; ***India:*** Grisactin; Walavin; ***Indon.:*** Fulcin; Fungistop; Griseofort; Mycostop; ***Irl.:*** Fulcin†; ***Israel:*** Grifulin; ***Ital.:*** Fulcin; Grisovina FP; ***Malaysia:*** Grisuvin; Grivin; Krisovin; Medofulvin†; Myconil†; ***Mex.:*** Fulcin; Fulsivin; Fulvina†; Grisovin; ***Philipp.:*** Grisovin; ***Port.:*** Fulcin†; Grisomicon†; Grisovin; ***S.Afr.:*** Microcidal; ***Singapore:*** Grivin†; Krisovin; Medofulvin†; ***Spain:*** Fulcin; Greosin†; ***Switz.:*** Grisol†; ***Thai.:*** Aofen; Grifulvin; Grisflavin; Grivin; Neofulvin; Trivanex; ***Turk.:*** Gefulvin; Grisovin; ***UK:*** Grisol; Grisovin†; ***USA:*** Gris-PEG; ***Venez.:*** Fulvin†; Grisovin.

Multi-ingredient: ***Arg.:*** Griseoplus.

Isoconazole *(BAN, USAN, rINN)*

Isoconazol; Isoconazolum; Isokonatsoli; Isokonazol; Izokonazol; Izokonazolas. 1-[2,4-Dichloro-β-(2,6-dichlorobenzyloxy)phenethyl]imidazole.

Изоконазол

$C_{18}H_{14}Cl_4N_2O$ = 416.1.

CAS — 27523-40-6.

ATC — D01AC05; G01AF07.

ATC Vet — QD01AC05; QG01AF07.

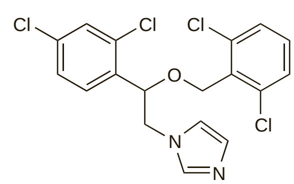

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Isoconazole). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Protect from light.

Isoconazole Nitrate *(BANM, rINNM)*

Isoconazole, bitrate d'; Isoconazole, Nitrate d'; Isoconazoli nitras; Isokonatsolinitraatti; Isokonazolnitrat; Isokonazol-nitrát; Izokonazol Nitrat; Izokonazol-nitrát; Izokonazolo nitratas; Nitrato de isoconazol; R-15454.

Изоконазола Нитрат

$C_{18}H_{14}Cl_4N_2O,HNO_3$ = 479.1.

CAS — 24168-96-5 (isoconazole mononitrate); 40036-10-0 (isoconazole nitrate).

ATC — D01AC05; G01AF07.

ATC Vet — QD01AC05; QG01AF07.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Isoconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Local reactions including burning or itching may occur after application of isoconazole.

Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Antimicrobial Action

Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including *Candida* spp., dermatophytes, and *Malassezia furfur*. It is also active against some Gram-positive bacteria.

Uses and Administration

Isoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vaginal mycoses, particularly due to *Candida* spp. (p.518) and in fungal skin infections (p.521). For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 1% or 2% cream or other topical formulation has been used.

Preparations

BP 2008: Isoconazole Pessaries.

Proprietary Preparations (details are given in Part 3)
Arg.: Isomicot; Mupaten; ***Austria:*** Gyno-Travogen; Travogen; ***Belg.:*** Travogen; ***Braz.:*** Gino Monipax†; Gino-Isomax; Ginotrax; Gyno Icaden; Gyno-Mycel†; Gynoplus†; Icaden; Isomax; Micaden; Mycel Gyno; Neo Isocaden; ***Chile:*** Ufarin; ***Fr.:*** Fazol; Fazol G; ***Ger.:*** Travogen†; ***Gr.:*** Travogen; ***Hong Kong:*** Gyno-Travogen†; Travogen; ***Israel:*** Isogen; ***Ital.:*** Isogyn; Travogen; ***Malaysia:*** Travogen; ***Mex.:*** Icaden; Nocazin; ***Philipp.:*** Travogen; ***Pol.:*** Gyno-Travogen; Travogen; ***Port.:*** Gino-Travogen; ***Rus.:*** Gyno-Travogen (Гино-травоген); Travogen (Травоген); ***Singapore:*** Gyno-Travogen; Travogen; ***Switz.:*** Gyno-Travogen; Travogen; ***Thai.:*** Nacozil†; Travogen; ***Turk.:*** Gyno-Travogen; Travogen; ***Venez.:*** Icaden; Noginox.

Multi-ingredient: ***Arg.:*** Scheriderm; ***Austria:*** Travocort; ***Belg.:*** Travocort; ***Ger.:*** Bi-Vaspit†; Travocort; ***Gr.:*** Travocort; ***Hong Kong:*** Travocort; ***Indon.:*** Travocort; ***Irl.:*** Travocort; ***Israel:*** Isocort; Tevaderm; ***Ital.:*** Travocort; ***Malaysia:*** Isoradin; Travocort; ***Mex.:*** Scheriderm; ***Philipp.:*** Travocort; ***Pol.:*** Travocort; ***Port.:*** Travocort; ***Rus.:*** Travocort (Травокорт); ***S.Afr.:*** Travocort; ***Singapore:*** Travocort; ***Switz.:*** Travocort; ***Thai.:*** Travocort; ***Turk.:*** Travazol; Travocort.

Itraconazole *(BAN, USAN, rINN)*

Itraconazol; Itraconazolum; Itrakonatsoli; Itrakonazol; Itrakonazolas; Oriconazole; R-51211. (±)-2-*sec*-Butyl-4-[4-(4-{4-[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}-piperazin-1-yl)phenyl]-2,4-dihydro-1,2,4-triazol-3-one.

Итраконазол

$C_{35}H_{38}Cl_2N_8O_4$ = 705.6.

CAS — 84625-61-6.

ATC — J02AC02.

ATC Vet — QJ02AC02.

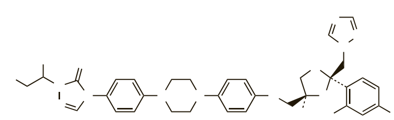

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Itraconazole). A white or almost white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane; sparingly soluble in tetrahydrofuran. Protect from light.

Adverse Effects

The most common adverse effects associated with itraconazole include dyspepsia, abdominal pain, nausea, vomiting, constipation, diarrhoea, headache, and dizziness. Others include allergic reactions such as pruritus, rash, urticaria, and angioedema. Isolated cases of the Stevens-Johnson syndrome have been associated with itraconazole.

An increase in liver enzyme values has occurred in some patients and cases of hepatitis and cholestatic jaundice have been observed, especially in those treated for more than one month. There have been rare cases of liver failure and death.

Heart failure and pulmonary oedema have been reported rarely and serious cardiovascular events including arrhythmias and sudden death have been attributed to drug interactions in patients receiving itraconazole (see Interactions, below).

Alopecia, oedema, and hypokalaemia have also been associated with prolonged use. Menstrual disorders and peripheral neuropathy have been reported in a few patients.

Incidence of adverse effects. Itraconazole 50 to 400 mg daily for a median of 5 months was considered to be well tolerated in 189 patients with systemic fungal infections.[1] Of 86 patients with underlying disease, including 49 with AIDS, 16 with diabetes, and 23 with malignancy, nausea and vomiting occurred in 19 patients, hypertriglyceridaemia in 16, hypokalaemia in 11, and elevated liver enzyme values in 13. The role of itraconazole in hypertriglyceridaemia could not be assessed because all the samples were not drawn in the fasting state and hypertriglyceridaemia is a complication of HIV infection. Gynaecomastia occurred in 2 patients, 1 of whom also took spironolactone. Rash occurred in 4 patients.

Of 49 patients taking itraconazole 100 to 400 mg daily for up to 39 months, 23 did not experience adverse effects during treatment,[2] while 6 had nausea and vomiting, 5 developed oedema, and 2 developed hypertension; 3 of the patients who developed oedema and 1 who became hypertensive were diabetic. Three patients stopped itraconazole, 1 due to vomiting, 1 to leucopenia, and 1 to nephrotic syndrome. The patient with nephrotic syndrome had pre-existing oedema and hypertension; the syndrome cleared when itraconazole was stopped.

1. Tucker RM, *et al.* Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990; **26:** 561–6.
2. Graybill JR, *et al.* Itraconazole treatment of coccidioidomycosis. *Am J Med* 1990; **89:** 282–90.

Effects on the heart. Between September 1992, when itraconazole was approved in the USA, and April 2001, the FDA had received 58 reports of potential cases of heart failure associated with itraconazole.[1] There had been 28 patients admitted to hospital, and 13 had died. However, a causal relationship was difficult to prove. Overall, 43 patients had risk factors or diseases which might confound an association between the use of itraconazole and development of heart failure. Unpublished studies in *dogs* and humans had suggested a negative inotropic effect with intravenous itraconazole.

In August 2001, the UK CSM published a similar alert.[2] By this time, about 67 million patients worldwide had received itraconazole and there had been 75 spontaneously reported cases of suspected heart failure and an additional 63 reports of oedema suggestive of heart failure associated with oral formulations; there had been only 1 report of suspected heart failure in the UK. The CSM considered that the risk of heart failure with itraconazole was low, especially in young healthy patients receiving short courses of treatment (e.g. for vulvovaginal candidiasis). However, the risks appeared to be higher for older patients, patients with pre-existing heart disease or risk factors for heart failure, and for those receiving high doses and longer treatment courses (e.g. for onychomycosis).

The CSM[2] therefore advised caution when prescribing itraconazole to patients at risk of heart failure, whereas the FDA[1] contra-indicated it for the treatment of onychomycosis in patients with evidence of ventricular dysfunction.

1. Ahmad SR, *et al.* Congestive heart failure associated with itraconazole. *Lancet* 2001; **357:** 1766–7.
2. Committee on Safety of Medicines. Cardiodepressant effect of itraconazole (Sporanox). *Current Problems* 2001; **27:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 04/06/06)

Precautions

Itraconazole has caused abnormalities in fetal development in *rodents* and is therefore contra-indicated in pregnancy. For further information, see Pregnancy, under Precautions of Fluconazole, p.532.

Itraconazole should be avoided in patients with hepatic impairment. Liver function should be monitored if treatment lasts more than one month or if there are symptoms suggestive of hepatitis. Treatment should be stopped if abnormal liver function is detected. Plasma-itraconazole concentrations should be monitored in patients with active liver disease and the dosage adjusted if necessary.

Dose adjustments may also be required in some patients with renal impairment. Licensed product information warns that the use of intravenous preparations of itraconazole formulated with hydroxypropylbetadex is contra-indicated in patients with a creatinine clearance of less than 30 mL/minute.

Itraconazole should be stopped if neuropathy develops.

Itraconazole should not be used for the treatment of less severe fungal infections such as onychomycosis in patients with evidence of, or a history of, ventricular dysfunction such as heart failure.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of itraconazole. In this case absorption may be improved by giving itraconazole with an acidic drink, such as a cola beverage.

Breast feeding. Breast feeding while receiving itraconazole is not recommended by the manufacturer although only small amounts of itraconazole are distributed into breast milk.

Interactions

Enzyme-inducing drugs such as carbamazepine, isoniazid, nevirapine, phenobarbital, phenytoin, rifabutin, or rifampicin may *decrease* plasma concentrations of itraconazole sufficiently to reduce its effectiveness. Conversely, enzyme inhibitors such as clarithromycin, erythromycin, HIV-protease inhibitors, including ritonavir-boosted HIV-protease inhibitors, may *increase* plasma concentrations of itraconazole. Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, proton pump inhibitors, and histamine H_2-receptor antagonists, may reduce the absorption of itraconazole. Like other triazole antifungals, itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, and may increase plasma concentrations of other drugs reliant upon it for their metabolism. This increases the risk of adverse effects and such combinations should be given with caution and careful monitoring, if at all. Drugs so affected may include:

- *antiarrhythmics* such as dofetilide and quinidine
- *antiepileptics* such as carbamazepine (which in turn decreases the concentration of the antifungal, see above)
- *antihistamines* such as astemizole and terfenadine
- the *antimycobacterial* rifabutin (which again also decreases antifungal concentrations)
- *antineoplastics* such as busulfan, docetaxel, and the vinca alkaloids
- *antipsychotics* such as pimozide and sertindole
- *anxiolytics and sedatives* such as buspirone
- *benzodiazepines* such as alprazolam, diazepam, midazolam, and triazolam
- *calcium channel blockers* such as verapamil, and the dihydropyridines felodipine, nifedipine, and nisoldipine (see also below)
- *cardiac glycosides* such as digoxin
- some *corticosteroids* such as budesonide, dexamethasone, fluticasone and methylprednisolone
- the *coumarin anticoagulant* warfarin
- *ergot alkaloids* such as dihydroergotamine, ergometrine, ergotamine, and methylergometrine
- the *gastrointestinal prokinetic* cisapride
- *HIV-protease inhibitors* such as indinavir, ritonavir, and saquinavir (concentrations of the antifungal may be increased in turn by indinavir, ritonavir, or co-formulated lopinavir-ritonavir, but not by saquinavir)
- *immunosuppressants* such as ciclosporin, sirolimus, and tacrolimus
- *opioids* such as alfentanil and levacetylmethadol
- some *oral hypoglycaemics*
- the *phosphodiesterase inhibitors* sildenafil and vardenafil
- *statins* (HMG Co-A reductase inhibitors) such as atorvastatin, lovastatin, and simvastatin

Where drugs metabolised via CYP3A4 also prolong the QT interval, the risk of serious cardiovascular effects such as torsade de pointes means that the combination should be avoided; this includes astemizole, cisapride, dofetilide, levacetylmethadol, pimozide, quinidine, sertindole, and terfenadine. Care is also required with calcium channel blockers, which may increase the risk of congestive heart failure if given together, and nisoldipine in particular is considered contra-indicated. Use with the statins is also best avoided because of the risk of muscle damage.

◊ Reviews of drug interactions with azole antifungals.

1. Baciewicz AM, Baciewicz FA. Ketoconazole and fluconazole drug interactions. *Arch Intern Med* 1993; **153:** 1970–6.
2. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. *Ann Pharmacother* 1998; **32:** 915–28.
3. Venkatakrishnan K, *et al.* Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38:** 111–80.

Immunosuppressants. Fatal hepatitis occurred in a 68-year-old woman[1] after 2 months of use of itraconazole and *leflunomide*. The authors suggested that the combined hepatotoxicity of both drugs might have accounted for this.

1. Legras A, *et al.* Fatal hepatitis with leflunomide and itraconazole. *Am J Med* 2002; **113:** 352–3.

Metal ions. Didanosine in a formulation containing aluminium and magnesium ion buffering agents could reduce the absorption of itraconazole due to the resultant increase in gastric pH.[1]

1. Moreno F, *et al.* Itraconazole-didanosine excipient interaction. *JAMA* 1993; **269:** 1508.

Antimicrobial Action

Itraconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. It has a slightly wider spectrum of activity than ketoconazole. It is active against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Malassezia furfur*, *Microsporum* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, and *Trichophyton* spp. Itraconazole also has some antiprotozoal activity against *Leishmania* spp.

Acquired resistance to itraconazole is rare but ketoconazole-resistant strains of *Candida albicans* have been found to be cross resistant to itraconazole.

Microbiological interactions. Synergistic antifungal effects were seen *in vitro* with terbinafine and itraconazole against strains of *Candida albicans*[1] and *Scedosporium prolificans*.[2] For effects on the antifungal activity of azoles when given with amphotericin B, see p.525.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44:** 470–2.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles, see under Antimicrobial Action of Fluconazole, p.533. Decreased susceptibility to itraconazole and cross-resistance to fluconazole has been reported in *C. albicans* isolated from patients with AIDS given long-term prophylaxis with itraconazole.[1] *Aspergillus fumigatus* resistant to itraconazole has also been seen.[2,3]

1. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; **44:** 1585–7.
2. Denning DW, *et al.* Itraconazole resistance in Aspergillus fumigatus. *Antimicrob Agents Chemother* 1997; **41:** 1364–8.
3. Dannaoui E, *et al.* Acquired itraconazole resistance in Aspergillus fumigatus. *J Antimicrob Chemother* 2001; **47:** 333–340.

Pharmacokinetics

Itraconazole is absorbed from the gastrointestinal tract when given orally either as capsules containing itraconazole coated onto sugar spheres or as an oral liquid formulated with hydroxypropylbetadex. Absorption from the capsule formulation is enhanced by an acidic gastric environment and is greatest when doses are taken with food; absorption from the oral liquid is not dependent on an acid environment, and absorption is greatest in the fasting state. Peak plasma concentrations are achieved between 1.5 and 5 hours after a dose of either formulation, and steady state is reached within 15 days during daily dosing. Peak plasma concentrations at steady state of about 2 micrograms/mL have been reported after daily doses of 200 mg.

Bioavailability increases with doses of 100 to 400 mg in such a manner as to suggest that itraconazole undergoes saturable metabolism. Itraconazole is highly protein bound; only 0.2% circulates as free drug. Itraconazole is widely distributed but only small amounts diffuse into the CSF. Concentrations attained in the skin, sebum, pus, and many organs and tissues are several times higher than simultaneous plasma concentrations. Therapeutic concentrations of itraconazole remain in the skin and mucous membranes for 1 to 4 weeks after the drug is stopped. Small amounts are distributed into breast milk.

Itraconazole is metabolised in the liver mainly by cytochrome P450 isoenzyme CYP3A4. The major metabolite, hydroxyitraconazole, has antifungal activity comparable with that of itraconazole. Itraconazole is also excreted as inactive metabolites in the bile or urine; 3 to 18% is excreted in the faeces as unchanged drug. Small amounts are eliminated in the stratum corneum and hair. Itraconazole is not removed by dialysis.

The elimination half-life following a single 100-mg dose has been reported as 20 hours, increasing to 30 to 40 hours with continued use.

Uses and Administration

Itraconazole is a triazole antifungal given orally for the treatment of oropharyngeal and vulvovaginal candidiasis, for pityriasis versicolor, for dermatophytoses unresponsive to topical treatment, for onychomycosis, and for systemic infections including aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis. It is also given for the prophylaxis of fungal infections in immunocompromised patients. The place of itraconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

Doses of itraconazole oral liquid and capsules are not equivalent and may not be used interchangeably.

In the UK, itraconazole **oral liquid** is licensed for use in oral and oesophageal candidiasis in a dose of 200 mg daily for 1 week; it may be taken as a single daily dose, or, preferably, in 2 divided doses, the liquid being retained in the mouth for 20 seconds before swallowing. If there is no response after a week, treatment may be continued for a further week. In the USA, a similar regimen is licensed for oropharyngeal candidiasis, but in oesophageal candidiasis an alternative regimen of 100 mg daily for at least 3 weeks is preferred, although the dose may be increased to 200 mg daily if necessary.

For patients with fluconazole-resistant infections the dose in the UK is 100 to 200 mg twice daily for 2 weeks; if there is no response, 100 mg twice daily may be given for a further 2 weeks. In the USA the recommended dose is 100 mg twice daily.

Itraconazole oral liquid is also licensed in the UK for prophylaxis of susceptible fungal infections in immunocompromised patients, in doses of 5 mg/kg daily, in 2 divided doses.

The following oral doses all apply to itraconazole **capsules**. The dose in oropharyngeal candidiasis is 100 mg (or 200 mg in patients with AIDS or neutropenia) daily for 15 days. Vulvovaginal candidiasis may be treated with itraconazole 200 mg twice daily for 1 day. Pityriasis versicolor may be treated with itraconazole 200 mg daily for 7 days. For dermatophytoses the dose is 100 mg daily for 15 days or 200 mg daily for 7 days in tinea corporis or tinea cruris; doses are 100 mg daily for 30 days or 200 mg twice daily for 7 days in tinea pedis or tinea manuum. For nail infections the dose is 200 mg daily for 3 months or pulse therapy with 200 mg twice daily for 7 days repeated once (for fingernails) or twice (for toenails) after drug-free intervals of 21 days.

For systemic infections, itraconazole capsules are given in usual doses of 100 to 200 mg once daily, increased to 200 mg twice daily for invasive or disseminated infections, including cryptococcal meningitis. In life-threatening infections a loading dose of 200 mg three times daily for 3 days has been given. A dose of 200 mg daily is used for primary or secondary prophylaxis in neutropenic patients or those with AIDS. Absorption may be impaired in these patients and monitoring of plasma concentrations is advised with an increase in dose to 200 mg twice daily if necessary. This higher dose is recommended routinely by some authorities in the USA such as the *Centers for Disease Control and Prevention*.

Itraconazole may also be given by **intravenous infusion** in a dose of 200 mg given twice daily over 1 hour for two days, then 200 mg daily thereafter.

◊ Reviews.

1. Haria M, *et al.* Itraconazole: a reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* 1996; **51:** 585–620.
2. Pierard GE, *et al.* Itraconazole. *Expert Opin Pharmacother* 2000; **1:** 287–304.
3. Stevens DA (ed). Managing fungal infections in the 21st century: focus on itraconazole. *Drugs* 2001; **61** (suppl 1): 1–56.
4. Slain D, *et al.* Intravenous itraconazole. *Ann Pharmacother* 2001; **35:** 720–9.
5. Boogaerts M, Maertens J. Clinical experience with itraconazole in systemic fungal infections. *Drugs* 2001; **61** (suppl 1): 39–47.
6. Maertens J, Boogaerts M. The place for itraconazole in treatment. *J Antimicrob Chemother* 2005; **56** (suppl 1): i33–i38.
7. Potter M. Strategies for managing systemic fungal infection and the place of itraconazole. *J Antimicrob Chemother* 2005; **56** (suppl 1): i49–i54.

Administration. ***HIGH DOSES.*** Doses of itraconazole 600 mg daily in two divided doses for 3 to 16 months were used in 8 patients with systemic mycoses resistant to conventional therapy.[1] Two patients with AIDS and cryptococcal meningitis failed to respond and 2 who responded initially later relapsed or developed progressive disease when the dose was reduced. The main adverse effects were hypokalaemia, hypertension, and oedema possibly associated with adrenal suppression.

In a patient with cerebral aspergillosis, itraconazole 800 mg daily for 5 months then 400 mg daily for a further 4 ⁄ months produced complete resolution of cerebral lesions.[2]

1. Sharkey PK, *et al.* High-dose itraconazole in the treatment of severe mycoses. *Antimicrob Agents Chemother* 1991; **35:** 707–13.
2. Sánchez C, *et al.* Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; **21:** 1485–7.

Administration in children and neonates. Itraconazole has been used in children in the treatment of tinea capitis.[1] Doses were 50 mg daily by mouth for those below 20 kg and 100 mg daily for those weighing 20 kg or more.

A review of the use of itraconazole in children[2] considered oral itraconazole to be safe and effective against most fungal organisms causing superficial infections.

Itraconazole was given to 2 premature infants with disseminated candidiasis in a dose of 10 mg/kg daily in two divided doses for 3 or 4 weeks without adverse effects.[3] Treatment was successful in both infants.

Although itraconazole oral liquid is not licensed for use in children in the UK, and the capsules are only licensed from 12 years of age, the *BNFC* suggests the following daily ***oral*** doses, given as a single dose (unless otherwise specified):

for **oropharyngeal candidiasis**:

- 1 month to 12 years of age, 3 to 5 mg/kg (to a maximum of 100 mg) daily for 15 days; up to 200 mg daily may be given to patients with neutropenia or AIDS
- 12 to 18 years of age, 100 mg (200 mg in those with neutropenia or AIDS) daily for 15 days

for **dermatophyte infections**:

- 1 month to 12 years of age, 3 to 5 mg/kg daily; this is given to a maximum of 200 mg daily for 7 days (pityriasis versicolor), to a maximum of 100 mg daily for 15 days (tinea corporis and tinea cruris), or to a maximum of 100 mg daily for 30 days (tinea pedis and tinea manuum)
- 12 to 18 years of age, 200 mg daily for 7 days (pityriasis versicolor); 100 mg daily for 15 days or as in pityriasis (tinea corporis and tinea cruris); or 100 mg daily for 30 days or 200 mg *twice* daily for 7 days (tinea pedis and tinea manuum)

for **onychomycosis**, from 1 year of age:

- 1 to 12 years, courses of 5 mg/kg daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections
- 12 to 18 years, either 200 mg daily for 3 months, or courses of 200 mg *twice* daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections

for **histoplasmosis** or for **systemic fungal infections** such as aspergillosis, candidiasis, and cryptococcosis (including cryptococcal meningitis) where other antifungal drugs are inappropriate or ineffective:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) once or twice daily; the *twice* daily dose should be used in invasive or disseminated disease or cryptococcal meningitis. For intravenous doses see below

for **maintenance in AIDS patients** to prevent relapse of underlying fungal infection, or for **prophylaxis in neutropenia** when standard therapy is inappropriate:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) daily, increased to *twice* daily if plasma-itraconazole concentrations are low

for **prophylaxis in haematological malignancy or bone-marrow transplantation** (in patients expected to become neutropenic), where standard therapy is inappropriate the *oral liquid* may be given as follows:

- from 1 month of age to 18 years, 2.5 mg/kg *twice* daily, starting before transplantation or chemotherapy and continued until the neutrophil count recovers

Like the oral liquid the intravenous product is not licensed in children in the UK; the *BNFC* suggests the following ***intravenous*** doses by infusion in children with **systemic fungal infections**:

- from 1 month of age to 18 years, 2.5 mg/kg (to a maximum of 200 mg) every 12 hours for 2 days, then the same dose once daily for a maximum of 12 days. Doses should be given by diluting 250 mg as the intravenous concentrate in 50 mL of sodium chloride 0.9% and infusing over 60 minutes

1. Möhrenschlager M, *et al*. Optimizing the therapeutic approach in tinea capitis of childhood with itraconazole. *Br J Dermatol* 2000; **143:** 1011–15.
2. Gupta AK, *et al.* Efficacy and safety of itraconazole use in children. *Dermatol Clin* 2003; **21:** 521–35.
3. Bhandari V, Narang A. Oral itraconazole therapy for disseminated candidiasis in low birth weight infants. *J Pediatr* 1992; **120:** 330.

Amoebic infections. Itraconazole has been suggested for *Acanthamoeba* keratitis (p.822), when it is given orally with topical miconazole.

Leishmaniasis. When systemic therapy is required for the treatment of leishmaniasis (p.824), pentavalent antimonials are most commonly used. The successful use of itraconazole has been reported in a few patients[1-4] with cutaneous disease but infections with *Leishmania aethiopica* may not respond.[5] Although a pilot study[6] in patients with mucocutaneous leishmaniasis reported benefit with itraconazole this was not confirmed in another study[7] where the response was only transient in the majority of patients. Similarly, itraconazole with terbinafine has been found to be ineffective in post kala-azar dermal leishmaniasis.[8]

1. Albanese G, *et al.* Cutaneous leishmaniasis: treatment with itraconazole. *Arch Dermatol* 1989; **125:** 1540–2.
2. Pialoux G, *et al.* Cutaneous leishmaniasis in an AIDS patient: cure with itraconazole. *J Infect Dis* 1990; **162:** 1221–2.
3. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol* 1996; **26:** 1413–15.
4. Consigli J, *et al.* Cutaneous leishmaniasis: successful treatment with itraconazole. *Int J Dermatol* 2006; **45:** 46–9.
5. Akuffo H, *et al.* The use of itraconazole in the treatment of leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1990; **84:** 532–4.
6. Amato VS, *et al.* Use of itraconazole in the treatment of mucocutaneous leishmaniasis: a pilot study. *Int J Infect Dis* 2000; **4:** 153–7.
7. Calvopina M, *et al.* Itraconazole in the treatment of New World mucocutaneous leishmaniasis. *Int J Dermatol* 2004; **43:** 659–63.
8. Khalil EAG, *et al.* Failure of a combination of two antifungal drugs, terbinafine plus itraconazole, in Sudanese post kala-azar dermal leishmaniasis. *Trans R Soc Trop Med Hyg* 1996; **90:** 187–8.

Trypanosomiasis. Itraconazole, alone or with allopurinol, may produce beneficial responses in American trypanosomiasis (p.827).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: ITC†; Itrac; Micotenk; Nitridazol; Panastat; Salimidin; Sporanox; ***Austral.:*** Sporanox; ***Austria:*** Itrabene; Sporanox; ***Belg.:*** Sporanox; ***Braz.:*** Estiranox; Fungonax; Itracotan; Itrahexal†; Itranax†; Itraspor; Itrazol; Neo Itrax; Sporanox; Spozol; Tracnox†; Traconal; Traconax†; Tracozon; Tranazol†; Tratzol; Traxonol†; ***Canad.:*** Sporanox; ***Chile:*** Itodal; Sporanox; Teramic; ***Cz.:*** Cladostad; Prokanazol; Sporanox; ***Denm.:*** Niddazol; Sporanox; ***Fin.:*** Sporanox; ***Fr.:*** Sporanox; ***Ger.:*** Canifug Itra; Itracol; Sempera; Siros; ***Gr.:*** Assosept-S; Bevonazole; Brovicton; Deratil; Etrel; Flunol; Idranox; Isoflon; Itrabest; Itracon; Itraconal; Itralfa; Itraviron; Itrazol; Laverio; Lorenzol; Mesmor; Micronazol; Prominox; Soprazon; Sporanox; Sporizole; Stas; Sterginox; Zetilox; ***Hong Kong:*** Aranox; Quali-itrazole; Sporanox; ***Hung.:*** Cladostad; Omicral; Orungal; ***India:*** Candistat; Canditral; Itracan; ***Indon.:*** Forcanox; Fungitrazol; Furolnok; Itzol; Nufatrac; Sporacid; Sporanox; Spyrocon; Trachon; Unitrac; Zitrazol; ***Irl.:*** Sporanox; ***Israel:*** Itranol; Sporanox; ***Ital.:*** Sporanox; Trazer; Triasporin; ***Jpn:*** Itrizole; ***Malaysia:*** Canditral; Inox; Sporanox; Unitrac; ***Mex.:*** Carexan; Conamed; Congox; Derusil; Ergospharma; Fitocyd; Fulzoltec†; Fuzoltec; Imazol; Iqcona; Isoporum; Isox; Itranax; Lozartil; Rixtal; Seritral; Silicsan; Sinozol; Solmavin; Sporanox; Steitraz; Trax; Z-Fin; Zolken; ***Neth.:*** Trisporal; ***Norw.:*** Sporanox; ***NZ:*** Sporanox; ***Philipp.:*** Sporanox; ***Pol.:*** Orungal; Trioxal; ***Port.:*** Sporanox; ***Rus.:*** Irunine (Ирунин); Orungal (Орунгал); Orungamin (Орунгамин); Orunit (Орунит); Rumycoz (Румикоз); ***S.Afr.:*** Adco-Sporozole; Sporanox; ***Singapore:*** Canditral†; Sporanox; ***Spain:*** Canadiol; Hongoseril; Oromic; Sporanox; ***Swed.:*** Sporanox; ***Switz.:*** Sporanox; ***Thai.:*** Canditral; Icona; Itra; Itracon; Norspor; Spazol; Sporal; Sporlab; Spornar; ***Turk.:*** Funit; Itraspor; Sporex; ***UK:*** Sporanox; ***USA:*** Sporanox; ***Venez.:*** Fungosin; Sporanox.

Multi-ingredient: ***Mex.:*** Sepia; Sporasec; ***Venez.:*** Sporasec.

Ketoconazole *(BAN, USAN, rINN)*

Ketoconazol; Kétoconazole; Ketoconazolum; Ketokonatsoli; Ketokonazol; Ketokonazolas; R-41400. (±)-*cis*-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-yl-methoxy]phenyl}piperazine.

Кетоконазол

$C_{26}H_{28}Cl_2N_4O_4$ = 531.4.

CAS — 65277-42-1.

ATC — D01AC08; G01AF11; J02AB02.

ATC Vet — QD01AC08; QG01AF11; QJ02AB02.

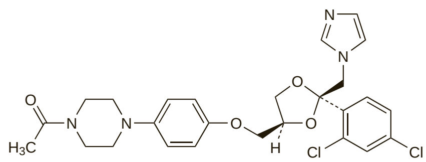

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Ketoconazole). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects

Gastrointestinal disturbances are the most frequently reported adverse effect after the oral use of ketoconazole. Nausea and vomiting have been reported in about 3% of patients, and abdominal pain in about 1%. These adverse effects are dose-related and may be minimised by giving ketoconazole with food. Asymptomatic, transient elevations in serum concentrations of liver enzymes may occur in about 10% of patients. Hepatitis has been reported and the risk appears to increase if treatment with ketoconazole is continued for longer than 2 weeks; it is usually reversible on stopping ketoconazole but fatalities have occurred. Ketoconazole interferes with steroid biosynthesis and adverse endocrine effects include gynaecomastia, oligospermia, menstrual irregularities, and adrenal cortex suppression, especially at high doses.

Other adverse effects include allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis after the first dose have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur. Thrombocytopenia, paraesthesia, raised intracranial pressure, and photophobia have been reported rarely.

After topical use of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Effects on the blood. A case of fatal aplastic anaemia was reported[1] in a 23-year-old woman who had taken ketoconazole for 4 days for the treatment of vaginal discharge.

1. Duman D, *et al.* Fatal aplastic anemia during treatment with ketoconazole. *Am J Med* 2001; **111:** 737.

Effects on endocrine function. Oral ketoconazole blocks testosterone synthesis and adrenal response to corticotropin, resulting in azospermia and oligospermia, gynaecomastia, impotence and decreased libido, and adrenal insufficiency.[1-8] As an inhibitor of steroid production, ketoconazole is valuable in controlling hypercortisolism and is used therapeutically in some endocrine disorders and prostatic cancer. For further discussion see under Uses and Administration, below.

1. DeFelice R, *et al.* Gynecomastia with ketoconazole. *Antimicrob Agents Chemother* 1981; **19:** 1073–4.
2. Pont A, *et al.* High-dose ketoconazole therapy and adrenal and testicular function in humans. *Arch Intern Med* 1984; **144:** 2150–3.
3. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i:** 44–5.
4. Dandona P, *et al.* Non-suppression of cortisol secretion by long term treatment with ketoconazole in patients with acute leukaemia. *J Clin Pathol* 1985; **38:** 677–8.
5. Pillans PI, *et al.* Hyponatraemia and confusion in a patient taking ketoconazole. *Lancet* 1985; **i:** 821–2.
6. McCance DR, *et al.* Acute hypoadrenalism and hepatotoxicity after treatment with ketoconazole. *Lancet* 1987; **i:** 573.
7. Best TR, *et al.* Persistent adrenal insufficiency secondary to low-dose ketoconazole therapy. *Am J Med* 1987; **82:** 676–80.
8. Khosla S, *et al.* Adrenal crisis in the setting of high-dose ketoconazole therapy. *Arch Intern Med* 1989; **149:** 802–4.

Effects on the liver. Hepatic adverse reactions to oral ketoconazole are well known.[1-4] Transient minor elevations of liver enzymes without clinical signs or symptoms of hepatic disease occur in about 10% of patients and may occur at any stage of treatment. Although this reaction is not usually clinically important it may signal the onset of more serious hepatic injury and indicates the need for close monitoring of liver function. Symptomatic hepatic reactions are much rarer (less than 0.1% of patients) but are potentially fatal. There is usually a hepatocellular pattern of damage and sometimes cholestasis. Patients at increased risk of hepatic injury include those with a history of liver disease, those aged over 50, especially women, and those requiring prolonged treatment. It is important to monitor liver function during treatment as well as to limit the length of treatment. If liver enzyme values continue to rise or jaundice or hepatitis occur, ketoconazole should be withdrawn immediately since fatalities have occurred in patients who continued treatment after signs of hepatic injury developed.

1. Janssen PA, Symoens JE. Hepatic reactions during ketoconazole treatment. *Am J Med* 1983; **74:** 80–5.
2. Lewis JH, *et al.* Hepatic injury associated with ketoconazole therapy. *Gastroenterology* 1984; **86:** 503–13.
3. Lake-Bakaar G, *et al.* Hepatic reactions associated with ketoconazole in the United Kingdom. *BMJ* 1987; **294:** 419–21.
4. García Rodríguez LA, *et al.* A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999; **48:** 847–52.

Precautions

Since ketoconazole has been reported to cause hepatotoxicity it should not be given to patients with pre-existing liver disease. Patients given ketoconazole should be monitored for symptoms of hepatitis; also, liver function tests should be performed before starting oral treatment with ketoconazole lasting for more than 14 days and then at least monthly throughout therapy.

Ketoconazole has been shown to be teratogenic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of ketoconazole. In this case absorption may be improved by giving ketoconazole with an acidic drink, such as a cola beverage.

Breast feeding. Ketoconazole is excreted in breast milk and licensed product information states that oral use should be avoided during breast feeding. However, no adverse effects were seen in a breast-fed infant whose mother was receiving ketoconazole;[1] it was calculated that the infant was exposed to about 0.4% of the usual therapeutic dose of ketoconazole for this age group. The American Academy of Pediatrics considers[2] that use of ketoconazole is therefore usually compatible with breast feeding.

1. Moretti ME, *et al.* Disposition of maternal ketoconazole in breast milk. *Am J Obstet Gynecol* 1995; **173:** 1625–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/06/05)

Porphyria. Ketoconazole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce the absorption of ketoconazole. Absorption of ketoconazole may also be reduced by sucralfate. Enzyme-inducing drugs such as rifampicin, isoniazid, efavirenz, nevirapine, or phenytoin may reduce plasma-ketoconazole concentrations. Concentrations of isoniazid and rifampicin may also be reduced by ketoconazole.

Ketoconazole inhibits certain hepatic oxidase enzymes, especially the cytochrome P450 isoenzyme CYP3A4, in a similar way to itraconazole (p.537) and similar care should be taken to avoid adverse effects due to increased plasma concentrations of the interacting drugs.

A disulfiram-like reaction may occur in patients taking ketoconazole after drinking alcohol. The efficacy of oral contraceptives may be reduced.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Ketoconazole is an imidazole antifungal that interferes with ergosterol synthesis and therefore alters the permeability of the cell membrane of sensitive fungi. It is reported to be fungistatic at concentrations achieved clinically. Ketoconazole has a wide spectrum of antimicrobial activity including activity against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Epidermophyton floccosum*, *Histoplasma capsulatum*, *Malassezia* spp., *Microsporum canis*, *Paracoccidioides brasiliensis*, *Trichophyton mentagrophytes*, and *T. rubrum*. Some strains of *Aspergillus* spp., *Cryptococcus neoformans*, and *Sporothrix schenckii* are sensitive.

Ketoconazole has activity against some Gram-positive bacteria and some antiprotozoal activity against *Leishmania* spp.

There are rare reports of *Candida albicans* acquiring resistance to ketoconazole.

Microbiological interactions. For the effect of imidazoles and amphotericin B on each other's antimicrobial activity, see Amphotericin B, p.525.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles see Fluconazole, Antimicrobial Action, p.533.

Pharmacokinetics

The absorption of ketoconazole from the gastrointestinal tract is variable and increases with decreasing stomach pH. Mean peak plasma concentrations of about 3.5 micrograms/mL have been obtained 2 hours after an oral dose of 200 mg. Systemic absorption after topical or vaginal application in healthy subjects is minimal. Ketoconazole is more than 90% bound to plasma proteins, mainly albumin. It is widely distributed and appears in breast milk. Penetration into the CSF is poor. The elimination of ketoconazole is reported to be biphasic, with an initial half-life of 2 hours and a terminal half-life of about 8 hours.

Ketoconazole is metabolised in the liver to inactive metabolites. It is excreted as metabolites and unchanged drug chiefly in the faeces; some is excreted in the urine.

◊ References.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. *Clin Pharmacokinet* 1988; **14:** 13–34.
2. Lelawongs P, *et al.* Effect of food and gastric acidity on absorption of orally administered ketoconazole. *Clin Pharm* 1988; **7:** 228–35.
3. Lake-Bakaar G, *et al.* Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; **109:** 471–3.
4. Daneshmend TK. Diseases and drugs but not food decrease ketoconazole 'bioavailability'. *Br J Clin Pharmacol* 1990; **29:** 783–4.
5. Hurwitz A, *et al.* Gastric function in the elderly: effects on absorption of ketoconazole. *J Clin Pharmacol* 2003; **43:** 996–1002.

Uses and Administration

Ketoconazole is an imidazole antifungal used topically or orally. It is given orally in chronic mucocutaneous or vaginal candidiasis, in fungal infections of the gastrointestinal tract, in dermatophyte infections of the skin and fingernails not responding to topical treatment, and in systemic infections including blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis. It has been given for the prophylaxis of fungal infections in immunocompromised patients, although fluconazole or itraconazole are usually preferred. It has been recommended that, because of its erratic absorption and slow therapeutic response, ketoconazole should not be used for the treatment of life-threatening fungal infections, including fungal meningitis, or for severe infections in immunocompromised patients. Also, because of the risk of hepatotoxicity the use of ketoconazole in nonsystemic fungal infections tends to be restricted to serious infections resistant to other treatment.

The place of ketoconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

The usual oral dose for treatment and prophylaxis of fungal infections is 200 mg once daily taken with food. This may be increased to 400 mg daily if an adequate response is not obtained; in some infections even higher doses have been used. Children may be given about 3 mg/kg daily, or 50 mg for those aged 1 to 4 years and 100 mg for children aged 5 to 12 years. Treatment should usually be continued for 14 days and for at least one week after symptoms have cleared and cultures have become negative. Some infections may require several months of treatment and giving ketoconazole for such prolonged periods may increase the risk of hepatotoxicity.

A dose of 400 mg once daily for 5 days is used for the treatment of chronic vaginal candidiasis.

Ketoconazole is applied topically as a 2% cream in the treatment of candidal or dermatophyte infections of the skin, or in the treatment of pityriasis versicolor. It is used once or twice daily and continued for at least a few days after the disappearance of symptoms. A foam containing 2% ketoconazole applied twice daily for 4 weeks may be used in the treatment of seborrhoeic dermatitis. A shampoo containing 1 or 2% ketoconazole is also used; it is applied twice weekly for 2 to 4 weeks (or occasionally longer) in the treatment of dandruff or seborrhoeic dermatitis. The 2% shampoo is used once daily for up to 5 days in pityriasis versicolor. For prophylaxis of seborrhoeic dermatitis the 2% shampoo is used once every 1 to 2 weeks; for prophylaxis of pityriasis versicolor it may be used once daily for a maximum of 3 days before exposure to sunshine.

Acanthamoeba infections. Although there is currently no established treatment for granulomatous amoebic encephalitis, ketoconazole may have some activity against the *Acanthamoeba* spp. responsible for this infection and has been applied topically to skin lesions. Ketoconazole has also been suggested for *Acanthamoeba* keratitis (p.822), when it has been given orally with topical miconazole.

Acute respiratory distress syndrome. In two small double-blind, controlled trials,[1,2] the development of acute respiratory distress syndrome (ARDS—p.1498) and mortality rates were lower in high-risk patients given ketoconazole than in those given placebo. An accompanying editorial[3] commented that adequate blood concentrations appeared to be essential. The mode of action could be associated with inhibition of leukotriene and thromboxane synthesis.[2,3] Nevertheless, in a study in 234 patients,[4] ketoconazole failed to reduce mortality or improve clinical outcomes when given early in the course of ARDS. Some centres have developed guidelines for ketoconazole prophylaxis in patients at risk of ARDS.[5]

1. Slotman GJ, *et al.* Ketoconazole prevents acute respiratory failure in critically ill surgical patients. *J Trauma* 1988; **28:** 648–54.
2. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21:** 1635–42.
3. Slotman GJ. Ketoconazole: maybe it isn't the magic potion, but ... *Crit Care Med* 1993; **21:** 1642–4.
4. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283:** 1995–2002.
5. Sinuff T, *et al.* Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14:** 1–6.

Blastomycosis. Ketoconazole has largely been replaced by itraconazole as the azole of choice in the treatment of blastomycosis (p.518) because of its higher incidence of adverse effects, and lower efficacy. If used as an alternative it is given in doses of 400 to 800 mg daily.[1]

1. Chapman SW, *et al.* Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46:** 1801–12. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/588300 (accessed 03/07/08)

Endocrine disorders and malignant neoplasms. Ketoconazole has been reported to impair steroid hormone synthesis[1] and to blunt the response of cortisone to adrenocorticotrophic hormone (ACTH)[2] and has been tried in the management of a number of endocrine disorders.

In **Cushing's syndrome** (p.2344), ketoconazole in doses of up to 1200 mg daily has been used successfully as an alternative or adjuvant to definitive therapies such as surgery or radiotherapy.[3-6]

Treatment of **hirsutism** is usually with an anti-androgen (see under Cyproterone, p.2089), but ketoconazole has been tried in small numbers of women at a dose of 300 mg daily[7] or 400 mg daily,[8,9] with variable results.

Ketoconazole has been reported to produce a beneficial response in some forms of **precocious puberty** (p.2081) that do not generally respond to gonadorelin analogues; cessation of menstruation and regression of pubertal signs in girls[10] and reduced testosterone secretion and increase in adult height in boys[11-13] has been noted in small numbers of patients studied.

The anti-androgenic effects of ketoconazole have also been found useful in the management of **prostatic cancer** (p.671) in selected patients,[14-18] although there have been some concerns about its tolerability,[17] and it is not generally used as a first-line treatment.

Ketoconazole was ineffective in suppressing **postoperative erection** in patients undergoing penile reconstructive surgery.[19]

1. Pont A, *et al.* Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97:** 370–2.
2. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i:** 44–5.
3. Winquist EW, *et al.* Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. *J Clin Oncol* 1995; **13:** 157–64.
4. Estrada J, *et al.* The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* 1997; **336:** 172–7.
5. Berwaerts JJ, *et al.* Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutical use of ketoconazole. *J Am Geriatr Soc* 1998; **46:** 880–4.
6. Chou SC, Lin JD. Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J* 2000; **47:** 401–6.
7. Venturoli S, *et al.* A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *J Clin Endocrinol Metab* 1999; **84:** 1304–10.
8. Sonino N, *et al.* Low-dose ketoconazole treatment in hirsute women. *J Endocrinol Invest* 1990; **13:** 35–40.
9. Venturoli S, *et al.* Ketoconazole therapy for women with acne and/or hirsutism. *J Clin Endocrinol Metab* 1990; **71:** 335–9.
10. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12:** 81–3.
11. Bertelloni S, *et al.* Long-term outcome of male-limited gonadotropin-independent precocious puberty. *Horm Res* 1997; **48:** 235–9.
12. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.
13. Almeida MQ, *et al.* Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. *Clin Endocrinol (Oxf)* 2008; **69:** 93–98.
14. Lowe FC, Bamberger MH. Indications for use of ketoconazole in management of metastatic prostate cancer. *Urology* 1990; **36:** 541–5.
15. Mahler C, *et al.* Ketoconazole and liarozole in the treatment of advanced prostatic cancer. *Cancer* 1993; **71:** 1068–73.
16. Small EJ, *et al.* Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. *J Urol (Baltimore)* 1997; **157:** 1204–7.
17. Bok RA, Small EJ. The treatment of advanced prostate cancer with ketoconazole: safety issues. *Drug Safety* 1999; **20:** 451–8.
18. Pettaway CA, *et al.* Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000; **18:** 1050–7.
19. DeCastro BJ, *et al.* Oral ketoconazole for prevention of postoperative penile erection: a placebo controlled, randomized, double-blind trial. *J Urol (Baltimore)* 2008; **179:** 1930–2.

Hypercalcaemia. Ketoconazole has been used[1,2] in the treatment of hypercalcaemia (p.1668). It acts to reduce 1,25-dihydroxycholecalciferol concentrations by inhibiting cytochrome P450-dependent 1α-hydroxylation of vitamin D.

1. Yavuz H. Familiar drugs for the treatment of hypercalcemia. *J Pediatr* 1998; **133:** 311.
2. Young C, *et al.* Hypercalcaemia in sarcoidosis. *Lancet* 1999; **353:** 374.

Leishmaniasis. As discussed on p.824, ketoconazole has been tried as an alternative to conventional first- and second-line therapy for visceral leishmaniasis,[1,2] although reports of treatment have not all been favourable.[3,4]

It has also been tried in cutaneous leishmaniasis. A cure rate of 70% was reported in over 100 patients with *Leishmania major* infections treated with oral ketoconazole 200 to 400 mg daily for 4 to 6 weeks. Ketoconazole was not considered to be effective in infections due to *L. tropica*, *L. aethiopica*,[5] or *L. guyanensis*.[6] Ketoconazole 600 mg daily for 28 days has produced similar results to sodium stibogluconate intramuscularly for 20 days in patients with cutaneous leishmaniasis due to *L. panamensis*.[7] A further comparative study[8] of 96 patients being treated for cutaneous leishmaniasis, caused mainly by *L. major* or *L. tropica*, found ketoconazole given in doses of 600 mg in adults or 10 mg/kg in children for 30 days to be more effective than 6 to 8 bi-weekly intralesional injections of meglumine antimonate. In another study,[9] ketoconazole was less effective than sodium stibogluconate when cutaneous leishmaniasis was due to *L. braziliensis*, but more effective when *L. mexicana* was the cause.

1. Wali JP, *et al.* Ketoconazole in treatment of visceral leishmaniasis. *Lancet* 1990; **330:** 810–11.
2. Wali JP, *et al.* Ketoconazole in the treatment of antimony- and pentamidine-resistant Kala-azar. *J Infect Dis* 1992; **166:** 215–16.
3. Sundar S, *et al.* Ketoconazole in visceral leishmaniasis. *Lancet* 1990; **336:** 1582–3.
4. Rashid JR, *et al.* The efficacy and safety of ketoconazole in visceral leishmaniasis. *East Afr Med J* 1994; **71:** 392–5.
5. Weinrauch L, *et al.* Ketoconazole in cutaneous leishmaniasis. *Br J Dermatol* 1987; **117:** 666–7.
6. Dedet J-P, *et al.* Failure to cure Leishmania braziliensis guyanensis cutaneous leishmaniasis with oral ketoconazole. *Trans R Soc Trop Med Hyg* 1986; **80:** 176.
7. Saenz RE, *et al.* Efficacy of ketoconazole against Leishmania braziliensis panamensis cutaneous leishmaniasis. *Am J Med* 1990; **89:** 147–55.
8. Salmanpour R, *et al.* Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (Glucantime) for the treatment of cutaneous leishmaniasis. *J Dermatol Treat* 2001; **12:** 159–62.
9. Navin TR, *et al.* Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis* 1992; **165:** 528–34.

Preparations

USP 31: Ketoconazole Oral Suspension; Ketoconazole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: C-86; Cetonil; Eumicel; Faction; Fangan; Fitonal; Fungicil†; Grenfung; Keduo; Ketogel†; Ketolef; Ketonazol; Ketozol†; Krol†; Micoespec K; Micoral; Orifungal; Perative; Quadion; Socosep; Tersoderm Plus†; Tikl; Triatop†; ***Austral.:*** Daktagold†; Hexal Konazol Shampoo; Nizoral; Sebizole; ***Austria:*** Fungoral; Nizoral; ***Belg.:*** Docketoral; Nizoral; ***Braz.:*** Aciderm; Arcolan; Candiderm; Candoral; Cetocona†; Cetoconalab; Cetohexal†; Cetomed; Cetomicoss†; Cetomizol; Cetonax; Cetoneo; Cetonil; Cetonin; Cetozan; Cetozaz†; Cetozol; Fungoral†; Ketomicol†; Ketonan†; Ketonazol; Lozan; Miconan; Micoral; Nizoral; Nizoretic; Noriderm; Noronal; Sioconazol†; Tonazox†; Zanoc; Zolmicol; ***Canad.:*** Ketoderm; Nizoral; ***Chile:*** Arcolane; Biogel; Eprofil†; Fungarest; Fungium; Ketonil†; Soridermal; TKC; ***Cz.:*** Asquam; Nizoral; Orozanol†; ***Denm.:*** Kezoral; Nizoral; ***Fin.:*** Nizoral; ***Fr.:*** Ketoderm; Ketolium; Nizoral; ***Ger.:*** Nizoral; Terzolin; ***Gr.:*** Abba; Adenosan; Aquarius; Botaderm; Cezolin; Ebersept; Flidaphen; Fungoral; Ilgem; Libroman; Mycofebrin; Neo-egmol; Nyoxep; Scalpin; Sostatin; Vafluson†; ***Hong Kong:*** Diazon; Fluzoral; Fungazol; Ketozol; Ketozole; Larry; Nizoral; Pristine; Pristinex; Sebizole†; Stada K; Synizoral; ***Hung.:*** Ketospor; Nizoral; ***India:*** Arcolane; Danfree; Danruf; Funazole; Fungicide; Hyphoral; Keto; ***Indon.:*** Anfuhex; Dermaral; Dexazol; Dysfungal; Fexazol; Formyco; Funet; Fungasol; Fungoral; Interzol; Ketomed; Lusanoc; Micoticum; Muzoral; Mycoderm; Mycoral; Mycozid; Nizol; Nizoral; Nofung; Picamic; Profungal; Solinfec; Sporex; Thicazol; Wizol; Zoloral; Zoralin; Zumazol; ***Irl.:*** Nizoral; ***Israel:*** Nizoral; ***Ital.:*** Nizoral; Triatop; ***Malaysia:*** Dezor; Fungazol; Funginox; Ketozole†; Kezoral; Larry; Nizoral; Pristine†; Pristinex†; Sebizole†; Sunazol†; Yucomy; Ziconal†; ***Mex.:*** Akorazol; Apo-Kesol†; Biozoral; Conazol; Cremosan; Ergomicon; Eurolat; Fungipar; Fungoral; Fungosine; Honzil; Keprobiozol†; Kestomicol†; Ketofar; Ketomed; Ketomizol; Ketoril; Konaderm; Konaturil; Lemyken†; Lizovag; Lornazol†; Messelzol; Mi-Ke-Sons; Micoser; Micozol; Mycodib; Nastil; Nazolfarm; Nazoltec; Nizoral; Onofin-K; Prenalon; Remecon; Strizole; Termizol; Tiniasil; Tiniazol; Tocomizol†; Toconal; Tolcrem; Tomiko; Triatop; ***Neth.:*** Nizoral; ***Norw.:*** Fungoral; Konazal; ***NZ:*** Daktagold; Ketopine; Nizoral; Sebizole; ***Philipp.:*** Ketovid; Nizoral; ***Pol.:*** Fungores; Nizoral; Noell; ***Port.:*** Farmorol; Frisol†; Frisolac; Micopar; Nizale; Nizoral; Rapamic; Tedol; ***Rus.:*** Livarole (Ливарол); Mycosoral (Микозорал); Nizoral (Низорал); ***S.Afr.:*** Adco-Dermed; Ketazol; Kez; Nizcreme; Nizoral; Nizorelle; Nizovules; Nizshampoo; ***Singapore:*** Antanazol; Beatoconazole; Dezor; Dezoral†; Diazon; Ketozole; Kezoral; Nicozone; Nitozol; Nizoral; Pristine; Pristinex; Profungal†; Sebizole; Yucomy; ***Spain:*** Fungarest; Fungo Farmasierra; Fungo Zeus; Keto-Cure; Ketoderma; Ketoisdin; Medezol; Micoticum; Panfungol; ***Swed.:*** Fundan; Fungoral; Ketoson; ***Switz.:*** Ketozol; Nizoral; Terzolin; ***Thai.:*** AC-FA; Chintaral; Dezor; Diazon; Fungazol; Fungiderm-K; Funginox; Kara†; Katsin; Kazinal; Kenalyn; Kenazol; Kenazole†; Kenoral; Ketazol†; Ketazon; Ketocine; Ketolan; Ketomed; Ketonazole; Ketoral†; Ketosil; Ketozal; Kezon; Konazol†; Lama; Larry; Manoketo; Masarol; Mizoron; Mycella; Myco; Mycoral; Ninazol; Nizoral; Nora†; Pasalen; Sporaxyl; Sporoxyl; Triatop†; ***Turk.:*** Fungoral; Ketoral; Konazol; Nizoral; ***UK:*** Daktarin Gold; Dandrazol; Dandrid; Nizoral; ***USA:*** Extina; Nizoral; Xolegel; ***Venez.:*** Arcolane; Danfree†; Freetop; Kenazol; Ketazol; Ketocoval†; Ketomed; Napox†; Nizoral; Noractin†; Topstar†.

Multi-ingredient: ***Arg.:*** Aeromicrosona C†; Bactisona; Ciprocort; Dercotex; Duo Minoxi†; Gentacler; Gynerium; Ketohair†; Linfol Dermico; Micozol Compuesto†; Microsona C; Ovogin; Prurisedan Biotic†; Start NP†; Torgyn Duo; Tricur; Tridermal; Triefect†; ***Braz.:*** Betazol Cort; Candicort; Capel; Celocort; Cetobeta; Cetocort; Cetocorten; Cimecort; Emscort; Naderm; Novacort; Trok; Trok-N; ***Chile:*** KPL†; ***India:*** Hyphoral; Scalpe; ***Ital.:*** Keto Z; Ketomousse; ***Malaysia:*** Ketoplus; ***Mex.:*** Femisan; Gynoclin-V; Trexen Duo; ***Philipp.:*** Scalpex; ***Rus.:*** Keto Plus (Кето Плюс); ***USA:*** Xolegel Duo.

Lanoconazole *(rINN)*

Lanoconazol; Lanoconazolum; Latoconazole; NND-318; TJN-318. (±)-α-[(*E*)-4-(*o*-Chlorophenyl)-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile.

Ланоконазол

$C_{14}H_{10}ClN_3S_2$ = 319.8.

CAS — 101530-10-3.

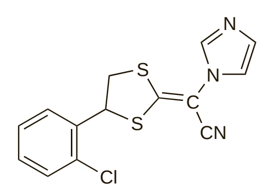

Profile

Lanoconazole is an imidazole antifungal used topically in the treatment of fungal skin infections as a 1% cream, ointment, or solution, applied once daily. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Astat; ***Port.:*** Micoder.

Liranaftate *(rINN)*

Liranaftato; Liranaftatum; M-732; Piritetrate. *O*-5,6,7,8-Tetrahydro-2-naphthyl 6-methoxy-*N*-methylthio-2-pyridinecarbamate.

Лиранафтат

$C_{18}H_{20}N_2O_2S$ = 328.4.

CAS — 88678-31-3.

Profile

Liranaftate is an antifungal related to tolnaftate (p.548) and is applied once daily as a 2% cream or solution in the treatment of superficial dermatophyte infections (p.521).

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Zefnart.

Mepartricin *(BAN, USAN, rINN)*

Mepartricina; Mépartricine; Mepartricinum; Methylpartricin; SN-654; SPA-S-160.

Мепартрицин

CAS — 11121-32-7.

ATC — A01AB16; D01AA06; G01AA09; G04CX03.

ATC Vet — QA01AB16; QD01AA06; QG01AA09; QG04CX03.

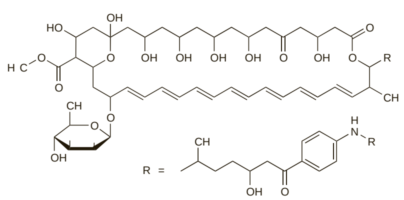

Mepartricin A: R = CH
Mepartricin B: R = H

Profile

Mepartricin is a mixture of the methyl esters of 2 related polyene antibiotics that may be obtained from a strain of *Streptomyces aureofaciens*. It has antifungal and antiprotozoal activity and has been used in vaginal candidiasis and trichomoniasis as pessaries or as a vaginal cream. A cream is also available for the treatment of superficial candidiasis. An oral form of mepartricin sodium laurilsulfate is also used. Oral mepartricin 40 mg daily is used in the treatment of some prostate disorders.

Prostate disorders. Studies[1,2] have shown that mepartricin given by mouth is effective in the treatment of *benign prostatic hyperplasia* (see p.2178 for the more usual treatments); a dose of 40 mg daily is commonly used.[2] Mepartricin is thought to reduce cholesterol, oestrogen, and androgen binding to the prostate. Similarly, another study[3] has shown that the same dose of mepartricin provides symptomatic improvement in the management of *chronic prostatitis/chronic pelvic pain syndrome* (see Prostatitis, p.2181).

1. Tosto A, *et al.* A double-blind study of the effects of mepartricin in the treatment of obstruction due to benign prostatic hyperplasia. *Curr Ther Res* 1995; **56:** 1270–75.
2. Denis L, *et al.* Double-blind, placebo-controlled trial to assess the efficacy and tolerability of mepartricin in the treatment of BPH. *Prostate* 1998; **37:** 246–52.
3. De Rose AF, *et al.* Role of mepartricin in category III chronic nonbacterial prostatitis/chronic pelvic pain syndrome: a randomized prospective placebo-controlled trial. *Urology* 2004; **63:** 13–16.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Iperplasin; Prostec; ***Belg.:*** Tricandil†; ***Braz.:*** Montricin†; ***Chile:*** Normoprost†; ***Cz.:*** Ipertrofan; ***Ital.:*** Ipertrofan; Tricandil; ***Philipp.:*** Ipertrofan; ***Pol.:*** Ipertrofan; ***Port.:*** Iperplasin; Ipertrofan; Tricandil.

Multi-ingredient: ***Braz.:*** Tricangine†.

Micafungin Sodium *(USAN, rINNM)*

FK-463; Micafungina sódica; Micafungine Sodique; Natrii Micafunginum. 5-((1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(1*R*)-3-Amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(1*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-[(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzoyl)amino]tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2′,1′-*l*][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl)-2-hydroxyphenyl sodium sulfate.

Натрий Микафунгин

$C_{56}H_{70}N_9NaO_{23}S$ = 1292.3.

CAS — 235114-32-6 (micafungin); 208538-73-2 (micafungin sodium).

ATC — J02AX05.

ATC Vet — QJ02AX05.

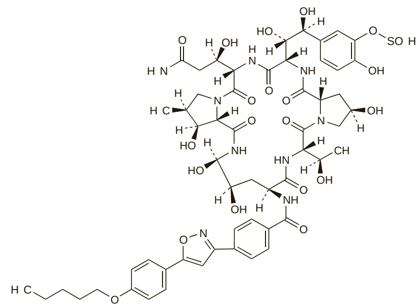

Adverse Effects

As for Caspofungin, p.528. Isolated cases of renal dysfunction or acute renal failure have also occurred in patients taking micafungin.

Precautions

Patients who develop abnormal liver or renal function tests while taking micafungin should be monitored for deterioration in hepatic or renal function respectively.

Interactions

Micafungin may increase the area under the concentration-time curve for nifedipine and sirolimus.

Antimicrobial Action

As for Caspofungin, p.528.

Pharmacokinetics

Micafungin is absorbed from the gastrointestinal tract after oral doses. It is more than 99% bound to plasma proteins, mainly albumin.

Micafungin is metabolised by arylsulfatase to its catechol form and further metabolised to the methoxy form by catechol-*O*-methyltransferase. Some hydroxylation to micafungin via cytochrome P450 isoenzymes also occurs.

After 28 days about 71% of a dose is recovered in the faeces and 12% in the urine. Mean half-lives of 14.0 to 17.2 hours have been reported.

Uses and Administration

Micafungin is an echinocandin antifungal with general properties similar to those of caspofungin (p.528). It is used for the treatment and prophylaxis of candidiasis and also in the treatment of aspergillosis. It is given as the sodium salt by intravenous infusion in doses of 50 mg once daily for candidiasis. For the treatment of oesophageal candidiasis the recommended dose is 150 mg daily. For aspergillosis 50 to 150 mg is given once daily. Doses up to 300 mg daily have been used in severe or refractory disease. A dose of 50 mg daily is used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation.

◊ Reviews.

1. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **362:** 1142–51.
2. Jarvis B, *et al.* Micafungin. *Drugs* 2004; **64:** 969–84.
3. Carver PL. Micafungin. *Ann Pharmacother* 2004; **38:** 1707–21.
4. van Burik JA, *et al.* Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; **39:** 1407–16.
5. Chandrasekar PH, Sobel JD. Micafungin: a new echinocandin. *Clin Infect Dis* 2006; **42:** 1171–8.
6. Fritz JM, *et al.* Micafungin for the prophylaxis and treatment of Candida infections. *Expert Rev Anti Infect Ther* 2008; **6:** 153–62.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Funguard; ***UK:*** Mycamine; ***USA:*** Mycamine.

Miconazole *(BAN, rINN)*

Miconazol; Miconazolum; Mikonatsoli; Mikonazol; Mikonazolas; R-18134. 1-[2,4-Dichloro-β-(2,4-dichlorobenzyloxy)phenethyl]imidazole.

Миконазол

$C_{18}H_{14}Cl_4N_2O$ = 416.1.

CAS — 22916-47-8.

ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.

ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.

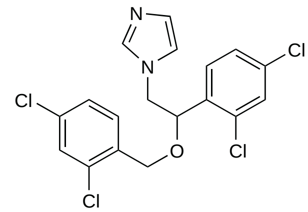

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Miconazole). A white or almost white powder. It exhibits polymorphism. M.p. 83° to 87°. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 31 (Miconazole). A white to pale cream powder. It may exhibit polymorphism. M.p. 78° to 88°. Insoluble in water; soluble 1 in 9.5 of alcohol, 1 in 2 of chloroform, 1 in 15 of ether, 1 in 4 of isopropyl alcohol, 1 in 5.3 of methyl alcohol, and 1 in 9 of propylene glycol; freely soluble in acetone and in dimethylformamide. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Miconazole Nitrate *(BANM, USAN, rINNM)*

Miconazole, nitrate de; Miconazoli nitras; Mikonatsolinitraatti; mikonazol Nitrat; Mikonazolnitrat; Mikonazol-nitrát; Mikonazolo nitratas; Mikonazolu azotan; Nitrato de miconazol; R-14889.

Миконазола Нитрат

$C_{18}H_{14}Cl_4N_2O,HNO_3$ = 479.1.

CAS — 22832-87-7.

ATC — A01AB09; A07AC01; D01AC02; G01AF04; J02AB01; S02AA13.

ATC Vet — QA01AB09; QA07AC01; QD01AC02; QG01AF04; QJ02AB01; QS02AA13.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Miconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Miconazole Nitrate). A white or practically white, crystalline powder, with not more than a slight odour. Soluble 1 in 6250 of water, 1 in 312 of alcohol, 1 in 75 of methyl alcohol, 1 in 525 of chloroform, 1 in 1408 of isopropyl alcohol, 1 in 119 of propylene glycol; freely soluble in dimethyl sulfoxide; soluble in dimethylformamide; insoluble in ether. Protect from light.

Adverse Effects

After oral use of miconazole, nausea and vomiting have been reported, and also diarrhoea (usually on long-term treatment). There have been allergic reactions, rarely, and isolated reports of hepatitis.

Local irritation and sensitivity reactions may occur when miconazole nitrate is used topically; contact dermatitis has been reported.

After the intravenous infusion of miconazole, phlebitis, nausea, vomiting, diarrhoea, anorexia, pruritus, rash, febrile reactions, flushes, drowsiness, and hyponatraemia have been reported. Other effects include hyperlipidaemia, aggregation of erythrocytes, anaemia, and thrombocytosis. Transient tachycardia and other cardiac arrhythmias have followed the rapid intravenous injection of miconazole (but see also Effects on the Heart, below). Rare adverse effects include acute psychosis, arthralgia, and anaphylaxis. Many of these adverse effects have been associated with the injection vehicle, which contains polyoxyl castor oil (p.1918).

Effects on the heart. Bradycardia, progressing to fatal ventricular fibrillation and cardiac arrest, occurred in a heart transplant patient during intravenous infusion of miconazole for an invasive fungal infection.[1]

1. Coley KC, Crain JL. Miconazole-induced fatal dysrhythmia. *Pharmacotherapy* 1997; **17:** 379–82.

Overdosage. A report[1] of a generalised tonic-clonic convulsion that occurred in an infant 10 to 15 minutes after the inadvertent infusion of miconazole 500 mg instead of 50 mg.

1. Coulthard K, *et al.* Convulsions after miconazole overdose. *Med J Aust* 1987; **146:** 57–8.

Precautions

Miconazole oral gel should be avoided in patients with hepatic impairment.

Intravaginal preparations of miconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

Miconazole has been fetotoxic at high doses in *animals* and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Porphyria. Miconazole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Miconazole can inhibit the metabolism of drugs metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and may thus have effects similar to those of fluconazole (p.532). Miconazole may enhance the activity of oral anticoagulants, sulfonylurea hypoglycaemics, or phenytoin. Adverse effects have been reported when miconazole was given with carbamazepine.

There is a risk of cardiac arrhythmias if miconazole is used with astemizole, cisapride, or terfenadine and such combinations should be avoided.

Anticoagulants. The anticoagulant activity of coumarin anticoagulants can be potentiated by miconazole given orally,[1] intravaginally,[2] or topically.[3] As of December 2002 the Australian Adverse Drug Reactions Advisory Committee had received 18 reports of significant increases in the INR of patients previously stabilised on warfarin within 1 to 2 weeks of starting treatment with miconazole oral gel.[4]

1. Ortín M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; **33:** 175–7.
2. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; **47:** 225–26.
3. Devaraj A, *et al.* Interaction between warfarin and topical miconazole cream. *BMJ* 2002; **325:** 77.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Miconazole oral gel elevates INR—a reminder. *Aust Adverse Drug React Bull* 2002; **21:** 14. Available at: http://www.tga.gov.au/adr/aadrb/aadr0212.pdf (accessed 28/06/05)

Antimicrobial Action

Miconazole is an imidazole antifungal with similar antimicrobial activity to that of ketoconazole (p.539). It also has some activity against *Aspergillus* spp., *Cryptococcus neoformans, Pseudallescheria boydii,* and some Gram-positive bacteria including staphylococci and streptococci.

◊ References.

1. Barasch A, Griffin AV. Miconazole revisited: new evidence of antifungal efficacy from laboratory and clinical trials. *Future Microbiol* 2008; **3:** 265–9.

Microbiological interactions. A study *in vitro* indicating antimicrobial synergism of miconazole and benzoyl peroxide against *Staphylococcus* spp. and *Propionibacterium acnes.*[1]

For the effect on antifungal activity of giving azoles and amphotericin B together, see p.525.

1. Vanden Bossche H, *et al.* Synergism of the antimicrobial agents miconazole and benzoyl peroxide. *Br J Dermatol* 1982; **107:** 343–8.

Pharmacokinetics

Miconazole is incompletely absorbed from the gastrointestinal tract. Peak plasma concentrations of 1 microgram/mL are achieved about 4 hours after a dose of 1 g daily. Over 90% is reported to be bound to plasma proteins.

Miconazole is metabolised in the liver to inactive metabolites. From 10 to 20% of an oral dose is excreted in the urine, mainly as metabolites, within 6 days. About 50% of an oral dose may be excreted unchanged in the faeces. The elimination pharmacokinetics of miconazole have been described as triphasic, with a biological half-life of about 24 hours.

Very little miconazole is removed by haemodialysis.

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

◊ Reviews.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. *Clin Pharmacokinet* 1983; **8:** 17–42.

Uses and Administration

Miconazole is an imidazole antifungal used as miconazole base or nitrate in the treatment of superficial candidiasis (p.518), and of the skin infections dermatophytosis and pityriasis versicolor (p.521). It has also been given intravenously by infusion in the treatment of disseminated fungal infections, but other azoles are now more commonly used.

Miconazole may be given orally as a gel containing 20 mg/g (24 mg/mL) for the treatment of oropharyngeal and intestinal candidiasis. The usual adult dose is 5 to 10 mL four times daily (equivalent to a total of about 15 mg/kg daily). Children under the age of 2 years may be given the oral gel in a dose of 2.5 mL twice daily; those aged between 2 and 6 years, 5 mL twice daily; and those aged over 6 years, 5 mL four times daily. For the treatment of oral lesions the oral gel is applied directly.

Miconazole nitrate is usually applied twice daily as a 2% cream, lotion, or powder in the treatment of fungal infections of the skin including candidiasis, dermatophytosis, and pityriasis versicolor. In the treatment of vaginal candidiasis, 5 g of a 2% intravaginal cream is inserted into the vagina once daily for 10 to 14 days or twice daily for 7 days. Miconazole nitrate pessaries may be inserted in dosage regimens of 100 mg once daily for 7 or 14 days, 100 mg twice daily for 7 days, 200 or 400 mg daily for 3 days, or in a single dose of 1200 mg.

Acanthamoeba keratitis. Miconazole has been applied topically in *Acanthamoeba* keratitis (p.822) in combination with systemic treatment with either ketoconazole or itraconazole.

Skin disorders. Topical preparations containing an imidazole such as ketoconazole or miconazole, usually with hydrocortisone, are used in the management of *seborrhoeic dermatitis* (p.1584). A cream containing miconazole nitrate 2% and benzoyl peroxide 5% has been used topically in the treatment of *acne* (p.1577).

Preparations

BP 2008: Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment; Miconazole Cream; Miconazole Oromucosal Gel;
USP 31: Miconazole Injection; Miconazole Nitrate Cream; Miconazole Nitrate Topical Powder; Miconazole Nitrate Vaginal Suppositories.

Proprietary Preparations (details are given in Part 3)

Arg.: Daktarin; Deralbine; Gynotran; Miconol; Micotgez; Micotral; Micotrim P; Micotrim S†; Monizol; Nedis; Salicrem Miconazol†; ***Austral.:*** Daktarin; Eulactol Antifungal†; Hairscience Anti-Dandruff; Monistat†; Resolve; Resolve Thrush; ***Austria:*** Daktarin; Gyno-Daktarin; ***Belg.:*** Daktar†; Daktarin; Gyno-Daktarin; Zimycan; ***Braz.:*** Anfugitarin; Biodol†; Ciconazol; Daknax†; Daktarin; Daktazol; Ginedak; Gino-Daczol; Ginotarin; Gyno-Daktarin; Micofim; Micogyn; Micotarin; Micozen; Mycosin; Vodol; ***Canad.:*** Micatin; Micozole; Monazole†; Monistat; ***Chile:*** Daktarin; Fungos†; ZeaSorb AF; ***Cz.:*** Daktarin†; ***Denm.:*** Brenazol†; Brentan; ***Fin.:*** Daktarin; Gyno-Daktarin; Medizol†; ***Fr.:*** Daktarin; Gyno-Daktarin; ***Ger.:*** Amykon†; Castellani mit Miconazol; Daktar; Decomyk; Derma-Mykotral; Fungur M; Gyno-Daktar; Gyno-Mykotral; InfectoSoor; Micobeta; Micotar; Mykoderm; Mykoderm Mund-Gel; Mykotin; Vobamyk; ***Gr.:*** Daktarin; Fantersol; Medacter; Mezolitan; Untano; ***Hong Kong:*** Daktarin; Dermon; Funga; Fungo†; Gyno-Daktarin†; ***India:*** Daktarin; Gyno-Daktarin; Micogel; Zole; ***Indon.:*** Daktarin; Fungares; Micoskin; Micrem; Moladerm; Mycorine; Sporend; Zolagel; ***Irl.:*** Daktarin; Gyno-Daktarin; ***Israel:*** Daktarin; Fungiderm; Gyno-Daktarin; Pitrion; ***Ital.:*** Daktarin; Miconal; Micotef; Miderm; Nizacol; Pivanozolo; Prilagin; ***Jpn:*** Florid; ***Malaysia:*** Antifungal; Becarin; Daktarin; Decozol; Fungo†; Resolve; Setarin†; Uniderm†; Zarin†; ***Mex.:*** Aloid; Biodantyl-C; Daktarin; Dermifun; Falernol; Fucoderm; Fungicrem; Fungiquim; Ginazol; Gyno-Daktarin; Hipo Femme; K-Mizol; Lotrimin AF; Micoffen; Mindosan V†; Nacomic; Neomicol; Nimicon; Niscamil; Oz Crema; Piat†; Vigasil; ***Neth.:*** Daktarin; Dermacure; Gyno-Daktarin; Kruidvat Antischimmelcreme; Zimycan; ***Norw.:*** Daktar; ***NZ:*** Daktarin; Fungo; Hairscience Antidandruff†; Micozole; Micreme; Monistat; ***Philipp.:*** Daktarin; De-Ol; Defungin; Fungtopic; Monistat; ***Pol.:*** Daktarin; Gyno-Femidazol; Miconal; ***Port.:*** Daktarin; Gyno-Daktarin; Micane; Zimycan; ***Rus.:*** Daktarin (Дактарин); Gynezol (Гинезол); ***S.Afr.:*** Covarex; Daktarin; Dermazole; Gyno-Daktarin; Gynospor; ***Singapore:*** Antifungal; Daktarin; Decozol; Fungo†; Hairscience†; Liconar; Micon; Minazol; Mycoban; Resolve; Zarin; ***Spain:*** Daktarin; Fungisdin; Pasedon; Tremix; ***Swed.:*** Daktar; ***Switz.:*** Daktarin; Dumicoat†; Monistat; ***Thai.:*** Daktarin; Dermon; Funcort†; Fungi-M; Fungisil; Liconar†; Micazin; Misone†; Mysocort; Nikarin; Noxraxin; Podakrin; Ranozol; Skindure; Tara; ***Turk.:*** Fungucit; Miko-Penetran; ***UAE:*** Gyno-Mikozal; Mikozal; ***UK:*** Daktarin; Gyno-Daktarin; Loramyc; ***USA:*** Absorbine Antifungal Foot Powder†; Breezee Mist Antifungal†; Femizol-M; Fungoid; Lotrimin AF; M-Zole; Maximum Strength Desenex Antifungal†; Micatin; Monistat; Neosporin AF; Podactin; Prescription Strength Desenex; Ting; Vagistat-3; ZeaSorb AF; ***Venez.:*** Canidazol†; Daktarin; Drinax†; Gyno-Daktarin.

Multi-ingredient: ***Arg.:*** Adenil; Betacort Plus; Blamy; Ciprocort; Cuta Crema; Daktozin; Delisan; Denvercrem; Dermizol Trio; Dermosona; Factor Dermico; Gentasol; Ginal Cent; Ginkan; Gynormal; Hifamonil Crema; Ladylen; Lazar-Cort Complex; Linfol Cicatrizante; Macril; Mailen; Miklogen; Monizol Cort; Monizol Cort Crema; Ovumix; Pentol; Protiderm; Septigyn; Tribiocort; Triliver; Triplex; Vagicural Plus; ***Austral.:*** Daktozin; Resolve; Resolve Plus; Resolve Tinea; ***Austria:*** Acne Plus; ***Belg.:*** Acneplus; Daktacort; Daktozin; ***Braz.:*** Amplium-G; Anfugine; Daktozin; Facyl M; Gino Pletil; Ginosutin M; Tizonil M†; Trinizol M†; ***Chile:*** Doxifen; Famidal; Famidal Ad†; Ginecopast; Ginecopast Dual; Ginedazol; Ginedazol Dual; Medidos; Mizonase; ***Cz.:*** Daktozin†; Klion-D; Mycosolon†; ***Denm.:*** Brentacort; ***Fin.:*** Daktacort; ***Fr.:*** Squaphane; Squaphane E; Squaphane Masque-Creme; Squaphane P; Squaphane S; ***Ger.:*** Acne Plus; Decoderm tri; InfectoSoor; Micotar ZP; Vobaderm; ***Gr.:*** Antimycotic; Catrigel; Combi; Conazol; Daktodor; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Fluniprol; Flunovon; Fosemyk; Fumicon; Micoflup; Micogen; Mifler; Oxigon; Panderm; Panmyk; Sarmel; Verdal; ***Hong Kong:*** Conazole; Daktacort; Fungo Soothing Balm; Hydro-Funga; Micosone; ***Hung.:*** Klion-D; Mycosolon; ***India:*** Betamil-GM; Betamil-M; Betnederm GM; Betnovate-GM; Betnovate-M; Candizole-T; Cloderm GM; Daktacort; Eumosone-M; Flucort-MZ; Flucreme NM; Lobate-GM; Lobate-M; Micogel F; Stecort-NM; Tenovate M; Valbet; Zole-F; ***Indon.:*** Benoson M; Brentan; Daktarin Diaper; Thecort; Zolacort; ***Irl.:*** Daktacort; ***Israel:*** Daktacort; ***Ital.:*** Acnidazil; ***Malaysia:*** Becacort†; Daktacort; Decocort; Miconazole H†; Neo-Penotran; Setarin H†; Zaricort†; ***Mex.:*** Bebektin; Daktacort; Gynotran; ***Neth.:*** Acnecare; Acnecure†; Acnidazil†; Daktacort; ***Norw.:*** Daktacort; ***NZ:*** Daktacort; Daktozin†; Fungocort†; Micreme H; ***Philipp.:*** Acne Plus; Daktacort; Neo-Penotran; ***Pol.:*** Daktacort†; Mycosolon; ***Port.:*** Daktacort; Zacne; ***Rus.:*** Klion-D (Клион-Д); Mycosolon (Микозолон); Neo-Penotran (Нео-Пенотран); ***S.Afr.:*** Acneclear; Acnidazil; Daktacort; Trialone; ***Singapore:*** Conazole; Daktacort; Decocort; Micon-H; Neo-Penotran; Tri-Micon; Zaricort; ***Spain:*** Bexicortil; Blastoestimulina; Brentan; Dermisdin†; Nutracel; ***Swed.:*** Cortimyk; Daktacort; ***Switz.:*** Acne Creme Plus; Daktacort; Decoderm bivalent; ***Thai.:*** Daktacort; Decocort; Fungisil-T; Kelaplus; Ladocort; Tara-Plus; Timi; Trimicon; ***Turk.:*** Neo-Penotran; Nidazol-M; ***UK:*** Acorvio Plus; Daktacort; Daktacort HC; ***USA:*** Fungoid HC; ***Venez.:*** Daktozin.

Naftifine Hydrochloride *(BANM, USAN, rINNM)*

AW-105-843; Hidrocloruro de naftifina; Naftifin Hidroklorür; Naftifine, Chlorhydrate de; Naftifini Hydrochloridum; Naftifungin Hydrochloride; SN-105-843 (naftifine). (*E*)-*N*-Cinnamyl-*N*-methyl(1-naphthylmethyl)amine hydrochloride.

Нафтифина Гидрохлорид

$C_{21}H_{21}N,HCl = 323.9.$

CAS — 65472-88-0 (naftifine); 65473-14-5 (naftifine hydrochloride).

ATC — D01AE22.

ATC Vet — QD01AE22.

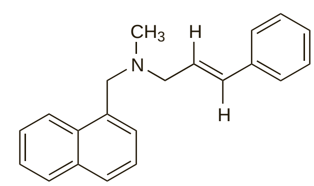

(naftifine)

Pharmacopoeias. In *US.*

USP 31 (Naftifine Hydrochloride). Store in airtight containers.

Profile

Naftifine hydrochloride is an allylamine derivative (see Terbinafine, p.546) which is fungicidal against dermatophytes, but only fungistatic against *Candida* spp.

Naftifine hydrochloride 1% is applied topically once or twice daily for fungal skin infections, particularly dermatophytosis (see Skin Infections, p.521).

Local reactions such as burning or stinging may occur.

◊ Reviews.

1. Gupta AK, *et al.* Naftifine: a review. *J Cutan Med Surg* 2008; **12:** 51–8.

Preparations

USP 31: Naftifine Hydrochloride Cream; Naftifine Hydrochloride Gel.

Proprietary Preparations (details are given in Part 3)

Austria: Benecut; Exoderil; ***Canad.:*** Naftin; ***Cz.:*** Exoderil; ***Ger.:*** Exoderil; ***Hong Kong:*** Exoderil; ***Hung.:*** Exoderil; ***Indon.:*** Exoderil; ***Israel:*** Exoderil; ***Ital.:*** Suadian; ***Malaysia:*** Exoderil; ***Pol.:*** Exoderil; ***Rus.:*** Exoderil (Экзодерил); ***Singapore:*** Exoderil†; ***Spain:*** Micosona; ***Turk.:*** Exoderil; ***USA:*** Naftin.

Natamycin *(BAN, USAN, pINN)*

Antibiotic A-5283; CL-12625; E235; Natamicina; Natamycine; Natamycinum; Natamycyna; Natamysiini; Pimaricin; Pimarisin.

Натамицин

$C_{33}H_{47}NO_{13}$ = 665.7.

CAS — 7681-93-8.

ATC — A01AB10; A07AA03; D01AA02; G01AA02; S01AA10.

ATC Vet — QA01AB10; QA07AA03; QD01AA02; QG01AA02; QS01AA10.

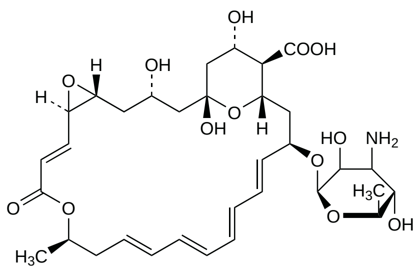

Pharmacopoeias. In *Jpn*, *Pol.*, and *US*.

USP 31 (Natamycin). An off-white to cream-coloured powder. It may contain up to 3 moles of water. Practically insoluble in water; soluble in glacial acetic acid and in dimethylformamide; slightly soluble in methyl alcohol. A 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Gastrointestinal disturbances have occurred after oral use of natamycin. Local application has sometimes produced irritation.

Porphyria. Natamycin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Antimicrobial Action

Natamycin is a polyene antifungal active against *Candida* and *Fusarium* spp. In addition it is active against the protozoan *Trichomonas vaginalis*.

Pharmacokinetics

Natamycin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically. After ocular use, natamycin is present in therapeutic concentrations in corneal stroma but not in intra-ocular fluid; systemic absorption does not usually occur.

Uses and Administration

Natamycin is a polyene antifungal antibiotic produced by the growth of *Streptomyces natalensis*. It is used for the local treatment of candidiasis (p.518) and fungal keratitis (see Eye Infections, p.519). It has also been used in vaginal trichomoniasis (p.827).

A 5% ophthalmic suspension or a 1% ointment of natamycin is used in the treatment of blepharitis, conjunctivitis, or keratitis due to susceptible fungi, including *Fusarium solani*.

Natamycin lozenges are used for the treatment of oral candidiasis in a dose of 10 mg every 4 to 6 hours. Tablets have been given orally for the treatment of intestinal candidiasis. Natamycin has also been used topically for fungal skin infections and for candidal and trichomonal infections of the vagina.

Preparations

USP 31: Natamycin Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Natacyn; ***Cz.:*** Pimafucin; ***Fin.:*** Pimafucin; ***Ger.:*** Deronga Heilpaste†; Pima Biciron N; Pimafucin; ***Hung.:*** Pimafucin; ***India:*** Natadrops; ***Indon.:*** Fukricin; ***Ital.:*** Natafucin†; ***Malaysia:*** Natacyn; ***Mex.:*** Miconacina; ***Neth.:*** Pimafucin; ***Pol.:*** Pimafucin; ***Rus.:*** Piamfucin (Пимафуцин)†; Pimafucin (Пимафуцин); ***S.Afr.:*** Natacyn; ***Singapore:*** Natacyn; ***Thai.:*** Natacyn; ***Turk.:*** Pimafucin; ***USA:*** Natacyn.

Multi-ingredient: *Cz.:* Pimafucort; ***Fin.:*** Pimafucort; ***Hung.:*** Pimafucort; ***Neth.:*** Pimafucort; ***NZ:*** Pimafucort; ***Pol.:*** Pimafucort; ***Port.:*** Pimafucort; ***Rus.:*** Pimafucort (Пимафукорт).

Neticonazole Hydrochloride *(rINNM)*

Hidrocloruro de neticonazol; Néticonazole, Chlorhydrate de; Neticonazoli Hydrochloridum; SS-717. (*E*)-1-{2-(Methylthio)-1-[*o*-(pentyloxy)phenyl]vinyl}imidazole hydrochloride.

Нетиконазола Гидрохлорид

$C_{17}H_{22}N_2OS,HCl$ = 338.9.

CAS — 130726-68-0 (neticonazole); 130773-02-3 (neticonazole hydrochloride).

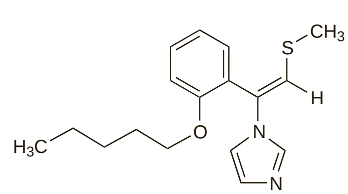

(neticonazole)

Profile

Neticonazole is an imidazole antifungal that has been used topically as the hydrochloride in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Atolant.

Nystatin *(BAN, USAN, rINN)*

Fungicidin; Nistatin; Nistatina; Nistatinas; Nisztatin; Nystatiini; Nystatine; Nystatinum; Nystatyna.

Нистатин

CAS — 1400-61-9.

ATC — A07AA02; D01AA01; G01AA01.

ATC Vet — QA07AA02; QD01AA01; QG01AA01.

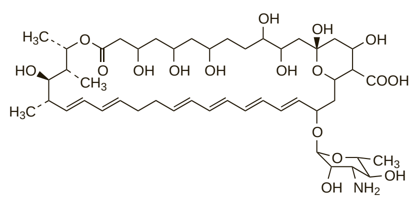

(nystatin A_1)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Nystatin). An antifungal substance obtained by fermentation using certain strains of *Streptomyces noursei*. It contains mainly tetraenes, the principal component being nystatin A_1. The potency is not less than 4400 units/mg and not less than 5000 units/mg if intended for oral use, calculated with reference to the dried substance. It is a yellow or slightly brownish hygroscopic powder. Practically insoluble in water and in alcohol; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Nystatin). A substance, or a mixture of two or more substances, produced by the growth of *Streptomyces noursei* (Streptomycetaceae). It has a potency of not less than 4400 units/mg, or, where intended for use in extemporaneous preparation of oral suspensions, not less than 5000 units/mg. A yellow to light tan, hygroscopic powder, with an odour suggestive of cereals; it is affected by long exposure to light, heat, and air. Practically insoluble in water and in alcohol; insoluble in chloroform and in ether; freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly to sparingly soluble in methyl alcohol, in *n*-butyl alcohol, and in *n*-propyl alcohol. A 3% suspension in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

Adverse Effects

Nausea, vomiting, and diarrhoea have occasionally been reported after oral use of nystatin. Oral irritation or sensitisation may occur. Rashes, including urticaria, have occurred and Stevens-Johnson syndrome has been reported rarely. Irritation may occur rarely after the topical use of nystatin.

Effects on the skin. Generalised pustular eruptions were reported in 3 patients after oral nystatin.[1] Subsequent sensitivity testing revealed delayed (type IV) hypersensitivity to nystatin.

1. Küchler A, *et al.* Acute generalized exanthematous pustulosis following oral nystatin therapy: a report of three cases. *Br J Dermatol* 1997; **137:** 808–11.

Precautions

Some intravaginal preparations of nystatin may damage latex contraceptives and additional contraceptive precautions may be necessary during treatment.

Antimicrobial Action

Nystatin is a polyene antifungal antibiotic that interferes with the permeability of the cell membrane of sensitive fungi by binding to sterols, chiefly ergosterol. Its main action is against *Candida* spp.

Pharmacokinetics

Nystatin is poorly absorbed from the gastrointestinal tract. It is not absorbed through the skin or mucous membranes when applied topically.

Uses and Administration

Nystatin is a polyene antifungal antibiotic used for the prophylaxis and treatment of candidiasis of the skin and mucous membranes (see p.518). It has been used with antibacterials in various regimens to suppress the overgrowth of gastrointestinal flora and as part of selective decontamination regimens (see Intensive Care, p.175).

For the treatment of intestinal or oesophageal candidiasis, nystatin is given in oral doses of 500 000 or 1 000 000 units, as a tablet or capsule, 3 or 4 times daily. In infants and children a dosage of 100 000 units or more may be given 4 times daily, as an oral suspension.

For the treatment of lesions of the mouth, pastilles or a suspension may be given in a dosage of 100 000 units 4 times daily. Higher doses of, for example, 500 000 units 4 times daily, may be needed in immunocompromised patients (but see also Candidiasis, below). The formulation should be kept in contact with the affected area for as long as possible, and patients should avoid taking food or drink for one hour after a dose. In the USA, doses of 400 000 to 600 000 units 4 times daily of the suspension, or 200 000 to 400 000 units 4 or 5 times daily as lozenges, are used.

For prophylaxis of intestinal candidiasis in patients given broad-spectrum antibacterials, tablets to a total dose of 1 000 000 units daily may be given. A prophylactic dose for infants born to mothers with vaginal candidiasis is 100 000 units daily of the oral suspension.

For the treatment of vaginal infections, nystatin is given in a dosage of 100 000 to 200 000 units daily for 14 days or longer as pessaries or vaginal cream. For cutaneous lesions, ointment, gel, cream, or dusting powder containing 100 000 units/g may be applied 2 to 4 times daily.

A liposomal formulation of nystatin for *parenteral* use is under investigation.

Candidiasis. A systematic review[1] of 14 studies (12 of prophylaxis, 2 of treatment) considered that nystatin could not be recommended for prophylaxis or treatment of *Candida* infections in patients with immunosuppression. In practice, fluconazole is usually preferred in such patients (see p.518).

1. Gøtzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 28/06/05).

Preparations

BP 2008: Nystatin Ointment; Nystatin Oral Suspension; Nystatin Pastilles; Nystatin Pessaries; Nystatin Tablets;
USP 31: Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin Cream; Nystatin for Oral Suspension; Nystatin Lotion; Nystatin Lozenges; Nystatin Ointment; Nystatin Oral Suspension; Nystatin Tablets; Nystatin Topical Powder; Nystatin Vaginal Suppositories; Nystatin Vaginal Tablets; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Tetracycline Hydrochloride and Nystatin Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Candermil; Candidias; Dipni; Micostatin; Neostatin; Nistagrand; Nistamed; Nistat; ***Austral.:*** Mycostatin; N-Statin†; Nilstat; ***Austria:*** Candio; Mycostatin; Nystaderm; ***Belg.:*** Nilstat; Sterostatine†; ***Braz.:*** Albistin; Candistatin†; Canditrat; Hidrotiazida†; Inofungin; Kandistat; Kolpazol†; Micostal; Micostalab; Micostatin; Neo Mistatin; Neostatin; Nicostat; Nidazolin; Nifatin†; Nistagen†; Nistagyn; Nistanil†; Nistatin; Nistaval; Nistax†; Nistomic; Tricocet; ***Canad.:*** Candistatin; Mycostatin; Nadostine†; Nilstat†; Nyaderm; ***Chile:*** Micostatin; Nistoral; ***Cz.:*** Fungicidin; ***Denm.:*** Mycostatin; ***Fin.:*** Mycostatin; ***Fr.:*** Mycostatine; ***Ger.:*** Adiclair; Biofanal; Candio; Fungireduct†; Lederlind; Moronal; Mykoderm Heilsalbe; MykoPosterine N†; Mykundex; Mykundex mono; Nystaderm; ***Gr.:*** Mycostatin; Nystamont†; Nystamysyn; ***Hong Kong:*** Lystin; Mycostatin; ***India:*** Mycostatin; ***Indon.:*** Candistin; Enystin; Fungatin; Kandistatin; Mycostatin; Nymiko; ***Irl.:*** Mycostatin; ***Ital.:*** Mycostatin; ***Malaysia:*** Mikostat; Mycostatin; Uphastatin†; ***Mex.:*** Aponistan V; Bistatin V; Mibesan-S; Micostatin; Nistan; Nistaquim; Nizin-V; ***Norw.:*** Mycostatin; ***NZ:*** Mycostatin; Nilstat; ***Philipp.:*** Afunginal; Mycostatin;

The symbol † denotes a preparation no longer actively marketed

Port.: Mycostatin; ***S.Afr.:*** Candacide; Canstat; Mycostatin; Nystacid; ***Singapore:*** Mycostatin†; ***Spain:*** Mycostatin; ***Swed.:*** Mycostatin; ***Switz.:*** Mycostatine; ***Thai.:*** Lystin†; Mycostatin; ***Turk.:*** Fungostatin; Mikostatin; ***UAE:*** Mikostat; ***UK:*** Nystamont†; Nystan; ***USA:*** Mycostatin; Nilstat; Nystop; Pedi-Dri; ***Venez.:*** Micostatin; Nistafesa†; Romalina†.

Multi-ingredient: ***Arg.:*** Bacticort Complex; Bexon; Biotaer Gamma†; Biotaer Nebulizable; Dermadex NN; Farm-X Duo; Fasigyn Nistatina; Flagystatin; Kenacomb; Linfol; Min O; Naxo TV; Neocolpoben†; Nistinol; O-Biol; O-Biol P; Pelvicillin NF; Polygynax; Terra-Cortril Nistatina†; Tratomax; ***Austral.:*** Kenacomb; Otocomb Otic; ***Austria:*** Mycostatin V; Mycostatin-Zinkoxid; Topsym polyvalent; ***Belg.:*** Eoline†; Mycolog; Polygynax†; ***Braz.:*** Benzevit; Bio-Vagin; Colpagex N; Colpatrin; Colpist; Colpistar; Colpistatin; Colpolase; Dermodex; Dermokin; Donnagel; Flagyl Nistatina; Fungimax; Ginec†; Ginestatin; Gynax-N; Londerm-N; Minegyl C/Nistatina†; Mud; Naxogin Composto; Neolon-D; Nistazol†; Omcilon A M; Onciplus; Oxyderme; Poliginax; Tricolpex; Tricomax; Trivagel N; Vagi Biotic; Vagimax; Vagitrin-N; ***Canad.:*** Flagystatin; Kenacomb†; ratio-Triacomb; Triacomb†; Viaderm-KC; ***Chile:*** Multilind; Naxogin Compositum; Naxogin Dos†; Nistaglos; ***Cz.:*** Macmiror Complex; Polygynax; ***Denm.:*** Kenalog Comp med Mycostatin; ***Fin.:*** Flagyl Comp; ***Fr.:*** Auricularum; Mycolog†; Polygynax; Polygynax Virgo; Tergynan; ***Ger.:*** Aureomycin N†; Candio-Hermal Plus; Halog Tri†; Jellin polyvalent†; Lokalison-antimikrobiell Creme N; Moronal V; Multilind; Mykoproct sine; Mykundex Heilsalbe; Nystaderm comp; Nystalocal; Penanyst; Polygynax†; Topsym polyvalent; Volonimat Plus N; ***Gr.:*** Kenacomb; ***Hong Kong:*** Kenacomb; Macmiror Complex; Polygynax; Triacomb; ***India:*** Kenacomb; ***Indon.:*** Fasigyn-Nystatin; Fladystin; Flagystatin; Gynoxa; Myco-Z; Naxogin Complex; New Kenacomb; Trichostatic; Vagistin; ***Irl.:*** Kenacomb; Nystaform-HC†; Nystaform†; Timodine; Tinaderm-M; ***Israel:*** Auricularum; Dermacombin; Kenacomb†; ***Ital.:*** Assocort; Fasigin N; Macmiror Complex; ***Malaysia:*** Kenacomb; ***Mex.:*** Acenil; Bidrozil; Decadron con Nistatina; Dermalog-C; Flagystatin V; Kenacomb; Macmiror Complex V; Metrofur; Micostatin Baby; Novageon; Nysmosons-V; Promibasol-Plus; Vagitrol-V; ***Neth.:*** Mycolog; ***NZ:*** Kenacomb; Viaderm-KC; ***Philipp.:*** Dermovate-NN; Flagystatin; Kenacomb; Lidex NGN; ***Pol.:*** Macmiror Complex; Triacomb; ***Port.:*** Dafnegil; Dermovate-NN†; Kenacomb; ***Rus.:*** Macmiror Complex (Макмирор Комплекс); Polygynax (Полижинакс); Tergynan (Тержинан); ***S.Afr.:*** Duoderm†; Hiconcil-NS; Kenacomb; Riostatin; Tetrex-F; ***Singapore:*** Flagystatin; Kenacomb†; Polygynax; ***Spain:*** Interderm; Intradermo Cort Ant Fung†; Milrosina Nistatina; Positon; ***Swed.:*** Kenacombin Novum; ***Switz.:*** Dermovate-NN; Multilind; Mycolog N; Mycolog†; Nystacortone†; Nystalocal; Topsym polyvalent; ***Thai.:*** Dermacombin; Gynecon; Gynecon-T; Gynoco; Gynova; Gyracon; Kenacomb; Nystin; Quinradon-N; Vagicin; ***UAE:*** Mikostat Baby Ointment; Panderm; ***UK:*** Dermovate-NN; Gregoderm†; Nystaform; Nystaform-HC; Timodine; Tinaderm-M; Tri-Adcortyl; Trimovate; ***USA:*** Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; Mytrex†; NGT; Tri-Statin II; ***Venez.:*** Halcicomb; Kenacomb.

Omoconazole Nitrate *(USAN, rINNM)*

10-80-07; Nitrato de omoconazol; Omoconazole, Nitrate d'; Omoconazoli Nitras. (*Z*)-1-{2,4-Dichloro-β-[2-(*p*-chlorophenoxy)ethoxy]-α-methylstyryl}imidazole nitrate.

Омоконазола Нитрат

$C_{20}H_{17}Cl_3N_2O_2,HNO_3 = 486.7.$

CAS — 74512-12-2 (omoconazole); 83621-06-1 (omoconazole nitrate).

ATC — D01AC13; G01AF16.

ATC Vet — QD01AC13; QG01AF16.

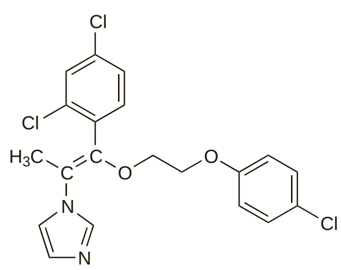

(omoconazole)

Profile

Omoconazole is an imidazole antifungal used locally for fungal skin infections (p.521) and for vaginal candidiasis (p.518). It is applied topically as the nitrate as a 1% cream, powder, or solution in the treatment of cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. For vaginal candidiasis, omoconazole nitrate is given as pessaries in doses of 150 mg daily for 6 days, 300 mg daily for 3 days, or 900 mg as a single dose.

Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Afongan; ***Fr.:*** Fongamil; Fongarex; ***Gr.:*** Fongamil; ***Hung.:*** Mikogal; ***Mex.:*** Afongan; ***Port.:*** Afongan†; Fongamil; ***Rus.:*** Mikogal (Микогал).

Oxiconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de oxiconazol; Oxiconazole, Nitrate d'; Oxiconazoli Nitras; Ro-13-8996; Ro-13-8996/001; Ro-13-8996/000 (oxiconazole); SGD-301-76; ST-813. 2′,4′-Dichloro-2-imidazol-1-ylacetophenone (*Z*)-*O*-(2,4-dichlorobenzyl)oxime mononitrate.

Оксиконазола Нитрат

$C_{18}H_{13}Cl_4N_3O,HNO_3 = 492.1.$

CAS — 64211-45-6 (oxiconazole); 64211-46-7 (oxiconazole nitrate).

ATC — D01AC11; G01AF17.

ATC Vet — QD01AC11; QG01AF17.

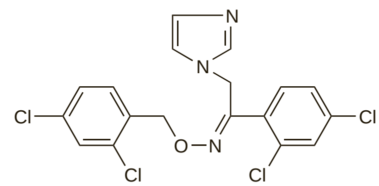

(oxiconazole)

Profile

Oxiconazole is an imidazole antifungal applied topically as the nitrate as a cream, solution, or powder equivalent to oxiconazole 1% in the treatment of fungal infections of the skin (p.521). It is also given as a pessary in a single dose equivalent to 600 mg of oxiconazole in the treatment of vaginal candidiasis (p.518).

Local reactions including burning and itching have been reported. Intravaginal preparations of azoles may damage latex contraceptives.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

◊ Reviews.

1. Jegasothy BV, Pakes GE. Oxiconazole nitrate: pharmacology, efficacy, and safety of a new imidazole antifungal agent. *Clin Ther* 1991; **13:** 126–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Oxistat; ***Austria:*** Gyno-Liderman; Liderman; Oceral; ***Braz.:*** Micotin; Oceral; Oxipelle; Oxitrat†; ***Canad.:*** Oxizole†; ***Cz.:*** Gyno-Myfungar†; Myfungar; ***Fr.:*** Fonx; ***Ger.:*** Myfungar; Oceral GB†; ***Mex.:*** Gyno-Myfungar†; Myfungar; Oxistat; ***Rus.:*** Myfungar (Мифунгар); ***Spain:*** Salongo; ***Switz.:*** Oceral; ***Turk.:*** Oceral; ***USA:*** Oxistat.

Multi-ingredient: ***India:*** Zoderm.

Parconazole Hydrochloride *(USAN, rINNM)*

Hidrocloruro de parconazol; Parconazole, Chlorhydrate de; Parconazoli Hydrochloridum; R-39500. *cis*-1-{[2-(2,4-Dichlorophenyl)-4-[(2-propynyloxy)methyl]-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole hydrochloride.

Парконазола Гидрохлорид

$C_{17}H_{16}Cl_2N_2O_3. HCl = 403.7.$

CAS — 61400-59-7 (parconazole); 68685-54-1 (parconazole); 62973-77-7 (parconazole hydrochloride).

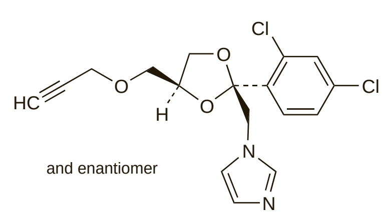

(parconazole)

Profile

Parconazole is an antifungal that has been used as the hydrochloride in the treatment of gastrointestinal candidiasis in veterinary medicine.

Pentamycin

Fungichromin; Lagosin; Pentamicina.

Пентамицин

$C_{35}H_{58}O_{12} = 670.8.$

CAS — 6834-98-6.

ATC — G01AA11.

ATC Vet — QG01AA11.

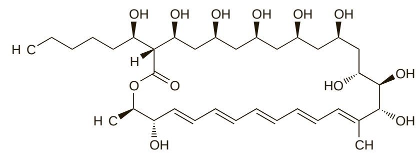

Profile

Pentamycin is a polyene antifungal antibiotic obtained from *Streptomyces pentaticus*. It has been used in the treatment of vaginal candidiasis and for the protozoal infection trichomoniasis.

Posaconazole *(BAN, USAN, rINN)*

Posaconazol; Posaconazolum; Sch-56592. 4-{*p*-[4-(*p*-{[(3*R*,5*R*)-5-(2,4-Difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furyl]methoxy}phenyl)-1-piperazinyl]phenyl}-1-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-Δ^2-1,2,4-triazolin-5-one.

Позаконазол

$C_{37}H_{42}F_2N_8O_4 = 700.8.$

CAS — 171228-49-2.

ATC — J02AC04.

ATC Vet — QJ02AC04.

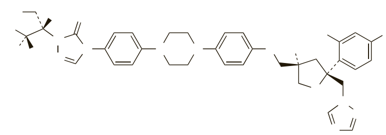

Adverse Effects

The most commonly reported adverse effects with posaconazole are headache and nausea. Other common adverse effects include abdominal pain, anorexia, asthenia, back pain, diarrhoea, dyspepsia, dizziness, dry mouth, dry skin, fatigue, fever, flatulence, hot flushes, insomnia, neutropenia, paraesthesia, pruritus, rash, somnolence, and vomiting. An increase in liver enzyme values has occurred in some patients, especially in those with serious underlying disease. Hypersensitivity and allergic reactions, including Stevens-Johnson syndrome, have occurred rarely.

Precautions

Some azoles have been associated with QT interval prolongation and licensed product information therefore advises that posaconazole should be used with caution in patients with potentially proarrhythmic conditions. Patients who develop abnormal liver function tests while being treated with posaconazole should be routinely monitored for the development of more serious liver injury.

Breast feeding. Breast feeding while taking posaconazole is not recommended by licensed product information.

Pregnancy. Posaconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with posaconazole.

Interactions

Posaconazole is metabolised by the uridine diphosphate glucuronosyltransferase UGT1A4, and is a substrate for p-glycoprotein. The use of drugs that either inhibit (for example, clarithromycin, erythromycin, ciclosporin, and verapamil) or induce (see below) enzymes in this pathway may increase or decrease plasma-posaconazole concentrations, respectively. Rifabutin and phenytoin have been shown to decrease plasma-posaconazole concentrations and a similar effect may be expected with rifampicin, carbamazepine, primidone, and phenobarbital. Concentrations of posaconazole are reduced by cimetidine possibly due to reduced absorption of posaconazole as a result of decreased acid production and reduced posaconazole concentrations may also be expected with other H_2-antagonists and proton pump inhibitors.

Posaconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and concentrations of other drugs that are metabolised by this enzyme pathway may be increased by posaconazole. Increased plasma concentrations of astemizole, cisapride, halofantrine, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. HMG-CoA reductase inhibitors such as atorvastatin, lovastatin, and simvastatin are contra-indicated as concomitant use as been associated with rhabdomyolysis. Increased plasma concentrations of sirolimus and tacrolimus have been noted; doses of sirolimus and tacrolimus may need to be reduced and concentrations monitored. Similarly, dose reduction with monitoring is recommended for ciclosporin. Close monitoring of blood glucose is necessary if posaconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for calcium-channel blockers, digoxin, vinca alkaloids, and some benzodiazepines (such as alprazolam, midazolam, and triazolam). It is expected that posaconazole will increase the concentrations of HIV-protease inhibitors and NNRTIs.

Interactions may occur where both posaconazole and the other drug are affected. Examples are ciclosporin (where concentrations of both posaconazole and ciclosporin are increased) and rifabutin (where concentrations of posaconazole are reduced but those of rifabutin are increased).

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Posaconazole is a triazole antifungal drug that in sensitive fungi inhibits the enzyme lanosterol 14α-demethylase (CYP51) resulting in the impairment of ergosterol synthesis in fungal cell membranes. Posaconazole has activity against *Candida* spp., *Aspergillus* spp., *Coccidioides immitis*, *Fonsecaea pedrosoi*, and some species of *Fusarium* and zygomycetes.

Pharmacokinetics

Posaconazole exhibits linear pharmacokinetics after single and multiple doses with a high fat meal. No further increases in plasma concentration are seen with doses above 800 mg daily. It is slowly absorbed from the gastrointestinal tract and has a large volume of distribution. Peak plasma concentrations occur about 5 hours after an oral dose. Steady state plasma-posaconazole concentrations occur after 7 to 10 days of multiple dosage. Plasma protein binding is over 98%.

Metabolism plays only a minor role in the elimination of posaconazole; most circulating metabolites are glucuronide conjugates with only small amounts of oxidative metabolites. Posaconazole is slowly eliminated with a mean elimination half-life of 35 hours. The main elimination route of posaconazole is via the faeces (77%) where 66% of a dose is excreted unchanged. About 14% of a dose is excreted in the urine with only trace amounts excreted unchanged.

◊ Reviews.

1. Courtney R, *et al.* Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; **47:** 2788–95.

Uses and Administration

Posaconazole is an oral triazole antifungal used in the treatment of severe oropharyngeal candidiasis. It is also indicated in the treatment of invasive aspergillosis, chromoblastomycosis, coccidioidomycosis, fusariosis, or mycetoma infections in patients who are resistant to, or intolerant of, other antifungals. Posaconazole is also given for the prophylaxis of fungal infections in patients who are at high risk for invasive fungal disease due to prolonged neutropenia.

Posaconazole is given orally as a suspension; doses should be given with a meal, or a nutritional supplement in those who cannot tolerate food, in order to enhance oral absorption and ensure adequate exposure.

For the treatment of **oropharyngeal candidiasis** posaconazole is given in a loading dose of 200 mg on the first day, followed by 100 mg daily for 13 days. In patients with oropharyngeal candidiasis refractory to itraconazole and/or fluconazole, posaconazole is given at a dose of 400 mg twice daily.

In patients with refractory **invasive systemic fungal infections**, it is given at a dose of 400 mg twice daily. Patients not tolerating food or nutritional supplements should take 200 mg four times daily.

In the **prophylaxis** of invasive fungal infections, the recommended dose is 200 mg three times daily. Treatment is continued until recovery from neutropenia or immunosuppression. In patients undergoing cytotoxic chemotherapy for haematological malignancies, or haematopoietic stem-cell transplantation, treatment should begin several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells/mm^3.

◊ References.

1. Herbrecht R. Posaconazole: a potent, extended-spectrum triazole anti-fungal for the treatment of serious fungal infections. *Int J Clin Pract* 2004; **58:** 612–24.
2. Segal BH, *et al.* Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis* 2005; **40:** 1684–8.
3. Keating GM. Posaconazole. *Drugs* 2005; **65:** 1553–67.
4. Raad II, *et al.* Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis* 2006; **42:** 1726–34.
5. Nagappan V, Deresinski S. Posaconazole: a broad-spectrum triazole antifungal agent. *Clin Infect Dis* 2007; **45:** 1610–7.
6. Frampton JE, Scott LJ. Posaconazole : a review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008; **68:** 993–1016.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Noxafil; ***Cz.:*** Noxafil; ***Fr.:*** Noxafil; ***Gr.:*** Noxafil; ***Neth.:*** Noxafil; ***NZ:*** Noxafil; ***Pol.:*** Noxafil; ***Swed.:*** Noxafil; ***UK:*** Noxafil; ***USA:*** Noxafil.

Propionic Acid

E280; E283 (potassium propionate); Kwas propionowy; Propanoico, ácido. Propanoic acid.

Пропионовая Кислота

$C_2H_5.CO_2H$ = 74.08.

CAS — 79-09-4.

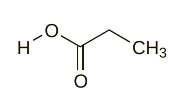

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 26 (Propionic Acid). An oily liquid having a slight pungent, rancid odour. Miscible with water, with alcohol, and with various other organic solvents. Store in airtight containers.

Calcium Propionate

E282. Calcium propanoate.

Пропионат Кальция

$(C_3H_5O_2)_2Ca$ = 186.2.

CAS — 4075-81-4 (anhydrous calcium propionate); 56744-45-7 (calcium propionate monohydrate).

Sodium Propionate

E281; Natrii propionas; Natrio propionatas; Natriumpropionaatti; Natriumpropionat; Nátrium-propionát; Propionan sodný; Propionato de sodio; Sodium, propionate de. Sodium propanoate.

Пропионат Натрия

$C_3H_5NaO_2$ = 96.06.

CAS — 137-40-6 (anhydrous sodium propionate); 6700-17-0 (sodium propionate hydrate).

ATC — S01AX10.

ATC Vet — QA16QA02; QS01AX10.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Propionate). Slightly hygroscopic colourless crystals or white or almost white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 7.8 to 9.2. Store in airtight containers.

USNF 26 (Sodium Propionate). Colourless transparent crystals or a granular crystalline powder; odourless or with a faint acetic-butyric odour. Deliquescent in moist air. Soluble 1 in 1 of water, 1 in 0.65 of boiling water, and 1 in 24 of alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Profile

Propionic acid and its salts are antifungals. Calcium and sodium propionate have been used topically, usually with other antimicrobials for the treatment of dermatophyte infections. Eye drops containing sodium propionate have also been used.

Propionic acid and its calcium, sodium, and potassium salts are used in the baking industry as inhibitors of moulds.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Propionat.

Multi-ingredient: ***Arg.:*** Cicatrol; Farm-X; Fungicida†; Hipoglos Cicatrizante; Novo Miconol; Piecidex†; Plusderm†; ***Austral.:*** Mycoderm; ***Austria:*** Dermowund; ***Braz.:*** Andriodermol; Colpagex N; Gynax-N; Micotox†; Vagitrin-N; ***Canad.:*** Amino-Cerv; ***Chile:*** Fittig; ***Fr.:*** Dermacide; Otoralgyl a la phenylephrine†; ***Hong Kong:*** Mycoderm; ***Indon.:*** Decyline; ***Israel:*** Otomycin; ***Malaysia:*** Mycoderm; ***S.Afr.:*** Neopan; ***USA:*** Amino-Cerv; Prophyllin; ***Venez.:*** Diodonato†.

Pyrrolnitrin *(USAN, rINN)*

52230; NSC-107654; Pirrolnitrina; Pyrrolnitrine; Pyrrolnitrinum. 3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole.

Пирролнитрин

$C_{10}H_6Cl_2N_2O_2$ = 257.1.

CAS — 1018-71-9.

ATC — D01AA07.

ATC Vet — QD01AA07.

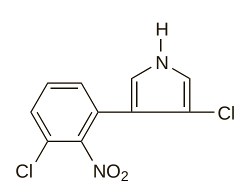

Pharmacopoeias. In *Jpn.*

Profile

Pyrrolnitrin is an antifungal antibiotic isolated from *Pseudomonas pyrrocinia* and applied topically in the treatment of superficial fungal infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Micutrin.

Multi-ingredient: ***Ital.:*** Micutrin Beta†; ***Port.:*** Pirrolfungin†.

The symbol † denotes a preparation no longer actively marketed

Ravuconazole *(pINN)*

BMS-207147; ER-30346; Ravuconazol; Ravuconazolum. 4-{2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-thiazolyl}-benzonitrile.

Равуконазол

$C_{22}H_{17}F_2N_5OS$ = 437.5.

CAS — 182760-06-1.

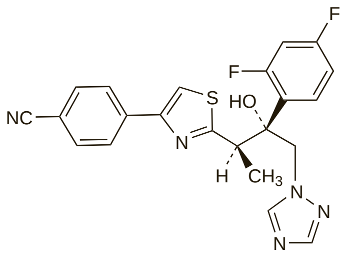

Profile

Ravuconazole is a triazole antifungal said to possess a broader spectrum of activity than fluconazole or itraconazole. It is under investigation for the treatment of systemic fungal infections.

Sertaconazole Nitrate *(BANM, rINNM)*

Nitrato de sertaconazol; Sertaconazole, nitrate de; Sertaconazoli nitras; Sertakonatsolinitraatti; Sertakonazol Nitrat; Sertakonazol-nitrat; Sertakonazol-nitrát; Sertakonazolo nitratas; Szertakonazol-nitrát. (±)-1-{2,4-Dichloro-β-[(7-chlorobenzo[*b*]thien-3-yl)-methoxy]phenethyl}imidazole nitrate.

Сертаконазола Нитрат

$C_{20}H_{15}Cl_3N_2OS,HNO_3$ = 500.8.

CAS — 99592-32-2 (sertaconazole); 99592-39-9 (sertaconazole nitrate).

ATC — D01AC14.

ATC Vet — QD01AC14.

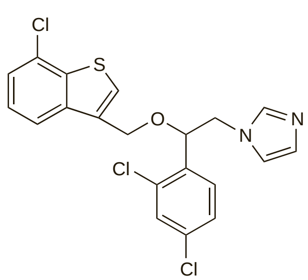

(sertaconazole)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sertaconazole Nitrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol and in dichloromethane; soluble in methyl alcohol. Protect from light.

Profile

Sertaconazole is an imidazole antifungal used topically as the nitrate as a 2% cream, gel, solution, or powder in the treatment of superficial candidiasis, dermatophytosis, seborrhoeic dermatitis, and pityriasis versicolor. In the treatment of vaginal candidiasis it is used as a 2% vaginal cream daily for 7 or 8 days or as a single dose of a 300-mg or 500-mg pessary.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Zalain†; ***Austria:*** Zalain†; ***Braz.:*** Gyno Zalain; Zalain; ***Chile:*** Tromderm; Zalain; ***Cz.:*** Zalain†; ***Ger.:*** Mykosert; Zalain; ***Gr.:*** Fuganol†; ***Hong Kong:*** Zalain; ***Hung.:*** Zalain; ***Indon.:*** Dermofix; ***Ital.:*** Sertacream; Sertaderm; Sertadie; Sertagyn; Zalain†; ***Malaysia:*** Zalain†; ***Philipp.:*** Zalain; ***Port.:*** Dermofix; Sertopic; ***Rus.:*** Zalain (Залаин); ***Singapore:*** Zalain; ***Spain:*** Dermofix; Dermoseptic; Gine Zalain; Ginedermofix; Zalain; ***Thai.:*** Zalain; ***Turk.:*** Zalain; ***USA:*** Ertaczo; ***Venez.:*** Zalain.

Siccanin *(rINN)*

Sicanina; Siccanine; Siccaninum. (13a*S*)-1,2,3,4,4a*β*-5,6,6a,11b*β*,13b*β*-Decahydro-4-4-6a*β*,9-tetramethyl-13*H*-benzo[*a*]furo[2,3,4-*mn*]xanthen-11-ol.

Сикканин

$C_{22}H_{30}O_3$ = 342.5.

CAS — 22733-60-4.

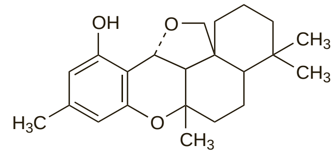

Pharmacopoeias. In *Jpn.*

Profile

Siccanin is obtained from *Helminthosporium siccans*, a parasitic organism of rye grass It has antifungal activity and is used topically as a 1% ointment for dermatophyte infections.

Sodium Parachlorobenzoate

Sodium *p*-Chlorobenzoate.

Натрий Парахлорбензоат

$C_7H_4ClNaO_2$ = 178.5.

CAS — 3686-66-6.

Profile

Sodium parachlorobenzoate has antifungal activity and is used as a 4% powder in the treatment of fungal skin infections (p.521).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hung.:*** Mycosid.

Sulconazole Nitrate *(BANM, USAN, rINNM)*

Nitrato de sulconazol; RS-44872; RS-44872-00-10-3; Sulconazole, Nitrate de; Sulconazoli Nitras; Sulkonazol Nitrat. 1-[2,4-Dichloro-β-(4-chlorobenzyl)thiophenethyl]imidazole nitrate.

Сульконазола Нитрат

$C_{18}H_{15}Cl_3N_2S,HNO_3$ = 460.8.

CAS — 61318-90-9 (sulconazole); 61318-91-0 (sulconazole nitrate).

ATC — D01AC09.

ATC Vet — QD01AC09.

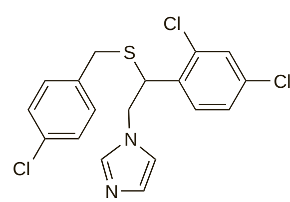

(sulconazole)

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Sulconazole Nitrate). A white to off-white crystalline powder. Soluble 1 in 3333 of water, 1 in 100 of alcohol, 1 in 130 of acetone, 1 in 333 of chloroform, 1 in 286 of dichloromethane, 1 in 2000 of dioxan, 1 in 71 of methyl alcohol, 1 in 10 of pyridine, and 1 in 2000 of toluene. Protect from light.

Adverse Effects and Precautions

Local reactions including blistering, burning, itching, and erythema have been reported after sulconazole use.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Antimicrobial Action

Sulconazole is an imidazole antifungal with activity against dermatophytes, *Candida* spp., and *Malassezia furfur.*

Uses and Administration

Sulconazole is an imidazole antifungal used topically as the nitrate once or twice daily as a 1% cream or solution in the treatment of fungal skin infections including dermatophyte infections and pityriasis versicolor (p.521), and candidiasis (p.518).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Antifungal; Minot†; ***Belg.:*** Myk-1; ***Fr.:*** Myk; ***Irl.:*** Exelderm†; ***Neth.:*** Myk-1; ***Turk.:*** Exelderm; ***UK:*** Exelderm; ***USA:*** Exelderm.

Terbinafine *(BAN, USAN, rINN)*

SF-86-327; SF-86327; Terbinafiini; Terbinafin; Terbinafina; Terbinafinum. (*E*)-6,6-Dimethylhept-2-en-4-ynl(methyl)-(1-naphthylmethyl)amine.

Тербинафин

$C_{21}H_{25}N$ = 291.4.

CAS — 91161-71-6.

ATC — D01AE15; D01BA02.

ATC Vet — QD01AE15; QD01BA02.

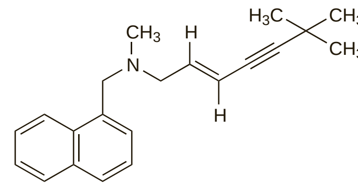

Terbinafine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de terbinafina; Terbinafiinihydrokloridi; Terbinafin Hidroklorür; Terbinafine, chlorhydrate de; Terbinafin-hydrochlorid; Terbinafinhydroklorid; Terbinafini hydrochloridum; Terbinafiny chlorowodorek.

Тербинафина Гидрохлорид

$C_{21}H_{26}ClN$ = 327.9.

CAS — 78628-80-5.

ATC — D01AE15; D01BA02.

ATC Vet — QD01AE15; QD01BA02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Terbinafine Hydrochloride). A white or almost white powder. Very slightly or slightly soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone. Protect from light.

USP 31 (Terbinafine Hydrochloride). A white or off-white powder. Very slightly or slightly soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in acetone; Protect from light.

Adverse Effects

The most frequent adverse effects after oral use of terbinafine hydrochloride are gastrointestinal disturbances such as nausea, diarrhoea, and mild abdominal pain. Loss or disturbance of taste may occur and occasionally may be severe enough to lead to anorexia and weight loss. Other frequent adverse effects include headache and skin reactions, including rash or urticaria, sometimes with arthralgia or myalgia. Severe skin reactions including angioedema, photosensitivity, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Liver dysfunction with isolated reports of cholestasis, hepatitis, and jaundice, has occurred and there have also been rare cases of hepatic failure, sometimes leading to death or needing liver transplantation, in patients both with and without pre-existing liver disease. Other rare adverse effects include paraesthesia, hypoaesthesia, dizziness, malaise, fatigue, and alopecia. Haematological disorders including neutropenia, thrombocytopenia, and agranulocytosis, psychiatric disturbances such as depression and anxiety, and precipitation or exacerbation of cutaneous and systemic lupus erythematosus have been reported very rarely.

There may be local reactions after topical use of terbinafine.

Incidence of adverse effects. Postmarketing surveillance of about 10 000 patients[1] suggested the following incidences of adverse effects to oral terbinafine: gastrointestinal symptoms, 4.7%; dermatological effects, 3.3%; CNS symptoms (commonly headache), 1.8%; taste disturbances, 0.6%; and transient disturbances in liver function, 0.1%. Serious adverse effects possibly or probably related to terbinafine included angioedema, bronchospasm, erythema multiforme, extended stroke, and unilateral leg oedema. Combined data from 25 884 patients from this and 3 further studies[2] generally confirmed these results. Overall, adverse effects were reported in 10.5% of patients and caused treatment to be stopped in 5.3%. Serious adverse effects probably or possibly related to terbinafine occurred in 12 patients (0.046%).

1. O'Sullivan DP, *et al.* Postmarketing surveillance of oral terbinafine in the UK: report of a large cohort study. *Br J Clin Pharmacol* 1996; **42:** 559–65.
2. O'Sullivan DP. Terbinafine: tolerability in general medical practice. *Br J Dermatol* 1999; **141** (suppl 56): 21–5.

Effects on the blood. Up to August 2006, the Australian Adverse Drug Reactions Advisory Committee had received 16 reports of blood dyscrasias attributed to oral terbinafine including agranulocytosis (7 reports), neutropenia (7), and pancytopenia (2).[1] The reactions generally occurred within 4 to 6 weeks of starting therapy. Eleven patients recovered, 4 within one week of stopping treatment. However, a 79-year-old patient who developed agranulocytosis about 2 months after starting terbinafine died from septic shock.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Life threatening blood dyscrasias with oral terbinafine. *Aust Adverse Drug React Bull* 2006; **25:** 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.htm (accessed 02/05/08)

Effects on the eyes. The US manufacturer has noted that changes in the lens and retina of the eye have sometimes been associated with oral terbinafine, although the significance of these changes is not known.

Effects on the salivary glands. Bilateral parotid swelling was associated with terbinafine in a 38-year-old man.[1] Information from the manufacturer and the UK CSM indicated that this effect had occurred in other patients but was very rare. More recently, severe sialadenitis as a complication of drug reaction with eosinophilia and systemic complications (DRESS—a type of hypersensitivity reaction) was reported in an 80-year-old woman treated with terbinafine.[2] She also had severe xerostomia, lachrymal gland swelling, dry eyes, and keratitis.

1. Torrens JK, McWhinney PH. Parotid swelling and terbinafine. *BMJ* 1998; **316:** 440–1.
2. Abecassis S, *et al.* Severe sialadenitis: a new complication of drug reaction with eosinophilia and systemic symptoms. *J Am Acad Dermatol* 2004; **51:** 827–30.

Effects on the skin. Serious skin reactions are occasionally reported in patients receiving terbinafine and have included erythema multiforme,[1,2] erythroderma,[1] severe urticaria,[1] pityriasis rosea,[1] worsening of pre-existing psoriasis,[1,3] acrodermatitis continua of Hallopeau,[4] bullous pemphigoid,[5] acute generalised exanthematous pustulosis,[6] and lupus erythematosus.[7-10] Several of these patients had a history of auto-immune disease[2,9] and it has been suggested that this could be a risk factor for developing severe reactions.[2]

1. Gupta AK, *et al.* Cutaneous adverse effects associated with terbinafine therapy: 10 case reports and a review of the literature. *Br J Dermatol* 1998; **138:** 529–32.
2. Goeteyn V, *et al.* Is systemic autoimmune disease a risk factor for terbinafine-induced erythema multiforme? *Br J Dermatol* 2000; **142:** 578–9.
3. Wilson NJE, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; **139:** 168.
4. Nishiwaki F, *et al.* Acrodermatitis continua of Hallopeau due to oral terbinafine. *Br J Dermatol* 2007; **157:** 1073–4.
5. Aksakal BA, *et al.* Oral terbinafine-induced bullous pemphigoid. *Ann Pharmacother* 2003; **37:** 1625–7.
6. Beltraminelli HS, *et al.* Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: case report and review of the literature. *Br J Dermatol* 2005; **152:** 780–3.
7. Murphy M, Barnes L. Terbinafine-induced lupus erythematosus. *Br J Dermatol* 1998; **138:** 708–9.
8. Brooke R, *et al.* Terbinafine-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 1998; **139:** 1132–3.
9. Holmes S, Kemmett D. Exacerbation of systemic lupus erythematosus induced by terbinafine. *Br J Dermatol* 1998; **139:** 1133.
10. Hill VA, *et al.* Subacute lupus erythematosus-like eruption due to terbinafine: report of three cases. *Br J Dermatol* 2003; **148:** 1056.

Effects on taste. Disturbance and loss of taste have been reported in about 0.6% of patients taking terbinafine. While this usually resolves gradually once the drug is withdrawn, persistent impairment of taste has been reported.[1,2]

1. Bong JL, *et al.* Persistent impairment of taste resulting from terbinafine. *Br J Dermatol* 1998; **139:** 747–8.
2. Duxbury AJ, *et al.* Persistent impairment of taste associated with terbinafine. *Br Dent J* 2000; **188:** 295–6.

Precautions

Terbinafine should not be used in patients with existing liver disease and liver function tests should be performed in all patients before starting oral therapy. Terbinafine should be stopped if clinical or biochemical evidence of hepatotoxicity develops. It should also be stopped if any progressive skin rash occurs and should be used with caution in patients with psoriasis.

Terbinafine should be given in reduced doses to patients with renal impairment (see Administration in Renal Impairment, under Uses and Administration, below).

Breast feeding. Terbinafine is excreted in breast milk and licensed product information states that it should be avoided during breast feeding.

Interactions

Plasma concentrations of terbinafine may be increased by drugs that inhibit its metabolism by cytochrome P450, such as cimetidine, and decreased by drugs that induce cytochrome P450 enzymes, such as rifampicin.

Menstrual disturbances including breakthrough bleeding have been reported in patients taking oral contraceptives and terbinafine.

Terbinafine has been shown *in vitro* to inhibit metabolism mediated by the cytochrome P450 isoenzyme CYP2D6. Hence it may affect the plasma concentrations of drugs predominantly metabolised by this enzyme such as tricyclic antidepressants, beta blockers, SSRIs, and type B MAOIs.

For the effects of terbinafine on some other drugs, see carbamazepine (p.475), ciclosporin (p.1826), nortriptyline (p.380), and warfarin (p.1429).

Antimicrobial Action

Terbinafine is an allylamine derivative reported to have a broad spectrum of antifungal activity. It is considered to act through inhibition of fungal sterol synthesis. Terbinafine is fungicidal against dermatophytes, moulds, and certain dimorphic fungi and some yeasts.

Microbiological interactions. Additive and synergistic activity was reported with terbinafine plus fluconazole or itraconazole against strains of *Candida albicans* that had reduced susceptibility to azoles *in vitro*.[1] Terbinafine was also reported to enhance the activity of azoles against *Scedosporium prolificans*[2] and against the protozoan *Leishmania braziliensis*.[3]

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44:** 470–2.
3. Rangel H, *et al.* Naturally azole-resistant Leishmania braziliensis promastigotes are rendered susceptible in the presence of terbinafine: comparative study with azole-susceptible Leishmania mexicana promastigotes. *Antimicrob Agents Chemother* 1996; **40:** 2785–91. Correction. *ibid.* 1997; **41:** 496.

Pharmacokinetics

Terbinafine hydrochloride is well absorbed from the gastrointestinal tract. The bioavailability is about 40% because of first-pass hepatic metabolism. Mean peak plasma concentrations of about 1 microgram/mL occur within 2 hours of a single oral dose of 250 mg. Steady state concentrations are about 25% higher than those seen after a single dose and are reached in 10 to 14 days. Terbinafine is extensively bound to plasma proteins. Terbinafine is distributed into the stratum corneum of the skin, the nail plate, and hair where it reaches concentrations considerably higher than those found in plasma. It appears in breast milk.

Terbinafine is metabolised in the liver to inactive metabolites which are excreted mainly in the urine. A plasma elimination half-life varying from 17 to 36 hours has been reported and a terminal elimination half-life of up to 400 hours in patients given prolonged therapy, probably representing elimination from skin and adipose tissue. Fungicidal concentrations in nails are maintained for several weeks after therapy is stopped. The elimination rate may be altered in patients with liver or kidney disease. Less than 5% of a topical dose of terbinafine hydrochloride is absorbed.

◊ References.

1. Kovarik JM, *et al.* Multiple-dose pharmacokinetics and distribution in tissue of terbinafine and metabolites. *Antimicrob Agents Chemother* 1995; **39:** 2738–41.

Uses and Administration

Terbinafine is an allylamine antifungal given by mouth as the hydrochloride in the treatment of dermatophyte infections of the skin and nails (p.521). Oral doses are stated in terms of the base. Terbinafine hydrochloride 1.13 g is equivalent to about 1 g of terbinafine. It is also applied, as the hydrochloride, to the skin in dermatophytoses, in pityriasis versicolor (see Skin Infections, p.521), and in cutaneous candidiasis (p.518).

An oral dose of 250 mg is given once daily for 2 to 4 weeks for tinea cruris; treatment may be continued for up to 6 weeks for tinea pedis infections; a 4-week course is used in tinea corporis infections. A cream, gel, or solution containing 1% terbinafine hydrochloride is applied once or twice daily for 1 to 2 weeks to treat tinea corporis and tinea cruris; a 1-week course is recommended for tinea pedis. A 2-week course of treatment is used in cutaneous candidiasis and pityriasis versicolor.

Dermatophyte infections of the nails are treated with the equivalent of terbinafine 250 mg orally once daily for 6 to 12 weeks although longer treatment may be necessary in toe-nail infections.

Dosage should be reduced in patients with renal impairment (see below).

◊ References.

1. Balfour JA, Faulds D. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* 1992; **43:** 259–84.
2. Abdel-Rahman SM, Nahata MC. Oral terbinafine: a new antifungal agent. *Ann Pharmacother* 1997; **31:** 445–56.
3. McClellan KJ, *et al.* Terbinafine: an update of its use in superficial mycoses. *Drugs* 1999; **58:** 179–202.
4. Darkes MJ, *et al.* Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol* 2003; **4:** 39–65.
5. Fleece D, *et al.* Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114:** 1312–15.
6. Gupta AK, *et al.* The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. *J Drugs Dermatol* 2005; **4:** 302–8.
7. Revankar SG, *et al.* Use of terbinafine in rare and refractory mycoses. *Future Microbiol* 2008; **3:** 9–17.

Administration in children. Although terbinafine is not currently licensed in the UK for use in children, the *BNFC* suggests the following oral doses for the treatment of tinea capitis in children over 1 year of age:

- in those weighing 10 to 20 kg: the equivalent of terbinafine 62.5 mg once daily
- in those weighing 20 to 40 kg: 125 mg once daily
- in those weighing over 40 kg: 250 mg once daily Treatment is usually given for 4 weeks for tinea capitis, 2 to 4 weeks for tinea cruris, 4 weeks for tinea corporis, and may be continued for up to 6 weeks in tinea pedis. Infections of the nails are treated for 6 weeks to 3 months, although longer treatment may occasionally be required for toe-nail infections.

Similar regimens have been reported in the literature.[1,2] A review on the use of terbinafine in children considered it both safe and effective in the management of tinea capitis and onychomycosis.[3]

1. Jones TC. Overview of the use of terbinafine (Lamisil) in children. *Br J Dermatol* 1995; **132:** 683–9.
2. Fuller LC, *et al.* A randomized comparison of 4 weeks of terbinafine vs 8 weeks of griseofulvin for the treatment of tinea capitis. *Br J Dermatol* 2001; **144:** 321–7.
3. Gupta AK, *et al.* The efficacy and safety of terbinafine in children. *J Eur Acad Dermatol Venereol* 2003; **17:** 627–40.

Administration in renal impairment. The UK licensed product information recommends that in patients with renal impairment (creatinine clearance less than 50 mL/minute or serum creatinine greater than 300 micromol/litre) usual oral doses should be halved to the equivalent of 125 mg of terbinafine daily.

Leishmaniasis. An inadvertent beneficial response has been reported[1] in an HIV-positive patient with cutaneous leishmaniasis (p.824) who was taking terbinafine 250 mg daily for tinea corporis and onychomycosis. Beneficial results were also reported in a pilot study[2] in which patients with cutaneous leishmaniasis took either terbinafine 125 mg twice daily (those aged 5 to 15 years), or terbinafine 250 mg twice daily (those over 15 years), for 4 weeks.

1. González-Rupérez J, *et al.* Remission of localized cutaneous leishmaniasis in a HIV-positive patient using systemic terbinafine. *Dermatology* 1997; **194:** 85–6.
2. Bahamdan KA, *et al.* Terbinafine in the treatment of cutaneous leishmaniasis: a pilot study. *Int J Dermatol* 1997; **36**: 59–60.

Non-dermatophyte fungal infections. Beneficial responses to oral terbinafine have been reported in candidal infections of the nails and mouth,[1-3] aspergillosis, chromoblastomycosis, paracoccidioidomycosis, and sporotrichosis.[3]

1. Nolting S, *et al.* Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. *Br J Dermatol* 1994; **130** (suppl 43): 16–21.
2. Segal R, *et al.* Treatment of Candida nail infection with terbinafine. *J Am Acad Dermatol* 1996; **35:** 958–61.
3. Pérez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. *Mycoses* 1999; **42** (suppl 2): 111–4.

Seborrhoeic dermatitis. Terbinafine has been tried in the treatment of seborrhoeic dermatitis (p.1584). In one study, 60 patients were randomised to receive oral terbinafine 250 mg daily or a placebo cream applied twice daily for 4 weeks.[1] Clinical improvement, maintained 8 weeks after completing treatment, in the terbinafine group led the investigators to conclude that oral terbinafine is an effective treatment for seborrhoeic dermatitis, and to suggest that this might be due to its activity against *Malassezia ovalis* (*Pityrosporum ovale*) as well as to some anti-inflammatory action. However, the methodology of this study has been questioned[2] and further investigation is needed. A further, uncontrolled, study[3] of 661 patients who received oral terbinafine 250 mg daily for 12 days each month for 3 months concluded that intermittent oral terbinafine could be effective for seborrhoeic dermatitis, at least in severe or recalcitrant forms. It has also been tried topically as a 1% cream.[4]

1. Scaparro E, *et al*. Evaluation of the efficacy and tolerability of oral terbinafine (Daskil) in patients with seborrhoeic dermatitis: a multicentre, randomized, investigator-blinded, placebo-controlled trial. *Br J Dermatol* 2001; **144:** 854–7.
2. Faergemann J. Treatment of seborrhoeic dermatitis with oral terbinafine? *Lancet* 2001; **358:** 170.
3. Cassano N, *et al*. Oral terbinafine for the treatment of seborrheic dermatitis in adults. *Int J Dermatol* 2002; **41:** 821–2.
4. Gündüz K, *et al*. Efficacy of terbinafine 1% cream on seborrhoeic dermatitis. *J Dermatol* 2005; **32:** 22–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Fungueal; Lamisil; Maditez; Piecidex NF; Tacna; Terbi-Derm; Terekol; Terfin; ***Austral.:*** Lamisil; SolvEasy; Tamsil; Zabel; ***Austria:*** Daskil; Lamisil; ***Belg.:*** Lamisil; ***Braz.:*** Binafin†; Finex†; Funtyl; Lamisil; Micosil; ***Canad.:*** Lamisil; ***Chile:*** Dermoxyl; Dicil; Elater; Finex; Lamisil; Micoset; Micostop†; Terfex; ***Cz.:*** Atifan; Brinaf†; Lamisil; Mycodekan; Onychon; Tefine; Terbihexal; Terbisil; Terbistad; Terfimed; Verbinaf; ***Denm.:*** Lamisil; ***Fin.:*** Lamisil; ***Fr.:*** Lamisil; Lamisilate; LamisilDermgel; ***Ger.:*** Amiada; Dermatin; Lamisil; Myconormin; Onymax; Terbiderm; Terbigalen; ***Gr.:*** Anaplas; Chemiderm; Demsil; Drogenil; Ealk; Flixid; Frezylin; Fungitherapy; Lamigen; Lamisil; Mycutol; Optimus; Pavlinox; Pro-Misil; Romiver; Seralon; Soluteb; Terbafin; Terbigram; Terbin; Terbiprol; Terbiskin; Terbisol; Terfinil; Terfinor; Termisil; Thateron; Vifaderm; ***Hong Kong:*** Lamisil; Terbifin; ***Hung.:*** Lamisil; Terbigen; Terbisil; Terfin; Tineal; ***India:*** Exifine; Lamisil†; Terbifin; ***Indon.:*** Interbi; Lamisil; Termisil; ***Irl.:*** Fungafine; Fungasil; Lamisil; Lanafine; Nailderm; Ternaf; ***Israel:*** Lamisil; ***Ital.:*** Daskil; Lamisil; ***Malaysia:*** Dermafin; Exifine; Lamisil; Lisim; ***Mex.:*** Binafex; Erbitrax; Fyterdin; Lamisil; Losil-T; Mycelvan; Unasal; Xilatril; ***Neth.:*** Binanidda; Finanidda; Finavita†; Fungitif; Lamisil; Niddafin; Niddavita; Terbiderm; Terbinavita; Terfungin; Tiebinafin; Vitabin; ***Norw.:*** Lamisil; ***NZ:*** Lamisil†; Terbafin; ***Philipp.:*** Lamifen; Lamisil; ***Pol.:*** Afugin; Lamisil; Lamisilatt; Myconafine; Onymax; Tenasil; Terbiderm; TerbiGen; Terbisil; ***Port.:*** Daskyl; Lamisil; ***Rus.:*** Binafin (Бинафин); Exifine (Экзифин); Fungoterbine (Фунготербин); Lamican (Ламикан); Lamisil (Ламизил); Medofloran (Медофлоран); Terbinox (Тербинокс); Terbisil (Тербизил); Termicon (Термикон); ***S.Afr.:*** Dermax; Lamisil; Terbicil; ***Singapore:*** Lamisil; ***Spain:*** Lamicosil; Lamisil; ***Swed.:*** Lamisil; ***Switz.:*** Lamisil; Myconormin; Onymax; Terbifil; Tineafine; ***Thai.:*** EU 2000; Lamisil; ***Turk.:*** Lamisil; Mycocur; Terafin; Terbin; Terbisil; Tigal; ***UK:*** Lamisil; ***USA:*** DesenexMax; Lamisil; ***Venez.:*** Exifine†; Funtopic†; Lamisil; Nafina; Terfex.

Terconazole *(BAN, USAN, rINN)*

R-42470; Terconazol; Terconazolum; Terkonatsoli; Terkonazol; Terkonazolas; Triaconazole. 1-{4-[[2-(2,4-Dichlorophenyl)-*r*-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-*c*-4-yl]methoxy]phenyl}-4-isopropylpiperazine.

Терконазол

$C_{26}H_{31}Cl_2N_5O_3$ = 532.5.
CAS — 67915-31-5.
ATC — G01AG02.
ATC Vet — QG01AG02.

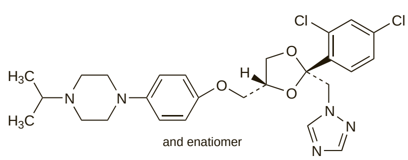

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Terconazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

Adverse Effects

Local reactions including burning and itching have been reported with vaginal use of terconazole. Other adverse effects have included dysmenorrhoea and genital, body, and abdominal pain. A flu-like syndrome with headache, fever, chills, and hypotension has been reported in some patients and may be more prevalent with vaginal pessaries providing doses larger than 80 mg.

Flu-like syndrome. References.

1. Moebius UM. Influenza-like syndrome after terconazole. *Lancet* 1988; **ii:** 966–7.

Precautions

Intravaginal preparations of terconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Antimicrobial Action

Terconazole is a triazole derivative that is thought to disrupt normal fungal cell membrane permeability. Terconazole is active *in vitro* against *Candida* spp. and other fungi. It has some antibacterial activity *in vitro* but not against usual vaginal flora such as lactobacilli.

Pharmacokinetics

After intravaginal use, 5 to 16% of terconazole is absorbed. Systemically absorbed drug is metabolised by the liver and excreted in urine and faeces.

Uses and Administration

Terconazole is a triazole antifungal used in the local treatment of vulvovaginal candidiasis (p.518). Intravaginal dosage regimens are terconazole 40 mg (as 0.8% vaginal cream) or 80 mg (as a pessary) at bedtime for 3 nights or 20 mg (as 0.4% cream) at bedtime for 7 nights.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Gyno-Terazol†; ***Braz.:*** Ginconazol†; Gyno-Fungix; ***Canad.:*** Terazol; ***Mex.:*** Fungistat; ***S.Afr.:*** Terazol; ***Switz.:*** Gyno-Terazol; ***USA:*** Terazol; Zazole; ***Venez.:*** Fungistat.

Tioconazole *(BAN, USAN, rINN)*

Tioconazol; Tioconazolum; Tiokonatsoli; Tiokonazol; Tiokonazolas; UK-20349. 1-[2,4-Dichloro-β-(2-chloro-3-thenyloxy)phenethyl]imidazole.

Тиоконазол

$C_{16}H_{13}Cl_3N_2OS$ = 387.7.
CAS — 65899-73-2.
ATC — D01AC07; G01AF08.
ATC Vet — QD01AC07; QG01AF08.

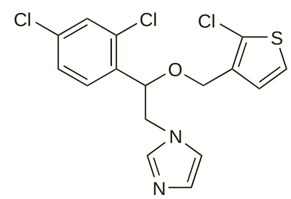

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Tioconazole). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Tioconazole). Store in airtight containers.

Adverse Effects and Precautions

Local reactions to tioconazole including burning, itching, and erythema have been reported.

Intravaginal preparations of tioconazole may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Hypersensitivity. Tioconazole, an imidazole antifungal widely used in Finland, appeared to be an important cause of contact allergy in that country, since an incidence of more than 1% was reported in patients undergoing routine patch testing.[1] There may be cross-reactivity with other commonly used imidazole derivatives.

1. Heikkilä H, *et al*. A study of 72 patients with contact allergy to tioconazole. *Br J Dermatol* 1996; **134:** 678–80.

Antimicrobial Action

Tioconazole is an imidazole antifungal with a broad spectrum of activity including action against dermatophytes, *Malassezia furfur*, and *Candida albicans.* Tioconazole is active *in vitro* against some Gram-positive bacteria.

Uses and Administration

Tioconazole is an imidazole antifungal used in the treatment of superficial candidiasis (p.518), and dermatophytoses and pityriasis versicolor (see Skin Infections, p.521).

For vaginal candidiasis it is used as pessaries or vaginal ointment usually as a single 300-mg dose.

It has been used topically as a 1% cream, lotion, or powder in the treatment of superficial fungal infections. Tioconazole has also been used for nail infections as a 28% w/w topical solution, although systemic treatment is generally preferred.

Preparations

BP 2008: Tioconazole Cream; Tioconazole Nail Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Honguil; Niofen; Tiomicol; Trosyd; ***Austria:*** Trosyd; ***Braz.:*** Gino Conazol; Gino Tralen; Neo Tionazol; Tioconax; Tionazen; Tralen; ***Canad.:*** Gynecure†; Trosyd†; ***Chile:*** Telset; ***Fin.:*** Gyno-Trosyd; Trosyd; ***Fr.:*** Gyno-Trosyd; Trosyd; ***Ger.:*** Mykontral; ***Gr.:*** Cotinazin; ***Hong Kong:*** Gyno-Trosyd; Trosyd; ***Indon.:*** Prodermal; Trosyd; ***Irl.:*** Trosyl; ***Ital.:*** Gino-Trosyd†; Trosyd; ***Malaysia:*** Gyno-Trosyd; Trosyd; ***NZ:*** Gyno-Trosyd†; ***Philipp.:*** Trosyd; ***Port.:*** Gino-Trosyd; Trosyd; ***S.Afr.:*** Gyno-Trosyd; Trosyd; ***Singapore:*** Gyno-Trosyd; Trosyd; ***Spain:*** Trosderm; Trosid; ***Switz.:*** Gyno-Trosyd; Trosyd; ***Thai.:*** Trosyd; ***Turk.:*** Dermo-Rest; Dermo-Trosyd; Gyno-Trosyd; Tiocan; Tiocell; ***UK:*** Trosyl; ***USA:*** Vagistat-1; ***Venez.:*** Gino-Tralen; Tralen.

Multi-ingredient: ***Braz.:*** Cartrax; Duozol; Gynomax; Gynopac; Seczol; Takil; Travogyn; ***Fin.:*** Trosycort; ***Mex.:*** Fasigyn VT; ***Switz.:*** Trosyd†.

Tolciclate *(USAN, rINN)*

K-9147; KC-9147; Tolciclato; Tolciclatum. *O*-(1,2,3,4-Tetrahydro-1,4-methano-6-naphthyl) *m*,*N*-dimethylthiocarbanilate.

Тольциклат

$C_{20}H_{21}NOS$ = 323.5.
CAS — 50838-36-3.
ATC — D01AE19.
ATC Vet — QD01AE19.

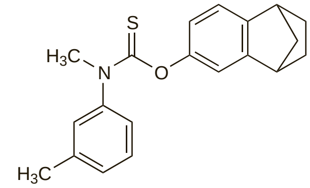

Profile

Tolciclate is an antifungal with activity against *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. It is used topically as a 1% cream or lotion, or as a 0.5% powder in the treatment of various dermatophyte infections and in pityriasis versicolor.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Tolmicol†; ***Ger.:*** Fungifos†; ***Gr.:*** Tolmicil†; ***Ital.:*** Tolmicen†; ***Mex.:*** Kilmicen†; ***NZ:*** Tolmicen; ***Port.:*** Tolmicen†.

Tolnaftate *(BAN, USAN, rINN)*

Sch-10144; Tolnaftaatti; Tolnaftát; Tolnaftat; Tolnaftatas; Tolnaftato; Tolnaftatum. *O*-2-Naphthyl *m*,*N*-dimethylthiocarbanilate.

Тольнафтат

$C_{19}H_{17}NOS$ = 307.4.
CAS — 2398-96-1.
ATC — D01AE18.
ATC Vet — QD01AE18.

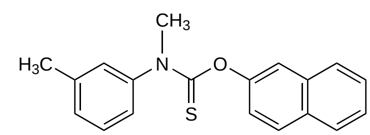

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Tolnaftate). A white or yellowish-white powder. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 31 (Tolnaftate). A white to creamy-white, fine powder, with a slight odour. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in chloroform; sparingly soluble in ether. Store in airtight containers.

Adverse Effects

Skin reactions occur rarely with tolnaftate and include irritation and contact dermatitis.

Antimicrobial Action

Tolnaftate inhibits the growth of the dermatophytes *Epidermophyton, Microsporum, Trichophyton* spp., and *Malassezia furfur*, but is not active against *Candida* spp. or bacteria.

Uses and Administration

Tolnaftate is an antifungal used topically as a 1% gel, solution, powder, ointment, or cream in the treatment or prophylaxis of superficial dermatophyte infections and of pityriasis versicolor (see Skin Infections, p.521). Tolnaftate is applied twice daily for 2 to 6 weeks. Repeat treatment may be required.

Preparations

USP 31: Tolnaftate Cream; Tolnaftate Gel; Tolnaftate Topical Aerosol; Tolnaftate Topical Powder; Tolnaftate Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Athletes Foot†; Tinaderm†; ***Austral.:*** Antifungal Foot Deodorant†; Curatin; Ringworm Ointment; Tinaderm; Tineafax; ***Canad.:*** Absorbine Jr Antifungal; Footworks; Pitrex; Scholl Athlete's Foot; Tinactin; ZeaSorb AF; ***Chile:*** Tinaderm; ***Fr.:*** Sporiline†; ***Ger.:*** Tinatox; Tonoftal; ***Hong Kong:*** Aftate; ***Hung.:*** Athletes Foot†; Chinofungin; Digifungin; ***India:*** Tinaderm; Tolnaderm; ***Indon.:*** Naftate; ***Irl.:*** Mycil; Tinaderm†; ***Israel:*** Athletes Foot; Pitrex; Tinasol; ***Ital.:*** Tinaderm†; ***Malaysia:*** Dermoplex Antifungal; Myco-Aid; Tinaderm†; Tolnaderm; ***Mex.:*** Excelsior†; Tinaderm; Tinoxal; ***NZ:*** Tinaderm†; ***Philipp.:*** Tinactin; Tolnaderm; ***Port.:*** Tinaderm; ***S.Afr.:*** Tinaderm; ***Singapore:*** Tinaderm†; ***Spain:*** Micoisdin†; Tinaderm; ***Thai.:*** Ezon-T; Tono; ***Turk.:*** Mikoderm; ***UK:*** Mycil; Scholl Athlete's Foot; Tinaderm;

USA: Aftate; Blis-To-Sol; Dr Scholl's Athlete's Foot; Genaspor; Lamisil AF Defense; Podactin; Quinsana Plus; Tinactin; ***Venez.:*** Tinaderm; Tolnaftan.

Multi-ingredient: ***Arg.:*** Bacticort Complex; Cevaderm; Quadriderm†; ***Austral.:*** Mycil Healthy Feet; ***Braz.:*** Cremederme; Permut; Poliderms; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Tetraderm; ***Hong Kong:*** Alber T†; Dermafacte; Mycil; Quadriderm; Triditol-G; ***India:*** Fourderm; Quiss; ***Irl.:*** Mycil; Tinaderm-M; ***Israel:*** Phytoderm Compositum; ***Malaysia:*** Elan-Forte; ***Philipp.:*** Quadriderm; Quadrotopic; ***S.Afr.:*** Duoderm†; Quadriderm; ***Singapore:*** Quadriderm†; ***Spain:*** Cuatroderm; ***Switz.:*** Quadriderm; ***Thai.:*** Alber T; Ezon-T; ***UK:*** Mycil; Tinaderm-M; ***USA:*** Absorbine Athletes Foot Care; Dermasept Antifungal.

Triacetin *(rINN)*

E1518; Glicerin-triacetát; Glycerol Triacetate; Glycerolum Triacetas; Glyceryl Triacetate; Triacetina; Triacetinas; Triacétine; Triacetinum; Triacetyna; Triasetiini. 1,2,3-Propanetriol triacetate.

Триацетин

$C_9H_{14}O_6$ = 218.2.

CAS — 102-76-1.

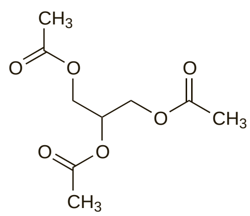

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Triacetin). A clear, colourless, slightly viscous, oily liquid. Soluble in water; miscible with dehydrated alcohol and with toluene. Store in well-filled containers.

USP 31 (Triacetin). A colourless, somewhat oily liquid with a slight, fatty odour. Soluble in water; slightly soluble in carbon disulfide; miscible with alcohol, with chloroform, and with ether. Store in airtight containers.

Profile

Triacetin is reported to possess fungistatic properties based on the liberation of acetic acid. It has been applied topically in the treatment of superficial dermatophyte infections. It has also been used as a plasticiser in oral preparations.

Triacetin may destroy rayon fabric. It should not come into contact with metals.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Micosan†; ***Hong Kong:*** Alber T†; ***Thai.:*** Alber T; Ezon-T.

Trimetrexate Glucuronate *(BANM, USAN, rINNM)*

CI-898 (trimetrexate); Glucuronato de trimetrexato; JB-11 (trimetrexate); NSC-352122; NSC-249008 (trimetrexate); NSC-328564 (trimetrexate); Trimétrexate, Glucuronate de; Trimetrexati Glucuronatum. 5-Methyl-6-(3,4,5-trimethoxyanilinomethyl)quinazolin-2,4-diyldiamine mono-D-glucuronate.

Триметрексата Глюкуронат

$C_{19}H_{23}N_5O_3,C_6H_{10}O_7$ = 563.6.

CAS — 52128-35-5 (trimetrexate); 82952-64-5 (trimetrexate glucuronate).

ATC — P01AX07.

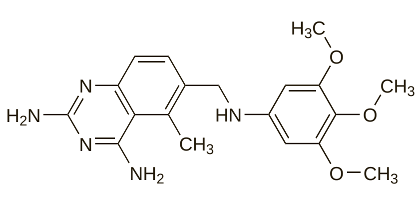

(trimetrexate)

Incompatibility. Trimetrexate is reported to be incompatible with foscarnet. Trimetrexate should not be mixed with folinic acid or chloride ions, since precipitation occurs instantly.

Adverse Effects, Treatment, and Precautions

Trimetrexate is a dihydrofolate reductase inhibitor and therefore adverse effects and precautions are similar to those of methotrexate, p.745. It must be given with folinic acid, which should be continued for 72 hours after the last dose of trimetrexate.

Interactions

Studies in *animals* suggest that cimetidine and imidazole antifungals such as clotrimazole and ketoconazole may inhibit trimetrexate metabolism, and there is a risk of possible interactions with all drugs that affect hepatic cytochrome P450 systems.

Antimicrobial Action

Trimetrexate is an inhibitor of dihydrofolate reductase and consequently prevents formation of the active coenzyme tetrahydrofolate and production of DNA and RNA precursors, leading to cell death. At therapeutic doses the selective transport of trimetrexate, but not folinic acid, into *Pneumocystis jirovecii* allows folinic acid to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting its antifungal activity. *In-vitro* trimetrexate has shown dose-related inhibition of growth of the trophozoite stage of *P. jirovecii.*

Pharmacokinetics

The pharmacokinetics of intravenous trimetrexate have been described as both biphasic and triphasic, with a terminal elimination half-life of about 16 to 18 hours. After use with folinic acid a biphasic disposition with a terminal half-life of 11 hours has also been reported. It is extensively protein bound; reports suggest that it is 95 to 98% bound at low serum concentrations, but that binding is saturable, with free fraction increasing at plasma concentrations above 1 microgram/mL. Trimetrexate is excreted mainly in the urine, as unchanged drug and metabolites, some of which may be active. The major metabolic pathway appears to be oxidative O-demethylation followed by conjugation to the sulfate or glucuronide.

Uses and Administration

Trimetrexate is a dihydrofolate reductase inhibitor with general properties similar to those of methotrexate (p.749). It is used in the management of moderate to severe pneumocystis pneumonia in immunocompromised patients, notably patients with AIDS, where other therapy has proved ineffective (see also p.521). It has also been tried as an antineoplastic in the management of various solid tumours.

Trimetrexate is given as the glucuronate but doses are stated in terms of trimetrexate. Trimetrexate glucuronate 1.53 mg is equivalent to about 1 mg of trimetrexate. It is given by intravenous infusion, over 60 to 90 minutes. The schedule in pneumocystis pneumonia is 45 mg/m^2 daily for 21 days, in association with folinic acid rescue for 24 days. The dosage of trimetrexate and folinic acid should be adjusted according to the results of blood tests, which should be performed at least twice a week during therapy. Renal and hepatic function and haemoglobin values should also be monitored. Treatment with zidovudine and other myelosuppressive drugs should be interrupted to allow full doses of trimetrexate to be given.

◊ Reviews.

1. Fulton B, *et al.* Trimetrexate: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of Pneumocystis carinii pneumonia. *Drugs* 1995; **49:** 563–76.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Neutrexin†; ***Irl.:*** Neutrexin†; ***Spain:*** Neutrexin†; ***Thai.:*** Neutrexin†; ***USA:*** Neutrexin†.

Undecenoic Acid

Acide Undécylénique; Acidum undecylenicum; 10-Hendecenoic Acid; Kyselina undecylenová; Undecilénico, ácido; Undecileno rūgštis; Undecilénsav; Undecylenic Acid; Undecylensyra; Undesenoatlar; Undesilenatlar; Undesyleenihappo. Undec-10-enoic acid.

Ундеценовая Кислота

$C_{11}H_{20}O_2$ = 184.3.

CAS — 112-38-9.

ATC — D01AE04.

ATC Vet — QD01AE04.

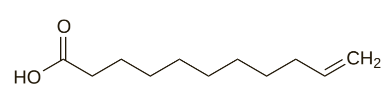

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Undecylenic Acid; Undecenoic Acid BP 2008). A colourless or pale yellow liquid or a white or very pale yellow crystalline mass. Practically insoluble in water; freely soluble in alcohol and in fatty and essential oils. Store in nonmetallic containers. Protect from light.

USP 31 (Undecylenic Acid). A clear, colourless to pale yellow liquid with a characteristic odour. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils. Store in airtight containers. Protect from light.

Calcium Undecenoate

Calcium Undecylenate *(USAN)*; Undecilenato de calcio. Calcium di(undec-10-enoate).

Ундециленат Кальция

$(C_{11}H_{19}O_2)_2Ca$ = 406.6.

ATC — D01AE04.

ATC Vet — QD01AE04.

Pharmacopoeias. In *US.*

USP 31 (Calcium Undecylenate). A fine white powder with a characteristic odour and no grit. Practically insoluble in water, in cold alcohol, in acetone, in chloroform, and in ether; slightly soluble in hot alcohol.

Zinc Undecenoate

Cinko undecilenatas; Çinko Undesilenat; Cink-undecilenát; Sinkkiundesylenaatti; Undecilenato de zinc; Undecilinato de Zinco; Undecylenan zinečnatý; Zinc Undecylenate; Zinc, undécylénate de; Zinci undecylenas; Zinkundecylenat. Zinc di(undec-10-enoate).

Ундециленат Цинка

$(C_{11}H_{19}O_2)_2Zn$ = 431.9.

CAS — 557-08-4.

ATC — D01AE04.

ATC Vet — QD01AE04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Zinc Undecylenate; Zinc Undecenoate BP 2008). A fine white or almost white powder. Practically insoluble in water and in alcohol. Protect from light.

USP 31 (Zinc Undecylenate). A fine, white powder. Practically insoluble in water and in alcohol.

Adverse Effects

Irritation may rarely occur after the topical application of undecenoic acid or its salts.

Antimicrobial Action

Undecenoic acid and its derivatives are active against some pathogenic fungi, including the dermatophytes *Epidermophyton, Trichophyton,* and *Microsporum* spp.

Uses and Administration

Undecenoic acid and its zinc salt are applied topically in the prophylaxis and treatment of superficial dermatophytoses, particularly tinea pedis (p.521). Typical concentrations are undecenoic acid 2 to 5% and zinc undecenoate 20%. They are used in creams, ointments, solutions, or powders, often with each other. Calcium undecenoate is used as a 10 or 15% powder.

Several other salts and derivatives of undecenoic acid including methyl, phenyl, and propyl undecenoate, disodium sulfosuccinated undecenoic acid monoethanolamide, and undecenoic acid monoethanolamide and diethanolamide have been used similarly.

◊ A systematic review[1] of topical treatments for fungal skin or nail infections considered undecenoates to be effective, although comparative studies with other classes of topical antifungal were largely lacking.

1. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/07/08).

Preparations

USP 31: Compound Undecylenic Acid Ointment.

Proprietary Preparations (details are given in Part 3)

Arg.: Bentophyto; Sinamida Pies; Umasam; ***Austria:*** Crino Cordes; Mayfung; Pelsana Med; ***Canad.:*** Desenex; ***Cz.:*** Mykoseptin; ***Fr.:*** Mycodecyl; ***Hung.:*** Lubex; ***Indon.:*** Decyline; Topix; Undecyl; ***Irl.:*** Caldesene; Desenex; ***Israel:*** Undecyl; ***Mex.:*** Derman; ***Pol.:*** Mykodermina; Unguentum Undecylenicum; ***Rus.:*** Mykoseptin (Микосептин); ***S.Afr.:*** Mycota; ***Switz.:*** Fungex; Lubex; Turexan Creme; Turexan Douche; ***Turk.:*** Undo-Pate; Utalk; ***UK:*** Mycota; ***USA:*** Blis-To-Sol; Caldesene; Cruex; Decylenes; Desenex; Elon Dual Defense; Protectol; Undelenic.

Multi-ingredient: ***Arg.:*** Bacteroskin†; Bentophyto; Bifena; Champuacid; Cicatrol; Clevosan; Dettonjab; Farm-X; Fungicida†; Fungocop; Hipoglos Cicatrizante; Laurinol Plus; LB Jabon con Purcelin†; Novo Miconol; Novofarma Champu; Piecidex†; Plusderm†; Tersoderm Anticaspa†; ***Austral.:*** Mycoderm†; Pedoz; Sebitar; Seborrol†; ***Austria:*** Dequafungan; Mycopol; Pelsana Med; Salvyl; ***Braz.:*** Andriodermol; Micosan†; Micotox†; Micoz†; ***Chile:*** Fittig; Hansaplast Footcare†; Lady Fittig†; NP-27; ***Cz.:*** Hexadecyl†; ***Fr.:*** Paps; ***Ger.:*** Gehwol Fungizid†; Gehwol Nagelpilz†; Skinman Soft; ***Gr.:*** Ekzegamma†; ***Hong Kong:*** Acnederm; Fungifax†; Mycoderm†; Sebitar; ***Hung.:*** Squa-med; ***Indon.:*** Decyline; Mikorex; Skintex; ***Irl.:*** Ceanel†; ***Israel:*** Fungimon; Pedisol; Pitrisan; ***Ital.:*** Balta Intimo†; Foot Zeta; Genisol; Micofoot; Propast; ***Malaysia:*** Acnederm†; Sebitar; ***Mex.:*** Micotex; ***NZ:*** Acnederm†; Egomycol†; Grans Remedy; Sebitar; Seborrol†; ***Pol.:*** Undofen; ***Port.:*** Edoltar†; Micaveen; ***S.Afr.:*** AF; Mycota†; ***Singapore:*** Sebitar; ***Switz.:*** Crimanex; Ederphyt; Fungex; Pelsano; Pruri-med; Sebo Shampooing; Trosyd†; Turexan Emulsion†; ***Turk.:*** Fungecyl; Undo-Talk; ***UK:*** Ceanel; Healthy Feet; Monphytol†; Mycota; ***USA:*** Breezee Mist Foot Powder; Dermasept Antifungal; Gordochom; Phicon-F; ***Venez.:*** Diodonato†.

The symbol † denotes a preparation no longer actively marketed

Voriconazole *(BAN, USAN, rINN)*

UK-109496; Voriconazol; Voriconazolum; Vorikonazol. (2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

Вориконазол

$C_{16}H_{14}N_5F_3O = 349.3$.

CAS — 137234-62-9.

ATC — J02AC03.

ATC Vet — QJ02AC03.

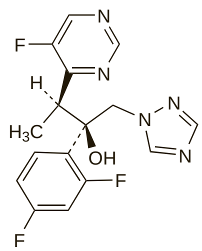

Adverse Effects

The most commonly reported adverse effects with voriconazole are visual disturbances, fever, rashes, nausea, vomiting, diarrhoea, abdominal pain, headache, sepsis, respiratory disorders, and peripheral oedema. There have been some serious hepatic reactions including fatalities. Skin reactions have included rare cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions may occur and are more likely during long-term treatment.

Other adverse effects reported as being common during treatment with voriconazole include: chills, flu-like syndrome, asthenia, back pain, chest pain, injection site reactions, facial oedema, hypotension, sinusitis, altered liver function tests, jaundice, cheilitis, blood disorders, hypokalaemia, hypoglycaemia, dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia, pruritus, alopecia, exfoliative dermatitis, acute renal failure, and haematuria. Hypersensitivity reactions, including anaphylaxis, have occurred rarely.

Effects on the blood. Fever and leucocytosis with eosinophilia in one patient has been attributed to voriconazole treatment.[1]

1. Vishnubhotla P, *et al.* Fever and eosinophilia associated with voriconazole. *Ann Pharmacother* 2004; **38:** 900–901.

Effects on the heart. Bradycardia with a prolonged QT interval and asymptomatic episodes of torsade de pointes occurred in a 15-year-old patient, after 3 weeks of voriconazole therapy at usual doses.[1] All drug treatment was stopped but the effects recurred on rechallenge with a small dose of voriconazole.

1. Alkan Y, *et al.* Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; **39:** e49–e52.

Effects on mental function. There have been reports[1,2] of patients experiencing hallucinations (auditory or visual) during treatment with voriconazole. In one study 18 of 415 patients (4.3%) given voriconazole had visual hallucinations compared with 2 of 422 (0.5%) given amphotericin B.[1]

1. Walsh TJ, *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346:** 225–34.
2. Agrawal AK, Sherman LK. Voriconazole-induced musical hallucinations. *Infection* 2004; **32:** 293–5.

Precautions

Acute renal failure may occur with voriconazole and renal function should be monitored during treatment. Liver function should also be monitored before and during treatment with voriconazole. It should be used with caution in patients with hepatic impairment and doses may need to be adjusted (see under Uses and Administration, below). Patients should avoid sunlight during treatment as photosensitivity reactions have been reported. Visual disturbances may occur and patients affected should not drive or operate hazardous machinery. In addition, all patients, whether affected by visual disturbances or not, should not drive at night, and should have their visual function monitored if they are receiving voriconazole for more than 28 days. Voriconazole has been associated with QT interval prolongation and should therefore be given with caution to patients with potentially pro-arrhythmic conditions.

Voriconazole has been shown to be teratogenic and embryotoxic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532. Licensed product information recommends that women of child-bearing potential should use effective contraception during treatment with voriconazole.

Interactions

Voriconazole is metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. Use of drugs that either inhibit or induce these isoenzymes may increase or decrease plasma concentrations of voriconazole, respectively. Rifampicin has been shown to decrease voriconazole plasma concentrations and a similar effect may be expected with carbamazepine or phenobarbital; use of voriconazole with these drugs is therefore not recommended.

Concentrations of other drugs that are metabolised by CYP2C19, CYP2C9, or CYP3A4 may be increased by voriconazole. Increased plasma concentrations of astemizole, cisapride, pimozide, quinidine, and terfenadine could be expected and concomitant use is contra-indicated because of the risk of cardiac arrhythmias including torsade de pointes. Use with ergot alkaloids such as ergotamine and dihydroergotamine is also contra-indicated because of the possible risk of ergotism. Increased plasma concentrations of sirolimus and tacrolimus have been noted; use with sirolimus is contra-indicated, although tacrolimus may be used providing its dose is reduced and concentrations monitored. Similarly, reduced dose with monitoring is recommended for ciclosporin. Likewise, monitoring and possible dose reductions of methadone are recommended during concomitant use. Concentrations of oral anticoagulants may be affected and increased prothrombin time has occurred with warfarin; monitoring should therefore be carried out. Close monitoring of blood glucose is necessary if voriconazole is used with oral hypoglycaemics such as the sulfonylureas. Dose reductions may be needed for some statins, calcium-channel blockers, vinca alkaloids, and some benzodiazepines (such as midazolam and triazolam) if their plasma concentrations are increased.

Interactions may occur where both voriconazole and the other drug are affected. Examples are phenytoin and rifabutin (where concentrations of voriconazole are reduced but those of phenytoin or rifabutin are increased). If it is essential to give either drug with voriconazole, then an increase in the dose of voriconazole is recommended. With omeprazole, the plasma concentration of both drugs may be increased and a reduced dose of omeprazole is recommended.

Voriconazole may inhibit metabolism of non-nucleoside reverse transcriptase inhibitors and they in turn may either inhibit the metabolism of voriconazole (e.g. delavirdine and efavirenz) or induce the metabolism of voriconazole (e.g. efavirenz and nevirapine). Co-administration of voriconazole and efavirenz is contra-indicated. Similarly, voriconazole may inhibit metabolism of HIV-protease inhibitors (e.g. saquinavir, amprenavir, and nelfinavir) while they may in turn inhibit the metabolism of voriconazole. High doses of ritonavir (400 mg twice daily) significantly decrease plasma concentrations of voriconazole and co-administration is contra-indicated. Similar effects have been seen with low doses of ritonavir (100 mg twice daily) and use with voriconazole should be avoided where possible. Indinavir, however, does not appear to interact with voriconazole.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Voriconazole is a triazole antifungal that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in the impairment of ergosterol synthesis in fungal cell membranes. Voriconazole has a broad spectrum of activity against all *Candida* species, including fluconazole-resistant strains, as well as *Aspergillus* spp., *Scedosporium* spp., and *Fusarium* spp.

◊ Reports of breakthrough zygomycosis and other fungal infections in immunocompromised patients treated empirically or prophylactically with voriconazole.[1-5]

1. Marty FM, *et al.* Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004; **350:** 950–2.
2. Siwek GT, *et al.* Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis* 2004; **39:** 584–7.
3. Imhof A, *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis* 2004; **39:** 743–6.
4. Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. *Clin Infect Dis* 2005; **40:** 770–1.
5. Vigouroux S, *et al.* Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. *Clin Infect Dis* 2005; **40:** e35-e37.

Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. It is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma protein binding of voriconazole is about 58%. Voriconazole diffuses into CSF.

Voriconazole is metabolised by hepatic cytochrome P450 isoenzyme CYP2C19; the major metabolite is the inactive *N*-oxide. Metabolism via isoenzymes CYP2C9 and CYP3A4 has also been demonstrated *in vitro*. About 80% of voriconazole is excreted in the urine.

◊ References.

1. Purkins L, *et al.* Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46:** 2546–53.
2. Johnston A. The pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; **56** (suppl 1): 1.
3. Walsh TJ, *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; **48:** 2166–72.
4. Theuretzbacher U, *et al.* Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; **45:** 649–63.

Uses and Administration

Voriconazole is a triazole antifungal used mainly in immunocompromised patients for the treatment of invasive aspergillosis (p.517), candidaemia (p.518) in non-neutropenic patients, fluconazole-resistant serious invasive candidiasis, oesophageal candidiasis, and serious fungal infections due to *Scedosporium* and *Fusarium* spp.

Voriconazole may be given orally or intravenously.

Oral doses as film-coated tablets should be taken at least 1 hour before, or 1 hour after, a meal; oral suspensions should be taken at least 1 hour before, or 1 to 2 hours after, a meal. The oral suspension may be preferred in children.

The following ***oral loading doses*** of voriconazole are given every 12 hours for the first 24 hours:

- adults and adolescents weighing more than 40 kg: 400 mg
- under 40 kg: 200 mg
- children aged 2 to 12 years: no loading dose

Subsequent ***oral maintenance doses*** are:

- adults and adolescents over 40 kg: 200 mg twice daily, increased to 300 mg twice daily if the response is inadequate
- under 40 kg: 100 mg twice daily, increased to 150 mg twice daily if the response is inadequate
- children aged 2 to 12 years: 200 mg twice daily

US licensed product information does not suggest a loading dose for oesophageal candidiasis; oral maintenance doses are as above and treatment should be given for a minimum of 14 days and continued for at least 7 days after resolution of symptoms.

Intravenous loading doses of voriconazole are:

- adults and adolescents: 6 mg/kg every 12 hours for the first 24 hours
- children aged 2 to 12 years: no loading dose

Intravenous maintenance doses are:

- adults and adolescents: 4 mg/kg twice daily; a lower dose of 3 mg/kg twice daily may be suitable for candidaemia in non-neutropenic patients or for deep tissue *Candida* infections, or for patients unable to tolerate the higher dose
- children aged 2 to 12 years: 7 mg/kg twice daily; 4 mg/kg twice daily may be used in those unable to tolerate the higher dose

Intravenous infusions should be given at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. UK licensed product information recommends that intravenous therapy should not be given for longer than 6 months.

Doses of voriconazole should be modified in patients with hepatic or renal impairment (see below). For a suggested dose in patients taking the NNRTI efavirenz see Interactions, Antifungals, p.873.

◊ Reviews.

1. Muijsers RBR, *et al.* Voriconazole: in the treatment of invasive aspergillosis. *Drugs* 2002; **62:** 2655–64.
2. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003; **36:** 630–7.
3. Pearson MM, *et al.* Voriconazole: a new triazole antifungal agent. *Ann Pharmacother* 2003; **37:** 420–32.
4. Gothard P, Rogers TR. Voriconazole for serious fungal infections. *Int J Clin Pract* 2004; **58:** 74–80.
5. Donnelly JP, De Pauw BE. Voriconazole—a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004; **10** (suppl 1): 107–17.
6. Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* 2007; **67:** 269–98.

Administration in hepatic impairment. No dosage adjustment is necessary when voriconazole is given to patients with acute hepatic impairment but doses should be modified in patients with chronic disease. Patients with mild to moderate hepatic cirrhosis (Child-Pugh category A and B) should receive the standard loading doses of voriconazole (see above) but maintenance doses should be halved. Doses for patients with severe hepatic cirrhosis (Child-Pugh category C) have not been established.

Administration in renal impairment. No dose adjustment is needed for oral voriconazole in patients with renal impairment. Patients with a creatinine clearance less than 50 mL/minute should receive oral voriconazole instead of intravenous voriconazole, as accumulation of the intravenous vehicle, sulfobutyl ether beta-cyclodextrin sodium (SBECD), may occur. When intravenous voriconazole is considered justified in such patients, serum creatinine should be closely monitored and consideration given to changing to the oral route if increases occur.

Although voriconazole is haemodialysed, no dose adjustment is required for patients on haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Vfend; ***Austral.:*** Vfend; ***Austria:*** Vfend; ***Belg.:*** Vfend; ***Braz.:*** Vfend; ***Canad.:*** Vfend; ***Chile:*** Vfend; ***Cz.:*** Vfend; ***Denm.:*** Vfend; ***Fin.:*** Vfend; ***Fr.:*** Vfend; ***Ger.:*** Vfend; ***Gr.:*** Vfend; ***Hong Kong:*** Vfend; ***Hung.:*** Vfend; ***Indon.:*** Vfend; ***Irl.:*** Vfend; ***Israel:*** Vfend; ***Ital.:*** Vfend; ***Malaysia:*** Vfend; ***Mex.:*** Vfend; ***Neth.:*** Vfend; ***Norw.:*** Vfend; ***NZ:*** Vfend; ***Pol.:*** Vfend; ***Port.:*** Vfend; ***S.Afr.:*** Vfend; ***Singapore:*** Vfend; ***Spain:*** Vfend; ***Swed.:*** Vfend; ***Switz.:*** Vfend; ***Thai.:*** Vfend; ***UK:*** Vfend; ***USA:*** Vfend; ***Venez.:*** Vorcum.

Antigout Drugs

This chapter deals with the treatment of gout and hyperuricaemia and the drugs used mainly for these disorders.

Gout and hyperuricaemia

Uric acid is the final product of the metabolism of endogenous and exogenous purine in man. An excess of uric acid, measured in the plasma as sodium urate, constitutes **hyperuricaemia**. This excess may be caused by an overproduction or underexcretion of urate. It is influenced by genetic and environmental factors and may be classified as primary (mainly idiopathic) or secondary. An increase in urate production may be caused by excessive dietary purine intake, certain cancers or their treatment, or, more rarely, enzyme defects of purine metabolism. Reduced urate excretion may be caused by renal disease, hypertension, or the intake of certain drugs such as thiazide diuretics. Other factors contributing to hyperuricaemia include hyperlipidaemia, obesity, alcohol consumption, and lead exposure.

A patient is usually considered to be hyperuricaemic when plasma-urate concentrations exceed 0.42 mmol/litre (7 mg per 100 mL) in men and postmenopausal women or 0.36 mmol/litre (6 mg per 100 mL) in premenopausal women. At these high concentrations there is a risk of crystals of monosodium urate monohydrate being formed and deposited in synovial fluid and various tissues. However, some subjects may have supersaturated plasma-urate concentrations without any crystal deposits, while others may suffer from deposits in the absence of apparent hyperuricaemia.

The presence of urate crystals in the synovial fluid leads to an inflammatory response in the affected joint, commonly at the base of the big toe (podagra). The ensuing exquisite pain, tenderness, erythema, and swelling constitute the clinical manifestations of **acute inflammatory gouty arthritis**. Repeated acute attacks may be associated with a visible or palpable build up of crystal deposits (**tophi**) at various sites including in and around the affected joint. Tophi release urate crystals into the synovial fluid after various stimuli and so cause further acute attacks, leading to **chronic tophaceous gout**. Intra-articular and peri-articular tophi may cause gradual joint erosion, which, without treatment, results in disabling **chronic gouty arthritis**. Rarely, the kidney can be affected by urate deposits producing a gouty nephropathy or by uric acid calculi or stones (uric acid nephrolithiasis or urolithiasis).

Treatment aims to alleviate the acute attack, prevent future attacks, and lower plasma-urate concentration.

Plasma-urate concentrations may be reduced by control of obesity and modification of diet and alcohol intake. Drug treatment can relieve the pain of acute attacks but more prolonged therapy for hyperuricaemia is generally only considered if there are recurrent attacks of gout or there is renal involvement (see under Chronic Gout, below).

Acute gout. An attack of acute inflammatory gouty arthritis is best treated as soon as possible with an NSAID. Aspirin or other salicylates are not suitable since they may increase plasma-urate concentrations. Treatment is started with high doses of an NSAID, the doses being reduced as the patient responds. Usually treatment can be withdrawn within 1 to 2 weeks. Colchicine is an effective alternative; it may be used alone, or with an NSAID. Patients who do not respond to NSAIDs or colchicine, or for whom these drugs are contra-indicated, may be treated with a systemic corticosteroid. Intra-articular corticosteroids are effective in acute monoarticular gout, or when used adjunctively in patients with polyarticular gout; infection of joints should be excluded prior to injection. Intravenous, intramuscular, or subcutaneous corticotropin has been reported to alleviate pain and inflammation in acute gout. It may be used alone or adjunctively, and may be a useful alternative in patients with renal and gastrointestinal contra-indications to other therapies. Other therapies for acute gout include adjunctive analgesics and topical ice. Drugs used for chronic gout (allopurinol or the uricosurics) should not be started during an acute attack since they can exacerbate and prolong it (see below).

Chronic gout. If the patient suffers frequent acute attacks or develops tophaceous gout, or has renal complications as a result of urate overproduction, then long-term treatment of hyperuricaemia may be needed. Such **urate-lowering therapy** should not be started during an acute attack, or for 2 to 3 weeks thereafter, as fluctuations in urate concentration may prolong the existing attack or initiate a new one. Treatment involves inhibiting the production of uric acid or enhancing its urinary excretion, in order to maintain a serum urate concentration at or below 0.3 or 0.36 mmol/litre. Hyperuricaemia due to overproduction of urate is treated with allopurinol which inhibits the enzyme xanthine oxidase, involved in purine metabolism. Hyperuricaemia associated with underexcretion of uric acid can be treated with either allopurinol or a uricosuric such as benzbromarone, probenecid or sulfinpyrazone. Allopurinol is most commonly given as first-line therapy, but may be combined with or replaced by uricosurics if treatment fails. Allopurinol should also be used for patients with renal urate deposits or with uric acid renal calculi as it reduces urolithiasis. Febuxostat is an alternative xanthine oxidase inhibitor under investigation.

With either treatment there is mobilisation of urate crystals from established tophi, as the plasma-urate concentration falls, which can trigger further acute attacks of gout. Patients are thus also given **prophylaxis** with an NSAID or colchicine from the start of urate-lowering treatment until at least a month after the plasma-urate has been reduced to an acceptable concentration; up to 6 months of prophylactic cover has been recommended.

Once the hyperuricaemia is corrected, the patient continues to receive therapy with allopurinol or uricosurics indefinitely. If an acute attack occurs during such maintenance therapy, this therapy should be continued to avoid fluctuations in urate concentration, and the acute attack treated in its own right.

Surgery may have to be considered for patients severely affected by chronic tophaceous gout.

References[1-18] to gout and its management are given below.

1. Agudelo CA, Wise CM. Gout: diagnosis, pathogenesis, and clinical manifestations. *Curr Opin Rheumatol* 2001; **13:** 234–9.
2. Schlesinger N, Schumacher HR. Gout: can management be improved? *Curr Opin Rheumatol* 2001; **13:** 240–4.
3. Terkeltaub RA. Gout. *N Engl J Med* 2003; **349:** 1647–55.
4. Rott KT, Agudelo CA. Gout. *JAMA* 2003; **289:** 2857–60.
5. Snaith ML, Adebajo AO. Gout and hyperuricaemia. In: Snaith ML, ed. *ABC of rheumatology.* 3rd ed. London: BMJ Publishing Group, 2004: 39–44.
6. Anonymous. Gout in primary care. *Drug Ther Bull* 2004; **42:** 37–40.
7. Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 2004; **64:** 2399–2416.
8. Wortmann RL. Recent advances in the management of gout and hyperuricemia. *Curr Opin Rheumatol* 2005; **17:** 319–24.
9. Underwood M. Gout. *Clin Evid* 2005; **13:** 1435–44.
10. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J* 2005; **81:** 572–9.
11. Stamp L, *et al.* Gout in solid organ transplantation: a challenging clinical problem. *Drugs* 2005; **65:** 2593–2611.
12. Choi HK, *et al.* Pathogenesis of gout. *Ann Intern Med* 2005; **143:** 499–516.
13. Lee SJ, *et al.* Recent developments in diet and gout. *Curr Opin Rheumatol* 2006; **18:** 193–8.
14. Teng GG, *et al.* Pathophysiology, clinical presentation and treatment of gout. *Drugs* 2006; **66:** 1547–63.
15. Underwood M. Diagnosis and management of gout. *BMJ* 2006; **332:** 1315–19.
16. Zhang W, *et al.* EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; **65:** 1312–24.
17. Jordan KM, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; **46:** 1372–4. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/46/8/1372 (accessed 22/04/08)
18. Schlesinger N. Overview of the management of acute gout and the role of adrenocorticotropic hormone. *Drugs* 2008; **68:** 407–15.

Allopurinol *(BAN, USAN, rINN)*

Allopürinol; Allopurinoli; Allopurinolum; Allopurynol; Alopurinol; Alopurinolis; BW-56-158; HPP; NSC-1390.

Аллопуринол

$C_5H_4N_4O$ = 136.1.

CAS — 315-30-0 (allopurinol); 17795-21-0 (allopurinol sodium).

ATC — M04AA01.

ATC Vet — QM04AA01.

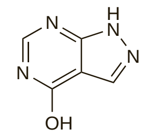

Description. Allopurinol is a tautomeric mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Allopurinol). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides.

USP 31 (Allopurinol). A fluffy white to off-white powder having only a slight odour. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of potassium and sodium hydroxides.

Incompatibility. Allopurinol sodium as a 3 mg/mL solution in 0.9% sodium chloride was visually incompatible with amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlormethine hydrochloride, chlorpromazine hydrochloride, cimetidine hydrochloride, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin hydrochloride, diphenhydramine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine hydrochloride, idarubicin hydrochloride, imipenem with cilastatin sodium, methylprednisolone sodium succinate, metoclopramide hydrochloride, minocycline hydrochloride, nalbuphine hydrochloride, netilmicin sulfate, ondansetron hydrochloride, pethidine hydrochloride, prochlorperazine edisilate, promethazine hydrochloride, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.[1]

1. Trissel LA, Martinez JF. Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1792–9.

Adverse Effects

The most common adverse effect of allopurinol is skin rash. Rashes are generally maculopapular or pruritic, sometimes purpuric, but more serious hypersensitivity reactions may occur and include exfoliative rashes, the Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is therefore recommended that allopurinol be withdrawn immediately if a rash occurs (see Precautions, below). Further symptoms of hypersensitivity include fever and chills, lymphadenopathy, leucopenia or leucocytosis, eosinophilia, arthralgia, and vasculitis leading to renal and hepatic damage and, very rarely, seizures. These hypersensitivity reactions may be severe, even fatal, and patients with hepatic or renal impairment are at special risk.

Hepatotoxicity and signs of altered liver function may also be found in patients who are not hypersensitive. Haematological effects include thrombocytopenia, aplastic anaemia, agranulocytosis, and haemolytic anaemia.

Many other adverse effects have been noted rarely and include paraesthesia, peripheral neuropathy, alopecia, gynaecomastia, hypertension, taste disturbances, nausea, vomiting, abdominal pain, diarrhoea, headache, malaise, drowsiness, vertigo, and visual disturbances.

Patients with gout may have an increase in acute attacks on beginning treatment with allopurinol, although attacks usually subside after several months.

Incidence of adverse effects. A Boston Collaborative Drug Surveillance Program involving 29 524 hospitalised patients found that, with the exception of skin reactions, 33 of 1835 patients treated with allopurinol (1.8%) had adverse effects. These effects were dose-related and the most frequent were haematological (11 patients, 0.6%), diarrhoea (5 patients, 0.3%), and drug fever (5 patients, 0.3%). Hepatotoxicity was reported in 3 patients (0.2%). Two patients developed possible hypersensitivity reactions to allopurinol.[1]

A further analysis involving 1748 outpatients indicated no instances of acute blood disorders, skin diseases, or hypersensitivity that warranted hospital treatment. Liver disease, although found, was not considered to be associated with allopurinol.

There were only 2 patients in whom renal disease could possibly have been caused by allopurinol.[2]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Jick H, Perera DR. Reactions to allopurinol. *JAMA* 1984; **252:** 1411.

Effects on the blood. In addition to the haematological abnormalities of leucopenia, thrombocytopenia, haemolytic anaemia, and clotting abnormalities noted in the Boston Collaborative Drug Surveillance Program,[1] aplastic anaemia has also been reported, sometimes in patients with renal impairment.[2] Pure red cell aplasia has also been reported.[3,4]

1. McInnes GT, *et al*. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40:** 245–9.
2. Anonymous. Allopurinol and aplastic anaemia. *WHO Drug Inf* 1989; **3:** 26.
3. Lin Y-W *et al.* Acute pure red cell aplasia associated with allopurinol therapy. *Am J Hematol* 1999; **61:** 209–11.
4. Chao S-C, *et al.* Hypersensitivity syndrome and pure red cell aplasia following allopurinol therapy in a patient with chronic kidney disease. *Ann Pharmacother* 2005; **39:** 1552–6.

Effects on the eyes. Some case reports have suggested an association between allopurinol use and the development of cataracts,[1] but a detailed ophthalmological survey involving 51 patients who had taken allopurinol failed to confirm this.[2] However, a large retrospective case-control study in elderly patients concluded that long-term, or high-dose, allopurinol therapy did increase the risk of cataract extraction.[3]

1. Fraunfelder FT, *et al.* Cataracts associated with allopurinol therapy. *Am J Ophthalmol* 1982; **94:** 137–40.
2. Clair WK, *et al.* Allopurinol use and the risk of cataract formation. *Br J Ophthalmol* 1989; **73:** 173–6.
3. Garbe E, *et al.* Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; **116:** 1652–6.

Effects on the skin. Skin reactions are the most common adverse effects of allopurinol.

One report calculated that of 215 adverse effects noted over a 16-year period 188 (87.4%) were related to the skin or mucous membranes.[1] An analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 6 allergic skin reactions attributed to allopurinol among 784 recipients of the drug.[2] Desensitisation protocols[3] and alternative drugs[4] have been used after cutaneous reactions to allopurinol.

Serious skin reactions to allopurinol may occur as part of a generalised hypersensitivity reaction. A review of the literature between 1970 and the end of 1990 revealed 101 cases of allopurinol hypersensitivity syndrome, 94 of which involved the skin.[5] Skin reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or a diffuse maculopapular or exfoliative dermatitis; 27 of the 101 patients died. The relative risk of toxic epidermal necrolysis or Stevens-Johnson syndrome occurring with allopurinol was high (calculated to be 5.5) in a case-control study including 13 patients with these cutaneous reactions who had received allopurinol.[6] This risk was not constant over time, being higher during the first 2 months of treatment. During these 2 months the estimated excess risk was 1.5 cases per million users per week. Another case-control study,[7] involving 379 patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, found that allopurinol was the drug most frequently associated with these reactions. The risk again appeared to be restricted to short-term use (less than 8 weeks) and was greater in patients taking 200 mg or more daily.

1. Vinciullo C. Allopurinol hypersensitivity. *Med J Aust* 1984; **141:** 449–50.
2. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.
3. Fam AG, *et al.* Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; **44:** 231–8.
4. Fam AG. Difficult gout and new approaches for control of hyperuricemia in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; **3:** 29–35.
5. Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; **27:** 337–43.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–1607.
7. Halevy S, *et al.* EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008; **58:** 25–32.

Precautions

Allopurinol should not be used for the treatment of an acute attack of gout; additionally, allopurinol therapy should not be begun for any purpose during an acute attack. However, allopurinol is continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately.

Treatment should be stopped immediately if any skin reactions or other signs of hypersensitivity develop. A cautious reintroduction at a low dose may be attempted when mild skin reactions have cleared (see Effects on the Skin, above); allopurinol should not be reintroduced in those patients who have experienced other forms of hypersensitivity reaction. Dosage should be reduced in renal or hepatic impairment. Care is advised in patients being treated for hypertension or cardiac insufficiency, who may also have renal impairment.

To reduce the risk of renal xanthine deposition an adequate fluid intake (2 to 3 litres daily) is required. In addition, a neutral or slightly alkaline urine may be desirable.

Breast feeding. Allopurinol and its metabolite, oxipurinol, are distributed into breast milk, and licensed product information recommends that allopurinol should be used with caution in breast-feeding women. Although oxipurinol was detected in the plasma of a breast-fed infant, no adverse effects were noted in the infant during 6 weeks of maternal treatment with allopurinol.[1] The American Academy of Pediatrics noted that there had been no documented problems with allopurinol and considered its use to be usually compatible with breast feeding.[2]

1. Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. *Clin Investig* 1993; **71:** 161–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Interactions

Drugs that can increase uric acid concentrations may decrease the efficacy of allopurinol. Aspirin and the salicylates possess this activity and should generally be avoided in hyperuricaemia and gout. An increase in hypersensitivity reactions, and possibly also other adverse effects, has been reported in patients taking allopurinol with ACE inhibitors or thiazide diuretics, particularly in patients with renal impairment.

The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and their doses should be markedly reduced when either of them is given with allopurinol to avoid potentially life-threatening toxicity. There have also been reports of allopurinol enhancing the activity of, and possibly increasing the toxicity of, a number of other drugs including some antibacterials, some anticoagulants, some other antineoplastics, ciclosporin, some sulfonylurea antidiabetics, theophylline, and vidarabine.

ACE inhibitors. An apparent interaction between allopurinol and *captopril* has been reported in patients with chronic renal failure. In one patient it was suggested that the development of fatal Stevens-Johnson syndrome after the introduction of allopurinol was due to potentiation by captopril.[1] In the second patient hypersensitivity, characterised by fever, arthralgia, and myalgia, occurred and was believed to be due to captopril, or one of its metabolites, potentiated by the addition of allopurinol.[2] Care is advised if allopurinol is used with captopril, especially in patients with chronic renal failure.

1. Pennell DJ, *et al.* Fatal Stevens-Johnson syndrome in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 463.
2. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* 1984; **i:** 679.

Antacids. Allopurinol failed to reduce blood-uric-acid concentrations when given at the same time as *aluminium hydroxide* in 3 patients on chronic haemodialysis. However, if allopurinol was given 3 hours before aluminium hydroxide the expected decrease in uric acid concentration did occur.[1]

1. Weissman I, Krivoy N. Interaction of aluminium hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* 1987; **107:** 787.

Antibacterials. Although an increased incidence of skin rashes has been noted when allopurinol has been used with *ampicillin* or *amoxicillin*, data currently available are insufficient to confirm whether this is due to allopurinol or not. For further details, see Ampicillin, p.204.

Anticoagulants. For the effect of allopurinol on *dicoumarol*, *phenprocoumon*, or *warfarin*, see Warfarin, p.1429.

Antiepileptics. For a report of allopurinol possibly inhibiting the metabolism of *phenytoin*, see under Antigout Drugs, p.499.

Antigout drugs. Uricosuric drugs are likely to increase the renal elimination of oxipurinol (the major active metabolite of allopurinol). For example, *benzbromarone* lowered plasma concentrations of oxipurinol by about 40% when used with allopurinol, although plasma concentrations of allopurinol itself were not affected.[1] The interaction was not of concern, since the combination was more effective than allopurinol alone in lowering serum concentrations of uric acid. Licensed product information recommends reassessing the dosage of allopurinol on an individual basis when a uricosuric drug is added.

Probenecid has been reported to decrease the clearance of oral allopurinol riboside.[2] In a pharmacokinetic study in healthy subjects,[3] giving allopurinol and probenecid together significantly reduced oxipurinol concentrations; however, this combination had a greater hypouricaemic effect than either drug given alone.

1. Müller FO, *et al.* The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* 1993; **44:** 69–72.
2. Were JBO, Shapiro TA. Effects of probenecid on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* 1993; **37:** 1193–6.
3. Stocker SL, *et al.* Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects. *Clin Pharmacokinet* 2008; **47:** 111–18.

Antineoplastics. Allopurinol inhibits the metabolism of *mercaptopurine* and marked dosage reduction of this drug to one-quarter to one-third of the usual dose is required if it is used with allopurinol. There are also reports of interactions between allopurinol and other antineoplastics. Mild chronic allopurinol-induced hepatotoxicity has been reported in a male patient to have been exacerbated by *tamoxifen*.[1] Hypersensitivity vasculitis resulting in the death of a patient receiving allopurinol and *pentostatin* has been described. Although it could not be ascertained whether this effect was due to one of the drugs alone or to an interaction it was believed that this combination should not be used.[2]

For a report of an increased incidence of bone-marrow toxicity in patients given allopurinol with *cyclophosphamide*, see p.703.

1. Shah KA, *et al.* Allopurinol hepatotoxicity potentiated by tamoxifen. *N Y State J Med* 1982; **82;** 1745–6.
2. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86:** 499.

Antivirals. For the effect of allopurinol on *didanosine*, see p.871.

Immunosuppressants. Allopurinol inhibits the metabolism of mercaptopurine, the metabolite of *azathioprine*, and marked dosage reduction of azathioprine to one-quarter to one-third of the usual dose is required if it is used with allopurinol. Similar caution is also required with mercaptopurine itself (see Antineoplastics, above). The effects of allopurinol on *ciclosporin* concentrations (a marked increase) are reported on p.1826.

Xanthines. For the effect of allopurinol on the pharmacokinetics of *caffeine* and *theophylline*, see p.1117 and p.1144 respectively.

Pharmacokinetics

Up to 90% of an oral dose of allopurinol is rapidly absorbed from the gastrointestinal tract; its plasma half-life is about 1 to 2 hours. Allopurinol's major metabolite is oxipurinol (alloxanthine), which is also an inhibitor of xanthine oxidase with a plasma half-life of about 15 or more hours in patients with normal renal function, although this is greatly prolonged by renal impairment. Both allopurinol and oxipurinol are conjugated to form their respective ribonucleosides. Allopurinol and oxipurinol are not bound to plasma proteins.

Excretion is mainly through the kidney, but it is slow since oxipurinol undergoes tubular reabsorption. About 70% of a daily dose may be excreted in the urine as oxipurinol and up to 10% as allopurinol; prolonged use may alter these proportions, as allopurinol inhibits its own metabolism. The remainder of the dose is excreted in the faeces. Allopurinol and oxipurinol have also been detected in breast milk.

◊ References.

1. Murrell GAC, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986; **11:** 343–53.
2. Turnheim K, *et al.* Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. *Br J Clin Pharmacol* 1999; **48:** 501–9.
3. Day RO, *et al.* Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin Pharmacokinet* 2007; **46:** 623–44.

Uses and Administration

Allopurinol is used to treat hyperuricaemia (p.552) associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme disorders, or cancer and its treatment (see Tumour Lysis Syndrome, p.639). It is not used for asymptomatic hyperuricaemia. Allopurinol is also used in the management of renal calculi caused by the deposition of calcium oxalate (in the presence of hyperuricosuria) and of 2,8-dihydroxyadenine (see Renal Calculi, below). It may have the potential to reduce oxidative stress by blocking the production of free radicals and is an ingredient of kidney preservation solutions. In addition allopurinol has antiprotozoal activity and has been used in leishmaniasis and American trypanosomiasis.

Allopurinol is used in **gout and hyperuricaemia** to inhibit the enzyme xanthine oxidase, thus preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby divided between hypoxanthine, xanthine, and uric acid, each with its independent solubility. This results in the reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming. At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor. However, most of its activity is due to the metabolite oxipurinol which is a non-competitive inhibitor of xanthine oxidase.

Allopurinol is used in chronic gout to correct hyperuricaemia, reduce the likelihood of acute attacks, and prevent the sequelae of chronic gout. Initially, it may increase plasma-concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence allopurinol should not be started until an acute attack has completely subsided, and treatment should be started with a low dose increased gradually; an NSAID (but not aspirin or salicylates) or colchicine should also be given for at least 1 month after hyperuricaemia is corrected, usually 3 months. It may take several months to deplete the uric acid level sufficiently to control acute attacks.

A suggested oral starting dose of allopurinol is 100 mg daily, gradually increased by 100 mg for example at weekly intervals until the concentration of urate in plasma is reduced to 0.36 mmol/litre (6 mg per 100 mL) or less. A daily dose range of 100 to 300 mg may be adequate for those with mild gout and up to 600 mg for those with moderately severe tophaceous gout. The maximum recommended daily dose is 800 mg in the USA and 900 mg in the UK. Up to 300 mg may be taken as a single daily dose; larger amounts should be taken in divided doses to reduce the risk of gastric irritation. Taking allopurinol after food will also minimise gastric irritation. Patients should maintain an adequate fluid intake to prevent renal xanthine deposition.

Doses of allopurinol should be reduced in patients with renal impairment (see below)

When used for the prevention of uric acid nephropathy associated with cancer therapy 600 to 800 mg may be given daily, generally for 2 or 3 days before starting the cancer treatment. A high fluid intake is essential. In hyperuricaemia secondary to cancer or cancer chemotherapy, maintenance doses of allopurinol are similar to those used in gout and are given according to the response.

The main use of allopurinol in children is for hyperuricaemia associated with cancer or cancer chemotherapy or with enzyme disorders. The dosage used may vary: in the UK a dose of 10 to 20 mg/kg daily up to a maximum of 400 mg daily is recommended for children under 15 years of age, while in the USA the dose is 150 mg daily for children under 6 years of age and 300 mg daily for those aged 6 to 10 years, adjusted if necessary after 48 hours.

Allopurinol sodium has been given by intravenous infusion in sodium chloride 0.9% or glucose 5% to patients (usually cancer patients) unable to take allopurinol orally. The recommended dose in adults is the equivalent of allopurinol 200 to 400 mg/m^2 daily up to a maximum of 600 mg daily. Allopurinol sodium 116.2 mg is equivalent to 100 mg of allopurinol.

Administration in renal impairment. Excretion of allopurinol and its active metabolite oxipurinol is primarily via the kidneys and therefore the dosage should be reduced in renal impairment according to creatinine clearance (CC).

In the USA the following doses are suggested for oral and intravenous use:
- CC 10 to 20 mL/minute: 200 mg daily
- CC less than 10 mL/minute: no more than 100 mg daily
- CC less than 3 mL/minute: consider also a longer dosage interval

In the UK a maximum initial oral daily dosage of 100 mg is recommended for those with renal impairment, increased only if the response is inadequate. Doses less than 100 mg daily or 100 mg at intervals longer than 1 day are recommended for those with severe renal insufficiency. Because of the imprecision of low creatinine clearance values, it is suggested that, if facilities are available for monitoring, the allopurinol dose should be adjusted to maintain plasma-oxipurinol concentrations below 100 micromoles/litre (15.2 micrograms/mL). A suggested alternative dose for patients requiring dialysis two or three times weekly is 300 to 400 mg allopurinol immediately after dialysis only.

The difficulties of maintaining an appropriate dose in such patients were illustrated by a study[1] in New Zealand involving 227 allopurinol-treated patients. The guidelines used suggested maintenance doses based on CC as follows:
- less than 10 mL/minute: 100 mg every 3 days
- 10 mL/minute: 100 mg every 2 days
- 20 mL/minute: 100 mg daily
- 40 mL/minute: 150 mg daily
- 60 mL/minute: 200 mg daily

The recommended dose or less was used in the majority of cases (183 of 227). However, of 214 patients for whom serum-uric acid concentrations were available, only 48 achieved values of 0.36 mmol/litre or less. The proportion of patients achieving acceptable serum-uric acid concentrations was higher (38%) in patients given higher than recommended doses than in those on doses recommended by the guidelines (19%). Although guidelines might be useful for initial dosing, longer term use could lead to inadequate control of hyperuricaemia.

1. Dalbeth N, *et al.* Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; **33:** 1646–50.

Diagnosis and testing. Deficiency of the enzyme ornithine carbamoyltransferase can result in severe CNS dysfunction or even in death, and identification of women at risk of being carriers of this genetic enzyme deficiency has been described.[1] The enzyme deficiency causes carbamoyl phosphate to accumulate, which stimulates the synthesis of orotidine. The test relies on giving a single dose of allopurinol, which will, in carriers, greatly increase the urinary excretion of orotidine. However, mutation analysis is now more usually used to establish the diagnosis.

1. Hauser ER, *et al.* Allopurinol-induced orotidinuria. *N Engl J Med* 1990; **322:** 1641–5. Correction. *ibid.* 1997; **336:** 1335.

Duchenne muscular dystrophy. Controlled studies of the use of allopurinol in an attempt to increase muscle ATP in Duchenne muscular dystrophy (p.1507) failed to show any benefit from treatment.[1-3]

1. Stern LM, *et al.* The progression of Duchenne muscular dystrophy: clinical trial of allopurinol therapy. *Neurology* 1981; **31:** 422–6.
2. Hunter JR, *et al.* Effects of allopurinol in Duchenne's muscular dystrophy. *Arch Neurol* 1983; **40:** 294–9.
3. Bertorini TE, *et al.* Chronic allopurinol and adenine therapy in Duchenne muscular dystrophy: effects on muscle function, nucleotide degradation, and muscle ATP and ADP content. *Neurology* 1985; **35:** 61–5.

Epilepsy. Reduction in the frequency of seizures has been described in some patients with severe or intractable epilepsy (p.465) when allopurinol was added to their existing antiepileptic therapy.[1-4] Although the mode of action was not known it was noted that the patients were not hyperuricaemic and that allopurinol did not affect plasma concentrations of existing antiepileptics.[1] However, others[5] have seen no benefit.

1. DeMarco P, Zagnoni P. Allopurinol and severe epilepsy. *Neurology* 1986; **36:** 1538–9.
2. Tada H, *et al.* Clinical effects of allopurinol on intractable epilepsy. *Epilepsia* 1991; **32:** 279–83.
3. Zagnoni PG, *et al.* Allopurinol as an add-on therapy in refractory epilepsy—a double-blind placebo-controlled randomised study. *Epilepsia* 1994; **35:** 107–12.
4. Togha M, *et al.* Allopurinol as adjunctive therapy in intractable epilepsy: a double-blind and placebo-controlled trial. *Arch Med Res* 2007; **38:** 313–16.
5. Coppola G, Pascotto A. Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* 1996; **18:** 50–2.

Organ and tissue transplantation. Allopurinol 25 mg on alternate days has been added to the immunosuppressive treatment for renal transplantation,[1] and is reported to reduce the frequency of acute rejection. One possible explanation for this effect is allopurinol's ability to suppress the production of free radicals (see Oxidative Stress, below). Organ and tissue transplantation, and the more usual drugs used in immunosuppressive regimens are discussed on p.1810. It should be noted that allopurinol interacts with azathioprine (see Immunosuppressants, under Interactions, above) and ciclosporin (p.1826).

1. Chocair P, *et al.* Low-dose allopurinol plus azathioprine/cyclosporin/prednisolone, a novel immunosuppressive regimen. *Lancet* 1993; **342:** 83–4.

Oxidative stress. Allopurinol, through its inhibition of xanthine oxidase, can block the development of superoxide free radicals during reperfusion after an ischaemic episode. Consequently, the ability of allopurinol to reduce oxidative stress has been investigated in a number of clinical situations.

In a small study[1] of patients with idiopathic dilated cardiomyopathy, short-term intracoronary allopurinol improved myocardial efficiency by decreasing the oxygen demand of left ventricular contraction.

In patients undergoing coronary artery bypass graft surgery, perioperative allopurinol reduced hospital mortality, the incidence of arrhythmias, the number of ischaemic events, and the need for inotropic support, although the findings were not consistent in all studies.[2]

Improved endothelial dysfunction has been found in patients with chronic heart failure given allopurinol.[3,4]

A large study[5] in neonates undergoing cardiac surgery found that allopurinol caused a reduction in seizures and cardiac events in those with hypoplastic left heart syndrome. No benefit was found in neonates with less severe forms of congenital heart disease, considered to be at lower risk of adverse surgical outcome or reperfusion injury. Allopurinol also failed to reduce the incidence of periventricular leucomalacia (thought to represent ischaemic infarction of the developing brain) in preterm infants compared with placebo in a large study.[6] Similarly, allopurinol did not reduce the incidence of infarct extension in patients with acute myocardial infarction.[7]

The possibility that allopurinol limits the production of free radicals has also led to allopurinol sodium being included as an ingredient of the University of Wisconsin solution [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)], which is used for the preservation of organs for transplantation.[8]

A pilot study using allopurinol showed a beneficial effect on free radical formation, cerebral blood volume, and electrical brain activity in severely asphyxiated newborns.[9] However, a systematic review[10] of this and 2 other studies in such infants was unable to determine whether allopurinol produced clinically important benefits.

1. Cappola TP, *et al.* Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; **104:** 2407–11.
2. Weimert NA, *et al.* Allopurinol as a cardioprotectant during coronary artery bypass graft surgery. *Ann Pharmacother* 2003; **37:** 1708–11.
3. Doehner W, *et al.* Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricaemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105:** 2619–24.
4. Farquharson CAJ, *et al.* Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; **106:** 221–6.
5. Clancy RR, *et al.* Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; **108:** 61–70.
6. Russell GAB, Cooke RWI. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73:** F27–F31.
7. Parmley LF, *et al.* Allopurinol therapy of ischemic heart disease with infarct extension. *Can J Cardiol* 1992; **8:** 280–6.
8. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995; **46:** 235–47.
9. Van Bel F, *et al.* Effect of allopurinol on postasphyxial free radical formation, cerebral haemodynamics, and electrical brain activity. *Pediatrics* 1998; **101:** 185–93.
10. Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 14/07/08).

Prostatitis. Although allopurinol has been reported to be of benefit[1] in a small study in patients with chronic prostatitis (p.2181), a systematic review[2] found no other satisfactory evidence of benefit, and considered that the clinical relevance of the original study results was unclear.

1. Persson BE, *et al.* Ameliorative effect of allopurinol on nonbacterial prostatitis: a parallel double-blind controlled study. *J Urol (Baltimore)* 1996; **155:** 961–4.
2. McNaughton Collins M, Wilt T. Allopurinol for chronic prostatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 18/05/06).

Protozoal infections. Allopurinol has been widely used as an adjunct to pentavalent antimonials in the treatment[1,2] of Old World *visceral leishmaniasis* (p.824), particularly where resistance to antimony alone is likely, although the degree of benefit has been called into question.[3] It has also been used with other drugs such as pentamidine[4] or azole antifungals[5-8], including in transplant patients[7] or those with AIDS,[5] or in whom antimonials were otherwise poorly tolerated.[8] Allopurinol has also been tried alone[9,10] or with other drugs in both Old World[11] and New World[12-14] *cutaneous* or *mucocutaneous leishmaniasis*; results, particularly in the latter, have been variable.

Some beneficial results have been noted[15-17] in indeterminate and chronic Chagas' disease (*American trypanosomiasis*, p.827), although it may be less effective than itraconazole.

The selective antiparasitic action of allopurinol is believed to be due to its incorporation into the protozoal, but not the mammalian, purine salvage pathway. This leads to the formation of 4-aminopyrazolopyrimidine ribonucleotide triphosphate, a highly toxic analogue of adenosine triphosphate, that is incorporated into ribonucleic acid. This action of allopurinol is shared by allopurinol riboside, one of the minor metabolites in man, but not by oxipurinol, the major human metabolite. Thus, some studies have been conducted with allopurinol riboside, rather than allopurinol, in an attempt to enhance activity by avoiding host-mediated inactivation.[18]

1. di Martino L, *et al.* Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. *Trans R Soc Trop Med Hyg* 1990; **84:** 534–5.
2. Gradoni L, *et al.* Treatment of Mediterranean visceral leishmaniasis. *Bull WHO* 1995; **73:** 191–7.
3. Singh NKP, *et al.* Combination therapy in kala-azar. *J Assoc Physicians India* 1995; **43:** 319–20.
4. Das VNR, *et al.* A randomized clinical trial of low dosage combination of pentamidine and allopurinol in the treatment of antimony unresponsive cases of visceral leishmaniasis. *J Assoc Physicians India* 2001; **49:** 609–13.
5. Raffi F, *et al.* Use of an itraconazole/allopurinol combination for the treatment of visceral leishmaniasis in a patient with AIDS. *Clin Infect Dis* 1995; **21:** 1338–9.
6. Torrus D, *et al.* Fluconazole plus allopurinol in treatment of visceral leishmaniasis. *J Antimicrob Chemother* 1996; **37:** 1042–3.
7. Hueso M, *et al.* The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. *Nephrol Dial Transplant* 1999; **14:** 2941–3.
8. Kuyucu N, *et al.* Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in an infant who developed pancreatitis caused by meglumine antimoniate. *Pediatr Infect Dis J* 2001; **20:** 455–7.
9. Halbert AR, *et al.* Allopurinol for Old World cutaneous leishmaniasis. *Pediatr Dermatol* 1995; **12:** 287–8.
10. D'Oliveira A, *et al.* Evaluating the efficacy of allopurinol for the treatment of cutaneous leishmaniasis. *Int J Dermatol* 1997; **36:** 938–40.
11. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2002; **41:** 521–4.
12. Velez I, *et al.* Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 232–6.
13. Martinez S, *et al.* Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clin Infect Dis* 1997; **24:** 165–9.
14. Llanos-Cuentas A, *et al.* Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clin Infect Dis* 1997; **25:** 677–84.
15. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; **59:** 133–8.
16. Amato Neto V. Etiological treatment for infection by Trypanosoma cruzi. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 211–3.
17. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; **97:** 23–9.
18. Shapiro TA, *et al.* Pharmacokinetics and metabolism of allopurinol riboside. *Clin Pharmacol Ther* 1991; **49:** 506–14.

Renal calculi. In conjunction with a reduced dietary purine intake, high fluid intake, and potassium citrate, allopurinol may be used to prevent the recurrence of calcium oxalate renal calculi (p.2181) in patients with hyperuricosuria.[1,2] The recommended oral dose of allopurinol is 200 to 300 mg daily adjusted on the basis of subsequent 24-hour urinary urate excretion. Allopurinol is also advocated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with deficient activity of the enzyme adenine phosphoribosyltransferase.

1. Ettinger B, *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986; **315:** 1386–9.
2. Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002; **31:** 915–25.

Sarcoidosis. Although corticosteroids remain the mainstay of drug therapy for sarcoidosis (p.1512), and other drugs are very much second line, there are reports[1-3] of benefit in cutaneous disease from the use of allopurinol.

1. Brechtel B, *et al.* Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; **135:** 307–9.
2. Antony F, Layton AM. A case of cutaneous acral sarcoidosis with response to allopurinol. *Br J Dermatol* 2000; **142:** 1052–3.
3. Bregnhoej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; **16:** 125–7.

Schizophrenia. Involvement of purinergic neurotransmission has been hypothesised to play some role in schizophrenia (p.955), and allopurinol has been investigated as a possible adjunctive treatment, with some evidence of benefit, especially in patients with refractory positive symptoms.[1]

1. Buie LW, *et al.* Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. *Ann Pharmacother* 2006; **40:** 2200–4.

Skin disorders. Reactive perforating collagenosis (RPC) is a condition in which altered collagen is eliminated through the epidermis; it may be inherited or acquired. In 3 of 4 patients with RPC refractory to antibacterials and oral and topical corticosteroids, significant improvement was seen with allopurinol, in terms of reduction of new lesions, improvement of existing lesions, and reduction of pruritus. The fourth patient died from unrelated causes before review.[1]

1. Hoque SR, *et al.* Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. *Br J Dermatol* 2006; **154:** 759–62.

Preparations

BP 2008: Allopurinol Tablets;
USP 31: Allopurinol Oral Suspension; Allopurinol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alfadiman; Alloboxal†; Gotir†; Puritenk; ***Austral.:*** Allohexal; Allorin†; Allosig; Capurate†; Progout; Zyloprim; ***Austria:*** Allostad; Allotyrol†; Apurin†; Gewapurol; Gichtex; Purinol; Urosin; Zyloric; ***Belg.:*** Alpuric; Docallopu; Zyloric; ***Braz.:*** Labopurinol†; Lopurax; Uricemil†; Zilopur; Zyloric; ***Canad.:*** Novo-Purol; Zyloprim; ***Chile:*** Talol; Urogotan A; Zyloric; ***Cz.:*** Apurol†; Milurit; Purinol; ***Denm.:*** Abopur; Apurin; Hexanurat; ***Fin.:*** Allonol; Apurin; Arturic; Zyloric; ***Fr.:*** Zyloric; ***Ger.:*** Allo; Allo-Efeka; Allo-Puren†; Allobeta; Bleminol; Cellidrin; dura AL; Epidropal; Foligan; Jenapurinol; Milurit; Pureduct†; Remid; Uribenz; Uripurinol†; Zyloric; ***Gr.:*** Soluric; Zylapour; Zyloric; ***Hong Kong:*** Allnol†; Marinol; Mephanol†; Milurit; Progout; Zyloric; ***Hung.:*** Harpagin†; Milurit; ***India:*** Ciploric; Zyloric; ***Indon.:*** Algut; Benoxuric; Hycemia; Isoric; Licoric; Llanol; Nilapur; Pritanol; Puricemia; Reucid; Rinolic; Sinoric; Tylonic; Urica; Uricnol; Xanturic; Zyloric; ***Irl.:*** Purinol; Tipuric; Zyloric; ***Israel:*** Alloril; Zylol; Zyloric†; ***Ital.:*** Allurit; Uricemil†; Zyloric; ***Malaysia:*** Harpagin†; Uritab†; Zyloric; ***Mex.:*** Acyprin; Apo-Tinole†; Atisuril; Aurigen†; Bionol; Darzune; Etindrax; Unizuric; Zyloprim; ***Neth.:*** Apurin; Zyloric; ***Norw.:*** Allopur; Arturic; Zyloric; ***NZ:*** Allohexal; Allorin; Progout; ***Philipp.:*** Allurase; Alpurase; Elavil; Llanol; Lopric; Loricid; Purinase; Purispec; Puristen; Synol; Trianol; Xanurace; Zyloprim; ***Pol.:*** Allupol; Milurit; Zyloric; ***Port.:*** Alosfar; Uriprim; Zurim; Zyloric; ***Rus.:*** Purinol (Пуринол); ***S.Afr.:*** Lonol; Puricos; Redurate; Urinol; Zyloprim; ***Singapore:*** Erloric†; Progout; Valeric†; Zyloric; ***Spain:*** Zyloric; ***Swed.:*** Zyloric; ***Switz.:*** allo-basan†; Allopur; Cellidrine; Mephanol; Sigapurol N†; Uriconorme; Zyloric; ***Thai.:*** Alinol; Allopin; Apnol; Apurol; Loporic†; Medoric; Puricin†; Puride; Uricad; Valeric†; Xanol; Zyloric; ***Turk.:*** Allo-Urik; Allogut; Urikoliz; ***UK:*** Caplenal; Cosuric; Rimapurinol; Xanthomax†; Zyloric; ***USA:*** Aloprim; Zyloprim; ***Venez.:*** Aluprol†; Aluron; Zyloric.

Multi-ingredient: ***Arg.:*** Artrex; Colpuril; Xuric-A; ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Ital.:*** Uricodue; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

Benzbromarone *(BAN, USAN, rINN)*

Bensbromaron; Bentsbromaroni; Benzbromaron; Benzbromarona; Benzbromaronas; Benzbromaronum; L-2214; MJ-10061. 3,5-Dibromo-4-hydroxyphenyl 2-ethylbenzofuran-3-yl ketone.

Бензбромарон

$C_{17}H_{12}Br_2O_3$ = 424.1.
CAS — 3562-84-3.
ATC — M04AB03.
ATC Vet — QM04AB03.

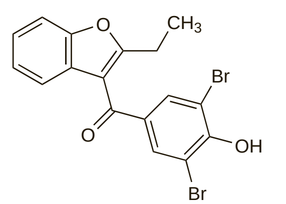

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Benzbromarone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Adverse Effects

Benzbromarone may cause gastrointestinal adverse effects, especially diarrhoea. It may precipitate an acute attack of gout and cause uric acid renal calculi and renal colic. Hepatotoxicity has occurred and monitoring of liver function has been recommended.

Effects on the liver. Benzbromarone-induced liver damage has been reported.[1-4]

1. Van Der Klauw MM, *et al.* Hepatic injury caused by benzbromarone. *J Hepatol* 1994; **20:** 376–9.
2. Anonymous. Benzbromarone and hepatitis. *WHO Drug Inf* 2000; **14:** 29.
3. Wagayama H, *et al.* Fatal fulminant hepatic failure associated with benzbromarone. *J Hepatol* 2000; **32:** 874.
4. Arai M, *et al.* Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* 2002; **17:** 625–6.

Precautions

Benzbromarone should be avoided in patients with moderate or severe renal impairment, in those with uric acid renal calculi, and in those with urinary uric acid excretion rates of greater than 700 mg per 24 hours. Like other uricosurics, treatment with benzbromarone should not be started during an acute attack of gout. Similarly, an adequate fluid intake should be maintained to reduce the risk of uric acid renal calculi; additionally, alkalinisation of the urine may be considered.

Porphyria. Benzbromarone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Aspirin and other salicylates antagonise the effect of benzbromarone. Benzbromarone may increase the anticoagulant activity of coumarin oral anticoagulants (see under Interactions of Warfarin, p.1429).

Antigout drugs. For mention of the effects of benzbromarone on the clearance of oxipurinol, the major active metabolite of *allopurinol*, and the view that this was not clinically significant, see under Interactions of Allopurinol, p.553.

Pharmacokinetics

Benzbromarone is only partially absorbed from the gastrointestinal tract, reaching peak plasma concentrations about 2 to 4 hours after an oral dose. Benzbromarone is extensively bound to plasma proteins. It is metabolised in the liver, and is excreted mainly in the faeces; a small amount appears in the urine.

◊ References.

1. Maurer H, Wollenberg P. Urinary metabolites of benzbromarone in man. *Arzneimittelforschung* 1990; **40:** 460–2.
2. Walter-Sack I, *et al.* Variation of benzbromarone elimination in man—a population study. *Eur J Clin Pharmacol* 1990; **39:** 173–6.

Uses and Administration

Benzbromarone is a uricosuric drug that reduces plasma concentrations of uric acid by blocking renal tubular reabsorption. It has been suggested that benzbromarone may also increase the intestinal elimination of uric acid. It has been used to treat hyperuricaemia including that associated with chronic gout (p.552) although it has been withdrawn in many countries due to reports of hepatotoxicity.

Benzbromarone is not used to treat acute attacks of gout and may exacerbate and prolong them if given during an attack; treatment should not start therefore until an acute attack has subsided.

The usual oral dose has been 50 to 200 mg daily. An NSAID or colchicine should be given initially to reduce the risk of precipitating acute gout. An adequate fluid intake should be maintained. Lower doses of benzbromarone (20 mg) have also been used in the form of a combination product with allopurinol.

◊ References.

1. Hanvivadhanakul P, *et al.* Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 2002; **85** (suppl 1): S40–S47.
2. Kumar S, *et al.* Benzbromarone therapy in management of refractory gout. *N Z Med J* 2005; **118:** U1528.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Max Uric†; ***Austria:*** Uricovac; ***Belg.:*** Desuric†; ***Braz.:*** Narcaricina†; ***Ger.:*** Narcaricin†; ***Hung.:*** Harpagin†; ***Jpn:*** Urinorm; ***Malaysia:*** Harpagin†; ***Mex.:*** Desuric†; ***Neth.:*** Desuric; ***S.Afr.:*** Minuric†; ***Singapore:*** Narcaricin†; ***Spain:*** Urinorm; ***Switz.:*** Desuric†; Obaron†; ***Thai.:*** Narcaricin†.

Multi-ingredient: ***Austria:*** Allobenz; Duovitan; Gichtex plus; ***Belg.:*** Comburic; ***Ger.:*** Allo.comp.; Allomaron†; Harpagin; ***Philipp.:*** Allomaron; ***Port.:*** Acifugan†; ***S.Afr.:*** Allomaron†; ***Spain:*** Acifugan†; Facilit†; ***Thai.:*** Allomaron.

Benziodarone *(BAN, rINN)*

Benciodarona; Bentsiodaroni; Benziodaron; Benziodaronum; L-2329. 2-Ethylbenzofuran-3-yl 4-hydroxy-3,5-di-iodophenyl ketone.

Бензйодарон

$C_{17}H_{12}I_2O_3$ = 518.1.
CAS — 68-90-6.
ATC — C01DX04.
ATC Vet — QC01DX04.

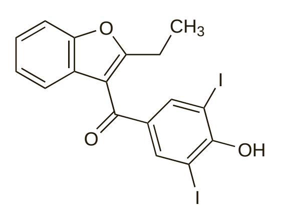

Profile

Benziodarone is a uricosuric drug structurally related to benzbromarone (see above) that has been given orally to reduce hyperuricaemia in chronic gout.

Benziodarone has been associated with jaundice and thyroid disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Dilafurane†.

Multi-ingredient: ***Ital.:*** Uricodue.

Colchicine

Colchicina; Colchicinum; Kolchicin; Kolchicinas; Kolkicin; Kolkisiini; Kolşisin. (*S*)-*N*-(5,6,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[α]heptalen-7-yl)acetamide.

Колхицин

$C_{22}H_{25}NO_6$ = 399.4.

CAS — 64-86-8.

ATC — M04AC01.

ATC Vet — QM04AC01.

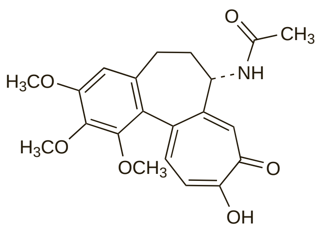

Description. Colchicine is an alkaloid obtained from various *Colchicum* spp.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*
Chin. also has a monograph for colchicine amide.

Ph. Eur. 6.2 (Colchicine). A yellowish-white amorphous or crystalline powder. Very soluble in water, rapidly recrystallising from concentrated solutions as the sesquihydrate; freely soluble in alcohol and in chloroform. Protect from light.

USP 31 (Colchicine). An alkaloid obtained from various *Colchicum* spp. and other genera. Pale yellow to pale greenish-yellow amorphous scales, or powder or crystalline powder. Is odourless or nearly so, and darkens on exposure to light. Soluble 1 in 25 of water and 1 in 220 of ether; freely soluble in alcohol and in chloroform. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

The most frequent adverse effects of oral colchicine are those involving the gastrointestinal tract and may be associated with its antimitotic action. Diarrhoea, nausea, vomiting, and abdominal pain are often the first signs of toxicity and are usually an indication that colchicine therapy should be stopped or the dose reduced. Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, skin rashes, and renal and hepatic damage.

Rarely, bone marrow depression with agranulocytosis, thrombocytopenia, and aplastic anaemia have occurred on prolonged treatment as have peripheral neuropathy, myopathy, rashes, and alopecia.

Adverse effects after intravenous use include cardiac arrhythmias and local reactions such as thrombophlebitis and neuritis. Extravasation may cause tissue necrosis.

Symptoms of acute **overdosage** with oral colchicine often do not appear for 2 to 12 hours. The first signs of toxicity are nausea, vomiting, and diarrhoea; a burning sensation of the throat, stomach, and skin may also occur. The diarrhoea may be severe and haemorrhagic and, coupled with vascular damage or paralytic ileus can lead to dehydration, hypotension, and shock. Multiple organ failure may occur, manifest as CNS toxicity (confusion, delirium, sometimes coma), bone marrow depression, hepatocellular damage, muscle damage, neuropathy, respiratory distress, myocardial depression, and renal damage. A toxic epidermal necrolysis-like reaction has also been reported. Death may be due to respiratory depression, cardiovascular collapse, or sepsis after pancytopenia. In surviving patients, alopecia, rebound leucocytosis, and stomatitis may occur about 10 days after the acute overdose. The lethal dose varies: 7 mg of colchicine has caused death, yet recovery has occurred after much larger doses.

When treating colchicine overdosage or acute poisoning patients should be carefully monitored for some time to take account of the delayed onset of symptoms. The stomach may be emptied by lavage in adults within 1 hour of acute poisoning; multiple dose activated charcoal should be given to adults and children who have ingested more than 300 micrograms/kg of colchicine provided vomiting has not started. Treatment is primarily symptomatic and supportive with attention being given to the control of respiration, maintenance of blood pressure and the circulation, and correction of fluid and electrolyte imbalance.

Effects on the neuromuscular system. Colchicine-induced myoneuropathy may be a common but unrecognised condition in patients with *reduced* renal function who receive usual doses of colchicine.[1] Although both skeletal muscles and peripheral nerves are affected, myopathy is most prominent and associated axonal neuropathy is mild. The condition usually presents with proximal muscle weakness and is always accompanied by elevations in serum creatine kinase concentrations. Withdrawal of colchicine leads to spontaneous remission of these symptoms within a few weeks but resolution of the polyneuropathy is slow. Examination of proximal muscles shows marked abnormal spontaneous activity and, because of the features of the condition, it is often initially misdiagnosed as probable polymyositis or uraemic myopathy. A literature review[2] identified renal impairment as the primary risk factor for the development of colchicine-induced myopathy; dosage adjustment is advised in these patients.

There have been reports suggesting colchicine-induced myopathy may develop in patients who have *normal* renal function.

A patient with normal renal function but chronic alcohol-induced liver disease developed an unusual form of myoneuropathy after receiving only a short course of colchicine. This patient was also taking tolbutamide, the microsomal enzyme-inhibiting activity of which may have exacerbated the toxicity of colchicine.[3] A teenager with familial Mediterranean fever who had normal renal and hepatic function developed toxic myopathy due to colchicine use. Myopathy improved after colchicine was stopped and recurred when it was restarted at a lower dose.[4]

Rhabdomyolysis has also been reported.[5,6]

1. Kuncl RW, *et al.* Colchicine myopathy and neuropathy. *N Engl J Med* 1987; **316:** 1562–8.
2. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 2004; **24:** 1784–92.
3. Besana C, *et al.* Colchicine myoneuropathy. *Lancet* 1987; **ii:** 1271–2.
4. Sayarlioglu M, *et al.* Colchicine-induced myopathy in a teenager with familial Mediterranean fever. *Ann Pharmacother* 2003; **37:** 1821–4.
5. Chattopadhyay I, *et al.* Colchicine induced rhabdomyolysis. *Postgrad Med J* 2001; **77:** 191–2.
6. Boomershine KH. Colchicine induced rhabdomyolysis. *Ann Pharmacother* 2002; **36:** 824–6.

Effects on the reproductive system. UK licensing information states that colchicine may adversely affect spermatogenesis under certain conditions of therapy. *Animal* data has shown that colchicine in high doses may arrest spermatogenesis and lead to azoospermia. However, in clinical practice male infertility does not seem to be common in patients given colchicine, and may be related in some cases to the underlying disease rather than the drug.[1] Similarly, although colchicine is not recommended in the first trimester of pregnancy, it may improve fertility in women with familial Mediterranean fever, and results in women who have been taking colchicine at conception and during pregnancy have been relatively reassuring[1] (see also under Pregnancy, below).

1. Mijatovic V, *et al.* Familial Mediterranean fever and its implications for fertility and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2003; **108:** 171–6.

Inappropriate administration. Intravenous use of colchicine is associated with a risk of severe or fatal adverse effects (see Administration, below). Although unlicensed either orally or parenterally for use in back pain, intravenous colchicine has apparently been used in alternative medicine for this indication. As of February 2008, the FDA had received reports of 50 adverse events, including 23 deaths, associated with the unapproved use of intravenous colchicine. Three of the reported deaths were associated with compounded colchicine that, due to preparation errors, was 8 times more potent than the amount stated on the label. Potentially fatal effects include neutropenia, thrombocytopenia, pancytopenia, acute renal failure, and congestive heart failure.[1,2]

1. FDA. FDA takes action to stop the marketing of unapproved injectable drugs containing colchicine (issued 6th February 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01791.html (accessed 21/04/08)
2. FDA. Questions and answers about FDA's enforcement action against unapproved injectable colchicine products (issued 6th February 2008). Available at: http://www.fda.gov/cder/drug/unapproved_drugs/colchicine_qa.htm (accessed 21/04/08)

Overdosage. References.

1. McIntyre IM, *et al.* Death following colchicine poisoning. *J Forensic Sci* 1994; **39:** 280–6.
2. Hood RL. Colchicine poisoning. *J Emerg Med* 1994; **12:** 171–7.
3. Baud FJ, *et al.* Brief report: treatment of severe colchicine overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; **332:** 642–5.
4. Critchley JAJH, *et al.* Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol* 1997; **16:** 229–32.
5. Milne ST, Meek PD. Fatal colchicine overdose: report of a case and review of the literature. *Am J Emerg Med* 1998; **16:** 603–8.
6. Kubler PA. Fatal colchicine toxicity. *Med J Aust* 2000; **172:** 498–9.
7. Harris R, *et al.* Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med* 2000; **18:** 435–40.
8. Mullins ME, *et al.* Fatal cardiovascular collapse following acute colchicine ingestion. *J Toxicol Clin Toxicol* 2000; **38:** 51–4.
9. Arroyo MP, *et al.* Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; **150:** 581–8.
10. Ataş B, *et al.* Four children with colchicine poisoning. *Hum Exp Toxicol* 2004; **23:** 353–6.
11. Miller MA, *et al.* Colchicine-related death presenting as an unknown case of multiple organ failure. *J Emerg Med* 2005; **28:** 445–8.
12. Borras-Blasco J, *et al.* Acute renal failure associated with an accidental overdose of colchicine. *Int J Clin Pharmacol Ther* 2005; **43:** 480–4.

Precautions

Colchicine should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity. It should also be used with caution in patients with cardiac, hepatic, renal, or gastrointestinal disease. Colchicine should be avoided in patients with blood disorders. It should also generally be avoided in pregnancy since it is known to be teratogenic in *animals* and there have also been some suggestions of a risk of fetal chromosome damage in humans.

Colchicine should not be given by subcutaneous or intramuscular injection as it causes severe local irritation.

Breast feeding. Colchicine is distributed into breast milk,[1-3] and some have recommended waiting for 8 hours[2] or 12 hours[3] after a dose before breast feeding to minimise exposure of the infant. However, since no adverse effects on the infant have been noted in these reports, the American Academy of Pediatrics considered its use to be usually compatible with breast feeding.[4]

1. Milunsky JM, Milunsky A. Breast-feeding during colchicine therapy for familial Mediterranean fever. *J Pediatr* 1991; **119:** 164.
2. Guillonneau M, *et al.* Colchicine is excreted at high concentrations in human breast milk. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 177–8.
3. Ben-Chetrit E, *et al.* Colchicine in breast milk of patients with familial Mediterranean fever. *Arthritis Rheum* 1996; **39:** 1213–17.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)

Pregnancy. Colchicine is contra-indicated in pregnancy because of *animal* teratogenicity. However, it has been used during pregnancy in women with familial Mediterranean fever (see under Uses, below). There was no increase in abnormality rate of the newborns and no problems were detected in 130 offspring.[1]

1. Rabinovitch O, *et al.* Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *Am J Reprod Immunol* 1992; **28:** 245–6.

Interactions

Use of colchicine with clarithromycin, erythromycin, or tolbutamide may cause colchicine toxicity. Thiazide diuretics may increase serum uric acid and interfere with the activity of colchicine. Muscle disorders have been reported when colchicine is used with ciclosporin. Colchicine may impair the absorption of vitamin B_{12}.

Cardiovascular drugs. Acute myopathy has been reported in patients with chronic renal impairment given colchicine with *simvastatin*.[1,2] Similar effects have been seen in patients with renal impairment given colchicine with *fluvastatin*[3], or *pravastatin*.[4] Since many statins are metabolised by the cytochrome P450 isoenzyme CYP3A4, as is colchicine, this has been proposed as one possible mechanism.[3,4] However, fluvastatin and pravastatin are cleared through different isoenzymes. Alternative proposed mechanisms are synergistic myopathy[2,3] or interference with transport mediated by P-glycoprotein.[4] Tetraparesis developed in a patient who took colchicine with *verapamil*; this was considered to be due to a pharmacokinetic interaction which increased serum and CSF concentrations of colchicine.[5]

1. Hsu W-C, *et al.* Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002; **25:** 266–8.
2. Baker SK, *et al.* Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004; **30:** 799–802.
3. Atasoyu EM, *et al.* Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005; **39:** 1368–9.
4. Alaylı G, *et al.* Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005; **39:** 1358–61.
5. Tröger U, *et al.* Tetraparesis associated with colchicine is probably due to inhibition by verapamil of the P-glycoprotein efflux pump in the blood-brain barrier. *BMJ* 2005; **331:** 613. Correction. *ibid.* 2006; **332:** 882.

Ciclosporin. There is a need for caution if colchicine is used with ciclosporin. Myopathies or rhabdomyolysis[1] may be a problem, especially in transplant patients[2] or those with renal impairment.[3] In addition, increased blood-ciclosporin concentrations and nephrotoxicity developed in a renal transplant patient after the introduction of colchicine therapy.[4]

1. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337:** 915.
2. Simkin PA, Gardner GC. Colchicine use in cyclosporine treated transplant recipients: how little is too much? *J Rheumatol* 2000; **27:** 1334–7.
3. Rumpf KW, Henning HV. Is myopathy in renal transplant patients induced by cyclosporin or colchicine? *Lancet* 1990; **335:** 800–1.
4. Menta R, *et al.* Reversible acute cyclosporin nephrotoxicity induced by colchicine administration. *Nephrol Dial Transplant* 1987; **2:** 380–1.

Macrolides. Life-threatening colchicine toxicity has been described after use for 2 weeks with *erythromycin* in a patient with hepatic and renal impairment.[1] In a patient with end-stage renal disease, but no hepatic impairment, fatal colchicine toxicity developed after 4 days of *clarithromycin* therapy.[2] A patient with moderate chronic renal impairment developed acute but non-fatal colchicine intoxication on day 4 of a 7-day *Helicobacter pylori* treatment course containing clarithromycin.[3] A retrospective study in 116 patients given both drugs concluded that clarithromycin increased the risk of colchicine toxicity, especially in those patients with renal impairment, and that the two drugs should not be used together.[4]

1. Caraco Y, *et al.* Acute colchicine intoxication—possible role of erythromycin administration. *J Rheumatol* 1992; **19:** 494–6.
2. Dogukan A, *et al.* Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD): possible role of clarithromycin administration. *Clin Nephrol* 2001; **55:** 181–2.
3. Rollot F, *et al.* Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004; **38:** 2074–7.
4. Hung IFN, *et al.* Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005; **41:** 291–300.

Tolbutamide. For a suggestion that tolbutamide may have exacerbated the toxicity of colchicine in a patient with liver disease, see under Effects on the Neuromuscular System, above.

Pharmacokinetics

Peak plasma concentrations of colchicine are reached within 2 hours of oral use. Colchicine is partially deacetylated in the liver and the unchanged drug and its metabolites are excreted in the bile and undergo intestinal reabsorption. Colchicine is found in high concentrations in leucocytes, kidneys, the liver, and spleen. Most of the drug is excreted in the faeces but 10 to 20% is excreted in the urine and this proportion rises in patients with liver disorders. Colchicine is distributed into breast milk.

◊ References.

1. Rochdi M, *et al.* Pharmacokinetics and absolute bioavailability of colchicine after iv and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol* 1994; **46:** 351–4.
2. Ferron GM, *et al.* Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol* 1996; **36:** 874–83.

Uses and Administration

Colchicine is used for the relief of acute gout (p.552) and for the prophylaxis of acute attacks, particularly during the first few months of treatment with allopurinol or uricosurics. Colchicine produces a dramatic response in acute gout, probably by reducing the inflammatory reaction to urate crystals; this effect might be due to several actions including decreased leucocyte mobility. It is not an analgesic and has no effect on blood concentrations of uric acid, or on the excretion of uric acid. Colchicine also has an antimitotic action.

Colchicine has also been used in several other conditions including amyloidosis, Behçet's syndrome, familial Mediterranean fever, idiopathic thrombocytopenic purpura, pericarditis, primary biliary cirrhosis, and pyoderma gangrenosum.

If colchicine is used for acute attacks of **gout**, then treatment should be started as soon as possible and an effect may be expected within 12 hours. The recommended oral dose in the UK is 1 mg initially, then 500 micrograms every 2 to 3 hours until pain relief is obtained or gastrointestinal adverse effects occur (but see also Administration, below). Although some licensed products allow doses up to a maximum of 10 mg, the *BNF* considers that the total dose should not exceed 6 mg. At least 3 days should elapse before another course is given. In the USA the oral dose is 1 to 1.2 mg initially; this may be repeated every 2 hours, or 500 or 600 micrograms may be taken every hour (or even every 2 or 3 hours if sufficient), until pain is relieved or gastrointestinal adverse effects occur. The maximum total dose for an acute attack should not exceed 8 mg.

Colchicine has sometimes been given intravenously in a dose of 1 or 2 mg over 2 to 5 minutes with additional doses of 0.5 or 1 mg every 6 hours as required to a total dose of not more than 4 mg in 24 hours; once this amount of colchicine has been given further doses should not then be given by any route for at least 7 days. For the view that the intravenous route should be avoided, see Administration, below.

When used for the prophylaxis of gout oral doses are 500 or 600 micrograms once daily; some patients may require doses up to 1.8 mg daily.

Consideration should be given to using reduced dosages in patients with renal impairment, see below.

◊ References.

1. Lange U, *et al.* Current aspects of colchicine therapy: classical indications and new therapeutic uses. *Eur J Med Res* 2001; **6:** 150–60.
2. Schlesinger N, *et al.* Colchicine for acute gout. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/04/08).

Administration. Although colchicine 1 mg orally, followed by 500 micrograms every 2 to 3 hours, is recommended in the UK for the treatment of acute gout, many rheumatologists consider this excessive; a low-dose regimen of 500 micrograms no more than 3 times daily has been advocated in preference.[1] It has also been suggested that intravenous colchicine, although undoubtedly effective, should not be used because of the risk of severe or fatal adverse effects.[2] For reports of fatalities with intravenous colchicine during unlicensed use, see Inappropriate Administration, above.

1. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2003; **327:** 1275–6.
2. Morris I, *et al.* Colchicine in acute gout. *BMJ* 2004; **328:** 289.

Administration in renal impairment. Some licensed product information in the UK recommends that the dose of colchicine given *orally* should be reduced by up to 50% in patients with mild to moderate renal impairment, and that it should not be used in those with severe impairment. Similar recommendations have been made by various sources in the USA; for example, the *American Hospital Formulary Service* notes that some recommend the prophylactic oral dose should not exceed 600 micrograms daily in patients with a serum creatinine of 1.6 mg per 100 mL or greater, or with a creatinine clearance (CC) of 50 mL/minute or less. Some patients may only need 600 micrograms every alternate day. The *intravenous* dose should be reduced by 50% in patients with a CC of between 10 and 50 mL/minute, and it is contra-indicated in those patients with a CC less than 10 mL/minute.

Amyloidosis. Colchicine is well known to have a useful role in amyloidosis (p.743) secondary to familial Mediterranean fever, where results have suggested the possibility of reversing nephropathic changes due to renal amyloid deposition (see below). However, combination therapy with melphalan and prednisone was found to be more effective than colchicine alone in primary amyloidosis,[1] and a later study[2] found no benefit in adding colchicine to the standard therapy. The mechanism of the anti-amyloid effect of colchicine is not clear.

1. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomised trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100:** 290–8.
2. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336:** 1202–7.

Behçet's syndrome. Behçet's syndrome (p.1499) has been treated with numerous drugs. Where possible, topical treatment of local lesions should be tried before starting systemic therapy. Corticosteroids are favoured for systemic treatment in many countries, but colchicine has also been widely used. Beneficial responses have been described for most of the symptoms including the arthritic, ocular, and cutaneous manifestations, although a systematic review has questioned colchicine's efficacy.[1] The mechanism of action in this condition is believed to be based on the effect on polymorphonuclear leucocytes and other cellular effects.[2] Colchicine has also been used with corticosteroids for acute exacerbations, followed by colchicine maintenance;[3] colchicine with aspirin has also been recommended in acute disease,[4] and colchicine with benzathine benzylpenicillin has been tried.[5]

1. Saenz A, *et al.* Pharmacotherapy for Behcet's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 27/04/05).
2. Schattner A. Colchicine—expanding horizons. *Postgrad Med J* 1991; **67:** 223–6.
3. Rakover Y, *et al.* Behcet disease: long-term follow-up of three children and review of the literature. *Pediatrics* 1989; **83:** 986–92.
4. Wechsler B, Piette JC. Behçet's disease. *BMJ* 1992; **304:** 1199–1200.
5. Çalgüneri M, *et al.* Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996; **192:** 125–8.

Diffuse parenchymal lung disease. Colchicine is a potential alternative to corticosteroid therapy in patients with cryptogenic fibrosing alveolitis (see Diffuse Parenchymal Lung Disease, p.1502). However the degree of benefit, if any, is unclear although colchicine does appear to be safer and better tolerated than corticosteroid therapy.[1]

1. Davies HR, *et al.* Immunomodulatory agents for idiopathic pulmonary fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 27/04/05).

Familial Mediterranean fever. Familial Mediterranean fever (recurrent or paroxysmal polyserositis; periodic disease) is an inherited disorder that primarily affects Sephardic Jews or persons of Arab, Armenian, or Turkish ancestry.[1,2] It is characterised by attacks of acute abdominal pain, fever, and signs of peritonitis, which resolve spontaneously, usually in 24 to 48 hours. Pleuritic chest pain, arthritis, skin rash, pericarditis, and headache may occur. The most dangerous complication, however, is type AA amyloidosis (see also p.743), which can lead to nephrotic syndrome, renal failure, and death.

Familial Mediterranean fever is managed with colchicine.[1-3] Colchicine cannot stop an established attack, but, given prophylactically in oral adult doses of 1 to 3 mg daily, it reduces the frequency of attacks, prevents amyloidosis and reverses proteinuria. An initial daily dose of 500 micrograms or less has been suggested for children younger than 5 years of age, 1 mg for those aged 5 to 10 years, and 1.5 mg for children aged over 10 years; doses may be increased in a stepwise fashion to a maximum of 2 mg daily if needed.[3] Attacks are usually treated with NSAIDs[2,3] or, in severe cases, opioids.[3] Anecdotal evidence has suggested that prazosin may also be of benefit,[4] but initial reports of improvement with interferon alfa have not been borne out.[2] Anakinra has also been investigated.[5]

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet* 1998; **351:** 659–63.
2. Drenth JPH, van der Meer JWM. Hereditary periodic fever. *N Engl J Med* 2001; **345:** 1748–57.
3. Kallinich T, *et al.* Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; **119:** e474–e483. Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/2/e474 (accessed 21/04/08)
4. Kataoka H, *et al.* Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.
5. Roldan R, *et al.* Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; **75:** 504–5.

Idiopathic thrombocytopenic purpura. In idiopathic thrombocytopenic purpura (p.1505), refractory to standard therapy, a few patients have had partial or complete response to colchicine[1,2] and further studies have been suggested.[2,3]

1. Strother SV, *et al.* Colchicine therapy for refractory idiopathic thrombocytopenic purpura. *Arch Intern Med* 1984; **144:** 2198–2200.
2. Bonnotte B, *et al.* Efficacy of colchicine alone or in combination with vinca alkaloids in severe corticoid-resistant thrombocytopenic purpura: six cases. *Am J Med* 1999; **107:** 645–6.
3. McMillian R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126:** 307–14.

Pericarditis. Mild cases of recurrent pericarditis may be treated with colchicine, as an adjunct to NSAID therapy.[1-3] It may also provide effective prophylaxis, allowing the tapering of corticosteroids, which are usually reserved for the treatment of severe acute attacks.[2,3] The drug has also been used successfully in children.[4] In an open-label study, colchicine added to conventional therapy with aspirin or prednisone significantly decreased the recurrence rate in patients with a first episode of recurrent pericarditis, compared with conventional therapy alone.[5] Another open-label study had similar results using adjunctive colchicine for the first episode of acute pericarditis.[6] In patients with two or more relapses of acute pericarditis, colchicine was found to be highly effective in preventing recurrence.[7] The proportion of patients with relapses during or after colchicine therapy was significantly higher, and the duration of colchicine therapy significantly longer, in those who had pre-treatment with corticosteroids.

1. Millaire A, *et al.* Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15:** 120–4.
2. Adler Y, *et al.* Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97:** 2183–5.
3. Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84:** 449–54.
4. Yazigi A, *et al.* Colchicine for recurrent pericarditis in children. *Acta Paediatr Scand* 1998; **87:** 603–4.
5. Imazio M, *et al.* Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; **165:** 1987–91.
6. Imazio M, *et al.* Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005; **112:** 2012–16.
7. Artom G, *et al.* Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis. *Eur Heart J* 2005; **26:** 723–7.

Peyronie's disease. Beneficial effects have been reported with colchicine in men with Peyronie's disease. Small studies show colchicine to be most effective in reducing pain during penile erection.[1] A combination of vitamin E and colchicine has also been suggested as an alternative in early disease.[2]

1. Kadioğlu A, *et al.* Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res* 2000; **12:** 169–75.
2. Prieto Castro RM, *et al.* Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 2003; **91:** 522–4.

Primary biliary cirrhosis. Primary biliary cirrhosis (p.2408) is a chronic progressive liver disease with no specific treatment, and in general drug therapy has been poor or largely ineffective. Reviewers have noted[1-3] that several studies have been conducted with colchicine, and, although biochemical parameters were improved, a beneficial effect on clinical symptoms or liver histology was not found. A comparative study of colchicine and methotrexate showed that while both drugs improved biochemical test results and symptoms, the response to methotrexate was greater.[4] Some consider that combination therapy with colchicine, methotrexate, and ursodeoxycholic acid may be more promising than monotherapy.[2]

1. Heathcote EJ. Evidence-based therapy of primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999; **11:** 607–15.
2. Holtmeier J, Leuschner U. Medical treatment of primary biliary cirrhosis and primary sclerosing cholangitis. *Digestion* 2001; **64:** 137–50.
3. Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 27/04/05).
4. Kaplan MM, *et al.* A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. *Gastroenterology* 1999; **117:** 1173–80.

Pyoderma gangrenosum. Pyoderma gangrenosum (p.1583) associated with inflammatory bowel disease has been successfully treated with colchicine in 2 patients.[1,2] Colchicine was also of benefit in 3 patients with pyoderma associated with familial Mediterranean fever.[3] Other isolated reports include the use of low-dose colchicine in idiopathic pyoderma gangrenosum.[4]

1. Paolini O, *et al.* Treatment of pyoderma gangrenosum with colchicine. *Lancet* 1995; **345:** 1057–8.
2. Rampal P, *et al.* Colchicine in pyoderma gangrenosum. *Lancet* 1998; **351:** 1134–5.
3. Lugassy G, Ronnen M. Severe pyoderma associated with familial Mediterranean fever: favourable response to colchicine in three patients. *Am J Med Sci* 1992; **304:** 29–31.
4. Kontochristopoulos GJ, *et al.* Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209:** 233–6.

Preparations

BP 2008: Colchicine Tablets;
USP 31: Colchicine Injection; Colchicine Tablets; Probenecid and Colchicine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Xuric; ***Austral.:*** Colgout; Lengout; ***Braz.:*** Cixin; Colchin; Colchis; ***Hong Kong:*** Colcina; Colgout; CP-Colchi; ***Hung.:*** Colchicum-Dispert; ***India:*** Goutnil; ***Indon.:*** Recolfar; ***Malaysia:*** Goutnil†; ***Mex.:*** Colchiquim; Sixol; Ticolcin; ***NZ:*** Colgout; ***Thai.:*** Cochic; Colchily; Colcine; Goutichine; Prochic; Tolchicine; ***Turk.:*** Colchicum-Dispert; Kolsin.

Multi-ingredient: ***Arg.:*** Artrex; Colpuril; Xuric-A; ***Fr.:*** Colchimax; ***Mex.:*** Butayonacol; ***Spain:*** Colchimax; ***USA:*** ColBenemid.

Colchicum

Colchico; Colchique.

Безвременник

Profile

Colchicum, the dried ripe seeds or dried corm of the meadow saffron, *Colchicum autumnale*, contains colchicine (p.556) and has been used similarly for the prophylaxis and relief of acute gout.

It is also included in several herbal preparations.

Homoeopathy. Colchicum has been used in homoeopathic medicines under the following names: Colchicinum; Colchicum autumnale; Colchicum, tuber; Colch. at.

Poisoning. *Colchicum autumnale* is quite similar to a species of garlic *Allium ursinum*, especially in leaf appearance, and both plants grow in the same areas at the same time of year. There are reports of colchicine poisoning, some of them fatal, after accidental ingestion of *C. autumnale*.[1-6] Colchicine poisoning should be considered in patients with gastroenterocolitis after a wild plant meal.

1. Brnčić N, *et al.* Accidental plant poisoning with Colchicum autumnale: report of two cases. *Croat Med J* 2001; **42:** 673–5.
2. Sannohe S, *et al.* Colchicine poisoning resulting from accidental ingestion of meadow saffron (Colchicum autumnale). *J Forensic Sci* 2002; **47:** 1391–6.
3. Gabrscek L, *et al.* Accidental poisoning with autumn crocus. *J Toxicol Clin Toxicol* 2004; **42:** 85–8.
4. Brvar M, *et al.* Case report: fatal poisoning with Colchicum autumnale. *Crit Care* 2004; **8:** R56–R59.
5. Brvar M, *et al.* Acute poisoning with autumn crocus (Colchicum autumnale L.). *Wien Klin Wochenschr* 2004; **116:** 205–8.
6. Sundov Z, *et al.* Fatal colchicine poisoning by accidental ingestion of meadow saffron-case report. *Forensic Sci Int* 2005; **149:** 253–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Colchysat.
Multi-ingredient: ***Ger.:*** Unguentum lymphaticum; ***Venez.:*** Linfoderm.

Febuxostat *(USAN, rINN)*

Febuxostatum; TMX-67. 2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

Фебуксостат

$C_{16}H_{16}N_2O_3S$ = 316.4.
CAS — 144060-53-7.
ATC — M04AA03.
ATC Vet — QM04AA03.

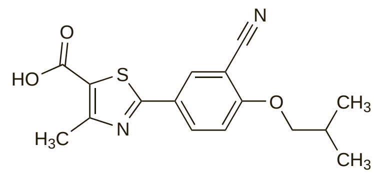

Profile

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase, and is under investigation for the treatment of hyperuricaemia in patients with chronic gout.

◊ References.

1. Mayer MD, *et al.* Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther* 2005; **12:** 22–34.
2. Schumacher HR. Febuxostat: a non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout. *Expert Opin Invest Drugs* 2005; **14:** 893–903.
3. Becker MA, *et al.* Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005; **353:** 2450–61. Correction. *ibid.* 2006; **354:** 1533.
4. Khosravan R, *et al.* The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol* 2006; **46:** 88–102.
5. Khosravan R, *et al.* Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacokinet* 2006; **45:** 821–41.
6. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. *Ann Pharmacother* 2006; **40:** 2187–94.

Probenecid *(BAN, rINN)* ⊗

Probenecidas; Probénécide; Probenecidum; Probenesid; Probenesidi. 4-(Dipropylsulphamoyl)benzoic acid.

Пробенецид

$C_{13}H_{19}NO_4S$ = 285.4.
CAS — 57-66-9.
ATC — M04AB01.
ATC Vet — QM04AB01.

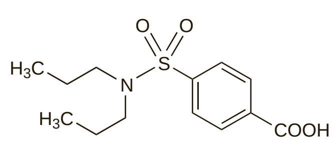

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Probenecid). A white or almost white crystalline powder or small crystals. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone.

USP 31 (Probenecid). A white or practically white, fine, practically odourless, crystalline powder. Practically insoluble in water and in dilute acids; soluble in alcohol, in acetone, in chloroform, and in dilute alkali.

Adverse Effects and Treatment

Probenecid may cause nausea, vomiting, anorexia, headache, sore gums, flushing, alopecia, dizziness, anaemia, and urinary frequency. Hypersensitivity reactions, with fever, dermatitis, pruritus, urticaria, and, rarely, anaphylaxis, and Stevens-Johnson syndrome have occurred. There have been reports of leucopenia, hepatic necrosis, nephrotic syndrome, and aplastic anaemia. Haemolytic anaemia has also occurred, and may be associated with G6PD deficiency.

When used in chronic gout, and particularly during the first few months of therapy, probenecid may precipitate acute attacks. Uric acid renal calculi, with or without haematuria, costovertebral pain and renal colic may occur.

In massive overdosage probenecid causes stimulation of the CNS, with convulsions and death from respiratory failure. Severe overdosage should be managed by lavage and symptomatic treatment.

Precautions

Probenecid therapy should not be started during an acute attack of gout; however treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Probenecid is also unsuitable for the control of hyperuricaemia secondary to cancer or cancer chemotherapy. Probenecid should not be given to patients with a history of uric acid renal calculi or blood disorders. It should be used with caution in patients with a history of peptic ulceration. Probenecid should not be used as an antibacterial adjunct in patients with known renal impairment, and it is ineffective in gout in patients with severe renal impairment.

To reduce the risk of uric acid renal calculi in patients with gout an adequate fluid intake (2 to 3 litres daily) is required, and, if necessary, especially during the first few months of treatment, sodium bicarbonate or potassium citrate may be given to render the urine alkaline.

A reducing substance has been found in the urine of some patients taking probenecid, and may give false positive results with some tests for glucose in the urine. Probenecid reduces the excretion of some iodinated contrast media and may interfere with laboratory tests by decreasing the excretion of aminohippuric acid, phenolsulfonphthalein, and sulfobromophthalein.

Abuse. It has been alleged that some athletes using banned anabolic steroids have taken probenecid in an attempt to inhibit the urinary excretion of steroid metabolites in order to avoid detection by urine screening tests.[1]

1. Anonymous. Does probenecid mask steroid use? *Pharm J* 1987; **239:** 299.

Porphyria. Probenecid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

The dose of probenecid may need to be increased if patients are also given drugs, such as diuretics or pyrazinamide, that increase the blood concentration of uric acid. Salicylates, including aspirin, and probenecid are mutually antagonistic and should not be given together.

Probenecid may also affect many other drugs. By inhibiting renal tubular secretion, it has the potential to increase the toxicity and/or to enhance the therapeutic efficacy of drugs excreted by that route. In some instances a reduction in dose is essential to counteract an increase in toxicity, as is the case with methotrexate. Some combinations, such as that with ketorolac, should be avoided. Conversely, probenecid may be given with some antibacterials such as the penicillins and cephalosporins to increase their effects.

Altered excretion may also increase serum concentrations of other antibacterials (aminosalicylic acid, conjugated sulfonamides, dapsone, meropenem, some quinolones, rifampicin), some antivirals (aciclovir, ganciclovir, zalcitabine, zidovudine, and possibly famciclovir), some benzodiazepines (adinazolam, lorazepam, and nitrazepam), some ACE inhibitors (captopril and enalapril), some NSAIDs (diflunisal, indometacin, ketoprofen, meclofenamate, naproxen), paracetamol, and sulfonylurea hypoglycaemic drugs. The clinical significance of such interactions is not entirely clear although the possibility of the need for a reduction in dosage of these drugs should be borne in mind.

It has been reported that patients receiving probenecid require lower doses of thiopental for induction of anaesthesia. Probenecid may increase the speed of induction of anaesthesia with midazolam.

Reducing the urinary concentration of some drugs could diminish their activity in certain diseases as might happen with nitrofurantoin or some quinolones in urinary-tract infections and penicillamine in cystinuria.

Allopurinol. Probenecid may increase the clearance of allopurinol despite an increased hypouricaemic effect when these 2 drugs are given together (see Antigout Drugs, under Allopurinol, p.553).

Pharmacokinetics

Probenecid is completely absorbed from the gastrointestinal tract with peak plasma concentrations achieved 2 to 4 hours after a dose. It is extensively bound to plasma proteins (85 to 95%). The plasma half-life is dose-dependent and ranges from less than 5 to more than 8 hours. Probenecid crosses the placenta. It is metabolised by the liver, and excreted in the urine mainly as metabolites. Excretion of unchanged probenecid is increased in alkaline urine.

Uses and Administration

Probenecid is a uricosuric drug used to treat hyperuricaemia (p.552) associated with chronic gout; it has also been used to treat hyperuricaemia caused by diuretic therapy. It is also used as an adjunct to some antibacterials to reduce their renal tubular excretion and is given with the antiviral cidofovir to reduce nephrotoxicity.

Probenecid is used in **chronic gout and hyperuricaemia** to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. Probenecid is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production, and is not used for hyperuricaemia associated with cancer or cancer therapy.

Probenecid has no analgesic or anti-inflammatory action and is of no value in acute gout. Initially it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence probenecid should not be started until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

It is usual to start treatment for gout with oral doses of 250 mg twice daily increased after a week to 500 mg twice daily and later, if the therapeutic effects are inadequate, by increments of 500 mg every 4 weeks, up to 2 g daily. Probenecid may not be effective in chronic renal impairment particularly when the glomerular filtration rate is less than 30 mL/minute. An adequate fluid intake is required to reduce the risk of uric acid renal calculi.

When the patient has been free from acute attacks for at least 6 months, and provided that the plasma-urate concentration is within acceptable limits, the daily dose may be gradually reduced, by 500 mg every 6 months, to the lowest effective maintenance dose which is then given indefinitely.

Probenecid may also be used as an **adjunct to antibacterial therapy** particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500 mg four times daily, or less in elderly patients with suspected renal impairment. When renal impairment is sufficient to retard the excretion of antibacterials, probenecid should not be given.

The dosage for children over 2 years of age and weighing less than 50 kg is 25 mg/kg (700 mg/m^2) initially, followed by 10 mg/kg (300 mg/m^2) every 6 hours.

Single oral doses of probenecid 1 g are given with a suitable oral antibacterial, or at least 30 minutes before an injected antibacterial, in the single-dose treatment of gonorrhoea (p.191).

Doses of probenecid to be used with cidofovir are given on p.868.

Preparations

BP 2008: Probenecid Tablets;
USP 31: Ampicillin and Probenecid for Oral Suspension; Probenecid and Colchicine Tablets; Probenecid Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pro-Cid; ***Canad.:*** Benuryl; ***Fin.:*** Probecid†; ***Fr.:*** Benemide; ***Gr.:*** Benemid; ***India:*** Bencid; ***Mex.:*** Benecid; ***Norw.:*** Probecid; ***S.Afr.:*** Proben; ***Swed.:*** Probecid; ***Thai.:*** Benacid; Bencid; Benemid†; ***USA:*** Benemid.

Multi-ingredient: ***USA:*** ColBenemid.

Used as an adjunct in: ***Braz.:*** Emicilin; Gonol; ***Spain:*** Blenox.

Sulfinpyrazone *(BAN, rINN)*

G-28315; Sulfinpirazona; Sulfinpirazonas; Sulfinpyratsoni; Sulfinpyrazon; Sulfinpyrazonum; Sulphinpyrazone; Sulphoxyphenylpyrazolidine; Szulfinpirazon. 1,2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3,5-dione.

Сульфинпиразон

$C_{23}H_{20}N_2O_3S$ = 404.5.

CAS — 57-96-5.

ATC — M04AB02.

ATC Vet — QM04AB02.

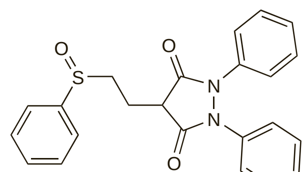

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Sulfinpyrazone). A white or almost white powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Sulfinpyrazone). A white to off-white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol and in acetone; sparingly soluble in dilute alkali.

Adverse Effects and Treatment

The most frequent adverse effects of sulfinpyrazone involve the gastrointestinal tract, and include nausea, vomiting, diarrhoea and abdominal pain. It may cause gastric bleeding or aggravate existing peptic ulcers. Skin rashes have been reported, and may be associated with a hypersensitivity reaction. Aplastic anaemia, agranulocytosis, leucopenia, and thrombocytopenia have been reported rarely as have raised liver enzyme values, jaundice, and hepatitis, renal impairment, salt and water retention, and acute renal failure.

When used in chronic gout, particularly during the first few months of treatment, sulfinpyrazone may precipitate acute attacks and there is a risk of uric acid renal calculi developing.

Symptoms of overdosage include hypotension, acute renal failure, arrhythmias, respiratory disorders, convulsions, and coma, as well as gastrointestinal effects. Treatment of overdose may involve activated charcoal if a substantial amount has been ingested within 1 hour of presentation, followed by symptomatic and supportive therapy.

Effects on the kidneys. Although renal failure has been reported occasionally in patients receiving sulfinpyrazone for gout[1] many of the cases have occurred in those given the drug for myocardial infarction.[2,3] Acute renal failure may also occur after overdose or in patients with intravascular volume depletion.[4,5]

1. Durham DS, Ibels LS. Sulphinpyrazone-induced acute renal failure. *BMJ* 1981; **282:** 609.
2. Boelaert J, *et al.* Sulphinpyrazone-induced decrease in renal function: a review of reports with discussion of pathogenesis. *Acta Clin Belg* 1982; **37:** 368–75.
3. Lijnen P, *et al.* Decrease in renal function due to sulphinpyrazone treatment early after myocardial infarction. *Clin Nephrol* 1983; **19:** 143–6.
4. Florkowski CM, *et al.* Acute non-oliguric renal failure secondary to sulphinpyrazone overdose. *J Clin Pharm Ther* 1992; **17:** 71.
5. Walls M, *et al.* Acute renal failure due to sulfinpyrazone. *Am J Med Sci* 1998; **315:** 319–21.

Precautions

Sulfinpyrazone should not be started during an acute attack of gout; however, treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Sulfinpyrazone is not suitable for the control of hyperuricaemia associated with cancer or cancer chemotherapy.

Sulfinpyrazone should be given with care to patients with renal impairment or heart failure and is contra-indicated in those with severe renal or hepatic impairment. It is also contra-indicated in patients with blood dyscrasias or blood coagulation disorders, and in patients with uric acid renal calculi or peptic ulcer disease or a history of such disorders.

Sulfinpyrazone should not be given to patients hypersensitive to it or to other pyrazole derivatives such as phenylbutazone; nor should it be given to patients in whom hypersensitivity reactions (including bronchospastic reactions in asthmatics) have been provoked by aspirin or by other drugs with prostaglandin-synthetase inhibiting activity.

To reduce the risk of uric acid renal calculi an adequate fluid intake (2 to 3 litres daily) is required; alkalinising the urine with sodium bicarbonate or potassium citrate may also be considered. It is recommended that patients have periodic full blood counts to detect any haematological abnormalities.

Renal-function tests involving aminohippuric acid or phenolsulfonphthalein may be invalidated.

Porphyria. Sulfinpyrazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Doses of sulfinpyrazone may need to be increased if it is given with other drugs, such as diuretics or pyrazinamide, that increase uric acid concentrations. Sulfinpyrazone and salicylates including aspirin are mutually antagonistic and should not be used together. There may also be an increased risk of bleeding when sulfinpyrazone is used with other drugs such as aspirin that inhibit platelet function.

Sulfinpyrazone's renal tubular secretion is inhibited by probenecid although with little clinical effect. Since sulfinpyrazone, like probenecid, inhibits the tubular secretion of weak organic acids, interactions can be expected with penicillins although the effect is not considered to be clinically useful.

Sulfinpyrazone can potentiate the action of some drugs. The most significant interaction of this type involves warfarin, acenocoumarol, and possibly other coumarin anticoagulants (p.1429). Patients receiving sulfinpyrazone and such an anticoagulant should have their prothrombin times monitored and the anticoagulant dosage reduced as appropriate. Similarly, sulfinpyrazone may potentiate the effects of phenytoin (see Antigout Drugs, p.499), and possibly some sulfonamides and sulfonylureas.

In contrast, sulfinpyrazone may increase the metabolism of theophylline (p.1144) and diminish its activity.

Pharmacokinetics

Sulfinpyrazone is readily absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins and has a plasma half-life of about 2 to 4 hours. Sulfinpyrazone is partly metabolised in the liver and some of the metabolites are active. On long-term therapy, sulfinpyrazone induces its own metabolism. Unchanged drug and metabolites are mainly excreted in the urine.

◊ References.

1. Bradbrook ID, *et al.* Pharmacokinetics of single doses of sulphinpyrazone and its major metabolites in plasma and urine. *Br J Clin Pharmacol* 1982; **13:** 177–85.
2. Schlicht F, *et al.* Pharmacokinetics of sulphinpyrazone and its major metabolites after a single dose and during chronic treatment. *Eur J Clin Pharmacol* 1985; **28:** 97–103.

Uses and Administration

Sulfinpyrazone is a uricosuric drug used to treat hyperuricaemia associated with chronic gout (p.552). It also has some antiplatelet activity.

Sulfinpyrazone is used in chronic gout to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. It is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production and is not used for hyperuricaemia associated with cancer or cancer therapy.

Sulfinpyrazone has little analgesic or anti-inflammatory action and is of no value in acute gout. Initially, it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence sulfinpyrazone should not be given until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

The initial oral dose of sulfinpyrazone in the UK is 100 to 200 mg daily (the USA allows up to 200 mg twice daily), taken with meals or milk. This may be gradually increased over 1 to 3 weeks until a daily dosage of 600 mg is reached; up to 800 mg daily may be given if necessary. After the plasma-urate concentration has been controlled, the daily maintenance dose may be reduced to as low as 200 mg. An adequate fluid intake is required to prevent formation of uric acid renal calculi.

Antiplatelet therapy. Sulfinpyrazone inhibits platelet function, thereby inhibiting thrombosis. A meta-analysis of studies, conducted by the Antiplatelet Trialists' Collaboration, has shown that it reduces the risk of myocardial infarction, stroke, or vascular death in patients at high risk of occlusive vascular disease[1] and also reduces the risk of occlusion in patients undergoing arterial reperfusion and revascularisation procedures.[2] However, aspirin is the most widely used antiplatelet therapy, as discussed under Cardiovascular Risk Reduction, on p.1164.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.
2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; **308:** 159–68.

Preparations

BP 2008: Sulfinpyrazone Tablets;
USP 31: Sulfinpyrazone Capsules; Sulfinpyrazone Tablets.

Proprietary Preparations (details are given in Part 3)
Ital.: Enturen; ***Port.:*** Sulfinona†; ***UK:*** Anturan; ***USA:*** Anturane.

Tisopurine *(rINN)*

MPP; Thioallopurinol; Thiopurinol; Tisopurina; Tisopurinum. 1*H*-Pyrazolo[3,4-*d*]pyrimidine-4-thiol.

Тизопурин

$C_5H_4N_4S$ = 152.2.
CAS — 5334-23-6.
ATC — M04AA02.
ATC Vet — QM04AA02.

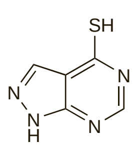

Profile

Tisopurine, an analogue of allopurinol, is an inhibitor of uric acid synthesis. It is used orally in the treatment of disorders associated with hyperuricaemia (p.552), including gout, in doses of 100 to 400 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exuracid.

Urate Oxidase

CB-8129; Uricasa; Uricase.

Уратоксидаза

CAS — 9002-12-4.
ATC — M04AX01.
ATC Vet — QM04AX01.

Rasburicase *(BAN, USAN, rINN)*

Rasburicasa; Rasburicasum; Rasburikaasi; Rasburikas; Rasburikaz; SR-29142.

Разбуриказа

CAS — 134774-45-1.
ATC — V03AF07.
ATC Vet — QV03AF07.

Description. Rasburicase is a recombinant form of the enzyme urate oxidase.

Adverse Effects

The most serious adverse effects of rasburicase involve hypersensitivity reactions, including anaphylaxis, rashes, bronchospasm, rhinitis, urticaria, hypotension, dyspnoea, and chest pain and tightness. Haemolysis and methaemoglobinaemia have also been reported. Other adverse effects are nausea, vomiting, abdominal pain, constipation, diarrhoea, headache, fever, respiratory distress, sepsis, neutropenia, and mucositis.

Precautions

Treatment with rasburicase should be immediately and permanently stopped if hypersensitivity reactions, methaemoglobinaemia, or haemolysis develop. Rasburicase is contra-indicated in patients with G6PD deficiency or other cellular metabolic disorders known to cause haemolytic anaemia; hydrogen peroxide, which is produced during oxidation of uric acid to allantoin, can induce haemolytic anaemia in these patients. Patients at higher risk of having G6PD deficiency should be screened before receiving rasburicase.

Uses and Administration

Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin. It is used in the treatment and prophylaxis of severe hyperuricaemia (p.552) associated with the treatment of malignancy. It is given by intravenous infusion before and during the start of chemotherapy, in a dose of 150 or 200 micrograms/kg daily over 30 minutes. Duration of treatment may vary from 5 to 7 days.

The native form of urate oxidase has also been used.

Gout. Rasburicase has been used successfully to treat gout in patients allergic to allopurinol.[1,2]

1. Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* 2005; **20:** 431–3.
2. Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; **2:** 338–42.

Tumour lysis syndrome. The tumour lysis syndrome (p.639) represents a biochemical disturbance after massive release of cellular breakdown products from tumour cells sensitive to therapy; hyperuricaemia is a cardinal feature. Rasburicase was effective in the prophylaxis or treatment of hyperuricaemia in children and young adults with leukaemia or lymphoma who either presented with abnormally high plasma concentrations of uric acid or had large tumour cell burdens.[1] Treatment was mostly well tolerated; one patient developed nausea and vomiting and one experienced bronchospasm and hypoxaemia 3 hours after infusion. Antibodies to rasburicase were seen in 17 of 121 assessable patients. Safety and efficacy were confirmed in further studies of children[2] and adults[2,3] considered to be at particularly high risk of tumour lysis syndrome. In children[4] with haematologic malignancies at high risk for tumour lysis, rasburicase given intravenously achieved more rapid control and lower levels of plasma uric acid than oral allopurinol. No antibodies to rasburicase were detected at day 14. In 3 children with acute lymphoblastic leukaemia, hyperuricaemia was reportedly controlled with oral allopurinol and a single dose of rasburicase, although subclinical tumour lysis was apparent.[5] Rasburicase has also been used for tumour lysis syndrome in neonates. One infant was given a single dose of rasburicase after 2 days of induction chemotherapy for neuroblastoma, started on day 21 of life; serum urate normalised and chemotherapy was completed without further incident. A second infant, with acute lymphoblastic leukaemia and renal dysfunction, presented with tumour lysis syndrome, and had 6 doses of intravenous rasburicase plus aggressive supportive therapy, but died of complications on day 7 of life.[6] Reviews[7,8] have concluded that rasburicase is highly effective at decreasing uric acid concentrations rapidly and thoroughly; there is some suggestion that shorter durations of treatment (between 1 and 3 days as opposed to 5 days) may be sufficient even in high-risk patients.

1. Pui C-H, *et al.* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukaemia or lymphoma. *J Clin Oncol* 2001; **19:** 697–704.
2. Pui C-H, *et al.* Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia* 2001; **15:** 1505–9.
3. Coiffier B, *et al.* Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; **21:** 4402–6.
4. Goldman SC, *et al.* A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001; **97:** 2998–3003.
5. Lee ACW, *et al.* Treatment of impending tumor lysis with single-dose rasburicase. *Ann Pharmacother* 2003; **37:** 1614–17.
6. McNutt DM, *et al.* Rasburicase for the management of tumor lysis syndrome in neonates. *Ann Pharmacother* 2006; **40:** 1445–50.
7. Bessmertny O, *et al.* Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. *Curr Pharm Des* 2005; **11:** 4177–85.
8. Oldfield V, Perry CM. Rasburicase: a review of its use in the management of anticancer therapy-induced hyperuricaemia. *Drugs* 2006; **66:** 529–45.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Fasturtec; ***Belg.:*** Fasturtec; ***Braz.:*** Fasturtec; ***Canad.:*** Fasturtec; ***Chile:*** Fasturtec†; ***Cz.:*** Fasturtec; ***Denm.:*** Fasturtec; ***Fin.:*** Fasturtec; ***Fr.:*** Fasturtec; ***Ger.:*** Fasturtec; ***Gr.:*** Fasturtec; ***Hong Kong:*** Fasturtec; ***Hung.:*** Fasturtec; ***Irl.:*** Fasturtec; ***Ital.:*** Fasturtec; Uricozyme†; ***Neth.:*** Fasturtec; ***Norw.:*** Fasturtec; ***NZ:*** Fasturtec; ***Pol.:*** Fasturtec; ***Port.:*** Fasturtec; ***Singapore:*** Fasturtec; ***Spain:*** Fasturtec; ***Swed.:*** Fasturtec; ***Switz.:*** Fasturtec; ***UK:*** Fasturtec; ***USA:*** Elitek; ***Venez.:*** Fasturtec.

Antihistamines

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The peripheral effects of histamine are chiefly mediated by 2 sets of receptors termed H_1 and H_2. Effects mediated by the H_1 receptors include the contraction of smooth muscle and the dilatation and increased permeability of the capillaries. The effects of histamine on vascular smooth muscle are mediated by H_2 as well as H_1 receptors. Other effects that are mediated by H_2 receptors include cardiac accelerating effects and, in particular, the stimulating action of histamine on the secretion of gastric acid. An H_3 receptor has also been identified in a number of systems including the CNS and peripheral nerves. It is thought that H_3 receptors are involved in the autoregulation of the release of histamine and other neurotransmitters from neurones.

The term 'antihistamines' is normally reserved for histamine H_1-antagonists and this is the convention used in *Martindale*. H_2-antagonists, typified by cimetidine (p.1716), are described in the chapter on Gastrointestinal Drugs. H_3-antagonists are under investigation.

The older antihistamines are associated with troublesome sedative and antimuscarinic effects, and are often termed 'sedating antihistamines'. The newer antihistamines, which are essentially devoid of these effects, are correspondingly termed 'non-sedating antihistamines' and include acrivastine, astemizole, cetirizine, loratadine, and terfenadine.

On the basis of their chemical structure most antihistamines can be classified into one of 6 groups:

- *Alkylamines:* drugs within this group typically possess significant sedative actions, although paradoxical stimulation can occur, especially in children. They are highly potent H_1-antagonists. Brompheniramine and chlorphenamine are typical alkylamines; acrivastine is a non-sedating alkylamine antihistamine.
- *Monoethanolamines:* monoethanolamine derivatives have pronounced sedative and antimuscarinic actions but a low incidence of gastrointestinal effects. Examples include clemastine and diphenhydramine.
- *Ethylenediamines:* these antihistamines are selective H_1-antagonists. They cause moderate sedation (despite having weak CNS effects), gastric disturbances, and skin sensitisation. Antazoline and mepyramine are examples.
- *Phenothiazines:* phenothiazine antihistamines have significant sedative, and pronounced antiemetic and antimuscarinic effects. Photosensitivity reactions have occurred. Promethazine is a typical phenothiazine.
- *Piperazines:* this group of antihistamines possesses moderate sedative and significant antiemetic actions. Piperazine derivatives include cetirizine, cyclizine, and hydroxyzine. Cetirizine causes less sedation than other members of this group.
- *Piperidines:* piperidines cause moderate or low sedation and are highly selective for H_1 receptors. Examples include azatadine, cyproheptadine, and the non-sedating antihistamines astemizole, loratadine, and terfenadine.

Although characteristic pharmacological properties have been described for members of each group it should be noted that many of the effects of antihistamines vary as much with each patient as with each drug and that, in particular, some of the newer non-sedating antihistamines may share the chemical structure of a group in which the other members have sedative effects.

◊ References.

1. Hill SJ, *et al.* International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* 1997; **49:** 253–78.
2. Leurs R, *et al.* Therapeutic potential of histamine H receptor agonists and antagonists. *Trends Pharmacol Sci* 1998; **19:** 177–83.

Hypersensitivity. Hypersensitivity may be defined as an exaggerated or inappropriate immune response causing tissue damage. Hypersensitivity reactions are generally classified into 4 types (types I to IV) although this may be considered an over simplification and more than one type can often be postulated for a patient's hypersensitivity. In each of the 4 types, prior sensitisation of the patient to the specific antigen is required. The term *'allergy'* by definition originally covered all types of hypersensitivity reactions as well as the induction of immunity in an individual. Nowadays, the term is more commonly applied to type I hypersensitivity reactions.

Type I, immediate hypersensitivity reactions occur after exposure to an antigen (the allergen) in a sensitised subject; that is, one in whom the initial exposure to the antigen has caused the production of specific antibodies, mainly IgE (immunoglobulin E), which are bound to the surface of mast cells and basophils. At subsequent exposure, antigen binds to antibody resulting in degranulation of mast cells and basophils with release of mediators. These include preformed mediators such as histamine and chemotactic factors, and newly synthesised mediators such as leukotrienes, platelet-activating factor, and prostaglandins. Although type I reactions are usually described as being acute and short-lived, clinically there may often also be a late-phase and more prolonged reaction affecting the skin and bronchi. Examples of type I hypersensitivity reactions discussed below include allergic conjunctivitis, allergic rhinitis, urticaria and angioedema, and anaphylactic shock.

Type II, cell-surface hypersensitivity reactions are caused by the interaction of circulating antibodies, mainly IgG (immunoglobulin G) and IgM (immunoglobulin M), with antigens that are on the surface of specific cells or tissues. This interaction results in activation of complement and of phagocytic and killer cells leading to cell damage or lysis. Type II reactions are responsible for blood transfusion reactions, some drug-induced blood disorders, and many auto-immune disorders.

Type III, immune complex hypersensitivity reactions, are caused by the interaction of fixed or circulating antigens with circulating antibodies, mainly IgG and IgM (either soluble or particulate), resulting in formation of immune complexes. The immune complexes trigger a variety of inflammatory processes including complement activation, mediator release from mast cells and basophils, and platelet aggregation. Examples of type III reactions include serum sickness, some auto-immune and neoplastic disorders, type 2 lepra reactions (see Leprosy, p.176), and reactions, particularly in the lung, to some particulate antigens such as micro-organisms.

Type IV, cell-mediated or delayed hypersensitivity reactions, are caused by interaction of an antigen with sensitised T-lymphocytes; lymphokines are released by T-lymphocytes and inflammation ensues. Type IV reactions usually occur at least 24 hours after contact with the antigen. A type IV reaction is responsible for tuberculin reactions used for sensitivity testing, contact dermatitis, and some reactions to chronic infectious disease for example type 1 lepra reactions (p.176).

An **anaphylactoid** (pseudoallergic) reaction produces similar symptoms to those of anaphylaxis (see below), but is caused by direct release of histamine provoked by an unclear, non-immune mechanism. There is thus no requirement for prior exposure to the triggering factor, commonly a drug.

Adverse Effects of Antihistamines

The most common adverse effect of the *sedating antihistamines* is CNS depression, with effects varying from slight drowsiness to deep sleep, and including lassitude, dizziness, and incoordination (although paradoxical stimulation may occasionally occur, especially at high doses and in children or the elderly). These sedative effects, when they occur, may diminish after a few days of treatment. A major advantage of the *non-sedating antihistamines* is that they generally cause little or no drowsiness (but see Sedation, below).

Other adverse effects that are more common with the *sedating antihistamines* include headache, psychomotor impairment, and antimuscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation, and increased gastric reflux. Another major advantage of the *non-sedating antihistamines* is that most have little or no antimuscarinic effect.

Occasional gastrointestinal adverse effects of antihistamines include nausea, vomiting, diarrhoea, or epigastric pain. Those with antiserotonin actions, such as cyproheptadine, may cause an increase in appetite with resultant weight gain, whereas anorexia has been reported with some other antihistamines.

Palpitations and arrhythmias have been reported occasionally with most antihistamines, but a major disadvantage of the *non-sedating antihistamines* astemizole and terfenadine is the rare occurrence of hazardous ventricular arrhythmias which has led to important restrictions on their use (see Precautions, below).

Antihistamines sometimes cause rashes and hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis) and cross-sensitivity to related drugs may occur. Photosensitivity can be a problem, particularly with the phenothiazine antihistamines.

Blood disorders, including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia, although rare, have been reported. Jaundice has also been observed, particularly with the phenothiazine antihistamines.

Other adverse effects that have been reported with the antihistamines include convulsions, sweating, myalgia, paraesthesias, extrapyramidal effects, tremor, sleep disturbances, depression, confusion, tinnitus, hypotension, and hair loss.

Despite reports suggesting a possibility of human fetal abnormalities resulting from the use of some antihistamines, especially the piperazine derivatives, a causal relationship has largely been rejected; for details see Pregnancy, under Precautions, below.

Some antihistamines have been abused for their CNS effects.

Antihistamines available as preparations for application to the skin may occasionally cause skin sensitisation; systemic adverse effects have been reported after topical application to large areas of the skin.

Overdosage with *sedating antihistamines* is associated with antimuscarinic, extrapyramidal, and CNS effects. When CNS stimulation predominates over CNS depression, which is more likely in children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations, and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, CNS depression is more common with drowsiness, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse. In the case of the *non-sedating antihistamines*, antimuscarinic effects are less marked, but hazardous ventricular arrhythmias (below) may be a special problem with astemizole and terfenadine, even in modest overdoses, and have led to restrictions on their use.

◊ Reviews.

1. Simons FER. H -receptor antagonists: comparative tolerability and safety. *Drug Safety* 1994; **10:** 350–80.
2. Horak F, Stübner UP. Comparative tolerability of second generation antihistamines. *Drug Safety* 1999; **20:** 385–401.

Arrhythmias. Ventricular arrhythmias have been reported rarely with astemizole and terfenadine particularly in association with increased blood concentrations. For full details and specific warnings see under Astemizole, p.567, and Terfenadine, p.590.

The suspicion that such life-threatening arrhythmias may be a class effect of the non-sedating antihistamines has so far proven unfounded. Data[1] from the WHO adverse drug reaction database showed that cardiac events had been reported with the 5 most widely prescribed non-sedating antihistamines at that time (acrivastine, astemizole, cetirizine, loratadine, and terfenadine), and an attempt to quantify the risk[2] suggested that use of these drugs was associated overall with a fourfold increase in likelihood of developing ventricular arrhythmias, although the absolute risk remained low. However, other centres[3] have argued that definitive causality has only been proven for astemizole and terfenadine. In addition, a possible mechanism for drug-induced cardiac toxicity has only been found with astemizole and terfenadine;[4] both drugs have been shown to block cardiac potassium channels *in vitro*, a phenomenon that results in prolongation of the QT interval, which is a risk factor for developing ventricular arrhythmias. Studies[5] with loratadine and cetirizine have found that neither drug blocked potassium channels *in vitro*, and a similar lack of activity might be expected with desloratadine and levocetirizine; however, there is some evidence that mizolastine can block potassium channels at high concentrations *in vitro*[6] (although a small study in healthy subjects noted no adverse effects on cardiac conduction at doses up to 4 times those normally given).[7] A case report[8] of arrhythmias in a patient with pre-existing QT-prolongation given fexofenadine, did not appear to be associated with blocking of potassium channels.[9]

1. Lindquist M, Edwards IR. Risks of non-sedating antihistamines. *Lancet* 1997; **349:** 1322. Correction. *ibid.;* 1482.
2. de Abajo FJ, García Rodrígues LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol* 1999; **47:** 307–13.
3. Himmel MH, *et al.* Dangers of non-sedating antihistamines. *Lancet* 1997; **350:** 69.
4. Salata JJ, *et al.* Cardiac electrophysiological actions of the histamine H -receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. *Circ Res* 1995; **76:** 110–19.
5. Woosley RL. Cardiac actions of antihistamines. *Ann Rev Pharmacol Toxicol* 1996; **36:** 233–52.
6. Taglialatela M, *et al.* Inhibition of HERG1 K channels by the novel second-generation antihistamine mizolastine. *Br J Clin Pharmacol* 2000; **131:** 1081–8.
7. Chaufour S, *et al.* Study of cardiac repolarization in healthy volunteers performed with mizolastine, a new H -receptor antagonist. *Br J Clin Pharmacol* 1999; **47:** 515–20.
8. Pinto YM, *et al.* QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 980.
9. Scherer CR, *et al.* The antihistamine fexofenadine does not affect I currents in a case report of drug-induced cardiac arrhythmia. *Br J Clin Pharmacol* 2002; **137:** 892–900.

Reye's syndrome. For criticism of a suggested link in children between antihistamines and Reye's syndrome, see p.22.

Sedation. CNS depression is a common adverse effect of the sedating antihistamines and sedative effects can range from slight drowsiness to deep sleep. Daytime sedation can be a problem especially for those who have to drive or operate machinery. When sedative effects do occur they are most apparent at the start of treatment and often diminish after a few days despite continued use. Sedation caused by alcohol or other CNS depressants is enhanced. Many studies have attempted to quantify and compare the sedative effects of the older antihistamines, but results vary widely and classifications are difficult to make. Theoretically, the onset, degree, and persistence of sedation depend on factors such as penetration of the blood-brain barrier and on the relative affinity for central and peripheral histamine H_1 receptors. In general, antihistamines of the monoethanolamine and phenothiazine classes cause the most sedation.

In view of these problems, non-sedating antihistamines have been developed. These compounds have poor penetration into the CNS and/or higher affinity for peripheral rather than central histamine H_1 receptors. Studies with acrivastine,[1] astemizole,[2] fexofenadine,[3] loratadine,[4] and terfenadine[5] have generally indicated a lower incidence of sedation and related CNS effects than that observed with older antihistamines and comparable with that of placebo; prescription-event monitoring suggested that sedation was lower with fexofenadine and loratadine than with acrivastine or cetirizine, although the risk was low with all 4 drugs.[6] In a study[7] to compare the effects of acrivastine, terfenadine, and diphenhydramine on driving performance, terfenadine had no significant effect on driving performance. Acrivastine's effects were dose-related, but with little effect at the normal therapeutic dose, whereas diphenhydramine profoundly impaired all the measures of driving performance. In another study,[8] the effects of fexofenadine on driving performance were comparable with placebo. Studies with terfenadine[5] suggest that the incidence of sedation does not increase significantly with increased dose or duration of administration. Cetirizine appears to be more sedating than loratadine or terfenadine but less sedating than older antihistamines; the effect appears to be dose dependent.[9] Limited data with azelastine[10] indicate a similar incidence of drowsiness to that with terfenadine. An incidence of sedation comparable with that caused by terfenadine has also been seen for mequitazine when given in the recommended dosage of 5 mg twice daily.[5] Sedation has, however, occurred after doses of 10 mg twice daily.[11] Other newer antihistamines claimed to produce no troublesome sedation include ebastine, epinastine, mizolastine, and setastine. A review[12] of studies in drivers divided antihistamines into:

- first-generation (such as clemastine, diphenhydramine, and triprolidine), which produced significant impairment of driving ability
- second-generation (acrivastine, cetirizine, ebastine, emedastine, loratadine, mizolastine, and terfenadine), which produced more modest degrees of impairment; higher doses than normal produced significant impairment
- third-generation (levocetirizine, fexofenadine), which seemed to produce little or no impairment

A number of studies have indicated that the non-sedating antihistamines do not seem to enhance the effects of alcohol and other CNS depressants.

A few patients treated with non-sedating antihistamines have experienced drowsiness. Therefore it is prudent to exercise caution before driving or operating machinery; the effect of a drug on a particular patient can be ascertained after the first few doses.

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Precautions for Antihistamines

Drowsiness is a major problem with the *sedating antihistamines* and those affected should not drive or operate machinery; alcohol should be avoided. In the case of *non-sedating antihistamines*, although drowsiness is rare, it can occur and may affect the performance of skilled tasks.

Because of their antimuscarinic actions the *sedating antihistamines* should be used with care in conditions such as angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyloroduodenal obstruction; antimuscarinic adverse effects are not a significant problem with the *non-sedating antihistamines.*

Occasional reports of convulsions in patients taking antihistamines suggest a need for caution in patients with epilepsy.

Many antihistamines are excreted in the urine in the form of active metabolites so that dosage reduction may be necessary in renal impairment (see individual monographs for specific advice). Caution is also needed in hepatic impairment, notably with phenothiazine antihistamines (for further details, see Effects on the Liver, under Chlorpromazine, p.971) and, above all, with the *non-sedating antihistamines*, astemizole and terfenadine (hazardous ventricular arrhythmias may occur in the presence of excessive blood concentrations). Other important cautions for astemizole and terfenadine include avoidance of use with drugs liable to interfere with their hepatic metabolism or otherwise increase the risk of arrhythmias, and contra-indication in patients with cardiac disease, known or suspected prolongation of the QT interval, or hypokalaemia or other electrolyte imbalances. For full details see under Astemizole, p.567, and Terfenadine, p.590.

Antihistamines should not be given to neonates because the latter are more susceptible to antimuscarinic effects. It has also been recommended that antihistamines should be avoided in young children (see Children, below, and under Promethazine, p.589, and Alimemazine, p.566). Elderly patients are also more susceptible to many of the adverse effects of antihistamines and, in particular, their inappropriate use for postural giddiness should be avoided (see Vertigo, below).

Topical preparations containing antihistamines should not be used on broken or eczematous skin.

A number of large studies have failed to find any strong associations between fetal abnormalities and antihistamines taken during pregnancy (see under Pregnancy, below).

Asthma. Antihistamines are not considered effective in the management of asthma[1] and their use has often been contra-indicated in patients with asthma because of fears that they may cause airway obstruction. However, antihistamine-induced airway obstruction has rarely been noted clinically and many patients with asthma tolerate concurrent treatment with antihistamines without obvious adverse effects. Therefore the American Academy of Allergy and Immunology has recommended that antihistamines are not contra-indicated in patients with asthma, unless an adverse reaction has previously been demonstrated, and the FDA no longer warns against the use of over-the-counter antihistamines by people with asthma.[2]

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Children. In 2004, the FDA[1] reviewed all reports that it had received, between 1969 and 2003, of serious adverse events in children (aged from birth to 16 years) given promethazine. Of 125 reports there were 38 cases of respiratory depression, apnoea, or cardiac arrest; 29 cases of extrapyramidal dystonic reactions; 24 cases of other CNS reactions; 15 cases of seizures or seizure-like activity; 12 cases of dermatological reactions; and 5 cases of neuroleptic malignant syndrome. These reports included 22 cases of respiratory depression in patients aged 1.5 months to 2 years, 7 of which were fatal. Doses received in these 22 cases ranged from 0.45 to 6.4 mg/kg. Serious outcomes occurred with all routes of administration (oral, rectal, and parenteral). US licensed product information for promethazine hydrochloride now contra-indicates its use in children under 2 years of age because of the potential for fatal respiratory depression; a strengthened warning regarding use in children aged 2 years and older advises use of the lowest effective dose and to avoid concomitant use of other drugs with respiratory depressant effects. UK licensed product information for phenothiazine antihistamines, such as promethazine and alimemazine, also warns that these should not be given to children under 2 years of age, and the *BNFC* advises that sedating antihistamines such as these should not be given to children under 2 years of age, except on specialist advice, because safety has not been established.

Concern has also been expressed about the safety in children of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[2] has also found no good evidence for or against the effectiveness of over-the-counter preparations in acute cough. In early 2008, the FDA[3] and MHRA[4] both advised that over-the-counter cough and cold preparations should not be given to children under 2 years of age. They warn of the potential for serious and potentially life-threatening adverse effects and that such preparations provide only symptomatic relief, at best. If these products are used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing. For the MHRA's suggested management of the symptoms of coughs and colds, see Cough, p.1547.

An association between phenothiazine antihistamines and sudden infant death syndrome has also been investigated—see p.588.

1. Starke PR, *et al.* Boxed warning added to promethazine labeling for pediatric use. *N Engl J Med* 2005; **352:** 2653.

2. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
3. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01778.html (accessed 15/04/08)
4. MHRA/CHM. Updated advice—over-the-counter cough and cold medicines for children. *Drug Safety Update* 2008; **1** (9): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 15/04/08)

Pregnancy. Antihistamines have been used for antiemetic therapy during pregnancy, but considerable anxiety has surrounded such use and its potential for risk to the fetus. The most widely studied preparation was *Debendox* which contained doxylamine, dicycloverine, and pyridoxine, and was known as *Bendectin* in some countries. Dicycloverine was removed from the preparation in 1976 in the USA and subsequently in other countries, and the product was withdrawn from the market in 1983 because of threatened litigation.[1] By that time *Debendox* had been used for over 27 years and in over 33 million pregnancies worldwide.[1]

Initial concern came from anecdotal reports of malformations in infants whose mothers had taken *Debendox* during pregnancy.[2,3] Evidence was found[4] of an association between prenatal exposure to the 3-component formulation of *Bendectin* and an increased risk of pyloric stenosis and possibly also defective heart valves in a study of 1369 malformed infants and 2968 healthy control cases. Other studies have suggested an increased incidence of oral clefts,[5] gastrointestinal atresia,[6] and genital tract disorders,[7] but generally such increases have been small. No overall pattern of malformations appears to have emerged, and many large studies have failed to confirm an association between doxylamine use and congenital malformations.[8-13]

A prospective study of 11 481 pregnancies found no increased incidence of either severe congenital abnormalities or perinatal mortality rates in women who had been prescribed prochlorperazine, meclozine, cyclizine, or *Bendectin* during pregnancy, although there was some evidence of an excess number of congenital abnormalities in patients taking trimethobenzamide.[14]

The Collaborative Perinatal Project[15] monitored the mothers of 50 282 children between 1958 and 1965. Of these, 5401 were exposed to antihistamines and 1309 to phenothiazines during the first 4 months of pregnancy. There was no evidence to suggest that exposure to these drugs was related to malformations, although there were slight suggestions of associations between respiratory malformations and pheniramine, inguinal hernia and meclozine, inguinal hernia or genito-urinary malformations and diphenhydramine, and cardiovascular deformities and phenothiazines. A report[16] on the same study found no effects of phenothiazines on perinatal mortality, birth-weight, or IQ scores at the age of 4 years. The Collaborative Perinatal Project also noted a relationship between cardiovascular defects and inguinal hernia and dimenhydrinate exposure.[15]

Both the UK CSM[17] and the FDA in the USA[18] reviewed the literature in 1981 and concluded that while the scientific evidence did not show an increase in birth defects with *Debendox*, the risk of teratogenicity could not be completely excluded. A subsequent review[19] by the FDA in 1999 into the reasons for withdrawal stated that the evidence supported the conclusion that the combination had not been withdrawn from the market for reasons of safety or efficacy. In some countries a combination preparation of doxylamine and pyridoxine remains available for the treatment of nausea and vomiting in pregnancy. There has been a study indicating that vomiting itself is not teratogenic.[20]

A number of other studies have been carried out on meclozine prompted by reports of fetal abnormalities in 10 patients associated with a preparation of meclozine and pyridoxine;[21] these studies have not supported the original reports.[22-24]

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2. Paterson DC. Congenital deformities associated with Bendectin. *Can Med Assoc J* 1977; **116:** 1348.
3. Donnai D, Harris R. Unusual fetal malformations after antiemetics in early pregnancy. *BMJ* 1978; **1:** 691–2.
4. Eskenazi B, Bracken MB. Bendectin (Debendox) as a risk factor for pyloric stenosis. *Am J Obstet Gynecol* 1982; **144:** 919–24.
5. Golding J, *et al.* Maternal anti-nauseants and clefts of lip and palate. *Hum Toxicol* 1983; **2:** 63–73.
6. Jick H, *et al.* First-trimester drug use and congenital disorders. *JAMA* 1981; **246:** 343–6.
7. Gibson GT, *et al.* Congenital anomalies in relation to the use of doxylamine/dicyclomine and other antenatal factors: an ongoing prospective study. *Med J Aust* 1981; **i:** 410–4.
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Interactions of Antihistamines

Sedating antihistamines may enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and antipsychotics. Sedative interactions apply to a lesser extent with the *non-sedating antihistamines*; they do not appear to potentiate the effects of alcohol, but it should be avoided in excess.

Sedating antihistamines have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and some antidepressants (both tricyclics and MAOIs).

Potentially hazardous ventricular arrhythmias have occurred when the *non-sedating antihistamines* astemizole and terfenadine have been given with drugs liable to interfere with their hepatic metabolism, with other potentially arrhythmogenic drugs including those that prolong the QT interval, or with those likely to cause electrolyte imbalance. For full details see under Astemizole, p.567, and Terfenadine, p.591.

It has been suggested that some *sedating antihistamines* could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibiotics.

Antihistamines may suppress the cutaneous histamine response to allergen extracts and should be stopped several days before skin testing.

Uses of Antihistamines

Histamine H_1-antagonists (termed 'antihistamines' in *Martindale*) diminish or abolish the major actions of histamine in the body by competitive, reversible blockade of histamine H_1-receptor sites on tissues; they do not inactivate histamine or prevent its synthesis, nor, in most cases, its release (although some are claimed to have mast-cell stabilising properties). Histamine H_1 receptors are responsible for vasodilatation, increased capillary permeability, flare and itch reactions in the skin, and to some extent for contraction of smooth muscle in the bronchi and gastrointestinal tract.

Many of the *sedating antihistamines* also possess antimuscarinic, adrenaline-antagonising, serotonin-antagonising, and local anaesthetic effects. Some have calcium-channel blocking activity.

Antihistamines are used primarily for the alleviation of conditions such as urticarial **rashes** and **nasal allergy** that are characterised by type I hypersensitivity (see above), but by virtue of their associated pharmacological actions they are also used to alleviate the symptoms of a wide range of other conditions (such as pruritus and nausea and vomiting).

The antihistamines can improve or relieve the symptoms of **seasonal allergic rhinitis** ('hay fever') in many patients. They alleviate rhinorrhoea and sneezing (and ocular symptoms such as conjunctivitis) but may be less effective for nasal congestion. The relief obtained is dependent on the severity and nature of the symptoms, being greater in the milder stages. The *non-sedating antihistamines* are preferred for daytime control, but a *sedating antihistamine* may be preferred at night. Antihistamines may also be of value in **vasomotor rhinitis**, despite the fact that this is not primarily an allergic condition. *Sedating antihistamines* are widely marketed, often with a decongestant, in compound preparations for the symptomatic treatment of coughs and **colds** although there is little evidence of value.

Antihistamines are of value in preventing **urticaria** and are used to treat urticarial rashes and mild **angioedema**. They are also used as adjuncts to adrenaline in the emergency treatment of **anaphylaxis** and severe angioedema. However, the use of an antihistamine is not appropriate for the control of blood transfusion reactions caused by ABO incompatibility.

The *sedating antihistamines* are of value in the alleviation of **pruritus** both of allergic and of non-allergic origin; they have a major role in pruritus associated with atopic eczema. The *non-sedating antihistamines* do not alleviate pruritus of non-allergic origin owing to their poor penetration of the blood-brain barrier.

Sedating antihistamines have marked antiemetic activity and are used to control **nausea and vomiting** caused by a variety of vestibular disorders. In the case of motion sickness a sedating antihistamine, such as dimenhydrinate or promethazine, is used if severe drowsiness (or even sleep) is not considered undesirable, but generally a less sedative antihistamine, such as cyclizine, cinnarizine, or meclozine may be preferred. Sedating antihistamines are similarly used to control the vertigo and nausea associated with **Ménière's disease** and related conditions, with cinnarizine promoted as a specific treatment. Sedating antihistamines also have an important role in the alleviation of the nausea and vomiting of **migraine**, and buclizine or cyclizine are marketed in some countries in a combination preparation for this purpose; cyproheptadine, which has serotonin antagonist and calcium-channel blocking activity, may be of value in the prophylaxis of migraine. Sedating antihistamines have a very limited role in the short-term management of vomiting of pregnancy but are no longer considered appropriate for nausea alone. *Sedating antihistamines* have also been widely used for **premedication** in anaesthetic practice and still have a major role in the prevention of postoperative nausea and vomiting.

Some of the antihistamines with very pronounced sedative effects, such as diphenhydramine and promethazine, have been marketed for treatment of occasional **insomnia** but their long duration of action can cause hangover effects. Some antihistamines are also available as preparations for topical application for the alleviation of **insect bites**, but there is little evidence of any real value and such use may be associated with sensitisation.

◊ General references.

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2. Slater JW, *et al.* Second-generation antihistamines: a comparative review. *Drugs* 1999; **57:** 31–47.
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4. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs* 2005; **65:** 341–84.

Anaesthesia

Phenothiazine antihistamines have been used for anaesthetic premedication (p.1780) and to relieve anxiety during surgical and obstetric procedures, but benzodiazepines are now used more routinely. However, sedating antihistamines such as promethazine and cyclizine do have a role in the control of postoperative vomiting (below). Alimemazine is licensed for premedication in children, although when given alone it may cause postoperative restlessness if pain is present.

Anaphylaxis

Anaphylaxis is commonly a type I (immediate) hypersensitivity reaction (see above) to various allergens such as drugs, foods, and insect venoms. A clinically identical reaction can, however, be provoked by some other immune mechanisms, or by non-immune mechanisms (an anaphylactoid reaction). Symptoms of anaphylaxis and anaphylactoid reactions include erythema, pruritus, urticaria, and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension, and coma can occur in severe reactions.

Patients with severe anaphylactic or anaphylactoid reactions should be given immediate treatment with adrenaline (see Anaphylaxis and Anaphylactic Shock, p.1205). Addition of a parenteral antihistamine such as chlorphenamine maleate or diphenhydramine hydrochloride and a corticosteroid such as hydrocortisone after the acute episode may decrease the duration and severity of symptoms and prevent relapse. The use of antihistamines in treating the symptoms of milder forms of anaphylaxis is discussed under individual symptoms such as Pruritus (below) and Urticaria and Angioedema (below).

Angioedema

See under Urticaria and Angioedema, below.

Asthma

Antihistamines appear to have no place in the treatment of asthma (p.1108). A meta-analysis[1] of double-blind randomised placebo-controlled studies published since 1980 did not support the use of antihistamines in the treatment of asthma, although the quality of the studies was generally considered to be poor.

1. Van Ganse E, *et al.* Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997; **10:** 2216–24.

Conjunctivitis

Allergic conjunctivitis is a type I hypersensitivity reaction (above). It is usually seasonal but perennial attacks due to allergens such as house dust mites can occur. Itching, tears, and burning are common symptoms and frequently rhinitis (below) will co-exist. Conjunctivitis can also be caused by pathogenic micro-organisms (see Eye Infections, p.171).

Avoidance of unnecessary exposure to aeroallergens is of prime importance in the management of allergic conjunctivitis. Since a large number of inflammatory mediators are involved in its pathogenesis no single drug will be completely effective. Systemic sedating and non-sedating antihistamines are effective in reducing allergic symptoms and preventing attacks; the choice of drug depends on the degree of sedation required. Ophthalmic antihistamine preparations such as antazoline, azelastine, emedastine, levocabastine, and olopatadine may also be used for acute attacks. Ophthalmic corticosteroids may reduce inflammation, but should be restricted to severe cases only and limited to 5 to 7 days of use because of the risk of local adverse effects such as cataract or raised intra-ocular pressure. Mast-cell stabilisers including ketotifen, lodoxamide, nedocromil, and sodium cromoglicate have been widely used for prophylaxis; some antihistamines also have mast-cell stabilising properties. Diclofenac and ketorolac eye drops are available for the treatment of allergic conjunctivitis. Combined preparations of astringents such as zinc sulfate and sympathomimetics or other conjunctival decongestants such as naphazoline may also be used for symptomatic relief.

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Coughs and colds

Sedating antihistamines are frequently used in combination preparations for the treatment of coughs and colds (p.1547 and p.850 respectively). The mechanism of their antitussive action may involve reduction in cholinergic nerve transmission or may simply result from their sedative effects; reduction of nasal secretions may be of value in treating cough caused by postnasal drip. Antihistamines should not be used to treat productive coughs because reduction in bronchial secretions may cause formation of viscid mucus plugs. The sedative effects of antihistamines may prove troublesome for daytime use but may be a short-term advantage for night coughs.

Antihistamines may be useful in the management of children with an acute allergic cough in the pollen season. They may also be used, with allergen avoidance and intranasal corticosteroids, in children with a chronic throat clearing type of cough and signs of allergic rhinitis.[1]

1. Shields MD, *et al.* British Thoracic Society Cough Guideline Group. Recommendations for the assessment and management of cough in children. *Thorax* 2008; **63** (suppl III): iii1–iii15. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 01/08/08)

Food allergy

The term food allergy (food hypersensitivity) should be reserved for instances in which an immune mechanism for the reaction is proven, as may occur, for example, with nuts; food intolerance is used to describe a non-immune reaction. Food allergy may be the result of a type I (immediate), or possibly a type III (immune complex), hypersensitivity reaction (see above). Management revolves around the identification of the provoking food allergen and its subsequent avoidance. Individualised diets are designed and patients are educated about possible hidden sources of the allergen. Drug therapy has a very limited role in the prevention of food allergy; oral sodium cromoglicate has been used but efficacy has not been unequivocally established.

Inadvertent exposure to an allergen resulting in anaphylactic shock (p.1205) requires immediate treatment with adrenaline. Milder symptoms may be controlled by antihistamines and corticosteroids. Allergen immunotherapy (p.2251) plays no role in the routine management of food allergy.

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Hay fever

Hay fever is a seasonal form of allergic rhinitis in which symptoms of conjunctivitis are also present. Management is symptomatic and therapies used are discussed under Conjunctivitis, above and Rhinitis, below.

Insomnia

Some of the older sedating antihistamines including diphenhydramine and promethazine, have been promoted to the public for occasional insomnia (p.957), although their long duration of action may cause hangover effects. Promethazine was formerly popular for children but the use of hypnotics in this age group is not usually justified. Moreover a possible association between phenothiazines and sudden infant death syndrome (see under the Adverse Effects of Promethazine, p.588) contributed to the recommendation that such antihistamines should not be used in young children.

Ménière's disease

Ménière's disease is a disorder of the labyrinth (the inner ear) characterised by recurrent attacks of vertigo, progressive hearing loss, and worsening tinnitus (p.1866). It usually presents in middle age and may equally affect men and women. The main pathological feature is an excess of endolymph fluid producing an increase in pressure in the membranous labyrinth (endolymphatic hydrops). Attacks occur in clusters over a few weeks with periods of remission lasting weeks or months.

The aims of treatment are to alleviate symptoms and preserve hearing if possible. It is therefore important to assess how far the disease has progressed, particularly in terms of hearing loss. In addition to conventional hearing tests, cochlear dysfunction may be assessed pharmacologically. Hypertonic glycerol has been given orally to reduce the endolymphatic fluid volume by osmotic diuresis, any temporary improvement in hearing indicating reversible impairment. However, this test is associated with adverse effects that some consider unacceptable. Urea has been used as an alternative to glycerol. Intravenous acetazolamide has been used diagnostically to increase endolymphatic pressure temporarily in order to produce transient hearing loss in patients in the reversible stages of the disease.

Acute attacks of vertigo in the early stages may be treated with the same drugs used for vertigo of any cause (see below).

Vasodilators have been advocated for maintenance treatment because ischaemia of the labyrinth has been postulated as a factor in the aetiology. Betahistine, a histamine analogue, is used. Restriction of dietary sodium and administration of diuretics, such as chlortalidone, furosemide, and hydrochlorothiazide, has also been used traditionally to reduce the amount of fluid in the endolymphatic spaces.

As the disease progresses, vestibular ablation with aminoglycosides may be indicated. Systemic streptomycin has been used but the risk of further hearing loss and other serious adverse effects has limited its use. Intratympanic use of gentamicin is now preferred, and can improve vertigo in up to 90% of patients, although exacerbation of hearing loss is still a risk, albeit at a lower incidence than that with systemic streptomycin.

Surgical treatment remains an option for patients with Ménière's disease refractory to medical interventions.

References.

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Migraine

Antihistamines have a number of uses in the management of migraine (p.616). Those with antiemetic activity such as buclizine and cyclizine are used to alleviate the nausea and vomiting associated with migraine; they are common ingredients of compound analgesic preparations given for the initial treatment of migraine.

Those antihistamines with antiserotonin actions, including cyproheptadine and flunarizine, have been used for the prophylaxis of migraine.

Nausea and vomiting

The management of various types of nausea and vomiting is discussed in detail on p.1700.

The older antihistamines such as cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine are among the principal drugs used for **motion sickness**. They are all of similar efficacy but may differ in onset and duration of action and in the extent of adverse effects such as drowsiness. If a sedative effect is desired dimenhydrinate and promethazine are useful, otherwise a slightly less sedating antihistamine such as cinnarizine, cyclizine, or meclozine may be preferred. The aim is prevention of motion sickness since antiemetics are more effective for prophylaxis than for treatment; intramuscular promethazine may be effective as a treatment if injection is feasible. Antihistamines may be slightly less effective against motion sickness than the antimuscarinic hyoscine (p.1733), but are often better tolerated. Non-sedating antihistamines such as terfenadine, which penetrate poorly into the CNS, do not appear to be effective against motion sickness.

Diphenhydramine has been included in antiemetic regimens for the control of nausea and vomiting associated with **cancer chemotherapy** to reduce the extrapyramidal reactions associated with metoclopramide; it may also improve overall antiemetic control. Cyclizine is used as an antiemetic in **palliative care**.

Cyclizine is given as a supplement to opioids for premedication and has been effective prophylactically as well as in established **postoperative nausea and vomiting**. Promethazine has also been used for the prevention and treatment of postoperative nausea and vomiting, but has marked sedative effects. Dimenhydrinate is also effective for prophylaxis.

Nausea in the first trimester of **pregnancy** does not require drug therapy, but on rare occasions if vomiting is severe an antihistamine such as promethazine may be required pending specialist advice. See under Precautions for Antihistamines, above, for a discussion of the risks of antiemetic therapy during pregnancy.

Otitis media

Acute otitis media (p.182) and otitis media with effusion may resolve without treatment although antibacterials are often given. Antihistamines and decongestants, alone or in combination, have been widely given to children for symptomatic management of acute otitis media and associated respiratory symptoms, but studies have failed to show benefit and their use is not recommended.[1] Indeed in one study,[2] adjunctive treatment with chlorphenamine was found to prolong the duration of middle ear effusion.

1. Griffin GH, *et al.* Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 07/03/07).
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Pruritus

The sedating antihistamines are commonly used to relieve pruritus (itching) (p.1582) from a variety of causes. They are effective in relieving pruritus associated with urticaria (below) but are also used for itching associated with dermatoses such as atopic eczema (p.1579), where the degree of benefit is less certain. They are given in the latter to control nocturnal itching and for severe pruritus associated with relapse.

The exact pathophysiology of itching remains unclear.[1-3] Although histamine release is associated with itching in atopic eczema different inflammatory mediators are involved in other dermatoses. The CNS is also thought to play a part in the perception of itch. Hence, the relative roles of CNS sedation and peripheral histamine-receptor blockade in the mode of action of antihistamines in these conditions is a matter of debate. Although sedation has generally been considered the more important, the benefits of sedating antihistamines appear to be less in eczema than in urticaria. In addition, clemastine has been reported to provide no antipruritic benefit, yet it induces significant sedation. Studies with non-sedating antihistamines have been inconclusive; most found no benefit in pruritus associated with atopic eczema, although one early study has shown a slight benefit from the addition of acrivastine or terfenadine to treatment with a topical corticosteroid and an emollient.[4] Some have questioned whether any antihistamine offers much benefit in pruritus.[5]

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Rhinitis

Rhinitis may be allergic or non-allergic in origin. Allergic rhinitis is a type I hypersensitivity reaction (see above); both early (sneezing, rhinorrhoea, and nasal congestion) and late (nasal congestion) reactions may be provoked. It may be seasonal (as in hay fever) or perennial and, in some patients, will frequently co-exist with conjunctivitis (above). Non-allergic rhinitis may be divided into eosinophilic non-allergic rhinitis or non-eosinophilic non-allergic rhinitis. The term vasomotor rhinitis has been used to describe the latter although its use is best avoided since no vasomotor dysfunction has been clearly identified.

In the management of **allergic rhinitis**, avoidance of unnecessary exposure to aeroallergens is of prime importance. However, in most sufferers this is not possible and some form of drug therapy will be necessary. A large number of inflammatory mediators are involved in the pathogenesis of rhinitis and no single drug is completely effective in the alleviation of symptoms.

- Some antihistamines may nonetheless be useful in reducing secretions, nasal itching, sneezing, and ocular symptoms such as conjunctivitis, but are less effective for relief of nasal congestion. Non-sedating antihistamines such as acrivastine, cetirizine, ebastine, fexofenadine, loratadine, and mizolastine are now considered the first-choice treatment for mild and/or intermittent allergic rhinitis. They are also used for the management of breakthrough symptoms in those sufferers using prophylactic intranasal corticosteroids or sodium cromoglicate (see below). Since the maximum effect of antihistamines occurs several hours after peak serum concentrations have been obtained, they should be given in anticipation of a reaction to achieve the maximum response. Most antihistamines are unsuitable for topical use in the nose or eye since they are generally ineffective at the concentrations suitable for local therapy; also there is the potential for sensitisation. However, the antazoline salts, azelastine and levocabastine have been used topically in the nose for control of symptoms. Such preparations are considered less effective than intra-nasal corticosteroids but probably more effective than cromoglicate.
- The actions of topical corticosteroids in allergic rhinitis include relief of inflammation, a decrease in capillary permeability and in mucus production, and vasoconstriction; they inhibit both the early and late response to allergen exposure. Corticosteroids are first-line treatment for the prophylaxis of moderate and/or persistent allergic rhinitis. In seasonal allergic rhinitis, they should be started at least 2 weeks before the pollen season and taken regularly throughout the season. Those applied intranasally include beclometasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone. At recommended dosage, local adverse effects are mild and transient, and systemic effects are not a risk; aqueous sprays may cause less local effects than pressurised aerosols. Treatment of allergic rhinitis with oral or parenteral corticosteroids has been reserved for short-term treatment in special circumstances only, although some have contested even this practice.
- Mast-cell stabilisers such as ketotifen, nedocromil, and sodium cromoglicate are thought to act primarily by preventing release of inflammatory mediators from sensitised mast cells through stabilisation of mast-cell membranes. They are an alternative to corticosteroids in the prophylactic treatment of allergic rhinitis and may be preferred for therapy in children. They may also be useful in controlling mild to moderate symptoms.
- The leukotriene receptor antagonist montelukast has produced benefits comparable to those seen with antihistamines, and is licensed in some countries for management of seasonal allergic rhinitis.
- Intranasal sympathomimetics such as phenylephrine, naphazoline, oxymetazoline, and xylometazoline may be useful for short-term treatment of allergic rhinitis to relieve severe nasal congestion which can be painful and may impede delivery of sodium cromoglicate or a corticosteroid to the mucosal surfaces. Oral sympathomimetic decongestants such as pseudoephedrine and phenylpropanolamine are less effective than topical sympathomimetics and adverse effects may be troublesome.
- Ipratropium bromide given intranasally may be useful as adjunctive therapy in patients with rhinorrhoea as it has a localised parasympathetic blocking action which reduces watery hypersecretion from nasal mucosa.

Allergen immunotherapy (p.2251) is generally only indicated in severe allergic rhinitis when sensitivity testing demonstrates sensitivity to one allergen and when exposure to the allergen is unavoidable or symptomatic treatment has failed.

The management of **non-allergic rhinitis** is similar to that of allergic rhinitis despite different mechanisms being involved in its aetiology. Topical corticosteroids are often first-line therapy especially if nasal congestion is a dominant feature. The role of antihistamines is more limited; sedating antihistamines are useful in reducing nasal secretions because of their antimuscarinic actions; however, non-sedating antihistamines are relatively ineffective. In patients in whom rhinorrhoea is a particular problem, intranasal ipratropium is of value. Although intranasal sympathomimetics have also been used they should generally be avoided because of the risk of rebound congestion. Oral sympathomimetics are largely ineffective.

Other therapies tried include topical capsaicin, to induce local desensitisation, and nasal douching with a saline and sodium bicarbonate solution.

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4. Parikh A, Scadding GK. Seasonal allergic rhinitis. *BMJ* 1997; **314:** 1392–5.
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6. Durham S. Summer hay fever. *BMJ* 1998; **316:** 843–5.
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Urticaria and angioedema

Most patients with urticaria or angioedema (p.1584) derive some benefit from oral antihistamines, especially in relief of pruritus. However, patients who are severely affected, particularly those with laryngeal oedema, are allergic emergencies and require immediate treatment with adrenaline (see Anaphylaxis and Anaphylactic Shock, p.1205). Also, large doses of antihistamines are sometimes required and urticarias with a type I immunological origin and iatrogenic urticarias respond better than physical urticarias. If attacks of urticaria are frequent, antihistamines may be given prophylactically. Sedating antihistamines such as chlorphenamine and diphenhydramine have been widely used in the treatment of urticaria but non-sedating antihistamines are now generally preferred. Hydroxyzine has been used particularly in dermographism and cholinergic urticaria. Cyproheptadine has generally been considered the drug of choice for cold urticaria, although appetite stimulation may be a problem.

Some drugs with both H_1-antagonist and mast-cell stabilising actions, such as ketotifen, oxatomide, and azatadine have shown efficacy in the treatment of urticaria; the role of mast-cell stabilisation is unknown.

Topical treatment is rarely effective except for cases of mild urticaria; topical antihistamines carry a risk of sensitisation.

References.

1. Monroe EW. Chronic urticaria: review of nonsedating H anti-histamines in treatment. *J Am Acad Dermatol* 1988; **19:** 842–9.
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Vertigo

Vertigo is a symptom of vestibular disorders. It is characterised by a sensation of rotation of the surroundings or of movement of static objects. Dizziness is considered to be a wider term, although some use it as a synonym for vertigo.

A variety of disorders may affect the vestibular system and produce vertigo, including cerebrovascular disorders, epilepsy, head injury, malignant neoplasms, Ménière's disease, migraine, multiple sclerosis, and infections. Motion sickness can induce vertigo. Ototoxic drugs may also cause vestibular damage and precipitate vertigo.

Patients suffering from vertigo should undergo thorough investigations to identify any underlying cause. Simple measures to improve the integration of sensory input from visual, proprioceptive, and vestibular receptors may prove effective, especially in the elderly, in whom the inappropriate prescribing of drugs for postural instability needs to be avoided. Such measures include improving visual acuity, balance exercises, and the use of walking aids.

The most widely used drugs for acute vertigo are the antihistamines. They may have a direct action on the inner ear besides acting centrally. Antimuscarinic actions may contribute to their activity; antimuscarinics, especially hyoscine, have a long history of use in vertigo. Antihistamines used in the treatment of vertigo include buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclozine, and promethazine. Cinnarizine and flunarizine are also used for vertigo although they are devoid of any significant antimuscarinic actions; their activity may be due to calcium-channel blockade. Phenothiazines such as prochlorperazine are also used to control any associated vomiting. Benzodiazepines including diazepam have been given in acute severe attacks. However their prolonged use in those with chronic symptoms is of questionable value.

Vasodilators may be of benefit in the treatment of vertigo of vascular aetiology. Parenteral or sublingual histamine was formerly widely used, and betahistine is still advocated especially for vertigo associated with Ménière's disease. Nicotinyl alcohol has also been used.

References.

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; **50:** 777–91.
2. Luxon LM. Vertigo: new approaches to diagnosis and management. *Br J Hosp Med* 1996; **56:** 519–20 and 537–41.
3. Luxon LM. Assessment and management of vertigo. *Prescribers' J* 1998; **38:** 87–97.
4. Baloh RW. Vertigo. *Lancet* 1998; **352:** 1841–6.
5. Hain TC, Uddin M. Pharmacological treatment of vertigo. *CNS Drugs* 2003; **17:** 85–100.

Acrivastine *(BAN, USAN, rINN)*

Acrivastin; Acrivastina; Acrivastinum; Akrivastiini; Akrivastin; BW-825C. (*E*)-3-{6-[(*E*)-3-Pyrrolidin-1-yl-1-*p*-tolylprop-1-enyl]-2-pyridyl}acrylic acid.

Акривастин

$C_{22}H_{24}N_2O_2$ = 348.4.

CAS — 87848-99-5.

ATC — R06AX18.

ATC Vet — QR06AX18.

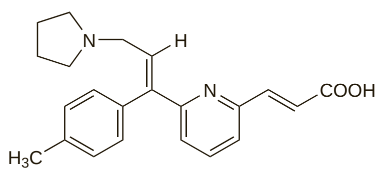

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Acrivastine should be given with care in renal impairment; UK licensed product information recommends that it should not be given to patients with significant renal impairment, while product information in other countries, such as Switzerland for example, contra-indicates its use in those with a creatinine clearance of less than 50 mL/minute. Acrivastine should not be used in patients hypersensitive to triprolidine.

Sedation. For a discussion of the sedative effects of antihistamines see p.562.

Interactions

As for the non-sedating antihistamines in general, p.563.

Pharmacokinetics

Acrivastine is well absorbed from the gastrointestinal tract; peak plasma concentrations are achieved in about 1.5 hours. The plasma half-life of acrivastine is about 1.5 hours and the drug does not appear to cross the blood-brain barrier to a significant extent. Acrivastine along with an active metabolite is excreted principally in the urine.

Uses and Administration

Acrivastine is a non-sedating antihistamine structurally related to triprolidine. It does not have any significant sedative or antimuscarinic actions. It is used for the symptomatic relief of allergic conditions such as rhinitis (p.565) and various types of urticaria (p.565) when it is given in oral doses of 8 mg three times daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

Administration in renal impairment. See Precautions, above

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Semprex; ***Cz.:*** Semprex†; ***Denm.:*** Benadryl; ***Fin.:*** Benadryl; Semprex†; ***Hong Kong:*** Semprex; ***Ital.:*** Semprex; ***Malaysia:*** Semprex; ***Neth.:*** Semprex; ***Philipp.:*** Semprex; ***Rus.:*** Semprex (Семпрекс); ***S.Afr.:*** Semprex; ***Singapore:*** Semprex; ***Swed.:*** Semprex; ***Switz.:*** Semprex; ***Thai.:*** Semprex†; ***Turk.:*** Semprex; ***UK:*** Benadryl Allergy Relief.

Multi-ingredient: ***Austria:*** Duact; ***Denm.:*** Duact; ***Fin.:*** Duact; ***Turk.:*** Duact; ***UK:*** Benadryl Plus; ***USA:*** Semprex-D.

Alimemazine Tartrate *(BANM, rINNM)*

Alimémazine, Tartrate d'; Alimemazini Tartras; Tartrato de alimemazina; Trimeprazine Tartrate. *NN*-Dimethyl-2-methyl-3-(phenothiazin-10-yl)propylamine tartrate.

Алимемазина Тартрат

$(C_{18}H_{22}N_2S)_2,C_4H_6O_6$ = 747.0.

CAS — 84-96-8 (alimemazine); 4330-99-8 (alimemazine tartrate).

ATC — R06AD01.

ATC Vet — QR06AD01.

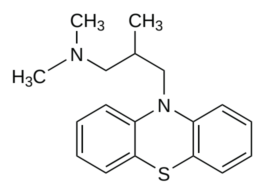

(alimemazine)

Pharmacopoeias. In *Br.*, *Fr.*, *Jpn*, and *US.*

BP 2008 (Alimemazine Tartrate). A white or slightly cream powder. It darkens on exposure to light. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Trimeprazine Tartrate). A white to off-white, odourless, crystalline powder. Soluble 1 in 2 of water, 1 in 20 of alcohol, 1 in 5 of chloroform, and 1 in 1800 of ether; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Children. There have been reports of adverse effects in children given alimemazine tartrate orally. Fatal malignant hyperthermia[1] and severe cardiovascular depression[2] have occurred after its use for premedication, and severe respiratory and CNS depression[3] after use as a postoperative sedative. Doses in these 3 reports ranged from 2.4 to 4.4 mg/kg. Although unconfirmed, a possible association between phenothiazine sedatives and sudden infant death syndrome has also been suggested (see Promethazine Hydrochloride, p.588). Alimemazine tartrate is no longer licensed in the UK for short-term sedation in children and it is recommended that it should not be used in infants less than 2 years of age (but see below). The maximum recommended oral dose for premedication of children aged 2 to 7 years is 2 mg/kg. There has been a warning[4] that the use of alimemazine for deep sedation in diagnostic and therapeutic procedures in children is associated with prolonged drowsiness and that standards of monitoring, starvation, and postprocedural care should be similar to those with general anaesthesia.

1. Moyes DG. Malignant hyperpyrexia caused by trimeprazine. *Br J Anaesth* 1973; **45:** 1163–4.
2. Loan WB, Cuthbert D. Adverse cardiovascular response to oral trimeprazine in children. *BMJ* 1985; **290:** 1548–9.
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Pregnancy. For a discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Alimemazine, a phenothiazine derivative, is a sedating antihistamine with antiemetic activity and pronounced sedative effects. It also has some antimuscarinic actions. It is used mainly for the relief of urticaria (p.565) and pruritus (p.565), and, in the UK, for pre-operative medication in children. Alimemazine may also be used in compound preparations for the symptomatic treatment of coughs (p.564).

Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25 mg is equivalent to about 20 mg of alimemazine.

- The adult dose of alimemazine tartrate used for the relief of **urticaria** and **pruritus** in the *UK* is 10 mg two or three times daily; up to 100 mg daily has been given in refractory cases. Elderly patients are given 10 mg once or twice daily and children over 2 years of age 2.5 to 5 mg three or four times daily. Despite the view that alimemazine should not be given to younger children (see above), and although not licensed in the UK, the *BNFC* suggests that 250 micrograms/kg (maximum of 2.5 mg) three or four times daily may be given to those aged 6 months to 2 years for the relief of urticaria and pruritus, but only under specialist care.
- Doses used in the *USA* have been lower, even allowing for them being expressed in terms of alimemazine. The adult dose was the equivalent of alimemazine 2.5 mg four times daily. Children in the USA 3 years of age and over have been given 2.5 mg at night or three times daily. However, it appears that proprietary preparations are no longer available in the USA.
- The usual recommended dose in the UK for **premedication** in children aged 2 to 7 years is up to 2 mg/kg given about one to two hours before the operation.

Anaesthesia. Alimemazine tartrate may be used for anaesthetic premedication (see p.563) in children if the oral route is preferred to the more usual parenteral route of other phenothiazine antihistamines. Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, above), and in the UK alimemazine tartrate is not licensed for use in infants less than 2 years of age.

Insomnia. Antihistamines such as alimemazine tartrate have been used as alternatives to benzodiazepines for the short-term treatment of insomnia (p.564), particularly for children. However, their antimuscarinic side-effects may prove troublesome.

Regimens involving a short course of alimemazine tartrate in high dosage were tried in order to alter the sleep pattern of children with sleeping difficulties.[1,2] Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, above). The UK product is no longer indicated for short-term sedation in children and should not be used in infants less than 2 years of age.

1. Valman HB. ABC of 1 to 7 (revised): sleep problems. *BMJ* 1987; **294:** 828–30.
2. Anonymous. What can be done for night waking in children? *Lancet* 1987; **ii:** 948–9.

Preparations

BP 2008: Alimemazine Tablets; Paediatric Alimemazine Oral Solution; Strong Paediatric Alimemazine Oral Solution;
USP 31: Trimeprazine Tartrate Syrup; Trimeprazine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Chemists Own Peetalix†; Vallergan; ***Belg.:*** Theralene; ***Canad.:*** Panectyl; ***Fr.:*** Theralene; ***Ger.:*** Repeltin†; ***Irl.:*** Vallergan; ***Neth.:*** Nedeltran; ***Norw.:*** Vallergan; ***NZ:*** Vallergan; ***S.Afr.:*** Vallergan; ***Spain:*** Variargil; ***Swed.:*** Theralen; ***UK:*** Vallergan.

Multi-ingredient: ***Fr.:*** Sirop Teyssedre; Theralene Pectoral Nourrisson†.

Antazoline *(BAN, rINN)*

Antatsoliini; Antazolin; Antazolina; Antazolinum. *N*-Benzyl-*N*-(2-imidazolin-2-ylmethyl)aniline.

Антазолин

$C_{17}H_{19}N_3$ = 265.4.
CAS — 91-75-8.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

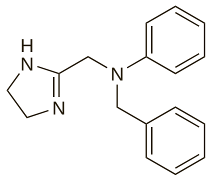

Antazoline Hydrochloride *(BANM, rINNM)*

Antatsoliinihydrokloridi; Antazolin hydrochlorid; Antazoline, chlorhydrate d'; Antazolin-hidroklorid; Antazolinhydroklorid; Antazolini Hydrochloricum; Antazolini hydrochloridum; Antazolinium Chloride; Antazolino hidrochloridas; Antazoliny chlorowodorek; Hidrocloruro de antazolina; Imidamine Hydrochloride; Phenazolinum.

Антазолина Гидрохлорид

$C_{17}H_{19}N_3$,HCl = 301.8.
CAS — 2508-72-7.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Antazoline Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in dichloromethane.

Antazoline Mesilate *(BANM, rINNM)*

Antazoline, Mésilate d'; Antazoline Mesylate; Antazoline Methanesulphonate; Antazolini Mesilas; Antazoliny mezylan; Imidamine Mesylate; Mesilato de antazolina.

Антазолина Мезилат

$C_{17}H_{19}N_3$,CH_3SO_3H = 361.5.
CAS — 3131-32-6.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *Pol.*

Antazoline Phosphate *(BANM, rINNM)*

Antazolin Fosfat; Antazoline, Phosphate d'; Antazolini Phosphas; Fosfato de antazolina; Imidamine Phosphate.

Антазолина Фосфат

$C_{17}H_{19}N_3$,H_3PO_4 = 363.3.
CAS — 154-68-7.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *US.*
USP 31 (Antazoline Phosphate). A white to off-white crystalline powder. Soluble in water; practically insoluble in ether and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 4.0 and 5.0. Store in airtight containers.

Antazoline Sulfate *(rINNM)*

Antazoline, Sulfate d'; Antazoline Sulphate *(BANM)*; Antazolini Sulfas; Imidamine Sulphate; Sulfato de antazolina.

Антазолина Сульфат

$(C_{17}H_{19}N_3)_2H_2SO_4$,$2H_2O$ = 664.8.
CAS — 24359-81-7 (anhydrous antazoline sulfate).
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

NOTE. The above molecular formula is that provided in the *It. P.* Other sources give a molecular formula of $C_{17}H_{19}N_3$,H_2SO_4.

Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for the antihistamines in general, p.561.

Hypersensitivity. Reports of acute interstitial pneumonitis (with fever, rash, and dyspnoea)[1] and of immune thrombocytopenic purpura[2] were attributed to hypersensitivity reactions after the oral use of antazoline.

1. Pahissa A, *et al.* Antazoline-induced allergic pneumonitis. *BMJ* 1979; **2:** 1328.
2. Nielsen JL, *et al.* Immune thrombocytopenia due to antazoline (Antistina). *Allergy* 1981; **36:** 517–19.

Uses and Administration

Antazoline, an ethylenediamine derivative, is an antihistamine used topically for the treatment of allergic conjunctivitis (p.564). It is used as the hydrochloride, phosphate, or sulfate in eye drops, most commonly in a concentration of 0.5%; the mesilate has also been used. Antazoline salts are often used with a vasoconstrictor such as naphazoline hydrochloride or nitrate or xylometazoline hydrochloride.

The hydrochloride and sulfate salts of antazoline have been used topically for the treatment of minor skin irritations, but as with other antihistamines there is a risk of sensitisation. The hydrochloride has also been given by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Albalon-A; Antistine-Privine; In A Wink Allergy†; ***Austria:*** Histophtal; ***Belg.:*** Zincfrin Antihistaminicum†; ***Canad.:*** Albalon-A; Vasocon-A†; Zincfrin-A; ***Chile:*** Albasol A†; Bacitopic Compuesto; Nasomin; Oftalirio; Red Off Plus; Rinobanedif; Spersallerg; ***Cz.:*** Sanorin-Analergin; Spersallerg; ***Denm.:*** Ansal; Antistina-Privin; Sesal; ***Fin.:*** Antistin-Privin†; Zincfrin-A†; ***Ger.:*** Allergopos N; Antistin-Privin; Spersallerg; ***Gr.:*** Spersallerg; ***Hong Kong:*** Spersallerg; ***Hung.:*** Spersallerg; ***Indon.:*** Indofrin-A; ***Irl.:*** Otrivine-Antistin; RBC; ***Israel:*** Antistin-Privin†; ***Ital.:*** Antistin-Privina; ***Malaysia:*** Alergoftal; Napha A; Spersallerg; ***Mex.:*** Midazol Ofteno; Oftalirio†; Zincfrin-A; ***Norw.:*** Spersallerg; ***NZ:*** Albalon-A†; Otrivine-Antistin; ***Philipp.:*** Spersallerg; ***Pol.:*** Dermophenazol; Oftophenazol; Rhinophenazol; Spersallerg; ***Port.:*** Alergiftalmina; ***Rus.:*** Sanorin-Analergin (Санорин-аналергин); Spersallerg (Сперсаллерг); ***S.Afr.:*** Albalon-A†; Antistin-Privin; Covosan; Gemini; Oculerge; Safyr Bleu Antihistamine†; Spersallerg; Zincfrin-A; ***Singapore:*** Antistin-Privin; Spersallerg; ***Spain:*** Alergoftal; ***Swed.:*** Antasten-Privin; ***Switz.:*** Antistin-Privin; Spersallerg; ***Thai.:*** Antazallerge; Histaoph; Opsa-His†; Opsil-A; Spersallerg; ***Turk.:*** Alergoftal; Sulfarhin; ***UK:*** Otrivine-Antistin; ***USA:*** Antazoline-V; Vasocon-A.

Astemizole *(BAN, USAN, rINN)*

Astemitsoli; Astemizol; Astemizolas; Astémizole; Astemizolum; Asztemizol; MJD-30. 1-(4-Fluorobenzyl)-2-{[1-(4-methoxyphenethyl)-4-piperidyl]amino}benzimidazole.

Астемизол

$C_{28}H_{31}FN_4O$ = 458.6.
CAS — 68844-77-9.
ATC — R06AX11.
ATC Vet — QR06AX11.

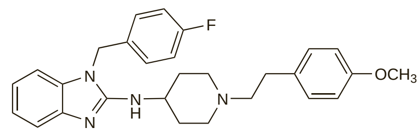

NOTE. The code R-43512 has been used to describe both astemizole and its metabolite tecastemizole (norastemizole).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Astemizole). A white or almost white powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane and in methyl alcohol. Protect from light.
USP 31 (Astemizole). Store in airtight containers.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Increased appetite and weight gain have been reported with astemizole.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with astemizole, particularly in association with raised blood concentrations (see Arrhythmias below) and as a result the drug has been withdrawn from the market in most countries. To reduce the risk of developing such arrhythmias recommendations were that licensed doses should **not** be exceeded, and that it should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of astemizole, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance, is **contra-indicated** (see Interactions below).

Arrhythmias. Although severe life-threatening cardiovascular effects including torsade de pointes and other ventricular arrhythmias were initially reported mainly after substantial overdoses of astemizole, such reactions have also occurred rarely with doses as low as 20 to 30 mg daily and even as low as 10 mg daily in those with possible predisposing factors. There has been a report[1] of astemizole-induced torsade de pointes in a 15-year-old girl who claimed to have taken 10 mg daily for 10 weeks but pharmacokinetic data were more consistent with acute ingestion of higher doses. There have also been several reports of cardiotoxicity after accidental overdosage with astemizole in children.[2-4]

Although the drug is now withdrawn in the UK, recommendations were made by the UK CSM to reduce the risk of developing serious arrhythmias[5-7] (see Adverse Effects above for details). It was considered that astemizole should be stopped immediately in patients who experience syncope, and appropriate clinical evaluation including ECG monitoring instituted, because syncope has preceded or accompanied severe arrhythmias in some cases. Convulsions in patients taking astemizole may also be related to cardiovascular effects.[8]

Studies have suggested that astemizole induces ventricular arrhythmias by inhibiting cardiac potassium channels which results in prolongation of the QT interval, a risk factor for developing arrhythmias.[9] For further discussion, see p.562.

1. Simons FER, *et al.* Astemizole-induced torsade de pointes. *Lancet* 1988; **ii:** 624.
2. Hoppu K, *et al.* Accidental astemizole overdose in young children. *Lancet* 1991; **338:** 538–40.
3. Tobin JR, *et al.* Astemizole-induced cardiac conduction disturbances in a child. *JAMA* 1991; **266:** 2737–40.
4. Wiley JF, *et al.* Cardiotoxic effects of astemizole overdose in children. *J Pediatr* 1992; **120:** 799–802.
5. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems* **35** 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
6. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. CSM/MCA. Astemizole (Hismanal): only available on prescription. *Current Problems* 1999; **25:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 19/05/06)
8. Clark A, Love H. Astemizole-induced ventricular arrhythmias: an unexpected cause of convulsions. *Int J Cardiol* 1991; **33:** 165–7.
9. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Overdosage. Severe cardiac events have been associated with astemizole overdosage (see Arrhythmias, above); management is mainly supportive. The absorption of astemizole from the gastrointestinal tract can be prevented by giving activated charcoal[1] but because astemizole is rapidly absorbed it would need to be given as soon as possible after poisoning. Haemodialysis does not appear to increase the clearance of astemizole.

1. Laine K, *et al.* The effect of activated charcoal on the absorption and elimination of astemizole. *Hum Exp Toxicol* 1994; **13:** 502–5.

Porphyria. Astemizole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Sedation. For discussion of the sedative effects of antihistamines see p.562.

Interactions

As for the non-sedating antihistamines in general, p.563.

Astemizole should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the imidazole and triazole antifungals such as ketoconazole and itraconazole, and the macrolide antibacterials clarithromycin, erythromycin, troleandomycin, and possibly other macrolides. Others, similarly to terfenadine (p.591), may include serotonin reuptake inhibitors, HIV-protease inhibitors, NNRTIs, and zileuton. The metabolism of astemizole may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, and the beta blocker sotalol should be avoided, as should diuretics that cause electrolyte imbalances such as hypokalaemia. The use of terfenadine and astemizole together is not recommended.

Pharmacokinetics

Absorption of astemizole from the gastrointestinal tract is rapid and is reduced by food. First-pass metabolism is extensive, therefore plasma concentrations of unchanged drug are very low. The plasma concentration of astemizole plus metabolites takes about 4 to 8 weeks to reach steady state. The metabolism of astemizole is mediated through the cytochrome P450 enzyme system by the isoenzymes CYP3A4, CYP2D6, and CYP2A6. The elimination half-life of astemizole and its metabolites at steady state is about 19 days. Unchanged astemizole is highly bound to plasma proteins and does not appear to cross the blood-brain barrier to a significant extent. Desmethylastemizole, the major metabolite of astemizole, has histamine H_1-receptor-blocking activity; tecastemizole (norastemizole) is another active metabolite. The metabolites of astemizole are excreted slowly in the urine and faeces, and undergo enterohepatic recycling. Virtually none of an oral dose is excreted as unchanged drug.

Uses and Administration

Astemizole, a piperidine derivative, is a non-sedating antihistamine with a very long duration of action. It does not have significant sedative or antimuscarinic actions. Astemizole has been used for the symptomatic relief of allergic conditions including rhinitis (p.565) and conjunctivitis (p.564), and skin disorders such as urticaria (p.565). Preparations of astemizole have now been withdrawn from the market in most countries because of the risk of adverse effects.

Astemizole has been given in an oral dose of 10 mg once daily, or 5 mg daily in children aged 6 to 12 years. These doses must not be exceeded because of the risk of cardiac arrhythmias with higher doses.

The active metabolite of astemizole, tecastemizole (norastemizole) has been investigated for the treatment of allergic rhinitis.

Preparations

USP 31: Astemizole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alermizol†; Astezol†; Cezane†; Mudantil†; ***Cz.:*** Hismanal†; ***Gr.:*** Mibiron†; Tulipe-R†; Tyrenol†; Waruzol†; ***India:*** Astizole; Stemiz†; ***Mex.:*** Adistan†; Alerfur; Alerken; Alermi; Aleztem; Anerzol; Antagon 1; Astemina; Astesen; Aztemin; Aztil; Aztrolen; Biostan; Dexodin; Emdar; Emizol; Farmidal S; Fustermizol; Ginomizol†; Histalino; Histaser; Novasten; Practizol; Ulcoid-Zol†; Urtigen; ***Port.:*** Perifer H1†; ***Spain:*** Alermizol†; Esmacen†; Hubermizol†; Narvizol†; Rifedot†; Simprox†; Urdrim†; ***Venez.:*** Asemin†; Corexan†; Histalong†; Prevan†.

Multi-ingredient: *Arg.:* Bio Cabal†; Bronco Biotaer†; Dallamizol-D†; Gentiabron†; Muco Cortos†; Predual Descongestivo†; Wilpan C†.

Azatadine Maleate *(BANM, USAN, rINNM)*

Atsatadiinimaleaatti; Azatadine, Maléate d'; Azatadini Maleas; Azatadinmaleat; Maleato de azatadina; Sch-10649. 6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine dimaleate.

Азатадина Малеат

$C_{20}H_{22}N_2,2C_4H_4O_4 = 522.5.$

CAS — 3964-81-6 (azatadine); 3978-86-7 (azatadine maleate).

ATC — R06AX09.

ATC Vet — QR06AX09.

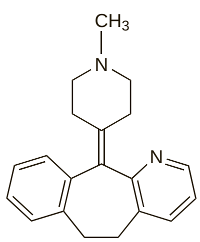

(azatadine)

Pharmacopoeias. In *US.*

USP 31 (Azatadine Maleate). A white to light cream-coloured, odourless powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; practically insoluble in ether and in benzene.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Extrapyramidal effects. An acute dystonic reaction was reported in a patient who had taken azatadine maleate 20 to 30 mg orally over a 24-hour period.[1] The condition was reversed by intravenous injection of benzatropine 2 mg.

1. Joske DJL. Dystonic reaction to azatadine. *Med J Aust* 1984; **141:** 449.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Azatadine maleate is readily absorbed from the gastrointestinal tract and is partly metabolised. Peak plasma concentrations are achieved in about 4 hours. The elimination half-life has been reported to be 9 to 12 hours. Excretion of unchanged drug and metabolites is via the urine.

Uses and Administration

Azatadine maleate is a piperidine derivative closely related to cyproheptadine. It is a sedating antihistamine with a long duration of action; it also has antimuscarinic and antiserotonin properties.

Azatadine maleate is used for the symptomatic relief of allergic conditions including rhinitis (p.565) and urticaria (p.565); it is also used for other pruritic skin disorders as well as reactions to insect bites and stings. It is given in usual oral doses of 1 mg twice daily; if necessary 2 mg twice daily may be given. Children aged 6 to 12 years may be given 0.5 to 1 mg twice daily.

It is also used with a decongestant such as pseudoephedrine sulfate.

Preparations

USP 31: Azatadine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Zadine; ***Canad.:*** Optimine; ***Hong Kong:*** Zadine†; ***Malaysia:*** Zadine†; ***Mex.:*** Idulamine†; ***NZ:*** Zadine†; ***Singapore:*** Zadine†; ***Spain:*** Lergocil.

Multi-ingredient: *Braz.:* Cedrin; ***Canad.:*** Trinalin; ***Mex.:*** Trinalin†; ***Spain:*** Atiramin; Idulanex; ***USA:*** Rynatan†; Trinalin†.

Azelastine Hydrochloride

(BANM, USAN, rINNM)

A-5610 (azelastine or azelastine hydrochloride); Atselastiinihydrokloridi; Azelastin Hidroklorür; Azélastine, chlorhydrate d'; Azelastin-hydrochlorid; Azelastinhydroklorid; Azelastini hydrochloridum; Azelastino hidrochloridas; E-0659 (azelastine or azelastine hydrochloride); Hidrocloruro de azelastina; W-2979M (azelastine or azelastine hydrochloride). 4-(*p*-Chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone monohydrochloride.

Азеластина Гидрохлорид

$C_{22}H_{24}ClN_3O,HCl = 418.4.$

CAS — 58581-89-8 (azelastine); 79307-93-0 (azelastine hydrochloride).

ATC — R01AC03; R06AX19; S01GX07.

ATC Vet — QR01AC03; QR06AX19; QS01GX07.

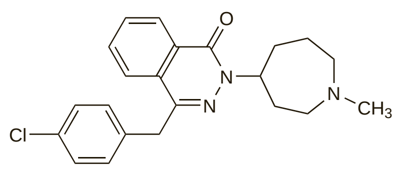

(azelastine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Azelastine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in dehydrated alcohol and in dichloromethane.

Adverse Effects and Precautions

As for the antihistamines in general, p.561.

When given intranasally, irritation of the nasal mucosa and taste disturbances have been reported; somnolence, headache, and dry mouth have also been noted in some patients. Taste disturbance can occur after use in the eye.

Pharmacokinetics

About 40% of an intranasal dose of azelastine reaches the systemic circulation. Elimination is via hepatic metabolism with excretion mainly in the faeces.

◊ Azelastine is rapidly and almost completely absorbed when given *orally*, peak plasma concentrations being achieved in 4 to 5 hours. Azelastine undergoes hepatic metabolism; the major metabolite, demethylazelastine, has antihistamine activity. The elimination half-life of azelastine is about 25 hours, increasing to 35.5 hours after multiple oral doses, possibly as a result of accumulation of the demethyl metabolite. Azelastine and its metabolites are excreted predominantly in the faeces and also in urine.

Uses and Administration

Azelastine hydrochloride is an antihistamine that, in addition to its histamine H_1-receptor-blocking activity, appears to inhibit the release of inflammatory mediators from mast cells. It is used topically in the symptomatic relief of allergic conditions including rhinitis (p.565) and conjunctivitis (p.564). It is also used in the treatment of non-allergic rhinitis.

In the treatment of allergic **rhinitis** in adults and children aged 5 years and over, the usual dose in the UK is 140 micrograms by nasal spray into each nostril twice daily. In the USA, however, 2 sprays of a similar preparation (supplying 137 micrograms per spray) may be given into each nostril twice daily; children aged 5 years and over may be given 1 spray into each nostril twice daily. In the USA, azelastine is also used in the treatment of non-allergic rhinitis in adults and children aged 12 years and over. The dose is 2 sprays into each nostril twice daily. In the treatment of **conjunctivitis**, azelastine is licensed in the UK for the treatment of seasonal allergic conjunctivitis in adults and children aged 4 years and over and for the treatment of perennial allergic conjunctivitis in adults and children aged 12 years and over. In the USA, it is licensed for the treatment of allergic conjunctivitis in adults and children aged 3 years and over. Regardless of the age and indication, a 0.05% solution is instilled into each eye twice daily; this may be increased to four times daily in severe conditions.

Azelastine hydrochloride has also been given by mouth.

◊ References.

1. Wober W, *et al*. Efficacy and tolerability of azelastine nasal spray in the treatment of allergic rhinitis: large scale experience in community practice. *Curr Med Res Opin* 1997; **13:** 617–26.
2. McNeely W, Wiseman LR. Intranasal azelastine: a review of its efficacy in the management of allergic rhinitis. *Drugs* 1998; **56:** 91–114.
3. Lenhard G, *et al.* Double-blind, randomised, placebo-controlled study of two concentrations of azelastine eye drops in seasonal allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin* 1997; **14:** 21–8.
4. Sabbah A, Marzetto M. Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children. *Curr Med Res Opin* 1998; **14:** 161–70.
5. Duarte C, *et al.* Treatment of severe seasonal rhinoconjunctivitis by a combination of azelastine nasal spray and eye drops: a double-blind, double-placebo study. *J Investig Allergol Clin Immunol* 2001; **11:** 34–40.
6. Canonica GW, *et al.* Topical azelastine in perennial allergic conjunctivitis. *Curr Med Res Opin* 2003; **19:** 321–9.
7. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy* 2007; **27:** 852–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alager; Allergodil; Brixia; Xanaes; ***Austral.:*** Azep; ***Austria:*** Allergodil; Allergospray; Lasticom; Oculastin; ***Belg.:*** Allergodil; Otrivine Anti-Allergie; ***Braz.:*** Azelast†; Rino-Azetin†; Rino-Lastin; ***Chile:*** Allergodil†; Az Ofteno; Brixia; ***Cz.:*** Allergodil; ***Denm.:*** Allergodil; ***Fin.:*** Lastin; ***Fr.:*** Alerdual; Allergodil; Prorhinite; ***Ger.:*** Allergodil; Loxin; Vividrin akut Azelastin; ***Gr.:*** Afluon; ***Hong Kong:*** Azep; ***Hung.:*** Allergodil; ***India:*** Azep; ***Irl.:*** Rhinolast; ***Israel:*** Optilast; Rhinolast; ***Ital.:*** Allergodil; Lasticom; ***Malaysia:*** Azep†; ***Mex.:*** Astelin; AZ Ofteno; ***Neth.:*** Allergodil; Oculastin; Otrivin neusallergie azelastine; ***Norw.:*** Azelvin; Lastin; ***NZ:*** Eyezep; ***Philipp.:*** Azelone; Azep; ***Pol.:*** Allergodil; ***Port.:*** Allergodil; Azep; Oculastin; ***Rus.:*** Allergodil (Аллергодил); ***S.Afr.:*** Rhinolast; ***Singapore:*** Azep†; ***Spain:*** Afluon; Corifina; ***Swed.:*** Azelvin; Lastin; ***Switz.:*** Allergodil; Oculastin; Otrivin rhume des foins; ***Thai.:*** Azep†; ***Turk.:*** Allergodil; ***UK:*** Aller-Eze; Optilast; Rhinolast; ***USA:*** Astelin; Optivar; ***Venez.:*** Alergot; Allergodil; AZ; Brixia.

Multi-ingredient: *India:* Duonase.

Bamipine *(BAN, rINN)*

Bamipiini; Bamipin; Bamipina; Bamipinum. *N*-Benzyl-*N*-(1-methyl-4-piperidyl)aniline.

Бамипин

$C_{19}H_{24}N_2 = 280.4.$

CAS — 4945-47-5.

ATC — D04AA15; R06AX01.

ATC Vet — QD04AA15; QR06AX01.

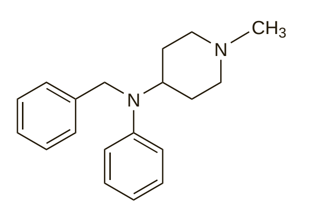

Profile

Bamipine is a sedating antihistamine (p.561) with pronounced sedative effects.

Bamipine and its salts are used mainly for the symptomatic relief of allergic conditions such as urticaria (p.565) and in pruritic skin disorders. Bamipine hydrochloride has been given by mouth. Bamipine, bamipine lactate, and bamipine salicylate have all been applied topically.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Soventol; ***Ger.:*** Soventol; ***Gr.:*** Soventol†; ***Neth.:*** Soventol; ***Pol.:*** Soventol.

Multi-ingredient: *India:* Multifungin H†; Multifungin†; Soventol†.

Bepotastine *(rINN)*

Bepotastina; Bépotastine; Bepotastinum; Betotastine. (+)-4-{[(S)-p-Chloro-α-2-pyridylbenzyl]oxy}-1-piperidinebutyric acid.

Бепотастин

$C_{21}H_{25}ClN_2O_3$ = 388.9.

CAS — 125602-71-3; 190786-43-7.

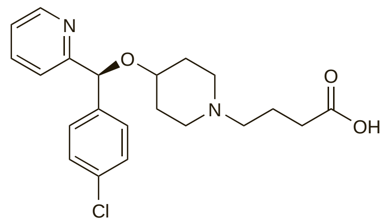

Bepotastine Besilate *(rINNM)*

Bépotastine, Bésilate de; Bepotastini Besilas; Besilato de bepotastina; Betotastine Besilate; TAU-284.

Бепотастина Безилат

$C_{21}H_{25}ClN_2O_3,C_6H_6O_3S$ = 547.1.

CAS — 190786-44-8.

Profile

Bepotastine is an antihistamine (p.561) used as the besilate in the treatment of allergic rhinitis. It is also used for the symptomatic relief of urticaria and pruritic skin disorders. The usual oral dose is 10 mg of bepotastine besilate twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Talion.

Bisulepin

4-[3-(Dimethylamino)propylidene]-4,9-dihydrothienol[2,3-b]benzo[e]thiepin.

$C_{17}H_{19}NS_2$ = 301.5.

CAS — 5802-61-9 (bisulepin); 1154-12-7 (bisulepin hydrochloride).

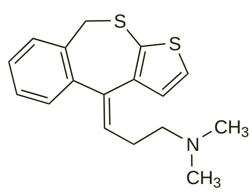

Profile

Bisulepin is given orally as an antihistamine; the hydrochloride salt is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dithiaden; ***Hung.:*** Dithiaden†.

Bromazine Hydrochloride *(BANM, rINNM)*

Bromazine, Chlorhydrate de; Bromazini Hydrochloridum; Bromodiphenhydramine Hydrochloride; Hidrocloruro de bromazina. 2-(4-Bromobenzhydryloxy)-NN-dimethylethylamine hydrochloride.

Бромазина Гидрохлорид

$C_{17}H_{20}BrNO,HCl$ = 370.7.

CAS — 118-23-0 (bromazine); 1808-12-4 (bromazine hydrochloride).
ATC — R06AA01.
ATC Vet — QR06AA01.

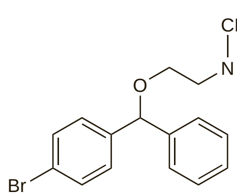

(bromazine)

Pharmacopoeias. In *US.*

USP 31 (Bromodiphenhydramine Hydrochloride). A white to pale buff-coloured, crystalline powder having no more than a faint odour. Soluble 1 in less than 1 of water, 1 in 2 of alcohol and of chloroform, 1 in 3500 of ether, and 1 in 31 of isopropyl alcohol; insoluble in petroleum spirit. Store in airtight containers.

Profile

Bromazine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p.561) with antimuscarinic and marked sedative actions. It is used in combination preparations for the symptomatic treatment of coughs and the common cold (p.564) in an oral dose of 12.5 to 25 mg every 4 to 6 hours. The recommended maximum dose in such preparations is 150 mg daily. Children over 6 years of age may be given 6.25 to 12.5 mg every 6 hours.

Preparations

USP 31: Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Bromodiphenhydramine Hydrochloride Elixir.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Ambenyl Cough Syrup; Amgenal Cough; Bromotuss with Codeine.

Brompheniramine Maleate

(BANM, rINNM)

Bromfeniramin Maleat; Bromfeniraminmaleat; Brómfeniramin-maleát; Bromfeniramin-maleinát; Bromfeniramino maleatas; Bromifeniramiinimaleaatti; Bromphéniramine, maléate de; Brompheniramini maleas; Maleato de bromfeniramina; Parabromdylamine Maleate. (±)-3-(4-Bromophenyl)-NN-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.

Бромфенирамина Малеат

$C_{16}H_{19}BrN_2,C_4H_4O_4$ = 435.3.

CAS — 86-22-6 (brompheniramine); 980-71-2 (brompheniramine maleate).
ATC — R06AB01.
ATC Vet — QR06AB01.

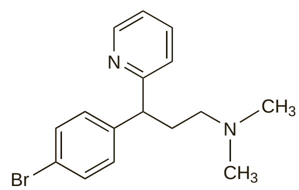

(brompheniramine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Brompheniramine Maleate). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Brompheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 5 of water, 1 in 15 of alcohol and of chloroform; slightly soluble in ether and in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Incompatibility. Brompheniramine maleate has been reported to be incompatible with some amidotrizoate, adipiodone, and iotalamate salts.

Dexbrompheniramine Maleate *(BANM, rINNM)*

Dexbromphéniramine, Maléate de; Dexbrompheniramini Maleas; Maleato de dexbromfeniramina.

Дексбромфенирамина Малеат

CAS — 2391-03-9.
ATC — R06AB06.
ATC Vet — QR06AB06.

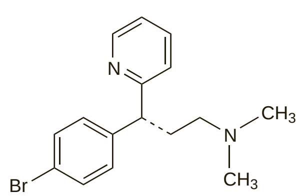

(dexbrompheniramine)

Pharmacopoeias. In *US.*

USP 31 (Dexbrompheniramine Maleate). A white, odourless, crystalline powder. It exists in two polymorphic forms, one melting between 106° and 107°, and the other between 112° and 113°; a mixture of the two forms may melt between 105° and 113°. Soluble 1 in 1.2 of water, 1 in 2.5 of alcohol, 1 in 2 of chloroform, and 1 in 3000 of ether. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers which contain dexbrompheniramine maleate with pseudoephedrine have resulted in crying, irritability, and poor sleep patterns in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Effects on the blood. A report[1] that agranulocytosis in a 34-year-old alcoholic man was possibly associated with brompheniramine therapy.

1. Hardin AS, Padilla F. Agranulocytosis during therapy with a brompheniramine-medication. *J Arkansas Med Soc* 1978; **75:** 206–8.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after use of antihistamines including brompheniramine or dexbrompheniramine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; **293:** 486–7 (brompheniramine maleate, chlorpheniramine maleate, and phenindamine tartrate).
2. Barone DA, Raniolo J. Facial dyskinesia from overdose of an antihistamine. *N Engl J Med* 1980; **303:** 107 (dexbrompheniramine maleate).

Withdrawal. Withdrawal symptoms have been reported[1] after stopping long-term therapy with brompheniramine maleate. A patient had been taking 48 mg almost every day for 20 years and developed tremor, nausea, depression, and apyrexial sweating within 48 hours of stopping treatment; symptoms resolved over the following weeks.

1. Kavanagh GM, *et al.* Withdrawal symptoms after discontinuation of long-acting brompheniramine maleate. *Br J Dermatol* 1994; **131:** 913–14.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Brompheniramine maleate appears to be well absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations are achieved within about 5 hours. An elimination half-life of about 25 hours has been reported. Unchanged drug and metabolites are excreted primarily in the urine.

◊ References.

1. Simons FER, *et al.* The pharmacokinetics and antihistaminic effects of brompheniramine. *J Allergy Clin Immunol* 1982; **70:** 458–64.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.

Uses and Administration

Brompheniramine maleate, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions.

Brompheniramine is a racemic mixture; dexbrompheniramine, the dextrorotatory isomer, has about twice the activity of brompheniramine by weight. Brompheniramine maleate and dexbrompheniramine maleate are used for the symptomatic relief of allergic conditions, mainly rhinitis (p.565) and conjunctivitis (p.564). They are common ingredients of compound preparations for the symptomatic treatment of coughs and the common cold (p.564). However, such preparations should be used with caution in children, and generally avoided in those under 2 years of age (see p.562). Brompheniramine tannate has been used similarly.

Brompheniramine maleate is given in usual oral doses of 4 to 8 mg three or four times daily. Children up to 3 years of age are given 0.4 to 1 mg/kg over 24 hours in four divided doses. Children aged 3 to 6 years are given 1 to 2 mg three or four times daily and those aged 6 to 12 years 2 to 4 mg three or four times daily.

Brompheniramine maleate has also been given by subcutaneous, intramuscular, or slow intravenous injection; the dose is usually 10 mg every 8 to 12 hours as necessary and the total parenteral dose should not exceed 40 mg in 24 hours.

The symbol † denotes a preparation no longer actively marketed

Dexbrompheniramine maleate is normally given as an ingredient of decongestant preparations containing pseudoephedrine. The dose of dexbrompheniramine maleate by mouth in these combinations is 2 mg up to four times daily. Children over 6 years can be given 1 mg up to four times daily.

Modified-release oral preparations of brompheniramine maleate or dexbrompheniramine maleate are available in some countries; dosage is specific to a particular formulation.

Preparations

BP 2008: Brompheniramine Tablets;
USP 31: Brompheniramine Maleate Elixir; Brompheniramine Maleate Injection; Brompheniramine Maleate Tablets; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Dimegan; ***Malaysia:*** Bomex; ***Singapore:*** Bomex†; ***Thai.:*** Babycold; Bomine; Dimetane; ***UK:*** Dimotane†; ***USA:*** Bidhist; Dimetane†; J-Tan; Lodrane 12; Lodrane 24; Oraminic II; P-Tex.

Multi-ingredient: ***Arg.:*** Factus; ***Austral.:*** Dimetapp; Dimetapp DM; ***Braz.:*** Bialerge; Decongex Plus; Decongex Plus Expectorante†; Dimetapp; Winter AP; ***Canad.:*** Dimetane Expectorant C; Dimetane Expectorant DC; Dimetapp Cold; Dimetapp DM Cough & Cold; Dimetapp Oral Infant Cold & Fever Drops; Dimetapp Oral Infant Drops; Dimetapp-C; Drixoral; Drixoral Day/Night; ***Chile:*** Disofrin†; ***Cz.:*** Disophrol; ***Fin.:*** Disofrol†; ***Fr.:*** Dimetane Expectorant Enfant†; Martigene†; ***Gr.:*** Dimetapp New†; ***Hong Kong:*** Brom-PP; Brom-Ramine Compound; Bromhexine Compound; Brompheneх; DF Multi-Symptom; Dimaxin†; Dimeta-2; Dimetapp; Drixoral; Eascold; ENT†; Eurotapp; Unihist; Vidatapp; Vidatapp Forte; ***Hung.:*** Disophrol†; ***Indon.:*** Alco Plus; Alco Plus DMP; Drixoral; ***Irl.:*** Dimotane Co; ***Malaysia:*** Drixoral†; Rinafort; ***Mex.:*** Afrinex; Cripofen; Dimetapp; ***NZ:*** Dimetapp; Dimetapp DM Cold & Cough; ***Philipp.:*** Dimerrin; Dimetapp; Hisdec; Nasatapp; Nostero; Penbrosol; PPB; Rhinodec; Rhinotapp; Snizee; Zeditapp; ***Pol.:*** Disophrol; ***Port.:*** Constipal; Ilvico N; ***S.Afr.:*** Dimetapp; Ilvico; ***Singapore:*** Dimetapp; Drixoral†; Rinafort; ***Spain:*** Disofrol; Ilvico; ***Swed.:*** Disofrol; ***Switz.:*** Disofrol; Rupton†; ***Thai.:*** Asiatapp; Bepeno; Bepeno-G; Bluco; Bromavon; Bromesep Elixir; Bromesep Expectorant; Bromped; Bromtussia; Bromtussia DC†; Brontus; Centapp; Daminate; Dimetapp; Meditapp; Meditapp Expectorant; MEXY; Minra†; Nartap; Nasorest†; Pharfed; Polamine; Polydine; Polydrop; Postap; Postap Expectorant; Rhinadine; Rhinophen-C†; Unihist; ***Turk.:*** Disophrol; ***UK:*** Dimotane Co; Dimotane Expectorant; Dimotane Plus†; ***USA:*** 12 Hour Antihistamine Nasal Decongestant; 12 Hour Cold; Accuhist; Accuhist DM Pediatric; Accuhist PDX; Alacol DM; Allent; Anaplex DM; Anaplex HD; Andehist DM†; Andehist†; Brofed; Bromadine-DM; Bromarest DX; Bromatan-DM; Bromatane DX; Bromfed; Bromfed-DM; Bromfed-PD; Bromfenex; Bromhist; Bromhist PDX; Bromhist-DM; Bromhist-NR; Bromphen DX Cough; Brompheniramine Cough; Brovex PD; C-Tan D; Carbodex DM; Coldec DM; Comtrex Acute Head Cold; CPB WC; Cytuss-HC NR; Dallergy DM; DEKA; Dexaphen-SA; Dimetane Decongestant†; Dimetapp; Dimetapp Cold & Fever; Dimetapp DM; Dimetapp Nighttime Flu; Disobrom; Disophrol; Dristan Allergy; Dristan Cold Maximum Strength Multi-symptom Formula; Drixomed; Drixoral; Drixoral Cold & Allergy; Drixoral Cold & Flu; Drixoral Plus; Drocon-CS; Endafed; Histacol DM; Histussin HC; Iofed; Lodrane; Lodrane 12D; Lodrane D; Lortuss DM; M-END WC; Maximum Strength Dristan Cold; Myphetane DX; Nalex AC; Neo DM; P-Hist DM; PBM Allergy; Pediahist DM; Q-Tapp DM; Respahist; Resperal-DM; Rondamine-DM; Rondec; Seradex-LA; Sildec-DM; Sinadrin Plus; Touro A & H; Touro Allergy; Tusdec-DM; Tusnel-HC; Tussall; ULTRAbrom; VaZol-D; Vazotab; Vazotan; Vazotuss HC; Zotex-PE; ***Venez.:*** Dimetapp; Ilvico; Metorfedrin.

Buclizine Hydrochloride *(BANM, USAN, rINNM)*

Buclizine, Chlorhydrate de; Buclizini Hydrochloridum; Buklizin Hidroklorür; Hidrocloruro de buclizina; NSC-25141; UCB-4445. (*RS*)1-(4-*tert*-Butylbenzyl)-4-(4-chlorobenzhydryl)piperazine dihydrochloride.

Буклизина Гидрохлорид

$C_{28}H_{33}ClN_2,2HCl = 505.9.$

CAS — 82-95-1 (buclizine); 129-74-8 (buclizine hydrochloride).

ATC — R06AE01.

ATC Vet — QR06AE01.

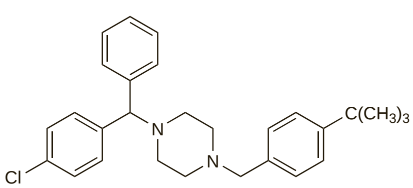

(buclizine)

Pharmacopoeias. In *Br.*

BP 2008 (Buclizine Hydrochloride). A white or slightly yellowish, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; sparingly soluble in chloroform and in propylene glycol.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Buclizine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative actions. It is used mainly for its antiemetic action, particularly in the prevention of motion sickness (p.564) and with analgesics in the treatment of migraine (p.616). In some countries it is given in the management of allergic conditions and in pruritic skin disorders (p.565). Buclizine has also been used in the treatment of vertigo (p.565) associated with disorders of the vestibular system, although its value in these conditions remains to be established.

To prevent motion sickness, buclizine hydrochloride is given at least 30 minutes before travelling in an oral dose of 25 or 50 mg, which may be repeated, if necessary, after 4 to 6 hours. The usual dose to alleviate nausea is 25 or 50 mg daily up to 100 mg daily in divided doses; in severe cases up to 150 mg daily has been given.

In the treatment of migraine, buclizine hydrochloride is given in usual doses of 12.5 mg at the start of an attack or when one is known to be imminent; children aged 10 to 14 years may be given 6.25 mg and older children the usual adult dose.

In pruritic skin disorders the usual dose of buclizine hydrochloride is 25 to 50 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Longifene; ***Braz.:*** Buclina; Postafen; ***Fr.:*** Aphilan; ***Hong Kong:*** Longifene†; ***India:*** Longifene; ***Malaysia:*** Buchzine†; Longifene†; Longimin†; ***Port.:*** Buclina; Postafeno†; ***S.Afr.:*** Longifene; ***Singapore:*** Longifene†; Panzimine†; ***Turk.:*** Longifene; ***USA:*** Bucladin-S Softab.

Multi-ingredient: ***Braz.:*** Apetibe†; Apetil; Buclamin†; Buclifen-Vit†; Buclimax; Bucliplex†; Carnabol; Complevit; Klizin; Nutri-Ped†; Nutrimaiz SM; Pepsivit†; Pondusvitam; Profol; Propan†; Vitaler†; ***Ger.:*** Migralave N†; ***Irl.:*** Migraleve; ***Israel:*** Migraleve; ***Philipp.:*** Appebon; Appebon with Iron; Appetason; Biotermin AS; Ferlette; Medifortan-AS; Pediafortan-AS; Propan; Propan with Iron; Regeron-E Plus; ***Port.:*** Migraleve; ***S.Afr.:*** Vomifene; ***Spain:*** Migraleve; ***Switz.:*** Migraleve; ***UK:*** Migraleve; ***Venez.:*** Dexapostafen.

Carbinoxamine Maleate *(BANM, rINNM)*

Carbinoxamine, Maléate de; Carbinoxamini Maleas; Karbinoksamin Maleat; Maleato de carbinoxamina. 2-[4-Chloro-α-(2-pyridyl)benzyloxy]-*NN*-dimethylethylamine hydrogen maleate.

Карбиноксамина Малеат

$C_{16}H_{19}ClN_2O,C_4H_4O_4 = 406.9.$

CAS — 486-16-8 (carbinoxamine); 3505-38-2 (carbinoxamine maleate).

ATC — R06AA08.

ATC Vet — QR06AA08.

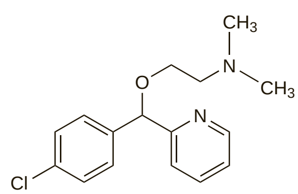

(carbinoxamine)

Pharmacopoeias. In *US.*

USP 31 (Carbinoxamine Maleate). A white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 1.5 of alcohol and of chloroform, and 1 in 8300 of ether. pH of a 1% solution in water is between 4.6 and 5.1. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Carbinoxamine maleate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and serotonin antagonist effects. Carbinoxamine maleate is used for the relief of allergic conditions such as rhinitis (p.565), and is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p.564).

Dose recommendations for carbinoxamine maleate may vary between preparations. Licensed US product information suggests a usual oral dose of carbinoxamine maleate in adults of 4 to 8 mg given 3 or 4 times daily. Children of 2 to 3 years of age may be given a dose of 2 mg three or four times daily, children aged 3 to 6 years given 2 to 4 mg three or four times daily, and those above 6 years given 4 to 6 mg three or four times daily. Lower doses, sometimes less than half these licensed in the US, may be used in other countries. Carbinoxamine polistirex has also been given by mouth.

Preparations

USP 31: Carbinoxamine Maleate Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Omega 100; ***Mon.:*** Allergefon; ***Thai.:*** Histin; Sinumine†; ***USA:*** Carboxine†; Histex CT; Histex I/E; Histex PD; Palgic; Pediatex.

Multi-ingredient: ***Arg.:*** Aseptobron C; Cobenzil Compuesto†; Omega 100 Expectorante†; Rondec Compositum†; Rondec†; Torfan H†; ***Austria:*** Rhinopront; ***Belg.:*** Rhinopront†; ***Braz.:*** Afebrin†; Gegrip†; Iodeto de Potassio Composto†; Naldecon; Naldecon Pediatrico; Nasaliv; Neolefrin; Neolefrin Baby; Resprin; ***Chile:*** Matinor; Rhinopront†; Rinofrim†; ***Cz.:*** Rhinopront†; Rhinotussal†; ***Ger.:*** Rhinopront†; Rhinotussal†; ***Gr.:*** Rhinopront-S†; Rhinopront†; Rondec; ***Hong Kong:*** Became; Coritussal; Metoplex; Rhinopront; ***Hung.:*** Rhinopront†; ***India:*** Clistin; ***Indon.:*** Kenantist; ***Israel:*** Rhinovis†; ***Malaysia:*** Became; Rhinopront†; ***Mex.:*** Lentostamin; Prindex; ***Singapore:*** Became; Rhinopront†; ***Spain:*** Rinomax; Rinoretard†; ***Switz.:*** Rhinopront†; Rhinotussal; ***Thai.:*** Rhinar; Rhinohist; Rhinopront†; Rondec-DM†; ***Turk.:*** Rhinopront; Rhinotussal; ***UAE:*** Fluzal†; ***USA:*** Andehist DM†; Andehist†; Aridex; Carbinoxamine Compound†; Carbiset; Carbodec; Carbodec DM; Carbodex DM; Carboxine-PSE; Coldec D; Cordron-D; Cordron-DM; Cydec DM†; Cydec†; Dacex-A; Decahist-DM†; DMax; Histex HC; Nacon; Norel LA; Palgic DS; Palgic-D; Pediatex-D; Pediatex-DM; Pseudo-Car DM; Rondec; Sildec-DM; Trituss-A; XiraHist DM; ***Venez.:*** Aurimel†; Resprin; Rhinopront†; Rondec†; Sondinal†.

Cetirizine Hydrochloride

(BANM, USAN, rINNM)

Cetirizin-dihidroklorid; Cetirizin-dihydrochlorid; Cetirizindihydroklorid; Cétirizine, Chlorhydrate de; Cétirizine, dichlorhydrate de; Cetirizini dihydrochloridum; Cetirizini Hydrochloridum; Cetirizino dihidrochloridas; Cetyryzyny dichlorowodorek; Hidrocloruro de cetirizina; P-071; Setiritsiinidihydrokloridi; Setirizin Hidroklorür; UCB-P071. The dihydrochloride of 2-[4-(4-chlorobenzhydryl)piperazin-1-yl]ethoxyacetic acid.

Цетиризина Гидрохлорид

$C_{21}H_{25}ClN_2O_3,2HCl = 461.8.$

CAS — 83881-51-0 (cetirizine); 83881-52-1 (cetirizine hydrochloride).

ATC — R06AE07.

ATC Vet — QR06AE07.

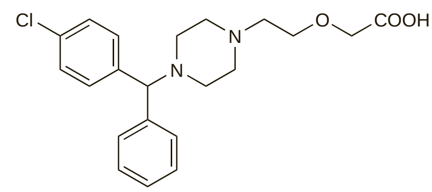

(cetirizine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cetirizine Dihydrochloride; Cetirizine Hydrochloride BP 2008). A white or almost white powder. Freely soluble in water; practically insoluble in acetone and in dichloromethane. A 5% solution in water has a pH of 1.2 to 1.8. Protect from light.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Reduced dosage is recommended for patients with hepatic or renal impairment (see under Uses and Administration, below).

Arrhythmias. The ECG effects of cetirizine were studied[1] in normal subjects; doses of up to six times the usual recommended dose did not prolong the QT interval. Additionally, the FDA[2] in the USA and representatives of the manufacturers[3] in Belgium did not find any association between cetirizine and the development of ventricular arrhythmias. However, there has been a subsequent report[4] of torsade de pointes after overdosage with cetirizine in a hypokalaemic patient undergoing haemodialysis for chronic renal failure. See also p.562.

1. Sale ME, *et al.* The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther* 1994; **56:** 295–301.
2. Himmel MH, *et al.* Dangers of non-sedating antihistamines. *Lancet* 1997; **350:** 69.
3. Coulie P, *et al.* Non-sedating antihistamines and cardiac arrhythmias. *Lancet* 1998; **351:** 451.
4. Renard S, *et al.* Torsades de pointes induites par surdosage en cétirizine. *Arch Mal Coeur Vaiss* 2005; **98:** 157–61.

Effects on the liver. Life-threatening hepatitis developed in a 23-year-old man who had been taking cetirizine long-term for atopic dermatitis.[1] He recovered after treatment with prednisolone.

There has been a report of recurrent acute hepatitis associated with the short-term use of cetirizine for seasonal allergic rhinitis in a 26-year-old man.[2]

1. Watanabe M, *et al.* Severe hepatitis in a patient taking cetirizine. *Ann Intern Med* 2001; **135:** 142–3.
2. Pompili M, *et al.* Recurrent acute hepatitis associated with use of cetirizine. *Ann Pharmacother* 2004; **38:** 1844–7.

Hypersensitivity. Hypersensitivity reactions manifesting as urticaria[1,2] and fixed drug eruptions[3] have been reported with cetirizine.

1. Karamfilov T, *et al.* Cetirizine-induced urticarial reaction. *Br J Dermatol* 1999; **140:** 979–80.
2. Calista D, *et al.* Urticaria induced by cetirizine. *Br J Dermatol* 2001; **144:** 196.
3. Inamadar AC, *et al.* Multiple fixed drug eruptions due to cetirizine. *Br J Dermatol* 2002; **147:** 1025–6.

Sedation. For discussion of the sedative effects of antihistamines see p.562.

Interactions

As for the non-sedating antihistamines in general, p.563. However, some interactions are less likely with cetirizine than with non-sedating antihistamines such as astemizole and terfenadine, since cetirizine appears to have low hepatic metabolism and little arrhythmogenic potential (see Arrhythmias, above).

Anticoagulants. For a report of an interaction between cetirizine and *acenocoumarol*, see under Interactions in Warfarin, p.1429.

Pharmacokinetics

Cetirizine is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being attained within about an hour. Food delays the time to peak plasma concentrations but does not decrease the amount of drug absorbed. Cetirizine is highly bound to plasma proteins and has an elimination half-life of about 10 hours. It has been detected in breast milk. Cetirizine is excreted primarily in the urine mainly as unchanged drug. It does not appear to cross the blood-brain barrier to a significant extent.

◊ References.

1. Awni WM, *et al.* Effect of haemodialysis on the pharmacokinetics of cetirizine. *Eur J Clin Pharmacol* 1990; **38:** 67–9.
2. Desager JP, *et al.* A pharmacokinetic evaluation of the second-generation H -receptor antagonist cetirizine in very young children. *Clin Pharmacol Ther* 1993; **53:** 431–5.
3. Pitsiu M, *et al.* Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. *Br J Clin Pharmacol* 2004; **57:** 402–11.
4. Hussein Z, *et al.* Retrospective population pharmacokinetics of levocetirizine in atopic children receiving cetirizine: the ETAC study. *Br J Clin Pharmacol* 2005; **59:** 28–37.

Uses and Administration

Cetirizine hydrochloride, a piperazine derivative and metabolite of hydroxyzine (p.581), is described as a long-acting non-sedating antihistamine with some mast-cell stabilising activity. It appears to have a low potential for drowsiness in usual doses and to be virtually free of antimuscarinic activity. It is used for the symptomatic relief of allergic conditions including rhinitis (p.565) and chronic urticaria (p.565).

In adults and children aged 6 years and over, cetirizine hydrochloride is given in an oral dose of 10 mg once daily or 5 mg twice daily. Children aged 2 to 5 years may be given cetirizine 5 mg once daily or 2.5 mg twice daily. In the USA, children aged 6 months to 2 years may be given a dose of 2.5 mg once daily, increased to a maximum of 2.5 mg twice daily in those aged 12 months and over, for the treatment of perennial allergic rhinitis and chronic urticaria.

It is also used with a decongestant such as pseudoephedrine hydrochloride.

Dosage of cetirizine should be reduced in patients with hepatic or renal impairment, see below.

◊ References.

1. Curran MP, *et al.* Cetirizine: a review of its use in allergic disorders. *Drugs* 2004; **64:** 523–61.

Administration in hepatic or renal impairment. In patients with hepatic impairment, US licensed product information recommends that the dosage of cetirizine may need to be reduced to half the usual oral daily dose (see above). Similarly in patients with renal impairment, both the UK and US product information recommends a dosage reduction to half the usual daily dose.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cabal; Cetidac; Cetizine; Cetriler; Salvalerg; Stopaler; Zyrtec; ***Austral.:*** Alzene; Zyrtec; ***Austria:*** Alerid; Cetiderm; Cetirhexal; Cetiristad; Cetyrol†; ratioAllerg; Reactine; Rigix; Tirizin; Virlix; Zirtek†; Zyrtec; ***Belg.:*** Histimed; Reactine; Zyrtec; ***Braz.:*** Aletir; Cetihexal†; Cetrizin; Zetalerg†; Zetir; Zinetrin; Zyrtec; ***Canad.:*** Allergy Relief; Reactine; ***Chile:*** Alertop; Coolips; Findaler; Histalen; Histax; Remitex; Rigotax; Sanaler; Sixacina; Zyrtec; ***Cz.:*** Alerid; Analergin; Cerex; Letizen; Parlazin; Reactine; Virlix†; Zodac; Zyrtec; ***Denm.:*** Alnok; Asytec; Benaday; Cidron; Gardex; Virlix†; Zyrtec; ***Fin.:*** Alzyr; Cidron†; Gardex; Heinix; Histec; Senirex; Siterin; Zyrtec; ***Fr.:*** Humex Rhinite Allergique†; Reactine; Virlix; Zyrtec; ***Ger.:*** Alerid†; Cetalerg†; Ceterifug†; Ceti-Puren; Ceti†; Cetiderm; Cetidura†; Cetil; CetiLich; Cetirigamma; Cetirlan†; Reactine; Zetir; Zyrtec; ***Gr.:*** Agelmin; Alenstran; Alergoxal; Arzedyn; Bebexin; Blezamont; Cetialfa; Cetiram; Cetirgen; Ceziren†; Cirizine; Dermizin; Enahimine; Gentiran; Habitek; Hamiltosin; Histafren; Kilsol; Lambeta; Ralizon; Remezine; Rezerc; Spatanil; Tasker; Telarix; Vitinelin; Zeda; Zepholin; Ziptek; Zirtek†; Znupril; ***Hong Kong:*** Adezio; Cetihis; Cetirin; Cety; Histacet; Histazine; Marizine; Rhinil; Ryvel; Simtec; Vick-Zyrt; Zertine; Zicet; Zyrtec; ***Hung.:*** Alerid; Cetigen; Cetrin; Cetripharm; Merzin; Parlazin; Zyrtec; ***India:*** Alerid; Cetcip; Ceticad; Cetriwal; Cetrizet; Cetrizine; CTZ; ELG Nil; LGNil; Rinitrin; Zyrtec; ***Indon.:*** Betarhin; Cerini; Cetrixal; Cetryn; Cetymin; Estin; Falergi; Histrine; Incidal-OD; Ozen; Risina; Rydian; Ryvel; Ryzen; Ryzo; Tiriz; Zenriz; ***Irl.:*** Cetrine; Histek; Zirpine; Zirtek; Zynor; ***Israel:*** Histazine; Zyllergy; ***Ital.:*** Formistin; Virlix†; Zirtec; ***Jpn:*** Zyrtec; ***Malaysia:*** Adezio; Ceritec; Simtec; Zicet; Zyrtec; ***Mex.:*** Apoliz; Cethexal; Kenicet; Reactine; Trizinet; Virlix; Zyrtec; ***Neth.:*** Reactine; Revalintabs; Zyrtec; ***Norw.:*** Acura; Reactine; Virlix†; Zyrtec; ***NZ:*** Razene; Zyrtec; ***Philipp.:*** Brellercet; Cet-10; Cetimin; Prixlae; Unizef; Virlix; Zinex; Zyrrigin; Zyrtec; ***Pol.:*** Acer; Alermed; Alerzina; Allertec; Amertil; Ceratio; CetAlergin; Cetrivax; Cetrizen; Cetyryzyna; Letizen; Virlix; Zyrtec; Zyx; ***Port.:*** Cetix; Cinaz; Rinoliber; Virlix; Zyrtec; ***Rus.:*** Alerza (Алерза); Allertec (Аллертек); Analergin (Аналергин); Cetirinax (Цетиринак); Cetrine (Цетрин); Letizen (Летизен); Parlazin (Парлазин); Zetrinal (Зетринал); Zodac (Зодак); Zyncet (Зинцет); Zyrtec (Зиртек); ***S.Afr.:*** Allecet; Allermine; Texa; Zetop; Zyrtec; ***Singapore:*** Adezio; Agelmin†; Allertec†; Alzytec; Cetihis; Cetrine; Rhizin†; Sancotec; Terizin; Zyrtec; ***Spain:*** Alercina; Alerlisin; Coulergin; Reactine Plus; Reactine†; Virdox†; Virlix; Voltric†; Zyrtec; ***Swed.:*** Acura; Alerid; Cidron; Reactine; Zyrlex; ***Switz.:*** Cerzine; Cet eco; Cetallerg; Cetrine; Histatec; Tobin; Zyrtec; ***Thai.:*** Allercet; Cetihis; Cetrimed; Cetrine; Cetrizet; Cetrizin; Ceza; Cistamine; Cyzine; Fatec; Histica; Incidal-OD†; Rentrex; Setin; Sutac; Terzine; Tizine; Triz; Unicet; Zensil; Zermed; Zertine; Zittec; Zymed; Zyrac; Zyrazine; Zyrcon; Zyrex; Zyrtec; ***Turk.:*** Allerset; Cetryn; Hitrizin; Ressital; Setiral; Virlix; Yenizin; Zyrtec; ***UAE:*** Cetralon; ***UK:*** AllerTek; Benadryl Allergy Oral Solution; Benadryl One A Day; Cetirocol†; Hayfever & Allergy Relief; Hayfever Relief; Piriteze; Pollenshield; Zirtek; ***USA:*** Zyrtec; ***Venez.:*** Celay; Cetirex; Cetirivax; Cetral; Cetrine†; Talzic; Virlix†; Zyrtec.

Multi-ingredient: ***Arg.:*** Cabal-D; Cetriler D; Zyrtec-D; ***Austria:*** Cirrus; ***Belg.:*** Cirrus; Reactine Pseudoephedrine; ***Braz.:*** Zyrtec-D; ***Canad.:*** Reactine Allergy & Sinus; ***Chile:*** Alertop-D; Findaler-D; Histalen D; Remitex D; Rigotax-D; Sanaler-D; Zyrtec-D†; ***Cz.:*** Pronose†; ***Fin.:*** Cirrus; ***Fr.:*** Actifed-duo; Humex Rhinite Allergique; ***Ger.:*** Reactine duo; Zyrtec Duo†; ***Hong Kong:*** Cirrus; Zyrtec-D; ***Hung.:*** Zyrtec-D; ***India:*** Alerid Cold; Alerid D; Amcold; Cheston Cold; ***Indon.:*** Cirrus; ***Ital.:*** Naristar; Pronose†; Reactine; ***Malaysia:*** Cirrus; Zyrtec-D; ***Mex.:*** Virlix-D; Zyrtec-D; ***NZ:*** Zyrtec Decongestant; ***Pol.:*** Cirrus; Zyrtec D; ***Port.:*** Cirrus; ***Singapore:*** Cirrus†; ***Spain:*** Naristar†; Stopcold; Virlix Plus; ***Thai.:*** Zyrtec-D; ***Turk.:*** Cirrus; ***USA:*** Zyrtec-D; ***Venez.:*** Cetirivax D; Zyrtec-D.

Chlorcyclizine Hydrochloride *(BANM, rINNM)*

Chlorciklizino hidrochloridas; Chlorcyclizine, chlorhydrate de; Chlorcyclizini hydrochloridum; Chlorcyclizinium Chloride; Chlorcyklizin-hydrochlorid; Hidrocloruro de clorciclizina; Kloorisyklitsiinihydrokloridi; Klórciklizin-hidroklorid; Klorcyklizinhydroklorid. 1-(4-Chlorobenzhydryl)-4-methylpiperazine hydrochloride.

Хлорциклизина Гидрохлорид

$C_{18}H_{21}ClN_2,HCl = 337.3.$

CAS — 82-93-9 (chlorcyclizine); 1620-21-9 (chlorcyclizine hydrochloride).

ATC — R06AE04.

ATC Vet — QR06AE04.

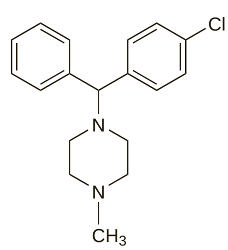

(chlorcyclizine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Chlorcyclizine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.0. Protect from light.

Profile

Chlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p.561). It has been given orally for the symptomatic relief of hypersensitivity reactions; it has also been used as an antiemetic. It has been used in topical preparations, although as with other antihistamines, there is a risk of sensitisation.

Chlorcyclizine dibunate (naftoclizine) has been used as a cough suppressant similarly to sodium dibunate (p.1573).

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Trihistan†; ***Norw.:*** Trihistan†.

Multi-ingredient: ***Fin.:*** Anervan; ***Israel:*** Temigran; ***Neth.:*** Primatour; ***Norw.:*** Anervan; ***Spain:*** Diminex Antitusigeno; ***Swed.:*** Anervan; Exolyt.

Chloropyramine Hydrochloride *(BANM, rINNM)*

Chloropyramine, Chlorhydrate de; Chloropyramini Hydrochloridum; Halopyramine Hydrochloride; Hidrocloruro de cloropiramina. *N*-(4-Chlorobenzyl)-*N′N′*-dimethyl-*N*-(2-pyridyl)ethylenediamine hydrochloride.

Хлоропирамина Гидрохлорид

$C_{16}H_{20}ClN_3,HCl = 326.3.$

CAS — 59-32-5 (chloropyramine); 6170-42-9 (chloropyramine hydrochloride).

ATC — D04AA09; R06AC03.

ATC Vet — QD04AA09; QR06AC03.

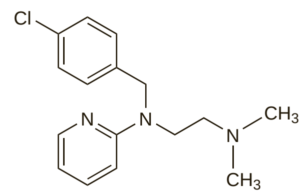

(chloropyramine)

Profile

Chloropyramine hydrochloride, an ethylenediamine derivative, is an antihistamine (p.561). It has been given orally and by injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Hung.: Suprastin; ***Mex.:*** Avapena; ***Rus.:*** Suprastin (Супрастин).

Chlorphenamine Maleate

(BANM, rINNM)

Chlorfenamin-maleinát; Chlorfenamino maleatas; Chlorofenaminy maleinian; Chlorphénamine, maléate de; Chlorphenamini maleas; Chlorpheniramine Maleate; Chlorprophenpyridamine Maleate; Kloorifenamiinimaleaatti; Klorfenaminmaleat; Klórfenamin-maleát; Maleato de clorfenamina. (±)-3-(4-Chlorophenyl)-*NN*-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.

Хлорфенамина Малеат

$C_{16}H_{19}ClN_2,C_4H_4O_4 = 390.9.$

CAS — 132-22-9 (chlorphenamine); 113-92-8 (chlorphenamine maleate).

ATC — R06AB04.

ATC Vet — QR06AB04.

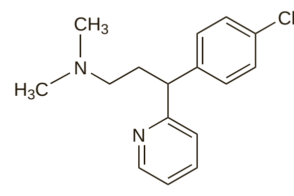

(chlorphenamine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Chlorphenamine Maleate). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 31 (Chlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 4 of water and 1 in 10 of alcohol and of chloroform; slightly soluble in ether and in benzene. Its solutions in water have a pH between 4 and 5. Store in airtight containers. Protect from light.

Incompatibility. Chlorphenamine maleate has been reported to be incompatible with calcium chloride, kanamycin sulfate, noradrenaline acid tartrate, pentobarbital sodium, and meglumine adipiodone.

Dexchlorpheniramine Maleate *(BANM, rINNM)*

Dekschlorfeniramino maleatas; Dekskloorifeniramiinimaleaatti; Dexchlorfeniramin-maleinát; Dexchlorphenamine Maleate; Dexchlorphéniramine, Maléate de; Dexchlorpheniramini maleas; Dexklorfeniraminmaleat; Dexklórfeniramin-maleát; Maleato de dexclorfeniramina.

Дексхлорфенирамина Малеат

CAS — 25523-97-1 (dexchlorpheniramine); 2438-32-6 (dexchlorpheniramine maleate).
ATC — R06AB02.
ATC Vet — QR06AB02.

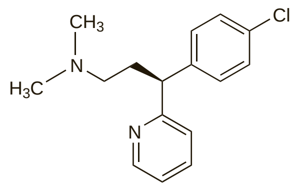

(dexchlorpheniramine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Dexchlorpheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 31 (Dexchlorpheniramine Maleate). A white, odourless, crystalline powder. Soluble 1 in 1.1 of water, 1 in 2 of alcohol, 1 in 1.7 of chloroform, and 1 in 2500 of ether; slightly soluble in benzene. pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Exfoliative dermatitis may develop. Injections may be irritant and cause transient hypotension or stimulation of the CNS.

Effects on the blood. There are several old and isolated reports of blood dyscrasias after use of chlorphenamine maleate; these include agranulocytosis,[1,2] thrombocytopenia,[3] pancytopenia,[4] and aplastic anaemia.[5] Haemolytic anaemia has occurred after use of dexchlorpheniramine maleate.[6] The association with antihistamine use has been questioned in some of these cases.[7]

1. Shenfield G, Spry CJF. Unusual cause of agranulocytosis. *BMJ* 1968; **ii:** 52–3.
2. Hardin AS. Chlorpheniramine and agranulocytosis. *Ann Intern Med* 1988; **108:** 770.
3. Eisner EV, *et al.* Chlorpheniramine-dependent thrombocytopenia. *JAMA* 1975; **231:** 735–6.
4. Deringer PM, Maniatis A. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; **i:** 432.
5. Kanoh T, *et al.* Aplastic anaemia after prolonged treatment with chlorpheniramine. *Lancet* 1977; **i:** 546–7.
6. Duran-Suarez JR, *et al.* The I antigen as an immune complex receptor in a case of haemolytic anaemia induced by an antihistaminic agent. *Br J Haematol* 1981; **49:** 153–4.
7. Spry CJF. Chlorpheniramine-induced bone-marrow suppression. *Lancet* 1976; **i:** 545.

Effects on the senses. Chlorphenamine has been reported to affect the senses of smell and taste.[1]

1. Schiffman SS. Taste and smell in disease. *N Engl J Med* 1983; **308:** 1275–9.

Extrapyramidal disorders. Facial dyskinesias have been reported[1,2] after oral doses of chlorphenamine maleate.

1. Thach BT, *et al.* Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. *N Engl J Med* 1975; **293:** 486–7.
2. Davis WA. Dyskinesia associated with chronic antihistamine use. *N Engl J Med* 1976; **294:** 113.

Interactions

As for the sedating antihistamines in general, p.563.

Antiepileptics. For a report of the effect of chlorphenamine on *phenytoin*, see p.499.

Pharmacokinetics

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide interindividual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS.

Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

◊ References.

1. Rumore MM. Clinical pharmacokinetics of chlorpheniramine. *Drug Intell Clin Pharm* 1984; **18:** 701–7.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
3. Yasuda SU, *et al.* The roles of CYP2D6 and stereoselectivity in the clinical pharmacokinetics of chlorpheniramine. *Br J Clin Pharmacol* 2002; **53:** 519–25.

Uses and Administration

Chlorphenamine maleate, an alkylamine derivative, is a sedating antihistamine that causes a moderate degree of sedation; it also has antimuscarinic activity.

Chlorphenamine is a racemic mixture; the dextrorotatory isomer, dexchlorpheniramine, has about twice the activity of chlorphenamine by weight.

Chlorphenamine maleate and dexchlorpheniramine maleate are used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565), and conjunctivitis (p.564), and in pruritic skin disorders (p.565). They are common ingredients of compound preparations for symptomatic treatment of coughs and the common cold (p.564). However, such preparations should be used with caution in children, and generally avoided in those under 2 years of age (see p.562). Chlorphenamine may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p.563).

Chlorphenamine maleate is given in oral doses of 4 mg every 4 to 6 hours up to a maximum of 24 mg daily. Doses for children, according to age, are: 1 to 2 years, 1 mg twice daily; 2 to 5 years, 1 mg every 4 to 6 hours (maximum 6 mg daily); 6 to 12 years, 2 mg every 4 to 6 hours (maximum 12 mg daily). Although not licensed in the UK, the *BNFC* suggests that children aged 1 month and over may be given 1 mg twice daily.

Chlorphenamine maleate may be given by intramuscular, by subcutaneous, or by slow intravenous injection over a period of 1 minute. The usual dose is 10 to 20 mg and the total dose given by these routes in 24 hours should not normally exceed 40 mg. For children, doses of 87.5 micrograms/kg subcutaneously four times daily have been suggested. The following parenteral doses may also be used in children: the usual dose in those aged 1 month to 1 year is 250 micrograms/kg; those aged 1 to 5 years may be given a dose of 2.5 to 5 mg and those aged 6 to 12 years, 5 to 10 mg. Alternatively, children and adolescents aged 1 to 18 years may be given a dose of 200 micrograms/kg. The *BNFC* suggests that doses for children may be repeated if necessary up to 4 times in 24 hours.

Dexchlorpheniramine maleate is given in oral doses of 2 mg every 4 to 6 hours up to a maximum of 12 mg daily. Children aged 2 to 5 years may be given 0.5 mg every 4 to 6 hours (maximum 3 mg daily), and those aged 6 to 12 years, 1 mg every 4 to 6 hours (maximum 6 mg daily).

Modified-release oral preparations of chlorphenamine maleate or dexchlorpheniramine maleate are available in some countries; dosage is specific to a particular formulation.

Dexchlorpheniramine maleate has been applied topically in some countries, although as with other antihistamines there is a risk of sensitisation. Chlorphenamine polistirex (a sulfonated diethenylbenzene-ethenylbenzene copolymer complex), chlorphenamine tannate, and dexchlorpheniramine tannate are given orally and are used similarly to the maleate.

Malaria. Chlorphenamine may be tried in patients with malaria who have chloroquine-induced pruritus (see Effects on the Skin, p.600), but additionally it has been shown to have some promise as an adjunct in the treatment of chloroquine-resistant malaria itself. Early studies indicated that chlorphenamine was only one of a number of drugs that reversed chloroquine resistance *in vitro* in isolates of *Plasmodium falciparum*. Later clinical studies in children in Nigeria showed enhanced efficacy when chlorphenamine was given with chloroquine.[1-5] The overall management of malaria is discussed on p.594.

1. Sowunmi A, *et al.* Enhanced efficacy of chloroquine-chlorpheniramine combination in acute uncomplicated falciparum malaria in children. *Trans R Soc Trop Med Hyg* 1997; **91:** 63–7.
2. Sowunmi A, Oduola AMJ. Comparative efficacy of chloroquine/chlorpheniramine combination and mefloquine for the treatment of chloroquine-resistant Plasmodium falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1997; **91:** 689–93.
3. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and pyrimethamine/sulfadoxine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; **92:** 77–81.
4. Sowunmi A, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine and halofantrine in acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1998; **92:** 441–5.
5. Okonkwo CA, *et al.* Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. *Trans R Soc Trop Med Hyg* 1999; **93:** 306–11.

Preparations

BP 2008: Chlorphenamine Injection; Chlorphenamine Oral Solution; Chlorphenamine Tablets;
USP 31: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Chlorpheniramine Maleate Extended-release Capsules; Chlorpheniramine Maleate Injection; Chlorpheniramine Maleate Syrup; Chlorpheniramine Maleate Tablets; Dexchlorpheniramine Maleate Syrup; Dexchlorpheniramine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afeme; Alergidryl†; Alergitrat; Isomerine†; Qura Plus; ***Austral.:*** Polaramine; ***Austria:*** Polaramin; ***Belg.:*** Polaramine†; ***Braz.:*** Alergonil; Alergovalle†; Alergyo; Alermine†; Deflux†; Dexclor†; Dexlerg; Dexmin†; Expectamin F; Histamin; Hystin; Polamin†; Polaramine; Polaren; Polaryn; ***Canad.:*** Chlor-Tripolon; Novo-Pheniram; ***Chile:*** Asafen Nueva Formula†; Clorprimeton; Nipolen; Prodel; Scadan; ***Denm.:*** Polaramin; ***Fr.:*** Polaramine; ***Ger.:*** Polaronil; ***Gr.:*** Istamex; Polaramine†; ***Hong Kong:*** Allermin; Apomin; Chlorpyrimine; Dapriton; Kenyamine; Medifen†; Pirimat; Piriton†; Polaramine; Rhiniramine; Sprinsol†; Synchloramin; Uni-Ramine; ***India:*** Cofton; ***Indon.:*** Chlorphenon; Cohistan; CTM; Orphen; Pehachlor; Polamec; Polaramine; Polarist; Polofar; ***Irl.:*** Piriton; ***Israel:*** Ahiston; Anaphyl†; ***Ital.:*** Polaramin; Trimeton; ***Malaysia:*** Chloramine†; Chlormine; Chlorpyrimine; D-Antihist†; Dex-Antihist†; Dexchloramine; Polamine†; Polaramine; Somin; ***Mex.:*** Alerdil; Antadex-H; Blendox; Cloro-Trimeton; Cronal; Docsi; Hierbal; Histadryl; Polaramine†; ***Neth.:*** Polaramine; ***Norw.:*** Phenamin; Polaramin; ***NZ:*** Histafen; Polaramine; ***Philipp.:*** Antamin; Barominic; Chlor-Trimeton; Valemine; Virgomine; ***Port.:*** Trenelone; ***S.Afr.:*** Allergex; Chlor-Trimeton†; Chlorhist†; Polaramine†; Rhineton; ***Singapore:*** Allerphen†; Chloramine; Chlorpyrimine; Dexchloramine; Dextramine; Piriton; Polaramine; Rhiniramine; Somin; ***Spain:*** Antihistaminico; Polaramine; ***Swed.:*** Polaramin; ***Switz.:*** Polaramine; ***Thai.:*** Allergin†; Chlorleate; Chlorpheno; Chlorpyrimine; Cohistan; Histatab; Histatapp; Icolid Plus; Kloramin; Nasamine†; Piriton†; ***UAE:*** Chlorohistol; ***UK:*** Allercalm; Allergy Relief; Allerief; Calimal; Hayleve; Piriton; Pollenase Antihistamine; ***USA:*** Aller-Chlor; Allergy; Allergy Relief; Chlo-Amine; Chlor-Pro; Chlor-Trimeton; ChlorTan; Ed-Chlor-Tan; Efidac 24 Chlorpheniramine; PediaCare Allergy Formula; Pediatan; Pediox-S; QDALL AR; TanaHist PD; Teldrin; ***Venez.:*** Clorotrimeton; Inquiramin†; Liramin.

Multi-ingredient: numerous preparations are listed in Part 3.

Chlorphenoxamine Hydrochloride *(BANM, rINNM)*

Chlorphénoxamine, Chlorhydrate de; Chlorphenoxamini Hydrochloridum; Hidrocloruro de clorfenoxamina; Klorfenoksamin Hidroklorür. 2-(4-Chloro-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

Хлорфеноксамина Гидрохлорид

$C_{18}H_{22}ClNO,HCl = 340.3.$

CAS — 77-38-3 (chlorphenoxamine); 562-09-4 (chlorphenoxamine hydrochloride).
ATC — D04AA34; R06AA06.
ATC Vet — QD04AA34; QR06AA06.

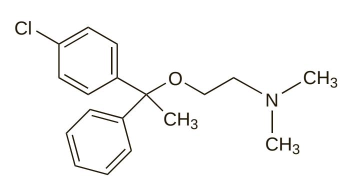

(chlorphenoxamine)

Profile

Chlorphenoxamine, a congener of diphenhydramine (p.577), has antimuscarinic and antihistaminic properties. It has been used in nausea, vomiting, and vertigo, and was formerly used in the symptomatic treatment of parkinsonism. Chlorphenoxamine has also been used in hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Systral; ***Hong Kong:*** Systral†; ***Indon.:*** Systral; ***Philipp.:*** Systral; ***Port.:*** Systral; ***Thai.:*** Systral; ***Turk.:*** Sistral; Systral.

Multi-ingredient: ***Austria:*** Spirbon; ***Ger.:*** Systral C†; ***S.Afr.:*** Analgen-SA†.

Cinnarizine *(BAN, USAN, rINN)*

Cinarizin; Cinarizina; Cinarizinas; Cinnarizin; Cinnarizinum; Cynaryzyna; 516-MD; R-516; R-1575; Sinarizin; Sinnaritsiini. 1-Benzhydryl-4-cinnamylpiperazine; (*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

Циннаризин

$C_{26}H_{28}N_2$ = 368.5.

CAS — 298-57-7.

ATC — N07CA02.

ATC Vet — QN07CA02.

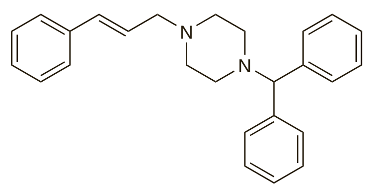

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cinnarizine). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

There have been rare reports of extrapyramidal symptoms after taking cinnarizine, sometimes associated with depressive feelings.

High doses of cinnarizine should be used with caution in patients with hypotension because of the possibility of decreasing blood pressure further.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of cinnarizine, see Flunarizine, p.580.

Hypersensitivity. Immunologically-defined lichen planus pemphigoides has been reported[1] in a 72-year-old woman taking cinnarizine. Lesions began to clear when treatment was stopped but challenge with cinnarizine provoked severe itching and reactivation of pigmented lesions. Another case[2] has also been described.

1. Miyagawa S, *et al.* Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; **112:** 607–13.
2. Ramallal M, *et al.* Lichenoid eruption associated with cinnarizine use. *Pharm World Sci* 2002; **24:** 215–16.

Porphyria. Cinnarizine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Tinnitus. The Spanish System of Pharmacovigilance had received reports[1] of tinnitus associated with calcium-channel blockers; some of the reports, including the one relating to cinnarizine, were in patients also receiving other ototoxic drugs. WHO was said to have additional reports of tinnitus associated with calcium-channel blockers including cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Weight gain. There has been a report[1] of weight gain in 4 patients who had taken cinnarizine for 1 to 2 years; in all cases the weight gain was associated with increased appetite.

1. Navarro-Badenes J, *et al.* Weight-gain associated with cinnarizine. *Ann Pharmacother* 1992; **26:** 928–30.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Cinnarizine is absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. It undergoes metabolism and has a half-life of 3 to 6 hours. Cinnarizine is excreted in the faeces mainly as unchanged drug, and in the urine predominantly as metabolites.

Uses and Administration

Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p.565) and for the prevention and treatment of motion sickness (p.564). It is also used in the management of various peripheral and cerebral vascular disorders.

In the UK, the usual oral dose for vertigo and vestibular disorders is 30 mg three times daily. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. Children aged 5 to 12 years are given half the adult dose for both indications. In other European countries, a dose of 75 mg once or twice daily has been given for vertigo and vestibular disorders. Doses of 75 mg have also been given 1 to 3 times daily for cerebrovascular disorders and 2 or 3 times daily for peripheral vascular disorders.

◊ References.

1. Shupak A, *et al.* Cinnarizine in the prophylaxis of seasickness: laboratory vestibular evaluation and sea study. *Clin Pharmacol Ther* 1994; **55:** 670–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dismaren; Fabracin; Folcodal; Iroplex†; Natropas; Stugeron; ***Austria:*** Cinnabene; Pericephal; Stutgeron; ***Belg.:*** Stugeron; ***Braz.:*** Antigeron; Cinaran; Cinarivert†; Cinarix†; Cinazin†; Cinazon; Civertim; Cronogeron; Fluxon; Laberitin†; Labigeron; Nerizina†; Stugerina†; Stugeron; Vertigeron; Verzum; Vessel†; ***Chile:*** Cinergil; Siridone; Stugeron; ***Cz.:*** Cinedil†; Cinnabene; Stugeron; ***Denm.:*** Sepan; ***Gr.:*** Derozin; Stugeron; ***Hong Kong:*** Celenid†; Medozine; Stugeron; ***Hung.:*** Stugeron; ***India:*** Avidazine; Cintigo; Diziron; Stugeron; Vertiron; ***Indon.:*** Merron; Nariz; Perifas; Stugeron; Vertizine; ***Irl.:*** Stugeron; ***Israel:*** Stunarone; ***Ital.:*** Cinazyn; Stugeron; Toliman; ***Malaysia:*** Celenid†; Cereron†; Cinna; Cinnaron; Stugeron; Uphageron; ***Mex.:*** Bulasan; Cisaken; Dilateron-F; Dilper-INA; Karilex; Oblant; Stugeron; Venoxil; Winpar; ***Philipp.:*** Dizzinon; Niziran; Stugeron; Vertisin; ***Port.:*** Cinon; Stugeron; ***Rus.:*** Phezam (Фезам); Stugeron (Стугерон); ***S.Afr.:*** Purazine; Stugeron; ***Singapore:*** Celenid; Cinna; Cinnar; Cinnaron; Stugeron†; Urizine†; ***Spain:*** Stugeron; ***Switz.:*** Cerepar; Cinnageron; Cinnamed†; Stugeron; ***Thai.:*** C-Pela†; Celenid; Cenai; Cerebroad; Ceremin; Cinerine; Cinna; Cinnar; Cinnaza; Cinrizine; CN-25†; Linazine; Manoron; Med-Circuron†; Medozine; Siarizine; Silicin; Sorebral; Stugeron; Stugin; Stuno; Urizine; Vernarin; ***Turk.:*** Sefal; ***UK:*** Arlevert; Cinaziere†; Stugeron; ***Venez.:*** Cinaren; Cinarin; Sinver; Stugeron; Vericin.

Multi-ingredient: ***Arg.:*** Cadencial Plus; Cinacris; Difusil; Ribex; Vasodual†; ***Austria:*** Cinnarplus; ***Belg.:*** Touristil; ***Braz.:*** Coldrin; Exit; Forgrip†; Sureptil; ***Cz.:*** Arlevert; ***Fin.:*** Rinomar; ***Ger.:*** Arlevert; ***Hong Kong:*** C-Sik†; ***Hung.:*** Arlevert; ***India:*** Vertigil; ***Neth.:*** Primatour; ***Rus.:*** Omaron (Омарон); Piracezine (Пирацезин); ***Spain:*** Clinadil; Clinadil Compositum; Diclamina; ***Swed.:*** Rinomar.

Clemastine Fumarate

(BANM, USAN, rINNM)

Clémastine, fumarate de; Clemastini fumaras; Fumarato de clemastina; HS-592 (clemastine); Klemastiinifumaraatti; Klemastin fumarát; Klemastin Hidrojen Fumarat; Klemastinfumarat; Klemastino fumaratas; Klemastyny fumaran; Klemasztin-fumárát; Meclastine Fumarate; Mecloprodine Fumarate. (+)-(2*R*)-2-{2-[(*R*)-4-Chloro-α-methylbenzhydryloxy]ethyl}-1-methylpyrrolidine hydrogen fumarate.

Клемастина Фумарат

$C_{21}H_{26}ClNO,C_4H_4O_4$ = 460.0.

CAS — 15686-51-8 (clemastine); 14976-57-9 (clemastine fumarate).

ATC — D04AA14; R06AA04.

ATC Vet — QD04AA14; QR06AA04.

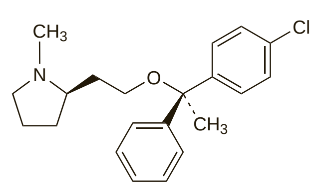

(clemastine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Clemastine Fumarate). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol (70%); slightly soluble in alcohol (50%) and in methyl alcohol. A 10% suspension in water has a pH of 3.2 to 4.2.

USP 31 (Clemastine Fumarate). A colourless to faintly yellow, odourless, crystalline powder. Very slightly soluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. pH of a 10% suspension in water is between 3.2 to 4.2. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Breast feeding. The American Academy of Pediatrics[1] considers that clemastine should be given with caution to breast-feeding mothers, since it has been associated with adverse effects in the infant. Drowsiness, irritability, a high-pitched cry, neck stiffness, and refusal to feed in a 10-week-old breast-fed baby occurred 12 hours after her mother started treatment with clemastine.[2] Clemastine was detected in the mother's breast milk. The baby recovered and was feeding normally on the day after the drug was stopped.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Kok THHG, *et al.* Drowsiness due to clemastine transmitted in breast milk. *Lancet* 1982; **i:** 914–15.

Porphyria. Clemastine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Clemastine fumarate is rapidly and almost completely absorbed from the gastrointestinal tract; peak plasma concentrations are achieved in 2 to 4 hours. Unchanged drug and metabolites are excreted principally in the urine. An elimination half-life of about 21 hours has been reported. Clemastine is distributed into breast milk.

◊ References.

1. Schran HF, *et al.* The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. *J Clin Pharmacol* 1996; **36:** 911–22.

Uses and Administration

Clemastine fumarate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It has been reported to have a duration of action of about 10 to 12 hours. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565).

Clemastine is given as the fumarate although doses are expressed in terms of the base. Clemastine fumarate 1.34 mg is equivalent to about 1 mg of clemastine base. The usual oral dose is 1 mg twice daily. Up to 6 mg daily has been given, particularly for urticaria and angioedema. Children aged 1 to 3 years may be given 250 to 500 micrograms twice daily; those aged 3 to 6 years, 500 micrograms twice daily; and those aged 6 to 12 years, 0.5 to 1 mg twice daily.

Clemastine fumarate may be given by intramuscular or slow intravenous injection in a total daily dose equivalent to 4 mg of clemastine for acute allergic reactions; for prophylaxis 2 mg is given by intravenous injection. The dose for children is 25 micrograms/kg daily in two divided doses by intramuscular injection.

Clemastine fumarate has also been used topically, although as with other antihistamines, there is a risk of sensitisation.

Preparations

BP 2008: Clemastine Oral Solution; Clemastine Tablets;
USP 31: Clemastine Fumarate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Tavegyl; ***Braz.:*** Agasten; ***Canad.:*** Tavist; ***Cz.:*** Tavegyl; ***Denm.:*** Tavegyl; ***Ger.:*** Tavegil; ***India:*** Clamist; ***Indon.:*** Tavegyl; ***Ital.:*** Tavegil†; ***Mex.:*** Tavist; ***Neth.:*** Tavegil; ***Philipp.:*** Marsthine; Tavegyl; Tavist; ***Port.:*** Tavegyl; Tavist; ***Rus.:*** Tavegyl (Тавегил); ***S.Afr.:*** Tavegyl; ***Spain:*** Tavegil; ***Swed.:*** Tavegyl; ***Switz.:*** Tavegyl; ***Turk.:*** Tavegyl; ***UK:*** Tavegil; ***USA:*** Contac 12 Hour Allergy; Dayhist-1; Tavist Allergy.

Multi-ingredient: ***Braz.:*** Emistin; ***Ger.:*** Corto-Tavegil†; ***Mex.:*** Tavist-D†; ***Spain:*** Dexa Tavegil.

Clemizole Hydrochloride *(BANM, rINNM)*

AL-20; Clémizole, Chlorhydrate de; Clemizoli Hydrochloridum; Hidrocloruro de clemizol. 1-(4-Chlorobenzyl)-2-(pyrrolidin-1-ylmethyl)benzimidazole hydrochloride.

Клемизола Гидрохлорид

$C_{19}H_{20}ClN_3,HCl = 362.3.$

CAS — 442-52-4 (clemizole); 1163-36-6 (clemizole hydrochloride).

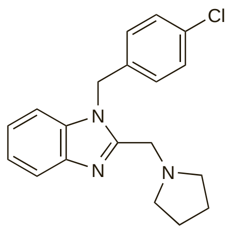

(clemizole)

Profile

Clemizole hydrochloride is a sedating antihistamine (p.561). It has been used for the symptomatic relief of allergic conditions, in pruritic skin disorders, and in combination preparations for the treatment of symptoms of the common cold. Clemizole has also been applied topically as the hexachlorophene, the sodium sulfate, and the undecylate derivatives in topical and rectal preparations combined with corticosteroids and local anaesthetics, although as with other antihistamines, there is a risk of sensitisation.

See p.251 for the use of clemizole penicillin.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Apracur†; ***Braz.:*** Ultraproct; ***Hong Kong:*** Ultraproct†; ***Indon.:*** Ultraproct; ***Thai.:*** Apracur; Scheriproct†.

Clocinizine Hydrochloride *(rINNM)*

Chlorcinnazine Dihydrochloride; Clocinizine, Chlorhydrate de; Clocinizini Hydrochloridum; Hidrocloruro de clonizina. 1-(4-Chlorobenzhydryl)-4-cinnamylpiperazine dihydrochloride.

Клоцинизина Гидрохлорид

$C_{26}H_{27}ClN_2,2HCl = 475.9.$

CAS — 298-55-5 (clocinizine).

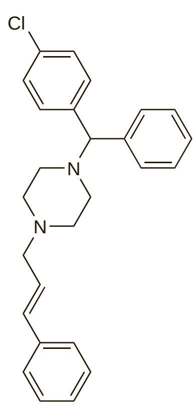

(clocinizine)

Profile

Clocinizine hydrochloride, a piperazine derivative, is an antihistamine (p.561) given by mouth in combination preparations for the symptomatic treatment of upper respiratory-tract disorders, often with a decongestant.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Denoral†; ***Ital.:*** Denoral†; ***Spain:*** Senioral.

Cyclizine *(BAN, rINN)*

Ciclizina; Cyclizinum; Cyklizin; Siklizin; Syklitsiini. 1-Benzhydryl-4-methylpiperazine.

Циклизин

$C_{18}H_{22}N_2 = 266.4.$
CAS — 82-92-8.
ATC — R06AE03.
ATC Vet — QR06AE03.

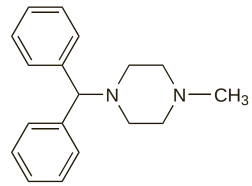

Pharmacopoeias. In *Br.*
BP 2008 (Cyclizine). A white or creamy white, crystalline powder. Practically insoluble in water. It dissolves in most organic solvents and in dilute acids. M.p. about 107°. A saturated solution in water has a pH of 7.6 to 8.6.

Cyclizine Hydrochloride *(BANM, rINNM)*

Ciklizin-hidroklorid; Ciklizino hidrochloridas; Cyclizine, chlorhydrate de; Cyclizini hydrochloridum; Cyklizin hydrochlorid; Cyklizinhydroklorid; Hidrocloruro de ciclizina; Syklitsiinihydrokloridi.

Циклизина Гидрохлорид

$C_{18}H_{22}N_2,HCl = 302.8.$
CAS — 303-25-3.
ATC — R06AE03.
ATC Vet — QR06AE03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Cyclizine Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol. A 2% solution in alcohol 2 vol. and water 3 vol. has a pH of 4.5 to 5.5. Protect from light.
USP 31 (Cyclizine Hydrochloride). A white, odourless, crystalline powder or small colourless crystals. Soluble 1 in 115 of water and of alcohol and 1 in 75 of chloroform; insoluble in ether. pH of a 2% solution in alcohol 2 vol. and water 3 vol. is between 4.5 and 5.5. Store in airtight containers. Protect from light.

Cyclizine Lactate *(BANM, rINNM)*

Cyclizine, Lactate de; Cyclizini Lactas; Lactato de ciclizina.

Циклизина Лактат

$C_{18}H_{22}N_2,C_3H_6O_3 = 356.5.$
CAS — 5897-19-8.
ATC — R06AE03.
ATC Vet — QR06AE03.

Pharmacopoeias. *Br.* includes an injection of cyclizine lactate.

Incompatibility. Cyclizine lactate is reported to be incompatible with oxytetracycline hydrochloride, chlortetracycline hydrochloride, benzylpenicillin, and solutions with a pH of 6.8 or more.

Cyclizine Tartrate *(BANM, rINNM)*

Cyclizine, Tartrate de; Cyclizini Tartras; Tartrato de ciclizina.

Циклизина Тартрат

$C_{18}H_{22}N_2,C_4H_6O_6 = 416.5.$
ATC — R06AE03.
ATC Vet — QR06AE03.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Cyclizine may aggravate severe heart failure. Hypotension may occur on injection.

Abuse. Cyclizine tablets have been abused either alone or with opioids for their euphoric effects.[1-7] They have been taken by mouth or used to make injections. It has been suggested that cyclizine dependence may occur when it is used with opioids in the treatment of chronic pain.[8]

1. Gott PH. Cyclizine toxicity—intentional drug abuse of a proprietary antihistamine. *N Engl J Med* 1968; **279:** 596.
2. Kahn A, Harvey GJ. Increasing misuse of cyclizine. *Pharm J* 1985; **235:** 706.
3. Atkinson MK. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
4. Halpin D. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
5. Council of the Pharmaceutical Society of Great Britain. Sales of preparations containing cyclizine. *Pharm J* 1985; **235:** 797.
6. Ruben SM, *et al.* Cyclizine abuse among a group of opiate dependents receiving methadone. *Br J Addict* 1989; **84:** 929–34.
7. Bassett KE, *et al.* Cyclizine abuse by teenagers in Utah. *Am J Emerg Med* 1996; **14:** 472–4.
8. Hughes AM, Coote J. Cyclizine dependence. *Pharm J* 1986; **236:** 130.

Effects on the blood. Agranulocytosis occurred in a patient after 6 weeks of treatment with cyclizine 50 mg three times daily.[1] The blood count returned to normal once cyclizine was withdrawn.

1. Collier PM. Agranulocytosis associated with oral cyclizine. *BMJ* 1986; **292:** 174.

Effects on the heart. In a study[1] of 11 patients with severe heart failure, cyclizine produced detrimental haemodynamic effects including increased systemic and pulmonary artery pressures and ventricular filling pressures, and negated the vasodilator effects of diamorphine. It was suggested that the use of cyclizine should be avoided in patients with acute myocardial infarction or severe heart failure.

1. Tan LB, *et al.* Detrimental haemodynamic effects of cyclizine in heart failure. *Lancet* 1988; **i:** 560–1.

Effects on the liver. An 8-year-old girl developed jaundice on 2 occasions after taking cyclizine hydrochloride 25 mg daily by mouth. 'Hypersensitivity hepatitis' was considered responsible.[1]

1. Kew MC, *et al.* "Hypersensitivity hepatitis" associated with administration of cyclizine. *BMJ* 1973; **2:** 307.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving cyclizine, see p.563.

Interactions

As for the sedating antihistamines in general, p.563. Cyclizine may counteract the haemodynamic benefits of opioids (see Effects on the Heart, above) and this should be considered before using preparations that contain a combination of cyclizine and an opioid analgesic.

General anaesthetics. For a possible interaction between cyclizine premedication and *barbiturate anaesthetics* see under Thiopental, p.1795.

Pharmacokinetics

Cyclizine is absorbed from the gastrointestinal tract and has an onset of action within 2 hours. The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine. Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1% of the total oral dose is eliminated in the urine in 24 hours.

Uses and Administration

Cyclizine, a piperazine derivative, is a sedating antihistamine with antimuscarinic activity, although the sedative effects are not marked.

It is used as an antiemetic in the management of nausea and vomiting (p.564) including motion sickness, postoperative nausea and vomiting, after radiotherapy, and in drug-induced nausea and vomiting. It is included as an antiemetic with some opioids, and in combination preparations for the treatment of migraine attacks (p.616). Cyclizine is also used for the symptomatic treatment of vertigo (p.565) caused by Ménière's disease and other vestibular disturbances.

In the management of nausea and vomiting, cyclizine hydrochloride is given in a usual oral dose of 50 mg up to three times daily, although up to 200 mg may be given in 24 hours if necessary. For the prevention of motion sickness, the first dose should be given about 30 minutes before travelling. Children aged 6 to 12 years may be given 25 mg up to three times daily. Although not licensed in the UK, the *BNFC* suggests that those aged 1 month to 6 years may be given 0.5 to 1 mg/kg (maximum of 25 mg) up to 3 times daily.

Cyclizine is given intramuscularly or intravenously as the lactate. Doses of cyclizine lactate are similar to those of cyclizine hydrochloride given orally. For the prevention of postoperative nausea and vomiting the first dose of cyclizine lactate should be given about 20 minutes before the anticipated end of surgery.

Although not licensed in the UK, cyclizine is also available as suppositories on a named-patient basis. The *BNFC* suggests that children aged 2 to 6 years may be given rectal doses of 12.5 mg; those aged 6 to 12 years, 25 mg; and those aged 12 to 18 years, 50 mg. Doses may be given up to 3 times daily.

Cyclizine salts are used as antiemetics in combination with morphine or dipipanone; the use of such fixed-combination opioid preparations is considered to be unsuitable for the prolonged treatment that may be required in palliative care. See also under Interactions, above.

Preparations

BP 2008: Cyclizine Injection; Cyclizine Tablets; Dipipanone and Cyclizine Tablets;
USP 31: Cyclizine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Echnatol; ***Denm.:*** Marzine; ***Fin.:*** Marzine; ***Hong Kong:*** Marzine†; Valoid†; ***India:*** Medazine; ***Irl.:*** Valoid; ***Neth.:*** Kruidvat Reistabletten; ***Norw.:*** Marzine; ***NZ:*** Marzine; Nausicalm; Valoid; ***S.Afr.:*** Aculoid; Covamet; Emitex†; Medazine; Nauzine; Norizine†; Triazine; Valoid; ***Singapore:*** Marzine†; ***Swed.:*** Marzine†; ***Switz.:*** Marzine; ***UK:*** Valoid; ***USA:*** Bonine for Kids; Marezine.

Multi-ingredient: ***Austria:*** Echnatol B ; Migril; ***Fin.:*** Vertipam; ***Hong Kong:*** Migril†; Wellconal†; ***Irl.:*** Cyclimorph; Diconal†; Migril†; ***Neth.:*** Ercycof†; ***S.Afr.:*** Cyclimorph; Migril; Wellconal; ***UK:*** Cyclimorph; Diconal; Migril.

Cyproheptadine Hydrochloride

(BANM, rINNM)

Ciproheptadin-hidroklorid; Ciproheptadino hidrocloridas; Cyproheptadine, chlorhydrate de; Cyproheptadin-hydrochlorid seskvihydrát; Cyproheptadinhydroklorid; Cyproheptadini hydrochloridum; Cyproheptadini Hydrochloridum Sesquihydricum; Hidrocloruro de ciproheptadina; Siproheptadin Hidroklorür; Syproheptadiinihydrokloridi. 4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate.

Ципрогептадина Гидрохлорид

$C_{21}H_{21}N,HCl,1\frac{1}{2}H_2O = 350.9.$

CAS — 129-03-3 (cyproheptadine); 969-33-5 (anhydrous cyproheptadine hydrochloride); 41354-29-4 (cyproheptadine hydrochloride sesquihydrate).

ATC — R06AX02.

ATC Vet — QR06AX02.

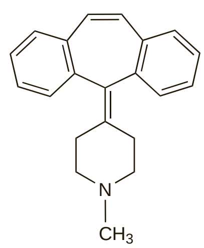

(cyproheptadine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Cyproheptadine Hydrochloride). A white or slightly yellow, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 31 (Cyproheptadine Hydrochloride). A white to slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 275 of water, 1 in 35 of alcohol, 1 in 26 of chloroform, and 1 in 1.5 of methyl alcohol; practically insoluble in ether.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Increased appetite and weight gain may occur with cyproheptadine.

Abuse. Dependence developed in a patient who took about 180 mg of cyproheptadine daily by mouth for 5 years.[1]

1. Craven JL, Rodin GM. Cyproheptadine dependence associated with an atypical somatoform disorder. *Can J Psychiatry* 1987; **32:** 143–5.

Effects on the nervous system. Antimuscarinic toxicity manifest by hallucinations and agitation developed in a 9-year-old child taking cyproheptadine 4 mg twice daily for migraine prophylaxis.[1]

1. Watemberg NM, *et al.* Central anticholinergic syndrome on therapeutic doses of cyproheptadine. *Pediatrics* 1999; **103:** 158–60.

Interference with diagnostic tests. Cyproheptadine reduced hypoglycaemia-induced growth hormone secretion by between 5 and 97% in 8 healthy subjects.[1] It was suggested that if patients receiving cyproheptadine were given a pituitary function test that used growth hormone response to insulin-induced hypoglycaemia, then cyproheptadine therapy should be stopped before the test.

UK licensed product information states that cyproheptadine may cause a false positive test result for tricyclic antidepressants in urine.

1. Bivens CH, *et al.* Inhibition of hypoglycaemia-induced growth hormone secretion by the serotonin antagonists cyproheptadine and methysergide. *N Engl J Med* 1973; **289:** 236–9.

Interactions

As for the sedating antihistamines in general, p.563.

Antidepressants. For reports suggesting that cyproheptadine can reduce the effectiveness of *SSRIs*, see under Fluoxetine, p.396.

Pharmacokinetics

After absorption from the gastrointestinal tract, cyproheptadine hydrochloride undergoes almost complete metabolism. Metabolites are excreted principally in the urine as conjugates, and also in the faeces.

Uses and Administration

Cyproheptadine, a piperidine derivative, is a sedating antihistamine with antimuscarinic, serotonin-antagonist, and calcium-channel blocking actions. It is used as the hydrochloride for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). Other uses include the management of migraine (p.564). Cyproheptadine hydrochloride is given as the sesquihydrate although doses are expressed in terms of the anhydrous substance. Anhydrous cyproheptadine hydrochloride 10 mg is equivalent to about 11 mg of cyproheptadine hydrochloride sesquihydrate.

For allergic conditions and pruritus the oral dose in adults is initially 4 mg three times daily, adjusted as necessary. The average dose requirement is 12 to 16 mg daily in three or four divided doses, but up to 32 mg daily may occasionally be necessary. The dose for children aged 2 to 6 years is 2 mg two or three times daily increasing to a maximum of 12 mg daily and for children aged 7 to 14 years, 4 mg two or three times daily up to a maximum of 16 mg daily. Cyproheptadine is not recommended in debilitated elderly patients.

A dose of 4 mg is used for both prophylaxis and treatment of migraine and other vascular headaches and may be repeated after 30 minutes; patients who respond usually obtain relief with 8 mg, and this dose should not be exceeded within a 4- to 6-hour period. A maintenance dose of 4 mg may be given every 4 to 6 hours.

Other cyproheptadine salts that have been given orally include the acetylaspartate, aspartate, cyclamate, orotate, acefyllinate (7-theophyllineacetate), and the pyridoxal phosphate salt (dihexazine).

Abdominal migraine. Cyproheptadine has been tried in the prophylactic treatment of children with abdominal migraine (see Pizotifen, p.624).

Angina pectoris. Cyproheptadine was used successfully to treat 2 patients with Prinzmetal's angina (p.1157) refractory to standard treatment with calcium-channel blockers and nitrates.[1] Serotonin is an important endocrine mediator of coronary vasospasm and the beneficial effects of cyproheptadine were attributed to its activity as a serotonin antagonist.

1. Schecter AD, *et al.* Refractory Prinzmetal angina treated with cyproheptadine. *Ann Intern Med* 1994; **121:** 113–14.

Appetite disorders. Cyproheptadine has been widely used as an appetite stimulant, including for anorexia nervosa and cachexia (see under Megestrol, p.2115), but in the long-term appears to have little value in producing weight gain and such use is no longer generally recommended. There has been concern that cyproheptadine was being promoted and used inappropriately as an appetite stimulant in some developing countries.[1]

1. Anonymous. Cyproheptadine: no longer promoted as an appetite stimulant. *WHO Drug Inf* 1994; **8:** 66.

Carcinoid syndrome. The management of carcinoid tumours (p.643) is largely symptomatic. Cyproheptadine hydrochloride, a serotonin antagonist, has had limited success in relieving symptoms such as diarrhoea but somatostatin analogues may now be preferred.[1] It has been used successfully with fenclonine, aprotinin, methylprednisolone, and antibacterials to prevent complications arising from release of tumour metabolites during hepatic embolisation, a procedure sometimes used to relieve the symptoms of carcinoid syndrome.[2] There have been a few reports of tumour regression, in addition to symptomatic control, after treatment of carcinoid tumours with cyproheptadine.[3,4]

1. Caplin ME, *et al.* Carcinoid tumour. *Lancet* 1998; **352:** 799–805.
2. Maton PN, *et al.* Role of hepatic arterial embolisation in the carcinoid syndrome. *BMJ* 1983; **287:** 932–5. Correction to dosage. ibid.; 1664.
3. Harris AL, Smith IE. Regression of carcinoid tumour with cyproheptadine. *BMJ* 1982; **285:** 475.
4. Leitner SP, *et al.* Partial remission of carcinoid tumor in response to cyproheptadine. *Ann Intern Med* 1989; **111:** 760–1.

Serotonin syndrome. Cyproheptadine has been successfully used to treat the serotonin syndrome (p.416) in patients who have developed the syndrome after overdoses involving serotonergic drugs or who have had their antidepressant therapy changed without an adequate wash-out period.[1,2]

1. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med* 1994; **331:** 1021–2.
2. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother* 2001; **35:** 870–3.

Sexual dysfunction. Cyproheptadine has been tried in the management of sexual dysfunction induced by SSRIs (see Effects on Sexual Function under Fluoxetine, p.393) but may possibly reduce the effectiveness of the SSRI.

Preparations

BP 2008: Cyproheptadine Tablets;
USP 31: Cyproheptadine Hydrochloride Syrup; Cyproheptadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Periactin; ***Austria:*** Periactin; ***Belg.:*** Periactin; ***Braz.:*** Periatin; Preptin†; ***Chile:*** Viternum; ***Cz.:*** Peritol; ***Denm.:*** Periactin†; ***Fr.:*** Periactine; ***Ger.:*** Peritol; ***Hong Kong:*** Cyprogin; ***Hung.:*** Peritol; ***India:*** Apenorm†; Ciplactin; Peritol; Practin; ***Indon.:*** Alphahist; Apeton; Cydifar; Cylat; Ennamax; Esprocy; Glocyp; Heptasan; Lexahist; Poncohist; Profut; Prohessen; Pronicy; Sinapdin; ***Irl.:*** Periactin; ***Ital.:*** Periactin; ***Mex.:*** Viternum; ***Neth.:*** Periactin; ***NZ:*** Periactin; ***Pol.:*** Peritol; ***Port.:*** Trimetabol†; Viternum; ***Rus.:*** Peritol (Перитол); ***S.Afr.:*** Cipla-Actin; Periactin; ***Singapore:*** Cyprotin; ***Spain:*** Klarivitina†; Periactin; Viternum; ***Swed.:*** Periactin; ***Switz.:*** Periactin†; ***Thai.:*** Cyheptine; Cyprogin; Cyprono; Cyprosian; Cyprotec; Hepdine; Periactin; Polytab; ***Turk.:*** Prakten; Sipraktin; ***UK:*** Periactin; ***Venez.:*** Cyprodin; Eptacor†; Periactin†.

Multi-ingredient: ***Arg.:*** Apeplus; Apetitol Forte; Ciprocort; Ciprovit Calcio; Ciprovit Energizante; Ciprovit Magnesico; Mikesan; Nipiol†; Potencil; Sudevil Vita; ***Braz.:*** Apetivit BC; Apetiviton BC; Apevitin BC; Apmed; Bonapetit†; Cobactin; Cobaglobal; Cobavit; Cobavital; Polivitam†; Trimetabol; ***Chile:*** Apetrol; Grisetin Con Carnitina†; Orodina; Peracon; Revil; Rodepan; Viternum Vitaminado; ***Hong Kong:*** Petina Compound; Tres Orix Forte; ***Ital.:*** Carpantin†; ***Mex.:*** Cipro-Dexol†; Ciprolisina; Pangavit Pediatrico; Rocavit; ***Spain:*** Anti Anorex Triple; Childrevit†; Covitasa B12; Desarrol; Enoton; Glotone; Medenorex; Pantobamin; Pranzo; Stolina; Tonico Juventus; Tres Orix Forte†; Trimetabol; Troforex Pepsico; Vita Menal; ***Venez.:*** Cipromet†; Cyprodex.

Deptropine Citrate *(BANM, rINNM)*

Citrato de deptropina; Deptropiinisitraatti; Deptropincitrat; Deptropin-citrát; Deptropine, citrate de; Deptropini citras; Deptropino citratas; Dibenzheptropine Citrate. (1*R*,3*r*,5*S*)-3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yloxy)tropane dihydrogen citrate.

Дептропина Цитрат

$C_{23}H_{27}NO,C_6H_8O_7 = 525.6.$

CAS — 604-51-3 (deptropine); 2169-75-7 (deptropine citrate).

ATC — R06AX16.

ATC Vet — QR06AX16.

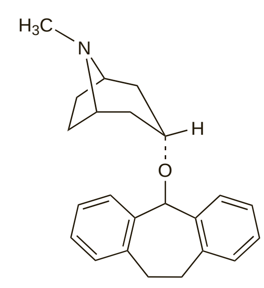

(deptropine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Deptropine Citrate). A white or almost white, microcrystalline powder. Very slightly soluble in water and in dehydrated alcohol; practically insoluble in dichloromethane. A saturated solution in water has a pH of 3.7 to 4.5. Protect from light.

Profile

Deptropine citrate is a sedating antihistamine (p.561) with a marked antimuscarinic action. It was given by mouth mainly in the treatment of respiratory-tract disorders.

Desloratadine *(BAN, USAN, rINN)*

Descarboethoxyloratadine; Desloratadin; Desloratadina; Desloratadinum; Sch-34117. 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

Дезлоратадин

$C_{19}H_{19}ClN_2$ = 310.8.

CAS — 100643-71-8.

ATC — R06AX27.

ATC Vet — QR06AX27.

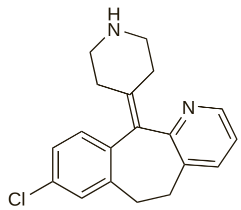

Profile

Desloratadine, the major, active metabolite of loratadine (p.583), is a non-sedating antihistamine. Desloratadine is used in the symptomatic relief of allergic conditions including rhinitis (p.565) and urticaria (p.565).

Desloratadine is given in an oral dose of 5 mg once daily.

It is also used with a decongestant such as pseudoephedrine sulfate.

For dosage in children, and in hepatic or renal impairment, see below.

◊ References.

1. McClellan K, Jarvis B. Desloratadine. *Drugs* 2001; **61:** 789–96.
2. Simons FER, ed. Desloratadine: clinical pharmacokinetics of a novel H receptor antagonist. *Clin Pharmacokinet* 2002; **41** (suppl 1): 1–44.
3. Limon L, Kockler DR. Desloratadine: a nonsedating antihistamine. *Ann Pharmacother* 2003; **37:** 237–46. Correction. *ibid.*; 454.
4. Murdoch D, *et al.* Desloratadine: an update of its efficacy in the management of allergic disorders. *Drugs* 2003; **63:** 2051–77.
5. Berger WE. The safety and efficacy of desloratadine for the management of allergic disease. *Drug Safety* 2005; **28:** 1101–18.
6. Canonica GW, *et al.* Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy* 2007; **62:** 359–66.

Administration in children. In the UK, desloratadine is licensed for use in children aged 1 year and over in the treatment of allergic rhinitis and urticaria; in the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Regardless of indication, oral doses of desloratadine are as follows:

- children aged 6 to 11 months: 1 mg once daily
- those aged 1 to 5 years: 1.25 mg once daily
- those aged 6 to 11 years: 2.5 mg once daily.

Administration in hepatic or renal impairment. US licensed product information recommends that patients with hepatic or renal impairment should be given desloratadine 5 mg orally on alternate days initially.

Breast feeding. Desloratadine is distributed into breast milk and consequently UK and US licensed product information does not recommend its use during breast feeding. For a discussion of the use of *loratadine* in breast feeding, see under Adverse Effects and Precautions, p.583.

Pregnancy. Desloratadine was not teratogenic in *animal* studies; however, product information recommends it should be used with caution, if at all, in pregnant women.

For a discussion of the use of loratadine in pregnancy, see under Adverse Effects and Precautions, p.583.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aerius; Azomyr†; Frenaler; Hexaler; Novo Alerpriv; ***Austral.:*** Claramax; ***Austria:*** Aerius; ***Belg.:*** Aerius; ***Braz.:*** Desalex; ***Canad.:*** Aerius; ***Chile:*** Aerius; Mailen; Neo Larmax; Neoclaritine; Neohysticlar; Rinaid; Rinoflax; ***Cz.:*** Aerius; Azomyr; Neoclarityn; ***Denm.:*** Aerius; ***Fin.:*** Aerius; ***Fr.:*** Aerius; ***Ger.:*** Aerius; ***Gr.:*** Aerius; Neoclarityn†; ***Hong Kong:*** Aerius; ***Hung.:*** Aerius; ***India:*** D-Loratin; Des-OD; Deslor; ***Indon.:*** Aerius; ***Irl.:*** Neoclarityn; ***Israel:*** Aerius; ***Ital.:*** Aerius; Azomyr; ***Malaysia:*** Aerius; ***Mex.:*** Aviant; Azomyr; ***Neth.:*** Aerius; Azomyr; Neoclarityn; ***Norw.:*** Aerius; ***NZ:*** Aerius; Claramax; ***Philipp.:*** Aerius; ***Pol.:*** Aerius; ***Port.:*** Aerius; Azomyr; Neoclarityn; ***Rus.:*** Aerius (Эриус); ***S.Afr.:*** Deselex; ***Singapore:*** Aerius; Desalex†; ***Spain:*** Aerius; Azomyr; ***Swed.:*** Aerius; ***Switz.:*** Aerius; ***Thai.:*** Aerius; ***Turk.:*** Aerius; ***UK:*** Neoclarityn; ***USA:*** Clarinex; ***Venez.:*** Aerius; Desalex; Deslorat; Esparflin; Mailen.

Multi-ingredient: ***Cz.:*** Aerinaze; ***USA:*** Clarinex-D.

Dimebolin

Dimebol; Dimeboline; Dimebon; Dimebone. 2,3,4,5-Tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1*H*-pyrido[4,3-*b*]indole.

Димеболин

$C_{21}H_{25}N_3$ = 319.4.

CAS — 3613-73-8 (dimebolin); 14292-23-0 (dimebolin x-hydrochloride).

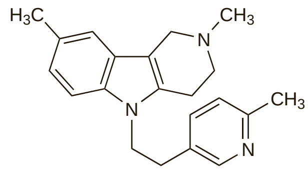

Profile

Dimebolin is an antihistamine that is reported to also have neuroprotective effects. It is under investigation as the dihydrochloride in the treatment of Alzheimer's disease and Huntington's disease.

◊ References.

1. Doody RS, *et al.* Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet* 2008; **372:** 207–15.

Dimenhydrinate *(BAN, rINN)*

Chloranautine; Dimenhidrinát; Dimenhidrinat; Dimenhidrinatas; Dimenhidrinato; Dimenhydramina; Dimenhydrinaatti; Dimenhydrinát; Dimenhydrinat; Diménhydrinate; Dimenhydrinatum; Diphenhydramine Teoclate; Diphenhydramine Theoclate. The diphenhydramine salt of 8-chlorotheophylline .

Дименгидринат

$C_{17}H_{21}NO,C_7H_7ClN_4O_2$ = 470.0.

CAS — 523-87-5.

ATC — R06AA02.

ATC Vet — QR06AA02.

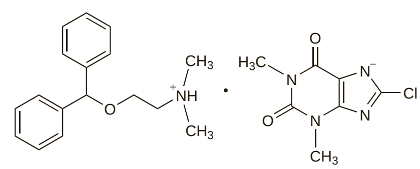

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Dimenhydrinate). A white or almost white, crystalline powder or colourless crystals. M.p. 102° to 106°. Slightly soluble in water; freely soluble in alcohol. A saturated solution in water has a pH of 7.1 to 7.6.

USP 31 (Dimenhydrinate). A white, odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether.

Incompatibility. Dimenhydrinate has been reported to be incompatible in solution with a wide range of compounds; those most likely to be encountered include: aminophylline, glycopyrronium bromide, hydrocortisone sodium succinate, hydroxyzine hydrochloride, meglumine adipiodone, some phenothiazines, and some soluble barbiturates.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Effects on the eyes. Dimenhydrinate 100 mg, given at 4-hourly intervals for 3 doses, was found to affect colour discrimination, night vision, reaction time, and stereopsis.[1]

1. Luria SM, *et al.* Effects of aspirin and dimenhydrinate (Dramamine) on visual processes. *Br J Clin Pharmacol* 1979; **7:** 585–93.

Porphyria. Dimenhydrinate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between cardiovascular defects or inguinal hernia and dimenhydrinate exposure, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Dimenhydrinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and significant sedative effects. It is used mainly as an antiemetic in the prevention and treatment of motion sickness (p.564). It is also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disturbances (see Vertigo, p.565).

The usual oral dose of dimenhydrinate is 50 to 100 mg, given 3 or 4 times daily. For the prevention of motion sickness, the first dose should be given at least 30 minutes before travelling. Typical doses for children, according to age, are: 2 to up to 6 years, 12.5 to 25 mg every 6 to 8 hours to a maximum of 75 mg daily (in some countries lower doses of 6.25 to 12.5 mg are given two or three times daily); 6 to 12 years, 25 to 50 mg every 6 to 8 hours to a maximum of 150 mg daily (again lower doses are used in some countries).

Dimenhydrinate may be given parenterally in usual doses of 50 mg, a concentration of 5% being used for intramuscular injection and 0.5% for slow intravenous injection (usually over 2 minutes). Children have been given dimenhydrinate by intramuscular or slow intravenous injection in a dose of 1.25 mg/kg four times daily to a maximum of 300 mg daily.

Dimenhydrinate has also been given by the rectal route.

Preparations

BP 2008: Dimenhydrinate Tablets;
USP 31: Dimenhydrinate Injection; Dimenhydrinate Syrup; Dimenhydrinate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dr Amin; Dramamine; Marine†; ***Austral.:*** Dramamine; ***Austria:*** Emedyl; Nausex; Travel-Gum; Vertirosan; ***Belg.:*** Paranausine; Vagomine†; ***Braz.:*** Dimedril†; Dramamine; Dramavit†; Dramin; Emebrid†; Neodrin; ***Canad.:*** Anti-Nauseant; Childrens Motion Sickness Liquid; Dinate; Gravol; Nauseatol; Novo-Dimenate; Travamine†; Travel Aid†; ***Chile:*** Mareamin; ***Cz.:*** Travel-Gum; ***Denm.:*** Anautin; ***Fr.:*** Dramamine; Nausicalm; ***Ger.:*** Dimen†; Reisegold†; Reisetabletten; Rodavan S; RubieMen†; Superpep; Vertigo-Vomex; Vomacur; Vomex A; ***Gr.:*** Dravom†; Drimen; Travelgum; Vomex A; ***Hong Kong:*** Dimate; Dimenate; Garcol; Gravol; Novomin; ***Hung.:*** Daedalon; Daedalonetta; ***India:*** Dramnate; Gravol; ***Indon.:*** Dramamine; Stopmun; ***Irl.:*** Dramamine†; ***Israel:*** Dramamine†; Travamin; ***Ital.:*** Lomarin; Motozina; Travelgum; Valontan; Xamamina; ***Malaysia:*** Dimenate; Dramamine; Driminate; Hydrinate; Novomin†; Setmenate†; ***Mex.:*** Apo-Mina; Dimetin-F†; Dimicaps; Dramamine; Unitril†; Vomisin; ***NZ:*** Dramamine; ***Philipp.:*** Gravol; ***Pol.:*** Aviomarin; ***Port.:*** Dramamine†; Draminal; Enjomin; Viabom; Vomidrine; ***Rus.:*** Dramina (Драмина); ***Singapore:*** Dimenate; Dramamine†; ***Spain:*** Biodramina; Cinfamar; Contramareo; Travel Well; ***Swed.:*** Amosyt; ***Switz.:*** Antemin; Dramamine†; Trawell; ***Thai.:*** Denim; Dimeno; Dimin†; Dramamine; Gravol; Motivan; Nausamine; Navamin; Phrachedi; Vominar†; ***Turk.:*** Anti-Em; Dramamine; Xamamine; ***UAE:*** Dizinil; ***UK:*** Arlevert; ***USA:*** Calm-X; Dimetabs; Dinate; Dramamine; Dramanate; Dymenate; Hydrate†; Triptone; ***Venez.:*** Dramamine†; Viajesan.

Multi-ingredient: ***Austral.:*** Travacalm; ***Austria:*** Neo-Emedyl; Synkapton; Vertirosan Vitamin B ; ***Braz.:*** Dramavit B6†; Dramin B-6; Dramin B-6 DL; Nausicalm; Nausilon B6; ***Canad.:*** Gravergol†; ***Cz.:*** Arlevert; Migraeflux; ***Fr.:*** Mercalm; ***Ger.:*** Arlevert; Migraeflux N; Migraeflux orange N; ***Gr.:*** Vertigo-Vomex; ***Hong Kong:*** Gravergol†; Rhinocap; ***Hung.:*** Arlevert; ***Indon.:*** Dramasine; ***Mex.:*** Bomine; ***Spain:*** Acetuber; Biodramina Cafeina; Cinfamar Cafeina; Saldeva; Salvarina; Sin Mareo x 4; ***Switz.:*** Agorhino†; Antemin compositum; Dramamine-compositum†; Gem Voyage Dragees contre les maux de voyage; Rhinocap; Trawell compositum; ***Thai.:*** Roxine.

Dimetindene Maleate *(BANM, rINNM)*

Dimethindene Maleate *(USAN)*; Dimethpyrindene Maleate; Dimethylpyrindene Maleate; Dimetindeenimaleaatti; Dimetinden Maleat; Dimétindène, maléate de; Dimetindeni maleas; Dimetindenmaleat; Dimetindén-maleát; Dimetinden-maleinát; Dimetindeno maleatas; Maleato de dimetindeno; NSC-107677; Su-6518. *NN*-Dimethyl-2-{3-[1-(2-pyridyl)ethyl]-1*H*-inden-2-yl}ethylamine hydrogen maleate.

Диметиндена Малеат

$C_{20}H_{24}N_2,C_4H_4O_4$ = 408.5.

CAS — 5636-83-9 (dimetindene); 3614-69-5 (dimetindene maleate).

ATC — D04AA13; R06AB03.

ATC Vet — QD04AA13; QR06AB03.

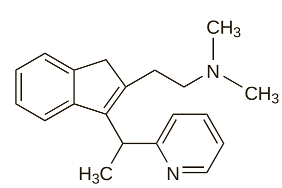

(dimetindene)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dimetindene Maleate). A white to almost white, crystalline powder. Slightly soluble in water; soluble in methyl alcohol. Protect from light.

Profile

Dimetindene maleate, an alkylamine derivative, is a sedating antihistamine (p.561); it is mildly sedative and is reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565) and rhinitis (p.565), and in pruritic skin disorders (p.565). It is also used in compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Dimetindene maleate is given in an oral dose of 1 to 2 mg three times daily; modified-release preparations are also available. It may also be given by the intravenous route. Dimetindene maleate is applied topically as a 0.1% gel or lotion although, as with other antihistamines, there is a risk of sensitisation. It is used in a strength of 0.025% in compound nasal preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Fenistil; ***Belg.:*** Fenistil; ***Cz.:*** Fenistil; ***Ger.:*** Fenistil; ***Gr.:*** Fenistil; ***Hung.:*** Fenistil; ***India:*** Foristal; ***Indon.:*** Fenistil; ***Israel:*** Fenistil; ***Ital.:*** Fenistil; ***Neth.:*** Fenistil; ***Norw.:*** Fenistil†; ***Philipp.:*** Fenistil; ***Pol.:*** Fenistil; ***Port.:*** Fenistil; Neostil; ***Rus.:*** Fenistil (Фенистил); ***Spain:*** Fenistil; ***Switz.:*** Fenistil; ***Thai.:*** Fenistil; ***Turk.:*** Fenistil; ***Venez.:*** Fenistil†.

Multi-ingredient: ***Arg.:*** Vibragel; ***Austria:*** Trimedil; Vibrocil; ***Belg.:*** Vibrocil; ***Braz.:*** Gripen; Trimedal; ***Cz.:*** Vibrocil; ***Ger.:*** Vibrocil†; ***Gr.:*** Vibrocil-S; ***Hong Kong:*** Vibrocil†; ***Hung.:*** Otrivin Allergia; Vibrocil; ***Israel:*** Vibrocil; ***Ital.:*** Vibrocil; ***Pol.:*** Otrivin Allergy; ***Port.:*** Vibrocil; ***Rus.:*** Vibrocil (Виброцил); ***S.Afr.:*** Vibrocil; Vibrocil-S; ***Switz.:*** Vibrocil.

Dimetotiazine Mesilate *(BANM, rINNM)*

Dimethothiazine Mesylate; Dimétotiazine, Mésilate de; Dimetotiazini Mesilas; Fonazine Mesylate *(USAN)*; IL-6302 (dimetotiazine); Mesilato de dimetotiazina; 8599-RP (dimetotiazine). 10-(2-Dimethylaminopropyl)-*NN*-dimethylphenothiazine-2-sulphonamide methanesulphonate.

Диметотиазина Мезилат

$C_{19}H_{25}N_3O_2S_2,CH_3SO_3H = 487.7.$

CAS — 7456-24-8 (dimetotiazine); 7455-39-2 (dimetotiazine mesilate).

ATC — N02CX05.

ATC Vet — QN02CX05.

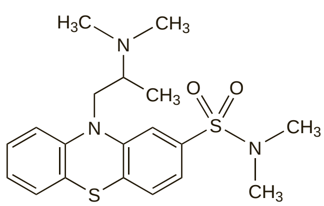

(dimetotiazine)

Profile

Dimetotiazine mesilate, a phenothiazine derivative, is a sedating antihistamine (p.561). It has been used for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders, and in the management of headaches including migraine.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Migristene; ***Mex.:*** Migristene.

Diphenhydramine *(BAN, rINN)*

Benzhydramine; Difenhidramina; Difenhydramiini; Difenhydramin; Diphénhydramine; Diphenhydraminum. 2-Benzhydryloxy-*NN*-dimethylethylamine.

Дифенгидрамин

$C_{17}H_{21}NO = 255.4.$

CAS — 58-73-1.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

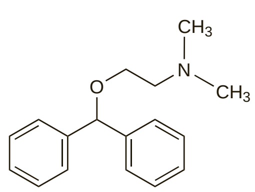

Pharmacopoeias. In *Jpn.*

Diphenhydramine Citrate *(BANM, rINNM)*

Benzhydramine Citrate; Citrato de difenhidramina; Diphénhydramine, Citrate de; Diphenhydramini Citras.

Дифенгидрамина Цитрат

$C_{17}H_{21}NO,C_6H_8O_7 = 447.5.$

CAS — 88637-37-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

Pharmacopoeias. In *US.*

USP 31 (Diphenhydramine Citrate). Store in airtight containers. Protect from light.

Diphenhydramine Di(acefyllinate) *(rINNM)*

Benzhydramine Di(acefyllinate); Bietanautine; Di(acefilinato) de difenhidramina; Diphénhydramine Diacéfylline; Diphenhydramine Di(acephyllinate); Diphenhydramini Diacefyllinas. Diphenhydramine bis(theophyllin-7-ylacetate).

Дифенгидрамина Диацефиллинат

$C_{17}H_{21}NO,2C_9H_{10}N_4O_4 = 731.8.$

CAS — 6888-11-5.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

NOTE. The name Etanautine has been applied both to diphenhydramine monoacefyllinate and to ethylbenzhydramine, an antimuscarinic formerly used in the symptomatic treatment of parkinsonism.

Diphenhydramine Hydrochloride *(BANM, rINNM)*

Benzhydramine Hydrochloride; Difenhidramin Hidroklorür; Difenhidramin-hidroklorid; Difenhidramino hidrochloridas; Difenhydramiinihydrokloridi; Difenhydramin-hydrochlorid; Difenhydraminhydroklorid; Difenhydraminy chlorowodorek; Dimedrolum; Diphénhydramine, chlorhydrate de; Diphenhydramini hydrochloridum; Diphenhydraminium Chloride; Hidrocloruro de difenhidramina.

Дифенгидрамина Гидрохлорид

$C_{17}H_{21}NO,HCl = 291.8.$

CAS — 147-24-0.

ATC — D04AA32; R06AA02.

ATC Vet — QD04AA32; QR06AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Jpn also includes Diphenhydramine Tannate.

Ph. Eur. 6.2 (Diphenhydramine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 31 (Diphenhydramine Hydrochloride). A white, odourless, crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 50 of acetone; very slightly soluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Diphenhydramine hydrochloride has been reported to be incompatible with amphotericin B, cefmetazole sodium, cefalotin sodium, hydrocortisone sodium succinate, some soluble barbiturates, some contrast media, and solutions of alkalis or strong acids.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Abuse. Reports of the abuse of diphenhydramine hydrochloride.

1. Anonymous. Is there any evidence that Benylin syrup is addictive? *BMJ* 1979; **1:** 459.
2. Smith SG, Davis WM. Nonmedical use of butorphanol and diphenhydramine. *JAMA* 1984; **252:** 1010.
3. Feldman MD, Behar M. A case of massive diphenhydramine abuse and withdrawal from use of the drug. *JAMA* 1986; **255:** 3119–20.
4. de Nesnera AP. Diphenhydramine dependence: a need for awareness. *J Clin Psychiatry* 1996; **57:** 136–7.
5. Dinndorf PA, *et al.* Risk of abuse of diphenhydramine in children and adolescents with chronic illnesses. *J Pediatr* 1998; **133:** 293–5.

Extrapyramidal disorders. Reports of dystonic extrapyramidal reactions to diphenhydramine.

1. Lavenstein BL, Cantor FK. Acute dystonia: an unusual reaction to diphenhydramine. *JAMA* 1976; **236:** 291.
2. Santora J, Rozek S. Diphenhydramine-induced dystonia. *Clin Pharm* 1989; **8:** 471.
3. Roila F, *et al.* Diphenhydramine and acute dystonia. *Ann Intern Med* 1989; **111:** 92–3.

Overdosage. In an evaluation of 136 cases, one fatal, of intoxication with diphenhydramine, the plasma concentration was correlated with frequency or extent of symptoms.[1] The most common symptom was impaired consciousness; psychosis, seizures, antimuscarinic symptoms such as mydriasis, tachycardia, and tachyarrhythmias, and respiratory failure were also observed. The positive association between dose and frequency and severity of symptoms was confirmed in a more recent study;[2] it was also found that severe symptoms were more likely to occur when 1 g or more of diphenhydramine had been taken.

There have been reports[3,4] of rhabdomyolysis as an effect of oral diphenhydramine overdosage. The liberal application of a lotion containing diphenhydramine produced acute delirium with visual and auditory hallucinations in a 9-year-old boy[5] and similar effects were seen in 3 children with varicella-zoster infection following the topical application of diphenhydramine (2 of these children also received oral diphenhydramine).[6]

1. Köppel C, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. *Clin Toxicol* 1987; **25:** 53–70.
2. Radovanovic D, *et al.* Dose-dependent toxicity of diphenhydramine overdose. *Hum Exp Toxicol* 2000; **19:** 489–95.
3. Hampel G, *et al.* Myoglobinuric renal failure due to drug-induced rhabdomyolysis. *Hum Toxicol* 1983; **2:** 197–203.
4. Haas CE, *et al.* Rhabdomyolysis and acute renal failure following an ethanol and diphenhydramine overdose. *Ann Pharmacother* 2003; **37:** 538–42.
5. Filloux F. Toxic encephalopathy caused by topically applied diphenhydramine. *J Pediatr* 1986; **108:** 1018–20.
6. Chan CYJ, Wallander KA. Diphenhydramine toxicity in three children with varicella-zoster infection. *DICP Ann Pharmacother* 1991; **25:** 130–2.

Porphyria. Diphenhydramine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. A pregnant woman who was receiving diphenhydramine hydrochloride 150 mg daily for a pruritic rash gave birth to an infant who developed diarrhoea and generalised tremulousness 5 days later.[1] The delay in appearance of withdrawal symptoms was considered to be due to reduced activity of glucuronyl conjugating enzymes in the first few days of life.

For discussion of the use of antihistamines in pregnancy, including a suggestion of a relationship between inguinal hernia or genito-urinary malformations and diphenhydramine exposure, see p.563. See also under Interactions, below, for a report of perinatal death possibly associated with temazepam and diphenhydramine.

1. Parkin DE. Probable Benadryl withdrawal manifestations in a new-born infant. *J Pediatr* 1974; **85:** 580.

Interactions

As for the sedating antihistamines in general, p.563. Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 that is partly responsible for the metabolism of some beta blockers including metoprolol and the antidepressant venlafaxine.

Benzodiazepines. There has been a report[1] suggesting that a reduction in *temazepam* metabolism caused by diphenhydramine may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Pharmacokinetics

Diphenhydramine hydrochloride is well absorbed from the gastrointestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral doses. Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Metabolism is extensive. Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged drug. The elimination half-life has been reported to range from 2.4 to 9.3 hours.

◊ References.

1. Glazko AJ, *et al.* Metabolic disposition of diphenhydramine. *Clin Pharmacol Ther* 1974; **16:** 1066–76.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97. (includes studies indicating a correlation between plasma concentrations and both antihistaminic and sedative effects).
3. Simons KJ, *et al.* Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990; **30:** 665–71.
4. Scavone JM, *et al.* Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharmacol* 1998; **38:** 603–9.

Uses and Administration

Diphenhydramine, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). It is also used for its antiemetic properties in the treatment of nausea and vomiting (p.564), particularly in the prevention and treatment of motion sickness (when it should be given at least 30 minutes before travelling), and in the treatment of vertigo of various causes (p.565). Diphenhydramine is used for its antimuscarinic properties in the control of parkinsonism (p.791) and drug-induced extrapyramidal disorders (p.971) (although the possibility that diphenhydramine itself may cause extrapyramidal symptoms should be remembered). Diphenhydramine has pronounced central sedative properties and may be used as a hypnotic in the short-term management of insomnia (p.564). It is a common ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p.564). However, such preparations should be used with caution in children, and generally avoided in those under 2 years of age (see p.562). It may also be given in combination preparations containing analgesics, particularly paracetamol. Diphenhydramine may be used parenterally as an adjunct in the emergency treatment of anaphylactic shock (p.563) or when oral therapy is not feasible.

For most indications, diphenhydramine hydrochloride is given in usual oral doses of 25 to 50 mg three or four times daily. The dose for children is 6.25 to 25 mg three or four times daily, or a total daily dose of 5 mg/kg may be given in divided doses. The maximum dose in adults and children is about 300 mg daily. A dose of 20 to 50 mg may be used as a hypnotic in adults and children over 12 years old.

When oral therapy is not feasible, diphenhydramine hydrochloride may be given by deep intramuscular injection or by intravenous injection using concentrations of 1% or 5%. Usual doses are 10 to 50 mg, although doses of 100 mg have been given. No more than 400 mg should be given in 24 hours. Children may be given 5 mg/kg daily in divided doses to a maximum of 300 mg in 24 hours. Diphenhydramine hydrochloride is applied topically, usually in preparations containing 1 to 2% although, as with other antihistamines, there is a risk of sensitisation.

Diphenhydramine citrate is given orally in a dose of 76 mg at night in combination preparations for its hypnotic action. Diphenhydramine di(acefyllinate) is given as an antiemetic for the prevention and treatment of motion sickness. The usual oral dose is 90 to 135 mg, which may be repeated if necessary at intervals of at least 6 hours, to a maximum of 540 mg daily. Other diphenhydramine salts that have been used include the polistirex, the salicylate, and the tannate by mouth, the methylbromide rectally, and the metilsulfate applied topically.

Dimenhydrinate (p.576) is diphenhydramine teoclate and mefenidramium metilsulfate is diphenhydramine methylsulfomethylate.

Preparations

BP 2008: Diphenhydramine Oral Solution;
USP 31: Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Diphenhydramine and Pseudoephedrine Capsules; Diphenhydramine Hydrochloride Capsules; Diphenhydramine Hydrochloride Elixir; Diphenhydramine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Alermina; Amodormin; Benadryl; Benadryl Antialergico†; Caladryl D; Drepatil†; Fabolergic; Histaler; Klonadryl; Mudantos H†; ***Austral.:*** Snuzaid; Unisom; ***Austria:*** Calmaben; Dermodrin; Dibondrin; Histaxin; Noctor; Sleepia†; ***Belg.:*** Azaron; Benylin; Diphamine; Nuicalm†; Nustasium; R Calm; ***Braz.:*** Difenidrin; ***Canad.:*** Aller-Aide; Allerdryl; Allergy Caplets; Allergy Elixir; Allergy Formula; Allernix; Benadryl; Calmex; Children's Allergy Formula; Dormex; Dormiphen; Insomnal; Jack & Jill Bedtime; Jack & Jill Thin Strips Cough & Cold; Neo Citran Nighttime Cough; Nytol; Simply Sleep; Sleep Aid; Sleep-Eze D; Sominex; Triaminic Thin Strips Nighttime Cough & Runny Nose; Unisom; ***Chile:*** Jaquedryl; Pasifen†; Somol; ***Cz.:*** Benadryl N†; Psilo-Balsam; ***Fr.:*** Butix; Nautamine; ***Ger.:*** Benadryl N†; Betadorm D; Dolestan; Dormutil N†; Emesan; Halbmond†; Hevert-Dorm; Moradorm; nervo OPT N; ratioAllerg†; S.8; Sedativum-Hevert; Sediat; Sedopretten; Sleepia†; Vivinox Sleep; ***Gr.:*** Benadryl; ***Hong Kong:*** Benadryl†; Calox†; Hydramine Cream†; Unisom; ***Hung.:*** Psilo-Balsam; ***India:*** Benadryl; Cofryl; Dimiril†; ***Indon.:*** Arcodryl; Benadryl; Otede; Paradryl; Recodryl; Sidiadryl; ***Israel:*** Nytol; ***Ital.:*** Aliserin; Allergan; Nytol†; ***Mex.:*** Benadryl; Bionaryl; Bonanoti; Drafen; Glicodril; Histadryl; Indumir; Lurispan; Nytol; Tzoali†; Ulcoid; Unisom†; ***NZ:*** Unisom; ***Philipp.:*** Allerin AH; Benadryl Antihistamine; Benaxil; Dramelin; ***Port.:*** Benaderma; Benergina; Codilergi; Nytol†; ***Rus.:*** Psilo-Balsam (Псило-Бальзам); ***S.Afr.:*** Betasleep; Sleepeze-PM; ***Singapore:*** Benocten; Paxidorm; ***Spain:*** Benadryl; Neosayomol; Nytol; Sonodor; ***Swed.:*** Desentol; ***Switz.:*** Bedorma; Benocten; Comprimes somniferes "S"; Dobacen†; Sleepia†; ***Thai.:*** Benadryl; ***Turk.:*** Allenik; Allerjin; Benison; Fenotral; ***UAE:*** Amydramine II; ***UK:*** Adult Chesty Cough; Child Chesty Cough; Dreemon; Histergan; Mandalyn Paediatric; Nightcalm; Nytol; Paxidorm; Sleep Aid; Sleepeaze; ***USA:*** 40 Winks; Aler-Dryl; AllerMax; Altaryl Childrens Allergy; Banophen Allergy; Ben-Tann; Benadryl; Benadryl Allergy; Benadryl Childrens Allergy; Benadryl Itch; Childrens PediaCare Nighttime Cough; Compoz Night-time Sleep Aid; Dermamycin; Diphen AF; Diphenhist; Dormin; Dytan; Dytuss; Genahist; Maximum Strength Sleepinal; Maximum Strength Unisom SleepGels; Miles Nervine; MouthKote P/R†; Nytol; Scot-Tussin Allergy; Siladryl; Silphen; Simply Sleep; Sleep-Ettes D; Sleepwell 2-nite; Snooze Fast; Sominex; Triaminic Cough & Runny Nose; Tusstat; Twilite; ***Venez.:*** Benadryl; Di-Fedril†; Ystal†.

Multi-ingredient: numerous preparations are listed in Part 3.

Diphenylpyraline Hydrochloride *(BANM, rINNM)*

Diphénylpyraline, Chlorhydrate de; Diphenylpyralini Hydrochloridum; Hidrocloruro de difenilpiralina. 4-Benzhydryloxy-1-methylpiperidine hydrochloride.

Дифенилпиралина Гидрохлорид

$C_{19}H_{23}NO,HCl = 317.9.$

CAS — 147-20-6 (diphenylpyraline); 132-18-3 (diphenylpyraline hydrochloride).

ATC — R06AA07.

ATC Vet — QR06AA07.

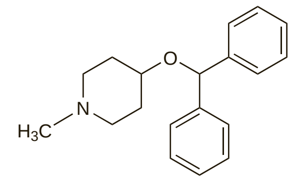

(diphenylpyraline)

Pharmacopoeias. In *Br.*

BP 2008 (Diphenylpyraline Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

◊ References.

1. Graham G, Bolt AG. Half-life of diphenylpyraline in man. *J Pharmacokinet Biopharm* 1974; **2:** 191–5 (ranged from 24 to 40 hours).

Uses and Administration

Diphenylpyraline hydrochloride, a piperidine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties.

It has been given for the symptomatic relief of allergic conditions including rhinitis (p.565), and in pruritic skin disorders (p.565). It has also been used in compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Diphenylpyraline hydrochloride has been given in an oral dose of up to 6 mg daily in 3 or 4 divided doses. Diphenylpyraline and diphenylpyraline hydrochloride have been applied topically although, as with other antihistamines, there is a risk of sensitisation.

Diphenylpyraline teoclate is piprinhydrinate (p.588).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Arbid N†.

Multi-ingredient: ***Austria:*** Arbid; Astronautal; Eucillin; Prurimix; Tropoderm; ***Belg.:*** Bicold†; Rhini-San; ***Braz.:*** Ornatrol†; ***Canad.:*** Creo-Rectal; Vito Bronches†; ***Cz.:*** Proctospre†; Prurimix†; ***Ger.:*** Perdiphen†; Proctospre†; Tempil N; ***Hong Kong:*** Phenahist; ***India:*** Eskold Expectorant†; Eskold†; ***Mex.:*** Flumil; ***S.Afr.:*** Actophlem; Eskornade; Solphyllex; Theophen Comp; ***Switz.:*** Arbid.

Doxylamine Succinate *(BANM, rINNM)*

Doksilamin Süksinat; Doksilamino-vandenilio sukcinatas; Doksylamiinivetysuksinaatti; Doxilamin-hidrogén-szukcinát; Doxylamine Hydrogen Succinate; Doxylamine, hydrogénosuccinate de; Doxylamine, Succinate de; Doxylamin-hydrogen-sukcinát; Doxylamini hydrogenosuccinas; Doxylamini Succinas; Doxylaminium Succinate; Doxylaminvätesuccinat; Histadoxylamine Succinate; Succinato de doxilamina. *NN*-Dimethyl-2-[α-methyl-α-(2-pyridyl)benzyloxy]ethylamine hydrogen succinate.

Доксиламина Сукцинат

$C_{17}H_{22}N_2O,C_4H_6O_4 = 388.5.$

CAS — 469-21-6 (doxylamine); 562-10-7 (doxylamine succinate).

ATC — R06AA09.

ATC Vet — QR06AA09.

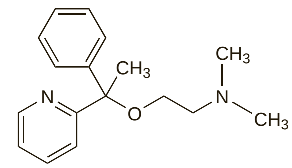

(doxylamine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Doxylamine Hydrogen Succinate; Doxylamine Succinate BP 2008). A white or almost white powder. Very soluble in water; freely soluble in alcohol.

USP 31 (Doxylamine Succinate). A white or creamy-white powder having a characteristic odour. Soluble 1 in 1 of water, 1 in 2 of alcohol and of chloroform, and 1 in 370 of ether; very slightly soluble in benzene. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. The controversy surrounding the use in pregnancy of combination products of doxylamine is discussed on p.563.

Overdosage. In an evaluation of 109 cases of intoxication with doxylamine,[1] no correlation was found between the amount ingested or plasma concentration and the frequency or extent of symptoms. The most common symptom was impaired consciousness. Psychotic behaviour, seizures, and antimuscarinic symptoms such as tachycardia and mydriasis were also observed. Rhabdomyolysis occurred in one patient and was accompanied by transient impairment of renal function. The same group commented[2] that rhabdomyolysis had been noted in 7 of 442 cases of doxylamine overdosage, with an associated rise in plasma creatine kinase and myoglobinuria, and suggested that doxylamine has a direct toxic effect on striated muscle.

1. Köppel C, *et al.* Poisoning with over-the-counter doxylamine preparations: an evaluation of 109 cases. *Hum Toxicol* 1987; **6:** 355–9.
2. Köppel C, *et al.* Rhabdomyolysis in doxylamine overdose. *Lancet* 1987; **i:** 442–3.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

After oral doses of doxylamine succinate peak plasma concentrations occur after 2 to 3 hours. An elimination half-life of about 10 hours has been reported.

◊ References.

1. Friedman H, *et al.* Clearance of the antihistamine doxylamine: reduced in elderly men but not in elderly women. *Clin Pharmacokinet* 1989; **16:** 312–16.

Uses and Administration

Doxylamine succinate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and pronounced sedative effects.

Doxylamine succinate is given for the symptomatic relief of hypersensitivity reactions, in pruritic skin disorders (p.565), as a hypnotic in the short-term treatment of insomnia (p.564), and as an ingredient of compound preparations for symptomatic treatment of coughs and the common cold (p.564).

In general it is no longer used in the management of nausea and vomiting of early pregnancy (see p.563 for the controversy that has surrounded the use in pregnancy of combination products of doxylamine).

Oral doses of up to 25 mg of doxylamine succinate have been given every 4 to 6 hours to a maximum of 150 mg daily. The usual hypnotic dose is 25 mg orally at night.

Preparations

USP 31: Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Doxylamine Succinate Syrup; Doxylamine Succinate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dozile; Restavit; ***Canad.:*** Unisom-2; ***Chile:*** Calmex; Dorminoctil; Nocpaz; Trimepaz†; Zarcop; ***Cz.:*** Hoggar N†; ***Fr.:*** Donormyl; Lidene; Noctyl; ***Ger.:*** Gittalun; Hewedormir doxyl intens†; Hoggar Night; Mereprine; Munleit†; SchlafTabs; Sedaplus; ***India:*** Rest-Aid; ***Israel:*** Sleep Aid; Unisom; ***NZ:*** Dozile; ***Philipp.:*** Unisom; ***Port.:*** Dormidina; ***S.Afr.:*** Equi-Sleep†; Restwel; Somnil; ***Spain:*** Dormidina; ***Switz.:*** Sanalepsi N; ***Turk.:*** Unisom; ***USA:*** Aldex AN; Unisom SleepTabs.

Multi-ingredient: ***Austral.:*** Analgesic/Calmative; Codalgin Plus; Dimetapp Cold, Cough & Flu; Dolased Analgesic Calmative; Dolased Day/Night Pain Relief; Fiorinal; Mersyndol; Ordov Migradol†; Panadeine Plus; Panalgesic; ***Austria:*** Wick Erkaltungs-Saft fur die Nacht; Wick Hustensaft; ***Belg.:*** Pholco-Mereprine; ***Braz.:*** Broncolex†; EMS Expectorante; Hytos Plus; Revenil; Revenil Dospan; Revenil Expectorante; Silencium; Silomat Plus†; ***Canad.:*** Dalmacol; Diclectin; Mersyndol with Codeine; Neo Citran Cold & Flu†; Nighttime; Nighttime Cold & Flu; Nyquil Sinus; NyQuil†; ratio-Calmydone; Regular Strength Sinus Medication; Tylenol Sinus (Nighttime Relief); Vicks Nyquil Cold & Flu; ***Cz.:*** Wick Medinait†; ***Fr.:*** DolirhumePro; ***Ger.:*** Paedisup; Wick Medinait; ***India:*** Doxinate; Vominate; ***Indon.:*** Dexmolex; Siladex; ***Irl.:*** Syndol; ***Ital.:*** Vicks Medinait; ***NZ:*** Dimetapp Cold, Cough & Flu Day & Night†; Mersyndol; Pryndette†; ***Pol.:*** Tabcin Impakt; ***Port.:*** Nausefe; ***S.Afr.:*** Abflex; Acurate; Adco-Dol; Asic; B-Dol; Betapyn; Cepacol; Codoxol; Doxsyn; Forpyn†; Lenapain; Nethaprin Dospan; Nethaprin Expectorant; Nomopain; Paxidal; Pynclear†; Pynstop; Sedapain; Sedinol; Syndol; Tensopyn; Vicks Medinite; Xerotens†; ***Spain:*** Cariban; Medinait; Vicks Medinait†; ***Switz.:*** Vicks Medinait; ***Turk.:*** Vicks MediNait; ***UK:*** Painex; Propain Plus; Syndol; Vicks Medinite; ***USA:*** Alka-Seltzer Plus Night-Time Cold; All-Nite Cold Formula; Genite; Night Time Cold/Flu Relief; Nite Time Cold Formula; NyQuil Hot Therapy; NyQuil Nighttime Cold/Flu; Nytcold Medicine; Vicks NyQuil LiquiCaps; Vicks NyQuil Multi-Symptom Cold Flu Relief; Vicks NyQuil Sinus; ***Venez.:*** Mercindol.

Ebastine *(BAN, USAN, rINN)*

Ebastiini; Ebastin; Ebastina; Ebastinas; Ébastine; Ebastinum; LAS-W-090; W-090. 4′-*tert*-Butyl-4-[4-(diphenylmethoxy)piperidino]butyrophenone.

Эбастин

$C_{32}H_{39}NO_2$ = 469.7.
CAS — 90729-43-4.
ATC — R06AX22.
ATC Vet — QR06AX22.

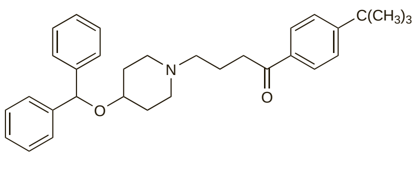

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ebastine). A white or almost white crystalline powder. M.p. about 86°. Practically insoluble in water; very soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

Profile

Ebastine, a piperidine derivative, is a non-sedating antihistamine (p.561) with a long duration of action. It does not have significant sedative or antimuscarinic actions.

Ebastine is given for the symptomatic relief of allergic conditions including rhinitis (p.565) and in pruritic skin disorders (p.565). The usual oral dose is 10 to 20 mg daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

◊ References.

1. Luria X. Comparative clinical studies with ebastine: efficacy and tolerability. *Drug Safety* 1999; **21** (suppl 1): 63–7.
2. Hurst M, Spencer CM. Ebastine: an update of its use in allergic disorders. *Drugs* 2000; **59:** 981–1006.
3. Lasseter KC, *et al.* Pharmacokinetics and safety of ebastine in patients with impaired hepatic function compared with healthy volunteers: a phase I open-label study. *Clin Pharmacokinet* 2004; **43:** 121–9.
4. Noveck RJ, *et al.* Pharmacokinetics and safety of ebastine in healthy subjects and patients with renal impairment. *Clin Pharmacokinet* 2007; **46:** 525–34.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ebastel†; ***Belg.:*** Estivan; ***Braz.:*** Ebastel; ***Chile:*** Ebastel†; ***Cz.:*** Kestine†; ***Denm.:*** Kestine; ***Fin.:*** Kestine; ***Fr.:*** Kestin; ***Ger.:*** Ebastel; ***Gr.:*** Kestine; ***Hong Kong:*** Kestine; ***Ital.:*** Clever; Kestine; ***Jpn:*** Ebastel; ***Mex.:*** Evastel; ***Neth.:*** Kestine; Netan; ***Norw.:*** Kestine; ***Philipp.:*** Aleva; ***Port.:*** Estivan; Kestine; ***Rus.:*** Kestine (Кестин); ***S.Afr.:*** Kestine; ***Singapore:*** Kestine; ***Spain:*** Bactil; Busidril†; Ebastel; ***Swed.:*** Kestine; ***Venez.:*** Ebastel.

Multi-ingredient: ***Arg.:*** Ebastel D†; ***Braz.:*** Ebastel D; ***Mex.:*** Evastel-D; ***Spain:*** Rino Ebastel; Rinobactil.

Embramine Hydrochloride *(BANM, rINNM)*

Embramine, Chlorhydrate d'; Embramini Hydrochloridum; Embraminium Chloratum; Hidrocloruro de embramina; Mebrophenhydramine Hydrochloride; Mebrophenhydraminium Chloratum. 2-(4-Bromo-α-methylbenzhydryloxy)-*NN*-dimethylethylamine hydrochloride.

Эмбрамина Гидрохлорид

$C_{18}H_{22}BrNO,HCl$ = 384.7.
CAS — 3565-72-8 (embramine); 13977-28-1 (embramine hydrochloride); 21661-63-2 (embramine teoclate).

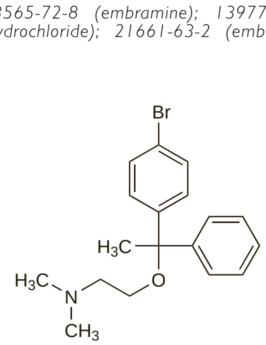

(embramine)

Profile

Embramine hydrochloride, a monoethanolamine derivative, is a sedating antihistamine (p.561). Embramine hydrochloride and embramine teoclate have been given orally for their antihistamine and antiemetic properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Medrin; ***India:*** Mebryl.

Emedastine Fumarate *(BANM, rINNM)*

AL-3432A; Emedastiinidifumaraatti; Emedastin difumarát; Emedastin Fumarat; Emedastindifumarat; Emedastine Difumarate *(USAN)*; Émédastine, difumarate d'; Émédastine, Fumarate d'; Emedastini difumaras; Emedastini Fumaras; Emedastyny difumaran; Fumarato de emedastina; KB-2413; KG-2413; LY-188695. 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)benzimidazole fumarate (1:2).

Эмедастина Фумарат

$C_{17}H_{26}N_4O,2C_4H_4O_4$ = 534.6.
CAS — 87233-61-2 (emedastine); 87233-62-3 (emedastine fumarate).
ATC — S01GX06.
ATC Vet — QS01GX06.

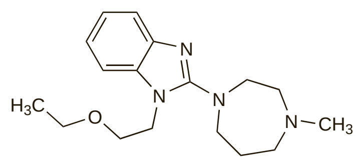

(emedastine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Emedastine Difumarate). A white or yellowish powder. It exhibits polymorphism. Soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 0.2% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 31 (Emedastine Difumarate). A white to faintly yellow crystalline powder. Soluble in water. pH of a 0.2% solution in water is between 3.0 and 4.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the antihistamines in general, p.561.

Ocular corneal infiltrates, local irritation, photophobia, rhinitis, and headaches have been reported after use of emedastine eye drops. Treatment should be stopped if corneal infiltrates develop.

Pharmacokinetics

Emedastine is absorbed from the gastrointestinal tract, peak plasma concentrations being attained about 3 hours after an oral dose. It is mainly metabolised in the liver to two primary metabolites 5- and 6-hydroxyemedastine which are excreted in the urine along with a small amount of unchanged drug. Small amounts of emedastine are absorbed after application to the eye. The elimination half-life is reported to be 7 hours after an oral dose and 10 hours following topical use.

Uses and Administration

Emedastine is an antihistamine. It is instilled twice daily as the fumarate as eye drops containing the equivalent of 0.05% of emedastine for the symptomatic relief of allergic conjunctivitis (p.564). It is also given orally in usual doses of 2 to 4 mg of the fumarate daily in two divided doses for allergic rhinitis (p.565), urticaria (p.565), and pruritic skin disorders (p.565).

Preparations

USP 31: Emedastine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austria: Emadine; ***Belg.:*** Emadine; ***Braz.:*** Emadine; ***Canad.:*** Emadine; ***Cz.:*** Emadine; ***Denm.:*** Emadine; ***Fin.:*** Emadine; ***Fr.:*** Emadine; ***Ger.:*** Emadine; ***Gr.:*** Emadine; ***Hong Kong:*** Emadine; ***Hung.:*** Emadine; ***Irl.:*** Emadine; ***Israel:*** Emadine; ***Ital.:*** Emadine; ***Jpn:*** Daren; Remicut; ***Malaysia:*** Emadine; ***Neth.:*** Emadine; ***Norw.:*** Emadine; ***Pol.:*** Emadine; ***Port.:*** Emadine; ***S.Afr.:*** Emadine; ***Spain:*** Emadine; ***Swed.:*** Emadine; ***Switz.:*** Emadine; ***Thai.:*** Emadine; ***Turk.:*** Emadine; ***UK:*** Emadine; ***USA:*** Emadine.

Epinastine Hydrochloride *(rINNM)*

Épinastine, Chlorhydrate d'; Epinastine, chlorhydrate d'; Epinastini hydrochloridum; Hidrocloruro de epinastina; WAL-801-Cl. 3-Amino-9,13b-dihydro-1*H*-dibenz[*c,f*]imidazo[1,5-*a*]azepine hydrochloride.

Эпинастина Гидрохлорид

$C_{16}H_{15}N_3,HCl$ = 285.8.
CAS — 80012-43-7 (epinastine).
ATC — R06AX24; S01GX10.
ATC Vet — QR06AX24; QS01GX10.

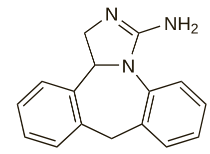

(epinastine)

Profile

Epinastine hydrochloride is an antihistamine (p.561) reported to have no significant sedative activity. It has been given orally in the management of allergic rhinitis and pruritic skin disorders. It is also used twice daily as eye drops, usually in a concentration of 0.05%, in the symptomatic relief of allergic conjunctivitis.

◊ References.

1. Sarashina A, *et al.* Population pharmacokinetics of epinastine, a histamine H receptor antagonist, in adults and children. *Br J Clin Pharmacol* 2005; **59:** 43–53.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alket; Flurinol; ***Belg.:*** Relestat; ***Braz.:*** Talerc; ***Chile:*** Flurinol; ***Cz.:*** Purivist; ***Fr.:*** Purivist; ***Ger.:*** Relestat; ***Gr.:*** Relestat; ***Hung.:*** Relestat; ***Irl.:*** Relestat; ***Ital.:*** Relestat; ***Jpn:*** Alesion; ***Mex.:*** Flurinol; ***Neth.:*** Relestat; ***Pol.:*** Relestat; ***Port.:*** Relestat; ***Spain:*** Relestat; ***Swed.:*** Relestat; ***Switz.:*** Relestat; ***UK:*** Relestat; ***USA:*** Elestat; ***Venez.:*** Flurinol.

Multi-ingredient: ***Arg.:*** Flurinol D; ***Mex.:*** Flurinol D.

Fexofenadine Hydrochloride

(BANM, USAN, rINNM)

Feksofenadiinihydrokloridi; Feksofenadin Hidroklorür; Fexofénadine, chlorhydrate de; Fexofenadinhydroklorid; Fexofenadini hydrochloridum; Hidrocloruro de fexofenadina; MDL-16455A; Terfenadine Carboxylate Hydrochloride. (±)-*p*-{1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-piperidino]butyl}-α-methylhydratropic acid hydrochloride.

Фексофенадина Гидрохлорид

$C_{32}H_{39}NO_4,HCl$ = 538.1.
CAS — 138452-21-8.
ATC — R06AX26.
ATC Vet — QR06AX26.

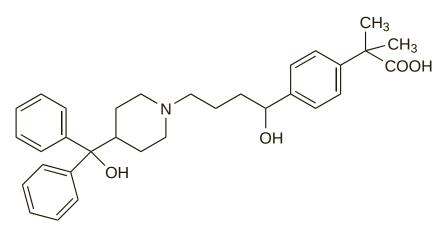

(fexofenadine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fexofenadine Hydrochloride). A white or almost white powder. Slightly soluble in water; freely soluble in methyl alcohol; very slightly soluble in acetone. It exhibits polymorphism.

USP 31 (Fexofenadine Hydrochloride). Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561.

Arrhythmias. A 67-year-old man suffered syncope after taking fexofenadine 180 mg daily for 2 months.[1] His ECG showed an abnormally prolonged QT interval which shortened once fexofenadine was stopped, although the interval tended to be long even without drug therapy. Nonetheless rechallenge was positive. The manufacturers of fexofenadine have commented[2] that the patient was at risk of developing arrhythmias before taking the drug.

The symbol † denotes a preparation no longer actively marketed

The ECG effects of fexofenadine have been studied[3] in normal subjects and doses of up to 480 mg daily [4 times the recommended dose for seasonal allergic rhinitis] did not prolong the QT interval. See also p.562.

1. Pinto YM, *et al.* QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 980.
2. Giraud T. QT lengthening and arrhythmias associated with fexofenadine. *Lancet* 1999; **353:** 2072.
3. Pratt CM, *et al.* Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999; **83:** 1451–4.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving fexofenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

See also under Adverse Effects and Precautions, in Terfenadine, p.590.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)

Psoriasis. Exacerbation of psoriasis has been reported[1] in association with the use of fexofenadine.

1. Saraswat A, Saraswat M. Pustular exacerbation of psoriasis due to fexofenadine. *Clin Exp Dermatol* 2006; **31:** 477–8.

Interactions

As for the non-sedating antihistamines in general, p.563.

Plasma concentrations of fexofenadine have been increased when given with erythromycin or ketoconazole, but, unlike terfenadine, licensed product information states that this was not associated with adverse effects on the QT interval.

Antacids containing aluminium and magnesium hydroxide have reduced the absorption of fexofenadine. Fruit juices including grapefruit may reduce the bioavailability of fexofenadine and use together should be avoided.

◊ References.

1. Dresser GK, *et al.* Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 2005; **77:** 170–7.

Pharmacokinetics

Fexofenadine is rapidly absorbed after oral doses with peak plasma concentrations being reached in 2 to 3 hours. It is about 60 to 70% bound to plasma proteins. About 5% of the total dose is metabolised, mostly by the intestinal mucosa, with only 0.5 to 1.5% of the dose undergoing hepatic biotransformation by the cytochrome P450 system. Elimination half-life of about 14 hours has been reported although this may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine does not appear to cross the blood-brain barrier.

Fexofenadine is a metabolite of terfenadine and as such has been detected in breast milk after the administration of terfenadine.

◊ References.

1. Russell T, *et al.* Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. *Clin Pharmacol Ther* 1998; **64:** 612–21.

Uses and Administration

Fexofenadine, an active metabolite of terfenadine (p.590), is a non-sedating antihistamine. It does not possess significant sedative or antimuscarinic actions. Fexofenadine is used as the hydrochloride in the symptomatic relief of allergic conditions including seasonal allergic rhinitis (p.565) and chronic urticaria (p.565).

In the UK a dose of fexofenadine hydrochloride 120 mg once daily is given orally in the treatment of seasonal allergic rhinitis; the recommended dose in chronic idiopathic urticaria is 180 mg once daily. US licensed product information suggests a dose of 60 mg twice daily or 180 mg once daily for both indications.

Fexofenadine is also used with a decongestant such as pseudoephedrine hydrochloride.

For doses in children or in patients with renal impairment, see below.

◊ References.

1. Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; **55:** 269–74.
2. Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 2000; **59:** 301–21.
3. Kawashima M, *et al.* Review of fexofenadine in the treatment of chronic idiopathic urticaria. *Int J Dermatol* 2002; **41:** 701–6.
4. Meeves SG, Appajosyula S. [Aventis, USA]. Efficacy and safety profile of fexofenadine HCl: a unique therapeutic option in H1-receptor antagonist treatment. *J Allergy Clin Immunol* 2003; **112** (suppl): S69–S77.
5. Mansfield LE. Once-daily immediate-release fexofenadine and sustained-release pseudoephedrine combination: a new treatment option for allergic rhinitis. *Expert Opin Pharmacother* 2006; **7:** 941–51.

Administration in children. Fexofenadine hydrochloride is used in children for the treatment of seasonal allergic rhinitis in an oral dose of 30 mg twice daily; in the UK it is licensed for use in children aged 6 to 11 years whereas in the USA it may be used in children as young as 2 years.

In the USA, fexofenadine is also licensed for use in paediatric chronic idiopathic urticaria. The dose in children aged 6 months to less than 2 years is 15 mg twice daily; older children may be given 30 mg twice daily.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. US licensed product information recommends that initial oral doses of fexofenadine hydrochloride in adults with renal impairment should be reduced to 60 mg once daily. In children with renal impairment, the initial dose should be reduced to 30 mg once daily in patients aged 2 to 11 years, and to 15 mg once daily in children aged 6 months to less than 2 years.

UK product information advises that fexofenadine should be given with caution to patients with renal impairment; however, it also states that dose adjustment is not considered to be necessary in such patients.

Preparations

USP 31: Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Fexofenadine Hydrochloride Capsules; Fexofenadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alerfedine; Allegra; Fexofen†; ***Austral.:*** Fexotabs; Telfast; Xergic; ***Austria:*** Telfast; ***Belg.:*** Telfast; ***Braz.:*** Allegra; Altiva; ***Canad.:*** Allegra; ***Chile:*** Aerodan; Alexia; Allegra; Fenax; ***Cz.:*** Afexil; Ewofex; Telfast; ***Denm.:*** Telfast; ***Fin.:*** Telfast; ***Fr.:*** Telfast; ***Ger.:*** Telfast; ***Hong Kong:*** Telfast; ***Hung.:*** Altiva; Telfast; ***India:*** Alernex†; Allegra; Fexigra; Fexofen; Fexova; Odifex; ***Indon.:*** Telfast; ***Irl.:*** Telfast; ***Israel:*** Telfast; ***Ital.:*** Kalicet†; Telfast; ***Malaysia:*** Telfast; ***Mex.:*** Allegra; ***Neth.:*** Telfast; ***Norw.:*** Telfast; ***NZ:*** Telfast; Xergic; ***Philipp.:*** Telfast; ***Pol.:*** Telfast; ***Port.:*** Telfast; ***Rus.:*** Fexadin (Фексадин); Telfast (Телфаст); ***S.Afr.:*** Telfast; ***Singapore:*** Telfast; ***Spain:*** Telfast; ***Swed.:*** Telfast; ***Switz.:*** Telfast; ***Thai.:*** Fenafex; Telfast; ***Turk.:*** Fexadyne; Fexofen; Telfast; ***UK:*** Telfast; ***USA:*** Allegra; ***Venez.:*** Allegra; Fexidine; Fexoril; Rinolast.

Multi-ingredient: ***Arg.:*** Alerfedine D; Allegra-D; ***Austral.:*** Telfast Decongestant; ***Braz.:*** Allegra-D; ***Canad.:*** Allegra-D; ***Chile:*** Alexia D; Allegra-D; ***Hong Kong:*** Telfast-D; ***Indon.:*** Telfast Plus; ***Malaysia:*** Altiva-D; Telfast-D; ***Mex.:*** Allegra-D; ***NZ:*** Telfast Decongestant†; ***Singapore:*** Telfast-D; ***USA:*** Allegra-D; ***Venez.:*** Allegra-D; Rinolast D.

Flunarizine Hydrochloride *(BANM, USAN, rINNM)*

Flunaritsiinidihydrokloridi; Flunarizin-dihydrochlorid; Flunarizindihydroklorid; Flunarizine, Chlorhydrate de; Flunarizine, dichlorhydrate de; Flunarizini dihydrochloridum; Flunarizini Hydrochloridum; Flunarizino dihidrochloridas; Hidrocloruro de flunarizina; R-14950. *trans*-1-Cinnamyl-4-(4,4′-difluorobenzhydryl)piperazine dihydrochloride.

Флунаризина Гидрохлорид

$C_{26}H_{26}F_2N_2,2HCl = 477.4.$

CAS — 52468-60-7 (flunarizine); 30484-77-6 (flunarizine hydrochloride).

ATC — N07CA03.

ATC Vet — QN07CA03.

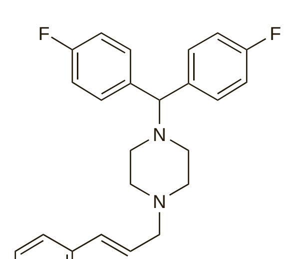

(flunarizine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flunarizine Dihydrochloride). A white or almost white hygroscopic powder. Slightly soluble in water, in alcohol, and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Adverse effects also seen with flunarizine include weight gain, extrapyramidal symptoms (sometimes associated with depression), and, rarely, galactorrhoea.

Extrapyramidal disorders. Extrapyramidal motor signs (including parkinsonism, orofacial tardive dyskinesia, and akathisia) have been reported in 12 patients given flunarizine 10 to 40 mg daily for between 3 weeks and 15 months; 11 also had mental depression.[1] Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects,[2-5] but the association with flunarizine has not always been certain. Some workers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extrapyramidal symptoms (geriatric patients)[2,6] or that flunarizine may unmask subclinical idiopathic Parkinson's disease.[6,7]

Extrapyramidal signs, including parkinsonism, have also been associated with the related drug, cinnarizine.[3-5] It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.[3]

1. Chouza C, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **i:** 1303–4.
2. Meyboom RHB, *et al.* Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. *Lancet* 1986; **ii:** 292.
3. Laporte J-R, Capella D. Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet* 1986; **ii:** 853–4.
4. Laporte J-R, Capella D. Useless drugs are not placebos. *Lancet* 1987; **i:** 1324.
5. Teive HAG, *et al.* Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord* 2004; **10:** 243–5.
6. Amery W. Side-effects of flunarizine. *Lancet* 1986; **i:** 1497.
7. Benvenuti F, *et al.* Side-effects of flunarizine. *Lancet* 1986; **ii:** 464.

Porphyria. Flunarizine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

As for the sedating antihistamines in general, p.563.

Hepatic enzyme inducers such as carbamazepine, phenytoin, and valproate may interact with flunarizine by increasing its metabolism; an increase in dosage of flunarizine may be required.

Pharmacokinetics

Flunarizine hydrochloride is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. Flunarizine hydrochloride is very lipophilic and is more than 90% bound to plasma proteins. It appears to undergo extensive metabolism; metabolites are excreted principally in the bile. Flunarizine hydrochloride has an elimination half-life of about 18 days.

Uses and Administration

Flunarizine is the difluorinated derivative of cinnarizine. It has antihistamine, sedative, and calcium-channel blocking activity. Flunarizine hydrochloride is used for migraine prophylaxis, for vertigo and vestibular disorders, and for peripheral and cerebral vascular disorders. It has also been used as adjunctive antiepileptic therapy in patients refractory to standard regimens.

Flunarizine is given orally as the hydrochloride although doses are expressed in terms of the base. Flunarizine hydrochloride 11.8 mg is equivalent to about 10 mg of flunarizine. The usual dose is 5 to 10 mg daily, usually given at night to minimise the effects of drowsiness.

Epilepsy. A number of drugs with calcium-channel blocking activity have been investigated as adjuncts in epilepsy (p.465), including flunarizine. Some individual studies have reported benefit, but a systematic review[1] concluded that although flunarizine might have a weak effect on seizure frequency the evidence was not convincing, and the withdrawal rate was significant, probably because of poor tolerability; it should therefore not be recommended as adjunctive antiepileptic therapy. The pharmacokinetic profile of flunarizine may in any case be too complex for clinical use as an antiepileptic.[2]

1. Chaisewikul R, *et al.* Calcium antagonists as an add-on therapy for drug-resistant epilepsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/05).
2. Hoppu K, *et al.* Flunarizine of limited value in children with intractable epilepsy. *Pediatr Neurol* 1995; **13:** 143–7.

Migraine. Flunarizine reduces the frequency of migraine attacks in both adult and paediatric patients and is used for the prophylaxis of migraine (p.616) in some countries. Its effects are comparable with several other prophylactic antimigraine drugs, including the generally preferred propranolol,[1-4] but it is more likely to be reserved for use when first-line drugs have proved to be ineffective or unsuitable. Its mode of action in migraine is unclear; possible mechanisms are inhibition of vasospasm induced by mediators such as serotonin and prostaglandins, inhibition of cellular hypoxia, and improved blood viscosity and erythrocyte deformability. Calcium-channel blocking activity might have a role, but evidence for the efficacy of other calcium-channel blockers in migraine prophylaxis (see Nifedipine, p.1355) is less convincing than for flunarizine.

Case reports have indicated benefit with flunarizine in the prophylaxis of the rare disorder of alternating hemiplegia in childhood[5,6] but a subsequent study[7] in 12 children did not produce conclusive findings. A later long-term study[8] reported that 7 of 9 children given flunarizine for up to 5 years for hemiplegia showed a reduction in the duration of attacks, and 3 had a reduction in frequency, but only 1 of these obtained a complete cessation of episodes.

The role of antihistamines in general in the management of migraine is discussed briefly on p.564.

1. Todd PA, Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; **38:** 481–99.
2. Andersson K-E, Vinge E. β-Adrenoceptor blockers and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs* 1990; **3:** 355–73.
3. Soelberg Sørensen P, *et al.* Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; **31:** 650–7.
4. Gawel MJ, *et al.* Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; **19:** 340–5.
5. Casaer P, Azou M. Flunarizine in alternating hemiplegia in childhood. *Lancet* 1984; **ii:** 579.
6. Curatolo P, Cusmai R. Drugs for alternating hemiplegic migraine. *Lancet* 1984; **ii:** 980.
7. Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics* 1987; **18:** 191–5.
8. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. *Neurology* 1993; **43:** 36–41.

Tourette's syndrome. A small unblinded study[1] involving 7 patients has suggested that flunarizine is more effective than placebo in the treatment of Tourette's syndrome (see Tics, p.954).

1. Micheli F, *et al.* Treatment of Tourette's syndrome with calcium antagonists. *Clin Neuropharmacol* 1990; **13:** 77–83.

Vertigo. Antihistamines are the mainstay of the treatment of vertigo (p.565). However, their antimuscarinic adverse effects may prove troublesome, particularly in the elderly, and they produce central sedation. Flunarizine is devoid of antimuscarinic properties, although it may produce central sedation.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bercetina; Coromert; Flufenal; Mondus; Niflucan; Sibelium; Vasculoflex†; ***Austria:*** Amalium; Flunarium; Sibelium; ***Belg.:*** Flunarimed; Flunatop; Kelamigra; Sibelium; ***Braz.:*** Flunarin; Fluvert; Fluzix; Sibelium; Vertigium; Vertix; ***Canad.:*** Sibelium; ***Chile:*** Flerox; Fluxus; Irrigor; Sibelium; Zentralin; ***Cz.:*** Sibelium; ***Denm.:*** Sibelium; ***Fr.:*** Sibelium; ***Ger.:*** Flunavert; Natil-N; Sibelium; ***Gr.:*** Sibelium; ***Hong Kong:*** Fludan; Sibelium†; ***Hung.:*** Sibelium; ***India:*** Migarid; Nomigrain; ***Indon.:*** Bartolium; Cevadil; Degrium; Dizilium; Frego; Sibelium; Siberid; Silum; Sinral; Unalium; Xepalium; ***Irl.:*** Sibelium; ***Ital.:*** Flugeral; Flunagen; Fluxarten; Gradient; Issium; Sibelium; Vasculene; ***Malaysia:*** Fludan; Forknow; Migarid; Sibelium; ***Mex.:*** Axilin; Fasolan; Nafluryl; Sibelium; ***Neth.:*** Sibelium; ***Philipp.:*** Sibelium; ***Port.:*** Sibelium; Vasilium; Zinasen; ***S.Afr.:*** Sibelium; ***Singapore:*** Forknow; Narizine†; Sibelium†; ***Spain:*** Flerudin; Flurpax; Sibelium; ***Switz.:*** Sibelium; ***Thai.:*** Cedelate†; Finelium†; Floxin; Fludan; Flulium; Flunarium; Flunaza†; Flunazine†; Fluricin; Hexilium; Liberal; Medilium; Poli-Flunarin; Seabell†; Sibelium; Simoyiam; Sobelin; Vanid; Vertilium; Zelium; ***Turk.:*** Sibelium; ***Venez.:*** Fludil; Sibelium.

Multi-ingredient: ***Arg.:*** Angiolit†; CCK Flunarizina†; Sibelium Plus; ***Braz.:*** Vertizine D.

Homochlorcyclizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de homoclorciclizina; Homochlorcyclizine, Chlorhydrate d'; Homochlorcyclizini Hydrochloridum. 1-(4-Chlorobenzhydryl)perhydro-4-methyl-1,4-diazepine dihydrochloride.

Гомохлорциклизина Гидрохлорид

$C_{19}H_{23}ClN_2,2HCl$ = 387.8.

CAS — 848-53-3 (homochlorcyclizine); 1982-36-1 (homochlorcyclizine hydrochloride).

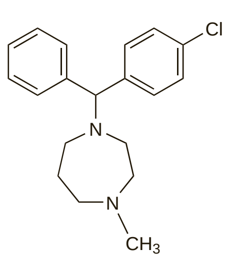

(homochlorcyclizine)

Pharmacopoeias. In *Jpn.*

Profile

Homochlorcyclizine hydrochloride, a piperazine derivative, is a sedating antihistamine (p.561) with antimuscarinic and moderate sedative properties. It is used for the symptomatic relief of allergic conditions including urticaria (p.565) and rhinitis (p.565), and in pruritic skin disorders (p.565). It is given in oral doses of 10 to 20 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Homoclomin; ***Indon.:*** Homoclomin; ***Jpn:*** Homoclomin; ***Thai.:*** Homoclomin.

Hydroxyzine *(BAN, rINN)*

Hidroxizina; Hydroksitsiini; Hydroxizin; Hydroxyzinum. (*RS*)-2-{2-[4-(*p*-Chloro-α-phenylbenzyl)piperazin-1-yl]ethoxy}ethanol.

Гидроксизин

$C_{21}H_{27}ClN_2O_2$ = 374.9.

CAS — 68-88-2.

ATC — N05BB01.

ATC Vet — QN05BB01.

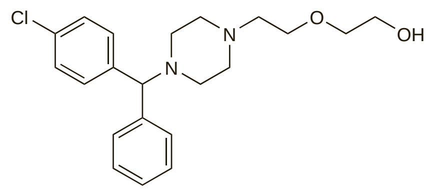

Hydroxyzine Embonate *(BANM, rINNM)*

Embonato de hidroxizina; Hydroxyzine, Embonate d'; Hydroxyzine Pamoate; Hydroxyzini Embonas; Pamoato de hidroxizina. 2-{2-[4-(4-Chlorobenzhydryl)piperazin-1-yl]ethoxy}ethanol 4,4′-methylenebis(3-hydroxy-2-naphthoate).

Гидроксизина Эмбонат

$C_{21}H_{27}ClN_2O_2,C_{23}H_{16}O_6$ = 763.3.

CAS — 10246-75-0.

ATC — N05BB01.

ATC Vet — QN05BB01.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Hydroxyzine Pamoate). A light yellow, practically odourless powder. Soluble 1 in more than 1000 of water, of chloroform, and of ether, 1 in 700 of alcohol, 1 in 10 of dimethylformamide, and 1 in 3.5 of 10M sodium hydroxide solution; practically insoluble in methyl alcohol. Store in airtight containers.

Hydroxyzine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidroxizina; Hidroksizin Hidroklorür; Hidroksizino hidrochloridas; Hidroxizin-hidroklorid; Hydroksitsiinihydrokloridi; Hydroxizinhydroklorid; Hydroxyzin dihydrochlorid; Hydroxyzine, chlorhydrate d'; Hydroxyzini Dihydrochloridum; Hydroxyzini hydrochloridum.

Гидроксизина Гидрохлорид

$C_{21}H_{27}ClN_2O_2,2HCl$ = 447.8.

CAS — 2192-20-3.

ATC — N05BB01.

ATC Vet — QN05BB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Hydroxyzine Hydrochloride). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in acetone. Store in airtight containers. Protect from light.

USP 31 (Hydroxyzine Hydrochloride). A white, odourless, powder. Soluble 1 in 1 of water, 1 in 4.5 of alcohol, and 1 in 13 of chloroform; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Incompatibility. Hydroxyzine hydrochloride has been reported to be incompatible with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), thioridazine, and some soluble barbiturates.

Stability. A mixture of hydroxyzine hydrochloride, chlorpromazine hydrochloride, and pethidine hydrochloride stored in glass or plastic syringes was found[1] to be stable for 366 days at 4° and 25°.

1. Conklin CA, *et al.* Stability of an analgesic-sedative combination in glass and plastic single-dose syringes. *Am J Hosp Pharm* 1985; **42:** 339–42.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Intramuscular injection of hydroxyzine has been reported to cause marked local discomfort. Intravenous use has been associated with haemolysis.

Amputation. Accidental intra-arterial injection of hydroxyzine has led to necrosis of the extremity requiring amputation of the digits of the affected limb.[1]

1. Hardesty WH. Inadvertent intra-arterial injection. *JAMA* 1970; **213:** 872.

Arrhythmias. ECG abnormalities, particularly alterations in T-waves, were associated with anxiolytic doses of hydroxyzine hydrochloride and were similar to those produced by thioridazine and tricyclic antidepressants.[1]

1. Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacol Comm* 1975; **1:** 61–5.

Effects on sexual function. A 32-year-old man had prolonged penile erections (priapism) after taking two separate doses of hydroxyzine for a skin rash.[1] It was suggested that the effect might be due to a hydroxyzine metabolite that was found to be structurally similar to a metabolite of trazodone, a drug known to induce penile erections.

1. Thavundayil JX. *et al.* Prolonged penile erections induced by hydroxyzine: possible mechanism of action. *Neuropsychobiology* 1994; **30:** 4–6.

Effects on the skin. Four children given hydroxyzine hydrochloride for restlessness developed a fixed drug eruption of the penis.[1] All recovered on drug withdrawal and subsequently had positive rechallenges.

1. Cohen HA, *et al.* Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother* 1997; **31:** 327–9.

Liver disorders. A study[1] has suggested that hydroxyzine should only be given once daily for the relief of pruritus in patients with primary biliary cirrhosis. The mean serum elimination half-lives of hydroxyzine and its metabolite cetirizine in 8 patients with primary biliary cirrhosis were 36.6 and 25.0 hours respectively.

1. Simons FER, *et al.* The pharmacokinetics and pharmacodynamics of hydroxyzine in patients with primary biliary cirrhosis. *J Clin Pharmacol* 1989; **29:** 809–15.

Porphyria. Hydroxyzine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Hydroxyzine is rapidly absorbed from the gastrointestinal tract and is metabolised. Metabolites include cetirizine (p.570), which has antihistaminic activity. An elimination half-life of about 20 hours has been reported.

◊ References.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.

Liver disorders. For reference to a prolonged half-life of hydroxyzine in patients with primary biliary cirrhosis, see under Adverse Effects and Precautions, above.

Uses and Administration

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. Its main use is as an anxiolytic (p.952) but see Anxiety Disorders below. It is also used as an adjunct to pre- and postoperative medication (see Anaesthesia, p.563) and in the management of pruritus (p.565) and urticaria (p.565) and has been used as an adjunct to opioid analgesia in the management of cancer pain (p.5).

Hydroxyzine may be given orally as the hydrochloride or the embonate; doses are expressed in terms of the hydrochloride. Hydroxyzine embonate 170 mg is equivalent to about 100 mg of hydroxyzine hydrochloride.

The usual oral doses in adults are: 50 to 100 mg four times daily for the short-term management of anxiety; for pruritus an initial dose of 25 mg given at night, increased if necessary to 25 mg three or four times daily; and 50 to 100 mg for pre- or postoperative sedation. For pruritus in children over 6 years of age the initial dose is 15 to 25 mg daily increased if necessary to 50 to 100 mg daily in divided doses; for children 6 months to 6 years old the initial dose is 5 to 15 mg daily increased if necessary to 50 mg daily in divided doses.

Alternatively, 1 mg/kg daily may be given in divided doses, to a maximum of 2.5 mg/kg daily in children aged 1 to 6 years, and to a maximum of 2 mg/kg daily in those aged 6 years and over. The pre- or postoperative sedative dose in children is 600 micrograms/kg. Dosage should be reduced in patients with hepatic or renal impairment, see below.

Hydroxyzine hydrochloride may also be given by deep intramuscular injection. For prompt control of anxiety or agitation in adults 50 to 100 mg is injected intramuscularly initially, and the dose may be repeated every four to six hours as required. For other indications when oral dosage is not practical, the intramuscular dose is 25 to 100 mg for adults and 1.1 mg/kg for children. Hydroxyzine should not be given by intravenous injection since haemolysis may result.

Administration in hepatic or renal impairment. In patients with hepatic impairment, UK licensed product information recommends a 33% reduction in the total oral daily dose of hydroxyzine. In patients with moderate or severe renal impairment, a dose reduction of 50% is recommended.

Anxiety disorders. Although hydroxyzine is used in the management of anxiety, there is little evidence to support its efficacy in anxious patients,[1] and the *BNF* considers that use of antihistamines solely for their sedative effect in anxiety is not appropriate.

1. Ballenger JC, *et al.* Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry* 2001; **62** (suppl 11): 53–8. Available at: http://www.psychiatrist.com/private/supplenet/v62s11/v62s1108.pdf (accessed 15/08/08)

Preparations

USP 31: Hydroxyzine Hydrochloride Injection; Hydroxyzine Hydrochloride Syrup; Hydroxyzine Hydrochloride Tablets; Hydroxyzine Pamoate Capsules; Hydroxyzine Pamoate Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Ataraxone; Hidroxina†; Hyderax; ***Austria:*** Atarax; ***Belg.:*** Atarax; ***Braz.:*** Hixizine; Prurizin; ***Canad.:*** Atarax; ***Chile:*** Dalun; Fasarax; Nexit†; ***Cz.:*** Atarax; ***Denm.:*** Atarax; ***Fin.:*** Atarax; ***Fr.:*** Atarax; ***Ger.:*** AH 3 N; Atarax; Elroquil N; ***Gr.:*** Atarax; Iremofar; ***Hong Kong:*** Atarax; Qualidrozine; ***Hung.:*** Atarax; ***India:*** Atarax; ***Indon.:*** Bestalin; Iterax; ***Israel:*** Otarex; ***Ital.:*** Atarax; ***Malaysia:*** Atarax; ***Mex.:*** Atarax; ***Neth.:*** Atarax; Navicalm†; ***Norw.:*** Atarax; ***NZ:*** Serecid; ***Philipp.:*** Iterax; ***Pol.:*** Atarax; ***Port.:*** Atarax; Coraphene; ***Rus.:*** Atarax (Атаракс); ***S.Afr.:*** Aterax; Neurax; ***Singapore:*** Atarax; Hizin; Phymorax†; ***Spain:*** Atarax; ***Swed.:*** Atarax; ***Switz.:*** Atarax; ***Thai.:*** Abacus; Allerax; Antizine; Atano; Atarax; Cerax; Darax†; Drazine; Hadarax; Histan; Hizin; Honsa; Hydroxin†; Katrax; Masarax†; Med-Xyzarax†; Polizine†; Postarax†; R-Rax; Taraxin; Trandrozine; Unamine; ***Turk.:*** Atarax; Validol; ***UK:*** Atarax; Ucerax; ***USA:*** Atarax†; Vistaril; Vistazine†.

Multi-ingredient: ***Austria:*** Diligan; ***Braz.:*** Marax; ***Ger.:*** Diligan†; ***India:*** Marax; ***Port.:*** Diligan†; Vesparax†; ***S.Afr.:*** Geratar; ***Spain:*** Calmoplex; Dolodens; ***USA:*** Hydrophed; Marax; Theomax DF; ***Venez.:*** Marax†.

Isothipendyl Hydrochloride *(BANM, rINNM)*

Hidrocloruro de isotipendil; Isothipendyl, Chlorhydrate d'; Isothipendyli Hydrochloridum. *NN*-Dimethyl-1-(pyrido[3,2-*b*][1,4]benzothiazin-10-ylmethyl)ethylamine hydrochloride.

Изотипендила Гидрохлорид

$C_{16}H_{19}N_3S,HCl = 321.9.$

CAS — 482-15-5 (isothipendyl); 1225-60-1 (isothipendyl hydrochloride).

ATC — D04AA22; R06AD09.

ATC Vet — QD04AA22; QR06AD09.

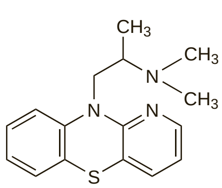

(isothipendyl)

Profile

Isothipendyl hydrochloride, an azaphenothiazine derivative, is an antihistamine (p.561) that has been applied topically for hypersensitivity and pruritic skin disorders although as with any antihistamine there is a risk of sensitisation. It has also been given orally and by the rectal route.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Actapront; ***Braz.:*** Andantol; ***Fr.:*** Sedermyl; ***Indon.:*** Andantol; ***Israel:*** Thiodantol; ***Ital.:*** Calmogel; ***Mex.:*** Andantol.

Ketotifen Fumarate *(BANM, USAN, rINNM)*

Fumarato de ketotifeno; HC-20511 (ketotifen); Ketotifeenivetyfumaraatti; Ketotifen Hydrogen Fumarate; Kétotifène, Fumarate de; Kétotifène, hydrogénofumarate de; Ketotifen-fumarát; Ketotifén-hidrogén-fumarát; Ketotifeni Fumaras; Ketotifeni hydrogenofumaras; Ketotifeno-vandenilio fumaratas; Ketotifenvätefumarat. 4-(1-Methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10(9*H*)-one hydrogen fumarate.

Кетотифена Фумарат

$C_{19}H_{19}NOS,C_4H_4O_4 = 425.5.$

CAS — 34580-13-7 (ketotifen); 34580-14-8 (ketotifen fumarate).

ATC — R06AX17; S01GX08.

ATC Vet — QR06AX17; QS01GX08.

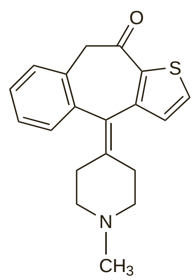

(ketotifen)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Ketotifen Hydrogen Fumarate; Ketotifen Fumarate BP 2008). A white to brownish-yellow, fine crystalline powder. Sparingly soluble in water; very slightly soluble in acetonitrile; slightly soluble in methyl alcohol.

Adverse Effects and Precautions

As for the antihistamines in general, p.561; drowsiness may be a problem, and dry mouth and dizziness may occur at the beginning of treatment but usually resolve with continued use. Weight gain and CNS stimulation have been reported. Isolated cases of severe skin reactions, cystitis, and hepatitis have been reported. Irritation, pain, and punctate keratitis are commonly reported after topical application to the eye.

For precautions to be observed in asthmatic patients, see Sodium Cromoglicate, p.1136. Ketotifen may take several weeks to exert its full effect; existing anti-asthma treatment should not be abruptly withdrawn after starting ketotifen therapy. It should not be used for the treatment of acute asthma attacks.

Overdosage. Overdoses of ketotifen ranging from 10 to 120 mg were reported in 8 patients.[1] Symptoms included drowsiness, confusion, dyspnoea, bradycardia or tachycardia, disorientation, and convulsions. Gastric lavage was performed in 6 patients, and all 8 recovered within 12 hours after supportive treatment.

In an overview of 21 cases of overdosage (including those reported above) the manufacturers stated that no serious signs or symptoms had been reported with doses below 20 mg, and there had been no fatalities.[2] The most serious effects reported had included unconsciousness, convulsions, bradycardia and tachycardia, and a severe hypotensive reaction. Management is essentially supportive and symptomatic.

1. Jefferys DB, Volans GN. Ketotifen overdose: surveillance of the toxicity of a new drug. *BMJ* 1981; **282:** 1755–6.
2. Le Blaye I, *et al.* Acute ketotifen overdosage: a review of present clinical experience. *Drug Safety* 1992; **7:** 387–92.

Interactions

As for the sedating antihistamines in general, p.563.

A reversible fall in the platelet count has been seen in a few patients receiving ketotifen with oral antidiabetics and it has been suggested that this combination should therefore be avoided.

Pharmacokinetics

Ketotifen fumarate is almost completely absorbed from the gastrointestinal tract after oral doses, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. Peak plasma concentrations occur 2 to 4 hours after an oral dose. It is mainly excreted in the urine as inactive metabolites with a small amount of unchanged drug; the terminal elimination half-life is about 21 hours.

Uses and Administration

Ketotifen is a sedating antihistamine (p.563) that also has a stabilising action on mast cells analogous to that of sodium cromoglicate (p.1137). It is used in the treatment of allergic conditions such as rhinitis (p.565) and conjunctivitis (p.564). Ketotifen has also been used in the prophylactic management of asthma, when it may take several weeks to exert its full effect; it should not be used to treat acute asthma attacks.

Ketotifen is given as the fumarate, but doses are expressed in terms of the base; ketotifen fumarate 1.38 mg is equivalent to about 1 mg of ketotifen.

Ketotifen fumarate is taken in oral doses equivalent to 1 mg of ketotifen twice daily with food, increased if necessary to 2 mg twice daily; 0.5 to 1 mg at night may be preferable for the first few days of treatment if drowsiness is likely to be a problem.

Ketotifen fumarate has also been applied topically, as eye drops equivalent to 0.025% ketotifen, used twice daily.

For children's doses, see below.

Action. It has been suggested that the anti-allergic action of ketotifen was independent of its antihistaminic properties.[1] This might be due to its effect on responses to platelet-activating factor (PAF).[2] However, the significance of PAF in the pathogenesis of asthma has been questioned.

1. Greenwood C. The pharmacology of ketotifen. *Chest* 1982; **82** (suppl): 45S–8S.
2. Morley J, *et al.* Effects of ketotifen upon responses to platelet activating factor: a basis for asthma prophylaxis. *Ann Allergy* 1986; **56:** 335–40.

Administration in children. Ketotifen fumarate can be given to children for the treatment of allergic conditions such as rhinitis (p.565) or conjunctivitis (p.564), and has been used in the prophylactic management of asthma. Oral doses equivalent to 1 mg of ketotifen twice daily with food may be used from 3 years of age. A dose equivalent to 500 micrograms ketotifen twice daily has been suggested in children between 6 months and 3 years of age.

Ketotifen fumarate has also been applied topically twice daily, as eye drops equivalent to 0.025% ketotifen, in children from 3 years of age.

Asthma. Results of studies on the effectiveness of ketotifen in the treatment of asthma (p.1108) have been conflicting; although some have found it effective in reducing symptoms[1-4] and in enabling a reduction in use of other anti-asthmatic drugs,[2,4] others have reported no significant benefits,[5,6] and UK guidelines on the management of asthma consider ketotifen to be ineffective.[7] A systematic review[8] found that it was of benefit in improving control of asthma and wheezing in children with mild to moderate disease, but noted that the high prevalence of atopy in several of the studies reviewed meant that the results might not be generalisable to children with asthma in general. A study in children described as 'preasthmatic' (that is, being at high risk of developing asthma) suggested that long-term therapy with ketotifen decreased the risk of asthma onset.[9]

1. Paterson JW, *et al.* Evaluation of ketotifen (HC20-511) in bronchial asthma. *Eur J Clin Pharmacol* 1983; **25:** 187–93.
2. Tinkelman DG, *et al.* A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma. *J Allergy Clin Immunol* 1985; **76:** 487–97.
3. Miraglia Del Giudice M, *et al.* Study of the efficacy of ketotifen treatment in asthmatic children under 3 years of age. *Curr Ther Res* 1986; **40:** 685–93.
4. Rackham A, *et al.* A Canadian multicenter study with Zaditen (ketotifen) in the treatment of bronchial asthma in children aged 5 to 17 years. *J Allergy Clin Immunol* 1989; **84:** 286–96.
5. White MP, *et al.* Ketotifen in the young asthmatic—a double-blind placebo-controlled trial. *J Int Med Res* 1988; **16:** 107–13.
6. Volovitz B, *et al.* Efficacy and safety of ketotifen in young children with asthma. *J Allergy Clin Immunol* 1988; **81:** 526–30.
7. Scottish Intercollegiate Guidelines Network/British Thoracic Society. British guideline on the management of asthma: a national clinical guideline. Revised edition May 2008. Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 23/06/08)
8. Bassler D, *et al.* Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
9. Bustos GJ, *et al.* Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; **25:** 568–73.

Conjunctivitis. References.

1. Martín AP, *et al.* The effect of ketotifen on inflammatory markers in allergic conjunctivitis: an open, uncontrolled study. *BMC Ophthalmol* 2003; **3:** 2. Available at: http://www.biomedcentral.com/1471-2415/3/2 (accessed 14/04/08)
2. Kidd M, *et al.* Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *Br J Ophthalmol* 2003; **87:** 1206–11.
3. Ganz M, *et al.* Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. *Adv Therapy* 2003; **20:** 79–91.
4. Abelson MB, *et al.* Efficacy and safety of single- and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatr Allergy Immunol* 2004; **15:** 551–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Antilerg; Bilozen; Biomira; Ketocev; Ketokid†; Respimex; Zaditen; ***Austral.:*** Zaditen; ***Austria:*** Ketotisan; Zaditen; ***Belg.:*** Zaditen; ***Braz.:*** Asdron; Asmalergin; Asmanon; Asmax; Asmen; Asmifen; Asmofen; Biatos; Broncoten†; Profilasmim-Ped†; Uni Cetotifen†; Zaditen; Zetitec†; ***Canad.:*** Zaditen; Zaditor; ***Chile:*** Ketotisin; Oftaler; Zaditen; ***Cz.:*** Ketof; Zaditen; ***Denm.:*** Zaditen; ***Fin.:*** Zaditen; ***Fr.:*** Zaditen; ***Ger.:*** Astifat†; Ketof; Pädiatifen†; Zaditen; Zatofug†; ***Gr.:*** Dovidin; Ecradin; Eucycline; Fental; Frenasma; Isocaren; K-Drops; Kathricol; Klevistamin; Labelphen; Lavoptik; Nostimex†; Noxtor; Orpidix; Pellexeme; Urpem; Zaditen; Zeoklamin; Zethrinal; Zidofen; ***Hong Kong:*** Amitone; Asmafen; Asmaten; Astifen; Dhatifen; Ketifen; Vidatifen; Zaditen; ***Hung.:*** Zaditen; ***India:*** Ketasma; ***Indon.:*** Astifen; Intifen; Nortifen; Prevas; Profilas; Scanditen; Zaditen; ***Irl.:*** Zaditen; ***Israel:*** Profiten; Zaditen; ***Ital.:*** Alleal; Allerket; Bentifen; Chetofen; Ketoftil; Sosefen; Stamifen; Zaditen; ***Malaysia:*** Asmafen; Asumalife; Denerel; Dhatifen; Ketifen; Licofen; Xidanef†; Zaden†; Zaditen; ***Mex.:*** Asmaral-K; Biotifen; Cantel; Kasmal; Kedrop; Keraffler; Ketaxal†; Nemodine; Nomotec; Osaten; Pretifen; Saluket-H1; Ventisol; Zaditen; ***Neth.:*** Bentifen; Zaditen; ***Norw.:*** Zaditen;

NZ: Asmafen; Zaditen; ***Philipp.:*** Zadec; Zaditen; ***Pol.:*** Zaditen; ***Port.:*** Bentifen; Cipanfeno; Quefeno†; Zaditen; ***Rus.:*** Zaditen (Задитен); Zetifen (Зетифен); ***S.Afr.:*** Ketohexal; Zaditen; Zetofen; ***Singapore:*** Asmafen†; Asumalife; Beatifen; Dhatifen; Erliten†; Tofen†; Zaditen; ***Spain:*** Ketasma†; Zaditen; Zasten; ***Swed.:*** Zaditen; ***Switz.:*** Zaditen; ***Thai.:*** Asmanoc†; Denerel†; Ibis; Katifen; Kenefen; Keten; Ketifen; Keto; Ketofen; Medkofen; Medotifen†; Politifen; Sykofen; Xidanef†; Zadino; Zaditen; Zytofen; ***Turk.:*** Astafen; Zaditen; ***UAE:*** Asmafort; ***UK:*** Zaditen; ***USA:*** Alaway; Zaditor; ***Venez.:*** Cosolve; Ketoptic; Ketotisin; Musibon†; Zaditen.

Multi-ingredient: ***Arg.:*** Airbronal†; Fatigan Bronquial†; Hyalcrom NF; Inastmol†; ***Mex.:*** Hyalcrom NF.

Levocabastine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levocabastina; Lévocabastine, chlorhydrate de; Levocabastini hydrochloridum; Levokabastiinihydrokloridi; Levokabastin-hydrochlorid; Levokabastinhydroklorid; Levokabastino hidrochloridas; Levokabasztin-hidroklorid; R-50547. (−)-*trans*-1-[*cis*-4-Cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid hydrochloride.

Левокабастина Гидрохлорид

$C_{26}H_{29}FN_2O_2,HCl$ = 457.0.

CAS — 79516-68-0 (levocabastine); 79547-78-7 (levocabastine hydrochloride); 79449-98-2 (cabastine).

ATC — R01AC02; S01GX02.

ATC Vet — QR01AC02; QS01GX02.

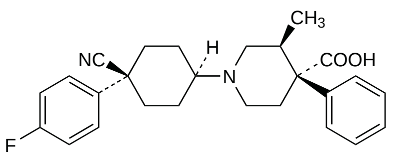

(levocabastine)

NOTE. Cabastine *(rINN)* is the racemate of levocabastine.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Levocabastine Hydrochloride). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in a 0.2% solution of sodium hydroxide; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Levocabastine Hydrochloride). Protect from light.

Adverse Effects and Precautions

As for the antihistamines in general, p.561. The most common adverse effects reported with levocabastine eye drops are transient stinging and burning of the eyes, urticaria, dyspnoea, drowsiness, and headache. With nasal use headache, nasal irritation, somnolence, and fatigue have been noted. The use of levocabastine nasal spray is not recommended in those with significant renal impairment.

Pharmacokinetics

Levocabastine is absorbed after both nasal and ocular use. Systemic availability has been estimated at 60 to 80% after nasal doses and 30 to 60% after ocular use. However absolute peak plasma concentrations are low. Plasma protein binding is about 55%. An elimination half-life of 35 to 40 hours has been reported for all routes of delivery. Elimination of levocabastine is primarily renal with 70% excreted as unchanged drug and 10% as an inactive acetylglucuronide metabolite; the remaining 20% is excreted unchanged in the faeces.

Trace amounts of levocabastine have been found in breast milk after ocular and nasal use.

◊ References.

1. Heykants J, *et al.* The pharmacokinetic properties of topical levocabastine: a review. *Clin Pharmacokinet* 1995; **29:** 221–30.

Uses and Administration

Levocabastine, a piperidine derivative, is a long-acting and potent antihistamine with a rapid onset of action. Levocabastine hydrochloride equivalent to 0.05% levocabastine is used topically twice daily as eye drops or as a nasal spray in the treatment of allergic conjunctivitis (p.564) and rhinitis (p.565), respectively, in adults and children aged 9 years and over. The frequency of the dose in both conditions may be increased to 3 or 4 times daily if necessary. In conjunctivitis it is recommended that treatment should be stopped if there is no improvement within 3 days.

◊ References.

1. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinically efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. *Drugs* 1995; **50:** 1032–49.
2. Doughty MJ. Levocabastine, a topical ocular antihistamine available as a pharmacy medicine – a literature review. *Pharm J* 2002; **268:** 367–70.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Histimet; ***Austral.:*** Livostin; ***Austria:*** Livostin; ***Belg.:*** Livostin; ***Braz.:*** Livostin; ***Canad.:*** Livostin; ***Cz.:*** Livostin; ***Denm.:*** Livostin; ***Fin.:*** Livostin; ***Fr.:*** Levophta; ***Ger.:*** Levophta†; Livocab; ***Gr.:*** Livostin; ***Hung.:*** Livostin†; ***Israel:*** Livostin; ***Ital.:*** Levostab; Livocab; Livostin; ***Jpn:*** Livostin; ***Mex.:*** Livostin; ***Neth.:*** Livocab; ***Norw.:*** Livostin; ***NZ:*** Livostin; ***Port.:*** Livostin; ***S.Afr.:*** Livostin; ***Spain:*** Bilina; Livocab; ***Swed.:*** Livostin; ***Switz.:*** Livostin; ***Thai.:*** Livostin†; ***Turk.:*** Livostin; ***UK:*** Livostin; ***USA:*** Livostin†; ***Venez.:*** Livostin.

Multi-ingredient: ***Chile:*** Livostin.

Levocetirizine *(BAN, USAN, rINN)*

Levocetirizina; Lévocétirizine; Levocetirizinum. (2-{4-[(*R*)-*p*-Chloro-α-phenylbenzyl]-1-piperazinyl}ethoxy)acetic acid.

Левоцетиризин

$C_{21}H_{25}ClN_2O_3$ = 388.9.

CAS — 130018-77-8.

ATC — R06AE09.

ATC Vet — QR06AE09.

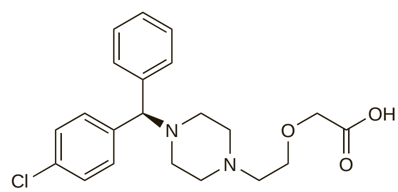

Levocetirizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocetirizina; Lévocétirizine, Chlorhydrate de; Levocetirizine Dihydrochloride *(USAN)*; Levocetirizini Hydrochloridum; UCB-28556.

Левоцетиризина Гидрохлорид

$C_{21}H_{25}ClN_2O_3,2HCl$ = 461.8.

CAS — 130018-87-0.

ATC — R06AE09.

ATC Vet — QR06AE09.

Profile

Levocetirizine is the *R*-enantiomer of cetirizine (p.570) and is used similarly, as the hydrochloride, for the symptomatic relief of allergic conditions including rhinitis (p.565) and chronic urticaria (p.565). The usual oral dose of levocetirizine hydrochloride is 5 mg once daily. US licensed product information suggests that the dose should be given in the evening, and that a dose of 2.5 mg may be adequate in some patients.

For doses in children or in patients with renal impairment, see below.

◊ References.

1. Scheinfeld N. The new antihistamines—desloratadine and levocetirizine: a review. *J Drugs Dermatol* 2002; **1:** 311–16.
2. Tillement JP, *et al.* Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists. *Biochem Pharmacol* 2003; **66:** 1123–6.
3. Horak F, *et al.* Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. *Br J Clin Pharmacol* 2005; **60:** 24–31.
4. Nettis E, *et al.* Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **154:** 533–8.
5. Hair PI, Scott LJ. Levocetirizine: a review of its use in the management of allergic rhinitis and skin allergies. *Drugs* 2006; **66:** 973–96.

Administration in children. Levocetirizine hydrochloride may be given orally to children for the symptomatic relief of allergic rhinitis and chronic idiopathic urticaria, although licensed doses may vary between countries. In the UK, children aged 2 to 6 years may be given a dose of 2.5 mg daily in 2 divided doses, and those older than 6 years may be given the adult dose of 5 mg daily. In the USA, however, levocetirizine hydrochloride is not recommended for children under 6 years of age. In those aged 6 to 11 years, a dose of 2.5 mg once daily in the evening may be given, and the adult dose of 5 mg daily only given to children aged 12 years and older.

For doses in children with renal impairment, see below.

Administration in renal impairment. The dose of levocetirizine hydrochloride should be reduced in patients with renal impairment according to creatinine clearance (CC), although recommendations can vary between countries. The following oral doses have been suggested for adults in the UK and for adults and adolescents aged 12 years and over in the USA:

- CC 50 to 79 mL/minute: 5 mg once daily in the UK; 2.5 mg once daily in the USA
- CC 30 to 49 mL/minute: 5 mg every other day in the UK; 2.5 mg every other day in the USA
- CC 10 to 29 mL/minute: 5 mg once every 3 days in the UK; 2.5 mg once every 3 or 4 days in the USA
- CC less than 10 mL/minute and patients undergoing dialysis: contra-indicated in both the UK and USA

Data are lacking for the use of levocetirizine in children with renal impairment. UK licensed product information suggests that the dose should be adjusted on an individual basis, taking into account the patient's renal clearance and body-weight.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Levomine; Supraler; ***Austria:*** Xyzall; ***Belg.:*** Xyzall; ***Braz.:*** Zyxem; ***Chile:*** Degraler; Neo Alertop; ***Cz.:*** Xyzal; ***Denm.:*** Xyzal; ***Fin.:*** Xyzal; ***Fr.:*** Xyzall; ***Ger.:*** Xusal; ***Gr.:*** Xozal; ***Hong Kong:*** Xyzal; ***Hung.:*** Xyzal; ***India:*** L-Cetridoc†; Leset; Levorid; Teczine; ***Indon.:*** Xyzal; ***Irl.:*** Xyzal; ***Ital.:*** Xyzal; ***Malaysia:*** Xyzal; ***Mex.:*** Xuzal; Zyxem; ***Neth.:*** Sopras; Virdos; Xyzal; ***Norw.:*** Xyzal; ***Philipp.:*** Xyzal; ***Pol.:*** Xyzal; ***Port.:*** Levrix; Xyzal; ***Rus.:*** Xyzal (Ксизал); ***S.Afr.:*** Xyzal; ***Singapore:*** Muntel; Sopras; Xazal; ***Switz.:*** Xyzal; ***Thai.:*** Xyzal; ***UK:*** Xyzal; ***USA:*** Xyzal.

Multi-ingredient: ***India:*** Levorid D.

Loratadine *(BAN, USAN, rINN)*

Loratadiini; Loratadin; Loratadina; Loratadinum; Loratadyna; Sch-29851. Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate.

Лоратадин

$C_{22}H_{23}ClN_2O_2$ = 382.9.

CAS — 79794-75-5.

ATC — R06AX13.

ATC Vet — QR06AX13.

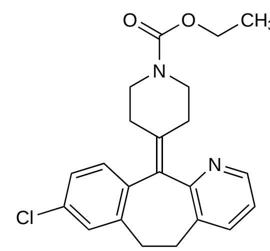

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Loratadine). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in acetone and in methyl alcohol.

USP 31 (Loratadine). A white to off-white powder. Insoluble in water; freely soluble in acetone, in chloroform, in methyl alcohol, and in toluene.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving loratadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding. However, UK licensed product information recommends that loratadine should not be used in breast-feeding mothers.

A study[2] in 6 women reported that about 0.03% of a single 40-mg oral dose of loratadine was distributed into breast milk over 48 hours as loratadine and its active metabolite, desloratadine.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Hilbert J, *et al.* Excretion of loratadine in human breast milk. *J Clin Pharmacol* 1988; **28:** 234–9.

Effects on the liver. Two patients[1] developed severe necroinflammatory liver injury after receiving loratadine 10 mg daily for allergic rhinitis. Although both recovered after drug withdrawal, one patient required a liver transplantation and recovery was prolonged.

The product information notes that abnormal hepatic function including jaundice, hepatitis, and hepatic necrosis has been reported rarely.

1. Schiano TD, *et al.* Subfulminant liver failure and severe hepatotoxicity caused by loratadine use. *Ann Intern Med* 1996; **125:** 738–40.

Pregnancy. UK product information does not recommend the use of loratadine in pregnancy.

Analysis of data collected by the Swedish Medical Birth Registry between 1994 and 2001 revealed 15 cases of hypospadias among a cohort of 2780 newborns exposed to loratadine during the first trimester of pregnancy.[1] The authors noted that the individual risk for having an infant with hypospadias after loratadine use is small (less than 1%) and the attributive risk of extra cases in the population is low. The US CDC has also analysed data from the National Birth Defects Prevention study;[2] they found no increase in the risk of second- or third-degree hypospadias in the infants of women who used loratadine in early pregnancy. In addition, an earlier prospective multicentre study[3] in 161 women taking a median dose of loratadine 10 mg daily in the first trimester of pregnancy suggested that its use was not associated with a significant risk of major congenital malformations.

1. Källén B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? *Int J Risk Safety Med* 2001; **14:** 115–19.
2. CDC. Evaluation of an association between loratadine and hypospadias — United States, 1997-2001. *MMWR* 2004; **53:** 219–21. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5310.pdf (accessed 11/05/04)
3. Moretti ME, *et al.* Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol* 2003; **111:** 479–83.

Sedation. For discussion of the sedative effects of antihistamines see p.562.

Interactions

As for the non-sedating antihistamines in general, p.563.

Loratadine is metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Drugs known to inhibit one or other of these enzymes include cimetidine, erythromycin, ketoconazole, quinidine, fluconazole, and fluoxetine.

Antibacterials. Data held on file by the manufacturer show that *erythromycin* can inhibit the metabolism of loratadine. However, even when given in large doses loratadine does not appear to cause the cardiac conduction disorders associated with the non-sedating antihistamines astemizole (see p.567) and terfenadine (see p.590).[1] Similarly, *clarithromycin* seemed to inhibit the metabolism of loratadine and its active metabolite desloratadine.[2]

1. Affrime MB, *et al.* Three month evaluation of electrocardiographic effects of loratadine in humans. *J Allergy Clin Immunol* 1993; **91:** 259.
2. Carr RA, *et al.* Steady-state pharmacokinetics and electrocardiographic pharmacodynamics of clarithromycin and loratadine after individual or concomitant administration. *Antimicrob Agents Chemother* 1998; **42:** 1176–80.

Antifungals. *Ketoconazole* also appears to be able to inhibit the metabolism of loratadine and at therapeutic doses, is about 3 times more inhibitory than erythromycin.[1] However, the concentrations of ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemizole or terfenadine. Clearance of the active metabolite desloratadine is also reduced.

1. Brannan MD, *et al.* Effects of various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; **57:** 193.

Gastrointestinal drugs. *Cimetidine* appears to have an inhibitory effect on the metabolism of loratadine and also attenuates the clearance of its active metabolite desloratadine although no clinically significant consequences have been seen.[1]

1. Brannan MD, *et al.* Effects of various cytochrome P450 inhibitors on the metabolism of loratadine. *Clin Pharmacol Ther* 1995; **57:** 193.

Pharmacokinetics

Loratadine is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being attained in about 1 hour. Bioavailability is increased and time to peak plasma concentrations is delayed when taken with food. Loratadine undergoes extensive metabolism. The major metabolite, desloratadine (p.576), has potent antihistaminic activity. Reported mean elimination half-lives for loratadine and desloratadine are 8.4 and 28 hours, respectively. Loratadine is about 98% bound to plasma proteins; desloratadine is less extensively bound. Loratadine and its metabolites have been detected in breast milk, but do not appear to cross the blood-brain barrier to a significant extent. Most of a dose is excreted equally in the urine and faeces, mainly in the form of metabolites.

Renal impairment. The disposition of loratadine does not appear to be significantly altered in patients with severe renal impairment and haemodialysis does not appear to be an effective means of removing loratadine or its metabolite desloratadine from the body.[1]

1. Matzke GR, *et al.* Pharmacokinetics of loratadine in patients with renal insufficiency. *J Clin Pharmacol* 1990; **30:** 364–71.

Uses and Administration

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity. It is used for the symptomatic relief of allergic conditions including rhinitis (p.565) and chronic urticaria (p.565).

Loratadine is given in an oral dose of 10 mg once daily. Children aged 2 to 5 years may be given 5 mg once daily and those aged 6 to 12 years may be given 10 mg once daily for seasonal allergic rhinitis and chronic idiopathic urticaria.

It is also used with a decongestant such as pseudoephedrine sulfate.

For dosage in hepatic or renal impairment, see below.

◊ References.

1. Haria M, *et al.* Loratadine: a reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994; **48:** 617–37.

Administration in hepatic or renal impairment. US product information recommends that patients with hepatic failure or renal impairment (glomerular filtration rate less than 30 mL/minute) should be given an initial oral dose of loratadine 10 mg on alternate days.

Preparations

USP 31: Loratadine Oral Solution; Loratadine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aerotina; Alergipan; Alermuc; Alerpriv; Algistop; Aseptobron Descongestivo; Bedix; Benadryl 24; Biloina; Bioaler†; Clarityne; Devedryl; Hisplex; Lertamine†; Lisaler; Loisan; Loratex†; Loratine; Loremex Antialergico; Nastizol Antialergico†; Negalerg L†; Niltro; Novo Vagran†; Nularef; Omega 100 L; Pulmosan Aller; Sinaler; Tabcin Alergia; Vagran; Vixidone L; ***Austral.:*** Alledine; AllerEze; Claratyne; Lorano; Lorastyne†; ***Austria:*** Allernon; Clarityn; Lictyn; Lorano; Loratyn; ***Belg.:*** Claritine; Rupton; Sanelor; ***Braz.:*** Alergaliv; Atinac†; Clarilerg†; Claritin; Clistin†; Histadin; Histamix†; Loradine; Loralerg; Loranil; Lorasc†; Loratamed; Loremix; Loritil; Neo Loratadin; ***Canad.:*** Claritin; ***Chile:*** Alergan; Alledryl; Clarityne; Frenaler; Histaplus†; Hysticlar; Larmax†; Lontadex; ***Cz.:*** Claritine; Erolin; Flonidan; Loranol; Roletra; ***Denm.:*** Clarityn; Geklimon†; Loritin; Mildin; Oratyn; Versal†; ***Fin.:*** Clarityn; Geklimon†; Tuulix; ***Fr.:*** Clarityne; ***Ger.:*** Lisino; Livotab†; Lobeta; Lora; Lora-Lich; Lora-Puren; Loraclar†; Loraderm; Loragalen; Loralerg†; Lorano; Loratadura; Loratagamma; Loravis; Vividrin Loratadin†; ***Gr.:*** Allerdrug; Allergofact; Biliranin†; Bollinol; Clarityne; Difmedol; Helporigin; Horestyl; Igir; Latoren; Lora; Loratab; Novacloxab; Ralinet; Ristotadin; Tirlor; Utel; Zelmar; ***Hong Kong:*** Allertyn; Ambrace; Carin; Clarityne; CP-Loradine; Erolin; Ezede; Loradin; Loraton; Lotadine; Lotin; Marlora; Rinityn; Rotifar; Voratadine; ***Hung.:*** Claritine; Erolin; Flonidan; Lorano; Roletra; ***India:*** Awayke†; Loratin; Lorfast; Loridin; Lorin; ***Indon.:*** Alernitis; Allohex; Alloris; Anhissen; Anlos; Clarihis; Claritin; Clatatin; Cronitin; Folerin; Hislorex; Histaritin; Imunex; Inclarin; Klinset; Lergia; Lesidas; Lolergi; Loran; Lorapharm; Lorihis; Nosedin; Prohistin; Pylor; Rahistin; Rihest; Safetin; Sohotin; Tinnic; Winatin; ***Irl.:*** Clarityn†; Histaclar; ***Israel:*** Lorastine; Loratrim; ***Ital.:*** Alorin†; Clarityn; Fristamin; ***Jpn:*** Claritin; ***Malaysia:*** Carin; Clarityne; Ezede†; Loradine; Lorastyne†; Loratyn†; Ridamin; Roletra; Tirlor; ***Mex.:*** Alerfin; Aludix; Antilergal; Biolorat; Clarityne; Curyken; Dimegan; Dissen; Ditana; Doralan; Dotagil; Dymaten; Efectine; Fartadin; Grimeral; Histina; Histox; Inigrin; Laritol; Lertamine; Lictyn; Liferamin; Lotan; Lovarin; Neoalexil; Nidatar; Quimtadine; Rodakin; Rokadin†; Sensibit; Serralsina; Sitinir; Vincidal; ***Neth.:*** Allerfre; Claritine; Kruidvat Hooikoortstabletten; Lorastad; Otrivin neusallergie loratadine; Sanelor; ***Norw.:*** Clarityn; Versal†; ***NZ:*** Claratyne; Lora-Tabs; ***Philipp.:*** Allerta; Claritin; Lergicyl; Loradex; Lorahist; Lorano; Loratyne; Lordam; Lordane; Onemin; Rinityn; Zylohist; ***Pol.:*** Alerfan; Aleric; Claritine; Flonidan; Lorahexal; Loram; Loratan; Loratine; Nalergine; Rotadin; ***Port.:*** Alertrin; Claritine; Evertine; Histadin; Profenox; Zolargene; ***Rus.:*** Alerpriv (Алерприв); Clargotil (Кларготил); Clarisens (Кларисенс); Claritine (Кларитин); Clarotadine (Кларотадин); Erolin (Эролин); Klallergine (Клаллергин); Klarfast (Кларфаст); Klaridol (Кларидол); Lomilan (Ломилан); Lorahexal (Лорагексал); Lorid (Лорид); Loridin (Лоридин); ***S.Afr.:*** Clarinese; Clarityne; Demazin Anti-Allergy†; Laura; Lorahist; Lorano; Loratyne†; Polaratyne†; Pollentyme; Rhinigine; ***Singapore:*** Allertyn; Ardin; Carin; Clarityne; Ezede; Histalor; Lorfast; Loridin; Lotadine; Ridamin; Rinityn; Roletra; Tirlor; ***Spain:*** Civeran; Clarityne; Fadina†; Optimin†; Velodan; ***Swed.:*** Clarityn; Versal; ***Switz.:*** Claritine; ***Thai.:*** Aller-Tab; Allerdine; Allersil; Caradine; Carinose†; Clalodine; Clarid; Clarityne; Halodin; Hisracon; Klaryne; Lindine; Loracine; Loradine; Loranox; Lordin; Lorin; Lorita; Lorityne†; Lorsedin; Lortadine; Ridamin; Rityne; Roletra; Tiradine; Tirlor; ***Turk.:*** Alarin; Claritine; Histadin; Loradif; Lorantis; Loritine; Ritin; ***UAE:*** Loratin; ***UK:*** Clarityn; ***USA:*** Alavert; Claritin; Clear-Atadine; Non-Drowsy Allergy; Tavist ND; ***Venez.:*** Alerdina; Alertidine†; Biolorat; Clarityne; Loradin†; Lorat; Loraval; Lorex; Loriden; Lotal; Polaramine Reformulado; Proactin†; Tirlor.

Multi-ingredient: ***Arg.:*** Alerpriv D; Bedix-D; Benadryl 24 D; Celestamine-L; Ciprocort D; Ciprocort L; Clarifriol; Clarityne Cort; Clarityne D; Cortistamin L; Decidex Plus; Dexaprof D; Histamino Corteroid L; Ideogrip; Lertamine D†; Lisaler Beta; Loisan-D; Loremex Descongestivo; Nastizol-L; Negalerg†; Novo Vagran D†; Novo-Nastizol†; Nularef Cort; Nularef-D; Paracetamol Grip NF; Pulmonix Grip; Pulmonix Plus; Sinaler B; Toraxan; Vagran D; Vixidone LB; ***Austral.:*** Clarinase; Sinease†; ***Austria:*** Clarinase; ***Belg.:*** Clarinase; ***Braz.:*** Claritin-D; Cloratadd D; Histadin D; Loralerg-D; Loranil D; Loremix D; Neofedrin; ***Canad.:*** Chlor-Tripolon ND; Claritin Allergy & Sinus; Claritin Extra†; Liberato; ***Chile:*** Alledryl D; Clarinase; Frenaler-D; Larmax D; Lertamine; Lertamine Extra; Lontadex D†; Rinomex; ***Cz.:*** Clarinase; ***Denm.:*** Clarinase; ***Fin.:*** Clarinase; ***Fr.:*** Clarinase; ***Gr.:*** Clarityne D; ***Hong Kong:*** Clariflu; Clarinase; Rhinos; ***Hung.:*** Clarinase; ***India:*** Loratin D; Lorfast-D; Loridin-D; ***Indon.:*** Aldisa; Clarinase; Glanos; Rhinos; ***Israel:*** Clarinase; ***Malaysia:*** Carinox; Clarinase; ***Mex.:*** Alerfin Ex; Alvium†; Alviumito†; Alviumthe†; Bisincof; Bramin; Bronar; Broquixol; Celestamine NS; Claricort†; Clariflu; Clarifriol; Clarinase†; Clarityne D; Coricidin Expec; Dimegan D; Doralan-Ax; Efectine D; Farmalor; Fluxibit; Gralddep; Laritol D; Laritol Ex; Laritol G; Lertamine D; Linfarden; Lovarin P†; Lyrsedin; Neoalexil P†; Quimtadine DSQ; Quimtafriol; Sensibit D; Sensibit XP; Sibilex; Tadinar-C; Tamex; Tavexyl; TheraFlu 24; TheraFlu N 12; TheraFlu TD; ***NZ:*** Clarinase†; Demazin Non-Drowsy†; ***Philipp.:*** Claricort; Clarinase; Rhinase; ***Pol.:*** Clarinase; ***Port.:*** Claridon; ***S.Afr.:*** Clarityne D; Demazin NS; Polaratyne D†; ***Singapore:*** Clarinase; ***Spain:*** Narine; ***Thai.:*** Clarinase; ***Turk.:*** Clarinase; ***USA:*** Alavert Allergy & Sinus D; Claritin-D; ***Venez.:*** Ambroclar; Celestamincort; Claricort; Claridex; Claridexultra; Clariflu; Clarigrip; Clarinase†; Fedyclar; Lokarin; Loracert; Rinase†.

Mebhydrolin *(BAN, rINN)*

Mebhidrolina; Mebhydroline; Mebhydrolinum. 5-Benzyl-1,2,3,4-tetrahydro-2-methyl-γ-carboline.

Мебгидролин

$C_{19}H_{20}N_2$ = 276.4.

CAS — 524-81-2.

ATC — R06AX15.

ATC Vet — QR06AX15.

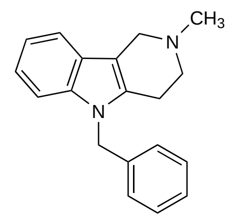

Mebhydrolin Napadisilate *(BANM, rINNM)*

Diazolinum; Mebhydrolin Napadisylate; Mebhydrolin Naphthalenedisulphonate; Mebhydroline, Napadisilate de; Mebhydrolini Napadisilas; Napadisilato de mebhidrolina. Mebhydrolin naphthalene-1,5-disulphonate.

Мебгидролина Нападизилат

$(C_{19}H_{20}N_2)_2,C_{10}H_8O_6S_2$ = 841.0.

CAS — 6153-33-9.

ATC — R06AX15.

ATC Vet — QR06AX15.

Profile

Mebhydrolin, an ethylenediamine derivative, is a sedating antihistamine (p.561) with antimuscarinic and sedative properties. It has been given orally as the base or as the napadisilate salt for the symptomatic relief of allergic conditions including urticaria and rhinitis, and in pruritic skin disorders. Granulocytopenia and agranulocytosis have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Biolergy; Gabiten; Histapan; Incitin; Interhistin; Tralgi; Zoline; ***Israel:*** Cidalin; ***Rus.:*** Diazolin (Диазолин); ***S.Afr.:*** Fabahistin; ***Thai.:*** Dalhis; Dayhist; Manocidal; Manoeidai; Posidol.

Meclozine Hydrochloride

(BANM, pINNM)

Hidrocloruro de meclozina; Meclizine Hydrochloride; Meclizinium Chloride; Méclozine, chlorhydrate de; Meclozini Dihydrochloridum; Meclozini hydrochloridum; Meklotsiinihydrokloridi; Meklozin Hidroklorür; Meklozin-dihydrochlorid; Meklozin-hidroklorid; Meklozinhydroklorid; Meklozino hidrochloridas; Meklozyny chlorowodorek; Parachloramine Hydrochloride. 1-(4-Chlorobenzhydryl)-4-(3-methylbenzyl)piperazine dihydrochloride.

Меклозина Гидрохлорид

$C_{25}H_{27}ClN_2,2HCl$ = 463.9.

CAS — 569-65-3 (meclozine); 1104-22-9 (anhydrous meclozine hydrochloride); 31884-77-2 (meclozine hydrochloride monohydrate).

ATC — R06AE05.

ATC Vet — QR06AE05.

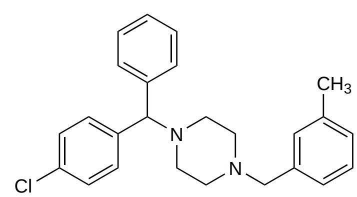

(meclozine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
US specifies the monohydrate.

Ph. Eur. 6.2 (Meclozine Hydrochloride). A yellow or yellowish-white, crystalline powder. Slightly soluble in water; soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 31 (Meclizine Hydrochloride). The monohydrate is white or slightly yellowish crystalline powder that has a slight odour. Practically insoluble in water and in ether; freely soluble in chloroform, in pyridine, and in acid-alcohol-water mixtures; slightly soluble in dilute acids and in alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. For reports of the use of antihistamines, including meclozine, in pregnancy, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Meclozine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It is mainly used for its antiemetic action, which may last for up to 24 hours. Meclozine hydrochloride is used in the prevention and treatment of nausea and vomiting associated with a variety of conditions including motion sickness (p.564) and for the symptomatic treatment of vertigo (p.565) caused by Ménière's disease and other vestibular disorders. Meclozine hydrochloride has also been used for the symptomatic relief of hypersensitivity reactions and pruritic skin disorders (p.565).

The usual oral dose of meclozine hydrochloride for motion sickness is 25 to 50 mg taken about one hour before travelling and repeated every 24 hours if necessary; up to 100 mg daily in divided doses has been given for the treatment of vertigo and vestibular disorders. In the prevention and treatment of motion sickness in children aged 6 to 12 years, 12.5 mg is given once daily; for children aged 2 to 6 years the dose is 6.25 mg once daily.

Both meclozine hydrochloride and meclozine base have been given by the rectal route; doses are similar to those given orally.

Preparations

USP 31: Meclizine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Agyrax; Postafene; ***Braz.:*** Meclin; ***Canad.:*** Bonamine; ***Chile:*** Bonamina; ***Cz.:*** Postafen†; ***Denm.:*** Postafen; ***Fin.:*** Postafen; ***Fr.:*** Agyrax; ***Ger.:*** Peremesin N†; Peremesin†; Postadoxin N; Postafen†; ***Gr.:*** Emetostop; Postafene†; ***Hong Kong:*** Postafene; ***Mex.:*** Chiclida; Marenin; ***Neth.:*** Suprimal; ***Norw.:*** Peremesin; Postafen; ***NZ:*** Sea-Legs; ***Philipp.:*** Bonamine; Postadoxine; ***Port.:*** Navicalm; ***Rus.:*** Bonine (Бонин); ***Spain:*** Chiclida; Dramine; Navicalm†; ***Swed.:*** Postafen; ***Switz.:*** Duremesan; ***Turk.:*** Postadoxine; ***UK:*** Sea-Legs; ***USA:*** Antivert; Antrizine; Bonine; Dizmiss; Dramamine II; Meni-D; Vergon†.

Multi-ingredient: ***Austria:*** Contravert B ; Diligan; ***Ger.:*** Diligan†; ***Hong Kong:*** Navidoxine; ***India:*** Diligan; Pregnidoxin; ***Malaysia:*** Becoloxin†; Navidoxine†; ***Mex.:*** Bonadoxina; Bonalen; Bonazin; Emediba; Liatriz; Meclifar; Meclison; Pidoxina; Vo-Remi; ***Neth.:*** Emesafene; ***Port.:*** Diligan†; ***S.Afr.:*** Geratar; ***Singapore:*** Navidoxine†; ***Switz.:*** Duremesan; Itinerol B ; ***UK:*** Traveleeze; ***Venez.:*** Bonadoxina; Etizil†; Mebax†.

Mepyramine *(BAN, rINN)*

Mepiramina; Mepyramiini; Mepyramin; Mépyramine; Mepyraminum; Pyranisamine; Pyrilamine. 2-(*N*-*p*-Anisyl-*N*-2-pyridylamino)ethyldimethylamine.

Мепирамин

$C_{17}H_{23}N_3O$ = 285.4.
CAS — 91-84-9.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.

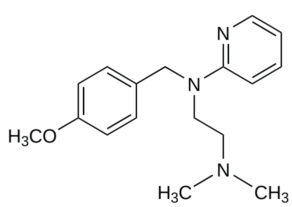

Mepyramine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mepiramina; Mépyramine, Chlorhydrate de; Mepyramini Hydrochloridum; Pyranisamine Hydrochloride; Pyrilamine Hydrochloride.

Мепирамина Гидрохлорид

$C_{17}H_{23}N_3O,HCl$ = 321.8.
CAS — 6036-95-9.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.

Mepyramine Maleate *(BANM, rINNM)*

Maleato de mepiramina; Mepiramin Maleat; Mepiramin-maleát; Mepiramino maleatas; Mepyramiinimaleaatti; Mepyramin maleinát; Mépyramine, maléate de; Mepyramini maleas; Mepyraminmaleat; Pyranisamine Maleate; Pyrilamine Maleate. Mepyramine hydrogen maleate.

Мепирамина Малеат

$C_{17}H_{23}N_3O,C_4H_4O_4$ = 401.5.
CAS — 59-33-6.
ATC — D04AA02; R06AC01.
ATC Vet — QD04AA02; QR06AC01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mepyramine Maleate). A white or slightly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol. M.p. 99° to 103°. A 2% solution in water has a pH of 4.9 to 5.2. Protect from light.

USP 31 (Pyrilamine Maleate). A white crystalline powder usually having a faint odour. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, 1 in 15 of dehydrated alcohol, and 1 in 2 of chloroform; slightly soluble in ether and in benzene. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Mepyramine, an ethylenediamine derivative, is a sedating antihistamine with antimuscarinic and sedative properties. Mepyramine maleate is used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p.565). Mepyramine maleate is also a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Mepyramine maleate has been given in an oral dose of 50 mg at night as a hypnotic in the short-term management of insomnia (p.564).

A cream containing 2% mepyramine maleate is used locally for insect bites or stings, and for hypersensitivity and pruritic skin conditions but, as with any antihistamine, there is a risk of sensitisation. It has also been used in eye drops.

In some countries mepyramine maleate is available for parenteral use. Mepyramine hydrochloride has also been given parenterally or by the rectal route. Mepyramine tannate and mepyramine acefyllinate have been used orally.

Preparations

BP 2008: Mepyramine Tablets;
USP 31: Pyrilamine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Relaxa-Tabs; ***Braz.:*** Alergitanil; ***Hong Kong:*** Anthisan; ***Irl.:*** Anthisan; ***NZ:*** Anthisan; ***S.Afr.:*** Anthisan; Antihist; Mepyraderm; Mepyrimal; ***Spain:*** Fluidasa; ***UK:*** Anthisan; ***USA:*** Pyrlex.

Multi-ingredient: ***Arg.:*** Bajumol†; Drynisan; Everfem; Fadanasal; Piracalamina; Polipectol†; Rynatanic†; ***Austral.:*** Neo-Diophen†; ***Belg.:*** Nortussine; ***Braz.:*** Alergitrat†; Alergo Glucalbet†; Beclase; Benistina†; Benzomel†; Conidrin; Expectussin†; Ginometrim Oral†; Gripanil†; Gripsay; Killgrip†; Naridrin; Nariflux; Nasogrip; Posdrink; ***Canad.:*** Extra Strength Multi-Symptom PMS Relief†; Hycomine; Jack and Jill; Midol Extra Strength; Midol PMS Extra Strength; Pamprin; Prefrin A; ratio-Theo-Bronc; Relievol PMS; Trendar PMS†; Tylenol Menstrual; ***Chile:*** Alerzona; Kitadol Periodo Menstrual; Minfaden; Predual; Rinolergan; Tapsin Periodo Menstrual; ***Fr.:*** Nortussine; ***Hong Kong:*** Easiko†; ***Israel:*** Aforinol; Alnase; Phenyphrine-Azol†; ***Ital.:*** Balsamina Kroner; Triaminic; Vasofen; ***Malaysia:*** Prefrin A†; ***Mex.:*** Femsedin Kutz; Lentostamin; ***Pol.:*** Kato-Nasal; Pro-Miss; ***Port.:*** Antigrippine; Naso-Prieulina†; Profrin-A†; Solpic†; ***S.Afr.:*** Antiflu†; Bronchiflu†; Codef; Codomill†; Colcaps; Coughcod; Docsed; Expectotussin C†; Flucol; Histodor; Meditussi†; Metaxol; Sinu-Flu†; ***Singapore:*** Prefrin A†; ***Spain:*** Amplidermis; Pectobal Dextro†; ***Switz.:*** Calpred; Demostan N; Escogripp sans codeine; Euceta Pic; Histacyl Compositum†; Histacylettes†; Stilex; ***Thai.:*** Antergan†; ***Turk.:*** Peditus; Stilex; ***UAE:*** Profinal FM; ***UK:*** Anthisan Plus; Wasp-Eze; ***USA:*** 4-Way Fast Acting; AlleRx; C-Tanna 12D; Calamycin; Codal-DH; Codal-DM; Codimal DM; Codimal PH; Conal; De-Chlor MR; Derma-Pax; Duonate; Gelhist; HC Derma-Pax; Midol Maximum Strength Multi-Symptom Menstrual; Midol Pre-Menstrual Syndrome; Myci-Spray; MyHist-DM; MyHist-PD; Nalex-A 12; ND-Gesic; P-Hist; P-Tanna; Pamprin; Poly-Histine†; Premsyn PMS; Pro-Red; Pyrlex CB; R-Tanna; R-Tannamine; R-Tannate; R-Tannic-S†; Rectagene Medicated Rectal Balm; Resperal; Rhinatate; Robitussin Night Relief; Ryna-12; Soothaderm; Tanoral; Tri-Tannate; Tricodene Cough & Cold; Triotann; Triplex AD; Tritan; Tussi-12 D; Tussi-12D S; Tussplex; Viravan; Viravan-DM; Z-Xtra; ***Venez.:*** Fesanol†; Metilcodin†; Metilfedrin†; Pi-Fedrin; Pinazo.

Mequitazine *(BAN, rINN)*

LM-209; Mekitatsiini; Mekitazin; Mequitazina; Méquitazine; Mequitazinum. 10-(Quinuclidin-3-ylmethyl)phenothiazine.

Мехитазин

$C_{20}H_{22}N_2S$ = 322.5.
CAS — 29216-28-2.
ATC — R06AD07.
ATC Vet — QR06AD07.

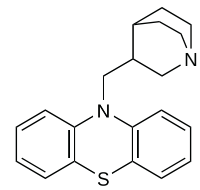

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Sedation. For discussion of the sedative effects of antihistamines, see p.562. When mequitazine is given in the recommended dosage of 5 mg twice daily the incidence of sedation appears comparable with that of terfenadine. Sedation has, however, occurred after doses of 10 mg twice daily.

Interactions

As for the sedating antihistamines in general, p.563.

Antibacterials. For a report of torsade de pointes in a patient taking *spiramycin* and mequitazine, see Cytochrome P450 Isoenzymes under Interactions of Spiramycin, p.333.

Pharmacokinetics

After absorption from the gastrointestinal tract, mequitazine is metabolised. Unchanged drug and metabolites are excreted principally in the bile.

Uses and Administration

Mequitazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic and mild sedative properties.

Mequitazine is used for the symptomatic relief of allergic conditions including urticaria (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). It has been given in usual oral doses of 5 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Primalan; ***Chile:*** Mircol; ***Fr.:*** Primalan; Quitadrill; ***Ger.:*** Metaplexan; ***Ital.:*** Primalan†; ***Mex.:*** Primalan; ***Philipp.:*** Primalan; ***Port.:*** Primalan; ***Rus.:*** Primalan (Прималан); ***Spain:*** Mircol.

Methdilazine *(BAN, rINN)*

Metdilatsiini; Metdilazin; Metdilazina; Methdilazinum; Metodilazina. 10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine.

Метдилазин

$C_{18}H_{20}N_2S$ = 296.4.
CAS — 1982-37-2.
ATC — R06AD04.
ATC Vet — QR06AD04.

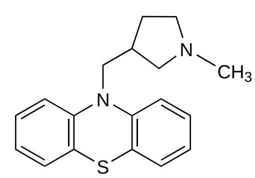

Methdilazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metodilazina; Methdilazine, Chlorhydrate de; Methdilazini Hydrochloridum.

Метдилазина Гидрохлорид

$C_{18}H_{20}N_2S,HCl$ = 332.9.
CAS — 1229-35-2.
ATC — R06AD04.
ATC Vet — QR06AD04.

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeias. In *US.*

USP 31 (Methdilazine Hydrochloride). A light tan crystalline powder having a slight characteristic odour. Soluble 1 in 2 of water and of alcohol, 1 in 6 of chloroform, and 1 in 1 of 0.1N hydrochloric acid and of 0.1N sodium hydroxide solution; practically insoluble in ether. pH of a 1% solution in water is between 4.8 and 6.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Methdilazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic and sedative activity. Methdilazine is also reported to have serotonin-antagonist properties.

Methdilazine hydrochloride is used for the symptomatic relief of hypersensitivity reactions and particularly for the control of pruritic skin disorders (p.565). An oral dose of 8 mg has been given 2 to 4 times daily. Methdilazine base has been used in similar doses. For children's doses, see below.

Administration in children. Methdilazine hydrochloride has been used in children for symptomatic relief of hypersensitivity reactions and particularly for the control of pruritic skin disorders. Oral doses of 4 mg given 2 to 4 times daily have been used in children aged 3 to 12 years. However, lower daily doses have also been used: children aged 3 to 6 years may be given 300 micrograms/kg daily (maximum 8 mg daily) and those aged 6 to 12 years, 4 mg twice daily.

Preparations

USP 31: Methdilazine Hydrochloride Syrup; Methdilazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Dilosyn†; ***Denm.:*** Tacryl†; ***India:*** Dilosyn.

Multi-ingredient: ***India:*** Dilosyn Expectorant.

Mizolastine *(BAN, rINN)*

Mitsolastiini; Mizolastin; Mizolastina; Mizolastinum; SL-85.0324-00. 2-{1-[1-(4-Fluorobenzyl)-1*H*-benzimidazol-2-yl]-4-piperidyl(methyl)amino}pyrimidin-4(1*H*)-one.

Мизоластин

$C_{24}H_{25}FN_6O$ = 432.5.

CAS — 108612-45-9.

ATC — R06AX25.

ATC Vet — QR06AX25.

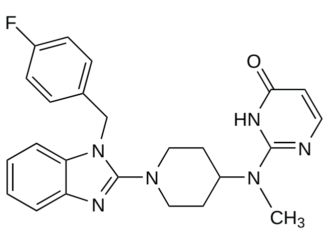

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Mizolastine has only a weak potential to prolong the QT interval (see also Arrhythmias, p.562) and has not been associated with arrhythmias. However, the manufacturers have warned against the use of mizolastine in patients with significant cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected QT prolongation. Use with drugs liable to interfere with the hepatic metabolism of mizolastine or with other potentially arrhythmogenic drugs should also be avoided (see under Interactions, below).

Interactions

As for the non-sedating antihistamines in general, p.563. Moderate increases in plasma concentrations of mizolastine have been reported with erythromycin and ketoconazole; use with macrolide antibacterials or systemic imidazole antifungals is contra-indicated by the manufacturer. They also advise against use of mizolastine with drugs known to prolong the QT interval, such as class I and III antiarrhythmics.

Other potent inhibitors of or substrates for the hepatic metabolism of mizolastine include cimetidine, ciclosporin, and nifedipine; caution is advised if given together.

Pharmacokinetics

Mizolastine is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations being reached after about 1.5 hours. Plasma protein binding is about 98%. The mean elimination half-life is about 13 hours. Mizolastine is mainly metabolised by glucuronidation although other metabolic pathways are involved, including metabolism by the cytochrome P450 isoenzyme CYP3A4, with the formation of inactive hydroxylated metabolites.

◊ References.

1. Rosenzweig P, *et al.* Pharmacodynamics and pharmacokinetics of mizolastine (SL 85.0324), a new nonsedative H antihistamine. *Ann Allergy* 1992; **69:** 135–9.
2. Lebrun-Vignes B, *et al.* Clinical pharmacokinetics of mizolastine. *Clin Pharmacokinet* 2001; **40:** 501–7.

Uses and Administration

Mizolastine is a non-sedating antihistamine with a long duration of action. It does not have significant antimuscarinic actions; it is reported to have mast-cell stabilising properties. Mizolastine is used for the symptomatic relief of allergic conditions including rhinitis (p.565), conjunctivitis (p.564), and skin disorders such as urticaria (p.565). The oral dose is 10 mg daily.

◊ References.

1. Leynadier F, *et al.* Efficacy and safety of mizolastine in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1996; **76:** 163–8.
2. Brostoff J, *et al.* Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. *Allergy* 1996; **51:** 320–5.
3. Stern MA, *et al.* Can an antihistamine delay appearance of hayfever symptoms when given prior to pollen season? *Allergy* 1997; **52:** 440–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Mistamine†; ***Austria:*** Mizollen; ***Belg.:*** Mistamine†; Mizollen; ***Chile:*** Mistamine†; ***Cz.:*** Mizollen†; ***Denm.:*** Mizollen; ***Fin.:*** Mizollen†; ***Fr.:*** Mizollen; ***Ger.:*** Mizollen; Zolim; ***Gr.:*** Mizollen; Oriens; ***Hung.:*** Mizollen†; ***India:*** Elina; ***Irl.:*** Mistamine†; ***Israel:*** Mizollen; ***Ital.:*** Mizollen; Zolistam; ***Mex.:*** Mistamine; ***Neth.:*** Mizollen; ***Pol.:*** Mizollen; ***Port.:*** Mistamine†; Mizollen; Zolistam; ***S.Afr.:*** Mizollen; ***Spain:*** Mistamine†; Mizolen; Zolistam; ***Swed.:*** Mizollen; ***Switz.:*** Mistamine†; Mizollen; ***UK:*** Mizollen.

Moxastine Teoclate *(rINNM)*

Mephenhydramine Theoclate; Mephenhydrinate; Moxastine, Téoclate de; Moxastine Theoclate; Moxastini Teoclas; Teoclato de moxastina. 2-(1,1-Diphenylethoxy)-*N*,*N*-dimethylethylamine 8-chlorotheophyllinate.

Моксастина Теоклат

$C_{18}H_{23}NO,C_6H_7ClN_4O_2$ = 472.0.

CAS — 3572-74-5 (moxastine); 21661-62-1 (moxastine teoclate).

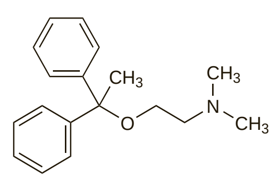

(moxastine)

Profile

Moxastine teoclate is an antihistamine with antiemetic properties. It is used to treat nausea and vertigo associated with Ménière's disease and other vestibular disorders, and for the prevention and treatment of motion sickness.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Kinedryl.

Multi-ingredient: ***Cz.:*** Nokinal†.

Niaprazine *(rINN)*

1709-CERM; Niaprazina; Niaprazinum. *N*-[3-(4-*p*-Fluorophenylpiperazin-1-yl)-1-methylpropyl]nicotinamide.

Ниапразин

$C_{20}H_{25}FN_4O$ = 356.4.

CAS — 27367-90-4.

ATC — N05CM16.

ATC Vet — QN05CM16.

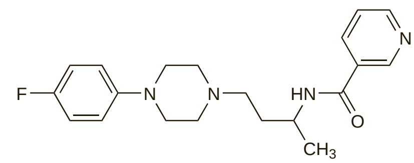

Profile

Niaprazine, a piperazine derivative, is an antihistamine (p.561) used in children for its sedative and hypnotic properties. The usual oral dose is 1 mg/kg at night.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Nopron; ***Ital.:*** Nopron.

Olopatadine Hydrochloride *(BANM, USAN, pINNM)*

ALO-4943A; Hidrocloruro de olopatadina; KW-4679; Olopatadin Hidroklorür; Olopatadine, Chlorhydrate d'; Olopatadini Hydrochloridum. 11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid hydrochloride.

Олопатадина Гидрохлорид

$C_{21}H_{23}NO_3,HCl$ = 373.9.

CAS — 113806-05-6 (olopatadine); 140462-76-6 (olopatadine hydrochloride).

ATC — R01AC08; S01GX09.

ATC Vet — QS01GX09.

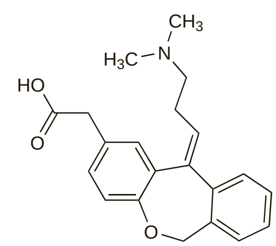

(olopatadine)

Adverse Effects and Precautions

As for the antihistamines in general, p.561. Headache and stinging or burning of the eye have occurred after ocular use.

Uses and Administration

Olopatadine hydrochloride is an antihistamine with mast-cell stabilising properties. It is used twice daily as eye drops containing the equivalent of 0.1% of olopatadine base in the treatment of allergic conjunctivitis (p.564) in adults and children aged three years and over.

◊ References.

1. Anonymous. Olopatadine for allergic conjunctivitis. *Med Lett Drugs Ther* 1997; **39:** 108–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Patanol; ***Austral.:*** Patanol; ***Belg.:*** Opatanol; ***Braz.:*** Patanol; ***Canad.:*** Patanol; ***Chile:*** Patanol; ***Cz.:*** Opatanol; ***Denm.:*** Opatanol; ***Fin.:*** Opatanol; ***Fr.:*** Opatanol; ***Ger.:*** Opatanol; ***Gr.:*** Opatanol; ***Hong Kong:*** Patanol; ***Hung.:*** Opatanol; ***Indon.:*** Patanol; ***Irl.:*** Opatanol; ***Israel:*** Patanol; ***Ital.:*** Opatanol; ***Jpn:*** Allelock; ***Malaysia:*** Patanol; ***Mex.:*** Patanol; ***Neth.:*** Opatanol; ***Norw.:*** Opatanol; ***NZ:*** Patanol; ***Philipp.:*** Patanol; ***Port.:*** Opatanol; ***Rus.:*** Opatanol (Опатанол); ***S.Afr.:*** Patanol; ***Singapore:*** Patanol; ***Spain:*** Opatanol; ***Swed.:*** Opatanol; ***Switz.:*** Opatanol; ***Thai.:*** Patanol; ***Turk.:*** Patanol; ***UK:*** Opatanol; ***USA:*** Pataday; Patanol; ***Venez.:*** Patanol.

Oxatomide *(BAN, USAN, rINN)*

Oksatomidi; Oxatomid; Oxatomida; Oxatomidum; R-35443. 1-[3-(4-Benzhydrylpiperazin-1-yl)propyl]benzimidazolin-2-one.

Оксатомид

$C_{27}H_{30}N_4O$ = 426.6.
CAS — 60607-34-3.
ATC — R06AE06.
ATC Vet — QR06AE06.

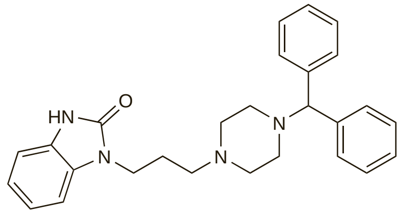

Profile

Oxatomide, a piperazine derivative, is a sedating antihistamine (p.561) that has also been reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria (p.565), rhinitis (p.565), and conjunctivitis (p.564). Oxatomide is given as the anhydrous substance or as the monohydrate; doses are expressed as the anhydrous substance. Oxatomide monohydrate 1.04 mg is equivalent to about 1 mg of anhydrous oxatomide. The usual oral dose is 30 mg twice daily. The hydrate has also been applied topically but, as with other antihistamines, there is a risk of sensitisation.

Effects on the nervous system. Acute dystonic reactions and long-lasting impaired consciousness were associated with oxatomide therapy in 6 children.[1] Impaired consciousness varied from lethargy and somnolence to a clinical picture resembling encephalitis and persisted for 2 days or more in 3 patients. Plasma-oxatomide concentrations were measured in 3 patients and found to be high, although 2 of these had been given the recommended dose.

1. Casteels-Van Daele M, *et al.* Acute dystonic reactions and long-lasting impaired consciousness associated with oxatomide in children. *Lancet* 1986; **i:** 1204–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cenacert†; Fensedyl; Tinset; ***Austria:*** Tinset; ***Belg.:*** Tinset†; ***Chile:*** Tinset; ***Fr.:*** Tinset; ***Gr.:*** Tinset; ***Hong Kong:*** Tinset†; ***Indon.:*** Oxtin; Tinset; ***Ital.:*** Tinset; ***Jpn:*** Celtect; ***Mex.:*** Tinset; ***Neth.:*** Tinset; ***Port.:*** Tinset; ***S.Afr.:*** Tinset; ***Spain:*** Cobiona; Oxatokey; ***Thai.:*** Tinset.

Multi-ingredient: ***Arg.:*** Causalon Bronquial; Causalon Grip; Letondal.

Oxomemazine *(rINN)*

Oxomemazina; Oxomémazine; Oxomemazinum; RP-6847; Trimeprazine SS-Dioxide. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.

Оксомемазин

$C_{18}H_{22}N_2O_2S$ = 330.4.
CAS — 3689-50-7.
ATC — R06AD08.
ATC Vet — QR06AD08.

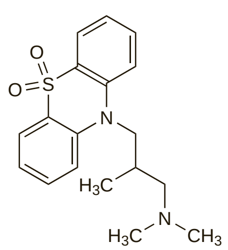

Oxomemazine Hydrochloride *(rINNM)*

Hidrocloruro de oxomemazina; Oxomémazine, Chlorhydrate d'; Oxomemazini Hydrochloridum.

Оксомемазина Гидрохлорид

$C_{18}H_{22}N_2O_2S,HCl$ = 366.9.
CAS — 4784-40-1.
ATC — R06AD08.
ATC Vet — QR06AD08.

Pharmacopoeias. In *Fr.*

Profile

Oxomemazine, a phenothiazine derivative, is a sedating antihistamine (p.561) used for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders (p.565). It is also an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Oxomemazine has been given orally in doses ranging from about 5 to 13 mg daily in divided doses. It has also been given by the rectal route. Oxomemazine hydrochloride has been used similarly by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Toplexil; ***Neth.:*** Toplexil.

Multi-ingredient: ***Belg.:*** Toplexil; ***Braz.:*** Expec; Iodesin; Iodeto de Potassium Composto†; Kl-Expectorante; Tiratosse†; Toplexil; Tussol†; ***Indon.:*** Comtusi; Toplexil; ***Israel:*** Oxacatin; Toplexil; ***Switz.:*** Toplexil.

Phenindamine Tartrate *(BANM, USAN, rINNM)*

Phenindamine Acid Tartrate; Phénindamine, Tartrate de; Phenindamini Tartras; Phenindaminium Tartrate; Tartrato de fenindamina. 1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-c]pyridine hydrogen tartrate.

Фениндамина Тартрат

$C_{19}H_{19}N,C_4H_6O_6$ = 411.4.
CAS — 82-88-2 (phenindamine); 569-59-5 (phenindamine tartrate).
ATC — R06AX04.
ATC Vet — QR06AX04.

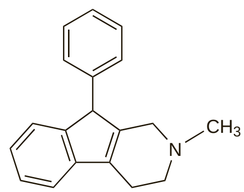

(phenindamine)

Pharmacopoeias. In *Br.*

BP 2008 (Phenindamine Tartrate). A white or almost white, odourless or almost odourless, voluminous powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 1% solution in water has a pH of 3.4 to 3.9. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Phenindamine tartrate may have a stimulant effect in certain individuals; to avoid the possibility of insomnia patients may be advised to take the last dose of the day several hours before retiring.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Phenindamine, a piperidine derivative, is a sedating antihistamine; however it may be mildly stimulating in certain individuals. It is used as the tartrate for the symptomatic relief of allergic conditions including urticaria (p.565) and rhinitis (p.565), and as an ingredient of compound preparations for coughs and the common cold (p.564).

Phenindamine tartrate is given in oral doses of 25 mg every 4 to 6 hours, up to a maximum of 150 mg daily. Children over 6 years of age have been given half these doses.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Nolahist.

Multi-ingredient: ***USA:*** P-V-Tussin.

Pheniramine *(BAN, rINN)*

Feniramiini; Feniramin; Feniramina; Phéniramine; Pheniraminum; Prophenpyridamine. *NN*-Dimethyl-3-phenyl-3-(2-pyridyl)propylamine.

Фенирамин

$C_{16}H_{20}N_2$ = 240.3.
CAS — 86-21-5.
ATC — R06AB05.
ATC Vet — QR06AB05.

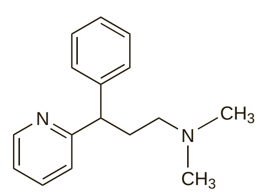

Pheniramine Aminosalicylate *(BANM, rINNM)*

Aminosalicilato de feniramina; Pheniramine *p*-Aminosalicylate; Pheniramine 4-Aminosalicylate; Phéniramine, Aminosalicylate de; Pheniramine Para-aminosalicylate; Pheniramini Aminosalicylas. Pheniramine 4-amino-2-hydroxybenzoate.

Фенирамина Аминосалисилат

$C_{16}H_{20}N_2,C_7H_7NO_3$ = 393.5.
CAS — 3269-83-8.
ATC — R06AB05.
ATC Vet — QR06AB05.

Pheniramine Maleate *(BANM, USAN, rINNM)*

Feniramiinimaleaatti; Feniramin Hidrojen Maleat; Feniramin Maleat; Feniramin maleinát; Feniraminmaleat; Feniramin-maleát; Feniramino maleatas; Maleato de feniramina; Phéniramine, maléate de; Pheniramini maleas; Pheniraminium Maleate; Prophenpyridamine Maleate. Pheniramine hydrogen maleate.

Фенирамина Малеат

$C_{16}H_{20}N_2,C_4H_4O_4$ = 356.4.
CAS — 132-20-7.
ATC — R06AB05.
ATC Vet — QR06AB05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pheniramine Maleate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol, in dichloromethane, and in methyl alcohol. M.p. 106° to 109°. A 1% solution in water has a pH of 4.5 to 5.5. Protect from light.

USP 31 (Pheniramine Maleate). A white crystalline powder having a faint amine-like odour. Soluble in water and in alcohol. pH of a 1% solution in water is between 4.5 and 5.5.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Abuse. References to the abuse of oral pheniramine.

1. Jones IH, *et al.* Pheniramine as an hallucinogen. *Med J Aust* 1973; **1:** 382–6.
2. Csillag ER, Landauer AA. Alleged hallucinogenic effect of a toxic overdose of an antihistamine preparation. *Med J Aust* 1973; **1:** 653–4.
3. Buckley NA, *et al.* Pheniramine—a much abused drug. *Med J Aust* 1994; **160:** 188–92.

Pregnancy. For discussion of the use of antihistamines, including pheniramine, in pregnancy, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

◊ The pharmacokinetics of pheniramine and its metabolites, *N*-desmethylpheniramine and *N*-didesmethylpheniramine, were investigated in 6 healthy subjects.[1] After oral doses of pheniramine aminosalicylate, peak-plasma pheniramine concentrations were reached in 1 to 2.5 hours. The terminal half-life ranged between 8 and 17 hours after intravenous doses (pheniramine maleate) and 16 and 19 hours after oral doses. The total recovery of pheniramine as unchanged drug and metabolites from the urine was 68 to 94% of the intravenous dose and 70 to 83% of the oral dose.

1. Witte PU, *et al.* Pharmacokinetics of pheniramine (Avil) and metabolites in healthy subjects after oral and intravenous administration. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 59–62.

Uses and Administration

Pheniramine, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties.

It is used as the maleate for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565), and conjunctivitis (p.564), and in pruritic skin disorders (p.565). It has also been used for its antiemetic properties in the prevention and control of motion sickness (p.564). Pheniramine maleate is used as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p.564). It is also used in combination with a decongestant in eye and nasal preparations.

Pheniramine maleate is given as a syrup in usual oral doses of 15 to 30 mg two or three times daily. It may also be given as a tablet in doses up to about 45 mg three times daily. In some countries pheniramine maleate has been given parenterally.

The aminosalicylate, the hydrochloride, and the tannate have also been used.

Preparations

USP 31: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Avil; Fenamine†; ***Austria:*** Avil; ***India:*** Avil; ***Indon.:*** Avil; ***Ital.:*** Inhiston†; ***Mex.:*** Histatex†; ***NZ:*** Avil†; ***Turk.:*** Avil; ***UAE:*** Histol.

Multi-ingredient: ***Arg.:*** Mira Klonal; Mirus; Refenax Colirio; ***Austral.:*** Avil Decongestant; Naphcon-A; Visine Allergy with Antihistamine; ***Austria:*** Neo Citran; ***Belg.:*** Naphcon-A; ***Braz.:*** Claril; ***Canad.:*** Ak Vernacon; Calmylin Ace; Citron Chaud DM; Diopticon A; Diorouge; Dristan; Hot Lemon; Hot Lemon Cough and Colds Relief DM; Hot Lemon Relief; Hot Lemon Relief for Cough and Cold; Naphcon-A; Neo Citran A†; Neo Citran Calorie Reduced†; Neo Citran Colds & Flu; Neo Citran DM; Neo Citran Extra Strength; Neo Citran†; Opcon-A; Pulmorphan; Pulmorphan Pediatrique; Robitussin AC; Robitussin with Codeine†; Visine Advance Allergy; ***Chile:*** Clarimir F; Dessolets; Miral; Mirus†; Naphcon-A; ***Cz.:*** Fervex; ***Fr.:*** Fervex; ***Ger.:*** Konjunktival Thilo†; Rhinosovil†; ***Hong Kong:*** Konjunktival†;

Naphcon-A; Opcon-A; ***Hung.:*** Fervex; Neo Citran; ***India:*** Avil Expectorant; Cosavil; Dristan Nasal Drops; ***Indon.:*** Flamergi; Isotic Azora; Naphcon-A; ***Israel:*** Tussosedan; ***Ital.:*** Nafcon A†; Senodin-AN; Stillergy; Tetramil; Triaminic; Triaminicflu; ***Malaysia:*** Naphcon-A; ***Mex.:*** Eyrasil; Istasol; Mirus; Opcon-A; Solutina; ***NZ:*** Naphcon-A; Visine Allergy; ***Philipp.:*** Decocon A; Naphcon-A; Optaphen; ***Pol.:*** Fervex; Theraflu ExtraGRIP; ***Rus.:*** Rinzasip (Ринзасип); TheraFlu Flu and Cold (ТераФлю от Гриппа и Простуды Экстра); ***S.Afr.:*** Calasthetic; Coff-Up; Degoran; Dristan Decongestant Nasal Mist; ***Singapore:*** Naphcon-A; ***Switz.:*** Neo Citran Grippe/refroidissement; ***Thai.:*** Naphcon-A; ***Turk.:*** Antibeksin; ***UAE:*** Histol Exp; ***USA:*** Dristan Nasal Spray; Nafazair A†; Naphazoline Plus; Naphcon-A; Naphoptic-A; Ocuhist; Opcon-A; Poly-Histine†; Scot-Tussin Original 5-Action; TheraFlu Cold & Cough; Tussirex; Visine-A; ***Venez.:*** Robitessin AC†; Soluclear; Tempragrip.

Phenyltoloxamine Citrate *(BANM, rINNM)*

C-5581H (phenyltoloxamine); Citrato de feniltoloxamina; Phényltoloxamine, Citrate de; Phenyltoloxamini Citras; Phenyltoloxamine Citrate; PRN (phenyltoloxamine). 2-(2-Benzylphenoxy)-*NN*-dimethylethylamine dihydrogen citrate.

Фенилтолоксамина Цитрат

$C_{17}H_{21}NO,C_6H_8O_7$ = 447.5.

CAS — 92-12-6 (phenyltoloxamine); 1176-08-5 (phenyltoloxamine citrate).

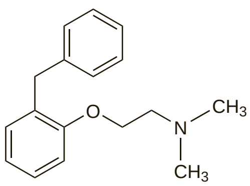

(phenyltoloxamine)

Pharmacopoeias. In *US.*

USP 31 (Phenyltoloxamine Citrate). A white crystalline powder. Very soluble in boiling water; slightly soluble in cold water and in alcohol; practically insoluble in cold acetone, in solvent ether, and in toluene. pH of a 1% solution in water is between 3.2 and 4.2.

Profile

Phenyltoloxamine citrate, a monoethanolamine derivative, is a sedating antihistamine (p.561). It is usually given orally in combination preparations with a decongestant or analgesic. Phenyltoloxamine citrate has been used in nasal preparations. Phenyltoloxamine polistirex has also been given orally.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Codipront; ***Braz.:*** Afebrin†; Setux; Setux Expectorante; ***Canad.:*** Omni-Tuss†; Tussionex; ***Chile:*** Codipront†; Matinor; Rinofrim†; Sinutab; Tossin†; ***Cz.:*** Codipront†; ***Fr.:*** Biocidan; Netux†; ***Ger.:*** Codipront†; ***Hong Kong:*** Codipront; ***Indon.:*** Codipront; Codipront cum Expectorant; ***Israel:*** Codivis; ***Ital.:*** Codipront†; ***Philipp.:*** Sinutab; ***Port.:*** Codipront; ***S.Afr.:*** Adco-Sinal Co; Dequa-Flu; Pholtex Linctus; Sinustop; Sinustop with Codeine; Sinutab; Sinutab with Codeine; Suncodin; ***Singapore:*** Codipront†; ***Spain:*** Codipront†; ***Switz.:*** Codipront; Codipront cum Expectorans†; ***Thai.:*** Codipront†; ***Turk.:*** Benzoleks; ***USA:*** Aceta-Gesic; Anabar; Be-Flex Plus; BP Poly-650; By-Ache; Cafgesic Forte; Chlorex-A; Combiflex; Combiflex ES; Comhist LA; Durabac Forte; Duraxin; Flextra; Hyflex; Lagesic; Levacet; Lobac; Major-gesic; Mobigesic; Momentum; Nalex-A; Pain-gesic; Percogesic; Phenylgesic; Poly-Histine†; Relagesic; Staflex; Tetra-Mag; ***Venez.:*** Codipront; Efoxamina†.

Pimethixene *(rINN)*

BP-400; Piméthixène; Pimethixenum; Pimetixene; Pimetixeno. 9-(1-Methyl-4-piperidylidene)thioxanthene.

Пиметиксен

$C_{19}H_{19}NS$ = 293.4.

CAS — 314-03-4.

ATC — R06AX23.

ATC Vet — QR06AX23.

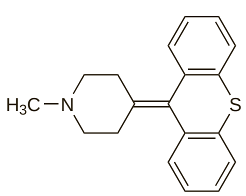

Profile

Pimethixene is reported to be a sedating antihistamine (p.561) and an inhibitor of serotonin. It is given to children in usual oral doses of about 1.8 to 5.5 mg daily for coughs. It has been used as a sedative and for the treatment of respiratory disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Ansiotex; Muricalm; Sonin†; ***Fr.:*** Calmixene.

Multi-ingredient: ***Braz.:*** Santussal.

Piprinhydrinate *(BAN, rINN)*

Diphenylpyraline Teoclate; Diphenylpyraline Theoclate; Piprinhidrinato; Piprinhydrinatum. The diphenylpyraline salt of 8-chlorotheophylline; 4-Benzhydryloxy-1-methylpiperidine salt of 8-chlorotheophylline.

Пипрингидринат

$C_{19}H_{23}NO,C_7H_7ClN_4O_2$ = 496.0.

CAS — 606-90-6.

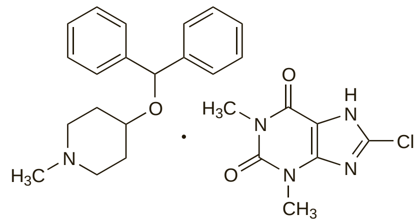

Profile

Piprinhydrinate, a piperidine derivative, is an antihistamine (p.561) given orally as an ingredient of compound preparations for the symptomatic relief of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Plokon†; ***Thai.:*** Plokon.

Multi-ingredient: ***Austria:*** Waldheim Influvidon; ***Ger.:*** Kolton grippale N†.

Promethazine *(BAN, rINN)*

Prometatsiini; Prometazin; Prometazina; Prométhazine; Promethazinum. Dimethyl (1-methyl-2-phenothiazin-10-ylethyl)amine.

Прометазин

$C_{17}H_{20}N_2S$ = 284.4.

CAS — 60-87-7.

ATC — D04AA10; R06AD02.

ATC Vet — QD04AA10; QR06AD02.

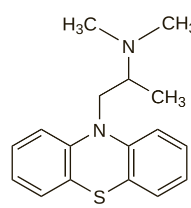

Promethazine Hydrochloride *(BANM, rINNM)*

Diprazinum; Hidrocloruro de prometazina; Proazamine Chloride; Prometatsiinihydrokloridi; Prometazin Hidroklorür; Prometazin-hidroklorid; Prometazinhydroklorid; Prometazino hidrochloridas; Prometazyny chlorowodorek; Prométhazine, chlorhydrate de; Promethazin-hydrochlorid; Promethazini hydrochloridum; Promethazinium Chloride.

Прометазина Гидрохлорид

$C_{17}H_{20}N_2S,HCl$ = 320.9.

CAS — 58-33-3.

ATC — D04AA10; R06AD02.

ATC Vet — QD04AA10; QR06AD02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Promethazine Hydrochloride). A white or faintly yellowish, crystalline powder. Very soluble in water; freely soluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Promethazine Hydrochloride). A white to faint yellow, practically odourless, crystalline powder. Slowly oxidises and acquires a blue colour on prolonged exposure to air. Freely soluble in water, in hot dehydrated alcohol, and in chloroform; practically insoluble in acetone, in ether, and in ethyl acetate. pH of a 5% solution in water is between 4.0 to 5.0. Store in airtight containers. Protect from light.

Adsorption. The adsorption of promethazine hydrochloride onto various glass and plastic containers and infusion systems has been studied.[1-4] Factors affecting the degree of adsorption included the particular material tested and the pH of the solution.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
3. Rhodes RS, *et al.* Stability of meperidine hydrochloride, promethazine hydrochloride, and atropine sulfate in plastic syringes. *Am J Hosp Pharm* 1985; **42:** 112–5.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Incompatibility. Solutions of promethazine hydrochloride are incompatible with alkaline substances, which precipitate the insoluble promethazine base. Compounds reported to be incompatible with promethazine hydrochloride include aminophylline, barbiturates, benzylpenicillin salts, carbenicillin sodium, chloramphenicol sodium succinate, chlorothiazide sodium, cefmetazole sodium, cefoperazone sodium, cefotetan disodium, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), furosemide, heparin sodium, hydrocortisone sodium succinate, meticillin sodium, morphine sulfate, nalbuphine hydrochloride, and some contrast media and parenteral nutrient solutions.

Promethazine Teoclate *(BAN, rINN)*

Prométhazine, Téoclate de; Promethazine Theoclate; Promethazini Teoclas; Teoclato de prometazina. The promethazine salt of 8-chlorotheophylline .

Прометазина Теоклат

$C_{17}H_{20}N_2S,C_7H_7ClN_4O_2$ = 499.0.

CAS — 17693-51-5.

ATC — D04AA10; R06AD02.

ATC Vet — QD04AA10; QR06AD02.

Pharmacopoeias. In *Br.*

BP 2008 (Promethazine Teoclate). A white or almost white, odourless or almost odourless powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. Protect from light.

Adverse Effects

As for the sedating antihistamines in general, p.561.

Cardiovascular adverse effects are more commonly seen after injection, and bradycardia, tachycardia, transient minor increases in blood pressure, and occasional hypotension have all been reported with promethazine hydrochloride. Jaundice and blood dyscrasias have been reported, and extrapyramidal effects may occur at high doses.

Venous thrombosis has been reported at the site of intravenous injections, and arteriospasm and gangrene may follow inadvertent intra-arterial injection.

Overdosage. A toxic neurological syndrome, which included CNS depression, acute excitomotor manifestations, ataxia and visual hallucinations, plus peripheral antimuscarinic effects developed in 2 children aged 44 months and 16 months after topical application of a 2% promethazine cream providing between 12.9 and 26 mg/kg.[1] The older child had also received hydroxyzine 10 mg orally 1 hour earlier.

1. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. *Can Med Assoc J* 1984; **130:** 1460–1.

Sudden infant death syndrome. Although some early reports raised the possibility of an association between the use of phenothiazine antihistamines and the sudden infant death syndrome (SIDS) this has not been confirmed. Following an initial report that 4 of 7 infants with SIDS had been given alimemazine before death and that a series of severe apnoeic crises had been observed in the twin of a SIDS victim given promethazine,[1] the same workers studied 52 SIDS victims, 36 near-miss infants (those who had experienced severe unexplained episodes of cyanosis or pallor during sleep), and 175 control subjects to investigate the role of nasopharyngitis and phenothiazines in this syndrome.[2] They found that there was no difference in the incidence of nasopharyngitis between the 3 groups, but the proportion of infants given phenothiazines was higher in both the SIDS group (23%) and the near-miss group (22%) than in the control group (2%). In a subsequent study,[3] they found that the incidence of central and obstructive sleep apnoeas was increased in 4 healthy infants given promethazine for 3 days, although the duration of the attacks was unaltered and generally short, with a range of 3 to 10 seconds. A report on behalf of the European Commission,[4] stated that no link between sudden deaths in infants and drug use had been confirmed by national drug monitoring centres. It was likely that the risk of apnoea was associated with all sedative drugs, especially in overdose.[4] Previously, phenothiazine-induced hyperthermia had been proposed as a contributory factor in SIDS.[5]

For general precautions regarding the use of antihistamines in children, see p.562.

1. Kahn A, Blum D. Possible role of phenothiazines in sudden infant death. *Lancet* 1979; **ii:** 364–5.

2. Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. *Pediatrics* 1982; **70:** 75–8.
3. Kahn A, *et al.* Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 1985; **75:** 844–7.
4. Cockfield. Phenergan, Theralene, Algotropyl—drugs responsible for the death of new-born babies. *Off J EC* 1986; **29:** C130/25–6.
5. Stanton AN. Sudden infant death syndrome and phenothiazines. *Pediatrics* 1983; **71:** 986–7.

Precautions

As for the sedating antihistamines in general, p.562.

Intravenous injections of promethazine hydrochloride must be given slowly and extreme care must be taken to avoid extravasation or inadvertent intra-arterial injection, because of the risk of severe irritation. Intramuscular injection may be painful, and it should not be given by subcutaneous injection.

False negative and positive results have been reported with some pregnancy tests.

Anaesthesia. In 8 healthy subjects promethazine 25 mg intravenously decreased lower oesophageal sphincter pressure and increased the incidence of gastro-oesophageal reflux.[1] It might, therefore, increase the risk of regurgitation and aspiration of gastric contents during induction of and recovery from anaesthesia. The effect was attributed to the antimuscarinic properties of promethazine.

1. Brock-Utne JG, *et al.* The action of commonly used antiemetics on the lower oesophageal sphincter. *Br J Anaesth* 1978; **50:** 295–8.

Children. A possible association between phenothiazine sedatives and sudden infant death syndrome has been suggested, but has not been confirmed (see under Adverse Effects, above). The current view in the UK and USA is that promethazine should not be given to children under 2 years of age.

Porphyria. Promethazine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p.563.

Renal impairment. Phenothiazine-induced toxic psychosis occurred in a patient with chronic renal failure who had been given promethazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

Promethazine is well absorbed after oral or intramuscular doses. Peak plasma concentrations have been seen 2 to 3 hours after a dose by these routes, although there is low systemic bioavailability after oral doses, due to high first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Values ranging from 76 to 93% have been reported for plasma-protein binding. Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to *N*-desmethylpromethazine. It is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

◊ References.

1. Taylor G, *et al.* Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. *Br J Clin Pharmacol* 1983; **15:** 287–93.
2. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
3. Stavchansky S, *et al.* Bioequivalence and pharmacokinetic profile of promethazine hydrochloride suppositories in humans. *J Pharm Sci* 1987; **76:** 441–5.
4. Strenkoski-Nix LC, *et al.* Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. *Am J Health-Syst Pharm* 2000; **57:** 1499–1505.

Uses and Administration

Promethazine, a phenothiazine derivative, is a sedating antihistamine with antimuscarinic, significant sedative, and some serotonin-antagonist properties. It is usually given as the hydrochloride or teoclate. Promethazine embonate and promethazine maleate have also been given orally. Promethazine dioxide (dioxopromethazine) has been used as the hydrochloride in eye and nasal drops. The antihistamine action has been reported to last for between 4 and 12 hours.

Promethazine hydrochloride is used for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). It may be given intravenously as an adjunct in the emergency treatment of anaphylactic shock (p.563).

Promethazine hydrochloride and promethazine teoclate are used for their antiemetic action in the prevention and treatment of nausea and vomiting in conditions such as motion sickness, drug-induced vomiting, and postoperative vomiting (p.564). They are also used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p.565). Promethazine hydrochloride is also employed pre- and postoperatively in surgery and obstetrics for its sedative effects and for the relief of apprehension (see Anaesthesia, p.563); it is often given with pethidine hydrochloride. Promethazine hydrochloride may be used for night-time sedation (see Insomnia, p.564).

Promethazine hydrochloride is a common ingredient of compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

The following doses have been given **orally**.

- For the treatment of *allergic conditions* promethazine hydrochloride is usually given in a dose of 25 mg at night increased to 25 mg twice daily if necessary; owing to its pronounced sedative effect it is preferably given at night but an alternative dose is 10 to 20 mg two or three times daily.
- Promethazine hydrochloride is given in doses of 20 to 50 mg at night for the short-term management of *insomnia* although its prolonged duration of action can lead to considerable drowsiness the following day.
- For the prevention of *motion sickness* promethazine hydrochloride can be given in a dose of 20 or 25 mg the night before travelling followed by a similar dose the following morning if necessary. The teoclate is used similarly. For the prevention of motion sickness the dose of promethazine teoclate is 25 mg at night or 25 mg one to two hours before travelling.
- For nausea and vomiting arising from causes such as *labyrinthitis* a dose of promethazine teoclate 25 mg at night is usually adequate; this may be increased to 50 or 75 mg at night or to 25 mg two or three times daily if necessary to a maximum of 100 mg daily.
- For *severe vomiting in pregnancy* the *BNF* recommends a dose of promethazine teoclate 25 mg at night, increased if necessary to a maximum of 100 mg.

In *children* the following oral doses of promethazine hydrochloride have been recommended.

- For allergic conditions: 2 to 5 years, 5 to 15 mg daily in one or two divided doses; 5 to 10 years, 10 to 25 mg daily in one or two divided doses.
- For night sedation or premedication: 2 to 5 years, 15 to 20 mg; 5 to 10 years, 20 to 25 mg.
- For the prevention of motion sickness the following doses of promethazine hydrochloride may be given the night before the journey and repeated on the following morning if necessary: 2 to 5 years, 5 mg; 5 to 10 years, 10 mg. Promethazine teoclate may also be given to children aged 5 to 10 years for the prevention of motion sickness in a dose of 12.5 mg daily, starting either on the night before travelling for long journeys or one to two hours before short journeys.
- Children aged 5 to 10 years may also receive promethazine teoclate for nausea and vomiting from causes such as labyrinthitis in a dose of 12.5 to 37.5 mg daily.

Promethazine hydrochloride is also given by the **rectal** route as suppositories. Doses are similar to those given orally.

Promethazine hydrochloride is given **parenterally** by deep intramuscular injection as a solution of 25 or 50 mg/mL. It may also be given by slow intravenous injection or injected into the tubing of a freely running infusion in a concentration of not more than 25 mg/mL, although it is usually diluted to 2.5 mg/mL. The rate of infusion should not exceed 25 mg/minute. The usual parenteral dose for all indications apart from nausea and vomiting is 25 to 50 mg; a dose of 100 mg should not be exceeded. Doses of 12.5 to 25 mg, repeated at intervals of not less than 4 hours, may be given for the treatment of nausea and vomiting, although not more than 100 mg is usually given in 24 hours.

Children aged 5 to 10 years may be given 6.25 to 12.5 mg of promethazine hydrochloride by deep intramuscular injection.

Promethazine has been used **topically** to provide relief in hypersensitivity disorders of the skin and for burns but, as with other antihistamines, it may produce skin sensitisation.

Sedation. For reference to the use of lytic cocktails of chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see under Pethidine, p.115.

Preparations

BP 2008: Promethazine Hydrochloride Tablets; Promethazine Injection; Promethazine Oral Solution; Promethazine Teoclate Tablets;
USP 31: Promethazine Hydrochloride Injection; Promethazine Hydrochloride Suppositories; Promethazine Hydrochloride Syrup; Promethazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Fenergan; ***Austral.:*** Avomine; Gold Cross Antihistamine Elixir†; Insomn-Eze†; Nyal Plus+ Allergy Relief†; Phenergan; ***Belg.:*** Phenergan; ***Braz.:*** Alergiderm; Alergosan†; Fenergan; Pamergan; Profergan; Prometazol; ***Canad.:*** Histantil; Phenergan†; ***Cz.:*** Prothazin; ***Denm.:*** Phenergan; ***Fr.:*** Phenergan; ***Ger.:*** Atosil; Closin; Eusedon mono†; Promethawern†; Proneurin; Prothanon; ***Gr.:*** Phenergan; Titanox; ***Hong Kong:*** Anvomin; Fenazin; Synvomin; ***Hung.:*** Pipolphen; ***India:*** Avomine; Emin; Phenergan; ***Indon.:*** Nufapreg; Phenergan; ***Irl.:*** Phenergan; ***Israel:*** Prothiazine; ***Ital.:*** Allerfen†; Fargan; Farganesse; Fenazil; ***Malaysia:*** Prothazine†; ***Norw.:*** Phenergan; ***NZ:*** Allersoothe; Avomine; Phenergan; ***Philipp.:*** Zinmet; ***Pol.:*** Diphergan; ***Port.:*** Fenergan; ***Rus.:*** Pipolphen (Пипольфен); ***S.Afr.:*** Avomine; Brunazine; Daralix; Lenazine; Phenergan; Prohist; Receptozine; ***Spain:*** Fenergan Topico; Frinova; ***Swed.:*** Lergigan; ***Thai.:*** Meta; Phenergan; Titanox†; ***UAE:*** Histaloc; ***UK:*** Avomine; Phenergan; Sominex; Ziz; ***USA:*** Phenadoz; Phenergan; Promethegan; ***Venez.:*** Diven†; Fenergan†.

Multi-ingredient: ***Austral.:*** Painstop; Painstop Night-Time Pain Reliever; Panquil; Phensedyl†; Tixylix Nightime; ***Braz.:*** Dorilen; Doriless; Fenergan Expectorante; Lisador; ***Canad.:*** Promatussin DM†; ***Cz.:*** Coldrex Nite; ***Fr.:*** Algotropyl†; Fluisedal; Rhinathiol Promethazine; Transmer†; Tussisedal; ***Ger.:*** Prothazin; ***Hong Kong:*** Dhasedyl; Ephedyl; Fendyl; Marsedyl; Methorsedyl; PEC; Phensedyn; Procodine†; Promethazine Compound Linctus†; Rhinathiol Promethazine; Super Cough†; Tripe P; ***Hung.:*** Tardyl†; ***India:*** Tixylix; ***Indon.:*** Berlifed; Fludexin; Halmezin; Neo Davenol; Phenadex; Prome; Promedex; Promethazine Ikapharmindo; ***Irl.:*** Night Nurse; ***Israel:*** Promethazine Expectorants; Prothiazine Expectorant; ***Ital.:*** Bronconait†; Nuleron; Tachinotte; ***Malaysia:*** Axcel Dextrozine; Dextrodyl; Dextromethorphan Compound; Dhasedyl DM; Hosedyl DM; Mucoease Plus; Phensedyl Dry Cough; Phensedyl†; Promedyl†; Rhinathiol Promethazine; Russedyl Plus; Russedyl†; SCMC Promethazine†; Sedilix DM†; Sedilix†; Tixylix†; ***NZ:*** Phensedyl Dry Family Cough†; Tixylix; ***Rus.:*** Prothiazine Expectorant (Протиазин Экспекторант); ***S.Afr.:*** Acustop; Adco-Kiddipayne; Antipyn†; Ban Pain; Brunacod; Colcaps; Dequa-Coff; Fevapar; Go-Pain; Goldgesic†; Histodor; Infacet; Infapain Forte; Kid-Eeze; Lenazine Forte; Lentogesic; Lesspain†; Medipyn; Megapyn; Mepromol; Painagon; Pedpain; Phensedyl; Propain†; Pynmed; Salterpyn; Stilpane; Stopayne; Tenston; Tixylix; Vacudol; Xeramax†; ***Singapore:*** Beacodyl; Cophadyl; Cophadyl-E; Dhasedyl; Dhasedyl DM; PCL†; Phensedyl†; Procodin; Promedyl†; Rhinathiol Promethazine; Sedilix; Sedilix DM; Unisedyl†; ***Spain:*** Actithiol Antihist; Antihemorroidal†; Fenergan Expectorante; Psicosoma Solucion; ***Swed.:*** Lergigan comp; ***Switz.:*** Linervidol†; Lysedil; Nardyl; Rhinathiol Promethazine; ***Thai.:*** Decos; Nordyl; Nortuss; Phencodin; Phensedyl†; Poly-Cof; Teradyl; ***Turk.:*** Artu; ***UAE:*** Flukit; ***UK:*** Day & Night Nurse; Night Nurse; Pamergan P100; Tixylix Night-Time; ***USA:*** Pentazine VC with Codeine; Phenameth DM; Pherazine DM; Pherazine VC; Pherazine VC with Codeine; Pherazine with Codeine; Prometh VC Plain; Prometh with Dextromethorphan; Promethazine VC with Codeine; ***Venez.:*** Preveral con Codeina; Preveral con Dextrometorfano.

Propiomazine *(BAN, USAN, rINN)*

CB-1678 (propiomazine or propiomazine maleate); Propiomatsiini; Propiomazin; Propiomazina; Propiomazinum; Wy-1359 (propiomazine or propiomazine maleate). 1-[10-(2-Dimethylaminopropyl)phenothiazin-2-yl]propan-1-one.

Пропиомазин

$C_{20}H_{24}N_2OS = 340.5.$
CAS — 362-29-8.
ATC — N05CM06.
ATC Vet — QN05CM06.

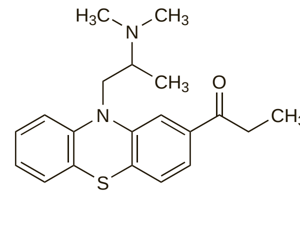

Propiomazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propiomazina; Propiomazine, Chlorhydrate de; Propiomazini Hydrochloridum.

Пропиомазина Гидрохлорид

$C_{20}H_{24}N_2OS,HCl = 376.9.$
CAS — 1240-15-9.
ATC — N05CM06.
ATC Vet — QN05CM06.

Propiomazine Maleate *(BANM, rINNM)*

CB-1678 (propiomazine or propiomazine maleate); Maleato de propiomazina; Propiomazine Hydrogen Maleate; Propiomazine, Maléate de; Propiomazini Maleas; Wy-1359 (propiomazine or propiomazine maleate).

Пропиомазина Малеат

$C_{20}H_{24}N_2OS,C_4H_4O_4 = 456.6.$
CAS — 3568-23-8.
ATC — N05CM06.
ATC Vet — QN05CM06.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Local irritation may occur at the site of intravenous injection of propiomazine hydrochloride and there may be thrombophlebitis.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Propiomazine, a phenothiazine derivative, is a sedating antihistamine that has been used for its sedative and antiemetic properties in insomnia (p.564) and nausea and vomiting (p.564).

Propiomazine is given as the maleate but doses are expressed in terms of the base; propiomazine maleate 1.3 mg is equivalent to about 1 mg of propiomazine. Doses equivalent to 25 to 50 mg orally at night have been given as a hypnotic.

Propiomazine hydrochloride has been given parenterally.

Preparations

Proprietary Preparations (details are given in Part 3)
Swed.: Propavan.

Quifenadine Hydrochloride *(rINNM)*

Hidrocloruro de quifenadina; Quifénadine, Chlorhydrate de; Quifenadini Hydrochloridum. α,α-Diphenyl-3-quinuclidinemethanol hydrochloride.

Хифенадина Гидрохлорид

$C_{20}H_{23}NO,HCl = 329.9.$
CAS — 10447-39-9 (quifenadine); 10447-38-8 (quifenadine hydrochloride).

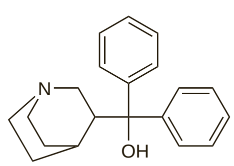

(quifenadine)

Profile

Quifenadine is an antihistamine given orally as the hydrochloride.

Rupatadine *(rINN)*

Rupatadina; Rupatadinum; UR-12592 (rupatadine fumarate). 8-Chloro-6,11-dihydro-11-{1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene}-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

Рупатадин

$C_{26}H_{26}ClN_3 = 416.0.$
CAS — 158876-82-5 (rupatadine); 182349-12-8 (rupatadine fumarate).
ATC — R06AX28.
ATC Vet — QR06AX28.

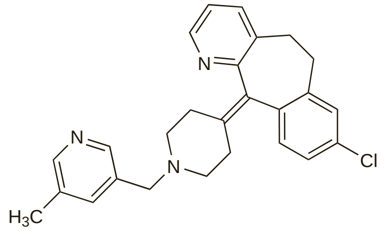

Profile

Rupatadine is an antihistamine with platelet-activating factor (PAF) antagonist activity that is used for the treatment of allergic rhinitis (p.565) and chronic idiopathic urticaria (p.565). It is given as the fumarate although doses are expressed in terms of the base; rupatadine fumarate 12.8 mg is equivalent to about 10 mg of rupatadine. The usual oral dose is the equivalent of 10 mg once daily of rupatadine.

◊ References.

1. Izquierdo I, *et al.* Rupatadine: a new selective histamine H1 receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today* 2003; **39:** 451–68.
2. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; **67:** 457–74.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Rupafin; ***Cz.:*** Tamalis; ***Gr.:*** Rupafin; ***Port.:*** Rinialer; ***Spain:*** Alergoliber; Rinialer; Rupafin.

Sequifenadine *(rINN)*

Bicarphene (sequifenadine or sequifenadine hydrochloride); Bikarfen (sequifenadine or sequifenadine hydrochloride); Sequifenadina; Séquifénadine; Sequifenadinum. α,α-Di-*o*-tolyl-3-quinuclidinemethanol.

Сехифенадин

$C_{22}H_{27}NO = 321.5.$
CAS — 57734-69-7.

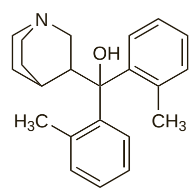

Profile

Sequifenadine is an antihistamine used in a wide range of allergic conditions. A usual dose is 50 to 100 mg given orally 2 or 3 times daily. Sequifenadine is reported also to have antiserotonin properties.

Setastine Hydrochloride *(rINNM)*

EGIS-2062; EGYT-2062; Hidrocloruro de setastina; Sétastine, Chlorhydrate de; Setastini Hydrochloridum. 1-{2-[(*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl}hexahydro-1*H*-azepine hydrochloride.

Сетастина Гидрохлорид

$C_{22}H_{28}ClNO,HCl = 394.4.$
CAS — 64294-95-7 (setastine).

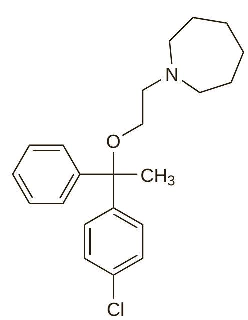

(setastine)

Profile

Setastine hydrochloride, a derivative of clemastine, is an antihistamine (p.561) claimed to have no sedative activity. It has been given orally for the symptomatic relief of hypersensitivity disorders.

Terfenadine *(BAN, USAN, rINN)*

MDL-9918; RMI-9918; Terfenadiini; Terfenadin; Terfenadina; Terfenadinas; Terfénadine; Terfenadinum. 1-(4-*tert*-Butylphenyl)-4-[4-(α-hydroxybenzhydryl)piperidino]butan-1-ol.

Терфенадин

$C_{32}H_{41}NO_2 = 471.7.$
CAS — 50679-08-8.
ATC — R06AX12.
ATC Vet — QR06AX12.

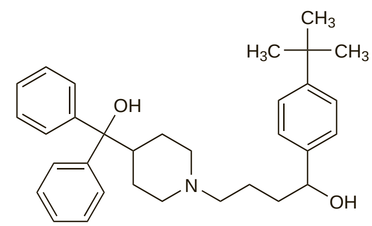

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Terfenadine). A white or almost white, crystalline powder. It shows polymorphism. Very slightly soluble in water and in dilute hydrochloric acid; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Erythema multiforme and galactorrhoea have also been reported.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with terfenadine, particularly in association with raised blood concentrations (see Arrhythmias, below). To *reduce the risk* of developing such arrhythmias the recommended dose should **not** be exceeded and terfenadine should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of terfenadine, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance is **contra-indicated** (see under Interactions, below). If palpitations, dizziness, syncope, or convulsions occur terfenadine should be withdrawn and the patient investigated for potential arrhythmias.

Alopecia. Hair loss was associated with use of terfenadine in a 24-year-old patient.[1] Regrowth occurred when treatment was stopped.

1. Jones SK, Morley WN. Terfenadine causing hair loss. *BMJ* 1985; **291:** 940.

Arrhythmias. Ventricular arrhythmias including torsade de pointes have occurred with terfenadine at doses greater than those recommended[1] and also at normal doses in patients whose metabolism of terfenadine is impaired by drugs or by liver disease. Generalised convulsions and a quinine-like effect on the ECG have also been reported after a presumed overdose of terfenadine.[2] Consequently a number of recommendations have been made to *reduce the risk* of developing serious arrhythmias (see Adverse Effects and Precautions, above, for details), including those from the UK CSM.[3,4] Terfenadine should be stopped immediately, and the patient evaluated for potential arrhythmias, in those who experience syncope, palpitations, dizziness, or convulsions after taking terfenadine.

Studies[5] have suggested that the ventricular arrhythmias are due to terfenadine itself rather than its active metabolite fexofenadine (p.579). Terfenadine has been shown to inhibit cardiac potassium channels, which results in prolongation of the QT interval, a risk factor for developing arrhythmias, while the non-sedating antihistamines cetirizine, fexofenadine, and loratadine have had no demonstrable effect[5,6] (see also p.562).

1. MacConnell TJ, Stanners AJ. Torsades de pointes complicating treatment with terfenadine. *BMJ* 1991; **302:** 1469.
2. Davies AJ, *et al.* Cardiotoxic effect with convulsions in terfenadine overdose. *BMJ* 1989; **298:** 325.
3. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
4. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
5. Woolsey RL, *et al.* Mechanism of the cardiotoxic actions of terfenadine. *JAMA* 1993; **269:** 1532–6.
6. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Breast feeding. No adverse effects have been observed in breast-fed infants whose mothers were receiving terfenadine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] of 4 healthy lactating women given 60 mg of terfenadine every 12 hours for 48 hours, terfenadine was undetected in breast milk; its active metabolite, fexofenadine, was excreted in limited amounts.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/04/04)
2. Lucas BD, *et al.* Terfenadine pharmacokinetics in breast milk in lactating women. *Clin Pharmacol Ther* 1995; **57:** 398–402.

Effects on the liver. Three episodes of acute hepatitis with jaundice occurred in a patient taking terfenadine intermittently over a period of 17 months.[1] Liver function tests returned to normal after the drug was stopped. Two further cases[2] of cholestatic hepatitis associated with terfenadine have been reported. Again, liver function tests returned to normal after drug withdrawal. A study[3] by the Boston Collaborative Drug Surveillance Program of 210 683 patients who had received prescriptions for terfenadine concluded that the use of terfenadine was rarely associated with important idiopathic liver disease. The investigators found only 3 cases of acute liver disease where a causal connection to terfenadine could not be ruled out; all these patients had also received a hepatotoxic drug and had made a full recovery.

1. Larrey D, *et al.* Terfenadine and hepatitis. *Ann Intern Med* 1985; **103:** 634.
2. Sahai A, Villeneuve JP. Terfenadine-induced cholestatic hepatitis. *Lancet* 1996; **348:** 552–3.
3. Myers MW, Jick H. Terfenadine and risk of acute liver disease. *Br J Clin Pharmacol* 1998; **46:** 251–3.

Effects on the nervous system. Non-sedating effects on the CNS have been reported after a single dose of terfenadine;[1] these have included anxiety, palpitations, and insomnia. The UK manufacturers commented that clinical studies suggest that the incidence of such effects is similar to that seen after placebo.[2]

Workers who had described a generalised tonic-clonic seizure in a patient taking terfenadine[3] later reported that the patient had subsequently had a second unprovoked seizure[4] and now considered that terfenadine may not have been the cause of his original seizure. Convulsions have been reported after overdosage with terfenadine (see under Arrhythmias, above).

The sedative effects of the older antihistamines and the lack of such effects with the non-sedating antihistamines including terfenadine are discussed under Sedation on p.562.

1. Napke E, Biron P. Nervous reactions after first dose of terfenadine in adults. *Lancet* 1989; **ii:** 615–16.
2. Masheter HC. Nervous reactions to terfenadine. *Lancet* 1989; **ii:** 1034.
3. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 241.
4. Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993; **307:** 736.

Hypersensitivity. Terfenadine use was associated with 108 reports of skin reactions, including rashes, urticaria, angioedema, photosensitivity reactions and peeling of the skin of the hands or feet.[1]

1. Stricker BHCh, *et al.* Skin reactions to terfenadine. *BMJ* 1986; **293:** 536.

Porphyria. Terfenadine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for the non-sedating antihistamines in general, p.563.

Terfenadine should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the triazole and imidazole antifungals such as itraconazole and ketoconazole, the macrolide antibacterials including clarithromycin, erythromycin, josamycin, and troleandomycin, the streptogramin antibacterial quinupristin/dalfopristin, the serotonin reuptake inhibitors citalopram, fluoxetine, fluvoxamine, nefazodone, and paroxetine, the HIV-protease inhibitors, the NNRTIs delavirdine and efavirenz, and zileuton. The metabolism of terfenadine may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, probucol, pentamidine isetionate, and the beta blocker sotalol should be avoided as should diuretics that cause electrolyte imbalances especially hypokalaemia. The use of terfenadine and astemizole together is not recommended.

◊ General references.

1. Kivistö KT, *et al.* Inhibition of terfenadine metabolism: pharmacokinetic and pharmacodynamic consequences. *Clin Pharmacokinet* 1994; **27:** 1–5.

Antibacterials. Pharmacokinetic studies have shown that the macrolide antibiotics *erythromycin*[1] and *clarithromycin*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with erythromycin[3] or *troleandomycin*.[4]

1. Honig PK, *et al.* Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; **52:** 231–8.
2. Honig P, *et al.* Effect of erythromycin, clarithromycin and azithromycin on the pharmacokinetics of terfenadine. *Clin Pharmacol Ther* 1993; **53:** 161.
3. Biglin KE, *et al.* Drug-induced torsades de pointes: a possible interaction of terfenadine and erythromycin. *Ann Pharmacother* 1994; **28:** 282.
4. Fournier P, *et al.* Une nouvelle cause de torsades de pointes: association terfenadine et troleandomycine. *Ann Cardiol Angeiol (Paris)* 1993; **42:** 249–52.

Antidepressants. Cardiac abnormalities have been reported in 2 patients taking *fluoxetine* with terfenadine.[1,2] Similarly, the use of *nefazodone* with terfenadine has resulted in prolongation of the QT interval.[3]

1. Swims MP. Potential terfenadine-fluoxetine interaction. *Ann Pharmacother* 1993; **27:** 1404–5.
2. Marchiando RJ, Cook MD. Probable terfenadine-fluoxetine-associated cardiac toxicity. *Ann Pharmacother* 1995; **29:** 937–8.
3. Abernethy DR, *et al.* Loratadine and terfenadine interaction with nefazodone: both antihistamines are associated with QTc prolongation. *Clin Pharmacol Ther* 2001; **69:** 96–103.

Antiepileptics. For reference to an interaction between terfenadine and *carbamazepine*, see p.475.

Antifungals. Pharmacokinetic studies have shown that *itraconazole*[1] and *ketoconazole*[2] interfere with the metabolism of terfenadine leading to its accumulation. A high plasma-terfenadine concentration is associated with prolongation of the QT interval, and arrhythmias such as torsade de pointes have been reported in patients given terfenadine with ketoconazole[3] or itraconazole.[1,4] While there has been a pharmacokinetic study[5] that suggested that the interaction between terfenadine and *fluconazole* might not be clinically significant, as the mechanism of the interaction appeared to involve the metabolite of terfenadine and did not lead to accumulation of the cardiotoxic parent compound, this may not always be the case. Studies in a small group of patients who had abnormal patterns of terfenadine metabolism found increases in terfenadine concentrations associated with ECG abnormalities when terfenadine was given with high doses of fluconazole.[6]

1. Pohjola-Sintonen S, *et al.* Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. *Eur J Clin Pharmacol* 1993; **45:** 191–3.
2. Honig PK, *et al.* Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. *JAMA* 1993; **269:** 1513–18.
3. Monahan BP, *et al.* Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990; **264:** 2788–90.
4. Crane JK, *et al.* Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. *Am J Med* 1993; **95:** 445–6.
5. Honig PK, *et al.* The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993; **53:** 630–6.
6. Cantilena LR, *et al.* Fluconazole alters terfenadine pharmacokinetics and electrocardiographic pharmacodynamics. *Clin Pharmacol Ther* 1995; **57:** 185.

Calcium-channel blockers. For reference to an interaction between terfenadine and *nifedipine*, see p.1353.

Grapefruit juice. A study[1] in healthy subjects given terfenadine and grapefruit juice for 7 days found raised plasma-terfenadine concentrations and prolongation of the QT interval. These effects were less pronounced when terfenadine was given 2 hours before grapefruit juice, but were nevertheless quantifiable in some subjects. In another study QT interval changes were not found in healthy subjects given single doses of terfenadine and grapefruit juice.[2] However, the highly variable pharmacokinetics between individuals led the authors to conclude that prolongation of the QT interval was possible following single doses. The probable mechanism of the interaction is inhibition of the metabolism of terfenadine by the cytochrome P450 isoenzyme CYP3A4.

1. Benton RE, *et al.* Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. *Clin Pharmacol Ther* 1996; **59:** 383–8.
2. Rau SE, *et al.* Grapefruit juice-terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clin Pharmacol Ther* 1997; **61:** 401–9.

Pharmacokinetics

Terfenadine is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are achieved within about 2 hours. It is a prodrug and undergoes extensive first-pass metabolism in the liver to its active metabolite the carboxylic acid derivative fexofenadine (p.579). The other main metabolite is an inactive piperidine-carbinol derivative. About 97% of terfenadine is bound to plasma proteins; fexofenadine is reported to be less extensively bound. Terfenadine does not appear to cross the blood-brain barrier to a significant extent; limited amounts of fexofenadine, but not the parent drug, have been detected in breast milk. An elimination half-life of 16 to 23 hours has been reported for terfenadine. The metabolites, and traces of unchanged drug, are excreted in the urine and the faeces.

◊ References.

1. Eller MG, *et al.* Pharmacokinetics of terfenadine in healthy elderly subjects. *J Clin Pharmacol* 1992; **32:** 267–71.

Uses and Administration

Terfenadine, a piperidine derivative, is a non-sedating antihistamine. It does not have significant antimuscarinic actions. It is used for the symptomatic relief of allergic conditions including rhinitis (p.565) and conjunctivitis (p.564) and skin disorders such as urticaria (p.565).

The maximum oral dose of terfenadine is 120 mg daily given either as 60 mg twice daily or 120 mg in the morning; a starting dose of 60 mg daily in a single dose or in two divided doses is recommended for rhinitis and conjunctivitis. Children who are over 12 years of age and weigh more than 50 kg may receive the usual adult dosage.

For dosage in renal impairment see below.

Administration in renal impairment. Half the usual oral daily dose of terfenadine has been suggested for patients with creatinine clearance less than 40 mL/minute.

Preparations

BP 2008: Terfenadine Oral Suspension; Terfenadine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Terfemax†; ***Cz.:*** Lotanax†; Tergal†; Teridin†; ***Denm.:*** Teldanex†; Tenadin†; Terfin†; ***Ger.:*** Hisfedin†; Terfedura†; Terfemundin†; ***Hong Kong:*** Fenason†; Hisdane†; Histafen; Tamagon; Vida Fenadine†; ***India:*** Trexyl†; ***Indon.:*** Alpenaso; Histastop; Terfin; ***Ital.:*** Allerzil†; ***Malaysia:*** Neutramine†; Tamagon†; ***Mex.:*** Teldane†; ***Norw.:*** Teldanex†; ***Port.:*** Triludan†; ***S.Afr.:*** Fendin; Triludan†; ***Spain:*** Cyater; Rapidal†; Ternadin; ***Swed.:*** Teldanex†; ***Turk.:*** Teradin; ***Venez.:*** Terfanil†; Tetram†; Tirfen†.

Multi-ingredient: ***Arg.:*** Cortaler Novo†; Cortistamin NF†; Sinlergia†; Terfenadina DG†; Vixidone T†; ***India:*** Alpha-Zedex†; Teguphen†; Tusant†; ***Indon.:*** Rhinofed; ***Malaysia:*** Trexydin†; ***Mex.:*** Teldane D†; ***Venez.:*** Rinodrina†; Rinotirfen†.

Thenyldiamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tenildiamina; Thényldiamine, Chlorhydrate de; Thenyldiamini Hydrochloridum; Thenyldiaminium Chloride. *NN*-Dimethyl-*N*′-(2-pyridyl)-*N*′-(3-thenyl)ethylenediamine hydrochloride.

Тенилдиамина Гидрохлорид

$C_{14}H_{19}N_3S,HCl = 297.8.$

CAS — 91-79-2 (thenyldiamine); 958-93-0 (thenyldiamine hydrochloride).

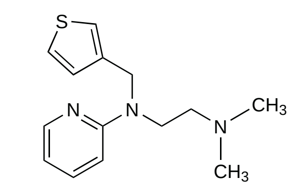

(thenyldiamine)

Profile

Thenyldiamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p.561). It is given by mouth as an ingredient of compound preparations for the symptomatic treatment of coughs and the common cold.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** NTR.

Thiethylperazine *(BAN, USAN, rINN)*

Thiéthylpérazine; Thiethylperazinum; Tietilperazina; Tietylperazin; Tietyyliperatsiini. 2-Ethylthio-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine.

Тиэтилперазин

$C_{22}H_{29}N_3S_2 = 399.6.$

CAS — 1420-55-9.

ATC — R06AD03.

ATC Vet — QR06AD03.

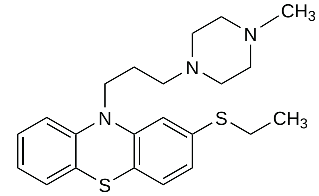

Thiethylperazine Malate *(BANM, rINNM)*

Malato de tietilperazina; Thiéthylpérazine, Malate de; Thiethylperazini Malas.

Тиэтилперазина Малат

$C_{22}H_{29}N_3S_2,2C_4H_6O_5 = 667.8.$

CAS — 52239-63-1.

ATC — R06AD03.

ATC Vet — QR06AD03.

Thiethylperazine Maleate *(BANM, USAN, rINNM)*

GS-95; Maleato de tietilperazina; NSC-130044; Thiethylperazine Dimaleate; Thiéthylpérazine, Maléate de; Thiethylperazini Maleas.

Тиэтилперазина Малеат

$C_{22}H_{29}N_3S_2,2C_4H_4O_4$ = 631.8.

CAS — 1179-69-7.

ATC — R06AD03.

ATC Vet — QR06AD03.

Pharmacopoeias. In *Swiss* and *US*.

USP 31 (Thiethylperazine Maleate). A yellowish granular powder, odourless or has not more than a slight odour. Soluble 1 in 1700 of water and 1 in 530 of alcohol; practically insoluble in chloroform and in ether; slightly soluble in methyl alcohol. pH of a 0.1% solution in water is between 2.8 and 3.8. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between injections of thiethylperazine maleate and nalbuphine hydrochloride.[1]

1. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Thiethylperazine, a phenothiazine derivative with a piperazine side-chain, is a sedating antihistamine used as an antiemetic for the control of nausea and vomiting (p.564) associated with surgical procedures and cancer therapy. It has also been used for the management of vertigo (p.565) and motion sickness although there is some doubt over its efficacy for these indications.

Thiethylperazine is given as the maleate or malate and doses are expressed in terms of the appropriate salt. Thiethylperazine maleate 10 mg is equivalent to about 10.53 mg of thiethylperazine malate.

Thiethylperazine *maleate* is given in usual oral doses of 10 mg up to three times daily; the maleate has also been given rectally. Where oral dosage is impractical similar doses of the *malate* may be given by deep intramuscular injection. Thiethylperazine is not recommended for use in children.

Preparations

USP 31: Thiethylperazine Maleate Suppositories; Thiethylperazine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Torecan; ***Chile:*** Torecan; ***Cz.:*** Torecan; ***Hung.:*** Torecan; ***Ital.:*** Torecan; ***Mex.:*** Torecan; ***Pol.:*** Torecan; ***Rus.:*** Torecan (Торекан); ***Spain:*** Torecan; ***Swed.:*** Torecan; ***Switz.:*** Torecan; ***USA:*** Torecan.

Thonzylamine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de tonzilamina; Thonzylamine, Chlorhydrate de; Thonzylamini Hydrochloridum. *N*-*p*-Anisyl-*N'N'*-dimethyl-*N*-(pyrimidin-2-yl)ethylenediamine hydrochloride.

Тонзиламина Гидрохлорид

$C_{16}H_{22}N_4O,HCl$ = 322.8.

CAS — 91-85-0 (thonzylamine); 63-56-9 (thonzylamine hydrochloride).

ATC — D04AA01; R01AC06; R06AC06.

ATC Vet — QD04AA01; QR01AC06; QR06AC06.

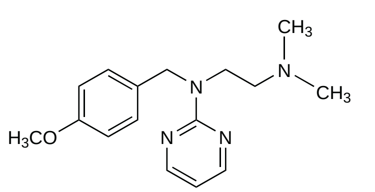

(thonzylamine)

Profile

Thonzylamine hydrochloride, an ethylenediamine derivative, is an antihistamine (p.561) given for the symptomatic relief of hypersensitivity disorders in oral doses of 50 to 100 mg daily; a 0.1% nasal solution and 2.5% ointment are also available. As with other antihistamines, there is a risk of skin sensitisation with the ointment. It is also used in eye drops with a vasoconstrictor such as naphazoline nitrate for allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tonamil.

Multi-ingredient: ***Ital.:*** Ascotodin; Collirio Alfa Antistaminico; Imidazyl Antistaminico; Iristamina; Narlisim; Pupilla Antistaminico; ***Port.:*** Narizima; ***Spain:*** Normo Nar†.

Trimethobenzamide Hydrochloride *(rINNM)*

Hidrocloruro de trimetobenzamida; Triméthobenzamide, Chlorhydrate de; Trimethobenzamidi Hydrochloridum; Trimetobenzamid Hidroklorür. *N*-[4-(2-Dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride.

Триметобензамида Гидрохлорид

$C_{21}H_{28}N_2O_5,HCl$ = 424.9.

CAS — 138-56-7 (trimethobenzamide); 554-92-7 (trimethobenzamide hydrochloride).

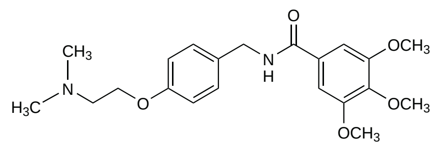

(trimethobenzamide)

Pharmacopoeias. In *US*.

USP 31 (Trimethobenzamide Hydrochloride). A white crystalline powder having a slight phenolic odour. Soluble 1 in 2 of water, 1 in 59 of alcohol, 1 in 67 of chloroform, and 1 in 720 of ether; insoluble in benzene.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Pain at the site of intramuscular injection and local irritation after rectal use have been noted.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including some evidence of an excess number of congenital abnormalities in infants born to mothers exposed to trimethobenzamide, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Trimethobenzamide hydrochloride, a monoethanolamine derivative, is a sedating antihistamine used as an antiemetic in the control of nausea and vomiting (p.564) including postoperative nausea and vomiting.

The usual dose is 250 or 300 mg orally or 200 mg by deep intramuscular injection or rectally three or four times daily. Children weighing more than about 15 kg have been given 100 to 200 mg three or four times daily by the oral or rectal route. Children weighing less than this have been given 100 mg three or four times daily by the rectal route.

Preparations

USP 31: Trimethobenzamide Hydrochloride Capsules; Trimethobenzamide Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Turk.: Ametik; Anti-Vomit; Emedur; Vomet; Vomitin; ***USA:*** T-Gen†; Tebamide†; Ticon; Tigan; Trimazide†.

Multi-ingredient: ***Turk.:*** Emedur; ***USA:*** Emergent-Ez; Tigan†; Triban†.

Tripelennamine Citrate *(BANM, rINNM)*

Citrato de tripelenamina; Tripélennamine, Citrate de; Tripelennamini Citras; Tripelennaminium Citrate. *N*-Benzyl-*N'N'*-dimethyl-*N*-(2-pyridyl)ethylenediamine dihydrogen citrate.

Трипеленнамина Цитрат

$C_{16}H_{21}N_3,C_6H_8O_7$ = 447.5.

CAS — 91-81-6 (tripelennamine); 6138-56-3 (tripelennamine citrate).

ATC — D04AA04; R06AC04.

ATC Vet — QD04AA04; QR06AC04.

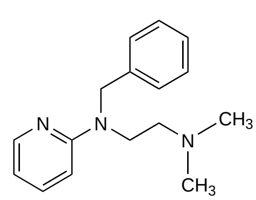

(tripelennamine)

Tripelennamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tripelenamina; Tripélennamine, Chlorhydrate de; Tripelennamini Hydrochloridum; Tripelennaminium Chloride.

Трипеленнамина Гидрохлорид

$C_{16}H_{21}N_3,HCl$ = 291.8.

CAS — 154-69-8.

ATC — D04AA04; R06AC04.

ATC Vet — QD04AA04; QR06AC04.

Pharmacopoeias. In *US*.

USP 31 (Tripelennamine Hydrochloride). A white crystalline powder. It slowly darkens on exposure to light. Soluble 1 in 1 of water, 1 in 6 of alcohol and of chloroform, 1 in 350 of acetone; insoluble in ether, in ethyl acetate, and in benzene. Its solutions are practically neutral to litmus. Protect from light.

Profile

Tripelennamine, an ethylenediamine derivative, is a sedating antihistamine (p.561) with antimuscarinic and moderate sedative properties. It has been used for the symptomatic relief of hypersensitivity reactions. It may also be used in compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

Tripelennamine has been given orally as the citrate or the hydrochloride. Tripelennamine hydrochloride has also been applied topically to the skin, although, as with other antihistamines, there is a risk of sensitisation.

Abuse. References to the intravenous abuse of tripelennamine alone[1] or with pentazocine in the combination known as T's and blues.[2-4]

1. Addington J, el-Guebaly N. Intravenous tripelennamine abuse in schizophrenia. *Can J Psychiatry* 1996; **41:** 63.
2. Showalter CV. T's and blues: abuse of pentazocine and tripelennamine. *JAMA* 1980; **244:** 1224–5.
3. von Almen WF, Miller JM. "Ts and Blues" in pregnancy. *J Reprod Med* 1986; **31:** 236–9.
4. McGwier BW, *et al.* Acute myocardial infarction associated with intravenous injection of pentazocine and tripelennamine. *Chest* 1992; **101:** 1730–2.

Overdosage. A severe toxic reaction, including agitation, hallucinations, and myoclonic jerks occurred in an 8-year-old child who was sprayed over the trunk and extremities with tripelennamine hydrochloride 2.1375 g in the treatment of severe poison ivy poisoning.[1] It was likely that inhalation of the fine mist of the aerosol spray contributed to the reaction but in this patient the initial reaction began 3 hours after exposure suggesting that percutaneous absorption through the multiple skin lesions probably contributed significantly. The original reaction was inadvertently prolonged by subsequent treatment with diphenhydramine hydrochloride and promethazine hydrochloride.

1. Schipior PG. An unusual case of antihistamine intoxication. *J Pediatr* 1967; **71:** 589–91.

Preparations

USP 31: Tripelennamine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Azaron; ***Cz.:*** Azaron†; ***Fin.:*** Etono; ***Ger.:*** Azaron; Fenistil†; ***Indon.:*** Tripel; ***Neth.:*** Azaron; ***Spain:*** Azaron; ***USA:*** Vaginex.

Multi-ingredient: ***Arg.:*** Quemicetina Nasal Compuesta; ***Braz.:*** Alergitrat†; ***Ital.:*** Anticorizza†; ***Pol.:*** Viosept; ***USA:*** Di-Delamine.

Triprolidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de triprolidina; Triprolidine, Chlorhydrate de; Triprolidini Hydrochloridum. (*E*)-2-[3-(Pyrrolidin-1-yl)-1-*p*-tolylprop-1-enyl]pyridine hydrochloride monohydrate.

Трипролидина Гидрохлорид

$C_{19}H_{22}N_2,HCl,H_2O$ = 332.9.

CAS — 486-12-4 (triprolidine); 550-70-9 (anhydrous triprolidine hydrochloride); 6138-79-0 (triprolidine hydrochloride monohydrate).

ATC — R06AX07.

ATC Vet — QR06AX07.

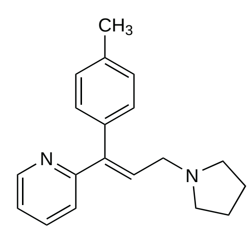

(triprolidine)

Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Triprolidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in alcohol; very soluble in chloroform; practically insoluble in ether.

USP 31 (Triprolidine Hydrochloride). A white crystalline powder, having no more than a slight, but unpleasant, odour. Soluble 1 in 2.1 of water, 1 in 1.8 of alcohol, 1 in 1 of chloroform, and 1 in 2000 of ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. UK product information for acrivastine has warned that acrivastine should not be used in patients hypersensitive to triprolidine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving triprolidine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] in 3 women of the excretion of triprolidine and pseudoephedrine, taken orally in a combined preparation, triprolidine was found to reach concentrations in breast milk similar to those found in plasma in one subject, and slightly lower than in plasma in the others. It was calculated that 0.06 to 0.2% of the ingested dose was distributed into breast milk over 24 hours. Concentrations of pseudoephedrine in breast milk exceeded those in plasma in all 3 women.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/01/04)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; **18:** 901–6.

Interactions

As for the sedating antihistamines in general, p.563.

Pharmacokinetics

After absorption from the gastrointestinal tract, triprolidine is metabolised; a carboxylated derivative accounts for about half the dose excreted in the urine. Reported half-lives vary from 3 to 5 hours or more. Triprolidine is distributed into breast milk.

◊ General references.

1. Paton DM, Webster DR. Clinical pharmacokinetics of H -receptor antagonists (the antihistamines). *Clin Pharmacokinet* 1985; **10:** 477–97.
2. Miles MV, *et al.* Pharmacokinetics of oral and transdermal triprolidine. *J Clin Pharmacol* 1990; **30:** 572–5.

Uses and Administration

Triprolidine hydrochloride, an alkylamine derivative, is a sedating antihistamine with antimuscarinic and mild sedative effects. It is used for the symptomatic relief of allergic conditions including urticaria (p.565) and rhinitis (p.565), and in pruritic skin disorders (p.565). It is often used in combination with pseudoephedrine hydrochloride for rhinitis and in other compound preparations for the symptomatic treatment of coughs and the common cold (p.564).

It is given orally, the usual dose for adults being 2.5 mg up to four times daily.

Triprolidine tannate has been used similarly.

Triprolidine hydrochloride has also been applied topically to the skin although, as with other antihistamines, there is a risk of sensitisation.

Preparations

BP 2008: Triprolidine Tablets;
USP 31: Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets; Triprolidine Hydrochloride Syrup; Triprolidine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Israel: Pro-Actidil†; ***Ital.:*** Actidil†; ***Spain:*** Pro-Actidil†; ***UAE:*** Sedofan T; ***USA:*** Zymine.

Multi-ingredient: ***Arg.:*** Actifedrin; ***Austral.:*** Actifed; Actifed CC Junior; Codral Original Day & Night Cold & Flu; Sudafed Sinus Day & Night Relief; Sudafed Sinus Pain & Allergy Relief; ***Belg.:*** Actifed; ***Braz.:*** Actifedrin; Trifedrin; ***Canad.:*** Actifed; Actifed Plus; CoActifed; Covan†; ratio-Cotridin; ratio-Cotridin Expectorant; ***Chile:*** Actifedrin; Actifedrin Antitusivo; ***Cz.:*** Trifed Expectorant†; Trifed†; ***Fr.:*** Actifed; Actifed Toux Seche†; ***Ger.:*** Rhinopront Kombi; ***Hong Kong:*** Actifed; Actifed Compound; Actifed DM†; Actihist-Co†; Antifort; Cough-EN†; Fedac; Fedac Compound; Prolifed; Setprodine†; Syncofit; Uni-Fedra Compound; Vidalidine; ***India:*** Actifed DM†; Actifed Plus†; Actifed†; Actiflu; Actiflu Plus; Ascoril-D+; Deletus; Deletus D; Nocold Plus; ***Indon.:*** Actifed; Actifed DM; Actifed Expectorant; Actigesic; Alerfed; Crofed; Eflin; Flutrop; Lapifed; Lapifed DM; Lapifed Expectorant; Nasafed; Nasafed Plus; Nichofed; Nostel; Protifed; Stop Cold; Tremenza; Trifed; Trifedrin; Valved; Valved DM; ***Irl.:*** Actifed; Actifed Chesty†; Actifed Compound†; Benylin Childrens Cough and Cold; Benylin Dual Action Dry; ***Israel:*** Actifed Compound†; Actifed DM†; Actifed Expectorant†; Actifed†; Histafed; Histafed Comp; Histafed Expectorant; Sinufed Kid Night†; ***Ital.:*** Actifed; Actifed Composto; Actigrip; ***Malaysia:*** Actifed; Actifed DM; Actifed Expectorant; Actihist; Actihist Expectorant; Actihist-Co; Axcel Tridine; Beatafed; Beatafed Compound†; Cough-EN; Decol; Fedac; Pabron Cold & Flu; Pabron Cough & Sinus; Pabron Cough-D; Peace; Pseudoephedrine T; Rhynacol; ***Mex.:*** Actifed; Actifed DM; Giparlix; ***NZ:*** Actifed; Codral Daytime/Nightime; Sudafed Day/Nightime Relief; Sudafed Sinus Pain & Allergy Relief; ***Pol.:*** Actifed; Actitrin; ***Port.:*** Actifed; Dinaxil; ***S.Afr.:*** Actifed; Actifed Cold & Fever; Actifed Dry Cough Regular; Actifed Dry Cough Sugar Free; Acuflu P; Acugest; Acugest Co; Acugest DM; Acugest Expect; Acutussive; Adco-Flupain; Adco-Tussend; Betafed; Coff-Rest†; Coryx; Endcol Cough Linctus†; Endcol DM†; Endcol Expectorant†; Fludactil Co; Fludactil Expectorant†; Fludactil†; Linctifed; Medifed; Merck-Cough Linctus; Merck-Expectorant; Merck-Fed; Neofed†; Sinuclear; Tixylix Flu; Trifen; ***Singapore:*** 3P†; Actifed; Actifed Compound; Actifed DM; Actifed Expectorant; Beactafed; Beactafed Co; Cough-EN; Fedac; Fedac Compound; Peacef; Trodrine†; Unitifed†; ***Spain:*** Iniston Antitusivo y Descongestivo; Iniston Descongestivo; Iniston Expectorante y Descongestivo; ***Thai.:*** Actifed; Actifed Compound†; Actifed DM; Actil; Actiplex; Clinikold; Cofed; Consudine; Hiscifed; Med-Actigen†; Medofed; Milafed; Nanafed†; Nasolin†; Nostrilet; Policol; Policold; Polyfed; Pondactil; Profed; Prophedin; Sinusaid; Sufed; Trifed; Triofed; Tripo; Triprodrine; Vefed†; Vesprolid-HCL; ***Turk.:*** A-ferin; Actidem; Actifed; ***UAE:*** Sedofan; Sedofan DM; ***UK:*** Benylin Childrens Coughs & Colds; Multi-Action Actifed; Multi-Action Actifed Chesty Coughs Expectorant; Multi-Action Actifed Dry Coughs; Sudafed Plus; ***USA:*** Actagen; Actagen-C Cough; Actifed; Actifed Cold & Allergy; Actifed Cold & Sinus; Actifed Plus; Allercon; Allerfrim; Allerfrim with Codeine; Allerphed; Aprodine; Aprodine with Codeine; Bayer Select Night Time Cold; Cenafed Plus; Genac; Silafed; Trifed-C Cough; Triofed; Tripohist D; Triposed; Zymine HC; Zymine-D; ***Venez.:*** Actifed†.

Tritoqualine *(rINN)*

L-554; Tritocualina; Tritoqualinum. 7-Amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)phthalide.

Тритоквалин

$C_{26}H_{32}N_2O_8$ = 500.5.
CAS — 14504-73-5.
ATC — R06AX21.
ATC Vet — QR06AX21.

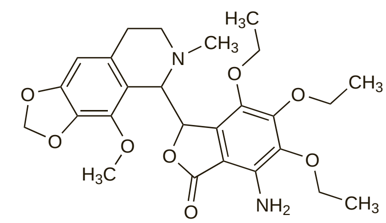

Profile

Tritoqualine is stated to inhibit histidine decarboxylase which catalyses the conversion of histidine to histamine. It has no action on histamine H_1-receptors and at therapeutic doses has no sedative or antimuscarinic effects. It has the uses of antihistamines (p.563) and has been given orally in usual doses of 200 to 600 mg daily in 2 or 3 divided doses for the symptomatic relief of hypersensitivity reactions including allergic rhinitis and urticaria.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Hypostamin; ***Fr.:*** Hypostamine; ***Ger.:*** Inhibostamin†.

Antimalarials

This chapter describes the main drugs used in the treatment and prophylaxis of malaria, one of the most serious protozoal infections in man. An estimated 40% of the world's population may be at risk of malaria; more than 500 million develop clinical infection, which is often very severe, and 1 to 3 million die each year. WHO produces guidelines for its strategic control and the management of malaria is under constant review. Measures to control malaria include *protection* from mosquito bites, *prophylaxis* with antimalarial drugs, and prompt *treatment* of any infection that develops. They also involve *vector control*; it is now recognised that for many countries vector eradication is an unrealistic aim.

Malaria

Malaria is a serious and potentially fatal disease, particularly in the case of falciparum malaria (see below) and especially in non-immune individuals (patients are classified as *non-immune* if they have not previously or recently been exposed to *Plasmodium* infection and as *semi-immune* or *immune* if they have a history of prolonged exposure). It is such a problem in many parts of the world that a global partnership named Roll Back Malaria[1] has been founded by WHO, United Nations Development Programme, UNICEF, and the World Bank with the aim of significantly reducing the world's malaria burden and halving the number of deaths due to malaria by 2010. Prompt diagnosis and effective treatment of malaria are crucial.[2,3]

Malaria is caused by infection by any of 4 species of *Plasmodium* protozoa. *P. falciparum* causes falciparum (malignant tertian or subtertian) malaria, which is the most serious form and can be rapidly fatal in non-immune individuals if not treated promptly. The other 3 species cause what are often termed 'benign' malarias: *P. vivax* causes vivax (benign tertian) malaria, which is widespread but rarely fatal, although symptoms during the primary attack can be severe; *P. malariae* causes quartan malaria, which is generally mild, but can cause fatal nephrosis; and *P. ovale* causes ovale (ovale tertian) malaria, which is the least common type of malaria and produces clinical features similar to *P. vivax*.[4]

The **life cycle** of *Plasmodium* is complex, comprising a sexual phase (sporogony) in the mosquito (vector) and an asexual phase (schizogony) in man (see Figure 1, below).

- Infection in man is usually caused by *sporozoites* from the bite of an infected female anopheline mosquito. It may rarely be acquired in other ways, congenitally via the placenta, or through blood transfusion, needlestick injuries, or organ transplantation.
- After an infected mosquito bite, sporozoites rapidly enter liver parenchymal cells, where they undergo *exoerythrocytic* or *pre-erythrocytic schizogony* forming *tissue schizonts* which mature and release thousands of *merozoites* into the blood on rupture of the cell.
- Merozoites enter erythrocytes where they transform into *trophozoites*. These produce *blood schizonts* which, as they mature, rupture and release merozoites into the circulation, which can infect other erythrocytes.
  This is termed the *erythrocytic cycle* and it is this periodic release of merozoites that is responsible for the characteristic periodicity of the fever in malaria.
- After several erythrocytic cycles, depending on the type of malaria, some erythrocytic forms develop into sexual *gametocytes*. Ingestion of infected blood containing gametocytes by a biting female mosquito allows the life cycle to be completed with the sexual phase in the mosquito.
- In *P. vivax* and *P. ovale* infections, some of the sporozoites entering the liver cells enter a latent tissue stage in the form of *hypnozoites* which are responsible for recurrence of malaria caused by these organisms.

Recurrences resulting from the persistence of latent tissue forms are often referred to as *relapses* while renewed attacks caused by persistent residual erythrocytic forms are termed *recrudescences*. True relapses do not occur with falciparum or quartan malarias.

CLINICAL MANIFESTATIONS OF MALARIA

The clinical symptoms of malaria are varied and non-specific; they usually include fever, fatigue, malaise, headache, myalgia, and sweating. Vomiting occurs in about 20% of patients, and mild diarrhoea in less than 5%. As the infection progresses, the spleen enlarges and the patient may develop anaemia and thrombocytopenia. The prognosis worsens with increasing parasite counts, more mature parasites, and more neutrophils containing malaria pigment.[5] Severe falciparum malaria may be complicated by acute renal failure, pulmonary oedema, and cerebral dysfunction. Since none of the clinical features of malaria are diagnostic, a definitive diagnosis depends upon the demonstration of parasites in stained blood films. However, antimalarial drug treatment should not be withheld in the absence of positive blood films if there is clinical suspicion of malaria. Any patient who has been in a malaria area in the previous two months should be considered to have malaria until proved otherwise.

ANTIMALARIAL DRUGS

Antimalarial drugs can be classified by the stage of the parasitic life cycle they affect. Thus:

Figure 1. Life cycle of the malaria parasite *Plasmodium*.

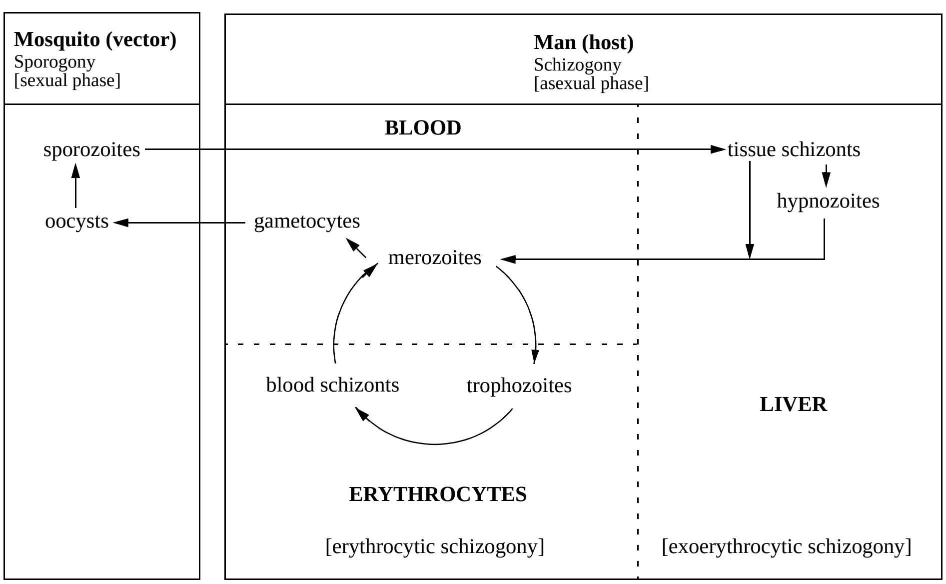

Blood schizontocides act on the erythrocytic stages of the parasite that are directly responsible for the clinical symptoms of the disease. They can produce a clinical cure or suppression of infection by susceptible strains of all 4 species of malaria parasite but, since they have no effect on exoerythrocytic forms, do not produce a radical cure of ovale or vivax malarias.

Tissue schizontocides act on the exoerythrocytic stages of the parasite and are used for causal prophylaxis to prevent invasion of the blood cells, or as anti-relapse drugs to produce radical cures of vivax and ovale malarias.

Gametocytocides destroy the sexual forms of the parasite to interrupt transmission of the infection to the mosquito vector.

Sporontocides have no direct effect on the gametocytes in the human host but prevent sporogony in the mosquito.

Antimalarial drugs can also be classified by the chemical group to which they belong, which in turn determines the stage of the life cycle they affect. The principal antimalarial drugs, classified according to *drug group* and *activity*, are listed in Table 1 p.595.

The naphthyridine derivative pyronaridine is under investigation for its use as an antimalarial. The quinolone antibacterials, and the 4-piperazinoquinoline derivatives, piperaquine and hydroxypiperaquine, have also been studied for their antimalarial activity. The 9-aminoacridines, such as mepacrine, are no longer used in the treatment of malaria.

The differing mechanisms of action of antimalarial drugs sometimes allow the use of combinations of antimalarials to improve efficacy. Such combinations are usually designed to potentiate each other, for instance by acting at sequential steps in the parasite's folic acid pathway (e.g. pyrimethamine with sulfadoxine or dapsone). Alternatively, a combination may be complementary, when the drugs involved act against different stages in the life cycle of the parasite (e.g. the use of chloroquine with primaquine to produce radical cure of *P. vivax* or *P. ovale* infections). The rationale behind the use of such combinations may be to enhance efficacy, particularly when drug resistance is a problem (see below), or it may be an attempt to delay the development of resistance to one or more of the drugs concerned.

Resistance.

Resistance to antimalarials has been documented for *P. falciparum*, *P. vivax*, and *P. malariae* and is seen with all classes of antimalarials except artemisinin and its derivatives.[3] Chloroquine resistance in *P. falciparum* now occurs virtually everywhere that *P. falciparum* malaria is transmitted, with the exception of certain parts of Central America and the Caribbean.[3,6] Resistance in *P. falciparum* to proguanil and pyrimethamine is apparent in many endemic areas. Cross-resistance between proguanil and pyrimethamine may also occur. Resistance in *P. falciparum* to the combination pyrimethamine-sulfadoxine (*Fansidar*) has spread rapidly in South-East Asia, but also occurs in other parts of the world including parts of South America, southern China, and Africa.[3,6] Mefloquine resistance is frequent in some areas of South-East Asia and migrant workers are thought to have spread mefloquine resistance to India and Bangladesh. Resistance has also occurred in the Amazon region of South America and, sporadically, in Africa, but generally, clinical mefloquine resistance outside South-East Asia is rare.[3,6] Resistance to quinine and halofantrine has also been noted. Cross-resistance between halofantrine and mefloquine may occur, as evidenced by reduced responses to halofantrine in some patients who have experienced treatment failure with mefloquine.[6] The emergence of multidrug resistance in *P. falciparum* makes the selection of effective prophylaxis and treatment difficult.

Multidrug resistance is defined as resistance to three or more antimalarial compounds from different chemical classes, of which two of the classes are the 4-aminoquinolines (e.g. chloroquine) and diaminopyrimidines (e.g. pyrimethamine-sulfadoxine (*Fansidar*)). Multidrug resistance occurs in South-East Asia (particularly along the borders of Thailand with Burma and Cambodia) and in the Amazon basin.[3]

P. vivax has developed resistance rapidly to pyrimethamine-sulfadoxine (*Fansidar*) in many areas and resistance to chloroquine and primaquine has also been reported

Table 1. Principal antimalarial drugs.

Antimalarial groups	Principal drugs	Activity
4-Aminoquinolines	Chloroquine Hydroxychloroquine Amodiaquine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
8-Aminoquinolines	Primaquine Tafenoquine	Tissue schizontocide. Also gametocytocidal activity and some activity at other stages of the parasite's life-cycle.
Artemisinin and its derivatives (Sesquiterpene lactones)	Artemether Artesunate	Blood schizontocide.
Biguanides	Proguanil Chlorproguanil	Tissue schizontocides and slow-acting blood schizontocides. Some sporontocidal activity. Dihydrofolate reductase inhibitors.
Diaminopyrimidines	Pyrimethamine	Tissue schizontocide and slow-acting blood schizontocide. Some sporontocidal activity. Dihydrofolate reductase inhibitor. Usually used with antimalarials that inhibit different stages of folate synthesis (sulfonamides or sulfones) to form synergistic combinations.
Dichlorobenzylidines	Lumefantrine	Blood schizontocide.
Hydroxynaphthoquinones	Atovaquone	Blood schizontocide. Usually given in combination with proguanil.
Lincosamides	Clindamycin	Blood schizontocides. Some tissue schizontocidal activity.
4-Methanolquinolines	Cinchona alkaloids Quinine Quinidine	Rapid-acting blood schizontocides. Some gametocytocidal activity.
	Mefloquine	Blood schizontocide.
9-Phenanthrenemethanols	Halofantrine	Blood schizontocide.
Sulfonamides	Sulfadoxine Sulfametopyrazine	Blood schizontocides. Dihydropteroate and folate synthesis inhibitors. Usually given in combination with pyrimethamine.
Sulfones	Dapsone	Blood schizontocide. Folate synthesis inhibitor. Usually given in combination with pyrimethamine
Tetracyclines	Doxycycline Tetracycline	Blood schizontocides. Some tissue schizontocidal activity..

in several parts of the world.[3,6] However, it remains sensitive to chloroquine in South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.[3] Resistance of *P. malariae* to chloroquine was seen recently in Indonesia.[3]

A knowledge of the geographical distribution and degree of resistance is important for the selection of appropriate control measures and for the development of policies for the rational use of antimalarial drugs. Resistance can be prevented, or slowed considerably, by selecting effective drugs and drug combinations according to local patterns of resistance, combining antimalarials with different mechanisms of action, preventing indiscriminate and uncontrolled use, and ensuring very high cure rates through full compliance with the correct antimalarial dose regimens. Malaria control strategies also need to involve other measures such as vector control and health education.[3,7]

TREATMENT OF MALARIA

Malaria is treated with a *blood schizontocide*, selected with due regard to the prevalence of specific patterns of drug resistance in the area of infection. In the case of vivax and ovale malarias (see below) subsequent treatment with a *tissue schizontocide* is needed where it is considered appropriate to prevent relapse.

Antimalarials are generally given orally, although in order to obtain a rapid response in patients with severe or complicated falciparum malaria (see below) it may be necessary to start with parenteral therapy, the patient being transferred to oral therapy when feasible.[3] Where there are only minimal health care facilities and parenteral therapy is not possible or may be delayed, artemisinin or artesunate suppositories may be given.

Treatment of falciparum malaria.

In most parts of the world *P. falciparum* is now resistant to chloroquine and therefore, apart from the rare circumstance of exposure in one of the few remaining areas of chloroquine sensitivity, chloroquine is **not** suitable for treatment. Resistance to pyrimethamine-sulfadoxine (*Fansidar*) has also occurred in most countries where it was used in place of chloroquine.[4]

In **uncomplicated falciparum malaria** (symptomatic malaria without signs of severity or evidence of vital organ dysfunction) combination drug therapy is recommended by WHO[3] for treatment in all *malaria endemic areas* experiencing resistance to monotherapy with chloroquine, amodiaquine, or pyrimethamine-sulfadoxine (*Fansidar*). Drugs with differing mechanisms of action but with similar half-lives should be used to avoid exposure of the parasite to a single drug for a prolonged period and to prevent the emergence and spread of drug-resistant parasites. Pyrimethamine-sulfadoxine (*Fansidar*) and atovaquone-proguanil (*Malarone*) rely on synergy between the 2 components and are operationally considered single products; they should not be considered combination therapy when used alone. The most widely recommended combinations are those that include an artemisinin-based drug as one of the components (ACT). Recommended ACTs are:

- artemether-lumefantrine (*Riamet*)
- artesunate and amodiaquine (in areas where resistance to amodiaquine is low)
- artesunate and pyrimethamine-sulfadoxine (*Fansidar*) (in areas where pyrimethamine-sulfadoxine efficacy is still high)
- artesunate and mefloquine (should only be used in areas of low transmission)
- amodiaquine and pyrimethamine-sulfadoxine (*Fansidar*) is still an effective option for some areas in West Africa where susceptibility remains high and for those countries unable to supply ACTs

In *non-endemic areas* the British Infection Society[8] and the Health Protection Agency Advisory Committee on Malaria Prevention in UK Travellers[9] recommend treating uncomplicated falciparum malaria or mixed infections with one of the following:

- oral quinine sulfate plus follow-on treatment with either doxycycline or clindamycin
- atovaquone-proguanil (*Malarone*)
- artemether-lumefantrine (*Riamet*)

In the USA, the CDC[10] recommends that uncomplicated falciparum malaria acquired in a chloroquine-sensitive area may be treated with oral chloroquine. Hydroxychloroquine may be used as an alternative. Malaria acquired in chloroquine-resistant areas is treated with one of the following:

- quinine sulfate plus doxycycline, tetracycline, or clindamycin
- atovaquone-proguanil (*Malarone*)
- mefloquine (although it should only be considered as a treatment option in patients who cannot use quinine sulfate or atovaquone-proguanil (*Malarone*) due to a higher rate of severe neuropsychiatric events associated with treatment doses)

In **severe or complicated falciparum malaria** including cerebral malaria, parenteral treatment is required to produce adequate blood concentrations as quickly as possible.[3] Patients need to be closely monitored while undergoing parenteral therapy and treatment is changed to an oral antimalarial as soon as the patient's condition permits.

In *malaria endemic areas* that are chloroquine-resistant, or where sensitivity to chloroquine is not known, quinine is usually given intravenously, starting with a loading dose. Intramuscular artemether is an alternative to intravenous quinine. In areas of low transmission intravenous artesunate is the recommended first choice. Intramuscular artemotil should only be used if other above alternatives are not available and intravenous quinidine should only be used if parenteral quinine or artemisinin derivatives are not available. Where there are only minimal health care facilities or when parenteral therapy is not possible or may be delayed, artemisinin, artesunate, artemether, or arterimol suppositories may be given[3]; the nasogastric route may also be used. Follow-on treatment is with either doxycycline or clindamycin (in pregnant women and in children) for 7 days.

In *non-endemic areas* intravenous quinine plus either oral doxycycline or oral clindamycin are recommended by authorities in the UK;[8,9] intravenous artesunate may be available on a named patient basis for the most severe cases if they are not responding to quinine therapy, are possibly infected with quinine-resistant falciparum, or quinine is contra-indicated. In the USA,[10] intravenous quinidine gluconate is used in place of intravenous quinine and intravenous artesunate is under investigation.

Supportive therapy in patients with severe or complicated malaria needs to be directed at reducing hyperpyrexia, controlling convulsions, maintaining fluid balance, and correcting hypoglycaemia. Severe malaria is associated with rapid development of anaemia, and blood transfusions are recommended for children with a haemoglobin concentration of less than 5 g per 100 mL (haematocrit less than 15%) living in areas of high transmission or for those with a haemoglobin level of 7 g per 100 mL (haematocrit threshold of 20%) living in an area of low transmission.[3] Although the benefit of exchange transfusion has not been proven in comparative studies,UK and US guidelines recommend that it be considered for patients with a parasite density of more than 10% or if the patient has cerebral malaria, renal complications, or non-volume overload pulmonary oedema.[9,10] Prophylactic use of anticonvulsants is not recommended and the use of intravenous or intramuscular phenobarbital resulted in increased mortality due to respiratory arrest.[3] Since iron might be involved in the pathogenesis of cerebral malaria, the iron chelator desferrioxamine has been tried in addition to standard antimalarial therapy, but any benefit is yet to be established and WHO advises against its use.[3] Anecdotal reports of the value of corticosteroids in cerebral malaria have not been substantiated by controlled studies and they have no place in the management of this condition.[3,11] Other approaches such as the use of hyperimmune serum or monoclonal antibody to tumour necrosis factor have also been unsuccessful.

Treatment of benign malarias. Benign malarias, which are usually caused by *P. vivax* or, less commonly, by *P. ovale* or *P. malariae*, can be debilitating but are usually less severe than falciparum malaria. Treatment for *P. vivax* and *P. ovale* includes a *radical cure*: that is, cure of both the blood and liver stage infections in order to prevent relapse and recrudescence. Treatment of *P. malariae* does not include radical cure as no hypnozoites are formed during infection. Chloroquine is still generally the drug of choice (but chloroquine-resistant vivax infection has been reported from some areas—notably Papua New Guinea, Indonesia, Myanmar, and Vanuatu). Chloroquine alone is adequate for *P. malariae* infections; for those caused by *P. vivax* or *P. ovale* a tissue schizontocide, usually primaquine, is added for radical cure.[3,8-10] In areas where ACTs are being used as first-line treatment for *P. falciparum* malaria, they may be given with primaquine for *P. vivax* infection as an alternative to chloroquine, with the exception of artesunate and pyrimethamine-sulfadoxine (*Fansidar*) as *P. vivax* resistance to pyrimethamine-sulfadoxine (*Fansidar*) is rapidly developing.[3] WHO[3] recommends that chloroquine-resistant *P. vivax* may be treated with amodiaquine followed by primaquine, while the CDC[10] recommends that patients not responding to chloroquine monotherapy or those with chloroquine-resistant infections should be given quinine sulfate plus doxycycline (or tetracycline) followed by primaquine; an alternative is mefloquine followed by primaquine. UK[9] guidelines recommend that resistant vivax malaria be treated with one of the 3 regimens used for the treatment of uncomplicated falciparum malaria (see above). Radical cure is inappropriate for patients living within an endemic area since re-infection is likely and therefore WHO[3] recommends that it should be limited to patients resident in areas where transmission is *very low* or *absent,* and it may be attempted *during an epidemic*; other patients should simply be treated with a further course of chloroquine in the event of relapse or re-infection. Severe vivax malaria should be treated the same way as severe and complicated falciparum malaria (see above).[3]

Treatment of malaria during pregnancy. Malaria is especially dangerous during pregnancy and the seriousness of the disease usually outweighs any potential risk from treatment. Malaria infection during pregnancy can result in maternal anaemia, hypoglycaemia, pulmonary oedema, miscarriage, premature birth, congenital malaria infection, low birth-weight, and neonatal death.[10,12] Pregnant women living in areas where malaria transmission is low or unstable have little or no acquired immunity and are 2 to 3 times more likely to develop severe disease than non-pregnant women living in the same area;[3,10] however, those living in endemic areas where malaria transmission is high have often acquired partial immunity.

For pregnant women living in *endemic areas* quinine plus follow-on treatment with clindamycin may be given for treatment of uncomplicated falciparum malaria in the first trimester. Data regarding the use of artemisinin derivatives in the first trimester is at present limited; however, ACTs may be given if no other effective treatment is available. In the second or third trimester ACTs, artesunate, or quinine may be given, plus follow-on treatment with clindamycin.[3] For the treatment of severe malaria in the first trimester quinine or artesunate may be used;[2,3] however, care should be taken that patients given quinine do not become hypoglycaemic. Artemisinin derivatives (particularly artesunate) are the drugs of choice for treatment of severe malaria in the second and third trimesters.[2,3]

In *non-endemic areas* it is recommended that falciparum malaria in pregnancy be treated with quinine plus follow-on treatment with clindamycin.[8-10] Atovaquone-proguanil (*Malarone*) or mefloquine may be given as alternatives where first-line treatment is not tolerated or no other treatment options are available.[10] Although fetal abnormalities have been associated with the use of high doses of chloroquine, extensive clinical experience suggests it is safe; its value is limited, however, due to resistance. The CDC recommends oral chloroquine for pregnant women with malaria infections acquired in chloroquine-sensitive areas and with non-falciparum malaria, although chloroquine-resistant *P. vivax* should be treated with quinine.[10] Radical cure for patients with vivax or ovale malaria during pregnancy should be postponed until after delivery due to the risk of intravascular haemolysis in the mother and fetus;[10,12] weekly chloroquine can be given during the remaining weeks of pregnancy. WHO recommends chloroquine or amodiaquine for pregnant women with *P. vivax* malaria.[2]

There may be difficulty if other drugs are required as opinion varies over their suitability. The tetracyclines are contra-indicated due to adverse effects on bone growth and teeth.

Treatment of splenomegaly syndrome. A few individuals infected with *Plasmodium* develop chronic hyperreactive malarial splenomegaly syndrome, an aberrant immunological response formerly known as the tropical splenomegaly syndrome. Traditionally, patients have first received a full course of antimalarial chemotherapy appropriate to the causative species followed by lengthy and probably lifelong chemoprophylaxis; however, a study in 312 patients suggested that pyrimethamine given with folinic acid for 30 days could produce a rapid reduction of splenomegaly which persisted for at least 3 months.[13]

PROPHYLAXIS OF MALARIA

Chemoprophylaxis of malaria may refer to absolute prevention of infection (*causal prophylaxis*) or to suppression of parasitaemia and its symptoms (*clinical prophylaxis*). Causal prophylaxis is provided by tissue schizontocides which destroy the exoerythrocytic forms of the parasite. Clinical prophylaxis is provided by blood schizontocides which, if continued until all exoerythrocytic forms of the parasite are destroyed, will ultimately produce a *suppressive cure*. In *P. falciparum* infections this would be achieved by about a month after the last infected bite, but relapses with *P. vivax* and *P. ovale* may still occur after standard clinical prophylactic regimens due to the presence of latent exoerythrocytic forms (hypnozoites).

The continuing increase in the prevalence of strains of *P. falciparum* resistant to chloroquine and other antimalarials, along with growing evidence of toxicity of some regimens, make recommendations for malaria prophylaxis increasingly difficult. Absolute protection cannot be guaranteed by any chemoprophylactic regimen currently in use and the importance and effectiveness of methods of avoiding bites from infected mosquitoes, such as the use of *protective clothing, bed netting, insect repellents*, and *insecticides* must be stressed.[2,7] WHO recommends the following measures to protect against mosquito bites:

- application of an effective insect repellent to exposed skin, especially between dusk and dawn when mosquitoes commonly bite
- accommodation in buildings with screens over doors and windows
- use of mosquito nets at night, preferably impregnated with pyrethroid insecticides such as permethrin or deltamethrin
- and use of anti-mosquito sprays or insecticide dispensers, or mosquito coils in bedrooms at night

Studies have shown that insecticide-impregnated mosquito nets can reduce mortality substantially.[14] In addition to these measures, travellers should be advised, even if chemoprophylaxis has been taken regularly, to regard **any** fever *after the first week (especially within 3 months)* and for *up to 1 year following possible exposure* as being caused by malaria and to seek medical advice **immediately**. Some authorities advise that travellers should also have antimalarial drugs ready for emergency self-treatment (*standby treatment*) when prompt medical attention is not available (see below).

Chemoprophylaxis should be reserved for those at high **risk**, notably *non-immune visitors*; widespread chemoprophylaxis in *immune or semi-immune* populations is no longer recommended except for women who are *pregnant*. For the elderly, pregnant women, and children, careful consideration should be given as to whether travel to areas where falciparum malaria occurs is absolutely necessary. WHO specifically advises pregnant women not to travel to areas where transmission of *P. falciparum* occurs and also advises against taking babies and young children to malarious areas (particularly where there is transmission of *P. falciparum*).[2] Advice on chemoprophylaxis must be based on a knowledge of the occurrence and susceptibility of *Plasmodium* strains in specific geographical areas. Local variations due to altitude, seasonal variations in temperature and rainfall, the degree of urbanisation, and many other factors further complicate the issue. WHO collates information provided by national health administrations and regularly publishes this information to assist in advising international travellers on the current situation; similar information is provided at national level by local institutes specialising in tropical diseases. However, the situation is so complex that advice differs. Recommendations issued by various authorities are usually for short-term stays and expert advice should be sought if long-term cover is required.

It is generally recommended that chemoprophylaxis should start about 1 week (or longer for mefloquine) before exposure to malaria, or if this is not possible at the earliest opportunity up to 1 or 2 days before exposure; this is partly to ensure that the patient is able to tolerate the drug. Chemoprophylaxis should continue throughout exposure and for at least 4 weeks after leaving the malarious area, with the exception of atovaquone-proguanil (*Malarone*) which may be stopped one week after leaving.

Prophylactic regimens.

Depending upon the risk of infection and the availability and standard of local medical care, WHO[2] has made recommendations on chemoprophylaxis and/or standby treatment for non-immune travellers:

- in areas where there is limited risk of any malaria transmission no chemoprophylaxis is needed; measures to protect against mosquito bites should be used
- in areas where *P. falciparum* is *absent* or still *sensitive to chloroquine*, or there is a risk of *P. vivax*, travellers can take chloroquine for prophylaxis
- in areas with a risk of *P. vivax* and *P. falciparum*, as well as *emerging resistance* to chloroquine, travellers can take chloroquine plus proguanil
- in areas of high risk of *P. falciparum* and where there is *multidrug resistance*, or in areas of low to moderate risk of *P. falciparum* but high levels of multidrug resistance, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) is recommended. These recommendations are subject to the local patterns of drug resistance

WHO[2] also recommends that for the small number of travellers who would be unable to obtain prompt medical attention when malaria is suspected (within 24 hours of the onset of symptoms), it may be necessary to provide for a course of self-treatment (**standby treatment**). Clear instructions must be given and persons taking standby medication must seek medical advice as soon as possible and resume any prophylaxis on completing the course. The basis upon which the choice of prophylaxis is made (as detailed above) in turn broadly determines the appropriate choice of standby treatment. Thus one of the following treatment regimens can be used:

- artemether-lumefantrine
- atovaquone-proguanil
- quinine plus doxycycline or clindamycin

In each instance, prophylaxis should be resumed 1 week after the *first* standby treatment dose, except for mefloquine prophylaxis which should be resumed at least 12 hours after the *last* treatment dose of quinine.

In the USA, recommendations for prophylaxis are provided by the CDC.[15] For chloroquine-sensitive malaria, chloroquine alone is advised; hydroxychloroquine is suggested as an alternative. Travellers unable to take either of these 2 options should take atovaquone-proguanil (*Malarone*), doxycycline, or mefloquine. For all areas with chloroquine-resistant malaria, 3 alternatives are available, mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*). Atovaquone-proguanil (*Malarone*) is recommended for emergency standby treatment. The use of primaquine is also advocated during the last 2 weeks of prophylaxis to prevent relapses due to *P. vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic.

UK experts[16] have also published guidelines for the prophylaxis of malaria. In areas where *P. falciparum* is sensitive to chloroquine, travellers can either take chloroquine or proguanil for prophylaxis. In areas of little chloroquine resistance travellers can take chloroquine plus proguanil, while travellers to areas of high infection risk or where there is chloroquine resistance may take mefloquine, doxycycline, or atovaquone-proguanil (*Malarone*) as prophylaxis. Standby treatment with chloroquine is recommended for travellers to chloroquine-sensitive areas who do not take any prophylaxis or who take proguanil as prophylaxis. Atovaquone-proguanil (*Malarone*), artemether-lumefantrine (*Riamet*), or quinine plus doxycycline are recommended in areas with chloroquine resistance.

Malaria vaccines are under development and several are currently undergoing clinical evaluation (see p.2221).

Prophylaxis during pregnancy. The choice of drugs for prophylaxis during pregnancy is limited and whenever possible women who are pregnant or likely to become so should avoid travelling to malarious areas (see also above). In pregnant women who cannot avoid travelling to endemic areas, chloroquine may be given alone for prophylaxis in the few areas where *P. falciparum* is sensitive to chloroquine, or with proguanil where resistance exists.[2] Folate supplements (folic acid 5 mg daily) need to be taken with proguanil. Mefloquine is normally avoided during the first trimester but may be given during the second and third trimesters and CDC[15] and UK[16] guidelines consider that it may be used *with caution* in the first trimester, especially in areas where there is a high risk of acquiring falciparum malaria. Doxycycline, atovaquone-proguanil (*Malarone*), or primaquine are contra-indicated in pregnant women by most experts; the *BNF* considers that atovaquone-proguanil (*Malarone*) should be avoided during pregnancy unless there is no suitable alternative. In non-pregnant women of child-bearing potential, pregnancy needs to be avoided for 3 months after completing mefloquine prophylaxis and for one week following doxycycline prophylaxis.

For those living in endemic areas, WHO[7] recommends that, in areas of stable transmission of *P. falciparum* malaria, pregnant women and their newborn should sleep under insecticide-treated nets; pregnant women should also be given intermittent preventative treatment (IPT) with an antimalarial drug, usually pyrimethamine-sulfadoxine (*Fansidar*). The first dose should be given after quickening in the second trimester and further doses should be given at intervals at least one month apart. For maximum benefit 2 to 3 doses of IPT should be given. For further information on the use of pyrimethamine in pregnancy, see under Precautions for Pyrimethamine, p.611. In areas of low or unstable malaria transmission, where pregnant women have low immunity to malaria, use of insecticide-treated nets and prompt case management of pregnant women with fever and malarial illness is recommended. In addition, all pregnant women should take iron and folate supplements.

Prophylaxis during breast feeding. It is generally accepted for most antimalarials that the amounts distributed into breast milk and consumed by nursing infants are too small to be harmful, although they are also too small to provide protection.[2,15] However, doxycycline is contra-indicated during breast feeding, and advice regarding atovaquone-proguanil varies: in the UK it is contra-indicated, though it may be used if no suitable alternative is available,[16] but in the USA it may be given once the infant weighs over 5 kg.[15] Although there has been concern that infants given prophylaxis with mefloquine who also ingested the drug from breast milk might be receiving excessive quantities,[15] mefloquine is probably safe to use in breast-feeding mothers.[16]

Prophylaxis in children. Chloroquine and proguanil may be given in scaled down doses to children of all ages but the choice of alternative drugs may be restricted, especially in very young children, and consideration should be given to whether their travel to malarious areas is absolutely necessary (see also above). Mefloquine is an option for use in children and infants weighing 5 kg or more if travelling to areas with chloroquine-resistant *P. falciparum* and atovaquone-proguanil (*Malarone*) may be given to children weighing 11 kg or more; the CDC considers that it may be used in infants weighing at least 5 kg. Doxycycline is contra-indicated in children less than 8 years of age, and higher age limits may apply in some countries such as the UK.[2,15,16]

Prophylaxis in epilepsy. In subjects with a history of epilepsy, the UK guidelines[16] advise that both chloroquine and mefloquine are unsuitable for prophylaxis. In areas without chloroquine resistance, proguanil alone is recommended. In areas with a high risk of chloroquine resistance, atovaquone-proguanil (*Malarone*) or doxycycline may be considered, but the metabolism of doxycycline may be influenced by antiepileptics. Dapsone with pyrimethamine (*Maloprim*) was considered to have been of particular value in travellers with epilepsy, especially children, but is no longer available in the UK.

Prophylaxis in HIV-infected travellers. HIV-infected travellers may take chloroquine routinely for antimalarial prophylaxis but its potential immunosuppressive effects should be recognised; proguanil, mefloquine, or doxycycline can also be used. Although patients with AIDS may be at increased risk of adverse effects to sulfonamides, a combination such as pyrimethamine-sulfadoxine (*Fansidar*) can be used for standby treatment if an alternative is not available.

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Amodiaquine *(BAN, rINN)*

Amodiaquina; Amodiaquinum. 4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl)phenol.

Амодиахин

$C_{20}H_{22}ClN_3O$ = 355.9.
CAS — 86-42-0.
ATC — P01BA06.

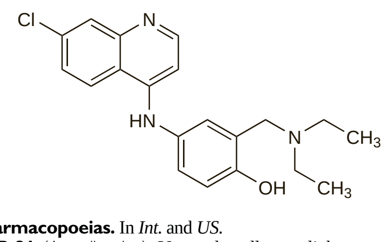

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Amodiaquine). Very pale yellow to light tan-yellow, odourless, powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in 1.0N hydrochloric acid. Store in airtight containers.

Amodiaquine Hydrochloride *(BANM, rINNM)*

Amodiaquine, Chlorhydrate d'; Amodiaquini Hydrochloridum; Hidrocloruro de amodiaquina. 4-(7-Chloro-4-quinolylamino)-2-(diethylaminomethyl)phenol dihydrochloride dihydrate.

Амодиахина Гидрохлорид

$C_{20}H_{22}ClN_3O,2HCl,2H_2O$ = 464.8.
CAS — 69-44-3 (anhydrous amodiaquine hydrochloride); 6398-98-7 (amodiaquine hydrochloride dihydrate).
ATC — P01BA06.

Pharmacopoeias. In *Fr.*, *Int.*, and *US.*

USP 31 (Amodiaquine Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 78 of alcohol; very slightly soluble in chloroform, in ether, and in benzene. Store in airtight containers.

Sorption. For reference to loss of amodiaquine hydrochloride from solutions during membrane filtration, see Chloroquine, p.599.

Adverse Effects and Precautions

As for Chloroquine, p.599, although amodiaquine was associated with hepatitis and a much higher incidence of agranulocytosis when it was used for the prophylaxis of malaria.

Incidence of adverse effects. Early isolated reports of severe neutropenia with amodiaquine usually concerned use in anti-inflammatory doses for rheumatoid arthritis, but there was a cluster of cases in 1986 associated with its use in malaria prophylaxis.[1] In all, 23 cases of agranulocytosis, 7 of which were fatal, were reported in the UK, USA, and Switzerland during a 12-month period ending March 1986. Nearly all of these patients had used the drug at a dosage of 400 mg weekly and the periods of exposure ranged from 3 to 24 weeks.[1] Some of these patients also had evidence of liver damage[1] and there have been other reports of hepatotoxicity associated with the prophylactic use of amodiaquine.[2] Examination of data submitted to the UK CSM[3] suggested that the frequency of adverse reactions to amodiaquine was about 1 in 1700 for serious reactions, 1 in 2200 for blood disorders, 1 in 15 650 for serious hepatic disorders, and 1 in 15 650 for fatal reactions. In contrast the frequency of agranulocytosis in users in France[4] has been estimated to be 1 in 25 000. Worldwide[4] the risk of severe reactions appears to be between 1 in 1000 and 1 in 5000. The manufacturers reportedly had 42 cases of serious adverse effects during amodiaquine prophylaxis, between 1985 and 1991; there were 28 cases of agranulocytosis (9 deaths) and 14 of hepatitis (3 deaths).[5] Whether there was significantly less risk when amodiaquine was given for treatment of malaria rather than prophylaxis was not certain.[6]

It has been suggested that an immunological reaction to amodiaquine quinone imine, which can be produced by autoxidation among other processes, may partially account for amodiaquine's greater tendency to induce agranulocytosis compared with chloroquine.[7,8]

The acute toxicity of amodiaquine appears to differ from that of chloroquine in that there have been no reports of cardiovascular symptoms after overdosage with amodiaquine[9] but intoxication with amodiaquine is also far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions, and involuntary movements.[9]

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Pregnancy. A study[1] to assess the safety and efficacy of amodiaquine or amodiaquine plus sulfadoxine-pyrimethamine in 900 pregnant women (in their second or third trimester) reported that PCR-corrected parasitological failure by day 28 was 14%, 11%, 3%, and 0% in those given chloroquine, sulfadoxine-pyrimethamine, amodiaquine alone, and amodiaquine plus sulfadoxine-pyrimethamine, respectively. No serious adverse effects were reported.

WHO considers that amodiaquine may be an alternative to chloroquine for treatment of malaria due to *P. vivax* during pregnancy (see Treatment of Malaria during Pregnancy, under Malaria, p.594).

1. Tagbor H, *et al.* Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet* 2006; **368:** 1349–56.

Pharmacokinetics

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. Amodiaquine is rapidly converted in the liver to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. Amodiaquine and desethylamodiaquine have been detected in the urine several months after use.

◊ References.

1. Winstanley P, *et al.* The disposition of amodiaquine in man after oral administration. *Br J Clin Pharmacol* 1987; **23:** 1–7.
2. White NJ, *et al.* Pharmacokinetics of intravenous amodiaquine. *Br J Clin Pharmacol* 1987; **23:** 127–35.
3. Winstanley PA, *et al.* The disposition of amodiaquine in Zambians and Nigerians with malaria. *Br J Clin Pharmacol* 1990; **29:** 695–701.
4. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.

Uses and Administration

Amodiaquine is a 4-aminoquinoline antimalarial with an action similar to that of chloroquine (p.602). It is as effective as chloroquine against chloroquine-sensitive strains of *Plasmodium falciparum* and is also effective against some chloroquine-resistant strains, although resistance to amodiaquine has developed and there may be partial cross-resistance between amodiaquine and chloroquine. To prevent the emergence and spread of drug resistant parasites WHO recommends that amodiaquine be given with an artemisinin derivative, such as artesunate, for the treatment of falciparum malaria. Amodiaquine is not recommended for the prophylaxis of malaria because of resistance and the risk of major toxicity.

Amodiaquine is given orally as the hydrochloride, but doses are expressed in terms of amodiaquine base; amodiaquine hydrochloride 260 mg is equivalent to about 200 mg of amodiaquine base. For the treatment of falciparum malaria and uncomplicated chloroquine-resistant vivax malaria a total dose of 30 mg/kg is given over 3 days (10 mg/kg daily for 3 days). Treatment of vivax malaria must be followed by radical cure with primaquine.

A fixed-dose combination product of amodiaquine and artesunate (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

◊ References.

1. Olliaro P, Mussano P. Amodiaquine for treating malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 17/05/05).
2. McIntosh HM, Jones KL. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/07/06).
3. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).

Preparations

USP 31: Amodiaquine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Fr.: Flavoquine; ***India:*** Basoquin; Camoquin; Ipcaquin†.

Multi-ingredient: ***Belg.:*** Amonate; ***China:*** Artemodi; ***India:*** Larimal†.

Artemisinin Derivatives

Artemisinina, derivados.

Artemether *(BAN, rINN)*

Artemeetteri; Artemeter; Artemetero; Artéméther; Artemetherum; Dihydroartemisinin Methyl Ether; Dihydroqinghaosu Methyl Ether; *o*-Methyldihydroartemisinin; SM-224. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

Артеметер

$C_{16}H_{26}O_5$ = 298.4.
CAS — 71963-77-4.
ATC — P01BE02.

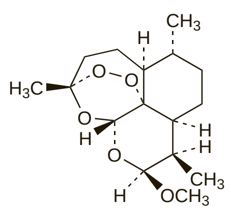

Pharmacopoeias. In *Chin.* and *Int.*

Artemisinin *(rINN)*

Arteannuin; Artemisinina; Artémisinine; Artemisinine; Artemisininum; Huanghuahaosu; Qinghaosu. (3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one.

Артемизинин

$C_{15}H_{22}O_5$ = 282.3.
CAS — 63968-64-9.
ATC — P01BE01.

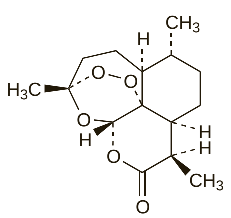

Pharmacopoeias. In *Chin.*, *Int.*, and *Viet.*

Artemotil *(rINN)*

Artémotil; Artemotilo; Artemotilum; Beta-arteether; Dihydroartemisinin Ethyl Ether; Dihydroqinghaosu Ethyl Ether; SM-227. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-10-ethoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin.

Артемотил

$C_{17}H_{28}O_5$ = 312.4.
CAS — 75887-54-6.
ATC — P01BE04.

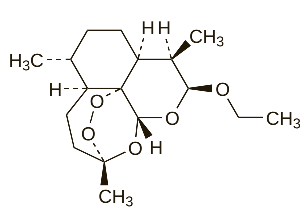

Pharmacopoeias. In *Int.*

Artenimol *(USAN, rINN)*

Arténimol; Artenimolum; Dihydroartemisinin; Dihydroqinghaosu. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol.

Артенимол

$C_{15}H_{24}O_5$ = 284.3.
CAS — 81496-81-3.
ATC — P01BE05.

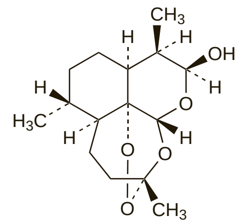

Pharmacopoeias. In *Chin.* and *Int.*

Artesunate *(BAN, USAN, rINN)*

Artésunate; Artesunato; Artesunatum. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate.

Артезунат

$C_{19}H_{28}O_8$ = 384.4.
CAS — 83507-69-1; 88495-63-0; 182824-33-5.
ATC — P01BE03.

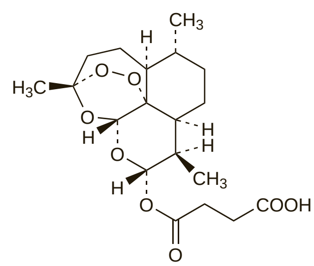

Pharmacopoeias. In *Int.* and *Viet.*

Sodium Artesunate *(BANM, rINNM)*

Artésunate de Sodium; Artesunato sódico; Dihydroartemisinin Hemisuccinate Sodium; Dihydroqinghaosu Hemisuccinate Sodium; Natrii Artesunatum; SM-804. (3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10-ol hydrogen succinate sodium.

Натрий Артезунат

$C_{19}H_{27}O_8Na$ = 406.4.

Adverse Effects and Precautions

Artemisinin and its derivatives appear to be generally well tolerated, although there have been reports of mild gastrointestinal disturbance (including nausea, vomiting, diarrhoea, and abdominal pain), dizziness, headache, tinnitus, neutropenia, elevated liver enzyme values, and ECG abnormalities including prolongation of the QT interval.

Evidence of severe neurotoxicity has been seen in *animals* given high doses.

◊ General references to adverse effects associated with artemisinin derivatives.

1. Price R, *et al.* Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg* 1999; **60:** 547–55.

Effects on the blood. For a report of severe haemolytic anaemia occurring in patient after taking artemether-lumefantrine, see p.605.

Effects on the heart. Bradycardia was reported in 10 of 34 patients who received artemether orally for 4 days.[1]

1. Karbwang J, *et al.* Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; **340:** 1245–8.

Effects on the nervous system. Neurotoxicity has been reported in *animals* given artemotil or artemether.[1] An *in-vitro* study[2] has shown that artenimol (dihydroartemisinin), the metabolite common to all artemisinin derivatives currently used, is neurotoxic. There has been a report[3] of acute cerebellar dysfunction manifesting as ataxia and slurred speech in a patient who took a 5-day course of artesunate by mouth.

1. Brewer TG, *et al.* Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg* 1994; **88** (suppl 1): 33–6.
2. Wesche DL, *et al.* Neurotoxicity of artemisinin analogs in vitro. *Antimicrob Agents Chemother* 1994; **38:** 1813–19.
3. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Engl J Med* 1997; **336:** 1328.

Pregnancy. Artesunate or artemether was used to treat multidrug-resistant falciparum malaria in 83 pregnant women in Thailand; of 73 pregnancies resulting in live births none showed evidence of any congenital abnormality.[1] Sixteen of the women were given artesunate during the first trimester; of these, 12 had normal deliveries, 1 was lost to study, and 3 had spontaneous abortions.

No undue adverse effects on the neonates occurred in a study[2] involving 45 women treated for multidrug-resistant malaria during their second or third trimester of pregnancy with either artemether or artemether plus mefloquine. Intramuscular artemether was also used to treat chloroquine/quinine-resistant falciparum malaria in 28 pregnant women in eastern Sudan. Artemether was given to 1 woman during the first trimester, to 12 during the second trimester, and to 15 during the third trimester. One baby was delivered at 32 weeks but died 6 hours later; all the other babies were delivered at full term and there were no reports of congenital abnormalities.[3]

WHO[4] recommends that, where available, artesunate is the first option, and artemether is the second, for the parenteral treatment of severe falciparum malaria during the second and third trimesters. In the first trimester, until more evidence becomes available, artesunate may be considered as an option.

1. McGready R, *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 1998; **92:** 430–3.
2. Sowunmi A, *et al.* Randomised trial of artemether versus artemether and mefloquine for the treatment of chloroquine/sufadoxine[sic]-pyrimethamine-resistant falciparum malaria during pregnancy. *J Obstet Gynaecol* 1998; **18:** 322–7.
3. Adam I, *et al.* Artemether in the treatment of falciparum malaria during pregnancy in eastern Sudan. *Trans R Soc Trop Med Hyg* 2004; **98:** 509–13.
4. WHO. *Guidelines for the treatment of malaria.* Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 21/06/06)

Interactions

Use of artemisinin derivatives with drugs that prolong the QT interval should be avoided if possible; caution is advised when artemisinin derivatives are given with other antimalarials that have this propensity.

Grapefruit juice. The oral bioavailability of artemether may be increased if taken with grapefruit juice.[1]

1. van Agtmael MA, *et al.* The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. *Clin Pharmacol Ther* 1999; **66:** 408–14.

Pharmacokinetics

Peak plasma concentrations have been achieved in about 3 hours after oral doses of artemether, in about 6 hours after intramuscular injection of artemether, and in about 11 hours after rectal artemisinin. Artemisinin derivatives (but not artemisinin) are rapidly hydrolysed to various extents to the active metabolite arterimol (dihydroartemisinin). Reported elimination half-lives have been about 45 minutes after intravenous doses of artesunate, about 4 hours after rectal artemisinin, and about 4 to 11 hours after intramuscular or oral artemether. There are very few published data on the pharmacokinetics of artemotil, but its elimination half-life appears to be longer than that of artemether.

◊ Reviews.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Navaratnam V, *et al.* Pharmacokinetics of artemisinin-type compounds. *Clin Pharmacokinet* 2000; **39:** 255–70.

Uses and Administration

Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua*, a herb that has traditionally been used in China for the treatment of malaria. It is a potent and rapidly acting blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*.

Artemisinin has been given orally or rectally in the treatment of malaria; regimens were often empirical with typical rectal doses ranging from 10 to 40 mg/kg daily over a variable number of days. However, it has largely been replaced in practice by its derivatives such as artemether and artesunate.

The following doses are recommended by WHO for the treatment of uncomplicated falciparum malaria.

Artesunate, when used with other antimalarials (amodiaquine, mefloquine, or pyrimethamine-sulfadoxine), is given orally to adults and children in a dose of 4 mg/kg daily, as a single dose, for 3 days.

Artemether is given orally with lumefantrine; 6 doses in total are given, the first at diagnosis and repeated after 8, 24, 36, 48, and 60 hours. Each dose is:

- adults and children weighing over 34 kg, artemether 80 mg with lumefantrine 480 mg
- children 5 to 14 kg, artemether 20 mg with lumefantrine 120 mg
- children 15 to 24 kg, artemether 40 mg with lumefantrine 240 mg
- children 25 to 34 kg, artemether 60 mg with lumefantrine 360 mg

For parenteral use in severe malaria, WHO recommends:

- for adults or children, **artesunate** 2.4 mg/kg intravenously or intramuscularly, repeated after 12 and 24 hours and then once daily thereafter
- as an alternative in children, **artemether** 3.2 mg/kg intramuscularly, followed by 1.6 mg/kg daily thereafter. For both drugs the patient should be transferred to oral therapy as soon as possible

A fixed-dose combination product containing artesunate and amodiaquine (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

Other derivatives of artemisinin, such as artemotil and alpha-beta arteether, are under investigation or commercial development (see Administration of Artemisinin Derivatives, below).

◊ Reviews.

1. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 17/05/05).
2. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 17/05/05).
3. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: a review. *J Postgrad Med* 2004; **50:** 40–4.
4. Ashley EA, White NJ. Artemisinin-based combinations. *Curr Opin Infect Dis* 2005; **18:** 531–6.
5. Davis TME, *et al.* Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; **182:** 181–5.
6. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).
7. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet* 2008; **47:** 91–102.

Administration of artemisinin derivatives. To overcome the poor solubility of *artemisinin* in water a number of dosage forms and routes have been tried. Also, several more potent derivatives with more suitable pharmaceutical properties have been developed, notably the methyl ether derivative, *artemether*, and the ethyl ether derivative, *artemotil*, which are more lipid soluble; the sodium salt of the hemisuccinate ester, *sodium artesunate*, which is soluble in water but appears to have poor stability in aqueous solutions; and *sodium artelinate*, which is both soluble and stable in water. Other derivatives that have been studied include *arteflene.*

Several preparations of artemisinin derivatives are available either commercially or for studies organised by bodies such as WHO. These include oral formulations of artemether, artesunate, artemisinin itself, and *artenimol*; intramuscular formulations of artemotil, artemether, and artesunate; intravenous formulations of *artelinic acid* and artesunate; and suppositories of artemisinin, artesunate, and artinimol.

Malaria. The overall management of malaria and the place of artemisinin derivatives in current recommendations are discussed on p.594. In an attempt to delay the development of resistance to these compounds, WHO at one time recommended that their use be restricted to the treatment of malaria in areas of documented multidrug resistance and that they should not be used at all for prophylaxis. However, the development of resistance to conventional treatment has now led WHO to recommend the use in such circumstances of combination therapies containing artemisinin derivatives (artemisinin-based combination therapies, also known as ACTs). The following combination therapies are recommended:

- artemether-lumefantrine
- artesunate plus amodiaquine
- artesunate plus pyrimethamine-sulfadoxine (*Fansidar*)
- artesunate plus mefloquine

Artemether-lumefantrine is now also recommended in the UK as an alternative to quinine-based therapy for uncomplicated falciparum malaria.

In acute uncomplicated malaria artemisinin derivatives are usually given by mouth. Those used have been artemisinin, artemether, or artesunate. Parenteral therapy is generally necessary in severe malaria and WHO recommends[1] artesunate intravenously or intramuscularly in adults and children, or artemether intramuscularly in children, as alternatives to quinine for severe malaria. A systematic review[2] has suggested that intravenous artesunate should be the drug of choice in adults with severe malaria, particularly if acquired in Asia. Rectal artesunate has been successful and is recommended by WHO[1] if parenteral therapy is not possible.

1. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 21/06/06)
2. Jones KL, *et al.* Artesunate versus quinine for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 05/06/08).

Schistosomiasis. Findings of a reduced intensity of *Schistosoma mansoni* infection in patients treated with sodium artesunate for malaria[1] prompted further investigation into the use of artemisinin derivatives for the control of schistosomiasis (p.138). A double-blind placebo-controlled study[2] in children negative for *S. mansoni* found a significantly lower incidence of infection in those given artemether orally. There was also a significant reduction in the prevalence of *Plasmodium falciparum* infection. A number of studies in China have confirmed the benefits of artemether or artesunate, often with praziquantel, against *S. japonicum*.[3]

1. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94:** 90–1.
2. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355:** 1320–5.
3. Xiao S-H. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop* 2005; **96:** 153–67.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Arinate; Artesiane; ***Braz.:*** Paluther; Plasmotrim; ***China:*** Cotecxin; ***India:*** Betamotil; E Mal; Falcigo; Falcinil; Larinate; Larither; Mosether; Rapither-AB; ***Neth.:*** Artecef; ***Thai.:*** Plasmotrim†.

Multi-ingredient: ***Austral.:*** Riamet; ***Austria:*** Riamet; ***Belg.:*** Amonate; Co-Arinate; Co-Artesiane; ***China:*** Artemodi; Duo-Cotecxin; ***Cz.:*** Riamet; ***Fr.:*** Riamet; ***Ger.:*** Riamet; ***Gr.:*** Riamet; ***Hong Kong:*** Riamet†; ***India:*** Artemal†; Larimal†; ***Neth.:*** Riamet; ***Norw.:*** Riamet†; ***Port.:*** Riamet; ***S.Afr.:*** Coartem; ***Swed.:*** Riamet; ***Switz.:*** Riamet; ***Thai.:*** Coartem; ***UK:*** Riamet.

Chloroquine *(BAN, rINN)*

Chloroquinum; Cloroquina; Klorokiini; Klorokin. 4-(7-Chloro-4-quinolylamino)pentyldiethylamine; 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

Хлорохин

$C_{18}H_{26}ClN_3$ = 319.9.
CAS — 54-05-7.
ATC — P01BA01.

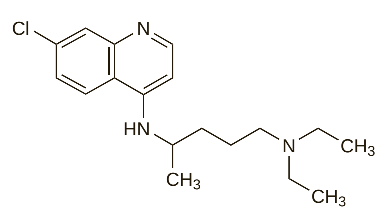

Pharmacopoeias. In *US.*
USP 31 (Chloroquine). A white or slightly yellow, odourless, crystalline powder. M.p. 87° to 92°. Very slightly soluble in water; soluble in chloroform, in ether, and in dilute acids. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Chloroquine Hydrochloride *(BANM, rINNM)*

Chloroquine, Chlorhydrate de; Chloroquini Hydrochloridum; Hidrocloruro de cloroquina.

Хлорохина Гидрохлорид

$C_{18}H_{26}ClN_3,2HCl$ = 392.8.
CAS — 3545-67-3.
ATC — P01BA01.

Pharmacopoeias. *US* includes an injection.

Chloroquine Phosphate *(BANM, rINNM)*

Chingaminum; Chlorochin-difosfát; Chlorochinium Phosphoricum; Chlorochinum Diphosphoricum; Chlorochiny fosforan; Chlorokvino fosfatas; Chloroquine, phosphate de; Chloroquini Diphosphas; Chloroquini phosphas; Fosfato de cloroquina; Klorokiinifosfaatti; Klorokinfosfat; Klorokin-foszfát; Quingamine; SN-7618.

Хлорохина Фосфат

$C_{18}H_{26}ClN_3,2H_3PO_4$ = 515.9.
CAS — 50-63-5.
ATC — P01BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Chloroquine Phosphate). A white or almost white, hygroscopic, crystalline powder. It exists in two forms, one melting at about 195° and the other at about 218°. Freely soluble in water; very slightly soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 3.8 to 4.3. Store in airtight containers. Protect from light.
USP 31 (Chloroquine Phosphate). A white, odourless, crystalline powder, which slowly discolours on exposure to light. It exists in two polymorphic forms, one melting between 193° and 195° and the other between 210° and 215°; mixture of the two forms melts between 193° and 215°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions have a pH of about 4.5.

Chloroquine Sulfate *(rINNM)*

Chlorochin-sulfát monohydrát; Chlorochiny siarczan; Chlorokvino sulfatas; Chloroquine, sulfate de; Chloroquine Sulphate *(BANM)*; Chloroquini sulfas; Chloroquini Sulfas Monohydricus; Chloroquini Sulphas; Klorokiinisulfaatti; Klorokinsulfat; Klorokin-szulfát; RP-3377; Sulfato de cloroquina.

Хлорохина Сульфат

$C_{18}H_{26}ClN_3,H_2SO_4,H_2O$ = 436.0.
CAS — 132-73-0 (anhydrous chloroquine sulfate).
ATC — P01BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*
Ph. Eur. 6.2 (Chloroquine Sulphate). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in alcohol. An 8% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

Sorption. Studies using low concentrations of chloroquine phosphate or chloroquine sulfate indicate that chloroquine exhibits pH-dependent binding to several materials used in medical equipment and membrane filters, including soda glass and various plastics such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, PVC, ethylvinyl acetate, and polyethylene.[1-3] Although this effect may not be of relevance at doses used clinically,[4] laboratory workers undertaking assays and sensitivity testing must recognise that significant reductions in concentrations can occur when chloroquine is prepared or stored in equipment made from these materials.[2,3] As the effect of borosilicate glass or polystyrene appears to be minimal, it has been suggested that they may be suitable for use in such procedures.[2,3]

Similar sorption has also been reported during membrane filtration of solutions of amodiaquine hydrochloride, mefloquine hydrochloride, or quinine sulfate.[1]

1. Baird JK, Lambros C. Effect of membrane filtration of antimalarial drug solutions on in vitro activity against Plasmodium falciparum. *Bull WHO* 1984; **62:** 439–44.
2. Yahya AM, *et al.* Binding of chloroquine to glass. *Int J Pharmaceutics* 1985; **25:** 217–23.
3. Yahya AM, *et al.* Investigation of chloroquine binding to plastic materials. *Int J Pharmaceutics* 1986; **34:** 137–43.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Adverse Effects

Adverse effects experienced with dosage regimens of chloroquine used in the treatment and prophylaxis of malaria are generally less common and less severe than those associated with the higher doses used for prolonged periods in rheumatoid arthritis.

Frequent adverse effects of chloroquine include headache, various skin eruptions, pruritus, and gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. More rarely, mental changes including psychotic episodes, agitation, and personality changes may occur. Convulsions have been reported.

Visual disturbances such as blurred vision and difficulties in focusing have occurred but these are more common with higher doses, when they may be associated with keratopathy or retinopathy, as discussed under Effects on the Eyes, below. Keratopathy usually occurs in the form of corneal opacities and is normally reversible when chloroquine is withdrawn. Retinopathy is the most serious adverse effect of chloroquine on the eyes and it can result in severe visual impairment. Changes may be irreversible and can even progress after chloroquine is stopped. Those taking high doses of chloroquine for prolonged periods appear to be at greatest risk of developing retinopathy.

Other uncommon adverse effects from prolonged use include loss of hair, bleaching of hair pigment, bluish-black pigmentation of the mucous membranes and skin, photosensitivity, tinnitus, reduced hearing, nerve deafness, neuromyopathy, and myopathy, including cardiomyopathy.

Blood disorders have been reported rarely. They include aplastic anaemia, reversible agranulocytosis, thrombocytopenia, and neutropenia.

There have also been rare reports of changes in liver function, including hepatitis and abnormal liver function tests.

Parenteral therapy with chloroquine can be hazardous and rapid intravenous dosage or the use of high doses can result in cardiovascular toxicity and other symptoms of acute overdosage.

Acute overdosage with chloroquine is extremely dangerous and death can occur within a few hours. Initial effects include headache, gastrointestinal disturbances, drowsiness, and dizziness. Hypokalaemia may occur within a few hours of ingestion of chloroquine. Visual disturbances may be dramatic with a sudden loss of vision. However, the main effect of overdosage with chloroquine is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, coma, and death.

Effects on the blood. Aplastic anaemia was associated with the use of chloroquine in 3 patients.[1] Two patients had received treatment over several months and one of these was later found to have acute myeloblastic leukaemia after receiving chloroquine treatment initially for discoid lupus erythematosus, and later for cerebral malaria. In the third patient aplastic anaemia developed 3 weeks after a short course of chloroquine for malaria.

1. Nagaratnam N, *et al.* Aplasia and leukaemia following chloroquine therapy. *Postgrad Med J* 1978; **54:** 108–12.

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy.

Keratopathy, characterised by corneal deposits, may occur within a few weeks of starting treatment. However, patients are often asymptomatic and fewer than 50% of affected patients complain of visual symptoms such as photophobia, haloes around lights, or blurred vision. Keratopathy is completely reversible on withdrawal of treatment and is not usually considered to be a contraindication to continued treatment.[1]

Retinopathy is potentially more serious. The outcome on stopping treatment is unpredictable and changes may be irreversible or may even progress.[2,3] Delayed-onset retinopathy has also been reported in patients many years after cessation of treatment.[4] The reported incidence of retinopathy varies according to the methodology and criteria used.[1,5,6] From studies in patients on long-term antimalarial treatment, it was reported[1] that an accumulation of 100 g of chloroquine [phosphate] (250 mg daily for 1 year) might cause retinopathy; the risk was significantly increased as the total dosage exceeded 300 g. Experience in rheumatology also indicates that the incidence of retinal toxicity is dose-related. While the total cumulative dose, the duration of treatment, and the age of the patient might all affect the incidence of retinal toxicity,[7,8] the daily dose might be the most important factor.[9] It has been suggested that the risk of retinal damage is small with daily doses of up to 4.0 mg of chloroquine phosphate per kg body-weight (= chloroquine base approximately 2.5 mg per kg daily) or up to 6.5 mg of hydroxychloroquine sulfate per kg.[9] In obese patients, excessive dosage should be avoided by calculating dosage on the basis of lean body-weight. It appears that retinopathy is rarely, if ever, associated with the weekly dosages of chloroquine recommended for the prophylaxis of malaria.[10,11]

In the UK, a review group[12] convened by the Royal College of Ophthalmologists made **recommendations** regarding use by rheumatologists and dermatologists. Chloroquine should only be used if hydroxychloroquine or other preferred drugs have failed as there is inadequate data to advise on a safe maximum dose; thus the following recommendations relate only to *hydroxychloroquine* as no guidelines have been published for chloroquine.

- Baseline assessment before treatment with hydroxychloroquine is commenced (maximum daily dosage 6.5 mg/kg lean body-weight) should consist of checking renal and hepatic function, questioning the patient about visual impairment not corrected by glasses, and recording near visual acuity.
- Thereafter, patients should be monitored annually with enquiry about visual symptomatology, rechecking of acuity, and assessment for blurred vision.
- Patients should be referred to an ophthalmologist if problems are detected either before or during treatment.
- Those taking long-term hydroxychloroquine should be subject to occasional ophthalmological review after 5 years' continuous treatment.

UK licensed product information for *chloroquine* recommends ophthalmic examination at 3 to 6 monthly intervals in patients receiving continuous high doses for more than a year, or weekly treatment for more than 3 years, or for those in whom total consumption exceeds 100 g or 1.6 g/kg.

1. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; **75** (suppl 1A): 25–34.
2. Ogawa S, *et al.* Progression of retinopathy long after cessation of chloroquine therapy. *Lancet* 1979; **i:** 1408.
3. Easterbrook M. Ocular effects and safety of antimalarial agents. *Am J Med* 1988; **85** (suppl 4A): 23–9.
4. Ehrenfeld M, *et al.* Delayed-onset chloroquine retinopathy. *Br J Ophthalmol* 1986; **70:** 281–3.
5. Finbloom DS, *et al.* Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; **12:** 692–4.
6. Morsman CDG, *et al.* Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* 1990; **4:** 572–6.
7. Elman A, *et al.* Chloroquine retinopathy in patients with rheumatoid arthritis. *Scand J Rheumatol* 1976; **5:** 161–6.
8. Marks JS, Power BJ. Is chloroquine obsolete in treatment of rheumatic disease? *Lancet* 1979; **i:** 371–3.
9. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; **75** (suppl 1A): 40–5.
10. Breckenridge A. Risks and benefits of prophylactic antimalarial drugs. *BMJ* 1989; **299:** 1057–8.
11. Lange WR, *et al.* No evidence for chloroquine-associated retinopathy among missionaries on long-term malaria chemoprophylaxis. *Am J Trop Med Hyg* 1994; **51:** 389–92.
12. Buckley R, *et al.* Royal College of Ophthalmologists, British Association of Dermatologists, and British Society for Rheumatology. Ocular toxicity and hydroxychloroquine: guidelines for screening 2004 (replacing The Royal College of Ophthalmologists Guidelines 1998). Available at: http://www.bad.org.uk/healthcare/guidelines/Ocular_toxicity_and_hydroxychloroquine_guidelines_for_screening_20041.pdf (accessed 09/06/05)

Effects on glucose metabolism. While hypoglycaemia has occurred with quinine (see p.613), it was not generally thought to be associated with chloroquine; however, there has been a report of its occurrence in a patient with reactive hypoglycaemia.[1]

1. Abu-Shakra M, Lee P. Hypoglycemia: an unusual adverse reaction to chloroquine. *Clin Exp Rheumatol* 1994; **12:** 95.

Effects on the heart. Studies in patients with malaria[1] and in healthy subjects[2] indicate that the acute cardiovascular toxicity that may be associated with parenteral use of chloroquine is related to transiently high plasma concentrations produced during the early part of the distribution phase; these findings appear to confirm that the dosage rate is a major determinant of this toxicity. Cardiac conduction abnormalities, including heart block, have also occurred in patients receiving long-term oral therapy with chloroquine,[3] including use in lupus erythematosus,[4,5] as well as after chloroquine overdosage or abuse.[6] Histological changes in endomyocardial biopsy specimens from 2 patients with cardiomyopathy associated with chloroquine or hydroxychloroquine therapy were found to be virtually identical to those seen in the skeletal muscle of patients with chloroquine-induced myopathy[7] (see also Effects on the Muscles, below).

1. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
2. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
3. Ogola ESN, *et al.* Chloroquine related complete heart block with blindness: case report. *East Afr Med J* 1992; **69:** 50–2.
4. Piette J-C, *et al.* Chloroquine cardiotoxicity. *N Engl J Med* 1987; **317:** 710–11.
5. Baguet J-P, *et al.* Chloroquine cardiomyopathy with conduction disorders. *Heart* 1999; **81:** 221–3.
6. Ihenacho HNC, Magulike E. Chloroquine abuse and heart block in Africans. *Aust N Z J Med* 1989; **19:** 17–21.
7. Ratliff NB, *et al.* Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. *N Engl J Med* 1987; **316:** 191–3.

Effects on mental function. Serious psychotic effects (depersonalisation and anxiety) developed in a healthy subject who took a standard 3-day course of oral chloroquine for the treatment of *Plasmodium falciparum* malaria, as part of a clinical study. Three weeks after completing the course she still had serious concentration problems and her symptoms gradually resolved over the next 4 months.[1]

1. Telgt DS, *et al.* Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. *Ann Pharmacother* 2005; **39:** 551–4.

Effects on the muscles. The myopathy induced by chloroquine is characterised by progressive weakness and atrophy of proximal muscles and can develop insidiously after periods of therapy ranging from a few weeks to a few years.[1] There are often mild sensory changes, depression of tendon reflexes, and abnormal nerve conduction studies suggestive of an associated peripheral neuropathy. The myopathy is reversible on withdrawal of treatment but recovery may take several months. Cardiomyopathy may also occur (see under Effects on the Heart, above). Similar effects have been reported with hydroxychloroquine.[2] In a retrospective review of 4405 patients with rheumatic disorders, 214 had received chloroquine or hydroxychloroquine and, of these, 3 developed myopathy.[3]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Estes ML, *et al.* Chloroquine neuromyotoxicity. *Am J Med* 1987; **82:** 447–55.
3. Avina-Zubieta JA, *et al.* Incidence of myopathy in patients treated with antimalarials: a report of three cases and a review of the literature. *Br J Rheumatol* 1995; **34:** 166–70.

Effects on the nervous system. Apart from neuropathies (see Effects on the Muscles, above) other adverse effects of chloroquine on the nervous system have included isolated reports of extrapyramidal symptoms and other involuntary movements[1,2] (in patients being treated for malaria), nystagmus[3] (in a patient on prolonged treatment for rheumatoid arthritis), and convulsions[4,5] and nonconvulsive status epilepticus[6] (in patients on malaria prophylaxis).

1. Umez-Eronini EM, Eronini EA. Chloroquine induced involuntary movements. *BMJ* 1977; **1:** 945–6.
2. Singhi S, *et al.* Chloroquine-induced involuntary movements. *BMJ* 1977; **2:** 520.
3. Marks JS. Motor polyneuropathy and nystagmus associated with chloroquine phosphate. *Postgrad Med J* 1979; **55:** 569.
4. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
5. Fish DR, Espri MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
6. Mülhauser P, *et al.* Chloroquine and nonconvulsive status epilepticus. *Ann Intern Med* 1995; **123:** 76–7.

Effects on the skin. *Pruritus* is common in patients given chloroquine for the treatment of malaria and it may become so severe as to compromise treatment. Itching starts a few hours after use but usually remits spontaneously within 72 hours. Although antihistamines are generally thought ineffective,[1,2] a few patients may obtain some relief.[3] The incidence of pruritus is purported to be higher in black patients, but this may only reflect the greater number of black patients surveyed. The aetiology of this reaction is unknown, but this apparent higher incidence has prompted suggestions that it may have a genetic basis[4] or be related to the affinity of chloroquine for melanin.[2] Chloroquine's main metabolite, monodesethylchloroquine, has been implicated,[5] although there is also some evidence suggesting that patients with pruritus metabolise chloroquine more slowly.[6] A survey[1] in Nigeria found that, of 1100 patients, 74% had pruritus during antimalarial therapy; 61% of these reacted to chloroquine, 30% reacted to amodiaquine, 2.5% to Fansidar (pyrimethamine-sulfadoxine), and, 6.5% reacted to all three. In another study in Nigeria,[4] the incidence of pruritus was reported to be 14% (8 of 56 patients) for chloroquine, 27% (14 of 52) for amodiaquine, and 13% (7 of 53) for halofantrine; none of 58 patients receiving quinine or 82 patients receiving mefloquine had pruritus. In contrast, in a study in Thailand only 1.9% of 1189 chloroquine-treated patients reported pruritus.[7]

There have been rare reports of more severe cutaneous reactions associated with chloroquine, including *toxic epidermal necrolysis*,[8,9] *erythema multiforme*,[10] and *Stevens-Johnson syndrome*,[11] although the causal role of chloroquine is not always clear as some of these patients also received other antimalarials, sometimes at an inappropriate dosage. In a more recent case of toxic epidermal necrolysis,[12] chloroquine given alone for malaria prophylaxis was the probable cause. A young patient receiving radiotherapy developed a localised bullous eruption and rapid progressive moist desquamation on the third day of treatment with oral chloroquine for malaria.[13] For a discussion including the possible effect of chloroquine on the incidence of erythema multiforme in patients taking pyrimethamine with sulfadoxine, see Adverse Effects with Sulfonamides, under Pyrimethamine, p.610.

1. Ajayi AA, *et al.* Epidemiology of antimalarial-induced pruritus in Africans. *Eur J Clin Pharmacol* 1989; **37:** 539–40.
2. Osifo NG. Chloroquine-induced pruritus among patients with malaria. *Arch Dermatol* 1984; **120:** 80–2.
3. Okor RS. Responsiveness of chloroquine-induced pruritus to antihistamine therapy—clinical survey. *J Clin Pharm Ther* 1990; **15:** 147–50.
4. Sowunmi A, *et al.* Pruritus and antimalarial drugs in Africans. *Lancet* 1989; **ii:** 213.
5. Essien EE, *et al.* Chloroquine disposition in hypersensitive and non-hypersensitive subjects and its significance in chloroquine-induced pruritus. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 71–7.
6. Ademowo OG, *et al.* The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine-induced pruritus: evidence for decreased chloroquine metabolism in volunteers with pruritus. *Clin Pharmacol Ther* 2000; **67:** 237–41.
7. Bussaratid V, *et al.* Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. *Trop Doct* 2000; **30:** 211–14.
8. Kanwar AJ, Singh OP. Toxic epidermal necrolysis—drug induced. *Indian J Dermatol* 1976; **21:** 73–7.
9. Phillips-Howard PA, Warwick Buckler J. Idiosyncratic reaction resembling toxic epidermal necrolysis caused by chloroquine and Maloprim. *BMJ* 1988; **296:** 1605.
10. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.

11. Bamber MG, *et al.* Fatal Stevens-Johnson syndrome associated with Fansidar and chloroquine. *J Infect* 1986; **13:** 31–3.
12. Boffa MJ, Chalmers RJG. Toxic epidermal necrolysis due to chloroquine phosphate. *Br J Dermatol* 1994; **131:** 444–5.
13. Rustogi A, *et al.* Unexpected skin reaction induced by radiotherapy after chloroquine use. *Lancet Oncol* 2006; **7:** 608–9.

Overdosage. For adverse effects associated with chloroquine overdosage, see Treatment of Adverse Effects, below.

Treatment of Adverse Effects

Acute overdosage with chloroquine can be rapidly lethal and intensive symptomatic supportive treatment should be started immediately. The first steps should be to maintain adequate respiration and to correct any cardiovascular disturbances. Early use of adrenaline with diazepam (see below) may minimise the cardiotoxicity of chloroquine and control arrhythmias. Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting more than the equivalent of 15 mg/kg of chloroquine base; activated charcoal may be left in the stomach to limit any further absorption. Intravenous sodium bicarbonate should be given to correct metabolic acidosis. Other methods to increase the elimination of chloroquine, such as dialysis, are probably of little use.

◊ Chloroquine overdosage is the most severe and frequent cause of intoxication with antimalarial drugs and chloroquine is often used for suicide attempts. Severe toxic manifestations may occur within 1 to 3 hours and fatal outcomes usually occur within 2 to 3 hours of drug ingestion. The major clinical symptoms are of neurological, respiratory, and cardiovascular toxicity;[1] death is usually due to cardiac arrest related to the direct effect of chloroquine on the myocardium.[2] Chloroquine has a low safety margin: doses of 20 mg/kg are considered toxic and 30 mg/kg may be lethal. The mortality rate in some published studies has ranged from 10 to 30%.[1] If gastric lavage is attempted it should be preceded by correction of severe cardiovascular disturbances and institution of artificial ventilation because insertion of the stomach tube may induce sudden cardiac arrest or convulsions; induction of emesis is contra-indicated because of the risk of lung aspiration. Activated charcoal has been recommended to limit absorption of chloroquine that may be left in the gut.[3] There is no evidence to indicate that attempts to increase chloroquine elimination such as acidification of the urine, haemodialysis, peritoneal dialysis, or exchange transfusion, are effective in overdosage. Elimination in the urine is more dependent on haemodynamic status than on infusion of osmotic solutions or acidification. Any clearance achieved by haemoperfusion or haemodialysis is low in comparison with the normal total body clearance.[1]

It is not clear if correction of hypokalaemia is essential, but giving potassium should be avoided in the initial phases of intoxication when conduction disturbances still exist. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication and might be useful diagnostically.[4] However, chloroquine-induced hypokalaemia may be due to a transport-dependent mechanism rather than to true potassium depletion and overzealous correction could result in hyperkalaemia.[4]

Since there had been no effective treatment for severe chloroquine poisoning, one group of workers tried using early mechanical ventilation, together with adrenaline and high doses of diazepam, both given intravenously, to counteract cardiotoxicity, with encouraging results.[2] Diazepam had earlier been shown to decrease the cardiotoxicity of chloroquine in *animal* studies and there had been several clinical reports of beneficial responses. It was considered that routine use of adrenaline before the onset of cardiac arrhythmia might be beneficial in the treatment of severe chloroquine poisoning.[2] UK licensed product information for chloroquine suggests giving adrenaline by intravenous infusion in a dose of 250 nanograms/kg per minute initially, with increments of 250 nanograms/kg per minute until adequate systolic blood pressure is restored, and diazepam by intravenous infusion in a dose of 2 mg/kg over 30 minutes as a loading dose, followed by 1 to 2 mg/kg per day for up to 2 to 4 days.

Overdosage with hydroxychloroquine has responded to measures similar to those used in the management of chloroquine overdosage.[5]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Riou B, *et al.* Treatment of severe chloroquine poisoning. *N Engl J Med* 1988; **318:** 1–6.
3. Neuvonen PJ, *et al.* Prevention of chloroquine absorption by activated charcoal. *Hum Exp Toxicol* 1992; **11:** 117–20.
4. Clemessy J-L, *et al.* Hypokalaemia related to acute chloroquine ingestion. *Lancet* 1995; **346:** 877–80.
5. Jordan P, *et al.* Hydroxychloroquine overdose: toxicokinetics and management. *J Toxicol Clin Toxicol* 1999; **37:** 861–4.

Precautions

Excessive doses of chloroquine and hydroxychloroquine are associated with retinal or visual field changes and the precautions to be taken in order to minimise such toxicity are discussed under Effects on the Eyes in Adverse Effects, above. There may be a temporary effect on visual accommodation.

Care is necessary when giving chloroquine to patients with hepatic or renal impairment, or to those with severe gastrointestinal disorders, a history of psoriasis, or neurological disorders, especially a history of epilepsy (see below for advice not to use for malaria prophylaxis). Chloroquine should be used with caution in patients with myasthenia gravis as it may aggravate the condition. Patients with G6PD deficiency should be observed for haemolytic anaemia during chloroquine treatment. Full blood counts should be performed at regular intervals during extended treatment with chloroquine. Although there have been reports of fetal abnormalities associated with the use of chloroquine during pregnancy, the risks of malaria are considered to be greater and there appears to be no justification for withholding chloroquine for the treatment or prophylaxis of malaria.

It is important that if chloroquine is given intravenously it should be by slow infusion (typically around 0.8 to 1.25 mg/kg per hour) otherwise severe cardiotoxicity may develop.

Breast feeding. Chloroquine is distributed into breast milk, but not in an amount adequate to provide chemoprophylaxis against malaria for the infant (see under Pharmacokinetics, below). Furthermore, no adverse effects have been seen in breast-feeding infants whose mothers were receiving chloroquine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/04/04)

Epilepsy. After reports[1,2] of convulsions associated with the use of chloroquine for malaria prophylaxis in 4 previously healthy patients and in 2 patients with a history of seizures, it has been suggested that prospective travellers who have a history of epilepsy should be warned of the risk. Although it was initially considered[3] that this should not restrict the use of chloroquine, UK malaria experts have recommended that it should be avoided for malaria prophylaxis in patients with epilepsy.[4]

1. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
2. Fish DR, Espir MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
3. Hellgren U, Rombo L. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
4. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Porphyria. Although chloroquine is probably safe in porphyric patients, some authorities consider its use to be contentious. Pyrimethamine is also probably safe in porphyric patients. Other drugs used for prophylaxis, such as dapsone and sulfadoxine and combinations containing them, are definitely contra-indicated in porphyric patients. Quinine is of proven safety in patients with porphyria and cell-culture tests have suggested that proguanil and mefloquine may also be safe.

Chloroquine has been tried in the treatment of porphyria cutanea tarda, but this may be associated with hepatotoxicity (see under Uses, below).

Pregnancy. There has been concern about the potential teratogenic effects of chloroquine because of a few case reports including defects in hearing and vision.[1] Two of 169 infants, born to women given chloroquine 300 mg weekly throughout pregnancy, had birth defects compared with 4 of 454 control infants whose mothers had not received antimalarials; the difference was not significant. The data suggested that chloroquine in the recommended prophylactic doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low-grade teratogenicity. Also it has been reported that chloroquine prophylaxis during pregnancy did not affect the birth-weight of neonates, compared with a control group.[2]

1. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. *BMJ* 1985; **290:** 1466–7.
2. Cot M, *et al.* Effect of chloroquine chemoprophylaxis during pregnancy on birth weight: results of a randomized trial. *Am J Trop Med Hyg* 1992; **46:** 21–7.

Psoriatic arthritis. It is recommended that chloroquine and hydroxychloroquine should not be used in the treatment of psoriatic arthritis as exacerbations of skin lesions can occur. Some patients may go on to develop generalised erythroderma with subsequent exfoliative dermatitis.[1] However, there has been controversy over the reported incidence of this adverse effect.[2,3]

1. Slagel GA, James WD. Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985; **12:** 857–62.
2. Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbations of psoriatic skin lesions. *J Rheumatol* 1982; **9:** 462–4.
3. Sayers ME, Mazanec DJ. Use of antimalarial drugs for the treatment of psoriatic arthritis. *Am J Med* 1992; **93:** 474–5.

Renal impairment. Although the elimination of chloroquine is prolonged in renal impairment no dosage adjustment is required in the treatment of malaria. Similarly, dosage reduction is not required for chloroquine prophylaxis except in those with severe renal impairment. Doses tend to be reduced when it is given for longer periods to patients with renal impairment.

Interactions

There is an increased risk of inducing ventricular arrhythmias if chloroquine is used with halofantrine (see p.604) or other arrhythmogenic drugs such as amiodarone and moxifloxacin. There is an increased risk of convulsions when chloroquine is given with mefloquine. The absorption of chloroquine can be reduced by antacids or kaolin and its metabolism may be inhibited by cimetidine.

Agalsidase. For the effect of using chloroquine with *agalsidase alfa* or *beta*, see p.2252.

Antiepileptics. Chloroquine may antagonise the antiepileptic activity of *carbamazepine* and *valproate* by lowering the convulsive threshold.

Antimalarials. Chloroquine should not be used with *halofantrine* since the latter prolongs the QT interval and therefore there is an increased potential to induce arrhythmias (see p.604). Use of chloroquine with *mefloquine* increases the risk of convulsions. Also use of chloroquine with *proguanil* may increase the incidence of proguanil-associated mouth ulceration.[1] The activity of chloroquine may be affected when it is given with other *antimalarials*. *Quinine* and chloroquine when used together may be antagonistic.[2] Mixtures of chloroquine with *quinine, mefloquine, amodiaquine, artemisinin,* or *pyrimethamine-sulfadoxine* were antagonistic *in vitro* against *Plasmodium falciparum*.[3]

1. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
2. Hall AP. Quinine and chloroquine antagonism in falciparum malaria. *Trans R Soc Trop Med Hyg* 1973; **67:** 425.
3. Stahel E, *et al.* Antagonism of chloroquine with other antimalarials. *Trans R Soc Trop Med Hyg* 1988; **82:** 221.

Antimicrobials. A woman who had previously tolerated chloroquine alone had acute dystonic reactions when also given *metronidazole*.[1] Chloroquine may also reduce the gastrointestinal absorption of *ampicillin* (see p.204).

1. Achumba JI, *et al.* Chloroquine-induced acute dystonic reactions in the presence of metronidazole. *Drug Intell Clin Pharm* 1988; **22:** 308–10.

Ciclosporin. Chloroquine has been reported to increase plasma concentrations of ciclosporin (see p.1826).

Digoxin. Hydroxychloroquine has been reported to increase plasma concentrations of digoxin (see p.1262).

Gastrointestinal drugs. Patients often wish to take chloroquine with food, antacids, or other gastrointestinal drugs to alleviate gastrointestinal irritation. Dosage with *food* may be beneficial as it appears to improve the absorption of chloroquine.[1,2] However, *antacids* or *kaolin* can reduce the absorption of chloroquine and it is therefore recommended that they should be given at least 4 hours apart.[3,4]

Cimetidine and chloroquine should be used with caution as *cimetidine* can significantly reduce the metabolism and elimination of chloroquine and increase its volume of distribution;[5] *ranitidine*, however, appears to have little effect on the pharmacokinetics of chloroquine.[6]

1. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
2. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
3. McElnay JC, *et al.* In vitro experiments on chloroquine and pyrimethamine absorption in the presence of antacid constituents or kaolin. *J Trop Med Hyg* 1982; **85:** 153–8.
4. McElnay JC, *et al.* The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg* 1982; **85:** 159–63.
5. Ette EI, *et al.* Chloroquine elimination in humans: effect of low-dose cimetidine. *J Clin Pharmacol* 1987; **27:** 813–16.
6. Ette EI, *et al.* Effect of ranitidine on chloroquine disposition. *Drug Intell Clin Pharm* 1987; **21:** 732–4.

Levothyroxine. For a report of a possible interaction of chloroquine with levothyroxine, see p.2172.

Praziquantel. For a report of possible reduced bioavailability of praziquantel when given with chloroquine, see p.154.

Vaccines. Although chloroquine has been reported to reduce the antibody response to *human diploid rabies vaccine* (see p.2234), the immune response to other vaccines used in routine immunisation schedules (tetanus, diphtheria, measles, poliomyelitis, typhoid, and BCG) has not been found to be altered by chloroquine prophylaxis.[1,2]

1. Greenwood BM. Chloroquine prophylaxis and antibody response to immunisation. *Lancet* 1984; **ii:** 402–3.
2. Wolfe MS. Precautions with oral live typhoid (Ty 21a) vaccine. *Lancet* 1990; **336:** 631–2.

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when given orally. Absorption is also rapid after intramuscular or subcutaneous use. It is widely distributed into body tissues and has a large apparent volume of distribution. It accumulates in high concentrations in some tissues, such as the kidneys, liver, lungs, and spleen and is strongly bound in melanin-containing cells such as those in the eyes and the skin. It also crosses the placenta. Chloroquine is eliminated very slowly from the body and it may persist in tissues for months or even years after stopping therapy.

Chloroquine is extensively metabolised in the liver, mainly to monodesethylchloroquine with smaller amounts of bisdesethylchloroquine (didesethylchloroquinine) and other metabolites being formed. Monodesethylchloroquine has been reported to have some activity against *Plasmodium falciparum*. Chloroquine and its metabolites are excreted in the urine, with about half of a dose appearing as unchanged drug and about 10% as the monodesethyl metabolite. Chloroquine and its monodesethyl metabolite are both distributed into breast milk.

◊ General references.

1. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine; clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.
2. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine: focus on recent advancements. *Clin Pharmacokinet* 1996; **31:** 257–74.

◊ Chloroquine is rapidly absorbed from the gastrointestinal tract but peak plasma concentrations after oral doses can vary considerably.[1] A mean peak plasma concentration of 76 nanograms/mL has been obtained in healthy adults a mean of 3.6 hours after giving the equivalent of 300 mg of chloroquine base orally as tablets.[2] In children with uncomplicated malaria given the equivalent of 10 mg/kg peak plasma concentrations of 250 nanograms/mL have been reached after 2 hours;[3] a mean peak of 134 nanograms/mL has been obtained after 5 hours in healthy children given a similar dose.[4] Nasogastric use has also produced therapeutic concentrations in children with severe falciparum malaria.[5]

Oral bioavailability is increased if chloroquine is taken with food[6,7] and some beverages[8] and may also be affected by the state of health of the patient; mean values have ranged from about 70% in patients with malaria[9] to 78 or 89% in healthy adults.[2] Although oral bioavailability appears to be unaltered in moderately undernourished adults[10] it has been reported that it may be significantly reduced in children with kwashiorkor.[4]

Preliminary studies with chloroquine suppositories indicated that, although rectal bioavailability is less than half of that of oral chloroquine, sustained therapeutic concentrations may be achieved.[11]

Absorption is also rapid after subcutaneous or intramuscular injection and mean peak plasma concentrations of chloroquine have been obtained within about 30 minutes.[5,9,12]

Chloroquine has a large apparent volume of distribution. A multicompartmental model appears to be necessary to describe the distribution kinetics of chloroquine.[2,13] After intravenous dosage there is a multi-exponential decline in plasma concentrations as chloroquine distributes out of a central compartment that has been estimated to be several orders of magnitude smaller than the total volume of distribution.[5,14] This slow distribution out of the central compartment produces transiently high cardiotoxic concentrations of chloroquine if the overall rate of parenteral delivery is not carefully controlled.

Reported mean values for protein binding have ranged from about 58 to 64%.[15,16] Chloroquine is also bound to platelets and granulocytes so that the plasma concentration is only 10 to 15% of that in whole blood.[17] If these cells are not removed by gentle centrifugation during analysis, erroneously high plasma concentrations will be reported. Furthermore, as chloroquine concentrations determined in serum are higher than those in plasma, probably due to release of chloroquine from platelets during coagulation, it is crucial to state whether analysis has been done on whole blood, serum, or properly separated plasma.

About 50% of a dose of chloroquine is metabolised in the liver, mainly to the *N*-dealkylated metabolite monodesethylchloroquine; smaller amounts of bisdesethylchloroquine, 7-chloro-4-aminoquinoline, and *N*-oxidation products are formed. Some of these metabolites may contribute to the cardiotoxicity associated with chloroquine. In one study, peak plasma concentrations of 7-chloro-4-aminoquinoline were found to be twice those of unchanged chloroquine despite the fact that only relatively small amounts are formed; this appears to be due to its fast rate of formation and long elimination half-life.[18]

A mean of 42 to 47% of a dose has been reported to be excreted in the urine as unchanged chloroquine and 7 to 12% as monodesethylchloroquine.[2] Various estimates of the terminal elimination half-life of chloroquine range from several days to up to 2 months, but its slow release from tissues ensures that small amounts may still be detected after a year.[18,19]

1. Hellgren U, *et al.* On the question of interindividual variations in chloroquine concentrations. *Eur J Clin Pharmacol* 1993; **45:** 383–5.
2. Gustafsson LL, *et al.* Disposition of chloroquine in man after single intravenous and oral doses. *Br J Clin Pharmacol* 1983; **15:** 471–9.
3. Adelusi SA, *et al.* Kinetics of the uptake and elimination of chloroquine in children with malaria. *Br J Clin Pharmacol* 1982; **14:** 483–7.
4. Walker O, *et al.* Single dose disposition of chloroquine in kwashiorkor and normal children—evidence for decreased absorption in kwashiorkor. *Br J Clin Pharmacol* 1987; **23:** 467–72.
5. White NJ, *et al.* Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. *N Engl J Med* 1988; **319:** 1493–1500.
6. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
7. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
8. Mahmoud BM, *et al.* Significant reduction in chloroquine bioavailability following coadministration with the Sudanese beverages aradaib, karkadi and lemon. *J Antimicrob Chemother* 1994; **33:** 1005–9.
9. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
10. Tulpule A, Krishnaswamy K. Chloroquine kinetics in the undernourished. *Eur J Clin Pharmacol* 1983; **24:** 273–6.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Phillips RE, *et al.* Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria. *BMJ* 1986; **293:** 13–16.
13. Frisk-Holmberg M, *et al.* The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in healthy subjects. *Eur J Clin Pharmacol* 1984; **26:** 521–30.
14. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
15. Walker O, *et al.* Characterization of chloroquine plasma protein binding in man. *Br J Clin Pharmacol* 1983; **15:** 375–7.
16. Ofori-Adjei D, *et al.* Protein binding of chloroquine enantiomers and desethylchloroquine. *Br J Clin Pharmacol* 1986; **22:** 356–8.
17. Gustafsson LL, *et al.* Pitfalls in the measurement of chloroquine concentrations. *Lancet* 1983; **i:** 126.
18. Ette EI, *et al.* Pharmacokinetics of chloroquine and some of its metabolites in healthy volunteers: a single dose study. *J Clin Pharmacol* 1989; **29:** 457–62.
19. Gustafsson LL, *et al.* Chloroquine excretion following malaria prophylaxis. *Br J Clin Pharmacol* 1987; **24:** 221–4.

Distribution into breast milk. Studies[1,2] have suggested that it is safe for mothers to breast feed when they are receiving chloroquine for treatment of malaria. Although chloroquine and its monodesethyl metabolite are distributed into breast milk, it has been estimated that the amount that would be consumed by an infant is well below the therapeutic range and separate chemoprophylaxis for the infant is required.

There appears to be no data on the excretion of hydroxychloroquine in milk after doses appropriate for the prevention or treatment of malaria, but hydroxychloroquine has been detected in breast milk from 2 mothers receiving doses of 400 mg daily for SLE or rheumatoid arthritis.[3,4] One group of workers estimated that, calculated on a body-weight basis, a 9-month-old infant could receive about 2% of a maternal dose via breast feeding.[3]

1. Ogunbona FA, *et al.* Excretion of chloroquine and desethylchloroquine in human milk. *Br J Clin Pharmacol* 1987; **23:** 473–6.
2. Akintonwa A, *et al.* Placental and milk transfer of chloroquine in humans. *Ther Drug Monit* 1988; **10:** 147–9.
3. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; **17:** 368–9.
4. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; **28:** 357.

Uses and Administration

Chloroquine is a 4-aminoquinoline antimalarial used in the treatment and prophylaxis of malaria. It has also been used in the treatment of hepatic amoebiasis, lupus erythematosus, light-sensitive skin eruptions, and rheumatoid arthritis.

Chloroquine is used for the prophylaxis and treatment of malaria due to susceptible strains of *Plasmodium ovale, P. vivax*, and *P. malariae*. It has also been used for susceptible strains of *P. falciparum* but in most of the world *P. falciparum* is now resistant to chloroquine, which should *not* therefore be given for treatment. Chloroquine is a rapid-acting blood schizontocide with some gametocytocidal activity against *P. ovale, P. vivax, P. malariae*, and immature gametocytes of *P. falciparum*. Since it has no activity against exoerythrocytic forms, it does not produce a radical cure of vivax or ovale malarias. The mechanism of action of chloroquine against blood schizonts remains unclear, but it may influence haemoglobin digestion by raising intravesicular pH in malaria parasite cells. It also interferes with synthesis of nucleoproteins by the parasite.

Chloroquine may be given as the phosphate, sulfate, or hydrochloride. Doses are normally expressed in terms of chloroquine base, and as a general guide:

- chloroquine base 300 mg is equivalent to about chloroquine phosphate 500 mg or chloroquine sulfate 400 mg
- chloroquine base 40 mg is equivalent to about chloroquine hydrochloride 50 mg

Oral bioavailability is increased when chloroquine is taken with food.

For the **treatment of malaria** caused by *P. vivax*, *P. ovale*, *P. malariae*, and the few remaining strains of chloroquine-sensitive *P. falciparum*, the usual total oral dose for adults and children is the equivalent of a total of about 25 mg of chloroquine base per kg bodyweight given over 3 days. This total dose has been given in a variety of ways. One way is to give 10 mg/kg, followed after 6 to 8 hours by 5 mg/kg, then 5 mg/kg daily for the next 2 days; alternatively, 10 mg/kg may be given daily for the first 2 days and 5 mg/kg on the third day. Sometimes the adult doses are not expressed in terms of body-weight but as 600 mg followed after 6 to 8 hours by 300 mg, then 300 mg daily for the next 2 days.

In severe and complicated malaria when the patient is unable to take oral medication, if chloroquine is to be used it can be given by injection. The intravenous route is preferred and a slow rate of infusion is essential, the required dose of 25 mg/kg being given in several infusions over 30 to 32 hours. Should the patient recover sufficiently to be able to take chloroquine orally then the intravenous regimen should be halted and oral therapy started.

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or in one of the few remaining areas where it is still sensitive to chloroquine, a dose equivalent to 300 mg of chloroquine base is given once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. For children, a weekly dose of 5 mg/kg has been recommended (but see also under Malaria, below). In areas of chloroquine-resistant malaria, but with a low risk of infection, chloroquine is given with proguanil; where there is a high risk of infection alternative antimalarial regimens are recommended.

In the treatment of **hepatic amoebiasis**, chloroquine is used with an intestinal amoebicide. The usual dose is the equivalent of 600 mg of chloroquine base daily for 2 days then 300 mg daily for 2 or 3 weeks. A dose of 6 mg/kg daily up to a maximum of 300 mg daily has been suggested for children.

When chloroquine is used for *long-term therapy* in conditions such as rheumatoid arthritis or lupus erythematosus, the dosage in obese patients should be calculated on the basis of lean body-weight in order to avoid excessive dosage.

In **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months, but if there is no improvement by then treatment should be stopped. The usual dose is the equivalent of chloroquine base 150 mg daily (maximum 2.5 mg/kg daily) or up to 3 mg/kg daily in children. For precautions and guidelines concerning use by rheumatologists see under Effects on the Eyes, above.

In discoid and systemic **lupus erythematosus** chloroquine is used in a dose equivalent to 150 mg (maximum 2.5 mg/kg) of base daily; children are given a dose of up to 3 mg/kg daily.

In the management of **light-sensitive skin eruptions**, adults may be given the equivalent of 150 to 300 mg of chloroquine base daily during periods of intense light exposure; children may be given up to 3 mg/kg.

Amoebiasis. For a discussion of the treatment of amoebiasis with mention of chloroquine for hepatic amoebiasis, see p.822.

Inflammatory disorders. Chloroquine and hydroxychloroquine possess anti-inflammatory properties and they have been tried or used with some benefit in a range of inflammatory conditions which often have an immunological basis, although they rarely constitute first-line therapy in these disorders. Such conditions include rheumatoid arthritis and SLE (see under Hydroxychloroquine, p.604), ulcerative colitis,[1] infantile interstitial pneumonitis,[2,3] asthma,[4] giant cell arteritis,[5] and various skin disorders (see below). The mode of action in these conditions is unclear. Results of studies have been conflicting but it does appear that chloroquine and hydroxychloroquine might have some immunosuppressive effects.[6,7]

1. Mayer L, Sachar DB. Efficacy of chloroquine in the treatment of inflammatory bowel disease. *Gastroenterology* 1988; **94:** A293.
2. Springer C, *et al.* Chloroquine treatment in desquamative interstitial pneumonia. *Arch Dis Child* 1987; **62:** 76–7.
3. Kerem E, *et al.* Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. *J Pediatr* 1990; **116:** 61–7.
4. Charous BL. Open study of hydroxychloroquine in the treatment of severe symptomatic or corticosteroid-dependent asthma. *Ann Allergy* 1990; **65:** 53–8.
5. Le Guennec P, *et al.* Management of giant cell arteritis: value of synthetic antimalarial agents: a retrospective study of thirty six patients. *Rev Rhum* 1994; **61:** 423–8.
6. Bygbjerg IC, Flachs H. Effect of chloroquine on human lymphocyte proliferation. *Trans R Soc Trop Med Hyg* 1986; **80:** 231–5.
7. Prasad RN, *et al.* Immunopharmacology of chloroquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 168–9.

Malaria. The overall treatment and prophylaxis of malaria and the place of chloroquine in current recommendations are discussed on p.594.

TREATMENT. In the treatment of patients with chloroquine-sensitive falciparum malaria studies have found chloroquine to be at least as effective as quinine in both uncomplicated and severe infections. However, very few areas exist where *Plasmodium falciparum* remains sensitive to chloroquine. There are also reports of resistance to chloroquine in *P. vivax*.[1]

Treatment with chloroquine is usually by mouth, adults and children being given the equivalent of 25 mg of chloroquine base per kg body-weight over 3 days. Any chloroquine lost through vomiting needs to be replaced by additional doses.[2]

Intravenous therapy has been used if the infection is severe or oral dosage is not possible. There should be close monitoring for hypotension and other signs of cardiovascular toxicity. The intramuscular or subcutaneous routes have been used if intravenous dosage is not possible. Patients should be transferred to oral therapy as soon as possible and treatment continued until a total dose equivalent to 25 mg of the base per kg has been given.

If injections cannot be given a chloroquine suspension or syrup appears to be well absorbed when given by nasogastric tube even in comatose patients. Rectal use in young children has also produced beneficial responses.[3,4]

PROPHYLAXIS. The widespread prevalence of strains of *P. falciparum* resistant to chloroquine has considerably diminished the value of chloroquine for malaria chemoprophylaxis and has made recommendations increasingly complex (see p.594). If chloroquine is used for prophylaxis it is usually given with proguanil. For **adults** a dose equivalent to 300 mg of chloroquine base is given by mouth once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. Some countries advise the use of 100 mg daily for 6 days a week. For **children**, a weekly dose of chloroquine base 5 mg/kg has been recommended, although UK malaria experts[5] have suggested the following prophylactic doses for children based on fractions of the adult dose of 300 mg weekly:

- under 6.0 kg (0 to 12 weeks of age), one-eighth the adult dose
- 6.0 to 9.9 kg (3 to 11 months), one-quarter the adult dose
- 10.0 to 15.9 kg (1 year to 3 years 11 months), three-eighths the adult dose
- 16.0 to 24.9 kg (4 years to 7 years 11 months), half the adult dose
- 25.0 to 44.9 kg (8 years to 12 years 11 months), three-quarters the adult dose
- over 45 kg (13 years and over), the adult dose

They noted that body-weight was a better guide to dosage than age for children over 6 months.

1. Whitby M. Drug resistant Plasmodium vivax malaria. *J Antimicrob Chemother* 1997; **40:** 749–52.
2. WHO. *WHO model formulary.* Geneva: WHO, 2004.
3. Westman L, *et al.* Rectal administration of chloroquine for treatment of children with malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 446.
4. Antia-Obong OE, *et al.* Chloroquine phosphate suppositories in the treatment of childhood malaria in Calabar, Nigeria. *Curr Ther Res* 1995; **56:** 928–35.
5. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Porphyria cutanea tarda. Chloroquine and hydroxychloroquine have been used with some benefit in the treatment of porphyria cutanea tarda (p.1448) and low doses (such as chloroquine phosphate 125 mg or hydroxychloroquine sulfate 200 mg given twice weekly) have been considered by some to be useful in patients unsuitable for phlebotomy.[1-4] However, the acute increase in urinary porphyrins and fall in hepatic porphyrin content produced by these drugs have been associated with a variable degree of hepatotoxicity[5,6] and others prefer to use desferrioxamine.[7]

1. Grossman ME, *et al.* Porphyria cutanea tarda. *Am J Med* 1979; **67:** 277–86.
2. Cainelli T, *et al.* Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1983; **108:** 593–600.
3. Ashton RE, *et al.* Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; **111:** 609–13.
4. Stölzel U, *et al.* Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. *Arch Dermatol* 2003; **139:** 309–13.
5. Scholnick PL, *et al.* The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol* 1973; **61:** 226–32.
6. Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. *Acta Derm Venereol* 2007; **87:** 401–5.
7. Rocchi E. Treatment of porphyria cutanea tarda. *Br J Dermatol* 1987; **116:** 139–40.

Rheumatoid arthritis. For reference to the use of chloroquine in the treatment of rheumatoid arthritis, see under Hydroxychloroquine, p.604.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p.1512) as alternatives or adjuncts to corticosteroid therapy.

References.

1. O'Leary TJ, *et al.* The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; **315:** 727–30.
2. Adams JS, *et al.* Effective reduction in the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia with short-course chloroquine therapy. *Ann Intern Med* 1989; **111:** 437–8.
3. DeSimone DP, *et al.* Granulomatous infiltration of the talus and abnormal vitamin D and calcium metabolism in a patient with sarcoidosis: successful treatment with hydroxychloroquine. *Am J Med* 1989; **87:** 694–6.
4. Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. *J Am Acad Dermatol* 1990; **23:** 487–9.
5. Zic JA, *et al.* Treatment of cutaneous sarcoidosis with chloroquine: review of the literature. *Arch Dermatol* 1991; **127:** 1034–40.
6. Baltzan M, *et al.* Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999; **160:** 192–7.

Skin disorders. In addition to their use in lupus erythematosus hydroxychloroquine and chloroquine have been tried in a number of other skin disorders including polymorphic light eruptions[1] (see Photosensitivity Disorders, p.1581), lichen planus[2,3] (p.1580), cutaneous symptoms of dermatomyositis (p.1510), erythema nodosum,[4,5] and recurrent erythema multiforme (p.1580). It has also been tried in mild type 2 lepra reactions (erythema nodosum leprosum, see p.176).

1. Murphy GM, *et al.* Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; **116:** 379–86.
2. Mostafa WZ. Lichen planus of the nail: treatment with antimalarials. *J Am Acad Dermatol* 1989; **20:** 289–90.
3. De Argila D, *et al.* Isolated lichen planus of the lip successfully treated with chloroquine phosphate. *Dermatology* 1997; **195:** 284–5.
4. Alloway JA, Franks LK. Hydroxychloroquine in the treatment of chronic erythema nodosum. *Br J Dermatol* 1995; **132:** 661–2.
5. Jarrett P, Goodfield MJD. Hydroxychloroquine and chronic erythema nodosum. *Br J Dermatol* 1996; **134:** 373.

Systemic lupus erythematosus. For reference to the use of chloroquine in cutaneous and systemic lupus erythematosus, see Hydroxychloroquine, p.605.

Preparations

BP 2008: Chloroquine Phosphate Tablets; Chloroquine Sulphate Injection; Chloroquine Sulphate Tablets;
USP 31: Chloroquine Hydrochloride Injection; Chloroquine Phosphate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Nivaquine; ***Austral.:*** Chlorquin; ***Austria:*** Resochin; ***Belg.:*** Nivaquine; ***Braz.:*** Clopirim†; Diclokin; Quinacris; ***Canad.:*** Aralen†; ***Cz.:*** Delagil; ***Denm.:*** Malarex; ***Fin.:*** Heliopar; ***Fr.:*** Nivaquine; ***Ger.:*** Resochin; Weimerquin; ***Hong Kong:*** Syncoquin; ***Hung.:*** Delagil; ***India:*** Clo-Kit; Emquin; Lariago; Maliago; Melubrin; Nivaquine-P; Resochin; ***Indon.:*** Avloclor; Malarex; Mexaquin; Resochin; Riboquin; ***Irl.:*** Avloclor; ***Israel:*** Avloclor; ***Mex.:*** Aralen; Maclorex; Paluken†; ***Neth.:*** Nivaquine; ***NZ:*** Chlorquin; Nivaquine; ***Philipp.:*** Aralen; Chlorofoz; ***Pol.:*** Arechin; ***Port.:*** Resochina; ***Rus.:*** Delagil (Делагил); ***S.Afr.:*** Daramal; Mirquin; Nivaquine; Plasmoquine; ***Spain:*** Resochin; ***Switz.:*** Chlorochin; Nivaquine; ***Thai.:*** Diroquine; Genocin; Maliaquine; P-Roquine†; ***UK:*** Avloclor; Malarivon; Malaviron; Nivaquine; ***USA:*** Aralen.

Multi-ingredient: ***Arg.:*** Tri-Emcortina†; ***Fr.:*** Savarine; ***S.Afr.:*** Daramal-Paludrine†.

Chlorproguanil Hydrochloride *(BANM, rINNM)*

Chlorproguanil, Chlorhydrate de; Chlorproguanili Hydrochloridum; Hidrocloruro de clorproguanil; M-5943. 1-(3,4-Dichlorophenyl)-5-isopropylbiguanide hydrochloride.

Хлорпрогуанила Гидрохлорид

$C_{11}H_{15}Cl_2N_5,HCl = 324.6.$

CAS — 537-21-3 (chlorproguanil); 15537-76-5 (chlorproguanil hydrochloride).

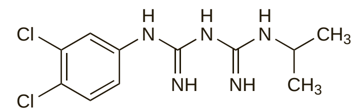

(chlorproguanil)

Profile

Chlorproguanil is a biguanide antimalarial used for malaria prophylaxis similarly to proguanil (p.609). It is sometimes given with dapsone. Combination with both dapsone and artesunate is also being investigated for malaria treatment.

◊ Reviews.

1. Bukirwa H, *et al.* Chlorproguanil-dapsone for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 17/05/05).

Halofantrine Hydrochloride *(BANM, USAN, rINNM)*

Halofantriinihydrokloridi; Halofantrin hydrochlorid; Halofantrine, Chlorhydrate d'; Halofantrine, chlorhydrate de; Halofantrin-hidroklorid; Halofantrinhydroklorid; Halofantrini hydrochloridum; Halofantrino hidrochloridas; Hidrocloruro de halofantrina; WR-171669. (*RS*)-3-Dibutylamino-1-(1,3-dichloro-6-trifluoromethyl-9-phenanthryl)propan-1-ol hydrochloride; 1,3-Dichloro-α-[2-(dibutylamino)ethyl]-6-trifluoromethyl-9-phenanthrene-methanol hydrochloride.

Галофантрина Гидрохлорид

$C_{26}H_{30}Cl_2F_3NO,HCl = 536.9.$

CAS — 69756-53-2 (halofantrine); 36167-63-2 (halofantrine hydrochloride); 66051-63-6 (±-halofantrine).

ATC — P01BX01.

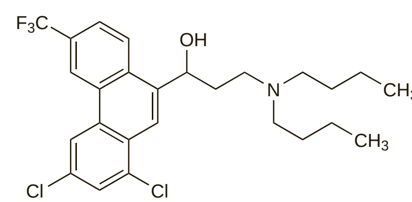

(halofantrine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Halofantrine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Adverse effects associated with halofantrine include diarrhoea, abdominal pain, nausea, vomiting, pruritus, and skin rash. Transient elevation of serum transaminases, intravascular haemolysis, and hypersensitivity reactions have also been reported.

Halofantrine can adversely affect the heart particularly by prolonging QT interval. Serious ventricular arrhythmias have been reported and fatalities have occurred. As a result it is contra-indicated in patients known to have a prolonged QT interval or those with cardiac disease or a family history of congenital QT prolongation, and also in those with unexplained syncopal attacks, thiamine deficiency, or electrolyte disturbances, or taking other arrhythmogenic drugs (see also Effects on the Heart, below, and Interactions, below).

Halofantrine is not recommended during pregnancy or breast feeding. It should not be taken on a full stomach since this increases its bioavailability and thus the risk of toxicity; after taking halofantrine, fatty food should be avoided for 24 hours.

Effects on the blood. Halofantrine has been associated with acute intravascular haemolysis.[1,2]

1. Vachon F, *et al.* Halofantrine and acute intravascular haemolysis. *Lancet* 1992; **340:** 909–10.
2. Mojon M, *et al.* Intravascular haemolysis following halofantrine intake. *Trans R Soc Trop Med Hyg* 1994; **88:** 91.

Effects on the heart. Prolonged PR[1,2] and QT[1-5] intervals have been reported in patients given halofantrine and there are individual reports of fatal cardiac arrest[1,5] and of torsade de pointes.[4] In 1994, the UK CSM[6] noted that QT interval prolongation occurred at recommended doses of halofantrine in the majority of patients and that worldwide there had been 14 reports of cardiac arrhythmias associated with halofantrine; 8 patients were known to have died. To reduce the risk of arrhythmias they stressed that halofantrine should *not* be taken with meals, with other drugs that may induce arrhythmias (e.g. quinine, chloroquine, and mefloquine; tricyclic antidepressants; antipsychotics; certain antiarrhythmics; and the antihistamines terfenadine and astemizole), or with drugs causing electrolyte disturbances. They also stated that it should *not* be given to patients known to have prolongation of the QT interval or with any form of cardiac disease associated with QT interval prolongation or ventricular arrhythmia (e.g. coronary heart disease, cardiomyopathy, or congenital heart disease). Some workers[2] have suggested ECG screening of all patients before starting treatment with halofantrine. Others[7] found pretreatment ECGs to be poorly predictive of QT lengthening during treatment. Children may experience serious cardiac effects at standard doses.[8]

1. Nosten F, *et al.* Cardiac effects of antimalarial treatment with halofantrine. *Lancet* 1993; **341:** 1054–6.
2. Monlun E, *et al.* Cardiac complications of halofantrine: a prospective study of 20 patients. *Trans R Soc Trop Med Hyg* 1995; **89:** 430–3.
3. Castot A, *et al.* Prolonged QT interval with halofantrine. *Lancet* 1993; **341:** 1541.
4. Monlun E, *et al.* Prolonged QT interval with halofantrine. *Lancet* 1993; **341:** 1541–2.
5. Anonymous. Halofantrine: revised data sheet. *WHO Drug Inf* 1993; **7:** 66–7.
6. Committee on Safety of Medicines/Medicines Control Agency. Cardiac arrhythmias with halofantrine (Halfan). *Current Problems* 1994; **20:** 6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023215 (accessed 18/06/08)
7. Matson PA, *et al.* Cardiac effects of standard-dose halofantrine therapy. *Am J Trop Med Hyg* 1996; **54:** 229–31.
8. Sowunmi A, *et al.* Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 446–8.

Effects on the skin. For a comparison of the incidence of pruritus associated with halofantrine and other antimalarials, see Effects on the Skin under Adverse Effects of Chloroquine, p.600.

Interactions

Halofantrine prolongs the QT interval and should not be used with other drugs that have the potential to induce cardiac arrhythmias, in particular the antimalarials mefloquine, chloroquine, and quinine, and also tricyclic antidepressants, phenothiazine antipsychotics, some antiarrhythmics (including amiodarone, disopyramide, flecainide, procainamide, quinidine, and the beta blocker sotalol), cisapride, and the antihistamines astemizole and terfenadine. Also, halofantrine should not be given with drugs that cause electrolyte disturbances (such as diuretics) or with HIV-protease inhibitors.

Grapefruit juice. In a study in 12 healthy patients, the bioavailability of halofantrine was reported to be increased when taken with grapefruit juice and this was found to accentuate halofantrine-associated QT prolongation.[1] It was suggested that grapefruit juice should be contra-indicated during use of halofantrine.

1. Charbit B, *et al.* Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. *Clin Pharmacol Ther* 2002; **72:** 514–23.

Tetracycline. Plasma concentrations of halofantrine were increased in 8 healthy subjects who were also given tetracycline.[1]

1. Bassi PU, *et al.* Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* 2004; **58:** 52–5.

Pharmacokinetics

Halofantrine is slowly and erratically absorbed after oral dosage, although it appears in the circulation within about 1 hour, peak concentrations occurring in 3 to 7 hours. Bioavailability of halofantrine is increased when given with or after food, particularly food high in fat content, and it must therefore be taken on an empty stomach because of the risk of cardiac toxicity. The elimination half-life of halofantrine varies considerably between individuals, but is generally about 1 to 2 days. Halofantrine is metabolised in the liver, its major metabolite being desbutylhalofantrine, which appears to be as active as the parent compound. Excretion of halofantrine is primarily via the faeces.

◊ References.

1. Karbwang J, Na Bangchang K. Clinical pharmacokinetics of halofantrine. *Clin Pharmacokinet* 1994; **27:** 104–19.
2. Watkins WM, *et al.* Halofantrine pharmacokinetics in Kenyan children with non-severe and severe malaria. *Br J Clin Pharmacol* 1995; **39:** 283–7.
3. Ohrt C, *et al.* Pharmacokinetics of an extended-dose halofantrine regimen in patients with malaria and in healthy volunteers. *Clin Pharmacol Ther* 1995; **57:** 525–32.

Uses and Administration

Halofantrine is a 9-phenanthrenemethanol antimalarial that has been used in the *treatment* of uncomplicated chloroquine-resistant falciparum and of chloroquine-resistant vivax malaria. Halofantrine is a blood schizontocide but has no activity against exoerythrocytic forms. Its value is limited by its unpredictable bioavailability and by cardiotoxicity. It should *not* be used where mefloquine has been used for prophylaxis (for cardiac hazard, see Effects on the Heart, above). Halofantrine should also *not* be used for malaria prophylaxis and is no longer recommended for standby treatment.

In the treatment of malaria, halofantrine hydrochloride has been given orally as 3 doses of 500 mg at intervals of 6 hours, on an empty stomach. Dosage for children is based on 24 mg/kg divided into 3 doses. The following doses have been recommended: 23 to 31 kg body-weight, 3 doses of 250 mg at intervals of 6 hours; 32 to 37 kg, 3 doses of 375 mg at intervals of 6 hours; over 37 kg, adult dose. A second course should be given after a week to patients with little or no previous exposure to malaria.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Halfan†; ***Fr.:*** Halfan; ***Ger.:*** Halfan†; ***Port.:*** Halfan; ***S.Afr.:*** Halfan; ***Spain:*** Halfan; ***Switz.:*** Halfan†.

Hydroxychloroquine Sulfate *(rINNM)*

Hydroxychloroquine, Sulfate d'; Hydroxychloroquine Sulphate *(BANM)*; Hydroxychloroquini Sulfas; Oxichlorochin Sulphate; Sulfato de hidroxicloroquina; Win-1258-2. 2-{*N*-[4-(7-Chloro-4-quinolylamino)pentyl]-*N*-ethylamino}ethanol sulphate.

Гидроксихлорохина Сульфат

$C_{18}H_{26}ClN_3O,H_2SO_4$ = 434.0.

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (hydroxychloroquine sulfate).

ATC — P01BA02.

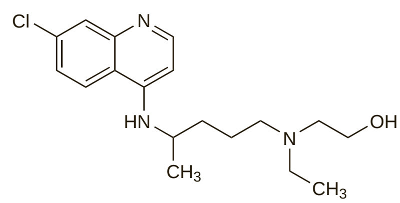

(hydroxychloroquine)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Hydroxychloroquine Sulphate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.5 to 5.5. Protect from light.

USP 31 (Hydroxychloroquine Sulfate). A white or practically white, odourless, crystalline powder. It exists in two forms, the usual form melting at about 240° and the other form at about 198°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions in water have a pH of about 4.5. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chloroquine, p.599.

Breast feeding. Hydroxychloroquine has been detected in human breast milk[1,2] but no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; **17:** 368–9.
2. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; **28:** 357.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy. With respect to retinopathy, precautions should be taken in patients undergoing long-term treatment, as described under Chloroquine on p.600.

Pregnancy. In a study[1] of 133 pregnancies in 90 women treated with hydroxychloroquine, no statistical difference in pregnancy outcome was found compared with a control group consisting of 70 pregnancies in 53 women. It was concluded that the findings supported preliminary evidence for the safety of hydroxychloroquine treatment in pregnancy, and that treatment should probably therefore be maintained during pregnancy in patients with SLE.

1. Costedoat-Chalumeau N, *et al.* Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum* 2003; **48:** 3207–11.

Interactions

As for Chloroquine, p.601.

Pharmacokinetics

The pharmacokinetics of hydroxychloroquine are similar to those of chloroquine (see p.602).

◊ References.

1. Tett SE, *et al.* Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 771–9.
2. Miller DR, *et al.* Steady-state pharmacokinetics of hydroxychloroquine in rheumatoid arthritis. *DICP Ann Pharmacother* 1991; **25:** 1302–5.
3. Ducharme J, *et al.* Enantioselective disposition of hydroxychloroquine after a single oral dose of the racemate to healthy subjects. *Br J Clin Pharmacol* 1995; **40:** 127–33.

Uses and Administration

Hydroxychloroquine sulfate is a 4-aminoquinoline antimalarial with actions similar to those of chloroquine (p.602), but is mainly used in the treatment of systemic and discoid lupus erythematosus and rheumatoid arthritis. It is also used in the treatment of light-sensitive skin eruptions.

Hydroxychloroquine sulfate is given orally.

In **lupus erythematosus** and **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months but if there is no improvement by then, treatment should be stopped. In the UK, treatment is usually started with 400 mg daily in divided doses with meals. In the USA, recommended initial doses are 400 to 600 mg daily for rheumatoid arthritis and 400 mg once or twice daily for lupus erythematosus. Doses are reduced to the minimum effective dose for maintenance; this is usually 200 to 400 mg daily but should not exceed 6.5 mg/kg daily (or 400 mg daily whichever is the smaller). To avoid excessive dosage in obese patients, special care is needed to calculate the dosage on the basis of lean body-weight. For further details, see under Effects on the Eyes in Chloroquine, p.600. In children, the minimum effective dose should be used up to a maximum of 6.5 mg/kg daily (or 400 mg daily whichever is the smaller).

Hydroxychloroquine sulfate is also used in similar doses for the treatment of **light-sensitive skin eruptions**, but treatment should only be given during periods of maximum exposure to light.

Hydroxychloroquine sulfate may be used in **malaria** both for treatment and prophylaxis, when chloroquine is not available, with the same limitations as for chloroquine. In the USA, a licensed dose for *prophylaxis* of malaria is 400 mg every 7 days; children may be given a weekly prophylactic dose of 6.5 mg/kg (up to a maximum of 400 mg). In *treating* an acute malarial attack, a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days; alternatively, a single dose of 800 mg has been given. In children, an initial dose of 13 mg/kg may be given, followed by 6.5 mg/kg after 6 hours and again on the second and third days.

Inflammatory disorders. For the use of hydroxychloroquine and chloroquine in a range of inflammatory conditions, see under Chloroquine, p.603 and under Rheumatoid Arthritis, below.

Malaria. The role of chloroquine and potentially therefore of hydroxychloroquine in the treatment and prophylaxis of malaria is discussed on p.594.

Porphyria cutanea tarda. For reference to the use of hydroxychloroquine in the treatment of porphyria cutanea tarda, see under the Uses and Administration of Chloroquine, p.603.

Rheumatoid arthritis. Hydroxychloroquine and chloroquine are used orally as disease-modifying antirheumatic drugs (DMARDs) in the management of **rheumatoid arthritis** (p.11) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease.[1] They are considered to be less effective than the other DMARDs but they are usually better tolerated and so may be preferred in patients with milder forms of the disease.[2] Additional benefit has been obtained using antimalarials with other DMARDs especially methotrexate and sulfasalazine,[3-5] although adverse effects may be more common. For reference to precautions to reduce the incidence of retinopathy, see under Effects on the Eyes in Adverse Effects of Chloroquine, p.600.

Generally the lowest effective dose should be used for maintenance to minimise toxicity; for hydroxychloroquine sulfate this should not exceed 6.5 mg/kg lean body-weight daily. Daily doses of 200 or 400 mg are commonly used but one study indicates that there is little advantage in using the higher dose.[6]

Experience with antimalarials to treat **juvenile idiopathic arthritis** (p.10) is limited and the results have been variable.[7,8]

Chloroquine and hydroxychloroquine have also been reported to be of use in **palindromic rheumatism**.[9-11]

1. Suarez-Almazor ME, *et al.* Antimalarials for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 17/05/05).
2. HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. *Am J Med* 1995; **98:** 156–68.
3. Clegg DO, *et al.* Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997; **24:** 1896–1902.
4. O'Dell JR. Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine in patients with rheumatoid arthritis. *Rheum Dis Clin North Am* 1998; **24:** 465–77.
5. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.
6. Pavelka K, *et al.* Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens. *Ann Rheum Dis* 1989; **48:** 542–6.
7. Brewer EJ, *et al.* Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. *N Engl J Med* 1986; **314:** 1269–76.
8. Grondin C, *et al.* Slow-acting antirheumatic drugs in chronic arthritis of childhood. *Semin Arthritis Rheum* 1988; **18:** 38–47.
9. Richardson MR, Zalin AM. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 741.
10. Hanonen P, *et al.* Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; **294:** 1289.
11. Youssef W, *et al.* Palindromic rheumatism: a response to chloroquine. *J Rheumatol* 1991; **18:** 35–7.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p.1512) as alternatives or adjuncts to corticosteroid therapy. For references to the use of hydroxychloroquine, see under Chloroquine, p.603.

Skin disorders. For reference to the use of hydroxychloroquine in a variety of skin disorders, see under Chloroquine, p.603.

Systemic lupus erythematosus. Antimalarials have been widely used in the treatment of lupus erythematosus (p.1513), particularly its cutaneous manifestations, although much of the evidence is based on case series and reports.[1] Hydroxychloroquine is most widely used, as it is thought to have fewer adverse effects than chloroquine, although any benefit with chloroquine generally starts to become evident within several weeks of starting treatment, whereas it may take up to 2 months for any effect of hydroxychloroquine to be seen. For extracutaneous disease, antimalarials are often combined with other drugs; treatment may be continued for many years. For reference to precautions to reduce the risk of retinopathy see Effects on the Eyes, under Adverse Effects of Chloroquine, p.600.

1. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol* 2005; **6:** 1–11.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p.1189) is usually with an anticoagulant. Hydroxychloroquine has been described by some as an antiplatelet agent[1] and although its mechanism of action is uncertain the incidence of fatal pulmonary embolism has been reduced in patients given hydroxychloroquine prophylactically after total hip replacement;[2] the usual daily divided oral dose was about 800 mg from the day before surgery until discharge; larger doses had been used.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308:** 235–46.
2. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. *Am J Med* 1988; **85:** (suppl 4A): 57–61.

Preparations

BP 2008: Hydroxychloroquine Tablets;
USP 31: Hydroxychloroquine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Axokine; Evoquin; Metirel; Narbon; Plaquenil; Polirreumin; ***Austral.:*** Plaquenil; ***Austria:*** Plaquenil; ***Belg.:*** Plaquenil; ***Braz.:*** Plaquinol; Reuquinol; ***Canad.:*** Apo-Hydroxyquine; Plaquenil; ***Chile:*** Plaquinol; ***Cz.:*** Plaquenil; ***Denm.:*** Ercoquin; Plaquenil; ***Fin.:*** Oxiklorin; Plaquenil†; ***Fr.:*** Plaquenil; ***Ger.:*** Quensyl; ***Gr.:*** Plaquenil; ***Hong Kong:*** Plaquenil; ***India:*** HCQS; ***Irl.:*** Plaquenil; ***Israel:*** Plaquenil; ***Ital.:*** Plaquenil; ***Malaysia:*** Plaquenil; ***Mex.:*** Plaquenil; ***Neth.:*** Plaquenil; ***Norw.:*** Plaquenil; ***NZ:*** Plaquenil; ***Philipp.:*** Plaquenil; ***Port.:*** Plaquinol; ***Rus.:*** Plaquenil (Плаквенил); ***Singapore:*** Plaquenil; ***Spain:*** Dolquine; ***Swed.:*** Plaquenil; ***Switz.:*** Plaquenil; ***Thai.:*** Hydroquin; Plaquenil; ***UK:*** Plaquenil; ***USA:*** Plaquenil; ***Venez.:*** Plaquinol.

Lumefantrine *(BAN, rINN)*

Benflumelol; Benflumetol; Lumefantrina; Luméfantrine; Lumefantrinum. 2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol.

Люмефантрин

$C_{30}H_{32}Cl_3NO$ = 528.9.

CAS — 82186-77-4.

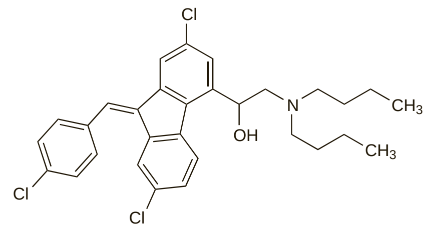

Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

Adverse effects associated with lumefantrine in combination with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue. Lumefantrine-artemether should be given with caution in severe hepatic or renal impairment and ECG and blood potassium monitored.

Effects on the blood. Severe haemolytic anaemia necessitating corticosteroid treatment, blood transfusion, and haemodialysis occurred in a patient after taking 8 lumefantrine-artemether tablets after a malarial attack.[1] It was considered that, given its molecular similarity to other antimalarials known to cause haemolysis, the causative drug was probably lumefantrine.

1. Mérat S, *et al.* Case report: combination artemether-lumefantrine and haemolytic anaemia following a malarial attack. *Trans R Soc Trop Med Hyg* 2003; **97:** 433–4.

Pharmacokinetics

The bioavailability of lumefantrine after oral doses is variable; absorption begins after a lag-time of up to 2 hours and bioavailability is substantially increased when given with food, particularly meals high in fat. Peak plasma concentrations occur after about 6 to 8 hours. Lumefantrine is almost completely protein bound. It is considered to be metabolised mainly in the liver and is excreted in the faeces. The elimination half-life is reported to be between 4 to 6 days in patients with malaria.

◊ References.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; **37:** 105–25.
2. Ezzet F, *et al.* Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 2000; **44:** 697–704.

Uses and Administration

Lumefantrine is a dichlorobenzylidine derivative given by mouth in combination with artemether (p.598) for the treatment of uncomplicated falciparum malaria. It is a blood schizontocide with a relatively slow onset of action but it has a longer duration of action than artemether.

The following doses are recommended by WHO; 6 doses in total are given, starting at diagnosis and repeated after 8, 24, 36, 48, and 60 hours. Each dose is:

- adults and children weighing over 34 kg, lumefantrine 480 mg with artemether 80 mg
- children 5 to 14 kg, lumefantrine 120 mg with artemether 20 mg
- children 15 to 24 kg, lumefantrine 240 mg with artemether 40 mg
- children 25 to 34 kg, lumefantrine 360 mg with artemether 60 mg

◊ References.

1. Omari AAA, *et al.* Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 19/07/06).
2. Omari AAA, *et al.* Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/07/06).
3. Kokwaro G, *et al.* Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. *Expert Opin Pharmacother* 2007; **8:** 75–94.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Riamet; ***Austria:*** Riamet; ***Belg.:*** Co-Artesiane; ***Cz.:*** Riamet; ***Fr.:*** Riamet; ***Ger.:*** Riamet; ***Gr.:*** Riamet; ***Hong Kong:*** Riamet†; ***Neth.:*** Riamet; ***Norw.:*** Riamet†; ***Port.:*** Riamet; ***S.Afr.:*** Coartem; ***Swed.:*** Riamet; ***Switz.:*** Riamet; ***Thai.:*** Coartem; ***UK:*** Riamet.

Mefloquine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mefloquina; Meflochin-hydrochlorid; Meflokiini-hydrokloridi; Meflokin-hidroklorid; Meflokinhydroklorid; Meflokvino hidrochloridas; Méfloquine, chlorhydrate de; Mefloquini hydrochloridum; Ro-21-5998 (mefloquine); Ro-21-5998/001 (mefloquine hydrochloride); WR-142490 (mefloquine). (*RS*)-[2,8-Bis(trifluoromethyl)-4-quinolyl]-(*SR*)-(2-piperidyl)methanol hydrochloride.

Мефлохина Гидрохлорид

$C_{17}H_{16}F_6N_2O,HCl$ = 414.8.

CAS — 53230-10-7 (mefloquine); 51773-92-3 (mefloquine hydrochloride).

ATC — P01BC02.

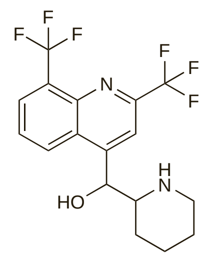

(mefloquine)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 31 (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Sorption. For reference to loss of mefloquine hydrochloride from solutions during membrane filtration, see Chloroquine, p.599.

Stability. A report of the photolytic degradation of mefloquine hydrochloride in water.[1]

1. Tønnesen HH, Grislingaas A-L. Photochemical stability of biologically active compounds II: photochemical decomposition of mefloquine in water. *Int J Pharmaceutics* 1990; **60:** 157–62.

Adverse Effects

Since mefloquine has a long elimination half-life, adverse effects may occur or persist up to several weeks after the last dose.

The most frequent adverse effects of mefloquine are nausea, diarrhoea, vomiting, abdominal pain, anorexia, headache, dizziness, loss of balance, somnolence, and sleep disorders, notably insomnia and abnormal dreams.

Neurological or psychiatric disturbances have also been reported with mefloquine and include sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus and hearing impairment, convulsions, anxiety, depression, confusion, hallucinations, panic attacks, emotional instability, aggression and agitation, and acute psychosis. There have been rare reports of suicidal ideation.

Other adverse effects include skin rashes, pruritus and urticaria, hair loss, muscle weakness, myalgia, liver function disturbances, and very rarely thrombocytopenia and leucopenia. There have been rare occurrences of erythema multiforme and Stevens-Johnson syndrome. Anaphylaxis has occurred rarely. Cardiovascular effects have included hypotension, hypertension, tachycardia or palpitations, bradycardia, QT prolongation, and other minor ECG changes. There have been isolated cases of atrioventricular block.

Incidence of adverse effects. The frequencies of adverse effects reported[1] in 134 soldiers given mefloquine hydrochloride 250 mg weekly for malaria chemoprophylaxis were: diarrhoea (48%), nausea (13%), vomiting (2%), headache (13%), and dizziness (7%). All of 7 healthy subjects who received a dose of mefloquine hydrochloride 15 mg/kg had symptoms that included vertigo, nausea, dizziness, and lightheadedness.[2] The manufacturers reported that dizziness occurred in 24% of patients with malaria treated with 750 mg of mefloquine, in 38% treated with 1000 mg, and in 96% treated with 1500 mg; splitting a dose into two doses given 8 hours apart can reduce the incidence of dizziness.[3] A prospective study involving 3673 patients found that anorexia, nausea, vomiting, dizziness, and sleep disorders were 1.1 to 1.4 times more frequent in patients receiving mefloquine 25 mg/kg for treatment of malaria than in those receiving 15 mg/kg, and that vomiting could be reduced by 40% if the higher dose was split and given as 15 mg/kg followed by a further 10 mg/kg after 16 to 24 hours.[4] The frequency of adverse effects is reported to be higher in subjects who become dehydrated.[5]

There has been concern that the adverse effects of mefloquine, especially neuropsychiatric reactions, might limit its use for the prophylaxis of malaria but, as discussed under Effects on the Nervous System, below, the incidence of adverse effects does not appear to be greater than with other prophylactic schedules.

1. Arthur JD, *et al.* Mefloquine prophylaxis. *Lancet* 1990; **335:** 972.
2. Patchen LC, *et al.* Neurologic reactions after a therapeutic dose of mefloquine. *N Engl J Med* 1989; **321:** 1415.
3. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
4. ter Kuile FO, *et al.* Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bull WHO* 1995; **73:** 631–42.
5. Perry IC. Malaria prophylaxis. *BMJ* 1995; **310:** 1673.

Effects on the blood. Agranulocytosis was reported[1] in a patient with malaria 48 hours after treatment with a 1250-mg course of mefloquine. The patient had previously taken 250 mg of mefloquine weekly for 7 weeks without side-effects. Thrombotic thrombocytopenic purpura has been reported[2] in a patient after taking two standard weekly doses of mefloquine for malaria prophylaxis. Symptoms improved after plasmapheresis.

1. Hennequin C, *et al.* Agranulocytosis during treatment with mefloquine. *Lancet* 1991; **337:** 984.
2. Fiaccadori E, *et al.* Thrombotic-thrombocytopenic purpura following malaria prophylaxis with mefloquine. *J Antimicrob Chemother* 2006; **57:** 160–1.

Effects on the liver. Acute fatty liver was reported[1] in a patient who had recently received mefloquine 250 mg weekly for 5 weeks for malaria prophylaxis. Symptoms resolved with fluid, electrolyte, and albumin replacement, after stopping mefloquine. In another report,[2] acute elevation of liver transaminases, associated with severe acute hepatitis, occurred in a patient with pre-existing mild hepatic impairment following a 6-week course of mefloquine 250 mg weekly.

1. Grieco A, *et al.* Acute fatty liver after malaria prophylaxis with mefloquine. *Lancet* 1999; **353:** 295–6.
2. Gotsman I, *et al.* Mefloquine-induced acute hepatitis. *Pharmacotherapy* 2000; **20:** 1517–19.

Effects on the nervous system. Neuropsychiatric reactions have been associated with the use of mefloquine although various figures have been reported for their frequency. The UK CSM has quoted[1] figures of 1 in 10 000 to 1 in 20 000 for severe reactions to *prophylactic* doses and similarly the manufacturers report that 1 in 10 000 patients given mefloquine prophylaxis will have serious problems. Others consider that the incidence of serious reactions is extremely low,[2] with a frequency of about 1 in 80 000. The manufacturers have also reported that most reactions in patients taking mefloquine for prophylaxis appear to occur after the first dose and have suggested that monitoring after the first dose could identify 40% of those at risk of neuropsychiatric effects.[3] Some authorities consider that over 75% of such reactions to mefloquine are apparent by the third dose.[4] This may allow for tolerability problems with mefloquine prophylaxis to be identified before travel. There has been much discussion on the comparative tolerability of antimalarials used for chemoprophylaxis. The incidence of adverse events, including neuropsychiatric events, was comparable for mefloquine and chloroquine in 2 uncontrolled questionnaire studies, one in tourists[5] and one in US Peace Corps volunteers.[6] However, in a more recent questionnaire in travellers,[7] although the incidence of reported adverse events was similar for mefloquine and chloroquine plus proguanil, neuropsychiatric adverse events were significantly more common in mefloquine recipients. In two randomised controlled studies,[8,9] both in military personnel, there was no difference between CNS symptoms in those given weekly mefloquine and those receiving chloroquine (with or without proguanil). In one of these studies,[9] a subgroup receiving a loading dose of mefloquine daily for 3 days initially had a higher incidence of CNS events. A review[10] of 10 controlled studies found no significant difference in the rates of withdrawal and overall incidence of adverse effects for mefloquine and alternative prophylactic regimens, but mefloquine was more likely than other drugs to cause insomnia and fatigue. Women may be at greater risk of adverse effects than men, and WHO has commented that the occurrence of such adverse effects may mean that only highly motivated occupational subgroups or individuals at high risk of infection with chloroquine-resistant malaria will be willing to continue with mefloquine prophylaxis.[11]

Neuropsychiatric reactions are more frequent after the higher doses of mefloquine used for *treatment* than those used for prophylaxis. Some workers have estimated that overall 1 in 8000 mefloquine users have such reactions, with the incidence 60 times higher after treatment than after prophylaxis.[12] Other workers who have used mefloquine in nearly 14 000 treatments calculated that the overall frequency of serious neuropsychiatric reactions was 1 per 1754 treatments; it therefore appeared that serious neuropsychiatric reactions were 10 times more probable after treatment than with prophylactic use of mefloquine.[13]

A severe neurological syndrome associated with mefloquine treatment, with agitation, delirium, stupor, hyperpyrexia, mydriasis, and generalised rigors responded rapidly to treatment with physostigmine, suggesting a central anticholinergic aetiology.[14]

A discrete post-malaria neurological syndrome (including an acute confusional state or acute psychosis, convulsions, and tremor) has been seen on recovery from falciparum malaria and there appeared to be a strong association with mefloquine although it was not the only risk factor.[15] Nevertheless the risk was considered unacceptable and the recommendation made[15] that, where there was an effective alternative drug, mefloquine should not be used after initial treatment of severe malaria.

Emergence delirium during recovery from general anaesthesia after mefloquine prophylaxis has been reported in 3 cases.[16]

1. Committee on Safety of Medicines. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems* 1996; **22:** 6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023214 (accessed 18/06/08)
2. Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996; **347:** 326.
3. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; **322:** 1752–3.
4. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. *Commun Dis Public Health* 2003; **6:** 180–99. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol6/No3/6(3)p180-99.pdf (accessed 06/07/06)
5. Steffen R, *et al.* Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341:** 1299–1303.
6. Lobel HO, *et al.* Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341:** 848–51.
7. Barrett PJ, *et al.* Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996; **313:** 525–8. Correspondence. *ibid.*; 1552–4.
8. Croft AMJ, *et al.* Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997; **91:** 199–203.
9. Boudreau E, *et al.* Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol* 1993; **44:** 257–65.
10. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *BMJ* 1997; **315:** 1412–16. Correspondence. *ibid.* 1998; **316:** 1980–1.
11. Anonymous. Mefloquine effectiveness impaired by high withdrawal rates. *WHO Drug Inf* 1998; **12:** 7–8.
12. Weinke T, *et al.* Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991; **45:** 86–91.
13. Luxemburger C, *et al.* Mefloquine for multidrug-resistant malaria. *Lancet* 1991; **338:** 1268.
14. Speich R, Haller A. Central anticholinergic syndrome with the antimalarial drug mefloquine. *N Engl J Med* 1994; **331:** 57–8.
15. Mai NTH, *et al.* Post-malaria neurological syndrome. *Lancet* 1996; **348:** 917–21.
16. Gullahorn GM, *et al.* Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet* 1993; **341:** 632.

Effects on the oesophagus. Oesophageal ulceration in one patient and discomfort in another 4 was attributed to swallowing mefloquine tablets with insufficient fluid.[1]

1. Phillips M. Antimalarial mefloquine. *Med J Aust* 1994; **161:** 227–8.

Effects on the skin. Isolated cases of Stevens-Johnson syndrome,[1] severe facial lesions,[2] exfoliative dermatitis,[3] toxic epidermal necrolysis,[4] and cutaneous vasculitis[5] have been associated with use of mefloquine for malaria prophylaxis.

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p.600.

1. Van den Enden E, *et al.* Mefloquine-induced Stevens-Johnson syndrome. *Lancet* 1991; **337:** 683.
2. Shlim DR. Severe facial rash associated with mefloquine. *JAMA* 1991; **266:** 2560.
3. Martin GJ, *et al.* Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; **16:** 341–2.
4. McBride SR, *et al.* Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997; **349:** 101.
5. White AC, *et al.* Cutaneous vasculitis associated with mefloquine. *Ann Intern Med* 1995; **123:** 894.

Overdosage. Cardiac, hepatic, and neurological symptoms have been reported in a patient who inadvertently received 5.25 g of mefloquine over 6 days.[1] All symptoms disappeared rapidly when mefloquine was stopped.

1. Bourgeade A, *et al.* Intoxication accidentelle à la méfloquine. *Presse Med* 1990; **19:** 1903.

Precautions

Tasks requiring fine coordination such as driving should not be undertaken during treatment with mefloquine or for at least 3 weeks afterwards; in the case of prophylactic use, care should be exercised while taking mefloquine and for at least 3 weeks after stopping it. The use of mefloquine for malaria prophylaxis is contra-indicated in patients with a history of psychiatric (including depression) or convulsive disorders. Increased plasma concentrations may occur in patients with hepatic impairment. Mefloquine should be stopped should symptoms suggestive of psychiatric disturbance occur during prophylaxis, and an alternative antimalarial substituted. Mefloquine is teratogenic in *animals* and its use during pregnancy is best avoided; however, in areas of chloroquine-resistant *Plasmodium falciparum*, WHO states that mefloquine may normally be taken for malaria prophylaxis during the second and third trimesters of pregnancy. It is recommended that women should also avoid becoming pregnant during, and for 3 months after, mefloquine use and that mothers should not breast feed while taking mefloquine. Mefloquine should be used with caution in patients with renal impairment and in those with cardiac conduction disorders.

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that mefloquine may be safe for use in such patients, see under Precautions for Chloroquine, p.601.

Pregnancy. Licensed product information for mefloquine reports that it is teratogenic in *rodents*. There is limited information on its effects in humans. One study in Thailand cited by WHO[1] found no difference between mefloquine and quinine in pregnancy outcome, but the numbers of treated patients who were in their first trimester were very small and its use should be kept to a minimum in that stage of pregnancy. Further spontaneous reports of exposure to mefloquine during the first trimester of pregnancy collected by the manufacturer revealed 24 fetal abnormalities and 17 spontaneous or missed abortions in 358 pregnancies, although a causal relationship was not established,[2] and a later study by the manufacturer involving 1627 reports of exposure during pregnancy appeared to show a similar incidence of congenital malformation to that in offspring of unexposed women.[3] In 53 army service women who inadvertently used mefloquine in pregnancy, and for whom pregnancy outcome was known, there were 17 elective abortions, 12 spontaneous abortions, one molar pregnancy, and 23 healthy live births, with no major congenital malformations.[4] The rate of spontaneous abortions was considered high.[4] A prospective cohort study involving 236 pregnant women who received an antimalarial in the first trimester did not find an increased risk of spontaneous abortion or anomaly in women who took mefloquine compared with other antimalarials, and the rate of spontaneous abortion was comparable with background rates.[5]

Confidence in the safety of mefloquine has increased, and WHO now considers mefloquine suitable for malaria prophylaxis in the second and third trimesters;[6] WHO has stated its use is not recommended in the first trimester because of limited information on its safety. Authorities in the UK consider that use may sometimes be justified in the first trimester in areas of high risk of acquiring falciparum malaria; inadvertent use is not an indication to terminate pregnancy.[7]

Pregnancy should be avoided during and for 3 months after prophylactic use.

1. WHO. Practical chemotherapy of malaria: report of a WHO scientific group. *WHO Tech Rep Ser 805* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_805.pdf (accessed 18/06/05)
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Vanhauwere B, *et al.* Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. *Am J Trop Med Hyg* 1998; **58:** 17–21.
4. Smoak BL, *et al.* The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army service women. *J Infect Dis* 1997; **176:** 831–3.
5. Phillips-Howard PA, *et al.* Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Travel Med* 1998; **5:** 121–6.
6. WHO. *International travel and health.* 2008 ed. Available at: http://www.who.int/ith/ (accessed 18/06/08)
7. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Interactions

Halofantrine should not be given with or after mefloquine because of the increased potential to induce hazardous cardiac arrhythmias, as discussed under Effects on the Heart on p.603. There is an increased risk of convulsions when mefloquine is used with chloroquine, quinidine, or quinine.

Alcohol. There has been a case report[1] of a patient who had neuropsychiatric disturbances after consuming a large quantity of alcohol with mefloquine; subsequent abstinence from alcohol led to complete reversal of the reactions.

1. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. *Can Med Assoc J* 1995; **152:** 515–17.

Antibacterials. Studies in healthy subjects have indicated that *ampicillin*[1] or *tetracycline*[2] could increase blood concentrations of mefloquine. Convulsions have been precipitated in 3 non-epileptic patients who were given mefloquine and the quinolone antibacterials *ciprofloxacin*, *ofloxacin*, or *sparfloxacin*.[3]

1. Karbwang J, *et al.* Effect of ampicillin on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1991; **40:** 631–3.
2. Karbwang J, *et al.* Effect of tetracycline on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1992; **43:** 567–9.
3. Mangalvedhekar SS, *et al.* Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. *Natl Med J India* 2000; **13:** 47.

Antidepressants. Licensed product information for mefloquine states that in patients taking tricyclic antidepressants use of mefloquine may theoretically contribute to prolongation of the QT interval.

Antiepileptics. Licensed product information states that mefloquine may reduce seizure control by lowering the plasma concentration of antiepileptics, including carbamazepine, phenobarbital, and phenytoin. For the effect of mefloquine on *valproate*, see p.511. For its effect on *carbamazepine*, see p.475.

Antihistamines. Giving mefloquine with antihistamines may theoretically contribute to the prolongation of QT intervals; however, this is not considered to be an absolute contra-indication.

Antimalarials. It is well established that the use of *halofantrine* with or after mefloquine is contra-indicated because of the risk of hazardous cardiac arrhythmias. Mefloquine and other related compounds such as *quinine*, *quinidine*, and *chloroquine* may be given together only under close medical supervision because of possible additive cardiac toxicity; there is also an increased risk of convulsions.

A study in healthy subjects indicated that use of *primaquine* could increase blood concentrations of mefloquine and might increase the incidence of adverse effects due to mefloquine,[1] but others reported no such interaction.[2]

1. MacLeod CM, *et al.* Interaction of primaquine with mefloquine in healthy males. *J Clin Pharmacol* 1990; **30:** 841.
2. Karbwang J, *et al.* Pharmacokinetics of mefloquine in the presence of primaquine. *Eur J Clin Pharmacol* 1992; **42:** 559–60.

Antipsychotics. The use of mefloquine with *phenothiazines* or *pimozide* may theoretically contribute to prolonged QT intervals, although this is not considered to be an absolute contra-indication.

Cardiovascular drugs. It has been recommended that mefloquine should be used with extreme caution in patients also taking *antiarrhythmics*, *beta blockers*, *calcium-channel blockers*, or *digitalis*, until more was known about the risks of cardiotoxicity, since theoretically these drugs might contribute to prolongation of the QT interval. An increased risk of ventricular arrhythmias has been reported when mefloquine is given with *amiodarone*.

Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient who was taking *propranolol*.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Metoclopramide. Use with metoclopramide may increase plasma concentrations of mefloquine.[1]

1. Na Bangchang K, *et al.* The effect of metoclopramide on mefloquine pharmacokinetics. *Br J Clin Pharmacol* 1991; **32:** 640–1.

Vaccines. Unfortunately, conflicting advice has been issued concerning the use of mefloquine after typhoid vaccination, for details see p.2241.

Pharmacokinetics

The pharmacokinetics of mefloquine may be altered by malaria infection in a manner similar to those of quinine, the main effects being reductions in both its volume of distribution and its overall clearance.

Mefloquine is well absorbed from the gastrointestinal tract but there is marked interindividual variation in the time required to achieve peak plasma concentrations. Mefloquine is about 98% bound to plasma proteins and high concentrations have been reported in red blood cells. It is widely distributed throughout the body. Mefloquine has a long elimination half-life; mean values of about 21 days have been reported for some patients, although like other pharmacokinetic data on mefloquine there is considerable variation in reported figures. Subtherapeutic concentrations of mefloquine may persist in the blood for several months. Mefloquine is metabolised in the liver. Little of a dose is excreted in the urine and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.

Mefloquine is distributed into breast milk in small amounts.

◊ Reviews of pharmacokinetic studies of mefloquine reveal considerable interindividual variation for several pharmacokinetic parameters and some evidence that there might be pharmacokinetic differences between ethnic groups.[1,2] Mefloquine is well absorbed by healthy subjects and by patients with uncomplicated malaria after oral doses.[3,4] In patients with complicated malaria adequate blood concentrations have been obtained by the nasogastric route but this route cannot be relied upon for seriously ill patients[5] as absorption may be incomplete.[1] Mefloquine has a large apparent volume of distribution but this is reduced in the presence of malaria.[6,7] In children given mefloquine with sulfadoxine and pyrimethamine as tablets crushed and mixed with a glucose syrup, maximum blood-mefloquine concentrations were higher and reached in a shorter time compared with equivalent doses in adults.[8] In pregnant women with uncomplicated malaria blood concentrations were lower than in non-pregnant women and the apparent volume of distribution was larger.[9] Once-weekly prophylactic doses of mefloquine resulted in steady-state conditions at about 10 doses with no evidence of subsequent accumulation.[10]

Mefloquine is metabolised in the liver[11] largely into 2,8-bis(trifluoromethyl)-4-quinoline carboxylic acid [Ro-21-5104][12] but this metabolite appears to be inactive against *Plasmodium falciparum*.[13] Only a small percentage of a dose is excreted in the urine[14] and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.[1] Mefloquine has an extremely long plasma elimination half-life; again there is considerable interindividual variation and mean values ranging from 13.9 to 27.5 days have been quoted, the smaller figure of the range referring to a formulation that did not provide as good absorption as the preparation now in use.[1]

Mefloquine is distributed into breast milk, but a single dose study in 2 women[15] indicated that the concentration of mefloquine in milk was only a small proportion of that seen in plasma.

1. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. *Clin Pharmacokinet* 1990; **19:** 264–79.
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 430–75.
3. Karbwang J, *et al.* The pharmacokinetics of mefloquine when given alone or in combination with sulphadoxine and pyrimethamine in Thai male and female subjects. *Eur J Clin Pharmacol* 1987; **32:** 173–7.
4. Looareesuwan S, *et al.* Studies of mefloquine bioavailability and kinetics using a stable isotope technique: a comparison of Thai patients with falciparum malaria and healthy caucasian volunteers. *Br J Clin Pharmacol* 1987; **24:** 37–42.
5. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
6. Juma FD, Ogeto JO. Mefloquine disposition in normals and in patients with severe Plasmodium falciparum malaria. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 15–17.
7. Karbwang J, *et al.* A comparison of the pharmacokinetics of mefloquine in healthy Thai volunteers and in Thai patients with falciparum malaria. *Eur J Clin Pharmacol* 1988; **35:** 677–80.
8. Singhasivanon V, *et al.* Pharmacokinetic study of mefloquine in Thai children aged 5-12 years suffering from uncomplicated falciparum malaria treated with MSP or MSP plus primaquine. *Eur J Drug Metab Pharmacokinet* 1994; **19:** 27–32.
9. Na Bangchang K, *et al.* Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 321–3.
10. Pennie RA, *et al.* Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg* 1993; **87:** 459–62.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.
13. Håkanson A, *et al.* Comparison of the activity in vitro of mefloquine and two metabolites against Plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1990; **84:** 503–4.
14. Schwartz DE, *et al.* Urinary excretion of mefloquine and some of its metabolites in African volunteers at steady state. *Chemotherapy* 1987; **33:** 305–8.
15. Edstein MD, *et al.* Excretion of mefloquine in human breast milk. *Chemotherapy* 1988; **34:** 165–9.

Uses and Administration

Mefloquine is a 4-methanolquinoline antimalarial related to quinine. It is a blood schizontocide effective against all forms of malaria including chloroquine- or multidrug-resistant strains of *Plasmodium falciparum*, although some strains are naturally resistant to mefloquine. It is used for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, and also for malaria prophylaxis. Mefloquine is also used after treatment with an artemisinin derivative for acute uncomplicated malaria, to reduce the risk of recrudescence.

Mefloquine is given orally as the hydrochloride but variation in the way doses are expressed could lead to confusion. In the UK and elsewhere, doses are expressed in terms of the base and a dose of 250 mg base is equivalent to about 274 mg of mefloquine hydrochloride. In the USA, doses are expressed in terms of the hydrochloride and a dose of 250 mg is therefore equivalent to only about 228 mg of mefloquine base. Doses in the USA could therefore be about 10% less than elsewhere.

Doses recommended in the UK are as follows.

- For the *treatment of malaria*, mefloquine base 20 to 25 mg/kg (up to a maximum of 1.5 g) as a single dose or preferably in 2 or 3 divided doses 6 to 8 hours apart
- For the *prophylaxis of malaria*, a dose of mefloquine base 250 mg once weekly in adults and children over 45 kg. Children weighing 5 to 19 kg may be given one-quarter the adult dose; those weighing 20 to 30 kg, half the adult dose; and those weighing 31 to 45 kg three-quarters the adult dose

  Prophylaxis should be started 1 to 3 weeks before exposure and continued for 4 weeks after leaving the malarious area

For other dosage recommendations, see under Malaria, below.

Malaria. The overall treatment and prophylaxis of malaria and the place of mefloquine in current recommendations are discussed on p.594.

TREATMENT. Clinical studies have shown mefloquine to be effective in the treatment of chloroquine- or multidrug-resistant falciparum malaria. It is also effective in benign malarias, but is not normally required since they usually respond to chloroquine.

Mefloquine has been widely used as an alternative to regimens using quinine for the treatment of chloroquine-resistant or multidrug-resistant strains of *Plasmodium falciparum*. It is now also used with an artemisinin derivative in multidrug resistance (see p.599).

As there is no parenteral formulation of mefloquine currently available it can only be used in patients who can take oral medication and is therefore unsuitable for sole treatment in severe infections. Mefloquine has produced adequate blood concentrations by the nasogastric route, but this route cannot be relied upon in seriously ill patients.[1] If mefloquine is given to patients after parenteral doses of quinine, it is recommended that a period of 12 hours should be allowed after the last dose of quinine to avoid toxicity.

In the UK, the recommended dose for the treatment of malaria is the equivalent of 20 to 25 mg of mefloquine base per kg bodyweight, as a single dose or preferably in two or three divided doses 6 to 8 hours apart, to a maximum of 1.5 g. The manufacturers recommend a lower dose of 15 mg/kg for the partially immune. In the USA, the manufacturers recommend 1250 mg of mefloquine hydrochloride given as a single dose. WHO[2] recommends a dose of mefloquine base of 25 mg/kg given over 2 or 3 days (15 mg/kg followed by 10 mg/kg a day later, or 8.3 mg/kg daily for 3 days).

WHO[3] considers that drugs used for the treatment of uncomplicated falciparum malaria may in principle be carried as a *standby* for use in similar doses for the emergency self-treatment of malaria, although mefloquine is not recommended by WHO as a first-line regimen.

PROPHYLAXIS. It had been hoped that mefloquine could be reserved for the treatment of malaria, but increasing drug resistance to chemoprophylactic regimens has led to it being widely used for malaria prophylaxis. WHO recommends[3] that mefloquine should be used where there is a high risk of falciparum malaria and drug resistance or a moderate to low risk but with high drug resistance. For **adults** the equivalent of 250 mg of mefloquine base is given every week, starting 1 to 3 weeks before departure, and continuing throughout the period of exposure and for 4 weeks after leaving the malarious area. Starting mefloquine prophylaxis 2 to 3 weeks before exposure allows for detection of possible adverse effects before travelling (see Effects on the Nervous System, above, for concerns about neurotoxicity). It is now considered that mefloquine prophylaxis can be given for periods of up to one year instead of the previous limit of 3 months.

Mefloquine is considered to be suitable[3] for prophylaxis in the second and third trimesters of pregnancy. Pregnancy should be avoided during and for 3 months after stopping the drug.

Recommended dosages of mefloquine for prophylaxis in **children** are generally based on 5 mg/kg as a single weekly dose in children weighing over 5 kg.[3] The doses now usually used in the

UK[4] for infants and children from 6 kg body-weight and above 3 months of age are as follows:

- 6 to 15.9 kg (3 months to 3 years 11 months), one-quarter the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months), half the adult dose
- 25 to 44.9 kg (8 years to 12 years 11 months), three-quarters the adult dose
- 45 kg and over (13 years or more), the adult dose

In the event of breakthrough malaria during malaria prophylaxis there may be a delay of up to several months before the onset of symptoms in contrast to that seen with other forms of prophylaxis.[5] Mefloquine should not be used for treatment if it has been used for prophylaxis.

1. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34:** 1028–36.
2. WHO. *Guidelines for the treatment of malaria.* Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 05/06/06)
3. WHO. *International travel and health.* 2008 ed. Available at: http://www.who.int/ith/ (accessed 18/06/08)
4. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)
5. Day JH, Behrens RH. Delay in onset of malaria with mefloquine prophylaxis. *Lancet* 1995; **345:** 398.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tropicur; ***Austral.:*** Lariam; ***Austria:*** Lariam; ***Belg.:*** Lariam; ***Braz.:*** Mephaquin; ***Canad.:*** Lariam; ***Chile:*** Lariam; ***Cz.:*** Lariam; Mephaquin†; ***Denm.:*** Lariam; ***Fin.:*** Lariam; ***Fr.:*** Lariam; ***Ger.:*** Lariam; ***Gr.:*** Lariam; ***Hong Kong:*** Lariam; Mephaquin; ***Hung.:*** Lariam; ***India:*** Larimef; Mefliam; Mefloc; Meflotas; ***Irl.:*** Lariam; ***Israel:*** Lariam; Mephaquin; ***Ital.:*** Lariam; ***Malaysia:*** Lariam; Mephaquin; ***Neth.:*** Lariam; ***Norw.:*** Lariam; ***NZ:*** Lariam; ***Philipp.:*** Lariam; ***Port.:*** Mephaquin; ***S.Afr.:*** Lariam; Mefliam; ***Singapore:*** Lariam; Mephaquin; ***Swed.:*** Lariam; ***Switz.:*** Lariam; Mephaquine; ***Thai.:*** Mephaquin†; Mequin; ***UK:*** Lariam; ***USA:*** Lariam.

Multi-ingredient: *Switz.:* Fansimef†.

Piperaquine Phosphate

Piperaquina, fosfato de; Piperaquini Phosphas; 13228-RP. 1,3-Bis[1-(7-chloro-4-quinolyl)-4′-piperazinyl]propane.

$C_{29}H_{32}Cl_2N_6,4H_3PO_4,4H_2O$ = 999.6.

CAS — 85547-56-4.

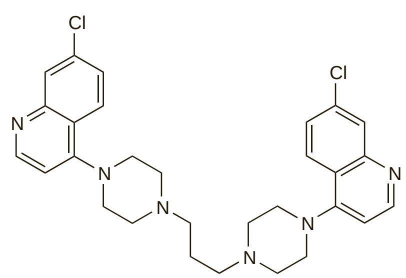

(piperaquine)

Pharmacopoeias. In *Chin.*

Profile

Piperaquine phosphate is a 4-piperazinoquinoline derivative which has been studied in the treatment and prophylaxis of falciparum malaria. Combined treatment with artenimol is also being investigated. A combination of piperaquine, artinimol, and trimethoprim (*Artecom*) is available in some countries.

◊ References.

1. Davis TME, *et al.* Piperaquine: a resurgent antimalarial drug. *Drugs* 2005; **65:** 75–87.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *China:* Duo-Cotecxin.

Primaquine Phosphate *(BANM, rINNM)*

Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakiinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini Phosphas; Primaquinum Phosphoricum; SN-13,272. (*RS*)-8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate.

Примахина Фосфат

$C_{15}H_{21}N_3O,2H_3PO_4$ = 455.3.

CAS — 90-34-6 (primaquine); 63-45-6 (primaquine phosphate).

ATC — P01BA03.

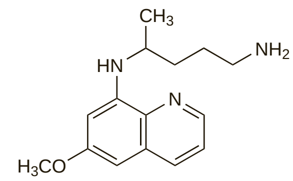

(primaquine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Primaquine Diphosphate). An orange crystalline powder. Soluble in water; practically insoluble in alcohol. Protect from light.

USP 31 (Primaquine Phosphate). An orange-red, odourless, crystalline powder. Soluble 1 in 15 of water; insoluble in chloroform and in ether. Its solutions are acid to litmus. Protect from light.

Adverse Effects

Adverse effects with therapeutic doses of primaquine are usually minimal but abdominal pain and gastric distress are more common if taken on an empty stomach. Larger doses may cause nausea and vomiting. Methaemoglobinaemia may occur occasionally. Haemolytic anaemia can occur in persons with G6PD deficiency (see below). Other uncommon effects include mild anaemia and leucocytosis. Hypertension and cardiac arrhythmias have been reported on rare occasions. Primaquine may rarely produce leucopenia or agranulocytosis, usually after overdosage. Other effects associated with overdosage include gastrointestinal symptoms, haemolytic anaemia, and methaemoglobinaemia with cyanosis.

◊ Many adverse effects have been reported after use of primaquine[1] but some, including pruritus and disturbances of visual accommodation, are considered to be inadequately documented or doubtfully attributed to the drug.

Acute intravascular haemolysis is the most serious toxic hazard of primaquine, especially in people with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some types of haemoglobinopathy. In individuals with G6PD deficiency the severity of haemolysis is directly related to the degree of deficiency and to the quantity of primaquine given. In patients with the African variant the standard course of primaquine generally produces a moderate and self-limiting anaemia, while in those with the Mediterranean and related Asian variants, haemolysis can result in progressive haemoglobinaemia and haemoglobinuria which can be fatal. Whenever possible, therapy with primaquine should be delayed until the acute stage of malaria has been brought under control by a blood schizontocide because of the risk of inducing haemolysis and compromising the gastrointestinal tolerance of therapy.

1. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizontocidal and gametocytocidal drug. *Bull WHO* 1981; **59:** 391–5.

Precautions

Primaquine should be used cautiously in acutely ill patients with any serious systemic disease characterised by a tendency to granulocytopenia such as rheumatoid arthritis or lupus erythematosus. It should also be used with care in patients with G6PD deficiency. Primaquine should be withdrawn if signs of haemolysis or methaemoglobinaemia occur and the blood count should be monitored periodically.

Pregnancy. Radical cure of vivax or ovale malarias with primaquine should be delayed in pregnant women until after delivery.[1]

1. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.

Interactions

Primaquine should not be used with drugs liable to induce haemolysis or bone marrow depression. Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Antimalarials. The pharmacokinetics of primaquine were not altered by *mefloquine* in healthy subjects,[1] although the effect of primaquine on mefloquine pharmacokinetics is uncertain (see under Mefloquine, p.607). In a study in patients with malaria, *quinine* reduced the plasma concentrations of primaquine, although the clinical importance of the interaction was unclear.[1]

1. Edwards G, *et al.* Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* 1993; **35:** 193–8.

Pharmacokinetics

Primaquine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after a dose is taken and then rapidly diminish with a reported elimination half-life of 3 to 6 hours. It is widely distributed into body tissues.

Primaquine is rapidly metabolised in the liver, its major metabolite being carboxyprimaquine, and little unchanged drug is excreted in the urine. Carboxyprimaquine accumulates in the plasma on repeated dosage.

◊ References.

1. Fletcher KA, *et al.* Studies on the pharmacokinetics of primaquine. *Bull WHO* 1981; **59:** 407–12.
2. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
3. Mihaly GW, *et al.* Pharmacokinetics of primaquine in man, I: studies of the absolute bioavailability and effects of dose size. *Br J Clin Pharmacol* 1985; **19:** 745–50.
4. Ward SA, *et al.* Pharmacokinetics of primaquine in man, II: comparison of acute vs chronic dosage in Thai subjects. *Br J Clin Pharmacol* 1985; **19:** 751–5.
5. Bhatia SC, *et al.* Pharmacokinetics of primaquine in patients with P. vivax malaria. *Eur J Clin Pharmacol* 1986; **31:** 205–10.
6. Rønn A, Bygbjerg I. Unexpected high primaquine concentrations in acutely ill malaria patients. *Lancet* 1993; **341:** 305.

Uses and Administration

Primaquine is an 8-aminoquinoline antimalarial that is effective as a tissue schizontocide against intrahepatic forms of all types of malaria parasite and is used to produce radical cure of vivax and ovale malarias.

Primaquine phosphate is given orally and doses may be expressed in terms of the base; primaquine phosphate 26.4 mg is equivalent to about 15 mg of primaquine base.

When used for *radical cure* of vivax or ovale **malaria**, a course of treatment with a blood schizontocide must be given first to kill any erythrocytic parasites. Primaquine phosphate is then given orally, usually in a dose equivalent to 15 mg of the base daily for 14 days but higher doses or longer courses may be required to overcome resistance in some strains of *P. vivax* (see below); WHO has advised that for uncomplicated malaria in travellers, infections acquired south of the equator should be treated with primaquine 500 micrograms/kg daily for 14 days and those acquired north of the equator with 250 micrograms/kg daily for 14 days. A dose for children is 250 micrograms/kg daily for 14 days.

For patients with G6PD deficiency the use of up to 45 mg (children 750 micrograms/kg) once every 7 days for 8 weeks has been suggested to minimise haemolysis (but see under Adverse Effects, above).

Primaquine is also gametocytocidal and a single dose of 750 micrograms/kg (to a maximum of 45 mg) has been suggested to *prevent transmission* of falciparum malaria particularly in areas where there is potential for re-introduction of malaria.

Primaquine is also used with clindamycin in the treatment of **pneumocystis pneumonia** in AIDS patients (below).

Malaria. The overall treatment and prophylaxis of malaria and the place of primaquine in current recommendations are described on p.594.

Despite the generally successful use of oral primaquine for radical cure of benign malarias,[1] there has been a report[2] of a patient weighing 84 kg who had relapse of vivax malaria after treatment including primaquine 15 mg given daily for 21 days; no further symptoms occurred after a second course of 15 mg given daily for 3 months. It was suggested that a daily dose of 15 mg might be inadequate for patients weighing more than 50 kg and that patients with vivax malaria who have relapsed after the standard course of primaquine, and possibly those with vivax malaria acquired in South-East Asia or Melanesia, should receive a total dose of 6 mg/kg in daily doses of 15 to 22.5 mg. A report from Thailand,[3] where primaquine-resistant strains of *Plasmodium vivax* are increasing, showed that a dose of primaquine 22.5 mg daily for 14 days was safe and more effective in preventing relapses than 15 mg daily in patients with an average body-weight of about 51 kg. There have been several other reports of primaquine-resistant *P. vivax*,[4-7] and the suggestion has been made that higher doses of primaquine (15 mg twice daily for 14 days, to give a total dose of 6 mg/kg assuming a body-weight of 70 kg) should be considered wherever the vivax malaria was acquired.[7,8] A systematic review[9] concluded that when used with chloroquine, a 14-day course of primaquine 15 mg daily was more effective than a 5-day course in preventing relapses of vivax malaria. The 5-day course of primaquine plus chloroquine appeared to be no better than chloroquine alone.

Variable responses to primaquine in the Amazonian region were attributed to considerable variation in the content of primaquine both between and within batches of tablets; primaquine content ranged from 19 to 168% of the labelled content.[10]

In the USA, the CDC[11] have suggested the use of primaquine at the end of prophylaxis to prevent relapses due to *P. vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic. In those who have taken chloroquine, doxycycline, or mefloquine as prophylaxis, primaquine is usually given during the last 2 weeks of prophylaxis, but may also be taken immediately after prophylaxis is completed. When atovaquone plus proguanil is taken as prophylaxis, primaquine may be given either during the last 7 days and then for an additional 7 days, or for 14 days after atovaquone plus proguanil prophylaxis is completed. The recommended daily dose of primaquine for terminal prophylaxis is 30 mg for adults and 600 micrograms/kg for children.

Primaquine has also been tried for prophylaxis of falciparum and vivax malaria; use for a year produced effective cover and was well tolerated by Javanese men without G6PD deficiency.[12] It was also effective for prophylaxis in Colombian military personnel; it was noted that primaquine prophylaxis could be stopped 1 week after departing the endemic area.[13]

1. Molyneux M, Fox R. Diagnosis and treatment of malaria in Britain. *BMJ* 1993; **306:** 1175–80.
2. Luzzi GA, *et al.* Treatment of primaquine-resistant Plasmodium vivax malaria. *Lancet* 1992; **340:** 310.
3. Bunnag D, *et al.* High dose of primaquine in primaquine resistant vivax malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 218–19.
4. Collins WE, Jeffrey GM. Primaquine resistance in Plasmodium vivax. *Am J Trop Med Hyg* 1996; **55:** 243–9.
5. Signorini L, *et al.* Short report: primaquine-tolerant Plasmodium vivax in an Italian traveler from Guatemala. *Am J Trop Med Hyg* 1996; **55:** 472–3.
6. Smoak BL, *et al.* Plasmodium vivax infections in US Army troops: failure of primaquine to prevent relapse in studies from Somalia. *Am J Trop Med Hyg* 1997; **56:** 231–4.
7. Doherty JF, *et al.* Treatment of Plasmodium vivax malaria—time for a change? *Trans R Soc Trop Med Hyg* 1997; **91:** 76.
8. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; **39:** 1336–45.
9. Galappaththy GNL, *et al.* Primaquine for preventing relapses in people with Plasmodium vivax malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/03/08).
10. Petralanda I. Quality of antimalarial drugs and resistance to Plasmodium vivax in Amazonian region. *Lancet* 1995; **345:** 1433.
11. CDC. Malaria. In: *The Yellow Book: CDC Health Information for International Travel; 2008.* Available at: http://wwwn.cdc.gov/travel/yellowBookCh4-Malaria.aspx (accessed 10/03/08)
12. Fryauff DJ, *et al.* Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* 1995; **346:** 1190–3.
13. Soto J, *et al.* Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann Intern Med* 1998; **129:** 241–4.

Pneumocystis pneumonia. Primaquine with clindamycin is used in the treatment of pneumocystis pneumonia as an alternative to co-trimoxazole[1] (see p.521). Treatment has usually lasted 3 weeks, with primaquine being given by mouth in daily doses equivalent to 30 mg of the base, and clindamycin usually being given intravenously in doses of 600 mg four times daily or 300 to 450 mg four times daily by mouth.[2] The *BNF* suggests clindamycin 600 mg by mouth every 8 hours with primaquine 30 mg daily by mouth for mild to moderate disease.

A randomised multicentre study[3] compared this latter regimen (primaquine 30 mg daily and clindamycin 600 mg three times daily) with co-trimoxazole and with a combination of dapsone and trimethoprim in 181 AIDS patients who had confirmed mild to moderate pneumocystis pneumonia. Primaquine-clindamycin was as effective as the other two regimens, although the authors suggested that the combination might be best avoided in patients with severe myelosuppression.

Primaquine with clindamycin is not normally recommended for prophylaxis although there are reports of it being tried.[4] A retrospective examination[5] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48:** 63–7.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter 2007.
3. Safrin S, *et al.* Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS: a double-blind, randomized trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. *Ann Intern Med* 1996; **124:** 792–802.
4. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
5. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Preparations

USP 31: Primaquine Phosphate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Primacin; ***Braz.:*** Primakinder; ***India:*** Malirid; PMQ-INGA; Primacip.

Proguanil Hydrochloride *(BANM, rINNM)*

Bigumalum; Chloriguane Hydrochloride; Chloroguanide Hydrochloride; Hidrocloruro de proguanil; Proguanide Hydrochloride; Proguaniilihydrokloridi; Proguanil, chlorhydrate de; Proguanil hydrochlorid; Proguanil-hidroklorid; Proguanilhydroklorid; Proguanili hydrochloridum; Proguanilo hidrochloridas; RP-3359; SN-12,837. 1-(4-Chlorophenyl)-5-isopropylbiguanide hydrochloride.

Прогуанила Гидрохлорид

$C_{11}H_{16}ClN_5,HCl = 290.2.$

CAS — 500-92-5 (proguanil); 637-32-1 (proguanil hydrochloride).

ATC — P01BB01.

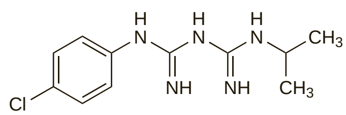

(proguanil)

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Ph. Eur. 6.2 (Proguanil Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane. Protect from light.

Stability. Although the Ph. Eur. 6.2 directs that proguanil hydrochloride should be protected from light, stability studies[1,2] suggest that it is a very stable compound with only small amounts of its major decomposition product 4-chloroaniline being formed during thermal and photochemical stress.

1. Owoyale JA, Elmarakby ZS. Effect of sunlight, ultraviolet irradiation and heat on proguanil. *Int J Pharmaceutics* 1989; **50:** 219–21.
2. Taylor RB, *et al.* A chemical stability study of proguanil hydrochloride. *Int J Pharmaceutics* 1990; **60:** 185–90.

Adverse Effects and Precautions

Apart from mild gastric intolerance, diarrhoea, and some reports of aphthous ulceration there appear to be few adverse effects associated with usual doses of proguanil hydrochloride. There have been rare reports of hypersensitivity reactions including urticaria and angioedema. Rare cases of seizures and psychotic events have also been reported. Haematological changes have been reported in patients with severe renal impairment. Overdosage may produce epigastric discomfort, vomiting, and renal irritation leading to haematuria.

Proguanil should be used with caution in patients with renal impairment; dosage should be reduced accordingly (see under Uses and Administration, below).

Proguanil may be taken during pregnancy, but UK guidelines recommend that folate supplements (folic acid 5 mg daily) should also be given; however, the combination of proguanil with atovaquone should be avoided as data regarding the safety of atovaquone are lacking.

◊ Until 1985 proguanil was generally taken in a dose of 100 mg daily for malaria prophylaxis with few adverse effects. Although there was no increase in serious adverse effects when the dose was increased to 200 mg daily, and it began to be used with chloroquine, there were an increasing number of reports of reversible aphthous ulceration.[1] Chloroquine may exacerbate this effect.[2] There has also been a report of reversible alopecia in women and scaling of the skin in both men and women using proguanil.[3]

Megaloblastic anaemia and pancytopenia were associated with proguanil accumulation in 2 patients with renal failure.[4]

Stevens-Johnson syndrome has been reported[5] in a patient taking proguanil with atovaquone.

1. Peto TEA. Toxicity of antimalarial drugs. *J R Soc Med* 1989; **82** (suppl 17): 30–4.
2. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
3. Hanson SN, *et al.* Hairloss and scaling with proguanil. *Lancet* 1989; **i:** 225.
4. Boots M, *et al.* Megaloblastic anemia and pancytopenia due to proguanil in patients with chronic renal failure. *Clin Nephrol* 1982; **18:** 106–8.
5. Emberger M, *et al.* Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. Abstract: *Clin Infect Dis* 2003; **37:** 158. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/06/08)

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that proguanil may be safe for use in such patients, see under Precautions for Chloroquine, p.601.

Interactions

Fluvoxamine. Fluvoxamine can virtually abolish[1] the metabolism of proguanil to its active metabolite cycloguanil via an inhibitory effect on the cytochrome P450 isoenzyme CYP2C19.

1. Jeppesen U, *et al.* The CYP2C19 catalyzed bioactivation of proguanil is abolished during fluvoxamine intake. *Eur J Clin Pharmacol* 1997; **52** (suppl): A134.

Warfarin. For a report of haematuria and high prothrombin ratio in a patient stabilised on warfarin who took proguanil for malaria prophylaxis, see p.1429.

Pharmacokinetics

Proguanil is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring within about 4 hours. Proguanil is metabolised in the liver to the active metabolite cycloguanil. Peak plasma concentrations of cycloguanil occur approximately 1 hour after those of the parent drug. The elimination half-lives of both proguanil and cycloguanil are about 20 hours. About 40 to 60% of proguanil is eliminated in the urine, of which 60% is unchanged and 30% cycloguanil. There is also some elimination via the faeces. Proguanil is distributed into breast milk in small amounts (which are not adequate to provide chemoprophylaxis for the infant).

◊ Early studies found proguanil to be well absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours.[1] In more recent studies, peak plasma concentrations of proguanil have been achieved within 2 to 4 hours.[2-4] Plasma protein binding for proguanil is 75%.[5] Proguanil is metabolised in the liver[3] to the active metabolite cycloguanil and to *p*-chlorophenylbiguanide which is inactive. Peak plasma concentrations of cycloguanil occur about 5.3 hours after doses of proguanil.[4] Unlike proguanil and *p*-chlorophenylbiguanide, cycloguanil is not concentrated in erythrocytes and thus concentrations of cycloguanil in plasma and whole blood are similar.[4] The elimination half-lives for proguanil and cycloguanil are about 20 hours.[3,4] A review of early studies states that 40 to 60% of a dose of proguanil is excreted in the urine, 60% of this as the unchanged drug, 30% as cycloguanil, and 8% as *p*-chlorophenylbiguanide.[1] About 10% of a dose is excreted in the faeces.[1] However, these values can vary greatly and wide interindividual variations in the ability to metabolise proguanil to cycloguanil have been reported.[3,6,7] Malaria prophylaxis with proguanil might be less effective in poor metabolisers although this has not been proved conclusively[8] and, anyway, other factors such as lack of protection against mosquitoes and sensitivity of the malaria parasite might be more important.[9]

Plasma concentrations of cycloguanil may be reduced in the third trimester of pregnancy.[10]

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Kelly JA, *et al.* The kinetics of proguanil during prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 338.
3. Watkins WM, *et al.* Variability in the metabolism of proguanil to the active metabolite cycloguanil in healthy Kenyan adults. *Trans R Soc Trop Med Hyg* 1990; **84:** 492–5.
4. Wattanagoon Y, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in healthy subjects. *Br J Clin Pharmacol* 1987; **24:** 775–80.
5. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
6. Ward SA, *et al.* Inter-subject variability in the metabolism of proguanil to the active metabolite cycloguanil in man. *Br J Clin Pharmacol* 1989; **27:** 781–7.
7. Helsby NA, *et al.* The multiple dose pharmacokinetics of proguanil. *Br J Clin Pharmacol* 1993; **35:** 653–6.
8. Mberu EK, *et al.* Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. *Trans R Soc Trop Med Hyg* 1995; **89:** 658–9.
9. Skjelbo E, *et al.* Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther* 1996; **59:** 304–11.
10. Wangboonskul J, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. *Eur J Clin Pharmacol* 1993; **44:** 247–51.

Uses and Administration

Proguanil is a biguanide compound that has little antimalarial activity until metabolised in the body to the active antimalarial drug cycloguanil. Cycloguanil, like pyrimethamine, inhibits plasmodial dihydrofolate re-

The symbol † denotes a preparation no longer actively marketed

ductase and thus disrupts synthesis of nucleic acids in the parasite. Cycloguanil is active against pre-erythrocytic forms and is a slow-acting blood schizontocide. It also has some sporontocidal activity, rendering the gametocytes non-infective to the mosquito vector.

The value of proguanil is limited by the rapid development of resistance.

Proguanil is used orally as the hydrochloride for the chemoprophylaxis of malaria, with chloroquine or atovaquone. The schizontocidal activity of cycloguanil on erythrocytic forms is too slow for cycloguanil or proguanil to be used alone for the treatment of malaria, but proguanil hydrochloride is given combined with atovaquone for the treatment of uncomplicated falciparum malaria.

For *prophylaxis* of malaria in combination with chloroquine, the usual adult daily dose of proguanil hydrochloride is 200 mg taken after food. For prophylaxis in combination with atovaquone 250 mg, the daily dose of proguanil hydrochloride is 100 mg. It is generally recommended that chemoprophylaxis for travellers should start 1 week before exposure to malaria, but if this is not possible it can be started 1 to 2 days prior to travel. Use should continue throughout exposure and for at least 4 weeks (1 week when proguanil is given with atovaquone) after leaving a malarious area.

In the *treatment* of uncomplicated falciparum malaria, adult doses are proguanil hydrochloride 400 mg together with atovaquone 1 g, each orally as a single dose for 3 consecutive days.

For children's doses in the prophylaxis and treatment of malaria, see below.

Cycloguanil was also formerly given by intramuscular injection as an oily suspension of the embonate.

◊ Reviews.

1. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
2. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.
3. Nakato H, *et al.* A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; **60:** 929–36.

Administration in children. Dosage recommendations for proguanil with **chloroquine** for **malaria prophylaxis** in children have varied. UK malaria experts[1] have suggested the following prophylactic oral doses for children based on fractions of the adult dose of 200 mg daily:

- under 6.0 kg (0 to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months): half the adult dose
- 25 to 44.9 kg (8 years to 12 years 11 months): three-quarters the adult dose
- 45 kg and over (13 years or more): the adult dose

They noted that body-weight was a better guide to dosage than age for children over 6 months.

Children may be given proguanil with **atovaquone** for the **prophylaxis** of malaria in the following doses, based on the adult dose of 100 mg of proguanil hydrochloride daily:

- children weighing 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose

Doses of proguanil with atovaquone for the **treatment** of malaria, based on the adult dose of 400 mg of proguanil hydrochloride daily, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- 40 kg and over: the adult dose

1. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Administration in renal impairment. Proguanil is excreted by the kidneys and should be given in reduced dosage or avoided in patients with renal impairment. The following oral doses have been recommended based on creatinine clearance (CC):

- CC 20 to 59 mL/minute: 100 mg daily
- CC 10 to 19 mL/minute: 50 mg every other day
- CC less than 10 mL/minute: 50 mg once weekly

Preparations

BP 2008: Proguanil Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Paludrine; ***Austria:*** Paludrine; ***Belg.:*** Paludrine; ***Denm.:*** Paludrine; ***Fin.:*** Paludrine†; ***Fr.:*** Paludrine; ***Ger.:*** Paludrine; ***India:*** Laveran; ***Irl.:*** Paludrine; ***Israel:*** Paludrine; ***Ital.:*** Paludrine; ***Malaysia:*** Paludrine†; ***Neth.:*** Paludrine; ***Norw.:*** Paludrine; ***Port.:*** Paludrine; ***S.Afr.:*** Paludrine†; ***Swed.:*** Paludrine; ***Switz.:*** Paludrine; ***UK:*** Paludrine.

Multi-ingredient: ***Austral.:*** Malarone; ***Austria:*** Malarone; Promal; ***Belg.:*** Malarone; ***Canad.:*** Malarone; ***Cz.:*** Malarone; ***Denm.:*** Malarone; ***Fr.:*** Malarone; Savarine; ***Ger.:*** Malarone; ***Gr.:*** Malarone; ***Hong Kong:*** Malarone; ***Hung.:*** Malarone; ***Irl.:*** Malarone; ***Israel:*** Malarone; ***Ital.:*** Malarone; ***Malaysia:*** Malarone; ***Neth.:*** Malarone; ***Norw.:*** Malarone; ***NZ:*** Malarone; ***Pol.:*** Malarone; ***S.Afr.:*** Daramal-Paludrine†; Malanil; ***Singapore:*** Malarone; ***Spain:*** Malarone; ***Swed.:*** Malarone; ***Switz.:*** Malarone; ***UK:*** Malarone; ***USA:*** Malarone.

Pyrimethamine *(BAN, rINN)*

BW-50-63; Pirimetamin; Pirimetamina; Pirimetaminas; Pirymetamina; Pyrimetamiini; Pyrimetamin; Pyrimethamin; Pyriméthamine; Pyrimethaminum; RP-4753. 5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine.

Пириметамин

$C_{12}H_{13}ClN_4$ = 248.7.

CAS — 58-14-0.

ATC — P01BD01.

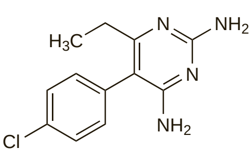

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Pyrimethamine). An almost white crystalline powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Pyrimethamine). A white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 125 of chloroform; slightly soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Use of pyrimethamine for prolonged periods, as used to be the case when it was **given alone** for the prophylaxis of malaria, can cause depression of haematopoiesis due to interference with folic acid metabolism. Skin rashes and hypersensitivity reactions also occurred.

Larger doses, such as those used in the treatment of toxoplasmosis, may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain, and vomiting; haematological effects such as megaloblastic anaemia, leucopenia, thrombocytopenia, and pancytopenia are also more likely to occur. CNS effects including headache, dizziness, and insomnia have also been reported.

Pulmonary eosinophilia has been reported in patients taking pyrimethamine **with other antimalarials**. Severe and sometimes fatal reactions have occurred when pyrimethamine has been used with sulfadoxine (*Fansidar*), including erythema multiforme and the Stevens-Johnson syndrome, and toxic epidermal necrolysis; there have also been isolated reports of hepatotoxicity. Agranulocytosis occurs more frequently when pyrimethamine is used with dapsone (*Maloprim*) and fatalities have been reported.

Acute overdosage with pyrimethamine can cause gastrointestinal effects and CNS stimulation with vomiting, excitability, and convulsions. Tachycardia, respiratory depression, circulatory collapse, and death may follow. Treatment of overdosage is symptomatic.

Adverse effects with dapsone. Between 1972 and 1988, the UK CSM received 76 reports of reactions that were attributed to the use of pyrimethamine with dapsone (*Maloprim*), of which 40 (53%) were considered to be serious, including 6 deaths.[1] The incidence was estimated to be 1 in 9100 for serious reactions and 1 in 60 200 for fatalities. Serious blood disorders including agranulocytosis, granulocytopenia, or leucopenia occurred in 15 patients (estimated incidence of 1 in 20 000), five of whom died. The other death was in a patient with myocarditis. Three patients had cyanosis due to methaemoglobinaemia. Respiratory disorders such as pulmonary eosinophilia, flu-like syndrome, and dyspnoea occurred in 6 patients. In 4 patients skin disorders were the principal effect and included epidermal necrolysis, angioedema, and bullous eruptions. Hepatic disorders were also reported in 4 patients. Three women using pyrimethamine-dapsone during pregnancy delivered malformed babies, one of them being stillborn. Other effects in 4 patients included convulsions, exacerbated epilepsy, pancreatitis, or a generalised allergic reaction.

A review[2] of 21 cases of agranulocytosis associated with pyrimethamine-dapsone concluded that, although agranulocytosis can occur very rarely in patients taking pyrimethamine or dapsone alone, agranulocytosis due to the combination appears to be caused by an idiosyncratic reaction to dapsone exacerbated by pyrimethamine. Of the 18 individuals for whom dosage was certain, 12 had been taking one tablet of pyrimethamine-dapsone twice weekly, twice the recommended dose of one tablet once weekly. Of the 9 patients who died, 6 had been taking one tablet twice weekly and one patient had taken one tablet once weekly; the dosage was uncertain in the remaining patients. The time of onset of symptoms had been 7 to 9 weeks after starting therapy in 16 of 19 of the patients.

Some consider that pyrimethamine with dapsone may produce some degree of immunosuppression and render users more susceptible to common infections. A higher incidence of non-specific upper respiratory-tract infections occurred in military recruits taking the combination than in those not given antimalarial prophylaxis.[3]

Pulmonary eosinophilia has also occurred in patients taking pyrimethamine with dapsone but, as there have also been similar reports of pulmonary toxicity in patients taking pyrimethamine with sulfadoxine (see below) or pyrimethamine with chloroquine, it has been suggested that pyrimethamine is probably the causative agent.[4]

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
2. Hutchinson DBA, *et al.* Agranulocytosis associated with Maloprim: review of cases. *Hum Toxicol* 1986; **5:** 221–7.
3. Lee PS, Lau EYL. Risk of acute non-specific upper respiratory tract infections in healthy men taking dapsone–pyrimethamine for prophylaxis against malaria. *BMJ* 1988; **296:** 893–5.
4. Davidson AC, *et al.* Pulmonary toxicity of malaria prophylaxis. *BMJ* 1988; **297:** 1240–1.

Adverse effects with sulfonamides. Severe and potentially fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been associated with the combined use of pyrimethamine with sulfadoxine (*Fansidar*) for malaria prophylaxis. The reported incidence of these reactions has varied with surveys in the UK,[1] USA,[2] and Sweden[3] yielding similar results and a survey from Switzerland[4] finding a much lower incidence. The overall rate of serious reactions to pyrimethamine-sulfadoxine in the UK has been estimated to be 1 in 2100. The estimates for severe cutaneous reactions were 1 in 4900 in the UK, 1 in 5000 to 1 in 8000 in the USA, 1 in 10 000 in Sweden, and 1 in 150 000 in Switzerland, and the death rates were 1 in 11 100 in the UK, 1 in 11 000 to 1 in 25 000 in the USA, and 1 in 35 000 in Sweden; no fatalities were reported in Switzerland. Workers on the Swiss survey had suggested that the high incidence of cutaneous reactions reported in the USA might have been due to concurrent therapy with chloroquine but this has been disputed.[5] The authors of the UK survey[1] suggested that the lower incidence reported in Switzerland may have been due to the different methods used to estimate the amount of drug usage. Whether this toxicity is due to the combined use of pyrimethamine and sulfadoxine is unclear as the estimated frequency of fatal reactions associated with the use of sulfadoxine alone in Mozambique[6] was 1 in 50 000.

There have been isolated reports of other severe or life-threatening reactions associated with the use of pyrimethamine-sulfadoxine when used alone or with chloroquine, including hepatotoxicity[7-9] (estimated incidence of 1 in 11 100 in the UK[1]), fatal multisystem toxicity,[10] drug fever and photodermatitis,[11] agranulocytosis,[11] and erythroderma resembling Sézary syndrome.[12] Severe pulmonary reactions have also occurred[3,13] but, as similar reactions have also been reported when pyrimethamine has been used with other antimalarials, including dapsone, it has been suggested that pyrimethamine is the causative agent (see Adverse Effects with Dapsone, above). Hyperammonaemia and carnitine deficiency with deterioration in mental status has been reported in a patient given pyrimethamine and sulfadiazine for the treatment of toxoplasmosis.[14]

Severe megaloblastic anaemia in a patient taking pyrimethamine and sulfadiazine for toxoplasmosis of the CNS[15] was treated by withdrawing pyrimethamine and giving folinic acid orally, together with a single platelet infusion.

For a comparison of the incidence of pruritus induced by various antimalarials including pyrimethamine with sulfadoxine, see Effects on the Skin under Chloroquine, p.600.

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–5.
2. Miller KD, *et al.* Severe cutaneous reactions among American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35:** 451–8.

3. Hellgren U, *et al.* Adverse reactions to sulphadoxine–pyrimethamine in Swedish travellers: implications for prophylaxis. *BMJ* 1987; **295:** 365–6.
4. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine–pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.
5. Rombo L, *et al.* Does chloroquine contribute to the risk of serious adverse reactions to Fansidar? *Lancet* 1985; **ii:** 1298–9.
6. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985; **ii:** 1072–3.
7. Lazar HP, *et al.* Fansidar and hepatic granulomas. *Ann Intern Med* 1985; **102:** 722.
8. Wejstal R, *et al.* Liver damage associated with Fansidar. *Lancet* 1986; **i:** 854–5.
9. Zitelli BJ, *et al.* Fatal hepatic necrosis due to pyrimethamine–sulfadoxine (Fansidar). *Ann Intern Med* 1987; **106:** 393–5.
10. Selby CD, *et al.* Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). *BMJ* 1985; **290:** 113–14.
11. Olsen VV, *et al.* Serious reactions during malaria prophylaxis with pyrimethamine–sulfadoxine. *Lancet* 1982; **ii:** 994.
12. Langtry JAA, *et al.* Erythroderma resembling Sézary syndrome after treatment with Fansidar and chloroquine. *BMJ* 1986; **292:** 1107–8.
13. Svanbom M, *et al.* Unusual pulmonary reaction during short term prophylaxis with pyrimethamine–sulfadoxine (Fansidar). *BMJ* 1984; **288:** 1876.
14. Sekas G, Harbhajan PS. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95:** 112–13.
15. Chute JP, *et al.* Severe megaloblastic anemia complicating pyrimethamine therapy. *Ann Intern Med* 1995; **122:** 884–5.

Overdosage. Reports of overdosage with pyrimethamine in infants.

1. Akinyanju O, *et al.* Pyrimethamine poisoning. *BMJ* 1973; **4:** 147–8.
2. Elmalem J, *et al.* Les accidents graves lors de la prescription de pyriméthamine chez les nourrissons traités pour une toxoplasmose. *Therapie* 1985; **40:** 357–9.

Precautions

Pyrimethamine may aggravate subclinical folic acid deficiency and it should not be given to patients with conditions associated with folate deficiency such as megaloblastic anaemia. Blood counts are required with prolonged treatment, and when large doses of pyrimethamine are used, as in the treatment of toxoplasmosis, blood counts should be checked twice weekly. Folinic acid, which does not interfere with the action of pyrimethamine against malaria or toxoplasmosis, has been given to prevent haematological toxicity due to pyrimethamine and its use is especially recommended if pyrimethamine is given during pregnancy. (Folic acid may be used as an alternative to folinic acid in malaria, but it interferes with the action of pyrimethamine against toxoplasmosis). For further information concerning use during pregnancy, see below.

Pyrimethamine should be given with caution to patients with renal or hepatic impairment. When patients with convulsive disorders need to receive large doses, as in the treatment of toxoplasmosis, it is recommended that small starting doses should be used.

When pyrimethamine is used with sulfonamides or dapsone, the general precautions applicable to those drugs should also be taken (see under Sulfamethoxazole, p.340 and under Dapsone, p.262) and treatment should be stopped immediately if any skin reactions, sore throat, or shortness of breath occurs.

Breast feeding. Pyrimethamine is distributed into breast milk[1] but as no adverse effects have been reported in breast-fed infants, the American Academy of Pediatrics considers breast feeding to be compatible with the use of pyrimethamine for malaria prophylaxis.[2] However, exposure of the infant to other folate antagonists should be avoided. The large doses of pyrimethamine used for treating toxoplasmosis may distribute into breast milk in sufficient quantities to interfere with folic acid metabolism in nursing infants.

1. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that pyrimethamine is probably safe for use in such patients, see under Precautions for Chloroquine, p.601.

Pregnancy. There have been concerns over the use of pyrimethamine during pregnancy as it has been shown to be teratogenic in *animal* studies.[1] In one report, severe congenital defects in a stillborn infant were attributed to the use of pyrimethamine in early pregnancy,[2] but the association was considered to be questionable.[3] Other instances of congenital malformations with pyrimethamine and dapsone are given under Adverse Effects with Dapsone, above.

Others[4] suggest that intermittent preventive therapy for malaria with pyrimethamine-sulfadoxine has a favourable safety profile in pregnancy. WHO considers that pyrimethamine combinations may be used after the first trimester of pregnancy in the treatment of toxoplasmosis,[5] and that pyrimethamine-sulfadoxine may be used in all trimesters for treatment in high-risk malaria-endemic regions.[6]

1. Anonymous. Pyrimethamine combinations in pregnancy. *Lancet* 1983; **ii:** 1005–7. Correction. *ibid.*; 1378.
2. Harpey J-P, *et al.* Teratogenicity of pyrimethamine. *Lancet* 1983; **ii:** 399.
3. Smithells RW, Sheppard S. Teratogenicity of Debendox and pyrimethamine. *Lancet* 1983; **ii:** 623–4.
4. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; **30:** 481–501.
5. WHO. *WHO model formulary.* Geneva: WHO, 2004.
6. WHO. *Guidelines for the treatment of malaria.* Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 16/06/06)

Interactions

Use of pyrimethamine with other folate antagonists such as co-trimoxazole, trimethoprim, methotrexate, or phenytoin may exacerbate bone marrow depression.

Lorazepam. Signs of mild liver toxicity in 2 of 5 subjects who received lorazepam and pyrimethamine appeared to confirm earlier suspicions that giving these drugs together could cause hepatotoxicity. Both patients tolerated each drug when given separately.[1]

1. Briggs M, Briggs M. Pyrimethamine toxicity. *BMJ* 1974; **1:** 40.

Zidovudine. Studies *in vitro* and in *animals* suggest that zidovudine could reduce the effectiveness of pyrimethamine in the treatment of toxoplasmic encephalitis.[1] Furthermore, the dose of zidovudine may need to be altered if these drugs are used together as there has been a report that pyrimethamine with sulfadoxine (*Fansidar*) prolonged the serum half-life of zidovudine.[2]

1. Israelski DM, *et al.* Zidovudine antagonizes the action of pyrimethamine in experimental infection with Toxoplasma gondii. *Antimicrob Agents Chemother* 1989; **33:** 30–4.
2. Klein RS. Prophylaxis of opportunistic infections in individuals infected with HIV. *AIDS* 1989; **3** (suppl 1): S161–S173.

Pharmacokinetics

Pyrimethamine is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations of about 200 nanograms/mL are obtained 2 to 6 hours after a dose of 25 mg orally. It is mainly concentrated in the kidneys, lungs, liver, and spleen and about 80 to 90% is bound to plasma proteins.

It is metabolised in the liver and slowly excreted via the kidney, the average half-life in plasma being about 4 days. Several metabolites have been detected in the urine. Pyrimethamine crosses the placenta. It is distributed into breast milk (see under Breast Feeding in Precautions, above).

◊ References.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Cook IF, *et al.* Race-linked differences in serum concentrations of dapsone, monoacetyldapsone and pyrimethamine during malaria prophylaxis. *Trans R Soc Trop Med Hyg* 1986; **80:** 897–901.
3. Weiss LM, *et al.* Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. *J Infect Dis* 1988; **157:** 580–3.
4. Hellgren U, *et al.* Plasma concentrations of sulfadoxine-pyrimethamine, mefloquine and its main metabolite after regular malaria prophylaxis for two years. *Trans R Soc Trop Med Hyg* 1991; **85:** 356–7.
5. Winstanley PA, *et al.* The disposition of oral and intramuscular pyrimethamine/sulphadoxine in Kenyan children with high parasitaemia but clinically non-severe falciparum malaria. *Br J Clin Pharmacol* 1992; **33:** 143–8.
6. Newton CRJC, *et al.* A single dose of intramuscular sulfadoxine-pyrimethamine as an adjunct to quinine in the treatment of severe malaria: pharmacokinetics and efficacy. *Trans R Soc Trop Med Hyg* 1993; **87:** 207–10.
7. Jacobson JM, *et al.* Pyrimethamine pharmacokinetics in human immunodeficiency virus-positive patients seropositive for Toxoplasma gondii. *Antimicrob Agents Chemother* 1996; **40:** 1360–5.
8. Klinker H, *et al.* Plasma pyrimethamine concentrations during long-term treatment for cerebral toxoplasmosis in patients with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 1623–7.
9. Trenque T, *et al.* Human maternofoetal distribution of pyrimethamine-sulphadoxine. *Br J Clin Pharmacol* 1998; **45:** 179–80.
10. Trenque T, *et al.* Population pharmacokinetics of pyrimethamine and sulfadoxine in children with congenital toxoplasmosis. *Br J Clin Pharmacol* 2004; **57:** 735–41.
11. Barnes KI, *et al.* Sulfadoxine-pyrimethamine pharmacokinetics in malaria: pediatric dosing implications. *Clin Pharmacol Ther* 2006; **80:** 582–96.

Uses and Administration

Pyrimethamine is a diaminopyrimidine antimalarial used with a sulfonamide in the treatment of malaria and toxoplasmosis. Pyrimethamine with sulfadoxine has been tried in the treatment of actinomycetoma and for prophylaxis of pneumocystis pneumonia. Pyrimethamine alone or with sulfadoxine has also been tried in the treatment of isosporiasis.

Pyrimethamine exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase, thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is active against pre-erythrocytic forms and is also a slow-acting blood schizontocide. It also has some sporontocidal activity; it does not prevent the formation of gametocytes but renders them non-infective to the mosquito vector. It is mainly effective against *Plasmodium falciparum* but has some activity against *P. vivax*.

The development of plasmodial resistance has rendered obsolete the use of pyrimethamine on its own in malaria. Combinations of pyrimethamine with long-acting sulfonamides, such as sulfadoxine or sulfametopyrazine, are now used, although resistance has also developed to them.

For the *treatment* of uncomplicated falciparum **malaria**, pyrimethamine is given orally with sulfadoxine in a fixed dose ratio of 1 to 20 (*Fansidar*). WHO recommends that a single dose of pyrimethamine-sulfadoxine be used with artesunate given for 3 days; in areas of susceptibility and where artesunate is unavailable, amodiaquine may be used with pyrimethamine-sulfadoxine. The following doses of pyrimethamine-sulfadoxine are recommended:

- adults and children aged over 13 years, pyrimethamine 75 mg with sulfadoxine 1.5 g
- infants 5 to 11 months, pyrimethamine 12.5 mg with sulfadoxine 250 mg
- children 1 to 6 years, pyrimethamine 25 mg with sulfadoxine 500 mg
- children 7 to 13 years, pyrimethamine 50 mg with sulfadoxine 1 g

A combination of pyrimethamine with sulfametopyrazine has been used similarly.

Pyrimethamine and pyrimethamine combinations are no longer recommended for *prophylaxis* of malaria. Combined preparations of pyrimethamine with sulfadoxine (*Fansidar*), and with dapsone in a fixed ratio of 1 to 8 (*Maloprim*), have been used in areas of chloroquine or multidrug resistance, although other antimalarials are now preferred.

Pyrimethamine given with a sulfonamide such as sulfadiazine is used in the treatment of **toxoplasmosis**. Alternatively, pyrimethamine may be given with clindamycin in AIDS patients with toxoplasmosis unable to tolerate a sulfonamide. For details of dosage regimens used, see below.

Isosporiasis. Isosporiasis (p.824) usually responds well to treatment with co-trimoxazole, but there is a high incidence of recurrence in immunocompromised patients, such as those with AIDS, and some form of maintenance therapy is generally required. Oral therapy with co-trimoxazole 960 mg given three times weekly or pyrimethamine 25 mg with sulfadoxine 500 mg given weekly were found to be equally effective maintenance regimens.[1] Pyrimethamine given alone in daily doses of 50 to 75 mg with folate therapy may be of use in the treatment of patients sensitive to sulfonamides.[2]

1. Pape JW, *et al.* Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **320:** 1044–7.
2. Weiss LM, *et al.* Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med* 1988; **109:** 474–5.

Malaria. The overall treatment and prophylaxis of malaria and the place of pyrimethamine-sulfadoxine (Fansidar) in current recommendations are discussed on p.594.

Mycetoma. For reference to the use of pyrimethamine as part of the treatment of actinomycetoma, see under Mycetoma, p.180.

Pneumocystis pneumonia. For a mention of pyrimethamine with either dapsone or sulfadoxine for the prophylaxis of pneumocystis pneumonia, and a discussion of conventional prophylaxis and treatment, see p.521.

Toxoplasmosis. Pyrimethamine is given, usually with sulfadiazine or another appropriate sulphonamide, in the treatment of toxoplasmosis (p.826). Folinic acid is also given to counteract the megaloblastic anaemia associated with these drugs.

Oral doses suggested by WHO[1] are:

- in *pregnancy* (second and third trimesters), pyrimethamine 25 mg daily for 3 to 4 weeks with sulfadiazine 3 g daily in 4 divided doses
- in *neonates*, pyrimethamine 1 mg/kg daily, with sulfadiazine 85 mg/kg daily in 2 divided doses; treatment should be given for 6 months if there is overt neonatal disease, or for 4 weeks to those without overt disease but whose mother was infected during pregnancy
- in *immunodeficiency*, pyrimethamine 200 mg in divided doses on the first day, then 75 to 100 mg daily for at least 6 weeks, followed by a suppressive dose of 25 to 50 mg daily; sulfadiazine is also given in a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily
- in *chorioretinitis*, pyrimethamine 75 mg daily for 3 days, then 25 mg daily for 4 weeks, followed in unresponsive patients by 50 mg daily for a further 4 weeks; sulfadiazine is also given in a dose of 2 g daily in 4 divided doses

Pyrimethamine with clindamycin is an alternative in patients unable to tolerate a sulfonamide.

Other drugs that have been tried with pyrimethamine include azithromycin,[2] clarithromycin,[3] and doxycycline.[4,5]

Alternative regimens tried for long-term maintenance therapy in patients with AIDS have included pyrimethamine plus sulfadiazine given twice weekly[6,7] or pyrimethamine alone in doses of 25 mg or 50 mg daily or 50 mg three times weekly.[8-10] However, results from a study involving 396 patients suggested that the mortality rate was higher in those receiving pyrimethamine 25 mg three times weekly for primary prophylaxis than in those receiving placebo.[11] Pyrimethamine with dapsone given once a week can provide effective prophylaxis but was not well tolerated.[12] Pyrimethamine with sulfadoxine, also given once weekly, was of benefit in bone-marrow transplant recipients.[13]

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Saba J, *et al.* Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis* 1993; **12:** 853–6.
3. Fernandez-Martin J, *et al.* Pyrimethamine-clarithromycin combination therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1991; **35:** 2049–52.
4. Morris JT, Kelly JW. Effective treatment of cerebral toxoplasmosis with doxycycline. *Am J Med* 1992; **93:** 107–8.
5. Hagberg L, *et al.* Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis* 1993; **25:** 157–60.
6. Pedrol E, *et al.* Central nervous system toxoplasmosis in AIDS patients: efficacy of an intermittent maintenance therapy. *AIDS* 1990; **4:** 511–17.
7. Podzanczer D, *et al.* Twice-weekly maintenance therapy with sulfadiazine-pyrimethamine to prevent recurrent toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1995; **123:** 175–80.
8. Murphy K, *et al.* Pyrimethamine alone as long-term suppressive therapy in cerebral toxoplasmosis. *Am J Med* 1994; **96:** 95–6.
9. de Gans J, *et al.* Pyrimethamine alone as maintenance therapy for central nervous system toxoplasmosis in 38 patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1992; **5:** 137–42.
10. Leport C, *et al.* Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. *J Infect Dis* 1996; **173:** 91–7.
11. Jacobson MA. *et al.* Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced human immunodeficiency virus disease: results of a randomized trial. *J Infect Dis* 1994; **169:** 384–94.
12. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20:** 531–41.
13. Foot ABM, *et al.* Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. *Bone Marrow Transplant* 1994; **14:** 241–5.

Preparations

BP 2008: Pyrimethamine Tablets;
USP 31: Pyrimethamine Tablets; Sulfadoxine and Pyrimethamine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Daraprim; ***Austral.:*** Daraprim; ***Austria:*** Daraprim; ***Belg.:*** Daraprim; ***Braz.:*** Daraprin; ***Canad.:*** Daraprim; ***Chile:*** Daraprim; ***Fr.:*** Malocide; ***Ger.:*** Daraprim; ***Irl.:*** Daraprim†; ***Israel:*** Daraprim†; ***Malaysia:*** Fansidar; ***Mex.:*** Daraprim; ***Neth.:*** Daraprim; ***Pol.:*** Daraprim; ***S.Afr.:*** Daraprim; ***Spain:*** Daraprim; ***Switz.:*** Daraprim; ***Thai.:*** Daraprim†; ***UK:*** Daraprim; ***USA:*** Daraprim.

Multi-ingredient: ***Austral.:*** Fansidar; Maloprim; ***Belg.:*** Co-Arinate; Dafrafin; Malastop†; ***Braz.:*** Fansidar; ***Canad.:*** Fansidar†; ***Denm.:*** Fansidar†; ***Fr.:*** Fansidar; ***India:*** Artemal†; Laridox; Pyralfin; Pyramet; Rimodar; ***Indon.:*** Fansidar; Suldox; ***Irl.:*** Fansidar; Maloprim†; ***Israel:*** Fansidar; ***Ital.:*** Metakelfin; ***Malaysia:*** Madomine; ***Philipp.:*** Fansidar; ***S.Afr.:*** Fansidar; Maloprim†; ***Singapore:*** Madomine†; Pyrisone; ***Switz.:*** Fansidar; Fansimef†; ***Thai.:*** Vivaxine†; ***UK:*** Fansidar; ***USA:*** Fansidar.

Pyronaridine Phosphate *(rINNM)*

Fosfato de pironaridina; Malaridine Phosphate; Pyronaridine, Phosphate de; Pyronaridini Phosphas. 7-Chloro-2-methoxy-10-[3,5-bis(pyrrolidinomethyl)-4-hydroxyanilino]benzo-[*b*]-1,5-naphthyridine phosphate.

Пиронаридина Фосфат

$C_{29}H_{32}ClN_5O_2,4H_3PO_4 = 910.0.$

CAS — 74847-35-1 (pyronaridine); 76748-86-2 (pyronaridine phosphate).

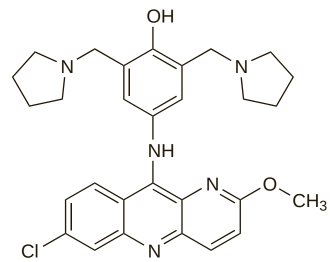

(pyronaridine)

Pharmacopoeias. In *Chin.*

Profile

Pyronaridine is a naphthyridine derivative used in China in the treatment of vivax malaria and chloroquine-resistant falciparum malaria. Its use has also been investigated in Africa and in Thailand. Combination of pyronaridine with artesunate is also being investigated. Pyronaridine has been given as the phosphate by mouth or by intramuscular or intravenous injection.

◊ References.

1. Shao B-R. A review of antimalarial drug pyronaridine. *Chin Med J* 1990; **103:** 428–34.
2. Shao B-R, *et al.* A 5-year surveillance of sensitivity in vivo of Plasmodium falciparum to pyronaridine/sulfadoxine/pyrimethamine in Diaoluo area, Hainan province. *Southeast Asian J Trop Med Public Health* 1991; **22:** 65–7.
3. Chen C, *et al.* Studies on a new antimalarial compound: pyronaridine. *Trans R Soc Trop Med Hyg* 1992; **86:** 7–10.
4. Winstanley P. Pyronaridine: a promising drug for Africa? *Lancet* 1996; **347:** 2–3.
5. Ringwald P, *et al.* Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet* 1996; **347:** 24–8.
6. Looareesuwan S, *et al.* Pyronaridine. *Lancet* 1996; **347:** 1189–90.
7. Anonymous. Pyronaridine: yet another promising antimalarial substance from China. *WHO Drug Inf* 1996; **10:** 9–10.
8. Looareesuwan S, *et al.* Clinical study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 205–9.
9. Ringwald P, *et al.* Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis* 1998; **26:** 946–53.

Quinine *(BAN)*

China; Chininum; Kiniini; Kinin; Quinina. (8*S*,9*R*)-6′-Methoxycinchonan-9-ol; (α*R*)-α-(6-Methoxy-4-quinolyl)-α-[(2*S*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2 = 324.4.$

CAS — 130-95-0 (anhydrous quinine).

ATC — P01BC01.

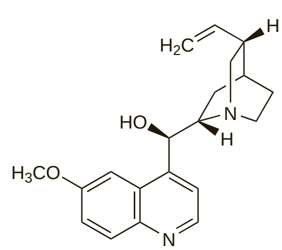

Description. Quinine is the chief alkaloid of various species of *Cinchona* (Rubiaceae). It is an optical isomer of quinidine.

Quinine Bisulfate

Chininum Bisulfuricum; Neutral Quinine Sulphate; Quinina, bisulfato de; Quinine Acid Sulphate; Quinine Bisulphate *(BANM)*; Quinini Bisulfas.

$C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O = 548.6.$

CAS — 549-56-4 (anhydrous quinine bisulfate).

ATC — P01BC01.

Pharmacopoeias. In *Br., Int.*, and *Viet.*

BP 2008 (Quinine Bisulphate). Colourless crystals or a white crystalline powder. It effloresces in dry air. Freely soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 2.8 to 3.4. Protect from light.

Quinine Dihydrochloride *(BANM)*

Chinini Dihydrochloridum; Neutral Quinine Hydrochloride; Quinina, dihidrocloruro de; Quinine Acid Hydrochloride; Quinini Dihydrochloridum.

$C_{20}H_{24}N_2O_2,2HCl = 397.3.$

CAS — 60-93-5.

ATC — P01BC01.

Pharmacopoeias. In *Br., Chin.*, and *Int.*

Viet. includes the injection.

BP 2008 (Quinine Dihydrochloride). A white or almost white powder. Very soluble in water; soluble in alcohol. A 3% solution in water has a pH of 2.0 to 3.0. Protect from light.

Quinine Etabonate

Euquinina; Euquinine; Quinina, etilcarbonato de; Quinine Ethyl Carbonate.

$C_{23}H_{28}N_2O_4 = 396.5.$

CAS — 83-75-0.

ATC — P01BC01.

Pharmacopoeias. In *Jpn.*

Quinine Hydrobromide *(BANM)*

Basic Quinine Hydrobromide; Chinini Bromidum; Quinina, hidrobromuro de; Quinine Monohydrobromide.

$C_{20}H_{24}N_2O_2,HBr,H_2O = 423.3.$

CAS — 549-49-5 (anhydrous quinine hydrobromide).

ATC — P01BC01.

Pharmacopoeias. In *Fr.*

Quinine Hydrochloride *(BANM)*

Basic Quinine Hydrochloride; Chinin hydrochlorid dihydrát; Chinini hydrochloridum; Chininii Chloridum; Chininium Chloratum; Chinino hidrochloridas; Chininum Hydrochloricum; Chininy chlorowodorek; Kiniinihydrokloridi; Kinin-hidroklorid; Kininhydroklorid; Quinina, hidrocloruro de; Quinine, chlorhydrate de; Quinine Monohydrochloride; Quinini Hydrochloridum; Quinini Hydrochloridum Dihydricum.

$C_{20}H_{24}N_2O_2,HCl,2H_2O = 396.9.$

CAS — 130-89-2 (anhydrous quinine hydrochloride); 6119-47-7 (quinine hydrochloride dihydrate).

ATC — P01BC01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn*, and *Viet.*

Ph. Eur. 6.2 (Quinine Hydrochloride). White or almost white, or colourless, fine, silky needles, often grouped in clusters. Soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

Quinine Sulfate

Basic Quinine Sulphate; Chinin sulfát dihydrát; Chinini sulfas; Chinino sulfatas; Chininum Sulfuricum; Chininy siarczan; Kiniinisulfaatti; Kininsulfat; Kinin-szulfát; Quinina, sulfato de; Quinine, sulfate de; Quinine Sulphate *(BANM)*; Quinini Sulfas; Quinini Sulfas Dihydricus.

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O = 782.9.$

CAS — 804-63-7 (anhydrous quinine sulfate); 6119-70-6 (quinine sulfate dihydrate).

ATC — P01BC01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US*, and *Viet.*

Ph. Eur. 6.2 (Quinine Sulphate). A white or almost white, crystalline powder or fine, colourless needles. Slightly soluble in water; sparingly soluble in boiling water and in alcohol. A 1% suspension in water has a pH of 5.7 to 6.6. Protect from light.

USP 31 (Quinine Sulfate). It is the sulfate of an alkaloid obtained from the bark of species of *Cinchona*. White, odourless, fine needle-like crystals, usually lusterless, making a light and readily compressible mass. It darkens on exposure to light. Soluble 1 in 500 of water and 1 in 120 of alcohol; sparingly soluble in water at 100°; slightly soluble in chloroform; freely soluble in alcohol at 80° and in a mixture of 2 parts of chloroform and one part of dehydrated alcohol; very slightly soluble in ether; Its saturated solution in water is neutral or alkaline to litmus. Protect from light.

Sorption. For reference to loss of quinine sulfate from solutions during membrane filtration, see Chloroquine, p.599.

Adverse Effects

Quinine or its salts given in usual therapeutic doses may give rise to a train of symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo.

Cinchonism may also occur after small doses in patients hypersensitive to quinine, but urticaria and flushing of the skin with intense pruritus are the most frequent reactions seen in these patients. Other effects include fever, skin rashes, and dyspnoea. Angioedema may also occur and asthma can be precipitated. Thrombocytopenia and other blood disorders have been reported. Thrombocytopenic purpura has been associated with quinine hypersensitivity. Haemoglobinuria occurs rarely.

Other adverse effects of quinine include hypoglycaemia, hypoprothrombinaemia, and renal failure.

The main symptoms of overdosage, which can be fatal, include gastrointestinal effects, oculotoxicity, CNS disturbances, and cardiotoxicity. Visual disturbances including sudden blindness are usually slowly reversible but there may be residual damage. Overdosage is discussed in detail below. Quinine can produce cardiovascular toxicity similar to that seen with quinidine, including conduction disturbances, arrhythmias, anginal symptoms, and hypotension leading to cardiac arrest and circulatory failure. Severe or even fatal cardiovascular toxicity can result from rapid intravenous dosage of quinine.

Large amounts of quinine can induce abortion; congenital malformations, particularly of the optic and auditory nerves, have been reported after failure to induce abortion with quinine. However, quinine should not be withheld from pregnant women with life-threatening malaria (see also under Pregnancy in Precautions, below).

Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; tetanus has developed in some patients (see under Malaria in Uses and Administration, below).

Effects on the blood. Between 1966 and 1975 the Swedish Adverse Drug Reaction Committee received 43 reports of *thrombocytopenia* attributable to quinine or quinidine[1] and the Boston Collaborative Drug Surveillance Program had 11 similar reports in patients studied between 1972 and 1981.[2] The FDA in the USA subsequently received details of 2 fatalities due to quinine-induced thrombocytopenia.[3] Up to October 2004, there had also been 228 cases of thrombocytopenia reported to the Australian Adverse Drug Reactions Advisory Committee, including 6 fatalities.[4] Quinine-induced thrombocytopenia appears to be a hypersensitivity reaction and beverages containing quinine as a bitter in concentrations as low as 20 micrograms/mL have precipitated thrombocytopenic purpura in previously sensitised individuals.[5]

Although quinine can cause *haemolysis*, there is some doubt over the traditional view that irregular dosage with quinine predisposes patients with malaria to *blackwater fever*, a syndrome of severe haemolytic anaemia, haemoglobinuria, oliguria, and renal failure.[6] Some of the patients affected may have had G6PD deficiency.[6] Haemolytic-uraemic syndrome[7-9] and pancytopenia with coagulopathy and renal impairment[10,11] have also been associated with the use of quinine.

There have also been reports of *disseminated intravascular coagulation*, including one fatality, after use of quinine by patients with quinine hypersensitivity.[12-14] In one case[14] the hypersensitivity reaction closely mimicked septic shock.

There have been isolated reports of *agranulocytosis* due to quinine.[15]

1. Böttiger LE, *et al.* Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Danielson DA, *et al.* Drug-induced blood disorders. *JAMA* 1984; **252:** 3257–60.
3. Freiman JP. Fatal quinine-induced thrombocytopenia. *Ann Intern Med* 1990; **112:** 308–9.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 01/11/04)
5. Murray JA, *et al.* Bitter lemon purpura. *BMJ* 1979; **2:** 1551–2.
6. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
7. Hagley MT, *et al.* Hemolytic-uremic syndrome associated with ingestion of quinine. *Am J Nephrol* 1992; **12:** 192–5.
8. Gottschall JL, *et al.* Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. *Am J Hematol* 1994; **47:** 283–9.
9. McDonald SP, *et al.* Quinine-induced hemolytic uremic syndrome. *Clin Nephrol* 1997; **47:** 397–400.
10. Maguire RB, *et al.* Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. *Ann Intern Med* 1993; **119:** 215–17.
11. Schmitt SK, Tomford JW. Quinine-induced pancytopenia and coagulopathy. *Ann Intern Med* 1994; **120:** 90–1.
12. Spearing RL, *et al.* Quinine-induced disseminated intravascular coagulation. *Lancet* 1990; **336:** 1535–7.
13. Barr E, *et al.* Recurrent acute hypersensitivity to quinine. *BMJ* 1990; **301:** 323.
14. Schattner A. Quinine hypersensitivity simulating sepsis. *Am J Med* 1998; **104:** 488–90.
15. Sutherland R, *et al.* Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. *BMJ* 1977; **1:** 605–7.

Effects on the ears. Although ototoxicity such as tinnitus or deafness is known to be a possible adverse effect of quinine, reversible hearing loss may also occur. While one group of workers[1] found the reduction in auditory acuity to be greatest at higher frequencies, another group[2] have found that hearing loss was generally equal across the range of frequencies tested and appeared to be related to the plasma concentration of quinine.

1. Roche RJ, *et al.* Quinine induces reversible high-tone hearing loss. *Br J Clin Pharmacol* 1990; **29:** 780–2.
2. Karlsson KK, *et al.* Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 765–7.

Effects on the eyes. Oculotoxicity after overdosage with quinine is well recognised (see below), but there has also been a report of blindness in two patients occurring during supposedly routine therapy.[1]

1. Waddell K. Blindness from quinine as an antimalarial. *Trans R Soc Trop Med Hyg* 1996; **90:** 331–2.

Effects on glucose metabolism. Hypoglycaemia is now recognised to be a frequent complication encountered in falciparum malaria and it is often associated with a poor prognosis. Children, pregnant women, and patients with severe disease appear to be particularly at risk. It is important to recognise that hypoglycaemia rather than cerebral malaria may be the cause of coma. Hypoglycaemia may also be induced by antimalarial therapy; first episodes of hypoglycaemia have been detected after patients received quinine[1-3] or quinidine[4] intravenously, although others have not found that quinine led to the development of hypoglycaemia.[5,6]

Quinine has also been reported to induce hypoglycaemia during treatment for leg cramps.[7]

1. White NJ, *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; **309:** 61–6.
2. Okitolonda W, *et al.* High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *BMJ* 1987; **295:** 716–18.
3. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
4. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.
5. Taylor TE, *et al.* Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988; **319:** 1040–7.
6. Kawo NG, *et al.* The metabolic effects of quinine in children with severe and complicated Plasmodium falciparum malaria in Dar es Salaam. *Trans R Soc Trop Med Hyg* 1991; **85:** 711–13.
7. Limburg PJ, *et al.* Quinine-induced hypoglycemia. *Ann Intern Med* 1993; **119:** 218–19.

Effects on the heart. Cardiotoxicity after overdosage with quinine is well recognised, and prolongation of the QT interval has been noted with therapeutic doses. There has also been a report[1] of fatal ventricular fibrillation with QT prolongation in an elderly patient who received standard doses of quinine by slow intravenous infusion for falciparum malaria. It was noted that the patient had some prolongation of the QT interval before starting quinine and also that her free quinine concentrations were unusually high despite total quinine concentrations considered to be within the therapeutic range.

1. Bonington A, *et al.* Fatal quinine cardiotoxicity in the treatment of falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 305–7.

Effects on the kidneys. See Effects on the Blood, above.

Effects on the liver. Although hepatitis has been associated with quinidine therapy (see p.1383), there appear to be few reports of hepatotoxicity due to quinine usage. Granulomatous hepatitis has been reported in 2 patients taking quinine,[1,2] but the diagnosis in the first of these cases was challenged as the histological findings were considered to be more indicative of non-specific reactive hepatitis.[3] Hepatotoxicity due to quinine hypersensitivity has been reported in another patient.[4] Symptoms of hepatotoxicity occurred within 24 hours in a further patient taking quinine for nocturnal leg cramps.[5]

1. Katz B, *et al.* Quinine-induced granulomatous hepatitis. *BMJ* 1983; **286:** 264–5.
2. Mathur S, *et al.* Quinine induced granulomatous hepatitis and vasculitis. *BMJ* 1990; **300:** 613.
3. Nirodi NS. Quinine induced granulomatous hepatitis. *BMJ* 1983; **286:** 647.
4. Punukollu RC, *et al.* Quinine hepatotoxicity: an underrecognized or rare phenomenon? *Arch Intern Med* 1990; **150:** 1112–13.
5. Farver DK, Lavin MN. Quinine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 32–4.

Effects on the skin. Urticaria, cutaneous flushing, various skin rashes, and pruritus are the commonest symptoms of hypersensitivity reactions to quinine.

Topical contact with quinine may cause contact as well as photocontact allergy, but quinine can also induce photosensitivity reactions after systemic dosage.[1,2] Photosensitivity associated with quinine intake from excessive consumption of tonic water has been reported.[3] There have also been reports of eczematous dermatitis,[1] oedema and erythema,[4] and lichen planus.[4] Both phototoxic[4] and photoallergic[1] mechanisms have been suggested. Fatal cutaneous vasculitis related to quinine treatment for nocturnal cramps has been reported.[5]

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p.600.

1. Ljunggren B, Sjövall P. Systemic quinine photosensitivity. *Arch Dermatol* 1986; **122:** 909–11.
2. Ljunggren B, *et al.* Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact Dermatitis* 1992; **26:** 1–4.
3. Wagner GH, *et al.* 'I'll have mine with a twist of lemon': quinine photosensitivity from excessive intake of tonic water. *Br J Dermatol* 1994; **131:** 734–5.
4. Ferguson J, *et al.* Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol* 1987; **117:** 631–40.
5. Price EJ, *et al.* Quinine-induced cutaneous vasculitis. *Br J Clin Pract* 1992; **46:** 138–9.

Hypersensitivity. For reference to hypersensitivity reactions associated with quinine, see Effects on the Blood, Effects on the Liver, and Effects on the Skin, above.

Overdosage. Cinchonism may occur with therapeutic doses of quinine and symptoms include nausea, vomiting, tinnitus, deafness, headache, vasodilatation, and slightly disturbed vision. These symptoms may also occur in acute overdosage, but the visual disorders may be severe and there may be CNS disturbances and cardiotoxicity. A lethal dose or lethal plasma-quinine concentration has not been established but fatalities have been reported[1] in adults after doses of 2 to 8 g and in children after 1 g.

An analysis[2] of 165 cases of acute quinine poisoning revealed that: 21% had no symptoms, nausea with or without vomiting occurred in 47%, visual disturbances in 42%, tinnitus in 38%, other auditory disturbances in 23%, sinus tachycardia in 23%, and other ECG abnormalities in 8%. Mild impairment of consciousness was reported in 14% of the patients while 7 (4%) patients had deeper grades of coma. Of the 5 patients who died, 4 developed intractable ventricular arrhythmias and the fifth had a Jacksonian fit followed by cardiac arrest.

The effects of oculotoxicity may include blurred vision, defective colour perception, visual field constriction, and total blindness.[2,3] The onset of symptoms may vary from a few hours to a day or more after ingestion.[2,3] Suggested mechanisms for the oculotoxicity of quinine include an action on the retinal vasculature to produce ischaemia or a direct toxic effect on the retina.[1] Visual loss in one group of patients[3] was associated with plasma-quinine concentrations in excess of 10 micrograms/mL. However, in another group plasma-quinine concentrations were considered to be an imprecise guide to predicting visual disturbances.[2] The speed and degree of visual recovery varies. Of 70 patients with visual disturbances after quinine poisoning, 39 subsequently had a period of total blindness.[2] Permanent visual deficits remained in 19 of these but no patient had permanent bilateral blindness. All of the 31 patients who had had blurred vision recovered full visual acuity.

It is considered that the actions of quinine on the myocardium are similar to those of quinidine but that it is less potent.[1] Sinus tachycardia and minor ECG changes are the most common cardiovascular effects. Conduction abnormalities and ventricular dysrhythmias may occur with severe poisoning. Ventricular tachycardia is mostly associated with cardiogenic shock or circulatory collapse. Hypokalaemia may also occur.[1]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
3. Dyson EH, *et al.* Death and blindness due to overdose of quinine. *BMJ* 1985; **291:** 31–3.

Treatment of Adverse Effects

In acute overdosage with quinine or its salts multiple doses of activated charcoal may be given to adults or children who present within one hour of ingesting more than the equivalent of 30 mg/kg of quinine base or any amount in a child under 2 years of age; gastric lavage may also be considered for use in adults. Other measures aimed at enhancing the elimination of quinine are largely ineffective. Treatment is mostly symptomatic with attention being given to maintaining blood pressure, respiration, and renal function, and to treating arrhythmias.

Vasodilators and stellate ganglion block have been used to prevent or reverse visual impairment but there is little evidence to support their use.

◊ It has been suggested that, as quinine has antimuscarinic effects, gastric emptying may be delayed and considerable amounts of drug might be removed from the stomach beyond the usual 4 hours.[1] Others consider that gastric lavage is of doubtful value as quinine is rapidly absorbed and vomiting has often occurred before admission.[2] However, studies in healthy subjects and poisoned patients suggest that oral activated charcoal may increase the elimination of quinine.[3,4] Other methods of increasing elimination are probably ineffective. In a study involving 16 patients with quinine poisoning forced acid diuresis, haemodialysis, haemoperfusion, or plasma exchange were all found to be ineffective in increasing quinine elimination.[5]

Stellate ganglion block has been recommended to prevent or reverse retinal damage, the rationale being that quinine-induced oculotoxicity might arise from retinal arteriolar constriction. However, clinical studies have failed to find sufficient improvement to justify its use.[6,7] Intravenous nitrates produced beneficial responses in 2 patients.[8]

1. Boland M, Volans G. ABC of poisoning: miscellaneous drugs. *BMJ* 1984; **289:** 1361–5.
2. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
3. Lockey D, Bateman DN. Effect of oral activated charcoal on quinine elimination. *Br J Clin Pharmacol* 1989; **27:** 92–4.
4. Prescott LF, *et al.* Treatment of quinine overdosage with repeated oral charcoal. *Br J Clin Pharmacol* 1989; **27:** 95–7.
5. Bateman DN, *et al.* Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. *Q J Med* 1985; **54:** 125–31.
6. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
7. Dyson EH, *et al.* Quinine amblyopia: is current management appropriate? *J Toxicol Clin Toxicol* 1985–6; **23:** 571–8.
8. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Precautions

Quinine and its salts are contra-indicated in patients with a history of hypersensitivity to quinine or quinidine and in patients with tinnitus or optic neuritis. They should not be used in the presence of haemolysis. They should be used with caution in patients with atrial fibrillation, cardiac conduction defects, or heart block. Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition.

Pregnancy in a patient with malaria is not generally regarded as a contra-indication to the use of quinine.

As quinine has been implicated in precipitating blackwater fever it is generally contra-indicated in patients who have already suffered an attack. Quinine may also cause haemolysis in some types of G6PD deficiency and should be used with care.

It is important that when quinine is given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity. Blood-glucose concentrations should also be monitored. Problems that have been associated with intramuscular use are discussed under Malaria in Uses and Administration, below.

Breast feeding. Although quinine is distributed into breast milk in small amounts,[1] the American Academy of Pediatrics considers that the use of quinine is probably compatible with breast feeding.[2]

1. Phillips RE, *et al.* Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br J Clin Pharmacol* 1986; **21:** 677–83.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/04/04)

Liver disease. See under Pharmacokinetics, below.

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that quinine is considered to be safe for use in such patients, see under Precautions for Chloroquine, p.601.

Pregnancy. The use of quinine in large doses as an abortifacient in the past has led to concern over its use during pregnancy, but no evidence of an oxytocic effect was found when it was used to treat severe falciparum malaria in women in the third trimester of pregnancy.[1]

Congenital abnormalities including damage to the auditory and optic nerves have been seen, usually after attempted abortions, but WHO[2] considers quinine to be safe when used in normal therapeutic doses during pregnancy (although the problem of hypoglycaemia in the second and third trimesters may mean that artemisinin derivatives are preferred). Jitteriness attributed to quinine withdrawal has been reported in an infant whose mother had drunk large quantities of tonic water containing quinine during the last 17 weeks of pregnancy.[3]

As malaria is potentially serious during pregnancy and poses a threat to the mother and fetus, there appears to be little justification for withholding treatment in the absence of a suitable alternative. However, pregnant patients treated for malaria are at special risk from hypoglycaemia exacerbated or caused by quinine-induced hyperinsulinaemia (see under Effects on Glucose Metabolism in Adverse Effects, above) and should be managed appropriately.

1. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 07/07/06)
3. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.

Renal impairment. See under Pharmacokinetics, below.

Interactions

As quinine shares many of the actions of quinidine, interactions seen between quinidine and other drugs (see p.1384) might also occur with quinine. Both have actions on skeletal muscle and may potentiate the effects of drugs with neuromuscular-blocking activity (see under Antiarrhythmics on p.1903). There is an increased risk of inducing ventricular arrhythmias if quinine is given with halofantrine (see p.604) or other arrhythmogenic drugs such as amiodarone, the antihistamines astemizole and terfenadine, cisapride, and the antipsychotic pimozide. There may be an increased risk of convulsions when quinine is given with mefloquine.

Amantadine. For a report of quinine reducing renal clearance of amantadine, see Antiarrhythmics, p.793.

Anticoagulants. Quinine can cause hypoprothrombinaemia and thereby enhance the effect of anticoagulants. In one report, reductions in *warfarin* dosage were necessary after ingestion of large amounts of tonic water containing quinine (see p.1429).

Antimalarials. Quinine and *chloroquine* may be antagonistic when used for falciparum malaria (see p.601). For a report of quinine reducing plasma concentrations of *primaquine*, see p.608.

Ciclosporin. For a report of quinine decreasing plasma concentrations of ciclosporin, see p.1826.

Digoxin. Quinidine has been reported to increase serum-digoxin concentrations (see Quinidine under Antiarrhythmics, p.1261) and quinine has reduced total body clearance of digoxin (see Antimalarials, p.1262).

Flecainide. For a report of quinine inhibiting the metabolism of flecainide, see p.1289.

Histamine H_2-antagonists. *Cimetidine* has been reported to reduce the clearance of quinine and prolong its elimination half-life in a study in healthy subjects; no significant effect was seen with *ranitidine*.[1]

1. Wanwimolruk S, *et al.* Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1986; **22:** 346–50.

Rifampicin. Elimination of quinine has been reported to increase in patients also receiving rifampicin.[1]

1. Wanwimolruk S, *et al.* Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* 1995; **40:** 87–91.

Tobacco smoking. A single-dose study in healthy subjects has suggested that blood concentrations of quinine are lower in heavy smokers than in non-smokers, potentially impairing efficacy.[1]

1. Wanwimolruk S, *et al.* Cigarette smoking enhances the elimination of quinine. *Br J Clin Pharmacol* 1993; **36:** 610–14.

Pharmacokinetics

The pharmacokinetics of quinine are altered significantly by malaria infection, the major effects being reductions in both its apparent volume of distribution and its clearance.

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation are attained about 1 to 3 hours after oral doses of the sulfate or bisulfate. Plasma protein binding is about 70% in healthy subjects and rises to 90% or more in patients with malaria. Quinine is widely distributed throughout the body. Concentrations attained in the CSF of patients with cerebral malaria have been reported to be about 2 to 7% of those in the plasma.

Quinine is extensively metabolised in the liver and rapidly excreted mainly in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5 to 20%. Excretion is increased in acid urine. The elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Small amounts of quinine also appear in the bile and saliva.

Quinine crosses the placenta and is distributed into breast milk (see Breast Feeding, above).

◊ References.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Supanaranond W, *et al.* Disposition of oral quinine in acute falciparum malaria. *Eur J Clin Pharmacol* 1991; **40:** 49–52.
3. Wanwimolruk S, *et al.* Pharmacokinetics of quinine in young and elderly subjects. *Trans R Soc Trop Med Hyg* 1991; **85:** 714–17.
4. Dyer JR, *et al.* The pharmacokinetics and pharmacodynamics of quinine in the diabetic and non-diabetic elderly. *Br J Clin Pharmacol* 1994; **38:** 205–12.
5. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol* 1996; **49:** 383–6.
6. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.
7. Boele van Hensbroek M, *et al.* Quinine pharmacokinetics in young children with severe malaria. *Am J Trop Med Hyg* 1996; **54:** 237–42.
8. Zhang H, *et al.* Evidence for involvement of human CYP3A in the 3-hydroxylation of quinine. *Br J Clin Pharmacol* 1997; **43:** 245–52.
9. Viriyayudhakorn S, *et al.* Pharmacokinetics of quinine in obesity. *Trans R Soc Trop Med Hyg* 2000; **94:** 425–8.

Administration in liver disease. Reduced clearance of quinine and prolonged elimination half-life have been reported in patients with acute hepatitis B given a single intravenous dose.[1] The results suggested that quinine accumulation after multiple doses could be greater in patients with hepatitis, even once hepatic function had returned to normal. In another study[2] patients with moderate chronic liver disease were given quinine orally; the half-life was prolonged but total clearance was not affected.

1. Karbwang J, *et al.* The pharmacokinetics of quinine in patients with hepatitis. *Br J Clin Pharmacol* 1993; **35:** 444–6.
2. Auprayoon P, *et al.* Pharmacokinetics of quinine in chronic liver disease. *Br J Clin Pharmacol* 1995; **40:** 494–7.

Administration in renal impairment. As urinary clearance comprises only 20% of total clearance of quinine, it appears that high plasma concentrations reported in patients with severe falciparum malaria and acute renal failure may be related more to the severity of the malaria, and associated pharmacokinetic changes, rather than to any reduction in the glomerular filtration rate.[1] There were significant changes in the pharmacokinetics of quinine in 6 patients with chronic renal failure after a single oral dose.[2] The changes included a prolonged half-life, but there was no clear relationship between severity of renal failure and the degree of impairment of quinine clearance.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Rimchala P, *et al.* Pharmacokinetics of quinine in patients with chronic renal failure. *Eur J Clin Pharmacol* 1996; **49:** 497–501.

Uses and Administration

Quinine is a cinchona alkaloid and a 4-methanolquinoline antimalarial that is a rapid-acting blood schizontocide with activity against *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. It is active against the gametocytes of *P. malariae* and *P. vivax*, but not against mature gametocytes of *P. falciparum*. The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias. The increasing spread of resistance to chloroquine has been responsible for the re-emergence of quinine as an important drug in the treatment of falciparum malaria. Quinine is not generally used for malaria prophylaxis.

Quinine is also used to treat the protozoal infection babesiosis and for the relief of nocturnal leg cramps.

Quinine has mild analgesic and antipyretic properties and is sometimes included in preparations used for the symptomatic relief of the common cold and influenza; additional salts that have been used for this purpose include the camsilate and the gluconate.

Quinine is also used as a bitter and a flavour.

Quinine is given as a number of salts and 100 mg of anhydrous quinine is equivalent to about:

- 169 mg of quinine bisulfate
- 122 mg of quinine dihydrochloride
- 122 mg of quinine etabonate
- 130 mg of quinine hydrobromide
- 122 mg of quinine hydrochloride
- 121 mg of quinine sulfate

For the treatment of **malaria** quinine is given orally, usually as the sulfate, hydrochloride, or dihydrochloride, or parenterally as the dihydrochloride; quinine etabonate is sometimes used orally because unlike other quinine salts, which are intensely bitter, it is tasteless. They all contain about the same amount of quinine and any of them can be used when the dose is cited in terms of "quinine salt"; this is not the case for the bisulfate, which contains a correspondingly smaller amount of quinine. Quinine formate is sometimes given parenterally.

A course of treatment with quinine for falciparum malaria usually lasts 7 days and in uncomplicated infections treatment should preferably be given by the oral route. The usual *oral* dose is 600 mg of quinine salt given every 8 hours for 7 days. For children, a dose of 10 mg of quinine salt per kg body-weight given every 8 hours for 7 days is recommended.

In severe or complicated falciparum malaria, or when the patient is unable to take oral medication, quinine should be given parenterally by slow intravenous infusion, but this can be hazardous and patients generally need monitoring, particularly for signs of cardiotoxicity. Therapy should be changed to the oral route as soon as possible to complete the course. To obtain therapeutic concentrations rapidly with parenteral therapy, quinine is often given in an initial loading dose followed by maintenance doses. A recommended *intravenous* dosage regimen suggested by WHO is an initial loading dose of 20 mg of quinine dihydrochloride per kg (up to a maximum of 1.4 g) given over 4 hours with maintenance infusions being started 8 hours later, calculated from the start of the previous infusion. Alternatively, in intensive care units, an initial loading dose of 7 mg/kg may be given over 30 minutes followed immediately by the first of the maintenance infusions. Maintenance infusions consist of 10 mg/kg (up to a maximum of 700 mg) given over 4 hours every 8 hours. A loading dose should not be given if the patient has received quinine, quinidine, mefloquine, or halofantrine, during the previous 24 hours. If parenteral therapy is required for more than 48 hours the maintenance dose of quinine dihydrochloride should be reduced to 5 to 7 mg/kg.

If intravenous infusion is not possible, quinine dihydrochloride has been given *intramuscularly*. Doses, including the loading dose, are the same as those used intravenously; the drug should be diluted in sodium chloride 0.9% to a concentration of 60 to 100 mg of the dihydrochloride per mL, and the total dose divided between two injection sites, preferably each anterior thigh (not the buttock). However, intramuscular injection can be irritant and there have been concerns regarding its safety and efficacy (see under Malaria, below).

When used for the relief of nocturnal **leg cramps**, quinine is given at night in an oral dose of 200 to 300 mg of the sulfate or bisulfate. Quinine benzoate has also been used.

Babesiosis. Although there is no established specific treatment for babesiosis (p.823), a combination of quinine and clindamycin has been used for *Babesia microti* infections.[1,2] For suggested doses see under Clindamycin, p.253. Quinine with azithromycin was reported to be effective in a patient who had not responded to quinine with clindamycin.[3]

1. Abramowicz M., ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter. 2007.
2. Wormser GP, *et al*. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/06/08)
3. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.

Flavouring. The Joint FAO/WHO Expert Committee on Food Additives concluded that quinine levels in soft drinks of up to 100 mg/litre (as quinine base) were not of toxicological concern.[1] However, because of the possibility of hypersensitivity reactions in some individuals, the committee recommended that consumers be informed of the presence of quinine in food or beverages.

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993.

Malaria. Quinine has had an important role in the treatment of falciparum malaria (see p.594) being used where there is chloroquine or multidrug *Plasmodium falciparum* resistance,[1-4] and also (in view of the widespread problem of *P. falciparum* resistance) where the infective species is not known, or if the infection is mixed. Treatment should be with one of the quinine salts given orally, with a dose of 600 mg of quinine salt for adults, or 10 mg/kg for children, every 8 hours for 7 days. The dose of quinine salt applies to the hydrochloride, dihydrochloride, sulfate, and etabonate, but not to the bisulfate. Any quinine lost through vomiting within one hour of an oral dose should be replaced by additional doses.[1]

The oral route may not provide effective treatment in severe infection and in such cases quinine should be given as the dihydrochloride by slow intravenous infusion, with the patient being observed closely, particularly for any signs of cardiotoxicity.[4] Loading doses of quinine are often used to obtain therapeutic blood concentrations as soon as possible in severely ill patients but they should not be given to patients who have received quinine, quinidine, mefloquine, or halofantrine, within the previous 24 hours.

WHO[3,4] has given recommendations for intravenous regimens comprising an initial loading dose and maintenance infusions (for details see Uses and Administration, above). Patients are transferred to oral therapy as soon as possible, and treatment continued until a total of at least 7 days of therapy has been given. If intravenous formulations of quinine are unavailable quinidine may be used as an alternative; for further details, see under the Uses and Administration of Quinidine, p.1385.

If facilities for intravenous infusion, including monitoring, are not available quinine may be given by deep intramuscular injection.[4] A loading dose of quinine dihydrochloride 20 mg/kg is given by injection in divided sites followed by injections of 10 mg/kg every 8 hours;[4] a dose interval of 12 hours has also been used. Patients should be transferred to oral therapy as soon as possible. The use of the intramuscular route has been controversial because of concerns over safety and efficacy. However, some studies have shown that it can safely be used in adults and children with severe infections.[5-8] Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; fatal tetanus has developed in some patients.[9] It has been suggested that some such reactions may be related to the use of preparations formulated in urethane or other irritant substances. Diluted solutions of quinine dihydrochloride 60 mg/mL adjusted to neutral pH appear to be less painful than the usual undiluted preparation of 300 mg/mL.

If facilities do not exist to give quinine parenterally then patients with severe malaria should receive quinine by mouth or nasogastric tube.

Quinine as formerly standardised used to contain a higher concentration of cinchona alkaloids and there might be synergy between mixtures of these alkaloids.[10] In practice no advantage has been shown by such mixtures over quinine alone in the treatment of chloroquine-resistant falciparum malaria.[11]

1. WHO. *WHO model formulary*. Geneva: WHO, 2004.
2. Molyneux M, Fox R. Diagnosis and treatment of malaria in Britain. *BMJ* 1993; **306:** 1175–80.
3. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO, 2000. Available at: http://www.who.int/malaria/docs/hbsm_toc.htm (accessed 16/07/07)
4. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 05/06/06)
5. Wattanagoon Y, *et al*. Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity. *BMJ* 1986; **293:** 11–13. Correction. *ibid.*; 362.
6. Mansor SM, *et al*. The safety and kinetics of intramuscular quinine in Malawian children with moderately severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 482–7.
7. Waller D, *et al*. The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 488–91.
8. Schapira A, *et al*. Comparison of intramuscular and intravenous quinine for the treatment of severe and complicated malaria in children. *Trans R Soc Trop Med Hyg* 1993; **87:** 299–302.
9. Yen LM, *et al*. Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet* 1994; **344:** 786–7.
10. Druilhe P, *et al*. Activity of a combination of three cinchona bark alkaloids against Plasmodium falciparum in vitro. *Antimicrob Agents Chemother* 1988; **32:** 250–4.
11. Bunnag D, *et al*. A combination of quinine, quinidine and cinchonine (LA 40221) in the treatment of chloroquine resistant falciparum malaria in Thailand: two double-blind trials. *Trans R Soc Trop Med Hyg* 1989; **83:** 66.

Muscle spasm. Quinine (usually as quinine sulfate or bisulfate) has traditionally been used for nocturnal cramps (p.1887) but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. In the USA, for example, the FDA ruled that quinine products should no longer be used for the management of nocturnal cramps.[1,2] A similar ban has been imposed in Australia.[3] Meta-analyses[4,5] concluded that although quinine was effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind. It was recommended that patients should be closely monitored while the efficacy of quinine is assessed over a period of at least 4 weeks. Some[6] have recommended that treatment be stopped every 3 months to see whether it is still needed.

Haemodialysis-induced cramp (p.1671) has been reported to respond to treatment with quinine[7,8] but similar concerns apply.

1. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
2. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 01/11/04)
4. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
5. Man-Son-Hing M, *et al*. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
6. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
7. Kaji DM, *et al*. Prevention of muscle cramps in haemodialysis patients by quinine sulphate. *Lancet* 1976; **ii:** 66–7.
8. Roca AO, *et al*. Dialysis leg cramps; efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.

Preparations

BP 2008: Quinine Bisulphate Tablets; Quinine Dihydrochloride Intravenous Infusion; Quinine Sulphate Tablets;
USP 31: Quinine Sulfate Capsules; Quinine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Circonyl; ***Austral.:*** Biquinate; Myoquin†; Quinate; Quinbisul; Quinoctal†; Quinsul; ***Braz.:*** Palukin; Paluquina†; ***Denm.:*** Kinin; ***Fr.:*** Quinoforme†; Surquina; ***Ger.:*** Limptar N; ***Gr.:*** Kinin†; ***India:*** Cinkona; Quinarsol; Quiningа; ***NZ:*** Q200; Q300; ***Swed.:*** Kinin; ***Thai.:*** Genin; ***USA:*** Qualaquin.

Multi-ingredient: ***Austria:*** Dilatol-Chinin; Iromin-Chinin-C; Limptar; Seltoc; ***Braz.:*** Monotrean; Monotrean B6; ***Fin.:*** Crampiton; Relapamil; ***Fr.:*** Dinacode†; Hexaquine; Okimus; Quinimax; ***Ger.:*** Limptar†; Togal Classic; ***Irl.:*** Anadin; ***Ital.:*** Monotrean†; ***Neth.:*** Aflukin C; ***NZ:*** Nicobrevin; ***Port.:*** Broncosil†; Rectopulmo Adultos†; ***Rus.:*** Analgin-Chinin (Анальгин-Хинин); ***S.Afr.:*** Ilvico; ***Spain:*** Brota Rectal Balsamico; ***UK:*** Nicobrevin.

Tafenoquine *(BAN, rINN)*

Tafenoquina; Tafénoquine; Tafenoquinum; WR-238605. (±)-8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[(α,α,α-trifluoro-*m*-tolyl)oxy]quinoline; (*RS*)-N^4-[2,6-Dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-yl]pentane-1,4-diamine.

Тафенохин

$C_{24}H_{28}F_3N_3O_3$ = 463.5.
CAS — 106635-80-7.

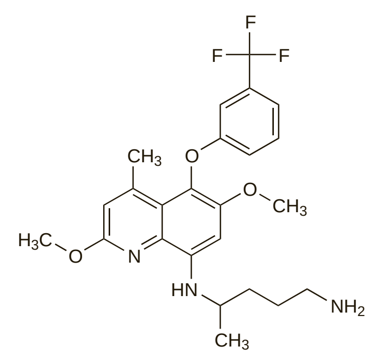

Profile

Tafenoquine is an 8-aminoquinoline antimalarial. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria.

◊ References.

1. Walsh DS, *et al*. Randomized dose-ranging study of the safety and efficacy of WR 238605 (tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. *J Infect Dis* 1999; **180:** 1282–7.
2. Lell B, *et al*. Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 2000; **355:** 2041–5.
3. Shanks GD, *et al*. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. *Clin Infect Dis* 2001; **33:** 1968–74.
4. Nasveld P, *et al*. Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. *Trans R Soc Trop Med Hyg* 2002; **96:** 683–4.
5. Hale BR, *et al*. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. *Clin Infect Dis* 2003; **36:** 541–9.
6. Walsh DS, *et al*. Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing Plasmodium vivax malaria relapse. *Clin Infect Dis* 2004; **39:** 1095–1103.
7. Walsh DS, *et al*. Efficacy of monthly tafenoquine for prophylaxis of Plasmodium vivax and multidrug-resistant P. falciparum malaria. *J Infect Dis* 2004; **190:** 1456–63.

Antimigraine Drugs

Cluster headache, p.616
Medication-overuse headache, p.616
Migraine, p.616
Post-dural puncture headache, p.617
Tension-type headache, p.617

This chapter reviews the management of headache, in particular migraine and cluster headache, and the drugs used mainly for their treatment. The mechanisms of head pain or headache are not fully understood but may involve neurovascular changes (as in migraine and cluster headache), muscle contraction (tension headache), nerve lesions (neuralgias), direct head injury, infection (meningitis), or referred pain (sinusitis, toothache, eye disorders). Headache is also an adverse effect of many drugs including, paradoxically, those used to treat it. The International Headache Society has published guidelines to aid the diagnosis of the various headache types. Patients may have more than one headache disorder simultaneously and require separate treatment for each.

◊ References.

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://216.25.100.131/ihscommon/guidelines/pdfs/ihc_II_main_no_print.pdf (accessed 01/10/04)

Cluster headache

Cluster headache (migrainous neuralgia, histaminic cephalalgia, Horton's syndrome) is of unknown aetiology but may be neurovascular in origin.[1-5] Patients experience one or more short-lived attacks of intense unilateral head pain, usually at the same time of day (often at night). These are associated with autonomic symptoms such as conjunctival injection or lachrymation, miosis or ptosis, nasal congestion or rhinorrhoea, forehead or facial sweating, and eyelid oedema. Restlessness during the attacks is characteristic. The period during which attacks occur is called a cluster period; it may last several weeks or months. In the typical episodic form of cluster headache, cluster periods are followed by periods of remission lasting for months or years but in the more rare chronic form, patients may have cluster periods lasting for more than a year, or with short periods of remission in between. Substances such as alcohol, histamine, or glyceryl trinitrate can precipitate headache attacks during cluster periods, but not during periods of remission. There is speculation that sleep-disordered breathing[6] and increased body heat[7] may also trigger cluster headaches.

The **treatment** of individual acute attacks during a cluster period is difficult because the headache is short-lived and oral analgesics are unlikely to be absorbed fast enough to produce much benefit.[1,3,4] Inhalation of 100% oxygen is rapid and effective in aborting attacks, but has practical difficulties; inhaled ergotamine has also been used. Some consider subcutaneous sumatriptan to be the acute therapy of choice in cluster attacks.[4,5] Dihydroergotamine is also effective but generally has to be given by injection and is usually reserved for use in emergency settings. Intranasal dihydroergotamine and intranasal sumatriptan have also been used.[1,4] Oral zolmitriptan may be considered for patients who cannot tolerate subcutaneous or intranasal sumatriptan and oxygen, or who prefer oral medication.[4] Intranasal instillation of lidocaine has been reported to be of some benefit but most patients do not obtain complete pain relief.[1,3,4]

Since individual attacks are difficult to treat it is probably more effective to manage cluster headache by **prophylaxis** once a cluster period has started. Ergotamine may be used for prevention in episodic cluster headache; it is given by mouth or rectally for limited periods of up to 2 weeks. It is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended. Other drugs that have been used, either alone or with ergotamine, include verapamil, lithium carbonate, and prednisolone. Some consider verapamil to be the preventive therapy of choice[1,4,8] particularly in patients with chronic long-lasting cluster periods.[5] Lithium may also be useful for the chronic form of the disorder. Methysergide and corticosteroids are considered by some to be the drugs of choice in those with short-lasting cluster periods (less than 2 months).[5] Pizotifen and valproate have also been tried;[1,3,5] other drugs under investigation include gabapentin, melatonin, and topiramate.[4]

Paroxysmal hemicrania is a rare variant of cluster headache and differs mainly in the high frequency and shorter duration of individual attacks. One of its features, which may be diagnostic, is its invariable response to indometacin.

1. Dodick DW, Capobianco DJ. Treatment and management of cluster headache. *Curr Pain Headache Rep* 2001; **5:** 83–91.
2. Zakrzewska JM. Cluster headache: review of literature. *Br J Oral Maxillofac Surg* 2001; **39:** 103–13.
3. Ekbom K, Hardebo JE. Cluster headache: aetiology, diagnosis and management. *Drugs* 2002; **62:** 61–9.
4. Matharu MS, *et al.* Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; **63:** 1637–77.
5. May A. Cluster headache: pathogenesis, diagnosis, and management. *Lancet* 2005; **366:** 843–55.
6. Chervin RD, *et al.* Sleep disordered breathing in patients with cluster headache. *Neurology* 2000; **54:** 2302–6.
7. Blau JN, Engel HO. A new cluster headache precipitant: increased body heat. *Lancet* 1999; **354:** 1001–2.
8. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January 2007). Available at: http://216.25.100.131/upload/NS_BASH/BASH_guidelines_2007.pdf (accessed 22/08/08)

Medication-overuse headache

Overuse of drugs such as ergotamine, triptans, and analgesics (including opioids and combination preparations containing caffeine or butalbital) to treat headache or migraine can lead to dependence and paradoxical chronic daily headache in headache-prone patients.[1-3] Such headaches do not appear to occur with regular use of analgesics to treat other disorders except occasionally in patients with a history of migraine.[1] Medication-overuse headaches, also referred to as rebound, analgesic abuse, or analgesic-induced headaches, can be difficult to treat and are relieved by withdrawal of the offending drug, but the primary headache may still persist and revert to its previous pattern of occurrence. Furthermore, stopping abruptly can exacerbate headache and produce other symptoms of withdrawal. This may then lead the patient to resume treatment to relieve the headache thereby setting up a vicious circle.

Options for outpatient treatment include either abrupt[4] or gradual withdrawal of the overused drug. Substitution with long-acting NSAID or intramuscular dihydroergotamine has been tried in withdrawal from ergotamine or analgesics;[4-6] prednisolone has also been used.[4] However, withdrawal symptoms may persist for up to 2 weeks and detoxification from ergotamine or analgesics may require hospitalisation; intravenous metoclopramide and repetitive intravenous dihydroergotamine may be required to control nausea and vomiting and intractable headache, respectively.[5] Although withdrawal from triptans has been reported to be of shorter duration with no intensive withdrawal symptoms, triptan overuse produces headaches at a faster rate and at lower dosages compared with ergotamine and analgesics, and is associated with an increase in migraine attack frequency.[1] General advice on the prevention of medication-overuse headache has included limiting the frequency of use of such drugs,[1,3,5] and starting prophylactic therapy in migraine patients having more than 2 headache days a week.[3,4]

1. Limmroth V, Katsarava Z. Medication overuse headache. *Curr Opin Neurol* 2004; **17:** 301–6.
2. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://216.25.100.131/ihscommon/guidelines/pdfs/ihc_II_main_no_print.pdf (accessed 05/10/04)
3. Smith TR, Stoneman J. Medication overuse headache from antimigraine therapy: clinical features, pathogenesis and management. *Drugs* 2004; **64:** 2503–14.
4. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January 2007). Available at: http://216.25.100.131/upload/NS_BASH/BASH_guidelines_2007.pdf (accessed 22/08/08)
5. Silberstein SD, Young WB. Analgesic rebound headache. *Drug Safety* 1995; **13:** 133–44.
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Migraine

Migraine is characterised by recurrent attacks of headache which typically last 4 to 72 hours. Attacks persisting for longer than 72 hours are referred to as status migrainosus. The headache is usually a unilateral pulsating pain that is aggravated by movement and is usually of sufficient severity to disturb or prevent daily activities. It is frequently accompanied by nausea, vomiting, or other gastrointestinal disturbances and there may be photophobia and phonophobia. Migraine with aura (classic migraine) is characterised by an aura consisting of visual or sensory symptoms that lasts less than an hour. The headache usually follows the aura directly, or within 1 hour, but may begin simultaneously with the aura. In addition, aura can occur without headache. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients with migraine. Premonitory symptoms may occur before a migraine attack (with or without aura). Familial hemiplegic migraine is a rare syndrome in which migraine with aura may be preceded or accompanied by dysphasia, confusion, and hemiparesis. Basilar-type migraine is another rare form of migraine with aura in which there may be disturbances of the brain stem or occipital lobes accompanied by symptoms such as decreased level of consciousness, vertigo, ataxia, dysarthria, and diplopia.

Migraine is described as a neurovascular headache. Traditionally, intracranial vasoconstriction was considered responsible for the aura and extracranial vasodilatation for the headache. However, it appears that vascular events may be secondary to neuropathic changes and the liberation of vasoactive substances including serotonin (5-HT), catecholamines, histamine, kinins, neuropeptides such as calcitonin gene-related peptide (CGRP), and prostaglandins.

There are several factors that may precipitate migraine attacks. These include anxiety, physical and emotional stress, a change in sleep pattern, bright lights, fasting, some foods, and menstruation. Menstrual migraine has no specific definition, but it is believed to occur around the time of menstruation and to be characterised by attacks without aura. Migraine may also be precipitated by drugs including combined oral contraceptives and oestrogens, and glyceryl trinitrate. The frequency of migraine attacks can be reduced if such precipitating factors can be identified and avoided. Quiet, darkness, and sleep can ease an attack, with sleep heralding recovery.

Treatment. There is evidence that therapy tailored to the severity of individual disease from the outset (stratified care) is preferable to beginning with simple analgesics and adjusting treatment subsequently according to response (step strategy).

Simple **analgesics** (paracetamol or aspirin and other NSAIDs) are effective if taken at the earliest signs of an attack. Weak opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations. However, many consider that opioids are best avoided, especially in patients who experience frequent headaches, to decrease the risk of medication-overuse headaches. Other drugs used with analgesics in antimigraine preparations have included caffeine and the sympathomimetic vasoconstrictor isometheptene.

If the initial treatment of migraine is delayed, absorption of oral drugs may be compromised by development of gastric stasis and nausea and vomiting; **antiemetics** such as buclizine and cyclizine, and the **prokinetic** drugs metoclopramide and domperidone are often included in compound antimigraine preparations. Prokinetic drugs also have the advantage of promoting gastric emptying and normal peristalsis. Dispersible and effervescent analgesic preparations are preferable because of their more rapid absorption. If nausea and vomiting are prominent rectal administration may be necessary.

Attacks not responding to simple analgesics or NSAIDs may be treated with specific antimigraine drugs such as the selective serotonin ($5\text{-}HT_1$) agonists (e.g. sumatriptan) or the ergot derivatives ergotamine and dihydroergotamine; poor absorption and adverse effects limit the use of ergot derivatives and selective serotonin ($5\text{-}HT_1$) agonists are generally preferred.

Serotonin ($5\text{-}HT_1$) agonists are highly effective in relieving the pain and nausea of a migraine attack. There are a number of **triptans** available; patient characteristics and preferences vary in response to use and can sometimes be unpredictable. Some patients experience recurrence of the headache within 24 to 48 hours and often respond to a second dose. Finding the best triptan to suit the individual patient may involve trial and error. Triptans should not be used in patients with major risk factors for, or suffering from, cardiovascular disease. The main concern with all triptans is their potential for coronary vasoconstriction and no triptan appears to be safer than the others.

If **ergotamine** is used it should be given at the first warning of an attack; the earlier it is given, the more effective the treatment. Since its oral bioavailability is poor and may be reduced further during a migraine attack, ergotamine has sometimes been given in sublingual or rectal preparations. Ergotamine can also exacerbate nausea and vomiting; metoclopramide or domperidone, or in severe cases the phenothiazines chlorpromazine or prochlorperazine, may be given. Dihydroergotamine may be of use if parenteral treatment is required; it can also be given intranasally but there is less experience with this route.

Patients who rapidly develop severe migraine may be given **parenteral** dihydroergotamine or sumatriptan. Some consider parenteral metoclopramide to be suitable first-line treatment. If there is no response to these drugs, dopamine antagonists such as chlorpromazine or prochlorperazine given parenterally may be effective in relieving the pain of acute migraine attacks. Prolonged attacks (status migrainosus) may require intravenous administration of dihydroergotamine with metoclopramide.

Other drugs that may be given alone or in combination include corticosteroids or pethidine. Lidocaine has been given intravenously for the emergency treatment of migraine; intranasal lidocaine has also been tried. The opioid agonist-antagonist butorphanol, given by nasal spray, has been advocated, but its place in therapy, if any, remains to be established. Other drugs under investigation include botulinum A toxin and CGRP antagonists; intravenous valproic acid has also shown promise in aborting acute attacks.

Guidelines have been issued for the treatment of migraine in **children and adolescents**. For acute treatment, ibuprofen and paracetamol were found to be effective in children aged 6 years and over; sumatriptan nasal spray should be considered in those aged 12 years and over.

Prophylactic treatment should be considered for patients in whom abortive measures are ineffective or migraine attacks occur frequently, or for those with less frequent but severe or prolonged attacks. Some recommend prophylaxis if attacks occur more often than once or twice a month. Prophylaxis can reduce the severity and/or frequency of attacks but does not eliminate them completely and patients still need additional abortive or symptomatic treatment. Drugs suggested for prophylaxis have a range of actions which reflects uncertainty over the pathogenesis of migraine. It is important to give prophylactic drugs for an adequate period before assessing their efficacy. Once an optimum effect has been achieved the need for continuing prophylaxis should be reviewed at intervals of about 3 to 6 months.

The main prophylactic drugs are **beta blockers**, tricyclic **antidepressants**, and the **antiepileptics**, topiramate and valproate. Propranolol is considered by many to be the prophylactic drug of choice. Lethargy appears to be the most common adverse effect. Other beta blockers reported to be effective are those that, like propranolol, possess no intrinsic sympathomimetic activity, which include atenolol, metoprolol, nadolol, and timolol. The potential for beta blockers to interact with some serotonin ($5\text{-}HT_1$) agonists and ergotamine should be borne in mind. Tricyclic antidepressants, particularly amitriptyline, given in gradually increasing doses at night are useful for preventing migraine, especially in patients who also have depression or tension-type headache, although antimuscarinic adverse effects may occur. Valproate is also used for preventing migraine. Nausea appears to be the most common adverse effect. Topiramate is the main alternative to valproate. Weight loss and paraesthesia are commonly reported adverse effects. Topiramate and valproate are particularly useful in patients who also have epilepsy or bipolar disorder.

Other drugs have been used for the prophylaxis of migraine: pizotifen, an antihistamine and serotonin antagonist, has been widely used but evidence for its efficacy is limited; it may be tried in children. Of the drugs with calcium-channel blocking activity, flunarizine appears to be effective, and has been suggested for use in children, and verapamil may be useful, but evidence for the efficacy of other calcium-channel blockers such as diltiazem, nifedipine, or nimodipine is less convincing; NSAIDs may be worth trying. The use of methysergide, a potent serotonin antagonist, has declined because of serious adverse effects, in particular retroperitoneal fibrosis. MAOIs such as phenelzine have been used occasionally but are best reserved for severe cases refractory to other forms of prophylactic treatment. Cyproheptadine, an antihistamine and serotonin antagonist, has been used for migraine prophylaxis, particularly in children. Other drugs used for the prophylaxis of migraine have included butterbur, clonidine, cyclandelate, indoramin, feverfew, and the ergot derivative metergoline. Positive results have been seen with magnesium and riboflavin. Other drugs still under investigation, which have shown potential for prevention of migraine attacks are: baclofen, botulinum A toxin, candesartan, gabapentin, lisinopril, and venlafaxine.

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Post-dural puncture headache

For the management of headache associated with lumbar puncture or spinal anaesthesia, see Post-dural Puncture Headache under Local Anaesthetics, p.1851.

Tension-type headache

Tension-type headaches, also referred to as muscle-contraction headaches, are probably the commonest form of headache. They are characterised by bilateral pain, which unlike migraine is continuous and non-pulsatile. The pain is often described by the patient as feeling like a tight band pressed around the head. Headaches of this type may be precipitated by many factors including psychosocial stress or muscular stress. Many patients also have associated symptoms of anxiety or depression. Tension-type headaches and migraine often co-exist and may then be referred to as combination or mixed headaches. Some patients only experience isolated acute attacks of tension-type headache (episodic tension-type headache), but others may develop chronic tension-type headache which is difficult to treat.

Treatment is aimed at removing the underlying causes where these can be identified. Simple massage may help if muscle contraction is a prominent component of the pain. Non-opioid analgesics, such as aspirin or other NSAIDs and paracetamol, may be tried for individual acute attacks of headache, but analgesic overuse must be avoided as this can lead to chronic headache resistant to other measures (see Medication-overuse Headache, above). Opioids alone or in combination preparations with other analgesics should also be avoided. Hypnotics or sedatives have sometimes been used in combination preparations with analgesics in the management of tension-type headache that disrupts sleep but, because of the potential for abuse, they should be avoided in chronic headaches. Muscle relaxants appear to have little place in the management of tension-type headache; although some patients may respond, results are generally disappointing. Other drugs that have been tried include valproate and botulinum A toxin. **Prophylaxis** is preferable to regular short-term use of analgesics in controlling chronic tension-type headache. Tricyclic antidepressants, particularly amitriptyline, are generally considered as first choice, although benefit is rarely complete. The mode of action is unclear and appears to be independent of any antidepressant action. In most cases, improvement is seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Addition of a beta blocker such as propranolol may sometimes be of benefit for patients with some migraine features.

References.

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2. Kumar KL, Cooney TG. Headaches. *Med Clin North Am* 1995; **79:** 261–86.
3. Anonymous. Management of tension-type headache. *Drug Ther Bull* 1999; **37:** 41–4.
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Almotriptan Malate *(BANM, USAN, rINNM)*

Almotriptan, Malate d'; Almotriptani Malas; LAS-31416 (almotriptan); Malato de almotriptán; PNU-180638E (almotriptan malate). 1-[({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)sulfonyl]pyrrolidine malate (1:1).

Альмотриптана Малат

$C_{17}H_{25}N_3O_2S,C_4H_6O_5$ = 469.6.

CAS — 154323-57-6 (almotriptan); 181183-52-8 (almotriptan malate).

ATC — N02CC05.

ATC Vet — QN02CC05.

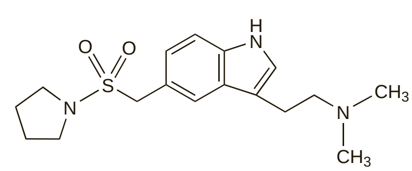

(almotriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Almotriptan should not be used in patients with severe hepatic impairment since clearance is likely to be markedly impaired, and should be given with caution, and in reduced doses, to patients with mild to moderate hepatic impairment. The dose of almotriptan should also be reduced in patients with severe renal impairment.

Patients with hypersensitivity to sulfonamides may theoretically exhibit a similar reaction to almotriptan.

Incidence of adverse effects. Results from studies involving more than 2500 patients with migraine suggested that adverse effects of almotriptan were infrequent.[1] The commonest adverse effects reported were dizziness, nausea and vomiting, headache, paraesthesia, fatigue, and drowsiness, all of which occurred in less than 3% of patients. The incidence of chest symptoms was 0.2% in 2 large phase III studies.

1. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001; **41:** 449–55.

Interactions

As for Sumatriptan, p.626.

Pharmacokinetics

After oral doses, peak plasma-almotriptan concentrations are obtained in about 1 to 3 hours, with a bioavailability of about 70%. Protein binding is about 35%. Almotriptan is metabolised, mainly by monoamine oxidase type A to the inactive indole acetic acid derivative and to a lesser extent by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to the inactive gamma-aminobutyric acid derivative. More than 75% of an oral dose is excreted in the urine and the remainder in faeces. About 40 to 50% of the dose in the urine and 5% in the faeces is excreted as unchanged drug. The plasma elimination half-life is about 3.5 hours in healthy subjects, increasing to about 7 hours in severe renal impairment.

Distribution into milk has been found in studies in *rats*.

◊ References.

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2. McEnroe JD, Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-HT receptor agonist for the treatment of migraine. *Clin Pharmacokinet* 2005; **44:** 237–46.

Uses and Administration

Almotriptan malate is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and doses are expressed in terms of the base; almotriptan malate 8.75 mg is equivalent to about 6.25 mg of almotriptan.

The usual dose of almotriptan is 12.5 mg in the UK and 6.25 or 12.5 mg in the USA. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. No more than 2 doses should be taken in a 24-hour period. For doses in hepatic and renal impairment see below.

◊ References.

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2. Keam SJ, *et al.* Almotriptan: a review of its use in migraine. *Drugs* 2002; **62:** 387–414.

Administration in hepatic or renal impairment. In patients with hepatic or severe renal impairment, no more than 12.5 mg of almotriptan should be taken in 24 hours; a starting dose of 6.25 mg may be used. Almotriptan is contra-indicated in patients with severe hepatic disease.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

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Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Almogran; ***Canad.:*** Axert; ***Denm.:*** Almogran; ***Fin.:*** Almogran; ***Fr.:*** Almogran; ***Ger.:*** Almogran; ***Irl.:*** Almogran; ***Ital.:*** Almogran; Almotrex; ***Neth.:*** Almogran; ***Norw.:*** Almogran; ***Port.:*** Almogran; Amignul; ***Spain:*** Almogran; Amignul; ***Swed.:*** Almogran; ***UK:*** Almogran; ***USA:*** Axert.

Alpiropride *(rINN)*

Alpiroprida; Alpipropridum. (±)-*N*-[(1-Allyl-2-pyrrolidinyl)methyl]-4-amino-5-(methylsulfamoyl)-*o*-anisamide.

Альпироприд

$C_{17}H_{26}N_4O_4S = 382.5.$

CAS — 81982-32-3.

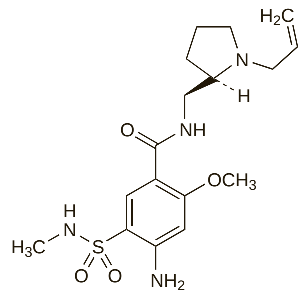

Profile

Alpiropride is a dopamine antagonist that has been given orally for the treatment and prophylaxis of migraine.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Rivistel†.

Dihydroergotamine *(BAN, rINN)*

Dihidroergotamina; Dihydroergotamiini; Dihydroergotamin; Dihydroergotaminum. (5′*S*,8*R*)-5′-Benzyl-9,10-dihydro-12′-hydroxy-2′-methyl-3′,6′,18-trioxoergotaman.

Дигидроэрготамин

$C_{33}H_{37}N_5O_5 = 583.7.$

CAS — 511-12-6.
ATC — N02CA01.
ATC Vet — QN02CA01.

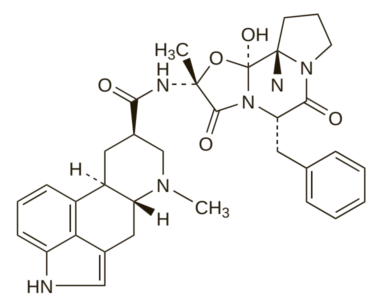

Dihydroergotamine Mesilate *(BANM, rINNM)*

Dihidroergotamin-mezilát; Dihidroergotamino mesilatas; Dihydroergotamiinimesilaatti; Dihydroergotamine, mésilate de; Dihydroergotamine Mesylate *(USAN)*; Dihydroergotamine Methanesulphonate; Dihydroergotamini mesilas; Dihydroergotamin-mesilát; Dihydroergotamin-mesylát; Dihydroergotaminy mezylan; Mesilato de dihidroergotamina.

Дигидроэрготамина Мезилат

$C_{33}H_{37}N_5O_5,CH_4O_3S = 679.8.$

CAS — 6190-39-2.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Dihydroergotamine Mesilate). Colourless crystals or a white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 4.4 to 5.4. Protect from light.

USP 31 (Dihydroergotamine Mesylate). A white to slightly yellowish powder, or off-white to faintly red powder, having a faint odour. Soluble 1 in 125 of water, 1 in 90 of alcohol, 1 in 175 of chloroform, and 1 in 2600 of ether. pH of a 0.1% solution in water is between 4.4 and 5.4. Protect from light.

Dihydroergotamine Tartrate *(BANM, rINNM)*

Dihidroergotamino tartratas; Dihidroergotamin-tartarát; Dihydroergotamiinitartraatti; Dihydroergotamine, tartrate de; Dihydroergotamini tartras; Dihydroergotamin-tartarát; Dihydroergotamintartrat; Tartrato de dihidroergotamina.

Дигидроэрготамина Тартрат

$(C_{33}H_{37}N_5O_5)_2,C_4H_6O_6 = 1317.4.$

CAS — 5989-77-5.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dihydroergotamine Tartrate). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. A 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p.620, although vasoconstriction may be less pronounced and the frequency of nausea and vomiting lower with dihydroergotamine mesilate than with ergotamine tartrate. Dihydroergotamine does not appear to produce physical dependence.

Effects on the cardiovascular system. There are conflicting reports on the risk of vasospasm in patients given dihydroergotamine with heparin for thromboembolism prophylaxis. Vasospastic or necrotic reactions have been reported on several occasions during such therapy.[1-4] In an Austrian study of 147 290 patients given drug prophylaxis for thromboembolism, complications attributable to ergotism were seen in 142 of 61 092 (0.23%) who received dihydroergotamine and heparin.[5] Others,[6] however, observed only 1 case of vasospasm in 5100 trauma patients (0.02%) given the combination. In 1989 the Swedish Adverse Drug Reactions Advisory Committee reported[7] that up to the end of September 1987 the manufacturer had received 201 reports of vasospastic reactions associated with the use of *Orstanorm* (dihydroergotamine + lidocaine) with heparin. Permanent damage occurred in 59% of these patients. Vasospastic reactions had occurred more frequently in patients who had undergone surgery for trauma and the prognosis for such patients was generally poorer than for others. Since the risk of permanent damage appeared to be related to treatment length the Committee recommended that this preparation should not be given for more than 7 days. The possibility of such reactions and the contra-indications of dihydroergotamine should be borne in mind when using this form of prophylaxis (see Venous Thromboembolism, under Uses, below).

1. van den Berg E, *et al.* Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. *Lancet* 1982; **i:** 955–6.
2. van den Berg E, *et al.* Vascular spasm during thromboembolism prophylaxis with heparin-dihydroergotamine. *Lancet* 1982; **ii:** 268–9.
3. Monreal M, *et al.* Skin and muscle necrosis during heparin-dihydroergotamine prophylaxis. *Lancet* 1984; **ii:** 820.
4. Kilroy RA, *et al.* Vascular spasm during heparin-dihydroergotamine prophylaxis. *Clin Pharm* 1987; **6:** 575–7.
5. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* 1986; **ii:** 638–9.
6. Schlag G, *et al.* Risk/benefit of heparin-dihydroergotamine thromboembolic prophylaxis. *Lancet* 1986; **ii:** 1465.
7. Swedish Adverse Drug Reaction Advisory Committee. Dihydroergotamine + lidocaine – vasospasm. *Bull Swed Adverse Drug React Advisory Committee* 1989; (54): 1.

Fibrosis. For reference to fibrosis associated with the administration of dihydroergotamine, see Methysergide Maleate, p.623.

Precautions

As for Ergotamine Tartrate, p.620.

Cardiovascular disorders. For specific contra-indications and precautions in cardiovascular disorders, see under Ergotamine, p.621.

Porphyria. Dihydroergotamine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Ergotamine (p.621).

Use with other vasoconstrictive drugs, including supplementary antimigraine treatment with ergotamine or sumatriptan, should be avoided.

Pharmacokinetics

Peak plasma-dihydroergotamine concentrations have been attained within about 1 to 2 hours after oral doses, about 30 minutes after intramuscular injection, about 15 to 45 minutes after subcutaneous injection, and about 45 to 55 minutes after intranasal doses. However, the bioavailability of dihydroergotamine after oral doses is very low; values ranging from less than 0.1 to 1.5% have been reported. Although dihydroergotamine is incompletely absorbed from the gastrointestinal tract, the low bioavailability is considered to be determined primarily by extensive first-pass hepatic metabolism. Bioavailability after intranasal doses is 43%. Dihydroergotamine is 90 to 95% bound to plasma proteins.

Dihydroergotamine undergoes extensive metabolism, the major metabolite, 8′-β-hydroxydihydroergotamine, being active. Plasma concentrations of this metabolite are greater than those of dihydroergotamine. A further oxidation step produces 8′,10′-dihydroxydihydroergotamine, which is also active. Other metabolites are also formed. Most of a dose is excreted as metabolites, mainly in the bile; 5 to 10% is excreted in the urine of which only trace amounts are of unchanged drug. The elimination of dihydroergotamine is biphasic; half-lives of about 1 to 2 hours and 22 to 32 hours have been reported for the 2 phases, respectively.

◊ References.

1. Little PJ, *et al.* Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 1982; **13:** 785–90.
2. Müller-Schweinitzer E. Pharmacological actions of the main metabolites of dihydroergotamine. *Eur J Clin Pharmacol* 1984; **26:** 699–705.
3. de Marées H, *et al.* Relationship between the venoconstrictor activity of dihydroergotamine and its pharmacokinetics during acute and chronic oral dosing. *Eur J Clin Pharmacol* 1986; **30:** 685–9.
4. Humbert H, *et al.* Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther* 1996; **60:** 265–75.

Uses and Administration

Dihydroergotamine is a semisynthetic ergot alkaloid that has weaker oxytocic and vasoconstrictor effects than ergotamine (p.621). Its activity as a 5-HT_1 agonist is believed to contribute to its antimigraine action. It is used in the treatment of migraine and cluster headache, and in the treatment of orthostatic hypotension. It has also been used for the prophylaxis of venous thromboembolism (see below).

Dihydroergotamine is commonly used as the mesilate by subcutaneous, intramuscular, or intravenous injection, although it may also be given as a nasal spray or orally.

For the treatment of migraine and to terminate an acute attack of cluster headache, dihydroergotamine mesilate is usually given by subcutaneous or intramuscular injection in doses of 1 mg repeated, if necessary, after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg up to a maximum daily dose of 2 mg. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 500 micrograms sprayed into each nostril as a 0.4% solution followed after 15 minutes by an additional 500 micrograms in each nostril. A total intranasal dose of 2 mg per attack should not be exceeded. In the USA, the maximum dose in 24 hours is 3 mg and in a 7-day period is 4 mg, while maximum daily doses of up to 4 mg with a maximum dose of 12 mg in a 7-day period have been given in other countries. In some countries it is given orally; up to 10 mg daily has been given orally for the treatment of acute attacks of migraine. Lower oral doses have been given in some countries for migraine prophylaxis.

Dihydroergotamine mesilate has also been used alone or with etilefrine hydrochloride (p.1284) in the treatment of orthostatic hypotension, in usual oral doses of up to 10 mg daily in divided doses. Doses of up to 40 to 60 mg have been used in some patients.

Dihydroergotamine tartrate has been used for indications similar to those of the mesilate.

Medication-overuse headache. Dihydroergotamine may be used in the treatment of medication-overuse headache (p.616), including symptoms of ergotamine withdrawal.

Migraine and cluster headache. Although sumatriptan is often the treatment of choice to abort acute attacks of migraine (p.616) that do not respond to simple analgesic preparations, parenteral dihydroergotamine, especially with an antiemetic, is an alternative for patients who develop severe or refractory migraine.[1-3] Preparations for intranasal[4,5] use are also available; in some countries, it is given orally. In a comparative study, relief of migraine was slower after subcutaneous dihydroergotamine than after subcutaneous sumatriptan, but headache recurred less often.[6] In other studies, intranasal dihydroergotamine was not as effective as subcutaneous[5] or intranasal[7] sumatriptan.

Dihydroergotamine is also used in the treatment of cluster headache (p.616), usually in emergency settings, where it is given to abort individual headache attacks.

1. Scott AK. Dihydroergotamine: a review of its use in the treatment of migraine and other headaches. *Clin Neuropharmacol* 1992; **15:** 289–96.
2. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
3. Colman I, *et al.* Parenteral dihydroergotamine for acute migraine headache: a systematic review of the literature. *Ann Emerg Med* 2005; **45:** 393–401.
4. Ziegler D, *et al.* Dihydroergotamine nasal spray for the acute treatment of migraine. *Neurology* 1994; **44:** 447–53.
5. Touchon J, *et al.* A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996; **47:** 361–5.
6. Winner P, *et al.* A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; **53:** 180–4.
7. Boureau F, *et al.* A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract* 2000; **54:** 281–6.

Orthostatic hypotension. Dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p.1530). It is sometimes used in preparations with sympathomimetics such as etilefrine. After parenteral dihydroergotamine, standing blood pressure is increased, but total peripheral resistance and supine blood pressure are also increased.[1] It does not prevent postprandial hypotension, presumably because it does not constrict the splanchnic veins, although use with caffeine may overcome this problem. The main disadvantage of dihydroergotamine, however, is that it is ineffective, or at best weakly effective, when given by mouth, although there has been some evidence that oral ergotamine tartrate may be of value.

Dihydroergotamine has been suggested for use in the prevention of hypotension associated with epidural[2] or spinal anaesthesia,[3] the usual management of which is discussed in Treatment of Adverse Effects of Local Anaesthetics, p.1851. It has also been tried in the management of hypotension associated with haemodialysis.[4]

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Mattila M, *et al.* Dihydroergotamine in the prevention of hypotension associated with extradural anaesthesia. *Br J Anaesth* 1985; **57:** 976–82.
3. Critchley LAH, Woodward DK. Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia. *Br J Anaesth* 2001; **87:** 499–501.
4. Milutinovic S. Dihydroergotamin in der Behandlung von Patienten mit symptomatischer Hypotonie während Dauerhämodialyse. *Arzneimittelforschung* 1987; **37:** 554–6.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism is usually with heparin or low-molecular-weight heparin (p.1189). Dihydroergotamine can reduce venous stasis by vasoconstriction of capacitance vessels and has enhanced postoperative prophylaxis when used with heparin.[1] Doses of dihydroergotamine mesilate 500 micrograms with heparin 5000 units, both given subcutaneously 2 hours before surgery, have been used. This regimen has then been given every 8 to 12 hours for 5 to 14 days depending on the risk of thrombosis. The use of dihydroergotamine with low-molecular-weight heparin has been shown to be of similar efficacy to dihydroergotamine with heparin[2,3] but might offer a more convenient dosing schedule. However, although dihydroergotamine might enhance the effect of heparin, a US National Institutes of Health consensus conference warned of the potential risk associated with its vasoconstrictive effects, and the contraindications to its use.[4] In 1989 the Swedish Adverse Drug Reactions Advisory Committee recommended that dihydroergotamine with heparin should not be given for more than 7 days (see Effects on the Cardiovascular System, under Adverse Effects, above).

1. Lindblad B. Prophylaxis of postoperative thromboembolism with low dose heparin alone or in combination with dihydroergotamine: a review. *Acta Chir Scand* 1988; (suppl 543): 31–42.
2. Sasahara AA, *et al.* Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg* 1986; **73:** 697–700.
3. Haas S, *et al.* Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittelforschung* 1987; **37:** 839–43.
4. NIH Consensus Development. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; **256:** 744–9.

Preparations

USP 31: Dihydroergotamine Mesylate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Dihydergot; ***Austria:*** Detemes; DHE; Dihydergot; Divegal; Ergont; Ergovasan; Migranal; ***Belg.:*** Diergo; Dihydergot; Dystonal; ***Braz.:*** Dihydergot†; ***Canad.:*** Migranal; ***Cz.:*** Clavigrenin†; Dihydergot; ***Fin.:*** Orstanorm; ***Fr.:*** Ikaran; Seglor; Tamik; ***Ger.:*** Agit; Angionorm; Clavigrenin†; DET MS; DET MS spezial†; DHE; Dihydergot†; Dihytamin; Erganton†; Ergomimet†; Ergont†; ergotam; Verladyn; ***Gr.:*** Dihydergot; Pervone†; Verteblan†; ***Hong Kong:*** Tamik†; ***India:*** Dihydergot†; Migranil; ***Indon.:*** Dihydergot; ***Ital.:*** Diidergot; Ikaran; Migranal†; Seglor; ***Mex.:*** Dihydergot; ***Port.:*** Dihydergot†; Seglor; ***Spain:*** Dihydergot; ***Swed.:*** Migranal†; Orstanorm; ***Switz.:*** Dihydergot; Ergotonine; Ikaran†; ***Thai.:*** Poligot†; ***USA:*** DHE; Migranal; ***Venez.:*** Dihydergot.

Multi-ingredient: *Arg.:* Parsel†; Polper Vascular; ***Austria:*** Agilan; Defluina; Dihydergot; Effortil comp; Hypodyn; Tonopan; Troparin compositum; Venotop; ***Braz.:*** Cefalium; Cefaliv; Enxak; Migraliv; Parcel; Tonopan; ***Chile:*** Emagrip; Migratapsin; Migrax; Parsel†; ***Fr.:*** Diergospray; ***Ger.:*** Agit plus†; Dihydergot plus; Effortil plus; Embolex NM†; Ergo-Lonarid PD†; Ergolefrin; Ergomimet plus†; Optalidon special NOC†; ***Mex.:*** Parsel; Tonopan; ***Spain:*** Tonopan; ***Switz.:*** Dihydergot; Dihydergot plus; Effortil plus; Tonopan†; ***Venez.:*** Brudol; Difen; Dol; Ivagan; Letydol; Parsel; Tainol†.

Eletriptan Hydrobromide

(BANM, USAN, rINNM)

Eletriptaanihydrobromidi; Élétriptan, Bromhydrate d'; Eletriptanhydrobromid; Eletriptani Hydrobromidum; Hidrobromuro de eletriptán; UK-116044-04. 3-{[(*R*)-1-Methyl-2-pyrrolidinyl]methyl}-5-[2-(phenylsulfonyl)ethyl]indole hydrobromide.

Элетриптана Гидробромид

$C_{22}H_{26}N_2O_2S,HBr = 463.4.$

CAS — 143322-58-1 (eletriptan); 177834-92-3 (eletriptan hydrobromide).

ATC — N02CC06.

ATC Vet — QN02CC06.

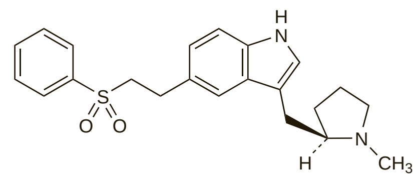

(eletriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Eletriptan should not be used in patients with severe hepatic or severe renal impairment. Blood pressure effects of eletriptan are increased in renal impairment and therefore the dose should be reduced in patients with mild to moderate renal impairment. No dosage adjustment is needed in mild or moderate hepatic impairment.

Breast feeding. Eletriptan is distributed into breast milk and the manufacturer has suggested that infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Interactions

As for Sumatriptan, p.626.

Eletriptan should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as erythromycin and ketoconazole; increased plasma levels of eletriptan have been noted after such combinations. It is recommended that eletriptan should not be taken within at least 72 hours of treatment with such drugs.

Pharmacokinetics

After oral doses eletriptan is rapidly and well absorbed (at least 81%) and has a bioavailability of about 50%. Peak plasma concentrations are attained within 1.5 hours. Eletriptan is about 85% protein bound. It is primarily metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4. Non-renal clearance accounts for about 90% of the elimination of eletriptan and the plasma elimination half-life is about 4 hours. A small amount is distributed into breast milk.

◊ References.

1. Shah AK, *et al.* Pharmacokinetics and safety of oral eletriptan during different phases of the menstrual cycle in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 1339–44.
2. Shah AK, *et al.* The pharmacokinetics and safety of single escalating oral doses of eletriptan. *J Clin Pharmacol* 2002; **42:** 520–7.
3. Milton KA, *et al.* Pharmacokinetics, pharmacodynamics, and safety of the 5-HT agonist eletriptan following intravenous and oral administration. *J Clin Pharmacol* 2002; **42:** 528–39.

Uses and Administration

Eletriptan hydrobromide is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Eletriptan is given orally as the hydrobromide, but doses are expressed in terms of the base; eletriptan hydrobromide 24.2 mg is equivalent to about 20 mg of eletriptan.

The usual dose is 40 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. Doses of 80 mg may be used in subsequent attacks, but should not be repeated within a 24-hour period. For doses in renal impairment, see below.

Administration in renal impairment. In the UK, a dose of 20 mg of eletriptan is recommended in patients with mild to moderate renal impairment. The maximum daily dose should not exceed 40 mg. Eletriptan should not be used in severe impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Mathew NT, *et al.* Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. *Headache* 2003; **43:** 962–74.
2. Takiya L, *et al.* Safety and efficacy of eletriptan in the treatment of acute migraine. *Pharmacotherapy* 2006; **26:** 115–28.
3. McCormack PL, Keating GM. Eletriptan: a review of its use in the acute treatment of migraine. *Drugs* 2006; **66:** 1129–49.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Relpax; ***Belg.:*** Relert; ***Canad.:*** Relpax; ***Chile:*** Relpax; ***Cz.:*** Relpax; ***Denm.:*** Relpax; ***Fin.:*** Relert; ***Fr.:*** Relpax; ***Ger.:*** Relpax; ***Gr.:*** Relpax; ***Hung.:*** Relpax; ***Israel:*** Relert; ***Ital.:*** Relpax; ***Mex.:*** Relpax; ***Neth.:*** Relpax; ***Norw.:*** Relpax; ***Pol.:*** Relpax; ***Port.:*** Relert; ***Rus.:*** Relpax (Релпакс); ***S.Afr.:*** Relpax; ***Singapore:*** Relpax; ***Spain:*** Relert; Relpax; ***Swed.:*** Relpax; ***Switz.:*** Relpax; ***Turk.:*** Relpax; ***UK:*** Relpax; ***USA:*** Relpax.

Ergotamine Tartrate *(BANM, rINNM)*

Ergotamiinitartraatti; Ergotamin Tartarat; Ergotamin Tartrat; Ergotamine, tartrate d'; Ergotamini tartras; Ergotamino tartratas; Ergotamin-tartarát; Ergotamintartrat; Ergotaminy winian; Tartrato de ergotamina. (5′*S*)-12′-Hydroxy-2′-methyl-5′-benzylergotaman-3′,6′,18-trione tartrate; (5′*S*)-12′-Hydroxy-2′-methyl-3′,6′,18-trioxo-5-benzylergotaman (+)-tartrate.

Эрготамина Тартрат

$(C_{33}H_{35}N_5O_5)_2,C_4H_6O_6$ = 1313.4.

CAS — 113-15-5 (ergotamine); 379-79-3 (ergotamine tartrate).

ATC — N02CA02.

ATC Vet — QN02CA02.

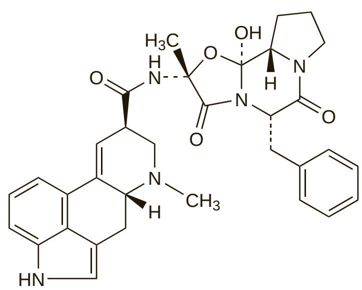

(ergotamine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Ergotamine Tartrate). Slightly hygroscopic, colourless crystals or a white or almost white crystalline powder. It may contain 2 molecules of methanol of crystallisation. Slightly soluble in alcohol. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Ergotamine Tartrate). Colourless odourless crystals or a white or yellowish-white crystalline powder. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol. Store at a temperature not exceeding 8°. Protect from light.

Stability in solution. References.

1. Kreilgård B, Kisbye J. Stability of ergotamine tartrate in aqueous solution. *Arch Pharm Chemi (Sci)* 1974; **2:** 1–13 and 38–49.

Adverse Effects

The adverse effects of ergotamine may be attributed either to its effects on the CNS, or to vasoconstriction of blood vessels and possible thrombus formation.

After therapeutic doses nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine; some patients may also experience abdominal pain. Weakness and muscle pains in the extremities and numbness and tingling of the fingers and toes may occur. There may occasionally be localised oedema and itching in hypersensitive patients. Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine.

Symptoms of acute overdosage include nausea, vomiting, diarrhoea, extreme thirst, coldness, tingling, and itching of the skin, a rapid and weak pulse, hypertension or hypotension, shock, confusion, convulsions, and unconsciousness; fatalities have been reported. Further symptoms of peripheral vasoconstriction or of cardiovascular disturbances, as seen in chronic ergotamine poisoning, may also occur but may be delayed.

In chronic poisoning or ergotism, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbances may develop. The extremities, especially the feet and legs, become numb, cold, tingling, and pale or cyanotic, with muscle pain; there may be no pulse in the affected limb. Eventually gangrene develops in the toes and sometimes the fingers. Anginal pain, tachycardia or bradycardia, and hypertension or hypotension have been reported. Myocardial infarction has occurred rarely. Pleural and peritoneal fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Chronic, intractable headache (rebound headache) may occur and is also a major withdrawal symptom following the development of ergotamine dependence (see under Precautions, below). Other adverse effects include confusion and convulsions. On rare occasions symptoms of vasoconstriction of blood vessels in the brain, eye, intestines, and kidneys occur. Anorectal ulceration, sometimes leading to rectal necrosis and stenosis or rectovaginal fistula, has been reported after excessive use of suppositories containing ergotamine.

Effects on the cardiovascular system. Reports[1-9] of adverse cardiovascular effects associated with ergotamine, including mention of fatalities.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.
2. Corrocher R, *et al.* Multiple arterial stenoses in chronic ergot toxicity. *N Engl J Med* 1984; **310:** 261.
3. Fisher PE, *et al.* Ergotamine abuse and extra-hepatic portal hypertension. *Postgrad Med J* 1985; **61:** 461–3.
4. Deviere J, *et al.* Ischemic pancreatitis and hepatitis secondary to ergotamine poisoning. *J Clin Gastroenterol* 1987; **9:** 350–2.
5. Galer BS, *et al.* Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* 1991; **31:** 446–50.
6. Redfield MM, *et al.* Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992; **117:** 50–2.
7. Lazarides MK, *et al.* Severe facial ischaemia caused by ergotism. *J Cardiovasc Surg* 1992; **33:** 383–5.
8. Hillis W, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
9. Zavaleta EG, *et al.* St. Anthony's fire (ergotamine induced leg ischemia)—a case report and review of the literature. *Angiology* 2001; **52:** 349–56.

Fibrosis. For reference to fibrosis associated with the use of ergotamine tartrate, see Methysergide Maleate, p.623.

Treatment of Adverse Effects

Treatment of acute poisoning with ergotamine is symptomatic. Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to patients who present within 1 hour of ingesting a toxic dose (more than 125 micrograms/kg in adults) or any amount in a child or adult with peripheral vascular disease, ischaemic heart disease, severe infection, or hepatic or renal impairment. Alternatively, gastric lavage may be considered in adults within 1 hour of ingesting a potentially life-threatening overdose. In chronic poisoning, withdrawal of ergotamine may be all that is required in some patients.

In both acute and chronic poisoning, attempts must be made to maintain an adequate circulation to the affected parts of the body in order to prevent the onset of gangrene. In severe arterial vasospasm vasodilators such as sodium nitroprusside by intravenous infusion have been given; heparin and dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Cardiovascular effects. Sodium nitroprusside has been used in severe ergotamine poisoning for its vasodilating and hypotensive actions; it should, however, be used with care if hypotension is a symptom of poisoning. It is usually given by intravenous infusion[1-4] although there have also been reports of intra-arterial infusion for ergotamine-induced ischaemia;[5,6] for details of precautions to be observed, see p.1397.

Many other drugs have been used in the treatment of circulatory disturbances induced by ergotamine. These include captopril by mouth,[7] alprostadil by intra-arterial infusion,[8,9] and glyceryl trinitrate by intravenous infusion.[10,11]

1. Carliner NH, *et al.* Sodium nitroprusside treatment of ergotamine-induced peripheral ischemia. *JAMA* 1974; **277:** 308–9.
2. Andersen PK, *et al.* Sodium nitroprusside and epidural blockade in the treatment of ergotism. *N Engl J Med* 1977; **296:** 1271–3.
3. Eurin B, *et al.* Ergot and sodium nitroprusside. *N Engl J Med* 1978; **298:** 632–3.
4. Carr P. Self-induced myocardial infarction. *Postgrad Med J* 1981; **57:** 654–5.
5. O'Dell CW, *et al.* Sodium nitroprusside in the treatment of ergotism. *Radiology* 1977; **124:** 73–4.
6. Whitsett TL, *et al.* Nitroprusside reversal of ergotamine-induced ischemia. *Am Heart J* 1978; **96:** 700.
7. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.
8. Levy JM, *et al.* Prostaglandin E for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7:** 28–30.
9. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus: Behandlung mit intraarterieller Prostaglandin-E -Infusion. *Dtsch Med Wochenschr* 1993; **118:** 1067–71.
10. Husum B, *et al.* Nitroglycerin infusion for ergotism. *Lancet* 1979; **ii:** 794–5.
11. Tfelt-Hansen P, *et al.* Nitroglycerin for ergotism: experimental studies in vitro and in migraine patients and treatment of an overt case. *Eur J Clin Pharmacol* 1982; **22:** 105–9.

Precautions

Ergotamine tartrate is contra-indicated in patients with severe or uncontrolled hypertension, shock, severe or persistent sepsis, peripheral vascular disease, ischaemic heart disease, temporal arteritis, hyperthyroidism, or hepatic or renal impairment. It is also contra-indicated in those with basilar or hemiplegic migraine. Ergotamine tartrate should be used with care in patients with anaemia. It is contra-indicated in pregnancy because of its oxytocic effect (see also below).

Patients should be warned to keep within the recommended dosage. Some symptoms of overdosage may mimic those of migraine. Numbness or tingling of the extremities generally indicates that ergotamine should be stopped. Although ergotamine is used for limited periods in the prevention of episodic cluster headache, it should not be given prophylactically in other circumstances, as prolonged use may give rise to gangrene. Dependence has occurred with regular use of ergotamine tartrate even if dosage recommendations are adhered to (see below).

Dizziness and feelings of anxiety have been reported; if affected, patients should avoid driving or operating machinery.

Breast feeding. Although the American Academy of Pediatrics includes ergotamine among those drugs that may be given with caution to breast-feeding mothers,[1] it notes that maternal use in doses equivalent to those given for the treatment of migraine has been associated with vomiting, diarrhoea, and convulsions in nursing infants. UK licensed product information recommends that ergotamine tartrate should be avoided during breast feeding; the distribution of unchanged drug and metabolites into breast milk presents a risk of ergotism in the infant and repeated doses of ergotamine may impair lactation.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)

Cardiovascular disorders. In the USA, dihydroergotamine is contra-indicated in patients with ischaemic heart disease and other cardiovascular disorders such as hypertension, peripheral arterial disease, or coronary artery vasospasm and it is also recommended that it should not be given to those with a family history of ischaemic heart disease, to postmenopausal women or men aged over 40, or to those with other ischaemic risk factors such as hypertension, hypercholesterolaemia, smoking, diabetes, or obesity, unless cardiovascular evaluation to exclude such disease has been carried out. Similar precautions and contra-indications, which resemble those that apply to serotonin (5-HT_1) agonists such as sumatriptan (p.626), may be applicable to other ergot derivatives used in migraine such as ergotamine.

In other countries, warnings concerning the use of ergot derivatives in patients with risk factors for myocardial ischaemia appear to be less stringent, although caution is clearly advisable.

Dependence. Dependence can develop insidiously when ergotamine tartrate is used for more than 2 days each week, even if total daily or weekly dosage recommendations are observed.[1] Individual reports indicate a state of addiction characterised by a predictable and irresistible pattern of drug usage, the development of tolerance to adverse effects, and a syndrome of withdrawal on stopping the drug. Ergotamine-dependent patients suffer from daily, or almost daily, migraine headaches, often referred to as medication-overuse headaches or 'rebound headaches', which are only alleviated by ergotamine. Intensifying headache with autonomic disturbances occurs within 24 to 48 hours of withdrawal of ergotamine and may continue for 72 hours or longer. As with other medication-overuse headaches (p.616), supportive and symptomatic measures should be taken to treat the withdrawal syndrome.

1. Saper JR. Ergotamine dependency—a review. *Headache* 1987; **27:** 435–8.

Porphyria. Ergotamine tartrate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Ergotamine is contra-indicated in pregnancy because of its oxytocic effect. Accidental dosage of ergotamine in the form of a *Cafergot* suppository (ergotamine tartrate 2 mg and caffeine 100 mg) to a patient at 39 weeks of pregnancy caused uterine contractions and fetal tachycardia.[1] An emergency caesarean section was undertaken because of suspected placental abruption but no clear signs of retroplacental haemorrhage were found. The neonate recovered quickly after delivery and had developed normally during the next 10 years.

Jejunal atresia has been reported[2] in an infant born prematurely to a woman who had taken ergotamine tartrate 6 to 8 mg daily, as *Cafergot* tablets, throughout her pregnancy. Two cases of Möbius syndrome (a condition characterised by facial paralysis as a result of hypoplasia of cranial nerve nuclei) have been associated with exposure to ergotamine during the first trimester of pregnancy.[3,4] In the first report[3] the mother had inadvertently been given three *Cafergot* suppositories within a period of 1 to 2 hours and at the time had experienced uterine cramping and a bloody vaginal discharge. The second mother[4] had used 2-mg ergotamine suppositories on a regular basis during the first 8 weeks of pregnancy.

1. de Groot ANJA, *et al.* Ergotamine-induced fetal stress: review of side effects of ergot alkaloids during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **51:** 73–7.
2. Graham JM, *et al.* Jejunal atresia associated with Cafergot ingestion during pregnancy. *Clin Pediatr (Phila)* 1983; **22:** 226–8.
3. Graf WD, Shepard TH. Uterine contraction in the development of Möbius syndrome. *J Child Neurol* 1997; **12:** 225–7.
4. Smets K, *et al.* Ergotamine as a possible cause of Möbius sequence: additional clinical observation. *J Child Neurol* 2004; **19:** 398.

Interactions

The vasoconstrictor effects of ergotamine are enhanced by sympathomimetics such as adrenaline. There is also an increased risk of peripheral vasoconstriction during use of ergotamine with beta blockers.

Ergotamine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and consequently it should not be given with potent inhibitors of this isoenzyme; elevated ergotamine concentrations sufficient to cause ergotism may occur with azole antifungals, macrolide antibacterials such as erythromycin and clarithromycin, and HIV-protease inhibitors including indinavir and ritonavir. Use of tetracycline with ergotamine may also increase the risk of ergotism and should be avoided.

Ergotamine should not be used with or given until several hours after stopping a serotonin (5-HT_1) agonist, since there is an additional risk of prolonged vasospastic reactions; at least 6 hours is advised for almotriptan, rizatriptan, sumatriptan, and zolmitriptan, and at least 24 hours for eletriptan and frovatriptan. Conversely, a delay is advised before starting a serotonin agonist in patients who have been receiving ergotamine: almotriptan, eletriptan, frovatriptan, rizatriptan, sumatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine.

Antibacterials. Acute reactions ranging from minor ergotism[1] to severe vasospasm[2] have been reported in patients given *erythromycin* in addition to ergotamine. There are also reports of acute ergotism in patients receiving ergotamine tartrate and *clarithromycin*[3,4] or *troleandomycin*.[5] The theoretical possibility exists that there may be a similar interaction with *azithromycin*. Ergotism has also been reported in patients receiving erythromycin[6] or troleandomycin[7] with dihydroergotamine.

1. Lagier G, *et al.* Un cas d'ergotisme mineur semblant en rapport avec une potentialisation de l'ergotamine par l'éthylsuccinate d'érythromycine. *Therapie* 1979; **34:** 515–21.
2. Ghali R, *et al.* Erythromycin-associated ergotamine intoxication: arteriographic and electrophysiologic analysis of a rare cause of severe ischemia of the lower extremities and associated ischemic neuropathy. *Ann Vasc Surg* 1993; **7:** 291–6.
3. Horowitz RS, *et al.* Clinical ergotism with lingual ischemia induced by clarithromycin-ergotamine interaction. *Arch Intern Med* 1996; **156:** 456–8.
4. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. *J Emerg Med* 2001; **21:** 411–13.
5. Matthews NT, Havill JH. Ergotism with therapeutic doses of ergotamine tartrate. *N Z Med J* 1979; **89:** 476–7.
6. Leroy F, *et al.* Dihydroergotamine-erythromycin-induced ergotism. *Ann Intern Med* 1988; **109:** 249.
7. Franco A, *et al.* Ergotisme aigu par association dihydroergotamine-triacétyloléandomycine. *Nouv Presse Med* 1978; **7:** 205.

Antidepressants. There have been isolated case reports[1] of the serotonin syndrome (p.416) in patients receiving dihydroergotamine with *amitriptyline*, *imipramine*, *paroxetine*, or *sertraline*.

1. Mathew NT, *et al.* Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* 1996; **16:** 323–7.

Antimigraine drugs. Arterial occlusion has been reported[1] in 2 patients given *methysergide* with a high parenteral dosage of ergotamine for cluster headache; the combination should be avoided. Use of ergotamine as supplementary antimigraine medication in patients receiving *dihydroergotamine* is not recommended.

For reports of arterial vasoconstriction in patients taking *beta blockers* and antimigraine drugs, see below. See also Interactions, above for a comment on the risk of vasospastic reactions with serotonin (5-HT_1) agonists such as *sumatriptan*.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.

Antivirals. There have been reports of ergotism in patients who received ergotamine and combination antiviral treatment for HIV infection. It was suggested that the ergotism might have been caused by inhibition of ergotamine metabolism by *ritonavir* in 4 cases,[1-4] *indinavir* in one,[5] and *nelfinavir*[6] in another. One of the patients receiving ritonavir,[4] who had taken three 1-mg tablets of ergotamine tartrate over the 4 days before presentation, also developed signs of cerebrovascular involvement and eventually went into an irreversible coma.

The metabolism of ergot alkaloids may be inhibited by *delavirdine* or *efavirenz*.

1. Caballero-Granado FJ, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. *Antimicrob Agents Chemother* 1997; **41:** 1207.
2. Montero A, *et al.* Leg ischemia in a patient receiving ritonavir and ergotamine. *Ann Intern Med* 1999; **130:** 329–30.
3. Liaudet L, *et al.* Severe ergotism associated with interaction between ritonavir and ergotamine. *BMJ* 1999; **318:** 771.
4. Pardo Rey C, *et al.* Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; **37:** e72–e73.
5. Rosenthal E, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and indinavir. *JAMA* 1999; **281:** 987.
6. Mortier E, *et al.* Ergotism related to interaction between nelfinavir and ergotamine. *Am J Med* 2001; **110:** 594.

Beta blockers. Peripheral vasoconstriction was reported in a patient with migraine after addition of *propranolol* to regular use of *Cafergot* (ergotamine and caffeine) suppositories twice daily.[1] This combination has been used without complication by others, who suggested that excessive dosage of ergotamine tartrate, rather than an interaction between ergotamine and propranolol, was responsible.[2] However, arterial vasoconstriction has been reported after use of methysergide with propranolol and *oxprenolol* with ergotamine.[3] Such combinations should therefore be used with caution.

1. Baumrucker JF. Drug interaction—propranolol and Cafergot. *N Engl J Med* 1973; **288:** 916–17.
2. Diamond S. Propranolol and ergotamine tartrate. *N Engl J Med* 1973; **289:** 159.
3. Venter CP, *et al.* Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids. *BMJ* 1984; **289:** 288–9.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to increase the oral bioavailability and plasma concentrations of dihydroergotamine in patients with orthostatic hypotension.[1]

1. Bobik A, *et al.* Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. *Clin Pharmacol Ther* 1981; **30:** 673–9.

Tacrolimus. Ergotamine may inhibit the metabolism of tacrolimus by cytochrome P450 isoenzymes (see p.1845).

Pharmacokinetics

Absorption of ergotamine from the gastrointestinal tract is poor and may be further decreased by the occurrence of gastric stasis during migraine attacks. Bioavailability is also diminished by a high first-pass hepatic metabolism. Ergotamine has been given rectally or by inhalation in an attempt to overcome these effects, with some improvement in absorption, but bioavailability is still about 5% or less. Absorption of sublingual ergotamine is very poor. There is considerable interindividual variation in the bioavailability of ergotamine, regardless of the route. Caffeine is sometimes included in oral and rectal preparations of ergotamine to improve the latter's absorption, although whether it does so is not clear. Drugs such as metoclopramide are sometimes given with the aim of alleviating gastric stasis and thus improve the absorption of ergotamine.

Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4; the majority of metabolites are excreted in the bile. About 4% of a dose is excreted in the urine. Some of the metabolites are pharmacologically active. The elimination of ergotamine is biphasic; half-lives of about 2 and 21 hours have been reported for the 2 phases, respectively. Ergotamine or its metabolites have been detected in breast milk.

◊ References.

1. Schmidt R, Fanchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. *Eur J Clin Pharmacol* 1974; **7:** 213–16.
2. Eadie MJ. Ergotamine pharmacokinetics in man: an editorial. *Cephalalgia* 1983; **3:** 135–8.
3. Perrin VL. Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clin Pharmacokinet* 1985; **10:** 334–52.

Uses and Administration

Ergotamine is an alkaloid derived from ergot (p.2010). It has marked vasoconstrictor effects, and a partial agonist action at serotonin (5-HT) receptors; it also has a powerful oxytocic action on the uterus, although less so than ergometrine (p.2009). It is used in migraine and cluster headache, and has been tried in orthostatic hypotension.

Ergotamine is commonly used as the tartrate. It is usually given orally, but has also been given sublingually, rectally, and by oral inhalation. It was formerly given by subcutaneous or intramuscular injection. Caffeine is sometimes given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear. Antiemetics such as cyclizine hydrochloride are sometimes included in combination preparations with ergotamine tartrate.

Ergotamine is used in migraine unresponsive to non-opioid analgesics. However, its adverse effects limit its use and prevent use for prophylaxis. It is most effective when given as early as possible in a migraine attack, preferably during the prodromal phase.

The usual oral dose is 1 to 2 mg of ergotamine tartrate, repeated, if necessary, half an hour later. Usually not more than 6 mg should be given in 24 hours, although some manufacturers recommend not more than 4 mg in 24 hours and others not more than 8 mg per attack. The recommended minimum interval between successive 24-hour courses is 4 days, and the total weekly dose is limited to a maximum of 12 mg, although again some manufacturers recommend a lower weekly limit of 8 mg. It is also recommended that patients should receive no more than 2 courses per month. Similar doses may be given sublingually.

Ergotamine tartrate may also be given rectally as suppositories, especially if the oral route is not effective or not practicable. The rectal dose of ergotamine tartrate is 2 mg repeated, if necessary, one hour later. Usually, not more than 4 mg should be given in 24 hours and not more than 8 mg in one week with an interval of at least 4 days between successive 24-hour courses.

A more rapid onset of action may be achieved by oral inhalation. One dose containing 360 micrograms of ergotamine tartrate has been inhaled at the onset of the attack and repeated, if necessary, at 5-minute intervals. Not more than 6 inhalation doses should be taken in 24 hours and not more than 12 in one week, with an interval of at least 4 days between successive 24-hour courses.

Ergotamine is used in patients with cluster headache to treat individual attacks of headache but since such attacks are short-lived oral inhalation may be preferable to oral, sublingual, or rectal routes. Doses used are similar to those given to treat migraine. It has also been used to prevent headache attacks during cluster periods, when it is usually given daily in low doses for up to 2 weeks, either orally or rectally (see below).

Migraine and cluster headache. Ergotamine was formerly one of the main drugs used to treat acute attacks of migraine (p.616) unresponsive to non-opioid analgesics, but triptan serotonin (5-HT_1) agonists such as sumatriptan are now preferred. Since ergotamine may exacerbate the nausea and vomiting that commonly develops as a migraine attack progresses it is often necessary to give an antiemetic as well. Poor oral bioavailability may be reduced further during a migraine attack and ergotamine has sometimes been given sublingually, rectally, or by inhalation. Adverse effects limit the dose that can be used for an individual attack and prevent the long-term use that would be required for migraine prophylaxis.

Ergotamine may be used similarly in cluster headache (p.616) to treat individual headaches during a cluster period. Ergotamine is also used in low doses given by mouth or rectally for limited periods of up to 2 weeks in the prophylaxis of headache attacks during a cluster period. Regimens that have been tried for such prophylaxis include 1 to 2 mg of ergotamine tartrate given 1 to 2 hours before an expected attack or 1 to 2 hours before bedtime for nocturnal attacks. The total maximum dose of ergotamine tartrate that may be given weekly for the prevention of cluster headache is less well established than for the treatment of migraine. Ergotamine is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended.

References.

1. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45:** 577–84.
2. Tfelt-Hansen P, *et al.* Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; **123:** 9–18.

Orthostatic hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p.1530). Ergotamine is believed[1] to be less selective than dihydroergotamine (p.619) in its actions and affects both venous capacitance and peripheral resistance.[2,3] However, the oral bioavailability of ergotamine is greater[2] than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled[3,4] or rectal[5] ergotamine.

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i:** 197–8.
2. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
3. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Toh V, *et al.* Ergotamine use in severe diabetic autonomic neuropathy. *Diabet Med* 2006; **23:** 574–6.

Preparations

BP 2008: Ergotamine Sublingual Tablets;
USP 31: Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Ergotamine Tartrate Inhalation Aerosol; Ergotamine Tartrate Injection; Ergotamine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ergodryl Mono†; ***Austria:*** Ergokapton; ***Chile:*** Jaquedryl; ***Ger.:*** ergo sanol spezial N; Ergo-Kranit Migrane; Migrexa†; ***Hung.:*** Ergam; ***Ital.:*** Ergotan; ***Philipp.:*** Avamigran; ***Thai.:*** Ergosia; Gynaemine; ***USA:*** Ergomar.

Multi-ingredient: ***Arg.:*** Cafergot; Cefalex; Ibu-Tetralgin; Ibumar Migra†; Ibupirac Migra; Integrobe Plus; Jaquedryl†; Migra Dioxadol; Migra Dorixina; Migral; Migral Compositum; Migral II; Mikesan; Solacil; Tetralgin; Tetralgin Novo; Zilactin-E†; ***Austral.:*** Cafergot; Ergodryl†; ***Austria:*** Avamigran; Cafergot; Migril; Secokapton; Synkapton; ***Belg.:*** Cafergot; ***Braz.:*** Migrane; Neogrein; Ormigrein; ***Canad.:*** Bellergal; Cafergot; Cafergot-PB†; Ergodryl; Gravergol†; ***Chile:*** Bellergal Retardado†; Cafergot-PB†; Cefalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Fredol; Migra-Nefersil; Migragesic; Migranol; Migratam; Ultrimin; ***Cz.:*** Bellaspon†; ***Denm.:*** Ergokoffin; Gynergen Comp; ***Fin.:*** Anervan; ***Fr.:*** Gynergene Cafeine; ***Ger.:*** Avamigran N†; Cafergot N†; Ergo-Kranit†; Ergoffin†; Migratan S†; RubieNex spezial†; ***Gr.:*** Cafergot; ***Hong Kong:*** Cafergot; Gravergol†; Migril†; ***Hung.:*** Kefalgin; ***India:*** Migranil; ***Indon.:*** Bellapheen; Cafergot; Ericaf; ***Irl.:*** Migranat; Migril†; ***Israel:*** Cafergot; Temigran; ***Ital.:*** Cafergot; Virdex; ***Malaysia:*** Cafergot; ***Mex.:*** Cafergot; Caftar; Ergocaf; Optium; Sydolil; Trinergot; ***Neth.:*** Cafergot; Ercycof†; ***Norw.:*** Anervan; ***NZ:*** Cafergot; ***Pol.:*** Bellergot; Coffecorn; ***Port.:*** Avamigran†; Migretil; ***S.Afr.:*** Cafergot; Cafergot-PB†; Migril; ***Singapore:*** Cafergot; ***Spain:*** Cafergot; Cafergot-PB†; Hemicraneal; ***Swed.:*** Anervan; Cafergot; ***Switz.:*** Bellagotin†; Cafergot; Cafergot-PB; ***Thai.:*** Avamigran; Bellergal†; Benera; Cafergot; Degran; Neuramizone; Poligot-CF; Polygot; Tofago; ***Turk.:*** Avmigran; Bellergal; Cafergot; Ergafein; ***UK:*** Cafergot; Migril; ***USA:*** Bel-Phen-Ergot S; Bellamine; Bellergal-S; Cafatine; Cafatine-PB; Cafergot; Ercaf; Folergot-DF; Phenerbel-S; Wigraine†; ***Venez.:*** Cafergot†; Ervostal; Migradorixina; Traveget.

Feverfew

Camomille, grande; Matricaria; Mattram; Nat' kopretiny řimbaby; Őszi margitvirág; Reunuspäivänkakkara; Tanaceti parthenii herba; Vaistinių skaistenių žolė.

Pharmacopoeias. In *Eur.* (see p.vii) and in *US*. US also describes Powdered Feverfew.

Ph. Eur. 6.2 (Feverfew). The dried, whole or fragmented aerial parts of *Tanacetum parthenium*. It contains not less than 0.2% of parthenolide ($C_{15}H_{20}O_3$ = 248.3), calculated with reference to the dried drug. It has a camphoraceous odour. Protect from light.

USP 31 (Feverfew). It consists of the dried leaves of *Tanacetum parthenium* (Asteraceae), collected when the plant is in flower. Store in a dry place. Protect from light.

Adverse Effects and Precautions

Mouth ulceration and soreness have been reported following ingestion of feverfew, and may be due to sensitisation; if they occur feverfew should be withdrawn. Contact dermatitis has been reported. Feverfew is reputed to have abortifacient properties and it is suggested that preparations should not be used in pregnancy.

Effects on the blood. There have been suggestions that feverfew may increase the risk of bleeding during surgery or in patients taking anticoagulants. However, although inhibition of platelet aggregation has been reported *in vitro* or in *animals* a review[1] of clinical studies noted that feverfew did not appear to affect haematological safety parameters.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Interactions

It has been suggested that feverfew may enhance the effects of anticoagulants (but see Effects on the Blood, above).

Uses and Administration

Feverfew consists of the dried leaves of the plant *Tanacetum parthenium* (Asteraceae). It is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, notably parthenolide. A preparation of the dried leaf powder, which has been standardised to provide a minimum of 0.2% parthenolide, is available in some countries. A suggested oral dose is 250 mg daily; a lower dose of 100 mg daily has also been given..

Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine (p.616). Studies of standardised preparations of the freeze-dried powdered leaf have produced variable results in preventing or ameliorating migraine attacks, and systematic reviews[1,2] suggest that its effectiveness in preventing migraine remains to be established.

1. Vogler BK, *et al.* Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998; **18:** 704–8.
2. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Rheumatoid arthritis. Feverfew has been used as a herbal medicine for the treatment of arthritis but although it has anti-inflammatory activity *in vitro*, a clinical trial[1] found it to be ineffective in rheumatoid arthritis.

1. Pattrick M, *et al.* Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989; **48:** 547–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Herbal Headache Relief†; ***Braz.:*** Tanaceto; Tenliv; ***Canad.:*** Tanacet; ***UK:*** Migraherb; Tanacet.

Multi-ingredient: ***Austral.:*** Albizia Complex; Extralife Arthri-Care; Extralife Migrai-Care; Guaiacum Complex†; ***Ital.:*** Neuralta Migren.

Frovatriptan *(BAN, rINN)*

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate). (6*R*)-5,6,7,8-Tetrahydro-6-methylamino-carbazole-3-carboxamide.

Фроватриптан

$C_{14}H_{17}N_3O$ = 243.3.
CAS — 158747-02-5.
ATC — N02CC07.
ATC Vet — QN02CC07.

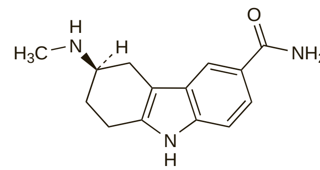

Frovatriptan Succinate *(BANM, USAN, rINNM)*

Frovatriptan, Succinate de; Frovatriptani Succinas; SB-209509AX (frovatriptan or frovatriptan succinate); Succinato de frovatriptán; VML-251 (frovatriptan or frovatriptan succinate).

Фроватриптана Суксинат

$C_{14}H_{17}N_3O,C_4H_6O_4,H_2O$ = 379.4.
CAS — 158930-17-7.
ATC — N02CC07.
ATC Vet — QN02CC07.

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Frovatriptan should not be used in patients with severe hepatic impairment. No dosage adjustment is needed in mild or moderate hepatic impairment.

Interactions

As for Sumatriptan, p.626.

Fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2 and has been shown to increase the blood levels of frovatriptan by 27 to 49%.

Pharmacokinetics

After oral doses, peak plasma-frovatriptan concentrations are attained in 2 to 4 hours, and bioavailability is about 20% in men and 30% in women. Food may delay the time to peak plasma concentrations by about 1 hour. Frovatriptan is 15% protein bound. It is primarily metabolised by the hepatic cytochrome P450 isoenzyme CYP1A2. About 32% of an oral dose is excreted in the urine and 62% in faeces. The plasma elimination half-life of frovatriptan is about 26 hours.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Buchan P, *et al.* Clinical pharmacokinetics of frovatriptan. *Headache* 2002; **42** (suppl 2): S54–S62.
2. Elkind AH, *et al.* Pharmacokinetics of frovatriptan in adolescent migraineurs. *J Clin Pharmacol* 2004; **44:** 1158–65.

Uses and Administration

Frovatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Frovatriptan is given orally as the succinate although doses are expressed in terms of the base; frovatriptan succinate 3.9 mg is equivalent to about 2.5 mg of frovatriptan.

The recommended dose is 2.5 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of at least 2 hours. The maximum dose of frovatriptan in 24 hours is 5 mg in the UK although, in the USA, a maximum daily dose of 7.5 mg is allowed.

◊ References.

1. Goldstein J. Frovatriptan: a review. *Expert Opin Pharmacother* 2003; **4:** 83–93.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Rapoport A, *et al.* Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache* 2002; **42** (suppl 2): S74–S83.
2. Ryan R, *et al.* Clinical efficacy of frovatriptan: placebo-controlled studies. *Headache* 2002; **42** (suppl 2): S84–S92.
3. Poolsup N, *et al.* Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005; **30:** 521–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Eumitan; ***Cz.:*** Fromen; Recur; ***Fin.:*** Migard; ***Fr.:*** Tigreat; ***Ger.:*** Allegro; ***Gr.:*** Migard; Migralin; ***Irl.:*** Frovex; ***Ital.:*** Auradol; Rilamig; ***Neth.:*** Fromirex; Migard; ***Port.:*** Dorlise; Migard; ***Spain:*** Forvey; Perlic; ***Switz.:*** Menamig; ***UK:*** Migard; ***USA:*** Frova.

Iprazochrome *(rINN)*

Ipratsokromi; Iprazochromum; Iprazocromo; Iprazokrom. 3-Hydroxy-1-isopropyl-5,6-indolinedione 5-semicarbazone.

Ипразохром

$C_{12}H_{16}N_4O_3$ = 264.3.
CAS — 7248-21-7.
ATC — N02CX03.
ATC Vet — QN02CX03.

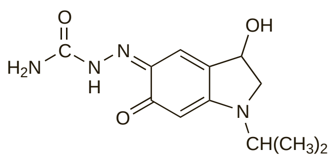

Profile

Iprazochrome is a serotonin antagonist used in the prophylaxis of migraine (p.616) and in the management of diabetic retinopathy. It has been given in usual oral doses of 2.5 to 5 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Divascan†; ***Hung.:*** Divascan; ***Pol.:*** Divascan.

Methysergide *(BAN, USAN, rINN)*

1-Methyl-D-lysergic Acid Butanolamide; Méthysergide; Methysergidum; Metisergida; Metysergid; Metysergidi. *N*-[1-(Hydroxymethyl)propyl]-1-methyl-D-lysergamide; 9,10-Didehydro-*N*-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide.

Метизергид

$C_{21}H_{27}N_3O_2$ = 353.5.
CAS — 361-37-5.
ATC — N02CA04.
ATC Vet — QN02CA04.

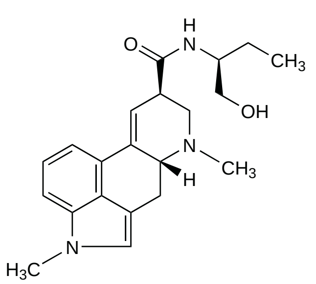

Methysergide Maleate *(BANM, rINNM)*

Maleato de metisergida; Méthysergide, Maléate de; Methysergidi Maleas.

Метизергида Малеат

$C_{21}H_{27}N_3O_2,C_4H_4O_4$ = 469.5.
CAS — 129-49-7.
ATC — N02CA04.
ATC Vet — QN02CA04.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Methysergide Maleate). A white or almost white crystalline powder which may have a yellow or pink tinge; odourless or almost odourless. Slightly soluble in water and in methyl alcohol; practically insoluble in chloroform and in ether. A 0.2% solution in water has a pH of 3.7 to 4.7. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Methysergide Maleate). A white to yellowish-white or reddish-white, crystalline powder. Is odourless or has not more than a slight odour. Soluble 1 in 200 of water and 1 in 165 of alcohol; soluble 1 in 3400 of chloroform; practically insoluble in ether. pH of a 1 in 500 solution is between 3.7 and 4.7. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Adverse Effects

Gastrointestinal effects such as nausea, vomiting, heartburn, and abdominal pain are common on initial treatment with methysergide maleate, as are dizziness and drowsiness. Other CNS effects reported include ataxia, insomnia, weakness, restlessness, lightheadedness, euphoria, and hallucinations. Peripheral or localised oedema, leg cramps, and weight gain have occurred and there have been occasional reports of skin rashes, loss of hair, joint and muscle pain, neutropenia, and eosinophilia. Orthostatic hypotension and tachycardia have been observed. There have been isolated reports of myocardial infarction particularly in patients with ischaemic heart disease or when given with other vasoconstrictive drugs, both of which are contra-indications for methysergide therapy.

Arterial spasm has occurred in some patients, and may present as paraesthesia of the extremities or anginal pain, as with ergotamine (p.620); if such symptoms occur methysergide should be withdrawn, although rebound headaches may be experienced if it is withdrawn suddenly. Vascular insufficiency of the lower limbs may represent arterial spasm or fibrotic changes. Treatment should be stopped at the first signs of impaired peripheral circulation. Retroperitoneal fibrosis, with obstruction of abdominal blood vessels and ureters, pleuropulmonary fibrosis, and fibrotic changes in heart valves have occurred in patients on long-term treatment. Methysergide must be withdrawn immediately if fibrosis occurs. Retroperitoneal fibrosis is usually reversible, but other fibrotic changes are less readily reversed.

Fibrosis. Fibrosis has been associated with the long-term use of methysergide maleate. In one early report[1] in 27 patients retroperitoneal fibrosis was attributed to use of methysergide for periods of 9 to 54 months in doses ranging from 2 to 28 mg daily. There was partial or complete regression of fibrosis in 13 of the patients whose treatment was withdrawn. Improvement usually began within a few days, in some cases with the aid of prednisone. The other 14 patients were treated by surgery; those few who continued taking methysergide had difficult postoperative courses. Cardiac murmurs occurred in 7 patients, and regressed wholly or partially in 3 after therapy was stopped. Fibrotic changes affecting the aorta, heart valves, and pulmonary tissues occurred in a few of the patients. Others have reported the development of endocardial fibrosis indicated by cardiac murmurs in 48 patients receiving methysergide.[2] The murmurs gradually regressed in 27 when methysergide was stopped. Retroperitoneal fibrosis was present in 9 patients and pleuropulmonary fibrosis in 2. A patient with fibrosis of the iliac vein has been described.[3]

A few cases of retroperitoneal fibrosis associated with ergotamine tartrate or dihydroergotamine have also been noted.[1] These 2 drugs have also been implicated in a few other cases of retroperitoneal fibrosis or other fibrotic disorders in patients taking high doses for long periods.[4-7]

1. Graham JR, *et al.* Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; **274:** 359–68.
2. Bana DS, *et al.* Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974; **88:** 640–55.
3. Bucci JA, Manoharan A. Methysergide-induced retroperitoneal fibrosis: successful outcome and two new laboratory features. *Mayo Clin Proc* 1997; **72:** 1148–50.
4. Lepage-Savary D, Vallières A. Ergotamine as a possible cause of retroperitoneal fibrosis. *Clin Pharm* 1982; **1:** 179–80.
5. Robert M, *et al.* Fibrotic processes associated with long-term ergotamine therapy. *N Engl J Med* 1984; **311:** 601 and 602.
6. Damstrup L, Jensen TT. Retroperitoneal fibrosis after long-term daily use of ergotamine. *Int Urol Nephrol* 1986; **18:** 299–301.
7. Malaquin F, *et al.* Pleural and retroperitoneal fibrosis from dihydroergotamine. *N Engl J Med* 1989; **321:** 1760.

Treatment of Adverse Effects

As for Ergotamine Tartrate, p.620.

Methysergide maleate should be withdrawn immediately if fibrosis develops. Corticosteroids have been used to treat fibrosis, although surgery may be required.

Precautions

As for Ergotamine Tartrate, p.620.

In addition, methysergide maleate is contra-indicated in valvular heart disease, pulmonary and collagen diseases, diseases of the urinary tract, phlebitis and cellulitis of the lower extremities, and debilitated states. It should be used with caution in patients with peptic ulcer disease because it may increase gastric acidity. Patients should be closely supervised. Methysergide should not be given continuously for more than 6 months and should normally be withdrawn gradually (see Uses and Administration, below). However, it should be withdrawn immediately if symptoms of fibrosis or arterial spasm develop.

Porphyria. Methysergide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

Interactions involving those ergot alkaloids used primarily in the management of migraine are discussed under ergotamine (p.621). References specific to methysergide may be found there under the headings Antimigraine Drugs and Beta Blockers.

Pharmacokinetics

Methysergide maleate is rapidly absorbed from the gastrointestinal tract with maximum plasma concentrations being obtained within about one hour of ingestion. It is 66% bound to plasma proteins. Methysergide undergoes extensive first-pass hepatic metabolism to methylergometrine (p.2011). About 50% of an oral dose is excreted in the urine as unchanged drug and metabolites. The elimination of methysergide is biphasic; half-lives of about 2.7 hours and 10 hours have been reported for the 2 phases respectively.

◊ References.

1. Bredberg U, *et al.* Pharmacokinetics of methysergide and its metabolite methylergometrine in man. *Eur J Clin Pharmacol* 1986; **30:** 75–7.

Uses and Administration

Methysergide maleate is a semisynthetic ergot alkaloid. It is a potent serotonin antagonist and, compared with ergotamine, has only weak vasoconstrictor and oxytocic effects. It may be used to prevent severe recurrent migraine (p.616) and headache attacks during cluster periods (p.616), although its use has declined because of adverse effects. It is ineffective in the treatment of acute attacks.

Methysergide is given orally as the maleate but doses are often expressed in terms of the base; 1.33 mg of methysergide maleate is equivalent to about 1 mg of methysergide. A usual dosage is 2 to 6 mg daily given in divided doses with meals. It is suggested that treatment should be started with 1 mg at bedtime and doses increased gradually over about 2 weeks; the minimum effective dose should be used. In some other countries doses are expressed in terms of the maleate, a usual dose of which is 4 to 8 mg daily. Careful and regular observation of the patient is essential because of the high incidence of adverse effects and it is recommended that treatment should only be carried out under hospital supervision. If treatment still proves to be ineffective after 3 weeks, further use is unlikely to be of benefit. Treatment should not be continued for more than 6 months, after which it should be gradually withdrawn over 2 or 3 weeks and then stopped for at least a month for reassessment. Some have considered that treatment courses should not exceed 3 months without a break.

Methysergide maleate has also been used to control diarrhoea associated with carcinoid syndrome (p.643) in high doses equivalent to 12 to 20 mg of methysergide daily.

As a serotonin antagonist, methysergide might be expected to help reverse the serotonin syndrome (p.416).

Preparations

BP 2008: Methysergide Tablets;
USP 31: Methysergide Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Deseril; ***Belg.:*** Deseril; ***Braz.:*** Deserila; ***Canad.:*** Sansert; ***Fr.:*** Desernil; ***Ger.:*** Deseril†; ***Neth.:*** Deseril; ***S.Afr.:*** Deseril†; ***Switz.:*** Deseril†; ***UK:*** Deseril.

Naratriptan Hydrochloride

(BANM, USAN, rINNM)

GR-85548A; GR-85548X (naratriptan); Hidrocloruro de naratriptán; Naratriptan, Chlorhydrate de; Naratriptani Hydrochloridum. *N*-Methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide hydrochloride.

Наратриптана Гидрохлорид

$C_{17}H_{25}N_3O_2S,HCl$ = 371.9.
CAS — 121679-13-8 (naratriptan); 121679-19-4 (naratriptan hydrochloride); 143388-64-1 (naratriptan hydrochloride).
ATC — N02CC02.
ATC Vet — QN02CC02.

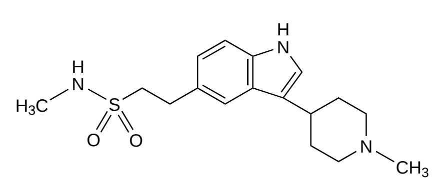

(naratriptan)

Pharmacopoeias. In *US.*

USP 31 (Naratriptan Hydrochloride). A white to pale yellow solid. Soluble in water. Store in airtight containers at a temperature not exceeding 30°.

The symbol † denotes a preparation no longer actively marketed

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Naratriptan should not be used in patients with severe hepatic or renal impairment (creatinine clearance less than 15 mL/minute) and should be used with caution in mild or moderate renal or hepatic impairment. Patients with hypersensitivity to sulfonamides may theoretically exhibit a similar reaction to naratriptan.

Medication-overuse headache. For a report of an association between naratriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p.626.

Interactions

As for Sumatriptan, p.626.

Pharmacokinetics

After oral doses, peak plasma-naratriptan concentrations occur at 2 to 3 hours, and bioavailability is reported to be 63% in men and 74% in women. Plasma protein binding is about 29%. Naratriptan undergoes some hepatic metabolism by a wide range of cytochrome P450 isoenzymes. It is mainly excreted in the urine with 50% of a dose being recovered as unchanged drug and 30% as inactive metabolites. The elimination half-life is 6 hours, and is significantly prolonged in patients with renal or hepatic impairment.

Distribution into milk has been found in studies in *rats*.

Uses and Administration

Naratriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. It is given orally as the hydrochloride, and doses are expressed in terms of the base; naratriptan hydrochloride 1.11 mg is equivalent to about 1 mg of naratriptan.

The recommended dose of naratriptan in the UK is 2.5 mg, and in the USA it is 1 or 2.5 mg. If no response is obtained with the initial dose, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of 4 hours, to a maximum of 5 mg in any 24-hour period. For doses in hepatic or renal impairment see below.

Administration in hepatic or renal impairment. Naratriptan is contra-indicated in patients with severe hepatic or severe renal impairment (creatinine clearance less than 15 mL/minute). In patients with mild to moderate hepatic or renal impairment, the recommended maximum dose in 24 hours is 2.5 mg and a lower starting dose should be considered.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Safety* 2004; **13:** 73–82.

Preparations

USP 31: Naratriptan Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Naramig; ***Austral.:*** Naramig; ***Austria:*** Antimigrin; Naramig; ***Belg.:*** Naramig; ***Braz.:*** Naramig; ***Canad.:*** Amerge; ***Chile:*** Miragran; Naramig; ***Cz.:*** Naramig; ***Denm.:*** Naragran; ***Fin.:*** Naramig; ***Fr.:*** Naramig; ***Ger.:*** Naramig; ***Gr.:*** Naramig; ***Hung.:*** Naramig†; ***Israel:*** Naramig; ***Mex.:*** Naramig; ***Neth.:*** Naramig; ***Norw.:*** Naramig; ***NZ:*** Naramig; ***Port.:*** Naramig; ***Rus.:*** Naramig (Нарамиг); ***S.Afr.:*** Naramig; ***Singapore:*** Naramig; ***Spain:*** Colatan†; Naramig; ***Swed.:*** Naramig; ***Switz.:*** Naramig; ***Thai.:*** Naramig†; ***Turk.:*** Naramig; ***UK:*** Naramig; ***USA:*** Amerge.

Oxetorone Fumarate *(USAN, rINNM)*

Fumarato de oxetorona; L-6257; Oxétorone, Fumarate d'; Oxetoroni Fumaras. 3-(6,12-Dihydrobenzofuro[3,2-*c*][1]benzoxepin-6-ylidene)-*NN*-dimethylpropylamine hydrogen fumarate.

Оксеторона Фумарат

$C_{21}H_{21}NO_2,C_4H_4O_4$ = 435.5.
CAS — 26020-55-3 (oxetorone); 34522-46-8 (oxetorone fumarate).
ATC — N02CX06.
ATC Vet — QN02CX06.

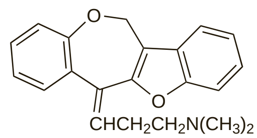

(oxetorone)

Profile

Oxetorone fumarate is an antihistamine and serotonin antagonist used orally in the treatment of migraine (p.616) and cluster headache (p.616) in doses of up to 180 mg daily. Oxetorone was reported to have induced hyperplastic changes in breast tissue and the uterine endometrium of *rodents*.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Nocertone; ***Cz.:*** Nocertone†; ***Fr.:*** Nocertone.

Pizotifen *(BAN, rINN)*

BC-105; Pitsotifeeni; Pizotifène; Pizotifeno; Pizotifenum; Pizotyline *(USAN)*. 9,10-Dihydro-4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene.

Пизотифен

$C_{19}H_{21}NS$ = 295.4.
CAS — 15574-96-6.
ATC — N02CX01.
ATC Vet — QN02CX01.

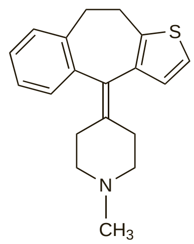

Pharmacopoeias. In *Chin.*

Pizotifen Malate *(BANM, rINNM)*

Malato de pizotifeno; Pizotifen Hydrogen Malate; Pizotifène, Malate de; Pizotifeni Malas; Pizotyline Malate.

Пизотифена Малат

$C_{19}H_{21}NS,C_4H_6O_5$ = 429.5.
CAS — 5189-11-7.
ATC — N02CX01.
ATC Vet — QN02CX01.

Pharmacopoeias. In *Br.*

BP 2008 (Pizotifen Malate). A white or slightly yellowish-white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, see p.561.

Increased appetite and weight gain may occur with pizotifen. Drowsiness may be troublesome.

Incidence of adverse effects. Adverse effects were noted in 22 of 47 patients with severe migraine given pizotifen 1 to 2 mg daily.[1] These reactions included weight increase (15), muscle pain or cramps (3), heavy or restless legs (3), fluid retention (3), drowsiness (2), more frequent milder headaches (2), facial flushing (1), reduced libido (1), exacerbation of epilepsy (1), and dreaming (2). Adverse effects necessitating withdrawal occurred in 11 patients.

1. Peet KMS. Use of pizotifen in severe migraine: a long-term study. *Curr Med Res Opin* 1977; **5:** 192–9.

Interactions

As for the sedating antihistamines in general, see p.563.

Antihypertensives. After a report[1] of loss of blood pressure control when treatment with pizotifen was started in a patient receiving *debrisoquine* the manufacturer suggested that since pizotifen had a similar chemical structure to the tricyclic antidepressants it might antagonise the actions of adrenergic neurone blockers in a similar manner.

1. Bailey RR. Antagonism of debrisoquine sulphate by pizotifen (Sandomigran). *N Z Med J* 1976; **1:** 449.

Pharmacokinetics

Pizotifen is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 5 hours after a single oral dose. Over 90% is bound to plasma proteins. Pizotifen undergoes extensive metabolism. Over half of a dose is excreted in the urine, chiefly as metabolites; a significant proportion is excreted in the faeces. The primary metabolite of pizotifen (*N*-glucuronide conjugate) has a long elimination half-life of about 23 hours.

Distribution into milk has been found in *animal* studies.

Uses and Administration

Pizotifen is a sedating antihistamine (p.561) that has strong serotonin antagonist and weak antimuscarinic properties. It also antagonises the action of tryptamine. Pizotifen is used, usually as the malate, for the prophylaxis of migraine and for the prevention of headache attacks during cluster periods. It is not effective in treating an acute attack. Doses of pizotifen malate are expressed in terms of the base; pizotifen malate 1.45 mg is equivalent to about 1 mg of pizotifen.

The usual adult oral dose is 1.5 mg daily either in three divided doses or as a single dose at night; children aged over 2 years may also be given up to 1.5 mg daily, although the maximum single dose (at night) should not exceed 1 mg. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness. Doses in adults may vary from 500 micrograms up to a maximum of 4.5 mg daily; not more than 3 mg should be given as a single dose.

Pizotifen hydrochloride has also been used in the management of migraine.

Abdominal migraine. Abdominal migraine is a recurrent disorder seen mainly in children and characterised by episodic midline abdominal pain lasting for up to 72 hours. The pain is severe enough to disrupt normal activities and may be associated with pallor, anorexia, nausea, and vomiting.[1,2] Sleep, and sometimes vomiting, terminate the attack.

Pizotifen was found to be effective for the prophylaxis of abdominal pain in children with abdominal migraine.[3] Prophylactic treatment with propranolol or cyproheptadine may also be of benefit.[4]

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://216.25.100.131/ihscommon/guidelines/pdfs/ihc_II_main_no_print.pdf (accessed 01/10/04)
2. Russell G, *et al.* The child with recurrent abdominal pain: is it abdominal migraine? *Br J Hosp Med* 2007; **68:** M110–M113.
3. Symon DNK, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995; **72:** 48–50.
4. Worawattanakul M, *et al.* Abdominal migraine: prophylactic treatment and follow-up. *J Pediatr Gastroenterol Nutr* 1999; **28:** 37–40.

Migraine and cluster headache. Pizotifen has been widely used for the prophylaxis of migraine (p.616) but evidence for its efficacy is limited. It has also been tried in the management of cluster headache (p.616) to prevent headache attacks during a cluster period.

References.

1. Cleland PG, *et al.* Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997; **38:** 31–8.
2. Barnes N, Millman G. Do pizotifen or propranolol reduce the frequency of migraine headache? *Arch Dis Child* 2004; **89:** 684–5.

Preparations

BP 2008: Pizotifen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Sandomigran; ***Austral.:*** Sandomigran; ***Belg.:*** Sandomigran; ***Braz.:*** Sandomigran; ***Canad.:*** Sandomigran; ***Cz.:*** Sandomigran; ***Denm.:*** Sandomigrin; ***Fr.:*** Sanmigran; ***Ger.:*** Mosegor†; ***Gr.:*** Mosegor†; ***Hong Kong:*** Sandomigran; ***Hung.:*** Sandomigran†; ***Indon.:*** Lysagor; ***Irl.:*** Sanomigran; ***Ital.:*** Sandomigran; ***Malaysia:*** Sandomigran; ***Neth.:*** Sandomigran; ***NZ:*** Sandomigran; ***Philipp.:*** Litec; Mosegor; ***Pol.:*** Polomigran; ***S.Afr.:*** Sandomigran; ***Spain:*** Mosegor; Sandomigran; ***Swed.:*** Sandomigrin; ***Switz.:*** Mosegor; ***Thai.:*** Anorsia; Mosegor; Moselar; Pizomed; Zofen; ***Turk.:*** Sandomigran; ***UK:*** Sanomigran; ***Venez.:*** Sandomiran†.

Multi-ingredient: ***Philipp.:*** Appetens; Mosegor Vita.

Rizatriptan Benzoate *(BANM, USAN, pINNM)*

Benzoato de rizatriptán; MK-0462; MK-462; Rizatriptan, Benzoate de; Rizatriptani Benzoas. 3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)indole monobenzoate; Dimethyl{2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)indol-3-yl]ethyl}amine monobenzoate.

Ризатриптана Бензоат

$C_{15}H_{19}N_5,C_7H_6O_2$ = 391.5.

CAS — 144034-80-0 (rizatriptan); 145202-66-0 (rizatriptan benzoate).

ATC — N02CC04.

ATC Vet — QN02CC04.

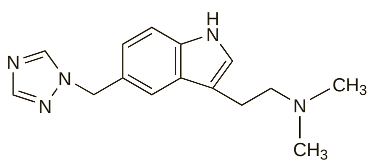

(rizatriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625. Toxic epidermal necrolysis has also been reported with rizatriptan.

Rizatriptan should not be used in patients with severe hepatic or renal impairment and should be given with caution to patients with mild or moderate hepatic or renal impairment.

Interactions

As for Sumatriptan, p.626.

Propranolol increases plasma-rizatriptan concentrations and it is recommended that lower doses of rizatriptan should be used in patients receiving both drugs (see Uses and Administration, below).

Pharmacokinetics

After oral doses, peak plasma-rizatriptan concentrations are obtained in about 1 to 1.5 hours or 1.6 to 2.5 hours depending on the formulation. Bioavailability is about 40 to 45%. Food may delay the time to peak plasma concentrations of the tablet formulation by about 1 hour. Plasma protein binding is low (14%).

Rizatriptan is metabolised primarily by monoamine oxidase type A to the inactive indole acetic acid derivative. The active metabolite *N*-monodesmethyl-rizatriptan is formed to a minor degree; other minor metabolites are also produced. About 14% of an oral dose is excreted in the urine as unchanged rizatriptan, 51% as the indole acetic acid metabolite, and 1% as *N*-monodesmethyl-rizatriptan. The plasma half-life is about 2 to 3 hours.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Lee Y, *et al.* Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. *Br J Clin Pharmacol* 1999; **47:** 373–8.
2. Goldberg MR, *et al.* Rizatriptan, a novel 5-HT agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2000; **40:** 74–83.
3. Vyas KP, *et al.* Disposition and pharmacokinetics of the antimigraine drug, rizatriptan, in humans. *Drug Metab Dispos* 2000; **28:** 89–95.
4. Swan SK, *et al.* Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: an open-label, randomized, single-dose, 3-period crossover study. *J Clin Pharmacol* 2006; **46:** 172–8.

Uses and Administration

Rizatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Rizatriptan is given as the benzoate, and doses are expressed in terms of the base; rizatriptan benzoate 14.53 mg is equivalent to about 10 mg of rizatriptan.

The usual dose in the UK of rizatriptan is 10 mg orally. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, a further dose of 10 mg may be taken after an interval of at least 2 hours. In the USA a dose of 5 or 10 mg is used. The recommended maximum dose in 24 hours is 20 mg in the UK and 30 mg in the USA. A reduced dose of 5 mg is recommended in patients also receiving propranolol, with the maximum dose in 24 hours reduced to 10 mg in the UK and 15 mg in the USA. It is also recommended that doses of the 2 drugs should be separated by at least 2 hours. For doses in hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. In patients with mild to moderate hepatic or renal impairment, the dose of rizatriptan should be reduced to 5 mg. If the headache recurs following an initial response, a further dose of 5 mg may be taken after an interval of at least 2 hours. The recommended maximum dose in 24 hours in these patients is 10 mg in the UK. Rizatriptan should not be used in patients with severe hepatic or renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Dooley M, Faulds D. Rizatriptan: a review of its efficacy in the management of migraine. *Drugs* 1999; **58:** 699–723. Correction. *ibid.* 2000; **59:** 179.
2. Wellington K, Plosker GL. Rizatriptan: an update of its use in the management of migraine. *Drugs* 2002; **62:** 1539–74.
3. Pascual J. A review of rizatriptan, a quick and consistent 5-HT1B/1D agonist for the acute treatment of migraine. *Expert Opin Pharmacother* 2004; **5:** 669–77.
4. Ahonen K, *et al.* A randomized trial of rizatriptan in migraine attacks in children. *Neurology* 2006; **67:** 1135–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Maxalt†; ***Austria:*** Maxalt; Rizalief; ***Belg.:*** Maxalt; ***Braz.:*** Maxalt; ***Canad.:*** Maxalt; ***Chile:*** Maxalt; ***Cz.:*** Maxalt†; ***Denm.:*** Maxalt; ***Fin.:*** Maxalt; ***Ger.:*** Maxalt; ***Gr.:*** Maxalt; Modinol†; ***Hung.:*** Maxalt†; ***India:*** Rizact; ***Israel:*** Rizalt; ***Ital.:*** Maxalt; Rizaliv; ***Mex.:*** Maxalt; ***Neth.:*** Maxalt; Rizatan; ***Norw.:*** Maxalt; ***NZ:*** Maxalt; ***Pol.:*** Maxalt; ***Port.:*** Maxalt; Migrof; ***S.Afr.:*** Maxalt; ***Spain:*** Maxalt; ***Swed.:*** Maxalt; ***Switz.:*** Maxalt; ***UK:*** Maxalt; ***USA:*** Maxalt; ***Venez.:*** Maxalt.

Sumatriptan *(BAN, rINN)*

GR-43175X; Sumatriptaani; Sumatriptán; Sumatriptanum. 3-(2-Dimethylaminoethyl)indol-5-yl-*N*-methylmethanesulfonamide.

Суматриптан

$C_{14}H_{21}N_3O_2S$ = 295.4.

CAS — 103628-46-2.

ATC — N02CC01.

ATC Vet — QN02CC01.

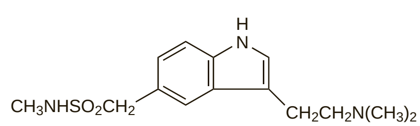

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Protect from light.

USP 31 (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Store in airtight containers at below 30°. Do not allow to freeze. Protect from light.

Sumatriptan Succinate *(BANM, USAN, rINNM)*

GR-43175C; Succinato de sumatriptán; Sumatriptaanisuksinaatti; Sumatriptan, succinate de; Sumatriptani Succcinas; Sumatriptani succinas; Sumatriptano sukcinatas; Sumatriptansuccinat; Sumatriptan-sukcinát; Sumatriptanum Succinas; Sumatryptanu bursztynian; Szumatriptánszukcinát.

Суматриптана Суксинат

$C_{14}H_{21}N_3O_2S,C_4H_6O_4$ = 413.5.

CAS — 103628-47-3 (sumatriptan hemisuccinate); 103628-48-4 (sumatriptan succinate).

ATC — N02CC01.

ATC Vet — QN02CC01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.3. Protect from light.

USP 31 (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers at a temperature not exceeding 30°. Do not allow to freeze. Protect from light.

Stability. Oral liquid preparations of sumatriptan 5 mg/mL prepared from crushed sumatriptan succinate tablets in 3 different syrups were stable for at least 21 days when stored at 4° and protected from light.[1]

1. Fish DN, *et al.* Stability of sumatriptan succinate in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 1619–22.

Adverse Effects

The most commonly reported adverse effects of serotonin (5-HT_1) agonists such as sumatriptan include dizziness, flushing, weakness, drowsiness, and fatigue. Nausea and vomiting may occur. Dyspnoea and sensory disturbance including paraesthesia and hypoaesthesia have been reported. Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. Transient increases in blood pressure may occur soon after treatment. Hypotension, bradycardia or tachycardia, palpitations, Raynaud's syndrome, and ischaemic colitis have been reported. Visual disturbances have also occurred.

Medication-overuse headache has been reported with sumatriptan and may necessitate withdrawal of the drug. Sumatriptan has occasionally been associated with minor disturbances in liver function. There have also been rare reports of seizures with sumatriptan. Hypersensitivity reactions ranging from skin rashes to, more rarely, anaphylaxis have occurred.

Transient pain at the injection site is common after subcutaneous sumatriptan injections; stinging, burning, erythema, bruising, and bleeding have also been reported. Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use.

Incidence of adverse effects. In a Dutch postmarketing survey[1] completed by 1187 patients the most common adverse reactions attributed to sumatriptan were paraesthesia (reported by 11.7% of patients), dizziness (8.1%), feeling of heaviness (8.0%), chest pain (7.9%), nausea and/or vomiting (7.3%), drowsiness/sedation (7.0%), flushing (5.1%), fatigue (4.6%), pressure in throat (3.3%), headache (3.1%), injection site reaction (3.0%), palpitations (2.8%), abdominal pain (2.6%), muscle pain (2.4%), and dyspnoea (2.2%).

The safety and tolerability of the triptans have been reviewed.[2]

1. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47:** 305–9.
2. Nappi G, *et al.* Tolerability of the triptans: clinical implications. *Drug Safety* 2003; **26:** 93–107.

Effects on the cardiovascular system. About 10 months after sumatriptan injection had been made available commercially, the UK CSM noted that it had received 34 reports of pain or tightness in the chest and 2 reports of myocardial ischaemia.[1] The Netherlands Centre for Monitoring of Adverse Reactions to Drugs declared about the same time that it had received 12 reports of chest or anginal pain mostly associated with oral sumatriptan.[2] A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients,[3] a figure considered to be lower than that seen in earlier studies, but in a subsequent questionnaire completed by 1187 of these patients 7.9% reported chest pain.[4] The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[5] stated in December 1994 that it had received 114 reports of chest pain since sumatriptan had been marketed in mid 1992. Most patients had recovered quickly but 2 had died. The first developed a fatal myocardial infarction after coronary artery dissection but the causal relation with sumatriptan was unclear. The second patient who had hypertrophic obstructive cardiomyopathy developed ventricular fibrillation a few hours after the onset of chest pain and this led to fatal cardiac arrest.

One group of workers[6] who studied the effect of sumatriptan 16 mg given subcutaneously suggested that the symptoms of chest pain might be due to an effect of sumatriptan on oesophageal function, but others have argued against this suggestion.[7] ADRAC[5] considered that the reaction in the 28 reports of throat tightness they had received by December 1994 was a different reaction to that of chest pain, and probably resulted from changes in oesophageal motility.

Several reports have provided details of individual cases of the adverse cardiovascular effects of sumatriptan including arrhythmias (ventricular tachycardia,[8] ventricular fibrillation,[8,9] or atrial fibrillation[10]), acute myocardial infarction,[11-15] and unstable an-

The symbol † denotes a preparation no longer actively marketed

gina.[16] Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction occurred in 1 case,[13] and fatal cardiac arrhythmia in another,[9] after oral use. Acute myocardial infarction[11] and cardiac arrhythmias[9] have been reported in patients with no predisposing factors.

A review[17] of published reports on chest pain as well as relevant data held by the UK manufacturer considered that the risk of myocardial ischaemia following vasoconstriction induced by sumatriptan was small. However, the contra-indications and cautions given under Precautions, below, should be observed. A recent study[18] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of cardiovascular death in those patients treated with serotonin agonists.

1. CSM. Sumatriptan (Imigran) and chest pain. *Current Problems 34* 1992. Also available at: http:// www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)
2. Stricker BHC. Coronary vasospasm and sumatriptan. *BMJ* 1992; **305:** 118.
3. Ottervanger JP, *et al.* Postmarketing study of cardiovascular adverse reactions associated with sumatriptan. *BMJ* 1993; **307:** 1185.
4. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47:** 305–9.
5. Boyd IW, Rohan AP. Sumatriptan-induced chest pain. *Lancet* 1994; **344:** 1704–5.
6. Houghton LA, *et al.* Is chest pain after sumatriptan oesophageal in origin? *Lancet* 1994; **344:** 985–6.
7. Hood S, *et al.* Sumatriptan-induced chest pain. *Lancet* 1994; **344:** 1500–1.
8. Curtin T, *et al.* Cardiorespiratory distress after sumatriptan given by injection. *BMJ* 1992; **305:** 713–14.
9. Laine K, *et al.* Fatal cardiac arrhythmia after oral sumatriptan. *Headache* 1999; **39:** 511–12.
10. Morgan DR, *et al.* Atrial fibrillation associated with sumatriptan. *BMJ* 2000; **321:** 275.
11. Ottervanger JP, *et al.* Transmural myocardial infarction with sumatriptan. *Lancet* 1993; **341:** 861–2.
12. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology* 1995; **45:** 1211–13.
13. O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. *Neurology* 1995; **45:** 2274–6.
14. Mueller L, *et al.* Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996; **36:** 329–31.
15. Main ML, *et al.* Cardiac arrest and myocardial infarction immediately after sumatriptan injection. *Ann Intern Med* 1998; **128:** 874.
16. Walton-Shirley M, *et al.* Unstable angina pectoris associated with Imitrex therapy. *Cathet Cardiovasc Diagn* 1995; **34:** 188.
17. Hillis WS, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
18. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the cerebrovascular system. Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis,[1] stroke,[2,3] and intracerebral haemorrhage.[4] Cerebral vasospasm has also been reported[5] with the use of oral sumatriptan. However, a study[6] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of stroke in those patients treated with serotonin agonists.

1. Luman W, Gray RS. Adverse reactions associated with sumatriptan. *Lancet* 1993; **341:** 1091–2.
2. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.
3. Meschia JF, *et al.* Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. *Arch Neurol* 1998; **55:** 712–14.
4. Edwards KR, *et al.* Intracerebral hemorrhage associated with sumatriptan. *Headache* 1995; **35:** 309.
5. Dash S, *et al.* Cerebral vasospasm from sumatriptan. *Neurology* 2004; **63:** 2128.
6. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the gastrointestinal tract. Ischaemic colitis and mesenteric ischaemia have been reported in a few patients receiving sumatriptan,[1-3] including repeated episodes in 2 patients,[2] each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum.[2]

Oesophageal constriction or throat tightness has been reported in some patients taking sumatriptan and may be due to a direct effect on the oesophagus (see Effects on the Cardiovascular System, above).

1. Knudsen JF, *et al.* Ischemic colitis and sumatriptan use. *Arch Intern Med* 1998; **158:** 1946–8.
2. Liu JJ, Ardolf JC. Sumatriptan-associated mesenteric ischemia. *Ann Intern Med* 2000; **132:** 597.
3. Naik M, *et al.* Sumatriptan-associated ischemic colitis. *Dig Dis Sci* 2002; **47:** 2015–16.

Effects on the respiratory system. See Asthma under Precautions, below.

Hypersensitivity. Reactions to sumatriptan such as skin rashes and, more rarely, anaphylaxis have been noted by the manufacturer. Published reports include angioedema occurring in a patient 5 minutes after subcutaneous sumatriptan,[1] and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient.[2]

1. Dachs R, Vitillo J. Angioedema associated with sumatriptan administration. *Am J Med* 1995; **99:** 684–5.
2. Pradalier A, *et al.* Delayed urticaria with sumatriptan. *Cephalalgia* 1996; **16:** 280–1.

Medication-overuse headache. Sumatriptan may have a similar risk of misuse to that associated with analgesics and ergotamine compounds in patients with medication-overuse headache (p.616). There have been reports[1-3] of patients using one or more daily doses of sumatriptan to control migraine. Many of the patients had a history of abuse of other antimigraine drugs and were using sumatriptan to prevent recurrence of headache. Whether misuse of sumatriptan was due to addiction or rebound headache as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache.[4] One study[5] and an anecdotal report[6] suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation.

The development of medication-overuse headache has also been reported with naratriptan and zolmitriptan.[7]

1. Osborne MJ, *et al.* Is there a problem with long term use of sumatriptan in acute migraine? *BMJ* 1994; **308:** 113.
2. Kaube H, *et al.* Sumatriptan. *BMJ* 1994; **308:** 1573–4.
3. Gaist D, *et al.* Misuse of sumatriptan. *Lancet* 1994; **344:** 1090.
4. Ottervanger JP, *et al.* Pattern of sumatriptan use and overuse in general practice. *Eur J Clin Pharmacol* 1996; **50:** 353–5.
5. Sullivan JT, *et al.* Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992; **52:** 635–42.
6. Bakshi R, Yan-Go FL. Prolonged marijuana-like dysphoria after subcutaneous sumatriptan. *Ann Pharmacother* 1996; **30:** 683.
7. Limmroth V, *et al.* Headache after frequent use of serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; **353:** 378.

Precautions

Sumatriptan and other serotonin ($5-HT_1$) agonists should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine.

Serotonin ($5-HT_1$) agonists are contra-indicated in patients with uncontrolled hypertension, ischaemic heart disease (coronary artery disease), a history of myocardial infarction, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease, or a previous cerebrovascular accident or transient ischaemic attack. Unrecognised cardiovascular disease should be excluded before the use of serotonin ($5-HT_1$) agonists in postmenopausal women, men over 40 years of age, and those with risk factors for ischaemic heart disease. If chest pain and tightness occur during use, appropriate investigations should be performed. Sumatriptan should not be used intravenously because of the increased risk of producing coronary vasospasm.

Drowsiness may occur after treatment with serotonin ($5-HT_1$) agonists and patients thus affected should not drive or operate machinery.

Sumatriptan should be used with caution in patients with hepatic or renal impairment, and should generally be avoided if impairment is severe.

There have been rare reports of seizures after use of sumatriptan and it should therefore be used with caution in patients with a history of epilepsy or other conditions predisposing to seizures. Patients with hypersensitivity to sulfonamides may exhibit a similar reaction to sumatriptan.

Asthma. The manufacturers reviewed data from more than 75 clinical studies of sumatriptan involving 12 701 patients and reported[1] that the incidence of adverse events related to asthma did not differ between patients with or without the condition. Earlier there had been concern over the safety of sumatriptan in patients with asthma after 2 reports of bronchospasm and a report of a patient with asthma who died during a study of sumatriptan although the patient had not received sumatriptan in the month before her death.

1. Lloyd DK, Pilgrim AJ. The safety of sumatriptan in asthmatic migraineurs. *Cephalalgia* 1993; **13:** 201–4.

Breast feeding. No adverse effects have been observed in breast-feeding infants whose mothers were receiving sumatriptan, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1] However, the manufacturers have suggested that infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment.

The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 lactating mothers.[2] The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight-adjusted basis an infant could receive a maximum of 3.5% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)
2. Wojnar-Horton RE, *et al.* Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; **41:** 217–21.

Cerebrovascular disorders. A patient with a superior sagittal sinus thrombosis who presented with headache and was misdiagnosed as having migraine variant developed a cortical stroke within minutes of a second 6-mg subcutaneous injection of sumatriptan.[1] The importance of establishing a diagnosis of typical migraine or cluster headache before using sumatriptan was emphasised and caution given against its use in any patient who may have unstable cerebrovascular disease or raised intracranial pressure. Additionally, there was no clinical evidence that a second injection would relieve a headache when the initial injection had been ineffective.

1. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.

Pregnancy. Sumatriptan crosses the placenta; however, only a very small quantity reaches the fetus. A literature review concluded that exposure to sumatriptan in pregnancy posed no additional risk of birth defects compared with that in the general population,[1] but as for other drugs sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the fetus.

1. Hilaire ML, *et al.* Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004; **38:** 1726–30.

Interactions

Sumatriptan and other serotonin ($5-HT_1$) agonists should not be given with ergotamine or related compounds (including methysergide) since there is an increased risk of vasospastic reactions. In addition, a delay is advised before starting a serotonin ($5-HT_1$) agonist in patients who have been receiving ergotamine or related compounds: sumatriptan, almotriptan, eletriptan, frovatriptan, rizatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine. Conversely, ergotamine should not be given until 6 hours after stopping these drugs or at least 24 hours in the case of eletriptan and frovatriptan. Serotonin ($5-HT_1$) agonists should not be given together.

Sumatriptan or rizatriptan should not be used with, and for 2 weeks after stopping, an MAOI. Use with the selective monoamine oxidase type B inhibitor selegiline is thought unlikely to provoke an interaction, but see p.817. Opinion varies on the concomitant use of zolmitriptan and inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A whereas in the USA it contra-indicates such combinations. There have been rare reports of serotonin syndrome associated with the use of triptan serotonin ($5-HT_1$) agonists with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), but see also under Antidepressants, below.

◊ Oral sumatriptan appeared to delay gastric emptying and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients.[1]

1. Rani PU, *et al.* Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest* 1996; **11:** 300–304.

Antidepressants. Sumatriptan and rizatriptan are metabolised mainly by monoamine oxidase type A and licensed product information advises that patients taking *MAOIs*, including reversible selective type A inhibitors such as moclobemide, should not be given triptan serotonin ($5-HT_1$) agonists. Clearance of zolmitriptan was decreased after moclobemide and in the UK a reduced dose of zolmitriptan is advised if the drug is used with an inhibitor of monoamine oxidase type A; in the USA, the use of these drugs together is contra-indicated. *SSRIs* such as fluoxetine may also interact with serotonin ($5-HT_1$) agonists with an increased risk of serotonin syndrome (p.416), and it has been suggested that *lithium* and sumatriptan may interact similarly. However, a review of the use of sumatriptan with MAOIs, SSRIs, or lithium found little evidence of an increased risk of serotonin syndrome.[1] It was concluded that most patients tolerate the combination of sumatriptan and an SSRI or lithium without incident. However, it was suggested that the use of sumatriptan with an MAOI should continue to be avoided until further data supporting safety becomes available. As there have since been rare reports of serotonin syndrome associated with the use of triptans with SSRIs or *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, licensed product information for the triptans states that when such use is clinically warranted, appropriate observation of the patient is advised, particularly when starting treatment, with dose increases, or with addition of another serotonergic drug. Product information for zolmitriptan also advises a reduction in dosage if it is given with fluvoxamine as the latter may inhibit zolmitriptan metabolism through its effects on the cytochrome P450 isoenzyme CYP1A2.

Increased serotonergic effects with increased incidence of adverse effects have been reported following the use of *St John's wort* with triptans.[2] Patients should be advised to stop taking St John's wort if treatment with a serotonin ($5-HT_1$) agonist is necessary.

1. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* 1998; **32:** 33–8.
2. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Antimigraine drugs. Although the efficacy and tolerability of subcutaneous sumatriptan in the acute treatment of migraine did not appear to be affected in patients already taking *dihydroergotamine* orally for migraine prophylaxis,[1] the bioavailability of oral dihydroergotamine is low and it could not be assumed that it was safe to use parenteral dihydroergotamine with sumatriptan.[2] Licensed product information for sumatriptan contra-indicates its use with *ergotamine* or other related compounds and also recommend that it should not be given until at least 24 hours after stopping ergotamine or related compounds (see Interactions, above).

Acute myocardial infarction has been reported[3] in a premenopausal woman with controlled hypertension and no known coronary artery disease after subcutaneous use of sumatriptan within a few hours of taking *methysergide* by mouth.

1. Henry P, *et al.* Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* 1993; **33:** 432–5.
2. Campbell JK. [Editor's comment]. *Headache* 1993; **33:** 435.
3. Liston H, *et al.* The association of the combination of sumatriptan and methysergide in myocardial infarction in a premenopausal woman. *Arch Intern Med* 1999; **159:** 511–13.

Antipsychotics. For reference to a potential interaction between sumatriptan and *loxapine*, see Chlorpromazine, p.974.

Pharmacokinetics

Sumatriptan is rapidly but incompletely absorbed when given orally and undergoes first-pass metabolism, resulting in a low absolute bioavailability of about 14%. Peak plasma concentrations after oral doses are achieved in about 2 hours. Bioavailability is much higher (96%) after subcutaneous doses with peak concentrations occurring within 25 minutes. Bioavailability after intranasal doses is 16% of that achieved subcutaneously, with peak concentrations occurring in about 1.5 hours. Plasma protein binding is low at about 14 to 21%.

The elimination half-life of sumatriptan is about 2 hours. Sumatriptan is extensively metabolised in the liver predominantly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the faeces. Small amounts of sumatriptan are distributed into breast milk (see Breast Feeding, above).

◊ Reviews.

1. Scott AK. Sumatriptan clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **27:** 337–44.
2. Lacey LF, *et al.* Single dose pharmacokinetics of sumatriptan in healthy volunteers. *Eur J Clin Pharmacol* 1995; **47:** 543–8.
3. Fuseau E, *et al.* Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002; **41:** 801–11.
4. Moen MD, Keating GM. Sumatriptan fast-disintegrating/rapid-release tablets. *Drugs* 2006; **66:** 883–90.

Uses and Administration

Sumatriptan is a selective serotonin agonist that acts at $5-HT_1$ receptors and produces vasoconstriction of cranial arteries. Drugs like sumatriptan, which are commonly known as triptans, are believed to act mainly at $5-HT_{1B}$ and $5-HT_{1D}$ subtype receptors and are therefore sometimes referred to as $5HT_{1B/1D}$-receptor agonists.

Sumatriptan is used for the acute treatment of migraine attacks and of cluster headache. It should not be used for prophylaxis. It may be given orally or subcutaneously as the succinate and intranasally as the base. Doses are expressed in terms of the base; sumatriptan succinate 70 mg is equivalent to about 50 mg of sumatriptan.

For the acute treatment of **migraine** sumatriptan should be used as soon as possible after the onset of the headache phase, but efficacy is independent of the duration of the attack before starting treatment. If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

- It is given *orally* to adults aged 18 years and over; the recommended dose in the UK is 50 mg, although some patients may require 100 mg. A clinical response can be expected after about 30 minutes. If symptoms recur after an initial response, further doses may be given provided that there is a minimum interval of 2 hours between doses and that not more than 300 mg is taken in any 24-hour period. In the USA a lower dose of 25 mg may be used, although some patients require 50 or 100 mg. This may be followed by a second dose of up to 100 mg if the headache returns or the patient has a partial response provided that the total daily dose does not exceed the recommended maximum of 200 mg. A minimum interval of 2 hours is recommended between doses. For oral doses in children and hepatic impairment, see below.
- When used *intranasally* a clinical response can be expected in 15 minutes. In the UK, patients aged 18 years and over may be given a single dose of 20 mg into one nostril, although 10 mg may be effective in some patients. In the USA, a dose of 5, 10, or 20 mg may be used. If symptoms recur, a second dose may be given at least 2 hours after the first dose. Not more than 40 mg should be used in a 24-hour period. For intranasal doses in adolescents, see below.
- In patients aged 18 years and over sumatriptan may be self-administered by *subcutaneous injection* in a single dose of 6 mg; a clinical response may be expected after 10 to 15 minutes. If symptoms recur, a second dose of 6 mg may be injected at least one hour after the first dose; not more than 12 mg should be given in a 24-hour period. In the USA, it may also be used in single doses of 4 mg if adverse effects are dose-limiting.

For the acute treatment of **cluster headache,** sumatriptan succinate is given by subcutaneous injection in similar doses to those used for migraine.

Administration in children. Sumatriptan may be given for the treatment of acute migraine in children and adolescents. Although not licensed for oral paediatric use in the UK, the *BNFC* suggests that a single *oral* dose of 25 mg may be given to children aged 6 to 10 years and 50 mg to those aged 10 to 12 years, repeated once after at least 2 hours if symptoms recur after an initial response; older children may be given the usual adult dose (see above).

In the UK, *intranasal* sumatriptan is licensed for use in adolescents aged 12 to 17 years in a dose of 10 mg into one nostril; the dose may be repeated after at least 2 hours if symptoms recur within 24 hours although not more than 20 mg should be used within a 24-hour period. The *BNFC* suggests that either this dose or an unlicensed dose equivalent to the usual adult dose (see above) may be used in those aged 12 years and over.

If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Administration in hepatic impairment. Sumatriptan should be used with caution in patients with hepatic impairment. A dose of up to 50 mg by mouth is considered suitable. It should not be given to patients with severe impairment.

High-altitude disorders. Sumatriptan has been tried with some success in a small study[1] for the prevention of symptoms of acute mountain sickness (p.1168).

1. Jafarian S, *et al.* Sumatriptan for prevention of acute mountain sickness: randomized clinical trial. *Ann Neurol* 2007; **62:** 273–7.

Migraine and cluster headache. The use of sumatriptan and other triptans in the treatment of cluster headache (p.616) and migraine (p.616) has been reviewed.[1-8]

In **migraine** serotonin ($5-HT_1$) agonists are preferred to ergotamine for the treatment of acute attacks unresponsive to non-opioid analgesics.

There are several *different triptans* clinically available. In a meta-analysis of 53 trials (involving 24 089 patients) and a separate analysis of all direct comparative trials of 5 of the triptans and sumatriptan, all were found to be more effective than placebo.[5] At the marketed doses, all oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) were effective and well tolerated. Almotriptan, eletriptan, or rizatriptan were considered to provide the highest likelihood of consistent success. A review of the efficacy of the 5 triptans available in the USA also showed pain relief at 2 hours was comparable for all.[6] Almotriptan 12.5 mg offered high tolerability and good efficacy; eletriptan 80 mg provided high efficacy and low recurrence; and rizatriptan 10 mg was associated with consistent and rapid freedom from pain.[5] Frovatriptan was not included in the analyses, but publicly available data suggested lower efficacy. Only sumatriptan, though, has parenteral formulations and the 6-mg subcutaneous formulation is still the fastest and most effective acute treatment.[5]

About 21 to 57% of patients who initially respond to sumatriptan have a *recurrence* of their headache within 24 to 48 hours; this may be related in part to its short half-life. Such recurrences usually respond to a second dose[9,10] but if a first dose is ineffective subsequent doses for the same attack are of no benefit and should not be given. Sumatriptan is considered[11] to be effective when given at any time once the headache phase of migraine has started but giving it during migraine aura appears to be of little benefit since it does not affect the aura or prevent or delay the development of headache.[12] Repeated or long-term use does not appear to be associated with reduced efficacy.[13,14] For reports of an association between sumatriptan and medication-overuse headache, see under Adverse Effects, above.

Sumatriptan's effectiveness appears to be maintained in *menstrual migraine*, a condition which is considered to be less responsive to treatment than nonmenstrual migraine.[15] Frovatriptan,[16] rizatriptan,[17] and zolmitriptan[18] have also been found to be effective in menstrual migraine.

Experience of subcutaneous use in *children* has been reported.[19] Results of a randomised, placebo-controlled study[20] of intranasal sumatriptan in adolescents aged 12 to 17 years showed evidence of efficacy, tolerability, and safety in this age group; it was felt that the nasal spray might be particularly well suited for adolescent use. Intranasal sumatriptan has also been tried in younger children (aged 8 years and over) with some success.[21]

Subcutaneous sumatriptan has also been shown to be effective in relieving acute attacks of headache in patients with **cluster headache**. In studies about 75% of patients have obtained relief within 15 minutes of a 6-mg subcutaneous injection;[22,23] the use of higher doses was found to be of no advantage. Long term efficacy appears to be maintained[24] but the significance of the transient increase in the frequency of attacks seen in some patients remains to be determined.[25] It does not appear to be effective for the prevention of headache during cluster periods.[26] Another triptan found to be effective in the treatment of episodic cluster headache is zolmitriptan.[27]

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Preparations

BP 2008: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Tablets;
USP 31: Sumatriptan Nasal Spray; Sumatriptan Succinate Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Imigran; Imitrex†; Micranil; Migraneitor; ***Austral.:*** Imigran; Sumatab; Suvalan; ***Austria:*** Glaxotriptan; Imigran; ***Belg.:*** Imitrex; ***Braz.:*** Imigran; Sumax; ***Canad.:*** Imitrex; ***Chile:*** Imigran; Liotrex†; Somatran; ***Cz.:*** Cinie; Dolorstad; Imigran; Rosemig; Sumamigren; Sumigra; ***Denm.:*** Imigran; ***Fin.:*** Imigran; ***Fr.:*** Imigrane; Imiject; ***Ger.:*** Imigran; ***Gr.:*** Imigran; Sutriptan; ***Hong Kong:*** Imigran; ***Hung.:*** Cinie; Illument; Imigran; ***India:*** Suminat; ***Indon.:*** Cetatrex; Imitrex; Triptagic; ***Irl.:*** Imigran; ***Israel:*** Imitrex; ***Ital.:*** Imigran; Sumigrene†; ***Malaysia:*** Imigran; ***Mex.:*** Imigran; Sumitrex; Tebegran; ***Neth.:*** Imigran; ***Norw.:*** Imigran; ***NZ:*** Imigran; Sumagran; ***Philipp.:*** Imigran; ***Pol.:*** Cinie; Imigran; Sumamigren; Sumigra; ***Port.:*** Diletan†; Imigran; ***Rus.:*** Amigrenin (Амигренин); Imigran (Имигран); ***S.Afr.:*** Imigran; ***Singapore:*** Imigran; ***Spain:*** Arcoiran; Dolmigral†; Imigran; ***Swed.:*** Imigran; ***Switz.:*** Imigran; ***Thai.:*** Imigran; ***Turk.:*** Imigran; Sumatran; ***UK:*** Imigran; ***USA:*** Imitrex; ***Venez.:*** Imigran; Migraval.

Zolmitriptan *(BAN, USAN, rINN)*

311C90; Tsolmitriptaani; Zolmitriptán; Zolmitriptanum. (*S*)-4-{3-[2-(Dimethylamino)ethyl]indol-5-ylmethyl}-1,3-oxazolidin-2-one.

Золмитриптан

$C_{16}H_{21}N_3O_2$ = 287.4.

CAS — 139264-17-8.

ATC — N02CC03.

ATC Vet — QN02CC03.

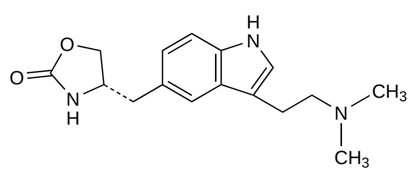

Adverse Effects and Precautions

As for Sumatriptan, p.625.

Zolmitriptan should also be avoided in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways. It should be given with caution in patients with moderate to severe hepatic impairment.

Ischaemia. A spinal cord lesion related to the use of zolmitriptan has been reported in a 50-year-old woman;[1] clinical features suggested that the lesion was an ischaemic infarct.

1. Vijayan N, Peacock JH. Spinal cord infarction during use of zolmitriptan: a case report. *Headache* 2000; **40:** 57–60.

Medication-overuse headache. For a report of an association between zolmitriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p.626.

Interactions

As for Sumatriptan, p.626.

It is recommended that the maximum dose of zolmitriptan in 24 hours should be reduced in patients receiving cimetidine (see Uses and Administration, below). A similar reduction in zolmitriptan dosage is anticipated if it is given with drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A (see Uses and Administration, below), whereas in the USA such combinations are contra-indicated.

◊ References.

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Beta blockers. *Propranolol* increased plasma-zolmitriptan concentrations in a study in 12 healthy subjects, but the changes were not thought to be clinically important enough to warrant dosage adjustment during concomitant use.[1]

1. Peck RW, *et al.* The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **44:** 595–9.

Pharmacokinetics

The absolute bioavailability of zolmitriptan after oral and intranasal doses is about 40%, and peak plasma concentrations are achieved in about 1.5 to 3 hours after oral doses, depending on the formulation, and in about 3 hours with the intranasal spray. Plasma protein binding is about 25%. Zolmitriptan undergoes hepatic metabolism, principally to the indole acetic acid, and also the *N*-oxide and *N*-desmethyl analogues. The *N*-desmethyl metabolite (183C91) was more active than the parent compound in *animal* studies, and would be expected to contribute to the therapeutic effect of zolmitriptan. The primary metabolism of zolmitriptan is mediated mainly by the cytochrome P450 isoenzyme CYP1A2 while monoamine oxidase type A is responsible for further metabolism of the *N*-desmethyl metabolite. Over 60% of a dose is excreted in the urine, mainly as the indole acetic acid, and about 30% appears in the faeces, mainly as unchanged drug. The elimination half-life is 2.5 to 3 hours, and is prolonged in patients with liver disease.

Distribution into milk has been found in studies in *rats*.

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Uses and Administration

Zolmitriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of migraine attacks. Zolmitriptan should not be used for prophylaxis.

The recommended dose in the UK is 2.5 mg orally. A clinical response can be expected within 1 hour. If symptoms persist or return within 24 hours, a second dose may be taken not less than 2 hours after the first dose. If a patient does not achieve satisfactory relief with a dose of 2.5 mg, subsequent attacks may be treated with doses of 5 mg. The maximum dose of zolmitriptan in 24 hours is 10 mg. Recommended doses in the USA are somewhat lower; the dose is 1.25 or 2.5 mg with a maximum dose of 10 mg in 24 hours.

When used intranasally a clinical response can be expected in 15 minutes. The usual dose is 5 mg as a single dose into one nostril. If symptoms persist or return within 24 hours, a second dose may be given after at least 2 hours, up to a maximum of 10 mg daily.

Dose reductions are recommended in patients taking certain other drugs. The maximum dose of zolmitriptan in 24 hours should be 5 mg in those receiving cimetidine or an inhibitor of monoamine oxidase type A (although use with inhibitors of monoamine oxidase type A is contra-indicated in the USA). A similar reduction is also recommended in those taking drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2.

For dosage in hepatic or renal impairment see below.

Administration in hepatic impairment. A study[1] has indicated that while there is no need to reduce the size of the initial dose of zolmitriptan in patients with moderate or severe hepatic impairment, accumulation may occur with repeated doses in patients with severe impairment and their total daily dosage should be reduced.

A maximum oral dose of 5 mg in 24 hours is recommended by licensed product information in the UK in patients with moderate to severe impairment. A dose of less than 2.5 mg is recommended in the USA.

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Administration in renal impairment. Although renal clearance of zolmitriptan and its metabolites was reduced in patients with moderate to severe impairment,[1] the resulting effect was unlikely to be of clinical importance and adjustment of zolmitriptan dosage in patients with renal impairment was considered unnecessary.

1. Gillotin C, *et al.* No need to adjust the dose of 311C90 (zolmitriptan), a novel anti-migraine treatment in patients with renal failure not requiring dialysis. *Int J Clin Pharmacol Ther* 1997; **35:** 522–6.

Migraine and cluster headache. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

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Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zomigon; ***Austral.:*** Zomig; ***Austria:*** Zomig; ***Belg.:*** Zomig; ***Braz.:*** Zomig†; ***Canad.:*** Zomig; ***Cz.:*** Zomig; ***Denm.:*** Zomig; ***Fin.:*** Zomig; ***Fr.:*** Zomig; Zomigoro; ***Ger.:*** AscoTop; ***Gr.:*** Zomigon; ***Hong Kong:*** Zomig; ***Hung.:*** Zomig; ***Irl.:*** Zomig; ***Israel:*** Zomig; ***Ital.:*** Zomig; ***Mex.:*** Zomig; ***Neth.:*** Zomig; ***Norw.:*** Zomig; ***Philipp.:*** Zomig; ***Pol.:*** Zomig; ***Port.:*** Zomig; ***Rus.:*** Zomig (Зомиг); ***S.Afr.:*** Zomig; ***Singapore:*** Zomig; ***Spain:*** Flezol†; Zomig; ***Swed.:*** Zomig; ***Switz.:*** Zomig; ***Thai.:*** Zomig; ***Turk.:*** Zomig; ***UK:*** Zomig; ***USA:*** Zomig; ***Venez.:*** Zomig.

Antimyasthenics

This chapter includes those drugs used for their anticholinesterase action in the treatment of myasthenia gravis and related neuromuscular disorders. Other groups of drugs playing an important role in the management of myasthenia are the corticosteroids (p.1490) and some drugs with immunosuppressant actions discussed in the chapters on Antineoplastics (p.635) and Immunosuppressants (p.1810).

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare auto-immune disease of the neuromuscular junction. Unlike myasthenia gravis (below), in which autoantibodies affect acetylcholine receptors, antibodies in Eaton-Lambert syndrome act presynaptically to reduce release of acetylcholine. Weakness mostly affects the proximal muscles, particularly those of the limbs; respiratory and ocular muscles are usually spared. Autonomic symptoms including dry mouth, constipation, and impotence are common. Over half of patients also have small cell carcinoma of the lung. Successful treatment of the tumour often leads to some improvement in symptoms.

The symptomatic treatment of Eaton-Lambert syndrome involves the use of drugs that increase the availability of acetylcholine at the neuromuscular junction. Response to treatment with *anticholinesterases* alone is poor and treatment with *amifampridine*, which increases acetylcholine release, appears to be more effective, particularly when given with an anticholinesterase such as *pyridostigmine*. The use of similar drugs such as *guanidine* and *fampridine* is limited by severe adverse effects. Low-dose guanidine has been tried with pyridostigmine where amifampridine is not readily available. Although there has been some improvement with the combination, the incidence of adverse effects, especially gastrointestinal reactions, is still high. Immunosuppressants including *azathioprine* and *corticosteroids* are also used, and unlike in treatment for myasthenia gravis, corticosteroids do not appear to induce an initial exacerbation of symptoms. Plasma exchange or high-dose intravenous *normal immunoglobulin* have been tried in patients with severe weakness.

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Myasthenia gravis

Myasthenia gravis is an auto-immune disorder characterised by defective neuromuscular transmission and consequent muscular weakness. It is caused by the formation of autoantibodies to elements of the neuromuscular junction. In most patients, antibodies to the nicotinic acetylcholine receptor are present. However, about 10 to 15% of patients have so-called 'seronegative myasthenia', in whom antibodies to other elements such as muscle-specific tyrosine kinase (MuSK) may be present instead; the proportion of such patients is much higher among those with ocular myasthenia (disease confined to the extra-ocular muscles). The thymus appears to be involved in many patients and some have a thymoma. Classifications of the disease may be based on the distribution and severity of symptoms, on the age of onset, and on the presence or absence of thymoma. Other types of myasthenia include transient neonatal myasthenia due to transplacental passage of receptor antibodies, which may persist for 1 to 6 weeks in the infants of myasthenic mothers, penicillamine-induced myasthenia, and congenital myasthenia (see under Amifampridine, p.630).

Diagnosis of myasthenia gravis.

Antibody testing remains the gold standard for diagnosis of myasthenia gravis. Patients may often be tested first for their reaction to an anticholinesterase. Intravenous edrophonium preceded by atropine (Tensilon test) is the most commonly used anticholinesterase test because of its rapid onset and short duration of action. Severe adverse effects can occasionally occur so testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available. A positive result is considered to be a rapid but temporary increase in muscle strength. Repetitive nerve stimulation is also used as a diagnostic test but, like the anticholinesterase test, is not specific for myasthenia gravis. Computed tomography or magnetic resonance imaging may be used to detect thymoma.

Treatment of myasthenia gravis.

- Symptomatic treatment is with an *anticholinesterase*; pyridostigmine and neostigmine are those most commonly used. Most patients prefer pyridostigmine as it produces less muscarinic adverse effects and has a longer duration of action, although the quicker onset of action of neostigmine may offer an advantage at the beginning of the day. The dose must be adjusted to give the optimum therapeutic response but muscle strength may not be restored to normal and some patients must live with a degree of disability. The effect may vary for different muscles and the dosage should be adjusted so that the bulbar and respiratory muscles receive optimum treatment. Generally, anticholinesterases only provide partial remission and their effects tend to diminish with continued treatment. Overdosage may lead to a 'cholinergic crisis' (see Adverse Effects of Neostigmine, p.631). Edrophonium may be employed to establish whether the patient is underdosed or overdosed.
- *Corticosteroids* are the main immunosuppressive drugs used for treatment. They are also useful in patients with ocular myasthenia, who as a group respond poorly to anticholinesterases and to thymectomy, provided that their disability is severe enough to warrant long-term corticosteroid treatment with its attendant adverse effects. Many start with low doses such as 5 to 20 mg of prednisolone daily or on alternate days, to reduce the risk of steroid-induced exacerbations of weakness, and increase the dose slowly thereafter according to response; an improvement is usually seen after a few weeks. Others use more aggressive regimens to obtain a more rapid response and start with large doses such as 60 to 80 mg of prednisolone daily. Whichever method is used, once clinical benefit has been obtained the regimen should be modified to alternate-day dosage, with the dose being slowly tapered when the patient is in remission. Patients taking corticosteroids require less anticholinesterase therapy and, if the dosage of the anticholinesterase is not reduced, an initial deterioration in the myasthenia may occur in the first few weeks of treatment (see also under Interactions of Neostigmine, p.632). It is rarely possible to withdraw corticosteroids completely but some patients may be maintained satisfactorily on as little as 10 mg on alternate days. If remission cannot be maintained on low-dose prednisolone, addition of azathioprine at a dosage of 2 to 3 mg/kg daily may be considered.
- Addition of *azathioprine* to treatment may allow a reduction in the dose of both corticosteroids and anticholinesterases. Azathioprine may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient, but it has a much slower onset of action than corticosteroids and is not usually used alone. *Ciclosporin* is effective in some patients unresponsive to standard combinations but serious adverse effects including nephrotoxicity may limit its use; the time to response is similar to that with corticosteroids. Other drugs such as *cyclophosphamide* and *methotrexate* have also been tried and benefit has been reported with *mycophenolate mofetil* and *tacrolimus*. However, a recent systematic review has found that only a small number of randomised controlled studies have been conducted on the use of immunosuppressive drugs for myasthenia gravis and most have been short-term. The review of this limited evidence concluded that, apart from cyclophosphamide used alone or ciclosporin used alone or with corticosteroids, there was no clear evidence of benefit from use of other immunosuppressants.
- Plasma exchange provides a dramatic but short-lived improvement and is useful as a short-term measure in myasthenic crisis to improve ill patients while other therapies take effect, but there is no evidence that repeated plasma exchange combined with immunosuppression is superior to immunosuppression alone. A similar short-term benefit has been seen from the use of high-dose intravenous *normal immunoglobulins*; however, a systematic review considered further study to be warranted.
- Thymectomy may be offered to all patients sufficiently fit to undergo surgery unless they have minimal symptoms, purely ocular disease, or late onset or seronegative disease. Thymectomy is usually avoided in prepubertal children because of concern over the effect on growth and the developing immune system; it has been suggested that symptomatic treatment with anticholinesterases should be continued until adolescence, when the disease often improves spontaneously. After thymectomy, remission or improvement may be expected in about 80% of patients without thymomas, although this may take some years; the response is poorer in those with thymomas.

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14. Benatar M, Kaminski H. Medical and surgical treatment for ocular myasthenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 26/05/06).
15. Hart IK, *et al.* Immunosuppressive agents for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
16. Gajdos P, *et al.* Intravenous immunoglobulin for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 28/05/08).

Ambenonium Chloride *(BAN, rINN)*

Ambenonii Chloridum; Ambénonium, Chlorure d'; Ambenoniumklorid; Ambenoniumkloridi; Ambestigmini Chloridum; Cloruro de ambenonio; Win-8077. *N,N'*-Oxalylbis(*N*-2-aminoethyl-*N*-2-chlorobenzyldiethylammonium) dichloride.

Амбенония Хлорид

$C_{28}H_{42}Cl_4N_4O_2$ = 608.5.

CAS — 7648-98-8 (ambenonium); 115-79-7 (anhydrous ambenonium chloride); 52022-31-8 (ambenonium chloride tetrahydrate).

ATC — N07AA30.

ATC Vet — QN07AA30.

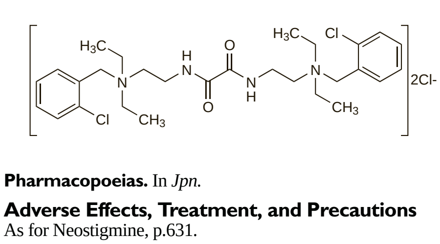

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631.

Ambenonium produces fewer muscarinic adverse effects than neostigmine. As there is only slight warning of overdosage, routine use of atropine with ambenonium is contra-indicated because the muscarinic symptoms of overdosage may be suppressed leaving only the more serious nicotinic effects (fasciculation and paralysis of voluntary muscle).

Pharmacokinetics

Ambenonium chloride is poorly absorbed from the gastrointestinal tract. It does not appear to be hydrolysed by cholinesterases.

Uses and Administration

Ambenonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632), but of longer duration. Ambenonium chloride is given orally in the treatment of myasthenia gravis (p.629) in usual doses of 5 to 25 mg three or four times daily, adjusted according to response. It may be of value in patients who cannot tolerate neostigmine or pyridostigmine.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Mytelase; ***Fr.:*** Mytelase; ***Gr.:*** Mytelase; ***Hung.:*** Mytelase; ***Pol.:*** Mytelase; ***Swed.:*** Mytelase; ***USA:*** Mytelase.

Amifampridine *(rINN)*

Amifampridina; Amifampridinum; 3,4-Diaminopyridine. Pyridine-3,4-diamine.

Амифампридин

$C_5H_7N_3$ = 109.1.

CAS — 54-96-6.

ATC — N07XX05.

ATC Vet — QN07XX05.

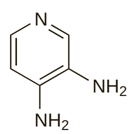

Profile

Amifampridine has similar actions and uses to fampridine (p.631) but is reported to be more potent in enhancing the release of acetylcholine from nerve terminals. It is used in the Eaton-Lambert myasthenic syndrome (below) and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism. There have been isolated reports of seizures and amifampridine is therefore contra-indicated in patients with epilepsy.

Congenital myasthenia. Congenital or hereditary myasthenia is a heterogeneous group of rare disorders associated with various defects in neuromuscular transmission including presynaptic impairment of acetylcholinesterase release, postsynaptic abnormality of acetylcholine receptors, or a deficiency of acetylcholinesterase.[1] Symptoms may be similar to those of myasthenia gravis (p.629) but there are no immunological abnormalities. Although some forms may respond to anticholinesterases, therapy is usually unsatisfactory. Experience in 16 patients[2] has suggested that amifampridine used alone or with anticholinesterases may be of benefit. Clinical improvement was seen in 5 of 11 patients with congenital myasthenia who were given amifampridine as part of a placebo-controlled study; 3 of the 11 responded to placebo.[3] There have also been reports of benefit from the use of quinidine sulfate in patients with the slow-channel congenital myasthenic syndrome.[4]

1. Engel AG. Congenital myasthenic syndromes. *Neurol Clin North Am* 1994; **12:** 401–37.
2. Palace J, *et al.* 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* 1991; **54:** 1069–72.
3. Anlar B, *et al.* 3,4-Diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* 1996; **11:** 458–61.
4. Harper CM, Engel AG. Quinidine sulfate therapy for the slow-channel congenital myasthenic syndrome. *Ann Neurol* 1998; **43:** 480–4.

Eaton-Lambert myasthenic syndrome. Daily doses of up to 100 mg of amifampridine by mouth have been found[1] to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome (p.629). A usual starting dose of 10 mg given three or four times daily increasing if necessary to a maximum of 20 mg given five times daily has been used.[2] However, some workers have recommended limiting the dose to 80 mg daily because of the increased risk of seizures with higher doses.[3] Adverse effects appear to be mainly mild and dose related,[1] although there is a report of cardiac arrest following toxicity.[4] Most patients experience some form of paraesthesia up to 60 minutes after a dose.[1-3] Amifampridine can produce mild excitatory effects and some patients may experience difficulty in sleeping.

1. McEvoy KM, *et al.* 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; **321:** 1567–71.
2. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–212.
3. Sanders DB, *et al.* A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; **54:** 603–7.
4. Boerma CE, *et al.* Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* 1995; **33:** 249–51.

Multiple sclerosis. Amifampridine has been tried in the management of multiple sclerosis (p.892). In a crossover study[1] involving 36 patients with multiple sclerosis, amifampridine given in a dosage of up to 100 mg daily improved symptoms of leg weakness to a greater extent than placebo but paraesthesia and abdominal pain which occurred in most patients were dose-limiting in some. A systematic review[2] of the use of aminopyridines for symptomatic management of multiple sclerosis was unable to come to any conclusion, and commented on the problem of publication bias in this area.

1. Bever CT, *et al.* Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* 1996; **47:** 1457–62.
2. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Distigmine Bromide *(BAN, rINN)*

BC-51; Bispyridostigmine Bromide; Bromuro de distigmina; Distigmiinibromidi; Distigminbromid; Distigmine, Bromure de; Distigmini Bromidum; Hexamarium Bromide. 3,3′-[*N,N′*-Hexamethylenebis(methylcarbamoyloxy)]bis(1-methylpyridinium bromide).

Дистигмина Бромид

$C_{22}H_{32}Br_2N_4O_4$ = 576.3.

CAS — 15876-67-2.

ATC — N07AA03.

ATC Vet — QN07AA03.

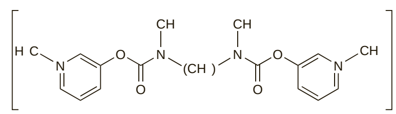

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631. The anticholinesterase action of distigmine, and hence its adverse effects, may be prolonged, and if treatment with atropine is required it should be maintained for at least 24 hours. Distigmine may stimulate uterine contractions and UK licensed product information has advised that it should be avoided in pregnancy.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Distigmine is poorly absorbed from the gastrointestinal tract.

Uses and Administration

Distigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

Although it is rarely used, distigmine bromide may be given orally with short-acting parasympathomimetics for the treatment of **myasthenia gravis** (p.629); patients being treated with parasympathomimetics tend to prefer pyridostigmine. The initial dose is 5 mg daily before breakfast, increased at intervals of 3 to 4 days if necessary to a maximum of 20 mg daily; children may be given up to 10 mg daily according to age.

Distigmine is one of several drugs that have been used in the prevention and treatment of **postoperative gastrointestinal atony** (see Decreased Gastrointestinal Motility, p.1694). It has also been used in **postoperative urinary retention** (p.2180), although it has been superseded by catheterisation. A dose of 500 micrograms of distigmine bromide was injected intramuscularly about 24 to 72 hours after surgery and repeated at intervals of 1 to 3 days until normal function was restored. Alternatively it has been given orally in a dose of 5 mg daily thirty minutes before breakfast. A similar oral dose, given daily or on alternate days, has been used in the management of **neurogenic bladder**.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Ubretid; ***Cz.:*** Ubretid; ***Fin.:*** Ubretid†; ***Ger.:*** Ubretid; ***Gr.:*** Ubretid; ***Hong Kong:*** Ubretid; ***Hung.:*** Ubretid†; ***Neth.:*** Ubretid; ***Pol.:*** Ubretid; ***Port.:*** Tonus†; ***Rus.:*** Ubretid (Убретид); ***Singapore:*** Ubretid; ***Switz.:*** Ubretid; ***UK:*** Ubretid.

Edrophonium Chloride *(BAN, rINN)*

Cloruro de edrofonio; Edrofonio chloridas; Edrofonium-chlorid; Edrofoniumklorid; Edrofoniumkloridi; Edrofonyum Klorür; Edrophonii chloridum; Édrophonium, chlorure d'. Ethyl(3-hydroxyphenyl)dimethylammonium chloride.

Эдрофония Хлорид

$C_{10}H_{16}ClNO$ = 201.7.

CAS — 312-48-1 (edrophonium); 116-38-1 (edrophonium chloride).

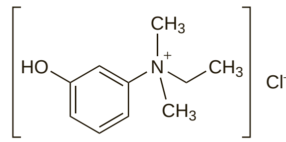

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Edrophonium Chloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Edrophonium Chloride). A white odourless crystalline powder. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; insoluble in chloroform and in ether. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631.

Interactions

As for Neostigmine, p.632.

Uses and Administration

Edrophonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity. It has actions similar to those of neostigmine (p.632) but its effect on skeletal muscle is claimed to be particularly prominent. It has a rapid onset but short duration of action. In patients with myasthenia gravis, there is immediate subjective improvement and muscle strength increases. This effect usually lasts only for about 5 to 15 minutes, after which time the typical signs and symptoms return; because of its brief action the drug is not suitable for the routine treatment of myasthenia gravis.

Edrophonium chloride is used in **myasthenia gravis** (p.629) both diagnostically and to distinguish between under- or over-treatment with other anticholinesterases.

- The usual *diagnostic procedure* is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg. In the UK the recommended total dose for children is 100 micrograms/kg, one-fifth of the dose being given initially, followed 30 seconds later by the remainder if no adverse effects develop; the *BNFC* suggests that this dose may be given to those aged from 1 month to 12 years. In the USA a total dose of 5 mg for children weighing less than 34 kg and 10 mg for heavier children is recommended, with one-fifth of the dose being given initially followed by increments of 1 mg every 30 to 45 seconds; the recommended total dose for infants is 500 micrograms.

  When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; the usual dose in adults is 10 mg while children below 34 kg in weight may be given 2 mg and heavier children 5 mg; a suggested dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously. Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
- To *detect under- or over-treatment*, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treat-

ment has been inadequate, edrophonium chloride will produce an immediate amelioration of symptoms, whereas in cholinergic crises due to over-treatment the symptoms will be temporarily aggravated. In the UK, the *BNFC* recommends that edrophonium chloride may be used in children aged from 1 month to 12 years to detect under- or over-treatment in a dose of 20 micrograms/kg. Licensed product information suggests testing one hour after the last dose of treatment but the *BNF* and the *BNFC* recommend testing just before the next dose is due. Testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available.

Edrophonium chloride was originally introduced for the **reversal of neuromuscular blockade** in anaesthesia. In the UK, the recommended dose in adults and children for the reversal of the effects of competitive neuromuscular blockers is 500 to 700 micrograms/kg given by intravenous injection over several minutes either with or after atropine sulfate 7 micrograms/kg; the *BNFC* suggests that this dose may be given to children as young as 1 month of age. In the USA, a dose of 10 mg of edrophonium chloride is given over 30 to 45 seconds and repeated as required up to a maximum of 40 mg. The brevity of its action limits its value. Prolonged apnoea may occur in patients treated with a depolarising neuromuscular blocker, such as suxamethonium; to determine if this is caused by a phase II block (see p.1912), edrophonium chloride 10 mg may be given intravenously with atropine.

Edrophonium bromide has been used similarly to edrophonium chloride.

Reversal of neuromuscular blockade. For a discussion of whether edrophonium might be more suitable than neostigmine for reversal of residual block after the use of the shorter-acting competitive neuromuscular blockers, see under Uses and Administration of Neostigmine, p.633.

Snake bite. For the use of anticholinesterases in the treatment of snake bite, see under Uses and Administration of Neostigmine, p.633.

Tetrodotoxin poisoning. Management of poisoning due to tetrodotoxin, a heat stable neuromuscular blocking toxin found in various marine animals, such as puffer fish, is mainly symptomatic and supportive. Reports[1,2] on the effectiveness of intravenous anticholinesterases such as edrophonium or neostigmine in reversing muscle weakness in tetrodotoxin poisoning have been conflicting. Although it appears that anticholinesterases may only be effective during partial block produced by tetrodotoxin, some consider[3] that, as there is no specific antidote, any measure that brings about improvement may be tried.

1. Chew SK, *et al*. Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; **ii:** 108.
2. Tibballs J. Severe tetrodotoxic fish poisoning. *Anaesth Intensive Care* 1988; **16:** 215–17.
3. Karalliedde L. Management of puffer fish poisoning. *Br J Anaesth* 1995; **75:** 500.

Preparations

BP 2008: Edrophonium Injection;
USP 31: Edrophonium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Canad.: Enlon; ***Gr.:*** Anticude; ***Spain:*** Anticude; ***USA:*** Enlon-Plus†; Enlon†; Reversol; Tensilon.

Fampridine *(USAN, rINN)*

EL-970; Fampridina; Fampridinum. 4-Aminopyridine; 4-Pyridinamine.

Фампридин

$C_5H_6N_2$ = 94.11.
CAS — 504-24-5.

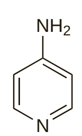

Profile

Fampridine enhances the release of acetylcholine from nerve terminals and has been used intravenously to reverse the effects of competitive neuromuscular blockers. It has also been tried orally and intravenously in the management of neurological disorders such as Eaton-Lambert myasthenic syndrome (p.629), Guillain-Barré syndrome (p.2228), multiple sclerosis (p.892), spinal cord injury, and Alzheimer's disease (see Dementia, p.362), and for the reversal of neuromuscular blockade in patients with botulism (p.2207). Typical oral doses appear to be around 30 to 50 mg daily.

Fampridine has also been considered as a specific antidote in poisoning with calcium-channel blockers (see Overdosage under Treatment of Adverse Effects of Nifedipine, p.1352).

Adverse effects seen in clinical trials include insomnia, seizures, paraesthesia, dizziness, and nausea; these effects, especially seizures, may limit its use.

◊ References.

1. Ter Wee PM, *et al.* 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum Toxicol* 1985; **4:** 327–9.
2. Davidson M, *et al.* 4-Aminopyridine in the treatment of Alzheimer's disease. *Biol Psychiatry* 1988; **23:** 485–90.
3. Hansebout RR, *et al.* 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *J Neurotrauma* 1993; **10:** 1–18.
4. Hayes KC, *et al.* Pharmacokinetics of an immediate-release oral formulation of fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *J Clin Pharmacol* 2003; **43:** 379–85.

Multiple sclerosis. Fampridine has potassium-channel blocking activity and has been tried in the treatment of multiple sclerosis to improve conduction in demyelinated fibres. Improvements have been reported in walking, dexterity, and vision, but only small numbers of patients have been studied. A systematic review[1] was unable to come to a conclusion about its safety and efficacy, noting that publication bias posed a problem in this area.

1. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Overdosage. An 8-month-old boy experienced dramatic opisthotonic posturing and vermiform tongue fasciculations after ingestion of up to 20 mg of fampridine;[1] the child was also noted to be tachycardic and tachypnoeic. His symptoms resolved after treatment with benzodiazepines.

1. Velez L, *et al.* Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. Abstract: *Pediatrics* 2003; **111:** 192–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/1/e82 (accessed 15/02/06)

Ipidacrine *(rINN)*

Amiridin (base or hydrochloride); Ipidacrina; Ipidacrinum; NIK-247 (hydrochloride). 9-Amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline.

Ипидакрин

$C_{12}H_{16}N_2$ = 188.3.
CAS — 62732-44-9 (ipidacrine); 90043-86-0 (ipidacrine hydrochloride); 118499-70-0 (ipidacrine hydrochloride monohydrate).

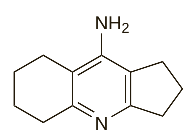

Profile

Ipidacrine, an analogue of tacrine (p.370), is a cholinesterase inhibitor. It is used in the management of various neurological disorders including CNS and peripheral nervous system disorders, demyelinating disease, myasthenia gravis (p.629) and other myasthenic syndromes, Alzheimer's disease (see Dementia, p.362), and gastrointestinal atony. For myasthenic syndromes an oral dose of 20 to 40 mg has been given up to 5 times daily. A usual dosage in Alzheimer's disease is 10 to 20 mg given 2 or 3 times daily but this may be increased gradually up to 200 mg daily given in divided doses.

Ipidacrine has also been given by injection as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Axamon (Аксамон).

Neostigmine *(BAN)*

Neostigmiini; Neostigmin; Neostigmina; Neostigminum. 3-(Dimethylcarbamoyloxy)trimethylanilinium ion.

$C_{12}H_{19}N_2O_2$ = 223.3.
CAS — 59-99-4.
ATC — N07AA01; S01EB06.
ATC Vet — QA03AB93; QN07AA01; QS01EB06.

Neostigmine Bromide *(BANM, pINN)*

Bromuro de neostigmina; Neostig. Brom.; Neostigmiinibromidi; Neostigminbromid; Néostigmine, bromure de; Neostigmini bromidum; Neostigminii Bromidum; Neostigminium-bromid; Neostigmino bromidas; Neostigminum Bromatum; Neosztigmin-bromid; Synstigminium Bromatum.

Неостигмина Бромид

$C_{12}H_{19}BrN_2O_2$ = 303.2.
CAS — 114-80-7.
ATC — N07AA01; S01EB06.
ATC Vet — QN07AA01; QS01EB06.

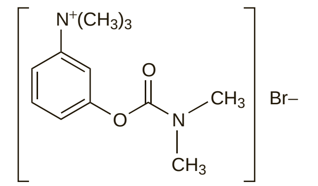

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Neostigmine Bromide). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Neostigmine Bromide). Store in airtight containers.

Stability. References.

1. Porst H, Kny L. Kinetics of the degradation of neostigmine bromide in aqueous solution. *Pharmazie* 1985; **40:** 713–17.

Neostigmine Metilsulfate *(BANM)*

Neostig. Methylsulph.; Neostigmiinimetilsulfaatti; Neostigmina, metilsulfato de; Neostigmine Methylsulfate; Neostigmine Methylsulphate; Néostigmine, métilsulfate de; Neostigmini metilsulfas; Neostigminii Metilsulfas; Neostigminium-methylsulfát; Neostigminmetilsulfat; Neostigminmetylsulfat; Neostigmino metilsulfatas; Neostygminy metylosiarczan; Neosztigmin-metilszulfát; Proserinum.

$C_{13}H_{22}N_2O_6S$ = 334.4.
CAS — 51-60-5.
ATC — N07AA01; S01EB06.
ATC Vet — QN07AA01; QS01EB06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Neostigmine Metilsulfate). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Neostigmine Methylsulfate). Store in airtight containers.

Adverse Effects

The adverse effects of neostigmine are chiefly due to excessive cholinergic stimulation and most commonly include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea. Allergic reactions have been reported; rashes have been associated with the use of the bromide salt. Neostigmine penetrates the blood-brain barrier poorly and CNS effects are usually only seen with high doses.

Overdosage may lead to a 'cholinergic crisis', characterised by both muscarinic and nicotinic effects. These effects may include excessive sweating, lachrymation, increased peristalsis, involuntary defaecation and urination or desire to urinate, miosis, ciliary spasm, nystagmus, bradycardia and other arrhythmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear. Death may result from respiratory failure, due to a combination of the muscarinic, nicotinic, and central effects, or cardiac arrest.

It has been reported that a paradoxical increase in blood pressure and heart rate may result from nicotinic stimulation of sympathetic ganglia, especially where atropine has been given to reverse the muscarinic effects (see Treatment of Adverse Effects, below).

In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased muscular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself (myasthenic crisis).

The adverse effects of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p.1885.

Treatment of Adverse Effects

If a life-threatening amount of neostigmine has been taken by mouth and the patient presents within 1 hour, the stomach may be emptied by lavage; giving activated charcoal to decrease absorption should also be considered. When necessary maintenance of respiration should take priority. Atropine sulfate should be given in usual doses of 1 to 2 mg, preferably intravenously, or else intramuscularly and repeated as necessary to control the muscarinic effects; doses of up to 4 mg have been suggested. Nicotinic effects, including muscle weakness and paralysis, are not antagonised by atropine; small doses of a competitive neuromuscular blocker have been suggested for the control of muscle twitching. Use of the cholinesterase reactivator pralidoxime as an adjunct to atropine has also been suggested (see p.1460). Further supportive treatment should be given as required.

Precautions

Neostigmine is contra-indicated in patients with mechanical gastrointestinal or urinary-tract obstruction, or peritonitis. It should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma. It should be used with caution in patients with cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction, and hypotension, as well as in patients with vagotonia, epilepsy, hyperthyroidism, parkinsonism, renal impairment, or peptic ulcer disease. When neostigmine is given by injection, atropine should always be available to counteract any excessive muscarinic reactions; atropine may also be given before, or with, neostigmine to prevent or minimise muscarinic adverse effects but this may mask the initial symptoms of overdosage and lead to cholinergic crisis.

UK licensed product information states that as the severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has also been reported that neonatal myasthenia may follow large doses during pregnancy. The amount of neostigmine distributed into breast milk is very small but breast-fed infants need to be monitored.

Large oral doses of neostigmine should be avoided in conditions where there may be increased absorption from the gastrointestinal tract. It should be avoided in patients known to be hypersensitive to neostigmine; the bromide ion from neostigmine bromide may contribute to any allergic reaction.

The precautions of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p.1885.

Neuromuscular disorders. Residual non-depolarising neuromuscular block in a patient with dystrophia myotonica was only partly reversed by neostigmine and atropine, and following a second dose of both drugs complete neuromuscular block developed.[1] In a second patient, with a history of progressive muscle dystrophy, the use of neostigmine to reverse residual non-depolarising blockade gave rise to a tonic response in the indirectly stimulated muscle. The type and degree of the response to neostigmine, and probably other anticholinesterases, cannot be predicted in patients with neuromuscular disease.

A patient with sero-negative ocular myasthenia gravis had exaggerated responses to both vecuronium and neostigmine.[2] The dose of neuromuscular blockers and their antagonists used in patients with myasthenia gravis should be titrated carefully regardless of the severity of the condition.

1. Buzello W, *et al*. Hazards of neostigmine in patients with neuromuscular disorders: report of two cases. *Br J Anaesth* 1982; **54:** 529–34.
2. Kim J-M, Mangold J. Sensitivity to both vecuronium and neostigmine in a sero-negative myasthenic patient. *Br J Anaesth* 1989; **63:** 497–500.

Interactions

Drugs with neuromuscular blocking activity, such as the aminoglycosides, clindamycin, colistin, cyclopropane, and the halogenated inhalational anaesthetics, may antagonise the effects of neostigmine. Those such as quinine, chloroquine, hydroxychloroquine, quinidine, procainamide, propafenone, lithium, and the beta blockers, that have the potential to aggravate myasthenia gravis, can reduce the effectiveness of treatment with parasympathomimetics. Prolonged bradycardia has also occurred in patients receiving beta blockers when given neostigmine. Anticholinesterases, such as neostigmine, can inhibit the metabolism of suxamethonium and enhance and prolong its action; combined use is not recommended.

Ophthalmic use of anticholinesterases, such as ecothiopate, should be undertaken with care in patients receiving neostigmine systemically for myasthenia gravis, because of possible additive toxicity.

Antimuscarinics such as atropine antagonise the muscarinic effects of neostigmine.

Beta blockers. There have been several reports of bradycardia and hypotension when neostigmine or physostigmine were given to patients receiving beta blockers[1-4] but no significant changes in heart rate were noted in a study of pyridostigmine given to 8 patients taking beta blockers.[5] Beta blockers have the potential to aggravate the symptoms of myasthenia gravis and may therefore reduce the effectiveness of parasympathomimetic treatment.

1. Sprague DH. Severe bradycardia after neostigmine in a patient taking propranolol to control paroxysmal atrial tachycardia. *Anesthesiology* 1975; **42:** 208–10.
2. Seidl DC, Martin DE. Prolonged bradycardia after neostigmine administration in a patient taking nadolol. *Anesth Analg* 1984; **63:** 365–7.
3. Baraka A, Dajani A. Severe bradycardia following physostigmine in the presence of beta-adrenergic blockade: a case report. *Middle East J Anesthesiol* 1984; **7:** 291–3.
4. Eldor J, *et al.* Prolonged bradycardia and hypotension after neostigmine administration in a patient receiving atenolol. *Anaesthesia* 1987; **42:** 1294–7.
5. Arad M, *et al.* Safety of pyridostigmine in hypertensive patients receiving beta blockers. *Am J Cardiol* 1992; **69:** 518–22.

Calcium-channel blockers. Use of calcium-channel blockers such as *verapamil* with neuromuscular blockers may produce an enhanced muscle block which is resistant to reversal with neostigmine[1] but which can be reversed by edrophonium.[2]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.

Corticosteroids. Although use of glucocorticoids alone may improve strength in myasthenic patients, use of *methylprednisolone* in patients receiving neostigmine or pyridostigmine has exacerbated symptoms and produced profound weakness needing assisted ventilation.[1] Since the adverse effects of combined therapy usually occur before any expected benefits it has been suggested that the glucocorticoid should be given on alternate days in small doses which are increased gradually until the optimal effect is achieved.[2]

1. Brunner NG, *et al.* Corticosteroids in management of severe, generalized myasthenia gravis: effectiveness and comparison with corticotrophin therapy. *Neurology* 1972; **22:** 603–10.
2. Jubiz W, Meikle AW. Alterations of glucocorticoid actions by other drugs and disease states. *Drugs* 1979; **18:** 113–21.

Pharmacokinetics

Neostigmine is a quaternary ammonium compound and, as the bromide, is poorly absorbed from the gastrointestinal tract. After parenteral doses as the metilsulfate, neostigmine is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Protein binding to human serum albumin is reported to range from 15 to 25%. Penetration into the CNS is poor. Neostigmine crosses the placenta and very small amounts are distributed into breast milk.

◊ Neostigmine appears to be poorly and variably absorbed when given orally. In 3 myasthenic patients peak plasma concentrations were obtained 1 to 2 hours after a single 30-mg dose by mouth and the mean plasma half-life was 0.87 hours; bioavailability was estimated to be 1 to 2%.[1] Mean plasma half-lives of 0.89 and 1.20 hours have been obtained after intravenous[1] and intramuscular[2] injections of neostigmine metilsulfate, respectively, although again only a few patients were studied. Metabolism and biliary excretion may play significant roles in the elimination of neostigmine.[2] About 80% of a dose may be excreted in the urine within 24 hours: about 50% of a dose as unchanged drug and 15% as 3-hydroxyphenyltrimethylammonium.[2] Mean plasma elimination half-lives for neostigmine have been found to be shorter in infants (0.65 hours) and children (0.80 hours) compared with adults (1.12 hours) but this does not appear to be related to its duration of effect in antagonising neuromuscular blockade.[3] For the half-life in anephric patients, see Administration in Renal Impairment, below.

1. Aquilonius S-M, *et al.* A pharmacokinetic study of neostigmine in man using gas chromatography–mass spectrometry. *Eur J Clin Pharmacol* 1979; **15:** 367–71.
2. Somani SM, *et al.* Kinetics and metabolism of intramuscular neostigmine in myasthenia gravis. *Clin Pharmacol Ther* 1980; **28:** 64–8.
3. Fisher DM, *et al.* The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; **59:** 220–5.

Uses and Administration

Neostigmine is a quaternary ammonium compound that inhibits cholinesterase activity and thus prolongs and intensifies the physiological actions of acetylcholine (p.1877). It probably also has direct effects on skeletal muscle fibres. The anticholinesterase actions of neostigmine are reversible.

Neostigmine is used in the treatment of myasthenia gravis, and has been used as an alternative to edrophonium in the diagnosis of myasthenia gravis (p.629). It is used in anaesthesia to reverse the neuromuscular blockade produced by competitive neuromuscular blockers (see below). It is also used in the management of paralytic ileus. Neostigmine has been used in the management of postoperative urinary retention (p.2180) but has generally been superseded by catheterisation. It has also been used to lower intra-ocular pressure in the management of glaucoma and to reduce rises in intra-ocular pressure associated with ophthalmic surgery, although other parasympathomimetics are usually used when such miotics are required.

Neostigmine is given as the bromide and as the metilsulfate. Neostigmine bromide is given orally and has been used topically as eye drops; the metilsulfate is given by intramuscular, intravenous, or subcutaneous injection.

Licensed product information states that 500 micrograms of neostigmine metilsulfate by intravenous injection is equivalent in effect to about 1 to 1.5 mg of neostigmine metilsulfate by intramuscular or subcutaneous injection, or 15 mg of neostigmine bromide orally.

In the treatment of **myasthenia gravis**, neostigmine bromide is given orally in a total daily dose usually between 75 and 300 mg, divided throughout the day, and if necessary the night, according to response; larger portions of the total dose may be given at times of greater fatigue. The maximum daily dose that most patients can tolerate is 180 mg. A usual total daily oral dose in children is 15 to 90 mg. In patients in whom oral therapy is impractical neostigmine metilsulfate may be given in doses of 0.5 to 2.5 mg by intramuscular or subcutaneous injection at intervals, giving a total daily dose usually in the range 5 to 20 mg. Single doses in children have ranged from 200 to 500 micrograms.

In the treatment of neonatal myasthenia gravis doses in the range 50 to 250 micrograms of the metilsulfate by intramuscular or subcutaneous injection, or 1 to 5 mg of the bromide orally, have been given usually every 4 hours (30 minutes before feeds); treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, the usual adult dose in the UK is 50 to 70 micrograms/kg given by intravenous injection over a period of 60 seconds; in the USA lower doses of 0.5 to 2 mg are used. Additional neostigmine may be given until the muscle power is normal but a total of 5 mg should not be exceeded. Similar doses may be used in children; the *BNFC* recommends a dose of 50 to 80 micrograms/kg in neonates and children, to a maximum of 2.5 mg in those under 12 years of age. The patient should be well ventilated until complete recovery of normal respiration is assured. To counteract any muscarinic effects in adults 0.6 to 1.2 mg of atropine sulfate is given by intravenous injection with or before the dose of neostigmine;

neonates and children up to 18 years of age may be given 20 micrograms/kg of atropine sulfate (to a maximum of 600 micrograms in those aged 1 month and over). It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.

In the treatment of paralytic **ileus** and postoperative **urinary retention**, oral doses of 15 to 30 mg of the bromide, or more usually 500 micrograms of the metilsulfate by subcutaneous or intramuscular injection, have been used.

Administration in renal impairment. The dosage of neostigmine may need to be adjusted in patients with renal impairment. The mean serum elimination half-life of 79.8 minutes obtained in patients with normal renal function was found to be prolonged to 181.1 minutes in anephric patients.[1]

1. Cronnelly R, *et al.* Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology* 1979; **51:** 222–6.

Decreased gastrointestinal motility. Parasympathomimetics enhance gastric contractions and increase intestinal motility and have been used in conditions associated with decreased gastrointestinal motility (p.1694). Good results have been reported with intravenous neostigmine in the treatment of acute colonic pseudo-obstruction,[1,2] a condition that appears to be due to parasympathomimetic dysfunction. These results have been confirmed in a randomised double-blind study.[3] It has therefore been suggested that parasympathomimetics should be tried before colonic decompression or surgery when conservative management has failed or a rapid resolution is required.[3] Neostigmine has also been used in the treatment of severe constipation due to disrupted intestinal motility.[4,5]

1. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl* 1992; **74:** 364–7.
2. Stephenson BM, *et al.* Parasympathomimetic decompression of acute colonic pseudo-obstruction. *Lancet* 1993; **342:** 1181–2.
3. Ponec RJ, *et al.* Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341:** 137–41.
4. Miller LS. Neostigmine for severe constipation with spinal cord lesions. *Ann Intern Med* 1984; **101:** 279.
5. Thurtle OA, *et al.* Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinergic drugs. *J R Soc Med* 1984; **77:** 327–8.

Local anaesthesia. Intrathecal neostigmine has been added to spinal local anaesthetics or opioids as an adjunct to prolong regional analgesia and improve haemodynamic stability. A systematic review[1] of studies of such use found that although neostigmine in doses up to 500 micrograms produced a very modest increase in analgesia in the perioperative and peripartum setting, it did not appear to improve haemodynamic stability and the incidence of adverse effects was greatly increased, even at low doses. The disadvantages were felt to outweigh whatever benefits such therapy might have.

1. Ho, KM, *et al.* Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* 2005; **33:** 41–53.

Reversal of neuromuscular blockade. Anticholinesterases have often been used after surgery to antagonise residual neuromuscular block induced by long-acting competitive neuromuscular blockers. However, there has been continuing debate[1-3] on whether anticholinesterases can be used in reduced doses or even omitted for intermediate-acting blockers such as atracurium and vecuronium and shorter-acting blockers such as mivacurium.

Decreasing the anticholinesterase dose may reduce adverse effects. Although it is not clear whether omitting neostigmine reversal reduces nausea and vomiting,[3,4] it avoids any adverse effects neostigmine may have on gut anastomoses. One commentator[1] considered that the wide variation in recovery time with aminosteroid blockers such as rocuronium was an indication for always using at least a small dose of anticholinesterase when these drugs were used. However, it was suggested that, if the block was being carefully monitored and recovery was established, a reduced dose of 1.25 mg of neostigmine might be preferable after a benzylisoquinolinium blocker such as atracurium or mivacurium. In children, smaller doses of an anticholinesterase could be used, even after an aminosteroid blocker, and after a blocker such as mivacurium, they might not be needed at all.

Others have preferred to reserve neostigmine reversal for cases where it was deemed clinically necessary: in a study[4] using such a protocol, 68% of those receiving rocuronium were given neostigmine, against 10% of those receiving mivacurium.

It has been suggested that because of its shorter duration of action edrophonium might be more suitable than neostigmine to antagonise residual block for neuromuscular blockers with shorter action and in particular, that edrophonium might be more appropriate than neostigmine for use with mivacurium. Neostigmine inhibits the plasma cholinesterase responsible for the metabolism of mivacurium and its use can in theory delay rather than speed recovery, although in practice there is considered to be little evidence for such an effect.[1] Edrophonium also has lesser effects on the vagus, a more rapid onset of action, and may be associated with a lower incidence of nausea and vomiting than neostigmine.[5] Neostigmine can cause clinically significant neuromuscular blockade if it is given to a patient who has already recovered a large degree of neuromuscular function[6,7] but edrophonium appears not to have this effect.[8] However, the antagonism produced by edrophonium is not adequately and reliably sustained especially after profound block.[9,10]

1. Hunter JM. Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults? *Br J Anaesth* 1996; **77:** 707–9.
2. Fawcett WJ. Neuromuscular block in children. *Br J Anaesth* 1997; **78:** 627.
3. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). *Eur J Anaesthesiol* 2001; **18** (suppl 23): 53–9.
4. Joshi GP, *et al.* The effects of antagonizing residual neuromuscular blockade by neostigmine and glycopyrrolate on nausea and vomiting after ambulatory surgery. *Anesth Analg* 1999; **89:** 628–31.
5. Watcha MF, *et al.* Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. *Anesth Analg* 1995; **80:** 713–17.
6. Hughes R, *et al.* Neuromuscular blockade by neostigmine. *Br J Anaesth* 1979; **51:** 568P.
7. Payne JP, *et al.* Neuromuscular blockade by neostigmine in anaesthetized man. *Br J Anaesth* 1980; **52:** 69–75.
8. Astley BA, *et al.* Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *Br J Anaesth* 1987; **59:** 983–8.
9. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; **58:** 1285–9.
10. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; **59:** 473–7.

Snake bite. The general management of snake bites is discussed on p.2239. Numerous reports from India have claimed benefit for anticholinesterases in the treatment of neurotoxic snake bites but failure to distinguish between cobra and krait bites, lack of controls, and inadequate information about other therapy weaken the claims.[1] However, edrophonium has been shown in 2 double-blind studies to be more effective than placebo[2] and antivenom[3] in the treatment of snake bite due to the Philippine cobra (*Naja naja philippinensis*). Neostigmine has also been reported[4] to have been effective in reversing paralysis in 2 patients bitten by *Micrurus frontalis* (a coral snake). Similarly, another patient made a remarkable recovery when treated with neostigmine after being bitten by an Asiatic cobra (*Naja naja kaouthia*).[5] Anticholinesterases would be expected to be of little value for bites from snakes whose venom contains neurotoxins which act presynaptically, including the Asian krait, the Australian tiger snake, and the taipan[6] and, although beneficial results have been reported in individual patients,[7] overall results are considered to be inconsistent.[2,8] However, it is recommended that a test dose of edrophonium preceded by atropine should be given to patients with neurological signs after a snake bite by any species and if improvement occurs, a longer acting anticholinesterase such as neostigmine can be given.[2,3]

1. Reid HA. Venoms and antivenoms. *Trop Dis Bull* 1983; **80:** 23.
2. Watt G, *et al.* Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). *N Engl J Med* 1986; **315:** 1444–8.
3. Watt G, *et al.* Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans R Soc Trop Med Hyg* 1989; **83:** 570–3.
4. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. *Rev Inst Med Trop Sao Paulo* 1996; **38:** 61–7.
5. Gold BS. Neostigmine for the treatment of neurotoxicity following envenomation by the Asiatic cobra. *Ann Emerg Med* 1996; **28:** 87–9.
6. Brophy T, Sutherland SK. Use of neostigmine after snake bite. *Br J Anaesth* 1979; **51:** 264–5.
7. Warrell DA, *et al.* Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; **286:** 678–80.
8. Trevett AJ, *et al.* Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (Oxyuranus scutellatus carini). *Trans R Soc Trop Med Hyg* 1995; **89:** 444–6.

Tetrodotoxin poisoning. For reference to the use of neostigmine in the treatment of tetrodotoxin poisoning caused by eating puffer fish, see under Uses and Administration of Edrophonium Chloride, p.631.

Preparations

BP 2008: Neostigmine Injection; Neostigmine Tablets;
USP 31: Neostigmine Bromide Tablets; Neostigmine Methylsulfate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Fadastigmina; Prostigmin; ***Austral.:*** Prostigmin; ***Austria:*** Normastigmin; Prostigmin; ***Belg.:*** Prostigmine; Robinul-Neostigmine; ***Braz.:*** Normastig; Prostigmine; ***Canad.:*** Prostigmin; ***Chile:*** Prostigmine†; ***Cz.:*** Syntostigmin; ***Denm.:*** Robinul-Neostigmin; ***Fin.:*** Glycostigmin; Robinul-Neostigmin; ***Fr.:*** Prostigmine; ***Ger.:*** Neostig; ***Gr.:*** Prostigmine; ***Hong Kong:*** Prostigmin†; ***Hung.:*** Stigmosan; ***India:*** Tilstigmin; ***Indon.:*** Prostigmin; ***Israel:*** Prostigmine†; ***Ital.:*** Intrastigmina; Prostigmina; ***Malaysia:*** Prostigmin†; ***Mex.:*** Prostigmine; ***Neth.:*** Prostigmin; ***Norw.:*** Robinul-Neostigmin; ***Philipp.:*** Prostigmin; ***Pol.:*** Polstigminum; ***Port.:*** Intrastigmina; Prostigmine; ***Spain:*** Prostigmine; ***Swed.:*** Robinul-Neostigmin; ***Switz.:*** Prostigmin; Robinul-Neostigmine; ***Thai.:*** Prostigmin; ***UK:*** Robinul-Neostigmine; ***USA:*** Neostigmine Min-I-Mix; Prostigmin.

Multi-ingredient: ***Austria:*** Normastigmin mit Pilocarpin; Pilostigmin Puroptal; ***Ger.:*** Syncarpin-N†.

Pyridostigmine Bromide *(BAN, rINN)*

Bromuro de piridostigmina; Piridostigmin Bromür; Piridostigmino bromidas; Piridosztigmin-bromid; Pyridostig. Brom.; Pyridostigmiinibromidi; Pyridostigminbromid; Pyridostigmine, bromure de; Pyridostigmini bromidum; Pyridostigminii Bromidum; Pyridostigminium-bromid. 3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.

Пиридостигмина Бромид

$C_9H_{13}BrN_2O_2 = 261.1.$

CAS — 155-97-5 (pyridostigmine); 101-26-8 (pyridostigmine bromide).

ATC — N07AA02.

ATC Vet — QN07AA02.

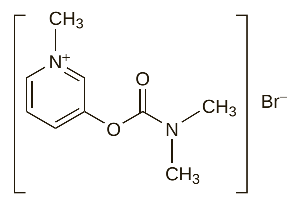

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Pyridostigmine Bromide). A white or almost white deliquescent crystalline powder. Very soluble in water and in alcohol. Store in airtight containers. Protect from light.

USP 31 (Pyridostigmine Bromide). A white or practically white, hygroscopic, crystalline powder, having an agreeable characteristic odour. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether; slightly soluble in petroleum spirit. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631. It has been stated that muscarinic adverse effects occur less frequently with pyridostigmine treatment than with neostigmine.

Breast feeding. Pyridostigmine was present in the breast milk of 2 nursing mothers, receiving maintenance therapy for myasthenia gravis, in a concentration between 36 and 113% of that in maternal plasma,[1] but in both cases the dose ingested per kg body-weight by the nursing infant was 0.1% or less of that ingested by the mother. Maternal medication with pyridostigmine should be no obstacle to breast feeding, at least with doses in the range of 180 to 300 mg daily.

On the basis of this study, the American Academy of Pediatrics considers[2] that pyridostigmine is usually compatible with breast feeding.

1. Hardell L-I, *et al.* Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; **14:** 565–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/02/06)

Effects on the joints. Several years after starting oral pyridostigmine bromide 60 mg five times daily, a middle-aged woman had episodes of bilateral arthralgia and hyperalgesia of her hips, knees, toes, and shoulders.[1] Symptoms resolved when pyridostigmine was stopped and rechallenge was positive on several occasions.

1. Rostedt A, Stålberg E. Joint pain and hyperalgesia due to pyridostigmine bromide in a patient with myasthenia gravis. *Neurology* 2004; **62:** 835–6.

Psychosis. Postoperative psychosis in a patient with myasthenia gravis who received large doses of pyridostigmine bromide was attributed to bromide intoxication,[1] but this diagnosis has been challenged.[2]

1. Rothenberg DM, *et al.* Bromide intoxication secondary to pyridostigmine bromide therapy. *JAMA* 1990; **263:** 1121–2.
2. Senecal P-E, Osterloh J. Confusion from pyridostigmine bromide: was there bromide intoxication? *JAMA* 1990; **264:** 454–5.

Renal impairment. During use of pyridostigmine for the reversal of neuromuscular blockade produced by competitive neuromuscular blockers, pyridostigmine kinetics were not significantly different after renal transplantation in 5 patients compared with those in 5 patients with normal renal function. However, in 4 anephric patients the elimination half-life was significantly increased and the plasma clearance significantly decreased.[1] It appeared that about 75% of the plasma clearance of pyridostigmine depended on renal function.

1. Cronnelly R, *et al.* Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; **28:** 78–81.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Pyridostigmine bromide is poorly absorbed from the gastrointestinal tract. It undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Pyridostigmine is excreted mainly in the urine as unchanged drug and metabolites. Pyridostigmine crosses the placenta and very small amounts are distributed into breast milk (see Breast Feeding, above). Penetration into the CNS is poor.

◊ It has been suggested[1] that data from pharmacokinetic studies of pyridostigmine might have varied because of the analytical methods used or inappropriate storage conditions of plasma samples; it was recommended that samples should be acidified and stored at −75°. Mean terminal elimination half-life was 200 minutes in 11 healthy subjects given 60 mg of pyridostigmine by mouth; maximum plasma concentrations were obtained 1 to 5 hours after dosing. The mean terminal elimination half-life after a 4-mg intravenous infusion in 10 of these subjects was 97 minutes.[1] Oral bioavailability was calculated to vary from 11.5 to 18.9%. In an earlier study food did not appear to affect bioavailability but did delay the time taken to achieve peak plasma concentrations.[2] It appears that 75% of the plasma clearance of pyridostigmine depends on renal function.[3] 3-Hydroxy-*N*-methylpyridinium has been identified as one of the 3 metabolites isolated from the urine of patients taking pyridostigmine.[4]

1. Breyer-Pfaff U, *et al.* Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther* 1985; **37:** 495–501.
2. Aquilonius S-M, *et al.* Pharmacokinetics and oral bioavailability of pyridostigmine in man. *Eur J Clin Pharmacol* 1980; **18:** 423–8.
3. Cronnelly R, *et al.* Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980: **28:** 78–81.
4. Somani SM, *et al.* Pyridostigmine in man. *Clin Pharmacol Ther* 1972; **13:** 393–9.

Uses and Administration

Pyridostigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632), but is slower in onset and of longer duration. It is given as the bromide.

Pyridostigmine is mainly used in the treatment of myasthenia gravis (p.629) although its use in neonatal myasthenia has declined in favour of neostigmine. It has also been used in the treatment of paralytic ileus. Pyridostigmine is sometimes used to reverse the neuromuscular blockade produced by competitive neuromuscular blockers but is generally considered less satisfactory than neostigmine. It has also been used as prophylaxis against the neuromuscular effects of nerve gas poisoning (below). Pyridostigmine has been used in the management of postoperative urinary retention (p.2180) but has generally been superseded by catheterisation.

For **myasthenia gravis**, total daily oral doses in the UK may range from 300 mg to 1.2 g; however, the *BNF* states that daily doses of 450 mg should not be exceeded in order to avoid receptor downregulation. It also notes that patients receiving pyridostigmine in doses over 360 mg daily may need more aggressive therapy. In the USA, licensed doses are somewhat higher, ranging up to 1.5 g daily.

The dose should be divided throughout the day and, if necessary, the night, according to response; larger portions of the total daily dose may be given at times of greater fatigue.

A suggested oral dose in the USA for children is 7 mg/kg daily in 5 or 6 divided doses. An alternative regimen used in the UK is an initial dose of 30 mg for children under 6 years or 60 mg for those aged 6 to 12 years. This is increased gradually by increments of 15 to 30 mg daily until a satisfactory response is obtained, which is usually within the dosage range of 30 to 360 mg daily.

Pyridostigmine has also been given as modified-release tablets, usually once or twice daily but these offer less flexibility of dosage. If necessary it has also been given by intramuscular injection or in severe cases by very slow intravenous injection. However, the intravenous route is hazardous and, if used, atropine must be available to counteract any severe muscarinic reactions.

In the treatment of neonatal myasthenia doses in the range of 50 to 150 micrograms/kg by intramuscular injection or 5 to 10 mg orally (30 to 60 minutes before feeds) have been given every 4 to 6 hours. Alternatively, oral doses may be based on neonatal weight: in the UK, the *BNFC* recommends an initial dose of 1 to 1.5 mg/kg, increased gradually to a maximum of 10 mg and repeated throughout the day. Treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by *competitive neuromuscular blockers*, doses of 10 to 20 mg have been given intravenously, with or preceded by atropine sulfate 0.6 to 1.2 mg to counteract any muscarinic effects. Glycopyrronium bromide has been used as an alternative to atropine.

In the USA pyridostigmine is licensed for prophylaxis against the neuromuscular effects of the nerve gas poison *soman* in military combat use only; the recommended oral dose is 30 mg every 8 hours started at least several hours before exposure to soman. If nerve gas poisoning occurs, pyridostigmine should be stopped and the patient should be treated with atropine and pralidoxime immediately.

In the treatment of paralytic **ileus** and postoperative **urinary retention** pyridostigmine bromide has been given in oral doses of 60 to 240 mg.

Decreased gastrointestinal motility. Parasympathomimetics such as pyridostigmine enhance gastric contractions and increase intestinal motility; they have been used in conditions associated with decreased gastrointestinal motility (p.1694).

Pyridostigmine, generally in doses of 60 mg up to 3 times daily, has been used to relieve severe constipation in patients with impaired intestinal motility due to Parkinson's disease.[1]

1. Sadjadpour K. Pyridostigmine bromide and constipation in Parkinson's disease. *JAMA* 1983; **249:** 1148.

Growth hormone deficiency. Although the value of stimulated growth hormone secretion tests in children has been questioned (see Growth Retardation, p.1798), pyridostigmine with somatorelin has been found to be a potent and reproducible test for distinguishing adults with severe growth hormone deficiency from normal subjects.[1] However, the combination is not effective in patients over 55 years of age,[2] and somatorelin with arginine is generally preferred where an alternative to the gold standard of the insulin-tolerance test is required.[1]

1. Ghigo E, *et al.* Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly subjects. *Baillieres Clin Endocrinol Metab* 1998; **12:** 341–58.
2. Vierhapper H, *et al.* The use of the pyridostigmine growth hormone-releasing hormone stimulation test to detect growth hormone deficiency in patients with pituitary adenomas. *Metabolism* 2002; **51:** 34–7.

Nerve gas poisoning. Pyridostigmine has been used prophylactically to protect soldiers against attack with nerve gas agents (p.2351) that inhibit acetylcholinesterase.[1] Pyridostigmine binds reversibly to acetylcholinesterase and provides a protected store from which acetylcholinesterase is later released.[1-3] Prophylaxis with pyridostigmine greatly enhances the efficacy of treatment with atropine and pralidoxime against exposure to *soman* but it is not effective alone and may not be uniformly effective against other nerve agents.[1] Giving 30 mg of pyridostigmine every 8 hours provides the optimum level of protection[2] and, although adverse effects are common at this dosage, the performance of military duties is not impaired.[4] However, neurological symptoms in veterans suffering the so-called Gulf War Syndrome appear to be more common in those who reported exposure to a range of potentially toxic substances which include pyridostigmine.[5] It has been suggested that these symptoms may be evidence of organophosphate-induced polyneuropathy resulting from exposure to a combination of organophosphorus compounds and other cholinesterase inhibitors such as pyridostigmine.[6] A study in *hens*[7] (a species susceptible to anticholinesterases) has also found symptoms of enhanced neurotoxicity when pyridostigmine, the insect repellent diethyltoluamide, and the pyrethroid insecticide permethrin were used together.

1. United States Army. *Medical management of chemical casualties handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense; 1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/RedHandbook/001TitlePage.htm (accessed 15/02/06)
2. Ministry of Defence. *Medical manual of defence against chemical agents.* London: HMSO, 1987. (JSP312).
3. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–4.
4. Keeler JR, *et al.* Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA* 1991; **266:** 693–5.
5. The Iowa Persian Gulf Study Group. Self-reported illness and health status among gulf war veterans: a population-based study. *JAMA* 1997; **277:** 238–45.
6. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the gulf war: a cross-sectional epidemiologic study. *JAMA* 1997; **277:** 231–7.
7. Abou-Donia MB, *et al.* Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET, and permethrin: implications of gulf war chemical exposure. *J Toxicol Environ Health* 1996; **48:** 35–56.

Orthostatic hypotension. Pyridostigmine has been investigated in the treatment of orthostatic hypotension (p.1530). A review[1] of 4 single-dose studies and a follow-up survey (involving a total of 106 patients and generally reporting an improvement in haemodynamic measurements) concluded that there was insufficient long-term data to support the routine use of pyridostigmine in the treatment of orthostatic hypotension.

1. Gales BJ, Gales MA. Pyridostigmine in the treatment of orthostatic intolerance. *Ann Pharmacother* 2007; **41:** 314–18.

Post-poliomyelitis syndrome. Although pyridostigmine has been reported[1] in some patients to reduce fatigue associated with post-poliomyelitis syndrome a double-blind placebo-controlled study failed to find any benefit.[2] Doses used[3] have included 30 mg daily increased gradually to about 60 mg three times daily but adverse effects are common.

1. Trojan DA, Cashman NR. Anticholinesterases in post-poliomyelitis syndrome. *Ann N Y Acad Sci* 1995; **753:** 285–95.
2. Trojan DA, *et al.* A multicenter, randomized, double-blinded trial of pyridostigmine in postpolio syndrome. *Neurology* 1999; **53:** 1225–33.
3. Thorsteinsson G. Management of postpolio syndrome. *Mayo Clin Proc* 1997; **72:** 627–38.

Preparations

BP 2008: Pyridostigmine Tablets;
USP 31: Pyridostigmine Bromide Injection; Pyridostigmine Bromide Syrup; Pyridostigmine Bromide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Mestinon; Piridos; ***Austral.:*** Mestinon; ***Austria:*** Mestinon; ***Belg.:*** Mestinon; ***Braz.:*** Mestinon; ***Canad.:*** Mestinon; ***Chile:*** Mestinon; ***Cz.:*** Mestinon; ***Denm.:*** Mestinon; ***Fin.:*** Mestinon; ***Fr.:*** Mestinon; ***Ger.:*** Kalymin; Mestinon; ***Gr.:*** Mestinon; ***Hong Kong:*** Mestinon; ***Hung.:*** Mestinon; ***India:*** Distinon; ***Indon.:*** Mestinon; ***Irl.:*** Mestinon; ***Israel:*** Mestinon; ***Ital.:*** Mestinon; ***Malaysia:*** Mestinon; ***Mex.:*** Mestinon; ***Neth.:*** Mestinon; ***Norw.:*** Mestinon; ***NZ:*** Mestinon; ***Philipp.:*** Mestinon; ***Pol.:*** Mestinon; ***Port.:*** Mestinon; ***Rus.:*** Kalymin (Калимин); ***S.Afr.:*** Mestinon; ***Singapore:*** Mestinon; ***Spain:*** Mestinon; ***Swed.:*** Mestinon; ***Switz.:*** Mestinon; ***Thai.:*** Mestinon; ***Turk.:*** Mestinon; ***UK:*** Mestinon; Nerve Agent Pre-Treatment Tablet Set L1A1; ***USA:*** Mestinon; ***Venez.:*** Mestinon.

Antineoplastics

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Antineoplastic drugs are used in the treatment of malignant neoplasms when surgery or radiotherapy is not possible or has proved ineffective, as an adjunct to surgery or radiotherapy, or, as in leukaemia, as the initial treatment. Therapy with antineoplastics is notably successful in a few malignant conditions and may be used to palliate symptoms and prolong life in others.

The two main groups of cytotoxic drugs used in the treatment of malignant disease are the alkylating agents and the antimetabolites. Nitrogen mustards, ethyleneimine compounds, and alkyl sulfonates are the main **alkylating agents**. Other compounds with an alkylating action are the various nitrosoureas. Cisplatin and dacarbazine appear to act similarly.

The **antimetabolites** may be subdivided into folic acid, purine, or pyrimidine antagonists.

Several natural products, or their derivatives, are used for their actions as **mitotic inhibitors**; they include the vinca alkaloids and the taxanes. Other drugs act as **topoisomerase inhibitors**, interfering with the coiling and uncoiling of DNA during replication. Drugs thought to act in this way include the podophyllotoxin derivatives such as etoposide, and camptothecin derivatives such as irinotecan and topotecan.

Some **antibiotics** such as the anthracyclines, bleomycin, and mitomycin C, also interfere with nucleic acids and are effective as antineoplastics.

Further described in this section are **other drugs** that act by various routes to affect the growth and proliferation of malignant cells. Better understanding of the biology of tumour cells has led to the development of new classes of these, including **tyrosine kinase inhibitors** such as imatinib. Some neoplasms express receptors to endogenous sex hormones, and various **hormone antagonists**, including, notably, the **aromatase inhibitors** are used in their management.

In recent years considerable interest has focused on immunological approaches to the treatment of malignant disease and a number of **monoclonal antibodies** have been, or are being, developed. The use of biological response modifiers such as interleukins continues to be the subject of investigation and attempts to develop vaccines against individual neoplasms also continue.

Glucocorticoids (see Corticosteroids, p.1495) are used with antineoplastics in the treatment of malignant disease, especially in acute leukaemias and lymphomas. Other agents used in antineoplastic therapy include sex hormones (p.2058) and radiopharmaceuticals (p.2052).

Adverse Effects

The acute effects of antineoplastic drugs often include nausea and vomiting, sometimes extremely severe. In addition, many of these compounds are irritant or vesicant, and produce local pain, irritation, and inflammation at the administration site; extravasation may lead to ulceration and necrosis. Hypersensitivity reactions may also occur.

Many of the adverse effects of antineoplastics are an extension of their therapeutic action, which is not selective for malignant cells but affects all rapidly-dividing cells: antineoplastic therapy is made possible only by increased sensitivity or less effective recovery of malignant cells compared with normal cells, and dosage is carefully controlled and timed, and, where possible, localised, to maximise the differences.

In consequence, adverse effects may be expected from most antineoplastics in tissues where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastrointestinal mucosa, skin, and gonads, as well as in the fetus. The effects may not manifest for days or weeks, depending both on the drugs used and the rate of division in the tissue concerned, and may sometimes be cumulative. Perhaps the most common serious effect, and one which has often limited the doses that can be given, is bone-marrow depression. Because of their effects on the various types of white blood cell many antineoplastics also cause profound suppression of normal immunity, and patients may be at greatly increased risk of severe and disseminated infection.

The rapid destruction of large numbers of cells during antineoplastic therapy of certain highly sensitive tumours, and the consequent release of breakdown products, may also lead to problems with hyperuricaemia and acute renal failure due to uric acid nephropathy (the 'tumour lysis syndrome').

Additionally, some drugs may have specific toxicities that are not necessarily related to their therapeutic action, such as cardiotoxicity due to anthracycline antibiotics, nephrotoxicity with cisplatin, or the effects of bleomycin on the lung. Again these can be cumulative, and may limit the total lifetime dose that can be given.

In the very long term, patients who have undergone successful antineoplastic chemotherapy may develop secondary malignancies, suggesting that antineoplastics may themselves be carcinogenic. In addition, most are potentially mutagenic and teratogenic, and use in pregnancy, particularly in the first trimester, may lead to fetal abortion, stunting, or malformation.

Carcinogenicity. There is clear evidence that some antineoplastic drugs may themselves be carcinogenic, although it is difficult to control for the possible effects of primary disease, combination chemotherapy, and combined treatment with radiotherapy.[1]

Most convincingly associated with secondary malignancies are the various **alkylating agents**[2-5] including the nitrosoureas, and the topoisomerase II inhibitor **podophyllotoxin derivatives** such as etoposide and teniposide.[2,3,5,6] Leukaemias, particularly acute myeloid leukaemia, are the most common forms of secondary disease.[1-3] Leukaemia associated with alkylating agents usually occurs about 5 to 7 years after treatment, and is often preceded by a preleukaemic myelodysplasia.[2,3] The nitrosoureas are associated with a relatively high frequency of secondary leukaemia, and busulfan and melphalan are considered to be more leukaemogenic than cyclophosphamide.[3] Leukaemia associated with the podophyllotoxin derivatives has a shorter latency period of 2 to 3 years, with sudden onset and no myelodysplastic phase.[2,3] Solid tumours can also occur as secondary malignancies and include bladder cancer associated with cyclophosphamide used to treat non-Hodgkin's lymphoma,[4] and bone sarcomas, and breast and lung cancers after the use of various alkylating agents.[4,7]

There is little evidence of carcinogenicity associated with **antimetabolites** such as methotrexate, although it has been suggested that they may act as co-carcinogens.[8] Fludarabine therapy has been reported to be associated with the development of myelodysplasia and acute myeloid leukaemias,[9] although a review of the purine nucleoside analogues, cladribine and fludarabine, concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients was needed.[10] Immunosuppression caused by antimetabolites including methotrexate, cladribine, and fludarabine, may also allow the development of Epstein-Barr virus-related lymphoma.[10,11] **Platinum derivatives** such as carboplatin and cisplatin have been found in large cohort studies[12,13] to have a dose-response relationship with the development of secondary leukaemia. Combinations that may also be associated with leukaemias include cisplatin with doxorubicin,[14] and other anthracycline-based regimens.[15] Another drug that has been associated with the development of secondary malignancies is **procarbazine**.[3,4,16,17]

Estimates of **risk** have varied very widely between studies, and have been calculated in various ways, making direct comparison impossible. Factors influencing the incidence of secondary malignancy include the use of combination chemotherapy regimens, combined treatment modalities, exposure to environmental carcinogens, predisposing genetic risk factors, ethnicity, age at time of treatment, gender, and spontaneous occurrence.[2,3]

The risk of secondary acute myeloid leukaemia appears to be associated primarily with the **cumulative dose** of antineoplastics.[2] Of patients at risk for secondary leukaemias, those with Hodgkin's disease have been most extensively studied. The cumulative 10-year incidence of secondary myeloid leukaemia has been reported to range from less than 1% up to 10%.[2,3] The highest risk is associated with the use of MOPP (chlormethine, vincristine, procarbazine, prednisone) and relative risk increases with cumulative dose of chlormethine.[2,3] Splenectomy or radiation of the spleen doubles the risk of leukaemia, as does an age of more than 45 years at the time of treatment.[2] Secondary solid tumours, such as lung cancer, in patients with Hodgkin's disease have also been attributed to the use of regimens such as MOPP.[4] The risk of secondary acute myeloid leukaemia, in patients treated with adjuvant chemotherapy for breast cancer, increases with cumulative doses of melphalan and cyclophosphamide, and high-dose regimens of doxorubicin with cyclophosphamide.[2,3] In patients treated for multiple myeloma, the increased risk of secondary leukaemia has been attributed to the prolonged use of melphalan.[2,3] Patients treated for testicular cancer appear to be at increased risk of secondary leukaemia associated with cumulative doses of podophyllotoxin derivatives (more than 2 g/m^2 etoposide), and the addition of high cisplatin doses may increase this risk.[2,3] Another review[18] of studies using etoposide or teniposide for various cancers found no relationship between the cumulative dose of these and secondary leukaemia, and suggested that other drugs used in treatment regimens had a greater effect on the development of secondary malignancy. There is growing evidence that the use of high-dose therapy with alkylating agents and/or anthracyclines, followed by autologous stem cell transplantation, is associated with an increased risk of secondary myelodysplasias and leukaemias, and a cumulative incidence of about 9% at 5 years.[2] However, it is unclear whether this is due to the high-dose therapy or to previous chemotherapy that has caused bone-marrow damage.[2,3]

Radiotherapy is an established cause of secondary malignancy. It remains unclear, however, to what extent the use of chemotherapy combined **with radiotherapy** could have an additive effect on the risk of secondary leukaemias, and how dose and treatment regimen influence this effect.[3] Similarly, the role of combined modality treatment in the development of secondary solid tumours has not been defined, even though the radiation-enhancing effect of some antineoplastics is known and used in chemoradiation regimens for this reason.[4]

In many cases the risk of secondary malignancy is far less than that of undertreating, or of failing to treat, the primary disease.[2,4] However, secondary malignancies may be more resistant to treatment and more aggressive than primary disease,[3,19] and the risk of inducing malignant neoplasia is certainly a consideration in the use of alkylating agents and podophyllotoxin derivatives to treat non-malignant disease,[3] and is an increasing challenge in the design of suitable treatment regimens for primary neoplastic disease.

1. Curtis RE, *et al.* Risk of leukemia associated with the first course of cancer treatment: an analysis of the surveillance, epidemiology, and end results program experience. *J Natl Cancer Inst* 1984; **72:** 531–44.
2. Kollmannsberger C, *et al.* Risk of secondary myeloid leukemia and myelodysplastic syndrome following standard-dose chemotherapy or high-dose chemotherapy with stem cell support in patients with potentially curable malignancies. *J Cancer Res Clin Oncol* 1998; **124:** 207–14.
3. Leone G, *et al.* Therapy related leukemias: susceptibility, prevention and treatment. *Leuk Lymphoma* 2001; **41:** 255–76.
4. Travis LB. Therapy-associated solid tumors. *Acta Oncol* 2002; **41:** 323–33.
5. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics* 2007; **119:** 554–68. Correction. *ibid.*; 1045.
6. Hawkins MM, *et al.* Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. *BMJ* 1992; **304:** 951–8.
7. Neglia JP, *et al.* Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2001; **93:** 618–29.
8. Zumtobel U, *et al.* Widespread cutaneous carcinomas associated with human papillomaviruses 5, 14 and 20 after introduction of methotrexate in two long-term PUVA-treated patients. *Dermatology* 2001; **202:** 127–30.
9. Micallef INM, *et al.* Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. *J Clin Oncol* 2000; **18:** 947–55.
10. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40:** 541–50.
11. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328:** 1317–21.
12. Travis LB, *et al.* Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999; **340:** 351–7.
13. Travis LB, *et al.* Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst* 2000; **92:** 1165–71.
14. Kaldor JM, *et al.* Leukemia following chemotherapy for ovarian cancer. *N Engl J Med* 1990; **322:** 1–6.
15. Levine MN, *et al.* Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol* 1998; **16:** 2651–8.
16. Kaldor JM, *et al.* Leukemia following Hodgkin's disease. *N Engl J Med* 1990; **322:** 7–13.
17. Lee IP, Dixon RL. Mutagenicity, carcinogenicity and teratogenicity of procarbazine. *Mutat Res* 1978; **55:** 1–14.
18. Smith MA, *et al.* Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol* 1999; **17:** 569–77.
19. Neugut AI, *et al.* Poor survival of treatment-related acute nonlymphocytic leukemia. *JAMA* 1990; **264:** 1006–8.

EFFECTS ON CHROMOSOMES. Visible chromosome gaps, breaks, and structural rearrangements are found in blood lymphocytes from patients who have received substantial doses of combination chemotherapy, and the changes persist for years after the end of treatment. A more sensitive, if transient, measure of genetic damage is the increased rate of sister chromatid exchange (SCE) that occurs with even quite small doses of cytotoxic drugs.[1] Evidence from a study[2] in patients given chlorambucil suggests that as the dose increases so the capacity of the cells to cope with induced genetic damage is progressively exceeded, and thus SCE frequency reflects cumulative toxicity throughout the course of treatment.

In patients who develop acute myeloid leukaemia after alkylating agent therapy, the most common chromosomal losses involve deletions of chromosome 13, loss of the entire chromosomes 5 and 7, or deletions of part or the whole long arm of chromosomes 5 and 7. Molecular alterations of the suppressor gene p53 have also been found.[3] Balanced translocations, usually involving chromosomes 11 and 21, are associated with treatment using topoisomerase II inhibitors.[3,4]

See also under Effects on Reproductive Potential, below.

1. Anonymous. Drugs that can cause cancer. *Lancet* 1984; **i:** 261–2.
2. Palmer RG, *et al.* Chlorambucil-induced chromosome damage to human lymphocytes is dose-dependent and cumulative. *Lancet* 1984; **i:** 246–9.
3. Leone G, *et al.* Therapy related leukemias: susceptibility, prevention and treatment. *Leuk Lymphoma* 2001; **41:** 255–76.
4. Rowley JD, Olney HJ. International workshop on the relationship of prior therapy to balanced chromosome aberrations in therapy-related myelodysplastic syndromes and acute leukemia: overview report. *Genes Chromosomes Cancer* 2002; **33:** 331–45.

Effects on the bladder. Cyclophosphamide (p.702) and ifosfamide (p.731) are the antineoplastics most frequently associated with adverse effects on the bladder, but see also Busulfan, p.690, Chlorambucil, p.696, and Mitomycin, p.752.

Effects on the blood. ***BONE-MARROW DEPRESSION.*** Bone-marrow depression, or myelosuppression, is common to the majority of cytotoxic antineoplastics, and is probably the single most important dose-limiting adverse effect, although its significance has been somewhat reduced in recent years by improvements in supportive care, including the availability of colony-stimulating factors and the development of techniques such as peripheral blood stem cell transfusion.

The formation and development of blood cells takes place in the bone marrow. A common progenitor, the pluripotent stem cell, gives rise to 3 major cell lines from which red cells, white cells, and platelets are derived (see Haematopoiesis, p.1042). All the cellular elements of blood may be affected by antineoplastic therapy, resulting in pancytopenia, but in many cases the toxicity appears to be greater for particular cell types. In addition, the different cell types have very different half-lives in the circulation. White blood cells and platelets tend to have the shortest half-lives in circulation. Hence the most usual manifestation of bone-marrow depression is leucopenia, leading to an increased risk of infection; thrombocytopenia is also fairly common. Erythrocytes have the longest life (about 120 days) and anaemia is somewhat less frequent, and may be associated with megaloblastic changes in the bone marrow.

The onset, duration, and severity of bone-marrow depression vary considerably with different antineoplastics. Relatively mild myelosuppression at worst seems to occur with conventional regimens of bleomycin (p.687), mitotane (p.753), streptozocin (p.771), and vincristine (p.787). Megaloblastic anaemia occurring with hydroxycarbamide (p.729) may be treatable by blood transfusions, if necessary, without interrupting therapy.

Many of the alkylating agents are associated with severe and sometimes irreversible bone-marrow depression, particularly at high doses. Busulfan (p.690) and the nitrosoureas such as carmustine (p.694) pose a particular problem because the nadir of white-blood cell and platelet counts may not be reached for up to 6 weeks after a dose. These drugs affect both resting and actively cycling stem cells.

Many antimetabolites are also associated with myelosuppression and some such as cytarabine (p.705) may produce megaloblastic anaemia in addition to leucopenia and thrombocytopenia. Cytarabine has a biphasic effect on granulocytes, producing an initial nadir about 7 to 9 days after a dose, and a second and more severe one after 15 to 24 days. Unlike alkylating agents, antimetabolites affect actively proliferating, but not resting, stem cells. Cladribine (p.701) and fludarabine (p.721) produce a prolonged and profound lymphopenia.

Of the other drugs mitomycin (p.752) and procarbazine (p.765) in particular have both been associated with prolonged, delayed myelosuppression. Recovery from the bone-marrow toxicity of mitomycin may take months and about 25% of cases do not recover. Cisplatin (p.698) and anthracyclines such as doxorubicin (p.712) can cause severe myelosuppression, although other toxic effects may be more important in determining dose; myelosuppression is dose-limiting with carboplatin (p.693). Cisplatin-induced renal toxicity may lead to anaemia by decreasing erythropoietin production. Bone-marrow depression is also a significant adverse effect of vinblastine (p.786) vindesine, and vinorelbine, although the effects of vincristine on the bone marrow are much less marked, as mentioned above. Neutropenia is common with the camptothecin derivatives irinotecan (p.737) and topotecan (p.780) and can be dose-limiting. The monoclonal antibody alemtuzumab (p.677) and the conjugated antibody gemtuzumab ozogamicin (p.728) also produce severe and prolonged myelosuppression.

For further details, see under the individual monographs. For the management of bone-marrow depression, including discussion of the appropriate thresholds for treatment, see under Treatment of Adverse Effects, below.

See also Effects on Immune Response, below.

Effects on body-weight. Although the effects of antineoplastics on the gastrointestinal tract (below) may lead to anorexia, malabsorption, and malnutrition, and hence to weight loss, antineoplastic therapy for breast cancer has also been associated with weight gain, sometimes dramatic.[1] Weight gain appeared to be more likely in premenopausal women, in those receiving multidrug regimens, and in those treated for longer periods of time. A study of premenopausal women found that reduced physical activity may be a contributing factor to the development of this form of weight gain.[2] A subsequent small study has suggested that adjuvant regimens based on doxorubicin and cyclophosphamide, with or without a taxane, may not be associated with significant weight gain, although patients may undergo unfavourable changes in body-mass composition.[3] Weight gain has also been noted after long-term follow-up of paediatric leukaemia patients.[4,5] Causes include cranial irradiation and corticosteroid therapy,[6] although some have suggested that weight gain depends more on inherent characteristics of the patients than the treatment given.[7]

Concurrent use of corticosteroids may also lead to weight gain.

1. Demark-Wahnefried W, *et al.* Why women gain weight with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1993; **11:** 1418–29.
2. Demark-Wahnefried W, *et al.* Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2001; **19:** 2381–9.
3. Freedman RJ, *et al.* Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab* 2004; **89:** 2248–53.
4. Birkebæk NH, Clausen N. Height and weight pattern up to 20 years after treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1998; **79:** 161–4.
5. Nysom K, *et al.* Degree of fatness after treatment for acute lymphoblastic leukaemia in childhood. *J Clin Endocrinol Metab* 1999; **84:** 4591–6.
6. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics* 2007; **119:** 554–68. Correction. *ibid.*; 1045.
7. Razzouk BI, *et al.* Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. *J Clin Oncol* 2007; **25:** 1183–9.

Effects on bones and joints. Osteoporosis occurs as both an acute[1] and late complication of chemotherapy, but as multicomponent regimens are used and because the pathogenesis of osteoporosis is likely to be multifactorial, it is difficult to assess the impact of individual drugs.[2] However, chemotherapy that causes hypogonadism will decrease bone mineral density in the majority of patients.[2] This includes regimens for a variety of neoplasms, including breast, prostate and testicular cancers, lymphomas, and haematological malignancies. In particular, regimens containing cyclophosphamide, chlormethine, busulfan, or procarbazine may cause ovarian insufficiency and therefore have the potential to lead to osteoporosis in females. Males may be protected from the effects of pronounced hypogonadism, as the cells that produce testosterone only replicate slowly.[2]

In addition, several drugs may exert direct effects on the bone. Methotrexate has been found to increase bone resorption and inhibit bone formation to produce a massive uncoupling of bone turnover.[2] Other drugs, including doxorubicin, have been shown to be toxic to bone in *animals*.[2] High-dose conditioning regimens used for bone marrow transplantation may have a direct dose-dependent toxicity on bone marrow osteoprogenitor cells, contributing to osteopenia.[3]

Corticosteroids are believed to cause bone loss by decreasing osteoblast activity, an effect which may be alleviated by chlorambucil. Surprisingly, corticosteroids have not been implicated in bone loss for most chemotherapy regimens, perhaps because the duration of treatment is short.[2] Nevertheless, osteoporosis and fractures have occurred in young patients with acute lymphoblastic leukaemia, treated with regimens containing high total doses of corticosteroids.[4,5] However, the disease itself, other chemotherapy, and radiotherapy are also likely to be contributory factors in the development of osteopenia in these patients. Osteonecrosis has also been reported with high doses of corticosteroids used in the treatment of leukaemias and solid tumours in adults and children.[4,6,7] Adolescent patients may be at increased risk because their bones are in the process of maturation.[4,6]

A study in children with leukaemia has suggested that the effects of chemotherapy on gastrointestinal and renal handling of nutrients may lead to alterations in calcium and magnesium homoeostasis and hence to abnormal turnover of bone mineral.[8] Renal phosphate loss following damage to the renal tubule caused by ifosfamide can lead to osteomalacia.[2]

1. Arikoski P, *et al.* Reduced bone density at completion of chemotherapy for a malignancy. *Arch Dis Child* 1999; **80:** 143–8.
2. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; **18:** 1570–93.
3. Banfi A, *et al.* High-dose chemotherapy shows a dose-dependent toxicity to bone marrow osteoprogenitors: a mechanism for post-bone marrow transplantation osteopenia. *Cancer* 2001; **92:** 2419–28.
4. Strauss AJ, *et al.* Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol* 2001; **19:** 3066–72.
5. van der Sluis IM, *et al.* Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. *J Pediatr* 2002; **141:** 204–10.
6. Mattano LA, *et al.* Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol* 2000; **18:** 3262–72.
7. Winquist EW, *et al.* Nontraumatic osteonecrosis after chemotherapy for testicular cancer: a systematic review. *Am J Clin Oncol* 2001; **24:** 603–6.
8. Atkinson SA, *et al.* Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukemia. *J Pediatr* 1989; **114:** 793–800.

Effects on the cardiovascular system. ***THROMBOEMBOLISM.*** Patients with cancer are at increased risk of thromboembolic disease, and thrombosis can be the earliest clinical sign of malignancy.[1] The risk of thromboembolism may be further increased by the use of antineoplastics. Deep-vein thrombosis and pulmonary embolism have been reported with a variety of chemotherapeutic regimens. Studies in patients with breast cancer have found that adjuvant chemotherapy can significantly increase the risk of venous thromboembolism.[2] An increase in venous thromboembolism, including CNS thromboses, has also been found with the use of asparaginase in the treatment of acute lymphoblastic leukaemia[2] (see also Effects on the Blood, under Asparaginase, p.682). Regimens that include bevacizumab, lenalidomide, or thalidomide have also reported high rates of venous thromboembolism.[3] Arterial thrombosis, including acute myocardial infarction, angina, stroke, and peripheral artery thrombosis, has also been reported with various regimens.[2] Mechanisms proposed for the possible role of antineoplastics in these effects include activation of coagulation, suppression of anticoagulant proteins and fibrinolysis, and a direct toxic effect on vascular endothelium.[1,2]

Several reports of arterial and venous thromboembolism have implicated combinations of bleomycin with cisplatin and another drug such as a vinca alkaloid or etoposide.[4-6] Such combinations, widely used for testicular cancer, have also been implicated in producing vasospastic reactions including angina[7] and Raynaud's syndrome,[8,9] although there is no evidence of a relationship between thromboembolism and vasospasm.[4]

In men with germ cell cancer there is some evidence that those with liver metastases, or receiving high-dose dexamethasone as antiemetic therapy, are at increased risk of thromboembolic complications.[10]

Treatment of venous thrombosis usually consists of low-molecular-weight or unfractionated heparin therapy and long-term secondary prophylaxis with warfarin,[11] but patients with cancer may be at greater risk of recurrent thrombosis. A multicentre, randomised study found that a low-molecular-weight heparin was more effective than an oral anticoagulant in reducing the risk of recurrent venous thromboembolism without increasing the risk of bleeding,[12] and many now recommend low-molecular-weight heparin therapy for both initial and continuing treatment of cancer patients with venous thromboembolism.[3,11] Patients with arterial thrombosis may require heparin and warfarin, or anti-platelet therapy.[13]

Thromboembolic complications may also be associated with the indwelling catheters used to provide vascular access for antineoplastic therapy.[14,15] Prophylaxis with low-dose warfarin or a low-molecular-weight heparin may reduce the risk.[15]

For a discussion of the cardiotoxicity of antineoplastics see Effects on the Heart, below.

1. Falanga A, Donati MB. Pathogenesis of thrombosis in patients with malignancy. *Int J Hematol* 2001; **73:** 137–44.
2. Lee AYY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. *Semin Thromb Hemost* 1999; **25:** 137–45.
3. Lyman GH, *et al.* American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* 2007; **25:** 5490–5505. Also available at: http://jco.ascopubs.org/cgi/reprint/25/34/5490.pdf (accessed 05/08/08)
4. Cantwell BMJ, *et al.* Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii:** 1086–7.
5. Hall MR, *et al.* Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii:** 1259.
6. Garstin IWH, *et al.* Arterial thrombosis after treatment with bleomycin and cisplatin. *BMJ* 1990; **300:** 1018.
7. Rodriguez J, *et al.* Angina pectoris following cisplatin, etoposide, and bleomycin in a patient with advanced testicular cancer. *Ann Pharmacother* 1995; **29:** 138–9.
8. Vogelzang NJ, *et al.* Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* 1981; **95:** 288–92.
9. Pechère M, *et al.* Fingertip necrosis during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma. *Br J Dermatol* 1996; **134:** 378–9.
10. Weijl NI, *et al.* Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Oncol* 2000; **18:** 2169–78.
11. Lee A, Levine M. Treatment of venous thromboembolism in cancer patients. *Cancer Control* 2005; **12** (suppl 1): 17–21.
12. Lee AYY, *et al.* Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349:** 146–53.
13. Sutherland DE, *et al.* Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis, and treatment. *Am J Hematol* 2003; **72:** 43–52.
14. Monreal M, Davant E. Thrombotic complications of central venous catheters in cancer patients. *Acta Haematol (Basel)* 2001; **106:** 69–72.
15. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol* 2003; **21:** 3665–75.

Effects on electrolytes. Fluid and electrolyte disturbances are common in patients with cancer.[1,2] These can be caused by the disease process, or adverse effects of treatment such as surgery, chemotherapy, antibacterials and diuretics. Mechanisms of chemotherapy-induced electrolyte disturbances include loss of appetite, gastrointestinal electrolyte loss due to vomiting and diarrhoea, impaired intestinal absorption due to mucosal damage, direct nephrotoxicity causing renal electrolyte loss, and a syndrome of inappropriate antidiuretic hormone secretion or a condition resembling it. Hypoparathyroidism, which may be a complication of neck surgery, also affects electrolyte balance and is associated with hyperphosphataemia and hypocalcaemia. As well as the acute signs and symptoms of electrolyte disturbances, changes in electrolyte homoeostasis may result in abnormal bone turnover (see Effects on Bones and Joints, above). Release of the contents of cells destroyed by chemotherapy is well-known to be associated with hyperuricaemia, hyperphosphataemia, hyperkalaemia, and hypocalcaemia (see Tumour Lysis Syndrome, below).

Disturbances of electrolyte homoeostasis have been reported particularly with cisplatin (p.699), cyclophosphamide (p.702), and ifosfamide (see Effects on the Kidneys, p.731).

1. Kapoor M, Chan GZ. Fluid and electrolyte abnormalities. *Crit Care Clin* 2001; **17:** 503–29.
2. Filippatos TD, *et al.* Alterations in electrolyte equilibrium in patients with acute leukemia. *Eur J Haematol* 2005; **75:** 449–60.

Effects on the gastrointestinal tract. Apart from anorexia, and nausea and vomiting (see below), many antineoplastics produce gastrointestinal disturbances. Mucosal inflammation (mucositis), notably as stomatitis and sometimes proctitis, is quite common, as are mucosal cellular changes, xerostomia, impaired absorption, and diarrhoea. In some cases gastrointestinal damage may progress to ulceration, haemorrhage, and perforation.

Antimetabolites affecting pyrimidine metabolism, such as cytarabine (p.705) and fluorouracil (p.722), and the antifolates such as methotrexate (p.745), seem to be particularly associated with severe gastrointestinal effects, especially at high doses, but there appear to be few antineoplastics that do not cause some degree of gastrointestinal disturbance. Irinotecan (p.737) can produce both an initial transient diarrhoea related to cholinergic stimulation, and more severe prolonged diarrhoea with a delayed onset, which may be dose-limiting and potentially fatal.

Use with radiotherapy may increase the toxicity of some drugs on the gastrointestinal tract. The neutropenia induced by many antineoplastic regimens can also lead to secondary gastrointestinal effects, such as stomatitis and gastrointestinal inflammation, associated with infection.

CLOSTRIDIUM DIFFICILE INFECTION. Antineoplastic therapy has occasionally been associated with the development of *Clostridium difficile*-induced gastrointestinal disease, even in the absence of concomitant antibacterial therapy.[1] Most patients had received multiple drug regimens. Methotrexate, fluorouracil, cyclophosphamide, and doxorubicin have all been associated with a number of cases but this may simply reflect the frequency of their use. A retrospective analysis[2] of a group of patients treated for acute leukaemia or receiving bone marrow transplantation found that predictive variables for *C. difficile* diarrhoea included the use of low intensity chemotherapy, but speculated that patients receiving high intensity chemotherapy may be subjected to more strict isolation and infection control procedures, thereby reducing the risk of nosocomial transmission. Another review[3] of 875 courses of myelosuppressive chemotherapy found 61 episodes of *C. difficile* diarrhoea, and that in 36% of those episodes the patients had received high-dose cytarabine. In 35 of the 61 episodes, patients had also received prior intravenous antibacterials.

For discussion of the treatment of such disease, see Antibiotic-associated Colitis, p.171

1. Anand A, Glatt AE. Clostridium difficile infection associated with antineoplastic chemotherapy: a review. *Clin Infect Dis* 1993; **17:** 109–13.
2. Hornbuckle K, *et al.* Determination and validation of a predictive model for Clostridium difficile diarrhea in hospitalized oncology patients. *Ann Oncol* 1998; **9:** 307–11.
3. Gorschlüter M, *et al.* Clostridium difficile infection in patients with neutropenia. *Clin Infect Dis* 2001; **33:** 786–91.

MUCOSITIS. The suffering associated with oral mucositis is by far the worst part of treatment for many patients undergoing curative chemotherapy or bone marrow transplantation, and for those undergoing oral radiotherapy.[1-3] Apart from pain and dysphagia the ulcerated mucosa provides a portal of entry for infection; loss of weight and malnutrition can further impair immune function, and if symptoms are severe enough the treatment cycle may have to be interrupted. Before the patient starts any intensive chemotherapy or local or systemic radiotherapy the oral cavity must be assessed with a view to eliminating sources of infection and chronic irritation. For comment on the prophylaxis and treatment of mucositis, see under Treatment of Adverse Effects, below.

1. Calman FMB, Langdon J. Oral complications of cancer. *BMJ* 1991; **302:** 485–6.
2. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998; **34:** 39–43.
3. Sonis ST, *et al.* The Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004; **100** (suppl): 1995–2025.

NAUSEA AND VOMITING. Nausea and vomiting are common adverse effects of antineoplastic therapy, and for many patients, represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff, or a needle. The problem may be severe enough in some cases to hinder or completely prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. Several neurotransmitters have been implicated over the years including acetylcholine, histamine, enkephalins, dopamine, and serotonin or 5-hydroxytryptamine (5-HT). The cerebral cortex is probably responsible for anticipatory vomiting. Antineoplastics may not all induce emesis by a common pathway, but 5-HT_3-receptor mechanisms are clearly important in the pathogenesis of *acute* cisplatin-associated vomiting. This was suspected when the antiemetic metoclopramide, a dopamine antagonist, was found to have serotonin (5-HT) antagonist activity at the high doses used against cisplatin emesis and confirmed when specific 5-HT_3 antagonists such as ondansetron proved to be effective. Different mechanisms are probably involved in *delayed* emesis since 5-HT_3 antagonists are less effective.

Some patients are more susceptible to emesis than others. The emetic potential of antineoplastics also varies in terms of severity and incidence, and may depend to some extent on the dose, route, and schedule of administration. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

- Vomiting may be *very severe* with cisplatin, dacarbazine, dactinomycin, chlormethine, high-dose cyclophosphamide, and streptozocin, and occurs in most patients.
- *Moderate* vomiting is likely with the taxanes, doxorubicin, more modest doses of cyclophosphamide, and high-dose methotrexate.
- Vinca alkaloids, fluorouracil, lower doses of methotrexate, chlorambucil, bleomycin, and etoposide have *low* emetogenic potential.

The *onset and duration* of vomiting also varies from drug to drug. With cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. Acute emesis (that occurring within 24 hours) has generally been easier to control than delayed emesis (that occurring more than 24 hours after chemotherapy) or anticipatory emesis.

The management of chemotherapy-induced nausea and vomiting is discussed on p.1700.

Effects on the heart. The cardiotoxicity of antineoplastics has been reviewed.[1-3] Cardiotoxicity is the major dose-limiting toxicity with anthracyclines such as doxorubicin and daunorubicin, manifesting most seriously as drug-induced cardiomyopathy, which is frequently fatal, and for which no specific treatment exists. Some of the newer anthracycline analogues such as epirubicin or idarubicin were developed to be less toxic to the heart, although this has not always been easy to prove in controlled studies. Dexrazoxane may prevent heart damage in patients taking anthracyclines, but has no effect on survival.[4] Cardiotoxicity has also been associated with other antineoplastics, although less frequently. High-dose cyclophosphamide or ifosfamide may produce myocarditis, arrhythmias, and congestive heart failure, sometimes delayed by up to 2 weeks, while fluorouracil has been associated with angina pectoris and myocardial infarction, perhaps due to a combination of vasospastic effects and activation of coagulation. Amsacrine has been associated with arrhythmias, sometimes fatal. As well as cardiac effects associated with a capillary leak syndrome, arrhythmias can occur with interleukin-2. Trastuzumab use can be associated with cardiomyopathy resulting in heart failure. Occasional reports of cardiotoxicity associated with busulfan, carmustine, cisplatin, cytarabine, etoposide, mitomycin, paclitaxel, pentostatin, and vincristine also exist. Newer drugs that have been associated with cardiotoxicity include bevacizumab, sorafenib, and sunitinib.

For a discussion of the thromboembolic events seen with antineoplastics see Effects on the Cardiovascular System, above.

1. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Safety* 2000; **22:** 263–302.
2. Floyd JD, *et al.* Cardiotoxicity of cancer therapy. *J Clin Oncol* 2005; **23:** 7685–96.
3. Sereno M, *et al.* Cardiac toxicity: old and new issues in anti-cancer drugs. *Clin Transl Oncol* 2008; **10:** 35–46.
4. van Dalen EC, *et al.* Cardioprotective interventions for cancer patients receiving anthracyclines. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/07/08).

Effects on immune response. Lymphocytes are produced by stem cells in the bone marrow and at other sites, including the thymus, and are involved in humoral and cell-mediated immunity. Most antineoplastics have a depressant effect on bone marrow (see Effects on the Blood, above) and many have immunosuppressant properties although the degree of suppression varies considerably and may depend on the dose and schedule used. Immunosuppression decreases the patient's resistance to infection and has been implicated in the development of malignancies. Response to vaccines may also be reduced, and there is a possibility of generalised infections with live viral vaccines (see Interactions, p.2202).

For a discussion on the effects of immunosuppressant therapy on the immune response and the infections associated with it, see Corticosteroids, p.1492.

Effects on the kidneys. Nephrotoxicity is well-recognised as an adverse effect of cisplatin (p.699), ifosfamide (p.731), and methotrexate (p.746), but renal toxicity may occur with other antineoplastics including the nitrosoureas, mitomycin (due to haemolytic-uraemic syndrome), azacitidine, gemcitabine, and pentostatin.[1]

1. Kintzel PE. Anticancer drug-induced kidney disorders: incidence, prevention and management. *Drug Safety* 2001; **24:** 19–38.

Effects on the liver. Occasional reports of hepatotoxicity exist for many antineoplastics including aminoglutethimide (p.679), busulfan (p.690), dacarbazine (p.707), dactinomycin (p.707), doxorubicin (p.713), floxuridine (p.720), flutamide (p.725), gemtuzumab, (p.728), hydroxycarbamide (p.729), imatinib (p.733), methotrexate (p.746), mitomycin (p.752), mitoxantrone (p.754), oxaliplatin (p.758), tamoxifen (p.773), and tioguanine (p.779). However, the relationship of the drug to the adverse effect is not always easy to establish.

An early but detailed review suggested that methotrexate, mercaptopurine, cytarabine, carmustine, streptozocin, asparaginase, and plicamycin could probably be classified as hepatotoxic. There was considered to be insufficient evidence to classify fluorouracil, cyclophosphamide, busulfan, dacarbazine, the anthracyclines, the vinca alkaloids, and the podophyllum derivatives as hepatotoxic, although this classification was not definitive.[1] Hepatic veno-occlusive disease has occurred after the use of high doses of chemotherapy for conditioning regimens before bone marrow transplantation.[2] Chemotherapy used in combination or with radiotherapy may also increase the risk of hepatotoxicity.[2] Liver toxicity may not be confined to patients: one report described 3 cases of liver damage in nurses working on an oncology ward.[3]

1. Ménard DB, *et al.* Antineoplastic agents and the liver. *Gastroenterology* 1980; **78:** 142–64.
2. King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist* 2001; **6:** 162–76.
3. Sotaniemi EA, *et al.* Liver damage in nurses handling cytostatic agents. *Acta Med Scand* 1983; **214:** 181–9.

Effects on the lungs. Lung injury leading to pulmonary fibrosis occurs in about 10% of all patients who receive bleomycin, being fatal in 1 to 2%. Clinically, the reaction usually presents several months after completion of therapy as non-productive cough and dyspnoea. The reaction is dose-related, being more likely at total doses over 400 000 international units (400 USP units), although it has occurred at much lower doses, and is more common in elderly patients. Injury may be exacerbated by the use of combination chemotherapy regimens and radiotherapy, and supplemental oxygen given even years after the use of bleomycin may precipitate pulmonary oedema.[1] Hypersensitivity pneumonitis, which is more amenable to treatment, has also been reported.[2]

Pulmonary damage has also been reported with an increasing number of antineoplastics apart from bleomycin.[1,3,4] Among the alkylating agents cyclophosphamide has been reported to produce lung injury in less than 1% of cases, although this may be increased where it is a component of combination regimens or given with radiotherapy. Busulfan may produce lung toxicity including insidious pulmonary fibrosis in as many as 4% of patients, usually developing several years after initiation of therapy, and with increased risk the longer that therapy lasts. A few reports exist of interstitial pneumonitis and fibrosis associated with chlorambucil and melphalan, but these appear to be extremely rare. The prognosis in patients with alkylating-agent-induced fibrosis is often poor, with mortality rates of 50% or more.

The antimetabolite methotrexate can produce symptoms similar to hypersensitivity pneumonitis in up to 7% of patients, sometimes with pleuritis and acute respiratory failure due to pulmonary oedema, but it is not clear whether a true hypersensitivity mechanism is involved, and symptoms are usually reversible even without stopping therapy. High-dose cytarabine has also been associated with pulmonary oedema. Gemcitabine (p.727) has been associated with interstitial pneumonitis and potentially life-threatening symptoms have occurred when given with thoracic radiotherapy.

Other antineoplastics known to be associated with pulmonary toxicity include mitomycin (usually in less than 10% of patients though the incidence may be much higher in combination regimens); the vinca alkaloids (generally in combination, and usually producing acute respiratory failure); chlorozotocin; procarbazine; and possibly teniposide. The nitrosoureas, and particularly carmustine, have also emerged as pulmonary toxins. Carmustine has been associated with an insidious chronic pulmonary fibrosis, which in some early studies occurred in as many as 30% of patients and had a high mortality. Symptoms are associated particularly with cumulative doses in excess of about 1.4 g/m^2, although toxicity has occurred at cumulative doses as low as 240 mg/m^2. The onset of symptoms may be very delayed: some workers reported fibrosis occurring up to 17 years after treatment in patients who received carmustine as children.[5] Pneumonia and fibrosis have also been reported in patients receiving rituximab (p.767), and fatal lung disease has occurred in patients given gefitinib (p.727).

1. Abid SH, *et al.* Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol* 2001; **13:** 242–8.
2. Holoye PY, *et al.* Bleomycin hypersensitivity pneumonitis. *Ann Intern Med* 1978; **88:** 47–9.
3. Twohig KJ, Matthay RA. Pulmonary effects of cytotoxic agents other than bleomycin. *Clin Chest Med* 1990; **11:** 31–54.
4. Fennell DA, Rudd RM. Pulmonary toxicity and cancer treatment. *Hosp Med* 2004; **65:** 462–5.
5. O'Driscoll BR, *et al.* Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990; **323:** 378–82.

Effects on mental function. Combination chemotherapy has been associated with psychiatric morbidity (anxiety, depression, behavioural changes) in both adults[1] and children.[2] It has been pointed out that patients receiving cancer chemotherapy inevitably suffer emotional distress, associated in part with the adverse effects of treatment. Patients should be fully informed of aims and likely outcomes of treatment, and adverse effects minimised, in order to keep emotional distress to a minimum.[3] Chemotherapy can also cause cognitive impairment,[4,5] affecting functions such as memory, reasoning, concentration, and language skills. Drugs may have direct central neurological toxic effects, or may indirectly affect brain function through adverse effects such as anaemia. Most studies have examined cognitive impairment in women being treated with chemotherapy for breast cancer, but many other cancer patients experience cognitive impairment, which they describe as 'chemo-brain' or 'chemo-fog'.

A number of individual antineoplastics have been associated with mental symptoms, including methotrexate (p.746), mitotane (p.753), and the vinca alkaloids (see Vinblastine, p.786). In many cases such symptoms can be attributed to direct central neurotoxicity (see also under Effects on the Nervous System, below).

1. Maguire GP, *et al.* Psychiatric morbidity and physical toxicity associated with adjuvant chemotherapy after mastectomy. *BMJ* 1980; **281:** 1179–80.
2. Dolgin MJ, *et al.* Behavioral distress in pediatric patients with cancer receiving chemotherapy. *Pediatrics* 1989; **84:** 103–10.
3. Brinkley D. Emotional distress during cancer chemotherapy. *BMJ* 1983; **286:** 663–4.
4. Tannock IF, *et al.* Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004; **22:** 2233–9.
5. Minisini A, *et al.* What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncol* 2004; **5:** 273–82.

Effects on the nervous system. Neurotoxic effects have been reported for many antineoplastics, including altretamine (p.678), asparaginase (p.682), busulfan (p.690), carboplatin (see under Incidence of Adverse Effects, p.693), carmustine (p.694), chlorambucil (p.696), chlormethine (p.697), cisplatin (p.698), cladribine (p.701), cytarabine (p.705), etanidazole (p.718), etoposide (p.718), fludarabine (p.721), fluorouracil (p.723), gemcitabine (p.728), hydroxycarbamide (p.729), ifosfamide (p.732), lomustine (p.741), methotrexate (p.746), mitotane (p.753), mitoxantrone (p.754), oxaliplatin (p.758), paclitaxel (p.759), pentostatin (p.763), procarbazine (p.765), tegafur (p.776), vinblastine (p.786), vincristine (p.787), and vindesine (p.788). In some cases these effects may be associated with particular routes such as the intrathecal. See under the individual monographs for further details. Radiotherapy can also cause damage to the nervous system so combination of the two modalities may lead to additive effects.

Reviews.

1. Verstappen CCP, *et al.* Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003; **63:** 1549–63.
2. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006; **24:** 1633–42.

EFFECTS ON THE EARS. Several antineoplastics have been associated with ototoxicity,[1] including vincristine and vinblastine, but cisplatin in particular is associated with high-frequency hearing loss and tinnitus. In addition, agents such as the nitrogen mustards and bleomycin are potentially ototoxic.

1. Seligmann H, *et al.* Drug-induced tinnitus and other hearing disorders. *Drug Safety* 1996; **14:** 198–212.

Effects on reproductive potential. ***CHROMOSOMES.*** If patients are fertile after treatment with antineoplastics, no significant increase has been seen in fetal chromosome damage, fetal abnormality, or the miscarriage rate. A review[1] of reports of survivors of *childhood cancers* found that adverse pregnancy outcomes were limited to particular groups of survivors. Female survivors of Wilms' tumours who had been treated with abdominal radiation, with or without chemotherapy, appeared to be at increased risk of complications including miscarriage, low birth-weight neonates, and neonatal death. After treatment of childhood Hodgkin's disease using both radiotherapy and chemotherapy, female survivors and partners of male survivors might be at increased risk of miscarriage; however, treatment with radiotherapy or chemotherapy alone did not increase this risk. For other cancers, data were more limited, but suggested that the risk of adverse pregnancy outcomes was not increased in survivors.

Regarding the risk of congenital abnormalities in the offspring of survivors of childhood cancers, most studies have shown no excess of major or minor malformations.[1,2] There was also no evidence that the risk of cancer is increased in the offspring. However, because of the small numbers in many studies and heterogeneity regarding treatments used, it is possible that effects of individual drugs could have been masked. Long-term follow-up is needed as increasing numbers of children survive to adulthood after successful chemotherapy.

For *adult patients*, there is also a lack of evidence of adverse pregnancy outcomes and congenital abnormalities in offspring after chemotherapy. In a large series[3] of women treated with methotrexate, alone or in combination, for gestational trophoblastic tumours, there was no evidence of an increase in adverse outcomes or abnormalities, although women who had received three or more drugs in combination were less likely to have a live birth. A large case-control study carried out in Canada, and involving over 85 000 parents of children with congenital anomalies, also has failed to confirm a higher incidence of congenital abnormality in the offspring of patients treated with radiotherapy or alkylating agents.[4] However, despite these generally reassuring results, it has been suggested that women should delay conception for a year after cessation of chemotherapy to allow mature ova that might have been damaged to be eliminated,[5] and that monitoring outcomes in patients who become pregnant shortly after exposure to cytotoxic drugs is desirable.[2]

See also Effects on Chromosomes under Carcinogenicity, above.

1. Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol* 1999; **33:** 29–33.
2. Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. *J Natl Cancer Inst Monogr* 2005; **34:** 21–5.
3. Rustin GJS, *et al.* Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours. *BMJ* 1984; **288:** 103–6.
4. Dodds L, *et al.* Case-control study of congenital anomalies in children of cancer patients. *BMJ* 1993; **307:** 164–8.
5. Walden PAM, Bagshawe KD. Pregnancies after chemotherapy for gestational trophoblastic tumours. *Lancet* 1979; **ii:** 1241.

GONADS. The effects of cytotoxic drugs on the gonads have been reviewed.[1-7] In male patients, antineoplastic drugs may damage the seminiferous tubules, resulting in testicular atrophy with decreased sperm count and motility. Testosterone secretion may also be reduced after damage to Leydig cells. In women, cytotoxic drugs act on the ovary to produce loss of primordial follicles with failure of ovulation, oligomenorrhoea or amenorrhoea, and failure of endocrine function resulting in loss of libido and menopausal symptoms. The degree of damage and its reversibility depend on the drug and its dose and the age and sex of the patient. Age is particularly important for women at the time of treatment, with older women (35 to 40 or over) being more sensitive, probably a reflection of the decrease in oocyte numbers with age.

Although dose also plays a role, estimates of the toxicity of various antineoplastics (as single agents) have been published.[4-6] The risk of gonadal dysfunction is high with alkylating agents (busulfan, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan), nitrosoureas (carmustine, lomustine), and procarbazine. Medium risk drugs include carboplatin, cisplatin, and doxorubicin. Low risk drugs include bleomycin, dactinomycin, fluorouracil, mercaptopurine, methotrexate, vinblastine, and vincristine.

Severe gonadal dysfunction in both men and women has been associated with combination chemotherapy regimens for Hodgkin's disease. Chlormethine and procarbazine are thought to be mainly responsible for the infertility produced. There is some evidence that currently favoured regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) result in less damage to gonadal cells than the earlier MOPP regimen (chlormethine, vincristine, procarbazine, and prednisone). Prolonged gonadal dysfunction has also been seen in patients given combination chemotherapy for acute lymphoblastic leukaemia; girls appear to be at less risk than boys, especially if treated in the prepubertal period.

Techniques for fertility preservation have been reviewed.[3-6] Established methods with the highest likelihood of success are sperm cryopreservation (sperm banking) for men and IVF with embryo cryopreservation for women. Other methods for women, for which there is less experience and investigation is underway, include oocyte cryopreservation for future IVF, gonadal tissue cryopreservation for autologous transplantation, and ovarian suppression using oral contraceptives or gonadotrophin-releasing hormone analogues. Such techniques are of little benefit for the preservation of fertility in patients treated as young children, however, because of gonadal immaturity.

1. Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. *Endocrinol Metab Clin North Am* 1993; **22:** 617–29.
2. Kovacs GT, Stern K. Reproductive aspects of cancer treatment: an update. *Med J Aust* 1999; **170:** 495–7.
3. Thomson AB, *et al.* Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. *Best Pract Res Clin Endocrinol Metab* 2002; **16:** 311–34.
4. Wallace WHB, *et al.* Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol* 2005; **6:** 209–18. Correction. *ibid.*; 922.
5. Magelssen H, *et al.* The effects of cancer and cancer treatments on male reproductive function. *Nat Clin Pract Urol* 2006; **3:** 312–22.
6. Lee SJ, *et al.* American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; **24:** 2917–31. Correction. *ibid.*; 5790.
7. Walshe JM, *et al.* Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; **24:** 5769–79.

SEXUAL FUNCTION. Loss of libido and decline in sexual performance seem to be relatively common in men receiving combination chemotherapy,[1,2] and may persist after chemotherapy has ended.[1] However, it may sometimes be difficult to distinguish the effects of chemotherapy from those of the disease and the patient's reaction to it: at least one study has shown that gonadal function is disturbed in patients with Hodgkin's disease before treatment.[2] Erectile dysfunction can also result from local damage caused by pelvic surgery or irradiation.[3] Evidence for decreased libido in women is harder to find, but failure of endocrine function after chemotherapy may lead to loss of libido and menopausal symptoms.[4]

1. Chapman RM, *et al*. Cyclical combination chemotherapy and gonadal function: retrospective study in males. *Lancet* 1979; **i:** 285–9.
2. Chapman RM, *et al*. Male gonadal dysfunction in Hodgkin's disease: a prospective study. *JAMA* 1981; **245:** 1323–8.
3. Costabile RA. Cancer and male sexual dysfunction. *Oncology (Huntingt)* 2000; **14:** 195–205.
4. Shalet SM. Effects of cancer chemotherapy on gonadal function of patients. *Cancer Treat Rev* 1980; **7:** 141–52.

Effects on the skin and nails. Alopecia occurs with many antineoplastics, and may be severe with doxorubicin and other anthracyclines, cyclophosphamide, ifosfamide, etoposide, or teniposide, the taxanes docetaxel and paclitaxel, and topotecan. The alkylating agents and some antibiotic antineoplastics are often associated with hyperpigmentation, most commonly of skin, although pigmentation of nails, hair, and teeth has occurred. Some drugs, such as the taxanes, cause dystrophic changes in the nails. Certain drugs may interact with UV light or x-ray radiation to enhance its effects on the skin and may cause radiation recall, photosensitivity, or, in the case of methotrexate, reactivation of UV light burns. Hypersensitivity to antineoplastics may produce cutaneous reactions including allergic rashes, angioedema, and pruritus. In addition to the above there may be local reactions to irritant and vesicant drugs after extravasation. Finally, certain drugs are associated with specific dermatological reactions: acneform follicular rashes have been reported with cetuximab, bleomycin may produce hyperkeratotic and sclerotic lesions, dactinomycin is associated with an erythematous papular or pustular rash mimicking septic emboli, fluorouracil may produce inflammation of solar keratoses, and plicamycin is associated with a distinctive flushing phenomenon. A palmar-plantar erythrodysesthesia syndrome has been seen with a number of antineoplastics (see below).

See also Local Toxicity, below. References may also be found under individual monographs.

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME. Palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) associated with chemotherapy[1] usually presents as a tingling sensation in the palms and soles, which progresses in a few days to burning pain and well-defined swelling and erythema. In severe cases there is desquamation, ulceration, blistering, and severe pain. The reaction appears to be caused by a direct toxic effect and seems to be dose-dependent, affected by both peak drug concentration and total cumulative dose. The drugs most often associated with PPE or similar syndromes are cytarabine (p.705), docetaxel (p.711), doxorubicin (p.712), and fluorouracil (p.723). PPE also occurs with the tyrosine kinase inhibitors, such as lapatinib (p.739), sorafenib (p.770), and sunitinib (p.771). It has also been reported for bevacizumab (p.684), capecitabine (p.692), cisplatin (see under Hypersensitivity, p.699), cyclophosphamide (p.702), and methotrexate (p.746). PPE is usually managed by reducing the drug dose, increasing the dosage interval, or withdrawing the drug, along with symptomatic treatment and wound care. Systemic corticosteroids and pyridoxine have been used in prophylaxis and treatment. Topical dimethyl sulfoxide has been used for PPE caused by liposomal doxorubicin.

1. Nagore E, *et al*. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; **1:** 225–34.

Hyperuricaemia. Overproduction of purines is a known complication of antineoplastic therapy and may result in hyperuricaemia (p.552). Hyperuricaemia is also an important part of the tumour lysis syndrome—see below.

Local toxicity. Local toxicity due to intravenous cancer chemotherapy may include local irritation, extravasation necrosis, and hypersensitivity. **Venous irritation**, presenting as vasospasm and pain or endothelial chemical burn of the vessel, resulting in a painful, streaky, long-lasting sterile phlebitis, may be due to the drug, or, as with carmustine, due to the diluent (alcohol). Irritation and phlebitis have been reported particularly with fluorouracil, carmustine, vinorelbine, and chlormethine.

Up to 6% of patients treated with peripheral intravenous chemotherapy experience **extravasation** (see below), usually with pain, erythema, and swelling at the site of injection. Severe necrosis requiring surgical intervention can develop, particularly with antibiotic antineoplastics such as doxorubicin.

Local **hypersensitivity** reactions, usually self-limiting, must be distinguished from extravasation. In hypersensitivity reactions there is no swelling at the injection site, and pain is felt as a dull ache along the course of the vein, as opposed to the stinging commonly noted after extravasation.

Tumour lysis syndrome. The tumour lysis syndrome represents a biochemical disturbance due to massive release of cellular breakdown products from tumour cells sensitive to therapy. The amount of breakdown products is sufficient to overwhelm normal excretory and metabolic mechanisms for their clearance, and the cardinal features of the syndrome are hyperkalaemia, hyperuricaemia, and hyperphosphataemia accompanied by hypocalcaemia. Clinical symptoms may include urate nephropathy or nephrocalcinosis leading to renal impairment, and cardiac arrhythmias associated with the potassium abnormalities. The syndrome is seen particularly when bulky chemosensitive disease is present, and may be more likely in patients with pre-existing renal impairment or hyperuricaemia. It is most frequent in patients with Burkitt's or lymphoblastic lymphoma, or an acute leukaemia. Of patients with solid tumours, reports have implicated those with germ-cell tumours, small-cell lung cancer, or neuroblastoma although, surprisingly, the syndrome has also been reported in patients with breast cancer, which is normally less rapidly responsive to chemotherapy. For comment on prevention and treatment, see under Treatment of Adverse Effects, below.

References.

1. Kalemkerian GP, *et al*. Tumor lysis syndrome in small cell carcinoma and other solid tumors. *Am J Med* 1997; **103:** 363–7.
2. Jeha S. Tumor lysis syndrome. *Semin Hematol* 2001; **38** (suppl 10): 4–8.
3. Baeksgaard L, Sørensen JB. Acute tumor lysis syndrome in solid tumors–a case report and review of the literature. *Cancer Chemother Pharmacol* 2003; **51:** 187–92.

Treatment of Adverse Effects

Intensive supportive care may be necessary to prevent or control the adverse effects of antineoplastic therapy. Antiemetic therapy should be given to reduce, and if possible prevent, nausea and vomiting, since once experienced it may become a conditioned response, and may not respond to antiemetics. Intensive oral care is desirable to minimise the effects of stomatitis (see also Mucositis, below), while corticosteroids, and if necessary nutritional supplements, may be of some help in patients with anorexia. Chemotherapy-induced diarrhoea may also require treatment (see below).

Techniques attempting to prevent the occurrence of alopecia have met with varying success (see below). Scalp tourniquets and local hypothermia have been used to minimise concentrations of antineoplastics in the scalp after intravenous injection. However, such methods may allow the development of a cancer-cell sanctuary and should not be used in patients with leukaemia or other conditions with circulating malignant cells.

Of particular importance is the management of bone-marrow depression. Colony-stimulating factors and epoetins can be used to promote the formation of replacement blood elements (see Anaemia, below). Active measures may be necessary to combat infection and bleeding. Transfusions of blood products may be required; granulocyte transfusions have been given for infections unresponsive to antibiotics, although their value is a matter of debate, while transfusion of blood platelets or use of growth factors such as oprelvekin (interleukin-11) may be of value in preventing thrombocytopenia-induced bleeding.

Extravasation of antineoplastics can pose serious problems. Infusion should be stopped immediately once extravasation is noticed and any drug remaining at the site aspirated if possible but the details of treatment are controversial (see below). If ulceration occurs plastic surgery may be required.

Hyperuricaemia secondary to tumour lysis in patients with leukaemias or lymphomas can be prevented by the addition of allopurinol or rasburicase to treatment schedules, and by adequate hydration and, if necessary, alkalinisation of the urine (see Tumour Lysis Syndrome, below). Good hydration is also important to minimise the nephrotoxic effects of drugs such as cisplatin and methotrexate.

Specific treatments exist for the toxicity of certain antineoplastics (for example the use of calcium folinate to reduce methotrexate toxicity, or mesna to control the bladder toxicity of cyclophosphamide or ifosfamide). For further details of the treatment of specific adverse effects see under the individual monographs.

Alopecia. Attempts to prevent or reduce chemotherapy-induced alopecia have relied on either restriction of scalp blood flow with a tourniquet or the use of local hypothermia.[1] Both of these techniques have been based on the rationale that a temporary decrease in blood flow to the scalp will decrease the exposure of hair follicles to the antineoplastic. Therefore, most benefit would be expected for alopecia caused by drugs with a short half-life and for which both active drug and metabolites are rapidly cleared from the circulation.

Studies of scalp tourniquets carried out in the 1970s found head discomfort to be the main side-effect. They used different chemotherapy regimens, definitions for success, and tourniquet techniques, making conclusions difficult, and tourniquets were largely replaced by local hypothermia techniques.

Most studies of local hypothermia have attempted to prevent doxorubicin-induced alopecia. Again, chemotherapy regimens, devices used, and exposure times have varied between studies. Varying degrees of efficacy have been reported, but hypothermia has generally been of benefit, particularly with single-agent chemotherapy. The dose of chemotherapy may be relevant, with hypothermia being less effective at doxorubicin doses above 50 mg. Headache and cold intolerance may occur, but scalp hypothermia is generally well tolerated.

Despite the successes there is concern that this technique may provide a sanctuary for circulating malignant cells, with the potential risk of metastasis, and there are reports of scalp metastases after the use of hypothermia.[1,2] One reviewer suggested that the use of scalp hypothermia might therefore be restricted to patients receiving single-agent chemotherapy with a palliative intent, or those with solid tumours that rarely metastasise to the scalp.[1] The technique should probably be avoided in patients with leukaemias.[2]

In the USA commercial distribution of cooling caps designed to produce localised scalp hypothermia was halted by the FDA in 1990 because of concerns about their effectiveness and their potential to create sanctuary sites and interfere with drug distribution elsewhere in the head. However, they continue to be available in many countries.

For reference to the use of minoxidil to decrease the duration of alopecia after doxorubicin-containing chemotherapy, see p.1343.

1. Dorr VJ. A practitioner's guide to cancer-related alopecia. *Semin Oncol* 1998; **25:** 562–70.
2. Forsberg SA. Scalp cooling therapy and cytotoxic treatment. *Lancet* 2001; **357:** 1134.

Bone-marrow depression. Bone-marrow depression in patients receiving chemotherapy may require a modification of the dose regimen in subsequent cycles, either by delaying or reducing doses, although it is recognised that this may sometimes reduce efficacy.

Licensed drug information for a number of myelosuppressive antineoplastics recommends that if neutropenia or thrombocytopenia occurs subsequent doses should be withheld until white cell counts have returned to 3000 to 3500 cells/mm^3 or more, and blood platelets to about 100 000 cells/mm^3. In practice, however, improved supportive care means that many expert centres routinely give treatment at lower blood counts than these. The values at which it is acceptable to treat will be influenced by whether the regimen is likely to result in further significant falls, and whether the intent is curative (in which case maintaining treatment intensity is particularly important) or palliative (when avoiding toxicity becomes a prime consideration); local protocols may contain further guidance and should be consulted where available. However, it has been suggested[1] that with appropriate management treatment is usually possible at neutrophil counts of 1500 cells/mm^3 and platelet counts above 100 000 cells/mm^3.

For guidelines on the use of haematopoietic growth factors in the management of anaemia, neutropenia, and thrombocytopenia, see below.

1. Summerhayes M, Daniels S. *Practical chemotherapy: a multidisciplinary guide*. Oxford: Radcliffe Medical Press, 2003.

ANAEMIA. Chemotherapy-induced anaemia can be managed with transfusion of red cells (p.1078), or treatment with epoetin (p.1061) or darbepoetin (p.1058).[1-4] Iron supplementation may be of benefit in anaemic cancer patients receiving erythropoietic therapy, even in those who are iron-replete.[4]

Guidelines for the use of epoetins and darbepoetin have been issued jointly by the American Society of Clinical Oncology and the American Society of Hematology,[5] and guidelines have also been issued by the US National Comprehensive Cancer Network.[3] In the treatment of chemotherapy-induced anaemia, the use of epoetins or darbepoetin can improve haemoglobin concentration and reduce the need for transfusion of red cells, but whether this improves symptoms and quality of life requires further study. The use of epoetins or darbepoetin is recommended when haemoglobin has fallen to 10 g per 100 mL or less. For patients with a concentration between 10 and 12 g per 100 mL, the decision to use epoetins depends on clinical circumstances, and may be considered for patients at a higher risk of adverse effects related to anaemia, including elderly patients with limited cardiopulmonary reserve, or patients with underlying coronary artery disease and symptomatic angina. In the UK, the use of epoetins or their analogues is not generally recommended[4] for chemotherapy-related anaemia except, in combination with intravenous iron, in patients in whom anaemia is profound and likely to affect survival, and who cannot be given blood transfusions, or in women given platinum-based chemotherapy for ovarian cancer in whom haemoglobin has fallen to 8 g per 100 mL or less.

1. Littlewood TJ. Management options for cancer therapy-related anaemia. *Drug Safety* 2002; **25:** 525–35.

2. Bohlius J, *et al.* Erythropoietin or darbepoetin for patients with cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 16/07/08).
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: cancer- and chemotherapy-induced anemia (version 1.2009). Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf (accessed 16/07/08)
4. NICE. Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia (TA 142, issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA142Guidance.pdf (accessed 28/07/08)
5. Rizzo JD, *et al.* Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol* 2008; **26:** 132–49. Correction. *ibid.*; 1192. Also published in *Blood* 2008; **111:** 25–41. Correction. *ibid.*; 3909. Also available at: http://jco.ascopubs.org/cgi/reprint/26/1/132 (accessed 16/07/08)

NEUTROPENIA. Use of granulocyte or granulocyte-macrophage colony-stimulating factors (G-CSF or GM-CSF), alone or with autologous bone marrow transplants or peripheral blood stem-cells, can markedly reduce the period of neutropenia after high-dose chemotherapy regimens (see Filgrastim, p.1070, and Molgramostim, p.1073).

The American Society of Clinical Oncology has issued detailed guidelines for the use of colony-stimulating factors (CSFs) in patients receiving chemotherapy.[1] These point out that in current practice infectious mortality resulting from febrile neutropenia is rare, and that the incidence with common chemotherapy regimens seldom exceeds 20% in previously untreated patients; however, episodes of febrile neutropenia prolong hospital stay, expose the patient to further interventions, and may result in delay or dose-reduction of further chemotherapy cycles. Unfortunately, although colony-stimulating factors can markedly reduce the incidence of febrile neutropenia, there was little evidence of improved clinical outcomes from the use of CSFs in most situations.

- Use of colony-stimulating factors for **primary prophylaxis** in previously untreated patients should not normally be considered except where the risk of febrile neutropenia was 20% or more, or where the risk was less than 20% but bone-marrow compromise or comorbidity indicated a patient at high risk (and even here the evidence for improved clinical outcome was modest).
- There was no evidence of clinical benefit from the use of colony-stimulating factors in **secondary prophylaxis**. In patients with a previous episode of febrile neutropenia the usual option (except where it would compromise the chances of cure) was dose reduction of the chemotherapy regimen.
- For adjunctive **treatment** of episodes of neutropenia, it was recommended that CSFs should not be routinely used for patients who were *afebrile*; there was also strong and consistent evidence against routine use for uncomplicated fever and neutropenia in *febrile* patients. Use might be considered in high-risk patients with febrile neutropenia.
- Although CSFs could permit **increased dose-density or dose-intensity** of chemotherapy, this was considered only justified within the context of a clinical study, since the limited data suggest survival benefit from dose-dense regimens with CSF support in only a few specific settings. Use in patients receiving combined **chemoradiotherapy** was not recommended.
- In patients with **haematological malignancies**, CSFs should be considered after induction chemotherapy in patients with acute myeloid leukaemias (patients aged over 55 may be most likely to benefit), after consolidation chemotherapy, and after initial induction or postremission chemotherapy in patients with acute lymphoblastic leukaemia; a subset of patients with myelodysplastic syndrome, severe neutropenia, and recurrent infection, might also benefit, but use in patients with refractory or relapsed myeloid leukaemia was not thought to be of benefit.
- CSFs were recommended as adjuncts to **progenitor cell transplantation** to help mobilise peripheral blood stem cells and to speed autologous engraftment.
- As **older patients** treated with curative chemotherapy for diffuse aggressive lymphoma are at increased risk of febrile neutropenia and infections, and dose reduction strategies have been associated with a reduced response rate and survival, prophylactic CSF was recommended for such patients aged 65 and older.
- Although the guidelines in adults were held to be generally applicable to **children**, it was noted that the potential for secondary myeloid leukaemia or myelodysplastic syndrome associated with CSFs was of concern in children with acute lymphoblastic leukaemia.

Guidelines issued by the US National Comprehensive Cancer Network[2] adopt a similar attitude to the use of CSFs, and suggest that they should be used for prophylaxis in all patients with a more than 20% risk of febrile neutropenia or neutropenia sufficient to compromise treatment, and may be considered in patients in whom this risk is judged to be between 10 and 20%. Factors that contribute to risk categorisation include the type of chemotherapy regimen and patient risk factors such as age, type of disease, disease stage, general health, and performance status.

For details on the management of infections in neutropenic patients, see Infections in Immunocompromised Patients, p.174.

1. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://www.jco.org/cgi/reprint/24/19/3187 (accessed 16/07/08)
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: myeloid growth factors (version 1.2008). Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf (accessed 16/07/08)

THROMBOCYTOPENIA. Chemotherapy-induced thrombocytopenia can be managed with transfusion of platelets (p.1076). Recombinant thrombopoietin[1] (p.1080), interleukin-3 (p.1073), and interleukin-6 have been evaluated for their ability to increase platelet numbers *in vivo*. Interleukin-11 has also been studied and is now available as oprelvekin (p.1074), which can reduce chemotherapy-induced thrombocytopenia.[2,3] Interleukin-1 (p.2325) has also been investigated in the prevention or treatment of thrombocytopenia.

The American Society of Clinical Oncology has issued guidelines for the use of platelet transfusion.[4] They recommend that prophylactic platelet transfusion be given for thrombocytopenia resulting from impaired bone-marrow function to reduce the risk of haemorrhage when the platelet count falls below a predefined threshold. This threshold will vary depending on the patient's diagnosis, clinical condition, and treatment modality. A threshold of 10 000 cells/mm^3 has been recommended for patients being treated for acute leukaemia, with haematopoietic stem cell transplantation, or for solid tumours. A higher threshold of 20 000 cells/mm^3 may need to be considered for patients with signs of haemorrhage, high fever, rapid fall of platelet count, coagulation abnormalities, patients receiving aggressive therapy for bladder tumours, or those with necrotic solid tumours who are at increased risk of bleeding from these sites.

1. Vadhan-Raj S, *et al.* Recombinant human thrombopoietin attenuates carboplatin-induced severe thrombocytopenia and the need for platelet transfusions in patients with gynecologic cancer. *Ann Intern Med* 2000; **132:** 364–8.
2. Gordon MS, *et al.* A phase I trial of recombinant human interleukin-11 (Neumega rhIL-11 growth factor) in women with breast cancer receiving chemotherapy. *Blood* 1996; **87:** 3615–24.
3. Isaacs C, *et al.* Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; **15:** 3368–77.
4. Schiffer CA, *et al.* Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38. Also available at: http://www.jco.org/cgi/reprint/19/5/1519.pdf (accessed 04/04/06)

Diarrhoea. Patients receiving chemotherapy should be monitored for onset, duration, and severity of diarrhoea. Uncomplicated mild to moderate diarrhoea may be managed conservatively with dietary modification and loperamide. Severe diarrhoea, and mild to moderate cases that are complicated by moderate to severe cramping, nausea and vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration, may require more aggressive management including intravenous fluids, octreotide, and antibacterials.[1]

1. Benson AB, *et al.* Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004; **22:** 2918–26.

Extravasation. Extravasation is the leakage of a drug into subcutaneous tissue during parenteral dosage. Extravasation injuries can range from mild erythema to ulceration, and severe necrosis in some cases if not dealt with promptly. Antineoplastics vary in their propensity to cause extravasation injury:[1]

- *vesicant antineoplastics* cause pain, inflammation and blistering of the local skin, tissue death and necrosis; they include amsacrine, the anthracyclines (doxorubicin and its derivatives), carmustine, dacarbazine, dactinomycin, mitomycin, chlormethine, paclitaxel, plicamycin, streptozocin, and the vinca alkaloids
- *exfoliants* can cause inflammation and exfoliation, but are less likely to cause tissue death, and include cisplatin, docetaxel, mitoxantrone, oxaliplatin, and topotecan
- carboplatin, irinotecan, and the podophyllotoxin derivatives (etoposide and teniposide) are examples of *irritant* drugs which may cause inflammation and irritation, but rarely cause breakdown of tissue. Fluorouracil, methotrexate, and raltitrexed can cause mild to moderate inflammation of local tissue.

Measures to prevent the occurrence of extravasation include giving vesicant or irritant drugs via a central line, or peripherally via a recently sited cannula; vesicants are generally given by intravenous injection into a fast-running infusion. Glyceryl trinitrate patches applied distally to the cannula may be used to dilate veins where venous access is a problem. The site of administration should be regularly checked, and the patient asked to report any untoward sensations.

If extravasation should occur the infusion should be stopped immediately and as much as possible of the infiltrating drug removed by aspiration. Beyond this, however, the management of extravasation is not well standardised and there has been disagreement as to the most appropriate course; there is little data from controlled studies and much practice is based on anecdotal reports and individual experience. Intravenous and subcutaneous injection of a corticosteroid (usually hydrocortisone) has been suggested, although some consider it ineffective or possibly even disadvantageous. Topical application of a 1% hydrocortisone cream to inflamed skin has also been suggested, and antihistamines and, if necessary, analgesics, may be given orally. In most cases application of a cold dressing or ice pack is appropriate. However, after extravasation of the taxanes, vinca alkaloids, or cisplatin, the use of warm packs with hyaluronidase to enhance uptake from the skin has been recommended; a similar procedure has been suggested for large volume extravasations of the podophyllotoxin derivatives.

The use of specific antidotes is a particularly contentious area, since few are clinically validated and some (such as the use of sodium bicarbonate 8.4% for anthracycline extravasations) may do more harm than good. Brief infiltration of a less concentrated (2.1%) sodium bicarbonate solution, followed after a few minutes by aspiration, is still, however, advocated by some in the management of extravasations of the anthracyclines, carmustine, and plicamycin. Better accepted in the management of anthracycline and mitomycin extravasation is the topical application of dimethyl sulfoxide about every 6 hours, sometimes alternated with hydrocortisone 1% cream. Dexrazoxane is also used for the management of anthracycline extravasation. Sodium thiosulfate 3 or 4% has been used to infiltrate the site of extravasations of cisplatin, dactinomycin, or chlormethine.

The role of surgery is also important. It is unequivocally necessary in cases where other methods have failed to prevent evolving tissue damage, but there is some dispute as to the role of early surgery to remove drug-laden tissue and prevent the development of more serious ulceration and necrosis. Techniques of saline flushout and liposuction have been developed for removing drug and non-viable tissue while preserving overlying skin.

Some references to the management of extravasation are given below.[1-6]

1. Stanley A. Managing complications of chemotherapy administration. In: Allwood M, *et al.*, eds. *The Cytotoxics Handbook*. 4th ed. Oxford: Radcliffe Medical Press, 2002: 119–93.
2. Dorr RT. Antidotes to vesicant chemotherapy extravasations. *Blood Rev* 1990; **4:** 41–60.
3. Gault DT. Extravasation injuries. *Br J Plast Surg* 1993; **46:** 91–6.
4. Bertelli G. Prevention and management of extravasation of cytotoxic drugs. *Drug Safety* 1995; **12:** 245–55.
5. Kassner E. Evaluation and treatment of chemotherapy extravasation injuries. *J Pediatr Oncol Nurs* 2000; **17:** 135–48.
6. Ener RA, *et al.* Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004; **15:** 858–62.

Hypersensitivity. Desensitisation protocols have been described for cancer patients with hypersensitivity reactions to chemotherapy, including taxanes, platinum agents, and monoclonal antibodies.[1]

1. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006; **6:** 271–7.

Mucositis. Many drugs have been tried for the *prophylaxis* of mucositis caused by antineoplastic therapy, by modifying exposure of the oral mucosa to chemotherapy, modifying epithelial proliferation, or reducing the potential for infection and inflammatory complications of mucositis.[1] Some drugs showed limited evidence of benefit in small studies, including benzydamine, betacarotene, granulocyte-macrophage colony-stimulating factor, povidone-iodine, propantheline bromide, vitamin E, and tretinoin. There are conflicting reports of benefit from studies of sucralfate and chlorhexidine. Other options that have been tried with less success include aciclovir, allopurinol, dinoprostone, glutamine, misoprostol, pentoxifylline, and bacterial and fungal decontamination.

A large systematic review[2] considered many of these and found that some drugs showed evidence of benefit, albeit weak, including amifostine, benzydamine, calcium phosphate, honey, hydrolytic enzymes, iseganan, and zinc sulfate; local cooling with ice chips and Chinese medicinal herb mixtures also showed some benefit. Practice guidelines[3] also suggested that local cooling may prevent oral mucositis associated with bolus fluorouracil or edatrexate; that ranitidine or omeprazole may prevent epigastric pain after treatment with cyclophosphamide, methotrexate, and fluorouracil, or after fluorouracil with or without folinic acid; and that amifostine may reduce oesophagitis associated with chemoradiotherapy for non-small cell lung cancer. Palifermin may prevent oral mucositis in patients with haematological neoplasms given high-dose chemotherapy and total body irradiation before autologous stem cell transplantation. Local cooling may be used in patients given high-dose melphalan.

There will be some overlap between measures for prophylaxis and treatment of mucositis, and another systematic review[4] of *treatment* strategies found that there was some evidence that topical allopurinol or granulocyte-macrophage colony-stimulating factor might improve chemotherapy-induced oral mucositis, but the evidence was weak and unreliable. Given the number of variables involved in the development of mucositis it is unlikely that any one prophylactic or treatment regimen will prove suitable for all patients.

1. Knox JJ, *et al.* Chemotherapy-induced oral mucositis: prevention and management. *Drugs Aging* 2000; **17:** 257–67.

2. Worthington HV, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 16/07/08).
3. Keefe DM, *et al.* The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; **109:** 820–31. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/114078093/PDFSTART (accessed 16/07/08)
4. Clarkson JE, *et al.* Interventions for treating oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 16/07/08).

Nausea and vomiting. For a detailed discussion of the management of chemotherapy-induced nausea and vomiting, see p.1700.

Osteoporosis. For a detailed discussion on the management of osteoporosis, see p.1084.

Further references.

1. Michaud LB, Goodin S. Cancer-treatment-induced bone loss, part 1. *Am J Health-Syst Pharm* 2006; **63:** 419–30.
2. Michaud LB, Goodin S. Cancer-treatment-induced bone loss, part 2. *Am J Health-Syst Pharm* 2006; **63:** 534–46.

Tumour lysis syndrome. Management of tumour lysis syndrome is based on hydration, correction of metabolic abnormalities, and supportive treatment of renal failure.[1-3] Aggressive hydration with isotonic sodium chloride reduces concentrations of uric acid, phosphate, and potassium, and should be considered in all patients at risk of the syndrome, except those at risk of volume overload. Management of acute hyperkalaemia may include cardiac membrane stabilisation with calcium gluconate, intracellular shift of potassium using insulin (with glucose) or inhaled beta$_2$ agonists, and increased excretion of potassium by diuretics or dialysis. In the management of hyperuricaemia[1,3,4] allopurinol may be given prophylactically to reduce the formation of uric acid, and rasburicase may be used for both prophylaxis and treatment by increasing uric acid oxidation. Adequate hydration, sometimes with urinary alkalinisation using sodium bicarbonate, also improves the solubility and hence renal excretion of uric acid.

1. Davidson MB, *et al.* Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 2004; **116:** 546–54.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; **127:** 3–11.
3. Coiffier B, *et al.* Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; **26:** 2767–78.
4. Holdsworth MT, Nguyen P. Role of i.v. allopurinol and rasburicase in tumor lysis syndrome. *Am J Health-Syst Pharm* 2003; **60:** 2213–24.

Precautions

In view of their severe toxicity and possible carcinogenicity these drugs should generally be reserved for severe or life-threatening disease, and it is widely suggested that their use should be confined to experienced staff in specialised centres.

Immunosuppression and bone-marrow depression are features of many of these drugs and their use is associated with an increased risk of infections caused by pathogenic or opportunistic micro-organisms, and a reduced capacity to cope with them. Where possible, immunosuppressant drugs should not be given to patients with acute infections, and dosage reduction or withdrawal should be considered if infection develops, until the infection has been controlled. For cautions regarding the use of vaccines in patients receiving these drugs see Interactions, below. For discussion of the treatment of infections in immunosuppressed patients, see p.174. Special care is necessary in debilitated patients.

Blood counts and measurement of haemoglobin concentrations should be carried out routinely to help predict the onset of bone-marrow depression. Great caution is needed when the marrow is already depressed from radiotherapy or therapy with other antineoplastics, and modification of dosage regimens may be required. The blood counts below which treatment is contra-indicated will vary depending on the regimen to be used and the therapeutic intent of that treatment (see Bone-Marrow Depression, above); local protocols, including those for the use of colony-stimulating factors, should always be consulted.

Although positive evidence of teratogenicity in humans is not available for all antineoplastics, pregnancy should be avoided in women receiving them: in particular they should not be given, if possible, during the first trimester. Mothers receiving antineoplastic therapy should not breast feed. Because some regimens may result in permanent infertility, the storage of semen samples for male patients, and embryos for females before such therapy may be desirable.

Many antineoplastics are vesicant or irritant. Care must be taken to avoid extravasation since severe pain and tissue damage may ensue. They must be handled with great care and contact with skin and eyes avoided; they should not be inhaled. In many countries official or professional guidelines on precautions for the safe handling of cytotoxic drugs have been issued.

For precautions specific to particular drugs, see under the individual monographs.

Administration in the elderly. The use of antineoplastics in the elderly should take into consideration age-related physiological changes including decline in renal and hepatic function, reduced haematopoietic reserve, and reduced gastrointestinal and cardiac function. Other factors to consider are comorbid conditions and potential drug interactions with associated medications.[1-4] Neoplastic disorders in the elderly have been undertreated because of an impression that these diseases are less aggressive,[5] and the effects of chemotherapy more likely to be severe.[1,2,5,6] Elderly patients have often been excluded from clinical trials for reasons that included physician bias, protocol eligibility criteria with restrictions on comorbidities, and poor patient functional status.[7] There is evidence, however, that healthy older patients can tolerate chemotherapy as well as younger patients.[1,2] However, there have been few studies of chemotherapy specifically in elderly patients,[4,5] and selection of a suitable dosage regimen is more difficult as a consequence, although there is increasing effort to address this lack of data.[2,5,6] Old people vary as much as any other group in their response to drugs, and the consensus is that they should not be excluded from any form of treatment on the grounds of age alone.

1. Kimmick GG, *et al.* Cancer chemotherapy in older adults: a tolerability perspective. *Drugs Aging* 1997; **10:** 34–49.
2. Lichtman SM, Skirvin JA. Pharmacology of antineoplastic agents in older cancer patients. *Oncology (Huntingt)* 2000; **14:** 1743–55.
3. Wildiers H, *et al.* Pharmacology of anticancer drugs in the elderly population. *Clin Pharmacokinet* 2003; **42:** 1213–42.
4. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25:** 1832–43.
5. Balducci L, Beghe' C. Cancer and age in the USA. *Crit Rev Oncol Hematol* 2001; **37:** 137–45.
6. Muss HB. Older age—not a barrier to cancer treatment. *N Engl J Med* 2001; **345:** 1128–9.
7. Townsley CA, *et al.* Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23:** 3112–24.

Administration at home. Outpatients taking oral antineoplastic therapy at home do not receive the same level of monitoring as inpatients, and should be cautioned to report any adverse effects, since such treatments may still produce severe toxicity.

Contraception. The *BNF* recommends that intra-uterine devices for contraception be used with caution in patients with drug- or disease-induced immunosuppression, because of the risk of infection; such devices are contra-indicated in marked immunosuppression.

Handling and disposal. Many antineoplastics are potent and potentially highly toxic drugs that must be handled with due care. In many countries official or professional guidelines are available for the handling, reconstitution, and disposal of antineoplastics, and most centres or institutions in which these drugs are used will have individual handling policies based on these.[1]

Recommendations generally include:

- that these drugs be reconstituted by trained personnel;
- that reconstitution take place in designated areas, designed to protect personnel and the environment—for example, the use of safety cabinets;
- that protective clothing be worn, including gloves, eye protection, and masks if necessary (it should be noted that gloves may vary in their resistance to penetration, depending upon their thickness, the material of which they are made, and the drug in question[1,2]);
- that waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patient's body fluids and excreta may contain appreciable amounts of antineoplastic agents and it has been suggested that they and materials such as bed linen contaminated with them should also be treated as hazardous waste[3,4]);
- that adequate procedures should be in place for accidental contamination due to spillages;
- that staff exposure to antineoplastic agents be recorded and monitored;
- that pregnant staff should avoid handling these drugs if possible.

1. Allwood M, *et al.* eds. *The Cytotoxics Handbook.* 4th ed. Oxford: Radcliffe Medical Press, 2002.
2. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health-Syst Pharm* 1999; **56:** 2450–3.
3. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.
4. Cass Y, Musgrave CF. Guidelines for the safe handling of excreta contaminated by cytotoxic agents. *Am J Hosp Pharm* 1992; **49:** 1957–8.

Pregnancy. Antineoplastics may be used during pregnancy for their immunosuppressant properties in auto-immune disease, and for the treatment of cancer, which can complicate 1 in 1000 pregnancies.[1-3] Although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus.[1]

The highest incidence of adverse effects appears to occur after exposure during the first trimester:[1-4] about 10 to 20% of fetuses exposed to cytotoxics during this period have major malformations, compared with 3% in the general population.[1] Malformations reflect the gestational age at exposure. The fetus is particularly vulnerable when exposed during organogenesis (weeks 2 to 8 after conception), and the heart, neural tube, and limbs are affected earlier than the palate and ear; after organogenesis, the eyes, genitalia, haematopoietic system, and CNS remain vulnerable to continued exposure.[3]

The risk of fetal malformations after exposure during the second and third trimesters is probably no higher than the background rate, but there may still be an increased risk of still-birth, fetal growth restriction, premature birth, and maternal or fetal myelosuppression.[1-3]

The delayed effects of antineoplastics on development have not been well-documented. Despite concerns that premature birth and low birth-weight could contribute to retardation of growth, development, and intellect,[5] long-term follow-up of a limited number of children has not shown any evidence of abnormalities.[3-5] Similarly, although maternal antineoplastic therapy has been implicated in a case of childhood neuroblastoma and papillary thyroid cancer, the child's fraternal twin, exposed to the same drugs *in utero*, was healthy.[3] There have been no reports of secondary leukaemias in exposed offspring, but the longer term risk is unknown.[3]

The teratogenicity of any drug depends on the timing of exposure, the dose, and the characteristics affecting placental transfer,[3] as well as the actions of the drug. Of the antineoplastics, the greatest risk seems to be associated with alkylating agents and antimetabolites, in particular aminopterin, fluorouracil, and methotrexate.[1,2,6] The vinca alkaloids and doxorubicin (but not epirubicin or idarubicin) may entail less risk,[2,3] although the former have produced malformations in *animals*.[1] Other drugs reported to be teratogenic or potentially teratogenic include busulfan,[1] chlorambucil,[1,6] chlormethine,[1] cyclophosphamide,[1,6] cytarabine,[1] mercaptopurine,[6] and the podophyllotoxin derivatives.[1] The problems with thalidomide and its congeners are well known.

There are no specific dosage recommendations for the use of antineoplastics during pregnancy, but physiological changes occurring in the mother can alter the pharmacokinetics of drugs.[1-3] This could potentially increase the toxicity of the antineoplastic, or decrease its efficacy.[2] Anecdotal evidence suggests that adverse effects may be less marked during pregnancy, perhaps reflecting reduced peak or free-drug concentrations in the blood.[3] Myelosuppressive chemotherapy should be avoided 3 weeks before the anticipated delivery so that the mother is neither neutropenic nor thrombocytopenic.[1-3] For the same reason, chemotherapy should be avoided after 35 weeks of gestation, when spontaneous delivery is more likely to occur.[3] The timing of delivery is also critical for the neonate, as chemotherapy given shortly before delivery may not be eliminated through the placenta, prolonging exposure in the newborn.[1,3]

There has also been concern that long-term *occupational exposure* to antineoplastics might have an adverse effect on the fetus of pregnant healthcare workers: a study in 650 Finnish nurses found that women who experienced fetal loss were more than twice as likely to have had first trimester exposure to antineoplastic drugs as women who successfully gave birth.[7] These results have been criticised on the grounds that such results are not generally seen in cancer patients,[8,9] who presumably are exposed to much higher doses of antineoplastics. However, similar results were seen in a cross-sectional analysis of 7094 pregnancies involving 2815 nursing and pharmacy staff.[10] Another study[11] has suggested that the rate of ectopic pregnancy may be increased in nurses occupationally exposed to antineoplastics, but the small number of ectopic pregnancies involved (15 in 734 pregnancies) means that the association with antineoplastics may be due to chance. A further, larger, case-control study[12] by the same investigators found no evidence of an increased rate of ectopic pregnancy, and suggested that occupational exposure to higher levels of antineoplastics in the past possibly explained the earlier findings. Again, such an effect does not appear to have been reported in women treated with antineoplastics.

See also Effects on Reproductive Potential, above.

1. Buekers TE, Lallas TA. Chemotherapy in pregnancy. *Obstet Gynecol Clin North Am* 1998; **25:** 323–9.

2. Falkenberry SS. Cancer in pregnancy. *Surg Oncol Clin N Am* 1998; **7:** 375–97.
3. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; **5:** 283–91.
4. Gwyn K. Children exposed to chemotherapy in utero. *J Natl Cancer Inst Monogr* 2005; 69–71.
5. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. *Semin Oncol* 2000; **27:** 712–26.
6. Østensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? *Drug Safety* 1998; **19:** 389–410.
7. Selevan SG, *et al.* A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med* 1985; **313:** 1173–8.
8. Kalter H. Antineoplastic drugs and spontaneous abortion in nurses. *N Engl J Med* 1986; **314:** 1048–9.
9. Mulvihill JJ, Stewart KR. Antineoplastic drugs and spontaneous abortion in nurses. *N Engl J Med* 1986; **314:** 1049.
10. Valanis B, *et al.* Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999; **41:** 632–8.
11. Saurel-Cubizolles MJ, *et al.* Ectopic pregnancy and occupational exposure to antineoplastic drugs. *Lancet* 1993; **341:** 1169–71.
12. Bouyer J, *et al.* Ectopic pregnancy and occupational exposure of hospital personnel. *Scand J Work Environ Health* 1998; **24:** 98–103.

Interactions

Because of their effects on the gastrointestinal mucosa antineoplastics have the potential to interfere with the absorption of drugs given orally. Antineoplastics that have an immunosuppressant effect may reduce the response to vaccines, and there is a possibility of generalised infection with live vaccines. Use with live vaccines should generally be avoided.

Many antineoplastics are inhibitors of certain isoenzymes of cytochrome P450 and some antineoplastics are also metabolised by these enzymes, and in consequence the possibility of interactions between antineoplastics, or between antineoplastics and other medication, cannot be discounted.

Interactions affecting specific drugs are covered under the individual monographs.

◊ References.

1. Le Blanc GA, Waxman DJ. Interaction of anticancer drugs with hepatic monooxygenase enzymes. *Drug Metab Rev* 1989; **20:** 395–439.
2. Loadman PM, Bibby MC. Pharmacokinetic drug interactions with anticancer drugs. *Clin Pharmacokinet* 1994; **26:** 486–500.
3. Kivistö KT, *et al.* The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br J Clin Pharmacol* 1995; **40:** 523–30.
4. McLeod HL. Clinically relevant drug-drug interactions in oncology. *Br J Clin Pharmacol* 1998; **45:** 539–44.
5. Beijnen JH, Schellens JHM. Drug interactions in oncology. *Lancet Oncol* 2004; **5:** 489–96.
6. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: underlying mechanisms and implications for oral chemotherapy. *Clin Pharmacokinet* 2004; **43:** 1127–56.

Antiepileptics. Retrospective review of outcomes in children treated for acute lymphoblastic leukaemia indicated that long-term antiepileptic therapy increased the clearance of several antileukaemic drugs and reduced the efficacy of therapy.[1]

1. Relling MV, *et al.* Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* 2000; **356:** 285–90.

Antivirals. The potential for interaction between antiretrovirals and antineoplastics has been reviewed.[1] Although clinical evidence of interactions is scanty, various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and thus have the potential to interact with a number of antineoplastics including taxanes, vinca alkaloids, and cyclophosphamide.

1. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet* 2005; **44:** 111–45.

Effects on other drugs. Antineoplastics have been reported to affect a number of drugs including:

- digoxin (reduced absorption, see p.1262)
- oral anticoagulants (increased or decreased effect, see Warfarin, p.1429)
- phenytoin (increased or decreased effect, see p.499)
- suxamethonium (prolonged effect, see p.1911)
- vaccines (decreased response, see p.2202).

Herbal medicines. The potential for interactions between antineoplastics and herbal medicines has been reviewed.[1] There is a general lack of information and reports, and warnings are largely based on theory and extrapolation from herbal interactions with other drugs.

1. Sparreboom A, *et al.* Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004; **22:** 2489–2503.

Pharmacokinetics

Many antineoplastics have intra- and interindividual pharmacokinetic variability that can be influenced by a number of factors. Patient age, disease state, and drug interactions can affect drug absorption, distribution, metabolism, and excretion. Genetic polymorphisms also affect drug disposition and are under investigation, but the clinical use of such information is currently limited. Various methods have been tried or are being investigated as ways of tailoring initial drug dosage and therapeutic drug monitoring for individual patients in order to improve treatment efficacy and minimise toxicity. Such methods include population pharmacokinetic modelling and individual pharmacogenetic typing; examples include carboplatin dosing based on glomerular filtration rate (p.693) and genotyping of patients thought to be at increased risk of irinotecan toxicity (p.737).

◊ Reviews.

1. Schrijvers D. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. *Clin Pharmacokinet* 2003; **42:** 779–91.
2. Tomita M, *et al.* Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet* 2004; **43:** 515–27.
3. Fleischhack G, *et al.* Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. *Clin Pharmacokinet* 2005; **44:** 1–31.
4. de Jonge ME, *et al.* Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet* 2005; **44:** 147–73.
5. Undevia SD, *et al.* Pharmacokinetic variability of anticancer agents. *Nat Rev Cancer* 2005; **5:** 447–58.
6. Scripture CD, *et al.* Modulation of cytochrome P450 activity: implications for cancer therapy. *Lancet Oncol* 2005; **6:** 780–9.
7. Bosch TM, *et al.* Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer. *Clin Pharmacokinet* 2006; **45:** 253–85.
8. Yong WP, *et al.* The role of pharmacogenetics in cancer therapeutics. *Br J Clin Pharmacol* 2006; **62:** 35–46.

Action

Much of the development of cancer chemotherapy has been based on an understanding of the way in which tumour cells grow, and the way in which the drugs affect this growth.

After cell division the daughter cells enter a period of growth, $\mathbf{G_1}$, which lasts for different lengths of time in different tissues. This is followed by a period of DNA synthesis, **S**, in which the amount of chromosomal material is doubled, then a postsynthetic, or premitotic, phase, $\mathbf{G_2}$, then finally by mitotic cell division, **M**. As an alternative to re-entering the cycle, the products of cell division may enter a kinetically-dormant, nonproliferative stage, $\mathbf{G_0}$, although it is not exactly clear what recruits such 'resting' cells back into the cell cycle.

The rate of cell division varies for different tumours; the doubling time for Burkitt's lymphoma and acute lymphoblastic leukaemia is less than 5 days, whereas the mean doubling time for seminoma is about 20 days, that for small-cell lung cancer about 50 days, and those for colon cancer and advanced breast cancer about 100 and 150 days respectively. The range of reported doubling times may also vary widely for a particular tumour type. Most common cancers increase very slowly in size in comparison with sensitive normal tissues, including those from which they derive, and the rate may decrease further in large tumours. This difference allows normal cells to recover more quickly than malignant ones from chemotherapy, and is the rationale behind cyclic dosage schedules. The lethal body tumour burden is reached when the tumour cell mass approaches or exceeds 1×10^{12} cells, equivalent to about 1 kg of tissue, and representing about 40 doublings.

Cell killing by cytotoxic agents is generally a first order process, so a given dose or course of antineoplastic kills a fixed percentage of tumour cells rather than a fixed number. Thus a drug that killed 99% of tumour cells would leave behind 10^{10} cells from a tumour containing 10^{12} cells, but only 10^2 cells from one containing 10^4, reinforcing the importance of treating malignant neoplasms as early as possible.

Cytotoxic drugs act to damage the reproductive integrity of cells. Some are active at a particular stage of the cell cycle. The antimetabolites interfere with DNA synthesis, as does hydroxycarbamide, and are thus active against cells in S phase, while the vinca alkaloids inhibit microtubular function and act on cells in phase M. Other drugs such as the alkylating agents, the anthracyclines, and cisplatin are not phase-specific, but since their actions are dependent at least in part on damaging DNA they are more effective against proliferating cells, particularly in S phase. It is now thought that many antineoplastics exert their ultimate effect by inducing cellular apoptosis (programmed cell death). Some drugs, such as bleomycin or vinblastine also have the property of arresting the cycle in a particular phase, and attempts have been made to synchronise tumour cell division in this way, to maximise the number of cells in a sensitive phase when a particular drug is used. However, in practice this approach has been less successful than early experimental results suggested.

Some drugs used in the treatment of neoplasms do not attack the tumour cells directly but are given in order to increase cell vulnerability to other modalities: these include radiosensitisers (which have proved of only limited benefit to date), and photosensitisers such as porfimer sodium, used in photodynamic therapy (PDT).

Apart from attacking cell division, increased understanding of the molecular biology of tumour cells has begun to open the possibility of other approaches to the treatment of malignant neoplasms. Some monoclonal antibodies are designed to bind to specific cell-surface proteins or receptors, enabling the immune system to recognise and attack tumour cells (targeted therapy). Control of tumour growth through inhibition of angiogenesis is also being used. Other areas of investigation include inducing tumour cells to differentiate into non-malignant forms, manipulation of cellular apoptosis and signal transduction, inhibiting the expression of abnormal growth factors, telomerases and other oncogene products (including the use of ribozymes or of 'antisense' compounds which inhibit oncogenic messenger RNA), and prevention or inhibition of metastasis. Gene therapy (p.2310) is another form of treatment under consideration. However, such approaches remain largely experimental.

◊ References to investigational modes of cancer therapy.

1. Noonberg SB, Benz CC. Tyrosine kinase inhibitors targeted to the epidermal growth factor receptor subfamily: role as anticancer agents. *Drugs* 2000; **59:** 753–67.
2. Vile RG, *et al.* Cancer gene therapy: hard lessons and new courses. *Gene Ther* 2000; **7:** 2–8.
3. Bodey B, *et al.* Failure of cancer vaccines: the significant limitations of this approach to immunotherapy. *Anticancer Res* 2000; **20:** 2665–76.
4. Green MC, *et al.* Monoclonal antibody therapy for solid tumors. *Cancer Treat Rev* 2000; **26:** 269–86.
5. Cox AD. Farnesyltransferase inhibitors: potential role in the treatment of cancer. *Drugs* 2001; **61:** 723–32.
6. Miller KD, *et al.* Redefining the target: chemotherapeutics as antiangiogenics. *J Clin Oncol* 2001; **19:** 1195–1206.
7. Kerbel RS. Clinical trials of antiangiogenic drugs: opportunities, problems, and assessment of initial results. *J Clin Oncol* 2001; **19** (suppl): 45s–51s.
8. Dermime S, *et al.* Cancer vaccines and immunotherapy. *Br Med Bull* 2002; **62:** 149–62.
9. Pirollo KF, *et al.* Antisense therapeutics: from theory to clinical practice. *Pharmacol Ther* 2003; **99:** 55–77.
10. Grunwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. *J Natl Cancer Inst* 2003; **95:** 851–67.
11. Dancey JE, Freidlin B. Targeting epidermal growth factor receptor—are we missing the mark? *Lancet* 2003; **362:** 62–4.
12. Kerbel RS. Antiangiogenic drugs and current strategies for the treatment of lung cancer. *Semin Oncol* 2004; **31** (suppl 1): 54–60.
13. Sattler M, *et al.* Therapeutic targeting of the receptor tyrosine kinase Met. *Cancer Treat Res* 2004; **119:** 121–38.
14. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med* 2005; **353:** 172–87.
15. Bianco R, *et al.* Key cancer cell signal transduction pathways as therapeutic targets. *Eur J Cancer* 2006; **42:** 290–4.
16. Chernajovsky Y, *et al.* Fighting cancer with oncolytic viruses. *BMJ* 2006; **332:** 170–2.
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18. Eastman A, Perez RP. New targets and challenges in the molecular therapeutics of cancer. *Br J Clin Pharmacol* 2006; **62:** 5–14.
19. Dangoor A, *et al.* Cancer vaccines: a clinical perspective. *Br J Hosp Med* 2006; **67:** 365–9.
20. Jordan CT, *et al.* Cancer stem cells. *N Engl J Med* 2006; **355:** 1253–61.
21. Eccles SA, Welch DR. Metastasis: recent discoveries and novel treatment strategies. *Lancet* 2007; **369:** 1742–57.

22. Hinnen P, Eskens FALM. Vascular disrupting agents in clinical development. *Br J Cancer* 2007; **96:** 1159–65.
23. Hsieh AC, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer* 2007; **97:** 453–7.
24. Press MF, Lenz H-J. EGFR, HER2 and VEGF pathways: validated targets for cancer treatment. *Drugs* 2007; **67:** 2045–75.
25. Croce CM. Oncogenes and cancer. *N Engl J Med* 2008; **358:** 502–11.
26. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008; **358:** 1160–74.

Resistance

Resistance to antineoplastics is one of the greatest limitations to the use of chemotherapy in malignant disease. Resistance may be intrinsic to the tumour or may be acquired during chemotherapy, which effectively acts to select resistant cells from a heterogeneous population; the latter is one reason that relapses, or malignancies in heavily-pretreated patients, may be particularly difficult to treat.

The mechanisms of resistance in cancer cells are complex and imperfectly understood, but appear to include:

- hypoxia and imperfect drug penetration in the centre of large, solid tumours
- the small proportion of cells actively dividing and thus vulnerable to antineoplastics (particularly in slow-growing tumours)
- decreased cellular uptake or increased efflux of antineoplastic
- increased metabolic breakdown or decreased activation of antineoplastic
- increased expression of target enzymes
- metabolism via alternative biochemical pathways to those blocked by the antineoplastic
- more efficient repair of damaged DNA
- possibly the expression of genes which inhibit drug-induced apoptosis.

Several of these mechanisms may be in operation at one time. Much interest has been expressed in the potential use of drugs which can modulate or inhibit mechanisms of resistance, and in particular in compounds such as valspodar, verapamil, quinidine, and ciclosporin, which have the ability to block the action of p-glycoprotein, a membrane glycoprotein which acts as an efflux pump for a range of cytotoxic substances and which is responsible for the multi-drug resistant (MDR) phenotype. However, for sustained benefit it seems likely that several drugs would be required, each to overcome a different mechanism of resistance, and it would be necessary to ensure that toxicity of antineoplastics to normal cells was not also enhanced.

If the emergence of heritable resistant phenotypes is a natural part of tumour-cell biology (the Goldie-Coldman hypothesis) it implies that the larger and older the tumour, the more likely is resistance to occur. This would confirm the benefits of surgery and radiotherapy to shrink the primary tumour, and of starting chemotherapy as soon as possible after (a preferably early) diagnosis.

Antiresistance agents. Some drugs have been reported to partially abolish multidrug resistance to antineoplastics *in vitro*.[1,2] These include:

- verapamil, its enantiomers and analogues such as Ro-11-2933
- other calcium-channel blockers including prenylamine, diltiazem, nifedipine analogues such as nicardipine and bepridil
- various phenothiazines and thioxanthenes including trifluoperazine and the *trans*-isomer of flupentixol
- structural analogues of the anthracyclines and vinca alkaloids
- progesterone and other steroid hormones, as well as, to some extent, anti-oestrogens such as tamoxifen
- ciclosporin and various of its nonimmunosuppressive analogues (such as valspodar)
- miscellaneous drugs including amiodarone, quinidine, propranolol, reserpine, yohimbine, dipyridamole, erythromycin, cefoperazone, and ceftriaxone

However, despite reported effects on resistance *in vitro* clinical results may be less impressive: studies in which verapamil was added to therapy for small cell lung cancer[3] or multiple myeloma[4] failed to show any benefit, and second-generation P-glycoprotein inhibitors such as valspodar have unpredictable pharmacokinetic interactions with cytotoxics.[5] Nevertheless, there is ongoing development of P-glycoprotein inhibitors, and drugs such as tariquidar are undergoing clinical studies.[5] It has been suggested that tumour growth may rely on a malignant equivalent of stem cells, with innate multi-drug resistance, and that this may make overcoming resistance without damaging normal stem cells particularly difficult.[6]

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Choice of Antineoplastic

The following section describes the treatment of some of the major malignant neoplasms, and in particular the role of combination chemotherapy with antineoplastics.

Table 1 (p.644) lists published initial doses for some well-known combination chemotherapy regimens. Doses may be modified (particularly in subsequent cycles) to allow for patient status and toxic effects, although in some cases this may be at the expense of efficacy. Regimens can also vary slightly between institutions, or may be modified as part of the ongoing evolution of cancer chemotherapy; such therapy should preferably take place only in expert centres. The same acronym has sometimes been used for regimens containing different drugs, or using the same drugs in different doses or in different ways, and the reader should consult the literature for further details.

Role of chemotherapy

In 1999, in an update of a previous consultation document on cancer chemotherapy,[1] WHO listed those drugs it considered essential for the rational management of malignant neoplasms.

The list divides drugs into 3 categories [note: drugs in italics in this list were not in the previous 1994 list]:

- 17 essential drugs that are used to treat curable cancers or cancers for which the cost-benefit ratio clearly favours drug treatment (bleomycin, *chlorambucil*, cisplatin, cyclophosphamide, *cytarabine*, dactinomycin, daunorubicin, doxorubicin, etoposide, fluorouracil, mercaptopurine, methotrexate, prednisolone, procarbazine, tamoxifen, vinblastine, and vincristine)
- 12 drugs that may have advantages in certain clinical situations (*busulfan*, *carboplatin*, *flutamide*, folinic acid, *gonadorelin analogues*, *interferon alfa*, *melphalan*, *megestrol*, mitomycin, *mitoxantrone*, *paclitaxel*, and *vinorelbine*)
- 13 drugs judged as not essential for the effective delivery of cancer care (*aminoglutethimide*, *anastrozole*, *altretamine*, *carmustine*, dacarbazine, *docetaxel*, *epirubicin*, *gemcitabine*, *ifosfamide*, *irinotecan*, *lomustine*, *raltitrexed*, and *topotecan*).

WHO considers that for some tumours such as hepatocellular carcinoma and lung cancer the development of effective prevention programmes through hepatitis B immunisation and tobacco control is currently of greater priority than therapy.[1]

Despite the real benefits achieved in selected conditions, reassessment of the role and value of chemotherapy for malignant neoplasms led a number of oncologists in the 1980s and 90s to express the view that it had not lived up to its promise. Braverman[2] suggested in 1991 that for many or most patients medical management should be confined to symptom management and enrolment in a hospice programme, with a considerable reduction in the prescription of antineoplastics and a confinement of studies to drugs with novel mechanisms of action, or refinement of regimens known to be effective, a view he subsequently re-iterated.[3] Similar views were expressed by others, pointing out the failure of treatment for most common adult tumours,[4] and suggesting that widespread use of chemotherapy was not justified outside clinical trials or specialised centres.[5,6] Bailar and Smith, in a statistical review in 1986, suggested that the 'war against cancer' was being lost, and that concentration on prevention rather than treatment might produce more promising results.[7] Despite acknowledging some areas of progress, an update of this review including data up to the end of 1994 came to the same conclusion.[8] Others also pointed out the failure to adequately address methods for cancer prevention.[9]

Such views naturally provoked controversy, and others considered that developments in the use of adjuvant and intensive regimens, as well as the continuing development of new agents, were significant and should not be denigrated.[10-14] However, the frequent reference to the hoped-for benefits of a greatly-improved knowledge of the molecular biology of cancer, and in particular the use of biological response modifiers,[11,15] or gene therapy,[16] did seem to concede that chemotherapeutic regimens could be improved. Whether dose intensification is one appropriate route for improvement is a matter of some debate,[17,18] and, so far, clear evidence of effectiveness has been reported only for certain leukaemias and lymphomas.[1]

It has been suggested that perhaps attempts to destroy cancer cells are based on a false analogy between oncology and microbiology, and that a more appropriate goal would be the restoration of mechanisms of cellular control, enabling the patient to live with their cancer. Understanding of malignancy as a process, involving complex interactions between the malignant cell and its environment, in which intervention may be feasible to restore regulation of cellular growth, offers a potentially useful approach to cancer treatment. Although such an approach remains largely theoretical at present,[9,19,20] some drugs currently available, such as imatinib and trastuzumab, offer glimpses of its potential.

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Management of malignant disease

Carcinoid tumours and other secretory neoplasms. All neoplastic cells have some abnormalities of metabolism, and many secrete characteristic metabolic products. Where the substance secreted has hormonal or pharmacological properties profound clinical effects may result, particularly since secretion is generally unregulated by normal homoeostatic mechanisms. Examples of syndromes associated with such secretory neoplasms include acromegaly (p.1798), Cushing's syndrome (p.2344), hyperprolactinaemia (p.2079), and other endocrine disorders associated with pituitary adenomas; phaeochromocytoma (p.1179); and carcinoid syndrome and the various syndromes associated with pancreatic endocrine tumours. Multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2) are inherited conditions in which many tumours occur in often more than one endocrine organ; tumours in this disorder are often secretory.[1,2]

Table 1. Common chemotherapy regimens for malignant disease.

Regimen	Drugs and Administration	Cycle	Typically used for	References
ABCM	Doxorubicin 30 mg/m^2 iv day 1; carmustine 30 mg/m^2 iv day 1; cyclophosphamide 100 mg/m^2 oral days 22–25; and melphalan 6 mg/m^2 oral days 22–25.	42 days	Multiple myeloma	1
ABVD	Doxorubicin 25 mg/m^2 iv days 1, 15; bleomycin 10 000 IU/m^2 iv[(b)] days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; and dacarbazine 375 mg/m^2 iv days 1, 15.	28 days	Lymphomas	2, 3
AC	Doxorubicin 60 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1.	21 days (for 4 cycles; some studies used up to 8 cycles)	Breast cancer	4–6
AC + paclitaxel	As above, then followed by paclitaxel 175 mg/m^2 iv day 1.	21 days (further 4 cycles)	Breast cancer	7
AC + trastuzumab	Doxorubicin 60 mg/m^2 iv day 1; cyclophosphamide 600 mg/m^2 iv day 1; and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days (for 6 cycles)	Breast cancer (HER2 overexpressing)	8
ACE	Doxorubicin 45 mg/m^2 iv day 1; cyclophosphamide 1 g/m^2 iv day 1; and etoposide 50 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer	9
AT	Doxorubicin 60 mg/m^2 iv day 1 and paclitaxel 200 mg/m^2 iv day 1.	21 days (for 4 cycles)	Breast cancer	4
AT	Doxorubicin 50 mg/m^2 iv day 1 and docetaxel 75 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Breast cancer (metastatic)	5
BEAM (Mini-BEAM)	Carmustine 60 mg/m^2 iv day 1; etoposide 75 mg/m^2 iv days 2–5; cytarabine 100 mg/m^2 twice daily iv days 2–5; and melphalan 30 mg/m^2 iv day 6.	usually 28 to 42 days	Lymphomas (salvage)	10
BEP	Bleomycin 30 000 IU iv[(b)] days 2, 9, 16; etoposide 100 mg/m^2 iv days 1–5; and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Testicular cancer	11
CAF	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and fluorouracil 500 mg/m^2 iv day 1.	21 days	Breast cancer	12
CAP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and prednisone 40 mg/m^2 oral days 1–5.	28 days	Chronic lymphocytic leukaemia	13
CAP	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1 (these doses are optimised from the original 600 mg/m^2, 45 mg/m^2, and 50 mg/m^2 respectively).	21 days (for 6 cycles)	Ovarian cancer	14, 15
CAV	Cyclophosphamide 900 mg/m^2 iv day 1; doxorubicin 45 mg/m^2 iv day 1; and vincristine 2 mg iv day 1.	21 days (for 6 cycles)	Small cell lung cancer	16
CHOP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 (max. 2 mg) iv day 1; and prednisone 100 mg oral days 1–5.	21 days (for 6 to 8 cycles)	Lymphomas, chronic lymphocytic leukaemia	17, 18
CMF	Cyclophosphamide 100 mg/m^2 oral days 1–14; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6, 19

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease.*(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
CMF	Cyclophosphamide 600 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv day 1.	21 days	Breast cancer	20
CMF	Cyclophosphamide 750 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6
CMV	Cisplatin 100 mg/m^2 iv day 2; methotrexate 30 mg/m^2 iv days 1, 8; and vinblastine 4 mg/m^2 iv days 1, 8.	21 days	Bladder cancer	21
COP (CVP)	Cyclophosphamide 800 mg/m^2 iv day 1; vincristine 2 mg iv day 1; and prednisone 60 mg/m^2 oral days 1–5, then tapered over days 6–8.	21 days (for 6 cycles)	Lymphomas (the original report of this regimen used a 14-day cycle)	22
CP	Cisplatin 100 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1 *or* carboplatin 300 mg/m^2 iv day1 and cyclophosphamide 600 mg/m^2 iv day 1.	28 days (for 6 cycles)	Ovarian cancer	23
CYVADIC	Cyclophosphamide 500 mg/m^2 iv day 1; vincristine 1.5 mg/m^2 iv[a] days 1, 5; doxorubicin 50 mg/m^2 iv day 1; and dacarbazine 250 mg/m^2 iv days 1–5.	21 days	Sarcoma (alternative versions of this regimen using vincristine on day 1 only have also been reported)	24
Dartmouth regimen	Dacarbazine 220 mg/m^2 iv days 1–3, 22–24; cisplatin 25 mg/m^2 iv days 1–3, 22–24; carmustine 150 mg/m^2 iv day 1; and tamoxifen 10 mg oral twice daily.	42 days	Melanoma (metastatic)	25, 26
DHAP	Dexamethasone 40 mg oral or iv days 1–4; cytarabine 2 g/m^2 iv over 3 hrs, repeated after 12 hrs, day 2; and cisplatin 100 mg/m^2 iv over 24 hrs, day 1.	21–28 days	Lymphomas (salvage)	27
EAP	Etoposide 120 mg/m^2 iv days 4–6; doxorubicin 20 mg/m^2 iv days 1, 7; and cisplatin 40 mg/m^2 iv days 2, 8.	21–28 days	Stomach cancer	28, 29
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 450 mg/m^2 iv day 1.	28 days	Small cell lung cancer	30
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 325 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	31
ECF	Epirubicin 50 mg/m^2 iv day 1; cisplatin 60 mg/m^2 iv day 1; and fluorouracil 200 mg/m^2 daily continuous iv.	21 days (for up to 8 cycles)	Stomach cancer	32
EDAP	Etoposide 100–200 mg/m^2 continuous iv, days 1–4; dexamethasone 40 mg oral or iv days 1–5; cytarabine 1 g/m^2 iv day 5; and cisplatin 20 mg/m^2 continuous iv, days 1–4.	21–28 days	Multiple myeloma (salvage), lymphomas	33
EMA-CO (or EMA-EP)	Etoposide 100 mg/m^2 iv days 1, 2; methotrexate 300 mg/m^2 iv over 12 hrs, day 1; folinic acid 15 mg oral or im, twice daily for 4 doses, starting day 2; and dactinomycin 500 micrograms iv days 1, 2. *with* cyclophosphamide 600 mg/m^2 iv day 8 and vincristine 1 mg/m^2 iv[a] day 8. *or* etoposide 150 mg/m^2 iv day 8 and cisplatin 75 mg/m^2 iv day 8.	14 days	Gestational trophoblastic tumours	34
EP (PE)	Etoposide 80 mg/m^2 iv days 1–3 and cisplatin 80 mg/m^2 iv day 1.	21 days	Small cell lung cancer (standard dose – other versions exist)	35

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease.*(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
EP (PE)	Etoposide 80 mg/m^2 iv days 1–5 and cisplatin 27 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer (high dose)	35
EP (PE)	Etoposide 100 mg/m^2 iv day 1, *then* 200 mg/m^2 oral days 2–4 and cisplatin 75 mg/m^2 iv day 1.	21 days	Small cell lung cancer	36
EPOCH	Etoposide 50 mg/m^2 continuous iv days 1–4; vincristine 400 micrograms/m^2 continuous iv[(a)] days 1–4; doxorubicin 10 mg/m^2 continuous iv days 1–4; cyclophosphamide 750 mg/m^2 iv day 5; and prednisone 60 mg/m^2 oral days 1–5.	21 days	Lymphomas (salvage)	37
ESHAP	Etoposide 40 mg/m^2 iv days 1–4; methylprednisolone 250–500 mg iv days 1–5; cisplatin 25 mg/m^2 continuous iv days 1–4; and cytarabine 2 g/m^2 iv day 5.	21–28 days (for up to 8 cycles)	Lymphomas (salvage)	38
FAM	Fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36; doxorubicin 30 mg/m^2 iv days 1, 29; and mitomycin 10 mg/m^2 iv day 1.	56 days	Stomach cancer, pancreatic cancer	39–41
FAMTX	Fluorouracil 1.5 g/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 15; methotrexate 1.5 g/m^2 iv day 1, 1 hour before fluorouracil; and folinic acid 15 mg/m^2 oral every 6 hrs for 3 days, starting 24 hrs after methotrexate.	28 days	Stomach cancer	29, 32
FOLFIRI	Irinotecan 180 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
FOLFOX4	Oxaliplatin 85 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv days 1, 2; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2.	14 days	Colorectal cancer (in addition to FOLFOX6, below, other variants of the FOLFOX regimen exist; combination with bevacizumab or cetuximab is also being tried)	70
FOLFOX6	Oxaliplatin 100 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
5FU/Folinic acid	Fluorouracil 370 mg/m^2 iv days 1–5 and folinic acid 200 mg/m^2 iv days 1–5.	28–35 days	Colorectal cancer	42
5FU/Folinic acid (Mayo regimen, Poon regimen)	Fluorouracil 425 mg/m^2 iv days 1–5 and folinic acid 20 mg/m^2 iv day 1–5.	28–35 days	Stomach cancer, colorectal cancer	42, 43
5FU/Folinic acid (de Gramont regimen)	Fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2 and folinic acid 200 mg/m^2 iv days 1, 2.	14 days	Colorectal cancer	44
Gemcitabine + cisplatin	Gemcitabine 1 g/m^2 iv days 1, 8, 15 and cisplatin 70 mg/m^2 iv day 2.	28 days	Bladder cancer (metastatic)	45
ICE (ICbE)	Ifosfamide 5 g/m^2 iv over 24 hrs, day 1 (with mesna); carboplatin 400 mg/m^2 iv day 1; and etoposide 100 mg/m^2 iv days 1–3.	28 days (for 6 cycles)	Small cell lung cancer	46
IFL (Douillard 1-week regimen)	Irinotecan 80 mg/m^2 iv, day 1; fluorouracil 2.3 g/m^2 continuous iv infusion, day 1; folinic acid 500 mg/m^2 iv, day 1.	7 days	Colorectal cancer	71
IFL (Douillard 2-week regimen)	Irinotecan 180 mg/m^2 iv, day 1; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2; folinic acid 200 mg/m^2 iv, days 1, 2.	14 days	Colorectal cancer	71
Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous				

Table 1. Common chemotherapy regimens for malignant disease.*(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
IFL (Saltz regimen)	Irinotecan 125 mg/m^2 iv; fluorouracil 500 mg/m^2 iv; and folinic acid 20 mg/m^2 iv all once a week for 4 weeks.	42 days	Colorectal cancer	47
Hyper-CVAD	*Course A:* Cyclophosphamide 300 mg/m^2 iv every 12 hrs, days 1–3; doxorubicin 50 mg/m^2 iv day 4; vincristine 2 mg iv days 4, 11; and dexamethasone 40 mg iv or oral, days 1–4, 11–14. *CNS prophylaxis* Methotrexate 12 mg intrathecal, day 2 and cytarabine 100 mg intrathecal, day 8. *Course B:* Methotrexate 200 mg/m^2 iv over 2 hrs, then 800 mg/m^2 iv over 24 hrs, day 1; folinic acid 15 mg iv every 6 hrs for 8 doses, from 24 hrs after methotrexate (increased to 50 mg iv every 6 hrs if methotrexate levels are high); methylprednisolone 50 mg iv every 12 hrs, days 1–3; and cytarabine 3 g/m^2 every 12 hrs, days 2, 3.	4 cycles of A alternated with 4 cycles of B, given over as short a period as possible; the number of A cycles in which CNS prophylaxis is given varies with expected risk of CNS disease	Lymphomas, adult acute lymphoblastic leukaemia (some variants of this regimen exist, including the substitution of daunorubicin 60mg/m^2 for doxorubicin in course A, the omission of methylprednisolone and addition of oral bicarbonate in course B, and simplification of methotrexate and folinic acid dosing; mesna, which was given in course A of the original regimen, is usually omitted)	48
M2	Vincristine 30 micrograms/kg iv[(a)] day 1; carmustine 500 micrograms/kg iv day 1; cyclophosphamide 10 mg/kg iv day 1; melphalan 250 micrograms/kg oral days 1–4 *or* 100 micrograms/kg oral days 1–7 *or* 1–10; and prednisone 1 mg/kg oral, days 1–7, then taper and discontinue by day 21 unless hypercalcaemia or bone disease persist.	35 days	Multiple myeloma	49
MACOP-B	Methotrexate 400 mg/m^2 iv days 8, 36, 64 (as 100 mg/m^2 iv bolus, then 300 mg/m^2 iv over 4 hrs); folinic acid 15 mg oral every 6 hrs for 6 doses, from 24 hrs after methotrexate; doxorubicin 50 mg/m^2 iv days 1, 15, 29, 43, 57, 71; cyclophosphamide 350 mg/m^2 iv days 1, 15, 29, 43, 57, 71; vincristine 1.4 mg/m^2 iv[(a)] days 8, 22, 36, 50, 64, 78; bleomycin 10 000 IU/m^2 iv[(b)] days 22, 50, 78; and prednisone 75 mg oral, daily for 10 weeks then tapered over 15 days.	12 weeks	Lymphomas	50
MIC	Mitomycin 6 mg/m^2 iv day 2; ifosfamide 3 g/m^2 iv day 2; and cisplatin 120 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	51
MIC	Mitomycin 6 mg/m^2 iv day 1; ifosfamide 3 g/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	52
MOPP	Chlormethine 6 mg/m^2 iv days 1, 8; vincristine 1.4 mg/m^2 (max. 2 mg), days 1, 8; procarbazine 100 mg/m^2 oral days 1–14; and prednisone 40 mg/m^2 oral days 1–14, cycles 1, 4.	28 days (for 6 cycles)	Lymphomas, Hodgkin's disease	3, 53
M-VAC	Methotrexate 30 mg/m^2 iv days 1, 15, 22; vinblastine 3 mg/m^2 iv days 2, 15, 22; doxorubicin 30 mg/m^2 iv day 2; and cisplatin 70 mg/m^2 iv day 2.	usually 28 days	Bladder cancer	45, 54, 55
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinblastine 4 mg/m^2 iv day 1, cycle 1 2 mg/m^2 iv day 8, cycle 1 4.5 mg/m^2 iv days 15, 22, cycle 1 4.5 mg/m^2 iv days 1, 15, cycle 2 and later; and cisplatin 120 mg/m^2 iv day 1	28 days	Non-small cell lung cancer (neoadjuvant)	56
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vindesine 3 mg/m^2 iv days 1, 8, 15, 22, day 1 of cycle 2, then every 2 weeks until the 15th week; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	56, 57
Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous				

Table 1. Common chemotherapy regimens for malignant disease.*(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinorelbine 25 mg/m^2 iv once a week for 16 weeks; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	57
PAC	Cisplatin 50 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cyclophosphamide 500 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Thymoma	58
Paclitaxel and carboplatin	Paclitaxel 175 mg/m^2 iv day 1 and carboplatin – adjust dose to AUC of 7.5 mg/mL/minute by Calvert formula, iv day 1.	21 days (for 6 cycles)	Ovarian cancer	59
Paclitaxel and cisplatin	Paclitaxel 135 mg/m^2 continuous iv over 24 hrs, day 1 and cisplatin 75 mg/m^2 iv day 1.	21 days (for 6 cycles)	Ovarian cancer	60
Paclitaxel (standard) and trastuzumab	Paclitaxel 175 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days	Breast cancer (HER2 overexpressing)	8
Paclitaxel (weekly) and trastuzumab	Paclitaxel 90 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	7 days	Breast cancer (HER2 overexpressing)	61
PCV	Procarbazine 60 mg/m^2 oral days 8–21; lomustine 110 mg/m^2 oral day 1; and vincristine 1.4 mg/m^2 iv[a] days 8, 29.	42–56 days	Gliomas (adjuvant)	62
PE	*See* EP			
ProMACE-CytaBOM	Prednisone 60 mg/m^2 oral days 1–14; doxorubicin 25 mg/m^2 iv day 1; cyclophosphamide 650 mg/m^2 iv day 1; etoposide 120 mg/m^2 iv day 1; cytarabine 300 mg/m^2 iv day 8; bleomycin 5000 IU/m^2 iv[b] day 8; vincristine 1.4 mg/m^2 iv[a] day 8; methotrexate 120 mg/m^2 iv day 8; and folinic acid 25 mg/m^2 oral every 6 hrs for 4 doses, from 24 hrs after methotrexate.	21 days	Lymphomas	63
PVB	See VBP			
SMF	Streptozocin 1 g/m^2 iv days 1, 8, 29, 36; mitomycin 10 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36.	56 days	Pancreatic cancer	41
Stanford V regimen	Doxorubicin 25 mg/m^2 iv days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; chlormethine 6 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 iv (max 2mg) days 8, 22; bleomycin 5000 IU/m^2 iv[b] days 8, 22; etoposide 60 mg/m^2 iv days 15, 16; prednisone 40 mg/m^2 oral on alternate days for 10 weeks then tapered by 10 mg on alternate days.	28 days (for 3 cycles)	Hodgkin's disease	64
VAD	Vincristine 400 micrograms iv days 1–4; doxorubicin 9 mg/m^2 iv days 1–4; and dexamethasone 40 mg oral days 1–4, 9–12, 17–20.	28 days (usually for 4 cycles)	Multiple myeloma	65
VBAP	Vincristine 1 mg iv day 1; carmustine 30 mg/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral (may be rounded to 100 mg oral) days 1–4.	21 or 28 days	Multiple myeloma	66, 67
VBP	Vinblastine 150 micrograms/kg iv days 1, 2; bleomycin 30 000 IU iv[b] days 2, 9, 16; and cisplatin 20 mg/m^2 iv days 1–5.	21 days	Germ-cell (ovarian, testicular) cancer	11
VCMP	Vincristine 1 mg iv day 1; melphalan 9 mg/m^2 oral days 1–4; cyclophosphamide 500 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral, days 1–4.	28 days	Multiple myeloma	67

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease.*(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
VeIP	Vinblastine 110 micrograms/kg iv days 1, 2; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68
VIP	Etoposide 75mg/m^2 iv days 1–5; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68
Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous				

(a) Although not always reflected in the original papers it is now generally accepted that the total dose of vincristine should not exceed 2 mg, in order to minimise neurotoxicity
(b) Doses of bleomycin have been given in international units (IU) in this table, but doses in the original papers may be quoted in mg-potency or USP units. One mg-potency or one USP unit is equivalent to 1000 international units

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Carcinoid syndrome. Carcinoid tumours (also known as gastroenteropancreatic neuroendocrine tumours) occur mainly in the gastrointestinal tract or lungs (bronchi), although they occasionally arise in other organs with a common embryological origin. Although they are relatively common, accounting for about 30% of all small bowel tumours, symptomatic carcinoid syndrome is rare, both because the tumours vary in their behaviour depending on their embryological origin and because the liver is capable of metabolising those tumour products which are secreted into the portal circulation; only if the carcinoid tumour secretes into the systemic circulation, notably after metastasis to the liver, do symptoms occur. Tumours of embryological fore-gut origin, usually found in the lung or stomach, predominantly secrete histamine or serotonin (5-HT); mid-gut tumours, with a usual primary site in the small intestine, are the most likely to metastasise and produce carcinoid syndrome, and predominantly secrete serotonin; hind-gut tumours, in the distal colon or rectum, are commonly benign, and do not secrete active substances.

The characteristic symptoms of carcinoid syndrome include episodic flushing of the face and upper trunk (which may be provoked by alcohol, food, or stress), secretory diarrhoea, wheezing and dyspnoea, weight loss, pellagra, painful hepatomegaly, and right-sided valvular heart disease, which sometimes progresses to right heart failure and death.[3,4]

The management of carcinoid tumours usually involves surgical resection,[3,4] and this can be curative, particularly if the primary tumour has not metastasised.[2,5-7] Antineoplastic chemotherapy has limited benefit,[2,5] except perhaps in patients with atypical variants of carcinoid tumours.[6] There is some evidence that treatment with interferon alfa can stabilise the disease or occasionally produce tumour regression,[7] but its value has not been borne out in practice[4] and adverse effects have limited its use.[6] Hepatic arterial occlusion by ligation or embolisation to destroy the blood supply of hepatic metastases has produced symptomatic palliation, but its effects are temporary,[5,6] and do not improve survival.[4] Results may be better in combination with systemic chemotherapy in selected patients.[8] Antineoplastics such as doxorubicin have also been given into the hepatic artery for treating hepatic metastases.[6] There is growing interest in the use of radiolabelled somatostatin analogues for the management of tumours that express high levels of somatostatin receptors;[3,4,9] promising results have been reported with palliative use in inoperable or metastatic disease.[2] Newer therapies such as gefitinib and bevacizumab are also being tried.[4] Radiofrequency ablation is also under investigation.[2]

For symptomatic relief of carcinoid syndrome somatostatin analogues such as octreotide or lanreotide are highly effective[4,10] and are the treatment of choice.[2,5-7] The availability of depot intramuscular preparations has simplified treatment, removing the need for multiple daily subcutaneous injections. However, with prolonged use a few patients develop resistance even to the highest doses.[5] Octreotide is also used in the perioperative management of these patients to treat or prevent carcinoid crisis, when it may be given intravenously.[2,5,11] Other drugs that reduce the effects of serotonin have been tried, including cyproheptadine, ondansetron, ketanserin, and methysergide.[4,5]

Apart from such specific pharmacological therapies, antidiarrhoeals such as codeine and loperamide are sometimes helpful in controlling diarrhoea. Wheezing (bronchoconstriction) and heart failure are managed conventionally. Supplementation with nicotinamide is advisable to prevent pellagra. It is also important to avoid provocative factors such as stress, alcohol, and particular foods.[4,5]

Pancreatic endocrine tumours. Neoplasms of the pancreatic islet cells (pancreatic endocrine tumours) are uncommon compared with those of the exocrine pancreas (see Malignant Neoplasms of the Pancreas, p.671). Pancreatic endocrine tumours, whether benign or malignant, often secrete clinically significant amounts of hormone; the hormone secreted, and hence the resultant clinical syndrome, depends on which of the several types of hormone-secreting islet cells is the origin of the tumour (for example, insulinomas arise in islet beta cells).[12] Primary therapy for solitary pancreatic endocrine tumours is surgical resection;[3] metastatic tumours may require a combination of symptomatic drug therapy, chemotherapy, radiotherapy, and surgical debulking. The most frequently used antineoplastic is streptozocin, either alone or with other drugs such as fluorouracil or doxorubicin.[12-14] Chlorozotocin is also active.[13] As with carcinoid tumours, hepatic metastases may be treated with hepatic artery embolisation.[7,8,12] Improved results have been reported with the combination of hepatic artery embolisation and chemotherapy.[2] Somatostatin analogues and interferon alfa may be used to control symptoms of pancreatic endocrine tumours.[7] Other therapies depend on the specific tumour type. In patients with **insulinoma** (tumours originating in the islet beta cells) excessive insulin secretion results in hypoglycaemia. Where surgical resection is not feasible or not successful diazoxide may be used to control hypoglycaemia.[2,3] Beneficial results have also been achieved with octreotide. Intake of frequent small meals containing complex carbohydrates is also important.[12] Up to 90% of insulinomas are benign and do not metastasise. In **glucagonoma** the primary neoplasm derives from the alpha cell[12] and the clinical syndrome (a characteristic skin rash known as necrolytic migratory erythema, diabetes mellitus or glucose intolerance, weight loss, and anaemia) results from excessive glucagon secretion. Surgical resection is indicated for localised disease but 50 to 80% of cases have metastasised at presentation. Octreotide usually decreases glucagon secretion and improves symptoms. Another well-characterised syndrome results from tumours which release vasoactive intestinal polypeptide (VIP). Such **VIPomas** result in profound but intermittent secretory diarrhoea, with consequent hypokalaemia and acidosis;[12] the syndrome is sometimes known as pancreatic cholera. Metabolic imbalances should be corrected by fluid and electrolyte supplementation. Octreotide controls the secretory diarrhoea, and it may be useful for symptom control before surgery as well as for palliation in metastatic disease. About 80% of vipomas are malignant.[12]

Of the other pancreatic endocrine tumours **gastrinoma** is the commonest: it results in Zollinger-Ellison syndrome, the treatment of which is discussed on p.1704. Rarer tumours include **somatostatinoma** and **PPoma** (secreting pancreatic polypeptide).[12]

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Gestational trophoblastic tumours. The gestational trophoblastic diseases arise from the trophoblast, the first tissue to differentiate in the early embryo: they are associated with conception and pregnancy and affect women of reproductive age. They may be divided into molar pregnancy (complete or partial hydatidiform mole), invasive mole (chorioadenoma destruens), choriocarcinoma, and placental site trophoblastic tumour. A persistent gestational trophoblastic tumour (invasive mole or choriocarcinoma) may develop in about 25% of women after evacuation of a complete molar pregnancy, and about 2 to 4% after a partial molar pregnancy.[1] Choriocarcinoma may also occur after normal delivery, abortion, or ectopic pregnancy.

All these tumours secrete human chorionic gonadotrophin (hCG), and measurement of the urinary or serum concentrations, which are generally proportional to the total tumour mass, is important in diagnosis of disease and monitoring of treatment.

The trophoblastic tumours vary in aggressiveness but some, such as choriocarcinoma, are highly invasive and rapidly fatal if untreated; however, appropriate treatment, based on the perceived risk category, can result in an excellent prognosis. Prognostic factors for increased risk include high titres of hCG, liver or brain metastases, and failure of previous single-agent chemotherapy as well as, perhaps, greater age. With current treatment, including local irradiation for metastases, virtually 100% of patients with localised disease should be cured, as are over 70% of patients with more advanced stages.

Prophylactic chemotherapy has been used in women considered at particular risk of persistent gestational trophoblastic tumour after evacuation of a complete molar pregnancy, but the practice is controversial.[1,2]

In patients who develop low- or moderate-risk choriocarcinoma or invasive mole, the treatment of choice is single-agent chemotherapy with methotrexate or dactinomycin.[1-7] The combination EMA-CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine) is probably the current preferred treatment in high-risk patients.[1,2,4,5,7-9] Methotrexate, dactinomycin, and etoposide is also used.[5,7] A combination of methotrexate, dactinomycin, and either cyclophosphamide or chlorambucil was the preferred combination in the past. Comparative studies are lacking.[9] In refractory disease, the salvage regimen EMA-EP uses etoposide and cisplatin in place of cyclophosphamide and vincristine in EMA-CO. Other regimens have used etoposide and cisplatin with either bleomycin or ifosfamide.[8]

Brain metastases are generally treated by local irradiation, given with chemotherapy. Modified EMA-CO, using a higher dose of systemic methotrexate and adding intrathecal methotrexate, is also used.[7] Liver metastases have been treated with irradiation, local chemoembolisation, or surgical resection.[2,7,8]

Patients with placental site trophoblastic tumour, which is relatively insensitive to chemotherapy, may be best treated by hysterectomy in the early stages.[1,2] In high-risk patients, a platinum-based regimen is preferred to EMA-CO.[4]

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Histiocytic syndromes. Histiocytic syndromes cover a broad range of proliferative disorders of histiocytes (macrophages and dendritic cells), for which the classification and diagnostic criteria are evolving.[1] Langerhans-cell histiocytosis (histiocytosis X) is one such disorder characterised by proliferation of CD1 positive Langerhans cells (a form of dendritic cell).[1] Terms that were formerly used for different clinical manifestations of Langerhans-cell histiocytosis include eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe syndrome,[1-4] but these are now considered obsolete.[1] Langerhans-cell histiocytosis mainly presents in childhood, and is of uncertain aetiology: it is not clear whether it should be considered a malignancy.[4,5]

The clinical presentation of Langerhans-cell histiocytosis is highly variable.[2,3,6,7] The classic feature is single or multiple bone lesions, and skin lesions may also occur (single system, localised, or restricted disease).[3-5,7] The disorder may also involve lymph nodes or visceral organs, ultimately causing dysfunction of the liver, lungs, or bone marrow (extensive or multisystem disease).[4,5] Sequelae to the disease include diabetes insipidus, growth failure, and orthopaedic handicap.[3,6] The morbidity and prognosis depends upon the number of organ systems involved, and whether normal function of these organs is affected. Patients with restricted disease have a generally benign course, and single lesions often regress spontaneously. However, if a bone lesion does not resolve, or risks causing fracture or deformity before it resolves, or is causing disabling symptoms, it may be treated with curettage, intralesional corticosteroids, or radiotherapy.[3-5,7] Systemic chemotherapy may be suitable in some patients with multifocal bone disease; vinblastine with prednisone or prednisolone is a suggested regimen.[4] Similarly, single skin lesions may be allowed to resolve without treatment or treated with surgery, topical corticosteroids, methoxsalen plus UV light (PUVA), or topical chlormethine.[4,5]

In more extensive disease the prognosis is not as good, mainly due to organ dysfunction.[3,6,7] Systemic chemotherapy has been widely used, because the disease tends to be progressive in these patients, but its degree of benefit is uncertain.[2,3,6,7] Corticosteroids and vinblastine for about 6 to 12 months are the most commonly used drugs; 6-mercaptopurine and methotrexate have also been used with reports of efficacy.[4] A comparative study in children with multisystem disease found treatment with vinblastine or etoposide for 6 months to be equally effective.[8] The overall response rate was 62%, but about half of the patients had switched to the alternate arm or other therapy during the drug treatment period. Half of those patients who became disease-free did have a reactivation, but these were generally milder than the original disease. Patients who failed to respond within the first 6 weeks of therapy were at increased risk for treatment failure. Subsequent study showed that vinblastine with etoposide was not superior to vinblastine alone (when combined with corticosteroids and 6-mercaptopurine).[4] Systemic corticosteroids have also been used for recalcitrant skin disease or multisystem disease in children[9] and for pulmonary Langerhans-cell histiocytosis in adults.[10] In patients who have not responded to combination chemotherapy, a number of treatments may be considered including ciclosporin,[4,7] the nucleoside analogues cladribine or pentostatin,[11] thalidomide,[9] and bone marrow transplantation.[4,6,7] Anti-CD1 monoclonal antibodies[5] may offer improved therapeutic or diagnostic options in the future.

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Leukaemias, acute. The acute leukaemias are malignancies affecting haematopoietic precursor cells. They are relatively rare (about 1 to 3 cases per 100 000 of population), and of uncertain cause in the majority of cases, although radiation, carcinogenic substances, or oncogenic retroviruses have been implicated in some types, and certain individuals appear to have a genetic predisposition to these diseases.

After the initiating event or events the progeny of the affected cell do not differentiate normally but proliferate in an uncontrolled fashion. The result is the accumulation in the blood and bone marrow of immature cell types (blasts) at the expense of normal functional blood cells.

The acute leukaemias may be broadly divided into **acute lymphoblastic leukaemia** (ALL), in which the neoplastic proliferation affects lymphoid cell lines, and the **acute myeloid leukaemias** (AML), variously known as acute myelogenous leukaemias or acute non-lymphoblastic leukaemias, which affect myeloid cell lines. These broad groups can be divided in various ways. ALL is subdivided by an immunophenotypic classification that distinguishes disease of B- and T-cell lineage; it was formerly divided morphologically into L1, L2, and L3 subtypes. For AML the French-American-British (FAB) classification has been widely used. This distinguishes, by lineage and estimated degree of differentiation:

- M0, undifferentiated AML
- M1, AML with minimal maturation
- M2, AML with maturation
- M3, acute promyelocytic leukaemia
- M4, acute myelomonocytic leukaemia
- M5, acute monocytic leukaemia
- M6, erythroid leukaemia
- M7, megakaryocytic leukaemia.

However, knowledge of the genotype, via cytogenetic or molecular analysis, is becoming increasingly important in the treatment of leukaemia. Consequently, a revised classification system has been proposed under the auspices of WHO, which uses a combination of morphology, immunophenotype, genetic, biological, and clinical features. In this classification,[1,2] AML is divided into 4 main groups:

- AML with recurrent cytogenic translocations
- AML with myelodysplasia-related features
- AML, therapy-related
- AML not otherwise specified.

The terms *de novo* and secondary AML are widely used but are without standardised definitions. It has been proposed that *de novo* AML should refer to AML in patients with no clinical history of myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukaemogenic agents; secondary AML should refer to patients with AML secondary to these disorders or proven leukaemogenic exposure.[3]

In the WHO classification of lymphoid neoplasms, the Revised European-American Lymphoma (REAL) classification has been adopted, in which acute lymphoblastic leukaemias and lymphoblastic lymphomas are considered to be a single disease with different presentations.[1]

Acute leukaemia usually presents with fatigue, anaemia, infection (due to granulocytopenia), and easy bruisability or bleeding (mainly due to thrombocytopenia). Onset is usually rapid with ALL, although AML may be preceded by myelodysplasia lasting months or years. Bone pain, and enlargement of liver, spleen and lymph nodes due to infiltration of leukaemic cells may occur. Other organs may also be affected, and various metabolic disturbances, including hyperuricaemia, hyponatraemia, and hypokalaemia may be present.

If untreated the acute leukaemias are normally fatal, usually within months. However, these malignancies are among those in which medical treatment can make a substantial difference to life expectancy, and in some cases a permanent remission may be effected.

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ACUTE LYMPHOBLASTIC LEUKAEMIA. With current chemotherapy regimens, long-term disease free survival can be achieved in over 80% of children and 30 to 40% of adults with acute lymphoblastic leukaemia (ALL).[1] While there is a lack of consensus on some prognostic factors, it is generally accepted that age less than 1 year or greater than 10 years, and high white cell count at the time of diagnosis indicate patients at higher risk of relapse.[2] These factors probably reflect the presence of specific genotypes. Chromosomal translocations that activate specific genes are a defining characteristic of ALL; although genetic abnormalities do not entirely account for treatment outcome they do provide prognostic information. In general, patients with changes such as hyperdiploidy, TEL-AML1 fusion, or t(1;19)/E2A-PBX1 fusion have the most favourable outcome, whereas those with t(9;22)/BCR-ABL fusion (the Philadelphia chromosome) or t(4;11)/MLL-AF4 fusion have a poorer outcome. More than 50% of cases of T-cell ALL have activating mutations that involve NOTCH1, a gene encoding a receptor that regulates normal T-cell development.[2]

Standard treatment regimens for T-cell and precursor B-cell ALL generally consist of 2 to 3 years of therapy divided into several phases: a short remission-induction phase; an intensification (consolidation) phase; therapy for prophylaxis of CNS disease, starting during the induction phase, and sometimes continuing for an extended period; and a prolonged continuation (maintenance) phase, sometimes including re-induction therapy.[1-3] Treatment for mature B-cell ALL (Burkitt cell leukaemia or lymphoma, see Burkitt's Lymphoma, below) is different in terms of the drugs used, and the maintenance phase is not required.[1,2]

The aim of **induction therapy** is to induce complete remission, and a slow early response to this therapy has been reported to be an indicator of poor prognosis.[4] Measurement of minimal residual disease at completion of induction therapy is particularly useful in determining prognosis.[3]

Standard induction regimens include vincristine and a corticosteroid (prednisolone or prednisone, or dexamethasone), plus asparaginase in children and an anthracycline such as doxorubicin in adults. However, it is now accepted that better remission rates and more prolonged remissions can be achieved with more intensive induction therapy using 4 to 5 drugs—often vincristine, a corticosteroid, asparaginase, and an anthracycline, with or without cyclophosphamide.[3] The use of imatinib in Philadelphia chromosome-positive ALL has greatly enhanced remission-induction rates and duration of disease-free survival.[2]

The use of dexamethasone, rather than prednisolone, in the induction regimen appears to yield improved event-free survival and a lower incidence of CNS relapse,[5] and increasing its dose may result in a greater marrow blast response.[6] However, some have reported a higher incidence of fatal sepsis with the use of dexamethasone.[7] There was some suggestion that use of asparaginase derived from *Escherichia coli* may be associated with better event-free survival than that derived from *Erwinia chrysanthemi*,[8] and that pegaspargase may be more effective than asparaginase.[9] However, the dose intensity and duration of asparaginase treatment appears to be more important than the type of asparaginase used.[2]

For mature B-cell ALL, a short-term intensive regimen of cyclophosphamide, high-dose methotrexate, and cytarabine is commonly used,[2] sometimes with the addition of ifosfamide and/or etoposide.[4]

About 60% of children and 35% of adults who achieve an initial remission will subsequently relapse with meningeal involvement unless **CNS therapy** directed at the sanctuary sites in the meninges is undertaken. Effective prophylaxis can reduce the incidence of CNS relapse to around 2 to 5%.[4,5] Standard therapy consisted of cranial irradiation and intrathecal methotrexate. However, concerns regarding the neurotoxicity of cranial irradiation and its ability to cause secondary brain tumours have led to the investigation of chemotherapy alone, particularly in children.[3,5,10] Regimens include intrathecal methotrexate combined with high-dose systemic methotrexate, and triple intrathecal chemotherapy with methotrexate, cytarabine and a corticosteroid. These regimens are started during induction therapy and continued intermittently for an extended period. Early intensification of triple intrathecal chemotherapy may be important in the prevention of CNS relapse, and successful CNS therapy may in turn prevent bone-marrow relapse.[11] Cranial irradiation may still be required in high-risk patients.[2,5]

Intensification (consolidation) therapy involves continuation of intensive chemotherapy regimens after the achievement of complete remission. Although the importance of this phase is rarely disputed, consensus is lacking on the best regimens and duration of treatment.[2] Drugs used in intensification regimens include high-dose cytarabine, etoposide, teniposide, high-dose methotrexate, mercaptopurine, tioguanine, and the antineoplastics used in induction regimens; often 4- to 5-drug combinations are used. The UKALL Trial X showed that addition of intensification therapy at 5 and 20 weeks from the beginning of induction, (using cytarabine, etoposide, tioguanine, and daunorubicin), produced 5-year disease-free survival of 71% compared with 57% in those who received only maintenance therapy.[10] Benefit was seen even in children considered at low risk of treatment failure. Further intensification may benefit those children with a slow response to initial therapy and high-risk of relapse.[12]

Continuation (maintenance) therapy is generally given for some 2 to 3 years after remission;[1-3,10] three years rather than two years of maintenance therapy is associated with a lower risk of relapse but not a markedly different survival rate.[13] The standard combination of drugs consists of daily mercaptopurine and weekly methotrexate.[2] Many protocols provide for periods of **re-induction** therapy (repeating induction therapy),[2] and such intensive therapy is associated with an absolute improvement of about 4% in long-term survival.[13] It has been suggested that individualisation of methotrexate dosage to take account of the patient's ability to clear the drug can improve the outcome.[14]

It is generally agreed that patients who maintain remission for 4 years after the end of maintenance therapy are at little risk of relapse and may be regarded as effectively cured.

Patients who relapse after stopping treatment can usually be brought to **second remission**, often by a repeat of their original induction therapy. However, if relapse occurs during treatment the prognosis is poor, and chemotherapy is unlikely to bring lasting benefit. However, clofarabine monotherapy can induce remission in some children with refractory or relapsed ALL.[15] Newer drugs that have been investigated with promising initial results include nelarabine, sphingosomal vincristine, and novel BCR-ABL inhibitors.[1]

The role of **stem cell transplantation** (p.1811) in the treatment of ALL is a matter of some controversy. Comparisons between transplantation and intensive chemotherapy have yielded inconsistent results.[2] Consequently, allogeneic transplantation is usually reserved for high-risk patients such as those who do not have a complete remission with induction therapy, and those with Philadelphia-positive ALL (who remain at high-risk even when treated with a tyrosine kinase inhibitor).[2] The lack of suitable HLA-matched family donors has led to the investigation of autologous purged marrow, or the use of marrow from mismatched family donors; however, generally neither of these options has proved more effective than chemotherapy.[16] Studies suggest that matched unrelated donors or cord-blood transplantation have results comparable with those obtained with matched related donors.[2]

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ACUTE MYELOID LEUKAEMIAS. Treatment of acute myeloid leukaemias (AML) is problematic because normal stem-cell precursors are sensitive to the drugs used, and therapy aimed at myeloid leukaemic clones results in destruction of part of the normal stem-cell pool. Wherever possible, treatment of AML should be in the context of clinical studies.[1-3]

Induction of remission is usually possible with intensive chemotherapy. Complete remission has been stated to be achievable in up to 80% of younger patients and about 50% of older patients (who form the majority of those with AML), but patients suffer severe neutropenia during induction and remission rate is to some extent dependent upon the standard of supportive care. Remission rates are lower in those with adverse prognostic factors such as poor performance status, AML secondary to myelodysplasia or antineoplastics, high white cell count, features of multidrug resistance, and unfavourable cytogenetics.[4,5] Established regimens are based on cytarabine with the anthracycline daunorubicin.[1-4,6,7] Although idarubicin may be preferred to daunorubicin,[8] especially in younger adult patients,[9] in children it is no more effective but may be associated with more toxicity.[10] Mitoxantrone is another alternative to daunorubicin,[8] and there is little evidence[1,4,8] that one anthracycline is better than another for induction protocols. Addition of etoposide or tioguanine to induction protocols of cytarabine and daunorubicin appears to be equally effective in younger adults and children,[11,12] but in older patients an induction regimen which added tioguanine was found to be more effective than one with etoposide.[13]

As in acute lymphoblastic leukaemia (see above) there is a trend towards the use of more intensive induction regimens.[6,12] Use of high-dose cytarabine compared with standard doses potentially improves survival in younger patients with favourable cytogenetics, but in the elderly neurotoxicity outweighs any benefit;[8] a combination of cytarabine with fludarabine may be an alternative in these patients.[5] The use of haematopoietic growth factors is controversial; some allow for their use as an optional adjunct to intensive chemotherapy,[2] while others recommend against their routine use in AML.[1]

Once remission is induced, consolidation or **postremission therapy** is essential in preventing relapse.[1,6,8] Options include further chemotherapy, or allogeneic or autologous bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811).[1,2,7] There is no consensus on the best postremission therapy.[2,7] Some advocate the use of high-dose cytarabine in those with favourable or intermediate risk; others are candidates for allogeneic stem cell transplantation.[2,7]

Patients who relapse or who fail to achieve complete remission will require **salvage** therapy. Standard salvage regimens can include high-dose cytarabine or fludarabine plus cytarabine.[7] Allogeneic stem cell transplantation can also be used for salvage therapy or for those in second or subsequent remission.[2,7] Investigational therapy is also an option.[7] Gemtuzumab ozogamicin may be useful in elderly patients.[1] Non-myeloablative chemotherapy with allogeneic transplantation may be an alternative in older patients.[5,7,14] Low-dose **maintenance** chemotherapy (with cytarabine and tioguanine) may improve disease-free survival but not overall survival,[4] and prolonged maintenance therapy is generally considered unnecessary in patients with AML.[1,6,12] Where debility or other medical conditions make standard or investigational therapy impossible in the elderly, **palliative** treatment with oral hydroxycarbamide, is often given; low-dose cytarabine may also be of benefit.[1,3,7] Good results have been reported with a combination of idarubicin and etoposide in elderly patients.[5]

Acute promyelocytic leukaemia (APL) is a subtype of AML accounting for 10% of AML cases in adults. It is important to distinguish APL from other forms since, unlike other subtypes, standard therapy is tretinoin **differentiation** therapy. Although most patients with APL can achieve complete remission after treatment with tretinoin alone, remission durations are short and most patients relapse.[15] Induction therapy with tretinoin and chemotherapy (an anthracycline and cytarabine) improved event-free survival compared with chemotherapy alone, and has become routine in APL,[16] although there is good evidence that cytarabine can be omitted.[8,15,17] Anthracycline-based consolidation therapy is mandatory,[16] and, again, although most studies have included cytarabine, the role of high-dose cytarabine has been questioned.[15,17] Although maintenance therapy with tretinoin alone has been reported to be of benefit,[17,18] resistance has developed with continuous treatment,[19] and retinoic acid syndrome is a major toxicity.[15,17] Prolonged maintenance therapy (intermittent tretinoin plus continuous mercaptopurine and methotrexate for 2 years) also appears to reduce the rate of relapse in APL.[19] The synthetic retinoid, tamibarotene (AM-80), has been used to induce remission in patients who relapsed after successful remission induction with tretinoin.[20] Low doses of arsenic trioxide have also been effective in inducing complete remission in patients with APL who have relapsed,[17,21] although fatalities have been reported with its use.[15] Arsenic trioxide has been successfully combined with tretinoin for induction and consolidation.[8] It has also been used alone as first-line therapy, but current recommendations tend to restrict such use to patients for whom chemotherapy is contra-indicated.[16] Autologous and allogeneic stem cell transplantation have also been tried as salvage therapy.[16,22]

The efficacy of tretinoin appears to be achievable only because the characteristic chromosomal abnormalities in APL result in an abnormal retinoic acid receptor. The development of drugs that can effect differentiation in other forms of AML, and indeed in other neoplasms, seems likely to be a long and difficult task.

Other experimental therapies under investigation for AML include clofarabine,[3,7,23] azacitidine, imatinib,[12] and decitabine.[3] The ciclosporin analogue valspodar, an inhibitor of multidrug resistance, has been investigated, but was associated with excessive early mortality.[24]

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Leukaemias, chronic. The chronic leukaemias may be broadly divided into those in which the neoplastic proliferation affects lymphoid cell lines, and those affecting the myeloid cell lines.

Chronic leukaemias affecting the *lymphoid cell lines* include chronic lymphocytic leukaemia (CLL), which is B-cell in about 95% of cases and T-cell in about 5%, and hairy-cell leukaemia, which affects B-cells. The revised European-American lymphoma classification,[1] and a proposed WHO classification of haematologic malignancies,[2] consider lymphoid leukaemias and lymphomas of the same cell type to be one disease with different clinical presentations. Thus B-cell CLL is the same disease as B-cell small lymphocytic lymphoma.

Chronic neoplasms affecting the *myeloid cell lines* include the myeloproliferative disorders chronic myeloid leukaemia (CML), polycythaemia vera, and primary (essential) thrombocythaemia, and the myelodysplastic syndromes. All of these may undergo transformation to acute myeloid leukaemia.

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CHRONIC LYMPHOCYTIC LEUKAEMIA. Chronic lymphocytic leukaemia (CLL) typically occurs in people over 60 years of age, and accounts for about 30% of leukaemias in the West although it is rarer in the Far East. Stages of CLL are defined according to the American Rai system or the European Binet system, with both having prognostic value.[1-6] The clinical course is variable: low-risk patients (Rai stage O; Binet stage A) have a median survival of about 10 years, while high-risk patients (Rai stage III/IV; Binet stage C) have a median survival of about 1.5 years; median survival in the intermediate stages is about 6 years.[1,2] The mutational status of the immunoglobulin IGHV gene also affects prognosis; attempts to use surrogate markers of this status included CD38 and ZAP-70, and these have assisted in further risk stratification.[6-9]

In patients at low risk and those at intermediate risk with indolent disease cytotoxic chemotherapy is usually deferred until signs and symptoms of disease progression occur.[1,2,4-7] In these patient groups, trials of immediate versus deferred chemotherapy for early-stage CLL have shown no significant advantage, or disadvantage, for immediate chemotherapy in terms of 10-year survival.[10] Patients with high-risk or progressive disease are usually treated with immediate chemotherapy.

When therapy is required, it is essentially symptomatic and palliative. Continuous or intermittent chlorambucil has been most widely used, and is given for as long as the patient responds; response rates range from about 40 to 70%.[2,3,7] Fludarabine is also used as initial therapy, and while response rates have been found to be higher than with chlorambucil,[11] there appears to be no overall advantage in terms of survival.[1,2,4,5,7,12] Compared with chlorambucil, the increased incidence of opportunistic infections is a disadvantage of fludarabine treatment.[4] The order in which alkylating agents and purine analogues are given is not thought important, provided patients who relapse on one treatment then receive the other.[9]

Although chlorambucil is often used with a corticosteroid (prednisone or prednisolone), there is some doubt as to whether this has a real advantage over chlorambucil alone.[1,2,10] Corticosteroid therapy is, however, the treatment of choice where patients present with cytopenias due to an immune mechanism.[1] The most commonly used combination chemotherapy is with cyclophosphamide and prednisone or prednisolone plus either vincristine (COP or CVP) or doxorubicin (CAP), or both (CHOP).[1-3] However, combination chemotherapy does not appear to offer any advantage over chlorambucil alone.[10] Similarly, comparisons of fludarabine with CAP and CHOP found fludarabine gave better response rates in patients with advanced disease, but similar survival-times.[1,2,5,8] The combination of fludarabine and cyclophosphamide may be synergistic,[13] and produced good overall response rates,[12] although overall survival did not differ compared with fludarabine alone.[6] However, consistent benefit from this combination in terms of progression-free survival has led some to consider it the first-line treatment of choice,[7,14] except for poor-risk patients, in whom response is unlikely.[14] Cladribine with or without corticosteroids has also been used in previously untreated patients; results were comparable with single-agent fludarabine.[8] Cladribine may also be used for CLL refractory to alkylating agents. Compared with chlorambucil and prednisone, cladribine and prednisone gave higher response rates but increased toxicity, and overall survival was not statistically different.[15] Pentostatin has also been investigated.[1] Pentostatin with cyclophosphamide was well-tolerated and produced good overall response rates in a small group of patients refractory to fludarabine.[7,12]

In patients who fail treatment with conventional therapy, the monoclonal antibodies alemtuzumab and rituximab have produced encouraging results.[3,6,12,16-18] Combinations of these antibodies with other drugs have been studied in CLL,[4,5,7,8,19] and the use of rituximab with fludarabine especially has shown marked clinical efficacy.[6,7,9,20] Alemtuzumab may be used as first-line therapy in patients with certain cytogenetic abnormalities associated with a poor prognosis, or as consolidation therapy after fludarabine-based induction therapy.[7] It is also effective in refractory patients with high-risk disease.[7]

Treatment of relapses depends upon response to initial therapy.[6,8] After long remissions, patients will usually respond again to induction treatment.[6] Alternative agents, or combination chemotherapy with or without monoclonal antibodies may then be tried.[6,8]

Haematopoietic stem cell transplantation (HSCT) has been investigated for CLL.[6] Autologous HSCT is unlikely to provide a cure[8] and relapse is inevitable.[7] The principles of allogeneic HSCT include the graft-versus-leukaemia effect and the absence of stem cell contamination.[8] However, transplant-related mortality has been high. Non-myeloablative conditioning protocols are under investigation.[6-8] Allogeneic HSCT is suggested for younger patients with non-response or early relapse after purine analogues, or those who relapse within 2 years of an initial response with purine-analogue based therapy or autologous HSCT, or in patients with certain cytogenetic abnormalities with a poor prognosis.[7]

Other drugs that have been investigated for CLL include bortezomib,[7] denileukin diftitox,[7] lenalidomide,[6,7,21] lumiliximab,[6,7] oblimersen sodium,[7] ofatumumab,[6] and thalidomide.[21]

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CHRONIC MYELOID LEUKAEMIA. Chronic myeloid (myelogenous) or chronic granulocytic leukaemia (CML) is a rare disease, occurring usually in older patients, and representing about 15% of all adult leukaemias. It is associated in over 90% of cases with the presence in blood cells of an abnormal chromosome, the Philadelphia chromosome (Ph), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22, with the fusion of the BCR gene and the ABL gene. The product of this gene, the protein BCR-ABL, is leukaemogenic. Ph-negative disease (atypical CML) carries a worse prognosis, and some classification systems consider it to be a separate disease.[1-3]

CML occurs in 3 different phases. It is usually diagnosed in the chronic phase, which may last for several years, which when untreated, progresses to an advanced phase; this consists of an often rapidly fatal blastic phase (blast crisis), which is often preceded by a transition period, the accelerated phase.[1,3-7]

The development of imatinib, an inhibitor of the BCR-ABL protein tyrosine kinase, constituted a revolutionary change in the management of CML.[1-5,8,9] The International Randomized Study of Interferon and STI571 (IRIS), found imatinib to be better than interferon alfa with low-dose cytarabine for newly diagnosed CML in **chronic phase**.[10,11] Follow-up study found responses to be durable in a high proportion of patients.[12] The optimal dose has not been determined, and high-dose imatinib is under investigation.[4,8] However, since relapse is common after stopping imatinib, therapy should be continued indefinitely in responsive patients.[1,8] Resistance may also be a problem.[2,3,5,7-9,13-15] For patients who do not respond to initial therapy with imatinib, or are in haematological relapse, options include increasing the dose of imatinib, the use of second-generation tyrosine kinase inhibitors such as dasatinib or nilotinib, considering allogeneic haematopoietic stem cell transplantation (HSCT), or investigational therapy.[1,3,6,7] For patients unable to tolerate imatinib or other tyrosine kinase inhibitors, interferon alfa (with or without low-dose cytarabine) or hydroxycarbamide may be reasonable alternatives.[1,2,4,8]

Early allogeneic HSCT (p.1811) has the potential to cure CML due to a graft-versus-leukaemia effect, but it is still associated with appreciable morbidity and mortality, including graft-versus-host disease,[9] and results with imatinib have challenged the role of HSCT as first-line therapy for chronic phase CML.[1] While HSCT is still an option in suitable patients such as younger patients with HLA-identical sibling donors,[4,5] or those with high-risk disease and low transplantation risk,[2] most recommend an initial period of therapy with imatinib since the response can either reinforce or weaken the indication for HSCT.[6,8,9] Ongoing advances in alternative donor sources (such as the use of HLA-matched unrelated donors and cord blood), improved HLA typing techniques, and less toxic non-myeloablative regimens are broadening the use of HSCT.[1,5] Autologous HSCT has also been investigated, but no advantage over interferon-based regimens has been shown.[8] Options in patients who relapse after HSCT include the use of donor lymphocyte infusions, tyrosine kinase inhibitors, or interferon alfa.[1,2]

Although now no longer a first-line treatment, in most patients, interferon alfa is associated with improved survival compared with busulfan or hydroxycarbamide,[16] and the addition of low-dose cytarabine to interferon alfa improves response rates but increases toxicity compared with interferon alfa alone.[17] Hydroxycarbamide is somewhat more effective, and better tolerated, than busulfan.[18]

Occasionally, patients present in **advanced phase**. Those in early blast crisis may be treated initially with imatinib or other tyrosine kinase inhibitors, and then proceed to allogeneic HSCT.[4,8] A longer trial of imatinib is possible for patients diagnosed in accelerated phase.[8] For those who progress to advanced disease while on imatinib, options include dasatinib or nilotinib, HSCT, or investigational therapy.[1]

Investigational therapies for CML include omacetaxine mepesuccinate, farnesyl transferase inhibitors such as lonafarnib and tipifarnib, hypomethylating agents such as azacitidine and decitabine, histone deacetylase inhibitors, and vaccines.[5,15] Combinations of imatinib with other drugs are also under investigation.[2]

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HAIRY-CELL LEUKAEMIA. Hairy-cell leukaemia is a rare, chronic, B-cell lymphoproliferative disorder marked by the presence of white blood cells with prominent cytoplasmic villi, pancytopenia, and splenomegaly. Many patients are asymptomatic and there is no clear advantage to early treatment before symptoms appear.[1-3] When treatment is required, splenectomy was formerly used as initial therapy, but response duration tended to be short. Interferon alfa-2a or -2b given for one year produces at least a partial response in most cases but patients have a tendency to relapse once therapy is stopped,[1,2,4] although maintenance therapy with low-dose interferon alfa may prolong remission.[4]

Better results have been reported with the purine analogues cladribine and pentostatin, and these have now emerged as first-line treatments for this disease.[1,2,4-6] Durable complete remission rates of 50% or more are seen after relatively short courses of therapy.[4,7-9] Toxicity is generally acceptable.[4,8] They do not appear to show cross-resistance; cladribine has been used successfully in patients resistant to, or intolerant of, pentostatin,[2,4] and others[6] have used pentostatin in patients who do not respond to cladribine. For patients who relapse, re-treatment with initial therapy is advocated, although interferon alfa is an option in those patients relapsing after treatment with a purine analogue.[2] There are reports of remission after use of rituximab in patients with refractory disease,[2,4,10,11] and it has been suggested for use in those who fail cladribine and pentostatin.[6] Other immunotherapy under investigation for hairy-cell leukaemia includes the recombinant immunotoxins LMB-2[12] and BL22.[13]

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MYELODYSPLASTIC SYNDROMES. Myelodysplastic syndromes are low-grade neoplasms of haematopoietic stem cells characterised by ineffective haematopoiesis that results in anaemia, neutropenia, or thrombocytopenia in various combinations. They have been described as smouldering leukaemia or preleukaemia, and transformation to acute myeloid leukaemia (AML) occurs in some patients.

The clinical course of myelodysplastic syndromes is variable, and a precise individual determination of prognostic score is important in planning treatment.[1-3] In the few younger patients with suitable HLA-matched siblings, allogeneic haematopoietic stem cell transplantation (HSCT) has curative potential.[1,2,4-6] As most patients are older, with medical conditions precluding the use of standard conditioning regimens, novel transplant conditioning regimens of reduced intensity are being investigated.[6,7]

Patients who are likely to have an indolent course are best treated conservatively with observation and supportive care (transfusions, antibacterials, or epoetins plus colony-stimulating factors).[1-5,7] Iron chelation therapy may be needed in patients who develop iron overload (p.1442) from blood transfusions.[3,7] Azacitidine, decitabine, or lenalidomide may be considered where a low serum-erythropoietin concentration does not respond to epoetins (with or without colony-stimulating factors). Patients with serum-erythropoietin above 500 mU/mL and a good probability of response to immunosuppressive therapy should be given antilymphocyte immunoglobulins with or without ciclosporin, or possibly ciclosporin alone.[3,7] Those likely to have a poor response to immunosuppressants should be given treatment with azacitidine, decitabine, lenalidomide, investigational agents, or considered for allogeneic HSCT.[3] Azacitidine or decitabine are also treatment options for patients with serious cytopenias; if not responsive, immunosuppressive therapy, investigational agents, or allogeneic HSCT can be tried.[3] Lenalidomide is effective for patients with chromosome 5q deletions,[8-10] and is recommended as first-line therapy in these patients.[3,7]

The treatment of progressive or advanced myelodysplastic syndromes or those that have transformed to AML may involve intensive chemotherapy similar to that for AML (see p.652), but remission rates are lower,[1,2,4,5] and relapse common.[7] However, many patients are elderly with poor performance status, and are unable to tolerate intensive chemotherapy. They may be treated with supportive care and haematopoietic growth factors alone.[7] Low-intensity chemotherapy such as azacitidine or decitabine may be tried in such patients,[3] but has had limited success.[2,4] Other antineoplastics and immunomodulating agents investigated for use in myelodysplastic syndromes include amifostine, arsenic trioxide, thalidomide, and topotecan.[2,4-7,11] Attempts to induce cellular differentiation have generally been disappointing.[4]

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POLYCYTHAEMIA VERA. Polycythaemia vera (polycythaemia rubra vera) is a Philadelphia-negative chronic myeloproliferative disorder,[1] associated in about 95% of patients with a mutation in the Janus kinase 2 (JAK2) gene.[1-3] It is characterised by an increased red cell mass and packed cell volume, and is often associated with increases in white cell and platelet counts and splenomegaly.[1,4] It is a disease of later life, with a median age at presentation of about 60 years.[4] The symptoms are related to hyperviscosity due to the increased number of cells in the blood, with the most common features being fatigue, headache, visual disturbances, paraesthesia, pruritus (characteristically exacerbated by warmth), and erythromelalgia (burning pain and erythema of the hands and feet). More serious symptoms include intermittent claudication, angina pectoris, and transient ischaemic attacks.[1] Patients often present with either arterial or venous thrombosis (cerebrovascular accident, myocardial infarction, pulmonary embolism) or occasionally, with haemorrhage, particularly involving the skin and gastrointestinal tract; splenic pain or gout may also be presenting features.[1,4]

Untreated, the disease is associated with a high risk of morbidity and mortality, and patients can undergo myelofibrotic transformation into blast crisis and acute myeloid leukaemia.[1,4] The aims of treatment are therefore to reduce the risk of thrombosis and haemorrhage, minimise transformation risk, and manage complications, or pregnancy.[4]

The mainstay of treatment is periodic phlebotomy to maintain the haematocrit within normal values,[5,6] along with aspirin in low doses (40 to 100 mg daily)[1] sufficient to reduce thrombosis without increasing the risk of major bleeding.[7] This may be all that is required in younger patients at low risk of thrombosis. In patients at high risk of thrombosis, including those who have a high phlebotomy requirement, some form of myelosuppressive therapy may also be considered. Chlorambucil, which was formerly used for this purpose, has largely been stopped because of a high incidence of leukaemia in patients so treated.[4-6] In patients with a life expectancy of less than 10 years, radioactive phosphorus-32 is probably appropriate, and produces good results with few immediate adverse effects.[5,8] However, like the alkylating agents it is associated with an increased risk of secondary malignancies.[6] In younger patients hydroxycarbamide,[1,4,6,8] busulfan,[5,6] or in some countries pipobroman,[5,9] have been preferred because they were considered to have lower risk of inducing leukaemia. However, there is some evidence[9,10] that they too may have leukaemogenic potential, especially when used in combination,[11] and some recommend that busulfan and pipobroman be reserved for elderly patients.[1,4] Non-cytotoxic therapies that have been shown to be effective include interferon alfa.[1,4-6,10,12] This may be preferred in younger patients requiring treatment.[4,5,8] Anagrelide, another antiplatelet drug, has also been tried in polycythaemia vera. It is effective in controlling the platelet count, but does not control progression of polycythaemia vera, and its adverse effects may make it difficult for some patients to tolerate.[4]

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PRIMARY THROMBOCYTHAEMIA. Primary thrombocythaemia (essential thrombocythaemia) is a rare Philadelphia-negative myeloproliferative disorder in which abnormal platelet production results in elevated platelet counts.[1,2] The Janus kinase 2 (JAK2) genetic mutation occurs in about 50 to 60% of patients.[3] The disorder occurs mainly during later life and unlike other myeloproliferative disorders, is associated with generally near-normal life expectancy.[1] However, microvascular occlusion marked by conditions such as erythromelalgia (burning pain and erythema of the hands and feet), paraesthesia, or migraine, and arterial or venous thrombosis (e.g. cerebrovascular accident, myocardial infarction, pulmonary embolism) may occur. The risk for thrombosis is highest in patients with a history of thrombosis and in those aged over 60 years. In less than 10% of patients the disease eventually enters a spent phase marked by fibrosis and marrow hypoplasia, or transforms to acute leukaemia.

Asymptomatic patients and those at low risk of thrombosis are generally not treated, but when to begin treatment is controversial.[1,4-6] Some consider that primary antithrombotic prophylaxis seems rational even in asymptomatic patients if there are no contra-indications to this therapy. Low-dose aspirin (40 to 100 mg daily) is considered to be effective, without increasing the risk of major bleeding. Acute microvascular symptoms may be managed with higher doses of aspirin (100 to 300 mg daily).[2] In patients at risk of thrombosis, drugs that lower platelet counts are used, including cytotoxics.[1,2,4,6,7] Phosphorus-32 and alkylating agents such as busulfan or pipobroman are little used now because of their known potential to induce leukaemia.[2,7,8] Hydroxycarbamide can reduce thrombotic events,[7,9] and has tended to be preferred because it was thought to have lower risk of inducing leukaemia, but it too appears to have leukaemogenic potential.[6-11] The increased risk of leukaemia from therapy is particularly relevant in younger patients, for whom non-cytotoxic drugs may be preferred. Some non-cytotoxic therapies have also been shown to reduce platelet counts. Anagrelide[8,10] is often substituted for hydroxycarbamide,[2,6,7,9] but its value has been questioned by a comparison[12] of 2 regimens using aspirin with either anagrelide or hydroxycarbamide. Although the reductions in platelet count were similar for both groups, patients taking anagrelide were found to be at greater risk of arterial thrombosis, serious haemorrhage, and transformation to myelofibrosis (but the rate of venous thromboembolism was lower). Interferon alfa can also effectively reduce platelet counts;[6,7,10] it is a good alternative for younger patients who face lifelong treatment,[2] and is the treatment of choice in pregnant women.[2,6,8,9] Haematopoietic stem cell transplantation may be considered in younger patients who have advanced, complicated disease.[6]

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Lymphomas. The malignant lymphomas are neoplastic disorders of the lymphoreticular cells. These cells are primarily located in the lymph nodes, but because of their wide distribution in the body lymphomas may arise in extranodal and extralymphatic tissues such as lung, gastrointestinal tract, and skin.

The term covers a heterogeneous group of diseases, comprising two main subgroups: Hodgkin's disease, and the non-Hodgkin's lymphomas (NHL). The cellular origin of Hodgkin's disease is uncertain; the NHL are monoclonal malignancies arising from B cells in about 80% of cases, with the remainder from cells of T lineage and from undifferentiated cells.

Management of patients with malignant lymphoma is largely determined by interpretation of histological features, and, especially for NHL, by an allocation of subtype and grade. Various classification systems have been proposed for NHL of which the National Cancer Institute Working Formulation has been widely used.[1] Under the Working Formulation, NHL are divided into:

- *low grade*, including small lymphocytic, follicular small cleaved cell, and follicular mixed small cleaved and large cell lymphoma
- *intermediate grade*, including follicular large cell, diffuse large cell, diffuse small cleaved cell, and diffuse mixed types
- *high grade*, including large cell immunoblastic, lymphoblastic, and small non-cleaved cell (including Burkitt's) lymphomas

The International Lymphoma Study Group has proposed a revised European-American lymphoma (REAL) classification,[2] and this has subsequently also been published under the auspices of WHO.[3] It is based on a division into B-cell, T-cell and natural killer cell, and Hodgkin's neoplasms. In this classification, B-cell lymphomas include B-cell small lymphocytic lymphoma, MALT lymphoma, follicular lymphoma (35% of adult NHL, rare in children), diffuse large B-cell lymphoma (30% of adult NHL, 5% of NHL in children), and Burkitt's lymphoma (rare in adults; 30% of NHL in children) and Waldenström's macroglobulinaemia (lymphoplasmacytic lymphoma). Plasma-cell myeloma (multiple myeloma) is also a B-cell neoplasm. T-cell lymphomas include precursor T-cell lymphoblastic lymphoma (rare in adults; 45% of NHL in children) and mycosis fungoides; and Hodgkin's lymphoma is subdivided into nodular lymphocyte-predominant and classical (nodular sclerosis and mixed cellularity) forms.

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HODGKIN'S DISEASE. Hodgkin's disease (Hodgkin's lymphoma) is characterised histologically by the presence of a particular type of giant cell, the Reed-Sternberg cell. It is more common in males than in females, and in the West is seen particularly in young adults and in the elderly, although the age distribution differs elsewhere.

It usually presents as painless enlargement of one or more lymph nodes, particularly in the neck or axillae. About a third of all patients also have constitutional symptoms of fever, weight loss, and night sweats, which indicate poorer prognosis. In advanced disease, signs of organ infiltration may occur, as may infectious complications. The mass of the tumour may result in compression of vital organs.

Hodgkin's disease can be treated by radiotherapy or chemotherapy or both, and the choice of treatment depends on the volume and histological subtype of the tumour, the age of the patient, and, particularly, the stage of the disease.[1-3] The Ann Arbor classification (with Cotswold modifications) recognises 4 stages:

- Stage I, with involvement of a single lymph node region or extralymphatic site
- Stage II, in which spread is restricted to lymph nodes and sites on one side of the diaphragm only
- Stage III, involving spread on both sides of the diaphragm with possible splenic and extralymphatic involvement
- Stage IV, where the patient has diffuse or disseminated disease in one or more extralymphatic organs or tissues.

Stages are subclassified A or B according to the absence or presence respectively of the aforementioned constitutional symptoms. X indicates bulky disease and E the involvement of single extranodal sites. Survival rates after treatment for Hodgkin's disease are generally excellent, and there is increasing emphasis on tailoring therapy to decrease early and late treatment-related morbidity while not compromising survival.[1,2] For prognostic and therapeutic considerations, patients are grouped into early stage favourable, early stage unfavourable or intermediate, and advanced stage disease.

In the treatment of early stage disease (stages I, II, and IIIA), radiotherapy alone was standard therapy for adult patients with limited disease, especially in those with good prognosis. However, there have been concerns about relapse rates and an increased risk of secondary malignancy after radiotherapy. Adjuvant chemotherapy (combined modality treatment) has been investigated in order to improve disease-free survival, reduce doses and volumes of radiotherapy, and avoid the need for surgical staging. A comprehensive meta-analysis of adjuvant chemotherapy in patients with early stage disease found a reduced risk of resistant or recurrent disease, but this did not translate to a significant improvement in 10-year survival.[4] A systematic review[5] came to the same conclusion. Most patients in the meta-analysis received the MOPP regimen (see below) and extended field radiotherapy, and some feel that the ABVD regimen (see below) and involved field radiotherapy may prove more effective in terms of toxicity and survival.[6] Combined modality treatment is now the preferred treatment for favourable early stage disease,[3,6-9] although the optimal chemotherapy regimen and radiation dose have yet to be determined. It is also generally accepted as the treatment of choice in those with unfavourable early stage disease, using the ABVD regimen.[3,6-9] Combined modality treatment is also preferred in children,[2,10] although evidence to support this is scanty.[11]

Chemotherapy alone is generally considered to be the treatment of choice in advanced disease (stages IIIB and IV), although the value of adding radiotherapy has still been debated. Meta-analyses or systematic reviews of combined modality therapy in advanced disease have found no survival benefit from additional radiotherapy, although it may have a role in initial bulky or residual disease.[5,12]

There are several 4-drug standard regimens available and the choice lies between one of these, alternating cycles of 2 different regimens, or a hybrid cycle that involves giving 7 or 8 drugs in the same course of treatment. However, the single most important factor governing the outcome of chemotherapy is thought to be dose intensity of the drugs given.

The earliest of the successful 4-drug regimens was combination chemotherapy with chlormethine, vincristine, procarbazine, and prednisone or prednisolone (MOPP). A number of MOPP-variant regimens exist which may be as effective and less toxic; these include substitution of chlorambucil or cyclophosphamide for chlormethine (LOPP or COPP, respectively), vinblastine for vincristine (MVPP), and both chlorambucil and vinblastine substituted in one regimen (ChlVPP). However, an alternative to the MOPP-based regimens, a non-cross resistant combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was found to be as effective as MOPP with a reduced risk of inducing sterility or secondary leukaemia. Better results were later reported with ABVD alone, or with MOPP/ABVD, than with MOPP alone, and ABVD has become the basis of standard treatment for advanced stage Hodgkin's disease.[3,10,13,14]

Attempts to improve the results of ABVD or MOPP have centred on dose intensified hybrid regimens. The German Hodgkin's Lymphoma study group found improved results with a hybrid regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) compared with COPP/ABVD; overall survival was highest with an increased dose of BEACOPP, although toxicity was increased.[15] The Stanford V regimen (doxorubicin, vinblastine, chlormethine, vincristine, bleomycin, etoposide and prednisone, with consolidative radiotherapy) is also used,[3,14] although a randomised study[16] comparing ABVD, Stanford V, and a MOPP-hybrid regimen found Stanford V to be inferior in terms of response and survival rates. Further comparative studies of ABVD versus BEACOPP or Stanford V are underway.[3,17]

Salvage treatment options for patients who relapse depend on the initial treatment and the interval between treatment and relapse. Patients who are candidates for salvage therapy can be divided into 4 groups:

- those initially treated with radiotherapy who have a recurrence, in whom standard chemotherapy regimens are effective
- those who never achieve complete remission with standard chemotherapy, in whom prognosis is very poor, and who are candidates for an intensive salvage chemotherapy regimen with autologous haematopoietic stem cell transplantation (HSCT)
- those whose original remission lasted for over a year, of whom some will respond to re-treatment with standard therapy, but in whom intensive salvage chemotherapy regimens with HSCT may be considered
- and those whose remission is short, less than one year, in whom standard chemotherapy may be used to reduce tumour volume before intensive salvage chemotherapy and HSCT.[8,18]

A common intensive salvage regimen consists of carmustine, etoposide, cytarabine, and melphalan (BEAM). Although intensive chemotherapy and HSCT is considered by some[8,14] to be the treatment of choice in relapsed patients, others[5] note that benefit on overall survival remains to be established.

Immunotherapies under investigation for Hodgkin's disease include the anti-CD20 monoclonal antibody rituximab,[6] and other monoclonal antibodies, some radiolabelled, to CD25 and CD30.[10] Gemcitabine is also being studied in refractory disease.[10]

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NON-HODGKIN'S LYMPHOMAS. The non-Hodgkin's lymphomas are a heterogeneous group of malignancies that vary considerably in their behaviour, prognosis, and management.[1] Classifications have grouped them by grade (low, intermediate, or high) or cellular origin (B-cell or T-cell), and histology (see Lymphomas, above). The most recent WHO classification, while still separating B- and T-cell lymphoid neoplasms, does not group the non-Hodgkin's lymphomas into a distinct clinical framework.[2] The non-Hodgkin's lymphomas include Burkitt's lymphoma, MALT lymphoma, and mycosis fungoides, all of which are discussed separately.

The usual presentation of lymphomas is lymphadenopathy, which in low-grade lymphoma may develop insidiously over a long period. There may be constitutional symptoms of fever, night sweats, and weight loss. Extranodal involvement may occur, as may symptoms due to organ compression by the tumour mass. Lymphomas of T-cell origin have a worse prognosis than B-cell lymphomas of the same type, and excess tumour bulk, involvement of bone marrow or gastrointestinal tract, and elevated serum-lactic dehydrogenase concentrations are also adverse prognostic factors. Staging is of somewhat less importance as a determinant of treatment and prognosis than in Hodgkin's disease.

About 40% of all lymphomas seen in North America and western Europe are *indolent* and of low grade; **follicular lymphoma** is the commonest form.[3] Follicular lymphomas may be subclassified histologically into 3 grades according to the number of centroblasts, and grade 3, which is more aggressive, should be treated as for diffuse large B-cell lymphoma[2,4] (see below). The approach to therapy of other follicular lymphoma differs dramatically in patients with localised or disseminated (advanced) disease.[2]

In the few patients with limited disease at presentation, radiotherapy is potentially curative,[1,5-8] with most patients achieving long-term freedom from disease, and low rates of relapse.[1] The addition of chemotherapy to radiotherapy does not convincingly prolong remission or improve overall survival.[2,6] Patients who do relapse after therapy should be treated as those with more disseminated disease.[2] Even in more advanced disease, which is rarely curable,[1,5,7] follicular lymphoma may follow a fairly chronic course, with a median survival of 8 or more years[4,5,8] although transformation to more aggressive forms may occur.[1]

Treatment in advanced disease has not been shown to affect survival, and a conservative approach of withholding treatment until symptoms require it is considered viable.[2,3,5,6,8,9] The choice of first-line chemotherapy for advanced disease is controversial.[4] Single-agent therapy with chlorambucil or cyclophosphamide, sometimes with a corticosteroid such as prednisone in the initial stages, may be preferred.[5,6,9] However, others[2] recommend this only for elderly or infirm patients, and then only after rituximab, which is the preferred first-line treatment in these patients. Patients treated with combination chemotherapy tend to have remission earlier but the remissions do not last longer than those achieved more slowly with single-agent therapy,[1] and overall survival has not improved.[5,6] Nonetheless, because intensification of chemotherapy has improved response rates, combination therapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) has become widely used.[5] Some[9] consider this regimen too toxic for indolent lymphomas unless rapid tumour debulking is required. CVP (cyclophosphamide, vincristine, and prednisone) has also been used.[4] The addition of rituximab to combination chemotherapy has increased overall response rate, response duration, and progression-free survival and hence some recommend rituximab either alone or with other regimens (chemoimmunotherapy) as first-line options; caution is advised in patients with hepatitis B.[2] The use of interferon alfa with chemotherapy for first-line treatment has produced conflicting results. However, when interferon alfa was used with anthracycline-containing regimens, improvements in response rate and prolonged remission were reported;[5,9] prolonged survival has not been proven.[6] Interferon alfa as maintenance therapy appears to improve disease-free survival, but only if complete remission has been obtained with initial chemotherapy.[1,5] Overall, a meta-analysis[10] of 10 studies found that the ability of interferon alfa to prolong remission duration and survival may depend on it being used with relatively intensive chemotherapy and given in unit doses of at least 5 million units (at least 36 million units/month). Results using the purine analogues, fludarabine and cladribine, for initial therapy have been promising, with high remission rates.[5]

Relapse of indolent lymphomas is generally inevitable. Although further remissions can be achieved with repeat of the initial alkylating agent, or an alternative alkylator, response rates and duration of remission tend to decrease.[6] Fludarabine and cladribine have shown responses in about half of those relapsing or refractory to initial chemotherapy.[5,6] Pentostatin has also been tried, with less response, but most studies were in patients refractory to the purine analogues, which show cross-resistance.[5] Radioimmunotherapy with radiolabelled monoclonal antibodies such as tositumomab and ibritumomab are alternative options for relapsed or refractory follicular lymphoma,[2,11] although myelosuppression may be a problem[8,11] and there may be practical difficulties to their use. High-dose chemotherapy followed by autologous[12,13] or allogeneic[14,15] haematopoietic stem cell transplantation (HSCT) may be an appropriate option for relapsed patients.[2,4,6] In those candidates considered for autologous HSCT, initial therapy should not be excessively myelotoxic, and in the case of allogeneic HSCT, nonmyeloablative approaches may be considered.[2]

Intermediate- to high-grade lymphomas, of which **diffuse large B-cell lymphoma** (DLCL) is the most common form,[2,16] are *aggressive*, and survival is measured in months in untreated patients. However, unlike indolent lymphomas, they are potentially curable with intensive therapy.[7] DLCL occurs most often in patients aged 50 to 60 years, but also occurs in children. As with follicular lymphoma, approach to therapy differs in patients with localised or advanced disease.[2] Up to 20% of patients with aggressive lymphomas have localised disease at presentation, and combined modality treatment with a brief course of CHOP (see above) and rituximab followed by involved field radiotherapy is the treatment of choice.[2,4] Combination chemotherapy is also the treatment of choice in advanced aggressive lymphomas: cure can be achieved in about 35% of patients. Many of the regimens used have included the vinca alkaloids and doxorubicin with alkylating agents: CHOP and CVP (cyclophosphamide, vincristine, and prednisone) have been widely used.[3,16] More intensive second and third generation regimens such as MACOP-B (an intensive 12-week programme of cyclic methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), m-BACOD (with dexamethasone rather than prednisone), and ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate), were then developed, and showed initial promising results. However, randomised studies failed to show any advantage for these second and third generation regimens over the less toxic and simpler CHOP regimen,[9,16,17] and many consider CHOP plus rituximab to be the standard for care.[2,4,18,19] High-dose chemotherapy with autologous HSCT has been tried for initial therapy in patients with diffuse aggressive non-Hodgkin's lymphoma, but remains investigational.[2,9,12,17]

On relapse, patients are treated with salvage chemotherapy regimens such as miniBEAM, (carmustine, etoposide, cytarabine, melphalan), DHAP (dexamethasone, cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, etoposide), ESHP or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), or MINE (mitoxantrone, ifosfamide, mesna, etoposide); all these regimens may be given with or without rituximab.[2,16] Patients are then evaluated for high-dose chemotherapy and autologous HSCT, which is considered the treatment of choice in suitable patients who respond to the salvage regimens.[1,2,16] In a randomised study, it was found to be superior to further courses of DHAP.[20] However, in disease resistant to salvage chemotherapy, its role has not been established,[16] and patients whose disease progresses are considered not likely to benefit from currently available standard therapy.[2]

High-grade lymphomas such as **precursor T-lymphoblastic lymphoma** (T-LBL) and Burkitt's lymphoma (see below) are *highly aggressive* and untreated patients survive only weeks. They occur mainly in children and young adults, and are often widely disseminated with bone marrow, peripheral blood, and CNS involvement. In children with lymphoblastic lymphoma, good results have been seen with protocols based on those used for acute lymphoblastic leukaemia (see above), including the use of CNS prophylaxis.[21] It is unclear whether a similar approach would be beneficial in adults with lymphoblastic leukaemia: CHOP continues to be widely used, with generally poor results.[21] HSCT is an option in lymphoblastic lymphoma.[12]

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AIDS-related lymphomas. Non-Hodgkin's lymphoma is often a late complication of AIDS,[1] and its incidence in HIV-infected individuals is about 60 times greater than in the general population.[1-3] Histologically, it is usually diffuse large cell lymphoma (see Non-Hodgkin's Lymphomas, above) or small non-cleaved lymphoma (Burkitt's lymphoma—see below).[1,2,4] About 50% of these are associated with the presence of Epstein-Barr virus. The other common HIV-associated lymphoma is primary CNS lymphoma, which is invariably associated with Epstein-Barr virus.[1,4] More recently, primary effusion lymphoma or body cavity-based lymphoma has been identified,[1,2,4] which is associated with human herpes virus 8. Although Hodgkin's disease (see above) is not considered an AIDS-defining illness, epidemiological studies have shown it to be associated with HIV infection.[5] The introduction of HAART for HIV infection (p.856) may reduce the risk of lymphomas by improving immune function,[2,4,6] but, conversely, may increase the incidence by allowing patients to survive long enough for lymphoma to develop.[1,2] The incidence of primary CNS lymphoma has decreased with the advent of HAART.[1,6] There is some evidence of tumour response when antiretroviral therapy is started in a patient who already has a lymphoma.[4]

A few patients with AIDS-related non-Hodgkin's lymphomas present with localised disease, and may benefit from radiotherapy, but most have disseminated disease, often extranodal, at presentation.[1,2,4] Optimal management is not established.[7] The common chemotherapy regimens used are similar to those used in non-HIV infected patients, combining cyclophosphamide, vincristine, doxorubicin, and corticosteroids (CHOP), and sometimes additional drugs such as bleomycin and methotrexate (m-BACOD).[1,3,4,6,7] However, although standard dose or even intensive chemotherapy regimens have been used successfully in selected patients, in general patients with AIDS tolerate chemotherapy poorly, and intensive regimens may even shorten their survival. The addition of rituximab has been investigated, but results have been disappointing and there is an increased risk of neutropenic sepsis and death in these patients.[6] A low-dose modification of m-BACOD has produced responses and survival comparable to standard dose m-BACOD,[8] and low-dose chemotherapy is likely to be preferred in patients with relatively poor immune function (CD4 cell count less than 200 cells/microlitre[3]).[3] Results of trials using cyclophosphamide, doxorubicin, and etoposide (CDE), sometimes with didanosine, have been promising.[1] A dose-adjusted regimen of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) has also been studied,[6] and has been given with HAART.[1] The use of colony-stimulating factors with chemotherapy has reduced neutropenia and febrile episodes, but there has been no effect on remission rates or overall survival.[1] Most studies used granulocyte-macrophage colony-stimulating factor, but this may increase HIV-1 replication.[1] The prognosis for patients with poor immune status remains poor, and median survival remains only about 4 to 8 months.[3]

Primary CNS lymphoma has a very poor prognosis in patients with HIV infection, with a median survival of 3 months. Palliative radiotherapy is commonly used,[2,4] and may be combined with chemotherapy,[1,3] but it remains uncertain whether therapy improves survival.[6] Intrathecal cytarabine or methotrexate may be used to treat the meningitis associated with primary CNS lymphoma.[1]

Patients with Hodgkin's disease are more likely to present with B symptoms, at an advanced stage, with extranodal disease, and concomitant Epstein-Barr virus infection. Bone marrow involvement may be found in more than 50% of patients. Before HAART, patients with Hodgkin's disease and infected with HIV had a median survival of 1 to 2 years. Outcomes in the HAART era may be improving, although optimal treatment is undecided. Regimens that have been tried include the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and Stanford V regimens.[5]

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Burkitt's lymphoma. Burkitt's lymphoma is a small non-cleaved cell lymphoma (SNCL) of B-cell origin, which is highly aggressive and is seen particularly in children; the rare cases in adults are most often associated with immunodeficiency such as AIDS. There is an endemic form in equatorial Africa, which is associated with Epstein-Barr virus and often involves the jaws and other facial bones.

The main treatment for Burkitt's lymphoma is chemotherapy. Regimens are generally based on high-dose cyclophosphamide, in various combinations with high-dose methotrexate, high-dose cytarabine, vincristine, doxorubicin, etoposide, and prednisone or prednisolone. Ifosfamide may be substituted for cyclophosphamide.[1-3] Cytarabine and methotrexate are also given intrathecally for CNS prophylaxis.[1,4] Although some groups have used an initial phase of low-intensity chemotherapy to reduce the risk of tumour lysis syndrome,[1] others[3] have shown that shorter duration, dose-intensive chemotherapy has resulted in improved survival.

In children complete remission is common and prognosis good: probability of long-term disease-free survival is usually greater than 80%.[3] Prognosis has been less good in adults, but with the increasing use of more intensive regimens similar to those used in children, is improving. About half of all adult cases are reported to be curable with intensive chemotherapy regimens.[2,4] It is possible that intensive regimens coupled with haematopoietic stem cell transplantation or monoclonal antibodies such as rituximab may improve results further.[2]

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MALT lymphoma. Marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) occur most commonly in the stomach, but may also occur in the salivary gland, breast, thyroid, eye, or lung. They tend to be indolent and remain localised for long periods of time, but can transform to a more aggressive type.

Most gastric MALT lymphomas are associated with *Helicobacter pylori* infection.[1,2] The bacterium stimulates the formation of MALT in the stomach, which normally lacks organised lymphoid tissue, and there is evidence that it indirectly stimulates tumour growth. Eradication of *H. pylori* infection using antibacterial and antisecretory therapy, as described in Peptic Ulcer Disease, p.1702, has been shown to result in regression of gastric MALT lymphoma in a number of patients.[1-4] Increasing experience of the use of *H. pylori* eradication indicates that the lymphoma regression after eradication can take up to 14 months; eradication suppresses but does not necessarily eradicate the neoplastic clone; only lymphomas limited to the mucosa or submucosa regress after eradication; and that lymphoma can recur.[5] Thus, patients who are *H. pylori*-positive with early stage primary gastric MALT lymphomas may be treated solely with *H. pylori* eradication regimens and long-term endoscopic follow-up.[2,6] The best treatment for patients without *H. pylori* infection, those whose tumours do not respond to eradication, and those with more advanced tumour stage at presentation remains to be established. Surgery has been widely used, but radiation therapy is the treatment of choice for localised disease.[2,6] Rituximab monotherapy may be considered for early stage disease if radiation therapy is contra-indicated; single-agent or combination chemotherapy is recommended in advanced disease.[2]

It has been suggested that screening for and eradication of *H. pylori* is worth investigating as a means of preventing gastric cancer.[7]

Non-gastrointestinal low-grade MALT lymphomas have been treated with surgery or radiation therapy if localised, and with single-agent or combination chemotherapy (similar to that used for other low-grade non-Hodgkin's lymphomas—see above) if advanced.[2,6,8]

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Mantle cell lymphoma. Mantle cell lymphoma is a rare, aggressive lymphoma of B-cell origin. Patients are often elderly and more often male. Most patients present with advanced stage disease. Clinical features include fever, weight loss, drenching night sweats, and gastrointestinal symptoms.[1]

There is no established standard of care for mantle cell lymphoma.[2] For the few patients presenting with localised disease, radiotherapy significantly improves progression-free survival, and is recommended first-line, with or without chemotherapy.[1,2] Systemic combination chemotherapy, although non-curative, is recommended in advanced disease.[1,2] Rituximab plus chemotherapy is recommended first-line.[1-3] Chemotherapy options include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), HyperCVAD/MA (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).[1-3] An alternative first-line treatment in suitable patients is high-dose radiochemotherapy and autologous haematopoietic stem cell transplantation (HSCT).[1-3] Allogeneic HSCT may be curative, but only a few patients are suitable and it is associated with considerable morbidity and mortality; it may be considered in suitable patients with relapsed disease after first-line therapy.[1] For patients who cannot tolerate more intensive therapy, some recommend CHOP with or without rituximab[2] or anthracycline- or fludarabine-containing regimens.[1] Patients who relapse after initial therapy or with progressive disease may be treated with bendamustine (with or without rituximab), bortezomib, purine analogue-containing regimens (with or without rituximab), or thalidomide (alone or with rituximab).[1-3] Radioimmunotherapy, with radiolabelled monoclonal antibodies ibritumomab and tositumomab, has also been investigated for relapsed or refractory disease.[1,3]

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Mycosis fungoides. Mycosis fungoides is the most common of the cutaneous T-cell lymphomas. It is considered to have 3 stages: a premycotic erythematous or patch phase, characterised by a pruritic rash resembling psoriasis, which may persist for years or even decades; an infiltrative or plaque phase, in which some patches become thickened, darker plaques with marked T-cell infiltration; and a tumour phase where lesions enlarge and ulcerate. Ultimately there may be visceral involvement or potentially fatal sepsis secondary to skin breakdown. A variant of mycosis fungoides presents as widespread pruritic erythroderma, accompanied by abnormal T-cells in the blood, and is known as the Sézary syndrome.

There are many therapeutic options for mycosis fungoides, but few have been evaluated in controlled trials. Treatment depends on disease stage and spread.[1-7] Patients with limited and slowly progressive *patch phase disease* have a good prognosis (median survival similar to age-matched controls) and may be managed with topical and local therapies. Topical therapies include emollients, corticosteroids, chlormethine, carmustine, or bexarotene. Phototherapy, using UV B light, or a psoralen plus UV A light

(PUVA), is a useful alternative when topical treatments are ineffective or not tolerated. Mycosis fungoides is very radiosensitive, and for clearly localised patches, or isolated patches that have failed to respond to other treatments, local x-ray or electron beam radiotherapy may be used.

The initial therapy for patients with widespread *patch/plaque phase disease* is also topical, using chlormethine or PUVA. Topical retinoids are not recommended for generalised skin involvement, as they can cause irritation.[7] Patients who fail to respond to a single drug may be treated with combinations such as chlormethine with either PUVA or electron beam therapy,[1] or PUVA with interferon alfa.[1,4] Total skin electron beam therapy may be used, but it may not be widely available and is usually only given once; it is generally used for thickened plaques or for disease that has not responded to other local therapies.

In the *tumour phase*, combination therapy as described above is often used initially. Alternatively, systemic retinoids (such as bexarotene, isotretinoin, or tretinoin), interferons, vorinostat, denileukin diftitox, or low-dose methotrexate may be tried.[7] Systemic chemotherapy may be used for palliation in recalcitrant disease and advanced disease with extracutaneous involvement, but responses are often of short duration. Options include single-agent liposomal doxorubicin, gemcitabine, chlorambucil, pentostatin, etoposide, cyclophosphamide, and temozolomide.[7] Combination regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (CHOP without doxorubicin), or CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide).[1]

Mycosis fungoides with erythrodermic features is treated similarly except that skin irradiation tends to be avoided or used in very low doses as it causes severe desquamation.[1] Extracorporeal photopheresis may be useful for disease with erythrodermic features.[1,4,6,7]

Therapies for *persistent or recurrent* mycosis fungoides include denileukin diftitox, bexarotene, and vorinostat.[2,3,5,6,8-11] Allogeneic haematopoietic stem cell transplant may be considered for patients with advanced disease that is progressive or refractory to multiple treatment options.[7]

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Waldenström's macroglobulinaemia. Waldenström's macroglobulinaemia (primary macroglobulinaemia) is a clinical syndrome associated with lymphoplasmacytic lymphoma in which the abnormal lymphocytes secrete a monoclonal serum paraprotein of immunoglobulin M type resulting in increased plasma viscosity. Patients are mainly elderly, and more often male. Although often asymptomatic, patients can present with weakness and fatigue, anaemia, hepatosplenomegaly, and lymphadenopathy. Some develop the hyperviscosity syndrome (characterised by oronasal bleeding, visual disturbances and retinal haemorrhage, neurological disturbances such as headache, vertigo, peripheral neuropathy, and hearing loss, and, rarely, heart failure).

Asymptomatic patients require no treatment and may remain stable for some years. Where treatment is required, it has usually been with alkylating agents such as chlorambucil (with or without prednisone, or prednisolone) or, more recently, with cladribine or fludarabine.[1-8] Single-agent oral cyclophosphamide has also been used.[3,8,9] Rituximab is also recommended by some as a reasonable first choice, although patients should be closely monitored for symptoms of hyperviscosity;[5-8,10] plasmapheresis may be performed to reduce plasma viscosity.[3,4,6-10] Data on the use of rituximab are limited, and others consider its role has yet to be defined.[4,9]

When disease stabilises, treatment may be stopped and begun again on relapse, with either the same drug, or an alternative first-line agent.[3,10] Autologous haematopoietic stem cell transplantation (HSCT) may be considered for relapsed disease, although studies are limited and complete response rare;[3,4,8] it is recommended that exposure to alkylating agents or nucleoside analogues be limited if HSCT is considered.[5,6,9,10] Although there are few studies, combination chemotherapy does not appear to produce better responses than single-agent chlorambucil;[1,2,4] combination therapy with newer drugs remains investigational.[9,10] However, cyclophosphamide-containing regimens[10] are recommended in relapsed or refractory disease, if the re-use of a first-line drug is not feasible.

High-dose corticosteroids may be used to treat systemic vasculitis arising from deposition of paraproteins.[9,10] Splenectomy, although rarely indicated, may be used to manage painful splenomegaly and hypersplenic syndromes.[4,9,10] Small studies have reported benefit with thalidomide (with or without dexamethasone and/or clarithromycin),[3-6,8-10] high-dose dexamethasone,[10] or interferon alfa.[3,5,9,10]

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PLASMA CELL NEOPLASMS. *Multiple myeloma.* Multiple myeloma (myelomatosis) is a lymphoproliferative disorder of B-cell origin, involving the development of an abnormal plasma-cell precursor. It occurs mainly in the elderly, and accounts for only 1% or less of all malignancies. It is more common in black than in white patients and in men than in women.

The proliferation of the abnormal clone tends to suppress normal haematopoiesis, resulting in anaemia and immunosuppression, with an increased risk of serious infection. Perhaps the most characteristic complication, however, is skeletal destruction, apparently due to release of an osteoclast stimulating factor, resulting in osteoporosis, lytic lesions and fractures, and bone pain, as well as consequent hypercalcaemia. In addition, the plasma cells release large quantities of monoclonal immunoglobulins, known as paraproteins, which can produce a hyperviscosity syndrome and in some cases may interfere with platelet function. Renal failure of various causes and neurological problems due to compression are also common.

Multiple myeloma is not curable with presently-available treatment, and **therapy** is concerned with prolongation of survival and alleviation of symptoms.[1-3] Those patients with stable, indolent or smouldering myeloma, or benign monoclonal gammopathy, are followed carefully but not treated until overt progressive disease occurs. Early treatment may inhibit disease progression, but overall survival and response rates are not affected.[4]

In patients with overt disease some form of haematopoietic stem cell **transplantation** (HSCT) may now be the treatment of choice.[5,6] If a syngeneic transplant (from an identical twin) is unavailable, high-dose chemotherapy combined with autologous peripheral blood stem cell (PBSC) transplantation improves response rate, event-free survival, and overall survival compared with standard chemotherapy. Evidence for these benefits is strongest for patients younger than 55 years old.[7] Although some[8] consider standard-dose chemotherapy to be the preferred initial treatment in patients older than 70 years, other reviews[5,6] have concluded that autologous PBSC transplantation is safe for the majority of patients older than 65 years, and guidelines have suggested its consideration in this group[3] if they have good functional status and limited co-morbidity. With tandem transplantation, patients receive a second planned autologous HSCT,[9] since it was shown that patients who did not enter remission after one transplant could achieve remission after another.[10] Some recommend tandem transplants in those who do not have at least a very good partial response after the first,[11] and as such, some centres routinely collect enough stem cells for two transplants.[9,12] Allogeneic HSCT has been used for multiple myeloma, sometimes after autologous HSCT, but few patients are suitable, and transplant-related morbidity and mortality are high with conventional myeloablative chemotherapy regimens; non-myeloablative regimens (miniallogeneic HSCT) are under investigation.[9-12]

Patients may be treated with vincristine, doxorubicin, and dexamethasone (VAD) for 3 to 4 months before transplantation,[11,12] although dexamethasone alone, or with thalidomide, has become a standard induction therapy.[2,9] Liposomal doxorubicin has been substituted for standard doxorubicin in the VAD regimen.[2] Some recommend lenalidomide with dexamethasone as standard induction therapy,[11] and other options include bortezomib-based regimens.[2,9,11] Oral induction with cyclophosphamide, idarubicin, and dexamethasone has also been tried.[13] Peripheral stem cells are collected after giving high-dose cyclophosphamide and granulocyte colony-stimulating factor.[5,8] Although some suggest the use of alkylating agents and interferon alfa after stem cell collection,[8] earlier alkylator therapy interferes with stem cell mobilisation,[2,9,11,12] and can result in poor engraftment.[6,7] The standard conditioning regimen before transplantation is considered to be high-dose melphalan.[3,5,6,8,9,12] Total body irradiation is no longer recommended, as combined with lower dose melphalan, it resulted in higher toxicity and no significant survival benefit compared with high-dose melphalan alone.[5-7] Similarly, stem cells are not purged of contaminating myeloma cells as a randomised study[14] showed no benefit.

Where transplantation is infeasible or inappropriate, **chemotherapy** may be given to induce remission and prolong survival. The standard first-line regimen has long been a combination of oral melphalan and corticosteroids, usually prednisolone or prednisone.[1,3,6,9,10,12] This MP regimen produces an objective response in about half of all patients, and prolongs median survival to between 2 and 3 years.[1,6] The contribution of corticosteroids to the regimen has been controversial although a trend towards increased survival was noted[5] compared with melphalan alone, and high-dose dexamethasone given alone has been reported to be effective in producing remissions.[6] Cyclophosphamide is active,[5] and has been substituted for melphalan.[1,3] The addition of thalidomide to melphalan and prednisone has led to better response rates and progression-free survival, and it is recommended as standard induction for elderly patients ineligible for HSCT; however, toxicity is higher than with the MP regimen.[11,15] More intensive first-line combination regimens have also been used, particularly in younger, fitter patients. Examples include the ABCM regimen (doxorubicin, carmustine, cyclophosphamide, and melphalan), alternating combinations of VMCP (vincristine, melphalan, cyclophosphamide, and prednisone) with VBAP (vincristine, carmustine, doxorubicin, and prednisone), the VAD regimen (vincristine, doxorubicin, and dexamethasone), and the M2 or VBMCP protocol (vincristine, carmustine, melphalan, cyclophosphamide, and prednisolone).[1,6] However, although response rates are higher, meta-analysis[16] has not shown these combination regimens to be more effective than melphalan and prednisone in terms of survival. The use of interferon alfa as induction therapy is controversial, although a systematic review[5] found it improved progression-free survival. The combination of thalidomide and dexamethasone has also shown promise for initial therapy in advanced disease, although toxicity may limit its use.[2]

Maintenance chemotherapy has not been shown convincingly to improve total duration of remissions or survival,[1] and although progression-free survival improved with interferon alfa treatment, overall survival benefit was considered to be minimal.[5] A study[17] found prednisone given on alternate days to be effective maintenance treatment in those patients responding to induction therapy. Some recommend no maintenance therapy for standard risk patients except within investigational studies; high-risk patients may be given thalidomide and prednisone as maintenance if not previously treated with thalidomide.[11] Thalidomide has also been used as maintenance after autologous HSCT,[2] and may be offered to patients not achieving a very good partial response after tandem HSCT.[15] Lenalidomide and bortezomib are under investigation as maintenance therapies.[2]

In patients who fail to respond to initial treatment, or who subsequently **relapse**, various regimens have been tried. A systematic review found no particular regimen to be more effective than another.[5] Salvage regimens for progressive disease include VAD with the addition of cyclophosphamide, EDAP (etoposide, dexamethasone, cytarabine, and cisplatin), and high-dose cyclophosphamide.[1,2] About 60 to 70% of patients who relapse more than 6 months after stopping first-line therapy will respond to re-use of the initial regimen.[1,9] Thalidomide, with or without dexamethasone, has been shown to be effective in refractory myeloma.[2,3,5,18] Good responses have been reported with bortezomib[2,3,19,20] in relapsed, refractory myeloma, and there is some suggestion of an additive response with dexamethasone. Bortezomib is also used with liposomal doxorubicin, as is lenalidomide, with or without dexamethasone.[2]

Although chemotherapy aimed at the myelomatous clone will produce symptomatic relief as disease is brought under control, **supportive and symptomatic care** is also important. Bisphosphonates such as clodronate, pamidronate, and zoledronate have been found to be effective in reducing skeletal complications,[21,22] and are recommended in those patients with bone disease.[2,3,23] Some recommend that bisphosphonate therapy be stopped after 2 years in patients with responsive or stable disease.[23,24] Radiotherapy is used for impending fracture or impending spinal cord compression, and is often effective in relieving uncontrolled bone pain.[2,6] Erythropoietin therapy can improve anaemia and reduce the need for transfusion.[1,2,5,6,8] A high fluid intake is essential in patients with renal dysfunction or hypercalcaemia (for the appropriate management of the latter, see p.1668). Vigorous antibacterial treatment may be needed if infection occurs (see Infections in Immunocompromised Patients, p.174) and plasma exchange may alleviate the hyperviscosity syndrome.[2,8,9]

Drugs under investigation for the treatment of multiple myeloma include oblimersen, and arsenic trioxide.[12]

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Malignant effusions. The amount of interstitial fluid is normally regulated by a complex equilibrium between capillary filtration, osmotic pressure, and physical hydrostatic or hydraulic forces. Malignant neoplasms can disturb this equilibrium by obstruction of capillary or lymphatic drainage as well as causing active exudation of additional fluid after metastatic implantation. Malignant effusions are associated most often with lung, breast, and ovarian malignancies and lymphomas. Symptoms vary, and the fluid build-up may be asymptomatic; both pleural and pericardial effusions can produce cough, pleuritic chest pain, and dyspnoea and pericardial effusions may progress to cardiac tamponade. Peritoneal effusions may lead to malignant ascites. The main aim of treatment for malignant effusions is effective palliation of symptoms, and depends in part on the tumour type, patient performance status, and prognosis.[1-7] If the tumour is chemosensitive, systemic chemotherapy may resolve the effusion. Simple fluid drainage (thoracentesis or pericardiocentesis) will relieve symptoms until fluid build-up recurs, and in patients with very poor prognosis (life expectancy less than 1 month), may suffice for palliation.

In malignant ascites, paracentesis is usually effective temporarily; evidence for the value of diuretics is weak, but spironolactone may be of benefit in some patients, either alone or with a loop diuretic. In other patients with refractory tumours, fluid drainage followed by sclerotherapy is likely to be preferred. The principle involved is the instillation of an irritant agent into the pleural or pericardial cavity to promote inflammatory and fibrotic changes which result in the membranes adhering together and abolition of the space between the membranes in which fluid accumulates. When this is done to treat pleural effusions (pleurodesis) success of sclerotherapy is dependent on adequate fluid drainage beforehand and full re-expansion of the lung to bring the pleural surfaces together. Intrapleural thrombolytics such as streptokinase have been used to improve fluid drainage in cases of loculation of the effusion.[6,7]

Many drugs have been used for sclerotherapy, and the most common are a tetracycline (doxycycline or tetracycline), bleomycin, or talc. The choice between these three remains controversial, and opinions on the preferred option differ.[1,4-8] However, a systematic review[9] found talc to be the sclerosant of choice for malignant pleural effusions. Other sclerosants that have been used, with varying reported rates of success, include interferon alfa, mepacrine, mitoxantrone, picibanil, povidone-iodine, silver nitrate, *Corynebacterium parvum*, and *Staphylococcus aureus* superantigen.[8] Following drainage of the effusions the sclerosant is instilled in a small volume (20 to 50 mL) of liquid through the drainage tube. Talc may also be given as a powder insufflation (rather than slurry), but this involves a surgical procedure under general anaesthesia. Sclerotherapy results in painful inflammation, and local anaesthetics or analgesics should be given. For patients who fail sclerotherapy, or for whom this is not considered suitable, there are various surgical options to manage effusions.[1-7,10]

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Malignant neoplasms of the bladder. Cancer of the bladder is the fourth or fifth most common cancer in Europe and the USA, where over 90% of bladder cancers are transitional cell in type. About two-thirds of all cases occur in men, and the median age at diagnosis is 65 years. Known risk factors include smoking and exposure to aniline dyes. In countries where it is endemic, schistosomiasis is an important cause of squamous cell bladder cancer. Most patients present with haematuria; there may also be urinary frequency or dysuria.

Urothelial tumours fall into 3 major groups, non-invasive, invasive, and metastatic, which differ in prognosis and management.[1] About 70% of cases are non-muscle-invasive (superficial), 25% are muscle-invasive, and 5% are metastatic.[2]

Of the *non-muscle invasive* tumours, about 70% are low-grade transitional cell carcinomas confined to the mucosa (Ta), and have a low risk of progression to muscle invasive disease and a 50% chance of recurrence. Most of the remainder are higher-grade transitional cell carcinomas that have invaded the submucosa (T1), and a small percentage are high-grade carcinoma in situ (CIS). These high-grade tumours have a high risk of progression to muscle invasive disease, and a 50 to 90% chance of recurrence. The standard initial treatment for primary or recurrent superficial disease is surgery, in the form of transurethral resection. In an attempt to prolong remission and reduce the recurrence rate antineoplastics have been instilled into the bladder after complete resection (prophylactic or adjuvant intravesical therapy).[2] Effective agents include doxorubicin, epirubicin, mitomycin, and thiotepa. These increase the disease-free interval, but do not reduce the risk of progression to invasive disease, nor prolong survival.[3] Good results have also been reported with intravesical BCG,[2,4] and meta-analyses[5,6] have found it to produce lower recurrence rates than mitomycin. A single dose of intravesical chemotherapy may be given within 24 hours of resection in patients with primary resected low-grade tumours.[1] Adjuvant intravesical therapy with an antineoplastic (usually mitomycin) or BCG is recommended for patients with recurrent Ta tumours or primary higher grade T1, and BCG is generally preferred to antineoplastics in primary CIS.[1,7] Maintenance intravesical BCG therapy for CIS is recommended for those showing a complete response. Those with recurrent or persistent disease can be given a second course of BCG or mitomycin. If residual disease is still present, cystectomy should be considered; intravesical therapy with a different agent (mitomycin, valrubicin, interferon alfa, or BCG plus interferon alfa) is an alternative to cystectomy. Radical cystectomy is recommended if disease progresses.[1] Photodynamic therapy using porfimer sodium or 5-aminolevulinic acid has also been investigated.[8]

Management of *muscle-invasive* bladder cancer that has not yet metastasised is a matter of some controversy, but conventional therapy has revolved around radical surgery.[1,2] However, such conventional therapy offers a 5-year survival rate of only about 50%.[9] Alternatives include systemic chemotherapy before or after cystectomy,[1,7] or bladder-sparing options such as chemotherapy with radiotherapy.[1] The optimal regimen remains to be defined but regimens incorporating cisplatin and methotrexate, such as M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin), appear to be widely used. These can delay recurrence of disease, but evidence for improved survival has been conflicting. For example, a large study comparing neoadjuvant therapy using CMV (cisplatin, methotrexate, and vinblastine) before cystectomy or radiotherapy, found this regimen to result in a higher response rate, but not to significantly prolong survival.[10] Although another study[11] has reported that neoadjuvant M-VAC provides a survival benefit over cystectomy alone, the strength of these results has been questioned.[12,13] A meta-analysis[14] that included both these studies concluded that neoadjuvant platinum-based combination chemotherapy did improve survival. However, the benefit was only modest, and there was no evidence of benefit for single-agent platinum therapy.

Patients with unresectable or *metastatic* disease, or who subsequently develop metastatic disease, are usually treated with systemic chemotherapy or radiotherapy.[1] For patients with good prognosis, a combination regimen such as

M-VAC or CMV may be used. Various combinations of gemcitabine, taxanes, and cisplatin have shown clinical benefit,[1] and gemcitabine plus cisplatin has been shown to provide similar survival advantage to M-VAC with better tolerability: some now consider that it should be the preferred regimen in advanced disease.[1,9,15,16]

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Malignant neoplasms of the bone. Solid cancers often metastasise to the skeleton and metastatic bone disease is a common problem with cancers of the breast, prostate, and lung. Bone metastases are often responsible for cancer pain (the general management of which is discussed on p.5) and also result in immobility, bone fractures, bone-marrow failure, spinal cord compression, and hypercalcaemia.[1] The most common sites of metastasis are the spine, hip, and femur. Primary bone malignancies are rare, and are usually sarcomas. Multiple myeloma (see Plasma Cell Neoplasms, p.658) also produces bone involvement.

Management of **bone metastases** is essentially palliative since cure is rarely possible.[1,2] External beam radiotherapy is the best treatment for localised metastatic bone pain, with responses occurring in over 70% of patients. Radiation delivered by bone seeking isotopes such as samarium-153 or strontium-89 is an alternative.[3-6] Bisphosphonates are of benefit in patients with severe bone pain that is too widespread for local use of radiotherapy and does not respond to other analgesics.[2,7]

Structural weakness due to extensive bone loss may require structural support.[1,2] Surgical fixation or stabilisation can treat or prevent fractures. Surgical excision and reconstruction with methylmethacrylate bone cement may also be required.

Bone metastases cause local osteolysis and various inhibitors of bone resorption have been tried, not only to correct hypercalcaemia of malignancy (p.1083), but also to relieve bone pain and reduce the risk of fractures. Several randomised studies in patients with metastatic bone disease from breast cancer or multiple myeloma have shown 25 to 50% reductions in skeletal events with the use of the bisphosphonates, clodronate or pamidronate.[2,8] Similar results have also been reported for zoledronate.[9,10] Ibandronate is also used.[11,12] A systematic review[13] concluded that bisphosphonates significantly decrease skeletal morbidity, except for spinal cord compression. Various organisations have produced guidelines to suggest which patients are best treated with bisphosphonates.[2,14,15] The clearest evidence is in patients who already have lytic destruction of bone. Treatment should start when bone metastases are diagnosed and continue until no longer clinically relevant; they do not affect survival.[13] Benefits in terms of skeletal events are only seen after about 6 months of treatment.[12] There is much interest in the use of bisphosphonates to prevent the development of bone metastases. However, preliminary evidence of their efficacy is conflicting,[16] and further large controlled studies are considered warranted.[2,15]

Systemic antineoplastic therapy should also be given if the primary tumour is chemosensitive. Endocrine treatment is usually preferred for patients with breast and prostatic cancers, and can produce useful control of symptoms from bone metastases.[1,2] Patients who also have visceral metastases or who have hormone resistant tumours should probably be treated with cytotoxic antineoplastics.[2]

New drugs under investigation include denosumab and atrasentan.[11]

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Malignant neoplasms of the brain. Most primary brain malignancies are gliomas, such as astrocytoma and glioblastoma multiforme. The frequency and natural history of brain tumours differ between children and adults. Low-grade astrocytomas, and medulloblastomas are the commonest primary brain tumours in children and anaplastic astrocytomas and glioblastoma multiforme are the most common in adults. However, metastatic brain cancer is the most common cause of intracranial tumours in adults, being up to ten times more common than primary brain tumours. The cancers that most often metastasise to the brain are lung cancer, breast cancer, and melanoma. CNS involvement in patients with acute leukaemia (see Acute Lymphoblastic Leukaemia, p.651) or lymphoma (see Non-Hodgkin's Lymphomas, p.656) is also quite common.

The symptoms of primary and metastatic cranial neoplasms are those of local pressure and damage to the brain (such as focal seizures and visual field defects), of displacement of brain structures (like oculomotor paresis with tentorial herniation), and of raised intracranial pressure (such as impaired consciousness and papilloedema). The single most frequent symptom is headache, which is seen in about 60% of cases.

The mainstay of treatment for most primary brain tumours is surgery to relieve compression and cerebral oedema, establish diagnosis, and where feasible resect as much of the tumour as possible.[1-7] High-dose corticosteroids and computed tomography have reduced the morbidity of surgery, both for biopsy and excision. For benign tumours (such as pilocytic astrocytomas) resection may be curative; for malignant tumours (such as anaplastic astrocytomas, glioblastoma multiforme, and medulloblastomas) there is some evidence that extensive resection prolongs survival, but this may be biased by the selection of younger fitter patients for surgery. Adjuvant radiotherapy is widely used after surgical resection for malignant tumours in adults and children. Surgery alone or with radiotherapy is also used for single brain metastases.[8] For multiple brain metastases, most patients are treated with radiotherapy and corticosteroids. Radiosurgery is an investigational technique developed to reduce the radiation dose received by normal brain tissue. Radioactive implants (brachytherapy) are also being investigated.

The role of adjuvant chemotherapy for primary brain malignancies has been less certain, in part because of the difficulty in finding drugs that can cross the blood-brain barrier; until the advent of temozolomide, treatment was usually based on nitrosoureas such as carmustine and lomustine. The PCV regimen, in which procarbazine, lomustine, and vincristine are given, has often been preferred in the treatment of gliomas after surgical resection and radiation therapy.[2] The value of this regimen was called into question by a large randomised trial of adjuvant PCV plus radiotherapy versus radiotherapy alone in high-grade astrocytoma, in which PCV provided no additional survival benefit.[9] However, a meta-analysis including this and 11 smaller studies found that giving some form of adjuvant chemotherapy (usually based on nitrosoureas) modestly improved survival in adults with high-grade glioma.[10] Temozolomide, an oral alkylating agent, is also being used for the treatment of recurrent gliomas.[11] Its use during and after radiotherapy in newly diagnosed glioblastoma, usually after debulking surgery, has improved survival,[12] and it has increasingly replaced the nitrosoureas in the management of glioma.[7,13-15]

In young children chemotherapy may be used as a stopgap measure to delay, or reduce the frequency of, radiotherapy, which can cause neurodevelopmental damage.[1,3] Studies in children under 3 years of age given combination chemotherapy regimens (often including cyclophosphamide, vincristine, cisplatin or carboplatin, and etoposide or methotrexate), after surgical resection of tumour found that radiotherapy could be safely delayed in most and that a few children might never require it.[3] Adjuvant chemotherapy (for example, vincristine and lomustine with or without cisplatin) has also been used to allow a reduction in radiation therapy in children aged between 3 and 10 years.[3] This chemotherapy regimen has also been used in children with poor-risk medulloblastoma.

Since present regimens for primary brain tumours are far from optimal, alternatives continue to be tried.[7] Newer antineoplastics include bevacizumab and irinotecan.[7,13,15] Newer delivery techniques include implantation of biodegradable polymers impregnated with carmustine (which has been shown to improve survival in patients with malignant glioma),[7] and the transient disruption of the blood-brain barrier to allow cytotoxics to cross. Other treatments investigated include single or multitargeted kinase inhibitors, ligand-toxin conjugates, antisense oligonucleotides, and gene therapy.

Whole-brain radiation therapy is the common choice for most patients with brain metastases. Surgery may be suitable for those with a single brain metastasis, especially if prognosis is favourable and systemic disease controlled.[16]

The value of chemotherapy in cerebral metastatic disease remains to be defined:[8,17] the primary tumour may be intrinsically resistant to chemotherapy, or metastasis may develop despite treatment of the primary tumour, which will encourage the selection of resistant species. Furthermore, although the blood-brain barrier may not be completely intact in these patients, allowing some passage of antineoplastics into the brain, drug delivery of the less lipid-soluble drugs to cerebral metastases may not be sufficient, or sufficiently consistent, to produce a response. Nonetheless cerebral metastases of some chemosensitive primary tumours may respond to therapy. Temozolomide with or without radiotherapy is under investigation, as are other agents such as topotecan, paclitaxel, gefitinib, and radiosensitisers.[16]

A brain cancer vaccine (DCVax®-Brain) is also being investigated.

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Malignant neoplasms of the breast. Cancer of the breast is the most common malignant neoplasm in women. The disease is rare under the age of 25, and increases in incidence with age, although the rate of increase slows after the menopause. Risk factors include a family history (women with inherited BRCA1 or BRCA2 mutations are at higher risk), and reproductive hormonal factors such as early menarche, late menopause, nulliparity, and older age at birth of first child. Oral contraceptives and postmenopausal HRT are also associated with a small excess risk (see Carcinogenicity, Breast, on p.2059 and p.2071 respectively).

Ductal carcinoma in situ (DCIS) is a tumour localised to the breast ducts with no evidence of invasion. Invasive breast cancer can be divided into three main groups:

- early breast cancer (operable, primary, stage I/II)
- locally advanced disease (inoperable local, stage III)
- advanced disease (metastatic; stage IV)

Breast cancer is an extremely heterogeneous disorder, and the clinical course is consequently very variable; such factors as patient age and menopausal status, tumour size and grade, involvement of axillary lymph nodes or skin, and presence of hormone receptors within the tumour may be a guide to the extent and aggressiveness of disease, and hence have prognostic significance for treatment.[1-3] Early testing for overexpression of HER2 (human epidermal growth factor receptor-2) is increasingly important, since it is of value in determining response to certain treatments.[3]

Up to 20% of all cancers of the breast detected by mammographic screening are **ductal carcinoma in situ** (DCIS),[4-7] the management of which still has some areas of controversy. Most patients with DCIS will be offered breast-conserving surgery,[3,6,8] although mastectomy, which was historically preferred, is still the treatment of choice in high-risk patients.[3-7] Radiotherapy is usually recommended after successful breast-conserving surgery,[3,6,8] as it reduces the rate of recurrence and the risk of developing invasive disease (although it does not affect survival); there may be a subgroup of women in whom it is unnecessary, but there is controversy as to how to define the group. In the USA the use of adjuvant tamoxifen is also suggested,[3-5] but studies have produced conflicting reports of benefit on recurrence,[5,7] and again, there is no proven effect on survival; French guidelines suggest that the use of adjuvant hormonal therapy be confined to clinical trials.[6] Adjuvant use of newer oestrogen modulators such as anastrozole is also under investigation.[5,7]

In patients with **early disease** (stage I or II; a relatively small tumour with no or limited nodal involvement) the prognosis is fairly good. Primary treatment is surgical.[1,3,9] Breast-conserving surgery followed by postoperative radiotherapy has been shown to have equivalent local recurrence rates and 10-year survival (about 60%) to mastectomy.[10] The use of postoperative radiotherapy after breast-conserving surgery reduces local recurrence rates, but does not appear to affect overall survival.[10,11] Radiotherapy is not usually used after mastectomy, but there are some studies indicating that it may have additional benefits in patients at high risk of recurrence.[12,13]

Further adjuvant therapy with cytotoxic chemotherapy or hormonal manipulations such as tamoxifen and ovarian ablation by surgery, radiotherapy, or gonadorelin analogues has been given to try to eradicate the micrometastases which cause relapses. Overviews of a large number of trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have confirmed the benefits of adjuvant therapy and attempted to determine which women derive most benefit and which regimens are most effective.[14-18] Analyses from these[18] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials[19] permitting up to 15 years of follow-up have shown that:

- all women with early-stage breast cancer benefit from adjuvant therapy (although the size of the benefit varies)
- the benefit continues to increase with time, suggesting that adjuvant therapy is curative in a proportion of women who would otherwise relapse
- about 6 months of anthracycline-based chemotherapy reduces the annual death rate due to breast cancer by about 38% in women under 50 years of age at diagnosis, and about 20% in those aged 50 to 69 at diagnosis (too few women over 70 were given chemotherapy to estimate benefit in this group)
- this survival advantage occurs largely independent of oestrogen receptor (ER) status, nodal status, or other tumour characteristics
- adjuvant regimens including an anthracycline are more effective than those without a drug of this class
- in women with ER-positive disease, about 5 years of treatment with adjuvant tamoxifen reduces the annual death rate due to breast cancer by around 31%, largely independent of age, other tumour characteristics, or the use of chemotherapy
- combined chemotherapy and tamoxifen therefore increases the survival benefit further: for middle-aged women with ER-positive disease the breast-cancer mortality rate over 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen
- ovarian ablation (by surgery or irradiation) or ovarian suppression with a gonadorelin analogue also appear to reduce the mortality due to breast cancer, but that the advantage only applies where other adjuvant therapies are not given

Although these data help in making therapeutic decisions, the size of the benefit will always be less in patients with good prognosis; in the most favourable cases (small tumours with no involved nodes) the incremental benefit may be too small to warrant adjuvant treatment.[3] Tailoring systemic adjuvant therapy to the patient is important, and age and clinical characteristics alone are not adequate grounds to make the judgement: appropriate prognostic markers should be considered.[19,20]

The large analyses have led to the widespread adoption of anthracycline-based regimens for adjuvant *chemotherapy*, replacing earlier historical regimens such as CMF (cyclophosphamide, methotrexate, and fluorouracil) with those such as FAC or CAF (cyclophosphamide, doxorubicin, fluorouracil), AC (doxorubicin plus cyclophosphamide), and their many variants. However, they do not take account of more recent developments in molecular profiling of the tumour, nor of newer drugs that have become available for adjuvant therapy.

The EBCTCG analysis could not show any difference in effectiveness between anthracycline regimens,[18] but regimens based on epirubicin have gained in popularity in many centres, since its lower cardiotoxicity compared with doxorubicin means that higher doses can be given. Addition of a taxane (docetaxel or paclitaxel) to an anthracycline-based regimen appears to improve disease-free and overall survival.[21,22] There is evidence that HER2-receptor status is prognostic for response to anthracycline-based regimens.[3] There is also increasing interest in the early use of trastuzumab in women with HER2-overexpressing tumours. Studies of adjuvant trastuzumab have shown significant improvements in disease-free survival and overall survival,[3,23-26] although there are concerns about cardiotoxicity.[27] The benefits of trastuzumab are independent of ER status.[3]

Reducing dose intensity of chemotherapy results in poorer survival, and this has led to the hypothesis that higher doses may offer more benefit, particularly in patients at high risk of recurrence. However, despite some positive reports of high-dose chemotherapy with stem-cell support, randomised studies have largely failed to show any benefit of high-dose over standard-dose therapy.[28,29]

The results of the analyses above established 5 years of tamoxifen as the standard of care for adjuvant *hormonal therapy* in ER-positive disease (it is now accepted that it should not be given to women with ER-negative tumours,[1,3,9] in whom it is of little value). However, some guidelines now suggest that aromatase inhibitors should be substituted for, or added to, tamoxifen, in postmenopausal women with ER-positive disease,[3,30] an area that is still being intensively studied.[31] There is evidence that 5 years of anastrozole is an effective alternative to tamoxifen,[31,32] and 2 years of treatment with letrozole was found to further reduce the risk of recurrence compared with tamoxifen.[33] Two to 3 years of tamoxifen followed by an aromatase inhibitor (anastrozole, exemestane, or letrozole) has also been investigated and appears promising.[31,34-36] In addition, although extending tamoxifen beyond 5 years is not advocated, there may be significant benefits to following a full course of tamoxifen with extended therapy with an aromatase inhibitor;[31] the optimum length of such therapy has yet to be determined. US guidelines allow for 5 years of letrozole after a full course of tamoxifen.[3] The relative efficacy of the different aromatase inhibitors available (and whether steroidal and nonsteroidal inhibitors vary in their effects and could beneficially be combined) is also under investigation.[31]

Aromatase inhibitors are not effective for hormonal therapy in premenopausal women with ER-positive disease,[3] although combination of ovarian suppression with a gonadorelin analogue (or ovarian ablation by surgery or irradiation) and aromatase inhibitor therapy is being studied.[37]

The optimum sequencing of surgery, radiotherapy, and chemotherapy/hormonal therapy continues to be investigated. Concurrent chemo- and radiotherapy is not feasible with current regimens because of toxicity; on the basis of limited data,[38,39] radiotherapy given after chemotherapy is preferred,[3] as it appears to be more effective. Whether tamoxifen should be given concurrently or sequentially with radiotherapy remains unclear, despite several studies addressing the question.[39] Where both chemotherapy and hormonal therapy are given, it is recommended that chemotherapy should precede hormonal therapy.[3] The use of neoadjuvant chemotherapy before surgery in locally advanced disease (see below) has led to its investigation in early disease. While studies have shown its use allows an increase in breast-conserving surgery, there is no clear evidence of an improvement in disease-free or overall survival.[40]

In **locally advanced** breast cancer (stage III) the few patients for whom initial surgery is feasible may be treated as those with high-risk early breast cancer (see above). However, most patients begin with anthracycline-based neoadjuvant chemotherapy, which usually results in sufficient tumour shrinkage to allow surgical management, as well as allowing assessment of the responsiveness of the tumour to subsequent treatment.[3,8] Radiotherapy and adjuvant chemotherapy are used after surgery, and tamoxifen is also added if the disease is oestrogen-receptor positive.[3]

The aims of therapy in **advanced disease** (stage IV) are palliation and prolongation of life; cure is generally not possible with current regimens,[1,3] and it is often appropriate to select therapy on the basis of its adverse effects, to achieve optimal risk/benefit ratios.[41] In women with ER-positive, limited, or asymptomatic disease, *hormonal therapy* is preferred: US guidelines advocate an aromatase inhibitor (anastrozole, letrozole, or exemestane), or an antioestrogen (usually tamoxifen) for first-line hormonal therapy in postmenopausal patients; second-line therapy options include fulvestrant, toremifene, progestogens such as megestrol, androgens such as fluoxymesterone, or oestrogens such as ethinylestradiol.[3,36] Premenopausal women should undergo ovarian ablation (by surgery or irradiation) or suppression with a gonadorelin analogue, and then be treated as for postmenopausal women. Initial hormonal therapy is continued until disease progression or unacceptable adverse effects occur at which point up to 2 further hormonal regimens may be tried. If these fail, or symptomatic visceral disease develops, the patient is a candidate for chemotherapy.

A number of drugs have some activity in *chemotherapy* of metastatic breast cancer. The taxanes, and in particular docetaxel (which is considered the reference drug in metastatic breast cancer[42]) are acknowledged to be effective,[43] and anthracyclines (doxorubicin, epirubicin, and the related drug mitoxantrone) are also widely used, although a systematic review suggested that their benefits in terms of tumour response did not extend to improved survival.[44] The benefits of platinum-based therapy have not been established.[45] Capecitabine, gemcitabine, and vinorelbine are active agents.[3]

There is considerable uncertainty as to whether combination regimens offer any substantial benefit over sequential use of single drugs.[3,42,46] Although a systematic review of older regimens suggested benefit from combination chemotherapy,[46] and this is the usual standard of care where therapy has curative intent,[42] some do not consider the evidence of benefit from combination therapy persuasive,[3] and toxicity is likely to be increased. Nonetheless, established combination regimens, including CMF and various anthracycline- and taxane-based regimens are in use,[3,8] along with newer combinations, such as gemcitabine plus paclitaxel, vinorelbine plus epirubicin, or paclitaxel plus bevacizumab.[3] Ixabepilone with or without capecitabine, is another option.[3,47] In patients with HER2-overexpressing tumours, trastuzumab may be added to chemotherapy:[3] the combination is markedly more effective in this group than chemotherapy alone,[42] although use with anthracyclines may be problematic because of the increased risk of cardiotoxicity.[3]

Higher response rates have been achieved by intensive regimens, combined with autologous bone marrow transplants or stem cells in some studies. However, the results of randomised trials have been disappointing, and a systematic review found no improvement in overall survival with the use of stem-cell supported high-dose therapy in metastatic breast cancer.[48]

The use of bisphosphonates in women with bone metastases reduces bone pain and skeletal complications such as fracture, spinal cord compression, and hypercalcaemia (see Malignant Neoplasms of the Bone, above). Radiotherapy is also used for bone pain, and for the treatment of brain metastases (see Malignant Neoplasms of the Brain, above).

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PROPHYLAXIS OF BREAST CANCER. The recognition of factors increasing the risk of breast cancer, and particularly the identification of specific genes that confer a high risk, has spurred the search for effective ways of preventing the disease. Current options, other than regular screening to detect the cancer at early stages, include surgery (prophylactic mastectomy and/or oophorectomy), drug therapy (below), and possibly some life-style modifications.[1-3]

Treatment with tamoxifen as part of the adjuvant management of early breast cancer is associated with a reduced risk of developing cancer in the other breast (see above). This led to the suggestion that prophylactic tamoxifen might prevent the development of breast cancer in women at risk, and to trials to test this hypothesis. These studies were not without controversy, since the risk/benefit for tamoxifen use in healthy women differed from that in women with breast cancer. The first study to be reported was the US National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study,[4] which randomised 13 388 women to 5 years of treatment with tamoxifen or placebo. Participants were either aged 60 years or older, had a history of lobular carcinoma in situ, or had a 5-year predicted risk of developing breast cancer of greater than 1.66% (as assessed by number of first-degree relatives with breast cancer, number of previous breast biopsies, presence of atypical hyperplasia, and reproductive factors). In this study there was a highly significant 49% reduction in the occurrence of invasive breast cancer in women given tamoxifen (21.4 cancers prevented per 1000 women treated). The incidence of non-invasive breast cancer was reduced to a similar extent. Tamoxifen reduced the incidence of oestrogen-receptor positive, but not oestrogen-receptor negative, tumours. Adverse effects of tamoxifen included a modest increase in the risk of endometrial cancer and vascular events (stroke and pulmonary embolism). Although this study was prematurely unblinded, and all women were offered a 5-year course of tamoxifen, follow-up continued for 7 years and the incidence of breast cancer remained relatively constant for the 2 years after tamoxifen therapy was stopped.[5] Preliminary results from 2 smaller randomised European studies did not confirm the benefit of tamoxifen in breast cancer prevention. The Italian study[6] was in hysterectomised women with no particular risk for breast cancer, and because of its size may not have been sufficiently powered to detect an effect of tamoxifen. The full follow-up[7] of 5 years of treatment in this study found no difference in breast cancer incidence between tamoxifen and placebo groups. A subgroup analysis of women at high risk of oestrogen-receptor positive breast cancer did find a protective effect from tamoxifen, and there was an apparent protective effect for women in this group who used HRT. However, this group was not identified at randomisation of the study and these results need to be confirmed. The British study[8] of 8 years of tamoxifen or placebo was in women with a first-degree family history of breast cancer, and their median age was younger than in the US study. Although preliminary results showed no benefit from tamoxifen, follow-up for a median of about 13 years did find a reduction in the risk of oestrogen-receptor positive tumours.[9] This reduced risk also appeared to improve with longer follow-up. Initial results of a further placebo-controlled study (IBIS-I)[10] of women at increased risk of breast cancer found that during 5 years of tamoxifen use, the risk of all breast cancers was reduced by 32%. As in other studies, the reduction occurred in oestrogen-receptor positive tumours. Similar adverse effects were found with tamoxifen use, but there was also an unexpected increase in deaths from all causes in tamoxifen users. This may be associated with the excess in thromboembolic events reported, although statistical variability could not be ruled out. Extended follow-up[11] for a further median of 8 years found that the beneficial effect of tamoxifen was maintained, and that reduction in the risk of oestrogen-receptor positive tumours increased with longer follow-up. However, the rate of adverse effects of tamoxifen reduced after treatment stopped. A retrospective analysis[12] of the NSABP P-1 data for women who had developed invasive breast cancer found that in carriers of the oncogene BRCA2, but not BRCA1 carriers, there was a reduction in breast cancer similar to the reduction in oestrogen-receptor positive cancer among all women in the study. The numbers available, however, were too small to be statistically significant, and it is therefore still not known if tamoxifen can reduce the risk of breast cancer in patients with these mutations.

Another anti-oestrogen, raloxifene, has reportedly shown a reduction in breast cancer risk while its effects on osteoporosis were being studied.[13] A further large placebo-controlled study[14] that included the incidence of breast cancer as a primary outcome also found a reduction with about 5 years of raloxifene use. There was a 55% lower risk of invasive oestrogen-receptor positive cancer (absolute risk reduction of 1.2 cancers per 1000 women treated for 1 year), but there was no effect on oestrogen-receptor negative disease. The effect of raloxifene has also been directly compared with tamoxifen in women with a predicted increased risk of breast cancer.[15] After up to 5 years of use, the incidence of invasive disease was similar in both groups, suggesting that raloxifene is as effective as tamoxifen in reducing the risk of developing invasive breast cancer in this group of women. The aromatase inhibitors, anastrozole and exemestane, are also under investigation.[16]

From these studies, tamoxifen prophylaxis has been shown to reduce the incidence of oestrogen-receptor breast cancer in women at increased risk, but there are limited data for women with BRCA1 and 2 mutations. Although the follow-up studies to date suggest that a course of tamoxifen is not merely delaying the development of breast cancer during treatment, it is not known whether this is a life-long effect; it is also not known whether overall survival will be improved. Long-term follow-up of large placebo-controlled studies is needed to provide answers to these questions. Until then, it is likely there will be continued disagreement on whether tamoxifen should be used for primary prevention, and if so, in whom, and for how long. Nevertheless, the use of tamoxifen for 5 years has been recommended for women who meet specified criteria for increased risk.[2,17] Raloxifene has been proposed by some as an alternative for women who are postmenopausal,[2] but others[17] do not recommend its use for breast cancer prevention. Surgery is often considered for women at high risk associated with genetic factors such as BRCA1 and 2 mutations,[2,3] and women with a history of lobular carcinoma in situ or thoracic radiation.[2]

Other candidates for the prevention of breast cancer include plant oestrogens (phytoestrogens) such as those in soya. Epidemiological evidence suggests that diets high in these compounds may be protective, but there are many confounding factors and inconsistencies in the data available.[18] It was thought that retinoids might also be protective, but a secondary prevention trial of fenretinide failed to show any benefit.[19]

Epidemiological data suggests that life-style modifications have the potential to reduce breast cancer risk. These include weight loss, increase in exercise, and dietary factors.[1,2] They may be proposed as part of an approach to a healthy life-style, but their real value in reducing breast cancer risk is unproven.

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MALIGNANT NEOPLASMS OF THE MALE BREAST. Breast cancer can occur in men, although it has a much lower incidence than in women. Risk factors are not well understood, but it may sometimes be associated with abnormalities of sex hormone metabolism, including those acquired through liver disease or testicular trauma. In addition, the inherited mutation BRCA2, which is associated with an increased risk of breast cancer in women, also increases the risk of breast cancer in men. Breast cancer in men occurs at a slightly older median age than in women (60 to 70 years), and is more likely to be oestrogen-receptor positive. Survival by stage appears to be similar to that in women, with an overall 5-year survival about 40 to 65%.

Treatment is similar to that for women.[1-5] Primary management is mastectomy and axillary lymph node dissection. Because of the rarity of the disease large controlled trials are lacking but studies in limited numbers of men and extrapolation from results in women suggest that adjuvant therapy should be considered on the same basis as for women. Radiotherapy may be used to reduce the rate of local recurrence in those considered at high risk. Adjuvant tamoxifen or chemotherapy may also be used, with tamoxifen being the most common. Chemotherapy is probably more appropriate in those with oestrogen-receptor negative tumours, locally advanced disease, or positive nodes. Adjuvant trastuzumab should be considered for men with high-risk HER2-positive disease. In advanced metastatic disease tamoxifen is generally the first choice treatment although there is evidence of benefit from aromatase inhibitors such as anastrozole or letrozole. Combination chemotherapy is reserved for unresponsive or relapsing disease; regimens that have been used include cyclophosphamide, methotrexate, and fluorouracil (CMF), cyclophosphamide, doxorubicin, and fluorouracil (CAF), or doxorubicin and vincristine. Hormonal ablation by adrenalectomy or orchidectomy is also effective, but has become less popular since the advent of tamoxifen. Any role of trastuzumab or bevacizumab in men with metastatic breast cancer has yet to be established.

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Malignant neoplasms of the cervix. Cancer of the uterine cervix is one of the most common cancers in women, accounting for about 12% of all female malignancies. It is associated with vaginal intercourse and the presence of human papillomavirus (HPV); high-risk types of the virus (HPV-16 and 18) that produce proteins E6 and E7 inactivate host tumour suppressor proteins and thus encourage malignant transformation. Smoking and long-term use of oral contraceptives (p.2060) may also be risk factors. Widespread screening has meant that in many women the disease has been detected in the preinvasive or early stages, when the prognosis is excellent to good.

Preinvasive cervical lesions (cervical intraepithelial neoplasia; CIN) may resolve spontaneously if low-grade, and may be monitored by repeat screening.[1] High-grade CIN (cervical dysplasia) and cervical carcinoma in situ may progress to invasive carcinoma and are usually excised using diathermy or laser techniques. Conisation of the cervix (cone biopsy) may be used to rule out the presence of invasive disease. Investigational therapies include photodynamic therapy, and topical fluorouracil.

Invasive cervical cancers are mostly squamous cell in origin (80 to 90%), with 10 to 20% being adenocarcinoma. Invasive cervical cancers may be divided into early-stage (I and IIA), locally advanced (stages IIB to IVA), and metastatic (IVB). The earliest stage of invasive cervical cancer may be treated by conisation of the cervix (which maintains fertility) or simple hysterectomy.[1-3] Other early-stage cancers may be treated by surgery (radical hysterectomy) or by radiotherapy.[3] Some patients treated with surgery may require adjuvant radiotherapy. Early-stage patients with poor prognostic factors have better survival if both chemotherapy and radiotherapy are given after surgery (adjuvant chemoradiotherapy).[2,4] Most regimens include cisplatin alone or combined with fluorouracil.[3,5,6] Hydroxycarbamide has also been used by some centres, but is less effective than cisplatin.[5] Patients with locally advanced cervical cancer are usually treated with primary chemoradiotherapy using cisplatin-based regimens.[2,4-7] The evidence for chemotherapy is stronger for stage IIB than for stages III/IVA. Neoadjuvant chemotherapy has been tried and although there is some indication that its use before surgery might be of benefit, no survival advantage has been shown; it does not appear to be beneficial before radiotherapy.[8] For local recurrence of disease, treatment options include radiotherapy if it has not already been used, more extensive surgery, or cisplatin-based chemoradiotherapy.[2,3,9] Treatment for metastatic disease consists of palliative radiotherapy, chemotherapy, or chemoradiotherapy.[2] Cisplatin, carboplatin, paclitaxel, or topotecan may all be considered for first-line therapy; if cisplatin has previously been used as a radiosensitiser a combination regimen of cisplatin with paclitaxel, topotecan, or gemcitabine, or carboplatin with paclitaxel, may be favoured.[3] Drugs that have been tried for second-line treatment include docetaxel, epirubicin, fluorouracil, ifosfamide, irinotecan, mitomycin, and vinorelbine.[3,9] Combination chemotherapy has been investigated and many regimens have shown higher response rates and improvements in progression-free survival but not overall survival; however, cisplatin plus topotecan has shown an improvement in overall survival.[10] Scottish guidelines[7] recommend offering treatment with cisplatin plus topotecan (in cisplatin-naïve patients), or cisplatin plus paclitaxel, to all women with stage IVB or recurrent disease.

An HPV vaccine has been developed to prevent cervical cancer.[11]

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Malignant neoplasms of the endometrium. Cancer of the endometrium is a disease primarily of postmenopausal women, and is more common in developed than developing countries. Most of the risk factors for endometrial cancer are associated with increased oestrogen exposure. Factors resulting in increased endogenous exposure include obesity, anovulatory infertility, early menarche, and late menopause. Exogenous factors include use of oestrogens without progestogens for hormone replacement therapy (p.2072), and tamoxifen therapy (see Carcinogenicity, p.773). Postmenopausal vaginal bleeding is the most common sign of endometrial cancer, and allows the disease to be diagnosed at an early stage when the prognosis is good (80% of women have early stage disease at presentation). In menopausal or premenopausal women, diagnosis may be delayed because abnormal bleeding patterns may not be so obvious. Most endometrial cancers are adenocarcinomas. A small percentage are clear-cell or serous carcinomas, which are highly aggressive and have a poorer prognosis. Endometrial hyperplasia is generally regarded as a precancerous lesion; endometrial hyperplasia with cytological atypia, in particular, is associated with progression to adenocarcinoma.

Surgery is the primary therapy for endometrial cancers that are stage I to III;[1-5] oophorectomy is performed, as well as total abdominal hysterectomy, because of the significant incidence of ovarian metastases. No further treatment is required in women with stage I disease who are at low risk of recurrence. In those with stage I disease and a higher risk of recurrence, adjuvant brachytherapy or pelvic irradiation are used. In all other women, adjuvant radiotherapy is given, the field being tailored depending on the disease stage. Adjuvant progestogen therapy has not been shown to be effective.[6] There are a few studies of adjuvant chemotherapy in women at high risk of recurrence, but further data from randomised trials are required to assess its role.[7] For women with advanced disease (stage IV), systemic therapy with progestogens or cytotoxic chemotherapy can be considered, although response rates are only up to 30%,[1,3] and evidence for a survival benefit is questionable.[8] Progestogens are likely to be preferred because of their better tolerability. Tamoxifen also produces minor benefit; alternation with progestogens may prolong the response to hormonal therapy.[5] Well-differentiated tumours, long disease-free interval, and positive hormone receptor status are factors that suggest increased response to progestogens. When progestogens are ineffective, chemotherapy may be tried. The drugs of choice are probably doxorubicin, cisplatin or carboplatin, paclitaxel, and cyclophosphamide.[5,8,9] The combination of carboplatin and paclitaxel has become standard in many centres in the management of advanced or recurrent endometrial cancer.[5,9] Investigational therapies include dactinomycin, gonadorelin analogues such as goserelin, and anastrozole.[3]

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Malignant neoplasms of the eye. Tumours of the orbit of the eye in adults are most commonly metastases from primary lesions elsewhere in the body, usually in the breast or lung, and local radiotherapy (external beam radiation or plaque radiotherapy) may be required for control of visual symptoms unresponsive to chemotherapeutic treatment of primary disease.[1]

Primary eye tumours are rare. In children, the most common intra-ocular tumour is retinoblastoma (see below), and the most common orbital tumour is rhabdomyosarcoma (see Soft-tissue Sarcomas, below). In adults, primary CNS lymphoma can originate in the eye (ocular lymphoma), and is treated with radiotherapy to the globe. However, the most common primary ocular cancer in adults is **intra-ocular melanoma** (posterior uveal melanoma), which accounts for 80% of all primary ocular cancers. Treatment options for small ocular melanomas include observation or local treatment (radiation, brachytherapy, cryotherapy, local resection, photocoagulation, or hyperthermia).[2,3] Large melanomas are treated by removal of the eye (enucleation). Treatment of medium-sized tumours is controversial, with some preferring treatments that preserve vision, and some enucleation. At present there are no good data to support the use of adjuvant chemotherapy. In the few patients with metastatic uveal melanoma, resection and intra-arterial chemotherapy or chemoembolisation may be used for isolated hepatic metastases.[2] Most of the combination chemotherapy regimens for palliative therapy have included dacarbazine.[2]

Ocular surface neoplasms (lesions of the conjunctival or corneal epithelium) are usually treated with local excision. Where surgery is not feasible, topical application of mitomycin (0.04%) or fluorouracil (1%) has been tried.[4]

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Malignant neoplasms of the gastrointestinal tract. Considered as a whole (and excluding skin cancers, which are often poorly registered) the gastrointestinal tract is the most frequent site of malignancies worldwide, although the frequencies of the various types of gastrointestinal cancer vary greatly from country to country. Direct exposure to various environmental carcinogens is thought to play an important role in many of these cancers. Treatment may include surgery, radiotherapy, and chemotherapy, but the prognosis in most forms of gastrointestinal cancer is not encouraging.

Gastrointestinal cancers vary in their management depending on the site. Discussed in more detail below are:

- oesophageal cancer
- stomach cancer
- colorectal cancerand its prophylaxis
- anal cancer

Other cancers may sometimes manifest in the gastrointestinal tract, including the various endocrine neoplasms responsible for carcinoid syndrome (p.643), and MALT lymphomas (p.657).

MALIGNANT NEOPLASMS OF THE OESOPHAGUS. Oesophageal cancer has perhaps the greatest variation in incidence between different geographical regions of any cancer, and is endemic in many parts of the world. The two major histological types are squamous cell carcinoma and adenocarcinoma.[1-3] Squamous cell carcinoma is strongly associated with tobacco and alcohol use, and may occur as a second primary tumour in patients with tumours of the upper aerodigestive tract (see Malignant Neoplasms of the Head and Neck, below). Adenocarcinoma is more common in non-endemic regions, including many developed countries,[2] and is associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p.1696). Oesophageal cancer usually develops as a growth or ulcerative lesion of the oesophagus with extensive infiltration of the mucosa and invasion of neighbouring structures. Lymphatic and blood-borne metastasis occurs at a relatively early stage. Symptoms of pain and dysphagia due to obstruction occur late, and overall, more than half of all patients have unresectable or metastatic disease at initial presentation. Metastatic disease is associated with a median survival of less than 1 year.[1]

Patients with stages I to III disease may be offered either surgical resection or a combination of chemotherapy (with cisplatin and fluorouracil) and radiotherapy.[2-4] Surgical patients who are node-positive, or otherwise considered to be at higher risk, may be given postoperative chemotherapy with radiotherapy.[2] The 5-year survival rate varies with the stage of the disease at initial presentation, from about 50 to 80% in the few with stage I disease, to 10 to 15% in those with stage III disease.[1] In consequence, there has been great interest in adjuvant treatment (pre-operative or postoperative).[5]

There is no clear evidence that pre-operative radiotherapy alone improves survival.[1,3,6] However, there has been conflicting evidence on the value of chemoradiotherapy or chemotherapy used before surgery, with some trials showing improved survival, and others no additional benefit.[1,3] A systematic review[7] found that pre-operative chemoradiotherapy significantly improved the 3-year mortality rates compared with surgery alone, and a later meta-analysis[8] found a significant survival benefit for neoadjuvant chemoradiotherapy (versus surgery alone) in patients with oesophageal adenocarcinoma or squamous cell carcinoma. Pre-operative chemoradiotherapy has thus become a common approach for patients with resectable oesophageal cancer.[2,4] Meta-analysis[8] also suggested some survival benefit of neoadjuvant chemotherapy without radiotherapy in those with adenocarcinoma, but not for those with squamous cell carcinoma. A systematic review[9] found that pre-operative chemotherapy may offer a survival advantage compared with surgery alone, although the evidence was considered to be inconclusive. However, some do not recommend the use of chemotherapy, either pre- or post-operatively, as standard of care.[2]

In half to two-thirds of patients the disease is too advanced at presentation for anything but palliation. Those with poor performance status should be offered supportive care.[2] This may include brachytherapy, laser therapy, stent placement, or photodynamic therapy with photosensitisers such as porfimer sodium to relieve obstruction.[2] Brachytherapy may be a better primary therapy for obstruction than a stent.[10] In those patients with good performance status, chemotherapy may also offer some palliation of the disease. Standard options include cisplatin-based, fluoropyrimidine-based, irinotecan-based, oxaliplatin-based or taxane-based combinations.[2,5,11] Chemoradiotherapy may also be used.[5]

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MALIGNANT NEOPLASMS OF THE STOMACH. Cancer of the stomach is one of the most common cancers worldwide, with particularly high incidence in the Far East, Russia, and parts of Latin America, although the incidence is declining almost everywhere. (In contrast the incidence of cancers at the gastro-oesophageal junction appears to be increasing.[1]) Over 90% of malignant gastric neoplasms are adenocarcinomas. Less frequent gastric neoplasms include lymphomas (see MALT lymphoma, above) and carcinoid tumours (see above). Dietary factors, such as high consumption of salted or smoked foods, are thought to play a role in the development of gastric cancer. *Helicobacter pylori* infection, and resultant gastritis, plays a role in gastric lymphomas, and may also be a factor in gastric cancer. However, it is not yet clear if elimination of *Helicobacter pylori* infection will prove useful in preventing the development of gastric cancer.[2,3]

Early disease is relatively asymptomatic or produces nonspecific gastrointestinal symptoms such as dyspepsia. There is concern that the use of antisecretory drugs for these symptoms may delay the diagnosis of gastric cancer (see Gastric Carcinoma, under Omeprazole Precautions, p.1754). Gastric epithelial dysplasia is a premalignant condition, and warrants follow-up and possible surgical intervention. Similarly, persistent gastric ulcers may be malignant. More advanced disease, which is the norm at presentation in most western countries, may produce discomfort or pain, anaemia, weight loss, and anorexia; obstruction, haemorrhage, and perforation may develop. Extension to the liver and pancreas, and lymphatic and blood-borne (portal) metastases may occur.

Surgery is the mainstay of treatment for locoregional disease.[4,5] There is some uncertainty, however, about the appropriate extent of surgery and associated lymph-node dissection.[1,5,6] Typical 5-year survival rates in western patients have ranged from about 50 to 80% in those with stage I disease to 13% in those with stage III;[6,7] although much higher survival rates (over 96% in stage I disease and nearly 45% in stage III) have been reported in Japan,[6] Japanese and western patients may not be equivalent, a fact that has made comparisons difficult.

Because of the poorer survival rates in patients with more advanced locoregional disease, adjuvant treatments have been tried.[1,6,7] Postoperative radiotherapy has not been shown to produce a survival benefit, and the value of pre-operative radiotherapy is uncertain. However, there has been considerable interest in the possible value of pre- or postoperative chemotherapy or chemoradiotherapy.[1,6,7] Postoperative (adjuvant) chemotherapy has failed to show a significant survival benefit, except for results with tegafur (plus gimestat and potassium oxonate: S-1) in a Japanese population;[5,8] it has not become standard practice in western countries.[8] Perioperative chemotherapy with preoperative and postoperative cycles of epirubicin, cisplatin, and fluorouracil (ECF) has, however, improved progression-free and overall survival in patients with operable adenocarcinomas.[9] This strategy is recommended for centres with a multi-disciplinary approach.[5,8] A large US study[10] found that median survival was improved from 27 to 36 months in patients given postoperative chemoradiotherapy (using a fluorouracil and folinic acid regimen), and this strategy is recommended for centres where surgery is used as the primary therapy.[5,8] Chemoradiotherapy is also an option for primary treatment of inoperable locoregional disease.[5] Palliative chemotherapy with any of the regimens used for metastatic disease is also an option in these patients.[5]

Treatment for advanced disease is purely palliative, and options include supportive care with or without chemotherapy.[5] Supportive care includes the relief of luminal obstruction with, for example, stent placement, laser surgery, or photodynamic therapy. Chemotherapy may have substantial palliative effect and modest survival gains, and may be considered in those with good performance status. There is no gold standard regimen, although combination therapy is preferred to single-agent therapy for palliation.[5,11] A systematic review[12] found that combination regimens including fluorouracil, anthracyclines, and cisplatin produced significant survival benefits; ECF was considered the regimen of choice since it was best tolerated, and it is considered standard therapy in some countries.[11] Fluorouracil, doxorubicin, and mitomycin (FAM) has been widely used;[5] other combinations include the substitution of methotrexate for mitomycin, or cisplatin for doxorubicin, in the FAM regimen (FAMTX, and MFC, respectively),[5,11] and the use of docetaxel instead of epirubicin in ECF (DCF).[5] However, ECF has shown better response and median survival than FAMTX.[5,11] Investigational drugs include docetaxel, paclitaxel, gemcitabine, irinotecan, raltitrexed, and oral drugs such as capecitabine, etoposide, oxaliplatin, and rubitecan. Bevacizumab is also under investigation.[5,7,11]

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MALIGNANT NEOPLASMS OF THE COLON AND RECTUM. Colorectal cancers are very common in developed areas such as the USA and western Europe, but rare among African and Asian populations. Genetic and dietary factors are thought to be related to development of the disease.[1] Inherited predisposition syndromes include familial adenomatous polyposis and hereditary non-polyposis colorectal cancer.[2,3] Most large bowel cancers arise within pre-existing intestinal polyps. Over 50% occur in the rectum and about 20% in the sigmoid colon. There may be direct invasion of neighbouring structures and metastatic spread to the lymph nodes, and to lungs, bone, and in particular, liver. Signs and symptoms include blood in the stools, altered bowel habit, anaemia, and weight loss; there may be local obstruction (depending on location) or perforation.

The first-line treatment for **early-stage** and **locally-advanced** disease (stages I to III; Dukes A to C) is surgery.[4,5] Survival in early-stage disease is good: published 5-year overall survival rates are 80 to 95% in patients with stage I disease, but fall to 25 to 60% (depending on prognostic factors such as nodal involvement and degree of tumour invasiveness) in those with stage III disease.[2] Adjuvant or neoadjuvant therapies have thus been widely investigated and incorporated into treatment.[4,5]

US guidelines for *colon cancer*[4] consider adjuvant therapy unnecessary in stage I disease, but recommend adjuvant chemotherapy in most patients with resectable stage II or stage III disease.

There is good evidence that fluorouracil-based adjuvant therapy improves survival in stage III disease,[6-10] and it has been regarded as the standard of care.[2,9,11,12] Recent results with the FOLFOX regimen (infusional fluorouracil, folinic acid, and oxaliplatin) have suggested that it can improve disease-free (but not overall) survival in this group.[13] Oral fluoropyrimidines have also been shown to improve survival after resection;[14] guidelines suggest that intravenous fluorouracil plus folinic acid, FOLFOX, or oral capecitabine are all suitable adjuvant regimens.[4] Results with the IFL regimen, which adds irinotecan to bolus fluorouracil and folinic acid, have not proved satisfactory because of its toxicity,[2,10,12] and FOLFIRI (infusional fluorouracil with folinic acid and irinotecan) has not been shown to be superior to fluorouracil/folinic acid in the adjuvant setting.[4]

In contrast, the evidence in favour of adjuvant therapy in patients with stage II colon cancer is much weaker:[12,15] US guidelines recommend its consideration, particularly in patients with poor prognostic features and within the context of a clinical study,[4] but its routine use is not advised:[16] such therapy would not improve survival by more than 5%.

Neoadjuvant therapy and radiotherapy seem to play little role in the management of early colon cancer, and the latter is not generally recommended,[2] although it may be considered where there is tumour penetration of fixed structures.[4] In contrast, in the management of early stage *rectal cancer* they play an important role. Local recurrence is common with rectal cancer, and radiotherapy or chemoradiotherapy can help reduce this. US guidelines suggest that surgery alone may be considered in patients with stage I disease.[5] Traditionally, adjuvant chemoradiotherapy was considered the standard of care for patients with stage II or stage III rectal cancer, but more recently neoadjuvant (pre-operative) treatment has been advocated on the basis of better local tumour control and lower morbidity:[2] it decreases tumour volume and thus enhances sphincter preservation.[5] A meta-analysis[17] found that adjuvant radiotherapy reduced the risk of local recurrence; the risk of death from rectal cancer may have been reduced, particularly for pre-operative radiotherapy but there was little impact on overall survival. A subsequent large randomised study also found that pre-operative chemoradiotherapy (fluorouracil infusion plus fractionated pelvic radiotherapy) improved local control and was associated with less toxicity than postoperative treatment, but did not improve overall survival.[18]

US guidelines recommend pre-operative chemoradiotherapy with fluorouracil, alone or with folinic acid, as the chemotherapy component in most patients with stage II or III disease;[5] it is suggested that oral capecitabine may be a valid alternative to fluorouracil. After surgery, adjuvant chemotherapy with a fluorouracil regimen, FOLFOX, or capecitabine is recommended, although the latter 2 options are extrapolations from results in colon cancer; a combined chemoradiotherapy regimen may be used in some patients.

Palliative treatments for **advanced** colorectal cancer (stage IV; metastatic disease) include surgery, radiotherapy, and chemotherapy.[1,2,4,5,10,19,20] Metastasis usually occurs first to the liver: about 20 to 25% of patients have detectable liver metastases at initial diagnosis in the UK, and a further 40 to 50% develop metastases within 3 years of primary surgery. Somewhat under 10% of these cases are localised and resectable,[19] and surgery offers a chance of prolonged survival.[2,19] Systemic neoadjuvant chemotherapy can reduce tumour volume and render some previously unresectable metastases suitable candidates for surgery.[2,4] Another potential approach is the adjuvant use of intraportal chemotherapy directed at the liver. In a meta-analysis of 10 studies,[21] the reduction in hepatic metastases with intraportal vein chemotherapy given for about 1 week after surgery was not significant, although there was a trend towards increased 5-year survival. It was concluded that additional trial evidence was required.[21]

Conventional palliative chemotherapy is based on the use of fluorouracil, and has been shown to produce modest survival benefits.[22] Adding folinic acid improves the efficacy,[23] and the combination has long been regarded as standard. Although it has been suggested that regimens based on continuous infusion of fluorouracil are more effective than those using bolus dosage,[2,24] others consider that although response rates are improved, median survival is similar, and that differences in toxicity and convenience of administration are more significant in making the choice.[20] Oral fluorouracil prodrugs such as capecitabine, or tegafur with uracil, are considered a valid alternative to intravenous fluorouracil.[3,25,26]

Several newer drugs have now been shown to improve response rates and survival when used for chemotherapy in these patients. In particular, regimens including irinotecan or oxaliplatin, such as FOLFIRI or FOLFOX, are now considered options for first-line management of metastatic colorectal cancer.[3-5,11,27,28] There is also evidence for both improved response and survival when bevacizumab (an antagonist of vascular endothelial growth factor) is added to chemotherapy.[29-31] Similarly, cetuximab, a blocker of the epidermal growth factor receptor, appears to improve response rate and decrease the rate of progression if given with irinotecan,[32] and preliminary results suggest that it is effective when combined with a FOLFOX regimen.[28] US guidelines currently recommend combining bevacizumab with one of the first-line regimens—FOLFOX, FOLFIRI, a fluorouracil/folinic acid regimen, or Cape Ox (capecitabine plus oxaliplatin)—in patients with metastatic disease who are able to tolerate intensive therapy,[4,5] although the data to support some of these combinations are not yet available. An alternative regimen (without the bevacizumab), or cetuximab plus irinotecan, or monotherapy with a drug not included in the original regimen (such as irinotecan, cetuximab, or panitumumab), may be tried in those who fail to respond. Capecitabine, or fluorouracil/folinic acid with or without bevacizumab, are options in those unable to tolerate the more intensive regimens.[4,5,11]

Other drugs and regimens continue to be investigated. Immunological therapies under investigation include monoclonal antibodies, and vaccination with autologous tumour cells or against tumour-associated antigens; gene therapy is another area of research.[33]

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Prophylaxis of cancer of the colon and rectum. Various drugs and dietary factors have been shown in epidemiological studies to be associated with a reduced risk of colorectal cancer, and some of these have been investigated in prospective randomised trials.[1-3]

- Aspirin and NSAIDs are the most widely studied.[1-10] In short-term randomised trials, both sulindac and celecoxib have reduced the size and number of colonic polyps in patients with familial adenomatous polyposis.[4] However, prophylactic surgical removal of the colon is still considered the standard of care for these patients.[1,11] Furthermore, despite significant reductions in adenoma formation in high-risk patients, cyclo-oxygenase-2 (COX-2) inhibitors have also been associated with cardiovascular toxicity.[12] There is some evidence of a dose-response effect, since the greatest prophylactic effect of aspirin in average-risk populations appears to be associated with doses substantially greater than those required for prevention of cardiovascular disease.[5,6,8,13] The effect of aspirin may depend on COX-2 expression: it appears only to reduce the risk of colorectal cancers that overexpress COX-2.[14]
- Calcium supplementation has shown a moderate reduction in the formation of new adenomas in patients with a history of colorectal adenomas,[15] and is well tolerated, but the evidence is not strong enough to recommend general supplementation to prevent colorectal cancer.
- Despite the epidemiological evidence for dietary fibre, a number of large randomised studies of fibre supplements or high-fibre diets have not found any reduction in the formation of new adenomas in patients with a history of colorectal adenomas.[1,2,16]
- Antoxidant vitamins have also been investigated, but evidence for their benefit is conflicting (see Prophylaxis of Malignant Neoplasms, p.1927).
- Epidemiological evidence[17] suggests that long-term use of statins is associated with a marked reduction in the risk of colorectal cancer. Prospective studies are required to confirm these results. A meta-analysis[18] did not support this hypothesis, although a modest reduction in risk or an effect with higher doses of statins could not be ruled out.
- Other potential chemopreventive agents on the basis of epidemiological evidence include folic acid, selenium, and menopausal HRT.[1-3] For the suggestion that folate may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p.1940.

An important component of the care of patients with inherited predisposition or other risk factors for colon cancer is regular screening.[2,11,19] Various screening methods are also under investigation for use in normal risk individuals.[20,21]

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MALIGNANT NEOPLASMS OF THE ANUS. Cancers of the anal canal mucosa are most commonly squamous cell carcinomas. Risk factors include immunosuppression, genital human papillomavirus infection, and sexual activity. Combined chemotherapy and radiotherapy is the usual primary treatment.[1,2] Fluorouracil with mitomycin is often used, and the combination of fluorouracil and cisplatin is also used in locally advanced disease. For patients who do not respond, or who subsequently relapse, surgical resection with the formation of a colostomy is preferred, possibly with further fluorouracil and cisplatin therapy. There is no standard therapy for metastatic disease,[1] although platinum-based regimens may be preferable.[2]

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Malignant neoplasms of the head and neck. Cancers of the head and neck are classically defined as those of the mucosal surfaces of the upper aerodigestive tract and include neoplasms of the oral cavity (accounting for 40%), pharynx (15%), and larynx (25%). Most are squamous cell carcinomas, and the highest incidence is in men aged over 50 years. Overall, cancers of the head and neck account for about 5% of all malignant neoplasms in the West, but are the most common causes in other parts of the world. The major risk factor for these cancers is the use of tobacco (whether chewed, inhaled, or smoked). Alcohol acts synergistically with tobacco to increase the risk. Human papillomavirus infection appears to be a risk factor for some squamous cancers of the oropharynx. Endemic nasopharyngeal cancer in parts of India, China, and North Africa is associated with Epstein-Barr virus and the consumption of salt-cured fish.

Premalignant lesions include leucoplakia and erythroplakia, and these can progress to invasive cancer. About one-third of cancers are diagnosed at early stages (I and II), and the rest are usually locally advanced (stage III and IVA). Although early-stage disease can be successfully treated, there is a high incidence of second primary cancers in the head and neck, lung, or oesophagus. Therefore, there is interest in the development of chemopreventive drugs to reduce this risk. Fewer than 30% of patients with locally advanced disease are cured. The treatment of head and neck cancer is complex, and is affected by the site and extent of disease, pathological findings, lymph node involvement, the patient's functional status, and comorbidities; the experience and skill of the team carrying out surgery and radiotherapy will also influence treatment recommendations.[1]

In early-stage resectable cancers, such as those of the oral cavity and oropharynx, surgery or radiotherapy (external beam irradiation or brachytherapy) are the mainstays of treatment.[1,2] Postoperative chemoradiotherapy may be used when extracapsular nodal spread or positive margins are found.[1] For anatomically unresectable early-stage disease, such as in the nasopharynx, radiotherapy alone is generally used, but primary chemoradiotherapy should be considered for patients with adverse prognostic factors such as nodal spread.[1]

Locally advanced disease is usually treated with combination therapy. Resectable disease is managed with surgery and adjuvant radiotherapy.[1] The addition of chemotherapy has been studied in resectable disease, but induction chemotherapy (given before surgery and radiotherapy) has not been found to consistently improve survival rates.[3] Postoperative chemoradiotherapy has produced inconsistent results, and there is insufficient evidence that it has any advantage over adjuvant radiotherapy.[3] In unresectable locally advanced disease, and in resectable disease when the aim is to avoid the need for surgery and thereby allow organ preservation, chemotherapy with radiotherapy is generally used, and different regimens have been tried. Concurrent chemoradiotherapy, without surgery, has increased survival compared with radiotherapy alone,[3,4] and concurrent treatment appears to improve overall survival more than radiotherapy with either neoadjuvant or adjuvant chemotherapy.[5] Induction chemotherapy followed by concurrent chemoradiotherapy has also been studied; limited data suggest that it may reduce distant failure rates and improve survival.[3] Some therefore recommend concurrent chemoradiotherapy as the most effective treatment for cancers of the nasopharynx[1,6] and larynx.[1]

Palliative chemotherapy is used in metastatic or recurrent disease.[1,3,6] Salvage surgery or a repeat course of radiotherapy are other options, depending on previous treatment. Drugs used for single-agent treatment include cisplatin, carboplatin, paclitaxel, docetaxel, fluorouracil, methotrexate, ifosfamide, bleomycin, cetuximab, and gemcitabine (for nasopharyngeal cancer). Combination regimens such as cisplatin and fluorouracil are commonly used and produce more responses, but no clear improvement in survival. Other common combinations include cisplatin or carboplatin with a taxane, and cisplatin plus cetuximab. The choice of best supportive care or single-agent or combination chemotherapy should be dictated by the patient's performance status, as the benefits of chemotherapy are limited.[1]

A local injection of cisplatin in a gel formulation containing adrenaline has been investigated in recurrent and refractory head and neck cancer.[7] Photodynamic therapy (see under Porfimer Sodium, p.764) using temoporfin is a more recent development for palliative management. Head and neck cancers have high levels of p53 gene mutations, and gene therapy is under investigation.[8] Chemoprevention by treatment of pre-malignant disease is also under investigation (see Leucoplakia, p.688).

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Malignant neoplasms of the kidney. Cancer of the kidney is relatively uncommon. About 80% of such cancers in adults are renal cell carcinoma, with the remainder mostly cancer of the renal pelvis. The disease is about twice as common in men as in women. Risk factors include smoking, obesity, hypertension, and phenacetin use. Disease is often clinically silent; there may however be haematuria, flank and back pain, and a palpable mass in the flank or abdomen. About 45% of patients have early-stage disease at presentation (I and II), 25% have locally advanced disease (stage III), and 30% metastatic disease (stage IV). The most common sites for metastases are the lung, liver, and bone, although unusual sites for metastases are a known feature of renal cancer.

Radical nephrectomy is the main treatment for early-stage disease although partial nephrectomy may be considered in some patients.[1-4] Minimally invasive procedures such as radiofrequency ablation and cryotherapy are under investigation for treatment of small tumours.[4,5] Radical nephrectomy is also used in selected patients with stage III disease. After radical nephrectomy 20 to 30% of patients with localised tumours will relapse, usually at distant sites.[3] This suggests that adjuvant therapy could be useful in reducing the risk of relapse.[1] However, radiotherapy is not beneficial, and no systemic therapy has been shown to reduce relapse (interferon alfa or interleukin-2 are not effective).[1,3,4] Standard care therefore remains close observation.[3]

In metastatic disease, nephrectomy may be considered in a few patients for palliation of symptoms. In addition, nephrectomy and surgical removal of solitary metastases may be appropriate in some patients.[3,6,7] In patients with minimal disease volume and good performance status, cytokine therapy with interleukin-2 or interferon alfa may be considered.[1,3,8] These cytokines have resulted in overall response rates of 10 to 20%, with a few long-term responses.[6,9] Higher response rates have been reported with high-dose interleukin-2 than low-dose therapy,[3,10] although overall survival is not improved.[11] A modest survival benefit has been suggested for interferon alfa.[11] Two studies[12,13] of nephrectomy before interferon alfa therapy compared with interferon alone, in patients with good performance status, found that although overall response rates were similar there was a small survival benefit from nephrectomy. Attempts have been made to improve the response rates to interleukin-2 and interferon alfa by combining them, or adding antineoplastics or retinoids, but responses have generally been poor or toxicity significant.[6,9] There are also attempts to improve the tolerability of interleukin-2 by the use of continuous infusion, lower doses given by the subcutaneous route,[1,2,9,14] and inhalation.[9,14] Renal cell carcinoma is largely resistant to chemotherapy with conventional antineoplastics, and hormonal therapy with progestogens or anti-oestrogens has also had poor success.[1,2,9] The most extensively studied antineoplastics are vinblastine, fluorouracil, and floxuridine. However, reviews of up to 83 studies involving thousands of patients and over 70 different drugs found that only floxuridine and fluorouracil appeared to have even modest activity.[6,15] No antineoplastic can be considered standard in the treatment of metastatic disease,[2,9,16] and supportive care remains a mainstay of therapy.[3]

Because of the treatment resistance of renal cell carcinoma, there is an urgent need to develop innovative approaches. Targeted therapies block angiogenesis and can induce tumour shrinkage and/or tumour necrosis;[8] there is evidence of efficacy with the tyrosine kinase inhibitors sorafenib and sunitinib, and promising results have been seen with temsirolimus and bevacizumab.[3,4,8,17,18] Evolving therapies include vaccination therapy with autologous or allogeneic dendritic cell vaccines, or peptides, and allogeneic haematopoietic stem cell transplantation.[4,10,19,20]

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WILMS' TUMOUR. In children most cases of renal tumours are due to Wilms' tumour (nephroblastoma). This is one of the most frequent solid tumours in childhood with a peak incidence between 1 and 5 years of age and accounting for about 6% of all childhood malignancies. The usual presentation is an asymptomatic abdominal mass; abdominal pain is less frequent and haematuria occurs only in about a quarter of patients. Metastasis in advanced disease is usually to the lungs and liver. Most primary tumours occur in one kidney, but some 5% involve both kidneys.

Unlike other forms of renal cancer Wilms' tumour responds well to chemotherapy. The basis of treatment is surgery, combined with chemotherapy, and if necessary radiotherapy. Management varies with disease stage and also varies between different study groups.[1-7] The US National Wilms' Tumour Study (NWTS) group and some other groups recommend initial surgery (nephrectomy) to confirm diagnosis and perform precise staging.[1,2] Postoperative chemotherapy regimens and radiotherapy are based on stage and histology.[5,7] Others, including the European Société Internationale d'Oncologie Pédiatrique (SIOP), use neoadjuvant chemotherapy to reduce the tumour size and make surgery easier.[4,5,7] Although there continues to be controversy about the relative merits of the two approaches,[7] overall survival for patients treated by either approach is very similar, being more than 90% for patients with favourable histology. The aim of the various study protocols has been to identify low-risk children who require less intensive therapy, and those with poor prognosis who require more intensive therapy or alternative investigative regimens.

Current SIOP neoadjuvant chemotherapy consists of 4 weeks of dactinomycin and vincristine for clinically localised disease, and 6 weeks of dactinomycin, vincristine, and epirubicin for metastatic disease.[3,4] Adjuvant chemotherapy regimens for disease with favourable histology are broadly similar between NWTS and SIOP.[2-4] In early disease, chemotherapy consists of vincristine combined with dactinomycin; in more advanced disease radiotherapy, and an anthracycline (doxorubicin or epirubicin) are added. Patients with unfavourable histology and stage I disease are treated the same as those with favourable histology early-stage disease.[3] Combination adjuvant chemotherapy regimens for patients with unfavourable histology and a poorer prognosis add drugs such as etoposide, carboplatin, and an alkylating agent (cyclophosphamide or ifosfamide), which may be combined with an anthracycline or vincristine; radiotherapy may also be used.[2-4] The duration of adjuvant chemotherapy is dependent on the disease stage. In children with recurrent disease, survival is usually poor: salvage rates of about 20 to 30% have been reported for those with favourable histology. A regimen of cyclophosphamide, carboplatin, and etoposide is being investigated.[3] Treatment with high-dose chemotherapy and autologous haematopoietic stem-cell rescue has shown promising results.[5] Bilateral Wilms' tumour is not usually treated with primary bilateral nephrectomy because of the need to retain renal function. It may be biopsied to assess histology and stage and then treated with neoadjuvant chemotherapy.[2,3,5] Surgery is then performed, preserving as much of the kidneys as is possible. Survival has been reported to be comparable with that in other patients.[2] Because of these results, some have suggested the use of partial nephrectomy in patients with small unilateral tumours.[2] However, most tumours are too large or too centrally located for partial nephrectomy to be routinely indicated.[5]

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Malignant neoplasms of the liver. Hepatocellular carcinoma (hepatoma) accounts for more than 90% of primary liver cancers. It is relatively uncommon in northern Europe and America but is the most common cancer among men in large parts of Africa and Asia. The incidence in men ranges from 2 to 8 times that in women. Chronic infection with hepatitis B or hepatitis C virus is by far the most important factor associated with development of liver cancer, although other risk factors include ingestion of foodstuffs contaminated with aflatoxins (see p.2249), alcoholic liver disease, haemochromatosis, and the long-term use of anabolic steroids (see Effects on the Liver, under Testosterone, p.2130) and, rarely, combined oral contraceptives, (see p.2060). Over 70% of patients with hepatocellular carcinoma have cirrhosis of the liver.

Clinical manifestations of liver cancer include increasing obstructive jaundice, pain, malaise, and the presence of an epigastric mass; there may be metastasis to the lungs, kidney, bones, brain or other sites, or invasion of local structures.

Although diagnosis of *early disease* may be improved by screening at-risk groups, few patients have their tumours identified at a stage allowing prolongation of survival with surgical resection or liver transplantation.[1-3] **Liver transplantation** (p.1815) may be considered in those patients with very small tumours (stage I) and who have advanced cirrhosis and are therefore not suitable for surgical resection.[1,4] Patients with larger tumours or more advanced stages of disease are not candidates for transplantation because of the high rates of recurrence in the transplanted liver.[2,3] **Surgical resection** is considered in patients with no cirrhosis or mild liver impairment whose tumours are considered resectable (stages I to III). However, recurrence rates are high, and 5-year survival is only about 30%.[1,3,5]

As a result, **adjuvant** or **neoadjuvant chemotherapy** has been investigated in early-stage disease. Hepatocellular carcinoma is relatively resistant to chemotherapy, and a review of 8 studies concluded that none of the regimens of adjuvant or neoadjuvant therapy examined produced improvement in survival or disease-free survival.[6] However, a later review[7] of 21 studies found that chemotherapy injected into the hepatic artery after curative resection, usually with embolisation (see below), did improve survival and decrease recurrence. Neoadjuvant therapy may be considered to reduce tumour burden before transplantation[5] or to permit resection.[8] In patients who have small tumours and are not candidates for surgery or transplantation, percutaneous intratumoral alcohol injection is an option.[1,3-5,8,9] Other ablative therapies include radiofrequency ablation and cryosurgery.[5,9,10]

Most patients present with *advanced stage* cancer and significant liver impairment. Options in unresectable disease include palliative medical treatments or supportive care.[1-3,5] **Systemic chemotherapy** has been tried, but has no standard role. Treatment with doxorubicin alone has been associated with a response rate of 3 to 30% and no increase in survival,[1,3,11] and this has not been bettered by combination chemotherapy. More recently, a significant survival benefit in selected patients has been seen with sorafenib.[10] Doxorubicin has also been given by intra-arterial infusion into the hepatic artery, as have fluorouracil, floxuridine, and other drugs such as cisplatin and mitomycin.[1,3] Transcatheter arterial **chemoembolisation** combines intra-arterial chemotherapy with temporary occlusion of the artery (embolisation) using substances such as gelatine foam or iodised oil; this prolongs the duration of contact between drug and tumour, and attempts to induce tumour necrosis by ischaemia.[1,3,5] Although use of these techniques has given higher response rates than systemic therapy, there has been no evidence of an improvement in survival.[1-3,11] However, repeated chemoembolisation was shown to improve survival compared with conservative treatment without chemotherapy in a study of selected patients with small unresectable tumours.[12] Systematic review[13] confirmed a survival benefit with chemoembolisation, using doxorubicin or cisplatin, and suggested this method as standard therapy for selected patients with small unresectable tumours, and well-preserved liver function. **Other options** that have been tried include interferon alfa and tamoxifen.[1,3-5,11] Despite some initial positive data for tamoxifen, large randomised clinical trials failed to show any survival benefit for therapy at conventional doses,[14,15] and meta-analyses[13,16] confirmed this. Adoptive immunotherapy, using activated T-cells cultured with interleukin-2 and a monoclonal anti-CD3 antibody, has been reported to lower recurrence after resection.[17] Trials of octreotide have produced conflicting results.[4]

In contrast to the poor response of hepatocellular carcinoma to therapy, better progress has been made in strategies for its **prevention**. Neonatal vaccination against hepatitis B has dramatically decreased the incidence of chronic infection in children in Taiwan, and reduced the incidence of hepatocellular carcinoma. This may be a more promising approach in areas where the disease is common.[2] There is evidence that interferon alfa can delay or prevent the development of hepatocellular carcinoma in cirrhotic patients with hepatitis C infection.[18] Chemoprevention may also be a useful approach after surgical resection: use of a synthetic retinoid, peretinoin, was found to reduce the development of second primary tumours after resection.[19,20]

The liver is the most common site of *metastatic disease*.[21] For most malignancies the presence of liver metastases is indicative of generalised dissemination, but isolated metastatic liver disease is common in colorectal cancer (p.665) and rarer cancers such as some neuroendocrine tumours (see Carcinoid Tumours, above). In contrast to disseminated disease, treatment of such isolated liver metastases can prolong survival. Surgical resection is the preferred treatment if feasible. Palliative or cytoreductive surgery is beneficial in hepatic metastases from neuroendocrine tumours because of their slow growth.[21] Combined resection and adjuvant chemotherapy (hepatic arterial or systemic) is under investigation for colorectal liver metastases. Unresectable colorectal liver metastases have been treated with systemic or hepatic intra-arterial chemotherapy, with modest survival benefits.[22] Neoadjuvant chemotherapy, given either systemically or intra-arterially, has also shown some promise in rendering metastatic colorectal cancer resectable.[23]

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Malignant neoplasms of the lung. Lung cancer is the most common non-skin cancer in the developed countries and the second most common overall worldwide. About 20 to 25% of all lung cancers are small cell lung cancers (SCLC) derived from endocrine cells in the bronchial mucosa; the remainder, comprising chiefly squamous cell carcinomas (40 to 45% of cases), adenocarcinoma (25 to 30%), and large-cell carcinoma (about 10%), are known collectively as non-small cell lung cancer (NSCLC). More than 80% of all lung cancers are associated with tobacco smoking, and there is also evidence that exposure to the cigarette smoke of others can increase the risk in non-smokers. Other risk factors may include occupational exposure to substances such as asbestos, and the effects of environmental toxins such as air pollutants.

Symptoms due to a lesion in a main bronchus (the most common site) include persistent cough, dyspnoea, haemoptysis, weight loss and sometimes chest pain. Metastatic spread is common, and may affect sites such as brain, liver, and bone. It occurs early with adenocarcinoma and SCLC, but late with squamous cell carcinoma.

Disease staging plays an important role in determining treatment. The management of SCLC differs significantly from that of non-small cell types.

The mainstay of treatment for **small cell lung cancer** is chemotherapy.[1-5] In limited disease (disease limited to one hemithorax with hilar and mediastinal lymph node involvement that can be encompassed within one tolerable radiotherapy field) the combination of chemotherapy and chest radiotherapy has been shown to improve survival[6,7] and is recommended therapy.[2-5] The most common chemotherapy regimen is 4 to 6 cycles of etoposide and cisplatin (EP or PE),[1,3-5,7,8] which offers a survival advantage over the previously used regimen of cyclophosphamide, doxorubicin, and vincristine (CAV). The optimum scheduling of chemotherapy and radiotherapy has been investigated and concurrent therapy found to be superior to sequential radiotherapy.[3,5] In comparing early and late concurrent therapy, a meta-analysis[9] of 7 studies found that a small improvement in overall survival at 2 years was associated with early radiotherapy (begun within 9 weeks of starting chemotherapy, or before the third cycle of chemotherapy) compared with late radiotherapy. There was also evidence that the use of hyperfractionated radiotherapy (given twice daily) and platinum-based regimens contributed to this benefit. In general, for limited disease it is recommended[2,3,5,7] that concurrent chest radiotherapy should be started with the first or second chemotherapy cycle. Response rates of 70 to 90% are reported, but median survival rates are only 14 to 20 months and the 2-year survival rate is about 40%.[5]

Only a few patients present with resectable early stage disease. Careful pre-operative staging is essential to rule out nodal involvement, and all patients should receive adjuvant chemotherapy. If nodal metastases are found, the addition of postoperative chest radiotherapy should be considered. Patients with later disease stages do not benefit from surgery.[3,5]

In extensive SCLC (spread beyond one hemithorax and may include malignant pleural or pericardial effusion or haematogenous spread) chemotherapy alone is used to palliate symptoms and prolong survival. The combination of etoposide and cisplatin (or carboplatin) is also used in these patients[3,5,7] but response is poorer than that for limited disease, with response rates of 60 to 70% and a 2-year survival rate of less than 5%.[5] The use of consolidation or maintenance chemotherapy has been studied in both limited and extensive disease. Most studies have found no improvement in progression-free or overall survival, and the general recommendation is that such extra therapy, with its associated toxicity, should not be used.[1-5,8] This view has been challenged by a meta-analysis[10] of 14 studies suggesting that there is evidence for benefit from maintenance therapy, although it is unclear which patients might benefit and which regimen would be most effective. Other strategies that have been tried, but with little consistent evidence of improved results, include the combination of irinotecan and cisplatin, the addition of further drugs to EP (such as ifosfamide, paclitaxel, or cyclophosphamide plus an anthracycline), and the use of dose-intense or dose-dense regimens.[1,5,8]

Patients who have responded to initial treatment still have a more than 50% risk of developing brain metastases. Prophylactic cranial irradiation reduces this risk and improves survival in patients in complete remission.[11] It is generally recommended for all patients with limited disease who achieve remission, and for those with extensive disease who achieve remission and have good prognostic factors and performance status.[2-5,7,8]

The value of chemotherapy in relapsed SCLC depends in part on the duration of remission before relapse, with greater responses the longer the remission.[3,5,7,8] UK guidelines recommend second-line chemotherapy only in patients whose disease responded to first-line treatment.[2] Patients may be given the same initial therapy if they have relapsed after more than 6 months. Patients who relapse within 3 months of achieving remission are considered to have refractory disease; second-line drugs include ifosfamide, paclitaxel, docetaxel, and gemcitabine, although response is likely to be poor. Response rates are better if relapse occurs between 3 and 6 months after remission, and topotecan has been suggested as the best option. Other drugs that may be considered include irinotecan, gemcitabine, a taxane, ifosfamide, oral etoposide, vinorelbine, or the CAV regimen.[5,7,8] Drugs under investigation for SCLC include amrubicin, pemetrexed, and picoplatin.[7,8] Second-line chemotherapy should be given until the patient receives maximal benefit, becomes refractory, or develops unacceptable toxicity. Radiotherapy may also be given for localised symptomatic palliation.[5]

In patients with **non-small cell lung cancer** presenting with tumour localised to the lung (generally stage I and II), the treatment of choice is surgery.[2,12-15] In patients with resectable disease who have medical contra-indications to surgery, radical radiotherapy is used with curative intent. In patients who are surgically staged, about 26 to 47% of patients with localised disease are still alive after 5 years.[14] To improve on these results, there has been great interest in the role of adjuvant therapies. In early-stage disease, use of radiotherapy after complete resection has been shown to result in worse survival than surgery alone,[16] and is not recommended.[13] Conversely, some recommend[2,14] that postoperative radiotherapy be considered if there is residual disease after surgery, although there is a lack of good evidence for a reduction in local recurrence in this setting. Chemotherapy has also been investigated as an adjuvant therapy and is recommended after complete resection.[2,12-15] There is some evidence that cisplatin-based postoperative therapy improves survival, but that alkylating agent-based therapy decreases survival.[17] Results of a large international trial suggest that 5-year survival and disease-free survival were significantly increased in patients given adjuvant chemotherapy compared with those given surgery alone. Chemotherapy consisted of 3 to 4 cycles of cisplatin combined with etoposide or a vinca alkaloid (vinblastine, vindesine, or vinorelbine).[18] A further study[19] of cisplatin with vinorelbine conducted in north America also supported these findings. Reviews[20-22] of these and other studies have concluded that adjuvant cisplatin-based chemotherapy does offer a survival benefit after complete resection of NSCLC. There is also some evidence of improved survival from studies in Japan[23,24] using continuous postoperative oral tegafur with uracil. In resectable disease, the use of pre-operative (neo-adjuvant) therapy is being investigated in an attempt to treat micrometastases and improve resection by tumour shrinkage;[12,25,26] effects on overall survival are conflicting.[22,25,26]

The choice of treatment will be affected by the site of the tumour and nodal spread, with some guidelines[13] suggesting pre-operative chemotherapy while others[14] recommend pre-operative concurrent chemoradiotherapy in selected patients. UK guidelines[2] only recommend such treatment as part of a clinical study.

In patients with unresectable locally advanced disease (stage IIIB and unresectable IIIA), the use of platinum-based chemotherapy either before or with radiotherapy has resulted in a modest increase in survival according to the findings of a number of meta-analyses[17,27-29] and has become recommended therapy.[13,30] Regimens usually include cisplatin plus either etoposide, a vinca alkaloid, or a taxane. The issue of dosage and sequencing has been investigated;[30,31] concurrent chemotherapy with radiotherapy (chemoradiotherapy) is considered by some to be superior to sequential therapy,[12,14,31,32] but others[2] recommend sequential chemoradiotherapy or caution[29] that the magnitude of increased benefit with concurrent therapy is not yet clear. Chemoradiotherapy followed by surgery (trimodality therapy) is also under investigation.[30] Encouraging results[32] suggest that this approach of chemotherapy, radiation, and surgery may improve progression-free survival when compared with chemotherapy and radiation alone.

Chemotherapy may also be used for advanced metastatic disease (stage IV), which is detected in 40 to 50% of patients at presentation, although response is poor with a 5-year survival rate of only about 1%. Meta-analyses have shown a modest improvement in survival and symptom control in patients given chemotherapy compared with those given best supportive care.[17,33] Furthermore, combination chemotherapy has improved responses compared with single drug therapy,[34] particularly platinum-based combinations.[35] When compared with combinations of newer drugs (including vinorelbine, gemcitabine, taxanes, and irinotecan), platinum-based regimens still have a higher response, but they cause more toxicity and 1-year survival is not significantly different.[35] In general, cisplatin-based chemotherapy has become the standard of care for advanced disease,[2,12-15,30] although no particular regimen has been identified as superior.[36,37] Regimens include cisplatin or carboplatin combined with either gemcitabine, irinotecan, etoposide, vinblastine, vinorelbine, docetaxel, or paclitaxel.[14,15] Older triple regimens such as mitomycin, vinblastine, and cisplatin (MVP) or mitomycin, ifosfamide, and cisplatin (MIC) are no better and are no longer advocated.[12,37] A combination of carboplatin and paclitaxel with the monoclonal antibody bevacizumab may be an option for patients with non-squamous cell histology and good performance status.[14] For patients who fail initial therapy for advanced disease, docetaxel[13,14,30] as a single agent is generally recommended for second-line treatment. Alternative drugs that may be considered include erlotinib, gemcitabine, or pemetrexed.[12-15,38,39] Topotecan is also under investigation.[40] Despite initial promise, disappointing results using gefitinib either alone[15,41] or with platinum-based chemotherapy[42,43] have been reported. The success of gefitinib may depend on identifying patients with specific mutations of the epidermal growth factor receptor (EGFR) gene.[44]

Bronchoscopic photodynamic therapy, with porfimer sodium, may be considered for the palliative treatment of bronchial obstruction.[14,45] Photodynamic therapy may also be used as an alternative to surgery in patients with very early-stage (in situ) endobronchial NSCLC.[45] Other palliative options for obstructed airways include endobronchial brachytherapy or stent placement, or laser treatment. External beam radiotherapy may be useful for symptom control and surgery may be suitable in some cases of resectable local recurrence.[14]

Despite the recent advances in chemotherapy for NSCLC, the median survival for this disease remains poor, and there is a need to identify alternative approaches to treatment. Those in preclinical development include gene therapy[46] with the tumour suppressor gene p53, and cancer vaccine immunotherapy.[47]

Given the poor prognosis of lung cancers, and the high incidence of second primaries in patients curatively treated for early-stage disease, there has been great interest in **prophylaxis.** The most important factor in primary and secondary prevention is cessation of tobacco smoking, for which a number of interventions may be tried (see Smoking Cessation, p.2354). Diets rich in fruit and vegetables have been associated with a lower incidence of malignant disease, and have prompted the investigation of antioxidant vitamins. However, primary prevention studies in those at risk of lung cancer have failed to show any benefit for vitamin supplements, and in the case of betacarotene, an increase in lung cancer was seen in those most at risk (see Prophylaxis of Malignant Neoplasms, p.1927). Other drugs under investigation are retinoids and NSAIDs.[48]

While a meta-analysis[49] concluded that screening of patients with chest radiography or sputum cytology was ineffective, the Early Lung Cancer Action Project found that computed tomography improves the likelihood of detection of nodules suggestive of lung cancer in high-risk patients.[50] Since most of those cancers detected were at an early stage, resection was possible, and it is theorised that this technique may reduce mortality,[51] although it remains investigational.

Metastatic lung disease. The lung is the second most frequent site for metastatic disease, occurring in about 30% of cancer patients. Surgical resection may be used to treat pulmonary metastases when there are no effective systemic therapies, no extrapulmonary metastases, the pulmonary metastasis is completely resectable, and the patient is able to undergo surgery.[52] Specific cancers for which surgical resection of pulmonary metastases is considered include soft-tissue sarcoma, osteosarcoma, and sometimes breast cancer.

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MALIGNANT MESOTHELIOMA. Malignant mesothelioma is a relatively rare tumour of the lining of the lung, yet its incidence is increasing. Occupational exposure to asbestos is the causative factor in most cases, with a mean latent interval of about 40 years between first exposure and death. Typical clinical manifestations include chest pain or dyspnoea or both. Neurological entrapment and pericardial involvement may occur. The disease is progressive, and median survival is poor. Histologically, disease may be epithelioid, sarcomatoid, or a mixture of the two. The epithelioid type is the most common, and may be confused with adenocarcinoma (see non-small cell lung cancer, above). In patients with small epithelioid tumours, radical surgery may be considered, but otherwise is seldom appropriate. Pleurodesis is usually the treatment of choice in the management of pleural effusions associated with mesothelioma; pleurectomy is an alternative. Palliative radiotherapy may be effective for pain relief,[1] but is generally of limited value.[2,3]

Responses to single-agent chemotherapy have been in the region of 10 to 20%. Doxorubicin, epirubicin, mitomycin, cyclophosphamide, ifosfamide, cisplatin, and carboplatin have all been tried.[1,4] Irinotecan, topotecan, gemcitabine, vinorelbine, docetaxel, and paclitaxel have also been investigated.[1,4] Combination chemotherapy, mostly with doxorubicin- or cisplatin-based regimens, have not shown any survival advantage over single-agent therapy.[4] However, encouraging results were obtained in a large phase 3 study using pemetrexed and cisplatin, and this combination is generally considered to be standard first-line therapy.[1,2,4-6] The addition of raltitrexed to cisplatin has also improved response rates and overall survival,[7] and some benefits have been seen with gemcitabine plus cisplatin,[2,3] which has been suggested as second-line therapy.[2,6] Other regimens, including vinorelbine compared with mitomycin, vinblastine, and cisplatin (MVP),[5] and raltitrexed with oxaliplatin[4] are being investigated. Gene therapy, immunomodulation, and angiogenesis inhibitors are also being tried.[1-3]

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Malignant neoplasms of the ovary. Ovarian cancers account for about 5% of all malignancies in women. The most common form (90% of cases) is **epithelial ovarian cancer**, which ranks as fourth in the leading causes of cancer deaths in women. The lethality of this disease is related to the absence of symptoms in most women during its early stages: in about three-quarters of all patients disease is advanced at diagnosis and has spread to the peritoneum or beyond. It is predominantly a disease of older women, the median age at diagnosis being 61 years. The risk of epithelial ovarian cancer appears to be related to the number of ovulatory cycles a women has in her lifetime, thus nulliparity increases the risk, whereas multiparity, breast feeding, and combined oral contraceptives (p.2061) decrease the risk. Other risk factors are a family history (particularly when associated with the BRCA1 and BRCA2 genes), and possibly fertility drugs (see Clomifene, p.2086), perineal talc use (p.1615), and menopausal HRT (p.2073).

The main treatment for epithelial ovarian cancer in most patients is surgical removal of womb, ovaries and fallopian tubes, and omentum, with debulking of any remaining gross disease.[1-3] The use of adjuvant chemotherapy depends on disease stage.

The minority of patients who have localised disease at diagnosis have a good prognosis. Patients with well differentiated early disease (stage IA) have a 5-year disease-free survival of at least 90%; adjuvant therapy has not been shown to improve survival in this group,[4] and conservative fertility-sparing surgery is possible in women of childbearing age.[1,3] In those subgroups with poorly differentiated or more extensive localised disease (stage IC and II) postoperative platinum-based chemotherapy has been reported to improve both recurrence-free and overall survival at 5 years,[5] and is usually considered appropriate.[1-3,6] Adjuvant intraperitoneal phosphorus-32 and oral melphalan have also been used.

Prognosis is less good in patients with advanced disease (stage III and IV), who presently form the majority at diagnosis. Patients with extra-pelvic disease or positive nodes who have only minimal residual disease after surgery have a 5-year survival rate of less than 30% but in patients with distant metastases or suboptimal debulking there is a less than 10% chance of long-term survival. Many adjuvant regimens have been tried in advanced ovarian cancer, often based on platinum derivatives, alkylating agents, and sometimes also anthracyclines. Cisplatin or carboplatin with cyclophosphamide (CP) and sometimes doxorubicin (CAP) have been widely used. In 1991, a meta-analysis[7] failed to reach any definite conclusions about the relative benefits of differing chemotherapeutic regimens, but did suggest that immediate treatment was better than delaying until relapse, that platinum-based regimens were probably better than those without a platinum derivative, that combination regimens were better than single-agent platinum where the doses were equivalent, and that carboplatin was as effective as cisplatin. A later updated analysis[8] by the same group reached similar conclusions. Two similar analyses in 1991 and 1992 suggested that regimens of cisplatin, doxorubicin, and cyclophosphamide offered a survival advantage over cisplatin with cyclophosphamide alone.[9,10] Subsequent to these analyses, a large randomised study (ICON2) was instigated to compare carboplatin alone with cyclophosphamide, doxorubicin and cisplatin. This study[11] found no difference in progression-free or overall survival (median 33 months) between the 2 treatment arms, and single-agent carboplatin was less toxic. In the early 1990s, the finding of significant activity for paclitaxel in ovarian cancer led to various studies incorporating this drug. Two studies[12,13] comparing cisplatin plus cyclophosphamide with cisplatin plus paclitaxel found improved overall survival for the paclitaxel-containing arm (median 38 and 36 months versus 24 and 26 months). Substitution of carboplatin for cisplatin resulted in similar overall survival,[14] and subsequently a number of reviews and guidelines have recommended paclitaxel plus cisplatin or carboplatin as the first-line adjuvant treatment of ovarian cancer.[1-3] Conversely, another study[15] found cisplatin alone (100 mg/m^2) to be no different to cisplatin (75 mg/m^2) plus paclitaxel (135 mg/m^2) in terms of overall survival (median 30 versus 26 months) and progression-free survival, although cisplatin alone was poorly tolerated. This study also contained a single-agent paclitaxel arm (200 mg/m^2), which had poorer progression-free survival, but similar overall survival (26 months) to the other arms. Results of a further study (ICON3)[16] also failed to demonstrate an improvement in progression-free or overall survival for carboplatin plus paclitaxel (median 17 and 36 months) compared with carboplatin alone or cisplatin-based CAP (median 16 and 35 months); single-agent carboplatin had a more favourable toxicity profile. Subsequent guidelines[6,17] have recommended that platinum-based therapy alone or with paclitaxel are both reasonable options for first-line adjuvant therapy.

Other therapies used in the adjuvant setting include interval surgical debulking in those with suboptimal debulking at primary surgery,[3,18] and intraperitoneal chemotherapy in those with minimal residual disease after primary surgery.[3,19-21] The use of neoadjuvant chemotherapy is controversial,[3] although it has been suggested to reduce morbidity and permit subsequent surgical debulking, and studies of this strategy followed by interval surgery are underway.[18,19]

In patients with recurrent disease, the choice of therapy depends on the time since initial therapy and the drugs used.[1,3,22] Relapse occurring more than 6 months after initial therapy is potentially platinum-sensitive and may be re-treated with the initial therapy. In patients who are potentially not sensitive to platinum derivatives, paclitaxel may be used if it was not used previously. Combining paclitaxel with platinum chemotherapy may further improve survival in patients who are platinum-sensitive.[23] Other drugs with activity include topotecan, liposomal doxorubicin, altretamine, capecitabine, cyclophosphamide, docetaxel, epirubicin, oral etoposide, gemcitabine, ifosfamide, irinotecan, tamoxifen, and vinorelbine.[3,18,19,22,24] Bevacizumab is also active.[3,19] The monoclonal antibodies oregovomab and pemtumomab are under investigation, as are ovarian cancer vaccines.[25] Some success has been reported using high-dose chemotherapy followed by autologous stem cell transplantation,[26] although an improvement in survival has not been shown.[3,18]

Prophylaxis. The identification of genes conferring an inherited predisposition to ovarian cancer, and the difficulty in identifying the disease and its poor prognosis has led to increased interest in prevention. Oral contraceptives are known to be protective in the general population, and there is growing evidence that women with mutation of the BRCA1 or BRCA2 gene might benefit similarly (see Ovary, under Carcinogenicity in Hormonal Contraceptives, p.2061). Prophylactic oophorectomy may be considered in women with BRCA1 mutations after child-bearing or at age 35 years.[27,28] The risk/benefit ratio of this procedure is not known, and a few women who undergo this procedure subsequently develop a primary peritoneal cancer.

Ovarian germ-cell cancers account for less than 3% of ovarian cancers and typically occur in women aged 20 to 30 years. Unlike epithelial ovarian cancer, most patients present with early disease, and even in advanced disease, combination chemotherapy can be curative.[3,29] Conservative fertility-sparing surgery is the main therapy. Adjuvant chemotherapy is used except in those with stage I disease able to undergo frequent follow-up. Common regimens are similar to those used in male germ-cell tumours, such as bleomycin, etoposide, and cisplatin (BEP) or vinblastine, bleomycin, and cisplatin (VBP).[3,29,30]

Ovarian stromal tumours account for about 7% of ovarian cancers[31] and are mainly treated with fertility-sparing surgery.[3] For those with high-risk stage I tumours, recommendations include observation, radiotherapy, or cisplatin-based chemotherapy. For those with tumour stages II to IV, options include radiotherapy for limited disease, or platinum-based regimens such as BEP, paclitaxel plus carboplatin, or docetaxel plus carboplatin.[3]

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Malignant neoplasms of the pancreas. Pancreatic adenocarcinoma (cancer of the exocrine pancreas) accounts for about 95% of pancreatic tumours. A very small percentage of pancreatic tumours arise in the endocrine pancreas, and have different clinical features and treatment (see under Carcinoid Tumours and Other Secretory Neoplasms, above). Although rare below the age of 30 the incidence of pancreatic adenocarcinoma rises steadily with age; overall, it accounts for about 3% of all cancers, but is the fifth leading cause of cancer deaths. Pancreatic adenocarcinoma is ductal in origin and metastasises early to the lymph nodes, and by the time of diagnosis more than half of all patients have liver metastases, more than a quarter have peritoneal seeding, and a third have invasion of the duodenum causing ulceration. The most frequent symptom at presentation in patients with cancer of the pancreatic head is jaundice, often with other symptoms indicative of obstruction of the bile duct. In lesions of the body and tail of the pancreas severe and relentless pain may develop. Diabetes mellitus is a manifestation of the disease, but there is also some evidence that it may be a predisposing factor. About 30% of pancreatic cancers are probably due to tobacco smoking.

Pancreatic adenocarcinoma has a very poor prognosis because of its usually advanced stage at diagnosis and lack of effective therapies.[1] Apart from a small number of patients with resectable carcinoma of the head of the pancreas, in whom radical surgery results in a 5-year survival of about 10 to 20% most patients with pancreatic adenocarcinoma will be dead within 1 year. Adjuvant therapy with irradiation and fluorouracil has been used in those with resectable disease,[1] based on early evidence that it optimised the chance for long-term survival. However, the results of a large randomised study[2,3] suggested that there was no benefit from adjuvant fluorouracil-based chemoradiotherapy but that there might be a survival benefit from prolonged chemotherapy alone. A subsequent review[4] that included this later study concluded that there was benefit with the use of adjuvant fluorouracil, but that chemoradiotherapy should not yet be dismissed from further study because trials to date had used radiotherapy regimens that were now considered to be suboptimal, a view also adopted by US guidelines.[5] Adjuvant gemcitabine is also effective,[6] and some consider it the preferred drug if single-agent therapy is used.[5,7] It is also recommended for use with fluorouracil-based chemoradiation. Capecitabine is an alternative to gemcitabine or fluorouracil for monotherapy.[5] Pre-operative (neoadjuvant) chemoradiotherapy is also under investigation, but a survival benefit has not been proven, and toxicity can be severe.[1,8,9]

In patients with symptomatic localised unresectable disease, chemoradiotherapy may be used.[5] Most studies have reported a modest survival benefit from the combination of radiotherapy and fluorouracil.[1,5,9,10] Evidence suggests that radiotherapy with gemcitabine can yield similar outcomes.[5] A period of chemotherapy followed by chemoradiation may be preferable to first-line chemoradiation. Chemotherapy alone is also an option in these patients,[5] and a systematic review[11] found insufficient evidence to recommend chemoradiation over chemotherapy alone; gemcitabine monotherapy or gemcitabine-based combination therapy is advocated.[5] Use of neoadjuvant chemoradiotherapy to improve resectability rates in locally advanced disease is investigational.[5,8,10] In patients with advanced (metastatic) disease, supportive care alone remains appropriate for those with poor performance status. Palliative chemotherapy may be considered in those with adequate performance status,[5] but benefits are modest (pancreatic adenocarcinoma is a chemoresistant tumour).[1,12] Despite this, a meta-analysis[13] found a survival advantage for chemotherapy over best supportive care. Single-agent fluorouracil has been widely used.[6,8,14] Combination regimens, such as FAM (fluorouracil, doxorubicin, mitomycin) SMF (streptozocin, mitomycin, fluorouracil), and FAP (fluorouracil, doxorubicin, cisplatin), have not proved more effective than fluorouracil alone.[8,9] However, there is evidence[5,15] that gemcitabine can produce slightly better survival than fluorouracil in patients who can tolerate it, and it has been recommended as the standard of care.[1,5,8,9,16] There is also some evidence that its effectiveness may be improved if it is given at a fixed dose rate of 10 mg/m^2 per minute, rather than by conventional infusion.[5,14] Gemcitabine has also been investigated in combination with other drugs such as cisplatin, docetaxel, irinotecan, oxaliplatin, or capecitabine, as well as with newer targeted therapies such as bevacizumab, cetuximab, trastuzumab, or erlotinib.[5,14,17] A meta-analysis[13] found a survival benefit for gemcitabine-based combination therapy compared with gemcitabine alone. Combinations showing benefit in terms of progression-free survival or overall survival include gemcitabine with capecitabine (GEMCAP), cisplatin (GEMCIS), oxaliplatin (GEMOX), or erlotinib.[5,6,14,18] The combination of cisplatin, epirubicin, fluorouracil, and gemcitabine (PEFG) has also shown impressive results.[14] Rubitecan is one of many other antineoplastics under investigation for advanced pancreatic cancer,[12,14] and other therapies that have been investigated include somatostatin analogues, other hormonal strategies, and biological therapies.[19] A preliminary study suggested that flutamide (an anti-androgen) might be beneficial[20] but flutamide with gemcitabine proved of no more benefit than gemcitabine alone.[21] Pancreatic cancer vaccines are also under investigation.[6,17]

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Malignant neoplasms of the prostate. Prostatic cancer is the most commonly diagnosed non-skin malignancy in men in the western world, and the second most common cause of cancer deaths in men: about one in 6 men can be expected to develop clinically evident carcinoma of the prostate during his lifetime. The incidence rises steadily with age. More than 95% of all prostate cancer is adenocarcinoma, which begins as a hard mass in the peripheral portion of the gland and infiltrates surrounding tissues slowly. Metastasis may occur in advanced disease, notably to bone. Presenting symptoms of advanced disease are usually those of urinary outflow obstruction, or pelvic or back pain due to bone metastases. However, as a result of the slow rate of tumour growth and usually advanced age at diagnosis, many patients die of other illnesses without having suffered significant disability from the cancer.

Controversy exists regarding all aspects of the management of prostate cancer, from screening to the best treatment for each stage of the disease. Much of this is because of the lack of clear data to guide treatment decisions. Factors that guide treatment decisions include the extent (stage) of the tumour, tumour grade (Gleason score), the patient's life expectancy (based on age and comorbid conditions), and patient preference.[1-4]

There is great controversy over the value of **screening** for early disease by detection of prostate specific antigen (PSA), and other tests, because of the uncertainties regarding interpretation of the test results, and controversy over the management of asymptomatic early localised disease.[5-8] Screening studies are currently underway.

In patients with **localised disease**, detected incidentally or by screening, the choices are radical prostatectomy, radical external beam radiotherapy, brachytherapy, or deferred treatment (watchful waiting).[8-10] There is currently no evidence to suggest one form of therapy is more effective than another, except perhaps for poorly differentiated tumours, which have a faster rate of progression and may benefit from earlier therapy.[4] Because of the lack of differences in efficacy, treatment morbidity and patient preferences are particularly important. Adverse effects of surgery include impotence and incontinence, and for radiotherapy, radiation proctitis, impotence and incontinence, and these complications may be severe in up to 5% of patients.[4] In medically fit patients with a life expectancy of 10 years or more many clinicians would consider radical prostatectomy or radiotherapy with curative intent,[1,4,8,11] although it should be noted that these patients are the ones for whom treatment complications are likely to have the most impact on quality of life.[4] In men with a life expectancy of less than 10 years and with low-grade tumours, there is a definite role for deferring treatment.[1,4,9,11] Interstitial implantation of radioisotopes (brachytherapy) is an alternative to external beam radiotherapy; a more localised dose is possible but inadequate dose distribution can occur and some patients may also need adjuvant external beam radiotherapy.[11] Cryosurgery, and ultrasound or radiofrequency interstitial tumour ablation are other options for localised disease, but are less well investigated.[11] In patients who undergo radical surgery and who are found to have positive margins, adjuvant radiotherapy or hormonal therapy may be used. Neoadjuvant hormonal therapy has been used before radiotherapy, but its role in early disease remains to be established. Hormonal therapy has also been used alone when there is a risk of disease progression but local therapy is not deemed necessary.[11]

For patients with **locally advanced disease**, options include radiotherapy with or without neoadjuvant or adjuvant hormonal therapy, hormonal treatment alone, or, in those who are asymptomatic, deferred treatment.[1,4,12,13] Although radiotherapy alone produces good local control, most patients eventually develop metastatic disease. There is increasing evidence that the use of hormonal therapy before or after radiotherapy improves disease-free and overall survival.[12-14] Deferred treatment was less effective than immediate treatment in one study,[15] but the form of follow-up for deferred treatment was not regulated. In patients for whom deferred treatment is considered, close surveillance is required. Surgery alone is rarely used in locally advanced disease[1] but there is some evidence to suggest that adjuvant hormonal therapy may delay disease progression, and neoadjuvant hormonal therapy is under investigation.[12]

PSA may be used to monitor the efficacy of therapy and detect biochemical relapse, but the interpretation of the test and when to instigate further treatment in patients with no clinical evidence of disease is controversial.[12,16]

For patients with **metastatic disease** cure is not possible and therapy is aimed at prolonging survival and palliating symptoms. The basis of therapy is hormonal manipulation: about 80% of patients will respond to such therapy, but resistance eventually develops. The first choice is between orchidectomy or a gonadorelin analogue, which have been shown to be equally effective.[4,17,18]

An alternative to orchidectomy or gonadorelin analogues is the use of an anti-androgen (such as flutamide, nilutamide, or bicalutamide) alone.[18] However, there is some evidence that these may be less effective and cause more treatment withdrawals (due to gastrointestinal intolerance),[17] although they may have less adverse effect on libido. Although historically oestrogens such as diethylstilbestrol have been used in patients with prostate cancer they are now less favoured because of their cardiovascular adverse effects.

The combined use of anti-androgens such as flutamide with ablation of testicular androgen production (by surgery or gonadorelin analogues) has the advantage of blocking the effects of adrenal androgen production as well (maximal or complete androgen blockade). An early meta-analysis[19] seemed to indicate that this approach did not produce a better survival rate compared with conventional castration, and an update of this meta-analysis[20] confirmed that any survival advantage from maximum androgen blockade using nonsteroidal anti-androgens was likely to be in the region of 3%. Any benefit also seems to appear only after 5 years of follow-up.[8]

The gonadorelin antagonist abarelix can also be used for hormone suppression. It has a more rapid onset of effect than the gonadorelin analogue leuprorelin and does not stimulate tumour flare.[21,22] Abarelix may be an alternative for men who are not suitable candidates for orchidectomy or gonadorelin analogue therapy.

In patients who relapse after or during hormonal therapy, second-line hormonal therapy may be tried, although responses are variable. Drugs that have been used include aminoglutethimide, high-dose bicalutamide, corticosteroids, ketoconazole, and megestrol.[16] Some patients treated with anti-androgens have a paradoxical response to withdrawal of the drug, but it is not possible to predict which patients will respond. Gonadorelin analogue therapy must be continued, to maintain testosterone suppression.[23]

Chemotherapy for recurrent **hormone-refractory prostate cancer** is still in clinical trials and has no routine place in therapy. Some patients with soft-tissue disease may benefit from an anthracycline.[4] Mitoxantrone has a palliative benefit and improves quality of life, but does not prolong survival.[24] Docetaxel given every 3 weeks improved survival compared with mitoxantrone,[25] both in a regimen with continuous prednisone. Docetaxel also reduced pain, but was associated with a higher incidence of adverse effects; a regimen using docetaxel weekly had a similar outcome to mitoxantrone. A combination of docetaxel with estramustine also improved survival[26] compared with mitoxantrone plus prednisone, but again with an increased incidence of adverse effects. Some consider docetaxel-based chemotherapy to be the standard of care.[24] Combinations of docetaxel are under investigation, including with vinorelbine, capecitabine, or high-dose calcitriol.[24] Combinations of estramustine with etoposide, vinblastine, or vinorelbine have also shown favourable results.[16,27] Other drugs that might reasonably be used after initial treatment with docetaxel-based therapy include oral cyclophosphamide, either alone or with vincristine and dexamethasone. Newer drugs under investigation include satraplatin and ixabepilone.[24,28]

Preliminary results have indicated that a herbal combination preparation, PC-SPES, may have beneficial effects in both androgen-dependent and androgen-independent disease. It has been used widely as a complementary medicine, but there have been reports of adverse cardiovascular effects and contamination with diethylstilbestrol and warfarin, resulting in the withdrawal of this product from most markets.[29,30] Although suramin originally showed promise, later results were less favourable, and it appears its development has ceased. Bone metastases are usually treated with palliative radiotherapy (see p.660). Bone-targeted therapy with strontium-89 has been tried,[27,31] and gene therapy is under investigation.[32] Prostate cancer growth is thought to be stimulated by endothelin-1, a small peptide that acts at endothelin-A receptors; atrasentan is an endothelin-A receptor antagonist under investigation, and early studies have shown improvements in time to disease progression and markers of bone metastases.[24,27] Vaccines are also under development for treatment of prostate cancer.[8,24,33]

Because of the difficulties involved in managing prostate cancer there has been interest in the concept of disease **prophylaxis**. One small study of finasteride in men at high risk of prostate cancer showed little evidence to support such use.[34] In healthy men, a large controlled trial[35] found that seven years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. Dutasteride is also under investigation.[36] Results from a case-control study have suggested an association between warfarin use and a decreased risk of prostate cancer.[37] There is preliminary evidence that selenium (see p.1961) or vitamin E (see p.1927) supplementation may also reduce the risk of prostate cancer, and a large randomised study is underway to further investigate this.

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Malignant neoplasms of the skin. Basal cell carcinoma is the most common form of skin cancer, accounting for about 80% of cases. The second most common skin cancer is squamous cell carcinoma. These 2 types of carcinoma (collectively referred to as nonmelanoma skin cancers) are the most common malignancies among white populations, but because many are not recorded the exact incidence is uncertain and they are often omitted from calculations of the relative frequency of malignancy. A small but increasing proportion of all skin cancers are melanomas, arising from melanocytes (pigment cells). Other cancers that manifest in the skin include cutaneous T-cell lymphomas (see Mycosis Fungoides, above) and Kaposi's sarcoma (see below).

Nonmelanoma and melanoma skin cancers are related to solar radiation, and the incidence is greatest in those regions where light-skinned populations live closest to the equator. Individuals at particular risk include those with fair skin, blue eyes, red hair, a tendency to freckle, and to burn rather than tan. Use of methoxsalen with ultraviolet light (PUVA) has also been associated with an increased incidence of skin cancers (see Effects on the Skin, under Methoxsalen, p.1605). Other risk factors for nonmelanoma skin cancers include various inherited disorders such as xeroderma pigmentosum (see Photosensitivity Disorders, p.1581) and albinism (see Pigmentation Disorders, p.1582). Immunosuppressive therapy, as used after solid organ transplantation (see p.1810 *et seq.*), is associated with a very large increase in risk of squamous cell carcinoma.

Prophylaxis. Although nonmelanoma and melanoma skin cancers are related to solar radiation, and measures to reduce sun exposure are therefore advocated for prophylaxis, the relationship appears to differ between the types.

- Squamous cell carcinoma and its precursor lesions are clearly linked to cumulative chronic sun exposure.[1,2] These lesions are more common on frequently exposed skin (head, neck, and back of hands), and are more common in individuals with outdoor occupations. In addition, there is evidence that regular sunscreen use can reduce the incidence of new actinic keratoses and increase remission of existing lesions,[3] and reduce incident squamous cell carcinomas.[4]
- Although basal cell carcinomas are also common on sun-exposed skin (head and neck), it appears that they may be more related to a history of severe sunburns, particularly in childhood and adolescence, rather than to cumulative sun exposure.[1] In 1 study,[4] there was no difference in incidence of basal cell carcinomas between sunscreen users and non-users.
- Cutaneous melanoma is more common on skin exposed to the sun occasionally (particularly the legs in women, and the back in men), and appears to be more common in indoor than outdoor workers. This suggests that intermittent sun exposure may be more risky than regular exposure for this cancer.[1,2] Although the use of sunscreens is advocated for protection against melanoma, some reports have suggested that sunscreen use may actually increase the risk. However, systematic reviews[5,6] have found no good evidence for an association between sunscreens and the increasing incidence of melanoma, but did find that studies varied in accounting for confounding factors such as patient complexion and recall bias. Also, people at higher risk of sunburn and melanoma may also be more likely to use sunscreens, and some people may use sunscreens to allow for prolonged sun exposure, thus receiving a higher cumulative amount of UV radiation. Sunscreen formulation, sun protection factor (SPF) rating, and protection against UVA, have also changed considerably over the last few decades, making it difficult to compare study results.

Chemoprevention has also been investigated as a means of reducing the incidence of squamous and basal cell cancers, particularly in those most at risk. Retinoids such as acitretin, etretinate, and isotretinoin have been shown to reduce the incidence of new squamous cell carcinomas in individuals with xeroderma pigmentosum, and in renal transplant recipients.[7] Conversely, neither betacarotene (p.1927) nor selenium (p.1961) has reduced the incidence of squamous or basal cell carcinomas in patients previously treated for these disorders. There is some evidence that a low-fat diet may reduce the incidence of actinic keratosis in patients with a history of nonmelanoma skin cancer.[8]

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BASAL CELL AND SQUAMOUS CELL CARCINOMA. The great majority of skin cancers are basal cell carcinomas, which are completely curable if diagnosed early and treated appropriately. Although they rarely metastasise, they have a tendency to be locally destructive. The remainder are mainly squamous cell carcinomas, which, although curable when treated early, have a greater risk of metastatic spread. Common precursor lesions for squamous cell carcinoma are actinic keratosis (solar keratosis) and Bowen's disease (squamous cell carcinoma in situ).

- Treatments for **actinic keratosis** and **Bowen's disease** include cryosurgery, curettage, excision, radiotherapy, laser treatment, photodynamic therapy (see Porfimer Sodium, p.764) using 5-aminolevulinic acid or methyl aminolevulinate, and topical fluorouracil or topical imiquimod.[1-5] Topical diclofenac or topical salicylic acid may be used for actinic keratosis.[2-4] The choice of treatment depends on the site and size of the lesion, evidence for efficacy, ease of application, and availability.[1]
- Treatment options for superficial low-risk **basal cell carcinomas** include curettage and electrodesiccation or cryosurgery.[6-9] Topical fluorouracil may be used for superficial lesions in some instances, as are topical imiquimod or photodynamic therapy using 5-aminolevulinic acid, methyl aminolevulinate, or porfimer.
- For superficial tumours at high-risk sites, and for most **squamous cell carcinomas**, excision with postoperatively determined margins or Mohs' micrographic surgery (tumour margins examined during the procedure) is more appropriate.[6-11] Radiotherapy is an alternative in patients at risk of surgical complications or where surgery would be difficult or extensive.

The prognosis with appropriate treatment is good, with 5-year disease free survival of over 90%. However, about 50% of patients will subsequently develop another skin cancer, and regular monitoring to detect this as early as possible is desirable.[7] In addition, patients should be educated about sun protection measures, and chemoprevention with retinoids may be appropriate for some high-risk patients (see Prophylaxis, in Malignant Neoplasms of the Skin, above).

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MELANOMA. Although cutaneous melanoma is rare it is the most aggressive skin cancer, accounting for the majority of all skin cancer deaths. Melanoma may arise in apparently normal skin or from an existing naevus. Early signs of a naevus that may indicate development of a melanoma are change in size, shape, or colour. Other signs include itching, ulceration, and bleeding. The most common site in women is the legs, and in men the back. For a discussion of sun protection measures in the prevention of melanoma, see Prophylaxis, in Malignant Neoplasms of the Skin, above.

Surgical resection is the mainstay of curative treatment for melanomas, and the margins of excision are determined by tumour depth.[1-6] Patients with thin tumours (less than 1 mm) can be treated with wide local excision only; patients with intermediate (1 to 4 mm) or thick (more than 4 mm) melanoma are at high risk for nodal disease, and lymph node dissection may also be performed if node biopsy is positive. Because of the high risk of recurrence after surgery in the latter group, there is great interest in adjuvant therapies. The most common adjuvant treatment is interferon alfa;[3,5,6] high-dose interferon has shown a clinical benefit in terms of relapse-free survival, but the effect on overall survival is less clear.[4,7-10] As toxicity is a significant problem with high-dose therapy, both low-dose extended-duration[11] and intermediate[12] dosage regimens have been studied, but neither have shown benefit in relapse-free or overall survival. Isolated limb perfusion with melphalan has been used as adjuvant therapy, but a review of four randomised trials failed to show any survival benefit for this compared with surgery alone.[13] Similarly, systemic chemotherapy has not proved useful in the adjuvant setting.[14] Various melanoma vaccines (e.g. GM2 ganglioside, autologous melanoma-associated antigens) are being investigated for adjuvant use,[15] but high-dose interferon alfa has been shown to produce greater clinical benefit than vaccination with GM2.[9] Isolated recurrences are treated with surgical resection.

For patients who present with metastatic melanoma the 5-year survival rate is poor.[14] There is no evidence to show that any systemic treatments are better than best supportive care in these patients.[16] Because of this, surgery is still considered an option, and a few patients may survive long term after resection of isolated metastases. For patients with a finite number of in-transit metastases (tumour involves skin or subcutaneous tissue more than 2 cm from the primary tumour but not beyond the regional lymph nodes) that cannot be fully excised or are unresectable, options include intralesional injection with BCG vaccine or interferon alfa, topical imiquimod, isolated limb perfusion with melphalan, or radiation therapy.[3] Chemotherapy has been tried in disseminated disease,[4-6,17] and dacarbazine, with a response rate of about 20%, is the most common single agent. However, the response duration is usually only 4 to 6 months, and complete responses are rare. The orally active analogue temozolomide produces similar responses,[18] and is an alternative.[3] Nitrosoureas (such as carmustine, lomustine, and semustine) have response rates around 15% as single agents.[17] Fotemustine appears to be more active, particularly in the treatment of brain metastases. Other drugs with a response rate of about 15% include cisplatin, vinblastine, vindesine, docetaxel, and paclitaxel; response duration has generally been poor.

Combination regimens have been used, such as CVD (cisplatin, a vinca alkaloid, and dacarbazine). Tamoxifen has also been added to regimens, on the hypothesis that melanoma is oestrogen-dependent; an example is the CDBT or Dartmouth regimen (cisplatin, dacarbazine, carmustine, and tamoxifen). However, a randomised study found that this regimen was no more effective than dacarbazine alone,[19] and there is a lack of evidence that tamoxifen potentiates the action of cytotoxics in melanoma.[17] Although the combination of temozolomide and interferon alfa has been reported to increase response rates compared with temozolomide alone, overall survival was no different and toxicity was worse.[20]

Cytokines such as interferon alfa and interleukin-2 have similar activity to chemotherapy in metastatic melanoma.[17] Cytotoxic chemotherapy has been given with these cytokines and there have been some reports of improved response rates, but large controlled studies are needed to confirm a benefit. Melanoma vaccines are also being used or investigated in metastatic or recurrent disease,[15] as are gene therapy, antiangiogenic agents such as thalidomide,[17] and the antisense oligonucleotide oblimersen.[21]

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Malignant neoplasms of the testis. Testicular cancer only accounts for about 1% of all male malignancies but it is the most common cancer in young men. Patients with a history of cryptorchidism are at increased risk. About 95% of testicular tumours arise in germ cells, and 40% or so of these are pure seminomas. The remainder are collectively known as nonseminomatous germ cell tumours (NSGCT) in the WHO classification, and are commonly of mixed cell types with or without a seminoma component. Nonseminomatous tumours have been referred to as teratomas in the British classification system, but this term has a more specific meaning in the WHO classification.[1]

Metastasis first occurs to the lymph nodes, then, in advanced disease, to distant sites such as lung, liver, brain, and bones. The leading symptom is a hard, painless swelling of the testis, but once metastasis occurs the patient may present with back pain (due to enlargement of retroperitoneal lymph nodes), cough, dyspnoea, gynaecomastia due to chorionic gonadotrophin production, or weight loss.

Surgical removal of the testis (orchidectomy) when diagnosis is confirmed is fundamental to the treatment of all types of testicular cancer, but further therapy depends upon the disease type and stage.[1-4]

In patients with **nonseminomatous** disease with the tumour confined to the testis (stage I), options after orchidectomy include surveillance or a short course of adjuvant chemotherapy. With surveillance, about 20 to 30% of patients will relapse and are subsequently treated with curative chemotherapy. Surveillance is thus not appropriate for patients who are unable to undergo regular follow-up. Similarly, in the UK, patients who have prognostic factors suggesting a high risk of relapse such as vascular or lymphatic invasion have been treated with adjuvant chemotherapy with 2 cycles of BEP (bleomycin, etoposide, and cisplatin),[1,3] which will prevent relapse in the vast majority of cases.[1] In the USA, retroperitoneal lymph-node dissection may be carried out to further stage the disease before making a decision regarding surveillance or adjuvant chemotherapy.[4] If resected nodes are clear, patients undergo surveillance, but if they involve tumour (stage II) the decision to give adjuvant chemotherapy is based on the degree of nodal involvement and the ability of the patient to undergo regular follow-up.[4]

Where metastasis to the lymph nodes (stage II) or beyond (stage III) has occurred, standard postorchidectomy therapy is now combination chemotherapy with BEP,[1,3,4] or EP (etoposide and cisplatin),[4] which have largely replaced the effective but more toxic PVB regimen (cisplatin, vinblastine, and bleomycin).[2,5] Based on serum markers and the presence or absence of non-pulmonary visceral metastases, patients with metastatic disease can be categorised into good, intermediate, and poor-risk groups.[4] Consequently, there has been interest in minimising the treatment in patients with good prognosis in order to reduce long-term morbidity. In such patients, 3 cycles of BEP,[1,4,6,7] or 4 cycles of EP, may be adequate.[2,4,6] The substitution of carboplatin for cisplatin has resulted in a 10% lower relapse-free survival, and slightly reduced overall survival, and is not usually recommended,[2,6] although some have reported good results with such a regimen in children.[8] There is evidence that overall survival is improved by increased dose-intensity of etoposide and perhaps bleomycin.[9] Standard management for patients with intermediate- or poor-risk disease is 4 cycles of BEP.[1,4,6,7] However, less than 50% of poor-risk patients achieve a durable response and they may be offered more intensive chemotherapy such as accelerated therapy, dose escalation with use of haematopoietic growth factors, or high-dose chemotherapy with stem cell support, with the aim of improving responses. So far, those intensive treatments evaluated in randomised clinical studies have not proved more effective than BEP, and have often been more toxic.[2,3] Studies are ongoing.[2] Secondary resection of residual tumour after chemotherapy is usual.[1-4]

Patients who fail, or who relapse after, standard chemotherapy have a poor prognosis, with an overall survival of only 20 to 25%.[2] A common salvage regimen is cisplatin and ifosfamide with either vinblastine or paclitaxel.[4,6] High-dose chemotherapy with stem cell support may also be considered.[1,2,4,6,7,10] Drugs with activity as single agents in relapsed disease include paclitaxel, oxaliplatin, and gemcitabine.[1,2,6,7]

Seminoma is extremely sensitive to radiation, and adjuvant radiotherapy is the treatment of choice after orchidectomy in limited disease (stage I) and disease with low tumour burden (stages IIA and IIB).[1-4,6,7] About three-quarters of patients have stage I disease at diagnosis and cure rates are between 95 and 100%. However, seminoma also responds very well to chemotherapy such as adjuvant single-agent carboplatin;[6,7] it has been compared with adjuvant radiotherapy for stage I disease. One study[11] found that after 4 years the relapse rates were similar, but long-term follow-up was required. Chemotherapy is also being used in some patients with stage IIB disease.[1] Patients with stages IIC to III seminoma have a relapse rate of over 35% after adjuvant radiotherapy, and adjuvant chemotherapy is preferred.[1,2,4] Standard regimens are BEP (3 cycles for good prognosis patients and 4 cycles for others[4]), or EP,[1,4] which produce survival rates of about 90%.[2] Salvage regimens for relapsed or unresponsive seminoma are similar to those used for nonseminomatous disease.[4]

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Malignant neoplasms of the thymus. Thymomas are tumours of the mediastinum, arising from thymic tissue. They are rare, and most commonly present in patients between 40 and 60 years of age. Thymoma originates from the epithelium of the thymus but may also contain a lymphocyte component, which is probably not neoplastic. Up to 50% of patients are asymptomatic, and others have local symptoms such as cough, chest pain, dyspnoea, and obstruction of the vena cava; paraneoplastic syndromes such as myasthenia gravis, red cell aplasia, and hypogammaglobulinaemia may also develop.

Thymomas may be classified based on cell type; they are also staged as non-invasive (encapsulated, stage I), invasive (localised, stage II; extensive, stage III; and disseminated, IVa), and metastatic (IVb). The majority of patients present with non-invasive disease, and can be treated solely by surgical resection with low recurrence rates and long-term survival approaching 100%.[1-3] Use of adjuvant radiation therapy for stage II and III thymoma is controversial.[4] Some recommend postoperative radiotherapy after complete surgical resection,[1,2] whereas others consider it to be beneficial only in patients with incomplete resection; late complications of radiation therapy may occur.[4]

In patients with unresectable invasive disease, primary radiation therapy has been used to shrink the thymoma to make it resectable.[2] Radiotherapy alone has also been used, with conflicting results.[2] There is increasing interest in combined modality approaches to improve survival in this group.[1-4] Chemotherapy has also been used to shrink tumours, allowing for resection.[2] Postoperative radiotherapy and/or chemotherapy is then given.[2,4,5] Chemotherapy regimens used in this approach are similar to those used in metastatic disease.

Therapy for recurrent or metastatic disease is not well established because of the rarity of the condition.[1-3] Case series and phase II studies have shown that the tumour is chemosensitive. Evidence that cisplatin had activity against thymoma has led to much interest in cisplatin-containing regimens such as cisplatin, doxorubicin, and cyclophosphamide (PAC), and the same drugs with addition of vincristine.[1-4] Ifosfamide is also active as a single agent against thymoma, and has been given with cisplatin and etoposide.[1,3] A combination of carboplatin and paclitaxel is under investigation.[3] Interleukin-2 has not proved beneficial.[1,3] There is some evidence that thymomas possess somatostatin receptors, and there have been a few reports of the benefit of octreotide.[1,3]

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Malignant neoplasms of the thyroid. Thyroid cancer accounts for only about 1% of all malignancies. The incidence is reportedly higher in women than men, in patients who received irradiation of the thyroid during childhood, and in populations where goitre is endemic. The natural history varies with the cell type and degree of differentiation. Well-differentiated papillary or follicular tumours (which constitute about 70% and 15% of cases, respectively) are very slow to grow and metastasise, sometimes persisting for years with little change in size and extent, although they may prove more aggressive in children. In contrast medullary carcinomas (5 to 10% of cases), which develop from the cells responsible for calcitonin secretion, and undifferentiated (anaplastic) tumours (5%) metastasise early and follow a much more rapid and aggressive course. About 25% of medullary cancers are hereditary, including those due to multiple endocrine neoplasia type 2.

The well-differentiated types usually present as a thyroid nodule, although most nodules are not malignant, while with anaplastic tumours there is usually bulky disease and often difficulty in breathing due to encroachment on the tracheal lumen.

In patients with **well-differentiated tumours** total or partial thyroidectomy is the treatment of choice.[1-6] This may be followed by a course of iodine-131 to destroy any residual tumour, although in low-risk patients the prognosis after surgery alone is so favourable that iodine-131 is not usually recommended.[1-6] Levothyroxine treatment should be given to all patients to suppress thyroid stimulating hormone (TSH) production, and must be continued for life.[1-7] Ten-year survival of up to 85% in patients with follicular tumours and up to 93% with papillary tumours has been seen.[4] External radiation therapy may be considered in patients with evidence of extrathyroid extension at the time of surgery.[4,5] Disease recurrence is commonly treated with further surgery, ablative iodine-131 therapy or external radiation therapy.[1,2,4-6]

In patients with **medullary cancers** total thyroidectomy and neck dissection are indicated, with levothyroxine treatment if needed.[2-4] Ten-year survival of 60 to 70% has been reported.[7,8] Adjuvant external beam radiotherapy may be used in patients at high risk of regional recurrence[3,4] but routine use has not shown any survival benefit.[2] Prophylactic thyroidectomy may be considered in patients with a hereditary predisposition to medullary cancer.[3,8] Resection may relieve symptoms in patients with **anaplastic tumours**, but cure is impossible and treatment is purely palliative, with survival measured in months.[3,4,7,9] Neither medullary[8] nor anaplastic tumours[7] are sensitive to iodine-131. External radiation therapy is commonly used.[2,3,9]

Chemotherapy has been tried in anaplastic thyroid cancer, as well as in unresponsive disease of other cell types, with limited benefit.[2,6] Drugs tried, often in combination regimens, include cisplatin, cyclophosphamide, bleomycin, dacarbazine, doxorubicin, fluorouracil, paclitaxel, and vincristine.[4,7-9] The vascular targeting agent combretastatin A4 phosphate is under investigation.[4]

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Neuroblastoma. Neuroblastoma accounts for about 7% of all childhood malignancies overall but is probably the most frequent neoplasm in the first year of life. Three-quarters of all cases present before the age of 5 years. The tumour is derived from cells of the neural crest, and may occur anywhere within the sympathetic nervous system, notably the sympathetic ganglia and the adrenal medulla. Clinical behaviour ranges from spontaneous remission to rapid metastatic progression and death. Sites of metastasis include lymph nodes, bone marrow, liver, and skin. Adverse prognostic factors include age over 1 year at diagnosis, stage IV (distant metastases), and amplification of the oncogene MYCN.

Progress in the treatment of neuroblastoma over the last 20 years has increased 10-year survival to about 60% overall, although in patients with disseminated disease the gains have been modest.[1]

In those with localised disease (stage I or II) surgical resection alone is appropriate, with good long-term survival prospects. In addition, asymptomatic infants less than one year of age with localised tumours and limited dissemination (stage IV special) usually have a high rate of tumour regression, and can be considered for surgical resection then close observation.[1] Low-dose chemotherapy generally arrests tumour progression should this occur.

In those with localised but unresectable disease (stage II and III), subtotal surgical resection may be followed by standard-dose chemotherapy.[1] Chemotherapy regimens include cyclophosphamide and doxorubicin, sometimes with vincristine for good prognosis patients, and with the addition of cisplatin and etoposide (or teniposide) for poorer prognosis patients. Further surgery may be given, with further chemotherapy and/or radiotherapy used in those with residual disease.[1]

Disseminated disease (stage IV) and tumours with adverse prognostic features such as MYCN amplification are often more resistant to chemotherapy, and more intensive therapy is used.[1,2] Surgery and radiation therapy may be combined with chemotherapy. Regimens used for remission induction include cyclophosphamide, doxorubicin, cisplatin, etoposide or teniposide, and vincristine. Another option is cisplatin, etoposide, and vindesine alternating with vincristine, dacarbazine, ifosfamide, and doxorubicin.[1] After remission induction, consolidation with myeloablative chemotherapy and autologous stem cell or bone marrow rescue may be used. Maintenance therapy with oral cyclophosphamide is being investigated. Isotretinoin, fenretinide, and monoclonal antibodies are also being investigated for their ability to maintain remissions after chemotherapy.[1,3] Targeted radiation, using iodine-131-labelled *m*-iodobenzylguanidine, which is actively taken up by cells synthesising catecholamines, may be used for scanning, and is also being investigated for treatment.[4]

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Retinoblastoma. Retinoblastoma is the most common eye tumour in children and accounts for about 3% of all childhood malignancies (for other malignant neoplasms of the eye, see above). In 60 to 70% of cases the tumour is sporadic and non-hereditary, producing a unilateral, unifocal lesion. In the remaining 30 to 40% of cases there is an abnormal tumour suppressor gene (RB1) inherited: these tumours are typically bilateral and are sometimes associated with an intracranial neuroblastic tumour (trilateral retinoblastoma or pinealoblastoma). In addition, patients with the hereditary form are at very high risk of secondary primary malignancies, particularly osteosarcoma and soft tissue sarcomas. The most common manifestations of retinoblastoma are leukocoria (white pupil), strabismus (squint) and nystagmus. Retinoblastoma is confined to the eye(s) (intra-ocular) at presentation in about 80% of patients, although the majority have extensive disease within the eye. Nevertheless, 5-year disease-free survival after treatment in these patients is over 90%. In contrast, patients with extra-ocular disease in the tissues around the eye, or with metastatic spread to the CNS and beyond, have a 5-year survival of less than 10% despite treatment.

The aim of treatment for intra-ocular retinoblastoma is to cure the disease, and to preserve as much vision as possible.[1-5] In patients with unilateral tumours, enucleation (removal of the eye) is the standard primary treatment when there is no expectation of useful vision (e.g. extensive disease within the eye). In bilateral retinoblastoma, standard treatment was enucleation of the advanced eye and external beam radiation therapy in the less advanced eye. However, there is increasing use of therapies to preserve the eye and to reduce the use of external radiotherapy which further increases the risk of secondary malignancies.[2-4,6] These include local treatments such as cryotherapy, thermotherapy, and plaque radiotherapy. Intravenous neoadjuvant chemotherapy may be given before local treatment to reduce tumour size (chemoreduction); regimens usually include carboplatin, etoposide (or teniposide), and vincristine.[2-4] Ciclosporin has also been included to overcome the multidrug resistance gene, P-glycoprotein.[3,6]

Patients who are found to have optic nerve involvement (micrometastatic retinoblastoma) on enucleation are at high risk of recurrence. Although there is no consensus on further treatment, these patients are often given adjuvant chemotherapy (cyclophosphamide, doxorubicin, and vincristine) and radiotherapy.[3]

Patients with orbital extension may be treated with enucleation, radiotherapy, and intensive chemotherapy.[3] Regimens typically include cyclophosphamide, doxorubicin, and vincristine, and may include carboplatin and etoposide. Intrathecal methotrexate and cranial irradiation may be added for CNS involvement or trilateral retinoblastoma. Metastatic disease may be treated similarly, but although combination chemotherapy may produce a response it is rarely curative in such advanced disease. High-dose chemotherapy with autologous stem cell rescue has been tried in metastatic disease, but it has not been effective for disease involving the CNS.[4]

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Sarcomas. The sarcomas are tumours arising from mesodermal cells which form the bone and connective tissue (as opposed to carcinomas, which arise from ectodermal and endodermal cells, and leukaemias and lymphomas which arise from the bone marrow and immune system).

Sarcomas are uncommon, and vary considerably in their sites, presentation, and prognosis. The primary malignancies of bone include osteosarcoma and Ewing's sarcoma, which most often occur in older children and adolescents, and chondrosarcoma which is most common in later life. Soft tissue sarcomas include those of fibrous tissue (fibrosarcoma), skeletal muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma), adipose tissue (liposarcoma), and blood vessels (a group which includes Kaposi's sarcoma).

BONE SARCOMA. The commonest primary malignant tumour of bone is **osteosarcoma** (osteogenic sarcoma) which accounts for about 3 to 4% of all childhood malignancies. It is composed of malignant osteoblasts which form an osteoid matrix within which new bone formation may occur. Most osteosarcomas are aggressive high-grade malignancies which destroy overlying cortical bone and invade adjacent soft tissue, as well as spreading along the medulla. Metastasis, almost exclusively via the vascular system to the lungs and other distant sites, is usual and occurs early.

The main therapy is surgery, with an increasing trend to more conservative, limb-sparing operations rather than amputation. Adjuvant chemotherapy is an important component of therapy, however, as metastasis of the tumour is common.[1-4] Combinations of cisplatin, doxorubicin, ifosfamide, and high-dose methotrexate are recommended.[3,4] Neoadjuvant chemotherapy is often given before surgery to attack micrometastases, shrink the primary tumour and enable evaluation of the tumour response.[3,5] Aggressive treatment regimens can result in long-term relapse-free survival rates of 70%, although patients with overt metastatic disease at presentation have a poorer prognosis.[4,5] Osteosarcomas are relatively resistant to radiation therapy;[4] however, for unresectable high-grade osteosarcoma, radiotherapy followed by adjuvant chemotherapy is recommended.[3]

Like osteosarcoma, **Ewing's sarcoma** is seen mainly in adolescents and older children. It is a round cell tumour that most often arises in the pelvis or the long bones of the limbs. There may be diffuse erosion of the bone and marked periosteal reaction. It spreads through the medullary cavity, and metastases to lung and other bones are common.

Initial treatment is neoadjuvant chemotherapy for several months.[3,4] Combinations of cyclophosphamide, ifosfamide, etoposide, doxorubicin, and vincristine are recommended,[3,4] given good results from addition of ifosfamide and etoposide to standard regimens.[4,6] Dactinomycin has also been used in standard regimens,[4,6] although its use for localised disease is controversial.[4] Typically, patients are then given local therapy (surgery, radiation, or both), with additional adjuvant chemotherapy.[3,4] Ewing's sarcoma is relatively radiosensitive,[4] and unresponsive or progressive disease is best managed with radiation therapy with or without surgery, followed by chemotherapy or best supportive care.[3] The prognosis of recurrent Ewing's sarcoma is poor.[3] High-dose chemotherapy with stem cell rescue has been investigated for relapsed or progressive disease, with promising initial results.[3,4]

Chemotherapy appears to have little place in the treatment of other bone sarcomas such as **chondrosarcoma**[3,4] or **osteoclastoma** (giant cell tumours of bone);[4] it has been used in high-grade **fibrosarcomas** and in **histiocytoma** but its value is uncertain.

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KAPOSI'S SARCOMA. Kaposi's sarcoma is a tumour of endothelial or spindle cell origin. In its classical form it manifests as red or violet cutaneous lesions of the limbs in elderly men, usually of Jewish or Mediterranean ancestry. An endemic form is also seen in certain areas of Africa.[1] Lesions may eventually affect the whole of the skin, upper airways, gastrointestinal tract, lungs, and lymph nodes, but in general disease is only very slowly progressive, and may require no treatment. Patients given immunosuppressive therapy may be at greater risk of developing Kaposi's sarcoma, particularly if they are from ethnic groups that are susceptible to the classic or endemic forms of the disease.[1] In recent years an epidemic form of the disease has appeared in patients with disease due to HIV infection (p.856). HIV-associated Kaposi's sarcoma is more aggressive, with a greater tendency to disseminated and metastatic disease.

A novel herpesvirus (human herpesvirus 8, HHV8) has been implicated in the pathogenesis of Kaposi's sarcoma. HHV8 induces changes in endothelial cells that make them more susceptible to inflammatory cytokines and angiogenesis.[2] Some antivirals, such as cidofovir and to a lesser extent foscarnet and ganciclovir, have shown activity against HHV8 *in vitro*, but they have not been equally successful in treating Kaposi's sarcoma *in vivo*. Treatment with HAART has greatly reduced the occurrence of Kaposi's sarcoma in AIDS patients, and may cause regression of milder forms of the disease, but this is thought to be due to improvements in immune function rather than a direct effect on Kaposi's sarcoma.[3] The development of Kaposi's sarcoma is likely to be multifactorial, and as infection with HHV8 alone does not produce disease, and the replication of HHV8 in sarcoma cells is low, antiviral therapy alone is unlikely to be sufficient to control symptoms.[3]

Patients with classic or endemic Kaposi's sarcoma are often treated with surgery or radiotherapy of individual lesions.[1] Extensive or recurrent disease may be treated with vinca alkaloids, bleomycin, doxorubicin, and dacarbazine, alone or in combination.[1] Etoposide and interferon alfa have also been tried.[1] Patients with immunosuppression-associated Kaposi's sarcoma may be treated similarly to those with the classic form, or preferably by alteration of the immunosuppressive regimen if this can be done without graft loss.[1] Clinical and histological regression of cutaneous Kaposi's sarcoma has been described in a small number of renal transplant recipients when ciclosporin and mycophenolate mofetil were replaced with sirolimus.[4]

The epidemic form of Kaposi's sarcoma is associated with HIV infection, and seen particularly in homosexual patients. HAART may control Kaposi's sarcoma, and is considered first-line therapy,[5-7] but the response is unpredictable, so specific therapy is often needed.[1] Localised disease may be managed with cryotherapy or radiotherapy, but intralesional vinblastine, interferon alfa, and topical alitretinoin are also used.[2,5-8] Photodynamic therapy is also used.[6,7]

Systemic chemotherapy is generally reserved for patients with more extensive disease or mucosal or visceral involvement.[5,7] In patients with a CD4 cell count of 200 cells/mm^3 or above, treatment with interferon alfa, in combination with zidovudine, has been advocated by some, but systemic chemotherapy is the treatment of choice.[1-3,5,6] The main combination regimens use a vinca alkaloid and bleomycin, with or without doxorubicin.[2,3] Liposomal formulations of doxorubicin and daunorubicin have produced response rates of 40-85%, and may be less toxic than conventional chemotherapy;[2,3,8] it has been suggested that a liposomal anthracycline is the drug of choice in extensive disease.[1,2,5-7] Paclitaxel is also used as a single agent in advanced disease.[2,3,7,8] However, although highly effective, doses may need to be reduced if given to patients taking HAART because of the risk of drug interactions.[5,7] Although data are limited, docetaxel may be a reasonable alternative.[7] Some response has also been reported for oral etoposide.[1]

Control of Kaposi's sarcoma has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but tumour regression ceased and regrowth occurred when dosage was reduced or withdrawn.[9] Further reports of intralesional or systemic use have included partial remissions and disease stabilisation, as well as no effect or disease progression. The reasons for these contradictory results are unclear, but they may be due to variability in chorionic gonadotrophin preparations, which contain a mixture of biological contaminants. A cytotoxic ribonuclease and the degradation product of the β-hCG subunit have been proposed as active contaminants against Kaposi's sarcoma, but other contaminants may stimulate the tumour.[10] Other lines of investigation include the use of sulfated polysaccharide peptidoglycans, imatinib, other inhibitors of angiogenesis including thalidomide, and the retinoids.[1,5-8]

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9. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; **346:** 118–19.
10. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; **204:** 330–3.

SOFT-TISSUE SARCOMA. Soft-tissue sarcomas are a varied group of malignant tumours that originate from mesenchymal stem cells residing in muscle, fat, or connective tissue,[1,2] and whose subtypes vary in terms of prognosis and response to different treatments.[3] The majority of soft-tissue sarcomas occur in the limb or limb girdle; some occur within the abdomen (retroperitoneal), in the head or neck, or in the gastrointestinal tract.[4,5] Patients have a 5-year survival rate of about 50 to 60%;[4] survival in those with extremity sarcomas is better than that in patients with retroperitoneal sarcomas.[2] Tumours often metastasise to the lung; those arising in the abdomen metastasise to the liver and peritoneum.[4]

Rhabdomyosarcoma is the commonest soft-tissue sarcoma in childhood, and is thought to arise from progenitor cells for skeletal muscle. The most frequent sites are the head and neck, genito-urinary tract, and extremities. Some genetic disorders are associated with rhabdomyosarcoma.[6,7] All patients are presumed to have micrometastatic disease at diagnosis; histologically the most common types are embryonal, which occurs at an earlier age, and alveolar, which is more common in adolescents.[7]

The **gastrointestinal stromal tumours** (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel.[4,8,9] Symptoms may include abdominal pain, anorexia, weight loss, haemorrhage, changes in bowel movements, bowel obstruction, or perforation. Patients with liver metastases may have oedema of the lower extremity, ascites, or jaundice.[10] Spread to the lungs and other locations is seen only in advanced cases.[4]

Surgery is the primary **therapy** for soft-tissue sarcomas,[1,2,4,8] and may be curative for localised disease.[5,11] Radiotherapy, as external-beam therapy or brachytherapy, may be given with surgery, or alone if surgery is inappropriate or declined by the patient.[5] Radiation may be given pre-operatively, during surgery, or postoperatively;[1] optimal timing is unclear.[5,8] Similar rates of local control and progression-free survival have been reported for pre- and postoperative radiotherapy, although pre-operative treatment has been associated with a greater incidence of wound complications, especially in lower extremity tumours.[4] Postoperative radiation can cause acute and delayed bowel toxicity in those with retroperitoneal tumours, and significant toxicity has occurred with the use of brachytherapy, especially when used in the upper abdomen.[2]

Surgery and/or radiotherapy may be combined with chemotherapy. Pre-operative chemotherapy may allow for more efficient resection of the tumour.[1,8] The use of postoperative chemotherapy is controversial,[5,8] except for some tumours such as extraosseous Ewing's sarcoma or rhabdomyosarcoma. For these tumours, combinations of vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, or etoposide form the basis of most regimens.[5-8]

For those with unresectable or metastatic disease, chemotherapy may be palliative; ifosfamide and doxorubicin are routinely used in this setting.[5] These may be used as single agents or in combination; other acceptable single agent choices are dacarbazine, gemcitabine, or liposomal doxorubicin.[4] Data support the use of adjuvant doxorubicin-based chemotherapy to improve disease-free survival;[12] however, overall survival is not improved. For palliative treatment in advanced soft-tissue sarcoma, a systematic review[13] concluded that combination chemotherapy did not significantly increase survival rates compared with single-agent doxorubicin. A retrospective analysis[14] found that, in patients with high-risk disease, clinical benefits of doxorubicin-based chemotherapy were not sustained beyond 1 year. There is no consensus on the best second-line chemotherapy regimen for patients with metastatic disease refractory to doxorubicin- or ifosfamide-based regimens.[2,3] Dose-intensified combination regimens, with colony-stimulating factor support, have been investigated as adjuvant therapy[15] and in advanced disease;[16] although both these studies found a delay in disease progression, a beneficial effect on overall survival was only found in the former. Intensive combination chemotherapy benefited a subgroup of children with metastatic rhabdomyosarcoma and fewer than 2 unfavourable risk factors, in terms of event-free survival and overall survival. However, most patients have more than 2 risk factors; these patients should be considered for novel first-line therapies. No evidence was found for improved outcome after consolidation therapy with high-dose melphalan and autologous bone marrow or peripheral-blood stem cell rescue.[17] Response to topotecan has been reported in a study of metastatic rhabdomyosarcoma,[18] and trabectedin has shown some activity in advanced soft-tissue sarcomas.[3,5] Tasonermin and melphalan can be used together for isolated limb perfusion of unresectable soft-tissue sarcomas, but severe toxicity may limit use of this regimen. Potential salvage therapy options after failure of first-line therapy include paclitaxel, docetaxel, gemcitabine, trofosfamide, temozolomide, and various combinations thereof.[3]

Surgery is used for localised, resectable disease arising in the gastrointestinal tract, although this does not routinely cure GISTs; median time to recurrence after resection is about 2 years. Adjuvant imatinib is under investigation in this setting. Imatinib produces durable clinical benefit and objective responses in most patients with GISTS, including those with metastatic or unresectable disease. If the tumour responds to imatinib, surgical resection may be indicated. In patients with imatinib-resistant GIST, or who experience life-threatening adverse effects such as hepatotoxicity and fluid retention with imatinib, sunitinib may be considered.[4,8,9,19]

1. Mankin HJ, Hornicek FJ. Diagnosis, classification, and management of soft tissue sarcomas. *Cancer Control* 2005; **12:** 5–21.
2. Windham TC, Pisters PWT. Retroperitoneal sarcomas. *Cancer Control* 2005; **12:** 36–43.
3. Hartmann JT, Patel S. Recent developments in salvage chemotherapy for patients with metastatic soft tissue sarcoma. *Drugs* 2005; **65:** 167–78.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: soft tissue sarcoma (version 2.2008). Available at: http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf (accessed 17/06/08)
5. Clark MA, *et al.* Soft-tissue sarcomas in adults. *N Engl J Med* 2005; **353:** 701–11.
6. McDowell HP. Update on childhood rhabdomyosarcoma. *Arch Dis Child* 2003; **88:** 354–7.
7. Breitfeld PP, Meyer WH. Rhabdomyosarcoma: new windows of opportunity. *Oncologist* 2005; **10:** 518–27.
8. Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clin Proc* 2007; **82:** 1409–32.
9. Rubin BP, *et al.* Gastrointestinal stromal tumour. *Lancet* 2007; **369:** 1731–41. Correction. *ibid.*; **370:** 388.
10. D'Amato G, *et al.* Update on the biology and therapy of gastrointestinal stromal tumors. *Cancer Control* 2005; **12:** 44–56.
11. Pellitteri PK, *et al.* Management of sarcomas of the head and neck in adults. *Oral Oncol* 2003; **39:** 2–12.
12. Sarcoma Meta-analysis Collaboration (SMAC). Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 06/09/06).
13. Bramwell VHC, *et al.* Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 06/09/06).
14. Cormier JN, *et al.* Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: chemotherapy-associated outcomes. *J Clin Oncol* 2004; **22:** 4567–74.
15. Frustaci S, *et al.* Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol* 2001; **19:** 1238–47.
16. Le Cesne A, *et al.* Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 2000; **18:** 2676–84.
17. Carli M, *et al.* European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. *J Clin Oncol* 2004; **22:** 4787–94. Correction. *ibid.* 2005; **23:** 248.
18. Pappo AS, *et al.* Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. *J Clin Oncol* 2001; **19:** 213–19.
19. Cowie F. Treatment of rare cancers: gastrointestinal stromal tumours. *Br J Hosp Med* 2006; **67:** 361–4.

Aclarubicin *(BAN, USAN, rINN)*

Aclacinomycin A; Aclarubicina; Aclarubicine; Aclarubicinum; Aklarubicin; Aklarubisiini; Aklarubisin; NSC-208734. Methyl (1*R*,2*R*,4*S*)-4-(*O*-{2,6-dideoxy-4-*O*-[(2*R*,6*S*)-tetrahydro-6-methyl-5-oxopyran-2-yl]-α-L-*lyxo*-hexopyranosyl}-(1→4)-2,3,6-trideoxy-3-dimethylamino-L-*lyxo*-hexopyranosyloxy)-2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxonaphthacene-1-carboxylate.

Акларубицин

$C_{42}H_{53}NO_{15}$ = 811.9.
CAS — 57576-44-0.
ATC — L01DB04.
ATC Vet — QL01DB04.

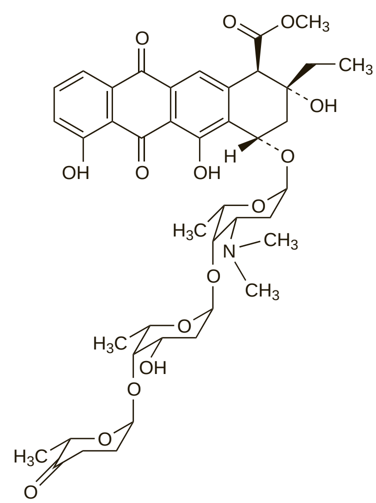

Description. Aclarubicin is an anthracycline antineoplastic antibiotic isolated from *Streptomyces galilaeus*.

Aclarubicin Hydrochloride *(BANM, rINNM)*

Aclarubicine, Chlorhydrate d'; Aclarubicini Hydrochloridum; Hidrocloruro de aclarubicina.

Акларубицина Гидрохлорид

$C_{42}H_{53}NO_{15}$,HCl = 848.3.
CAS — 75443-99-1.
ATC — L01DB04.
ATC Vet — QL01DB04.

Pharmacopoeias. In *Jpn.*

Stability. In a study of the stability of anthracycline antineoplastic agents in 4 infusion fluids—glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid—stability appeared to be partly related to pH; aclarubicin was most stable in sodium chloride injection, with a pH of 6.2, and any increase or decrease in pH appeared to affect stability adversely.[1]

1. Poochikian GK, *et al*. Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin Hydrochloride, p.712. Alopecia and cardiotoxicity may be less pronounced than with doxorubicin, and extravasation of aclarubicin causes less local tissue inflammation. Bone-marrow depression is dose-limiting, with platelet counts reaching a nadir 1 to 2 weeks after dosage, while leucopenia is greatest after 2 to 3 weeks; recovery generally occurs within 4 weeks. Myelosuppression may be particularly severe in patients who have received mitomycin or a nitrosourea.

Incidence of adverse effects. An early review[1] noted that a strikingly high incidence of ECG changes had been seen with aclarubicin, but that although acute cardiotoxicity occurred, the chronic cardiomyopathy classically associated with the anthracyclines (see p.713) appeared to be rare. Alopecia was also rare, although gastrointestinal disturbances and mucositis were as common or more common than with doxorubicin.

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.

Pharmacokinetics

Aclarubicin is rapidly distributed into tissues after intravenous injection. Clearance is triphasic, with a terminal elimination half-life of about 3 hours; the principal active metabolite has a terminal half-life of about 13 hours. Aclarubicin is extensively metabolised and only about 1% of the total dose is eliminated unchanged. It is excreted in urine, chiefly as metabolites; some is also eliminated in bile.

Uses and Administration

Aclarubicin is an anthracycline antibiotic with antineoplastic actions similar to those of the other anthracyclines (see Doxorubicin Hydrochloride, p.714), although it inhibits RNA synthesis more strongly than DNA synthesis. It has been used as the hydrochloride in the treatment of malignant blood disorders, such as acute myeloid leukaemia (p.652). Aclarubicin hydrochloride 104 mg is equivalent to about 100 mg of aclarubicin. The usual initial dose as a single agent has been the equivalent of 175 to 300 mg/m^2 of aclarubicin, divided over 3 to 7 consecutive days, as intravenous infusions over 30 to 60 minutes. Where appropriate and tolerated, maintenance doses of the equivalent of 25 to 100 mg/m^2 may be given as a single infusion every 3 to 4 weeks. The total dose that can be given over the patient's life-time depends upon cardiological status but most patients have not received more than 400 mg/m^2. Dosages may need to be reduced when given as part of a combination regimen.

◊ An early review of studies in patients with relapsed acute myeloid leukaemia confirmed the activity of aclarubicin, with reported complete remission rates of the order of 12 to 24%.[1] Doses varied from 10 to 30 mg/m^2 daily to higher doses of 75 to 120 mg/m^2 for 2 to 4 days; in general a total dose of about 300 mg/m^2 appeared to be necessary to induce remission. Less information was available concerning activity in acute lymphoblastic leukaemia, but response rates were lower than those in acute myeloid leukaemia. Results in the malignant lymphomas were generally disappointing.

Longer-term follow-up has confirmed that remission rates and survival are similar for induction regimens in acute myeloid leukaemia using either aclarubicin or daunorubicin.[2,3]

1. Warrell RP. Aclacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; **12:** 275–82.
2. de Nully Brown P, *et al*. Long-term survival and development of secondary malignancies in patients with acute myeloid leukemia treated with aclarubicin or daunorubicin plus cytosine arabinoside followed by intensive consolidation chemotherapy in a Danish national phase III trial. *Leukemia* 1997; **11:** 37–41.
3. Öberg G, *et al*. Long-term follow-up of patients ≥60 yr old with acute myeloid leukaemia treated with intensive chemotherapy. *Eur J Haematol* 2002; **68:** 376–81.

AE-941

Profile

AE-941 is an angiogenesis inhibitor derived from shark cartilage extract. It has been investigated for the treatment of non-small cell lung cancer and some other neoplasms.

◊ References.

1. Sauder DN, *et al*. Neovastat (AE-941), an inhibitor of angiogenesis: randomized phase I/II clinical trial results in patients with plaque psoriasis. *J Am Acad Dermatol* 2002; **47:** 535–41.
2. Gingras D, *et al*. Neovastat—a novel antiangiogenic drug for cancer therapy. *Anticancer Drugs* 2003; **14:** 91–6.

Alemtuzumab *(BAN, rINN)*

Alemtutsumabi; Alemtuzumabum; Campath-1; Campath-1H. Immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H γ1-chain antihuman antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer.

Алемтузумаб

CAS — 216503-57-0.
ATC — L01XC04.
ATC Vet — QL01XC04.

NOTE. The name FluCam has been used for a regimen of alemtuzumab with fludarabine. Distinguish from Flucam, which is ampiroxicam (p.19).

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641.

Alemtuzumab commonly causes bone marrow depression, which may be severe and prolonged; fatalities have occurred. Auto-immune anaemia and auto-immune thrombocytopenia and haemolytic anaemia have been reported less commonly; however, fatalities have been reported. Single doses greater than 30 mg, or cumulative weekly doses greater than 90 mg should not be used, because of the increased incidence of pancytopenia. Complete blood and platelet counts should be measured weekly during alemtuzumab therapy, and more frequently if anaemia, neutropenia, or thrombocytopenia occur. Treatment should be interrupted if severe myelosuppression or evidence of haematological toxicity are seen and stopped permanently if auto-immune anaemia or auto-immune thrombocytopenia develops. Lymphopenia may be profound with alemtuzumab therapy, and opportunistic infections are common, and occasionally life-threatening. Antimicrobial prophylaxis is recommended from the start of therapy until after completion; if serious infection occurs, treatment should be interrupted. Recovery of lymphocyte counts may take 6 months or longer after stopping treatment.

Alemtuzumab commonly causes an acute cytokine release syndrome. The reaction usually includes rigors, fever, nausea and vomiting, hypotension, rash, urticaria, pruritus, shortness of breath, headache, and diarrhoea. Rarer, more serious reactions may include bronchospasm, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, and cardiac arrest. Cardiac adverse effects have been fatal in some instances. These infusion-related reactions are most common at the start of therapy: the dose must be increased gradually when beginning treatment, or if it is interrupted for 7 days or more. Pre-medication with an oral or intravenous corticosteroid, oral antihistamine, and analgesic should also be used, particularly before the first dose, and with dose increases. If acute infusion reactions persist, the infusion time may be extended to 8 hours from the time of reconstitution.

Other adverse effects include fatigue, anorexia, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, chest pain, hypertension, cyanosis, and bradycardia or tachycardia. Localised oedema, stomatitis, mucositis, and abdominal pain have been reported, as have dizziness, paraesthesia, tremor, and taste loss. Confusion, insomnia or somnolence, depression, or anxiety may occur. Electrolyte disturbances include hyponatraemia and hypocalcaemia. Coughing, haemoptysis, sinusitis, bronchitis, and pharyngitis have been reported.

Alemtuzumab is contra-indicated for patients with active systemic infection, or underlying immunodeficiency.

Infection. Reactivation of hepatitis B[1] and CMV[2] has been reported with the use of alemtuzumab. Patients who have been pretreated with purine analogues or those with advanced disease and not responding to alemtuzumab therapy appear to be at highest risk for infectious complications. Recommendations for screening and prophylaxis[3] and guidelines for management[4] have been published. Six infection-related deaths have been reported[5] after previously untreated patients with B-cell chronic lymphocytic leukaemia were treated with fludarabine and rituximab, followed by alemtuzumab. These deaths may have resulted from a prolonged period of immunosuppression due to the sequencing of these drugs without sufficient recovery time. In the EU, alemtuzumab is licensed for use in patients for whom fludarabine combination chemotherapy is not appropriate.

1. Iannitto E, *et al*. Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; **74:** 254–8.
2. Laurenti L, *et al*. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. *Haematologica* 2004; **89:** 1248–52.
3. Thursky KA, *et al*. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol* 2006; **132:** 3–12.
4. O'Brien SM, *et al*. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clin Lymphoma Myeloma* 2006; **7:** 125–30.
5. Bayer, UK; Genzyme, UK. Important safety information: six infection-related deaths reported after treatment with MabCampath (alemtuzumab) following Fludarabine+Rituximab induction in patients with B-Cell Chronic Lymphocytic Leukemia (CLL) (issued 11th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014104&RevisionSelectionMethod=Latest (accessed 12/05/08)

Interactions

There are no formal interaction studies with alemtuzumab; however, it is recommended that it should not be given within 3 weeks of other chemotherapy drugs, and that patients should not receive live viral vaccines for at least 12 months after receiving alemtuzumab.

Pharmacokinetics

In patients with B-cell chronic lymphocytic leukaemia, distribution of alemtuzumab is mainly to the extracellular fluid and plasma. Over 12 weeks, clearance has been found to decrease with repeated dosing, with consequent accumulation in plasma, and the rate of elimination to approach zero-order kinetics. The half-life is reported to be 8 hours after a first dose of 30 mg, and 6 days after the last 30 mg dose. Steady-state concentrations are reached after about 6 weeks of therapy.

◊ References.

1. Rebello P, *et al*. Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy* 2001; **3:** 261–7.
2. Mould DR, *et al*. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007; **64:** 278–91.

Uses and Administration

Alemtuzumab is a humanised derivative of campath-1G, a rat monoclonal antibody to the CD52 antigen found on lymphocytes. Alemtuzumab is used in the treatment of B-cell chronic lymphocytic leukaemia (p.653). The dose of alemtuzumab must be increased gradually to avoid infusion-related reactions (see above). Alemtuzumab should be diluted in 100 mL sodium chloride 0.9% or glucose 5%. The initial dose is 3 mg daily, given as an intravenous infusion over 2 hours (it may be increased up to 8 hours in some patients, see above). This dose should be repeated daily until it is tolerated; the dose should then be increased to 10 mg daily. When this dose is tolerated, the maintenance dose of 30 mg can be started; this dose escalation usually takes 3 to 7 days. A maximum maintenance dose of 30 mg given three times weekly on alternate days can then be used for up to 12 weeks. The dose should be modified according to haematological toxicity.

Alemtuzumab is under investigation for induction therapy in transplantation (see Organ and Tissue Transplantation, p.1810, *et seq*). It is also under investigation for the treatment of multiple sclerosis.

◊ References.

1. Keating MJ, *et al*. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* 2002; **99:** 3554–61.
2. Osterborg A, *et al*. Clinical effects of alemtuzumab (Campath-1H) in B-cell chronic lymphocytic leukemia. *Med Oncol* 2002; **19** (suppl): S21–S26.
3. Dearden CE, *et al*. Alemtuzumab in T-cell malignancies. *Med Oncol* 2002; **19** (suppl): S27–S32.
4. Kennedy B, Hillmen P. Immunological effects and safe administration of alemtuzumab (MabCampath) in advanced B-cLL. *Med Oncol* 2002; **19** (suppl): S49–S55.
5. Rai KR, *et al*. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. *J Clin Oncol* 2002; **20:** 3891–7.

6. Hale G, *et al.* Alemtuzumab (Campath-1H) for treatment of lymphoid malignancies in the age of nonmyeloablative conditioning? *Bone Marrow Transplant* 2002; **30:** 797–804.
7. Frampton JE, Wagstaff AJ. Alemtuzumab. *Drugs* 2003; **63:** 1229–43.
8. Keating M, *et al.* Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. *Clin Lymphoma* 2004; **4:** 220–7.
9. Faderl S, *et al.* The evolving role of alemtuzumab in management of patients with CLL. *Leukemia* 2005; **19:** 2147–52.
10. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. *Transplantation* 2006; **81:** 1361–7.
11. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; **19:** 705–14.
12. Ravandi F, O'Brien S. Alemtuzumab in CLL and other lymphoid neoplasms. *Cancer Invest* 2006; **24:** 718–25.
13. Hillmen P, *et al.* Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 5616–23.

Administration. Subcutaneous use of alemtuzumab has been investigated as a means of reducing adverse infusion reactions associated with intravenous dosage. Studies have found it to be safe and effective.[1,2] Similar blood concentrations are achieved to those after intravenous use, although accumulation in the blood took longer to achieve with subcutaneous use, and higher cumulative doses were required.[3] Prolonged treatment with subcutaneous low-dose alemtuzumab (10 mg three times weekly for 18 weeks) has been reported to be as effective as intravenous infusion in patients with chronic lymphocytic leukaemia and a poor prognosis.[4]

1. Montillo M, *et al.* Safety and efficacy of subcutaneous Campath-1H for treating residual disease with chronic lymphocytic leukemia responding to fludarabine. *Haematologica* 2002; **87:** 695–700.
2. Lundin J, *et al.* Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood* 2002; **100:** 768–73.
3. Hale G, *et al.* Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood* 2004; **104:** 948–55.
4. Cortelezzi A, *et al.* A pilot study of low-dose subcutaneous alemtuzumab therapy for patients with hemotherapy-refractory [sic] chronic lymphocytic leukemia. *Haematologica* 2005; **90:** 410–12.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Campath; ***Austria:*** MabCampath; ***Belg.:*** MabCampath; ***Braz.:*** Campath; ***Cz.:*** MabCampath; ***Denm.:*** MabCampath; ***Fin.:*** MabCampath; ***Fr.:*** MabCampath; ***Ger.:*** MabCampath; ***Gr.:*** MabCampath; ***Hung.:*** MabCampath; ***Irl.:*** MabCampath; ***Israel:*** MabCampath; ***Ital.:*** MabCampath; ***Malaysia:*** MabCampath; ***Neth.:*** MabCampath; ***Norw.:*** MabCampath; ***Pol.:*** MabCampath; ***Port.:*** MabCampath; ***Rus.:*** Campath (Кэмпас); ***S.Afr.:*** MabCampath; ***Singapore:*** MabCampath; ***Spain:*** MabCampath; ***Swed.:*** MabCampath; ***Switz.:*** MabCampath; ***UK:*** MabCampath; ***USA:*** Campath.

Alitretinoin *(BAN, USAN, rINN)*

AGN-192013; Alitretinoiini; Alitretinoína; Alitrétinoïne; Alitretinoinum; ALRT-1057; BAL-4079; LG-100057; LGD-1057; NSC-659772; 9-*cis*-Retinoic Acid. (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

Алитретиноин

$C_{20}H_{28}O_2$ = 300.4.
CAS — 5300-03-8.
ATC — L01XX22.
ATC Vet — QL01XX22.

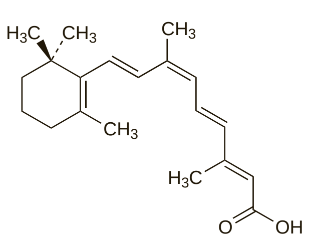

Adverse Effects and Precautions

Local skin toxicity may occur with topical application of alitretinoin, in particular erythema and oedema, and in some patients this may be dose-limiting. Pain, paraesthesia, rashes, pruritus, exfoliative dermatitis, and other skin disorders may also occur locally. Lymphadenopathy, phlebitis, cellulitis, and bacterial infections have been reported. Alitretinoin may have a weak photosensitising effect, and patients should minimise exposure of treated areas to sunlight or other ultraviolet light during therapy.

Interactions

Use of products containing diethyltoluamide is not recommended during alitretinoin therapy, as *animal* studies indicate an increase in diethyltoluamide toxicity with concurrent use.

Pharmacokinetics

Systemic absorption of topical alitretinoin is not considered to be extensive. *In-vivo* studies of oral doses indicate that alitretinoin is metabolised to 4-oxo-9-*cis*-retinoic acid.

Uses and Administration

Alitretinoin is a retinoid related to tretinoin (p.1618). It is used topically, as a 0.1% gel, in the management of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (p.675). It is applied directly to the lesions twice daily, increasing to up to 4 times daily if tolerated. Doses should be increased at intervals of at least 2 weeks. If local toxicity occurs, application frequency should be reduced, or treatment temporarily stopped, until the symptoms subside. EU licensed product information states that if no response is seen after 12 weeks, therapy should be stopped; however, US licensed product information states that some patients have required over 14 weeks to respond. Treatment may be continued as long as the patient responds. Oral formulations of alitretinoin are under investigation for the treatment of chronic hand dermatitis refractory to topical corticosteroids.

◊ References.

1. Cheer SM, Foster RH. Alitretinoin. *Am J Clin Dermatol* 2000; **1:** 307–14.
2. Bodsworth NJ, *et al.* Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol* 2001; **2:** 77–87.
3. Miles SA, *et al.* Antitumor activity of oral 9-cis-retinoic acid in HIV-associated Kaposi's sarcoma. *AIDS* 2002; **16:** 421–9.
4. Kurie JM, *et al.* Treatment of former smokers with 9-cis-retinoic acid reverses loss of retinoic acid receptor-beta expression in the bronchial epithelium: results from a randomized placebo-controlled trial. *J Natl Cancer Inst* 2003; **95:** 206–14.
5. Aboulafia DM, *et al.* 9-cis-Retinoic acid capsules in the treatment of AIDS-related Kaposi sarcoma: results of a phase 2 multicenter clinical trial. *Arch Dermatol* 2003; **139:** 178–86.
6. Ruzicka T, *et al.* Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; **140:** 1453–9.
7. Ruzicka T, *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158:** 808–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Panretin; ***Cz.:*** Panretin; ***Fr.:*** Panretin; ***Ger.:*** Panretin; ***Gr.:*** Panretin; ***Neth.:*** Panretin; ***Port.:*** Panretin; ***USA:*** Panretin.

Altretamine *(BAN, USAN, rINN)*

Altretamiini; Altretamin; Altretamina; Altrétamine; Altretaminum; Hexamethylmelamine; HMM; NSC-13875; WR-95704. 2,4,6-Tris(dimethylamino)-1,3,5-triazine; N^2,N^2,N^4,N^4,N^6,N^6-Hexamethyl-1,3,5-triazine-2,4,6-triamine.

Альтретамин

$C_9H_{18}N_6$ = 210.3.
CAS — 645-05-6.
ATC — L01XX03.
ATC Vet — QL01XX03.

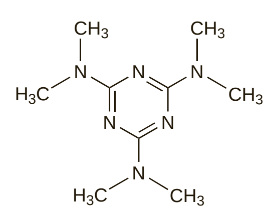

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Altretamine). A white crystalline powder. Insoluble in water; soluble in chloroform. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression is usually moderate, manifesting as leucopenia, thrombocytopenia, and anaemia, and may require dosage reduction; blood counts should be monitored regularly. Nausea and vomiting are common and usually moderate although they may be dose-limiting. Prolonged or high-dose therapy may be associated with neurotoxicity, both peripheral (neuropathies) and central (ataxia, depression, confusion, drowsiness, and hallucinations); neurological examination should be performed regularly and treatment interrupted or the dose reduced as appropriate. Renal toxicity may also be dose-limiting. Other rare adverse effects include rashes, alopecia, and hepatic toxicity.

Handling. Altretamine is irritant; avoid contact with skin and mucous membranes.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Pyridoxine appears to reduce the activity of altretamine.

Antidepressants. Severe and potentially life-threatening orthostatic hypotension developed in 3 patients who took *amitriptyline* or *imipramine* with altretamine and in a fourth patient who took *phenelzine* and altretamine.[1] One patient was able to tolerate the antineoplastic with *nortriptyline.*

1. Bruckner HW, Schleifer SJ. Orthostatic hypotension as a complication of hexamethylmelamine antidepressant interaction. *Cancer Treat Rep* 1983; **67:** 516.

Pharmacokinetics

Altretamine is well absorbed from the gastrointestinal tract after oral doses, but is rapidly demethylated in the liver producing variation in plasma-altretamine concentrations. The principal metabolites are pentamethylmelamine and tetramethylmelamine, which are excreted in urine. The elimination half-life has been reported to be 4 to 10 hours.

◊ References.

1. Damia G, D'Incalci M. Clinical pharmacokinetics of altretamine. *Clin Pharmacokinet* 1995; **28:** 439–48.

Uses and Administration

Altretamine is an antineoplastic agent structurally similar to the alkylating agent tretamine (triethylenemelamine) although its mode of action may be different. It is given orally and is licensed for use as a single agent in the palliative treatment of ovarian carcinoma (p.670). Altretamine has also been tried in lung cancer. The usual dose as a single agent in ovarian cancer is 260 mg/m^2 daily in four divided doses, for 14 or 21 consecutive days out of a 28-day cycle. Up to 12 cycles may be given. Therapy should be interrupted for at least 14 days, and subsequently restarted at a lower dose of 200 mg/m^2 daily, if the white cell count falls below 2000 cells/mm^3 or the platelet count below 75 000 cells/mm^3 or if neurotoxic or intolerable gastrointestinal symptoms occur. Lower doses are also used in combination regimens.

◊ Reviews.

1. Lee CR, Faulds D. Altretamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cancer chemotherapy. *Drugs* 1995; **49:** 932–53.
2. Manetta A, *et al.* Hexamethylmelamine as a single second-line agent in ovarian cancer: follow-up report and review of the literature. *Gynecol Oncol* 1997; **66:** 20–6.

Preparations

USP 31: Altretamine Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Hexalen; ***Cz.:*** Tretax†; ***Neth.:*** Hexalen; ***Norw.:*** Hexalen†; ***NZ:*** Hexalen†; ***Rus.:*** Hexalen (Гексален); ***Swed.:*** Hexalen†; ***Thai.:*** Hexalen; ***USA:*** Hexalen.

Alvocidib *(rINN)*

Alvocidibum; Avodenib; Flavopiridol. (−)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one.

Альвоцидиб

$C_{21}H_{20}ClNO_5$ = 401.8.
CAS — 146426-40-6.

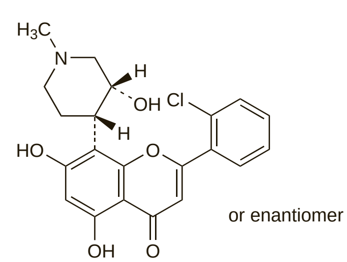

Alvocidib Hydrochloride *(rINNM)*

Alvocidib *(USAN)*; Alvocidib, Chlorhydrate d'; Alvocidibi Hydrochloridum; Hidrocloruro de alvocidib; HL-275; HMR-1275; L-868275; MDL-107826A; NSC-649890. (−)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one hydrochloride.

Альвоцидиба Гидрохлорид

$C_{21}H_{20}ClNO_5,HCl$ = 438.3.
CAS — 131740-09-5.

Profile

Alvocidib is an inhibitor of cyclin-dependent kinase that is under investigation as an antineoplastic for the treatment of chronic lymphocytic leukaemia.

Aminoglutethimide *(BAN, rINN)* ⊗

Aminoglutethimid; Aminoglutéthimide; Aminoglutethimidum; Aminoglutetimid; Aminoglutetimida; Aminoglutetimidas; Aminoglutetimidi; Aminoglutethimide; Ba-16038. 2-(4-Aminophenyl)-2-ethylglutarimide; 3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione.

Аминоглутетимид

$C_{13}H_{16}N_2O_2$ = 232.3.
CAS — 125-84-8.
ATC — L02BG01.
ATC Vet — QL02BG01.

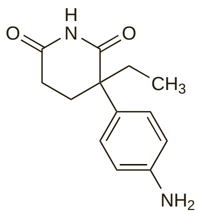

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Aminoglutethimide). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol.

USP 31 (Aminoglutethimide). A white or creamy-white, fine, crystalline powder. Very slightly soluble in water; readily soluble in most organic solvents. It forms water-soluble salts with strong acids. The pH of a 0.1% solution in dilute methyl alcohol (1 in 20) is between 6.2 and 7.3.

Adverse Effects

The most frequent adverse effects reported with aminoglutethimide include drowsiness, lethargy, and skin rashes (sometimes with fever); these generally diminish after the first 6 weeks of therapy. Dizziness and nausea occasionally occur. Leucopenia, thrombocytopenia, agranulocytosis, or severe pancytopenia have occurred rarely. Adrenal insufficiency may rarely occur, and there have been reports of other endocrine disturbances including hypothyroidism, and virilisation. Other rare effects include ataxia, headache, depression, gastrointestinal disturbances, hypercholesterolaemia, and orthostatic hypotension.

Overdosage may lead to CNS depression and impairment of consciousness, electrolyte disturbances, and respiratory depression.

Effects on the liver. Aminoglutethimide has been associated with reports of cholestatic jaundice, accompanied by rash[1,2] and fever,[2] and probably due to an idiosyncratic hypersensitivity reaction.[1] It has been suggested that liver function tests should be carried out in patients receiving aminoglutethimide who develop fever and eruptions.[2]

1. Gerber SB, Miller KB. Cholestatic jaundice and aminoglutethimide. *Ann Intern Med* 1982; **97:** 138.
2. Perrault DJ, Domovitch E. Aminoglutethimide and cholestasis. *Ann Intern Med* 1984; **100:** 160.

Effects on the lungs. Pulmonary infiltrates in a patient who developed progressive dyspnoea on starting therapy with aminoglutethimide were found to be due to diffuse alveolar damage and haemorrhage; thrombocytopenia was present but prothrombin and bleeding times were normal. The patient's gas exchange and chest radiographs improved on stopping aminoglutethimide and giving corticosteroids.[1] Blood and pulmonary eosinophilia, which resolved on stopping aminoglutethimide therapy, has also been reported.[2]

1. Rodman DM, *et al.* Aminoglutethimide, alveolar damage, and hemorrhage. *Ann Intern Med* 1986; **105:** 633.
2. Bell SC, Anderson EG. Pulmonary eosinophilia associated with aminoglutethimide. *Aust N Z J Med* 1998; **28:** 670–1.

Lupus. SLE occurred in a patient who received aminoglutethimide, and resolved when the drug was withdrawn.[1] In another report, however, a patient with a lupus-like syndrome had a reduction in disease activity when tamoxifen therapy was changed to aminoglutethimide.[2]

1. McCraken M, *et al.* Systemic lupus erythematosus induced by aminoglutethimide. *BMJ* 1980; **281:** 1254.
2. Etherington J, *et al.* Effect of aminoglutethimide on the activity of a case of a connective tissue disorder with features of systemic lupus erythematosus. *Lupus* 1993; **2:** 387.

Precautions

Aminoglutethimide inhibits adrenal steroid production so supplementary glucocorticoid therapy with hydrocortisone must normally be given, although supplementation may not be necessary in patients with Cushing's syndrome. Some patients also require a mineralocorticoid. It has been suggested that aminoglutethimide should be temporarily withdrawn in patients who undergo shock or trauma, or develop intercurrent infection.

Blood pressure, blood counts, and serum electrolytes should be regularly monitored during aminoglutethimide therapy and periodic monitoring of liver and thyroid function is recommended.

Aminoglutethimide should not be given during pregnancy as pseudohermaphroditism may occur in the fetus.

Aminoglutethimide frequently causes drowsiness: patients so affected should not drive or operate machinery.

Porphyria. Aminoglutethimide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The rate of metabolism of some drugs is increased by aminoglutethimide; patients also taking warfarin or other coumarin anticoagulants, theophylline, tamoxifen, medroxyprogesterone, or oral hypoglycaemics, may require increased dosages of these drugs. The metabolism of dexamethasone is also accelerated, which limits its value for corticosteroid supplementation in patients receiving aminoglutethimide. Use with diuretics may lead to hyponatraemia, while alcohol may potentiate the central effects of aminoglutethimide.

◊ See also references to aminoglutethimide's interactions with *digitoxin* (p.1259), *theophylline* (p.1144), *progestogens* (p.2126), *tamoxifen* (see Antineoplastics, p.774), and *anticoagulants* (under Warfarin, p.1429).

Pharmacokinetics

Aminoglutethimide is well absorbed after oral doses, with peak plasma concentrations occurring after 1 to 4 hours. It is metabolised in the liver, primarily to *N*-hydroxylaminoglutethimide and *N*-acetylaminoglutethimide, and appears to induce its own metabolism. The half-life, which is reported to be about 13 hours after a single dose, is decreased to around 9 hours after about 2 weeks of continuous therapy. Aminoglutethimide is excreted in urine, about half a dose being excreted unchanged and the remainder as metabolites. Only about 20 to 25% of a dose is bound to plasma protein.

Half-life. A study in 17 patients showed that the plasma half-life of aminoglutethimide had a mean value of 15.5 hours after single doses but fell to 8.9 hours during multiple-dose therapy.[1] This marked reduction could largely be attributed to a decrease in the volume of distribution; auto-induction of metabolism might be of less importance in decreasing half-life than had been previously suggested.

1. Lønning PE, *et al.* Single-dose and steady-state pharmacokinetics of aminoglutethimide. *Clin Pharmacokinet* 1985; **10:** 353–64.

Uses and Administration

Aminoglutethimide is an analogue of glutethimide (p.1000) and was formerly used for its weak anticonvulsant properties. Aminoglutethimide blocks the production of adrenal steroids and acts as an aromatase inhibitor to block the conversion of androgens to oestrogens (the major source of oestrogens in women without ovarian function). It was used in the treatment of metastatic breast cancer (p.661) in postmenopausal or oophorectomised women and as palliative treatment in men with advanced prostatic cancer (p.671).

Aminoglutethimide has also been used in the treatment of Cushing's syndrome (p.2344). Usual oral doses range from 1 to 2 g daily, in divided doses.

The *dextro*-isomer of aminoglutethimide, dexaminoglutethimide has been investigated.

Preparations

BP 2008: Aminoglutethimide Tablets;
USP 31: Aminoglutethimide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Orimeten†; ***Austral.:*** Cytadren; ***Austria:*** Orimeten†; ***Belg.:*** Orimeten†; ***Braz.:*** Orimeten†; ***Chile:*** Orimeten†; ***Cz.:*** Orimeten†; ***Fr.:*** Orimetene†; ***Ger.:*** Orimeten†; ***Hong Kong:*** Orimetene; ***Ital.:*** Orimeten†; ***Malaysia:*** Orimetene†; ***Neth.:*** Orimeten†; ***NZ:*** Cytadren†; ***Rus.:*** Mamomit (Мамомит); Orimeten (Ориметен)†; ***S.Afr.:*** Orimeten†; ***Spain:*** Orimeten†; ***Switz.:*** Orimetene†; ***UK:*** Orimeten†; ***USA:*** Cytadren†.

5-Aminolevulinic Acid

ALA; 5-ALA; δ-Aminolaevulinic Acid; 5-Aminolaevulinic Acid; 5-Aminolevulínico, ácido. 5-Amino-4-oxopentanoic acid.

$C_5H_9NO_3$ = 131.1.
CAS — 106-60-5.
ATC — L01XD04.
ATC Vet — QL01XD04.

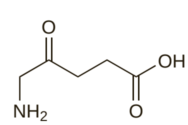

Aminolevulinic Acid Hydrochloride *(USAN)*

Aminolaevulinic Acid Hydrochloride; Aminolevulínico, hidrocloruro ácido. 5-Aminolevulinic acid hydrochloride.

$C_5H_9NO_3$, HCl = 167.6.
CAS — 5451-09-2.
ATC — L01XD04.
ATC Vet — QL01XD04.

Hexaminolevulinate Hydrochloride *(USAN)*

P-1026. Hexyl 5-amino-4-oxopentanoate hydrochloride.

$C_{11}H_{21}NO_3$,HCl = 251.8.
CAS — 140898-91-5.

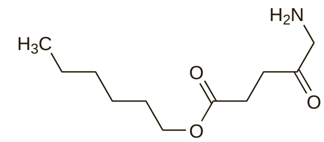

(hexaminolevulinate)

Methyl Aminolevulinate Hydrochloride *(USAN)*

Methyl Aminolaevulinate Hydrochloride; Metilaminolevulinato, hidrocloruro de; P-1202. Methyl 5-amino-4-oxopentanoate hydrochloride.

$C_6H_{11}NO_3$,HCl = 181.6.
CAS — 79416-27-6.
ATC — L01XD03.
ATC Vet — QL01XD03.

Adverse Effects and Precautions

The mechanism of action of topical 5-aminolevulinic acid or its derivatives generally results in local phototoxicity, manifest as a localised burning or stinging sensation, erythema, oedema, pruritus, scabbing, or pain. Symptoms are usually mild to moderate, and transient. During treatment, patients should be advised to avoid sunlight or prolonged exposure to bright light.

Other common adverse effects on the skin include scaling or crusting, ulceration, suppuration, blistering, bleeding, sensation of heat, erosion or exfoliation, and skin infection. Urticaria, rash, and changes in skin pigmentation may also occur. Application site discharge, eczema, and allergic contact dermatitis have been reported. Other common adverse effects include paraesthesia and headache. Nausea, fatigue, eye swelling or eye pain, and wound haemorrhage have been reported.

Handling. US licensed product information warns that nitrile gloves should be worn during application and removal of methyl aminolevulinate hydrochloride cream; vinyl or latex gloves do not provide adequate protection.

Hypersensitivity. Allergic reactions to aminolevulinic acid[1] and methyl aminolevulinate[2] have been reported.

1. Gniazdowska B, *et al.* Allergic contact dermatitis from δ-aminolevulinic acid used for photodynamic therapy. *Contact Dermatitis* 1998; **38:** 348–9.
2. Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevulinic acid methylester but not to 5-aminolaevulinic acid after photodynamic therapy. *Br J Dermatol* 2004; **150:** 143–5.

Porphyria. 5-Aminolevulinic acid and its derivatives are considered to be unsafe in patients with porphyria.

Interactions

Use with other known photosensitisers such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction commonly seen with 5-aminolevulinic acid or its derivatives.

St John's wort. A patient taking St John's wort had a pronounced phototoxic reaction consisting of an erythematous rash and swelling of the face, neck, and hands, 6 hours after receiving oral aminolevulinic acid. Although both drugs have been associated with photosensitivity, the authors suggested a synergistic effect had occurred. Tests *in vitro* appeared to confirm this.[1]

1. Ladner DP, *et al.* Synergistic toxicity of δ-aminolaevulinic acid-induced protoporphyrin IX used for photodiagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol* 2001; **144:** 916–8.

Pharmacokinetics

After intravenous and oral doses of aminolevulinic acid hydrochloride equivalent to 100 mg of aminolevulinic acid, the mean half-life of aminolevulinic acid is stated to be about 0.83 hours and 0.7 hours, respectively; oral bioavailability is about 50 to 60%. *In-vitro* studies of dermal absorption found that the mean cumulative absorption of methyl aminolevulinate through healthy human skin after 24 hours was 0.26% of a dose and a skin depot containing 4.9% of the dose was formed.

◊ References.

1. Juzeniene A, *et al.* Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. *Br J Dermatol* 2006; **155:** 791–9.

Uses and Administration

5-Aminolevulinic acid is a naturally occurring haem precursor that is metabolised in the body to protoporphyrin IX, a photosensitiser, and then to haem. It has been formulated for topical use in photodynamic therapy (see under Porfimer Sodium, p.764). It is used to treat actinic keratoses and basal cell carcinoma (see below). Aminolevulinic acid hydrochloride is applied topically as a 20% solution in the treatment of non-hyperkeratotic actinic keratoses of the face or scalp. This is followed, 14 to 18 hours later, by illumination with blue wavelength light sufficient to supply a dose of 10 J/cm^2. Treatment may be repeated once after 8 weeks if necessary.

Methyl aminolevulinate hydrochloride is a derivative of 5-aminolevulinic acid that is applied topically for the treatment of non-hyperkeratotic, non-pigmented actinic keratoses of the face or scalp when other therapies are considered inappropriate. It is also used for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other therapies. In some countries, methyl aminolevulinate is licensed for the treatment of Bowen's disease (squamous cell carcinoma *in situ*) when surgical excision is inappropriate. A cream containing the equivalent of 16% methyl aminolevulinate is applied to the lesions and covered with an occlusive dressing. After 3 hours the cream is removed and the lesions are exposed to red wavelength light in a dose of 75 J/cm^2; exposure to the cream for more than 4 hours should be avoided. For actinic keratoses, one session of photodynamic therapy is given, and again after 3 months if necessary. For basal cell carcinoma or Bowen's disease two sessions are given a week apart.

Patients should avoid sunlight or bright light sources for about 2 days after application.

Hexaminolevulinate hydrochloride is used as a diagnostic agent for the detection of bladder cancer (p.659), and is under investigation for the photodynamic therapy of bladder cancer.

Malignant neoplasms. The use of topical aminolevulinic acid or methyl aminolevulinate in the photodynamic therapy (PDT) of *actinic keratosis* and *basal cell carcinoma* (p.673) has been reviewed.[1-5] Both aminolevulinic acid and methyl aminolevulinate are considered to be effective in clearing non-hyperkeratotic actinic keratoses of the face and scalp, with response rates comparable to topical 5-fluorouracil and cryotherapy; cosmetic response is superior to that with cryotherapy.[6,7] More than 80% of lesions cleared completely after 2 treatments with aminolevulinic acid PDT; a recurrence rate of 19% was reported over 12 months.[8] Single treatment with methyl aminolevulinate is effective for thin lesions but thicker, non-responsive lesions may benefit from repeated treatment.[9] No significant differences in efficacy were seen between PDT with aminolevulinic acid or methyl aminolevulinate in the treatment of scalp actinic keratosis.[10] Aminolevulinic acid is considered as effective as cryotherapy but with superior healing and cosmetic results for superficial basal cell carcinoma; it is less effective for nodular disease.[6] Intralesional use has been investigated to improve penetration of the photosensitiser, with good preliminary results.[11] Methyl aminolevulinate topical PDT may be preferable for difficult-to-treat basal cell carcinoma.[12,13] Aminolevulinic acid is as effective in *Bowen's disease* (squamous cell carcinoma *in situ*) as cryotherapy or 5-fluorouracil, but with fewer adverse effects.[6] Topical methyl aminolevulinate PDT was more effective and cosmetically acceptable compared with topical 5-fluorouracil for pre-malignant skin disease in a small study in organ transplant recipients.[14]

PDT using oral 5-aminolevulinic acid as the photosensitiser, at doses of 30 or 60 mg/kg, has been used to treat *Barrett's oesophagus*, which is a major risk factor for oesophageal adenocarcinoma (p.664).[15,16] A small study found similar clinical responses with low-dose (30 mg/kg) and high-dose (60 mg/kg) aminolevulinic acid protocols.[17] Good long-term results have been reported with aminolevulinic acid PDT in patients with early neoplasia or high-grade intraepithelial neoplasia.[18]

Aminolevulinic acid is also under investigation for the photodynamic detection and treatment of *brain tumours* (p.660).[19] It has also been used for the fluorescence detection of *pleural malignancies*.[20]

An intravesical solution of aminolevulinic acid has been instilled for the detection[21] and management[22] of superficial *bladder cancer* (p.659). Hexaminolevulinate is used for the diagnosis of bladder cancer, and it appears to be more effective than standard white light cystoscopy.[23-25]

A topical application of 5-aminolevulinic acid 3% has been tried in the treatment of *cervical intraepithelial neoplasia*, with poor response.[26]

1. Ormrod D, Jarvis B. Topical aminolevulinic acid HCl photodynamic therapy. *Am J Clin Dermatol* 2000; **1:** 133–9.
2. Gupta AK, Ryder JE. Photodynamic therapy and topical aminolevulinic acid: an overview. *Am J Clin Dermatol* 2003; **4:** 699–708.
3. Siddiqui MAA, *et al.* Topical methyl aminolevulinate. *Am J Clin Dermatol* 2004; **5:** 127–37.
4. Marmur ES, *et al.* A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. *Dermatol Surg* 2004; **30:** 264–71.
5. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; **156:** 793–801.
6. Morton CA, *et al.* Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2002; **146:** 552–67. Also available at: http://www.bad.org.uk/healthcare/guidelines/topical_photodynamic_therapy.pdf (accessed 09/05/08)
7. Morton C, *et al.* AKtion Investigators. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155:** 1029–36.
8. Tschen EH, *et al.* Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155:** 1262–9.
9. Tarstedt M, *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; **85:** 424–8.
10. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol* 2007; **157:** 87–91.
11. Cappugi P, *et al.* New proposal for the treatment of nodular basal cell carcinoma with intralesional 5-aminolevulinic acid. *J Chemother* 2004; **16:** 491–3.
12. Horn M, *et al.* Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003; **149:** 1242–9.
13. Vinciullo C, *et al.* Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; **152:** 765–72.
14. Perrett CM, *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; **156:** 320–8.
15. Ackroyd R, *et al.* Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. *Gut* 2000; **47:** 612–17.
16. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid photodynamic therapy. *Gastrointest Endosc Clin N Am* 2000; **10:** 421–37.
17. Kelty CJ, *et al.* Comparison of high- vs low-dose 5-aminolevulinic acid for photodynamic therapy of Barrett's esophagus. *Surg Endosc* 2004; **18:** 452–8.
18. Pech O, *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest Endosc* 2005; **62:** 24–30.
19. Friesen SA, *et al.* 5-Aminolevulinic acid-based photodynamic detection and therapy of brain tumors (review). *Int J Oncol* 2002; **21:** 577–82.
20. Baas P, *et al.* Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid. *Chest* 2006; **129:** 718–24.
21. Zaak D, *et al.* Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. *Cancer* 2002; **95:** 1234–8. Correction. *ibid.*; 2580.
22. Kriegmair M, *et al.* Early clinical experience with 5-aminolevulinic acid for the photodynamic therapy of superficial bladder cancer. *Br J Urol* 1996; **77:** 667–71.
23. Anonymous. Hexyl aminolevulinate: 5-ALA hexylester, 5-ALA hexylesther, aminolevulinic acid hexyl ester, hexaminolevulinate, hexyl-5-aminolevulinate, P 1206. *Drugs R D* 2005; **6:** 235–8.
24. Jocham D, *et al.* Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol (Baltimore)* 2005; **174:** 862–6.
25. Frampton JE, Plosker GL. Hexyl aminolevulinate: in the detection of bladder cancer. *Drugs* 2006; **66:** 571–8.
26. Barnett AA, *et al.* A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia. *Int J Cancer* 2003; **103:** 829–32.

Skin disorders. 5-Aminolevulinic acid has been used topically in the photodynamic therapy (PDT) of skin conditions such as psoriasis, recalcitrant viral warts, acne vulgaris, and cutaneous T-cell lymphoma.[1] Variable results have been reported with this therapy in patients with plaque psoriasis; in one study therapy was generally well-tolerated,[2] but in the other all patients reported stinging or burning during irradiation.[3] A study comparing 5-aminolevulinic acid and methyl aminolevulinate for PDT of acne found both to be equally effective, although methyl aminolevulinate seemed to be better tolerated.[4] Topical methyl aminolevulinate-based PDT has been found to be effective in the treatment of facial acne vulgaris.[5,6] PDT with 5-aminolevulinic acid has been reported to significantly improve an infected leg ulcer resistant to conventional therapies.[7] A topical 10% solution has been used with intraurethral PDT to treat condylomata acuminata.[8]

1. Ibbotson SH. Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. *Br J Dermatol* 2002; **146:** 178–88.
2. Smits T, *et al.* A placebo-controlled randomized study on the clinical effectiveness, immunohistochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolevulinic acid-photodynamic therapy in patients with psoriasis. *Br J Dermatol* 2006; **155:** 429–36.
3. Radakovic-Fijan S, *et al.* Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol* 2005; **152:** 279–83.
4. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006; **54:** 647–51.
5. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol* 2006; **154:** 969–76.
6. Hörfelt C, *et al.* Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol* 2006; **155:** 608–13.
7. Clayton TH, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007; **156:** 384–5.
8. Wang XL, *et al.* Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; **151:** 880–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Metvix; ***Belg.:*** Metvix; ***Cz.:*** Hexvix; MC 506; Metvix; ***Denm.:*** Metvix; ***Fin.:*** Hexvix; Metvix; ***Fr.:*** Metvixia; ***Ger.:*** Metvix; ***Gr.:*** Hexvix; ***Ital.:*** Metvix; ***Neth.:*** Hexvix; Metvix; ***Norw.:*** Hexvix; Metvix; ***NZ:*** Metvix; ***Port.:*** Gliolan; Hexvix; Metvix; ***S.Afr.:*** Metvix; ***Spain:*** Metvix; ***Swed.:*** Hexvix; Metvix; ***Switz.:*** Metvix; ***UK:*** Metvix; Porphin; ***USA:*** Levulan Kerastick; Metvixia.

Amonafide *(rINN)*

Amonafida; Amonafidum; M-FA-142; Nafidimide; NSC-308847.
3-Amino-*N*-[2-(dimethylamino)ethyl]naphthalimide.

Амонафид

$C_{16}H_{17}N_3O_2$ = 283.3.
CAS — 69408-81-7.

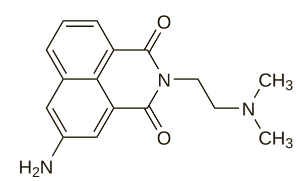

Profile

Amonafide is a topoisomerase inhibitor. Amonafide malate is under investigation for the treatment of acute myeloid leukaemia. Amonafide hydrochloride has also been investigated, but studies were stopped due to serious adverse effects.

Amrubicin *(USAN, rINN)*

Amrubicina; Amrubicine; Amrubicinum; SM-5887. (+)-(7*S*,9*S*)-9-Acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)-oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione.

Амрубицин

$C_{25}H_{25}NO_9$ = 483.5.
CAS — 110267-81-7 (amrubicin); 110311-30-3 (amrubicin hydrochloride).

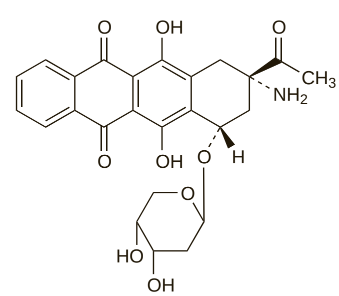

Profile

Amrubicin is a synthetic anthracycline derivative related to compounds such as doxorubicin (p.712). Amrubicin hydrochloride is used as an antineoplastic in the treatment of lung cancer, and is under investigation in the treatment of superficial bladder cancers, and lymphomas.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Calsed.

Amsacrine *(BAN, USAN, pINN)*

Acridinyl Anisidide; *m*-AMSA; Amsacrina; Amsacrinum; Amsakriini; Amsakrin; CI-880; NSC-249992. 4′-(Acridin-9-ylamino)methanesulphon-*m*-anisidide.

Амсакрин

$C_{21}H_{19}N_3O_3S$ = 393.5.
CAS — 51264-14-3.
ATC — L01XX01.
ATC Vet — QL01XX01.

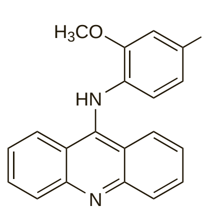

Incompatibility. Amsacrine is incompatible with sodium chloride 0.9% injection and with other chloride-containing solutions,[1,2] apparently because of the poor solubility of the hydrochloride salt in aqueous solution.[2] Amsacrine reacts with certain plastics.[1]

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
2. Trissel LA, *et al.* Visual compatibility of amsacrine with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2525–8.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression is usually dose-limiting and may be severe. The nadir of the white cell count has been reported at about 12 days after treatment, with recovery usually by the 25th day. Pancytopenia and haemorrhage may develop. Nausea and vomiting (mild to moderate), stomatitis (mild to life-threatening), rashes, and alopecia may occur. Grand mal seizures, renal dysfunction, hepatotoxicity, and cardiotoxicity have also been reported. Amsacrine is irritant: there may be phlebitis and local tissue necrosis particularly when given in high concentrations.

Amsacrine should be given with caution to patients with liver or kidney disease, who may require dosage adjustments.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with diuretics or nephrotoxic drugs such as the aminoglycosides may theoretically increase the risk of cardiotoxicity with amsacrine by precipitating hypokalaemia.

Pharmacokinetics

Amsacrine is poorly absorbed after oral doses. When given intravenously it has a reported terminal half-life of about 5 to 8 hours. It is metabolised in the liver and excreted primarily in the bile, mostly as metabolites. It is reported to be about 98% protein bound.

Uses and Administration

Amsacrine is an antineoplastic agent that appears to act by intercalation with DNA and inhibition of nucleic acid synthesis. It may also exert an action on cell membranes. Cells in G_2 or S phases may be most sensitive to its actions.

It is used for the induction and maintenance of remission in adult acute leukaemias, particularly acute myeloid leukaemia.

Amsacrine is prepared as a solution in lactic acid and dimethylacetamide, and is given, diluted in glucose 5%, by intravenous infusion over 60 to 90 minutes.

For the induction of remission, amsacrine may be given at a dose of 90 mg/m^2 daily for 5 to 8 days, depending on clinical response. Courses may be repeated at 2- to 4-week intervals according to response, and the dose may be increased to 120 mg/m^2 daily in subsequent courses if tolerated. Maintenance doses of 150 mg/m^2 as a single dose or divided over 3 consecutive days have been given every 3 to 4 weeks, adjusted if necessary according to response.

Complete blood counts should be performed regularly, and cardiac, liver, kidney, and CNS function should be monitored.

Doses should be reduced in patients with hepatic or renal impairment (see below).

◊ References.

1. Ghaddar HM, *et al.* Amsacrine and continuous-infusion high-dose cytosine arabinoside as induction therapy for patients with newly-diagnosed acute myelogenous leukemia. *Leuk Lymphoma* 1996; **22:** 71–6.
2. Reman O, *et al.* Groupe d'Étude et de Traitement de la Leucémie Aiguë Lymphoblastique de l'Adulte. Rescue therapy combining intermediate-dose cytarabine with amsacrine and etoposide in relapsed adult acute lymphoblastic leukemia. *Hematol J* 2004; **5:** 123–9.
3. Sung WJ, *et al.* Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. *Jpn J Clin Oncol* 2005; **35:** 612–16.
4. Horstmann MA, *et al.* Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children. *Haematologica* 2005; **90:** 1701–3.
5. Kessler T, *et al.* Amsacrine containing induction therapy in elderly AML patients: comparison to standard induction regimens in a matched-pair analysis. *Leuk Res* 2008; **32:** 491–4.

Administration in hepatic impairment. In moderate to severe hepatic impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Administration in renal impairment. In moderate to severe renal impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m^2 daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Amsidyl; ***Belg.:*** Amsidine; ***Canad.:*** Amsa PD; ***Cz.:*** Amsidyl†; ***Denm.:*** Amekrin; ***Fin.:*** Amekrin†; ***Fr.:*** Amsalyo†; ***Ger.:*** Amsidyl†; ***Irl.:*** Amsidine; ***Neth.:*** Amsidine; ***Swed.:*** Amekrin; ***Switz.:*** Amsidyl; ***UK:*** Amsidine.

Anastrozole *(BAN, USAN, rINN)* ⊗

Anastrotsoli; Anastrozol; Anastrozolum; ICI-D1033; ZD-1033. 2,2′-Dimethyl-2,2′-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(propiononitrile); α,α,α′,α′-Tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile.

Анастрозол

$C_{17}H_{19}N_5$ = 293.4.
CAS — 120511-73-1.
ATC — L02BG03.
ATC Vet — QL02BG03.

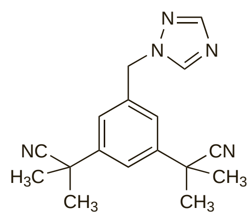

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects are gastrointestinal disturbances including anorexia, nausea and vomiting, and diarrhoea; asthenia; hot flushes; dizziness; drowsiness; headache; and rash. Other reported effects include hair thinning, vaginal dryness or bleeding, myalgia, arthralgia, and bone fractures, Abnormalities in liver enzyme values, thromboembolism, and increases in total cholesterol, have occurred in some patients receiving anastrozole. Very rare cases of erythema multiforme, Stevens-Johnson syndrome, and allergic reactions (including angioedema, urticaria, and anaphylaxis) have occurred.

Reductions in bone mineral density can occur during use of anastrozole. Patients with or at risk of osteoporosis should therefore have their bone density assessed at the start of therapy and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be started as appropriate and carefully monitored.

The use of anastrozole is contra-indicated in premenopausal women (particularly in pregnancy).

Effects on the liver. A case of acute hepatitis was attributed to anastrozole, 3 weeks after starting therapy.[1]

1. de la Cruz L, *et al.* Severe acute hepatitis in a patient treated with anastrozole. *Lancet* 2007; **369:** 23–4.

Effects on the musculoskeletal system. In a series of 77 postmenopausal women treated with anastrozole for metastatic breast cancer, 12 complained of joint pains within 2 months of beginning therapy. Based on this experience and the incidence of arthralgia reported during clinical studies, the authors estimated that arthralgia occurs in 10 to 15% of patients treated with anastrozole, possibly as a result of the very low oestrogen concentrations achieved.[1]

Adjuvant anastrozole therapy for postmenopausal women with early breast cancer was associated with accelerated bone loss, but the risk appeared to be confined to those with osteopenia at baseline.[2] These patients should be assessed for the risk of osteoporosis before starting therapy, and the decision to treat should be made on an individual basis.[3]

1. Donnellan PP, *et al.* Aromatase inhibitors and arthralgia. *J Clin Oncol* 2001; **19:** 2767.
2. Eastell R, *et al.* Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008; **26:** 1051–8.
3. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Oncol* 2006; **24:** 5305–12.

Pharmacokinetics

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations within about 2 hours. Food decreases the rate of absorption, though this is not considered clinically significant. Anastrozole is 40% bound to plasma proteins. It is metabolised in the liver, and excreted in urine, chiefly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations are achieved after about 7 days in patients receiving once-daily doses.

Uses and Administration

Anastrozole is a potent and selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. It is used in the treatment of advanced or locally advanced breast cancer, and as adjuvant treatment in early breast cancer (p.661), in postmenopausal women in an oral dose of 1 mg daily. Responses are unlikely in patients with oestrogen receptor-negative disease. Adjuvant therapy may be continued for up to 5 years, although the optimum duration is uncertain.

◊ References.

1. Bonneterre J, *et al.* Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; **18:** 3748–57.
2. Nabholtz JM, *et al.* Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000; **18:** 3758–67.
3. The ATAC (Arimidex, Tamoxifen Alone or in Combination) trialists' group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359:** 2131–9.
4. Wellington K, Faulds DM. Anastrozole in early breast cancer. *Drugs* 2002; **62:** 2483–90.
5. Baum M, *et al.* Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003; **98:** 1802–10.
6. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365:** 60–2.
7. Jakesz R, *et al.* Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; **366:** 455–62.
8. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; **7:** 633–43.
9. Jonat W, *et al.* Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; **7:** 991–6. Correction. *ibid.* 2007; **8:** 6.
10. Jakesz R, *et al.* Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* 2007; **99:** 1845–53. Correction. *ibid.* 2008; **100:** 226.
11. Forbes JF, *et al.* Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008; **9:** 45–53.

Endometriosis. In a small, open-label study,[1] *oral* anastrozole 1 mg, given daily with a low-strength oral contraceptive for 6 months, reduced pelvic pain scores in women with refractory endometriosis (p.2091). Adverse effects were mild, although most patients had breakthrough bleeding, which exacerbated pain. The authors supposed that a higher dose of oral contraceptive should be considered in future studies.

In a small pilot study of patients with rectovaginal endometriosis,[2] anastrozole 250 micrograms was given *vaginally* once daily for 6 months. Dysmenorrhoea improved significantly although chronic pelvic pain was unchanged. Adverse effects were mild.

1. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; **84:** 300–4.
2. Hefler LA, *et al.* Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* 2005; **84:** 1033–6.

Gynaecomastia. Anastrozole has been reported[1] to be under investigation for the treatment of gynaecomastia, but controlled studies suggest that it may be no better than placebo—see Gynaecomastia (p.2092) and Gynaecomastia under Adverse Effects and Precautions of Flutamide (p.725).

1. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; **2:** 643–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anaskebir; Anastraze; Anebol; Arimidex; Aromenal; Asiolex†; Distalene; Gondonar; Leprofen; Lezole†; Pantestone; Puricap; Trozolite; ***Austral.:*** Arimidex; ***Austria:*** Arimidex; ***Belg.:*** Arimidex; ***Braz.:*** Arimidex; ***Canad.:*** Arimidex; ***Chile:*** Arimidex; Trozolet; ***Cz.:*** Anabrest; Anaya; Arimidex; Egistrozol; OncoFem; Zynzol; ***Denm.:*** Arimidex; ***Fin.:*** Arimidex; ***Fr.:*** Arimidex; ***Ger.:*** Arimidex; ***Gr.:*** Arimidex; ***Hong Kong:*** Arimidex; ***Hung.:*** Arimidex; ***India:*** Altraz; Armotraz; ***Indon.:*** Arimidex; ***Irl.:*** Arimidex; ***Israel:*** Arimidex; ***Ital.:*** Arimidex; ***Malaysia:*** Arimidex; ***Mex.:*** Arimidex; ***Neth.:*** Arimidex; ***Norw.:*** Arimidex; ***NZ:*** Arimidex; ***Philipp.:*** Arimidex; ***Pol.:*** Arimidex; Atrozol; ***Port.:*** Arimidex; Remidex; ***Rus.:*** Arimidex (Аримидекс); ***S.Afr.:*** Arimidex; ***Singapore:*** Arimidex; ***Spain:*** Arimidex; ***Swed.:*** Arimidex; ***Switz.:*** Arimidex; ***Thai.:*** Arimidex; ***Turk.:*** Arimidex; ***UK:*** Arimidex; ***USA:*** Arimidex; ***Venez.:*** Arimidex; Trozolet.

Antineoplaston A10

3-Phenylacetylamino-2,6-piperidinedione.
$C_{13}H_{14}N_2O_3$ = 246.3.

Profile

Antineoplaston A10, one of a group of peptide derivatives isolated from blood and urine, has been investigated for the treatment of breast cancer, brain stem glioma, and other malignant neoplasms although its value has been questioned (see below).

◊ A critical review of the antineoplastons[1] noted that most work had been done with antineoplaston A10, which is insoluble in aqueous solutions, and its derivatives antineoplaston AS2.5 (phenylacetylglutamine), and antineoplaston AS2.1 (a 4:1 mixture of phenylacetic acid and phenylacetylglutamine), which had not been independently shown to be active against cancer. However, some interest in the antineoplastons subsequently continued.[2-4]

1. Green S. Antineoplastons: an unproved cancer therapy. *JAMA* 1992; **267:** 2924–8.
2. Buckner JC, *et al.* Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999; **74:** 137–45.
3. Badria F, *et al.* Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Lett* 2000; **157:** 57–63.
4. Burzynski SR, *et al.* Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. *Integr Cancer Ther* 2006; **5:** 40–7.

AP-12009

TGF-β2 antisense oligonucleotide; Transforming growth factor-β2-specific phosphorothioate antisense oligodeoxynucleotide.

Profile

AP-12009 is an antisense oligonucleotide that specifically suppresses the production of transforming growth factor-beta-2, an immunosuppressive protein produced by tumour cells. It is under investigation for the treatment of high-grade glioma (see Malignant Neoplasms of the Brain, p.660).

AS-1411

AGRO-100.

Profile

AS-1411 is a selective oligonucleotide ligand (aptamer) that binds to the protein nucleolin, inducing apoptosis in cancer cells. It is under investigation for the treatment of renal cell carcinoma, pancreatic cancer, and acute myelogenous leukaemia.

Asparaginase *(USAN)*

Asparaginasa; L-Asparaginase; L-Asparagine Amidohydrolase; L-Asparaginaz; L-Asparaginaasi; L-Asparaginas; L-Asparaginasum; MK-965; NSC-109229; Re-82-TAD-15.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Asparaginase (*USAN*) is an enzyme isolated from *Escherichia coli*, or obtained from other sources. See also Colaspase and Crisantaspase, below.

Incompatibility. Asparaginase is incompatible with rubber. Licensed product information recommends that it should not be mixed with other drugs.

Storage. Asparaginase should be stored at 2° to 8° (see also Stability, below).

Colaspase *(BAN)*

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Colaspase (*BAN*) is asparaginase obtained from selected strains of *Escherichia coli*, such as ATCC 9637.

Pharmacopoeias. *Chin.* includes Asparaginase obtained from *Escherichia coli* ASI 357.

Crisantaspase *(BAN)*

Crisantaspasum; Erwinia L-asparaginase; Krisantaspaasi; Krisantaspas.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Crisantaspase (*BAN*) is asparaginase obtained from cultures of *Erwinia chrysanthemi* (*E. carotovora*).

Pegaspargase *(USAN, rINN)*

PEG-L-asparaginase; Pegaspargasa; Pégaspargase; Pegaspargasum. A conjugate of colaspase with a polyethylene glycol of molecular weight 5000; Monomethoxypolyethylene glycol succinimidyl L-asparaginase.
Пэгаспаргаза
CAS — 130167-69-0.
ATC — L01XX24.
ATC Vet — QL01XX24.

Stability. Although asparaginase was routinely kept under refrigeration,[1] information from a manufacturer (*Merck Sharp & Dohme*) indicated that it would remain stable for 48 hours at 15° to 30°. Licensed product information for pegaspargase states it should not be used if stored at room temperature for more than 48 hours.

1. Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; **40:** 101–2.

Storage. Pegaspargase should be stored at 2° to 8°.

Units

One international unit of asparaginase splits 1 micromole of ammonia from L-asparagine in 1 minute under standard conditions.

Adverse Effects

Asparaginase is a protein and may produce anaphylaxis and other hypersensitivity reactions including fever, rashes, and bronchospasm; there does not appear to be cross-sensitivity between asparaginase derived from *Escherichia coli* and that from *Erwinia chrysanthemi*. Hypersensitivity to pegaspargase is less common, but about 30% of patients hypersensitive to the native enzyme experience hypersensitivity to pegaspargase treatment.

Liver function abnormalities occur in many patients, and there may be decreased blood concentrations of fibrinogen and clotting factors, alterations in blood lipids and cholesterol, and hypoalbuminaemia. Hyperammonaemia, due to the production of ammonia from asparagine, may occur. Uraemia, and occasionally renal failure, have been reported. Pancreatitis may occur and may be fatal: there may also be hyperglycaemia due to decreased insulin production, and death from ketoacidosis has occurred.

Gastrointestinal disturbances, including nausea and vomiting, and CNS disturbances, including drowsiness, depression, coma, hallucinations, and a Parkinson-like syndrome, have also been reported. Transient bone-marrow depression has occurred rarely, as has marked leucopenia.

Effects on the blood. Central thrombosis or intracranial haemorrhage as well as peripheral thrombosis and haemorrhage have been reported after asparaginase therapy.[1-4] Although the precise mechanism for this effect remains unclear, asparaginase appears to deplete certain clotting factors as well as antithrombin III, plasminogen, and fibrinogen.[4] These decreases may be dependent on the formulation and resultant asparaginase activity of preparations,[5] and there is some suggestion that crisantaspase may affect coagulation factors less severely than colaspase.[6] A multicentre, retrospective survey[3] of paediatric patients with acute lymphoblastic leukaemia found that use of corticosteroids with colaspase may be an additional risk factor for thromboembolic events.

1. Priest JR, *et al.* A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr* 1982; **100:** 984–9.
2. Ott N, *et al.* Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1988; **10:** 191–5.
3. Sutor AH, *et al.* Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr* 1999; **211:** 201–4.
4. Alberts SR, *et al.* Thrombosis related to the use of L-asparaginase in adults with acute lymphoblastic leukemia: a need to consider coagulation monitoring and clotting factor replacement. *Leuk Lymphoma* 1999; **32:** 489–96.
5. Nowak-Göttl U, *et al.* Influence of two different Escherichia coli asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica* 1996; **81:** 127–31.
6. Carlsson H, *et al.* Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol* 1995; **55:** 289–93.

Precautions

Asparaginase is contra-indicated in patients with pancreatitis, and should be avoided in pregnancy. It should be given cautiously to patients with hepatic impairment. Facilities for the management of anaphylaxis (see p.1205) should be available during treatment. Some manufacturers recommend an intradermal test dose at the start of asparaginase treatment to check for hypersensitivity, as described under Uses, below, although such tests may not always be predictive. Retreatment with asparaginase may be associated with an increased risk of allergic reactions. Serum amylase concentrations should be monitored regularly as should blood glucose concentrations. Asparaginase has been reported to interfere with tests of thyroid function by transient reduction of concentrations of thyroxine-binding globulin.

Interactions

If asparaginase is given before, rather than after, methotrexate the activity of the latter may be reduced (see below). Vincristine neurotoxicity may possibly be increased by use with intravenous asparaginase (see p.787).

Methotrexate. Asparaginase inhibits protein synthesis and cell replication, and therefore may interfere with the action of drugs such as methotrexate that require cell replication for their antineoplastic effect.[1] It has been suggested that a 24-hour interval between methotrexate and a subsequent dose of asparaginase permits at least an additive therapeutic effect.[2]

1. Jolivet J, *et al.* Prevention of methotrexate cytotoxicity by asparaginase inhibition of methotrexate polyglutamate formation. *Cancer Res* 1985; **45:** 217–20.
2. Capizzi RL. Asparaginase-methotrexate in combination chemotherapy: schedule-dependent differential effects on normal versus neoplastic cells. *Cancer Treat Rep* 1981; **65** (suppl 4): 115–21.

Pharmacokinetics

After intravenous injection the plasma half-life of the native enzyme has varied from about 8 to 30 hours; half-lives of up to 49 hours may be seen after intramuscular dosage. The mean half-life of pegaspargase is reported to be between 6 and 14 days. Asparaginase is found in the lymph at about 20% of the concentration in plasma. There is virtually no diffusion into the CSF. Little is excreted in the urine.

Uses and Administration

Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of those malignant cells which, unlike most healthy cells, are unable to synthesise L-asparagine for their metabolism, but resistance to its action develops fairly rapidly. Its action is reportedly specific for the G_1 phase of the cell cycle.

Asparaginase is used mainly for the induction of remissions in acute lymphoblastic leukaemia (p.651). Regimens vary, and dosage should follow local protocols, but it may be given intravenously in a dose of 1000 units/kg daily for 10 days after treatment with vincristine and prednisone or prednisolone, or intramuscularly in a dose of 6000 units/m^2 given every third day for 9 doses during treatment with vincristine and prednisone or prednisolone. Alternatively it may be given as pegaspargase, in doses of 2500 units/m^2 every 14 days, preferably by intramuscular injection although the intravenous route may also be used.

Asparaginase is not generally used alone as an induction agent but doses of 200 units/kg daily have been given intravenously for 28 days to adults and children. If pegaspargase is used alone doses are the same as for combination regimens. Children appear to tolerate asparaginase better than adults.

Although not entirely reliable, an intradermal test dose of about 2 units has been recommended in the USA, to test for hypersensitivity, before treatment with colaspase or where more than a week has elapsed between doses. Desensitisation has been advocated if no alternative antineoplastic treatment is available. Anaphylaxis with crisantaspase is stated to be rare; however, in the UK if there has been an interruption in treatment, therapy should be resumed with a low dose of 10 units/kg daily and increased to the full dose over 5 days if tolerated. A test dose is not advocated, although reference to local leukaemia protocols is recommended. The incidence of hypersensitivity is also lower in patients given pegaspargase, and again a test dose is not advocated. Pegaspargase has been successfully used in patients hypersensitive to the native enzyme.

For intravenous use a solution of asparaginase in Water for Injections or sodium chloride 0.9% should be given over not less than 30 minutes through a running infusion of sodium chloride 0.9% or glucose 5%. When given intramuscularly no more than 2 mL of a solution in sodium chloride 0.9% should be injected at a single site.

◊ References.

1. Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol* 1998; **28:** 97–113.
2. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999; **457:** 621–9.
3. Abshire TC, *et al.* Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 2000; **96:** 1709–15.
4. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet* 2005; **44:** 367–93.
5. Fu CH, Sakamoto KM. PEG-asparaginase. *Expert Opin Pharmacother* 2007; **8:** 1977–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kidrolase; L-Asp†; Oncaspar; ***Austral.:*** Leunase; ***Belg.:*** Paronal; ***Braz.:*** Elspar; ***Canad.:*** Kidrolase; ***Cz.:*** Erwinase†; Kidrolase; ***Denm.:*** Erwinase†; ***Fin.:*** Erwinase†; ***Fr.:*** Kidrolase; ***Ger.:*** Erwinase†; Oncaspar; ***Gr.:*** Erwinase; Oncaspar; ***Hong Kong:*** Elspar†; Leunase; ***India:*** Leunase; ***Indon.:*** Leunase; ***Irl.:*** Erwinase; ***Israel:*** Kidrolase; ***Jpn:*** Leunase; ***Malaysia:*** Erwinase†; Leunase; ***Mex.:*** Leunase; ***Neth.:*** Erwinase; Paronal; ***NZ:*** Erwinase; Leunase; ***Philipp.:*** Leunase; ***Pol.:*** Oncaspar; ***Port.:*** Erwinase; ***Rus.:*** Oncaspar (Онкаспар); ***S.Afr.:*** Laspar; ***Singapore:*** Erwinase†; Leunase; ***Swed.:*** Erwinase; ***Thai.:*** Erwinase†; Leunase; ***Turk.:*** Leunase; ***UK:*** Erwinase; ***USA:*** Elspar; Oncaspar.

Atiprimod *(rINN)*

Atiprimodum. 2-[3-(Diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane.

Атипримод

$C_{22}H_{44}N_2$ = 336.6.

CAS — 123018-47-3 (atiprimod); 130065-61-1 (atiprimod hydrochloride); 183063-72-1 (atiprimod maleate).

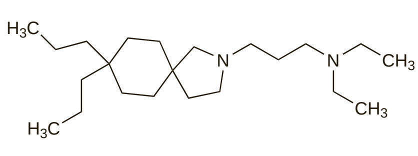

Profile

Atiprimod is an antineoplastic that is under investigation for the treatment of carcinoid tumours and multiple myeloma.

Atrasentan Hydrochloride *(USAN, rINNM)*

A-147627.1; Abbott-147627; ABT-627; Atrasentan, Chlorhydrate d'; Atrasentani Hydrochloridum; Hidrocloruro de atrasentán. (2*R*,3*R*,4*S*)-1-[(Dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid hydrochloride.

Атразентана Гидрохлорид

$C_{29}H_{38}N_2O_6$,HCl = 547.1.

CAS — 173937-91-2 (atrasentan); 195733-43-8 (atrasentan hydrochloride).

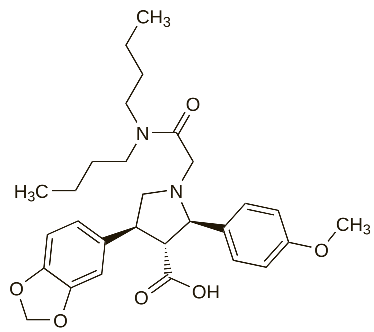

(atrasentan)

Profile

Atrasentan hydrochloride is a selective endothelin-A receptor antagonist that inhibits the effect of endothelin-1, a protein that may be involved in cancer progression. It is under investigation in the treatment of prostate cancer, and has been tried in other malignant neoplasms.

◊ References.

1. Samara E, *et al.* Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist. *J Clin Pharmacol* 2001; **41:** 397–403.
2. Carducci MA, *et al.* Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol* 2002; **20:** 2171–80.
3. Carducci MA, *et al.* Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003; **21:** 679–89.
4. Zonnenberg BA, *et al.* Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: an endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 2003; **9:** 2965–72.
5. Ryan CW, *et al.* Dose-ranging study of the safety and pharmacokinetics of atrasentan in patients with refractory malignancies. *Clin Cancer Res* 2004; **10:** 4406–11.
6. Michaelson MD, *et al.* Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006; **107:** 530–5.
7. Carducci MA, *et al.* Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007; **110:** 1959–66.
8. Chiappori AA, *et al.* Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res* 2008; **14:** 1464–9.
9. Phuphanich S, *et al.* New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Phase I safety study of escalating doses of atrasentan in adults with recurrent malignant glioma. *Neuro-oncol* 2008; **10:** 617–623.

Axitinib *(USAN, rINN)*

AG-013736; Axitinibum. *N*-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl}sulfanyl)benzamide.

Акситиниб

$C_{22}H_{18}N_4OS$ = 386.5.

CAS — 319460-85-0.

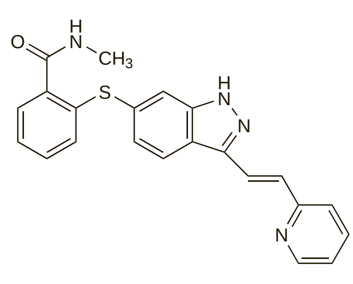

Profile

Axitinib is a tyrosine kinase inhibitor that is under investigation as an antineoplastic for the treatment of various cancers, including pancreatic, lung, gastrointestinal, and breast cancer, as well as melanoma.

◊ Reviews.

1. Sonpavde G, *et al.* Axitinib for renal cell carcinoma. *Expert Opin Invest Drugs* 2008; **17:** 741–8.
2. Choueiri TK. Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. *Curr Opin Investig Drugs* 2008; **9:** 658–71.

Azacitidine *(USAN, rINN)*

Azacitidina; 5-Azacitidina; Azacitidinum; 5-Azacytidine; Ladakamycin; NSC-102816; U-18496. 4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one.

Азацитидин

$C_8H_{12}N_4O_5$ = 244.2.

CAS — 320-67-2.

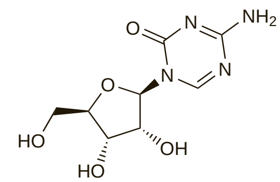

Adverse Effects and Precautions

The adverse effects of azacitidine are generally similar to those seen with cytarabine (p.705). Hypokalaemia, dyspnoea, and bruising are common.

Pharmacokinetics

Azacitidine is rapidly absorbed after subcutaneous use; the bioavailability relative to intravenous use is about 89%. The mean plasma half-life after subcutaneous injection is about 40 minutes. Azacitidine and its metabolites are excreted primarily in the urine; about 50% and 85% is recovered after subcutaneous and intravenous dosing, respectively. The mean elimination half-life is about 4 hours after subcutaneous or intravenous use.

◊ References.

1. Marcucci G, *et al.* Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. *J Clin Pharmacol* 2005; **45:** 597–602.
2. Tsao CF, *et al.* Azacitidine pharmacokinetics in an adolescent patient with renal compromise. *J Pediatr Hematol Oncol* 2007; **29:** 330–3.

Uses and Administration

Azacitidine is an antimetabolite antineoplastic with general properties similar to those of cytarabine (p.705). It also inhibits cellular pyrimidine synthesis. Azacitidine is used in myelodysplastic syndromes (p.654); it has also been used in the treatment of acute myeloid leukaemia (p.652).

For the treatment of myelodysplastic syndromes, azacitidine is given subcutaneously or intravenously in a dose of 75 mg/m^2 daily for 7 days, in 4-week cycles. If there is no benefit after 2 cycles, and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m^2 daily. Treatment for at least 4 cycles is usually needed.

Azacitidine should be used with caution in renal impairment and doses adjusted accordingly (see below).

◊ References.

1. Anonymous. Azacitidine (Vidaza) for myelodysplastic syndrome. *Med Lett Drugs Ther* 2005; **47:** 11.
2. Sullivan M, *et al.* Azacitidine: a novel agent for myelodysplastic syndromes. *Am J Health-Syst Pharm* 2005; **62:** 1567–73.
3. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
4. Siddiqui MAA, Scott LJ. Azacitidine: in myelodysplastic syndromes. *Drugs* 2005; **65:** 1781–9.
5. Kaminskas E, *et al.* FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 2005; **10:** 176–82.
6. Silverman LR, *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.
7. Abdulhaq H, Rossetti JM. The role of azacitidine in the treatment of myelodysplastic syndromes. *Expert Opin Invest Drugs* 2007; **16:** 1967–75.
8. O'Dwyer K, Maslak P. Azacitidine and the beginnings of therapeutic epigenetic modulation. *Expert Opin Pharmacother* 2008; **9:** 1981–6.

Administration in renal impairment. Adverse renal effects of azacitidine include abnormalities in renal-function tests, renal tubular acidosis, renal failure, and death. US licensed product information recommends that if serum-bicarbonate concentrations fall to below 20 mEq/litre, the dose of azacitidine should be halved for the next course. If there are rises in serum concentrations of urea or creatinine, the next cycle of azacitidine should be delayed until these return to normal or baseline, and the dose should be halved on the next treatment course.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Vidaza.

Becatecarin *(USAN, rINN)*

Becatecarina; Bécatécarine; Becatecarinum; BMS-181176; BMY-27557; NSC-655649; XL-119. 1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione.

Бекатекарин

$C_{33}H_{34}Cl_2N_4O_7$ = 669.6.
CAS — 119673-08-4.

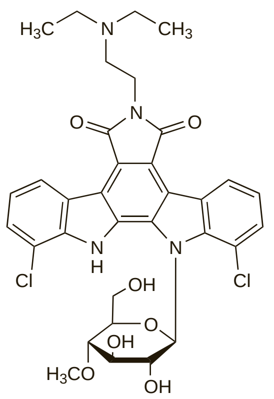

Profile

Becatecarin is an antineoplastic under investigation in the treatment of bile-duct and other tumours.

◊ References.

1. Merchant J, *et al.* Phase I clinical and pharmacokinetic study of NSC 655649, a rebeccamycin analogue, given in both single-dose and multiple-dose formats. *Clin Cancer Res* 2002; **8:** 2193–2201.
2. Goel S, *et al.* A phase II study of rebeccamycin analog NSC 655649 in patients with metastatic colorectal cancer. *Invest New Drugs* 2003; **21:** 103–7.
3. Langevin AM, *et al.* Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003; **25:** 526–33.
4. Hussain M, *et al.* A phase II study of rebeccamycin analog (NSC-655649) in metastatic renal cell cancer. *Invest New Drugs* 2003; **21:** 465–71.
5. Ricart AD, *et al.* Phase I and pharmacokinetic study of sequences of the rebeccamycin analogue NSC 655649 and cisplatin in patients with advanced solid tumors. *Clin Cancer Res* 2005; **11:** 8728–36.
6. Langevin AM, *et al.* Children's Oncology Group. A phase II trial of rebeccamycin analogue (NSC #655649) in children with solid tumors: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; **50:** 577–80.

Bendamustine Hydrochloride *(USAN, rINNM)*

Bendamustine, Chlorhydrate de; Bendamustini Hydrochloridum; Hidrocloruro de bendamustina; IMET-3393; SDX-105. 5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride.

Бендамустина Гидрохлорид

$C_{16}H_{21}Cl_2N_3O_2$, HCl = 394.7.
CAS — 16506-27-7 (bendamustine); 3543-75-7 (bendamustine hydrochloride).

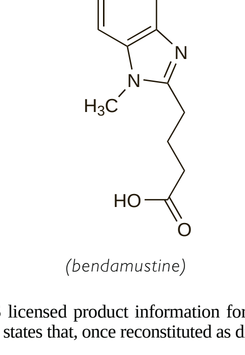

(bendamustine)

Stability. US licensed product information for bendamustine hydrochloride states that, once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2° to 8°) or for 3 hours when stored at room temperature (15° to 30°) and exposed to light.

Adverse Effects, Treatment, and Precautions

Bendamustine commonly causes myelosuppression and doses may need to be reduced (see Uses and Administration, below); patients are therefore susceptible to infection. Other common adverse effects include gastrointestinal disturbances, fever, asthenia, fatigue, malaise, dry mouth, somnolence, cough, headache, mucosal inflammation, and stomatitis. Infusion reactions are common; symptoms include fever, chills, pruritus, and rash. Anaphylactic reactions have been reported rarely, especially during the second and subsequent cycles of therapy. Prophylactic antihistamines, antipyretics, and corticosteroids should be considered. If severe infusion reactions occur, stopping therapy should be considered. Tumour lysis syndrome has been reported, usually within the first treatment cycle, and may lead to acute renal failure and death. Adequate volume status should be maintained and potassium and uric acid concentrations should be monitored; allopurinol may be used in patients at high risk. Skin reactions such as bullous exanthema can occur with bendamustine; therapy may need to be withheld or stopped. Worsening hypertension, including hypertensive crisis, has also occurred. Increases in creatinine concentrations and liver enzyme values have been reported; bendamustine should be used with caution in patients with renal or hepatic impairment.

Interactions

Bendamustine is extensively metabolised by cytochrome P450 isoenzyme CYP1A2. Inhibitors of CYP1A2, such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine; tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics

Bendamustine is about 95% bound to plasma proteins; data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolised by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28-day cycle. About 90% of the drug is eliminated, mainly via the faeces.

Uses and Administration

Bendamustine is an antineoplastic alkylating agent. It is given intravenously as the hydrochloride for the treatment of chronic lymphocytic leukaemia (p.653); it may also be used in non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and breast cancer.

For the treatment of chronic lymphocytic leukaemia, bendamustine hydrochloride is given in a dose of 100 mg/m^2, in 500 mL of sodium chloride 0.9%, infused over 30 minutes on days 1 and 2 of a 28-day cycle, for up to 6 cycles.

Doses are modified if toxicity occurs; dose delays may be warranted until neutrophils and platelets have recovered to acceptable concentrations. For severe haematological or non-haematological toxicity, doses should be reduced to 50 mg/m^2 on days 1 and 2 of each cycle. If severe haematological toxicity recurs, the dose should be further reduced to 25 mg/m^2. Dose re-escalation in subsequent cycles may be considered.

◊ References.

1. Barman Balfour JA, Goa KL. Bendamustine. *Drugs* 2001; **61:** 631–8.
2. Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. *Semin Oncol* 2002; **29** (4 suppl 13): 4–11.
3. Rummel MJ, *et al.* Bendamustine in the treatment of non-Hodgkin's lymphoma: results and future perspectives. *Semin Oncol* 2002; **29** (4 suppl 13): 27–32.
4. Rummel MJ, *et al.* Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 3383–9.
5. von Minckwitz G, *et al.* Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. *Anticancer Drugs* 2005; **16:** 871–7.
6. Herold M, *et al.* Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO 19). *J Cancer Res Clin Oncol* 2006; **132:** 105–12.
7. Ponisch W, *et al.* Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone—a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). *J Cancer Res Clin Oncol* 2006; **132:** 205–12.
8. Eichbaum MH, *et al.* Weekly administration of bendamustine as salvage therapy in metastatic breast cancer: final results of a phase II study. *Anticancer Drugs* 2007; **18:** 963–8.
9. Friedberg JW, *et al.* Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J Clin Oncol* 2008; **26:** 204–10. Correction. *ibid.*; 1911.
10. Apostolopoulos C, *et al.* Bendamustine as a model for the activity of alkylating agents. *Future Oncol* 2008; **4:** 323–32.

Administration in hepatic impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

Administration in renal impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, data are limited, and therefore caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40 mL/minute, due to a lack of data.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Ribomustin; ***USA:*** Treanda.

Bevacizumab *(rINN)*

Bévacizumab; Bevacizumabum; rhuMAb-VEGF. Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer.

Бевацизумаб

CAS — 216974-75-3.
ATC — L01XC07.
ATC Vet — QL01XC07.

Stability. UK licensed product information states that bevacizumab is chemically and physically stable for 48 hours at 2° to 30° in sodium chloride 0.9%, although immediate use is recommended from a microbiological point of view. If the solution is not used immediately, storage for longer than 24 hours at 2° to 8° cannot be recommended, unless dilution has taken place in controlled and validated aseptic conditions. In the USA, licensed product information states that bevacizumab solutions for infusion may be stored at 2° to 8° for up to 8 hours.

Bevacizumab should not be mixed with glucose.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bevacizumab may impair wound healing; therapy should not be started for at least 28 days after major surgery or until the surgical incision is fully healed; it should also be withheld before elective surgery. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation is more common in patients receiving bevacizumab; fatalities have been reported. Bevacizumab should be stopped permanently in patients who develop gastrointestinal perforation, or fistulas, or wound dehiscence needing medical intervention. Very rare cases of nasal septum perforation have been reported.

Leucopenia, anaemia, neutropenia, thrombocytopenia, and febrile neutropenia have also occurred; severe neutropenia with infection has caused fatalities. Haemorrhage may occur; fatal pulmonary haemorrhage presenting as haemoptysis has been reported. There is an increased risk of serious thromboembolic events associated with the use of bevacizumab including stroke, transient ischaemic attacks, myocardial infarction, angina, and death. Bevacizumab may cause congestive heart failure; the risk is higher in those patients who have concurrent or previous treatment with anthracyclines. Hypertension, possibly dose-dependent, has occurred; blood pressure should be monitored, and therapy stopped in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria may develop; bevacizumab should be stopped in patients who develop nephrotic syndrome. Other adverse effects include asthenia, pain, abdominal pain, gastrointestinal disturbances, stomatitis, headache, epistaxis, dyspnoea, upper respiratory infection, and exfoliative dermatitis. Peripheral sensory neuropathy, syncope, somnolence, supraventricular tachycardia, palmar-plantar erythrodysesthesia syndrome, and muscular weakness have been commonly reported. Infusion reactions, manifesting as hypertension, wheezing, chest pain, headaches, rigors, and diaphoresis may occur rarely with the first dose of bevacizumab; treatment should be interrupted.

There have been rare reports of reversible posterior leukoencephalopathy syndrome, a neurological disorder; this may present as seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Bevacizumab therapy should be stopped, and patients treated symptomatically.

◊ References.

1. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin Oncol* 2006; **33** (suppl 10): S26–S34.
2. Saif MW, Mehra R. Incidence and management of bevacizumab-related toxicities in colorectal cancer. *Expert Opin Drug Saf* 2006; **5:** 553–66.

Effects on the cardiovascular system. For a discussion of the incidence of hypertension associated with use of bevacizumab, see Effects on the Kidneys, below.

Effects on the kidneys. A systematic review and subsequent meta-analysis of 7 studies in 1850 patients with various cancers estimated the incidence and risk of developing hypertension and proteinuria with bevacizumab therapy.[1] The relative risk (RR) of developing proteinuria was 1.4 with low-dose bevacizumab (95% confidence interval 1.1 to 1.7) and even higher with high-dose therapy (RR 2.2; 95% confidence interval 1.6 to 2.9). For hypertension, the RR was 3.0 for low-dose bevacizumab (95% confidence interval 2.2 to 4.2) and 7.5 for high-dose therapy (95% confidence interval 4.2 to 13.4). US licensed product information states that hypertension can persist after stopping bevacizumab; therapy should be stopped permanently in those with hypertensive crisis or hypertensive encephalopathy. (For the suggestion that hypertension is a problem with angiogenesis inhibitors in general see Effects on the Cardiovascular System in Sorafenib, p.770.) The safety of continued treatment in patients with moderate to severe proteinuria has not been evaluated; therapy should be interrupted if proteinuria is equal to or greater than 2 g per 24 hours, and may be resumed when it is less than this.

Nephrotic syndrome has also been reported with use of bevacizumab;[2,3] therapy should be stopped in these patients. In one case,[3] there was evidence of a haemolytic-uraemic syndrome; renal biopsy revealed a glomerular thrombotic microangiopathy. Bevacizumab was stopped, with favourable response; however, sunitinib therapy was started but had to be stopped due to a recurrence of severe haemolytic-uraemic syndrome.

A patient who received 3 doses of bevacizumab was diagnosed with acute renal failure secondary to interstitial nephritis. His renal function resolved slowly after stopping therapy; haemodialysis was required.[4]

1. Zhu X, *et al.* Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; **49:** 186–93.
2. George BA, *et al.* Nephrotic syndrome after bevacizumab: case report and literature review. *Am J Kidney Dis* 2007; **49:** e23–e29.
3. Frangié C, *et al.* Renal thrombotic microangiopathy caused by anti-VEGF-antibody treatment for metastatic renal-cell carcinoma. *Lancet Oncol* 2007; **8:** 177–8.
4. Barakat RK, *et al.* Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. *Ann Pharmacother* 2007; **41:** 707–10.

Effects on the nervous system. There are reports of reversible posterior leukoencephalopathy syndrome (RPLS) attributed to bevacizumab.[1,2] Presenting symptoms included lethargy, seizures, hypertension, acute bilateral loss of vision, headache, and confusion. Recovery was rapid after symptomatic treatment.

The symptoms of RPLS may be difficult to distinguish from those of uncontrolled hypertension, and patients presenting with the above signs and symptoms should be examined neurologically.[3]

1. Glusker P, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 980–1.
2. Ozcan C, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 981–2.
3. Health Canada. Association of AVASTIN (bevacizumab) with hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome (RPLS) (issued 24th October 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2006/avastin_pc-cp-eng.php (accessed 30/07/08)

Effects on the spleen. Splenic infarction has been reported in a patient given bevacizumab, fluorouracil, folinic acid, and irinotecan. Bevacizumab was stopped. Four further chemotherapy cycles were given. The splenic infarcts partially regressed, although the patient died from metastatic progression. The authors attributed the splenic infarction to bevacizumab, which has been associated with arterial thromboembolic events.[1]

1. Malka D, *et al.* Splenic infarction and bevacizumab. *Lancet Oncol* 2006; **7:** 1038.

Fistula formation. US licensed product information for bevacizumab states that the incidence of gastrointestinal perforation, including fistula formation and/or intra-abdominal abscess, in bevacizumab-treated patients with colorectal cancer or non-small cell lung cancer was 2.4% and 0.9%, respectively. The Canadian manufacturer (*Roche, Canada*) has stated that there have been uncommon reports of other types of fistulas such as bronchopleural, urogenital, and biliary fistulas, across various indications. While cancer itself might have been a risk factor for fistula formation, a role for bevacizumab could not be excluded; most events occurred within the first 6 months of therapy.[1] There have been reports of tracheo-oesophageal fistula formation in association with use of bevacizumab, including some fatalities.[1,2] Therapy should be permanently stopped in patients with tracheo-oesophageal or gastrointestinal fistulas.

1. Roche, Canada. Health Canada endorsed important safety information on AVASTIN (bevacizumab): association of AVASTIN (bevacizumab) with tracheo-esophageal fistula (issued June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avastin_hpc-cps_2_e.pdf (accessed 13/06/07)
2. Genentech, USA. Important drug warning regarding AVASTIN (bevacizumab) (issued April 2007). Available at: http://www.fda.gov/medwatch/safety/2007/Avastin_DHCP_TEF_Final_April2007.pdf (accessed 13/06/07)

Interactions

◊ The US manufacturer of bevacizumab has recommended that it should not be used with *sunitinib* after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf (accessed 30/07/08)

Pharmacokinetics

Bevacizumab has an initial half-life of 1.4 days and a terminal half-life of about 20 days. The predicted time to steady state is about 100 days. Male patients and those with a higher tumour burden have higher clearances of bevacizumab than females and those with tumour burdens below the median, respectively; although no evidence of lesser efficacy has been seen due to this higher clearance, the relationship between exposure to bevacizumab and clinical outcome is not known.

Uses and Administration

Bevacizumab is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting the angiogenesis that occurs during tumour growth. Bevacizumab is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer (p.665). It is also used with paclitaxel for the first-line treatment of patients with metastatic breast cancer (p.661), and with platinum-based chemotherapy in the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (p.668). Bevacizumab is used with interferon alfa for the first-line treatment of advanced and/or metastatic renal cell cancer (p.667).

Bevacizumab is usually given diluted in 100 mL of sodium chloride 0.9%; the final concentration should be kept within the range of 1.4 to 16.5 mg/mL. The first dose should be given as an intravenous infusion over 90 minutes; if this is well tolerated the second dose should be given over 60 minutes, and if this is well tolerated then subsequent doses may be given over 30 minutes.

In the treatment of **colorectal cancer**, bevacizumab is given in a dose of 5 or 10 mg/kg once every 2 weeks, or 7.5 or 15 mg/kg once every 3 weeks; doses depend on the combination of drugs used in the regimen.

For **breast cancer**, the recommended dose of bevacizumab is 10 mg/kg given once every 2 weeks, or 15 mg/kg given once every 3 weeks.

For **non-small cell lung cancer**, the recommended dose of bevacizumab is 7.5 or 15 mg/kg given once every 3 weeks. In the UK, combination therapy is given for up to 6 cycles, followed by bevacizumab monotherapy until disease progression.

For **renal cell carcinoma**, bevacizumab is given in a dose of 10 mg/kg once every 2 weeks.

There are no recommended dose reduction regimens should adverse effects occur with bevacizumab; therapy should either be permanently stopped or temporarily suspended.

Bevacizumab is under investigation for various other neoplasms, such as head and neck, ovarian, and prostate cancer. A related monoclonal antibody, ranibizumab (p.2377) has been developed for the treatment of neovascular (wet) age-related macular degeneration, and it has been suggested that bevacizumab might also be of benefit.

◊ References.

1. Hurwitz H, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350:** 2335–42.
2. Johnson DH, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol* 2004; **22:** 2184–91.
3. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. *Ann Pharmacother* 2004; **38:** 1258–64.
4. Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am J Health-Syst Pharm* 2005; **62:** 1021–32. Correction. *ibid.*; 1241.
5. Kabbinavar FF, *et al.* Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23:** 3706–12.
6. Midgley R, Kerr D. Bevacizumab—current status and future directions. *Ann Oncol* 2005; **16:** 999–1004.
7. Lyseng-Williamson KA, Robinson DM. Spotlight on bevacizumab in advanced colorectal cancer, breast cancer, and non-small cell lung cancer. *BioDrugs* 2006; **20:** 193–5.
8. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006; **28:** 1779–1802.
9. Pañares RL, Garcia AA. Bevacizumab in the management of solid tumors. *Expert Rev Anticancer Ther* 2007; **7:** 433–45.
10. Cilley JC, *et al.* Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2007; **7:** 739–49.
11. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol* 2007; **25:** 2902–8.
12. Escudier B, *et al.* AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370:** 2103–11.
13. Miller K, *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357:** 2666–76.
14. Scott LJ. Bevacizumab: in first-line treatment of metastatic breast cancer. *Drugs* 2007; **67:** 1793–9.
15. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. *Drugs* 2008; **68:** 487–506.
16. Di Costanzo F, *et al.* Bevacizumab in non-small cell lung cancer. *Drugs* 2008; **68:** 737–46.
17. Norden AD, *et al.* Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008; **70:** 779–87.

Administration. It has been suggested that bevacizumab may be safely given at an infusion rate of 500 micrograms/kg per minute; this means a dose of 5 mg/kg could be given over 10 minutes.[1]

1. Reidy DL, *et al.* Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007; **25:** 2691–5.

Age-related macular degeneration. Short-term results with intravenous[1] or intravitreal[2-7] bevacizumab to treat age-related macular degeneration (p.785) are promising, although it is unlicensed for this use. Ranibizumab (p.2377) is a humanised antibody fragment derived from bevacizumab that is used for the treatment of this disease.

1. Michels S, *et al.* Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005; **112:** 1035–47.
2. Avery RL, *et al.* Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113:** 363–72.
3. Bashshur ZF, *et al.* Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006; **142:** 1–9.
4. Spaide RF, *et al.* Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; **26:** 383–90.
5. Fung AE, *et al.* The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90:** 1344–9.
6. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother* 2007; **41:** 614–25.
7. Madhusudhana KC, *et al.* Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases. *Br J Ophthalmol* 2007; **91:** 1716–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avastin; ***Austral.:*** Avastin; ***Belg.:*** Avastin; ***Braz.:*** Avastin; ***Canad.:*** Avastin; ***Chile:*** Avastin; ***Cz.:*** Avastin; ***Denm.:*** Avastin; ***Fin.:*** Avastin; ***Fr.:*** Avastin; ***Ger.:*** Avastin; ***Gr.:*** Avastin; ***Hong Kong:*** Avastin; ***Hung.:*** Avastin; ***Indon.:*** Avastin; ***Irl.:*** Avastin; ***Israel:*** Avastin; ***Ital.:*** Avastin; ***Jpn:*** Avastin; ***Mex.:*** Avastin; ***Neth.:*** Avastin; ***Norw.:*** Avastin; ***NZ:*** Avastin; ***Philipp.:*** Avastin; ***Pol.:*** Avastin; ***Port.:*** Avastin; ***Rus.:*** Avastin (Авастин); ***S.Afr.:*** Avastin; ***Singapore:*** Avastin; ***Spain:*** Avastin; ***Swed.:*** Avastin; ***Switz.:*** Avastin; ***Thai.:*** Avastin; ***UK:*** Avastin; ***USA:*** Avastin.

Bexarotene *(BAN, USAN, rINN)*

Beksaroteeni; Beksaroten; Bexaroten; Bexarotène; Bexaroteno; Bexarotenum; LG-100069; LGD-1069. *p*-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)vinyl]benzoic acid.

Бексаротен

$C_{24}H_{28}O_2$ = 348.5.

CAS — 153559-49-0.

ATC — L01XX25.

ATC Vet — QL01XX25.

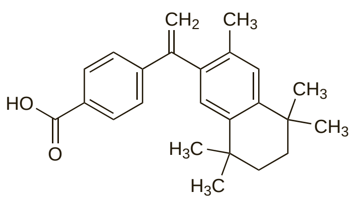

Adverse Effects and Precautions

The main adverse effects noted after oral therapy with bexarotene include hyperlipidaemia, hypothyroidism, leucopenia, headache, oedema, altered liver function, rash, and pruritus. Exfoliative dermatitis, alopecia, and skin disorders may occur. Other common adverse effects include anaemia, insomnia, dizziness, eye or ear disorders, gastrointestinal disturbances, arthralgia, and myalgia. Acute pancreatitis has been associated with hypertriglyceridaemia, and patients with risk factors for pancreatitis should generally not be given bexarotene. If triglyceride concentrations rise during therapy, dose reductions are recommended, and lipid-lowering therapy may be instituted (with the exception of gemfibrozil, see below). The most common adverse events associated with topical therapy are rash, pruritus, and pain. Bexarotene capsules and gel should not be used during pregnancy because of the risk of fetal malformation.

◊ References.

1. Assaf C, *et al.* Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; **155:** 261–6.

Interactions

Gemfibrozil. Gemfibrozil inhibits clearance of bexarotene, resulting in extremely high triglyceride levels and pancreatitis.[1]

1. Talpur R, *et al.* Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; **47:** 672–84.

Uses and Administration

Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is used in the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p.657), in a usual initial oral dose of 300 mg/m^2 daily as a single dose taken with a meal. Dosage is adjusted according to toxicity. For the topical treatment of refractory disease a 1% gel may be applied on alternate days for the first week, gradually increased at weekly intervals to up to 4 times daily, depending on tolerance.

◊ References.

1. Anonymous. Bexarotene (Targretin) for cutaneous T-cell lymphoma. *Med Lett Drugs Ther* 2000; **42:** 31–2.
2. Lowe MN, Plosker GL. Bexarotene. *Am J Clin Dermatol* 2000; **1:** 245–50.
3. Duvic M, *et al.* Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001; **19:** 2456–71.
4. Wong S-F. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001; **35:** 1056–65.
5. Heald P, *et al.* Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003; **49:** 801–15.
6. Hanifin JM, *et al.* Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 2004; **150:** 545–53.
7. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther* 2004; **4:** 180–8.
8. Gniadecki R, *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157:** 433–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Targretin; ***Chile:*** Targretin; ***Cz.:*** Targretin; ***Denm.:*** Targretin; ***Fr.:*** Targretin; ***Ger.:*** Targretin; ***Gr.:*** Targretin; ***Hung.:*** Targretin; ***Irl.:*** Targretin; ***Ital.:*** Targretin; ***Neth.:*** Targretin; ***Port.:*** Targretin; ***Spain:*** Targretin; ***UK:*** Targretin; ***USA:*** Targretin.

Bicalutamide *(BAN, USAN, rINN)*

Bicalutamida; Bicalutamidum; Bikalutamid; Bikalutamidi; ICI-176334. (*RS*)-4′-Cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

Бикалутамид

$C_{18}H_{14}F_4N_2O_4S$ = 430.4.

CAS — 90357-06-5.

ATC — L02BB03.

ATC Vet — QL02BB03.

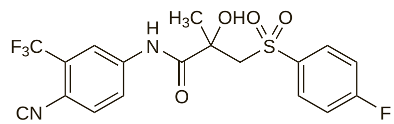

Pharmacopoeias. In *US.*

USP 31 (Bicalutamide). A fine, white to off-white powder. Sparingly to slightly soluble in alcohol; freely soluble in acetone and in tetrahydrofuran; soluble in acetonitrile. Store in airtight containers.

Adverse Effects and Precautions

As for Flutamide, p.725. Pruritus, asthenia, alopecia, hair regrowth, and dry skin occur commonly with bicalutamide. Hypersensitivity reactions, including angioedema and urticaria, have been reported infrequently.

Cardiovascular effects including angina, heart failure, arrhythmias, and ECG changes have been reported rarely. Interstitial pneumonitis and pulmonary fibrosis have also been reported rarely.

Effects on the gastrointestinal tract. There is some evidence that bicalutamide is associated with a lower incidence of diarrhoea than flutamide.[1]

1. Schellhammer P, *et al.* A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. *Urology* 1995; **45:** 745–52.

Effects on the lungs. For a review of cases of pneumonitis associated with anti-androgens including bicalutamide, see under Flutamide, p.725.

Gynaecomastia. For a discussion of gynaecomastia, a frequent adverse effect of anti-androgen therapy, and its management, see under Flutamide, p.725.

Interactions

Bicalutamide inhibits various cytochrome P450 isoenzymes, particularly CYP3A4, *in vitro*, and licensed product information recommends that terfenadine, astemizole, and cisapride should not be given with bicalutamide, and that other drugs with a narrow therapeutic index that are metabolised by cytochrome P450 isoenzymes should be used with caution. *In vitro* studies have shown that bicalutamide can displace warfarin from its protein binding sites (see also Antineoplastics, p.1429).

Pharmacokinetics

Bicalutamide is well absorbed after oral doses. It undergoes extensive metabolism in the liver, the active *R*-enantiomer mainly by oxidation, the inactive *S*-enantiomer mainly by glucuronidation. It is excreted as metabolites in urine and faeces. The half-life of the *R*-enantiomer is about 6 to 7 days, and may be prolonged still further in severe hepatic impairment. The *S*-enantiomer is cleared more rapidly. Bicalutamide is about 96% bound to plasma proteins.

◊ References.

1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* 2004; **43:** 855–78.

Uses and Administration

Bicalutamide is a nonsteroidal anti-androgen with actions and uses similar to those of flutamide (p.725). It is used orally in the treatment of prostatic cancer (p.671). When used with a gonadorelin analogue in the palliative treatment of advanced prostatic cancer the usual dose is 50 mg daily. In the UK treatment is started at least 3 days before starting the gonadorelin analogue to suppress any flare reaction, but in the USA treatment is started at the same time. A similar dose is used with surgical castration, starting on the same day as surgery.

Bicalutamide in a dose of 150 mg daily may be given as monotherapy or adjuvant therapy to surgery or radiotherapy in men with locally advanced disease at high risk for disease progression. It has been used as monotherapy in localised disease, but there is some evidence to suggest that in men without high risk of disease progression, who would otherwise be managed with watchful waiting, the immediate use of bicalutamide may increase the risk of death.

◊ References.

1. Wirth M, *et al.* Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001; **58:** 146–51.
2. Boccardo F, *et al.* Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. *Eur Urol* 2002; **42:** 481–90.
3. See WA, *et al.* Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *J Urol (Baltimore)* 2002; **168:** 429–35.
4. See W, *et al.* Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer. *Eur Urol* 2003; **44:** 512–17.
5. Fradet Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2004; **4:** 37–48.
6. Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2004; **2:** 213–19.
7. Wirth MP, *et al.* Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol (Baltimore)* 2004; **172:** 1865–70.
8. Iversen P, *et al.* Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol (Baltimore)* 2004; **172:** 1871–6.
9. Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. *Clin Prostate Cancer* 2005; **3:** 215–19.
10. Wirth M, *et al.* Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. *Prostate Cancer Prostatic Dis* 2005; **8:** 194–200.
11. Tyrell CJ, *et al.* Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005; **76:** 4–10.
12. McLeod DG, *et al.* Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97:** 247–54.
13. Wellington K, Keam SJ. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs* 2006; **66:** 837–50.
14. Iversen P, Roder MA. The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer. *Expert Rev Anticancer Ther* 2008; **8:** 361–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Androxinon†; Bicaprost†; Bidrostat; Biolutam; Bitakebir; Bosconar; Casodex; Codebup; Dimalan; Finaband; Gepeprostin; Imda†; Liberprost; Raffolutil; ***Austral.:*** Cosudex; ***Austria:*** Casodex; ***Belg.:*** Casodex; ***Braz.:*** Casodex; Gepeprostin; Lutamidal; ***Canad.:*** Casodex; ***Chile:*** Casodex; Lutamidal; ***Cz.:*** Bicaluplex; Calumid; Casodex; Lanbica; ***Denm.:*** Casodex; ***Fin.:*** Casodex; ***Fr.:*** Casodex; ***Ger.:*** Casodex; ***Gr.:*** Bicalut; Bicamide; Casodex; Verodex; ***Hong Kong:*** Casodex; ***Hung.:*** Bicatlon; Bilutamid; Calumid; Casodex; ***India:*** Caluran; Calutide; ***Indon.:*** Casodex; ***Irl.:*** Casodex; ***Israel:*** Casodex; ***Ital.:*** Casodex; ***Malaysia:*** Casodex; ***Mex.:*** Casodex; ***Neth.:*** Casodex; ***Norw.:*** Casodex; ***NZ:*** Cosudex; ***Philipp.:*** Casodex; ***Pol.:*** Casodex; ***Port.:*** Casodex; ***Rus.:*** Bilumid (Билумид); Calumid (Калумид); Casodex (Касодекс); ***S.Afr.:*** Casodex; ***Singapore:*** Casodex; ***Spain:*** Casodex; ***Swed.:*** Casodex; ***Switz.:*** Casodex; ***Thai.:*** Casodex; ***Turk.:*** Casodex; ***UK:*** Casodex; ***USA:*** Casodex; ***Venez.:*** Calutol; Casodex.

Multi-ingredient: ***Austral.:*** Zolacos CP.

Bleomycin Sulfate *(USAN, pINNM)*

Bleomicino sulfatas; Bleomicin-szulfát; Bleomycin Sulphate *(BANM)*; Bléomycine, sulfate de; Bleomycini sulfas; Bleomycinsulfat; Bleomycin-sulfát; Bleomysiinisulfaatti; Sulfato de bleomicina.

Блеомицина Сульфат

CAS — 11056-06-7 (bleomycin); 67763-87-5 (bleomycin hydrochloride); 9041-93-4 (bleomycin sulfate).

ATC — L01DC01.

ATC Vet — QL01DC01.

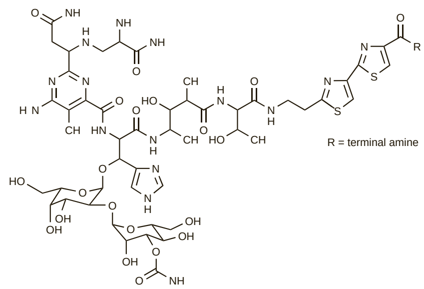

(bleomycin)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Int. and *Jpn* also include Bleomycin Hydrochloride. *Chin.* includes Bleomycin A5 Hydrochloride for Injection.

Ph. Eur. 6.2 (Bleomycin Sulphate). The sulfate of a mixture of glycopeptides obtained by the growth of *Streptomyces verticillus* or by any other means; the two principal components of the mixture are *N*-[3-(dimethylsulphonio)propyl]bleomycinamide (bleomycin A_2) and *N*-[4-(carbamimidoylamino)butyl]bleomycinamide (bleomycin B_2). A white or yellowish-white, very hygroscopic powder. It loses not more than 3% of its weight when dried. Very soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.0. Store in airtight containers at a temperature of 2° to 8°.

USP 31 (Bleomycin Sulfate). The sulfate salt of a mixture of basic cytotoxic glycopeptides, produced by the growth of *Streptomyces verticillus* or produced by other means. It has a potency of not less than 1.5 units and not more than 2.0 units/mg. It contains between 55 and 70% of bleomycin A_2 and between 25 and 32% of bleomycin B_2; the content of bleomycin B_4 is not more than 1%. The combined percentage of bleomycin A_2 and B_2 is not less than 90%. A cream-coloured, amorphous powder. It loses not more than 6% of its weight when dried. Very soluble in water. A solution in water containing 10 units/mL has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility. A loss of bleomycin activity was reported when bleomycin sulfate solutions were mixed with solutions of carbenicillin, cefazolin or cefalotin sodium, nafcillin sodium, benzylpenicillin sodium, methotrexate, mitomycin, hydrocortisone sodium succinate, aminophylline, ascorbic acid, or terbutaline.[1] The interactions of bleomycin have been summarised as the chelation of divalent and trivalent cations (especially copper), inactivation by compounds containing sulfhydryl groups, and precipitation by hydrophobic anions; solutions of bleomycin should not be mixed with solutions of essential amino acids, riboflavin, dexamethasone, or furosemide.[2]

1. Dorr RT, *et al.* Bleomycin compatibility with selected intravenous medications. *J Med* 1982; **13:** 121–30.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. Bleomycin sulfate solutions appear to be equally stable in plastic or glass,[1,2] despite some earlier studies suggesting loss of potency in plastic.[3,4] There is some evidence[5] that bleomycin is more stable in sodium chloride 0.9% than glucose 5%, and sodium chloride 0.9% is the diluent recommended by the licensed product information. UK licensed product information states that bleomycin sulfate is chemically and physically stable, once reconstituted and diluted as directed, for 10 days when refrigerated at 2° to 8° and protected from light. From a microbiological point of view, solutions should be used immediately; storage for longer than 24 hours at 2° to 8° is not recommended, unless prepared under controlled and validated aseptic conditions.

1. De Vroe C, *et al.* A study on the stability of three antineoplastic drugs and on their sorption by iv delivery systems and end-line filters. *Int J Pharmaceutics* 1990; **65:** 49–56.
2. Stajich GV, *et al.* In vitro evaluation of bleomycin-induced cell lethality from plastic and glass containers. *DICP Ann Pharmacother* 1991; **25:** 14–16.
3. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
4. Adams J, *et al.* Instability of bleomycin in plastic containers. *Am J Hosp Pharm* 1982; **39:** 1636.
5. Koberda M, *et al.* Stability of bleomycin sulfate reconstituted in 5% dextrose injection or 0.9% sodium chloride injection stored in glass vials or polyvinyl chloride containers. *Am J Hosp Pharm* 1990; **47:** 2528–9.

Units

8910 units of bleomycin complex A_2/B_2 are contained in 5 mg of bleomycin complex in one ampoule of the first International Reference Preparation (1980). The Ph. Eur. 6.2 specifies a potency of not less than 1500 international units per mg, calculated with reference to the dried substance. These units differ from those used by the USP: Bleomycin Sulfate (USP 31) contains 1.5 to 2.0 units of bleomycin in each mg. A change in the labelling of preparations in the UK, from units equivalent to those of the USP to international units in line with the Ph. Eur., resulted in an apparent but artefactual increase in UK doses by a factor of 1000.

In some countries doses were *formerly* described in terms of mg-potency, where 1 mg-potency corresponded to 1 unit. In the original preparation 1 mg-potency was equivalent to 1 mg-weight but improvements in purification of the product led to a situation in which ampoules labelled as containing 15 mg (i.e. 15 units) contained far fewer mg-weight of bleomycin.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

The most frequent adverse effects with bleomycin involve the skin and mucous membranes and include rash, erythema, pruritus, vesiculation, hyperkeratosis, nail changes, alopecia, hyperpigmentation, striae, and stomatitis. Fever is also common, and acute anaphylactoid reactions with hyperpyrexia and cardiorespiratory collapse have been reported in about 1% of patients with lymphoma. There is little depression of the bone marrow. Local reactions and thrombophlebitis may occur at the site of parenteral dosage.

The most serious delayed effect is pulmonary toxicity; interstitial pneumonitis occurs in about 10% of patients and progresses to fibrosis and death in about 1% of patients treated with bleomycin. Pulmonary toxicity is more likely in elderly patients and those given total doses greater than 400 000 international units (400 USP units). It is also more likely in patients who have had previous radiotherapy to the chest.

Effects on the lungs. Pneumonitis induced by bleomycin can progress to fatal pulmonary fibrosis. The presentation is often delayed; clinical manifestations include non-productive cough, dyspnoea, and sometimes fever (see Effects on the Lungs, p.638). Pneumomediastinum has also been reported as an initial manifestation of fatal pulmonary toxicity due to bleomycin.[1] Risk factors for toxicity include increased age,[2,3] deteriorating renal function,[2] and concurrent or previous radiotherapy. The reaction is dose-related, and maximum doses have been set (see Uses and Administration, below). Other factors that may be implicated include the regimen used, concomitant oxygen supplementation, smoking history, underlying lung disease, and growth factor support.[2,3] For further details of some of these risk factors, see under Interactions, below. There is no standard treatment for bleomycin-induced pneumonitis. Bleomycin therapy is usually stopped, and corticosteroids may be given[3] although strong evidence to support their use is lacking.[2] There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection may reduce pulmonary toxicity.[2]

1. Keijzer A, Kuenen B. Fatal pulmonary toxicity in testis cancer with bleomycin-containing chemotherapy. *J Clin Oncol* 2007; **25:** 3543–4.
2. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
3. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Effects on the skin, hair, and nails. Permanent nail loss and nail loss followed by regrowth with dystrophy have been reported after intralesional injection of bleomycin for periungual warts.[1-3] In 2 cases this was preceded by blistering and ulceration,[1] or swelling, severe pain, and a burning sensation.[2] All 3 patients had received injections on one or two previous occasions when 2 patients had reported only mild pain.[1,3] Other reported cutaneous adverse effects of bleomycin include flagellate erythema, Raynaud's phenomenon, gangrene, fibrotic or sclerotic skin changes, hyperpigmentation, and neutrophilic eccrine hidradenitis (an inflammatory dermatosis with erythematous plaques and nodules, neutrophilic infiltrates of eccrine glands, and degeneration of eccrine cells). Acute generalised exanthematous pustulosis and alopecia have also been reported.[4]

1. Czarnecki D. Bleomycin and periungual warts. *Med J Aust* 1984; **141:** 40.
2. Miller RAW. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. *Arch Dermatol* 1984; **120:** 963–4.
3. Urbina González F, *et al.* Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. *Arch Dermatol* 1986; **122:** 974–5.
4. Yamamoto T. Bleomycin and the skin. *Br J Dermatol* 2006; **155:** 869–75.

Effects on the vascular system. Although thromboembolic disorders and Raynaud's syndrome have been associated with use of bleomycin in combination regimens, particularly with cisplatin and the vinca alkaloids or etoposide (see Effects on the Cardiovascular System, p.636) there is some evidence for an association of Raynaud's syndrome with the use of bleomycin alone.[1,2]

There have also been cases of Raynaud's phenomenon reported after intralesional injection of bleomycin for treatment of warts on the hands and feet.[3-6] See also Effects on the Skin, Hair, and Nails, above.

1. Sundstrup B. Raynaud's phenomenon after bleomycin treatment. *Med J Aust* 1978; **2:** 266.
2. Adoue D, Arlet P. Bleomycin and Raynaud's phenomenon. *Ann Intern Med* 1984; **100:** 770.
3. Epstein E. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1991; **24:** 785–6.
4. Gregg LJ. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1992; **26:** 279–80.
5. de Pablo P, *et al.* Raynaud's phenomenon and intralesional bleomycin. *Acta Derm Venereol (Stockh)* 1992; **72:** 465.
6. Vanhooteghem O, *et al.* Raynaud phenomenon after treatment of verruca vulgaris of the sole with intralesional injection of bleomycin. *Pediatr Dermatol* 2001; **18:** 249–51.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641.

Bleomycin should be used with caution in the elderly, in patients with renal impairment or pulmonary infection or pre-existing impairment of pulmonary function, and in those who have received radiotherapy, particularly to the thorax. Patients should undergo regular chest X-rays. If these show infiltrates, or if breathlessness occurs, bleomycin should be stopped.

In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below).

AIDS. Cutaneous adverse effects occurred in 12 of 50 patients being treated with bleomycin for AIDS-associated Kaposi's sarcoma and increased in severity until bleomycin was withdrawn.[1] Bleomycin should be stopped in people with AIDS if cutaneous adverse effects are seen, and rechallenge should be avoided. However, the incidence of adverse effects did not appear to be higher in these patients than in cancer patients, and patients with AIDS seem to be less sensitive to bleomycin than to antibacterials such as co-trimoxazole and penicillins.

1. Caumes E, *et al.* Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990; **336:** 1593.

Diving. Since the partial pressure of oxygen in the inspired air of a scuba diver increases with increasing depth, a theoretical possibility exists of a toxic [pulmonary] reaction to oxygen in bleomycin-treated patients who subsequently go diving, and such a risk would increase with the depth and duration of each dive.[1] However, the risks associated with diving after uncomplicated bleomycin-based treatment have been questioned;[2] the authors considered that resuming diving was acceptable 6 to 12 months after completing treatment with BEP (bleomycin, etoposide, and cisplatin), and recommended caution only in those who developed pulmonary function impairment when given bleomycin.

1. Zanetti CL. Scuba diving and bleomycin therapy. *JAMA* 1990; **264:** 2869.
2. de Wit R, *et al.* Bleomycin and scuba diving: where is the harm? *Lancet Oncol* 2007; **8:** 954–5.

Handling and disposal. *Urine* produced for up to 72 hours after a dose of bleomycin should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. For a report of use of a bleomycin-containing chemotherapy regimen in a pregnant woman and subsequent adverse effects on the infant, see Pregnancy, under Cisplatin, p.699.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. There may be an increased risk of pulmonary toxicity in patients given bleomycin who receive oxygen, for example as part of a general anaesthetic procedure; a reduction in inspired oxygen concentration has been recommended.

Antineoplastics. Enhanced pulmonary toxicity, in some cases fatal, has been reported in patients given bleomycin and *cisplatin*,[1-4] presumably because cisplatin-induced renal impairment led to a decrease in bleomycin elimination. It seems reasonable to assume that similar interactions might occur if bleomycin were given with other nephrotoxic agents. It has been suggested that apart from a decrease in bleomycin dosage if nephrotoxicity occurs with such a combination, giving bleomycin by constant infusion rather than intermittent bolus might be less toxic.[1,5]

A study to investigate whether substitution of etoposide with *gemcitabine* would lead to a less leukaemogenic BEACOPP regimen was stopped early because of unexpectedly common pulmonary toxicity; one patient died. This toxicity was considered to be due to the use of gemcitabine with bleomycin.[6]

1. Bennett WM, *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep* 1980; **64:** 921–4.
2. van Barneveld PWC, *et al.* Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* 1984; **41:** 4–7.
3. Brodsky A, *et al.* Stevens-Johnson syndrome, respiratory distress and acute renal failure due to synergic bleomycin-cisplatin toxicity. *J Clin Pharmacol* 1989; **29:** 821–3.
4. Sleijfer S, *et al.* Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* 1996; **32A:** 550–2.
5. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
6. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004; **22:** 2424–9.

Colony-stimulating factors. An increased incidence of pulmonary toxicity has been reported in patients receiving bleomycin as part of the ABVD regimen (with doxorubicin, vinblastine, and dacarbazine) who were given granulocyte colony-stimulating factor to alleviate neutropenia.[1] Another case of rapidly developing and fatal pneumonitis in a patient given BEP (bleomycin, etoposide, and cisplatin) with granulocyte colony-stimulating factor has been reported.[2]

Analyses of study data failed to show increased pulmonary toxicity when granulocyte colony-stimulating factor was added to bleomycin-containing regimens in patients with germ cell tumours or non-Hodgkin's lymphomas.[3-5] In a retrospective review of patients with Hodgkin's lymphoma, however, use of bleomycin with granulocyte colony-stimulating factor was associated with a statistically significant increase of pulmonary toxicity.[6]

1. Matthews JH. Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* 1993; **342:** 988.
2. Dirix LY, *et al.* Pulmonary toxicity and bleomycin. *Lancet* 1994; **344:** 56.
3. Bastion Y, *et al.* Possible toxicity with the association of G-CSF and bleomycin. *Lancet* 1994; **343:** 1221–2.
4. Bastion Y, Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? *Lancet* 1994; **344:** 474.
5. Saxman SB, *et al.* Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* 1997; **111:** 657–60.
6. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 7614–20.

Oxygen. Because bleomycin is thought to cause pulmonary toxicity partly by induction of free radicals, use with high concentrations of oxygen could be hazardous,[1] and reductions in inspired oxygen concentration have been recommended by licensed product information where oxygen supplementation is unavoidable. *Animal* studies show an increased risk of mortality with use of bleomycin and oxygen, although data in humans are lacking. The need for oxygen restriction in bleomycin-treated patients has, however, been questioned.[2]

1. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.
2. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? *J Urol (Baltimore)* 1998; **160:** 1347–52.

Pharmacokinetics

Bleomycin is thought to be poorly absorbed from the gastrointestinal tract. Absorption is rapid after parenteral, intraperitoneal, or intrapleural use. Bioavailability is 100% and 70% after intramuscular and subcutaneous dosage, respectively. A bioavailability of 45% has been reported after intraperitoneal or intrapleural use. Plasma protein binding is low. Enzymic degradation of bleomycin occurs, primarily in plasma, the liver and other organs, and to a much lesser extent in skin and lungs. Elimination is biphasic: mean initial and terminal half-lives of 0.5 and 4 hours respectively have been reported after an intravenous bolus. Elimination may be more prolonged after continuous intravenous infusion and mean half-lives of 1.3 and 9 hours respectively have been reported. About two-thirds of a dose is excreted unchanged in the urine; the rate of excretion is determined by renal function. Drug concentrations in the CSF are low. Bleomycin crosses the placenta.

◊ References.

1. Broughton A, *et al.* Clinical pharmacology of bleomycin following intravenous infusion as determined by radioimmunoassay. *Cancer* 1977; **40:** 2772–8.
2. Alberts DS, *et al.* Bleomycin pharmacokinetics in man I: intravenous administration. *Cancer Chemother Pharmacol* 1978; **1:** 177–81.
3. Yee GC, *et al.* Bleomycin disposition in children with cancer. *Clin Pharmacol Ther* 1983; **33:** 668–73.

Uses and Administration

Bleomycin is an antineoplastic antibiotic that binds to DNA and causes strand scissions, and is probably most effective in the G_2 and M phases of the cell cycle. It is widely used to treat malignant disease; particularly squamous cell carcinomas, including those of the cervix and external genitalia, oesophagus, skin, and head and neck; Hodgkin's disease and other lymphomas; malignant neoplasms of the testis, and malignant effusions. It has also been tried in other malignancies, including carcinoma of the bladder, lung, and thyroid, and some sarcomas, including Kaposi's sarcoma.

Bleomycin is often used with other antineoplastics, notably with doxorubicin, vinblastine, and dacarbazine (ABVD) for Hodgkin's disease, and with etoposide and cisplatin (BEP) in testicular tumours. Bleomycin is given as the sulfate by either the intramuscular, intravenous, or subcutaneous route. It may also be given intra-arterially or instilled intrapleurally or intraperitoneally. If intramuscular injections are painful they may be given in a 1% solution of lidocaine.

Doses are calculated in terms of the base, and are given in ***units****, but the units used for preparations in the UK, which were formerly equivalent to those of the USP, are now international units equivalent to those of the Ph. Eur. (see Units, above). Since 1000 international units is equivalent to 1 USP unit, UK doses now appear to be 1000 times greater than those previously in use, or than those in use in the USA, and care is recommended in evaluating the literature.*

In the UK the licensed dose as a single agent for **squamous cell** or **testicular tumours** is 15 000 international units (15 USP units) three times a week, or 30 000 international units twice a week, by intramuscular or intravenous injection, although in practice treatment of malignancy will generally be with combination regimens. This may be repeated, at usual intervals of 3 to 4 weeks, up to a total cumulative dose of 500 000 international units. The dose and total cumulative dose should be reduced in those over 60 years of age (see below). Doses should be adjusted according to tolerance, and may need to be adjusted as part of combination chemotherapy. Continuous intravenous infusion at a rate of 15 000 international units per 24 hours for up to 10 days or 30 000 international units per 24 hours for up to 5 days may also be used. In patients with **lymphoma** a dose of 15 000 international units once or twice weekly by intramuscular injection has been suggested, to a total dose of 225 000 international units. Again, dosage should be reduced in older patients and in combination regimens if necessary. In the treatment of **malignant effusions** a solution of 60 000 international units in 100 mL of sodium chloride 0.9% may be instilled into the affected serous cavity. Treatment may be repeated as necessary up to a total cumulative dose of 500 000 international units depending on the patient's age. Local anaesthetics or analgesics are given concomitantly.

In the USA licensed doses for **lymphomas** as well as **squamous cell** and **testicular** neoplasms are 250 to 500 international units/kg (0.25 to 0.5 USP units/kg), or 10 000 to 20 000 international units/m^2 (10 to 20 USP units/m^2), given once or twice weekly. In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below). In patients with Hodgkin's disease, once a 50% response has been achieved it may be maintained with 1000 international units (1 USP unit) of bleomycin daily, or 5000 international units (5 USP units) weekly.

In the UK, licensed product information suggests that a **total dose** of 500 000 international units (500 USP units) should not be exceeded. Total cumulative dose should not exceed 300 000 international units in those aged 60 to 69 years, 200 000 international units in those 70 to 79, and 100 000 international units in those 80 and over; the weekly dose should be no more than 60 000, 30 000 and 15 000 international units respectively. In the USA the recommended maximum total dose is 400 000 international units (400 USP units); it is generally agreed that patients receiving 400 000 international units or more are at increased risk of pulmonary toxicity (see Adverse Effects, above).

Dosage should be reduced in patients with renal impairment (see below).

Bleomycin hydrochloride has also been given parenterally for malignant neoplasms, and bleomycin sulfate has been applied topically for the local treatment of skin tumours.

Administration. Although test doses have been suggested as a way of avoiding anaphylactoid reactions in patients with lymphoma being treated with bleomycin, a review[1] of the literature concluded that the evidence did not support such a strategy, since the onset of the reaction was unpredictable, and not associated with any particular dose. It had also been suggested that reactions were less frequent with intramuscular rather than intravenous dosage, but evidence for this was conflicting.

There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection in combination regimens may result in reduced pulmonary toxicity.[2,3]

1. Lam MSH. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother* 2005; **39:** 1897–1902.
2. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; **30:** 158–60.
3. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; **120:** 617–24.

Administration in renal impairment. A significant portion of a dose of bleomycin is excreted largely unchanged in the urine, and dose reduction should be considered in patients with renal impairment. UK licensed product information suggests a 50% dose reduction when the serum creatinine concentration is between 20 and 40 micrograms/mL and further reduction for serum creatinine above this. US licensed product information gives the following proposed percentages of the initial dose, based on creatinine clearance (CC):

- CC 5 to 10 mL/minute: 40%
- CC 10 to 20 mL/minute: 45%
- CC 20 to 30 mL/minute: 55%
- CC 30 to 40 mL/minute: 60%
- CC 40 to 50 mL/minute: 70%
- CC 50 mL/minute and above: 100%

Leucoplakia. Leucoplakia is used to describe a white patch or plaque in the mouth which cannot be otherwise characterised. Such lesions are of concern because they may be pre-malignant, and patients with evidence of dysplasia may be at higher risk of transformation (see also Malignant Neoplasms of the Head and Neck, p.666). Leucoplakia must be distinguished from other conditions such as candidiasis, lichen planus, and oral hairy leucoplakia which is associated with HIV infection.[1]

Leucoplakia is often associated with tobacco smoking, and smoking cessation can result in regression.[1] Where active treatment is desirable, small and easily accessible lesions can be removed surgically or by laser therapy, although they may recur.[1] For extensive patches or those in which surgery would be difficult, the treatments described include topical bleomycin 1%, dissolved in dimethyl sulfoxide and applied for 5 minutes daily for 14 consecutive days. In a group of 19 patients with dysplastic leucoplakia, improvement in the appearance of lesions and histological evidence of remission of the dysplasia occurred in the majority of patients. Sustained effects were also found on long-term follow-up for up to 10 years.[2]

There have been reports of partial or complete remission of leucoplakia in studies of vitamin A or betacarotene given orally long-term,[3-5] but lesions have recurred when supplementation was stopped.[4] Topical treatment with retinoids such as tretinoin or isotretinoin has also been tried, with similar results to those of oral vitamin A and retinoid treatments.[6,7] A small open study has also suggested that topical calcipotriol may be effective.[8]

A systematic review of treatments for leucoplakia found that there were few controlled trials reported, and that although these treatments might be effective in the resolution of lesions, the rate of relapse was high, and there was no evidence that they prevent malignant transformation.[9]

1. Scully C, Porter S. ABC of oral health: swellings and red, white, and pigmented lesions. *BMJ* 2000; **321:** 225–8.
2. Epstein JB, *et al.* Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer* 1998; **83:** 629–34.
3. Issing WJ, *et al.* Long-term follow-up of larynx leukoplakia under treatment with retinyl palmitate. *Head Neck* 1996; **18:** 560–5.
4. Sankaranarayanan R, *et al.* Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. *Oral Oncol* 1997; **33:** 231–6.
5. Garewal HS, *et al.* β-Carotene produces sustained remissions in patients with oral leukoplakia: results of a multicenter prospective trial. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 1305–10.
6. Epstein JB, Gorsky M. Topical application of vitamin A to oral leukoplakia: a clinical case series. *Cancer* 1999; **86:** 921–7.
7. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
8. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30:** 402–6.
9. Lodi G, *et al.* Interventions for treating oral leukoplakia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/05/08).

Malignant effusions. Bleomycin is used for the sclerotherapy of malignant pleural and pericardial effusions (p.659).

Malignant neoplasms. Bleomycin is used in regimens for the management of Hodgkin's disease (p.655), non-Hodgkin's lymphomas, including AIDS-related lymphomas (see p.656 and p.657), and for germ-cell tumours of the ovary and testis (see p.670, and p.673), as well as for some other malignancies including those of the head and neck, (p.666), and Kaposi's sarcoma (p.675).

Pneumothorax. In a patient with AIDS and pneumocystis pneumonia who developed pneumothorax, instillation of bleomycin into each pleural cavity was successful in resolving the pneumothorax after tetracycline sclerotherapy failed to do so.[1]

1. Hnatiuk OW, *et al.* Bleomycin sclerotherapy for bilateral pneumothoraces in a patient with AIDS. *Ann Intern Med* 1990; **113:** 988–90.

Warts. A number of studies have examined the local use of bleomycin sulfate to treat severe or resistant warts (p.1584) of the common, plane, plantar, eponychial, and mosaic types, usually by intralesional injection.[1-3] At the doses used, adverse effects, other than pain at the injection site,[1-3] do not seem to be common; however, nail dystrophy and Raynaud's phenomenon have been reported (see under Effects on the Nails and Effects on the Vascular System, under Adverse Effects, above). Bleomycin has also been applied as a pressure-sensitive adhesive tape,[4] and various techniques for better intralesional use have been investigated.[5-7]

1. Shumack PH, Haddock MJ. Bleomycin: an effective treatment for warts. *Australas J Dermatol* 1979; **20:** 41–2.
2. Bunney MH, *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **111:** 197–207.
3. Munkvad M, *et al.* Locally injected bleomycin in the treatment of warts. *Dermatologica* 1983; **167:** 86–9.
4. Takigawa M, *et al.* Treatment of viral warts with pressure-sensitive adhesive tape containing bleomycin sulfate. *Arch Dermatol* 1985; **121:** 1108.
5. Munn SE, *et al.* A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135:** 969–71.
6. van der Velden EM, *et al.* Dermatography with bleomycin as a new treatment for verrucae vulgaris. *Int J Dermatol* 1997; **36:** 145–50.
7. Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol [sic] hand warts. *Lasers Surg Med* 2002; **30:** 135–40.

Preparations

BP 2008: Bleomycin Injection;
USP 31: Bleomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Bileco; Bleocris; Blocamicina; Cytorich; ***Austral.:*** Blenamax; Blenoxane; ***Belg.:*** Bleomin; ***Braz.:*** Blenoxane; Bonar; Tecnomicina; ***Canad.:*** Blenoxane; ***Chile:*** Blexit; Nikableomicina; Oncobleocin; ***Cz.:*** Bleocin; ***Ger.:*** Bleo-cell; Bleomedac; ***Gr.:*** Bleocin; ***Hong Kong:*** Bleocin; ***Hung.:*** Bleocin; ***India:*** Bleochem; Bleocin; Bleocip; ***Indon.:*** Blenamax; Bleocin; ***Jpn:*** Bleo-S; Bleocin; ***Malaysia:*** Blenamax; Bleocin; ***Mex.:*** Blanoxan; Bleolem; ***NZ:*** Blenoxane; ***Philipp.:*** Blenoxane; Bloicin-S; ***Pol.:*** Bleocin; ***Port.:*** Blio†; ***Rus.:*** Blenamax (Бленамакс); ***S.Afr.:*** Blenoxane; Bleolem; ***Singapore:*** Bleocin; ***Thai.:*** Bleo-S; Bleocin; Bleolem; ***Turk.:*** Bleocin; Bleolem; ***UK:*** Bleo; ***USA:*** Blenoxane.

Bortezomib *(BAN, USAN, rINN)*

Bortézomib; Bortezomibum; LDP-341; MG-341; MLN-341; PS-341. *N*-((1*S*)-1-Benzyl-2-{[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino}-2-oxoethyl)pyrazinecarboxamide; {(1*R*)-3-Methyl-1-[(2*S*)-3-phenyl-2-(pyrazin-2-carboxamido)propanamido]butyl}boronic acid; .

Бортезомиб

$C_{19}H_{25}BN_4O_4$ = 384.2.

CAS — 179324-69-7.

ATC — L01XX32.

ATC Vet — QL01XX32.

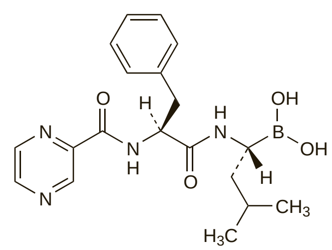

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects of bortezomib include haematological toxicities (especially transient thrombocytopenia), decreased appetite, gastrointestinal disturbances, peripheral neuropathy, fatigue, fever, dyspnoea, rash, and myalgia. Complete blood counts including platelet counts should be monitored and therapy withheld or given at reduced doses if necessary. Peripheral neuropathy may also be dose-limiting.

Other common adverse effects include hyperglycaemia, hypokalaemia, insomnia, anxiety, confusion, depression, blurred vision, eye pain, dizziness, dysgeusia, tremor, epistaxis, cough, rhinorrhoea, pruritus, arthralgia, oedema, and orthostatic hypotension. Tumour lysis syndrome, hypersensitivity, and seizures have been reported. Tachycardia, arrhythmias, palpitations, angina pectoris, and myocardial infarction have occurred. Congestive heart failure may be exacerbated and pulmonary oedema has been reported. There have been rare reports of acute respiratory distress syndrome, some of them fatal.

Renal impairment is common in patients with multiple myeloma and acute renal failure has developed in patients on bortezomib. Licensed product information in the UK considers that patients with compromised renal function should be monitored, and dose reductions considered if needed although in the USA this is considered unnecessary. Hepatotoxicity, which may be reversible, has included increases in liver enzyme values, hyperbilirubinaemia, and acute liver failure; bortezomib should be used with caution in hepatic impairment.

The impact of proteasome inhibition by bortezomib on disorders associated with protein accumulation such as amyloidosis is unknown and caution is advised in these patients.

Effects on the nervous system. Treatment with bortezomib is often associated with peripheral neuropathy, mainly sensory, although cases of motor neuropathy have been reported. Results from an analysis[1] found that the peripheral neuropathy associated with bortezomib seemed to be cumulative and dose-related, and increased in prevalence through the first 5 treatment cycles. Prolonged bortezomib exposure beyond this time did not seem to increase the incidence or severity of neuropathy. Development of neuropathy appeared to be independent of the previous neurotoxic therapy. In most patients, neuropathic pain resolved or improved after dose modification or upon completion of therapy.

1. Richardson PG, *et al.* Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol* 2006; **24:** 3113–20.

Effects on the skin. In 3 studies of bortezomib in patients with non-Hodgkin's lymphoma, 26 of 140 patients developed an erythematous maculopapular rash. Six patients underwent biopsy; all cases revealed a small vessel necrotising vasculitis. Although some patients had dosage reductions implemented or therapy interrupted upon development of the rash, others were treated continuously without dose reduction, with no apparent adverse clinical consequences. In fact, analysis of the data supported a strong relationship between bortezomib-associated cutaneous vasculitis and a positive clinical response in patient with non-Hodgkin's lymphoma.[1] A macular brown-red eruption developed in a patient at the site of bortezomib infusions; abundant venous flushing was given from the fourth infusion, and the eruption did not recur, although hyperpigmentation persisted for several months.[2]

1. Gerecitano J, *et al.* Drug-induced cutaneous vasculitis in patients with non-Hodgkin lymphoma treated with the novel proteasome inhibitor bortezomib: a possible surrogate marker of response? *Br J Haematol* 2006; **134:** 391–8.
2. Mataix J, *et al.* Persistent supravenous eruption induced by intravenous bortezomib therapy. *Br J Dermatol* 2008; **158:** 863–4.

Interactions

Bortezomib is metabolised in the liver via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; CYP2D6 and CYP2C9 are also thought to play minor roles. Consequently, patients should be monitored closely when bortezomib is used with other drugs that induce or inhibit these isoenzymes. Hypoglycaemia and hyperglycaemia have occurred in diabetic patients receiving oral antidiabetics who were given bortezomib. Caution may be required if bortezomib is used with drugs that are associated with peripheral neuropathy or hypotension.

Pharmacokinetics

After a single intravenous dose of bortezomib, plasma concentrations decline in a biphasic manner; a distribution phase with a half-life of less than 10 minutes is followed by a terminal elimination phase of about 5 to 15 hours. After multiple doses, clearance decreases and there is an increase in the terminal elimination phase. Protein binding has been reported to be over 80%. *In-vitro* studies indicate that bortezomib is primarily oxidatively metabolised via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; minor metabolism via CYP2D6 and CYP2C9 also occurs. The major metabolic pathway is deboronation to inactive metabolites.

◊ References.

1. Pekol T, *et al.* Human metabolism of the proteasome inhibitor bortezomib: identification of circulating metabolites. *Drug Metab Dispos* 2005; **33:** 771–7.

Uses and Administration

Bortezomib is an inhibitor of the 26S proteasome, a large protein complex in cells that is responsible for breaking down regulatory proteins of the cell cycle. Such inhibition disrupts tumour cell turnover and induces apoptosis. Bortezomib is used for the treatment of multiple myeloma (p.658) in patients who have failed at least one previous therapy. In the USA, it is also used similarly for mantle cell lymphoma in patients given at least one previous therapy. Bortezomib is given in initial doses of 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of a 21-day cycle. At least 72 hours should elapse between consecutive doses of bortezomib. In the UK, licensed product information recommends that patients with a confirmed complete response should receive 2 additional cycles of bortezomib, and that those who respond but do not achieve complete remission receive a total of 8 cycles. In the USA, extended therapy of more than 8 cycles may be given, either on the standard schedule recommended above, or on a maintenance schedule of one dose weekly for 4 weeks (days 1, 8, 15, and 22 of a 35-day cycle).

The dose should be reduced, or treatment withdrawn, according to toxicity, particularly when peripheral neuropathy, neuropathic pain, and haematological toxicity occur.

◊ References.

1. Goy A, Gilles F. Update on the proteasome inhibitor bortezomib in hematologic malignancies. *Clin Lymphoma* 2004; **4:** 230–7.
2. Orlowski RZ. Bortezomib and its role in the management of patients with multiple myeloma. *Expert Rev Anticancer Ther* 2004; **4:** 171–9.
3. Jagannath S, *et al.* Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005; **103:** 1195–1200.

4. Richardson PG, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352:** 2487–98.
5. O'Connor OA. Marked clinical activity of the proteasome inhibitor bortezomib in patients with follicular and mantle-cell lymphoma. *Clin Lymphoma Myeloma* 2005; **6:** 191–9.
6. Popat R, *et al.* Bortezomib for multiple myeloma. *Expert Opin Pharmacother* 2006; **7:** 1337–46.
7. Wang M, *et al.* Use of bortezomib in B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2006; **6:** 983–91.
8. NICE. Bortezomib monotherapy for relapsed multiple myeloma (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf (accessed 23/05/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Velcade; ***Austral.:*** Velcade; ***Belg.:*** Velcade; ***Canad.:*** Velcade; ***Chile:*** Velcade; ***Cz.:*** Velcade; ***Denm.:*** Velcade; ***Fin.:*** Velcade; ***Fr.:*** Velcade; ***Ger.:*** Velcade; ***Gr.:*** Velcade; ***Hong Kong:*** Velcade; ***Hung.:*** Velcade; ***Indon.:*** Velcade; ***Israel:*** Velcade; ***Ital.:*** Velcade; ***Malaysia:*** Velcade; ***Mex.:*** Velcade; ***Neth.:*** Velcade; ***Norw.:*** Velcade; ***NZ:*** Velcade; ***Philipp.:*** Velcade; ***Pol.:*** Velcade; ***Port.:*** Velcade; ***Rus.:*** Velcade (Велкейд); ***Singapore:*** Velcade; ***Spain:*** Velcade; ***Swed.:*** Velcade; ***Switz.:*** Velcade; ***Thai.:*** Velcade; ***UK:*** Velcade; ***USA:*** Velcade; ***Venez.:*** Velcade.

Bropirimine *(BAN, USAN, rINN)*

ABPP; Bropirimina; Bropiriminum; U-54461; U-54461S. 2-Amino-5-bromo-6-phenyl-4(3*H*)-pyrimidinone.

Бропиримин

$C_{10}H_8BrN_3O$ = 266.1.
CAS — 56741-95-8.

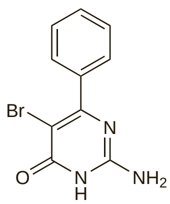

Profile

Bropirimine is reported to have immunomodulatory actions, possibly due to the induction of interferons. It has been investigated in the management of carcinoma in situ of the bladder (p.659).

Brostallicin *(rINN)*

Brostalicina; Brostallicine; Brostallicinum; PNU-166196 (hydrochloride). 4-(2-Bromoacrylamido)-*N*‴-(2-guanidinoethyl)-1,1′,1″,1‴-tetramethyl-*N*,4′:*N*′,4″:*N*″,4‴-quater[pyrrole-2-carboxamide].

Бростальлицин

$C_{30}H_{35}BrN_{12}O_5$ = 723.6.
CAS — 203258-60-0.

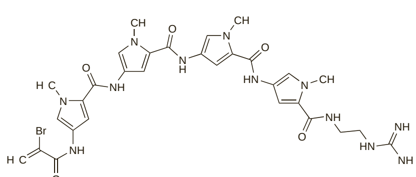

Profile

Brostallicin is an antineoplastic that binds to DNA. It is under investigation for the treatment of soft-tissue sarcomas.

◊ References.

1. ten Tije AJ, *et al.* Phase I and pharmacokinetic study of brostallicin (PNU-166196), a new DNA minor-groove binder, administered intravenously every 3 weeks to adult patients with metastatic cancer. *Clin Cancer Res* 2003; **9:** 2957–64.
2. Broggini M, *et al.* Brostallicin: a new concept in minor groove DNA binder development. *Anticancer Drugs* 2004; **15:** 1–6.
3. Leahy M, *et al.* Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2007; **43:** 308–15.

Broxuridine *(rINN)*

Bromodeoxyuridine; Broxuridina; Broxuridinum; BUDR; NSC-38297. 5-Bromo-2′-deoxyuridine; 5-Bromo-1-(2-deoxy-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Броксуридин

$C_9H_{11}BrN_2O_5$ = 307.1.
CAS — 59-14-3.

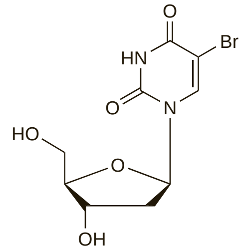

Profile

Broxuridine is a thymidine analogue which acts as a radiosensitiser to enhance the effects of radiotherapy. It is also reported to possess antiviral activity. A related compound brivudine (p.867) is used as an antiviral.

Broxuridine has been given by intra-arterial infusion, with radiotherapy and other antineoplastic agents, in the treatment of tumours of the brain, head, and neck. It has also been used diagnostically.

◊ References.

1. Freese A, *et al.* The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neurooncol* 1994; **20:** 81–95.
2. Phillips TL, *et al.* Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995; **33:** 339–48.
3. Prados MD, *et al.* Influence of bromodeoxyuridine radiosensitization on malignant glioma patient survival: a retrospective comparison of survival data from the Northern California Oncology Group (NCOG) and Radiation Therapy Oncology Group trials (RTOG) for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1998; **40:** 653–9.
4. Prados MD, *et al.* Phase III randomized study of radiotherapy plus procarbazine, lomustine, and vincristine with or without BUdR for treatment of anaplastic astrocytoma: final report of RTOG 9404. *Int J Radiat Oncol Biol Phys* 2004; **58:** 1147–52.

Busulfan *(BAN, rINN)*

Bussulfam; Busulfaani; Busulfanas; Busulfano; Busulfanum; Busulphan; Buszulfán; CB-2041; GT-41; Myelosan; NSC-750; WR-19508. Tetramethylene di(methanesulphonate); Butane-1,4-diol di(methanesulphonate).

Бусульфан

$C_6H_{14}O_6S_2$ = 246.3.
CAS — 55-98-1.
ATC — L01AB01.
ATC Vet — QL01AB01.

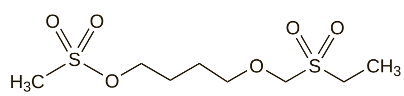

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Busulfan). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; freely soluble in acetone and in acetonitrile. Store in airtight containers. Protect from light.

USP 31 (Busulfan). A white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble 1 in 45 of acetone. Store in airtight containers.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

The major adverse effect of busulfan with standard doses is bone-marrow depression, manifest as leucopenia, thrombocytopenia, and sometimes, anaemia. The nadir of the granulocyte count usually occurs after about 10 to 30 days with recovery occurring over up to 5 months, but busulfan has sometimes caused irreversible or extremely-prolonged bone-marrow depression.

Hyperpigmentation is common, and in a few cases after long-term therapy may be part of a syndrome simulating Addison's disease.

Rarely, progressive interstitial pulmonary fibrosis, known as 'busulfan lung', can occur on prolonged treatment. Gastrointestinal disturbances are rare at usual therapeutic doses but may be dose-limiting where high doses are given before bone marrow transplantation. Other rare adverse effects include dry skin and other skin reactions, liver damage, gynaecomastia, cataract formation, and, at high doses, CNS effects including convulsions.

Busulfan may result in impaired fertility and gonadal function. As with other alkylating agents, it is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. Haemorrhagic cystitis occurred in a patient who had received prolonged therapy with busulfan.[1] High-dose busulfan used in conditioning regimens for haematopoietic stem cell transplantation may increase the risk of late-onset haemorrhagic cystitis.[2,3]

1. Pode D, *et al.* Busulfan-induced hemorrhagic cystitis. *J Urol (Baltimore)* 1983; **130:** 347–8.
2. Kondo M, *et al.* Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; **22:** 995–8.
3. Leung AYH, *et al.* Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 509–13.

Effects on the liver. Jaundice in the terminal phase of chronic myeloid leukaemia in a 31-year-old man was attributed to busulfan which had been taken for 6 years.[1] Busulfan toxicity involving the liver was also reported in a patient who had taken busulfan for 54 months,[2] while hepatitis possibly associated with busulfan therapy has also been described.[3] Dose-dependent veno-occlusive disease (VOD) has been reported in 20 to 40% of patients receiving high-dose busulfan before bone marrow transplantation.[4] Licensed product information from 1 manufacturer (*Pierre Fabre, UK*) states that previous radiotherapy, progenitor cell transplantation, or three cycles of chemotherapy or more, can increase the risk of hepatic VOD; another (*GSK*) lists concurrent use of multiple alkylating agents, or total doses of busulfan in excess of 16 mg/kg, as possible risk factors. A reduced incidence of hepatic VOD has been seen in those patients given high-dose busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for more than 24 hours after the last dose of busulfan.

1. Underwood JCE, *et al.* Jaundice after treatment of leukaemia with busulphan. *BMJ* 1971; **1:** 556–7.
2. Foadi MD, *et al.* Portal hypertension in a patient with chronic myeloid leukaemia. *Postgrad Med J* 1977; **53:** 267–9.
3. Morris L, Guthrie T. Busulfan-induced hepatitis. *Am J Gastroenterol* 1988; **83:** 682–3.
4. Hassan M. The role of busulfan in bone marrow transplantation. *Med Oncol* 1999; **16:** 166–76.

Effects on the nervous system. High-dose busulfan, used in conditioning regimens for bone marrow transplantation, has been associated with the development of convulsions,[1-4] both generalised[1,3,4] and myoclonic.[2,4] As a result, the use of prophylactic antiepileptic therapy has been suggested as a component of such regimens.[1,3,4] However, some do not consider the routine use of prophylactic antiepileptics justified,[5] and the potential for phenytoin to increase the metabolism of busulfan, thereby possibly decreasing its myeloablative efficacy, has been pointed out.[6] In addition, phenytoin plasma concentrations have been found to be subtherapeutic in patients who developed convulsions despite a standard prophylactic dose,[4] and the regimen was subsequently adjusted to take account of plasma concentrations. Clobazam has been suggested as an alternative to phenytoin for prophylaxis of busulfan-induced seizures.[7] Licensed product information from one manufacturer (*GSK, UK*) recommends the use of prophylactic anticonvulsants, and prefers a benzodiazepine to phenytoin. However, other manufacturers suggest use with phenytoin; *Otsuka* in the USA state that the recommended dose of their parenteral product is based on studies in which phenytoin was given, and that if other anticonvulsants are used exposure should be monitored, as a 15% increase in plasma-busulfan may be expected, with increased risk of toxicity.

1. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. *Lancet* 1984; **ii:** 1463.
2. Martell RW, *et al.* High-dose busulfan and myoclonic epilepsy. *Ann Intern Med* 1987; **106:** 173.
3. Sureda A, *et al.* High-dose busulfan and seizures. *Ann Intern Med* 1989; **111:** 543–4.
4. Grigg AP, *et al.* Busulphan and phenytoin. *Ann Intern Med* 1989; **111:** 1049–50. Correction. *ibid.*; **112:** 313.
5. Hugh-Jones K, Shaw PJ. No convulsions in children on high-dose busulphan. *Lancet* 1985; **i:** 220.
6. Fitzsimmons WE, *et al.* Anticonvulsants and busulfan. *Ann Intern Med* 1990; **112:** 552–3.
7. Schwarer AP, *et al.* Clobazam for seizure prophylaxis during busulfan chemotherapy. *Lancet* 1995; **346:** 1238.

Effects on the skin and hair. For the effect of radiotherapy in activating skin lesions in busulfan-treated patients, see under Precautions, below.

Permanent alopecia has been reported after use of busulfan.[1]

1. Tosti A, *et al.* Permanent alopecia after busulfan chemotherapy. *Br J Dermatol* 2005; **152:** 1056–8.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Careful attention should be given to monitoring blood counts during therapy. This should be done at least weekly at the start of standard dose therapy. With high dose therapy blood counts should be monitored daily, as should liver function. Prophylactic anticonvulsants should be used during high dose therapy (see Effects on the Nervous System, above).

Busulfan should be stopped if lung toxicity develops. The use of oxygen may exacerbate possible lung toxicity; if anaesthesia is required the concentration of oxygen should be minimised.

Handling. Busulfan is irritant; avoid contact with skin and mucous membranes.

Porphyria. Busulfan is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Radiotherapy. Severe cutaneous reactions occurred in patients given radiotherapy at least 30 days after combined chemotherapy with high-dose busulfan.[1]

It is possible that radiotherapy could worsen subclinical lung injury caused by busulfan.

1. Vassal G, *et al*. Radiosensitisation after busulphan. *Lancet* 1987; **i:** 571.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Phenytoin increases the clearance of busulfan (see Effects on the Nervous System, above).

Antifungals. Giving *itraconazole* with busulfan resulted in a decrease in the clearance of busulfan; *fluconazole* had no such effect.[1] Busulfan doses may need to be decreased if itraconazole is also given.

1. Buggia I, *et al*. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. *Anticancer Res* 1996; **16:** 2083–8.

Antineoplastics. When *tioguanine* was given with busulfan for chronic myeloid leukaemia, a number of cases of hepatic nodular regenerative hyperplasia, with abnormal liver function tests, portal hypertension, and oesophageal varices were noted. There were no cases in patients treated with busulfan alone, and the mechanism of this possible interaction is unclear.[1,2]

1. Key NS, *et al*. Oesophageal varices associated with busulfan-thioguanine combination therapy for chronic myeloid leukaemia. *Lancet* 1987; **ii:** 1050–2.
2. Shepherd PCA, *et al*. Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. *Br J Haematol* 1991; **79:** 185–92.

Antiprotozoals. In a study[1] of patients who received high-dose busulfan as part of a myeloablative regimen before stem cell transplantation, the use of *metronidazole* significantly increased plasma concentrations of busulfan and the degree of associated toxicity, including elevation of liver function tests, veno-occlusive disease, and mucositis.

1. Nilsson C, *et al*. The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **31:** 429–35.

Pharmacokinetics

Busulfan is readily absorbed from the gastrointestinal tract and rapidly disappears from the blood with a half-life of 2 to 3 hours. It is extensively metabolised, and excreted in the urine almost entirely as sulfur-containing metabolites. It crosses the blood-brain barrier.

Metabolism. In a study of the pharmacokinetics of high-dose busulfan in 5 patients receiving 1 mg/kg orally every six hours for 4 days, the mean elimination half-life decreased from about 3.4 hours after the first dose to about 2.3 hours after the final dose, suggesting that busulfan may induce its own metabolism.[1]

1. Hassan M, *et al*. Pharmacokinetic and metabolic studies of high-dose busulphan in adults. *Eur J Clin Pharmacol* 1989; **36:** 525–30.

Therapeutic drug monitoring. A review concluded that therapeutic drug monitoring of busulfan would maximise engraftment and minimise toxicity and relapse in haematopoietic stem cell transplantation. In regimens using busulfan with cyclophosphamide, steady-state plasma concentrations of busulfan above 600 micrograms/litre appeared to favour engraftment.[1] A pharmacokinetic analysis found that in patients with graft rejections, busulfan trough concentrations were below 150 nanograms/mL; steady state concentrations also tended to be lower in this group but not significantly so.[2]

The bioavailability of oral busulfan is variable, particularly in children; intravenous conditioning regimens, adjusted on the basis of first-dose pharmacokinetics and therapeutic drug monitoring, have been used to overcome this problem.[3,4] A study found a significant correlation between busulfan concentration in plasma and saliva after oral dosing in children; busulfan saliva analysis may therefore be a useful, non-invasive alternative to plasma analysis.[5]

1. McCune JS, *et al*. Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin Pharmacokinet* 2000; **39:** 155–65.
2. Chandy M, *et al*. Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia—the role of busulfan pharmacokinetics in determining outcome. *Bone Marrow Transplant* 2005; **36:** 839–45.
3. Tran H, *et al*. Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2004; **10:** 805–12.
4. Kletzel M, *et al*. Pharmacokinetics of a test dose of intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006; **12:** 472–9.
5. Rauh M, *et al*. Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children : validation of liquid chromatography tandem mass spectrometry method. *Clin Pharmacokinet* 2006; **45:** 305–16.

Uses and Administration

Busulfan is an antineoplastic with a cell-cycle non-specific alkylating action unlike that of the nitrogen mustards, and having a selective depressant action on bone marrow. In small doses, it depresses granulocytopoiesis and to a lesser extent thrombocytopoiesis but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues.

Because of its selective action, busulfan has been used in the palliative treatment of chronic myeloid leukaemia (p.653). It provides symptomatic relief with a reduction in spleen size and a general feeling of well-being. The fall in leucocyte count is usually accompanied by a rise in the haemoglobin concentration. Permanent remission is not induced and resistance to its beneficial effects gradually develops.

Busulfan may be used in patients with polycythaemia vera (p.654) and in some patients with myelofibrosis and primary thrombocythaemia (p.654). It is also used at high doses as part of a conditioning regimen to prepare patients for bone marrow transplantation, a procedure discussed on p.1811 under Haematopoietic Stem Cell Transplantation.

The licensed initial oral dosage of busulfan in **chronic myeloid leukaemia** is 60 micrograms/kg daily, with a usual maximum single daily dose of 4 mg. This is continued until the white cell count has fallen to between 15 000 and 25 000 cells/mm^3 (typically 12 to 20 weeks). It should be stopped earlier if the platelet count falls below 100 000 cells/mm^3. Higher doses may be given if the response after 3 weeks is inadequate but this increases the risk of irreversible damage to the bone marrow and calls for special vigilance. Complete blood counts should be made at least every week and the trends followed closely; if haemorrhagic tendencies occur or there is a steep fall in the white cell count indicating severe bone-marrow depression, busulfan should be withdrawn until marrow function has returned.

Once an initial remission has been attained treatment is stopped and not resumed until the white cell count returns to 50 000 cells/mm^3. If this occurs within 3 months continuous maintenance treatment with a usual dose of 0.5 to 2 mg daily may be given.

In patients with **polycythaemia vera** the usual oral dose is 4 to 6 mg daily, continued for 4 to 6 weeks with careful monitoring of blood counts. Further courses are given when relapse occurs; alternatively, maintenance therapy may be given at half the dose required for induction. Doses of 2 to 4 mg daily have been given for **essential thrombocythaemia** or myelofibrosis.

In conditioning regimens for **bone marrow transplantation** busulfan has been given in usual doses of 3.5 to 4 mg/kg daily in divided doses for 4 days orally (total dose 14 to 16 mg/kg), with cyclophosphamide, for ablation of the recipient's bone marrow. When given by intravenous infusion in a regimen with phenytoin (see Effects on the Nervous System, above), a recommended dose is 3.2 mg/kg ideal body-weight daily for 4 days (total dose 12.8 mg/kg); actual body-weight is used for the calculation if it is less than the ideal weight. The daily dose is given as 4 infusions of 800 micrograms/kg at intervals of 6 hours; each dose should be diluted in sodium chloride 0.9% or glucose 5% to a final concentration of about 500 micrograms/mL, and given over 2 hours through a central venous catheter using an infusion pump. UK licensed product information states that cyclophosphamide dosing should not be started for at least 24 hours after the last dose of busulfan; US information permits use no sooner than 6 hours after the last busulfan dose.

In the UK, busulfan is licensed for use with cyclophosphamide or melphalan as a conditioning regimen prior to haematopoietic stem cell transplantation in children. The recommended dose for children up to 17 years of age is weight-based as follows:

- less than 9 kg: busulfan 1 mg/kg
- 9 to 16 kg: busulfan 1.2 mg/kg
- 16 to 23 kg: busulfan 1.1 mg/kg
- 23 to 34 kg: busulfan 950 micrograms/kg
- greater than 34 kg: busulfan 800 micrograms/kg

This dose is given every 6 hours over 4 days to a total of 16 doses, diluted and infused as for adults. Cyclophosphamide or melphalan should not be started for at least 24 hours after the last dose of busulfan.

◊ References.

1. Buggia I, *et al*. Busulfan. *Ann Pharmacother* 1994; **28:** 1055–62.
2. Socié G, *et al*. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood* 2001; **98:** 3569–74.
3. Ferry C, Socié G. Busulfan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol* 2003; **31:** 1182–6.

Preparations

BP 2008: Busulfan Tablets;
USP 31: Busulfan Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Myleran; ***Austral.:*** Myleran; ***Austria:*** Myleran; ***Belg.:*** Myleran; ***Braz.:*** Myleran; ***Canad.:*** Busulfex; Myleran; ***Chile:*** Myleran; ***Cz.:*** Busilvex; Myleran; ***Denm.:*** Busilvex; ***Fr.:*** Busilvex; Myleran; ***Ger.:*** Busilvex; Myleran; ***Gr.:*** Busilvex; Myleran; ***Hong Kong:*** Busulfex; Myleran; ***India:*** Myleran; ***Irl.:*** Myleran; ***Israel:*** Busulfex; Myleran; ***Ital.:*** Busilvex; Myleran; ***Malaysia:*** Myleran; ***Mex.:*** Myleran; ***Neth.:*** Busilvex; Myleran; ***Norw.:*** Busilvex; ***NZ:*** Myleran; ***Pol.:*** Busilvex; Myleran; ***Port.:*** Busilvex; Myleran; ***Rus.:*** Myleran (Милеран); ***S.Afr.:*** Myleran; ***Singapore:*** Myleran; ***Spain:*** Busilvex; ***Swed.:*** Busilvex; Myleran; ***Switz.:*** Busilvex; Myleran†; ***Thai.:*** Myleran; ***Turk.:*** Busulfex; Myleran; ***UK:*** Busilvex; Myleran; ***USA:*** Busulfex; Myleran.

Capecitabine *(BAN, USAN, rINN)*

Capecitabina; Capécitabine; Capecitabinum; Kapecitabin; Kapesitabiini; Kapesitabin; Ro-09-1978/000. Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate.

Капецитабин

$C_{15}H_{22}FN_3O_6$ = 359.4.

CAS — 154361-50-9; 158798-73-3.

ATC — L01BC06.

ATC Vet — QL01BC06.

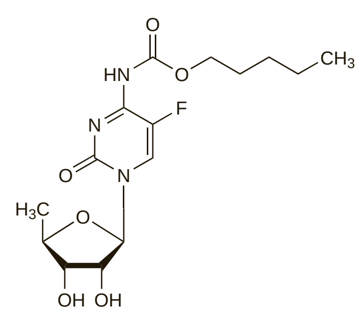

Pharmacopoeias. In *US*.

USP 31 (Capecitabine). A white to off-white crystalline powder. Sparingly soluble in water; soluble in alcohol and in acetonitrile; freely soluble in methyl alcohol. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for Fluorouracil, p.722. Diarrhoea (which may be severe), nausea and vomiting, abdominal pain, stomatitis, and palmar-plantar erythrodysesthesia syndrome (erythema and desquamation of hands and feet) occur commonly with capecitabine, and may be dose-limiting. Other common adverse effects include fatigue, asthenia, and anorexia. Rashes, alopecia, erythema, dryness of the skin, pruritus, skin pigmentation disorders, and nail disorders can occur. Other adverse effects are fever, pain, arthralgia, constipation, dyspepsia, paraesthesia, headache, dizziness, insomnia, hypo- or hypercalcaemia, and dehydration. Dermatitis, cardiotoxicity, and bone-marrow depression have all been reported. Hyperbilirubinaemia has occurred. Doses should be reduced in patients with moderate renal impairment and the drug is contra-indicated in those with severe renal or hepatic impairment.

Effects on blood lipids. Severe hypertriglyceridaemia has been reported with oral capecitabine;[1] patients had high baseline triglyceride concentrations at the start of capecitabine. Despite the introduction of lipid-lowering therapy, triglyceride concentrations remained above baseline, and only decreased several weeks after stopping capecitabine.

1. Kurt M, *et al.* Capecitabine-induced severe hypertriglyceridemia: report of two cases. *Ann Pharmacother* 2006; **40:** 328–31.

Effects on the eyes. A report of severe ocular irritation with corneal deposits and impaired visual acuity in 2 patients given capecitabine.[1] Symptoms resolved within several weeks of stopping the drug.

1. Walkhom B, *et al.* Severe ocular irritation and corneal deposits associated with capecitabine use. *N Engl J Med* 2000; **343:** 740–1.

Effects on the heart. Acute ischaemic chest pain has been reported, usually within a few days of starting capecitabine.[1-3] Symptoms from case reports[1] and incidence in Phase III studies[4] were similar to those in patients given fluorouracil. While symptoms have generally been reported to be reversible, fatal myocardial infarction has occurred.[2] One patient had also had cardiotoxicity with fluorouracil treatment,[1] but others had no apparent risk factors.[2]

1. Frickhofen N, *et al.* Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002; **13:** 797–801.
2. Kuppens IELM, *et al.* Capecitabine induces severe angina-like chest pain. *Ann Intern Med* 2004; **140:** 494–5.
3. Bertolini A, *et al.* Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori* 2001; **87:** 200–6.
4. van Cutsem E, *et al.* Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol* 2002; **13:** 484–5.

Effects on the nervous system. Peripheral neuropathy[1] and encephalopathy[2,3] have been reported in association with capecitabine use.

1. Saif MW, *et al.* Peripheral neuropathy associated with capecitabine. *Anticancer Drugs* 2004; **15:** 767–71.
2. Niemann B, *et al.* Toxic encephalopathy induced by capecitabine. *Oncology* 2004; **66:** 331–5.
3. Videnovic A, *et al.* Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. *Neurology* 2005; **65:** 1792–4.

Effects on the skin and nails. While hand-foot syndrome appears to be common in patients treated with capecitabine (see Palmar-plantar Erythrodysesthesia Syndrome, below), other skin eruptions have been rarely reported.[1] Onychomadesis (total separation of the nail-bed) and onycholysis have occurred.[2,3] Pyogenic granuloma has been seen with the use of capecitabine,[1] as has re-pigmentation of chemotherapy-induced vitiligo.[4]

1. Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; **147:** 1270–2.
2. Chen G-Y, *et al.* Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol* 2001; **145:** 521–2.
3. Chen G-Y, *et al.* Exudative hyponychial dermatitis associated with capecitabine and docetaxel combination chemotherapy for metastatic breast carcinoma: report of three cases. *Br J Dermatol* 2003; **148:** 1071–3.
4. Schmid-Wendtner M-H, *et al.* Leopard-like vitiligo with capecitabine. *Lancet* 2001; **358:** 1575.

Hypersensitivity. A patient was successfully given fluorouracil by continuous infusion despite previous hypersensitivity to capecitabine. The authors supposed that the hypersensitivity was likely to have been caused by capecitabine or intermediate metabolites, and suggested a lack of cross-sensitivity between capecitabine and fluorouracil.[1]

1. Liu CY. Fluorouracil for allergic reactions to capecitabine. *Ann Pharmacother* 2002; **36:** 1897–9.

Palmar-plantar erythrodysesthesia syndrome. Hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome, p.639) has been reported to be common with use of capecitabine given either as monotherapy[1] or as part of combination chemotherapy regimens.[2,3] The syndrome developed within the first 2 cycles of monotherapy,[1] but within the first 3 cycles in combination therapy,[3] which was attributed to dose modifications of capecitabine in the latter case. Use with docetaxel, and previous chemotherapy-induced stomatitis were found to be significant risk factors for its occurrence.[3] The only effective management is treatment interruption and dose modification.[4] Supportive measures to reduce pain and discomfort and prevent secondary infection are important.[5] General recommended strategies include submersion of hands and feet in cold water, wound care, and avoidance of extreme temperature changes, tight-fitting clothing, or skin friction. Emollient creams may be of benefit for both prophylaxis and treatment. Other strategies that have been proposed include the use of amifostine, topical or systemic corticosteroids, and nicotine patches; however, use of these drugs for capecitabine-induced hand-foot syndrome remains unproven. While pyridoxine cannot be recommended for prophylaxis, some consider it a reasonable choice for treatment, since benefit has been reported with its use with topical emollients.[4] Concurrent treatment with celecoxib has been reported to reduce the incidence of hand-foot syndrome induced by capecitabine.[6,7] For reference to the use of vitamin E to alleviate hand-foot syndrome caused by capecitabine and docetaxel, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p.1994.

As a result of capecitabine-induced hand-foot syndrome, fingerprint misidentification has been reported.[8]

1. Abushullaih S, *et al.* Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest* 2002; **20:** 3–10.
2. Park YH, *et al.* High incidence of severe hand-foot syndrome during capecitabine-docetaxel combination chemotherapy. *Ann Oncol* 2003; **14:** 1691–2.
3. Heo YS, *et al.* Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol* 2004; **44:** 1166–72.
4. Gressett SM, *et al.* Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract* 2006; **12:** 131–41.
5. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome: insights from clinical trials evaluating capecitabine. *Oncology (Huntingt)* 2004; **18:** 1161–8, 1173.
6. Lin E, *et al.* Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Huntingt)* 2002; **16** (12 suppl 14): 31–7.
7. Lin EH, *et al.* Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? *Am J Clin Oncol* 2006; **29:** 232–9.
8. García-Saénz JA, *et al.* Elementary, my dear Watson. *J Clin Oncol* 2007; **25:** 1815–6.

Tumour lysis syndrome. A fatal case of tumour lysis syndrome (p.639) has been reported after the use of capecitabine.[1]

1. Kurt M, *et al.* Tumor lysis syndrome following a single dose of capecitabine. *Ann Pharmacother* 2004; **38:** 902.

Interactions

As for Fluorouracil, p.723. Altered coagulation parameters and bleeding have occurred in patients on warfarin or phenprocoumon given capecitabine. Increased phenytoin plasma concentrations and symptoms of toxicity during use with capecitabine have been reported. Capecitabine must not be given with sorivudine or its analogues as fatal fluoropyrimidine toxicity may occur (see also Antivirals, under Interactions of Fluorouracil, p.723). Antacids containing aluminium or magnesium hydroxides cause a small increase in capecitabine plasma concentration. The maximum tolerated dose of capecitabine is reduced when it is given with either folinic acid or interferon alfa.

Pharmacokinetics

Capecitabine is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring at about 1.5 hours. Food reduces the rate and extent of absorption. Plasma protein binding of capecitabine is less than 60%. Capecitabine is hydrolysed in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR; doxifluridine—p.712) and subsequently to 5-fluorouracil in body tissues. 5-Fluorouracil is further metabolised, as discussed on p.723. About 3% of a dose of capecitabine is excreted in the urine unchanged.

◊ References.

1. Reigner B, *et al.* Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998; **4:** 941–8.
2. Reigner B, *et al.* Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet* 2001; **40:** 85–104.

Uses and Administration

Capecitabine is a prodrug that is converted to fluorouracil (p.723) in body tissues. It is given orally for the treatment of metastatic colorectal cancer (p.665) and is also used for the adjuvant treatment of patients after surgery for Dukes C colon cancer. Capecitabine is given with docetaxel for the treatment of locally advanced or metastatic breast cancer (p.661) after failure of anthracycline-containing chemotherapy. It may be given as monotherapy after failure of taxanes and anthracycline-containing regimens for patients with breast cancer and for whom further anthracycline-containing therapy is not indicated. Capecitabine with lapatinib (p.739) is used for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress human epidermal receptor type 2 (HER2). Capecitabine is also used with a platinum-based regimen for the first-line treatment of gastric cancer (p.664).

For *monotherapy* in **colon**, **colorectal**, or in **breast** cancer, the recommended initial oral dose is 1.25 g/m^2 given twice daily; doses are given for 14 days, followed by a 7-day rest period. Adjuvant treatment for colon cancer is recommended for a total of 6 months. For *combination* therapy in **breast** cancer, when given with docetaxel, capecitabine is given in the same dose as listed above; docetaxel is given at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. However, when used with lapatinib tosilate, a different regimen is used, see Uses and Administration, under Lapatinib Tosilate, p.739.

In *combination* therapy in **colorectal** or **gastric** cancer, the recommended initial oral dose of capecitabine is 0.8 to 1 g/m^2 twice daily for 14 days, followed by a 7-day rest period. Alternatively, capecitabine 625 mg/m^2 twice daily is given continuously.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Doses should be modified in subsequent cycles according to toxicity. Capecitabine doses should be reduced in patients with renal impairment (see below).

Capecitabine is also under investigation in the treatment of other malignancies.

◊ References.

1. Walko CM, Lindley C. Capecitabine: a review. *Clin Ther* 2005; **27:** 23–44.
2. Saif MW. Capecitabine versus continuous-infusion 5-fluorouracil for colorectal cancer: a retrospective efficacy and safety comparison. *Clin Colorectal Cancer* 2005; **5:** 89–100.
3. Glynne-Jones R, *et al.* The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? *Ann Oncol* 2006; **17:** 361–71.
4. Ershler WB. Capecitabine use in geriatric oncology: an analysis of current safety, efficacy, and quality of life data. *Crit Rev Oncol Hematol* 2006; **58:** 68–78.
5. Mandelblat J, *et al.* Capecitabine-docetaxel combination treatment. *Expert Rev Anticancer Ther* 2006; **6:** 1169–78.
6. Ershler WB. Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. *Oncologist* 2006; **11:** 325–35.
7. Schmoll HJ, Arnold D. Update on capecitabine in colorectal cancer. *Oncologist* 2006; **11:** 1003–9.
8. Pandor A, *et al.* The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. *Health Technol Assess* 2006; **10:** 1–185.
9. Schellens JHM. Capecitabine. *Oncologist* 2007; **12:** 152–5.
10. Tripathy D. Capecitabine in combination with novel targeted agents in the management of metastatic breast cancer: underlying rationale and results of clinical trials. *Oncologist* 2007; **12:** 375–89.
11. Dhillon S, Scott LJ. Capecitabine: in advanced gastric or oesophagogastric cancer. *Drugs* 2007; **67:** 601–10.
12. Glen H, Cassidy J. Redefining adjuvant chemotherapy in patients with stage III colon cancer: X-ACT trial. *Expert Rev Anticancer Ther* 2008; **8:** 547–51.
13. Comella P, *et al.* Capecitabine, alone and in combination, in the management of patients with colorectal cancer: a review of the evidence. *Drugs* 2008; **68:** 949–61.

Administration in renal impairment. Renal impairment increases systemic exposure to 5′-deoxy-5-fluorouridine, a metabolite of capecitabine. An increase in the severity of adverse effects appears to correlate with decreased renal function and increased exposure to this metabolite.[1]

Licensed product information suggests the following dosage adjustments based on creatinine clearance (CC):

- mild renal impairment, CC 51 to 80 mL/minute: no dosage adjustment necessary
- moderate renal impairment, CC 30 to 50 mL/minute: when the starting dose is 1.25 g/m^2 twice daily, a dose reduction of 25%, to about 950 mg/m^2 twice daily is recommended; however, when the starting dose is 1 g/m^2 twice daily, no dose reduction is required
- severe renal impairment, CC below 30 mL/minute: capecitabine is contra-indicated

1. Poole C, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. *Cancer Chemother Pharmacol* 2002; **49:** 225–34.

Preparations

USP 31: Capecitabine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Apecitab†; Categor; Xeloda; ***Austral.:*** Xeloda; ***Austria:*** Xeloda; ***Belg.:*** Xeloda; ***Braz.:*** Xeloda; ***Canad.:*** Xeloda; ***Chile:*** Xeloda; ***Cz.:*** Xeloda; ***Denm.:*** Xeloda; ***Fin.:*** Xeloda; ***Fr.:*** Xeloda; ***Ger.:*** Xeloda; ***Gr.:*** Xeloda; ***Hong Kong:*** Xeloda; ***Hung.:*** Xeloda; ***Indon.:*** Xeloda; ***Irl.:*** Xeloda; ***Israel:*** Xeloda; ***Ital.:*** Xeloda; ***Jpn:*** Xeloda; ***Malaysia:*** Xeloda; ***Mex.:*** Xeloda;

Neth.: Xeloda; **Norw.:** Xeloda; **NZ:** Xeloda; **Philipp.:** Xeloda; **Pol.:** Xeloda; **Port.:** Xeloda; **Rus.:** Xeloda (Кселода); **S.Afr.:** Xeloda; **Singapore:** Xeloda; **Spain:** Xeloda; **Swed.:** Xeloda; **Switz.:** Xeloda; **Thai.:** Xeloda; **Turk.:** Xeloda; **UK:** Xeloda; **USA:** Xeloda; **Venez.:** Xeloda.

Carboplatin *(BAN, USAN, rINN)*

Carboplatine; Carboplatino; Carboplatinum; CBDCA; JM-8; Karboplatiini; Karboplatin; Karboplatina; NSC-241240. *cis*-Diammine(cyclobutane-1,1-dicarboxylato)platinum.

Карбоплатин

$C_6H_{12}N_2O_4Pt$ = 371.3.

CAS — 41575-94-4.

ATC — L01XA02.

ATC Vet — QL01XA02.

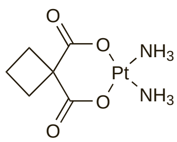

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Carboplatin). A colourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

USP 31 (Carboplatin). A 1% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. Carboplatin reacts with aluminium causing loss of potency and forming a precipitate. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving carboplatin.

Stability. About 5% of the initial carboplatin concentration was lost over 24 hours when solutions were diluted in sodium chloride 0.9% and stored at 25°; lesser amounts of degradation were seen at lower sodium chloride concentrations, but carboplatin was apparently stable over this period if diluted with glucose 5%.[1] The authors suggested that chloride-containing infusion solutions are not suitable for carboplatin, not only because of the loss of active drug but because of the possibility that conversion to cisplatin may be occurring, with a risk of increased toxicity.[1] This has been contested by the manufacturers (*Bristol-Myers, USA*), who found that only 0.5% or 0.7%, depending on formulation, of a carboplatin solution in sodium chloride 0.9%, had been converted to cisplatin after 24 hours.[2] However, the total degradation of carboplatin was not measured. In another study, the authors calculated the time to 5% degradation of carboplatin at 25° as 29.2 hours in sodium chloride 0.9% compared with 52.7 hours in water.[3] They concluded that carboplatin should not be diluted in sodium chloride 0.9% when intended for continuous infusion over a prolonged period.[3] Carboplatin in glucose 5% was reported to be stable for 7 days at 25° in PVC bags when protected from light.[4]

1. Cheung Y-W, *et al.* Stability of cisplatin, iproplatin, carboplatin, and tetraplatin in commonly used intravenous solutions. *Am J Hosp Pharm* 1987; **44:** 124–30.
2. Perrone RK, *et al.* Extent of cisplatin formation in carboplatin admixtures. *Am J Hosp Pharm* 1989; **46:** 258–9.
3. Allsopp MA, *et al.* The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int J Pharmaceutics* 1991; **69:** 197–210.
4. Diaz Amador F, *et al.* Stability of carboplatin in polyvinyl chloride bags. *Am J Health-Syst Pharm* 1998; **55:** 602, 604.

Adverse Effects, Treatment, and Precautions

As for Cisplatin, p.698; nephrotoxicity and gastrointestinal toxicity are less severe than with cisplatin and reversible myelosuppression is the dose-limiting toxicity; platelet counts reach a nadir between 14 and 21 days after a dose, with recovery within 35 days, but recovery from leucopenia may be slower. Myelosuppression may be more severe and prolonged in patients with impaired renal function. Carboplatin should therefore be given at reduced doses to these patients and should be avoided if creatinine clearance is 20 mL/minute or less. Weekly blood counts and regular renal and hepatic function tests are recommended in all patients during therapy. Neurological function including assessment of hearing should also be monitored.

Incidence of adverse effects. The manufacturers analysed the adverse effects of carboplatin in studies involving 710 patients.[1] Myelosuppression was the dose-limiting toxicity: leucopenia occurred in 55% of the evaluable patients. Leucopenia and thrombocytopenia result in symptomatic events such as infection or bleeding in a minority of patients. Anaemia was frequent (59%) and required transfusional support in about one-fifth of the patients. Nephrotoxicity and serum electrolyte loss were much less of a problem; no high-volume fluid hydration or electrolyte supplementation was given during treatment. Vomiting occurred in about half the patients, and a further 25% had nausea without vomiting. Peripheral neurotoxicity was reported in 6% of evaluable patients and clinical ototoxicity occurred in only 8 cases or about 1% (but see also Effects on the Ears, below). Increases in liver enzyme values have also been reported, as well as, more rarely, alopecia, skin rash, a flu-like syndrome, and local effects at the injection site.

1. Canetta R, *et al.* Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985; **12** (suppl A): 125–36.

Effects on the ears. Carboplatin is less ototoxic than cisplatin, but ototoxicity is still common with carboplatin when used in high doses, for example, as part of conditioning regimens for bone marrow transplantation.[1,2] There was some evidence that sodium thiosulfate reduced carboplatin-induced hearing loss, when carboplatin was used for CNS malignancy.[3,4]

1. Freilich RJ, *et al.* Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. *Med Pediatr Oncol* 1996; **26:** 95–100.
2. Parsons SK, *et al.* Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant* 1998; **22:** 669–74.
3. Neuwelt EA, *et al.* First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. *J Pharmacol Exp Ther* 1998; **286:** 77–84.
4. Doolittle ND, *et al.* Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001; **7:** 493–500.

Effects on the eyes. Cortical blindness developed in 2 patients with impaired renal function receiving high-dose carboplatin;[1] although 10 cases of visual disturbances in patients receiving carboplatin had been reported to the manufacturers, none of these had sudden blindness and it was thought that the effect represented CNS toxicity in the presence of poor renal excretion. It was concluded that it was unwise to give high-dose carboplatin to patients whose glomerular filtration rate is less than 50 mL/minute.

1. O'Brien MER, *et al.* Blindness associated with high-dose carboplatin. *Lancet* 1992; **339:** 558.

Effects on the kidneys. Although carboplatin is reported to be much less nephrotoxic than cisplatin it is not devoid of adverse effects on the kidney.[1-8] Salt wasting nephropathy (similar to that seen with cisplatin),[1] and decreased creatinine clearance[2] and glomerular filtration rate[3] have occurred, as has acute renal failure, including in 2 patients given intraperitoneal carboplatin[4] (although these patients had been heavily pretreated with cisplatin). It has been suggested that renal toxicity may be more likely at cumulative carboplatin doses of about 750 mg/m^2 or more,[3] and there is some evidence to suggest that intensive hydration may ameliorate nephrotoxic effects.[2]

1. Welborn J, *et al.* Renal salt wasting and carboplatinum. *Ann Intern Med* 1988; **108:** 640.
2. Reed E, Jacob J. Carboplatin and renal dysfunction. *Ann Intern Med* 1989; **110:** 409.
3. Smit EF, *et al.* Carboplatin and renal function. *Ann Intern Med* 1989; **110:** 1034.
4. McDonald BR, *et al.* Acute renal failure associated with the use of intraperitoneal carboplatin: a report of two cases and review of the literature. *Am J Med* 1991; **90:** 386–91.
5. Frenkel J, *et al.* Acute renal failure in high dose carboplatin chemotherapy. *Med Pediatr Oncol* 1995; **25:** 473–4.
6. Agraharkar M, *et al.* Carboplatin-related hematuria and acute renal failure. *Am J Kidney Dis* 1998; **32:** E5.
7. Butani L, *et al.* End-stage renal disease after high-dose carboplatinum in preparation of autologous stem cell transplantation. *Pediatr Transplant* 2003; **7:** 408–12.
8. Tarrass F, *et al.* End-stage renal disease following carboplatin chemotherapy for a nasopharyngeal carcinoma. *Ren Fail* 2007; **29:** 1049–51.

Hypersensitivity. In one series, 12% of 205 patients treated with carboplatin developed a hypersensitivity reaction after a median of 8 courses of platinum therapy.[1] Symptoms were at least moderately severe in half of the patients. Reactions to cisplatin would be anticipated in patients who have been previously sensitised to carboplatin—for 1 such case see p.699. In another study,[2] patients receiving more than 7 courses of carboplatin therapy were given a skin test before each course in an attempt to identify patients at risk for hypersensitivity reactions. The test consisted of 0.02 mL of an undiluted aliquot of their planned infusion, injected intradermally 1 hour before the dose. A negative skin test accurately predicted the absence of a hypersensitivity reaction. In a further extended report[3] by the same group, the skin test had been given about 30 minutes before carboplatin doses in 126 women who had already received at least 6 courses of a platinum-based regimen for a gynaecological cancer. Of 668 negative skin tests, a hypersensitivity reaction developed on 10 occasions (in 7 patients), giving a false-negative rate of 1.5%. None of the reactions were severe. Of the 39 patients who had a positive skin test, 7 elected to receive the dose of carboplatin; 6 of these developed a hypersensitivity reaction but none were severe.

The use of a desensitisation regimen has been successful in a small number of patients,[4] although others have not found it useful.[5]

1. Markman M, *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; **17:** 1141–5.
2. Zanotti KM, *et al.* Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001; **19:** 3126–9.
3. Markman M, *et al.* Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003; **21:** 4611–14.
4. Markman M, *et al.* Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004; **130:** 25–8.
5. Lafay-Cousin L, *et al.* Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer* 2008; **112:** 892–9.

Pregnancy. For a report of the successful use of carboplatin-based chemotherapy during pregnancy, with no adverse effects on the infant, see Pregnancy, under Cisplatin, p.699.

Interactions

As for Cisplatin, p.700.

Pharmacokinetics

Intravenous carboplatin exhibits a biphasic elimination and is excreted primarily in the urine, about 70% of a dose being excreted within 24 hours, almost all unchanged. The terminal half-life of intact carboplatin is reported to be about 1.5 to 6 hours. Platinum from carboplatin slowly becomes protein bound, and is subsequently excreted with a half-life of 5 days or more.

◊ References.

1. van der Vijgh WJF. Clinical pharmacokinetics of carboplatin. *Clin Pharmacokinet* 1991; **21:** 242–61.

Uses and Administration

Carboplatin is an analogue of cisplatin with similar actions and uses (see p.700). It is used in the treatment of advanced ovarian cancers and of small-cell lung cancer, both alone and combined with other antineoplastics. It has also been tried as an alternative to cisplatin in other solid tumours (see below).

Carboplatin is given by intravenous infusion over 15 minutes to 1 hour. In the UK an initial dose of 400 mg/m^2 is licensed for use as a single agent in previously untreated patients with normal renal function, reduced by 20 to 25% (300 to 320 mg/m^2) in patients who have previously been treated with myelosuppressive therapy or who have poor performance status. In the USA an initial dose of 360 mg/m^2 is licensed as a single agent in previously treated patients with recurrent disease, and an initial dose of 300 mg/m^2 when used with cyclophosphamide in previously untreated patients.

Dosage adjustments are necessary in patients with renal impairment (see below) and when carboplatin is given as part of a combination regimen. The dose in mg may be calculated using the Calvert formula as described under Administration, below. Subsequent doses should be adjusted according to the nadir of the white cell and platelet counts (see also Bone-marrow Depression, p.639), and should not be given more frequently than every 4 weeks.

Administration. Pharmacokinetic studies by Calvert and colleagues[1] have indicated that the dose of carboplatin to produce a desired area under the concentration-time curve (AUC) could be calculated, based on the patient's glomerular filtration rate (GFR), as:

$$\text{Dose in mg} = \text{target AUC} \times (\text{GFR} + 25)$$

It should be noted that the resultant dose is given in mg and not in mg/m^2. This formula was found to be useful in patients with higher than normal as well as reduced GFR. Suggested target AUCs were 5 mg/mL per minute in previously treated patients and 7 mg/mL per minute in those who had not previously received chemotherapy. In combination therapy the appropriate AUC value depended on the other drugs used: an AUC of 4.5 mg/mL per minute gave acceptable results when carboplatin was used with bleomycin and etoposide for testicular teratoma.

However, determination of GFR may be a problem: clearance of technetium-99m-labelled diethylenetriamine penta-acetic acid (DTPA) or chromium-51-labelled edetic acid is more accurate than 24-hour creatinine clearance, with the first of these more convenient than the second.[2] (It has been suggested that creatinine clearance should not be used to estimate GFR for the Calvert equation.[3]) Nonetheless, radioisotopic determination of

GFR is still an elaborate procedure, and may be less accurate in children than adults.[4] Chatelut and colleagues have proposed formulae for determining clearance of carboplatin in both adults[5] and children.[4]

It has been suggested that the Calvert and Chatelut formulae are not sufficiently accurate for use in children, or in adults with very severe renal impairment. Bayesian methods are the technique of choice where serum carboplatin concentrations can be monitored.[3] However, a study in children showed that dosage based on determination of the GFR results in more consistent carboplatin exposure than dosage based on body-surface area.[6]

1. Calvert AH, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7:** 1748–56.
2. Millward MJ, *et al.* Carboplatin dosing based on measurement of renal function—experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med* 1996; **26:** 372–9.
3. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997; **33:** 161–83.
4. Chatelut E, *et al.* Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther* 1996; **59:** 436–43.
5. Chatelut E, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; **87:** 573–80.
6. Thomas H, *et al.* Prospective validation of renal-function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group Trial. *J Clin Oncol* 2000; **18:** 3614–21.

Administration in renal impairment. The initial dose of carboplatin is usually determined using a formula (see Administration, above). If this approach is not adopted, the UK licensed product information recommends the following doses based on the patient's creatinine clearance (CC):

- CC 40 mL/minute or more: 400 mg/m^2
- CC 20 to 39 mL/minute: 250 mg/m^2

However, in the USA, the licensed information recommends:

- CC 41 to 59 mL/minute: 250 mg/m^2
- CC 16 to 40 mL/minute: 200 mg/m^2

Malignant neoplasms. A preliminary review[1] of carboplatin, concluded that it was active in ovarian cancer (p.670), with similar responses to those seen with cisplatin; its activity in small-cell lung cancer (p.668), seminoma, and squamous cell carcinomas of the head and neck seemed likely to be comparable, whereas results in gastrointestinal and breast cancers, lymphomas and leukaemias, melanoma, mesothelioma, renal carcinoma, and sarcoma were, generally unimpressive. A subsequent review[2] suggested that in testicular cancer, where there was a prospect of cure, cisplatin, which appeared to give better results in some studies should be preferred. However, in ovarian cancer, where treatment was largely palliative, carboplatin had the advantage of being better tolerated. A further review[3] of randomised studies concurred that carboplatin was equivalent to cisplatin in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer, and was inferior to cisplatin in testicular cancer. It was also concluded that carboplatin was inferior to cisplatin in head and neck and oesophageal cancers. There was insufficient comparative evidence for other cancers for which cisplatin has a role.

1. Wagstaff AJ, *et al.* Carboplatin: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Drugs* 1989; **37:** 162–90.
2. Anonymous. Cisplatin or carboplatin for ovarian and testicular cancer? *Drug Ther Bull* 1994; **32:** 62–3.
3. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; **17:** 409–22.

Preparations

BP 2008: Carboplatin Injection;
USP 31: Carboplatin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Carbokebir; Carboplat; Carboxtie; Omilipis; Paraplatin†; ***Austria:*** Carbosol; Paraplatin; ***Belg.:*** Carbosin; Paraplatin; ***Braz.:*** B-Platin; Biocarbo; Displata†; Evocarb†; Oncocarb†; Oncoplatin; Paraplatin; Platamine; Platicarb†; Tecnocarb; Vancel; ***Canad.:*** Paraplatin; ***Chile:*** Blastocarb†; Oncocarb; Paraplatin; ***Cz.:*** Cycloplatin; Paraplatin†; ***Denm.:*** Paraplatin; ***Fin.:*** Carbosin†; Paraplatin; ***Fr.:*** Paraplatine; ***Ger.:*** Carbo-cell; Carbomedac; Carboplat; Neocarbo; Ribocarbo; ***Gr.:*** Carboplamin; Carbosin; Emorzim; Megaplatin; Paraplatin; ***Hong Kong:*** Paraplatin; ***Hung.:*** Cycloplatin; Paraplatin; ***India:*** Biocarb; Cytocarb; Kemocarb; ***Indon.:*** Carbosin; Paraplatin; ***Irl.:*** Paraplatin; ***Israel:*** Paraplatin†; ***Ital.:*** Paraplatin; ***Malaysia:*** Carbosin; Paraplatin†; ***Mex.:*** Blastocarb; Boplatex; Carboplat; Carbotec; Ifacap; Kemocarb; Novoplat†; Paraplatin; ***Neth.:*** Carbosin; Paraplatin†; ***Norw.:*** Carbosin; Paraplatin; ***NZ:*** Carbosin†; Paraplatin; ***Philipp.:*** Biovinate; Bonaplatin; Carbotinol; Crobextin; Kemocarb; Paraplatin; ***Pol.:*** Cycloplatin; Paraplatin; ***Port.:*** Nealorin; Novoplatinum; Paraplatin; ***Rus.:*** Blastocarb (Бластокарб); Cycloplatin (Циклоплатин); Paraplatin (Параплатин); ***S.Afr.:*** Carbosin; Paraplatin; ***Singapore:*** Paraplatin; ***Spain:*** Ercar†; Nealorin; Paraplatin; Platinwas; ***Swed.:*** Paraplatin; ***Switz.:*** Paraplatin; ***Thai.:*** Blastocarb; Carbosin; Kemocarb; Paraplatin; ***Turk.:*** Carbosin; Paraplatin; Platinwas; ***UK:*** Paraplatin; ***USA:*** Paraplatin†; ***Venez.:*** Bioplatinex; Oplat.

Carboquone *(rINN)*

Carbazilquinone; Carbocuona; Carboquonum; Karbokvon; Karbokvoni. 2,5-Bis(aziridin-1-yl)-3-(2-hydroxy-1-methoxyethyl)-6-methyl-*p*-benzoquinone carbamate.

Карбохон

$C_{15}H_{19}N_3O_5$ = 321.3.
CAS — 24279-91-2.
ATC — L01AC03.
ATC Vet — QL01AC03.

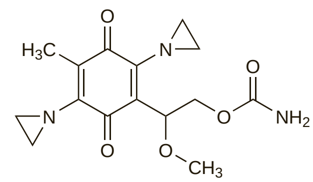

Profile

Carboquone is an alkylating agent that has been used in the treatment of a variety of malignant neoplasms including those of the lung, stomach, and ovary; it has also been used in lymphomas and in chronic myeloid leukaemia. It has been given by the intravenous or intra-arterial route, or orally.

Carmofur *(rINN)*

Carmofurum; HCFU; Karmofuuri. 5-Fluoro-*N*-hexyl-3,4-dihydro-2,4-dioxo-1-(2*H*)-pyrimidinecarboxamide; 1-Hexylcarbamoyl-5-fluorouracil.

Кармофур

$C_{11}H_{16}FN_3O_3$ = 257.3.
CAS — 61422-45-5.
ATC — L01BC04.
ATC Vet — QL01BC04.

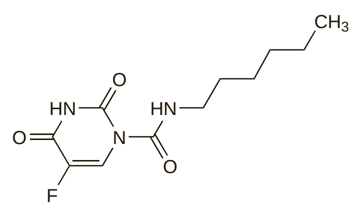

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Carmofur is an orally active derivative of fluorouracil (p.722) and has similar actions. It is used in the adjuvant treatment of colorectal cancer, and has been used in breast and ovarian cancers. Carmofur has been associated with the development of neurological disorders including leukoencephalopathy.

◊ References.

1. Yamada T, *et al.* Leukoencephalopathy following treatment with carmofur: a case report and review of the Japanese literature. *Asia Oceania J Obstet Gynaecol* 1989; **15:** 161–8.
2. Sakamoto J, *et al.* An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer. *Oncol Rep* 2001; **8:** 697–703.
3. Nakamura T, *et al.* Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III. *Int J Oncol* 2001; **19:** 291–8.
4. Tominaga T, *et al.* Postoperative chemoendocrine therapy for women with node-positive stage II breast cancer with combined cyclophosphamide, tamoxifen, and 1-hexylcarbamoyl-5-fluorouracil. *Eur J Surg* 2001; **167:** 598–604.
5. Iwagaki H, *et al.* Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection. *Anticancer Res* 2001; **21:** 4163–8.
6. Morimoto K, Koh M. Postoperative adjuvant use of carmofur for early breast cancer. *Osaka City Med J* 2003; **49:** 77–83.
7. Tominaga T, *et al.* 1-Hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep* 2004; **12:** 797–803.
8. Sakamoto J, *et al.* An individual patient data meta-analysis of adjuvant therapy with carmofur in patients with curatively resected colon cancer. *Jpn J Clin Oncol* 2005; **35:** 536–44.

Preparations

Proprietary Preparations (details are given in Part 3)

Fin.: Mirafur.

Carmustine *(BAN, USAN, rINN)*

BCNU; BiCNU; Carmustina; Carmustinum; Karmustiini; Karmustin; Karmustinas; Karmusztin; NSC-409962; WR-139021. 1,3-Bis(2-chloroethyl)-1-nitrosourea.

Кармустин

$C_5H_9Cl_2N_3O_2$ = 214.0.
CAS — 154-93-8.
ATC — L01AD01.
ATC Vet — QL01AD01.

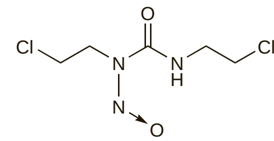

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Carmustine). A yellowish, granular powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. It melts at about 31° with decomposition. Store at a temperature of 2° to 8° in airtight containers. Protect from light.

Stability. The manufacturers state that, when reconstituted, resulting carmustine solutions (undiluted or further diluted in sodium chloride 0.9% or glucose 5%) are stable for 8 hours at room temperature, or 24 hours at 2° to 8°, when protected from light. There is some evidence that carmustine interacts with plastic giving sets and containers, and licensed product information recommends the use of polyethylene or glass.

A study has indicated that diluted solutions of carmustine undergo increased degradation in the presence of sodium bicarbonate, with only 73% of the original concentration of carmustine remaining after 90 minutes, much of the loss being in the first 15 minutes.[1]

1. Colvin M, *et al.* Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 1980; **37:** 677–8.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639. Delayed and cumulative bone-marrow depression is the most frequent and serious adverse effect of intravenous carmustine. Platelets and leucocytes are mainly affected, with platelet nadirs occurring at 4 to 5 weeks after a dose and leucocyte nadirs at 5 to 6 weeks; although thrombocytopenia is usually more severe, leucopenia may also be dose-limiting. Other adverse effects include pulmonary fibrosis (mainly but not exclusively at high cumulative doses—see also Effects on the Lungs, p.638), renal and hepatic damage, and neuroretinitis. Nausea and vomiting, beginning up to 2 hours after a dose, is common but can be reduced by prophylactic antiemetic therapy. Venous irritation may follow intravenous injection and transient hyperpigmentation has been noted after contact of a solution with the skin. Flushing of the skin and suffusion of the conjunctiva may occur on rapid intravenous infusion. Hypotension, tachycardia, chest pain, headache, and hypersensitivity reactions have been reported.

Convulsions, cerebral oedema, and various neurological symptoms have been reported in patients given carmustine-containing polymer implants; abnormalities of wound healing at the site of implantation, and an increased incidence of intracranial infection have also been reported.

As with other alkylating agents, carmustine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the eyes. Ocular toxicity has been reported in patients given carmustine,[1,2] and seems to be more likely when given into the carotid artery,[1,2] although it was also seen with high-dose intravenous therapy. There is some evidence that the alcohol diluent used to prepare carmustine solutions may contribute to the retinopathy.[2]

1. Shingleton BJ, *et al.* Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 1982; **100:** 1766–72.
2. Greenberg HS, *et al.* Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; **61:** 423–9.

Effects on the lungs. Studies have found a high incidence of fatal pulmonary fibrosis (see also Effects on the Lungs, p.638) in patients treated with carmustine for gliomas during childhood; patients who were treated before 5 or 6 years of age were more likely to die of pulmonary fibrosis than those treated at a later age.[1,2] However, there are reports of pulmonary toxicity and upper lobe pulmonary fibrosis occurring in adults given carmustine and high-dose chemotherapy.[3]

1. O'Driscoll BR, *et al.* Late carmustine lung fibrosis: age at treatment may influence severity and survival. *Chest* 1995; **107:** 1355–7.
2. Lohani S, *et al.* 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004; **126:** 1007.
3. Parish JM, *et al.* Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003; **78:** 630–4.

Extravasation. For mention of the use of sodium bicarbonate as a specific antidote after carmustine extravasation, see under Treatment of Adverse Effects of Antineoplastics, p.640.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Carmustine should be used with extreme caution in children, who are at particular risk of severe delayed pulmonary toxicity. It should also be used with caution in patients with reduced lung function. Lung function should be monitored before and frequently during therapy. Blood counts should be monitored weekly during therapy, and for at least 6 weeks after the last dose. Renal and hepatic function should also be monitored periodically.

Handling and disposal. Carmustine has been shown to permeate latex, PVC, and rubber gloves, the degree of permeation tending to increase with time,[1-3] up to an equilibrium value.[2] The permeation rate appears not to depend solely on glove thickness and material, and may be different for different gloves made from the same material.[2] The time for initial penetration was reported to vary between 4.7 and 66.0 minutes in one study,[2] and gloves could be chosen accordingly depending on the anticipated length of exposure. Double-gloving, particularly with thicker PVC[1] or ethylmethacrylate[3] gloves, may offer some additional protection.

1. Connor TH, *et al.* Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 1984; **41:** 676–9.
2. Thomas PH, Fenton-May V. Protection offered by various gloves to carmustine exposure. *Pharm J* 1987; **238:** 775–7.
3. Mellström GA, *et al.* Barrier effect of gloves against cytostatic drugs. *Curr Probl Dermatol* 1996; **25:** 163–9.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Cimetidine. Reductions in white cell counts and platelet counts well below those normally attributed to treatment with carmustine alone were seen in 6 of 8 patients receiving their first course of carmustine and steroids with cimetidine given prophylactically,[1] and in 9 patients in a further study.[2] Cimetidine was also reported to exacerbate the neutropenia and leucopenia in a patient receiving lomustine.[3]

1. Selker RG, *et al.* Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* 1978; **299:** 834.
2. Volkin RL, *et al.* Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* 1982; **142:** 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* 1985; **69:** 733.

Pharmacokinetics

Intravenous carmustine is rapidly metabolised, and no intact drug is detectable after 15 minutes; metabolites have a much longer half-life and are presumed to be responsible for its activity. It is primarily excreted in the urine; some is also excreted as carbon dioxide, via the lungs. Carmustine readily crosses the blood-brain barrier, appearing in CSF in substantial concentrations almost immediately after intravenous injection. Carmustine diffuses from polymer implants into surrounding brain tissue; however, tissue and plasma concentrations after implantation have not been determined.

Uses and Administration

Carmustine is a cell-cycle phase non-specific antineoplastic belonging to the nitrosourea group of compounds, which are considered to function as alkylating agents. It is believed to alkylate DNA and RNA, and may also inhibit enzymatic processes by carbamoylation of amino acids in proteins. Carmustine is used in the treatment of brain tumours, and in combination chemotherapy for multiple myeloma. It may be given as second-line therapy in Hodgkin's disease, non-Hodgkin's lymphoma, and some other malignancies (see below).

Carmustine is licensed for use as a single agent either as a single dose of 150 to 200 mg/m^2 or divided into doses of 75 to 100 mg/m^2 given on 2 successive days. Doses are given by intravenous infusion over 1 to 2 hours in sodium chloride 0.9% or glucose 5%. Lower doses are usually given in combination therapy, except for conditioning before stem-cell transplantation. Doses may be repeated every 6 weeks provided that blood counts have returned to acceptable levels. Subsequent doses must be adjusted according to the haematological response (see also Bone-marrow Depression, p.639).

Polymer implants containing carmustine have been developed for implantation into the brain in the localised treatment of high-grade malignant glioma or recurrent glioblastoma multiforme. Each implant contains 7.7 mg of carmustine: up to 8 such implants are inserted into the cavity left by surgical removal of the tumour.

Amyloidosis. For mention of chemotherapy with epirubicin, cyclophosphamide, and carmustine to suppress amyloidosis after cardiac transplantation, see p.743.

Malignant neoplasms. Carmustine has been used in chemotherapeutic regimens for a number of malignancies. Because of its ability to pass the blood-brain barrier it has been extensively used in malignant neoplasms of the brain (p.660). As an extension of such use, carmustine-releasing wafers have been implanted directly into the brain.[1] In a multicentre study[2] in patients with recurrent malignant glioma, biodegradable poly(carboxyphenoxypropane/sebacic acid)anhydride polymer wafers containing carmustine implanted into the brain after tumour resection produced a median survival of 31 weeks compared with 23 weeks for placebo. A subsequent small cohort study[3] failed to find a clear survival benefit associated with wafer implantation in recurrent glioma, and reported a higher rate of complications including seizures, cerebral oedema, CSF leaks, sepsis, and wound infections. The limitations of this small study were acknowledged by the authors, and a review[4] that included these studies concluded that despite limited data, carmustine wafers do provide some survival benefit. A randomised trial in 240 patients found that treatment with carmustine wafers reduced the risk of death by 28% compared with placebo;[5] this survival advantage was maintained at 1, 2, and 3 years, with statistical significance at 3 years.[6] The adverse effect profile was similar for carmustine and placebo groups,[5] and a retrospective review[7] found carmustine wafers to be well tolerated with a low incidence of surgical complications such as infection. However, it was noted that, in some patients, neurological symptoms developed during an attempted tapering of dexamethasone dosage after carmustine with radiotherapy and that close supervision of patients is warranted. Treatment effects or necrosis can radiographically mimic recurrent tumour in a proportion of patients;[7] implantation of wafers caused morphological changes of the brain immediately adjacent to the implants.[8]

Other conditions in which carmustine has been employed, include malignant melanoma (p.673), Hodgkin's disease (p.655), and multiple myeloma (p.658).

1. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther* 2008; **8:** 343–59.
2. Brem H, *et al.* Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995; **345:** 1008–12.
3. Subach BR, *et al.* Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; **45:** 17–23.
4. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000; **53:** 458–64.
5. Westphal M, *et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; **5:** 79–88.
6. Westphal M, *et al.* Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148:** 269–75.
7. Kleinberg LR, *et al.* Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; **22:** 1–9.
8. Giese A, *et al.* Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004; **66:** 351–60.

Mycosis fungoides. Topical application of carmustine has been used successfully[1-5] in early mycosis fungoides (p.657). Erythema and telangiectasia were the most frequent adverse effects.

1. Zackheim HS, *et al.* Topical carmustine (BCNU) for mycosis fungoides and related disorders: a 10-year experience. *J Am Acad Dermatol* 1983; **9:** 363–74.
2. Zackheim HS, *et al.* Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; **22:** 802–10.
3. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. *Semin Dermatol* 1994; **13:** 202–6.
4. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol* 2000; **42:** 283–5.
5. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. *Dermatol Ther* 2003; **16:** 299–302.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: BiCNU; ***Austral.:*** BiCNU; Gliadel; ***Austria:*** Carmubris; ***Belg.:*** Nitrumon†; ***Braz.:*** Becenun; ***Canad.:*** BiCNU; ***Chile:*** BiCNU; Gliadel†; ***Cz.:*** BiCNU; ***Fr.:*** BiCNU; Gliadel; ***Ger.:*** Carmubris; ***Gr.:*** Carmubris; Gliadel; Nitrumon†; ***Hong Kong:*** BiCNU; ***Hung.:*** BiCNU; ***Irl.:*** BiCNU; ***Israel:*** BiCNU†; Gliadel; ***Ital.:*** Gliadel; ***Malaysia:*** BiCNU†; Gliadel; ***Mex.:*** BiCNU; ***Neth.:*** Gliadel; ***NZ:*** BiCNU; ***Philipp.:*** BiCNU; ***Port.:*** Gliadel; ***S.Afr.:*** BiCNU; Gliadel; ***Singapore:*** BiCNU; ***Spain:*** Gliadel; ***Turk.:*** Nitrumon; ***UK:*** BiCNU†; Gliadel; ***USA:*** BiCNU; Gliadel.

Cetuximab *(USAN, rINN)*

C-225; Cétuximab; Cetuximabum. Immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain, dimer.

Цетуксимаб

CAS — 205923-56-4.

ATC — L01XC06.

ATC Vet — QL01XC06.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Adverse effects associated with cetuximab include skin reactions, asthenia, and gastrointestinal disturbances. Skin reactions present mainly as an acneform rash, and, if severe, require dosage adjustment (see Uses and Administration, below). Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. Mild reactions include chills, fever, and dyspnoea; severe reactions include bronchospasm, urticaria, hypotension, and loss of consciousness, and fatalities have occurred. Premedication with a histamine H_1-antagonist is recommended, and dose adjustment may be necessary (see below). Cardiopulmonary arrest and/or sudden death has been reported in patients treated with cetuximab and radiation therapy, and cetuximab should be given with caution to head and neck cancer patients with coronary artery disease, congestive cardiac failure, or arrhythmias. Hypomagnesaemia can occur; patients should be monitored for this and accompanying hypocalcaemia and hypokalaemia both during, and for up to 8 weeks after stopping, cetuximab therapy. Interstitial lung disease and pneumonitis have been reported rarely.

Effects on the skin, hair, and nails. Acneform follicular rashes have been reported with cetuximab therapy;[1,2] lesions were pustular and papular,[2-4] and commonly occurred on the face, scalp, chest, and upper back.[1-5] It has been suggested that there is a relationship between rash and response to therapy or survival, i.e. that rash might be a surrogate marker of cetuximab activity;[6] doubling the cetuximab dose in patients without severe initial skin reactions is reported to increase their response rate to therapy.[7] A few cases of lengthening eyelash and eyebrow hair[8] and abnormal growth of chest hair[9] have been described. Paronychia has also been reported,[1,5,10] as have intraoral aphthous ulcers.[1]

Treatment with oral isotretinoin 500 micrograms/kg daily has been reported to successfully clear acneform skin lesions in 2 patients; topical therapy with metronidazole 0.75% gel or erythromycin 1% was also used.[11] Prophylactic oral minocycline 100 mg daily, started on the same day as cetuximab and given for 8 weeks, significantly reduced total facial lesion counts in the first 4 weeks when compared with placebo; this difference tapered by the end of 8 weeks of treatment. Topical tazarotene showed no clinical benefit and caused local irritation that forced tazarotene to be stopped in many patients.[12]

Some have suggested that the clinical findings of papulopustular rash, nail and periungual abnormalities, alterations in hair texture and growth, and dry skin and pruritus, constitute a syndrome unique to the epidermal growth factor receptor (EGFR) inhibitors, believed to be due to EGFR inhibition in the epidermis, hair follicle, and nail matrix.[13]

Erythema and focal epidermolysis, progressing to severe radiation dermatitis with necrosis, has been reported in patients given radiation therapy with cetuximab.[14]

1. Busam KJ, *et al.* Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; **144:** 1169–76.
2. Walon L, *et al.* Éruptions acnéiformes induites par le cétuximab. *Ann Dermatol Venereol* 2003; **130:** 443–6.
3. Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. *Arch Dermatol* 2002; **138:** 129–31.
4. Jacot W, *et al.* Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol* 2004; **151:** 238–41.
5. Monti M, *et al.* Cutaneous toxicity induced by cetuximab. *J Clin Oncol* 2003; **21:** 4651–3.
6. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol* 2005; **23:** 5235–46.
7. Anonymous. Data support scaling cetuximab dose to provoke rash. *Pharm J* 2006; **277:** 474.
8. Dueland S, *et al.* Epidermal growth factor receptor inhibition induces trichomegaly. *Acta Oncol* 2003; **42:** 345–6.
9. Montagut C, *et al.* Abnormal hair growth in a patient with head and neck cancer treated with the anti-epidermal growth factor receptor monoclonal antibody cetuximab. *J Clin Oncol* 2005; **23:** 5273–5.
10. Boucher KW, *et al.* Paronychia induced by cetuximab, an antiepidermal growth factor receptor antibody. *J Am Acad Dermatol* 2002; **47:** 632–3.
11. Gutzmer R, *et al.* Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol* 2005; **153:** 849–51.
12. Scope A, *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 2007; **25:** 5390–6.
13. Lacouture ME, Lai SE. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol* 2006; **155:** 852–4.
14. Budach W, *et al.* Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 2007; **357:** 514–5.

Hypomagnesaemia. A patient given cetuximab developed profound hypomagnesaemia, requiring intravenous supplementation with up to 10 g magnesium sulfate daily, throughout the duration of cetuximab therapy. This case prompted a review of 154 patients treated with cetuximab, of whom 34 had their magnesium concentrations measured at least once. Among these 34 patients, 6 had grade 3 and 2 had grade 4 hypomagnesaemia; this equated to an incidence of 24% of grade 3/4 hypomagnesaemia. In each of these cases the need for supplementation subsided after stopping cetuximab, with resolution of the hypomagnesaemia within several weeks.[1] However, it was not clear whether all patients had a normal magnesium concentration before treatment, nor was there any indication of the median time to development of hypomagnesaemia.

Another retrospective review of 114 patients did address these issues.[2] It found 48 patients had normal baseline magnesium concentrations before starting cetuximab. Of these 48 evaluable patients, 13 developed grade 3 or grade 4 hypomagnesaemia (27%); median time to onset of grade 3/4 hypomagnesaemia was 5.5 months. There was a significant association between duration of cetuximab therapy and grade of hypomagnesaemia. Magnesium replacement therapy was given to those patients with grade 3/4 toxicity. Initial attempts at oral replacement with up to 1.6 g magnesium oxide three times daily were ineffective, and intravenous supplementation was needed. However, the effects of infusion did not extend beyond 48 to 72 hours, with some patients requiring daily magnesium sulfate infusions of up to 10 g daily. Furthermore, in some patients, magnesium supplementation became less effective with continued cetuximab treatment. Of 3 patients evaluable for recovery from hypomagnesaemia after stopping cetuximab, 2 were found to correct their magnesium concentrations without supplementation after 1 month. However, 1 patient required prolonged and ongoing supplementation for more than 5 months, at 4 g infused 3 times weekly (having received 8 g daily while on cetuximab).[2] A prospective study[3] found that a progressive decrease in serum magnesium concentrations was seen in 97% of patients after treatment with cetuximab, panitumumab, or matuzumab. The authors concluded that magnesium wasting was specifically due to inhibition of the epidermal growth factor receptor (EGFR), and suggested hypomagnesaemia might be a class effect of the monoclonal antibodies directed against EGFR. However, incidence and severity may vary between products. There was also high interindividual variability; increasing age was associated with more severe hypomagnesaemia.

1. Schrag D, *et al.* Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; **97:** 1221–4.
2. Fakih MG, *et al.* Cetuximab-induced hypomagnesemia in patients with colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 152–6.
3. Tejpar S, *et al.* Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 2007; **8:** 387–94.

Pharmacokinetics

The pharmacokinetics of cetuximab have been reported to be non-linear and dose-dependent. Steady-state concentrations are reached after 3 weeks. Cetuximab has a long elimination half-life of about 70 to 100 hours.

Uses and Administration

Cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in the treatment of EGFR-expressing metastatic colorectal cancer (p.665), either with irinotecan in patients refractory to irinotecan-based chemotherapy, or as monotherapy in patients intolerant to irinotecan. Cetuximab with radiotherapy is also used for the treatment of locally advanced squamous cell cancer of the head and neck (p.666). It is also approved as monotherapy for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. It is under investigation for non-small cell lung cancer and other solid tumours.

Cetuximab 400 mg/m^2 is given as a loading dose by intravenous infusion over 2 hours. This is followed by once weekly maintenance doses of 250 mg/m^2 given over 1 hour. Premedication with a histamine H_1-antagonist is recommended, and patients should be closely monitored for at least 1 hour after the end of the cetuximab infusion. A low-protein-binding 0.22-micrometre in-line filter should be used, and the infusion given via an infusion or syringe pump.

In combined therapy for colorectal cancer, irinotecan should not be given for at least 1 hour after the end of cetuximab infusion. In head and neck carcinoma, cetuximab therapy is started one week before radiation therapy and continued until the end of the radiation therapy period. Cetuximab is usually given 1 hour before radiation therapy. When used as monotherapy, cetuximab is continued until disease progression or unacceptable toxicity occurs.

Cetuximab doses should be permanently halved in patients who have experienced a mild to moderate infusion reaction, and stopped permanently if a severe reaction has occurred (see Adverse Effects and Precautions, above). When a severe acneform rash has occurred, the next dose should be delayed by 1 to 2 weeks. After the first occurrence, the full maintenance dose may be given if there has been improvement in the rash; after a second occurrence the next dose should be delayed and reduced to 200 mg/m^2; after a third occurrence the next dose should be delayed and reduced to 150 mg/m^2. If there is no improvement in the rash when therapy has been delayed, or if the rash has occurred 4 times, cetuximab should be stopped.

◊ References.

1. Cunningham D, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351:** 337–45.
2. Ng M, Cunningham D. Cetuximab (Erbitux)—an emerging targeted therapy for epidermal growth factor receptor-expressing tumours. *Int J Clin Pract* 2004; **58:** 970–6.
3. Wong S-F. Cetuximab: an epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. *Clin Ther* 2005; **27:** 684–94.
4. Chung KY, *et al.* Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 2005; **23:** 1803–10.
5. Nygren P, *et al.* Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab: an Acta Oncologica expert report. *Acta Oncol* 2005; **44:** 203–17.
6. Bonner JA, *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354:** 567–78.
7. Frieze DA, McCune JS. Current status of cetuximab for the treatment of patients with solid tumors. *Ann Pharmacother* 2006; **40:** 241–50.
8. Blick SKA, Scott LJ. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck and metastatic colorectal cancer. *Drugs* 2007; **67:** 2585–2607.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Erbitux; ***Austral.:*** Erbitux; ***Belg.:*** Erbitux; ***Chile:*** Erbitux; ***Cz.:*** Erbitux; ***Denm.:*** Erbitux; ***Fin.:*** Erbitux; ***Fr.:*** Erbitux; ***Gr.:*** Erbitux; ***Hong Kong:*** Erbitux; ***Hung.:*** Erbitux; ***Irl.:*** Erbitux; ***Israel:*** Erbitux; ***Ital.:*** Erbitux; ***Malaysia:*** Erbitux; ***Neth.:*** Erbitux; ***Norw.:*** Erbitux; ***NZ:*** Erbitux; ***Philipp.:*** Erbitux; ***Port.:*** Erbitux; ***Singapore:*** Erbitux; ***Spain:*** Erbitux; ***Swed.:*** Erbitux; ***Switz.:*** Erbitux; ***UK:*** Erbitux; ***USA:*** Erbitux.

Chlorambucil *(BAN, rINN)*

CB-1348; Chlorambucilis; Chlorambucilum; Chlorambucyl; Chloraminophene; Chlorbutinum; Clorambucilo; Klórambucil; Klorambucil; Klorambusiili; Klorambusil; NSC-3088; WR-139013.
4-[4-Bis(2-chloroethyl)aminophenyl]butyric acid.
Хлорамбуцил
$C_{14}H_{19}Cl_2NO_2$ = 304.2.
CAS — 305-03-3.
ATC — L01AA02.
ATC Vet — QL01AA02.

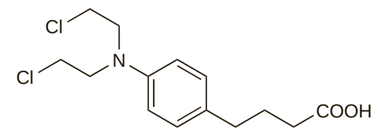

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Chlorambucil). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.
USP 31 (Chlorambucil). An off-white, slightly granular powder. M.p. 65° to 69°. Very slightly soluble in water; soluble 1 in 2 of acetone; soluble in dilute alkali. Store in airtight containers. Protect from light.

Storage. The manufacturers recommend that tablets of chlorambucil should be stored at 2° to 8° and kept dry.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

A reversible progressive lymphocytopenia tends to develop during treatment with chlorambucil. Neutropenia may continue to develop up to 10 days after the last dose. Irreversible bone-marrow depression can occur particularly when the total dosage for the course approaches 6.5 mg/kg.

Other reported adverse effects include gastrointestinal disturbances, hepatotoxicity, skin rashes (rarely Stevens-Johnson syndrome or toxic epidermal necrolysis), peripheral neuropathy, and central neurotoxicity, including seizures. Interstitial pneumonia and pulmonary fibrosis have occurred; the latter is usually reversible but fatalities have been recorded. Chlorambucil in high doses may produce azoospermia and amenorrhoea; sterility has developed particularly when chlorambucil has been given to boys at or before puberty.

Overdosage may result in pancytopenia and in neurotoxicity, including agitation, ataxia, and grand mal seizures.

Like other alkylating agents, chlorambucil is potentially mutagenic, teratogenic, and carcinogenic, and an increased incidence of acute leukaemias and other secondary malignancies has been reported in patients who have received the drug.

Effects on the bladder. Chlorambucil-induced cystitis was reported in a 73-year-old woman given 2 mg daily for over 2 years for the treatment of lymphocytic lymphoma.[1]

1. Daoud D, *et al.* Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; **11:** 491.

Effects on the eyes. Visual impairment and optic atrophy in a patient who had been receiving chlorambucil for 5 years to control non-Hodgkin's lymphoma were thought to be due to the drug,[1] although ocular effects are extremely rare with chlorambucil.

1. Yiannakis PH, Larner AJ. Visual failure and optic atrophy associated with chlorambucil therapy. *BMJ* 1993; **306:** 109.

Effects on the nervous system. There have been a small number of reports of seizures in patients given chlorambucil. A review[1] of these suggested that in adults, patients with a history of seizures, or those given high doses of chlorambucil may be at increased risk. The reports in children consisted mainly of patients being treated for nephrotic syndrome, possibly because the condition may alter the pharmacokinetics of chlorambucil.

1. Salloum E, *et al.* Chlorambucil-induced seizures. *Cancer* 1997; **79:** 1009–13.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Chlorambucil should be avoided, or given with great care and at reduced doses, for at least 4 weeks after treatment with radiotherapy or other antineoplastics (unless only low doses of radiation have been given to parts remote from the bone marrow and the neutrophil and platelet counts are not depressed). The dose should be reduced if there is lymphocytic involvement of the bone marrow or if it is hypoplastic. Chlorambucil should be given with care to patients with impaired renal function; consideration should also be given to dose reduction in patients with gross hepatic dysfunction. Children with nephrotic syndrome, patients receiving high-dose pulse therapy with chlorambucil, and those with a history of seizures, may be at increased risk of seizures. Regular blood counts are required during therapy.

Handling and disposal. Chlorambucil is irritant; avoid contact with skin and mucous membranes.

Urine produced for up to 48 hours after a dose of chlorambucil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Chlorambucil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals.*

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Pharmacokinetics

Chlorambucil is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and is reported to have a terminal half-life in plasma of about 1.5 hours. It is extensively metabolised in the liver, primarily to active phenylacetic acid mustard, which has a slightly longer plasma half-life of about 1.8 to 2.5 hours, and which like chlorambucil also undergoes some spontaneous degradation to further derivatives. Chlorambucil and its metabolites are extensively protein bound. It is excreted in the urine almost entirely as metabolites with less than 1% unchanged.

Uses and Administration

Chlorambucil is an antineoplastic derived from chlormethine (p.697) and has a similar mode of action. It acts on lymphocytes and to a lesser extent on neutrophils and platelets. Chlorambucil is most valuable in those conditions associated with the proliferation of white blood cells, especially lymphocytes, and is used in the treatment of chronic lymphocytic leukaemia and lymphomas, including Hodgkin's disease. It is also used in Waldenström's macroglobulinaemia and has been given in gestational trophoblastic tumours. Although formerly widely used in the management of polycythaemia vera it has largely been superseded.

Chlorambucil also has immunosuppressant properties and has been given in auto-immune disorders including amyloidosis, Behçet's syndrome, glomerular kidney disease, primary biliary cirrhosis, polymyositis, rheumatoid arthritis, and sarcoidosis.

The use of chlorambucil in these disorders is discussed further elsewhere, as indicated by the cross-references given below.

Chlorambucil is better tolerated than chlormethine hydrochloride and serious bone-marrow toxicity is not usually a problem with normal doses. When used as a single-agent antineoplastic for chronic lymphocytic leukaemia and lymphomas, chlorambucil is licensed for oral use in usual initial doses of 100 to 200 micrograms/kg daily (usually 4 to 10 mg once daily), for 3 to 8 weeks. A dose of 100 micrograms/kg daily may be adequate for the treatment of non-Hodgkin's lymphoma; 150 micrograms/kg daily until the total leukocyte count falls below 10 000 cells/mm^3 may be used in chronic lymphocytic leukaemia; and in Hodgkin's disease, 200 micrograms/kg daily is usually required. Lower doses may be given as part of a combination regimen. If lymphocytic infiltration of the bone marrow is present or if the bone marrow is hypoplastic, the daily dose should not exceed 100 micrograms/kg. Alternatively, high-dose chlorambucil may be given intermittently. For example, in chronic lymphocytic leukaemia it may be given in an initial single dose of 400 micrograms/kg increased by 100 micrograms/kg at each 2- or 4-week dose interval until control of lymphocytosis is achieved or toxicity occurs.

Once a remission has been established the patient may receive continuous maintenance with 30 to 100 micrograms/kg daily. However, short intermittent courses appear to be safer and are generally preferred for maintenance.

In patients with Waldenström's macroglobulinaemia chlorambucil is licensed in an initial oral dose of 6 to 12 mg daily until leucopenia develops. Maintenance therapy with doses of 2 to 8 mg daily may then be given indefinitely.

Total and differential white cell counts and haemoglobin and platelet examinations are recommended each week during treatment with chlorambucil.

Amyloidosis. Chlorambucil may be of use in preserving kidney function and improving survival in patients with amyloidosis secondary to rheumatic disease,[1-4] the management of which is discussed in more detail on p.743.

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. David J, *et al.* Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. *Clin Exp Rheumatol* 1993; **11:** 85–90.
4. Savolainen HA. Chlorambucil in severe juvenile chronic arthritis: longterm followup with special reference to amyloidosis. *J Rheumatol* 1999; **26:** 898–903.

Blood disorders, non-malignant. Chlorambucil may produce a response in cold auto-immune haemolytic anaemia (p.1043).

Connective tissue and muscular disorders. Chlorambucil has been used as a corticosteroid-sparing agent in patients with Behçet's syndrome (p.1499). It has occasionally been tried in polymyositis (p.1510). In both these conditions, the potential benefits must be weighed against the possibility of toxicity.

Kidney disorders, non-malignant. Chlorambucil has been used in some forms of glomerular kidney disease (p.1504). In minimal change nephropathy, in which cytotoxics are reserved for the most severe cases because of fears about toxicity, cyclophosphamide is generally preferred to chlorambucil because it is perceived as entailing somewhat less risk; chlorambucil has been used with corticosteroids in patients with membranous nephropathy,[1-3] but again cyclophosphamide may be better tolerated.

1. Ponticelli C, *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 1992; **327:** 599–603.
2. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
3. Ponticelli C, *et al.* A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995; **48:** 1600–4.

Liver disorders, non-malignant. No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p.2408). Chlorambucil is one of a number of drugs for which reports of benefit exist.[1]

1. Hoofnagle JH, *et al.* Randomized trial of chlorambucil for primary biliary cirrhosis. *Gastroenterology* 1986; **91:** 1327–34.

Malignant neoplasms. Chlorambucil is used in the management of a number of haematological malignancies including chronic lymphocytic leukaemia (p.653), Hodgkin's disease (p.655), indolent low-grade non-Hodgkin's lymphomas (p.656), and Waldenström's macroglobulinaemia (p.658). It was formerly used in polycythaemia vera (p.654) but is now largely superseded.

Ocular disorders, non-malignant. Chlorambucil is one of the immunosuppressants that may be considered for patients with uveitis (p.1515) unresponsive to corticosteroids in tolerable doses.[1-3]

1. Mudun AB, *et al.* Short-term chlorambucil for refractory uveitis in Behcet's disease. *Ocul Immunol Inflamm* 2001; **9:** 219–29.
2. Miserocchi E, *et al.* Efficacy and safety of chlorambucil in intractable noninfectious uveitis. *Ophthalmology* 2002; **109:** 137–42.
3. Goldstein DA, *et al.* Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. *Ophthalmology* 2002; **109:** 370–7.

Pemphigus and pemphigoid. Chlorambucil with prednisone or prednisolone has been reported[1,2] to be effective in the treatment of pemphigus and pemphigoid (p.1582).

1. Shah N, *et al.* The use of chlorambucil with prednisone in the treatment of pemphigus. *J Am Acad Dermatol* 2000; **42:** 85–8.
2. Chave TA, *et al.* Chlorambucil as a steroid-sparing agent in bullous pemphigoid. *Br J Dermatol* 2004; **151:** 1107–8.

Rheumatoid arthritis. Chlorambucil has been used for its immunosuppressant properties in a few patients with severe rheumatoid arthritis (p.11), especially with vasculitis, who have failed to respond to other drugs. However, the use of cytotoxic immunosuppressants other than methotrexate is considered debatable.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. Chlorambucil is one of a number of cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy.

Preparations

BP 2008: Chlorambucil Tablets;
USP 31: Chlorambucil Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Leukeran; ***Austral.:*** Leukeran; ***Austria:*** Leukeran; ***Belg.:*** Leukeran; ***Braz.:*** Leukeran; ***Canad.:*** Leukeran; ***Chile:*** Leukeran; ***Cz.:*** Leukeran; ***Denm.:*** Leukeran; ***Fin.:*** Leukeran; ***Ger.:*** Leukeran; ***Gr.:*** Leukeran; ***Hong Kong:*** Leukeran; ***India:*** Leukeran; ***Irl.:*** Leukeran; ***Israel:*** Leukeran; ***Ital.:*** Leukeran; ***Malaysia:*** Leukeran; ***Mex.:*** Leukeran; ***Neth.:*** Leukeran; ***Norw.:*** Leukeran; ***NZ:*** Leukeran; ***Philipp.:*** Leukeran; ***Pol.:*** Leukeran; ***Port.:*** Leukeran; ***Rus.:*** Leukeran (Лейкеран); ***S.Afr.:*** Leukeran; ***Singapore:*** Leukeran; ***Spain:*** Leukeran; ***Swed.:*** Leukeran; ***Switz.:*** Leukeran; ***Thai.:*** Leukeran; ***Turk.:*** Leukeran; ***UK:*** Leukeran.

Chlormethine Hydrochloride *(BANM, rINNM)*

Chlorethazine Hydrochloride; Chlorméthine, Chlorhydrate de; Chlormethini Hydrochloridum; Hidrocloruro de clormetina; HN2 (chlormethine); Klormetin Hidroklorür; Mechlorethamine Hydrochloride; Mustin Hidroklorür; Mustine Hydrochloride; Nitrogen Mustard (chlormethine); NSC-762; WR-147650. Bis(2-chloroethyl)methylamine hydrochloride; 2,2′-Dichloro-*N*-methyldiethylamine hydrochloride.

Хлорметина Гидрохлорид

$C_5H_{11}Cl_2N,HCl = 192.5.$
CAS — 51-75-2 (chlormethine); 55-86-7 (chlormethine hydrochloride).
ATC — L01AA05.
ATC Vet — QL01AA05.

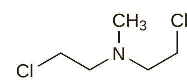

(chlormethine)

Pharmacopoeias. In *Br., Chin., Int.,* and *US.*

BP 2008 (Chlormethine Hydrochloride). A white or almost white, hygroscopic, vesicant, crystalline powder or mass. Very soluble in water. Store at a temperature of 8° to 15°.

USP 31 (Mechlorethamine Hydrochloride). A white, hygroscopic, crystalline powder. A 0.2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Stability. Solutions of chlormethine hydrochloride lose their activity very rapidly, particularly at neutral or alkaline pH.

A study[1] using an assay specific for chlormethine found that a 0.1% solution in Water for Injections or sodium chloride 0.9% injection underwent a loss of about 10% when stored for 6 hours at room temperature, and of about 4 to 6% when stored for the same period at 4°; similar results were obtained whether the solution was stored in glass vials or plastic syringes. Solutions in 500 mL of sodium chloride or glucose 5% injection and stored in PVC infusion bags were still less stable, with 15% and 10% degradation respectively after 6 hours at room temperature.

Chlormethine hydrochloride has been used in extemporaneous ointment preparations in the treatment of mycosis fungoides.[2] One formulation of chlormethine hydrochloride, dissolved in acetone and worked into white soft paraffin, was reported[3] to be stable for at least 84 days when stored at 4°, and for at least 40 days at 37°.

1. Kirk B. Stability of reconstituted Mustine Injection BP during storage. *Br J Parenter Ther* 1986; **7:** 86–92.
2. Price NM, *et al.* Ointment-based mechlorethamine treatment for mycosis fungoides. *Cancer* 1983; **52:** 2214–19.
3. Cummings J, *et al.* The long term stability of mechlorethamine hydrochloride (nitrogen mustard) ointment measured by HPLC. *J Pharm Pharmacol* 1993; **45:** 6–9.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Chlormethine hydrochloride is extremely toxic and its use is invariably accompanied by adverse effects. Severe nausea and vomiting may begin within an hour of injection of the drug and last for some hours; antiemetics should be given before treatment. It causes varying degrees of bone-marrow depression depending on the dose. In heavily pretreated patients, or when the total dose for a single course exceeds 400 micrograms/kg, there is a risk of severe and possibly fatal depression with anaemia, lymphocytopenia, granulocytopenia, and thrombocytopenia with consequent haemorrhage. Depression of lymphocytes may be apparent within 24 hours of a dose and maximum suppression of granulocytes and platelets occurs within 7 to 21 days; haematological recovery may be adequate after 4 weeks.

Tinnitus, vertigo, deafness, headache, drowsiness, and other neurological symptoms have been reported, as have episodes of jaundice. Skin reactions to chlormethine hydrochloride include maculopapular rashes. Hypersensitivity is frequent when topical preparations are used.

Chlormethine hydrochloride has a powerful vesicant action on the skin and mucous membranes and great care must be taken to avoid contact with the eyes. Thrombophlebitis is a potential hazard of chlormethine particularly if it is not sufficiently diluted. Extravasation of the injection causes severe irritation and even sloughing. If extravasation occurs during injection, it has been suggested that the involved area should be infiltrated with an isotonic 4% solution of sodium thiosulfate, followed by the application of an ice compress intermittently for 6 to 12 hours, although the role of specific antidotes in antineoplastic extravasation is somewhat contentious (see p.640).

Chlormethine hydrochloride may produce temporary or permanent inhibition of fertility. There is some evidence of mutagenicity, teratogenicity, and carcinogenicity.

Effects on the nervous system. Severe immediate neurotoxicity developed[1] in 14 of 21 evaluable patients who underwent bone marrow transplantation after preparation with cytotoxic regimens including chlormethine 0.3 to 2 mg/kg. Symptoms developed a median of 4 days after treatment and included headache, hallucinations, confusion, convulsions, paraplegia, and tremor. Symptoms resolved in most, although in some they had not done so before their death. Six of the patients who recovered from acute toxicity developed a delayed neurotoxicity, beginning a median of 169 days after the first chlormethine injection and characterised by symptoms including confusion, somnolence, personality change, dementia, focal motor seizures, and hydrocephalus. Patients older than 21 years, those who had received CNS irradiation, and those treated concomitantly with other cytotoxic agents were at increased risk of neurotoxicity.

1. Sullivan KM, *et al.* Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. *Ann Intern Med* 1982; **97:** 182–9.

Handling and disposal. Chlormethine hydrochloride is a strong vesicant; avoid contact with skin and mucous membranes.

The manufacturers state that *unused injection* solutions of chlormethine hydrochloride may be neutralised by mixing with an equal volume of a solution containing sodium thiosulfate 5% and sodium bicarbonate 5% and allowing to stand for 45 minutes. Equipment used in the preparation and administration of such solutions may be treated similarly. Alternatively a solution containing sodium carbonate 2.5% or sodium hydroxide in a mixture of industrial methylated spirit and water has been suggested for the decontamination of equipment.

Urine produced for up to 48 hours after a dose of chlormethine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pharmacokinetics

On intravenous injection, chlormethine is rapidly converted to a reactive ethyleneimmonium ion. It usually disappears from the blood in a few minutes. A very small proportion is excreted unchanged in the urine.

Uses and Administration

Chlormethine belongs to the group of antineoplastic drugs described as alkylating agents. It also possesses weak immunosuppressant properties.

Chlormethine hydrochloride has been used in the treatment of advanced Hodgkin's disease (p.655), historically with a vinca alkaloid, procarbazine, and prednisone or prednisolone (the MOPP regimen). Chlormethine has also been tried in non-Hodgkin's lymphomas, notably mycosis fungoides (p.657), and some other malignancies including chronic leukaemias, tumours of the breast, ovary, and lung, and in polycythaemia vera. Chlormethine has been used in the management of malignant effusions but is not the agent of choice.

In the MOPP regimen chlormethine hydrochloride has been given in doses of 6 mg/m^2. However, when licensed for use as a single agent, the usual dose of chlormethine hydrochloride is 400 micrograms/kg, preferably as a single dose, although it may be divided into 2 or 4 equal doses on successive days. It is given by intravenous injection in a strength of 1 mg/mL in Water for Injections or sodium chloride 0.9%. Injection over 2 minutes into the tubing of a fast running intravenous infusion of sodium chloride 0.9% or glucose 5% may reduce the incidence of thrombophlebitis and the risk of extravasation.

The response should be assessed by the trend of the blood counts. Treatment with chlormethine may be repeated when the bone-marrow function has recovered.

Intracavitary injections of 200 to 400 micrograms/kg have been given in the treatment of malignant, especially pleural, effusions. In mycosis fungoides with extensive skin involvement, very dilute solutions of chlormethine (e.g. 200 micrograms/mL) have been applied topically.

Histiocytic syndromes. Dilute solutions of chlormethine (200 micrograms/mL) have been applied topically for the cutaneous symptoms of Langerhans-cell histiocytosis (p.650).[1,2] Such therapy was reported to effectively clear skin lesions in most patients, and be well tolerated. However, although no malignant skin disease developed during the follow-up of one group of children, the long-term effects of topical chlormethine are of concern in young patients.[2]

1. Sheehan MP, *et al.* Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; **119:** 317–21.
2. Hoeger PH, *et al.* Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; **82:** 483–7.

Mycosis fungoides. Chlormethine is used topically in the management of mycosis fungoides (p.657). A retrospective cohort analysis[1] of 203 patients treated with chlormethine found a partial response rate of 33% and a complete response rate of 50%. The median time to achieve complete response was 12 months and the time to relapse was also 12 months. Mild disease of limited skin involvement responded better than generalised patch/plaque disease, and more patients with mild disease obtained long-term remission. Maintenance therapy was used in some patients, but on cessation the relapse rate was similar to patients who did not receive maintenance therapy. Treatment had usually been applied as either an aqueous solution or an ointment containing chlormethine 100 to 200 micrograms/mL.

1. Kim YH, *et al.* Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; **139:** 165–73.

Preparations

BP 2008: Chlormethine Injection;
USP 31: Mechlorethamine Hydrochloride for Injection.

Proprietary Preparations (details are given in Part 3)
Canad.: Mustargen; ***Fr.:*** Caryolysine; ***Gr.:*** Caryolysine; ***Israel:*** Mustargen; ***Switz.:*** Mustargen; ***USA:*** Mustargen.

Cilengitide *(USAN, rINN)*

Cilengitida; Cilengitidum; EMD-121974. Cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-N-methyl-L-valyl).

Циленгитид

$C_{27}H_{40}N_8O_7$ = 588.7.
CAS — 188968-51-6.

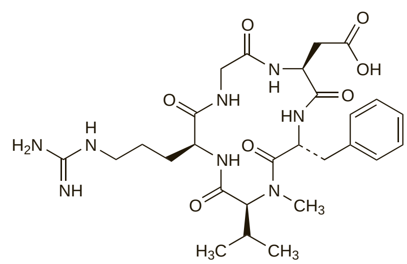

Profile

Cilengitide is an angiogenesis inhibitor under investigation in the treatment of glioma, pancreatic cancer, and non-small cell lung cancer.

◊ References.

1. Friess H, *et al.* A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; **6:** 285.
2. Hariharan S, *et al.* Assessment of the biological and pharmacological effects of the αvβ and αvβ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; **18:** 1400–7.
3. MacDonald TJ, *et al.* Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *J Clin Oncol* 2008; **26:** 919–24.
4. Reardon DA, *et al.* Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. *Expert Opin Invest Drugs* 2008; **17:** 1225–35.

Cisplatin *(BAN, USAN, rINN)*

CDDP; Cisplatina; Cisplatine; Cisplatino; Cisplatinum; Cis-platinum; Ciszplatin; DDP; *cis*-DDP; NSC-119875; Peyrone's Salt; Platinum Diamminodichloride; Sisplatiini; Sisplatin. *cis*-Diamminedichloroplatinum.

Цисплатин

$(NH_3)_2.PtCl_2$ = 300.1.
CAS — 15663-27-1.
ATC — L01XA01.
ATC Vet — QL01XA01.

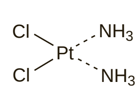

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Cisplatin). A yellow powder or yellow or orange-yellow crystals. Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation. Store in airtight containers. Protect from light.

USP 31 (Cisplatin). Store in airtight containers. Protect from light.

Incompatibility. Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite,[1,2] and admixture with preparations containing these as preservatives may result in loss of activity.[2] Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation.[3] The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours.[4] Mixtures with etoposide[5] in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives, but not when the diluent was glucose 5% with sodium chloride 0.45%. Turbidity has been reported[6] within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature.[7]

Cisplatin reacts with aluminium causing loss of potency and precipitate formation. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving cisplatin.

1. Hussain AA, *et al.* Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; **69:** 364–5.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
4. Stewart CF, Fleming RA. Compatibility of cisplatin and fluorouracil in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1990; **47:** 1373–7.
5. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 1400–4.
6. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.
7. Zhang Y, *et al.* Compatibility and stability of paclitaxel combined with cisplatin and with carboplatin in infusion solutions. *Ann Pharmacother* 1997; **31:** 1465–70.

Stability. Decomposition of cisplatin in aqueous solutions is primarily due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.[1,2] A solution in sodium chloride 0.9% injection has been reported to lose 3% of the drug in less than one hour and to remain stable at this equilibrium value for 24 hours at room temperature.[1] Stability is decreased if exposed to intense light, but the effect of normal lighting conditions is apparently smaller.[1,2] It has been recommended that admixtures of cisplatin with mannitol and magnesium sulfate (in glucose 5% with sodium chloride 0.45%) stored at room temperature in PVC bags should be used within 48 hours, but may be stored for 4 days at 4° or frozen and stored at –15° for up to 30 days.[3] However, solutions containing 600 micrograms/mL or more of cisplatin precipitate out when refrigerated and are slow to redissolve.[1]

1. Greene RF, *et al.* Stability of cisplatin in aqueous solution. *Am J Hosp Pharm* 1979; **36:** 38–43.
2. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
3. LaFollette JM, *et al.* Stability of cisplatin admixtures in polyvinyl chloride bags. *Am J Hosp Pharm* 1985; **42:** 2652.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

Severe nausea and vomiting occur in most patients during treatment with cisplatin; nausea may persist for up to a week.

Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Damage to the renal tubules may be evident during the second week after a dose of cisplatin and renal function must return to normal before further cisplatin is given. Adequate hydration, and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity. Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia, may occur, possibly as a result of renal tubular damage. Hyperuricaemia is also seen.

Bone-marrow depression may be severe with higher doses of cisplatin. Nadirs in platelet and leucocyte counts occur between days 18 and 23 and most patients recover by day 39; anaemia is common and may be partly related to decreased production of erythropoietin after renal damage.

Ototoxicity may be more severe in children. It can manifest as tinnitus, loss of hearing in the high frequency range, and occasionally deafness or vestibular toxicity. Other neurological effects reported include peripheral neuropathies, loss of taste, and seizures. Ocular toxicities include optic neuritis, papilloedema, and cerebral blindness.

Anaphylactoid reactions and cardiac abnormalities have occurred. Injection site reactions, including localised oedema, pain, erythema, skin ulceration and phlebitis may occur. Extravasation may lead to tissue cellulitis, fibrosis, and necrosis.

Platinum derivatives are potentially mutagenic and teratogenic, and there is some evidence they may be associated with the development of secondary leukaemias—see Carcinogenicity, p.635.

Effects on the blood. Cisplatin-induced anaemia appears to be disproportionate to the effects on other blood cells, and to correlate with renal tubular dysfunction.[1] It may therefore be due to an erythropoietin deficiency state resulting from cisplatin-induced renal tubular damage. Haemolysis has also been reported.[2]

1. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome *J Clin Invest* 1995; **95:** 1650–9.
2. Rothmann SA, Weick JK. Cisplatin toxicity for erythroid precursors. *N Engl J Med* 1981; **304:** 360.

THROMBOEMBOLISM. For discussion of thromboembolic events possibly associated with cisplatin-containing chemotherapy regimens see Effects on the Cardiovascular System, p.636.

Effects on the ears. Ototoxicity is a well-established adverse effect of cisplatin.[1] It appears to be due to generation of reactive oxygen species that cause apoptosis of hair cells in the cochlea,[1] and results in hearing loss, particularly at high frequencies.[1,2] Risk factors include younger age,[1] larger cumulative doses[1] (one study[2] identified doses above 60 mg/m^2 as risk factors), pre-existing hearing loss or renal disease,[1] and irradiation of the brain or base of the skull.[1,3] Various substances including thiols, amifostine, ebselen, allopurinol, and salicylates have been investigated in *animals* for their protective effect against cisplatin-induced neurotoxicity[1] but although some promising results have been seen, benefit is yet to be demonstrated in large clinical studies, and there is some concern about the risk of reducing the antineoplastic effect of cisplatin as well. However, a small study comparing cisplatin chemoradiation with or without sodium thiosulfate tentatively concluded that thiosulfate did seem to offer some protection against hearing loss.[4]

1. Rybak LP, *et al.* Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2007; **226:** 157–67.
2. Rademaker-Lakhai JM, *et al.* Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol* 2006; **24:** 918–24.
3. Low WK, *et al.* Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol* 2006; **24:** 1904–9.
4. Zuur CL, *et al.* Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol* 2007; **25:** 3759–65.

Effects on electrolytes. Renal-magnesium wasting and, less commonly, symptomatic hypomagnesaemia occurs with cisplatin therapy.[1,2] Adding magnesium to the pre- and posthydration fluids has been suggested.[2] When hypocalcaemia is also present, tetany may result,[1,3] although this has responded to electrolyte infusion without the need to interrupt chemotherapy.[1] Cisplatin therapy may also be associated with significant hypokalaemia[1] and hyponatraemia.[4,5]

See also Effects on the Kidneys, below.

1. Winkler CF, *et al.* Cisplatin and renal magnesium wasting. *Ann Intern Med* 1979; **91:** 502.
2. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev* 1999; **25:** 47–58.
3. Stuart-Harris R, *et al.* Tetany associated with cis-platin. *Lancet* 1980; **ii:** 1303.
4. Hutchison FN, *et al.* Renal salt wasting in patients treated with cisplatin. *Ann Intern Med* 1988; **108:** 21–5.
5. Mariette X, *et al.* Cisplatin and hyponatremia. *Ann Intern Med* 1988; **108:** 770–1.

Effects on the kidneys. Nephrotoxicity is a well-established adverse effect of cisplatin, may be dose-limiting, and can manifest as acute or chronic renal failure, polyuria, or chronic hypomagnesaemia.[1] The mechanism appears to involve primarily damage to the proximal renal tubule; selective magnesium loss may be due to a specific membrane or transport system abnormality. Sulfhydryl metabolism and oxidative stress play a role in toxicity, and measures that reduce glutathione depletion and scavenge intracellular free oxygen radicals have been tried in an attempt to modulate nephrotoxicity.[1-3] However, the primary measures for reducing renal damage have been aggressive hydration with chloride-containing solutions, and the use of mannitol (see also Prophylaxis, below). It has been suggested that cisplatin may mobilise lead accumulated in bone and cause temporary accumulation in the kidney, with concomitant toxicity,[4] but this has been vigorously disputed.[5-7]

See also under Effects on Electrolytes, above.

1. Anand AJ, Bashey B. Newer insights into cisplatin nephrotoxicity. *Ann Pharmacother* 1993; **27:** 1519–25.
2. Meyer KB, Madias NE. Cisplatin nephrotoxicity. *Miner Electrolyte Metab* 1994; **20:** 201–13.
3. Kuhlmann MK, *et al.* Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. *Nephrol Dial Transplant* 1997; **12:** 2478–80.
4. El-Sharkawi AM, *et al.* Unexpected mobilisation of lead during cisplatin chemotherapy. *Lancet* 1986; **ii:** 249–50.
5. Tothill P, *et al.* Is lead mobilised by cisplatin? *Lancet* 1989; **ii:** 333.
6. Tothill P, *et al.* Mobilisation of lead by cisplatin. *Lancet* 1989; **ii:** 1342.
7. Hainsworth IR, Morgan WD. Plasma lead and cisplatin. *Lancet* 1989; **ii:** 624.

PROPHYLAXIS. Hydration with 1 to 2 litres of fluid before treatment, and infusion of cisplatin in a further 2 litres of infusion fluid containing an osmotic diuretic such as mannitol reduces the nephrotoxicity of cisplatin, but does not abolish it. Maintaining adequate hydration and urinary output post-treatment is also important. Giving cisplatin over 6 to 8 hours rather than 1 to 2 hours may also decrease renal toxicity.

Sulfur-containing nucleophiles can inactivate cisplatin, and have therefore been investigated for their chemoprotective potential. Amifostine is a prodrug that is selectively activated by normal tissue, and has been shown to protect normal tissue (principally the kidney) against the cytotoxicity of cisplatin without affecting antitumour activity (for references, see Cytoprotection, p.1437). Glutathione (p.1448) is a similar agent, which may be selectively taken up by kidney and neural tissue. Sodium thiosulfate (p.1466) does not show selective activation or uptake, and its use is therefore limited to situations where cisplatin is given locally (e.g. intraperitoneal[1,2]) or directly (e.g. intra-arterial[3]).

1. Malmstrom H, *et al.* Intraperitoneal high-dose cisplatin and etoposide with systemic thiosulfate protection in second-line treatment of advanced ovarian cancer. *Gynecol Oncol* 1993; **49:** 166–71.
2. van Rijswijk RE, *et al.* Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. *Ann Oncol* 1997; **8:** 1235–41.
3. Rohde S, *et al.* Intra-arterial high-dose chemotherapy with cisplatin as part of a palliative treatment concept in oral cancer. *Am J Neuroradiol* 2005; **26:** 1804–9.

Effects on the nervous system. The features of cisplatin-induced peripheral neuropathy are consistent with damage predominantly to sensory fibres, with numbness, tingling, and decreased vibratory sensation and deep tendon reflexes, progressing in severe cases to disabling sensory ataxia.[1] The toxicity is dose-dependent, with symptoms usually appearing in patients who have received cumulative doses of 300 to 600 mg/m^2, although individuals vary in susceptibility. Neuropathy is reversible but recovery may take a year or more. The pathophysiology is unknown. Peripheral neuropathy can be a dose-limiting toxicity for cisplatin and agents such as Org-2766 (a corticotropin analogue) and amifostine (p.1436) have been investigated for their potential in protecting peripheral nerves.[1-3] Vitamin E has been reported to be effective in reducing peripheral neuropathy.[4] Glutathione is also under investigation for the prevention of neurotoxicity (see p.1448). However, a systematic review considered that the evidence for most of the interventions intended to reduce cisplatin neurotoxicity was insufficient to demonstrate benefit.[5] Autonomic neuropathy, with, in some cases, consequent orthostatic hypotension, has also been described after treatment with cisplatin-containing regimens.[6] Apart from ototoxicity (see above), cisplatin has also been associated with central neurotoxicity, including focal encephalopathy, seizures, aphasia, confusion, agitation, and cortical blindness.[7-10] It has been suggested that the mechanism of focal encephalopathy may be vascular,[7] although this is uncertain.

1. Mollman JE. Cisplatin neurotoxicity. *N Engl J Med* 1990; **322:** 126–7.
2. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs* 1995; **6:** 369–83.
3. Cavaletti G, *et al.* Neuroprotectant drugs in cisplatin neurotoxicity. *Anticancer Res* 1996; **16:** 3149–59.
4. Pace A, *et al.* Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003; **21:** 927–31.
5. Albers J, *et al.* Interventions for preventing neuropathy caused by cisplatin and related compounds. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 25/07/08).
6. Richardson P, Cantwell BMJ. Autonomic neuropathy after cisplatin based chemotherapy. *BMJ* 1990; **300:** 1466–7.
7. Lindeman G, *et al.* Cisplatin neurotoxicity. *N Engl J Med* 1990; **323:** 64–5.
8. Philip PA, *et al.* Convulsions and transient cortical blindness after cisplatin. *BMJ* 1991; **302:** 416.
9. Higa GM, *et al.* Severe, disabling neurologic toxicity following cisplatin retreatment. *Ann Pharmacother* 1995; **29:** 134–7.
10. Steeghs N, *et al.* Cisplatin-induced encephalopathy and seizures. *Anticancer Drugs* 2003; **14:** 443–6.

Extravasation. For discussion of the management of extravasation, including methods to manage cisplatin extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p.640.

Hypersensitivity. Anaphylactoid reactions to intravenous cisplatin generally appear within a few minutes of dosage and have manifested as facial oedema, wheezing, tachycardia, and hypotension.[1] A high incidence of anaphylactoid reaction has also been seen after intravesical instillation in patients with bladder cancer,[2] but intraperitoneal or intrapleural use does not seem to be associated with an enhanced risk of hypersensitivity,[3] although anaphylactoid reactions have occurred when cisplatin is given intraperitoneally.[4] Anaphylactoid symptoms and ischaemia of the hands accompanied severe exfoliative dermatitis in one patient on the second cycle of cisplatin-based chemotherapy;[5] she had earlier experienced exfoliative dermatitis associated with carboplatin. Palmar-plantar erythrodysesthesia (p.639) has also occurred.[6]

1. Von Hoff DD, *et al.* Allergic reactions to cis platinum. *Lancet* 1976; **i:** 90.
2. Denis L. Anaphylactic reactions to repeated intravesical instillation with cisplatin. *Lancet* 1983; **i:** 1378–9.
3. Markman M. No increase in allergic reactions with intracavitary administration of cisplatin. *Lancet* 1984; **ii:** 1164.
4. Hebert ME, *et al.* Anaphylactoid reactions with intraperitoneal cisplatin. *Ann Pharmacother* 1995; **29:** 260–3.
5. Lee TC, *et al.* Severe exfoliative dermatitis associated with hand ischemia during cisplatin therapy. *Mayo Clin Proc* 1994; **69:** 80–2.
6. Vakalis D, *et al.* Acral erythema induced by chemotherapy with cisplatin. *Br J Dermatol* 1998; **139:** 750–1.

Nausea and vomiting. For discussion of the management of chemotherapy-induced nausea and vomiting, see under Nausea and Vomiting, p.1700.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Cisplatin is generally contra-indicated in patients with renal or hearing impairment, or bone-marrow depression. Renal and neurological function and hearing should be monitored during treatment, and regular blood counts performed. Electrolytes should be measured before starting therapy, and before each subsequent course. Adequate hydration and urinary output must be maintained before, and for 24 hours after, a dose.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment.

Breast feeding. Platinum concentrations in a patient receiving cisplatin were 0.9 micrograms/mL in breast milk and 0.8 micrograms/mL in plasma.[1] Although most of the platinum in breast milk is probably protein-bound the authors considered that a mother should not breast feed while receiving cisplatin chemotherapy. However, in another report,[2] cisplatin was undetectable in breast milk and the American Academy of Pediatrics[3] considers its use to be compatible with breast feeding.

1. de Vries EGE, *et al.* Excretion of platinum into breast milk. *Lancet* 1989; **i:** 497. Correction. *ibid.*; 798.
2. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. Methods for the destruction of *cisplatin wastes* by reduction with zinc powder under acidic conditions or by reaction with ditiocarb sodium have been described.[1] Residue produced by the degradation of cisplatin by either method showed no mutagenicity *in vitro*.

Urine produced for up to 7 days after a dose of cisplatin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. Cisplatin was given with etoposide and bleomycin to a pregnant woman at 26 weeks of gestation for carcinoma of uncertain primary origin. At 27 weeks of gestation, she developed profound neutropenia followed by septicaemia and went into premature labour. The infant developed profound leucopenia and neutropenia by day 3, which was attributed to chemotherapy given 6 days before delivery; prophylactic antibacterials including gentamicin were given. Hair loss at the age of 10 days was attributed to etoposide. At 1 year of age, the child exhibited moderate bilateral sensorineural hearing loss; this was considered to be either due to cisplatin exposure *in utero* or to gentamicin use.[1] However, there are other reports of cisplatin use during the second or third trimester of pregnancy with no subsequent apparent adverse effects on the infant.[2-5] In most cases, cisplatin had been given with cyclophosphamide,[2-4] although in one instance it was given with paclitaxel.[5] In one report, cisplatin-induced maternal ototoxicity led to it being replaced after 2 courses by carboplatin.[4]

1. Raffles A, *et al.* Transplacental effects of maternal cancer chemotherapy: case report. *Br J Obstet Gynaecol* 1989; **96:** 1099–1100.
2. Malfetano JH, Goldkrand JW. Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma. *Obstet Gynecol* 1990; **75:** 545–7.
3. King LA, *et al.* Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. *Gynecol Oncol* 1991; **41:** 78–80.
4. Henderson CE, *et al.* Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. *Gynecol Oncol* 1993; **49:** 92–4.
5. Sood AK, *et al.* Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; **83:** 599–600.

Radiotherapy. Enhanced ototoxicity has been reported in patients given cisplatin for brain tumours who also had cranial irradiation.[1,2]

1. Granowetter L, *et al.* Enhanced cis-platinum neurotoxicity in pediatric patients with brain tumors. *J Neurooncol* 1983; **1:** 293–7.
2. Mahoney DH, *et al.* Ototoxicity with cisplatin therapy. *J Pediatr* 1983; **103:** 1006.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with other myelosuppressive, nephrotoxic or ototoxic drugs may exacerbate the adverse effects of cisplatin. The effects of cisplatin on renal function may also affect the pharmacokinetics of other drugs excreted by the renal route.

Antibacterials. Although the use of cisplatin with other nephrotoxic or ototoxic drugs requires great caution, there is some evidence that *aminoglycosides* can be used in patients who have recently received cisplatin if appropriate supportive care is available.[1]

1. Cooper BW, *et al.* Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy. *Am J Med* 1993; **94:** 497–504.

Antineoplastics. The ototoxicity of cisplatin was reportedly enhanced by *ifosfamide*,[1] a drug that is not ototoxic when given alone, although it does have nephrotoxic potential, making reports of increased nephrotoxicity in patients who have received both unsurprising.[2,3]

For a report of increased toxicity with *etoposide*, see p.718. Cisplatin may reduce the clearance of *paclitaxel*, see p.759.

1. Meyer WH, *et al.* Ifosfamide and exacerbation of cisplatin-induced hearing loss. *Lancet* 1993; **341:** 754–5.
2. Rossi R, Ehrich JHH. Partial and complete de Toni-Debré-Fanconi syndrome after ifosfamide chemotherapy of childhood malignancy. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S43–S45.
3. Martinez F, *et al.* Ifosfamide nephrotoxicity: deleterious effect of previous cisplatin administration. *Lancet* 1996; **348:** 1100–1.

Cardiovascular drugs. A patient whose renal function was unaffected by cisplatin alone developed nephrotoxicity when given cisplatin and antihypertensive therapy with *furosemide, hydralazine, diazoxide*, and *propranolol*.[1] Previous results in *animals* suggest that furosemide may aggravate cisplatin nephrotoxicity, while the other antihypertensives might have contributed to a transient fall in renal-blood flow with resultant increased renal-tubular cisplatin concentration.

1. Markman M, Trump DL. Nephrotoxicity with cisplatin and antihypertensive medications. *Ann Intern Med* 1982; **96:** 257.

Gastrointestinal drugs. For mention of 2 retrospective studies, one showing a decreased area under the plasma-concentration time curve of high-dose cisplatin with *ondansetron* and the other an increase, see p.703.

Pharmacokinetics

After intravenous doses cisplatin disappears from the plasma in a biphasic manner and half-lives of 25 to 49 minutes and 3 to 4 days have been reported for total platinum. More than 90% of the platinum from a dose is protein bound within 2 to 4 hours; only the unbound fraction has significant antineoplastic activity. Cisplatin is concentrated in the liver, kidneys, and large and small intestines. Penetration into the CNS appears to be poor. Excretion is mainly in the urine but is incomplete and prolonged: up to about 50% of a dose has been reported to be excreted in urine over 5 days, and platinum may be detected in tissue for several months afterwards. The unbound fraction, which is more rapidly cleared, may be actively secreted by the renal tubules. Cisplatin is well-absorbed on intraperitoneal use. Cisplatin may be distributed into breast milk (see Breast Feeding, above).

◊ References.

1. Loh GW, *et al.* A systematic review of limited sampling strategies for platinum agents used in cancer chemotherapy. *Clin Pharmacokinet* 2007; **46:** 471–94.
2. Jehn CF, *et al.* Pharmacokinetics of liposomal cisplatin (lipoplatin) in combination with 5-FU in patients with advanced head and neck cancer: first results of a phase III study. *Anticancer Res* 2007; **27:** 471–5.

Uses and Administration

The antineoplastic cisplatin is a platinum-containing complex that may act similarly to the alkylating agents. Its antineoplastic actions are cell-cycle non-specific and are dependent upon its *cis* configuration; they appear to be related to its hydrolysis in the body to form reactive aquated species. Although it causes immunosuppression, stimulation of the host immune response against the tumour has been suggested as contributing to cisplatin's antineoplastic action.

Cisplatin is of value in the treatment of tumours of the testis, usually as a major component of combination chemotherapy regimens, and particularly with bleomycin and etoposide (BEP), or with bleomycin and a vinca alkaloid. It is also used in metastatic ovarian tumours, cervical tumours, lung cancer, advanced bladder cancer, and squamous cell carcinoma of the head and neck. It has been reported to be active against many other solid tumours, as indicated by the cross references given below.

Cisplatin is given by intravenous infusion in sodium chloride 0.9% or in a mixture of sodium chloride and glucose. In monotherapy, it is usually given as a single dose of 50 to 120 mg/m^2 every 3 to 4 weeks. Alternatively, 15 to 20 mg/m^2 is given daily for 5 days, every 3 to 4 weeks. Lower doses are generally used for combination chemotherapy regimens than for single agent therapy; 20 mg/m^2 or more is given once every 3 to 4 weeks. A dose of 20 mg/m^2 daily for 5 days every 3 to 4 weeks has been used in combination chemotherapy of testicular tumours.

Licensed product information recommends that cisplatin is given in 2 litres of chloride-containing infusion fluid. In practice, volumes of less than 2 litres have been used in expert centres. The infusion may be given over 1 to 2 hours, although licensed product information generally recommends a longer infusion time of 6 to 8 hours in order to reduce renal and gastrointestinal toxicities.

To aid diuresis and protect the kidneys, 37.5 g of mannitol (e.g. 375 mL of mannitol 10%) is usually added to the infusion or is infused separately immediately before cisplatin. In order to begin diuresis the patient is usually hydrated by the infusion of 1 to 2 litres of a suitable fluid over several hours before giving cisplatin. Adequate hydration must also be maintained for up to 24 hours after a dose. Renal, haematological, auditory, and neurological function should be monitored during therapy, and dosage adjusted accordingly.

Cisplatin has also been given by the intra-arterial and intraperitoneal routes, and by instillation into the bladder. It is being investigated as a liposomal formulation, and as a collagen-based injectable gel containing cisplatin and adrenaline (MPI-5010) to localise the effect. An oral formulation of cisplatin is also under investigation.

Various analogues of cisplatin have been developed or investigated including those with fewer adverse effects (e.g. carboplatin, p.693; nedaplatin, p.755), an altered spectrum of activity (oxaliplatin, p.757), or activity on oral dosage (satraplatin, p.769).

Administration. Various adjustments to the administration of cisplatin have been suggested in an attempt to improve effectiveness while reducing toxicity.

Hydration before and after a dose of cisplatin, together with the use of mannitol to promote diuresis, is now standard (see Uses and Administration, above). Higher doses of cisplatin (up to 200 mg/m^2 per treatment cycle) have been successfully given by infusion in hypertonic sodium chloride, accompanied by intensive hydration.[1,2] Sodium chloride 3% infusion solution has been used.[3] However, while such a regimen may limit nephrotoxicity, other toxic effects, such as peripheral neuropathy, are not prevented;[1,2,4,5] myelosuppression may be less if the total dose is given in 2 divided doses rather than divided over 5 days.[2] High-dose cisplatin has been given once weekly; haematological toxicity may be dose-limiting with this regimen.[3]

Toxicity has been reported to be reduced when cisplatin was given by continuous intra-arterial[6] or intravenous[7] infusion. It has also been suggested that giving cisplatin in the evening rather than the morning results in less damage to renal function, apparently because of circadian variations in urine production.[8] However, another study[9] found that morning, rather than evening, doses of cisplatin resulted in less renal damage. Noting the inconsistency with previous reports, the authors concluded that use of a prolonged hydration protocol and concomitant furosemide might have been responsible for these results (see also under Interactions, Cardiovascular Drugs, above). It was also found that morning dosage of cisplatin may be more emetogenic than evening dosage, although the use of prophylactic ondansetron before cisplatin reduced this apparent circadian effect on vomiting.

A suggested alternative way to increase the platinum dose without producing incapacitating toxicity has been the combination of cisplatin and carboplatin.[10]

Various drugs have been investigated to reduce toxicity, including amifostine, glutathione, and thiosulfate, as discussed under Effects on the Kidneys, and Effects on the Nervous System, above.

A retrospective study of patients with bladder cancer found that calculation of creatinine clearance (CC) by mathematical formulas was inadequate in determining renal eligibility for treatment with cisplatin, especially in patients over 65 years of age; up to 44% of patients who were treated with cisplatin based on measured CC would have been deemed ineligible using mathematical calculations.[11]

1. Ozols RF, *et al.* High-dose cisplatin in hypertonic saline. *Ann Intern Med* 1984; **100:** 19–24.
2. Gandara DR, *et al.* Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. *J Natl Cancer Inst* 1989; **81:** 790–4.
3. de Jongh FE, *et al.* Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. *Br J Cancer* 2003; **88:** 1199–1206.
4. Bagley CM, *et al.* High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
5. Ozols RF, Young RC. High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; **102:** 719.
6. Jacobs SC, *et al.* Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. *Cancer* 1989; **64:** 388–91.
7. Salem P, *et al.* Cis-diamminedichloroplatinum (II) by 5-day continuous infusion: a new dose schedule with minimal toxicity. *Cancer* 1984; **53:** 837–40.
8. Hrushesky WJM, *et al.* Circadian time dependence of cisplatin urinary kinetics. *Clin Pharmacol Ther* 1982; **32:** 330–9.
9. Kobayashi M, *et al.* Cisplatin-induced vomiting depends on circadian timing. *Chronobiol Int* 2001; **18:** 851–63.
10. Piccart MJ, *et al.* Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990; **82:** 703–7.
11. Raj GV, *et al.* Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006; **24:** 3095–3100.

Malignant neoplasms. Cisplatin is used in the management of many solid malignancies, notably those of the bladder, cervix, lung, ovary, and testis, as discussed on p.659, p.663, p.668, p.670, and p.673 respectively. Other malignancies where cisplatin may be employed, as discussed in the introduction to this chapter, include non-Hodgkin's lymphomas (p.656), tumours of brain (p.660), endometrium (p.663), oesophagus, stomach, and anus (p.664, p.664, and p.666), head and neck (p.666), and thymus (p.674), neuroblastoma (p.674), and sarcoma of bone and soft tissue (p.675 and p.676).

Preparations

BP 2008: Cisplatin Injection;
USP 31: Cisplatin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Ciskebir; Elvecis; Platamine; Platino II; Platinol†; Sicatem; ***Austria:*** Cishexal; Platinol; Platosin; ***Belg.:*** Platinol; Platistine†; Platosin; ***Braz.:*** Astaplatin†; Bioplatino†; C-Platin; Cisplatex; Citoplax; Incel; Laxifos†; Platiran; Platistine; Tecnoplatin; Unistin†; ***Chile:*** Blastolem; ***Cz.:*** Cisanplat†; Platidiam; ***Denm.:*** Lederplatin; Platinol; ***Fin.:*** Platinol; ***Fr.:*** Cisplatyl; ***Ger.:*** Cis-Gry; Platinex; ***Gr.:*** Cisplamol; Cisplatyl†; Oncoplat; Platamine; Platinol; Platosin; ***Hung.:*** Platidiam; ***India:*** Cisplat; Cytoplatin; Kemoplat; Platin; ***Indon.:*** Platinox; Platosin; ***Israel:*** Abiplatin; ***Ital.:*** Citoplatino; Platamine; Platinex; Pronto Platamine; ***Jpn:*** Platosin; Randa; ***Malaysia:*** Platosin; ***Mex.:*** Blastolem; Metalino†; Niyaplat†; Noveldexis; Platinol; Platistil†; Tecnoplatin; ***Neth.:*** Platosin; ***Norw.:*** Platinol; Platistin; ***NZ:*** Platinol; ***Philipp.:*** Ciplexal; Cytosplat; Docistin; Kemoplat; Platamine; Platinol; Platinoxan; Platosin; ***Pol.:*** Platidiam; ***Port.:*** Faulplatin; ***Rus.:*** Blastolem (Бластолем); Platidiam (Платидиам); ***S.Afr.:*** Abiplatin; Platosin; ***Spain:*** Neoplatin; Placis; Platistil†; ***Swed.:*** Platinol; ***Switz.:*** Platiblastin-S; Platinol; ***Thai.:*** Abiplatin; Blastolem; Kemoplat; Platinol; Platosin; ***Turk.:*** Placis; Platosin-S; ***UK:*** Platinex†; ***USA:*** Platinol†; ***Venez.:*** Cytoplatin.

Cladribine *(BAN, USAN, rINN)*

2-Chlorodeoxyadenosine; Cladribina; Cladribinum; Kladribiini; Kladribin; RWJ-26251; RWJ-26251-000. 2-Chloro-2′-deoxyadenosine.

Кладрибин

$C_{10}H_{12}ClN_5O_3$ = 285.7.

CAS — 4291-63-8.

ATC — L01BB04.

ATC Vet — QL01BB04.

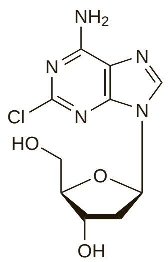

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cladribine). A white or almost white crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; soluble in dimethyl sulfoxide; practically insoluble in acetonitrile. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Cladribine). Store at a temperature of 2° to 8°. Protect from light.

Stability. Cladribine shows increased degradation in glucose 5%, therefore this diluent should not be used. Cladribine in sodium chloride 0.9% is stable for at least 24 hours at room temperature and ambient lighting in PVC infusion containers.

The manufacturers recommend that cladribine should be stored at 2° to 8° and protected from light.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

Cladribine produces severe myelosuppression, including neutropenia, anaemia, and thrombocytopenia, especially at high doses. Transfusion of blood products may be required. Prolonged CD4 lymphopenia with a nadir at 4 to 6 months also develops. Prolonged bone-marrow hypocellularity may also occur, although it is not clear if this is due to the drug or underlying disease. Haemolytic anaemia has also been reported. Severe infections can occur, and may be fatal. Myelodysplastic syndrome has been reported rarely.

Other adverse effects include fever, chills, diaphoresis, fatigue, malaise, mild nausea and gastrointestinal disturbances, rashes, pruritus, purpura, headache, anxiety, dizziness, abnormal breath and/or chest sounds, cough, dyspnoea, oedema, tachycardia, hypotension, arthralgia, and myalgia. Reversible, mild increases in bilirubin and hepatic transaminases are common. Rare adverse events include hepatic, renal, or cardiac failure, atrial fibrillation, and hypereosinophilia; tumour lysis syndrome can occur, and may be fatal.

Very high doses of cladribine have been associated with severe renal and nervous system toxicity as well as myelosuppression. Severe neurotoxicity is rare at currently recommended doses, but confusion, neuropathy, ataxia, insomnia, and somnolence have occurred.

Carcinogenicity. As with some other antimetabolites (see p.635), Epstein-Barr virus-related lymphoma has been reported after cladribine therapy.[1] A study found that in patients with chronic lymphocytic leukaemia, treatment with cladribine did not increase the risk of secondary malignancies when compared with treatment with alkylating agents and combination therapy. However, lung cancers occurred more frequently with cladribine treatment.[2]

1. Niesvizky R, *et al.* Epstein-Barr virus-associated lymphoma after treatment of macroglobulinemia with cladribine. *N Engl J Med* 1999; **341:** 55.
2. Robak T, *et al.* Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 2004; **40:** 383–9.

Precautions

For the precautions necessary with antineoplastics, see p.641. Careful haematological monitoring is recommended, especially during the first 4 to 8 weeks of therapy. Renal and hepatic function should also be monitored periodically.

Pharmacokinetics

Plasma-cladribine concentrations after intravenous infusion show either a biphasic or triphasic decline, with terminal half-lives ranging from 3 to 22 hours. A biexponential decline has been reported after subcutaneous injection, with an initial and terminal half-life of about 2 and 11 hours, respectively. Cladribine is extensively distributed and penetrates into the CNS. It is about 20% bound to plasma proteins. Cladribine is phosphorylated within cells by deoxycytidine kinase to form 2-chlorodeoxyadenosine-5′-monophosphate which is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine-5′-triphosphate (CdATP) by nucleoside diphosphate kinase.

◊ References.

1. Liliemark J. The clinical pharmacokinetics of cladribine. *Clin Pharmacokinet* 1997; **32:** 120–31.

Uses and Administration

Cladribine is a chlorinated purine nucleoside analogue that inhibits DNA synthesis and repair, particularly in lymphocytes and monocytes. It is used as an antimetabolite antineoplastic for the treatment of lymphoid malignancies including hairy-cell leukaemia (p.654) and chronic lymphocytic leukaemia (p.653). It has also been used in indolent low-grade non-Hodgkin's lymphomas (p.656), histiocytic syndromes (p.650), and in Waldenström's macroglobulinaemia (p.658).

The recommended intravenous dose of cladribine in hairy-cell leukaemia is a single course of 90 micrograms/kg (3.6 mg/m^2) daily for 7 days by continuous infusion. If the patient does not respond to the initial course, they are unlikely to respond to further doses. Cladribine is also given subcutaneously in a dose of 140 micrograms/kg (5.6 mg/m^2) daily for 5 consecutive days.

For the treatment of chronic lymphocytic leukaemia the recommended intravenous dose is 120 micrograms/kg (4.8 mg/m^2) daily for 5 consecutive days of a 28-day cycle; the infusion is given over 2 hours. Response should be determined every 2 cycles, and once maximum response has occurred a further 2 cycles of treatment are recommended, up to a maximum of 6 cycles. Patients who do not respond with a lymphocyte reduction of 50% or more after 2 cycles should not receive further therapy. Cladribine is also given subcutaneously in a dose of 100 micrograms/kg (4 mg/m^2) daily for 5 consecutive days. This dose of subcutaneous cladribine is also licensed in some countries for the treatment of indolent non-Hodgkin's lymphoma and Waldenström's macroglobulinaemia.

An oral formulation of cladribine is under investigation for the management of multiple sclerosis (see below); parenteral cladribine has also been used. Oral cladribine has also been investigated for chronic lymphocytic leukaemia.

◊ Reviews.

1. Robak T. Cladribine in the treatment of chronic lymphocytic leukemia. *Leuk Lymphoma* 2001; **40:** 551–64.
2. Goodman GR, *et al.* Cladribine in the treatment of hairy-cell leukaemia. *Best Pract Res Clin Haematol* 2003; **16:** 101–16.
3. Armitage JO, *et al.* Treatment of indolent non-Hodgkin's lymphoma with cladribine as single-agent therapy and in combination with mitoxantrone. *Int J Hematol* 2004; **79:** 311–21.
4. Robak T. The place of cladribine in the treatment of chronic lymphocytic leukemia: a 10-year experience in Poland. *Ann Hematol* 2005; **84:** 63–70.
5. Belani R, Saven A. Cladribine in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; **20:** 1109–23.
6. Sigal DS, Saven A. Cladribine in indolent non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2008; **8:** 535–45.

Multiple sclerosis. Parenteral cladribine has shown some evidence of benefit in multiple sclerosis (p.892) but it is not clear whether it improves attack rate or disease progression. An oral formulation is under investigation.

References.

1. Sipe JC, *et al.* Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet* 1994; **344:** 9–13.
2. Romine JS, *et al.* A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. *Proc Assoc Am Physicians* 1999; **111:** 35–44.
3. Rice GPA, *et al.* Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. *Neurology* 2000; **54:** 1145–55.
4. Janiec K, *et al.* Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic progressive multiple sclerosis. *Med Sci Monit* 2001; **7:** 93–8.
5. Sipe JC. Cladribine for multiple sclerosis: review and current status. *Expert Rev Neurother* 2005; **5:** 721–7.
6. Brousil JA, *et al.* Cladribine: an investigational immunomodulatory agent for multiple sclerosis. *Ann Pharmacother* 2006; **40:** 1814–21.
7. Leist TP, Vermersch P. The potential role for cladribine in the treatment of multiple sclerosis: clinical experience and development of an oral tablet formulation. *Curr Med Res Opin* 2007; **23:** 2667–76.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Intocel; Leustat; ***Austral.:*** Leustatin; Litak; ***Austria:*** Leustatin; ***Belg.:*** Leustatin; ***Braz.:*** Leustatin; ***Canad.:*** Leustatin; ***Cz.:*** Leustatin; Litak; ***Denm.:*** Leustatin; Litak; ***Fin.:*** Leustatin; Litak; ***Fr.:*** Leustatine; Litak; ***Ger.:*** Leustatin; Litak; ***Gr.:*** Leustatin; ***Hong Kong:*** Leustatin; ***Israel:*** Leustatin; Litak; ***Ital.:*** Leustatin; ***Neth.:*** Leustatin; Litak; ***Norw.:*** Leustatin; ***NZ:*** Leustatin; ***Philipp.:*** Leustatin; ***Pol.:*** Biodribin; ***Port.:*** Litak; ***S.Afr.:*** Leustatin; ***Spain:*** Leustatin; ***Swed.:*** Leustatin; ***Switz.:*** Leustatin; Litak; ***Thai.:*** Leustatin†; ***UK:*** Leustat; Litak; ***USA:*** Leustatin; ***Venez.:*** Leustatin.

Clofarabine *(BAN, USAN, rINN)*

Cl-F-Ara-A; Clofarabina; Clofarabinum. 2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine.

Кьофарабин

$C_{10}H_{11}ClFN_5O_3$ = 303.7.

CAS — 123318-82-1.

ATC — L01BB06.

ATC Vet — QL01BB06.

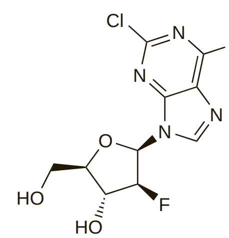

Adverse Effects, Treatment, and Precautions

As for Fludarabine Phosphate, p.721, although neurotoxicity is less severe. Capillary leak syndrome resulting from cytokine release has occurred with clofarabine, causing respiratory distress, hypotension, pleural and pericardial effusions, and multi-organ failure. Prophylactic corticosteroids may be useful, but clofarabine must be stopped immediately if signs or symptoms of capillary leak syndrome develop (respiratory status and blood pressure should be monitored during infusion). Other adverse effects include anxiety, flushing, tachycardia, hypotension, hepatotoxicity, haematuria, myalgia, arthralgia, and headache.

Renal and hepatic function, and complete blood counts, should be monitored during clofarabine therapy. Hydration should be maintained during treatment to minimise the risk of tumour lysis syndrome and other adverse effects.

Pharmacokinetics

Clofarabine is about 47% bound to plasma proteins. About 50 to 60% of a dose is excreted unchanged in the urine and it has a terminal half-life of about 5 hours.

Uses and Administration

Clofarabine, a purine nucleoside analogue, is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory acute lymphoblastic leukaemia (p.651) in patients aged 1 to 21 years. A dose of 52 mg/m^2 is given daily for 5 days, by intravenous in-

The symbol † denotes a preparation no longer actively marketed

fusion over 2 hours. A longer infusion time should be considered in children weighing less than 20 kg to reduce anxiety and irritability, and to avoid high clofarabine concentrations. The course may be repeated every 2 to 6 weeks, depending on the patient's recovery from bone-marrow depression and other adverse effects. Treatment is usually assessed after 2 treatment cycles.

Clofarabine is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and solid tumours.

◊ References.

1. Kantarjian HM, *et al.* Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. *J Clin Oncol* 2003; **21:** 1167–73.
2. Gandhi V, *et al.* Pharmacokinetics and pharmacodynamics of plasma clofarabine and cellular clofarabine triphosphate in patients with acute leukemias. *Clin Cancer Res* 2003; **9:** 6335–42.
3. Kantarjian H, *et al.* Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood* 2003; **102:** 2379–86.
4. Bonate PL, *et al.* Population pharmacokinetics of clofarabine, a second-generation nucleoside analog, in pediatric patients with acute leukemia. *J Clin Pharmacol* 2004; **44:** 1309–22.
5. Jeha S, *et al.* Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. *Blood* 2004; **103:** 784–9.
6. Faderl S, *et al.* Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias. *Blood* 2005; **105:** 940–7.
7. Curran MP, Perry CM. Clofarabine: in pediatric patients with acute lymphoblastic leukemia. *Paediatr Drugs* 2005; **7:** 259–64.
8. Kline JP, Larson RA. Clofarabine in the treatment of acute myeloid leukaemia and acute lymphoblastic leukaemia: a review. *Expert Opin Pharmacother* 2005; **6:** 2711–18.
9. Kantarjian HM, *et al.* Clofarabine: past, present, and future. *Leuk Lymphoma* 2007; **48:** 1922–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Evoltra; ***Fr.:*** Evoltra; ***Port.:*** Evoltra; ***UK:*** Evoltra; ***USA:*** Clolar.

Combretastatin A4 Phosphate

CS-A4 (combretastatin A4); NSC-348103 (combretastatin). 2-Methoxy-5-[(1*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl]-phenol dihydrogen phosphate.

$C_{18}H_{21}O_8P$ = 396.3.

CAS — 82855-09-2 (combretastatin); 117048-59-6 (combretastatin A4); 222030-63-9 (combretastatin A4 phosphate).

Profile

Combretastatin A4 phosphate is a synthetic derivative of combretastatin compounds originally isolated from the African bush-willow tree (Cape bush-willow; *Combretum caffrum*). It is described as a vascular targeting agent that reduces blood flow to tumours by disrupting the endothelial cells of newly formed blood vessels, and is under investigation for the treatment of thyroid and ovarian cancers.

Corynebacterium parvum

C. parvum; NSC-220537; *Propionibacterium acnes.*

Profile

Inactivated *Corynebacterium parvum* has been used in the treatment of malignant effusions, and has been tried as an adjuvant to cancer chemotherapy for its immunostimulant properties. It has also been used in the treatment of musculoskeletal and joint disorders.

Fever and pain have occurred after intracavitary injection. There have been reports of nephrotoxicity after intravenous use.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Arthrokehlan A.

Cyclophosphamide *(BAN, rINN)*

B-518; Ciclofosfamida; Ciklofosfamidas; Ciklofoszfamid; Cyclophosphamidum; Cyclophosphamidum Monohydricum; Cyclophosphanum; Cyklofosfamid; Cyklofosfamid monohydrát; NSC-26271; Siklofosfamid; Syklofosfamidi; WR-138719. 2-[Bis(2-chloroethyl)amino]perhydro-1,3,2-oxazaphosphorinan 2-oxide monohydrate.

Циклофосфамид

$C_7H_{15}Cl_2N_2O_2P,H_2O$ = 279.1.

CAS — 6055-19-2 (cyclophosphamide monohydrate); 50-18-0 (anhydrous cyclophosphamide).

ATC — L01AA01.

ATC Vet — QL01AA01.

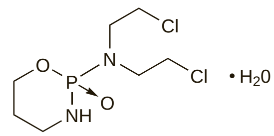

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Cyclophosphamide). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. A freshly prepared 2% solution in water has a pH of 4.0 to 6.0.

USP 31 (Cyclophosphamide). A white, crystalline powder. It liquefies upon loss of its water of crystallisation. Soluble in water and in alcohol. A 1% solution in water has a pH of 3.9 to 7.1 when determined 30 minutes after preparation. Store in airtight containers at 2° to 30°.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639. The major dose-limiting effect is myelosuppression. After single doses the nadir of the white cell count may occur in around 1 to 2 weeks with full recovery usually in 3 to 4 weeks. Thrombocytopenia and anaemia may occur but tend to be less common and less severe.

Haemorrhagic cystitis may develop after high or prolonged dosage, and can be life-threatening. Adequate hydration to maintain urine output at 100 mL/hour and use of mesna (see p.1449) are generally recommended in an attempt to reduce urotoxicity. If mesna is used, frequent emptying of the bladder should be avoided. Doses of cyclophosphamide should be given early in the day.

Alopecia occurs in about 20% of patients given low doses and in practically all patients given high doses. Hair loss starts after 3 weeks of treatment but regrowth is usually evident after 3 months, even with continued treatment. Hyperpigmentation of skin, especially that of the palms and soles, and of the nails, has been reported.

Nausea and vomiting commonly occur, and may be reduced by prophylactic antiemetics. Mucositis may also occur.

Other adverse effects include a syndrome resembling inappropriate secretion of antidiuretic hormone (which may require diuretic therapy), disturbances of carbohydrate metabolism, gonadal suppression (common and occasionally resulting in sterility), interstitial pulmonary fibrosis, and, especially at high doses, cardiotoxicity.

Cyclophosphamide, in common with other alkylating agents, has carcinogenic, mutagenic, and teratogenic potential and secondary malignancies have occurred in patients given previous antineoplastic therapy including cyclophosphamide—see p.635.

Effects on the bladder. *Sterile haemorrhagic cystitis* (p.2178) can occur after high-dose infusions of cyclophosphamide or after prolonged low-dose oral use.[1,2] It is believed to be secondary to renal excretion of alkylating metabolites, particularly the acrolein metabolite, that cause sloughing, thinning, and inflammation of the bladder wall. Damage ranges from minor bleeding to diffuse necrotic ulceration, and can lead to anaemia, constriction of the bladder, bladder perforation, and death.[2] Symptoms may be delayed, and have been reported to occur up to 6 months after stopping the drug.[3] An increased incidence of cystitis when patients on a high-dose cyclophosphamide regimen were transferred from one brand to another has been reported,[4] apparently because one was labelled in terms of the anhydrous substance and one as the monohydrate, resulting in a 6.4% difference in the content of active substance.[5]

Measures used to prevent haemorrhagic cystitis include intravenous hydration with diuresis, frequent voiding, or bladder catheterisation with irrigation, to increase urine output and dilute the excreted metabolites. Mesna may be used as a uroprotectant to reduce exposure to the metabolites.[2] If bleeding occurs, various drugs have been instilled intravesically, including sodium chloride 0.9%, alum, or prostaglandins.[2,6-9] Silver nitrate, formaldehyde, or phenol instillations have been used but are painful and patients require anaesthesia.[2] There is limited information to suggest that conjugated oestrogens given orally or intravenously may be effective.[2,10] Nonpharmacological techniques are reserved for refractory cases and include arterial embolisation or surgery.[2]

In addition to the shorter term effects, cyclophosphamide has been reported to be associated with the development of *bladder carcinoma.*[1,11-14] A history of cyclophosphamide-induced cystitis may be associated with an increased risk of bladder carcinoma[1,11] but some studies have not found a link,[13] and bladder malignancies can develop in patients who have not experienced cystitis while receiving cyclophosphamide.[12] For a discussion of the carcinogenic effects of antineoplastics, including cyclophosphamide, see p.635.

1. Talar-Williams C, *et al.* Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; **124:** 477–84.
2. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; **17:** 696–706.
3. Armstrong B, *et al.* Delayed cystitis due to cyclophosphamide. *N Engl J Med* 1979; **300:** 45.
4. Shaw IC, *et al.* Difference in bioactivity between two preparations of cyclophosphamide. *Lancet* 1983; **i:** 709.
5. Hilgard P, *et al.* Bioactivity of cyclophosphamide preparations. *Lancet* 1983; **i:** 1436.
6. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E . *Ann Intern Med* 1984; **101:** 142.
7. Miller LJ, *et al.* Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. *Ann Pharmacother* 1994; **28:** 590–4.
8. Ippoliti C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46:** 811–15.
9. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.
10. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen – report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
11. Wall RL, Clausen KP. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. *N Engl J Med* 1975; **293:** 271–3.
12. Plotz PH, *et al.* Bladder complications in patients receiving cyclophosphamide for systemic lupus erythematosus or rheumatoid arthritis. *Ann Intern Med* 1979; **91:** 221–3.
13. Pedersen-Bjergaard J, *et al.* Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med* 1988; **318:** 1028–32.
14. Travis LB, *et al.* Bladder cancer after chemotherapy for non-Hodgkin's lymphoma. *N Engl J Med* 1989; **321:** 544–5.

Effects on the blood. Amifostine has been reported to protect against the myelosuppressive effects of cyclophosphamide, and may be used to reduce neutropenia-related infection associated with the combination of cyclophosphamide and cisplatin (see p.1437).

Effects on carbohydrate metabolism. Acute onset type 1 diabetes occurred in a patient treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), and was thought to be due to the cyclophosphamide.[1]

1. Atlan-Gepner C, *et al.* A cyclophosphamide-induced autoimmune diabetes. *Lancet* 1998; **352:** 373–4.

Effects on electrolytes. Water intoxication has been reported with cyclophosphamide,[1-4] usually in high doses (30 to 50 mg/kg or more) although symptoms have been reported after a dose of 20 mg/kg in a patient with renal disease,[3] and in another patient with SLE but apparently normal renal function who received 10 mg/kg.[4] One case of severe hyponatraemia leading to convulsions and death has been reported.[5] Symptoms resemble the syndrome of inappropriate antidiuretic hormone secretion (SIADH)[5] but plasma concentrations of antidiuretic hormone do not appear to be raised in these patients.[3]

1. DeFronzo RA, *et al.* Water intoxication in man after cyclophosphamide therapy: time course and relation to drug activation. *Ann Intern Med* 1973; **78:** 861–9.
2. Green TP, Mirkin BL. Prevention of cyclophosphamide-induced antidiuresis by furosemide infusion. *Clin Pharmacol Ther* 1981; **29:** 634–42.
3. Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. *Arch Intern Med* 1985; **145:** 548–9.
4. McCarron MO, *et al.* Water intoxication after low dose cyclophosphamide. *BMJ* 1995; **311:** 292.
5. Harlow PJ, *et al.* A fatal case of inappropriate ADH secretion induced by cyclophosphamide therapy. *Cancer* 1979; **44:** 896–8.

Effects on the eyes. Recurrent transient myopia, apparently due to increased hydration of the lens of the eye, was induced by an intravenous bolus of cyclophosphamide in an adolescent with SLE.[1]

CMV retinitis has occurred in patients during or after cyclophosphamide therapy; presenting symptoms included floaters and blurred or decreased vision.[2]

1. Arranz JA, *et al.* Cyclophosphamide-induced myopia. *Ann Intern Med* 1992; **116:** 92–3.
2. Agrawal A, *et al.* Visual symptoms in patients on cyclophosphamide may herald sight threatening disease. *Br J Ophthalmol* 2003; **87:** 122–3.

Effects on reproductive potential. Severe gonadal failure with transient or permanent azoospermia is common in men treated with cyclophosphamide. Suppression of germ-cell function with intramuscular testosterone in 5 men during cyclophosphamide therapy for nephrotic syndrome was associated with a more rapid return of spermatogenesis compared with 10 patients who did not receive the androgen.[1]

1. Masala A, *et al.* Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997; **126:** 292–5.

Effects on the skin. An erythematous pruritic rash, similar to the palmar-plantar erythrodysesthesia syndrome (p.639) but occurring on the dorsal surfaces of the hands and feet, occurred 6 days after the first high dose of cyclophosphamide in a patient being prepared for bone marrow transplantation.[1] Previous cyclophosphamide-containing chemotherapy did not produce this reaction. The symptoms improved somewhat on treatment with triamcinolone ointment, and subsequently desquamation of the hands occurred with decreased purplish discoloration and oedema of the feet. There has also been a report of 2 patients who developed Stevens-Johnson syndrome, with some features suggestive of overlapping toxic epidermal necrolysis.[2]

1. Matsuyama JR, Kwok KK. A variant of the chemotherapy-associated erythrodysesthesia syndrome related to high-dose cyclophosphamide. *DICP Ann Pharmacother* 1989; **23:** 776–9.
2. Assier-Bonnet H, *et al.* Stevens-Johnson syndrome induced by cyclophosphamide: report of two cases. *Br J Dermatol* 1996; **135:** 864–6.

Hypersensitivity. Occasional anaphylaxis has been reported with cyclophosphamide;[1] analysis of data by the Boston Collaborative Drug Surveillance Program detected only one allergic skin reaction among 210 patients given cyclophosphamide, resulting in a calculated incidence of 4.8 reactions per 1000 recipients.[2]

1. Jones JB, *et al.* Cyclophosphamide anaphylaxis. *DICP Ann Pharmacother* 1989; **23:** 88–9.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641.

Cyclophosphamide should not be given to patients with bone-marrow aplasia, acute infection, or drug- or radiation-induced urothelial toxicity. It should be given with care to those with diabetes mellitus. Care is also needed in elderly or debilitated patients, or those with renal or hepatic impairment or who have undergone adrenalectomy. Liberal fluid intake and frequent micturition are advised to reduce the risk of cystitis but care must be taken to avoid water retention and intoxication. Urine should be examined regularly for red cells, which may precede haemorrhagic cystitis. The haematological profile should be monitored regularly.

The use of cyclophosphamide in pregnancy should be avoided where possible.

Breast feeding. Cyclophosphamide has been detected in breast milk,[1] and there are reports of neutropenia,[2] and leucopenia and thrombocytopenia,[3] in infants who have been breast fed by women receiving cyclophosphamide. The American Academy of Pediatrics considers[4] that cyclophosphamide may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Wiernik PH, Duncan JH. Cyclophosphamide in human milk. *Lancet* 1971; **1:** 912.
2. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust* 1977; **1:** 383–4.
3. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* 1979; **71:** 165–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. *Residues* of cyclophosphamide or ifosfamide destroyed using alkaline hydrolysis in the presence of dimethylformamide showed no mutagenicity *in vitro*.[1] An alternative method, involving refluxing of cyclophosphamide with hydrochloric acid, neutralising, and then reacting with sodium thiosulfate, was effective for the degradation of cyclophosphamide, but residues from ifosfamide were still highly mutagenic *in vitro* and this second method should therefore not be used to degrade ifosfamide.

Urine and faeces produced for up to 72 hours and 5 days respectively after an oral dose of cyclophosphamide should be handled wearing protective clothing.[2] As cyclophosphamide was present in sweat and saliva, protective clothing was advised for 72 hours after a dose when bathing the patient or carrying out oral procedures.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Cyclophosphamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Since cyclophosphamide must undergo hepatic metabolism before it is active, interactions are possible with drugs that inhibit or stimulate the mixed function oxidase enzymes responsible. There may be an increased risk of cardiotoxicity in patients who have also received doxorubicin or other cardiotoxic drugs.

Allopurinol. Although the Boston Collaborative Drug Surveillance Program reported an increased incidence of bone-marrow depression in patients given allopurinol with cyclophosphamide than in those given cyclophosphamide without allopurinol (15 of 26 compared with only 6 of 32),[1] a subsequent study in patients given combination chemotherapy, including cyclophosphamide, for lymphomas failed to find any difference in the nadirs of the platelet and white blood cell counts in cycles in which allopurinol was given.[2] Although allopurinol pretreatment in 4 patients resulted in a longer cyclophosphamide half-life in a study in 26 patients given cyclophosphamide, urinary excretion of cyclophosphamide was unchanged.[3] A longer cyclophosphamide half-life was also seen in a study in children given allopurinol.[4]

1. Boston Collaborative Drug Surveillance Program. Allopurinol and cytotoxic drugs: interaction in relation to bone marrow depression. *JAMA* 1974; **227:** 1036–40.
2. Stolbach L, *et al.* Evaluation of bone marrow toxic reaction in patients treated with allopurinol. *JAMA* 1982; **247:** 334–6.
3. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.
4. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Antibacterials. *Chloramphenicol* given before cyclophosphamide prolonged the mean cyclophosphamide serum half-life from 7.5 to 11.5 hours and reduced the peak activity in all of 5 subjects.[1] Giving *sulfaphenazole* before cyclophosphamide significantly inhibited the rate of biotransformation of cyclophosphamide in 2 of 7 subjects and enhanced it in 2; it remained unchanged in 3. A study in patients with non-Hodgkin's lymphoma found that giving *ciprofloxacin* before cyclophosphamide affected pharmacokinetic parameters of cyclophosphamide. The area under the concentration-time curve (AUC) of cyclophosphamide was increased and clearance was lower; AUC of the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, was decreased and clearance increased.[2]

1. Faber OK, *et al.* The effect of chloramphenicol and sulphaphenazole on the biotransformation of cyclophosphamide in man. *Br J Clin Pharmacol* 1975; **2:** 281–5.
2. Afsharian P, *et al.* The effect of ciprofloxacin on cyclophosphamide pharmacokinetics in patients with non-Hodgkin lymphoma. *Eur J Haematol* 2005; **75:** 206–11.

Anticoagulants. For reference to the interaction of cyclophosphamide with *warfarin*, see p.1429.

Antifungals. Analysis of cyclophosphamide metabolism in patients enrolled in a study comparing itraconazole with fluconazole found that those given itraconazole had higher exposure to toxic metabolites of cyclophosphamide. Both the antifungals appeared to alter cyclophosphamide metabolism and the authors cautioned against use of azole antifungals with antineoplastics that are metabolised via cytochrome P450 isoenzymes.[1]

1. Marr KA, *et al.* Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; **103:** 1557–9.

Barbiturates. Although patients receiving cyclophosphamide developed higher peak plasma concentrations of active cyclophosphamide metabolites when given enzyme-inducing agents such as barbiturates, the active metabolites also disappeared rapidly.[1]

1. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.

Chlorpromazine. The half-life of cyclophosphamide was about 200% greater in 2 children also taking chlorpromazine than in children not given the phenothiazine.[1]

1. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Ciclosporin. For reference to the effect of cyclophosphamide on ciclosporin concentrations, see Interactions, Antineoplastics, p.1826.

Colony-stimulating factors. Fatal respiratory insufficiency associated with alveolar fibrosis developed in an infant given cyclophosphamide and doxorubicin followed by *filgrastim*.[1] Since pulmonary toxicity with cyclophosphamide is normally associated with high cumulative doses it was suggested that in this case the effects might have been exacerbated by the granulocyte colony-stimulating factor. (The pulmonary toxicity of bleomycin has also been suggested to be exacerbated by colony-stimulating factors, as discussed on p.688).

1. van Woensel JBM, *et al.* Acute respiratory insufficiency during doxorubicin, cyclophosphamide, and G-CSF therapy. *Lancet* 1994; **344:** 759–60.

Corticosteroids. Single doses of *prednisone* have been found to inhibit the activation of cyclophosphamide but after longer-term treatment the rate of activation has increased.[1] A study in children found that pretreatment with *dexamethasone* was associated with increased clearance of cyclophosphamide and a decrease in its half-life relative to children not given the corticosteroid.[2]

1. Faber OK, Mouridsen HT. Cyclophosphamide activation and corticosteroids. *N Engl J Med* 1974; **291:** 211.
2. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Gastrointestinal drugs. In a retrospective study in patients receiving high-dose cyclophosphamide, cisplatin, and carmustine,[1] the area under the plasma-concentration time curve (AUC) for cyclophosphamide (measured as the parent compound) was 17% lower when *ondansetron* rather than prochlorperazine was added to the antiemetic regimen. In addition, the AUC for cisplatin was 10% higher with the ondansetron regimen. In a similar study,[2] the AUCs for both cyclophosphamide and cisplatin were lower in patients receiving an antiemetic regimen including ondansetron rather than prochlorperazine. The authors of both studies noted that the relevance of these findings to toxicity and antitumour effect of the antineoplastics remained to be determined.

1. Gilbert CJ, *et al.* Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 1998; **42:** 497–503.
2. Cagnoni PJ, *et al.* Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant* 1999; **24:** 1–4.

NSAIDs. Acute life-threatening water intoxication was reported in a patient given low-dose cyclophosphamide with *indometacin*.[1] The patient had previously received treatment with cyclophosphamide (for multiple myeloma) without significant adverse effect.

1. Webberley MJ, Murray JA. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* 1989; **65:** 950–2.

Suxamethonium. For reference to a possible interaction between cyclophosphamide and suxamethonium, see under Suxamethonium Chloride, p.1911.

Pharmacokinetics

After oral doses, cyclophosphamide is well absorbed from the gastrointestinal tract with a bioavailability greater than 75%. It is widely distributed in the tissues and crosses the blood-brain barrier. It undergoes activation by the mixed function oxidase systems in the liver. The initial metabolites are 4-hydroxycyclophosphamide and its acyclic tautomer, aldophosphamide, which both undergo further metabolism; aldophosphamide may undergo non-enzymatic conversion to active phosphoramide mustard. Acrolein is also produced and may be responsible for bladder toxicity. Cyclophosphamide is excreted principally in urine, as metabolites and some unchanged drug. It crosses the placenta, and is found in breast milk.

◊ Reviews.

1. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
2. de Jonge ME, *et al.* Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet* 2005; **44:** 1135–64.

Absorption. Cyclophosphamide was detected in the urine of 5 patients after application to intact skin, showing that cyclophosphamide can be absorbed via this route.[1] Absorption continued after the site of application had been cleaned, suggesting that cyclophosphamide had penetrated subcutaneous lipid and was slowly released to the circulation from this depot. Cyclophosphamide was also identified in the urine of 2 oncology nurses but appeared more quickly than in patients, suggesting a faster route of absorption, perhaps by inhalation of aerosols generated during dissolution of the drug.

1. Hirst M, *et al.* Occupational exposure to cyclophosphamide. *Lancet* 1984; **i:** 186–8.

Uses and Administration

Cyclophosphamide is an antineoplastic that is converted in the body to active alkylating metabolites with properties similar to those of chlormethine (p.698). It also possesses marked immunosuppressant properties.

Cyclophosphamide is widely used, often with other agents, in the treatment of malignant diseases as indicated by the cross-references below. It is given for Burkitt's and other non-Hodgkin's lymphomas, multiple myeloma, and mycosis fungoides. It is also used in gestational trophoblastic tumours and malignancies of the brain, breast, endometrium, lung, and ovary; in childhood malignancies such as neuroblastoma, retinoblastoma, Wilms' tumour; and in sarcomas and some leukaemias.

The immunosuppressant properties of cyclophosphamide have been used in organ and tissue transplantation. It has also been used in the management of disorders thought to have an auto-immune component including amyloidosis, Behçet's syndrome, glomerular kidney disease, idiopathic thrombocytopenic purpura, aplastic anaemia, cryptogenic fibrosing alveolitis, polymyositis, scleroderma, SLE, and vasculitic syndromes including the Churg-Strauss syndrome, polyarteritis nodosa, and Wegener's granulomatosis, as indicated by the cross references below.

Cyclophosphamide is usually given orally or by intravenous injection.

In the BP 2008 the content of Cyclophosphamide Injection is expressed in terms of the equivalent amount of anhydrous cyclophosphamide whereas the content of Cyclophosphamide Tablets is given in terms of the monohydrate; the USP 31 expresses content in terms of anhydrous cyclophosphamide for both injection and tablets. Confusion has arisen when patients were changed from a preparation in which the content was expressed as the monohydrate to one in which it was expressed as the anhydrous substance (see Effects on the Bladder, above). 53.45 mg of cyclophosphamide monohydrate is equivalent to 50 mg of anhydrous cyclophosphamide. *Doses below are given in terms of anhydrous cyclophosphamide.*

The dosage given may vary considerably depending on the disease being treated, the condition of the patient including the state of the bone marrow, and use with radiotherapy or other chemotherapy. The white cell count is usually used to guide the dose.

In the UK, examples of licensed regimens are:

- *low-dose*: cyclophosphamide 2 to 6 mg/kg weekly as a single intravenous dose or in divided oral doses
- *moderate-dose*: 10 to 15 mg/kg weekly as a single intravenous dose.
- *high-dose*: 20 to 40 mg/kg as a single intravenous dose every 10 to 20 days, although higher doses have been used

Alternative regimens include:

- 100 to 300 mg daily in divided oral doses
- 80 to 300 mg/m^2 daily as a single intravenous dose
- 300 to 600 mg/m^2 weekly as a single intravenous dose
- 600 to 1500 mg/m^2 as a single intravenous dose or short infusion at 10 to 20 day intervals

The use of mesna is generally recommended with single doses of cyclophosphamide over 2 g, but one manufacturer suggests its use with doses as low as 10 mg/kg.

In the USA, an initial dose of 40 to 50 mg/kg has been licensed for single agent therapy of malignancy, given intravenously in divided doses over 2 to 5 days although in practice treatment of malignancy will generally be with combination regimens. Other licensed regimens include:

- 3 to 5 mg/kg twice weekly intravenously
- 10 to 15 mg/kg every 7 to 10 days intravenously
- 1 to 5 mg/kg daily orally

A daily oral dose of 2 to 3 mg/kg has been used in children with minimal change nephropathy leading to the nephrotic syndrome, in whom corticosteroids have been unsuccessful.

In patients who are to undergo bone marrow transplantation very high doses of cyclophosphamide such as 60 mg/kg daily for 2 days may be given as part of the conditioning regimen.

Cyclophosphamide has also been given intramuscularly, intraperitoneally, and intrapleurally, as well as intra-arterially, and by local perfusion (but passage through the liver is required for its activation—see Pharmacokinetics, above). A liquid preparation of cyclophosphamide for oral use may be prepared using the powder for injection.

Regular blood counts are essential during therapy with cyclophosphamide and treatment should be withdrawn or delayed if leucopenia or thrombocytopenia becomes severe (see also Bone-marrow Depression, p.639). Patients should be adequately hydrated and urine output maintained.

Amyloidosis. Although there is no unequivocally effective treatment for amyloidosis (p.743), cyclophosphamide may reduce the decline in renal function and prolong survival;[1-3] it has also been used with epirubicin and carmustine to suppress the disease in a patient who had undergone heart transplantation for cardiac amyloid.[4] Good responses have also been reported to cyclophosphamide given in a regimen with thalidomide and dexamethasone.[5]

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. Chevrel G, *et al.* Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatology (Oxford)* 2001; **40:** 821–5.
4. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
5. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.

Blood disorders, non-malignant. Cyclophosphamide has been used in patients with idiopathic thrombocytopenic purpura (p.1505), but cytotoxic immunosuppressants tend to be a treatment of last resort. Responses generally occur within 8 weeks.[1] In patients with refractory life-threatening disease, high-dose cyclophosphamide[1] may be tried. Combination chemotherapy including cyclophosphamide has also produced responses in a few patients.[2]

In the management of warm auto-immune haemolytic anaemia (p.1043) low-dose cyclophosphamide may be used in patients refractory to corticosteroids and splenectomy. A small number of patients with severe refractory disease have been treated with high-dose cyclophosphamide with some success.[3]

Cyclophosphamide is often used in preparation for bone marrow transplantation in patients with aplastic anaemia (p.1042), and complete remission has also been reported with high-dose cyclophosphamide alone.[4,5] However, a randomised trial[6] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those given cyclophosphamide. Further follow-up[7] also found that relapse rates were no different.

Cyclophosphamide with a corticosteroid has been tried in the rare condition of acquired haemophilia (p.1048).

1. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126:** 307–14.
2. Figueroa M, *et al.* Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; **328:** 1226–9.
3. Moyo VM, *et al.* High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. *Blood* 2002; **100:** 704–6.
4. Brodsky RA, *et al.* Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med* 2001; **135:** 477–83.
5. Savage WJ, *et al.* Treatment of hepatitis-associated aplastic anemia with high-dose cyclophosphamide. *Pediatr Blood Cancer* 2007; **49:** 947–51.
6. Tisdale JF, *et al.* High-dose cyclophosphamide in severe aplastic anaemia: a randomised trial. *Lancet* 2000; **356:** 1554–9.
7. Tisdale JF, *et al.* Late complications following treatment for severe aplastic anemia (SAA) with high-dose cyclophosphamide (Cy): follow-up of a randomized trial. *Blood* 2002; **100:** 4668–70.

Cogan's syndrome. For reference to the use of cyclophosphamide with corticosteroids for Cogan's syndrome, see p.1502.

Connective tissue and muscular disorders. Cyclophosphamide is one of a number of immunosuppressants that have been tried for disease control in Behçet's syndrome (p.1499); such drugs may permit a reduction in the use of corticosteroids, although they carry their own risks of toxicity. In polymyositis (p.1510) cyclophosphamide may have a role where there is lung disease; the role of immunosuppressants other than azathioprine or methotrexate is poorly defined. In patients with SLE (p.1513), cyclophosphamide has been used with some success for severe disease or disease refractory to corticosteroids alone, and appears to be more effective than corticosteroids for lupus nephritis.

Kidney disorders, non-malignant. Cyclophosphamide is used with corticosteroids in the treatment of some forms of glomerular kidney disease (p.1504). In children with nephrotic syndrome, oral cyclophosphamide 2 to 3 mg/kg daily for 8 weeks may be added to a course of corticosteroid therapy in relapsing disease; intravenous cyclophosphamide 500 mg/m^2 monthly for 6 months also substantially reduces the risk of relapse.[1] Addition of cyclophosphamide to corticosteroid therapy also improves the prospect of remission in focal glomerulosclerosis. Oral cyclophosphamide helps to stabilise progressive disease in patients with membranous nephropathy[2] although intermittent intravenous pulses are reported to be ineffective.[3] Such treatment is usually reserved for those whose disease is severe and progressive enough to justify it, but is probably better tolerated than other alkylating agents such as chlorambucil.[4] Cyclophosphamide has been given with methylprednisolone for rapidly progressive glomerulonephritis,[5] and has been used as part of the aggressive management of renal lesions in Goodpasture's syndrome.

1. Hodson EM *et al.* Non-corticosteroid treatment for nephrotic syndrome in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 24/07/08).
2. Falk RJ, *et al.* Treatment of progressive membranous glomerulopathy: a randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. *Ann Intern Med* 1992; **116:** 438–45.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
4. Schieppati A, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester; John Wiley; 2004 (accessed 12/05/05).
5. Bruns FJ, *et al.* Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 1989; **86:** 400–6.

Liver disorders, non-malignant. For mention of the use of cyclophosphamide in auto-immune hepatitis inadequately controlled by corticosteroids and azathioprine see Chronic Active Hepatitis, p.1501.

Lung disorders, non-malignant. Cyclophosphamide may be useful with corticosteroids in patients with cryptogenic fibrosing alveolitis, as mentioned under Diffuse Parenchymal Lung Disease, p.1502.

Malignant neoplasms. Cyclophosphamide is one of the most widely used drugs for the chemotherapy of malignancy, and mention of its role may be found in the discussions of the management of gestational trophoblastic tumours (p.650); the non-Hodgkin's lymphomas, including AIDS-related lymphoma, Burkitt's lymphoma, and mycosis fungoides (p.656, p.657, p.657, p.657); malignancies of the brain (p.660), breast (p.661), endometrium (p.663), lung (p.668), ovary (p.670) and thymus (p.674); multiple myeloma (p.658); Wilms' tumour, neuroblastoma, and retinoblastoma (p.667, p.674, and p.675 respectively); and sarcomas of bone (p.675) and rhabdomyosarcoma (p.676). Cyclophosphamide is also used in the management of acute lymphoblastic leukaemia (p.651) and chronic lymphocytic leukaemia (p.653).

Neuromuscular disorders. Cyclophosphamide has been tried in myasthenia gravis (p.629) in patients who require immunosuppressants but are intolerant of or unresponsive to corticosteroids and azathioprine. Cyclophosphamide has also been tried in regimens for the management of multiple sclerosis (p.892), but the reported benefits have generally been slight and outweighed by toxicity, such that it is usually reserved for patients with severe disease resistant to standard therapies.

References.

1. De Feo LG, *et al.* Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle Nerve* 2002; **26:** 31–6.
2. Drachman DB, *et al.* Treatment of refractory myasthenia: "rebooting" with high-dose cyclophosphamide. *Ann Neurol* 2003; **53:** 29–34.
3. Portaccio E, *et al.* Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. *Multiple Sclerosis* 2003; **9:** 446–50.
4. Zephir H, *et al.* Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. *J Neurol Sci* 2004; **218:** 73–7.
5. La Mantia L, *et al.* Cyclophosphamide for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Ocular disorders, non-malignant. Immunosuppressive agents, including cyclophosphamide, have been used in scleritis and uveitis (see p.1512 and p.1515) unresponsive to corticosteroids in tolerable doses.

Organ and tissue transplantation. Cyclophosphamide is used in high doses, usually with busulfan or irradiation, in conditioning regimens for bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811). It has been tried as part of immunosuppressant regimens after transplantation of heart grafts (p.1812).

Paraquat poisoning. For reference to the use of cyclophosphamide in paraquat poisoning, see p.2048.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Immunosuppressive therapy, including cyclophosphamide,[1,2] has been used with corticosteroids to permit a reduction in corticosteroid dosage. Cyclophosphamide with a corticosteroid is also reported to be of value in ocular mucous membrane pemphigoid,[3] although treatment may not completely prevent cicatrisation.[4] Oral cyclophosphamide is considered an alternative to azathioprine in pemphigus vulgaris and pulsed intravenous doses might be considered in severe or recalcitrant cases.[5] There is less support for cyclophosphamide in bullous pemphigoid and it should only be considered if other treatments have failed or are contra-indicated.[6] However, oral or intravenous cyclophosphamide with corticosteroids may be considered for first-line treatment of severe or rapidly progressive mucous membrane pemphigoid.[7]

1. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; **128:** 1626–30.
2. Itoh T, *et al.* Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; **134:** 931–3.
3. Kirtschig G, *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138:** 380–4.
4. Elder MJ, *et al.* Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; **79:** 264–6.
5. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37.
Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 21/02/07)
6. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21.
Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 21/02/07)
7. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; **6:** 93–103.

Rheumatoid arthritis. Cyclophosphamide has been used as a disease-modifying antirheumatic drug in rheumatoid arthritis (p.11), usually in patients with severe disease unresponsive to other drugs; its severe toxicity limits its usefulness.[1] It is of most value in controlling antibody-mediated systemic complications of the disease such as vasculitis[2] through inhibition of B-cell function.

1. Suarez-Almazor ME, *et al.* Cyclophosphamide for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
2. Choy E, Kingsley G. How do second-line agents work? *Br Med Bull* 1995; **51:** 472–92.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. Cyclophosphamide is one of a number of cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy; its use has been limited by toxicity.

Scleroderma. As discussed on p.1817 the role of drug treatment for scleroderma is not well determined, but cyclophosphamide may be useful with or without a corticosteroid for patients with lung involvement.

Vasculitic syndromes. Treatment of the systemic vasculitides has revolved around the use of corticosteroids and cyclophosphamide. The benefits are uncertain in polyarteritis nodosa (p.1510) and Takayasu's arteritis (p.1514), but the benefits of combined therapy are generally accepted in Churg-Strauss syndrome (p.1501) and microscopic polyangiitis (p.1510), and cyclophosphamide is the mainstay of effective treatment of Wegener's granulomatosis (p.1515). A number of regimens are in use; in particular intermittent high-dose intravenous ('pulsed') use is being evaluated in comparison with continuous therapy.[1]

1. Richmond R, *et al.* Optimisation of cyclophosphamide therapy in systemic vasculitis. *Clin Pharmacokinet* 1998; **34:** 79–90.

Preparations

BP 2008: Cyclophosphamide Injection; Cyclophosphamide Tablets;
USP 31: Cyclophosphamide for Injection; Cyclophosphamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciclokebir; Endoxan†; Genoxal†; ***Austral.:*** Cycloblastin; Endoxan; ***Austria:*** Endoxan; ***Belg.:*** Endoxan; ***Braz.:*** Ciclodrax†; Cyclan†; Fosfaseron†; Genuxal; ***Canad.:*** Cytoxan; Procytox; ***Chile:*** Endoxan; Ledoxina; ***Cz.:*** Cytoxan†; Endoxan; ***Denm.:*** Carloxan†; Sendoxan; ***Fin.:*** Sendoxan; ***Fr.:*** Endoxan; ***Ger.:*** Cyclostin†; Endoxan; ***Gr.:*** Endoxan; ***Hong Kong:*** Endoxan; ***Hung.:*** Cytoxan; Endoxan; ***India:*** Cycloxan; Endoxan; Oncophos; ***Indon.:*** Endoxan; ***Irl.:*** Endoxana; ***Israel:*** Cytophosphan; Cytoxan†; Endoxan; ***Ital.:*** Endoxan; ***Jpn:*** Endoxan†; ***Malaysia:*** Endoxan†; ***Mex.:*** Genoxal†; Hidrofosmin; Ledoxina; ***Neth.:*** Endoxan; ***Norw.:*** Sendoxan; ***NZ:*** Cycloblastin; Cytoxan; Endoxan; ***Philipp.:*** Cytoxan; Endoxan; Ledoxan; Xyclomed; ***Pol.:*** Endoxan; ***Port.:*** Endoxan; ***S.Afr.:*** Cycloblastin; Endoxan; ***Singapore:*** Alkyloxan†; Endoxan; ***Spain:*** Genoxal; ***Swed.:*** Sendoxan; ***Switz.:*** Endoxan; ***Thai.:*** Endoxan; Ledoxan; ***Turk.:*** Alkyloxan; Endoxan; ***UK:*** Endoxana†; ***USA:*** Cytoxan†; Neosar; ***Venez.:*** Biodoxan.

Cytarabine *(BAN, USAN, rINN)*

Arabinosylcytosine; Ara-C; Citarabin; Citarabina; Citarabinas; Cytarabin; Cytarabina; Cytarabinum; Cytosine Arabinoside; NSC-63878 (cytarabine hydrochloride); Sitarabin; Sytarabiini; U-19920; U-19920A (cytarabine hydrochloride); WR-28453. 1-β-D-Arabinofuranosylcytosine; 4-Amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one.

Цитарабин

$C_9H_{13}N_3O_5$ = 243.2.

CAS — 147-94-4 (cytarabine); 69-74-9 (cytarabine hydrochloride).

ATC — L01BC01.

ATC Vet — QL01BC01.

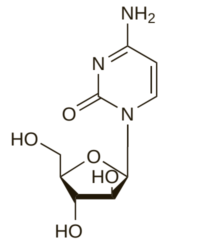

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Chin. includes the hydrochloride.

Ph. Eur. 6.2 (Cytarabine). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cytarabine). An odourless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform. Protect from light.

Incompatibility. Although cytarabine has been stated in the literature to be incompatible with solutions of fluorouracil[1,2] and methotrexate[2] some studies have reported it to be stable for some hours when mixed with the latter.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The major dose-limiting adverse effect of cytarabine is bone-marrow depression, manifest as leucopenia (particularly granulocytopenia), thrombocytopenia, and anaemia, sometimes with striking megaloblastic changes. Myelosuppression appears to be more evident after continuous infusions. Leucopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further 10 days.

Gastrointestinal disturbances may occur: nausea and vomiting may be more severe when doses are given rapidly (but other adverse effects are reported to be worse when the drug is given by infusion). Other adverse effects reported include hepatic dysfunction, renal dysfunction, neurotoxicity, bleeding complications, rashes, oral and anal ulceration, gastrointestinal haemorrhage, oesophagitis, and conjunctivitis. A syndrome of bone and muscle pain, fever, malaise, conjunctivitis, and rash, sometimes described as flu-like, has been reported 6 to 12 hours after cytarabine doses, and may be treated or prevented with corticosteroids. Anaphylactoid reactions and pancreatitis have occurred rarely. There may be local pain, cellulitis, and thrombophlebitis at the site of injection.

Intrathecal use of the liposomal cytarabine formulation commonly causes chemical arachnoiditis manifesting as neck stiffness or pain, nausea, vomiting, headache, and fever. Dexamethasone should be used prophylactically to reduce the incidence and severity of this complication. Other rare adverse effects include encephalopathy, and focal seizures. Intrathecal use of conventional cytarabine formulations has rarely been associated with severe spinal cord toxicity, necrotising encephalopathy, blindness, and other neurotoxicities. If given intrathecally, preservative-free diluents must be used.

High-dose therapy has been associated with particularly severe gastrointestinal and CNS effects, including severe ulceration of the gastrointestinal tract, pneumatosis cystoides leading to peritonitis, necrotising colitis and bowel necrosis, peripheral neuropathy, and cerebral and cerebellar dysfunction, with personality changes, somnolence, and coma. There may also be corneal toxicity leading to punctate keratitis and haemorrhagic conjunctivitis, sepsis, liver abscess, severe skin rash leading to desquamation, alopecia, and cardiac disorders including pericarditis and fatal cardiomyopathy. Pulmonary oedema, sometimes fatal, has occurred.

Cytarabine is teratogenic in *animals* (but see Pregnancy, below).

In addition to frequent white blood cell and platelet counts, blood-uric acid should be monitored because of the risk of hyperuricaemia secondary to lysis of neoplastic cells, and renal and hepatic function should be periodically assessed. Cytarabine should be given with care to patients with impaired liver function; dosage reduction may be necessary.

◊ The toxicity of cytarabine has been reviewed.[1] The principal toxicity of standard dosage regimens is myelosuppression but bleeding complications and gastrointestinal toxicity are also major problems at standard doses. With the high-dose regimens neurological toxicity may be dose-limiting: severe and sometimes irreversible symptoms have been seen in some 6 to 10% of patients receiving a cumulative dose of 36 g/m^2. Ocular toxicity may occur in up to 80% of patients at the highest doses. Since cytarabine toxicity is largely dose-related, low-dose cytarabine is generally well tolerated, even in elderly patients (who are more susceptible): its only significant toxicity is myelosuppression.

1. Stentoft J. The toxicity of cytarabine. *Drug Safety* 1990; **5:** 7–27.

Effects on the nervous system. Although paraplegia has been reported with intrathecal cytarabine[1] (see also under Benzyl Alcohol, p.1631) and peripheral neuropathy has occurred in a patient who had received only conventional intravenous doses,[2] the majority of cases of neurotoxicity associated with cytarabine appear to be in patients given high-dose regimens.[3-7] Although some cases have manifested as demyelinating peripheral neuropathy,[3,4] including a syndrome of painful legs and involuntary movements in the toes which showed some response to carbamazepine,[3] most studies have reported in particular a syndrome of cerebellar toxicity,[5-8] with symptoms such as dysarthria, nystagmus, and ataxia. Toxicity appears to be dose-related: in one series[5] CNS toxicity occurred in none of 12 patients given total doses of up to 24 g/m^2 of cytarabine, 3 of 19 receiving 36 g/m^2, and 1 of 12 given 48 g/m^2, none of which were life-threatening or irreversible, whereas 4 of 6 given 54 g/m^2 (as 4.5 g/m^2 every 12 hours for 12 doses) developed neurotoxicity, which was fatal in one and irreversible in another. However, persistent, severe cerebellar toxicity has also been reported in a patient who had received a total dose of only 36 g/m^2 (as 3 g/m^2 every 12 hours).[8] There is some evidence[6] that patients aged over 50, and those who have recently received conventional-dose cytarabine[7] may be at increased risk. Intracranial hypertension (pseudotumor cerebri) has occurred rarely.[9]

1. Saleh MN, *et al.* Intrathecal cytosine arabinoside-induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86:** 729–30.
2. Russell JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974; **4:** 652–3.
3. Malapert D, Degos JD. Jambes douloureuses et orteils instables: neuropathie induite par la cytarabine. *Rev Neurol (Paris)* 1989; **145:** 869–71.
4. Openshaw H, *et al.* Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia. *Cancer* 1996; **78:** 1899–1905.
5. Lazarus HM, *et al.* Central nervous system toxicity of high-dose systemic cytosine arabinoside. *Cancer* 1981; **48:** 2577–82.
6. Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9:** 23–8.
7. Barnett MJ, *et al.* Neurotoxicity of high-dose cytosine arabinoside. *Prog Exp Tumor Res* 1985; **29:** 177–82.
8. Dworkin LA, *et al.* Cerebellar toxicity following high-dose cytosine arabinoside. *J Clin Oncol* 1985; **3:** 613–16.
9. Fort JA, Smith LD. Pseudotumor cerebri secondary to intermediate-dose cytarabine HCl. *Ann Pharmacother* 1999; **33:** 576–8.

Effects on the skin. A syndrome of pain and erythema of the palms and soles, progressing to bullae and desquamation, has been seen in patients receiving intermediate- or high-dose cytarabine.[1-3] The syndrome is similar to the palmar-plantar erythrodysesthesia syndrome (p.639) reported in patients receiving chemotherapy not including cytarabine,[4] although some considered the two forms of toxicity distinct.[5] Cutaneous small vessel necrotising vasculitis has been reported after high-dose therapy with cytarabine.[6]

1. Baer MR, *et al.* Palmar-plantar erythrodysesthesia and cytarabine. *Ann Intern Med* 1985; **102:** 556.
2. Peters WG, Willemze R. Palmar-plantar skin changes and cytarabine. *Ann Intern Med* 1985; **103:** 805.
3. Calista D, Landi C. Cytarabine-induced acral erythema: a localized form of toxic epidermal necrolysis? *J Eur Acad Dermatol Venereol* 1998; **10:** 274–5.
4. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
5. Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103:** 303–4.
6. Ahmed I, *et al.* Cytosine arabinoside-induced vasculitis. *Mayo Clin Proc* 1998; **73:** 239–42.

The symbol † denotes a preparation no longer actively marketed

Pregnancy. Although there has been a report of limb and ear deformities in the infant of a woman given cytarabine at the estimated time of conception and 4 to 8 weeks later,[1] no congenital abnormalities were noted in 17 infants, 5 therapeutic abortions, and one still-birth (after pre-eclamptic toxaemia) resulting from over 20 known cases in which cytarabine was given during pregnancy.[2]

1. Wagner VM, *et al.* Congenital abnormalities in baby born to cytarabine treated mother. *Lancet* 1980; **ii:** 98–9.
2. Morgenstern G. Cytarabine in pregnancy. *Lancet* 1980; **ii:** 259.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antifungals. Cytarabine has been reported to inhibit the action of *flucytosine*—see p.534.

Antineoplastics. Acute pancreatitis has been reported in patients given cytarabine who had previously received *asparaginase* therapy.[1] Subclinical damage to the pancreas by asparaginase may have rendered it susceptible to cytarabine.

For a report of hepatic dysfunction in patients who had received cytarabine and *daunorubicin* see under Daunorubicin Hydrochloride, p.709.

Giving cytarabine after *fludarabine* is reported to result in a fivefold increase in intracellular cytarabine concentrations in leukaemic cells,[2] producing improved clinical response rates.

1. Altman AJ, *et al.* Acute pancreatitis in association with cytosine arabinoside therapy. *Cancer* 1982; **49:** 1384–6.
2. Avramis VI, *et al.* Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. *Clin Cancer Res* 1998; **4:** 45–52.

Pharmacokinetics

Cytarabine is not effective orally due to rapid deamination in the gastrointestinal tract; less than 20% of an oral dose is absorbed. After intravenous injection it disappears rapidly from the plasma with an initial half-life of about 10 minutes; the terminal elimination half-life ranges from 1 to 3 hours. It is converted by phosphorylation to an active form, which is rapidly deaminated, mainly in the liver and the kidneys, to inactive 1-β-D-arabinofuranosyluracil (uracil arabinoside, ara-U). The majority of an intravenous dose is excreted in the urine within 24 hours, mostly as the inactive metabolite with about 10% as unchanged cytarabine.

There is only moderate diffusion of cytarabine across the blood-brain barrier after intravenous injection, but, because of low deaminase activity in the CSF, concentrations achieved after continuous intravenous infusion or intrathecal injection are maintained for longer in the CSF than are those in plasma, with a terminal elimination half-life of 3.5 hours. After intrathecal doses of the liposomal formulation, a terminal elimination half-life of 100 to 263 hours was seen. Cytarabine also crosses the placenta.

◊ References.

1. Slevin ML, *et al.* The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. *Br J Clin Pharmacol* 1981; **12:** 507–10.
2. DeAngelis LM, *et al.* Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992; **29:** 173–7.
3. Hamada A, *et al.* Clinical pharmacokinetics of cytarabine formulations. *Clin Pharmacokinet* 2002; **41:** 705–18.

Uses and Administration

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits the synthesis of deoxyribonucleic acid. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Cytarabine is one of the mainstays of the treatment of acute myeloid leukaemias, together with an anthracycline, (see p.652), and is used for the prophylaxis of meningeal leukaemia, as well as in regimens for consolidation, in patients with acute lymphoblastic leukaemia (p.651). It has also been investigated in the blast crisis of chronic myeloid leukaemia (p.653) and the myelodysplasias (p.654) (see also Low-dose Therapy, under Administration, below). It may be used in salvage regimens for Hodgkin's disease (p.655), as part of the complex regimens sometimes employed in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p.656), and for meningeal lymphoma.

Cytarabine is usually given intravenously. Higher doses can be tolerated when given by rapid injection rather than slow infusion, because of the rapid clearance of cytarabine, but there is little evidence of clinical advantage either way. Cytarabine may be given intrathecally for leukaemic or lymphomatous meningitis.

For the induction of remission in adults and children with acute leukaemias many dosage regimens have been used: 100 mg/m^2 twice daily by rapid intravenous injection, or 100 mg/m^2 daily by continuous intravenous infusion, have often been employed. These doses are generally given for 5 to 10 days, depending on therapeutic response and toxicity. Children reportedly tolerate high doses better than adults.

For maintenance 1 to 1.5 mg/kg once or twice weekly has been given intravenously or subcutaneously; other regimens have been used.

In the treatment of refractory disease high-dose regimens have been used, with cytarabine given in doses of up to 3 g/m^2 every 12 hours for up to 6 days. These doses should be given by intravenous infusion over at least 1 hour.

In leukaemic meningitis cytarabine has been given intrathecally, often in a dose of 10 to 30 mg/m^2 every 2 to 4 days; it has also been used prophylactically. A liposomal formulation is available in some countries for intrathecal use, and permits less frequent dosing because of its longer duration of action: the recommended dose for lymphomatous meningitis is 50 mg intrathecally every 2 weeks for 5 doses then every 4 weeks for 5 doses.

White cell and platelet counts should be determined regularly during treatment with cytarabine and therapy should be stopped immediately if the count falls rapidly or to low values (see also Bone-marrow Depression, p.639).

Cytarabine ocfosfate is an orally active prodrug of cytarabine under investigation in chronic myeloid leukaemia.

Administration. INTRATHECAL. Intrathecal doses of the liposomal formulation of cytarabine result in prolonged drug exposure when compared with intrathecal doses of the conventional formulation (see Pharmacokinetics, above). In a randomised study,[1] the liposomal formulation given once every 2 weeks produced a higher response rate and improved Karnofsky score compared with the conventional formulation given twice a week in patients with lymphomatous meningitis secondary to lymphoma. The use of liposomal formulations intrathecally to treat leukaemic or lymphomatous meningitis has been reviewed.[2,3]

1. Glantz MJ, *et al.* Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol* 1999; **17:** 3110–16.
2. Rueda Domínguez A, *et al.* Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 2005; **7:** 232–8.
3. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother* 2008; **9:** 301–9.

LOW-DOSE THERAPY. Because of initial suggestions that low doses of cytarabine might induce differentiation and maturation of leukaemic cells, low-dose therapy has been tried in patients with myelodysplastic syndrome and acute myeloid leukaemia. Although complete remission may occur in about 20% of patients with myelodysplastic syndromes a similar proportion succumb to treatment-related mortality, and remissions do not appear to be particularly long-lasting. Bone-marrow suppression may be marked even at these doses.[1] Low-dose subcutaneous cytarabine (20 mg twice daily for 10 days, at intervals of 4 to 6 weeks) was found to be superior to hydroxycarbamide (with or without all-trans retinoic acid) in elderly patients with acute myeloid leukaemia. Although the authors considered the prognosis for these patients to still be unsatisfactory, they suggested that therapy with low-dose cytarabine could represent a baseline against which other promising treatments might be compared.[2]

1. Aul C, Gattermann N. The role of low-dose chemotherapy in myelodysplastic syndrome. *Leuk Res* 1992; **16:** 207–15.
2. Burnett AK, *et al.* The National Cancer Research Institute Haematological Oncology Study Group Adult Leukemia Working Party. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; **109:** 1114–24.

Leukoencephalopathy. There are anecdotal reports[1-3] of marked improvement in patients with progressive multifocal leukoencephalopathy secondary to AIDS or chemotherapy-induced immunosuppression who were given intravenous or intrathecal cytarabine. However, a randomised multicentre study[4] indicated that cytarabine was ineffective and had no role in this condition (see also Infections in Immunocompromised Patients, p.859). Others[5] have suggested that even intrathecal dosage may not provide adequate delivery of cytarabine to target cells, and that delivering the drug directly into the brain under pressure might be an alternative. Cytarabine has also been used with cidofovir.[6]

1. O'Riordan T, *et al.* Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* 1990; **20:** 51–4.
2. Portegies P, *et al.* Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1991; **337:** 680–1.
3. Nicoli F, *et al.* Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1992; **339:** 306.
4. Hall CD, *et al.* Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 1345–51.
5. Levy RM, *et al.* Convection-enhanced intraparenchymal delivery (CEID) of cytosine arabinoside (AraC) for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). *J Neurovirol* 2001; **7:** 382–5.
6. Terrier B, *et al.* Leucoencéphalite multifocale progressive en dehors du sida: efficacité de l'association cytarabine-cidofovir. *Rev Med Interne* 2007; **28:** 488–91.

Preparations

BP 2008: Cytarabine Injection;
USP 31: Cytarabine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aracytin†; Citagenin; ***Austria:*** Alexan; ARA-cell; ***Belg.:*** Cyta-Cell; Cytosar; DepoCyte; ***Braz.:*** Aracytin; Citab†; Citarax; Darbin; Serotabir†; Tabine†; ***Canad.:*** Cytosar; DepoCyt†; ***Chile:*** Alexan; Aracytin; Laracit; ***Cz.:*** Alcysten†; Alexan; Cytosar; DepoCyte; ***Denm.:*** Arabine; Cytosar†; DepoCyte; ***Fin.:*** Arabine; DepoCyte; ***Fr.:*** Aracytine; DepoCyte; ***Ger.:*** Alexan; ARA-cell; DepoCyte; Udicil; ***Gr.:*** Aracytin; Citabion; ***Hong Kong:*** Alexan; Cytosar; ***Hung.:*** Alexan; Cytosar; ***India:*** Biobin; Cytarine; ***Indon.:*** Cytosar-U; ***Irl.:*** Cytosar†; ***Israel:*** Alexan; Cytosar; ***Ital.:*** Aracytin; DepoCyte; Erpalfa; ***Jpn:*** Cylocide; Starasid; ***Malaysia:*** Cytosar-U; ***Mex.:*** Alexan†; Cytosar; Ifarab; Laracit; Medsara; Novumtrax; ***Neth.:*** Alexan; Cytosar; DepoCyte; ***Norw.:*** Cytosar†; DepoCyte; ***Philipp.:*** Cytosar-U; Leucyt; Tabine; ***Pol.:*** Alexan; Cytosar; DepoCyte; ***Port.:*** Alexan†; ARA-cell; Citaloxan; Cytosar; Depocyte; ***Rus.:*** Alexan (Алексан); Cytosar (Цитозар); ***S.Afr.:*** Alexan; Cytosar; ***Singapore:*** Alexan†; Cytosar†; ***Spain:*** DepoCyte; ***Swed.:*** Arabine; Cytosar†; DepoCyte; ***Switz.:*** Cytosar; ***Thai.:*** Alexan†; Cytarine; Cytosar; ***Turk.:*** Alexan; ARA-cell; Cytonal; ***UK:*** DepoCyte; ***USA:*** Cytosar-U†; DepoCyt; ***Venez.:*** Cytosar.

Dacarbazine *(BAN, USAN, rINN)*

Dacarbazina; Dacarbazinum; Dakarbatsiini; Dakarbazin; DIC; DTIC; Imidazole Carboxamide; NSC-45388; WR-139007. 5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide.

Дакарбазин

$C_6H_{10}N_6O$ = 182.2.

CAS — 4342-03-4 (dacarbazine); 64038-56-8 (dacarbazine citrate).

ATC — L01AX04.

ATC Vet — QL01AX04.

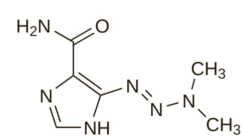

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Dacarbazine). A white or slightly yellowish, crystalline powder. Slightly soluble in water and in anhydrous alcohol; practically insoluble in dichloromethane. Store at 2° to 8°. Protect from light.

USP 31 (Dacarbazine). Store in airtight containers at 2° to 8°. Protect from light.

Incompatibility. Dacarbazine has been reported to be incompatible with hydrocortisone sodium succinate but not with the sodium phosphate.[1] It has been reported to be incompatible with heparin,[2] although only with concentrated dacarbazine solutions (25 mg/mL).

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Nelson RW, *et al.* Visual incompatibility of dacarbazine and heparin. *Am J Hosp Pharm* 1987; **44:** 2028.

Stability. References to the photodegradation of dacarbazine solution.[1-4] Dacarbazine is more sensitive to direct sunlight than to artificial lighting or diffuse daylight.

1. Stevens MFG, Peatey L. Photodegradation of solutions of the antitumour drug DTIC. *J Pharm Pharmacol* 1978; **30** (suppl): 47P.
2. Horton JK, Stevens MFG. Search for drug interactions between the antitumour agent DTIC and other cytotoxic agents. *J Pharm Pharmacol* 1979; **31** (suppl): 64P.
3. Kirk B. The evaluation of a light-protecting giving set. *Intensive Therapy Clin Monit* 1987; **8:** 78–86.
4. El Aatmani M, *et al.* Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2002; **59:** 1351–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Leucopenia and thrombocytopenia with dacarbazine, although usually moderate, may be severe. The nadir of the white cell count usually occurs 21 to 25 days after a dose. Anorexia, nausea, and vomiting occur in more than 90% of patients initially but tolerance may develop after repeated doses. Less frequent adverse effects include diarrhoea, skin reactions, alopecia, a flu-like syndrome, facial flushing and paraesthesia, headache, blurred vision, seizures, and rare but potentially fatal hepatotoxicity. There may be local pain at the injection site; extravasation produces pain and tissue damage. Anaphylaxis has occurred occasionally.

Dacarbazine should be used with caution in hepatic and renal impairment, and consideration given to reducing the dose. Haematological monitoring is required during therapy. Dacarbazine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. A report[1] of haemorrhagic cystitis associated with dacarbazine treatment for melanoma. The patient developed gross haematuria with inflammation and oedema of the bladder wall 2 weeks after completing 3 cycles of monotherapy with dacarbazine; the condition responded to symptomatic management with saline lavage and oral and intravenous hydration. Two subsequent transient episodes of haematuria resolved spontaneously.

1. Mohammadianpanah M, *et al.* Hemorrhagic cystitis in a patient receiving conventional doses of dacarbazine for metastatic malignant melanoma: case report and review of the literature. *Clin Ther* 2007; **29:** 1161–5.

Effects on the liver. Dacarbazine has been associated with fatal hepatic vascular toxicity, caused by thrombosis of the hepatic veins, necrosis, and extensive haemorrhage.[1] As the reaction usually occurs during the second course of dacarbazine it is thought to be immune mediated, and early corticosteroid treatment has been tried with a few reported cases of patient survival.[2] Other adverse hepatic effects have included[3] necrosis without inflammation, granulomatous hepatitis, and acute toxic hepatitis during the first course of dacarbazine. Morphological studies have suggested that dacarbazine may exert a toxic effect on the microfilamentous cytoskeleton of the hepatocytes.[3]

1. Ceci G, *et al.* Fatal hepatic vascular toxicity of DTIC: is it really a rare event? *Cancer* 1988; **61:** 1988–91.
2. Herishanu Y, *et al.* The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine. *Anticancer Drugs* 2002; **13:** 177–9.
3. Dancygier H, *et al.* Dacarbazine (DTIC)-induced human liver injury. *Gut* 1982; **23:** A447.

Handling. Dacarbazine is irritant; avoid contact with skin and mucous membranes.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Levodopa. For a report of dacarbazine reducing the effects of levodopa, see Antineoplastics, p.807.

Pharmacokinetics

Dacarbazine is poorly absorbed from the gastrointestinal tract. On intravenous injection it is rapidly distributed with an initial plasma half-life of about 20 minutes; the terminal half-life is reported to be about 5 hours. The volume of distribution is larger than body water content, suggesting localisation in some body tissues, probably mainly the liver. Only about 5% is bound to plasma protein. It crosses the blood-brain barrier to a limited extent; concentrations in CSF are about 14% of those in plasma. Dacarbazine is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP2E1 (and possibly in the tissues by CYP1A1) to its active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), which spontaneously decomposes to the major metabolite 5-aminoimidazole-4-carboxamide (AIC). About half of a dose is excreted unchanged in the urine by tubular secretion.

Uses and Administration

Dacarbazine is a cell-cycle non-specific antineoplastic that is thought to function as an alkylating agent after it has been activated in the liver. Dacarbazine is used mainly in the treatment of metastatic malignant melanoma (p.673). It is also given to patients with Hodgkin's disease (p.655), notably with doxorubicin, bleomycin, and vinblastine (ABVD). Dacarbazine is used with other drugs in the treatment of soft-tissue sarcoma (p.676), and may be given in neuroblastoma (p.674), Kaposi's sarcoma (p.675), and other tumours.

Dacarbazine is given by the intravenous route. Injections may be given over 1 to 2 minutes. The reconstituted solution can be further diluted with up to 300 mL of glucose 5% or sodium chloride 0.9% and given by infusion over 15 to 30 minutes.

Dacarbazine is licensed for use as a single agent for **metastatic melanoma** in doses of 2 to 4.5 mg/kg daily for 10 days, repeated at intervals of 4 weeks, or 200 to 250 mg/m^2 daily for 5 days, repeated at intervals of 3 weeks. It can also be given in a dose of 850 mg/m^2 by intravenous infusion at 3-week intervals. In the treatment of **Hodgkin's disease** doses of 150 mg/m^2 daily for 5 days repeated every 4 weeks, or 375 mg/m^2 every 15 days have been given with other agents. In the treatment of **soft-tissue sarcoma**, dacarbazine 250 mg/m^2 is given daily for 5 days repeated every 3 weeks; it is usually given with doxorubicin.

◊ References.

1. D'Incan M, Souteyrand P. Dacarbazine (Déticène). *Ann Dermatol Venereol* 2001; **128:** 517–25.
2. Eggermont AMM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? *Eur J Cancer* 2004; **40:** 1825–36.

Preparations

BP 2008: Dacarbazine Injection;
USP 31: Dacarbazine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Deticene†; Oncocarbil; ***Austral.:*** DTIC; ***Austria:*** DTIC-Dome; ***Braz.:*** Asercit†; Dacarb; ***Canad.:*** DTIC†; ***Chile:*** Deticene; ***Fin.:*** Dacatic; ***Fr.:*** Deticene; ***Ger.:*** Detimedac; ***Gr.:*** Dacarbion; Deticene; ***India:*** Dacarin; Decarb; DTIC†; ***Israel:*** Deticene; ***Ital.:*** Deticene; ***Malaysia:*** DTI†; ***Mex.:*** Deticene†; Detilem; Ifadac; ***Neth.:*** Deticene; ***NZ:*** DTIC-Dome†; ***Philipp.:*** Duticin; ***Port.:*** Deticene; Fauldetic; ***S.Afr.:*** DTIC-Dome; ***Swed.:*** DTIC; ***Switz.:*** Dacin; DTIC; ***Turk.:*** Deticene; ***UK:*** DTIC-Dome†; ***USA:*** DTIC-Dome.

Dactinomycin *(BAN, USAN, rINN)*

Actinomycin C_1; Actinomycin D; Dactinomicina; Dactinomycine; Dactinomycinum; Daktinomisin; Daktinomycin; Daktinomysiini; Daktynomycyna; Meractinomycin; NSC-3053. $N^{2.1},N^{2'.1'}$-(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyldicarbonyl)-bis[threonyl-D-valylprolyl(*N*-methylglycyl)(*N*-methylvaline) 1.5–3.1-lactone].

Дактиномицин

$C_{62}H_{86}N_{12}O_{16}$ = 1255.4.

CAS — 50-76-0.

ATC — L01DA01.

ATC Vet — QL01DA01.

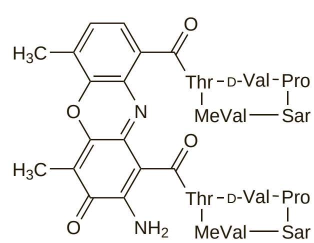

Description. Dactinomycin is an antineoplastic antibiotic produced by *Streptomyces parvulus* and other species of *Streptomyces.*

Cactinomycin (actinomycin C; HBF-386; NSC-18268) is a mixture of dactinomycin (actinomycin D) (10%), actinomycin C_2 (45%), and actinomycin C_3 (45%) produced by *Streptomyces chrysomallus.*

Pharmacopoeias. In *Chin., Int., Jpn, Pol.,* and *US.*

USP 31 (Dactinomycin). A bright red, somewhat hygroscopic, crystalline powder, affected by light and heat. It has a potency of not less than 950 and not more than 1030 micrograms/mg, calculated on the dried basis. Soluble in water at 10° and slightly soluble in water at 37°; freely soluble in alcohol; very slightly soluble in ether. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adsorption. Dactinomycin binds to cellulose ester filters,[1] and such filtration should be avoided.[2] Although it has been suggested that significant amounts of drug may be adsorbed to glass or plastic,[3] dactinomycin is reportedly compatible with glass and PVC infusion containers,[4] and giving into the tubing of a fast-running intravenous infusion is recommended—see Uses and Administration, below.

1. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Rapp RP, *et al.* Guidelines for the administration of commonly-used intravenous drugs—1984 update. *Drug Intell Clin Pharm* 1984; **18:** 218–32.
4. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Apart from nausea and vomiting adverse effects are often delayed, beginning 2 to 4 days after the completion of a course of treatment and reaching a maximum after 1 to 2 weeks. Fatalities have occurred. Bone-marrow depression and gastrointestinal effects (particularly stomatitis and diarrhoea) may prove dose-limiting. Bone-marrow depression is apparent 1 to 7 days after therapy and may be manifest first as thrombocytopenia; the nadir of the platelet and white cell counts usually occurs within 14 to 21 days, with recovery in 21 to 25 days. Other adverse effects include oral and gastrointestinal effects such as cheilitis, oesophagitis, gastrointestinal ulceration, and proctitis; fever, malaise, hypocalcaemia, erythema, myalgia, alopecia, pneumonitis, and kidney and liver abnormalities. Anaphylactoid reactions have occurred. Dactinomycin is very irritant and extravasation results in severe tissue damage.

The effects of radiotherapy are enhanced by dactinomycin and severe reactions may follow the use of high doses. Erythema and pigmentation of the skin may occur in areas previously irradiated. An increase in incidence of second primary tumours has been seen in patients treated with radiation and dactinomycin.

Dactinomycin should not be given to patients with varicella or herpes zoster, as severe and even fatal systemic disease may occur. Its use is best avoided in infants under 1 year as they are reported to be highly susceptible to the toxicity of dactinomycin. Blood counts and renal and hepatic function should be monitored frequently.

Effects on the liver. Although doses less than about 50 micrograms/kg or 1.5 mg/m^2 do not seem to be associated with an unacceptable degree of hepatotoxicity,[1] giving dactinomycin as a single dose of 60 micrograms/kg (about 1.8 mg/m^2) every 3 weeks to children with Wilms' tumour was associated with a high incidence of severe hepatotoxicity;[2] reduction of the dose to 45 micrograms/kg every 3 weeks reduced this incidence to levels comparable with a standard regimen of 15 micrograms/kg daily for 5 successive days.[3] Others have not seen such a high incidence of hepatotoxicity with doses of 60 micrograms/kg (despite some raised liver enzyme values), but in this case the high dose was given only every 6 weeks.[4] In general, dactinomycin should be given with caution to children with a history of antecedent liver damage, including abdominal irradiation or recent halothane anaesthesia.[1]

Reversible veno-occlusive disease has been seen particularly in children with Wilms' tumour who have received dactinomycin and vincristine. One study[5] found age of less than 1 year to be a risk factor and a study in children with rhabdomyosarcoma given dactinomycin, vincristine, and cyclophosphamide also found that young age (under 3 years) was associated with a greater risk of severe hepatic toxicity.[6] A literature review[7] noted a significant predominance of veno-occlusive disease in right-sided Wilms' tumour, possibly because the tumour mass could interfere with blood flow in the hepatic veins, which might make the liver more susceptible to the effects of dactinomycin.

1. Pritchard J, *et al.* Hepatotoxicity of actinomycin-D. *Lancet* 1989; **i:** 168.
2. D'Angio GJ. Hepatotoxicity with actinomycin D. *Lancet* 1987; **ii:** 104.
3. D'Angio GJ. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.
4. de Camargo B. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.

5. Bisogno G, *et al.* Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997; **29:** 245–51.
6. Arndt C, *et al.* Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; **22:** 1894–1901. Correction [dosage error]. *ibid.*; 3434.
7. Tornesello A, *et al.* Veno-occlusive disease of the liver in right-sided Wilms' tumours. *Eur J Cancer* 1998; **34:** 1220–3.

Handling. Dactinomycin is irritant; avoid contact with skin and mucous membranes.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Pharmacokinetics

Intravenous doses of dactinomycin are rapidly distributed with high concentrations in bone marrow and nucleated cells. It undergoes only minimal metabolism and is slowly excreted in urine and bile. The terminal plasma half-life is reported to be about 36 hours. It does not cross the blood-brain barrier but is thought to cross the placenta.

In children. A study[1] involving 31 patients aged between 1 and 20 years given dactinomycin in intravenous doses of 0.7 to 1.5 mg/m^2 found that the pharmacokinetics of the drug were variable, but could be described by a 3-compartment model. Peak plasma concentrations varied from 3.2 to 99.2 nanograms/mL, and both peak plasma concentration and exposure were inversely related to body-weight. Since there was evidence that exposure was also related to more severe toxicity, younger patients might be at greater risk with a regimen based on surface area; conversely the practice of capping the dose at 2 mg in older patients might result in underdosage.

For evidence that younger patients do experience more liver toxicity with dactinomycin, see Effects on the Liver, above.

1. Veal GJ, *et al.* Pharmacokinetics of dactinomycin in a pediatric patient population: a United Kingdom Children's Cancer Study Group Study. *Clin Cancer Res* 2005; **11:** 5893–9.

Uses and Administration

Dactinomycin is a highly toxic antibiotic with antineoplastic properties. It inhibits the proliferation of cells in a cell-cycle non-specific way by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It may enhance the cytotoxic effects of radiotherapy (see also Adverse Effects, above). Dactinomycin also has immunosuppressant properties.

It has been used, usually with other drugs or radiotherapy, in the treatment of Wilms' tumour (p.667), gestational trophoblastic tumours (p.650), nonseminomatous testicular cancer (p.673), and sarcomas such as rhabdomyosarcoma (p.676) and Ewing's sarcoma (p.675).

In the treatment of Wilms' tumour, childhood rhabdomyosarcoma, or Ewing's sarcoma, an intravenous dose of 15 micrograms/kg daily for 5 days has been used in combination regimens. In adults, gestational trophoblastic tumours have been treated with 12 micrograms/kg daily for 5 days as a single agent, or 500 micrograms on days 1 and 2 of combination regimens. Metastatic nonseminomatous testicular cancer has been treated with 1 mg/m^2 on day 1 of combination regimens. The dose intensity for adults or children should not exceed 15 micrograms/kg or 400 to 600 micrograms/m^2 daily for 5 days per 2-week cycle, and lower doses may need to be used in some chemotherapy combinations or with radiotherapy. Using a regional perfusion technique to localise the drug has permitted the use of higher doses, 50 micrograms/kg being suggested for an isolated lower extremity or pelvis and 35 micrograms/kg for an upper extremity.

Great care must be taken to avoid extravasation and it should be given, for preference, into the tubing of a fast-running intravenous infusion. Platelet and white cell counts should be performed frequently to detect bone-marrow depression; if either count shows a marked decrease the drug should be withheld until recovery occurs, which may take up to 3 weeks (see also Bone-marrow Depression, p.639).

Preparations

USP 31: Dactinomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Cosmegen; ***Austral.:*** Cosmegen; ***Austria:*** Cosmegen; ***Belg.:*** Lyovac Cosmegen; ***Braz.:*** Cosmegen; ***Canad.:*** Cosmegen; ***Fin.:*** Cosmegen; ***Fr.:*** Cosmegen; ***Ger.:*** Lyovac Cosmegen; ***Gr.:*** Cosmegen; ***Hong Kong:*** Cosmegen; ***India:*** Dacmozen; ***Irl.:*** Cosmegen; ***Ital.:*** Cosmegen; ***Malaysia:*** Cosmegen†; ***Mex.:*** Ac-De; ***Neth.:*** Lyovac Cosmegen; ***Norw.:*** Cosmegen; ***NZ:*** Cosmegen; ***Philipp.:*** Cosmegen; Trepar; ***Singapore:*** Cosmegen; ***Swed.:*** Cosmegen; ***Switz.:*** Cosmegen; ***Thai.:*** Cosmegen†; Lyovac Cosmegen; ***Turk.:*** Cosmegen; ***UK:*** Cosmegen; ***USA:*** Cosmegen.

Dasatinib *(USAN, rINN)*

BMS-354825; Dasatinibum. *N*-(2-Chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl}amino)-5-thiazolecarboxamide.

Дазатиниб

$C_{22}H_{26}ClN_7O_2S$ = 488.0.

CAS — 302962-49-8.

ATC — L01XE06.

ATC Vet — QL01XE06.

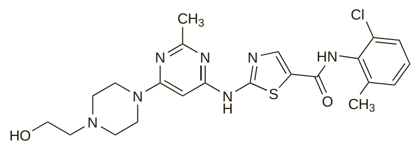

Adverse Effects, Treatment, and Precautions

The most common adverse effects of dasatinib include fluid retention, gastrointestinal disturbances, and bleeding. Fluid retention may be severe, and can result in pleural and pericardial effusion, pulmonary oedema, and ascites. Severe CNS haemorrhages, sometimes fatal, have been reported. Gastrointestinal haemorrhage may require interruption of therapy, and transfusions. Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in patients with advanced chronic myeloid leukaemia (CML) or acute lymphoblastic leukaemia than in patients in chronic phase. Recovery generally occurs after dose interruption and/or reduction, although treatment may need to be stopped. Febrile neutropenia has been reported. In patients with chronic phase CML, myelosuppression and fluid retention occur more often with twice daily dosing than once daily dosage. Other adverse effects include headache, pyrexia, musculoskeletal pain, fatigue, skin rashes, dyspnoea, cough, dizziness, chest pain, neuropathy, chills, and pruritus. Infections, including pneumonia, have been reported. Cardiac failure and arrhythmias can occur. Dasatinib has the potential to prolong the QT interval, and should be given with caution to patients at risk of this, such as those with hypokalaemia, hypomagnesaemia, or those on antiarrhythmic therapy, or receiving cumulative high doses of anthracyclines.

Effects on the skin. Panniculitis has been reported with the use of dasatinib, which resolved upon stopping therapy. In one case, dasatinib was restarted with prednisone, and no recurrence of panniculitis was noted. In another patient, however, a rash recurred on restarting therapy that was not sensitive to corticosteroid treatment.[1]

1. Assouline S, *et al.* Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006; **354:** 2623–4.

Interactions

Dasatinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals, macrolide antibacterials, HIV-protease inhibitors, and nefazodone may increase blood concentrations of dasatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of dasatinib. When use with such drugs cannot be avoided, dose adjustment of dasatinib may be necessary (see Uses and Administration, below). Since St John's wort may decrease dasatinib concentrations unpredictably, these drugs should not be given together.

Dasatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and may alter blood concentrations of other drugs that are substrates of this enzyme.

Since the solubility of dasatinib is dependent on pH, use with antacids should be avoided. If antacid therapy is needed, it should be given at least 2 hours before or 2 hours after the dose of dasatinib. Similarly, histamine H_2-receptor antagonists or proton pump inhibitors such as famotidine or omeprazole should not be given with dasatinib as long-term suppression of gastric acid secretion is likely to reduce dasatinib exposure.

Pharmacokinetics

Maximum plasma concentrations of dasatinib are achieved between 0.5 and 6 hours after an oral dose. The mean terminal half-life is about 5 hours. Consumption of a high-fat meal may increase exposure to dasatinib, but this effect is not considered to be of clinical significance. Dasatinib is extensively distributed and metabolised. Metabolism occurs primarily by the cytochrome P450 isoenzyme CYP3A4, forming an active metabolite. Plasma protein binding of dasatinib and its active metabolite is about 96% and 93%, respectively. Elimination is mainly via the faeces; about 4% is recovered in the urine.

Uses and Administration

Dasatinib is a tyrosine kinase inhibitor that is used for the treatment of adults with all phases of chronic myeloid leukaemia (CML; p.653) who have resistance or intolerance to previous therapy, including imatinib. It is also used for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL; p.651) who are resistant to or intolerant of prior therapy.

A recommended oral starting dose of dasatinib in chronic phase CML is 100 mg once daily: tablets, which should be swallowed whole, not crushed or chewed, should be taken consistently either in the morning or the evening. The recommended starting dose for accelerated, myeloid, or lymphoid blast phase CML or Philadelphia chromosome-positive ALL is 70 mg twice daily. Dosage may be adjusted according to response and tolerability; doses of up to 140 mg once daily have been used in patients with chronic phase CML, and up to 100 mg twice daily in those with advanced phase, or with ALL. Treatment is continued until disease progression or unacceptable toxicity occurs.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments are considered necessary. A dose increase should be considered in those patients given strong CYP3A4 inducers, and the patient should be monitored for toxicity. For those given a strong CYP3A4 inhibitor, the dose of dasatinib should be reduced to 20 mg daily. If this is not tolerated, then either drug should be stopped; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of dasatinib is increased.

◊ References.

1. Talpaz M, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; **354:** 2531–41.
2. Hochhaus A, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; **109:** 2303–9. Correction. *ibid.*; **110:** 1438.
3. Cortes J, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; **109:** 3207–13.
4. Guilhot F, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; **109:** 4143–50.
5. Ottmann O, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007; **110:** 2309–15.

6. Anonymous. Dasatinib (Sprycel) for CML and Ph+ALL. *Med Lett Drugs Ther* 2007; **49:** 6–7.
7. Olivieri A, Manzione L. Dasatinib: a new step in molecular target therapy. *Ann Oncol* 2007; **18** (suppl): vi42–vi46.
8. Keam SJ. Dasatinib: in chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. *BioDrugs* 2008; **22:** 59–69.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sprycel; ***Austral.:*** Sprycel; ***Cz.:*** Sprycel; ***Fr.:*** Sprycel; ***Gr.:*** Sprycel; ***Hung.:*** Sprycel; ***Indon.:*** Sprycel; ***Malaysia:*** Sprycel; ***NZ:*** Sprycel; ***UK:*** Sprycel; ***USA:*** Sprycel.

Daunorubicin Hydrochloride

(BANM, USAN, rINNM)

Cloridrato de Daunorrubicina; Daunomycin Hydrochloride; Daunoribisin Hidroklorür; Daunorubicin hydrochlorid; Daunorubicine, chlorhydrate de; Daunorubicin-hidroklorid; Daunorubicinhydroklorid; Daunorubicini hydrochloridum; Daunorubicino hidrochloridas; Daunorubisiinihydrokloridi; FI-6339 (daunorubicin); Hidrocloruro de daunorubicina; NDC-0082-4155; NSC-82151; RP-13057 (daunorubicin); Rubidomycin Hydrochloride. (1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-pyranoside hydrochloride; (8*S*-*cis*)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)]oxy-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

Даунорубицина Гидрохлорид

$C_{27}H_{29}NO_{10},HCl = 564.0.$

CAS — 20830-81-3 (daunorubicin); 23541-50-6 (daunorubicin hydrochloride).

ATC — L01DB02.

ATC Vet — QL01DB02.

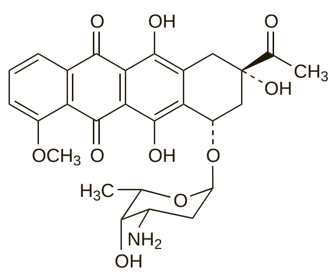

(daunorubicin)

NOTE. Daunorubicin citrate is used in the preparation of liposomal preparations (see Uses and Administration, below).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Daunorubicin Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It is manufactured by methods designed to minimise or eliminate the presence of histamine. An orange-red, hygroscopic, crystalline powder. It contains between 95 and 102% of the hydrochloride (anhydrous and solvent-free basis). Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Daunorubicin Hydrochloride). An orange-red, hygroscopic, crystalline powder. It has a potency equivalent to not less than 842 and not more than 1030 micrograms of the base per mg. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone; very slightly soluble in chloroform. A 0.5% solution in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Incompatibility. Daunorubicin is incompatible with heparin sodium,[1] and has also been reported to be incompatible with a solution of dexamethasone sodium phosphate.

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.

Stability. In a study[1] of the stability of anthracycline antineoplastic agents in 4 infusion fluids (glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid) daunorubicin hydrochloride was stable in all 4, the percentage remaining after 24 hours being 98.5%, 97.4%, 94.7%, and 95.4% respectively. Stability appeared to be partly related to pH; daunorubicin was more stable as the pH of the mixture became more acidic, with the best stability in glucose 5% with a pH of 4.5. Although daunorubicin solutions are degraded by light, the effect is reported not to be significant at concentrations of 500 micrograms/mL or above; however, below this concentration precautions should be taken to protect solutions from light, and storage should be in polyethylene or polypropylene containers to minimise adsorptive losses.[2] It has been suggested that formulation with the food colouring Scarlet GN, which absorbs light over the same spectral region as daunorubicin, would stabilise daunorubicin solutions to light.[3]

Liposomal daunorubicin should be diluted with glucose 5% solution as aggregation of the liposomes may result with sodium chloride. In addition, licensed product information advises that liposomal daunorubicin should not be mixed with substances containing benzyl alcohol or other detergent-like molecules, which can lead to premature rupture of the liposomes.

1. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
2. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
3. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712 and p.713.

Cardiotoxicity is more likely when the total cumulative dose of daunorubicin exceeds 550 to 600 mg/m^2 in adults, 300 mg/m^2 in children, or in children aged under 2 years, 10 mg/kg. The cumulative dose should be limited to 400 mg/m^2 in patients who have had previous radiation therapy to the mediastinum. Product information for liposomal daunorubicin recommends determining ventricular ejection fraction after cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter. Daunorubicin should be used in reduced doses in hepatic and renal impairment.

Liposomal formulations of daunorubicin may be associated with a reduced potential for local tissue necrosis although current clinical experience is limited and such toxicity remains a possibility. An acute syndrome of back pain, flushing, and chest tightness may occur during infusion, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. For a discussion of the cardiotoxicity of anthracyclines, and its management, see Effects on the Heart, under Doxorubicin, p.713.

Effects on the skin and nails. For reports of hyperpigmentation in patients given daunorubicin, see under Doxorubicin, p.713.

Handling and disposal. Daunorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

For a method for the destruction of daunorubicin in wastes see under Doxorubicin, p.713.

Interactions

As for Doxorubicin, p.713.

Antineoplastics. Hepatic dysfunction was reported[1] in 13 patients given daunorubicin 180 to 450 mg/m^2. Ten of them had also received *tioguanine* or *cytarabine*, or a combination of these. The authors also noted that other studies had suggested that the related drug doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, and thought that a similar interaction could occur between daunorubicin and tioguanine.

1. Penta JS, *et al.* Hepatotoxicity of combination chemotherapy for acute myelocytic leukemia. *Ann Intern Med* 1977; **87:** 247–8.

Pharmacokinetics

After intravenous injection, daunorubicin is rapidly distributed into body tissues, particularly the liver, lungs, kidneys, spleen, and heart with an initial distribution half-life of about 45 minutes. It is rapidly metabolised in the liver, and is excreted in bile and urine as unchanged drug and metabolites. The major metabolite, daunorubicinol, has antineoplastic activity. Up to 25% of a dose is excreted in urine in an active form over several days (the terminal plasma elimination half-lives of daunorubicin and its major metabolite are reported to be 18.5 and 26.7 hours respectively); an estimated 40% is excreted in bile. Daunorubicin does not appear to cross the blood-brain barrier, but crosses the placenta.

The pharmacokinetics of liposomal doxorubicin are significantly different from those of the conventional drug formulation, with a decreased uptake by normal tissues (although tumour neovasculature is reported to have increased permeability to the liposomes), and a terminal half-life of 4 to 5 hours.

Uses and Administration

Daunorubicin is an antineoplastic anthracycline antibiotic with actions similar to those of doxorubicin (p.714), to which it is closely related. It is used with other antineoplastics to induce remissions in acute leukaemias. Daunorubicin is given in combination regimens for acute lymphoblastic leukaemia (see p.651) and acute myeloid leukaemias (see p.652). It has also been tried in some other malignancies. A liposomal formulation of daunorubicin has been developed for use in the management of Kaposi's sarcoma in patients with AIDS (see also p.675).

Daunorubicin is usually given as the hydrochloride, but doses are expressed in terms of the base. Daunorubicin hydrochloride 21.4 mg is equivalent to about 20 mg daunorubicin.

In combination treatment regimens for adult acute leukaemia, the usual dose is 30 to 45 mg/m^2 daily on days 1 to 3 of the first course, and days 1 and 2 of subsequent courses. Daunorubicin is given as a solution in sodium chloride 0.9% into a fast-running infusion of sodium chloride or glucose. Courses may be repeated after 3 to 6 weeks. A dose of 25 mg/m^2 has been given intravenously once a week, in combination regimens, to children with acute lymphoblastic leukaemia. For children less than 2 years of age, or less than 0.5 m^2, a dose of 1 mg/kg has been used instead.

The total cumulative dose in adults should not exceed 550 to 600 mg/m^2; in patients who have received radiotherapy to the chest it may be advisable to limit the total dose to about 400 mg/m^2. Lower limits apply in children: a total cumulative dose of no more than 300 mg/m^2, or in children aged under 2 years 10 mg/kg, is recommended. Dosage should be reduced in patients with impaired hepatic or renal function (see below), and elderly patients with inadequate bone marrow reserves.

In the treatment of Kaposi's sarcoma, liposomal daunorubicin is given intravenously every 2 weeks starting with a dose of 40 mg/m^2, and continued for as long as disease control can be maintained. It is diluted with glucose 5% (sodium chloride 0.9% should not be used) to a concentration between 0.2 and 1 mg/mL, and given over 30 to 60 minutes.

Blood counts should be determined frequently during treatment as daunorubicin has a potent effect on bone-marrow function (see also Bone-marrow Depression, p.639). Cardiac function should be monitored at regular intervals to detect signs of cardiotoxicity.

Administration in hepatic impairment. Doses of daunorubicin should be reduced in hepatic impairment. Some licensed product information recommends that patients with serum-bilirubin concentrations of 12 to 30 micrograms/mL should receive 75% of the usual dose, and those with concentrations greater than 30 micrograms/mL should be given 50% of the usual dose.

Administration in renal impairment. Doses of daunorubicin should be reduced in renal impairment. Some licensed product information recommends that patients with serum-creatinine concentrations of 105 to 265 micromoles/litre should receive 75% of the usual dose, and those with concentrations greater than 265 micromoles/litre should be given 50% of the usual dose.

Preparations

USP 31: Daunorubicin Hydrochloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Daunoblastina; Maxidauno; ***Austral.:*** DaunoXome; ***Austria:*** Daunoblastin; DaunoXome; ***Belg.:*** Cerubidine; ***Braz.:*** Daunoblastina; Daunocin†; DaunoXome†; ***Canad.:*** Cerubidine; ***Chile:*** Cerubidine; Daurocina; Oncodaunotec; ***Cz.:*** Cerubidine†; ***Denm.:*** Cerubidin; DaunoXome; ***Fin.:*** DaunoXome; ***Fr.:*** Cerubidine; DaunoXome; ***Ger.:*** Daunoblastin; DaunoXome; ***Gr.:*** Cerubidine; DaunoXome; ***Hong Kong:*** Daunoblastina†; ***Hung.:*** Daunoblastina; ***India:*** Daunotec; Norubin; ***Irl.:*** Cerubidin; DaunoXome; ***Israel:*** Cerubidine; ***Ital.:*** Daunoblastina; DaunoXome; ***Mex.:*** Rubilem; ***Neth.:*** Cerubidine; DaunoXome; ***Norw.:*** Cerubidin; ***Port.:*** Daunoblastina†; DaunoXome; ***Rus.:*** DaunoXome (Даунозом); ***S.Afr.:*** Cerubidin†; Daunoblastin; ***Singapore:*** Daunoblastina; ***Spain:*** Daunoblastina; DaunoXome†; ***Swed.:*** Cerubidin†; DaunoXome; ***Switz.:*** Cerubidine; DaunoXome†; ***UK:*** DaunoXome; ***USA:*** Cerubidine; DaunoXome; ***Venez.:*** Daunoblastina.

The symbol † denotes a preparation no longer actively marketed

Decitabine (BAN, USAN, rINN)

5-Aza-2′-deoxycytidine; DAC; Decitabina; Décitabine; Decitabinum; NSC-127716. 4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.

Децитабин

$C_8H_{12}N_4O_4$ = 228.2.

CAS — 2353-33-5.

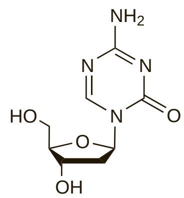

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. The most common adverse effect of decitabine is myelosuppression, which may be severe and dose-limiting. Fatalities have been reported. Other common adverse effects include fatigue, pyrexia, gastrointestinal disturbances, petechiae, and hyperglycaemia. Cardiorespiratory arrest, increased blood bilirubin, intracranial haemorrhage, abnormal liver function tests, pulmonary oedema, atrial fibrillation, central line infection, or febrile neutropenia may force treatment to be stopped or delayed. Other adverse effects which may be dose-limiting include lethargy, oedema, tachycardia, depression, or pharyngitis.

Pharmacokinetics

On intravenous dosage decitabine exhibits biphasic disposition. Plasma protein binding is negligible. The exact route of metabolism and excretion is not known; one pathway appears to be deamination by cytidine deaminase, which is found principally in the liver, but also in granulocytes, the intestinal epithelium, and whole blood. A terminal elimination half-life of about 0.5 hours has been reported after a 72-hour infusion.

Uses and Administration

Decitabine is an antineoplastic antimetabolite structurally related to cytarabine (p.705). It is reported to cause DNA hypomethylation by the inhibition of DNA methyltransferase, which has the potential to alter gene expression (re-activate silent genes) and limit disease progression and resistance. Decitabine is used in the treatment of myelodysplastic syndromes (p.654). It is given by intravenous infusion over 3 hours, diluted to a final concentration of 0.1 to 1 mg/mL in sodium chloride 0.9%, glucose 5%, or lactated Ringer's injection. The recommended dose is 15 mg/m^2 every 8 hours for 3 days; this 3-day cycle is repeated every 6 weeks, for a minimum of 4 cycles. Treatment may be continued as long as the patient continues to benefit. If haematological recovery from a cycle is incomplete, cycle length may be increased to as much as every 10 weeks and the dose reduced to 11 mg/m^2 every 8 hours upon restarting therapy; this dose may be maintained or increased in subsequent cycles as clinically indicated. Decitabine treatment should also be delayed if serum creatinine is 2 mg per 100 mL or greater, or if total bilirubin is 2 or more times the upper limit of normal, or if the patient has an active or uncontrolled infection.

Decitabine is also under investigation for the treatment of chronic myeloid leukaemia (p.653) and acute myeloid leukaemia (p.652). It is also reported to increase fetal haemoglobin in patients with sickle-cell disease (p.1044).

◊ References.

1. DeSimone J, *et al.* Maintenance of elevated fetal hemoglobin levels by decitabine during dose interval treatment of sickle cell anemia. *Blood* 2002; **99:** 3905–8.
2. Momparler RL. Pharmacology of 5-aza-2′-deoxycytidine (decitabine). *Semin Hematol* 2005; **42** (suppl 2): S9–S16.
3. Kantarjian HM, Issa JP. Decitabine dosing schedules. *Semin Hematol* 2005; **42** (suppl 2): S17–S22. Correction. *ibid.*; 274.
4. Lubbert M, Minden M. Decitabine in acute myeloid leukemia. *Semin Hematol* 2005; **42** (suppl 2): S38–S42.
5. Issa JP, Byrd JC. Decitabine in chronic leukemias. *Semin Hematol* 2005; **42** (suppl 2): S43–S49.
6. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
7. Momparler RL. Epigenetic therapy of cancer with 5-aza-2′-deoxycytidine (decitabine). *Semin Oncol* 2005; **32:** 443–51.
8. Kantarjian H, *et al.* Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 2006; **106:** 1794–1803.
9. McKeage K, Croom KF. Decitabine in myelodysplastic syndromes. *Drugs* 2006; **66:** 951–8.
10. Jabbour E, *et al.* Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer* 2008; **112:** 2341–51.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Dacogen.

Denileukin Diftitox (USAN, rINN)

$DAB_{389}IL2$; Denileucina diftitox; Denileukin Difitox (BAN); Dénileukine Diftitox; Denileukinum Diftitoxum; LY-335348.

Денилейкин Дифтитокс

CAS — 173146-27-5.
ATC — L01XX29.
ATC Vet — QL01XX29.

Adverse Effects and Precautions

Denileukin diftitox can cause an acute hypersensitivity reaction within 24 hours of infusion with symptoms reminiscent of a cytokine release syndrome. Anaphylaxis and death have also been reported. A more delayed flu-like syndrome may also occur up to several days after infusion. Vascular leak syndrome, characterised by hypotension, oedema, or hypoalbuminaemia, may also be delayed. Gastrointestinal disturbances, chills, fever, and asthenia are common. Other adverse effects include rash, predisposition to cutaneous infections, and thrombotic events. Visual loss has been reported; although recovery was reported in some patients, in most cases impairment persisted.

Uses and Administration

Denileukin diftitox is a recombinant interleukin fusion toxin comprised of interleukin-2 linked to the A and B fragments of diphtheria toxin. It is given by intravenous infusion for the management of persistent or recurrent cutaneous T-cell lymphoma (see Mycosis Fungoides, p.657), in patients whose malignant cells express the CD25 interleukin-2 receptor. The concentration of denileukin diftitox must be at least 15 micrograms/mL during all steps in the preparation of the solution for infusion. The recommended dose is 9 or 18 micrograms/kg daily, given over 15 minutes or more, for 5 consecutive days every 3 weeks.

◊ References.

1. Olsen E, *et al.* Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19:** 376–88.
2. Martin A, *et al.* A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol* 2001; **45:** 871–81.
3. Talpur R, *et al.* Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). *Leuk Lymphoma* 2002; **43:** 121–6.
4. Frankel AE, *et al.* A phase II study of DT fusion protein denileukin diftitox in patients with fludarabine-refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2003; **9:** 3555–61.
5. Eklund JW, Kuzel TM. Denileukin diftitox: a concise clinical review. *Expert Rev Anticancer Ther* 2005; **5:** 33–8.
6. Foss F. Clinical experience with denileukin diftitox (ONTAK). *Semin Oncol* 2006; **33** (suppl 3): 11–16.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ontak.

Diaziquone (USAN, rINN)

Aziridinylbenzoquinone; AZQ; CI-904; Diazicuona; Diaziquonum; NSC-182986. Diethyl 2,5-bis-(1-aziridinyl)-3,6-dioxo-1,4-cyclohexadiene-1,4-dicarbamate.

Диазихон

$C_{16}H_{20}N_4O_6$ = 364.4.

CAS — 57998-68-2.

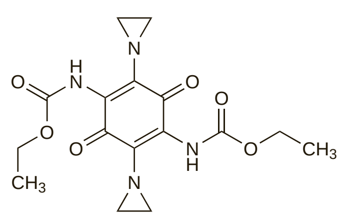

Profile

Diaziquone has been investigated as an antineoplastic in the treatment of malignant brain tumours and acute myeloid leukaemia. It is thought to act as an alkylating agent. Adverse effects include bone-marrow suppression, manifesting chiefly as leucopenia and thrombocytopenia, gastrointestinal disturbances, and alopecia. Anaphylactoid reactions have occurred.

Didemnin B

Didemnina B; NSC-325319.

$C_{57}H_{89}N_7O_{15}$ = 1112.4.

CAS — 77327-05-0.

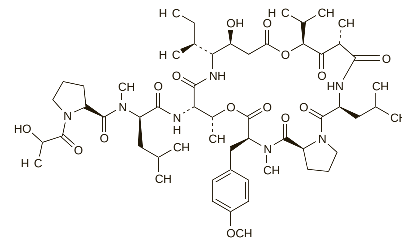

Profile

The didemnins are biologically active peptides extracted from a marine sea squirt of the genus *Trididemnum*. They possess antineoplastic and antiviral properties; didemnin B is reported to be more active than didemnin A or didemnin C and has been investigated as an antineoplastic, although results have not generally been favourable. Nausea and vomiting are dose-limiting; myelosuppression, cardiac and renal toxicity, liver dysfunction, other gastrointestinal disturbances, myalgia, fatigue, and phlebitis may occur. Hypersensitivity reactions, possibly due to the polyoxyl castor oil vehicle, are common.

Docetaxel (BAN, USAN, rINN)

Docétaxel; Docetaxelum; Docetaxol; Docetaxolum; Dosetaksel; Dosetaksoli; NSC-628503; RP-56976. (2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate; *tert*-Butyl {(1*S*,2*S*)-2-[(2*S*,5*R*,7*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-1,7,10-trihydroxy-9-oxo-5,20-epoxytax-11-en-13-yloxycarbonyl]-2-hydroxy-1-phenylethyl}carbamate.

Доцетаксел

$C_{43}H_{53}NO_{14}$ = 807.9.

CAS — 114977-28-5 (anhydrous docetaxel); 148408-66-6 (docetaxel trihydrate).
ATC — L01CD02.
ATC Vet — QL01CD02.

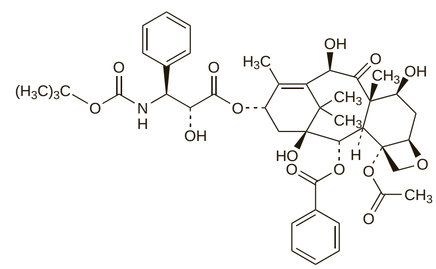

Adverse Effects, Treatment, and Precautions

As for Paclitaxel, p.759. Neutropenia, anaemia and skin reactions are common with docetaxel and may be severe. Fluid retention, resulting in oedema, ascites, pleural and pericardial effusion, and weight gain, is also common, and may be cumulative; premedication with a corticosteroid can reduce fluid retention as well as the severity of hypersensitivity reactions. Asthenia and fatigue have also been reported. Rare cases of ototoxicity, hearing impairment or loss have occurred. Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported with combination chemotherapy regimens containing docetaxel; haematological follow-up may be required.

Docetaxel should not be used in patients hypersensitive to polysorbate 80, which is contained in the formulation. Patients with hepatic impairment show increased sensitivity to toxic effects of docetaxel, and should be given the drug with great care and in reduced doses, if at all.

Effects on the eyes. Excessive tear formation (epiphora) severe enough to interfere with reading and driving has been reported in patients given docetaxel. Canalicular stenosis has been described as the mechanism for this effect, and docetaxel has been measured in tear fluid suggesting that irritation of the ocular surface and fibrosis of the tear drainage ducts may be caused by direct contact with docetaxel.[1] Epiphora and canalicular stenosis are more severe and occur more frequently in patients who receive weekly docetaxel than in those who receive the drug every 3 weeks.[2,3] The mean cumulative dose of docetaxel was found to be higher in those patients who developed stenosis.[2] Management of this adverse effect includes probing and irrigation of the lachrymal ducts and canalicular silicone tubing placement, or surgery followed by tube placement. The condition is generally reversible and tubing can be removed 4 to 6 weeks after stopping docetaxel therapy.[4] The use of topical tobramycin and dexamethasone on a tapering regimen can eliminate the need for silicone intubation or surgery in some patients.[3]

Very rare cases of transient visual disturbances such as flashing lights and scotomata have occurred during docetaxel infusion, and in association with hypersensitivity reactions. These were reversible upon stopping the infusion. For reference to a report of glaucoma possibly related to docetaxel, see Paclitaxel, p.759.

1. Esmaeli B, *et al.* Docetaxel secretion in tears: association with lacrimal drainage obstruction. *Arch Ophthalmol* 2002; **120:** 1180–2.
2. Esmaeli B, *et al.* Canalicular stenosis secondary to weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer. *Ophthalmology* 2002; **109:** 1188–91.
3. Esmaeli B, *et al.* Prospective study of incidence and severity of epiphora and canalicular stenosis in patients with metastatic breast cancer receiving docetaxel. *J Clin Oncol* 2006; **24:** 3619–22.
4. Ahmadi MA, Esmaeli B. Surgical treatment of canalicular stenosis in patients receiving docetaxel weekly. *Arch Ophthalmol* 2001; **119:** 1802–4.

Effects on the gastrointestinal tract. Ischaemic colitis has occurred in patients treated with docetaxel.[1-3] Some patients also received vinorelbine, which may have exacerbated this complication.[1,2]

1. Ibrahim NK, *et al.* Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. *Lancet* 2000; **355:** 281–3.
2. de Matteis A, *et al.* Intestinal side-effects of docetaxel/vinorelbine combination. *Lancet* 2000; **355:** 1098–9.
3. Hussein MAH, *et al.* Docetaxel-related ischemic colitis. *J Clin Oncol* 2005; **23:** 9424–5.

Effects on the heart. For comment on the increased risk of heart failure when docetaxel is given with trastuzumab and after anthracyclines, see under Interactions, below.

Effects on the musculoskeletal system. For reference to cases of taxane-induced arthralgia and myalgia successfully treated with gabapentin, see Paclitaxel, p.759.

Effects on the skin and nails. Palmar-plantar erythrodysesthesia syndrome (p.639) has been reported with the use of docetaxel.[1] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by docetaxel and capecitabine, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p.1994. Cases of radiation recall dermatitis associated with docetaxel have also been reported.[2-4] There is a further report of recall dermatitis at sites previously treated with a laser.[5] A hyperpigmented eruption developed in a patient at the site of docetaxel injection after insufficient venous flushing; no eruption occurred after a second infusion with abundant venous flushing.[6] Licensed drug information states that very rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with docetaxel, but that other factors may have contributed to the development of these reactions.

For further reference to reports of scleroderma and adverse effects on the nails after the use of docetaxel, see Paclitaxel, p.759.

In a multicentre study, patients given docetaxel wore a frozen glove on the right hand, leaving the left hand unprotected to serve as a control. The use of the glove significantly reduced skin and nail toxicity.[7]

1. Eich D, *et al.* Acral erythrodysesthesia syndrome caused by intravenous infusion of docetaxel in breast cancer. *Am J Clin Oncol* 2002; **25:** 599–602.
2. Piroth MD, *et al.* Radiation recall dermatitis from docetaxel. *Onkologie* 2002; **25:** 438–40.
3. Kandemir EG, *et al.* Docetaxel-induced radiation recall dermatitis. *Swiss Med Wkly* 2005; **135:** 34–5.
4. Borgia F, *et al.* Radiation recall dermatitis after docetaxel administration: absolute indication to replace the drug? *Br J Dermatol* 2005; **153:** 674–5.
5. Chu C-Y, Yang C-H. Docetaxel-induced recall dermatitis on previous laser treatment sites. *Br J Dermatol* 2005; **153:** 441–3.
6. Aydogan I, *et al.* Persistent serpentine supravenous hyperpigmented eruption associated with docetaxel. *J Eur Acad Dermatol Venereol* 2005; **19:** 345–7.
7. Scotté F, *et al.* Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol* 2005; **23:** 4424–9.

Hypersensitivity. For a discussion of taxane-induced hypersensitivity, including references to desensitisation protocols, see under Paclitaxel, p.759.

Tumour lysis syndrome. Fatal cases of tumour lysis syndrome (p.639) have been reported after the second-line use of docetaxel.[1,2]

1. Sorscher SM. Tumor lysis syndrome following docetaxel therapy for extensive metastatic prostate cancer. *Cancer Chemother Pharmacol* 2004; **54:** 191–2.
2. Ajzensztejn D, *et al.* Tumor lysis syndrome after treatment with docetaxel for non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 2389–91.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

◊ Docetaxel is metabolised by cytochrome P450 isoenzyme CYP3A, and theoretically has the potential to interact with other drugs that are inhibitors or inducers of this enzyme.[1]

1. Royer I, *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; **56:** 58–65.

Antifungals. In a pharmacokinetic study, no consistent effects on docetaxel concentrations were seen with the addition of *ketoconazole*. Significant inter- and intrapatient variability was observed and a potential interaction could not be excluded.[1] In another study in 7 patients, however, the clearance of docetaxel was significantly reduced by 49% when given with ketoconazole.[2]

1. Van Veldhuizen PJ, *et al.* Docetaxel and ketoconazole in advanced hormone-refractory prostate carcinoma: a phase I and pharmacokinetic study. *Cancer* 2003; **98:** 1855–62.
2. Engels FK, *et al.* Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* 2004; **75:** 448–54.

Antineoplastics. The clearance of a dose of docetaxel was markedly reduced[1] when it was given after 4 days of treatment with *topotecan,* rather than on day 1; this resulted in worsened neutropenia.

Sorafenib may increase systemic exposure to docetaxel.

An increased incidence of febrile neutropenia and gastrointestinal disorders, including 2 fatalities, was reported in patients given docetaxel with *doxorubicin,*[2] although others[3] considered this high incidence unrepresentative of usual toxicity rates with this combination.

Heart failure has been reported in patients given docetaxel with other cytotoxic drugs, especially *trastuzumab,* and particularly after anthracycline-containing therapy. UK licensed drug information therefore recommends that patients given docetaxel with trastuzumab should undergo baseline cardiac assessment and cardiac function should be monitored during treatment.

1. Zamboni WC, *et al.* Pharmacokinetic and pharmacodynamic study of the combination of docetaxel and topotecan in patients with solid tumors. *J Clin Oncol* 2000; **18:** 3288–94.
2. Brain EGC, *et al.* Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. *JAMA* 2005; **293:** 2367–71.
3. Martin M, *et al.* Life-threatening complications from doxorubicin-docetaxel chemotherapy for breast cancer. *JAMA* 2005; **294:** 2166.

Pharmacokinetics

On intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins. It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A4 and excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment.

◊ References.

1. Rudek MA, *et al.* Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur J Cancer* 2004; **40:** 1170–8.
2. Baker SD, *et al.* Clinical pharmacokinetics of docetaxel: recent developments. *Clin Pharmacokinet* 2006; **45:** 235–52.
3. Tran A, *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther* 2006; **79:** 570–80.
4. Charles KA, *et al.* Predicting the toxicity of weekly docetaxel in advanced cancer. *Clin Pharmacokinet* 2006; **45:** 611–22.

Uses and Administration

Docetaxel is a semisynthetic taxane similar to paclitaxel (see p.760). It is manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*. Docetaxel is used for locally advanced or metastatic breast cancer (p.661). It may be used as first-line treatment with doxorubicin; in the treatment of refractory disease, it is used alone or with capecitabine. In the treatment of metastatic breast cancer that overexpresses HER2 (human epidermal growth receptor 2), docetaxel may be used with trastuzumab as initial therapy. For adjuvant treatment of operable, node-positive breast cancer, docetaxel is given with doxorubicin and cyclophosphamide. Docetaxel is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (p.668), either with cisplatin for initial treatment of unresectable disease, or after failure of previous platinum-based chemotherapy. It is used with prednisone or prednisolone in hormone-refractory metastatic prostate cancer (p.671). Docetaxel is given with cisplatin and fluorouracil in the first-line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (p.664); it is also used in this combination for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (p.666).

Docetaxel is given by intravenous infusion in glucose 5% or sodium chloride 0.9% at a concentration not exceeding 0.74 mg/mL. Infusion is normally over 1 hour. Premedication with an oral corticosteroid, such as dexamethasone 16 mg daily, for 3 days starting 1 day before docetaxel is recommended with many regimens.

The licensed dose for docetaxel as a single agent in the treatment of **breast cancer** after failure of previous chemotherapy is 60 to 100 mg/m^2 once every 3 weeks. A dose of 75 mg/m^2 once every 3 weeks is given in combination therapy with doxorubicin, or capecitabine, or when used as adjuvant therapy with doxorubicin and cyclophosphamide. When used with trastuzumab, docetaxel is given at a dose of 100 mg/m^2 once every 3 weeks.

The dose for **non-small cell lung cancer** is 75 mg/m^2 once every 3 weeks, for both first-line combination therapy and monotherapy after failure of previous chemotherapy.

For **gastric adenocarcinoma** docetaxel 75 mg/m^2 is given before cisplatin and fluorouracil; treatment is repeated every 3 weeks.

In the induction treatment of **head and neck cancer**, the recommended dose of docetaxel is 75 mg/m^2, given before cisplatin and fluorouracil; treatment is given every 3 weeks for 3 cycles, followed by chemoradiotherapy, or for 4 cycles when followed by radiotherapy alone.

For **prostate cancer**, the dose of docetaxel is 75 mg/m^2 once every 3 weeks, with prednisone or prednisolone 5 mg orally twice daily given continuously. The use of prednisone or prednisolone reduces the need for a premedication corticosteroid; dexamethasone 8 mg may be given at 12 hours, 3 hours, and 1 hour before docetaxel.

Regular blood counts are required, and dosage in subsequent courses should be reduced in patients who experience severe or febrile neutropenia (see also Bone-marrow Depression, p.639), or severe cutaneous reactions or peripheral neuropathy. The dose of docetaxel should be reduced in hepatic impairment, see below.

◊ References. For references to taxanes as a class, see Paclitaxel, p.760.

1. Comer AM, Goa KL. Docetaxel: a review of its use in non-small cell lung cancer. *Drugs Aging* 2000; **17:** 53–80.
2. Shepherd FA, *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; **18:** 2095–2103.
3. Beer TM, *et al.* Docetaxel (Taxotere) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2003; **3:** 261–8.
4. Herbst RS, Khuri FR. Mode of action of docetaxel–a basis for combination with novel anticancer agents. *Cancer Treat Rev* 2003; **29:** 407–15.
5. Maenpaa JU. Docetaxel: promising and novel combinations in ovarian cancer. *Br J Cancer* 2003; **89** (suppl): S29–S34.
6. Tannock IF, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351:** 1502–12.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.
8. Montero A, *et al.* Docetaxel for treatment of solid tumours: a systematic review of clinical data. *Lancet Oncol* 2005; **6:** 229–39.
9. Martin M, *et al.* Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005; **352:** 2302–13.
10. Engels FK, *et al.* Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *Br J Cancer* 2005; **93:** 173–7.

11. McKeage K, Keam SJ. Docetaxel: in hormone-refractory metastatic prostate cancer. *Drugs* 2005; **65:** 2287–94.
12. Lyseng-Williamson KA, Fenton C. Docetaxel: a review of its use in metastatic breast cancer. *Drugs* 2005; **65:** 2513–31.
13. Ajani JA. Chemotherapy for advanced gastric or gastroesophageal cancer: defining the contributions of docetaxel. *Expert Opin Pharmacother* 2006; **7:** 1627–31.
14. Thuss-Patience PC, *et al.* Docetaxel in the treatment of gastric cancer. *Future Oncol* 2006; **2:** 603–20.
15. Deeks ED, Scott LJ. Docetaxel: in gastric cancer. *Drugs* 2007; **67:** 1893–1901.

Administration. Docetaxel has been investigated as a low-dose weekly infusion, in patient groups such as the elderly, those with poor performance status, or refractory disease.[1-6] Weekly doses of 30 to 40 mg/m^2 are considered to be of similar efficacy to the standard three-weekly dosage regimen.[7] A pharmacokinetic study in 20 elderly patients suggested that a suitable starting dose might be 26 mg/m^2, increased provided there was no toxicity.[8]

1. Hainsworth JD, *et al.* Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001; **19:** 3500–5.
2. Mekhail T, *et al.* Phase I trial of weekly docetaxel and gemcitabine in patients with refractory malignancies. *Cancer* 2003; **97:** 170–8.
3. Petrioli R, *et al.* Weekly low-dose docetaxel in advanced non-small cell lung cancer previously treated with two chemotherapy regimens. *Lung Cancer* 2003; **39:** 85–9.
4. Di Maio M, *et al.* Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007; **25:** 1377–82.
5. Abbrederis K, *et al.* Weekly docetaxel monotherapy for advanced gastric or esophagogastric junction cancer: results of a phase II study in elderly patients or patients with impaired performance status. *Crit Rev Oncol Hematol* 2008; **66:** 84–90.
6. Rivera E, *et al.* Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008; **112:** 1455–61.
7. Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. *Oncologist* 2004; **9:** 538–45.
8. Hurria A, *et al.* Pharmacokinetics and toxicity of weekly docetaxel in older patients. *Clin Cancer Res* 2006; **12:** 6100–5.

Administration in hepatic impairment. UK licensed product information recommends that doses of docetaxel monotherapy should be reduced from 100 mg/m^2 to 75 mg/m^2 in mild to moderate hepatic impairment, defined as alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) more than 1.5 times the upper limit of normal (ULN), and alkaline phosphatase more than 2.5 times the ULN. Hepatic function should be monitored; use should be avoided if possible in severe hepatic impairment. US licensed information advises against the use of docetaxel in patients with bilirubin above ULN, or in those with mild to moderate hepatic impairment (defined as for the UK, above).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Asodocel; Docekebir; Dolectran; Donataxel; Doxetal; Doxmil†; Eriox; Neocel†; Plustaxano; Taxotere; Texot; Trazoteva; Trixotene†; ***Austral.:*** Taxotere; ***Austria:*** Taxotere; ***Belg.:*** Taxotere; ***Braz.:*** Taxotere; ***Canad.:*** Taxotere; ***Chile:*** Taxotere; ***Cz.:*** Taxotere; ***Denm.:*** Taxotere; ***Fin.:*** Taxotere; ***Fr.:*** Taxotere; ***Ger.:*** Taxotere; ***Gr.:*** Taxotere; ***Hong Kong:*** Taxotere; ***Hung.:*** Taxotere; ***India:*** Daxotel; Docetax; ***Indon.:*** Taxotere; ***Irl.:*** Taxotere; ***Israel:*** Taxotere; ***Ital.:*** Taxotere; ***Jpn:*** Taxotere; ***Malaysia:*** Taxotere; ***Mex.:*** Taxotere; ***Neth.:*** Taxotere; ***Norw.:*** Taxotere; ***NZ:*** Taxotere; ***Philipp.:*** Taxotere; ***Pol.:*** Taxotere; ***Port.:*** Taxotere; ***Rus.:*** Tautax (Таутакс); Taxotere (Таксотер); ***S.Afr.:*** Taxotere; ***Singapore:*** Taxotere; ***Spain:*** Taxotere; ***Swed.:*** Taxotere; ***Switz.:*** Taxotere; ***Thai.:*** Daxotel†; Taxotere; ***Turk.:*** Taxotere; ***UK:*** Taxotere; ***USA:*** Taxotere; ***Venez.:*** Daxotel; Taxotere.

Doxifluridine *(rINN)*

5′-Deoxy-5-fluorouridine; 5-DFUR; Doxifluridina; Doxifluridinum; FUDR; Ro-21-9738.

Доксифлуридин

$C_9H_{11}FN_2O_5$ = 246.2.
CAS — 3094-09-5.

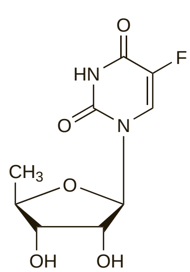

Pharmacopoeias. In *Jpn.*

Profile

Doxifluridine is an antineoplastic that probably acts through its conversion in the body to fluorouracil (p.722). It is given orally in the management of malignant neoplasms of the breast (p.661) and gastrointestinal tract (p.664), and of other solid tumours, in doses of 0.8 to 1.2 g daily in divided doses. It has also been given by the intravenous route.

Pharmacokinetics. Doxifluridine is metabolised to fluorouracil and 5,6-dihydrofluorouracil. It is orally active with a bioavailability of 34 to 47%.

References.

1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; **43:** 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol* 1999; **47:** 351–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Furtulon.

Doxorubicin *(BAN, USAN, rINN)*

Adriamycin; Doksorubisiini; Doxorubicina; Doxorubicine; Doxorubicinum; FI-106; 3-Hydroxyacetyldaunorubicin; 14-Hydroxydaunomycin. 8-Hydroxyacetyl (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione.

Доксорубицин

$C_{27}H_{29}NO_{11}$ = 543.5.
CAS — 23214-92-8.
ATC — L01DB01.
ATC Vet — QL01DB01.

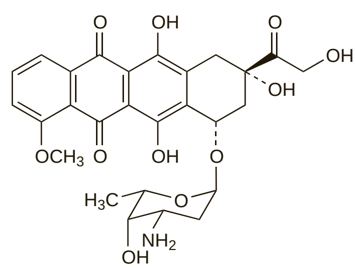

NOTE. In many countries the name Adriamycin is a trademark.

Doxorubicin Citrate *(BANM, rINNM)*

Citrato de doxorubicina; Doxorubicine, Citrate de; Doxorubicini Citras.

Доксорубицина Цитрат

$C_{27}H_{29}NO_{11},xC_6H_8O_7$.
CAS — 111266-55-8.
ATC — L01DB01.
ATC Vet — QL01DB01.

NOTE. Doxorubicin citrate complex is a constituent of some liposomal products. It is prepared from doxorubicin hydrochloride (below).

Doxorubicin Hydrochloride *(BANM, rINNM)*

Cloridrato de Doxorrubicina; Doksorubicino hidrochloridas; Doksorubicyny chlorowodorek; Doksorubisiinihydrokloridi; Doksorubisin Hidroklorür; Doxorubicine, chlorhydrate de; Doxorubicin-hidroklorid; Doxorubicin-hydrochlorid; Doxorubicinhydroklorid; Doxorubicini hydrochloridum; Hidrocloruro de doxorubicina; NSC-123127.

Доксорубицина Гидрохлорид

$C_{27}H_{29}NO_{11}$,HCl = 580.0.
CAS — 25316-40-9.
ATC — L01DB01.
ATC Vet — QL01DB01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Doxorubicin Hydrochloride). The hydrochloride of a substance isolated from certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It contains between 98 and 102% of the hydrochloride, calculated on the anhydrous substance. An orange-red, hygroscopic, crystalline powder. Soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers.

USP 31 (Doxorubicin Hydrochloride). A red-orange, hygroscopic, crystalline or amorphous powder. It contains not less than 98% and not more than 102% of $C_{27}H_{29}NO_{11}$,HCl, calculated on the anhydrous, solvent-free basis. Soluble in water, in sodium chloride 0.9%, and in methyl alcohol; practically insoluble in chloroform, in ether, and in other organic solvents. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. It may exist in an amorphous form, which should be stored at –25° to –10°.

Incompatibility. Admixture of doxorubicin hydrochloride with cefalotin sodium, dexamethasone, diazepam, or hydrocortisone sodium succinate is reported to result in immediate precipitation;[1] similarly precipitation has occurred when doxorubicin hydrochloride was mixed with furosemide or heparin sodium.[2] A mixture of fluorouracil or aminophylline with doxorubicin hydrochloride is reported to darken in colour from red to purple, indicating degradation of doxorubicin.[1] For mention of the compatibility of doxorubicin with paclitaxel, see p.759.

Liposomal doxorubicin differs in its incompatibilities from conventional formulations: whereas the latter are reportedly incompatible with allopurinol, cefepime, and ganciclovir, there was no visual evidence of this with the liposomal formulation. However, it was incompatible with a number of drug solutions including amphotericin B, docetaxel, gallium nitrate, hydroxyzine hydrochloride, metoclopramide hydrochloride, miconazole, mitoxantrone hydrochloride, morphine sulfate and some other opioids, paclitaxel, sodium bicarbonate, and some antibacterials.[3]

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
2. Cohen MH, *et al.* Drug precipitation within IV tubing: a potential hazard of chemotherapy administration. *Cancer Treat Rep* 1985; **69:** 1325–6.
3. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2708–13.

Stability. Although sensitive to light at low concentrations, doxorubicin is not subject to significant photodegradation at clinical concentrations and special precautions to protect solutions from light during administration do not appear to be necessary.[1,2] Solutions in sodium chloride solution 0.9% were reported[3] to be stable for 24 days when stored in PVC minibags at 25° and for even longer if stored in minibags or polypropylene syringes at 4°. Stability in solution seems to be partly related to pH, with doxorubicin becoming more stable[3-5] at acid pH. A fall in pH of the solution also significantly decreases the loss of doxorubicin by adsorption and precipitation onto the surface of a positively-charged in-line filter.[6]

Some liposomal doxorubicin formulations should be diluted only with glucose 5%. If not used immediately, they may be stored for 24 hours at 2° to 8°.

1. Tavoloni N, *et al.* Photolytic degradation of adriamycin. *J Pharm Pharmacol* 1980; **32:** 860–2.
2. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
3. Wood MJ, *et al.* Stability of doxorubicin, daunorubicin and epirubicin in plastic syringes and minibags. *J Clin Pharm Ther* 1990; **15:** 279–89.
4. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; **38:** 483–6.
5. Beijnen JH, *et al.* Stability of anthracycline antitumour agents in infusion fluids. *J Parenter Sci Technol* 1985; **39:** 220–2.
6. Francomb MM, *et al.* Effect of pH on the adsorption of cytotoxic drugs to a 96 hour intravenous filter. *Pharm J* 1991; **247:** R26.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p.635 and p.639.

Doxorubicin and other anthracyclines cause pronounced bone-marrow depression, which may be dose-limiting. White cell count reaches a nadir 10 to 15 days after a dose and usually recovers by about 21 days.

The anthracyclines may produce cardiac toxicity, both as an acute, usually transient disturbance of cardiac function marked by ECG abnormalities and, sometimes, arrhythmias; and as a delayed, sometimes fatal, irreversible congestive heart failure, which may occur suddenly. Severe cardiotoxicity is more likely in adults receiving total cumulative doses of doxorubicin greater than 450 to 550 mg/m^2, and may occur months or even years after use.

Gastrointestinal disturbances include moderate or sometimes severe nausea and vomiting; stomatitis and oesophagitis may progress to ulceration. More rarely, facial flushing, conjunctivitis, and lachrymation may occur. Alopecia occurs in the majority of patients. The urine may be coloured red. Occasional hypersensitivity reactions may occur. Hyperuricaemia may occur due to tumour lysis syndrome.

Doxorubicin and other anthracyclines are very irritant and thrombophlebitis and streaking of the skin over the vein used for injection has been reported; extravasation is serious and may produce extensive local necrosis and ulceration. Intravesical instillation can cause bladder and urethral irritation, haematuria, and haemorrhagic cystitis.

Combination therapy including doxorubicin has rarely been associated with secondary acute myeloid leukaemia (see also Carcinogenicity, p.635).

Formulations of liposomal doxorubicin may be associated with a reduced potential for local tissue necrosis, and possibly a reduced incidence of cardiotoxicity, although current clinical experience is limited, and such toxicity remains a possibility. Conversely, palmar-plantar erythrodysesthesia (p.639) appears to be more common, and may be dose-limiting. In addition, an acute pseudo-allergic reaction may be seen on initial infusion, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. Cardiotoxicity has been a major factor in limiting the use of the anthracyclines, doxorubicin and daunorubicin.[1-5] Toxicity is essentially of 2 kinds: acute, usually reversible ECG changes, including a wide range of arrhythmias, and a delayed, usually irreversible dose-related cardiomyopathy, resulting in congestive heart failure.[3-5] The latter may be further subdivided into chronic effects, occurring up to about a year afterwards, and late-onset toxicity occurring years after treatment.[4] Delayed toxicity may be fatal in as many as 60% of patients who develop it.[2]

The single most important determinant of cardiac toxicity appears to be the *cumulative dose*, with the risk of toxicity becoming ever greater at cumulative doxorubicin doses of 550 mg/m^2 or more,[2] and daunorubicin doses of 600 mg/m^2 or more.[1] However, patients vary widely in sensitivity,[4] and these values represent relatively arbitrary choices on a continuum of risk: there is no single safe dose.[2] Even at doses that produce no symptoms, subclinical myocardial damage may occur, and in children this may result in diminished cardiac reserve and heart disease in later life.[3,6,7] The *dosage schedule* also appears to be important; relatively high single doses on an infrequent schedule (presumably resulting in higher peak concentrations) appear to be more cardiotoxic than lower, weekly doses, or continuous infusion.[2,3,5,8-10] Cardiotoxicity is also reported to be more likely in *children and elderly* patients, and in those who have received prior *radiotherapy* to the chest.[1-5] There is reason to believe that previous *cardiovascular disease* may also increase the risk,[2-4] although such patients are commonly excluded from studies of anthracycline therapy.[2] *Females* may be at greater risk than males.[11] Use with cyclophosphamide, trastuzumab, or *other antineoplastics* with cardiotoxic potential may increase the likelihood of cardiomyopathy.

The late development of cardiac toxicity is of some concern: although in one study the mean time to development of symptoms was 33 days after a dose, with a range of 0 to 231 days,[2] several reports have indicated that late cardiac failure may occur up to 18 years after anthracycline therapy.[4,12,13]

Prevention. Given that doxorubicin-induced cardiac failure has been reported to occur in between 0.4 and 9% of all recipients, and that the fatality rate is high, much effort has gone into ways of predicting and preventing anthracycline-induced cardiotoxicity. Although ECG changes are commonly monitored, most of the changes are not predictive of cardiomyopathy and severe cardiac toxicity can occur without ECG changes. However, a persistent reduction in the voltage of the QRS wave is generally indicative of the need to perform further tests. Non-invasive cardiac monitoring, by means of echocardiography or radionuclide angiography, is useful in predicting the development of cardiomyopathy, but may give normal results until damage is quite advanced; sensitivity may be improved with exercise stress tests.[3-5] Endomyocardial biopsy is the most sensitive indicator of cardiomyopathy, but it is invasive and not widely available. The Childrens Cancer Study Group[14] has issued guidelines for monitoring using ECG, echocardiography, and radionuclide angiocardiography in patients receiving anthracyclines. The role of such techniques in predicting late-onset cardiotoxicity remains to be clarified.[4] There is some preliminary evidence to suggest that concentrations of cardiac troponins and natriuretic peptides could be used as predictive markers of myocardial damage.[15]

Dexrazoxane (p.1443) has shown some protective effect against the cardiotoxicity of doxorubicin and other anthracyclines, and is used to reduce cardiomyopathy in women receiving doxorubicin for metastatic breast cancer.

Alteration of the dosage schedule to weekly rather than three-weekly dosage, or the use of continuous infusion, has also been advocated as a way of reducing doxorubicin cardiotoxicity,[8-10] as has giving anthracyclines formulated in liposomes.[4]

Several anthracycline derivatives have been developed with the aim of reducing the inherent cardiotoxicity of this class of compounds, including aclarubicin (p.676), epirubicin (p.716), and mitoxantrone (p.754). However, although this strategy has met with some success, almost all these compounds exhibit some degree of cardiotoxicity.

Treatment. The result of treatment for such cardiotoxicity has generally been poor. Options have included digoxin, diuretics, low-salt diet, and bed rest. However, beta blockers may be useful, and results in patients with epirubicin-induced cardiotoxicity[16] have indicated that treatment with an ACE inhibitor can improve cardiac function and survival. Study is underway to determine whether ACE inhibitors can also prevent the initial toxicity if given immediately after an anthracycline.[17] Heart transplantation has been used.[5]

1. Von Hoff DD, *et al.* Daunomycin-induced cardiotoxicity in children and adults: a review of 110 cases. *Am J Med* 1977; **62:** 200–8.
2. Von Hoff DD, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91:** 710–17.
3. Hale JP, Lewis IJ. Anthracyclines: cardiotoxicity and its prevention. *Arch Dis Child* 1994; **71:** 457–62.
4. Shan K, *et al.* Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996; **125:** 47–58.
5. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; **339:** 900–905.
6. Yeung ST, *et al.* Functional myocardial impairment in children treated with anthracyclines for cancer. *Lancet* 1991; **337:** 816–18.
7. Lipschultz SE, *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991; **324:** 808–15.
8. Legha SS, *et al.* Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982; **96:** 133–9.
9. Torti FM, *et al.* Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule: assessment by endomyocardial biopsy. *Ann Intern Med* 1983; **99:** 745–9.
10. Lum BL, *et al.* Doxorubicin: alteration of dose scheduling as a means of reducing cardiotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 259–64.
11. Lipshultz SE, *et al.* Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995; **332:** 1738–43.
12. Goorin AM, *et al.* Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. *J Pediatr* 1990; **116:** 144–7.
13. Steinherz LJ, *et al.* Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991; **266:** 1672–7.
14. Steinherz LJ, *et al.* Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics* 1992; **89:** 942–9.
15. Sparano JA, *et al.* Predicting cancer therapy-induced cardiotoxicity: the role of troponins and other markers. *Drug Safety* 2002; **25:** 301–11.
16. Jensen BV, *et al.* Treatment with angiotensin-converting-enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. *Lancet* 1996; **347:** 297–9.
17. Jensen BV, *et al.* Angiotensin-converting enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. *Lancet* 1996; **347:** 1485.

Effects on the liver. Hepatitis and non-specific hepatocellular damage has been reported in patients receiving doxorubicin as part of combination therapy.[1] A characteristic hepatotoxicity can also be produced by the combination of radiotherapy with doxorubicin.[2]

1. Avilés A, *et al.* Hepatic injury during doxorubicin therapy. *Arch Pathol Lab Med* 1984; **108:** 912–13.
2. Price LA. Surviving malignant disease: medical and oncological aspects. *Br J Hosp Med* 1983; **30:** 8–12.

Effects on the skin and nails. Hyperpigmentation has occurred in patients given daunorubicin, doxorubicin, or idarubicin.[1-6] Reports described pigmentation of the skin and transverse hyperpigmented bands of the nails. Effects on the skin resolved over several weeks, and bands on the nails moved with normal nail growth. Dark-skinned patients appear to be more susceptible to this adverse effect. Biopsy has found an increase in melanin granules in the affected tissues. An unusual blue-grey pigmentation of the face was reported in a patient given doxorubicin.[7]

For specific reference to treatment of alopecia caused by doxorubicin, and for extravasation, see p.639.

1. Kelly TM, *et al.* Hyperpigmentation with daunorubicin therapy. *Arch Dermatol* 1984; **120:** 262–3.
2. Kumar L, Kochupillai V. Doxorubicin induced hyperpigmentation. *N Z Med J* 1990; **103:** 165.
3. Curran CF. Doxorubicin-associated hyperpigmentation. *N Z Med J* 1990; **103:** 517.
4. Anderson LL, *et al.* Cutaneous pigmentation after daunorubicin chemotherapy. *J Am Acad Dermatol* 1992; **26:** 255–6.
5. Borecky DJ, *et al.* Idarubicin-induced pigmentary changes of the nails. *Cutis* 1997; **59:** 203–4.
6. Kroumpouzos G, *et al.* Generalized hyperpigmentation with daunorubicin chemotherapy. *J Am Acad Dermatol* 2002; **46** (suppl): S1–S3.
7. Konohana A. Blue-gray pigmentation in a patient receiving doxorubicin. *J Dermatol* 1992; **19:** 250–2.

Palmar-plantar erythrodysesthesia syndrome. Discussion of palmar-plantar erythrodysesthesia syndrome (p.639) associated with the use of liposomal doxorubicin, and recommendations for its management.[1] The most effective way of preventing the syndrome was to maintain doses at not more than 10 mg/m^2 weekly (typically as a single infusion of 40 mg/m^2 every 4 weeks). At such doses, the syndrome, if it occurred was typically mild and easily managed. Dose-intensity modification was also thought likely to be beneficial in managing the syndrome if it developed, although evidence to support this was lacking.

1. von Moos R, *et al.* Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. *Eur J Cancer* 2008; **44:** 781–90.

Precautions

For a general discussion see Antineoplastics, p.641.

Doxorubicin and other anthracyclines are generally contra-indicated in patients with heart disease. The total cumulative dose should be limited, and cardiac function should be monitored during treatment (see Effects on the Heart, above). Blood counts should be monitored and doses should not be repeated while there is bone-marrow depression or ulceration of the mouth. Doxorubicin should be given with great care in reduced doses to patients with hepatic impairment; dosage reduction may also be necessary in children and the elderly. Extravasation results in severe tissue damage and doxorubicin and other anthracyclines should not be given by intramuscular or subcutaneous injection. The adverse effects of irradiation may be enhanced by doxorubicin and skin reactions previously induced by radiotherapy may recur; the maximum cumulative dose should be reduced to no more than 400 mg/m^2 in patients who have received radiotherapy to the chest or heart. Different liposomal formulations may not be interchangeable with conventional formulations, or with each other.

Breast feeding. Doxorubicin and its metabolites have been detected in breast milk.[1] The American Academy of Pediatrics considers[2] that doxorubicin is concentrated in breast milk, that it may possibly cause immune suppression in the infant, has unknown effects on growth, and an association with carcinogenesis.

1. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69:** 1387–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. Doxorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

A method for the destruction of doxorubicin or daunorubicin *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of daunorubicin by this method showed no mutagenicity *in vitro*; some mutagenicity was seen with high concentrations of residues from doxorubicin.

Urine and faeces produced for up to 7 days after a dose of doxorubicin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes; some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pregnancy. Although doxorubicin has been reported to be undetectable in amniotic fluid[1,2] it has been found in fetal tissue (liver, kidney, and lungs) at concentrations several times those in maternal plasma,[2] indicating that it does cross the placenta. The effect of anthracyclines on the outcome of 160 pregnancies has been analysed.[3] Most women had received combination chemotherapy that included doxorubicin or daunorubicin, for haematological malignancies or breast cancer. Most outcomes (73%) were normal. There were 5 malformations, most often associated with regimens that also included antimetabolites or alkylating agents; the malformations were highly variable. Fetal toxicity was associated with chemotherapy use for solid tumours during the first trimester, and the risk of severe fetal toxicity was significantly increased with doxorubicin doses above 70 mg/m^2 per cycle. Fetal cardiac toxicity occurred in 2 cases and was associated with anthracycline use during the second and third trimesters. It has been suggested that the use of epirubicin may reduce the risk of fetal myocardiopathy. Fetal death was more frequent in women with acute leukaemia; it was associated with disease progression and the authors recommended that chemotherapy should not be postponed.

1. Roboz J, *et al.* Does doxorubicin cross the placenta? *Lancet* 1979; **ii:** 1382–3.
2. D'Incalci M, *et al.* Transplacental passage of doxorubicin. *Lancet* 1983; **i:** 75.
3. Germann N, *et al.* Anthracyclines during pregnancy: embryo–fetal outcome in 160 patients. *Ann Oncol* 2004; **15:** 146–50.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. The cumulative dose of doxorubicin should be reduced in patients who have received other cardiotoxic drugs such as daunorubicin or cyclophosphamide. Doxorubicin is reported to inhibit the intracellular activation of stavudine and hence its antiviral effect.

Antibacterials. Hypersensitivity reactions to doxorubicin or daunorubicin have been reported in 2 patients with recent exposure to *clindamycin*, one of whom had exhibited hypersensitivity to that antibiotic.[1] The possibility of cross-sensitivity between anthracyclines and clindamycin should be considered.

1. Arena FP, Sherlock S. Doxorubicin hypersensitivity and clindamycin. *Ann Intern Med* 1990; **112:** 150.

Antineoplastics. Giving doxorubicin with or after drugs, such as *streptozocin*[1] or *methotrexate*,[2] that can impair hepatic function, has resulted in increased doxorubicin toxicity, possibly due to reduced hepatic clearance. A high incidence of cardiotoxicity (manifest as congestive heart failure) has been reported in patients given doxorubicin with *paclitaxel* (which also has cardiotoxic effects).[3] Any interaction may be schedule dependent.[4] Similarly an increased incidence of cardiotoxicity has been seen when *trastuzumab* was given with or after anthracyclines (see Effects on the Heart under Trastuzumab, p.782).

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[5] found that it decreased clearance of doxorubicin and prolonged the terminal half-life, increasing exposure to doxorubicin and myelosuppressive effects. The authors suggested that the dose of doxorubicin might need to be reduced by about 60%.

Sorafenib may increase systemic exposure to doxorubicin.

For a suggestion that doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, see under Daunorubicin Hydrochloride, p.709.

For a report of an increased incidence of febrile neutropenia and gastrointestinal complications when doxorubicin is used with *docetaxel*, see Antineoplastics, under Docetaxel, p.711.

In a pharmacokinetic study, both paclitaxel and docetaxel increased exposure to liposomal doxorubicin, although the effect was less pronounced with docetaxel.[6]

1. Anonymous. Two drugs may not be better than one. *JAMA* 1976; **236:** 913.
2. Robertson JH, *et al.* Toxicity of doxorubicin and methotrexate in osteogenic sarcoma. *BMJ* 1976; **1:** 23.
3. Gianni L, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13:** 2688–99.
4. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
5. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.
6. Briasoulis E, *et al.* Interaction pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel. *Cancer Chemother Pharmacol* 2004; **53:** 452–7.

Immunosuppressants. Increased plasma-doxorubicin concentrations and myelotoxicity have occurred when *ciclosporin* was used to modulate tumour resistance.[1] Severe neurological toxicity occurred in another patient given doxorubicin after long-term ciclosporin therapy.[2] It has been suggested that the use of ciclosporin or its analogues (see Antineoplastics, above for the effect of valspodar) to modulate doxorubicin resistance should be undertaken with caution.[3]

1. Rushing DA, *et al.* The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients with small cell lung cancer. *Cancer* 1994; **74:** 834–41.
2. Barbui T, *et al.* Neurological symptoms and coma associated with doxorubicin administration during chronic cyclosporin therapy. *Lancet* 1992; **339:** 1421.
3. Beck WT, Kuttesch JF. Neurological symptoms associated with cyclosporin plus doxorubicin. *Lancet* 1992; **340:** 496.

Thalidomide. In a comparison of two treatment regimens for multiple myeloma (thalidomide, dexamethasone, cisplatin, cyclophosphamide, and etoposide, with or without doxorubicin), there was an increased risk of deep-vein thrombosis in those patients who received the combination that included doxorubicin.[1] The authors cited a previous study[2] in which the addition of thalidomide to an antineoplastic regimen increased the risk of deep-vein thrombosis, and concluded that patients with multiple myeloma treated with the combination of doxorubicin and thalidomide are at increased risk.

1. Zangari M, *et al.* Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002; **100:** 1168–71.
2. Zangari M, *et al.* Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001; **98:** 1614–15.

Pharmacokinetics

After intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, and kidneys. It undergoes rapid metabolism in the liver to metabolites including the active metabolite doxorubicinol (adriamycinol). About 40 to 50% of a dose is stated to be excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5% of a dose is excreted in urine within 5 days. It does not cross the blood-brain barrier but may cross the placenta and is distributed into breast milk. The disappearance of doxorubicin from the blood is triphasic: mean half-lives are 12 minutes, 3.3 hours and about 30 hours.

The pharmacokinetics of liposomal formulations are somewhat different from the conventional drug. The use of macrogols in the surface layer of the liposomes (pegylation) reduces removal of liposomes by macrophages. This results in prolonged circulation in the plasma, with relatively little tissue distribution, but tumour neovasculature is reported to permit penetration of liposomes into tumour tissue. Pharmacokinetics are reported to be biphasic with mean half-lives of 5 hours and 55 to 75 hours respectively. A non-pegylated liposomal formulation also exists and is reported to produce higher peak plasma concentrations of total doxorubicin than conventional formulations, but lower free (not liposome-encapsulated) concentrations. Clearance is reduced, and peak plasma concentrations of doxorubicinol delayed.

◊ References.

1. Speth PAJ, *et al.* Clinical pharmacokinetics of doxorubicin. *Clin Pharmacokinet* 1988; **15:** 15–31.
2. Rushing DA, *et al.* The disposition of doxorubicin on repeated dosing. *J Clin Pharmacol* 1993; **33:** 698–702.
3. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. *Clin Pharmacol Ther* 1993; **53:** 555–61.
4. Amantea MA, *et al.* Population pharmacokinetics and pharmacodynamics of pegylated-liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma. *Clin Pharmacol Ther* 1997; **61:** 301–11.
5. Danesi R, *et al.* Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. *Clin Pharmacokinet* 2002; **41:** 431–44.
6. Swenson CE, *et al.* Pharmacokinetics of doxorubicin administered i.v. as Myocet (TLC D-99; liposome-encapsulated doxorubicin citrate) compared with conventional doxorubicin when given in combination with cyclophosphamide in patients with metastatic breast cancer. *Anticancer Drugs* 2003; **14:** 239–46.
7. Gabizon A, *et al.* Pharmacokinetics of pegylated liposomal doxorubicin : review of animal and human studies. *Clin Pharmacokinet* 2003 **42:** 419–36.

Uses and Administration

Doxorubicin is an anthracycline antineoplastic antibiotic. It is thought to have multiple modes of action including intercalation of DNA leading to an inhibition of DNA and RNA synthesis, inhibition of topoisomerase II, free radical formation, and alterations in cell membranes. Doxorubicin is a cell-cycle non-specific agent. It also has antibacterial and immunosuppressant properties.

Doxorubicin is effective against a wide range of tumours as indicated by the cross-references given below. Doxorubicin is used, often with other antineoplastics, in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, acute leukaemias, bone and soft-tissue sarcomas, neuroblastoma, Wilms' tumour, and malignant neoplasms of the bladder, breast, lung, ovary, and stomach. It has also been used in other tumours. Liposomal doxorubicin is used in the management of Kaposi's sarcoma in patients with AIDS, for the treatment of metastatic breast and ovarian cancers, and with bortezomib for the treatment of multiple myeloma.

Doxorubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 minutes or more. When used as a single agent, the dose is 60 to 75 mg/m^2, or 1.2 to 2.4 mg/kg, once every 3 weeks. Alternatively, doses of 20 to 25 mg/m^2 have been given daily for 3 days every 3 weeks, although dividing the dose in this way may increase the incidence of mucositis. A regimen of 20 mg/m^2 as a single weekly dose may be used, and is reported to be associated with a lower incidence of cardiotoxicity.

Doses may need to be reduced if doxorubicin is given with other antineoplastics: a dose of 30 to 60 mg/m^2 every 3 weeks has been suggested. Doses should also be reduced in patients with liver dysfunction (see below). The maximum total dose should not exceed 450 to 550 mg/m^2; in patients who have received radiotherapy to the chest, or other cardiotoxic drugs, it may be advisable to further limit the total dose.

In the management of AIDS-related Kaposi's sarcoma *pegylated liposomal* doxorubicin hydrochloride is given in an intravenous dose of 20 mg/m^2 infused over 30 minutes once every 2 to 3 weeks. For the treatment of breast and ovarian cancers, the suggested dose of this liposomal formulation is 50 mg/m^2 infused over 1 hour once every 4 weeks. In the treatment of multiple myeloma, liposomal doxorubicin hydrochloride is given at a dose of 30 mg/m^2 on day 4 of the bortezomib regimen (see p.689); it is given as an infusion over 1 hour immediately after the bortezomib infusion. In all these conditions, treatment should be continued for as long as the patient responds satisfactorily and tolerates treatment. The pegylated liposomal formulation should be diluted only with glucose 5%; generally, doses below 90 mg are diluted in 250 mL, and doses over 90 mg are diluted in 500 mL.

A *non-pegylated liposomal* formulation is also available and contains a doxorubicin citrate complex prepared with the aid of doxorubicin hydrochloride. It is given in the treatment of metastatic breast cancer in doses equivalent to doxorubicin hydrochloride 60 to 75 mg/m^2 every 3 weeks, with cyclophosphamide 600 mg/m^2. Doses are given by intravenous infusion over 1 hour, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of 0.4 to 1.2 mg/mL doxorubicin.

Blood counts should be made routinely during treatment with doxorubicin (see also Bone-marrow Depression, p.639) and cardiac function should be monitored at regular intervals for early signs of cardiotoxicity.

Doxorubicin hydrochloride has also been instilled into the bladder in the local treatment of malignant neoplasms. For this purpose 50 mL of a 1 mg/mL solution may be instilled into the bladder for about one hour; treatment may be given at weekly to monthly intervals. Doxorubicin has also been given intra-arterially.

Various novel formulations of doxorubicin have been investigated. Doxorubicin with carbon/iron carrier particles (MTC-DOX) is a magnetically targeted treatment, using an external magnet to keep the drug at the tumour site, that has been investigated for hepatocellular carcinoma. A polymer of doxorubicin and polyisohexylcyanoacrylate in nanoparticle form is under investigation for the treatment of hepatocellular carcinoma. Doxorubicin-eluting beads, for injection directly into the brain, are under investigation for the treatment of glioma.

◊ Reviews of liposomal formulations.

1. Working PK, Dayan AD. CPMP Preclinical Expert Report: Caelyx (Stealth liposomal doxorubicin HCL). *Hum Exp Toxicol* 1996; **15:** 752–85.
2. Sharpe M, *et al.* Polyethylene glycol-liposomal doxorubicin: a review of its use in the management of solid and haematological malignancies and AIDS-related Kaposi's sarcoma. *Drugs* 2002; **62:** 2089–2126.
3. Forbes C, *et al.* A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002; **6:** 1–119.
4. O'Shaughnessy JA. Pegylated liposomal doxorubicin in the treatment of breast cancer. *Clin Breast Cancer* 2003; **4:** 318–28.
5. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity. *Oncol Rep* 2004; **12:** 549–56.
6. Thigpen JT, *et al.* Role of pegylated liposomal doxorubicin in ovarian cancer. *Gynecol Oncol* 2005; **96:** 10–18.
7. Soloman R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal doxorubicin. *Clin Lymphoma Myeloma* 2008; **8:** 21–32.
8. Patil RR, *et al.* Engineered nanocarriers of doxorubicin: a current update. *Crit Rev Ther Drug Carrier Syst* 2008; **25:** 1–61.

Administration in hepatic impairment. Doses of doxorubicin should be adjusted as follows in patients with liver dysfunction:

- serum-bilirubin concentrations of 12 to 30 micrograms/mL: half the normal dose
- serum-bilirubin greater than 30 micrograms/mL: quarter of the usual dose.

Slightly different schedules may apply to liposomal products but may vary between preparations.

Amyloidosis. For mention of the use of doxorubicin in patients with amyloidosis (and of the increased risk this may carry in cardiac amyloidosis) see p.743.

Malignant neoplasms. Doxorubicin plays a major role in combination regimens for chemotherapy of solid malignancies; it is often employed for tumours of the breast and lung (see p.661 and p.668) and for Wilms' tumour and neuroblastoma or retinoblastoma in children (see p.667, p.674, and p.675) and has been used for malignancies of the bladder (p.659); for various gynaecological cancers including those of the endometrium, and ovary (see p.663, and p.670); for cancer of the liver, stomach, and pancreas (p.667, p.664, p.671); and for neoplasms of prostate, and thymus (p.671 and p.674). It is also used in the treatment of sarcomas of bone and soft-tissue (see p.675 and p.676) and liposomal doxorubicin is used in patients with Kaposi's sarcoma (see p.675).

In addition, doxorubicin is a component of the ABVD regimen used to treat Hodgkin's disease (see p.655) and is part of the CHOP regimen used for non-Hodgkin's lymphoma (p.656). Doxorubicin is also used in Burkitt's lymphoma (p.657), mycosis fungoides (p.657), and the lymphomas associated with AIDS (see p.657). It has been employed in acute lymphoblastic leukaemia (p.651), in chronic lymphocytic leukaemia as part of the CHOP regimen (though with uncertain benefit—see p.653), and in multiple myeloma (p.658).

Preparations

BP 2008: Doxorubicin Injection;
USP 31: Doxorubicin Hydrochloride for Injection; Doxorubicin Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Adriblastina; Caelyx†; Colhidrol; Dicladox; Doxocris; Doxokebir; Doxopeg; Doxorbin†; Doxtie; Flavicina†; Nagun; Onkostatil; Ranxas†; Roxorin; Varidoxo; ***Austral.:*** Caelyx; ***Austria:*** Adriblastin; Caelyx; DOXO-Cell; Doxolem; Doxorubin; Myocet; ***Belg.:*** Adriblastina; Caelyx; Doxorubin; Myocet; ***Braz.:*** Adriblastina; Biorrub; Caelyx; Doxofil†; Doxolem; Neoxane†; Rubex; Rubidox; ***Canad.:*** Caelyx; Myocet; ***Chile:*** Adriblastina; Caelyx; Daxotel; ***Cz.:*** Adriblastina; Caelyx; Doxolem; Myocet; Rastocin†; ***Denm.:*** Caelyx; ***Fin.:*** Caelyx; ***Fr.:*** Adriblastine; Caelyx; Myocet; ***Ger.:*** Adriblastin; Adrimedac; Caelyx; DOXO-Cell; Myocet; Onkodox; Ribodoxo-L; ***Gr.:*** Adriblastina; Caelyx; Doxorubin; Doxotil; Myocet; Rubidox; ***Hong Kong:*** Caelyx; ***Hung.:*** Adriblastina; Caelyx; Myocet; Pallagicin†; ***India:*** Adrim†; Cadria; Duxocin; Oncodox; ***Indon.:*** Caelyx; Pallagicin; Rubidox; ***Irl.:*** Caelyx; Myocet; ***Israel:*** Adriblastina; Caelyx†; Doxil; ***Ital.:*** Adriblastina; Caelyx; Myocet; ***Jpn:*** Adriacin; ***Malaysia:*** Caelyx; Doxorubin; ***Mex.:*** Adriblastina; Caelyx; Doxolem; Doxotec; Ifadox; Oxocina†; ***Neth.:*** Adriblastina; Caelyx; Doxorubin; Myocet; ***Norw.:*** Caelyx; ***NZ:*** Caelyx; Doxorubin; ***Philipp.:*** Adriblastina; Adrim; Axibin; Caelyx; Rubidox; ***Pol.:*** Adriblastina; Adrimedac; Biorubina; Caelyx; Rastocin; ***Port.:*** Adriblastina†; DOXO-cell; Fauldoxo; Myocet; ***Rus.:*** Caelyx (Келикс); Doxolem (Доксолем)†; Rastocin (Растоцин); ***S.Afr.:*** Adriblastina; Caelyx; ***Singapore:*** Adriblastina; Caelyx; Doxorubin†; ***Spain:*** Caelyx; Farmiblastina; Myocet; ***Swed.:*** Caelyx; ***Switz.:*** Adriblastin; Caelyx; ***Thai.:*** AD Mycin; Adriblastina; Adrim; Caelyx; Doxolem; Doxorubin; Lipo-Dox; ***Turk.:*** Adriblastina; Caelyx; ***UK:*** Caelyx; Myocet; ***USA:*** Doxil; Rubex†; ***Venez.:*** Adriblastina; Adrim; Caelyx; Doxonolver.

Droloxifene *(USAN, rINN)* ⊗

Droloxifène; Droloxifeno; Droloxifenum; 3-Hydroxytamoxifen; K-21060E. (*E*)-α-{*p*-[2-(Dimethylamino)ethoxy]phenyl}-α′-ethyl-3-stilbenol.

Дролоксифен

$C_{26}H_{29}NO_2$ = 387.5.
CAS — 82413-20-5.

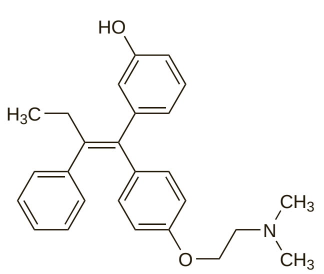

Profile

Droloxifene is a selective oestrogen receptor modulator related to tamoxifen (p.772) and with similar general properties. It has been investigated in the hormonal treatment and prophylaxis of breast cancer and is under study for osteoporosis.

Edatrexate *(USAN, rINN)*

CGP-30694; Édatrexate; Edatrexato; Edatrexatum. *N*-(*p*-{1-[(2,4-Diamino-6-pteridinyl)methyl]propyl}benzoyl)-L-glutamic acid.

Эдатрексат

$C_{22}H_{25}N_7O_5$ = 467.5.
CAS — 80576-83-6.

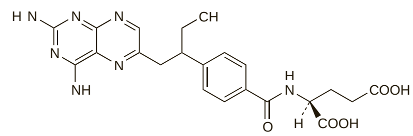

Profile

Edatrexate is an analogue of methotrexate (p.745) and has similar general properties. It has been investigated as an antineoplastic in the treatment of various malignant neoplasms. Mucositis may be dose limiting.

Edrecolomab *(USAN, rINN)*

17-1A Antibody; C1; Édrécolomab; Edrecolomabum; Monoclonal Antibody 17-1A. Immunoglobulin G2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer.

Эдреколомаб

CAS — 156586-89-9.
ATC — L01XC01.
ATC Vet — QL01XC01.

Profile

Edrecolomab is a monoclonal antibody of murine origin directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery in patients with colorectal cancer (p.665), although reports of improved survival do not seem to have been borne out. It has been given by intravenous infusion over 2 hours, in an initial dose of 500 mg, followed by 4 further doses of 100 mg at monthly intervals. The drug is of murine origin and most patients develop antibodies after use. Hypersensitivity reactions, including anaphylactic reactions, have occurred.

It has also been tried for other malignant neoplasms including pancreatic cancer and advanced breast cancer.

◊ References.

1. Riethmüller G, *et al.* Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 1994; **343:** 1177–83.
2. Riethmüller G, *et al.* Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J Clin Oncol* 1998; **16:** 1788–94.
3. Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A). *Drugs* 1998; **56:** 619–26.
4. Punt CJA, *et al.* Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 2002; **360:** 671–7.
5. Hartung G, *et al.* Adjuvant therapy with edrecolomab versus observation in stage II colon cancer: a multicenter randomized phase III study. *Onkologie* 2005; **28:** 347–50.

Efaproxiral *(USAN, rINN)* ⊗

Éfaproxiral; Efaproxiralum; RSR-13. 2-(4-{2-[(3,5-Dimethylphenyl)amino]-2-oxoethyl}phenoxy)-2-methyl propanoic acid.

Эфапроксирал

$C_{20}H_{23}NO_4$ = 341.4.
CAS — 131179-95-8.
ATC — L01XD06.
ATC Vet — QL01XD06.

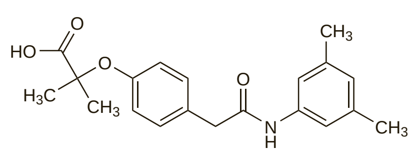

Efaproxiral Sodium *(USAN, rINNM)* ⊗

Efaproxiral sódico; Éfaproxiral Sodique; Natrii Efaproxiralum.

Натрий Эфапроксирал

$C_{20}H_{22}NNaO_4$ = 363.4.
CAS — 170787-99-2.
ATC — L01XD06.
ATC Vet — QL01XD06.

Profile

Efaproxiral is an allosteric modifier of haemoglobin that enhances the diffusion of oxygen to hypoxic tumour tissue, making it more sensitive to radiotherapy. It has been investigated in the treatment of brain metastases from solid tumours.

Enocitabine *(rINN)*

Behenoyl Cytarabine; Behenoylcytosine Arabinoside; BH-AC; Enocitabina; Énocitabine; Enocitabinum; NSC-239336. *N*-(1-β-D-Arabinofuranosyl-1,2-dihydro-2-oxo-4-pyrimidinyl)docosanamide.

Эноцитабин

$C_{31}H_{55}N_3O_6$ = 565.8.
CAS — 55726-47-1.

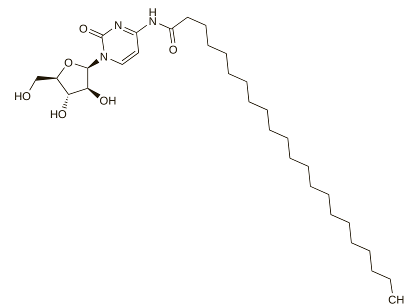

Profile

Enocitabine is an antineoplastic that is converted in the body to cytarabine (p.705). It has been used similarly in the treatment of acute leukaemias.

Enzastaurin Hydrochloride *(USAN, rINNM)*

Enzastaurine, Chlorhydrate d'; Enzastaurini Hydrochloridum; Hidrocloruro de enzastaurina; LY-317615. 3-(1-Methyl-1*H*-indol-3-yl)-4-{1-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1*H*-indol-3-yl}-1*H*pyrrole-2,5-dione hydrochloride.

Энзастаурина Гидрохлорид

$C_{32}H_{29}N_5O_2$,HCl = 552.1.
CAS — 359017-79-1.

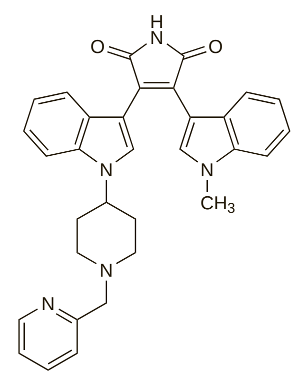

(enzastaurin)

Profile

Enzastaurin hydrochloride is a protein kinase C inhibitor that is under investigation for the treatment of gliomas and non-Hodgkin's lymphoma.

◊ References.

1. Sorbera LA, *et al.* Enzastaurin hydrochloride. *Drugs Of The Future* 2007; **32:** 297–309. Correction. *ibid.*; 751.
2. Ma S, Rosen ST. Enzastaurin. *Curr Opin Oncol* 2007; **19:** 590–5.
3. Chen YB, LaCasce AS. Enzastaurin. *Expert Opin Invest Drugs* 2008; **17:** 939–44.

Epirubicin Hydrochloride

(BANM, USAN, rINNM)

4′-Epiadriamycin Hydrochloride; 4′-Epidoxorubicin Hydrochloride; Épirubicine, chlorhydrate d′; Epirubicin-hidroklorid; Epirubicin-hydrochlorid; Epirubicinhydroklorid; Epirubicini hydrochloridum; Epirubicino hidrochloridas; Epirubisiinihydrokloridi; Epirubisin Hidroklorür; Hidrocloruro de epirubicina; IMI-28; Pidorubicin Hydrochloride. (8*S*,10*S*)-10-(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride.

Эпирубицина Гидрохлорид

$C_{27}H_{29}NO_{11},HCl = 580.0.$

CAS — 56420-45-2 (epirubicin); 56390-09-1 (epirubicin hydrochloride).

ATC — L01DB03.

ATC Vet — QL01DB03.

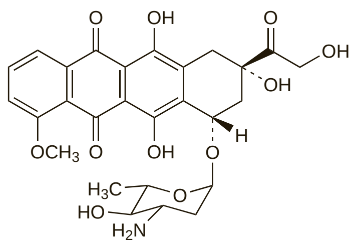

(epirubicin)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Epirubicin Hydrochloride). A substance obtained by chemical transformation of a substance produced by certain strains of *Streptomyces peucetius*. An orange-red powder. Soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.0 to 5.5. Store at 2° to 8° in airtight containers. Protect from light.

Incompatibility. Licensed product information states that epirubicin hydrochloride is incompatible with heparin or fluorouracil, resulting in precipitation, and that it is hydrolysed in alkaline solutions.

Stability. Epirubicin was not subject to significant photodegradation at clinical concentrations,[1,2] and special precautions to protect solutions from light during use do not appear to be necessary. However, photodegradation may be significant at lower concentrations (below 500 micrograms/mL).[1]

1. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
2. Pujol M, *et al.* Stability study of epirubicin in NaCl 0.9% injection. *Ann Pharmacother* 1997; **31:** 992–5.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Cardiotoxicity and myelotoxicity may be less than with doxorubicin. Cardiotoxicity is more likely when the cumulative dose exceeds 0.9 to 1 g/m^2.

Effects on the heart. For further discussion of the cardiotoxicity of anthracyclines, see under Adverse Effects of Doxorubicin, p.713.

Interactions

As for Doxorubicin, p.713.

Antineoplastics. Increased exposure to epirubicin, and a consequent increase in myelotoxicity, has been reported in patients given epirubicin immediately after *paclitaxel*, compared with patients who received epirubicin before paclitaxel.[1] Similar interactions have been seen when paclitaxel was given before other anthracyclines.[2] These and other studies[3,4] have suggested that paclitaxel given in this way is associated with a reduced conversion of epirubicin to the less myelotoxic metabolite, epirubicinol, although the interaction is complex, and may involve both disposition and pharmacodynamics.

1. Venturini M, *et al.* Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. *J Clin Oncol* 2000; **18:** 2116–25.
2. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
3. Grasselli G, *et al.* Clinical and pharmacologic study of the epirubicin and paclitaxel combination in women with metastatic breast cancer. *J Clin Oncol* 2001; **19:** 2222–31.
4. Danesi R, *et al.* Pharmacokinetics and pharmacodynamics of combination chemotherapy with paclitaxel and epirubicin in breast cancer patients. *Br J Clin Pharmacol* 2002; **53:** 508–18.

Cimetidine. Cimetidine increased the formation of the active metabolite of epirubicin in a study in 8 patients; there was also a substantial increase in systemic exposure to unchanged epirubicin.[1] The mechanisms and potential clinical significance of the interaction were unclear.

1. Murray LS, *et al.* The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common drug interaction. *Clin Oncol* 1998; **10:** 35–8.

Pharmacokinetics

After intravenous doses epirubicin is rapidly and extensively distributed into body tissues, and undergoes metabolism in the liver, with the formation of epirubicinol (13-hydroxyepirubicin) and appreciable amounts of glucuronide derivatives. Epirubicin is eliminated mainly in bile, with a terminal plasma elimination half-life of about 30 to 40 hours. About 10% of a dose is recovered in urine within 48 hours. Epirubicin does not cross the blood-brain barrier.

◊ References.

1. Morris RG, *et al.* Disposition of epirubicin and metabolites with repeated courses to cancer patients. *Eur J Clin Pharmacol* 1991; **40:** 481–7.
2. Robert J. Clinical pharmacokinetics of epirubicin. *Clin Pharmacokinet* 1994; **26:** 428–38.

Uses and Administration

Epirubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p.714). It is used, alone or with other antineoplastics, in acute leukaemias, lymphomas, multiple myeloma, and in solid tumours including Wilms' tumour (p.667), cancer of the bladder (p.659), breast (p.661), and stomach (p.664).

Epirubicin hydrochloride is given by intravenous injection of a solution in sodium chloride 0.9% or Water for Injections into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 to 5 minutes, or by infusion over up to 30 minutes. It is given as a single agent in usual doses of 60 to 90 mg/m^2 as a single dose every 3 weeks; this dose may be divided over 2 or 3 days if desired. A regimen of 12.5 to 25 mg/m^2 once a week has also been tried in palliative care. High-dose regimens, of 120 mg/m^2 or more every 3 weeks, or 45 mg/m^2 for 3 consecutive days every 3 weeks have been used.

Doses may need to be reduced if epirubicin is given with other antineoplastics. Doses should also be reduced in patients with liver impairment (see below) and in those whose bone-marrow function is impaired by age or previous chemotherapy or radiotherapy.

A total cumulative dose of 0.9 to 1 g/m^2 should not generally be exceeded, because of the risk of cardiotoxicity.

Epirubicin has also been given by intravesical instillation in the local treatment of bladder cancer. Instillation of 50 mg weekly as a 0.1% solution (in sodium chloride 0.9% or sterile water) for 8 weeks has been suggested, reduced to 30 mg in 50 mL weekly if chemical cystitis develops; for carcinoma *in-situ*, the dose may be increased, if tolerated, to 80 mg in 50 mL weekly. For the prophylaxis of recurrence in patients who have undergone transurethral resection, 50 mg weekly for 4 weeks, followed by 50 mg instilled once a month for 11 months is the suggested regimen. The solution should be retained in the bladder for 1 hour.

Blood counts should be made routinely during treatment with epirubicin (see also Bone-marrow Depression, p.639) and cardiac function should be carefully monitored. Liver function should be assessed before and if possible during therapy.

◊ References.

1. Plosker GL, Faulds D. Epirubicin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 1993; **45:** 788–856.
2. Coukell AJ, Faulds D. Epirubicin: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. *Drugs* 1997; **53:** 453–82.
3. Onrust SV, *et al.* Epirubicin: a review of its intravesical use in superficial bladder cancer. *Drugs Aging* 1999; **15:** 307–33.
4. Ormrod D, *et al.* Epirubicin: a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. *Drugs Aging* 1999; **15:** 389–416.
5. Earl H, Iddawela M. Epirubicin as adjuvant therapy in breast cancer. *Expert Rev Anticancer Ther* 2004; **4:** 189–95.

Administration in hepatic impairment. Doses of epirubicin should be halved in patients with moderate liver dysfunction (serum bilirubin concentrations of 12 to 30 micrograms/mL), while those with severe liver impairment (serum bilirubin greater than 30 micrograms/mL) should be given a quarter of the usual dose.

Amyloidosis. For reference to a regimen including epirubicin used to control disease in a patient with amyloidosis, see p.743.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Crisabon; Cuatroepi; Epidoxo; Epifil; Epikebir; EPR†; Farmorubicin; Robanul; Rubifarm†; ***Austral.:*** Pharmorubicin; ***Austria:*** Epi-Cell; Farmorubicin; ***Belg.:*** Farmorubicine; ***Braz.:*** Farmorubicina; Nuovodox; Rubina; Tecnomax; ***Canad.:*** Pharmorubicin; ***Chile:*** Farmorrubicina; ***Cz.:*** Farmorubicin; ***Denm.:*** Farmorubicin; ***Fin.:*** Farmorubicin; ***Fr.:*** Farmorubicine; ***Ger.:*** Epi-Cell; Epi-NC; Farmorubicin; Riboepi; ***Gr.:*** Ciazil; Epirub; Farmorubicin; Megarubicin; ***Hong Kong:*** Pharmorubicin; ***Hung.:*** Farmorubicin; ***Irl.:*** Pharmorubicin; ***Israel:*** Farmorubicin; ***Ital.:*** Farmorubicina; ***Jpn:*** Farmorubicin; ***Malaysia:*** Pharmorubicin; ***Mex.:*** Binarin; Epilem; Farmorubicin; ***Neth.:*** Farmorubicine; ***Norw.:*** Farmorubicin; ***NZ:*** Pharmorubicin; ***Philipp.:*** Pharmorubicin; ***Pol.:*** Bioepicyna; Farmorubicin; ***Port.:*** Epi-cell; Farmorubicina; ***Rus.:*** Epilem (Эпилем)†; Farmorubicin (Фарморубицин); ***S.Afr.:*** Farmorubicin; ***Singapore:*** Pharmorubicin; ***Spain:*** Farmorubicina; ***Swed.:*** Farmorubicin; ***Switz.:*** Farmorubicin; ***Thai.:*** Anthracin; E.P.Mycin; Epilem; Pharmorubicin; ***Turk.:*** Farmorubicin; ***UK:*** Pharmorubicin; ***USA:*** Ellence; ***Venez.:*** Farmorubicin.

Epratuzumab *(rINN)*

Épratuzumab; Epratuzumabum. Immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer.

Эпратузумаб

CAS — 205923-57-5.

Profile

Epratuzumab is a humanised anti-CD22 monoclonal antibody under investigation, alone or conjugated with yttrium-90, for the treatment of non-Hodgkin's lymphoma. It is also under investigation for the treatment of moderate to severe SLE.

◊ References.

1. Davies SL, Martin L. Epratuzumab. *Drugs Of The Future* 2005; **30:** 683–7.
2. Leonard JP, *et al.* Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 5044–51.
3. Lindén O, *et al.* Dose-fractionated radioimmunotherapy in non-Hodgkin's lymphoma using DOTA-conjugated, Y-radiolabeled, humanized anti-CD22 monoclonal antibody, epratuzumab. *Clin Cancer Res* 2005; **11:** 5215–22.
4. Goldenberg DM. Epratuzumab in the therapy of oncological and immunological diseases. *Expert Rev Anticancer Ther* 2006; **6:** 1341–53.
5. Leonard JP, Goldenberg DM. Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene* 2007; **26:** 3704–13.

Eptaplatin *(rINN)*

Eptaplatine; Eptaplatino; Eptaplatinum; Heptaplatin; SKI-2053R. *cis*-[(4*R*,5*R*)-2-Isopropyl-1,3-dioxolane-4,5-bis(methylamine)-*N*,*N*′][malonato(2−)-*O*,*O*′]platinum.

Эптаплатин

$C_{11}H_{20}N_2O_6Pt = 471.4.$

CAS — 146665-77-2.

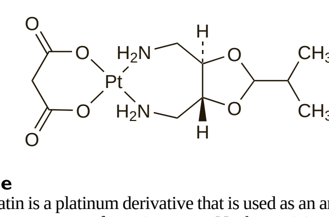

Profile

Eptaplatin is a platinum derivative that is used as an antineoplastic in the treatment of gastric cancer. Nephrotoxicity is the main adverse effect.

◊ References.

1. Ahn JH, *et al.* Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. *Cancer Chemother Pharmacol* 2002; **50:** 104–10.
2. Min YJ, *et al.* Combination chemotherapy with 5-fluorouracil and heptaplatin as first-line treatment in patients with advanced gastric cancer. *J Korean Med Sci* 2004; **19:** 369–73.

Preparations

Proprietary Preparations (details are given in Part 3)

Kor.: Sunpla.

Erlotinib Hydrochloride *(USAN, rINNM)*

CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774. *N*-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.

Эрлотиниба Гидрохлорид

$C_{22}H_{23}N_3O_4$,HCl = 429.9.

CAS — 183321-74-6 (erlotinib); 183319-69-9 (erlotinib hydrochloride).

ATC — L01XE03.

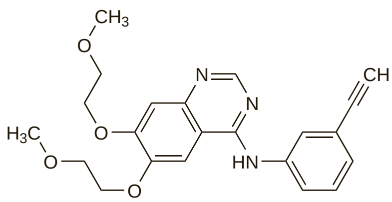

(erlotinib)

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with erlotinib hydrochloride are rash and diarrhoea. Moderate or severe diarrhoea should be treated with an appropriate antidiarrhoeal such as loperamide; dose reduction may be needed. In more severe or persistent cases leading to dehydration, therapy should be stopped temporarily. Other common adverse effects include other gastrointestinal disturbances, gastrointestinal bleeding, fatigue, alopecia, stomatitis, pruritus, dry skin, paronychia, conjunctivitis, keratoconjunctivitis sicca, epistaxis, and abdominal pain. Alterations in liver function tests have occurred. Rare cases of hepatic failure, including fatalities, have been reported. Interstitial lung disease has also been reported; fatalities have occurred. Erlotinib treatment should be interrupted if unexplained pulmonary symptoms occur, such as dyspnoea, cough, and fever.

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, can increase erlotinib concentrations and use with potent inhibitors should be avoided as increased toxicity may occur. Conversely, CYP3A4 inducers, such as rifampicin, can reduce erlotinib concentrations and may reduce its efficacy. Dose adjustments may be required (see Uses and Administration, below). Caution is also required with ciprofloxacin or potent inhibitors of CYP1A2, as erlotinib exposure may be increased, and dose reductions may be needed if adverse effects occur. Use with P-glycoprotein inhibitors such as ciclosporin and verapamil may cause altered distribution or elimination of erlotinib. Caution is advised when erlotinib is used with antacids, proton pump inhibitors, or histamine H_2-receptor antagonists, as erlotinib absorption may be impaired. Exposure to erlotinib is reduced in smokers compared with non-smokers.

Pharmacokinetics

Erlotinib is absorbed from the gastrointestinal tract, with a bioavailability of about 60%; this may increase up to almost 100% in the presence of food. Peak plasma concentrations are reached about 4 hours after a dose, and it is about 93% bound to plasma proteins. Erlotinib is metabolised predominantly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP1A2. Metabolic pathways include demethylation, to metabolites OSI-420 and OSI-413, oxidation, and aromatic hydroxylation. Erlotinib has an elimination half-life of about 36 hours. More than 80% of a dose is excreted as metabolites in the faeces.

Uses and Administration

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor. It is used for the management of locally advanced or metastatic non-small cell lung cancer (p.668) that is unresponsive to other therapy. It is also used with gemcitabine in the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer (p.671). It is given orally as the hydrochloride but doses are expressed in terms of the base: erlotinib hydrochloride 109 mg is equivalent to about 100 mg of erlotinib.

The usual dose for non-small cell lung cancer is 150 mg daily, taken at least 1 hour before or 2 hours after food. In the treatment of pancreatic cancer, the recommended dose is 100 mg daily, taken at least 1 hour before or 2 hours after food. Treatment is continued until disease progression or unacceptable toxicity occurs. Where dosage adjustment is necessary, reductions are made in 50 mg steps.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of erlotinib are considered necessary. When used with a potent CYP3A4 inhibitor, the dose of erlotinib may need to be reduced, especially if severe adverse effects occur. When given with a potent CYP3A4 inducer, increases in the dose of erlotinib should be considered at 2-week intervals with monitoring. The maximum dose of erlotinib when used with rifampicin is 450 mg. If the inducer is then stopped, the erlotinib dose will need to be immediately reduced to the indicated starting dose.

Erlotinib is also under investigation in the treatment of malignant glioma.

◊ References.

1. Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4238s–4240s.
2. Pérez-Soler R, *et al.* Determinants of tumor response and survival with erlotinib in patients with non—small-cell lung cancer. *J Clin Oncol* 2004; **22:** 3238–47.
3. Anonymous. Erlotinib. *Med Lett Drugs Ther* 2005; **47:** 25–6.
4. Smith J. Erlotinib: small-molecule targeted therapy in the treatment of non-small-cell lung cancer. *Clin Ther* 2005; **27:** 1513–34.
5. Brown ER, Shepherd FA. Erlotinib in the treatment of non-small cell lung cancer. *Expert Rev Anticancer Ther* 2005; **5:** 767–75.
6. Shepherd FA, *et al.* Erlotinib in previously treated non—small-cell lung cancer. *N Engl J Med* 2005; **353:** 123–32.
7. Tang PA, *et al.* A review of erlotinib and its clinical use. *Expert Opin Pharmacother* 2006; **7:** 177–93.
8. Gridelli C, *et al.* Erlotinib in non-small-cell lung cancer. *Expert Opin Pharmacother* 2007; **8:** 2579–92.
9. Saif MW, *et al.* Erlotinib: the first biologic in the management of pancreatic cancer. *Expert Opin Pharmacother* 2008; **9:** 1595–1607.

Administration in hepatic or renal impairment. Erlotinib is metabolised by the liver. UK licensed product information states that although erlotinib exposure was similar in patients with moderate hepatic impairment (Child-Pugh score 7 to 9) compared with those with adequate hepatic function, caution is advised when using erlotinib in hepatic impairment. Dose reduction or interruption of therapy should be considered if adverse effects occur. Use in severe hepatic impairment is not recommended due to a lack of data.

UK licensed product information also states that no dose adjustments appear necessary in patients with mild to moderate renal impairment, but that use of erlotinib in patients with severe renal impairment is not recommended. There are no data available for patients with a creatinine clearance less than 15 mL/minute or those with a serum creatinine concentration greater than 1.5 times the upper normal limit.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Tarceva; ***Austral.:*** Tarceva; ***Belg.:*** Tarceva; ***Canad.:*** Tarceva; ***Chile:*** Tarceva; ***Cz.:*** Tarceva; ***Fin.:*** Tarceva; ***Fr.:*** Tarceva; ***Ger.:*** Tarceva; ***Gr.:*** Tarceva; ***Hong Kong:*** Tarceva; ***Hung.:*** Tarceva; ***Irl.:*** Tarceva; ***Israel:*** Tarceva; ***Malaysia:*** Tarceva; ***Mex.:*** Tarceva; ***Neth.:*** Tarceva; ***NZ:*** Tarceva; ***Philipp.:*** Tarceva; ***Pol.:*** Tarceva; ***Port.:*** Tarceva; ***Rus.:*** Tarceva (Тарцева); ***Singapore:*** Tarceva; ***Swed.:*** Tarceva; ***Switz.:*** Tarceva; ***UK:*** Tarceva; ***USA:*** Tarceva.

Estramustine Sodium Phosphate *(BANM, rINNM)*

Estramustin Fosfat Sodyum; Estramustine, Phosphate Sodique de; Estramustine Phosphate Sodium *(USAN)*; Fosfato sódico de estramustina; Natrii Estramustini Phosphas; NSC-89199 (estramustine phosphate); Ro-21-8837/001; Ro-22-2296/000 (estramustine). Estra-1,3,5(10)-triene-3,17β-diol 3-[bis(2-chloroethyl)carbamate] 17-(disodium phosphate); Disodium 3-[bis(2-chloroethyl)-carbamoyloxy]estra-1,3,5(10)-trien-17β-yl orthophosphate.

Натрия Эстрамустина Фосфат

$C_{23}H_{30}Cl_2NNa_2O_6P$ = 564.3.

CAS — 2998-57-4 (estramustine); 4891-15-0 (estramustine phosphate); 52205-73-9 (estramustine sodium phosphate).

ATC — L01XX11.

ATC Vet — QL01XX11.

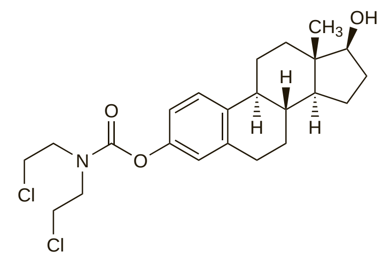

(estramustine)

Pharmacopoeias. In *Br.*

BP 2008 (Estramustine Sodium Phosphate). A white or almost white powder. Freely soluble in water and in methyl alcohol; very slightly soluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 8.5 to 10.0. Protect from light.

Adverse Effects, Treatment, and Precautions

Oestrogenic adverse effects are fairly common, and may include gynaecomastia, fluid retention, and cardiovascular effects. Gastrointestinal disturbances, hepatic dysfunction, loss of libido, hypersensitivity reactions, and occasionally leucopenia and thrombocytopenia may occur. Estramustine is contra-indicated in patients with peptic ulceration and severe hepatic or cardiovascular disease. Diabetes mellitus may be exacerbated, and the drug should be given with care to patients with disorders such as congestive heart failure, epilepsy, hypertension, migraine, and renal impairment which may be adversely affected by additional fluid retention. Care is also required in patients with conditions predisposing to hypercalcaemia, and serum calcium should be monitored in hypercalcaemic patients.

Porphyria. Estramustine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Estramustine sodium phosphate should not be given with milk products or products high in calcium, which may interfere with its absorption. Hypersensitivity reactions including angioedema have occurred rarely in patients given estramustine who were also receiving an ACE inhibitor.

Pharmacokinetics

Up to 75% of a dose of estramustine sodium phosphate is absorbed from the gastrointestinal tract and rapidly dephosphorylated. Estramustine is found in the body mainly as its oxidised isomer estromustine; both forms accumulate in the prostate. Some hydrolysis of the carbamate linkage occurs in the liver, releasing estradiol, estrone, and the normustine group. Estramustine and estromustine have plasma half-lives of 10 to 20 hours, and are excreted with their metabolites mainly in the faeces.

Uses and Administration

Estramustine is a combination of estradiol and normustine and has weaker oestrogenic activity than estradiol and weaker antineoplastic activity than most other alkylating agents. Estramustine phosphate is given orally as the disodium salt. Doses are calculated in terms of estramustine phosphate; 108 mg of estramustine sodium phosphate is equivalent to about 100 mg of estramustine phosphate. Estramustine phosphate with meglumine has been given by intravenous injection.

Estramustine sodium phosphate is licensed for use in the treatment of advanced prostatic carcinoma (p.671). An estramustine phosphate dose of about 14 mg/kg daily in divided doses is used. The usual initial dose is 560 to 840 mg daily, which may be adjusted to between 140 mg and 1.4 g daily according to the response and gastrointestinal tolerance. It should be given not less than 1 hour before or 2 hours after meals.

◊ References.

1. Bergenheim AT, Henriksson R. Pharmacokinetics and pharmacodynamics of estramustine phosphate. *Clin Pharmacokinet* 1998; **34:** 163–72.
2. Sangrajrang S, *et al.* Estramustine resistance. *Gen Pharmacol* 1999; **33:** 107–13.

3. Kreis W, Budman D. Daily oral estramustine and intermittent intravenous docetaxel (Taxotere) as chemotherapeutic treatment for metastatic, hormone-refractory prostate cancer. *Semin Oncol* 1999; **26** (suppl 17): 34–8.
4. Kitamura T. Necessity of re-evaluation of estramustine phosphate sodium (EMP) as a treatment option for first-line monotherapy in advanced prostate cancer. *Int J Urol* 2001; **8:** 33–6.
5. Hamilton A, Muggia F. Estramustine potentiates taxane in prostate and refractory breast cancers. *Oncology (Huntingt)* 2001; **15** (suppl 7): 40–3.
6. Kitamura T, *et al.* EMP combination chemotherapy and low-dose monotherapy in advanced prostate cancer. *Expert Rev Anticancer Ther* 2002; **2:** 59–71.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.
8. Fizazi K, *et al.* Meta-analysis of Estramustine in Prostate Cancer (MECaP) Trialists' Collaborative Group. Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data. *Lancet Oncol* 2007; **8:** 994–1000.

Preparations

BP 2008: Estramustine Phosphate Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Amsupros†; Estracyt; ***Austria:*** Estracyt; ***Belg.:*** Estracyt; ***Canad.:*** Emcyt; ***Chile:*** Estracyt; ***Cz.:*** Estracyt; ***Denm.:*** Estracyt; ***Fin.:*** Estracyt; ***Fr.:*** Estracyt; ***Ger.:*** cellmustin; Estracyt; Medactin; Multosin; Prostamustin†; ***Gr.:*** Estracyt; ***Hong Kong:*** Estracyt; ***Hung.:*** Estracyt; ***India:*** X-Trant; ***Irl.:*** Estracyt; ***Israel:*** Estracyt; ***Ital.:*** Estracyt; ***Jpn:*** Estracyt; ***Malaysia:*** Estracyt†; ***Mex.:*** Emcyt; ***Neth.:*** Estracyt; ***Norw.:*** Estracyt; ***Pol.:*** Estracyt; ***Port.:*** Estracyt; ***Rus.:*** Estracyt (Эстрацит); ***S.Afr.:*** Estracyt; ***Singapore:*** Estracyt; ***Spain:*** Estracyt; ***Swed.:*** Estracyt; ***Switz.:*** Estracyt; ***Turk.:*** Estracyt; ***UK:*** Estracyt; ***USA:*** Emcyt; ***Venez.:*** Estracyt.

Etanidazole *(USAN, rINN)*

Etanidazol; Étanidazole; Etanidazolum; NSC-301467; SR-2508. *N*-(2-Hydroxyethyl)-2-nitroimidazole-1-acetamide.

Этанидазол

$C_7H_{10}N_4O_4$ = 214.2.
CAS — 22668-01-5.

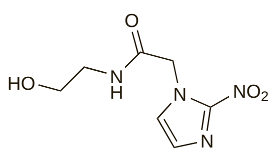

Profile

Etanidazole is a radiosensitiser, structurally related to metronidazole, that is under investigation as an adjunct to radiotherapy in the treatment of cancer. Peripheral neuropathy may be dose-limiting.

◊ References.

1. Lee DJ, *et al.* Results of an RTOG phase III trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1995; **32:** 567–76.
2. Eschwege F, *et al.* Results of a European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1997; **39:** 275–81.
3. Marcus KJ, *et al.* A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma. *Int J Radiat Oncol Biol Phys* 2003; **55:** 1182–5.
4. Drzymala RE, *et al.* Radiation Therapy Oncology Group. A phase I-B trial of the radiosensitizer: etanidazole (SR-2508) with radiosurgery for the treatment of recurrent previously irradiated primary brain tumors or brain metastases (RTOG Study 95-02). *Radiother Oncol* 2008; **87:** 89–92.

Etoposide *(BAN, USAN, rINN)*

EPEG; Etoposid; Étoposide; Etoposidi; Etopósido; Etoposidum; Etopozid; Etopozidas; NSC-141540; VP-16; VP-16-213. 4′-Demethylepipodophyllotoxin 9-[4,6-*O*-(*R*)-ethylidene-β-D-glucopyranoside]; (5*S*,5a*R*,8a*S*,9*R*)-9-(4,6-*O*-Ethylidene-β-D-glucopyranosyloxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

Этопозид

$C_{29}H_{32}O_{13}$ = 588.6.
CAS — 33419-42-0.
ATC — L01CB01.
ATC Vet — QL01CB01.

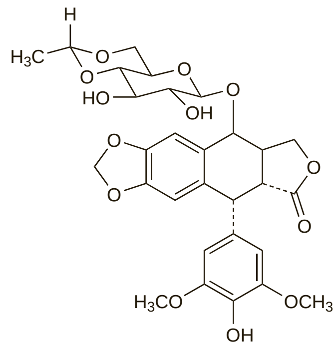

NOTE. The trivial name epipodophyllotoxin has occasionally been used incorrectly for this derivative.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Etoposide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers.

USP 31 (Etoposide). A fine, white to off-white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, in dichloromethane, and in ethyl acetate; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Etoposide Phosphate *(USAN)*

BMY-40481; Etopósido, fosfato de. {5*R*-[5α,5aβ,8aα,9β(*R**)]}-5-[3,5-Dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydrofuro-[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-Demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) 4′-(dihydrogen phosphate).

$C_{29}H_{33}O_{16}P$ = 668.5.
CAS — 117091-64-2.
ATC — L01CB01.
ATC Vet — QL01CB01.

Incompatibility. For reference to precipitation when mannitol or potassium chloride was added to mixtures of etoposide and cisplatin in sodium chloride injection, see Cisplatin, p.698.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The dose-limiting toxicity of etoposide is myelosuppression, mainly seen as leucopenia, but also thrombocytopenia, and sometimes anaemia. The nadir of the granulocyte count usually occurs 7 to 14 days after a dose, with recovery by about 21 days. Nausea and vomiting are common; there may also be anorexia, diarrhoea, and mucositis. Gastrointestinal toxicity may be more common after oral dosage. Reversible alopecia occurs in about two-thirds of all patients. Hypersensitivity or anaphylactoid reactions can occur, characterised by flushing, chills, fever, tachycardia, bronchospasm, dyspnoea, and hypotension. Apnoea and fatal reactions associated with bronchospasm have been reported. Peripheral or central neuropathies, including transient cortical blindness, have been reported rarely, as have weakness, fatigue, somnolence, aftertaste, fever, rashes, urticaria, skin pigmentation, pruritus, and dysphagia. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. Tumour lysis syndrome, sometimes fatal, has been reported after use of etoposide with other chemotherapeutic drugs. Disturbances of liver function have been reported, mainly at high doses. There have been occasional reports of cardiotoxicity. Local irritation and thrombophlebitis may occur at the site of injection. Care should be taken to avoid extravasation although tissue damage (possibly associated with the vehicle) is rare.

Rapid intravenous doses may cause hypotension; etoposide should be given by infusion over at least 30 minutes. Etoposide should not be given to patients with severe hepatic impairment nor by the intracavitary route.

Some adverse effects associated with intravenous etoposide may be due to the formulation of the vehicle.

There is evidence that etoposide may be associated with the development of secondary leukaemias—see Carcinogenicity, p.635.

Breast feeding. Some licensed product information states that it is not known whether etoposide is excreted into breast milk. However, in breast milk samples from a woman given consolidation therapy, including etoposide,[1] for acute promyelocytic leukaemia, etoposide concentrations were maximal just after a dose, but decreased rapidly to undetectable levels within 24 hours on each of three days. She started to breast feed her baby 3 weeks after the completion of therapy, and no abnormalities were observed in the infant up to 16 months of age.

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.

Effects on the gastrointestinal tract. Pneumatosis intestinalis (the presence of gas within the bowel wall), a rare condition, has been reported after intravenous[1] and oral[2] etoposide. It is supposed that myelosuppressive drugs might interfere with the mucosal integrity of the intestinal tract, and that the intestinal mucosa might be highly sensitive to etoposide.

1. Hashimoto S, *et al.* Pneumatosis cystoides intestinalis after chemotherapy for hematological malignancies: report of 4 cases. *Intern Med* 1995; **34:** 212–15.
2. Shih I-L, *et al.* Pneumatosis coli after etoposide chemotherapy for breast cancer. *J Clin Oncol* 2007; **25:** 1623–5.

Effects on the nervous system. A report of an acute dystonic reaction in a child given etoposide as part of a combined maintenance regimen for acute lymphoblastic leukaemia;[1] the patient had been receiving the same regimen uneventfully for over a year but symptoms (which responded to diphenhydramine) recurred on rechallenge with etoposide.

1. Ascher DP, Delaney RA. Acute dystonia from etoposide. *Drug Intell Clin Pharm* 1988; **22:** 41–2.

Handling and disposal. *Urine and faeces* produced for up to 4 and 7 days respectively after a dose of etoposide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hypersensitivity. Hypersensitivity reactions to intravenous etoposide are characterised by one or more of: hypotension, bronchospasm, flushing, exanthema, dyspnoea, fever, chills, tachycardia, tightness in the chest, cyanosis, and hypertension. Although originally thought rare, some investigators[1] have reported an incidence of up to about 50%, particularly in younger patients. The mechanism is uncertain, but a literature review[1] supported the hypothesis that it might not be antibody-mediated, since reducing the rate of infusion can prevent reactions, as can reducing etoposide concentration in the infusion solution. However, an immunogenic mechanism cannot be excluded as hypersensitivity appears to have been reported less frequently with the oral formulation, which unlike the infusion does not contain polysorbate 80. In addition, there are reports[2-4] of successful use of etoposide phosphate formulations (which do not contain polysorbate 80) after hypersensitivity reactions to etoposide, suggesting that the solvent may be responsible.

1. Hoetelmans RMW, *et al.* Hypersensitivity reactions to etoposide. *Ann Pharmacother* 1996; **30:** 367–71.
2. Bernstein BJ, Troner MB. Successful rechallenge with etoposide phosphate after an acute hypersensitivity reaction to etoposide. *Pharmacotherapy* 1999; **19:** 989–91.
3. Siderov J, *et al.* Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer* 2002; **86:** 12–13.
4. Collier K, *et al.* Successful treatment with etoposide phosphate in patients with previous etoposide hypersensitivity. *J Oncol Pharm Pract* 2008; **14:** 51–5.

Pregnancy. For a report of hair loss in an infant, attributed to etoposide given to the mother before delivery, see Pregnancy, under Cisplatin, p.699.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Phenylbutazone, salicylic acid, and sodium salicylate can affect the protein binding of etoposide. Caution is advised when etoposide phosphate is given with drugs such as levamisole hydrochloride that are known to inhibit phosphatase activities.

Antineoplastics. Giving etoposide 2 days after a dose of *cisplatin* was associated with a marked decrease in etoposide clearance and more toxicity, compared with the same dose given 21 days after a dose of cisplatin, in a study involving 17 children.[1] There was no evidence of a persistent decrease in etoposide clearance associated with the cumulative dose of cisplatin, however. In a randomised, crossover study,[2] cisplatin or *carboplatin* were given alternately during 2 courses of etoposide. Although increases in the area under the concentration-time curve of etoposide were seen in the second course, effects were modest and, given the pharmacokinetic variability seen with etoposide, the authors considered any clinical impact to be small.

1. Relling MV, *et al.* Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* 1994; **56:** 503–11.
2. Thomas HD, *et al.* Randomized cross-over clinical trial to study potential pharmacokinetic interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* 2002; **53:** 83–91.

Ciclosporin. High-dose ciclosporin therapy was found to increase the exposure to etoposide by 80%, and to reduce etoposide clearance by 38%. Leucopenia was increased. Etoposide doses should be halved when the drug is given with high-dose ciclosporin.[1] In a study[2] of children who received etoposide and mitoxantrone for acute myeloid leukaemia, the addition of ciclosporin with a 40% reduction in the doses of the antineoplastics still resulted in a 71% reduction in the clearance of etoposide, and a 42% reduction for mitoxantrone. However, there was wide interpatient variability, and the rates of stomatitis and infection were similar between the groups, with or without ciclosporin.

1. Lum BL, *et al.* Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate drug resistance. *J Clin Oncol* 1992; **10:** 1635–42.
2. Lacayo NJ, *et al.* Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* 2002; **16:** 920–7.

Grapefruit juice. In a randomised crossover study[1] of 6 patients, grapefruit juice appeared to reduce the oral bioavailability of etoposide. Initially the authors had expected the opposite since etoposide is demethylated by cytochrome P450 isoenzyme CYP3A4. Although no definite conclusions could be made due to the small number of patients studied, a possible mechanism might have been alteration of P-glycoprotein mediated transport.

1. Reif S, *et al.* Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol* 2002; **58:** 491–4.

Pharmacokinetics

Absorption after oral doses is variable, but on average about 50% of the dose of etoposide is absorbed. The pharmacokinetics of etoposide are subject to considerable interindividual variation. It is rapidly distributed, and concentrations in plasma fall in a biphasic manner, with a terminal half-life of 4 to 11 hours. Etoposide is about 94% bound to plasma protein. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Etoposide is excreted in urine and faeces as unchanged drug and metabolites: about 45% of a dose is reported to be excreted in urine over 72 hours. It crosses the blood-brain barrier poorly; concentrations in CSF are 1 to 10% of those in plasma. It is distributed into breast milk (see Breast Feeding, above).

◊ References.

1. Toffoli G, *et al.* Pharmacokinetic optimisation of treatment with oral etoposide. *Clin Pharmacokinet* 2004; **43:** 441–66.

Metabolism. Studies *in vitro* suggested that metabolic activation of etoposide by oxidation into the *O*-quinone derivative might play an essential role in its activity against DNA.[1]

1. van Maanen JMS, *et al.* Metabolic activation of anti-tumour agent VP 16-213. *Hum Toxicol* 1986; **5:** 136.

Uses and Administration

Etoposide is a semisynthetic derivative of podophyllotoxin with antineoplastic properties; it interferes with the function of topoisomerase II thus inhibiting DNA synthesis, and is most active against cells in the late S and G_2 phases of the cell cycle.

It is used, usually with other antineoplastics, in the treatment of tumours of the testis, small cell cancer of the lung, and in acute leukaemias. It has also been tried in other solid tumours including those of the brain, gastrointestinal tract, ovary, and thymus, and some childhood neoplasms; in lymphomas, and in the treatment of Kaposi's sarcoma associated with AIDS. For further discussion, see the cross-references indicated under Malignant Neoplasms, below.

Etoposide is given by slow intravenous infusion over at least 30 minutes, as a solution in sodium chloride 0.9% or glucose 5% injection. In general, the concentration of the infusion should be between 200 to 400 micrograms/mL, although recommendations vary depending on the preparation; precipitation may occur at higher concentrations. Etoposide phosphate, a prodrug, has improved solubility in water. 113.6 mg of etoposide phosphate is equivalent to 100 mg of etoposide. Intravenous doses are calculated in terms of etoposide, and are identical to those of the base, but it may be given in concentrations up to the equivalent of etoposide 20 mg/mL. Etoposide phosphate solutions may be infused over 5 minutes to 3.5 hours. Etoposide may also be given orally.

Regimens vary; the usual intravenous dose of etoposide ranges from 50 to 120 mg/m^2 daily for 5 days. Somewhat lower doses have been suggested in lung cancer. Alternatively, 100 mg/m^2 has been given on alternate days to a total of 300 mg/m^2. The usual oral dose of etoposide is 100 to 240 mg/m^2 daily for 5 consecutive days. Courses may be repeated after 3 to 4 weeks. Doses should be reduced in renal impairment (see below).

Administration. Although precipitation of etoposide may occur at high infusion concentrations (see Uses and Administration, above), high doses of etoposide have been infused undiluted to avoid giving large volumes of fluid to the patient.[1-3] Etoposide was infused through a central line, and this method has been reported to be safe and effective;[2] pharmacokinetic studies suggested unaltered systemic bioavailability when compared with diluted infusions.[3] However, cracking of plastic syringes and infusion cassettes has been reported, possibly due to the polyethylene glycol component of the formulation. This appears particularly problematic when devices containing ABS plastic (a polymer produced from acrylonitrile, butadiene, and styrene) are used; alternative devices may be preferable.[1]

Etoposide has been injected into the ventricles of the brain in the treatment of patients with neoplastic meningitis.[4]

1. Schwinghammer TL, *et al.* Cracking of ABS plastic devices used to infuse undiluted etoposide injection. *Am J Hosp Pharm* 1988; **45:** 1277.
2. Creger RJ, *et al.* Infusion of high doses of undiluted etoposide through central venous catheters during preparation for bone marrow transplantation. *Cancer Invest* 1990; **8:** 13–16.
3. Ehninger G, *et al.* Unaltered pharmacokinetics after the administration of high-dose etoposide without prior dilution. *Cancer Chemother Pharmacol* 1991; **28:** 214–16.
4. Chamberlain MC, *et al.* Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer* 2006; **106:** 2021–7.

Administration in renal impairment. Some licensed product information for etoposide or etoposide phosphate recommends that patients with a creatinine clearance of between 15 and 50 mL/minute be given 75% of the recommended dose. No recommendations are given for those patients having a creatinine clearance of below 15 mL/minute, although one product (*Vepesid; BMS, USA*) suggests that further dose reduction in these patients be considered.

Blood disorders, non-malignant. For reference to the use of combination chemotherapy, including etoposide, in a few patients with refractory idiopathic thrombocytopenic purpura, see p.1505.

Histiocytic syndromes. Systemic chemotherapy is often tried in patients with extensive Langerhans-cell histiocytosis (p.650), although its value is uncertain. Etoposide is one of the drugs widely used for this purpose.

Hypereosinophilic syndrome. Etoposide has been reported to produce clinical responses in patients with the hypereosinophilic syndrome.[1]

1. Bourrat E, *et al.* Etoposide for treating the hypereosinophilic syndrome. *Ann Intern Med* 1994; **121:** 899–900.

Malignant neoplasms. Etoposide has been used for a variety of solid tumours: in particular it is part of curative regimens used in the treatment of testicular cancer and germ-cell tumours of the ovary (see p.673 and p.670), and is used with cisplatin and other drugs in the treatment of lung cancer (p.668). Other solid neoplasms in which it is sometimes employed include those of the brain (p.660), stomach (p.664), and thymus (p.674), as well as in neuroblastoma (p.674), Wilms' tumour (p.667), retinoblastoma (p.675), and rhabdomyosarcoma (p.676); it has also formed part of systemic regimens for bone sarcomas (p.675), disseminated Kaposi's sarcoma (see p.675), and gestational trophoblastic tumours (p.650). Etoposide is used in regimens for Hodgkin's disease (see p.655); it is also sometimes used in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p.656), and may produce short-term responses in mycosis fungoides (p.657). It is also used in Burkitt's lymphoma (p.657). Etoposide may have benefits when added to induction protocols for acute myeloid leukaemia (p.652), and when used as part of intensification therapy in acute lymphoblastic leukaemia (p.651). It has formed part of salvage regimens in multiple myeloma (p.658).

Vasculitic syndromes. For mention of the use of etoposide to induce remission in patients with Wegener's granulomatosis resistant to standard therapy with cyclophosphamide and corticosteroids, see p.1515.

Preparations

BP 2008: Etoposide Capsules; Etoposide Intravenous Infusion;
USP 31: Etoposide Capsules; Etoposide Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Citodox; Etocris; Etopofos†; Euvaxon; Labimion†; Neoplaxol; Optasid†; Percas; Vepesid; VP-Gen; ***Austral.:*** Etopophos; Vepesid; ***Austria:*** Etopofos; Vepesid; ***Belg.:*** Celltop; Eposin; Etopophos†; Vepesid; ***Braz.:*** Eposido; Etopos†; Etopul†; Etosin; Eunades; Evoposdo†; Nexvep; Posidon; Vepesid; ***Canad.:*** Vepesid; ***Chile:*** Epsidox; Lastet†; ***Cz.:*** Etopophos†; Lastet; Vepesid; ***Denm.:*** Etopofos; Vepesid; ***Fin.:*** Eposin†; Etopofos; Exitop†; Vepesid; ***Fr.:*** Celltop; Etopophos; Vepeside; ***Ger.:*** ETO CS; Eto-cell; Eto-Gry; Etomedac; Etopophos; Exitop; Neoposid; Onkoposid; Riboposid; Vepesid; ***Gr.:*** Etobion; Vepesid; ***Hong Kong:*** Vepesid; ***Hung.:*** Lastet; Sintopozid; Vepesid; ***India:*** Bioposide; Etosid; Lastet†; Posid; ***Indon.:*** Posyd; ***Irl.:*** Etopophos†; Vepesid; ***Israel:*** Etopophos†; Vepesid†; ***Ital.:*** Lastet; Vepesid; ***Jpn:*** Lastet; ***Malaysia:*** Eposin; Lastet; Vepesid†; ***Mex.:*** Etonco; Etopos; Kenazol; Lastet†; Vepesid; VP-Tec; ***Neth.:*** Toposin; Vepesid; ***Norw.:*** Eposin; Etopofos; Vepesid; ***NZ:*** Etopophos; Vepesid; ***Philipp.:*** Etopoxan; Etopul; Fytosid; Lastet; Posid; Topresid; Vepesid; ***Pol.:*** Lastet; Sintopozid; Vepesid; ***Port.:*** Eposin; Lastet; Vepesid; ***Rus.:*** Etopos (Этопос)†; Vepesid (Вепезид); ***S.Afr.:*** Eposin; Etopophos; Vepesid; ***Singapore:*** Lastet; Vepesid†; ***Spain:*** Eposin†; Lastet; Vepesid; ***Swed.:*** Eposin; Etopofos; Exitop†; Vepesid; ***Switz.:*** Etopophos; Vepesid; ***Thai.:*** Eposin; Etopos; Fytosid; Lastet; Vepesid; ***Turk.:*** Eposin; Lastet; Vepesid; ***UK:*** Eposin; Etopophos; Vepesid; ***USA:*** Etopophos; Toposar; Vepesid; ***Venez.:*** Etonolver; Etosid; Fytosid.

Exemestane *(BAN, USAN, rINN)* ⊗

Eksemestaani; Eksemestan; Exemestan; Exémestane; Exemestano; Exemestanum; FCE-24304. 6-Methyleneandrosta-1,4-diene-3,17-dione.

Эксеместан

$C_{20}H_{24}O_2$ = 296.4.

CAS — 107868-30-4.

ATC — L02BG06.

ATC Vet — QL02BG06.

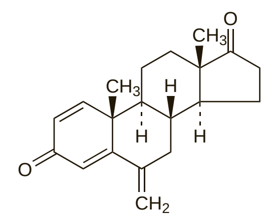

Adverse Effects and Precautions

The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg oedema. Thrombocytopenia and leucopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane. Density should therefore be assessed at the start of therapy, in those with osteoporosis or at risk of it, and patients monitored during therapy.

The use of exemestane is contra-indicated in premenopausal women (particularly in pregnancy).

Effects on the musculoskeletal system. Exemestane therapy has been found to decrease bone mineral density (BMD) in postmenopausal women with early breast cancer.[1,2] In one study, the decrease in BMD was seen within 6 months of switching therapy from tamoxifen, and was significant at the lumbar spine and hip.[2] In a Scandinavian study, BMD loss with exemestane compared with placebo was modest from the femoral neck, and not significant at the lumbar spine;[1] however, it was noted that the changes in the placebo group were greater than expected, possibly due to the lack of calcium and vitamin D supplementation, and that there is a high incidence of hip fracture in Scandinavia. Patients starting exemestane therapy should be assessed for baseline BMD;[1] while those with normal BMD are considered to not need further assessment beyond lifestyle advice, those with osteopenia should have their BMD monitored, and therapeutic interventions made as appropriate.[2]

1. Lønning PE, *et al.* Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; **23:** 5126–37.
2. Coleman RE, *et al.* Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; **8:** 119–27.

Interactions

The metabolism of exemestane is mediated by the cytochrome P450 isoenzyme CYP3A4. Rifampicin, a potent inducer of CYP isoenzymes, can decrease plasma concentrations of exemestane. Use with other drugs that induce this isoenzyme may reduce the efficacy of exemestane. Exemestane should also be used cautiously with drugs that are substrates for CYP3A4 and that have a narrow therapeutic index. Significant effects on exemestane clearance by cytochrome P450 isoenzyme inhibitors are considered unlikely. Exemestane should not be given with oestrogen-containing drugs as these would negate its pharmacological action.

Pharmacokinetics

Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. It is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4, and via reduction by aldoketoreductase. Metabolites are excreted in the urine and faeces, and less than 1% of a dose is excreted unchanged in the urine. Exemestane has a terminal elimination half-life of about 24 hours.

Uses and Administration

Exemestane is a selective inhibitor of the aromatase (oestrogen synthase) system, similar to formestane (p.726). It is used in the treatment of advanced breast cancer (p.661), in postmenopausal women who are no longer responsive to anti-oestrogen therapy. It is also used for adjuvant treatment of postmenopausal women with oestrogen-receptor positive early breast cancer, after 2 to 3 years of initial adjuvant tamoxifen treatment; a total of 5 years of adjuvant hormonal therapy should be given. The recommended oral dose is 25 mg once daily, preferably after a meal.

In patients receiving potent inducers of the cytochrome P450 isoenzyme CYP3A4 (such as rifampicin or phenytoin), the recommended oral dose of exemestane is 50 mg once daily, after a meal.

◊ References.

1. Clemett D, Lamb HM. Exemestane: a review of its use in postmenopausal women with advanced breast cancer. *Drugs* 2000; **59:** 1279–96.
2. Kaufmann M, *et al.* Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000; **18:** 1399–1411.
3. Lønning PE, *et al.* Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000; **18:** 2234–44.
4. Coombes RC, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350:** 1081–92. Corrections. *ibid.*; **351:** 2461 and *ibid.* 2006; **355:** 1746.
5. Bertelli G, *et al.* Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2006; **69:** 471–7.
6. Bundred N. The evolving role of exemestane in the management of breast cancer. *Br J Hosp Med* 2006; **67:** 427–30.
7. Coombes RC, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; **369:** 559–70. Correction. *ibid.*; 906.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aromasin; ***Austral.:*** Aromasin; ***Austria:*** Aromasin; ***Belg.:*** Aromasin; ***Braz.:*** Aromasin; ***Canad.:*** Aromasin; ***Chile:*** Aromasin; ***Cz.:*** Aromasin; ***Denm.:*** Aromasin; ***Fin.:*** Aromasin; ***Fr.:*** Aromasine; ***Ger.:*** Aromasin; ***Gr.:*** Aromasin; ***Hong Kong:*** Aromasin; ***Hung.:*** Aromasin; ***Indon.:*** Aromasin; ***Irl.:*** Aromasin; ***Israel:*** Aromasin; ***Ital.:*** Aromasin; ***Malaysia:*** Aromasin; ***Neth.:*** Aromasin; ***Norw.:*** Aromasin; ***NZ:*** Aromasin; ***Philipp.:*** Aromasin; ***Pol.:*** Aromasin; ***Port.:*** Aromasin; ***Rus.:*** Aromasin (Аромазин); ***S.Afr.:*** Aromasin; ***Singapore:*** Aromasin; ***Spain:*** Aromasil; ***Swed.:*** Aromasin; ***Switz.:*** Aromasin; ***Thai.:*** Aromasin; ***Turk.:*** Aromasin; ***UK:*** Aromasin; ***USA:*** Aromasin; ***Venez.:*** Aromasin.

Exisulind *(rINN)*

Exisulindum; FGN-1; Sulindac Sulfone. 5-Fluoro-2-methyl-1-[(*Z*)-*p*-(methylsulfonyl)benzylidene]indene-3-acetic acid.

Эксисулинд

$C_{20}H_{17}FO_4S$ = 372.4.

CAS — 59973-80-7.

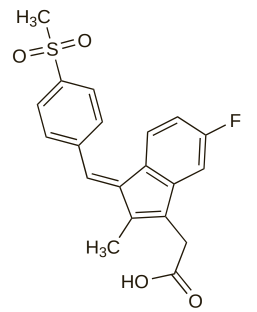

Profile

Exisulind is a sulfone metabolite of sulindac (p.126) that is reported to induce apoptosis in cancerous and precancerous cells. It has been studied for the treatment of familial adenomatous polyposis, with variable results. It is also being investigated for the prevention and treatment of malignant neoplasms, including those of the breast, prostate, and lung.

◊ References.

1. Goluboff ET. Exisulind, a selective apoptotic antineoplastic drug. *Expert Opin Invest Drugs* 2001; **10:** 1875–82.
2. Webster WS, Leibovich BC. Exisulind in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2005; **5:** 957–62.
3. Arber N, *et al.* Sporadic adenomatous polyp regression with exisulind is effective but toxic: a randomised, double blind, placebo controlled, dose-response study. *Gut* 2006; **55:** 367–73.

Fadrozole Hydrochloride *(USAN, rINNM)* ⊗

CGS-16949 (fadrozole); CGS-16949A; Fadrozole, Chlorhydrate de; Fadrozoli Hydrochloridum; Hidrocloruro de fadrozol. (±)-*p*-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile monohydrochloride.

Фадрозола Гидрохлорид

$C_{14}H_{13}N_3HCl$ = 259.7.

CAS — 102676-47-1 (fadrozole); 102676-96-0 (fadrozole hydrochloride).

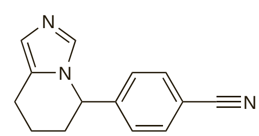

(fadrozole)

Profile

Fadrozole hydrochloride is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used for the treatment of breast cancer. It has been given in oral doses of 1 mg twice daily.

◊ References.

1. Buzdar AU, *et al.* Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma: results of two randomized double blind controlled multiinstitutional trials. *Cancer* 1996; **77:** 2503–13.
2. Miller AA, *et al.* Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996; **78:** 789–93.
3. Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996; **7:** 465–9.
4. Thurlimann B, *et al.* First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer: prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996; **7:** 471–9.
5. Tominaga T, *et al.* Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol* 2003; **14:** 62–70.

Fenretinide *(USAN, rINN)*

Fenretinida; Fenrétinide; Fenretinidum; 4-HPR; 4-Hydroxyphenylretinamide; McN-R-1967. *all-trans*-4′-Hydroxyretinanilide.

Фенретинид

$C_{26}H_{33}NO_2$ = 391.5.

CAS — 65646-68-6.

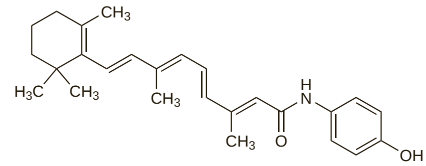

Profile

Fenretinide is a retinoid derivative that is given orally and is being studied in the management of breast and prostate cancer, malignant bone tumours, soft-tissue sarcoma, and some other malignancies. It has also been tried in oral lichen planus and leucoplakia. Fenretinide has been investigated in the treatment of psoriasis, but was associated with unacceptable adverse effects such as night blindness and severe toxic erythema.

◊ Fenretinide has been studied for the treatment of breast cancer and cutaneous malignancies but early results were disappointing and night blindness and mucocutaneous effects have been associated with this use.[1] Fenretinide has been investigated for the prevention of breast cancer (p.662), but a large randomised study of secondary prevention failed to show any benefit.[2] A follow-up of the same study[3] found that patients receiving fenretinide had a lower incidence of ovarian carcinoma during the 5-year treatment period, but that this apparently protective effect disappeared after treatment was stopped. Combinations of tamoxifen and fenretinide, given intermittently (for treatment or prevention), have been reported to be well tolerated.[4-6]

1. Modiano MR, *et al.* Phase II study of fenretinide (N-[4-hydroxyphenyl]retinamide) in advanced breast cancer and melanoma. *Invest New Drugs* 1990; **8:** 317–19.
2. Veronesi U, *et al.* Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; **91:** 1847–56.
3. De Palo G, *et al.* Effect of fenretinide on ovarian carcinoma occurrence. *Gynecol Oncol* 2002; **86:** 24–7.
4. Cobleigh MA, *et al.* Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. *J Clin Oncol* 1993; **11:** 474–7.
5. Conley B, *et al.* Pilot trial of the safety, tolerability, and retinoid levels of N-(4-hydroxyphenyl) retinamide in combination with tamoxifen in patients at high risk for developing invasive breast cancer. *J Clin Oncol* 2000; **18:** 275–83.
6. Guerrieri-Gonzaga A. *et al.* Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 2006; **24:** 129–35.

Floxuridine *(USAN, rINN)*

Floxuridina; Floxuridinum; 5-Fluorouracil Deoxyriboside; FUDR; NSC-27640; WR-138720. 2′-Deoxy-5-fluorouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione.

Флоксуридин

$C_9H_{11}FN_2O_5$ = 246.2.

CAS — 50-91-9.

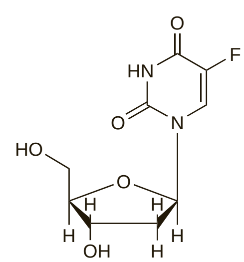

Pharmacopoeias. In *US.*

USP 31 (Floxuridine). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722. Adverse reactions after intra-arterial infusion often include local reactions, thromboembolic complications, and infection or bleeding at the catheter site, or blockage of the catheter. Erythema, stomatitis, and gastrointestinal disturbances are relatively common. There have also been signs of liver dysfunction.

Effects on the liver. Serious biliary toxicity has been reported in over half of all patients receiving hepatic arterial infusions of floxuridine, usually manifesting as sclerosing cholangitis or acalculous cholecystitis;[1] as a result some surgeons routinely remove the gallbladder at the time of infusion pump implantation.[2] Extrahepatic biliary stenosis with jaundice and cholestasis has also been described;[3] the authors suggest that this could lead to intrahepatic biliary damage from bile stasis and infection, recurrent cholangitis, and biliary sclerosis. Floxuridine infusions have also been associated with a case of fatal progressive cirrhosis of the liver in the absence of overt cholestasis.[4] Pseudoaneurysms of the hepatic artery, leading to serious retroperitoneal or gastrointestinal bleeding, have also been described.[5]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Anonymous. An implanted infusion pump for chemotherapy of liver metastases. *Med Lett Drugs Ther* 1984; **26:** 89–90.
3. Aldrighetti L, *et al.* Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FUdR) for liver metastases from colorectal cancer. *Hepatogastroenterology* 2001; **48:** 1302–7.
4. Pettavel J, *et al.* Fatal liver cirrhosis associated with long-term arterial infusion of floxuridine. *Lancet* 1986; **ii:** 1162–3.
5. Samaras P, *et al.* Hemorrhage associated with hepatic artery pseudoaneurysms after regional chemotherapy with floxuridine: case report. *Int Semin Surg Oncol* 2008; **5:** 17.

Interactions

As for Fluorouracil, p.723.

Pharmacokinetics

Floxuridine is poorly absorbed from the gastrointestinal tract and it is usually given by injection. Floxuridine is metabolised mainly in the liver to fluorouracil after rapid injection. When given by slow intra-arterial infusion, more of the drug is metabolised to floxuridine monophosphate (F-dUMP). It is excreted as carbon dioxide via the lungs; some is excreted, as unchanged drug and metabolites, in urine. Floxuridine crosses the blood-brain barrier to some extent and is found in CSF.

Uses and Administration

Floxuridine is an antineoplastic which acts as an antimetabolite, either by conversion to fluorouracil (after rapid injection), or, when given by slow intra-arterial infusion, partly via floxuridine monophosphate (F-dUMP), which produces greater inhibition of DNA synthesis.

Floxuridine is used in the palliative treatment of hepatic metastases of colorectal cancer—see Malignant Neoplasms of the Liver, p.667. It has been tried in some other solid neoplasms. Doses of 100 to 600 micrograms/kg daily are given by continuous hepatic arterial infusion, usually with the aid of an infusion pump, until toxicity occurs.

White cell and platelet counts should be carried out regularly during therapy and treatment should be stopped if the white cell count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p.639), or if major adverse effects occur.

◊ References.

1. Fordy C, *et al.* Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer* 1998; **78:** 1058–60.
2. Kemeny N, *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341:** 2039–48.
3. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; **18:** 243–54.
4. Fiorentini G, *et al.* Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48:** 305–12.
5. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; **352:** 734–5.

Preparations

USP 31: Floxuridine for Injection.

Proprietary Preparations (details are given in Part 3)
USA: FUDR.

Fludarabine Phosphate

(BAN, USAN, rINNM)

2-F-ara-AMP; Fludarabiinifosfaatti; Fludarabin Fosfat; Fludarabine Monophosphate; Fludarabine, phosphate de; Fludarabinfosfat; Fludarabin-fosfát; Fludarabini phosphas; Fludarabino fosfatas; 2-Fluoro-ara-AMP; Fosfato de fludarabina; NSC-312887. 9-β-D-Arabinofuranosyl-2-fluoroadenine 5′-dihydrogenphosphate.

Флударабина Фосфат

$C_{10}H_{13}FN_5O_7P$ = 365.2.

CAS — 21679-14-1 (fludarabine); 75607-67-9 (fludarabine phosphate).

ATC — L01BB05.

ATC Vet — QL01BB05.

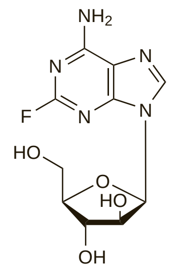

(fludarabine)

NOTE. The name FluCam has been used for a regimen of fludarabine with alemtuzumab. Distinguish from Flucam, which is ampiroxicam (p.19).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fludarabine Phosphate). A white or almost white, hygroscopic, crystalline powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Fludarabine Phosphate). A white to off-white, hygroscopic, crystalline powder. Slightly soluble in water and in 0.1M hydrochloric acid; practically insoluble in dehydrated alcohol; freely soluble in dimethylformamide. Store at 2° to 8°. Protect from light.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow suppression from fludarabine is dose-limiting, manifesting as neutropenia, thrombocytopenia, and anaemia; the nadir of the white cell and platelet counts usually occurs after about 13 to 16 days. Myelosuppression can be severe and cumulative; prolonged lymphopenia with concomitant risk of opportunistic infections may occur. Bone marrow hypoplasia or aplasia resulting in pancytopenia may sometimes be fatal.

Other common adverse effects include fever, fatigue, chills, cough, weakness, malaise, anorexia, gastrointestinal disturbances, mucositis, stomatitis, oedema, and skin rashes. Pulmonary toxicity, including pulmonary fibrosis, pneumonitis, and dyspnoea can occur. Other adverse effects include dysuria, haematuria, epistaxis, and abnormalities in hepatic or pancreatic enzymes. Tumour lysis syndrome has been reported, especially in patients with large tumour burdens. Auto-immune disorders, including auto-immune haemolytic anaemia, have been reported, and may be life-threatening or fatal. Patients should be monitored for signs of haemolysis and therapy stopped if it occurs. Rarely reported effects include heart failure, arrhythmias, anaphylaxis, and haemorrhagic cystitis. Neurological disturbances include peripheral neuropathy, agitation, confusion, visual disturbances, hearing loss, headache, sleep disorders, and seizures; high doses have been associated with progressive encephalopathy, blindness, coma, and death.

Exacerbation of existing skin cancer lesions as well as new onset of skin cancer has been reported in some patients. Transfusion-associated graft-versus-host disease has been seen after transfusion of non-irradiated blood in patients treated with fludarabine, and fatalities have occurred; patients should only receive irradiated blood.

Dosage should be reduced in renal impairment (see below). It should also be avoided in patients with decompensated haemolytic anaemia.

Carcinogenicity. A study in patients with chronic lymphocytic leukaemia who were treated with fludarabine found that there was no significantly increased risk of secondary malignancy following therapy, despite the immunosuppressive properties of this drug.[1] A review[2] of this and other studies concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients treated with fludarabine was needed.

1. Cheson BD, *et al.* Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukaemias. *J Clin Oncol* 1999; **17:** 2454–60.
2. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40:** 541–50.

Effects on the eyes. See under Effects on the Nervous System, below.

Effects on the lungs. Pulmonary toxicity manifest as dyspnoea, fever, hypoxaemia, and radiographic evidence of interstitial and alveolar infiltrates was diagnosed in 9 patients of a cohort of 105 treated with fludarabine.[1] Lung biopsies were performed in 6 patients and showed diffuse chronic interstitial inflammation and fibrosis. Patients with chronic lymphocytic leukaemia appeared to be at greater risk of developing this complication than those with non-Hodgkin's lymphoma.

1. Helman DL, *et al.* Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002; **122:** 785–90.

Effects on the nervous system. High doses (of the order of 100 mg/m^2 daily intravenously) of fludarabine are associated with severe, life-threatening neurotoxicity. However, a few cases of progressive multifocal leukoencephalopathy have also been reported in patients given fludarabine in usual doses.[1-4] The prolonged immunosuppression caused by fludarabine might increase the risk of developing this fatal demyelinating disease, which is caused by opportunistic JC virus infection. Ocular toxicity, including irreversible loss of vision, has also been reported occasionally, including with low-dose regimens.[5]

1. Zabernigg A, *et al.* Late-onset fatal neurological toxicity of fludarabine. *Lancet* 1994; **344:** 1780.
2. Gonzalez H, *et al.* Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999; **41:** 183–6.
3. Cid J, *et al.* Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000; **79:** 392–5.
4. Vidarsson B, *et al.* Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. *Am J Hematol* 2002; **70:** 51–4.
5. Ding X, *et al.* Ocular toxicity of fludarabine: a purine analog. *Expert Rev Ophthalmol* 2008; **3:** 97–109.

Graft-versus-host disease. Transfusion-associated graft-versus-host disease has been reported when blood products were used in patients treated with fludarabine.[1] Fludarabine-treated patients should receive irradiated red cells and platelets (to inactivate any viable T-cells) if they require a transfusion.

1. Williamson LM, *et al.* Fludarabine treatment and transfusion-associated graft-versus-host disease. *Lancet* 1996; **348:** 472–3.

Infection. A review[1] of patients treated with fludarabine-containing regimens showed that therapy was associated with serious infections including listeriosis, pneumocystis pneumonia, mycobacterial infections, and opportunistic fungal and viral infections. The risk was exacerbated by previous or current corticosteroid therapy. Prophylactic therapy with co-trimoxazole, triazole antifungals, aciclovir, and colony-stimulating factors was recommended in at-risk patients. A high incidence of herpesvirus infections was also found in another review[2] of patients treated with fludarabine. Combination therapy using chlorambucil and fludarabine resulted in more infections than when either was used alone,[3] but single-agent fludarabine was associated with more major infections and herpesvirus infections than chlorambucil alone. The frequency of serious infection has also been reported[4] to be increased in patients after their conditions became refractory to fludarabine and they were being treated with conventional chemotherapy.

For reports of progressive multifocal leukoencephalopathy caused by opportunistic JC virus infection in patients receiving fludarabine, see Effects on the Nervous System, above.

1. Anaissie EJ, *et al.* Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med* 1998; **129:** 559–66.
2. Byrd JC, *et al.* Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol* 1999; **105:** 445–7.
3. Morrison VA, *et al.* Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. *J Clin Oncol* 2001; **19:** 3611–21.
4. Perkins JG, *et al.* Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 2002; **94:** 2033–9.

Interactions

Increased pulmonary toxicity, sometimes fatal, has been reported in patients given fludarabine with pentostatin. Pretreatment with cytarabine may reduce the metabolic activation of fludarabine, but pretreatment with fludarabine results in increased intracellular concentrations of cytarabine—see p.706. The therapeutic efficacy of fludarabine may also be reduced by dipyridamole and other inhibitors of adenosine uptake.

Aminoglycosides. Severe ototoxicity occurred when a short course of *gentamicin* was given to a patient who had recently completed a course of fludarabine.[1]

1. O'Brien RK, Sparling TG. Gentamicin and fludarabine ototoxicity. *Ann Pharmacother* 1995; **29:** 200–1.

Corticosteroids. For a suggestion that use of fludarabine with corticosteroids may increase the risk of infection, see Infection, above.

Pharmacokinetics

Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate are seen about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after oral doses of the phosphate.

Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 60% of a dose is excreted in the urine. The pharmacokinetics of fludarabine exhibit considerable interindividual variation.

◊ References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. *Clin Pharmacokinet* 2002; **41:** 93–103.

Uses and Administration

Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine (p.912); it acts as a purine antagonist antimetabolite. It is used for its antineoplastic properties in the treatment of chronic lymphocytic leukaemia. Fludarabine phosphate is given by bolus injection or by intravenous infusion over 30 minutes in a usual dose of 25 mg/m^2 daily for 5 consecutive days. Alternatively it may be given orally in a dose of 40 mg/m^2 daily for 5 consecutive days. Courses may be repeated every 28 days, usually for up to 6 cycles.

Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression (see also Bone-marrow Depression, p.639). Doses should be reduced in renal impairment (see below).

◊ General references.

1. Adkins JC, *et al.* Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 1997; **53:** 1005–37.
2. Plosker GL, Figgitt DP. Oral fludarabine. *Drugs* 2003; **63:** 2317–23.

Administration in renal impairment. Doses of fludarabine phosphate should be reduced by up to 50% in patients with mild to moderate renal impairment (creatinine clearance between 30 and 70 mL/minute); the drug should not be given in more severe renal impairment.

Malignant neoplasms. Fludarabine is the preferred second-line therapy for chronic lymphocytic leukaemia once initial alkylating agent therapy fails,[1] and may also be used for initial therapy (see p.653). It has also been tried in other malignancies. Listed below are some references to the use of fludarabine phosphate for the treatment of chronic lymphocytic leukaemia,[2,3] and its potential activity against a variety of other malignancies, including indolent low-grade non-Hodgkin's lymphoma[4,5] (p.656), mycosis fungoides,[6] heavy chain disease,[7] prolymphocytic leukaemia,[8,9] hairy cell leukaemia,[10] and Waldenström's macroglobulinaemia.[11,12]

1. NICE. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (issued September 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/NICEfludarab_E_29guidance.pdf (accessed 31/07/08)
2. Zhu Q, *et al.* Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. *Leuk Lymphoma* 2004; **45:** 2239–45.
3. Richards S. Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev* 2005; **31:** 332–5.
4. Hiddemann W, Pott-Hoeck C. Fludarabine in the management of malignant lymphomas. *Drugs* 1994; **47** (suppl 6): 50–6.
5. Anderson VR, Perry CM. Fludarabine: a review of its use in non-Hodgkin's lymphoma. *Drugs* 2007; **67:** 1633–55.
6. Scarisbrick JJ, *et al.* A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma. *Br J Dermatol* 2001; **144:** 1010–15.
7. Agrawal S, *et al.* First report of fludarabine in gamma-heavy chain disease. *Br J Haematol* 1994; **88:** 653–5.
8. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukaemia. *Lancet* 1990; **336:** 820.
9. Kantarjian HM, *et al.* Efficacy of fludarabine, a new adenine nucleoside analogue, in patients with prolymphocytic leukemia and the prolymphocytoid variant of chronic lymphocytic leukemia. *Am J Med* 1991; **90:** 223–8.
10. Kantarjian HM, *et al.* Fludarabine therapy in hairy cell leukemia. *Cancer* 1991; **67:** 1291–3.
11. Dhodapkar MV, *et al.* Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; **98:** 41–8.
12. Leblond V, *et al.* Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood* 2001; **98:** 2640–4.

Preparations

USP 31: Fludarabine Phosphate for Injection; Fludarabine Phosphate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fludakebir; Fludara; Fluradosa; Forclina; ***Austral.:*** Fludara; ***Austria:*** Fludara; ***Belg.:*** Fludara; ***Braz.:*** Fludara; ***Canad.:*** Fludara; ***Chile:*** Fludara; ***Cz.:*** Fludara; Tazumara; ***Denm.:*** Fludara; ***Fin.:*** Fludara; ***Fr.:*** Fludara; ***Ger.:*** Fludara; ***Gr.:*** Fludara; ***Hong Kong:*** Fludara; ***Hung.:*** Fludara; ***India:*** Fludara; ***Indon.:*** Fludara; ***Irl.:*** Fludara; ***Israel:*** Fludara; ***Ital.:*** Fludara; ***Malaysia:*** Fludara; ***Mex.:*** Beneflur; Fludara; ***Neth.:*** Fludara; ***Norw.:*** Fludara; ***NZ:*** Fludara; ***Philipp.:*** Fludara; ***Pol.:*** Fludara; ***Port.:*** Fludara; ***Rus.:*** Fludara (Флудара); ***S.Afr.:*** Fludara; ***Singapore:*** Fludara; ***Spain:*** Beneflur; ***Swed.:*** Fludara; ***Switz.:*** Fludara; ***Thai.:*** Fludara; ***Turk.:*** Fludara; ***UK:*** Fludara; ***USA:*** Fludara; ***Venez.:*** Fludara.

Fluorouracil *(BAN, USAN, rINN)*

5-Fluorouracil; Fluorouracilas; Fluorouracile; Fluorouracilo; Fluorouracilum; Fluorouracyl; Fluorourasiili; Fluorourasil; 5-Fluorourasil; Fluoruracil; 5-FU; NSC-19893; Ro-2-9757; WR-69596. 5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

Флуороурацил

$C_4H_3FN_2O_2$ = 130.1.

CAS — 51-21-8.

ATC — L01BC02.

ATC Vet — QL01BC02.

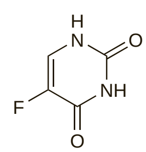

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Fluorouracil). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.0. Protect from light.

USP 31 (Fluorouracil). A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Incompatibility. Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is reported to be incompatible with cytarabine,[1] diazepam,[2] doxorubicin[2] (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate.[3] Although fluorouracil has been stated to be incompatible with methotrexate[1] a study of the long-term stability of an admixture of the 2 drugs in sodium chloride 0.9% injection suggests otherwise.[4]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
3. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.
4. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.

Stability. Despite one report[1] that fluorouracil had limited stability when dissolved in glucose 5% at room temperature (10% loss from solution in 43 hours when stored in PVC and in only 7 hours when stored in glass), others[2] found such a solution to be stable for at least 16 weeks when stored in PVC at 5°. When stored at room temperature in PVC, solutions of fluorouracil may lose water by evaporation, which slowly increases their concentration.[2,3] Results of a study of fluorouracil and methotrexate admixtures in sodium chloride 0.9% suggest that extended stability (up to 13 weeks) is possible in this diluent at 5° in PVC bags.[3] Commercial solutions of fluorouracil for injection have been reported to be stable for 7 days at 37° in a portable infusion pump, although at 25° one brand showed evidence of precipitation.[4] Fluorouracil solutions may be incompatible with synthetic elastomers: microscopic precipitation has been reported as soon as 4 hours after placement into polyisoprene reservoirs of elastomeric infusers and in polypropylene syringes with an elastomeric joint.[5] Some have questioned the validity of this finding.[6,7]

1. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
2. Quebbeman EJ, *et al.* Stability of fluorouracil in plastic containers used for continuous infusion at home. *Am J Hosp Pharm* 1984; **41:** 1153–6.
3. Vincké B, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
4. Stiles ML, *et al.* Stability of fluorouracil administered through four portable infusion pumps. *Am J Hosp Pharm* 1989; **46:** 2036–40.
5. Corbrion V, *et al.* Precipitation of fluorouracil in elastomeric infusers with a polyisoprene reservoir and in polypropylene syringes with an elastomeric joint. *Am J Health-Syst Pharm* 1997; **54:** 1845–8.
6. Trissel LA. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55:** 1314–15.
7. Allwood MC. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55;** 1315–16.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p.635 and p.639.

The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastrointestinal toxicity. With protracted continuous infusion in particular, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Leucopenia, thrombocytopenia, stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site, are signs that treatment should be stopped. The nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Nausea and vomiting, rashes, and alopecia are common. Ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischaemia have occurred.

Local inflammatory and photosensitivity reactions have occurred after topical use. Dermatitis and, rarely, erythema multiforme have been reported.

Effects on the eyes. Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lachrymation and watering of the eyes.[1] In one patient this was associated with symptoms suggesting fibrosis of the tear duct,[1] and possibly representing local irritation due to the presence of fluorouracil in tear fluid,[2] although symptoms have not always resolved on stopping the drug.[1] More seriously a case of bilateral total corneal epithelial erosion has been described.[3] Optic neuropathy, culminating in near blindness, has also occurred in a patient given fluorouracil as part of a combination regimen.[4] Severe ulceration and corneal abscess with hyopyon has followed local injection of fluorouracil into the eye in a diabetic patient with idiopathic band keratopathy.[5]

1. Haidak DJ, *et al.* Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med* 1978; **88:** 657.
2. Christophidis N, *et al.* Lacrimation and 5-fluorouracil. *Ann Intern Med* 1978; **89:** 574.
3. Hirsh A, *et al.* Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy. *Br J Ophthalmol* 1990; **74:** 638.
4. Adams JW, *et al.* Recurrent acute toxic optic neuropathy secondary to 5-FU. *Cancer Treat Rep* 1984; **68:** 565–6.
5. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol* 1993; **77:** 250–1.

Effects on the heart. Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil,[1] although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher.[1-3] Possible risk factors include pre-existing heart disease or mediastinal radiotherapy, and prolonged infusion of the drug, but symptoms can also occur in patients without these risk factors.[2-4] Therefore, at present, it is not possible to reliably predict patients at risk.[5] Some suggest that the use of a trometamol buffer in the fluorouracil formulation may contribute to the formation of cardiotoxic degradation products.[6]

1. Keefe DL, *et al.* Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol* 1993; **33:** 1060–70.
2. McLachlan SA, *et al.* The spectrum of 5-fluorouracil cardiotoxicity. *Med J Aust* 1994; **161:** 207–9.
3. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994; **28:** 374–8.

4. Hannaford R. Sudden death associated with 5-fluorouracil. *Med J Aust* 1994; **161:** 225.
5. Becker K, *et al.* Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs* 1999; **57:** 475–84.
6. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Effects on the nervous system. Central neurotoxicity, including cerebellar ataxia, confusion, disorientation, and emotional lability is reported to occur rarely in patients receiving fluorouracil, although the incidence may be increased with high-dose or intensive regimens. Patients with disorders of pyrimidine metabolism may be at increased risk of neurotoxicity.[1-3] It has also been suggested that fluorouracil may produce neurotoxicity by causing thiamine deficiency, and that thiamine may be used to treat it.[4]

1. Tuchman M, *et al.* Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985; **313:** 245–9.
2. Stéphan F, *et al.* Depressed hepatic dihydropyrimidine dehydrogenase activity and fluorouracil-related toxicities. *Am J Med* 1995; **99:** 685–8.
3. Takimoto C, *et al.* Reversible 5-fluorouracil-associated encephalopathy in a dihydropyrimidine dehydrogenase (DPD) deficient patient. *Clin Pharmacol Ther* 1996; **59:** 161.
4. Pirzada NA, *et al.* Fluorouracil-induced neurotoxicity. *Ann Pharmacother* 2000; **34:** 35–8.

Effects on the skin. In addition to reports of fluorouracil-associated dermatitis and photosensitivity a syndrome of erythema, pain, and desquamation of the skin of palms and soles has been reported[1-4] (the palmar-plantar erythrodysesthesia syndrome, p.639). Although particularly associated with continuous infusion[1,2] the syndrome can also occur after bolus doses.[3,4] Symptoms generally respond to stopping the drug, but addition of oral pyridoxine to chemotherapy regimens has been reported to prevent or resolve symptoms,[5] as has application of a nicotine patch in one patient.[6]

Rash and confusion developing in an elderly man with malabsorption and poor nutritional intake who received fluorouracil for a biliary-tract tumour were diagnosed as pellagra.[7] Symptoms responded to nicotinic acid therapy.

1. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
2. Feldman LD, Ajani JA. Fluorouracil-associated dermatitis of the hands and feet. *JAMA* 1985; **254:** 3479.
3. Atkins JN. Fluorouracil and the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1985; **102:** 419.
4. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. *Ann Intern Med* 1989; **111:** 858.
5. Vukelja SJ, *et al.* Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1989; **111:** 688–9.
6. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.
7. Stevens HP, *et al.* Pellagra secondary to 5-fluorouracil. *Br J Dermatol* 1993; **128:** 578–80.

Hypersensitivity. Although local hypersensitivity reactions are included in licensed product information as potential adverse effects of topical fluorouracil, hypersensitivity reactions to systemic fluorouracil have been reported very rarely.[1-6] For a report of the successful use of fluorouracil in a patient allergic to capecitabine, suggesting that cross-sensitivity does not occur between the two, see p.692.

1. Reed WP, Morris DM. Maculopapular eruption resulting from systemic administration of 5-fluorouracil. *Cutis* 1984; **33:** 381–2.
2. Sridhar KS. Allergic reaction to 5-fluorouracil infusion. *Cancer* 1986; **58:** 862–4.
3. Milla Santos A, Sanchiz Medina F. Anaphylactic reaction following iv administration of 5-fluorouracil. *Cancer Treat Rep* 1986; **70:** 1346.
4. Duley JA, Nethersell AB. Delayed hypersensitivity to 5-fluorouracil associated with reduced dihydropyrimidine dehydrogenase (DPD) activity. *Adv Exp Med Biol* 1998; **431:** 147–50.
5. Eppinger T, Sperber K. Desensitization to 5-fluorouracil. *Allergy Asthma Proc* 1999; **20:** 189–91.
6. Biswal BM. Anaphylaxis following continuous 5-fluorouracil infusion chemotherapy. *Aust N Z J Med* 1999; **29:** 743–4.

Precautions

For general discussions see Antineoplastics, p.641. Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. Patients with a history of high-dose pelvic irradiation or treatment with alkylating agents, and those with widespread metastases to the bone marrow should also be treated with extreme caution. Blood cell counts should be determined frequently during therapy. Fluorouracil should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency as this can lead to increased toxicity.

Topical fluorouracil should not be used on mucous membranes. There is a possibility of increased absorption if used excessively or on ulcerated or inflamed skin. Occlusive dressings may increase inflammatory actions. Exposure to UV light during treatment should be avoided. Creams are preferably applied using a non-metal applicator or gloved hand; if bare fingertips are used the hands must be washed immediately afterwards.

Handling and disposal. Fluorouracil is irritant; avoid contact with skin and mucous membranes.

Urine and faeces produced for up to 48 hours and 5 days respectively after an oral dose of fluorouracil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Metabolic disorders. For reference to increased risk of neurotoxicity in patients with a defect of pyrimidine metabolism given fluorouracil, see under Effects on the Nervous System, above.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642. The actions of fluorouracil may be modified by other drugs including allopurinol, cimetidine, folinic acid, methotrexate, and metronidazole (see also under Administration, below).

◊ References.

1. Jansman FGA, *et al.* Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. *Am J Health-Syst Pharm* 2005; **62:** 1788–93.

Antineoplastics. *Oxaliplatin*, which is given with fluorouracil and folinic acid in the treatment of colorectal cancer, reduced fluorouracil clearance in a study[1] of 29 patients with colorectal cancer. The effect was delayed and prolonged, lasting about 15 days, and an increase in toxicity correlated with raised fluorouracil concentrations. The mechanism of this interaction is unclear. In contrast, however, another study[2] found no effect of oxaliplatin on fluorouracil pharmacokinetics; the study was not designed to investigate a delayed effect and the dose of oxaliplatin was lower than that used in the first study.

Sorafenib has been reported to have variable effects on fluorouracil exposure.

For reference to the effect of fluorouracil on the action of *paclitaxel*, see Antineoplastics, p.759. For the increased risk of haemolytic-uraemic syndrome that may be seen if fluorouracil is used with *mitomycin*, see Effects on the Kidneys, p.752.

1. Boisdron-Celle M, *et al.* Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemother Pharmacol* 2002; **49:** 235–43.
2. Joel SP, *et al.* Lack of pharmacokinetic interaction between 5-fluorouracil and oxaliplatin. *Clin Pharmacol Ther* 2004; **76:** 45–54.

Antiprotozoals. *Metronidazole* increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. No enhanced antineoplastic effect was seen with the combination *in vitro*.[1]

1. Bardakji Z, *et al.* 5-Fluorouracil–metronidazole combination therapy in metastatic colorectal cancer. *Cancer Chemother Pharmacol* 1986; **18:** 140–4.

Antivirals. Giving *interferon alfa-2b* with fluorouracil has produced a marked increase in the initial plasma concentration of fluorouracil and a decrease in fluorouracil clearance.[1]

Severe leucopenia, fatal in some cases, has been reported in patients given fluorouracil or fluorouracil prodrugs (such as tegafur) with *sorivudine*.[2,3] A metabolite of sorivudine appears to inhibit dihydropyrimidine dehydrogenase, the primary enzyme responsible for the inactivation of fluorouracil.[3]

1. Czejka MJ, *et al.* Clinical pharmacokinetics of 5-fluorouracil: influence of the biomodulating agents interferon, dipyridamole and folic acid alone and in combination. *Arzneimittelforschung* 1993; **43:** 387–90.
2. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
3. Diasio RB. Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.

Gastrointestinal drugs. Pretreatment with *cimetidine* for 4 weeks increased plasma concentrations of fluorouracil after intravenous and oral doses in 6 patients.[1] The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen after single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6. Care is required in patients given both drugs together.

1. Harvey VJ, *et al.* The influence of cimetidine on the pharmacokinetics of 5-fluorouracil. *Br J Clin Pharmacol* 1984; **18:** 421–30.

Pharmacokinetics

Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin.

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids (including crossing the blood-brain barrier to appear in the CSF), and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine monophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate), the former undergoing conversion to the triphosphate which can be incorporated into RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose is excreted unchanged in the urine within 6 hours. The remainder is inactivated primarily in the liver and is catabolised via dihydropyrimidine dehydrogenase (DPD) similarly to endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and other metabolites are also produced.

◊ References.

1. Ploylearmsaeng S-A, *et al.* How may anticancer chemotherapy with fluorouracil be individualised? *Clin Pharmacokinet* 2006; **45:** 567–92.

Chronopharmacology. Plasma concentrations of fluorouracil during continuous intravenous infusion are reported to undergo circadian variations of as much as 50% of the mean, peak concentrations occurring in the middle of the night.[1] The variation may be due to a circadian variation in the activity of the enzyme dihydropyrimidine dehydrogenase in blood,[2] but striking inter-patient variations in peak concentrations of fluorouracil and peak enzyme activity suggest that any adjustment of infusion times would need to be individualised.[2] It has been suggested that pharmacokinetic monitoring should be investigated as a means of individualising fluorouracil doses with the aim of improving efficacy and reducing toxicity.[3]

1. Petit E, *et al.* Circadian rhythm-varying plasma concentration of 5-fluorouracil during a five-day continuous venous infusion at a constant rate in cancer patients. *Cancer Res* 1988; **48:** 1676–9.
2. Harris BE, *et al.* Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res* 1990; **50:** 197–201.
3. Young AM, *et al.* Can pharmacokinetic monitoring improve clinical use of fluorouracil. *Clin Pharmacokinet* 1999; **36:** 391–8.

Uses and Administration

Fluorouracil, an analogue of the pyrimidine uracil, is an antineoplastic that acts as an antimetabolite. After intracellular conversion to the active deoxynucleotide it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It can also interfere with RNA synthesis.

Fluorouracil is used alone or in combination in the adjuvant and palliative treatment of gastrointestinal cancer. In this setting it may be combined with folinic acid (see Administration, below). Fluorouracil is often given with cyclophosphamide and methotrexate or doxorubicin in the adjuvant treatment of breast cancer. It may also be used in the palliation of other malignant neoplasms such as those of the head and neck, liver, and pancreas. In addition, it may be used topically for treating malignant or premalignant lesions of the skin. Its use in these malignancies is further discussed under Choice of Antineoplastic as indicated by the cross-references given below.

Many dosage regimens have been used. Although it is most often given in combination regimens for the treatment of malignancy, many of the licensed dosage regimens relate to single-agent use. Such licensed regimens include:

- by *intravenous injection*, usual doses of 12 mg/kg daily (to a maximum of 0.8 to 1 g daily) for 3 or 4 days. If there is no evidence of toxicity, this may be followed after 1 day by 6 mg/kg on alternate days for 3 or 4 further doses. An alternative schedule is to give 15 mg/kg intravenously once a week throughout the course. The course may be repeated after 4 to 6 weeks or maintenance doses of 5 to 15 mg/kg to a maximum of 1 g may be given weekly.
- by *intravenous infusion*, usual doses of 15 mg/kg daily (to a maximum of 1 g daily) being infused in 500 mL of sodium chloride 0.9% or glucose 5% over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15 g has been given. *Continuous infusion* may also be used. The course may be repeated after 4 to 6 weeks.
- by continuous *intra-arterial infusion*, in doses of 5 to 7.5 mg/kg daily (regional perfusion).
- by *mouth*, although the parenteral route is generally preferred, a dose of 15 mg/kg, to a maximum of 1 g in one day, has been given once weekly for maintenance.

Suggested regimens with folinic acid include:

- 200 mg/m^2 of folinic acid (as calcium folinate) by slow intravenous injection followed immediately by an intravenous bolus of fluorouracil 370 mg/m^2; the treatment is given daily for 5 consecutive days, and may be repeated every 4 to 5 weeks
- lower doses of folinic acid (20 mg/m^2) followed by fluorouracil 425 mg/m^2 for 5 consecutive days, repeated every 4 to 5 weeks (the Mayo regimen)
- an initial dose of 200 mg/m^2 of folinic acid, followed by fluorouracil 400 mg/m^2 as an initial intravenous bolus injection and then 600 mg/m^2 by continuous intravenous infusion. This dosage is given for 2 consecutive days every 2 weeks (the de Gramont regimen)

The white cell count should be determined frequently during treatment with fluorouracil and therapy stopped immediately if the count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p.639) or if severe adverse effects occur. Doses should be reduced by up to half in patients with poor nutritional status, impaired bone-marrow, hepatic, or renal function, and within 30 days of major surgery.

Fluorouracil is used topically in the treatment of solar (actinic) keratoses and other superficial tumours and premalignant conditions of the skin including Bowen's disease and superficial basal cell carcinomas. For actinic keratosis it is usually applied as a 0.5 to 5% cream or as a 1 to 5% solution in propylene glycol once or twice daily for 2 to 4 weeks; the higher strength may be applied for at least 3 to 6 weeks for superficial basal cell carcinomas.

Administration. Modulation of fluorouracil by other drugs has been tried in an effort to enhance its effects, particularly in the treatment of colorectal cancer (p.665).

Folinic acid has been extensively used to modulate the effects of fluorouracil, and has become the agent of choice. Various regimens have been used, modifying the fluorouracil schedule (continuous infusion versus bolus), folinic acid dose (low-dose versus high-dose) and the regimen frequency (monthly, bimonthly, or weekly). Despite numerous studies, the optimum regimen in terms of efficacy and tolerability has yet to be determined.

In the adjuvant setting, a large-scale randomised trial[1] found no difference in efficacy between low-dose and high-dose folinic acid when added to fluorouracil given either once weekly for 30 doses, or for 5 consecutive days per month over 6 months. Fluorouracil and low-dose folinic acid may therefore become the preferred regimen in the adjuvant setting.

In the palliation of advanced disease, meta-analyses have revealed the value of the addition of folinic acid to fluorouracil,[2] and the use of infusions rather than bolus fluorouracil,[3] in terms of response rates. An updated meta-analysis confirmed the benefit of addition of folinic acid to fluorouracil in terms of response rate, and found a small but statistically significant advantage in terms of overall survival. Survival benefit was restricted to trials using the same dose of fluorouracil in the treatment arms (fluorouracil alone versus fluorouracil and folinic acid), suggesting that the benefit of modulation with folinic acid could be compensated by an increase of fluorouracil dose in the fluorouracil alone arm. However, increased toxicity from high-dose fluorouracil might occur.[4] The data for low-dose folinic acid versus high-dose are less clear.[5] In 1 randomised trial,[6] a bimonthly infusion regimen of fluorouracil plus high-dose folinic acid (the de Gramont regimen[7]) was more effective than a monthly bolus regimen of fluorouracil plus low-dose folinic acid. Further studies comparing the effect of high- and low-dose folinic acid added to the same schedule of continuous infusion fluorouracil are required.

Interferon alfa also appears to modify[8] the actions of fluorouracil (see also under Interactions, above), and has been investigated in combination with fluorouracil and folinic acid. Although some early results were promising, later randomised controlled trials failed to show any benefit for the addition of interferon alfa to fluorouracil or fluorouracil plus folinic acid.[8] It is not clear whether interferon beta will prove of any greater benefit.

Based on the results of early adjuvant studies, *levamisole* was used as standard therapy to modulate fluorouracil, particularly in the USA. However, more recent trials indicate that levamisole is no more effective than placebo when added to fluorouracil,[1] or to fluorouracil plus folinic acid.[9]

Methotrexate has also been used to modulate fluorouracil. Meta-analysis of several studies of fluorouracil preceded by methotrexate found that the combination doubled the response rate to fluorouracil in metastatic colorectal cancer and produced some survival benefits.[10] (Combination in the reverse order, i.e. methotrexate preceded by fluorouracil, may reduce methotrexate toxicity—see under Treatment of Adverse Effects, p.747.)

1. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355:** 1588–96.
2. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10:** 896–903.
3. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16:** 301–8.
4. The Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22:** 3766–75. Correction. *ibid.* 2005; **23:** 1337–8.
5. Rustum YM, *et al.* Rationale for treatment design: biochemical modulation of 5-fluorouracil by leucovorin. *Cancer J Sci Am* 1998; **4:** 12–18.
6. de Gramont A, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup study. *J Clin Oncol* 1997; **15:** 808–15.
7. de Gramont A, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; **34:** 619–26.
8. Makower D, Wadler S. Interferons as biomodulators of fluoropyrimidines in the treatment of colorectal cancer. *Semin Oncol* 1999; **26:** 663–71.
9. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; **17:** 3553–9.
10. Advanced Colorectal Cancer Meta-analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994; **12:** 960–9.

Darier's disease. Two patients with resistant Darier's disease (p.1578) receiving long-term oral retinoid therapy responded to treatment with topical fluorouracil applied as a 1% cream once daily.[1] There was complete clearance of skin lesions after 3 weeks of treatment.

1. Knulst AC, *et al.* Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; **133:** 463–6.

Eye disorders. Aside from its use in glaucoma surgery (below), fluorouracil has been used adjunctively in other ocular surgery. It has also shown promising results in the treatment of ocular surface malignancies.[1]

1. Abraham LM, *et al.* The clinical applications of fluorouracil in ophthalmic practice. *Drugs* 2007; **67:** 237–55.

Glaucoma. A regimen of subconjunctival injections of fluorouracil is effective in improving the outcome of glaucoma filtering surgery[1-3] in selected patients when used as an adjunct to prevent the formation of scar tissue (see p.1873). However, in view of the increased risk of late-onset conjunctival wound leaks caution has been suggested in its use in eyes with a good prognosis.[3] Although one study[4] found that fluorouracil improved the success rate of combined glaucoma filtering surgery and cataract surgery earlier studies had failed to demonstrate any advantage.[5,6] A systematic review[7] of these and 2 other studies concluded that fluorouracil reduced the risk of surgical failure of trabeculectomy in eyes at high risk of failure, and in those undergoing surgery for the first time, but noted that the methodological quality of the studies was not high, and that this practice has largely been superseded by the use of intra-operative mitomycin. However, a later survey[8] in the UK found that the use of antimetabolites in glaucoma surgery was much less common than in the USA or Japan, and that fluorouracil was strongly preferred to mitomycin.

Intra-operative topical application of fluorouracil has been tried as an alternative to subconjunctival injection with conflicting results.[9-11]

1. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. *Arch Ophthalmol* 1992; **110:** 1072–5.
2. Goldenfeld M, *et al.* 5-Fluorouracil in initial trabeculectomy: a prospective, randomized, multicenter study. *Ophthalmology* 1994; **101:** 1024–9.
3. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. *Am J Ophthalmol* 1996; **121:** 349–66.
4. Gandolfi SA, Vecchi M. 5-Fluorouracil in combined trabeculectomy and clear-cornea phacoemulsification with posterior chamber intraocular lens implantation: a one-year randomized, controlled clinical trial. *Ophthalmology* 1997; **104:** 181–6.
5. Wong PC, *et al.* 5-Fluorouracil after primary combined filtration surgery. *Am J Ophthalmol* 1994; **117:** 149–54.
6. O'Grady JM, *et al.* Trabeculectomy, phacoemulsification, and posterior chamber lens implantation with and without 5-fluorouracil. *Am J Ophthalmol* 1993; **116:** 594–9.
7. Wormald R, *et al.* Post-operative 5-fluorouracil for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 12/05/05).
8. Siriwardena D, *et al.* National survey of antimetabolite use in glaucoma surgery in the United Kingdom. *Br J Ophthalmol* 2004; **88:** 873–6.
9. Egbert PR, *et al.* A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. *Am J Ophthalmol* 1993; **116:** 612–16.
10. Lachkar Y, *et al.* Trabeculectomy with intraoperative sponge 5-fluorouracil in Afro-Caribbeans. *Br J Ophthalmol* 1997; **81:** 555–8.
11. Yorston D, Khaw PT. A randomised trial of the effect of intra-operative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001; **85:** 1028–30.

Malignant neoplasms. Fluorouracil plays an important role in the adjuvant treatment of gastrointestinal cancer, as discussed on p.664, and has been widely used in adjuvant regimens for early breast cancer (p.661). It may also be employed in the management of a wide variety of other malignancies including pancreatic endocrine tumours (p.643), cancers of the cervix (p.663) and head and neck (p.666), liver metastases (p.667), and tumours of the exocrine pancreas (p.671). It is reported to have only modest activity in neoplasms of the kidney (p.667). In addition, it is sometimes applied topically as part of the management of malignant or pre-malignant lesions of the skin (see Basal Cell and Squamous Cell Carcinoma, p.673), or surface neoplasia of the eye (p.664).

The role of fluorouracil in chemoradiotherapy of various malignancies has been reviewed.[1]

1. Rich TA, *et al.* Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol* 2004; **22:** 2214–32.

Toxoplasmosis. For mention of the use of fluorouracil with clindamycin to treat cerebral toxoplasmosis, see p.253.

Warts. Fluorouracil has been used, as a 1% or, more usually, a 5% cream or solution in the treatment of genital warts (condylomata acuminata).[1-3] It has been tried as an adjuvant to laser therapy in severe papillomavirus-associated vulvar disease,[4] with variable results, and in men with subclinical or clinically apparent penile lesions.[5] A preparation of fluorouracil 3% in a collagen gel basis, together with adrenaline as a local vasoconstrictor, has been tried by injection into genital warts.[6] A combination of fluorouracil 0.5% and salicylic acid 10% has also been stated to be effective in the topical treatment of common and plantar warts.[7] For a discussion of the various agents, including cytotoxics such as fluorouracil, employed to produce destruction of warts, see p.1584.

1. Kling AR. Genital warts—therapy. *Semin Dermatol* 1992; **11:** 247–55.
2. Stone KM. Human papillomavirus infection and genital warts: update on epidemiology and treatment. *Clin Infect Dis* 1995; **20** (suppl 1): S91–7.
3. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997; **102:** 28–37.
4. Reid R, *et al.* Superficial laser vulvectomy IV: extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus-associated vulvar disease. *Obstet Gynecol* 1990; **76:** 439–48.
5. Bergman A, Nalick R. Genital human papillomavirus infection in men: diagnosis and treatment with a laser and 5-fluorouracil. *J Reprod Med* 1991; **36:** 363–6.
6. Swinehart JM, *et al.* Intralesional fluorouracil/epinephrine injectable gel for treatment of condylomata acuminata: a phase 3 clinical study. *Arch Dermatol* 1997; **133:** 67–73.
7. Zschocke I, *et al.* Wirksamkeit und Nutzen eines 5-FU-/Salicylsäure-haltigen Präparates in der Therapie vulgärer und plantarer Warzen—systematische Literaturübersicht und Metaanalyse. *J Dtsch Dermatol Ges* 2004; **2:** 187–93.

Preparations

BP 2008: Fluorouracil Cream; Fluorouracil Injection;
USP 31: Fluorouracil Cream; Fluorouracil Injection; Fluorouracil Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cinco-Fu†; Efudix; Ifocid†; Oncofu†; Triosules; ***Austral.:*** Efudix; ***Belg.:*** Efudix; Fluracedyl; Fluroblastine; ***Braz.:*** Killit†; Utoral†; ***Canad.:*** Adrucil†; Efudex; ***Chile:*** Efudix; Fluoracilo; ***Cz.:*** La-Fu; ***Denm.:*** Flurablastin; ***Fin.:*** Flurablastin; ***Fr.:*** Efudix; ***Ger.:*** Efudix; Neofluor; O-fluor†; Onkofluor; Ribofluor; ***Gr.:*** Uraciflor; ***Hong Kong:*** Efudix†; ***Hung.:*** Efudix; ***India:*** Fivefluro; Florac; Fluracil; ***Indon.:*** Curacil; Fluracedyl; ***Irl.:*** Efudix; ***Israel:*** Efudix; ***Ital.:*** Efudix; ***Malaysia:*** Fluracedyl; ***Mex.:*** Efudix; Flurox; Ifacil†; Tecflu; ***Neth.:*** Efudix; Fluracedyl; ***Norw.:*** Flurablastin; ***NZ:*** Efudix; ***Philipp.:*** Fivoflu; Fluoxan; Fluracedyl; Fluroblastin; Uflahex; Utoral; ***Pol.:*** Efudix; ***Port.:*** Cinkef-U; ***Rus.:*** Flurox (Флурокс)†; ***S.Afr.:*** Efudix; Fluroblastin; ***Singapore:*** Efudix; ***Spain:*** Efudix†; ***Swed.:*** Flurablastin; Fluracedyl†; ***Switz.:*** Efudix; ***Thai.:*** Fivoflu; Fluracedyl†; Flurox; ***UK:*** Efudix; ***USA:*** Adrucil; Carac; Efudex; Fluoroplex; ***Venez.:*** Fivoflu; Fluroblastin.

Multi-ingredient: ***Austria:*** Verrumal; ***Braz.:*** Efurix; ***Cz.:*** Verrumal; ***Ger.:*** Verrumal; ***Gr.:*** Verruca Hermal; ***Hong Kong:*** Verrumal; ***Hung.:*** Verrumal; ***Israel:*** Verrumal; Verucid†; ***Malaysia:*** Verrumal; ***Pol.:*** Verrumal; ***Port.:*** Verrucare; Verrumal; ***Singapore:*** Verrumal; ***Switz.:*** Verrumal; ***Thai.:*** Verrumal; ***Turk.:*** Verrutol.

Flutamide *(BAN, USAN, rINN)*

Flutamid; Flutamida; Flutamidas; Flutamidi; Flutamidum; Sch-13521. α′,α′,α′-Trifluoro-4′-nitroisobutyro-*m*-toluidide; α,α,α-Trifluoro-2-methyl-4′-nitro-*m*-propionotoluidide.

Флутамид

$C_{11}H_{11}F_3N_2O_3$ = 276.2.

CAS — 13311-84-7.

ATC — L02BB01.

ATC Vet — QL02BB01.

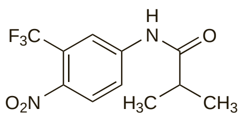

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.

USP 31 (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water, in liquid paraffin, and in petroleum spirit; freely soluble in acetone, in ethyl acetate, and in methyl alcohol; soluble in chloroform and in ether. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

The most frequently reported adverse effects with flutamide are hot flushes and reversible gynaecomastia or breast tenderness, sometimes accompanied by galactorrhoea. Nausea, vomiting, diarrhoea, increased appetite, anorexia, and sleep disturbances may occur. There have been reports of skin reactions, including epidermal necrolysis, and of liver damage, sometimes fatal. Other adverse effects reported in patients receiving flutamide include anaemias, haemolysis, headache, dizziness, malaise, blurred vision, anxiety, depression, decreased libido, impotence, and hypertension. Abdominal pain, chest pain, dyspnoea, and cough have been reported rarely. Discoloration of the urine to amber or yellow-green can be caused by the presence of flutamide and/or its metabolites.

Flutamide should be used with care in patients with cardiovascular disease because of the possibility of fluid retention. It should also be used with caution in patients with hepatic impairment and is contra-indicated in those with severe impairment. Regular liver function testing is recommended in all patients: therapy should be stopped or dosage reduced if there is evidence of hepatotoxicity.

Effects on the blood. A report[1] of methaemoglobinaemia in an elderly man was attributed to flutamide. A study[2] of 45 patients given flutamide found no cases of methaemoglobinaemia, but the authors noted a further 3 published case reports.

1. Schott AM, *et al.* Flutamide-induced methemoglobinemia. *DICP Ann Pharmacother* 1991; **25:** 600–1.
2. Schulz M, *et al.* Lack of methemoglobinemia with flutamide. *Ann Pharmacother* 2001; **35:** 21–5.

Effects on the liver. Hepatitis occurred in a 79-year-old man taking flutamide 750 mg daily as sole therapy after a prostatectomy,[1] but a subsequent study[2] in 1091 patients given flutamide 250 mg three times daily as part of a regimen for prostate cancer found marked signs of liver damage only in 4, of whom only 2 had clinical evidence of hepatotoxicity. In the USA, the FDA had 46 reports of patients with hepatotoxicity associated with flutamide up to December 1994. Of these patients, 20 died from progressive liver disease.[3] Further cases have continued to be reported.[4-6] Early tapering of the dose, stopping therapy, or switching to another anti-androgen may resolve hepatotoxic effects.[7] Patients with chronic viral hepatitis may be at higher risk of developing hepatotoxicity with anti-androgen therapy.[8]

1. Hart W, Stricker BHC. Flutamide and hepatitis. *Ann Intern Med* 1989; **110:** 943–4.
2. Gomez J-L, *et al.* Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am J Med* 1992; **92:** 465–70.
3. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol (Baltimore)* 1996; **155:** 209–12. Correction *ibid:* 396.
4. Garcia Cortes M, *et al.* Flutamide-induced hepatotoxicity: report of a case series. *Rev Esp Enferm Dig* 2001; **93:** 423–32. Correction. *ibid.*; 634.
5. Lubbert C, *et al.* Ikterus und schwere Leberfunktionsstorung bei der hormonablativen Behandlung des Prostatakarzinoms. *Internist (Berl)* 2004; **45:** 333–40.
6. Osculati A, Castiglioni C. Fatal liver complications with flutamide. *Lancet* 2006; **367:** 1140–1.
7. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
8. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.

Effects on the lungs. In a review[1] of 78 cases of pneumonitis reported to the FDA between 1998 and 2000 that were associated with bicalutamide, flutamide, or nilutamide, it was found that 14 patients had died of respiratory failure. It was estimated that the incidence of pneumonitis was highest for nilutamide (0.77%), but lower for flutamide (0.04%) and bicalutamide (0.01%).

1. Bennett CL, *et al.* Pneumonitis associated with nonsteroidal antiandrogens: presumptive evidence of a class effect. *Ann Intern Med* 2002; **137:** 625.

Effects on the skin. Photosensitivity reactions have been reported in patients receiving flutamide.[1,2] Some consider it to be an early manifestation of SLE.[2]

1. Fujimoto M, *et al.* Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; **135:** 496–7.
2. Kaur C, Thami GP. Flutamide-induced photosensitivity: is it a forme fruste of lupus? *Br J Dermatol* 2003; **148:** 603–4.

Gynaecomastia. Gynaecomastia (p.2092) and breast pain are frequent adverse effects of nonsteroidal anti-androgens used to treat prostate cancer. Nearly 90% of patients treated with bicalutamide in the Early Prostate Cancer programme experienced breast pain, gynaecomastia, or both.[1] Some patients who develop gynaecomastia will accept it as a tolerable adverse effect of therapy but others will require specific treatment, and a number of different measures have been tried for both prevention and treatment. The risk of breast changes can be reduced by the use of prophylactic low-dose irradiation of the breast area before nonsteroidal anti-androgen therapy is started. However, skin irritation can occur, and the long-term risk for development of breast cancer is unknown. Irradiation is unlikely to be effective once breast enlargement has occurred but it can help to reduce pain. Empirical use of oral analgesics or topical local anaesthetics may be considered for breast pain. Specific surgical treatment to reduce breast tissue includes liposuction and breast tissue excision.[2,3]

Hormonal therapy using tamoxifen or anastrozole has been suggested, largely based on reports of benefit in various patient groups with gynaecomastia.[1,2] Two randomised controlled studies[4,5] of men who were treated with bicalutamide for prostate cancer found that prophylactic tamoxifen was effective for the prevention of gynaecomastia and breast pain, but that anastrozole was no better than placebo. One of these studies[5] also assessed the use of these drugs as treatment and found that gynaecomastia and breast pain resolved in at least 65% of patients treated with tamoxifen, but only in about 18% of those treated with anastrozole. Tamoxifen is considered to be more effective than radiotherapy for prevention of gynaecomastia.[3]

1. Sieber PR. Treatment of bicalutamide-induced breast events. *Expert Rev Anticancer Ther* 2007; **7:** 1773–9.
2. Leibovitch I, *et al.* Management options for gynaecomastia and breast pain associated with nonsteroidal antiandrogen therapy: case studies in context. *Clin Drug Invest* 2003; **23:** 205–15.
3. Di Lorenzo G, *et al.* Management of gynaecomastia in patients with prostate cancer: a systematic review. *Lancet Oncol* 2005; **6:** 972–9.
4. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; **23:** 808–15.
5. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.

Interactions

Flutamide may increase the effect of warfarin, see Antineoplastics, p.1429.

Pharmacokinetics

Flutamide is reported to be rapidly and completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after a dose. It is rapidly and extensively metabolised; the major metabolite (2-hydroxyflutamide) possesses anti-androgenic properties. The half-life of the metabolite is about 6 hours. Both flutamide and 2-hydroxyflutamide are more than 90% bound to plasma proteins. Excretion is mainly in the urine with only minor amounts appearing in the faeces.

◊ References.

1. Radwanski E, *et al.* Single and multiple dose pharmacokinetic evaluation of flutamide in normal geriatric volunteers. *J Clin Pharmacol* 1989; **29:** 554–8.

Uses and Administration

Flutamide is a nonsteroidal compound with anti-androgenic properties which appears to act by inhibiting the uptake and/or binding of androgens in target tissues. It is used, usually with gonadorelin analogues, in the palliative treatment of prostatic carcinoma (p.671). The usual oral dose is 250 mg three times daily. When used in combination therapy UK licensed product information recommends that flutamide treatment should be started at least 3 days before the gonadorelin analogue to suppress any 'flare' reaction; however, in some other countries it is recommended that treatment with both agents be begun simultaneously for optimum effect.

Congenital adrenal hyperplasia. For mention of the use of flutamide with testolactone to block androgenic effects in congenital adrenal hyperplasia, see p.1502.

Hirsutism. Anti-androgens (usually cyproterone or spironolactone) are widely used for the drug treatment of hirsutism (p.2089). Flutamide has no particular advantage in this context;[1,2] one study has found flutamide to be more effective than spironolactone in inhibiting hirsutism,[3] but others found them to be of similar efficacy,[4,5] and the risk of hepatotoxicity with flutamide is a problem.[2] Nonetheless, flutamide has continued to be investigated.[6-8]

1. Rittmaster RS. Hyperandrogenism—what is normal? *N Engl J Med* 1992; **327:** 194–6.
2. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
3. Cusan L, *et al.* Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertil Steril* 1994; **61:** 281–7.
4. Erenus M, *et al.* Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertil Steril* 1994; **61:** 613–6.
5. Moghetti P, *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85:** 89–94.
6. Muderris II, *et al.* Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). *Gynecol Endocrinol* 2000; **14:** 38–41.
7. Venturoli S, *et al.* Low-dose flutamide (125 mg/day) as maintenance therapy in the treatment of hirsutism. *Horm Res* 2001; **56:** 25–31.
8. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.

Malignant neoplasms. Androgen blockade, which may include the use of flutamide, is used in the management of metastatic hormone-responsive prostate cancer (p.671); once the cancer begins to progress despite such therapy, stopping flutamide occasionally produces paradoxical disease regression. Promising preliminary results have also followed the use of flutamide in patients with adenocarcinoma of the pancreas (p.671).

Polycystic ovary syndrome. Flutamide has been used, usually with metformin, in the management of polycystic ovary syndrome (p.2080);[1-4] additive effects have been reported with this combination.

1. Ibáñez L, *et al.* Additive effects of insulin-sensitizing and anti-androgen treatment in young nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002; **87:** 2870–4.
2. Ibáñez L, *et al.* Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003; **88:** 2600–6.
3. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60:** 241–9.
4. Gambineri A, *et al.* Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006; **91:** 3970–80.

Preparations

USP 31: Flutamide Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Asoflut; Dedile; Eulexin†; Flutaplex; Flutax†; Flutepan; Flutrax; FTDA†; Olter†; ***Austral.:*** Eulexin; Flutamin; Fugerel†; ***Austria:*** Afluta; Androbloc; Flutabene; Flutahexal; Flutastad; Fugerel; ***Belg.:*** Eulexin; Flutaplex; ***Braz.:*** Biomida†; Eulexin; Tecnoflut; Teflut; ***Canad.:*** Euflex; ***Chile:*** Androdor†; Drogenil; Etaconil; Flulem; ***Cz.:*** Andraxan; Flucinom; Flumed; Flutacan†; Flutaplex; Prostandril; Xadaren†; ***Denm.:*** Eulexin; Fluprosin; Flutacan†; Profamid; ***Fin.:*** Eulexin; Profamid; ***Fr.:*** Eulexine; Prostadirex; ***Ger.:*** Apimid†; Flumid; Fluta; Flutexin†; Fugerel; Prostica; Prostogenat†; Testotard†; ***Gr.:*** Adiprost; Andraxan; Elbat; Flucinom; Flutaplex; Palistop; Prostamide; Rikital; Tremexal; ***Hong Kong:*** Flutan†; Fugerel; ***Hung.:*** Cytamid†; Fluprost; Flutam; Flutasin; Fugerel; ***India:*** Cytomid; Prostamid; ***Indon.:*** Flutaplex; Fugerel; ***Irl.:*** Androstat; Drogenil; ***Israel:*** Eulexin; ***Ital.:*** Drogenil†; Eulexin; Fluprost; Virflutam†; ***Malaysia:*** Flutan†; Flutaplex; Fugerel†; ***Mex.:*** Eulexin; Flimutal; Fluken†; Flulem; Tafenil; ***Neth.:*** Drogenil; Eulexin; Flutaplex; Prostatil; ***Norw.:*** Eulexin; ***NZ:*** Eulexin; Flutamin; Flutol†; ***Philipp.:*** Fugerel; Prostanon; ***Pol.:*** Apo-Flutam; Fugerel; Prostandril; ***Port.:*** Drogenil; Eulexin; Prosneo; ***Rus.:*** Flutamid (Флутамид); Flutaplex (Флутаплекс); ***S.Afr.:*** Eulexin; Flutahexal; Flutaplex; ***Singapore:*** Flutan; Fugerel†; ***Spain:*** Eulexin; Flutandrona; Flutaplex†; Grisetin; Oncosal; Prostacur; ***Swed.:*** Eulexin; Flutacan†; ***Switz.:*** Flucinome; ***Thai.:*** Andraxan; Flulem; Flutan; Flutaplex; Fugerel; ***Turk.:*** Andraxan; Eulexin; ***UK:*** Chimax; Drogenil; ***USA:*** Eulexin†; ***Venez.:*** Etaconil; Eulexin.

Formestane *(BAN, rINN)* ⊗

CGP-32349; Formestaani; Formestan; Formestano; Formestanum; 4-Hydroxyandrostenedione; 4-OHA; 4-OHAD. 4-Hydroxyandrost-4-ene-3,17-dione.

Форместан

$C_{19}H_{26}O_3$ = 302.4.
CAS — 566-48-3.
ATC — L02BG02.
ATC Vet — QL02BG02.

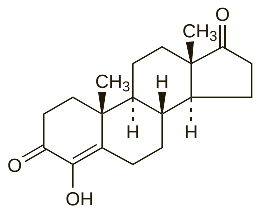

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of formestane are local irritation and pain at the site of injection. Patients may experience hot flushes due to oestrogen deprivation. Other occasional or rare adverse effects include rashes and pruritus, alopecia or hypertrichosis, drowsiness, dizziness, emotional lability, oedema of the leg, thrombophlebitis, vaginal spotting or bleeding, gastrointestinal disturbances, pelvic or muscle cramps, arthralgia, exacerbation of bone pain, and a vasovagal reaction. Hypersensitivity reactions to the drug or the formulation have occurred.

Care should be taken to avoid intravascular injection. Injection into or near the sciatic nerve may result in pain and nerve trauma. Caution is required if patients drive or operate machinery.

Effects on carbohydrate metabolism. Recurrent hypoglycaemic episodes developed in a diabetic patient previously well maintained on gliclazide after addition of formestane to treatment for metastatic breast cancer.[1] Episodic hypoglycaemia continued after dosage reduction, and eventually withdrawal, of gliclazide, suggesting that the effect was not simply an interaction with the sulfonylurea.

1. Brankin E, *et al.* Hypoglycaemia associated with formestane treatment. *BMJ* 1997; **314:** 869.

Pharmacokinetics

Intramuscular formestane is reported to form a depot that slowly releases active drug into the systemic circulation; maximum plasma concentrations occur about 30 to 48 hours after a single dose and then decline fairly rapidly over 2 to 4 days before declining more slowly, with an apparent elimination half-life of 5 to 6 days. The systemic uptake has been estimated at 20 to 25% of the dose in 14 days. Formestane is about 85% bound to plasma protein in the circulation. It is metabolised by conjugation to the inactive glucuronide: less than 1% of the dose is excreted in urine unchanged.

Uses and Administration

Formestane is an inhibitor of the aromatase (oestrogen synthetase) system which is responsible for the production of oestrogens from androgens. It has been used for its anti-oestrogenic properties in the endocrine treatment of advanced breast cancer in postmenopausal women (p.661).

It is given by intramuscular injection, as an aqueous suspension, in doses of 250 mg every 2 weeks. Injections should be given into each buttock alternately.

◊ Reviews.

1. Wiseman LR, McTavish D. Formestane: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of breast cancer and prostatic cancer. *Drugs* 1993; **45:** 66–84.
2. Anonymous. Formestane for advanced breast cancer in postmenopausal women. *Drug Ther Bull* 1993; **31:** 85–7.
3. Carlini P, *et al.* Formestane, a steroidal aromatase inhibitor after failure of non-steroidal aromatase inhibitors (anastrozole and letrozole): is a clinical benefit still achievable? *Ann Oncol* 2001; **12:** 1539–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lentaron†; ***Austria:*** Lentaron; ***Braz.:*** Lentaron†; ***Chile:*** Lentaron†; ***Cz.:*** Lentaron†; ***Denm.:*** Lentaron†; ***Ger.:*** Lentaron†; ***Gr.:*** Lentaron†; ***Hong Kong:*** Lentaron†; ***Ital.:*** Lentaron†; ***Malaysia:*** Lentaron†; ***S.Afr.:*** Lentare†; ***Spain:*** Lentaron†; ***Turk.:*** Lentaron.

Forodesine Hydrochloride *(USAN, rINNM)*

BCX-1777 (forodesine or forodesine hydrochloride); Forodésine, Chlorhydrate de; Forodesini Hydrochloridum; Hidrocloruro de forodesina. (–)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one hydrochloride.

Фородезина Гидрохлорид

$C_{11}H_{14}N_4O_4$,HCl = 302.7.
CAS — 209799-67-7 (forodesine); 284490-13-7 (forodesine hydrochloride).

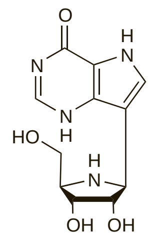

(forodesine)

Profile

Forodesine is an inhibitor of purine nucleoside phosphorylase. It is under investigation in the treatment of T-cell lymphomas, chronic lymphocytic leukaemia, and acute lymphoblastic leukaemia.

Fotemustine *(BAN, rINN)*

Fotemustin; Fotemustina; Fotémustine; Fotemustinum; S-10036. (±)-Diethyl {1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl}phosphonate.

Фотемустин

$C_9H_{19}ClN_3O_5P$ = 315.7.
CAS — 92118-27-9.
ATC — L01AD05.
ATC Vet — QL01AD05.

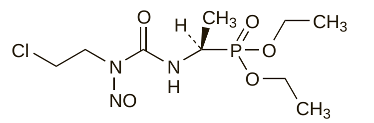

Profile

Fotemustine is a nitrosourea derivative and alkylating agent with actions similar to those of carmustine (p.694). It is used in the treatment of disseminated malignant melanoma, particularly where cerebral metastases are present (p.673) and has been tried in primary malignancies of the brain (p.660). When used as a single agent it is licensed for intravenous or intra-arterial infusion in usual doses of 100 mg/m^2 weekly for 3 weeks to induce remission, followed after 4 to 5 weeks, if blood counts permit, by maintenance dosage with 100 mg/m^2 every 3 weeks. Intravenous infusions are given over 1 hour and intra-arterial infusions over 4 hours. Liver function should be monitored regularly during induction treatment. Regular blood counts should be taken and dosage should be reduced or withheld if white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p.639). Bone-marrow suppression may be delayed, with the nadir of the white cell counts 5 or 6 weeks after dosing. Solutions for infusion must be freshly prepared and protected from light.

◊ References.

1. Rougier P, *et al.* Fotemustine in patients with advanced gastric cancer, a phase II trial from the EORTC-GITCCG. *Eur J Cancer* 1996; **32A:** 1432–3.
2. Marzolini C, *et al.* Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. *Cancer Chemother Pharmacol* 1998; **42:** 433–40.
3. Ulrich J, *et al.* Management of cerebral metastases from malignant melanoma: results of a combined, simultaneous treatment with fotemustine and irradiation. *J Neurooncol* 1999; **43:** 173–8.
4. Terheyden P, *et al.* Sequential interferon-alpha2b, interleukin-2 and fotemustine for patients with metastatic melanoma. *Melanoma Res* 2000; **10:** 475–82.
5. Frenay M, *et al.* Up-front chemotherapy with fotemustine (F) / cisplatin (CDDP) / etoposide (VP16) regimen in the treatment of 33 non-removable glioblastomas. *Eur J Cancer* 2000; **36:** 1026–31.
6. Mornex F, *et al.* A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003; **13:** 97–103.
7. Aapro MS, *et al.* Phase II study of fotemustine in patients with advanced ovarian carcinoma: a trial of the EORTC Gynecological Cancer Group. *Eur J Cancer* 2003; **39:** 1141–13.
8. Fazeny-Dorner B, *et al.* Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. *Anticancer Drugs* 2003; **14:** 437–42.
9. Avril MF, *et al.* Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; **22:** 1118–25.
10. Ozkan M, *et al.* Post-operative sequential chemo-radiotherapy in high-grade cerebral gliomas with fotemustine. *J Chemother* 2004; **16:** 298–302.
11. Bonenkamp JJ, *et al.* Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol* 2004; **30:** 1107–12.
12. Peters S, *et al.* Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006; **17:** 578–83.
13. Gill S, *et al.* Long-term survival and secondary acute leukemia after fotemustine therapy for metastatic melanoma. *J Clin Oncol* 2007; **25:** 4493–4.
14. Scoccianti S, *et al.* Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. *Anticancer Drugs* 2008; **19:** 613–20.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Muforan†; ***Austral.:*** Muphoran; ***Austria:*** Muphoran; ***Belg.:*** Muphoran; ***Braz.:*** Muphoran; ***Cz.:*** Mustophoran; ***Fr.:*** Muphoran; ***Gr.:*** Muphoran; ***Hung.:*** Mustophoran; ***Israel:*** Muphoran; ***Ital.:*** Muphoran; ***NZ:*** Muphoran; ***Pol.:*** Mustophoran; ***Port.:*** Muphoran; ***Rus.:*** Mustophoran (Мюстофоран); ***Spain:*** Mustoforan; ***Turk.:*** Muphoran.

Fulvestrant *(BAN, USAN, rINN)* ⊗

Fulvestrantum; ICI-182780; ZD-9238. 7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

Фульвестрант

$C_{32}H_{47}F_5O_3S$ = 606.8.
CAS — 129453-61-8.
ATC — L02BA03.
ATC Vet — QL02BA03.

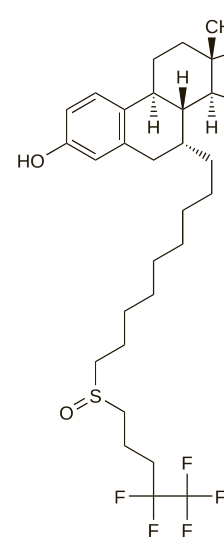

Pharmacopoeias. In *US.*

USP 31 (Fulvestrant). A mixture of the diastereoisomers A and B. A white powder. Freely soluble in alcohol. Store at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

The most commonly reported adverse effects of fulvestrant are nausea, vomiting, constipation, diarrhoea, abdominal pain, headache, back pain, hot flushes, and pharyngitis. Injection site reactions can occur. Other adverse effects include rash, asthenia, urinary-tract infections, venous thromboembolism, and elevations in liver enzyme values. Myalgia, vertigo, and leucopenia have been reported. Hypersensitivity reactions, including angioedema and urticaria, can occur. Vaginal bleeding has been reported rarely. Fulvestrant should be given with caution to those with severe renal impairment (creatinine clearance less than 30 mL/minute) and in those with mild to moderate hepatic impairment; use is contra-indicated in those with severe hepatic impairment. In patients with bleeding tendencies, thrombocytopenia, or taking anticoagulants, fulvestrant should also be used with caution, if at all.

Pharmacokinetics

Fulvestrant is slowly absorbed after intramuscular injection; maximum plasma concentrations are reached after about 7 days. Steady-state concentrations are reached after about 3 to 6 doses (given monthly). Fulvestrant is highly bound to plasma proteins. It is metabolised primarily in the liver to a number of metabolites, some of which have oestrogen antagonist activity, and is excreted in the faeces. After intramuscular injection fulvestrant has a half-life of about 40 to 50 days.

◊ References.

1. Robertson JFR, *et al.* Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 2004; **43:** 529–38.

Uses and Administration

Fulvestrant is an oestrogen antagonist that downregulates the oestrogen receptor and is used for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women (p.661); it is given when disease has relapsed or progressed during or after treatment with anti-oestrogens. The recommended dose is 250 mg, given intramuscularly at monthly intervals. It is injected into the buttock, either as a single injection or as two concurrent doses.

◊ References.

1. Osborne CK, *et al.* Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002; **20:** 3386–95.
2. Howell A, *et al.* Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002; **20:** 3396–3403.
3. Bross PF, *et al.* Fulvestrant in postmenopausal women with advanced breast cancer. *Clin Cancer Res* 2003; **9:** 4309–17.
4. Howell A, *et al.* Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004; **22:** 1605–13.
5. McKeage K, *et al.* Fulvestrant: a review of its use in hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. *Drugs* 2004; **64:** 633–48.
6. Buzdar AU. Fulvestrant: a new type of estrogen receptor antagonist for the treatment of advanced breast cancer. *Drugs Today* 2004; **40:** 751–64.
7. Robertson JF, *et al.* Endocrine treatment options for advanced breast cancer—the role of fulvestrant. *Eur J Cancer* 2005; **41:** 346–56.
8. Howell A, *et al.* Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005; **104:** 236–9.
9. Bundred N. Preclinical and clinical experience with fulvestrant (Faslodex) in postmenopausal women with hormone receptor-positive advanced breast cancer. *Cancer Invest* 2005; **23:** 173–81.
10. Buzdar AU, Robertson JFR. Fulvestrant: pharmacologic profile versus existing endocrine agents for the treatment of breast cancer. *Ann Pharmacother* 2006; **40:** 1572–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Faslodex; ***Austral.:*** Faslodex; ***Belg.:*** Faslodex; ***Braz.:*** Faslodex; ***Canad.:*** Faslodex; ***Cz.:*** Faslodex; ***Denm.:*** Faslodex; ***Fin.:*** Faslodex; ***Fr.:*** Faslodex; ***Ger.:*** Faslodex; ***Gr.:*** Faslodex; ***Hung.:*** Faslodex; ***Irl.:*** Faslodex; ***Israel:*** Faslodex; ***Ital.:*** Faslodex; ***Malaysia:*** Faslodex; ***Mex.:*** Faslodex; ***Neth.:*** Faslodex; ***Norw.:*** Faslodex; ***NZ:*** Faslodex; ***Pol.:*** Faslodex; ***Port.:*** Faslodex; ***Rus.:*** Faslodex (Фазлодекс); ***Spain:*** Faslodex; ***Swed.:*** Faslodex; ***Switz.:*** Faslodex; ***UK:*** Faslodex; ***USA:*** Faslodex; ***Venez.:*** Faslodex.

Gefitinib *(BAN, USAN, rINN)*

Géfitinib; Gefitinibum; ZD-1839. *N*-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

Гефитиниб

$C_{22}H_{24}ClFN_4O_3$ = 446.9.
CAS — 184475-35-2.
ATC — L01XE02.
ATC Vet — QL01XE02.

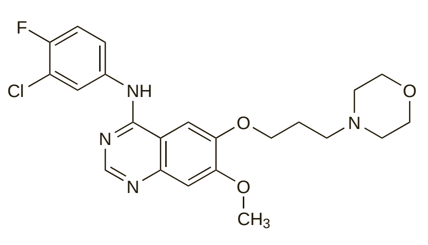

Profile

Gefitinib is a selective inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor. It blocks signal transduction pathways implicated in the growth of tumour cells. It is given orally for the management of locally advanced or metastatic non-small cell lung cancer (p.668) unresponsive to other therapy; the usual dose is 250 mg daily. In the USA, use is restricted to those patients who are currently receiving and benefiting from gefitinib, or to those who have previously benefited from therapy. Adverse effects include rashes and diarrhoea. There have been reports of severe diffuse parenchymal lung disease, including fatalities. There are also reports of tumour haemorrhage, sometimes fatal, after use of gefitinib in patients with head and neck cancer. Gefitinib is under investigation in the management of other solid tumours.

◊ References.

1. Culy CR, Faulds D. Gefitinib. *Drugs* 2002; **62:** 2237–48.
2. Inoue A, *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; **361:** 137–9.
3. Kris MG, *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non–small cell lung cancer: a randomized trial. *JAMA* 2003; **290:** 2149–58.
4. Liu CY, Seen S. Gefitinib therapy for advanced non–small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1644–53.
5. Cersosimo RJ. Gefitinib: a new antineoplastic for advanced non-small-cell lung cancer. *Am J Health-Syst Pharm* 2004; **61:** 889–98.
6. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA) monotherapy: clinical experience in non-small-cell lung cancer. *Drug Safety* 2004; **27:** 1081–92.
7. Frampton JE, Easthope SE. Gefitinib: a review of its use in the management of advanced non-small-cell lung cancer. *Drugs* 2004; **64:** 2475–92.
8. Tanovic A, Alfaro V. Gefitinib: current status in the treatment of non-small cell lung cancer. *Drugs Today* 2004; **40:** 809–27.
9. Birnbaum A, Ready N. Gefitinib therapy for non-small cell lung cancer. *Curr Treat Options Oncol* 2005; **6:** 75–81.
10. Shah NT, *et al.* Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005; **23:** 165–74.
11. Swaisland HC, *et al.* Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005; **44:** 1067–81.
12. Swaisland HC, *et al.* Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005; **44:** 1165–77.
13. Blackhall F, *et al.* Where next for gefitinib in patients with lung cancer? *Lancet Oncol* 2006; **7:** 499–507.

Effects on survival. In chemotherapy-naive patients with advanced non-small cell lung cancer, gefitinib, given with gemcitabine plus cisplatin,[1] or paclitaxel plus carboplatin,[2] showed no survival advantage over chemotherapy without gefitinib. In a large study in patients with non-small cell lung cancer given gefitinib or placebo, after failure of one or two previous treatment regimens, no survival benefit was shown with gefitinib;[3] recommendations restricting the use of gefitinib to selected patients have been made in the USA (see above).[4] However, a subset analysis of study data found an improvement in survival in a subgroup of patients of Asian origin.[5] In reports of the IMEX study in patients with head and neck cancer, no survival advantage for gefitinib was found when compared with methotrexate; an increased incidence of tumour haemorrhage was seen in those treated with gefitinib.[6] Studies have suggested that there are subgroups of patients with non-small cell lung cancer who have specific biomarkers or mutations in the epidermal growth factor receptor gene which correlate with clinical response to gefitinib.[7-10]

A small retrospective study found that further treatment with gefitinib prolonged survival in patients who were initially responsive, but who had subsequent disease progression upon stopping therapy.[11]

1. Giaccone G, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol* 2004; **22:** 777–84.
2. Herbst RS, *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* 2004; **22:** 785–94.
3. Thatcher N, *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.
4. FDA Public Health Advisory. New labeling and distribution program for gefitinib (Iressa) (issued 17/06/05). Available at: http://www.fda.gov/cder/drug/advisory/iressa.htm (accessed 13/03/06)
5. Chang A, *et al.* Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006; **1:** 847–55.
6. AstraZeneca, Canada. Health Canada endorsed important safety information on Iressa (gefitinib): lack of survival benefit and increased incidence of tumour haemorrhage in association with IRESSA in patients with squamous cell carcinoma of the head and neck (SCCHN) (issued 1st December 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/iressa_4_hpc-cps-eng.php (accessed 01/08/08)
7. Lynch TJ, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.
8. Paez JG, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–1500.
9. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non–small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005; **23:** 2556–68.
10. Hirsch FR, *et al.* Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.
11. Yokouchi H, *et al.* Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. *BMC Cancer* 2007; **7:** 51.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Iressa; ***Austral.:*** Iressa; ***Canad.:*** Iressa; ***Chile:*** Iressa; ***Fr.:*** Iressa†; ***Hong Kong:*** Iressa; ***India:*** Geftinat; ***Indon.:*** Iressa; ***Israel:*** Iressa; ***Malaysia:*** Iressa; ***Mex.:*** Iressa; ***NZ:*** Iressa; ***Philipp.:*** Iressa; ***Rus.:*** Iressa (Иресса); ***Singapore:*** Iressa; ***Switz.:*** Iressa; ***Thai.:*** Iressa; ***UK:*** Iressa; ***USA:*** Iressa; ***Venez.:*** Iressa.

Gemcitabine Hydrochloride

(BANM, USAN, rINNM)

Gemcitabine, chlorhydrate de; Gemcitabini hydrochloridum; Hidrocloruro de gemcitabina; LY-188011 (gemcitabine). 4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one hydrochloride; 2′-Deoxy-2′,2′-difluorocytidine hydrochloride.

Гемцитабина Гидрохлорид

$C_9H_{11}F_2N_3O_4,HCl$ = 299.7.
CAS — 95058-81-4 (gemcitabine); 122111-03-9 (gemcitabine hydrochloride).
ATC — L01BC05.
ATC Vet — QL01BC05.

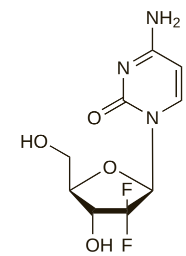

(gemcitabine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Gemcitabine Hydrochloride). A white or almost white powder. Soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 2.0 to 3.0.

USP 31 (Gemcitabine Hydrochloride). A white to off-white solid. Soluble in water; practically insoluble in alcohol and in polar organic solvents; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers.

Incompatibility. Gemcitabine hydrochloride was reported to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, cefotaxime sodium, furosemide, ganciclovir sodium, imipenem with cilastatin sodium, irinotecan, methotrexate sodium, methylprednisolone sodium succinate, mezlocillin sodium, mitomycin, piperacillin sodium, piperacillin sodium with tazobactam, and prochlorperazine edisilate during simulated Y-site administration.[1]

1. Trissel LA, *et al.* Compatibility of gemcitabine hydrochloride with 107 selected drugs during simulated Y-site injection. *J Am Pharm Assoc* 1999; **39:** 514–18.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The major dose-limiting adverse effect of gemcitabine is bone-marrow depression, although this is reported to be modest and rarely requires stopping therapy. Gastrointestinal disturbances occur, especially nausea and vomiting, but these are usually of mild to moderate severity. Rashes, often associated with pruritus, and flu-like symptoms are relatively common. Oedema, dyspnoea, and alopecia are also commonly reported. Pulmonary oedema has been reported infrequently; interstitial pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome have occurred. Therapy should be stopped if pulmonary toxicity occurs. There are rare cases of hypotension, anaphylactoid reactions, and severe desquamative and bullous skin eruptions. Haematuria, proteinuria, transient liver enzyme elevations, and serious hepatotoxicity, including liver failure and death, have been reported. It should therefore be used with caution in patients with impaired renal or hepatic function. Haemolytic-uraemic syndrome and/or thrombocytopenic purpura have been reported and have led to irreversible renal failure; gemcitabine should be stopped at the first signs of microangiopathic haemolytic anaemia. Congestive heart failure, myocardial infarction, or arrhythmias may occur rarely.

Gemcitabine may produce somnolence: patients so affected should not drive or operate machinery. Severe toxicity, in the form of potentially life-threatening oesophagitis and pneumonitis has been seen in patients given radical radiotherapy to the thorax concurrently with gemcitabine.

Effects on the nervous system. A report of autonomic neuropathy associated with gemcitabine therapy.[1] Symptoms resolved 4 weeks after stopping therapy.

1. Dormann AJ, *et al.* Gemcitabine-associated autonomic neuropathy. *Lancet* 1998; **351:** 644.

Effects on the skin. A patient who received gemcitabine 1 week after having had phototherapy developed a severe sunburn reaction in those areas exposed to UVB. The erythema resolved spontaneously, but recurred with each subsequent dose of gemcitabine, and became progressively more intense. A short course of high-dose prednisone was given with topical triamcinolone, and the patient was safely rechallenged with 2 further doses of gemcitabine.[1]

1. Badger J, *et al.* Photo therapy recall with gemcitabine following ultraviolet B treatment. *J Clin Oncol* 2005; **23:** 7224–5.

Peripheral ischaemia. Pain, coldness, colour changes, and distal claudication in the feet have been reported in patients treated with gemcitabine and cisplatin.[1] Pain and colour changes in the fingertips have also been reported after gemcitabine monotherapy.[2]

1. Barceló R, *et al.* Distal ischemic changes related to combination chemotherapy with cisplatin and gemcitabine: description of four cases. *Ann Oncol* 2000; **11:** 1191–4.
2. Yildiz R, *et al.* Digital ischemic changes after gemcitabine therapy in a patient with metastatic non-small-cell lung cancer. *Ann Pharmacother* 2007; **41:** 901–2.

Interactions

Antineoplastics. In a study[1] of 14 patients with lung cancer, the use of *paclitaxel* before gemcitabine caused a decrease in the systemic clearance, volume of distribution, and interpatient pharmacokinetic variability of gemcitabine. This resulted in plasma concentrations of gemcitabine slightly higher than the desired range. However, there was no apparent relationship between pharmacokinetic changes and toxicity, and the clinical significance of this possible interaction is unclear.

A trial investigating a modified chemotherapy regimen in which gemcitabine was substituted for etoposide was stopped because of unexpected pulmonary toxicity. This was considered to be due to the combination of gemcitabine and *bleomycin*, as the adverse effect was apparent in other studies using this combination.[2]

1. Shord SS, *et al.* Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003; **51:** 328–36.
2. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2004; **22:** 2424–9.

Pharmacokinetics

After intravenous doses gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues. Clearance is about 25% lower in women than in men. Almost all of the dose is excreted in urine as 2′-deoxy-2′,2′-difluorouridine (dFdU), only about 1% being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, the latter two active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender. The intracellular half-life of the triphosphate is stated to range from 0.7 to 12 hours.

◊ References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Shamseddine AI, *et al.* Comparative pharmacokinetics and metabolic pathway of gemcitabine during intravenous and intra-arterial delivery in unresectable pancreatic cancer patients. *Clin Pharmacokinet* 2005; **44:** 957–67.

Uses and Administration

Gemcitabine is an analogue of cytarabine (p.705) that is metabolised intracellularly to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis and induce apoptosis. It is primarily active against cells in S phase. It is given in the management of solid tumours including those of the bladder, breast, lung, ovary, and pancreas (see p.659, p.661, p.668, p.670, and p.671, respectively).

Gemcitabine is given intravenously as the hydrochloride. Doses are calculated in terms of the base; gemcitabine hydrochloride 1.14 g is equivalent to about 1 g of gemcitabine. Doses are reconstituted in sodium chloride 0.9%. The concentration of the infusion solution should not exceed the equivalent of gemcitabine 40 mg/mL. Gemcitabine is given by infusion over 30 to 60 minutes; doses are subsequently adjusted according to response and toxicity.

In the treatment of **pancreatic cancer**, an initial course of gemcitabine 1 g/m^2 once weekly for up to 7 weeks may be given, followed after a one-week recovery period by a regimen of infusions once weekly for 3 consecutive weeks out of 4.

In **non-small cell lung cancer**, gemcitabine may be given as a single agent; 1 g/m^2 once weekly for 3 consecutive weeks out of 4 is recommended. Alternatively, it may be given before cisplatin. Two schedules have been used; gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle, or gemcitabine 1 g/m^2 is given on days 1, 8 and 15 of a 28-day cycle.

In the treatment of **bladder cancer**, gemcitabine is given before cisplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1, 8, and 15 of a 28-day cycle.

In **breast cancer**, gemcitabine is usually given after a taxane such as paclitaxel. A dose of gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle.

In **ovarian cancer**, gemcitabine is given before carboplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1 and 8 of a 21-day cycle.

◊ References.

1. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 15–19.
2. Hussain M, *et al.* Novel gemcitabine-containing triplets in the management of urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 20–4.
3. Hochster HS. Newer approaches to gemcitabine-based therapy of pancreatic cancer: fixed-dose-rate infusion and novel agents. *Int J Radiat Oncol Biol Phys* 2003; **56** (suppl): 24–30.
4. Yardley DA. Gemcitabine and taxanes as a new standard of care in breast cancer. *Clin Breast Cancer* 2004; **4** (suppl 3): S107–S112.
5. Natale R. A ten-year review of progress in the treatment of non-small-cell lung cancer with gemcitabine. *Lung Cancer* 2005; **50** (suppl): S2–S4.
6. Saha A, Rudd R. Gemcitabine and carboplatin: is this the best combination for non-small cell lung cancer? *Expert Rev Anticancer Ther* 2006; **6:** 165–73.
7. Kose MF, *et al.* Gemcitabine plus carboplatin in platinum-sensitive recurrent ovarian carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 437–43.
8. Wirk B, Perez E. Role of gemcitabine in breast cancer management: an update. *Semin Oncol* 2006; **33** (suppl 2): S6–S14.
9. Pfisterer J, *et al.* Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006; **24:** 4699–4707.
10. Kiba T, *et al.* Single-agent gemcitabine for biliary tract cancers: study outcomes and systematic review of the literature. *Oncology* 2006; **70:** 358–65.
11. Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. *Oncologist* 2007; **12:** 999–1006.
12. El Karak F, Flechon A. Gemcitabine in bladder cancer. *Expert Opin Pharmacother* 2007; **8:** 3251–6.
13. Serrano A, Gerson R. Chemotherapy with gemcitabine in advanced biliary tract carcinoma. *Rev Recent Clin Trials* 2008; **3:** 70–8.
14. Hilbig A, Oettle H. Gemcitabine in the treatment of metastatic pancreatic cancer. *Expert Rev Anticancer Ther* 2008; **8:** 511–23.
15. Dent S, *et al.* Gemcitabine in the management of metastatic breast cancer: a systematic review. *Breast Cancer Res Treat* 2008; **108:** 319–31.

Preparations

USP 31: Gemcitabine for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Abine; Antoril; Eriogem; Gemtro; Gezt; Gramagen; ***Austral.:*** Gemzar; ***Austria:*** Gemzar; ***Belg.:*** Gemzar; ***Braz.:*** Gemzar; ***Canad.:*** Gemzar; ***Chile:*** Gemzar; ***Cz.:*** Gemzar; ***Denm.:*** Gemzar; ***Fin.:*** Gemzar; ***Fr.:*** Gemzar; ***Ger.:*** Gemzar; ***Gr.:*** Gemzar; ***Hong Kong:*** Gemzar; ***Hung.:*** Gemzar; ***India:*** Gemcite; Oncogem; ***Indon.:*** Gemzar; ***Irl.:*** Gemzar; ***Israel:*** Gemzar; ***Ital.:*** Gemzar; ***Malaysia:*** Gemzar; ***Mex.:*** Gemzar; ***Neth.:*** Gemzar; ***Norw.:*** Gemzar; ***NZ:*** Gemzar; ***Philipp.:*** Gemzar; ***Pol.:*** Gemzar; ***Port.:*** Gemzar; ***Rus.:*** Gemzar (Гемзар); ***S.Afr.:*** Gemzar; ***Singapore:*** Gemzar; ***Spain:*** Gemzar; ***Swed.:*** Gemzar; ***Switz.:*** Gemzar; ***Thai.:*** Gemzar; ***Turk.:*** Gemzar; ***UK:*** Gemzar; ***USA:*** Gemzar; ***Venez.:*** Gemzar.

Gemtuzumab Ozogamicin *(USAN, rINNM)*

CDP-771; CMA-676; Gemtuzumab ozogamicina; Gemtuzumab Ozogamicine; Gemtuzumab Zogamicin; Gemtuzumabum Ozogamicinum; WAY-CMA-676. Immunoglobulin G4 (human-mouse monoclonal hP67.6 κ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer conjugate with ozogamicin.

Гемтузумаб Озогамицин

CAS — 220578-59-6.

ATC — L01XC05.

ATC Vet — QL01XC05.

Adverse Effects and Precautions

For general discussions see Antineoplastics, p.635 and p.641.

Myelosuppression is common with gemtuzumab ozogamicin, and thrombocytopenia may be prolonged. Infusion-related reactions characteristic of a cytokine release syndrome (including fever, chills, dyspnoea, and hypotension) and hypersensitivity may occur; prophylactic use of an antihistamine and paracetamol is recommended. Pulmonary sequelae may be fatal. Hepatotoxicity, including severe veno-occlusive disease, has also been reported. Electrolyte imbalances, especially hypokalaemia and hypomagnesaemia, and gastrointestinal disturbances may occur.

Blood and platelet counts, electrolytes, and liver function tests should be regularly monitored.

Hypersensitivity. A 75-year-old man with acute myeloid leukaemia developed severe respiratory distress and died after being given gemtuzumab ozogamicin and platelets on the same day. He had previously had the drug and platelets on separate occasions with no untoward effects. It was suggested that this combination contributed to a fatal hypersensitivity reaction.[1]

1. Hanbali A, *et al.* Fatal hypersensitivity reaction to gemtuzumab ozogamicin associated with platelet transfusion. *Am J Health-Syst Pharm* 2007; **64:** 1401–2.

Uses and Administration

Gemtuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated with calicheamicin, a cytotoxic antibiotic. The antibody binds specifically to the CD33 antigen, which is expressed on leukaemic myeloblasts but not normal haematopoietic stem cells. Gemtuzumab ozogamicin is licensed for the second-line treatment of CD33-positive acute myeloid leukaemia (p.652) in elderly patients who are unable to tolerate conventional chemotherapy. It is given in 100 mL of sodium chloride 0.9% via an in-line 1.2 micron filter. The licensed dose is 9 mg/m^2 given by intravenous infusion over 2 hours, repeated once after 14 days. Lower doses are under investigation as part of combined induction or consolidation regimens.

◊ References.

1. McGavin JK, Spencer CM. Gemtuzumab ozogamicin. *Drugs* 2001; **61:** 1317–22.
2. Dowell JA, *et al.* Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 2001; **41:** 1206–14.
3. Sievers EL, *et al.* Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001; **19:** 3244–54.
4. Sievers EL, Linenberger M. Mylotarg: antibody-targeted chemotherapy comes of age. *Curr Opin Oncol* 2001; **13:** 522–7.
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6. Buckwalter M, *et al.* Pharmacokinetics of gemtuzumab ozogamicin as a single-agent treatment of pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Pharmacol* 2004; **44:** 873–80.
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8. Fenton C, Perry CM. Gemtuzumab ozogamicin: a review of its use in acute myeloid leukaemia. *Drugs* 2005; **65:** 2405–27.
9. Tsimberidou AM, *et al.* The role of gemtuzumab ozogamicin in acute leukaemia therapy. *Br J Haematol* 2006; **132:** 398–409.
10. Stasi R, *et al.* Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer Treat Rev* 2008; **34:** 49–60.
11. Leukaemia Research Fund. AML14: Leukaemia Research Fund Acute Myeloid Leukaemia and High Risk MDS Trial 14. Available at: http://www.download.bham.ac.uk/bctu/aml14/trial%20documentation/amendment%20january%202004/Protocol%20Jan%202004.pdf (accessed 30/07/08)
12. Medical Research Council. AML15: Medical Research Council Working Parties on Leukaemia in Adults and Children Acute Myeloid Leukaemia Trial 15. Available at: http://www.download.bham.ac.uk/bctu/AML15/Amendment%20Nov%202007/AML15%20protocol%20version%207%20Final%20200704201%20with%20no%20track%20changes.pdf (accessed 30/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Mylotarg; ***USA:*** Mylotarg; ***Venez.:*** Mylotarg.

Hydroxycarbamide *(BAN, rINN)*

Hidroksikarbamid; Hidroksikarbamidas; Hidroxicarbamida; Hidroxikarbamid; Hydroksikarbamidi; Hydroksiüre; Hydroxikarbamid; Hydroxycarbamidum; Hydroxymočovina; Hydroxyurea *(USAN)*; NSC-32065; SQ-1089; WR-83799.

Гидроксикарбамид

NH_2.CO.NHOH = 76.05.

CAS — 127-07-1.

ATC — L01XX05.

ATC Vet — QL01XX05.

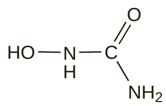

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Hydroxycarbamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Hydroxyurea). A white to off-white powder. It is somewhat hygroscopic and decomposes in the presence of moisture. Freely soluble in water and in hot alcohol. Store in airtight containers in a dry atmosphere.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow suppression, including megaloblastic changes, is the main adverse effect of hydroxycarbamide. The erythema caused by irradiation may be exacerbated. Other adverse effects reported have included gastrointestinal disturbances, impairment of renal function, pulmonary oedema, dermatological reactions, alopecia, and neurological reactions such as headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions. There are rare reports of acute pulmonary reactions consisting of pulmonary infiltrates or fibrosis, dyspnoea and fever. Symptoms resembling cutaneous vasculitis, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders treated with hydroxycarbamide, especially in those also given interferon. There are reports of hepatotoxicity and pancreatitis, some fatal, in patients with HIV infection, given hydroxycarbamide and antiretrovirals (see also HIV Infection and AIDS, below); peripheral neuropathy has also occurred.

Pre-existing anaemia should be corrected before beginning therapy with hydroxycarbamide and the haemoglobin concentration, white cell and platelet counts, and hepatic and renal function should be determined repeatedly during treatment. Treatment should be interrupted if the white cell or platelet count fall below acceptable levels (see also Bone-marrow Depression, p.639). If anaemia occurs when hydroxycarbamide is used as an antineoplastic, it may be corrected by transfusions of whole blood without stopping therapy. If anaemia (haemoglobin less than 4.5 g per 100 mL, or reticulocyte count less than 80 000 cells/mm^3 when haemoglobin is less than 9 g per 100 mL) occurs when the drug is used for sickle-cell disease, therapy should be interrupted. Megaloblastic changes are usually self-limiting.

Hydroxycarbamide should be used with caution in patients with impaired renal function. Uric acid concentrations should be monitored, and a high fluid intake maintained during treatment. The elderly may be more sensitive to its adverse effects.

Breast feeding. In breast-milk samples from a woman given hydroxycarbamide 500 mg three times daily, the mean concentration of the drug was found to be about 6 mg/litre. It was estimated that, had the infant been breast-fed, it would have received about 3 to 4 mg daily. Although this amount appears to be low, women are advised not to breast feed while taking hydroxycarbamide.[1]

1. Sylvester RK, *et al.* Excretion of hydroxyurea into milk. *Cancer* 1987; **60:** 2177–8.

Carcinogenicity. Secondary leukaemias have occurred in patients receiving hydroxycarbamide for myeloproliferative disorders, although the extent to which this is due to the treatment or the underlying disorder is unknown.

Skin cancers have also been associated with its use. These are often multiple and include both squamous cell and basal cell carcinomas.

References.

1. Liozon E, *et al.* Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature. *Hematol Cell Ther* 1997; **39:** 11–18.
2. Pearson TC, *et al.* Leukemic transformation in polycythemia vera. *Blood* 1998; **92:** 1837–8.
3. De Simone C, *et al.* Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. *Eur J Dermatol* 1998; **8:** 114–15.
4. Best PJM, Petitt RM. Multiple skin cancers associated with hydroxyurea therapy. *Mayo Clin Proc* 1998; **73:** 961–3.

Effects on the liver. Fever and hepatitis have been reported[1,2] in patients receiving hydroxycarbamide. Symptoms recurred when patients were rechallenged with the drug.

1. Heddle R, Calvert AF. Hydroxyurea induced hepatitis. *Med J Aust* 1980; **1:** 121.
2. Westerman DA, *et al.* Hydroxyurea-induced fever and hepatitis. *Aust N Z J Med* 1998; **28:** 657–9.

Effects on the skin and nails. Reports of skin reactions with hydroxycarbamide include hyperpigmentation of the skin,[1] and of nails (melanonychia).[2]

Hydroxycarbamide therapy has been associated with scaly erythematous skin lesions often resembling those of dermatomyositis.[1,3,4] Such lesions usually occur after several years of treatment and the course is usually benign. However, withdrawal of the drug is usually necessary for healing or improvement, in which case resolution may take several months.[1,4] Hydroxycarbamide can also cause painful leg ulcers, often on the malleoli, which may require stopping treatment.[1,5,6] Leg ulcers often coexist with dermatomyositis-like eruptions and may be caused by the same mechanism,[7] although mechanical injury may have a role in malleolar ulceration.[5] Licensed product information notes that vasculitic toxicities, including vasculitic ulceration and gangrene, have been associated with hydroxycarbamide use in patients with myeloproliferative disorders (particularly if also given interferon). However, histologically, perivascular lymphocytic infiltration without vasculitis has been reported in both early dermatomyositis-like lesions[1] and in leg ulcers.[5,8]

Skin cancers have also occurred, see Carcinogenicity above.

1. Vassallo C, *et al.* Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol* 2001; **26:** 141–8.
2. Aste N, *et al.* Nail pigmentation caused by hydroxyurea: report of 9 cases. *J Am Acad Dermatol* 2002; **47:** 146–7.
3. Senet P, *et al.* Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol* 1995; **133:** 455–9.
4. Daoud MS, *et al.*. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 1997; **36:** 178–82.
5. Best PJ, *et al.* Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* 1998; **128:** 29–32.
6. Chaine B, *et al.* Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137:** 467–70.
7. Suehiro M, *et al.* Hydroxyurea dermopathy with a dermatomyositis-like eruption and a large leg ulcer. *Br J Dermatol* 1998; **139:** 748–9.
8. Tarumoto T, *et al.* A case of bilateral heel ulcers associated with hydroxyurea therapy for chronic myelogenous leukemia. *Jpn J Clin Oncol* 2000; **30:** 159–62.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of hydroxycarbamide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642.

Pharmacokinetics

Hydroxycarbamide is readily absorbed from the gastrointestinal tract and distributed throughout the body. Peak plasma concentrations are reached within 2 hours. Up to 50% of a dose is metabolised by the liver; hydroxycarbamide is excreted in urine as metabolites and unchanged drug. Some is excreted as carbon dioxide via the lungs. About 80% of a dose is reported to be excreted in the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

◊ References.

1. Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin Pharmacokinet* 1998; **34:** 347–58.
2. Gwilt PR, *et al.* Pharmacokinetics of hydroxyurea in plasma and cerebrospinal fluid of HIV-1-infected patients. *J Clin Pharmacol* 2003; **43:** 1003–7.
3. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Uses and Administration

Hydroxycarbamide is an antineoplastic that may cause inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor. It is S-phase specific. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia, and may be used in the myeloproliferative disorders polycythaemia vera and primary (essential) thrombocythaemia. It has also been tried, often combined with radiotherapy, in some solid malignancies (see Malignant Neoplasms, below). Hydroxycarbamide has also produced benefit in the haemoglobinopathies, particularly in sickle-cell disease (see below).

In the treatment of chronic myeloid leukaemia and solid tumours, hydroxycarbamide is given orally, typically in a single dose of 20 to 30 mg/kg daily or in a single dose of 80 mg/kg every third day. Generally, the continuous regimen is used for chronic myeloid leukaemia, and the intermittent regimen for solid tumours. When used with radiotherapy, hydroxycarbamide is started 7 days before radiotherapy. If a beneficial effect is evident after 6 weeks, therapy may be continued indefinitely.

In essential thrombocythaemia, the initial dose of hydroxycarbamide is about 15 mg/kg daily; starting doses of 15 to 20 mg/kg daily are recommended for polycythaemia vera. Doses are subsequently adjusted according to platelet counts.

In sickle-cell disease initial doses of 15 mg/kg daily are suggested, increased if necessary by 5 mg/kg daily every 12 weeks according to response and blood counts, up to a maximum of 35 mg/kg daily. The *BNFC* recommends 10 to 20 mg/kg once daily initially for children aged from 1 to 18 years; increments thereafter are similar to those for adults.

Blood counts and hepatic and renal function should be monitored during therapy; treatment may need to be interrupted if leucopenia or thrombocytopenia occur (see Adverse Effects, Treatment, and Precautions, above).

Administration in renal impairment. Results from a single-dose study in patients with sickle-cell disease indicated that systemic exposure to hydroxycarbamide correlates to renal function.[1] An initial dose of 7.5 mg/kg daily was suggested for patients with sickle-cell disease and a creatinine clearance of less than 60 mL/minute.

1. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Haemoglobinopathies. Hydroxycarbamide is considered a promising treatment for the haemoglobinopathies. It can stimulate fetal haemoglobin production, which in turn can reduce haemoglobin polymerisation and the numbers of deformed, dense, and damaged erythrocytes.[1] In adult patients with **sickle-cell disease** (p.1044), a randomised controlled study produced evidence that initial doses of 15 mg/kg daily, adjusted according to response and tolerance to up to 35 mg/kg daily, reduced the rate of sickle-cell crisis compared with placebo.[2] An observational follow-up study[3] of this group found that patients taking hydroxycarbamide for frequent sickle-cell episodes appeared to have reduced mortality. A report in 2 adults has suggested that it might reverse splenic dysfunction.[4] A systematic review[5] has noted that despite the benefits, the paucity of long-term studies limits conclusions on the toxicity of treatment with hydroxycarbamide.

Despite some concerns about giving a potential carcinogen to children,[6] studies in paediatric populations have also reported evidence of benefit in terms of decreased hospitalisation[7,8] and sickle-cell crisis.[8,9] Hydroxycarbamide may be an alternative to blood transfusions in children who have had a stroke.[8,10,11] Although a small trial[12] has suggested benefit in paediatric patients in terms of splenic preservation, long-term prevention of organ damage remains to be established.[13,14]

It has been suggested that use of the drug with erythropoietin might enhance the production of fetal haemoglobin, but results from studies of the combination have been conflicting.[15,16]

There appear to have been few studies of hydroxycarbamide specifically in **thalassaemia** (p.1045). Initial oral doses of 8.2 to 10.3 mg/kg daily, increased until toxicity occurred, did produce increases in fetal haemoglobin in 3 patients, but these were not sustained.[17] Others have reported[18] that rises in fetal haemoglobin did not necessarily correlate with clinical improvement. Conversely, sustained responses have been seen in other studies.[19-22] Use with sodium phenylbutyrate has produced conflicting results.[23-25]

1. Halsey C, Roberts IAG. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003; **120:** 177–86.
2. Charache S, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332:** 1317–22.
3. Steinberg MH, *et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; **289:** 1645–51. Correction. *ibid.*; **290:** 756.
4. Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 1996; **88:** 1951–3.
5. Lanzkron S, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008; **148:** 939–55.
6. Zimmerman SA, *et al.* Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; **103:** 2039–45.
7. Scott JP, *et al.* Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996; **128:** 820–8.
8. Gulbis B, *et al.* Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005; **105:** 2685–90.
9. Jayabose S, *et al.* Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr* 1996; **129:** 559–65.
10. Ware RE, *et al.* Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; **94:** 3022–6.
11. Ware RE, *et al.* Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; **145:** 346–52.
12. Wang WC, *et al.* A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; **139:** 790–6.
13. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001; **139:** 763–4.
14. Kinney TR, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999; **94:** 1550–4.
15. Goldberg MA, *et al.* Treatment of sickle cell anemia with hydroxyurea and erythropoietin. *N Engl J Med* 1990; **323:** 366–72.
16. Rodgers GP, *et al.* Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle-cell disease. *N Engl J Med* 1993; **328:** 73–80.
17. Hajjar FM, Pearson HA. Pharmacologic treatment of thalassemia intermedia with hydroxyurea. *J Pediatr* 1994; **125:** 490–2.
18. de Paula EV, *et al.* Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003; **70:** 151–5.
19. Loukopoulos D, *et al.* Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998; **30:** 120–8.
20. Rigano P, *et al.* Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/β-thalassemia. *Hemoglobin* 2001; **25:** 9–17.
21. Loukopoulos D, *et al.* Reduction of the clinical severity of sickle cell/β-thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000; **26:** 453–66.
22. Bradai M, *et al.* Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia. *Blood* 2003; **102:** 1529–30.
23. Olivieri NF, *et al.* Treatment of thalassaemia major with phenylbutyrate and hydroxyurea. *Lancet* 1997; **350:** 491–2.
24. Hoppe C, *et al.* Hydroxyurea and sodium phenylbutyrate therapy in thalassemia intermedia. *Am J Hematol* 1999; **62:** 221–7.
25. Dover GJ. Hemoglobin switching protocols in thalassemia. *Ann N Y Acad Sci* 1998; **850:** 80–6.

HIV infection and AIDS. Unlike most drugs used to treat HIV, which target viral enzymes, hydroxycarbamide inhibits ribonucleotide reductase, a host cellular enzyme that is less prone to mutation and subsequent development of resistance.[1] The drug acts synergistically with didanosine (p.870). Of 25 HIV-positive patients given didanosine 200 mg twice daily with hydroxycarbamide 15 mg/kg daily in 2 divided doses, all showed a drop in viral load and an increase in CD4+ lymphocyte count.[2] Viraemia was not detectable in 13 of 24 patients evaluated at 6 months and 10 of 20 patients evaluated at 1 year. In 2 of these patients who subsequently received no antiviral treatments for 1 year there was no viral rebound, although some proviral DNA was detected.[3] In another study in 6 patients, didanosine 200 mg twice daily with hydroxycarbamide 250 mg four times daily (suggested to be a better regimen because of the short half-life of the antineoplastic) produced a sharp decrease in viraemia, which was maintained for up to 72 weeks.[4] A rebound occurred in 1 patient on interrupting treatment but viral replication was again suppressed when treatment was restarted.

Combinations with didanosine and other HIV drugs have also been tried.[1] A controlled study[5] of hydroxycarbamide, didanosine, and stavudine indicated significantly enhanced activity when the antivirals were used with the antineoplastic rather than placebo. However, in a long-term follow-up[6] there was a high withdrawal rate amongst patients receiving this combination, due to virological failure and adverse effects such as peripheral neuropathy and fatigue. Another study[7] (ACTG 5025) was terminated due to the high risk of toxicity, including fatal pancreatitis, in patients receiving the hydroxycarbamide regimens. The authors noted that the use of a higher daily dosage of 1200 mg of hydroxycarbamide (rather than the usual 1000 mg daily) and increased exposure to didanosine (itself associated with pancreatitis) may have contributed to toxicity. An analysis of 2613 patients[8] determined that the use of hydroxycarbamide with didanosine, or didanosine and stavudine, resulted in a fourfold increase in the risk for development of pancreatitis, compared to didanosine alone. In a study of patients who had failed protease-inhibitor based regimens,[9] the addition of the antineoplastic to reverse transcriptase inhibitor-based therapy significantly improved virologic response. Despite an increased incidence of adverse events associated with its use, hydroxycarbamide was considered to be a valuable alternative in these patients. A small randomised study[10] of patients with chronic HIV infection given structured treatment interruptions with cycles of HAART, or HAART and hydroxycarbamide, found that use of the latter decreased viral load. There is some suggestion that a lower dose of hydroxycarbamide (300 mg twice daily) may have better antiretroviral activity, and fewer adverse effects, than higher doses.[11] For further discussion of the management of HIV infection and AIDS, see p.856.

1. Gibbs MA, Sorensen SJ. Hydroxyurea in the treatment of HIV-1. *Ann Pharmacother* 2000; **34:** 89–93.
2. Vila J, *et al.* 1-year follow-up of the use of hydroxycarbamide and didanosine in HIV infection. *Lancet* 1996; **848:** 203–4.
3. Vila J, *et al.* Absence of viral rebound after treatment of HIV-infected patients with didanosine and hydroxycarbamide. *Lancet* 1997; **350:** 635–6.
4. Lori F, *et al.* Long-term suppression of HIV-1 by hydroxyurea and didanosine. *JAMA* 1997; **277:** 1437–8.
5. Rutschmann OT, *et al.* A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998; **12:** F71–7.
6. Rutschmann OT, *et al.* Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000; **14:** 2145–51.
7. Havlir DV, *et al.* Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; **15:** 1379–88.
8. Moore RD, *et al.* Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001; **15:** 617–20.
9. Lafeuillade A, *et al.* The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing protease inhibitor-based combinations. *HIV Clin Trials* 2002; **3:** 263–71.
10. García F, *et al.* A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* 2003; **17:** 43–51.
11. Lisziewicz J, *et al.* Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Safety* 2003; **26:** 605–24.

Malignant neoplasms. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia (p.653), and may be used in the myeloproliferative disorders polycythaemia vera (p.654) and primary (essential) thrombocythaemia (p.654). Hydroxycarbamide has been tried, often with radiotherapy, in some solid malignancies such as tumours of the cervix (p.663), head and neck (p.666), and ovary (p.670).

Psoriasis. An immunosuppressant (usually methotrexate or ciclosporin) may be useful in patients with severe refractory psoriasis (p.1583). Hydroxycarbamide has also been tried, although experience is limited.[1,2]

1. Layton AM, *et al.* Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121:** 647–53.
2. Smith CH, *et al.*. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24:** 2–6.

Preparations

BP 2008: Hydroxycarbamide Capsules;
USP 31: Hydroxyurea Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Dacrodil; Droxiurea†; Hydrea†; ***Austral.:*** Hydrea; ***Austria:*** Litalir; ***Belg.:*** Hydrea; ***Braz.:*** Hydrea; Hydrine†; Oxeron†; Ureax†; ***Canad.:*** Hydrea; ***Chile:*** Hydrea; ***Cz.:*** Litalir; Siklos; ***Denm.:*** Hydrea; ***Fin.:*** Hydrea; ***Fr.:*** Hydrea; Siklos; ***Ger.:*** Litalir; Syrea; ***Gr.:*** Hydrea†; Medroxyurea†; ***Hong Kong:*** Hydrea; ***Hung.:*** Litalir; ***India:*** Cytodrox; Hydab; Neodrea†; Oxyrea; ***Indon.:*** Hydrea; ***Irl.:*** Hydrea; ***Israel:*** Hydrea†; ***Ital.:*** Onco-Carbide; ***Malaysia:*** Hydrea†; ***Mex.:*** Hydrea; ***Neth.:*** Hydrea; ***NZ:*** Hydrea; ***Philipp.:*** Hydab; Krabinex; Litalir; ***Port.:*** Hydrea; Siklos; ***Rus.:*** Gidroxyurea (Гидроксиурея); ***S.Afr.:*** Hydrea; ***Singapore:*** Hydrea; ***Spain:*** Hydrea; ***Swed.:*** Hydrea; ***Switz.:*** Litalir; ***Thai.:*** Hydrea; ***Turk.:*** Hydrea; ***UK:*** Hydrea; ***USA:*** Droxia; Hydrea; Mylocel†.

Ibritumomab Tiuxetan *(BAN, USAN, rINN)*

Ibritumomab tiuxetán; Ibritumomab Tiuxétan; Ibritumomabum Tiuxetanum; IDEC-129; IDEC-Y2B8. Immunoglobulin G1, anti(human CD20 (antigen))(mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer tiuxetan conjugate.

Ибритумомаб Тиуксетан

CAS — 206181-63-7.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p.635 and p.641.

Myelosuppression is common after doses of ibritumomab tiuxetan, and may be prolonged. Fatal intracranial haemorrhage has occurred. Infections and hypersensitivity reactions may also be severe. As ibritumomab tiuxetan is given with rituximab, severe infusion reactions due to the cytokine release syndrome may occur (see under Rituximab, p.767). Severe cutaneous and mucocutaneous reactions, some fatal, have been reported and therapy should be stopped if they occur. Gastrointestinal disturbances are common. Other adverse effects include anorexia, asthenia, fever, cough, dyspnoea, dizziness, headache, insomnia, anxiety, arthralgia, myalgia, and peripheral oedema. Patients should be monitored for signs of extravasation in order to avoid radiation-associated tissue damage. If extravasation occurs, the infusion should be stopped immediately and restarted in another vein.

Complete blood and platelet counts should be monitored weekly, or more frequently if cytopenia is present, until haematological recovery. Ibritumomab tiuxetan should not be given to patients with extensive marrow involvement, impaired bone marrow reserve, or platelet or neutrophil counts below acceptable levels (see also Bone-marrow Depression, p.639). Care should be taken during and after radiolabelling with indium-111 or yttrium-90 to minimise radiation exposure.

Effects on the skin. Severe cutaneous and mucocutaneous reactions have been reported after use of ibritumomab tiuxetan with rituximab, some of them with a fatal outcome.[1,2] Reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset was reported to vary from days to months. Treatment should be stopped if any patient experiences such a reaction.

1. Kooijmans-Coutinho M [Biogen Idec (USA)]. Important drug warning (issued October 2005). Available at: http://www.fda.gov/medwatch/safety/2005/Zevalin_dearhcp.pdf (accessed 30/07/08)
2. Berlex, Canada. Association of severe mucocutaneous reactions with the ZEVALIN therapeutic regimen (issued 7th December 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zevalin_nth-aah_e.pdf (accessed 26/04/06)

Uses and Administration

Ibritumomab is a murine monoclonal antibody to CD20 antigen, which is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. Radiolabelled ibritumomab tiuxetan is used in the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (p.656). Patients are pretreated with a low dose of rituximab (p.767). In the USA this is followed by slow intravenous injection of ibritumomab tiuxetan chelated with indium-111 (p.2054) for imaging to confirm that biodistribution of tumour cells is acceptable. A second rituximab treatment is given 7 to 9 days after the first, followed by ibritumomab tiuxetan chelated with yttrium-90 (p.2057) for radio-immunotherapy.

◊ References.

1. Wiseman GA, *et al.* Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Crit Rev Oncol Hematol* 2001; **39:** 181–94.
2. Wagner HN, *et al.* Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002; **43:** 267–72.
3. Witzig TE, *et al.* Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 2453–63.
4. Witzig TE, *et al.* Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3262–9.
5. Ansell SM, *et al.* Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3885–90.
6. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today* 2004; **40:** 111–19.
7. Hagenbeek A, Lewington V. Report of a European consensus workshop to develop recommendations for the optimal use of Y-ibritumomab tiuxetan (Zevalin) in lymphoma. *Ann Oncol* 2005; **16:** 786–92.
8. Meredith RF. Logistics of therapy with the ibritumomab tiuxetan regimen. *Int J Radiat Oncol Biol Phys* 2006; **66** (suppl): S35–S38.
9. Cheung MC, *et al.* Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47:** 967–77. Correction. *ibid.*; 1719–20.
10. Gisselbrecht C, *et al.* Current status and future perspectives for yttrium-90 (Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Zevalin; ***Cz.:*** Zevalin; ***Denm.:*** Zevalin†; ***Fin.:*** Zevalin; ***Fr.:*** Zevalin; ***Ger.:*** Zevalin; ***Hung.:*** Zevalin; ***Irl.:*** Zevalin; ***Ital.:*** Zevalin; ***Neth.:*** Zevalin; ***Norw.:*** Zevalin; ***NZ:*** Zevalin; ***Pol.:*** Zevalin; ***Port.:*** Zevalin; ***Spain:*** Zevalin; ***Swed.:*** Zevalin; ***Switz.:*** Zevalin; ***UK:*** Zevalin; ***USA:*** Zevalin.

Idarubicin Hydrochloride

(BANM, USAN, rINNM)

4-Demethoxydaunorubicin Hydrochloride; Hidrocloruro de idarubicina; Idarubicine, chlorhydrate d'; Idarubicinhydroklorid; Idarubicini hydrochloridum; Idarubisiinihydrokloridi; Idarubisin Hidroklorür; IMI-30; NSC-256439 (idarubicin). (7*S*,9*S*)-9-Acetyl-7-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-7,8,9,10-tetrahydro-6,9,11-trihydroxynaphthacene-5,12-dione hydrochloride.

Идарубицина Гидрохлорид

$C_{26}H_{27}NO_9,HCl = 534.0.$

CAS — 58957-92-9 (idarubicin); 57852-57-0 (idarubicin hydrochloride).

ATC — L01DB06.

ATC Vet — QL01DB06.

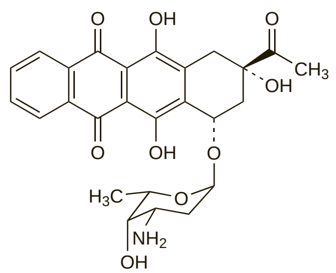

(idarubicin)

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Idarubicin Hydrochloride). A red-orange to red-brown powder. Slightly soluble in water; insoluble in acetone and in solvent ether; soluble in methyl alcohol. A 0.5% solution in water has a pH between 5.0 and 6.5. Store in airtight containers.

Incompatibility. Licensed product information states that precipitation occurs when idarubicin hydrochloride is mixed with heparin, and that it will degrade in alkaline solution.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Raised liver enzymes and bilirubin can occur with idarubicin. Severe enterocolitis with perforation has been reported rarely. A cumulative total dose limit has not yet been defined. UK licensed product information states that total cumulative oral doses up to 400 mg/m^2 have a low probability of cardiotoxicity, and no significant cardiotoxicity was seen in patients treated with mean cumulative intravenous doses of 93 mg/m^2. Cardiomyopathy has been reported in some patients with cumulative intravenous doses of 150 to 290 mg/m^2. It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. Idarubicin should be given with caution, and in reduced doses, to patients with renal or hepatic impairment.

Effects on the skin and nails. For a report of transverse hyperpigmented bands of the nails in a patient who received idarubicin, see under Doxorubicin, p.713.

Pharmacokinetics

On intravenous dosage idarubicin is rapidly distributed into body tissues and extensively tissue bound, with a volume of distribution which may be in excess of 2000 litres. It is extensively metabolised, both in the liver and extrahepatically; the principal metabolite, idarubicinol (13-dihydroidarubicin) has equal antineoplastic activity. Peak concentrations of idarubicin and idarubicinol in bone marrow and nucleated blood cells are 400 (idarubicin) and 200 (idarubicinol) times greater than those in plasma; cellular concentrations of drug and metabolite decline with apparent terminal half-lives of 15 and 72 hours respectively, whereas plasma half-lives are reported to be 20 to 22 hours and about 45 hours respectively. Idarubicin is excreted in bile, and to a lesser extent in urine, as unchanged drug and metabolites.

Idarubicin is also absorbed orally, but estimates of its oral bioavailability vary from about 20 to 50%.

◊ References.

1. Robert J. Clinical pharmacokinetics of idarubicin. *Clin Pharmacokinet* 1993; **24:** 275–88.

Uses and Administration

Idarubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p.714). It is used as the hydrochloride, alone or with other drugs, for the induction of remission in patients with acute myeloid leukaemias (p.652). It is also used as a second-line treatment in acute lymphoblastic leukaemia (p.651), and advanced breast cancer (p.661). It has been tried in multiple myeloma (p.658) and non-Hodgkin's lymphoma (p.656).

Idarubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 5 to 15 minutes. The suggested dose in adult acute myeloid leukaemia is 12 mg/m^2 daily for 3 days, with cytarabine. A similar dose, as a single agent, has been given in acute lymphoblastic leukaemia. An alternative dosage schedule in acute myeloid leukaemia is 8 mg/m^2 given daily for 5 days, either alone or in combination therapy. In children with acute lymphoblastic leukaemia a dose of 10 mg/m^2 daily for 3 days as a single agent has been suggested. When the intravenous route cannot be used, idarubicin hydrochloride may be given by mouth. A suggested dose in adult acute myeloid leukaemia as a single agent is 30 mg/m^2 daily for 3 days; 15 to 30 mg/m^2 may be given daily for 3 days when used with other drugs.

In patients with refractory breast cancer idarubicin hydrochloride has been given orally in doses of 45 mg/m^2, as a single dose or divided over 3 consecutive days; the treatment may be repeated every 3 or 4 weeks depending on the haematological recovery.

Blood counts should be performed frequently in patients receiving idarubicin, and monitoring of cardiac, hepatic, and renal function is recommended. Doses should be reduced in patients with hepatic or renal impairment (for further information on the former, see below). In patients who receive a second course of idarubicin dosage should be reduced by 25% if severe mucositis developed with the first course; therapy should be delayed until the patient has recovered from this toxicity.

◊ The actions and uses of idarubicin have been reviewed.[1] A study in leukaemia cells *in vitro* suggested that idarubicin was more active than a conventional anthracycline, daunorubicin, against cells with the multidrug resistance (MDR) phenotype.[2] A collaborative overview of randomised studies for acute myeloid leukaemia found that idarubicin-based therapy achieved better remission rates and overall survival than daunorubicin-based regimens.[3] Its oral bioavailability has been suggested to offer an advantage in the management of malignancies in older patients.[4]

1. Cersosimo RJ. Idarubicin: an anthracycline antineoplastic agent. *Clin Pharm* 1992; **11:** 152–67.
2. Berman E, McBride M. Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukaemia cells. *Blood* 1992; **79:** 3267–73.
3. AML Collaborative Group. A systematic collaborative overview of randomised trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol* 1998; **103:** 100–9.
4. Crivellari D, *et al.* New oral drugs in older patients: a review of idarubicin in elderly patients. *Crit Rev Oncol Hematol* 2004; **49:** 153–63.

Administration in hepatic impairment. UK licensed product information for idarubicin hydrochloride recommends that a dose reduction be considered in patients with hepatic impairment. Although no specific doses are suggested, it is noted that a 50% reduction in dosage has been used with some other anthracyclines in patients with acute leukaemias whose bilirubin levels were between 12 and 20 micrograms/mL. Furthermore, in studies in breast cancer a 50% dosage reduction of oral idarubicin has sometimes been used in those whose bilirubin rose to 20 to 30 micrograms/mL, with withdrawal if levels rose above this. However, in other studies idarubicin was not used if bilirubin values were above 20 micrograms/mL.

In the USA, similar cautions apply but product information only suggests that idarubicin should be withheld if bilirubin levels exceed 50 micrograms/mL.

Preparations

USP 31: Idarubicin Hydrochloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Idarrux†; Zavedos; ***Austral.:*** Zavedos; ***Austria:*** Zavedos; ***Belg.:*** Zavedos; ***Braz.:*** Zavedos; ***Canad.:*** Idamycin; ***Chile:*** Zavedos; ***Cz.:*** Zavedos; ***Denm.:*** Zavedos; ***Fin.:*** Zavedos; ***Fr.:*** Zavedos; ***Ger.:*** Zavedos; ***Gr.:*** Zavedos; ***Hong Kong:*** Zavedos; ***Hung.:*** Zavedos; ***Irl.:*** Zavedos; ***Israel:*** Zavedos; ***Ital.:*** Zavedos; ***Malaysia:*** Zavedos; ***Mex.:*** Idamycin; Idaralem; ***Neth.:*** Zavedos; ***Norw.:*** Zavedos; ***NZ:*** Zavedos; ***Philipp.:*** Zavedos; ***Pol.:*** Zavedos; ***Port.:*** Zavedos; ***Rus.:*** Zavedos (Заведос); ***S.Afr.:*** Zavedos; ***Singapore:*** Zavedos; ***Spain:*** Zavedos; ***Swed.:*** Zavedos; ***Switz.:*** Zavedos; ***Thai.:*** Idaralem; Zavedos; ***Turk.:*** Zavedos; ***UK:*** Zavedos; ***USA:*** Idamycin; ***Venez.:*** Zavedos.

Ifosfamide *(BAN, USAN, rINN)*

Ifosfamid; Ifosfamida; Ifosfamidas; Ifosfamidi; Ifosfamidum; Ifoszfamid; Iphosphamide; Isophosphamide; MJF-9325; NSC-109724; Z-4942. 3-(2-Chloroethyl)-2-(2-chloroethylamino)perhydro-1,3,2-oxazaphosphorinane 2-oxide.

Ифосфамид

$C_7H_{15}Cl_2N_2O_2P = 261.1.$

CAS — 3778-73-2.

ATC — L01AA06.

ATC Vet — QL01AA06.

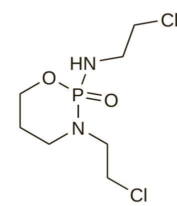

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ifosfamide). A white or almost white, hygroscopic, fine crystalline powder. Soluble in water; freely soluble in dichloromethane. Store in airtight containers.

USP 31 (Ifosfamide). A white, crystalline powder. M.p. about 40°. Freely soluble in water; very soluble in alcohol, in methyl alcohol, in isopropyl alcohol, in dichloromethane, and in ethyl acetate; very slightly soluble in hexanes. A 10% solution in water has a pH of between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 25°.

Incompatibility. Ifosfamide appears to be compatible when mixed in solution with mesna.[1,2] However, ifosfamide appears to be incompatible with benzyl alcohol used as a preservative in Water for Injections: solutions made up with water preserved in this way became turbid, with the formation of aqueous and oily phases, at concentrations of ifosfamide greater than 60 mg/mL.[3]

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Behme RJ, *et al.* Incompatibility of ifosfamide with benzyl-alcohol-preserved bacteriostatic water for injection. *Am J Hosp Pharm* 1988; **45:** 627–8.

Stability. Ifosfamide undergoes a reversible chemical rearrangement in aqueous solution, which is sensitive to changes in pH.[1] The ratio of these compounds to one another in biological fluids may have a bearing on the toxicity and efficacy of ifosfamide.

1. Küpfer A, *et al.* Intramolecular rearrangement of ifosfamide in aqueous solutions. *Lancet* 1990; **335:** 1461.

Adverse Effects, Treatment, and Precautions

As for Cyclophosphamide, p.702. Toxic effects on the urinary tract may be more severe with ifosfamide and may involve the kidneys as well as the bladder. CNS adverse effects have been reported, especially confusion, drowsiness, depressive psychosis, hallucinations, and rarely, seizures.

Effects on the heart. Severe myocardial depression, with heart failure and ventricular arrhythmias, has been reported in patients given high-dose ifosfamide.[1] Symptoms were reversible with appropriate treatment in most cases although one patient died of cardiogenic shock.

1. Quezado ZMN, *et al.* High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med* 1993; **118:** 31–6.

Effects on the kidneys. In addition to its effects on the bladder ifosfamide may be associated with serious nephrotoxicity. Both proximal and distal tubular damage,[1,2] and to a lesser extent glomerular effects,[2] are seen, and the Fanconi syndrome (with development of hypophosphataemic rickets in a number of children),[2-6] and nephrogenic diabetes insipidus[1,6] may result. Progressive chronic renal failure after high-dose ifosfamide has been described.[7] Life-threatening hypokalaemia possibly due to a renal lesion has also occurred.[8] Results in *rats* suggest that generation of toxic metabolites within the kidney itself may be responsible, and that repairable renal damage occurs after the first dose, which is aggravated by repeated toxic insults.[9] This is in agreement with clinical results, since although renal damage has been seen after a single dose, perhaps representing an idiosyncratic reaction,[10,11] most cases have been in children receiving relatively high doses long-term. Renal damage appears to persist after withdrawal of ifosfamide in these patients and may be largely irreversible.[12]

A combination of younger age and high cumulative doses of ifosfamide was found to convey the highest risk of toxicity, but use with cisplatin may also increase the risk.[13] The maximum safe dose of ifosfamide has been debated.[13-15] It has been suggested that cumulative doses of ifosfamide of 100 g/m^2 or more should be avoided in children in an attempt to reduce the incidence of nephrotoxicity,[14] although subsequent reviews have suggested that lower cumulative doses may be toxic, especially in younger children.[13,15]

1. Skinner R, *et al.* Nephrotoxicity after ifosfamide. *Arch Dis Child* 1990; **65:** 732–8.
2. Burk CD, *et al.* Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr* 1990; **117:** 331–5.
3. Skinner R, *et al.* Hypophosphataemic rickets after ifosfamide treatment in children. *BMJ* 1989; **298:** 1560–1.
4. Newbury-Ecob RA, Barbor PRH. Hypophosphataemic rickets after ifosfamide treatment. *BMJ* 1989; **299:** 258.
5. Newbury-Ecob RA, *et al.* Ifosfamide-induced Fanconi syndrome. *Lancet* 1989; **i:** 1328.
6. Skinner R, *et al.* Nephrotoxicity of ifosfamide in children. *Lancet* 1989; **ii:** 159.
7. Krämer A, *et al.* Progressive renal failure in two breast cancer patients after high-dose ifosfamide. *Lancet* 1994; **334:** 1569.
8. Husband DJ, Watkin SW. Fatal hypokalaemia associated with ifosfamide/mesna chemotherapy. *Lancet* 1988; **i:** 1116.
9. Graham MI, *et al.* A proposed mechanism for isophosphamide-induced kidney toxicity. *Hum Toxicol* 1985; **4:** 545–6.
10. Heney D, *et al.* Acute ifosfamide-induced tubular toxicity. *Lancet* 1989; **ii:** 103–4.
11. Devalck C, *et al.* Acute ifosfamide-induced proximal tubular toxic reaction. *J Pediatr* 1991; **118:** 325–6.
12. Heney D, *et al.* Progressive renal toxicity due to ifosfamide. *Arch Dis Child* 1991; **66:** 966–70.
13. Loebstein R, *et al.* Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol* 1999; **39:** 454–61.
14. Skinner R, *et al.* Risk factors for ifosfamide nephrotoxicity in children. *Lancet* 1996; **348:** 578–80.
15. Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. *Pediatrics* 1998; **101:** 1067. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/6/e8 (accessed 30/06/04)

Effects on the nervous system. Use of ifosfamide (with mesna for urothelial protection) may be associated with the development of severe encephalopathy, with EEG abnormalities, disorientation, hallucinations, catatonia, and coma; occasionally CNS depression has led to circulatory collapse and death.[1,2] The effect has been suggested to be due to a metabolite, perhaps chloroacetaldehyde,[3] a hypothesis supported by the increased incidence of encephalopathy after oral rather than intravenous doses.[4,5] Others suggest that the dechloroethylated metabolites may contribute, and in particular the *R*-enantiomer of 3-dechloroethyl-ifosfamide which is a metabolite of *S*-ifosfamide.[6] There is some uncertainty about the contributory role of mesna, if any: encephalopathy has not been seen when mesna is given with cyclophosphamide,[7] and has been seen when ifosfamide is given alone,[5] but an exacerbatory role for mesna cannot be ruled out,[8] perhaps via its chelating properties.[1,7]

A nomogram has been proposed to identify patients at greatest risk of toxicity,[9,10] such as those with renal or hepatic impairment,[9] although doubts have been raised as to its general applicability.[11] A retrospective review of 237 patients given ifosfamide, of whom 38 developed encephalopathy, found no evidence that age or ifosfamide dose influenced the development of the condition, and serum creatinine values were in the normal range in the affected group, although they were slightly higher than in those not affected; however, low serum albumin did seem to be associated with greater risk.[12] It has also been suggested that the drug be given by continuous infusion over several days where possible, since this route has by far the lowest incidence of encephalopathy (7%, versus 26% with intravenous bolus and 43% with oral doses).[4] Care may also be required when giving other antineoplastics to patients who have had encephalopathy after ifosfamide, since a case of encephalopathy with bleomycin (not normally associated with neurotoxicity) has been reported in such a patient.[13]

A few reports suggests that methylthioninium chloride can effectively prevent or reverse signs of encephalopathy, and a number of mechanisms have been proposed (see Glutaric Aciduria under Uses of Methylthioninium Chloride, p.1451)

1. Meanwell CA, *et al.* Encephalopathy associated with ifosphamide/mesna therapy. *Lancet* 1985; **i:** 406–7.
2. Cantwell BMJ, Harris AL. Ifosfamide/mesna and encephalopathy. *Lancet* 1985; **i:** 752.
3. Goren MP, *et al.* Dechloroethylation of ifosfamide and neurotoxicity. *Lancet* 1986; **ii:** 1219–20.
4. Cerny T, *et al.* Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet* 1990; **335:** 175.
5. Lewis LD, Meanwell CA. Ifosfamide pharmacokinetics and neurotoxicity. *Lancet* 1990; **335:** 175–6.
6. Wainer IW, *et al.* Ifosfamide stereoselective dichloroethylation [sic] and neurotoxicity. *Lancet* 1994; **343:** 982–3.
7. Osborne RJ, Slevin ML. Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1398–9.
8. Pinkerton R, *et al.* Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1399.
9. Meanwell CA, *et al.* Avoiding ifosfamide/mesna encephalopathy. *Lancet* 1986; **ii:** 406.
10. Perren TJ, *et al.* Encephalopathy with rapid infusion ifosfamide/mesna. *Lancet* 1987; **i:** 390–1.
11. McCallum AK. Ifosfamide/mesna encephalopathy. *Lancet* 1987; **i:** 987. Correction. *ibid.*; 1048.
12. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol* 2005; **28:** 277–80.
13. Atherton P, *et al.* Drug-induced encephalopathy after previous ifosfamide treatment. *Lancet* 1988; **ii:** 1084.

Handling and disposal. A study[1] found that ifosfamide 8% solution penetrated all of 4 brands of latex glove and one PVC glove, although the diffusion rate was 4 or more times slower than through cadaver skin. Permeation was greater through the PVC glove than the latex gloves, partly due to its lesser thickness, although permeation was not dependent on thickness alone and varied between gloves of the same brand as well as between brands. They recommended that latex gloves of a suitable brand should be worn when handling ifosfamide, and changed at least every 2 hours. For reference to a method for the destruction of ifosfamide waste, see under Cyclophosphamide, p.703.

1. Corlett SA, *et al.* Permeation of ifosfamide through gloves and cadaver skin. *Pharm J* 1991; **247:** R39.

Interactions

As for Cyclophosphamide, p.703. For a general outline of antineoplastic drug interactions, see p.642. For reference to the effects of ifosfamide on oral anticoagulants, see under Warfarin Sodium, p.1429. For a report of the enhancement of cisplatin-induced ototoxicity and nephrotoxicity, see under Cisplatin, p.700.

Antibacterials. Oral *rifampicin* given twice daily for 6 days, starting 3 days before intravenous ifosfamide (as a 24-hour infusion), increased the clearance of ifosfamide by over 100%; however, exposure to metabolites of ifosfamide was relatively unchanged. The authors considered that rifampicin might decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Antifungals. *Ketoconazole* given orally for 4 days, starting 1 day before intravenous ifosfamide (given as a 24-hour infusion), decreased ifosfamide clearance. However, ifosfamide metabolism to active metabolites was decreased, and urinary excretion of ifosfamide was increased. Ketoconazole may decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Pharmacokinetics

Ifosfamide is normally given intravenously, although it is well absorbed from the gastrointestinal tract. The pharmacokinetics of ifosfamide are reported to exhibit considerable interindividual variation. It is a prodrug that is extensively metabolised, chiefly by cytochrome P450 isoenzymes such as CYP3A4 and CYP2B6 in the liver, to a variety of active and inactive metabolites; there is some evidence that metabolism is saturated at very high doses. Although the manufacturers state that a mean terminal elimination half-life of about 15 hours has been reported after a single high-dose intravenous bolus, most studies at lower doses appear to have recorded elimination half-lives of about 4 to 8 hours. After repeated doses (fractionated therapy) there is a decrease in the elimination half-life, apparently due to autoinduction of metabolism. Ifosfamide is distributed into the CSF. It is excreted largely in urine, as unchanged drug and metabolites.

◊ General references.

1. Wagner T. Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 439–56.
2. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
3. Kerbusch T, *et al.* Clinical pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. *Clin Pharmacokinet* 2001; **40:** 41–62.

◊ In a study[1] in 20 patients receiving intravenous ifosfamide over 3 or 5 days, the median elimination half-life of ifosfamide was 3.85 hours in patients under 60 years of age compared with 6.03 hours in those over age 60; this difference appeared to be due to an increased volume of distribution in the older age group. The autoinduction of metabolism typically seen with multiple doses of ifosfamide was not affected by age. The increased clearance seen over time during a 5-day cycle of ifosfamide treatment[2] was not sustained over the 21 days between cycles, but was reproducible and of similar magnitude in the subsequent cycle.

In another study[3] the half-life of the *S*-enantiomer of ifosfamide was found to be 5.98 hours after an intravenous bolus of the racemate, compared with 7.12 hours for the *R*-enantiomer.

1. Lind MJ, *et al.* The effect of age on the pharmacokinetics of ifosfamide. *Br J Clin Pharmacol* 1990; **30:** 140–3.
2. Lewis LD. A study of 5 day fractionated ifosfamide pharmacokinetics in consecutive treatment cycles. *Br J Clin Pharmacol* 1996; **42:** 179–86.
3. Corlett SA, *et al.* Pharmacokinetics of ifosfamide and its enantiomers following a single 1h intravenous infusion of the racemate in patients with small cell lung carcinoma. *Br J Clin Pharmacol* 1995; **39:** 452–5.

Uses and Administration

Ifosfamide is an alkylating agent with properties similar to those of cyclophosphamide (p.703), of which it is a congener. It is used in the treatment of solid tumours including those of the cervix, lung, ovary, testis, and thymus, as well as in sarcoma and in the treatment of lymphomas. For further mention of these uses see the cross-references given below.

Ifosfamide is given intravenously, either by injection as a solution diluted to less than 4%, or by infusion. Licensed dosage regimens include a total dose of 8 to 12 g/m^2 divided over 3 to 5 days, with the course repeated at 2 to 4 week intervals; a total dose of 6 g/m^2 divided over 5 days, repeated every 3 weeks; and doses of 5 to 6 g/m^2, to a maximum of 10 g, given as a single 24-hour infusion, repeated at 3 to 4 week intervals. The interval between courses also depends on the blood count (see also Bone-marrow Depression, p.639). Oral ifosfamide has also been studied but is associated with neurotoxicity (see Effects on the Nervous System, above).

Ifosfamide should be given with mesna (see Administration, below), and adequate hydration should be maintained, to avoid urological toxicity; fluid intake should not be less than 2 litres daily.

Administration. Mesna (p.1449) can combine with urotoxic ifosfamide metabolites in the kidney to form stable and non-toxic compounds. It is therefore given prophylactically with ifosfamide. It has a shorter half-life than ifosfamide so repeated doses are needed to provide adequate protection of the bladder. A common schedule uses intravenous mesna at 60% of the ifosfamide dose, divided into 3 doses given with, or 15 minutes before, ifosfamide, then 4 and 8 hours after ifosfamide.[1] Mesna may also be given orally, but higher doses are required.

1. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.

Malignant neoplasms. Ifosfamide may be used as an alternative to cyclophosphamide in lymphomas such as Burkitt's lymphoma (p.657). It is also used in a variety of solid neoplasms, including in palliative regimens for advanced cervical cancer (p.663); in the treatment of lung cancer (p.668); in ovarian cancer (p.670) and second-line and salvage regimens for testicular cancer (p.673); in thymoma (p.674); in adjuvant therapy for bone sarcomas (p.675) and rhabdomyosarcoma (p.676).

Preparations

USP 31: Ifosfamide for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Asoifos†; Cuantil; Duvaxan†; Fentul; Holoxan†; Ifocris; Ifosmixan; IFX; ***Austral.:*** Holoxan; ***Austria:*** Holoxan; ***Belg.:*** Holoxan; ***Braz.:*** Holoxane; Seromida†; ***Canad.:*** Ifex; ***Chile:*** Holoxan; Ifolem; ***Cz.:*** Holoxan; ***Denm.:*** Holoxan†; ***Fin.:*** Holoxan; ***Fr.:*** Holoxan; ***Ger.:*** Holoxan; IFO-cell; ***Gr.:*** Holoxan; ***Hong Kong:*** Holoxan; ***Hung.:*** Holoxan; ***India:*** Ifos; Ipamide; ***Indon.:*** Holoxan; ***Irl.:*** Mitoxana; ***Israel:*** Ifoxan; ***Ital.:*** Holoxan; ***Malaysia:*** Holoxan†; ***Mex.:*** Alquimid; Ifolem; Ifomida; Ifoxan†; ***Neth.:*** Holoxan; ***Norw.:*** Holoxan; ***NZ:*** Holoxan; ***Philipp.:*** Holoxan; Iphox; ***Pol.:*** Holoxan; Macdafen; ***Port.:*** Holoxan; ***S.Afr.:*** Holoxan; ***Singapore:*** Holoxan; ***Spain:*** Tronoxal; ***Swed.:*** Holoxan; ***Switz.:*** Holoxan; ***Thai.:*** Holoxan; IFO-cell; Ifolem; ***Turk.:*** Holoxan; ***UK:*** Mitoxana†; ***USA:*** Ifex.

Multi-ingredient: ***India:*** Holoxan Uromitexan; Ifex-M; Ipamide with Mesna.

Imatinib Mesilate *(BANM, rINNM)*

CGP-57-148B; Imatinib, Mésilate d'; Imatinib Mesylate *(USAN)*; Imatinibi Mesilas; Mesilato de imatinib; STI-571. α-(4-Methyl-1-piperazinyl)-3′-{[4-(3-pyridyl)-2-pyrimidinyl]amino}-*p*-tolu-*p*-toluidide methanesulfonate.

Иматиниба Мезилат

$C_{29}H_{31}N_7O,CH_4O_3S = 589.7.$

CAS — 152459-95-5 (imatinib); 220127-57-1 (imatinib mesilate).

ATC — L01XE01.

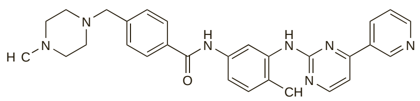

(imatinib)

Adverse Effects and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects of imatinib mesilate include gastrointestinal disturbances, superficial oedema, myalgia, muscle cramps, rashes, fatigue, and headache. There are reports of erythema multiforme and Stevens-Johnson syndrome. Other adverse effects include dizziness, taste disturbances, paraesthesia, insomnia, eye disorders or visual disturbances, epistaxis, dyspnoea, dry skin, alopecia, night sweats, pyrexia, weakness, and rigors. Hepatotoxicity may occur; fatal cases of hepatic necrosis have been reported. Aseptic necrosis of bone, mainly in the femoral head, has been reported rarely.

Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in leukaemic patients, and may be associated with the underlying disease. Gastrointestinal bleeding, however, is more frequent in those patients treated for stromal tumours. Ulceration can occur; gastrointestinal perforation, fatal in some cases, has been reported rarely.

Severe fluid retention can occur, which may result in pleural and pericardial effusion, pulmonary oedema, and ascites. Some fatalities have been reported, and treatment may need to be stopped if there is unexpected, rapid weight gain. Elderly patients and those with a history of cardiac disease may be at increased risk. Isolated cases of left ventricular dysfunction have been reported; patients with cardiac disease or risk factors for cardiac failure should be monitored. There are reports, including fatalities, of cerebral oedema, increased intracranial pressure and papilloedema.

Imatinib mesilate should be taken with food and a large glass of water to minimise gastrointestinal irritation. Complete blood counts and liver function should be monitored regularly.

Effects on the heart. Ten patients receiving imatinib developed severe congestive heart failure without obvious cause; all patients had normal left ventricular function before imatinib was started. Mitochondrial abnormalities were found after myocardial biopsy on 2 of the patients. These findings were confirmed by studies on *mice* and *in vitro*. The authors suggested that patients be closely followed for clinical manifestations of left ventricular dysfunction.[1]

Subsequent evaluation by the manufacturer (*Novartis*) established that the frequency of reported cardiac events was less than 1%. However, they recommended that patients with known cardiac disease or risk factors for cardiac failure be monitored accordingly, that those developing clinical manifestations suggestive of congestive cardiac failure be thoroughly evaluated and treated, and that elderly patients or those with underlying heart disease be evaluated for baseline left ventricular ejection fraction.[2]

1. Kerkelä R, *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; **12:** 908–16.
2. Novartis, Canada. Health Canada endorsed important safety information on Gleevec (imatinib mesylate): recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC (imatinib mesylate) (issued 21st September, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/gleevec_2_hpc-cps-eng.php (accessed 01/08/08)

Effects on the kidneys. Imatinib has been associated with the development of acute renal failure, requiring haemodialysis.[1-3]

1. Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; **17:** 685–7.
2. Pou M, *et al.* Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; **44:** 1239–41.
3. Foringer JR, *et al.* Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; **39:** 2136–8.

Effects on the lungs. Interstitial pneumonitis has been reported with imatinib;[1-8] presenting symptoms included dry cough and dyspnoea. Doses of imatinib ranged from 100 mg to 600 mg daily. In most cases, the pneumonitis resolved after stopping imatinib and starting corticosteroid therapy. The mechanism was unclear, and may involve a hypersensitivity reaction. In an analysis of 27 cases of interstitial lung disease associated with imatinib therapy,[8] 30% of patients showed a hypersensitivity reaction radiological pattern. Pre-existing lung disease may be a risk factor.

1. Bergeron A, *et al.* Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; **20:** 4271–2.
2. Rosado MF, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003; **21:** 3171–3.
3. Ma CX, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; **78:** 1578–9.
4. Yokoyama T, *et al.* Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia* 2004; **18:** 645–6.
5. Isshiki I, *et al.* Interstitial pneumonitis during imatinib therapy. *Br J Haematol* 2004; **125:** 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; **79:** 80–1.
7. Lin J-T, *et al.* Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; **47:** 1693–5.
8. Ohnishi K, *et al.* Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006; **20:** 1162–4.

Effects on reproductive potential. Oligospermia[1] and ovarian failure[2] have been reported after treatment with imatinib. Patients should be counselled before therapy about the risk of impaired fertility.

1. Seshadri T, *et al.* Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* 2004; **351:** 2134–5.
2. Christopoulos C, *et al.* Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* 2008; **358:** 1079–80.

Effects on the skin, hair, and nails. There are reports of acute generalised exanthematous pustulosis in patients receiving imatinib.[1,2] The authors noted that severe skin reactions had been reported in some other patients receiving the drug, and speculated that the effect might be dose-dependent and related to its pharmacological action. In subsequent reports[3-5] of cutaneous adverse effects, this dose-dependency has also been observed, with effects especially at doses of 600 mg daily and above. In a report of a livedoid pattern of rash in 3 patients taking imatinib, the authors noted that adverse skin reactions to imatinib tend to be strongly dose-dependent, are self-limiting, and do not usually affect the mucous membranes.[6] Epidermal necrolysis occurred in a patient who underwent stem cell transplantation after treatment with imatinib.[7] The authors suggested that prolonged inhibition of platelet-derived growth factor by imatinib may have impaired the repair of skin damage caused by the conditioning therapy. In a report of 19 patients exhibiting skin reactions, the authors suggested that the actions of imatinib on platelet-derived growth factor may have caused an increase in dermal interstitial fluid pressure, capable of inducing oedema and the subsequent erythema and desquamation that was observed. Rare reactions included psoriasis, hyaline cell syringoma, and malpighian epithelioma, all of which occurred after at least 1 year of therapy.[8] Follicular mucinosis[9] and panniculitis[10] have also been reported with use of imatinib, as has Stevens-Johnson syndrome.[11,12] Palmoplantar hyperkeratosis and nail dystrophy can occur.[13] Repigmentation of grey hair has also been reported.[14]

Oral corticosteroids have been used to resolve most cases of skin eruptions.[8] In other instances, re-introduction of imatinib at low doses, gradually increased to full dosage, has been successfully tolerated.[8,12,15] In one patient, who developed exfoliative dermatitis with imatinib and had recurrent reactions despite decreased doses, a once-weekly dose of imatinib was associated with a less severe rash that eventually disappeared over a period of 4 months.[16]

1. Brouard M, Saurat J-H. Cutaneous reactions to STI571. *N Engl J Med* 2001; **345:** 618–19.
2. Schwarz M, *et al.* Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; **69:** 254–6.
3. Valeyrie L, *et al.* Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48:** 201–6.
4. Drummond A, *et al.* A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; **120:** 911–13.
5. Ugurel S, *et al.* Dose-dependent severe cutaneous reactions to imatinib. *Br J Cancer* 2003; **88:** 1157–9.
6. Martínez-González MC, *et al.* Livedoid skin reaction probably due to imatinib therapy. *Ann Pharmacother* 2007; **41:** 148–52.
7. Schaich M, *et al.* Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2003; **82:** 303–4.
8. Breccia M, *et al.* Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; **74:** 121–3.
9. Yanagi T, *et al.* Follicular mucinosis associated with imatinib (STI571). *Br J Dermatol* 2004; **151:** 1276–8.
10. Ugurel S, *et al.* Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003; **149:** 678–9.
11. Hsiao L-T, *et al.* Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol* 2002; **117:** 620–2.
12. Rule SAJ, *et al.* Managing cutaneous reactions to imatinib therapy. *Blood* 2002; **100:** 3434–5.
13. Deguchi N, *et al.* Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. *Br J Dermatol* 2006; **154:** 1216–18.
14. Etienne G, *et al.* Imatinib mesylate and gray hair. *N Engl J Med* 2002; **347:** 446.
15. Park MA, *et al.* Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004; **25:** 345–7.
16. Tanvetyanon T, Nand S. Overcoming recurrent cutaneous reactions from imatinib using once-weekly dosing. *Ann Pharmacother* 2003; **37:** 1818–20.

Effects on the spleen. There are isolated reports of splenic rupture in patients receiving imatinib mesilate.[1]

1. Elliott MA, *et al.* Adverse events after imatinib mesylate therapy. *N Engl J Med* 2002; **346:** 712–13.

Gynaecomastia. Gynaecomastia was noted in 7 of 38 men assessed for hormone concentrations while enrolled in studies of imatinib; the authors attributed the disorder to reductions in testosterone concentrations due to imatinib.[1]

1. Gambacorti-Passerini C, *et al.* Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; **361:** 1954–56.

Hypophosphataemia. Hypophosphataemia and associated changes in bone and mineral metabolism were reported in a study of patients receiving imatinib. Patients with normal serum-phosphate concentrations also had similar changes in bone turnover. Hypophosphataemia was apparently related to patient age and imatinib dose; it was also associated with decreased serum concentrations of calcium and vitamin D.[1] In a review of data, the manufacturers (*Novartis*) noted an incidence of 50% of patients in 2 studies; overall 1.5% had grade 4 hypophosphataemia. However, the reported incidence of hypophosphataemia as an adverse effect of imatinib was only 3%. They suggested that phosphate concentrations be monitored in patients taking imatinib until further elucidation of the effect of the drug on bone is available.[2] While some have questioned the association between treatment with imatinib and hypophosphataemia,[3] others have also reported hypophosphataemia during treatment with the drug.[4] The effect, however, appears to be reversible on stopping imatinib.

1. Berman E, *et al.* Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; **354:** 2006–13.
2. Owen S, *et al.* Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
3. Tournis S, Lyritis GP. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
4. Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 628. Correction. *ibid.*; 1627.

Pregnancy. Two of 3 pregnancies in 2 patients taking imatinib were successful; the infants were both small for weight, but healthy and without congenital abnormalities. In the third case, a first trimester miscarriage occurred. Both women continued imatinib throughout their pregnancies.[1]

In another report,[2] 10 women became pregnant while being treated with imatinib for chronic myeloid leukaemia. Imatinib therapy was stopped upon discovery of the pregnancy; exposure to imatinib ranged from 4 to 9 weeks. Two patients had a spontaneous abortion shortly after stopping imatinib, and another patient elected to have a therapeutic abortion. Seven other pregnancies went to term, resulting in 8 babies. One infant had hypospadias which was surgically corrected without complications; all other infants were healthy. The partners of 8 male patients also conceived while the men were receiving imatinib, one of them twice. All male patients continued therapy with imatinib. One spontaneous abortion occurred. Of the 8 babies born, 1 was found to have a mild rotation of the small intestine requiring surgery shortly after birth. The authors considered it possible that the brief exposure to imatinib may have slightly increased the risk of spontaneous abortion. While concluding that normal pregnancies are possible during imatinib therapy, the authors of both reports emphasised that possible teratogenic effects cannot be ruled out, and that patients should still be advised to use appropriate and effective contraception.

A similar warning was issued in a review of outcome data from 125 pregnancies involving exposure to imatinib. The authors noted that 63 pregnancies had resulted in the live birth of normal infants; a further 35 women terminated the pregnancy (in 3 cases because fetal abnormalities were found), and 18 ended in spontaneous abortion.[3] However, there were 9 infants with congenital abnormalities, several of which were strikingly similar, a fact that was considered to be of some concern.

1. AlKindi S, *et al.* Imatinib in pregnancy. *Eur J Haematol* 2005; **74:** 535–7.

2. Ault P, *et al.* Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol* 2006; **24:** 1204–8.
3. Pye SM, *et al.* The effects of imatinib on pregnancy outcome. *Blood* 2008; **111:** 5505–8.

Interactions

Imatinib mesilate is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals and macrolide antibacterials, may increase blood concentrations of imatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of imatinib; imatinib dosage may need to be increased in these patients (see Uses and Administration, below).

In vitro studies have indicated that imatinib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6, and may increase blood concentrations of drugs that are substrates of these enzymes.

The dose of levothyroxine may need to be increased before imatinib is given to patients with hypothyroidism (see Antineoplastics under Interactions of Levothyroxine, p.2172).

Antifungals. In a small study in healthy subjects, *ketoconazole* significantly increased imatinib exposure; mean maximum plasma concentration and area under the concentration-time curve increased, and clearance of imatinib decreased. The half-life of imatinib appeared relatively unchanged. To avoid overexposure, single subtherapeutic doses of imatinib had been used (200 mg); the authors noted that clinical significance might arise with use of imatinib in daily doses of 800 mg or more.[1]

1. Dutreix C, *et al.* Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* 2004; **54:** 290–4.

St John's wort. Exposure to imatinib was significantly reduced when it was given after 2 weeks of treatment with St John's wort; area under the concentration-time curve was decreased, maximum plasma concentration and half-life of imatinib were reduced, and clearance increased.[1,2]

1. Frye RF, *et al.* Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004; **76:** 323–9.
2. Smith PF, *et al.* The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004; **24:** 1508–14.

Pharmacokinetics

Imatinib mesilate is well absorbed after oral doses with peak blood concentrations occurring after 2 to 4 hours. The mean bioavailability is about 98%. Imatinib is reported to be about 95% bound to plasma proteins. Plasma elimination half-lives of imatinib and its major active metabolite, the *N*-demethylated piperazine derivative, are about 18 and 40 hours respectively. The major enzyme responsible for the metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4; isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role. About 81% of a dose is eliminated within 7 days in the faeces (68%) and urine (13%). It is excreted mostly as metabolites, with only 25% as unchanged drug.

◊ References.

1. Peng B, *et al.* Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol* 2004; **44:** 158–62.
2. Peng B, *et al.* Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005; **44:** 879–94.

Uses and Administration

Imatinib mesilate is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (p.653) and acute lymphoblastic leukaemia (p.651). It also inhibits the tyrosine kinase for platelet-derived growth factor and stem cell factor, c-kit (CD117), which is overexpressed in gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p.676). Imatinib is also indicated for patients with myelodysplastic syndromes (p.654), hypereosinophilic syndrome, aggressive systemic mastocytosis (p.1138), and dermatofibrosarcoma protuberans. Imatinib is given orally as the mesilate but doses are expressed as the base. Imatinib mesilate 119.5 mg is equivalent to about 100 mg of imatinib.

In the treatment of **chronic myeloid leukaemia**, patients in chronic phase may be given the equivalent of 400 mg of the base daily, increased to 600 mg daily or 400 mg twice daily if required. Patients in blast crisis or accelerated phase are given 600 mg daily, increased to 400 mg twice daily if necessary.

In the treatment of patients with newly diagnosed **acute lymphoblastic leukaemia**, imatinib 600 mg daily may be given with induction, consolidation, or maintenance chemotherapy. The same dose may be given as monotherapy for patients with relapsed or refractory disease.

In the treatment of unresectable or metastatic malignant **gastrointestinal stromal tumours**, doses of 400 or 600 mg daily are recommended.

For patients with **myelodysplastic disease**, the recommended dose of imatinib is 400 mg daily. For **mastocytosis**, 400 mg daily is given, unless there is associated eosinophilia, in which case a starting dose of 100 mg daily is recommended, increased to 400 mg if response is inadequate. Similarly, the recommended dose for **hypereosinophilic syndrome** is 400 mg daily, although a subset of patients with FIP1L1-platelet-derived growth factor receptor-α fusion kinase should be started on 100 mg daily, increased to 400 mg if response is insufficient. Patients with **dermatofibrosarcoma protuberans** may be given 400 mg twice daily.

Doses should be taken with food, and accompanied by plenty of water, to minimise gastric irritation. Dose adjustments may be necessary if myelosuppression or hepatotoxicity occurs; blood counts and liver function should be regularly monitored (see Administration in Hepatic Impairment, below).

Doses of imatinib should be increased by 50%, and clinical response should be carefully monitored, in patients given potent CYP3A4 inducers such as rifampicin or phenytoin. For children's doses, see Administration in Children, below.

Administration in children. In the UK, the licensed dose of imatinib for children with chronic myeloid leukaemia (CML) is 340 mg/m^2 daily, for those in chronic or advanced phase; a total dose of 800 mg should not be exceeded. The dose may be increased to 570 mg/m^2 daily (maximum total dose 800 mg) in children with disease progression, with unsatisfactory haematological response after at least 3 months of treatment, with no cytogenetic response after 12 months of treatment, or with loss of a previously achieved haematological or cytogenetic response.

In the USA, the recommended dose of imatinib is 340 mg/m^2 daily in children with newly diagnosed CML; the dose should not exceed 600 mg. For children with chronic phase CML recurring after stem cell transplantation or who are resistant to interferon alfa therapy, the recommended dose of imatinib is 260 mg/m^2 daily.

Treatment can be given as a once-daily dose, or split into morning and evening doses. There is no experience with the use of imatinib in children under 2 years of age.

Administration in hepatic impairment. Imatinib is metabolised in the liver. Licensed product information in the UK recommends that patients with mild, moderate, or severe liver impairment should be given the minimum recommended dose of 400 mg daily. In the USA, patients with mild and moderate impairment should be given initial doses of 400 mg daily, but in those with severe hepatic impairment, 300 mg daily is recommended. In both countries, degrees of hepatic impairment are defined as:

- mild: total bilirubin equal to 1.5 times the upper limit of normal (ULN); aspartate aminotransferase (AST/SGOT) greater than ULN. AST/SGOT can be normal or less than ULN if the total bilirubin is greater than ULN
- moderate: total bilirubin greater than 1.5 to 3 times the ULN
- severe: total bilirubin greater than 3 to 10 times the ULN

If, during treatment, elevations in bilirubin greater than 3 times the ULN or in liver transaminases greater than 5 times the ULN occur, imatinib should be withheld until bilirubin levels have returned to less than 1.5 times the ULN and transaminase levels to less than 2.5 times the ULN. Treatment may then be continued at a reduced daily dose. In adults the dose is reduced from 800 mg to 600 mg, from 600 mg to 400 mg, and from 400 mg to 300 mg. In children, the dose should be reduced from 340 mg/m^2 daily to 260 mg/m^2 daily, or from 260 mg/m^2 daily to 200 mg/m^2 daily.

Hypereosinophilic syndrome. Imatinib has been reported to produce clinical responses in patients with the hypereosinophilic syndrome (HES).[1-4] Some reports suggest that imatinib also has activity in mast-cell disease, even in the absence of associated eosinophilia.[5] However, not all patients with HES respond to imatinib.[4] Many patients with the myelodysplastic variant of HES express a novel kinase derived from an abnormal fusion of platelet-derived growth factor receptor-α gene with a neighbouring gene, FIP1L1. Almost all patients with this FIP1L1-platelet-derived growth factor receptor-α fusion kinase will respond to imatinib, but a subset of patients with HES without known imatinib targets have also been reported to respond to the drug.[6,7]

1. Gleich GJ, *et al.* Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002; **359:** 1577–8.
2. Cools J, *et al.* A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348:** 1201–14.
3. Koury MJ, *et al.* Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; **115:** 587–9.
4. Payne SM, Kovacs MJ. Imatinib mesylate treatment in two patients with idiopathic hypereosinophilic syndrome. *Ann Pharmacother* 2004; **38:** 1215–18.
5. Pardanani A, *et al.* Imatinib for systemic mast-cell disease. *Lancet* 2003; **362:** 535–7.
6. Müller AMS, *et al.* Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. *Ann Hematol* 2006; **85:** 1–16.
7. Antoniu SA. Imatinib mesylate for the treatment of hypereosinophilic syndromes. *Curr Opin Investig Drugs* 2006; **7:** 980–4.

Malignant Neoplasms. References.

1. Druker BJ, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344:** 1031–7.
2. Druker BJ, *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; **344:** 1038–42.
3. Joensuu H, *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344:** 1052–6.
4. Demetri GD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347:** 472–80.
5. Kantarjian HM, *et al.* Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. *Blood* 2003; **101:** 473–5.
6. Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. *N Engl J Med* 2003; **348:** 1048–50.
7. Deininger MW, *et al.* Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; **21:** 1637–47.
8. Druker BJ. Imatinib mesylate in the treatment of chronic myeloid leukaemia. *Expert Opin Pharmacother* 2003; **4**: 963–71.
9. Borthakur G, Cortes JE. Imatinib mesylate in the treatment of chronic myelogenous leukemia. *Int J Hematol* 2004; **79:** 411–19.
10. Hochhaus A, La Rosee P. Imatinib therapy in chronic myelogenous leukemia: strategies to avoid and overcome resistance. *Leukemia* 2004; **18:** 1321–31.
11. Verweij J, *et al.* Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364:** 1127–34.
12. Deininger MWN, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. *Pharmacol Rev* 2003; **55:** 401–23.
13. Deininger M, *et al.* The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* 2005; **105:** 2640–53.
14. Kantarjian HM, *et al.* New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med* 2006; **145:** 913–23.
15. Moen MD, *et al.* Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs* 2007; **67:** 299–320.
16. Siddiqui MAA, Scott LJ. Imatinib: a review of its use in the management of gastrointestinal stromal tumours. *Drugs* 2007; **67:** 805–20.
17. Cross SA, Lyseng-Williamson KA. Imatinib: in relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Drugs* 2007; **67:** 2645–54.

Pulmonary hypertension. Imatinib has produced beneficial responses in patients with pulmonary arterial hypertension (p.1179) and may have a role, particularly in patients who fail to respond to other therapies.[1-3]

1. Ghofrani HA, *et al.* Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 1412–13.
2. Patterson KC, *et al.* Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006; **145:** 152–3.
3. Souza R, *et al.* Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006; **61:** 736.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Glivec; Ziatir; ***Austral.:*** Glivec; ***Belg.:*** Glivec; ***Braz.:*** Glivec; ***Canad.:*** Gleevec; ***Chile:*** Glivec; ***Cz.:*** Glivec; ***Denm.:*** Glivec; ***Fin.:*** Glivec; ***Fr.:*** Glivec; ***Ger.:*** Glivec; ***Gr.:*** Glivec; ***Hong Kong:*** Glivec; ***Hung.:*** Glivec; ***India:*** Imatib; Zoleta; ***Indon.:*** Glivec; ***Irl.:*** Glivec; ***Israel:*** Glivec; ***Ital.:*** Glivec; ***Jpn:*** Glivec; ***Malaysia:*** Glivec; ***Mex.:*** Glivec; ***Neth.:*** Glivec; ***Norw.:*** Glivec; ***NZ:*** Glivec; ***Philipp.:*** Glivec; ***Pol.:*** Glivec; ***Port.:*** Glivec; ***Rus.:*** Glivec (Гливек); ***S.Afr.:*** Gleevec; ***Singapore:*** Glivec; ***Spain:*** Glivec; ***Swed.:*** Glivec; ***Switz.:*** Glivec; ***Thai.:*** Glivec; ***Turk.:*** Glivec; ***UK:*** Glivec; ***USA:*** Gleevec; ***Venez.:*** Glivec.

Imexon *(rINN)*

BM-06002; Imexón; Imexonum. (5*R*,*S*)-4-Amino-1,3-diazabicyclo[3.1.0]hex-3-en-2-one.

Имексон

$C_4H_5N_3O$ = 111.1.

CAS — 59643-91-3.

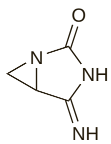

Profile

Imexon is a cyanoaziridine compound that appears to act as an antineoplastic in several ways, one of which is by causing mitochondrial disruption in the cancer cell, thus inducing apoptosis. It is under investigation for the treatment of malignant neoplasms, including ovarian cancer, pancreatic adenocarcinoma, multiple myeloma, and metastatic malignant melanoma.

Interleukin-2

BG-8301 (teceleukin); Epidermal Thymocyte Activating Factor; ETAF; IL-2; Interleucina 2; T-cell Growth Factor.

Description. Interleukin-2 is a naturally-occurring 133-amino-acid glycoprotein with a molecular weight of about 15 000. It is available from natural sources or as a product of recombinant DNA technology (rIL-2).

In addition to aldesleukin (below) modified forms of interleukin-2 produced by recombinant DNA technology have included celmoleukin and teceleukin.

Aldesleukin *(BAN, USAN, rINN)*

Aldesleukiini; Aldesleukina; Aldesleukine; Aldesleukinum; Aldeslökin; Des-alanyl-1, Serine-125 Human Interleukin-2; Recombinant Interleukin-2; 125-L-Serine-2–133-interleukin 2 (human reduced).

Альдеслейкин

CAS — 110942-02-4.

ATC — L03AC01.

ATC Vet — QL03AC01.

Description. Aldesleukin (modified human recombinant interleukin-2) is produced by recombinant DNA technology using an *Escherichia coli* strain containing an analogue of the human interleukin-2 gene. It differs from native interleukin-2 in that it is not glycosylated, it has no N-terminal alanine, and it has serine substituted for cysteine at position 125.

Incompatibility. Aldesleukin 33 800 units/mL in glucose 5% lost significant biological activity when mixed with other drugs including ganciclovir sodium, lorazepam, pentamidine isetionate, prochlorperazine edisilate, and promethazine hydrochloride.[1] However, the incompatibility was not detectable by spectrophotometric methods and only lorazepam was visually incompatible, suggesting that these methods may be invalid for assessing the compatibility of proteins.

1. Alex S, *et al.* Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: evaluation of three methods. *Am J Health-Syst Pharm* 1995; **52:** 2423–6.

Stability. Aldesleukin lost 75 to 100% of activity when reconstituted with glucose 5% or sodium chloride 0.9% in a plastic syringe and given over 24 hours with a syringe driver.[1,2] Loss of activity was not seen if aldesleukin was reconstituted with water alone[2] or with the addition of albumin.[1,2] It was suggested that loss of activity could be suspected because of lack of toxicity,[1,2] and that the lack of toxicity in some published studies could be due to this.[1,3] However, the authors of these studies indicated that they had reconstituted aldesleukin with albumin.[4,5] Reconstitution with low concentrations of albumin has been advocated to avoid bioavailability problems,[1,4,6] but is not recommended for currently licensed preparations. Vials of aldesleukin are reconstituted with water for injection.

However, UK licensed product information allows for further dilution of reconstituted aldesleukin with up to 500 mL of glucose 5%, containing human albumin 0.1%, when infused over a 24-hour period; the albumin should be added and mixed with the glucose before addition of the reconstituted aldesleukin.

For short intravenous infusion, the US licensed product information indicates that dilution in glucose 5% outside of a specified range (below 30 micrograms/mL and above 70 micrograms/mL) results in increased variability in drug delivery.

Reconstitution or dilution of aldesleukin preparations with sodium chloride 0.9% is not recommended because increased aggregation occurs.

1. Miles DW, *et al.* Reconstitution of interleukin 2 with albumin for infusion. *Lancet* 1990; **335:** 1602–3.
2. Vlasveld LT, *et al.* Reconstitution of interleukin-2. *Lancet* 1990; **336:** 446.
3. Miles DW, *et al.* Toxicity and reconstitution of recombinant interleukin-2 with albumin. *Lancet* 1991; **338:** 1464.
4. Franks CR. Reconstitution of interleukin-2. *Lancet* 1990; **336:** 445–6.
5. Hamblin T. Reconstitution of interleukin-2 with albumin for infusion. *Lancet* 1990; **336:** 251.
6. Lamers CHJ, *et al.* Bioavailability of interleukin-2 after reconstitution with albumin. *Lancet* 1992; **340:** 241.

Units

100 units of human interleukin-2 are contained in one ampoule of the first International Standard Preparation (1987). The activity of interleukin-2 has also been expressed in Nutley and Cetus units: 100 international units is reportedly equivalent to about 83.3 Nutley units and to about 16.7 Cetus units. US licensed product information states that 18 million international units of aldesleukin are equivalent to 1.1 mg of protein.

Adverse Effects and Treatment

Toxicity is related to dose and route and is often severe; fatalities have been recorded. Decreased vascular resistance and increased capillary permeability (the 'capillary leak syndrome') is common in patients given aldesleukin, and results in hypotension, reduced organ perfusion, and oedema. The incidence and severity of this syndrome is lower after subcutaneous than intravenous dosage. Fluid replacement may be necessary to treat the resultant hypovolaemia and dopamine or other pressor agents may be needed to help maintain organ perfusion. Capillary leak syndrome may also be associated with cardiac effects including tachycardia, angina, myocardial infarction; respiratory effects such as dyspnoea, pulmonary oedema, and respiratory failure; renal abnormalities including uraemia and oliguria or anuria; mental status changes including irritability, depression, confusion, and drowsiness. Therapy should be stopped if patients develop severe lethargy or somnolence, as continuing may result in coma. Raised liver enzymes, gastrointestinal disturbances, fever and flu-like symptoms (malaise, rigors, chills, arthralgia, and myalgia), rashes, pruritus, anaemia, leucopenia, and thrombocytopenia, are also relatively common. Paracetamol (but not NSAIDs, see Effects on the Kidneys, below) may be used prophylactically for fever. Pethidine may be used to control rigors. Antiemetics and antidiarrhoeals may also be required. Antihistamines may benefit some patients with pruritic rash. Injection site reactions are common after subcutaneous doses; necrosis has occurred. Aldesleukin therapy is associated with impaired neutrophil function, and an increased risk of bacterial infections (see below), including sepsis and bacterial endocarditis; this has been reported mainly after intravenous use, and antibacterial prophylaxis may be necessary.

◊ References.

1. Sundin DJ, Wolin MJ. Toxicity management in patients receiving low-dose aldesleukin therapy. *Ann Pharmacother* 1998; **32:** 1344–52.
2. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001; **24:** 287–93.
3. Dutcher J, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part II: management of IL-2 toxicity and studies with other cytokines. *Med Oncol* 2001; **18:** 209–19.
4. Schwartz RN, *et al.* Managing toxicities of high-dose interleukin-2. *Oncology (Huntingt)* 2002; **16** (suppl 13): 11–20.

Bacterial infections. The incidence of sepsis and bacteraemia is increased in patients receiving interleukin-2 via intravenous catheters,[1,2] and possibly subcutaneously,[3] although others have not found this to be the case.[4,5] The increased incidence of non-opportunistic bacterial infection may be a particular problem in patients with AIDS who are treated with interleukin-2.[6] The mechanism is uncertain, but may be related to impairment of neutrophil function by the cytokine.[7]

1. Snydman DR, *et al.* Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990; **112:** 102–7.
2. Shiloni E, *et al.* Interleukin-2 therapy, central venous catheters, and nosocomial sepsis. *Ann Intern Med* 1990; **112:** 882–3.
3. Jones AL, *et al.* Infectious complications of subcutaneous interleukin-2 and interferon-alpha. *Lancet* 1992; **339:** 181–2.
4. Buter J, *et al.* Infection after subcutaneous interleukin-2. *Lancet* 1992; **339:** 552.
5. Schomburg AG, *et al.* Cytokines and infection in cancer patients. *Lancet* 1992; **339:** 1061.
6. Murphy PM, *et al.* Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-γ. *Ann Intern Med* 1988; **108:** 36–41.
7. Klempner MS, *et al.* An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. *N Engl J Med* 1990; **322:** 959–65.

Effects on endocrine function. It has been suggested that patients with adrenal metastases may be particularly susceptible to adrenal haemorrhage and consequent failure during interleukin therapy.[1] Results also suggested that lack of endogenous steroid production may increase the risk of early severe interleukin-2 toxicity.[1]

Effects on thyroid function have also been reported, with the development of hypothyroidism[2-4] and goitre.[3]

1. VanderMolen LA, *et al.* Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med* 1989; **111:** 185.
2. Atkins MB, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318:** 1557–63.
3. van Liessum PA, *et al.* Hypothyroidism and goitre during interleukin-2 therapy without LAK cells. *Lancet* 1989; **i:** 224.
4. Sauter NP, *et al.* Transient thyrotoxicosis and persistent hypothyroidism due to acute autoimmune thyroiditis after interleukin-2 and interferon-α therapy for metastatic carcinoma: a case report. *Am J Med* 1992; **92:** 441–4.

Effects on the kidneys. Intravenous aldesleukin therapy was associated with varying degrees of acute renal dysfunction in almost all of 99 adult patients.[1] The clinical syndrome of hypotension, oliguria, fluid retention, and associated azotaemia with intense tubular avidity for filtered sodium all support prerenal acute renal failure as the cause of renal dysfunction. However, renal function values returned to baseline levels within 7 days in 62% of patients and in 95% by 30 days. Patients with elevated pretreatment serum-creatinine values, particularly those aged over 60 years, and those who had previously undergone a nephrectomy, were at risk of more severe and prolonged changes in renal function, and might be particularly vulnerable to the use of indometacin for associated fever and chills, which could potentiate renal impairment through its effects on intrarenal prostaglandin production. Similar effects were noted in a study[2] of 15 children given continuous infusion of aldesleukin. A further study[3] of the renal haemodynamic effects of aldesleukin infusion found it to have a specific renal vasoconstrictor effect; changes in renal prostaglandin synthesis contributed to the decreased renal blood flow.

1. Belldegrun A, *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106:** 817–22.
2. Cochat P, *et al.* Renal effects of continuous infusion of recombinant interleukin-2 in children. *Pediatr Nephrol* 1991; **5:** 33–7.
3. Geertsen PF, *et al.* Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2. *Clin Sci* 1998; **95:** 73–81.

Effects on the skin. Pseudosystemic sclerosis has been reported after use of aldesleukin; a reduction in skin thickening was seen after aldesleukin therapy was stopped and corticosteroids started.[1]

1. Marie I, *et al.* Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. *Br J Dermatol* 2007; **156:** 182–3.

Precautions

Aldesleukin should be given with great care, if at all, to patients with pre-existing cardiac or pulmonary disease, and those with severe renal or hepatic impairment. It should be avoided in patients with CNS metastases or seizure disorders.

Risk factors for toxicity and poor response include restricted physical activity (Eastern Cooperative Oncology Group performance status of 1 or greater), 2 or more metastatic sites, and a period of less than 24 months between diagnosis of primary tumour and consideration for aldesleukin therapy. UK licensed product information states that aldesleukin should not be used to treat metastatic renal cell carcinoma in patients with all three of these risk factors.

Aldesleukin may worsen auto-immune diseases, and should be used with caution in patients with these conditions. Bacterial infections should be adequately treated before beginning therapy. Aldesleukin may increase effusions from serosal surfaces, and these should generally be treated before starting aldesleukin therapy.

Vital signs, blood counts, renal and hepatic function, serum electrolytes, and pulmonary and cardiac function should be monitored before starting treatment and then regularly during therapy.

Activity. For mention of the loss of activity when aldesleukin was given by continuous infusion without albumin, see Stability above.

Inflammatory bowel disease. Two patients with a history of Crohn's disease had a recurrence of the condition when given aldesleukin. It was suggested that interleukin-2 should be contraindicated in such patients.[1]

1. Sparano JA, *et al.* Symptomatic exacerbation of Crohn disease after treatment with high-dose interleukin-2. *Ann Intern Med* 1993; **118:** 617–18.

Psoriasis. Exacerbations of psoriasis developed in 3 patients during therapy with aldesleukin alone or with lymphokine-activated killer cells. The psoriatic symptoms remitted with topical therapy.[1]

1. Lee RE, *et al.* Interleukin 2 and psoriasis. *Arch Dermatol* 1988; **124:** 1811–15.

Interactions

Corticosteroids (which reduce some of the adverse effects of interleukin-2) may also reduce its antineoplastic properties: use together should generally be avoided. The use of iodinated contrast media after aldesleukin therapy may result in symptoms resembling the immediate adverse effects of aldesleukin. Although most events were reported to occur within 2 to 4 weeks of the last dose of aldesleukin, some occurred several months afterward.

Antivirals. For the effect of interleukin-2 on plasma concentrations of *indinavir*, see p.884.

NSAIDs. NSAIDs are effective in preventing or reducing fever and myalgia caused by interleukin-2. However, there is concern that they could exacerbate renal toxicity (see also Effects on the Kidneys, above). Use of *indometacin* in patients receiving interleukin-2 led to more severe weight gain, oliguria, and azotaemia in 1 study.[1] However, *ibuprofen* was used successfully to reduce interleukin-2 toxicity in another study.[2]

1. Sosman JA, *et al.* Repetitive weekly cycles of interleukin-2 II: clinical and immunologic effects of dose, schedule, and addition of indomethacin. *J Natl Cancer Inst* 1988; **80:** 1451–61.
2. Eberlein TJ, *et al.* Ibuprofen causes reduced toxic effects of interleukin 2 administration in patients with metastatic cancer. *Arch Surg* 1989; **124:** 542–7.

Pharmacokinetics

After intravenous bolus, the serum distribution and elimination half-lives of aldesleukin are 13 and 85 minutes, respectively. After subcutaneous doses, the absorption half-life is 45 minutes and the elimination half-life is 5.3 hours, while bioavailability ranges between 35 and 47%.

Aldesleukin is metabolised to amino acids by the kidneys.

◊ References.

1. Anderson PM, Sorenson MA. Effects of route and formulation on clinical pharmacokinetics of interleukin-2. *Clin Pharmacokinet* 1994; **27:** 19–31.
2. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous interleukin-2 in HIV-infected patients. *Pharmacotherapy* 1996; **16:** 754–9.
3. Kirchner GI, *et al.* Pharmacokinetics of recombinant human interleukin-2 in advanced renal cell carcinoma patients following subcutaneous application. *Br J Clin Pharmacol* 1998; **46:** 5–10.

Uses and Administration

Interleukin-2 is a lymphokine which stimulates the proliferation of T-lymphocytes and thus amplifies immune response to an antigen; it also has actions on B-lymphocytes, and induces the production of interferon-γ and the activation of lymphokine-activated killer (LAK) cells and natural killer (NK) cells. Interleukin-2 is used in the immunotherapy of metastatic renal cell carcinoma in selected patients (see p.667). It is also used in metastatic melanoma (p.673), and has been tried in non-Hodgkin's lymphoma and acute myeloid leukaemia.

Interleukin-2 is usually given by intravenous infusion or subcutaneous injection of one of its recombinant forms, such as aldesleukin.

Many dosage regimens have been tried. In the UK, the recommended dose of aldesleukin for metastatic renal cell carcinoma is 18 million units given subcutaneously once daily for 5 days, followed by 2 days rest for the first week. For the next 3 weeks, 18 million units are then given on days 1 and 2 of each week, and 9 million units on days 3 to 5 of each week, followed by 2 days rest. This 4-week cycle may be repeated after an interval of 1 week. Doses may be delayed or reduced if the regimen is not tolerated.

Intravenous infusion of aldesleukin is now rarely used because of an association with capillary leak syndrome (see Adverse Effects and Treatment, above). If it is used, 18 million units/m^2 per 24 hours is given as a continuous intravenous infusion for 5 days, followed by 2 to 6 days of rest. Then another 5 days of infusion is given, followed by 3 weeks of rest. This constitutes one induction cycle; a second cycle may be given after the 3-week rest period of the first cycle. After either subcutaneous or intravenous use, up to 4 maintenance cycles may be given, at 4-week intervals, to patients who respond or whose disease stabilises. In the USA, aldesleukin is given by intravenous infusion for metastatic renal cell carcinoma or metastatic melanoma. The recommended dose is an infusion of 600 000 units/kg over 15 minutes, every 8 hours for up to 14 doses. This 5-day cycle is repeated after 9 days. Further courses may be given at intervals of at least 7 weeks in patients who respond. Doses should be withheld for toxicity.

Aldesleukin given by inhalation is being investigated in the treatment of renal cell carcinoma.

Interleukin-2 has also been given in adoptive immunotherapy with LAK cells or tumour-infiltrating lymphocytes (TIL), which are harvested from the patient, activated *ex vivo*, and then re-infused.

Interleukin-2 is also being tried in patients with HIV infection and AIDS in an attempt to restore immune response (see below) and has been given in some other infections or immune diseases.

Other interleukins are under investigation (see also Interleukin-1, p.2325). Conjugates of interleukin-2 with macrogol (PEG-IL2; pegaldesleukin) have also been investigated and liposome-encapsulated interleukin-2 has also been investigated for the treatment of renal, brain and CNS tumours.

A mixture of naturally occurring cytokines, including interleukins, interferons, chemokines, and colony-stimulating factors (Multikine®) is under investigation for neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck.

◊ Reviews.

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3. Malaguarnera M, *et al.* Use of interleukin-2 in advanced renal carcinoma: meta-analysis and review of the literature. *Eur J Clin Pharmacol* 2001; **57:** 267–73.
4. Atkins MB, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part I: IL-2-based clinical trials. *Med Oncol* 2001; **18:** 197–207.
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10. Petrella T, *et al.* Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. *Cancer Treat Rev* 2007; **33:** 484–96.

HIV infection and AIDS. The immunodeficiency of HIV infection and AIDS (p.856) has been associated with a defect in interleukin-2 production. Interleukin-2 stimulates the proliferation of lymphocytes and activates natural killer cells and a number of studies have therefore examined the potential benefits of adding interleukin-2 to the treatment of patients with HIV infection.[1,2] Following earlier pilot studies, trials of antiretroviral therapy plus interleukin-2 have shown it to produce a much greater increase in CD4 cell counts than antiretroviral therapy alone,[3-7] even where therapy included HAART. Given the efficacy of current therapies, demonstrating additional benefits on survival or disease progression is difficult, although some studies have been undertaken.[1] In the interim, a pooled analysis[8] of earlier results showed a non-significant trend towards improved clinical outcome.

Although teceleukin has been tried[3] most studies of interleukin-2 therapy in HIV have used aldesleukin. Doses and routes have varied: in general doses seem to have ranged from 6 to 18 million units daily by intravenous infusion, or 3 to 30 million units daily subcutaneously, given in most cases for a 5-day cycle every 8 weeks. Subcutaneous dosage appears to be as effective as intravenous,[4,9] is more convenient,[4] and may be less toxic.[10] There is evidence that 5-day dose cycles of 3, 4.5 or 7.5 million units twice daily by subcutaneous injection are effective,[5,6,9,11-13] whereas cycles with a lower dose of 1.5 million units twice daily are not.[5,11,13] A meta-analysis[14] of 3 trials found that subcutaneous doses of 7.5 million units twice daily for 5 days every 8 weeks resulted in greater increases in CD4 cell counts after 3 cycles of therapy than doses of 4.5 million units or 1.5 million units. However, others have reported benefit from a dose as low as 3 million units daily when used with HAART in patients with advanced disease.[15] Continuous low-dose daily therapy appears to accelerate the normalisation of T-cell and natural killer cell concentrations over the course of several months.[10]

Adverse effects are common, particularly at higher doses and with intravenous infusion rather than subcutaneous use.[7,10] However, concerns about a potential stimulant effect on viral replication with a consequent increase in viral load do not seem to have been borne out.[4-7,9] Some studies have reported reduced viral loads in interleukin-treated patients,[6,16] including decreases in hepatitis C viral load in those HIV patients co-infected with hepatitis C.[9,17]

The macrogol conjugate of interleukin-2, PEG-IL2, has also been investigated in this context, but results have been disappointing, since it appears markedly less effective than aldesleukin in stimulating CD4 counts.[4,18]

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2. Temesgen Z. Interleukin-2 for the treatment of human immunodeficiency virus infection. *Drugs Today* 2006; **42:** 791–801.
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4. Levy Y, *et al.* Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial. *Lancet* 1999; **353:** 1923–9.
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9. Tambussi G, *et al.* Efficacy of low-dose intermittent subcutaneous interleukin (IL)–2 in antiviral drug–experienced human immunodeficiency virus–infected persons with detectable virus load: a controlled study of 3 IL-2 regimens with antiviral drug therapy. *J Infect Dis* 2001; **183:** 1476–84.
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11. Davey RT, *et al.* A randomized trial of high- versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection. *J Infect Dis* 1999; **179:** 849–58.
12. David D, *et al.* Rapid effect of interleukin-2 therapy in human immunodeficiency virus–infected patients whose CD4 cell counts increase only slightly in response to combined antiretroviral treatment. *J Infect Dis* 2001; **183:** 730–5.
13. Ruxrungtham K, *et al.* A randomized, controlled 24-week study of intermittent subcutaneous interleukin-2 in HIV-1 infected patients in Thailand. *AIDS* 2000; **14:** 2509–13.
14. Arduino RC, *et al.* CD4 cell response to 3 doses of subcutaneous interleukin 2: meta-analysis of 3 Vanguard studies. *Clin Infect Dis* 2004; **39:** 115–22.
15. Arnó A, *et al.* Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ≤250/microlitre CD4 T cells and undetectable plasma virus load. *J Infect Dis* 1999; **180:** 56–60.
16. Lafeuillade A, *et al.* Pilot study of a combination of highly active antiretroviral therapy and cytokines to induce HIV-1 remission. *J Acquir Immune Defic Syndr* 2001; **26:** 44–55.
17. Schlaak JF, *et al.* Sustained suppression of HCV replication and inflammatory activity after interleukin-2 therapy in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr* 2002; **29:** 145–8.
18. Carr A, *et al.* Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in human immunodeficiency virus-infected patients: a randomized, controlled, multicenter study. *J Infect Dis* 1998; **178:** 992–9.

Postherpetic neuralgia. A 46-year-old HIV patient with chronic, treatment-resistant postherpetic neuralgia (p.9) received 1 cycle of subcutaneous interleukin-2 (7.5 million units twice daily for 5 consecutive days) within the context of a clinical HIV study. He reported immediate resolution of his postherpetic neuralgia, and no recurrence of pain occurred during 3 years of follow-up.[1]

1. Rotty J, *et al.* Interleukin-2: a potential treatment option for postherpetic neuralgia? *Clin Infect Dis* 2006; **43:** e109–e110.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ilgen; Proleukin; ***Austral.:*** Proleukin†; ***Austria:*** Proleukin; ***Belg.:*** Proleukin; ***Braz.:*** Proleukin; ***Canad.:*** Proleukin; ***Cz.:*** Proleukin; ***Denm.:*** Pro-

leukin; ***Fr.:*** Proleukin; ***Ger.:*** Proleukin; ***Gr.:*** Proleukin; ***Hong Kong:*** Proleukin; ***Hung.:*** Proleukin; ***Irl.:*** Proleukin; ***Israel:*** Proleukin; ***Ital.:*** Proleukin; ***Jpn:*** Celeuk; Imunace; ***Mex.:*** Proleukin; ***Neth.:*** Proleukin; ***NZ:*** Proleukin; ***Pol.:*** Proleukin; ***Port.:*** Proleukin; ***Rus.:*** Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.:*** Chiron IL-2; ***Singapore:*** Proleukin†; ***Spain:*** Proleukin; ***Switz.:*** Proleukin; ***Turk.:*** Proleukin; ***UK:*** Proleukin; ***USA:*** Proleukin.

Ipilimumab *(USAN, rINN)*

Ipilimumabum; MDX-010; MDX-CTLA-4. Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

Ипилимумаб

CAS — 477202-00-9.

Profile

Ipilimumab is an antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is under investigation for the treatment of melanoma and various solid tumours. Adverse effects include enterocolitis, hypophysitis, dermatitis, arthritis, uveitis, hepatitis, nephritis, and aseptic meningitis.

◊ References.

1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24:** 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12:** 864–72.

Iratumumab *(USAN, rINN)*

Iratumumabum; MDX-060. Immunoglobulin G1, anti-(tumor necrosis factor ligand superfamily member 8 (CD30 ligand)) (human monoclonal MDX-060 heavy chain), disulfide with human monoclonal MDX-060 light chain, dimer.

Иратумумаб

CAS — 640735-09-7.

Profile

Iratumumab is an anti-CD30 monoclonal antibody that is under investigation for the treatment of Hodgkin's disease. Reported adverse effects include a rise in liver transaminases, and acute respiratory distress syndrome.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekanhydroklorid; U-101440E. (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

Иринотекана Гидрохлорид

$C_{33}H_{38}N_4O_6,HCl,3H_2O = 677.2.$

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.

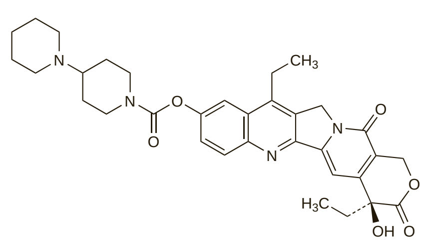

(irinotecan)

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Anaemia also occurs and, less commonly, thrombocytopenia. Gastrointestinal disturbances are common: acute diarrhoea, occurring within 24 hours of a dose, may be part of a cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, and miosis. These symptoms can be controlled with atropine. However a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Other adverse effects include nausea and vomiting, weakness, alopecia, and skin reactions. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions, interstitial pneumonia, pneumonitis, intestinal perforation, pancreatitis, muscular contraction or cramps, and paraesthesia.

Irinotecan should not be given to patients with inflammatory bowel disease. The risk of diarrhoea may be increased in the elderly and in patients who have had radiotherapy to the abdomen or pelvis. Radiotherapy also increases the risk of myelosuppression. Blood counts should be monitored weekly and liver function tests should be regularly performed.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, below).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, below.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients experiencing this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; **18:** 237.
2. Yang X, *et al.* Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; **12:** 1343–58.
3. Rothenberg ML, *et al.* Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; **19:** 3801–7.
4. Saliba F, *et al.* Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; **16:** 2745–51.
5. Lenfers BHM, *et al.* Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; **10:** 1251–3.
6. Savarese D, *et al.* Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; **18:** 450–1.
7. Ychou M, *et al.* Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; **23:** 143–8.
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9. Michael M, *et al.* Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; **22:** 4410–17.
10. Govindarajan R, *et al.* Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356:** 566–7.
11. Kehrer DFS, *et al.* Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; **7:** 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; while heterozygous patients may also be at risk, results of studies have been variable and such patients may tolerate normal initial doses of irinotecan. However, the most appropriate dose reduction in the homozygous population is not known. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m^2 daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity.

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44:** 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47:** 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22:** 1382–8.
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5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24:** 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24:** 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25:** 2594–2600.

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94:** 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 144–5.

3. Ledermann JA, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 145–6.
4. Van Cutsem E, *et al.* Toxicity of irinotecan in patients with colorectal cancer. *N Engl J Med* 2001; **345:** 1351–2.
5. Falcone A, *et al.* Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients. *J Clin Oncol* 2001; **19:** 3456–62.

Smoking. A study found that tobacco smoking significantly affected the pharmacokinetics and toxicity of irinotecan.[1] Clearance of irinotecan was faster in smokers, and systemic exposure to the active metabolite SN-38 (see Pharmacokinetics, below) was almost 40% lower in smokers. This effect probably contributed to the significantly lower haematological toxicity seen in smokers; no significant difference in diarrhoea was seen between smokers and non-smokers. Smoking may induce cytochrome P450 isoenzyme CYP3A, or possibly affect carboxylesterase activity. The study did not determine an effect of smoking on the outcome of treatment with irinotecan. However, smokers may need a higher dose of irinotecan relative to non-smokers, since the lower exposure to irinotecan and SN-38 may indicate a potential risk of treatment failure.

1. van der Bol JM, *et al.* Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* 2007; **25:** 2719–26.

Thalidomide. A pharmacokinetic study found that the metabolism of irinotecan to SN-38 was significantly decreased by thalidomide. Despite reports of reduced gastrointestinal toxicity when these 2 drugs were given together (see Effects on the Gastrointestinal System, above), 3 out of 19 patients enrolled in the study had severe delayed diarrhoea after being given irinotecan with thalidomide.[1]

1. Allegrini G, *et al.* Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation. *Cancer Chemother Pharmacol* 2006; **58:** 585–93.

Pharmacokinetics

Irinotecan exhibits biphasic or triphasic pharmacokinetics, with a terminal half-life of about 14 hours. After intravenous doses it is hydrolysed by carboxylesterase in body tissues to active SN-38 (7-ethyl-10-hydroxycamptothecin). SN-38 exhibits a biphasic elimination profile with a terminal half-life of about 14 hours. Plasma protein binding for irinotecan and SN-38 is about 65% and 95%, respectively. SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is also partly metabolised by cytochrome P450 isoenzymes CYP3A4 and perhaps CYP3A5. More than 50% of an intravenous dose of irinotecan is excreted as unchanged drug, with about 30% in the faeces via the bile and about 20% in the urine.

◊ References.

1. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet* 1997; **33:** 245–59.
2. Rivory LP. Metabolism of CPT-11: impact on activity. *Ann N Y Acad Sci* 2000; **922:** 205–15.
3. Mathijssen RH, *et al.* Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res* 2001; **7:** 2182–94.
4. Ma MK, McLeod HL. Lessons learned from the irinotecan metabolic pathway. *Curr Med Chem* 2003; **10:** 41–9.
5. Smith NF, *et al.* Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicol In Vitro* 2006; **20:** 163–75.

Uses and Administration

Irinotecan is a semisynthetic derivative of the alkaloid camptothecin, obtained from the shrub *Camptotheca acuminata*. The camptothecin derivatives are inhibitors of the enzyme topoisomerase I and thus interfere with the coiling and uncoiling of DNA during replication and prevent nucleic acid synthesis. This action is specific for S phase.

Irinotecan is used, alone or with fluorouracil-based chemotherapy, in the treatment of colorectal cancer (p.665). It is also indicated for use with cetuximab in the treatment of EGFR-expressing metastatic colorectal cancer, after the failure of other regimens containing irinotecan. It has been tried in the management of other solid tumours including those of the lung (p.668).

It is given as the hydrochloride, by intravenous infusion, in at least 250 mL of glucose 5%, or sodium chloride 0.9%. In the treatment of refractory colorectal malignancies one suggested single-agent dose regimen is irinotecan hydrochloride 125 mg/m^2 infused over 90 minutes once a week for 4 weeks, followed by a 2-week rest period. Additional courses may be given if required, with doses modified according to toxicity. Another regimen requires an initial dose of 350 mg/m^2 over 30 to 90 minutes repeated every 3 weeks and adjusted according to toxicity (for dosage in hepatic impairment, see below).

For the suggestion that initial doses should be modified to reduce toxicity in those with certain genotypes, see Genetic Factors, above.

Irinotecan may also be given as part of a regimen with fluorouracil and folinic acid in the first-line treatment of metastatic colorectal cancer. Numerous regimens exist. The irinotecan hydrochloride component of the course may be given at a dose of 180 mg/m^2 over 30 to 90 minutes every 2 weeks. Alternatively, 125 mg/m^2 may be given weekly, usually on days 1, 8, 15, and 22 of a 42-day cycle. (For reference to toxicity from such regimens see under Interactions, above.)

Treatment cycles may be continued indefinitely as long as patients continue to benefit.

In the treatment of EGFR-expressing metastatic colorectal cancer, when used with cetuximab, irinotecan is given usually at the same dose as was used in the last cycles of the previous irinotecan-containing regimen; irinotecan should not be given for at least 1 hour after the end of the cetuximab infusion.

A formulation of irinotecan with hyaluronic acid is being developed.

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1. Douillard JY, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355:** 1041–7. Correction. *ibid.*; 1372.
2. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
3. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions—colorectal cancer and beyond. *Oncologist* 2001; **6:** 66–80.
4. Saltz LB, *et al.* Irinotecan plus fluorouracil/leucovorin for metastatic colorectal cancer: a new survival standard. *Oncologist* 2001; **6:** 81–91.
5. Cunningham D, *et al.* Optimizing the use of irinotecan in colorectal cancer. *Oncologist* 2001; **6** (suppl 4): 17–23.
6. Vanhoefer U, *et al.* Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol* 2001; **19:** 1501–18.
7. Douillard JY, *et al.* Update on European adjuvant trials with irinotecan for colorectal cancer. *Oncology (Huntingt)* 2002; **16** (suppl 3): 13–15.
8. Ulukan H, Swaan PW. Camptothecins: a review of their chemotherapeutic potential. *Drugs* 2002; **62:** 2039–57.
9. Pizzolato JF, Saltz LB. The camptothecins. *Lancet* 2003; **361:** 2235–42.
10. Glimelius B. Benefit-risk assessment of irinotecan in advanced colorectal cancer. *Drug Safety* 2005; **28:** 417–33.
11. Fuchs C, *et al.* Irinotecan in the treatment of colorectal cancer. *Cancer Treat Rev* 2006; **32:** 491–503.
12. Sato T, *et al.* Treatment of advanced or recurrent colorectal cancer with irinotecan in Japan and elsewhere. *Expert Opin Pharmacother* 2008; **9:** 1223–8.

Administration in hepatic impairment. In patients with hyperbilirubinaemia, the clearance of irinotecan is decreased, exposure to the active metabolite SN-38 is increased, and the risk of haematological toxicity is increased. US licensed product information recommends a reduction in the initial dose of irinotecan for those patients with increased bilirubin concentrations. However, doses in patients with bilirubin greater than 2 mg/100 mL cannot be determined due to insufficient data.

In the UK, licensed product information recommends the following dosage reduction for monotherapy regimens in which irinotecan hydrochloride is normally given at 350 mg/m^2 every 3 weeks (see Uses and Administration, above):

- in patients with bilirubin up to 1.5 times the upper limit of normal range (ULN), no dosage reduction is considered necessary and irinotecan hydrochloride 350 mg/m^2 is recommended;
- in patients with bilirubin ranging from 1.5 to 3 times the ULN, irinotecan hydrochloride 200 mg/m^2 may be given;
- in patients with bilirubin over 3 times the ULN, the use of irinotecan is not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Biotecan; Camptosar; CPT†; Efixano; Irenax; Irinogen; Itoxaril; Kebirtecan; Pipetecan; Satigene; Sibudan; Trinotecan; Winol; ***Austral.:*** Camptosar; ***Austria:*** Campto; ***Belg.:*** Campto; ***Braz.:*** Biotecan; Camptosar; Irenax; Tecnotecan; ***Canad.:*** Camptosar; ***Chile:*** Camptosar; Linatecan; ***Cz.:*** Campto; Canri; ***Denm.:*** Campto; ***Fin.:*** Campto; ***Fr.:*** Campto; ***Ger.:*** Campto; ***Gr.:*** Campto; ***Hong Kong:*** Campto; ***Hung.:*** Campto; ***India:*** Irinotel; ***Indon.:*** Campto; ***Irl.:*** Campto; ***Israel:*** Campto; ***Ital.:*** Campto; ***Malaysia:*** Campto; ***Mex.:*** Camptosar; Daritex A; Terican; ***Neth.:*** Campto; ***Norw.:*** Campto; ***NZ:*** Camptosar; ***Philipp.:*** Campto; ***Pol.:*** Campto; ***Port.:*** Campto; Faultenocan; ***Rus.:*** Campto (Кампто); Iriten (Иритен); Irnocam (Ирнокам); ***S.Afr.:*** Campto; ***Singapore:*** Campto; ***Spain:*** Campto; ***Swed.:*** Campto; ***Switz.:*** Campto; ***Thai.:*** Campto; Irinotel; ***Turk.:*** Campto; ***UK:*** Campto; ***USA:*** Camptosar; ***Venez.:*** Camptosar; Elinatecan.

Ixabepilone *(USAN, rINN)*

Azaepothilone B; BMS-247550-01; Ixabepilona; Ixabépilone; Ixabepilonum. (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.
Иксабепильон
$C_{27}H_{42}N_2O_5S$ = 506.7.
CAS — 219989-84-1.
ATC — L01DC04.
ATC Vet — QL01DC04.

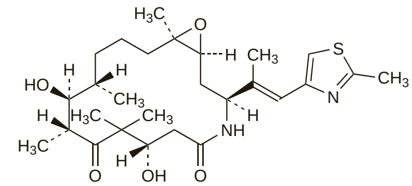

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Peripheral neuropathy is common with ixabepilone, and dose reduction, or delaying or stopping treatment may be necessary (see Uses and Administration, below). Dose-dependent myelosuppression can occur, manifested mainly as neutropenia; febrile neutropenia and fatalities have been reported. Frequent blood counts are recommended. Ixabepilone is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance; patients should be premedicated with a histamine H_1- and histamine H_2-antagonist about 1 hour before infusion. Therapy should be stopped if a hypersensitivity reaction occurs, and symptomatic treatment given. Subsequent cycles may be given with additional corticosteroid therapy, and extension of the infusion time should be considered.

Other adverse effects include gastrointestinal disturbances, anorexia, myalgia, arthralgia, fatigue, alopecia, insomnia, headache, taste disorders, dizziness, increased lachrymation, dyspnoea, cough, skin rashes, nail disorders, palmar-plantar erythrodysesthesia syndrome, pruritus, skin exfoliation or hyperpigmentation, and hot flushes.

Interactions

Ixabepilone undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to ixabepilone. Conversely, CYP3A4 inducers can reduce exposure to ixabepilone. Use of ixabepilone with strong inhibitors or inducers of CYP3A4 should be avoided. If strong inhibitors are used, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of ixabepilone and should be avoided. St John's wort may decrease plasma concentrations of ixabepilone unpredictably and should also be avoided.

Pharmacokinetics

Ixabepilone is extensively distributed. Plasma protein binding is about 67 to 77%. It is extensively metabolised in the liver, mainly by oxidation via cytochrome P450 isoenzyme CYP3A4. It is eliminated mainly as metabolites; about 86% of a dose is eliminated within 7 days, 65% in faeces, and 21% in the urine. The terminal elimination half-life is reported to be about 52 hours.

Uses and Administration

Ixabepilone is an analogue of the epothilone compound patupilone (p.761) that is used for the treatment of patients with metastatic or locally advanced breast cancer. It is given as monotherapy in those whose tumours are resistant or refractory to anthracyclines, taxanes, and capecitabine. Ixabepilone is also used with capecitabine in those whose tumours are resistant to anthracycline and taxanes, or in those with cancer resistant to taxanes, and for whom further anthracycline therapy is contra-indicated.

The recommended dose of ixabepilone is 40 mg/m^2 given by intravenous infusion over 3 hours every 3 weeks. Patients with a body-surface greater than 2.2 m^2 should be dosed as calculated for 2.2 m^2. Ixabepilone is diluted with lactated Ringer's solution to a final concentration of 200 to 600 micrograms/mL before infusion.

Doses are adjusted for toxicity. If moderate or severe neuropathy, or any severe toxicity (other than neuropathy) occurs, the dose should be decreased by 20%. If severe neuropathy lasts 7 days or more, or any disabling toxicity occurs, therapy should be stopped. If the neutrophil count falls below 500 cells/mm^3 for 7 days or more, if platelets fall below 25 000 cells/mm^3 (or below 50 000 cells/mm^3 with bleeding), or if febrile neutropenia occurs, the dose should be decreased by 20%. If toxicities recur, an additional 20% dose reduction should be made. Patients should not begin a new cycle of treatment unless the neutrophil count is at least 1500 cells/mm^3, the platelet count is at least 100 000 cells/mm^3, and non-haematological toxicities have improved to grade 1 (mild) or resolved.

Doses are also adjusted in hepatic impairment (see Administration in Hepatic Impairment, below).

Use of strong inhibitors of CYP3A4 should be avoided with ixabepilone. If no alternative is available, a dose reduction of ixabepilone to 20 mg/m^2 should be considered. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of ixabepilone is increased back to the original dose.

◊ References.

1. Gianni L. Ixabepilone and the narrow path to developing new cytotoxic drugs. *J Clin Oncol* 2007; **25:** 3389–91.
2. Fornier MN. Ixabepilone, first in a new class of antineoplastic agents: the natural epothilones and their analogues. *Clin Breast Cancer* 2007; **7:** 757–63.
3. Thomas ES, *et al.* Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007; **25:** 5210–17.

Administration in hepatic impairment. Therapy with ixabepilone and capecitabine *combination therapy* is contra-indicated in patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.5 times the upper limit of normal (ULN), or in those with bilirubin greater than the ULN. Patients with values equal to or below these figures may be given the standard dose of ixabepilone.

In *monotherapy*, the following doses of ixabepilone may be given:

- mild; AST and ALT equal to or less than 2.5 times the ULN, and bilirubin equal to or less than the ULN: 40 mg/m^2 *or* AST or ALT equal to or less than 10 times the ULN and bilirubin equal to or less than 1.5 times the ULN: 32 mg/m^2
- moderate; AST and ALT equal to or less than 10 times the ULN and bilirubin greater than 1.5 times the ULN, but equal to or less than 3 times the ULN: patients should be started at 20 mg/m^2, and the dosage in subsequent cycles escalated up to, but not exceeding, 30 mg/m^2 if tolerated
- severe; AST or ALT greater than 10 times the ULN or bilirubin greater than 3 times the ULN: not recommended

Data are limited for patients with a baseline AST or ALT greater than 5 times the ULN.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ixempra.

Lapatinib Tosilate *(rINNM)*

GW-572016F; Lapatinib Ditosylate *(USAN)*; Lapatinib, Tosilate de; Lapatinibi Tosilas; Tosilato de lapatinib. *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)furan-2-yl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate.

Лапатиниба Тозилат

$C_{29}H_{26}ClFN_4O_4S,2C_7H_8O_3S,H_2O$ = 943.5.

CAS — 231277-92-2 (lapatinib); 388082-78-8 (lapatinib tosilate).

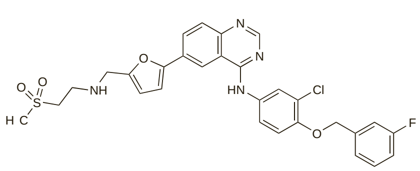

(lapatinib)

Adverse Effects, Treatment, and Precautions

The most common adverse effects of lapatinib tosilate are gastrointestinal disturbances, dermatological reactions such as palmar-plantar erythrodysesthesia and rash, and fatigue. Diarrhoea may be severe and dose-limiting. Decreases in left ventricular ejection fraction (LVEF) have been reported with lapatinib, usually within the first 9 weeks of treatment. LVEF should be evaluated in all patients before therapy is started, and periodically evaluated during treatment. Prolongation of the QT interval has also been reported, and lapatinib should be given with caution to those patients with relevant risk factors such as hypokalaemia or hypomagnesaemia, congenital QT prolongation, use of antiarrhythmics, or cumulative high-dose anthracycline therapy. Other reported adverse effects include stomatitis, mucosal inflammation, pain in extremities, back pain, dyspnoea, and insomnia. Lapatinib should be given with caution in severe hepatic impairment; doses may need to be reduced.

Interactions

Lapatinib tosilate undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to lapatinib. Conversely, CYP3A4 inducers, such as carbamazepine, can reduce exposure to lapatinib. Use of lapatinib with strong inhibitors or inducers of CYP3A4 should be avoided; if they are to be given together, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of lapatinib and should be avoided. *In vitro* studies indicate that lapatinib itself inhibits CYP3A4 and CYP2C8; it should be used cautiously with substrates of these isoenzymes that have a narrow therapeutic index.

Lapatinib is a substrate of P-glycoprotein and P-glycoprotein inhibitors can increase plasma concentrations of lapatinib. Lapatinib itself also inhibits human P-glycoprotein and may in turn increase plasma concentrations of drugs that are substrates of P-glycoprotein.

Pharmacokinetics

Absorption after an oral dose of lapatinib tosilate is variable and incomplete. Peak plasma concentrations occur after about 4 hours. Systemic exposure to lapatinib is increased when it is given with food. It is highly protein bound. Lapatinib undergoes extensive metabolism, mainly by cytochrome P450 isoenzymes CYP3A4 and CYP3A5; CYP2C19 and CYP2C8 account for some minor metabolism. The terminal half-life after a single dose has been reported to be about 14 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. About 27% and 14% of an oral dose is recovered in the faeces, as parent lapatinib and metabolites, respectively; renal excretion is negligible.

Uses and Administration

Lapatinib tosilate is a dual tyrosine kinase inhibitor directed against two members of the human epidermal growth factor receptor family, namely epidermal growth factor receptor (EGFR; ErbB1) and human epidermal receptor type 2 (HER2; ErbB2). Lapatinib is used with capecitabine (p.691) for the treatment of patients with advanced or metastatic breast cancer (p.661) whose tumours overexpress HER2, and who have had previous therapy including an anthracycline, a taxane, and trastuzumab.

Doses of lapatinib tosilate are expressed in terms of the base; lapatinib tosilate 405 mg is equivalent to about 250 mg of lapatinib.

The recommended dose of lapatinib is 1.25 g given orally once daily on days 1 to 21 of a 21-day cycle. Capecitabine is given at a dose of 2 g/m^2 daily (given orally in 2 doses about 12 hours apart) on days 1 to 14 of the cycle. Treatment may be continued until disease progression or unacceptable toxicity occurs. If a daily dose is missed, the next day's dose should not be doubled. Lapatinib is given at least one hour before or one hour after food.

Dosage should be reduced in patients with severe hepatic impairment (see Administration in Hepatic Impairment, below). Treatment with lapatinib should be stopped in patients who develop a decreased left ventricular ejection fraction (LVEF); however, patients may be restarted at a reduced dose of lapatinib 1 g daily after a minimum of 2 weeks if the LVEF recovers to normal and if the patient is asymptomatic. Lapatinib may need to be stopped or treatment interrupted if other severe toxicities develop. Patients can be restarted at the recommended dose when the toxicity improves. However, if toxicity recurs, lapatinib should be restarted at the lower dose of 1 g daily.

If use with potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of lapatinib are considered necessary, based on pharmacokinetic studies. Lapatinib should be given at a dose of 500 mg daily when given with a potent CYP3A4 inhibitor; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the lapatinib dose is increased to the usual recommended dose. When given with a potent inducer of this isoenzyme, the dose of lapatinib should be titrated gradually from 1.25 g daily up to 4.5 g daily, based on tolerability; if the inducer is stopped, the dose of lapatinib should be reduced to the usual recommended dose.

Lapatinib is also under investigation for the treatment of head and neck squamous cell carcinoma.

◊ References.

1. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. *Ann Pharmacother* 2006; **40:** 261–9.
2. Moy B, Goss PE. Lapatinib: current status and future directions in breast cancer. *Oncologist* 2006; **11:** 1047–57.
3. Geyer CE, *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355:** 2733–43.
4. Montemurro F, *et al.* Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Expert Opin Biol Ther* 2007; **7:** 257–68.
5. Ito Y, *et al.* Does lapatinib, a small-molecule tyrosine kinase inhibitor, constitute a breakthrough in the treatment of breast cancer? *Breast Cancer* 2007; **14:** 156–62.
6. Dhillon S, Wagstaff AJ. Lapatinib. *Drugs* 2007; **67:** 2101–8.

Administration in hepatic impairment. Systemic exposure to lapatinib after a single 100-mg oral dose increased by about 14% and 63% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, when compared with healthy control subjects. Caution is advised when lapatinib is given to patients with severe hepatic impairment. Oral doses should be reduced to 750 mg daily. However, licensed product information warns that there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Tykerb; ***Fr.:*** Tyverb; ***Switz.:*** Tyverb; ***UK:*** Tyverb; ***USA:*** Tykerb.

Lenalidomide *(BAN, USAN, rINN)*

CC-5013; CDC-501; Lénalidomide; Lenalidomidum. 3-(4-Amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione.

Леналидомид

$C_{13}H_{13}N_3O_3$ = 259.3.

CAS — 191732-72-6.

ATC — L04AX04.

ATC Vet — QL04AX04.

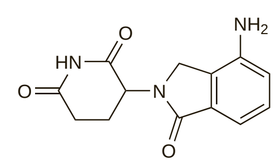

Adverse Effects, Treatment, and Precautions

Lenalidomide is associated with significant neutropenia and thrombocytopenia. Anaemia is also common. Patients may require dose reduction or therapy may need to be delayed or stopped. Full blood counts should be monitored weekly for the first 8 weeks of therapy, and monthly thereafter. There is also an increased risk of deep-vein thrombosis and pulmonary embolism with lenalidomide. Other adverse effects include gastrointestinal disturbances, pruritus, rash, and fatigue. Dyspnoea, muscle cramps, hypotension, tremor, hypoaesthesia, and infections such as pneumonia are common. Peripheral neuropathy has been reported, as have cases of hypothyroidism; thyroid function should be monitored. Cardiac disorders and hepatotoxicity have also been reported. Caution is advised in patients with renal impairment as lenalidomide is excreted via the kidneys.

The symbol † denotes a preparation no longer actively marketed

Because of potential teratogenicity lenalidomide use is restricted in women of child-bearing potential, see also under Thalidomide, p.2397.

Interactions

Lenalidomide may increase peak plasma concentrations of digoxin. Epoetins or other drugs that increase the risk of thrombosis should be used with caution in patients taking lenalidomide.

Pharmacokinetics

Lenalidomide is rapidly absorbed with maximum plasma concentrations occurring between about 0.6 and 1.5 hours after an oral dose. Giving lenalidomide with food may reduce plasma concentrations but not the extent of absorption. Binding to plasma proteins is about 30%. About two-thirds of a dose is eliminated unchanged through the kidneys. The elimination half-life is about 3 hours after a 5 mg-dose; half-life increases with dose. Clearance decreases proportionally with renal function.

Uses and Administration

Lenalidomide is an analogue of thalidomide (p.2397) that has immunomodulatory and antiangiogenic properties. It is given orally for the treatment of patients with transfusion-dependent anaemia due to myelodysplastic syndromes (p.654) associated with certain abnormalities of chromosome 5 (deletion 5q abnormalities). The recommended initial dose is 10 mg daily. Lenalidomide is also used orally with dexamethasone for the treatment of patients with multiple myeloma (p.658) who have received at least one prior therapy. The recommended starting dose of lenalidomide is 25 mg daily, given for 21 days of a 28-day cycle. The recommended oral dose of dexamethasone is 40 mg daily on days 1 to 4, days 9 to 12, and days 17 to 20 of each 28-day cycle, for the first 4 cycles, and then 40 mg daily on days 1 to 4 of each 28-day cycle thereafter.

Lenalidomide is associated with significant neutropenia and thrombocytopenia, and dosage is adjusted according to haematological toxicity.

◊ References.

1. List A, *et al.* Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005; **352:** 549–57.
2. Anderson KC. Lenalidomide and thalidomide: mechanisms of action—similarities and differences. *Semin Hematol* 2005; **42** (suppl 4): S3–S8.
3. Hideshima T, *et al.* Current therapeutic uses of lenalidomide in multiple myeloma. *Expert Opin Invest Drugs* 2006; **15:** 171–9.
4. List A, *et al.* Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006; **355:** 1456–65.
5. Shah SR, Tran TM. Lenalidomide in myelodysplastic syndrome and multiple myeloma. *Drugs* 2007; **67:** 1869–81.
6. Rao KV. Lenalidomide in the treatment of multiple myeloma. *Am J Health-Syst Pharm* 2007; **64:** 1799–1807.
7. Lacy MQ, *et al.* Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc* 2007; **82:** 1179–84.
8. Dimopoulos M, *et al.* Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357:** 2123–32.
9. Weber DM, *et al.* Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357:** 2133–42.
10. Chanan-Khan AA, Cheson BD. Lenalidomide for the treatment of B-cell malignancies. *J Clin Oncol* 2008; **26:** 1544–52.

Administration in renal impairment. Lenalidomide is eliminated mainly via the kidneys as unchanged drug. Clearance decreases as renal function decreases, prolonging the elimination half-life and increasing exposure to the drug. A study recommended that dose adjustments be made for patients with creatinine clearance (CC) less than 50 mL/minute; a 40% reduction to 60% of the starting dose was recommended for these patients. For those with CC less than 30 mL/minute, the reduced dose should be given at extended dosing intervals. About 30% of circulating lenalidomide was removed by a 4-hour session of haemodialysis.[1]

UK licensed product information makes the following recommendations at the start of oral therapy for patients with multiple myeloma and renal impairment:

- mild renal impairment (CC greater than or equal to 50 mL/minute): 25 mg once daily (full dose)
- moderate renal impairment (CC from 30 mL/minute to less than 50 mL/minute): 10 mg once daily. This dose may be increased to 15 mg once daily after 2 cycles if the patient is not responding to treatment, but is tolerating lenalidomide
- severe renal impairment (CC less than 30 mL/minute, not requiring dialysis): 15 mg every other day
- end-stage renal disease (CC less than 30 mL/minute, requiring dialysis): 15 mg, three times weekly, after dialysis

1. Chen N, *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; **47:** 1466–75.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Revlimid; ***Fr.:*** Revlimid; ***Port.:*** Revlimid; ***UK:*** Revlimid; ***USA:*** Revlimid.

Lestaurtinib *(USAN, rINN)*

A-154475.0; CEP-701; KT-5555; Lestaurtinibum; SP-924. (9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,-10,11,12-hexahydro-1*H*-9,12-epoxydiindolo[1,2,3-*fg*:3′,2′,1′-*kl*]-pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one.

Лестауртиниб

$C_{26}H_{21}N_3O_4$ = 439.5.
CAS — 111358-88-4.

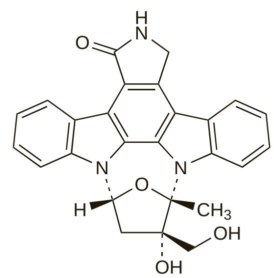

Profile

Lestaurtinib is a tyrosine kinase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

Letrozole *(BAN, USAN, rINN)* ⊗

CGS-20267; Letrotsoli; Letrozol; Létrozole; Letrozolum. 4,4′-(1*H*-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.

Летрозол

$C_{17}H_{11}N_5$ = 285.3.
CAS — 112809-51-5.
ATC — L02BG04.
ATC Vet — QL02BG04.

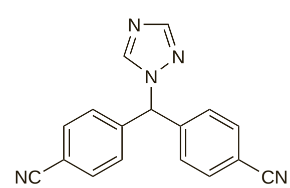

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Letrozole). A white or yellowish, crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol; freely soluble in dichloromethane.

USP 31 (Letrozole). A white to yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

Adverse Effects and Precautions

As for Anastrozole, p.681.

Effects on the musculoskeletal system. Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole therapy.[1]

1. Perez EA, *et al.* Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24:** 3629–35.

Effects on the skin. Toxic epidermal necrolysis, attributed to letrozole, has been reported in a patient with breast cancer who was also receiving dexamethasone and omeprazole.[1] She had been switched from tamoxifen to letrozole a few weeks before the reaction occurred.

1. Chia WK, *et al.* Toxic epidermal necrolysis in patient with breast cancer receiving letrozole. *Lancet Oncol* 2006; **7:** 184–5.

Interactions

Tamoxifen. In a study[1] of postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole plasma concentrations by a mean of about 38%, but the effect of letrozole on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

1. Dowsett M, *et al.* Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999; **5:** 2338–43.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. About 60% of letrozole in the circulation is bound to plasma protein, mainly albumin. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days.

Uses and Administration

Letrozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used in the treatment of advanced or locally advanced breast cancer (p.661) in postmenopausal women. It may be given as neoadjuvant (pre-operative) therapy to those with localised hormone-receptor positive disease, to allow subsequent breast-conserving surgery. Letrozole is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. In postmenopausal women given 5 years of adjuvant tamoxifen for early breast cancer, letrozole may be used as extended adjuvant therapy; treatment should continue for 4 years or until tumour relapse occurs, although optimal duration of therapy is unknown. The usual dose is 2.5 mg daily by mouth.

◊ References.

1. Mouridsen H, *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; **19:** 2596–2606.
2. Buzdar A, *et al.* Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001; **19:** 3357–66.
3. Ellis MJ, *et al.* Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001; **19:** 3808–16.
4. Goss PE, *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349:** 1793–1802.
5. Simpson D, *et al.* Letrozole: a review of its use in postmenopausal women with breast cancer. *Drugs* 2004; **64:** 1213–30.
6. Goss PE, *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97:** 1262–71.
7. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; **353:** 2747–57.
8. Scott LJ, Keam SJ. Letrozole: in postmenopausal hormone-responsive early-stage breast cancer. *Drugs* 2006; **66:** 353–62.
9. Gelmon K. Prescribing extended adjuvant letrozole. *Breast* 2007; **16:** 446–55.
10. Goss PE, *et al.* Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol* 2008; **26:** 1948–55.
11. Muss HB, *et al.* Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol* 2008; **26:** 1956–64.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dosage adjustment of letrozole is required for patients with mild to moderate hepatic impairment (Child-Pugh category A and B). While letrozole is contra-indicated in the UK in severe hepatic impairment (Child-Pugh category C), in the USA, it is recommended that the dose of letrozole be reduced by 50% in those patients with cirrhosis and severe hepatic impairment; the recommended dose for these patients is 2.5 mg given every other day.

Infertility. Letrozole has been investigated[1-4] as an adjunct to assisted reproduction technologies in the management of infertility (p.2080). However, concerns about this unlicensed use have been raised by the Canadian manufacturer (*Novartis, Canad.*) because of the potential for maternal and fetal toxicity, and fetal malformations:[5] licensed product information contra-indicates the use of letrozole in premenopausal women, and there have been reports of congenital anomalies in the infants of women treated with letrozole for infertility.

1. Healey S, *et al.* Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril* 2003; **80:** 1325–9.
2. Al-Fozan H, *et al.* A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004; **82:** 1561–3.
3. Garcia-Velasco JA, *et al.* The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. *Fertil Steril* 2005; **84:** 82–7.
4. Al-Fadhli R, *et al.* A randomized trial of superovulation with two different doses of letrozole. *Fertil Steril* 2006; **85:** 161–4.
5. Novartis, Canada. Health Canada endorsed important safety information: contraindication of Femara (letrozole) in premenopausal women (issued 17th November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/femara_hpc-cps-eng.pdf (accessed 31/07/08)

Preparations

USP 31: Letrozole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cendalon; Fecinole; Femara; Kebirzol; ***Austral.:*** Femara; ***Austria:*** Femara; ***Belg.:*** Femara; ***Braz.:*** Femara; ***Canad.:*** Femara; ***Chile:*** Femara; ***Cz.:*** Femara; ***Denm.:*** Femar; ***Fin.:*** Femar; ***Fr.:*** Femara; ***Ger.:*** Femara; ***Gr.:*** Femara; ***Hong Kong:*** Femara; ***Hung.:*** Femara; ***India:*** Femara; Fempro; Oncolet; Trozet; ***Indon.:*** Femara; ***Irl.:*** Femara; ***Israel:*** Femara; ***Ital.:*** Femara; ***Jpn:*** Femara; ***Malaysia:*** Femara; ***Mex.:*** Femara; ***Neth.:*** Femara; ***Norw.:*** Femar; ***NZ:*** Femara; ***Philipp.:*** Femara; ***Pol.:*** Aromek; Femara; Lametta; ***Port.:*** Femara; ***Rus.:*** Femara (Фемара); ***S.Afr.:*** Femara; ***Singapore:*** Femara; ***Spain:*** Femara; Insegar; ***Swed.:*** Femar; ***Switz.:*** Femara; ***Thai.:*** Femara; ***Turk.:*** Femara; ***UK:*** Femara; ***USA:*** Femara; ***Venez.:*** Femara.

Lobaplatin *(rINN)*

D-19466; Lobaplatine; Lobaplatino; Lobaplatinum. *cis*-[*trans*-1,2-Cyclobutanebis(methylamine)][(*S*)-lactato-*O*¹,*O*¹]platinum.

Лобаплатин

$C_9H_{18}N_2O_3Pt$ = 397.3.

CAS — 135558-11-1.

Profile

Lobaplatin is an analogue of cisplatin (p.698) that has been investigated for its antineoplastic properties. Thrombocytopenia is reported to be dose-limiting. It may be active against some cancer cells resistant to cisplatin or carboplatin.

◊ References.

1. Welink J, *et al.* Pharmacokinetics and pharmacodynamics of lobaplatin (D-19466) in patients with advanced solid tumors, including patients with impaired renal or liver function. *Clin Cancer Res* 1999; **5:** 2349–58.
2. McKeage MJ. Lobaplatin: a new antitumour platinum drug. *Expert Opin Invest Drugs* 2001; **10:** 119–28.
3. Anonymous. Lobaplatin: D 19466. *Drugs R D* 2003; **4:** 369–72.

Lomustine *(BAN, USAN, rINN)*

CCNU; Lomustiini; Lomustin; Lomustina; Lomustinas; Lomustinum; Lomustyna; Lomusztin; NSC-79037; RB-1509; WR-139017. 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.

Ломустин

$C_9H_{16}ClN_3O_2$ = 233.7.

CAS — 13010-47-4.

ATC — L01AD02.

ATC Vet — QL01AD02.

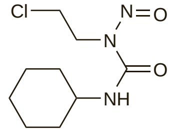

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lomustine). A yellow, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Carmustine, p.694. Neurological reactions such as confusion and lethargy have been reported.

Handling and disposal. A method for the destruction of lomustine *waste* by reaction with hydrobromic acid in glacial acetic acid has been described.[1] The residue produced by the degradation of lomustine by this method showed no mutagenicity. This method is not suitable for the degradation of carmustine or semustine.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.

Overdosage. A patient who inadvertently received 200 mg of lomustine for 7 days instead of a single 200-mg dose developed pancytopenia and subsequent multiorgan dysfunction including liver dysfunction, abdominal pain, pulmonary toxicity with tachypnoea and hypoxaemia, and CNS toxicity leading to confusion and disorientation.[1] Although the white cell count recovered other signs of toxicity did not and the patient developed fever and hypotension and died 59 days after the initial dose of lomustine. In another case of accidental overdose, a 30-year old female received a cumulative dose of 28 mg/kg over 7 days.[2] Severe myelosuppression developed soon after the overdose and lasted for 50 days. The patient was treated with granulocyte colony-stimulating factor and antibacterial cover, norethisterone (to prevent menstruation), and acetylcysteine (to protect against organ toxicity). Gastrointestinal necrosis occurred, and liver enzymes remained elevated even after recovery from the overdose, but the patient survived and her tumour regressed without further chemotherapy.

1. Trent KC, *et al.* Multiorgan failure associated with lomustine overdose. *Ann Pharmacother* 1995; **29:** 384–6.
2. Abele M, *et al.* CCNU overdose during PCV chemotherapy for anaplastic astrocytoma. *J Neurol* 1998; **245:** 236–8.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Cimetidine. For a report of a possible interaction between lomustine and cimetidine, see under Carmustine, p.695.

Theophylline. Leucopenia and thrombocytopenia in a 45-year-old woman were believed to have been secondary to an interaction between theophylline and lomustine.[1]

1. Zeltzer PM, Feig SA. Theophylline-induced lomustine toxicity. *Lancet* 1979; **ii:** 960–1.

Pharmacokinetics

Lomustine is absorbed from the gastrointestinal tract and is rapidly metabolised, with peak plasma concentrations of metabolites occurring within 4 hours of an oral dose. Metabolites have a prolonged plasma half-life reported to range from 16 to 48 hours. Active metabolites readily cross the blood-brain barrier and appear in the CSF in concentrations higher than those in plasma. About half a dose is excreted as metabolites in the urine within 24 hours and about 75% is excreted within 4 days.

Uses and Administration

Lomustine is a nitrosourea with actions and uses similar to those of carmustine (p.695). It has been used in the treatment of brain tumours (p.660) and resistant or relapsed Hodgkin's disease and other lymphomas (p.655), and also lung cancer (p.668), malignant melanoma (p.673), and various solid tumours.

When given as a single agent, lomustine is licensed for oral use in adults and children as a single dose of 120 to 130 mg/m²; division of the dose over 3 consecutive days may reduce gastrointestinal effects. A dose of 100 mg/m² should be given to patients with compromised bone-marrow function. Doses are also generally reduced when lomustine is given as part of a combination regimen. Providing blood counts have returned to acceptable levels, doses may be repeated every 6 to 8 weeks, and should be adjusted according to the haematological response (see also Bone-marrow Depression, p.639).

Preparations

BP 2008: Lomustine Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: CeeNU; ***Austral.:*** CeeNU; ***Braz.:*** Citostal; ***Canad.:*** CeeNU; ***Chile:*** CeeNU; ***Cz.:*** CeeNU; ***Ger.:*** Cecenu; ***Hong Kong:*** CeeNU; ***Israel:*** CeeNU†; ***Malaysia:*** CeeNU†; ***Mex.:*** CeeNU; ***Neth.:*** Belustine; ***NZ:*** CeeNU; ***Philipp.:*** CeeNU; ***S.Afr.:*** CeeNU; ***Singapore:*** CeeNU†; ***Switz.:*** Prava; ***UK:*** CCNU; ***USA:*** CeeNU.

Lonidamine *(BAN, rINN)*

AF-1890; Diclondazolic Acid; Lonidamina; Lonidaminum; TH-070. 1-(2,4-Dichlorobenzyl)indazole-3-carboxylic acid.

Лонидамин

$C_{15}H_{10}Cl_2N_2O_2$ = 321.2.

CAS — 50264-69-2.

ATC — L01XX07.

ATC Vet — QL01XX07.

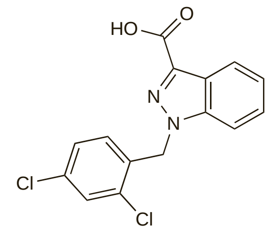

Profile

Lonidamine is an antineoplastic that is thought to act by inhibiting mitochondrial function in tumour cells. It has been given orally in the treatment of various solid neoplasms, including those of the lung, breast, prostate, and brain.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Doridamina†.

Mafosfamide *(rINN)*

Mafosfamid; Mafosfamida; Mafosfamidi; Mafosfamidum. (±)-2-({2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-4-yl}thio)ethanesulphonic acid *P-cis* oxide.

Мафосфамид

$C_9H_{19}Cl_2N_2O_5PS_2$ = 401.3.

CAS — 88859-04-5.

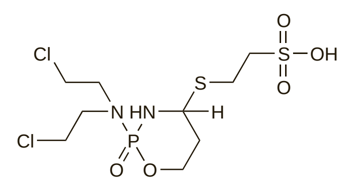

Profile

Mafosfamide is a derivative of cyclophosphamide (p.702) that has been used to treat bone marrow for transplantation. It is also under investigation in the treatment of neoplastic meningitis.

Marimastat *(BAN, USAN, rINN)*

BB-2516; Marimastatum. (2*S*,3*R*)-3-{(*S*)-[2,2-Dimethyl-1-(methylcarbamoyl)propyl]carbamoyl}-2-hydroxy-5-methylhexanohydroxamic acid.

Маримастат

$C_{15}H_{29}N_3O_5$ = 331.4.

CAS — 154039-60-8.

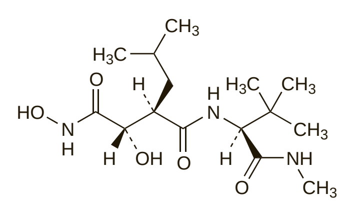

Profile

Marimastat is an oral inhibitor of matrix metalloproteinases, enzymes which are thought to play a role in the metastasis of cancer cells. It has been investigated in various malignant disorders.

Masoprocol *(USAN, rINN)*

CHX-10; CHX-100; Masoprocolum; Mesonordihydroguaiaretic Acid; *meso*-NDGA. *meso*-4,4′-(2,3-Dimethyltetramethylene)-dipyrocatechol.

Мазопрокол

$C_{18}H_{22}O_4$ = 302.4.

CAS — 27686-84-6.

ATC — L01XX10.

ATC Vet — QL01XX10.

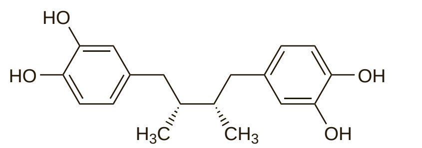

Profile

Masoprocol is a 5-lipoxygenase inhibitor isolated from the chaparral or creosote bush, *Larrea tridentata* (p.2280). It is reported to have antineoplastic activity. It has been used in the topical treatment of actinic (solar) keratoses. Local irritation and contact dermatitis have occurred.

Melanoma Vaccines

ATC — L03AX12.

Profile

A number of therapeutic vaccines designed to stimulate an antibody response are being developed for the treatment of melanoma (p.673).

One available preparation contains melanoma lysate (*Melacine*; *Schering, Canada*). It is used intramuscularly in a regimen with cyclophosphamide for the treatment of metastatic disease. Patients who show a clinical response may continue the melanoma vaccine as maintenance therapy. Adverse effects include injection site reactions such as granuloma formation, gastrointestinal disturbances, flu-like syndrome, and hypersensitivity reactions.

Other potential melanoma vaccines may be based on whole cells, GM2 ganglioside, heat shock proteins, or autologous tumour cells conjugated to an immunogenic hapten.

◊ Reviews.

1. Kim CJ, *et al.* Immunotherapy for melanoma. *Cancer Control* 2002; **9:** 22–30.
2. Minev BR. Melanoma vaccines. *Semin Oncol* 2002; **29:** 479–93.
3. Parmiani G, *et al.* Immunotherapy of melanoma. *Semin Cancer Biol* 2003; **13:** 391–400.
4. Sondak VK, Sosman JA. Results of clinical trials with an allogenic melanoma tumor cell lysate vaccine: Melacine. *Semin Cancer Biol* 2003; **13:** 409–15.
5. Castelli C, *et al.* Heat shock proteins: biological functions and clinical application as personalized vaccines for human cancer. *Cancer Immunol Immunother* 2004; **53:** 227–33.
6. Komenaka I, *et al.* Immunotherapy for melanoma. *Clin Dermatol* 2004; **22:** 251–65.
7. Oki Y, Younes A. Heat shock protein-based cancer vaccines. *Expert Rev Vaccines* 2004; **3:** 403–11.
8. Elliott B, Dalgleish A. Melanoma vaccines. *Hosp Med* 2004; **65:** 668–73.
9. Bystryn JC, Reynolds SR. Melanoma vaccines: what we know so far. *Oncology (Williston Park)* 2005; **19:** 97–108.
10. Saleh F, *et al.* Melanoma immunotherapy: past, present, and future. *Curr Pharm Des* 2005; **11:** 3461–73.
11. Lens M. The role of vaccine therapy in the treatment of melanoma. *Expert Opin Biol Ther* 2008; **8:** 315–23.
12. Rosenthal R, *et al.* Active specific immunotherapy phase III trials for malignant melanoma: systematic analysis and critical appraisal. *J Am Coll Surg* 2008; **207:** 95–105.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Melacine†.

Melphalan *(BAN, USAN, rINN)*

CB-3025; Melfalaani; Melfalán; Melfalan; Melphalanum; NSC-8806 (melphalan hydrochloride); PAM; Phenylalanine Mustard; Phenylalanine Nitrogen Mustard; L-Sarcolysine; WR-19813. 4-Bis(2-chloroethyl)amino-L-phenylalanine.

Мелфалан

$C_{13}H_{18}Cl_2N_2O_2$ = 305.2.

CAS — 148-82-3 (melphalan); 3223-07-2 (melphalan hydrochloride).

ATC — L01AA03.

ATC Vet — QL01AA03.

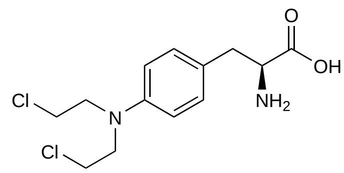

NOTE. Merphalan (CB-3007; NSC-14210; sarcolysine) is the racemic form of melphalan; Medphalan (CB-3026; NSC-35051) is the D-isomer of melphalan.

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Melphalan). A white or almost white powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Protect from light.

USP 31 (Melphalan). An off-white to buff powder with a faint odour. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol; soluble in dilute mineral acids. Store in airtight, glass containers. Protect from light.

Stability. A study of the stability of melphalan 40 and 400 micrograms/mL in infusion fluids reported that the time for a 10% loss of drug at 20° in sodium chloride 0.9% injection was 4.5 hours, compared with 2.9 hours in lactated Ringer's injection, which has a considerably lower chloride ion content, and only 1.5 hours in glucose 5% injection.[1] At 25° the corresponding figures were 2.4, 1.5, and 0.6 hours, and at 37° they were 0.6, 0.4, and 0.3 hours. It was concluded that melphalan is sufficiently stable at 20° in sodium chloride injection to permit infusion, but that increased temperature and decreased chloride ion concentration were associated with faster degradation rates.[1] Another study recommended that solutions of melphalan be handled at temperatures above 5° for the minimum time but found that a solution containing 20 micrograms/mL in sodium chloride 0.9% could be stored for at least 6 months at –20° without significant deterioration.[2] A more recent study, while recommending storage at 4° between preparation and use of the infusion, considered that giving it at a room temperature of 20° or below, and use of hypertonic (3%) saline as a diluent, would be sufficient to allow prolonged infusion.[3] The practicalities of such a procedure were not addressed.

1. Tabibi SE, Cradock JC. Stability of melphalan in infusion fluids. *Am J Hosp Pharm* 1984; **41:** 1380–2.
2. Bosanquet AG. Stability of melphalan solutions during preparation and storage. *J Pharm Sci* 1985; **74:** 348–51.
3. Pinguet F, *et al.* Effect of sodium chloride concentration and temperature on melphalan stability during storage and use. *Am J Hosp Pharm* 1994; **51:** 2701–4.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p.635 and p.639.

The onset of neutropenia and thrombocytopenia is variable; the nadir of bone-marrow depression usually occurs at 2 to 3 weeks after starting treatment with melphalan, with recovery after 4 to 5 weeks.

Skin rashes and hypersensitivity reactions, including anaphylaxis, may occur. Cardiac arrest has been reported in association with such effects. Gastrointestinal disturbances may sometimes occur, particularly at high doses where diarrhoea, vomiting, and stomatitis may become dose-limiting. Haemolytic anaemia, vasculitis, pulmonary fibrosis, and hepatic disorders including hepatitis and jaundice have been reported. Suppression of ovarian function is common in premenopausal women; temporary or permanent sterility may occur in male patients. Extravasation of melphalan injection can cause skin ulceration and necrosis. As with other alkylating agents, melphalan also has carcinogenic, mutagenic, and teratogenic potential.

Mucositis. Amifostine has been shown to reduce the frequency and severity of melphalan-induced oral mucositis.[1]

1. Spencer A, *et al.* Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplant* 2005; **35:** 971–7.

Overdosage. A 12-month old child given melphalan 140 mg intravenously (a tenfold overdose) developed pronounced lymphopenia within 24 hours but had no other significant adverse effects until the seventh day, when neutropenia, thrombocytopenia, oral ulceration, and diarrhoea developed.[1] Bone marrow recovered within 40 days. Treatment was by vigorous hyperalimentation and close surveillance during this period and the patient subsequently remained well 9 months afterwards, without complications. Cases of intravenous melphalan overdose have also been reported in adults,[2] resulting in bone-marrow depression, haemorrhagic diarrhoea, and electrolyte disturbances. Bone-marrow depression has also been reported after cumulative oral doses of 360 mg over 3 weeks,[3] and 560 mg over 2 weeks.[4] Filgrastim was used in one of these cases to stimulate bone-marrow recovery.[4]

1. Coates TD. Survival from melphalan overdose. *Lancet* 1984; **ii:** 1048.
2. Jost LM. Überdosierung von Melphalan (Alkeran): Symptome und Behandlung: eine Übersicht. *Onkologie* 1990; **13:** 96–101.
3. Grimes DJ, *et al.* Complete remission of paraproteinaemia and neuropathy following iatrogenic oral melphalan overdose. *Br J Haematol* 1993; **83:** 675–7.
4. Jirillo A, *et al.* Accidental overdose of melphalan per os in a 69-year-old woman treated for advanced endometrial carcinoma. *Tumori* 1998; **84:** 611.

Precautions

For general discussions see Antineoplastics, p.641.

Care is required in patients with impaired renal function.

Handling and disposal. *Urine and faeces* produced for up to 48 hours and 7 days respectively after a dose of melphalan by mouth should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

Use of nalidixic acid with high-dose intravenous melphalan in children has resulted in fatal haemorrhagic enterocolitis.

Ciclosporin. For reference to enhanced toxicity when melphalan was given with ciclosporin, see under Ciclosporin, p.1826.

Food. The bioavailability of oral melphalan is significantly reduced, by up to 45%, by food. Some recommend that melphalan should not be taken with food, and that if dosage is switched from after to before food patients should be monitored for increased toxicity.[1]

1. Nathan C, Betmouni R. Melphalan: avoid with food. *Pharm J* 1996; **257:** 264.

Interferons. The fever induced by interferon alfa resulted in a reduction in the area under the plasma concentration-time curve for melphalan in a study of 10 patients, although the peak plasma concentration and time to peak concentration were not affected.[1] The effect was thought to represent increased chemical reactivity of melphalan at the elevated temperature.

1. Ehrsson H, *et al.* Oral melphalan pharmacokinetics: influence of interferon-induced fever. *Clin Pharmacol Ther* 1990; **47:** 86–90.

Pharmacokinetics

Absorption of melphalan from the gastrointestinal tract is variable; the mean bioavailability is reported to be 56% but it may range from 25 to 89%. Absorption is reduced by the presence of food (see above). On absorption it is rapidly distributed throughout body water with a volume of distribution of about 0.5 litres/kg, and has been reported to be inactivated mainly by spontaneous hydrolysis. About 60 to 90% is bound to plasma proteins, mainly albumin. The terminal plasma half-life of melphalan has been reported to be of the order of 30 to 150 minutes. Melphalan is excreted in the urine, about 10% as unchanged drug.

◊ References.

1. Nath CE, *et al.* Melphalan pharmacokinetics in children with malignant disease: influence of body weight, renal function, carboplatin therapy and total body irradiation. *Br J Clin Pharmacol* 2005; **59:** 314–24.
2. Nath CE, *et al.* Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2007; **64:** 151–64.
3. Padussis JC, *et al.* Pharmacokinetics and drug resistance of melphalan in regional chemotherapy: ILP versus ILI. *Int J Hyperthermia* 2008; **24:** 239–49.

Uses and Administration

Melphalan is an antineoplastic that acts as a bifunctional alkylating agent. It is used mainly in the treatment of multiple myeloma. Melphalan has also been given to patients with carcinoma of the breast and ovary, neuroblastoma, Hodgkin's disease, and in polycythaemia vera, and has been given by intra-arterial regional perfusion for malignant melanoma and soft-tissue sarcomas. See also the cross-references given below. Melphalan is also used in the treatment of amyloidosis, see below.

Melphalan is usually given orally as a single daily dose or in divided doses; it is also given intravenously as the hydrochloride. Doses are calculated in terms of the base; 1.12 mg of melphalan hydrochloride is equivalent to about 1 mg of melphalan. Frequent blood counts are essential and dosage should be adjusted according to haematological response. Therapy should be interrupted if the platelet or white cell count fall below acceptable levels (see also Bone-marrow Depression, p.639). It should be given with great caution if the neutrophil count has recently been depressed by chemotherapy or radiotherapy.

Numerous conventional-dose regimens have been tried for the treatment of multiple myeloma and there is still uncertainty as to the best schedule. Licensed **oral** dosage regimens include:

- 150 micrograms/kg daily in divided doses for 4 to 7 days
- 250 micrograms/kg daily for 4 days
- 6 mg daily for 2 to 3 weeks

Melphalan is usually combined with corticosteroids. Courses are followed by a rest period of up to 6 weeks to allow recovery of haematological function and are then repeated, or maintenance therapy may be instituted, usually with a daily dose of 1 to 3 mg, or up to 50 micrograms/kg. For optimum effect, therapy is usually adjusted to produce a moderate leucopenia, with white cell counts in the range 3000 to 3500 cells/mm^3.

In the treatment of breast cancer, licensed doses are 150 micrograms/kg daily or 6 mg/m^2 daily for 5 days, repeated every 6 weeks. Doses of 200 micrograms/kg daily for 5 days every 4 to 8 weeks have been given to patients with ovarian carcinoma.

In patients with polycythaemia vera, doses of 6 to 10 mg daily for 5 to 7 days, and then 2 to 4 mg daily, have been used for remission induction; a dose of 2 to 6 mg weekly has been used for maintenance.

Melphalan is also given **intravenously**; a single dose of 1 mg/kg, repeated in 4 weeks if the platelet and neutrophil counts permit, has been licensed in ovarian adenocarcinoma. It may be infused in sodium chloride 0.9% or injected into the tubing of a fast-running drip; when given by infusion the time from reconstitution of the solution to completion of infusion should not exceed 1.5 hours and prolonged infusions should be carried out with several batches of solution, each freshly prepared. In multiple myeloma, the licensed dose for use as a single agent is an intravenous dose of 400 micrograms/kg or 16 mg/m^2, infused over 15 to 20 minutes; the first 4 doses may be given at 2-week intervals, but further doses should be given at 4-week intervals depending on toxicity.

High-dose melphalan has been given intravenously in some malignancies: doses of 100 to 240 mg/m^2 have been licensed in neuroblastoma, and 100 to 200 mg/m^2 in multiple myeloma, generally followed by autologous stem cell rescue, which becomes essential where doses exceed 140 mg/m^2. High doses should be given through a central venous catheter.

Melphalan may be given by **local arterial perfusion** in the management of melanoma and soft-tissue sarcomas. A typical dosage range for upper extremity perfusions is 0.6 to 1 mg/kg, whereas for lower extremity perfusions doses of 0.8 to 1.5 mg/kg (in melanoma) or 1 to 1.4 mg/kg (in sarcoma) are typically used.

The dose of melphalan should be reduced in patients with **renal impairment** (see below).

Administration in renal impairment. The initial dose of intravenous melphalan should be reduced by about 50% in patients with renal impairment and dosage reduction should be considered when giving it by mouth. High-dose regimens are not recommended in patients with moderate to severe renal impairment.

Amyloidosis. Amyloidosis refers to a group of conditions characterised by accumulation of a waxy proteinaceous infiltrate within body tissues. Various forms are known,[1-3] including:

- primary or AL amyloidosis, in which the amyloid is derived from immunoglobulin light chains
- ATTR amyloidosis (a familial form), in which amyloid is derived from transthyretin
- AA amyloidosis, which is most often secondary to chronic inflammation, such as that associated with rheumatoid arthritis, tuberculosis, or familial Mediterranean fever (p.557)

Symptoms vary, depending on where the amyloid is deposited. The organs most commonly affected are the heart and kidneys. Renal amyloidosis can present as proteinuria, leading to nephrotic syndrome and renal failure. While renal disease is common in the AA and AL forms, it is less prevalent in ATTR amyloidosis, which commonly presents with neuropathy. Cardiac involvement, rare in AA amyloidosis, is variable in the ATTR form, and common in the AL form; it manifests as restrictive cardiomyopathy, leading to congestive heart failure. Painful peripheral sensory neuropathy and carpal tunnel syndrome also occur frequently. Amyloid deposition in the gastrointestinal tract can lead to malabsorption. Hepatomegaly is common. Macroglossia, due to deposition of amyloid in the tongue, occurs only in the AL form.[1,2]

Management depends to some extent upon the type of amyloidosis involved, and the site, but no drug or combination of drugs is unequivocally effective. Treatment for AA amyloidosis secondary to chronic inflammation is aimed at the underlying disease; immunosuppressants such as chlorambucil, cyclophosphamide, and methotrexate have been used, as well as inhibitors of tumour necrosis factor and interleukin-1 receptor antagonists.[4] Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever, but is not considered to be of benefit in other forms of amyloidosis.[1,5] Melphalan plus prednisone or prednisolone has been shown to increase median survival in primary amyloidosis patients.[6] It is considered the treatment of choice in AL amyloidosis for patients in whom more intensive chemotherapy is not appropriate; evidence of benefit from the addition of a corticosteroid has not been evaluated and in some patients, it may be reasonable not to include a corticosteroid.[5] Melphalan, prednisone, and colchicine was found to be more effective than colchicine alone in the treatment of AL amyloidosis,[7] but a later trial[8] found no benefit in adding colchicine to the standard therapy. Addition of multiple alkylating agents such as vincristine, carmustine, and cyclophosphamide to the standard therapy[9] did not improve survival or response. Evidence to support the use of alkylating-based combination chemotherapy for primary amyloidosis is lacking.[5] Alternatively, cycles of vincristine, doxorubicin, and dexamethasone (VAD) may be effective, but patients with cardiac amyloidosis may be at increased risk of anthracycline toxicity.[10] In the UK, VAD is considered as first-line therapy in patients under the age of 70 years who do not have cardiac failure, autonomic neuropathy, or peripheral neuropathy.[5] High-dose intravenous melphalan with autologous haematopoietic stem cell transplantation (HSCT) has been used;[11] it may result in complete remission of primary amyloidosis,[12-14] and some[1] consider it the treatment of choice. While this may improve renal disease,[12] the therapy remains very toxic, and patient selection on the basis of limited organ disease and no significant cardiac involvement, may reduce morbidity and mortality.[5,13] The outcome of treatment with high-dose intravenous melphalan with autologous HSCT was not superior to standard-dose oral melphalan plus oral dexamethasone in patients with newly diagnosed AL amyloidosis.[15] High-dose dexamethasone or thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those refractory to chemotherapy;[5] good results have been reported in patients with AL amyloidosis given a regimen combining cyclophosphamide with dexamethasone and thalidomide.[16] Local application or oral dosage of dimethyl sulfoxide, and 4′-iodo-4′-deoxydoxorubicin has been investigated.[1,10]

Symptomatic management is also important. Care must be taken to avoid digitalis toxicity when cardiac amyloid is present, as well as to avoid salt and water depletion through injudicious use of diuretics. Calcium-channel blockers and beta blockers should be avoided.[1] Renal transplantation may be considered in end-stage renal failure due to amyloidosis, but unless amyloid production has been stopped disease is likely to recur in the new kidney. Cardiac transplantation, and subsequent chemotherapy with epirubicin, carmustine, and cyclophosphamide to suppress the underlying disease and control amyloid deposition in the graft has also been described.[17] Liver transplantation is the definitive therapy for patients with ATTR amyloidosis.[1,18] Because amyloid deposits contain a plasma glycoprotein serum amyloid P component (SAP) that contributes to the stability of the deposits, and thus contributes to the pathogenesis of amyloidosis, future therapeutic approaches include the targeting of SAP to deplete it from the tissues and clear it from the plasma. Ro-63-8695 (CPHPC) is being investigated.[3,19] Eprodisate disodium is under investigation for AA amyloidosis.[20]

1. Khan MF, Falk RH. Amyloidosis. *Postgrad Med J* 2001; **77:** 686–93.
2. Falk RH, Skinner M. The systemic amyloidoses: an overview. *Adv Intern Med* 2000; **45:** 107–37.
3. Gillmore JD, Hawkins PN. Drug Insight: emerging therapies for amyloidosis. *Nat Clin Pract Nephrol* 2006; **2:** 263–70.
4. Lachmann HJ, *et al.* Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356:** 2361–71.
5. British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. *Br J Haematol* 2004; **125:** 681–700. Also available at: http://www.bcshguidelines.com/pdf/ALamyloidosis_210604.pdf (accessed 07/03/06)
6. Gertz MA, Rajkumar SV. Primary systemic amyloidosis. *Curr Treat Options Oncol* 2002; **3:** 261–71.
7. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; **100:** 290–8.
8. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; **336:** 1202–7.
9. Gertz MA, *et al.* Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol* 1999; **17:** 262–7.
10. Sezer O, *et al.* New therapeutic approaches in primary systemic AL amyloidosis. *Ann Hematol* 2000; **79:** 1–6.
11. Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid* 2007; **14:** 261–9.
12. Dember LM, *et al.* Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. *Ann Intern Med* 2001; **134:** 746–53.
13. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002; **99:** 4276–82.
14. Skinner M, *et al.* High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; **140:** 85–93.
15. Jaccard A, *et al.* Myélome Autogreffe (MAG) and Intergroupe Francophone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357:** 1083–93.
16. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.
17. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
18. Suhr OB, *et al.* Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6:** 263–76.
19. Pepys MB, *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 2002; **417:** 254–9.
20. Dember LM, *et al.* Eprodisate for AA Amyloidosis Trial Group. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; **356:** 2349–60.

Bone disorders, non-malignant. Fibrogenesis imperfecta ossium is a rare progressive bone disease in which disorders of bone collagen and mineralisation, and subsequent abnormal bone structure, result in bone pain and fractures. A patient responded to treatment with melphalan 10 mg and prednisolone 20 or 30 mg daily, in 7-day courses every 2 months.[1,2] Another showed some improvement with intermittent 5-day courses of melphalan 10 mg daily and prednisolone 40 mg daily.[3] However, melphalan alone was reported to be ineffective in 2 other patients; both experienced bone-marrow depression.[3,4]

1. Stamp TCB, *et al.* Fibrogenesis imperfecta ossium: remission with melphalan. *Lancet* 1985; **i:** 582–3.
2. Ralphs JR, *et al.* Ultrastructural features of the osteoid of patients with fibrogenesis imperfecta ossium. *Bone* 1989; **10:** 243–9.
3. Carr AJ, *et al.* Fibrogenesis imperfecta ossium. *J Bone Joint Surg Br* 1995; **77:** 820–9.
4. Lafage-Proust M-H, *et al.* Fibrogenesis imperfecta ossium: ineffectiveness of melphalan. *Calcif Tissue Int* 1996; **59:** 240–4.

Malignant neoplasms. The important role played by melphalan in the management of multiple myeloma is discussed on p.658. Melphalan is also used as part of salvage regimens for relapsed Hodgkin's disease (see p.655), in ovarian cancer (p.670), and for local perfusion of melanoma (p.673).

Preparations

BP 2008: Melphalan Injection; Melphalan Tablets;
USP 31: Melphalan Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alkerana; ***Austral.:*** Alkeran; ***Austria:*** Alkeran; ***Belg.:*** Alkeran; ***Braz.:*** Alkeran; ***Canad.:*** Alkeran; ***Chile:*** Alkeran; ***Cz.:*** Alkeran; ***Denm.:*** Alkeran; ***Fin.:*** Alkeran; ***Fr.:*** Alkeran; ***Ger.:*** Alkeran; ***Gr.:*** Alkeran; ***Hong Kong:*** Alkeran; ***India:*** Alkeran; ***Irl.:*** Alkeran; ***Israel:*** Alkeran; ***Ital.:*** Alkeran; ***Malaysia:*** Alkeran; ***Mex.:*** Alkeran; ***Neth.:*** Alkeran; ***Norw.:*** Alkeran; ***NZ:*** Alkeran; ***Philipp.:*** Alkeran; ***Pol.:*** Alkeran; ***Port.:*** Alkeran; ***Rus.:*** Alkeran (Алкеран); ***S.Afr.:*** Alkeran; ***Singapore:*** Alkeran; ***Swed.:*** Alkeran; ***Switz.:*** Alkeran; ***Thai.:*** Alkeran; ***Turk.:*** Alkeran; ***UK:*** Alkeran; ***USA:*** Alkeran.

Mepolizumab *(USAN, rINN)*

Mépolizumab; Mepolizumabum; SB-240563. Immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 γ1-chain), disulfide with human-mouse monoclonal SB-240563 κ-chain, dimer.

Меполизумаб

CAS — 196078-29-2.

Profile

Mepolizumab is an anti-interleukin-5 monoclonal antibody. It is under investigation in the treatment of hypereosinophilic syndrome (chronic eosinophilic leukaemia), as well as eosinophilic oesophagitis, and asthma.

◊ References.

1. Leckie MJ, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356:** 2144–8.
2. Plötz S-G, *et al.* Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; **349:** 2334–9.
3. Braun-Falco M, *et al.* Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab). *Br J Dermatol* 2004; **151:** 1103–4.

4. Garrett JK, *et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; **113:** 115–19.
5. Rothenberg ME, *et al.* Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358:** 1215–28.

Mercaptopurine *(BAN, rINN)*

Mercaptopurina; Mercaptopurinum; Mercaptopurinum Monohydricum; Merkaptopuriini; Merkaptopürin; Merkaptopurin; Merkaptopurin monohydrát; Merkaptopurinas; Merkaptopuryna; NSC-755; 6MP; Purinethiol; WR-2785. 6-Mercaptopurine monohydrate; Purine-6-thiol monohydrate; 1,7-Dihydro-6*H*-purine-6-thione monohydrate.

Меркаптопурин

$C_5H_4N_4S,H_2O$ = 170.2.

CAS — 50-44-2 (anhydrous mercaptopurine); 6112-76-1 (mercaptopurine monohydrate).

ATC — L01BB02.

ATC Vet — QL01BB02.

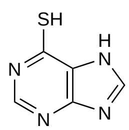

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine and mercaptamine (formerly cysteamine, p.2340) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Mercaptopurine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Mercaptopurine). A yellow, odourless or practically odourless, crystalline powder. Insoluble in water, in acetone, and in ether; soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2N sulfuric acid.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression with mercaptopurine, manifesting as leucopenia, thrombocytopenia, and anaemia, may be delayed; hypoplasia may occur. Mercaptopurine is less toxic to the gastrointestinal tract than the folic acid antagonists or fluorouracil but gastrointestinal disturbances may occur. Hepatotoxicity has been reported, with cholestatic jaundice and necrosis, sometimes fatal. Gastrointestinal and hepatic toxicity are reported to be more frequent in adults than in children, and are more likely at higher doses. Crystalluria with haematuria has been observed rarely as have skin disorders including hyperpigmentation. Fever may occur.

Mercaptopurine is potentially carcinogenic and mutagenic; an increased incidence of abortion has occurred in women given mercaptopurine during the first trimester of pregnancy.

Mercaptopurine should be used with care in patients with impaired hepatic or renal function. Hepatic function should be monitored periodically.

Effects on the blood. Measurement of the activity of thiopurine methyltransferase (TPMT) or the concentration of its substrate, tioguanine nucleotide, has been suggested as a way of predicting those individuals likely to have severe myelotoxicity with mercaptopurine and related drugs (see Azathioprine, p.1819). Patients with an inherited deficiency of the TPMT enzyme may be at increased risk of myelosuppression from mercaptopurine. US licensed product information suggests TPMT testing in patients with evidence of toxicity, and state that reductions in the dose of mercaptopurine may be necessary in those with TPMT deficiency, although optimal initial doses have not been established for these patients. The UK licensed information states that tests for TPMT deficiency have not been shown to identify all patients at risk of severe toxicity, and that close monitoring of blood counts should still be performed.

Effects on the pancreas. Pancreatitis occurred in 13 of 396 patients given mercaptopurine for inflammatory bowel disease.[1] Symptoms resolved on withdrawal but recurred in 7 who were re-challenged with mercaptopurine or azathioprine. Acute pancreatitis has also been reported in 2 children given mercaptopurine during maintenance chemotherapy for acute lymphoblastic leukaemia.[2] They had also suffered pancreatitis from asparaginase during earlier therapy, and the authors suggested that subclinical damage to the pancreas by asparaginase may have been exacerbated by mercaptopurine, but also noted that most patients who develop asparaginase-induced pancreatitis receive mercaptopurine without developing this complication.

1. Present DH, *et al.* 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111:** 641–9.
2. Willert JR, *et al.* Recurrent mercaptopurine-induced acute pancreatitis: a rare complication of chemotherapy for acute lymphoblastic leukemia in children. *Med Pediatr Oncol* 2002; **38:** 73–4.

Handling and disposal. A method for the destruction of mercaptopurine or tioguanine in *wastes* by oxidation with potassium permanganate in sulfuric acid.[1] Residues produced by this method had no mutagenic activity. *Urine and faeces* produced for up to 48 hours and 5 days, respectively after a dose of mercaptopurine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Overdosage. Despite substantial overdose, no acute renal or hepatic toxicity occurred in 2 children. In one case, in which no specific detoxification measures were implemented, neutrophils reached a nadir on day 11 followed by a gradual recovery to normal by day 46. In the other case, gastric lavage was performed and activated charcoal was given; no evidence of neutropenia was seen. The authors recommended that management of acute accidental ingestion should include gastric lavage if the patient presents within 1 hour or if the amount ingested is large. Haemodialysis may be considered if the patient presents within 3 hours of ingestion. Liver function should be monitored. Severe myelosuppression may be managed with granulocyte colony-stimulating factor and a bone-marrow harvest may be of benefit if performed within several hours of the overdose.[1]

1. Chow LML, *et al.* Toxic ingestion of 6-mercaptopurine by young siblings of pediatric oncology patients. *J Pediatr* 2004; **144:** 669–71.

Porphyria. Mercaptopurine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Mercaptopurine should be given with particular caution with other hepatotoxic drugs. Its effects are enhanced by allopurinol and the dose of mercaptopurine should be reduced to one-third to one-quarter of the usual dose when allopurinol is also given.

Allopurinol. Mercaptopurine plasma concentrations were markedly increased by allopurinol when mercaptopurine was given by mouth but not when it was given intravenously.[1] The results appear to indicate that allopurinol inhibits the first-pass metabolism of mercaptopurine.

1. Zimm S, *et al.* Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther* 1983; **34:** 810–17.

Anticoagulants. For reference to mercaptopurine diminishing the activity of *warfarin*, see p.1429.

Antineoplastics. For a suggestion that *doxorubicin* might enhance the hepatotoxicity of mercaptopurine, see under Daunorubicin Hydrochloride, p.709.

Giving mercaptopurine with low-dose oral *methotrexate* increased mean peak plasma concentrations of mercaptopurine by 26% compared with the same dose of mercaptopurine alone in a study in 14 patients with acute lymphoblastic leukaemia.[1] The effect was probably due to inhibition of the first-pass metabolism of mercaptopurine by methotrexate, which is a potent inhibitor of xanthine oxidase. In another study[2] of 10 children with acute lymphoblastic leukaemia, high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of mercaptopurine by 108 and 121% respectively. However, the clinical effect of this pharmacokinetic interaction is probably only minor because of the low, and highly variable, mercaptopurine bioavailability and the lack of correlation between mercaptopurine plasma concentrations and effect.[3] Mercaptopurine and methotrexate have been widely used in combination chemotherapy regimens for acute lymphoblastic leukaemia for their synergistic pharmacodynamic interaction.

1. Balis FM, *et al.* The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* 1987; **41:** 384–7.
2. Innocenti F, *et al.* Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* 1996; **37:** 409–14.
3. Giverhaug T, *et al.* The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* 1999; **33:** 341–6.

Azathioprine. For a report of a fatality when a patient was prescribed mercaptopurine and azathioprine by separate practitioners, see Interactions, under Azathioprine, p.1819.

Gastrointestinal drugs. The enzyme thiopurine methyltransferase is inhibited *in vitro* by *sulfasalazine* and *mesalazine*, raising the possibility of an interaction in patients treated simultaneously with an aminosalicylate and a thiopurine such as mercaptopurine or azathioprine.[1] Myelotoxicity has been reported in a patient receiving mercaptopurine and *olsalazine*.[2] Similarly, severe pancytopenia has occurred in a 13-year-old boy when azathioprine was added to mesalazine therapy.[3] In a study[4] of 34 patients with Crohn's disease in which *balsalazide*, mesalazine, or sulfasalazine was added to established azathioprine or mercaptopurine therapy, mild leucopenia was common in patients given mesalazine or sulfasalazine, and whole blood concentrations of tioguanine nucleotide were found to be increased, probably due to thiopurine methyltransferase inhibition. These effects were not statistically significant in patients given balsalazide.

1. Szumlanski C, Weinshilboum RM. Sulfasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39:** 456–9.
2. Lewis LD, *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; **62:** 464–75.
3. Chouragui JP, *et al.* Azathioprine toxicity in a child with ulcerative colitis: interaction with mesalazine. *Gastroenterology* 1996; **110** (suppl): A883.
4. Lowry PW, *et al.* Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; **49:** 656–64.

Pharmacokinetics

Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. Plasma half-lives ranging from about 20 to 90 minutes have been reported after intravenous injection and the drug is not found in plasma after about 8 hours but this is of limited significance since mercaptopurine is activated intracellularly by conversion to nucleotide derivatives which persist for much longer. It is rapidly and extensively metabolised in the liver, by methylation and oxidation as well as by the formation of inorganic sulfates. Thiol methylation is catalysed by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. Patients with little or no detectable enzyme activity may accumulate excessive cellular concentrations of active tioguanine nucleotides, predisposing them to mercaptopurine toxicity. Considerable amounts of mercaptopurine are also oxidised to thiouric acid by the enzyme xanthine oxidase. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Mercaptopurine crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

Therapeutic drug monitoring. For a discussion of therapeutic drug monitoring for mercaptopurine, see under Azathioprine, p.1819.

Uses and Administration

Mercaptopurine is an antineoplastic that acts as an antimetabolite. It is an analogue of the natural purines hypoxanthine and adenine. After the intracellular conversion of mercaptopurine to active nucleotides, including thioinosinic acid, it appears to exhibit a variety of actions including interfering with nucleic acid synthesis. It also has immunosuppressant properties. Its actions are specific for cells in S phase.

Mercaptopurine is used, usually with other agents, in the treatment of leukaemia. It induces remissions in acute lymphoblastic and myeloid leukaemias (p.651 and p.652, respectively) but other agents are generally preferred and mercaptopurine is chiefly employed in maintenance programmes, commonly with methotrexate. It may also be effective in chronic myeloid leukaemia (p.653). There is cross-resistance between mercaptopurine and tioguanine (p.779).

Mercaptopurine has been used for its immunosuppressant properties in the treatment of auto-immune disorders such as inflammatory bowel disease but has been largely replaced by azathioprine.

Mercaptopurine is given orally. The usual initial antineoplastic dose for children and adults is 2.5 mg/kg or 50 to 75 mg/m^2 daily but dosage varies according to individual response and tolerance. If there is no clinical improvement and no evidence of white-cell depression after 4 weeks, the dose may be cautiously increased up to 5 mg/kg daily. In maintenance schedules the dose may vary from 1.5 to 2.5 mg/kg daily. Blood counts should be taken at least once a week and if there is a steep fall in the white cell count or severe bone-marrow depression the drug should be withdrawn immediately. Therapy may be resumed carefully if the white cell count remains constant for 2 or 3 days or rises.

It has been used intravenously as mercaptopurine sodium. Thioinosine (mercaptopurine riboside) has also been used.

Administration. There is evidence[1] that the maintenance dosage of mercaptopurine should be tailored individually to achieve an appropriate systemic exposure in children with acute lymphoblastic leukaemia (although this would involve determining mercaptopurine pharmacokinetics in each child). Improvements in survival since 1980 may be associated with changes in the prescribing of mercaptopurine which have resulted in greater cumulative doses being given;[2] some children may have been undertreated in the past because of variations in the pharmacokinetics of mercaptopurine (particularly boys, who tolerate mercaptopurine better than girls,[3] but who have a poorer prognosis).[2] The concentration of tioguanine nucleotide metabolites in the erythrocytes has been shown to be directly related to the risk of relapse in children with acute lymphoblastic leukaemia.[4] Thiopurine methyltransferase (TPMT) activity (which results in methylation and inactivation of mercaptopurine rather than the formation of active nucleotides) may play a substantial role in this variation,[5] but titration of the dose of mercaptopurine until myelotoxicity occurs may prevent the problem:[2] despite gaps in therapy caused by more frequent drug withdrawal, it appears to result in greater accumulation of tioguanine nucleotides in the cells.[6]

1. Koren G, *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; **323:** 17–21.
2. Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Arch Dis Child* 1991; **66:** 462–6.
3. Lilleyman JS, *et al.* Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. *Br J Cancer* 1984; **49:** 703–7.
4. Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994; **343:** 1188–90.
5. Lennard L, *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; **336:** 225–9.
6. Lennard L, *et al.* Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites. *Br J Clin Pharmacol* 1996; **42:** 525–7.

Inflammatory bowel disease. Mercaptopurine has been reported to be of benefit in ulcerative colitis[1,2] and Crohn's disease,[3-5] although azathioprine has generally been preferred (see p.1820). The *BNF* considers that in resistant or frequently relapsing cases mercaptopurine 1 to 1.5 mg/kg given daily may be of use.

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85:** 717–22.
2. George J, *et al.* The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91:** 1711–14.
3. Present DH, *et al.* Treatment of Crohn's disease with 6-mercaptopurine: a long-term randomized, double-blind study. *N Engl J Med* 1980; **302:** 981–7.
4. Sandborn W, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 16/05/08).
5. Markowitz J, *et al.* A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119:** 895–902.

Polymyositis. Mercaptopurine has been tried in a few patients with polymyositis but has not been formally assessed.

Preparations

BP 2008: Mercaptopurine Oral Suspension; Mercaptopurine Tablets;
USP 31: Mercaptopurine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Puri-Nethol; Varimer; ***Austral.:*** Puri-Nethol; ***Austria:*** Puri-Nethol; ***Belg.:*** Puri-Nethol; ***Braz.:*** Puri-Nethol; ***Canad.:*** Purinethol; ***Chile:*** Puri-Nethol; ***Cz.:*** Puri-Nethol; ***Fr.:*** Puri-Nethol; ***Ger.:*** Puri-Nethol; ***Gr.:*** Puri-Nethol; ***Hong Kong:*** Puri-Nethol; ***India:*** Puri-Nethol; ***Irl.:*** Puri-Nethol; ***Israel:*** Puri-Nethol; ***Ital.:*** Puri-Nethol; ***Mex.:*** Puri-Nethol; ***Neth.:*** Puri-Nethol; ***Norw.:*** Puri-Nethol; ***NZ:*** Puri-Nethol; ***Philipp.:*** Capmerin; Empurine; Puri-Nethol; ***Rus.:*** Puri-Nethol (Пури-нетол); ***S.Afr.:*** Puri-Nethol; ***Singapore:*** Puri-Nethol; ***Swed.:*** Puri-Nethol; ***Switz.:*** Puri-Nethol; ***Thai.:*** Empurine; Puri-Nethol; ***Turk.:*** Puri-Nethol; ***UK:*** Puri-Nethol; ***USA:*** Purinethol.

Methotrexate *(BAN, USAN, rINN)*

Amethopterin; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic Acid; CL-14377; α-Methopterin; Methotrexát; Méthotrexate; Methotrexatum; Metotreksaatti; Metotreksatas; Metotrexát; Metotrexat; Metotrexato; MTX; NSC-740; WR-19039. *N*-{4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl}-L-glutamic acid.

Метотрексат

$C_{20}H_{22}N_8O_5$ = 454.4.

CAS — 59-05-2.

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

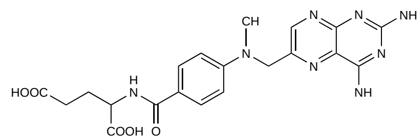

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Methotrexate). A yellow or orange, hygroscopic, crystalline powder. It contains not more than 13% of water. Practically insoluble in water, in alcohol, and in dichloromethane; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

USP 31 (Methotrexate). It is a mixture of 4-amino-10-methylfolic acid and closely related substances; it contains not less than 98% and not more than 102% of $C_{20}H_{22}N_8O_5$, calculated on the anhydrous basis. A yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

Methotrexate Sodium *(BANM, rINNM)*

Méthotrexate de Sodium; Methotrexate Disodium; Metotreksat Sodyum; Metotrexato sodium; Natrii Methotrexatum.

Натрий Метотрексат

$C_{20}H_{20}N_8Na_2O_5$ = 498.4.

CAS — 7413-34-5 (methotrexate disodium); 15475-56-6 (methotrexate sodium, xNa).

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

Incompatibility. Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate;[1] however, another study suggests it is compatible with fluorouracil.[2] Furthermore a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°, although precipitation did occur on storage for several days.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Stability to light. Methotrexate undergoes photodegradation when stored in the light in diluted solutions, although undiluted commercial preparations are reported to show negligible photodegradation.[1] The bicarbonate ion catalyses this reaction and such admixtures should be avoided if possible, although they may be stable in light for 12 hours. Storage of solutions diluted in sodium chloride 0.9% injection in PVC bags was reported to protect against photodegradation although the length of the study was only 4 hours.[2] Photodegradation can take place under normal lighting, but is more rapid in direct sunlight, with about 11% drug loss from a 1 mg/mL solution after 7 hours; storage under normal lighting resulted in little change in drug concentration over 24 hours with a decrease of up to 12% by 48 hours.[3] Loss was greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hours.

1. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J Pharm Sci* 1978; **67:** 526–31.
2. Dyvik O, *et al.* Methotrexate in infusion solutions—a stability test for the hospital pharmacy. *J Clin Hosp Pharm* 1986; **11:** 343–8.
3. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Adverse Effects

For general discussions see Antineoplastics, p.635.

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may exhibit an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with fetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned (see Carcinogenicity, below).

Carcinogenicity. There are reports of lymphomas associated with low-dose methotrexate therapy for rheumatic disorders,[1-4] which in some cases have been associated with concomitant Epstein-Barr virus infection.[2] Transitional cell bladder cancer has also been associated with such therapy.[5] However, a retrospective analysis involving 16 263 patients with rheumatoid arthritis found no evidence of a relationship between the use of methotrexate as an antirheumatic and the development of haematological malignancy.[6] Nonetheless, the spontaneous remission of lymphoma after withdrawal of methotrexate in some patients seems to support an association[7] A later prospective study[8] of all new cases of lymphoma, detected over 3 years in patients treated with methotrexate for rheumatoid arthritis, also found a higher incidence of Hodgkin's disease compared with the general population. The carcinogenic risk with antimetabolites such as methotrexate has generally been considered less than with alkylating agents (p.635).

1. Zimmer-Galler I, Lie JT. Choroidal infiltrates as the initial manifestation of lymphoma in rheumatoid arthritis after treatment with low-dose methotrexate. *Mayo Clin Proc* 1994; **69:** 258–61.
2. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328:** 1317–21.
3. Viraben R, *et al.* Reversible cutaneous lymphoma occurring during methotrexate therapy. *Br J Dermatol* 1996; **135:** 116–18.
4. Ebeo CT, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; **123:** 2150–3.
5. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids. *Lancet* 1994; **343:** 1222–3.
6. Moder KG, *et al.* Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995; **99:** 276–81.
7. Georgescu L, Paget SA. Lymphoma in patients with rheumatoid arthritis: what is the evidence of a link with methotrexate? *Drug Safety* 1999; **20:** 475–87.
8. Mariette X, *et al.* Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002; **99:** 3909–15.

Effects on the blood. Although serious and sometimes fatal blood dyscrasias are a well-known consequence of high-dose methotrexate therapy the UK CSM[1] stated in September 1997 that it was also aware of 83 reports of blood dyscrasias associated with low-dose methotrexate used to treat psoriasis or rheumatoid arthritis; there were 36 fatalities. Many of the cases had contributing factors such as advanced age, renal impairment, or use with interacting drugs.

1. Committee on Safety Medicines/Medicines Control Agency. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

Megaloblastic anaemia. Megaloblastic anaemia, usually with marked macrocytosis, has been reported in mainly elderly patients given long-term weekly methotrexate therapy.[1-3] It has been suggested that therapy should be withdrawn if the mean corpuscular volume exceeds 106 femtolitres.[1] Symptoms appear to be associated with folate depletion by methotrexate,[2,4,5] probably due to increased excretion,[6] and in one case megaloblastic anaemia developed after starting a weight-reducing diet poor in folate.[4] Folate supplementation, conversely, may permit continuation of methotrexate therapy with resolution of the anaemia.[5]

1. Dodd HJ, *et al.* Megaloblastic anaemia in psoriatic patients treated with methotrexate. *Br J Dermatol* 1985; **112:** 630.
2. Dahl MGC. Folate depletion in psoriatics on methotrexate. *Br J Dermatol* 1984; **111** (suppl 26): 18.
3. Casserly CM, *et al.* Severe megaloblastic anemia in a patient receiving low-dose methotrexate for psoriasis. *J Am Acad Dermatol* 1993; **29:** 477–80.
4. Fulton RA. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 267–8.
5. Oxholm A, Thomsen K. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; **114:** 268–9.
6. Duhra P, *et al.* Intestinal folate absorption in methotrexate treated psoriatic patients. *Br J Dermatol* 1988; **119:** 327–32.

Effects on the gastrointestinal tract. Although gastrointestinal toxicity is well recognised as an effect of high-dose regimens, oral ulceration has also been reported after low-dose (weekly) methotrexate use.[1,2] In some instances it was related to overdosage; symptoms resolved upon correction of the dose and with folate supplementation.[1] Folate deficiency may increase the oral toxicity of methotrexate, and folate supplementation may also avoid the need to stop low-dose methotrexate.[2]

1. Deeming GMJ, *et al.* Methotrexate and oral ulceration. *Br Dent J* 2005; **198:** 83–5.
2. Kalantzis A, *et al.* Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100:** 52–62.

Effects on the kidneys. High-dose methotrexate therapy can result in supersaturation of the urine with methotrexate and its metabolites leading to crystal formation.[1] These crystals can cause intrarenal obstruction and are a factor in the development of acute renal failure. Risk factors for crystal formation are acid urine, volume depletion, and renal impairment. Adequate hydration, and urinary alkalinisation with sodium bicarbonate or acetazolamide play an important role in minimising nephrotoxicity in high-dose methotrexate regimens. A study found that the incidence of severe toxicity was reduced in patients given greater hydration and alkalinisation. However, this more intensive hydration regimen also significantly lowered methotrexate plasma concentrations.[2] More recently glucarpidase (p.1447), a recombinant glutamate carboxypeptidase, has been developed and may be useful in the management of methotrexate-induced renal dysfunction when methotrexate concentrations are very high.[3]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Christensen ML, *et al.* Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J Clin Oncol* 1988; **6:** 797–801.
3. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006; **11:** 694–703.

Effects on the liver. Methotrexate is well established as a cause of hepatotoxicity, including periportal fibrosis, when given in relatively high doses as an antineoplastic, and it has become clear that its long-term use in lower doses for disorders such as psoriasis and rheumatoid arthritis can also be associated with liver toxicity.[1] There has been some difficulty in these patients in distinguishing the effects of the drug from the effects of the disease, but there is good evidence that the risk is increased in patients given doses on a daily rather than a weekly regimen, and in those with a high alcohol intake.[1] Pre-existing liver disease, obesity (especially if associated with diabetes mellitus), renal impairment, and increasing total cumulative dose may also increase the risk of hepatotoxicity.[1] A lower incidence of hepatotoxicity in patients with rheumatoid arthritis (compared with older studies in patients with psoriasis) may be due to improved dosage regimens and greater awareness of the risks.[1]

In order to minimise the risks of serious liver damage various guidelines and recommendations have been issued for the use of methotrexate in psoriasis and rheumatoid arthritis, and the appropriate monitoring.

- For patients with *psoriasis*, US guidelines[2] recommend a liver biopsy at the beginning of treatment and after each cumulative dose of 1 to 1.5 g, together with monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and albumin. The need to repeat routine liver biopsies has been questioned.[3] Some[4] recommend omitting the baseline biopsy in patients with no risk factors. Practice in the UK has been similar but monitoring of the aminoterminal peptide of type III procollagen (PIIINP), a serological marker of hepatic fibrosis,[5] is now recommended by the British Association of Dermatologists[6] as a safer alternative to liver biopsy. PIIINP values should be determined before starting methotrexate and then every 2 to 3 months during treatment. A liver biopsy may then be considered in those with persistently abnormal values. However, some[5] have said that larger studies of the value of PIIINP assays should be undertaken before definitive recommendations can be made.
- In patients with *rheumatoid arthritis* US guidelines[7] suggest an initial biopsy only in patients with a history of excessive alcohol consumption, persistently abnormal AST values or chronic hepatitis B or C infection. All patients should undergo monitoring of liver enzyme values (AST and ALT) and albumin every 4 to 8 weeks, and a biopsy should be performed if 5 of 9 or 6 of 12 measurements of AST are elevated in a 12-month interval; if liver changes are moderate to severe, methotrexate should be discontinued. However, some rheumatologists[8,9] consider that less stringent monitoring may be warranted, especially in those with no risk factors for hepatotoxicity. Similarly, although these guidelines have been widely adopted for use in children with juvenile idiopathic arthritis, some[10] consider that routine blood tests every 4 to 8 weeks are unnecessarily frequent.

The UK CSM advised in 1997 that liver-function tests (together with blood count and renal-function testing) should be performed before beginning long-term low-dose methotrexate therapy and repeated weekly until therapy was stabilised, and thereafter every 2 to 3 months.[11]

1. West SG, *et al.* Methotrexate hepatotoxicity. *Rheum Dis Clin North Am* 1997; **23:** 883–915.
2. Roenigk HH, *et al.* American Academy of Dermatology. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; **19:** 145–6.
3. Boffa MJ, *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133:** 774–8.
4. Roenigk HH, *et al.* Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998; **38:** 478–85.
5. Maurice PDL, *et al.* Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. *Br J Dermatol* 2005; **152:** 451–8.
6. British Association of Dermatologists. Psoriasis Guideline 2006. Available at: http://www.bad.org.uk/healthcare/guidelines/psoriasis_guideline_(Final_update)_280906.pdf (accessed 31/07/08)
7. Kremer JM, *et al.* American College of Rheumatology. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; **37:** 316–28.
8. Yazici Y, *et al.* Monitoring by rheumatologists for methotrexate-, etanercept-, infliximab-, and anakinra-associated adverse events. *Arthritis Rheum* 2003; **48:** 2769–72.
9. Yazici Y, *et al.* Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. *Clin Exp Rheumatol* 2005; **23:** 517–20.
10. Ortiz-Alvarez O,*et al.* Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol* 2004; **31:** 2501–6.
11. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

Effects on the lungs. Pulmonary toxicity due to methotrexate has been well described.[1,2] A review[1] of over 120 reports of methotrexate pneumonitis found that onset usually occurred during treatment, presenting as dyspnoea, cough, and fever. Examination often found tachypnoea and crackles, eosinophilia, reduced pulmonary function, interstitial and alveolar infiltrates on chest radiography, and interstitial inflammation and fibrosis. The majority of cases were managed with cessation of methotrexate with or without corticosteroid therapy; most patients improved, but there were 16 deaths caused by respiratory disease. Methotrexate was restarted in 16 patients, and pneumonitis recurred in 4 of these.

Up to 25 April 2003, the UK CSM had received 90 reports of parenchymal lung disorders, including 52 reports of pneumonitis, 21 of pulmonary fibrosis, 5 of interstitial lung disease, and 3 of interstitial pneumonitis. The CSM has suggested that patients should seek medical attention if symptoms such as dyspnoea, dry, nonproductive cough, or fever develop; methotrexate should be stopped and corticosteroids given in the event of suspected pneumonitis.[3]

A multicentre case-control study[4] which examined 29 cases of methotrexate-induced lung injury among rheumatoid arthritis patients reported a number of risk factors. These included age over 60 years, pleuropulmonary disease (or to a lesser extent other extra-articular disease), previous use of other disease-modifying antirheumatic drugs, and low serum-albumin; an association with smoking, nonsedentary occupations, and diabetes mellitus was also noted.

1. Imokawa S, *et al.* Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; **15:** 373–81.
2. Lateef O, *et al.* Methotrexate pulmonary toxicity. *Expert Opin Drug Saf* 2005; **4:** 723–30.
3. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Methotrexate and pneumonitis. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
4. Alarcón GS, *et al.* Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: a multicenter, case-control study. *Ann Intern Med* 1997; **127:** 356–64.

Effects on mental function. Children who had received intrathecal methotrexate with cranial irradiation for the prophylaxis of CNS leukaemia, had a significant intellectual deficit compared with their siblings.[1] There was no corresponding significant reduction in IQ in a group of children who had received systemic chemotherapy and radiotherapy when compared with their sibling controls. The results suggest that intrathecal methotrexate and cranial irradiation cause intellectual problems, particularly on the higher, more complex and integrated intellectual functions, and that the repercussions are greater in younger children. Subsequent results in these patients indicated that although the lowering of IQ had persisted, it had not progressed since the original study.[2] A further study confirmed the adverse neurological effects of leukaemia treatment, and its effects on IQ, and did not find a reduced radiation dose to be any less toxic.[3] Neurotoxicity appeared to be greater when systemic therapy with intramuscular rather than oral methotrexate was given with CNS prophylaxis. A study[4] of children who underwent surgery, chemotherapy, and craniospinal radiotherapy for medulloblastoma also found that those patients who received intrathecal methotrexate had significantly worse cognitive deficits than those who did not, and all patients performed worse than a control group of cousins and siblings.

In a small study[5] of children treated for leukaemia with chemotherapy that included intrathecal methotrexate, but without irradiation, there were lower cognitive scores in some measures compared with a group of healthy controls, but overall no major cognitive impairment was found.

A study in 20 patients receiving intermittent oral methotrexate for psoriasis found no evidence of psychological impairment.[6]

1. Twaddle V, *et al.* Intellectual function after treatment for leukaemia or solid tumours. *Arch Dis Child* 1983; **58:** 949–52.
2. Twaddle V, *et al.* Intellect after malignancy. *Arch Dis Child* 1986; **61:** 700–2.
3. Chessells JM, *et al.* Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation. *Arch Dis Child* 1990; **65:** 416–22.
4. Riva D, *et al.* Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology* 2002; **59:** 48–53.
5. Kingma A, *et al.* No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol* 2002; **24:** 106–14.
6. Duller P, van de Kerkhof PCM. The impact of methotrexate on psycho-organic functioning. *Br J Dermatol* 1985; **113:** 503–4.

Effects on the nervous system. Methotrexate has a cumulative toxic effect on the nervous system, and generalised and focal neurotoxic reactions are associated with intrathecal and high-dose intravenous use.[1] An immediate, usually transient, effect occurring within a day of high intravenous doses can cause nausea and vomiting, headache, somnolence, lethargy, confusion, disorientation, seizures, and increased intracranial pressure. Reversible acute meningitis can follow intrathecal use, with similar results.[1] Aseptic meningitis has also been reported after intramuscular methotrexate.[2] Spinal cord myelopathy resulting in transient or permanent paraplegia has also followed intrathecal methotrexate use, especially if other neurotoxic treatments have also been used. A subacute form of toxic reaction can occur up to several weeks after treatment. It is usually transient and characterised by seizures, varying degrees of paresis, aphasia, anaesthesia, blurred vision, and pseudobulbar palsy. A more delayed syndrome occurs weeks to months after treatment and is of variable severity, but can progress to lethargy, seizures, spasticity, paresis, drooling, and dementia. This condition is characterised by leukoencephalopathy and chronic calcification of brain tissue. It is dose-related, and more severe if the patient has also received radiotherapy.[1]

See also Effects on Mental Function, above.

1. Shuper A, *et al.* Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *J Child Neurol* 2000; **15:** 573–80.
2. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis. *Ann Pharmacother* 2007; **41:** 1906–11.

Effects on the skin. There are rare reports[1,2] of painful erythema of the hands and feet, particularly the fingertips, with progression to blistering and desquamation (palmar-plantar erythrodysesthesia syndrome, p.639) after the use of high-dose intravenous methotrexate. Purpuric skin lesions due to vasculitis have occurred after both high-dose[3] and low-dose[4,5] methotrexate. Accelerated rheumatoid nodulosis has been reported[6,7] after the use of methotrexate in patients with rheumatoid arthritis. Erosion of psoriatic plaques, accompanied by pain and erythema, has been seen[8,9] after low-dose methotrexate therapy; blistering and necrosis consistent with toxic epidermal necrolysis has occurred.[8] Possible exacerbation of a photosensitivity reaction to ciprofloxacin has been described,[10] and reactivation of sunburn has also been reported[11] in a number of cases where methotrexate was given within 2 to 5 days after the initial sunburn.

1. Doyle LA, *et al.* Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; **98:** 611–12.
2. Millot F, *et al.* Acral erythema in children receiving high-dose methotrexate. *Pediatr Dermatol* 1999; **16:** 398–400.
3. Navarro M, *et al.* Leukocytoclastic vasculitis after high-dose methotrexate. *Ann Intern Med* 1986; **105:** 471–2.
4. Marks CR, *et al.* Small-vessel vasculitis and methotrexate. *Ann Intern Med* 1984; **100:** 916.
5. Torner O, *et al.* Methotrexate related cutaneous vasculitis. *Clin Rheumatol* 1997; **16:** 108–9.
6. Williams FM, *et al.* Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. *J Am Acad Dermatol* 1998; **39:** 359–62.
7. Filosa G, *et al.* Accelerated nodulosis during methotrexate therapy for refractory rheumatoid arthritis: a case report. *Adv Exp Med Biol* 1999; **455:** 521–4.
8. Reed KM, Sober AJ. Methotrexate-induced necrolysis. *J Am Acad Dermatol* 1983; **8:** 677–9.
9. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. *J Am Acad Dermatol* 1996; **35:** 835–8.
10. Nedorost ST, *et al.* Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; **125:** 433–4.
11. Khan AJ, *et al.* Methotrexate and the photodermatitis reactivation reaction: a case report and review of the literature. *Cutis* 2000; **66:** 379–82.

Hypersensitivity. There are rare reports of anaphylactic reactions in patients given methotrexate. Reactions have usually occurred in patients who had previous exposure to methotrexate, but there are also reports of reaction during initial exposure to high-dose intravenous therapy.[1] Serious reactions have also been described after low-dose intravenous[2] and intrathecal[3] use.

1. Alkins SA, *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; **77:** 2123–6.
2. Cohn JR, *et al.* Systemic anaphylaxis from low dose methotrexate. *Ann Allergy* 1993; **70:** 384–5.
3. Devecioğlu Ö, *et al.* Systemic near-fatal anaphylactic reaction after intrathecal methotrexate administration. *Med Pediatr Oncol* 2000; **34:** 151–2.

Treatment of Adverse Effects

For general guidelines, see p.639.

Folinic acid neutralises the immediate toxic effects of methotrexate on the bone marrow. It is given as sodium or calcium folinate orally, intramuscularly, by intravenous bolus injection, or by infusion. When overdosage is suspected the dose of folinate should be at least as high as that of methotrexate and should be given as soon as possible; further doses are given as required preferably based on serum-methotrexate concentrations. Folinate should be continued until serum-methotrexate concentrations fall below 0.05 to 0.1 micromol/litre, which may necessitate prolonged treatment in patients with delayed elimination. Other dosage regimens, given intramuscularly or orally, may be appropriate for more modest toxicity associated with conventional doses of methotrexate. For details, see under Folinic Acid, p.1944. After intrathecal overdose, the drainage of 30 mL of CSF within 15 minutes removes about 95% of methotrexate; but methotrexate rapidly enters the systemic circulation and folinic acid treatment should be based on serum-methotrexate concentrations.

Folinic acid is usually given with high-dose methotrexate regimens to prevent damage to normal tissue ('folinic acid rescue') and this is discussed in Uses and Administration, below.

An adequate flow of alkaline urine should be maintained after high doses of methotrexate to prevent precipitation of methotrexate or its metabolites in the renal tubules; in addition to adequate hydration, the use of acetazolamide or sodium bicarbonate is recommended.

The recombinant glutamate carboxypeptidase glucarpidase (p.1447) rapidly hydrolyses methotrexate to inactive metabolites, and is under investigation in the management of methotrexate toxicity.

Folate supplementation. A discussion of the selection of the appropriate route for folinic acid rescue with *high-dose methotrexate* regimens.[1] The general objective is to give folinic acid (as folinate) at doses that maintain plasma concentrations of reduced folates at a level equivalent to or greater than the plasma-methotrexate concentration. In any clinical situation suggesting impaired gastrointestinal function calcium folinate should be given by injection. Although absorption of intramuscular doses is relatively complete and rapid the intravenous route is usually preferable for other reasons, such as a reduced risk of bleeding at injection sites. In the absence of impaired gastrointestinal function, and where there are no concomitant risk factors for methotrexate toxicity, the oral route may be used provided that methotrexate concentrations are expected to be less than 1 micromol/litre. For very high dose methotrexate regimens it is generally appropriate to begin folinic acid rescue intravenously to ensure adequate initial therapy, but the majority of the dosage regimen can generally be given orally.

There is no consensus on the use of folate supplementation in patients taking *low-dose methotrexate*,[2] although reviews have concluded that supplementation with either folic or folinic acid reduces adverse effects related to the liver function tests, gastrointestinal tract and oral mucosa.[2,3] However, a study found that while folate supplementation reduced the incidence of methotrexate-related liver enzyme elevations, it had no effect on incidence, severity, or duration of other adverse effects.[4] Effects of folate supplementation on the efficacy of methotrexate have been inconclusive;[3] some consider the effect to be small.[4,5] There is some suggestion that folinic acid, but not folic acid, may reduce the efficacy of methotrexate.[2] However, an analysis[6] of two studies found a reduction in efficacy with folic acid supplementation. The issue of supplementation remains controversial, with some recommending routine folic acid,[2,5,7] and others suggesting that folate only be added when demand for folate increases, such as during infection or with antibacterial use.[8]

1. Rodman JH, Crom WR. Selecting an administration route for leucovorin rescue. *Clin Pharm* 1989; **8:** 617, 621.
2. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; **43:** 267–71.
3. Ortiz Z, *et al.* Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 08/02/06).
4. van Ede AE, *et al.* Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; **44:** 1515–24.
5. Griffith SM, *et al.* Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue folic acid supplements long term? *Rheumatology (Oxford)* 2000; **39:** 1102–9.
6. Khanna D, *et al.* Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005; **52:** 3030–8.
7. Hornung N, *et al.* Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. *J Rheumatol* 2004; **31:** 2374–81.
8. Manna R, *et al.* Folic acid supplementation during methotrexate treatment: nonsense? *Rheumatology (Oxford)* 2005; **44:** 563–4.

Other drugs. Pretreatment with fluorouracil is reported to reduce the toxicity of methotrexate sufficiently to permit high-dose methotrexate without the need for folinic acid rescue.[1] Methotrexate has also been given before fluorouracil to modulate its activity (see Administration, in Fluorouracil, p.724).

The acute neurotoxic effects of methotrexate have been reported to be relieved by intravenous aminophylline or oral theophylline in some children.[2]

For reference to the ineffectiveness of diltiazem in preventing the nephrotoxicity due to high-dose methotrexate, see Kidney Disorders, under Diltiazem p.1267.

For evidence that colestyramine might decrease serum-methotrexate concentrations, see Interactions, below. For reference to the use of glucarpidase to manage methotrexate-induced renal toxicity see Effects on the Kidneys, above.

1. White RM. 5-Fluorouracil modulates the toxicity of high dose methotrexate. *J Clin Pharmacol* 1995; **35:** 1156–65.
2. Bernini JC, *et al.* Aminophylline for methotrexate-induced neurotoxicity. *Lancet* 1995; **345:** 544–7.

Precautions

For general discussions see p.641.

Methotrexate should be used with great care in patients with bone-marrow, hepatic, or renal impairment. It should also be used cautiously in ulcerative disorders of the gastrointestinal tract, and in the elderly and the very young. Pleural or ascitic effusions may act as a depot for methotrexate and produce enhanced toxicity, and should be drained before treatment.

Regular monitoring of haematological, renal, and hepatic function, and gastrointestinal toxicity is advisable. Treatment should be interrupted if myelosuppression, diarrhoea, or stomatitis occur. Dyspnoea or cough may be a sign of pulmonary toxicity and patients should be advised to contact their doctor if they develop these symptoms. Treatment should be withdrawn and the patient investigated to exclude infection. If methotrexate-induced lung disease is suspected corticosteroid therapy may be started and further treatment with methotrexate should not be given. Patients or their carers should report any symptoms or signs suggestive of infection, especially sore throat.

In patients receiving **low-dose methotrexate for psoriasis or rheumatoid arthritis** full blood counts and renal and liver function tests should be performed before starting treatment and repeated regularly thereafter (for discussion of guidelines for monitoring in these patients see Effects on the Liver, above). Treatment should be interrupted if myelosuppression, stomatitis, or any abnormality of liver function is detected. Methotrexate should not be used to treat rheumatoid arthritis or psoriasis in patients with alcoholism, liver disease or persistent abnormal liver function tests, or in those with significant renal impairment, immunodeficiency, or blood disorders. A test dose has been recommended. Severe or fatal toxicity has resulted from overdosage when doses intended for a low-dose weekly regimen were mistakenly taken daily, and particular care should be taken to avoid confusion about dosage frequency.

With **high-dose regimens**, serum concentrations of methotrexate should be monitored. Maintenance of an adequate flow of alkaline urine is essential (see Treatment of Adverse Effects, above).

Methotrexate is a potent teratogen and should be avoided in **pregnancy**. Some manufacturers advise that conception should be avoided for at least 6 months after therapy but others consider 3 months adequate.

Blood products. Enhanced toxicity was seen in 2 of 14 patients receiving methotrexate by 24-hour infusion when packed red cells were transfused immediately after the methotrexate infusion.[1] Erythrocytes act as reservoirs for methotrexate and probably resulted in the prolonged high serum-methotrexate concentrations seen in these patients. Great care should be exercised whenever packed red blood cells and methotrexate are given concurrently.

1. Yap AKL, *et al.* Methotrexate toxicity coincident with packed red cell transfusions. *Lancet* 1986; **ii:** 641.

Breast feeding. Methotrexate has been detected in breast milk in low concentrations.[1] The American Academy of Pediatrics considers[2] that methotrexate may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the nursing infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Johns DG, *et al.* Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972; **112:** 978–80.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/04)

Handling and disposal. Care should be taken to avoid inhalation of methotrexate or contact with skin and mucous membranes. It may cause irritation of the eyes.

Methods have been published for the oxidative destruction of methotrexate *wastes* using potassium permanganate and sulfuric acid, aqueous alkaline potassium permanganate, or sodium hypochlorite.[1] The first method may also be used for dichloromethotrexate. Residues produced by the degradation of methotrexate by these methods showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 72 hours and 7 days respectively after a dose of methotrexate should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.* eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hepatitis. Reactivation of hepatitis B infection, with the development of hepatocellular necrosis and fulminant hepatic failure requiring liver transplantation, developed on stopping low-dose methotrexate therapy in a patient with rheumatoid arthritis who was also an asymptomatic chronic hepatitis B carrier.[1] It was suggested that all patients being considered for low-dose methotrexate therapy should be screened for the presence of serum HBsAg before beginning therapy.

1. Flowers MA, *et al.* Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; **112:** 381–2.

Porphyria. Methotrexate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

PUVA. Of a total of 94 patients with psoriasis and 38 with mycosis fungoides treated with PUVA therapy (methoxsalen and ultraviolet light) 2 of the former also given methotrexate developed skin cancers.[1] It was suggested that the combination of methotrexate and PUVA may be synergistic in inducing cutaneous malignancy. However, in a cohort study[2] of patients with severe psoriasis, exposure to methotrexate for at least 4 years was associated with an increase in risk of squamous cell carcinoma but not basal cell carcinoma, and no interaction was found between methotrexate and PUVA.

1. Fitzsimons CP, *et al.* Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet* 1983; **i:** 235–6.
2. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73:** 2759–64.

Radiation. Analysis of neutrophil counts for 18 months in children with acute lymphoblastic leukaemia showed that methotrexate-induced neutropenia was significantly greater in patients given CNS irradiation and was considered to have contributed to 3 of 5 deaths during remission.[1]

For the effect of cranial irradiation and intrathecal methotrexate on intellectual development, see Effects on Mental Function, above.

1. Report to the Medical Research Council of the Working Party on Leukaemia in Childhood. Analysis of treatment in childhood leukaemia: I—predisposition to methotrexate-induced neutropenia after craniospinal irradiation. *BMJ* 1975; **3:** 563–6.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. The effects of methotrexate may be enhanced by drugs that decrease its renal excretion, such as NSAIDs and salicylates, probenecid, and some penicillins. Fatal toxicity has occurred in patients given NSAIDs with methotrexate (see below). Severe toxicity has occurred rarely when co-trimoxazole or trimethoprim was given with methotrexate. Use with other myelotoxic, hepatotoxic, or nephrotoxic agents may increase the risk of toxicity. Folic acid and its derivatives may decrease the effectiveness of methotrexate, although they are often used together to reduce methotrexate toxicity (see Treatment of Adverse Effects, above).

Animal studies suggested methotrexate toxicity may be increased by chloramphenicol, para-aminobenzoic acid, and hypoglycaemics, but there does not appear to be any evidence of this clinically.

Antibacterials. The oral *aminoglycosides* neomycin[1] and paromomycin[2] have been reported to reduce the gastrointestinal absorption of methotrexate. Various *penicillins* have been reported to markedly decrease the clearance of methotrexate given intravenously for treatment of neoplasms,[3-6] although *ceftazidime* may not.[4] There have also been a few reports of penicillins possibly exacerbating the toxicity of low-dose methotrexate in patients being treated for psoriasis or rheumatoid arthritis, but a small study found that although flucloxacillin decreased methotrexate clearance slightly, this was not clinically significant.[7] Methotrexate toxicity has been reported in a patient receiving low-dose methotrexate after a course of *tetracycline*.[8] In a patient receiving high-dose methotrexate, giving *doxycycline* before the eleventh cycle was believed to be responsible for an exacerbation of methotrexate toxicity, with raised plasma concentrations and reduced clearance of methotrexate.[9] *Sulfonamides* such as sulfafurazole and sulfamethoxazole may displace methotrexate from binding sites[10] and reduce renal clearance.[11] Megaloblastic pancytopenia has been reported on a number of occasions when methotrexate was given with *co-trimoxazole*[12-14] or *trimethoprim*;[13,15,16] possible mechanisms involved include an additive antifolate effect, in addition to the effect of the sulfamethoxazole component in the case of co-trimoxazole.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Cohen MH, *et al.* Effect of oral prophylactic broad spectrum nonabsorbable antibiotics on the gastrointestinal absorption of nutrients and methotrexate in small cell bronchogenic carcinoma patients. *Cancer* 1976; **38:** 1556.
3. Bloom EJ, *et al.* Delayed clearance (CL) of methotrexate (MTX) associated with antibiotics and antiinflammatory agents. *Clin Res* 1986; **34:** 560A.
4. Yamamoto K, *et al.* Delayed elimination of methotrexate associated with piperacillin administration. *Ann Pharmacother* 1997; **31:** 1261–2.
5. Dean R, *et al.* Possible methotrexate-mezlocillin interaction. *Am J Pediatr Hematol Oncol* 1992; **14:** 88–9.
6. Ronchera CL, *et al.* Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. *Ther Drug Monit* 1993; **15:** 375–9.
7. Herrick AL, *et al.* Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1996; **41:** 223–7.
8. Turck M. Successful psoriasis treatment then sudden 'cytotoxicity'. *Hosp Pract* 1984; **19:** 175–6.
9. Tortajada-Ituren JJ, *et al.* High-dose methotrexate—doxycycline interaction. *Ann Pharmacother* 1999; **33:** 804–8.
10. Liegler DG, *et al.* The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969; **10:** 849–57.
11. Ferrazzini G, *et al.* Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990; **117:** 823–6.
12. Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* 1989; **120:** 582–3.
13. Jeurissen ME, *et al.* Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1989; **111:** 261.
14. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim–sulphamethoxazole—a potentially hazardous combination. *Clin Exp Dermatol* 1990; **15:** 358–60.
15. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction. *Br J Rheumatol* 1998; **37:** 105–6.
16. Govert JA, *et al.* Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med* 1992; **117:** 877–8.

Antiepileptics. For mention of the reduction in serum-*valproate* concentration produced by methotrexate see p.511.

Antineoplastics. Enhanced methotrexate toxicity might be expected with nephrotoxic agents (such as *cisplatin*) that can reduce methotrexate excretion by impairing renal function. Sequential use of methotrexate and *fluorouracil* may result in synergistic enhancement of effect (see Administration, in Fluorouracil, p.724), and equally, fluorouracil before methotrexate may reduce its toxicity (see Other Drugs, under Treatment of Adverse Effects, above), but if *asparaginase* (p.682) is given before methotrexate the cytotoxic effect of methotrexate may be reduced.

Methotrexate may increase the bioavailability of *mercaptopurine*, probably by interference with first-pass metabolism (see p.744).

Colestyramine. Serum-methotrexate concentrations were markedly reduced in 3 patients given colestyramine to treat methotrexate toxicity.[1,2] Colestyramine appears to bind methotrexate and reduce its enterohepatic recirculation.

1. Erttmann R, Landbeck G. Effect of oral cholestyramine on the elimination of high-dose methotrexate. *J Cancer Res Clin Oncol* 1985; **110:** 48–50.
2. Shinozaki T, *et al.* Successful rescue by oral cholestyramine of a patient with methotrexate nephrotoxicity: nonrenal excretion of serum methotrexate. *Med Pediatr Oncol* 2000; **34:** 226–8.

Dantrolene. Dantrolene was considered to have caused methotrexate toxicity in a patient given high-dose methotrexate.[1]

1. André N, *et al.* Can dantrolene contribute to methotrexate toxicity? *Ann Pharmacother* 2006; **40:** 1695–6.

Gastrointestinal drugs. Elevated serum concentrations of methotrexate were reported when it was given to 2 patients also receiving *omeprazole*.[1,2] The effect was not seen with subsequent cycles of methotrexate therapy once omeprazole had been stopped. In another case[3] however, raised methotrexate concentrations were thought to be due to an interaction with omeprazole, but were identical during a second cycle after omeprazole had been withdrawn. Severe generalised myalgia and bone pain were reported in a patient who received methotrexate and *pantoprazole*.[4] The same reaction occurred on rechallenge with the combination, but not with methotrexate alone. Although methotrexate concentrations were unchanged, concentrations of the metabolite 7-hydroxymethotrexate were raised suggesting an interaction with its renal elimination. *Lansoprazole* has been reported not to affect the pharmacokinetics of methotrexate.[5]

1. Reid T, *et al.* Impact of omeprazole on the plasma clearance of methotrexate. *Cancer Chemother Pharmacol* 1993; **33:** 82–4.
2. Beorlegui B, *et al.* Potential interaction between methotrexate and omeprazole. *Ann Pharmacother* 2000; **34:** 1024–7.
3. Whelan J, *et al.* Omeprazole does not alter plasma methotrexate clearance. *Cancer Chemother Pharmacol* 1999; **44:** 88–9.
4. Tröger U, *et al.* Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. *BMJ* 2002; **324:** 1497.
5. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.

Immunosuppressants. For reports of enhanced toxicity with *ciclosporin* in patients who have received methotrexate see p.1826.

Leflunomide. For a report of the effect of methotrexate in patients receiving leflunomide, see p.76.

Nitrous oxide. Severe unpredictable myelosuppression and stomatitis have been attributed to the use of nitrous oxide anaesthesia in patients receiving methotrexate, potentiating the effects of methotrexate on folate metabolism.[1] The effect could be reduced by the use of folinic acid rescue.

1. Goldhirsch A, *et al.* Methotrexate/nitrous-oxide toxic interaction in perioperative chemotherapy for early breast cancer. *Lancet* 1987; **ii:** 151.

NSAIDs. Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when it was given with various NSAIDs including *aspirin* and other *salicylates*,[1,2] *azapropazone*,[3] *diclofenac*,[4] *indometacin*,[4,5] and *ketoprofen*.[6] The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion.[6,7] *Naproxen* has been reported not to affect the pharmacokinetics of methotrexate,[8,9] but a fatal interaction has nonetheless been reported.[10] Despite the risks, some commentators have pointed out that methotrexate and NSAIDs are frequently used together in the treatment of rheumatoid arthritis,[11,12] and that provided this is done with caution, in low doses, and patients are appropriately monitored and cautioned to avoid additional 'over-the-counter' analgesics, such combinations need not be contra-indicated. A study in patients receiving low-dose methotrexate for rheumatoid arthritis suggested that *flurbiprofen*, *ketoprofen*, or *piroxicam* did not influence methotrexate clearance.[13] A case of methotrexate toxicity has nevertheless been described[14] in an elderly woman when flurbiprofen was added to low-dose methotrexate therapy.

Manufacturers of methotrexate generally contra-indicate the use of NSAIDs with high-dose methotrexate.

1. Baker H. Intermittent high dose oral methotrexate therapy in psoriasis. *Br J Dermatol* 1970; **82:** 65–9.
2. Zuik M, Mandel MA. Methotrexate-salicylate interaction: a clinical and experimental study. *Surg Forum* 1975; **26:** 567–9.
3. Daly HM, *et al.* Methotrexate toxicity precipitated by azapropazone. *Br J Dermatol* 1986; **114:** 733–5.
4. Gabrielli A, *et al.* Methotrexate and nonsteroidal anti-inflammatory drugs. *BMJ* 1987; **294:** 776.
5. Maiche AG. Acute renal failure due to concomitant action of methotrexate and indomethacin. *Lancet* 1986; **i:** 1390.
6. Thyss A, *et al.* Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. *Lancet* 1986; **i:** 256–8.
7. Furst DE, *et al.* Effect of aspirin and sulindac on methotrexate clearance. *J Pharm Sci* 1990; **79:** 782–6.
8. Stewart CF, *et al.* Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 1990; **47:** 540–6.
9. Vakily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; **45:** 1179–86.
10. Singh RR, *et al.* Fatal interaction between methotrexate and naproxen. *Lancet* 1986; **i:** 1390.
11. Tully M. NSAIDs. *Pharm J* 1991; **247:** 746.
12. Zachariae H. Methotrexate and nonsteroidal anti-inflammatory drugs. *Br J Dermatol* 1992; **126:** 95.
13. Tracy TS, *et al.* Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1994; **37:** 453–6.
14. Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann Pharmacother* 1992; **26:** 234–7.

Probenecid. Probenecid can produce two- to fourfold increases in serum-methotrexate concentrations,[1-3] presumably by inhibiting renal excretion of methotrexate. Although probenecid has been shown to reduce protein binding of methotrexate,[4] usual doses of probenecid are unlikely to significantly affect methotrexate elimination by this mechanism. A woman receiving low-dose weekly methotrexate for rheumatoid arthritis developed severe pancytopenia when probenecid was given for asymptomatic hyperuricaemia.[5]

1. Aherne GW, *et al.* Prolongation and enhancement of serum methotrexate concentrations by probenecid. *BMJ* 1978; **1:** 1097–9.
2. Howell SB, *et al.* Effect of probenecid on cerebrospinal fluid methotrexate kinetics. *Clin Pharmacol Ther* 1979; **26:** 641–6.
3. Lilly MB, Omura GA. Clinical pharmacology of oral intermediate-dose methotrexate with or without probenecid. *Cancer Chemother Pharmacol* 1985; **15:** 220–2.
4. Paxton JW. Interaction of probenecid with the protein binding of methotrexate. *Pharmacology* 1984; **28:** 86–9.
5. Basin KS, *et al.* Severe pancytopenia in a patient taking low dose methotrexate and probenecid. *J Rheumatol* 1991; **18:** 609–10.

Retinoids. An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* are given together,[1] possibly due to increased plasma concentrations of methotrexate.[2,3]

1. Zachariae H. Dangers of methotrexate/etretinate combination therapy. *Lancet* 1988; **i:** 422.
2. Harrison PV, *et al.* Methotrexate and retinoids in combination for psoriasis. *Lancet* 1987; **ii:** 512.
3. Larsen FG, *et al.* Interaction of etretinate with methotrexate pharmacokinetics in psoriatic patients. *J Clin Pharmacol* 1990; **30:** 802–7.

Xanthines. For mention of the effect of methotrexate on the clearance of theophylline, see Antineoplastics, under Interactions of Theophylline, p.1144.

Pharmacokinetics

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less well absorbed. It is also rapidly and completely absorbed after intramuscular doses. Peak serum concentrations are achieved in 1 to 2 hours after an oral dose, and 30 to 60 minutes after an intramuscular one.

Methotrexate is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 litres/kg; it penetrates ascitic fluid and effusions, which may act as a depot and thus enhance toxicity. Clearance from plasma is reported to be triphasic, with a terminal elimination half-life of between 3 and 10 hours after doses less than 30 mg/m^2 or 8 to 15 hours after high-dose parenteral therapy. It is about 50% bound to plasma protein. Methotrexate enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates: bound drug may remain in the body for several months, particularly in the liver.

Only small or insignificant amounts cross the blood-brain barrier and enter the CSF after oral or parenteral doses although this may be increased by giving higher doses; however, after intrathecal doses there is significant passage into the systemic circulation.

Methotrexate has been detected in very small amounts in saliva and breast milk. It crosses the placenta.

Methotrexate does not appear to undergo significant metabolism at low doses; after high-dose therapy the 7-hydroxy metabolite has been detected. Methotrexate may be partly metabolised by the intestinal flora after oral doses. It is excreted primarily in the urine, by glomerular filtration and active tubular secretion. Small amounts are excreted in bile and found in faeces; there is some evidence for enterohepatic recirculation.

Considerable interindividual variation exists in the pharmacokinetics of methotrexate: those patients in whom clearance is delayed are at increased risk of toxicity.

◊ References.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; **3:** 1–13.
2. Balis FM, *et al.* Clinical pharmacokinetics of commonly used anticancer drugs. *Clin Pharmacokinet* 1983; **8:** 202–32.
3. Wang Y-M, Fujimoto T. Clinical pharmacokinetics of methotrexate in children. *Clin Pharmacokinet* 1984; **9:** 335–48.
4. Witter FR. Clinical pharmacokinetics in the treatment of rheumatoid arthritis in pregnancy. *Clin Pharmacokinet* 1993; **25:** 444–9.
5. Bannwarth B, *et al.* Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. *Clin Pharmacokinet* 1996; **30:** 194–210.
6. Chládek J, *et al.* Pharmacokinetics and pharmacodynamics of low-dose methotrexate in the treatment of psoriasis. *Br J Clin Pharmacol* 2002; **54:** 147–56.
7. Grim J, *et al.* Pharmacokinetics and pharmacodynamics of methotrexate in non-neoplastic diseases. *Clin Pharmacokinet* 2003; **42:** 139–51.
8. Aumente D, *et al.* Population pharmacokinetics of high-dose methotrexate in children with acute lymphoblastic leukaemia. *Clin Pharmacokinet* 2006; **45:** 1227–38.
9. Thompson PA, *et al.* Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2007; **59:** 847–53.

Uses and Administration

Methotrexate is an antineoplastic that acts as an antimetabolite of folic acid. It also has immunosuppressant properties. Within the cell, folic acid is reduced to dihydrofolic and then tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA. It is most active against cells in the S phase of the cell cycle. Folinic acid (the 5-formyl derivative of tetrahydrofolic acid) has been given after high doses to bypass the block in tetrahydrofolate production in normal cells and prevent the adverse effects of methotrexate. A suggested schedule for *folinic acid rescue* is described under Folinic Acid, p.1944. (See also Treatment of Adverse Effects, above). Methotrexate, in very high doses, followed by folinic acid rescue, is used in treating some malignant diseases.

Methotrexate is used in the management of acute lymphoblastic leukaemia. It is seldom used for the induction of remission but is employed in maintenance programmes and in the prophylaxis and treatment of meningeal leukaemia. It may be used for Burkitt's and other non-Hodgkin's lymphomas. In the solid neoplasms it is an important part of curative regimens for choriocarcinoma and other gestational trophoblastic tumours, and for the adjuvant therapy of osteosarcoma and breast cancer. It may also be used in malignant neoplasms of the bladder and head and neck, and some other neoplasms, as indicated by the cross references given below.

Methotrexate is of value in the treatment of psoriasis but because of the risks associated with this use, it should only be given when the disease is severe and has not responded to other forms of treatment. It is widely used as a disease-modifying antirheumatic drug in rheumatoid arthritis. Methotrexate may be used to prevent graft-versus-host disease after bone marrow transplantation and may be used as a cytotoxic immunosuppressant and corticosteroid-sparing agent in non-malignant diseases.

Methotrexate has a role in the management of ectopic pregnancy and in the termination of early pregnancy (see below).

Methotrexate may be given orally as the base or the sodium salt, or by injection as the sodium salt. Doses are calculated in terms of methotrexate. Methotrexate sodium 16.5 mg is equivalent to about 15 mg of methotrexate. The doses and regimens used vary enormously, and may need to be adjusted according to bone marrow or other toxicity (see also under Bone-marrow Depression, p.639). Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24 hours.

A common dose for maintenance therapy of acute lymphoblastic **leukaemia** is 15 mg/m^2 once or twice weekly, orally or intramuscularly, with other agents such as mercaptopurine; 20 to 30 mg/m^2 twice weekly has also been given. Alternatively, 2.5 mg/kg may be given intravenously every 14 days. Meningeal leukaemia may be treated by the intrathecal injection of 12 mg/m^2 (maximum 15 mg) once weekly for 2 to 3 weeks, then once monthly; an alternative is 200 to 500 micrograms/kg at intervals of 2 to 5 days until the cell count of the CSF returns to normal. Another regimen has been recommended for children based on age, with children under the age of 1 year receiving 6 mg, 8 mg for those 1 year of age, 10 mg in 2-year-olds, and 12 mg in those 3 years of age or older. Intrathecal doses have also sometimes been given prophylactically to patients with lymphoblastic leukaemia in association with intrathecal cytarabine and hydrocortisone. Methotrexate in intravenous doses of about 500 mg/m^2, followed by folinic acid rescue, may also produce effective concentrations in the CSF and has been used for meningeal leukaemia.

Choriocarcinoma has been treated with doses of 15 to 30 mg daily orally or intramuscularly for 5 days repeated after an interval of 1 week or more, for 3 to 5 courses. Alternatively 0.25 to 1 mg/kg up to a maximum of 60 mg has been given intramuscularly every 48 hours for 4 doses, followed by folinic acid rescue, and repeated at intervals of 7 days for 4 or more courses. Combination chemotherapy may be necessary in patients with metastases.

Doses of 10 to 60 mg/m^2 are given intravenously in the treatment of **breast cancer**, often with cyclophosphamide and fluorouracil.

In advanced **lymphosarcoma** doses of 0.625 to 2.5 mg/kg daily have been suggested with other antineoplastics. Alternatively, higher doses of up to 30 mg/kg have been given intravenously, followed by folinic acid rescue. For Burkitt's lymphoma 10 to 25 mg of oral methotrexate has been given daily for 4 to 8 days, repeated after an interval of 7 to 10 days, while patients with mycosis fungoides may be given an oral dose of 2.5 to 10 mg daily to induce remission; alternatively 50 mg may be given weekly as a single dose or two divided doses, by intramuscular injection.

Very high doses, in the range 12 to 15 g/m^2 have been given by intravenous infusion, followed by folinic acid, as part of combined adjuvant therapy in patients with **osteosarcoma**. High-dose regimens have been tried in other malignancies, including carcinoma of the lung and of the head and neck.

Single weekly doses of 10 to 25 mg may be given orally or by intramuscular or intravenous injection in the treatment of **psoriasis** and adjusted by response. Other, more frequent, regimens have been used but a weekly dosage regimen appears to be less hepatotoxic than a daily one. In the treatment of **rheumatoid arthritis** doses of 7.5 mg orally once weekly are used, adjusted by response and not exceeding 20 mg/week.

It is essential that blood counts and tests of renal and liver function should be made before, during, and after each course of treatment with methotrexate (see Precautions, above).

Asthma. Various immunosuppressants, including methotrexate, have been tried for their anti-inflammatory and corticosteroid-sparing properties in chronic asthma (p.1108), but because of fears about toxicity are largely reserved for certain patients dependent upon systemic corticosteroids. Results of individual studies with methotrexate have been conflicting, but it appears that some patients may benefit from the corticosteroid-sparing effects of methotrexate.[1,2] However, other reviewers considered that the reduction in corticosteroid dose was insufficient to offset the adverse effects of methotrexate.[3] Methotrexate therapy must be given for at least 3 months for an adequate assessment of efficacy.

1. Shulimzon TR, Shiner RJ. A risk-benefit assessment of methotrexate in corticosteroid-dependent asthma. *Drug Safety* 1996; **15:** 283–90.
2. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997; **112:** 29–33.
3. Davies H, *et al.* Methotrexate as a steroid sparing agent for asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 12/05/05).

Connective tissue and muscular disorders. Reports in a limited number of patients indicate that methotrexate given once weekly in low to moderate doses may be of benefit in patients with SLE (p.1513), with benefit reported particularly for joint and mucocutaneous symptoms.[1] In a retrospective analysis of patients with cutaneous lupus erythematosus, low doses of methotrexate significantly decreased disease activity.[2]

Methotrexate therapy has been investigated for its potential corticosteroid-sparing properties in polymyalgia rheumatica (p.1510). Different regimens have been tried and although one study[3] reported benefit, others[4,5] found no evidence of clinical efficacy or a corticosteroid-sparing effect.

Methotrexate is widely used in rheumatoid arthritis (see below) and in polymyositis (p.1510), and has been tried in Cogan's syndrome (p.1502).

1. Sato EI. Methotrexate therapy in systemic lupus erythematosus. *Lupus* 2001; **10:** 162–4.
2. Wenzel J, *et al.* Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005; **153:** 157–62.
3. Ferraccioli G, *et al.* Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol* 1996; **23:** 624–8.
4. Feinberg HL, *et al.* The use of methotrexate in polymyalgia rheumatica. *J Rheumatol* 1996; **23:** 1550–2.
5. van der Veen MJ, *et al.* Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996; **55:** 218–23.

Ectopic pregnancy. Ectopic pregnancy occurs when the fertilised ovum implants outside the uterus, usually in the fallopian tube itself (tubal pregnancy). Earlier detection has become possible due to improved diagnostic techniques. In many countries, there has been a rise in the rate of ectopic pregnancies followed by a decline; this may be partly due to increasing rates of infection with *Chlamydia*, followed by the effect of prevention, and changes in the popularity of intra-uterine devices.[1] Although ectopic pregnancies may spontaneously abort early, without clinical sequelae, the potential adverse effects are serious, ranging from pelvic pain and bleeding at 5 to 6 weeks of gestation (indistinguishable from spontaneous abortion), to potentially fatal intra-abdominal haemorrhage later in the course of an otherwise asymptomatic pregnancy.

Laparoscopic surgery remains the standard treatment.[1-3] In some countries non-surgical methods are increasing in popularity because of earlier diagnosis.[1,4] Perhaps the most experience of the latter has been with methotrexate. Management with intramuscular methotrexate may be appropriate for selected women with small unruptured tubal pregnancies who are haemodynamically stable, have low serum-chorionic gonadotrophin concentrations, and lack contra-indications to methotrexate use.[2-6] Surgery is preferred where there is cardiac activity in the conceptus, since a living embryo increases resistance to methotrexate.[5,6] Two regimens of intramuscular methotrexate have been described. A multiple-dose regimen of 1 mg/kg on 4 alternate days, with folinic acid rescue,[1] has similar efficacy to surgery.[3] A single dose of 50 mg/m^2 can be used instead[1,4] but systematic reviews have indicated that it has a higher failure rate than surgery[3,7] and about 20% of patients will require more than one cycle of treatment.[4] The addition of an oral dose of mifepristone to single-dose methotrexate has been investigated[1,8,9] and may reduce treatment failure rates.

Methotrexate has been given by local injection directly into the ectopic (salpingocentesis). Doses of 1 mg/kg or 50 mg have been used[10] but this technique is significantly less successful than surgery.[3] Systemic methotrexate (with folinic acid rescue) has also been reported to be effective in resolving persistent ectopic pregnancy unsuccessfully treated with surgery.

The role of other agents in the management of ectopic pregnancy is less well established. Local instillation of glucose 50% by salpingocentesis has also been used in the treatment of ectopic pregnancy,[10,11] but one study was stopped because of a higher failure rate with glucose treatment compared with local methotrexate.[12]

Methotrexate may also be used in the termination of early uterine pregnancy (see below).

1. Farquhar CM. Ectopic pregnancy. *Lancet* 2005; **366:** 583–91.
2. Tay JI, *et al.* Ectopic pregnancy. *BMJ* 2000; **320:** 916–9. Correction. *ibid.*; **321:** 424.
3. Hajenius PJ, *et al.* Interventions for tubal ectopic pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/05/08).
4. Lipscomb GH, *et al.* Nonsurgical treatment of ectopic pregnancy. *N Engl J Med* 2000; **343:** 1325–9.

5. Lipscomb GH, *et al.* Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999; **341:** 1974–8.
6. American College of Obstetricians and Gynecologists. ACOG practice bulletin: medical management of tubal pregnancy. Number 3, December 1998. *Int J Gynecol Obstet* 1999; **65:** 97–103.
7. Parker J, *et al.* A systematic review of single-dose intramuscular methotrexate for the treatment of ectopic pregnancy. *Aust N Z J Obstet Gynaecol* 1998; **38:** 145–50.
8. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
9. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
10. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42:** 39–47.
11. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76:** 797–800.
12. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265:** 82–4.

Inflammatory bowel disease. Methotrexate (given intramuscularly once weekly in a dose of 25 mg) was reported to improve symptoms and reduce corticosteroid requirements in a large controlled study in patients with chronic active Crohn's disease.[1] Those patients who were in remission after 16 weeks of methotrexate treatment were entered into a further placebo-controlled trial[2] of methotrexate 15 mg weekly by intramuscular injection. During 40 weeks of follow-up, a higher proportion of patients receiving methotrexate remained in remission, and had fewer relapses. Smaller studies have also reported modest benefit for oral methotrexate 12.5 to 22.5 mg/week in chronic active disease.[3,4] Subcutaneous methotrexate has also been used.[5] A review[6] concluded that low-dose methotrexate could be recommended for induction of remission and for its corticosteroid-sparing effect in refractory and corticosteroid-dependent Crohn's disease, although the precise indications, dose, and route for its use were still unclear. The value of methotrexate in ulcerative colitis is doubtful: although benefits have been seen in some patients,[5,7] a study in active ulcerative colitis found no significant differences between oral methotrexate 12.5 mg/week and placebo.[8] For a discussion of inflammatory bowel disease, see p.1697.

1. Feagan BG, *et al.* Methotrexate for the treatment of Crohn's disease. *N Engl J Med* 1995; **332:** 292–7.
2. Feagan BG, *et al.* A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N Engl J Med* 2000; **342:** 1627–32.
3. Oren R, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92:** 2203–9.
4. Arora S, *et al.* Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46:** 1724–9.
5. Egan LJ, *et al.* A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 1999; **13:** 1597–1604.
6. Egan LJ, Sandborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. *Mayo Clin Proc* 1996; **71:** 69–80.
7. Kozarek RA. Methotrexate for refractory Crohn's disease: preliminary answers to definitive questions. *Mayo Clin Proc* 1996; **71:** 104–5.
8. Oren R, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; **110:** 1416–21.

Malignant neoplasms. Methotrexate is extensively used in the management of malignant disease. In acute lymphoblastic leukaemia it is used for maintenance therapy, and intrathecally for prophylaxis of CNS relapse, as discussed on p.651, while it also forms part of a number of regimens used for Burkitt's and other aggressive, intermediate- to high-grade non-Hodgkin's lymphomas (see p.657 and p.656), including mycosis fungoides (p.657) and those associated with AIDS (p.657). In the solid neoplasms it is an important part of curative regimens for gestational trophoblastic tumours (p.650), the adjuvant therapy of osteosarcoma (p.675) and is used in regimens for tumours of the bladder (p.659), brain (p.660), breast (p.661), stomach (p.664), and head and neck (p.666).

Multiple sclerosis. Results suggest that methotrexate 7.5 mg by mouth weekly may be of benefit[1] in slowing the progression of multiple sclerosis (p.892). Although the results of studies of immunosuppressant therapy in this condition have tended to be disappointing, it has been pointed out that benefit was assessed differently in the methotrexate study,[2] which may have a bearing on its more favourable conclusions.

1. Goodkin DE, *et al.* Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol* 1995; **37:** 30–40.
2. Whitaker JN, *et al.* Clinical outcomes and documentation of partial beneficial effects of immunotherapy for multiple sclerosis. *Ann Neurol* 1995; **37:** 5–6.

Myasthenia gravis. Methotrexate has been tried in the management of myasthenia gravis (p.629) in patients who require immunosuppression but are intolerant of or unresponsive to corticosteroids and azathioprine.

Organ and tissue transplantation. For reference to the use of methotrexate (usually with ciclosporin) in bone marrow transplantation, see Haematopoietic Stem Cell Transplantation, p.1811.

Primary biliary cirrhosis. Like other drugs used for primary biliary cirrhosis (p.2408) methotrexate has been associated with biochemical improvement but evidence of clinical and in particular histological improvement is harder to demonstrate, and the toxicity of immunosuppressants such as methotrexate is problematic. A randomised study comparing methotrexate with colchicine found a slightly lower survival with methotrexate after 10 years of treatment;[1] a systematic review[2] concluded that methotrexate increased mortality in patients with primary biliary cirrhosis and that its use could not be recommended.

1. Kaplan MM, *et al.* A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cirrhosis: ten-year results. *Hepatology* 2004; **39:** 915–23.
2. Gong Y, Gluud C. Methotrexate for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 08/02/06).

Psoriatic arthritis. Methotrexate may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p.13) when the arthritis is not controlled by physical therapy and NSAIDs, although toxicity may limit long-term use in some patients.

Rheumatoid arthritis. Therapy of rheumatoid arthritis (p.11) is conventionally begun with an analgesic and an NSAID for symptomatic relief, to which a disease-modifying antirheumatic drug (DMARD) is subsequently added in an attempt to retard the disease process. It is now clear that irreversible joint damage commonly occurs in early disease and rheumatologists now generally add the DMARD shortly after rheumatoid arthritis has been diagnosed. Methotrexate is widely used,[1] and is the DMARD of first choice in many patients. Systematic review has confirmed that methotrexate has significant benefit in the short-term treatment of the disease.[2] Methotrexate has also been tried with ciclosporin, hydroxychloroquine and sulfasalazine, leflunomide, etanercept, and infliximab. Studies have shown improved responses to these combinations compared with methotrexate alone, but long-term efficacy and safety has not been studied.[3]

Methotrexate may be of benefit in juvenile idiopathic arthritis (p.10).[4-6]

Methotrexate may also be of value in the management of associated uveitis (see below).

1. Anonymous. Modifying disease in rheumatoid arthritis. *Drug Ther Bull* 1998; **36:** 3–6.
2. Suarez-Almazor ME, *et al.* Methotrexate for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 12/05/05).
3. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001; **134:** 695–706.
4. Ravelli A, *et al.* Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. *J Pediatr* 1998; **133:** 262–5.
5. Takken T, *et al.* Methotrexate for treating juvenile idiopathic arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 12/05/05).
6. Ramanan AV, *et al.* Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; **88:** 197–200.

Sarcoidosis. Where therapy is required for sarcoidosis (p.1512) corticosteroids are the first choice of drug; methotrexate is one of the preferred second-line immunosuppressants.

References.

1. Webster GF, *et al.* Methotrexate therapy in cutaneous sarcoidosis. *Ann Intern Med* 1989; **111:** 538–9.
2. Soriano FG, *et al.* Neurosarcoidosis: therapeutic success with methotrexate. *Postgrad Med J* 1990; **66:** 142–3.
3. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155:** 846–51.
4. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; **54:** 742–6.

Scleroderma. There is some evidence of benefit with methotrexate in patients with scleroderma (p.1817), particularly for cutaneous symptoms, although not all studies have shown clear value.

References.

1. van den Hoogen FH, *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; **35:** 364–72.
2. Seyger MMB, *et al.* Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; **39:** 220–5.
3. Uziel Y, *et al.* Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; **136:** 91–5.
4. Pope JE, *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44:** 1351–8.
5. Weibel L, *et al.* Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; **155:** 1013–20.

Skin disorders, non-malignant. Methotrexate is widely used in the treatment of severe refractory psoriasis. As discussed on p.1583 the aim of such therapy is to bring the disease under control, enabling a return to other therapy. For use in psoriatic arthritis see above. Methotrexate is also used with corticosteroids in the management of pemphigus and pemphigoid (p.1582).

Termination of pregnancy. Methotrexate has been investigated as an alternative to mifepristone for use with misoprostol for the termination of early pregnancy (p.2004). Intramuscular methotrexate followed 3 days later by intravaginal misoprostol was more effective than misoprostol alone for termination at 56 days or less;[1] the combination was reported to be less successful after 57 to 63 days of gestation.[2] Later studies[3,4] however found the combination to be safe and effective in terminating pregnancies up to 63 days of gestation; in these the misoprostol was given up to 7 days after the methotrexate. Oral methotrexate is also effective.[5-7] However, the efficacy of methotrexate followed by misoprostol does appear to diminish with increasing gestational age,[8] and the time to complete abortion generally takes longer with regimens using methotrexate compared with mifepristone.[9] The American College of Obstetricians and Gynecologists[10] recommends that methotrexate with misoprostol may be used in pregnancies of up to 49 days of gestation, the usual regimen being methotrexate, either 50 mg/m^2 intramuscularly or 50 mg orally, followed 3 to 7 days later by misoprostol 800 micrograms vaginally. The College also advises that it may take up to 4 weeks for complete abortion to occur in about 15 to 25% of women given such regimens.

For the role of methotrexate in the management of ectopic pregnancy, see above.

1. Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994; **272:** 1190–5.
2. Creinin MD. Methotrexate and misoprostol for abortion at 57-63 days gestation. *Contraception* 1994; **50:** 511–15.
3. Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. *N Engl J Med* 1995; **333:** 537–40.
4. Creinin MD, *et al.* A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *Am J Obstet Gynecol* 1995; **173:** 1578–84.
5. Creinin MD. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1996; **54:** 15–18.
6. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
7. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.
8. Creinin MD, *et al.* Methotrexate and misoprostol for early abortion: a multicenter trial. *Contraception* 1996; **53:** 321–7.
9. Wiebe E, *et al.* Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002; **99:** 813–19.
10. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, October 2005). *Obstet Gynecol* 2005; **106:** 871–82.

Uveitis. Methotrexate has been reported to be safe and effective[1-3] when used to treat uveitis (p.1515) in small numbers of patients.

1. Samson CM, *et al.* Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. *Ophthalmology* 2001; **108:** 1134–9.
2. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005; **32:** 362–5.
3. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol* 2005; **89:** 806–8.

Vasculitic syndromes. In giant cell arteritis (p.1503), improved clinical response and a corticosteroid-sparing effect have been reported with the addition of methotrexate to corticosteroid therapy,[1] but other studies using different designs and dosages[2,3] have failed to find any benefit. For the use of methotrexate in Takayasu's arteritis and Wegener's granulomatosis see p.1514 and p.1515, respectively.

1. Jover JA, *et al.* Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; **134:** 106–14.
2. Spiera RF, *et al.* A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; **19:** 495–501.
3. Hoffman GS, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; **46:** 1309–18.

Preparations

BP 2008: Methotrexate Injection; Methotrexate Tablets;
USP 31: Methotrexate for Injection; Methotrexate Injection; Methotrexate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Artrait; Ervemin; Trixate; Xantromid; ***Austral.:*** Ledertrexate; Methoblastin; ***Austria:*** Ebetrexat; Emthexate; ***Belg.:*** Emthexate; Ledertrexate; ***Braz.:*** Biometrox; Emthexate; Metrexato; Miantrex; Reutrexato; Tecnomet; Trexeron†; Unitrexate†; ***Chile:*** Trixilem; ***Cz.:*** Metoject; ***Denm.:*** Emthexate†; Metoject; ***Fin.:*** Emthexat†; Metoject; Trexan; ***Fr.:*** Ledertrexate†; Novatrex; ***Ger.:*** Farmitrexat†; Lantarel; Metex; MTX; O-trexat; ***Gr.:*** Emthexate; Methobion; Metoject; ***Hung.:*** Metoject; Trexan; ***India:*** Biotrexate; Caditrex; Imutrex; Methocip; Neotrexate; ***Indon.:*** Emthexate; ***Israel:*** Abitrexate; ***Jpn:*** Metolate; ***Malaysia:*** Emthexate; ***Mex.:*** Atrexel; Ifamet; Ledertrexate; Leulin†; Medsatrexate; Methoblastin†; Otaxem; Texate; Trixilem; ***Neth.:*** Emthexate; Ledertrexate†; Metoject; ***Norw.:*** Emthexat; Metoject; ***NZ:*** Emthexate; Ledertrexate†; Methoblastin; ***Philipp.:*** Emthexate; Hextrate; Methobax; Pterin; Zexate; ***Pol.:*** Trexan; ***Port.:*** Fauldexato; Metoject; ***Rus.:*** Trixilem (Триксилем)†; ***S.Afr.:*** Abitrexate; Emthexate; ***Spain:*** Emthexate; Metoject; ***Swed.:*** Emthexat†; Metoject; ***Thai.:*** Abitrexate; Emthexate; Trixilem; Zexate; ***Turk.:*** Emthexate; Trexan; ***UK:*** Maxtrex; Metoject; ***USA:*** Rheumatrex; Trexall; ***Venez.:*** Zexate.

2-Methoxyoestradiol

2-ME2; 2-Methoxyestradiol; NSC-659853. (17β)-2-Methoxyestra-1,3,5(10)-triene-3,17-diol.

$C_{19}H_{26}O_3$ = 302.4.

CAS — 362-07-2.

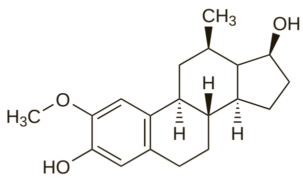

Profile

2-Methoxyoestradiol is a metabolite of oestradiol (p.2097). It does not exhibit direct oestrogenic activity, but works through multiple cellular pathways to produce antineoplastic effects, including inhibition of angiogenesis and induction of apoptosis. 2-Methoxyoestradiol is under investigation in the treatment of various diseases, including glioblastoma, multiple myeloma, carcinoid tumours, as well as ovarian, prostate, breast, and renal cell cancers. It is also under investigation for pulmonary arterial hypertension.

Mifamurtide *(rINN)*

Mifamurtida; Mifamurtidum; MTP-PE; Muramyl Tripeptide Phosphatidyl Ethanolamine; Muramyl Tripeptide Phosphatidyl Monoethanolamine. 2-[(N-{(2R)-2-[(2-Acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2R)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate.

Мифамуртид

$C_{59}H_{109}N_6O_{19}P$ = 1237.5.

CAS — 83461-56-7.

ATC — L03AX15.

ATC Vet — QL03AX15.

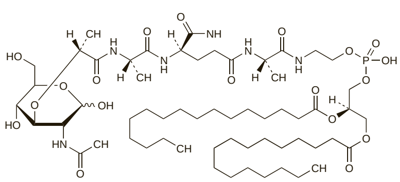

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Mifamurtide Sodium *(rINNM)*

CGP-19835A; L-MTP-PE (liposomal mifamurtide sodium); Mifamurtida sódica; Mifamurtide *(USAN)*; Mifamurtide Sodique; Mifamurtidum Natricum. 2-[(N-{(2R)-2-[(3R,4R,5S,6R)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yloxy]propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2R)-2,3-bis(hexanoyloxy)propyl sodium phosphate hydrate.

Мифамуртид Натрий

$C_{59}H_{108}N_6NaO_{19}P,xH_2O$.

CAS — 838853-48-8.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Profile

Mifamurtide is an immunomodulator that activates macrophages to increase their capacity to destroy cancer cells. It is under investigation for the treatment of osteosarcoma.

Miltefosine *(BAN, rINN)*

D-18506; HDPC; Hexadecylphosphocholine; Miltefosiini; Miltefosin; Miltefosina; Miltéfosine; Miltefosinum. [2-(Trimethylammonio)ethyl][hexadecyloxyphosphonate].

Мильтефозин

$C_{21}H_{46}NO_4P$ = 407.6.

CAS — 58066-85-6.

ATC — L01XX09.

ATC Vet — QL01XX09.

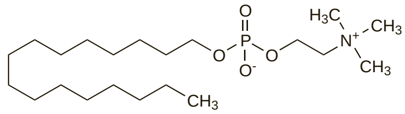

Profile

Miltefosine is a phospholipid derivative which is structurally related to the phospholipid components of the cell membrane and is thought to exert its antineoplastic actions by disruption of cell-membrane function. A 6% solution is applied once or twice daily as a topical antineoplastic agent for skin metastases of breast cancer. Miltefosine has also been tried orally for various malignant neoplasms. It is used for the treatment of visceral and cutaneous leishmaniasis in an oral dose of 1.5 to 2.5 mg/kg daily (maximum daily dose 150 mg) for 28 days.

Leishmaniasis. Miltefosine, given orally in doses of 50 to 150 mg daily, or about 2.5 mg/kg daily, for 28 days, appears to be of benefit[1-7] in the treatment of visceral leishmaniasis (p.824), and has been licensed for this purpose in India and Germany. Benefit has also been reported in patients given similar doses for New World cutaneous leishmaniasis,[8] and it has also been licensed in some South American countries, but success may depend on the infecting *Leishmania* species.[9] The use of longer courses of miltefosine in the treatment of patients with both leishmaniasis and HIV infection has been reported.[10]

1. Sundar S, *et al.* Trial of oral miltefosine for visceral leishmaniasis. *Lancet* 1998; **352:** 1821–3.
2. Jha TK, *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; **341:** 1795–1800.
3. Thakur CP, *et al.* Miltefosine in a case of visceral leishmaniasis with HIV co-infection; and rising incidence of this disease in India. *Trans R Soc Trop Med Hyg* 2000; **94:** 696–7.
4. Sundar S, *et al.* Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 2000; **31:** 1110–13.
5. Sundar S, *et al.* Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med* 2002; **347:** 1739–46.
6. Bhattacharya SK, *et al.* Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis* 2004; **38:** 217–21.
7. Ritmeijer K, *et al.* A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis* 2006; **43:** 357–64.
8. Soto J, *et al.* Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis* 2001; **33:** e57–e61. Available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/322689 (accessed 01/08/08)
9. Soto J, *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; **38:** 1266–72.
10. Sindermann H, *et al.* Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis* 2004; **39:** 1520–3.

Malignant neoplasms. References to the use of topical miltefosine in breast cancer.

1. Terwogt JM, *et al.* Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. *Br J Cancer* 1999; **79:** 1158–61.
2. Smorenburg CH, *et al.* Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. *Anticancer Drugs* 2000; **11:** 825–8.
3. Leonard R, *et al.* Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol* 2001; **19:** 4150–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Miltex†; ***Austria:*** Miltex; ***Braz.:*** Miltex; ***Chile:*** Miltex†; ***Cz.:*** Miltex†; ***Fin.:*** Miltex†; ***Fr.:*** Miltex; ***Ger.:*** Impavido; Miltex; ***Hung.:*** Miltex; ***Israel:*** Miltex; ***Ital.:*** Miltex; ***Malaysia:*** Miltex†; ***Philipp.:*** Miltex; ***Singapore:*** Miltex; ***Spain:*** Miltex; ***Swed.:*** Miltex; ***UK:*** Miltex.

Mitobronitol *(BAN, rINN)*

DBM; Dibromomannitol; Mitobronitolum; NSC-94100; R-54; WR-220057. 1,6-Dibromo-1,6-dideoxy-D-mannitol.

Митобронитол

$C_6H_{12}Br_2O_4$ = 308.0.

CAS — 488-41-5.

ATC — L01AX01.

ATC Vet — QL01AX01.

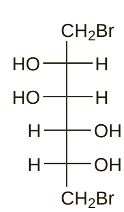

Pharmacopoeias. In *Br.*

BP 2008 (Mitobronitol). A white or almost white crystalline solid. Slightly soluble in water, in alcohol, and in acetone; practically insoluble in chloroform. Protect from light.

Profile

Mitobronitol is an antineoplastic which appears to act as an alkylating agent, perhaps by epoxide formation. It has been used in the management of thrombocythaemia, both primary, and secondary to chronic myeloid leukaemia or polycythaemia vera.

The usual oral dose is 250 mg daily until the platelet count falls to acceptable levels. Intermittent dosage has been given for maintenance therapy, adjusted according to the blood count. Frequent examination of the blood should be performed during treatment.

Mitobronitol is well absorbed from the gastrointestinal tract and is excreted through the liver into the bile, with reabsorption from the small intestine. It is eliminated as unchanged drug and some bromine-containing metabolites in the urine over several days.

Carcinogenicity. Long-term follow-up of a cooperative study[1] involving 350 patients with polycythaemia vera and treated with mitobronitol was thought to indicate that mitobronitol was less likely than phosphorus-32 or busulfan to induce acute myeloid leukaemia.

For a discussion of the usual management of polycythaemia vera, see p.654.

1. Kelemen E, *et al.* Decreasing risk of leukaemia during prolonged follow-up after mitobronitol therapy for polycythaemia vera. *Lancet* 1987; **ii:** 625.

Preparations

BP 2008: Mitobronitol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Myelobromol; ***UK:*** Myelobromol.

Mitoguazone Dihydrochloride *(rINNM)*

Dihidrocloruro de mitoguazona; Methyl-GAG; Methylglyoxal Bisguanylhydrazone (mitoguazone); MGBG; Mitoguazone, Dichlorhydrate de; Mitoguazoni Dihydrochloridum; NSC-32946. 1,1′-[(Methylethanediylidene)dinitrilo]diguanidine dihydrochloride.

Митогуазона Дигидрохлорид

$C_5H_{12}N_8,2HCl$ = 257.1.

CAS — 459-86-9 (mitoguazone); 7059-23-6 (mitoguazone dihydrochloride).

ATC — L01XX16.

ATC Vet — QL01XX16.

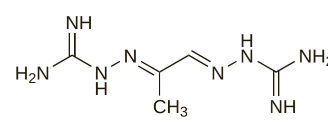

(mitoguazone)

Profile

Mitoguazone is an antineoplastic that may exert its cytotoxic effects by its ability to inhibit polyamine biosynthesis. It has been tried as the dihydrochloride monohydrate or the acetate, in the treatment of leukaemias, lymphomas, and some solid tumours.

Mitoguazone may produce hypoglycaemia and should be given dissolved in glucose-containing infusion fluids; sugar may be taken orally if hypoglycaemia develops during infusion. Granulocytopenia and thrombocytopenia are generally mild and reversible on stopping treatment. Gastrointestinal effects frequently occur.

Mitolactol *(rINN)*

DBD; Dibromodulcitol; Mitolactolum; NSC-104800; WR-138743. 1,6-Dibromo-1,6-dideoxy-D-galactitol.

Митолактол

$C_6H_{12}Br_2O_4$ = 308.0.

CAS — 10318-26-0.

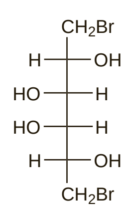

Profile

Mitolactol is an antineoplastic that may act by alkylation, probably as epoxide metabolites including dianhydrogalactitol. It has been given orally in the treatment of metastatic breast and cervical carcinoma, although other drugs are usually preferred, and has also been tried in other malignant neoplasms, notably those of the brain.

In addition to myelosuppression, which is usually dose-limiting, and manifests chiefly as leucopenia and thrombocytopenia, adverse effects include gastrointestinal disturbances, skin rashes, grey pigmentation of the skin, transient disturbances of hepatic function, elevated blood-urea nitrogen (BUN), and hypersensitivity reactions. Blood counts should be taken regularly during treatment and mitolactol withdrawn if bone-marrow depression occurs.

Mitomycin *(BAN, USAN, rINN)*

Mitomicina; Mitomicinas; Mitomicinum; Mitomisin; Mitomycin C; Mitomycine; Mitomycine C; Mitomycinum; Mitomysiini; NSC-26980. 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-hydroxymethyl-8a-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione carbamate; (1*S*,2*S*,9*S*,9a*R*)-7-Amino-2,3,5,8,9,9a-hexahydro-9a-methoxy-6-methyl-5,8-dioxo-1,2-epimino-1-*H*-pyrrolo[1,2-*a*]indol-9-ylmethyl carbamate.

Митомицин

$C_{15}H_{18}N_4O_5$ = 334.3.

CAS — 50-07-7.

ATC — L01DC03.

ATC Vet — QL01DC03.

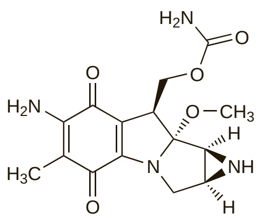

Description. Mitomycin is an antineoplastic antibiotic produced by the growth of *Streptomyces caespitosus*.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Mitomycin). A substance produced by a strain of *Streptomyces caespitotus.* Blue-violet crystals or crystalline powder. Slightly soluble in water and in acetone; freely soluble in dimethylacetamide; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 7.5. Protect from light.

USP 31 (Mitomycin). A blue-violet crystalline powder. It has a potency of not less than 970 micrograms/mg. Slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. A 0.5% suspension in water has a pH of 6.0 to 7.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Mitomycin may be incompatible with drugs that are acid in solution—for a report of incompatibility with topotecan, see p.780.

Stability. Mitomycin undergoes degradation in acid solution,[1] and two studies[2,3] suggested that mitomycin was much less stable in glucose 5% injection than in sodium chloride 0.9%. These findings were queried by a manufacturer (*Bristol, USA*) whose own results suggested[4] that mitomycin was stable for 48 hours in glucose injection 5% at 25°, and it is uncertain whether different manufacturers' formulations differ in stability, or, as has been suggested, that an unsuitable assay was used by the manufacturer to measure stability.[5]

1. Beijnen JH, Underberg WJM. Degradation of mitomycin C in acidic solution. *Int J Pharmaceutics* 1985; **24:** 219–29.
2. Benvenuto JA, *et al.* Stability and compatibility of antitumour agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
3. Quebbeman EJ, *et al.* Stability of mitomycin admixtures. *Am J Hosp Pharm* 1985; **42:** 1750–4.
4. Keller JH. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 59,64.
5. Quebbeman EJ, Hoffman NE. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; **43:** 64.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The main adverse effect of mitomycin is delayed cumulative bone-marrow suppression. Profound leucopenia and thrombocytopenia occurs after about 4 weeks with recovery in about 8 to 10 weeks after a dose. Blood counts may not recover in about one-quarter of patients. Other serious adverse effects include renal damage and pulmonary reactions; a potentially fatal haemolytic-uraemic syndrome has been reported in some patients. US licensed product information states that the degree of renal impairment does not appear to be related to dose or duration of therapy although it has been suggested that the incidence of renal toxicity is greatly increased if the total cumulative dose exceeds 120 mg (see also Effects on the Kidneys, below). Gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and rarely cardiotoxicity may also occur. Local tissue necrosis, ulceration, and cellulitis may follow extravasation.

Mitomycin is contra-indicated in patients with impaired renal function or coagulation disorders. Renal function should be tested before beginning treatment and after each course.

Effects on the bladder. Intravesical instillation of mitomycin after resection of superficial bladder tumours has led to the development of indolent asymptomatic ulcers at the resection site which may persist for months, and must be distinguished from persistent infiltrating bladder cancer.[1,2] Persistent ulceration, inflammation, necrosis, and pain has also occurred, possibly because of mitomycin extravasation at the resection site.[3] There are also a few reports[4] of eosinophilic cystitis, in which eosinophilic infiltration of the mucosa and muscle were accompanied by oedema, inflammation, muscle necrosis and fibrosis. Severe bladder contracture is a rare, and often irreversible, complication of intravesical mitomycin;[5] urinary diversion may be required in cases of intolerable urinary frequency.[6] Formation of papillary-like calcifications at the resection site,[7] and calcification of the bladder wall have also been described after the use of mitomycin for superficial transitional cell carcinoma of the bladder.

See also under Effects on the Skin, below.

1. Richards B, Tolley D. Benign ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 45.
2. Hetherington JW, Whelan P. Persistent ulcers after bladder instillation of mitomycin C. *Lancet* 1986; **i:** 324.
3. Cliff AM, *et al.* Perivesical inflammation after early mitomycin C instillation. *BJU Int* 2000; **85:** 556–7.
4. Ülker V, *et al.* Eosinophilic cystitis induced by mitomycin-C. *Int Urol Nephrol* 1996; **28:** 755–9.
5. Punga-Maole ML, *et al.* Rétraction vésicale, complication de la chimioprophylaxie du cancer vésical superficiel par mitomycine C endovésicale: a propos d'un cas et revue de la littérature. *Prog Urol* 1995; **5:** 580–5.
6. Wajsman Z, *et al.* Severely contracted bladder following intravesical mitomycin C therapy. *J Urol (Baltimore)* 1983; **130:** 340–1.
7. Fiore AA, *et al.* Papillary-like bladder calcifications following intravesical mitomycin C: a case report. *Minerva Urol Nefrol* 1993; **45:** 171–3.

Effects on the eyes. Early complications after the topical use of mitomycin with glaucoma filtering surgery (see Glaucoma, below) include hypotony, shallow anterior chamber, cataract formation, choroidal effusions, hypotonous maculopathy, and suprachoroidal haemorrhage.[1] Late complications include bleb leak, blebitis, and endophthalmitis.[2] Complications from the topical use of mitomycin with or after pterygium surgery (see Pterygium, below) commonly include irritation and photophobia. Other effects include delayed epithelial healing, avascularity of the sclera and cornea, scleral calcification and ulceration, necrotising scleritis, corneal or scleral perforation, iridocyclitis, cataract formation, glaucoma, and symblepharon.[1] Some of these effects may be severe and sight-threatening, and require further surgery.[3] Complications most commonly reported after the use of topical mitomycin in ocular surface neoplasia were hypersensitivity reactions and epiphora (an overflow of tears) secondary to stenosis of the lachrymal punctum.[4]

1. Hardten DR, Samuelson TW. Ocular toxicity of mitomycin-C. *Int Ophthalmol Clin* 1999; **39:** 79–90.
2. DeBry PW, *et al.* Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. *Arch Ophthalmol* 2002; **120:** 297–300.
3. Rubinfeld RS, *et al.* Serious complications of topical mitomycin C after pterygium surgery. *Ophthalmology* 1992; **99:** 1647–54.
4. Khong JJ, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006; **90:** 819–22.

Effects on the kidneys. A syndrome of thrombotic microangiopathy resembling the haemolytic-uraemic syndrome has been seen in patients receiving mitomycin, either alone[1] or more often with other drugs, particularly fluorouracil[2] or tamoxifen.[3,4] The syndrome is characterised by haemolytic anaemia, thrombocytopenia, and progressive renal failure, and may be accompanied by hypertension, pulmonary oedema, and neurological effects including confusion, headache, and seizures.[1,2] Onset is usually delayed, sometimes occurring several months after the end of a course of mitomycin.[1,2]

There is some uncertainty as to whether mitomycin dose is significant, but one study[1] found that all of 25 cases they reported had received total doses of 70 mg or more, and another[2] reported that 74 of 83 cases had received 60 mg or more.

Symptoms may be exacerbated by blood transfusions.[2] The use of erythropoietin allowed the cessation of blood transfusion, with subsequent haematological improvement and slower progression of chronic renal failure in one case report.[5] Plasma exchange has been suggested as possibly helpful,[1] although only a minority of patients may benefit from this treatment.[2] Captopril therapy may also be useful.[6]

1. Cordonnier D, *et al.* La néphrotoxicité de la mitomycine C (à propos de 25 observations): résultats d'une enquête multicentrique organisée par la société de néphrologie. *Nephrologie* 1985; **6:** 19–26.
2. Lesesne JB, *et al.* Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; **7:** 781–9.
3. Montes A, *et al.* A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. *Eur J Cancer* 1993; **29**A: 1854–7.
4. Ellis PA, *et al.* Haemolytic uraemic syndrome in a patient with lung cancer: further evidence for a toxic interaction between mitomycin-C and tamoxifen. *Clin Oncol (R Coll Radiol)* 1996; **8:** 402–3.
5. Catalano C, *et al.* Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron* 2002; **91:** 324–6.
6. Schiebe ME, *et al.* Mitomycin C-related hemolytic uremic syndrome in cancer patients. *Anticancer Drugs* 1998; **9:** 433–5.

Effects on the liver. Hepatic veno-occlusive disease developed in 6 of 29 patients given intensive mitomycin therapy and autologous bone marrow transplantation.[1] The effect was manifest as abdominal pain, hepatomegaly, and ascites, and liver failure was progressive and fatal in 3. A further patient, who had no symptoms, was found to have veno-occlusive disease at post mortem.

1. Lazarus HM, *et al.* Veno-occlusive disease of the liver after high-dose mitomycin C therapy and autologous bone marrow transplantation. *Cancer* 1982; **49:** 1789–95.

Effects on respiratory function. Mitomycin-induced pulmonary toxicity has been reviewed.[1,2] There have been reports of toxicity at total dosages as low as 20 mg/m^2 of mitomycin,[2] although others report[1] that the average cumulative dose associated with toxicity is 78 mg. Premedication with corticosteroids may reduce the incidence of lung toxicity.[2]

See also Effects on the Lungs, p.638. For reference to the respiratory effects of mitomycin used with a vinca alkaloid see Interactions, Antineoplastics, under Vinblastine Sulfate, p.786.

1. Linette DC, *et al.* Mitomycin-induced pulmonary toxicity: case report and review of the literature. *Ann Pharmacother* 1992; **26:** 481–4.
2. Okuno SH, Frytak S. Mitomycin lung toxicity: acute and chronic phases. *Am J Clin Oncol* 1997; **20:** 282–4.

Effects on the skin. Severe eczema of the hands and feet and generalised rash have been reported in patients receiving intravesical mitomycin.[1,2] These symptoms appear to be due to a delayed hypersensitivity (type IV) reaction,[1,2] which is probably also responsible for the bladder irritation and cystitis that may follow intravesical mitomycin[1] (see above). Leucocytoclastic vasculitis caused by an immune-complex mediated (type III) reaction and presenting as purpuric papules has also been described.[2]

1. Colver GB, *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; **122:** 217–24.
2. Kunkeler L, *et al.* Type III and type IV hypersensitivity reactions due to mitomycin C. *Contact Dermatitis* 2000; **42:** 74–6.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antineoplastics. Cardiotoxicity developed in 14 of 91 patients who received mitomycin therapy as second-line treatment for breast cancer after the failure of *doxorubicin*-containing regimens, compared with 3 of 89 similar patients whose second-line treatment did not include mitomycin.[1]

For reports of acute bronchospasm after injection of a *vinca alkaloid* in patients pretreated with mitomycin see Vinblastine Sulfate, p.786. For the increased risk of haemolytic-uraemic syndrome that may occur if mitomycin is given with *fluorouracil* or *tamoxifen* see under Effects on the Kidneys, above.

1. Buzdar AU, *et al.* Adriamycin and mitomycin C: possible synergistic cardiotoxicity. *Cancer Treat Rep* 1978; **62:** 1005–8.

Pharmacokinetics

Mitomycin disappears rapidly from the blood after intravenous injection with an initial (distribution) half-life of 17 minutes. It is widely distributed but does not appear to cross the blood-brain barrier. Mitomycin is metabolised mainly but not exclusively in the liver. The terminal half-life is about 50 minutes. After normal doses about 10% of a dose is excreted unchanged in the urine; small amounts are also present in bile and faeces. With increasing doses metabolic pathways are saturated, and more drug is excreted unchanged in the urine.

Uses and Administration

Mitomycin is a highly toxic antibiotic with antineoplastic properties. It acts as an alkylating agent after activation *in vivo* and suppresses the synthesis of nucleic acids. It is a cell-cycle non-specific agent, but is most active in the late G_1 and early S phases.

Mitomycin is used, with other antineoplastic agents, in the treatment of many solid tumours including those of the bladder, breast, cervix, eye, liver, lung, stomach, and prostate as indicated by the cross-references given below. Mitomycin has been tried in other neoplasms including those of the gastrointestinal tract, head and neck, pancreas, in melanoma, sarcomas, and in leukaemias.

Dosage regimens include an initial dose of 10 to 20 mg/m^2 intravenously; subsequent doses are repeated at intervals of 6 to 8 weeks if blood counts permit, and should be reduced according to the previous haematological response. Another suggested regimen is 2 mg/m^2 daily for 5 days, repeated after 2 days. Other regimens may be used, particularly in combination.

Doses are adjusted according to the effect on bone marrow and treatment should not be repeated until the leucocyte and platelet counts are above acceptable levels (see also Bone-marrow Depression, p.639).

Mitomycin is also used as a bladder instillation: 10 to 40 mg is instilled once weekly or three times a week for a total of 20 doses in the treatment of superficial bladder tumours. For the prevention of recurrent bladder tumours 20 mg may be instilled every 2 weeks, or 40 mg monthly or 3-monthly. Alternatively 4 to 10 mg may be instilled once weekly or three times a week. These doses are usually given in 10 to 40 mL of water for injection. The solution should be retained in the bladder for at least 1 hour.

Mitomycin has been given by the intra-arterial route in the treatment of liver tumours, sometimes as an infusion of microcapsules designed to produce localised embolisation.

Mitomycin is used for its effect on fibroblasts to improve outcomes and reduce scarring in certain types of surgery, notably in glaucoma (see below).

◊ References.

1. Abraham LM, *et al.* Mitomycin: clinical applications in ophthalmic practice. *Drugs* 2006; **66:** 321–40.
2. Bolenz C, *et al.* Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 1273–82.
3. Tabaee A, *et al.* Mitomycin C and endoscopic sinus surgery: where are we? *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 40–3.
4. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; **138:** 700–9.

Glaucoma. Mitomycin, like fluorouracil, is effective in improving the outcome of glaucoma filtering surgery in selected patients when used as an adjunct to prevent the formation of scar tissue (see p.1873). Fluorouracil is usually given as a regimen of multiple injections but mitomycin given as a single intra-operative topical application in usual concentrations ranging from 0.2 to 0.5 mg/mL appears to be of similar efficacy.[1,2] A systematic review of 11 studies concluded that intra-operative mitomycin reduced the chances of failure in high-risk patients, and in those having their first trabeculectomy.[3] However it was noted that the nature of the data might have led to overestimation of the effect and that there was some evidence of an increased risk of cataract with mitomycin. Late hypotony is also a problem.[4] For other potential complications see Effects on the Eye, above.

1. Skuta GL, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992; **99:** 438–44.
2. Katz GJ, *et al.* Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. *Ophthalmology* 1995; **102:** 1263–9.
3. Wilkins M, *et al.* Intra-operative mitomycin C for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/04/06).
4. Bindlish R, *et al.* Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up. *Ophthalmology* 2002; **109:** 1336–42.

Malignant neoplasms. Mitomycin is used in the prevention of recurrent bladder cancer (p.659), in the palliative therapy of advanced breast cancer (p.661), in malignancies of the cervix (p.663), eye (p.664), stomach and anus (p.664 and p.666), liver (p.667), and non-small cell lung cancer (p.668), and has been tried in advanced prostatic cancer (see p.671).

Pterygium. Pterygium is a degenerative condition of subconjunctival tissues that results in a vascularised overgrowth of the conjunctiva and cornea. It is cosmetically unappealing but does not usually require treatment. However, if it affects the pupillary area it can be treated surgically. Pterygium often recurs after removal and methods used to prevent recurrence include radiotherapy or the topical application of mitomycin or thiotepa.[1]

Thiotepa has been applied postoperatively as 0.05% eye drops for several weeks, but pterygium may still recur[2] and adverse effects include conjunctival injection, granuloma, hypertrophic conjunctiva, and black deposits in the conjunctival fornix.[1] Depigmentation of the eyelids may also be a problem, so patients should avoid direct sunlight during thiotepa use.[1]

Mitomycin has been applied topically to the surgical site, or given as eye drops postoperatively.[1] The optimal intra-operative exposure time and concentration are uncertain: concentrations of 0.02 or 0.04% have been applied for up to 5 minutes,[1,3] and low-dose treatment with mitomycin 0.02% for 30 seconds has been reported to be effective with few complications.[4] Postoperative treatment has generally been given as 0.02, 0.04, or 0.1% eye drops for up to 2 weeks, but the higher concentrations and longer treatment periods have been associated with more adverse effects,[1] some of which may be severe and sight-threatening (see also Effects on the Eyes, above). Comparisons of intra-operative with postoperative use suggest that pterygium recurrence rates are similar.[1,5]

A range of β-irradiation doses and fractionation methods have been used. Long-term complications include posterior subcapsular changes of the lens, atrophy and ulceration of the sclera, and scleral necrosis leading to endophthalmitis.[1] In one retrospective study,[6] intra-operative use of 0.04% mitomycin was more effective than β-irradiation in preventing recurrence after surgery. In another study,[7] postoperative mitomycin 0.02% for one week was less effective than radiation therapy.

1. Hoffman RS, Power WJ. Current options in pterygium management. *Int Ophthalmol Clin* 1999; **39:** 15–26.
2. Chapman-Smith JS. Pterygium treatment with triethylene thiophosphoramide. *Aust N Z J Ophthalmol* 1992; **20:** 129–31.
3. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. *Ophthalmic Surg Lasers* 2001; **32:** 341–5.
4. Cheng H-C, *et al.* Low-dose intraoperative mitomycin C as chemoadjuvant for pterygium surgery. *Cornea* 2001; **20:** 24–9.
5. Oguz H, *et al.* Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. *Acta Ophthalmol Scand* 1999; **77:** 147–50.
6. Amano S, *et al.* Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery. *Br J Ophthalmol* 2000; **84:** 618–21.
7. Şimşek T, *et al.* Comparative efficacy of β-irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol* 2001; **11:** 126–32.

Preparations

USP 31: Mitomycin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Asomutan; Crisofimina; Datisan†; Maximiton; Mitocyna; Mitokebir; Mitonovag; Mitotie; Oncotaxina†; Sintemicina; Vetio; ***Braz.:*** Mitocin; ***Canad.:*** Mutamycin; ***Chile:*** Metomit†; ***Fin.:*** Mitostat; Mutamycin; ***Fr.:*** Ametycine; ***Ger.:*** Ametycine; Mitem; Mito-extra; Mito-medac; ***India:*** Mitocin; ***Mex.:*** Ifamit†; Mitocin-C; Mitolem; Mitotie; Mixandex; ***Norw.:*** Mutamycin; ***Philipp.:*** Mytoxid; ***Swed.:*** Mutamycin; ***Switz.:*** Mutamycine†; ***USA:*** Mitozytrex; Mutamycin.

Mitotane *(USAN, rINN)*

CB-313; *o,p′*DDD; Mitotaani; Mitotan; Mitotano; Mitotanum; NSC-38721; WR-13045. 1,1-Dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane.

Митотан

$C_{14}H_{10}Cl_4$ = 320.0.

CAS — 53-19-0.

ATC — L01XX23.

ATC Vet — QL01XX23.

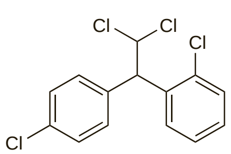

Pharmacopoeias. In *US.*

USP 31 (Mitotane). A white crystalline powder with a slight aromatic odour. M.p. is between 75° and 81°. Practically insoluble in water; soluble in alcohol, in ether, in petroleum spirit, and in fixed oils and fats. Store in airtight containers. Protect from light.

Adverse Effects

Almost all patients given mitotane have anorexia, nausea and vomiting, and sometimes diarrhoea, and about 40% suffer some central toxicity with dizziness, vertigo, sedation, lethargy, and depression. Permanent brain damage may develop with prolonged dosage. Bleeding time may be prolonged. Other common adverse effects include leucopenia, thrombocytopenia, anaemia, hypercholesterolaemia, hypertriglyceridaemia, mucositis, gynaecomastia, and headache. Ocular adverse effects may occur including blurred vision, diplopia, lenticular opacities, and retinopathy. Other adverse effects include hypersensitivity reactions, haematuria, albuminuria, skin rashes, fever, myalgia, haemorrhagic cystitis, flushing, hypertension, and orthostatic hypotension.

Precautions

Mitotane inhibits the adrenal cortex and adrenocortical insufficiency may develop during treatment; corticosteroid therapy is often required. In trauma, infection, or shock the drug should be temporarily withdrawn and corticosteroids should be given systemically. Mitotane should be given with care to patients with renal or hepatic impairment. Before mitotane therapy is begun, all possible tumour tissue from large metastases should be surgically removed, in order to minimise possible infarction or haemorrhage in the tumour. Patients should not drive or operate machinery. Behavioural and neurological assessments should be carried out regularly in patients who have been receiving treatment for 2 years or more. Plasma concentrations should be monitored to guide dosage; the therapeutic window lies between 14 and 20 micrograms/mL (see also Therapeutic Drug Monitoring, below).

Interactions

Mitotane may induce hepatic microsomal enzymes and enhance the metabolism of some other drugs, including coumarin anticoagulants.

Spironolactone. Mitotane in a dose of up to 3 g daily in a 65-year-old patient with Cushing's syndrome appeared to be ineffective and did not produce the usual adverse effects associated with mitotane while the patient was also receiving spironolactone.[1]

1. Wortsman J, Soler NG. Mitotane: spironolactone antagonism in Cushing's syndrome. *JAMA* 1977; **238:** 2527.

Pharmacokinetics

Up to 40% of a dose of mitotane is absorbed from the gastrointestinal tract; absorption increases with food. After daily doses of 5 to 15 g, concentrations in the blood of 7 to 90 micrograms/mL of unchanged drug and 29 to 54 micrograms/mL of metabolite have been reported. Mitotane has been detected in the blood for about 6 to 9 weeks after stopping treatment. It is widely distributed and appears to be stored mainly in fatty tissues. It is metabolised in the liver and other tissues and excreted as metabolites in urine and bile. From 10 to 25% of a dose has been recovered in the urine as a water-soluble metabolite.

Therapeutic drug monitoring. Monitoring of mitotane and its major metabolite *o,p′*-DDE in 2 patients receiving mitotane in low doses for Cushing's disease demonstrated that there is a prolonged lag time in the plasma concentration changes in response to alterations in dosage,[1] presumably because of the lipophilicity of both compounds which leads to accumulation in adipose tissue. A study[2] in adrenal carcinoma found that mitotane is preferentially distributed into the very-low-density lipoprotein (VLDL) fraction of the serum of patients with hypertriglyceridaemia, whereas under normolipidaemic conditions, it is bound to high-density lipoproteins and albumin. Because VLDL is not incorporated into the human adrenal cells, mitotane's lipophilicity has implications for treatment and monitoring in patients with hypertriglyceridaemia. In some studies[3,4] tumour responses were seen only in those patients achieving a serum concentration of mitotane above 14 micrograms/mL, and a small prospective study[5] found that therapeutic concentrations (defined as between 14 and 20 micrograms/mL) could be reached by sustained low doses (1 to 3 g daily), thus limiting side-effects.

1. Benecke R, *et al.* Plasma level monitoring of mitotane (o,p′-DDD) and its metabolite (o,p′-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol* 1991; **41:** 259–61.
2. Gebhardt DOE, *et al.* The distribution of *o,p′*-DDD (mitotane) among serum lipoproteins in normo- and hypertriglyceridemia. *Cancer Chemother Pharmacol* 1992; **29:** 331–4.
3. Haak HR, *et al.* Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. *Br J Cancer* 1994; **69:** 947–51.
4. Baudin E, *et al.* Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p′DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; **92:** 1385–92.
5. Terzolo M, *et al.* Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; **85:** 2234–8.

The symbol † denotes a preparation no longer actively marketed

Uses and Administration

Mitotane is an antineoplastic with a selective inhibitory action on adrenal cortex activity. It may also modify peripheral steroid metabolism. It is given in the treatment of inoperable adrenocortical tumours and has also been used in patients with Cushing's syndrome (p.2344). Dosing schedules vary. In the UK, mitotane is started at a dose of 2 to 3 g daily in patients with adrenocortical tumours, given orally in 2 or 3 divided doses, and preferably with meals. Doses may be reduced to 1 to 2 g daily after 2 months of treatment, or until a cumulative dose of 200 g, or in event of toxicity. If plasma monitoring is available, initial doses may be as high as 4 to 6 g daily in divided doses until a cumulative dose of 75 g is reached (over about 15 days). Children or adolescents may be given starting doses of 1.5 to 3.5 g/m^2 daily, in 2 or 3 divided doses, with meals; this is reduced after 2 to 3 months according to mitotane plasma concentrations. In the USA, the usual initial oral dosage is 2 to 6 g daily in 3 or 4 divided doses. Doses are usually increased to 9 to 10 g daily, unless adverse effects necessitate dose reduction. The maximum tolerated dose ranges from about 2 to 16 g daily. In some countries, mitotane may also be started at 9 to 10 g daily in 3 or 4 divided doses.

◊ A retrospective study involving 105 patients with adrenocortical carcinoma found the prognosis to be generally poor with a 5-year survival of 22% among 88 patients followed up.[1] Surgical resection was the treatment of choice; mitotane treatment had no effect on survival although 8 patients had transient tumour regression and it was of some benefit in controlling adrenal hypersecretion. However, others have previously reported improved survival in patients with adrenocortical carcinoma in whom mitotane serum concentrations were above 14 micrograms/mL, and some[2] have suggested that the poor results with mitotane in the retrospective study may have been due to low serum-mitotane concentrations (see Therapeutic Drug Monitoring, above). A further study[3] found mitotane to be of benefit only in patients with adrenocortical carcinoma undergoing palliative surgery, but of no additional benefit as an adjuvant therapy for survival amongst patients receiving curative surgical resection. However, a retrospective analysis[4] of adjuvant mitotane therapy after radical resection found that it significantly prolonged recurrence-free survival. A review[5] concluded that, although mitotane is recommended for patients with unresectable tumours, only about 35% of such tumours respond.

1. Luton J-P, *et al.* Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med* 1990; **322:** 1195–1201.
2. Haak HR, *et al.* Mitotane therapy of adrenocortical carcinoma. *N Engl J Med* 1990; **323:** 758.
3. Icard P, *et al.* Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001; **25:** 891–7.
4. Terzolo M, *et al.* Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007; **356:** 2372–80.
5. Wooten MD, King DK. Adrenal cortical carcinoma: epidemiology and treatment with mitotane and a review of the literature. *Cancer* 1993; **72:** 3145–55.

Preparations

USP 31: Mitotane Tablets.

Proprietary Preparations (details are given in Part 3)

Braz.: Lisodren; ***Canad.:*** Lysodren; ***Cz.:*** Lysodren; ***Denm.:*** Lysodren; ***Fin.:*** Lysodren; ***Fr.:*** Lysodren; ***Ger.:*** Lysodren; ***Gr.:*** Lysodren; ***Hong Kong:*** Lysodren; ***Neth.:*** Lysodren; ***Pol.:*** Lysodren; ***Spain:*** Lysodren; ***UK:*** Lysodren; ***USA:*** Lysodren.

Mitoxantrone Hydrochloride

(BANM, USAN, rINNM)

CL-232315; DHAD; Dihydroxyanthracenedione Dihydrochloride; Hidrocloruro de mitoxantrona; Mitoksantron Hidroklorür; Mitoksantronihydrokloridi; Mitoksantrono hidrochloridas; Mitoxantron dihydrochlorid; Mitoxantrone, chlorhydrate de; Mitoxantron-hidroklorid; Mitoxantronhydroklorid; Mitoxantroni Dihydrochloridum; Mitoxantroni hydrochloridum; Mitozantron Hidroklorür; Mitozantrone Hydrochloride; NSC-301739. 1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone dihydrochloride.

Митоксантрона Гидрохлорид

$C_{22}H_{28}N_4O_6,2HCl = 517.4.$

CAS — 65271-80-9 (mitoxantrone); 70476-82-3 (mitoxantrone hydrochloride).

ATC — L01DB07.

ATC Vet — QL01DB07.

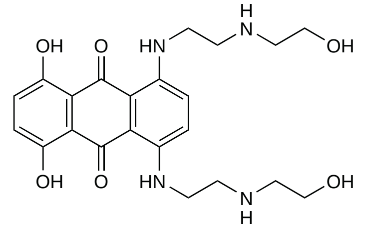

(mitoxantrone)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Mitoxantrone Hydrochloride). A dark-blue, electrostatic, hygroscopic powder. Sparingly soluble in water; practically insoluble in acetone; slightly soluble in methyl alcohol. Store in airtight containers.

USP 31 (Mitoxantrone Hydrochloride). A dark-blue powder. Sparingly soluble in water; practically insoluble in acetone, in acetonitrile, and in chloroform; slightly soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Mitoxantrone is reported to be better tolerated than doxorubicin. The nadir of the white cell count usually occurs about 10 days after a dose, with recovery by day 21. Elevation in liver enzyme values may occur; there are occasional reports of severe hepatic impairment in patients with leukaemia, in whom doses are generally higher and adverse effects of mitoxantrone may be more frequent and severe.

Transient blue-green coloration of the urine, and occasionally the sclerae, may occur. Tissue necrosis is rare after extravasation.

Severe neurotoxicity has resulted from erroneous intrathecal dosage; local or regional neuropathy has followed intra-arterial injection. Care is required in patients with pre-existing heart disease, or who have had prior anthracycline treatment or radiotherapy to the chest, as they are at increased risk of cardiotoxicity; regular cardiac examinations should be performed in such patients and in those who receive a total cumulative dose of mitoxantrone in excess of 160 mg/m^2. Care is also required in patients with hepatic impairment. Regular blood counts should be performed during treatment.

Alopecia. Two patients receiving therapy with mitoxantrone developed selective alopecia of white but not of dark hair.[1]

1. Arlin ZA, *et al.* Selective alopecia with mitoxantrone. *N Engl J Med* 1984; **310:** 1464.

Breast feeding. Mitoxantrone was detected in the breast milk of a woman with acute promyelocytic leukaemia in remission who was given consolidation chemotherapy that included mitoxantrone 6 mg/m^2 on days 1 to 3. Concentrations were 120 nanograms/mL just after the third dose and 18 nanograms/mL 28 days after treatment. Although the breast fed her neonate from 3 weeks after the completion of the course of treatment and no adverse effects were seen, the authors recommended that women treated with mitoxantrone should not breast feed.[1]

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.

Effects on the heart. Data from over 4000 patients treated with mitoxantrone included 172 reports of cardiac events, including 42 cases of congestive heart failure and 66 of decreased ejection fraction.[1] Previous anthracycline therapy increased the risk, and congestive heart failure seemed to be more likely in patients exposed to a cumulative mitoxantrone dose of 160 mg/m^2, or 100 mg/m^2 in those already given anthracyclines. In a further 78 patients,[2] clinical heart failure developed in 2 after cumulative doses of 174 and 243 mg/m^2. Four of 9 other patients given mitoxantrone in doses above 100 mg/m^2 showed signs of cardiotoxicity, and a further patient previously given doxorubicin 313 mg/m^2 had a fall in stress ejection fraction after only 47 mg/m^2 of mitoxantrone. However, sinus bradycardia has also been reported[3] in 2 previously untreated patients after starting continuous infusions of mitoxantrone 10 mg/m^2. For information on the cardiotoxicity of anthracyclines, to which mitoxantrone is structurally related, see under Adverse Effects and Treatment of Doxorubicin, p.713.

1. Crossley RJ. Clinical safety and tolerance of mitoxantrone. *Semin Oncol* 1984; **11:** (suppl 1): 54–8.
2. Stuart-Harris R, *et al.* Cardiotoxicity associated with mitoxantrone. *Lancet* 1984; **ii:** 219–20.
3. Benekli M, *et al.* Mitoxantrone-induced bradycardia. *Ann Intern Med* 1997; **126:** 409.

Handling and disposal. *Urine and faeces* produced for up to 7 days after a dose of mitoxantrone should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Hypersensitivity. In a report of 3 patients, allergic-type reactions to mitoxantrone included vasculitis, facial oedema and skin rashes, and in one, breathlessness, tachypnoea, cyanosis, and unrecordable pulse and blood pressure.[1] Allergic reactions to the drug appear to be rare.

1. Taylor WB, *et al.* Allergic reactions to mitoxantrone. *Lancet* 1986; **i:** 1439.

Interactions

For a report of the effect of ciclosporin in patients receiving mitoxantrone and etoposide, see p.719.

Pharmacokinetics

After intravenous doses mitoxantrone is rapidly and extensively distributed to body tissues, and slowly excreted in urine and bile as unchanged drug and metabolites. The elimination half-life is reported to range from 5 to 18 days. Between 6 and 11% of a dose has been recovered from urine, and 13 to 25% in faeces, within 5 days. It does not appear to cross the blood-brain barrier, but it is distributed into breast milk.

◊ References.

1. Ehninger G, *et al.* Pharmacokinetics and metabolism of mitoxantrone: a review. *Clin Pharmacokinet* 1990; **18:** 365–80.

Uses and Administration

Mitoxantrone is an antineoplastic structurally related to doxorubicin (p.712). Its mode of action has not been fully established but it inhibits topoisomerase II and causes DNA strand breakage, as well as intercalating with DNA. It is cell-cycle non-specific but is most active against cells in the late S phase.

It is used in the treatment of metastatic breast cancer (p.661), and of non-Hodgkin's lymphomas (p.656), alone or with other agents. It may also be given to treat adult acute myeloid leukaemias (p.652). Mitoxantrone has also been used in patients with hormone-refractory prostate cancer (p.671), liver cancer (p.667), and ovarian cancer (p.670).

In addition, mitoxantrone is used in the management of secondary progressive or relapsing multiple sclerosis (see below), to reduce neurological disability or the frequency of relapses.

Mitoxantrone is given as the hydrochloride, but doses are expressed in terms of the base; 1.2 mg of the hydrochloride is equivalent to about 1 mg of mitoxantrone. In the treatment of breast cancer, prostate cancer, liver cancer, and lymphomas, a dose equivalent to mitoxantrone 14 mg/m^2 is given initially, then repeated every 3 weeks. It is diluted to at least 50 mL in sodium chloride 0.9% or glucose 5% and injected over at least 3 minutes into a freely-running intravenous infusion of either. Subsequent doses may be adjusted according to the degree of myelosuppression produced. Initial dosage may need to be reduced to 12 mg/m^2 in debilitated patients or those who have had previous chemotherapy. Doses should also probably be reduced when mitoxantrone is given as part of a combination regimen: an initial dose of 10 to 12 mg/m^2 has been suggested.

In the treatment of patients with acute myeloid leukaemia a dose of 12 mg/m^2 daily for 5 days may be given to induce remission; alternatively a similar dose may be given for 3 days with cytarabine.

Cardiac examinations are recommended in all patients who receive a cumulative dose of mitoxantrone greater than 160 mg/m^2; left ventricular ejection fraction (LVEF) should be determined before each dose in patients who have received a cumulative dose in excess of 100 mg/m^2. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p.639).

In the management of multiple sclerosis, the recommended dose is the equivalent of mitoxantrone 12 mg/m^2 by intravenous infusion over 5 to 15 minutes. This dose may be given once every 3 months initially provided that neutrophil counts are above 1500 cells/mm^3 and that LVEF is greater than 50%. Blood counts should be monitored before each dose. LVEF should be evaluated before beginning mitoxantrone therapy and before all subsequent doses; a total cumulative lifetime dose in excess of 140 mg/m^2 should be avoided. LVEF should also be measured if signs or symptoms of heart failure develop.

◊ References.

1. Faulds D, *et al.* Mitoxantrone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991; **41:** 400–49.
2. Fox EJ. Mechanism of action of mitoxantrone. *Neurology* 2004; **63** (suppl): S15–S18.

Multiple sclerosis. Mitoxantrone has produced clinical benefit[1-4] in terms of reduced relapse rate and a slowing of disease progression in patients with multiple sclerosis (p.892). It has been given intravenously in doses of 5 or 12 mg/m^2 every 3 months, or 8 mg/m^2 every month. Patients with progressive relapsing disease may benefit from rapid induction with 12 mg/m^2 monthly for 3 months.[5] Benefit has also been shown in combination with corticosteroids,[6] although the combination was not compared with mitoxantrone alone. However, cardiotoxicity limits the dose that can be given.[7,8] Because of this and other adverse effects, such as possible secondary malignancy or potentially permanent amenorrhoea, some consider the use of mitoxantrone in multiple sclerosis to be unproven[9] and others have cautioned[10] that it should not be used before other immunomodulators. A systematic review[11] concluded that mitoxantrone was moderately effective in the short-term treatment of multiple sclerosis, but that information on its long-term effects was lacking; use should be limited to patients with worsening relapsing-remitting or secondary progressive disease with evidence of worsening disability.

1. Millefiorini E, *et al.* Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997; **244:** 153–9.
2. van de Wyngaert FA, *et al.* A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001; **101:** 210–16.
3. Hartung H-P, *et al.* Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; **360:** 2018–25.
4. Jeffery DR, Herndon R. Review of mitoxantrone in the treatment of multiple sclerosis. *Neurology* 2004; **63** (suppl): S19–S24.
5. Rizvi SA, *et al.* Mitoxantrone for multiple sclerosis in clinical practice. *Neurology* 2004; **63** (suppl): S25–S27.
6. Edan G, *et al.* Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; **62:** 112–118.
7. Ghalie RG, *et al.* Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002; **59:** 909–13.
8. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology* 2004; **63** (suppl): S28–S32.
9. Chaudhuri A, Behan PO. Mitoxantrone trial in multiple sclerosis. *Lancet* 2003; **361:** 1133–4.
10. Goodin DS, *et al.* The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003; **61:** 1332–8.
11. Martinelli Boneschi F, *et al.* Mitoxantrone for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/03/06).

Preparations

BP 2008: Mitoxantrone Intravenous Infusion;
USP 31: Mitoxantrone Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Batinel; Micraleve; Mitoxgen; Mitoxmar; ***Austral.:*** Novantrone; Onkotrone; ***Austria:*** Novantron; ***Belg.:*** Novantrone; Xantrosin; ***Braz.:*** Misostol; Mitaxis†; Mitoxal; ***Canad.:*** Novantrone†; ***Chile:*** Neotalem†; ***Cz.:*** Novantrone†; Onkotrone; Refador; ***Denm.:*** Novantrone; ***Fin.:*** Novantrone; ***Fr.:*** Elsep; Novantrone; ***Ger.:*** Neoxantron; Novantron; Onkotrone; Onkoxantron; Ralenova; ***Gr.:*** Genefadrone; Mitoxan; Novantrone; Zyneva; ***Hong Kong:*** Novantrone; ***Hung.:*** Novantrone; Onkotrone; Refador; ***India:*** Oncotron; ***Indon.:*** Norexan; ***Irl.:*** Novantrone; ***Israel:*** Novantrone; ***Ital.:*** Novantrone; Onkotrone; ***Malaysia:*** Novantrone†; ***Mex.:*** Formyxan; Mitoxgen; Mitroxone; Neotalem; ***Neth.:*** Novantrone†; ***Norw.:*** Novantrone; ***NZ:*** Novantrone; ***Philipp.:*** Domitrone; Onkotrone; ***Port.:*** Mitroxene; Novantrone; ***S.Afr.:*** Novantrone; ***Singapore:*** Novantrone; ***Spain:*** Novantrone; Pralifan; ***Swed.:*** Novantrone; ***Switz.:*** Novantron; ***Thai.:*** Neotalem; Novantrone†; ***Turk.:*** Neotalem; Novantrone; ***UK:*** Novantrone†; Onkotrone; ***USA:*** Novantrone; ***Venez.:*** Misostol.

Multialchilpeptide

Multialquilpéptido.

CAS — 9076-25-9.

Profile

Multialchilpeptide is a complex of metamelfalan, an analogue of melphalan (p.742), with peptides. It has been used in the treatment of malignant neoplasms of the blood and lymphatic systems.

Naptumomab Estafenatox *(rINN)*

ABR-217620; Naptumomab Estafénatox; Naptumomabum Estafenatoxum. Immunoglobulin fragment, anti-[trophoblast glycoprotein (TPBG, 5T4)] monoclonal 5T4 gamma1 heavy chain fragment fusion protein [*Mus musculus* VH (5T4V14: H41>P, S44>G, I69>T, V113>G)-IGHG1_CH1] - [Glycyl-Glycyl-Prolyl] - superantigen SEA/E-120 (synthetic), non-disulfide linked with monoclonal 5T4 kappa light chain [*Mus musculus* V-KAPPA (5T4V18: F10>S, T45>K, I63>S, F73>L, T77>S, L78>V, L83>A)-IGKC].

Наптумомаб Эстафенатокс

CAS — 676258-98-3.

Profile

Naptumomab estafenatox is a murine monoclonal antibody conjugated with a bacterial superantigen, a modified variant of Staphylococcal enterotoxin A that acts as a target for T-cell activation. The antibody is directed against a tumour-specific antigen 5T4. Naptumomab estafenatox is under investigation for the treatment of renal cell carcinoma.

Nedaplatin *(rINN)*

Nédaplatine; Nedaplatino; Nedaplatinum. *cis*-Diammine(glycolato-*O*^{1},*O*^{2})platinum.

Недаплатин

$C_2H_8N_2O_3Pt$ = 303.2.

CAS — 95734-82-0.

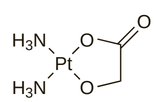

Profile

Nedaplatin is a platinum derivative with general properties similar to those of cisplatin (p.698) although it may be associated with less nephrotoxicity. It is used in the treatment of a variety of malignant neoplasms. It is given by intravenous infusion over 1 hour or more, dissolved in at least 300 mL of an appropriate infusion solution, in doses of 80 to 100 mg/m^2. The infusion should be followed by infusion of at least 1 litre of fluid to ensure adequate hydration and reduce the risk of renal damage.

◊ References.

1. Yoshioka T, *et al.* A new combination chemotherapy with cis-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for advanced esophageal cancers. *Intern Med* 1999; **38:** 844–8.
2. Adachi S, *et al.* Intravenous nedaplatin and intraarterial cisplatin with transcatheter arterial embolization for patients with locally advanced uterine cervical cancer. *Int J Clin Pharmacol Res* 2001; **21:** 105–10.
3. Kato H, *et al.* Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. *Anticancer Res* 2003; **23:** 3493–8.
4. Ishibashi T, *et al.* Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. *Anticancer Res* 2005; **25:** 1273–81.
5. Shirai T, *et al.* Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small-cell lung cancer. *Lung Cancer* 2006; **52:** 181–7.
6. Fuwa N, *et al.* Chemoradiation therapy using radiotherapy, systemic chemotherapy with 5-fluorouracil and nedaplatin, and intra-arterial infusion using carboplatin for locally advanced head and neck cancer–Phase II study. *Oral Oncol* 2007; **43:** 1014–20.
7. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer. *Cancer Chemother Pharmacol* 2008; **62:** 465–70.
8. Yokoyama Y, *et al.* A phase II multicenter trial of concurrent chemoradiotherapy with weekly nedaplatin in advanced uterine cervical carcinoma: Tohoku Gynecologic Cancer Unit Study. *Oncol Rep* 2008; **19:** 1551–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Aqupla.

Nelarabine *(BAN, USAN, rINN)*

GW-506U; GW-506U78; MAY; Nelarabina; Nélarabine; Nelarabinum; Nelzarabine; 506U; 506U78. 2-Amino-9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine.

Неларабин

$C_{11}H_{15}N_5O_5$ = 297.3.

CAS — 121032-29-9.

ATC — L01BB07.

ATC Vet — QL01BB07.

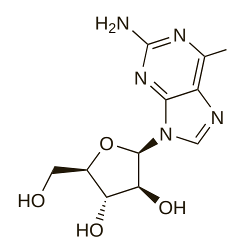

Adverse Effects, Treatment, and Precautions

Neurotoxicity is common with nelarabine and may be dose-limiting. Signs and symptoms include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoaesthesia. Severe toxicity can manifest as coma, status epilepticus (which may be fatal), craniospinal demyelination, or ascending neuropathy. Risk of neurotoxicity is increased by previous or current intrathecal chemotherapy or previous radiation to the spine or brain. Leucopenia, thrombocytopenia, anaemia, and neutropenia are common, especially in children. Full blood counts should be regularly monitored. Other common adverse events include fatigue, gastrointestinal disorders, respiratory disorders, pyrexia, headache, hypokalaemia, hypoalbuminaemia, hyperbilirubinaemia, and increased liver enzyme values. Fatal cerebral haemorrhage has been reported. Appropriate measures to avoid hyperuricaemia (especially in patients considered at risk for tumour lysis syndrome) include adequate hydration, urinary alkalinisation, and possible prophylaxis with allopurinol.

Pharmacokinetics

In adult patients with leukaemia or lymphoma, nelarabine is rapidly eliminated from the plasma, with a half-life of about 30 minutes; no data are available for paediatric patients although the mean clearance is reported to be about 30% higher in children. Nelarabine is rapidly and extensively converted by demethylation to the active metabolite 9-β-D-arabinofuranosylguanine (ara-G; arabinosylguanine; arabinofuranosylguanine; guanine arabinoside); both nelarabine and ara-G are widely distributed throughout the body. Ara-G has an elimination half-life from plasma of about 3 hours. Plasma protein binding is not significant. Nelarabine also undergoes hydrolysis to form methylguanine. Both methylguanine and ara-G undergo further metabolism to guanine, which is deaminated to form xanthine, itself further oxidised to uric acid. Nelarabine and ara-G are partially eliminated by the kidneys; mean apparent clearance is lower in patients with mild to moderate renal impairment.

◊ References.

1. Kisor DF, *et al.* Pharmacokinetics of nelarabine and 9-beta-D-arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. *J Clin Oncol* 2000; **18:** 995–1003.

Uses and Administration

Nelarabine is a prodrug of ara-G, a purine nucleoside analogue that is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. A dose of 1.5 g/m^2 is given undiluted by intravenous infusion over 2 hours in adults, on days 1, 3, and 5 of a 21-day cycle. In children, nelarabine is given undiluted by intravenous infusion over 1 hour, at a dose of 650 mg/m^2 daily for 5 days, and repeated every 21 days.

◊ References.

1. Gandhi V, *et al.* Evaluation of the combination of nelarabine and fludarabine in leukemias: clinical response, pharmacokinetics, and pharmacodynamics in leukemia cells. *J Clin Oncol* 2001; **19:** 2142–52.
2. Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacother* 2005; **39:** 1056–63.
3. Sanford M, Lyseng-Williamson KA. Nelarabine. *Drugs* 2008; **68:** 439–47.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Atriance; ***UK:*** Atriance; ***USA:*** Arranon.

Nilotinib *(USAN, rINN)*

AMN-107; Nilotinibum. 4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]-amino}benzamide.

Нильотиниб

$C_{28}H_{22}F_3N_7O$ = 529.5.
CAS — 641571-10-0.
ATC — L01XE08.
ATC Vet — QL01XE08.

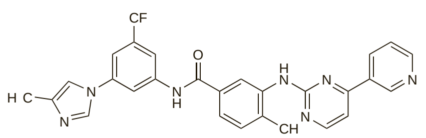

Nilotinib Hydrochloride *(rINNM)*

Hidrocloruro de nilotinib; Nilotinib, Chlorhydrate d'; Nilotinibi Hydrochloridum. Nilotinib Hydrochloride Monohydrate.

Нильотиниба Гидрохлорид

$C_{28}H_{22}F_3N_7O,HCl,H_2O$ = 584.0.
CAS — 923288-90-8.
ATC — L01XE08.
ATC Vet — QL01XE08.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of nilotinib are rash, pruritus, nausea, fatigue, headache, and gastrointestinal disturbances. Myelosuppression occurs, but is generally reversible and can be managed by temporary cessation of therapy or dose reduction. Complete blood counts should be performed every fortnight for the first 2 months and monthly thereafter. Nilotinib can prolong the QT interval, which may result in ventricular tachycardia (torsade de pointes), causing syncope, seizures, and/or death; nilotinib should not be used in patients with hypokalaemia or hypomagnesaemia or long QT syndrome. Electrolyte abnormalities including hypophosphataemia, hypokalaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia can occur, and should be monitored during therapy. Hepatotoxicity has been reported. Serum lipase should be monitored as increases can occur, and caution is recommended in patients with a history of pancreatitis.

Interactions

Nilotinib is a competitive inhibitor of several cytochrome P450 isoenzymes, particularly CYP3A4, which plays an important role in its metabolism. Use of nilotinib with strong inhibitors or inducers of CYP3A4 should be avoided. If they are used, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of nilotinib and should be avoided. St John's wort should also be avoided. Nilotinib should not be given with drugs that prolong the QT interval.

Pharmacokinetics

Peak plasma concentrations occur about 3 hours after an oral dose of nilotinib; bioavailability is increased almost twofold when given with food, especially a high-fat meal. Plasma protein binding is about 98%. The apparent elimination half-life is about 17 hours. It is metabolised in the liver via oxidation and hydroxylation, in which cytochrome P450 isoenzyme CYP3A4 plays an important role.

Uses and Administration

Nilotinib is a tyrosine kinase inhibitor that is used for the treatment of chronic myeloid leukaemia. In patients who are resistant or intolerant to prior treatment that included imatinib, nilotinib hydrochloride is given in an oral dose equivalent to nilotinib 400 mg every 12 hours, at least 1 hour before or 2 hours after food. Therapy is interrupted if toxicity occurs; treatment may be re-started at a lower dose of 400 mg once daily.

Nilotinib is a competitive inhibitor of cytochrome P450 isoenzymes, including CYP3A4. Use with strong CYP3A4 inhibitors or inducers should be avoided. If no alternative is available, a dose reduction to nilotinib 400 mg once daily should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period should be allowed before nilotinib is increased to the original dose. A dose increase of nilotinib may be needed if a strong CYP3A4 inducer is given; this depends on patient tolerability, and the nilotinib dose will need to be decreased once the inducer is stopped.

Nilotinib is also under investigation for the treatment of gastrointestinal stromal tumours.

◊ References.

1. Weisberg E, *et al.* AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006; **94:** 1765–9.
2. Kantarjian H, *et al.* Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354:** 2542–51.
3. Kantarjian HM, *et al.* Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; **110:** 3540–6.
4. Plosker GL, Robinson DM. Nilotinib. *Drugs* 2008; **68:** 449–59.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Tasigna; ***Port.:*** Tasigna; ***Switz.:*** Tasigna; ***UK:*** Tasigna; ***USA:*** Tasigna.

Nilutamide *(BAN, USAN, rINN)*

Nilutamid; Nilutamida; Nilutamidi; Nilutamidum; RU-23908. 5,5-Dimethyl-3-(α,α,α-trifluoro-4-nitro-*m*-tolyl)-imidazolidine-2,4-dione.

Нилутамид

$C_{12}H_{10}F_3N_3O_4$ = 317.2.
CAS — 63612-50-0.
ATC — L02BB02.
ATC Vet — QL02BB02.

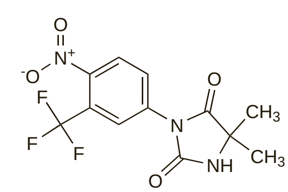

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nilutamide). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone; soluble in anhydrous ethanol. Protect from light.

Adverse Effects and Precautions

As for Flutamide, p.725. Interstitial pneumonitis has occurred in patients receiving nilutamide, and the drug is contra-indicated in those with severe respiratory insufficiency.

Effects on the eyes. Reversible visual disturbances, particularly delayed dark adaptation, have been associated with nilutamide.[1,2] Although some consider such visual disturbances to be mild and generally well tolerated,[3] others suggest that these, together with alcohol intolerance and, more seriously, effects on the lung, mean that other nonsteroidal anti-androgens should be preferred.[4]

1. Harnois C, *et al.* Ocular toxicity of Anandron in patients treated for prostatic cancer. *Br J Ophthalmol* 1986; **70:** 471–3.
2. Brisset JM, *et al.* Ocular toxicity of Anandron. *Br J Ophthalmol* 1987; **71:** 639.
3. Dijkman GA, *et al.* Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1550–1.
4. Dole EJ, Holdsworth MT. Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1551–2.

Interactions

Patients receiving nilutamide may exhibit intolerance to alcohol.

Pharmacokinetics

Nilutamide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively metabolised although it may inhibit its own metabolism to some extent after multiple doses. About 60% of an oral dose of nilutamide is eliminated in the urine and less than 10% in the faeces, with an elimination half-life of 41 to 49 hours.

Uses and Administration

Nilutamide is a nonsteroidal anti-androgen that is used similarly to flutamide (p.725) in the treatment of prostatic carcinoma (p.671). It is given orally in a dose of 300 mg daily, usually starting on the same day that the patient undergoes orchidectomy or receives treatment with a gonadorelin analogue. Dosage may be reduced to 150 mg daily after 1 month.

◊ References.

1. Dole EJ, Holdsworth MT. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31:** 65–75.
2. Desai A, *et al.* Nilutamide: possible utility as a second-line hormonal agent. *Urology* 2001; **58:** 1016–20.
3. Kassouf W, *et al.* Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol (Baltimore)* 2003; **169:** 1742–4.
4. Nakabayashi M, *et al.* Efficacy of nilutamide as secondary hormonal therapy in androgen-independent prostate cancer. *BJU Int* 2005; **96:** 783–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anandron†; ***Austral.:*** Anandron; ***Braz.:*** Anandron; ***Canad.:*** Anandron; ***Cz.:*** Anandron†; ***Fr.:*** Anandron; ***Gr.:*** Anandron; ***Hung.:*** Anandron; ***Mex.:*** Anandron; ***Neth.:*** Anandron; ***Port.:*** Anandron; ***Swed.:*** Anandron; ***USA:*** Nilandron.

Nimotuzumab *(rINN)*

Cimazumab; h-R3; Nimotutsumabi; Nímótúzúmab; Nimotuzumabas; Nimotuzumabs; Nimotuzumabum. Immunoglobulin G1, anti-(humanized mouse monoclonal hR3 β1 chain anti-human epidermal growth factor receptor), disulfide with humanized mouse monoclonal hR3 κ-chain, dimer.

Нимотузумаб

CAS — 828933-51-3.

Profile

Nimotuzumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in some countries for the treatment of glioma and cancers of the head and neck and pancreas.

Nimustine Hydrochloride *(rINNM)*

ACNU; Hidrocloruro de nimustina; Nimustiinihydrokloridi; Nimustine, Chlorhydrate de; Nimustinhydroklorid; Nimustini Hydrochloridum; NSC-245382; Pimustine Hydrochloride. 3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride.

Нимустина Гидрохлорид

$C_9H_{13}ClN_6O_2,HCl$ = 309.2.
CAS — 42471-28-3 (nimustine); 55661-38-6 (nimustine hydrochloride).
ATC — L01AD06.
ATC Vet — QL01AD06.

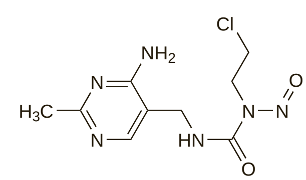

(nimustine)

Profile

Nimustine is a nitrosourea antineoplastic with actions and uses similar to those of carmustine (p.694). It is licensed for use in the treatment of malignant glioma. Nimustine hydrochloride is given in doses of 2 to 3 mg/kg or 90 to 100 mg/m^2 as a single dose by slow intravenous injection, repeated at intervals of 6 weeks depending on haematological response.

◊ References.

1. Anders K, *et al.* Accelerated radiotherapy with concomitant ACNU/Ara-C for the treatment of malignant glioma. *J Neurooncol* 2000; **48:** 63–73.
2. Kochii M, *et al.* Randomized comparison of intra-arterial versus intravenous infusion of ACNU for newly diagnosed patients with glioblastoma. *J Neurooncol* 2000; **49:** 63–70.

3. Silvani A, *et al.* Intra-arterial ACNU and carboplatin versus intravenous chemotherapy with cisplatin and BCNU in newly diagnosed patients with glioblastoma. *Neurol Sci* 2002; **23:** 219–24.
4. Weller M, *et al.* Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003; **21:** 3276–84.
5. Watanabe T, *et al.* Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. *J Neurooncol* 2005; **72:** 57–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: ACNU; ***Jpn:*** Nidran†; ***Neth.:*** ACNU†; ***Switz.:*** ACNU†.

Nolatrexed *(rINN)*

AG-337 (nolatrexed dihydrochloride); Nolatrexedum. 2-Amino-6-methyl-5-(4-pyridylthio)-4(3*H*)-quinazolinone.

Нолатрексед

$C_{14}H_{12}N_4OS = 284.3.$
CAS — 147149-76-6 (nolatrexed); 152946-68-4 (nolatrexed dihydrochloride).

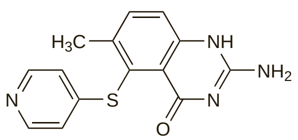

Profile

Nolatrexed is, like raltitrexed (p.766), a selective inhibitor of thymidylate synthase. It has been investigated as an antimetabolite antineoplastic for the treatment of hepatocellular carcinoma, although results of single-agent studies have been disappointing. It is also under investigation in combination therapy for other solid tumours.

◊ References.

1. Mok TS, *et al.* A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999; **44:** 307–11.
2. Hughes AN, *et al.* Clinical pharmacokinetic and in vitro combination studies of nolatrexed dihydrochloride (AG337, Thymitaq) and paclitaxel. *Br J Cancer* 2000; **82:** 1519–27.
3. Estlin EJ, *et al.* A phase I study of nolatrexed dihydrochloride in children with advanced cancer. *Br J Cancer* 2001; **84:** 11–18.
4. Pivot X, *et al.* Result of two randomized trials comparing nolatrexed (Thymitaq) versus methotrexate in patients with recurrent head and neck cancer. *Ann Oncol* 2001; **12:** 1595–9.
5. Jhawer M, *et al.* Phase II trial of nolatrexed dihydrochloride [Thymitaq, AG 337] in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2007; **25:** 85–94.
6. Gish RG, *et al.* Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25:** 3069–75.

Oblimersen Sodium *(USAN, rINNM)*

G-3139; Natrii Oblimersenum; Oblimersén sódico; Oblimersen Sodique.

Натрий Облимерсен

$C_{172}H_{204}N_{62}\text{-}Na_{17}O_{91}P_{17}S_{17} = 6058.3.$
CAS — 190977-41-4.

Profile

Oblimersen sodium is an antisense oligonucleotide that blocks the production of BCL-2, a mitochondrial protein that prevents apoptosis. It is under investigation for the treatment of various malignant neoplasms, including leukaemias, lung cancer, and malignant melanoma.

◊ References.

1. Frankel SR. Oblimersen sodium (G3139 Bcl-2 antisense oligonucleotide) therapy in Waldenstrom's macroglobulinemia: a targeted approach to enhance apoptosis. *Semin Oncol* 2003; **30:** 300–304.
2. Büchele T. Proapoptotische Therapie mit Oblimersen (bcl-2-Antisense-Oligonukleotid)—Übersicht über präklinische und klinische Daten. *Onkologie* 2003; **26** (suppl 7): 60–9.
3. Herbst RS, Frankel SR. Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): a rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4245s–4248s.
4. Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. *World J Urol* 2005; **23:** 33–7.
5. O'Brien SM, *et al.* Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23:** 7697–7702.
6. Mita MM, *et al.* A phase I, pharmacokinetic and biologic correlative study of oblimersen sodium (Genasense, G3139) and irinotecan in patients with metastatic colorectal cancer. *Ann Oncol* 2006; **17:** 313–21.
7. Bedikian AY, *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24:** 4738–45.
8. O'Brien S, *et al.* Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 1114–20. Correction. *ibid.* 2008; **26:** 820.

Ofatumumab *(rINN)*

HuMax-CD20; Ofatumumabum. Immunoglobulin G1, anti-(human CD20 (antigen))(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer.

Офатумумаб

CAS — 679818-59-8.

Profile

Ofatumumab is an anti-CD20 monoclonal antibody that is under investigation for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

◊ References.

1. Coiffier B, *et al.* Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 2008; **111:** 1094–1100.
2. Hagenbeek A, *et al.* First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; **111:** 5486–95.
3. Robak T. Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther* 2008; **10:** 294–309.

Olaparib *(rINN)*

Olaparibum. 4-[(3-{[4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one.

Олапариб

$C_{24}H_{23}FN_4O_3 = 434.5.$
CAS — 763113-22-0.

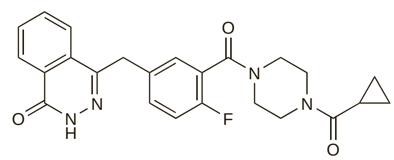

Profile

Olaparib is an antineoplastic that is under investigation for the treatment of ovarian cancer.

Omacetaxine Mepesuccinate *(pINN)*

CGX-635; HHT; Homoharringtonine; Mepesuccinato de omacetaxina; NSC-141633; Omacétaxine, Mépésuccinate d'; Omacetaxini mepesuccinas. 1-[(1*S*,3a*R*,14b*S*)-2-Methoxy-1,5,6,8,9,14b-hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)butanedioate.

Омацетаксин Мепесукцинат

$C_{29}H_{39}NO_9 = 545.6.$
CAS — 26833-87-4.

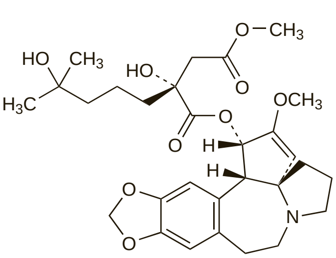

Pharmacopoeias. In *Chin.*

Profile

Omacetaxine mepesuccinate is a semisynthetic formulation of homoharringtonine, which is an alkaloid derived from the tree *Cephalotaxus harringtonia*, and related species. It is thought to induce apoptosis by inhibition of protein synthesis. It is under investigation for the treatment of chronic myeloid leukaemia (p.653). It has also been tried in the treatment of acute leukaemias and other neoplastic disorders.

The related compounds harringtonine, isoharringtonine, and deoxyharringtonine have also been investigated.

Adverse effects of omacetaxine mepesuccinate may include severe hypotension, cardiac arrhythmias, myelosuppression, gastrointestinal disturbances, chest pain, headache, fatigue, alopecia, rashes, and hyperglycaemia.

◊ References.

1. Kantarjian HM, *et al.* Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic myelogenous leukemia. *J Clin Oncol* 2000; **18:** 3513–21.
2. Kantarjian HM, *et al.* Homoharringtonine: history, current research, and future direction. *Cancer* 2001; **92:** 1591–1605.
3. O'Brien S, *et al.* Simultaneous homoharringtonine and interferon-alpha in the treatment of patients with chronic-phase chronic myelogenous leukemia. *Cancer* 2002; **94:** 2024–32.
4. Tang J, *et al.* A homoharringtonine-based regimen for childhood acute myelogenous leukemia. *Med Pediatr Oncol* 2003; **41:** 70–2.
5. O'Brien S, *et al.* Results of triple therapy with interferon-alpha, cytarabine, and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. *Cancer* 2003; **98:** 888–93.
6. Luo CY, *et al.* Homoharringtonine: a new treatment option for myeloid leukemia. *Hematology* 2004; **9:** 259–70.
7. Quintás-Cardama A, Cortes J. Homoharringtonine for the treatment of chronic myelogenous leukemia. *Expert Opin Pharmacother* 2008; **9:** 1029–37.
8. Quintás-Cardama A, Cortes J. Omacetaxine mepesuccinate - a semisynthetic formulation of the natural antitumoral alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. *IDrugs* 2008; **11:** 356–72.

Oregovomab *(USAN, rINN)*

MAb-B43.13; Orégovomab; Oregovomabum. Immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer.

Ореговомаб

CAS — 213327-37-8.

Profile

Oregovomab is a murine monoclonal antibody that binds to CA-125, an antigen that is overexpressed in the majority of ovarian cancer patients, and stimulates an immune response to the tumour cells. It is under investigation for the treatment of ovarian cancer.

Oxaliplatin *(BAN, USAN, rINN)*

JM-83; NSC-266046; *l*-OHP; Oksaliplatiini; Oksaliplatin; Oksaliplatina; Oxaliplatina; Oxaliplatine; Oxaliplatino; Oxaliplatinum; RP-54780; SR-96669. [(1*R*,2*R*)-1,2-Cyclohexanediamine-*N*,*N*′]-[oxalato(2-)-*O*,*O*′]platinum.

Оксалиплатин

$C_8H_{14}N_2O_4Pt = 397.3.$
CAS — 61825-94-3.
ATC — L01XA03.
ATC Vet — QL01XA03.

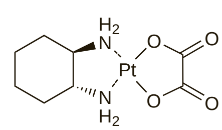

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oxaliplatin). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

Incompatibility. Licensed product information states that oxaliplatin should not be mixed with chloride-containing solutions (including sodium chloride) or alkaline drugs or solutions. In particular, oxaliplatin should not be mixed with fluorouracil or any trometamol salts. While oxaliplatin may be infused through a Y-site with folinic acid (in glucose 5% solution), they may not be mixed in the same infusion bag, and folinic acid must not contain trometamol as an excipient. The infusion line should be flushed with glucose 5% before giving any other medication. Oxaliplatin may degrade on contact with aluminium, and injection equipment containing aluminium should not be used.

Stability. UK licensed product information states that oxaliplatin must be diluted in glucose 5% to give a concentration not less than 200 micrograms/mL. From a microbiological point of view, the infusion preparation should be used immediately; the infusion should not be stored for longer than 24 hours at 2° to 8° unless it has been prepared in controlled and validated aseptic conditions. Chemical and physical stability has been shown for 48 hours at 2° to 8°, and for 24 hours at 25°. US licensed product information states that, after dilution in 250 to 500 mL of glucose

5%, oxaliplatin infusion solutions have a shelf-life of 6 hours at room temperature (20° to 25°) and up to 24 hours when refrigerated (2° to 8°), and that protection from light is not required.

A study[1] found that oxaliplatin solutions at 700 micrograms/mL in polyolefin infusion bags of glucose 5% were chemically stable for at least 30 days at both 3° to 7° and 20° to 24° without regard to light.

1. André P, *et al.* Stability of oxaliplatin in infusion bags containing 5% dextrose injection. *Am J Health-Syst Pharm* 2007; **64:** 1950–4.

Adverse Effects and Precautions

The adverse affects of oxaliplatin are similar to those of cisplatin (p.698) but nausea and vomiting, nephrotoxicity, and myelosuppression, seem to be less marked. Raised liver enzyme values may occur. Neurotoxicity can be dose-limiting. Peripheral neuropathy occurs in 85 to 95% of patients given oxaliplatin; pain, functional impairment, and loss of tendon reflexes may develop. Pulmonary fibrosis, potentially fatal, has also been reported. Extravasation of oxaliplatin can cause local pain and inflammation; complications may sometimes be severe, including necrosis.

Neurological examinations should be carried out at regular intervals during treatment and the dose should be reduced if symptoms are prolonged or severe. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p.639). Oxaliplatin should not be given to patients with pre-existing sensory neuropathies or myelosuppression, nor to those with severe renal impairment. Renal function and toxicity should be carefully monitored in those with more moderate degrees of renal impairment.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment for men and for 4 months for women.

Effects on the blood. Acute haemolysis, with[1-4] and without[5] anaemia, has been reported with the use of oxaliplatin. The reactions were considered to be immune-mediated. Evan's syndrome (immune-mediated thrombocytopenia and haemolytic anaemia) has also been reported.[6]

1. Desrame J, *et al.* Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; **354:** 1179–80.
2. Garufi C, *et al.* Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000; **11:** 497.
3. Hofheinz R-D, *et al.* Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient. *Cancer Chemother Pharmacol* 2004; **53:** 276–7.
4. Chen VMY, *et al.* An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; **44:** 838–43.
5. Koutras AK, *et al.* Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis: a case report and review of the literature. *Oncology* 2004; **67:** 179–82.
6. Earle CC, *et al.* Oxaliplatin-induced Evan's syndrome. *Br J Cancer* 2001; **84:** 441.

Effects on the liver. The development of ascites, portal hypertension, and hepatic lesions in a patient with colorectal cancer was considered to be due to oxaliplatin; metastatic or recurrent cancer had been originally suspected.[1]

1. Tisman G, *et al.* Oxaliplatin toxicity masquerading as recurrent colon cancer. *J Clin Oncol* 2004; **22:** 3202–4.

Effects on the nervous system. Neurological toxicity is the principal dose-limiting adverse effect with oxaliplatin.[1-3] The toxicity is biphasic:

- acute paraesthesias or dysaesthesias of the extremities, triggered or exacerbated by cold, are seen in 85 to 95% of patients within hours of infusion, but are normally mild and resolve within hours or days. Some patients also have distressing laryngopharyngeal symptoms, such as difficulty in breathing or swallowing.
- with increasing cumulative dose, peripheral sensory symptoms increase in duration and intensity. Symptoms are sometimes associated with pain and cramps, and may progress to functional impairment (loss of fine sensorimotor coordination). Dosage reduction may be required, but in clinical practice the onset of functional impairment often occurs after the maximum response to therapy has been attained. Cumulative neurotoxicity is reversible in most cases, and about 80% of patients exhibit symptom regression within 4 to 6 months.

The incidence of neurotoxicity may be higher when oxaliplatin is given with fluorouracil. There is some evidence that more prolonged infusion of oxaliplatin can reduce acute toxicity, particularly laryngopharyngeal symptoms. Antiepileptics such as carbamazepine (see Neuropathic Pain, p.477) or gabapentin have been investigated in the management of oxaliplatin-induced neurotoxicity and glutathione has been tried for prevention. Intravenous calcium gluconate and magnesium chloride infusions have been used to prevent acute oxaliplatin neuropathy with good initial results; similarly, intravenous calcium gluconate and magnesium sulfate have been reported to dramatically improve oxaliplatin-associated neuropathy.[4-6] However, a study designed to evaluate potential reduction of cumulative neurotoxicity associated with oxaliplatin, using calcium and magnesium salts, was terminated after those patients receiving calcium and magnesium reported a significantly lower response to chemotherapy (which consisted of oxaliplatin, folinic acid, fluorouracil, and bevacizumab). Although these results need confirmation, the possibility that calcium and magnesium may reduce the activity of certain drugs in the treatment of colorectal cancer should be considered.[7]

1. Extra JM, *et al.* Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol* 1998; **25** (suppl 5): 13–22.
2. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
3. Cassidy J, Misset J-L. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol* 2002; **29** (suppl 15): 11–20.
4. Gamelin L, *et al.* Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res* 2004; **10:** 4055–61.
5. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. *Ann Pharmacother* 2005; **39:** 128–35.
6. Gamelin L, *et al.* Neurotoxicité de l'oxaliplatine. *Bull Cancer* 2006; **93** (suppl 1): S17–S22.
7. Hochster HS, *et al.* Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol* 2007; **25:** 4028–9.

GUILLAIN-BARRÉ SYNDROME. A patient with metastatic colon cancer developed Guillain-Barré syndrome after weekly treatment with oxaliplatin-based chemotherapy;[1] he recovered after treatment with intravenous immunoglobulin.

1. Christodoulou C, *et al.* Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. *Anticancer Drugs* 2004; **15:** 997–9.

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME. Reversible posterior leukoencephalopathy syndrome (RPLS) was diagnosed in a woman given oxaliplatin with bevacizumab, and capecitabine. She tolerated further therapy with bevacizumab and irinotecan with no complications. The authors attributed the RPLS to oxaliplatin.[1]

1. Pinedo DM, *et al.* Reversible posterior leukoencephalopathy syndrome associated with oxaliplatin. *J Clin Oncol* 2007; **25:** 5320–1.

Extravasation. Although oxaliplatin was originally considered to be non-vesicant, there have been reports of extravasation causing inflammation, sclerosis, or, in some cases, severe necrosis.[1-4] Some consider it to be a vesicant drug,[1,2] although others state oxaliplatin extravasation to be less harmful than that of more classic vesicants.[4]

For discussion of the management of extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p.640.

1. Baur M, *et al.* Extravasation of oxaliplatin (Eloxatin)–clinical course. *Onkologie* 2000; **23:** 468–71.
2. Foo KF, *et al.* A case report of oxaliplatin extravasation. *Ann Oncol* 2003; **14:** 961–2.
3. Kennedy JG, *et al.* Vesicant characteristics of oxapliplatin [sic] following antecubital extravasation. *Clin Oncol (R Coll Radiol)* 2003; **15:** 237–9.
4. Kretzschmar A, *et al.* Extravasations of oxaliplatin. *J Clin Oncol* 2003; **21:** 4068–9.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, have been reported with oxaliplatin,[1-13] usually after several cycles of treatment. Symptoms include hypotension, tachycardia, dyspnoea, burning sensations, pruritus, erythema, sweating, and dizziness.[1,2,7,8] Rashes have also been reported[5,6,12] as have fever and chills.[9,10] While the mechanism of hypersensitivity to oxaliplatin is not clear, it has been suggested that reactions are characterised by development of symptoms during or shortly after the infusion, and are possibly due to a type I IgE-mediated reaction.[7,10] Idiosyncratic or infusional reactions, which are delayed until hours after the infusion,[6,10] are considered to be associated with cytokine release.[7,10] Cases have generally resolved on stopping oxaliplatin and giving appropriate treatment.

Prophylaxis before further oxaliplatin therapy, with corticosteroids and/or antihistamines, has shown variable efficacy.[4-7,9,10] Desensitisation protocols using dilute solutions and longer infusion times have been reported to be successful.[10,11,13]

Intradermal skin testing has been used to identify patients with suspected hypersensitivity to oxaliplatin; however, in some patients with negative skin tests, reactions have occurred upon rechallenge.[6,8]

1. Tournigand C, *et al.* Severe anaphylactic reactions to oxaliplatin. *Eur J Cancer* 1998; **34:** 1297–8.
2. Médioni J, *et al.* Anaphylaxis after oxaliplatin. *Ann Oncol* 1999; **10:** 610.
3. Larzillière I, *et al.* Anaphylactic reaction to oxaliplatin: a case report. *Am J Gastroenterol* 1999; **94:** 3387–8.
4. Stahl M, *et al.* Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001; **12:** 874.
5. Alliot C, *et al.* Severe anaphylactic reaction to oxaliplatin. *Clin Oncol (R Coll Radiol)* 2001; **13:** 236.
6. Thomas RR, *et al.* Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003; **97:** 2301–7.
7. Brandi G, *et al.* Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; **89:** 477–81.
8. Garufi C, *et al.* Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003; **14:** 497–8.
9. Lenz G, *et al.* Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer Drugs* 2003; **14:** 731–3.
10. Lim K-H, *et al.* Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs* 2004; **15:** 605–7.
11. Gammon D, *et al.* Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004; **9:** 546–9.
12. Ng CVT. Hypersensitivity reactions to oxaliplatin in two Asian patients. *Ann Pharmacother* 2005; **39:** 1114–18.
13. Mis L, *et al.* Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005; **39:** 966–9.

Interactions

For reference to the effect of oxaliplatin on fluorouracil, see Antineoplastics, p.723.

Pharmacokinetics

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours.

Oxaliplatin is extensively metabolised to both inactive and active compounds and is predominantly excreted in the urine.

◊ References.

1. Lévi F, *et al.* Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet* 2000; **38:** 1–21.
2. Graham MA, *et al.* Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res* 2000; **6:** 1205–18.

Uses and Administration

Oxaliplatin is a platinum-containing complex similar to cisplatin (see p.698). It is given with fluorouracil and folinic acid in the treatment of metastatic colorectal cancer and in the adjuvant treatment of stage III (Dukes C) colon cancer (p.665). The recommended dose is 85 mg/m^2 by intravenous infusion over 2 to 6 hours, dissolved in 250 to 500 mL of glucose 5%. The dose may be repeated at intervals of 2 weeks if toxicity permits, reduced according to tolerance. In the adjuvant setting, oxaliplatin is given for 12 cycles. After persistent neurotoxicity or recovery from severe adverse effects licensed product information recommends an initial reduction to 65 mg/m^2 in metastatic colorectal cancer, and to 75 mg/m^2 when given as adjuvant treatment. Oxaliplatin should always be given before fluoropyrimidines.

Oxaliplatin is under investigation for the treatment of ovarian and lung cancer. A liposomal formulation of oxaliplatin is in development.

◊ References.

1. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
2. Monnet I, *et al.* Oxaliplatin plus vinorelbine in advanced non-small-cell lung cancer: final results of a multicenter phase II study. *Ann Oncol* 2002; **13:** 103–7.
3. Louvet C, *et al.* Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002; **20:** 4543–8.
4. Simpson D, *et al.* Oxaliplatin: a review of its use in combination therapy for advanced metastatic colorectal cancer. *Drugs* 2003; **63:** 2127–56.
5. Winegarden JD, *et al.* A phase II study of oxaliplatin and paclitaxel in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2004; **15:** 915–20.
6. André T, *et al.* Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350:** 2343–51.
7. Chao Y, *et al.* Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. *Br J Cancer* 2004; **91:** 453–8.
8. Pectasides D, *et al.* Oxaliplatin plus high-dose leucovorin and 5-fluorouracil (FOLFOX 4) in platinum-resistant and taxane-pretreated ovarian cancer: a phase II study. *Gynecol Oncol* 2004; **95:** 165–72.
9. Keam SJ, *et al.* Oxaliplatin: in operable colorectal cancer. *Drugs* 2005; **65:** 89–96.
10. Fu S, *et al.* Clinical application of oxaliplatin in epithelial ovarian cancer. *Int J Gynecol Cancer* 2006; **16:** 1717–32.
11. Kim GP, Erlichman C. Oxaliplatin in the treatment of colorectal cancer. *Expert Opin Drug Metab Toxicol* 2007; **3:** 281–94.
12. Stordal B, *et al.* Oxaliplatin for the treatment of cisplatin-resistant cancer: a systematic review. *Cancer Treat Rev* 2007; **33:** 347–57.

Administration in renal impairment. The primary route of platinum elimination is renal, and clearance of platinum is decreased in patients with renal impairment. However, a study determined that increased platinum exposure in patients with renal impairment was not associated with increased oxaliplatin toxicity. Dose reduction was not considered to be necessary in patients with mild to moderate renal impairment (as defined by creatinine clearance of 20 mL/minute or more).[1] UK licensed product information concurs that no dose adjustment is necessary in mild to moderate renal impairment, but contra-indicates the use of oxaliplatin in severe renal impairment (defined as creatinine clearance of less than 30 mL/minute), due to lack of data.

1. Takimoto CH, *et al.* Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute organ dysfunction working group study. *J Clin Oncol* 2003; **21:** 2664–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Crisapla; Dabenzol; Dacplat; Goxyral; Kebir; Metaplatin; Mitog; O-Plat; Oxaltie; Platenk†; Platinostyl; Plusplatin; Uxalun; Xaliplat; ***Austral.:*** Eloxatin; ***Belg.:*** Eloxatin; ***Braz.:*** Eloxatin; Evoxali†; Ezulen; O-Plat; Uxalun; ***Chile:*** Eloxatin; O-Plat; ***Cz.:*** Ebeoxal; Eloxatin; Oxiplat; Platox; ***Fr.:*** Eloxatine; ***Ger.:*** Eloxatin; ***Hong Kong:*** Eloxatin; ***Hung.:*** Eloxatin; ***India:*** Dacotin; ***Indon.:*** Eloxatin; ***Ital.:*** Eloxatin; ***Malaysia:*** Eloxatin; ***Mex.:*** Eloxatin; Olipcis; Oxitan; Riptam; ***Neth.:*** Eloxatin; ***NZ:*** Eloxatin; ***Philipp.:*** Eloxatin; ***Pol.:*** Eloxatin; ***Port.:*** Eloxatin; ***Rus.:*** Eloxatine (Элоксатин); ***Singapore:*** Eloxatin; ***Spain:*** Eloxatin; ***Swed.:*** Eloxatin; ***Switz.:*** Eloxatine; ***Thai.:*** Eloxatin; Oxalip; Oxitan; ***Turk.:*** Eloxatin; ***UK:*** Eloxatin; ***USA:*** Eloxatin; ***Venez.:*** Eloxatin.

Paclitaxel *(BAN, USAN, rINN)*

BMS-181339-01; NSC-125973; Paclitaxelum; Paklitakselí; Paklitaksel; Paklitaxel; Taxol; Taxol A. (2S,5R,7S,10R,13S)-10,20-Bis(acetoxy)-2-benzoyloxy-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-13-yl (3S)-3-benzoylamino-3-phenyl-D-lactate.
Паклитаксел
$C_{47}H_{51}NO_{14}$ = 853.9.
CAS — 33069-62-4.
ATC — L01CD01.
ATC Vet — QL01CD01.

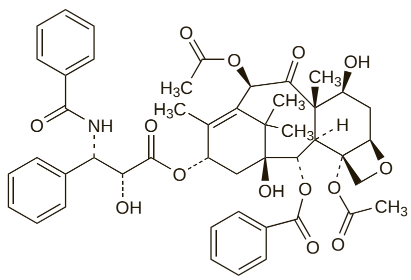

NOTE. Paclitaxel was formerly referred to as taxol, but the use of this name is now limited, as Taxol is a trademark.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Paclitaxel). Isolated from natural sources or produced by fermentation or by a semisynthetic process. A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Paclitaxel). A white to off-white powder. Insoluble in water; soluble in alcohol. Store in airtight containers at a temperature between 20° and 25°. Protect from light.

Incompatibility. The vehicle for paclitaxel injection, which contains alcohol and polyoxl castor oil, was found to leach the plasticiser diethylhexyl phthalate from some plastic giving sets.[1,2] Consequently, licensed product information recommends the use of non-PVC containers and giving sets.

Paclitaxel was found to be compatible with doxorubicin for at least 24 hours, but microcrystalline precipitation of paclitaxel occurred after 3 to 5 days.[3] For mention of the incompatibility of paclitaxel and cisplatin see p.698.

1. Trissel LA, *et al.* Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. *Am J Hosp Pharm* 1994; **51:** 2804–10.
2. Mazzo DJ, *et al.* Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. *Am J Health-Syst Pharm* 1997; **54:** 566–9.
3. Trissel LA, *et al.* Compatibility and stability of paclitaxel combined with doxorubicin hydrochloride in infusion solutions. *Ann Pharmacother* 1998; **32:** 1013–6.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

Paclitaxel produces severe dose-limiting bone marrow depression, the nadir of the white cell count usually occurring after about 11 days, with recovery usually by day 15 to 21 after a dose. Myelosuppression may be less frequent and less severe when infusions are given over 3 rather than 24 hours. Peripheral neuropathy can also be severe, and occasionally dose-limiting. Hypersensitivity reactions, with flushing, rash, dyspnoea, hypotension, chest pain, and angioedema may occur, and all patients should be given initial premedication with corticosteroids, antihistamines, and histamine H_2-antagonists. Other adverse effects include alopecia, arthralgia and myalgia, gastrointestinal disturbances, mucositis, bradycardia and ECG changes, nail dystrophies, and elevation of liver enzyme values. Infections are common, as are injection site reactions; extravasation may result in tissue damage. Rare adverse events include hypertension, severe thrombotic events, myocardial infarction, heart failure, severe cardiac conduction abnormalities, seizures, neuroencephalopathy, paralytic ileus, optic nerve disturbances, severe skin reactions, hepatic necrosis, and hepatic encephalopathy. There are rare reports of interstitial pneumonia and other lung disorders.

Paclitaxel is not recommended in patients with severely impaired hepatic function. The drug is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance. The formulation also contains alcohol, the CNS effects of which should be considered. Blood counts should be monitored frequently. Continuous cardiac monitoring is needed in patients who have had previous significant conduction abnormalities when given paclitaxel.

Alcohol intoxication. Acute alcohol intoxication resulting from high-dose paclitaxel infusion has been reported;[1] it was calculated that the dose used (348 mg/m²) supplied 50 mL of alcohol, or the equivalent of about 3 drinks (half a bottle of wine).

1. Wilson DB, *et al.* Paclitaxel formulation as a cause of ethanol intoxication. *Ann Pharmacother* 1997; **31:** 873–5.

Effects on the eyes. Optic neuritis has occurred with paclitaxel. There is a report of glaucoma possibly related to the use of docetaxel and paclitaxel in a patient also receiving corticosteroids.[1]

1. Fabre-Guillevin E, *et al.* Taxane-induced glaucoma. *Lancet* 1999; **354:** 1181–2.

Effects on the heart. Infusion of paclitaxel has been associated with sinus bradycardia, atrial arrhythmias, ventricular tachycardia, heart block, myocardial infarction, and sudden death.[1,2] Symptoms of heart failure have been reported.[3] In another report sudden death 7 days after paclitaxel treatment raised the question of whether paclitaxel might have had a delayed effect.[4] There is some evidence of cellular damage to the myocardium of a patient with paclitaxel-associated cardiac symptoms.[3] Licensed product information notes that severe cardiovascular events have been seen more frequently after the use of paclitaxel in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

1. Rowinsky EK, *et al.* Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991; **9:** 1704–12.
2. Arbuck SG, *et al.* A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst Monogr* 1993; **15:** 117–30.
3. Jekunen A, *et al.* Paclitaxel-induced myocardial damage detected by electron microscopy. *Lancet* 1994; **343:** 727–8.
4. Alagaratnam TT. Sudden death 7 days after paclitaxel infusion for breast cancer. *Lancet* 1993; **342:** 1232–3.

Effects on the musculoskeletal system. Gabapentin has been reported to be of benefit in the management of taxane-induced arthralgia and myalgia.[1,2]

1. van Deventer H, Bernard S. Use of gabapentin to treat taxane-induced myalgias. *J Clin Oncol* 1999; **17:** 434–5.
2. Nguyen VH, Lawrence HJ. Use of gabapentin in the prevention of taxane-induced arthralgias and myalgias. *J Clin Oncol* 2004; **22:** 1767–9.

Effects on the respiratory system. Acute bilateral interstitial pneumonitis has been reported rarely in patients receiving paclitaxel, despite premedication with corticosteroids and histamine antagonists.[1] Symptoms resolved on treatment with parenteral corticosteroids.

1. Khan A, *et al.* Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother* 1997; **31:** 1471–4.

Effects on the skin and nails. Nail changes, noted as pigmentation or discoloration of the nail-bed, may occur with paclitaxel. Onycholysis (separation of the nail from the nail-bed) has also been reported.[1] Discoloration and onycholysis can also occur after docetaxel use, and there are reports of subungual hyperkeratosis and haemorrhage.[2-4]

Localised oedema evolving into skin sclerosis, mimicking systemic sclerosis, has been reported after taxane use. In most patients, the sclerosis developed mainly on the extremities, and especially the lower extremities. Joint contracture may occur. The total cumulative dose of the taxane may contribute to the onset.[5]

1. Flory SM, *et al.* Onycholysis associated with weekly administration of paclitaxel. *Ann Pharmacother* 1999; **33:** 584–5.
2. Wasner G, *et al.* Clinical picture: nail changes secondary to docetaxel. *Lancet* 2001; **357:** 910.
3. Pavithran K, Doval DC. Nail changes due to docetaxel. *Br J Dermatol* 2002; **146:** 709–10.
4. Leonard GD, Zujewski JA. Docetaxel-related skin, nail, and vascular toxicity. *Ann Pharmacother* 2003; **37:** 148.
5. Itoh M, *et al.* Taxane-induced scleroderma. *Br J Dermatol* 2007; **156:** 363–7.

Hypersensitivity. Despite premedication with corticosteroids, antihistamines, and H_2-antagonists, hypersensitivity reactions are common in patients given paclitaxel; up to about 40% of patients may have a mild reaction and about 2% a severe reaction. Fatalities have been reported. There are rare reports of delayed hypersensitivity reactions with paclitaxel; necrotic ulceration has occurred, without evidence of extravasation.[1] Some consider the cause to be the polyoxyl castor oil diluent for paclitaxel, and docetaxel has been suggested as a suitable alternative.[2] However, hypersensitivity reactions have also occurred with docetaxel and taxane cross-reactivity has been reported.[3,4] Although the manufacturers of both drugs consider further use to be contra-indicated after a severe reaction, strategies for continuation of treatment and desensitisation have been described.[5,6]

Hypersensitivity reactions to paclitaxel-eluting stents have also been reported;[7] however, the incidence is low, and some consider the polymer coating of the stent to be the likely cause.[8]

1. Beri R, *et al.* Severe dermatologic reactions at multiple sites after paclitaxel administration. *Ann Pharmacother* 2004; **38:** 238–41.
2. Bernstein BJ. Docetaxel as an alternative to paclitaxel after acute hypersensitivity reactions. *Ann Pharmacother* 2000; **34:** 1332–5.
3. Denman JP, *et al.* Hypersensitivity reaction (HSR) to docetaxel after a previous HSR to paclitaxel. *J Clin Oncol* 2002; **20:** 2760–1.
4. Karacan Ö, *et al.* Acute interstitial pneumopathy associated with docetaxel hypersensitivity. *Onkologie* 2004; **27:** 563–5.
5. Markman M, *et al.* Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; **18:** 102–5.
6. Feldweg AM, *et al.* Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005; **96:** 824–9.
7. Nebeker JR, *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; **47:** 175–81.
8. Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: is it the pill or the polymer? *J Am Coll Cardiol* 2006; **47:** 182–3.

Pregnancy. Paclitaxel has been shown to be fetotoxic in *animal* studies, but although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus. Paclitaxel has been used in the treatment of a patient who presented at 27 weeks of gestation with ovarian cancer. She had cytoreductive surgery and then adjuvant chemotherapy consisting of 3 cycles of paclitaxel and cisplatin given every 3 weeks. A healthy child was delivered by caesarean section at 37 weeks, and showed normal growth and development at 30 months of age.[1]

Anhydramnios has been associated with the use of trastuzumab and paclitaxel, see Pregnancy, under Trastuzumab, p.783.

1. Sood AK, *et al.* Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; **83:** 599–600.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Pretreatment with cisplatin may reduce the clearance of paclitaxel, resulting in increased toxicity, and when both drugs are given, paclitaxel should be given first.

Antineoplastics. For reference to enhanced cardiotoxicity when paclitaxel was given with *doxorubicin*, see p.714. For the pharmacokinetic changes reported when paclitaxel was given with *gemcitabine*, see p.728.

Pretreatment with *fluorouracil* has been reported to inhibit paclitaxel's cytotoxic action, possibly by preventing tumour cells from entering the G_2-M phases of the cell cycle.[1] The effect also occurred when the 2 drugs were given simultaneously, suggesting that combination therapy might not be appropriate.

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[2] found that it decreased clearance of paclitaxel and prolonged the terminal half-life, increasing exposure to paclitaxel and myelosuppressive effects. The authors suggested that the dose of paclitaxel may need to be reduced by about 60%.

1. Johnson KR, *et al.* 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumor cells. *Clin Cancer Res* 1997; **3:** 1739–45.
2. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.

Antivirals. *HIV-PROTEASE INHIBITORS.* In a patient given various antiretrovirals during paclitaxel treatment for Kaposi's sarcoma, pharmacokinetic parameters of paclitaxel were not significantly different when compared with historical controls.[1] The first course of therapy combined paclitaxel with lamivudine, stavudine, and the HIV-protease inhibitors *ritonavir* and *saquinavir.* In subsequent courses, paclitaxel was given with nevirapine, and the final course consisted of paclitaxel given with ritonavir and *indinavir*. However, licensed product information for paclitaxel states that studies suggest that systemic clearance of paclitaxel was significantly lower in the presence of *nelfinavir* and ritonavir, but not indinavir, and that paclitaxel should be given with caution to patients taking HIV-protease inhibitors. HIV-protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, but are also reported to inhibit CYP3A activity. This may lead to increased adverse effects when given with taxanes; the combination of delavirdine and saquinavir has been reported to cause serious mucositis, severe myalgia, alopecia, and leucopenia when given with paclitaxel.[2]

1. Nannan Panday VR, *et al.* Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma—drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. *Cancer Chemother Pharmacol* 1999; **43:** 516–19.
2. Schwartz JD, *et al.* Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS* 1999; **13:** 283–4.

Immunosuppressants. *Ciclosporin* increased the oral absorption of paclitaxel, possibly by inhibiting the multidrug transporter P-glycoprotein in the gastrointestinal tract.[1]

For the effects of *valspodar* (an analogue of ciclosporin) on paclitaxel, see Antineoplastics, above.

1. Meerum Terwogt JM, *et al.* Co-administration of cyclosporin enables oral therapy with paclitaxel. *Lancet* 1998; **352:** 285. Correction. *ibid.*; 824.

Pharmacokinetics

Intravenous paclitaxel exhibits a biphasic decline in plasma concentrations, with a mean terminal half-life of anywhere between about 3 and 50 hours. The pharmacokinetics are non-linear. The steady-state volume of distribution is reported to range from 200 to 700 litres/m^2, indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is 89% or more bound to plasma protein *in vitro*. The elimination of paclitaxel has not been fully elucidated; only about 1 to 12% of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non-renal clearance. Paclitaxel is metabolised in the liver, with the major metabolic pathway apparently mediated by the cytochrome P450 isoenzyme CYP2C8, although CYP3A4 may play a minor role. Metabolites are excreted in the faeces via the bile, the primary metabolite being 6α-hydroxypaclitaxel.

◊ References.

1. Sonnichsen DS, Relling MV. Clinical pharmacokinetics of paclitaxel. *Clin Pharmacokinet* 1994; **27:** 256–69.
2. Walle T, *et al.* Taxol metabolism and disposition in cancer patients. *Drug Metab Dispos* 1995; **23:** 506–12.
3. Sonnichsen DS, *et al.* Variability in human cytochrome P450 paclitaxel metabolism. *J Pharmacol Exp Ther* 1995; **275:** 566–75.
4. Henningsson A, *et al.* Mechanism-based pharmacokinetic model for paclitaxel. *J Clin Oncol* 2001; **19:** 4065–73.

Uses and Administration

Paclitaxel is a taxane originally derived from the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae), and now obtained semisynthetically from a taxane precursor derived from the needles of the European yew, *Taxus baccata*. Paclitaxel's antineoplastic action arises from induction of microtubule formation and stabilisation of microtubules, thereby disrupting normal cell division in the G_2 and M phases of the cell cycle.

Paclitaxel is used for the primary treatment of advanced ovarian cancer (p.670) with cisplatin or carboplatin, and for secondary treatment. In the treatment of node-positive breast cancer (p.661), paclitaxel is used for primary adjuvant therapy after anthracycline-containing chemotherapy. In locally advanced or metastatic breast cancer, it is used first-line with an anthracycline, or as a second-line single-agent, usually after failure of anthracycline-based therapy. In patients with metastatic disease who overexpress HER2 (human epidermal growth receptor 2) it may be used with trastuzumab as initial therapy. Paclitaxel is used with cisplatin or carboplatin, for the primary treatment of advanced non-small cell lung cancer (p.668). It may be used for the second-line treatment of AIDS-related Kaposi's sarcoma (p.675), and has been tried in other neoplasms including cancers of the head and neck, and relapsed germ-cell tumours.

The recommended dose for the primary treatment of **ovarian cancer** is 135 mg/m^2 infused over 24 hours, followed by cisplatin, and repeated at 3-week intervals. Alternatively 175 mg/m^2 may be infused over 3 hours, followed by cisplatin, every 3 weeks. For the secondary treatment of ovarian cancer, the suggested dose as a single agent is 135 or 175 mg/m^2 infused over 3 hours once every 3 weeks.

For **breast cancer**, a dose of paclitaxel 175 mg/m^2 infused over 3 hours once every 3 weeks is recommended for adjuvant treatment (for 4 courses), for second-line monotherapy, and for first-line treatment with trastuzumab; paclitaxel is given the day after the first dose of trastuzumab, or immediately after subsequent doses if well-tolerated. When used first-line with doxorubicin, paclitaxel 220 mg/m^2 is infused over 3 hours once every 3 weeks; the dose is given 24 hours after doxorubicin.

In **non-small cell lung cancer**, the recommended dose is 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours, followed by cisplatin, and repeated at 3-week intervals.

A dose of 135 mg/m^2 over 3 hours once every 3 weeks has been suggested for AIDS-related **Kaposi's sarcoma**. Alternatively, 100 mg/m^2 over 3 hours every 2 weeks may be given, especially in patients with poor performance status.

Regular blood counts should be performed, and dosage should not be repeated until the neutrophil and platelet counts are at acceptable levels; the neutrophil count should be above 1000 cells/mm^3 in patients with AIDS (see also Bone-marrow Depression, p.639). The dose should be reduced by 20% in subsequent courses in patients who have severe neutropenia or peripheral neuropathy. Patients should be pretreated with corticosteroids, antihistamines, and histamine H_2-antagonists. The dose of paclitaxel may need to be reduced in patients with hepatic impairment (see below).

Various formulations have been developed to avoid the use of polyoxyl castor oil and improve the efficacy and safety of paclitaxel. An injectable suspension of albumin-bound paclitaxel nanoparticles (*Abraxane; Abraxis, USA*; ABI-007) is available for the treatment of refractory or relapsed breast cancer. The dose is 260 mg/m^2 given intravenously over 30 minutes every 3 weeks. Other formulations in development include paclitaxel linked to docosahexaenoic acid or biodegradable polymers (such as paclitaxel poliglumex), micellar and liposomal formulations, and an oral dosage form. An injectable vitamin E-based emulsion of paclitaxel has been investigated for the treatment of urothelial cancer and metastatic breast cancer.

Paclitaxel-releasing stents may be used to reduce restenosis after coronary artery stent placement.

◊ References to paclitaxel, and to taxanes as a class.

1. Gelmon K. The taxoids: paclitaxel and docetaxel. *Lancet* 1994; **344:** 1267–72.
2. Long HJ. Paclitaxel (Taxol): a novel anticancer chemotherapeutic drug. *Mayo Clin Proc* 1994: **69:** 341–5.
3. Spencer CM, Faulds D. Paclitaxel: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. *Drugs* 1994; **48:** 794–847.
4. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **332:** 1004–14. Correction. *ibid.*; **333:** 75.
5. Anonymous. Paclitaxel and docetaxel in breast and ovarian cancer. *Drug Ther Bull* 1997; **35:** 43–6.
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7. Crown J, O'Leary M. The taxanes: an update. *Lancet* 2000; **355:** 1176–8.
8. Michaud LB, *et al.* Risks and benefits of taxanes in breast and ovarian cancer. *Drug Safety* 2000; **23:** 401–28.
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10. Anonymous. Albumin-bound paclitaxel (Abraxane) for advanced breast cancer. *Med Lett Drugs Ther* 2005; **47:** 39–40.
11. Harries M, *et al.* Nanoparticle albumin-bound paclitaxel for metastatic breast cancer. *J Clin Oncol* 2005; **23:** 7768–71.
12. Robinson DM, Keating GM. Albumin-bound paclitaxel: in metastatic breast cancer. *Drugs* 2006; **66:** 941–8.
13. Hayes DF, *et al.* Cancer and Leukemia Group B (CALGB) Investigators. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med* 2007; **357:** 1496–1506.
14. Seidman AD, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; **26:** 1642–9.

Administration. Although many of the original studies of paclitaxel employed a 24-hour infusion regimen, the use of *3-hour infusions* has subsequently become widespread. A systematic review[1] noted that although it was difficult to compare efficacy in studies of unlike malignancies there was no conclusive evidence of a difference in effectiveness with differing length of infusion; however, there were differences in the adverse effect profile, neutropenia being much less marked with the shorter infusion, although neurotoxic effects were reduced with 24-hour administration.

There has also been considerable interest in evaluating the use of paclitaxel in reduced-dose *weekly* schedules.[2-12] Various dosage regimens have been tried: most have found that doses of between 50 and about 100 mg/m^2 weekly, usually by infusion over 1 hour rather than a conventional 3-hour infusion, can be given with relatively modest toxicity. Although higher doses have been tried, neurotoxicity and myelosuppression become problematic and tend to limit dose intensity. A number of studies have addressed the combination of weekly paclitaxel with other antineoplastics, for example with trastuzumab in breast cancer, estramustine in prostate cancer, and with platinum compounds or gemcitabine in other solid tumours such as those of the ovary or lung. Weekly paclitaxel is also under investigation in combination with radiotherapy in the management of lung cancer and glioblastoma multiforme.

1. Williams C, *et al.* Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/05/05).
2. Seidman AD, *et al.* Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; **16:** 3353–61.
3. Fountzilas G, *et al.* Radiation and concomitant weekly administration of paclitaxel in patients with glioblastoma multiforme: a phase II study. *J Neurooncol* 1999; **45:** 159–65.
4. Markman M. Weekly paclitaxel in the management of ovarian cancer. *Semin Oncol* 2000; **27** (suppl 7): 37–40.
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6. Langer CJ, *et al.* Paclitaxel by 1-h infusion in combination with carboplatin in advanced non-small cell lung carcinoma (NSCLC). *Eur J Cancer* 2000; **36:** 183–93.
7. Akerley W. Recent developments in weekly paclitaxel therapy in lung cancer. *Curr Oncol Rep* 2001; **3:** 165–9.
8. Haas N, *et al.* Phase I trial of weekly paclitaxel plus oral estramustine phosphate in patients with hormone-refractory prostate cancer. *Urology* 2001; **58:** 59–64.
9. Seidman AD, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; **19:** 2587–95.
10. Kouroussis C, *et al.* A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. *Am J Clin Oncol* 2001; **24:** 404–7.
11. Brambilla L, *et al.* Weekly paclitaxel for advanced aggressive classic Kaposi sarcoma: experience in 17 cases. *Br J Dermatol* 2008; **158:** 1339–44.
12. Sparano JA, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; **358:** 1663–71. Correction. *ibid.*; **359:** 106.

Administration in hepatic impairment. The US licensed product information makes recommendations for initial dosage adjustment of some paclitaxel regimens in patients with hepatic impairment, according to transaminase and bilirubin concentrations. They suggest paclitaxel should not be given if transaminase values are more than 10 times normal upper limits, or if bilirubin is more than 75 micrograms/mL or 5 times the normal upper limit.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Coronary stents that elute paclitaxel effectively reduce restenosis and have been widely used, although there is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis.[1-3] In a study compared with bare metal stents, paclitaxel-releasing stents reduced the risk of restenosis and the need for repeat revascularisation procedures, although the follow-up rates of death from cardiac causes or myocardial infarction were not significantly reduced at 9 months[4] and 1 year.[5] However, between 9 months and 1 year, major cardiac adverse events were significantly reduced in the paclitaxel-releasing stent group compared to controls.[5] A review[6] of various stent designs concluded that safety of paclitaxel-releasing stents was independent of design, dose-density, or presence or absence of a polymer carrier system; however, those without a polymer carrier were unable to show a positive effect on clinical outcome in patients with de novo coronary lesions. However, in a paclitaxel-releasing stent system, failure of the stent-delivery balloon to deflate has been associated with serious injuries and 1 fatality.[7] The risk of late stent thrombosis may also be increased with drug eluting stents,[8] although the evidence is controversial,[9] and their role in complex interventions is not yet established.[10,11]

Positive effects on restenosis have also been reported[12] with use of a paclitaxel-coated angioplasty balloon.

1. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
2. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
3. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
4. Stone GW, *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350:** 221–31.
5. Stone GW, *et al.* One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; **109:** 1942–7.
6. Silber S. Paclitaxel-eluting stents: are they all equal? An analysis of six randomized controlled trials in de novo lesions of 3,319 patients. *J Interv Cardiol* 2003; **16:** 485–90.
7. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; **351:** 1593–5.
8. Stone GW, *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
9. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
10. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
11. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
12. Scheller B, *et al.* Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006; **355:** 2113–24.

Preparations

USP 31: Paclitaxel Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Asotax; Clitaxel; Dalys; Drifen; Erioxal; Paclikebir; Pacliteva; Paklitaxfil; Panataxel; Tarvexol; Taxocris; Taxol; Taycovit; ***Austral.:*** Anzatax; Taxol; ***Austria:*** Ebetaxel; Taxol; ***Belg.:*** Paclitaxin; Paxene; Taxol; ***Braz.:*** Biopaxel; Onxel; Paclitax; Parexel; Paxel†; Taclipaxol†; Taclix†; Tarvexol; Taxilan; Taxol; ***Canad.:*** Taxol; ***Chile:*** Britaxol; Oncoplaxel; Praxel; Taxodiol; ***Cz.:*** Anzatax; OncoTax; Onxol; Paclimedac; Pacline; Paxene; Taxol; ***Denm.:*** Taxol; ***Fin.:*** Taxol; ***Fr.:*** Paxene; Taxol; ***Ger.:*** NeoTaxan; Ribotax; Taxol; ***Gr.:*** Biotaxel; Ovapac; Paclit; Paclitaxin; Paclitol; Paclixel; Pataxel; Paxene; Ribotal; Taxogen; Taxol; Taxoprol; ***Hong Kong:*** Anzatax; Taxol; ***Hung.:*** Genexol; Intaxel; Magytax; Paxene; Taxol; ***India:*** Intaxel; Paclitax; Petaxel; ***Indon.:*** Anzatax; Paxus; Taxol; ***Irl.:*** Paxene; Taxol; ***Israel:*** Biotax; Ebetaxel; Medixel; Taxol†; ***Ital.:*** Anzatax; Paxene; Taxol; ***Jpn:*** Taxol; ***Malaysia:*** Anzatax; Formoxol; Mitotax; Taxol; ***Mex.:*** Asotax; BrisTaxol; Cryoxet; Daburex; Ifaxol; Paclisan; Praxel; ***Neth.:*** Paclitaxin; Paxene; Taxol; ***Norw.:*** Taxol; ***NZ:*** Taxol; ***Philipp.:*** Intaxel; Taxol; Unitaxel; ***Pol.:*** Poltaxel; Sindaxel; Taxol; ***Port.:*** Paxene; Taxobine; Taxol; ***Rus.:*** Abitaxel (Абитаксел)†; Mitotax (Митотакс); Paxene (Паксен); Taxol (Таксол); ***S.Afr.:*** Anzatax; Biolyse; Taxol; ***Singapore:*** Anzatax; Genexol; Taxol; ***Spain:*** Paxene; Taxol; ***Swed.:*** Paxene; Taxol; ***Switz.:*** Taxol; ***Thai.:*** Anzatax; Intaxel; Oncotaxel; Praxel; Taxol; ***Turk.:*** Anzatax; Taxol; ***UK:*** Paxene; Taxol; ***USA:*** Abraxane; Onxol; Taxol; ***Venez.:*** Clitaxel; Intaxel; Paclitax.

Panitumumab *(USAN, rINN)*

ABX-EGF; E7.6.3; Panitumumabum. Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer.

Панитумумаб

CAS — 339177-26-3.

ATC — L01XC08.

ATC Vet — QL01XC08.

Adverse Effects, Treatment, and Precautions

As for Cetuximab, p.695, although the use of premedication for prevention of infusion reactions with panitumumab has not been standardised. The infusion rate should be reduced by 50% in patients who have mild to moderate infusion reactions; if a severe reaction occurs, immediate and permanent discontinuation is recommended. In patients who developed skin reactions, infectious complications including abscesses and sepsis, in some cases fatal, have been reported.

Interactions

Use of panitumumab with combination chemotherapy is not recommended. A high incidence of severe diarrhoea occurred in patients given panitumumab with fluorouracil, folinic acid, and irinotecan. Increased risk of death occurred when panitumumab was given with bevacizumab.

Pharmacokinetics

The pharmacokinetics of panitumumab are reported to be non-linear. Steady-state concentrations were reached by the third infusion with the recommended dose regimen. The elimination half-life was about 7.5 days.

Uses and Administration

Panitumumab is a recombinant human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in the treatment of EGFR-expressing metastatic colorectal cancer (p.665) in patients with disease progression after fluoropyrimidine-, oxaliplatin-, or irinotecan-containing regimens. In some countries it is licensed only in patients whose tumour contains a non-mutated *KRAS* gene (Kirsten rat sarcoma 2 viral oncogene homologue), which plays a role in cell growth regulation and angiogenesis; mutations in the *KRAS* gene occur frequently in various human tumours and are implicated in oncogenesis and tumour progression.

The recommended dose is 6 mg/kg given as an intravenous infusion every 14 days. Doses up to and including 1 g are given in 100 mL sodium chloride 0.9% over 60 minutes whereas doses above 1 g are diluted in 150 mL and given over 90 minutes; the final concentration of the infusion should not exceed 10 mg/mL. The infusion should be given via an infusion pump using a low-protein-binding 0.2 or 0.22 micrometre in-line filter. It may be given through a peripheral line or indwelling catheter; the line should be flushed with sodium chloride 0.9% before and after giving panitumumab. The infusion rate should be reduced by 50% in patients who have a mild to moderate infusion reaction, and stopped immediately and permanently if a severe reaction occurs.

Panitumumab should be withheld if severe dermatological toxicity develops, and permanently stopped if toxicity does not improve within 1 month. If toxicity improves after withholding no more than 2 doses of panitumumab, treatment may be restarted at half the original dose. If toxicity recurs, therapy should be permanently stopped. If toxicity does not recur, subsequent doses may be increased in increments of 25% until the recommended dose of 6 mg/kg is reached.

◊ References.

1. Gibson TB, *et al.* Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 29–31.
2. Saif MW, Cohenuram M. Role of panitumumab in the management of metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 118–24.
3. Hoy SM, Wagstaff AJ. Panitumumab: in the treatment of metastatic colorectal cancer. *Drugs* 2006; **66:** 2005–14.
4. Saadeh CE, Lee HS. Panitumumab: a fully human monoclonal antibody with activity in metastatic colorectal cancer. *Ann Pharmacother* 2007; **41:** 606–13.
5. Anonymous. Panitumumab (Vectibix) for metastatic colorectal cancer. *Med Lett Drugs Ther* 2007; **49:** 35–6. Correction. *ibid.*; 48. [dosage error]
6. Giusti RM, *et al.* FDA drug approval summary: panitumumab (Vectibix). *Oncologist* 2007; **12:** 577–83.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Vectibix; ***Port.:*** Vectibix; ***UK:*** Vectibix; ***USA:*** Vectibix.

Panobinostat *(rINN)*

Panobinostatum. (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide.

Панобиностат

$C_{21}H_{23}N_3O_2$ = 349.4.

CAS — 404950-80-7.

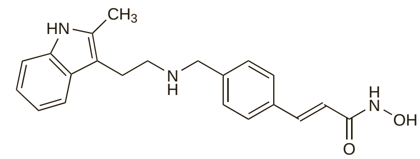

Profile

Panobinostat is a histone deacetylase inhibitor that is under investigation as an antineoplastic for the treatment of cutaneous T-cell lymphoma.

Patupilone *(rINN)*

EPO-906; Epothilone B; Patupilona; Patupilonum. (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Патупильон

$C_{27}H_{41}NO_6S$ = 507.7.

CAS — 152044-54-7.

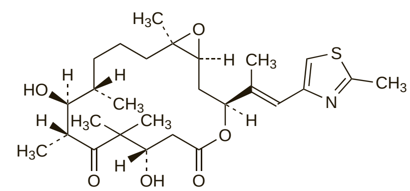

Profile

Patupilone is a metabolite isolated from the bacterium *Sorangium cellulosum*, with microtubule stabilising activity similar to that of the taxanes. It is under investigation as an antineoplastic for the treatment of ovarian cancer.

Pazopanib Hydrochloride *(USAN, rINNM)*

GW-786034B; Hidrocloruro de pazopanib; Pazopanib, Chlorhydrate de; Pazopanibi Hydrochloridum. 5-({4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide hydrochloride.

Пазопаниба Гидрохлорид

$C_{21}H_{23}N_7O_2S,HCl$ = 474.0.

CAS — 444731-52-6 (pazopanib); 635702-64-6 (pazopanib hydrochloride).

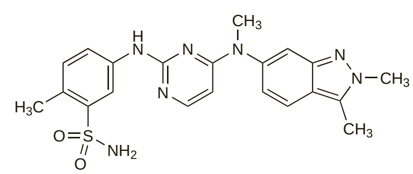

(pazopanib)

Profile

Pazopanib hydrochloride is an inhibitor of tyrosine kinase associated with the epidermal growth factor receptor. It is under investigation for the treatment of renal cell carcinoma.

Peldesine *(USAN, pINN)*

BCX-34; Peldesina; Peldésine; Peldesinum. 2-Amino-3,5-dihydro-7-(3-pyridylmethyl)-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one.

Пельдезин

$C_{12}H_{11}N_5O$ = 241.2.

CAS — 133432-71-0.

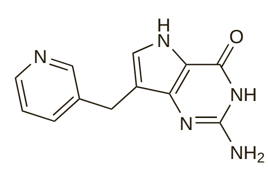

Profile

Peldesine is an inhibitor of the enzyme purine nucleoside phosphorylase and is reported to suppress T-cell proliferation. It has been investigated in the management of cutaneous T-cell lymphomas, and has also been tried topically in psoriasis and some T-cell mediated eye disorders.

Pemetrexed Disodium

(BANM, USAN, rINNM)

LY-231514 (pemetrexed or pemetrexed disodium); MTA; Multitargeted Antifolate; Pemetreksed Disodyum; Pemetrexed disódico; Pémétrexed Disodique; Pemetrexedum Dinatricum. Disodium *N*-{*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate.

Динатрий Пеметрексед

$C_{20}H_{19}N_5Na_2O_6$ = 471.4.

CAS — 137281-23-3 (pemetrexed); 150399-23-8 (pemetrexed disodium).

ATC — L01BA04.

ATC Vet — QL01BA04.

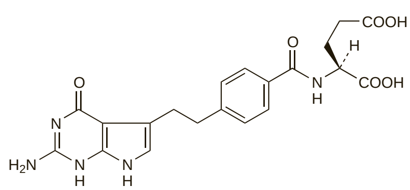

(pemetrexed)

NOTE. In practice, pemetrexed is given as the disodium heptahydrate ($C_{20}H_{19}N_5Na_2O_6$,$7H_2O$ = 597.5).

Incompatibility. Licensed product information states that pemetrexed is physically incompatible with diluents containing calcium, including Ringer's solution and lactated Ringer's solution. A study[1] found pemetrexed disodium 20 mg/mL to be physically incompatible with 24 drugs resulting in precipitation or colour change during simulated Y-site administration. These drugs include amphotericin B, some cephalosporin and cephamycin antibacterials, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisilate, tobramycin sulfate, and topotecan hydrochloride.

1. Trissel LA, *et al.* Physical compatibility of pemetrexed disodium with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; **61:** 2289–93.

Stability. Licensed product information states that pemetrexed is chemically and physically stable, once reconstituted and diluted, for 24 hours either refrigerated at 2° to 8° or at 25°; from a microbiological point of view, solutions should be used immediately, unless prepared under controlled and validated aseptic conditions.

Pemetrexed, reconstituted in polypropylene syringes with sodium chloride 0.9% to a concentration of 25 mg/mL, was found to be both chemically and physically stable for 2 days when stored at room temperature, and for 31 days when refrigerated.[1] Although pemetrexed solutions of 2, 10, and 20 mg/mL in glucose 5% and sodium chloride 0.9% in PVC bags were chemically stable for 90 days when frozen at −20°, microparticulates formed, possibly related to the PVC containers. Pemetrexed solutions should therefore not be frozen.[2]

1. Zhang Y, Trissel LA. Physical and chemical stability of pemetrexed solutions in plastic syringes. *Ann Pharmacother* 2005; **39:** 2026–8.
2. Zhang Y, Trissel LA. Physical instability of frozen pemetrexed solutions in PVC bags. *Ann Pharmacother* 2006; **40:** 1289–92.

Adverse Effects, Treatment, and Precautions

As for Raltitrexed, p.766.

Pemetrexed may also cause fatigue, stomatitis, pharyngitis, dyspnoea, chest pain, and neuropathy. Rare cases of hepatitis, colitis, and intestinal pneumonitis have occurred; fatalities have been reported. Serious renal events, including acute renal failure, have been reported with pemetrexed when it was used either alone or with other cytotoxic drugs; most patients had underlying risk factors such as dehydration, hypertension, or diabetes. Cardiovascular events, including myocardial infarction and cerebrovascular events, have occurred rarely, usually when pemetrexed was used with other cytotoxic drugs. Cases of radiation pneumonitis and radiation recall have been reported in patients treated with radiotherapy. Hypersensitivity reactions may occur.

Complete blood cell counts should be monitored, and folate and vitamin B_{12} are given as prophylaxis against haematological and gastrointestinal toxicity during pemetrexed therapy. Pre-treatment with a corticosteroid, such as oral dexamethasone, reduces the incidence and severity of skin reactions.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

High doses of NSAIDs and aspirin may decrease pemetrexed elimination. In patients with mild to moderate renal impairment (creatinine clearance 45 to 79 mL/minute) high doses of NSAIDs and aspirin should be avoided from 2 days before until 2 days after pemetrexed use, and NSAIDs that have longer half-lives, such as piroxicam, should be avoided from 5 days before until 2 days after pemetrexed.

Analgesics. Enteric-coated *aspirin* 325 mg given orally every 6 hours for a total of 9 doses before pemetrexed, did not affect the pharmacokinetic profile of pemetrexed in an interaction study; the authors considered no dose adjustment necessary when moderate doses of aspirin were given with pemetrexed. However, this result could not be extrapolated to high-dose aspirin regimens, as the interaction might be dependent on salicylate concentrations. In contrast, oral *ibuprofen* 400 mg every 6 hours for a total of 9 doses before pemetrexed significantly reduced systemic pemetrexed clearance. Despite an increase in pemetrexed exposure, no increase in toxicity was seen. Dose adjustments were not considered necessary in patients with normal renal function (defined as creatinine clearance of 80 mL/minute or greater). However, in patients with pre-existing reduced pemetrexed clearance due to renal impairment, giving ibuprofen may result in further increases in pemetrexed exposure; the authors advised caution when using these 2 drugs together in patients with a creatinine clearance of less than 80 mL/minute.[1] For licensed drug information regarding the use of aspirin and NSAIDs with pemetrexed, see above.

1. Sweeney CJ, *et al.* Two drug interaction studies evaluating the pharmacokinetics and toxicity of pemetrexed when coadministered with aspirin or ibuprofen in patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 536–42.

Pharmacokinetics

Pemetrexed has a plasma elimination half-life of 3.5 hours in patients with normal renal function. *In-vitro* data indicate that pemetrexed is about 81% bound to plasma proteins. It undergoes limited hepatic metabolism, and about 70 to 90% of a dose is eliminated unchanged in the urine within 24 hours.

Uses and Administration

Pemetrexed is primarily a thymidylate synthase inhibitor like raltitrexed (p.766), but it also inhibits other folate-dependent enzymes involved in purine synthesis such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. It is used as second-line monotherapy or first-line with cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer (p.668). It is also used with cisplatin in the first-line treatment of unresectable malignant pleural mesothelioma (p.669).

Pemetrexed is given as the disodium heptahydrate but doses are expressed in terms of the base: pemetrexed disodium heptahydrate 1.4 g is equivalent to about 1 g of pemetrexed. A dose of pemetrexed 500 mg/m^2 is given by intravenous infusion over 10 minutes. The dose may be repeated in 21-day cycles, and should be adjusted according to toxicity. In combination therapy, cisplatin is given about 30 minutes after the end of pemetrexed infusion.

Pre-treatment with oral dexamethasone 4 mg twice daily for 3 days is recommended, starting the day before pemetrexed. At least 5 doses of oral folic acid (350 micrograms to 1 mg) should be taken during the 7 days before the first dose of pemetrexed; dosing should continue throughout pemetrexed therapy, and for 21 days after the last pemetrexed dose. Patients should also receive an intramuscular injection of vitamin B_{12} 1 mg in the week before the first pemetrexed dose, and once every 3 cycles thereafter; subsequent injections may be given on the same day as pemetrexed.

Pemetrexed is under investigation as an antifolate antimetabolite in the treatment of colon, pancreatic, breast, and head and neck cancer.

◊ References.

1. Smit EF, *et al.* Alimta (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer: a phase II study. *Ann Oncol* 2003; **14:** 455–60.
2. Vogelzang NJ, *et al.* Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21:** 2636–44.
3. Hanna N, *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22:** 1589–97.
4. Hochster HS. The role of pemetrexed in the treatment of gastrointestinal malignancy. *Clin Colorectal Cancer* 2004; **4:** 190–5.
5. Hazarika M, *et al.* Pemetrexed in malignant pleural mesothelioma. *Clin Cancer Res* 2005; **11:** 982–92.
6. Puto K, Garey JS. Pemetrexed therapy for malignant pleural mesothelioma. *Ann Pharmacother* 2005; **39:** 678–83.
7. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. *Clin Ther* 2005; **27:** 1343–82.
8. Martin M. Clinical experience with pemetrexed in breast cancer. *Semin Oncol* 2006; **33** (suppl 2): S15–S18.
9. Anonymous. Can pemetrexed help in malignant mesothelioma? *Drug Ther Bull* 2006; **44:** 77–80.
10. Dundar Y, *et al.* Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. *Health Technol Assess* 2007; **11:** 1–90.
11. Green J, *et al.* Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/08/07).
12. Longo-Sorbello GS, *et al.* Role of pemetrexed in non-small cell lung cancer. *Cancer Invest* 2007; **25:** 59–66.

Administration in renal impairment. A pharmacokinetic study[1] found that pemetrexed clearance decreased with declining renal function. Although systemic exposure increased in these patients, this was not associated with an increase in drug-related dose-limiting toxicities for patients with a GFR of 40 mL/minute or more and receiving vitamin supplementation (folic acid and vitamin B_{12} supplementation appears to reduce toxicity without altering pemetrexed pharmacokinetics). Patients with a GFR of 80 mL/minute or more tolerated a dose of pemetrexed 600 mg/m^2, given intravenously every 3 weeks, whereas patients with a GFR of 40 to 79 mL/minute tolerated 500 mg/m^2 every 3 weeks. One patient with a GFR of 19 mL/minute died as a result of treatment-related toxicity and accrual into this group was stopped. As a result, no data were available for patients with a GFR below 40 mL/minute.

Licensed product information states that no dose adjustment is necessary in patients with a creatinine clearance (CC) of 45 mL/minute or more. Use in patients with a CC of less than 45 mL/minute is not recommended due to lack of data. Caution is advised when giving pemetrexed with NSAIDs in patients whose CC is less than 80 mL/minute (see Interactions, above).

1. Mita AC, *et al.* Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *J Clin Oncol* 2006; **24:** 552–62.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alimta; ***Austral.:*** Alimta; ***Belg.:*** Alimta; ***Canad.:*** Alimta; ***Chile:*** Alimta; Elimta†; ***Cz.:*** Alimta; ***Denm.:*** Alimta; ***Fin.:*** Alimta; ***Fr.:*** Alimta; ***Ger.:*** Alimta; ***Gr.:*** Alimta; ***Hong Kong:*** Alimta; ***Hung.:*** Alimta; ***Irl.:*** Alimta; ***Israel:*** Alimta; ***Ital.:*** Alimta; ***Malaysia:*** Alimta; ***Neth.:*** Alimta; ***Norw.:*** Alimta; ***NZ:*** Alimta; ***Pol.:*** Alimta; ***Rus.:*** Alimta (Алимта); ***Singapore:*** Alimta; ***Spain:*** Alimta; ***Swed.:*** Alimta; ***Switz.:*** Alimta; ***Thai.:*** Alimta; ***Turk.:*** Alimta; ***UK:*** Alimta; ***USA:*** Alimta.

Pemtumomab

Profile

Pemtumomab is a radiolabelled monoclonal antibody of murine origin that binds to muc-1, an epithelial cell surface protein on tumour cells. It has been investigated for the treatment of various cancers, including ovarian and gastric cancers, but results have been disappointing.

Pentostatin *(BAN, USAN, rINN)*

CI-825; Covidarabine; Co-vidarabine; Deoxycoformycin; 2′-Deoxycoformycin; NSC-218321; PD-81565; Pentostatina; Pentostatine; Pentostatinum. (*R*)-3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol; 1,2-Dideoxy-1-[(*R*)-3,6,7,8-tetrahydro-8-hydroxyimidazo[4,5-*d*][1,3]-diazepin-3-yl]-D-*erythro*-pentofuranose.

Пентостатин

$C_{11}H_{16}N_4O_4$ = 268.3.
CAS — 53910-25-1.
ATC — L01XX08.
ATC Vet — QL01XX08.

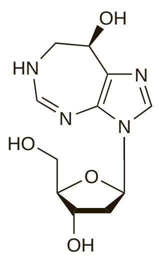

Adverse Effects and Precautions

The most common adverse effects in patients receiving pentostatin include myelosuppression (and in particular suppression of CD4+ lymphocyte subset), headache, abdominal pain, fever and chills, gastrointestinal disturbances (notably diarrhoea and nausea and vomiting), hypersensitivity reactions, and hepatotoxicity. Central neurotoxicity may be manifest as tiredness, anxiety, depression, sleep disturbances, and paraesthesias: treatment should be withheld or stopped in such patients. Impaired renal function and pulmonary toxicity (cough, dyspnoea, and pneumonia) may occur. Severe toxicity in early studies, affecting mainly the CNS, kidneys, liver, and lungs, was associated with the use of doses higher than those currently recommended and produced some fatalities.

Other adverse effects reported with pentostatin include dry skin and rashes (sometimes severe and worsening with continued treatment), pruritus, conjunctivitis, alopecia, arthralgia and myalgia, peripheral oedema, thrombophlebitis, and cardiovascular disorders including arrhythmias, angina pectoris, and heart failure.

Pentostatin should not be given to patients with impaired renal function, or in active infection. It is teratogenic in *animals* and potentially genotoxic: it is therefore contra-indicated in pregnancy and men receiving pentostatin should not father children for 6 months after therapy.

Interactions

Pentostatin should not be given with fludarabine, as the combination may increase pulmonary toxicity. A similar increase in toxicity is expected when pentostatin is used with vidarabine.

Use of pentostatin with carmustine, etoposide and high-dose cyclophosphamide, has produced acute pulmonary oedema and hypotension, leading to death. Pentostatin should therefore not be given with high-dose cyclophosphamide.

Allopurinol. Fatal acute necrotising arteritis developed in a patient given pentostatin and allopurinol.[1] Although the hypersensitivity vasculitis may have been due to allopurinol alone there is circumstantial evidence to suggest that pentostatin may predispose patients to drug hypersensitivity and it may be wise to avoid this combination, and to observe pentostatin-treated patients closely for allergic manifestations.

1. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; **86:** 498–9.

Pharmacokinetics

After intravenous injection, pentostatin has an elimination half-life of about 6 hours. Approximately 90% of a dose is excreted in the urine as unchanged drug and metabolites. Pentostatin crosses the blood-brain barrier and can be measured in the CSF.

Uses and Administration

Pentostatin is a potent inhibitor of the enzyme adenosine deaminase and probably exerts its cytotoxic actions through the interruption of normal purine metabolism and DNA synthesis. Lymphocytes are particularly sensitive to its actions.

Pentostatin is used as a single agent in the treatment of hairy-cell leukaemia (p.654), in usual doses of 4 mg/m^2 every other week. The dose is given as an intravenous bolus injection, or as an infusion over 20 to 30 minutes. Hydration with 500 mL to 1 litre of glucose 5% in sodium chloride 0.18 or 0.9%, or equivalent, is recommended beforehand; a further 500 mL of the hydration solution should be infused once the drug has been given.

Pentostatin has been tried in cutaneous T-cell lymphomas (see Mycosis Fungoides, p.657) and histiocytic syndromes (p.650). It is also under investigation in some other lymphoid malignancies, including chronic lymphocytic leukaemia (p.653) and non-Hodgkin's lymphomas (p.656) and for the management of chronic graft-versus-host disease following haematopoietic stem cell transplantation (p.1811).

◊ References.

1. Grever MR, *et al.* Pentostatin in the treatment of hairy-cell leukemia. *Best Pract Res Clin Haematol* 2003; **16:** 91–9.
2. Drapkin R, *et al.* Results of a phase II multicenter trial of pentostatin and rituximab in patients with low grade B-cell non-Hodgkin's lymphoma: an effective and minimally toxic regimen. *Clin Lymphoma* 2003; **4:** 169–75.
3. Tsimberidou AM, *et al.* Phase II study of pentostatin in advanced T-cell lymphoid malignancies: update of an MD Anderson Cancer Center series. *Cancer* 2004; **100:** 342–9.
4. Tsiara SN, *et al.* Treatment of resistant/relapsing chronic lymphocytic leukemia with a combination regimen containing deoxycoformycin and rituximab. *Acta Haematol (Basel)* 2004; **111:** 185–8.
5. Dillman RO. Pentostatin (Nipent) in the treatment of chronic lymphocyte leukemia and hairy cell leukemia. *Expert Rev Anticancer Ther* 2004; **4:** 27–36.
6. Higman M, *et al.* Pentostatin—pharmacology, immunology, and clinical effects in graft-versus-host disease. *Expert Opin Pharmacother* 2004; **5:** 2605–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Nipent†; ***Fr.:*** Nipent; ***Ger.:*** Nipent; ***Gr.:*** Nipent; ***Ital.:*** Nipent; ***Neth.:*** Nipent; ***Port.:*** Nipent; ***Spain:*** Nipent; ***UK:*** Nipent; ***USA:*** Nipent.

Peplomycin Sulfate *(USAN, rINNM)*

NK-631; Pepleomycin Sulphate; Peplomycin Sulphate; Péplomycine, Sulfate de; Peplomycini Sulfas; Sulfato de peplomicina. N^1-{3-[(*S*)-(α-Methylbenzyl)amino]propyl}bleomycinamide sulphate.

Пепломицина Сульфат

$C_{61}H_{88}N_{18}O_{21}S_2,H_2SO_4$ = 1571.7.
CAS — 68247-85-8 (peplomycin); 70384-29-1 (peplomycin sulfate).

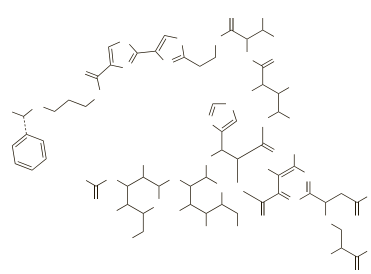

(peplomycin)

Pharmacopoeias. In *Jpn.*

Profile

Peplomycin is an antineoplastic derived from bleomycin (see p.687) and with similar properties. It has been given as the sulfate in the treatment of a variety of malignant neoplasms, including lymphomas and tumours of the head and neck, breast, cervix, lung, prostate, and skin.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Pepleo.

Peretinoin *(rINN)*

Ácido poliprénico; E-5166; Pérétinoin; Peretinoína; Peretinoinum; Polyprenic Acid; Polyprenoic Acid. (*all-E*)-3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoic acid.

Перетиноин; Полипреноевая Кислота

$C_{20}H_{30}O_2$ = 302.5.
CAS — 81485-25-8.

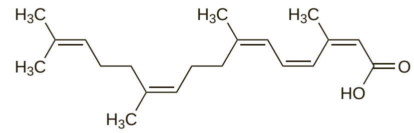

Profile

Peretinoin is a retinoid that has been tried in psoriasis and keratoderma and is being studied in the treatment of liver cancers.

◊ References.

1. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996; **334:** 1561–7.
2. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; **340:** 1046–7.
3. Takai K, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma: updated analysis of the long-term follow-up data. *Intervirology* 2005; **48:** 39–45.

Picoplatin *(BAN, USAN, rINN)*

AMD-473; NX-473; Picoplatine; Picoplatino; Picoplatinum; ZD-0473. *cis*-Amminedichloro(2-methylpyridine)platinum(II).

Пикоплатин

$C_6H_{10}Cl_2N_2Pt$ = 376.1.
CAS — 181630-15-9.

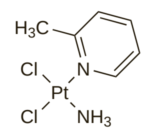

Profile

Picoplatin is a platinum derivative that is under investigation as an intravenous antineoplastic for the treatment of small-cell lung cancer. It is also under investigation for the treatment of colorectal cancer and prostate cancer. An oral dosage form is also being developed.

Pipobroman *(USAN, pINN)*

A-8103; NSC-25154; Pipobromán; Pipobromanum. 1,4-Bis(3-bromopropionyl)piperazine.

Пипоброман

$C_{10}H_{16}Br_2N_2O_2$ = 356.1.
CAS — 54-91-1.
ATC — L01AX02.
ATC Vet — QL01AX02.

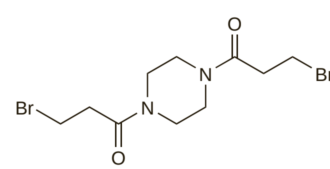

Profile

Pipobroman is an antineoplastic which appears to act by alkylation. It may be used in the treatment of polycythaemia vera (p.654), in patients requiring myelosuppressive therapy, and in refractory chronic myeloid leukaemia (p.653).

The usual initial dose for polycythaemia vera is 1 mg/kg daily, given orally, and increased to 3 mg/kg, if necessary, according to response. Maintenance dosage is 100 to 200 micrograms/kg daily.

The main adverse effect is moderate bone-marrow depression, which may develop 4 weeks or more from starting treatment. Anaemia may be marked at higher doses and is usually accompanied by leucopenia. Thrombocytopenia and haemolysis have occurred. In the initial stages of treatment, white cell and platelet counts should be determined on alternate days and complete blood counts once or twice weekly. Dosage should be stopped if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639).

The symbol † denotes a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Vercyte; ***Ital.:*** Vercite.

Pirarubicin *(rINN)*

Pirarubicina; Pirarubicine; Pirarubicinum; 1609-RB; Tepirubicin; THP-ADM; THP-doxorubicin. (8*S*,10*S*)-10-{[3-Amino-2,3,6-trideoxy-4-*O*-(2*R*-tetrahydro-2*H*-pyran-2-yl)-α-L-*lyxo*-hexopyranosyl]oxy}-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione.

Пирарубицин

$C_{32}H_{37}NO_{12}$ = 627.6.
CAS — 72496-41-4.
ATC — L01DB08.
ATC Vet — QL01DB08.

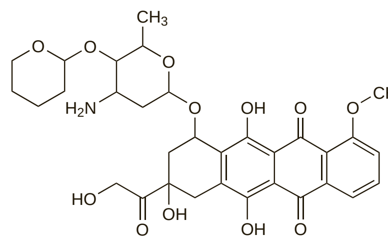

Pharmacopoeias. In *Jpn.*

Profile

Pirarubicin is an antineoplastic anthracycline antibiotic that is a structural analogue of doxorubicin (p.712), and has similar properties. It is used in the management of breast cancer and has also been tried in other solid neoplasms, acute leukaemias and lymphomas.

Pirarubicin is formulated as the hydrochloride but doses are in terms of the base. A usual dose of 25 to 50 mg/m^2 every 3 to 4 weeks has been recommended in breast cancer, but other dosage regimens have been used. Doses may be given by intravenous injection over 5 to 10 minutes into a rapidly-flowing intravenous infusion of glucose 5%. Patients should undergo regular blood counts and monitoring of cardiac function: at cumulative doses above 600 mg/m^2 ventricular ejection fraction should be checked before each course. Pirarubicin has also been given by the intra-arterial and intravesical routes.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Pinorubin†; ***Fr.:*** Theprubicine.

Piritrexim Isetionate *(rINNM)*

BW-301U (piritrexim); Isetionato de piritrexima; NSC-351521; Piritrexim Isethionate *(USAN)*; Piritrexime, Isétionate de; Piritreximi Isetionas. 2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine mono(2-hydroxyethanesulphonate).

Пиритрексима Изетионат

$C_{17}H_{19}N_5O_2,C_2H_6O_4S$ = 451.5.
CAS — 72732-56-0 (piritrexim); 79483-69-5 (piritrexim isetionate).

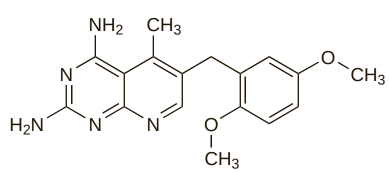

(piritrexim)

Profile

Piritrexim is a folate antagonist with general properties similar to those of methotrexate (p.745). It has been tried by mouth for its antineoplastic properties, and has also been used (as the isetionate) for the treatment of opportunistic infections in immunosuppressed patients. Myelosuppression, gastrointestinal disturbances, and hepatotoxicity have been reported.

Piritrexim isetionate has also been investigated for severe psoriasis.

◊ References.

1. Khorsand M, *et al.* Phase II trial of oral piritrexim in advanced, previously treated transitional cell cancer of bladder. *Invest New Drugs* 1997; **15:** 157–63.
2. Roth BJ, *et al.* Piritrexim in advanced, refractory carcinoma of the urothelium (E3896): a phase II trial of the Eastern Cooperative Oncology Group. *Invest New Drugs* 2002; **20:** 425–9.
3. Huie M, *et al.* Phase I study of piritrexim and gemcitabine in patients with advanced solid tumors. *Am J Clin Oncol* 2005; **28:** 613–17.
4. Lassiter LK, *et al.* Phase II open-label study of oral piritrexim in patients with advanced carcinoma of the urothelium who have experienced failure with standard chemotherapy. *Clin Genitourin Cancer* 2008; **6:** 31–5.

Pixantrone *(BAN, USAN, rINN)*

BBR-2778; Pixantrona; Pixantronum. 6,9-Bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione.

Пиксантрон

$C_{17}H_{19}N_5O_2$ = 325.4.
CAS — 144510-96-3 (pixantrone); 144675-97-8 (pixantrone maleate);.

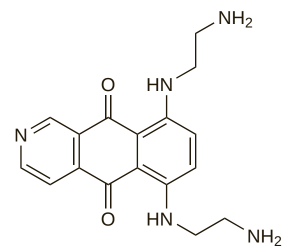

Profile

Pixantrone is an anthracycline antineoplastic that is under investigation for the treatment of non-Hodgkin's lymphoma.

◊ References.

1. Borchmann P, Schnell R. The role of pixantrone in the treatment of non-Hodgkin's lymphoma. *Expert Opin Invest Drugs* 2005; **14:** 1055–61.

Plitidepsin *(BAN, rINN)*

Aplidine; Dehydrodidemnin B; Plitidepsina; Plitidepsine; Plitidepsinum. 3,6-Anhydro(*N*-{(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-3-hydroxy-4-{[*N*-(2-oxopropanoyl)-L-prolyl-*N*-methyl-D-leucyl-L-threonyl]amino}-5-methylheptanoyloxy]-2,5-dimethyl-3-oxohexanoyl}-L-leucyl-L-prolyl-*N*,*O*-dimethyl-L-tyrosine).

Плитидепсин

$C_{57}H_{87}N_7O_{15}$ = 1110.3.
CAS — 137219-37-5.

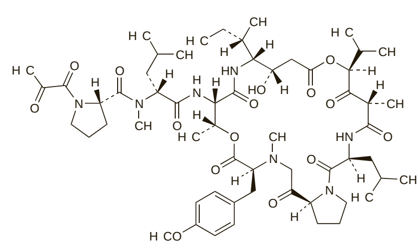

Profile

Plitidepsin is an antineoplastic isolated from the marine tunicate *Aplidium albicans*. It is under investigation in the treatment of acute lymphoblastic leukaemia, multiple myeloma, and solid tumours.

◊ References.

1. Faivre S, *et al.* Phase I and pharmacokinetic study of aplidine, a new marine cyclodepsipeptide in patients with advanced malignancies. *J Clin Oncol* 2005; **23:** 7871–80.
2. Maroun JA, *et al.* Phase I study of Aplidine in a daily×5 one-hour infusion every 3 weeks in patients with solid tumors refractory to standard therapy. A National Cancer Institute of Canada Clinical Trials Group study: NCIC CTG IND 115. *Ann Oncol* 2006; **17:** 1371–8.
3. Izquierdo MA, *et al.* Phase I clinical and pharmacokinetic study of plitidepsin as a 1-hour weekly intravenous infusion in patients with advanced solid tumors. *Clin Cancer Res* 2008; **14:** 3105–12.
4. Peschel C, *et al.* Phase II study of plitidepsin in pretreated patients with locally advanced or metastatic non-small cell lung cancer. *Lung Cancer* 2008; **60:** 374–80.

Porfimer Sodium *(BAN, USAN, rINN)*

CL-184116; Dihaematoporphyrin Ether; Porfimeerinatrium; Porfimère Sodique; Porfimernatrium; Porfímero sódico; Porfimerum Natricum.

Порфимер Натрий

CAS — 87806-31-3.
ATC — L01XD01.
ATC Vet — QL01XD01.

Adverse Effects and Precautions

Photosensitivity occurs in all patients treated with porfimer sodium. This effect is likely to be prolonged, and patients should avoid sunlight or bright indoor light for at least 30 days. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Other reported adverse effects include local inflammation, chest pain, respiratory insufficiency or distress (including dyspnoea), abdominal pain, dysphagia, constipation, nausea and vomiting, fever, tachycardia and atrial fibrillation, pleural effusion, mucositis, and anaemia due to tumour bleeding. Pneumonia and bronchitis may occur. Anxiety and insomnia have also been reported. Photodynamic therapy with porfimer sodium is contra-indicated in patients with severe hepatic impairment, oesophageal fistulae, erosion of major blood vessels, or severe acute respiratory distress. Sufficient time should be allowed between photodynamic therapy and radiotherapy to allow inflammatory reactions from either treatment to subside.

Porphyria. The use of porfimer sodium is contra-indicated in patients with porphyria.

Interactions

Use of porfimer sodium with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

Porfimer sodium is distributed and eliminated slowly after intravenous injection, with plasma elimination half-life reported to be between 11 and 28 days. *In vitro* studies indicate that plasma protein binding is about 90%. Excretion occurs primarily via the faeces.

Uses and Administration

Porfimer sodium is a haematoporphyrin derivative that reportedly accumulates in malignant tissue on injection. It is then activated by laser light to release oxygen radicals within malignant cells, producing cytotoxicity. Porfimer sodium is used as a photosensitiser in the photodynamic therapy of non-small cell lung cancer (p.668), oesophageal cancer (p.664), and superficial bladder cancer (p.659). It is also used for the treatment of dysplasia associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p.1696), and has been investigated in various other neoplasms, including tumours of the gastrointestinal tract and cervix.

Porfimer sodium should be reconstituted with glucose 5% to a final concentration of 2.5 mg/mL. It is given by slow intravenous injection at a dose of 2 mg/kg. This is followed, 40 to 50 hours later, by activation using a laser tuned to a wavelength of 630 nanometres and delivered to the area of the tumour using a fibre optic guide. Residual tumour may subsequently be debrided surgically. A second laser treatment may be given 96 to 120 hours after the original injection. A maximum of 3 courses of photodynamic therapy may be used, with each injection separated by a minimum of 30 days for oesophageal and endobronchial tumours, and a minimum of 90 days for dysplasia in Barrett's oesophagus. However, in the treatment of superficial bladder cancer, only one dose of drug and light is given due to an increased risk of bladder contracture, and no surgical debridement is performed.

Photodynamic therapy. Photodynamic therapy probably has the greatest potential of the various forms of light-activated treatment.[1] Photosensitising drugs are given intravenously, orally, or topically, and are selectively retained by tumour cells. When exposed to the correct wavelength of light the drug produces toxic oxygen radicals that destroy cell membranes and thereby kill the tumour cells. Vascular damage and immune-mediated injury may also occur.[2,3] Tumour cells must have an adequate supply of oxygen to be sensitive to photodynamic therapy,[2] and as light penetration is usually limited, early or superficial malignant lesions respond best to therapy.[1,2] Photodynamic therapy has been tried in skin, gastrointestinal, head and neck, bladder, gynaecological, pancreatic, pulmonary, and various intraperitoneal malignancies[2-11] It is also used for the treatment of Barrett's oesophagus[11-13] and for the treatment of age-related macular degeneration (p.785); it has been tried for other ocular disorders.[14] There is also an interesting report of cytotoxicity against leukaemic cells *in vitro* when exposure to porfimer sodium was combined with ultrasound.[5]

The main adverse effect of photosensitisers such as porfimer is photosensitivity lasting 4 to 8 weeks; patients should be advised to avoid sunlight during this period and therapy is best delayed until the darker winter months if possible.[1] Newer photosensitisers are being developed to show increased tissue penetration and less prolonged photosensitivity.[2] The natural haem precursor 5-aminolevulinic acid (p.679) has the advantage that photosensitivity lasts only a few hours.

1. Bown SG. New techniques in laser therapy. *BMJ* 1998; **316:** 754–7.
2. Hsi RA, *et al.* Photodynamic therapy in the treatment of cancer: current state of the art. *Drugs* 1999; **57:** 725–34.
3. Ost D, *et al.* Photodynamic therapy in lung cancer. *Oncology* 2000; **14:** 379–86.
4. Wilson JHP, *et al.* Photodynamic therapy for gastrointestinal tumors. *Scand J Gastroenterol* 1991; **26** (suppl 188): 20–5.
5. Tachibana K, *et al.* Eliminating adult T-cell leukaemia cells with ultrasound. *Lancet* 1997; **349:** 325.
6. Walther MM. The role of photodynamic therapy in the treatment of recurrent superficial bladder cancer. *Urol Clin North Am* 2000; **27:** 163–70.
7. Metz JM, Friedberg JS. Endobronchial photodynamic therapy for the treatment of lung cancer. *Chest Surg Clin North Am* 2001; **11:** 829–39.
8. Biel MA. Photodynamic therapy in head and neck cancer. *Curr Oncol Rep* 2002; **4:** 87–96.
9. Moghissi K. Role of bronchoscopic photodynamic therapy in lung cancer management. *Curr Opin Pulm Med* 2004; **10:** 256–60.
10. Bown SG, *et al.* Photodynamic therapy for cancer of the pancreas. *Gut* 2002; **50:** 549–57.
11. Brown SB, *et al.* The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol* 2004; **5:** 497–508.
12. Wolfsen HC, *et al.* Photodynamic therapy for dysplastic Barrett esophagus and early esophageal adenocarcinoma. *Mayo Clin Proc* 2002; **77:** 1176–81.
13. Kelty CJ, *et al.* Photodynamic therapy for Barrett's esophagus: a review. *Dis Esophagus* 2002; **15:** 137–44.
14. Sivaprasad S, Hykin P. The role of photodynamic therapy in ophthalmology. *Br J Hosp Med* 2006; **67:** 647–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Photofrin; ***Cz.:*** Photobarr; ***Fr.:*** Photobarr; ***Ger.:*** Photofrin; ***Gr.:*** Photofrin; ***Hung.:*** Photofrin; ***Israel:*** Photofrin; ***Neth.:*** Photobarr; Photofrin; ***Port.:*** Photobarr; Photofrin; ***USA:*** Photofrin.

Porfiromycin *(BAN, USAN, rINN)*

Methyl Mitomycin; NSC-56410; Porfiromicina; Porfiromycine; Porfiromycinum; U-14743. 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-1,5-dimethylazirino[2′,3′:3,4]-pyrrolo[1,2-*a*]-indole-4,7-dione carbamate ester.

Порфиромицин

$C_{16}H_{20}N_4O_5$ = 348.4.

CAS — 801-52-5.

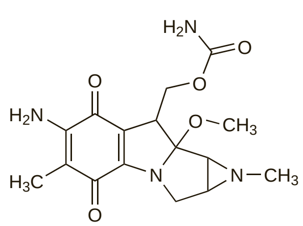

Profile

Porfiromycin is an antibiotic antineoplastic structurally related to mitomycin (p.752). It is being studied as a radiosensitiser in the management of malignant neoplasms of the head and neck.

◊ References.

1. Haffty BG, *et al.* Bioreductive alkylating agent porfiromycin in combination with radiation therapy for the management of squamous cell carcinoma of the head and neck. *Radiat Oncol Invest* 1997; **5:** 235–45.
2. Haffty BG, *et al.* Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2005; **61:** 119–28.

Prednimustine *(USAN, rINN)*

Leo-1031; NSC-134087; Prednimustiini; Prednimustin; Prednimustina; Prednimustinum. 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(4-{4-[bis(2-chloroethyl)amino]phenyl}butyrate).

Преднимустин

$C_{35}H_{45}Cl_2NO_6$ = 646.6.

CAS — 29069-24-7.

ATC — L01AA08.

ATC Vet — QL01AA08.

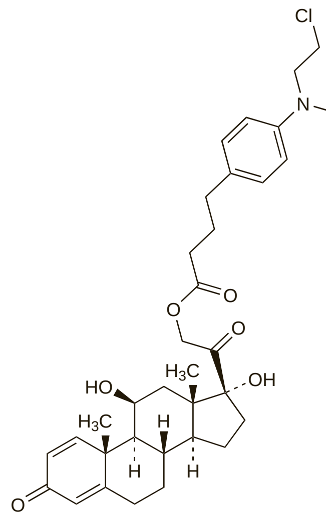

Profile

Prednimustine is the prednisolone ester of chlorambucil, (p.696) and has been given orally in the treatment of various malignant diseases.

Procarbazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de procarbazina; Ibenzmethyzin Hydrochloride; NSC-77213; Procarbazine, Chlorhydrate de; Procarbazini Hydrochloridum; Ro-4-6467/1. *N*-Isopropyl-α-(2-methylhydrazino)-*p*-toluamide hydrochloride.

Прокарбазина Гидрохлорид

$C_{12}H_{19}N_3O,HCl$ = 257.8.

CAS — 671-16-9 (procarbazine); 366-70-1 (procarbazine hydrochloride).

ATC — L01XB01.

ATC Vet — QL01XB01.

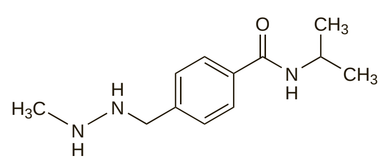

(procarbazine)

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US.*

USP 31 (Procarbazine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects associated with procarbazine are gastrointestinal disturbances such as anorexia, nausea and vomiting (although patients may soon become tolerant), and bone-marrow depression. Leucopenia and thrombocytopenia may be delayed with a nadir at about 4 weeks after a dose, and recovery usually within 6 weeks. Anaemia, haemolysis, and bleeding tendencies have been reported.

Neurotoxicity is also common, with central effects such as somnolence, depression, nervousness or confusion, headache, hallucinations, and dizziness, and peripheral neuropathies including paraesthesias and decreased reflexes. Lethargy, ataxia, and sleep disorders have also occurred, and tremors, convulsions, and coma have been reported.

Other adverse effects reported include fever and myalgia, pulmonary fibrosis or pneumonitis, haematuria, urinary frequency, skin reactions including dermatitis, pruritus, and hyperpigmentation, tachycardia, orthostatic hypotension, ocular defects, infertility, and hepatic impairment.

Procarbazine is a carcinogen, mutagen, and teratogen.

Procarbazine should be used with caution in patients with hepatic or renal impairment, and is contra-indicated if impairment is severe. The haematological status of the patient should be determined at least every 3 or 4 days and hepatic and renal function determined weekly. Care is also advisable in patients with phaeochromocytoma, epilepsy, or cardiovascular or cerebrovascular disease. Treatment should be interrupted if allergic skin reactions occur.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of procarbazine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Procarbazine is a weak MAOI and the possibility of reactions with other drugs and food, although very rare, must be borne in mind—for details of MAOI reactions see p.417. Procarbazine may enhance the sedative effects of other CNS depressants. A disulfiram-like reaction has been reported with alcohol and the effects of antihypertensive agents may be enhanced.

Antiepileptics. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine, possibly through a reactive intermediate generated by induction of the cytochrome P450 isoenzyme CYP3A subfamily.[1] Non-enzyme-inducing antiepileptics might be more appropriate in patients with brain tumours in whom procarbazine therapy is anticipated.

1. Lehmann DF, *et al.* Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther* 1997; **62:** 225–9.

Pharmacokinetics

Procarbazine is readily absorbed from the gastrointestinal tract. It crosses the blood-brain barrier and diffuses into the CSF. A plasma half-life of about 10 minutes has been reported. Procarbazine is rapidly metabolised (mainly in liver and kidneys) and only about 5% is excreted unchanged in the urine. The remainder is oxidised to *N*-isopropylterephthalamic acid and excreted in the urine, up to about 70% of a dose being excreted in 24 hours. Some of the drug is excreted as carbon dioxide and methane via the lungs. During oxidative breakdown in the body hydrogen peroxide is formed which may account for some of the drug's actions.

Uses and Administration

Procarbazine hydrochloride is a methylhydrazine derivative whose antineoplastic effect, although not fully understood, may resemble that of the alkylating agents; it appears to inhibit protein and nucleic acid synthesis and suppress mitosis. It does not exhibit cross-resistance with other cytotoxic drugs.

Its main use is the treatment of Hodgkin's disease (p.655) when it is usually given with other drugs, as in the MOPP regimen (with chlormethine, vincristine, and prednisone) and its variants. Procarbazine has also been used in the treatment of other lymphomas (p.656) and in some other malignant neoplasms including tumours of the brain (p.660).

Doses of procarbazine hydrochloride are calculated in terms of procarbazine; procarbazine hydrochloride 116 mg is equivalent to about 100 mg of procarbazine. In many of the combination regimens it has been given orally to adults and children in doses of the equivalent of procarbazine 100 mg/m^2 for 10 to 14 days of each 4- or 6-week cycle. If used as a single agent in adults a dose equivalent to 50 mg of procarbazine daily, increased by 50 mg daily to 250 to 300 mg daily in divided doses has been suggested in the UK, while in the USA the recommended regimen is 2 to 4 mg/kg daily for the first week, subsequently increased to 4 to 6 mg/kg daily, doses being given to the nearest 50 mg. These doses are continued until maximum response is achieved or leucopenia, thrombocytopenia, or other signs of toxicity ensue. Maintenance doses are usually 50 to 150 mg daily, or 1 to 2 mg/kg, daily, until a cumulative dose of at least 6 g has been given. In children, initial daily doses of the equivalent of 50 mg/m^2 have been suggested in the USA (UK product information simply suggests a dose of 50 mg), increased to 100 mg/m^2 and then adjusted according to response.

Blood disorders, non-malignant. Chemotherapy with regimens including procarbazine has been used in a few patients with refractory idiopathic thrombocytopenic purpura (p.1505), and has produced prolonged remission although in most cases of the disease such aggressive therapy is difficult to justify.

Preparations

USP 31: Procarbazine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Natulan; ***Canad.:*** Matulane; Natulan†; ***Fr.:*** Natulan; ***Ger.:*** Natulan; ***Gr.:*** Natulan; ***Hung.:*** Natulan†; ***Ital.:*** Natulan; ***Neth.:*** Natulan; ***NZ:*** Natulan†; ***Rus.:*** Natulan (Натулан); ***Spain:*** Natulan; ***USA:*** Matulane.

Raltitrexed *(BAN, USAN, rINN)*

D-1694; ICI-D1694; Raltitreksed; Raltitreksedi; Raltitrexedum; ZD-1694. *N*-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl(methyl)amino]-2-thenoyl}-L-glutamic acid.

Ралтитрексед

$C_{21}H_{22}N_4O_6S$ = 458.5.

CAS — 112887-68-0.

ATC — L01BA03.

ATC Vet — QL01BA03.

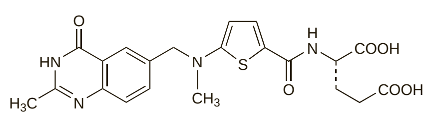

Adverse Effects, Treatment, and Precautions

Raltitrexed produces bone marrow depression, usually mild to moderate, with leucopenia, anaemia, and, less frequently, thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after a dose, with recovery by the third week. Gastrointestinal toxicity is also common, with nausea and vomiting, diarrhoea, and anorexia: mucositis may occur. Reversible increases in liver enzyme values have occurred. Other adverse effects include weakness and malaise, fever, pain, headache, skin rashes, desquamation, arthralgia, muscle cramps, weight loss, dehydration, peripheral oedema, alopecia, increased sweating, taste disturbance, and conjunctivitis. The use of folinic acid 25 mg/m^2 every 6 hours intravenously has been suggested in licensed product information for patients who develop very severe toxicity.

Raltitrexed should be given with care to patients with hepatic impairment and should be avoided if impairment is severe. It should also be avoided in severe renal impairment and be given in reduced doses in moderate impairment. Care is also advisable in debilitated or elderly patients or in patients who have had radiotherapy.

Raltitrexed is teratogenic; pregnancy should be avoided while either partner is receiving the drug and for at least 6 months after treatment. It may impair male fertility.

Toxicity. A large multicentre study comparing raltitrexed with fluorouracil plus folinic acid was suspended in 1999 due to an excess of deaths in the raltitrexed arm.[1] This decision has led to some controversy,[1-3] as in 11 of the 17 deaths in patients taking raltitrexed there was evidence that the dose had not been correctly adjusted to take account of renal function. In addition, and further confusing the issue, the incidence of reported serious adverse effects was lower in raltitrexed-treated patients than in controls. A further study[4] reported an increased rate of raltitrexed-related deaths compared with fluorouracil-based regimens. Almost all of the 18 deaths were caused by gastrointestinal and haematological toxicity, and in 3 of these the dose of raltitrexed had not been adjusted for toxicity.

1. Anonymous. Drug-company decision to end cancer trial. *Lancet* 1999; **354:** 1045.
2. Ford HER, Cunningham D. Safety of raltitrexed. *Lancet* 1999; **354:** 1824–5.
3. Kerr D. Safety of raltitrexed. *Lancet* 1999; **354:** 1825.
4. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.

Interactions

Raltitrexed should not be given with folic or folinic acid, which may impair its cytotoxic action. (For the deliberate use of folinic acid to counteract the effects of raltitrexed in patients with severe toxicity, see above.)

Pharmacokinetics

After intravenous doses raltitrexed exhibits triphasic pharmacokinetics, with an initial rapid decline from peak plasma concentrations followed by a slow terminal elimination phase. Raltitrexed is actively transported into cells and metabolised to active polyglutamate forms. The remainder of a dose is excreted unchanged, about 50% of a dose appearing in the urine, and about 15% in the faeces. The terminal elimination half-life is about 8 days. Clearance is markedly reduced in renal impairment.

◊ References.

1. Clarke SJ, *et al.* Clinical and preclinical pharmacokinetics of raltitrexed. *Clin Pharmacokinet* 2000; **39:** 429–43.

Uses and Administration

Raltitrexed is a folate analogue that is a potent and specific inhibitor of the enzyme thymidylate synthase, which is involved in the synthesis of DNA. It has been used in the treatment of advanced colorectal cancer (p.665) and has also been tried in breast cancer (p.661) and other solid neoplasms.

The recommended initial dose of raltitrexed in patients with normal renal function is 3 mg/m^2 given by intravenous infusion over 15 minutes. Subsequent doses, which should be reduced by up to 50% depending on the severity of initial toxicity, may be given at intervals of 3 weeks provided toxicity has resolved.

A full blood count should be performed before each dose and treatment withheld if the white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p.639). Hepatic and renal function should also be tested. It is essential that doses be adjusted in renal impairment (see below).

◊ References.

1. Gunasekara NS, Faulds D. Raltitrexed: a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1998; **55:** 423–35.
2. Cunningham D, *et al.* Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials. *Eur J Cancer* 2002; **38:** 478–86.
3. Scheithauer W, *et al.* Randomized multicenter phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002; **20:** 165–72.
4. Feliu J, *et al.* Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. *Eur J Cancer* 2002; **38:** 1204–11.
5. Comella P, *et al.* Oxaliplatin plus raltitrexed and leucovorin-modulated 5-fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002; **86:** 1871–5.
6. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.
7. van Meerbeeck JP, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23:** 6881–9.
8. Ducreux M, *et al.* FFCD 9601 Collaborative Group. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 trial. *Oncology* 2006; **70:** 222–30.
9. Wilson KS, *et al.* Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. *Cancer Invest* 2007; **25:** 711–14.
10. Hind D, *et al.* The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008; **12:** 1–182.

Administration in renal impairment. It is essential that doses of raltitrexed be adjusted in renal impairment (creatinine clearance less than 65 mL/minute) as fatalities have been associated with the failure to make such adjustments (see Toxicity, under Adverse Effects, above). The dosage interval should be increased from 3 to 4 weeks and the dose adjusted on the basis of creatinine clearance (CC) as follows:

- CC of 55 to 65 mL/minute, 2.25 mg/m^2
- CC of 25 to 54 mL/minute, 1.5 mg/m^2 (in some countries, adjustment of the dose to a percentage of the full dose equivalent to the value of the CC in mL/minute is suggested in this group, e.g. reduction to 30% in those with a CC of 30 mL/minute, or 40% if CC is 40 mL/minute)
- CC less than 25 mL/minute, treatment contra-indicated

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tomudex; ***Austral.:*** Tomudex; ***Austria:*** Tomudex; ***Belg.:*** Tomudex; ***Braz.:*** Tomudex; ***Canad.:*** Tomudex; ***Cz.:*** Tomudex; ***Fin.:*** Tomudex†; ***Fr.:*** Tomudex; ***Hong Kong:*** Tomudex†; ***Hung.:*** Tomudex; ***Irl.:*** Tomudex; ***Ital.:*** Tomudex; ***Mex.:*** Tomudex; ***Neth.:*** Tomudex; ***Norw.:*** Tomudex; ***Philipp.:*** Tomudex; ***Port.:*** Tomudex; ***Rus.:*** Tomudex (Томудекс); ***S.Afr.:*** Tomudex†; ***Singapore:*** Tomudex; ***Spain:*** Tomudex; ***Switz.:*** Tomudex; ***Turk.:*** Tomudex; ***UK:*** Tomudex; ***Venez.:*** Tomudex†.

Ranimustine *(rINN)*

MCNU; NSC-0270516; Ranimustina; Ranimustinum; Ranomustine. Methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside.

Ранимустин

$C_{10}H_{18}ClN_3O_7$ = 327.7.

CAS — 58994-96-0.

ATC — L01AD07.

ATC Vet — QL01AD07.

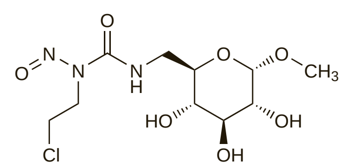

Profile

Ranimustine is a nitrosourea derivative with general properties similar to those of carmustine (p.694). It is used intravenously in the treatment of malignant neoplasms in usual doses of 50 to 90 mg/m^2 every 6 to 8 weeks according to haematological response.

◊ References.

1. Wada M, *et al.* Induction therapy consisting of alternating cycles of ranimustine, vincristine, melphalan, dexamethasone and interferon alpha (ROAD-IN) and a randomized comparison of interferon alpha maintenance in multiple myeloma: a co-operative study in Japan. *Br J Haematol* 2000; **109:** 805–14.
2. Hatano N, *et al.* Efficacy of post operative adjuvant therapy with human interferon beta, MCNU and radiation (IMR) for malignant glioma: comparison among three protocols. *Acta Neurochir (Wien)* 2000; **142:** 633–8.
3. Wakabayashi T, *et al.* Initial and maintenance combination treatment with interferon-beta, MCNU (ranimustine), and radiotherapy for patients with previously untreated malignant glioma. *J Neurooncol* 2000; **49:** 57–62.
4. Mizuno H, *et al.* Superior efficacy of MMCP regimen compared with VMCP and MMPP regimens in the treatment of multiple myeloma. *Intern Med* 2002; **41:** 290–4.
5. Takenaka T, *et al.* Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004; **79:** 165–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cymerin.

Ranpirnase *(USAN, rINN)*

P-30 Protein; Ranpirnasa; Ranpirnasum.

Ранпирназа

CAS — 196488-72-9.

NOTE. P-30 protein has been incorrectly stated to contain ergotamine.

Profile

Ranpirnase is a ribonuclease reported to have antineoplastic properties. It is under investigation in the treatment of malignant mesothelioma. Ranpirnase has also been investigated in the management of solid tumours. It is also reported to have activity *in vitro* against HIV.

Razoxane *(BAN, rINN)*

ICI-59118; ICRF-159; NSC-129943; Ratsoksaani; Razoxan; Razoxano; Razoxanum. (±)-4,4′-Propylenebis(piperazine-2,6-dione).

Разоксан

$C_{11}H_{16}N_4O_4$ = 268.3.

CAS — 21416-87-5.

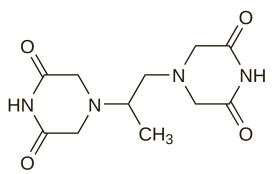

Profile

Razoxane is an antineoplastic with inhibitory activity during the pre-mitotic and early mitotic phases of cell growth (G_2-M). It enhances the effects of radiotherapy. It has been used with radiotherapy in the treatment of sarcomas, including Kaposi's sarcoma. Razoxane has also been tried in other malignant diseases including acute leukaemias and non-Hodgkin's lymphomas. However, it is no longer widely used. Razoxane was formerly used in psoriasis, but its carcinogenic properties militate against such use, as discussed below.

In the treatment of sarcomas it has generally been given orally in doses of 125 mg twice daily; higher doses have been given in the management of acute leukaemias and Kaposi's sarcoma. The peripheral blood count should be monitored during treatment.

The principal adverse effects of razoxane include bone-marrow depression, gastrointestinal disturbances, skin reactions, and alopecia. It may enhance the adverse effects of radiotherapy. Razoxane therapy has been associated with the development of secondary malignancies: it is contra-indicated in the treatment of non-malignant conditions.

Dexrazoxane (p.1443) is the (+)-enantiomer of razoxane. It is used to reduce anthracycline-induced cardiotoxicity.

Malignant neoplasms. References to the use of razoxane with radiotherapy.

1. Rhomberg W, *et al.* Radiotherapy vs radiotherapy and razoxane in the treatment of soft tissue sarcomas: final results of a randomized study. *Int J Radiat Oncol Biol Phys* 1996; **36:** 1077–84.
2. Rhomberg W, *et al.* A small prospective study of chordomas treated with radiotherapy and razoxane. *Strahlenther Onkol* 2003; **179:** 249–53.

Skin disorders, non-malignant. Razoxane was formerly used in the systemic treatment of psoriasis, and has been found to be extremely effective, with an initial response rate of 97% overall. It was found to be of use in all forms of cutaneous psoriasis and psoriatic arthropathy.[1] However, the development of acute myeloid leukaemias and other malignancies in patients given razoxane[2-5] has led to its being contra-indicated in non-malignant conditions.

For a discussion of psoriasis and its management, see p.1583.

1. Horton JJ, Wells RS. Razoxane: a review of 6 years' therapy in psoriasis. *Br J Dermatol* 1983; **109:** 669–73.
2. Horton JJ, *et al.* Epitheliomas in patients receiving razoxane therapy for psoriasis. *Br J Dermatol* 1983; **109:** 675–8.
3. Lakhani S, *et al.* Razoxane and leukaemia. *Lancet* 1984; **ii:** 288–9.
4. Caffrey EA, *et al.* Acute myeloid leukaemia after treatment with razoxane. *Br J Dermatol* 1985; **113:** 131–4.
5. Zuiable AG, *et al.* Razoxane and T-cell lymphoma. *Br J Dermatol* 1989; **121:** 149.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardioxane.

Rituximab *(BAN, USAN, rINN)*

IDEC-102; IDEC-C2B8; Rituksimab; Rituksimabi; Rituximabum. Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer.

Ритуксимаб

CAS — 174722-31-7.

ATC — L01XC02.

ATC Vet — QL01XC02.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Infusion of rituximab has been associated with a cytokine release syndrome of fever, chills, and rigors, usually within 2 hours of beginning therapy (see also below). Other reported symptoms include pruritus, urticaria, rashes, dyspnoea, bronchospasm, angioedema, transient hypotension, and flushing. Asthenia, headache, rhinitis, myalgia, dizziness, and hypertension may also be associated with infusion reactions. Severe cases may be associated with tumour lysis syndrome, acute renal failure, respiratory failure, and death. Hypersensitivity reactions manifest similarly to the cytokine release syndrome, but usually occur within minutes of starting infusion. Mucocutaneous reactions, some fatal, and including Stevens-Johnson syndrome or toxic epidermal necrolysis have also occurred.

Patients with an extensive tumour burden, pulmonary tumour infiltration or pulmonary insufficiency may be at increased risk of severe reactions and should be treated with caution and possibly a decreased initial infusion rate. Therapy should be interrupted in patients who develop severe symptoms and only resumed, at half the previous rate, once all signs and symptoms have resolved. Premedication with analgesics, antihistamines, and possibly corticosteroids is recommended in all patients before receiving rituximab.

Reactivation of hepatitis B virus (HBV) has occurred in some patients; fulminant hepatitis, hepatic failure, and fatalities have been reported. Patients at high risk of HBV infection should be screened before starting rituximab therapy and carriers should be monitored for signs of active infection or hepatitis during and for several months after therapy. Rituximab should be stopped if viral hepatitis develops. Other serious infections, which may be fatal, can occur with rituximab. Cases of progressive multifocal leukoencephalopathy, some fatal, have been reported with rituximab.

Haematological adverse effects including lymphopenia, leucopenia, neutropenia, thrombocytopenia, and anaemia have occurred in some patients; effects are considered mild and reversible. Complete blood and platelet counts should be monitored regularly. Exacerbation of heart failure and angina pectoris has also been reported, and other cardiac events include arrhythmias and tachycardia. Gastrointestinal disturbances may also occur. Abdominal pain, bowel obstruction, and perforation, in some cases fatal, have been reported with rituximab combination chemotherapy.

◊ References.

1. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; **7** (suppl 3): S19–S25.
2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; **31:** 456–73.

Effects on the blood. Late-onset neutropenia (defined as neutropenia occurring 30 days after the last dose) has been reported in patients receiving rituximab.[1]

1. Rios-Fernández R, *et al.* Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. *Br J Dermatol* 2007; **157:** 1271–3.

Effects on the eyes. About 20 minutes after the start of a rituximab infusion, a patient developed bilateral conjunctivitis without pain, lachrymation, or discharge. No other clinical manifestations of a hypersensitivity reaction were apparent, and the conjunctivitis resolved spontaneously, about 30 minutes after the end of the infusion. No recurrence was evident with subsequent rituximab therapy.[1]

1. Marinella MA. Bilateral conjunctivitis due to rituximab. *Ann Pharmacother* 2007; **41:** 1318.

Effects on the gastrointestinal tract. In November 2006 the manufacturer noted that 47 cases of bowel obstruction (9 fatal) and 37 cases of gastrointestinal perforation (4 fatal) had been reported in patients given rituximab.[1] Interpretation of data was difficult due to confounding factors; however, a contributory role of rituximab could not be excluded. The mean time to onset of symptoms was 6 days (range 1 to 77 days) for documented perforation. Complaints of abdominal pain, especially early in a course of rituximab treatment, should prompt thorough diagnostic evaluation and treatment.

1. Roche, Canada. Reports of bowel obstruction and gastrointestinal perforation with RITUXAN (rituximab) (issued 10th November 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rituxan_3_hpc-cps-eng.php (accessed 30/07/08)

Effects on the lungs. Pulmonary reactions have been reported with rituximab use,[1] including reversible interstitial pneumonia[2-4] and interstitial fibrosis.[5] A fatal intra-alveolar haemorrhage in 1 patient was attributed to a hypersensitivity reaction to rituximab.[6]

1. Wagner SA, *et al.* Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; **82:** 916–19.
2. Burton C, *et al.* Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003; **348:** 2690–1.
3. Jullien V, *et al.* Une pneumopathie alvéolo-interstitielle hypoxémiante associée à la prise de rituximab. *Rev Mal Respir* 2004; **21:** 407–10.
4. Swords R, *et al.* Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004; **77:** 103–4.
5. Leon RJ, *et al.* Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc* 2004; **79:** 949, 953.
6. Alexandrescu DT, *et al.* Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma* 2004; **45:** 2321–5.

Effects on the nervous system. As of December 2006, the FDA had received a total of 24 reports of progressive multifocal leukoencephalopathy (PML) in patients given rituximab.[1] PML is a fatal demyelinating disease that follows reactivation of latent JC or PK polyomavirus (also known as papovavirus) in the CNS; the virus is present in about 80% of adults. In the first 12 cases reported to the FDA, 10 patients tested positive for the JC virus and 1 had confirmed BK virus.

1. FDA. Rituximab (marketed as Rituxan): progressive multifocal leukoencephalopathy (PML). *FDA Drug Safety Newsletter* 2007; **1:** 3–5. Available at: http://www.fda.gov/cder/dsn/2007_fall/2007_fall.pdf (accessed 07/02/08)

Infusion-related reactions. By November 1998 there had been 74 cases of serious infusion-related reactions to rituximab reported worldwide, with 8 fatal cases.[1] An estimated 12 000 to 14 000 patients had been treated.

The reaction usually occurs within the first 2 hours of infusion and the underlying mechanism is believed to be a severe cytokine release syndrome, with some elements of tumour lysis syndrome.[1-3] In one series of cases tumour necrosis factor-α and interleukin-6 levels were found to peak 90 minutes after the onset of the infusion, and these elevated cytokine levels coincided with infusion-related symptoms.[2] The reaction is usually most marked after the first infusion and subsequent infusions are usually tolerated, emphasising that this is not a true hypersensitivity reaction.[4]

Patients with a high tumour burden (lesions over 10 cm in diameter or more than 500 000 circulating malignant cells/mm^3), a history of pulmonary infiltration or insufficiency, or underlying cardiac disease are believed to be at greater risk of severe reactions.[1,2,4] The UK CSM recommends that premedication with an analgesic and an antihistamine should always be given before rituximab, and corticosteroids should be considered.[1] However, serious or fatal reactions have occurred despite such premedication.[3,4] Alternative infusion schedules and/or combination therapy with chemotherapeutic drugs may be required to decrease the tumour burden before rituximab therapy.[2,4]

1. Committee on Safety of Medicines/Medicines Control Agency. Rituximab (MabThera): serious infusion-related adverse reactions. *Current Problems* 1999; **25:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 26/04/06)
2. Winkler U, *et al.* Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukaemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; **94:** 2217–24.
3. Lim L-C, *et al.* Fatal cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukaemia. *J Clin Oncol* 1999; **17:** 1962–3.
4. Byrd JC, *et al.* Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999; **17:** 791–5.

Pregnancy. Giving 4 cycles of rituximab (with doxorubicin, vincristine, and prednisolone) to a pregnant woman with lymphoma, from 21 weeks of gestation until delivery at 35 weeks, resulted in no adverse effects to either the mother or the infant.[1] In another report, a 31-year-old woman was diagnosed with non-Hodgkin's lymphoma during pregnancy. She received 6 cycles of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Two months after treatment, she spontaneously delivered a premature but healthy infant. Patient and child were clinically assessed every 3 months; the infant's B cells were severely diminished at birth but recovered over 6 to 12 weeks. Rituximab concentrations in both mother and child also decreased as expected. No adverse effects were seen during 16 months of follow-up.[2] In 2 case reports of rituximab use during the first trimester of pregnancy, no significant adverse effects on the neonates were seen; transient granulocytopenia and lymphopenia were reported.[3,4] A 35-year-old woman diagnosed with Burkitt's lymphoma in week 15 of pregnancy received 4 weekly infusions of rituximab starting in week 16, followed by four courses of rituximab with CHOP, and then 2 courses of CHOP alone. In week 41, a healthy infant was delivered by caesarean section. Both the mother and child had very high serum concentrations of rituximab at birth with a complete absence of B cells; rituximab levels in the cord blood serum were three times that in the mother's serum. However, B-cell recovery was reported to be rapid, and no overt infectious complications were seen in the child up to the age of 26 months; growth and developmental status were also normal.[5] Nonetheless, licensed product information advises against rituximab use during pregnancy, given the potential for B-cell depletion in the fetus; women of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months after therapy.

1. Herold M, *et al.* Efficacy and safety of a combined rituximab chemotherapy during pregnancy. *J Clin Oncol* 2001; **19:** 3439.
2. Decker M, *et al.* Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol* 2006; **7:** 693–4. Correction. *ibid.*; 706.
3. Kimby E, *et al.* Safety of rituximab therapy during the first trimester of pregnancy: a case history. *Eur J Haematol* 2004; **72:** 292–5.
4. Ojeda-Uribe M, *et al.* Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. *J Perinatol* 2006; **26:** 252–5.
5. Friedrichs B, *et al.* The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 2006; **91:** 1426–7.

Pharmacokinetics

The mean maximum plasma concentration of rituximab has been reported to increase with successive infusions; however, considerable interindividual variation is seen. Serum concentrations are negatively correlated with tumour burden and the number of circulating B-cells. The mean terminal half-life is about 20 days. Rituximab is bound to B lymphocytes, and is detectable in the body for 3 to 6 months after treatment.

Uses and Administration

Rituximab is a chimeric monoclonal antibody to CD20 antigen used in the treatment of non-Hodgkin's lymphomas (p.656). It is used as monotherapy in relapsed or refractory low-grade or follicular lymphoma, or as first-line treatment with combination chemotherapy, such as CVP (cyclophosphamide, vincristine, and prednisolone). Rituximab monotherapy may also be used in patients with low-grade stable disease after first-line treatment with CVP chemotherapy. It is also indicated for maintenance therapy in patients with refractory or relapsed follicular lymphoma who respond to induction chemotherapy that may or may not have contained rituximab. Rituximab is also used with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based regimens for CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. Rituximab also forms part of the combination regimen employing ibritumomab tiuxetan (p.730). Rituximab with methotrexate is used in adults with moderate to severely active rheumatoid arthritis (p.11) who have had an inadequate response to DMARDs, including tumour necrosis factor inhibitors.

Rituximab is given by intravenous infusion, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of between 1 and 4 mg/mL. The first infusion is given initially at a rate of 50 mg/hour; subsequently this may be increased in increments of 50 mg/hour every 30 minutes to a maximum of 400 mg/hour, if well tolerated. Subsequent doses may be begun at a rate of 100 mg/hour, and increased in increments of 100 mg/hour every 30 minutes to a maximum of 400 mg/hour.

In the UK for the treatment of refractory or relapsed follicular **lymphoma**, rituximab is given as a single agent in a usual dose of 375 mg/m^2 once weekly for 4 doses; in the USA 8 doses may be given. Patients in either country may be re-treated after relapse for a further 4 doses. When given with combination chemotherapy such as CVP (for follicular lymphoma) or CHOP (for diffuse large B-cell lymphoma), rituximab 375 mg/m^{2}is given on day 1 of the chemotherapy cycle, after the corticosteroid component of the regimen, for a total of 8 cycles. In patients previously treated with 6 to 8 cycles of CVP chemotherapy and who have not progressed, rituximab 375 mg/m^2 may be given once weekly for 4 doses, repeated every 6 months, for up to 16 doses. For maintenance treatment in those who have responded to induction chemotherapy, rituximab 375 mg/m^2 is given once every 3 months until disease progression or for a maximum period of 2 years.

In the regimen with ibritumomab tiuxetan, rituximab is usually given at a dose of 250 mg/m^2.

In the treatment of **rheumatoid arthritis**, rituximab is given in a dose of 1 g, for 2 doses; the infusions are separated by 2 weeks. It is given with methotrexate, and corticosteroids are recommended before each infusion to reduce the incidence and severity of infusion reactions.

Rituximab is also under investigation for the treatment of a number of **other conditions** including chronic lymphocytic leukaemia, multiple sclerosis, ANCA-associated vasculitis, and SLE, including lupus nephritis.

Administration. Rituximab has been used intralesionally in the treatment of cutaneous B-cell lymphoma. There are reports of benefit, with long-term remission in some patients,[1] but rapid recurrence in others.[2] In a study of 8 patients, intralesional rituximab was given to 6 patients, in doses of 10 to 30 mg per lesion, 3 times weekly; if clinical remission was incomplete, another cycle of 3 injections was given 1 month later. Two patients were treated intravenously with weekly infusions for 4 weeks. Complete remission was seen in all 8 patients. No relapse was seen in those given intravenous therapy, but recurrences were seen in 4 of the 6 patients treated intralesionally. Moderate pain was reported during intralesional injection.[3]

1. Paul T, *et al.* Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144:** 1239–43.
2. Roguedas AM, *et al.* Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2005; **152:** 541–4.
3. Kerl K, *et al.* Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. *Br J Dermatol* 2006; **155:** 1197–1200.

Administration in children. Although not licensed in the UK or the USA for use in children, there are reports of benefit in children with various diseases, such as auto-immune haemolytic anaemia, idiopathic thrombocytopenic purpura (see also below), and post-transplantation lymphoproliferative disease,[1] as well as rheumatoid arthritis, and SLE.[2] Standard doses of 375 mg/m^2 weekly have usually been given, in most cases for a median course of 4 doses.

1. Giulino LB, *et al.* Treatment with rituximab in benign and malignant hematologic disorders in children. *J Pediatr* 2007; **150:** 338–44.
2. El-Hallak M, *et al.* Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007; **150:** 376–82.

Eye disorders. Orbital pseudolymphomas are uncommon benign tumours which usually affect the lachrymal gland, orbital soft tissue, or extra-ocular muscles. Clinical presentation includes painless onset of ptosis, proptosis, diplopia, or eyelid swelling. There are reports of durable response to rituximab.[1]

1. Witzig TE, *et al.* Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. *Mayo Clin Proc* 2007; **82:** 692–9.

Glomerular kidney disease. In a report of 5 patients with corticosteroid-resistant nephrotic syndrome, 4 patients had a complete remission and 1 patient had a partial remission after treatment with rituximab in standard doses for 4 weeks. Complete remission was maintained in 3 patients, despite tapering of corticosteroids and calcineurin inhibitors.[1]

1. Bagga A, *et al.* Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; **356:** 2751–2.

Haemolytic anaemia. Rituximab has been used in the treatment of severe refractory auto-immune haemolytic anaemia (p.1043) of various causes, including warm,[1,2] cold,[3-5] and mixed[6,7] disease.

1. Quartier P, *et al.* Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001; **358:** 1511–13.
2. Gottardo NG, *et al.* Successful induction and maintenance of long-term remission in a child with chronic relapsing autoimmune hemolytic anemia using rituximab. *Pediatr Hematol Oncol* 2003; **20:** 557–61.
3. Sparling TG, *et al.* Remission of cold hemagglutinin disease induced by rituximab therapy. *Can Med Assoc J* 2001; **164:** 1405.
4. Engelhardt M, *et al.* Severe cold hemagglutinin disease (CHD) successfully treated with rituximab. *Blood* 2002; **100:** 1922–3.
5. Berentsen S, *et al.* Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004; **103:** 2925–8.
6. Morselli M, *et al.* Mixed warm and cold autoimmune hemolytic anemia: complete recovery after 2 courses of rituximab treatment. *Blood* 2002; **99:** 3478–9.
7. Webster D, *et al.* Prompt response to rituximab of severe hemolytic anemia with both cold and warm autoantibodies. *Am J Hematol* 2004; **75:** 258–9.

Haemorrhagic disorders. Although data are limited, reports suggest that rituximab may be an effective alternative for the treatment of acquired haemophilia (p.1048) after established therapies have failed.[1,2]

1. Maillard H, *et al.* Rituximab in postpartum-related acquired hemophilia. *Am J Med* 2006; **119:** 86–8.
2. Stachnik JM. Rituximab in the treatment of acquired hemophilia. *Ann Pharmacother* 2006; **40:** 1151–7.

Idiopathic thrombocytopenic purpura. Rituximab has been reported[1-3] to be effective in patients, including children and infants, with idiopathic thrombocytopenic purpura (p.1505) refractory to standard treatments. However, a review[4] cautioned against the indiscriminate use of rituximab in this patient population, given the lack of controlled data.

1. Zaja F, *et al.* The B-cell compartment as the selective target for the treatment of immune thrombocytopenias. *Haematologica* 2003; **88:** 538–46.
2. Bengtson KL, *et al.* Successful use of anti-CD20 (rituximab) in severe, life-threatening childhood immune thrombocytopenic purpura. *J Pediatr* 2003; **143:** 670–3.
3. Wang J, *et al.* Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr* 2005; **146:** 217–21.
4. Arnold DM, *et al.* Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; **146:** 25–33.

Malignant neoplasms. Reviews.

1. NICE. Rituximab for aggressive non-Hodgkin's lymphoma (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/65_rituximab_nonhodgkins_fullguidance.pdf (accessed 30/07/08)
2. Avivi I, *et al.* Clinical use of rituximab in haematological malignancies. *Br J Cancer* 2003; **89:** 1389–94.
3. Cvetković RS, Perry CM. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2006; **66:** 791–820.
4. Held G, *et al.* Rituximab for the treatment of diffuse large B-cell lymphomas. *Expert Rev Anticancer Ther* 2006; **6:** 1175–86.
5. van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. *Curr Oncol Rep* 2007; **9:** 378–83.
6. Schulz H, *et al.* Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/07/08).
7. Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. *Annu Rev Med* 2008; **59:** 237–50.

Pemphigus. Rituximab has been reported to be of benefit in pemphigus vulgaris (p.1582) and 17 cases have been reviewed.[1] It was used in patients with severe and widespread disease that had not responded to usual therapy with corticosteroids and immunosuppressants. A dose of 375 mg/m^2 once weekly was used and most patients were given a course of 4 doses. Most patients showed some improvement from rituximab, including 9 who were free of clinical disease for more than 6 months and 5 who had a partial response. However, although concomitant therapy could be reduced in 8 patients, only 2 were able to stop systemic corticosteroids and immunosuppressants; in 6 cases this information was not reported. Rituximab might therefore be useful for remission induction when corticosteroids have not been effective, but long-term follow-up is needed. Rituximab with normal immunoglobulins has also been reported to be effective in patients with refractory pemphigus vulgaris.[2]

Rituximab has been reported to be of benefit in pemphigus foliaceus,[3,4] a less common variant of pemphigus. A single cycle of 4 weekly infusions of rituximab was reported to achieve complete remission in 12 of 14 patients with pemphigus vulgaris and 6 of 7 patients with pemphigus foliaceus; 2 patients in the former group achieved delayed complete remission. Of these 20 patients, 6 with pemphigus vulgaris and 3 with pemphigus foliaceus had a relapse; 2 of these 9 patients were given a second course of rituximab and again achieved complete remission. After 34 months of follow-up, 18 patients were free of disease, and 8 of these were not receiving any systemic therapy.[5]

1. El Tal AK, *et al.* Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55:** 449–59.
2. Ahmed AR, *et al.* Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–9.
3. Goebeler M, *et al.* Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. *Br J Dermatol* 2003; **149:** 899–901.
4. Arin MJ, *et al.* Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. *Br J Dermatol* 2005; **153:** 620–5.
5. Joly P, *et al.* A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med* 2007; **357:** 545–52.

Rheumatoid arthritis. Rituximab is of benefit in patients with rheumatoid arthritis (p.11) refractory to standard therapy.[1-3] The ability of rituximab to prevent articular damage, its efficacy for extra-articular manifestations, the efficacy and safety of repeated courses, and long-term effects on the immune system remain to be determined.[4] Radiographic data from a placebo-controlled study showed a trend towards less progression of structural joint damage with a course of rituximab (2 doses); assessment was made at 24 weeks.[5] In a consensus statement, European and Canadian rheumatologists stated that re-treatment with rituximab may be considered after week 24 in those who respond to initial therapy.[6]

In the UK, NICE states that rituximab with methotrexate is a treatment option for adults with severe active rheumatoid arthritis who have had an inadequate response to DMARDs or are intolerant of them; previous therapy should have included at least one tumour necrosis factor α inhibitor. Treatment with rituximab and methotrexate should continue only if patients show an adequate response, and repeat courses should be given no more often than every 6 months; specialist supervision is advised.[7]

1. Edwards JCW, *et al.* Efficacy of B-cell—targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; **350:** 2572–81.
2. Summers KM, Kockler DR. Rituximab treatment of refractory rheumatoid arthritis. *Ann Pharmacother* 2005; **39:** 2091–5.
3. Higashida J, *et al.* Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-α treatment. *J Rheumatol* 2005; **32:** 2109–15.
4. Looney RJ. B cell-targeted therapy for rheumatoid arthritis: an update on the evidence. *Drugs* 2006; **66:** 625–39.
5. Cohen SB, *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54:** 2793–2806.
6. Smolen JS, *et al.* Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; **66:** 143–50.
7. NICE. Rituximab for the treatment of rheumatoid arthritis: Technology Appraisal 126 (issued August 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/word/TA126guidance.doc (accessed 13/05/08)

Scleroderma. Rituximab is under investigation for the management of scleroderma (p.1817).

Skin disorders. In addition to reports of efficacy in pemphigus (see above), rituximab has been reported to be of benefit in refractory cases of pemphigoid[1] and epidermolysis bullosa acquisita.[2,3]

1. Schmidt E, *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156:** 352–6.
2. Crichlow SM, *et al.* A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol* 2007; **156:** 194–6.
3. Sadler E, *et al.* Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; **157:** 417–19.

Systemic lupus erythematosus. Rituximab is under investigation for the treatment of SLE (p.1513).[1]

1. Sfikakis PP, *et al.* Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005; **17:** 550–7.

Thrombotic microangiopathies. Rituximab has been reported[1-3] to be of benefit in relapsed or refractory thrombotic thrombocytopenic purpura (see under Plasma, p.1076).

1. Zheng X, *et al.* Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. *Ann Intern Med* 2003; **138:** 105–8.
2. Reddy PS, *et al.* Rituximab in the treatment of relapsed thrombotic thrombocytopenic purpura. *Ann Hematol* 2005; **84:** 232–5.
3. Kosugi S, *et al.* Rituximab provided long-term remission in a patient with refractory relapsing thrombotic thrombocytopenic purpura. *Int J Hematol* 2005; **81:** 433–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: MabThera; ***Austral.:*** MabThera; ***Austria:*** MabThera; ***Belg.:*** MabThera; ***Braz.:*** MabThera; ***Canad.:*** Rituxan; ***Chile:*** MabThera; ***Cz.:*** MabThera; ***Denm.:*** MabThera; ***Fin.:*** MabThera; ***Fr.:*** MabThera; ***Ger.:*** MabThera; ***Gr.:*** MabThera; ***Hong Kong:*** MabThera; ***Hung.:*** MabThera; ***Indon.:*** MabThera; ***Irl.:*** MabThera; ***Israel:*** MabThera; ***Ital.:*** MabThera; ***Jpn:*** Rituxan; ***Malaysia:*** MabThera; ***Mex.:*** MabThera; ***Neth.:*** MabThera; ***Norw.:*** MabThera; ***NZ:*** MabThera; ***Philipp.:*** MabThera; ***Pol.:*** MabThera; ***Port.:*** MabThera; ***Rus.:*** MabThera (МабТера); ***S.Afr.:*** MabThera; ***Singapore:*** MabThera; ***Spain:*** MabThera; ***Swed.:*** MabThera; ***Switz.:*** MabThera; ***Thai.:*** MabThera; ***Turk.:*** MabThera; ***UK:*** MabThera; ***USA:*** Rituxan; ***Venez.:*** MabThera.

Roquinimex *(USAN, rINN)*

FCF-89; LS-2616; Roquinimexum. 1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxanilide.

Рохинимекс

$C_{18}H_{16}N_2O_3$ = 308.3.
CAS — 84088-42-6.
ATC — L03AX02.
ATC Vet — QL03AX02.

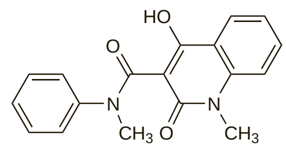

Profile

Roquinimex is an immunomodulator reported to stimulate various immune functions including macrophage cytotoxicity. It has been investigated for its potential against malignant neoplasms including as adjuvant therapy after bone marrow transplantation in acute leukaemia, to prolong the time to relapse. Roquinimex has also been investigated in immune and auto-immune disorders including multiple sclerosis. However serious cardiovascular toxicity after roquinimex therapy has led to several studies being terminated.

◊ References.

1. Coutant R, *et al.* Low dose linomide in type I juvenile diabetes of recent onset: a randomised placebo-controlled double blind trial. *Diabetologia* 1998; **41:** 1040–6.
2. Simonsson B, *et al.* Roquinimex (Linomide) vs placebo in AML after autologous bone marrow transplantation. *Bone Marrow Transplant* 2000; **25:** 1121–7.
3. Tan IL, *et al.* Linomide in the treatment of multiple sclerosis: MRI results from prematurely terminated phase-III trials. *Multiple Sclerosis* 2000; **6:** 99–104.
4. Noseworthy JH, *et al.* Linomide in relapsing and secondary progressive MS. Part 1: trial design and clinical results. *Neurology* 2000; **54:** 1726–33.

Rostaporfin *(USAN, rINN)*

Rostaporfina; Rostaporfine; Rostaporfinum; SnET2; Tin Ethyl Etiopurpurin; Tin etiopurpurin dichloride. (*OC*-6-13)-Dichloro[ethyl (18*RS*,19*SR*)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-N^{23},N^{24},N^{25},N^{26}]tin.

Ростапорфин

$C_{37}H_{42}Cl_2N_4O_2Sn$ = 764.4.
CAS — 284041-10-7; 114494-17-6.

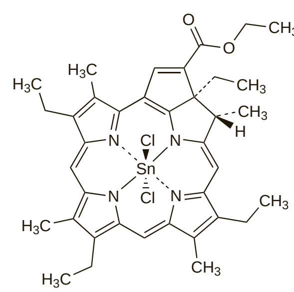

and enantiomer

Profile

Rostaporfin is a photosensitiser that is under investigation in the photodynamic therapy of neovascular (wet) age-related macular degeneration (p.785). It has also been investigated for photodynamic therapy of malignant neoplasms.

Rubitecan *(USAN, rINN)*

9-NC; 9-Nitrocamptothecin; RFS-2000; Rubitécan; Rubitecán; Rubitecanum. 9-Nitro-20(*S*)-camptothecin.

Рубитекан

$C_{20}H_{15}N_3O_6$ = 393.3.
CAS — 91421-42-0.

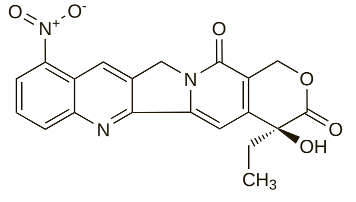

Profile

Like irinotecan (p.737), rubitecan is a topoisomerase I inhibitor related to camptothecin. It can be given orally and has been investigated for its antineoplastic properties particularly in the treatment of pancreatic cancer. It is also under investigation for the treatment of paediatric patients infected with HIV.

◊ References.

1. Clark JW. Rubitecan. *Expert Opin Invest Drugs* 2006; **15:** 71–9.

Sabarubicin *(rINN)*

MEN-10755; Sabarubicina; Sabarubicine; Sabarubicinum. (7*S*,9*S*)-7-{[4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]oxy}-6,9,11-trihydroxy-9-(hydroxyacetyl)-7,8,9,10-tetrahydrotetracene-5,12-dione.

Сабарубицин

$C_{32}H_{37}NO_{13}$ = 643.6.
CAS — 211100-13-9.

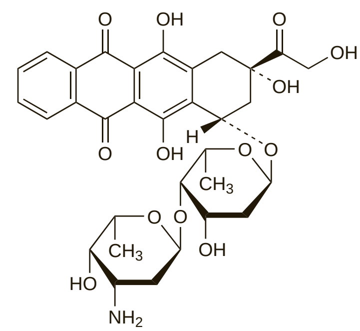

Profile

Sabarubicin, an anthracycline, is an analogue of doxorubicin (p.712). It acts as a potent topoisomerase II inhibitor and is under investigation for the treatment of various solid tumours, such as cancers of the lung, ovary, breast, and prostate. Myelosuppression is the main adverse effect.

◊ References.

1. Bos AM, *et al.* Pharmacokinetics of MEN-10755, a novel anthracycline disaccharide analogue, in two phase I studies in adults with advanced solid tumours. *Cancer Chemother Pharmacol* 2001; **48:** 361–9.
2. Schrijvers D, *et al.* Phase I study of MEN-10755, a new anthracycline in patients with solid tumours: a report from the European Organization for Research and Treatment of Cancer, Early Clinical Studies Group. *Ann Oncol* 2002; **13:** 385–91.
3. Jones K. MEN-10755. Menarini. *Curr Opin Investig Drugs* 2003; **4:** 1473–8.
4. Caponigro F, *et al.* A phase II study of sabarubicin (MEN-10755) as second line therapy in patients with locally advanced or metastatic platinum/taxane resistant ovarian cancer. *Invest New Drugs* 2005; **23:** 85–9.
5. Fiedler W, *et al.* A study from the EORTC new drug development group: open label phase II study of sabarubicin (MEN-10755) in patients with progressive hormone refractory prostate cancer. *Eur J Cancer* 2006; **42:** 200–204.

Satraplatin *(USAN, rINN)*

BMS-182751; BMY-45594; JM-216; Satraplatine; Satraplatino; Satraplatinum. (*OC*-6-43)-Bis(acetato)amminedichloro(cyclohexylamine)platinum.

Сатраплатин

$C_{10}H_{22}Cl_2N_2O_4Pt$ = 500.3.
CAS — 129580-63-8.

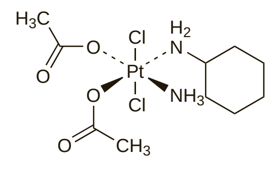

Profile

Satraplatin is an analogue of cisplatin (p.698) with generally similar properties, but which is well absorbed after oral dosage. It is under investigation for its antineoplastic properties in the treatment of various solid tumours.

◊ References.

1. Kelland LR. An update on satraplatin: the first orally available platinum anticancer drug. *Expert Opin Invest Drugs* 2000; **9:** 1373–82.
2. Vouillamoz-Lorenz S, *et al.* Pharmacokinetics of satraplatin (JM216), an oral platinum (IV) complex under daily oral administration for 5 or 14 days. *Anticancer Res* 2003; **23:** 2757–65.

3. Sternberg CN, *et al.* Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; **68:** 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; **96:** 990–4.
5. McKeage MJ. Satraplatin in hormone-refractory prostate cancer and other tumour types: pharmacological properties and clinical evaluation. *Drugs* 2007; **67:** 859–69.

Semustine *(USAN, rINN)*

Methyl Lomustine; Methyl-CCNU; NSC-95441; Semustiini; Semustin; Semustina; Sémustine; Semustinum; WR-220076. 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea.

Семустин

$C_{10}H_{18}ClN_3O_2$ = 247.7.
CAS — 13909-09-6.
ATC — L01AD03.
ATC Vet — QL01AD03.

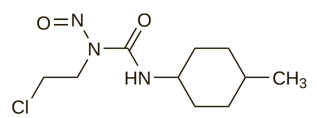

Pharmacopoeias. In *Chin.*

Adverse Effects, Treatment, and Precautions

As for Carmustine, p.694.

Effects on the kidneys. Nephrotoxicity has been reported in patients receiving high cumulative doses of semustine. Severe renal damage was reported in 6 of 17 children given semustine after radiotherapy for brain tumours; all 6 children had received a total dose above 1.5 g/m^2 in contrast to those not so affected, who had received lower doses.[1] A decrease in kidney size was seen in 2 patients who had received lower cumulative doses. There had been no evidence during treatment that patients were losing renal function. Similarly others have reported an increased risk of renal abnormalities in patients given a cumulative dose of 1.4 g/m^2 or more.[2] Some 25% of patients given higher doses were so affected, while those given lower doses were not. Overall, however, the problem may not be particularly frequent: in one study it was considered that only 4 of 857 patients treated with semustine over 6 years might have had delayed renal insufficiency possibly related to semustine.[3]

1. Harmon WE, *et al.* Chronic renal failure in children treated with methyl-CCNU. *N Engl J Med* 1979; **300:** 1200–3.
2. Micetich KC, *et al.* Nephrotoxicity of semustine (methyl-CCNU) in patients with malignant melanoma receiving adjuvant chemotherapy. *Am J Med* 1981; **71:** 967–72.
3. Nichols WC, Moertel CG. Nephrotoxicity of methyl-CCNU. *N Engl J Med* 1979; **301:** 1181.

Pharmacokinetics

Semustine is well absorbed from the gastrointestinal tract after oral doses, and is rapidly metabolised. The metabolites are reported to possess prolonged plasma half-lives, and cross the blood-brain barrier into the CSF. It is excreted in urine as metabolites: up to 60% of a dose is excreted in this way within 48 hours. Small amounts may be excreted in faeces and via the lungs as carbon dioxide.

Uses and Administration

Semustine is a nitrosourea with actions and uses similar to those of carmustine (p.695) and lomustine (p.741).

Seocalcitol *(BAN, rINN)*

EB-1089; Séocalcitol; Seocalcitolum. (5*Z*,7*E*,22*E*,24*E*)-24a,26a,27a-Trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1α,3β,25-triol.

Сеокальцитол

$C_{30}H_{46}O_3$ = 454.7.
CAS — 134404-52-7.

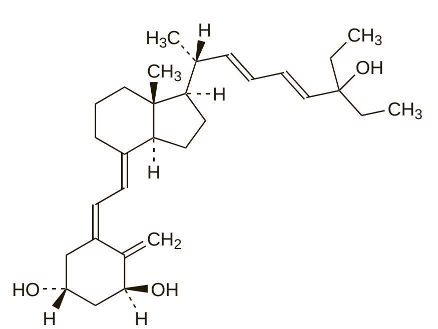

Profile

Seocalcitol is a vitamin D analogue that has been investigated for the treatment of hepatocellular carcinoma.

Sizofiran *(rINN)*

Schizophyllan; Sizofirán; Sizofiranum. Poly[3→-(*O*-β-D-glucopyranosyl-(1→3)-*O*-[β-D-glucopyranosyl-(1→6)]-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-glucopyranosyl)→1].

Сизофиран

$(C_{24}H_{40}O_{20})_n$.
CAS — 9050-67-3.

Profile

Sizofiran is a polysaccharide obtained from cultures of the basidiomycete fungus *Schizophyllum commune*. It is reported to have antineoplastic and immunomodulating activity and is given with radiotherapy in malignant neoplasms of the cervix (p.663). It is given by intramuscular injection in usual doses of 40 mg weekly. It has also been tried with chemotherapy or radiotherapy in other malignant neoplasms. Hypersensitivity reactions, including anaphylactoid shock, may occur.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Sonifilan.

Sobuzoxane *(rINN)*

MST-16; Sobuzoxano; Sobuzoxanum. 4,4′-Ethylenebis[1-(hydroxymethyl)-2,6-piperazinedione] bis(isobutyl carbonate).

Собузоксан

$C_{22}H_{34}N_4O_{10}$ = 514.5.
CAS — 98631-95-9.

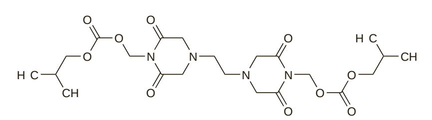

Profile

Sobuzoxane is an orally active inhibitor of topoisomerase II that has been used for its antineoplastic properties in the treatment of non-Hodgkin's lymphomas and adult T-cell leukaemia/lymphoma. Adverse effects include myelosuppression, bleeding tendency, renal and hepatic dysfunction, gastrointestinal disturbances, alopecia, headache, and fever.

◊ References.

1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104:** 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human herpesvirus 8-negative primary effusion lymphoma. *Int J Hematol* 2004; **79:** 271–5.

Sorafenib *(USAN, rINN)*

BAY-43-9006; Sorafénib; Sorafenibum. 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*^{2}-methylpyridine-2-carboxamide.

Сорафениб

$C_{21}H_{16}ClF_3N_4O_3$ = 464.8.
CAS — 284461-73-0.
ATC — L01XE05.
ATC Vet — QL01XE05.

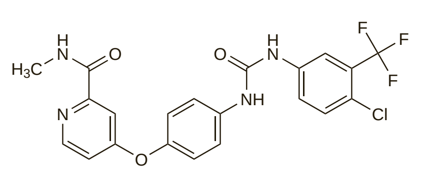

Sorafenib Tosilate *(rINNM)*

BAY-54-9085; Sorafénib, Tosilate de; Sorafenib, tosilato de; Sorafenib Tosylate *(USAN)*; Sorafenibi Tosilas. 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*^{2}-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Сорафениба Тозилат

$C_{21}H_{16}ClF_3N_4O_3,C_7H_8O_3S$ = 637.0.
CAS — 475207-59-1.
ATC — L01XE05.
ATC Vet — QL01XE05.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. Dermatological toxicities such as palmar-plantar syndrome and rash are the most common adverse effects with sorafenib. Treatment may include topical therapies, or dose adjustment, or temporary interruption of sorafenib. Mild to moderate hypertension can occur, which may be manageable with antihypertensive therapy, but severe or persistent hypertension or hypertensive crisis despite treatment, may force sorafenib to be stopped. Blood pressure should be regularly monitored. There is an increased risk of bleeding with sorafenib and fatalities have been reported; if severe enough to need intervention, the drug should be permanently stopped. Leucopenia, lymphopenia, anaemia, neutropenia, and thrombocytopenia are common. Hypophosphataemia and transient disturbances in liver function tests can occur. Elevations in lipase and amylase concentrations are very common. Pancreatitis has been reported. Other adverse effects include alopecia, pruritus, dry skin, erythema, acne, flushing, exfoliative dermatitis, hoarseness, gastrointestinal disturbances, arthralgia, myalgia, asthenia, pain, and peripheral neuropathy. Tinnitus, depression, and erectile dysfunction are often reported, as are pyrexia, flu-like illness, and weight decrease. Gastrointestinal perforation has been reported rarely; therapy should be stopped if it occurs. Reversible posterior leukoencephalopathy has also occurred rarely. Sorafenib therapy should be interrupted or stopped in patients who develop cardiac ischaemia and/or infarction.

◊ References.

1. Robert C, *et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; **6:** 491–500.
2. Strumberg D, *et al.* Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? *Eur J Cancer* 2006; **42:** 548–56.
3. Veronese ML, *et al.* Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006; **24:** 1363–9.
4. Yang C-H, *et al.* Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008; **158:** 592–6.

Effects on the cardiovascular system. A meta-analysis[1] of data involving 4599 patients indicated that 23.4% of those given sorafenib developed hypertension; about 5% of sorafenib-treated patients developed severe (grade 3 or 4) hypertension. This represented a relative risk of developing high blood pressure 6.1 times that of patients not given sorafenib. Hypertension may also develop with other angiogenesis inhibitors; relative risk has been shown to be similar with high-dose bevacizumab, and there is evidence of a slightly smaller risk (incidence of hypertension 22.5%, relative risk 3.89) with sunitinib.

1. Wu S, *et al.* Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol* 2008; **9:** 117–23.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642. Sorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Rifampicin can reduce exposure to sorafenib. Other inducers of this enzyme (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, and phenytoin) may also reduce blood concentrations of sorafenib. However, ketoconazole did not alter exposure to sorafenib and other drugs that inhibit CYP3A4 are considered unlikely to alter the metabolism of sorafenib.

In vitro studies have indicated that sorafenib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP2D6, but use of sorafenib with midazolam, or omeprazole, or dextromethorphan did not alter the exposure to any of these drugs; interactions with drugs that are substrates of these enzymes are considered unlikely.

Sorafenib inhibits the cytochrome P450 isoenzyme CYP2C9 *in vitro*, and may increase concentrations of its substrates. The effect of warfarin on mean PT-INR was not altered by sorafenib; however, patients taking warfarin or phenprocoumon with sorafenib should have their INR regularly checked.

Sorafenib also inhibits the isoenzymes CYP2B6 and CYP2C8 *in vitro*, and drug interactions with substrates of these may occur.

Sorafenib may increase exposure to docetaxel, doxorubicin, and irinotecan; variable effects on fluorouracil have been reported.

Pharmacokinetics

Sorafenib reaches peak plasma concentrations about 3 hours after an oral dose. Absorption is reduced by about 30% after a high-fat meal. Plasma protein binding is about 99.5%. Sorafenib is metabolised primarily in the liver via the cytochrome P450 isoenzyme CYP3A4. It also undergoes glucuronidation. The elimination half-life of sorafenib is about 25 to 48 hours. About 96% of a dose is excreted within 14 days, with 77%, mostly as unchanged drug, recovered in the faeces, and 19% in the urine as glucuronidated metabolites.

◊ References.

1. Clark JW, *et al.* Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res* 2005; **11:** 5472–80.

Uses and Administration

Sorafenib is an inhibitor of multiple intracellular and cell surface kinases thought to be involved in angiogenesis. It is given as the tosilate but doses are expressed in terms of the base; sorafenib tosilate 274 mg is equivalent to about 200 mg of sorafenib. Sorafenib is used in the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. The recommended oral dose is 400 mg twice daily, given at least 1 hour before or 2 hours after food. Treatment is continued until no clinical benefit is seen or until unacceptable toxicity occurs. Doses are reduced to 400 mg once daily if toxicity occurs; further reduction to a single dose of 400 mg every other day may be necessary.

Sorafenib is under investigation for the treatment of locally unresectable and metastatic melanoma.

◊ References.

1. Rini BI. Sorafenib. *Expert Opin Pharmacother* 2006; **7:** 453–61.
2. Escudier B, *et al.* TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356:** 125–34. Correction. *ibid.*; **357:** 203.
3. McKeage K, Wagstaff AJ. Sorafenib: in advanced renal cancer. *Drugs* 2007; **67:** 475–83.
4. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy* 2007; **27:** 1125–44.
5. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol* 2008; **61:** 535–48.
6. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health-Syst Pharm* 2008; **65:** 123–31.
7. Simpson D, Keating GM. Sorafenib: in hepatocellular carcinoma. *Drugs* 2008; **68:** 251–8.

Administration in hepatic or renal impairment. Sorafenib is primarily metabolised in the liver. Hepatic impairment may reduce exposure to sorafenib, compared with patients with normal hepatic function. In patients with hepatocellular carcinoma, exposure is comparable in patients with mild and moderate (Child-Pugh A and B) impairment. Licensed product information states that no dose adjustment is needed in patients with mild to moderate impairment. No data are available on patients with severe (Child-Pugh C) hepatic impairment.

Licensed product information states that no dose adjustment is needed in patients with mild, moderate, or severe renal impairment, but that no data are available for patients on dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nexavar; ***Austral.:*** Nexavar; ***Chile:*** Nexavar; ***Cz.:*** Nexavar; ***Fr.:*** Nexavar; ***Gr.:*** Nexavar; ***Hung.:*** Nexavar; ***Indon.:*** Nexavar; ***Malaysia:*** Nexavar; ***Mex.:*** Nexavar; ***NZ:*** Nexavar; ***Port.:*** Nexavar; ***UK:*** Nexavar; ***USA:*** Nexavar.

Streptozocin *(USAN, rINN)*

Estreptozocina; NSC-85998; Streptotsosiini; Streptozocine; Streptozocinum; Streptozosin; Streptozotocin; U-9889. 2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose.

Стрептозоцин

$C_8H_{15}N_3O_7$ = 265.2.
CAS — 18883-66-4.
ATC — L01AD04.
ATC Vet — QL01AD04.

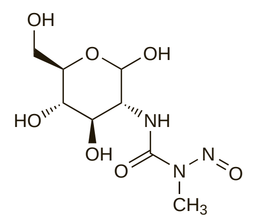

Storage. Licensed product information recommends that the freeze-dried streptozocin preparation be stored at 2° to 8° and protected from light.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Cumulative nephrotoxicity is common with streptozocin and may be severe and irreversible. Intra-arterial use may be associated with increased risk of nephrotoxicity.

Other adverse effects include severe nausea and vomiting and alterations in liver function or occasionally severe hepatotoxicity. Myelosuppression may occur but is rarely severe. Streptozocin may affect glucose metabolism. A diabetogenic effect has been reported; hypoglycaemia attributed to the release of insulin from damaged cells has also occurred.

Streptozocin is irritant to tissues and extravasation may lead to local ulceration and necrosis.

Streptozocin should be used with extreme care in patients with pre-existing renal impairment.

Handling and disposal. Methods for the destruction of streptozocin *waste* by reaction with hydrobromic acid in glacial acetic acid or by oxidation with a solution of potassium permanganate in sulfuric acid.[1] Residues produced by either method were free of mutagenic activity.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.

Interactions

Streptozocin should not be given with other potentially nephrotoxic drugs. For increased doxorubicin toxicity when given with streptozocin see p.714.

Phenytoin. It has been suggested that because phenytoin appeared to protect the beta cells of the pancreas from the cytotoxic effects of streptozocin, its use with streptozocin should be avoided in patients being treated for pancreatic tumours.[1]

1. Koranyi L, Gero L. Influence of diphenylhydantoin on the effect of streptozotocin. *BMJ* 1979; **1:** 127.

Pharmacokinetics

After intravenous doses streptozocin is rapidly cleared from the blood and distributed to body tissues, particularly the liver, kidneys, intestines, and pancreas. It is extensively metabolised, mainly in the liver and perhaps the kidney, and excreted principally in the urine as metabolites and a small amount of unchanged drug. About 60 to 70% of an intravenous dose is excreted in urine within 24 hours. Some is also excreted via the lungs. Streptozocin itself does not cross the blood-brain barrier but its metabolites are found in the CSF.

Uses and Administration

Streptozocin is an antibiotic antineoplastic belonging to the nitrosoureas (see Carmustine, p.695) and is used, alone or with other antineoplastics, mainly in the treatment of pancreatic endocrine (islet-cell) tumours (p.643). It has been tried in other tumours including exocrine pancreatic cancer and prostate cancer. It is licensed for intravenous injection or infusion in doses of 1 g/m^2 weekly, increased if necessary after 2 weeks to up to 1.5 g/m^2. Alternatively doses of 500 mg/m^2 may be given daily for 5 days and repeated every 6 weeks.

Streptozocin has also been given by intra-arterial infusion (but see Adverse Effects above).

Full blood counts, and renal and hepatic function tests should be performed routinely during treatment; doses should be reduced or treatment withdrawn if renal toxicity occurs.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Zanosar; ***Fr.:*** Zanosar; ***Gr.:*** Zanosar; ***Israel:*** Zanosar; ***USA:*** Zanosar.

Sunitinib Malate *(USAN, rINNM)*

Malato de sunitinib; PHA-290940AD; SU-010398; SU-011248 (sunitinib); Sunitinib, Malate de; Sunitinibi Malas. *N*-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide hydrogen (2*S*)-2-hydroxybutanedioate.

Сунитиниба Малат

$C_{22}H_{27}FN_4O_2,C_4H_6O_5$ = 532.6.
CAS — 557795-19-4 (sunitinib); 341031-54-7 (sunitinib malate).
ATC — L01XE04.
ATC Vet — QL01XE04.

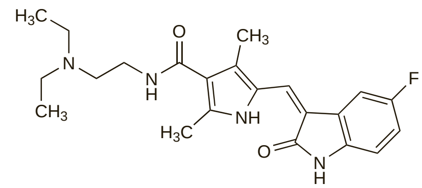

(sunitinib)

Adverse Effects, Treatment, and Precautions

Common adverse effects of sunitinib include gastrointestinal disturbances, anorexia, headache, fatigue, fever, hypertension, hypothyroidism, mouth pain or irritation, dry mouth, mucosal inflammation, oedema, taste disturbances, arthralgia, and myalgia. Myelosuppression is common, and complete blood counts should be performed at the beginning of each treatment cycle. Other effects include dizziness, paraesthesia, dyspnoea, alopecia, Yellow skin discoloration and chromaturia can occur. Other dermatological effects include depigmentation of the hair or skin, dryness, rash, exfoliative dermatitis, or palmar-planter syndrome. Gastrointestinal perforation has been reported rarely; fatalities have been reported in patients with intra-abdominal malignancies.

Decreases in left ventricular ejection fraction (LVEF) have occurred with sunitinib; baseline and periodic evaluations of LVEF should be taken. Patients should be monitored for signs of congestive cardiac failure and therapy interrupted or stopped if they occur. Dose reductions may be necessary in patients who show no signs of heart failure but who show decreases in LVEF. Sunitinib may prolong the QT interval and should be used with caution in patients with a history of this, who are taking antiarrhythmics, or who have pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

There is an increased risk of bleeding at all sites; epistaxis is the most common treatment-related bleeding event but fatal pulmonary haemorrhage has occurred in patients with lung cancer. Pulmonary embolism or venous thromboembolic events may occur. Patients under stresses such as surgery, trauma, or severe infection should be monitored for adrenal insufficiency. Increases in serum amylase and lipase concentrations have been seen and there are rare reports of pancreatitis and hepatic failure. There are also rare reports of seizures and reversible posterior leukoencephalopathy syndrome.

Effects on the cardiovascular system. A retrospective review in 75 patients given repeating cycles of sunitinib in phase I/II studies of its efficacy for gastrointestinal stromal tumours found that cardiovascular events occurred in 8, of whom 6 developed congestive heart failure.[1] Of 36 patients given the subsequently approved dose, 10 had reductions in left ventricular ejection fraction of at least 10%. Hypertension developed in 35 of the 75 patients, and it was suggested that left ventricular dysfunction might be due to a combination of hypertension and a direct toxic effect on heart muscle.

For the relative risk of developing hypertension with sunitinib, and the view that this may be an effect common to angiogenesis inhibitors, see under Sorafenib, p.770.

1. Chu TF, *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; **370:** 2011–19.

Effects on the kidneys. For a report of haemolytic-uraemic syndrome after the use of bevacizumab and sunitinib, see Effects on the Kidneys, under Bevacizumab, p.685.

Effects on the nervous system. Coma has been reported with sunitinib; therapy was immediately stopped and the patient regained consciousness within 24 hours.[1]

1. Arnaud L, *et al.* Transient sunitinib-induced coma in a patient with fibromyxoid sarcoma. *J Clin Oncol* 2008; **26:** 1569–71.

Effects on the skin. A patient developed palmar-plantar syndrome and rashes resembling seborrhoeic dermatitis while taking sunitinib. Therapy was stopped and the rash was treated with a topical corticosteroid; blisters on the palms and soles resolved with desquamation.[1]

1. Tsai K-Y, *et al.* Hand-foot syndrome and seborrheic dermatitis-like rash induced by sunitinib in a patient with advanced renal cell carcinoma. *J Clin Oncol* 2006; **24:** 5786–8.

Effects on thyroid function. Hypothyroidism is common after sunitinib therapy. A cohort study found that 36% of patients developed hypothyroidism after an average of 50 weeks of therapy. The incidence of hypothyroidism increased with the duration of therapy, and the effect was not transient; patients needed replacement therapy with levothyroxine. Mild thyrotoxicosis may precede the onset of hypothyroidism. Although the mechanism is not clear, the drug may cause destructive thyroiditis. Patients should be screened for hypothyroidism and serum concentrations of thyroid-stimulating hormone (TSH) measured at suggested intervals of 2 to 3 months.[1]

1. Desai J, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006; **145:** 660–4.

Tumour lysis syndrome. Tumour lysis syndrome has been reported after treatment with sunitinib; electrolytes and renal function should be closely monitored.[1,2]

1. Nicholaou T, *et al.* Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. *Lancet* 2007; **369:** 1923–4.
2. Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007; **25:** 3544–6.

Interactions

Sunitinib is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4 to produce an active metabolite, which is further metabolised by CYP3A4. Ketoconazole increased exposure to sunitinib, and use with other potent inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sunitinib concentrations. Conversely, use with rifampicin decreased exposure to sunitinib, and inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, phenobarbital, or St John's wort) may decrease plasma sunitinib concentrations. If the use of alternative drugs is not feasible, dose adjustments of sunitinib may be necessary (see Uses and Administration, below).

◊ The US manufacturer of *bevacizumab* has recommended that it should not be used with sunitinib after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf (accessed 30/07/08)

Pharmacokinetics

Maximum plasma concentrations occur 6 to 12 hours after an oral dose of sunitinib. Bioavailability is unaffected by food. Sunitinib is metabolised mainly via the cytochrome P450 isoenzyme CYP3A4 to its primary active metabolite, which itself is then further metabolised via CYP3A4. Plasma protein binding of sunitinib and its metabolite is about 95% and 90%, respectively; plasma elimination half-lives are 40 to 60 hours, and 80 to 110 hours, respectively. Sunitinib is excreted mainly in faeces; about 16% is found in urine, as unchanged drug and metabolites.

Uses and Administration

Sunitinib malate is an inhibitor of several receptor tyrosine kinases. It is used for the treatment of gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p.676) after disease progression during imatinib treatment, or in patients intolerant to imatinib. It is also used for the treatment of advanced and/or metastatic renal cell carcinoma (p.667).

Sunitinib is given orally as the malate, but doses are expressed in terms of the base; sunitinib malate 66.8 mg is equal to about 50 mg of sunitinib. The recommended dose is 50 mg once daily, for 4 weeks of a 6-week treatment cycle. Doses may be increased or decreased in steps of 12.5 mg, based on individual tolerability. UK licensed product information recommends that the daily dose should not normally exceed 75 mg nor be decreased below 25 mg.

Use of inhibitors or inducers of CYP3A4 may increase or decrease sunitinib plasma concentrations. If no alternative is available, a dose reduction of sunitinib to a minimum of 37.5 mg daily should be considered if it is given with a strong CYP3A4 inhibitor. Doses can be increased to a maximum of 87.5 mg daily if sunitinib is given with a CYP3A4 inducer; the patient should be closely monitored for toxicity.

◊ References.

1. Motzer RJ, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24:** 16–24.
2. Faivre S, *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24:** 25–35.
3. Motzer RJ, *et al.* Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Invest Drugs* 2006; **15:** 553–61.
4. Motzer RJ, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295:** 2516–24.
5. Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66:** 2255–66.
6. Demetri GD, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368:** 1329–38.
7. Motzer RJ, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356:** 115–24.
8. Goodman VL, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 1367–73.
9. O'Brien MF, *et al.* Sunitinib therapy in renal cell carcinoma. *BJU Int* 2008; **101:** 1339–42.
10. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S119–S123.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sutent; ***Austral.:*** Sutent; ***Braz.:*** Sutent; ***Cz.:*** Sutent; ***Fr.:*** Sutent; ***Gr.:*** Sutent; ***Hung.:*** Sutent; ***Malaysia:*** Sutent; ***NZ:*** Sutent; ***Port.:*** Sutent; ***UK:*** Sutent; ***USA:*** Sutent.

Talaporfin Sodium *(USAN, rINNM)*

LS-11; Monoaspartyl Chlorin e6 (talaporfin); Natrii Talaporfinum; NPe-6 (talaporfin); Talaporfina sódica; Talaporfine Sodique; Taporfin Sodium. Tetrasodium *N*-{[(7*S*,8*S*)-3-carboxy-7-(2-carboxyethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21*H*,23*H*-porphin-5-yl]acetyl}-L-aspartate.

Натрий Талапорфин

$C_{38}H_{41}N_5Na_4O_9$ = 803.7.

CAS — 110230-98-3 (talaporfin); 220201-34-3 (talaporfin sodium).

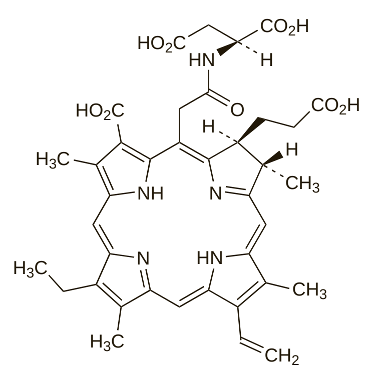

(talaporfin)

Profile

Talaporfin sodium is a photosensitiser that is used for the photodynamic therapy (see under Porfimer Sodium, p.764) of lung cancer. It is also under investigation for the treatment of other tumours.

Tamibarotene *(rINN)*

AM-80; Tamibarotène; Tamibaroteno; Tamibarotenum. *N*-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid.

Тамибаротен

$C_{22}H_{25}NO_3$ = 351.4.

CAS — 94497-51-5.

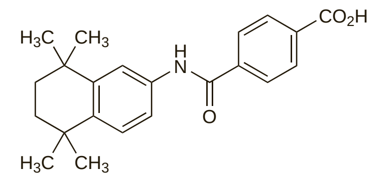

Profile

Tamibarotene is a synthetic retinoid that is given orally for the treatment of relapsed or refractory acute promyelocytic leukaemia.

Malignant neoplasms. Tamibarotene has been used to induce remission in patients with acute promyelocytic leukaemia (see Acute Myeloid Leukaemias, p.652) who relapsed after successful remission induction with tretinoin.[1,2] Twenty-four patients received tamibarotene at a daily oral dose of 6 mg/m^2; 14 patients obtained complete remission after a median of 41 days.[1] Reported adverse effects include hypercholesterolaemia, hypertriglyceridaemia,[1,3] cheilitis, xerosis, gastrointestinal disturbances, bone pain, headache, dermatitis, liver damage, and leucocytosis; in one case, retinoic acid syndrome occurred.[1]

1. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; **90:** 967–73.
2. Shinjo K, *et al.* Good prognosis of patients with acute promyelocytic leukemia who achieved second complete remission (CR) with a new retinoid, Am80, after relapse from CR induced by all-trans-retinoic acid. *Int J Hematol* 2000; **72:** 470–3.
3. Takeuchi M, *et al.* Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80. *Leuk Lymphoma* 1998; **31:** 441–51.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Amnolake.

Tamoxifen Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de tamoxifeno; ICI-46474; Tamoksifeenisitraatti; Tamoksifen Sitrat; Tamoksifeno citratas; Tamoxifen citrát; Tamoxifencitrat; Tamoxifén-citrát; Tamoxifène, citrate de; Tamoxifeni citras. (*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyldimethylamine citrate.

Тамоксифена Цитрат

$C_{26}H_{29}NO,C_6H_8O_7$ = 563.6.

CAS — 10540-29-1 (tamoxifen); 54965-24-1 (tamoxifen citrate).
ATC — L02BA01.
ATC Vet — QL02BA01.

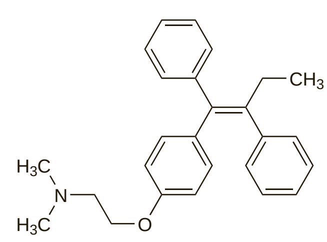

(tamoxifen)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Tamoxifen Citrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water and in acetone; soluble in methyl alcohol.
USP 31 (Tamoxifen Citrate). A white, fine, crystalline powder. Very slightly soluble in water, in alcohol, in acetone, and in chloroform; soluble in methyl alcohol. Protect from light.

Adverse Effects

The most frequent adverse effects of tamoxifen are hot flushes. Other adverse effects include fluid retention, nausea, gastrointestinal intolerance, vaginal bleeding or discharge, pruritus vulvae, rashes, dry skin, and alopecia. There have also been reports of dizziness, headache, depression, confusion, fatigue, and muscle cramps. There may be an increased tendency to thromboembolism, and pulmonary embolism has occurred. Tumour pain and flare may be a sign of response, but hypercalcaemia, sometimes severe, has developed in patients with bony metastases. Transient thrombocytopenia and leucopenia have been reported. Blurred vision and loss of visual acuity, corneal opacities, retinopathies, and cataracts have occurred rarely. Tamoxifen has been associated with increased liver enzymes, and rarely with cholestasis and hepatitis. Hypertriglyceridaemia has occurred. Uterine fibroids and endometrial changes including hyperplasia and polyps may occur, and an increased incidence of endometrial carcinoma, and rarely uterine sarcoma, has been reported. Suppression of menstruation may occur in premenopausal women and cystic ovarian swellings have occasionally occurred. Very rare cases of interstitial pneumonitis have been reported.

Carcinogenicity. Tamoxifen has a stimulant effect on the endometrium (probably by acting as a partial oestrogen agonist) and its use has been associated with the development of endometrial polyps[1,2] and endometriosis,[3] and an increased risk of endometrial cancer.[4-6] The risk, which increases with duration of therapy, is generally agreed to be modest, and the clinical benefit in women with breast cancer outweighs any increased risk of endometrial neoplasm.[7-10] Women taking tamoxifen to prevent breast cancer have been estimated to have a 2.53-fold greater risk of developing endometrial carcinoma than untreated women.[11] The risk may increase with more prolonged use and a case-control study has reported that long-term (over 2 years) users may have a worse prognosis if endometrial cancer develops, due to less favourable history and stage.[12] Another case-control study showed that the relative risk of endometrial cancer increased with duration of tamoxifen treatment, up to at least 10 years. Risk was not associated with the daily dose of tamoxifen, and was comparable in pre- and postmenopausal women.[13]

It has been recommended that women with breast cancer taking tamoxifen should have annual gynaecological examinations, and any unusual symptoms, including abnormal bleeding or spotting should be investigated promptly.[14] Women taking tamoxifen for prophylaxis of breast cancer should be monitored carefully for endometrial hyperplasia. If atypical hyperplasia develops, tamoxifen should be stopped while the condition is treated and a hysterectomy should be considered before tamoxifen is re-started.[14] However, up to 39% of postmenopausal women taking tamoxifen show endometrial changes and as these seldom progress to cancer, the value of routine endometrial biopsies has been questioned.[8,9,14,15] Transvaginal ultrasonography has been used as a noninvasive method of endometrial screening, but has a high rate of false-positive results.[16] It has been suggested that colour doppler ultrasonography, which distinguishes vascularised lesions such as polyps and carcinomas from avascular atrophic lesions, may be a useful alternative.[17] There is some evidence that a levonorgestrel-releasing intra-uterine device can protect against the uterine changes induced by tamoxifen.[18]

Although rare, there is an increase in the risk of uterine sarcoma in women receiving tamoxifen. Between 1978, when tamoxifen was first marketed in the USA, and April 2001, the FDA was aware of 43 cases in women who had been receiving tamoxifen; there had also been reports in 116 women in other countries.[19] Although less than the expected rate in this population, this was considered to be due to underreporting. An evaluation of data from 39 451 breast cancer patients initially treated with tamoxifen found that the overall risk of uterine corpus cancer was more than doubled with the use of tamoxifen; the risk of rare but aggressive forms of uterine tumours, notably malignant mixed mullerian tumours, was increased more than fourfold.[20]

Tamoxifen has been shown to form DNA adducts in *rat* livers, and there has been speculation that it may cause liver cancer in humans. However, there is considerable interspecies variation in the metabolism of tamoxifen and several large-scale clinical trials did not find an increase in liver carcinogenicity in humans.[10] There is also little evidence of an increased relative risk of other secondary malignancies such as gastrointestinal or ovarian cancers.[10]

1. Corley D, *et al.* Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992; **79:** 111–16.
2. Buijs C, *et al.* Tamoxifen and uterine abnormalities. *J Clin Oncol* 2004; **22:** 2505–7.
3. Cano A, *et al.* Tamoxifen and the uterus and endometrium. *Lancet* 1989; **i:** 376.
4. Fornander T, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989; **i:** 117–20.
5. Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. *Cancer* 1990; **65:** 1463–4.
6. van Leeuwen FE, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994; **343:** 448–52.
7. Baum M, *et al.* Endometrial cancer during tamoxifen treatment. *Lancet* 1994; **343:** 1291.
8. Bissett D, *et al.* Gynaecological monitoring during tamoxifen therapy. *Lancet* 1994; **344:** 1244.
9. Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; **351:** 155–7.
10. Stearns V, Gelmann EP. Does tamoxifen cause cancer in humans? *J Clin Oncol* 1998; **16:** 779–92.
11. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
12. Bergman L, *et al.* Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000; **356:** 881–7.
13. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. *J Natl Cancer Inst* 2005; **97:** 375–84.
14. American College of Obstetrics and Gynaecologists. ACOG Committee Opinion: tamoxifen and endometrial cancer. *Int J Gynaecol Obstet* 1996; **53:** 197–9.
15. Barakat RR, *et al.* Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000; **18:** 3459–63.
16. Gerber B, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000; **18:** 3464–70.
17. Aleem FA, Predanic M. Endometrial changes in patients on tamoxifen. *Lancet* 1995; **346:** 1292–3.
18. Gardner FJE, *et al.* Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet* 2000; **356:** 1711–17.
19. Wysowski DK, *et al.* Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002; **346:** 1832–3.
20. Curtis RE, *et al.* Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 70–4.

Effects on the blood. Pancytopenia developed shortly after beginning tamoxifen therapy in an elderly woman, and persisted for some years;[1] the patient eventually developed very severe leucopenia and died of infection. Thrombocytopenia has also been reported.[2]

1. Miké V, *et al.* Fatal neutropenia associated with long-term tamoxifen therapy. *Lancet* 1994; **344:** 541–2.
2. Nasiroğlu N, *et al.* Tamoxifen induced-thrombocytopenia: it does occur. *Med Oncol* 2007; **24:** 453–4.

Effects on blood lipids. Tamoxifen has been reported to have a generally favourable effect on serum lipid profiles.[1] Patients with breast cancer and subsequent chemotherapy-induced ovarian failure developed marked increases in total cholesterol and low-density lipoprotein levels; adjuvant tamoxifen was found to decrease these serum lipid concentrations to below baseline concentrations. No significant changes in high-density lipoprotein or serum triglyceride concentrations were observed.[2] However, some cases of increased serum triglycerides in women with pre-existing hypertriglyceridaemia have been reported. Pancreatitis has also resulted. It has been suggested that tamoxifen should be used with caution in patients with hypertriglyceridaemia.[3,4]

1. Love RR, *et al.* Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med* 1991; **115:** 860–4.
2. Vehmanen L, *et al.* Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids. *Br J Cancer* 2004; **91:** 476–81.
3. Kanel KT, *et al.* Delayed severe hypertriglyceridaemia from tamoxifen. *N Engl J Med* 1997; **337:** 281.
4. Colls BM, George PM. Severe hypertriglyceridaemia and hypercholesterolaemia associated with tamoxifen use. *Clin Oncol* 1998; **10:** 270–1.

Effects on the cardiovascular system. ***ISCHAEMIC HEART DISEASE.*** For discussion of whether the effects of tamoxifen on lipid profiles can alter the incidence of ischaemic heart disease, see Cardiovascular Disorders under Uses and Administration, below.

STROKE. An excess risk of stroke was seen in tamoxifen compared with placebo recipients (5 cases versus 1) in a study of adjuvant tamoxifen.[1] A statistically non-significant increase in stroke was also seen in a study on the use of tamoxifen for breast cancer prevention (0.5 excess cases per 1000 women per year).[2] A meta-analysis[3] of 9 trials for prevention or treatment of breast cancer, involved data from 39 601 women, of whom 19 954 received tamoxifen. It concluded that use of tamoxifen increased the risk of ischaemic stroke by 82%, and the risk of any stroke by 29%; however, the absolute increase in risk was small.

In contrast, a case-control study of 11 045 women with breast cancer, found that tamoxifen use was not associated with an increased risk of first stroke.[4]

1. Dignam JJ, Fisher B. Occurrence of stroke with tamoxifen in NSABP B-24. *Lancet* 2000; **355:** 848–9.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004; **63:** 1230–3.
4. Geiger AM, *et al.* Stroke risk and tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; **96:** 1528–36.

THROMBOEMBOLISM. A case control study,[1] involving 25 cases of deep-vein thrombosis or pulmonary embolism among more than 10 000 women with breast cancer, suggested that current use of tamoxifen was associated with an estimated relative risk of developing idiopathic venous thromboembolism of 7.1 (95% confidence interval 1.5 to 33). Past use of tamoxifen was not associated with a materially increased risk. In a randomised placebo-controlled study, there was an increase in pulmonary emboli in women receiving tamoxifen for cancer prevention (excess of 0.46 cases per 1000 women per year).[2] The fatality rate from pulmonary emboli in tamoxifen recipients was about 17%. In this study, there was also a trend towards more deep-vein thrombosis in tamoxifen recipients. In another controlled study[3] of breast cancer prevention, tamoxifen approximately doubled the risk of developing a major thromboembolic event such as pulmonary embolism, deep-vein thrombosis, or retinal thrombosis. Cerebral sinus thrombosis has also been reported.[4] An analysis[5] of 4 tamoxifen prevention studies also found that venous thromboembolic events were increased in all studies, with a relative risk of 1.9 for those taking tamoxifen compared with placebo. However, another randomised study[6] found only a borderline significantly higher risk of developing venous thromboembolic events in those women allocated to tamoxifen; most of these events were superficial thrombophlebitis. Furthermore, women already at risk for atherosclerosis had a higher risk of venous thromboembolism. While the authors could not exclude a selection bias for healthier subjects in the study, they commented that the prothrombotic effect of tamoxifen may depend on the patient's existing endocrine status, and may be attenuated in those women taking HRT, especially when it is used transdermally.

1. Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998; **45:** 608–12.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
3. Duggan C, *et al.* Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol* 2003; **21:** 3588–93.
4. Masjuan J, *et al.* Tamoxifen: a new risk factor for cerebral sinus thrombosis. *Neurology* 2004; **62:** 334–5.
5. Cuzick J, *et al.* Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; **361:** 296–300.
6. Decensi A, *et al.* Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. *Circulation* 2005; **111:** 650–6.

Effects on the eyes. Tamoxifen has been reported to be associated with decreased visual acuity, corneal opacities and cataract, and retinopathy. The latter is sometimes progressive although in most cases it has shown improvement once the drug was stopped.[1] A prospective study in 63 patients taking tamoxifen 20 mg daily found evidence of decreased visual acuity, macular oedema, and retinal opacities in 4, occurring after 10 to 35 months of therapy.[2] A small excess risk of developing cataracts (3.1 extra per year per 1000 women) and of requiring cataract surgery (1.7 per year per 1000 women) was found in women taking tamoxifen for up to 5 years to reduce the risk of breast cancer.[3] Studies *in vitro* have suggested that cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen or its hydroxy metabolite.[4] Retinopathy after high-dose tamoxifen treatment may be associated with crystalline deposition of the drug in the retina.[5]

1. Mihm LM, Barton TL. Tamoxifen-induced ocular toxicity. *Ann Pharmacother* 1994; **28:** 740–2.
2. Pavlidis NA, *et al.* Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. *Cancer* 1992; **69:** 2961–4.
3. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
4. Zhang JJ, *et al.* Tamoxifen blocks chloride channels: a possible mechanism for cataract formation. *J Clin Invest* 1994; **94:** 1690–7.
5. Bourla DH, *et al.* Peripheral retinopathy and maculopathy in high-dose tamoxifen therapy. *Am J Ophthalmol* 2007; **144:** 126–8.

Effects on the genito-urinary system. Persistent nocturnal priapism was reported in a man receiving tamoxifen 20 mg daily.[1] Symptoms abated within 24 hours of withdrawing the drug. Impotence has been reported in men receiving tamoxifen, and has been attributed to a paradoxical oestrogenic effect.[2]

1. Fernando IN, Tobias JS. Priapism in patient on tamoxifen. *Lancet* 1989; **i:** 436.
2. Collinson MP, *et al.* Two case reports of tamoxifen as a cause of impotence in male subjects with carcinoma of the breast. *Breast* 1993; **2:** 48–9.

Effects on the liver. Cholestasis and increased liver enzyme values have been reported on use of tamoxifen in a 75-year-old patient.[1] Enzyme activity rose again on rechallenge with tamoxifen. Fatal hepatocellular necrosis and agranulocytosis, possibly exacerbated by continuing to take the drug once jaundice developed, has also been reported;[2] the authors noted that 4 cases of hepatic failure (3 fatal) and 5 cases of hepatitis (1 fatal) had been reported to the UK CSM. Patients taking tamoxifen may also develop steatohepatitis,[3-7] which must be distinguished from alcohol-induced liver disease. Steatohepatitis is reversible on withdrawal of tamoxifen.[3,5,6] A study in healthy women who had had hysterectomies found the risk of steatohepatitis to be particularly high among obese women, moderately high among overweight women, and similar to that with placebo in women of normal weight.[8] Bezafibrate has been tried to prevent progression of steatohepatitis and permit continued use of tamoxifen.[9]

For a report of peliosis hepatis and liver haemorrhage in a patient receiving tamoxifen and warfarin, see under Interactions, below.

For reference to studies in *animals* suggesting that tamoxifen has the potential to cause liver cancer, see Carcinogenicity, above.

1. Blackburn AM, *et al.* Tamoxifen and liver damage. *BMJ* 1984; **289:** 288.
2. Ching CK, *et al.* Tamoxifen-associated hepatocellular damage and agranulocytosis. *Lancet* 1992; **339:** 940.
3. Pratt DS, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1995; **123:** 236.
4. Van Hoof M, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1996; **124:** 855–6.
5. Ogawa Y, *et al.* Tamoxifen-induced fatty liver in patients with breast cancer. *Lancet* 1998; **351:** 725.
6. Oien KA, *et al.* Cirrhosis with steatohepatitis after adjuvant tamoxifen. *Lancet* 1999; **353:** 36–7.
7. Osman KA, *et al.* Tamoxifen-induced non-alcoholic steatohepatitis: where are we now and where are we going? *Expert Opin Drug Saf* 2007; **6:** 1–4.
8. Bruno S, *et al.* Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. *BMJ* 2005; **330:** 932–5.
9. Saibara T, *et al.* Bezafibrate for tamoxifen-induced non-alcoholic steatohepatitis. *Lancet* 1999; **353:** 1802.

Effects on the ovaries. Ovarian cysts are relatively common as an adverse effect in women receiving adjuvant tamoxifen: a study[1] in 95 such women reported the development of ovarian cysts in 6 of 16 (37.5%) who were premenopausal and in 5 of 79 postmenopausal women (6.3%). In 2 of the premenopausal women the cysts were complex. Two women underwent laparotomy for persistent cysts that were found to be benign, and 1 for leiomyoma; the cysts in the other 8 women resolved after withdrawal of tamoxifen. A study of 142 breast cancer patients receiving tamoxifen found ovarian cysts in 24 patients after treatment. Cyst development was more common in pre-menopausal women, patients with high oestrogen levels, and patients who did not receive high-dose chemotherapy.[2] There is little evidence that tamoxifen increases the risk of ovarian cancer (see Carcinogenicity, above).

1. Shushan A, *et al.* Ovarian cysts in premenopausal and postmenopausal tamoxifen-treated women with breast cancer. *Am J Obstet Gynecol* 1996; **174:** 141–4.
2. Mourits MJE, *et al.* Ovarian cysts in women receiving tamoxifen for breast cancer. *Br J Cancer* 1999; **79:** 1761–64.

Effects on the skin and hair. Vasculitis has been reported in patients given tamoxifen.[1,2] Withdrawal of the drug resulted in complete clearance of the lesions;[1,2] in one case, on re-introduction, purpura developed again within a few days.[1] The results suggest that tamoxifen can produce immune-mediated vascular damage.

In another report a patient with white hair developed darkening and repigmentation of the hair after about 2½ years of tamoxifen therapy.[3] Alopecia has also been reported in women given tamoxifen,[4,5] and in older patients the follicle may not recover.[4]

1. Drago F, *et al.* Tamoxifen and purpuric vasculitis. *Ann Intern Med* 1990; **112:** 965–6.
2. Baptista MZ, *et al.* Tamoxifen-related vasculitis. *J Clin Oncol* 2006; **24:** 3504–5.
3. Hampson JP, *et al.* Tamoxifen-induced hair colour change. *Br J Dermatol* 1995; **132:** 483–4.
4. Gateley CA, Bundred NJ. Alopecia and breast disease. *BMJ* 1997; **314:** 481.
5. Ayoub J-PM, *et al.* Tamoxifen-induced female androgenetic alopecia in a patient with breast cancer. *Ann Intern Med* 1997; **126:** 745–6.

Precautions

All patients being considered for treatment with tamoxifen should be assessed for any increased risk of thromboembolism. Tamoxifen should not be used for treatment of infertility or the prophylaxis of breast cancer in women with a history of thromboembolic events. When used to treat breast cancer in such women, the risks and benefits should be considered; in some patients, especially those given cytotoxic drugs, prophylactic anticoagulation may be justified. Care is also needed during or immediately after major surgery or prolonged immobility; all patients should be given prophylaxis against thrombosis. In patients being treated for infertility, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility and only restarted when the patient is fully mobile. Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness or any pain in the calf of one leg. Tamoxifen should be withdrawn immediately in any patient developing thromboembolism and appropriate treatment given. Treatment should not usually be restarted for infertility therapy but resumption of tamoxifen with prophylactic anticoagulation may be justified in selected patients with breast cancer.

Women treated with tamoxifen should have routine gynaecological monitoring, and any abnormal symptoms such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain should be investigated (see also under Carcinogenicity, above). Periodic complete blood counts and liver function tests have been suggested.

Abuse. Although the supervised use of tamoxifen for the treatment of gynaecomastia resulting from the abuse of anabolic steroids has been reported[1] it also appears to be widely used without medical supervision. Tamoxifen can be used to treat idiopathic gynaecomastia and gynaecomastia resulting as an adverse effect of nonsteroidal anti-androgens used to treat prostate cancer (see under Breast Disorders, Non-malignant, below).

1. de Luis DA, *et al.* Anabolizantes esteroideos y ginecomastia: revisión de la literatura. *An Med Interna* 2001; **18:** 489–91.

Breast feeding. Tamoxifen was shown to inhibit lactation in 60 puerperal women.[1] Licensed product information recommends that it should not be given to lactating women.

1. Masala A, *et al.* Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. *Br J Obstet Gynaecol* 1978; **85:** 134–7.

Porphyria. Tamoxifen has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Tamoxifen is contra-indicated in pregnancy. Ambiguous genitalia have been reported in an infant exposed to tamoxifen *in utero*, although no causal link was demonstrated.[1] Another infant was born with Goldenhar's syndrome (oculoauriculovertebral dysplasia) after exposure to tamoxifen throughout a 26-week pregnancy.[2] The mother had also taken cocaine and marijuana during the first 6 weeks of pregnancy, and a bone scan using technetium Tc99m medronate had been performed. The US manufacturer of tamoxifen (*Zeneca, USA*) was aware of 50 pregnancies in patients taking tamoxifen, resulting in 19 normal births, 8 terminations, 13 unknown outcomes and 10 infants with fetal or neonatal abnormalities.[2]

Tamoxifen has also been used to stimulate ovulation in women with luteal phase dysfunction. In one study tamoxifen was given to 40 women, resulting in 14 pregnancies. Although 9 infants were born with no congenital abnormalities, there were 5 spontaneous abortions, which the authors felt was unacceptably high.[3] Another study, using lower doses of tamoxifen (in some cases sequentially with clomifene), reported 32 pregnancies and only 3 spontaneous abortions in 65 treated patients.[4]

1. Tewari K, *et al.* Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997; **350:** 183.
2. Cullins SL, *et al.* Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994; **271:** 1905–6.
3. Ruiz-Velasco V, *et al.* Chemical inducers of ovulation: comparative results. *Int J Fertil* 1979; **24:** 61–64.
4. Wu CH. Less miscarriage in pregnancy following tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. *Early Pregnancy* 1997; **3:** 301–5.

Radiotherapy. There are reports of radiation recall, with erythema at the site of previous radiotherapy, in patients receiving tamoxifen.[1,2]

1. Parry BR. Radiation recall induced by tamoxifen. *Lancet* 1992; **340:** 49.
2. Extermann M, *et al.* Radiation recall in a patient with breast cancer treated for tuberculosis. *Eur J Clin Pharmacol* 1995; **48:** 77–8.

Interactions

There is a risk of increased anticoagulant effect if tamoxifen is given with coumarin anticoagulants. Conversely, use with cytotoxic drugs may increase the risk of thromboembolic events; prophylactic anticoagulation should be considered. Tamoxifen increases the dopaminergic effect of bromocriptine. Use with inhibitors of cytochrome P450 isoenzyme CYP2D6 has been shown to reduce plasma concentrations of endoxifen, a tamoxifen metabolite (see Pharmacokinetics, below); the clinical relevance is unclear.

Allopurinol. For reference to exacerbation of hepatotoxicity when tamoxifen was given with allopurinol, see p.553.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of tamoxifen in 10 healthy subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Anticoagulants. Cases of a potentially life-threatening interaction between tamoxifen and *warfarin*, with marked prolongation of prothrombin times, haematuria, and haematoma, have been reported.[1-3] It has been suggested that in addition to enhancement of the effects of warfarin, competition for the same metabolic enzyme systems might reduce the activity of tamoxifen against tumours,[2] but this remains speculative.

Peliosis hepatis and fatal liver haemorrhage have been reported in a patient who was receiving tamoxifen with warfarin and a liothyronine-levothyroxine preparation.[4]

1. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
2. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
3. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
4. Loomus GN, *et al.* A case of peliosis hepatis in association with tamoxifen therapy. *Am J Clin Pathol* 1983; **80:** 881–3.

Antidepressants. The metabolism of tamoxifen to an active metabolite, 4-hydroxy-*N*-desmethyltamoxifen (endoxifen), may be inhibited by paroxetine, a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6.[1] However, the clinical consequences of this are, as yet, unclear.[1] In addition, a case-control study[2] found that patients taking tamoxifen with known inhibitors of CYP isoenzymes, including CYP2D6, were no more likely to relapse than those not receiving a CYP inhibitor.

1. Stearns V, *et al.* Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; **95:** 1758–64.
2. Lehmann D, *et al.* Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. *J Clin Pharmacol* 2004; **44:** 861–5.

Antineoplastics. *Aminoglutethimide* reduces serum tamoxifen concentrations, possibly by increasing its metabolism.[1] For mention of an increased risk of haemolytic-uraemic syndrome in patients who received therapy with tamoxifen and *mitomycin* see Effects on the Kidneys, under Mitomycin, p.752. Tamoxifen is reported to reduce plasma concentrations of *letrozole*, see p.740.

1. Lien EA, *et al.* Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. *Cancer Res* 1990; **50:** 5851–7.

Immunosuppressants. For the results of a study *in vitro* suggesting that tamoxifen might inhibit the metabolism of *tacrolimus* by inhibiting the cytochrome P450 isoenzyme system, see under Interactions of Tacrolimus, p.1845.

Neuromuscular blockers. For reference to prolonged neuromuscular blockade in a patient given *atracurium* while receiving tamoxifen, see p.1904.

Pharmacokinetics

Peak plasma concentrations of tamoxifen occur 4 to 7 hours after an oral dose. It is extensively protein bound. Plasma clearance is reported to be biphasic and the terminal half-life may be up to 7 days. It is extensively metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6. The major serum metabolite, *N*-desmethyltamoxifen, has a half-life at steady state of about 14 days. 4-Hydroxytamoxifen is a minor metabolite. *In-vitro* studies suggest that both these metabolites are further metabolised to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen). Several of the metabolites are stated to have similar pharmacological activity to the parent compound. Tamoxifen is excreted slowly in the faeces, mainly as conjugates. Small amounts are excreted in urine. Tamoxifen appears to undergo enterohepatic circulation.

Genetic factors. Tamoxifen is metabolised by the cytochrome P450 isoenzymes, and its metabolites may play a role in its antineoplastic effect. Studies have suggested that patients with low or absent CYP2D6 activity or who are being treated with CYP2D6 inhibitors have lower concentrations of endoxifen. Patients with CYP2D6*3, *4, *5, and *6 alleles are designated as poor metabolisers, those with *9, *10, *17, *29, and *41 as intermediate metabolisers, and those with *1, *2, and *35 as extensive metabolisers.[1,2] Genetic polymorphism in the enzymes responsible for tamoxifen biotransformation has the potential to affect clinical outcomes. While a small study[3] showed a decreased risk of breast cancer recurrence in patients with the CYP2D6*4 allele when treated with tamoxifen, another[4] found that this allele was an independent predictor of a higher risk of disease relapse and a lower incidence of hot flashes in postmenopausal women with breast cancer. A further study[5] found that carriers of CYP2D6 alleles *4 or *5 showed a greater risk for breast cancer relapse. Furthermore, carriers of the CYP2C19*17 genotype had a more favourable clinical outcome. These results prompted the Clinical Pharmacology Subcommittee of the US FDA Advisory Committee for Pharmaceutical Science to advise that availability of genotypic testing be included in licensed product information for tamoxifen.[6,7] Some have commented[7] that it would seem reasonable to confine CYP2D6 testing to situations where it might guide the choice between tamoxifen and an alternative.

1. Borges S, *et al.* Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther* 2006; **80:** 61–74.
2. Goetz MP, *et al.* Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 2008; **83:** 160–6.

3. Wegman P, *et al.* Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res* 2005; **7:** R284–R290.
4. Goetz MP, *et al.* Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; **23:** 9312–18.
5. Schroth W, *et al.* Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 2007; **25:** 5187–93.
6. Young D. Genetics examined in tamoxifen's effectiveness: recurrence warning urged for labeling. *Am J Health-Syst Pharm* 2006; **63:** 2286, 2296.
7. Desta Z, Flockhart DA. Germline pharmacogenetics of tamoxifen response: have we learned enough? *J Clin Oncol* 2007; **25:** 5147–9.

Metabolism. Tamoxifen is extensively metabolised by cytochrome P450 isoenzymes, to active metabolites that include *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen).[1] *In-vitro* studies suggest that both *N*-desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised to endoxifen.[2] However, the biotransformation of tamoxifen has not been fully elucidated, and there is growing interest in how genetic polymorphism might influence the efficacy and toxicity of tamoxifen and its metabolites (see Genetic Factors, above).

1. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. *Clin Pharmacokinet* 2005; **44:** 349–66.
2. Desta Z, *et al.* Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004; **310:** 1062–75.

Uses and Administration

Tamoxifen is an oestrogen antagonist with actions similar to those of clomifene citrate (see p.2086). It may also inhibit the production or release of cellular growth factors and induce apoptosis. It is used in the adjuvant endocrine therapy of node-positive breast cancer, in the treatment of metastatic disease, and for prophylaxis in women at increased risk including those with ductal carcinoma in situ. It has been tried in some other malignancies including tumours of the ovary and in malignant melanoma. Tamoxifen is also used to stimulate ovulation in women with anovulatory infertility. See also the cross-references below.

Tamoxifen is given orally as the citrate but doses are calculated in terms of the base; tamoxifen citrate 15.2 mg is equivalent to about 10 mg of tamoxifen. In the treatment of breast cancer, usual doses are tamoxifen 20 mg daily, in 2 divided doses or as a single daily dose. Doses of up to 40 mg daily may be given but no additional benefit has been demonstrated. Adjuvant therapy is normally continued for up to 5 years, although the optimum duration is still uncertain (p.661). To reduce breast cancer incidence in women at high risk of the disease, the licensed dose of tamoxifen is 20 mg daily for 5 years.

In the treatment of anovulatory infertility the usual dose is tamoxifen 20 mg daily on days 2 to 5 of the menstrual cycle, increased if necessary in subsequent cycles up to 80 mg daily. In women with irregular menstruation the initial course may be begun on any day, and a second course begun at a higher dose after 45 days if there has been no response. If the patient responds with menstruation, subsequent courses may begin on day 2 of the cycle.

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation for the treatment of cyclic mastalgia.

◊ Reviews.

1. Kramer R, Brown P. Should tamoxifen be used in breast cancer prevention? *Drug Safety* 2004; **27:** 979–89.
2. Singh Ranger G. Current concepts in the endocrine therapy of breast cancer: tamoxifen and aromatase inhibitors. *J Clin Pharm Ther* 2005; **30:** 313–17.
3. Morales L, *et al.* Choosing between an aromatase inhibitor and tamoxifen in the adjuvant setting. *Curr Opin Oncol* 2005; **17:** 559–65.
4. Poole R, Paridaens R. The use of third-generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. *Curr Opin Oncol* 2007; **19:** 564–72.
5. Munshi A, Singh P. Tamoxifen in breast cancer: not so easy to write off. *Breast* 2008; **17:** 121–4.

Breast disorders, non-malignant. *GYNAECOMASTIA.* Tamoxifen, usually in doses of 10 mg twice daily, has been reported to be effective[1-7] in reducing pain, swelling, and breast size in men or pubertal boys with gynaecomastia (p.2092). Tamoxifen has been recommended as a drug of choice in patients requiring drug therapy, given for 3 months to see if a response occurs.[7] It has also been reported to be effective for the prevention and treatment of gynaecomastia and breast pain caused by the nonsteroidal anti-androgen bicalutamide,[8-11] which is used in the treatment of prostate cancer (see Gynaecomastia under Adverse Effects and Precautions of Flutamide, p.725).

1. Jefferys DB. Painful gynaecomastia treated with tamoxifen. *BMJ* 1979; **1:** 1119–20.
2. Hooper PD. Puberty gynaecomastia. *J R Coll Gen Pract* 1985; **35:** 142.
3. McDermott MT, *et al.* Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; **83:** 1283–5.
4. Ting AC, *et al.* Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; **66:** 38–40.
5. Lawrence SE, *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; **145:** 71–6.
6. Hanavadi S, *et al.* The role of tamoxifen in the management of gynaecomastia. *Breast* 2006; **15:** 276–80.
7. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; **357:** 1229–37.
8. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; **8:** 75–83.
9. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; **6:** 295–300.
10. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; **174:** 2197–2203.
11. Fradet Y, *et al.* Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol* 2007; **52:** 106–14.

MASTALGIA. Tamoxifen 20 mg daily has been shown to be effective in patients with both cyclic and non-cyclic mastalgia,[1] and improvement has also been reported at a lower dose of 10 mg daily.[2] However, there is concern about the use of tamoxifen in otherwise healthy premenopausal women,[3-5] particularly since many patients relapse on withdrawal,[2] and it has been recommended[6,7] that tamoxifen be reserved for patients who fail to respond to other drugs (see p.2092).

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation in the treatment of cyclic mastalgia.

1. Fentiman IS, *et al.* Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; **i:** 287–8.
2. Fentiman IS, *et al.* Studies of tamoxifen in women with mastalgia. *Br J Clin Pract* 1989; **43** (suppl 68): 34–6.
3. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; **i:** 305.
4. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 680–1.
5. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; **i:** 681.
6. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
7. Anonymous. Cyclical breast pain: what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.

Cardiovascular disorders. Tamoxifen has been reported to have a generally favourable effect on lipid profiles (see Effects on Blood Lipids, under Adverse Effects, above) suggesting it may have cardiovascular benefits.[1] A cohort study of adjuvant tamoxifen found that the drug reduced the incidence of myocardial infarction,[2] and a randomised study of the same therapy also showed a trend towards a decrease in mortality from coronary heart disease.[3] However, in a much larger breast cancer prevention trial, tamoxifen did not reduce the risk of, and mortality from, ischaemic heart disease, neither of which differed between placebo and tamoxifen recipients.[4,5] This lack of difference was independent of pre-existing cardiovascular disease.[5] A review[6] noted that while the available data suggested an overall benefit, most of them came from studies in women at low absolute risk of myocardial infarction; studies in men at high absolute risk would be needed to determine whether tamoxifen and related drugs were suitable as cardioprotectants.

1. Pritchard KI, Abramson BL. Cardiovascular health and aromatase inhibitors. *Drugs* 2006; **66:** 1727–40.
2. McDonald CC, *et al.* Scottish Cancer Trials Breast Group. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. *BMJ* 1995; **311:** 977–80.
3. Costantino JP, *et al.* Coronary heart disease mortality and adjuvant tamoxifen therapy. *J Natl Cancer Inst* 1997; **89:** 776–82.
4. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; **90:** 1371–88.
5. Reis SE, *et al.* Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. *J Natl Cancer Inst* 2001; **93:** 16–21.
6. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. *Circulation* 2005; **112:** 3018–24.

Disorders related to the menstrual cycle. Apart from cyclic mastalgia (see above) tamoxifen has been used in a number of cases in which disorders were linked to the hormonal changes of the menstrual cycle, including menorrhagia due to myometrial hypertrophy,[1] an auto-immune dermatitis due to post-ovulatory rises in serum progesterone[2,3] (see Effects on the Skin under Progesterone, p.2125), and premenstrual migraine.[4] However, tamoxifen was thought to be a cause of recurrent migraines in another patient, because of its action at oestrogen receptors.[5]

1. Fraser IS. Menorrhagia due to myometrial hypertrophy: treatment with tamoxifen. *Obstet Gynecol* 1987; **70:** 505–6.
2. Wojnarowska F, *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78:** 407–8.
3. Stephens CJM, *et al.* Autoimmune progesterone dermatitis responding to tamoxifen. *Br J Dermatol* 1989; **121:** 135–7.
4. O'Dea JPK, Davis EH. Tamoxifen in the treatment of menstrual migraine. *Neurology* 1990; **40:** 1470–1.
5. Mathew P, Fung F. Recapitulation of menstrual migraine with tamoxifen. *Lancet* 1999; **353:** 467–8.

Infertility. Tamoxifen is reported to be as effective as clomifene in the treatment of anovulatory infertility (p.2080) in women,[1,2] and may be useful in women in whom abnormal cervical mucus acts as a barrier to spermatozoa.[3] In infertile men, however, results are reportedly contradictory, with some studies reporting increase in sperm density and improved pregnancy rates while others failed to demonstrate any effect.[4] The addition of testosterone may improve outcomes, however, and a later study of men with idiopathic oligozoospermia reported that tamoxifen with testosterone improved sperm variables and pregnancy rates compared with a placebo group (there was no comparison with tamoxifen alone).[5]

1. Messinis IE, Nillius SJ. Comparison between tamoxifen and clomiphene for induction of ovulation. *Acta Obstet Gynecol Scand* 1982; **61:** 377–9.
2. Boostanfar R, *et al.* A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril* 2001; **75:** 1024–6.
3. Annapurna V, *et al.* Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction. *Int J Fertil* 1997; **42:** 215–18.
4. Howards SS. Treatment of male infertility. *N Engl J Med* 1995; 312–17.
5. Adamopoulos DA, *et al.* Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003; **80:** 914–20.

Malignant neoplasms. For reference to the use of tamoxifen in malignant neoplasms of breast, ovary, and in cutaneous melanoma, see p.661, p.670, and p.673. The most common use of tamoxifen is for the endocrine therapy of oestrogen-receptor positive early or advanced breast cancer, where there seems to be a clear benefit. How long such therapy should be continued remains uncertain although continuing therapy beyond 5 years may not increase the overall benefit. However, extending therapy by following 5 years of tamoxifen therapy with several years of an aromatase inhibitor such as letrozole (see, p.740) does seem to provide additional benefit.

Extension of tamoxifen use to the attempted prophylaxis of breast cancer has proved controversial (see p.662). Nonetheless, evidence that tamoxifen can reduce short-term incidence of breast cancer in some women at increased risk has been seen, and tamoxifen has been approved for such use in the USA.

Despite some positive data, tamoxifen does not appear to be effective in the treatment of hepatocellular carcinoma (see p.667).

Osteoporosis. Tamoxifen has been reported to have favourable effects on bone mass,[1-3] but any general role in the prevention of osteoporosis (p.1084) seems unlikely given concerns about the carcinogenicity of tamoxifen. The effects are reported to be comparable in magnitude to those of calcium supplementation, and less than those of oestrogens (see also p.2077) or bisphosphonates. It has been suggested that such an effect on bone would provide an additional benefit in women receiving tamoxifen for the prophylaxis of breast cancer,[4] although others dispute the benefits.[5]

1. Love RR, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; **326:** 852–6.
2. Love RR, *et al.* Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Intern Med* 1994; **154:** 2585–8.
3. Grey AB, *et al.* The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995; **99:** 636–41.
4. Powles TJ. The case for clinical trials of tamoxifen for prevention of breast cancer. *Lancet* 1992; **340:** 1145–7.
5. Fugh-Berman A, Epstein S. Tamoxifen: disease prevention or disease substitution? *Lancet* 1992; **340:** 1143–5.

Precocious puberty. Tamoxifen has been reported to be beneficial in the treatment of precocious puberty (p.2081).

Preparations

BP 2008: Tamoxifen Tablets;
USP 31: Tamoxifen Citrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Crisafeno; Diemon; Farmifeno†; Ginarsan; Nolvadex; Rolap; Tamofen†; Tamoxis; Taxfeno; Trimetrox; ***Austral.:*** Genox; Nolvadex; Tamosin; Tamoxen; ***Austria:*** Ebefen; Kessar; Nolvadex; Tamax; Tamofen†; Tamoplex; ***Belg.:*** Doctamoxifene; Nolvadex; Tamizam; Tamoplex; ***Braz.:*** Bioxifeno; Estrocur†; Festone; Kessar; Nolvadex; Tamooex†; Tamoplex†; Tamox†; Tamoxin; Taxofen; Tecnotax; ***Canad.:*** Apo-Tamox; Nolvadex; Tamofen; ***Chile:*** Kessar; Nolvadex; Oncotamox; Tamolem†; Taxus; ***Cz.:*** Nolvadex; Tamifen†; Tamoplex; Zitazonium; ***Denm.:*** Tamofen†; ***Fin.:*** Nolvadex†; Tadex; Tamexin; Tamofen; ***Fr.:*** Kessar; Nolvadex; Oncotam†; Tamofene†; ***Ger.:*** Jenoxifen; Kessar†; Mandofen; Nolvadex; Nourytam; Tamokadin; Tamopham†; Tamox; Tamoxasta†; Tamoximerck; Tamoxistad; Zemide†; ***Gr.:*** Adifen; Defarol†; Kessar; Nolvadex; Puretam; Tamoplex; Zymoplex; ***Hong Kong:*** Apo-Tamox; Nolvadex; Novofen; Tamifen†; Zitazonium; ***Hung.:*** Zitazonium; ***India:*** Caditam; Cytotam; Mamofen; Nolvadex; Tamodex†; ***Indon.:*** Nolvadex; Tamofen; Tamoplex; Taxen; ***Irl.:*** Nolgen†; Nolvadex; Tamofen†; Tamox; ***Israel:*** Nolvadex; Tamofen; Tamoxen;

The symbol † denotes a preparation no longer actively marketed

Tamoxi; ***Ital.:*** Kessar; Ledertam†; Nolvadex; Nomafen; Tamoxene; Virtamox†; ***Malaysia:*** Genox; Nolvadex; Novofen; Tamoplex; Zitazonium; ***Mex.:*** Bilem; Cryoxifeno; Fenobest; Kessar†; Nolvadex; Ralsifen-X; Tamoxan†; Taxus; Tecnofen; ***Neth.:*** Nolvadex; ***Norw.:*** Nolvadex; ***NZ:*** Genox; Nolvadex; Tamofen; ***Philipp.:*** Fenahex; Gynatam; Gyraxen; Kessar; Nolvadex; Tamoplex; Tamoxsta; Zitazonium; ***Pol.:*** Nolvadex; ***Port.:*** Mastofen; Nolvadex; Tamoxan; ***Rus.:*** Bilem (Билем)†; Tamifen (Тамифен); Zitazonium (Зитазониум); ***S.Afr.:*** Kessar; Neophedan; Nolvadex; Tamoplex; ***Singapore:*** Apo-Tamox; Nolvadex; Tamofen; ***Spain:*** Nolvadex; Sinmaren†; Yacesal; ***Swed.:*** Nolvadex; ***Switz.:*** Kessar†; Nolvadex; Tamec; ***Thai.:*** Bilem; Gynatam; Nolvadex; Novofen; Tamofen†; Tamoplex; Tuosomin; Zitazonium; ***Turk.:*** Nolvadex; Tadex; Tamofen; ***UAE:*** Tamophar; ***UK:*** Nolvadex; Soltamox; ***USA:*** Nolvadex†; Soltamox; ***Venez.:*** Gynatam; Nolvadex; Taxus.

Tegafur *(BAN, USAN, rINN)*

FT-207; Ftorafur; MJF-12264; NSC-148958; Tégafur; Tegafurum; Tegafuuri; WR-220066. 5-Fluoro-1-(tetrahydro-2-furyl)uracil; 5-Fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Тегафур

$C_8H_9FN_2O_3$ = 200.2.
CAS — 17902-23-7.
ATC — L01BC03.
ATC Vet — QL01BC03.

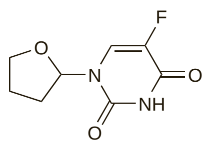

Pharmacopoeias. In *Chin.* and *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722.

Bone-marrow depression may be less severe with tegafur but gastrointestinal toxicity is often dose-limiting and central neurotoxicity is more common. Peripheral oedema and dyspnoea occur commonly. Increases in liver function test values are common and there are reports of fatal fulminant hepatitis. Liver function should be monitored in patients with hepatic impairment given tegafur; it should not be given in severe hepatic impairment.

Interactions

Tegafur should not be used with drugs that inhibit dihydropyrimidine dehydrogenase; fatalities have occurred in patients given tegafur and sorivudine (see Antivirals under Interactions of Fluorouracil, p.723). Increased plasma concentrations of phenytoin, and symptoms of toxicity during use with tegafur and uracil, have been reported.

Pharmacokinetics

Tegafur is well absorbed from the gastrointestinal tract after oral doses. After an intravenous dose it is reported to have a prolonged plasma half-life of 6 to 16 hours. Tegafur appears to be slowly metabolised in the liver to fluorouracil (p.723), and some intracellular conversion to fluorouracil may also occur. Tegafur crosses the blood-brain barrier and is found in the CSF.

◊ References.

1. Etienne-Grimaldi M-C, *et al.* A clinical pharmacokinetic analysis of tegafur-uracil (UFT) plus leucovorin given in a new twice-daily oral administration schedule. *Clin Pharmacokinet* 2007; **46:** 953–63.

Uses and Administration

Tegafur is considered to be an orally active prodrug of fluorouracil (p.723). It has been used in the management of malignant neoplasms including those of the breast, gallbladder, gastrointestinal tract, head and neck, liver, and pancreas. Tegafur has been given orally in doses up to 1 g/m^2 daily. It is often given with uracil (UFT; p.2407). Tegafur 300 mg/m^2 daily, with uracil 672 mg/m^2 daily, may be given in 3 divided oral doses, together with calcium folinate, in the management of metastatic colorectal cancer. Doses are given for a cycle of 28 days, followed by 7 days without treatment. The drugs should be taken 1 hour before or after meals, and doses modified according to toxicity. Doses of tegafur 1 to 3 g/m^2 daily for 5 days have been given intravenously.

Administration. Tegafur is an orally active prodrug of fluorouracil. Although it has been given as a single agent, it is more often used with drugs that modify its bioavailability and toxicity.[1] These include uracil (p.2407) and gimestat (5-chlorodihydropyrimidine, CDHP), which can increase fluorouracil concentrations by inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for its further catabolism,[1-3] and oxonic acid (otastat), which inhibits another enzyme, orotate pyrimidine phosphoribosyl transferase, thought to play a role in the gastrointestinal toxicity of fluorouracil and its prodrugs.[2]

UFT consists of tegafur and uracil in the optimal molar ratio 1:4.[1] It is available for the treatment of colorectal cancer (p.665)—for doses, see above. A preliminary analysis of a large study comparing oral UFT and calcium folinate therapy with intravenous fluorouracil and calcium folinate found both regimens to be well tolerated with similar levels of toxicity.[4] Adjuvant therapy with UFT appears to improve survival in patients with adenocarcinoma of the lung[5] and node-negative breast cancer.[6]

S-1 (TS-1, *Taiho Jpn*) is a combination of tegafur, gimestat and the potassium salt of oxonic acid in the molar ratio 10:4:10. It has been tried in gastric and colorectal cancers,[2,3,7,8] and initial results have suggested comparable activity to fluorouracil and calcium folinate in induction regimens, but the incidence of diarrhoea and stomatitis was reduced.

1. Adjei AA. A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. *Br J Clin Pharmacol* 1999; **48:** 265–77.
2. Sakata Y, *et al.* Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34:** 1715–20.
3. Sugimachi K, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57:** 202–10.
4. Smith R, *et al.* UFT plus calcium folinate vs 5-FU plus calcium folinate in colon cancer. *Oncology (Huntingt)* 1999; **13** (suppl 3): 44–7.
5. Kato H, *et al.* A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350:** 1713–21.
6. Noguchi S, *et al.* Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol* 2005; **23:** 2172–84.
7. Osugi H, *et al.* Oral fluoropyrimidine anticancer drug TS-1 for gastric cancer patients with peritoneal dissemination. *Oncol Rep* 2002; **9:** 811–15.
8. Shibahara K, *et al.* Retrospective study of S-1 versus tegafur/uracil and oral leucovorin in patients with metastatic colorectal cancer. *Anticancer Res* 2008; **28:** 1779–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ftorafur; UFT; ***Hong Kong:*** Futraful; ***Hung.:*** Ftorafur; ***Indon.:*** Futraful; ***Ital.:*** Citofur†; ***Jpn:*** Futraful; ***Rus.:*** Ftorafur (Фторафур); ***Spain:*** Utefos; ***Thai.:*** UFUR.

Multi-ingredient: ***Arg.:*** Asofurtal; UFT; ***Austria:*** UFT; ***Belg.:*** UFT; ***Braz.:*** UFT; ***Denm.:*** Uftoral; ***Fr.:*** UFT; ***Ger.:*** UFT; ***Gr.:*** UFT; ***Hong Kong:*** UFT; ***Hung.:*** UFT; ***Israel:*** UFT†; ***Ital.:*** UFT; ***Jpn:*** UFT; ***Malaysia:*** UFT; ***Mex.:*** UFT; ***Neth.:*** UFT; ***Norw.:*** UFT; ***NZ:*** Orzel†; ***Philipp.:*** Tefudex; UFT; ***Port.:*** UFT; ***Rus.:*** UFT (УФТ); ***S.Afr.:*** UFT; ***Singapore:*** UFT; ***Spain:*** UFT; ***Swed.:*** UFT; ***Thai.:*** UFT; ***Turk.:*** UFT; ***UK:*** Uftoral.

Temoporfin *(BAN, USAN, rINN)*

EF-9; mTHPC; Temoporfiini; Temoporfina; Témoporfine; Temoporfinum; *meso*-Tetrahydroxyphenylchlorin; *meta*-Tetrahydroxyphenylchlorin. 3,3′,3″,3‴-(7,8-Dihydroporphyrin-5,10,15,20-tetrayl)tetraphenol; 7,8-Dihydro-5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin.

Темопорфин

$C_{44}H_{32}N_4O_4$ = 680.7.
CAS — 122341-38-2.
ATC — L01XD05.
ATC Vet — QL01XD05.

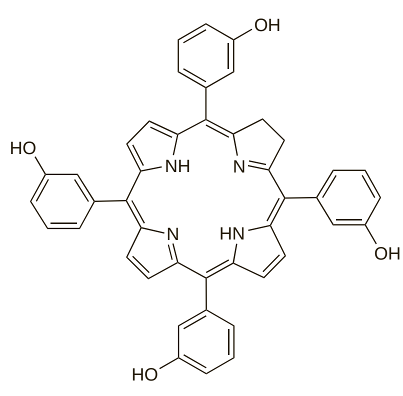

Adverse Effects and Precautions

Adverse effects of temoporfin include photosensitivity, local inflammatory reactions, and gastrointestinal disturbances. Patients should be advised to avoid direct sunlight or bright indoor light for 15 days, and to protect the injection site from light for at least 3 months if extravasation has occurred.

Porphyria. The use of temoporfin is contra-indicated in patients with porphyria.

Interactions

Use of temoporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased; this has been reported with topical fluorouracil.

Pharmacokinetics

Peak plasma concentrations of temoporfin are reached about 2 to 4 hours after intravenous infusion. Thereafter, elimination is biexponential, with a terminal plasma half-life of about 65 hours. Plasma protein binding is about 85%. *Animal* data indicate that temoporfin is metabolised in the liver and excreted in the faeces via the bile.

Uses and Administration

Temoporfin is a porphyrin derivative. It is used palliatively as a photosensitiser in the photodynamic therapy (see under Porfimer Sodium, p.764) of refractory squamous cell carcinoma of the head and neck (p.666), that cannot be treated with radiotherapy, surgery, or systemic chemotherapy. It is also under investigation in the treatment of various other malignant neoplasms. Temoporfin is given by slow intravenous injection over at least 6 minutes, at a dose of 150 micrograms/kg. This is followed 96 hours later by activation using a laser tuned to a wavelength of 652 nanometres for about 200 seconds, sufficient to supply a dose of 20 J/cm^2. Treatment may be repeated once after 4 weeks if necessary.

◊ References.

1. Kubler AC, *et al.* Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999; **25:** 60–8.
2. Baas P, *et al.* Photodynamic therapy with *meta*-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study. *Br J Dermatol* 2001; **145:** 75–8.
3. Kubler AC, *et al.* Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001; **30:** 504–9.
4. Javaid B, *et al.* Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. *Lasers Med Sci* 2002; **17:** 51–6.
5. Friedberg JS, *et al.* A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg* 2003; **75:** 952–9.
6. Copper MP, *et al.* Meta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2003; **129:** 709–11.
7. D'Cruz AK, *et al.* mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. *Head Neck* 2004; **26:** 232–40.
8. Etienne J, *et al.* Photodynamic therapy with green light and m-tetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2004; **59:** 880–9. Correction. *ibid.*; **60:** 1042.
9. Hopper C, *et al.* mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. *Int J Cancer* 2004; **111:** 138–46.
10. Lou PJ, *et al.* Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *Br J Cancer* 2004; **91:** 441–6.
11. Campbell SM, *et al.* Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151:** 1076–80.
12. Naim R. Photodynamische Therapie mit m-THPC (Foscan): Behandlung von Plattenepithelkarzinomen im Kopf-Hals-Bereich. *HNO* 2008; **56:** 490–2.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Foscan; ***Cz.:*** Foscan; ***Denm.:*** Foscan; ***Ger.:*** Foscan; ***Gr.:*** Foscan; ***Israel:*** Foscan; ***Neth.:*** Foscan; ***Port.:*** Foscan; ***UK:*** Foscan.

Temozolomide *(BAN, USAN, rINN)*

CCRG-81045; M&B-39831; NSC-362856; Sch-52365; Temotsolomidi; Temozolomid; Temozolomida; Témozolomide; Temozolomidum. 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide.

Темозоломид

$C_6H_6N_6O_2$ = 194.2.
CAS — 85622-93-1.
ATC — L01AX03.
ATC Vet — QL01AX03.

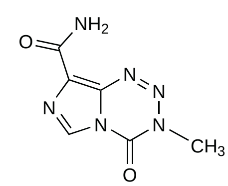

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641. Myelosuppression is common with temozolomide and is dose-limiting. The nadir of cell counts usually occurs 21 to 28 days after treatment, with recovery within the next 1 to 2 weeks. Patients over 70 years of age are thought to be more susceptible to severe myelosuppression. Prolonged pancytopenia may result in aplastic anaemia, and fatalities have been reported. Opportunistic infections can occur; *Pneumocystis jirovecii* pneumonia has been reported in patients also given radiotherapy or corticosteroids, or during a longer dosing regimen of temozolomide. Other common adverse effects include gastrointestinal disturbances, anorexia, alopecia, fatigue, headache, rashes, convulsions, and insomnia or somnolence. Anxiety, depression, confusion, dizziness, hemiparesis, aphasia, dysphagia, peripheral neuropathy, paraesthesia, neurological and/or speech disorders, tremor, and concentration or memory impairment can occur, as can visual field defects, blurred vision, diplopia, hearing impairment, or tinnitus. Deafness has been reported. Vascular disorders such as haemorrhage, deep venous thrombosis, and peripheral oedema can occur; pulmonary embolism has been reported. Other commonly reported adverse effects include dyspnoea, coughing, dry skin, pruritus, arthralgia and/or myalgia, urinary incontinence, fever, pain, and dysgeusia. Liver enzyme values can increase, and hyperglycaemia may occur. Cushingoid disorders have occurred uncommonly. Hypersensitivity reactions, including rare cases of anaphylaxis, have been reported. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported rarely. Temozolomide has carcinogenic, mutagenic, and teratogenic potential.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring 0.5 to 1.5 hours after a dose. Food reduces the rate and extent of absorption. It readily crosses the blood-brain barrier and can be detected in the CSF. The plasma elimination half-life is 1.8 hours. Temozolomide undergoes spontaneous hydrolysis to its active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), which is then further hydrolysed to active and inactive compounds. It is largely eliminated by the kidneys, about 5 to 10% as unchanged drug.

Uses and Administration

Temozolomide is a prodrug that is converted to MTIC (see Pharmacokinetics, above), the active metabolite of dacarbazine (p.706). MTIC acts as an alkylating agent. Temozolomide is given orally and is licensed for the treatment of malignant gliomas such as glioblastoma multiforme and anaplastic astrocytoma, and malignant melanoma (below).

In adult patients with *newly diagnosed* **glioblastoma multiforme**, temozolomide is given initially with focal radiotherapy (the *concomitant phase*) in an oral dose of 75 mg/m^2 daily for 42 days. Treatment may be interrupted or stopped depending on toxicity. Complete blood counts should be monitored weekly. Four weeks after completing the concomitant phase, temozolomide *monotherapy* is begun at an oral dose of 150 mg/m^2 once daily for 5 days of a 28-day cycle. In cycle 2, the dose is increased to 200 mg/m^2 for 5 days, if toxicity allows. If the dose cannot be increased in cycle 2, it should not be increased in subsequent cycles. The dose used at cycle 2 is then given every 28 days, toxicity allowing. Up to 6 cycles of temozolomide monotherapy may be given.

The usual oral dose for *recurrent or progressive* malignant gliomas in adults and children over 3 years of age (and previously untreated with chemotherapy) is 200 mg/m^2 daily for 5 days, repeated every 28 days. In patients who have received previous courses of chemotherapy the dose should be reduced to 150 mg/m^2 for the first cycle of therapy, but may be increased to 200 mg/m^2 for subsequent courses if there is no haematological toxicity.

A dose of 200 mg/m^2 daily for 5 days every 28 days is also used for metastatic **malignant melanoma**.

Malignant neoplasms. Temozolomide has been studied[1-9] particularly in the management of malignant neoplasms of the brain (p.660). In the UK, guidance has been issued[10] on its use in patients with recurrent progressive malignant glioma who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of adverse effects).

1. Dinnes J, *et al.* A rapid and systematic review of the effectiveness of temozolomide for the treatment of recurrent malignant glioma. *Br J Cancer* 2002; **86:** 501–5.
2. Wick W, *et al.* One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology* 2004; **62:** 2113–15.
3. Levin N, *et al.* Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide. *Neurology* 2004; **63:** 354–6.
4. Agarwala SS, *et al.* Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol* 2004; **22:** 2101–7.
5. Stupp R, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352:** 987–96.
6. Athanassiou H, *et al.* Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; **23:** 2372–7.
7. Tosoni A, *et al.* Is protracted low-dose temozolomide feasible in glioma patients? *Neurology* 2006; **66:** 427–9.
8. Wick A, *et al.* Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol* 2007; **25:** 3357–61.
9. Sher DJ, *et al.* The added value of concurrently administered temozolomide versus adjuvant temozolomide alone in newly diagnosed glioblastoma. *J Neurooncol* 2008; **88:** 43–50.
10. NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (issued April 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/temozolomideguidance.pdf (accessed 30/07/08)

Melanoma. Temozolomide has been studied[1-3] as a treatment for advanced metastatic melanoma (p.673). A phase III trial compared the overall survival-time in 305 patients treated with either oral temozolomide or intravenous dacarbazine in standard doses for up to 12 cycles of therapy. Temozolomide was found to be at least equivalent to dacarbazine in these patients, and there were no major differences in adverse effects.[2] However, median survival-times were short in both groups (7.7 months and 6.4 months respectively). Another phase III study comparing temozolomide alone or with interferon alfa in 282 patients also found modest median survival-times of 8.4 and 9.7 months respectively.[4] Temozolomide has also been investigated in *animals* for regional therapy of melanoma of the extremities by isolated limb infusion in combination with hyperthermia.[5]

1. Bleehen NM, *et al.* Cancer research campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol* 1995; **13:** 910–13.
2. Middleton MR, *et al.* Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; **18:** 158–66.
3. Quirt I, *et al.* Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist* 2007; **12:** 1114–23.
4. Kaufmann R, *et al.* Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. *J Clin Oncol* 2005; **23:** 9001–7.
5. Ko SH, *et al.* Optimizing a novel regional chemotherapeutic agent against melanoma: hyperthermia-induced enhancement of temozolomide cytotoxicity. *Clin Cancer Res* 2006; **12:** 289–97.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dralitem; Temodal†; ***Austral.:*** Temodal; ***Austria:*** Temodal; ***Belg.:*** Temodal; ***Braz.:*** Temodal; ***Canad.:*** Temodal; ***Chile:*** Temodal; ***Cz.:*** Temodal; ***Denm.:*** Temodal; ***Fin.:*** Temodal; ***Fr.:*** Temodal; ***Ger.:*** Temodal; ***Gr.:*** Temodal; ***Hong Kong:*** Temodal; ***Hung.:*** Temodal; ***Indon.:*** Temodal; ***Irl.:*** Temodal; ***Israel:*** Temodal; ***Ital.:*** Temodal; ***Malaysia:*** Temodal; ***Mex.:*** Temodal; ***Neth.:*** Temodal; ***Norw.:*** Temodal; ***NZ:*** Temodal; ***Philipp.:*** Temodal; ***Pol.:*** Temodal; ***Port.:*** Temodal; ***Rus.:*** Temodal (Темодал); ***S.Afr.:*** Temodal; Temoxol†; ***Singapore:*** Temodal; ***Spain:*** Temodal; ***Swed.:*** Temodal; ***Switz.:*** Temodal; ***Thai.:*** Temodal; ***Turk.:*** Temodal; ***UK:*** Temodal; ***USA:*** Temodar; ***Venez.:*** Temodal.

Temsirolimus *(BAN, USAN, rINN)*

CCI-779; Temsirolimusum. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4′[2,2-bis(hydroxymethyl)propionate].

Темсиролимус

$C_{56}H_{87}NO_{16}$ = 1030.3.

CAS — 162635-04-3.

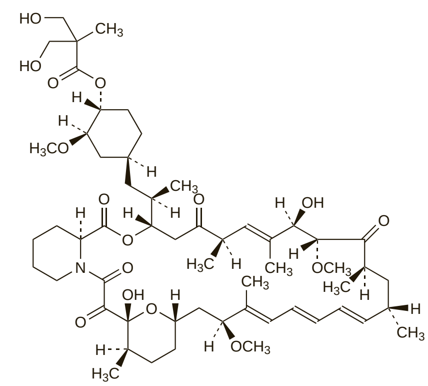

Incompatibility. The formulation of temsirolimus injection contains polysorbate 80, which increases the rate of extraction of the plasticiser di-2-ethylhexylphthalate (DEHP) from PVC. In order to minimise exposure to DEHP, the infusion should be given in glass, polyolefin, or polyethylene containers, through non-DEHP giving sets with an in-line polyethersulfone filter of not greater than 5 microns.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most frequent adverse effects of temsirolimus include rash, asthenia, mucositis, gastrointestinal disturbances, anaemia, leucopenia, thrombocytopenia, hyperglycaemia, hyperlipidaemia, hypertriglyceridaemia, lymphopenia, and hypophosphataemia. Raised liver transaminase concentrations are common. Hypersensitivity reactions, including anaphylaxis, dyspnoea, flushing, and chest pain have occurred. Antihistamines should be given about 30 minutes before the start of the infusion. If the patient develops a hypersensitivity reaction, the infusion should be stopped and the patient observed for 30 to 60 minutes, after which treatment may be resumed if appropriate, at a slower infusion rate; a further dose of an H_1- or H_2-receptor antagonist may be given. Infections, including urinary-tract infection, pharyngitis, rhinitis, and pneumonia can occur. Acute, and sometimes fatal, renal failure has been reported. Interstitial lung disease has been reported, including some fatalities, although other cases were asymptomatic. Manifestations included dyspnoea, cough, hypoxia, or fever. Cases of fatal bowel perforation have occurred; patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhoea, and/or acute abdomen. Abnormal wound healing has also been reported. Patients with CNS tumours given anticoagulants may be at increased risk of developing intracranial bleeding, which may be fatal.

Effects on the lungs. Eight out of 22 patients given temsirolimus developed pulmonary abnormalities compatible with drug-induced pneumonitis. Dyspnoea and dry cough were the most common symptoms, although 4 patients were asymptomatic. The risk of developing pulmonary toxicity is increased in those with abnormal pre-treatment pulmonary function, or a history of lung disease.[1]

1. Duran I, *et al.* Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; **42:** 1875–80.

Interactions

Temsirolimus is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4 to produce sirolimus. Ketoconazole had no effect on exposure to temsirolimus, but increased exposure to the metabolite. Use with other strong inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sirolimus concentrations. Rifampicin had no effect on exposure to temsirolimus, but decreased exposure to sirolimus. Strong inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, or phenobarbital) may also decrease exposure to sirolimus; St John's wort may decrease temsirolimus plasma concentrations unpredictably. If the use of alternative drugs is not feasible, dose adjustments of temsirolimus may be necessary (see Uses and Administration, below).

◊ References.

1. Boni J, *et al.* Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome P450-inducing medications. *J Clin Pharmacol* 2007; **47:** 1430–9.

Pharmacokinetics

Temsirolimus is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 to 5 metabolites; sirolimus is the main active metabolite. The mean half-lives of temsirolimus and sirolimus are about 17 hours and 55 hours, respectively. Exposure to sirolimus may be much greater than that of temsirolimus, due principally to the longer half-life of sirolimus. Elimination is mainly in faeces; about 5% is recovered in the urine.

The symbol † denotes a preparation no longer actively marketed

Uses and Administration

Temsirolimus is an ester analogue of sirolimus (p.1841) that is given intravenously for the treatment of advanced renal cell carcinoma in a dose of 25 mg once weekly. Treatment may continue until disease progression or toxicity occurs. Temsirolimus is given in 250 mL sodium chloride 0.9% and infused over 30 to 60 minutes, preferably via an infusion pump.

Treatment should be interrupted if the absolute neutrophil count falls below 1000 cells/mm^3, or the platelet count falls below 75 000 cells/mm^3, or if grade 3 toxicity occurs. Once these have resolved to grade 2 or less, temsirolimus may be restarted with the dose reduced by 5 mg weekly, to a dose no lower than 15 mg weekly.

Use of strong inhibitors or inducers of CYP3A4 may increase or decrease exposure to sirolimus, the active metabolite of temsirolimus. If no alternative is available, a dose reduction of temsirolimus to 12.5 mg weekly should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of temsirolimus is increased back to the original dose. A dose increase of temsirolimus to 50 mg weekly should be considered if it is given with a strong CYP3A4 inducer; once the inducer is stopped, the dose of temsirolimus should be decreased to the original dose.

Temsirolimus is also under investigation for the treatment of mantle cell lymphoma.

◊ References.

1. Anonymous. Temsirolimus: CCI 779, CCI-779, cell cycle inhibitor-779. *Drugs R D* 2004; **5:** 363–7.
2. Mounier N, *et al.* Activitié clinique du CCI779 (temsirolimus), inhibiteur de mTOR. *Bull Cancer* 2006; **93:** 1139–43.
3. Hudes G, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356:** 2271–81.
4. Simpson D, Curran MP. Temsirolimus: in advanced renal cell carcinoma. *Drugs* 2008; **68:** 631–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Torisel; ***Fr.:*** Torisel; ***Port.:*** Torisel; ***USA:*** Torisel.

Teniposide *(BAN, USAN, rINN)*

ETP; NSC-122819; Teniposid; Téniposide; Teniposidi; Tenipósido; Teniposidum; VM-26. (5*S*,5a*R*,8a*S*,9*R*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-(4,6-*O*-thenylidene-β-D-glucopyranosyloxy)isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

Тенипозид

$C_{32}H_{32}O_{13}S$ = 656.7.
CAS — 29767-20-2.
ATC — L01CB02.
ATC Vet — QL01CB02.

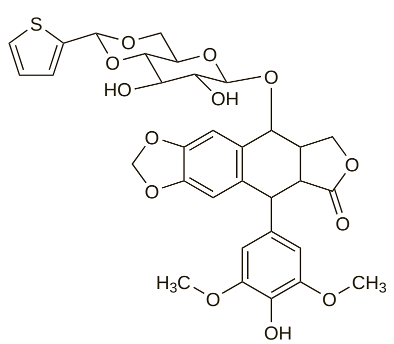

Stability. Precipitation occurred repeatedly in preparations for infusion containing teniposide 200 micrograms/mL in either glucose 5% or sodium chloride 0.9% injection, although previously such preparations had been used uneventfully.[1] Dilution of teniposide solutions to 100 micrograms/mL or less reduced the frequency of the problem, which could not be attributed to a change in formulation and remained unexplained.

1. Strong DK, Morris LA. Precipitation of teniposide during infusion. *Am J Hosp Pharm* 1990; **47:** 512,518.

Adverse Effects, Treatment, and Precautions

As for Etoposide, p.718. There is some evidence that teniposide may be a more potent mutagen and carcinogen than etoposide.

Hypersensitivity. Haemolytic anaemia and acute renal failure with tubular necrosis has been reported in a patient who developed an antibody to teniposide.[1] As with etoposide (p.718) hypersensitivity or infusion reactions occur, sometimes with the first dose, and may be severe;[2,3] the frequency may be as high as 13% in neuroblastoma patients.[2] Although it has been suggested that hypersensitivity reactions might be due to the polyoxyl castor oil in the injection vehicle,[2] studies *in vitro* suggest that it is the drug rather than the vehicle that is responsible.[3]

1. Habibi B, *et al.* Immune hemolytic anemia and renal failure due to teniposide. *N Engl J Med* 1982; **306:** 1091–3.
2. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; **i:** 394.
3. Carstensen H, *et al.* Teniposide-induced hypersensitivity reactions in children. *Lancet* 1989; **ii:** 55.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Antiepileptics. Clearance of teniposide was markedly increased by *phenytoin* or *phenobarbital*; the resultant decrease in systemic exposure to the antineoplastic might reduce its efficacy, and increased dosage would be needed in patients receiving these drugs to guarantee equivalent exposure.[1]

1. Baker DK, *et al.* Increased teniposide clearance with concomitant anticonvulsant therapy. *J Clin Oncol* 1992; **10:** 311–15.

Ciclosporin. Use of ciclosporin with teniposide has been reported[1] to produce a decrease in the clearance of the latter, with increased terminal half-life, peak plasma concentrations, and toxicity.

1. Toffoli G, *et al.* Cyclosporin A as a multidrug-resistant modulator in patients with renal cell carcinoma treated with teniposide. *Br J Cancer* 1997; **75:** 715–21.

Uses and Administration

Teniposide is an antineoplastic agent with general properties similar to those of etoposide (p.718). It has been given alone or with other antineoplastic agents in the treatment of refractory acute lymphoblastic leukaemia (p.651). Teniposide has been tried in solid tumours including neuroblastoma (p.674), and retinoblastoma (p.675).

Teniposide is given by slow intravenous infusion over at least 30 to 60 minutes, as a solution of up to 1 mg/mL in sodium chloride 0.9% injection or glucose 5% injection. Dosage regimens have ranged from 30 mg/m^2 every 5 days, to 180 mg/m^2 weekly, as a single agent. Doses of 165 mg/m^2 twice weekly for 8 or 9 doses with cytarabine, or up to 250 mg/m^2 weekly for 4 to 8 weeks with vincristine and prednisone have been given in the treatment of refractory acute lymphoblastic leukaemia.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vumon; ***Austral.:*** Vumon; ***Austria:*** Vumon; ***Belg.:*** Vumon; ***Braz.:*** Vumon; ***Canad.:*** Vumon; ***Chile:*** Vumon; ***Cz.:*** Vumon†; ***Ger.:*** VM 26; ***Gr.:*** Vumon; ***Hong Kong:*** Vumon; ***Israel:*** Vumon†; ***Ital.:*** Vumon; ***Malaysia:*** Vumon†; ***Mex.:*** Vumon; ***Neth.:*** Vumon; ***NZ:*** Vumon; ***Pol.:*** Vumon; ***Port.:*** Vumon; ***S.Afr.:*** Vumon; ***Singapore:*** Vumon†; ***Spain:*** Vumon; ***USA:*** Vumon.

Testolactone *(USAN, rINN)* ⊗

1-Dehydrotestololactone; NSC-23759; SQ-9538; Testolactona; Testolactonum; Testolakton; Testolaktoni. D-Homo-17a-oxaandrosta-1,4-diene-3,17-dione.

Тестолактон

$C_{19}H_{24}O_3$ = 300.4.
CAS — 968-93-4.

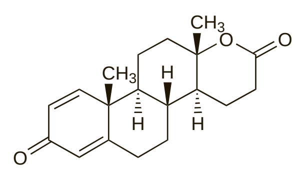

Pharmacopoeias. In *US.*

USP 31 (Testolactone). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 4050 of water; soluble in alcohol and in chloroform; slightly soluble in benzyl alcohol; insoluble in ether and in petroleum spirit. Store in airtight containers.

Profile

Testolactone is a derivative of testosterone (see p.2129). It is reported to be an aromatase inhibitor that reduces peripheral oestrogen synthesis but has no significant androgenic activity. It has been used in the palliative treatment of advanced breast cancer in postmenopausal women (p.661).

The usual oral dose is 250 mg four times daily.

It should not be given to men with breast cancer.

Peripheral neuropathies have occurred in patients given testolactone; gastrointestinal disturbances, pain or oedema of the extremities, hypertension, malaise, maculopapular erythema, and glossitis have also been reported.

Congenital adrenal hyperplasia. For mention of the use of testolactone with flutamide to block androgenic effects in congenital adrenal hyperplasia, see p.1502.

Precocious puberty. Encouraging results have been reported using testolactone in the treatment of 5 girls with precocious puberty (p.2081) due to the McCune-Albright syndrome.[1] Testolactone is an aromatase inhibitor and blocks the synthesis of oestrogens from androgens. Long-term therapy (for up to 5 years) was associated with continued benefit in many patients; however, signs of puberty were not always completely suppressed, in some cases perhaps because of difficulties in maintaining the dosage regimen.[2] Encouraging results were also obtained using testolactone with spironolactone in the treatment of familial precocious puberty in boys, although neither agent was successful when used alone.[3] Again, signs of a reduced response to longer-term therapy have occurred; in this case control was restored by addition of a gonadorelin analogue.[4] Another study[5] in 10 boys who were treated for at least 6 years with spironolactone and testolactone, with deslorelin added at the onset of secondary central precocious puberty, found normalisation in growth rate and bone maturation, and improvements in predicted adult height.

1. Feuillan PP, *et al.* Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med* 1986; **315:** 1115–19.
2. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
3. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
4. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
5. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Preparations

USP 31: Testolactone Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Teslac†; ***Ger.:*** Fludestrin†; ***USA:*** Teslac†.

Thiotepa *(BAN, rINN)*

NSC-6396; TESPA; Thiophosphamide; Thiotépa; Thiotepum; Tiotepa; Triethylenethiophosphoramide; TSPA; WR-45312. Phosphorothioic tri(ethyleneamide); Tris(aziridin-1-yl)phosphine sulphide.

Тиотепа

$C_6H_{12}N_3PS$ = 189.2.
CAS — 52-24-4.
ATC — L01AC01.
ATC Vet — QL01AC01.

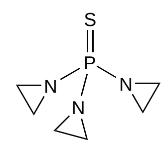

Pharmacopoeias. In *Br., Chin., Fr., Jpn,* and *US.*

BP 2008 (Thiotepa). Fine white, crystalline flakes. M.p. 52° to 57°. Freely soluble in water, in alcohol, and in chloroform. Store at 2° to 8°. At higher temperatures it polymerises and becomes inactive.

USP 31 (Thiotepa). Fine white, crystalline flakes, having a faint odour. M.p. 52° to 57°. Soluble 1 in 13 of water, 1 in about 8 of alcohol, 1 in about 2 of chloroform, and 1 in about 4 of ether. Store at 2° to 8° in airtight containers. Protect from light.

Incompatibility. Lyophilised thiotepa 1 mg/mL in glucose 5% was incompatible when mixed with solutions of cisplatin or minocycline hydrochloride.[1]

1. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.

Stability. A solution of a lyophilised thiotepa preparation 0.5 mg/mL in glucose 5% was considered to be stable (less than 10% loss of thiotepa) for 8 hours at both 4° and 23°.[1] After 24 hours losses ranged between about 10 and 17%. A higher thiotepa concentration (5 mg/mL) was stable for 3 days at 23° and 14 days at 4°. Another study found that solutions containing 1 or 3 mg/mL of thiotepa in sodium chloride 0.9% were stable for 24 hours at 25° and 48 hours at 8°, but solutions containing 0.5% thiotepa needed to be used immediately.[2]

1. Xu QA, *et al.* Stability of thiotepa (lyophilized) in 5% dextrose injection at 4 and 23°C. *Am J Health-Syst Pharm* 1996; **53:** 2728–30.
2. Murray KM, *et al.* Stability of thiotepa (lyophilized) in 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1997; **54:** 2588–91.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression may be delayed; the nadir of white cell and platelet counts may occur up to 30 days after therapy has been stopped. Bone-marrow depression has been reported after intravesical as well as parenteral use, and has occasionally been prolonged or fatal.

Gastrointestinal disturbances, fatigue, weakness, headache and dizziness, hypersensitivity reactions, blurred vision and conjunctivitis may occur. Amenorrhoea and impaired fertility have also been reported. Local irritation, and rarely frank chemical or haemorrhagic cystitis may follow intravesical instillation. Depigmentation of periorbital skin has occurred after the use of thiotepa eye drops. As with other alkylating agents, thiotepa is potentially mutagenic, teratogenic, and carcinogenic.

Thiotepa should be given with extreme care, if at all, to patients with pre-existing impairment of hepatic, renal, or bone-marrow function.

Pharmacokinetics

The absorption of thiotepa from the gastrointestinal tract is incomplete and unreliable; variable absorption also occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. After intravenous doses it is rapidly cleared from plasma, with an elimination half-life of about 2.4 hours. It is extensively metabolised: triethylenephosphoramide (TEPA), the primary metabolite, and some of the other metabolites have cytotoxic activity and are eliminated more slowly than the parent compound. It is excreted in the urine: less than 2% of a dose is reported to be present as unchanged drug or its primary metabolite.

Uses and Administration

Thiotepa is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It has generally been replaced by cyclophosphamide (p.703) or other drugs. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

Instillations of thiotepa may be used in the adjuvant treatment of superficial tumours of the bladder (p.659) and in the control of malignant effusions (p.659). It has been given parenterally in the palliative treatment of various solid tumours, including those of breast and ovary (p.661 and p.670). It has also been given intrathecally to patients with malignant meningeal disease, and has been used, in the form of eye drops, as an adjunct to the surgical removal of pterygium, to prevent recurrence (see p.753).

Thiotepa is given in a variety of dosage schedules. In general, initial doses to suit the individual patient are followed by maintenance doses given at intervals of 1 to 4 weeks. Blood counts are recommended before and during therapy and should continue for at least 3 weeks after stopping. Thiotepa should not be given if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639) and treatment should be stopped if the white cell count falls rapidly. Dosage should be reduced in patients with lesser degrees of leucopenia.

In the treatment of bladder cancer thiotepa in doses up to 60 mg may be instilled in 30 to 60 mL of sterile water or sodium chloride 0.9% into the bladder of a patient previously dehydrated for 8 to 12 hours, and retained if possible for 2 hours. The instillation may be repeated weekly for up to 4 weeks. Similar instillations have been given at intervals of 1 to 2 weeks, for up to 8 instillations in the prophylaxis of recurrence after surgical removal of bladder cancer. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically. For malignant effusions, doses of up to 60 mg of thiotepa in 20 to 60 mL of sterile water may be instilled after aspiration; in the USA the licensed dose is 600 to 800 micrograms/kg, a dose similar to that suggested for injection directly into tumours. Thiotepa for local use may be mixed with solutions of procaine and adrenaline.

Intramuscular and intravenous dosage regimens vary considerably; several regimens have used courses of 15 mg daily for 4 days. In the USA a licensed dose is 300 to 400 micrograms/kg given at 1- to 4-week intervals. A solution containing 1 mg/mL in sterile water has been tried intrathecally in doses of up to 10 mg given on alternate days, for up to 4 doses.

Thiotepa 0.05% in sterile Ringer's solution has been instilled as eye drops every 3 hours for up to 6 weeks after surgical removal of pterygium in order to reduce the likelihood of recurrence.

A dose of 60 mg weekly has been instilled into the urethra for the treatment of condylomata acuminata (genital warts). Topical application of thiotepa has also been used for condylomata.

Thiotepa is under investigation for use as conditioning therapy before haematopoietic stem cell transplantation.

Preparations

BP 2008: Thiotepa Injection;
USP 31: Thiotepa for Injection.

Proprietary Preparations (details are given in Part 3)

Gr.: Ledertepa†; ***Ital.:*** Thioplex; ***Neth.:*** Ledertepa; ***Spain:*** Onco Tiotepa†; ***USA:*** Thioplex.

Tioguanine *(BAN, rINN)*

NSC-752; 6-TG; Thioguanine *(USAN)*; 6-Thioguanine; Tioguaniini; Tioguanin; Tioguanina; Tioguaninum; WR-1141. 2-Aminopurine-6(1*H*)-thione; 2-Amino-6-mercaptopurine; 2-Aminopurine-6-thiol.

Тиогуанин

$C_5H_5N_5S$ = 167.2.

CAS — 154-42-7 (anhydrous tioguanine); 5580-03-0 (tioguanine hemihydrate).

ATC — L01BB03.

ATC Vet — QL01BB03.

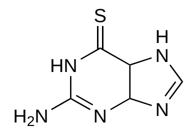

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2008 (Tioguanine). A pale yellow, crystalline powder. Practically insoluble in water, in alcohol, and in chloroform; dissolves in dilute solutions of alkali hydroxides.

USP 31 (Thioguanine). It is anhydrous or contains one-half molecule of water of hydration. A pale yellow, odourless or practically odourless, crystalline powder. Insoluble in water and in chloroform; soluble 1 in 7700 of alcohol; freely soluble in dilute solutions of alkali hydroxides. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Mercaptopurine, p.744.

In some patients, gastrointestinal reactions are reported to be less frequent than with mercaptopurine.

Effects on the blood. For the view that it may be possible to predict those individuals likely to have severe bone-marrow depression with tioguanine based on measurement of the activity of thiopurine methyltransferase or the concentration of tioguanine nucleotide, see under Azathioprine, p.1819.

Effects on the liver. The use of tioguanine has been limited by reports of hepatic veno-occlusive disease attributed to the drug.[1-4] The manufacturer (*GlaxoSmithKline*) has stated that, in most cases, liver toxicity is reversible upon withdrawal of chemotherapy. A comparison with mercaptopurine in the maintenance treatment of children with acute lymphoblastic leukaemia found that of 95 patients who developed veno-occlusive disease, 82 were receiving tioguanine, representing about 11% of all patients assigned to the drug.[5] In addition, although tioguanine was associated with fewer CNS relapses, patients in the tioguanine arm were more likely to develop fatal infections.

Centrilobular hepatic necrosis has also been reported; reports are confounded by the use of high doses of tioguanine, other antineoplastics, oral contraceptives, and chronic alcohol abuse.

1. Gill RA, *et al.* Hepatic veno-occlusive disease caused by 6-thioguanine. *Ann Intern Med* 1982; **96:** 58–60.
2. Krivoy N, *et al.* Reversible hepatic veno-occlusive disease and 6-thioguanine. *Ann Intern Med* 1982; **96:** 788.
3. Kao NL, Rosenblate HJ. 6-Thioguanine therapy for psoriasis causing toxic hepatic venoocclusive disease. *J Am Acad Dermatol* 1993; **28:** 1017–18.
4. Romagosa R, *et al.* Treatment of psoriasis with 6-thioguanine and hepatic venoocclusive disease. *J Am Acad Dermatol* 2002; **47:** 970–2.
5. Vora A, *et al.* Medical Research Council/National Cancer Research Network Childhood Leukaemia Working Party. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368:** 1339–48.

Handling and disposal. For reference to a method for the destruction of tioguanine in wastes, see Mercaptopurine, p.744.

Interactions

Unlike mercaptopurine (p.744), normal doses of tioguanine may be used with allopurinol.

A number of cases of portal hypertension with hepatic nodular regenerative hyperplasia have been reported in patients who received tioguanine with busulfan (see p.691).

It has been suggested that daunorubicin might enhance the hepatotoxicity of tioguanine (see p.709).

Pharmacokinetics

Tioguanine is incompletely and variably absorbed from the gastrointestinal tract; on average about 30% of a dose is absorbed after oral doses. It is rapidly activated in the body by intracellular conversion to its nucleotide, thioguanylic acid and its thioguanosine phosphate derivatives. With repeated doses increasing amounts of the nucleotide are incorporated into DNA. Very little unchanged tioguanine has been detected circulating in the blood but the half-life of the nucleotide in the tissues is prolonged. Tioguanine is inactivated primarily by methylation to aminomethylthiopurine; small amounts are deaminated to thioxanthine, and may go on to be oxidised by xanthine oxidase to thiouric acid, but inactivation is essentially independent of xanthine oxidase and is not affected by inhibition of the enzyme.

It is excreted in the urine almost entirely as metabolites; only negligible amounts of tioguanine have been detected. Tioguanine does not appear to cross the blood-brain barrier to a significant extent; very little is found in CSF after normal clinical doses. It crosses the placenta.

Uses and Administration

Tioguanine is an analogue of the naturally occurring purine, guanine, and is an antineoplastic with actions and uses similar to those of mercaptopurine (p.744). It appears to cause fewer gastrointestinal reactions but cross-resistance exists so that patients who do not respond to one are unlikely to respond to the other.

Tioguanine may be given orally, usually with other antineoplastics, in the induction of remissions in acute myeloid leukaemia (p.652). It has also been used in other malignancies including acute lymphoblastic leukaemia (p.651) and chronic myeloid leukaemia (p.653).

Doses of between 100 and 200 mg/m^2 daily have been given at various stages of treatment for short term cycles; similar doses have been used in children. A dose of 2 mg/kg daily increased after 4 weeks, if there is no response or toxicity allows, to 3 mg/kg daily may be given to adults and children in those rare cases when single agent therapy is considered appropriate.

Blood counts should be made frequently, particularly during induction and when tioguanine is given with other antineoplastics. Therapy should be withdrawn at the first sign of severe bone-marrow depression. Tioguanine is not recommended for long-term continuous therapy because of the high risk of hepatotoxicity (see Effects on the Liver, above).

Tioguanine has been given intravenously as the sodium salt.

Psoriasis. A report of the use of tioguanine, in doses ranging from 20 mg twice weekly to 120 mg daily, in the management of patients with refractory psoriasis.[1] Dramatic improvement occurred in 14 of 18 patients, but a further 2 were unable to tolerate the drug. Myelosuppression was the principal toxic effect and it was suggested that thiopurine methyltransferase activity could be measured as a basis to determine initial dosage and the risk of toxicity. For the conventional management of psoriasis see p.1583.

1. Mason C, Krueger GG. Thioguanine for refractory psoriasis. *J Am Acad Dermatol* 2001; **44:** 67–72.

Preparations

BP 2008: Tioguanine Tablets;
USP 31: Thioguanine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Lanvis; ***Austral.:*** Lanvis; ***Belg.:*** Lanvis; ***Braz.:*** Lanvis; ***Canad.:*** Lanvis; ***Chile:*** Lanvis; ***Cz.:*** Lanvis; ***Fr.:*** Lanvis; ***Gr.:*** Lanvis; ***Hong Kong:*** Lanvis; ***Irl.:*** Lanvis; ***Israel:*** Lanvis; ***Malaysia:*** Lanvis; ***Neth.:*** Lanvis; ***NZ:*** Lanvis; ***Pol.:*** Lanvis; ***S.Afr.:*** Lanvis; ***Singapore:*** Lanvis†; ***Swed.:*** Lanvis; ***Switz.:*** Lanvis; ***Thai.:*** Lanvis; ***UK:*** Lanvis; ***USA:*** Tabloid.

Tipifarnib *(USAN, rINN)*

R-115777; Tipifarnibum. (+)-6-[(*R*)-Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.

Типифарниб

$C_{27}H_{22}Cl_2N_4O$ = 489.4.

CAS — 192185-72-1.

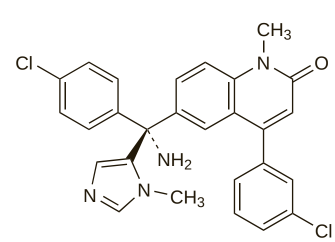

The symbol † denotes a preparation no longer actively marketed

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)

Profile

Tipifarnib is a farnesyl transferase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

◊ References.

1. Zhang S, *et al.* Pharmacokinetics of tipifarnib after oral and intravenous administration in subjects with advanced cancer. *J Clin Pharmacol* 2006; **46:** 1116–27.
2. Siegel-Lakhai WS, *et al.* Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. *J Clin Oncol* 2006; **24:** 4558–64.
3. Perez-Ruixo JJ, *et al.* Exposure-toxicity relationships for tipifarnib in cancer patients. *Br J Clin Pharmacol* 2007; **64:** 219–32.
4. Martinelli G, *et al.* Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. *Clin Adv Hematol Oncol* 2008; **6:** 303–10.

Tirapazamine *(USAN, rINN)*

SR-4233; Tirapazamina; Tirapazaminum; Win-59075. 3-Amino-1,2,4-benzotriazine 1,4-dioxide.

Тирапазамин

$C_7H_6N_4O_2$ = 178.1.

CAS — 27314-97-2.

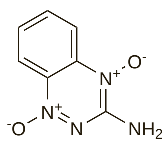

Profile

Tirapazamine is reported to be reduced in hypoxic cells to an active anion that causes DNA strand breaks. It sensitises hypoxic tumour cells to the cytotoxic activity of other drugs. It is under investigation for its cytotoxic actions, alone or with cisplatin or radiotherapy. Adverse effects reported with tirapazamine include nausea and vomiting, diarrhoea, skin rashes, muscle cramps and fatigue; myelosuppression is said to be rare.

◊ Reviews.

1. Gandara DR, *et al.* Tirapazamine: prototype for a novel class of therapeutic agents targeting tumor hypoxia. *Semin Oncol* 2002; **29** (suppl 4): 102–9.

Topotecan Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de topotecán; SKF-104864A; SKFS-104864-A; Topotécane, Chlorhydrate de; Topotecani Hydrochloridum; Topotekaanihydrokloridi; Topotekanhydroklorid. (*S*)-10-Dimethylaminomethyl-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2*b*]quinoline-3,14(4*H*,12*H*)-dione hydrochloride.

Топотекана Гидрохлорид

$C_{23}H_{23}N_3O_5$,HCl = 457.9.

CAS — 123948-87-8 (topotecan); 119413-54-6 (topotecan hydrochloride).

ATC — L01XX17.

ATC Vet — QL01XX17.

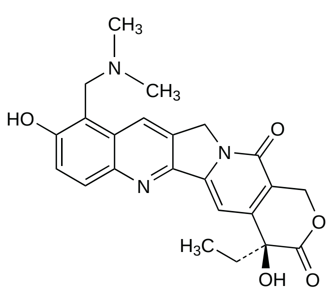

(topotecan)

Incompatibility. Topotecan hydrochloride was found to degrade to 88.7% of its original concentration over 4 hours when mixed with ticarcillin sodium or potassium clavulanate. It was also found to be incompatible with dexamethasone sodium phosphate and fluorouracil.[1] When mixed with mitomycin solution an immediate colour change took place and concentrations of mitomycin fell by 15 to 20% over 4 hours. The pH of the mixtures remained constant at 3.3 to 3.5.

1. Mayron D, Gennaro AR. Stability and compatibility of topotecan hydrochloride with selected drugs. *Am J Health-Syst Pharm* 1999; **56:** 875–81.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641.

Neutropenia is very common with topotecan and is usually dose-limiting. The nadir of white cell count usually occurs about 9 to 12 days after a dose. Febrile neutropenia, sepsis, and neutropenic colitis can occur; fatalities have been reported. Thrombocytopenia, anaemia, and leucopenia also occur commonly. Topotecan should not be given to those patients with pre-existing bone-marrow depression, and blood counts should be monitored regularly. Gastrointestinal disturbances and anorexia are also common with topotecan, and may be severe. Other adverse effects include fatigue and weakness, alopecia, malaise, pruritus, pyrexia, and hyperbilirubinaemia. Hypersensitivity reactions including rashes have been reported; anaphylaxis may occur rarely.

Licensed product information recommends that topotecan should not be given to patients with severe hepatic or renal impairment, due to a lack of data in these patients. Its use in breast feeding is contra-indicated for the same reason. Topotecan has been reported to produce fetal death and malformations in *animals*.

Interactions

For a report of topotecan reducing the clearance of docetaxel, see Antineoplastics, p.711.

Greater myelosuppression is seen when topotecan is used with other cytotoxic drugs, which may require dosage reductions of either drug. However, with platinum drugs, there is a sequence-dependent interaction; giving a platinum drug on the first day of topotecan dosage requires lower doses of each, compared with giving it on the fifth day.

Granulocyte colony-stimulating factor can prolong the duration of neutropenia if given with topotecan, so if used, it should not be started until, 24 hours after topotecan dosage is complete.

Ciclosporin has been reported to increase exposure to topotecan.

Pharmacokinetics

Topotecan is rapidly absorbed after oral doses; peak plasma concentrations occur after about 1 to 2 hours. The oral bioavailability is about 40%. Food does not appreciably affect topotecan pharmacokinetics. Topotecan is widely distributed after intravenous doses. Plasma protein binding is about 35%. The drug undergoes reversible hydrolysis of the lactone ring to the inactive hydroxy acid form; only small amounts are demethylated in the liver. A significant proportion of a dose is excreted in urine. The terminal half-life has been reported to be 2 to 3 hours for the intravenous formulation, and 3 to 6 hours for the oral formulation.

◊ References.

1. Herben VMM, *et al.* Clinical pharmacokinetics of topotecan. *Clin Pharmacokinet* 1996; **31:** 85–102.

Uses and Administration

Like irinotecan (p.738), topotecan is a semisynthetic derivative of the alkaloid camptothecin that exerts its antineoplastic activity by inhibition of topoisomerase I. It is used in the treatment of metastatic carcinoma of the ovary refractory to other therapy (see p.670) and in relapsed small cell lung cancer (p.668) after standard therapy. Topotecan is given with cisplatin in the treatment of metastatic, recurrent, or persistent carcinoma of the cervix (p.663) which is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is also under investigation in the management of myelodysplastic syndromes.

Topotecan is given as the hydrochloride but doses are calculated in terms of the base. Topotecan hydrochloride 1.09 mg is equivalent to about 1 mg of topotecan.

In **ovarian** and **small cell lung cancer**, topotecan hydrochloride may be given *intravenously* in an initial dose equivalent to topotecan 1.5 mg/m^2, infused over 30 minutes, on days 1 to 5 of a 21-day course. A minimum of 4 courses should be given, in the absence of tumour progression, and provided that blood counts and haemoglobin have recovered adequately (see also Bone-marrow Depression, p.639). If severe neutropenia occurs in any course the dose in the subsequent courses may be reduced by 250 micrograms/m^2, or a granulocyte colony-stimulating factor may be given from day 6 of the course, 24 hours after topotecan dosage is complete. If severe toxicity recurs once the dose has been reduced to 1 mg/m^2 withdrawal of topotecan may be required. Dosage should also be reduced after severe thrombocytopenia and in patients with renal impairment (see below).

Topotecan may also be given *orally* for small cell lung cancer. The recommended dose is 2.3 mg/m^2 once daily for 5 consecutive days, repeated every 21 days. If neutropenia occurs, or if the platelet count falls below 25 000 cells/mm^3, or for patients with severe diarrhoea, the daily dose should be reduced by 400 micrograms/m^2 for subsequent courses.

In **cervical cancer**, topotecan is given in an intravenous dose of 750 micrograms/m^2, infused over 30 minutes, on days 1, 2, and 3 of a 21-day course; cisplatin 50 mg/m^2 is given by intravenous infusion after topotecan on day 1. Dosage adjustments for subsequent courses are specific for each drug; for cisplatin, see p.700. If severe febrile neutropenia occurs, or if the platelet count falls below 10 000 cells/mm^3, the topotecan dose should be reduced to 600 micrograms/m^2. Alternatively, in the event of severe febrile neutropenia, granulocyte colony-stimulating factor may be given from day 4 of the course, 24 hours after completion of the topotecan infusion; if febrile neutropenia recurs despite this, topotecan dosage should be further reduced to 450 micrograms/m^2 for subsequent courses.

◊ References.

1. Rocha Lima CM, Chiappori A. Treatment of relapsed small-cell lung cancer—a focus on the evolving role of topotecan. *Lung Cancer* 2003; **40:** 229–36.
2. Armstrong DK. Topotecan dosing guidelines in ovarian cancer: reduction and management of hematologic toxicity. *Oncologist* 2004; **9:** 33–42.
3. Ahmad T, Gore M. Review of the use of topotecan in ovarian carcinoma. *Expert Opin Pharmacother* 2004; **5:** 2333–40.
4. Long HJ, *et al.* Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005; **23:** 4626–33.
5. Randall-Whitis LM, Monk BJ. Topotecan in the management of cervical cancer. *Expert Opin Pharmacother* 2007; **8:** 227–36.
6. Eckardt JR, *et al.* Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; **25:** 2086–92. Correction. *ibid.*; 3387.
7. Nicum SJ, O'Brien ME. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; **7:** 795–801.
8. O'Brien M, *et al.* Recent advances with topotecan in the treatment of lung cancer. *Oncologist* 2007; **12:** 1194–204.
9. Ackermann S, *et al.* Topotecan in cervical cancer. *Int J Gynecol Cancer* 2007; **17:** 1215–23.
10. Peng LH, *et al.* Topotecan for ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

Administration in renal impairment. Licensed product information for *intravenous* topotecan recommends the following for patients with **ovarian or small cell lung cancer** according to creatinine clearance (CC):

- mild renal impairment (CC 40 to 60 mL/minute): no dosage adjustment
- moderate renal impairment (CC 20 to 39 mL/minute): 0.75 mg/m^2 daily for 5 consecutive days

For patients with small cell lung cancer given *oral* topotecan, the following is suggested:

- mild renal impairment (CC 50 to 80 mL/minute): no dosage adjustment
- moderate renal impairment (CC 30 to 49 mL/minute): 1.8 mg/m^2 once daily for 5 consecutive days

Data are insufficient to make dose recommendations in patients with severe renal impairment.

In patients with **cervical cancer**, treatment with topotecan and cisplatin should only be started in those with a serum creatinine of 1.5 mg or less per 100 mL.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Asotecan; Hycamtin; Potekam; Tisogen; Topestin†; Topokebir; Topotag†; TPT†; ***Austral.:*** Hycamtin; ***Austria:*** Hycamtin; ***Belg.:*** Hycamtin; ***Braz.:*** Hycamtin; ***Canad.:*** Hycamtin; ***Chile:*** Hycamtin; ***Cz.:*** Hycamtin; ***Denm.:*** Hycamtin; ***Fin.:*** Hycamtin; ***Fr.:*** Hycamtin; ***Ger.:*** Hycamtin; ***Gr.:*** Hycamtin; ***Hong Kong:*** Hycamtin; ***Hung.:*** Hycamtin; Viatopin; ***India:*** Topotel; ***Irl.:*** Hycamtin; ***Israel:*** Hycamtin; ***Ital.:*** Hycamtin; ***Mex.:*** Toranex;

Neth.: Hycamtin; ***Norw.:*** Hycamtin; ***Pol.:*** Hycamtin; ***Port.:*** Hycamtin; ***Rus.:*** Hycamtin (Гикамтин); ***S.Afr.:*** Hycamtin; ***Singapore:*** Hycamtin; ***Spain:*** Hycamtin; ***Swed.:*** Hycamtin; ***Switz.:*** Hycamtin; ***Thai.:*** Hycamtin; Topotel; ***Turk.:*** Hycamptin; ***UK:*** Hycamtin; ***USA:*** Hycamtin; ***Venez.:*** Hycamtin†.

Toremifene Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de toremifeno; FC-1157a; Toremifen Sitrat; Torémifène, Citrate de; Toremifeni Citras. 2-{*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy}-*N*,*N*-dimethylethylamine citrate.

Торемифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7 = 598.1.$

CAS — 89778-26-7 (toremifene); 89778-27-8 (toremifene citrate).

ATC — L02BA02.

ATC Vet — QL02BA02.

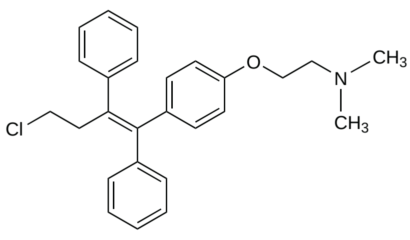

(toremifene)

Adverse Effects and Precautions

As for Tamoxifen Citrate, p.772.

Use of toremifene is contra-indicated in patients with pre-existing endometrial hyperplasia, or in those with severe thromboembolic disease or severe hepatic impairment. Toremifene must be used with caution in patients with uncompensated heart failure or severe angina. Patients with bone metastases should be monitored for signs and symptoms of hypercalcaemia.

Interactions

Toremifene is metabolised by cytochrome P450 isoenzyme CYP3A4, and potent enzyme-inducing drugs such as phenytoin, phenobarbital and carbamazepine, might be expected to increase toremifene metabolism, thereby lowering the serum concentration. Conversely, azole antifungals and macrolide antibacterials may inhibit toremifene metabolism by inhibiting the isoenzyme.

Use with drugs that decrease renal calcium excretion, such as thiazide diuretics, may increase the incidence of hypercalcaemia. Use with coumarin anticoagulants should be avoided as there is a risk of increased bleeding time.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of toremifene in 9 subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Pharmacokinetics

Toremifene citrate is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations of toremifene within 3 hours. Plasma concentration declines biexponentially; the mean distribution half-life is about 4 hours and the elimination half-life is about 5 days. It is extensively bound to plasma proteins, mainly albumin. Toremifene is metabolised principally by the cytochrome P450 isoenzyme CYP3A4; the main metabolite is N-demethyltoremifene, which is reported to have anti-oestrogenic activity but with weak anti-tumour activity. It undergoes enterohepatic circulation and is eliminated mainly in the faeces as metabolites. About 10% is excreted in the urine.

◊ Reviews.

1. Taras TL, *et al.* Clinical pharmacokinetics of toremifene. *Clin Pharmacokinet* 2000; **39:** 327–34.

Uses and Administration

Toremifene is an anti-oestrogen with properties similar to those of tamoxifen (p.775). It is used in the treatment of metastatic breast cancer (p.661) in postmenopausal women with oestrogen-receptor positive tumours. It is also being investigated for the treatment of lung tumours and for the management of prostate cancer.

Toremifene is given orally as the citrate, but doses are calculated in terms of the base; 88.4 mg of toremifene citrate is equivalent to about 60 mg of toremifene. A dose of toremifene 60 mg once daily is used.

◊ References.

1. Wiseman LR, Goa KL. Toremifene: a review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* 1997; **54:** 141–60.
2. Anonymous. Toremifene and letrozole for advanced breast cancer. *Med Lett Drugs Ther* 1998; **40:** 43–5.
3. Holli K. Adjuvant trials of toremifene vs tamoxifen: the European experience. *Oncology (Huntingt)* 1998; **12** (suppl 5): 23–7.
4. Holli K, *et al.* Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000; **18:** 3487–94.
5. Taneja SS, *et al.* Toremifene—a promising therapy for the prevention of prostate cancer and complications of androgen deprivation therapy. *Expert Opin Invest Drugs* 2006; **15:** 293–305.
6. Smith MR, *et al.* Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. *J Urol (Baltimore)* 2008; **179:** 152–5.
7. Smith MR, *et al.* Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. *J Clin Oncol* 2008; **26:** 1824–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Fareston†; ***Austral.:*** Fareston; ***Austria:*** Fareston; ***Belg.:*** Fareston; ***Cz.:*** Fareston; ***Fin.:*** Fareston; ***Fr.:*** Fareston; ***Ger.:*** Fareston; ***Gr.:*** Fareston; ***Hung.:*** Fareston; ***Irl.:*** Fareston; ***Ital.:*** Fareston; ***Mex.:*** Fareston; ***Neth.:*** Fareston; ***NZ:*** Fareston; ***Port.:*** Fareston; ***Rus.:*** Fareston (Фарестон); ***S.Afr.:*** Fareston; ***Spain:*** Fareston; ***Swed.:*** Fareston; ***Switz.:*** Fareston; ***Thai.:*** Fareston; ***Turk.:*** Fareston; ***UK:*** Fareston; ***USA:*** Fareston.

Tositumomab *(rINN)*

B-1; Tositumomabum. Immunoglobulin G2a anti-(human antigen CD 20) (mouse monoclonal clone B1R1 γ2a-chain), disulfide with mouse monoclonal clone B1R1 λ_x-chain, dimer.

Тоситумомаб

CAS — 192391-48-3.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Infusion reactions suggestive of a cytokine release syndrome, and other hypersensitivity reactions including anaphylaxis, have been reported with tositumomab. Prolonged and severe neutropenia, thrombocytopenia, and anaemia occur commonly; full blood counts should be monitored weekly for up to 12 weeks. Other adverse effects include gastrointestinal disturbances, dehydration, abdominal pain, pleural effusion, and increased susceptibility to infection. Delayed adverse effects such as the development of secondary malignancies, leukaemia, or myelodysplastic syndrome may occur. Patients receiving the radiolabelled regimen may be susceptible to hypothyroidism and pretreatment with thyroid blocking drugs is recommended (see Uses and Administration, below); levels of thyroid-stimulating hormone should be measured before treatment and annually thereafter.

Uses and Administration

Tositumomab is an anti-B1 monoclonal antibody that is directed against the CD20 antigen found on the surface of B lymphocytes. It is radiolabelled with iodine-131 (p.2054) for the treatment of patients with CD20 antigen-expressing, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma (p.656), and including those patients who have disease refractory to rituximab.

The regimen consists of a dosimetric step, followed 7 to 14 days later by a therapeutic step. The dosimetric step consists of 450 mg of tositumomab given intravenously in 50 mL sodium chloride 0.9% over 60 minutes. Tositumomab 35 mg radiolabelled with iodine-131 is then given intravenously in 30 mL sodium chloride 0.9% over 20 minutes. This is followed by whole body imaging to determine whether biodistribution is acceptable, and to allow calculation of the therapeutic dose of radiolabelled tositumomab. In the therapeutic step, tositumomab 450 mg is given again, and followed by the calculated dose of radiolabelled tositumomab.

The rate of infusion may be halved for mild to moderate infusional toxicity, and stopped if this is severe; the infusions may be restarted at half the rate once toxicity resolves. Patients are pretreated with thyroid protective agents at least 24 hours before the first radiolabelled dose of tositumomab; treatment is continued until 2 weeks after the radiolabelled therapeutic dose. Analgesics and antihistamines are also given by mouth 30 minutes before doses of tositumomab.

◊ References.

1. Kaminski MS, *et al.* Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; **19:** 3918–28.
2. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol* 2003; **30** (suppl): 31–8.
3. Anonymous. Iodine-131 tositumomab (Bexxar) for treatment of lymphoma. *Med Lett Drugs Ther* 2003; **45:** 86–7.
4. Friedberg JW, Fisher RI. Iodine-131 tositumomab (Bexxar): radioimmunoconjugate therapy for indolent and transformed B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2004; **4:** 18–26.
5. Davies AJ, *et al.* Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22:** 1469–79.
6. Vose JM. Bexxar : novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. *Oncologist* 2004; **9:** 160–72.
7. Horning SJ, *et al.* Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; **23:** 712–19.
8. Kaminski MS, *et al.* I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; **352:** 441–9.
9. Fisher RI, *et al.* Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol* 2005; **23:** 7565–73.
10. Dosik AD, *et al.* Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer* 2005; **106:** 616–22.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Bexxar.

Trabectedin *(USAN, rINN)*

Ecteinascidin-743; ET-743; NSC-648766; Trabectedina; Trabectédine; Trabectedinum. (1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6′,8,14-Trihydroxy-7′,9-dimethoxy-4,10,23-trimethyl-19-oxo-3′,4′,6,7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6a*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1′(2′*H*)-isoquinolin]-5-yl acetate.

Трабектедин

$C_{39}H_{43}N_3O_{11}S = 761.8.$

CAS — 114899-77-3.

ATC — L01CX01.

ATC Vet — QL01CX01.

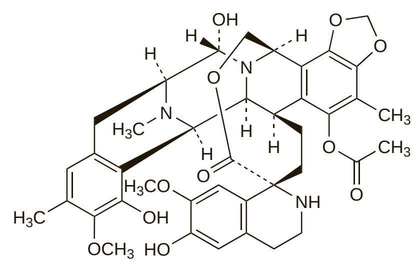

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia, thrombocytopenia, anaemia, and leucopenia are very common with trabectedin; febrile neutropenia often occurs. Full blood counts should be performed at baseline, weekly for the first 2 cycles, and then once between cycles thereafter. Dose reductions may be needed in those with haematological toxicity. Hepatobiliary disorders are also very common, and include hyperbilirubinaemia and alterations in liver function tests, which are mostly transient. Patients with liver disease should be closely monitored, and trabectedin should not be given to those with hyperbilirubinaemia.

Other very common adverse effects include gastrointestinal disturbances, anorexia, headache, and fatigue. Antiemetic prophylaxis with dexamethasone should be given to all patients. Peripheral sensory neuropathy, paraesthesia, dysgeusia, dizziness, pyrexia, and oedema are common, as are dyspnoea, cough, alopecia, myalgia, arthralgia, dehydration, hypokalaemia, hypotension, and flushing. Injection site reactions can occur, and the use of a central line is recommended.

Deaths associated with trabectedin treatment often involved a combination of adverse events including pancytopenia, febrile neutropenia, and in some cases sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Trabectedin may cause serious birth defects if given during pregnancy, although data are limited. Women and men of fertile age are advised to use effective contraception during treatment, and for 3 and 5 months, respectively, after stopping treatment. Breast feeding is contra-indicated due to lack of data, and should be avoided for the duration of treatment and for 3 months after therapy is stopped.

Interactions

Trabectedin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme (such as azole antifungals, macrolide antibacterials, or ritonavir) may increase blood concentrations of trabectedin. Equally, inducers of CYP3A4 (such as rifampicin, phenobarbital, and St John's wort) may decrease systemic exposure to trabectedin. Trabectedin is a substrate of P-glycoprotein, and use with P-glycoprotein inhibitors (such as ciclosporin and verapamil) may alter trabectedin pharmacokinetics, although the clinical significance of this interaction has not been established. Alcohol and other hepatotoxic drugs should be avoided during trabectedin treatment due to possible potentiation of hepatotoxicity. Use with live attenuated vaccines is not recommended, and use with yellow fever vaccine is specifically contra-indicated. For the effect of trabectedin on phenytoin, see p.499.

Pharmacokinetics

Trabectedin is extensively distributed in the tissues. Plasma protein binding is about 94 to 98%. It is metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4. The terminal half-life is about 180 hours. Trabectedin is excreted mainly in the faeces, with a small amount in the urine, of which less than 1% is unchanged drug.

◊ References.

1. Beumer JH, *et al.* Metabolism of trabectedin (ET-743, Yondelis) in patients with advanced cancer. *Cancer Chemother Pharmacol* 2007; **59:** 825–37.
2. Perez-Ruixo JJ, *et al.* Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet* 2007; **46:** 867–84.

Uses and Administration

Trabectedin is a novel DNA-binding agent derived from the marine tunicate, *Ecteinascidia turbinata*. It is used for the treatment of advanced soft-tissue sarcomas, after failure of anthracyclines or ifosfamide, or in patients for whom these drugs are unsuitable. The recommended dose is 1.5 mg/m^2, given as an intravenous infusion over 24 hours. The dose can be repeated at 3-week intervals as long as clinical benefit persists, provided haematological, hepatic, and renal function parameters are met. If these baseline criteria are not met, treatment must be delayed for up to 3 weeks, until the criteria are met. If haematological toxicity or hepatotoxicity occurs at any time between cycles, the dose for subsequent cycles must be reduced to 1.2 mg/m^2. Once a dose has been reduced, dose escalation for subsequent cycles is not recommended. If any toxicities recur in subsequent cycles, a further dose reduction to 1 mg/m^2 may be made; thereafter, if further toxicity occurs, treatment should be stopped. If trabectedin is given via a central venous line, which is the preferred method, the dose should be diluted in at least 500 mL of sodium chloride 0.9% or glucose 5%. If central access is unfeasible, and it is given peripherally, the dose should be diluted in at least 1 litre of diluent. Dexamethasone 20 mg is given intravenously 30 minutes before treatment with trabectedin, to reduce nausea and hepatotoxicity.

Trabectedin is also under investigation for the treatment of ovarian cancer.

◊ References.

1. van Kesteren C, *et al.* Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. *Anticancer Drugs* 2003; **14:** 487–502.
2. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Invest Drugs* 2003; **12:** 1843–53.
3. Beumer JH, *et al.* Hepatotoxicity and metabolism of trabectedin: a literature review. *Pharmacol Res* 2005; **51:** 391–8.
4. Fayette J, *et al.* ET-743: a novel agent with activity in soft tissue sarcomas. *Oncologist* 2005; **10:** 827–32.
5. Schöffski P, *et al.* Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. *Future Oncol* 2007; **3:** 381–92.
6. Carter NJ, Keam SJ. Trabectedin : a review of its use in the management of soft tissue sarcoma and ovarian cancer. *Drugs* 2007; **67:** 2257–76.
7. Schöffski P, *et al.* Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. *Expert Opin Pharmacother* 2008; **9:** 1609–18.

Administration in hepatic impairment. Licensed product information states that there are no studies of trabectedin in hepatic impairment and data are unavailable to recommend doses in these patients. However, since systemic exposure is likely to be increased in these patients, thus increasing the risk of hepatotoxicity, caution is advised and dose adjustments may be needed. Trabectedin should not be given to patients with hyperbilirubinaemia.

Administration in renal impairment. Licensed product information for trabectedin states that no dose adjustments are needed in patients with mild or moderate renal impairment, but that trabectedin should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) as no data are available for this population.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Yondelis; ***Fr.:*** Yondelis.

Trastuzumab *(BAN, rINN)*

HER-2 Monoclonal Antibody; rhuMAb HER2; Trastutsumabi; Trastuzumabum. Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ_1-chain anti-human p185$^{c\text{-}erbB2}$ receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer.

Трастузумаб

CAS — 180288-69-1.
ATC — L01XC03.
ATC Vet — QL01XC03.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639 and p.641.

Trastuzumab has been associated with fatal hypersensitivity reactions, infusion reactions characteristic of a cytokine release syndrome, and pulmonary events including acute respiratory distress syndrome. These usually occur after the first dose of trastuzumab and are more common in patients with reduced lung function. Use of trastuzumab is contra-indicated in patients with severe dyspnoea at rest. Cardiac dysfunction and congestive heart failure may also occur and left ventricular function should be monitored before and during therapy. The risk of cardiotoxicity is increased if trastuzumab is given with anthracyclines or cyclophosphamide (see below).

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common, as are chills, fever, headache, arthralgia, myalgia, and rashes. Asthenia, chest pain, and renal or liver disorders have also been reported.

Effects on the heart. Cardiac events related to the use of trastuzumab include asymptomatic decreases in left ventricular ejection fraction, tachycardia, palpitations, dyspnoea, and chest pain. Congestive heart failure may develop.[1]

In a pivotal comparative trial,[2] an increased incidence of cardiac adverse events prompted a retrospective analysis. This independent review identified cardiac dysfunction in 27% of patients receiving trastuzumab, an anthracycline, and cyclophosphamide, compared with only 8% receiving an anthracycline and cyclophosphamide. In patients given trastuzumab and paclitaxel, 13% developed cardiac dysfunction compared with 1% of patients given paclitaxel alone, although all these patients had previously received an anthracycline. The incidence of severe dysfunction was highest in those patients receiving trastuzumab, an anthracycline, and cyclophosphamide.

Further analysis[3] of this and 6 other studies found that, in a total of 1219 patients, 10 heart-related deaths had been reported, and that 9 of these were patients who had received trastuzumab. However, the risk of developing cardiotoxicity was less when trastuzumab was given alone than when given with anthracyclines. Advanced age was found to be a significant risk factor, whereas giving trastuzumab and the anthracycline at different times appeared to decrease the rate of cardiotoxicity.

Licensed product information for trastuzumab warns that patients who have previously received anthracyclines may also be at increased risk of cardiotoxicity with trastuzumab treatment. Furthermore, because the half-life of trastuzumab is about 28.5 days, trastuzumab may persist in the circulation for up to 24 weeks, and patients given anthracyclines after stopping trastuzumab may still be at increased risk of cardiotoxicity. If anthracyclines are used, the patient's cardiac function should be carefully monitored. Patients with pre-existing cardiovascular disease should also be treated with caution.

However, the majority of patients who develop congestive heart failure improve with standard treatment, including the use of ACE inhibitors, beta blockers, cardiac glycosides and diuretics.[1,4,5] Cardiotoxicity may improve even in those patients who continue with trastuzumab therapy.[4,5] A small retrospective study found that cardiotoxicity appeared to be largely reversible once trastuzumab was stopped, and that therapy might even be restarted. Findings from myocardial biopsy suggested that, while the mechanism of cardiotoxicity with trastuzumab remained uncertain, it differed from that with anthracyclines.[6] A retrospective review[7] of 173 patients with metastatic breast cancer who were treated with trastuzumab-based therapy for at least 1 year found that 28% of patients experienced a cardiac event; 10.9% had grade 3 cardiotoxicity, including 1 cardiac-related death. However, cardiotoxicity, whether symptomatic or not, was generally reversible, with or without specific therapy, suggesting that maintenance or re-treatment with trastuzumab may be feasible in those patients for whom no alternative therapeutic options are available.

The pathogenesis of the cardiotoxicity associated with trastuzumab is under investigation. A small study[8] showed specific uptake of a pretreatment tracer dose of radiolabelled trastuzumab into the myocardium of patients who subsequently developed cardiac adverse events. The human epidermal growth factor receptor 2 (HER2) gene appears essential for normal cardiac development; studies in *animals* suggest that trastuzumab may interfere with HER2 signalling and function in cardiomyocytes, and that loss of HER2 increases sensitivity to anthracycline toxicity.[4,5]

Analysis of symptomatic heart failure with trastuzumab suggests a lower incidence than that previously reported with retrospective data; however, this may be due to over-reported events in pivotal trials and the more recent exclusion of patients at risk of cardiotoxicity.[4] More recent analysis from a large study of patients given adjuvant chemotherapy with or without trastuzumab found a cumulative incidence of cardiac events (defined as confirmed New York Heart Association class III or IV cardiac dysfunction, or cardiac death) with trastuzumab of 4.1% at 3 years. The difference in cumulative incidence was 3.3% when compared with the control group.[9] Some have commented[10] that follow-up was relatively short and that long-term data on cardiac risks with trastuzumab are lacking. Reviews[11,12] have concluded that trastuzumab-induced cardiotoxicity is not dose-related and is generally reversible once the drug is stopped. However, others[13] have challenged the concept that cardiotoxicity is reversible, and the need for longer-term follow-up data, especially with respect to asymptomatic left ventricular dysfunction, has been emphasised.[11,13]

1. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; **95:** 1592–1600.
2. Slamon DJ, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
3. Seidman A, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20:** 1215–21.
4. Suter TM, *et al.* Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004; **13:** 173–83.
5. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22:** 322–9.
6. Ewer MS, *et al.* Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23:** 7820–6.
7. Guarneri V, *et al.* Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 2006; **24:** 4107–15.
8. Behr TM, *et al.* Trastuzumab and breast cancer. *N Engl J Med* 2001; **345:** 995–6.
9. Tan-Chiu E, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23:** 7811–19.
10. Levine MN. Trastuzumab cardiac side effects: only time will tell. *J Clin Oncol* 2005; **23:** 7775–6.
11. Sengupta PP, *et al.* Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc* 2008; **83:** 197–203.
12. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Safety* 2008; **31:** 459–67.
13. Telli ML, *et al.* Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007; **25:** 3525–33.

Metastatic disease. There is some suggestion that patients treated with trastuzumab for metastatic breast cancer have a higher incidence of cerebral metastases. This may reflect increased survival of patients given trastuzumab, and the lack of CNS penetration by the drug,[1,2] or tumours overexpressing human epidermal growth receptor 2 (HER2) may be more likely to metastasise to the CNS.[2] A comparison[1] of trastuzumab-treated patients with a control group found that, although trastuzumab reduced the incidence of bone metastases, the development of brain metastases was similar in both groups. However, trastuzumab improved overall survival in all patients developing metastases, including those with brain metastases. A retrospective review[2] found an association between the development of cerebral metastases and both hormone-receptor negative status and the presence of visceral disease.

1. Lower EE, *et al.* Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival. *Clin Breast Cancer* 2003; **4:** 114–19.
2. Clayton AJ, *et al.* Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004; **91:** 639–43.

Peripheral vascular toxicity. A woman developed a painless prominence of the veins in her left arm and hand 3 days after receiving trastuzumab via a left hand vein. The veins were thickened and rope-like on palpation but there was no tenderness, oedema, or skin changes; there was no evidence of thrombus. She had previously received intravenous chemotherapy into left hand veins without sequelae. Biopsy suggested venous wall injury. Cardiac function was preserved, suggesting the mechanism of vascular injury was unrelated to cardiac dysfunction. Trastuzumab therapy was stopped permanently and her symptoms gradually resolved over the course of a year.[1]

1. Pansegrau GK, *et al.* Trastuzumab-associated peripheral vascular toxicity. *J Clin Oncol* 2007; **25:** 1438–40.

Pregnancy. A 28-year-old woman who had been given trastuzumab 6 mg/kg every 3 weeks was found to be pregnant after 5 months of therapy. Trastuzumab was stopped at about 20 weeks of gestation. Ultrasound study of the fetus at 23 weeks indicated no amniotic fluid. On observation, the anhydramnios slowly resolved. No further complications occurred and a healthy female infant was induced at 37⁄ weeks; amniotic fluid was clear at delivery.[1] Similarly, 2 cycles of trastuzumab and paclitaxel were given to a 38-year-old pregnant woman between 26 and 32 weeks of gestation: fetal abdominal circumference stopped increasing and the volume of amniotic fluid decreased to almost total anhydramnios. There was also evidence of fetal renal failure. Fetal lung maturation was induced and a caesarean section done at about 32 weeks of gestation. The infant showed signs of bacterial sepsis with hypotension, transient renal failure, and respiratory failure necessitating mechanical ventilation. After antibacterial therapy, blood pressure normalised, ventilation was ended, and diuresis was deemed adequate. He was discharged at age 6 weeks in healthy condition and development at 12 weeks of age was deemed to be normal.[2] In another report, a 30-year-old patient conceived 3 days after her second cycle of trastuzumab; no further therapy was given. Her pregnancy went successfully to term and a healthy female was born with no sequelae.[3] Low amniotic fluid volume was seen in another case of trastuzumab use during pregnancy; at 5 years of age, the child was reported to have normal growth and development.[4]

1. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol* 2005; **105:** 642–3.
2. Bader AA, *et al.* Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007; **8:** 79–81.
3. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. *J Clin Oncol* 2006; **24:** 321–2.
4. Pant S, *et al.* Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 2008; **26:** 1567–9.

Interactions

For reports of trastuzumab enhancing the effect of warfarin, see p.1429.

Pharmacokinetics

The half-life of trastuzumab varies considerably: it has been reported to be 1.7 days after a 10-mg dose, 12 days after a 500-mg dose, and 5.8 days after the recommended dose (4 mg/kg followed by 2 mg/kg weekly); 28.5 days has also been reported after the recommended dose. Detectable concentrations of the cell surface protein of the HER2 receptor (shed antigen) have been found in patients' serum; those patients with higher baseline values for shed antigen had lower serum trough concentrations of trastuzumab, although target trastuzumab concentrations were still achieved after weekly dosing, and no relationship to clinical response was observed.

Uses and Administration

Trastuzumab is a humanised monoclonal antibody directed against a cell surface protein produced by the human epidermal growth factor receptor 2 (HER2) gene. HER2 protein is overexpressed in about one-third of all breast cancers. Trastuzumab is used in the treatment of breast cancer (p.661) with such characteristics.

The recommended dose in **metastatic** breast cancer, alone, with an aromatase inhibitor, or followed by a taxane, is 4 mg/kg initially, by intravenous infusion in 250 mL of sodium chloride 0.9% over 90 minutes. This may be followed by 2 mg/kg over 30 minutes at weekly intervals.

Trastuzumab is also given in **early** breast cancer after surgery, chemotherapy, and radiotherapy. There are 2 recommended schedules, with trastuzumab given either weekly or every 3 weeks.

- The recommended dose for the 3-weekly schedule is 8 mg/kg initially, by intravenous infusion in 250 mL sodium chloride 0.9% over 90 minutes. This may be followed by 6 mg/kg at 3-weekly intervals. Treatment is continued for 1 year or until disease recurrence.

  If the patient misses a dose of trastuzumab by 1 week or less, then the usual dose of 6 mg/kg should be given as soon as possible, without waiting until the next planned cycle. Subsequent cycles are then given according to the previous schedule.

  If the dose is missed by more than 1 week, a re-loading dose of trastuzumab 8 mg/kg should be given, and subsequent maintenance doses of 6 mg/kg should then be given every 3 weeks thereafter.
- In the weekly schedule, trastuzumab is given with paclitaxel after 4 cycles of the AC regimen (doxorubicin and cyclophosphamide). It is given at an initial loading dose of 4 mg/kg followed by 2 mg/kg weekly thereafter for 1 year; paclitaxel is given either weekly or 3-weekly for a total of 12 weeks.

HER2 may also be overexpressed in other epithelial cancers, and trastuzumab is under investigation for use in non-small cell lung cancer, pancreatic, prostate, and ovarian malignancies.

◊ References.

1. Spigel DR, Burstein HJ. Trastuzumab regimens for HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer* 2003; **4:** 329–37.
2. Ferrone M, Motl SE. Trastuzumab for the treatment of non-small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1904–8.
3. Langer CJ, *et al.* Trastuzumab in the treatment of advanced non—small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group Study 2598. *J Clin Oncol* 2004; **22:** 1180–7.
4. Tripathy D, *et al.* Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 2004; **22:** 1063–70.
5. Papazisis KT, *et al.* Safety and efficacy of the combination of trastuzumab with docetaxel for HER2-positive women with advanced breast cancer: a review of the existing clinical trials and results of the expanded access programme in the UK. *Int J Clin Pract* 2004; **58:** 581–6.
6. Jones RL, Smith IE. Efficacy and safety of trastuzumab. *Expert Opin Drug Saf* 2004; **3:** 317–27.
7. Piccart-Gebhart MJ, *et al.* HERA Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1659–72.
8. Romond EH, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.
9. Kabe KL, Kolesar JM. Role of trastuzumab in adjuvant therapy for locally invasive breast cancer. *Am J Health-Syst Pharm* 2006; **63:** 527–33.
10. Plosker GL, Keam SJ. Trastuzumab: a review of its use in the management of HER2-positive metastatic and early-stage breast cancer. *Drugs* 2006; **66:** 449–75.
11. Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369:** 29–36.
12. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007; **357:** 39–51.
13. Orman JS, Perry CM. Trastuzumab: in HER2 and hormone receptor co-positive metastatic breast cancer. *Drugs* 2007; **67:** 2781–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Herceptin; ***Austral.:*** Herceptin; ***Belg.:*** Herceptin; ***Braz.:*** Herceptin; ***Canad.:*** Herceptin; ***Chile:*** Herceptin; ***Cz.:*** Herceptin; ***Denm.:*** Herceptin; ***Fin.:*** Herceptin; ***Fr.:*** Herceptin; ***Ger.:*** Herceptin; ***Gr.:*** Herceptin; ***Hong Kong:*** Herceptin; ***Hung.:*** Herceptin; ***Indon.:*** Herceptin; ***Irl.:*** Herceptin; ***Israel:*** Herceptin; ***Ital.:*** Herceptin; ***Jpn:*** Herceptin; ***Malaysia:*** Herceptin; ***Mex.:*** Herceptin; ***Neth.:*** Herceptin; ***Norw.:*** Herceptin; ***NZ:*** Herceptin; ***Philipp.:*** Herceptin; ***Pol.:*** Herceptin; ***Port.:*** Herceptin; ***Rus.:*** Herceptin (Герцептин); ***S.Afr.:*** Herceptin; ***Singapore:*** Herceptin; ***Spain:*** Herceptin; ***Swed.:*** Herceptin; ***Switz.:*** Herceptin; ***Thai.:*** Herceptin; ***Turk.:*** Herceptin; ***UK:*** Herceptin; ***USA:*** Herceptin; ***Venez.:*** Herceptin.

Treosulfan *(BAN, rINN)*

Dihydroxybusulphan; NSC-39069; Treosulfaani; Tréosulfan; Treosulfano; Treosulfanum. L-Threitol 1,4-dimethanesulphonate.

Треосульфан

$C_6H_{14}O_8S_2$ = 278.3.
CAS — 299-75-2.
ATC — L01AB02.
ATC Vet — QL01AB02.

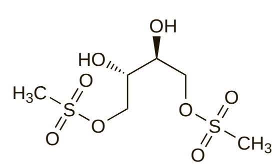

Profile

Treosulfan is an antineoplastic agent related to busulfan (p.690), which is reported to act by alkylation after conversion *in vivo* to epoxide compounds. It is used palliatively or as an adjunct to surgery mainly in the treatment of ovarian cancer (p.670).

Treosulfan 1 g daily is licensed for oral use in 4 divided doses for 2 or 4 weeks followed by the same period without treatment. Alternatively 1.5 g daily in 3 divided doses may be given for 1 week, followed by 3 weeks without therapy. The cycle is then repeated, the dose being adjusted if necessary according to the effect on bone marrow. Doses of 3 to 8 g/m^2 may instead be given intravenously every 1 to 3 weeks. Doses larger than 3 g/m^2 should be given by infusion at a rate of 3 g/m^2 every 5 to 10 minutes. Doses up to 1.5 g/m^2 have been given intraperitoneally. Lower doses should be used if treatment with other antineoplastic drugs or radiotherapy is being given.

Regular blood counts should be made and treatment should be interrupted if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639). Because bone-marrow depression may be cumulative the interval between blood counts should be reduced after the second course of treatment with treosulfan.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Ovastat.

Trofosfamide *(rINN)*

A-4828; NSC-109723; Trilophosphamide; Trofosfamid; Trofosfamida; Trofosfamidi; Trofosfamidum; Trophosphamide; Z-4828. 3-(2-Chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine-2-oxide.

Трофосфамид

$C_9H_{18}Cl_3N_2O_2P$ = 323.6.
CAS — 22089-22-1.
ATC — L01AA07.
ATC Vet — QL01AA07.

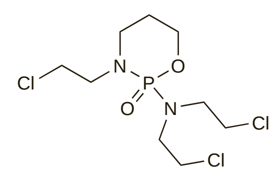

Profile

Trofosfamide is a derivative of cyclophosphamide (p.702) and has the same general properties. It is used in the treatment of malignant disorders in usual initial oral doses of 300 to 400 mg daily. Doses of 50 to 150 mg daily have been given for maintenance therapy.

Uses. References[1-10] to the use of trofosfamide, including its investigational use with pioglitazone and rofecoxib as antiangiogenic therapy.[4,5,7]

1. Gunsilius E, *et al.* Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. *Cancer Invest* 2001; **19:** 808–11.
2. Reichardt P, *et al.* Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas: results of a retrospective analysis. *Onkologie* 2002; **25:** 541–6.
3. Andersson PO, *et al.* Trofosfamide as salvage therapy for anaplastic large cell lymphoma relapsing after high-dose chemotherapy. *Leuk Lymphoma* 2002; **43:** 2351–3.
4. Vogt T, *et al.* Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer* 2003; **98:** 2251–6.
5. Reichle A, *et al.* Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer* 2004; **101:** 2247–56.
6. Latz D, *et al.* Trofosfamide in the palliative treatment of cancer: a review of the literature. *Onkologie* 2004; **27:** 572–6.
7. Coras B, *et al.* Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic kaposi sarcoma. *Arch Dermatol* 2004; **140:** 1504–7.
8. Jahnke K, *et al.* Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. *Ann Oncol* 2005; **16:** 1974–8.
9. Salminen EK, *et al.* Palliative chemotherapy with trofosfamide in advanced prostate cancer. *Anticancer Res* 2006; **26:** 539–42.
10. Görn M, *et al.* A pilot study of docetaxel and trofosfamide as second-line 'metronomic' chemotherapy in the treatment of metastatic non-small cell lung cancer (NSCLC). *Onkologie* 2008; **31:** 185–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ixoten; ***Ger.:*** Ixoten; ***Spain:*** Genoxal Trofosfamida.

Tumour Necrosis Factor

Factor de necrosis tumoral; TNF.

Tasonermin *(BAN, rINN)*

Tasonermiini; Tasonermina; Tasonermine; Tasonerminum; TNFα-1a.

Тасонермин

$C_{778}H_{1225}N_{215}O_{231}S_2$ = 17350.5.
CAS — 94948-59-1.
ATC — L03AX11.
ATC Vet — QL03AX11.

Profile

Tumour necrosis factor is a cytokine of which 2 forms have been identified with similar biological properties: TNFα or cachectin, which is produced mainly by macrophages, and TNFβ or lymphotoxin, which is produced by lymphocytes. Various recombinant forms of TNFα, both human and mouse, are available: the names sonermin and sertenef have been used for such products.

The antitumour effects of tumour necrosis factor *in vitro* and in *animals* have prompted investigation of recombinant TNFα in the treatment of cancer either alone or with other cytokines such as interleukin-2 or the interferons. Tasonermin is a recombinant TNFα used with melphalan (p.742) for soft tissue sarcomas. It is given by mild hyperthermic isolated limb perfusion at a total dose of 3 mg for an upper limb and 4 mg for a lower limb.

Leakage of tasonermin into the systemic circulation should not exceed 10%, as severe toxicity may occur. Local adverse effects include skin reactions, oedema, and pain; less commonly, vascular thrombosis, onycholysis, or severe tissue damage have occurred. Systemic effects include fever, chills, nausea and vomiting, arrhythmias, hepatotoxicity, and infections. Shock or hypotension, neurological disorders, thrombocytopenia, leucopenia, acute renal failure, and hypersensitivity reactions have all been reported.

◊ References.

1. van Der Veen AH, *et al.* An overview on the use of TNF-alpha: our experience with regional administration and developments towards new opportunities for systemic application. *Anticancer Res* 2000; **20:** 3467–74.
2. Libutti SK, *et al.* Technique and results of hyperthermic isolated hepatic perfusion with tumor necrosis factor and melphalan for the treatment of unresectable hepatic malignancies. *J Am Coll Surg* 2000; **191:** 519–30.
3. Lejeune FJ, *et al.* Limb salvage by neoadjuvant isolated perfusion with TNFα and melphalan for non-resectable soft tissue sarcoma of the extremities. *Eur J Surg Oncol* 2000; **26:** 669–78.
4. Eggermont AM, ten Hagen TL. Tumor necrosis factor-based isolated limb perfusion for soft tissue sarcoma and melanoma: ten years of successful antivascular therapy. *Curr Oncol Rep* 2003; **5:** 79–80.
5. ten Hagen TL, Eggermont AM. Solid tumor therapy: manipulation of the vasculature with TNF. *Technol Cancer Res Treat* 2003; **2:** 195–203.
6. Noorda EM, *et al.* Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. *Cancer* 2003; **98:** 1483–90.
7. Corti A. Strategies for improving the anti-neoplastic activity of TNF by tumor targeting. *Methods Mol Med* 2004; **98:** 247–64.

Units. The first International Standard for human tumour necrosis factor α, which contained 40 000 international units/ampoule, was considered unsuitable for the assay of recombinant *mouse* tumour necrosis factor α, for human tumour necrosis factor β, or for preparations of tumour necrosis factor α of modified structure.[1] The second International Standard for human tumour necrosis factor α has been established as having a potency of 46 500 international units/ampoule.[2]

The first Reference Reagent for tumour necrosis factor β had an assigned potency of 150 000 units/ampoule.[3]

1. WHO. WHO expert committee on biological standardization: forty-second report. *WHO Tech Rep Ser 822* 1992. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf (accessed 01/08/08)
2. WHO. WHO expert committee on biological standardization: fifty-fourth report. *WHO Tech Rep Ser 927* 2005. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_927_eng.pdf (accessed 01/08/08)
3. WHO. WHO expert committee on biological standardization: forty-seventh report. *WHO Tech Rep Ser 878* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_878.pdf (accessed 01/08/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Beromun†; ***Cz.:*** Beromun; ***Fr.:*** Beromun†; ***Gr.:*** Beromun; ***Ital.:*** Beromun; ***Neth.:*** Beromun; ***Port.:*** Beromun; ***Spain:*** Beromun; ***Swed.:*** Beromun.

Ubenimex *(rINN)*

NK-421; NSC-265489; Ubénimex; Ubenimexum. (−)-*N*-[(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine.

Убенимекс

$C_{16}H_{24}N_2O_4$ = 308.4.

CAS — 58970-76-6.

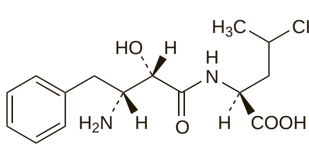

Pharmacopoeias. In *Chin.*

Profile

Ubenimex is a peptide derived from *Streptomyces olivoreticuli*. It is reported to have antineoplastic and immunostimulant properties. It has been used in the adjuvant treatment of acute myeloid leukaemia and is under investigation for the treatment of lung cancer. Adverse effects include gastrointestinal and hepatic function disturbances, skin rashes, headache, and paraesthesias.

◊ References.

1. Ichinose Y, *et al.* Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *J Natl Cancer Inst* 2003; **95:** 605–10.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Bestatin†; ***Jpn:*** Bestatin.

Valrubicin *(USAN, rINN)*

AD-32; NSC-246131; *N*-Trifluoroacetyladriamycin-14-valerate; *N*-Trifluoroacetyldoxorubicin-14-valerate; Valrubicina; Valrubicine; Valrubicinum. (8*S*,10*S*)-8-Glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-{[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy}-5,12-naphthacenedione 8^2-valerate.

Вальрубицин

$C_{34}H_{36}F_3NO_{13}$ = 723.6.

CAS — 56124-62-0.

ATC — L01DB09.

ATC Vet — QL01DB09.

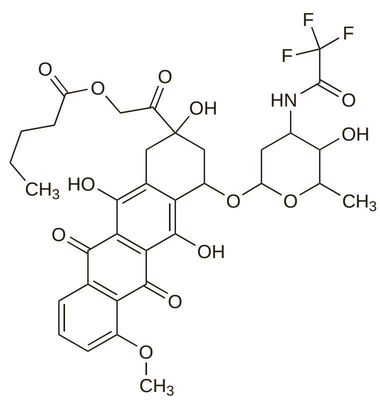

Pharmacopoeias. In *US.*

USP 31 (Valrubicin). An orange to orange-red crystalline powder. Very slightly soluble in water, in hexane, and in petroleum spirit; soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Increased urinary frequency and urgency, dysuria, bladder spasm and pain may follow intravesical use of valrubicin due to local irritation of the bladder, and usually resolve within 1 to 7 days of treatment. Gross haematuria has occurred rarely but should be distinguished from drug-induced red coloration of the urine. Abdominal pain and nausea may occur.

Myelosuppression similar to that seen with other anthracyclines (see Adverse Effects of Doxorubicin, p.712) is possible if significant systemic exposure occurs. Therefore valrubicin should not be given to patients with a perforated bladder or compromised bladder mucosa.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with carcinoma *in situ* who do not respond completely to valrubicin treatment after 3 months.

Pharmacokinetics

On intravesical use valrubicin penetrates the bladder wall but systemic absorption is low in patients who have an intact bladder mucosa. The drug is almost entirely excreted by voiding after the installation period.

Uses and Administration

Valrubicin is a semisynthetic analogue of the anthracycline doxorubicin (p.712). It is used for carcinoma *in situ* of the bladder (p.659) refractory to BCG vaccine, when surgery is contra-indicated, although only about 20% of such patients exhibit a complete response. A dose of 800 mg has been given intravesically once a week for 6 weeks, as 75 mL of a solution diluted with sodium chloride 0.9%. The solution should be retained for 2 hours if possible before voiding.

◊ References.

1. Steinberg G, *et al.* Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol (Baltimore)* 2000; **163:** 761–7.
2. Kuznetsov DD, *et al.* Intravesical valrubicin in the treatment of carcinoma in situ of the bladder. *Expert Opin Pharmacother* 2001; **2:** 1009–13.

Preparations

USP 31: Valrubicin Intravesical Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Valtaxin; ***Israel:*** Valstar; ***USA:*** Valstar†.

Verteporfin *(BAN, USAN, rINN)*

Benzoporphyrin Derivative; BPD; CL-318952; Verteporfiini; Verteporfina; Vertéporfine; Verteporfinum. *trans*-18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoic acid monomethyl ester.

Вертепорфин

$C_{41}H_{42}N_4O_8$ = 718.8.

CAS — 129497-78-5.

ATC — S01LA01.

ATC Vet — QS01LA01.

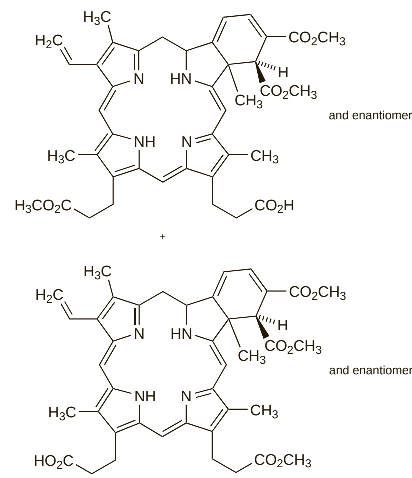

Pharmacopoeias. In *US.*

USP 31 (Verteporfin). Store at a temperature between −25° and −10° in airtight containers.

Adverse Effects and Precautions

Photosensitivity will occur in all patients treated with verteporfin and patients should not be exposed to direct sunlight for 2 to 5 days after treatment. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Headaches, injection site reactions, and visual disturbances occur frequently. Extravasation at the injection site may produce severe pain and inflammation and requires interruption of therapy. Patients who experience a severe decrease in vision should not be re-treated until their vision recovers. Other reported adverse effects include hypersensitivity, infusion-related pain (primarily presenting as back pain), chest pain, gastrointestinal disturbances, atrial fibrillation, hypertension, decreased hearing, and anaemia. Verteporfin should be used with care in patients with hepatic impairment and may be contra-indicated if impairment is severe.

Porphyria. The use of verteporfin is contra-indicated in patients with porphyria.

Interactions

Use of verteporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

After intravenous doses, elimination of verteporfin is bi-exponential, with a terminal plasma elimination half-life of about 5 to 6 hours. Protein binding is about 90%. It is metabolised in the liver. It is excreted in faeces via the bile, mostly as unchanged drug, with less than 1% of a dose recovered in the urine.

◊ References.

1. Houle J-M, Strong A. Clinical pharmacokinetics of verteporfin. *J Clin Pharmacol* 2002; **42:** 547–57.

Uses and Administration

Verteporfin is a photosensitiser used in photodynamic therapy (see under Porfimer Sodium, p.764). It is used to treat neovascular (wet) age-related macular degeneration (see below). After intravenous dosage verteporfin accumulates preferentially in the endothelial cells of actively growing blood vessels, including those in the choroid. When activated by laser light it produces local vascular occlusion and this inhibits neovascularisation and reduces the decline in visual acuity. It is given by intravenous infusion over 10 minutes at a dose of 6 mg/m^2. This is followed 15 minutes after the start of the infusion by activation using a laser tuned to a wavelength of 689 nanometres and delivered to the eye via a fibre optic device and a slit lamp, together with a suitable contact lens. The recommended light dose is 50 J/cm^2, given over 83 seconds. Therapy may be repeated every 3 months for recurrent choroidal neovascular leakage. Verteporfin has also been investigated in the photodynamic therapy of a variety of other disorders including malignant neoplasms.

Age-related macular degeneration. Age-related macular degeneration (AMD) is a degenerative disease usually occurring in people over the age of 50 years.[1-3] The central portion of the retina (the macula) deteriorates[2,4,5] and it is a major cause of severe visual loss in people over 60 years old in North America and Europe.[4,6] There are two main types of AMD.

- In geographic atrophy or *non-neovascular* or *non-exudative (dry) AMD*, which occurs at an early stage of AMD, the retinal pigment epithelium is lost completely in localised areas, causing a gradual loss of central vision in the affected eye(s). It is characterised by retinal hypo- or hyperpigmentation, and yellow deposits of acellular amorphous debris beneath the retina, called drusen. These are usually large, or soft (with indistinct margins); small hard drusen occur naturally with ageing but, unlike drusen in AMD, do not progress.
- In *neovascular* or *exudative (wet) AMD*, new blood vessels develop in the choroidal layer beneath the retina; leaks or haemorrhage from these lead to macular oedema, retinal scarring, and often acute, significant loss of vision.[2,4,5,7-10] This process of *choroidal neovascularisation* (CNV) is defined as classic or occult according to its appearance on fluorescein angiography;[2,5,9,11] the classic form is associated with more rapid progression than the occult form.[2,9] CNV lesions are also classified according to their location relative to the fovea.[1,2,12] Although the neovascular form accounts for only about 20% of all cases of AMD, the risk of severe visual loss with this form is much higher than with dry AMD.[1,9] However, about 10 to 20% of patients with dry AMD can progress to the neovascular form,[1,10] and both forms can occasionally co-exist in the same patient.[11]

Risk factors, besides older age, include a family history of the disorder, the presence of a mutation in the complement factor H (CFH) gene, smoking, white race, and increased body-mass index;[3,8,13] female sex, atherosclerosis, dietary fat or fish intake, alcohol or caffeine consumption, refractive error, iris colour, and increased exposure to sunlight have also been proposed as risk factors but have not consistently been related to development of AMD.[13]

There is currently no **treatment** that effectively prevents visual loss or improves vision in all patients with AMD.[14]

- Laser photocoagulation treatment is of proven efficacy for neovascular AMD, especially for extrafoveal CNV; however, rates of recurrence are high.[1,6,8,13,14]
- Photodynamic therapy (see under Porfimer Sodium, p.764) with verteporfin has been shown to decrease the risk of visual loss in patients with neovascular AMD, including subfoveal CNV.[1,4,8,9,11,12,14-18] Systematic reviews have noted that although photodynamic therapy with verteporfin is probably effective in preventing visual loss in those with classic and occult CNV due to AMD, the size of the effect remains in doubt.[5,19] Furthermore, the therapy can only be effective during the proliferative stage of the disease while the neovascular process is active.[5]

  In the UK, NICE guidelines considered the evidence to show a larger treatment effect in patients with classic CNV, and recommend photodynamic therapy in those patients with neovascular AMD with a confirmed diagnosis of classic, with no occult, subfoveal CNV.[2] However, other guidelines[20] on the use of verteporfin recommend that verteporfin treatment be considered for patients with minimally classic subfoveal CNV who have relatively small lesions, or where the proportion of classic CNV is increasing. For those patients with occult CNV and who are presumed to have recent disease progression, verteporfin may be considered in those with smaller lesions or lower levels of visual acuity; for those with large occult lesions, treatment may be considered if levels of visual acuity are rapidly decreasing. Patients should be followed up at least as often as every 3 months after initial therapy, and re-treated if necessary.[20]

  While photodynamic therapy is considered to have minimal adverse effects and a low complication rate, some have cautioned that patients should be counselled that verteporfin therapy rarely leads to an improvement in vision.[21]
- Vascular endothelial growth factor (VEGF) plays a role in the development of CNV secondary to AMD; pegaptanib and ranibizumab are VEGF inhibitors used in the treatment of neovascular (wet) AMD.[22-24] Systematic reviews[25,26] of randomised controlled studies of these drugs concluded that both show benefit in slowing or stopping the progression of disease. Greater effect was seen with ranibizumab than with pegaptanib, although head-to-head comparative studies are needed to confirm this. Bevacizumab has also been tried, although its use is controversial.[6,22,27] Triamcinolone acetonide, a corticosteroid that may also downregulate VEGF, has been given intravitreally with variable results; combination treatment with photodynamic therapy is under investigation.[10,13,28]
- Angiogenesis inhibitors such as anecortave are under investigation for neovascular AMD.[3,10,13,14,28] Interferon alfa showed encouraging preliminary results, but controlled data showed no benefit.[8,10,13] Thalidomide has been tried, but trials were stopped due to adverse effects.[10,13]
- Vitamin and mineral supplements may be of use in selected patients; the AREDS trial found that antoxidants (vitamin C, vitamin E, and betacarotene) plus zinc modestly benefited those with moderate to severe signs of the disease.[11,14] However, betacarotene should be avoided in smokers.[3,6,10] The carotenoids, lutein and zeaxanthin, have been promoted as retinal protectants, but controlled data are lacking.[10,11,14,29] Some recommend that those at risk of AMD should be encouraged to stop smoking and to consume a diet including vegetables, fish, nuts, and to reduce consumption of fats especially vegetable oil.[7,29] A prospective cohort study found that a high dietary intake of vitamin E and zinc, or an above-median intake of the combination of vitamins C and E, betacarotene, and zinc were associated with a lower risk of incident AMD.[30] However, systematic reviews[31,32] have found no evidence to support the role of antioxidant vitamin and mineral supplements in the primary prevention of AMD.
- Retinal or macular surgery, and transpupillary thermotherapy are under investigation.[1,8,11,13,14,28] Radiotherapy has also been tried with mixed results.[10,13] Retinal transplantation is under investigation.[6,8,11,14] Gene silencing with bevasiranib, a short interfering RNA (siRNA) therapeutic designed to turn off or silence the gene that produces VEGF, is also under investigation for wet AMD.[33]

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2. NICE. Guidance on the use of photodynamic therapy for age-related macular degeneration: Technology Appraisal 68 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/68_PDTGuidance.pdf (accessed 09/05/08)
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5. Wormald R, *et al.* Photodynamic therapy for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/08/08).
6. Cook HL, *et al.* Age-related macular degeneration: diagnosis and management. *Br Med Bull* 2008; **85:** 127–49.
7. Constable IJ. Age-related macular degeneration and its possible prevention. *Med J Aust* 2004; **181:** 471–2.
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9. Yang YC. Preserving vision with verteporfin photodynamic therapy. *Hosp Med* 2004; **65:** 39–43.
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12. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol* 1999; **117:** 1329–45.
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14. Lois N. Neovascular age-related macular degeneration. *Compr Ophthalmol Update* 2004; **5:** 143–61.
15. Blumenkranz MS, *et al.* Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials—TAP report no. 5. *Arch Ophthalmol* 2002; **120:** 1307–14.
16. Blinder KJ, *et al.* Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial—VIP report no. 3. *Ophthalmology* 2003; **110:** 667–73.
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19. Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *Br J Ophthalmol* 2004; **88:** 212–17.
20. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina* 2005; **25:** 119–34.
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22. Anonymous. A view on new drugs for macular degeneration. *Drug Ther Bull* 2007; **45:** 49–52.
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24. Brown DM, *et al.* ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1432–44.
25. Takeda AL, *et al.* Pegaptanib and ranibizumab for neovascular age-related macular degeneration: a systematic review. *Br J Ophthalmol* 2007; **91:** 1177–82.
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27. Wong TY, *et al.* Clinical update: new treatments for age-related macular degeneration. *Lancet* 2007; **370:** 204–6.
28. Liu M, Regillo CD. A review of treatments for macular degeneration: a synopsis of currently approved treatments and ongoing clinical trials. *Curr Opin Ophthalmol* 2004; **15:** 221–6.
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31. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; **335:** 755–9.
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33. Arjamaa O. Gene silencing in wet age-related macular degeneration. *Lancet* 2006; **368:** 630–1.

Preparations

USP 31: Verteporfin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Visudyne; ***Austral.:*** Visudyne; ***Austria:*** Visudyne; ***Belg.:*** Visudyne; ***Braz.:*** Visudyne; ***Canad.:*** Visudyne; ***Chile:*** Visudyne; ***Cz.:*** Visudyne; ***Denm.:*** Visudyne; ***Fin.:*** Visudyne; ***Fr.:*** Visudyne; ***Ger.:*** Visudyne; ***Gr.:*** Visudine; ***Hong Kong:*** Visudyne; ***Hung.:*** Visudyne; ***Indon.:*** Visudyne; ***Israel:*** Visudyne; ***Ital.:*** Visudyne; ***Jpn:*** Visudyne; ***Malaysia:*** Visudyne; ***Neth.:*** Visudyne; ***Norw.:*** Visudyne; ***NZ:*** Visudyne; ***Philipp.:*** Visudyne; ***Pol.:*** Visudyne; ***Port.:*** Visudyne; ***Rus.:*** Visudyne (Визудин); ***S.Afr.:*** Visudyne; ***Singapore:*** Visudyne; ***Spain:*** Visudyne; ***Swed.:*** Visudyne; ***Switz.:*** Visudyne; ***Thai.:*** Visudyne; ***Turk.:*** Visudyne; ***UK:*** Visudyne; ***USA:*** Visudyne; ***Venez.:*** Visudyne.

Vinblastine Sulfate *(USAN, rINNM)*

29060-LE; NSC-49842; Sulfato de Vimblastina; Sulfato de vinblastina; Vinblastiinisulfaatti; Vinblastin Sülfat; Vinblastine, sulfate de; Vinblastine Sulphate *(BANM)*; Vinblastini sulfas; Vinblastino sulfatas; Vinblastinsulfat; Vinblastin-sulfát; Vinblasztin-szulfát; Vincaleukoblastine Sulphate; VLB (vinblastine); Winblastyny siarczan.

Винбластина Сульфат

$C_{46}H_{58}N_4O_9,H_2SO_4 = 909.1.$

CAS — 865-21-4 (vinblastine); 143-67-9 (vinblastine sulfate).

ATC — L01CA01.

ATC Vet — QL01CA01.

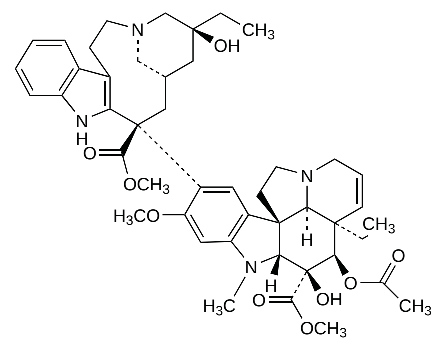

(vinblastine)

Description. Vinblastine sulfate is the sulfate of an alkaloid, vincaleukoblastine, extracted from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Vinblastine Sulphate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water; practically insoluble in alcohol. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature not exceeding −20° in airtight glass containers. Protect from light.

USP 31 (Vinblastine Sulfate). A white or slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature between −25° and −10° in airtight containers. Protect from light.

Stability. Between about 5 and 20% of active drug was lost from solution when a solution of vinblastine sulfate 3 micrograms/mL in glucose 5% injection was stored for 48 hours in a range of intravenous burette giving sets, the highest loss being from cellulose propionate sets and the lowest from one made from methacrylate butadiene styrene.[1] Similarly, storage in PVC tubing led to a 42 to 44% loss from solution whereas only about 6% was lost over the 48 hours in polybutadiene tubing. The losses appeared to be due to drug sorption, and were therefore greater from the tubing which had a greater surface-area-to-volume ratio than the burettes.

1. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression, especially leucopenia, is the most common adverse effect with vinblastine and tends to be dose-limiting. Maximum depression occurs 5 to 10 days after a dose with recovery in a further 7 to 14 days. Leucopenia may be more severe in patients with cachexia or extensive skin ulceration: vinblastine should not be used in elderly patients with these conditions. Stomatitis and gastrointestinal bleeding may occur; nausea and vomiting respond to treatment with antiemetics.

The vinca alkaloids can produce central and peripheral (including autonomic) neurotoxicity, although these effects are less frequent with vinblastine. Symptoms include malaise, weakness, headache, depression, paraesthesia and numbness, loss of deep tendon reflexes, peripheral neuropathies, constipation and adynamic ileus, jaw pain, and convulsions. Damage to the eighth cranial nerve may result in vestibular and auditory toxicity leading to dizziness, nystagmus, vertigo, and partial or total deafness. A routine prophylactic regimen against constipation is recommended in patients receiving high doses of vinblastine. Overdosage has caused permanent damage to the CNS. Intrathecal use of the vinca alkaloids is contra-indicated because of the likelihood of fatal neurotoxicity (see Administration Error, below).

Other reported effects include skin reactions, alopecia, ischaemic cardiac toxicity, hypertension, dyspnoea and bronchospasm, and bone and tumour pain. A syndrome of inappropriate secretion of antidiuretic hormone has occurred at high doses, and may be relieved by fluid restriction and, if necessary, a suitable diuretic. Rare cases of anaphylaxis and anaphylactoid-type reactions have been reported with the vinca alkaloids.

Vinblastine is irritant to the skin and mucous membranes and extravasation may cause necrosis, cellulitis, and sloughing. The application of warmth and local injection of hyaluronidase may be of benefit in relieving the effects of extravasation. By analogy with its use in the management of vincristine overdosage (see p.787), folinic acid has been suggested for use in overdosage with vinblastine.

Vinblastine should not be injected into an extremity with impaired circulation because of an increased risk of thrombosis. It should be given with caution and at reduced dosage to patients with hepatic impairment (see under Uses, below).

Administration error. *Intrathecal doses of vinca alkaloids, including vinblastine, result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK guidelines on dilution of vinca alkaloids to avoid intrathecal use, see p.787.

Handling and disposal. A method for the destruction of vincristine or vinblastine *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of either drug by this method showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vinblastine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Vinblastine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vinblastine and increased toxicity. For a report of the possible contribution of vinblastine to reduced plasma concentrations of phenytoin, see p.499.

Analgesics. A report of enhanced hepatotoxicity in patients treated with interferon alfa and vinblastine who were given *paracetamol*.[1]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.

Antibacterials. There is a report of severe vinblastine toxicity in 3 patients who received vinblastine and ciclosporin with *erythromycin*.[1] Adverse effects resolved on stopping erythromycin and recurred in 1 patient who was rechallenged with erythromycin.

1. Tobe SW, *et al.* Vinblastine and erythromycin: an unrecognised serious drug interaction. *Cancer Chemother Pharmacol* 1995; **35:** 188–90.

Antineoplastics. Acute bronchospastic reactions after injection of a vinca alkaloid have been reported, usually in patients who have also received *mitomycin*,[1] and presenting as acute respiratory distress, cyanosis, and dyspnoea, often with the development of pulmonary infiltrates and pneumonitis.[2,3] A number of fatalities due to respiratory complications have occurred. For reports of vascular toxicity and Raynauds syndrome associated with the use of vinca alkaloids with *bleomycin* and other drugs, see Effects on the Cardiovascular System, p.636.

1. Dyke RW. Acute bronchospasm after a vinca alkaloid in patients previously treated with mitomycin. *N Engl J Med* 1984; **310:** 389.
2. Konits PH, *et al.* Possible pulmonary toxicity secondary to vinblastine. *Cancer* 1982; **50:** 2771–4.
3. Ozols RF, *et al.* MVP (mitomycin, vinblastine, and progesterone): a second-line regimen in ovarian cancer with a high incidence of pulmonary toxicity. *Cancer Treat Rep* 1983; **67:** 721–2.

Antivirals. Severe myelosuppression has occurred in patients given relatively high doses of vinblastine with *interferon alfa-n1*.

A patient who had been given vinblastine 6 mg/m^2 every 3 weeks had severe gastrointestinal and haematological toxicity and moderate renal failure when *HAART* with zidovudine, lamivudine, abacavir, nevirapine, and lopinavir with ritonavir was reintroduced.[1] The vinblastine dosage was eventually stabilised at 2 mg/m^2 during HAART without toxicity.

1. Kotb R, *et al.* Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol* 2006; **76:** 269–71.

Pharmacokinetics

Vinblastine is not reliably absorbed from the gastrointestinal tract. After intravenous use it is rapidly cleared from the blood and distributed to tissues; it is reported to be concentrated in blood platelets. It is extensively protein bound. Vinblastine is metabolised in the liver, by cytochrome P450 isoenzymes of the CYP3A subfamily, to an active metabolite desacetylvinblastine, and is excreted in faeces via the bile, and in urine; some is excreted as unchanged drug. The terminal half-life is reported to be about 25 hours. It does not cross the blood-brain barrier in significant amounts.

◊ References.

1. Levêque D, Jehl F. Molecular pharmacokinetics of catharanthus (vinca) alkaloids. *J Clin Pharmacol* 2007; **47:** 579–88.

Uses and Administration

Vinblastine sulfate is an antineoplastic agent that apparently acts by binding to the microtubular proteins of the spindle and arresting mitosis at the metaphase; it is thus specific for the M phase of the cell cycle. It also interferes with glutamate metabolism and possibly nucleic acid synthesis, and has some immunosuppressant activity. Significant cross-resistance with vincristine has not been reported although pleiotropic resistance may occur.

Vinblastine sulfate is used, usually with other antineoplastics, in the treatment of Hodgkin's disease and other lymphomas, for some inoperable malignant neoplasms including those of the breast, bladder, and kidney, and in non-small cell lung cancer, choriocarcinoma, and Kaposi's sarcoma; vinblastine has also been employed in the management of Langerhans-cell histiocytosis. It was formerly used with bleomycin and cisplatin (PVB) for testicular cancer, but other regimens are now preferred. The management of these conditions is discussed under Choice of Antineoplastic, as indicated by the cross-references given below.

Vinblastine sulfate may be given by intravenous injection as a solution containing 1 mg/mL in sodium chloride 0.9%. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vinblastine should generally be diluted to a volume of at least 20 mL to avoid inadvertent intrathecal use; higher concentrations can be used for children under 10 years of age. Care should be taken to avoid extravasation and the intravenous injection may be given into a freely running infusion of sodium chloride injection if preferred. The usual dose is about 6 mg/m^2, not more often than every 7 days, although doses starting at 3.7 mg/m^2 and increasing to 18.5 mg/m^2 have been given as a single agent. If a maintenance dose is required, it may be given every 7 days provided white cell counts permit (see below), and should be the maximum dose that the patient is able to tolerate without serious leucopenia occurring.

Children may be given vinblastine sulfate in a usual maximum weekly dose of 7.5 mg/m^2. Doses of up to 12.5 mg/m^2 weekly as a single agent have been given.

White cell counts should be made before each injection and some sources suggest a repeat dose should not be given unless the count has risen to at least 4000 cells/mm^3 (but see also Bone-marrow Depression, p.639). A dosage reduction is advised in patients with hepatic impairment (see below).

Administration in hepatic impairment. UK licensed product information recommends that the dose of vinblastine be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL.

Blood disorders, non-malignant. The vinca alkaloids vinblastine and vincristine have been used experimentally in the treatment of auto-immune blood disorders such as idiopathic thrombocytopenic purpura (p.1505). There are also reports of the haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura responding to treatment with intravenous injection of vincristine.[1-3] For further details on the treatment of thrombotic microangiopathies, see under Plasma, p.1076. Vincristine has been given with normal immunoglobulin in the management of a patient with life-threatening thrombocytopenia due to sarcoidosis.[4] Vincristine has also been used for life-threatening haemangioma (p.1505).

1. Gutterman LA, *et al.* The hemolytic-uremic syndrome: recovery after treatment with vincristine. *Ann Intern Med* 1983; **98:** 612–13.
2. Ferrara F, *et al.* Vincristine as salvage treatment for refractory thrombotic thrombocytopenic purpura. *Ann Hematol* 1999; **78:** 521–3.
3. Ferrara F, *et al.* Vincristine as treatment for recurrent episodes of thrombotic thrombocytopenic purpura. *Ann Hematol* 2002; **81:** 7–10.
4. Larner AJ. Life threatening thrombocytopenia in sarcoidosis. *BMJ* 1990; **300:** 317–19.

Histiocytic syndromes. The value of systemic chemotherapy in patients with Langerhans-cell histiocytosis (p.650) is uncertain; however, it is certainly widely used in extensive disease, vinblastine being one of the drugs often employed.[1,2]

1. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996; **75:** 17–24.
2. Gadner H, *et al.* A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; **138:** 728–34. Correction. *ibid.*; **139:** 170.

Malignant neoplasms. Vinblastine plays an important role in the ABVD regimen in patients with Hodgkin's disease (p.655). It also formed part of the effective, if toxic, PVB regimen used to treat germ cell (ovarian or testicular) cancer, p.670 and p.673 respectively, although other regimens tend now to be preferred. The vinca alkaloids are also active in gestational trophoblastic tumours (p.650), and vinblastine is also used in the therapy of invasive bladder cancer (p.659); it may be used in the adjuvant or palliative treatment of non-small-cell lung cancer (p.668) and in the palliative care of advanced breast cancer (p.661) and mycosis fungoides (p.657). It has been used in malignancies of the kidney (p.667). Vinca alkaloids are also used to treat Kaposi's sarcoma (p.675).

Preparations

BP 2008: Vinblastine Injection;
USP 31: Vinblastine Sulfate for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Blastovin; Velbe†; Xintoprost†; ***Austral.:*** Velbe; ***Austria:*** Velbe; ***Belg.:*** Velbe; Vinblasin; ***Braz.:*** Rabinefil†; Velban†; ***Chile:*** Lemblastine; Velbe†; ***Denm.:*** Velbe; ***Fin.:*** Velbe†; ***Fr.:*** Velbe; ***Ger.:*** Cellblastin†; Velbe†; ***Gr.:*** Velbe; ***Hong Kong:*** Velbe†; ***India:*** Cytoblastin; ***Israel:*** Blastovin; ***Ital.:*** Velbe; ***Mex.:*** Ifabla†; Lemblastine; Velbe†; ***Neth.:*** Blastivin; Velbe; ***Norw.:*** Velbe; ***Philipp.:*** Velbastine; ***Port.:*** Solblastin; Velbe†; ***Swed.:*** Velbe; ***Switz.:*** Velbe; ***UK:*** Velbe; ***USA:*** Velban; ***Venez.:*** Velbe†.

Vincristine Sulfate *(USAN, rINNM)*

Compound 37231; Leurocristine Sulphate; NSC-67574; 22-Oxovincaleukoblastine Sulphate; Sulfato de vincristina; Vincristine, sulfate de; Vincristine Sulphate *(BANM)*; Vincristini sulfas; Vinkristiinisulfaatti; Vinkristin Sülfat; Vinkristino sulfatas; Vinkristinsulfat; Vinkristin-sulfát; Vinkrisztin-szulfát; Winkrystyny siarczan.

Винкристина Сульфат

$C_{46}H_{56}N_4O_{10},H_2SO_4 = 923.0.$

CAS — 57-22-7 (vincristine); 2068-78-2 (vincristine sulfate).

ATC — L01CA02.

ATC Vet — QL01CA02.

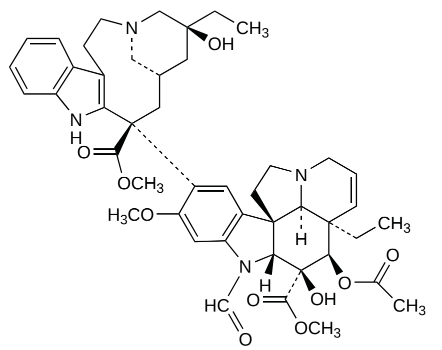

(vincristine)

Description. Vincristine sulfate is the sulfate of an alkaloid, 22-oxovincaleukoblastine, obtained from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Vincristine Sulphate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding −20° in airtight glass containers. Protect from light.

USP 31 (Vincristine Sulfate). A white to slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature between −25° and −20° in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786.

Bone-marrow depression occurs less commonly than with vinblastine but neurological and neuromuscular effects are more severe with vincristine and are dose-limiting. Walking may be impaired and the neurological effects may not be reversed for several months after the drug is stopped. Convulsions, often with hypertension, have occurred. Constipation is common and there may be abdominal pain. Urinary disturbances have occurred and alopecia is frequent.

Folinic acid has been given for the treatment of overdosage: suggested doses are as much as 100 mg of folinic acid intravenously every 3 hours for 24 hours, then every 6 hours for at least 48 hours. However, this is unlikely to be of benefit in reversing neuromuscular toxicity. For mention of the use of glutamic acid in managing the usually fatal consequences of inadvertent intrathecal dosage, see below.

Because severe constipation and impaction of faeces often occur with vincristine, laxatives or enemas may be necessary to ensure regular bowel function. Vincristine should be given with caution to patients with pre-existing neuromuscular disease and is contra-indicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (see under Effects on the Nervous System, below). Doses may need to be adjusted in patients with hepatic impairment. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity.

Administration error. *Inadvertent intrathecal doses of vincristine result in ascending paralysis and death.*[1,2] However, in one case[1] treatment immediately after the error, and consisting of removal of contaminated spinal fluid and flushing with lactated Ringer's solution and fresh frozen plasma diluted in lactated Ringer's solution, plus intravenous and oral glutamic acid, was reported successful in stabilising neurological dysfunction and preventing death. A similar case of successful treatment has subsequently been reported,[3] in which immediate CSF aspiration and irrigation (with lactated Ringer's solution containing fresh frozen plasma to bind vincristine) for 6 days was combined with intravenous folate, glutamic acid, and pyridoxine. The role of neuroprotectant drugs in these cases is uncertain, although a study involving 84 patients found that glutamic acid 1.5 g daily given orally in divided doses during a 6-week induction chemotherapy course decreased vincristine-induced neurotoxicity.[4] One manufacturer (*Lilly*) has stated that the roles of glutamic acid, folinic acid, and pyridoxine remain unclear.

While early recognition and immediate treatment with cerebrospinal fluid drainage and exchange may improve survival,[5] fatalities still occur despite these measures.[5,6] Recommendations[2,6] have been made in order to prevent further errors occurring, including restrictions on the prescription, administration, and storage of intrathecal drugs. In the UK, recommendations state that vinca alkaloids for intravenous use in adults or children over 10 years should be diluted to a maximum concentration of 100 micrograms/mL (vincristine) or a volume of at least 20 mL (vinblastine, vindesine, or vinorelbine) and labelled with a clear warning of the consequences of use by other routes. Higher concentrations may be used in children under 10 years, and in certain specialised centres.[2]

1. Dyke RW. Treatment of inadvertent intrathecal injection of vincristine. *N Engl J Med* 1989; **321:** 1270–1.
2. Department of Health. Updated national guidance on the safe administration of intrathecal chemotherapy (HSC 2003/010, 2 October 2003). Available at: http://www.dh.gov.uk/assetRoot/04/06/43/17/04064317.pdf (accessed 01/07/04)
3. Qweider M, *et al.* Inadvertent intrathecal vincristine administration: a neurosurgical emergency. Case report. *J Neurosurg Spine* 2007; **6:** 280–3.
4. Jackson DV, *et al.* Amelioration of vincristine neurotoxicity by glutamic acid. *Am J Med* 1988; **84:** 1016–22.
5. Alcaraz A, *et al.* Intrathecal vincristine: fatal myeloencephalopathy despite cerebrospinal fluid perfusion. *J Toxicol Clin Toxicol* 2002; **40:** 557–61.
6. Fernandez CV, *et al.* Intrathecal vincristine: an analysis of reasons for recurrent fatal chemotherapeutic error with recommendations for prevention. *J Pediatr Hematol Oncol* 1998; **20:** 587–90.

Effects on the nervous system. In its most typical form, vincristine neurotoxicity[1] manifests as a mixed sensorimotor neuropathy of the distal type. The earliest symptoms are sensory changes in the form of paraesthesias, accompanied by impairment and ultimately loss of deep tendon reflexes. In more severe forms, impairment of motor function occurs with wrist drop and foot drop, ataxia and gait abnormalities, and occasionally progressive quadriparesis.

In contrast to these peripheral neuropathies, which are usually associated with long-term usage, there may be short-term autonomic neuropathy resulting in constipation and occasionally ileus, abdominal pain, atony of the urinary bladder (which may lead to urinary retention), orthostatic hypotension, and rarely, impotence. Effects on the cranial nerves may result in ptosis, hoarseness (due to laryngeal nerve paralysis), or optic neuropathies. Effects on the CNS are rare, probably in part because of poor penetration into CSF, but include excessive release of antidiuretic hormone and consequent hyponatraemia.

Hallucinations have occurred[2] and effects on the special senses have been reported: both bilateral optic atrophy and blindness,[3] and profound neurological deafness (which was largely reversible on drug withdrawal)[4] have occurred. Convulsions associated with hypertension are another feature of vincristine toxicity.[5]

Toxicity is related to both the cumulative and the individual dose.[1] It usually begins in adults after receiving a total of 5 to 6 mg, and is significant by the time a cumulative dose of 15 to 20 mg is reached. If individual doses are low (less than 2 mg) or intervals between doses are longer than the usual week, patients can tolerate higher cumulative doses. Children tolerate vincristine better than adults, but the elderly are particularly prone to neurotoxicity. Patients with existing neurological disorders such as poliomyelitis or the Charcot-Marie-Tooth syndrome may be at increased risk of neurotoxicity.[6-9] It has been suggested that increased neurotoxicity may be associated with the use of ready-to-use solutions rather than reconstituted lyophilised preparations but this has not been proved.[10-14]

There is no good treatment for the effects of vincristine on the nervous system: symptoms are largely reversible once dosage is interrupted, and should be managed with appropriate symptomatic care.[1] However, there is some suggestion that glutamic acid may be of benefit in treating neurotoxicity—see Administration Error, above. For the use of dinoprost to alleviate ileus induced by vinca alkaloids, see p.2007.

1. Legha SS. Vincristine neurotoxicity: pathophysiology and management. *Med Toxicol* 1986; **1:** 421–7.
2. Holland JF, *et al.* Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res* 1973; **33:** 1258–64.
3. Awidi AS. Blindness and vincristine. *Ann Intern Med* 1980; **93:** 781.
4. Yousif H, *et al.* Partially reversible nerve deafness due to vincristine. *Postgrad Med J* 1990; **66:** 688–9.
5. Ito S, *et al.* Seizures and hypertension complicating vincristine therapy in children. *Clin Pharmacol Ther* 1995; **57:** 208.
6. Hogan-Dann CM, *et al.* Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. *JAMA* 1984; **252:** 2862–3.
7. Miller BR. Neurotoxicity and vincristine. *JAMA* 1985; **253:** 2045.
8. Chauncey TR, *et al.* Vincristine neurotoxicity. *JAMA* 1985; **254:** 507.
9. Griffiths JD, *et al.* Vincristine neurotoxicity in Charcot-Marie-Tooth syndrome. *Med J Aust* 1985; **143:** 305–6.
10. Arnold AM, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 346.
11. Jalihal S, Roebuck N. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637.
12. Davies CE, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 637–8.
13. Warrier RP, Ducos R. Acute vincristine neurotoxicity. *Lancet* 1985; **i:** 980.
14. Gennery BA. Vincristine neurotoxicity. *Lancet* 1985; **ii:** 385.

Handling and disposal. For a method for the destruction of vincristine *wastes*, see under Vinblastine Sulfate, p.786.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vincristine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Vincristine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Use of vincristine with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vincristine and increased toxicity. If vincristine is used with asparaginase it should be given 12 to 24 hours before the enzyme: giving asparaginase with or before vincristine may reduce vincristine clearance and increase toxicity. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with bleomycin and other drugs see Effects on the Cardiovascular System, p.636.

Antibacterials. Severe neurotoxicity has occurred when *isoniazid* was added to the regimen of a patient receiving vincristine.[1]

1. Carrión C, *et al.* Possible vincristine-isoniazid interaction. *Ann Pharmacother* 1995; **29:** 201.

Antiepileptics. A pharmacokinetic study showed that systemic clearance of vincristine was 63% higher when it was given with *phenytoin* or *carbamazepine*, two inducers of the cytochrome P450 isoenzyme CYP3A4. The clinical significance of this finding is unknown.[1]

1. Villikka K, *et al.* Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumours. *Clin Pharmacol Ther* 1999; **66:** 589–93.

Antifungals. Toxicity has been reported to be increased in children who received *itraconazole* with or without nifedipine during treatment involving vincristine.[1-4] Itraconazole is presumed to potentiate the toxicity of vincristine either by inhibition of cytochrome P450 isoenzymes, thus reducing the clearance of vincristine,[1-4] or by inhibiting the P-glycoprotein efflux pump,[2,3] and increasing intracellular concentrations of vincristine. Nifedipine also decreases the clearance of vincristine, by similar mechanisms,[1,3,4] and can theoretically further potentiate toxicity.

1. Murphy JA, *et al.* Vincristine toxicity in five children with acute lymphoblastic leukaemia. *Lancet* 1995; **346:** 443.
2. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2001; **18:** 137–42.
3. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. *Pediatr Hematol Oncol* 2001; **18:** 543–6.
4. Kamaluddin M, *et al.* Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. *Acta Paediatr* 2001; **90:** 1204–7.

Nifedipine. Vincristine toxicity may be potentiated by nifedipine, see Antifungals, above.

Pharmacokinetics

Vincristine is not reliably absorbed from the gastrointestinal tract. After intravenous injection it disappears rapidly from the blood. It is extensively protein bound and is reported to be concentrated in blood platelets. It is metabolised in the liver and excreted primarily in the bile; about 70 to 80% of a dose is found in faeces, as unchanged drug and metabolites, while 10 to 20% appears in the urine. The terminal half-life is reported to be about 85 hours but may range from about 19 to 155 hours. Vincristine does not appear to cross the blood-brain barrier in significant amounts.

Uses and Administration

Vincristine is an antineoplastic agent that may act similarly to vinblastine (p.786) by arresting mitosis at the metaphase. Significant cross-resistance with vinblastine has not been reported although pleiotropic resistance may occur.

Vincristine sulfate is used mainly in combination chemotherapy regimens for acute and chronic leukaemias, lymphomas, including Hodgkin's disease and non-Hodgkin's lymphomas, and multiple myeloma. It is also used for tumours of the breast, lung, head and neck, and soft-tissue sarcomas, as well as for paediatric solid tumours including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma, and medulloblastoma. Vincristine has also been used in idiopathic thrombocytopenic purpura refractory to other agents. See also the cross-references given below.

Vincristine sulfate is given by intravenous injection. It has been given as a solution containing 1 mg/mL. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vincristine should generally be diluted to a maximum concentration of 100 micrograms/mL and to a volume of at least 10 mL, to avoid inadvertent intrathecal use; higher concentrations can be used for children under 10 years of age. Care should be taken to avoid extravasation and the injection may be given over 1 minute into a freely-running intravenous infusion (usually sodium chloride 0.9%) if preferred.

The usual adult intravenous dose of vincristine sulfate is 1.4 to 1.5 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg (see also Administration, below). For children weighing over 10 kg, the suggested dose is 1.4 to 2 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg. For those weighing less than 10 kg, the suggested initial dose is 50 micrograms/kg, once weekly.

Blood counts should be carried out before giving each dose. Dosage reduction is recommended in patients with hepatic impairment (see below).

A liposomal formulation of vincristine is under investigation for the treatment of acute lymphoblastic leukaemia.

Action. Results *in vitro* suggested[1] a selective action of vincristine against lymphocytes of patients with chronic lymphocytic leukaemia; lymphocytes of healthy subjects were not so affected. A further study[2] confirmed these findings, and also found marked variation in vincristine susceptibility among individual chronic lymphocytic leukaemic cells. This suggests that vincristine may have effects other than arrest of mitosis.

1. Vilpo J, Vilpo L. Selective toxicity of vincristine against chronic lymphocytic leukaemia in vitro. *Lancet* 1996; **347:** 1491–2.
2. Vilpo JA, *et al.* Selective toxicity of vincristine against chronic lymphocytic leukemia cells in vitro. *Eur J Haematol* 2000; **65:** 370–8.

Administration. Although a maximum single dose of 2 mg is recommended for vincristine sulfate to reduce neurotoxicity, a review[1] has suggested that this guideline is overly rigid, since it does not take into account interindividual variations in pharmacokinetics and susceptibility to toxicity, which may be considerable. Furthermore the authors considered the evidence for effectiveness of this dosage limitation to be equivocal. They suggested beginning therapy at 1.4 mg/m^2 and adjusting subsequent doses according to toxicity.

For UK recommendations on dilution of intravenous vinca alkaloids see Administration Error, under Adverse Effects, above.

1. McCune JS, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm* 1997; **54:** 1755–8.

Administration in hepatic impairment. Licensed product information states that the dose of vincristine should be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL (51 micromoles/litre).

Amyloidosis. For mention of regimens including vincristine used in the management of amyloidosis, see p.743.

Blood disorders, non-malignant. Vincristine may be employed in the treatment of various auto-immune blood disorders, see under Vinblastine, p.786.

Malignant neoplasms. Vincristine is widely used in the treatment of malignant neoplasms. It is a fundamental part of potentially curative regimens for acute lymphoblastic leukaemia, Hodgkin's disease and aggressive non-Hodgkins lymphomas (see p.651, p.655 and p.656). It has also been used in chronic lymphocytic leukaemia (p.653) and in other non-Hodgkin's lymphomas including AIDS-related lymphoma (p.657), Burkitt's lymphoma (p.657) and mycosis fungoides (p.657). Other haematological malignancies in which it may be tried include multiple myeloma (p.658). Among the solid neoplasms, vincristine is used in regimens to treat gestational trophoblastic tumours (p.650), tumours of the brain (p.660), head and neck (p.666), Wilms' tumour (p.667), small-cell lung cancer (p.668), and thymoma (p.674). It is also employed in regimens for neuroblastoma (p.674), retinoblastoma (p.675), and some sarcomas including sarcomas of bone, Kaposi's sarcoma, and rhabdomyosarcoma (see p.675, p.675, and p.676).

Preparations

BP 2008: Vincristine Injection;
USP 31: Vincristine Sulfate for Injection; Vincristine Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Vinces; ***Austral.:*** Oncovin; ***Austria:*** Oncovin; ***Belg.:*** Oncovin; Vincrisin; ***Braz.:*** Biocrist†; Oncovin†; Tecnocris; Vincizina; Vincrifil†; Vincristex†; Vinracine†; ***Chile:*** Citomid; Oncovin†; ***Cz.:*** Citomid†; ***Denm.:*** Oncovin; ***Fin.:*** Oncovin†; ***Fr.:*** Oncovin; ***Ger.:*** Cellcristin; Farmistin†; Onkocristin; ***Gr.:*** Oncovin; ***India:*** Biocristine; Cytocristin; Neocristin; ***Malaysia:*** Vinracine; ***Mex.:*** Citomid; Ifavin†; Oncovin; Vinblax†; Vincasar†; Vintec; ***Norw.:*** Oncovin†; ***Philipp.:*** Alcavixin; Nevexitin; ***Port.:*** Faulcris†; Oncovin†; ***Rus.:*** Citomid (Цитомид)†; ***S.Afr.:*** Oncovin†; ***Spain:*** Vincrisul; ***Swed.:*** Oncovin; ***Switz.:*** Oncovin; ***Thai.:*** Citomid; ***UK:*** Oncovin; ***USA:*** Oncovin; Vincasar PFS; ***Venez.:*** Oncovin†.

Vindesine Sulfate *(USAN, rINNM)*

Compound 112531 (vindesine); Desacetyl Vinblastine Amide Sulfate; LY-099094; NSC-245467 (vindesine or vindesine sulfate); Sulfato de vindesina; Vindesiinisulfaatti; Vindésine, sulfate de; Vindesine Sulphate *(BANM)*; Vindesini sulfas; Vindesinsulfat; Vindesin-sulfát; Vindezino sulfatas; Vindezin-szulfát. 3-Carbamoyl-4-*O*-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate.

Виндезина Сульфат

$C_{43}H_{55}N_5O_7,H_2SO_4$ = 852.0.

CAS — 53643-48-4 (vindesine); 59917-39-4 (vindesine sulfate).

ATC — L01CA03.

ATC Vet — QL01CA03.

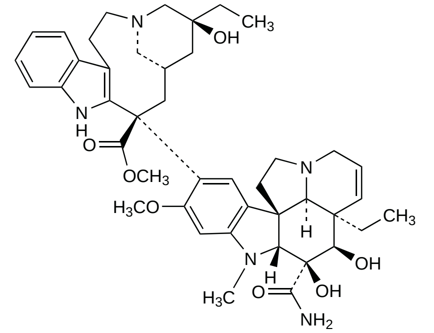

(vindesine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Vindesine Sulphate). A white or almost white, hygroscopic, amorphous substance. Freely soluble in water and in methyl alcohol; practically insoluble in cyclohexane. The pH of a 0.5% solution in water is 3.5 to 5.5. Store in airtight polypropylene containers with a polypropylene cap, at a temperature not exceeding –50°.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786.

The main dose-limiting effect of vindesine is granulocytopenia, with the nadir of the white cell count usually occurring 3 to 5 days after a dose and recovery after a further 4 to 5 days. Although neurotoxicity occurs it may be less severe than that seen with vincristine (see p.787). Alopecia is the most common adverse effect.

Folinic acid has been suggested for the treatment of overdosage by analogy with vincristine.

Vindesine should not be given by the intrathecal route, as this may produce fatal toxicity. Care should be taken if acute abdominal pain occurs: further doses may result in paralytic ileus.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* In a 10-year-old child accidentally given an intrathecal injection of vindesine, treatment with folinic acid and dexamethasone produced transient recovery but symptoms subsequently recurred and the patient died of progressive ascending paralysis.[1] The CNS showed changes at necropsy similar to those seen after intrathecal vincristine. Other fatal cases[2] have subsequently been reported. For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p.787.

1. Robbins G. Accidental intrathecal injection of vindesine. *BMJ* 1985; **291:** 1094.
2. Nisse P, *et al.* Administration accidentelle intrathécale de vindésine: à propos de 2 cas mortels. *Therapie* 2007; **62:** 360–1.

Interactions

As for Vinblastine Sulfate, p.786.

Pharmacokinetics

The pharmacokinetics of vindesine are similar to those of the other vinca alkaloids. After intravenous doses elimination from the blood is triphasic; the drug is rapidly distributed to body tissues. The terminal half-life is reported to be about 20 hours. It is metabolised primarily in the liver and excreted in bile and urine.

Uses and Administration

Vindesine sulfate is an antineoplastic agent derived from vinblastine (see p.785); like the other vinca alkaloids it causes mitotic arrest in metaphase by binding to microtubular protein. It is used in the treatment of refractory acute lymphoblastic or chronic myeloid leukaemias, and malignant melanoma. It has also been tried in malignant neoplasms of the breast, and lung. See also the cross references given below.

Vindesine sulfate is given weekly by intravenous injection. It may be given as a solution containing 1 mg/mL in sodium chloride injection 0.9%. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vindesine should generally be diluted to a volume of at least 20 mL to avoid inadvertent intrathecal use; higher concentrations can be used for children under 10 years of age. Care should be taken to avoid extravasation and it may be given into a fast-running infusion of sodium chloride, glucose 5%, or glucose-saline injection. The usual starting dose for adults is 3 mg/m^2 which may be raised by increments of 500 micrograms/m^2 weekly providing that the granulocyte and platelet counts do not fall below acceptable levels (see also Bone-marrow Depression, p.639), and acute abdominal pain is not experienced; weekly doses are usually between 3 and 4 mg/m^2. Children may be given 4 mg/m^2 initially, with weekly doses usually ranging between 4 and 5 mg/m^2. An alternative regimen for children with leukaemia is 2 mg/m^2 daily for 2 consecutive days, repeated after an interval of 5 to 7 days. Blood counts should be made before each injection. It may be necessary to reduce initial doses in patients with significantly impaired hepatic function.

Malignant neoplasms. Vindesine has been tried in refractory metastatic melanoma (p.673), childhood acute lymphoblastic leukaemia (p.651), chronic myeloid leukaemia in blastic crisis (p.653), and neuroblastoma (p.674). It is also under investigation in lung cancer, particularly non-small cell lung cancer (p.668) and responses have been reported in advanced breast cancer (p.661).

Preparations

BP 2008: Vindesine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Eldisine†; ***Austral.:*** Eldisine†; ***Austria:*** Eldisin; ***Belg.:*** Eldisine; ***Cz.:*** Eldisine†; ***Fin.:*** Eldisine†; ***Fr.:*** Eldisine; ***Ger.:*** Eldisine; ***Gr.:*** Eldisine; Enison; Gesidine; ***Irl.:*** Eldisine; ***Ital.:*** Eldisine; ***Neth.:*** Eldisine; ***Port.:*** Gesidine; ***S.Afr.:*** Eldisine†; ***Spain:*** Enison; ***Swed.:*** Eldisine; ***Switz.:*** Eldisine; ***UK:*** Eldisine.

Vinflunine *(rINN)*

F-12158; F-13840; L-0070; Vinflunina; Vinfluninum. 4′-Deoxy-20′,20′-difluoro-8′-norvincaleukoblastine.

Винфлунин

$C_{45}H_{54}F_2N_4O_8$ = 816.9.

CAS — 162652-95-1 (vinflunine); 194468-36-5 (vinflunine tartrate).

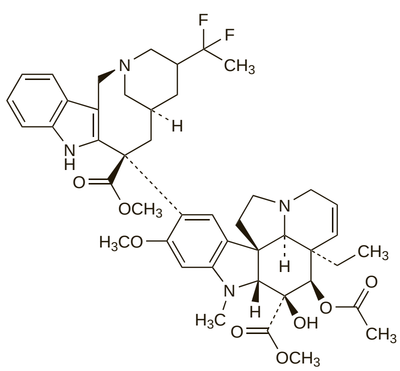

Profile

Vinflunine is a vinca alkaloid derived from vinorelbine (p.789) that is under investigation for the treatment of bladder cancer and non-small cell lung cancer.

Vinorelbine Tartrate *(BANM, USAN, rINNM)*

5′-Nor-anhydrovinblastine Tartrate; Tartrato de vinorelbina; Vinorelbiinitartraatti; Vinorelbin Bitartrat; Vinorelbin-ditartarát; Vinorelbine Ditartrate; Vinorelbine, tartrate de; Vinorelbini Ditartras; Vinorelbini tartras; Vinorelbino tartratas; Vinorelbintartrat. 3′,4′-Didehydro-4′-deoxy-8′-norvincaleukoblastine ditartrate.

Винорелбина Тартрат

$C_{45}H_{54}N_4O_8,2C_4H_6O_6$ = 1079.1.

CAS — 71486-22-1 (vinorelbine); 125317-39-7 (vinorelbine tartrate).

ATC — L01CA04.

ATC Vet — QL01CA04.

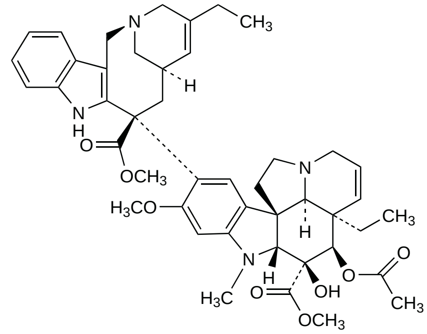

(vinorelbine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Vinorelbine Tartrate). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in hexane. A 1.4% solution in water has a pH of 3.3 to 3.8. Store under an inert gas at a temperature not exceeding −15°. Protect from light.

USP 31 (Vinorelbine Tartrate). A white to yellow or light brown amorphous powder. Freely soluble in water. pH of a 1% solution in water is between 3.3 and 3.8. Store at a temperature between −25° and −10° in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p.786. The main dose-limiting effect of vinorelbine is granulocytopenia. The nadir of the granulocyte count occurs 5 to 10 days after a dose, with recovery usually after a further 7 to 14 days. The drug should be stopped if moderate or severe neurotoxicity develops. Local pain and thrombophlebitis may be seen with repeated injection of vinorelbine. Gastrointestinal effects such as nausea and vomiting are common with the oral formulation.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p.787.

Effects on the gastrointestinal tract. For reference to a report of vinorelbine possibly exacerbating ischaemic colitis in patients receiving docetaxel, see p.711.

Interactions

As for Vinblastine Sulfate, p.786.

Pharmacokinetics

As with the other vinca alkaloids, vinorelbine exhibits triphasic pharmacokinetics after intravenous injection, and has a terminal half-life of between about 28 and 44 hours. It is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations achieved between 1.5 and 3 hours after oral doses. It is metabolised in the liver; deacetylvinorelbine has antineoplastic activity. Vinorelbine and its metabolites are excreted primarily in faeces via the bile but also in urine.

◊ References.

1. Levêque D, Jehl F. Clinical pharmacokinetics of vinorelbine. *Clin Pharmacokinet* 1996; **31:** 184–97.
2. Marty M, *et al.* Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors. *Ann Oncol* 2001; **12:** 1643–9.
3. Bugat R, *et al.* The effects of food on the pharmacokinetic profile of oral vinorelbine. *Cancer Chemother Pharmacol* 2002; **50:** 285–90.
4. Variol P, *et al.* A simultaneous oral/intravenous population pharmacokinetic model for vinorelbine. *Eur J Clin Pharmacol* 2002; **58:** 467–76.
5. Wong M, *et al.* Predictors of vinorelbine pharmacokinetics and pharmacodynamics in patients with cancer. *J Clin Oncol* 2006; **24:** 2448–55.

Uses and Administration

Vinorelbine is a semisynthetic derivative of vinblastine (p.786) with similar general properties. It is used in the treatment of advanced breast cancer and non-small cell lung cancers (see p.661 and p.668 respectively), and has been tried in other malignancies including lymphomas and tumours of ovary and prostate.

Vinorelbine is given as the tartrate but doses are calculated in terms of vinorelbine: vinorelbine tartrate 1.385 mg is equivalent to about 1 mg of vinorelbine. It may be given by intravenous injection over 5 to 10 minutes, as a solution containing the equivalent of vinorelbine 1.5 to 3 mg/mL in glucose 5% or sodium chloride 0.9% injection, directly or into a freely-running intravenous infusion. However, UK guidelines recommend that for patients over the age of 10 years, solutions of vinorelbine should generally be diluted to a volume of at least 20 mL to avoid inadvertent intrathecal use; higher concentrations can be used for children under 10 years of age. It may also be given by intravenous infusion over 20 to 30 minutes after dilution in 125 mL of glucose 5% or sodium chloride 0.9%.

The usual initial intravenous dose in the treatment of breast cancer or non-small cell lung cancer is the equivalent of vinorelbine 25 to 30 mg/m^2 weekly. In the UK, the manufacturers recommend that if the neutrophil count falls below 2000 cells/mm^3 subsequent doses should be delayed until recovery. In the USA it is suggested that subsequent doses should be halved if granulocyte counts fall to between 1000 and 1500 cells/mm^3; treatment should be interrupted if counts are below 1000 cells/mm^3 and stopped if granulocytopenia persists for more than 2 weeks (see also Bone-marrow Depression, p.639). Doses should also be reduced in hepatic impairment and in patients with massive liver metastases (but see also below).

In the treatment of non-small cell lung cancer, vinorelbine is also given orally at a dose of 60 mg/m^2 once weekly for 3 weeks. Subsequent doses may be increased to 80 mg/m^2, unless the neutrophil count falls below 500 cells/mm^3, or to between 500 and 1000 cells/mm^3 on two separate occasions, in which case the dose is kept at 60 mg/m^2 for the next 3 doses.

◊ References.

1. Gregory RK, Smith IE. Vinorelbine—a clinical review. *Br J Cancer* 2000; **82:** 1907–13.
2. Sarris AH, *et al.* Infusional vinorelbine in relapsed or refractory lymphomas. *Leuk Lymphoma* 2000; **39:** 291–9.
3. Sorensen P, *et al.* Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. *Gynecol Oncol* 2001; **81:** 58–62.
4. Oudard S, *et al.* Phase II study of vinorelbine in patients with androgen-independent prostate cancer. *Ann Oncol* 2001; **12:** 847–52.
5. Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. *Clin Breast Cancer* 2001; **2:** 113–28.
6. Aapro MS, *et al.* Developments in cytotoxic chemotherapy: advances in treatment utilising vinorelbine. *Crit Rev Oncol Hematol* 2001; **40:** 251–63.
7. Gridelli C, De Vivo R. Vinorelbine in the treatment of non-small cell lung cancer. *Curr Med Chem* 2002; **9:** 879–91.
8. Freyer G, *et al.* Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 2003; **21:** 35–40.
9. Gebbia V, Puozzo C. Oral versus intravenous vinorelbine: clinical safety profile. *Expert Opin Drug Saf* 2005; **4:** 915–28.
10. Aapro MS, *et al.* Oral vinorelbine: role in the management of metastatic breast cancer. *Drugs* 2007; **67:** 657–67.
11. Gralla RJ, *et al.* Oral vinorelbine in the treatment of non-small cell lung cancer: rationale and implications for patient management. *Drugs* 2007; **67:** 1403–10.

Administration in hepatic impairment. Clearance of vinorelbine was markedly reduced in patients with diffuse liver metastases and hence severely altered hepatic function: a 50% dose reduction was probably appropriate in such patients even if hyperbilirubinaemia was not marked.[1] However, reduced doses were not necessary in patients with moderate liver involvement in whom liver function, as measured by lidocaine metabolism, was not markedly reduced. Licensed product information in the UK suggests that the intravenous dose be reduced by one-third in patients with massive liver metastases (more than 75% of liver volume replaced by tumour cells).

In the USA, licensed information recommends that the intravenous dose of vinorelbine be reduced by 50% in patients with bilirubin values of 2.1 to 3 mg per 100 mL and by 75% in those with bilirubin greater than 3 mg per 100 mL.

1. Robieux I, *et al.* Pharmacokinetics of vinorelbine in patients with liver metastases. *Clin Pharmacol Ther* 1996; **59:** 32–40.

Preparations

USP 31: Vinorelbine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Filcrin; Navelbine; Neocitec; Sulcoline; Vilbine†; Vilne; Vinarine; Vinkebir; Vinorel; Vinorgen; ***Austral.:*** Navelbine; ***Austria:*** Navelbine; ***Belg.:*** Navelbine; ***Braz.:*** Navelbine; Neocitec; Norelbin; ***Canad.:*** Navelbine; ***Chile:*** Navelbine; ***Cz.:*** Navelbine; Navirel; Nibrevin; ***Denm.:*** Navelbine; Navirel; ***Fin.:*** Navelbine; ***Fr.:*** Navelbine; ***Ger.:*** Navelbine; ***Gr.:*** Navelbine; ***Hong Kong:*** Navelbine; ***Hung.:*** Navelbin; ***India:*** Vinelbine; ***Israel:*** Navelbine; ***Ital.:*** Navelbine; ***Jpn:*** Navelbine; ***Malaysia:*** Navelbine; ***Mex.:*** Navelbine;

Viessia; Vinilex; ***Neth.:*** Navelbine; ***Norw.:*** Navelbine; ***NZ:*** Navelbine; ***Philipp.:*** Navelbine; Vinotel; ***Pol.:*** Navelbine; Navirel; ***Port.:*** Navelbine; Vinorel; ***Rus.:*** Maverex (Маверекс); Navelbine (Навельбин); ***S.Afr.:*** Navelbine; ***Singapore:*** Navelbine; ***Spain:*** Navelbine; ***Swed.:*** Navelbine; ***Switz.:*** Navelbine; ***Thai.:*** Navelbine; Vinelbine; ***Turk.:*** Navelbine; ***UK:*** Navelbine; ***USA:*** Navelbine.

Vorinostat *(USAN, rINN)*

SAHA; Suberoylanilide Hydroxamic Acid; Vorinostatum. *N*-Hydroxy-*N′*-phenyl octanediamide.

Вориностат

$C_{14}H_{20}N_2O_3$ = 264.3.

CAS — 149647-78-9.

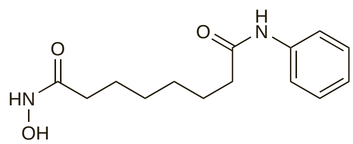

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects of vorinostat are gastrointestinal disturbances, fatigue, chills, dry mouth and taste disorders. Thrombocytopenia and anaemia also occur commonly, and are dose-related; dose reductions may be necessary and in some instances, therapy may need to be stopped. Pulmonary embolism has occurred. Other adverse effects include muscle spasms, alopecia, dizziness, peripheral oedema, headache, pruritus, cough, upper respiratory-tract infection, and pyrexia. Hypokalaemia and hyperglycaemia have been reported, as has prolongation of the QT interval. Blood cell counts, electrolytes, glucose, and serum creatinine should be monitored every 2 weeks during the first 2 months of therapy and monthly thereafter. Baseline and periodic ECG monitoring should be performed.

Interactions

Severe thrombocytopenia and gastrointestinal bleeding have been reported when vorinostat has been given with other histone deacetylase inhibitors such as valproic acid; platelet counts should be monitored every 2 weeks for the first 2 months of therapy. Vorinostat may prolong prothrombin time and affect the INR in patients receiving coumarin anticoagulants.

Pharmacokinetics

After an oral dose of vorinostat with a high-fat meal, mean time to maximum plasma concentration was about 4 hours; this was reduced to 1.5 hours after fasting. Aside from this decrease in the rate of absorption, a high-fat meal also increased the extent of absorption. While these results were stated not to be clinically significant, licensed product information recommends that vorinostat be taken with food. Plasma protein binding is about 71%. Vorinostat is metabolised by glucuronidation and hydrolysis followed by oxidation; metabolites are pharmacologically inactive. Less than 1% of a dose is recovered in the urine as unchanged drug. The mean terminal half-life is about 2 hours for vorinostat.

◊ References.

1. Rubin EH, *et al.* A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* 2006; **12:** 7039–45.

Uses and Administration

Vorinostat is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Non-Hodgkin's Lymphomas, p.656). The recommended dose is 400 mg orally, given once daily with food. This may be reduced to 300 mg once daily, with a further reduction to 300 mg once daily for 5 consecutive days of each week, if needed. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Vorinostat is also under investigation for the treatment of multiple myeloma and mesothelioma.

◊ References.

1. O'Connor OA. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol* 2006; **24:** 166–73.
2. Krug LM, *et al.* Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. *Clin Lung Cancer* 2006; **7:** 257–61.
3. Richon VM. Cancer biology: mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Br J Cancer* 2006; **95** (suppl): S2–S6.
4. O'Connor OA. Clinical experience with the novel histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in patients with relapsed lymphoma. *Br J Cancer* 2006; **95** (suppl): S7–S12.
5. Duvic M, Zhang C. Clinical and laboratory experience of vorinostat (suberoylanilide hydroxamic acid) in the treatment of cutaneous T-cell lymphoma. *Br J Cancer* 2006; **95** (suppl): S13–S19.
6. Anonymous. Vorinostat (Zolinza) for cutaneous T-Cell lymphoma. *Med Lett Drugs Ther* 2007; **49:** 23–4.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Zolinza.

Vorozole *(BAN, USAN, rINN)* ⊗

R-83842; Vorozol; Vorozolum. (+)-6-[4-Chloro-α-(1,2,4-triazol-1-yl)benzyl]-1-methyl-1*H*-benzotriazole.

Ворозол

$C_{16}H_{13}ClN_6$ = 324.8.

CAS — 129731-10-8.

ATC — L02BG05.

ATC Vet — QL02BG05.

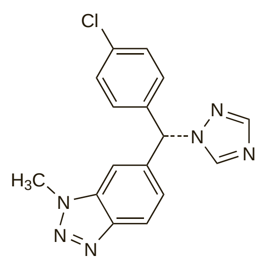

Profile

Vorozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system. It has been investigated in the treatment of breast cancer.

◊ References.

1. Goss PE, *et al.* Randomized phase III trial comparing the new potent and selective third-generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients. *J Clin Oncol* 1999; **17:** 52–63.
2. Harper-Wynne CL, *et al.* Comparison of the systemic and intratumoral effects of tamoxifen and the aromatase inhibitor vorozole in postmenopausal patients with primary breast cancer. *J Clin Oncol* 2002; **20:** 1026–35.

Zinostatin *(USAN, rINN)*

Neocarzinostatin; NSC-69856; NSC-157365; Zinostatina; Zinostatine; Zinostatinum.

Зиностатин

CAS — 9014-02-2.

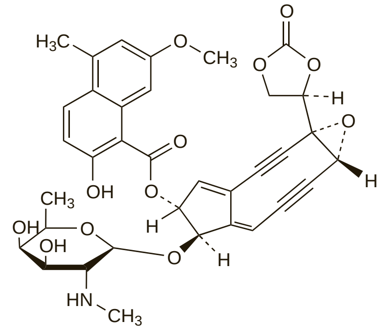

Description. Zinostatin is an antineoplastic antibiotic obtained from *Streptomyces carzinostaticus*.

Pharmacopoeias. *Jpn* includes zinostatin stimalamer.

Profile

Zinostatin is an antibiotic with antineoplastic activity and has been used in the treatment of malignant neoplasms.

Zinostatin stimalamer (SMANCS), a conjugate of zinostatin with a styrene-maleic acid polymer, is used for the treatment of liver cancer.

Zorubicin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de zorubicina; NSC-164011; RP-22050 (zorubicin); Zorubicine, Chlorhydrate de; Zorubicini Hydrochloridum. Benzoic acid (2*S*-*cis*)-{1-[4-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxonaphthacen-2-yl]ethylidene}hydrazide hydrochloride.

Зорубицина Гидрохлорид

$C_{34}H_{35}N_3O_{10},HCl$ = 682.1.

CAS — 54083-22-6 (zorubicin); 36508-71-1 (zorubicin hydrochloride).

ATC — L01DB05.

ATC Vet — QL01DB05.

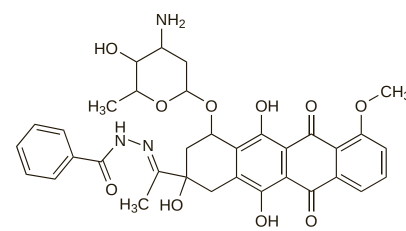

(zorubicin)

Profile

Zorubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (see p.712). It has been used as the hydrochloride in the treatment of acute leukaemias.

Antiparkinsonian Drugs

The antiparkinsonian drugs described in this chapter can be broadly divided into 2 groups; the **dopaminergics**, drugs that are used to potentiate the actions of dopamine, and the **antimuscarinics**, drugs that are used to reduce excessive central cholinergic effects.

Dopamine is a key neurotransmitter in the CNS; in particular, striatal dopamine depletion is associated with the clinical condition of parkinsonism. Dopamine also inhibits prolactin release from the pituitary and is believed to be the prolactin-release inhibiting factor (PRIF or PIF); dopamine deficiency in the pituitary is associated with conditions characterised by hyperprolactinaemia. Accordingly, drugs that replenish central dopamine or that can act as stimulants of dopamine receptors (dopamine agonists), may alleviate the symptoms of parkinsonism (see below), hyperprolactinaemia (p.2079), and related disorders.

At least 5 subtypes of dopamine receptor are thought to exist: D_1 receptors appear to stimulate adenylate cyclase activity; D_2 receptors activate various systems and inhibit adenylate cyclase activity. D_3, D_4, and D_5 receptors have been less well studied but D_3 and D_4 are similar to D_2, forming the D_2-like group, whereas D_1 and D_5 form the D_1-like group. D_2 receptors have been implicated in the pathophysiology of parkinsonism and schizophrenia.

Dopaminergics, or drugs that enhance their actions, described in this chapter include:

- levodopa, which is converted by decarboxylation into dopamine in the body, and which, unlike dopamine itself, can penetrate the blood-brain barrier and supply a source of dopamine to the brain
- the peripheral dopa-decarboxylase inhibitors, benserazide and carbidopa, which have no dopaminergic action of their own but increase the availability of levodopa
- apomorphine, which is structurally related to dopamine and acts as a dopamine agonist
- the adamantanamine, amantadine, which may augment dopaminergic activity
- the ergot derivatives, bromocriptine, cabergoline, lisuride, and pergolide, which act as dopamine agonists
- various other non-ergot dopamine agonists, such as piribedil, pramipexole, ropinirole, rotigotine, talipexole, and terguride
- the specific monoamine oxidase type B inhibitors, rasagiline and selegiline, which enhance the action of dopamine and levodopa
- the catechol-*O*-methyltransferase inhibitors (COMT-inhibitors), entacapone and tolcapone, which enhance the action of levodopa

Antimuscarinic drugs are used in Parkinson's disease (idiopathic or primary parkinsonism) and, particularly, drug-induced parkinsonism. They act by reducing the excessive central cholinergic effects of dopamine deficiency. Antimuscarinics described in this chapter include the tertiary amines, such as benzatropine, orphenadrine, procyclidine, and trihexyphenidyl, which are the most commonly used in the treatment of parkinsonism.

Parkinsonism

The syndrome of parkinsonism is characterised by tremor, rigidity, akinesia or bradykinesia, and loss of postural reflexes, associated with reduced dopamine activity in the brain. It may be **classified** as follows:

- primary (idiopathic) parkinsonism, usually referred to as Parkinson's disease (formerly paralysis agitans)
- secondary (acquired) parkinsonism, including postencephalitic parkinsonism, drug-induced parkinsonism, and symptoms associated with manganese poisoning
- 'parkinsonism-plus' syndromes where parkinsonism is a feature of other degenerative diseases of the CNS, such as progressive supranuclear palsy and multiple system atrophy

'Arteriosclerotic parkinsonism' has been used to describe parkinsonism associated with cerebrovascular disease, although this may be confusing since vascular brain damage is not a cause of Parkinson's disease.

The term parkinsonism is often used for the idiopathic form, that is, Parkinson's disease. Parkinson's disease and postencephalitic parkinsonism have been attributed primarily to depletion of striatal dopamine in the basal ganglia as a result of the loss of neurones in the substantia nigra. Striatal dopamine deficiency results in loss of the normal functional balance between dopaminergic and cholinergic activity and the aim of treatment is to increase the former and/or decrease the latter.

The **cause** of *Parkinson's disease* is not established, although environmental and genetic factors are probably superimposed on a background of neuronal loss related to ageing. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a contaminant of an illicitly produced pethidine analogue MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), causes irreversible parkinsonism similar to Parkinson's disease. This effect appears to follow conversion by monoamine oxidase B to the neurotoxic methylphenylpyridinium ion which is selectively concentrated in dopaminergic neurones in the substantia nigra. It has been proposed that free radicals produced during normal metabolism of dopamine in the brain by monoamine oxidase B might be similarly neurotoxic to dopaminergic neurones in the substantia nigra (the oxidant stress hypothesis). This has led to concern that use of levodopa, by increasing the supply of dopamine, might therefore exacerbate neurodegeneration and hasten the progression of Parkinson's disease but compelling evidence of such an effect is lacking.

Drug-induced parkinsonism (see Extrapyramidal Disorders, p.971) can arise from depletion of presynaptic dopamine, as with reserpine and tetrabenazine, or from blockade of postsynaptic dopamine receptors in the striatum, as by antipsychotics and some antiemetics such as metoclopramide. It is generally reversible on drug withdrawal or dose reduction and may sometimes disappear gradually despite continuous drug therapy. Although the use of levodopa to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, it has generally been reported to be ineffective or to increase psychiatric symptoms. Antimuscarinics may provide relief from the extrapyramidal symptoms that occur as adverse effects of antipsychotic therapy; however, they do not relieve the symptoms of tardive dyskinesia and should be withdrawn if it develops.

There is no cure for Parkinson's disease. Although the possibility of using drug therapy to slow neurodegeneration is being investigated, no drug so far has a proven neuroprotective effect. **Treatment** is palliative and symptomatic and consists mainly of drug therapy supplemented when necessary with physical treatment such as physiotherapy and speech therapy. Surgery is occasionally used and there is growing interest in the use of transplantation and in electrical devices for the control of tremor.

Drugs used in Parkinson's disease. Drug therapy consists largely of the use of dopaminergics or antimuscarinics in an attempt to restore the normal balance between dopaminergic and cholinergic activity. Dopaminergics may act by direct replacement of dopamine, by delaying the metabolism of endogenous dopamine, by stimulation of dopamine receptors directly, or by enhancement of release of endogenous dopamine. Drugs with differing actions are often used together to achieve optimum control of symptoms.

- *Levodopa* is the most effective symptomatic treatment. It is converted by decarboxylation into dopamine and, unlike dopamine, can penetrate the blood-brain barrier and supply a source of dopamine to the brain. Levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as *benserazide* or *carbidopa*. These drugs are unable to penetrate the blood-brain barrier and therefore prevent only extracerebral conversion of levodopa to dopamine. This allows effective concentrations of dopamine to be achieved in the brain with lower doses of levodopa and also reduces nausea and vomiting and other adverse effects associated with peripheral formation of dopamine.

  The majority of patients respond initially to levodopa and its use has improved the quality and duration of life. However, after 2 years or more, benefit is reduced as the disease progresses and late complications emerge. Apart from dyskinesias and psychiatric effects, a major problem with long-term levodopa treatment is the appearance of fluctuations in mobility, the two predominant forms being 'end-of-dose' deterioration ('wearing-off' effect) and the 'on-off' phenomenon (see Complications of Treatment, below). Thus, views differ as to the best time to start treatment and the dosage to use in order to limit the long-term complications.

  Catechol-*O*-methyltransferase (COMT) inhibitors, such as *entacapone* and *tolcapone*, are selective and reversible inhibitors of COMT, with mainly peripheral actions. They are given as adjunctive therapy to patients experiencing fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations; because of the risk of serious hepatotoxicity, tolcapone should be restricted to when other adjunctive therapy is ineffective or contra-indicated. When levodopa is used with a peripheral dopa-decarboxylase inhibitor, *O*-methylation becomes the predominant form of metabolism of levodopa; adding a peripheral COMT inhibitor can thus extend the duration and effect of levodopa in the brain, and allow lower and less frequent doses of levodopa. They therefore can help to stabilise patients, especially those experiencing 'end-of-dose' deterioration.
- *Rasagiline* and *selegiline* are selective inhibitors of monoamine oxidase type B, an enzyme involved in the metabolism of dopamine in the brain. When used with levodopa in severe parkinsonism they have a dose-sparing effect and are of value in patients experiencing fluctuations in mobility. Early treatment with selegiline may delay the need for levodopa and there has been much interest in the possibility that these drugs might have neuroprotective effects, but it is difficult to separate any putative effect on disease progression from symptomatic benefits, and at present there is insufficient evidence to show that any treatment can slow progression of the disease. Used alone, selegiline produces few adverse effects but when used with levodopa it can provoke or worsen dyskinesias or psychiatric symptoms and doubts have been expressed on the safety of long-term use.
- Dopamine agonists such as *bromocriptine, cabergoline, lisuride, pergolide, pramipexole,* and *ropinirole* act by direct stimulation of remaining postsynaptic dopamine receptors. Dopamine agonists are increasingly used in the early treatment of younger patients with parkinsonism in an attempt to delay therapy with levodopa (younger patients are at an increased risk of motor complications with levodopa). However, their efficacy often decreases after a few years. In older patients they may be reserved for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating fluctuations in mobility in the later stages of the disease. *Apomorphine* is a potent dopamine agonist, but must be given parenterally and with an antiemetic. Although this restricts its use, it has a role in stabilising patients who suffer unpredictable 'on-off' effects. It is also used in the differential diagnosis of parkinsonism. Transdermal patches containing *rotigotine*, another dopamine agonist, are available for use as monotherapy in the treatment of early-stage Parkinson's disease and as an adjunct to levodopa therapy in some countries.
- *Antimuscarinics* are considered to have a weak antiparkinsonian effect compared with levodopa. They may reduce tremor but have little effect on bradykinesia. They may be of use alone or with other drugs in the initial treatment of patients with mild symptoms, especially when tremor is pronounced, or later as an adjunct to levodopa, such as in patients with refractory tremor or dystonias. Antimuscarinic adverse effects, particularly cognitive impairment, occur frequently and can limit their use. However, some antimuscarinic effects can ameliorate complications associated with Parkinson's disease; dry mouth may be an advantage in patients with sialor-

rhoea. There appear to be no important differences in the efficacy of antimuscarinics for Parkinson's disease but some patients may tolerate one drug better than another. Those commonly used for Parkinson's disease include *benzatropine, orphenadrine, procyclidine,* and *trihexyphenidyl*.

- *Amantadine* is a weak dopamine agonist with some antimuscarinic activity although its activity as an antagonist of *N*-methyl-D-aspartate may also have a beneficial effect in Parkinson's disease. It has mild antiparkinsonian effects compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity but only a small proportion of patients derive much benefit. It is used similarly to antimuscarinics in early disease when symptoms are mild, but tolerance to its effects can occur rapidly.

Choice and implementation of drug treatment. If symptoms are mild, drug therapy may not be required in the early stages of the disease. When symptoms become troublesome but are still relatively mild *amantadine* or an *antimuscarinic* may be started; antimuscarinics are useful when tremor predominates but are generally more suitable for younger patients and in drug-induced rather than idiopathic parkinsonism. Some have begun treatment with *selegiline* immediately, but there have been doubts over whether it has a neuroprotective effect, as postulated, and also over long-term safety. There is no consensus on when to start dopaminergic treatment or whether to begin with *levodopa* or a *dopamine agonist*. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms.

When levodopa does become necessary, the usual practice is to start with small doses, together with a peripheral dopa-decarboxylase inhibitor, and increase slowly to a dose which reduces disability to an acceptable level. Variations in response and diminishing effectiveness over the years necessitate careful adjustment of the size and form of the dose and the dosage schedule.

Complications of treatment. Fluctuations in mobility have been reported in more than half of patients on levodopa after 5 years of therapy. They generally proceed through predictable **'end-of-dose'** deterioration to the **'on-off'** phenomenon with marked very sudden swings from mobility to immobility. The cause of the fluctuations is not known, but multiple factors including desensitisation of dopamine receptors, interference with the response to dopamine by other levodopa metabolites such as 3-*O*-methyldopa, fluctuating plasma concentrations, and erratic transport of levodopa from blood to the brain have been suggested. It appears that as the disease progresses the capacity of the nigrostriatal dopaminergic system to synthesise and store dopamine, and to act as a buffer in maintaining dopamine brain concentrations, declines. Dopamine concentrations therefore become more dependent on levodopa dosage and the pattern of response will come to reflect more closely the rise and fall in levodopa concentrations. Eventually the effect of various factors that produce even small changes in plasma concentrations of levodopa will progressively become more pronounced.

Approaches to the management of 'end-of-dose' fluctuations include more frequent but smaller doses and the use of modified-release preparations. Addition of selegiline or partial replacement of levodopa by a dopamine agonist with a more prolonged action may also be tried.

Various attempts have been made to overcome the 'on-off' phenomenon. Those speculating that long-term treatment results in altered dopamine receptor sensitivity have used controlled withdrawal of levodopa for short periods ('drug holidays') but it is a dangerous procedure of doubtful value and no longer recommended.

Others have linked the 'on-off' phenomenon to variable plasma concentrations although, since transfer of levodopa into the brain involves active transport mechanisms, concentrations in plasma may not necessarily reflect those in the brain. Continuous intraduodenal or intravenous infusion of levodopa has been shown to reduce fluctuations in mobility, which suggests that dopamine receptors are still sensitive, although this is not practical for day-to-day management (but see below). However, there is evidence that some patients may benefit from modified-release formulations of levodopa with a peripheral dopa-decarboxylase or COMT inhibitor. As levodopa competes with amino acids for uptake into the brain, attempts to lessen fluctuations in dopamine brain concentrations have included taking levodopa on an empty stomach and also delaying most of a day's protein consumption until the evening. Addition of entacapone, rasagiline, selegiline, or a dopamine agonist may also help to reduce 'on-off' phenomena. If fluctuations remain a problem subcutaneous apomorphine is often effective. In some countries a gel formulation of levodopa with carbidopa is available for continuous infusion by an ambulatory pump into the duodenum when other available combination therapy has not been satisfactory.

Other complications of treatment with levodopa can include **dyskinesia**, which may respond to dosage adjustment or partial replacement of levodopa with a dopamine agonist. Amantadine may also be considered, although evidence is lacking. Some patients with Parkinson's disease may experience **severe pain** and **dystonia**; measures to increase 'on' periods can help reduce or eliminate pain in most patients.

Patients with Parkinson's disease can suffer from a range of **psychiatric effects**, such as depression, dementia, sleep disturbances, and psychosis, due to the adverse effects of drug therapy and to disease progression. It has been recommended that if patients develop psychotic reactions, an attempt to adjust their antiparkinsonian drugs should be tried before resorting to the use of antipsychotics. Although classical antipsychotics are usually contra-indicated because they can exacerbate parkinsonism, the atypical antipsychotics clozapine and quetiapine may be used in treatment-resistant psychosis—see Disturbed Behaviour, p.954. The cholinesterase inhibitor rivastigmine is licensed in some countries for the symptomatic treatment of mild to moderately severe dementia in Parkinson's disease. **Excessive daytime sleepiness** and **sudden onset of sleep** have been reported with dopamine agonists and patients should be warned of the possible risks (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805). **Fibrotic reactions** resulting in cardiovascular and pulmonary adverse effects have been reported with ergot derivatives and patients should be monitored (see Fibrosis, under Adverse Effects of Bromocriptine, p.799). **Nausea and vomiting** induced by dopaminergics may be minimised by introducing the drug gradually and giving the dose with food, but if this is ineffective or apomorphine is being used these effects can be controlled by the antiemetic domperidone. Domperidone does not readily cross the blood-brain barrier and therefore acts mainly as a peripheral dopamine antagonist. Tolerance to the nausea usually develops after a few weeks and domperidone may then be withdrawn.

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Amantadine *(BAN, pINN)*

Amantadiini; Amantadin; Amantadina; Amantadinum. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine.

Амантадин

$C_{10}H_{17}N$ = 151.2.

CAS — 768-94-5.

ATC — N04BB01.

ATC Vet — QN04BB01.

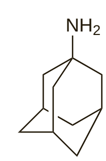

Amantadine Hydrochloride *(BANM, USAN, pINNM)*

1-Adamantanamine Hydrochloride; Amantadiinihydrokloridi; Amantadine, chlorhydrate d'; Amantadin-hidroklorid; Amantadin-hydrochlorid; Amantadinhydroklorid; Amantadini hydrochloridum; Amantadino hidrochloridas; EXP-105-1; Hidrocloruro de amantadina; NSC-83653. Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine hydrochloride.

Амантадина Гидрохлорид

$C_{10}H_{17}N,HCl$ = 187.7.

CAS — 665-66-7.

ATC — N04BB01.

ATC Vet — QN04BB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Amantadine Hydrochloride). A white or almost white crystalline powder. It sublimes on heating. Freely soluble in water and in alcohol.

USP 31 (Amantadine Hydrochloride). A white or practically white crystalline powder. Soluble 1 in 2.5 of water, 1 in 5.1 of alcohol, 1 in 18 of chloroform, and 1 in 70 of macrogol 400. pH of a 20% solution in water is between 3.0 and 5.5.

Amantadine Sulfate *(pINNM)*

Amantadine, Sulfate d'; Amantadine Sulphate; Amantadini Sulfas; Sulfato de amantadina.

Амантадина Сульфат

$(C_{10}H_{17}N)_2,SO_4$ = 398.6.
CAS — 31377-23-8.
ATC — N04BB01.
ATC Vet — QN04BB01.

Adverse Effects

Most adverse effects associated with amantadine therapy appear to be dose-related and relatively mild; some resemble those of antimuscarinic drugs. They may be reversed by withdrawing therapy but many resolve despite continuation.

Livedo reticularis, sometimes associated with ankle oedema, is quite common in patients given very high doses of amantadine or with long-term therapy. CNS effects such as anxiety, inability to concentrate, dizziness, insomnia, nightmares, headache, and changes in mood may occur. Psychotic reactions, hallucinations, and confusion have been reported, especially in the elderly, patients with renal impairment or psychiatric disorders, and those also receiving antimuscarinics.

Other adverse effects reported have included orthostatic hypotension, palpitations, urinary retention, slurred speech, ataxia, lethargy, anorexia, nausea, vomiting, dry mouth, constipation, skin rash, diaphoresis, photosensitisation, and blurred vision. There have been isolated reports of congestive heart failure, leucopenia, neutropenia, dyskinesias, oculogyric episodes, and convulsions.

Effects on the cardiovascular system. Congestive heart failure has been reported with amantadine;[1] the patient had been receiving combined treatment with amantadine, levodopa, and orphenadrine for 4 years. Others have considered that while amantadine sometimes causes ankle oedema, an association between amantadine and heart failure is not proven.[2] Livedo reticularis, a mottled blue discoloration of the skin due to prominence of the normal pattern of venous drainage, has been reported[2] to occur in about 50% of all elderly patients given amantadine 100 to 300 mg daily for 2 to 6 weeks and was associated with oedema in 5 to 10%. Both livedo and oedema have usually been confined to the legs and may result from the catecholamine-releasing action of amantadine in certain vascular beds; the oedema was unlikely to be due to heart failure. Angina, dyspnoea, pulmonary congestion, or distension of neck veins has also been reported[2] in 4 of 89 parkinsonian patients treated with amantadine; only 2 of these 4 had had ankle oedema before heart failure developed. No patient had been seen in whom heart failure seemed due directly to amantadine.

See also Overdosage, below.

1. Vale JA, Maclean KS. Amantadine-induced heart-failure. *Lancet* 1977; **i:** 548.
2. Parkes JD, *et al.* Amantadine-induced heart-failure. *Lancet* 1977; **i:** 904.

Effects on electrolytes. For a report of a patient who developed hyponatraemia when given amantadine or levodopa, see Effects on Kidney Function under Levodopa, p.805.

Effects on the eyes. Superficial punctate keratitis and corneal abrasion with loss of visual acuity was seen in both eyes of a 64-year-old man about 3 weeks after starting treatment with amantadine 100 mg daily.[1] Symptoms resolved on stopping amantadine but recurred when re-treatment with amantadine was attempted. In another report,[2] a 14-year-old boy developed bilateral corneal oedema with visual loss associated with amantadine treatment. He had been taking amantadine 300 mg daily for several months with numerous other drugs; symptoms resolved when amantadine was stopped.

1. Nogaki H, Morimatsu M. Superficial punctate keratitis and corneal abrasion due to amantadine hydrochloride. *J Neurol* 1993; **240:** 388–9.
2. Hughes B, *et al.* Reversible amantadine-induced corneal edema in an adolescent. *Cornea* 2004; **23:** 823–4.

Effects on mental function. It has been suggested[1] that the ability of amantadine and memantine to cause psychotic disturbances in patients with Parkinson's disease might be related to their action as *N*-methyl-D-aspartate antagonists.

1. Riederer P, *et al.* Pharmacotoxic psychosis after memantine in Parkinson's disease. *Lancet* 1991; **338:** 1022–3.

Effects on the nervous system. Peripheral sensory motor neuropathy secondary to long-term (8 years) use of amantadine has been reported[1] in a 48-year-old woman with parkinsonism. Trophic skin ulcers, paraesthesias, and distal weakness resolved on stopping amantadine.

1. Shulman LM, *et al.* Amantadine-induced peripheral neuropathy. *Neurology* 1999; **53:** 1862–5.

Overdosage. A patient with postencephalitic parkinsonism who had taken an estimated 2.8 g of amantadine hydrochloride in a suicide attempt developed acute toxic psychosis with disorientation, visual hallucinations, and aggressive behaviour.[1] Convulsions did not occur, possibly because he had been receiving phenytoin, which was continued. The patient was treated with hydration and chlorpromazine and recovered in 4 days.

A 2-year-old child who had ingested 600 mg of amantadine hydrochloride developed symptoms of acute toxicity, including agitation and dystonic posturing, despite emesis with 'syrup of ipecac'.[2] She responded immediately to a trial of physostigmine 500 micrograms intravenously, repeated after 10 minutes. Her pupils remained moderately dilated until about 20 hours after the ingestion; thereafter she made a full recovery.

Cardiac arrest developed 4 hours after a 37-year-old woman ingested 2.5 g of amantadine hydrochloride and was treated successfully.[3] However, ventricular arrhythmias, including torsade de pointes, continued over the ensuing 48 hours and may have been exacerbated by use of isoprenaline and dopamine. The patient was subsequently stabilised with lidocaine by intravenous infusion, but died of respiratory failure 10 days after admission.

1. Fahn S, *et al.* Acute toxic psychosis from suicidal overdosage of amantadine. *Arch Neurol*, 1971; **25:** 45–8.
2. Berkowitz CD. Treatment of acute amantadine toxicity with physostigmine. *J Pediatr* 1979; **95:** 144–5.
3. Sartori M, *et al*. Torsade de pointe: malignant cardiac arrhythmia induced by amantadine poisoning. *Am J Med* 1984; **77:** 388–91.

Precautions

Amantadine is usually contra-indicated in severe renal disease and in patients with a history of epilepsy or other seizure disorders, or gastric ulceration. It should also not be given to patients with untreated angle-closure glaucoma. Amantadine should be used with caution in patients with cardiovascular or liver disease, renal impairment, recurrent eczema, or psychiatric disorders. Suicide attempts, in some cases fatal, and suicidal ideation have been reported in patients taking amantadine. Care should be taken in all elderly patients, who may be more sensitive to antimuscarinic effects, and in whom renal clearance is likely to be reduced.

In common with other drugs having antimuscarinic properties amantadine may cause blurred vision or impair alertness; patients so affected should not drive or operate machinery.

Treatment with amantadine should not be stopped abruptly in parkinsonian patients since they may experience a sudden marked clinical deterioration. There have been isolated reports of a neuroleptic malignant-like syndrome associated with abrupt withdrawal of amantadine, especially in patients also receiving antipsychotics.

Antiviral resistance. See Influenza under Uses and Administration, below.

Breast feeding. Amantadine is distributed into breast milk and licensed product information states that adverse effects have occurred in infants being breast fed by mothers taking amantadine.

Pregnancy. Amantadine should not be used during pregnancy; embryotoxicity and teratogenicity have been reported in *rats* given high doses.[1]

A complex cardiovascular lesion occurred in an infant whose mother had taken amantadine hydrochloride 100 mg daily during the first 3 months of pregnancy.[1] In another case, tetralogy of Fallot and limb deformities were seen in the neonate of a mother who was given amantadine hydrochloride 100 mg daily for 7 days during the 4th and 6th weeks of gestation.[2] However, a report of the use of amantadine during 2 separate pregnancies by a woman with multiple sclerosis noted no abnormalities in either infant.[3]

1. Nora JJ, *et al.* Cardiovascular maldevelopment associated with maternal exposure to amantadine. *Lancet* 1975; **ii:** 607.
2. Pandit PB, *et al.* Tibial hemimelia and tetralogy of Fallot associated with first trimester exposure to amantadine. *Reprod Toxicol* 1994; **8:** 89–92.
3. Levy M, *et al.* Fetal outcome following intrauterine amantadine exposure. *Reprod Toxicol* 1991; **5:** 79–81.

Renal impairment. Evidence of extremely limited excretion of amantadine was found in 12 patients who were either anephric or had negligible renal function after a single 100-mg dose of amantadine hydrochloride.[1] Only small amounts were removed by dialysis. It was suggested that amantadine should be given with caution to patients requiring maintenance haemodialysis; a single dose may provide adequate plasma concentrations for many days.[1]

Dosage regimens based on creatinine clearance[2] or fixed doses at extended intervals[3] have been published. However, both regimens have been criticised and a conservative approach to amantadine dosage in these patients recommended[4] (for the regimens in licensed product information, see Administration in Renal Impairment, below). The need for caution in using amantadine in patients with renal impairment is highlighted by a report of a patient with end-stage renal disease who progressed from delirium to coma after receiving amantadine 100 mg twice daily for 3 days.[5]

1. Soung L-S, *et al.* Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med* 1980; **93:** 46–9.
2. Horadam VW, *et al.* Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. *Ann Intern Med* 1981; **94:** 454–8.
3. Wu MJ, *et al.* Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. *Clin Nephrol* 1982; **17:** 19–23.
4. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.
5. Macchio GJ, *et al.* Amantadine-induced coma. *Arch Phys Med Rehabil* 1993; **74:** 1119–20.

Withdrawal. Neuroleptic malignant syndrome occurred in a patient being treated for heat stroke when all his medication, including antipsychotics and amantadine, was withdrawn.[1] It is suggested that dopamine agonists should not be stopped in patients with hyperpyrexia at risk from this syndrome. In another report,[2] a 14-year-old boy being treated with amantadine for influenza A encephalopathy developed neuroleptic malignant syndrome when the drug was stopped after 5 days; the patient improved when amantadine treatment was resumed. The authors recommended a gradual reduction in dosage when stopping amantadine therapy.

Acute delirium developed in 3 elderly patients with Parkinson's disease after gradual withdrawal of long-term amantadine therapy;[3] symptoms resolved when amantadine was restarted.

1. Simpson DM, Davis GC. Case report of neuroleptic malignant syndrome associated with withdrawal from amantadine. *Am J Psychiatry* 1984; **141:** 796–7.
2. Ito T, *et al.* Neuroleptic malignant syndrome following withdrawal of amantadine in a patient with influenza A encephalopathy. *Eur J Pediatr* 2001; **160:** 401.
3. Factor SA, *et al.* Acute delirium after withdrawal of amantadine in Parkinson's disease. *Neurology* 1998; **50:** 1456–8.

Interactions

Amantadine may enhance the adverse effects of antimuscarinics and the dose of these drugs should be reduced when used with amantadine; adverse effects of levodopa may also be exacerbated.

Licensed product information states that amantadine should be used with caution in patients receiving drugs that affect the CNS. The rate of excretion of amantadine may be reduced by drugs that raise urinary pH.

Antiarrhythmics. *Quinine* and *quinidine* have been reported to reduce the renal clearance of amantadine in healthy male, but not female, subjects.[1] Patients taking these drugs together should be observed for signs of amantadine toxicity.

1. Gaudry SE, *et al.* Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. *Clin Pharmacol Ther* 1993; **54:** 23–7.

Antimalarials. For the possible effects of the use of *quinine* and *quinidine* with amantadine, see Antiarrhythmics, above.

Diuretics. A patient with Parkinson's disease, previously stabilised on amantadine hydrochloride 300 mg daily, developed symptoms of amantadine toxicity, including ataxia, myoclonus, and confusion, 7 days after starting treatment with a preparation containing *triamterene* and *hydrochlorothiazide* (*Dyazide*).[1] It was postulated that the effect was due to reduction of the tubular secretion of amantadine.

1. Wilson TW, Rajput AH. Amantadine-Dyazide interaction. *Can Med Assoc J* 1983; **129:** 974–5.

MAOIs. Hypertension occurred about 48 hours after starting treatment with *phenelzine sulfate* in a patient already receiving amantadine.[1]

1. Jack RA, Daniel DG. Possible interaction between phenelzine and amantadine. *Arch Gen Psychiatry* 1984; **41:** 726.

Pharmacokinetics

Amantadine hydrochloride is well absorbed from the gastrointestinal tract; peak concentrations in the plasma appear within about 4 hours after oral doses. Plasma protein binding is reported to be about 67%, with a substantial amount bound to erythrocytes; the concentration is about 2.7 times higher in erythrocytes than in plasma. It is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion although small amounts of an acetylated metabolite have also been detected in urine; the plasma elimination half-life is reported to be about 15 hours in patients with normal renal function but is significantly prolonged in the elderly and in patients with renal impairment. The rate of elimination may be increased by acidification of the urine. Amantadine crosses the placenta and the blood-brain barrier. It is also distributed into breast milk.

◊ References.

1. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; **14:** 35–51.

Uses and Administration

Amantadine is a weak dopamine agonist with some antimuscarinic activity; it is also an antagonist at *N*-methyl-D-aspartate receptors. Amantadine has mild antiparkinsonian activity and is used in the management of parkinsonism, mainly in early disease when symptoms are mild. It may improve bradykinesia, rigidity, and tremor but tolerance can develop.

Amantadine is also an antiviral that inhibits replication of influenza type A virus; it has very little or no activity against influenza type B virus. It is used prophylactically against infection with influenza type A virus and to ameliorate symptoms when given during the early stages of infection.

Amantadine has also been used in the management of herpes zoster.

Amantadine is usually given orally as the hydrochloride and the doses below are expressed in terms of this salt.

In **parkinsonism**, treatment is usually started with 100 mg daily, increasing to 100 mg twice daily after a week or more. Doses up to a maximum of 400 mg daily have occasionally been used. The lowest effective dose should be used in patients over 65 years of age because of the potential for reduced renal clearance in this age group. Withdrawal of amantadine treatment for parkinsonism should be gradual to avoid exacerbating the condition; UK licensed product information suggests decreasing the dose by half at weekly intervals.

The dose of amantadine in the UK for the treatment of **influenza A** is 100 mg daily, usually given for about 5 days. For the prophylaxis of influenza A the same dose is given for as long as protection from infection is required, which may be for about 6 weeks. If amantadine is being given with influenza vaccination then it is usually only given for up to 3 weeks after vaccination. Children aged 10 to 15 years may also be given 100 mg daily for the recommended period. A daily dose of less than 100 mg or 100 mg given at intervals greater than one day has been recommended for patients over 65 years of age.

Doses in the USA are higher than those in the UK: for the treatment of influenza A the daily dose is 200 mg daily as a single dose or in two divided doses, continued for 24 to 48 hours after the disappearance of symptoms. The same dose is given for the prophylaxis of influenza A for at least 10 days following exposure. If given with vaccination then amantadine should be taken for the next 2 to 4 weeks. The dose of amantadine should be reduced to 100 mg daily in patients aged 65 years and over, and in those who show intolerance to the higher dose. Children aged 1 to 9 years may be given 4.4 to 8.8 mg/kg daily to a maximum of 150 mg daily; older children may be given 100 mg twice daily.

In **herpes zoster**, treatment with 100 mg twice daily may be given for 14 days; if pain persists, treatment may be continued for a further 14 days.

The dosage of amantadine should be reduced in patients with renal impairment (see below).

Amantadine sulfate has been used similarly to the hydrochloride; it has been given by mouth or by intravenous infusion.

Administration. Amantadine sulfate has been used successfully in doses of up to 600 mg daily by intravenous infusion in the management of akinetic crisis in patients with Parkinson's disease.[1]

1. Gadoth N, *et al.* I.V. amantadine sulfate for extrapyramidal crisis. *Clin Pharm* 1985; **4:** 146.

Administration in renal impairment. The dose of amantadine should be reduced in patients with renal impairment by either reducing the total daily dose or by increasing the dosage interval in accordance with their creatinine clearance (CC).

In the UK the following doses are recommended:

- CC over 35 mL/min: 100 mg daily
- CC 15 to 35 mL/min: 100 mg every 2 to 3 days
- CC less than 15 mL/min: not recommended

In the USA the following doses are recommended:

- CC 30 to 50 mL/min: 200 mg on the first day followed by 100 mg daily thereafter
- CC 15 to 29 mL/min: 200 mg on the first day followed by 100 mg on alternate days
- CC less than 15 mL/min or those on haemodialysis: 200 mg every 7 days

See also under Precautions, above.

Extrapyramidal disorders. Amantadine has been used as an alternative to antimuscarinics[1] in the short-term management of *drug-induced extrapyramidal symptoms* (p.971). US licensed product information has recommended a usual dose of 200 mg daily in 2 divided doses increased up to 300 mg daily if necessary. However the development of tolerance has limited its usefulness. See also Parkinsonism, below.

Amantadine has been investigated in the management of *chorea* in patients with Huntington's disease.[2,3]

1. König P, *et al.* Amantadine versus biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 1996; **33:** 80–4.
2. Magnet MK, *et al.* Amantadine in the akinetic-rigid variant of Huntington's disease. *Ann Pharmacother* 2004; **38:** 1194–6.
3. Heckmann JM, *et al.* IV amantadine improves chorea in Huntington's disease: an acute randomized, controlled study. *Neurology* 2004; **63:** 597–8.

Hepatitis C. Amantadine has been investigated[1-4] as an addition to interferon-based antiviral regimens in the treatment of chronic hepatitis C infection (p.851). A meta-analysis[1] concluded that it was of no value in treatment-naive patients or relapsers, but that triple therapy with amantadine, ribavirin, and interferon improved sustained responses in patients previously unresponsive to therapy.

1. Deltenre P, *et al.* Evaluation of amantadine in chronic hepatitis C: a meta-analysis. *J Hepatol* 2004; **41:** 462–73.
2. Stauber RE, *et al.* Retreatment of patients with chronic hepatitis C not responding to interferon/ribavirin combination therapy with daily interferon plus ribavirin plus amantadine. *Wien Klin Wochenschr* 2004; **116:** 530–5.
3. Herrine SK, *et al.* Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci* 2005; **50:** 719–26.
4. Mangia A, *et al.* A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepatitis* 2005; **12:** 292–9.

Hiccup. Amantadine[1] has been reported to have produced beneficial results in patients with intractable hiccups (p.976).

1. Askenasy JJM, *et al.* Persistent hiccup cured by amantadine. *N Engl J Med* 1988; **318:** 711.

Influenza. Amantadine has been used similarly to rimantadine (p.904) in the prophylaxis and treatment of influenza A (p.859). In adults, the two drugs are equally effective, but amantadine is associated with more adverse effects;[1] further study on their safety and efficacy in children and the elderly is considered warranted.[2] Amantadine reduced the duration of influenza A symptoms when given in a dose of 200 mg daily within 48 hours of the onset of symptoms.[3] Vaccination is usually the method of choice for prophylaxis of influenza but amantadine has been used in addition to vaccination in certain individuals or when vaccination is contra-indicated. Although amantadine is licensed in the UK and USA for the prophylaxis and treatment of influenza A, its use for such purposes is not recommended.[4-6] Resistance to amantadine may occur rapidly.[7] For further information see Resistance, under Rimantadine, p.904.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 21/06/06).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 29/05/08).
3. Nicholson KG, Wiselka MJ. Amantadine for influenza A. *BMJ* 1991; **302:** 425–6.
4. NICE. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza: Technology Appraisal 58 (issued February 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/58_Flu_fullguidance.pdf (accessed 11/08/08)
5. NICE. Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza: Technology Appraisal 67 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/67_Flu_prophylaxis_guidance.pdf (accessed 11/08/08)
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 09/10/07)
7. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.

Multiple sclerosis. Amantadine has been used to alleviate fatigue associated with multiple sclerosis (p.892). However, a systematic review[1] concluded that there was insufficient evidence to support its use in reducing fatigue in patients with multiple sclerosis; further large controlled studies are considered warranted.

1. Pucci E, *et al.* Amantadine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 29/05/08).

Neuroleptic malignant syndrome. Amantadine has been tried[1-3] in the treatment of the neuroleptic malignant syndrome (p.972).

1. McCarron MM, *et al.* A case of neuroleptic malignant syndrome successfully treated with amantadine. *J Clin Psychiatry* 1982; **43:** 381–2.
2. Amdurski S, *et al.* A therapeutic trial of amantadine in haloperidol-induced malignant neuroleptic syndrome. *Curr Ther Res* 1983; **33:** 225–9.
3. Woo J, *et al.* Neuroleptic malignant syndrome successfully treated with amantadine. *Postgrad Med J* 1986; **62:** 809–10.

Parkinsonism. Amantadine's mechanism of action in parkinsonism (p.791) is unclear but may be due to its antimuscarinic activity and alterations in dopamine release and reuptake. It has also been suggested that amantadine's action as a non-competitive antagonist of *N*-methyl-D-aspartate may have a beneficial effect.[1,2] It has mild antiparkinsonian activity compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity and is used in a similar manner to antimuscarinics mainly in the treatment of patients with early Parkinson's disease when symptoms are mild. It may also be useful for dyskinesias in more advanced disease.[3] However, few patients obtain much benefit and tolerance to its effects can occur. Moreover, two systematic reviews[4,5] concluded that there was insufficient evidence from randomised controlled trials on the safety and efficacy of amantadine in the treatment of both Parkinson's disease and levodopa-induced dyskinesias in late disease.

Licensed product information suggests that the effectiveness of amantadine may be prolonged by withdrawing it for 3 to 4 weeks, continuing with existing antiparkinsonian therapy or starting low-dose levodopa treatment if clinically necessary in the meantime.

1. Laing P. Stroke treatment. *Lancet* 1991; **337:** 1601.
2. Greenamyre JT, O'Brien CF. N-Methyl- -aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991; **48:** 977–81.
3. Thomas A, *et al.* Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; **75:** 141–3.
4. Crosby N, *et al.* Amantadine in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).
5. Crosby NJ, *et al.* Amantadine for dyskinesia in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Withdrawal syndromes. *COCAINE.* Despite some early promising results a systematic review[1] considered that there was no evidence to support the use of dopamine agonists, including amantadine, in the treatment of cocaine dependence (p.1860).

1. Soares B, *et al.* Dopamine agonists for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Preparations

BP 2008: Amantadine Capsules; Amantadine Oral Solution;
USP 31: Amantadine Hydrochloride Capsules; Amantadine Hydrochloride Syrup.

Proprietary Preparations (details are given in Part 3)

Arg.: Actison; Ampakine; Virosol; ***Austral.:*** Symmetrel; ***Austria:*** Amant; Hofcomant; PK-Merz; Virucid†; ***Belg.:*** Amantan; ***Braz.:*** Mantidan; ***Canad.:*** Endantadine; Symmetrel; ***Chile:*** PK-Merz†; Prayanol; ***Cz.:*** Amantadol; PK-Merz; Viregyt-K; ***Fin.:*** Atarin; ***Fr.:*** Mantadix; ***Ger.:*** Adekin; Aman†; Amanta; Amantagamma; Amixx; AMT†; InfectoFlu; Infex; PK-Merz; tregor; ***Gr.:*** Hofcomant†; PK-Merz†; Symmetrel; ***Hong Kong:*** PK-Merz; Symmetrel†; ***Hung.:*** PK-Merz; Viregyt; ***India:*** Amantrel; ***Irl.:*** Symmetrel; ***Israel:*** A-Parkin; Influ-A†; Paritrel; PK-Merz; ***Ital.:*** Mantadan; ***Malaysia:*** PK-Merz; ***Mex.:*** Kinestrel; Padiken†; PK-Merz; ***Neth.:*** Symmetrel; ***NZ:*** Symmetrel; ***Philipp.:*** PK-Merz; ***Pol.:*** Amantix; Viregyt K; ***Port.:*** Parkadina; Profil†; ***S.Afr.:*** Antadine†; Symmetrel; ***Singapore:*** Symmetrel; ***Switz.:*** PK-Merz; Symmetrel; ***UK:*** Lysovir; Symmetrel; ***USA:*** Symmetrel; ***Venez.:*** Symmetrel†.

Multi-ingredient: *Mex.:* Antiflu-Des; Fluviatol; Rosel.

Apomorphine Hydrochloride *(BANM)*

Apomorfiinihydrokloridi; Apomorfin Hidroklorür; Apomorfina, hidrocloruro de; Apomorfin-hidroklorid; Apomorfin-hydrochlorid hemihydrát; Apomorfinhydroklorid; Apomorfino hidrochloridas; Apomorfiny chlorowodorek; Apomorphine, chlorhydrate d'; Apomorphini hydrochloridum; Apomorphini Hydrochloridum Hemihydricum. 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate; (*R*)-10,11-Dihydroxy-6a-aporphine hydrochloride hemihydrate; (6a*R*)-5,6,6a,7-Tetrahydro-6-methyl-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate.

$C_{17}H_{17}NO_2,HCl,{}^1\!/_2H_2O$ = 312.8.

CAS — 58-00-4 (apomorphine); 314-19-2 (anhydrous apomorphine hydrochloride); 41372-20-7 (apomorphine hydrochloride, hemihydrate).

ATC — G04BE07; N04BC07.

ATC Vet — QG04BE07; QN04BC07.

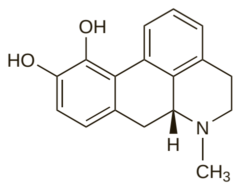

(apomorphine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Apomorphine Hydrochloride). White or faintly yellow to green-tinged greyish crystals or crystalline powder, the green tinge becoming more pronounced on exposure to air and light. Sparingly soluble in water and in alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

USP 31 (Apomorphine Hydrochloride). Odourless, minute white or greyish-white, glistening crystals or white powder. It gradually acquires a green colour on exposure to light and air. Soluble 1 in 50 of water and 1 in 20 of water at 80°; soluble 1 in 50 of alcohol; very slightly soluble in ether and in chloroform. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Stability. Aqueous solutions of apomorphine hydrochloride decompose on storage and should not be used if they turn green or brown or contain a precipitate.

Adverse Effects

Treatment of parkinsonism. Apomorphine usually produces nausea and vomiting when given in therapeutic doses but these effects can be controlled by treatment with domperidone or trimethobenzamide. Transient sedation can be common during the first few weeks of treatment. Increased salivation and perspiration have also been reported. Apomorphine can produce neuropsychiatric disturbances including increasing cognitive impairment, personality changes, confusion, and hallucinations. Signs of CNS stimulation including euphoria, lightheadedness, restlessness, tremor, tachycardia, and tachypnoea occur less frequently. Apomorphine may induce dyskinesias during 'on' periods in patients with parkinsonism and these may be severe enough to require stopping therapy; postural instability and falls may also be a problem. Transient orthostatic hypotension may also occur infrequently. Eosinophilia has occurred rarely. The use of apomorphine with levodopa may cause haemolytic anaemia and treatment may need to be stopped if this cannot be satisfactorily controlled through dosage adjustment. Induration, nodule formation, and panniculitis, sometimes leading to ulceration, often develops at the site of subcutaneous injection.

Management of erectile dysfunction. The most common adverse effects have been nausea, headache, and dizziness. Other effects reported include yawning, rhinitis, pharyngitis, somnolence, infection, pain, increased cough, flushing, taste disturbances, and sweating. Fainting and syncope (vasovagal syndrome) have also occurred.

Overdosage with apomorphine can produce persistent vomiting, respiratory depression, bradycardia, hypotension, and coma; death may occur.

Akinesia. A 60-year-old man who was being investigated for parkinsonian symptoms became totally immobile and mute 15 minutes after receiving apomorphine 4 mg subcutaneously.[1] He remained conscious but was drowsy and sweating. Similar profound akinesia occurred on rechallenge with 2- and 6-mg doses. A diagnosis of probable nigrostriatal degeneration was made as the patient had previously shown no improvement with levodopa, but the mechanism of the idiosyncratic reaction to apomorphine was unclear.

1. Jenkins JR, Pearce JMS. Paradoxical akinetic response to apomorphine in parkinsonism. *J Neurol Neurosurg Psychiatry* 1992; **55:** 414–15.

Effects on the heart. A 67-year-old man developed palpitations with cold perspiration and chest pain, in addition to asthenia, salivation, nausea and vomiting, 5 minutes after receiving 3 mg apomorphine subcutaneously. An ECG showed atrial fibrillation with a ventricular frequency of 140 beats/minute.[1]

1. Stocchi F, *et al.* Transient atrial fibrillation after subcutaneous apomorphine bolus. *Mov Disord* 1996; **11:** 584–5.

Effects on mental function. Severe confusion, hallucinations, and acute psychosis were reported in 4 of 6 parkinsonian patients given subcutaneous apomorphine.[1] Three of the 4 had previously experienced mental disturbances while receiving lisuride. However, other studies failed to note effects on mental function in parkinsonian patients given apomorphine[2,3] and it has been suggested that the risk of psychosis in patients with no history of confusion or hallucinations is low.[3] UK licensed product information notes that apomorphine has been reported to exacerbate neuropsychiatric disturbances in patients with parkinsonism.

1. Ruggieri S, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 566.
2. Stibe CMH, *et al.* Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988; **i:** 403–6.
3. Poewe W, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **i:** 1084–5.

Hypersensitivity. Allergic reactions including contact dermatitis, severe rhinitis, and respiratory distress have been reported in 2 workers who came into contact with apomorphine powder.[1] Contact allergy has also been reported in a patient who developed a swollen nose and lips after intranasal use of apomorphine.[2] Skin testing in all these cases[1,2] gave a positive reaction to apomorphine. Biopsy of subcutaneous nodules, which develop at the site of injection in most patients using apomorphine subcutaneously, has not been able to clarify what type of reaction was responsible for the development of panniculitis.[3] Although the nodules may slowly resolve the sites are often unsuitable for reuse as absorption from them is unpredictable; concern has been expressed that this may limit long-term use of apomorphine.[3]

1. Dahlquist I. Allergic reactions to apomorphine. *Contact Dermatitis* 1977; **3:** 349–50.
2. van Laar T, *et al.* Nasolabiale allergische reactie op intranasale toediening van apomorfine bij de ziekte van Parkinson. *Ned Tijdschr Geneeskd* 1992; **136** (suppl 47): 26–7.
3. Acland KM, *et al.* Panniculitis in association with apomorphine infusion. *Br J Dermatol* 1998; **138:** 480–2.

Oedema. Severe reversible oedema of the lower limbs developed in a patient receiving subcutaneous apomorphine.[1] Oedema recurred when apomorphine was reintroduced, but to a lesser extent.

1. Vermersch P. Severe oedema after subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; **ii:** 802.

Stomatitis. Stomatitis, severe enough to warrant stopping treatment, occurred in 4 of 8 patients after 2 to 6 months of therapy with sublingual apomorphine.[1]

1. Montastruc JL, *et al.* Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. *Clin Neuropharmacol* 1991; **14:** 432–7.

Treatment of Adverse Effects

In the UK, domperidone is usually given to control nausea and vomiting when apomorphine is used in the management of Parkinson's disease; pretreatment with domperidone for at least 2 days is advised before starting treatment with apomorphine. Usually domperidone can be withdrawn gradually over several weeks or longer although some patients may need to continue treatment indefinitely. In the USA, trimethobenzamide hydrochloride is used similarly, beginning 3 days before starting apomorphine treatment.

In overdosage an opioid antagonist such as naloxone has been given to treat excessive vomiting, and CNS and respiratory depression.

◊ References.

1. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.

Precautions

Apomorphine should not be given to patients with respiratory or CNS depression, hypersensitivity to opioids, neuropsychiatric problems, or dementia. It should be used with caution in patients prone to nausea and vomiting or when vomiting is likely to pose a risk. Apomorphine should also be used with care in patients with pulmonary, cardiovascular, or endocrine disease or with renal or hepatic impairment. Extra care is needed when starting treatment in elderly or debilitated patients and in those with a history of orthostatic hypotension. Patients who experience dizziness, lightheadedness, or syncope should not drive or operate machinery.

Treatment of parkinsonism. Apomorphine is not suitable for use in patients who have an 'on' response to levodopa marred by severe dyskinesia, hypotonia, or psychiatric effects; it should also not be used in those with hepatic impairment. Periodic monitoring of hepatic, renal, haematopoietic, and cardiovascular function has been advised and the *BNF* recommends that patients receiving apomorphine with levodopa should be screened for haemolytic anaemia on starting treatment and then every 6 months. Patients who develop anaemia, or those who have continuing confusion or hallucinations during treatment with apomorphine require observation and dosage adjustment under specialist supervision; treatment may need to be stopped. Excessive daytime sleepiness and sudden onset of sleep may also occur with apomorphine and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Local subcutaneous reactions can sometimes be reduced by using sodium chloride 0.9% to dilute injection solutions, by rotating injection sites, and possibly by use of ultrasound in areas of nodularity and induration.

Management of erectile dysfunction. UK licensed product information has warned that drugs for erectile dysfunction should be used with caution in patients with anatomical penile deformity.

Interactions

Apomorphine should be used with caution in patients receiving antihypertensives or organic nitrates as it may potentiate their hypotensive effects. Enhanced hypotensive effects may also occur when alcohol is given with apomorphine. The therapeutic effects of apomorphine may be antagonised by antipsychotics and other drugs that act as CNS dopamine inhibitors. The effect of apomorphine is possibly enhanced by entacapone and memantine.

Antiemetics. *Domperidone* (in the UK) and *trimethobenzamide* (in the USA) are used with apomorphine to control nausea and vomiting when it is prescribed for the management of parkinsonism. However, whether other antiemetics may safely be used is less clear. US licensed product information contra-indicates the use of *ondansetron* and related 5-HT_3 antagonists with apomorphine, on the grounds that profound hypotension and loss of consciousness has been reported in patients given this combination. However, UK licensed product information makes no mention of such a contra-indication, and licensed information for lower-dose products used in the management of erectile dysfunction notes that on the basis of interaction studies, ondansetron hydrochloride or *prochlorperazine maleate* may safely be given to patients receiving apomorphine for this indication.

Pharmacokinetics

Apomorphine is well absorbed after subcutaneous injection but undergoes extensive first-pass hepatic metabolism when given by mouth and oral bioavailability is low. However, it is readily absorbed after sublingual doses and peak plasma concentrations are achieved in about 40 to 60 minutes; bioavailability is reported to be about 17 to 18% compared with subcutaneous injection. Apomorphine is about 90% bound to plasma proteins, mainly to albumin.

Apomorphine is extensively metabolised in the liver, primarily by conjugation with glucuronic acid or sulfate; the major metabolite is apomorphine sulfate. It is also demethylated to produce norapomorphine. Most of a dose is excreted in urine, mainly as metabolites.

◊ References.

1. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. *Clin Pharmacokinet* 1999; **37:** 257–71.
2. Argiolas A, Hedlund H. The pharmacology and clinical pharmacokinetics of apomorphine SL. *BJU Int* 2001; **88** (suppl 3): 18–21.
3. LeWitt PA. Subcutaneously administered apomorphine: pharmacokinetics and metabolism. *Neurology* 2004; **62** (suppl 4): S8–S11.

Uses and Administration

Apomorphine is a morphine derivative with structural similarities to dopamine. It is a potent dopamine D_1- and D_2-receptor agonist used in the management of parkinsonism, especially in the control of the 'on-off' effect. It has also been used in the management of erectile dysfunction. Apomorphine is given as the hydrochloride and doses are expressed in terms of this salt. The regimen for parkinsonism given below applies to the UK preparation and doses are give subcutaneously; a similar preparation is available in the USA although the licensed maximum single and daily doses are less than those in the UK.

The optimal dose of apomorphine in the management of 'off' periods in **parkinsonism** should be established individually under specialist care. At least 2 days of pretreatment with the antiemetic domperidone is advised before starting apomorphine. After withholding antiparkinsonian therapy overnight to provoke an 'off' period, a test dose of 1 mg is given initially, followed by a second dose of 2 mg after 30 minutes, if necessary. Subsequent incremental increases should then be given at intervals of at least 40 minutes, as necessary, to determine the lowest dose producing a satisfactory motor response. Once the patient's normal antiparkinsonian therapy is re-established, the effective dose of apomorphine hydrochloride is given at the first signs of an 'off' period.

The dose and frequency are further adjusted according to response; patients typically require 3 to 30 mg daily in divided doses but individual injections should not be greater than 10 mg. Patients who require more than 10 injections daily or those whose overall control of symptoms remains unsatisfactory with intermittent injections may benefit from continuous subcutaneous infusion. The infusion is started at a rate of 1 mg/hour and this may be increased in steps of up to 0.5 mg/hour at intervals of not less than 4 hours to a maximum rate of 4 mg/hour. It is advised that infusions should only be given during waking hours and that the infusion site should be changed every 12 hours; 24-hour infusions are not advised unless there are severe night-time symptoms. Patients usually need to supplement the infusion with intermittent bolus injections but the recommended maximum total daily dose given by infusion and/or injection is 100 mg.

In the management of **erectile dysfunction** the usual initial dose has been 2 mg taken sublingually about 20 minutes before sexual activity. A dose of 3 mg was used on subsequent occasions if necessary with a minimum of 8 hours between doses. Reduced dosage is needed in patients with renal impairment (see below).

Apomorphine stimulates the chemoreceptor trigger zone in the brain and can produce emesis within a few minutes of a dose. However, the use of apomorphine for the induction of emesis in poisoning is considered dangerous owing to the risk of inducing protracted vomiting and shock, and is not recommended.

Administration in renal impairment. In the management of erectile dysfunction, the maximum dose of apomorphine hydrochloride has been limited to 2 mg sublingually in patients with severe renal impairment.

Erectile dysfunction. Apomorphine is among a wide range of drugs that has been used in the management of erectile dysfunction[1-5] (p.2179) with some beneficial results. It is usually given sublingually although it has also been given subcutaneously.[3] Inhaled apomorphine is also under investigation.

1. Heaton JPW, *et al.* Recovery of erectile function by the oral administration of apomorphine. *Urology* 1995; **45:** 200–6.
2. Dula E, *et al.* Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. *Urology* 2000; **56:** 130–5.
3. Segraves RT, *et al.* Effect of apomorphine on penile tumescence in men with psychogenic impotence. *J Urol (Baltimore)* 1991; **145:** 1174–5.
4. Martinez R, *et al.* Clinical experience with apomorphine hydrochloride: the first 107 patients. *J Urol (Baltimore)* 2003; **170:** 2352–5.
5. Gontero P, *et al.* Clinical efficacy of apomorphine SL in erectile dysfunction of diabetic men. *Int J Impot Res* 2005; **17:** 80–5.

DIAGNOSIS. Test doses of subcutaneous apomorphine have been used in the differential diagnosis of parkinsonian syndromes,[1-4] to distinguish forms responsive to dopaminergics from other parkinsonian syndromes such as Wilson's disease, corticobasal degeneration, and diffuse Lewy-body dementia. Oral challenge with levodopa is still the best test of dopaminergic responsiveness[5,6] but apomorphine has proved of value in re-assessing patients who have become less responsive to levodopa.[1,4]

1. Barker R, *et al.* Subcutaneous apomorphine as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1989; **i:** 675.
2. Oertel WH, *et al.* Apomorphine test for dopaminergic responsiveness. *Lancet* 1989; **i:** 1262–3.
3. Frankel JP, *et al.* Use of apomorphine to test for dopamine responsiveness in Wilson's disease. *Lancet* 1989; **ii:** 801–2.
4. Hughes AJ, *et al.* Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990; **336:** 32–4.
5. Steiger MJ, Quinn NP. Levodopa challenge test in Parkinson's disease. *Lancet* 1992; **339:** 751–2.
6. Müller T, *et al.* Repeated rating improves value of diagnostic dopaminergic challenge tests in Parkinson's disease. *J Neural Transm* 2003; **110:** 603–9.

Parkinsonism. ***TREATMENT.*** Although apomorphine has produced benefit in Parkinson's disease (p.791) when given orally, the high doses required to overcome extensive first-pass hepatic metabolism (up to 1.4 g daily in one study[1]), were associated with uraemia. The use of apomorphine in Parkinson's disease has therefore been limited by the need for parenteral dosage. The current main use of apomorphine in Parkinson's disease is for the stabilisation of patients with 'on-off' fluctuations unresponsive to other dopamine agonists. It is usually given subcutaneously either by injection or infusion but a review[2] of the use of apomorphine in Parkinson's disease also discussed studies of rectal, sublingual, and intranasal use. Inhaled apomorphine is also under investigation.

1. Cotzias GC, *et al.* Treatment of Parkinson's disease with aporphines. *N Engl J Med* 1976; **294:** 567–72.
2. Koller W, Stacy M. Other formulations and future considerations for apomorphine for subcutaneous injection therapy. *Neurology* 2004; **62** (suppl 4): S22–S26.

Preparations

USP 31: Apomorphine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Apokinon†; Uprima†; ***Austral.:*** Apomine; ***Austria:*** APO-go; Ixense†; Uprima†; ***Belg.:*** Uprima†; ***Braz.:*** Uprima; ***Chile:*** Noc; Uprima†; ***Cz.:*** APO-go; Uprima†; ***Denm.:*** Uprima†; ***Fin.:*** Uprima†; ***Fr.:*** Apokinon†; Ixense†; Uprima†; ***Ger.:*** APO-go; Ixense†; Uprima†; ***Gr.:*** APO-go; Taluvian†; Uprima†; ***Hong Kong:*** Uprima†; ***Hung.:*** APO-go†; Uprima†; ***Irl.:*** Uprima†; ***Israel:*** APO-go; ***Ital.:*** Apofin; Ixense†; Taluvian†; Uprima†; ***Jpn:*** Ixense; ***Mex.:*** Taluvian; ***Neth.:*** APO-go; Uprima†; ***Norw.:*** Uprima†; ***NZ:*** Apomine; Uprima†; ***Port.:*** APO-go; Uprima†; ***S.Afr.:*** Uprima†; ***Spain:*** APO-go; Taluvian†; Uprima†; ***Swed.:*** Uprima†; ***Switz.:*** Uprima†; ***Thai.:*** Ixense†; ***Turk.:*** APO-go; ***UK:*** APO-go; Uprima†; ***USA:*** Apokyn; ***Venez.:*** Uprima†.

Benserazide *(BAN, USAN, rINN)*

Benseratsidi; Benserazid; Benserazida; Bensérazide; Benserazidum; Ro-4-4602. DL-Serine 2-(2,3,4-trihydroxybenzyl)hydrazide; 2-Amino-3-hydroxy-2′-(2,3,4-trihydroxybenzyl)propionohydrazide.

Бенсеразид

$C_{10}H_{15}N_3O_5$ = 257.2.

CAS — 322-35-0.

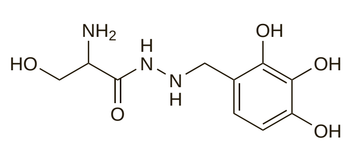

Benserazide Hydrochloride *(BANM, rINNM)*

Benseratsidihydrokloridi; Bensérazide, chlorhydrate de; Benserazid-hydrochlorid; Benserazidhydroklorid; Benserazidi hydrochloridum; Benserazido hidrochloridas; Benszerazid-hidroklorid; Hidrocloruro de benserazida; Serazide Hydrochloride.

Бенсеразида Гидрохлорид

$C_{10}H_{15}N_3O_5$,HCl = 293.7.

CAS — 14919-77-8; 14046-64-1.

NOTE. Compounded preparations of benserazide hydrochloride may be represented by the following names:

- Co-beneldopa *(BAN)*—benserazide 1 part and levodopa 4 parts (w/w).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Benserazide Hydrochloride). A white or yellowish-white or orange-white crystalline powder. It shows polymorphism. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

Solubility. Benserazide is unstable in a neutral, alkaline, or strongly acidic medium.[1]

1. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Adverse Effects and Precautions

◊ Early reports[1] noted developmental abnormalities of the *rat* skeleton, but others found no evidence of any disorder involving bone metabolism in man.[2] Nevertheless licensed product information recommends that benserazide should not be given to patients under 25 years of age, nor to pregnant women or to women of child-bearing potential in the absence of adequate contraception.

1. Theiss E, Schärer K. Toxicity of L-dopa and a decarboxylase inhibitor in animal experiments. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 497–504.
2. Ziegler WH, *et al.* Toxicity of L-dopa and a dopa decarboxylase inhibitor in humans. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 505–16.

Pharmacokinetics

◊ Pharmacokinetic and metabolic studies[1,2] in *animals* and man have shown that, after oral doses in parkinsonian patients, benserazide was rapidly absorbed to the extent of about 58%; giving it with levodopa tended to increase this slightly. Benserazide was rapidly excreted in the urine in the form of metabolites, mostly within the first 6 hours; 85% of urinary excretion had occurred within 12 hours. It is mainly metabolised in the gut and appears to protect levodopa against decarboxylation primarily in the gut, but also in the rest of the organism, mainly by way of its metabolite trihydroxybenzylhydrazine. Benserazide did not cross the blood-brain barrier in *rats*.

1. Schwartz DE, *et al.* Pharmacokinetics of the decarboxylase benserazide in man: its tissue distribution in the rat. *Eur J Clin Pharmacol* 1974; **7:** 39–45.
2. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; **28:** 302–7.

Uses and Administration

Benserazide hydrochloride is a peripheral dopa-decarboxylase inhibitor with actions similar to those of carbidopa (p.803) and is used similarly as an adjunct to levodopa in the treatment of parkinsonism (p.791). For details of dosage, see Levodopa, p.808.

◊ References.

1. Dingemanse J, *et al.* Pharmacodynamics of benserazide assessed by its effects on endogenous and exogenous levodopa pharmacokinetics. *Br J Clin Pharmacol* 1997; **44:** 41–8.

Preparations

BP 2008: Co-beneldopa Capsules; Dispersible Co-beneldopa Tablets.

Proprietary Preparations (details are given in Part 3)

Ger.: Restex.

Multi-ingredient: ***Arg.:*** Madopar; ***Austral.:*** Madopar; ***Austria:*** Dopamed; Levobens; Madopar; Restex; ***Belg.:*** Prolopa; ***Braz.:*** Prolopa; ***Canad.:*** Prolopa; ***Chile:*** Melitase; Prolopa; ***Cz.:*** Madopar; ***Denm.:*** Madopar; ***Fin.:*** Madopar; ***Fr.:*** Modopar; ***Ger.:*** Levodopa comp B; Levopar; Madopar; PK-Levo; ***Gr.:*** Madopar; ***Hong Kong:*** Madopar; ***Hung.:*** Madopar; ***Indon.:*** Leparson; Levazide; Levopar; Madopar; Pardoz; ***Irl.:*** Madopar; ***Israel:*** Levopar Plus; ***Ital.:*** Madopar; ***Malaysia:*** Madopar; ***Mex.:*** Madopar; ***Neth.:*** Madopar; Modopar; ***Norw.:*** Madopar; ***NZ:*** Madopar; ***Philipp.:*** Madopar; ***Pol.:*** Madopar; ***Port.:*** Madopar; ***Rus.:*** Madopar (Мадопар); ***S.Afr.:*** Madopar; ***Singapore:*** Madopar; ***Spain:*** Madopar; ***Swed.:*** Madopark; ***Switz.:*** Madopar; ***Thai.:*** Cenparkin†; Madopar; Vopar; ***Turk.:*** Madopar; ***UK:*** Madopar; ***Venez.:*** Madopar.

Benzatropine Mesilate *(BANM, rINNM)*

Benzatropine, Mésilate de; Benzatropine Methanesulfonate; Benzatropini Mesilas; Benztropine Mesylate; Mesilato de benzatropina. (1*R*,3*r*,5*S*)-3-Benzhydryloxytropane methanesulphonate.

Бензатропина Мезилат

$C_{21}H_{25}NO,CH_4O_3S = 403.5.$

CAS — 86-13-5 (benzatropine); 132-17-2 (benzatropine mesilate).

ATC — N04AC01.

ATC Vet — QN04AC01.

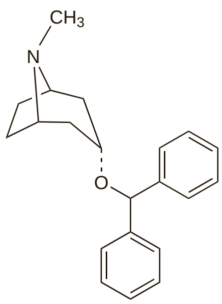

(benzatropine)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Benzatropine Mesilate). A white, odourless or almost odourless, crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in ether.

USP 31 (Benztropine Mesylate). A white, slightly hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Drowsiness may be severe in some patients and patients so affected should not drive or operate machinery. Mental disturbances and excitement may occur with large doses or in susceptible patients.

Abuse. For mention of abuse of benzatropine see under Trihexyphenidyl Hydrochloride, p.820.

Effects on the heart. Paradoxical sinus bradycardia in a patient with depression and psychotic symptoms was attributed to benzatropine since it persisted despite modification to other treatment and resolved only when benzatropine was withdrawn.[1]

1. Voinov H, *et al.* Sinus bradycardia related to the use of benztropine mesylate. *Am J Psychiatry* 1992; **149:** 711.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Antidepressants. A report[1] of 5 patients who developed delirium while taking an antipsychotic, an *SSRI,* and benzatropine suggested that there might be an interaction between SSRIs and benzatropine.

1. Roth A, *et al.* Delirium associated with the combination of a neuroleptic, an SSRI, and benztropine. *J Clin Psychiatry* 1994; **55:** 492–5.

Antipsychotics. Fatal heat stroke after exposure to an ambient temperature of over 29° has been reported[1,2] in patients receiving benzatropine with antipsychotics. Paralytic ileus, sometimes fatal, has also been seen in patients taking benzatropine with antipsychotics.[3]

1. Stadnyk AN, Glezos JD. Drug-induced heat stroke. *Can Med Assoc J* 1983; **128:** 957–9.
2. Tyndel F, Labonté R. Drug-facilitated heat stroke. *Can Med Assoc J* 1983; **129:** 680.
3. Wade LC, Ellenor GL. Combination mesoridazine- and benztropine mesylate-induced paralytic ileus: two case reports. *Drug Intell Clin Pharm* 1980; **14:** 17–22.

Uses and Administration

Benzatropine mesilate is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820); it also has antihistaminic properties.

Benzatropine is used for the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias (see under Uses and Administration of Levodopa, p.809).

Benzatropine mesilate is given orally or, if necessary, by intramuscular or intravenous injection.

In idiopathic **parkinsonism** benzatropine mesilate is usually given orally in an initial daily dose of 0.5 to 1 mg at bedtime. Its actions are cumulative, and may not be manifest for several days after beginning therapy. Patients with post-encephalitic parkinsonism often tolerate an initial daily dose of 2 mg. The dose may be gradually increased by 500 micrograms every 5 to 6 days to a maximum of 6 mg daily until the optimum dose is reached. Maintenance therapy may be given as a single daily dose at bedtime or in divided doses 2 to 4 times daily.

In the management of **drug-induced extrapyramidal symptoms** doses of 1 to 4 mg once or twice daily have been given orally or parenterally. Therapy may be withdrawn after 1 to 2 weeks to assess whether it is still necessary.

In an emergency, benzatropine mesilate may be injected intramuscularly or intravenously in a dose of 1 to 2 mg; intramuscular injection is reported to produce an effect as quickly as intravenous dosage so the latter is rarely necessary.

For management of **dystonias in children**, the *BNFC* suggests that in an emergency, single doses of 20 to 100 micrograms/kg (maximum of 2 mg) may be given by intravenous or intramuscular injection to children aged 3 to 12 years, and 1 to 2 mg to those aged 12 to 18 years.

Benzatropine has also been given as the hydrochloride.

Preparations

BP 2008: Benzatropine Injection; Benzatropine Tablets;
USP 31: Benztropine Mesylate Injection; Benztropine Mesylate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Benztrop; Cogentin; ***Austria:*** Cogentin; ***Canad.:*** Cogentin†; ***Cz.:*** Apo-Benztropine; ***Denm.:*** Cogentin†; ***Hong Kong:*** Cogentin; ***Irl.:*** Cogentin†; ***Norw.:*** Cogentin†; ***NZ:*** Benztrop; Cogentin; ***Port.:*** Cogentin†; ***Thai.:*** Cogentin; ***UK:*** Cogentin; ***USA:*** Cogentin.

Biperiden *(BAN, rINN)*

Biperideeni; Bipéridène; Biperideno; Biperidenum. 1-(Bicyclo-[2.2.1]hept-5-en-2-yl)-1-phenyl-3-piperidinopropan-1-ol.

Биперилен

$C_{21}H_{29}NO = 311.5.$

CAS — 514-65-8.

ATC — N04AA02.

ATC Vet — QN04AA02.

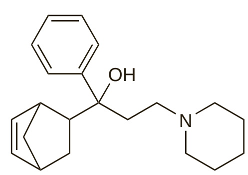

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Biperiden). A white, practically odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform. Protect from light.

Biperiden Hydrochloride *(BANM, rINNM)*

Biperideenihydrokloridi; Biperiden Hidroklorür; Bipéridène, chlorhydrate de; Biperidén-hidroklorid; Biperiden-hydrochlorid; Biperidenhydroklorid; Biperideni hydrochloridum; Biperideno hidrochloridas; Hidrocloruro de biperideno.

Биперидена Гидрохлорид

$C_{21}H_{29}NO,HCl = 347.9.$

CAS — 1235-82-1.

ATC — N04AA02.

ATC Vet — QN04AA02.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Biperiden Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol; very slightly soluble in dichloromethane. A 0.2% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Biperiden Hydrochloride). A white, practically odourless, crystalline powder. Slightly soluble in water, in alcohol, in chloroform, and in ether; sparingly soluble in methyl alcohol. Protect from light.

Biperiden Lactate *(BANM, rINNM)*

Biperiden Laktat; Bipéridène, Lactate de; Biperideni Lactas; Lactato de biperideno.

Биперидена Лактат

$C_{21}H_{29}NO,C_3H_6O_3 = 401.5.$

CAS — 7085-45-2.

ATC — N04AA02.

ATC Vet — QN04AA02.

Pharmacopoeias. *US* includes Biperiden Lactate Injection.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Parenteral use may be followed by slight transient hypotension.

Abuse. Abuse of biperiden has been reported in psychiatric patients.[1]

1. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289:** 612–13.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics

Biperiden is readily absorbed from the gastrointestinal tract, but bioavailability is only about 30% suggesting that it undergoes extensive first-pass metabolism. Biperiden has an elimination half-life of about 20 hours.

◊ References.

1. Hollmann M, *et al.* Biperiden effects and plasma levels in volunteers. *Eur J Clin Pharmacol* 1984; **27:** 619–21.
2. Grimaldi R, *et al.* Pharmacokinetic and pharmacodynamic studies following the intravenous and oral administration of the antiparkinsonian drug biperiden to normal subjects. *Eur J Clin Pharmacol* 1986; **29:** 735–7.

Uses and Administration

Biperiden is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820) but with more potent antinicotinic properties.

Biperiden is used in the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias.

Biperiden is given orally as the hydrochloride and by injection as the lactate; doses are expressed in terms of the relevant salt. The initial oral dose for **Parkinson's disease** is 2 mg of the hydrochloride three or four times daily increased according to response to a maximum of 16 mg daily. The dose for **drug-induced extrapyramidal symptoms** is 2 mg of the hydrochloride orally one to three times daily; alternatively, 2 mg of biperiden lactate may be given by intramuscular or slow intravenous injection and repeated every 30 minutes if needed up to a maximum of 4 doses in 24 hours.

Preparations

USP 31: Biperiden Hydrochloride Tablets; Biperiden Lactate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Akineton; Berofin; Darcipireno; Sinekin; ***Austral.:*** Akineton; ***Austria:*** Akineton; ***Belg.:*** Akineton; ***Braz.:*** Akineton; Cinetol; Parkinsol; ***Canad.:*** Akineton; ***Chile:*** Akineton; ***Cz.:*** Akineton; ***Denm.:*** Akineton; ***Fin.:*** Akineton; Ipsatol; ***Fr.:*** Akineton; ***Ger.:*** Akineton; Norakin N†; ***Gr.:*** Akineton; ***Hung.:*** Akineton; ***India:*** Dyskinon†; ***Irl.:*** Akineton; ***Israel:*** Dekinet; ***Ital.:*** Akineton; ***Mex.:*** Akineton; Bikipen; Kinex; ***Neth.:*** Akineton; ***Norw.:*** Akineton†; ***Philipp.:*** Akineton; ***Pol.:*** Akineton; ***Port.:*** Akineton; ***Rus.:*** Akineton (Акинетон)†; ***S.Afr.:*** Akineton; ***Spain:*** Akineton; ***Swed.:*** Akineton†; ***Switz.:*** Akineton; ***Turk.:*** Akineton; ***USA:*** Akineton; ***Venez.:*** Akineton.

Bornaprine Hydrochloride *(BANM, rINNM)*

Bornaprin Hidroklorür; Bornaprine, Chlorhydrate de; Bornaprini Hydrochloridum; Hidrocloruro de bornaprina. 3-Diethylaminopropyl 2-phenylbicyclo[2.2.1]heptane-2-carboxylate hydrochloride.

Борнаприна Гидрохлорид

$C_{21}H_{31}NO_2,HCl = 365.9.$

CAS — 20448-86-6 (bornaprine); 26908-91-8 (bornaprine hydrochloride).

ATC — N04AA11.

ATC Vet — QN04AA11.

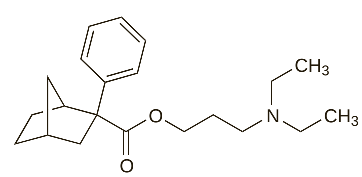

(bornaprine)

Profile

Bornaprine hydrochloride is a quaternary ammonium antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It is used in the symptomatic treatment of **parkinsonism** (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias; it is claimed to be mainly effective against tremor. Bornaprine hydrochloride is given orally in initial doses of 2 mg daily gradually increased to 6 to 12 mg daily according to response. It is also used in the treatment of **hyperhidrosis** (p.1580) in a dose of 4 to 8 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sormodren; ***Ger.:*** Sormodren; ***Ital.:*** Sormodren; ***Turk.:*** Sormodren.

Bromocriptine Mesilate *(BANM, rINNM)*

Bromocriptine, mésilate de; Bromocriptine Mesylate *(USAN)*; Bromocriptine Methanesulphonate; Bromocriptini mesilas; Bromocryptine Mesylate; 2-Bromo-α-ergocryptine Mesylate; 2-Bromoergocryptine Monomethanesulfonate; Bromokriptiinimesilaatti; Bromokriptin Mesilat; Bromokriptinmesilat; Bromokriptin-mesylát; Brómokriptin-mezilát; Bromokriptino mesilatas; CB-154 (bromocriptine); Mesilato de bromocriptina. (5′S)-2-Bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-ergotaman-3′,6′,18-trione methanesulphonate.

Бромокриптина Мезилат

$C_{32}H_{40}BrN_5O_5,CH_4O_3S$ = 750.7.

CAS — 25614-03-3 (bromocriptine); 22260-51-1 (bromocriptine mesilate).

ATC — G02CB01; N04BC01.

ATC Vet — QG02CB01; QN04BC01.

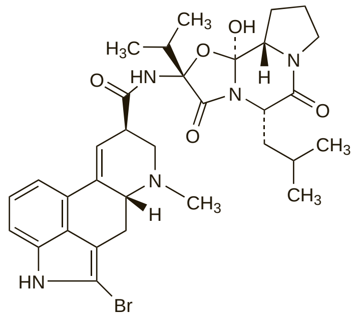

(bromocriptine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Bromocriptine Mesilate). A white or slightly coloured fine crystalline powder. Practically insoluble in water; soluble in alcohol; sparingly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in a mixture of 2 parts methyl alcohol to 8 of water has a pH of 3.1 to 3.8. Store in airtight containers at a temperature not exceeding −15°. Protect from light.

USP 31 (Bromocriptine Mesylate). A white or slightly coloured fine crystalline powder; odourless or having a weak characteristic odour. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Adverse Effects

Nausea is the most common adverse effect at the beginning of treatment with bromocriptine, but vomiting, dizziness, and orthostatic hypotension may also occur. Syncope has followed initial doses.

Adverse effects are generally dose-related and may therefore be more frequent with the higher doses that have been used in the treatment of parkinsonism and acromegaly. Reduction of the dosage, followed in a few days by a more gradual increase, may alleviate many adverse effects. Nausea may be reduced by taking bromocriptine with food; domperidone may also be given at least 1 hour before bromocriptine, for the first few days of therapy.

Bromocriptine and similar drugs are vasoconstrictors; Raynaud's syndrome or digital vasospasm, induced by cold, and leg cramps have been reported. Other cardiovascular effects have included erythromelalgia, prolonged severe hypotension, arrhythmias, and exacerbation of angina. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and psychiatric disorders have been reported in postpartum women given bromocriptine.

The use of ergot derivatives such as bromocriptine has been associated with retroperitoneal fibrosis, pleural thickening and effusions, and pericarditis and pericardial effusions.

Other adverse effects reported include headache, nasal congestion, drowsiness, dry mouth, constipation, diarrhoea, and altered liver-function tests. Dyskinesias and psychomotor excitation have occurred in patients suffering from parkinsonism. Gastrointestinal bleeding has been reported in acromegalic patients. Psychosis, with hallucinations, delusions, and confusion, occurs particularly when high doses are used to treat parkinsonism, but has also been reported with low doses. A neuroleptic malignant-like syndrome associated with abrupt withdrawal of bromocriptine has been reported very rarely.

Incidence of adverse effects. In 27 published studies of the treatment of Parkinson's disease, 217 of the 790 patients given bromocriptine had adverse effects.[1] Mental changes were noted in 90 patients, dyskinesia in 20, orthostatic hypotension in 40, and gastrointestinal effects in 40. The fewest adverse effects (9%) occurred with low-dose bromocriptine, more occurred with high-dose bromocriptine (27%) or with low-dose bromocriptine with levodopa (26%), and the most occurred with high-dose bromocriptine and levodopa (32%). However, those on high doses had more advanced disease and might have been more susceptible to mental changes and dyskinesias.

An analysis by the manufacturer of published reports on patients treated with bromocriptine for 1 to 10 years concluded that in general, adverse effects noted were no different from those associated with short-term treatment.[2]

1. Lieberman AN, Goldstein M. Bromocriptine in Parkinson disease. *Pharmacol Rev* 1985; **37:** 217–27.
2. Weil C. The safety of bromocriptine in long-term use: a review of the literature. *Curr Med Res Opin* 1986; **10:** 25–51.

Effects on the blood. Severe leucopenia and mild thrombocytopenia developed in a 23-year-old woman after treatment with bromocriptine 7.5 to 10 mg daily for about 3 months.[1]

1. Giampietro O, *et al*. Severe leukopenia and mild thrombocytopenia after chronic bromocriptine (CB-154) administration. *Am J Med Sci* 1981; **281:** 169–72.

Effects on the cardiovascular system. An early review noted that asymptomatic **hypotension** occurred in many subjects given bromocriptine.[1] However, faintness and dizziness, sometimes accompanied by *nausea* and *vomiting*, were common at the start of treatment with bromocriptine and these symptoms rather than an anaphylactic type of reaction were likely to account for the collapse that occurred in a few sensitive patients. Two of 53 patients with Parkinson's disease fainted after an initial dose of 1.25 or 2.5 mg, but the exact incidence of shock-like syndromes was difficult to assess; the manufacturers had stated that 22 of over 10 000 subjects given bromocriptine had had hypotension and collapse, mainly at the start of treatment.

- All patients starting treatment should be warned of the possibility of fainting. The initial dose should not exceed 1.25 to 2.5 mg and should be taken with food and in bed.

If fainting does occur recovery is usually rapid and spontaneous. Tolerance to adverse effects such as hypotension and nausea may develop rapidly.

Hypertension, seizures, stroke, and *myocardial infarction* have been associated with bromocriptine therapy, notably in postpartum women.[2-4] A study involving 1813 women suggested that the risk of **postpartum hypertension** was increased in women who had pregnancy-induced hypertension and that this risk was further increased in those who took bromocriptine for suppression of lactation.[5] A case-controlled study[6] involving 43 of the women who had had postpartum seizures while taking bromocriptine found that while the initial risk of seizures appeared to be lower in patients taking bromocriptine there was a small positive association with seizures occurring more than 72 hours after delivery.

- Although a causal relationship between the use of bromocriptine and these adverse effects in postpartum women has not been established, licensed product information recommends that bromocriptine should not be used post partum or in the puerperium in women with high blood pressure, coronary artery disease or other severe cardiovascular disorders, or symptoms or history of serious psychiatric disorders.
- It is also recommended that when bromocriptine is used in postpartum women blood pressure should be carefully monitored, especially during the first few days and if hypertension, unremitting headache, or signs of CNS toxicity develop, treatment should be discontinued immediately.

Severe dilated **cardiomyopathy** has been reported in a patient being treated with bromocriptine for microprolactinoma.[7]

For details of **fibrotic reactions** resulting in cardiovascular adverse effects, see Fibrosis, below.

1. Parkes D. Side effects of bromocriptine. *N Engl J Med* 1980; **302:** 749–50.
2. Anonymous. Postpartum hypertension, seizures, strokes reported with bromocriptine. *FDA Drug Bull* 1984; **14:** 3.
3. Ruch A, Duhring JL. Postpartum myocardial infarction in a patient receiving bromocriptine. *Obstet Gynecol* 1989; **74:** 448–51.
4. Larrazet F, *et al*. Possible bromocriptine-induced myocardial infarction. *Ann Intern Med* 1993; **118:** 199–200.
5. Watson DL, *et al*. Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989; **74:** 573–6.
6. Rothman KJ, *et al*. Bromocriptine and puerperal seizures. *Epidemiology* 1990; **1:** 232–8.
7. Kaushik P, *et al*. Acute onset of severe dilated cardiomyopathy during bromocriptine therapy. *Ann Pharmacother* 2004; **38:** 1219–21.

Effects on the ears. Audiometric evidence of bilateral sensorineural hearing loss was reported in 3 patients receiving bromocriptine 15 or 20 mg daily for chronic hepatic encephalopathy.[1] Hearing improved when the dose was reduced to 10 mg daily.

1. Lanthier PL, *et al*. Bromocriptine-associated ototoxicity. *J Laryngol Otol* 1984; **98:** 399–404.

Effects on electrolytes. There have been isolated reports of severe hyponatraemia associated with the use of bromocriptine.[1,2]

1. Marshall AW, *et al*. Bromocriptine-associated hyponatraemia in cirrhosis. *BMJ* 1982; **285:** 1534–5.
2. Damase-Michel C, *et al*. Hyponatraemia in a patient treated with bromocriptine. *Drug Invest* 1993; **5:** 285–7.

Effects on the eyes. Blurred vision and diplopia has been reported in several patients receiving bromocriptine.[1] Reversible myopia also developed in a patient with hyperprolactinaemia given bromocriptine.[2]

Licensed product information states that visual field impairment associated with macroprolactinoma usually resolves with bromocriptine treatment. However, in a patient with progressive visual loss due to compression of the optic chiasm by a large pituitary tumour, bromocriptine caused total visual loss within hours.[3] Vision slowly returned to normal when the patient was placed in the supine position; the most likely cause of the visual loss was thought to be orthostatic hypotension with resultant decrease in perfusion pressure to the visual system. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Bromocriptine has been reported to cause visual cortical disturbances.[4] In some cases blurred vision and transient cortical blindness have preceded seizures and strokes.

1. Calne DB, *et al*. Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Manor RS, *et al*. Myopia during bromocriptine treatment. *Lancet* 1981; **i:** 102.
3. Couldwell WT, Weiss MH. Visual loss associated with bromocriptine. *Lancet* 1992; **340:** 1410–11.
4. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on mental function. High doses of bromocriptine are well known to cause **psychotic reactions** in patients with parkinsonism.[1] However, mania has also been associated with the use of bromocriptine post partum[2,3] and it has been stated that psychological symptoms can occur with doses of only 2.5 to 5 mg daily.[4] It was also noted that, unlike the relatively mild and transient symptoms associated with levodopa, bromocriptine produces a severe psychosis in which the patient is violent and aggressive, suffering from intense delusions which are often hostile and violent; complete withdrawal of bromocriptine may still leave a residue of severe psychotic illness persisting for 1 to 3 weeks. Psychosis associated with low doses of bromocriptine has often occurred in patients with a history of psychotic illness or disturbances in behaviour and mood prior to treatment.[5-7] Drug-related psychotic reactions have also been reported in patients with no psychiatric history;[8,9] of 600 patients given bromocriptine or lisuride for the treatment of acromegaly or prolactinoma, 8 developed symptoms including anxiety, depression, auditory hallucinations, delusions, hyperactivity, disinhibition, euphoria, and insomnia and 4 had received doses only previously associated with psychosis in susceptible patients.[9]

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p.805.

For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including bromocriptine, see under Levodopa, p.805.

1. Calne DB, *et al*. Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Vlissides DN, *et al*. Bromocriptine-induced mania? *BMJ* 1978; **1:** 510.
3. Brook NM, Cookson IB. Bromocriptine-induced mania? *BMJ* 1978; **1:** 790.
4. Pearce I, Pearce JMS. Bromocriptine in parkinsonism. *BMJ* 1978; **1:** 1402–4.
5. Pearson KC. Mental disorders from low-dose bromocriptine. *N Engl J Med* 1981; **305:** 173.
6. Le Feuvre CM, *et al*. Bromocriptine-induced psychosis in acromegaly. *BMJ* 1982; **285:** 1315.
7. Procter AW, *et al*. Bromocriptine induced psychosis in acromegaly. *BMJ* 1983; **286:** 50. Correction. *ibid.*; 311.
8. Einarson TR, Turchet EN. Psychotic reaction to low-dose bromocriptine. *Clin Pharm* 1983; **2:** 273–4.
9. Turner TH, *et al*. Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *BMJ* 1984; **289:** 1101–3.

Effects on the nervous system. CSF rhinorrhoea has been associated with bromocriptine therapy in patients with invasive prolactinomas. A report of 3 cases found 13 further cases on reviewing the literature;[1] of these, 7 patients had developed rhinorrhoea within 1 month of starting bromocriptine and 2 cases developed after 12 months.

For reference to seizures associated with the use of bromocriptine in postpartum women, see Effects on the Cardiovascular System, above.

1. Barlas O, *et al.* Bromocriptine-induced cerebrospinal fluid fistula in patients with macroprolactinomas: report of three cases and a review of the literature. *Surg Neurol* 1994; **41:** 486–9.

Effects on the respiratory system. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including bromocriptine, see Fibrosis, below.

Effects on sexual function. For reports of the effects of dopamine agonists on sexual function, see under Levodopa, p.806.

Effects on the urinary tract. Constant dribbling urinary incontinence developed in a woman receiving bromocriptine 2.5 mg daily for a recurrent pituitary growth; symptoms resolved on stopping the drug and recurred on rechallenge.[1] Bromocriptine has been shown to have two effects, one on the bladder outflow tract and one on the detrusor muscle, that could predispose to urinary incontinence.[2]

1. Sandyk R, Gillman MA. Urinary incontinence in patient on long-term bromocriptine. *Lancet* 1983; **ii:** 1260–1.
2. Caine M. Bromocriptine and urinary incontinence. *Lancet* 1984; **i:** 228.

Fibrosis. Fibrosis has been associated with the long-term use of ergot derivatives (see under Methysergide, p.623). Fibrotic reactions such as cardiac valvulopathy and pleuropulmonary effusion have been reported with bromocriptine, cabergoline, lisuride, and pergolide therapy in patients with Parkinson's disease.

Constrictive pericarditis[1] was reported in 2 patients who had received *bromocriptine* for 2 and 4 years, respectively; the latter still had slight pleural effusion 13 months after the drug was stopped. Valvular heart disease[2] developed in another patient who had received bromocriptine for 5 years; symptoms resolved 6 months after stopping the drug. Interstitial lung disease, with dyspnoea, chest pain, cough, and pulmonary fibrosis was reported[3] in a patient after use of relatively high doses of bromocriptine (62 mg daily). Respiratory symptoms largely resolved on withdrawal of the drug, although functional respiratory changes and moderate dyspnoea persisted after 6 months. A review of the literature revealed several other reports of pleuropulmonary fibrosis associated with relatively high doses of bromocriptine which occurred after between 15 days and up to 3 years of treatment. Although the incidence of this effect did not seem to be high, similar cases have continued to be reported.[4-6] In June 2008 the EMEA recommended that for long-term use in conditions such as Parkinson's disease, the maximum dose should be 30 mg daily.[7]

A patient developed pleuropulmonary disease 16 months after starting treatment with *cabergoline*;[8] he had previously received bromocriptine for 10 years and had had a normal chest X-ray at the time of transfer to cabergoline treatment. In another report, 2 cases of pleural effusion/pulmonary fibrosis, occurring after 10 to 11 months of treatment, were described.[9] One patient had modest pretreatment lung alterations attributed to previous bromocriptine therapy. Withdrawal was associated with improvement in both cases. Congestive heart failure secondary to constrictive pericarditis, and severe pleuropulmonary fibrosis that resulted in dyspnoea, persistent in one case,[10] have also been reported in 2 patients receiving long-term cabergoline.[10,11] Another patient developed cardiac valvulopathy after taking cabergoline for a total of 20 months;[12] her dosage was 4 mg daily for the last 7 months. Cardiac symptoms slowly improved on withdrawal of the drug, although some evidence of valvular defects was still present 23 months later. Valvular heart disease has also been reported in a 74-year-old man after 4 months of therapy with cabergoline [dosage not stated].[13] By December 2005, 86 cases of suspected adverse reactions to cabergoline had been reported to the Australian Drug Reactions Advisory Committee (ADRAC),[14] of which 15 described pleural or pulmonary fibrosis/effusion, or pneumonitis; time to onset ranged from a few days to over 3 years with a median of 4 months. There had been no reports of fibrotic complications associated with low-dose cabergoline in the treatment of lactation suppression and hyperprolactinaemia. The UK MHRA considers the risk of cardiac valvulopathy to be high and UK labelling for cabergoline has been amended accordingly (see p.802) with the EMEA in June 2008 recommending a maximum dose of 3 mg daily.[7]

A woman developed bilateral pleural effusions after taking *lisuride* 4 mg daily for about 17 months.[8] Her condition improved on stopping lisuride.

The UK CSM[15] reported in 2003 that *pergolide* had been associated with cases of cardiac valvulopathy; since 1989, valvulopathy had been reported in fewer than 5 in 100 000 patients. The CSM also referred to a published case series[16] which reported on 3 patients with severe tricuspid regurgitation after long-term pergolide treatment. The authors of this case series and the CSM both considered that, based on the available evidence, there was a potential association between pergolide and cardiac valvulopathy. Subsequently, the FDA[17] stated that, up to the end of 2002, it was aware of 15 cases of valvular heart disease with pergolide treatment; this figure included the 3 cases reported in the above series and 4 cases from the UK. A later study[18] that examined 78 patients taking pergolide for Parkinson's disease found evidence of restrictive valvular heart disease in 15 of 52 (29%) patients taking doses less than 5 mg daily and in 11 of 26 (42%) receiving doses of 5 mg or more daily. Pulmonary fibrosis and retroperitoneal fibrosis have also been associated with pergolide treatment;[19-21] in most cases, symptoms improved when the drug was stopped. Duration of exposure to pergolide ranged from 6 months[20] to 11 years.[21]

In April 2002 the CSM[22] calculated crude reporting rates of fibrotic reactions associated with the ergot derivative dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide), based on data submitted to its Yellow Card scheme and estimated drug exposure. Pergolide was found to be associated with a higher reporting rate of fibrotic reactions compared with the other ergot derivatives; however, this result needed further investigation to see if it reflected a true increase in risk or was due to factors such as reporting biases. There is some evidence that the incidence of reactions to pergolide are dose-related, and doses are restricted in many countries (see p.812) and in June 2008 the EMEA recommended a maximum dose of 3 mg daily.[7] Pergolide was withdrawn from the market in the USA and Canada. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with this class of drugs.

1. Champagne S, *et al.* Chronic constrictive pericarditis induced by long-term bromocriptine therapy: report of two cases. *Ann Pharmacother* 1999; **33:** 1050–4.
2. Serratrice J, *et al.* Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002; **10:** 334–6.
3. Vergeret J, *et al.* Fibrose pleuro-pulmonaire et bromocriptine. *Sem Hop Paris* 1984; **60:** 741–4.
4. Kinnunen E, Viljanen A. Pleuropulmonary involvement during bromocriptine treatment. *Chest* 1988; **94:** 1034–6.
5. Macak IA, *et al.* Bromocriptine-induced pulmonary disease. *Can J Hosp Pharm* 1991; **44:** 37–8, xxiv.
6. Debove P, *et al.* Pleuropneumopathie à la bromocriptine chez un parkinsonien: revue de la littérature à propos d'une nouvelle observation. *Ann Med Interne (Paris)* 1998; **149:** 167–71.
7. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
8. Bhatt MH, *et al.* Pleuropulmonary disease associated with dopamine agonist therapy. *Ann Neurol* 1991; **30:** 613–16.
9. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.
10. Ling LH, *et al.* Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist therapy (cabergoline) for Parkinson's disease. *Mayo Clin Proc* 1999; **74:** 371–5.
11. Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart* 2004; **90:** e47.
12. Horvath J, *et al.* Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004; **19:** 656–62.
13. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
14. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Ergot derivatives and fibrotic reactions. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 30/05/08)
15. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Pergolide (Celance) and cardiac valvulopathy. *Current Problems* 2003; **29:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Pritchett AM, *et al.* Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; **77:** 1280–6.
17. Flowers CM, *et al.* The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. *Mayo Clin Proc* 2003; **78:** 730–1.
18. Van Camp G, *et al.* Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004; **363:** 1179–83.
19. Agarwal P, *et al.* Diagnosis and management of pergolide-induced fibrosis. *Mov Disord* 2004; **19:** 699–704.
20. Simcock D, Paviour D. Rapid onset of pergolide-induced pulmonary fibrosis in a patient with corticobasal degeneration. *Hosp Med* 2004; **65:** 372–3.
21. Tintner R, *et al.* Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson disease. *Arch Neurol* 2005; **62:** 1290–5.
22. Committee on Safety of Medicines/Medicines Control Agency. Fibrotic reactions with pergolide and other ergot-derived receptor agonists. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)

Hypersensitivity. An allergic reaction developed in a 26-year-old woman being treated with bromocriptine for a prolactin-secreting microadenoma.[1] The patient reacted similarly to lisuride and treatment was continued with quinagolide.

1. Merola B, *et al.* Allergy to ergot-derived dopamine agonists. *Lancet* 1992; **339:** 620.

Oedema. Oedema poorly responsive to diuretics has been reported[1] in a patient given bromocriptine as part of treatment for prolactinoma. The oedema improved on substitution of pergolide but worsened with higher doses. Oedema resolved when treatment was changed to quinagolide. The reaction was considered to be idiosyncratic since enquiries by the author of the report had revealed only one similar case. In a subsequent report[2] a patient with Parkinson's disease who had been receiving bromocriptine for 5 years developed marked lower leg oedema, and subsequently cough, dyspnoea, and chest pain associated with an exudative pleural effusion; there was no evidence of fibrosis. Both oedema and effusion had largely resolved within 4 weeks of stopping bromocriptine.

1. Blackard WG. Edema—an infrequently recognized complication of bromocriptine and other ergot dopaminergic drugs. *Am J Med* 1993; **94:** 445.
2. Messiaen T, *et al.* Épanchement pleural et importants œdèmes des membres inférieurs induits par la bromocriptine. *Rev Med Interne* 1996; **17:** 680–3.

Overdosage. The most striking symptom in two children aged 2 and 2½ years who accidentally ingested an estimated 25 and 7.5 mg of bromocriptine, respectively, was lethargy with altered mental status.[1] The first child vomited and became sleepy. On admission he was markedly lethargic, but combative when disturbed, and also had hypotension, shallow breathing, dilated pupils, and hyperreflexic lower extremities. Nasogastric lavage was promptly performed, and activated charcoal and then magnesium citrate given. Blood pressure and ECG were monitored, and glucose and sodium chloride solution infused. The other child vomited, became lethargic, and had dilated pupils. Ipecacuanha was given, and activated charcoal followed by magnesium citrate given by nasogastric tube. Both children recovered completely.

1. Vermund SH, *et al.* Accidental bromocriptine ingestion in childhood. *J Pediatr* 1984; **105:** 838–40.

Withdrawal syndromes. Transient galactorrhoea and hyperprolactinaemia occurred in a young woman after withdrawal of bromocriptine therapy for Parkinson's disease.[1] It was suggested the effects were due to a rebound phenomenon. For discussion of a syndrome resembling neuroleptic malignant syndrome that has developed on withdrawal of bromocriptine and other antiparkinsonian drugs, see under Levodopa, p.806.

1. Pentland B, Sawers JSA. Galactorrhoea after withdrawal of bromocriptine. *BMJ* 1980; **281:** 716.

Precautions

Patients with hyperprolactinaemia should be investigated for the possibility of a pituitary tumour before treatment with bromocriptine. Malignancy must be excluded in patients with cyclical benign breast disorders such as mastalgia. Annual gynaecological examinations (or every 6 months for postmenopausal women) are recommended. Treatment of women with hyperprolactinaemic amenorrhoea results in ovulation; patients not wishing to conceive should be advised to use contraceptive measures although oral contraceptives should be avoided because they may increase prolactin levels. Acromegalic patients should be checked for symptoms of peptic ulceration before therapy and should immediately report symptoms of gastrointestinal discomfort during therapy.

In general, bromocriptine should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, or a history of psychosis. It is contra-indicated in patients with hypersensitivity to bromocriptine or other ergot alkaloids, and in those with uncontrolled hypertension.

Bromocriptine is contra-indicated in the toxaemia of pregnancy. It should also not be used postpartum or in the puerperium in women with hypertension, coronary artery disease, or symptoms or a history of serious psychiatric disorders. When used, blood pressure should be monitored carefully, especially during the first few days in postpartum women. Particular caution is necessary in patients who are receiving or who have recently received drugs that can alter blood pressure; use with ergot alkaloids during the puerperium is not recommended. Treatment in postpartum women should be stopped immediately if hypertension, unremitting headache, or signs of CNS toxicity develop.

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and those who drive or operate machinery should be warned of the possibility of dizziness and fainting during this period. Excessive daytime sleepiness and sudden onset of sleep may also occur with bromocriptine and other dopaminergic agonists, and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring. A reduction in dosage or withdrawal of the drug may be appropriate. Because of the risk of fibrosis bromocriptine is contra-indicated in patients with pre-existing valve problems.

Patients on long-term, high-dose therapy should be monitored for signs of progressive fibrotic disorders such as retroperitoneal fibrosis and bromocriptine withdrawn if fibrotic changes are diagnosed or suspected. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with bromocriptine. Periodic monitoring of cardiovascular, haematopoietic, hepatic, and renal function is also recommended. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Breast feeding. The American Academy of Pediatrics[1] considers that bromocriptine should be given with caution to breast-feeding mothers, since it suppresses lactation and may be hazardous to the mother.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/02/06)

Porphyria. Bromocriptine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy. Details of various surveys of the effect of the use of bromocriptine during pregnancy have been published by the manufacturer.[1,2] The first survey was based on spontaneous reporting of all pregnancies between 1973 and 1980 in women who had taken bromocriptine after conception.[1] Information was obtained on 1410 pregnancies in 1335 women, the majority of whom had been treated for hyperprolactinaemic conditions, while in 256 pregnancies pituitary tumours and acromegaly were the primary diagnosis. Bromocriptine was generally taken at some time in the first 8 weeks after conception, the mean duration of treatment being 21 days. In 4 patients bromocriptine was not prescribed until late in pregnancy and in 9 with acromegaly and pituitary microadenoma it was taken continuously throughout gestation. There were 157 (11.1%) spontaneous abortions, 12 (0.9%) extrauterine pregnancies, 2 patients with 3 hydatidiform moles (0.2%), and an incidence of twin pregnancies of 1.8%. Major congenital abnormalities were detected in 12 (1%) infants at birth and minor abnormalities in 31 (2.5%). A second survey,[2] which consisted of formal monitoring of the use of bromocriptine at 33 clinics between 1979 and 1980, collected data on a further 743 pregnancies in 668 women and had similar findings. The incidence rates reported in these surveys were comparable with those quoted for normal populations and the data indicate that the use of bromocriptine in the treatment of women with infertility is not associated with an increased risk of abortion, multiple pregnancy, or congenital abnormalities. Furthermore, follow-up, for up to 9 years, of 546 children exposed to bromocriptine *in utero* found no evidence that bromocriptine had any adverse effect on postnatal development.[2] Nevertheless, since the risk of abortion is not increased by interruption of treatment, licensed drug information recommends that bromocriptine therapy be stopped as soon as pregnancy is confirmed unless there is a definite indication for its continuation.

See also Pregnancy under Hyperprolactinaemia and Prolactinomas, below.

1. Turkalj I, *et al.* Surveillance of bromocriptine in pregnancy. *JAMA* 1982; **247:** 1589–91.
2. Krupp P, Monka C. Bromocriptine in pregnancy: safety aspects. *Klin Wochenschr* 1987; **65:** 823–7.

Interactions

Dopamine antagonists such as the phenothiazines, butyrophenones, thioxanthenes, and metoclopramide (but see below) might be expected to reduce the prolactin-lowering and the antiparkinsonian effects of bromocriptine and domperidone might reduce its prolactin-lowering effect. Memantine may enhance the effects of bromocriptine. Stimulants of gastrointestinal motility such as macrolide antibacterials or octreotide can increase the bioavailability of bromocriptine.

Alcohol. Alcohol intolerance was noted in 5 of 73 patients receiving bromocriptine 10 to 60 mg daily for the treatment of acromegaly.[1] Two patients who had gastrointestinal adverse effects while taking low doses of bromocriptine had a marked reduction in their symptoms and were able to tolerate higher doses when they refrained completely from alcohol.[2]

1. Wass JAH, *et al.* Long-term treatment of acromegaly with bromocriptine. *BMJ* 1977; **1:** 875–8.
2. Ayres J, Maisey MN. Alcohol increases bromocriptine's side effects. *N Engl J Med* 1980; **302:** 806.

Antibacterials. Drowsiness, dystonia, choreoathetoid dyskinesias, and visual hallucinations occurred when *josamycin* was given to a patient receiving bromocriptine.[1]

The systemic bioavailability of a single oral dose of bromocriptine 5 mg was markedly increased in 5 healthy subjects after treatment with *erythromycin estolate* 250 mg four times daily for 4 days;[2] clearance of bromocriptine was decreased and peak plasma concentrations of bromocriptine were more than 4 times higher than when given alone.

1. Montastruc JL, Rascol A. Traitement de la maladie de Parkinson par doses élevées de bromocriptine: interaction possible avec la josamycine. *Presse Med* 1984; **13:** 2267–8.
2. Nelson MV, *et al.* Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; **47:** 694–7.

Antifungals. The response to bromocriptine was blocked in a patient who was also receiving *griseofulvin.*[1]

1. Schwinn G, *et al.* Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. *Eur J Clin Invest* 1977; **7:** 101–7.

Antipsychotics. Serum concentrations of prolactin rose and visual fields deteriorated when *thioridazine* was given to a 40-year-old man receiving bromocriptine therapy for a large prolactinoma.[1]

For a discussion of the effect of bromocriptine on patients receiving antipsychotics, see Antiparkinsonian Drugs under Chlorpromazine on p.974.

1. Robbins RJ, *et al.* Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. *Am J Med* 1984; **76:** 921–3.

Metoclopramide. As noted in Interactions, above, there are theoretical reasons to suppose that dopamine antagonists such as metoclopramide might reduce the effects of bromocriptine. However, an early study[1] in 10 patients with Parkinson's disease given single doses of bromocriptine 12.5 to 100 mg found that pretreatment with metoclopramide 60 mg had no consistent effect upon plasma concentrations of bromocriptine or growth hormone and no consistent effect upon clinical response.

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.

Sympathomimetics. There have been isolated reports[1,2] of severe hypertension, with headache and life-threatening complications, in patients taking bromocriptine with *isometheptene mucate* or *phenylpropanolamine*.

1. Kulig K, *et al.* Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. *Obstet Gynecol* 1991; **78:** 941–3.
2. Chan JCN, *et al.* Postpartum hypertension, bromocriptine and phenylpropanolamine. *Drug Invest* 1994; **8:** 254–6.

Pharmacokinetics

Bromocriptine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 1 to 3 hours after oral doses. However, only about 30% of an oral dose is absorbed and, owing to extensive first-pass metabolism, the bioavailability is only about 6%. It has been reported to be 90 to 96% bound to serum albumin *in vitro*. It is metabolised in the liver, mainly by hydrolysis to lysergic acid and peptides. The elimination of bromocriptine is biphasic; half-lives of about 4 to 4.5 hours and 15 hours, respectively have been reported for the 2 phases. It is excreted mainly in faeces via the bile, with small amounts in urine.

◊ In a study involving 10 patients with Parkinson's disease, single oral doses of bromocriptine 12.5, 25, 50, and 100 mg resulted in very variable peak plasma concentrations ranging from 1.3 to 5.3, 1.4 to 3.5, 2.6 to 19.7, and 6.5 to 24.6 nanograms/mL, respectively, 30 to 210 minutes (mean 102 minutes) after dosage.[1] After 4 hours plasma concentrations were about 75% of the peak values. Clinical improvement was evident within 30 to 90 minutes of a dose with peak effect at about 130 minutes and in most patients improvement persisted throughout the 4-hour study period. Peak clinical response, peak fall in blood pressure, and peak rise in plasma concentrations of growth hormone occurred about 30, 60, and 70 minutes, respectively after peak plasma-bromocriptine concentrations but there was no significant relationship between them. However, there was a significant relationship between plasma concentrations and concurrent changes in clinical response compared with pretreatment scores. Dyskinesias occurred within 90 to 180 minutes of dosage in 5 of 10 patients.

Bromocriptine is well absorbed from standard oral tablets placed in the vagina and plasma concentrations sufficient to lower plasma prolactin concentrations have been achieved using this route.[2,3]

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.
2. Vermesh M, *et al.* Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. *Obstet Gynecol* 1988; **72:** 693–8.
3. Katz E, *et al.* Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. *Obstet Gynecol* 1989; **73:** 517–20.

Uses and Administration

Bromocriptine, an ergot derivative (p.2010), is a dopamine D_2-agonist. It inhibits the secretion of prolactin (p.2017) from the anterior pituitary and is used in the treatment of prolactinoma and endocrinological disorders associated with hyperprolactinaemia, including amenorrhoea, galactorrhoea, hypogonadism, and infertility in both men and women. Bromocriptine is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Growth hormone secretion may be suppressed by bromocriptine in some patients with acromegaly. Because of its dopaminergic activity bromocriptine is also used in the management of Parkinson's disease.

Bromocriptine is usually given orally as the mesilate; doses are expressed in terms of the base. Bromocriptine mesilate 2.87 mg is equivalent to about 2.5 mg of bromocriptine. Oral doses should be taken with food. Bromocriptine mesilate has also been given intramuscularly as a depot injection for disorders associated with hyperprolactinaemia.

For the **prevention of puerperal lactation** bromocriptine 2.5 mg is given on the day of delivery followed by 2.5 mg twice daily for 14 days. The risk of hypotension and, more rarely, hypertension must be borne in mind and it has been recommended that bromocriptine should not be given until at least 4 hours after delivery. For the **suppression of established lactation** it is given in a dose of 2.5 mg daily for 2 to 3 days subsequently increased to 2.5 mg twice daily for 14 days.

For the treatment of other conditions (see below) the dose of bromocriptine is usually increased gradually. In the UK, typically, an initial dose of 1 to 1.25 mg at night is given, increased to 2 to 2.5 mg at night after 2 to 3 days, and subsequently increased by 1 mg every 2 to 3 days to a dose of 2.5 mg twice daily, or more if necessary. In the USA, a usual starting dose is 1.25 to 2.5 mg daily increased by 2.5 mg every 2 to 7 days.

In the **treatment of hypogonadism and galactorrhoea syndromes and infertility** bromocriptine is introduced gradually as described above. Most patients with hyperprolactinaemia respond to 7.5 mg daily but up to 30 mg daily may be required. Infertile patients without raised serum concentrations of prolactin are usually given 2.5 mg twice daily. In patients known to have **prolactinomas** the dose is also introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days to a dose of 5 mg every 6 hours but occasionally patients may require up to 30 mg daily. Although unlicensed in the UK and USA, bromocriptine is used in some countries for **cyclical benign breast and menstrual disorders**. In benign breast disease bromocriptine is introduced gradually up to a daily dosage of 5 to 7.5 mg if necessary. In the treatment of premenstrual symptoms therapy should begin on day 14 of the cycle and introduced gradually up to a usual dosage of 2.5 mg twice daily until menstruation begins.

Bromocriptine may be used as an adjunct to surgery and radiotherapy to reduce plasma-growth hormone concentrations in **acromegalic patients**. In the UK, it is introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days if necessary up to 5 mg every 6 hours, according to response. In the USA, the usual starting dose (see above) may be increased by 1.25 to 2.5 mg every 3 to 7 days to a maximum daily dose of 100 mg if necessary; the usual dosage range is 20 to 30 mg daily.

In **Parkinson's disease** bromocriptine has been used alone, although it is usually given as an adjunct to levodopa treatment. It should be introduced even more gradually than the regimen above, and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved. In the UK, a suggested initial dose is the equivalent of 1 to 1.25 mg of bromocriptine at night during week 1, increased to 2 to 2.5 mg at night for week 2, 2.5 mg twice daily for week 3, and for week 4, 2.5 mg three times daily; the dose may be increased thereafter by 2.5 mg every 3 to 14 days according to response. The EMEA has recommended a maximum dose of 30 mg daily. In the USA, a usual starting dose is 1.25 to 2.5 mg twice daily increased by 2.5 mg every 14 to 28 days to a maximum dose of 100 mg daily if necessary.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and bromocriptine has been used in acromegaly (p.1798) as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels. While it is less effective than somatostatin analogues, it can be given orally and is therefore more convenient to administer.

Cushing's syndrome. There have been occasional reports of benefit with the use of bromocriptine in the treatment of Cushing's syndrome (p.2344). Remission of ACTH-dependent Cushing's syndrome was maintained for 6 years by bromocriptine 2.5 mg twice daily in a patient who had initially received pituitary irradiation.[1] However, the same group subsequently reported that they had found that bromocriptine did not effectively reduce ACTH secretion following bilateral adrenalectomy.[2]

1. Atkinson AB, *et al.* Six year remission of ACTH-dependent Cushing's syndrome using bromocriptine. *Postgrad Med J* 1985; **61:** 239–42.
2. Atkinson AB. The treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)* 1991; **34:** 507–13.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as bromocriptine in the management of hepatic encephalopathy see p.1697.

Hyperprolactinaemia and prolactinomas. Prolactinomas (prolactin-secreting pituitary adenomas) are among the commonest causes of hyperprolactinaemia. Raised serum-prolactin concentrations can result in reduced gonadotrophin production, which in turn may suppress gonadal function. Consequences may include oligomenorrhoea or amenorrhoea, and infertility in either sex. Galactorrhoea may also result from high prolactin levels and can occur in men as well as women.

Dopamine is the major inhibitory factor in the hypothalamus and directly inhibits the secretion of prolactin. Bromocriptine, a dopamine agonist, has been the first choice of treatment in many centres for the treatment of hyperprolactinaemia secondary to a prolactinoma although cabergoline is now preferred by some. Bromocriptine is extremely effective in controlling elevated circulating prolactin concentrations and restoring gonadal function; although it is rarely curative, it may produce considerable shrinkage of the adenoma.[1]

The sensitivity of hyperprolactinaemia to bromocriptine therapy can vary considerably between patients and this is reflected in the wide range of oral doses required to reduce prolactin concentrations to normal levels. Although beginning therapy with gradually increasing doses can minimise adverse effects it has been reported that about 5 to 10% of patients are unable to tolerate oral bromocriptine;[2] other dosage routes have therefore been investigated. Bromocriptine is well absorbed from standard oral tablets placed in the vagina and appears to be both effective in lowering prolactin concentrations and well tolerated when given by this route.[3] However, limitations are considered to be the relatively short duration of action and the relatively low dose that can be given.[2] A depot preparation given intramuscularly in a dose of 50 to 250 mg monthly has been found to be effective and well tolerated in long-term studies;[4,5] it is reported to be used in some centres to begin treatment for macroprolactinomas.[2]

For discussions of the management of hyperprolactinaemia and associated disorders see p.2079 (hyperprolactinaemia), p.2078 (amenorrhoea), p.2079 (hypogonadism), p.2179 (erectile dysfunction), and p.2080 (infertility).

1. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 55–65.
2. Ciccarelli E, Camanni F. Diagnosis and drug therapy of prolactinoma. *Drugs* 1996; **51:** 954–65.
3. Ginsburg J, *et al.* Vaginal bromocriptine. *Lancet* 1991; **338:** 1205–6.
4. Ciccarelli E, *et al.* Long term therapy of patients with macroprolactinoma using repeatable injectable bromocriptine. *J Clin Endocrinol Metab* 1993; **76:** 484–8.
5. Ciccarelli E, *et al.* Double blind randomized study using oral or injectable bromocriptine in patients with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1994; **40:** 193–8.

PREGNANCY. References to the management of prolactinoma during pregnancy.[1-3] Bromocriptine has been successfully used for management in pregnant women, particularly if there is symptomatic enlargement of the tumour, although there continues to be debate on the appropriateness of continuous therapy in less high-risk individuals.

1. Randeva HS, *et al.* Prolactinoma and pregnancy *Br J Obstet Gynaecol* 2000; **107:** 1064–8.
2. Bronstein MD, *et al.* Medical management of pituitary adenomas: the special case of management of the pregnant woman. *Pituitary* 2002; **5:** 99–107.
3. Chiodini I, Liuzzi A. PRL-secreting pituitary adenomas in pregnancy. *J Endocrinol Invest* 2003; **26:** 96–9.

Lactation inhibition. Because of its effects on prolactin, bromocriptine is a potent suppressor of lactation and has been widely used for the prevention of lactation in women who choose not to breast feed post partum. However, bromocriptine has been associated with severe adverse effects in some women, and its use to suppress a physiological state has been criticised (see p.2003). Consequently, licensed product information from a number of countries recommends that bromocriptine should only be used to suppress puerperal lactation for medical reasons; it is also not recommended for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support.

Mastalgia. Since mastalgia (p.2092) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months. Bromocriptine is one of the drugs that may be used to treat mastalgia.[1,2] It may improve symptoms in up to about 50% of patients with cyclical mastalgia, but is less effective in the non-cyclical form.[3,4] Adverse effects can be severe in some patients.

1. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
2. Anonymous. Cyclical breast pain—what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.
3. Pye JK, *et al.* Clinical experience of drug treatments for mastalgia. *Lancet* 1985; **ii:** 373–7.
4. Mansel RE, Dogliotti L. European multicentre trial of bromocriptine in cyclical mastalgia. *Lancet* 1990; **335:** 190–3.

Neuroleptic malignant syndrome. Bromocriptine has been used in doses of up to 30 mg daily,[1-6] usually alone or with dantrolene, in the treatment of neuroleptic malignant syndrome (p.972) although some workers have not found it to be of use.[7]

1. Mueller PS, *et al.* Neuroleptic malignant syndrome: successful treatment with bromocriptine. *JAMA* 1983; **249:** 386–8.
2. Dhib-Jalbut S, *et al.* Treatment of the neuroleptic malignant syndrome with bromocriptine. *JAMA* 1983; **250:** 484–5.
3. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
4. Guerrero RM, Shifrar KA. Diagnosis and treatment of neuroleptic malignant syndrome. *Clin Pharm* 1988; **7:** 697–701.
5. Lo TCM, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
6. Chandran GJ, *et al.* Neuroleptic malignant syndrome: case report and discussion. *Can Med Assoc J* 2003; **169:** 439–42.
7. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.

Parkinsonism. Dopamine agonists such as bromocriptine are often used to begin treatment of parkinsonism (p.791), particularly in younger patients, in an attempt to delay therapy with levodopa. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease. However, in early disease, there is no evidence that adjunctive bromocriptine prevents or delays the onset of motor complications associated with levodopa monotherapy.

References.

1. Temlett JA, *et al.* Adjunctive therapy with bromocriptine in Parkinson's disease. *S Afr Med J* 1990; **78:** 680–5.
2. Hely MA, *et al.* The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* 1994; **57:** 903–10.
3. Montastruc JL, *et al.* A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1034–8.
4. Giménez-Roldán S, *et al.* Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clin Neuropharmacol* 1997; **20:** 67–76.
5. Ogawa N, *et al.* Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease: final report of a ten-year follow-up. *Eur Neurol* 1997; **38** (suppl 2): 37–49.
6. Lees AJ, *et al.* Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001; **57:** 1687–94.
7. van Hilten JJ, *et al.*. Bromocriptine versus levodopa in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).
8. van Hilten JJ, *et al.* Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).

Polycystic ovary syndrome. Bromocriptine has been tried in women with the polycystic ovary syndrome (p.2080) who have mild basal hyperprolactinaemia without evidence of a pituitary tumour.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical but dopaminergic therapy has emerged as a common first-line choice. Bromocriptine showed some benefit in a small study.[1]

1. Walters AS, *et al.* A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Ann Neurol* 1988: **24:** 455–8.

Withdrawal syndromes. ***ALCOHOL.*** Studies of the efficacy of bromocriptine as an aid in the maintenance of abstinence from alcohol (p.1626) have yielded conflicting results.[1-4] However, it has been suggested[3] that response to bromocriptine might be linked to a specific genotype of the D_2 dopamine receptor.

1. Dongier M, *et al.* Bromocriptine in the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1991; **15:** 970–7.
2. Naranjo CA, *et al.* Long-acting bromocriptine (B) does not reduce relapse in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
3. Lawford BR, *et al.* Bromocriptine in the treatment of alcoholics with the D dopamine receptor A1 allele. *Nat Med* 1995; **1:** 337–41.
4. Powell BJ, *et al.* A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol Clin Exp Res* 1995; **19:** 462–8.

Preparations

BP 2008: Bromocriptine Capsules; Bromocriptine Tablets;
USP 31: Bromocriptine Mesylate Capsules; Bromocriptine Mesylate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Parlodel; Serocryptin†; ***Austral.:*** Bromohexal; Bromolactin†; Kripton; Parlodel; ***Austria:*** Bromed; Cehapark; Parlodel; Umprel; ***Belg.:*** Parlodel; ***Braz.:*** Bagren; Parlodel; ***Canad.:*** Parlodel; ***Chile:*** Criten; Grifocriptina; Kriptonal; Parlodel; Prigost; ***Cz.:*** Medocriptine; Parlodel; Serocryptin†; ***Denm.:*** Bromergon†; Parlodel; ***Fin.:*** Parlodel; ***Fr.:*** Bromo-Kin; Parlodel; ***Ger.:*** Bromocrel†; kirim; kirim gyn; Pravidel; ***Gr.:*** Parlodel; ***Hong Kong:*** Bromtine; Medocriptine; Parlodel; Serocryptin†; ***Hung.:*** Serocryptin†; ***India:*** Sicriptin; ***Indon.:*** Cripsa; Parlodel; ***Irl.:*** Parlodel; ***Israel:*** Parilac; Parlodel; ***Ital.:*** Parlodel; ***Malaysia:*** Butin†; Criptamine†; Medocriptine; Parlodel; Zolac†; ***Mex.:*** Broptin; Crilem; Cryocriptina; Kriptiser; Mesiken; Parlodel; Serocryptin†; ***Neth.:*** Parlodel; ***Norw.:*** Parlodel; ***Philipp.:*** Parlodel; Provasyn; ***Pol.:*** Bromergon; Bromocorn; Ergolaktyna; Parlodel; ***Port.:*** Parlodel; ***Rus.:*** Bromergon (Бромэргон); Parlodel (Парлодел); ***S.Afr.:*** Parlodel; ***Singapore:*** Butin†; Parlodel; Suplac†; ***Spain:*** Parlodel; ***Swed.:*** Pravidel; ***Switz.:*** Parlodel; ***Thai.:*** Brocaden; Bromergon; Parlodel; Suplac; ***Turk.:*** Gynodel; Parlodel; ***UAE:*** Antiprotin; ***UK:*** Parlodel; ***USA:*** Parlodel; ***Venez.:*** Parlodel; Serocryptin†.

Budipine *(rINN)*

Budipino; Budipinum. 1-*tert*-Butyl-4,4-diphenylpiperidine.

Будипин

$C_{21}H_{27}N$ = 293.4.
CAS — 57982-78-2.
ATC — N04BX03.
ATC Vet — QN04BX03.

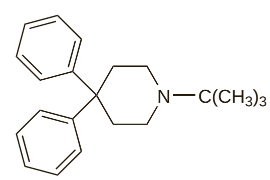

Profile

Budipine is a phenylpiperidine derivative used as an adjunct in the treatment of parkinsonism (p.791). It is given orally as the hydrochloride in daily doses of up to 60 mg.

◊ References.

1. Spieker S, *et al.* Tremorlytic activity of budipine: a quantitative study with long-term tremor recordings. *Clin Neuropharmacol* 1995; **18:** 266–72.
2. Groen H, *et al.* A study to investigate the pharmacokinetics and metabolism of budipine after administration of a single oral dose of [C]-B757-01 to six healthy volunteers. *Br J Clin Pharmacol* 1999; **48:** 771P–772P.
3. Malsch U, *et al.* Monotherapie der Parkinsonschen Erkrankung mit Budipin: ein randomisierter Doppelblindvergleich mit Amantadin. *Fortschr Neurol Psychiatr* 2001; **69:** 86–9.
4. Przuntek H, *et al.* Budipine provides additional benefit in patients with Parkinson disease receiving a stable optimum dopaminergic drug regimen. *Arch Neurol* 2002; **59:** 803–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Parkinsan.

Cabergoline *(BAN, USAN, rINN)*

Cabergolina; Cabergolinum; FCE-21336; Kabergoliini; Kabergolin; Kabergolina. 1-[(6-Allylergolin-8β-yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea; (8*R*)-6-Allyl-*N*-[3-(dimethylamino)-propyl]-*N*-(ethylcarbamoyl)ergoline-8-carboxamide.

Каберголин

$C_{26}H_{37}N_5O_2$ = 451.6.

CAS — 81409-90-7.

ATC — G02CB03; N04BC06.

ATC Vet — QG02CB03; QN04BC06.

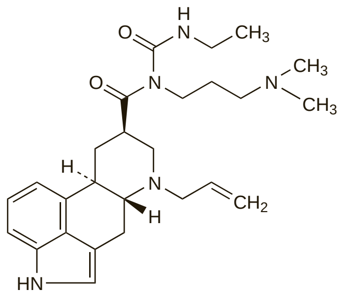

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cabergoline). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in alcohol; very slightly soluble in *n*-hexane. It is slightly soluble in 0.1M hydrochloric acid. Protect from light.

Adverse Effects and Precautions

As for Bromocriptine, p.798, although patients unable to tolerate bromocriptine may tolerate cabergoline (and *vice versa*).

Licensed product information states that conception should be avoided for at least one month after treatment.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including cabergoline, see under Levodopa, p.805.

For reference to **pathological gambling** reported in patients with Parkinson's disease receiving dopamine agonists including cabergoline, see under Levodopa, p.805.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including cabergoline, see under Bromocriptine, p.799.

In 2007, based on further evidence from 3 studies,[1-3] the UK MHRA[4] considered the risk of cardiac valvulopathy to be high and clinically significant with cabergoline and pergolide, and the risks of treatment with these 2 drugs to be similar. This resulted in the following changes to UK labelling for cabergoline products in Parkinson's disease:

- restricted to second-line treatment in patients intolerant of, or who do not respond to, non-ergot drug treatment
- contra-indicated in patients with a history of pulmonary, pericardial, and retroperitoneal fibrotic disorders, or in those with anatomical evidence of cardiac valvulopathy
- monitoring for development of valvular disease or fibrosis recommended: echocardiography should be performed within 3 to 6 months of starting treatment and every 6 to 12 months thereafter

In June 2008 the EMEA further recommended that the maximum dose should be 3 mg daily.[5]

1. Yamamoto M, *et al.* Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. *Neurology* 2006; **67:** 1225–9.
2. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; **356:** 29–38.
3. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; **356:** 39–46.
4. MHRA/CHM. Cabergoline: cardiovalvulopathy. *Drug Safety Update* 2007: **1** (1): 5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2031802 (accessed 30/05/08)
5. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)

Oedema. Three cases of lower limb oedema after chronic treatment with cabergoline have been reported.[1] In one case the oedema was severe enough to necessitate withdrawal of therapy.

1. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.

Interactions

As for Bromocriptine, p.800.

Pharmacokinetics

Cabergoline is absorbed from the gastrointestinal tract and mean peak plasma concentrations are achieved within 2 to 3 hours. It is subject to first-pass metabolism and is extensively metabolised to several metabolites that do not appear to contribute to its pharmacological activity. Plasma protein binding has been estimated to be about 40%. Cabergoline is mainly eliminated via the faeces; a small proportion is excreted in the urine. In *rats*, cabergoline has been reported to cross the placenta and to be distributed into breast milk.

◊ General references.

1. Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. *Clin Pharmacokinet* 2003; **42:** 633–45.

Half-life. Pharmacokinetic studies of cabergoline have been hampered by lack of an assay method sensitive enough to detect plasma concentrations of cabergoline after therapeutic doses. However, the plasma elimination half-life of cabergoline has been estimated indirectly to be 63 to 68 hours in healthy subjects and 79 to 115 hours in patients with hyperprolactinaemia.[1]

1. Rains CP, *et al.* Cabergoline: a review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. *Drugs* 1995; **49:** 255–79.

Uses and Administration

Cabergoline, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p.800). It is a potent and long-lasting inhibitor of prolactin secretion used in the management of disorders associated with hyperprolactinaemia. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Cabergoline is also used in the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK cabergoline is restricted to patients who are intolerant of, or who do not respond to, non-ergot drug treatment.

Cabergoline is given orally and should be taken with food.

To **inhibit physiological lactation**, cabergoline is given as a single 1-mg dose on the first day post partum. For **suppression of established lactation**, the dose is 250 micrograms every 12 hours for 2 days.

In the treatment of **disorders associated with hyperprolactinaemia**, the initial dose of cabergoline is 500 micrograms weekly. The dose is then increased at monthly intervals in increments of 500 micrograms weekly according to response. The weekly dose may be given on a single occasion or divided into 2 or more doses on separate days; doses over 1 mg should be given as divided doses. The usual dose is 1 mg weekly but up to 4.5 mg weekly has been used.

In **Parkinson's disease**, cabergoline should be introduced gradually and during this period the dose of levodopa may be reduced gradually until an optimal response is achieved. A suggested initial dose of cabergoline given as a single daily dose is 0.5 mg in monotherapy or 1 mg in adjunctive therapy. The dose may be increased in increments of 0.5 or 1 mg at intervals of 7 or 14 days. The EMEA has recommended a maximum dose of 3 mg daily.

Doses of cabergoline may need to be reduced in patients with severe hepatic impairment (see below).

Administration in hepatic impairment. Licensed drug information recommends caution in patients with severe hepatic impairment (Child-Pugh category C), and doses of cabergoline should be adjusted accordingly.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone concentrations, although they are less effective than somatostatin analogues (p.1798). Although a small study comparing cabergoline with depot bromocriptine and quinagolide failed to find evidence of its effectiveness (see p.2377), in a later open study[1] there was a good response in about 40% of patients treated with cabergoline, which is better than the response usually reported for bromocriptine. The addition of cabergoline has also been beneficial in acromegaly that is resistant to somatostatin analogue therapy.[2]

1. Abs R, *et al.* Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 1998; **83:** 374–8.
2. Cozzi R, *et al.* Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin Endocrinol (Oxf)* 2004; **61:** 209–15.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (see p.2079). Although bromocriptine has been the first choice for this indication, some now prefer cabergoline,[1] which appears to be more effective and better tolerated.[2,3]

Further references.[4-9]

1. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14:** 228–38. Correction. *ibid.*, 342.
2. Pascal-Vigneron V, *et al.* Amenorrhée hyperprolactinémique: traitement par cabergoline versus bromocriptine. *Presse Med* 1995; **24:** 753–7.
3. di Sarno A, *et al.* Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 2001; **86:** 5256–61.
4. Webster J, *et al.* The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinaemic disorders: an open, uncontrolled, multicentre study. *Clin Endocrinol (Oxf)* 1993; **39:** 323–9.
5. Webster J, *et al.* A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1994; **331:** 904–9.
6. Verhelst J, *et al.* Cabergoline in the treatment of hyperprolactinaemia: a study in 455 patients. *J Clin Endocrinol Metab* 1999; **84:** 2518–22.
7. Colao A, *et al.* Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrinol Metab* 2000; **85:** 2247–52.
8. Colao A, *et al.* Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003; **349:** 2023–33.
9. Colao A, *et al.* Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J Clin Endocrinol Metab* 2004; **89:** 1704–11.

Lactation inhibition. A single 1-mg dose of cabergoline was found to be as effective as bromocriptine 2.5 mg given twice daily for 14 days for preventing puerperal lactation in a double-blind multicentre study involving 272 women.[1] It has been suggested that cabergoline would be a better choice than bromocriptine for lactation inhibition.[2] However, as discussed on p.2003, the routine use of dopaminergics such as bromocriptine or cabergoline is not recommended for the suppression of physiological lactation.

1. European Multicentre Study Group for Cabergoline in Lactation Inhibition. Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study. *BMJ* 1991; **302:** 1367–71.
2. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14:** 228–38. Correction. *ibid.*; 342.

Parkinsonism. Cabergoline is used as a long-acting dopamine agonist in Parkinson's disease (p.791). Dopamine agonists are often used to begin treatment in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stages of the disease.

References.

1. Inzelberg R, *et al.* Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. *Neurology* 1996; **47:** 785–8.
2. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.
3. Hutton JT, *et al.* Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology* 1996; **46:** 1062–5.
4. Marsden CD. Clinical experience with cabergoline in patients with advanced Parkinson's disease treated with levodopa. *Drugs* 1998; **55** (suppl 1): 17–22.
5. Rinne UK, *et al.* Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications: results of a double-blind levodopa controlled trial. *Drugs* 1998; **55** (suppl 1): 23–30.
6. Clarke CE, Deane KHO. Cabergoline for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane KHO. Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Bracco F, *et al.* The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. *CNS Drugs* 2004; **18:** 733–46. Correction. *ibid.* 2005; **19:** 633.
9. Curran MP, Perry CM. Cabergoline: a review of its use in the treatment of Parkinson's disease. *Drugs* 2004; **64:** 2125–41.
10. Odin P, *et al.* Efficacy and safety of high-dose cabergoline in Parkinson's disease. *Acta Neurol Scand* 2006; **113:** 18–24.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p.958) is obscure and treatment has been largely empirical but dopaminergic therapy has emerged as a common first-line choice. Long-acting drugs such as cabergoline may be preferred in order to avoid the complications associated with levodopa therapy. Results from a 12-week open-label pilot study[1] in 9 patients with idiopathic RLS given cabergoline after insufficient response to levodopa therapy were promising; doses of cabergoline ranged from 1 to 4 mg. A later randomised multicentre study[2] in 85 patients concluded that a single evening dose of cabergoline for 5 weeks markedly reduced symptoms during the night and the next day compared with placebo. Results from the follow-up analysis of 66 patients after 1 year of treatment suggested that cabergoline at a median dose of 2 mg daily has a high rate of remission and is well tolerated. The authors recommended an initial dose of cabergoline 500 micrograms in the evening increased in increments of 500 micrograms weekly according to response.

1. Stiasny K, *et al.* Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline—an open clinical trial. *Sleep* 2000; **23:** 349–54.
2. Stiasny-Kolster K, *et al.* Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology* 2004; **63:** 2272–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cabaser; Caberpar; Cieldom; Dostinex; Lac Stop; Lactamax; Triaspar; ***Austral.:*** Cabaser; Dostinex; ***Austria:*** Cabaseril; Dostinex; ***Belg.:*** Dostinex; Sostilar; ***Braz.:*** Dostinex; ***Canad.:*** Dostinex; ***Chile:*** Dostinex; ***Cz.:*** Cabera; Dostinex; ***Denm.:*** Cabaser; Dostinex; ***Fin.:*** Cabaser; Dostinex; ***Fr.:*** Dostinex; ***Ger.:*** Cabaseril; Dostinex; ***Gr.:*** Dostinex; ***Hong Kong:*** Dostinex; ***India:*** Caberlin; Camforte†; ***Irl.:*** Cabaser; Dostinex; ***Israel:*** Cabaser; Dostinex; ***Ital.:*** Actualene; Cabaser; Dostinex; ***Malaysia:*** Dostinex; ***Mex.:*** Dostinex; ***Neth.:*** Dostinex; ***Norw.:*** Cabaser; Dostinex; ***NZ:*** Dostinex; ***Pol.:*** Dostinex; ***Port.:*** Dostinex; ***Rus.:*** Dostinex (Достинекс); ***S.Afr.:*** Dostinex; ***Singapore:*** Dostinex; ***Spain:*** Dostinex; Sogilen; ***Swed.:*** Cabaser; Dostinex; ***Switz.:*** Cabaser; Dostinex; ***Turk.:*** Cabaser; Dostinex; ***UK:*** Cabaser; Dostinex; ***USA:*** Dostinex†; ***Venez.:*** Dostinex.

Carbidopa *(BAN, USAN, rINN)*

Carbidopum; Carbidopum Monohydricum; Karbidopa; Karbidopa monohydrát; α-Methyldopa Hydrazine; MK-486. (+)-2-(3,4-Dihydroxybenzyl)-2-hydrazinopropionic acid monohydrate; (−)-L-α-Hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate.

Карбидопа

$C_{10}H_{14}N_2O_4,H_2O$ = 244.2.

CAS — 28860-95-9 (anhydrous); 38821-49-7 (monohydrate).

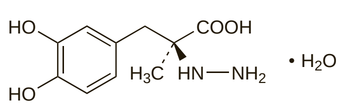

NOTE. The synonym MK-485 has been used for the racemic mixture.

Compounded preparations of carbidopa and levodopa may be represented by the following names:

- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Carbidopa). A white or yellowish-white powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane; dissolves in dilute solutions of mineral acids. Protect from light.

USP 31 (Carbidopa). A white to creamy-white, odourless or practically odourless powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in 3N hydrochloric acid. Protect from light.

Adverse Effects

Hypersensitivity. Henoch-Schönlein purpura that developed in a 68-year-old patient being treated for Parkinson's disease appeared to be due to either carbidopa or an excipient of the carbidopa preparation (*Sinemet*).[1]

1. Niedermaier G, Briner V. Henoch-Schönlein syndrome induced by carbidopa/levodopa. *Lancet* 1997; **349:** 1071–2.

Pharmacokinetics

Carbidopa is rapidly but incompletely absorbed from the gastrointestinal tract. It is rapidly excreted in the urine both unchanged and in the form of metabolites. It does not cross the blood-brain barrier. In *rats*, carbidopa has been reported to cross the placenta and to be distributed into breast milk.

Uses and Administration

Carbidopa is a peripheral dopa-decarboxylase inhibitor with little or no pharmacological activity when given alone in usual doses. It inhibits the peripheral decarboxylation of levodopa to dopamine and as, unlike levodopa, it does not cross the blood-brain barrier, effective brain concentrations of dopamine are produced with lower doses of levodopa. At the same time reduced peripheral formation of dopamine reduces peripheral adverse effects, notably nausea and vomiting, and cardiac arrhythmias, although the dyskinesias and adverse mental effects associated with levodopa therapy tend to develop earlier. Contrary to its effect in patients on levodopa alone, pyridoxine does not inhibit the response to levodopa in patients also receiving a peripheral dopa-decarboxylase inhibitor.

In the treatment of parkinsonism (p.791) carbidopa is given with levodopa to enable a lower dosage of the latter to be used, a more rapid response to be obtained, and to decrease adverse effects. For details of administration and dosage, see Levodopa, p.808.

Carbidopa also inhibits the peripheral decarboxylation of the serotonin precursor oxitriptan (p.414).

◊ General references.

1. Pinder RM, *et al*. Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. *Drugs* 1976; **11:** 329–77.
2. Boshes B. Sinemet and the treatment of parkinsonism. *Ann Intern Med* 1981; **94:** 364–70.

Preparations

BP 2008: Co-careldopa Tablets;
USP 31: Carbidopa and Levodopa Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Prikap; ***Pol.:*** Nakom; ***USA:*** Lodosyn.

Multi-ingredient: ***Arg.:*** Lebocar; Lecarge; Nervocur; Parkinel; Sinemet; Stalevo; ***Austral.:*** Kinson; Sinemet; Stalevo; ***Austria:*** Levocar; Sinemet; ***Belg.:*** Sinemet; Stalevo; ***Braz.:*** Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Sinemet; Stalevo; ***Canad.:*** Apo-Levocarb; Novo-Levocarbidopa; Nu-Levocarb; Sinemet; ***Chile:*** Grifoparkin; Levofamil†; Protonis; Saniter Compuesto; Sinemet; Stalevo; ***Cz.:*** Dopalux; Duodopa; Isicom; Lecardop; Nakom; Sinemet; Stalevo; ***Denm.:*** Duodopa; Sinemet; Stalevo; ***Fin.:*** Kardopal; Sinemet; Stalevo; ***Fr.:*** Duodopa; Sinemet; Stalevo; ***Ger.:*** Dopadura C; Isicom; Levo-C; Levobeta C; Levocarb; Levocomp; Levodop; Levodopa Comp; Levodopa comp C; Levodopa-Carbi†; Nacom; Stalevo; Striaton; Tremopar†; ***Gr.:*** Sinemet; Sinemet-CR; Stalevo; Zimox; ***Hong Kong:*** Apo-Levocarb; Levomed; Levomet; Sinedopa; Sinemet; Stalevo; ***Hung.:*** Duellin; Sinemet; Stalevo; ***India:*** Levopa-C†; Syndopa; ***Indon.:*** Stalevo; ***Irl.:*** Half Sinemet; Sinemet; Stalevo; ***Israel:*** Dopicar; Sinemet; Stalevo; ***Ital.:*** Duodopa; Sinemet; Sirio; Stalevo; ***Malaysia:*** Apo-Levocarb; Levomed; Sinemet; Stalevo; ***Mex.:*** Cloisone; Lemdopa; Racovel; Sinemet; Stalevo; Ternovag; ***Neth.:*** Duodopa; Sinemet; Stalevo; ***Norw.:*** Duodopa; Sinemet; Stalevo; ***NZ:*** Apo-Levocarb; Sindopa; Sinemet; ***Philipp.:*** Ledocar; Sinemet; Stalev; Tidomet; ***Pol.:*** Sinemet; Stalevo; ***Port.:*** Duodopa; Ledopsan; Sinemet; Stalevo; ***Rus.:*** Duellin (Дуэллин); Nakom (Наком); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); ***S.Afr.:*** Carbilev; Sinemet; ***Singapore:*** Cardopar; Levomet; Sinemet; Stalevo; Tidomet; ***Spain:*** Duodopa; Ledopsan; Sinemet; Stalevo; ***Swed.:*** Duodopa; Sinemet; Stalevo; ***Switz.:*** Sinemet; Stalevo; ***Thai.:*** Levomed†; Levomet; Sinemet; Stalevo; Syndopa; ***Turk.:*** Sinemet; Stalevo; ***UK:*** Duodopa; Half Sinemet; Sinemet; Stalevo; Tilolec†; ***USA:*** Atamet; Parcopa; Sinemet; Stalevo; ***Venez.:*** Sinemet; Stalevo.

Dexetimide *(BAN, USAN, rINN)*

Dexetimida; Dexétimide; Dexetimidum. (*S*)-2-(1-Benzyl-4-piperidyl)-2-phenylglutarimide; (*S*)-3-Phenyl-1′-(phenylmethyl)-(3,4′-bipiperidine)-2,6-dione.

Дексэтимид

$C_{23}H_{26}N_2O_2$ = 362.5.

CAS — 21888-98-2.

ATC — N04AA08.

ATC Vet — QN04AA08.

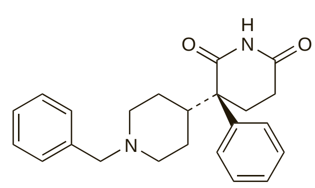

Dexetimide Hydrochloride *(BANM, rINNM)*

Dexbenzetimide Hydrochloride; Dexétimide, Chlorhydrate de; Dexetimidi Hydrochloridum; Hidrocloruro de dexetimida; R-16470.

Дексэтимида Гидрохлорид

$C_{23}H_{26}N_2O_2,HCl$ = 398.9.

CAS — 21888-96-0.

ATC — N04AA08.

ATC Vet — QN04AA08.

Profile

Dexetimide is a tertiary antimuscarinic with actions similar to those of trihexyphenidyl (p.820). It has been used to alleviate drug-induced extrapyramidal symptoms (see under Chlorpromazine, p.971), but, like other antimuscarinics, is of no value against tardive dyskinesias. Dexetimide is given as the hydrochloride although doses are expressed in terms of the base; dexetimide hydrochloride 1.1 mg is equivalent to about 1 mg of dexetimide. A usual oral dose is 0.5 to 1 mg once daily; it has also been given by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Tremblex; ***Neth.:*** Tremblex.

Diethazine Hydrochloride *(BANM, rINNM)*

Diaethazinium Chloratum; Diéthazine, Chlorhydrate de; Diethazini Hydrochloridum; Eazamine Hydrochloride; Hidrocloruro de dietazina; RP-2987. 10-(2-Diethylaminoethyl)phenothiazine hydrochloride.

Диэтазина Гидрохлорид

$C_{18}H_{22}N_2S,HCl$ = 334.9.

CAS — 60-91-3 (diethazine); 341-70-8 (diethazine hydrochloride).

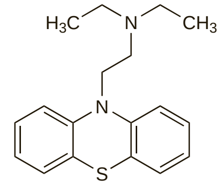

(diethazine)

Profile

Diethazine hydrochloride is an antimuscarinic with actions similar to those of profenamine hydrochloride (p.815), but it is more toxic and bone-marrow depression may occur. It has been used in the treatment of parkinsonism.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Deparkin†.

Droxidopa *(USAN, rINN)*

L-*threo*-3,4-Dihydroxyphenylserine; DOPS; Droxidopum; L-DOPS; L-*threo*-DOPS. (−)-*threo*-3-(3,4-Dihydroxyphenyl)-L-serine.

Дроксидопа

$C_9H_{11}NO_5$ = 213.2.

CAS — 23651-95-8.

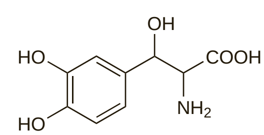

Profile

Droxidopa is a precursor of noradrenaline that is used in the treatment of parkinsonism (p.791) and some forms of orthostatic hypotension (p.1530). The usual oral maintenance dose is 600 mg daily for the treatment of parkinsonism and 300 to 600 mg daily in orthostatic hypotension; daily doses should be divided.

The racemic form (DL-*threo*-3,4-dihydroxyphenylserine) has also been studied for orthostatic hypotension.

◊ References.

1. Iida N, *et al.* Treatment of dialysis-induced hypotension with -threo-3, 4-dihydroxyphenylserine. *Nephrol Dial Transplant* 1994; **9:** 1130–5.
2. Freeman R, *et al.* The treatment of neurogenic orthostatic hypotension with 3,4-DL-threo-dihydroxyphenylserine: a randomized, placebo-controlled, crossover trial. *Neurology* 1999; **10:** 2151–7.
3. Akizawa T, *et al.* Clinical effects of L-threo-3,4-dihydroxyphenylserine on orthostatic hypotension in hemodialysis patients. *Nephron* 2002; **90:** 384–90.
4. Kaufmann H, *et al.* Norepinephrine precursor therapy in neurogenic orthostatic hypotension. *Circulation* 2003; **108:** 724–8.
5. Goldstein DS, *et al.* Clinical pharmacokinetics of the norepinephrine precursor L-threo-DOPS in primary chronic autonomic failure. *Clin Auton Res* 2004; **14:** 363–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Dops.

The symbol † denotes a preparation no longer actively marketed

Entacapone *(BAN, USAN, rINN)*

Entacapona; Entacaponum; Entakapon; Entakaponi; OR-611. (*E*)-α-Cyano-*N*,*N*-diethyl-3,4-dihydroxy-5-nitrocinnamamide; (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylacrylamide.

Энтакапон

$C_{14}H_{15}N_3O_5$ = 305.3.

CAS — 130929-57-6.

ATC — N04BX02.

ATC Vet — QN04BX02.

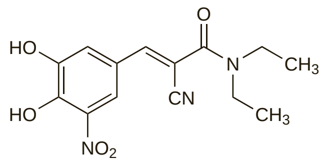

Adverse Effects

The most frequent adverse effects produced by entacapone relate to increased dopaminergic activity and occur most commonly at the start of treatment; reduction of the levodopa dosage may reduce the severity and frequency of such effects. Adverse effects may include nausea, vomiting, abdominal pain, constipation, diarrhoea, colitis, dry mouth, and dyskinesias. Other commonly reported adverse effects include dizziness, insomnia, nightmares, hallucinations, confusion, fatigue, and increased sweating. There have been rare reports of agitation, urticaria, erythematous or maculopapular rash, anorexia, and weight decrease. Increases in liver enzyme values have been reported rarely; there have also been isolated cases of cholestatic hepatitis. Isolated cases of neuroleptic malignant syndrome have been reported after abrupt reduction or withdrawal of entacapone; there have also been isolated cases of rhabdomyolysis. It may produce a harmless reddish-brown discoloration of the urine. Skin, hair, beard, and nail discolorations have been reported.

◊ References.

1. Brooks DJ. Safety and tolerability of COMT inhibitors. *Neurology* 2004; **62** (Suppl 1): S39–S46.

Precautions

Entacapone is contra-indicated in patients with phaeochromocytoma and in patients with a history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis. It should be avoided in patients with hepatic impairment, and given with caution to patients with biliary obstruction. A general medical evaluation, including liver function, should be considered in those who experience progressive anorexia, asthenia, and weight decrease within a relatively short period of time.Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, in Levodopa, p.805) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Treatment with entacapone should not be stopped abruptly; when necessary withdrawal should be made gradually, increasing the dose of levodopa as required.

Genetic polymorphism. For reference to slow metabolisers being more susceptible to COMT-inhibitor induced hepatotoxicity, see under Tolcapone, p.820.

Interactions

Use of entacapone with a non-selective MAOI is contra-indicated. Entacapone should be used with caution in patients receiving drugs metabolised by catechol-*O*-methyltransferase (COMT) including adrenaline, apomorphine, dobutamine, dopamine, isoprenaline, methyldopa, noradrenaline, paroxetine, and rimiterol. Caution is also advised when used with certain antidepressants including the tricyclics, reversible inhibitors of monoamine oxidase type A, and noradrenaline reuptake inhibitors such as venlafaxine.

Entacapone may aggravate levodopa-induced orthostatic hypotension and should be used cautiously in patients who are taking other drugs which may cause orthostatic hypotension.

Entacapone may form chelates with iron preparations in the gastrointestinal tract; the two drugs should be taken at least 2 to 3 hours apart.

Pharmacokinetics

There are large intra- and interindividual variations in the absorption of entacapone. Peak plasma concentrations are achieved about one hour after oral doses. Entacapone undergoes extensive first-pass metabolism and oral bioavailability is about 35%. Absorption is not affected significantly by food. Entacapone is about 98% bound to plasma proteins. It is eliminated mainly in the faeces with about 10 to 20% being excreted in the urine, mainly as glucuronide conjugates. Entacapone is thought to be distributed into breast milk on the basis of studies in *rats*.

◊ Entacapone is rapidly absorbed from the gastrointestinal tract and bioavailability after oral doses has been reported to range from 29 to 46%. It does not cross the blood-brain barrier. Over half of a dose appears in the faeces with smaller amounts being excreted in the urine as glucuronides of entacapone and its (*Z*)-isomer. Elimination half-lives of about 1.6 to 3.4 hours have been reported for entacapone.

References.

1. Wikberg T, *et al.* Identification of major metabolites of the catechol-O-methyltransferase inhibitor entacapone in rats and humans. *Drug Metab Dispos* 1993; **21:** 81–92.
2. Keränen T, *et al.* Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol* 1994; **46:** 151–7.

Uses and Administration

Entacapone is a selective, reversible, peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to combination preparations of levodopa and dopa-decarboxylase inhibitors, in patients with Parkinson's disease and 'end-of-dose' motor fluctuations who cannot be stabilised on levodopa combinations alone. Entacapone is given orally in a dosage of 200 mg at the same time as each dose of levodopa with dopa-decarboxylase inhibitor, up to a maximum of 200 mg ten times daily. It is often necessary to gradually reduce the dosage of levodopa by about 10 to 30% within the first few weeks after starting treatment with entacapone; this effect may be more marked in the presence of benserazide than of carbidopa.

Entacapone may also be given as a combination preparation with carbidopa and levodopa; for dosage details, see Levodopa, p.808.

Parkinsonism. Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT), with mainly peripheral actions. It is given as adjunctive therapy to patients with Parkinson's disease (p.791) experiencing fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. When levodopa is given with a peripheral dopa-decarboxylase inhibitor, *O*-methylation then becomes the predominant form of metabolism of levodopa; therefore adding a peripheral COMT inhibitor such as entacapone potentially extends the duration and effect of levodopa in the brain, and thus allows levodopa to be given less often and in lower doses.

References.

1. Holm KJ, Spencer CM. Entacapone: a review of its use in Parkinson's disease. *Drugs* 1999; **58:** 159–177.
2. Anonymous. Entacapone for Parkinson's disease. *Med Lett Drugs Ther* 2000; **42:** 7–8.
3. Chong BS, Mersfelder TL. Entacapone. *Ann Pharmacother* 2000; **34:** 1056–65.
4. Myllyla VV, *et al.* Twelve-month safety of entacapone in patients with Parkinson's disease. *Eur J Neurol* 2001; **8:** 53–60.
5. Poewe WH, *et al.* Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurol Scand* 2002; **105:** 245–55.
6. Brooks DJ, *et al.* Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1071–9.
7. Fenelon G, *et al.* Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations: a randomized, double-blind, multicentre study. *J Neural Transm* 2003; **110:** 239–51.
8. Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? *Neurology* 2004; **62** (suppl 1): S72–S81.
9. Deane KHO, *et al.* Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).
10. Poewe W. The role of COMT inhibition in the treatment of Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S31–S38.
11. Schrag A. Entacapone in the treatment of Parkinson's disease. *Lancet Neurol* 2005; **4:** 366–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Comtan; ***Austral.:*** Comtan; ***Austria:*** Comtan; ***Belg.:*** Comtan; ***Braz.:*** Comtan; ***Canad.:*** Comtan; ***Cz.:*** Comtan; Comtess; ***Denm.:*** Comtess; ***Fin.:*** Comtess; ***Fr.:*** Comtan; ***Ger.:*** Comtess; ***Gr.:*** Comtan; ***Hong Kong:*** Comtan; ***Hung.:*** Comtan; ***Indon.:*** Comtan; ***Irl.:*** Comtess; ***Israel:*** Comtan; ***Ital.:*** Comtan; ***Malaysia:*** Comtan; ***Mex.:*** Comtan; ***Neth.:*** Comtan; Comtess; ***Norw.:*** Comtess; ***NZ:*** Comtan; ***Philipp.:*** Comtan; ***Pol.:*** Comtan; ***Port.:*** Comtan; Comtess; ***S.Afr.:*** Comtan; ***Singapore:*** Comtan; ***Spain:*** Comtan; ***Swed.:*** Comtess; ***Switz.:*** Comtan; ***Thai.:*** Comtan; ***Turk.:*** Comtan; ***UK:*** Comtess; ***USA:*** Comtan; ***Venez.:*** Comtan.

Multi-ingredient: ***Arg.:*** Stalevo; ***Austral.:*** Stalevo; ***Belg.:*** Stalevo; ***Braz.:*** Stalevo; ***Chile:*** Stalevo; ***Cz.:*** Stalevo; ***Denm.:*** Stalevo; ***Fin.:*** Stalevo; ***Fr.:*** Stalevo; ***Ger.:*** Stalevo; ***Gr.:*** Stalevo; ***Hong Kong:*** Stalevo; ***Hung.:*** Stalevo; ***Indon.:*** Stalevo; ***Irl.:*** Stalevo; ***Israel:*** Stalevo; ***Ital.:*** Stalevo; ***Malaysia:*** Stalevo; ***Mex.:*** Stalevo; ***Neth.:*** Stalevo; ***Norw.:*** Stalevo; ***Philipp.:*** Stalev; ***Pol.:*** Stalevo; ***Port.:*** Stalevo; ***Rus.:*** Stalevo (Сталево); ***Singapore:*** Stalevo; ***Spain:*** Stalevo; ***Swed.:*** Stalevo; ***Switz.:*** Stalevo; ***Thai.:*** Stalevo; ***Turk.:*** Stalevo; ***UK:*** Stalevo; ***USA:*** Stalevo; ***Venez.:*** Stalevo.

Levodopa *(BAN, USAN, rINN)*

Dihydroxyphenylalanine; L-Dopa; 3-Hydroxy-L-tyrosine; Laevodopa; Lévodopa; Levodopum. (−)-3-(3,4-Dihydroxyphenyl)-L-alanine.

Леводопа

$C_9H_{11}NO_4$ = 197.2.

CAS — 59-92-7.

ATC — N04BA01.

ATC Vet — QN04BA01.

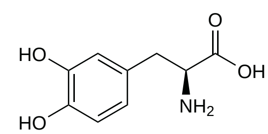

NOTE. Compounded preparations of levodopa may be represented by the following names:

- Co-beneldopa (*BAN*)—benserazide 1 part and levodopa 4 parts (w/w)
- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa, respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Levodopa). A white or slightly cream-coloured, crystalline powder. Slightly soluble in water; freely soluble in 1M hydrochloric acid but sparingly soluble in 0.1M hydrochloric acid; practically insoluble in alcohol. A 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 31 (Levodopa). A white to off-white, odourless, crystalline powder. In the presence of moisture, it is rapidly oxidised by atmospheric oxygen and darkens. Slightly soluble in water; freely soluble in 3N hydrochloric acid; insoluble in alcohol. Store in a dry place in airtight containers at a temperature not exceeding 40°. Protect from light.

Stability. Extemporaneously prepared oral liquid dosage forms may be unstable and manufacturers' formulations should be used where possible.[1] Water dispersible formulations of levodopa with benserazide are available in some countries but a method that can be used by patients to prepare daily solutions of levodopa with carbidopa has been suggested:[2] one litre of a solution in potable water may be prepared with ten crushed standard tablets of levodopa 100 mg with carbidopa 25 mg and 2 g of ascorbic acid added to stabilise the levodopa.

1. Walls TJ, *et al.* Problems with inactivation of drugs used in Parkinson's disease. *BMJ* 1985; **290:** 444–5.
2. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.

Adverse Effects

Gastrointestinal effects, notably nausea, vomiting, and anorexia are common early in treatment with levodopa, particularly if the dosage is increased too rapidly. Gastrointestinal bleeding has been reported in patients with a history of peptic ulcer disease.

The commonest cardiovascular effect is orthostatic hypotension, which is usually asymptomatic, but may be associated with faintness and dizziness. Cardiac arrhythmias have been reported and hypertension has occasionally occurred.

Psychiatric symptoms occur in a high proportion of patients, especially the elderly, and include agitation, anxiety, euphoria, nightmares, insomnia or sometimes drowsiness, and depression. More serious effects, usually requiring a reduction in dosage or withdrawal of levodopa, include aggression, paranoid delusions, hallucinations, delirium, severe depression, with or without suicidal behaviour, and unmasking of psychoses. Psychotic reactions are more likely in patients with postencephalitic parkinsonism or a history of mental disorders. Excessive daytime sleepiness and sudden onset of sleep have been reported very rarely.

Abnormal involuntary movements or dyskinesias are the most serious dose-limiting adverse effects of levodopa and are very common at the optimum dose required to control parkinsonism; their frequency increases with duration of treatment. Involuntary movements of the face, tongue, lips, and jaw often appear first and those of the trunk and extremities later. Severe generalised choreoathetoid and dystonic movements may occur after prolonged use. Muscle twitching and blepharospasm may be early signs of excessive dosage. Exaggerated respiratory movements and exacerbated oculogyric crises have been reported in patients with postencephalitic parkinsonism. Bradykinesia and akinesia, in the form of 'end-of-dose' deterioration and the 'on-off' phenomenon, may re-emerge in patients with parkinsonism as a complication of long-term treatment, but may be due to progression of the disease rather than to levodopa (see also Parkinsonism, p.791).

A positive response to the direct Coombs' test may occur, usually without evidence of haemolysis although auto-immune haemolytic anaemia has occasionally been reported. Transient leucopenia and thrombocytopenia have occurred rarely. The effects of levodopa on liver and kidney function are generally slight; transient increases in liver enzymes, and in blood-urea nitrogen and serum-uric acid concentrations, have been reported. Levodopa may cause discoloration of the urine; reddish at first then darkening on standing. Other body fluids may also be discoloured.

Some of the adverse effects reported may not be attributable directly to levodopa, but rather to the use of antimuscarinics, to increased mobility, or to the unmasking of underlying conditions as parkinsonism improves. Use with a peripheral dopa-decarboxylase inhibitor may reduce the severity of peripheral symptoms such as gastrointestinal and cardiovascular effects, but central effects such as dyskinesias and mental disturbances may occur earlier in treatment.

Incidence of adverse effects. The major adverse effects of levodopa are dyskinesia in 75% of patients and psychiatric disturbances in 25%.[1] Nausea and vomiting in 40 to 50% gradually regress and hypotension in 25 to 30% is generally asymptomatic. Less common adverse effects include cardiac arrhythmias, particularly atrial and ventricular ectopic beats and less commonly atrial flutter and fibrillation; palpitations and flushing often accompanied by excessive sweating; hypertension; polyuria, incontinence, and urinary retention, although antimuscarinic drugs often contribute to problems with micturition; and dark coloration of the urine and saliva. Rare adverse effects include abdominal pain, constipation, and diarrhoea; mydriasis, blurred vision, diplopia, and precipitation of glaucoma; headache; stridor; tachypnoea; and paraesthesias.

1. Calne DB, Reid JL. Antiparkinsonian drugs: pharmacological and therapeutic aspects. *Drugs* 1972; **4:** 49–74.

Abnormal coloration. Black pigmentation of rib cartilage has been noted at necropsy in patients treated with levodopa.[1,2] Abnormal pigmentation is generally not seen at other sites[2] but there have been isolated reports[2,3] of patients who also had pigmentation of the intervertebral discs. Although the pigmentation appears to be irreversible it was considered to be probably harmless.[2] It has been suggested that the pigmentation was due to deposition of dihydroxyphenylalanine (DOPA) in the cartilage.[1] It is known that DOPA will readily auto-oxidise *in vitro* in the presence of oxygen to a black pigment and this can also happen *in vivo* since black urine is a well known adverse effect of levodopa. Dark sweat and pigmentation of the skin and teeth are also known adverse effects.

See also Effects on the Skin and Hair, below.

1. Connolly CE, *et al.* Black cartilage associated with levodopa. *Lancet* 1986; **i:** 690.
2. Rausing A, Rosén U. Black cartilage after therapy with levodopa and methyldopa. *Arch Pathol Lab Med* 1994; **118:** 531–5.
3. Keen CE. *BMJ* 1998; **316:** 240.

Dysgeusia. A change in taste sensation was reported[1] in 23 of 514 patients treated with levodopa and a peripheral dopa-decarboxylase inhibitor; 2 of the 23 had total loss of taste initially. The altered taste, often described as insipid, metallic, or plastic, was first observed 3 to 32 weeks after beginning treatment, and lasted for 2 to 40 weeks. In an earlier report, 22 of 100 patients receiving levodopa alone had experienced changes in taste.[2]

1. Siegfried J, Zumstein H. Changes in taste under L-DOPA therapy. *Z Neurol* 1971; **200:** 345–8.
2. Barbeau A. L-DOPA therapy: past, present and future. *Ariz Med* 1970; **27:** 1–4.

Effects on the blood. Reports of effects of levodopa on the blood are mostly confined to individual case reports. A study in 365 patients, receiving levodopa in a mean daily dosage of 4.04 g, found that 32 developed a positive direct Coombs' test, the majority after between 3 and 12 months of therapy, but none developed haemolytic anaemia.[1] However, occasional cases of auto-immune haemolytic anaemia have been reported;[2-4] in one case, dosage reduction and addition of a peripheral dopa-decarboxylase inhibitor largely abolished haemolysis,[3] but in another, haemolysis recurred on re-institution of levodopa with carbidopa and required corticosteroid treatment.[4] A case of severe acute non-haemolytic anaemia related to levodopa therapy has also been reported.[5]

Although levodopa is widely stated to produce leucopenia in some patients, there are few published reports. However transient minor decreases in total leucocyte counts were reported in 3 of a group of 80 patients receiving levodopa.[6]

Severe thrombocytopenia has been reported in 2 patients who had received levodopa for 3 and 2 years respectively;[7,8] the condition was apparently an auto-immune response and responded to prednisone therapy and withdrawal of levodopa.

1. Joseph C. Occurrence of positive Coombs test in patients treated with levodopa. *N Engl J Med* 1972; **286:** 1401–2.
2. Territo MC, *et al.* Autoimmune hemolytic anemia due to levodopa therapy. *JAMA* 1973; **226:** 1347–8.
3. Lindström FD, *et al.* Dose-related levodopa-induced haemolytic anaemia. *Ann Intern Med* 1977; **86:** 298–300.
4. Bernstein RM. Reversible haemolytic anaemia after levodopa-carbidopa. *BMJ* 1979; **1:** 1461–2.
5. Alkalay I, Zipoli T. Levodopa-induced acute non-hemolytic anemia. *Ann Allergy* 1977; **39:** 191.
6. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–800.
7. Wanamaker WM, *et al.* Thrombocytopenia associated with long-term levodopa therapy. *JAMA* 1976; **235:** 2217–19.
8. Giner V, *et al.* Thrombocytopenia associated with levodopa treatment. *Arch Intern Med* 2003; **163:** 735–6.

Effects on the cardiovascular system. There have been conflicting reports on the effects of peripheral dopa-decarboxylase inhibitors on orthostatic hypotension attributed to levodopa therapy. In a study,[1] supine and erect systolic blood pressure was found to be significantly higher in parkinsonian patients given levodopa with carbidopa than in those receiving levodopa alone, suggesting that the peripheral actions of dopamine contribute to levodopa-induced hypotension. However, another study[2] found no change in the incidence and degree of orthostatic hypotension after giving levodopa with carbidopa and, similarly, no difference in the frequency of ventricular arrhythmias.

See also Effects on Kidney Function, below and Cardiovascular Disorders, under Precautions, below.

1. Calne DB, *et al.* Action of -α-methyldopahydrazine on the blood pressure of patients receiving levodopa. *Br J Pharmacol* 1972; **44:** 162–4.
2. Leibowitz M, Lieberman A. Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone on the cardiovascular system of patients with Parkinson's disease. *Neurology* 1975; **25:** 917–21.

Effects on electrolytes. See Effects on Kidney Function, below.

Effects on the endocrine system. Single doses of levodopa given to healthy subjects cause an increase in plasma concentrations of glucose, insulin, and glucagon, as well as of growth hormone[1] and there has been concern over the potential endocrine effects of levodopa therapy in patients with Parkinson's disease.[2] A study of carbohydrate metabolism in 24 patients with Parkinson's disease indicated that these patients had abnormally low rates of **glucose utilisation** when untreated, apparently due to impaired insulin release, and this was not altered when levodopa therapy was given.[3] However, a similar study completed by 19 patients[2] noted increased impairment of glucose utilisation after levodopa therapy for 1 year with a delayed hypersecretion of insulin in response to a glucose load similar to the metabolic changes of acromegaly. It was considered that patients given levodopa for parkinsonism should be monitored for evidence of diabetes mellitus or frank acromegaly.[2]

Postmenopausal bleeding occurred in varying degrees in 12 of 47 women treated with levodopa.[4] In one case bleeding was severe enough to warrant interrupting treatment and subsequent dosage reduction.

1. Rayfield EJ, *et al.* -Dopa stimulation of glucagon secretion in man. *N Engl J Med* 1975; **293:** 589–91.
2. Sirtori CR, *et al.* Metabolic responses to acute and chronic -dopa administration in patients with parkinsonism. *N Engl J Med* 1972; **287:** 729–33.
3. Van Woert MH, Mueller PS. Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa. *Clin Pharmacol Ther* 1971; **12:** 360–7.
4. Wajsbort J. Post-menopausal bleeding after -dopa. *N Engl J Med* 1972; **286:** 784.

Effects on the eyes. Both miosis[1] and mydriasis[2] have been reported with levodopa.

For a report of the exacerbation of oculogyric crises by levodopa, see Extrapyramidal Effects, below.

1. Spiers ASD, *et al.* Miosis during -dopa therapy. *BMJ* 1970; **2:** 639–40.
2. Weintraub MI, *et al.* Pupillary effects of levodopa therapy: development of anisocoria in latent Horner's syndrome. *N Engl J Med* 1970; **283:** 120–3.

Effects on the gastrointestinal tract. Although gastrointestinal bleeding has more commonly been reported in patients with a history of peptic ulceration, there is a rare report[1] of acute melaena and non-specific gastritis associated with levodopa therapy in a 56-year-old man without any previous evidence of a gastric disorder.

See also Dysgeusia, above.

1. Riddoch D. Gastritis and -dopa. *BMJ* 1972; **1:** 53–4.

Effects on kidney function. Levodopa 1 to 2 g given to 7 patients with idiopathic or postencephalitic Parkinson's disease produced significant increases in renal plasma flow, glomerular filtration rate, and sodium and potassium excretion.[1] It was considered that the natriuretic effects could contribute to the orthostatic hypotension commonly seen in patients receiving levodopa. There is a report of a patient who developed hyponatraemia when given levodopa with carbidopa.[2] The patient had previously had a similar reaction with amantadine. On each occasion symptoms disappeared when dopaminergic medication was withdrawn and recurred on rechallenge. Inappropriate secretion of antidiuretic hormone was suggested as a possible mechanism.

Levodopa has also been reported to have a kaliuretic effect, resulting in hypokalaemia, in some parkinsonian patients;[3] the effect could be prevented by also giving a peripheral dopa-decarboxylase inhibitor.

1. Finlay GD, *et al.* Augmentation of sodium and potassium excretion, glomerular filtration rate and renal plasma flow by levodopa. *N Engl J Med* 1971; **284:** 865–70.
2. Lammers GJ, Roos RAC. Hyponatraemia due to amantadine hydrochloride and L-dopa/carbidopa. *Lancet* 1993; **342:** 439.
3. Granérus A-K, *et al.* Kaliuretic effect of -dopa treatment in parkinsonian patients. *Acta Med Scand* 1977; **201:** 291–7.

Effects on mental function. Psychiatric complications were the single commonest reason for stopping levodopa treatment in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Within 2 years, levodopa was withdrawn because of toxic confusional states (21 patients), paranoid psychosis (6), unipolar depression (2), and mania (1). The incidence of visual hallucinations increased as treatment continued but, as with toxic confusional states, patients generally improved when levodopa was withdrawn. Before treatment, 40 patients had suffered severe depression and levodopa produced sustained improvement in only 2. After 6 years, 20 of the 81 patients remaining were moderately or severely depressed and were rarely improved by withdrawal or reduction in dosage of levodopa. Increasing dementia affected 26 of the 81 patients after 6 years; withdrawal of levodopa in 5 failed to improve cognitive disabilities, but increased parkinsonism.

Another study[2] reported that 141 of 400 patients being treated for Parkinson's disease developed mental disorders. In this study certain acute states, particularly anxiety, on-off hallucinations, and fits of delirium were linked to treatment with levodopa, whereas dementia and depression were not.

Long-term use of levodopa and dopamine agonists has been associated with a number of **behavioural disturbances**, including hypersexuality (see Effects on Sexual Function, below), punding (purposeless repetitive acts), excessive gambling or shopping (see below), and other obsessive behaviour such as compulsive eating.[3] Reduction in dopaminergic therapy can lead to cessation or improvement in symptoms. Some patients may develop dopamine dysregulation syndrome (see Abuse, under Precautions, below).

A 12-month study of 1281 patients in the USA treated with dopamine agonists for Parkinson's disease found that 9 were suffering from **excessive gambling**.[4] All patients had received levodopa, 8 pramipexole, and the remaining patient pergolide. The rate of pathological gambling was 1.5% in the 529 patients taking pramipexole. The authors considered that this was not unexpected given the general availability of casinos in the local area and an incidence in the general US population of 0.3 to 1.3%. An analysis[5] of 11 patients who began pathological gambling after starting therapy with pramipexole (9 cases) or ropinirole (2 cases) found that in 8 patients such behaviour resolved when the drug was tapered or stopped; follow-up was not available in the other 3. In 7 patients the symptoms had developed within 1 to 3 months of achieving maintenance dose or after dose increases of dopamine agonist therapy. Of the 11 patients, 3 had not received levodopa. Cabergoline therapy has also been associated with pathological gambling.[6] Similar behaviour described as being markedly increased in "on" periods has been reported in other patients treated with levodopa.[7] Pathological gambling has also been associated with misuse of dopaminergics.[8]

Sleep-related complaints have occurred and were reported by 74 of 100 patients with Parkinson's disease.[9] All 74 were on levodopa and the prevalence of symptoms increased with the duration of treatment. Symptoms included insomnia, excessive daytime somnolence, altered dream phenomena, nocturnal vocalisation, involuntary myoclonic movements, and rarely, sleepwalking. Sleep fragmentation, which includes insomnia and somnolence, was the most common symptom overall. It has been suggested[10] that in patients with mild to moderate disease levodopa and dopamine agonists could cause sleep disruption. However, these drugs produce beneficial effects on nocturnal disabilities in patients with more severe disease. Reports[11-17] of daytime somnolence or sudden onset of sleep with various other dopamine agonists, including apomorphine, bromocriptine, cabergoline, lisuride, pergolide, piribedil, pramipexole, quinagolide, and ropinirole, suggest that this is a class effect of dopaminergic antiparkinsonian therapy, and patients should be warned of the possible risks (see Precautions, below). The risk of somnolence may be increased in those patients taking combinations of dopaminergics.[15,18]

1. Shaw KM, *et al*. The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.
2. Rondot P, *et al.* Mental disorders in Parkinson's disease after treatment with -Dopa. *Adv Neurol* 1984; **40:** 259–69.
3. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
4. Driver-Dunckley E, *et al.* Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61:** 422–3.
5. Dodd ML, *et al.* Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62:** 1377–81.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Pathological gambling with cabergoline. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 16/02/06)
7. Molina JA, *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov Disord* 2000; **15:** 869–72.
8. Gschwandtner U, *et al.* Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 2001; **24:** 170–2.
9. Nausieda PA, *et al.* Psychiatric complications of levodopa therapy of Parkinson's disease. *Adv Neurol* 1984; **40:** 271–7.
10. van Hilten B, *et al.* Sleep disruption in Parkinson's disease: assessment by continuous activity monitoring. *Arch Neurol* 1994; **51:** 922–8.
11. Frucht S, *et al.* Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; **52:** 1908–10.
12. Schapira AHV. Sleep attacks (sleep episodes) with pergolide. *Lancet* 2000; **355:** 1332–3.
13. Ferreira JJ, *et al.* Sleep attacks and Parkinson's disease treatment. *Lancet* 2000; **355:** 1333–4.
14. Pirker W, Happe S. Sleep attacks in Parkinson's disease. *Lancet* 2000; **356:** 597–8.
15. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Dopaminergic drugs and sudden sleep onset. *Current Problems* 2003; **29:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Houmann CN. *et al.* Sleep attacks in patients taking dopamine agonists: review. *BMJ* 2002; **324:** 1483–7.
17. Plowman BK, *et al.* Sleep attacks in patients receiving dopamine-receptor agonists. *Am J Health-Syst Pharm* 2005; **62:** 537–40.
18. Etminan M, *et al.* Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomised controlled trials. *Drug Safety* 2001; **24:** 863–8.

Effects on respiration. Respiratory crises, including attacks of gasping, panting, sniffing, puffing, and breath-holding, occurred in 12 of 25 patients with postencephalitic parkinsonism during treatment with levodopa.[1] A further 8 developed respiratory and phonatory tics, including sudden deep breaths, yawns, coughs, giggles, sighing, grunting, and moaning. All 20 patients also suffered tachypnoea, bradypnoea, and asymmetrical movement of both sides of the chest, paradoxical diaphragmatic movements, and reversal of inspiratory and expiratory phases. The induction of respiratory crises may be prompt or greatly delayed; 3 patients only developed crises after more than 9 months of treatment with levodopa. Crises were readily precipitated by psychophysiological arousals such as rage and exertion. Most of the patients who developed marked respiratory disorders had shown slight irregularities of respiratory rhythm, rate, and force before receiving levodopa.

In another report a distressing dose-related irregularity in the rate and depth of breathing occurred when a patient with Parkinson's disease was given levodopa with benserazide.[2] The respiratory abnormality was completely suppressed by use of tiapride, with no reduction in the efficacy of levodopa.

1. Sacks OW, *et al*. Side-effects of L-dopa in postencephalitic parkinsonism. *Lancet* 1970; **i:** 1006.
2. De Keyser J, Vincken W. -Dopa-induced respiratory disturbance in Parkinson's disease suppressed by tiapride. *Neurology* 1985; **35:** 235–7.

Effects on sexual function. An increase in libido, over and above the effects of improved mobility and well-being, has been reported in parkinsonian patients receiving levodopa or dopamine agonists. One report noted increased libido but no improvement in sexual performance in 4 of 80 patients receiving levodopa[1] while another reported a moderate increase in sexual interest in 4 of 7 male patients.[2] There have also been reports of hypersexuality and deviant sexual behaviour in patients with Parkinson's disease receiving levodopa or dopamine agonists.[3-6] In some cases this was associated with increased dosage and possibly abuse of the drugs. Symptoms often improved on dosage reduction or withdrawal. Hypersexual behaviour and hypergenitalism have also been reported in a pre-pubertal boy given levodopa for behavioural disturbances.[7]

Some workers[8] have commented that dopaminergics such as cabergoline are being promoted illegally on the Internet for male sexual enhancement and warn of the potential for abuse and serious adverse effects.

Clitoral tumescence and increased libido has been noted in a woman receiving bromocriptine to suppress lactation[9] but there has been a report of sexual dissatisfaction and decreased libido in 3 women receiving bromocriptine for hyperprolactinaemia.[10]

1. Barbeau A. -Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101:** 791–9.
2. Brown E, *et al.* Sexual function and affect in parkinsonian men treated with -dopa. *Am J Psychiatry* 1978; **135:** 1552–5.
3. Vogel HP, Schiffter R. Hypersexuality—a complication of dopaminergic therapy in Parkinson's disease. *Pharmacopsychiatry* 1983; **16:** 107–10.
4. Jiménez-Jiménez FJ, *et al.* Possible zoophilia associated with dopaminergic therapy in Parkinson disease. *Ann Pharmacother* 2002; **36:** 1178–9.
5. Kaňovský P, *et al.* Penile erections and hypersexuality induced by pergolide treatment in advanced, fluctuating Parkinson's disease. *J Neurol* 2002; **249:** 112–14.
6. Berger C, *et al.* Sexuelle Delinquenz und Morbus Parkinson. *Nervenarzt* 2003; **74:** 370–5.
7. Korten JJ, *et al.* Undesirable prepubertal effects of levodopa. *JAMA* 1973; **226:** 355.
8. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
9. Blin O, *et al.* Painful clitoral tumescence during bromocriptine therapy. *Lancet* 1991; **337:** 1231–2.
10. Saleh AK, Moussa MAA. Sexual dysfunction in women due to bromocriptine. *BMJ* 1984; **289:** 228.

Effects on the skin and hair. Two women who were given levodopa, up to 3 g daily, developed diffuse alopecia in addition to other adverse effects.[1] Repigmentation of hair has occurred in a white-bearded man after being treated with levodopa 1.5 g daily for 8 months.[2] Vitiligo has been reported[3] in a patient with Parkinson's disease following addition of tolcapone to his levodopa/carbidopa regimen. The development of vitiligo was attributed to the increase in plasma-levodopa concentrations brought about by concomitant use of tolcapone.

See also Melanoma, under Precautions, below.

1. Marshall A, Williams MJ. Alopecia and levodopa. *BMJ* 1971; **2:** 47.
2. Grainger KM. Pigmentation in Parkinson's disease treated with levodopa. *Lancet* 1973; **i:** 97–8.
3. Sabaté M, *et al.* Vitiligo associated with tolcapone and levodopa in a patient with Parkinson's disease. *Ann Pharmacother* 1999; **33:** 1228–9.

Extrapyramidal effects. Choreiform movements were the major dose-limiting complication of long-term treatment with levodopa in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Dyskinesias usually appeared in the first year and became more severe and generalised with time. Certain distinctive patterns of involuntary movements occurred as follows:

- peak-dose movements affected 65 of the 81 patients and were dose-related. Movements were usually choreic, affecting the face and limbs, but dystonic and ballistic movements were also seen; characteristically they began 20 to 90 minutes after an oral dose and lasted from 10 minutes to 4 hours with a tendency to be more severe mid-way through the interdose period
- biphasic movements presenting as 2 distinct episodes of chorea or dystonia within each interdose period occurred in only 3 patients
- early morning and 'end-of-dose' dystonia was present in 15 patients after 6 years of treatment with levodopa, but rarely developed during the first 3 years
- nocturnal myoclonus occurred in 12 patients

The frequency, intensity, and complexity of spontaneous fluctuations in performance were greatly enhanced by long-term levodopa therapy. Two clinically distinct types of fluctuation, 'end-of-dose' deterioration and the 'on-off' phenomenon, were related to treatment. 'End-of-dose' deterioration or the 'wearing-off' effect affected 52 patients after 6 years of treatment and was characterised by progressive reduction in the duration of benefit from each dose with a gradual return of nocturnal and early morning disability in some patients. The 'on-off' phenomenon affected 14 patients who experienced completely unpredictable swings from relative mobility, usually accompanied by involuntary movements, to periods of profound bradykinesia and hypotonia. In addition, 'freezing episodes' and abrupt falls became increasingly common and affected 50 patients after 6 years compared with 33 before therapy.

1. Shaw KM, *et al*. The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49:** 283–93.

OCULOGYRIC CRISIS. After initial remission, oculogyric crises in 5 of 25 patients with postencephalitic parkinsonism recurred and were subsequently severely exacerbated during treatment with levodopa.[1] One patient, who previously had not had oculogyric crises, developed severe crises in the fourth month of therapy with levodopa. During these crises forced gaze deviation was always accompanied by severe neurological and mental symptoms, some of which were scarcely tolerable.

1. Sacks OW, Kohl M. -Dopa and oculogyric crises. *Lancet* 1970; **ii:** 215–16.

Gout. There have been reports of elevated serum uric acid concentrations in patients receiving levodopa, but some of these are of doubtful significance since levodopa has been shown to give falsely-elevated uric acid concentrations by colorimetric methods.[1] However, hyperuricaemia as measured by more specific methods,[2,3] with a few cases of overt gout,[2,3] has also been reported.

1. Cawein MJ, Hewins J. False rise in serum uric acid after -dopa. *N Engl J Med* 1969; **281:** 1489–90.
2. Honda H, Gindin RA. Gout while receiving levodopa for parkinsonism. *JAMA* 1972; **219:** 55–7.
3. Calne DB, Fermaglich J. Gout induced by -dopa and decarboxylase inhibitors. *Postgrad Med J* 1976; **52:** 232–3.

Hypersensitivity. Reports of hypersensitivity reactions to levodopa have included a vasculitis characterised by neuromyopathy, periarteriolitis with eosinophilia,[1] and a lupus-like auto-immune syndrome.[2]

1. Wolf S, *et al.* Neuromyopathy and periarteriolitis in a patient receiving levodopa. *Arch Intern Med* 1976; **136:** 1055–7.
2. Massarotti G, *et al.* Lupus-like autoimmune syndrome after levodopa and benserazide. *BMJ* 1979; **2:** 553.

Overdosage. Adverse effects after ingestion of 80 to 100 g of levodopa over a 12-hour period by a parkinsonian patient included hypertension initially, followed by hypotension of a few hours' duration, sinus tachycardia, and symptomatic orthostatic hypotension for more than a week.[1] Marked confusion, agitation, insomnia, and restlessness were the most prominent clinical symptoms and did not disappear completely for over a week; severe anorexia and insomnia persisted for 2 to 3 weeks. After the overdose the patient had virtually no signs of parkinsonism and received no levodopa or antimuscarinic medication for 6 days; rigidity and akinesia began to recur on the fourth day.

1. Hoehn MM, Rutledge CO. Acute overdose with levodopa: clinical and biochemical consequences. *Neurology* 1975; **25:** 792–4.

Withdrawal syndromes. Withdrawal of antiparkinsonian drugs, particularly levodopa, has been implicated in the development of a syndrome resembling the neuroleptic malignant syndrome,[1-6] characterised by fever, muscle rigidity, profuse sweating, tachycardia, tachypnoea, and elevated muscle enzyme values.[1] Several fatalities have occurred.[1,2] It has been suggested that the neuroleptic malignant syndrome is associated with blockade of dopamine receptors in the striatum, leading to increased rigidity and heat production, and in the hypothalamus, resulting in impaired thermoregulation[7] and it seems reasonable that withdrawal of levodopa might have a similar effect in patients with depleted central dopamine concentrations. Thus, the use of a 'drug holiday' to manage fluctuations in response to levodopa (see Parkinsonism, p.791) is no longer recommended.

Fever, extrapyramidal symptoms and raised creatine kinase concentrations, resembling a very mild form of the neuroleptic malignant syndrome, have also been reported in parkinsonian patients exposed to stress such as dehydration or infection but without any change in medication.[8]

1. Friedman JH, *et al.* A neuroleptic malignantlike syndrome due to levodopa therapy withdrawal. *JAMA* 1985; **254:** 2792–5.
2. Sechi GP, *et al.* Fatal hyperpyrexia after withdrawal of levodopa. *Neurology* 1984; **34:** 249–51.
3. Figà-Talamanca L, *et al.* Hyperthermia after discontinuance of levodopa and bromocriptine therapy: impaired dopamine receptors a possible cause. *Neurology* 1985; **35:** 258–61.
4. Gibb WRG, Griffith DNW. Levodopa withdrawal syndrome identical to neuroleptic malignant syndrome. *Postgrad Med J* 1986; **62:** 59–60.
5. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal: clinical features in 11 patients. *Parkinsonism Relat Disord* 2003; **9:** 175–8.
6. Mizuno Y, *et al.* Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord* 2003; **9** (suppl 1): S3–S9.
7. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981; **31:** 132–7.
8. Mezaki T, *et al.* Benign type of malignant syndrome. *Lancet* 1989; **i:** 49–50.

Treatment of Adverse Effects

Reduction in dosage reverses most of the adverse effects of levodopa. Nausea and vomiting may be diminished by increasing the dose of levodopa gradually, and/or by taking with or after meals, although taking levodopa on a full stomach may lead to lower plasma concentrations. Gastrointestinal effects may also be reduced by giving an antiemetic such as cyclizine or domperidone but not a phenothiazine (see Antipsychotics, under Interactions, below). Use with a peripheral dopa-decarboxylase inhibitor reduces peripheral but not central adverse effects. Orthostatic hypotension may respond to the use of elastic stockings.

The benefits of gastric decontamination are uncertain. However, activated charcoal should be considered in adults who have ingested more than 2 g (or more than the total daily dose, whichever is greater), and in children who have taken more than 200 mg, if they present within 1 hour of ingestion. Supportive measures should also be instituted. Pyridoxine may increase the metabolism of levodopa (see Nutritional Agents, under Interactions, below) but its value in overdosage has not been established; it does not reduce the effects of levodopa given with a peripheral dopa-decarboxylase inhibitor.

Nausea and vomiting. For reference to the use of domperidone in the management of nausea and vomiting associated with levodopa in patients with Parkinson's disease, see under Uses and Administration of Domperidone, p.1727.

Psychosis. Atypical antipsychotics such as clozapine (p.985) have been tried in the management of psychosis occurring as a complication of parkinsonism and of drugs such as levodopa used in its treatment.

Precautions

Levodopa is contra-indicated in patients with angle-closure glaucoma and should be used with caution in open-angle glaucoma. Caution is also required in patients with cardiovascular disease, pulmonary disease, endocrine disorders, psychiatric disturbances, osteomalacia, hepatic or renal disease, or a history of peptic ulceration. Periodic evaluations of hepatic, psychiatric, haematological, renal, and cardiovascular functions have been advised.

Since an association between levodopa and activation of malignant melanoma has been suspected (although not confirmed), it is generally recommended that levodopa should not be given to patients with (or with a history of) the disease or with skin disorders suggestive of it.

Parkinsonian patients who benefit from levodopa therapy should be warned to resume normal activities gradually to avoid the risk of injury. Treatment with levodopa should not be stopped abruptly.

Excessive daytime sleepiness and sudden onset of sleep may occur with levodopa and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Levodopa inhibits prolactin secretion and may therefore interfere with lactation.

Food interferes with the absorption of levodopa, though levodopa is usually given with or immediately after meals to reduce nausea and vomiting. However, patients experiencing the 'on-off' phenomenon may benefit from dosage on an empty stomach (see Parkinsonism, p.791).

Abuse. Abuse of levodopa and dopamine agonists in patients with Parkinson's disease has been reported.[1-6] The term dopamine dysregulation syndrome, has been used to describe a condition where there is a compulsive and dysregulated use of dopaminergic drugs beyond that needed to achieve relief of motor symptoms and which is harmful to the patient.[7] Patients have progressively increased the dosage of levodopa to obtain psychotropic effects such as euphoria despite accompanying dystonia and other extrapyramidal adverse effects. Withdrawal often led to craving, drug-seeking behaviour, and mood disturbances such as depression, features resembling a psychological dependence syndrome. Abuse in patients without parkinsonism has also occurred.[8]

See also Effects on Sexual Function under Adverse Effects, above.

1. Nausieda PA. Sinemet "abusers". *Clin Neuropharmacol* 1985; **8:** 318–27.
2. Soyka M, Huppert D. L-dopa abuse in a patient with former alcoholism. *Br J Addict* 1992; **87:** 117–18.
3. Spigset O, von Schéele C. Levodopa dependence and abuse in Parkinson's disease. *Pharmacotherapy* 1997; **17:** 1027–30.
4. Merims D, *et al.* Is there addiction to levodopa in patients with Parkinson's disease? *Mov Disord* 2000; **15:** 1014–16.
5. Müller U, *et al.* Levodopa-Abhängigkeit bei Parkinsonkrankheit: Fallbericht und Literaturübersicht. *Nervenarzt* 2002; **73:** 887–91.
6. Borek LL, Friedman JH. Levodopa addiction in idiopathic Parkinson disease. *Neurology* 2005; **65:** 1508.
7. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17:** 172–80.
8. Steiner I, Wirguin I. Levodopa addiction in non-parkinsonian patients. *Neurology* 2003; **61:** 1451.

Cardiovascular disorders. A high incidence of cardiovascular adverse effects was reported in early studies of levodopa, but both Parkinson's disease and heart disease are common in the elderly and adverse cardiac effects of levodopa may be less prevalent than was first thought. A study in 40 patients[1] concluded that, apart from those with severe orthostatic hypotension or unstable coronary disease, levodopa may be used safely in parkinsonian patients with heart disease. Others[2] noted that levodopa and bromocriptine cause cardiac arrhythmias in less than 1% of all patients, the incidence for levodopa with a peripheral dopa-decarboxylase inhibitor being lower still. Nevertheless, caution is advised in patients with cardiovascular disease.

1. Jenkins RB, *et al.* Levodopa therapy of patients with parkinsonism and heart disease. *BMJ* 1972; **3:** 512–14.
2. Parkes JD, *et al.* Amantadine-induced heart failure. *Lancet* 1977; **i:** 904.

Diabetes mellitus. For reference to concern over the potential of levodopa to impair glucose utilisation, see Effects on the Endocrine System under Adverse Effects, above.

Melanoma. There has been concern over the effects of levodopa on melanoma in view of the ability of malignant melanoma cells to convert levodopa to melanin and isolated reports of melanoma developing or being exacerbated during levodopa therapy continue to appear. However, in a survey of 1099 patients with primary cutaneous malignant melanoma only one had taken levodopa.[1] It was concluded that levodopa therapy is not an important factor in the induction of malignant melanoma. Furthermore, use of levodopa in daily doses of up to 4 g with carbidopa in 17 patients with metastatic melanoma failed to provide any evidence that levodopa accelerated the progression of the disease.[2] Reviews[3,4] of these and later reports concluded that the purported link between levodopa and malignant melanoma was tenuous.

For a report of antineoplastic chemotherapy used for the treatment of melanoma reducing the efficacy of levodopa, see under Interactions, below.

1. Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. *JAMA* 1978; **240:** 554–5.
2. Gurney H, *et al.* The use of L-dopa and carbidopa in metastatic malignant melanoma. *J Invest Dermatol* 1991; **96:** 85–7.
3. Siple JF, *et al.* Levodopa therapy and the risk of malignant melanoma. *Ann Pharmacother* 2000; **34:** 382–5.
4. Fiala KH, *et al.* Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Parkinsonism Relat Disord* 2003; **9:** 321–7.

Pregnancy. Levodopa alone and with carbidopa has been associated with fetal abnormalities in *animals* given high doses; no teratogenic effect has been noted with carbidopa alone. However, 2 women with parkinsonism who received levodopa with carbidopa or levodopa alone throughout their pregnancies gave birth to normal infants.[1]

1. Cook DG, Klawans HL. Levodopa during pregnancy. *Clin Neuropharmacol* 1985; **8:** 93–5.

Withdrawal. For adverse effects associated with withdrawal of levodopa, see under Adverse Effects, above.

Interactions

The therapeutic or adverse effects of levodopa may be affected by interactions with a variety of drugs. Mechanisms may include effects on catecholamine metabolising enzymes, neurotransmitters, or receptor sites, effects on the endocrine system, and effects on gastrointestinal absorption. Drugs that modify gastric emptying may affect the absorption of levodopa.

Antibacterials. A study[1] in 7 healthy subjects showed that use of *spiramycin* with levodopa and carbidopa resulted in reduced plasma-levodopa concentrations and an increase in its peripheral metabolism.

A hypertensive reaction and severe tremor occurred when *isoniazid* was given to a patient receiving levodopa;[2] it was not certain whether isoniazid was acting as an MAOI.

1. Brion N, *et al.* Effect of a macrolide (spiramycin) on the pharmacokinetics of -dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol* 1992; **15:** 229–35.
2. Morgan JP. Isoniazid and levodopa. *Ann Intern Med* 1980; **92:** 434.

Antidementia drugs. Increasing the dose of *tacrine* worsened parkinsonian symptoms in an elderly woman with Alzheimer's disease and mild parkinsonism; symptoms responded to levodopa with carbidopa, but recurred when the dose of tacrine was again increased.[1]

1. Ott BR, Lannon MC. Exacerbation of parkinsonism by tacrine. *Clin Neuropharmacol* 1992; **15:** 322–5.

Antidepressants. ***BUPROPION.*** Caution has been advised with bupropion because of reports of a higher incidence of adverse effects during use with levodopa.

MAOIS. Giving levodopa with non-specific MAOIs such as *phenelzine*, *pargyline*, *nialamide*, or *tranylcypromine* may cause dangerous hypertension;[1-4] it is recommended that levodopa should not be given with, or within at least 14 days of stopping, an MAOI. Hypertensive reactions to levodopa with tranylcypromine were inhibited by carbidopa,[5] but licensed product information for preparations containing levodopa with carbidopa or benserazide still contra-indicates their use with MAOIs. The incidence of adverse effects may be increased if levodopa is used with *moclobemide*, a monoamine oxidase type A inhibitor (see Dopaminergics, p.411). *Selegiline*, a monoamine oxidase type B inhibitor, is used to enhance the antiparkinsonian effect of levodopa, see p.818.

1. Hunter KR, *et al.* Monoamine oxidase inhibitors and -dopa. *BMJ* 1970; **3:** 388.
2. Hodge JV. Use of monoamine oxidase inhibitors. *Lancet* 1965; **i:** 764–5.
3. Friend DG, *et al.* The action of L-dihydroxyphenylalanine in patients receiving nialamide. *Clin Pharmacol Ther* 1965; **6:** 362–6.
4. Sharpe J, *et al.* Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. *Can Med Assoc J* 1972; **107:** 296–300.
5. Teychenne PF, *et al.* Interactions of levodopa with inhibitors of monoamine oxidase and -aromatic amino acid decarboxylase. *Clin Pharmacol Ther* 1975; **18:** 273–7.

SSRIS. There was some evidence from a prescribing study that SSRIs might exacerbate parkinsonism resulting in increased doses of levodopa or addition of adjunctive drugs.[1]

1. van de Vijver DAMC, *et al.* Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. *Br J Clin Pharmacol* 2002; **54:** 168–70.

TRICYCLIC ANTIDEPRESSANTS. Although tricyclic antidepressants have generally been used safely with levodopa,[1] hypertensive crises have occurred in some rare cases. Such events have been reported in patients receiving *amitriptyline* or *imipramine* and levodopa with carbidopa.[2,3] Imipramine has been reported to impair the rate of levodopa absorption,[4] presumably due to its antimuscarinic properties (for the effect of antimuscarinics on the absorption of levodopa, see below).

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Rampton DS. Hypertensive crisis in a patient given Sinemet, metoclopramide, and amitriptyline. *BMJ* 1977; **2:** 607–8.
3. Edwards M. Adverse interaction of levodopa with tricyclic antidepressants. *Practitioner* 1982; **226:** 1447–8.
4. Morgan JP, *et al.* Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology* 1975; **25:** 1029–34.

TRYPTOPHAN. See Amino Acids under Nutritional Agents, below.

Antiepileptics. *Phenytoin* has been shown to diminish the therapeutic effect of levodopa in patients with parkinsonism or chronic manganese poisoning.[1] The mechanism of the interaction was considered uncertain.

1. Mendez JS. Diphenylhydantoin: blocking of levodopa effects. *Arch Neurol* 1975; **32:** 44–6.

Antihypertensives. Use of levodopa with *guanethidine* may cause increased hypotension.[1] *Clonidine* has been reported to inhibit the therapeutic effect of levodopa, possibly by stimulating central alpha-adrenoceptors.[2] *Methyldopa* and levodopa may enhance each other's therapeutic or adverse effects, although there has been mention of the inhibitory effect of methyldopa on the therapeutic response to levodopa.[3,4] *Reserpine and other rauwolfia alkaloids* may oppose the antiparkinsonian effects of levodopa by central depletion of dopamine; UK licensed product information advises that use together should be avoided.

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Shoulson I, Chase TN. Clonidine and the anti-parkinsonian response to -dopa or piribedil. *Neuropharmacology* 1976; **15:** 25–7.
3. Cotzias GC, *et al.* -Dopa in Parkinson's syndrome. *N Engl J Med* 1969; **281:** 272.
4. Kofman O. Treatment of Parkinson's disease with -dopa: a current appraisal. *Can Med Assoc J* 1971; **104:** 483–7.

Antimuscarinics. Antimuscarinic antiparkinsonian drugs may enhance the therapeutic effects of levodopa but by delaying gastric emptying they may also reduce its absorption.[1]

1. Algeri S, *et al.* Effect of anticholinergic drugs on gastro-intestinal absorption of L-dopa in rats and in man. *Eur J Pharmacol* 1976; **35:** 293–9.

Antineoplastics. A patient with Parkinson's disease noted[1] that the efficacy of levodopa was reduced each time he received *dacarbazine* for the treatment of melanoma. As serum-dopamine concentrations were unchanged it was suggested[1] that dacarbazine might compete with levodopa at the blood-brain barrier.

1. Merello M, *et al.* Impaired levodopa response in Parkinson's disease during melanoma therapy. *Clin Neuropharmacol* 1992; **15:** 69–74.

Antipsychotics. The therapeutic effects of levodopa may be diminished by CNS dopamine inhibitors including phenothiazine derivatives[1] such as *prochlorperazine.*[2] Butyrophenones such as *haloperidol* and thioxanthenes such as *flupentixol* might be expected to have a similar effect due to their antidopaminergic properties.

1. Yahr MD, Duvoisin RC. Drug therapy of parkinsonism. *N Engl J Med* 1972; **287:** 20–4.
2. Duvoisin RC. Diphenidol for levodopa induced nausea and vomiting. *JAMA* 1972; **221:** 1408.

Anxiolytics. Reversible deterioration of parkinsonism has been reported in patients receiving levodopa who were also given *benzodiazepines* such as *diazepam*,[1,2] *nitrazepam*[1] (although the evidence was equivocal), or *chlordiazepoxide.*[3] In one case parkinsonian symptoms resolved without alteration in the medication.[1]

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii:** 1283–5.
2. Wodak J, *et al.* Review of 12 months' treatment with L-dopa in Parkinson's disease, with remarks on unusual side effects. *Med J Aust* 1972; **2:** 1277–82.
3. Yosselson-Superstine S, Lipman AG. Chlordiazepoxide interaction with levodopa. *Ann Intern Med* 1982; **96:** 259–60.

Baclofen. Adverse effects including hallucinations, confusion, headache, and nausea and worsening of symptoms have been reported[1,2] in patients with Parkinson's disease taking levodopa when also given baclofen.

1. Skausig OB, Korsgaard S. Hallucinations and baclofen. *Lancet* 1977; **i:** 1258.
2. Lees AJ, *et al.* Baclofen in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1978; **41:** 707–8.

Gastrointestinal drugs. *ANTACIDS.* Some studies have suggested that taking an antacid before a dose of levodopa enhances the absorption of levodopa, apparently by enhancing gastric emptying and reducing metabolism of levodopa in the stomach.[1,2] This was particularly marked in a case report in a patient with prolonged gastric emptying time.[1] However, another study in 8 patients with presumably normal gastric motility, only 3 of whom had Parkinson's disease, found no significant increase in overall absorption of levodopa when given with an antacid although there was some evidence of increased absorption in some of the patients.[3] UK licensed product information (*Madopar CR; Roche*) states that antacids reduce the absorption of levodopa from the modified-release preparation by 32%.

1. Rivera-Calimlim L, *et al.* -Dopa treatment failure: explanation and correction. *BMJ* 1970; **4:** 93–4.
2. Pocelinko R, *et al.* The effect of an antacid on the absorption and metabolism of levodopa. *Clin Pharmacol Ther* 1972; **13:** 149.
3. Leon AS, Spiegel HE. The effect of antacid administration on the absorption and metabolism of levodopa. *J Clin Pharmacol* 1972; **12:** 263–7.

ANTIEMETICS. *Metoclopramide* is a dopamine antagonist and may cause extrapyramidal symptoms including parkinsonism; however, it accelerates gastric emptying and has been reported[1] to increase the rate of levodopa absorption. The importance of timing has been noted[2] since levodopa delays gastric emptying and metoclopramide antagonises this effect. Licensed product information advises caution when using metoclopramide with levodopa. *Domperidone* has been reported to increase the bioavailability of levodopa slightly.[3]

1. Morris JGL, *et al.* Plasma dopa concentrations after different preparations of levodopa in normal subjects. *Br J Clin Pharmacol* 1976; **3:** 983–90.
2. Berkowitz DM, McCallum RW. Interaction of levodopa and metoclopramide on gastric emptying. *Clin Pharmacol Ther* 1980; **27:** 414–20.
3. Shindler JS, *et al.* Domperidone and levodopa in Parkinson's disease. *Br J Clin Pharmacol* 1984; **18:** 959–62.

PROKINETICS. Maximum plasma concentrations of levodopa are increased by *cisapride*.[1]

See also Metoclopramide and Domperidone, under Antiemetics, above.

1. Neira WD, *et al.* The effects of cisapride on plasma -dopa levels and the clinical response in Parkinson's disease. *Mov Disord* 1995; **10:** 66–70.

General anaesthetics. The general anaesthetics *cyclopropane* and *halothane* lower the threshold for ventricular arrhythmias to sympathomimetic amines, including dopamine, and should probably not be used within 6 to 8 hours of levodopa.[1,2] Although other general anaesthetics are now usually preferred, it was suggested that, in any case, levodopa could safely be taken before surgery when given with a peripheral dopa-decarboxylase inhibitor.[3]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.
2. Bianchine JR, Sunyapridakul L. Interactions between levodopa and other drugs: significance in the treatment of Parkinson's disease. *Drugs* 1973; **6:** 364–88.
3. Anonymous. Surgery and long-term medication. *Drug Ther Bull* 1984; **22:** 73–6.

Nutritional agents. *AMINO ACIDS.* The transport of levodopa into the brain is subject to competition from chemically related L-amino acids, especially the other aromatic amino acids *phenylalanine*, *tyrosine*, *tryptophan*, and *histidine*.[1] A high-protein diet or the large neutral amino acids phenylalanine, *leucine*, or *isoleucine* have been shown to reduce the therapeutic effect of levodopa given by intravenous infusion to parkinsonian patients; such alterations in the absorption and transport of levodopa may contribute to the fluctuating responses seen in Parkinson's disease, the so-called 'on-off' phenomenon[2] (see also Parkinsonism, p.791). In contrast, a study in healthy subjects[3] found that while a low-protein meal appeared to cause a small reduction in levodopa absorption, a high-protein meal had no such effect. Other reported interactions with amino acids include *methionine*-antagonism of the therapeutic effect of levodopa in parkinsonism[4] and *tryptophan*-reduced blood concentrations of levodopa.[5]

1. Daniel PM, *et al.* Do changes in blood levels of other aromatic aminoacids influence levodopa therapy? *Lancet* 1976; **i:** 95.
2. Nutt JG, *et al.* The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; **310:** 483–8.
3. Robertson DRC, *et al.* The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 1991; **31:** 413–17.
4. Pearce LA, Waterbury LD. L-methionine: a possible levodopa antagonist. *Neurology* 1974; **24:** 640–1.
5. Weitbrecht W-U, Weigel K. Der Einfluß von -Tryptophan auf die -Dopa-Resorption. *Dtsch Med Wochenschr* 1976; **101:** 20–2.

IRON SALTS. Levodopa forms complexes with iron salts and ferrous sulfate has reduced bioavailability of levodopa by about 50% in healthy subjects.[1] Giving *ferrous sulfate* to 9 patients with Parkinson's disease receiving levodopa with carbidopa reduced the area under the curve for levodopa by 30%; the reduction was greater than 75% for carbidopa. Although this was associated with deterioration in some patients' disability, the average reduction in efficacy of therapy did not achieve statistical significance.[2]

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.
2. Campbell NRC, *et al.* Sinemet-ferrous sulphate interaction in patients with Parkinson's disease. *Br J Clin Pharmacol* 1990; **30:** 599–605.

PYRIDOXINE. The enzyme responsible for the decarboxylation of levodopa, L-amino acid decarboxylase, is dependent on pyridoxine and pyridoxine supplements have been reported to enhance the peripheral metabolism of levodopa to dopamine leaving less available to cross the blood-brain barrier for central conversion to dopamine;[1-4] pyridoxine therefore inhibits the action of levodopa but this can be stopped by use of a peripheral dopa-decarboxylase inhibitor.[3,4]

1. Carter AB. Pyridoxine and parkinsonism. *BMJ* 1973; **4:** 236.
2. Leon AS, *et al.* Pyridoxine antagonism of levodopa in parkinsonism. *JAMA* 1971; **218:** 1924–7.
3. Cotzias GC, Papavasiliou PS. Blocking the negative effects of pyridoxine on patients receiving levodopa. *JAMA* 1971; **215:** 1504–5.
4. Yahr MD, Duvoisin RC. Pyridoxine, levodopa, and -α-methyldopa hydrazine regimen in parkinsonism. *JAMA* 1971; **216:** 2141.

Papaverine. Antagonism of the beneficial effects of levodopa in parkinsonism has been reported when patients were also given papaverine,[1,2] and it was recommended that the combination should be avoided. However, a later study[3] in 9 patients receiving levodopa with a peripheral dopa-decarboxylase inhibitor found no changes in the control of Parkinson's disease when they were also given papaverine for 3 weeks.

1. Duvoisin RC. Antagonism of levodopa by papaverine. *JAMA* 1975; **231:** 845.
2. Posner DM. Antagonism of levodopa by papaverine. *JAMA* 1975; **233:** 768.
3. Montastruc JL, *et al.* Does papaverine interact with levodopa in Parkinson's disease? *Ann Neurol* 1987; **22:** 558–9.

Penicillamine. Isolated case reports suggest that penicillamine increases plasma-levodopa concentrations.[1]

1. Mizuta E, *et al.* Effect of -penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol* 1993; **16:** 448–50.

Sympathomimetics. It has been suggested that sympathomimetics such as *adrenaline* or *isoprenaline* may enhance the cardiac adverse effects of levodopa.[1]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12:** 376–82.

Pharmacokinetics

Levodopa is rapidly absorbed from the gastrointestinal tract by an active transport system. Most absorption takes place in the small intestine; absorption is very limited from the stomach, and since decarboxylation may take place in the stomach wall, delays in gastric emptying may reduce the amount of levodopa available for absorption. Peak plasma concentrations are achieved within 2 hours of oral doses. Levodopa is about 10 to 30% bound to plasma proteins.

Levodopa is rapidly decarboxylated by the enzyme aromatic L-amino acid decarboxylase, mostly in the gut, liver, and kidney, to dopamine, which is metabolised in turn, principally to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Other routes of metabolism include *O*-methylation, transamination, and oxidation, producing a variety of minor metabolites including noradrenaline and 3-*O*-methyldopa; the latter may accumulate in the CNS due to its relatively long half-life. The elimination half-life of levodopa itself is reported to be about 30 to 60 minutes.

Unlike dopamine, levodopa is actively transported across the blood-brain barrier, but because of the extent of peripheral decarboxylation very little is available to enter the CNS unless it is given with a peripheral dopa-decarboxylase inhibitor. In the presence of a peripheral dopa-decarboxylase inhibitor the major route of metabolism of levodopa becomes the formation of 3-*O*-methyldopa by the enzyme catechol-*O*-methyltransferase.

About 80% of an oral dose of levodopa is excreted in the urine within 24 hours, mainly as dihydroxyphenylacetic and homovanillic acids. Only small amounts of levodopa are excreted unchanged in the faeces.

Levodopa crosses the placenta and is distributed into breast milk.

◊ General references.

1. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984; **7:** 35–49.
2. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987; **13:** 141–78.
3. Robertson DRC, *et al.* The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa. *Br J Clin Pharmacol* 1989; **28:** 61–9.
4. Robertson DRC, *et al.* The influence of levodopa on gastric emptying in man. *Br J Clin Pharmacol* 1990; **29:** 47–53.

Uses and Administration

Levodopa, a naturally occurring amino acid, is the immediate precursor of the neurotransmitter dopamine. The actions of levodopa are mainly those of dopamine (p.1273).

Unlike dopamine, levodopa readily enters the CNS and is used in the treatment of conditions, such as Parkinson's disease, that are associated with depletion of dopamine in the brain. Levodopa is rapidly decarboxylated by peripheral enzymes so that very little unchanged drug is available to cross the blood-brain barrier for central conversion into dopamine. Consequently, levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as benserazide (p.796) or carbidopa (p.803) to increase the proportion of levodopa that can enter the brain. This enables the dosage of levodopa to be reduced and may diminish peripheral adverse effects, such as nausea and vomiting and cardiac arrhythmias, by blocking the peripheral production of dopamine. It may also provide a more rapid response at the start of therapy.

The majority of patients with Parkinson's disease benefit from levodopa therapy, but after 2 years or more, improvement in disability is gradually lost as the disease progresses and fluctuations in mobility emerge. Postencephalitic parkinsonism responds to levodopa, but a higher incidence of adverse effects has been reported than in the idiopathic form so smaller doses are generally used. Levodopa has also been used to control the neurological symptoms of chronic manganese poisoning, which resemble those of parkinsonism. It should not be used in antipsychotic-induced parkinsonism.

Levodopa has an effect on pituitary function as a result of its conversion to dopamine. It may enhance growth hormone secretion and has been used diagnostically as a provocative test for growth hormone deficiency. Levodopa also inhibits prolactin secretion.

Response to levodopa varies considerably between patients. **Treatment of parkinsonism** should begin with small doses increased gradually, ideally to a dose that improves mobility without producing adverse effects. Levodopa should be taken with or after meals, although in later disease, it may be preferable to take it on an empty stomach (see Precautions, above). Once established, maintenance doses may need to be reduced as the patient ages. When given **without a peripheral dopa-decarboxylase inhibitor** (which is rare) a suggested initial oral dose is 125 mg twice daily increased gradually every 3 to 7 days, according to response, to up to 8 g daily in divided doses. The intervals between doses should be adjusted to meet individual needs; many patients find 4 or 5 divided doses daily to be satisfactory although some may require smaller, more frequent doses in order to control fluctuations in mobility. Maximum improvement may take up to 6 months or longer to occur.

When given **with a peripheral dopa-decarboxylase inhibitor** lower doses of levodopa are used. As high central dopamine concentrations can be achieved more quickly, both beneficial and adverse effects tend to occur more rapidly than with levodopa alone and patients should be monitored carefully. In those already receiving levodopa the drug should be stopped and benserazide or carbidopa with levodopa started on the next day or after 24 hours if the patient was receiving a modified-release preparation of levodopa.

Benserazide is given as the hydrochloride but doses are expressed in terms of the base. Benserazide hydrochloride 28.5 mg is equivalent to about 25 mg of benserazide. Benserazide is usually given with levodopa in the ratio of 1 part of benserazide base to 4 parts of levodopa (co-beneldopa) and the doses for co-beneldopa that follow are expressed in terms of the levodopa component.

- An initial oral dose for *patients not previously treated with levodopa* is levodopa 50 mg three or four times daily increased gradually in increments of levodopa 100 mg once or twice weekly, according to response. If the disease is at an advanced stage, the initial starting dose may be increased to levodopa 100 mg three times daily. For some elderly patients, an initial dose of levodopa 50 mg once or twice daily, increased by 50 mg every third or fourth day, may be suitable. Maintenance doses usually lie within the range of levodopa 400 to 800 mg daily in divided doses, although most patients require no more than 600 mg daily. If optimal improvement has not been achieved after several weeks at the average dose, further increases may be made with caution; it is rarely necessary to give more than 1 g of levodopa daily.
- The initial dose of levodopa given with benserazide in *patients previously treated with levodopa alone* should be about 10 to 15% of the dose previously being taken, thus levodopa 300 mg would be appropriate for a patient previously taking levodopa 2 g daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose is levodopa 50 mg given three or four times daily. In either situation, the dose may then be adjusted in a similar manner as described for previously untreated patients.
- Modified-release capsules containing the equivalent of benserazide 25 mg with levodopa 100 mg are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* the initial dose is one capsule three times daily adjusted every 2 to 3 days according to response; it is recommended that initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of levodopa with benserazide, initially one capsule should be substituted for every 100 mg of levodopa and should be given at the same dosage frequency as before; increases in dosage can then be made every 2 to 3 days according to response. An average of 50% more levodopa may be required compared with previous therapy and titration may take up to 4 weeks. *Supplementary doses* of an immediate-release preparation of benserazide with levodopa may also be required with the first morning dose.

Carbidopa is usually given with levodopa (co-careldopa) as tablets in the ratio of 1 to 4 or 1 to 10, which allows dosage adjustments of either drug for individual patients. Carbidopa is given as the hydrous base although doses are expressed in terms of the anhydrous base; hydrous carbidopa 10.8 mg is equivalent to about 10 mg of anhydrous carbidopa. Full inhibition of peripheral dopa-decarboxylase is reported to be achieved with 70 to 100 mg of carbidopa daily.

- A suggested initial oral dose for *patients not previously treated with levodopa* is carbidopa 25 mg with levodopa 100 mg three times daily, increased gradually, in increments of carbidopa 12.5 mg with levodopa 50 mg or carbidopa 25 mg with levodopa 100 mg every day or on alternate days, as necessary. The usual maintenance dosage range is carbidopa 75 to 200 mg with levodopa 750 mg to 2 g daily in divided doses. Carbidopa doses greater than 200 mg daily are not generally exceeded.
- The initial dose of levodopa with carbidopa in *patients previously treated with levodopa alone* should be about 20 to 25% of the dose previously being taken, thus for patients taking less than 1.5 g of levodopa daily a suggested initial dose is carbidopa 25 mg with levodopa 100 mg given three or four times daily; a suggested initial dose for patients taking more than 1.5 g of levodopa daily is carbidopa 25 mg with levodopa 250 mg given three or four times daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose should provide a similar daily amount of levodopa.
- Modified-release tablets containing carbidopa with levodopa in the ratio of 1 to 4 are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* therapy, or for *those currently receiving levodopa alone*, the initial dose is carbidopa 50 mg with levodopa 200 mg twice daily, adjusted according to response, at intervals of not less than 3 days. It is recommended that for patients who are not already receiving levodopa initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of carbidopa with levodopa, the initial dose of the modified-release preparation should provide a similar daily amount of levodopa, but the dosing intervals should be prolonged and are normally between 4 to 12 hours. The initial substitution dose of the modified-release preparation should provide no greater than 10% more levodopa than was previously given for doses of levodopa exceeding 900 mg daily. Doses and intervals may then be altered according to clinical response, allowing at least 3 days between adjustments. Up to 30% more levodopa may be required in the modified-release preparation than was previously given in the immediate-release preparation. Average maintenance doses of modified-release preparations lie within the range of carbidopa 100 mg with levodopa 400 mg to carbidopa 400 mg with levodopa 1.6 g daily in divided doses. *Supplementary doses* of an immediate-release preparation of carbidopa with levodopa may be required in some patients.

Combination preparations of levodopa with carbidopa and the catechol-*O*-methyltransferase (COMT) inhibitor **entacapone** are also available; each tablet contains levodopa and carbidopa in a ratio of 4 to 1 with entacapone 200 mg. Such preparations are indicated for patients with end-of-dose motor fluctuations not stabilised on levodopa/peripheral dopa-decarboxylase inhibitor treatment. Patients should only take one combination tablet for each dose.

- *Patients previously treated with an immediate-release preparation of levodopa with a peripheral dopa-decarboxylase inhibitor and separate entacapone* should be transferred to the combination preparation at a dose that provides similar or slightly higher amounts of levodopa.
- For *patients not currently taking entacapone*, the dose of the combination preparation should normally provide a similar or slightly lower dose of levodopa to that previously taken. However, patients with *dyskinesia* or taking *levodopa in doses above 800 mg daily* should start entacapone as a separate medication before being transferred to the combination preparation, as a 10 to 30% reduction in their levodopa dose may be needed when starting combination therapy, especially if levodopa is being given with benserazide.

In some countries a gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available for continuous infusion by an ambulatory pump into the duodenum. It is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations when other available combination therapy has not been satisfactory. A positive test of the clinical response via a temporary nasoduodenal tube is required before a permanent tube is inserted into the duodenum or upper jejunum. The total daily dose comprises of 3 individually-adjusted doses, which are expressed in terms of the levodopa component as follows:

- the *morning bolus dose*, based on the patient's previous morning intake of levodopa, is usually 100 to 200 mg infused over 10 to 30 minutes and should not exceed 300 mg
- the *continuous maintenance dose*, based on the patient's previous daily intake of levodopa, is usually 40 to 120 mg/hour infused over 16 hours, adjustable in steps of 2 mg/hour to within a range of 20 to 200 mg/hour; higher doses may be needed in exceptional cases
- *extra bolus doses*, given when required, are usually between 10 to 40 mg/hour although higher doses may be needed in exceptional cases; the maintenance dose should be increased if more than 5 bolus doses are needed daily

After the initial dose setting, further dose adjustments should be made over a few weeks. If medically justified, it may be administered during the night.

Melevodopa, the methyl ester of levodopa, has been used orally as the hydrochloride with carbidopa in some countries for parkinsonism. The ethyl ester of levodopa, etilevodopa, is under study.

Administration. A small crossover study involving 24 patients with severe Parkinson's disease found that intraduodenal infusion of a levodopa and carbidopa gel preparation for 3 weeks was clinically superior to individually optimised conventional regimens.[1] Long-term experience (up to 7 years) in a limited number of patients has suggested that intraduodenal infusion is a good alternative for those with advanced disease and disabling motor fluctuations.[2] A gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available in some countries for intraduodenal infusion.

1. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.
2. Nilsson D, *et al.* Duodenal levodopa infusion in Parkinson's disease: long-term experience. *Acta Neurol Scand* 2001; **104:** 343–8.

Drug-induced extrapyramidal disorders. The management of drug-induced extrapyramidal disorders is discussed under the Adverse Effects of Chlorpromazine on p.971. Although the use of dopamine agonists, especially levodopa, to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, levodopa has generally been reported to be ineffective or to increase psychiatric symptoms.

Dysphagia. Results of a small study[1] have suggested that levodopa may improve the impaired swallowing reflex in patients with basal ganglia infarctions and thereby help to prevent aspiration pneumonia.

1. Kobayashi H, *et al.* Levodopa and swallowing reflex. *Lancet* 1996; **348:** 1320–1.

Dystonias. A dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures; it may also have additional myoclonic or tremulous components. Typically it starts as a focal dystonia localised in one part of the body and to begin with may appear only during a specific motor act (action dystonia). If the syndrome is progressive the dystonias may become apparent at rest and spread first to more than one part of the body (segmental dystonia) and may eventually affect most or all of the body (generalised dystonia). Progression of the dystonia appears to be related to age of onset. Dystonia beginning in childhood usually starts in the legs and progresses to become segmental or generalised, whereas in adults the dystonia usually starts in other parts of the body and rarely becomes generalised. Examples of focal dystonias are blepharospasm (affecting the eye and surrounding facial muscles), writer's cramp (hand and arm), spasmodic torticollis (neck), spasmodic dysphonia, or dystonic dysphagia (larynx or pharynx), and leg dystonias. Some dystonias may be associated with metabolic disorders such as Wilson's disease or Lesch-Nyhan syndrome; with neurological disorders such as Huntington's disease; or with other causes including head trauma, manganese or carbon disulfide toxicity, or the adverse effects of antipsychotics or antiparkinsonian drugs. However, in the majority of cases the disease is idiopathic.

There are no cures for most types of dystonia, but with appropriate **management** symptomatic relief is possible in many patients.[1-5]

- It has been suggested that all children and adolescents presenting with dystonia, particularly starting in the legs, should first be given a trial with *levodopa*.[1,3,5] Although not licensed for children in the UK, the *BNFC* states that children aged 3 months and older with dopamine-sensitive dystonias, including dystonic cerebral palsy, may be given 250 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) two to three times daily increased according to response every 2 to 3 days to a maximum of 1 mg/kg of levodopa three times daily. Another suggested regimen is to gradually build up to a dose of levodopa 200 mg with carbidopa 50 mg given three times daily and to maintain this dose for 3 months; if there is no useful response in this period the drug is withdrawn.[1] Where there is benefit it is usually dramatic and is sustained as long as the drug is taken, which may be more than 10 years in some cases, in general without the long-term problems associated with levodopa for parkinsonism (see p.791).
- In children and adolescents who fail to respond to levodopa an *antimuscarinic* such as trihexyphenidyl is second choice; the *BNFC* also suggests using benzatropine or procyclidine. Adverse effects are minimised by starting with a low dose which is then gradually increased. General experience indicates that about half of all children and adolescents benefit from antimuscarinics; adults tolerate the drug less well and only about a fifth of adult patients with focal dystonia benefit.
- In patients who do not respond to levodopa or high-dose antimuscarinics other drugs may be used. Many benefit from *benzodiazepines* such as diazepam; a few have responded to *baclofen* or *carbamazepine*. *Antipsychotics* are sometimes useful but carry the risk of inducing tardive dyskinesia. *Tetrabenazine* carries less risk of tardive dyskinesia but may induce depression. In very severe dystonia combination therapy may be required: tetrabenazine with pimozide and trihexyphenidyl is sometimes effective.
- In patients refractory to oral therapy *intrathecal* baclofen, or surgery may be tried.
- The response in patients with adult onset focal dystonia is usually poor. However, the use of *botulinum A toxin* can produce relief in blepharospasm, spasmodic torticollis, and spasmodic dysphonia, and is under investigation for writer's cramp and other occupational dystonias. In some patients with generalised and segmental dystonia, botulinum A toxin injected into the most disabling or painful muscles has been used as adjunctive therapy. Local injections into the affected muscles produce weakness over the next week or so, thereby reducing or abolishing dystonic spasms. The effect lasts some 2 to 4 months. *Botulinum B toxin* has also been used in the management of spasmodic torticollis.

Further details of the management of blepharospasm and spasmodic torticollis can be found under Botulinum Toxins on p.1891. For a discussion of the management of antipsychotic-induced dystonic reactions, see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p.971.

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
2. Williams A. Consensus statement for the management of focal dystonias. *Br J Hosp Med* 1993; **50:** 655–9.
3. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000; **23:** 239–51.
4. Tarsy D, Simon DK. Dystonia. *N Engl J Med* 2006; **355:** 818–29.
5. Jankovic J. Treatment of dystonia. *Lancet Neurol* 2006; **5:** 864–72.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as levodopa in the management of hepatic encephalopathy see p.1697.

Neuroleptic malignant syndrome. There have been isolated reports[1-4] that levodopa used alone or with bromocriptine has been successful in the treatment of patients with neuroleptic malignant syndrome (p.972). However, bromocriptine is usually preferred when a dopaminergic is required for the treatment of this condition.

1. Knezevic W, *et al.* Neuroleptic malignant syndrome. *Med J Aust* 1984; **140:** 28–30.
2. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
3. Lo TCN, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
4. Shoop SA, Cernek PK. Carbidopa/levodopa in the treatment of neuroleptic malignant syndrome. *Ann Pharmacother* 1997; **31:** 119.

Parkinsonism. Levodopa is the mainstay in the treatment of Parkinson's disease (p.791) but opinion varies on when it should be used in the course of the disease. Most patients respond to levodopa initially but after a few years benefit may be reduced. There may be problems with dyskinesias and psychiatric effects and fluctuations in mobility necessitating careful dosage adjustment or the use of adjunctive drugs. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms. Levodopa should be given with a peripheral dopa-decarboxylase inhibitor; a peripheral catechol-*O*-methyltransferase (COMT) inhibitor may also be necessary for patients experiencing fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. The various methods used for the pharmacokinetic optimisation of levodopa therapy as Parkinson's disease progresses include timing of doses, the use of modified-release formulations, oral solutions (but see Stability, p.804) and dispersible formulations for immediate absorption, the timing of food intake, and the use of other drugs to increase the absorption of levodopa. In some countries a gel formulation of levodopa with carbidopa is available for intraduodenal infusion.

References.

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Contin M, *et al.* Pharmacokinetic optimisation in the treatment of Parkinson's disease. *Clin Pharmacokinet* 1996; **30:** 463–81.
3. Murer MG, *et al.* Levodopa in Parkinson's disease: neurotoxicity issue laid to rest? *Drug Safety* 1999; **21:** 339–52.
4. Furlanut M, *et al.* Monitoring of L-dopa concentrations in Parkinson's disease. *Pharmacol Res* 2001; **43:** 423–7. Correction. *ibid.*; **44:** 149.
5. Carlsson A. Treatment of Parkinson's with L-DOPA: the early discovery phase, and a comment on current problems. *J Neural Transm* 2002; **109:** 777–87.
6. Katzenschlager R, Lees AJ. Treatment of Parkinson's disease: levodopa as the first choice. *J Neurol* 2002; **249** (suppl 2): II19–II24.
7. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. *CNS Drugs* 2003; **17:** 475–89.
8. LeWitt PA, Nyholm D. New developments in levodopa therapy. *Neurology* 2004; **62** (suppl 1): S9–S16.
9. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S56–S63.
10. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64:** 216–23.

Pituitary and hypothalamic disorders. ***DIAGNOSIS AND TESTING.*** Diminished growth hormone reserve is one of the earliest functional abnormalities in anterior pituitary failure and, since dopamine is believed to stimulate growth hormone secretion, levodopa has been used as a provocative test for the diagnosis of growth hormone deficiency.[1,2] Levodopa 500 mg has been given orally after an overnight fast and serum concentrations of growth hormone measured hourly at 0 to 3 hours; children may be given 10 mg/kg to a maximum of 500 mg. Transient nausea, vomiting, vertigo, and hypotension may occur and the patient should be kept recumbent during the test. A normal response is an increase in serum concentration of growth hormone of more than 5 nanograms/mL or to a level of more than 10 nanograms/mL, although 10 to 15% of normal subjects may not respond. However, there is some dispute as to whether stimulated growth hormone secretion tests are superior to measurements of circulating somatomedins in detecting growth hormone deficiency.[3-5] For a discussion of the management of growth retardation, including the problems of accurate diagnosis, see p.1798.

1. Abboud CF. Laboratory diagnosis of hypopituitarism. *Mayo Clin Proc* 1986; **61:** 35–48.
2. Müller EE, *et al.* Involvement of brain catecholamines and acetylcholine in growth hormone deficiency states: pathophysiological, diagnostic and therapeutic implications. *Drugs* 1991; **41:** 161–77.
3. Hoffmann DM, *et al.* Diagnosis of growth-hormone deficiency in adults. *Lancet* 1994; **343:** 1064–8. Correction. *ibid.*, **344:** 206.
4. de Boer H, *et al.* Diagnosis of growth hormone deficiency in adults. *Lancet* 1994; **343:** 1645–6.
5. Rosenfeld RG, *et al.* Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995; **80:** 1532–40.

Sleep-associated movement disorders. The aetiology of *restless legs syndrome* and *periodic limb movements in sleep* is obscure and treatment has been largely empirical (p.958). Few of the treatments tried in these often co-existent disorders have been studied in a controlled manner but small controlled studies[1-6] have reported beneficial effects such as improved sleep quality and reduced leg movements from levodopa used with a peripheral dopa-decarboxylase inhibitor. Most patients received a bedtime dose of 50 to 200 mg of levodopa with possible additional doses during the night. A 1-year open-label extension study[7] confirmed the continued efficacy and safety of levodopa in patients with restless legs syndrome; the authors recommended a maximum daily dose of 400 mg levodopa to decrease the risk of exacerbation or rebound symptoms during the day. However, long-acting dopaminergic agonists are preferred in order to avoid the complications associated with levodopa.

Levodopa has also been reported to have been of benefit in a study of 10 patients with *sleep bruxism*.[8]

1. von Scheele C. Levodopa in restless legs. *Lancet* 1986; **ii:** 426–7.
2. Brodeur C, *et al.* Treatment of restless legs syndrome and periodic movements during sleep with -dopa: a double-blind controlled study. *Neurology* 1988; **38:** 1845–8.
3. Kaplan PW, *et al.* A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993; **16:** 717–23.
4. Trenkwalder C, *et al.* L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. *Sleep* 1995; **18:** 681–8.
5. Beneš H, *et al.* Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep* 1999; **22:** 1073–81.
6. Janzen L, *et al.* An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother* 1999; **33:** 86–92.
7. Trenkwalder C, *et al.* One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Mov Disord* 2003; **18:** 1184–9.
8. Lobbezoo F, *et al.* The effect of the catecholamine precursor -dopa on sleep bruxism: a controlled clinical trial. *Mov Disord* 1997; **12:** 73–8.

Strabismus. Experimental studies have shown that centrally acting drugs such as levodopa may improve vision in patients with amblyopia (see Strabismus, p.1874). However, their role in clinical practice remains to be established.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2:** 91–100.

Tourette's syndrome. Levodopa has been studied in the management of Tourette's syndrome (see Tics, p.954). A small pilot study[1] has produced encouraging results.

1. Black KJ, *et al.* Response to levodopa challenge in Tourette syndrome. *Mov Disord* 2000; **15:** 1194–8.

Preparations

BP 2008: Co-beneldopa Capsules; Co-careldopa Tablets; Dispersible Co-beneldopa Tablets; Levodopa Capsules; Levodopa Tablets;
USP 31: Carbidopa and Levodopa Tablets; Levodopa Capsules; Levodopa Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Prikap; ***Ger.:*** Dopaflex; Restex; ***Hung.:*** Dopaflex†; ***India:*** Levopa†; ***Ital.:*** Levomet†; ***Jpn:*** Doparl; ***Pol.:*** Nakom; ***USA:*** Dopar†; Larodopa†.

Multi-ingredient: ***Arg.:*** Lebocar; Lecarge; Madopar; Nervocur; Parkinel; Sinemet; Stalevo; ***Austral.:*** Kinson; Madopar; Sinemet; Stalevo; ***Austria:*** Dopamed; Levobens; Levocar; Madopar; Restex; Sinemet; ***Belg.:*** Prolopa; Sinemet; Stalevo; ***Braz.:*** Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Prolopa; Sinemet; Stalevo; ***Canad.:*** Apo-Levocarb; Novo-Levocarbidopa; Nu-Levocarb; Prolopa; Sinemet; ***Chile:*** Grifoparkin; Levofamil†; Melitase; Prolopa; Protonis; Saniter Compuesto; Sinemet; Stalevo; ***Cz.:*** Dopalux; Duodopa; Isicom; Lecardop; Madopar; Nakom; Sinemet; Stalevo; ***Denm.:*** Duodopa; Madopar; Sinemet; Stalevo; ***Fin.:*** Kardopal; Madopar; Sinemet; Stalevo; ***Fr.:*** Duodopa; Modopar; Sinemet; Stalevo; ***Ger.:*** Dopadura C; Isicom; Levo-C; Levobeta C; Levocarb; Levocomp; Levodop; Levodopa Comp; Levodopa comp B; Levodopa comp C; Levodopa-Carbi†; Levopar; Madopar; Nacom; NeyDop N (Revitorgan-Dilutionen N Nr 97)†; PK-Levo; Stalevo; Striaton; Tremopar†; ***Gr.:*** Madopar; Sinemet; Sinemet-CR; Stalevo; Zimox; ***Hong Kong:*** Apo-Levocarb; Levomed; Levomet; Madopar; Sinedopa; Sinemet; Stalevo; ***Hung.:*** Duellin; Madopar; Sinemet; Stalevo; ***India:*** Levopa-C†; Syndopa; ***Indon.:*** Leparson; Levazide; Levopar; Madopar; Pardoz; Stalevo; ***Irl.:*** Half Sinemet; Madopar; Sinemet; Stalevo; ***Israel:*** Dopicar; Levopar Plus; Sinemet; Stalevo; ***Ital.:*** Duodopa; Madopar; Sinemet; Sirio; Stalevo; ***Malaysia:*** Apo-Levocarb; Levomed; Madopar; Sinemet; Stalevo; ***Mex.:*** Cloisone; Lemdopa; Madopar; Racovel; Sinemet; Stalevo; Ternovag; ***Neth.:*** Duodopa; Madopar; Modopar; Sinemet; Stalevo; ***Norw.:*** Duodopa; Madopar; Sinemet; Stalevo; ***NZ:*** Apo-Levocarb; Madopar; Sindopa; Sinemet; ***Philipp.:*** Ledocar; Madopar; Sinemet; Stalev; Tidomet; ***Pol.:*** Madopar; Sinemet; Stalevo; ***Port.:*** Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; ***Rus.:*** Duellin (Дуэллин); Madopar (Мадопар); Nakom (Наком); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); ***S.Afr.:*** Carbilev; Madopar; Sinemet; ***Singapore:*** Cardopar; Levomet; Madopar; Sinemet; Stalevo; Tidomet; ***Spain:*** Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; ***Swed.:*** Duodopa; Madopark; Sinemet; Stalevo; ***Switz.:*** Madopar; Sinemet; Stalevo; ***Thai.:*** Cenparkin†; Levomed†; Levomet; Madopar; Sinemet; Stalevo; Syndopa; Vopar; ***Turk.:*** Madopar; Sinemet; Stalevo; ***UK:*** Duodopa; Half Sinemet; Madopar; Sinemet; Stalevo; Tilolec†; ***USA:*** Atamet; Parcopa; Sinemet; Stalevo; ***Venez.:*** Madopar; Sinemet; Stalevo.

Lisuride Maleate *(BANM, rINNM)*

Lisurid Maleat; Lisuride, Maléate de; Lisuridi Hydrogenomaleas; Lisuridi Maleas; Lisuridivetymaleaatti; Lisuridvätemaleat; Lysuride Maleate; Maleato de lisurida; Methylergol Carbamide Maleate. 3-(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea hydrogen maleate; 8-Decarboxamido-8-(3,3-diethylureido)-D-lysergamide maleate.

Лизурида Малеат

$C_{20}H_{26}N_4O,C_4H_4O_4$ = 454.5.

CAS — 18016-80-3 (lisuride); 19875-60-6 (lisuride maleate).

ATC — G02CB02; N02CA07.

ATC Vet — QG02CB02; QN02CA07.

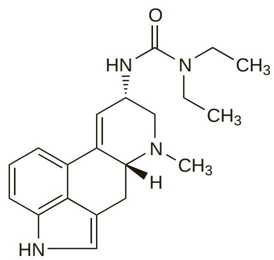

(lisuride)

Adverse Effects and Precautions

As for Bromocriptine, p.798. Infusion of lisuride in parkinsonian patients has been associated with severe psychiatric adverse effects.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including lisuride, see under Adverse Effects of Levodopa, p.805.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including lisuride, see under Adverse Effects of Bromocriptine, p.799.

Porphyria. Lisuride maleate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for Bromocriptine, p.800.

Pharmacokinetics

◊ Plasma concentrations varied widely after a single oral dose of lisuride maleate 300 micrograms in 11 patients with Parkinson's disease.[1] Absorption was rapid and the mean plasma elimination half-life was 2.2 hours. Only a mean of 0.05% of the dose was excreted unchanged in the urine in 24 hours. The mean oral bioavailability of lisuride maleate has been reported[2] to be 10% after a 100-microgram dose and 22% after a 300-microgram dose.

A single dose of lisuride 25 micrograms given by intravenous, intramuscular, or subcutaneous injection reduced plasma-prolactin concentrations by up to 60% in 11 of 12 healthy subjects, the effect lasting for about 10 hours.[3] Plasma-lisuride concentrations after intravenous injection fell in 2 phases with half-lives of 14 minutes and 1.5 hours, respectively. Peak plasma concentrations after subcutaneous and intramuscular injection were obtained after 12 and 15 minutes, respectively.

1. Burns RS, *et al*. Disposition of oral lisuride in Parkinson's disease. *Clin Pharmacol Ther* 1984; **35:** 548–56.
2. Hümpel M, *et al*. Radioimmunoassay of plasma lisuride in man following intravenous and oral administration of lisuride hydrogen maleate; effect on plasma prolactin level. *Eur J Clin Pharmacol* 1981; **20:** 47–51.
3. Krause W, *et al*. The pharmacokinetics and pharmacodynamics of lisuride in healthy volunteers after intravenous, intramuscular, and subcutaneous injection. *Eur J Clin Pharmacol* 1991; **40:** 399–403.

Uses and Administration

Lisuride maleate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p.798). It is also reported to have serotonergic activity. It is used similarly in the management of Parkinson's disease and has been used in disorders associated with hyperprolactinaemia. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that can be adequately relieved with simple analgesics and breast support. Lisuride has been used in some countries for the treatment of acromegaly, and for the prophylaxis of migraine.

In the management of **Parkinson's disease** lisuride maleate has been given alone or added to treatment in patients having 'on-off' fluctuations in control with levodopa. It is normally given orally; doses should be taken with food. Initially 200 micrograms is taken at bedtime and additional doses of 200 micrograms may be added, at intervals of one week, first at midday and then in the morning. Further increases are made, until an optimum response is obtained, by adding 200 micrograms each week using the same sequence of increases, starting with the bedtime dose; dosage should not normally exceed 5 mg daily in divided doses.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p.1798). While bromocriptine has been the main dopamine agonist used, lisuride has been used in some countries, typically in a dose of 100 micrograms three times daily.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p.2079). Lisuride has been used as an alternative to bromocriptine. There is a report of plasma-prolactin concentrations being reduced to normal in 4 female patients with macroprolactinomas given lisuride 400 to 800 micrograms daily for 2 years.[1] Subsequent dosage reduction in 3 was followed by a rise in prolactin values. In the fourth patient prolactin remained in the normal range when the dose was progressively reduced from 400 to 50 micrograms daily, although complete withdrawal was followed by an increase in prolactin concentration within 3 months.

Vaginal dosage of lisuride has been studied in an attempt to avoid adverse effects associated with oral therapy. In a study[2] involving 40 women with hyperprolactinaemia a 200-microgram standard oral tablet placed in the vagina at night produced a similar reduction in prolactin concentrations to that obtained with 400 micrograms taken orally and was better tolerated.

1. Liuzzi A, *et al*. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985; **313:** 656–9.
2. Tasdemir M, *et al*. Vaginal lisuride for hyperprolactinaemia. *Lancet* 1995; **346:** 1362.

Lactation inhibition. Lisuride is used in some countries for the prevention of puerperal lactation (p.2003). However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation.

References.

1. Venturini PL, *et al*. Effects of lisuride and bromocriptine on inhibition of lactation and on serum prolactin levels: comparative double-blind study. *Eur J Obstet Gynecol Reprod Biol* 1981; **11:** 395–400.

Mastalgia. In a small placebo-controlled study,[1] lisuride 200 micrograms daily was effective in the treatment of cyclical mastalgia. However, since mastalgia (p.2092) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months.

1. Kaleli S, *et al*. Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.

Migraine. Although lisuride has been used in some countries for the prophylaxis of migraine (p.616) it is not usually considered to be the drug of choice or even one of the main alternatives.

Parkinsonism. While some neurologists use dopamine agonists such as lisuride early in the treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, others reserve them for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease.

References.

1. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; **39:** 336–9.
2. Clarke CE, Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
3. Clarke CE, Speller JM. Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
4. Allain H, *et al*. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Eur Neurol* 2000; **44:** 22–30.

Administration. Lisuride has been of benefit when given by continuous intravenous or subcutaneous infusion in patients having fluctuations in mobility with levodopa therapy[1-4] but severe psychiatric effects have been associated with the use of these routes.[3] Transdermal lisuride is also being investigated for the treatment of Parkinson's disease and restless legs syndrome.[5,6]

1. Obeso JA, *et al*. Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986; **19:** 31–5.
2. Obeso JA, *et al*. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* 1986; **i:** 467–70.
3. Critchley P, *et al*. Psychosis and the lisuride pump. *Lancet* 1986; **i:** 349.
4. Stocchi F, *et al*. Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002; **125:** 2058–66.
5. Woitalla D, *et al*. Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl* 2004; **68:** 89–95.
6. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. *Sleep Med* 2006; **7:** 31–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dopagon†; ***Austria:*** Dopergin; Prolacam†; ***Fr.:*** Arolac; Dopergine; ***Ger.:*** Cuvalit†; Dopergin; ***Gr.:*** Dipergon; ***Ital.:*** Dopergin; ***Mex.:*** Dopergin; ***Neth.:*** Dopergin; ***NZ:*** Dopergin; ***Spain:*** Dopergin; ***Switz.:*** Dopergin†; ***Thai.:*** Dopergin†; ***Turk.:*** Dopergin.

Metixene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metixeno; Methixene Hydrochloride *(USAN)*; Methixene Hydrochloride Monohydrate; Metikseenihydrokloridi; Metikseno hidrochloridas; Métixène, chlorhydrate de; Metixén-hidroklorid; Metixen-hydrochlorid monohydrát; Metixenhydroklorid; Metixeni hydrochloridum; Metixeni Hydrochloridum Monohydricum; NSC-78194; SJ-1977. (*RS*)-9-(1-Methyl-3-piperidylmethyl)thioxanthene hydrochloride monohydrate.

Метиксена Гидрохлорид

$C_{20}H_{23}NS,HCl,H_2O$ = 363.9.

CAS — 4969-02-2 (metixene); 1553-34-0 (anhydrous metixene hydrochloride); 7081-40-5 (metixene hydrochloride monohydrate).

ATC — N04AA03.

ATC Vet — QN04AA03.

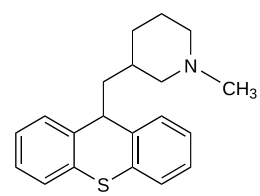

(metixene)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Metixene Hydrochloride). A white or almost white, crystalline or fine crystalline powder. Soluble in water, in alcohol, and in dichloromethane. A 1.8% solution in water has a pH of 4.4 to 5.8. Protect from light.

Profile

Metixene hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1219); it also has antihistaminic and direct antispasmodic properties.

It is used for the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The usual oral dose of metixene hydrochloride is 2.5 mg three times daily initially, gradually increased according to response to a total of 15 to 60 mg daily in divided doses.

Metixene hydrochloride has also been used in preparations to relieve gastrointestinal spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Tremarit; ***Hung.:*** Tremaril; ***Ital.:*** Tremaril; ***Swed.:*** Tremoquil†.

Multi-ingredient: ***Philipp.:*** Spasmo-Canulase; ***Port.:*** Espasmo Canulase; ***S.Afr.:*** Spasmo-Canulase; ***Switz.:*** Spasmo-Canulase.

Orphenadrine Citrate *(BANM, rINNM)*

Citrato de orfenadrina; Mephenamine Citrate; Orfenadriinisitraatti; Orfenadrincitrat; Orfenadrin-citrát; Orfenadrino citratas; Orphenadin Citrate; Orphénadrine, Citrate d'; Orphénadrine, citrate de; Orphenadrini citras. (*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine dihydrogen citrate.

Орфенадрина Цитрат

$C_{18}H_{23}NO,C_6H_8O_7$ = 461.5.

CAS — 83-98-7 (orphenadrine); 4682-36-4 (orphenadrine citrate).

ATC — M03BC01.

ATC Vet — QM03BC01.

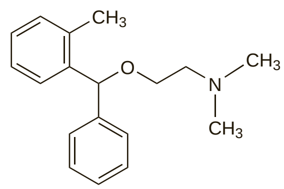

(orphenadrine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Orphenadrine Citrate). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Orphenadrine Citrate). A white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Orphenadrine Hydrochloride *(BANM, rINNM)*

BS-5930; Hidrocloruro de orfenadrina; Mephenamine Hydrochloride; Orfenadriinihydrokloridi; Orfenadrin-hidroklorid; Orfenadrin-hydrochlorid; Orfenadrinhydroklorid; Orfenadrino hidrochloridas; Orphenadin Hydrochloride; Orphénadrine, Chlorhydrate d'; Orphénadrine, chlorhydrate de; Orphenadrini hydrochloridum. (*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine hydrochloride.

Орфенадрина Гидрохлорид

$C_{18}H_{23}NO,HCl$ = 305.8.

CAS — 341-69-5.

ATC — N04AB02.

ATC Vet — QN04AB02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Orphenadrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Orphenadrine may cause insomnia.

Abuse. A 23-year-old schizophrenic man, whose treatment included orphenadrine 100 mg three times daily, obtained illicit supplies and increased the dose for euphoric effect.[1] On one occasion he had an epileptic convulsion after a 600-mg dose.

See also under Trihexyphenidyl Hydrochloride, p.820.

1. Shariatmadari ME. Orphenadrine dependence. *BMJ* 1975; **3:** 486.

Overdosage. A report[1] of acute poisoning with orphenadrine after massive overdosage in a schizophrenic patient, who responded to intensive supportive treatment, including large doses of adrenaline, dopamine, and dobutamine to restore blood pressure following asystole. Between 1977 and 1980 twelve deaths due to orphenadrine were recorded by the UK National Poisons Unit.

1. Clarke B, *et al*. Acute poisoning with orphenadrine. *Lancet* 1985; **i:** 1386.

Porphyria. Orphenadrine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Withdrawal. A suspected withdrawal syndrome was reported in a 56-year-old woman who showed slow neurological postoperative recovery after her orphenadrine treatment had been stopped abruptly;[1] her status improved when the drug was restarted.

1. Esler MD, *et al*. Postoperative orphenadrine withdrawal. *Br J Anaesth* 2000; **85:** 497.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Orphenadrine is an inhibitor of the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of bupropion to its major metabolite; licensed product information advises that orphenadrine should be used with caution in patients also receiving bupropion.

Chlorpromazine. For the effect of orphenadrine on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p.974.

Dextropropoxyphene. A suggested interaction between orphenadrine and dextropropoxyphene was open to question.[1,2]

1. Pearson RE, Salter FJ. Drug interaction? — orphenadrine with propoxyphene. *N Engl J Med* 1970; **282:** 1215.
2. Puckett WH, Visconti JA. Orphenadrine and propoxyphene (cont.). *N Engl J Med* 1970; **283:** 544.

Pharmacokinetics

Orphenadrine is readily absorbed from the gastrointestinal tract and after intramuscular injection. It is almost completely metabolised to at least 8 metabolites. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. The half-life of orphenadrine has been reported to be 14 hours (but see below).

Half-life. While the mean elimination half-life of orphenadrine in 5 healthy subjects given a single dose of the hydrochloride was found to be 15.5 hours, elimination half-lives of 30.5 and 40 hours were calculated in 2 patients given repeated oral doses.[1]

1. Labout JJM, *et al*. Difference between single and multiple dose pharmacokinetics of orphenadrine hydrochloride in man. *Eur J Clin Pharmacol* 1982; **21:** 343–50.

Uses and Administration

Orphenadrine, which is a congener of diphenhydramine (p.577) without sharing its soporific effect, is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It also has weak antihistaminic and local anaesthetic properties. Orphenadrine is used as the hydrochloride and the citrate; doses are expressed in terms of the relevant salt.

Orphenadrine is used as the hydrochloride in the symptomatic treatment of **parkinsonism** (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The initial oral dose of orphenadrine hydrochloride is 150 mg daily in divided doses gradually increased by 50 mg every 2 or 3 days according to response; the usual maintenance dose is in the range of 150 to 300 mg daily, but some patients may require a total of up to 400 mg daily. Orphenadrine hydrochloride has also been given intramuscularly.

Orphenadrine is also used as the citrate to relieve pain due to **skeletal muscle spasm**. It is given orally in a dose of 100 mg twice daily or by intramuscular or slow intravenous injection in a dose of 60 mg which has been repeated every 12 hours.

Combinations of orphenadrine with an NSAID, usually diclofenac, or with paracetamol, have been used in the treatment of musculoskeletal and joint disorders.

Hiccup. Orphenadrine citrate has been used in some countries for the treatment of intractable hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976.

Muscle and joint disorders. References to the use of orphenadrine in the management of leg cramps and other painful conditions associated with skeletal muscle spasm,[1,2] and with diclofenac in osteoarthritis and other musculoskeletal disorders.[3,4]

1. Latta D, Turner E. An alternative to quinine in nocturnal leg cramps. *Curr Ther Res* 1989; **45:** 833–7.
2. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. *J Int Med Res* 1991; **19:** 71–87.
3. Uitz E, *et al.* Diclofenac/Orphenadrin-Infusionstherapie bei Patienten mit aktivierten Arthrosen. *Wien Med Wochenschr* 1998; **148:** 179–82.
4. Aglas F, *et al.* Ergebnisse einer Anwendungsbeobachtung mit Diclofenac/Orphenadrin-Infusionen bei Patienten mit muskuloskelettalen Krankheiten und Funktionsstorungen. *Acta Med Austriaca* 1998; **25:** 86–90.

Preparations

BP 2008: Orphenadrine Hydrochloride Tablets;
USP 31: Orphenadrine Citrate Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Norflex; ***Belg.:*** Disipal; ***Canad.:*** Norflex; ***Chile:*** Plenactol; ***Denm.:*** Disipal; Lysantin; Norflex†; ***Fin.:*** Norflex; ***Ger.:*** Norflex; ***Gr.:*** Disipal; Norflex; ***India:*** Orphipal; ***Israel:*** Flexin; ***Ital.:*** Disipal; ***Malaysia:*** Norflex; ***Mex.:*** Norflex; ***Norw.:*** Disipal†; ***NZ:*** Disipal; Norflex; ***Port.:*** Norflex†; ***S.Afr.:*** Disipal; Norflex; Phenerine; ***Swed.:*** Disipal†; Norflex; ***Thai.:*** Norflex; Orfenal†; ***UK:*** Biorphen; Disipal; ***USA:*** Banflex; Flexon; Norflex; ***Venez.:*** Norflex.

Multi-ingredient: ***Arg.:*** Belmalen; Doloctaprin Plus†; Flogodisten; Metaflex Plus†; Mio Aldoron; Mio-Virobron; ***Austral.:*** Norgesic; ***Austria:*** Neodolpasse; Norgesic; ***Braz.:*** Anapirol†; Banidor†; Dalgex; Doralgex; Dorciflex; Dorflex; Doricin; Dorzone; Flexalgex; Flexdor; Itaiflex†; Miorrelax; Nevralgex; Relaflex; Rielex; Sedalex; Theopirina†; ***Canad.:*** Norgesic; ***Chile:*** Norgesic; ***Cz.:*** Neodolpasse; ***Fin.:*** Dolan; Norgesic; ***Ger.:*** Norgesic N†; ***Gr.:*** Norgesic; ***Hong Kong:*** Norgesic; ***Hung.:*** Neodolpasse; ***Irl.:*** Norgesic†; ***Israel:*** Muscol; Norgesic; ***Malaysia:*** Anarex; Norgesic; Orphenadol; Suniton; ***Mex.:*** Norflex Plus; ***NZ:*** Norgesic; ***Philipp.:*** Norgesic; ***Port.:*** Norgesic†; ***S.Afr.:*** Besemax; Besenol; Norflex Co; ***Singapore:*** Anarex; Camgesic; Norgesic; Norphen; Orphenadol; ***Swed.:*** Norgesic; ***Thai.:*** Cenasic; Corilax†; Dorpane; Med-Myolax†; Medgesic; Muscol†; Myodrine; Myoflex; Myosic; Myospa; Nabesac; Neosec; Norgesic; Norgic; Norphen; Nuosic; Nurasic; Orano; Orflex; Orpar; Orphengesic; Parina; Poli-Relaxane; Polydol; Pormus; Relar; Rena; ***UAE:*** Muscadol; ***USA:*** Norgesic; Orphengesic; ***Venez.:*** Norgesic.

Pergolide Mesilate *(BANM, rINNM)*

LY-127809; Mesilato de pergolida; Pergolid Mesilat; Pergolid mesylát; Pergolide, mésilate de; Pergolide Mesylate *(USAN)*; Pergolidi mesilas; Pergolidimesilaatti; Pergolidmesilat; Pergolid-mezilát; Pergolido mesilatas. 8β-Methylthiomethyl-6-propylergoline methanesulphonate; Methyl (8*R*,10*R*)-6-propylergolin-8-ylmethyl sulphide methanesulphonate.

Перголида Мезилат

$C_{19}H_{26}N_2S,CH_4O_3S$ = 410.6.

CAS — 66104-22-1 (pergolide); 66104-23-2 (pergolide mesilate).

ATC — N04BC02.

ATC Vet — QN04BC02.

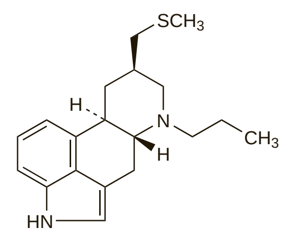

(pergolide)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pergolide Mesilate). A white or almost white crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane; very slightly soluble in acetone; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Pergolide Mesylate). A white to off-white powder. Slightly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Bromocriptine, p.798.

An increased incidence of uterine neoplasms has been reported in *rodents* given high doses of pergolide mesilate.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including pergolide, see under Adverse Effects of Levodopa, p.805.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including pergolide, see under Adverse Effects of Bromocriptine, p.799.

In Australia,[1] Canada,[2], and Europe[3] regulatory authorities recommended that patients undergo a cardiovascular evaluation before starting treatment with pergolide; periodic clinical monitoring for development of valvular disease or fibrosis is also recommended. Doses of pergolide above 3 mg daily are not recommended by the EMEA.[3] Furthermore, use is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment and it is contra-indicated in patients with a history of fibrotic disorders or in those with anatomical evidence of cardiac valvulopathy.[4] In 2007, based on further evidence from 2 studies,[5,6] pergolide was withdrawn from the market in the USA[7] and Canada.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cardiac valvulopathy with pergolide. *Aust Adverse Drug React Bull* 2004; **23:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.pdf (accessed 16/02/06)

2. Shire, Canada. New Safety information regarding Permax and occurrence of cardiac valvulopathy/fibrosis: update on the use of Permax (pergolide mesylate) (issued 12/10/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/shire_permax_2_hpc-cps-eng.pdf (accessed 12/08/08)

3. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)

4. MHRA. Dopamine agonists for Parkinson's disease (issued 30th March 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/DopamineagonistsforParkinson146sdisease/CON2030729 (accessed 03/06/08)

5. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; **356:** 29–38.

6. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; **356:** 39–46.

7. FDA. FDA public health advisory: pergolide (marketed as Permax) (issued 29th March 2007). Available at: http://www.fda.gov/cder/drug/advisory/pergolide.htm (accessed 03/06/08)

8. Eli Lilly, Canada. Health Canada-mandated important safety information on Permax (pergolide mesylate) (issued 10th August 2007). Available at: http://www.lilly.ca/searchable/media/hcp/permax.pdf (accessed 25/06/08)

Interactions

As for Bromocriptine, p.800.

Pharmacokinetics

Pergolide mesilate is absorbed from the gastrointestinal tract. It is reported to be about 90% bound to plasma proteins. It is excreted mainly in the urine in the form of metabolites.

◊ References.

1. Blin O. The pharmacokinetics of pergolide in Parkinson's disease. *Curr Opin Neurol* 2003; **16** (suppl 1): S9–S12.

Uses and Administration

Pergolide mesilate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p.800), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. Pergolide is used in the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK pergolide is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment. Pergolide is given by mouth as the mesilate with doses expressed as the base. Pergolide mesilate 65.3 mg is equivalent to about 50 mg pergolide.

For use as *monotherapy* an initial dose equivalent to 50 micrograms of pergolide is given on the first evening of therapy. The dose is thereafter gradually increased: 50 micrograms twice daily is taken on days 2 to 4, then increased by 100 to 250 micrograms every 3 or 4 days, given in 3 divided doses, up to a daily dose of 1.5 mg at day 28. After day 30, the dose should be increased further by a maximum of 250 micrograms twice a week until an optimum response is achieved. Usual maintenance doses are 2.1 to 2.5 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

For use as *adjunctive therapy* with levodopa, pergolide should be introduced gradually and during this period patients can have their levodopa dosage decreased gradually until an optimum response is achieved. The initial dose of pergolide is the equivalent of 50 micrograms daily for the first 2 days, increased gradually by 100 or 150 micrograms every third day over the next 12 days of therapy. Further increases of 250 micrograms may then be made every third day until an optimum response is achieved. A usual maintenance dose is 3 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p.1798). While bromocriptine has been the main dopamine agonist used pergolide has also been tried.[1]

1. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; **309:** 704–9.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p.2079). Pergolide has been suggested as an alternative to bromocriptine in this condition.

Studies[1-3] of pergolide mesilate in patients with hyperprolactinaemia indicate that single doses reduce serum-prolactin concentrations for more than 24 hours. In most patients, the effective dose was between 50 and 150 micrograms daily. Adverse effects were similar to those seen with bromocriptine, although some patients who could not take bromocriptine were able to tolerate pergolide (and *vice versa*). Pergolide reportedly lost favour for this indication after reports of an increased incidence of uterine neoplasms in *rodents* receiving high doses. However, licensed product information states that no cases of uterine malignancies have to date been reported in humans receiving pergolide. The long-term outcome of treatment of macroprolactinomas with pergolide has been examined in 23 patients,[4] and efficacy and relative safety of pergolide was demonstrated after an average of 27 months (range: 9 to 64 months) treatment.

1. Franks S, *et al.* Treatment of hyperprolactinaemia with pergolide mesylate: acute effects and preliminary evaluation of long-term treatment. *Lancet* 1981; **ii:** 659–61.

2. Franks S, *et al.* Effectiveness of pergolide mesylate in long-term treatment of hyperprolactinaemia. *BMJ* 1983; **286:** 1177–9.

3. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; **309:** 704–9.

4. Freda PU, *et al.* Long-term treatment of prolactin-secreting macroadenomas with pergolide. *J Clin Endocrinol Metab* 2000; **85:** 8–13.

Parkinsonism. Dopamine agonists such as pergolide are often used to begin the treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease. Pergolide has a relatively long duration of action compared with other dopamine agonists commonly used. Although the duration of the clinical antiparkinsonian effect of pergolide remains to be determined, studies suggest it is of the order of 5 to 8 hours. Depending on the dose used the response to other dopamine agonists in late parkinsonism is 1 to 4 hours for levodopa, 2 to 4 hours for lisuride, and 4 to 6 hours for bromocriptine.

References.

1. Anonymous. Pergolide (Celance)—a third dopamine agonist. *Drug Ther Bull* 1991; **29:** 79.

2. Markham A, Benfield P. Pergolide: a review of its pharmacology and therapeutic use in Parkinson's disease. *CNS Drugs* 1997; **7:** 328–40.

3. Barone P, *et al.* Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. *Neurology* 1999; **53:** 573–9.

4. Clarke CE, Speller JM. Pergolide for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews, Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).

5. Clarke CE, Speller JM. Pergolide versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Pergolide has produced some benefit in a number of studies.[1-6] In a randomised placebo-controlled study,[6] therapeutic effects were observed with mean daily doses of pergolide 400 micrograms after 6 weeks and maintained after 12 months with doses of up to 720 micrograms daily.

1. Silber MH, *et al.* Pergolide in the management of restless legs syndrome: an extended study. *Sleep* 1997; **20:** 878–82.

2. Winkelmann J, *et al.* Treatment of restless legs syndrome with pergolide—an open clinical trial. *Mov Disord* 1998; **13:** 566–9.

3. Earley CJ, *et al.* Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998; **51:** 1599–1602.

4. Wetter TC, *et al.*. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999; **52:** 944–50.

5. Stiasny K, *et al.* Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 2001; **56:** 1399–1402.

6. Trenkwalder C, *et al.* Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS study. *Neurology* 2004; **62:** 1391–7.

Tourette's syndrome. Pergolide has been studied in the management of Tourette's syndrome (see Tics, p.954). A preliminary study[1] produced encouraging results, subsequently confirmed by placebo-controlled trials in children and adolescents.[2,3]

1. Lipinski JF, *et al.* Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide. *Mov Disord* 1997; **12:** 402–7.

2. Gilbert DL, *et al.* Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial. *Neurology* 2000; **54:** 1310–15.

3. Gilbert DL, *et al.* Tic reduction with pergolide in a randomized controlled trial in children. *Neurology* 2003; **60:** 606–11.

Preparations

USP 31: Pergolide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aroltex; Breator†; Celance; Geranil†; Parlide†; ***Austral.:*** Permax; ***Austria:*** Permax; ***Belg.:*** Permax; ***Braz.:*** Celance; ***Canad.:*** Permax; ***Chile:*** Celance†; ***Cz.:*** Permax; ***Denm.:*** Permax; ***Fin.:*** Permax; ***Fr.:*** Celance; ***Ger.:*** Parkotil; ***Gr.:*** Celance; ***Hong Kong:*** Celance†; ***Hung.:*** Parkotil†; ***Irl.:*** Celance; ***Ital.:*** Nopar; ***Mex.:*** Permax; ***Neth.:*** Permax; ***NZ:*** Permax; ***Pol.:*** Hizest†; ***Port.:*** Permax; ***S.Afr.:*** Permax; ***Singapore:*** Celance†; ***Spain:*** Pharken; ***Switz.:*** Permax; ***Thai.:*** Celance†; ***Turk.:*** Permax; ***UK:*** Celance; ***USA:*** Permax†.

Piribedil *(rINN)*

ET-495; EU-4200; Piribédil; Piribedilum. 2-(4-Piperonylpiperazin-1-yl)pyrimidine.

Пирибедил

$C_{16}H_{18}N_4O_2$ = 298.3.

CAS — 3605-01-4.

ATC — N04BC08.

ATC Vet — QN04BC08.

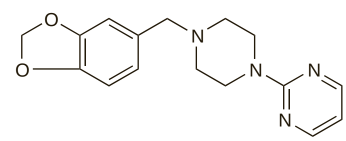

Profile

Piribedil is a non-ergot dopamine agonist that has been given orally in the treatment of parkinsonism and in circulatory disorders. Piribedil mesilate has been given by injection for circulatory disorders. Preparations of piribedil are licensed in some countries for the management of impaired memory and cognitive function in the elderly.

Adverse effects reported include nausea and vomiting, dizziness, hallucinations, confusion, drowsiness, hypothermia, dyskinesias, and occasional changes in liver function.

When used as monotherapy in Parkinson's disease a usual daily oral dose of piribedil is 150 to 250 mg in divided doses; a daily dose of 80 to 140 mg may be suitable when used as an adjunct to levodopa.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including piribedil, see under Adverse Effects of Levodopa, p.805.

Parkinsonism. Piribedil is a dopamine D_2-agonist while its metabolite is reported to act on D_1 receptors. It has been mainly used as an adjunct to levodopa therapy in the treatment of Parkinson's disease (p.791).

References.

1. Montastruc JL, *et al.* Current status of dopamine agonists in Parkinson's disease management. *Drugs* 1993; **46:** 384–93.

2. Montastruc JL, *et al.* A randomized, double-blind study of a skin patch of a dopaminergic agonist, piribedil, in Parkinson's disease. *Mov Disord* 1999; **14:** 336–41.

3. Ziegler M, Rondot P. Activité du piribédil dans la maladie de Parkinson: étude multicentrique. *Presse Med* 1999; **28:** 1414–18.

4. Ziegler M, *et al.* Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized, placebo-controlled study. *Mov Disord* 2003; **18:** 418–25.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Trivastal; ***Braz.:*** Trivastal; ***Fr.:*** Trivastal; ***Ger.:*** Trivastal; ***Gr.:*** Trivastal; ***India:*** Trivastal; ***Ital.:*** Trivastan; ***Malaysia:*** Trivastal; ***Philipp.:*** Trivastal; ***Pol.:*** Pronoran; ***Port.:*** Trivastal; ***Rus.:*** Pronoran (Проноран); ***Singapore:*** Trivastal; ***Thai.:*** Trivastal; ***Turk.:*** Trivastal; ***Venez.:*** Trivastal.

Pramipexole Hydrochloride

(BANM, rINNM)

Hidrocloruro de pramipexol; PNU-98528-E; Pramipexole, Chlorhydrate de; Pramipexole, dichlorhydrate de; Pramipexole Dihydrochloride *(USAN)*; Pramipexoli dihydrochloridum; Pramipexoli Hydrochloridum; SND-919-CL-2Y (pramipexole hydrochloride); SUD-919Y (pramipexole). (*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate.

Прамипексола Гидрохлорид

$C_{10}H_{17}N_3S,2HCl, H_2O = 302.3.$

CAS — 104632-26-0 (pramipexole); 104632-25-9 (anhydrous pramipexole hydrochloride); 191217-81-9 (pramipexole hydrochloride monohydrate).

ATC — N04BC05.

ATC Vet — QN04BC05.

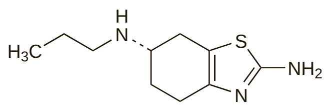

(pramipexole)

Adverse Effects and Precautions

As for Bromocriptine, p.798.

Pramipexole should be used with caution in patients with renal impairment and reduced doses are recommended.

Ophthalmological monitoring is recommended at regular intervals or if vision abnormalities occur.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26:** 439–44.

Effects on mental function. Pramipexole has been associated with attacks of sudden onset of sleep, sometimes without any prior feeling of drowsiness, that can occur at any time during treatment. Licensed product information states that the incidence of daytime **somnolence** is increased at daily doses of pramipexole hydrochloride higher than 1.5 mg. A retrospective analysis[1] of data to evaluate the incidence and nature of somnolence in patients receiving pramipexole in clinical studies showed that for patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean daily dose of around 4 mg (range: 0.75 to 4.5 mg).

For further reports of daytime somnolence occurring in patients receiving dopamine agonists including pramipexole, see under Adverse Effects of Levodopa, p.805.

For reference to **pathological gambling** reported in patients with Parkinson's disease receiving dopamine agonists, including pramipexole, see under Levodopa, p.805.

1. Hauser RA, *et al.* Pramipexole-induced somnolence and episodes of daytime sleep. *Mov Disord* 2000; **15:** 658–63.

Interactions

As for Bromocriptine, p.800. Cimetidine is reported to reduce the renal clearance of pramipexole.

Caution is advised when other sedating drugs or alcohol are used with pramipexole because of possible additive effects and the risk of precipitating sudden onset of sleep (see above).

◊ References.

1. Wright CE, *et al.* Influence of probenecid and cimetidine on pramipexole pharmacokinetics. *Clin Pharmacol Ther* 1996; **59:** 183.

Pharmacokinetics

Pramipexole is readily absorbed from the gastrointestinal tract and peak plasma concentrations have been reached within about 2 hours in fasting patients and in about 3 hours when given with food. Oral bioavailability is reported to be about 90%. Pramipexole is widely distributed throughout the body and plasma-protein binding is less than 20%. Metabolism is minimal and more than 90% of a dose is excreted via renal tubular secretion unchanged into the urine. Elimination half-lives of 8 to 12 hours have been reported. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

◊ References.

1. Wright CE, *et al.* Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. *J Clin Pharmacol* 1997; **37:** 520–5.

Uses and Administration

Pramipexole is a non-ergot dopamine agonist with actions similar to those of bromocriptine (p.800). It is used similarly in the management of Parkinson's disease, either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response. Pramipexole is also used for the treatment of moderate to severe restless legs syndrome. It is given orally as the hydrochloride; doses have been described in terms of the hydrochloride (as below) or of the base. In terms of equivalency:

- pramipexole hydrochloride 125 micrograms is equivalent to about 88 micrograms of pramipexole
- pramipexole hydrochloride 250 micrograms is equivalent to about 180 micrograms of pramipexole
- pramipexole hydrochloride 500 micrograms is equivalent to about 350 micrograms of pramipexole
- pramipexole hydrochloride 1 mg is equivalent to about 700 micrograms of pramipexole

In the treatment of **Parkinson's disease**, the dose of pramipexole should be increased gradually and the dose of levodopa gradually reduced during the dose-titration and maintenance phases until an optimum response is achieved. The initial dose of pramipexole *hydrochloride* is 125 micrograms three times daily increased to 250 micrograms three times daily in the second week and then to 500 micrograms three times daily in the third week according to response. Thereafter the daily dose may be increased if necessary by 750 micrograms at weekly intervals to a maximum of 4.5 mg daily. The dosage should be reduced in patients with renal impairment (see below).

If it is necessary to stop pramipexole therapy, it should be withdrawn gradually. UK licensed product information suggests tapering off the dose of pramipexole hydrochloride at a rate of 750 micrograms daily until a daily dose of 750 micrograms has been reached; thereafter, the dose should be reduced by 375 micrograms daily. US licensed product information suggests that withdrawal should be gradual over a period of 1 week.

Pramipexole is also given as a single daily dose, 2 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of pramipexole *hydrochloride* is 125 micrograms daily. This may be increased if necessary after 4 to 7 days to 250 micrograms daily. Subsequent doses may be increased if necessary by 250 micrograms every 4 to 7 days to a maximum of 750 micrograms daily. Response to therapy should be evaluated after 3 months; if treatment is interrupted for more than a few days, it should be restarted at 125 micrograms daily, and then increased, if required, as described above. For this indication, pramipexole may be withdrawn without gradual tapering of the dose.

Administration in renal impairment. The elimination of pramipexole is dependent on renal function and the dosage of pramipexole hydrochloride should therefore be reduced in patients with renal impairment.

In the treatment of *Parkinson's disease*, the following dosage schedule has been suggested in UK licensed product information for initial therapy adjusted according to the patient's creatinine clearance (CC):

- CC 20 to 50 mL/minute: 125 micrograms given twice daily
- CC less than 20 mL/minute: 125 micrograms once daily

Similar reductions are suggested in US licensed information for patients with a CC of 35 to 59 mL/minute and 15 to 34 mL/minute, respectively.

If renal function declines during maintenance therapy it is recommended that the daily dose of pramipexole should be reduced by the same percentage as the decline in CC.

Lower doses are used in the treatment of *restless legs syndrome* and UK licensed information considers dosage reductions unnecessary in patients with CC of more than 20 mL/minute. US licensed information recommends that the interval between titration steps is increased to 14 days in those patients with CC of 20 to 60 mL/minute.

Parkinsonism. Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease (p.791) as an adjunct to levodopa therapy to reduce 'off' periods with levodopa and ameliorate other fluctuations of mobility in the later stages of the disease. It is also used as monotherapy early in the course of the disease in an attempt to delay therapy with levodopa.

References.

1. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease: a randomized dose-ranging study. *JAMA* 1997; **278:** 125–30.
2. Lieberman A, *et al.* Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* 1997; **49:** 162–8.
3. Shannon KM, *et al.* Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997; **49:** 724–8.
4. Guttman M. International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997; **49:** 1060–5.
5. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000; **284:** 1931–8.
6. Clarke CE, *et al.* Pramipexole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
7. Clarke CE, *et al.* Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
8. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 2004; **61:** 1044–53. Correction. *ibid.* 2005; **62:** 430.
9. Moller JC, *et al.* Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord* 2005; **20:** 602–10.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical, although dopaminergic therapy has emerged as a common first-line choice. Low-dose pramipexole has produced some benefit in a number of studies[1-7] and is licensed for the treatment of moderate to severe RLS in some countries.

1. Lin S-C, *et al.* Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin Proc* 1998; **73:** 497–500.
2. Montplaisir J, *et al.* Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999; **52:** 938–43.
3. Montplaisir J, *et al.* Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* 2000; **7** (suppl 1): 27–31.
4. Saletu M, *et al.* Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci* 2002; **252:** 185–94.
5. Silber MH, *et al.* Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* 2003; **26:** 819–21.
6. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. *Neuropsychobiology* 2004; **50:** 65–70.
7. Winkelman JW, *et al.* Efficacy and safety of pramipexole in restless legs syndrome. *Neurology* 2006; **67:** 1034–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Maxtenk; Mirapex†; Nixol; Parfeno; Parxium; Portiv; Sifrol; ***Austral.:*** Sifrol; ***Austria:*** Sifrol; ***Belg.:*** Mirapexin; ***Braz.:*** Mirapex; Sifrol; ***Canad.:*** Mirapex; ***Chile:*** Sifrol; ***Cz.:*** Mirapexin; Sifrol; ***Denm.:*** Mirapexin; Sifrol; ***Fin.:*** Sifrol; ***Fr.:*** Sifrol; ***Ger.:*** Sifrol; ***Gr.:*** Mirapexin; ***Hung.:*** Mirapexin; ***Indon.:*** Sifrol; ***Irl.:*** Mirapexin; ***Ital.:*** Mirapexin; ***Jpn:*** BI-Sifrol; ***Malaysia:*** Sifrol; ***Mex.:*** Sifrol; ***Neth.:*** Daquiran†; Sifrol; ***Norw.:*** Sifrol; ***NZ:*** Sifrol; ***Philipp.:*** Sifrol; ***Pol.:*** Mirapexin; ***Port.:*** Mirapexin; Sifrol; ***Rus.:*** Mirapex (Мирапекс); ***S.Afr.:*** Pexola; ***Singapore:*** Sifrol; ***Spain:*** Mirapexin; ***Swed.:*** Sifrol; ***Switz.:*** Sifrol; ***Thai.:*** Sifrol; ***Turk.:*** Pexola; ***UK:*** Mirapexin; ***USA:*** Mirapex; ***Venez.:*** Sifrol/Mirapex.

Procyclidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de prociclidina; Procyclidine, Chlorhydrate de; Procyclidini Hydrochloridum. 1-Cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)propan-1-ol hydrochloride.

Проциклидина Гидрохлорид

$C_{19}H_{29}NO,HCl = 323.9.$

CAS — 77-37-2 (procyclidine); 1508-76-5 (procyclidine hydrochloride).

ATC — N04AA04.

ATC Vet — QN04AA04.

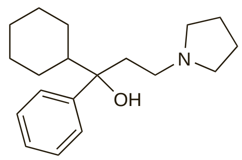

(procyclidine)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Procyclidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 6.5.

USP 31 (Procyclidine Hydrochloride). A white crystalline powder, having a moderate characteristic odour. Soluble 1 in 35 of water, 1 in 9 of alcohol, 1 in 6 of chloroform, and 1 in 11 000 of ether; insoluble in acetone. pH of a 1% solution in water is between 5.0 and 6.5. Store in a dry place in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Psychotic episodes may be precipitated in patients with mental disorders when procyclidine is used for the treatment of drug-induced extrapyramidal syndrome.

Abuse. Like other antimuscarinics (see also under Trihexyphenidyl Hydrochloride, p.820) procyclidine has been abused for its euphoriant effects.[1,2]

1. McGucken RB, *et al.* Teenage procyclidine abuse. *Lancet* 1985; **i:** 1514.
2. Dooris B, Reid C. Feigning dystonia to feed an unusual drug addiction. *J Accid Emerg Med* 2000; **17:** 311.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Paroxetine increases plasma-procyclidine concentrations and it is recommended that the dose of procyclidine should be reduced if antimuscarinic effects are seen in patients receiving both drugs.

Pharmacokinetics

Procyclidine hydrochloride is absorbed from the gastrointestinal tract and bioavailability has been reported to be 75% after oral doses; it disappears rapidly from the tissues. Procyclidine given intravenously acts within 5 to 20 minutes and has a duration of effect of up to 4 hours. The mean plasma elimination half-life after oral or intravenous doses is about 12 hours. About one-fifth of an oral dose is metabolised in the liver, mainly by the cytochrome P450 isoenzymes, followed by conjugation with glucuronic acid. A small amount of unchanged drug is excreted in the urine.

◊ References.

1. Whiteman PD, *et al.* Pharmacokinetics and pharmacodynamics of procyclidine in man. *Eur J Clin Pharmacol* 1985; **28:** 73–8.

Uses and Administration

Procyclidine hydrochloride is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It is used for the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias (but see under Uses and Administration of Levodopa, p.809).

In **parkinsonism**, the initial oral dose of 2.5 mg three times daily may be increased gradually by 2.5 to 5 mg every 2 or 3 days (or by 2.5 mg daily if used for drug-induced extrapyramidal syndrome) until the optimum maintenance dose, usually 10 to 30 mg daily in 3 (or occasionally 4) divided doses, is reached; daily doses of up to 60 mg have occasionally been required. As a rule, postencephalitic patients tolerate and require the larger doses; elderly and arteriosclerotic patients may require smaller doses.

In emergency, 5 to 10 mg may be given by intravenous injection; higher doses have sometimes been used. The intramuscular route has also been employed: 5 to 10 mg may be given as a single injection, repeated if necessary after 20 minutes to a maximum of 20 mg daily. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Although not licensed in the UK for management of **dystonias in children**, the *BNFC* suggests oral doses of 1.25 mg 3 times daily in those aged 7 to 12 years, and 2.5 mg 3 times daily in those aged 12 to 18 years. In an emergency, a single dose may be given by intramuscular or intravenous injection to children as follows: aged under 2 years, 0.5 to 2 mg; 2 to 10 years, 2 to 5 mg; 10 to 18 years, 5 to 10 mg or occasionally more.

Preparations

BP 2008: Procyclidine Injection; Procyclidine Tablets;
USP 31: Procyclidine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Kemadrin; ***Belg.:*** Kemadrin; ***Canad.:*** Kemadrin†; Procyclid†; ***Cz.:*** Kemadrin; ***Denm.:*** Kemadrin; ***Ger.:*** Osnervan; ***Hung.:*** Kemadrin; ***India:*** Kemadrin; ***Irl.:*** Kemadrin; ***Israel:*** Kemadrin; ***Ital.:*** Kemadrin†; ***Malaysia:*** Kemadrin†; ***NZ:*** Kemadrin; ***Spain:*** Kemadren; ***Switz.:*** Kemadrin; ***UK:*** Arpicolin; Kemadrin; Muscinil†; ***USA:*** Kemadrin.

Profenamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Profenamina; Ethopropazine Hydrochloride; Hidrocloruro de profenamina; Isothazine Hydrochloride; Profénamine, Chlorhydrate de; Profenamini Hydrochloridum; Prophenamini Chloridum. 10-(2-Diethylaminopropyl)phenothiazine hydrochloride.

Профенамина Гидрохлорид

$C_{19}H_{24}N_2S,HCl = 348.9.$

CAS — 522-00-9 (profenamine); 1094-08-2 (profenamine hydrochloride).

ATC — N04AA05.

ATC Vet — QN04AA05.

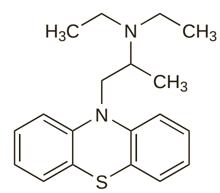

(profenamine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Profenamine may also cause muscle cramps, paraesthesia, and a sense of heaviness in the limbs, epigastric discomfort, and nausea.

Profenamine is a phenothiazine derivative; adverse effects associated with phenothiazines may occur, especially with high doses (see under Chlorpromazine, p.969).

Breast feeding. Profenamine is distributed into the milk of lactating mothers.[1]

1. Rowan JJ. Excretion of drugs in milk. *Pharm J* 1976; **217:** 184–7.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Profenamine hydrochloride is a phenothiazine derivative with antimuscarinic, adrenergic-blocking, antihistaminic, local anaesthetic, and ganglion-blocking properties. It has been used in the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as other phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in a usual initial oral dose of 50 mg three times daily, gradually increased to 500 mg or more daily in divided doses, according to response.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Parsitan.

Rasagiline Mesilate *(rINNM)*

Mesilato de rasagilina; Rasagiline, Mésilate de; Rasagiline Mesylate *(USAN)*; Rasagilini Mesilas; TVP-1012. (*R*)-*N*-2-Propynyl-1-indanamine methanesulfonate.

Разагилина Мезилат

$C_{12}H_{13}N,CH_4O_3S = 267.3.$

CAS — 136236-51-6 (rasagiline); 161735-79-1 (rasagiline mesilate).

ATC — N04BD02.

ATC Vet — QN04BD02.

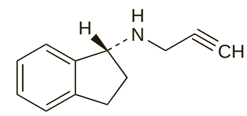

(rasagiline)

Adverse Effects and Precautions

Common adverse effects reported with rasagiline monotherapy include headache, flu-like syndrome, malaise, neck pain, angina pectoris, dyspepsia, anorexia, leucopenia, arthralgia, arthritis, depression, vertigo, rhinitis, conjunctivitis, skin rashes, melanoma, and urinary urgency. Cerebrovascular accidents and myocardial infarction have been reported rarely. Other adverse effects include orthostatic hypotension and hallucinations.

Rasagiline should not be used in patients with severe hepatic impairment; use in moderate impairment should also be avoided. It should be used with caution in patients with mild hepatic impairment and therapy should be stopped in those who progress to moderate impairment.

Interactions

As for Selegiline Hydrochloride, p.817. Unlike the non-selective MAOIs, such as phenelzine, rasagiline can be used safely without dietary tyramine restrictions, although these have been recommended in some countries.

Rasagiline should not be given with other MAOIs because of the risk of non-selective MAO inhibition that may lead to hypertensive reactions.

It is metabolised by the cytochrome P450 isoenzyme CYP1A2 and potent inhibitors of this enzyme such as ciprofloxacin may increase the plasma levels of rasagiline. UK licensed product information for rasagiline advises caution when such drugs are used with rasagiline whereas US licensed product information recommends that the dose of rasagiline be reduced to 0.5 mg daily when given with CYP1A2 inhibitors. Tobacco smoking induces hepatic metabolic enzymes and may decrease the plasma levels of rasagiline.

Entacapone has been reported to increase the clearance of oral rasagiline by 28% when used together.

Pharmacokinetics

Rasagiline is rapidly absorbed from the gastrointestinal tract, with peak plasma levels occurring in about 30 minutes to an hour. Bioavailability is reported to be about 36%. Rasagiline is about 60 to 70% bound to plasma proteins.

It is extensively metabolised in the liver by *N*-dealkylation and hydroxylation, via the cytochrome P450 isoenzyme CYP1A2, and conjugation. 1-Aminoindan is a major metabolite and is stated to be active although it is not a monoamine oxidase B inhibitor. Metabolites are excreted mainly in the urine and partly in the faeces; less than 1% of a dose is excreted as unchanged drug in the urine. The terminal half-life is 0.6 to 2 hours.

Uses and Administration

Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease (p.791), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' fluctuations in response. Rasagiline is given orally as the mesilate and doses are expressed in terms of the base; rasagiline mesilate 1.56 mg is equivalent to about 1 mg of rasagiline. The usual dose is the equivalent of rasagiline 1 mg once daily. In the USA, an initial daily dose of 0.5 mg is recommended for adjunctive therapy.

The dose of rasagiline may need to be reduced when given with drugs that inhibit the cytochrome P450 isoenzyme CYP1A2 (see Interactions, above for details) and in patients with hepatic impairment (see below).

◊ References.

1. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 2002; **59:** 1937–43.
2. Stern MB, *et al.* Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord* 2004; **19:** 916–23.
3. Thebault JJ, *et al.* Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. *Pharmacotherapy* 2004; **24:** 1295–1305.
4. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol* 2004; **61:** 561–6.

5. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005; **62:** 241–8.
6. Rascol O, *et al.* Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 2005; **365:** 947–54.
7. Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease: a review. *Expert Opin Pharmacother* 2005; **6:** 2061–75.
8. Chen JJ, *et al.* Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol* 2005; **45:** 878–94.
9. Siderowf A, Stern M. Clinical trials with rasagiline: evidence for short-term and long-term effects. *Neurology* 2006; **66** (suppl 4): S80–S88.
10. Oldfield V, *et al.* Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007; **67:** 1725–47.

Administration in hepatic impairment. UK licensed product information for rasagiline advises caution when used in patients with mild hepatic impairment whereas US licensed information recommends that the dose be reduced to 500 micrograms daily. Rasagiline should not be used in those with moderate or severe impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Elbrus; ***Belg.:*** Azilect; ***Cz.:*** Azilect; ***Denm.:*** Azilect; ***Fin.:*** Azilect; ***Fr.:*** Azilect; ***Ger.:*** Azilect; ***Gr.:*** Azilect; ***Irl.:*** Azilect; ***Israel:*** Azilect; ***Neth.:*** Azilect; ***Norw.:*** Azilect; ***Pol.:*** Azilect; ***Port.:*** Azilect; ***Spain:*** Azilect; ***UK:*** Azilect; ***USA:*** Azilect.

Ropinirole Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de ropinirol; Ropinirole, Chlorhydrate de; Ropiniroli Hydrochloridum; SKF-101468 (ropinirole); SKF-0101468-A (ropinirole hydrochloride). 4-[2-(Dipropylamino)ethyl]-2-indolinone hydrochloride.

Ропинирола Гидрохлорид

$C_{16}H_{24}N_2O,HCl = 296.8.$

CAS — 91374-21-9 (ropinirole); 91374-20-8 (ropinirole hydrochloride).

ATC — N04BC04.

ATC Vet — QN04BC04.

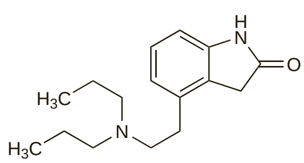

(ropinirole)

Adverse Effects and Precautions

As for Bromocriptine, p.798. Licensed product information states that the pharmacokinetics of ropinirole have not been studied in patients with hepatic or severe renal impairment and therefore it should be used with caution, if at all, in such patients. No pharmacokinetic changes were noted in those with mild to moderate renal impairment.

In the treatment of restless legs syndrome, earlier onset of symptoms in the afternoon or evening (augmentation) and recurrence of symptoms in the early morning hours (rebound) have been reported with ropinirole.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26:** 439–44.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including ropinirole, see under Adverse Effects of Levodopa, p.805.

Interactions

Since it is a dopamine agonist, ropinirole may share some of the pharmacological interactions of bromocriptine, p.800. In addition, high doses of oestrogens can increase plasma concentrations of ropinirole and dosage adjustments may be necessary if oestrogen therapy is started or withdrawn during treatment with ropinirole. Ropinirole is metabolised by the cytochrome P450 isoenzyme CYP1A2 and there is therefore the potential for interactions between ropinirole and other drugs that are metabolised similarly or more particularly with inducers or inhibitors of this enzyme. Dosage adjustments may be necessary if therapy with such drugs is started or withdrawn during treatment with ropinirole.

Pharmacokinetics

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have been achieved 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food. Bioavailability is reported to be about 50%. It is widely distributed throughout the body and plasma protein binding is low (10 to 40%).

Ropinirole is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP1A2, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported for ropinirole. It is thought to be distributed into breast milk on the basis of studies in *rats*.

◊ References.

1. Brefel C, *et al.* Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* 1998; **45:** 412–15.
2. Hubble J, *et al.* Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. *J Clin Pharmacol* 2000; **40:** 641–6.
3. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* 2000; **39:** 243–54.

Uses and Administration

Ropinirole is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p.800), but in contrast to bromocriptine it also has agonist properties at D_3 receptors. It is used similarly in the management of Parkinson's disease, either alone or as an adjunct to reduce 'on-off' fluctuations in levodopa response. Ropinirole is also used for the treatment of moderate to severe idiopathic restless legs syndrome. It is given by mouth as the hydrochloride; doses are expressed in terms of the base. Ropinirole hydrochloride 1.14 mg is equivalent to about 1 mg of ropinirole.

In the treatment of **Parkinson's disease**, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over the period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets.

Ropinirole is also given as a single daily dose, 1 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of ropinirole is 250 micrograms daily for 2 days; if tolerated, the dose is then increased to 500 micrograms daily for the rest of the first week. Subsequent increases may be made in weekly steps of 500 micrograms until a dose of 3 mg daily is reached; if necessary, the dose may then be increased after 1 further week to a maximum of 4 mg daily.

In the UK, it has been recommended that treatment should be re-assessed 3 months after starting therapy. For this indication, ropinirole may be withdrawn without gradual tapering of the dose.

If treatment with ropinirole is interrupted for more than a few days it should be restarted at the low initial dose and increased gradually as required.

◊ Reviews.

1. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; **49** (suppl 1): S58–S62.

Parkinsonism. Dopamine agonists such as ropinirole may be used to begin treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease.

References.

1. Rascol O, *et al.* A placebo-controlled study of ropinirole a new D agonist, in the treatment of motor fluctuations of -DOPA-treated parkinsonian patients. *Adv Neurol* 1996; **69:** 531–4.
2. Adler CH, *et al.* The Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49:** 393–9.
3. Rascol O, *et al.* Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13:** 39–45.
4. Korczyn AD, *et al.* A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53:** 364–70.
5. Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. *Drugs* 2000; **60:** 115–37.
6. Clarke CE, Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane KHO. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Whone AL, *et al.* Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54:** 93–101.
9. Pahwa R, *et al.* Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007; **68:** 1108–15.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Ropinirole is licensed for the treatment of moderate to severe RLS in some countries.

References.

1. Trenkwalder C, *et al.* Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004; **75:** 92–7.
2. Cheer SM, *et al.* Ropinirole: for the treatment of restless legs syndrome. *CNS Drugs* 2004; **18:** 747–54.
3. Walters AS, *et al.* Ropinirole is effective in the treatment of restless legs syndrome—TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004; **19:** 1414–23.
4. Bogan RK, *et al.* TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81:** 17–27.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Requip; ***Austral.:*** Repreve; ***Austria:*** Requip; ***Belg.:*** Requip; ***Canad.:*** Requip; ***Chile:*** Requip; ***Cz.:*** Adartrel; Requip; ***Denm.:*** Requip; ***Fin.:*** Requip; ***Fr.:*** Adartrel; Requip; ***Ger.:*** Requip; ***Gr.:*** Adartrel; Requip; ***Hong Kong:*** Requip; ***Hung.:*** Requip; ***Irl.:*** Requip; ***Israel:*** Requip; ***Ital.:*** Requip; ***Malaysia:*** Requip; ***Neth.:*** Requip; ***Norw.:*** Requip; ***NZ:*** Requip; ***Pol.:*** Requip; ***Port.:*** Requip; Zyatrol; ***S.Afr.:*** Requip; ***Singapore:*** Requip; ***Spain:*** Requip; ***Swed.:*** Requip; ***Switz.:*** Adartrel; Requip; ***Turk.:*** Requip; ***UK:*** Adartrel; Requip; ***USA:*** Requip.

Rotigotine *(USAN, rINN)*

N-0923; Rotigotina; Rotigotinum; SPM-962. (−)-(S)-5,6,7,8-Tetrahydro-6-{propyl[2-(2-thienyl)ethyl]amino}-1-naphthol.

Ротиготин

$C_{19}H_{25}NOS = 315.5.$

CAS — 99755-59-6 (rotigotine); 125572-93-2 (rotigotine hydrochloride).

ATC — N04BC09.

ATC Vet — QN04BC09.

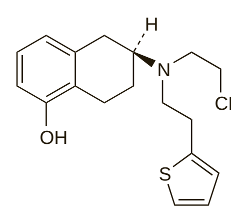

Adverse Effects and Precautions

As for Bromocriptine, p.798. Reactions may occur at the site of application and are usually mild or moderate in intensity. The site should be rotated on a daily basis and the same site should not be used within 14 days.

Licensed product information recommends that rotigotine should be used with caution in patients with severe hepatic impairment and reduced doses may be necessary in cases of worsening impairment; however, this is based on a lack of evidence in such patients.

Interactions

Since it is a dopamine agonist, rotigotine may share some of the pharmacological interactions of bromocriptine, p.800.

Caution is advised when other sedating drugs or alcohol are used with rotigotine because of possible additive effects.

Pharmacokinetics

Rotigotine has poor oral bioavailability as it undergoes extensive first-pass metabolism via glucuronidation in the gut wall and liver. Peak plasma concentrations are achieved 24 hours after transdermal application. Steady-state concentrations are reached after 24 to 48 hours of continuous daily application. It undergoes *N*-dealkylation and conjugation to form inactive metabolites. Rotigotine is excreted mainly in the urine and about 23% appears in the faeces. The elimination half-life is 5 to 7 hours. It is distributed into milk of *rats*.

Uses and Administration

Rotigotine is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p.798), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. It is used as monotherapy in the management of Parkinson's disease (p.791), mainly in the early stage. It may also be used as an adjunct to levodopa therapy. Rotigotine is given as transdermal patches delivering amounts ranging from 2 to 8 mg per 24 hours.

When given as *monotherapy*, the initial dose is 2 mg daily, increased in weekly steps of 2 mg if necessary to a maximum of 8 mg daily.

Rotigotine may also be used as *adjunctive therapy* with levodopa in an initial dose of 4 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 16 mg daily.

Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Treatment with rotigotine should be withdrawn gradually; the daily dose should be reduced in steps of 2 mg every other day until complete withdrawal is achieved.

Rotigotine is also being studied as a transdermal preparation in the treatment of restless legs syndrome.

◊ References.

1. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003; **60:** 1721–8.
2. Stiasny-Kolster K, *et al.* Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov Disord* 2004; **19:** 1432–8.
3. Poewe W, Leussi F. Clinical studies with transdermal rotigotine in early Parkinson's disease. *Neurology* 2005; **65** (suppl 1): S11–S14. Correction. *ibid.*; 1328.
4. Watts RL, *et al.* Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 2007; **68:** 272–6. Correction. *ibid.*; **69:** 617.
5. Splinter MY. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. *Ann Pharmacother* 2007; **41:** 285–95.
6. LeWitt PA, *et al.* Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 2007; **68:** 1262–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Neupro; ***Gr.:*** Neupro; ***Pol.:*** Neupro; ***Port.:*** Neupro; ***UK:*** Neupro; ***USA:*** Neupro†.

Selegiline Hydrochloride

(BANM, USAN, rINNM) ⊗

Deprenyl; L-Deprenyl; Hidrocloruro de selegilina; Selegiliinihydrokloridi; Selegilin Hidroklorür; Selegilin hydrochlorid; Sélégiline, chlorhydrate de; Selegilinhydroklorid; Selegilini hydrochloridum; Selegilino hidrochloridas; Szelegilin-hidroklorid. (−)-(*R*)-*N*,α-Dimethyl-*N*-(prop-2-ynyl)phenethylamine hydrochloride; (*R*)-Methyl(α-methylphenethyl)prop-2-ynylamine hydrochloride.

Селегилина Гидрохлорид

$C_{13}H_{17}N,HCl = 223.7.$

CAS — 14611-51-9 (selegiline); 2079-54-1 (selegiline hydrochloride); 14611-52-0 (selegiline hydrochloride).

ATC — N04BD01.

ATC Vet — QN04BD01.

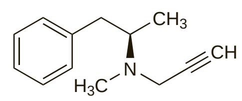

(selegiline)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Selegiline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in acetone. A 2% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 31 (Selegiline Hydrochloride). A white, odourless crystalline powder. Freely soluble in water, in chloroform, and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects

Selegiline is often given as an adjunct to levodopa therapy and many of the adverse effects reported may be attributed to enhanced levodopa activity; dosage of levodopa may have to be reduced. However, most reported adverse effects, with the possible exception of increased dyskinesias and cardiac arrhythmias, have also been seen with selegiline monotherapy. Adverse effects have included orthostatic hypotension, chest pain, nausea, vomiting, constipation, diarrhoea, confusion, headache, tremor, vertigo, dizziness, psychosis, depression, hallucinations, agitation, dry mouth, sore throat, difficulty in micturition, skin reactions, back pain, muscle cramps, joint pain, and myopathy. The amfetamine metabolites of selegiline may cause insomnia and abnormal dreams; evening doses should be avoided. Transient increases in liver enzymes have been reported. Mouth ulcers and stomatitis may occur with the oral lyophilisate.

Since the selectivity of selegiline is lost at higher doses, signs and symptoms of overdosage may resemble those of non-selective MAOIs such as phenelzine (see p.415).

Effects on carbohydrate metabolism. Profound hypoglycaemia developed in a 70-year-old man after selegiline was added to his existing medication for Parkinson's disease.[1] Hypoglycaemia was accompanied by hyperinsulinaemia and resolved 1 week after stopping selegiline.

1. Rowland MJ, *et al.* Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J Clin Pharmacol* 1994; **34:** 80–5.

Effects on mortality. For reference to a study which observed an increased mortality rate in patients with Parkinson's disease taking selegiline and levodopa compared with those taking levodopa alone, see Parkinsonism under Uses and Administration, below.

Precautions

Selegiline should be used with caution in patients with a history of peptic ulceration and avoided in those with active ulceration. It should also be used with caution in uncontrolled hypertension, arrhythmias, angina, severe liver or kidney dysfunction, or psychosis.

Cardiovascular disorders. An investigation[1] of the autonomic effects of selegiline as a potential cause of the unexpected mortality observed in a study[2] in patients with Parkinson's disease receiving selegiline and levodopa (see Parkinsonism, below) suggested that the risk of orthostatic hypotension with this combination may have been underestimated. It was considered prudent to withdraw selegiline from those with symptomatic orthostatic hypotension or cardiovascular or cerebrovascular disease. For those without symptomatic morbidity, but a greater than 20 mmHg fall in blood pressure on standing for 2 minutes, gradual withdrawal of selegiline with adjustment of levodopa dosage should be considered.

1. Churchyard A, *et al.* Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **63:** 228–34.
2. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.

Interactions

Selegiline is less likely than non-selective MAOIs, such as phenelzine, to interact with tyramine in food; such hypertensive reactions have been reported rarely at usual doses but UK licensed product information for oral formulations states that its selectivity is lost at higher doses and it must be assumed that selegiline can usually only be used safely without dietary restrictions at doses of up to 10 mg daily. US licensed information for the transdermal preparation states that dietary restrictions are necessary at doses of 9 mg daily and above. For dietary restrictions applicable to patients taking MAOIs, see p.417.

Even when given in therapeutic doses life-threatening interactions can occur between selegiline and pethidine. Serious reactions, sometimes fatal, have also been reported when selegiline was used with tricyclic antidepressants or serotonin reuptake inhibitors including the SSRIs and venlafaxine. Licensed drug information states that 14 days should elapse between stopping selegiline and starting treatment with tricyclic or serotonergic antidepressants. Conversely, selegiline should not be given to patients who have recently received these antidepressants; at least 5 weeks should elapse between stopping fluoxetine and starting treatment with selegiline. Use of selegiline with non-selective MAOIs may cause severe hypotension and such use is not recommended.

Antidepressants. Although there have been studies in which patients with parkinsonism have received selegiline with *SSRIs* such as fluoxetine[1] or paroxetine[2] (apparently without any problems) there have been reports of reactions[3-5] such as shivering and sweating, hypertension, hyperactivity, and ataxia occurring when selegiline and fluoxetine have been used together. The FDA noted[6] that reactions similar to those between SSRIs and non-selective MAOIs had also been reported in patients taking selegiline with paroxetine or sertraline.

Severe reactions, sometimes fatal, have also occurred in patients taking selegiline and *tricyclic antidepressants*.[6] For a report of serotonin syndrome developing when *venlafaxine* was given after selegiline (despite a drug-free period) see p.429.

There has been a report[7] of a patient receiving the non-selective MAOI *iproniazid* who experienced severe orthostatic hypotension when given selegiline. Selegiline given with the reversible MAOI *moclobemide* to healthy subjects markedly increased the pressor response to tyramine compared with the effects of each drug used alone.[8] The authors concluded that dietary restriction of tyramine-containing foods would be necessary if these drugs were to be used together.

One UK manufacturer (*Cephalon, UK*) states that oral selegiline should not be given with any type of antidepressant, while another (*Orion, UK*) advises that use with SSRIs or venlafaxine be avoided and recommends caution when used with the tricyclics. The US manufacturer of transdermal selegiline (*Bristol-Myers Squibb, USA*), used for depression, states that use with other antidepressants such as *bupropion*, *mirtazapine*, serotonin reuptake inhibitors, *St John's wort*, and tricyclics is contra-indicated.

1. Waters CH. Fluoxetine and selegiline—lack of significant interaction. *Can J Neurol Sci* 1994; **21:** 259–61.
2. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* 1994; **28:** 405–6.
3. Suchowersky O, de Vries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990; **35:** 571–2.
4. Jermain DM, *et al.* Potential fluoxetine-selegiline interaction. *Ann Pharmacother* 1992; **26:** 1300.
5. Montastruc JL, *et al.* Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* 1993; **341:** 555.
6. Anonymous. Eldepryl and antidepressant interaction. *FDA Med Bull* 1995; **25** (Feb.): 6.
7. Pare CMB, *et al.* Attempts to attenuate the 'cheese effect': combined drug therapy in depressive illness. *J Affect Disord* 1985; **9:** 137–41.
8. Korn A, *et al.* Tyramine pressor sensitivity in healthy subjects during combined treatment with moclobemide and selegiline. *Eur J Clin Pharmacol* 1996; **49:** 273–8.

Antimigraine drugs. Some serotonin agonists including *rizatriptan*, *sumatriptan*, and *zolmitriptan* are metabolised via monoamine oxidase type A and therefore it is considered unlikely that selegiline, a monoamine oxidase type B inhibitor, would interact with these drugs. Nevertheless, one manufacturer (*Cephalon, UK*) of oral selegiline contra-indicates its use in patients also receiving serotonin agonists; it is also recommended that at least 24 hours should elapse between stopping selegiline and starting treatment with these drugs.

Opioid analgesics. Selegiline can produce life-threatening reactions when given with *pethidine*.[1]

Some manufacturers contra-indicate use of selegiline with pethidine and other opioid analgesics such as *dextropropoxyphene*, *methadone*, and *tramadol*.

1. Zornberg GL, *et al*. Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337:** 246. Correction. *ibid.*; 440.

Oral contraceptives. The total area under the concentration-time curve for selegiline given in single doses of 5 to 40 mg was raised ten- to twentyfold in 4 women who were using oral hormonal contraceptives when compared with 4 women receiving no other medication.[1] It was suggested that use of selegiline and oral hormonal contraceptives should be avoided or the dosage of selegiline reduced.

1. Laine K, *et al.* Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol* 1999; **47:** 249–54.

Sympathomimetics. Licensed information for a US product (*Eldepryl; Somerset, USA*) states that there has been a report of hypertensive crisis in a patient taking recommended doses of selegiline and *ephedrine*. A hypertensive reaction after low-dose *dopamine* infusion has been reported[1] in a 75-year-old patient taking selegiline 10 mg daily for Parkinson's disease. The authors suggest that this may indicate a non-specific action of selegiline at usual doses on peripheral monoamine oxidase type-A. UK licensed product information states that dopamine should be used with caution in patients taking selegiline.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Pharmacokinetics

Selegiline is readily absorbed from the gastrointestinal tract and peak plasma concentrations are achieved in 30 minutes after oral doses of conventional preparations. Although subject to large interindividual variation, bioavailability is about 10% and is increased when given with food. Selegiline is rapidly distributed throughout the body and crosses the blood-brain barrier. It undergoes extensive first-pass metabolism in the liver to produce at least 5 metabolites, including *l*-(−)-desmethylselegiline (norselegiline), *l*-(−)-*N*-methylamfetamine, and *l*-(−)-amfetamine. Plasma concentrations of selegiline metabolites are greatly reduced after doses of the oral lyophilisate preparation, the majority of which undergoes absorption through the buccal mucosa. Selegiline is excreted as metabolites mainly in the urine and about 15% appears in the faeces. At steady state the elimination half-life is reported to be 10 hours.

◊ References.

1. Heinonen EH, *et al.* Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites. *Clin Pharmacol Ther* 1994; **56:** 742–9.
2. Mahmood I, *et al.* Clinical pharmacokinetics and pharmacodynamics of selegiline: an update. *Clin Pharmacokinet* 1997; **33:** 91–102.
3. Anttila M, *et al.* Marked effect of liver and kidney function on the pharmacokinetics of selegiline. *Clin Pharmacol Ther* 2005; **77:** 54–62.
4. Azzaro AJ, *et al.* Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. *J Clin Pharmacol* 2007; **47:** 1256–67.

Uses and Administration

Selegiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease mainly as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response, but see Parkinsonism, below. Addition of selegiline to levodopa therapy may enable the dosage of levodopa to be reduced by about 10 to 30%. Selegiline may be given alone in early Parkinson's disease in an attempt to delay the need for levodopa therapy. It is also used in the treatment of depression (see also below).

In the treatment of **Parkinson's disease**, selegiline hydrochloride is given by mouth as conventional preparations such as capsules, tablets, or liquid, or as lyophilisate tablets. The dose of the conventional preparations is 10 mg daily, either as a single dose in the morning or in 2 divided doses of 5 mg at breakfast and lunchtime. The initial dose of the oral lyophilisate tablets is 1.25 mg daily at least 5 minutes before breakfast; patients already receiving 10 mg of conventional preparations can be transferred to 1.25 mg of the oral lyophilisate. In the USA, the initial oral lyophilisate dose of 1.25 mg daily may be increased, after at least 6 weeks, to 2.5 mg given once daily, if necessary.

To avoid initial confusion and agitation, particularly in the elderly, the *BNF* suggests it may be appropriate when using conventional preparations to start treatment with a dose of 2.5 mg daily.

In the USA, transdermal patches delivering 6, 9, or 12 mg of selegiline over 24 hours are available for the treatment of **depression**. The initial dose is 6 mg daily, increased in steps of 3 mg every 2 weeks if necessary, to a maximum of 12 mg daily. Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Dose increases should be made with caution in the elderly and patients should be closely observed for postural changes in blood pressure during treatment. Dietary restrictions are necessary at doses of 9 mg daily and above, see p.417.

Other conditions in which selegiline has been tried include dementia.

◊ Some references to the actions of selegiline.

1. Youdim MBH, Finberg JPM. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine oxidase B inhibitors. *Clin Pharmacol Ther* 1994; **56:** 725–33.
2. Lange KW, *et al.* Biochemical actions of l-deprenyl (selegiline). *Clin Pharmacol Ther* 1994; **56:** 734–41.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; selegiline is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (p.1860).

References.

1. Houtsmuller EJ, *et al.* Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* 2004; **172:** 31–40.

Dementia. The hypothesis that neurodegeneration in Alzheimer's disease (p.362) might be due to free radical formation has led to drugs such as selegiline being tried as antioxidant therapy.

Early double-blind studies[1,2] indicated that oral selegiline 10 mg daily might produce beneficial effects in patients with Alzheimer's disease but it was suggested that improvements in mood and cognitive function may have been due to a reduction in tension and depression.[3] A 15-month study in Alzheimers's patients with mild cognitive impairment showed oral selegiline 10 mg daily to have little effect,[4] although the authors pointed out that those with more severe dementia have shown more response in other studies. The conclusion of a later study[5] that oral selegiline 10 mg daily slowed progression in patients with moderate disease has been criticised[6] on the grounds that any effect was only evident after statistical adjustment to the original analysis. In addition a systematic review[7] examining the effects of selegiline concluded that there was no meaningful evidence of a beneficial effect of oral selegiline in patients with Alzheimer's disease. They also considered that there was no longer any justification for its use in patients with Alzheimer's disease.

1. Piccinin GL, *et al.* Neuropsychological effects of -deprenyl in Alzheimer's type dementia. *Clin Neuropharmacol* 1990; **13:** 147–63.
2. Mangoni A, *et al.* Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. *Eur Neurol* 1991; **31:** 100–107.
3. Anonymous. Drugs for Alzheimer's disease. *Drug Ther Bull* 1990; **28:** 42–4.
4. Burke WJ, *et al.* L-Deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. *J Am Geriatr Soc* 1993; **41:** 1219–25.
5. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
6. Pincus MM. Alpha-tocopherol and Alzheimer's disease. *N Engl J Med* 1997; **337:** 572.
7. Birks J, Flicker L. Selegiline for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).

Depression. Selegiline is a selective inhibitor of monoamine oxidase type B and there are reports[1-3] of it producing improvement in depression (p.373). However, at the doses usually required to produce an antidepressant effect the specificity of oral selegiline is reported to be lost and it has been suggested that the efficacy of selegiline as an antidepressant might depend on inhibition of monoamine oxidase A rather than inhibition of monoamine oxidase B alone. Such a loss of specificity would mean that patients taking selegiline for depression would need to observe the dietary restrictions applicable to non-selective MAOIs.

To overcome the problems associated with the oral route, transdermal selegiline has also been tried and may be more effective than placebo in the treatment of depression.[4] The use of the transdermal route allows sustained blood levels of selegiline to be delivered without extensive inhibition of peripheral monoamine oxidase A. Transdermal patches of selegiline are licensed for the treatment of depression in the USA.

1. Mendlewicz J, Youdim MBH. L-Deprenil, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. *Br J Psychiatry* 1983; **142:** 508–11.
2. Mann JJ, *et al.* A controlled study of the antidepressant efficacy and side-effects of (−)-deprenyl. *Arch Gen Psychiatry* 1989; **46:** 45–50.
3. Sunderland T, *et al.* High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry* 1994; **51:** 607–15.
4. Frampton JE, Plosker GL. Selegiline transdermal system: in the treatment of major depressive disorder. *Drugs* 2007; **67:** 257–65.

Narcoleptic syndrome. Small controlled studies[1,2] have suggested that oral selegiline 20 to 40 mg daily has a beneficial effect on symptoms of narcolepsy and cataplexy (p.2148); at such a dosage a low-tyramine diet is considered necessary.

1. Hublin C, *et al.* Selegiline in the treatment of narcolepsy. *Neurology* 1994; **44:** 2095–2101.
2. Mayer G, *et al.* Selegeline [sic] hydrochloride treatment in narcolepsy: a double-blind, placebo-controlled study. *Clin Neuropharmacol* 1995; **18:** 306–19.

Parkinsonism. As a selective monoamine oxidase type B inhibitor, selegiline reduces the metabolism of dopamine and thereby enhances its actions. It reduces levodopa's 'end-of-dose' effect and has a dose-sparing effect. Some have used it as **monotherapy** in an attempt to delay the need for levodopa. If progression of Parkinson's disease (p.791) were due to a cytotoxic effect of free radicals, generated during the metabolism of dopamine, on dopaminergic neurones in the substantia nigra, selegiline might slow the process by reducing their formation. In a large early study,[1] the DATATOP study, selegiline monotherapy delayed the need to start levodopa in patients with early Parkinson's disease. These findings were corroborated by other smaller studies.[2,3] There has been much debate over whether the benefit was due to a neuroprotective or symptomatic effect. Re-analysis of the DATATOP data by independent workers[4,5] and findings of other studies[6] supported a symptomatic effect. Subsequent studies involving DATATOP patients were also consistent with a symptomatic effect; any benefit produced by selegiline appeared to be less pronounced as the duration of treatment increased[7] and was lost completely long term.[8,9] However, a later study[10] designed to minimise any symptomatic effect cast doubt on whether the delay in progression of the signs and symptoms of Parkinson's disease obtained with selegiline was entirely due to a symptomatic effect.

Studies of the use of selegiline as an **adjunct** to levodopa therapy[6,11,12] indicate that selegiline permits a modest reduction in the dosage requirements of levodopa. An interim analysis of a study of the early addition of selegiline to levodopa has also suggested that selegiline might stabilise the long-term daily levodopa dosage.[13] As with monotherapy, combined therapy has been reported to slow symptom progression.[14]

The use of selegiline in Parkinson's disease has been questioned after a UK study[11] found an unexpected increase in mortality in patients taking levodopa with selegiline compared with those taking levodopa alone. No difference in mortality had been detected at the 3-year follow-up[15] but after an average follow-up time of 5.6 years[11] mortality was 60% higher in the group also receiving selegiline. The study has been criticised on many grounds including the fact that mortality was very high in both arms of the study[16] and has been the subject of much debate.[17,18] The authors of the study[11] had stated that they would advise the study patients to withdraw selegiline therapy. Analysis of follow-up data[19] until the selegiline arm of the study was terminated (average 6.8 years) found an excess mortality of about 35%, a figure calculated[20] to be no longer significant. However, because of the premature termination of the study such results were considered[21] to be biased. Whether any excess in mortality is causally related to selegiline is still unclear. Some consider that changes in prescribing practice based on this study are not warranted.[17] Others[21] have made a cautious recommendation not to start combination treatment in patients with newly diagnosed Parkinson's disease but consider that there is little evidence to advise patients who have been using selegiline with levodopa for years without problem to change their treatment. An evaluation of mortality among patients taking antiparkinsonian drugs (using the UK General Practice Research Database) provided evidence against there being substantial excess mortality associated with the use of selegiline.[22] These results are supported by a systematic review[23] and meta-analyses[24,25] of randomised, double-blind studies which found no increase in mortality associated with selegiline treatment regardless of concurrent levodopa. Furthermore, increased mortality was not seen in patients in the original DATATOP trial[1] after an average follow-up time of 8.2 years. However, it was noted that the delay of disability observed in the early phase of selegiline therapy[1,7] was not associated with longer life during follow-up.[26] A recent systematic review[23] has also found no convincing evidence that selective monoamine oxidase type B inhibitors (selegiline and lazabemide) significantly delay disease progression in early Parkinson's disease and routine use is not recommended.

1. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; **321:** 1364–71.
2. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; **245:** 519–22.
3. Allain H, *et al.* Selegiline in de novo parkinsonian patients: the French selegiline multicenter trial (FSMT). *Acta Neurol Scand* 1991; **84** (suppl 136): 73–8.
4. Schulzer M, *et al.* The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992; **32:** 795–8.

5. Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; **57:** 217–20.
6. Brannan T, Yahr MD. Comparative study of selegiline plus -dopa–carbidopa versus -dopa–carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995; **37:** 95–8.
7. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; **39:** 29–36.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996; **39:** 37–45.
10. Olanow CW, *et al.* The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1996; **38:** 771–7.
11. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–7.
12. Myllylä VV, *et al.* Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995; **91:** 177–82.
13. Larsen JP, Boas J. Norwegian-Danish Study Group. The effects of early selegiline therapy on long-term treatment and parkinsonian disability: an interim analysis of a Norwegian-Danish 5-year study. *Mov Disord* 1997; **12:** 175–82.
14. Pålhagen S, *et al.* Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology* 2006; **66:** 1200–6.
15. Parkinson's Disease Research Group in the United Kingdom. Comparisons of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; **307:** 467–72.
16. Olanow CW, *et al.* Patients taking selegiline may have received more levodopa than necessary. *BMJ* 1996; **312:** 702–3.
17. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin Proc* 1996; **71:** 659–70.
18. Mizuno Y, Kondo T. Mortality associated with selegiline in Parkinson's disease: what do the available data mean? *Drug Safety* 1997; **16:** 289–94.
19. Ben-Shlomo Y, *et al.* Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998; **316:** 1191–6.
20. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998; **316:** 1183–4.
21. Breteler MMB. Selegiline, or the problem of early termination of clinical trials. *BMJ* 1998; **316:** 1182–3.
22. Thorogood M, *et al.* Mortality in people taking selegiline: observational study. *BMJ* 1998; **317:** 252–4.
23. Macleod AD, *et al.* Monoamine oxidase B inhibitors for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/02/06).
24. Olanow CW, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; **51:** 825–30.
25. Ives NJ, *et al.* Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; **329:** 593–6.
26. The Parkinson Study Group. Mortality in DATATOP: A multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; **43:** 318–25.

Smoking cessation. Selegiline has been investigated as an aid to smoking cessation (p.2354).

References.

1. George TP, *et al.* A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 2003; **53:** 136–43.
2. Biberman R, *et al.* A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction* 2003; **98:** 1403–7.

Preparations

BP 2008: Selegiline Oral Solution; Selegiline Tablets;
USP 31: Selegiline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Brintenal; Jumex; Kinabide†; Zelapar; ***Austral.:*** Eldepryl; Selgene; ***Austria:*** Amboneural; Cognitiv; Jumex; Regepar; Xilopar; ***Belg.:*** Eldepryl; ***Braz.:*** Deprilan; Elepril; Jumexil; Niar; Parkexin; ***Canad.:*** Eldepryl†; ***Chile:*** Selgina; ***Cz.:*** Apo-Seleg; Cognitiv; Jumex; Niar; Segalin†; Sepatrem†; ***Denm.:*** Eldepryl; ***Fin.:*** Eldepryl; ***Fr.:*** Deprenyl; Otrasel; ***Ger.:*** Amindan†; Antiparkin; Jutagilin; MAOtil†; Movergan; Selegam†; Selemerck; Selepark; Selgimed; Xilopar; ***Gr.:*** Cosmopril; Ermolax; Feliselin; Krautin; Legil; Procythol; Resostyl; ***Hong Kong:*** Julab; Jumex; Sefmex; Selegos; ***Hung.:*** Cognitiv; Jumex; Primulex†; ***India:*** Selerin; Selgin; ***Indon.:*** Jumex; ***Irl.:*** Eldepryl; ***Israel:*** Jumex; ***Ital.:*** Egibren; Jumex; Selecom; Seledat; Xilopar; ***Jpn:*** FP Tab; ***Malaysia:*** Ginex†; Jumex; Sefmex; Selegos†; ***Mex.:*** Niar; ***Neth.:*** Eldepryl; ***Norw.:*** Eldepryl; ***NZ:*** Eldepryl; Selgene†; ***Philipp.:*** Jumex; ***Pol.:*** Apo-Selin; Jumex; Parkinil†; Segan; Selerin; Selgin; Selgres; ***Port.:*** Jumex; Niponeurin; Xilopar; ***Rus.:*** Cognitiv (Когнитив); Segan (Сеган); Selegos (Селегос); ***S.Afr.:*** Eldepryl; Parkilyne; ***Singapore:*** Jumex; Selegos; ***Spain:*** Plurimen; ***Swed.:*** Eldepryl; ***Switz.:*** Jumexal; Selecim†; ***Thai.:*** Elegelin†; Julab; Jumex; Kinline†; Sefmex; Seline†; ***Turk.:*** Moverdin; Seldepar; ***UK:*** Eldepryl; Zelapar; ***USA:*** Atapryl; Carbex; Eldepryl; Emsam; Zelapar; ***Venez.:*** Jumex.

Talipexole Hydrochloride *(rINNM)*

Alefexole Hydrochloride; B-HT-920; Hidrocloruro de talipexol; Talipexole, Chlorhydrate de; Talipexoli Hydrochloridum. 6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.

Талипексола Гидрохлорид

$C_{10}H_{15}N_3S,2HCl = 282.2.$

CAS — 101626-70-4 (talipexole); 36085-73-1 (talipexole hydrochloride).

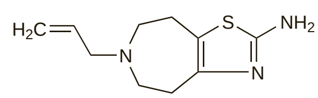

(talipexole)

Profile

Talipexole hydrochloride is a dopamine D_2-agonist that is used in the management of parkinsonism (p.791) in usual oral doses of 1.2 to 3.6 mg daily, in divided doses. It has also been investigated in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Domin.

Terguride *(rINN)*

Tergurida; Terguridum. 1,1-Diethyl-3-(6-methylergolin-8α-yl)urea.

Тергурид

$C_{20}H_{28}N_4O = 340.5.$

CAS — 37686-84-3.

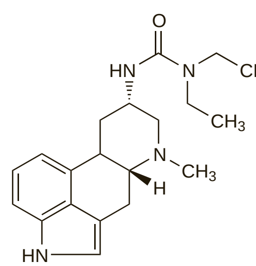

Profile

Terguride, an ergot derivative, is a partial dopamine agonist with general properties similar to those of bromocriptine (p.798). It is used in the treatment of disorders related to hyperprolactinaemia (p.2079) in a usual oral dose of 500 micrograms twice daily. It is also being investigated in the management of parkinsonism.

◊ References.

1. Krause W, *et al.* Pharmacokinetics and endocrine effects of terguride in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 609–15.
2. Baronti F, *et al.* Partial dopamine agonist therapy of levodopa-induced dyskinesias. *Neurology* 1992; **42:** 1241–3.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mysalfon†; ***Jpn:*** Teluron.

Tolcapone *(BAN, USAN, rINN)*

Ro-40-7592; Tolcapona; Tolcaponum; Tolkapon; Tolkaponi. 3,4-Dihydroxy-4′-methyl-5-nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl(4-methylphenyl)methanone.

Толкапон

$C_{14}H_{11}NO_5 = 273.2.$

CAS — 134308-13-7.
ATC — N04BX01.
ATC Vet — QN04BX01.

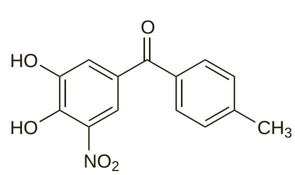

Pharmacopoeias. In *US.*

USP 31 (Tolcapone). A yellow, fine powder or fine powder with lumps. Insoluble in water and in *n*-hexane; Freely soluble in acetone and in tetrahydrofuran; sparingly soluble in chloroform and in dichloromethane; soluble in methyl alcohol and in ethyl acetate. Store in airtight containers at a temperature between 20° and 25°. Protect from light.

Adverse Effects

The most common adverse effects associated with tolcapone are diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, anorexia, dyskinesia, dystonia, dizziness, orthostatic hypotension, hallucinations, confusion, excessive dreaming, somnolence, headache, increased sweating, and sleep disorders. Diarrhoea may be severe enough for treatment to be stopped. Increases in liver enzyme values have occurred and hepatitis and hepatic failure, sometimes fatal, have been reported. Isolated cases of neuroleptic malignant syndrome have also been reported following dose reduction or stopping tolcapone; rhabdomyolysis may develop as a complication of the syndrome. Tolcapone and its metabolites can produce a yellow intensification in the colour of urine.

Effects on the liver. The UK CSM had noted[1] that, after a report[2] in September 1998 of fatal acute hepatic failure associated with tolcapone, the European Committee for Proprietary Medicinal Products (CPMP) had reviewed all reports of hepatic injury with tolcapone. There had been 10 reports of serious hepatic adverse reactions since tolcapone was marketed in October 1997, which included 7 reports of hepatitis, 3 of which had a fatal outcome. Serious hepatic reactions occurred unpredictably and their development was not always predicted by liver function monitoring. Consequently, in the EU, the marketing authorisation for tolcapone was suspended in November 1998. This suspension was lifted in April 2004 by the CPMP after further review.

In some countries such as the USA, tolcapone has always remained available albeit with restricted indications and strict monitoring requirements (see Precautions, below). Up to 2003, there had been no further reports of fatal hepatic failure following the introduction of these measures although the number of patients eligible to receive the drug has been reduced.[3]

1. CSM/MCA. Withdrawal of tolcapone (Tasmar). *Current Problems* 1999; **25:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. Assal F, *et al.* Tolcapone and fulminant hepatitis. *Lancet* 1998; **352:** 958.
3. Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Safety* 2003; **26:** 743–7.

Effects on the skin. For reference to the development of vitiligo in a patient following addition of tolcapone to levodopa/carbidopa treatment, see under Levodopa, p.806.

Precautions

Tolcapone should not be given to patients with hepatic impairment or raised liver enzyme values. Liver enzymes should be monitored:

- when starting treatment with tolcapone or on increasing the dose to 200 mg three times daily
- every 2 weeks during the first year of therapy
- every 4 weeks for a further 6 months
- every 8 weeks thereafter

Tolcapone should be stopped if liver enzyme levels exceed the upper limit of normal or if signs or symptoms suggestive of the onset of hepatic failure occur. Patients who have developed evidence of hepatic injury while receiving tolcapone should not be given the drug again.

Tolcapone should be used with caution in patients with severe renal impairment.

It is contra-indicated in patients with severe dyskinesia or with a history of neuroleptic malignant syndrome (NMS). It is also contra-indicated in patients with a history of nontraumatic rhabdomyolysis or symptoms of hyperpyrexia and confusion possibly related to NMS. Patients with phaeochromocytoma should not be given tolcapone.

Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p.805) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Abrupt withdrawal or dose reduction of tolcapone should be monitored carefully because of the risk of developing symptoms resembling NMS.

The elderly. Confusion occurred in 3 elderly patients with severe Parkinson's disease after the addition of tolcapone to their antiparkinsonian therapy.[1] It was suggested that a starting dose of tolcapone 100 mg daily might be more suitable in frail patients with severe disease. It was noted[2] that a reduction in levodopa dosage is generally recommended when tolcapone is given to patients such as these, who were receiving 500 to 600 mg of levodopa daily.

1. Henry C, Wilson JA. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **351:** 1965–6.
2. Harper J, Vieira B. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; **352:** 578.

Genetic polymorphism. Two patients who developed elevated liver enzyme values while receiving tolcapone, one of whom also had hepatic dysfunction while receiving entacapone, were found to be poor metabolisers with regard to UDP-glucuronosyltransferase activity.[1] Such patients may be predisposed to COMT-inhibitor induced hepatotoxicity.

1. Martignoni E, *et al.* Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. *Neurology* 2005; **65:** 1820–2.

Interactions

Tolcapone may influence the pharmacokinetics of drugs metabolised by catechol-*O*-methyltransferase; a dose reduction of such drugs should be considered when given with tolcapone. Increased concentrations of benserazide and its active metabolite have been reported when given with tolcapone. Licensed product information advises that non-selective MAOIs should not be used with tolcapone.

Pharmacokinetics

Tolcapone is rapidly absorbed from the gastrointestinal tract and maximum plasma concentrations have been obtained within 2 hours of an oral dose; food delays and decreases the absorption. Absolute bioavailability is reported to be about 65%. Tolcapone is more than 99% bound to plasma proteins (mainly albumin) and is not widely distributed into body tissues. It is extensively metabolised, mainly by conjugation to the inactive glucuronide, but methylation by catechol-*O*-methyltransferase to 3-*O*-methyltolcapone and metabolism by cytochrome P450 isoenzymes CYP3A4 and CYP2A6 also occurs. About 60% of a dose is excreted in the urine with the remainder appearing in the faeces. The elimination half-life has been reported to be about 2 to 3 hours. The clearance of unbound tolcapone may be reduced by 50% in patients with moderate cirrhotic liver disorders.

◊ References.

1. Dingemanse J, *et al.* Integrated pharmacokinetics and pharmacodynamics of the novel catechol-O-methyltransferase inhibitor tolcapone during first administration to humans. *Clin Pharmacol Ther* 1995; **57:** 508–17.
2. Jorga KM, *et al.* Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. *Clin Pharmacol Ther* 1998; **63:** 646–54.
3. Jorga K, *et al.* Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase. *Br J Clin Pharmacol* 1999; **48:** 513–20.
4. Jorga K, *et al.* Population pharmacokinetics of tolcapone in parkinsonian patients in dose finding studies. *Br J Clin Pharmacol* 2000; **49:** 39–48.

Uses and Administration

Tolcapone is a peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to levodopa and dopa-decarboxylase inhibitor combinations in the management of Parkinson's disease for patients who cannot be stabilised on these levodopa combinations or for those who experience 'end-of-dose' deterioration. Because of the risk of serious hepatotoxicity (see Effects on the Liver, above) the FDA in the USA restricted its use to when other adjunctive therapy was ineffective or contra-indicated. In the EU, tolcapone was withdrawn from the market in November 1998 and subsequently returned in 2004, its use being similarly restricted to patients who fail to respond to, or are intolerant of, other COMT inhibitors.

The usual recommended dosage of tolcapone is 100 mg given orally three times daily; up to a maximum of 200 mg three times daily may be considered if the clinical benefit justifies the increased risk of hepatotoxicity. The first dose of the day should be taken at the same time as the combined levodopa preparation. Most patients already taking more than 600 mg of levodopa daily will require a reduction in their dosage of levodopa; patients on lower levodopa doses may also require a dose reduction.

Tolcapone should be withdrawn if a substantial clinical benefit is not obtained within the first 3 weeks of treatment. An adjustment in the levodopa dose may be necessary following tolcapone withdrawal.

Parkinsonism. Tolcapone is a reversible peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of levodopa and dopamine.[1] It appears to differ from entacapone (p.804) by being a more potent COMT inhibitor in the periphery and by penetrating into the brain (although the significance of any central effects of COMT inhibition are not known).[1] When given to patients with Parkinson's disease (p.791) and levodopa-related fluctuations in disability or 'end-of-dose' effects, it has prolonged the clinical benefit obtained with levodopa and allowed the total daily dosage of levodopa to be reduced.[2,3] Benefit has also been reported[4] when added to levodopa therapy in patients with stable Parkinson's disease. However, a systematic review[5] concluded that there were insufficient data to demonstrate any significant difference in efficacy between tolcapone and bromocriptine or pergolide in the adjunctive treatment of levodopa-induced motor complications.

The use of tolcapone is restricted in some countries because of the risk of serious hepatotoxicity (see Effects on the Liver, above).

1. Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; **351:** 1221–2.
2. Kurth MC, *et al.* Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. *Neurology* 1997; **48:** 81–7.
3. Rajput AH, *et al.* Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind placebo-controlled, multicenter trial. *Neurology* 1997; **49:** 1066–71.
4. Waters CH, *et al.* Tolcapone Stable Study Group. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; **49:** 665–71.
5. Deane KHO, *et al.* Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).

Preparations

USP 31: Tolcapone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Tasmar; ***Austria:*** Tasmar; ***Belg.:*** Tasmar; ***Braz.:*** Tasmar; ***Chile:*** Tasmar; ***Cz.:*** Tasmar; ***Denm.:*** Tasmar; ***Fin.:*** Tasmar; ***Fr.:*** Tasmar; ***Ger.:*** Tasmar; ***Gr.:*** Tasmar; ***Hong Kong:*** Tasmar†; ***Hung.:*** Tasmar; ***Irl.:*** Tasmar; ***Ital.:*** Tasmar; ***Mex.:*** Tasmar; ***Neth.:*** Tasmar; ***NZ:*** Tasmar; ***Philipp.:*** Tasmar; ***Pol.:*** Tasmar; ***Port.:*** Tasmar; ***Rus.:*** Tasmar (Тасмар); ***S.Afr.:*** Tasmar; ***Spain:*** Tasmar; ***Swed.:*** Tasmar; ***Switz.:*** Tasmar; ***UK:*** Tasmar; ***USA:*** Tasmar.

Trihexyphenidyl Hydrochloride

(BANM, rINNM)

Benzhexol Hydrochloride; Cloridrato de Triexilfenidila; Cyclodolum; Hidrocloruro de trihexifenidilo; Triheksifenidilio hidrochloridas; Triheksyfenidylu chlorowodorek; Triheksyfenidyylihydrokloridi; Trihexifenidilhidroklorid; Trihexyfenidyl-hydrochlorid; Trihexyfenidylhydroklorid; Trihexyphénidyle, chlorhydrate de; Trihexyphénidyle, Chlorhydrate de; Trihexyphenidyli hydrochloridum; Trihexyphenidylium Chloratum. 1-Cyclohexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride.

Тригексифенидила Гидрохлорид

$C_{20}H_{31}NO,HCl = 337.9.$

CAS — 144-11-6 (trihexyphenidyl); 52-49-3 (trihexyphenidyl hydrochloride).

ATC — N04AA01.

ATC Vet — QN04AA01.

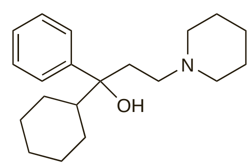

(trihexyphenidyl)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trihexyphenidyl: Artanes.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Trihexyphenidyl Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.2 to 6.2.

USP 31 (Trihexyphenidyl Hydrochloride). A white or slightly off-white, crystalline powder, having not more than a very faint odour. Slightly soluble in water; soluble in alcohol and in chloroform. Store in airtight containers.

Adverse Effects, Treatment and Precautions

As for Atropine Sulfate, p.1219. In some patients, such as those with arteriosclerosis or a history of drug idiosyncrasy, trihexyphenidyl may produce mental disturbances, excitement, or nausea and vomiting; such patients should be allowed to develop a tolerance by starting with a small initial dose and gradually increasing it until an effective level is reached. If a severe reaction occurs, trihexyphenidyl should be stopped for a few days and resumed at a lower dose. Trihexyphenidyl may provoke or exacerbate tardive dyskinesia.

Abuse. Trihexyphenidyl hydrochloride has been abused for its euphoric effect[1] especially by psychiatric patients.[2] Its abuse potential in schizophrenic patients has been questioned[3] and its unpleasant antimuscarinic effects tend to limit its repeated use,[4] but a small survey among psychiatric patients found that trihexyphenidyl was reported to be the antimuscarinic most frequently abused;[5] procyclidine, benzatropine, and orphenadrine (in decreasing order of frequency) were also misused. A later analysis of health insurance data from one region of France[6] examined prescriptions for trihexyphenidyl in 3028 subjects, most of whom were also receiving antipsychotics, and concluded that there was evidence of an abnormal pattern of use in about 2%. Patients in this subgroup were mostly young, male, and also receiving benzodiazepines or high doses of buprenorphine.

1. Crawshaw JA, Mullen PE. A study of benzhexol abuse. *Br J Psychiatry* 1984; **145:** 300–3.
2. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; **289:** 612–13.
3. Goff DC, *et al.* A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994; **151:** 429–31.
4. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.
5. Buhrich N, *et al.* Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; **51:** 928–9.
6. Frauger E, *et al.* Détournement d'usage du trihexyphénidyle (Artane , Parkinane): tendances récentes. *Therapie* 2003; **58:** 541–7.

Effects on the heart. Paradoxical sinus bradycardia developed in a schizophrenic patient after receiving trihexyphenidyl for extrapyramidal effects due to antipsychotic medication.[1] Normal sinus rhythm was restored after trihexyphenidyl was stopped. The patient had previously received trihexyphenidyl and suffered bradycardia which at the time was attributed to haloperidol.

1. Blumensohn R, *et al.* Bradycardia due to trihexyphenidyl hydrochloride. *Drug Intell Clin Pharm* 1986; **20:** 786–7.

Effects on mental function. Trihexyphenidyl 2 mg by mouth significantly impaired memory function compared with placebo in a study in 13 elderly patients.[1] Impairment of memory has also been observed in patients with Parkinson's disease given antimuscarinics such as trihexyphenidyl.[2] However, impairment may be reversible on stopping the antimuscarinic (see Atropine, p.1220).

1. Potamianos G, Kellett JM. Anti-cholinergic drugs and memory: the effects of benzhexol on memory in a group of geriatric patients. *Br J Psychiatry* 1982; **140:** 470–2.
2. Sadeh M, *et al.* Effects of anticholinergic drugs on memory in Parkinson's disease. *Arch Neurol* 1982; **39:** 666–7.

Overdosage. A 34-year-old woman developed a toxic reaction with widely dilated pupils, dry skin, and visual hallucinations within 24 hours of taking about 300 mg of trihexyphenidyl hydrochloride with suicidal intent.[1] After 3 to 4 days the hallucinations were replaced by illusions; complete recovery occurred after a week, with no special treatment. Death associated with moderate blood concentrations of trihexyphenidyl (0.12 micrograms/mL) has been reported[2] in a schizophrenic patient recovering from a respiratory infection. It was thought possible that he had increased his dose to counteract developing tardive dyskinesia, and that the toxic effects had been exacerbated by respiratory inflammation; there was no evidence of suicidal intent.

1. Ananth JV, *et al.* Toxic psychosis induced by benzhexol hydrochloride. *Can Med Assoc J* 1970; **103:** 771.
2. Gall JAM, *et al.* Death due to benzhexol toxicity. *Forensic Sci Int* 1995; **71:** 9–14.

Withdrawal. A 61-year-old woman who had taken trihexyphenidyl 6 mg daily for a year for Parkinson's disease developed encephalopathy and miosis on two occasions when treatment was abruptly withdrawn.[1] Slowly tapered withdrawal avoided these effects.

1. Johkura K, *et al.* Trihexyphenidyl withdrawal encephalopathy. *Ann Neurol* 1997; **41:** 133–4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Chlorpromazine. For the effect of trihexyphenidyl on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p.974.

Pharmacokinetics

Trihexyphenidyl hydrochloride is well absorbed from the gastrointestinal tract and has been stated to exert an effect within 1 hour of an oral dose.

Half-life. The reported half-life of trihexyphenidyl has varied according to the assay method used. Values reported when using radioreceptor and chromatographic techniques have ranged from about 1 to more than 24 hours[1] and from 10 to 29 hours,[2] respectively, but the sensitivity and specificity of these methods have been criticised.[3] With a more recently developed radio immunoassay it was found that after oral doses there was an initial elimination phase with an estimated half-life of 5.33 hours followed by a terminal elimination phase with an estimated half-life of 32.7 hours.

1. Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol* 1985; **18:** 35–40.
2. Garbarg S, *et al.* Comparaison pharmacoclinique de deux formes galéniques de trihexyphénidyle. *Encephale* 1983; **IX:** 167–74.
3. He H, *et al.* Development and application of a specific and sensitive radioimmunoassay for trihexyphenidyl to a pharmacokinetic study in humans. *J Pharm Sci* 1995; **84:** 561–7.

Uses and Administration

Trihexyphenidyl hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1220). It also has a direct antispasmodic action on smooth muscle.

Trihexyphenidyl hydrochloride is given orally in the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias, but see Extrapyramidal Disorders, below. Trihexyphenidyl hydrochloride is given in 3 or 4 divided doses daily before or with food.

In **Parkinson's disease** the usual initial dose of 1 mg daily is gradually increased at intervals of 3 to 5 days by increments of 2 mg to 6 to 10 mg daily according to response; for advanced cases, 12 to 15 mg daily or even more (up to 20 mg daily) may be needed. As a rule, postencephalitic patients tolerate and require the larger doses.

Usual doses for **drug-induced extrapyramidal symptoms** lie within the range of 5 to 15 mg daily, although as little as 1 mg daily may be sufficient in some cases.

Since the elderly and arteriosclerotic patients are more susceptible to the adverse effects of antimuscarinics a dose at the lower end of the range is usually recommended.

Antimuscarinic treatment of parkinsonism should never be terminated suddenly and it is usual when changing from one drug to another to withdraw one in small amounts while gradually increasing the dose of the other.

Trihexyphenidyl hydrochloride may be given with other drugs used for the relief of parkinsonism, such as levodopa, but the dose of each drug may need to be reduced. Trihexyphenidyl hydrochloride 3 to 6 mg daily is usually adequate.

Extrapyramidal disorders. Antimuscarinics such as trihexyphenidyl are used in the management of dystonias (p.809) although only about half of all children and adolescents, and fewer adults (who tolerate antimuscarinics less well) show any response. Adverse effects may be limited by starting with a low dose: one suggested regimen[1] starts with trihexyphenidyl 1 mg daily and rises up to 12 mg daily over the next 4 to 6 weeks; some patients may require up to 60 to 100 mg daily. The *BNFC* suggests that children aged 1 month to 18 years may be given oral doses of 1 to 2 mg daily in 1 or 2 divided doses, adjusted according to response.

1. Jankovic J. Dystonia: medical therapy and botulinum toxin. *Adv Neurol* 2004; **94:** 275–86.

Preparations

BP 2008: Trihexyphenidyl Tablets;
USP 31: Trihexyphenidyl Hydrochloride Elixir; Trihexyphenidyl Hydrochloride Extended-release Capsules; Trihexyphenidyl Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Artane; ***Austral.:*** Artane; ***Austria:*** Artane; ***Belg.:*** Artane; ***Braz.:*** Artane; Triexidyl; ***Canad.:*** Apo-Trihex; ***Chile:*** Artane†; Tenvatil; Tonaril; ***Denm.:*** Peragit; ***Fr.:*** Artane; Parkinane; ***Ger.:*** Artane; Parkopan; ***Gr.:*** Artane; ***Hong Kong:*** Apo-Trihex; Artandyl; Artane; ***India:*** Pacitane; Parnon; ***Indon.:*** Arkine; Artane; Hexymer; ***Irl.:*** Artane†; ***Israel:*** Artane†; Partane; Rodenal; ***Ital.:*** Artane; ***Malaysia:*** Aca; Apo-Trihex; Uphazhexol†; ***Mex.:*** Artane†; Hipokinon; Kexidil; ***Neth.:*** Artane; ***Pol.:*** Parkopan; ***Port.:*** Artane; ***S.Afr.:*** Artane; ***Singapore:*** Apo-Trihex; Beahexol; ***Spain:*** Artane; ***Swed.:*** Pargitan; ***Thai.:*** Aca; Acamed; Artane†; Pozhexol; Tridyl; ***UK:*** Broflex; ***USA:*** Trihexy.

Multi-ingredient: ***Ger.:*** Spasman†; ***India:*** Sycot; Trinicalm Forte; Trinicalm Plus; ***Spain:*** Largatrex†.

Tropatepine Hydrochloride *(rINNM)*

Hidrocloruro de tropatepina; SD-1248-17; Tropatépine, Chlorhydrate de; Tropatepini Hydrochloridum. 3-(Dibenzo[*b,e*]thiepin-11(6*H*)-ylidene)tropane hydrochloride.

Тропатепина Гидрохлорид

$C_{22}H_{23}NS,HCl = 370.0.$

CAS — 27574-24-9 (tropatepine); 27574-25-0 (tropatepine hydrochloride).

ATC — N04AA12.

ATC Vet — QN04AA12.

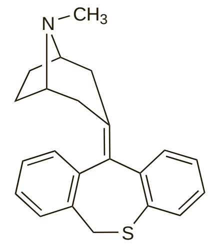

(tropatepine)

Profile

Tropatepine hydrochloride is an antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It is used in the management of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value in tardive dyskinesias. Tropatepine hydrochloride is given orally in usual doses of 10 to 30 mg daily; it is also given intramuscularly or by slow intravenous injection in doses of 10 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Lepticur.

Antiprotozoals

Amoebic infections, p.822
Acanthamoeba infections, p.822
Acanthamoeba keratitis, p.822
Disseminated acanthamoeba infection, p.822
Amoebiasis, p.822
Naegleria infections, p.822
Primary amoebic meningoencephalitis, p.822
Babesiosis, p.823
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Malaria, p.826
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Toxoplasmosis, p.826
Trichomoniasis, p.827
African trypanosomiasis, p.827
American trypanosomiasis, p.827

The drugs described in this chapter are those used mainly in the treatment of parasitic protozoal infections. In addition to their use as antiprotozoals, metronidazole and related nitroimidazole derivatives are also important in the treatment of anaerobic bacterial infections. Some veterinary antiprotozoal drugs are included. Drugs used in the treatment of malaria are described in the Antimalarials chapter; some of these are also used in other protozoal infections.

The principal antiprotozoal drugs are listed in Table 1, below.

Choice of Antiprotozoal

Protozoal infections occur throughout the world and are a major cause of morbidity and mortality in some regions. The choice of treatment for the principal protozoal diseases in humans is discussed below.

Amoebic infections

The most common amoebic infection of man is amoebiasis caused by infection with the protozoan parasite *Entamoeba histolytica* and related species. Free-living amoebae can also cause disease in man, though these infections are rare. Infection with *Naegleria fowleri* results in primary amoebic meningoencephalitis, while infection with *Acanthamoeba* species or leptomyxid amoebae leads to granulomatous amoebic encephalitis. *Acanthamoeba* is also a cause of keratitis.

Acanthamoeba infections. ***ACANTHAMOEBA KERATITIS.*** *Acanthamoeba* keratitis is usually associated with the wearing of soft contact lenses. It is treated by prompt topical antiamoebic therapy,[1-4] although an optimum regimen has yet to be determined. Surgery may be needed in severe cases. Propamidine isetionate applied topically was the first drug used with some success.[5,6] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. Due to surface toxicity and poor *in-vitro* sensitivity of neomycin, propamidine was later used with a biguanide such as chlorhexidine or polihexanide. However, poor cysticidal activity, chronic conjunctival infection, and resistance to some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine. Systemic itraconazole or ketoconazole with topical miconazole have also been tried with some success. Clotrimazole has also been used successfully. Biguanides may also be used alone,[4] and are particularly effective in early infection.

Acanthamoeba keratitis in contact lens wearers should be preventable by good lens hygiene (see Contact Lens Care, p.1622).

Table 1. Classification of principal antiprotozoals.

Antimony compounds	*Nitrofurans*
Meglumine antimonate	Furazolidone
Sodium stibogluconate	Nifuratel
	Nifurtimox
Aromatic diamidines	
Pentamidine	*5-Nitroimidazoles*
	Metronidazole
Arsenicals, pentavalent	Nimorazole
Acetarsol	Ornidazole
Tryparsamide	Secnidazole
	Tinidazole
Arsenicals, trivalent	
Melarsoprol	*Miscellaneous*
	Atovaquone
Dichloroacetamides	Benznidazole
Diloxanide	Dehydroemetine
	Eflornithine
Halogenated hydroxyquinolines	Mepacrine
Diiodohydroxyquinoline	Paromomycin
	Suramin

1. Illingworth CD, *et al.* Acanthamoeba keratitis: risk factors and outcome. *Br J Ophthalmol* 1995; **79:** 1078–82.
2. Elder MJ, Dart JKG. Chemotherapy for acanthamoeba keratitis. *Lancet* 1995; **345:** 791–2.
3. Lindquist TD. Treatment of Acanthamoeba keratitis. *Cornea* 1998; **17:** 11–16.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 1st ed. New Rochelle NY: The Medical Letter, 2007.
5. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; **26:** 231–6.
6. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; **17:** 893–905.

DISSEMINATED ACANTHAMOEBA INFECTION. Granulomatous amoebic encephalitis is caused by infection with free-living amoebae, usually *Acanthamoeba* spp. or sometimes leptomyxid amoebae. It is an opportunistic infection occurring mainly in debilitated or immunocompromised individuals. The protozoa spread to the CNS from pulmonary or skin lesions and produce focal neurological deficits that progress over days or weeks to a diffuse meningoencephalitis. The infection is usually fatal and most cases have been diagnosed postmortem so little is known about effective treatments; A few cases have been reported in which patients with encephalitis responded to combinations of pentamidine, sulfadiazine, flucytosine, and an azole such as itraconazole or fluconazole;[1] susceptibilities of species and strains appear to vary widely, and susceptibility testing is advisable.

Clinical responses to chemotherapy have also been reported in a few patients[2-4] with disseminated infection but no evidence of CNS involvement. Disseminated *Acanthamoeba* infection in an immunocompromised patient was successfully treated with intravenous pentamidine followed by maintenance therapy with oral itraconazole.[2] Skin lesions were treated topically with chlorhexidine and ketoconazole. Clinical improvement of disseminated acanthamoebiasis in a patient with AIDS followed treatment with intravenous pentamidine and oral flucytosine; an infant with HIV infection was treated with fluconazole, flucytosine, and sulfadiazine.[3] A lung transplant patient with disseminated acanthamoebiasis was also successfully treated with pentamidine, flucytosine, and azithromycin, plus topical chlorhexidine and ketoconazole.[4]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 1st ed. New Rochelle NY: The Medical Letter, 2007.
2. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.
3. Murakawa GJ, *et al.* Disseminated Acanthamoeba in patients with AIDS: a report of five cases and a review of the literature. *Arch Dermatol* 1995; **131:** 1291–6.
4. Oliva S, *et al.* Successful treatment of widely disseminated acanthamoebiasis. *South Med J* 1999; **92:** 55–7.

Amoebiasis. The term amoebiasis is generally applied to infections with obligate parasitic species of amoeba, principally *Entamoeba histolytica*.[1,2] Other parasitic species which occasionally cause human infections include *E. polecki* (primarily a parasite of pigs and reported mainly in Papua New Guinea) and *Dientamoeba fragilis* (often found in association with the helminth *Enterobius vermicularis* and now thought to be a trichomonad).

Transmission of *E. histolytica* is by the faeco-oral route and infection results from the ingestion of cysts, usually in contaminated food and drink. The cysts transform to trophozoites in the intestines and reproduction occurs by fission of the trophozoites. Further cysts develop and are excreted in the faeces. Amoebiasis occurs throughout the world. It is more prevalent and severe in the tropics and subtropics, but is more closely related to sanitation and socio-economic status than to climate. Colonisation with *E. histolytica* can result in asymptomatic infection, but in other cases the trophozoites invade the wall of the large intestine causing ulceration and may migrate to other tissues, especially the liver, where they continue to divide and destroy tissue. Factors increasing susceptibility to tissue invasion include malnutrition, immunosuppression, and pregnancy.

Symptomatic amoebiasis may be classified as intestinal or extra-intestinal amoebiasis. Intestinal amoebiasis comprises two main states, amoebic dysentery and non-dysenteric amoebic colitis; amoeboma, a localised form of intestinal amoebiasis, and amoebic appendicitis may also occur. Hepatic amoebiasis, the most common form of extra-intestinal amoebic disease, may present as acute non-suppurative disease or as amoebic liver abscess. Amoebic infection is a less common cause of liver abscess than bacterial infection. Amoebiasis may also involve the skin, genito-urinary tract, or organs such as the lungs and brain.

Drugs used in the **treatment** of amoebiasis may be classified according to their site of action as follows:

- *luminal amoebicides* acting principally in the bowel lumen.

  Diloxanide furoate is widely used as the luminal amoebicide of choice, although clefamide, etofamide, and teclozan are also effective.[3] Paromomycin and diiodohydroxyquinoline have also been used[1,2,4] although most oral preparations of halogenated hydroxyquinolines have been withdrawn because of the association between clioquinol and subacute myelo-opticoneuropathy
- *tissue* or *systemic amoebicides* acting principally in the intestinal wall and liver. These have included the alkaloid emetine, its synthetic derivative dehydroemetine, and the antimalarial chloroquine which acts principally in the liver
- *mixed amoebicides* acting at all sites of infection, that is within the intestinal lumen and in the intestinal wall and other tissues. These have included metronidazole and other 5-nitroimidazole derivatives. However, because of their rapid absorption from the gastrointestinal tract, the nitroimidazoles are less effective against parasites in the lumen

In non-endemic areas, patients with asymptomatic intestinal amoebiasis (cyst passers) are generally treated with a luminal amoebicide. The choice of drug is influenced by availability; diloxanide furoate is generally used in the UK while diiodohydroxyquinoline or paromomycin are used in the USA.[5] Standard treatment for invasive amoebiasis (amoebic dysentery; hepatic amoebiasis) is metronidazole, ornidazole, or tinidazole, followed by a luminal amoebicide to eradicate any surviving organisms from the lumen of the large intestine and prevent relapse. The majority of patients with amoebic liver abscess defervesce after 3 to 4 days of treatment with metronidazole. Addition of chloroquine is an option in patients who do not respond;[4] WHO recommends that hepatic abscesses should be lanced by needle aspiration.[3] Nitazoxanide has been used in mild to moderate intestinal disease.[5] In severe cases of amoebic dysentery tetracycline given with a systemic amoebicide lessens the risk of superinfection, intestinal perforation, and peritonitis.

In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p.1694.

Drugs suggested for the treatment of *Dientamoeba fragilis* infections include diiodohydroxyquinoline, metronidazole, paromomycin, or tetracycline.[5] Metronidazole has been suggested for *E. polecki* infections.[5]

1. Stanley SL. Amoebiasis. *Lancet* 2003; **361:** 1025–34.
2. Haque R, *et al.* Amebiasis. *N Engl J Med* 2003; **348:** 1565–73.
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4. Petri WA, Singh U. Diagnosis and management of amebiasis. *Clin Infect Dis* 1999; **29:** 1117–25.
5. Abramowicz M, ed. *Drugs for parasitic infections.* 1st ed. New Rochelle NY: The Medical Letter, 2007.

Naegleria infections. ***PRIMARY AMOEBIC MENINGOENCEPHALITIS.*** Primary amoebic meningoencephalitis is usually caused by the free-living amoeba *Naegleria fowleri*. It occurs mainly in healthy children and young adults and is usually associated with swimming in warm fresh water. The protozoa invade the CNS directly through the nasal mucosa to produce a meningoencephalitis that is usually rapidly fatal. Few cases of successful treatment have been reported, and have generally involved intravenous, and usually intrathecal, amphotericin B;[1-3] some patients were also given oral rifampicin.

1. Anderson K, Jamieson A. Primary amoebic meningoencephalitis. *Lancet* 1972; **i:** 902–3.
2. Seidel JS, *et al.* Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982; **306:** 346–8.
3. Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991; **151:** 1201–2.

Babesiosis

Babesiosis (piroplasmosis) is an infection caused by intraerythrocytic protozoa of the *Babesia* genus, which are transmitted to man by the bite of infected *Ixodes* ticks. Transmission by blood transfusion has also been reported. *Ixodes scapularis*, one of the ticks that may cause babesiosis, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* and therefore the bite from this tick may lead to babesiosis, human granulocytic anaplasmosis (see Ehrlichiosis, p.168), or Lyme disease (p.177) as a single infection or as a co-infection.[1] Babesiosis occurs worldwide in animals. In the US, human infection is most commonly due to *B. microti*; the disease is much rarer in Europe where it is usually caused by *B. divergens* or *B. bovis* .[1-3] Infection with the newly recognised babesia-like piroplasms WA-1 and MO-1 has also been reported in the USA.[1,2]

Clinical features of babesiosis acquired in the USA differ from that acquired in Europe. Infection in the USA is often asymptomatic and self-limiting, but may produce prolonged severe viral-like illness with fever and haemolytic anaemia, particularly in patients who are asplenic, elderly, debilitated, or immunocompromised (including those infected with HIV). Symptoms include chills, sweating, myalgia, arthralgia, weakness, fatigue, anorexia, nausea, vomiting, jaundice, and headache. The most common complications are heart failure, disseminated intravascular coagulation, acute respiratory distress syndrome, and renal failure.[1-3] Co-infection with *B. microti* and *Borrelia burgdorferi* has resulted in more severe symptoms. In Europe, infections have mostly been described in asplenic persons, in many of whom the infection was rapidly fatal. Clinical features include severe haemolytic anaemia, jaundice, pulmonary oedema, and renal failure.

There is no established specific **treatment** for babesiosis. Treatment is not recommended for asymptomatic patients although all symptomatic patients should be treated with antibacterials to prevent the development of complications.[1] For serious infections, supportive therapies include red blood cell exchange transfusions to reduce parasitaemia. Clindamycin with quinine was the first regimen used[4] for the treatment of *B. microti* infections, but has been associated with significant toxicity. A prospective randomised study[5] in 58 patients found azithromycin with atovaquone to be as effective as clindamycin and quinine and associated with less toxicity. Azithromycin with quinine has been reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[6,7] Pentamidine has also been reported to produce clinical improvement in patients with *B. microti* infection,[8] but the efficacy and safety of pentamidine has been questioned.[9] Other drugs that have been tried with variable results include chloroquine, primaquine, pyrimethamine, sulfadiazine, and tetracycline.[2,3] The Infectious Diseases Society of America[1] recommends a combination of either clindamycin plus quinine or atovaquone plus azithromycin, both orally for 7 to 10 days; the combination of intravenous clindamycin plus oral quinine should be used in severe babesiosis. In immunocompromised patients higher doses of azithromycin may be used; they are prone to relapsing disease, and treatment should be given for 6 weeks or more, including 2 weeks after parasites are no longer detectable in blood smears.[10] Partial or complete exchange transfusion may also be given. Patients with persistent infection should be re-treated.

Patients *co-infected* or suspected to be co-infected with *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* should also be given doxycycline for 10 days.[1,3] For information on the treatment of co-infected patients see Lyme Disease, p.177. In *B. divergens* infections, treatment is complicated by the rapid progression of the disease. Antiprotozoal and antimalarial drugs have been tried with limited success, although pentamidine with co-trimoxazole was successful in a patient,[11] and a marked reduction in parasite load was seen in a patient treated with pentamidine plus exchange transfusions.[12] The combination of clindamycin plus quinine with exchange transfusion has also been suggested.[2]

Preventive measures against babesiosis include the use of tick repellents, physical protection, and prompt removal of attached ticks.[1]

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/07/08)
2. Homer MJ, *et al.* Babesiosis. *Clin Microbiol Rev* 2000; **13:** 451–69.
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9. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; **95:** 241.
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11. Raoult D, *et al.* Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; **107:** 944.
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Balantidiasis

Infection with the ciliate protozoan *Balantidium coli* results from the ingestion of cysts, the commonest sources of which are pigs. Water-borne epidemics of balantidiasis have been reported. Most infections are asymptomatic and the organism lives in the large intestine as a luminal commensal, but those with symptomatic infections have diarrhoea. Colonic ulceration resulting in a severe dysenteric syndrome resembling amoebic dysentery may occur in some individuals, especially if malnourished. Treatment is with tetracycline; metronidazole or diiodohydroxyquinoline are alternatives.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Blastocystis hominis infection

There is controversy over whether the protozoan parasite *Blastocystis hominis* is a pathogen or a harmless commensal of the intestinal tract. It has increasingly been reported both in immunocompetent and immunocompromised subjects,[1] with transmission probably by the faeco-oral route. Diarrhoea and other gastrointestinal symptoms have been ascribed to the organism.

Treatment with standard antiprotozoals, especially metronidazole, has had variable success; metronidazole resistance may occur.[2] Diiodohydroxyquinoline[3] and nitazoxanide[4] may also be effective. Co-trimoxazole was reported to have eliminated *B. hominis* from the stools of all but one of 47 otherwise healthy subjects with diarrhoea in one study,[5] and similarly in 36 of 38 children, and 14 of 15 adults, in another.[6]

1. Anonymous. Blastocystis hominis: commensal or pathogen? *Lancet* 1991; **337:** 521–2.
2. Haresh K, *et al.* Isolate resistance of Blastocystis hominis to metronidazole. *Trop Med Int Health* 1999; **4:** 274–7.
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Coccidiosis

Coccidiosis is a term sometimes applied to infections with protozoa of the order *Eucoccidiorida*. The predominant coccidian infections in man are caused by *Cryptosporidium* (below), *Cyclospora cayetanensis* (below), *Isospora* (below), *Plasmodium* (see Malaria, p.594), and *Toxoplasma* (below). Coccidian protozoa, primarily *Eimeria*, cause economically important infections in domesticated animals.

Cryptosporidiosis

Cryptosporidiosis is a gastrointestinal infection caused by species of the coccidian protozoan parasite *Cryptosporidium*. It has a worldwide distribution and occurs in many animal species as well as in man. Infection is acquired through ingestion, and perhaps inhalation, of oocysts. Infection in immunocompetent individuals usually causes a self-limiting diarrhoea lasting up to 2 weeks. In immunocompromised patients there may be profuse and persistent diarrhoea, profound weight loss, and severe abdominal pain, and the infection may be life-threatening. Cryptosporidiosis is a cause of diarrhoea in patients with AIDS. Other sites of infection include the respiratory and biliary tracts.

There is currently no consistently effective specific therapy[1] (evidence is perhaps best for nitazoxanide.[2]) and priority should be given to maintaining hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p.1694. In patients with AIDS the best treatment is improvement of immune function with HAART, but where this is not possible therapy with an antimicrobial and an antidiarrhoeal drug continues to be standard.[1] Paromomycin,[3-10] azithromycin,[11,12] and nitazoxanide[13,14] are widely used, although benefits are at best moderate.[1] Therapy with paromomycin plus azithromycin has produced some beneficial responses in patients with AIDS-related cryptosporidiosis.[15] Other treatments reported to have produced benefit include hyperimmune bovine colostrum,[16-20] eflornithine,[21] normal immunoglobulin with high cryptosporidium antibody titres,[22] or letrazuril,[23,24] but again the numbers of patients involved are small. Responses to spiramycin have not been consistent.[25-27] Beneficial responses to octreotide have been reported in a few cases,[28,29] but a study in patients with refractory AIDS-related diarrhoea suggested that response was better in patients without identifiable pathogens.[30]

Clarithromycin and rifabutin may be useful for disease prophylaxis,[31] although the efficacy of clarithromycin has been questioned.[32]

1. Chen X-M, *et al.* Cryptosporidiosis. *N Engl J Med* 2002; **346:** 1723–31.
2. Abubakar I, *et al.* Prevention and treatment of cryptosporidiosis in immunocompromised patients. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley, 2007 (accessed 09/07/08)
3. Clezy K, *et al.* Paromomycin for the treatment of cryptosporidial diarrhoea in AIDS patients. *AIDS* 1991; **5:** 1146–7.
4. Armitage K, *et al.* Treatment of cryptosporidiosis with paromomycin: a report of five cases. *Arch Intern Med* 1992; **152:** 2497–9.
5. Danziger LH, *et al.* Treatment of cryptosporidial diarrhea in an AIDS patient with paromomycin. *Ann Pharmacother* 1993; **27:** 1460–2.
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18. Nord J, *et al.* Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients. *AIDS* 1990; **4:** 581–4.
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20. Greenberg PD, Cello JP. Treatment of severe diarrhea caused by Cryptosporidium parvum with oral bovine immunoglobulin concentrate in patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **13:** 348–54.
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Cyclosporiasis

An organism originally described as cyanobacterium-like or coccidian-like bodies, but now identified as the coccidian protozoan *Cyclospora cayetanensis*, has been reported to be a cause of diarrhoea in both immunocompromised and immunocompetent patients. Infection results from ingestion of spores or oocysts in contaminated food or water. In immunocompetent patients, infection may be asymptomatic or cause a self-limiting diarrhoeal illness. Immunocompromised patients may develop severe or persistent symptoms. Beneficial responses have been reported with co-trimoxazole.[1-3] Ciprofloxacin may be an alternative in those unable to tolerate co-trimoxazole, although it is somewhat less effective.[3]

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Gastro-enteritis

Although bacteria and viruses are responsible for many cases of infective diarrhoea, protozoal infections are also a cause of diarrhoea, which can be severe (especially in immunocompromised patients, including those with AIDS). In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p.1694. Specific therapy with antiprotozoals may also be necessary to control enteric protozoal infections. For the management of the protozoal infections that are generally associated with diarrhoea, see under Amoebiasis (above), Balantidiasis (above), *Blastocystis hominis* infections (above), Cryptosporidiosis (above), Cyclosporiasis (above), Giardiasis (below), Isosporiasis (below), and Microsporidiosis (below).

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Giardiasis

Infection with *Giardia intestinalis* (*G. lamblia*; *Lamblia intestinalis*) occurs throughout the world and is one of the commonest intestinal protozoal infections. Infection is acquired by oral ingestion of *Giardia* cysts, and transmission may be person-to-person or from contaminated drinking water or foodstuffs. Infected patients may have acute or chronic diarrhoea or they may be asymptomatic. In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p.1694.

Treatment is with metronidazole or another nitroimidazole derivative such as tinidazole.[1] Albendazole, furazolidone, mebendazole, and mepacrine have all also been used but some of them may be less well tolerated than the nitroimidazoles. Nitazoxanide is also effective[2-4] and some consider it a drug of choice.[1] Paromomycin has been suggested;[1] although it is less effective than other drugs, it is not absorbed systemically and may be a useful alternative during pregnancy. Treatment may sometimes need to be repeated, possibly due to resistance,[5,6] and drug combinations such as metronidazole with mepacrine[5,7] have been reported to be of value in these cases.

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Infections in immunocompromised patients

Patients with a defective immune system are at particular risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, and splenectomy may all cause neutropenia and impaired humoral and cellular immunity in varying degrees. The risk of infection is linked to the duration and severity of neutropenia. Most protozoal infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Those of particular concern in patients with HIV infection include Cryptosporidiosis (above), Isosporiasis (below), Leishmaniasis (below), Microsporidiosis (below), and Toxoplasmosis (below).

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Isosporiasis

Isosporiasis is a coccidian protozoal infection of the gastrointestinal tract caused by *Isospora belli*. Oocysts are excreted in faeces and infection is acquired when sporulated oocysts are ingested. In immunocompetent individuals the infection is usually mild and self-limiting but in immunocompromised patients there may be severe, chronic gastroenteritis. Treatment is usually with co-trimoxazole.[1,2] Ciprofloxacin may be an alternative in those unable to tolerate co-trimoxazole, although it is somewhat less effective.[2] Pyrimethamine has been used successfully in individual patients with sulfonamide sensitivity.[3] In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p.1694.

Recurrence of infection is common and long-term suppressive treatment with either co-trimoxazole or pyrimethamine plus sulfadoxine has been recommended.[4]

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Leishmaniasis

Leishmaniasis[1,2] is caused by parasitic protozoa of the genus *Leishmania*. It occurs throughout Africa, the Middle East, Central Asia, and the Mediterranean (Old World leishmaniasis), and throughout Central and South America (New World leishmaniasis). In endemic areas there is generally a reservoir of disease in a mammalian host, often dogs or rodents. The usual vectors are sandflies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Leishmaniasis can be categorised as cutaneous, mucosal, and visceral and ranges from self-limiting, localised, cutaneous ulcers to widely disseminated progressive disease and involvement of the reticuloendothelial system. Incubation periods can be prolonged, with clinical features not appearing until several months or even years after the primary infection.

In endemic areas an integrated approach to controlling leishmaniasis involves case detection and treatment of patients, vector and animal reservoir control, environmental management to reduce suitable vector habitats, and personal protection against sandfly bites including the use of insect repellents and bednets.[3] Strategies aimed at controlling malaria are believed to have reduced leishmaniasis transmission dramatically.[3]

Visceral leishmaniasis of the Old World is mainly caused by *L. donovani* and *L. infantum* and of the New World by *L. chagasi*. The onset of the disease is gradual in residents of an endemic area but may present as an acute illness in non-immune visitors to the region. Many infections result in sub-clinical or self-limiting disease. Fever, malaise, shivering or chills, weight loss, anorexia, and discomfort in the left hypochondrium are common; there is often non-tender splenomegaly with or without hepatomegaly, wasting, pallor of mucous membranes, anaemia, leucopenia, and lymphadenopathy. Continued deterioration can lead to potentially fatal secondary infection. Darkening of the skin of the face, hands, feet, and abdomen is common in endemic visceral leishmaniasis in India (kala-azar = black sickness). Rare complications can include severe acute haemolytic anaemia, acute renal damage, and severe mucosal haemorrhage. In recent years, visceral leishmaniasis has emerged as an opportunistic infection in patients with HIV or other conditions associated with reduced immunity, in whom it is particularly difficult to treat.

A small percentage of patients develop post-kala-azar dermal leishmaniasis after recovery from visceral leishmaniasis and such patients represent a human reservoir for the disease.

The pentavalent antimonials meglumine antimonate and sodium stibogluconate are the traditional first-line drugs for the treatment of visceral leishmaniasis.[3-5] Patients relapsing after the initial course of treatment may be given a further course, but there is growing evidence that responsiveness to the antimonials is declining. Resistance to antimonials is widespread in parts of India.[5] Miltefosine has been shown to be effective[6-8] and has recently been introduced in India for treatment. Four regimens have been suggested for the first-line treatment of visceral leishmaniasis due to *L. infantum* in Mediterranean countries.[9] They are:

- pentavalent antimonials
- pentavalent antimonials plus allopurinol
- liposomal amphotericin B
- paromomycin alone or with pentavalent antimonials

These regimens have also been evaluated in other regions and in patients with HIV infection.[10-16] Amphotericin B has been tried successfully as a second-line drug in drug-resistant infections[17-20] and increasingly as a useful alternative first-line drug.[4,5,21,22] Lipid formulations of amphotericin B are better tolerated than conventional amphotericin B, and are likely to be preferred when the toxicity and duration of therapy with conventional forms would compromise patient compliance.[4] Pentamidine has also been used as a second-line drug but its usefulness as alternative first-line therapy is doubtful[23] given its toxicity, increasing failure rates, and slow disease response. Nevertheless it has been tried as an adjunct to meglumine antimonate for first-line therapy[24] and alone for long-term secondary prophylaxis in patients with HIV infection.[25] Beneficial responses to ketoconazole have been reported in some patients[26,27] but unfavourable reports have also appeared.[28,29] Another line of investigation is to boost the immune response to the parasite by adding interferon gamma to conventional treatment, although results have been variable.[30-33]

Cutaneous leishmaniasis is caused by various species of *Leishmania* and a wide variety of clinical presentations is possible. A 'classical' lesion starts as a nodule at the site of inoculation. A crust develops centrally which may fall away exposing an ulcer which heals gradually. Satellite nodules at the edge of the lesion are common. Cutaneous leishmaniasis of the Old World is normally caused by *L. tropica*, *L. major*, or *L. aethiopica*, although cutaneous lesions due to *L. infantum* have been reported. New World cutaneous leishmaniasis (American cutaneous leishmaniasis) is caused by numerous species and subspecies of *Leishmania* including *L. braziliensis*, *L. mexicana*, *L. panamensis*, and *L. peruviana*. In general, New World forms tend to be more severe and longer lasting than Old World forms. The disease ranges from single, self-healing lesions which are troublesome and unsightly but not a threat to life, to multiple, deep, and destructive ulcers which cause considerable disfigurement and disability.

Diffuse cutaneous leishmaniasis occurs occasionally after infection with *L. aethiopica* or members of the *L. mexicana* complex and involves dissemination of the disease from the original site of infection to distant skin sites, typically the face and exterior surfaces of the limbs. The lesions resemble lepromatous leprosy, do not heal spontaneously, and are resistant to treatment.

Another variant is leishmaniasis recidivans which is a lupoid or tuberculoid form. This chronic disease often occurs as slowly progressive, destructive and disfiguring lesions on the face which are very resistant to most forms of therapy.

There is no established treatment for cutaneous leishmaniasis.[5] The decision to treat depends upon the site and extent of the lesions and the likelihood of dissemination. Small lesions, particularly in Old World cutaneous leishmaniasis, may be left untreated if they are not troublesome to the patient. Treatment for disfiguring or potentially disabling lesions may be local or systemic. Systemic treatment is required where there is a risk that the infecting organism may be one causing mucocutaneous leishmaniasis (see below) or where there is evidence of lymphatic spread or extensive local involvement.

WHO[3] suggested that early noninflamed nodular lesions due to *L. tropica*, *L. major*, *L. mexicana*, *L. panamensis*, or *L. peruviana* might be treated with intralesional injections of mepacrine, sodium stibogluconate, or meglumine antimonate, or removed by surgery and curettage. Benefit has been reported with this therapy.[5,34,35] However, local infiltration of drugs can be difficult as well as painful. Surgical curettage may promote dissemination of the parasite.[36] Other local treatments include cryotherapy or, alternatively, application of heat to bring the temperature of the lesion to about 40° which may aid healing.[37] Topical treatment with paromomycin sulfate 15% plus methylbenzethonium chloride 5 or 12% has produced promising responses;[38-41] paromomycin 12 to 15% with urea 10% was better tolerated.[42] However, not all studies have shown benefit.[43,44]

Systemic treatment is similar to that of visceral leishmaniasis[3,5,45,46] (see above). Topical paromomycin plus systemic meglumine antimonate was initially found to be promising in patients with New World infections,[47] but a subsequent randomised, controlled study[48] found that application of paromomycin sulfate 15% with methylbenzethonium chloride 12% did not augment the clinical response to parenteral meglumine antimonate. Cutaneous leishmaniasis due to *L. aethiopica*, including diffuse cutaneous leishmaniasis, does not generally respond to antimonials[3] although responses to antimonials with paromomycin have been reported.[49] It may also be treated with pentamidine.[3,5]

Other drugs tried in cutaneous leishmaniasis have included fluconazole,[50] itraconazole,[51-54] and ketoconazole.[41,55-58] Variable responses to allopurinol have been reported in patients with New World infections.[59-61] Dapsone was reported to be effective in a study in patients in India[62] but not in Colombia.[63] Among the non-specific therapies tried in cutaneous leishmaniasis, topical application of the nitric oxide donor *S*-nitroso-*N*-acetylpenicillamine (SNAP)[64] and intralesional injection of hypertonic sodium chloride solution[65] have produced beneficial responses. Immunomodulation using leishmania antigens mixed with BCG,[66,67] or interferon gamma,[68,69] has produced encouraging results.

While there has been some work on vaccines against cutaneous leishmaniasis much more needs to be done. However, leishmanisation (deliberate infection with *L. major*) has been used as a last resort in some countries when other measures have failed.

Mucocutaneous leishmaniasis of the New World (espundia) is caused by *L. braziliensis* or *L. panamensis*. In mucocutaneous leishmaniasis the primary lesions do not heal spontaneously. Metastatic spread to the mucosa may occur during the presence of the primary lesion or up to 30 years later. The nasal mucosa is always affected. Ulceration and erosion progressively destroy the soft tissue and cartilage of the oronasal/pharyngeal cavity. Mutilation is severe and secondary bacterial infection is frequent and can be fatal.

Mucocutaneous leishmaniasis responds poorly to treatment and relapses are common. Initial treatment is with pentavalent antimony;[5] failure to respond is an indication to use amphotericin B or pentamidine. Nifurtimox may be effective in some cases of mucocutaneous leishmaniasis.[3] Treatment with corticosteroids may be needed to control severe inflammation. Mucosal disease in Old World leishmaniasis is much less common than visceral or cutaneous forms, but treatment with antimony compounds or ketoconazole has been described.[70]

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Malaria

For a discussion of malaria, its prophylaxis and treatment, see p.594.

Microsporidiosis

Microsporidia are obligate intracellular spore-forming protozoal parasites. They were primarily regarded as a cause of disease in nonhuman species but some, including *Encephalitozoon*, *Enterocytozoon*, *Pleistophora*, and *Trachipleistophora* spp. and *Brachiola vesicularum* and *Vittaforma corneae (Nosema corneum)*, are now recognised as human pathogens. Transmission is believed to be predominantly faeco-oral although inhalation and direct inoculation also occur. Infections usually occur only in immunocompromised patients. Small bowel infection with *Enterocytozoon bieneusi* has been reported in AIDS patients as a cause of chronic diarrhoea and weight loss. Other manifestations of microsporidiosis in AIDS include keratoconjunctivitis, respiratory-tract infections, renal and urinary-tract infections, peritonitis, cholangitis, granulomatous hepatitis, and disseminated myositis.

There is no established treatment.[1] Beneficial responses have been reported with albendazole[2-6] and atovaquone.[7] Metronidazole has been reported to produce a transient symptomatic response in some patients[8] but not in those with severe diarrhoea.[9] There has also been a report of a patient treated successfully with nitazoxanide.[10] Fumagillin appears effective in the treatment of infection due to *E. bieneusi*.[11]

Topical treatment of keratoconjunctivitis has been disappointing, although there are reports of individual patients responding to topical propamidine isetionate,[12] topical fumagillin,[13,14] oral albendazole,[15] oral albendazole plus topical fumagillin,[16] or oral itraconazole plus topical antibacterials.[17]

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Pneumocystis pneumonia

Although *Pneumocystis jirovecii* was formerly classified as a protozoan, it is now accepted to be a fungus. For the management of pneumocystis pneumonia, see p.521.

Toxoplasmosis

Toxoplasmosis[1] is a zoonosis with a worldwide distribution caused by the protozoan parasite *Toxoplasma gondii*. There is a high incidence of *Toxoplasma* antibody, an indication of previous infection, in the general population, although infection will have been diagnosed in few individuals. Sexual reproduction of *T. gondii* occurs in the gastrointestinal tract of cats. Soil becomes contaminated from excretion of oocysts in cat faeces. Other animals, such as pigs and sheep, may become infected by ingestion of these oocysts and act as intermediate hosts. In man, infection is acquired through contact with infected cat faeces or contaminated soil, or from eating raw or undercooked meat from infected animals. Ingested oocysts rapidly transform into trophozoites which multiply in tissue macrophages. The intracellular trophozoites disseminate in the bloodstream and lymphatic system to reach the brain, heart, and lungs. As immunity develops the trophozoites form latent cystic aggregates (bradyzoites), mainly in the brain, heart, and skeletal muscle, and these are subject to reactivation throughout the life of the host.

Toxoplasma infection in immunocompetent individuals is usually asymptomatic and if symptomatic infection does occur it is usually self-limiting. Very rarely myocarditis or encephalitis may occur. Patients with impaired immunity may develop serious complications such as encephalitis, chorioretinitis, myocarditis, and pneumonitis. Toxoplasmic encephalitis is the most common presentation in patients with AIDS.

Congenital toxoplasmosis is not a problem in women who have *Toxoplasma* antibody before conception, but primary toxoplasmosis during early pregnancy is serious because of the risk of transplacental transmission which may result in fetal death or congenital toxoplasmosis. Primary infection during later pregnancy can also result in congenital infection, although this often only becomes symptomatic later in life. The sequelae in live-born infants with signs of infection are generally severe and include a potentially fatal syndrome in which hydrocephalus, hepatosplenomegaly with jaundice, mental retardation, and chorioretinitis may occur. Congenital disease that becomes clinically evident later in life is usually less severe, but often results in ocular or neurological impairment. Infection in the pregnant woman is usually asymptomatic and antenatal screening programmes have been set up in some countries for the diagnosis of acute infections during pregnancy. However, the value and practicality of such schemes has been debated.[2-6] Ocular toxoplasmosis causes chorioretinitis and is often a result of congenital infection; patients may be asymptomatic until later in life.

Treatment. Toxoplasmosis in immunocompetent patients is not usually treated unless symptoms are severe. Currently there is no drug active against the cystic form, so any treatment is directed against the acute forms of the disease. Active toxoplasmosis in immunocompromised patients requires prompt treatment. Toxoplasmosis is normally treated with pyrimethamine plus sulfadiazine.[7,8] Folinic acid should also be given during treatment to counteract the megaloblastic anaemia associated with these drugs. Clindamycin plus pyrimethamine and folinic acid has been used as an alternative in patients unable to take the sulfonamide.[8] Other drug combinations have been studied and have been found to have activity in toxoplasmic encephalitis, notably atovaquone plus pyrimethamine and folinic acid, or atovaquone plus sulfadiazine, or azithromycin plus pyrimethamine and folinic acid. Atovaquone has also been given alone in patients unable to tolerate pyrimethamine or sulfadiazine.[8] Severely ill patients needing parenteral therapy have been given intravenous co-trimoxazole or clindamycin with oral pyrimethamine.[8] Adjunctive corticosteroids may be given occasionally for treatment of a mass effect associated with focal lesions or oedema, but should be stopped as soon as possible because of their immunosuppressant effect. Anticonvulsants should be given to patients with a history of seizures.[8] Acute treatment is ideally continued for 6 weeks, or for longer if disease is extensive or response is incomplete.

Patients who have successfully completed a 6-week course of acute therapy should be given chronic maintenance therapy, which should ideally be with pyrimethamine plus sulfadiazine and folinic acid, but alternatives are pyrimethamine plus clindamycin and folinic acid, or atovaquone, with or without pyrimethamine and folinic acid.[8] Chronic maintenance therapy should be lifelong unless immune reconstitution occurs because of antiretroviral therapy, in which case consideration may be given to stopping prophylaxis. It should, however, be restarted if the CD4+ T lymphocyte count falls to below 200 cells/microlitre.[8]

A systematic review[9] of the treatment of women during **pregnancy** has involved small studies with variations in period of gestation, duration of follow-up, and other aspects of methodology, making comparison of data problematical; consequently the evidence is inconclusive as to whether treatment is effective in preventing fetal infection or overt neonatal disease. If treatment is given, pyrimethamine should not be used to treat primary toxoplasmosis during the first trimester of pregnancy in immunocompetent patients. Spiramycin has been used throughout the first trimester but, although it reduces the risk of congenital transmission, it does not readily penetrate the cerebrospinal space and does not prevent toxoplasmic encephalitis in immunocompromised women. After the first trimester pyrimethamine may be given with sulfadiazine and folinic acid and, when there is evidence of placental or fetal infection, this treatment may be alternated with courses of spiramycin until term. In **neonates** with congenital toxoplasmosis, the preferred treatment is pyrimethamine together with sulfadiazine and folinic acid.[7] Infants without HIV infection should be treated for 12 months. In infants with mild toxoplasmosis, some experts recommend alternating pyrimethamine-sulfadiazine with spiramycin on a monthly basis from months 7 to 12, in order to reduce the risk of bone marrow suppression. However, infants with HIV infection and moderate to severe toxoplasmosis should receive the full 12-month regimen of pyrimethamine-sulfadiazine.[7] Longer courses of treatment may be given in cases of extensive disease. A corticosteroid, usually dexamethasone or prednisolone, has been added in children with CNS involvement.[7]

In immunocompetent individuals, **ocular toxoplasmosis** is a self-limiting disease and requires no treatment, unless visual acuity is threatened or there is a large retinal lesion with marked vitritis.[10-12] A systematic review[13] found a lack of evidence to support routine treatment for acute toxoplasma retinochoroiditis in immunocompetent patients, but did find weak evidence to suggest that long-term treatment of patients with chronic recurrent disease may reduce recurrence. All immunocompromised patients should be treated and prolonged treatment is necessary to prevent recrudescence. The best drug regimen is unknown. The most commonly used regimens are pyrimethamine with sulfadiazine or pyrimethamine with clindamycin (which is concentrated in the choroid). Benefit has been reported from clindamycin with corticosteroids,[14] although corticosteroids should never be used alone since fulminant cases may occur. Spiramycin is not indicated for ocular toxoplasmosis.

Prophylaxis. Primary prophylaxis against *T. gondii* infection has been investigated in AIDS patients and recipients of organ transplants. In HIV-infected persons who are seropositive for *Toxoplasma* and who have a CD4+ T lymphocyte count of less than 100 cells/microlitre, primary prophylaxis against encephalitis should be given.[15] Co-trimoxazole, in regimens designed for pneumocystis pneumonia prophylaxis, was found to be effective and is therefore recommended.[15] Alternatively, pyrimethamine plus dapsone may be given.[15] Atovaquone with or without pyrimethamine can also be considered.[15] Pyrimethamine plus sulfadoxine has also been tried, with promising results.[16] *Toxoplasma*-seronegative persons who are not receiving a pneumocystis prophylactic regimen known to be active against toxoplasmic encephalitis should be retested for *Toxoplasma* should their CD4+ T lymphocyte count fall below 100 cells/microlitre and if they have seroconverted primary prophylaxis should be instigated.[15] Primary prophylaxis should be stopped in adult and adolescent patients whose CD4+ T lymphocyte count rises in response to antiretroviral therapy to more than 200 cells/microlitre for 3 months or more. If the count subsequently falls to below 200 cells/microlitre it should be reinstigated.[15]

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Trichomoniasis

Trichomoniasis is caused by invasion of the genito-urinary tract with the protozoan *Trichomonas vaginalis*. Transmission is primarily sexual. Trichomoniasis is a common cause of vaginitis and vaginal discharge; some infected women are asymptomatic but should still be treated to prevent sexual transmission and symptomatic infection. Men are usually asymptomatic, although they may experience urethritis.

Treatment is usually with a nitroimidazole such as metronidazole when a single oral dose can be effective.[1-4] Sexual partners should also be treated. The incidence of treatment failures appears to be increasing and some at least have been due to metronidazole resistance. Patients who do not respond to single-dose treatment may be given a more intensive course of metronidazole for 5 to 7 days. Tinidazole has been widely used as an alternative to metronidazole,[1] and may be effective in cases of metronidazole resistance.[5] A patient with metronidazole- and tinidazole-resistant infection was successfully treated with paromomycin.[6] Local application of paromomycin has also been tried in a small number of patients with moderate success.[7]

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African trypanosomiasis

African trypanosomiasis (sleeping sickness) is caused by subspecies of the protozoan *Trypanosoma brucei*, transmitted by the bite of infected tsetse flies (*Glossina* spp.). Gambian or West African sleeping sickness is caused by *T. brucei gambiense*, carried by riverine tsetse flies, and Rhodesian or East African sleeping sickness is caused by *T. brucei rhodesiense*, carried by savannah tsetse flies. Infection can follow blood transfusion and congenital trypanosomiasis has also occurred.

Although it has proven impractical to eliminate trypanosomiasis from endemic areas, the intensity of transmission can be reduced by detection and treatment of cases and vector control, including insecticide spraying of breeding sites and the use of insecticide-impregnated traps and screens.[1] Control of infection in domestic animals may also be beneficial.[1]

Trypanosomiasis can be divided into the early haematolymphatic stage (infection of the bloodstream and lymph nodes), with lymphadenopathy, pruritus, fever, headache, and muscle and joint pain, and the late or meningoencephalitic stage (infection of the CNS) which is marked by signs including sleep disturbances, confusion, incoordination, psychiatric disorders, and eventual deterioration of consciousness.[1-3] Trypanosomiasis due to *T. b. gambiense* develops slowly over several months or even years and the disease stages are relatively distinct. Infection with *T. b. rhodesiense* is more acute with a rapid onset of symptoms and indistinct disease stages and, if left untreated, will usually lead to death in a matter of weeks or months.

The **haematolymphatic** phase of African trypanosomiasis is treated with suramin or pentamidine.[1-3] Pentamidine may be used for treatment of *T. b. gambiense* infections, but increasing resistance makes it unsuitable for *T. b. rhodesiense* infections; suramin is used for *T. b. rhodesiense* infections and for *T. b. gambiense* infections which are resistant to pentamidine. Giving both pentamidine and suramin for *T. b. gambiense* infections has not been shown to reduce the incidence of relapse.[4]

Suramin and pentamidine penetrate the blood-brain barrier poorly and are only used in the **meningoencephalitic** stage as adjuncts before starting treatment with melarsoprol or eflornithine. Melarsoprol, which is effective against both *T. b. gambiense* and *T. b. rhodesiense*, is usually only given to treat the meningoencephalitic stage of the infection because it may produce potentially fatal encephalopathy. However, protection against this toxicity may be provided by prophylaxis with prednisolone.[5,6] Patients with *T. b. gambiense* infection may be treated more safely with eflornithine than melarsoprol on its own.[7-9] Combination therapy with melarsoprol and eflornithine was reported to be effective in a patient who had not responded to either drug alone.[10] Eflornithine given with suramin produced disappointing results in 6 patients with *T. b. rhodesiense*.[11]

Nifurtimox[1,12,13] is an alternative treatment to melarsoprol for relapse of *T. b. gambiense* infection. Promising results have been obtained from a randomised controlled study[14] for the treatment of second stage *T.b. gambiense* infection with oral nifurtimox plus intravenous eflornithine.

There is no established effective alternative treatment for melarsoprol-resistant *T. b. rhodesiense*, although suramin given with high-dose metronidazole was successful in a patient.[15]

Patients should be seen every 6 months for a follow-up period of at least 2 years, to ascertain if treatment has been successful.

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American trypanosomiasis

American trypanosomiasis (Chagas' disease) is caused by *Trypanosoma cruzi*, carried by reduviid or triatomine bugs which feed on human blood.[1] Infected bugs defecate on the human host while feeding and metacyclic trypanosomes are shed and enter the host via skin abrasions or by direct penetration of mucous membranes such as the conjunctiva. Transmission by blood transfusion has been a large problem. Congenital infection can also occur. Control measures include case detection and treatment, vector control by insecticide applications within domestic buildings, and screening of blood donors.[1]

Infection with *T. cruzi* is found throughout South and Central America and has been recorded in Mexico and Texas; there have also been reports of transfusion-induced infection in northern USA and Canada. Three phases of the disease are recognised. In the early acute phase of infection parasites are present in the blood; this phase may be asymptomatic or there may be a swelling or chagoma at the site of infection, allergic reactions, and more rarely acute heart failure or meningoencephalitis. The acute phase may be fatal in children, but patients usually survive to enter an indeterminate phase, in which infection may be present in tissue for years without clinical manifestations. Classical features of the final chronic phase are cardiomyopathy, megacolon, and mega-oesophagus. Parasitaemia falls to undetectable levels after the acute phase.

Available treatment is generally unsatisfactory but, despite their toxicity, nifurtimox or benznidazole are of value especially in the acute phase; it is not certain whether trypanocidal treatment during the indeterminate phase can prevent the development of chronic disease although favourable results were obtained in a small study in children given benznidazole.[2] Although it is generally felt that there is no benefit from treatment in the chronic phase, treatment during the early chronic phase was reported to be beneficial,[3] and long-term follow-up of patients who had received benznidazole showed a reduction in cardiac complications and parasitaemia.[4] Symptomatic treatment is often given, particularly in the chronic stage for cardiac and gastrointestinal lesions. A systematic review[5] considered that indications for treatment with benznidazole or nifurtimox included all cases of congenital infection, reactivated infection, and all children 18 years of age or less; antitrypanocidal treatment should also generally be offered to adults aged 19 to 50, and should be considered in older adults although the risks of drug therapy were greater in the last group. It was not recommended for advanced Chagasic cardiomyopathy, since the existing pathology would not benefit, but the potential to reduce development of cardiomyopathy should be considered in patients with gastrointestinal involvement.

The efficacy of treatment varies from country to country and may be linked to variations in the sensitivity of different strains of *T. cruzi*. Treatment is said to be successful when both parasitaemia and serological tests become negative and remain so for at least one year after the end of treatment.

Allopurinol and allopurinol riboside are under investigation for the treatment of American trypanosomiasis since they have shown trypanocidal activity. Allopurinol has been reported to be as effective as nifurtimox or benznidazole in reducing parasitaemia during the indeterminate phase and to be better tolerated.[6] Allopurinol and itraconazole, alone or in combination, have produced beneficial responses in patients with chronic disease.[7,8]

In areas where the proportion of seropositive blood donors is high, emergency blood supplies positive for *T. cruzi* have been made safe by the addition of methylrosanilinium chloride. It has been suggested that the risk of transmission to transplant recipients can be reduced considerably by nifurtimox or benznidazole treatment of the donor for 2 weeks before transplantation, and of the recipient for 2 weeks after transplantation. In laboratory workers at risk of an infection after an accident, treatment with benznidazole for 10 days should be started immediately.

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Acetarsol *(BAN, rINN)*

Acetaminohydroxyphenylarsonsäure; Acétarsol; Acetarsolum; Acetarsone; Acetphenarsinum; Asetarsoli; Osarsolum. 3-Acetamido-4-hydroxyphenylarsonic acid.

Ацетарсол

$C_8H_{10}AsNO_5$ = 275.1.

CAS — 97-44-9.

ATC — A07AX02; G01AB01; P01CD02.

ATC Vet — QA07AX02; QG01AB01; QP51AD05.

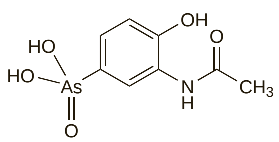

Profile

Acetarsol, a pentavalent organic arsenical derivative, was formerly given orally in the treatment of intestinal amoebiasis and vaginally in the treatment of trichomoniasis, but the use of pentavalent arsenical compounds has been abandoned in favour of more effective and less toxic drugs. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p.2260.

Acetarsol suppositories were once tried in the treatment of proctitis. Acetarsol lithium and acetarsol sodium have been included in some preparations for minor mouth infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Rus.:*** Osarbon (Осарбон).

Amprolium Hydrochloride *(BANM, rINNM)*

Amprolii Hydrochloridum; Amprolium, Chlorhydrate d'; Hidrocloruro de amprolio. 1-(4-Amino-2-propylpyrimidin-5-ylmethyl)-2-methylpyridinium chloride hydrochloride.

Амлролия Гидрохлорид

$C_{14}H_{19}ClN_4,HCl$ = 315.2.

CAS — 121-25-5 (amprolium); 137-88-2 (amprolium hydrochloride).

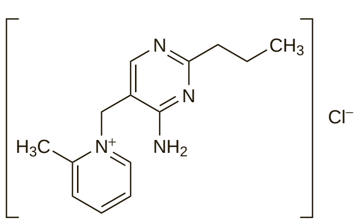

(amprolium)

Pharmacopoeias. In *Fr.* and *US* for veterinary use only. Also in *BP(Vet).*

BP(Vet) 2008 (Amprolium Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform; very slightly soluble in ether.

USP 31 (Amprolium). A white to light yellow powder. Freely soluble in water, in alcohol, in dimethylformamide and in methyl alcohol; sparingly soluble in dehydrated alcohol; practically insoluble in acetone, in butyl alcohol, and in isopropyl alcohol.

Profile

Amprolium hydrochloride is an antiprotozoal used in veterinary practice, alone or with other drugs such as ethopabate, for the control of coccidiosis in pigeons and in poultry.

Pentavalent Antimony Compounds

Antimonio pentavalente, compuestos de.

Meglumine Antimonate

Antimoniato de meglumina; Antimony Meglumine; Meglumine Antimoniate; Protostib; RP-2168. 1-Deoxy-1-methylamino-D-glucitol antimonate.

Меглумина Антимонат

$C_7H_{18}NO_8Sb$ = 366.0.

CAS — 133-51-7.

ATC — P01CB01.

ATC Vet — QP51AB01.

Sodium Stibogluconate *(BAN, rINN)*

Estibogluconato de sodio; Natrii Stibogluconas; Natriumstiboglukonaatti; Natriumstiboglukonat; Sod. Stibogluc.; Sodium Antimony Gluconate; Sodyum Stiboglukonat; Stibogluconate de Sodium; Stibogluconat-Natrium.

Натрия Стибоглюконат

CAS — 16037-91-5.

ATC — P01CB02.

ATC Vet — QP51AB02.

Description. A pentavalent antimony compound of indefinite composition. It has been represented by the formula $C_6H_9Na_2O_9Sb$ but usually there are less than 2 atoms of Na for each atom of Sb. Solutions may be sterilised by autoclaving.

Pharmacopoeias. In *Br., Chin., Int.,* and *It.*

BP 2008 (Sodium Stibogluconate). It is mainly the disodium salt of μ-oxy-bis[gluconato(3-)O^2,O^3,O^4-hydroxo-antimony]. It contains not less than 30.0% and not more than 34.0% of antimony(V), calculated with reference to the dried and methanol-free substance. It is a colourless, odourless or almost odourless, mostly amorphous powder. Very soluble in water; practically insoluble in alcohol and in ether. A solution in water containing 10% of pentavalent antimony has a pH of 5.0 to 5.6 after autoclaving.

Adverse Effects, Treatment, and Precautions

As for Trivalent Antimony Compounds, p.141.

Adverse effects are generally less frequent and less severe with the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate than with trivalent compounds such as antimony sodium tartrate. Nevertheless, similar precautions should be observed, especially in patients on high-dose therapy.

Intramuscular injections of sodium stibogluconate can be painful and intravenous use has been associated with thrombophlebitis.

◊ Common adverse effects of pentavalent antimony are anorexia, vomiting, nausea, malaise, arthralgia and myalgia, headache, lethargy, and pancreatitis. ECG changes are dose-dependent and most commonly include T-wave inversion and prolonged QT interval. Renal damage is a rarely reported toxic effect. Pentavalent antimony is usually well tolerated. Serious adverse effects when they occur usually involve the liver or the heart when it is prudent to interrupt the course temporarily.

References.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Aronson NE, *et al.* Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. *Clin Infect Dis* 1998; **27:** 1457–64.

Breast feeding. The amount of antimony distributed into the breast milk of a patient given sodium stibogluconate was considered not to constitute a hazard and oral absorption was not detected in an *animal* study.[1] The American Academy of Pediatrics also considers that the use of antimony is usually compatible with breast feeding.[2] Others, however, have felt that more safety evaluation was required before antimony could be considered completely safe during breast feeding.[3]

1. Berman JD, *et al.* Concentration of Pentostam in human breast milk. *Trans R Soc Trop Med Hyg* 1989; **83:** 784–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)
3. Verschoyle RD. Comment. *Trop Dis Bull* 1990; **87:** 919.

Effects on the blood. Although thrombocytopenia is associated with leishmaniasis, there are case reports of it also being associated with sodium stibogluconate.[1,2]

1. Braconier JH, Miörner H. Recurrent episodes of thrombocytopenia during treatment with sodium stibogluconate. *J Antimicrob Chemother* 1993; **31:** 187–8.
2. Hepburn NC. Thrombocytopenia complicating sodium stibogluconate therapy for cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1993; **87:** 691.

Effects on the heart. The ECG was monitored during 65 courses of treatment with sodium stibogluconate in 59 Kenyan patients with leishmaniasis.[1] ECG abnormalities developed during 35 treatment courses. They were qualitatively similar to those previously described during treatment with trivalent antimonial drugs, but occurred less frequently and later during the course of treatment. The most common abnormality was inversion and/or decreased amplitude of T waves. Incidence was related to total daily dose and duration of treatment. One patient died suddenly during the 4th week of treatment with antimony 60 mg/kg daily. Other deaths probably related to cardiac toxicity have been reported in patients receiving 60 mg/kg daily[2] and 30 mg/kg daily.[3] It has been recommended[1] that for treatment with sodium stibogluconate ECGs should be obtained every 3 to 4 days in patients given antimony 20 mg/kg daily for more than 20 days or a higher dose for more than 10 days. If Stokes-Adams attacks or ventricular tachyarrhythmias develop, sodium stibogluconate should be stopped and appropriate treatment given. A retrospective study[4] in patients treated with sodium stibogluconate for mostly cutaneous leishmaniasis found that the mean QT_c interval steadily increased throughout the period of treatment, reaching a potentially toxic threshold by the third week, but cardiotoxicity was seen only in one elderly patient who had hypokalaemia and pre-existing cardiovascular morbidity. Identification before treatment of factors that may increase cardiovascular risk is important.

1. Chulay JD, *et al.* Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). *Am J Trop Med Hyg* 1985; **34:** 702–9.
2. Bryceson ADM, *et al.* Visceral leishmaniasis unresponsive to antimonial drugs II: response to high dosage sodium stibogluconate or prolonged treatment with pentamidine. *Trans R Soc Trop Med Hyg* 1985; **79:** 705–14.
3. Thakur CP. Harmful effect of high stibogluconate treatment of kala-azar in India. *Trans R Soc Trop Med Hyg* 1986; **80:** 672–3.
4. Lawn SD, *et al.* Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg* 2006; **100:** 264–9.

Effects on the kidneys. Sodium stibogluconate given for 10 days to 16 young men with cutaneous leishmaniasis had no apparent adverse effect on glomerular or tubular renal function.[1] However, evidence of renal tubular dysfunction has been reported in patients with mucocutaneous leishmaniasis given meglumine antimonate or sodium stibogluconate for 30 days or more[2] and acute renal failure has occurred in patients both with,[3] and without,[4] pre-existing renal impairment, the latter resulting in death.

1. Joliffe DS. Nephrotoxicity of pentavalent antimonials. *Lancet* 1985; **i:** 584.
2. Veiga JPR, *et al.* Renal tubular dysfunction in patients with mucocutaneous leishmaniasis treated with pentavalent antimonials. *Lancet* 1983; **ii:** 569.
3. Balzan M, Fenech F. Acute renal failure in visceral leishmaniasis treated with sodium stibogluconate. *Trans R Soc Trop Med Hyg* 1992; **86:** 515–16.
4. Rodrigues MLO, *et al.* Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. *Rev Inst Med Trop Sao Paulo* 1999; **41:** 33–7.

Effects on the liver. WHO has reported that when serious adverse effects occur with sodium stibogluconate they usually involve the liver or the heart.[1] There have been reports of disturbed liver function[2,3] in patients given sodium stibogluconate, although there has also been a report[4] that signs of altered liver function, which may be a feature of visceral leishmaniasis, improved during treatment with sodium stibogluconate.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
3. Hepburn NC, *et al.* Hepatotoxicity of sodium stibogluconate in leishmaniasis. *Lancet* 1993; **342:** 238–9.
4. Misbahuddin M, *et al.* Stibogluconate for leishmaniasis. *Lancet* 1993; **342:** 804.

Effects on the musculoskeletal system. Arthralgia is common with pentavalent antimony compounds. It is usually dose-dependent[1] but a patient has been described who experienced symptoms early in treatment.[2] Palindromic arthropathy with effusion was associated with sodium stibogluconate treatment in another patient.[3]

1. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii:** 13–16.
2. Castro C, *et al.* Severe arthralgia, not related to dose, associated with pentavalent antimonial therapy for mucosal leishmaniasis. *Trans R Soc Trop Med Hyg* 1990; **84:** 362.
3. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.

Effects on the nervous system. Peripheral neuropathy developed in a patient about 8 days after starting therapy with sodium stibogluconate.[1] The symptoms were generally reversible when treatment was stopped (after 17 days), although there was some slight persistent hypoaesthesia in the toes. An interaction with a single dose of amitriptyline, taken on the second day of stibogluconate therapy, seemed unlikely but could not be ruled out.

1. Brummitt CF, *et al.* Reversible peripheral neuropathy associated with sodium stibogluconate therapy for American cutaneous leishmaniasis. *Clin Infect Dis* 1996; **22:** 878–9.

Effects on the pancreas. Pancreatitis has been associated with sodium stibogluconate treatment.[1-3] Withdrawing treatment usually resulted in resolution of pancreatitis.

1. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; **21:** 107–10.
2. Gasser RA, *et al.* Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis* 1994; **18:** 83–90.
3. Domingo P, *et al.* Treatment of Indian kala-azar with pentavalent antimony. *Lancet* 1995; **345:** 584–5.

Pharmacokinetics

The pentavalent antimony compounds are poorly absorbed from the gastrointestinal tract. After intravenous doses an initial distribution phase is followed by biexponential elimination by the kidneys. The elimination half-life of the initial phase is about 1.7 hours and that of the slow terminal phase is about 33 hours. The corresponding half-lives after intramuscular doses are reported to be 2 hours and 766 hours respectively. The slow elimination phase may reflect reduction to trivalent antimony. Accumulation occurs on daily use and maximum tissue concentrations may not be reached for 7 days or more. Antimony has been detected in breast milk (see Breast Feeding, above).

◊ References.

1. Rees PH, *et al.* Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet* 1980; **ii:** 226–9.
2. Chulay JD, *et al.* Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. *Trans R Soc Trop Med Hyg* 1988; **82:** 69–72.
3. Al Jaser M, *et al.* Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharm Res* 1995; **12:** 113–16.

Uses and Administration

Pentavalent antimony, as sodium stibogluconate or meglumine antimonate, is used as first-line treatment for all forms of leishmaniasis except *Leishmania aethiopica* infections.

For systemic use, sodium stibogluconate is given by intramuscular or intravenous injection as a solution containing the equivalent of pentavalent antimony 100 mg/mL. Intramuscular injection is generally preferable. Intravenous injections must be given very slowly (over at least 5 minutes) and preferably through a fine needle to avoid thrombophlebitis; as with trivalent antimony compounds, they should be stopped immediately if coughing, vomiting, or substernal pain occurs. Meglumine antimonate is given by deep intramuscular injection as a solution containing the equivalent of pentavalent antimony 85 mg/mL. Doses are expressed in terms of the equivalent amount of pentavalent antimony.

Local variations exist in treatment schedules but WHO recommends the following regimens:

- In **visceral leishmaniasis**, initial treatment is based on daily intramuscular injection of pentavalent antimony 20 mg/kg to a maximum of 850 mg (but see below) for at least 20 days. The length of treatment varies from one endemic area to another, but is continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals. Patients who relapse are re-treated at the same dose.
- Early non-inflamed lesions of **cutaneous leishmaniasis** due to all forms of *Leishmania* except *L. aethiopica*, *L. amazonensis*, and *L. braziliensis* may be treated by infiltration with intralesional injections of 1 to 3 mL of sodium stibogluconate or meglumine antimonate (about 100 to 300 mg of pentavalent antimony), repeated once or twice if necessary at intervals of 1 to 2 days. Systemic therapy with intramuscular pentavalent antimony 10 to 20 mg/kg daily is given if the lesions are more severe and continued until a few days after clinical and parasitological cure is achieved.

  Cutaneous leishmaniasis due to *L. aethiopica* is not responsive to antimonials at conventional doses. In cutaneous leishmaniasis due to *L. braziliensis*, prolonged systemic treatment with intramuscular pentavalent antimony 20 mg/kg daily for a minimum of 4 weeks is indicated. Similar doses are required for **diffuse cutaneous leishmaniasis** due to *L. amazonensis* and are continued for several months after clinical improvement occurs. Relapses should be expected until immunity develops.
- In **mucocutaneous leishmaniasis**, daily doses of intramuscular pentavalent antimony 20 mg/kg are given for a minimum of 4 weeks; if the response is poor, 10 to 15 mg/kg may be given every 12 hours for the same period. Relapses are well known and have generally been associated with inadequate or interrupted treatment; they are treated with the same drug given for at least twice as long as the original treatment. Only when that fails should alternative treatment be given.

Leishmaniasis. The main treatment for leishmaniasis (p.824) is a pentavalent antimony compound such as sodium stibogluconate. Higher doses of antimony compounds than those recommended by WHO (see above) have been tried in order to overcome the unresponsiveness of leishmaniasis to therapy. In the USA, the use of 20 mg/kg daily of pentavalent antimony has been recommended, without restriction to an 850-mg maximum daily dose.[1,2] At 20 mg/kg daily the most common adverse effects are musculoskeletal disorders, elevated liver enzyme values, and T-wave changes on the ECG, and the CDC recommends that the ECG, blood chemistry, and blood count should be monitored throughout therapy if resources permit.[1] Severe cardiotoxicity is rare at this dose but fatal cardiac toxicity has been reported with doses of up to 60 mg/kg daily (see under Effects on the Heart, above). Drug-resistant strains of *Leishmania infantum* have been associated with unresponsiveness to treatment with meglumine antimonate.[3] It was suggested[4] that the use of suboptimal doses may be increasing the prevalence of drug-resistant strains of the parasite. However, low doses of antimony compounds (5 mg/kg daily for 30 days) have produced long-term cure in patients with cutaneous *L. braziliensis* infection followed for up to 10 years.[5]

INTRALESIONAL ADMINISTRATION. Intralesional infiltration of 3 doses of sodium stibogluconate on alternate days or once weekly was more effective than daily treatment in a study of 96 patients in Saudi Arabia.[6] Local infiltration of meglumine antimonate in usual doses of 150 to 900 mg (maximum 1500 mg) once each week for up to 6 weeks produced microbiological and clinical cures in all of 45 patients in Italy with cutaneous leishmaniasis.[7]

1. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992; **46:** 296–306.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. Faraut-Gambarelli F, *et al.* In vitro and in vivo resistance of Leishmania infantum to meglumine antimoniate: a study of 37 strains collected from patients with visceral leishmaniasis. *Antimicrob Agents Chemother* 1997; **41:** 827–30.
4. Grogl M, *et al.* Drug resistance in leishmaniasis: its implication in systemic chemotherapy of cutaneous and mucocutaneous disease. *Am J Trop Med Hyg* 1992; **47:** 117–26.
5. Oliveira-Neto MP, *et al.* A low-dose antimony treatment in 159 patients with American cutaneous leishmaniasis: extensive follow-up studies (up to 10 years). *Am J Trop Med Hyg* 1997; **57:** 651–5.
6. Tallab TM, *et al.* Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* 1996; **35:** 594–7.
7. Aste N, *et al.* Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate. *Br J Dermatol* 1998; **138:** 370–1.

Preparations

BP 2008: Sodium Stibogluconate Injection.

Proprietary Preparations (details are given in Part 3)
Braz.: Glucantime; ***Fr.:*** Glucantime; ***Israel:*** Pentostam; ***Ital.:*** Glucantim†; ***Spain:*** Glucantime; ***UK:*** Pentostam; ***Venez.:*** Glucantime.

Atovaquone *(BAN, USAN, rINN)*

Atovacuona; Atovakon; Atovakvon; Atovakvoni; Atovaquonum; BW-A566C; BW-566C; BW-566C80; 566C; 566C80. 2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

Атоваxон

$C_{22}H_{19}O_3Cl$ = 366.8.

CAS — 95233-18-4.

ATC — P01AX06.

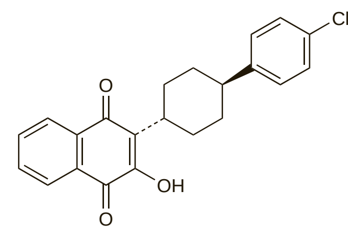

Pharmacopoeias. In *US.*

USP 31 (Atovaquone). A yellow powder. Insoluble in water; slightly soluble in alcohol, in butanediol, in ethyl acetate, in glycerol, in octanol, and in macrogol 200; sparingly soluble in acetone, in di-*n*butyl adipate, in dimethyl sulfoxide, and in macrogol 400; soluble in chloroform; freely soluble in *N*-methyl-2-pyrrolidone and in tetrahydrofuran; very slightly soluble in 0.1N sodium hydroxide. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse reactions to atovaquone include skin rashes, headache, fever, insomnia, and gastrointestinal effects such as nausea, diarrhoea, and vomiting. Raised liver enzyme values, hyponatraemia, and haematological disturbances such as anaemia and neutropenia may occur occasionally. Atovaquone should be avoided in patients with gastrointestinal disorders that may limit absorption of the drug.

Effects on the skin. Stevens-Johnson syndrome has been reported[1] in a patient taking atovaquone with proguanil.

1. Emberger M, *et al.* Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. Abstract: *Clin Infect Dis* 2003; **37:** 158. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/07/08)

Interactions

Use of atovaquone with either metoclopramide, tetracycline, or rifampicin (and possibly also rifabutin) may result in decreases in plasma-atovaquone concentrations. Other drugs which have produced small reductions in plasma-atovaquone concentrations include aciclovir, antidiarrhoeals, benzodiazepines, cephalosporins, laxatives, opioids, and paracetamol.

Atovaquone is reported to decrease the metabolism of zidovudine resulting in moderate increases in zidovudine plasma concentrations. A decrease in trough concentrations of indinavir, and in the area under the indinavir time-concentration curve has been reported when atovaquone was also given. Small decreases in the plasma concentrations of co-trimoxazole have been noted in patients taking atovaquone. There is a theoretical possibility that atovaquone could displace other highly protein-bound drugs from plasma-protein binding sites.

Pharmacokinetics

Atovaquone is poorly absorbed from the gastrointestinal tract after oral doses; bioavailability is especially poor in patients with AIDS. Bioavailability from commercial oral liquid formulations is better than from tablets and can be further improved if taken with food, particularly meals with a high fat content. Atovaquone is more than 99% bound to plasma proteins and has a long plasma half-life of 2 to 3 days, thought to be due to enterohepatic recycling. It is excreted almost exclusively in faeces as unchanged drug.

◊ References.

1. Hughes WT, *et al.* Safety and pharmacokinetics of 566C80, a hydroxynaphthoquinone with anti-Pneumocystis carinii activity: a phase I study in human immunodeficiency virus (HIV)-infected men. *J Infect Dis* 1991; **163:** 843–8.
2. Rolan PE, *et al.* Examination of some factors responsible for a food-induced increase in absorption of atovaquone. *Br J Clin Pharmacol* 1994; **37:** 13–20.
3. Dixon R, *et al.* Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. *Antimicrob Agents Chemother* 1996; **40:** 556–60.
4. Hussein Z, *et al.* Population pharmacokinetics of atovaquone in patients with acute malaria caused by Plasmodium falciparum. *Clin Pharmacol Ther* 1997; **61:** 518–30.
5. Rolan PE, *et al.* Disposition of atovaquone in humans. *Antimicrob Agents Chemother* 1997; **41:** 1319–21.

Uses and Administration

Atovaquone is a hydroxynaphthoquinone antiprotozoal that is also active against the fungus *Pneumocystis jirovecii*. It is used in the treatment and prophylaxis of pneumocystis pneumonia in patients unable to tolerate co-trimoxazole, and with proguanil in the treatment and prophylaxis of malaria.

In the treatment of mild to moderate **pneumocystis pneumonia**, atovaquone is given orally in a dose of 750 mg with food twice daily as a suspension, for 21 days. For prophylaxis 1500 mg of the suspension is given once daily with food.

Prophylaxis of falciparum **malaria** should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area. The following doses may be given once daily:

- adults and children over 40 kg: atovaquone 250 mg with proguanil hydrochloride 100 mg
- children 11 to 20 kg: one-quarter the adult dose
- children 21 to 30 kg: one-half the adult dose
- children 31 to 40 kg: three-quarters the adult dose

In the **treatment** of uncomplicated falciparum **malaria**, the following doses are given as a single daily dose for 3 days:

- adults and children over 40 kg: atovaquone 1000 mg with proguanil hydrochloride 400 mg
- children 5 to 8 kg: one-eighth the adult dose
- children 9 to 10 kg: three-sixteenths the adult dose
- children 11 to 20 kg: one-quarter the adult dose
- children 21 to 30 kg: one-half the adult dose
- children 31 to 40 kg: three-quarters the adult dose

Atovaquone with proguanil is one of the antimalarial drugs recommended by some experts to be carried as a **standby** for the emergency treatment of **malaria**. The dose recommended for self-treatment is the same as that for treatment of uncomplicated falciparum malaria.

◊ Reviews.

1. Haile LG, Flaherty JF. Atovaquone: a review. *Ann Pharmacother* 1993; **27:** 1488–94.
2. Artymowicz RJ, James VE. Atovaquone: a new antipneumocystis agent. *Clin Pharm* 1993; **12:** 563–70.
3. Spencer CM, Goa KL. Atovaquone: a review of its pharmacological properties and therapeutic efficacy in opportunistic infections. *Drugs* 1995; **50:** 176–96.
4. Baggish AL, Hill DR. Antiparasitic agent atovaquone. *Antimicrob Agents Chemother* 2002; **46:** 1163–73.
5. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
6. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.

Babesiosis. In a prospective, randomised study[1] involving 58 patients with babesiosis (p.823), atovaquone with azithromycin was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Atovaquone 750 mg twice daily with azithromycin 600 mg once daily, or 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, both orally for 7 to 10 days, has been recommended by some experts[2,3] in the USA for the treatment of *Babesia microti* infections. Children may be given atovaquone 20 mg/kg twice daily with azithromycin 12 mg/kg once daily, or 10 mg/kg on day 1 followed by 5 mg/kg once daily thereafter, both by mouth for 7 to 10 days.

1. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/07/08)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 1st ed. New Rochelle NY: The Medical Letter, 2007.

Malaria. Atovaquone with proguanil (*Malarone*) is used in the treatment and prophylaxis of uncomplicated malaria caused by *Plasmodium falciparum* (see p.594).

Atovaquone, a blood schizontocide, is associated with an unacceptably high rate of recrudescence when used alone[1,2] for *treatment* but is more successful in malaria when used with proguanil,[2,3] including that produced by multidrug-resistant strains.[4] Use of the combination to treat *P. ovale* and *P. malariae* malarias has also been studied.[5] Atovaquone with proguanil followed by primaquine may also be effective for the treatment of *P. vivax* malaria.[6]

Atovaquone with proguanil has also been found to be useful for *prophylaxis* of falciparum malaria in both children[7] and adults[8] in endemic areas. It may also be used for prophylaxis in non-immune travellers[9,10] and appears to be well tolerated.[10,11]

1. Chiodini PL, *et al.* Evaluation of atovaquone in the treatment of patients with uncomplicated Plasmodium falciparum malaria. *J Antimicrob Chemother* 1995; **36;** 1073–5.
2. Looareesuwan S, *et al.* Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 62–6.
3. Radloff PD, *et al.* Atovaquone and proguanil for Plasmodium falciparum malaria. *Lancet* 1996; **347:** 1511–14.
4. Sabchareon A, *et al.* Efficacy and pharmacokinetics of atovaquone and proguanil in children with multidrug-resistant Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 201–6.
5. Radloff PD, *et al.* Atovaquone plus proguanil is an effective treatment for Plasmodium ovale and P. malariae malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 682.
6. Looareesuwan S, *et al.* Atovaquone and proguanil hydrochloride followed by primaquine for treatment of plasmodium vivax malaria in Thailand. *Trans R Soc Trop Med Hyg* 1999; **93:** 637–40.
7. Lell B, *et al.* Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet* 1998; **351:** 709–13.
8. Shanks GD, *et al.* Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for Plasmodium falciparum malaria. *Clin Infect Dis* 1998; **27:** 494–9.
9. Overbosch D, *et al.* Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clin Infect Dis* 2001; **33:** 1015–21.
10. Nakato H, *et al.* A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; **60:** 929–36.
11. Høgh B, *et al.* Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. *Lancet* 2000; **356:** 1888–94.

Microsporidiosis. There is no established effective treatment for microsporidiosis (p.826). Beneficial responses were reported with atovaquone in a preliminary study.[1]

1. Anwar-Bruni DM, *et al.* Atovaquone is effective treatment for the symptoms of gastrointestinal microsporidiosis in HIV-1-infected patients. *AIDS* 1996; **10:** 619–23.

Pneumocystis pneumonia. Atovaquone is one alternative to co-trimoxazole for the treatment of pneumocystis pneumonia (p.521). In open studies, a clinical response to atovaquone was reported in 78% of patients with mild to moderate disease and in 56% of patients with severe disease who were intolerant of, or who failed to respond to, both co-trimoxazole and pentamidine.[1] Comparative studies have shown atovaquone to be less effective than co-trimoxazole[2] and probably less effective than pentamidine,[3,4] but to produce fewer treatment-limiting adverse effects than either.

Atovaquone is also an alternative to co-trimoxazole for both primary or secondary *prophylaxis*, and was as effective as dapsone[5] or inhaled pentamidine[6] in studies in patients intolerant of co-trimoxazole.

1. White A, *et al.* Clinical experience with atovaquone on a treatment investigational new drug protocol for Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **9:** 280–5.
2. Hughes W, *et al.* Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med* 1993; **328:** 1521–7.
3. Dohn MN, *et al.* Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. *Ann Intern Med* 1994; **121:** 174–80.
4. Lederman MM, van der Horst C. Atovaquone for Pneumocystis carinii pneumonia. *Ann Intern Med* 1995; **122:** 314.
5. El-Sadr WM, *et al.* Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998; **339:** 1889–95.
6. Chan C, *et al.* Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999; **180:** 369–76.

Toxoplasmosis. Atovaquone, either alone or with pyrimethamine or sulfadiazine, has produced encouraging results for treatment[1-3] or long-term suppression[2-4] of toxoplasmosis (p.826) in patients with AIDS.

1. Kovacs JA, *et al.* Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet* 1992; **340:** 637–8.
2. Torres RA, *et al.* Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1997; **24:** 422–9.
3. Chirgwin K, *et al.* Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002; **34:** 1243–50.
4. Katlama C, *et al.* Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. *AIDS* 1996; **10:** 1107–12.

Preparations

USP 31: Atovaquone Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Wellvone; ***Austria:*** Wellvone; ***Belg.:*** Wellvone; ***Canad.:*** Mepron; ***Fr.:*** Wellvone; ***Ger.:*** Wellvone; ***Gr.:*** Wellvone; ***Ital.:*** Wellvone; ***Neth.:*** Wellvone; ***Port.:*** Wellvone; ***S.Afr.:*** Wellvone; ***Spain:*** Wellvone; ***Swed.:*** Wellvone; ***Switz.:*** Wellvone; ***UK:*** Wellvone; ***USA:*** Mepron.

Multi-ingredient: ***Austral.:*** Malarone; ***Austria:*** Malarone; Promal; ***Belg.:*** Malarone; ***Canad.:*** Malarone; ***Cz.:*** Malarone; ***Denm.:*** Malarone; ***Fr.:*** Malarone; ***Ger.:*** Malarone; ***Gr.:*** Malarone; ***Hong Kong:*** Malarone; ***Hung.:*** Malarone; ***Irl.:*** Malarone; ***Israel:*** Malarone; ***Ital.:*** Malarone; ***Malaysia:*** Malarone; ***Neth.:*** Malarone; ***Norw.:*** Malarone; ***NZ:*** Malarone; ***Pol.:*** Malarone; ***S.Afr.:*** Malanil; ***Singapore:*** Malarone; ***Spain:*** Malarone; ***Swed.:*** Malarone; ***Switz.:*** Malarone; ***UK:*** Malarone; ***USA:*** Malarone.

Azanidazole *(BAN, USAN, rINN)*

Azanidazol; Azanidazolum; F-4. 4-[(*E*)-2-(1-Methyl-5-nitroimidazol-2-yl)vinyl]pyrimidin-2-ylamine.

Азанидазол

$C_{10}H_{10}N_6O_2$ = 246.2.
CAS — 62973-76-6.
ATC — G01AF13; P01AB04.
ATC Vet — QG01AF13; QP51AA04.

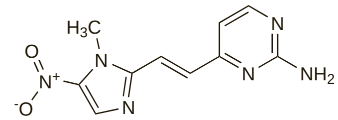

Profile

Azanidazole is a 5-nitroimidazole derivative similar to metronidazole (p.837) and is used in the treatment of trichomoniasis in usual oral doses of 200 mg twice daily or 250 mg once daily intravaginally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Triclose.

Benznidazole *(rINN)*

Benznidazol; Benznidazolum; Ro-7-1051. *N*-Benzyl-2-(2-nitroimidazol-1-yl)acetamide.

Бензнидазол

$C_{12}H_{12}N_4O_3$ = 260.2.
CAS — 22994-85-0.
ATC — P01CA02.

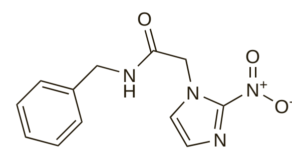

Pharmacopoeias. In *Int.*

Adverse Effects

Nausea, vomiting, abdominal pain, peripheral neuropathy, blood dyscrasias, and severe skin reactions have been reported with benznidazole.

◊ A study[1] involving 20 patients with chronic American trypanosomiasis given benznidazole 5 mg/kg daily had to be stopped because of the high incidence of skin rashes and neurological symptoms.

1. Apt W, *et al.* Clinical trial of benznidazole and an immunopotentiator against Chagas disease in Chile. *Trans R Soc Trop Med Hyg* 1986; **80:** 1010.

Pharmacokinetics

Benznidazole is absorbed from the gastrointestinal tract after oral doses.

◊ References.

1. Raaflaub J, Ziegler WH. Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. *Arzneimittelforschung* 1979; **29:** 1611–14.

Uses and Administration

Benznidazole is a 2-nitroimidazole derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection with *Trypanosoma cruzi*, especially during the early acute stage of the disease.

Benznidazole has been given orally in a dose of 5 to 7 mg/kg daily in two divided doses usually for 60 days (but see below). Children have been given 10 mg/kg daily in two divided doses.

American trypanosomiasis. Available treatment for American trypanosomiasis (p.827) is generally unsatisfactory, but benznidazole is of value especially in the acute phase. WHO[1] recommends that benznidazole should be given for 60 days but some in the USA[2] suggest courses of 30 to 90 days. Although treatment is usually confined to the acute phase of the disease, therapy during the early chronic phase was reported to be beneficial,[3] and long-term follow-up in patients who had received benznidazole has shown a reduction in cardiac complications and parasitaemia.[4]

1. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.
3. de Andrade ALSS, *et al*. Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. *Lancet* 1996; **348:** 1407–13.
4. Viotti R, *et al*. Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. *Am Heart J* 1994; **127:** 151–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Radanil; ***Braz.:*** Rochagan; ***Ecuad.:*** Ragonil.

Buparvaquone *(BAN, rINN)*

Buparvacuona; Buparvaquonum; BW-720C. *trans*-2-(4-*tert*-Butylcyclohexylmethyl)-3-hydroxy-1,4-naphthoquinone.

Бупарвахон

$C_{21}H_{26}O_3$ = 326.4.
CAS — 88426-33-9.
ATC Vet — QP51AX22.

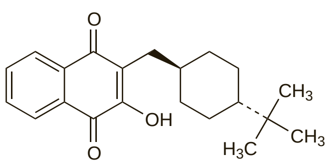

Profile

Buparvaquone is an antiprotozoal used in veterinary practice for the treatment of theileriosis in cattle.

Carnidazole *(BAN, USAN, pINN)*

Carnidazol; Carnidazolum; R-25831; R-28096 (carnidazole hydrochloride). *O*-Methyl [2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-thiocarbamate.

Карнидазол

$C_8H_{12}N_4O_3S$ = 244.3.
CAS — 42116-76-7.
ATC Vet — QP51AA09.

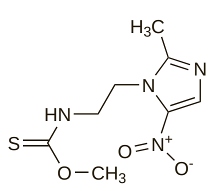

Profile

Carnidazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the control of trichomoniasis in pigeons.

Clazuril *(BAN, USAN, rINN)*

Clazurilo; Clazurilum; Klatsuriili; Klazuril; R-62690. (±)-[2-Chloro-4-(4,5-dihydro-3,5-dioxo-*as*-triazin-2(3*H*)-yl)phenyl]-(*p*-chlorophenyl)acetonitrile.

Клазурил

$C_{17}H_{10}Cl_2N_4O_2$ = 373.2.
CAS — 101831-36-1.
ATC Vet — QP51AJ02.

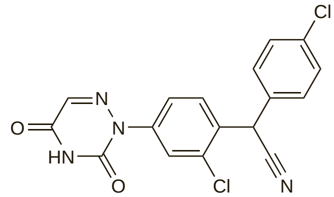

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Clazuril for Veterinary Use; Clazuril BP(Vet) 2008). A white or light yellow powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Clazuril is an antiprotozoal used in veterinary practice for the control of coccidiosis in pigeons.

Clefamide *(BAN, rINN)*

Chlorphenoxamide; Clefamida; Cléfamide; Clefamidum. 2,2-Dichloro-*N*-(2-hydroxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]-acetamide.

Клефамид

$C_{17}H_{16}Cl_2N_2O_5$ = 399.2.
CAS — 3576-64-5.
ATC — P01AC02.

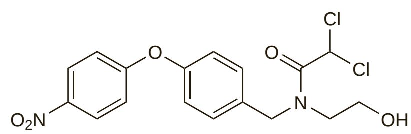

Profile

Clefamide is an antiprotozoal that has been used as a luminal amoebicide in the treatment of *Entamoeba histolytica* infections.

Clopidol *(BAN, USAN, rINN)*

Clopidolum; Clopindol; Meticlorpindol. 3,5-Dichloro-2,6-dimethylpyridin-4-ol.

Клопидол

$C_7H_7Cl_2NO$ = 192.0.
CAS — 2971-90-6.

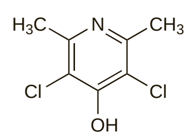

Profile

Clopidol is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry and rabbits either alone or with methyl benzoquate (p.837).

Decoquinate *(BAN, USAN, rINN)*

Décoquinate; Decoquinato; Decoquinatum; HC-1528; M&B-15497. Ethyl 6-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate.

Декохинат

$C_{24}H_{35}NO_5$ = 417.5.
CAS — 18507-89-6.
ATC Vet — QP51AX14.

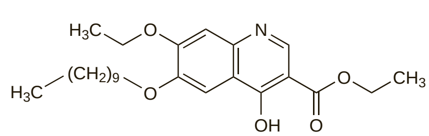

Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.
BP(Vet) 2008 (Decoquinate). A cream to buff-coloured, odourless or almost odourless, microcrystalline powder. Insoluble in water; practically insoluble in alcohol; very slightly soluble in chloroform and in ether.
USP 31 (Decoquinate). Store in airtight containers.

Profile

Decoquinate is an antiprotozoal used in veterinary practice for the control of coccidiosis in calves, sheep, and chickens. It is also used for toxoplasmosis in sheep.

Dehydroemetine Hydrochloride *(BANM, rINNM)*

BT-436; Déhydroémétine, Chlorhydrate de; 2,3-Dehydroemetine Hydrochloride; Dehydroemetini Hydrochloridum; DHE; Hidrocloruro de dehidroemetina; Ro-1-9334. 2,3-Didehydro-6′,7′,10,11-tetramethoxyemetan dihydrochloride; 3-Ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-4*H*-benzo[*a*]quinolizine dihydrochloride.

Дегидроэметина Гидрохлорид

$C_{29}H_{38}N_2O_4$,2HCl = 551.5.
CAS — 4914-30-1 (dehydroemetine); 2228-39-9 (dehydroemetine hydrochloride).

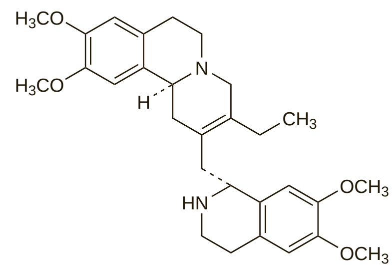

(dehydroemetine)

NOTE. The name DHE has been used to denote a preparation of dihydroergotamine mesilate.

Pharmacopoeias. In *Int.*

Profile

Dehydroemetine, a synthetic derivative of emetine (p.833), is a tissue amoebicide with similar actions and uses, although probably of a lower toxicity.

Dehydroemetine should be avoided in patients with cardiac, renal, or neuromuscular disease and patients should be monitored for cardiac toxicity during treatment.

When used in the treatment of amoebiasis (p.822), dehydroemetine hydrochloride is given by intramuscular injection in a dose of 1 mg/kg daily (maximum daily dose of 60 mg), generally for up to 4 to 6 days, but for no more than 5 days in children. A dose of 0.5 mg/kg has been suggested for elderly or severely ill patients. At least 6 weeks should elapse before treatment is repeated. Following treatment with dehydroemetine, all patients should receive a luminal amoebicide to eliminate organisms from the colon. Patients with hepatic amoebiasis may be given supplementary treatment with chloroquine.

Liver fluke infections. Dehydroemetine has been given[1] in the treatment of the liver fluke infection fascioliasis (see p.137).

1. Farid Z, *et al*. Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82:** 299.

Diaveridine *(BAN, USAN, rINN)*

BW-49-210; Diaveridina; Diavéridine; Diaveridinum; NSC-408735. 5-Veratrylpyrimidine-2,4-diyldiamine.

Диаверидин

$C_{13}H_{16}N_4O_2$ = 260.3.
CAS — 5355-16-8.
ATC Vet — QP51AX18.

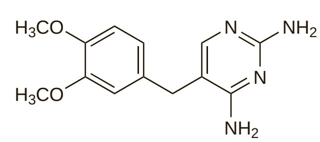

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Diaveridine is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Diclazuril *(BAN, USAN, rINN)*

Diclazurilo; Diclazurilum; Diklatsuriili; Diklazuril; R-64433. (±)-4-Chlorophenyl[2,6-dichloro-4-(2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-2-yl)phenyl]acetonitrile.

Диклазурил

$C_{17}H_9Cl_3N_4O_2$ = 407.6.

CAS — 101831-37-2.

ATC Vet — QP51AJ03.

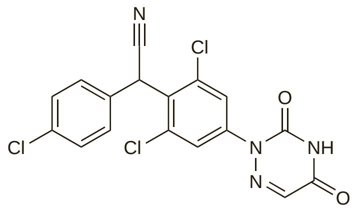

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Diclazuril for Veterinary Use; Diclazuril BP(Vet) 2008). A white or light yellow powder. Practically insoluble in water, in alcohol, and in dichloromethane; sparingly soluble in dimethylformamide. Protect from light.

Profile

Diclazuril is an antiprotozoal that has been tried in AIDS patients for the management of diarrhoea associated with protozoal infection. It is used in veterinary practice for the control of coccidiosis in lambs and poultry.

◊ References.

1. Kayembe K, *et al.* Diclazuril for Isospora belli infections in AIDS. *Lancet* 1989; **i:** 1397.
2. Connolly GM, *et al.* Diclazuril in the treatment of severe cryptosporidial diarrhoea in AIDS patients. *AIDS* 1990; **4:** 700–701.
3. Menichetti F, *et al.* Diclazuril for cryptosporidiosis in AIDS. *Am J Med* 1991; **90:** 271–2.
4. Limson-Pobre RNR, *et al.* Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis* 1995; **20:** 201–2.

Diiodohydroxyquinoline *(rINN)*

Diiodohidroxiquinoleína; Diiodohydroxyquin; Diiodohydroxyquinoléine; Di-iodohydroxyquinoline *(BAN)*; Diiodohydroxyquinolinum; Di-iodoxychinolinum; Diiodoxyquinoléine; Diiyodohidroksikinolin; Dijodhydroxikinolin; Dijodihydroksikinoliini; Iodoquinol *(USAN)*. 5,7-Di-iodoquinolin-8-ol.

Дийодогидроксихинолин

$C_9H_5I_2NO$ = 397.0.

CAS — 83-73-8.

ATC — G01AC01.

ATC Vet — QG01AC01.

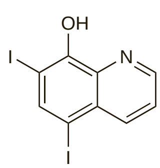

Pharmacopoeias. In *US.*

USP 31 (Iodoquinol). A light yellowish to tan, microcrystalline powder, not readily wetted in water, odourless or has a faint odour. Practically insoluble in water; sparingly soluble in alcohol and in ether.

Adverse Effects

Major concerns have been expressed about the safety of the halogenated hydroxyquinolines since the recognition of severe neurotoxicity with clioquinol (p.254). In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are principally those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms such as paraesthesias in the legs, progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disability.

It was suggested that the Japanese epidemic might have been due to genetic susceptibility, but a few cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, including broxyquinoline and diiodohydroxyquinoline, have been reported elsewhere.

Diiodohydroxyquinoline has also been associated with gastrointestinal effects such as abdominal cramps, nausea, and diarrhoea. Adverse effects which may be attributable to the iodine content of diiodohydroxyquinoline include pruritus ani, skin eruptions, and enlargement of the thyroid gland. Fever, chills, headache, and vertigo have also occurred.

Precautions

Diiodohydroxyquinoline is contra-indicated in patients known to be hypersensitive to iodine or halogenated hydroxyquinolines and in those with hepatic or renal impairment. It should be used with caution in thyroid disease and may interfere with determinations of protein-bound iodine in tests for thyroid function for up to 6 months after therapy. Its use is best avoided in patients with neurological disorders. Long-term use should be avoided.

Children. The Committee on Drugs of the American Academy of Pediatrics[1] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

WHO considers that the use of halogenated hydroxyquinolines for the treatment of acute diarrhoea or amoebiasis in children cannot be justified.[2] There is no evidence of their efficacy in acute diarrhoea and they have been associated with severe neurological effects. On the rare occasions when a luminal amoebicide is required, other less toxic and more effective agents are available.

1. Kauffman RE, *et al.* American Academy of Pediatrics Committee on Drugs. Clioquinol (iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86:** 797–8.
2. WHO. The rational use of drugs in the management of acute diarrhoea in children. Geneva: WHO, 1990.

Pharmacokinetics

Diiodohydroxyquinoline is poorly absorbed from the gastrointestinal tract. Concern has been expressed about possible absorption after application to the skin (see Children, under Precautions, above).

Uses and Administration

Diiodohydroxyquinoline, a halogenated hydroxyquinoline, is a luminal amoebicide acting principally in the bowel lumen and is used in the treatment of intestinal amoebiasis, although a less toxic amoebicide such as diloxanide furoate is usually preferred; children should not be treated with diiodohydroxyquinoline (see Precautions, above). It is given alone in the treatment of asymptomatic cyst passers and with an amoebicide that acts in the tissues, such as metronidazole, in patients with invasive amoebiasis (p.822). The usual oral dosage in the treatment of amoebiasis is 630 or 650 mg three times daily for 20 days.

Diiodohydroxyquinoline has also been given in the treatment of *Dientamoeba fragilis* infections, in balantidiasis (p.823) as an alternative to tetracycline, and in *Blastocystis hominis* infections (p.823).

Diiodohydroxyquinoline was formerly used in the treatment of acrodermatitis enteropathica; it is reported to act by enhancing zinc absorption and has now been superseded by oral zinc therapy.

Diiodohydroxyquinoline is claimed to have some antibacterial and antifungal activity and has been used topically (but see Children, under Precautions, above).

Preparations

USP 31: Iodoquinol Tablets.

Proprietary Preparations (details are given in Part 3)

Canad.: Diodoquin; ***Mex.:*** Ameban; Antidifar; Carsuquin; Diameb; Diodoquin; Diyosul; Drioquilen†; Entero-Diyod; Entodiba; Exoquin; Flanoquin†; Quinosul; Versamiv; ***Turk.:*** Floraquin; ***USA:*** Sebaquin; Yodoxin; ***Venez.:*** Diodoquin.

Multi-ingredient: ***Arg.:*** Hipoglos Cicatrizante; Plusderm†; ***Chile:*** Dexagin; Kordinol Compuesto†; ***Mex.:*** Ameban; Amebyl; Bontal; Coralzul; Depofin; Dialgin; Diodolina; Dipecfur; Facetin-D; Farmeban; Flagenase 400; Flagocil; Lambliquin; Metodine; Metrodiyod; Metroviform†; Norecil; Novageon; Stomffler Plus; Threchop; ***S.Afr.:*** Vagarsol; Viocort; Viodor; ***Thai.:*** Coccila†; Disento; Gynecon; Gynecon-T; Gynoco; Gynova; Gyracon; Medicin†; Nystin; Quinradon-N; Vagicin; ***USA:*** Alcortin; Vytone; ***Venez.:*** Diodonato†.

Diloxanide Furoate *(BANM, rINNM)*

Diloksanid Furoat; Diloxanide, Furoate de; Diloxanidi Furoas; Furoato de diloxanida. 4-(*N*-Methyl-2,2-dichloroacetamido)-phenyl 2-furoate.

Дилоксанида Фуроат

$C_{14}H_{11}Cl_2NO_4$ = 328.1.

CAS — 579-38-4 (diloxanide); 3736-81-0 (diloxanide furoate).

ATC — P01AC01.

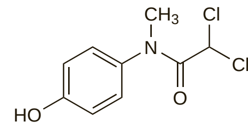

(diloxanide)

Pharmacopoeias. In *Br., Int.,* and *US.*

BP 2008 (Diloxanide Furoate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Protect from light.

USP 31 (Diloxanide Furoate). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Store in airtight containers. Protect from light.

Adverse Effects

Flatulence is the most common adverse effect during treatment with diloxanide furoate. Vomiting, pruritus, and urticaria may occasionally occur.

Pharmacokinetics

Diloxanide furoate is hydrolysed before absorption from the gastrointestinal tract. The resulting diloxanide is readily absorbed and excreted mainly in the urine as the glucuronide; less than 10% of a dose appears in the faeces.

Uses and Administration

Diloxanide furoate, a dichloroacetamide derivative, is a luminal amoebicide acting principally in the bowel lumen and is used in the treatment of intestinal amoebiasis (p.822). It is given alone in the treatment of asymptomatic cyst passers and with an amoebicide that acts in the tissues, such as metronidazole, in patients with invasive amoebiasis.

Diloxanide furoate is given orally in a dosage of 500 mg three times daily for 10 days; children weighing more than 25 kg may be given 20 mg/kg daily, in 3 divided doses, for 10 days. The course of treatment may be repeated if necessary.

Preparations

BP 2008: Diloxanide Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Aristogyl Plus; Dyrade-M; Entamizole; Entrolate†; Qugyl; Tinidafyl Plus; Wotinex.

Dimetridazole *(BAN, pINN)*

Dimetridatsoli; Dimetridazol; Dimétridazole; Dimetridazolum. 1,2-Dimethyl-5-nitroimidazole.

Диметридазол

$C_5H_7N_3O_2$ = 141.1.

CAS — 551-92-8.

ATC Vet — QP51AA07.

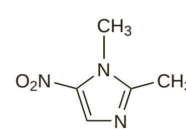

Pharmacopoeias. In *Fr.* for veterinary use. Also in *BP(Vet).*

BP(Vet) 2008 (Dimetridazole). An almost white to brownish-yellow, odourless or almost odourless powder which darkens on exposure to light. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light.

Profile

Dimetridazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the control of various protozoal infections in birds, fish, and reptiles. It is also used for swine dysentery.

Diminazene Aceturate (BANM, rINNM)

Aceturato de diminazeno; Diminazène, Acéturate de; Diminazeni Aceturas. 1,3-Bis(4-amidinophenyl)triazene bis(*N*-acetylglycinate).

Диминазена Ацетурат

$C_{22}H_{29}N_9O_6$ = 515.5.

CAS — 536-71-0 (diminazene); 908-54-3 (diminazene aceturate).

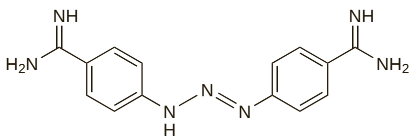

(diminazene)

NOTE. Diminazene aceturate is often referred to by its veterinary proprietary name Berenil.

Profile

Diminazene aceturate, an aromatic diamidine derivative related to pentamidine, is an antiprotozoal that has been used in veterinary practice in the treatment of trypanosomiasis and babesiosis. It has also been tried in human infections.

Dinitolmide (BAN, rINN)

Dinitolmida; Dinitolmidum; Dinitrotoluamide; Methyldinitrobenzamide. 3,5-Dinitro-*o*-toluamide.

Динитолмид

$C_8H_7N_3O_5$ = 225.2.

CAS — 148-01-6.

ATC Vet — QP51AX12.

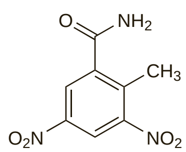

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Dinitolmide). A cream to light tan powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, and in ether; soluble in acetone.

Profile

Dinitolmide is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Eflornithine Hydrochloride

(BANM, USAN, rINNM)

DFMO; α-Difluoromethylornithine Hydrochloride; Éflornithine, Chlorhydrate d'; Eflornithini Hydrochloridum; Hidrocloruro de eflornitina; MDL-71782; MDL-71782A; RMI-71782. 2-(Difluoromethyl)-DL-ornithine monohydrochloride monohydrate.

Эфлорнитина Гидрохлорид

$C_6H_{12}F_2N_2O_2,HCl,H_2O$ = 236.6.

CAS — 67037-37-0 (eflornithine); 96020-91-6 (eflornithine hydrochloride).

ATC — D11AX16; P01CX03.

ATC Vet — QD11AX16.

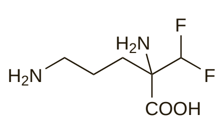

(eflornithine)

Adverse Effects and Precautions

Myelosuppression may lead to anaemia, leucopenia, and thrombocytopenia. Some patients have had hearing loss and alopecia. Gastrointestinal disturbances, especially diarrhoea, may occur. Seizures have occurred in about 8% of patients given eflornithine but they may have been related to the disease rather than treatment.

Dosage should be reduced in patients with renal impairment.

Skin irritation, such as erythema or a stinging or burning sensation, has been reported after topical application of eflornithine.

Effects on the ears. A study in 58 patients[1] receiving eflornithine alone or with interferon alfa for the treatment of metastatic melanoma found that hearing loss was related to the cumulative dose of eflornithine and was worse in patients with pre-existing hearing deficit.

1. Croghan MK, *et al.* Dose-related α-difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; **14:** 331–5.

Effects on the heart. Fatal cardiac arrest occurred in an AIDS patient with pneumocystis pneumonia during the intravenous infusion of eflornithine 100 mg/kg over 1 hour.[1] Sudden death after infusion of eflornithine had occurred in several other critically ill patients with AIDS.

1. Barbarash RA, *et al.* Alpha-difluoromethylornithine infusion and cardiac arrest. *Ann Intern Med* 1986; **105:** 141–2.

Pharmacokinetics

Eflornithine hydrochloride is absorbed from the gastrointestinal tract. After intravenous doses about 80% is excreted unchanged in the urine in 24 hours. The terminal elimination half-life is about 3 hours. It is distributed to the CSF.

Less than 1% of a dose is absorbed after topical application.

◊ References.

1. Haegele KD, *et al.* Kinetics of α-difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther* 1981; **30:** 210–17.
2. Milord F, *et al.* Eflornithine concentrations in serum and cerebrospinal fluid of 63 patients treated for Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1993; **87:** 473–7.
3. Malhotra B, *et al.* Percutaneous absorption and pharmacokinetics of eflornithine HCl 13.9% cream in women with unwanted facial hair. *J Clin Pharmacol* 2001; **41:** 972–8.

Uses and Administration

Eflornithine is an antiprotozoal that acts as an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis; trypanosomes are more susceptible to the effects of eflornithine than are humans, probably because of their slower turnover of this enzyme.

Eflornithine is used in African trypanosomiasis due to *Trypanosoma brucei gambiense*. It is effective in the early and, more importantly, in the late stage of the disease (when there is CNS involvement).

In the treatment of African trypanosomiasis, eflornithine hydrochloride is given by intravenous infusion. The dose is 100 mg/kg every 6 hours for at least 14 days. Each dose should be given over a period of at least 45 minutes. Dosage should be reduced in patients with renal impairment.

Eflornithine hydrochloride is also applied topically twice daily for the reduction of unwanted facial hair in women. It is available as a cream containing 15% eflornithine hydrochloride monohydrate; in the UK this content is expressed as 11.5% eflornithine and in the USA as 13.9% anhydrous eflornithine hydrochloride.

Cryptosporidiosis. Eflornithine has been tried in the treatment of cryptosporidiosis (p.823) in AIDS patients.[1]

1. Rolston KVI, *et al.* Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; **2:** 426–30.

Hirsutism. Topical eflornithine hydrochloride applied twice daily as a 13.9% cream is effective in reducing the growth of unwanted facial hair in females (see Hirsutism, p.2089), although it must be used indefinitely to prevent regrowth.[1] Its action is thought to be due to the irreversible inhibition of ornithine decarboxylase in hair follicles. It has also been used successfully in combination with laser hair removal.[2]

1. Barman Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol* 2001; **2:** 197–201.
2. Hamzavi I, *et al.* A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol* 2007; **57:** 54–9.

Malignant neoplasms. Eflornithine has antimetabolic activity and is being studied as a potential chemopreventive agent in patients at high risk of a variety of malignant diseases, including cancer of the bladder, breast, cervix, colon, oesophagus, prostate, and skin.[1]

1. Meyskens FL, Gerner EW. Development of difluoromethylornithine (DFMO) as a chemoprevention agent. *Clin Cancer Res* 1999; **5:** 945–51.

African trypanosomiasis. Eflornithine is effective in the treatment of *Trypanosoma brucei gambiense* infections (p.827), and is particularly valuable in providing an alternative to melarsoprol in meningoencephalitic disease.[1-3] Eflornithine 100 mg/kg intravenously every 6 hours for 7 days, rather than the standard 14 days, produced long-term responses in 42 of 47 patients who had relapsed after other treatment regimens.[4] Similar positive results in relapsing cases were obtained with a short 7-day course in a multicentre randomised controlled study,[5] although this short course was inferior to the 14-day course for new cases, in whom it could not be recommended. A patient who had relapsed after treatment with melarsoprol and eflornithine given singly was cured when the drugs were given together.[6] Eflornithine is not effective when given alone in *T. b. rhodesiense* infections, and early reports of its use with suramin were not encouraging.[7] However, benefit has been reported from use with nifurtimox.[8]

1. Chappuis F, *et al.* Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* 2005; **41:** 748–51.
2. Balasegaram M, *et al.* Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull WHO* 2006; **84:** 783–91.
3. Priotto G, *et al.* Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *BMJ* 2008; **336:** 705–8.
4. Khonde N, *et al.* A seven days course of eflornithine for relapsing Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1997; **91:** 212–13.
5. Pepin J, *et al.* Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bull WHO* 2000; **78:** 1284–95.
6. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 315.
7. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92:** 449–50.
8. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Vaniqa; ***Cz.:*** Vaniqa; ***Fr.:*** Vaniqa; ***Ger.:*** Vaniqa; ***Irl.:*** Vaniqa; ***Ital.:*** Vaniqa; ***Neth.:*** Vaniqa; ***Port.:*** Vaniqa; ***Spain:*** Vaniqa; ***UK:*** Vaniqa; ***USA:*** Ornidyl; Vaniqa.

Emetine Hydrochloride (BANM)

Cloridrato de Emetina; Emet. Hydrochlor.; Emetiinihydrokloridi; Emetina, hidrocloruro de; Emetin-dihydrochlorid; Émétine, chlorhydrate d'; Emetine Dihydrochloride; Emetin-hidroklorid; Emetinhydroklorid; Emetini Chloridum; Emetini Dihydrochloridum; Emetini hydrochloridum; Emetino hidrochloridas; Emetyny dichlorowodorek; Ipecine Hydrochloride; Methylcephaëline Hydrochloride. 6′,7′,10,11-Tetramethoxyemetan dihydrochloride heptahydrate; (2*S*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(1*R*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl]-2*H*-benzo[*a*]quinolizine dihydrochloride heptahydrate.

Эметина Гидрохлорид

$C_{29}H_{40}N_2O_4,2HCl,7H_2O$ = 679.7.

CAS — 483-18-1 (emetine); 316-42-7 (anhydrous emetine hydrochloride); 7083-71-8 (emetine hydrochloride, hydrate); 79300-08-6 (emetine hydrochloride, heptahydrate).

ATC — P01AX02.

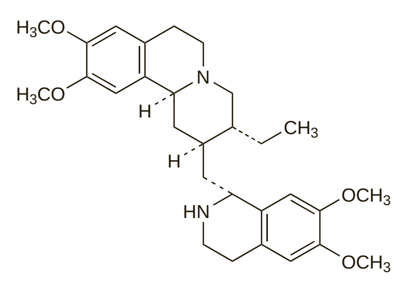

(emetine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Viet.*
Eur. also has a monograph for Emetine Hydrochloride Pentahydrate; *Int.* permits the heptahydrate or pentahydrate in the same monograph. *US* has a monograph for the anhydrous salt.

Ph. Eur. 6.2 (Emetine Hydrochloride Heptahydrate; Emetine Hydrochloride BP 2008). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

Ph. Eur. 6.2 (Emetine Hydrochloride Pentahydrate). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 31 (Emetine Hydrochloride). The hydrochloride of an alkaloid obtained from ipecacuanha, or prepared by methylation of cephaëline, or prepared synthetically. Anhydrous emetine hydrochloride is a white or slightly yellowish, odourless, crystalline powder. Freely soluble in water and in alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Emetine hydrochloride is commonly associated with aching, tenderness, stiffness, and weakness of the muscles in the area of the injection site; there may be necrosis and abscess formation. After injection, diarrhoea and nausea and vomiting, sometimes with dizziness and headache, are common. There may be generalised muscle weakness and muscular pain, especially in the neck and limbs, and, more rarely, mild sensory disturbances. Eczematous, urticarial, and purpuric skin lesions have been reported.

Cardiovascular effects are considered the most serious and include precordial pain, dyspnoea, tachycardia, and hypotension. Changes in the ECG, particularly flattening or inversion of the T-wave and prolongation of the QT interval, occur in many patients. Emetine accumulates in the body and large doses or prolonged use may cause lesions of the heart, gastrointestinal tract, kidneys, liver, and skeletal muscle. Severe acute degenerative myocarditis may occur and may give rise to sudden cardiac failure and death. In some patients cardiotoxic effects have appeared after the completion of treatment with therapeutic doses.

Emetine hydrochloride is very irritant and contact with mucous membranes should be avoided.

Precautions

Emetine is contra-indicated in cardiac, renal, or neuromuscular disease. Its use should be avoided during pregnancy and it should not be given to children, except in severe amoebic dysentery unresponsive to other drugs. It should be used with great caution in old or debilitated patients. Patients given emetine should be closely supervised; ECG monitoring is advisable during treatment.

Pharmacokinetics

After injection emetine hydrochloride is concentrated in the liver, and to some extent in kidney, lung, and spleen. Excretion is slow and detectable amounts may persist in urine 40 to 60 days after treatment has been stopped.

Uses and Administration

Emetine, an alkaloid of ipecacuanha (p.1562), is a tissue amoebicide acting principally in the bowel wall and in the liver. It has been given by deep subcutaneous or intramuscular injection in the treatment of severe invasive amoebiasis (p.822), including hepatic amoebiasis in patients who do not respond to metronidazole, although dehydroemetine has tended to replace it. Emetine was formerly given orally as emetine and bismuth iodide.

Emetine has also been included in combination preparations for the symptomatic relief of cough.

Preparations

USP 31: Emetine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Spirbon; ***Cz.:*** Ipecarin†; Kodynal†; ***Hung.:*** Radipon; ***Switz.:*** Ipeca†; Sano Tuss.

Ethopabate *(BAN)*

Etopabato. Methyl 4-acetamido-2-ethoxybenzoate.

$C_{12}H_{15}NO_4$ = 237.3.
CAS — 59-06-3.
ATC Vet — QP51AX17.

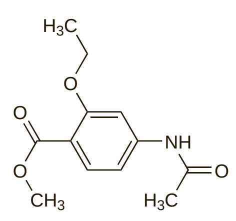

Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.
BP(Vet) 2008 (Ethopabate). A white or pinkish-white powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol; slightly soluble in ether.
USP 31 (Ethopabate). A white or pinkish-white, odourless or practically odourless, powder. Very slightly soluble in water; soluble in dehydrated alcohol, in acetone, in methyl alcohol, and in acetonitrile; slightly soluble in ether; sparingly soluble in dichloromethane, in dioxan, in ethyl acetate, and in isopropyl alcohol. Protect from light.

Profile

Ethopabate is an antiprotozoal used in veterinary practice with other drugs, such as amprolium, for the control of coccidiosis in poultry.

Etofamide *(rINN)*

Ethychlordiphene; Etofamida; Étofamide; Etofamidum; K-430. 2,2-Dichloro-*N*-(2-ethoxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]-acetamide.

Этофамид

$C_{19}H_{20}Cl_2N_2O_5$ = 427.3.
CAS — 25287-60-9.
ATC — P01AC03.

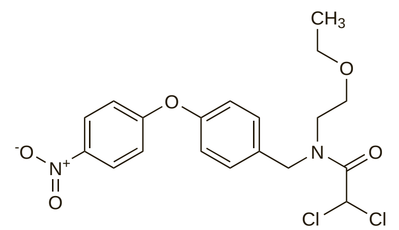

Profile

Etofamide, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p.832).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Kitnos; ***Mex.:*** Kitnos; ***Philipp.:*** Kitnos.

Fumagillin *(BAN, rINN)*

Fumagilina; Fumagilliini; Fumagilline; Fumagillinum. 4-(1,2-Epoxy-1,6-dimethylhex-4-enyl)-5-methoxy-1-oxaspiro[2.5]oct-6-yl hydrogen deca-2,4,6,8-tetraenedioate.

Фумагиллин

$C_{26}H_{34}O_7$ = 458.5.
CAS — 23110-15-8.
ATC — P01AX10.
ATC Vet — QP51AX23.

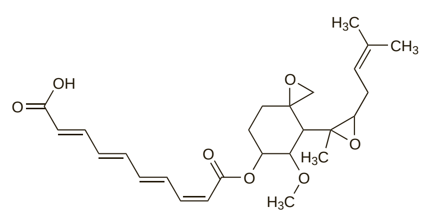

Profile

Fumagillin is an alicyclic antibiotic produced by certain strains of *Aspergillus fumigatus*. It has activity against Microsporidia and is used in veterinary practice to control *Nosema apis* infection in honeybees. Fumagillin is given in an oral dose of 20 mg three times daily for 14 days in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in patients with HIV infection. It has also been tried in humans in the topical treatment of microsporidial keratoconjunctivitis. It was formerly given orally in the treatment of intestinal amoebiasis, but produced an unacceptably high frequency of adverse effects. Analogues of fumagillin have been studied for effects on angiogenesis in solid tumours.

Microsporidiosis. As discussed on p.826, topical treatment of microsporidial keratoconjunctivitis has been disappointing. There have been several reports of successful treatment in individual patients using fumagillin topically,[1-3] usually as a solution of bicyclohexylammonium fumagillin containing the equivalent of fumagillin 70 micrograms/mL.

Oral fumagillin has been effective in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in patients with HIV infection.[4-7]

1. Rosberger DF, *et al.* Successful treatment of microsporidial keratoconjunctivitis with topical fumagillin in a patient with AIDS. *Cornea* 1993; **12:** 261–5.
2. Diesenhouse MC, *et al.* Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol* 1993; **115:** 293–8.
3. Garvey MJ, *et al.* Topical fumagillin in the treatment of microsporidial keratoconjunctivitis in AIDS. *Ann Pharmacother* 1995; **29:** 872–4.
4. Molina J-M, *et al.* Potential efficacy of fumagillin in intestinal microsporidiosis due to Enterocytozoon bieneusi in patients with HIV infection: results of a drug screening study. *AIDS* 1997; **11:** 1603–10.
5. Molina J-M, *et al.* Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. *AIDS* 2000; **14:** 1341–8.
6. Molina J-M, *et al.* Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med* 2002; **346:** 1963–9.
7. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Flisint.

Furazolidone *(BAN, rINN)*

Furatsolidoni; Furazolidon; Furazolidona; Furazolidonum; Nifurazolidonum. 3-(5-Nitrofurfurylideneamino)-2-oxazolidone.

Фуразолидон

$C_8H_7N_3O_5$ = 225.2.
CAS — 67-45-8.
ATC — G01AX06.
ATC Vet — QG01AX06.

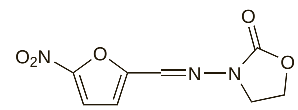

Pharmacopoeias. In *Br., Fr.,* and *US.*
BP 2008 (Furazolidone). A yellow odourless or almost odourless crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. The filtrate from a 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.
USP 31 (Furazolidone). A yellow, odourless, crystalline powder. Practically insoluble in water, in alcohol, and in carbon tetrachloride. Store in airtight containers. Protect from light and avoid exposure to direct sunlight.

Adverse Effects

The most common adverse effects of furazolidone involve the gastrointestinal tract and include nausea and vomiting. Dizziness, drowsiness, headache, and a general malaise have also been reported.

Allergic reactions, most commonly skin reactions such as rashes or angioedema, may occur. There have been instances of acute pulmonary reactions, similar to those seen with the structurally related drug nitrofurantoin, and of hepatotoxicity. Agranulocytosis has been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given furazolidone.

Darkening of the urine has been attributed to the presence of metabolites.

Precautions

Furazolidone should be used with caution in those with G6PD deficiency because of the risk of haemolytic anaemia. It should not be given to infants under 1 month of age since their enzyme systems are immature.

Interactions

A disulfiram-like reaction has been reported in patients taking alcohol while on furazolidone therapy; alcohol should be avoided during, and for a short period after, treatment with furazolidone.

Furazolidone is an MAOI and the cautions advised for these drugs regarding use with other drugs, especially indirect-acting sympathomimetic amines, and the consumption of food and drink containing tyramine, should be observed (see Phenelzine Sulfate, p.417). However, there appear to be no reports of hypertensive crises in patients receiving furazolidone and it has been suggested that, since furazolidone inhibits monoamine oxidase gradually over several days, the risks are small if treatment is limited to a 5-day course. Toxic psychosis has been reported in a patient receiving furazolidone and amitriptyline (see Antiprotozoals, under Interactions of Amitriptyline, p.380).

Pharmacokinetics

Although furazolidone has been considered to be largely unabsorbed when given orally, the occurrence of systemic adverse effects and coloured metabolites in the urine suggest that this may not be the case. Rapid and extensive metabolism, possibly in the intestine, has been proposed.

Uses and Administration

Furazolidone is a nitrofuran derivative with antiprotozoal and antibacterial activity. It is active against the protozoan *Giardia intestinalis* (*Giardia lamblia*) and against a range of enteric bacteria *in vitro*, including staphylococci, enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Vibrio cholerae*. Furazolidone is bactericidal and appears to act by interfering with bacterial enzyme systems. Resistance is reported to be limited. It is used in the treatment of giardiasis (p.824) and cholera (p.172). It has been suggested for other bacterial gastrointestinal infections, but antibacterial therapy is regarded as unnecessary in mild and self-limiting gastro-enteritis (see p.171).

Furazolidone is given orally in a dose of 100 mg four times daily; children and infants from 1 month of age may be given 1.25 mg/kg four times daily. It is usually given for 2 to 5 days, but may be given for up to 7 days in some patients, or for up to 10 days for giardiasis.

Peptic ulcer disease. Furazolidone is not one of the main antibacterials used in *Helicobacter pylori* eradication regimens for peptic ulceration (p.1702), but there are some studies suggesting its efficacy.[1-8]

1. Segura AM, *et al.* Furazolidone, amoxycillin, bismuth triple therapy for Helicobacter pylori infection. *Aliment Pharmacol Ther* 1997; **11:** 529–32.
2. Xiao S-D, *et al.* High cure rate of Helicobacter pylori infection using tripotassium dicitrato bismuthate, furazolidone and clarithromycin triple therapy for 1 week. *Aliment Pharmacol Ther* 1999; **13:** 311–15.
3. Liu W-Z, *et al.* Furazolidone-containing short-term triple therapies are effective in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 1999; **13:** 317–22.
4. Dani R, *et al.* Omeprazole, clarithromycin and furazolidone for the eradication of Helicobacter pylori in patients with duodenal ulcer. *Aliment Pharmacol Ther* 1999; **13:** 1647–52.
5. Graham DY, *et al.* Furazolidone combination therapies for Helicobacter pylori infection in the United States. *Aliment Pharmacol Ther* 2000; **14:** 211–15.
6. Liu W-Z, *et al.* A new quadruple therapy for Helicobacter pylori using tripotassium dicitrato bismuthate, furazolidone, josamycin and famotidine. *Aliment Pharmacol Ther* 2000; **14:** 1519–22.
7. Fakheri H, *et al.* Clarithromycin vs furazolidone in quadruple therapy regimens for the treatment of Helicobacter pylori in a population with a high metronidazole resistance rate. *Aliment Pharmacol Ther* 2001; **15:** 411–16.
8. Lu H, *et al.* One-week regimens containing ranitidine bismuth citrate, furazolidone and either amoxicillin or tetracycline effectively eradicate Helicobacter pylori: a multicentre, randomized, double-blind study. *Aliment Pharmacol Ther* 2001; **15:** 1975–9.

Preparations

USP 31: Furazolidone Oral Suspension; Furazolidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Giardil; ***Braz.:*** Enterolidon†; Giarcid†; Giarlam†; Neo Furasil; ***Chile:*** Furoxona; ***Ger.:*** Nifuran†; ***India:*** Furoxone; ***Indon.:*** Neo Prodiar; ***Mex.:*** Furoxona; Fuxol; Kaodin; Rolidan†; Salmocide; ***Philipp.:*** Diafuran; Diapectolin; Furoxone; ***Thai.:*** Furasian; Furion; ***USA:*** Furoxone†; ***Venez.:*** Furoxil; Furoxona; Onetil†.

Multi-ingredient: ***Arg.:*** Endomicina†; ***Braz.:*** Atapec†; Colestase; Enterobion†; ***Chile:*** Furazolidona; ***Hong Kong:*** Enterocin Compound; ***Hung.:*** Noditran†; ***India:*** Aristogyl-F; Dysfur-M†; Emantid†; Flagyl-F†; Kaltin MF; Lomofen; Metrogyl-F†; ***Mex.:*** Caopecfar; Colfur; Contefur†; Coralzul; Dialgin; Dibapec Compuesto; Estibal; Exofur; Furoxona CP; Fuzotyl†; Kapecfuran; Neokap; Optazol; Reuginal; Solfurol; Threchop; Trilor†; Yodozona; ***Spain:*** Desinvag; ***Thai.:*** Coccila†; Di-Su-Frone†; Difuran; Disento; Disento PF; Furasian; Furopectin†; Med-Kafuzone†; Mediocin†; ***Venez.:*** Sendafur†.

Halofuginone Hydrobromide *(BANM, USAN, rINNM)*

Halofuginone, Bromhydrate d'; Halofuginoni Hydrobromidum; Hidrobromuro de halofuginona; RU-19110. (±)-*trans*-7-Bromo-6-chloro-3-[3-(3-hydroxy-2-piperidyl)acetonyl]quinazolin-4(3*H*)-one hydrobromide.

Галофугинона Гидробромид

$C_{16}H_{17}BrClN_3O_3,HBr = 495.6.$

CAS — 55837-20-2 (halofuginone); 64924-67-0 (halofuginone hydrobromide).

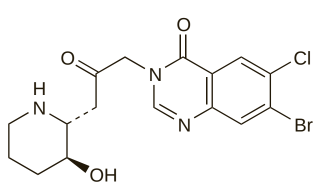

(halofuginone)

Profile

Halofuginone is an antiprotozoal used as the hydrobromide in veterinary practice for the prevention of coccidiosis in poultry and for the control of cryptosporidiosis in calves. It is also under investigation for use in neoplastic disease in humans and in the treatment of scleroderma (p.1817).

Imidocarb *(BAN, rINN)*

Imidocarbe; Imidocarbo; Imidocarbum. 1,3-Bis[3-(2-imidazolin-2-yl)phenyl]urea.

Имидокарб

$C_{19}H_{20}N_6O = 348.4.$

CAS — 27885-92-3.

ATC Vet — QP51AE01.

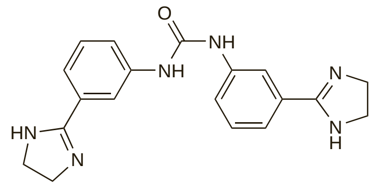

Imidocarb Dipropionate *(BANM, rINNM)*

Dipropionato de imidocarbo; Imidocarbe, Dipropionate d'; Imidocarbi Dipropionas.

Имидокарба Дипропионат

$C_{19}H_{20}N_6O,2C_3H_6O_2 = 496.6.$

CAS — 55750-06-6.

Imidocarb Hydrochloride *(BANM, USAN, rINNM)*

4A65; Hidrocloruro de imidocarbo; Imidocarbe, Chlorhydrate d'; Imidocarbi Hydrochloridum. 3,3′-Di(2-imidazolin-2-yl)carbanilide dihydrochloride.

Имидокарба Гидрохлорид

$C_{19}H_{20}N_6O,2HCl = 421.3.$

CAS — 5318-76-3.

Profile

Imidocarb has antiprotozoal and antibacterial activity and is used as the dipropionate in veterinary practice in the treatment of babesiosis and anaplasmosis in cattle. Imidocarb hydrochloride has also been used.

Isometamidium Chloride *(BAN, rINN)*

Cloruro de isometamidio; Isometamidii Chloridum; Isometamidium; Isométamidium, Chlorure d'. 8-[3-(*m*-Amidinophenyl)-2-triazeno]3-amino-5-ethyl-6-phenylphenanthridinium chloride.

Изометамидия Хлорид

$C_{28}H_{26}ClN_7 = 496.0.$

CAS — 34301-55-8.

Profile

Isometamidium is an antiprotozoal used as the chloride in veterinary practice for the control of trypanosomiasis.

Lasalocid *(BAN, USAN, rINN)*

Lasalocide; Lasalócido; Lasalocidum; Ro-02-2985.
6-[(3*R*,4*S*,5*S*,7*R*)-7-{(2*S*,3*S*,5*S*)-5-Ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-y]tetrahydro-3-methyl-2-fury1}4-hydroxy-3,5-dimethyl-6-oxononyl]-2-hydroxy-*m*-toluic acid.

Лазалоцид

$C_{34}H_{54}O_8 = 590.8.$

CAS — 11054-70-9; 25999-31-9.

ATC Vet — QP51AH02.

Lasalocid Sodium *(BANM, rINNM)*

Lasalocid sódico; Lasalocide Sodique; Lasalocidum Natricum.

Лазалоцид Натрий

$C_{34}H_{53}NaO_8 = 612.8.$

CAS — 25999-20-6.

ATC Vet — QP51AH02.

Profile

Lasalocid, an antibiotic produced by *Streptomyces lasaliensis*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in birds.

Letrazuril *(rINN)*

Létrazuril; Letrazurilo; Letrazurilum. (±)-[2,6-Dichloro-4-(4,5-dihydro-3,5-dioxo-*as*-triazin-2(3*H*)-yl)phenyl](*p*-fluorophenyl)acetonitrile.

Летразурил

$C_{17}H_9Cl_2FN_4O_2 = 391.2.$

CAS — 103337-74-2.

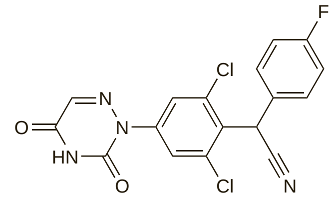

Profile

Letrazuril is an antiprotozoal that has been investigated in the treatment of cryptosporidiosis (p.823) in patients with AIDS.

Maduramicin *(BAN, USAN, rINN)*

CL-273703; Maduramicin Ammonium; Maduramicina; Maduramicine; Maduramicinum. Ammonium (2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2-hydroxy-6-{(*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-{(2*S*,2′*R*,3′*S*,5*R*,5′*R*)-octahydro-2-methyl-3′-[(2*R*,4*S*,5*S*,6*S*)-tetrahydro-4,5-dimethoxy-6-methyl-2*H*-pyran-2-yl]oxy}-5′-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl](2,2′-bifuran-5-yl)-1,6-dioxaspiro[4.5]dec-7-yl]ethyl}-4,5-dimethoxy-3-methyl-2*H*-pyran-2-acetate.

Мадурамицин

$C_{47}H_{80}O_{17},NH_3 = 934.2.$

CAS — 84878-61-5.

ATC Vet — QP51AX10.

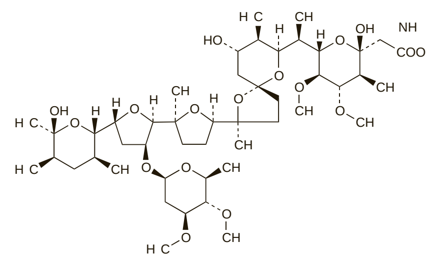

NOTE. The name maduramicin has also been used to denote the acid.

Profile

Maduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Melarsoprol *(BAN, rINN)*

Mel B; Melarsen Oxide-BAL; Mélarsoprol; Melarsoprolum; RP-3854. 2-[4-(4,6-Diamino-1,3,5-triazin-2-ylamino)phenyl]-1,3,2-dithiarsolan-4-ylmethanol.

Меларсопрол

$C_{12}H_{15}AsN_6OS_2 = 398.3.$

CAS — 494-79-1.

ATC — P01CD01.

ATC Vet — QP51AD04.

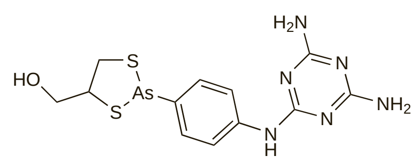

Adverse Effects and Treatment

Adverse effects are common and may be severe during the treatment of African trypanosomiasis with melarsoprol. It may be difficult to distinguish between effects of the disease, Jarisch-Herxheimer reactions resulting from the release of antigens from trypanosomes killed by melarsoprol, and adverse effects due to the drug's arsenic content or to hypersensitivity. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p.2260.

A severe febrile reaction may occur after the first injection of melarsoprol, especially in patients with large numbers of trypanosomes in their blood. It is therefore common practice to give 2 or 3 injections of suramin or pentamidine before starting melarsoprol therapy.

The greatest risk is from reactive encephalopathy which occurs in about 10% of patients treated with melarsoprol and is usually seen between the end of the first 3- or 4-day course of injections and the start of the second course. Encephalopathy may be sudden in onset or develop slowly. Symptoms include fever, headache, tremor, slurring of speech, convulsions, and coma; death has occurred in up to 5% of patients treated with melarsoprol. Less commonly, haemorrhagic encephalopathy may occur. The prophylactic use of corticosteroids has been suggested during treatment courses of melarsoprol (see African Trypanosomiasis, below). Treatment of reactive encephalopathy has included the use of corticosteroids, hypertonic solutions to combat cerebral oedema, anticonvulsants such as diazepam, and subcutaneous adrenaline; dimercaprol has been given on the assumption that encephalopathy resulted from arsenic poisoning, but has not generally been of benefit.

Hypersensitivity reactions to melarsoprol may occur during the second and subsequent courses of treatment. Desensitisation with gradually increasing doses of melarsoprol has been attempted; corticosteroids may help to control symptoms during this procedure. Some authorities consider that the use of small doses of melarsoprol may increase the risk of resistance.

Melarsoprol injection is very irritant and extravasation during intravenous use should be avoided. Vomiting and abdominal colic may occur if it is injected too rapidly. Other adverse effects reported include agranulocytosis, hypertension, peripheral neuropathy, proteinuria, severe diarrhoea, myocardial damage, exfoliative dermatitis, and hepatic disturbances.

◊ References.

1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **i:** 1246–50.
2. Pepin J, Milord F. African trypanosomiasis and drug-induced encephalopathy: risk factors and pathogenesis. *Trans R Soc Trop Med Hyg* 1991; **85:** 222–4.
3. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; **89:** 92–7.

Precautions

Use of melarsoprol in febrile patients has been associated with an increased incidence of reactive encephalopathy, and therefore it should not be given during epidemics of influenza. Intercurrent infections such as malaria and pneumonia should be treated before melarsoprol is used. Severe haemolytic reactions have been reported in patients with G6PD deficiency. It may precipitate erythema nodosum when given to patients with leprosy.

Patients should be in hospital when they are treated with melarsoprol and dosage decided after taking into account their general condition.

Treatment of pregnant women with trypanosomiasis should be deferred until after delivery. Pregnant women with meningoencephalitis may be treated with pentamidine (*Trypanosoma brucei gambiense*) or suramin (*T. b. rhodesiense*).

Pharmacokinetics

Melarsoprol is reported to be unreliably absorbed if given orally and is usually given by intravenous injection. A small amount penetrates into the CSF where it has a local trypanocidal action. It is rapidly metabolised and excreted in the faeces and urine so any prophylactic effect is short-lived.

Uses and Administration

Melarsoprol, a trivalent arsenical derivative, is a trypanocide which appears to act by inhibiting trypanosomal pyruvate kinase. It is effective in the treatment of all stages of African trypanosomiasis due to *Trypanosoma brucei gambiense* or *T. brucei rhodesiense*, but because of its toxicity its use is usually reserved for stages of the disease involving the CNS. Resistance has been reported to develop.

Patients undergoing therapy with melarsoprol should be treated in hospital. Melarsoprol is given by intravenous injection as a 3.6% solution in propylene glycol. The injection should be given slowly, care being taken to prevent leakage into the surrounding tissues, and the patient should remain supine and fasting for several hours after the injection.

Treatment protocols vary, but in general melarsoprol is given in low doses initially, especially in children and debilitated patients, increased gradually to the maximum daily dose of 3.6 mg/kg. Doses are given daily for 3 or 4 days and the course repeated 2 or 3 times with an interval of 7 to 10 days between courses. Since massive destruction of parasites resulting in a Jarisch-Herxheimer reaction is particularly dangerous during treatment with melarsoprol, several doses of suramin or pentamidine may be given to induce the reaction before melarsoprol is started.

Melarsonyl potassium is a water-soluble derivative of melarsoprol which was formerly used as an alternative to melarsoprol but was probably more toxic and less effective.

African trypanosomiasis. Melarsoprol, which is effective against both *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, is usually only given to treat the meningoencephalitic stage of African trypanosomiasis (p.827) because it may produce potentially fatal encephalopathy. However, protection against this toxicity may be provided by prophylaxis with prednisolone.[1,2] Therapy with melarsoprol and eflornithine was reported to be effective in a patient who had not responded to either drug alone.[3] A comparative study[4] in 500 patients with second-stage infection with *T. b. gambiense* found that a more concise dosage regimen of melarsoprol 2.2 mg/kg daily, as a single course over 10 days, was similar in efficacy to standard regimens of 1.2 to 3.6 mg/kg daily for 3 or 4 days repeated twice over a 26-day period with 7-day intervals between series, although there was no difference between the regimens in the incidence of associated encephalopathy.

1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **i:** 1246–50.
2. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; **89:** 92–7.
3. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 315.
4. Burri C, *et al.* Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by Trypanosoma brucei gambiense: a randomised trial. *Lancet* 2000; **355:** 1419–25.

Mepacrine Hydrochloride *(BANM, rINNM)*

Acrichinum; Acrinamine; Antimalarinae Chlorhydras; Chinacrina; Hidrocloruro de mepacrina; Mépacrine, Chlorhydrate de; Mepacrini Hydrochloridum; Mepakrin Hidroklorür; Quinacrine Hydrochloride. 6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.

Мепакрина Гидрохлорид

$C_{23}H_{30}ClN_3O,2HCl,2H_2O = 508.9.$

CAS — 83-89-6 (mepacrine); 69-05-6 (anhydrous mepacrine dihydrochloride); 6151-30-0 (mepacrine dihydrochloride dihydrate).

ATC — P01AX05.

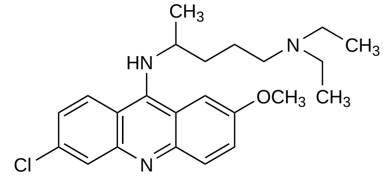

(mepacrine)

Adverse Effects

The most common adverse effects associated with mepacrine are dizziness, headache, and gastrointestinal disturbances such as nausea and vomiting. Reversible yellow discoloration of the skin, conjunctiva, and urine may occur during long-term use or after large doses; blue/black discoloration of the palate and discoloration of the nails have also been reported. Doses such as those used in the treatment of giardiasis may occasionally cause transient acute toxic psychosis and CNS stimulation. Convulsions have been reported at high doses. Ocular toxicity similar to that seen with chloroquine (p.600) and chronic dermatoses, including severe exfoliative dermatitis and lichenoid eruptions, have also occurred after prolonged use of mepacrine. Hepatotoxicity and aplastic anaemia occur rarely.

Effects on the nervous system. Two patients had convulsions a few hours after mepacrine hydrochloride 400 mg was given intrapleurally for malignant effusions. One developed status epilepticus and died and the other was successfully treated with anticonvulsants.[1]

1. Borda I, Krant M. Convulsions following intrapleural administration of quinacrine hydrochloride. *JAMA* 1967; **201:** 1049–50.

Precautions

Mepacrine should be used with caution in elderly patients or patients with a history of psychosis, or in the presence of hepatic disease. Mepacrine can cause exacerbation of psoriasis and should be avoided in psoriatic patients.

Porphyria. Mepacrine should be used with caution in patients with porphyria.

Interactions

Mepacrine has been reported to produce a mild disulfiram-like reaction (see p.2296) when taken with alcohol.

Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Pharmacokinetics

Mepacrine is readily absorbed from the gastrointestinal tract and widely distributed throughout the body. It accumulates in body tissues, particularly the liver, and is liberated slowly. It is excreted slowly mainly in the urine, and is still detectable in the urine after 2 months. Mepacrine crosses the placenta.

Intrapleural administration. Peak plasma concentrations of mepacrine far above those associated with CNS effects were rapidly attained in 3 of 4 patients after intrapleural instillation of a solution of mepacrine hydrochloride and remained at these levels for several hours.[1]

1. Björkman S, *et al.* Pharmacokinetics of quinacrine after intrapleural instillation in rabbits and man. *J Pharm Pharmacol* 1989; **41:** 160–73.

Uses and Administration

Mepacrine is a 9-aminoacridine antiprotozoal used as the hydrochloride mainly as an alternative to the nitroimidazoles in the treatment of giardiasis (p.824).

In giardiasis, mepacrine hydrochloride is given orally in doses of 100 mg three times daily after food for 5 to 7 days. A dose for children is 2 mg/kg given three times daily (maximum 300 mg daily).

Mepacrine hydrochloride may also be used, alone or with hydroxychloroquine, for the treatment of discoid and subcutaneous lupus erythematosus. It has also been used locally in the treatment of some forms of cutaneous leishmaniasis, as a sterilisation technique for contraception, and in the management of malignant effusions. It was formerly used to treat malaria.

The mesilate was also formerly used.

Mepacrine is under investigation for the treatment of variant Creutzfeldt-Jakob Disease.

Contraception. Sterilisation with intra-uterine mepacrine has been attempted as an irreversible method of contraception (p.2070). It produces occlusion of the fallopian tube and has been reported to be an effective nonsurgical means of female sterilisation,[1] although it may be less effective than other methods.[2] There has been speculation about the risk of cancer from this technique but there appeared to be no evidence to confirm such a risk.[3-5] However, the method remains controversial and a full evaluation of its safety and efficacy has been recommended.[6] The Indian government has banned the use of mepacrine for sterilisation.

1. Hieu DT, *et al.* 31 781 Cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; **342:** 213–17.
2. Sokal DC, *et al.* Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam. *Contraception* 2008; **78:** 61–5.
3. Anonymous. Death of a study: WHO, what, and why. *Lancet* 1994; **343:** 987–8.
4. Hieu DT. Quinacrine method of family planning. *Lancet* 1994; **343:** 1040.
5. Sokal DC, *et al.* Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. *Contraception* 2008; **78:** 66–72.
6. Benagiano G. Sterilisation by quinacrine. *Lancet* 1994; **344:** 689.

Leishmaniasis. Mepacrine has been suggested for intralesional injection in the treatment of early noninflamed nodular lesions of cutaneous leishmaniasis (p.824) due to *Leishmania tropica*, *L. major*, *L. mexicana*, *L. panamensis*, or *L. peruviana*.[1] The suggested course of treatment was 3 intralesional injections of a 5% solution of mepacrine given at intervals of 3 to 5 days. However, local infiltration of drugs can be difficult and painful.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990.

Sclerotherapy. Intrapleural instillations of mepacrine hydrochloride or mesilate have been used as sclerosants in the management of malignant pleural effusions (p.659) and recurrent pneumothorax but the treatment is associated with pain and a high frequency of toxic effects.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Maladin.

Methyl Benzoquate *(BAN)*

Nequinate *(USAN, pINN)*; AY-20385; ICI-55052; Néquinate; Nequinato; Nequinatum. Methyl 7-benzyloxy-6-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate.

Нехинат

$C_{22}H_{23}NO_4$ = 365.4.
CAS — 13997-19-8.

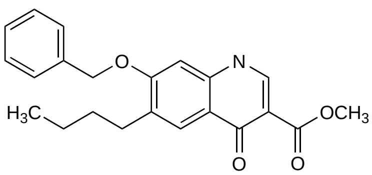

Profile

Methyl benzoquate is an antiprotozoal used in veterinary practice with clopidol (p.831) for the prevention of coccidiosis in poultry.

Metronidazole *(BAN, USAN, rINN)*

Bayer-5360; Metronidatsoli; Metronidazol; Metronidazolas; Métronidazole; Metronidazolum; NSC-50364; RP-8823; SC-10295. 2-(2-Methyl-5-nitroimidazol-1-yl)ethanol.

Метронидазол

$C_6H_9N_3O_3$ = 171.2.
CAS — 443-48-1.
ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.
ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

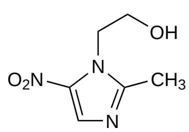

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Metronidazole). A white or yellowish, crystalline powder. Slightly soluble in water, in alcohol, in acetone, and in dichloromethane. Protect from light.

USP 31 (Metronidazole). White to pale yellow, odourless crystals or crystalline powder. It darkens on exposure to light. Sparingly soluble in water and in alcohol; slightly soluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. See below.

Metronidazole Benzoate *(BAN, rINNM)*

Benzoato de metronidazol; Benzoyl Metronidazole; Metronidatsolibentsoaatti; Metronidazolbensoat; Metronidazol-benzoát; Métronidazole, benzoate de; Metronidazoli benzoas; Metronidazolo benzoatas; RP-9712. 2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate.

Метронидазола Бензоат

$C_{13}H_{13}N_3O_4$ = 275.3.
CAS — 13182-89-3.
ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.
ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Metronidazole Benzoate). White or slightly yellowish, crystalline powder or flakes. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Metronidazole Benzoate). A white to slightly yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; very slightly soluble in solvent ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Metronidazole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de metronidazol; Métronidazole, Chlorhydrate de; Metronidazoli Hydrochloridum; SC-32642.

Метронидазола Гидрохлорид

$C_6H_9N_3O_3,HCl$ = 207.6.
CAS — 69198-10-3.
ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.
ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

Incompatibility. Solutions of metronidazole hydrochloride have a low pH, usually of less than 2.0, before dilution and neutralisation for intravenous use. These undiluted solutions react with aluminium in equipment such as needles to produce reddish-brown discoloration, and a precipitate has been reported with ready-to-use preparations of metronidazole hydrochloride, although this occurred after contact for 6 hours or more.[1,2]

Several studies have assessed the compatibility of antibacterial injections and other drugs when added to metronidazole solution for intravenous infusion.[3-7] Results have varied according to the criteria applied and the preparations and conditions used. Physical incompatibilities due to the low pH of metronidazole injections appear to be more of a problem than chemical incompatibility. Regardless of these studies, it is generally recommended that other drugs should not be added to intravenous solutions of metronidazole or its hydrochloride. Specific information on the compatibility of individual formulations may be found in the manufacturers' literature.

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bisaillon S, Sarrazin R. Compatibility of several antibiotics or hydrocortisone when added to metronidazole solution for intravenous infusion. *J Parenter Sci Technol* 1983; **37:** 129–32.
4. Gupta VD, Stewart KR. Chemical stabilities of hydrocortisone sodium succinate and several antibiotics when mixed with metronidazole injection for intravenous infusion. *J Parenter Sci Technol* 1985; **39:** 145–8.
5. Gupta VD, *et al.* Chemical stabilities of cefamandole nafate and metronidazole when mixed together for intravenous infusion. *J Clin Hosp Pharm* 1985; **10:** 379–83.
6. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
7. Nahata MC, *et al.* Stability of metronidazole and ceftizoxime sodium in ready-to-use metronidazole bags stored at 4 and 25° C. *Am J Health-Syst Pharm* 1996; **53:** 1046–8.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Vomiting, and diarrhoea or constipation may also occur. A furred tongue, glossitis, and stomatitis may be associated with an overgrowth of *Candida*. There have been rare reports of antibiotic-associated colitis associated with metronidazole, although it is also used in the treatment of this condition.

Weakness, dizziness, ataxia, headache, drowsiness, insomnia, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures have been associated with high doses of metronidazole or prolonged treatment.

Temporary moderate leucopenia and thrombocytopenia may occur in some patients receiving metronidazole. Skin rashes, urticaria, and pruritus occur occasionally and erythema multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, and jaundice have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some *animals*.

Carcinogenicity and mutagenicity. Metronidazole is mutagenic in bacterial assays, and its hydroxy metabolite even more so, but studies of mammalian cells *in vitro* and *in vivo* have not consistently demonstrated a mutagenic effect. Similarly, there is no uniformity in the limited data concerning genotoxicity in humans,[1] and although metronidazole has been classified as a carcinogen in *animals*, the evidence of human carcinogenicity is ambiguous. There was no appreciable increase in the incidence of cancer in a retrospective study of 771 patients given metronidazole for vaginal trichomoniasis,[2] nor in another similar study of 2460 patients.[3] The first study[2] did show an excess of cases of lung cancer, although all 4 were in women who were smokers. Subsequent follow-up[4] to 1984, covering a period of 15 to 25 years, still showed an excess of lung cancer cases even after allowing for smoking status. However, this follow-up also continued to show no significant increase overall in cancer-related morbidity or mortality. Follow-up[5] of the patients from the second study for 11 to 15 years to 1984 also showed no increase in the overall incidence of cancers nor did it confirm any increase in lung cancer.

Risks to the fetus are discussed under Pregnancy in Precautions, below.

1. Bendesky A, *et al.* Is metronidazole carcinogenic? *Mutat Res* 2002; **511:** 133–44.
2. Beard CM, *et al.* Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979; **301:** 519–22.
3. Friedman GD. Cancer after metronidazole. *N Engl J Med* 1980; **302:** 519.
4. Beard CM, *et al.* Cancer after exposure to metronidazole. *Mayo Clin Proc* 1988; **63:** 147–53.
5. Friedman GD, Selby JV. Metronidazole and cancer. *JAMA* 1989; **261:** 866.

Effects on the blood. Adverse haematological effects associated with metronidazole therapy include a report of bone marrow aplasia, with leucopenia and markedly reduced erythropoiesis and granulopoiesis,[1] aplastic anaemia,[2] and the haemolytic-uraemic syndrome.[3]

1. White CM, *et al.* Bone marrow aplasia associated with metronidazole. *BMJ* 1980; **280:** 647.
2. Raman R, *et al.* Metronidazole induced aplastic anaemia. *Clinician* 1982; **46:** 464–8.
3. Powell HR, *et al.* Haemolytic-uraemic syndrome after treatment with metronidazole. *Med J Aust* 1988; **149:** 222–3.

Effects on the ears. A review of reports of ototoxicity notified to the Australian Adverse Drug Reactions Advisory Committee revealed a number of cases of deafness associated with the use of metronidazole.[1]

1. Anonymous. Drug-induced ototoxicity. *WHO Drug Inf* 1991; **5:** 12.

Effects on the eyes. Myopia which developed in a patient after 11 days of oral metronidazole for trichomoniasis had resolved 4 days after withdrawal of treatment, but recurred when she resumed treatment.[1]

Optic neuropathies have also occurred.[2,3] In one report, retrobulbar or optic neuritis was seen in 7 patients given oral metronidazole.[2] Dosage varied from 0.75 to 1 g daily and duration of treatment from 7 days to a year. Abnormalities included defects in colour vision, decreased vision, and scotomas. Vision improved on withdrawal of metronidazole, although there was a residual deficit in 2 patients.

1. Grinbaum A, *et al.* Transient myopia following metronidazole treatment for Trichomonas vaginalis. *JAMA* 1992; **267:** 511–12.
2. Putnam D, *et al.* Metronidazole and optic neuritis. *Am J Ophthalmol* 1991; **112:** 737.
3. McGrath NM, *et al.* Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol* 2007; **35:** 585–6.

Effects on the gastrointestinal tract. ***ANTIBIOTIC-ASSOCIATED COLITIS.*** Reports of pseudomembranous colitis associated with the use of metronidazole.

1. Thomson G, *et al.* Pseudomembranous colitis after treatment with metronidazole. *BMJ* 1981; **282:** 864–5.
2. Daly JJ, Chowdary KVS. Pseudomembranous colitis secondary to metronidazole. *Dig Dis Sci* 1983; **28:** 573–4.

Effects on the liver. Severely elevated liver enzyme values, consistent with a drug-induced hepatitis, occurred in a patient given metronidazole hydrochloride 500 mg every 6 hours intravenously for 4 days. He was also receiving cefapirin sodium and tobramycin sulfate.[1] A case of reversible hepatotoxicity caused by an overdose of metronidazole 12.5 g has also been reported.[2]

1. Appleby DH, Vogtland HD. Suspected metronidazole toxicity. *Clin Pharm* 1983; **2:** 373–4.
2. Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. *Ann Intern Med* 1995; **122:** 803.

Effects on the nervous system. ***ASEPTIC MENINGITIS.*** A 42-year-old man had 3 episodes of aseptic meningitis during treatment with oral metronidazole as part of an eradication regimen for *Helicobacter pylori* infection.[1] On each occasion his symptoms resolved spontaneously when eradication treatment was stopped and recurred when treatment was restarted. The aseptic meningitis was attributed to the metronidazole and the patient later tolerated an eradication treatment regimen containing a proton-pump inhibitor and a macrolide.

1. Khan S, *et al.* Metronidazole-induced aseptic meningitis during Helicobacter pylori eradication therapy. *Ann Intern Med* 2007; **146:** 395–6.

CEREBELLAR TOXICITY. Ataxia and dysarthria have been reported in 2 patients taking oral metronidazole plus intravenous cefepime or oral levofloxacin.[1] Symptoms occurred about one month after starting treatment and resolved 2 to 5 weeks after stopping metronidazole.

1. Woodruff BK, *et al.* Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 2002; **346:** 68–9.

CONVULSIONS. Reports of convulsions associated with metronidazole therapy (usually in high doses or in patients with renal impairment).

1. Halloran TJ. Convulsions associated with high cumulative doses of metronidazole. *Drug Intell Clin Pharm* 1982; **16:** 409.

2. Wienbren M, *et al.* Convulsions and encephalopathy in a patient with leukemia after treatment with metronidazole. *J Clin Pathol* 1985; **38:** 1076.
3. Ferroir JP, *et al.* Polynévrite, crises convulsives et syndrome cérébelleux, complications d'un traitement par le métronidazole. *Presse Med* 1985; **14:** 2108.
4. Moulin B, *et al.* Risque neurotoxique du métronidazole (MN) au cours de l'insuffisance rénale sévère. *Ann Med Interne (Paris)* 1988; **139:** 369.
5. Sopena B, *et al.* Convulsiones inducidas por la asociación de metronidazol y cloroquina. *Med Clin (Barc)* 1990; **95:** 675.
6. Beloosesky Y, *et al.* Convulsions induced by metronidazole treatment for Clostridium difficile-associated disease in chronic renal failure. *Am J Med Sci* 2000; **319:** 338–9.

EFFECTS ON MENTAL FUNCTION. Although metronidazole is sometimes used to reduce colonic flora in the treatment of hepatic encephalopathy, impaired metabolism of metronidazole in such patients can result in elevated plasma concentrations and consequent toxicity. Psychosis and manic behaviour were reported in one such patient during treatment for hepatic encephalopathy with metronidazole and lactulose, although plasma-metronidazole concentrations were not found to be raised (24 micrograms/mL).[1] Symptoms resolved when metronidazole was stopped. Acute psychosis has also been reported in a patient following a 5-day course of intravenous metronidazole 1 g daily for a gynaecological disorder.[2]

1. Uhl MD, Riely CA. Metronidazole in treating portosystemic encephalopathy. *Ann Intern Med* 1996; **124:** 455.
2. Schreiber W, Spernal J. Metronidazole-induced psychotic disorder. *Am J Psychiatry* 1997; **154:** 1170–1.

PERIPHERAL NEUROPATHY. Peripheral neuropathy has been reported in patients receiving prolonged treatment with metronidazole.[1-4] Stopping metronidazole or lowering the dose usually results in complete resolution or improvement of the neuropathy but in some patients it may persist despite these measures. For reports of retrobulbar or optic neuritis associated with metronidazole, see Effects on the Eyes, above.

1. Duffy LF, *et al.* Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 1985; **88:** 681–4.
2. Boyce EG, *et al.* Persistent metronidazole-induced peripheral neuropathy. *DICP Ann Pharmacother* 1990; **24:** 19–21.
3. Learned-Coughlin S. Peripheral neuropathy induced by metronidazole. *Ann Pharmacother* 1994; **28:** 536.
4. Dreger LM, *et al.* Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother* 1998; **32:** 267–8.

Effects on the pancreas. A small number of cases of acute pancreatitis associated with metronidazole, in some cases recurrent on rechallenge, have been reported.[1-4] No cases were found in a retrospective study of about 6500 patients who had received metronidazole.[5]

1. Plotnick BH, *et al.* Metronidazole-induced pancreatitis. *Ann Intern Med* 1985; **103:** 891–2.
2. Sanford KA, *et al.* Metronidazole-associated pancreatitis. *Ann Intern Med* 1988; **109:** 756–7.
3. Sura ME, *et al.* Metronidazole-associated pancreatitis. *Ann Pharmacother* 2000; **34:** 1152–5.
4. Tsesmeli NE, *et al.* Acute pancreatitis as a possible consequence of metronidazole during a relapse of ulcerative colitis. *Eur J Gastroenterol Hepatol* 2007; **19:** 805–6.
5. Friedman G, Selby JV. How often does metronidazole induce pancreatitis? *Gastroenterology* 1990; **98:** 1702–3.

Gynaecomastia. Gynaecomastia occurred in a 36-year-old man with ulcerative colitis after taking metronidazole for about a month.[1]

1. Fagan TC, *et al.* Metronidazole-induced gynecomastia. *JAMA* 1985; **254:** 3217.

Hypersensitivity. A hypersensitivity reaction with chills, fever, generalised erythema, and a maculopapular rash developed after a single dose of metronidazole in a patient who had previously developed a rash during treatment with intravaginal metronidazole.[1]

1. Knowles S, *et al.* Metronidazole hypersensitivity. *Ann Pharmacother* 1994; **28:** 325–6.

Precautions

Peripheral neuropathy, transient epileptiform seizures, and leucopenia have sometimes been associated with prolonged or intensive treatment with metronidazole (see Adverse Effects, above). Clinical and laboratory monitoring is advised in patients given metronidazole for more than 10 days. Doses should be reduced in patients with severe hepatic impairment.

It is suggested that the use of metronidazole should be avoided during pregnancy, and this caution applies especially to use during the first trimester and to the use of high-dose regimens (see also below).

Patients are advised not to drink alcoholic beverages while taking metronidazole (see under Interactions, below).

Breast feeding. Metronidazole is distributed into breast milk giving it a bitter taste which may impair feeding.[1] The American Academy of Pediatrics considers that although the effects of metronidazole on breast-fed infants are unknown they may be of concern. It recommends that breast feeding should be stopped for 12 to 24 hours when single-dose therapy is used;[2] no specific recommendations are given for long-term treatment.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/02/04)

Pregnancy. Metronidazole is mutagenic in bacteria and carcinogenic in *rodents*. It readily crosses the placenta achieving similar concentrations in the placental cord and maternal plasma and its use in pregnancy is controversial. Meta-analyses of studies involving the use of metronidazole in the first trimester of pregnancy[1,2] concluded that there did not appear to be an increased risk of teratogenicity. However, in the USA licensed product information considers metronidazole to be contra-indicated during the first trimester in patients with trichomoniasis; use for trichomoniasis during the second and third trimesters may be acceptable. For other indications the risks and benefits of treatment with metronidazole should be weighed carefully, especially in the first trimester.

1. Burtin P, *et al.* Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995; **172:** 525–9.
2. Caro-Patón T, *et al.* Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997; **44:** 179–82.

Interactions

When given with alcohol, metronidazole may provoke a disulfiram-like reaction in some patients. Acute psychoses or confusion have been associated with the use of metronidazole and disulfiram together.

Metronidazole is reported to impair the metabolism or excretion of several drugs including warfarin (p.1429), phenytoin (p.499), lithium (see Antimicrobials, p.404), ciclosporin, and fluorouracil (p.723), with the consequent potential for an increased incidence of adverse effects. There is some evidence that phenytoin might accelerate the metabolism of metronidazole. Plasma concentrations of metronidazole are decreased by phenobarbital, with a consequent reduction in the effectiveness of metronidazole. Cimetidine has increased plasma concentrations of metronidazole and might increase the risk of neurological adverse effects. For references to some of these interactions, see below.

For incompatibilities between metronidazole and other drugs in solutions for injection, see above.

Alcohol. Metronidazole may provoke a disulfiram-like reaction in some individuals when given with alcohol; reactions have occurred after the use of preparations formulated with alcohol, including injections, as well as after drinking alcohol.[1] Acute psychosis or confusional state was reported in 6 of 29 alcoholic patients who were also taking disulfiram.[2] However, an analysis of published reports[3] and a study in healthy subjects[4] both found that there was no convincing evidence of a disulfiram-like reaction between metronidazole and alcohol although caution was still advised.

1. Edwards DL, *et al.* Disulfiram-like reaction associated with intravenous trimethoprim-sulfamethoxazole and metronidazole. *Clin Pharm* 1986; **5:** 999–1000.
2. Rothstein E, Clancy DD. Toxicity of disulfiram combined with metronidazole. *N Engl J Med* 1969; **280:** 1006–7.
3. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother* 2000; **34:** 255–7.
4. Visapää J-P, *et al.* Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother* 2002; **36:** 971–4.

Antineoplastics. For reference to the effect of metronidazole on busulfan, see p.691.

Carbamazepine. For a report of a possible interaction between metronidazole and carbamazepine, see p.475.

Cimetidine. In a study in 6 healthy subjects metronidazole plasma concentrations were increased by twice-daily doses of cimetidine. The effect was presumed to be due to inhibition of cytochrome P450 isoenzymes responsible for metronidazole metabolism.[1] However, cimetidine was not found to affect the pharmacokinetics of metronidazole in a study in patients with Crohn's disease[2] nor in a single-dose study in healthy subjects.[3]

1. Gugler R, Jansen JC. Interaction between cimetidine and metronidazole. *N Engl J Med* 1983; **309:** 1518–19.
2. Eradiri O, *et al.* Interaction of metronidazole with cimetidine and phenobarbital in Crohn's disease. *Clin Pharmacol Ther* 1987; **41:** 235.
3. Loft S, *et al.* Lack of effect of cimetidine on the pharmacokinetics and metabolism of a single oral dose of metronidazole. *Eur J Clin Pharmacol* 1988; **35:** 65–8.

Disulfiram. For a report of acute psychosis or confusional state following metronidazole treatment in alcoholic patients receiving disulfiram, see under Alcohol, above.

Mycophenolate mofetil. For details of a pharmacokinetic study reporting reduced exposure to mycophenolate mofetil when given with metronidazole or metronidazole plus norfloxacin, see Antibacterials, p.1837.

Omeprazole. Although concentrations in plasma and saliva of metronidazole and its hydroxy metabolite were unaffected by omeprazole in healthy subjects, those in gastric juice were substantially lowered, possibly as a result of a reduction in transfer from the plasma.[1] However, this may be of limited clinical significance during treatment of *Helicobacter pylori* infections.

1. Jessa MJ, *et al.* The effect of omeprazole on the pharmacokinetics of metronidazole and hydroxymetronidazole in human plasma, saliva and gastric juice. *Br J Clin Pharmacol* 1997; **44:** 245–53.

Phenobarbital. An increase in the rate of metabolism of metronidazole, resulting in treatment failure, was reported in a patient taking phenobarbital.[1] In a retrospective survey of patients who had not responded to treatment with metronidazole, 80% were found to be on long-term phenobarbital therapy.[2] It was found that up to 3 times the usual dose was required to produce a parasitological cure of giardiasis in such patients.

1. Mead PB, *et al.* Possible alteration of metronidazole metabolism by phenobarbital. *N Engl J Med* 1982; **306:** 1490.
2. Gupte S. Phenobarbital and metabolism of metronidazole. *N Engl J Med* 1983; **308:** 529.

Phenytoin. In addition to conflicting reports on the effects of metronidazole on the metabolism of phenytoin (p.499), increased metabolism of metronidazole was reported in a patient during treatment with phenytoin.[1]

1. Wheeler LA, *et al.* Use of high-pressure liquid chromatography to determine plasma levels of metronidazole and metabolites after intravenous administration. *Antimicrob Agents Chemother* 1978; **13:** 205–9.

Antimicrobial Action

Metronidazole is active against several protozoa including *Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia intestinalis* (*Giardia lamblia*), and *Trichomonas vaginalis*. Most obligate anaerobic bacteria, including *Bacteroides* and *Clostridium* spp., are sensitive *in vitro* to metronidazole. It is bactericidal. It also has activity against the facultative anaerobes *Gardnerella vaginalis* and *Helicobacter pylori* and against some spirochaetes. Resistance to metronidazole has been reported and cross-resistance to other nitroimidazoles, such as tinidazole, may occur.

◊ Metronidazole has well-established bactericidal activity against obligate anaerobic bacteria *in vitro*, including the Gram-negative organisms *Bacteroides fragilis* and other *Bacteroides* spp., *Fusobacterium* spp., and *Veillonella* spp., and the Gram-positive organisms *Clostridium difficile, Cl. perfringens,* and other *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp., and *Peptostreptococcus* spp.; *Propionibacterium* and *Actinomyces* spp. are often resistant.[1-6] It also has activity against the facultative anaerobe *Gardnerella vaginalis*, although its bactericidal effect is reported to be much slower than against obligate anaerobes,[7] against some strains of *Campylobacter* spp. including *C. fetus* subsp. *jejuni*,[8,9] and against *Helicobacter pylori*.[10,11]

The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of *G. vaginalis*.[12,13]

The mode of action of metronidazole is not entirely clear, but is thought to involve reduction by bacterial 'nitroreductases' to an unstable intermediate which interacts with DNA, effectively preventing further replication.[14] A number of factors affect the sensitivity of micro-organisms to metronidazole *in vitro*. Anaerobic conditions are important for optimal activity. Interactions between micro-organisms and metronidazole have been described, including inhibition of *Escherichia coli* by metronidazole in the presence of *B. fragilis* and enhancement of the rate of killing of *B. fragilis* by metronidazole in the presence of *E. coli*.

Resistance to metronidazole has developed in sensitive species. Although no resistance among the *B. fragilis* group was observed over several years,[15,16] there have been occasional reports of resistance in this group[17-22] and in other *Bacteroides* spp.[23-25] now known as *Prevotella* spp. Nitroimidazole resistance in *Helicobacter pylori* has been increasing and may be associated with reduced response rates to anti-*Helicobacter* therapy for peptic ulcer disease in some populations (see Peptic Ulcer Disease under Uses, below).

1. Wüst J. Susceptibility of anaerobic bacteria to metronidazole, ornidazole, and tinidazole and routine susceptibility testing by standardized methods. *Antimicrob Agents Chemother* 1977; **11:** 631–7.
2. Dubreuil L, *et al.* Susceptibility of anaerobic bacteria from several French hospitals to three major antibiotics. *Antimicrob Agents Chemother* 1984; **25:** 764–6.
3. Hill GB, Ayers OM. Antimicrobial susceptibilities of anaerobic bacteria isolated from female genital tract infections. *Antimicrob Agents Chemother* 1985; **27:** 324–31.

4. Chow AW, *et al.* In vitro susceptibility of Clostridium difficile to new β-lactam and quinolone antibiotics. *Antimicrob Agents Chemother* 1985; **28:** 842–4.
5. Brazier JS, *et al.* Antibiotic susceptibility of clinical isolates of clostridia. *J Antimicrob Chemother* 1985; **15:** 181–5.
6. Van der Auwera P, *et al.* Comparative serum bactericidal activity against test anaerobes in volunteers receiving imipenem, clindamycin, latamoxef and metronidazole. *J Antimicrob Chemother* 1987; **19:** 205–10.
7. Ralph ED, Amatnieks YE. Metronidazole in treatment against Haemophilus vaginalis (Corynebacterium vaginale). *Antimicrob Agents Chemother* 1980; **18:** 101–4.
8. Hof H, *et al.* Comparative in vitro activities of niridazole and metronidazole against anaerobic and microaerophilic bacteria. *Antimicrob Agents Chemother* 1982; **22:** 332–3.
9. Freydière AM, *et al.* In vitro susceptibilities of 40 Campylobacter fetus subsp jejuni strains to niridazole and metronidazole. *Antimicrob Agents Chemother* 1984; **25:** 145–6.
10. Marshall BJ, *et al.* Pyloric campylobacter infection and gastroduodenal disease. *Med J Aust* 1985; **142:** 439–44.
11. Howden A, *et al.* In-vitro sensitivity of Campylobacter pyloridis to furazolidone. *Lancet* 1986; **ii:** 1035.
12. Ralph ED, Amatnieks YE. Relative susceptibilities of Gardnerella vaginalis (Haemophilus vaginalis), Neisseria gonorrhoeae, and Bacteroides fragilis to metronidazole and its two major metabolites. *Sex Transm Dis* 1980; **7:** 157–60.
13. Shanker S, Munro R. Sensitivity of Gardnerella vaginalis to metabolites of metronidazole and tinidazole. *Lancet* 1982; **i:** 167.
14. Ingham HR, *et al.* Interactions between micro-organisms and metronidazole. *J Antimicrob Chemother* 1982; **10:** 84–7.
15. Tally FP, *et al.* Susceptibility of the Bacteroides fragilis group in the United States in 1981. *Antimicrob Agents Chemother* 1983; **23:** 536–40.
16. Tally FP, *et al.* Nationwide study of the susceptibility of the Bacteroides fragilis group in the United States. *Antimicrob Agents Chemother* 1985; **28:** 675–7.
17. Ingham HR, *et al.* Bacteroides fragilis resistance to metronidazole after long-term therapy. *Lancet* 1978; **i:** 214.
18. Eme A, *et al.* Bacteroides fragilis resistant to metronidazole. *J Antimicrob Chemother* 1983; **12:** 523–5.
19. Lamothe F, *et al.* Bacteroides fragilis resistant to both metronidazole and imipenem. *J Antimicrob Chemother* 1986; **18:** 642–3.
20. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
21. Hickey MM, *et al.* Metronidazole resistant Bacteroides fragilis infection of a prosthetic hip joint. *J Infect* 1990; **20:** 129–33.
22. Turner P, *et al.* Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; **345:** 1275–7.
23. Sprott MS, *et al.* Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
24. McWalter PW, Baird DR. Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
25. Sprott MS, Kearns AM. Metronidazole-resistant Bacteroides melaninogenicus. *J Antimicrob Chemother* 1988; **22:** 951–2.

Pharmacokinetics

Metronidazole is readily and almost completely absorbed after oral doses. Peak plasma concentrations of about 6 and 12 micrograms/mL are achieved, usually within 1 to 2 hours, after single doses of 250 and 500 mg respectively. Some accumulation occurs and consequently there are higher concentrations when multiple doses are given. Absorption may be delayed, but is not reduced overall by food. Metronidazole benzoate given orally is hydrolysed in the gastrointestinal tract to release metronidazole, which in turn is then absorbed.

Peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been reported in patients given an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours. The bioavailability of metronidazole from rectal suppositories is 60 to 80%; peak plasma concentrations are half those achieved with equivalent oral doses and effective concentrations occur after about 5 to 12 hours. Absorption from vaginal pessaries is poor with a reported bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of about 2 micrograms/mL after a dose of 500 mg. An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma concentrations of 0.3 micrograms/mL at 8 hours, with a bioavailability of 56%.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, cerebral abscesses, CSF, liver and liver abscesses, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins.

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The principal oxidative metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite), which has antibacterial activity and is detected in plasma and urine, and 2-methyl-5-nitroimidazole-1-acetic acid (the acid metabolite), which has virtually no antibacterial activity and is often not detected in plasma, but is excreted in urine. Small amounts of reduced metabolites, acetamide and *N*-(2-hydroxyethyl)oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora.

The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe hepatic impairment; that of the hydroxy metabolite is prolonged in patients with substantial renal impairment.

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

◊ References.

1. Cunningham FE, *et al.* Pharmacokinetics of intravaginal metronidazole gel. *J Clin Pharmacol* 1994; **34:** 1060–5.
2. Lamp KC, *et al.* Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999; **36:** 353–73.

Hepatic impairment. There have been differing results from pharmacokinetic studies of the elimination of metronidazole in patients with hepatic impairment. No marked difference was reported[1] between patients with cirrhosis or hepatosplenic schistosomiasis given a single 500-mg oral dose of metronidazole when compared with healthy subjects; this suggested that, in the absence of renal impairment, dosage adjustment was not needed in patients with hepatic impairment. However, others found[2] that elimination of metronidazole, given intravenously, was considerably impaired in a study of 10 patients with alcoholic liver disease or chronic active hepatitis, 7 of whom also had reduced creatinine clearance. Responding to the comment[3] that these differing results were probably due to impaired renal elimination, the authors suggested[4] that impaired elimination of metronidazole was due to impaired hepatic metabolism rather than decreased renal clearance; other studies have shown metronidazole clearance to be normal in renal impairment. They nevertheless agreed that reduction in the dosage of metronidazole is required only when hepatic function is very poor, particularly when renal function is impaired. A study in 10 severely ill patients with or without impaired hepatic and/or renal function[5] also suggested that hepatic function is a very important determinant of metronidazole elimination.

1. Daneshmend TK, *et al.* Disposition of oral metronidazole in hepatic cirrhosis and in hepatosplenic schistosomiasis. *Gut* 1982; **23:** 807–13.
2. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1983; **287:** 1845.
3. Daneshmend TK, Roberts CJC. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984; **288:** 405.
4. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984, **288:** 1009.
5. Ljungberg B, *et al.* Metronidazole: pharmacokinetic observations in severely ill patients. *J Antimicrob Chemother* 1984; **14:** 275–83.

Infants and children. A single intravenous dose of 15 mg/kg has been suggested for neonates[1] which would produce therapeutic concentrations of metronidazole for around 24 hours in term neonates and 48 hours in preterm neonates. Renal and hepatic function is incompletely developed in newborn infants and consequently the elimination half-life of metronidazole is prolonged and has been reported to range from 25 to 109 hours.[1] Elimination half-life is inversely proportional to gestational age[1,2] and as the infant matures half-life is reduced to values closer to those in adults.[1,3]

1. Jager-Roman E, *et al.* Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982; **100:** 651–4.
2. Hall P, *et al.* Intravenous metronidazole in the newborn. *Arch Dis Child* 1983; **58:** 529–31.
3. Amon I, *et al.* Disposition kinetics of metronidazole in children. *Eur J Clin Pharmacol* 1983; **24:** 113–19.

Renal impairment. Pharmacokinetic studies have indicated that doses of metronidazole need not be altered in patients with renal impairment,[1] although adjustments might be required in patients undergoing haemodialysis, since metronidazole and its hydroxy metabolite are efficiently cleared and extensively removed in such patients.[2] However, in another study[3] the amount of metronidazole and its hydroxy metabolite cleared was found to depend on the type of dialysis membrane used; the authors concluded that dosage supplementation may be needed only for seriously ill patients undergoing haemodialysis with a membrane having high metronidazole clearance.

Routine adjustment of dosage was not considered necessary in patients undergoing peritoneal dialysis.[4] However, the potential for metabolites to accumulate was noted in patients on continuous ambulatory peritoneal dialysis[5] and it was suggested that dosage reduction may be necessary if excessive concentrations of metabolites are found to be toxic.

1. Houghton GW, *et al.* Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol* 1985; **19:** 203–9.
2. Somogyi A, *et al.* Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol* 1983; **25:** 683–7.
3. Lau AH, *et al.* Hemodialysis clearance of metronidazole and its metabolites. *Antimicrob Agents Chemother* 1986; **29:** 235–8.
4. Cassey JG, *et al.* Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother* 1983; **24:** 950–1.
5. Guay DR, *et al.* Pharmacokinetics of metronidazole in patients undergoing continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 1984; **25:** 306–10.

Uses and Administration

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa (see Antimicrobial Action, above); it also has a radiosensitising effect on hypoxic tumour cells. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced.

Metronidazole is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, *Blastocystis hominis* infections, giardiasis, and trichomoniasis; it has also been tried in leishmaniasis and microsporidiosis. For details of these infections and their treatment see under Choice of Antiprotozoal, p.822. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections. Specific bacterial infections treated with metronidazole include bacterial vaginosis, acute necrotising ulcerative gingivitis, pelvic inflammatory disease, tetanus, and antibiotic-associated colitis. For details of these infections and their treatment see under Choice of Antibacterial, p.162.

Metronidazole is used to eradicate *Helicobacter pylori* in peptic ulcer disease (with other antimicrobials, and either bismuth compounds or proton pump inhibitors) and in the management of malodorous tumours and ulcers where there is anaerobic infection. It is also used in the treatment of rosacea and of dracunculiasis (guinea-worm infection) and has been given in the treatment of perianal Crohn's disease and hepatic encephalopathy. It has also been tried as an adjunct to the radiotherapy of malignant neoplasms. See also below for these miscellaneous uses.

ADMINISTRATION AND DOSAGE. Metronidazole is given orally in tablets or, as metronidazole benzoate, in oral suspension; the tablets are taken with or after food and the suspension at least 1 hour before food. Metronidazole is also given rectally in suppositories, applied topically as a cream or gel, or given by intravenous infusion of metronidazole or metronidazole hydrochloride. Doses are expressed in terms of metronidazole base.

In **amoebiasis**, metronidazole acts as an amoebicide at all sites of infection with *Entamoeba histolytica*. Because of its rapid absorption it is probably less effective against parasites in the bowel lumen and is therefore used with a luminal amoebicide such as diloxanide furoate or diiodohydroxyquinoline in the treatment of invasive amoebiasis. Metronidazole is given in oral doses of 400 to 800 mg three times daily for 5 to 10 days. Children aged 1 to 3 years may be given one-quarter, those aged 3 to 7 years one-third, and those aged 7 to 10 years one-half the total adult daily dose; alternatively 35 to 50 mg/kg daily in divided doses has been used. An alternative adult dose is 1.5 to 2.5 g as a single daily dose for 2 or 3 days.

In **balantidiasis** and ***Blastocystis hominis* infection**, metronidazole has been given orally in a dose of 750 mg three times daily for 5 and 10 days, respectively.

In **giardiasis**, the usual oral dose of metronidazole is 2 g once daily for 3 successive days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10 days. Dosage for children is proportional, as for amoebiasis (above). An alternative schedule for children is 15 mg/kg daily in divided doses.

In **trichomoniasis**, metronidazole is given orally either as a single 2-g dose, as a 2-day course of 800 mg in the morning and 1.2 g in the evening, or as a 7-day course of 600 mg to 1 g daily in two or three divided doses. Sexual partners should also be treated. If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended. Vaginal preparations containing metronidazole are available for the treatment of vaginal trichomoniasis in some countries. Children with trichomoniasis may be given a 7-day course of metronidazole by mouth as follows: 1 to 3 years, 50 mg three times daily; 3 to 7 years, 100 mg twice daily, and 7 to 10 years, 100 mg three times daily. An alternative children's dose is 15 mg/kg daily in 3 divided doses for 7 days.

Bacterial vaginosis is treated similarly to vaginal trichomoniasis with which it may co-exist; metronidazole is usually given orally as a single 2-g dose or as a 5 to 7-day course of 400 or 500 mg twice daily. Alternatively it may be applied locally as 5 g of a 0.75% gel once or twice daily for 5 days.

In **acute necrotising ulcerative gingivitis**, metronidazole 200 mg three times daily is given orally for 3 days; similar doses are used in acute dental infections. A 25% dental gel has also been used as an adjunct to the treatment of chronic periodontal infections.

For the treatment of most **anaerobic bacterial infections**, metronidazole is given orally in an initial dose of 800 mg followed by 400 mg every 8 hours, usually for about 7 days. A regimen of 500 mg every 8 hours is alternatively used. When oral therapy is precluded metronidazole may be given intravenously, 500 mg being infused as 100 mL of a 5 mg/mL solution at a rate of 5 mL/minute every 8 hours, or rectally as a 1-g suppository every 8 hours for 3 days, then every 12 hours; oral therapy should be substituted as soon as possible. Suppositories may be unsuitable for beginning therapy in serious infections because of the slower absorption of metronidazole. Children may be given 7.5 mg/kg every 8 hours by mouth or by intravenous infusion; recommended rectal doses for children, to be given every 8 hours for 3 days, then every 12 hours thereafter, are: for those aged under 1 year, 125 mg; 1 to 5 years, 250 mg; 5 to 10 years, 500 mg. In the USA recommended adult doses of metronidazole are 7.5 mg/kg every 6 hours by mouth or 15 mg/kg by intravenous infusion followed by 7.5 mg/kg every 6 hours, doses being infused over 1 hour; by either route a total dose of 4 g in 24 hours should not be exceeded. In mixed anaerobic and aerobic infections metronidazole is given with the appropriate antibacterials.

For the **prevention of postoperative anaerobic bacterial infections**, especially in patients undergoing abdominal or gynaecological surgery, metronidazole is given orally, intravenously, or rectally in doses similar to those used for treatment, usually with a beta-lactam or an aminoglycoside antibacterial. Various schedules have been employed. In the UK, licensed doses for adults are:

- orally 400 mg every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal dosage until oral therapy is possible
- by intravenous infusion, 500 mg shortly before operation and repeated every 8 hours, oral doses of 200 or 400 mg every 8 hours being substituted as soon as possible
- by rectum, 1 g every 8 hours starting 2 hours before surgery.

The *BNF*, however, recommends that oral doses should be started only 2 hours before the operation and that the number of doses for all dose routes be limited to a total of four. In the USA the recommended schedule for adults undergoing colorectal surgery is metronidazole 15 mg/kg by intravenous infusion over 30 to 60 minutes, completed about 1 hour before surgery, followed by two further intravenous doses of 7.5 mg/kg infused at 6 and 12 hours after the initial dose.

In **peptic ulcer disease**, metronidazole is used in combination therapy to eradicate *Helicobacter pylori*. Typical regimens include metronidazole plus another antibacterial (clarithromycin or amoxicillin) given with either a proton pump inhibitor (omeprazole or lansoprazole) or with ranitidine bismuth citrate. The usual dose of metronidazole is 400 mg twice daily except when given with omeprazole and amoxicillin, when metronidazole 400 mg three times daily is used. Treatment is continued for 1 week.

For **leg ulcers** and **pressure sores** infected with anaerobic bacteria, oral metronidazole 400 mg may be given three times daily for 7 days. Metronidazole is also applied topically as a 0.75% or 0.8% gel to reduce the odour associated with anaerobic infection in **fungating tumours**.

In the treatment of **rosacea** metronidazole is given orally or applied topically.

Administration in hepatic impairment. Since metronidazole is mainly metabolised by hepatic oxidation, accumulation of metronidazole and its metabolites is likely in patients with severely impaired hepatic function. Metronidazole should therefore be given with caution and at reduced doses to patients with severe hepatic impairment, and especially hepatic encephalopathy when adverse affects of metronidazole can add to the symptoms of the disease. One-third of the usual daily dose may be given once daily in these patients. For patients with lesser degrees of hepatic impairment, pharmacokinetic studies have not produced consistent results (see under Pharmacokinetics, above) and no recommendations about dosage reduction have been made by licensed product information.

Administration in renal impairment. The elimination of metronidazole is largely unchanged in patients with renal impairment, although metabolites may accumulate in patients with end-stage renal disease on dialysis (see under Pharmacokinetics, above). Dosage reductions are therefore not usually recommended for patients with renal impairment although, since both metronidazole and its metabolites are removed by haemodialysis, doses need to be given immediately after haemodialysis.

Dracunculiasis. Metronidazole may be beneficial in the management of dracunculiasis (p.136). It provides symptomatic relief and is also thought to weaken the anchorage of the worms within subcutaneous tissue, thus allowing them to be removed more quickly.

Metronidazole has been given in a variety of regimens, including doses of 400 mg three times daily for 5 days,[1] 40 mg/kg daily in three divided doses (to a maximum daily dose of 2.4 g) for 3 days,[2] and 400 mg daily for 10 to 20 days.[3] WHO recommends 25 mg/kg daily for 10 days;[4] a dose of 250 mg three times daily for 10 days has also been recommended.

1. Padonu KO. A controlled trial of metronidazole in the treatment of dracontiasis in Nigeria. *Am J Trop Med Hyg* 1973; **22:** 42–4.
2. Kale OO. A controlled field trial of the treatment of dracontiasis with metronidazole and niridazole. *Ann Trop Med Parasitol* 1974; **68:** 91–5.
3. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57:** 683–9.
4. WHO. *WHO model formulary.* Geneva: WHO, 2004.

Hepatic encephalopathy. The treatment of hepatic encephalopathy is discussed on p.1697. It includes the use of an antimicrobial such as metronidazole to reduce the intestinal flora.

Inflammatory bowel disease. Metronidazole is used in the treatment of perineal Crohn's disease (see Inflammatory Bowel Disease, p.1697) and may also be used in colonic Crohn's disease, when it has been tried with ciprofloxacin. It has also proved effective for the prevention of postsurgical recurrence. Duration of therapy is usually limited to 3 months.

References.

1. Bernstein LH, *et al.* Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79:** 357–65.
2. Brandt LJ, *et al.* Metronidazole therapy for perineal Crohn's disease: a follow-up study. *Gastroenterology* 1982; **83:** 383–7.
3. Ursing B, *et al.* A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. *Gastroenterology* 1982; **83:** 550–62.
4. Sutherland L, *et al.* Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; **32:** 1071–5.
5. Rutgeerts P, *et al.* Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108:** 1617–21.
6. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91:** 328–32.

Metabolic disorders. Children with excesses of methylmalonic[1,2] and propionic[3] acid in their blood or urine have shown clinical improvement when given metronidazole, which reduced the excretion of faecal propionate and urinary methylmalonate. Metronidazole is considered to act through its antimicrobial effect on gut anaerobes that are involved in propionate production; such propionate cannot be handled by these children who are deficient in the relevant enzyme.

1. Bain MD, *et al.* Contribution of gut bacterial metabolism to human metabolic disease. *Lancet* 1988; **i:** 1078–9.
2. Koletzko B, *et al.* Antibiotic therapy for improvement of metabolic control in methylmalonic aciduria. *J Pediatr* 1990; **117:** 99–101.
3. Mellon AF, *et al.* Effect of oral antibiotics on intestinal production of propionic acid. *Arch Dis Child* 2000; **82:** 169–72.

Mouth disorders and infections. Ciclosporin-induced gingival hyperplasia resolved in 4 patients after treatment with metronidazole.[1]

Metronidazole is considered to be effective for the treatment of acute necrotising ulcerative gingivitis and is an alternative to penicillin in other dental infections (see Mouth Infections, p.180).

1. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.

Peptic ulcer disease. The use of metronidazole is well established in regimens for eradicating *Helicobacter pylori* (see Peptic Ulcer Disease, p.1702). However, the emergence of metronidazole-resistant strains of *H. pylori* has been associated with an increased rate of treatment failures with some regimens.[1-4] Difficulties arise in assessing metronidazole resistance and in correlating *in-vitro* results with clinical response.[5] In populations in which the incidence of resistance is high, it may become necessary to use alternative regimens,[6] but in other areas, such as the UK, regimens including metronidazole continue to be among the standard alternatives (although the *BNF* recommends that they should not be used for initial treatment in patients who have been given metronidazole for other infections).

1. Buckley MJM, *et al.* Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci* 1997; **42:** 2111–15.
2. Lerang F, *et al.* Highly effective twice-daily triple therapies for Helicobacter pylori infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? *Am J Gastroenterol* 1997; **92:** 248–53.
3. Misiewicz JJ, *et al.* One week triple therapy for Helicobacter pylori: a multicentre comparative study. *Gut* 1997; **41:** 735–9.
4. van Zanten SV, *et al.* Adding once-daily omeprazole 20 mg to metronidazole/amoxicillin treatment for Helicobacter pylori gastritis: a randomized, double-blind trial showing the importance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 5–10.
5. Goddard AF, Logan RPH. Antimicrobial resistance and Helicobacter pylori. *J Antimicrob Chemother* 1996; **37:** 639–43.
6. Fennerty MB. Should we abandon metronidazole containing Helicobacter pylori treatment regimens? The clinical relevance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 2–3.

Skin disorders. Metronidazole may be effective in the management of malodorous anaerobic skin infections associated with ulceration (p.194), including *pressure sores* and *fungating tumours*. Both the oral and topical routes have been employed but the evidence in favour of its use is largely anecdotal as few randomised controlled studies have yet been performed.[1,2]

Metronidazole has also been used[3] in the treatment of *rosacea* (p.1583). Metronidazole 200 mg twice daily by mouth was more effective than placebo[4] and as effective as oral oxytetracycline.[5] Similarly, topical preparations (for example, 0.75% cream, gel, or lotion or 1% cream) have been found to be better than placebo and as effective as oral oxytetracycline.[6,7]

1. Clark J. Metronidazole gel in managing malodorous fungating wounds. *Br J Nurs* 2002 **11** (suppl): S54–S60.
2. Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage* 2008; **54:** 18–27.
3. Conde JF, *et al.* Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. *J Drugs Dermatol* 2007; **6:** 495–8.
4. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **i:** 1211–12.
5. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102:** 443–5.
6. McClellan KJ, Noble S. Topical metronidazole: a review of its use in rosacea. *Am J Clin Dermatol* 2000; **1:** 191–9.
7. Dahl MV, *et al.* Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol* 2001; **45:** 723–30.

Surgical infection. Metronidazole and related nitroimidazoles are used in surgical infection prophylaxis (p.195) to reduce the rate of wound infection.

HAEMORRHOIDECTOMY. Prophylactic metronidazole reduced pain following haemorrhoidectomy in a small study.[1]

1. Carapeti EA, *et al.* Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. *Lancet* 1998; **351:** 169–72.

African trypanosomiasis. Although there is no established alternative treatment for *Trypanosoma brucei rhodesiense* infections that are resistant to melarsoprol (see p.827), metronidazole and suramin were effective in 1 patient.[1]

1. Foulkes JR. Metronidazole and suramin combination in the treatment of arsenical refractory rhodesian sleeping sickness—a case study. *Trans R Soc Trop Med Hyg* 1996; **90:** 422.

Preparations

BP 2008: Metronidazole Gel; Metronidazole Intravenous Infusion; Metronidazole Oral Suspension; Metronidazole Suppositories; Metronidazole Tablets;
USP 31: Metronidazole Gel; Metronidazole Injection; Metronidazole Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bexon; Colpofilin; Dazotron; Epaq†; Etronil; Flagyl; Format; Ginkan; Gynotran; Metral; Metrocev; Metrolocal; Nalox; Noritate†; Padet; Repligen; Rozex; Taremis; Tolbin; Tricofin; Trimstat†; ***Austral.:*** Flagyl; Metrogyl; Metronide; Rozex; ***Austria:*** Acsacea; Anaerobex; Elyzol; Rozex; Trichex; ***Belg.:*** Anaeromet†; Flagyl; Pharmaflex†; Rosaced; Rozex; ***Braz.:*** Ambrosil†; Amebil†; Astergyl†; Canderm; Dalzolston; Flagyl; Flanizol; Helmizol; Metrizol†; Metrodax†; Metrogyl†; Metronib†; Metronide; Metroniflex; Metronil; Metronin; Metronix; Metrotix†; Metroval; Metrozol; Minegyl†; Neo Metrodazol; Odonid; Rozex; ***Canad.:*** Flagyl; Florazole; Metrocream; Metrogel; Metrolotion; NidaGel; Noritate; Novo-Nidazol†; Trikacide; ***Chile:*** Deprocid; Flagyl; Geloderm; Kabizol; Medazol; Metrocream; Metrogel; Metropast; Noritate†; ***Cz.:*** Deflamon†; Efloran; Entizol; Klion†; Medazol†; Rosalox; Rozex; ***Denm.:*** Elyzol; Flagyl; Metrogel†; Rozex; Zidoval; ***Fin.:*** Elyzol; Flagyl; Rosazol; Rozex; Trikozol; Zidoval; ***Fr.:*** Elyzol; Flagyl; Rosiced; Rozacreme; Rozagel; Rozex; ***Ger.:*** Arilin; Clont; Elyzol; Flagyl; Fossyol†; Infectoclont; Metrocreme; Metrogel; Metronid-Puren†; Metronimerck; Metronour; Metront†; Rosiced; Vagimid; ***Gr.:*** Colpocin-T; Elyzol Dental; Emedal; Flagolin; Flagyl; Gnostol; Metrazol; Metrogyl; Periotret; Robaz; Rosiced; Trichovagil; Tricodazole; Unitrim; ***Hong Kong:*** Elyzol; Flagyl; Gynoplix; Marphazole; Metole; Metrogyl; Noritate; Qualigyl; Rozex; Unigo; ***Hung.:*** Klion; Rozex; Supplin; ***India:*** Aristogyl; Flagyl; Giardyl†; Metrogyl; Monizole; Unimezol†; ***Indon.:*** Anmerob; Biatron; Corsagyl; Dumozol; Farnat; Fladex; Flagyl; Flametia; Fortagyl; Metrofusin; Molazol; Nidazole; Promuba; Supplin; Tismazol; Trichodazol; Trogiar; Trogyl; Vagizol; ***Irl.:*** Anabact†; Flagyl; Metronide; Metrotop; Rozex; ***Israel:*** Elyzol; Flagyl; Metrogyl; Noritate; Rozex; Venogyl; Zidoval; ***Ital.:*** Deflamon; Elyzol; Flagyl; Rosased†; Rozex; Vagilen; Zidoval; ***Malaysia:*** Flagyl; Frotin; Protogyl†; Ranigyl†; Rozex; Setrozole†; ***Mex.:*** Ameblin; Antral†; Biomona; Biotazol; Dasmetrol; Dualizol; Elyzol; Epaq; Fagizol; Fartricon; Flagenase; Flagenol; Flagepat; Flagyl; Flamin†; Flaxtec; Fresenizol; Hemestal; Laglan; Lamblit; Lozad; Medazol; Medizol; Messeldazol; Metosan†; Metricom; Metrizol; Metrobendizol; Metrocream; Metrogel; Metroson; Milezzol; Nidralon-V; Nidrozol; Nitromidager; Ortrizol; Otrozol; Ovazol-V; Planizol; Promibasol; Prozolin; Retofar†; Samonil; Selegil†; Servizol; Solumidazol; Stomffler; Valpar; Vanestrin-V; Vertisal; ***Neth.:*** Flagyl; Metrogel; Rosiced; Rozex; ***Norw.:*** Elyzol; Flagyl; Rozex; Zidoval; ***NZ:*** Flagyl; Rozex; Trichozole; ***Philipp.:*** Ameryl; Anerobia; Flagyl; Metrinox; Metrodal; Norstene; Patryl; Robaz; Rodazid; Servizol; Tricomycin; Triconex; Tridel; Vamogyl; Zol; ***Pol.:*** Metrosept; Rozex; ***Port.:*** Dumozol; Flagyl; Metroderme; Norstene; Rodermil; Roseless; Rosiced; ***Rus.:*** Efloran (Эфлоран); Flagyl (Флагил); Klion (Клион); Metrogyl (Метрогил); Metroseptol (Метросептол); Rosamet (Розамет); Trichopol (Трихопол); ***S.Afr.:*** Bemetrazole; Flagyl; Medamet; Metagyl†; Metazol; Metrazole; Metrostat; Narobic; Rozex; Trichazole; Zagyl; Zobacide; ***Singapore:*** Fladex; Flagyl; Medazole; Metrozole†; MND†; Nizole; Rozex; ***Spain:*** Amotein; Flagyl; Rozex; Tricowas B; Zidoval; ***Swed.:*** Elyzol†; Flagyl; Rozex; Zidoval; ***Switz.:*** Arilin; Elyzol; Flagyl; Metrolag; Perilox; Rivozol†; Rosalox; Rozex; ***Thai.:*** Asiazole; Biogyl; Elyzol†; Flagyl; Med-Tricocide†; Medazyl†; Mefiron; Menisole; Mepagyl†; Mesolex†; Metrazole; Metrocide; Metrogyl; Metrolex; Metrovid; Milanidazole; Robaz; Tricomed; Unigo; Vagil†; Vagyl; ***Turk.:*** Flagyl; Metrajil; Metrazol; Metrosel; Nidazol; Roza; ***UAE:*** Negazole; ***UK:*** Acea; Anabact; Elyzol; Flagyl; Metrogel; Metrolyl; Metrosa; Metrotop; Metrozol; Noritate; Norzol; Rozex; Vaginyl; Zidoval; Zyomet; ***USA:*** Flagyl; Metrocream; Metrogel; Metrogel Vaginal; Noritate; Protostat; Vandazole; ***Venez.:*** Bactrizol; Flegyl; Menizol; Metren; Metris; Metrogyl; Metrovax; Rozek.

Multi-ingredient: ***Arg.:*** Bexon; Ciprocort; Estilomicin; Farm-X Duo; Farm-X Ginecologico; Flagystatin; Ginal Cent; Ginkan; Linfol; Linfol Cicatrizante; Mailen; Monizol Cort; Naxo TV; Neocolpoben†; Ovumix; Pelvicillin NF; Pentol; Septigyn; Tratomax; Vagicural Plus; ***Austral.:*** Somac-MA; ***Austria:*** Helicocin; ***Braz.:*** Bio-Vagin; Colpatrin; Colpist; Colpistar; Colpistatin; Donnagel; Flagyl Nistatina; Fungimax; Ginestatin; Minegyl C/Nistatina†; Nistazol†; Periodontil; Profargil†; Tricolpex; Tricomax; Vagi Biotic; Vagimax; ***Canad.:*** Flagystatin; Losec 1-2-3 M; Rosasol; ***Cz.:*** Klion-D; Rodogyl†; ***Fin.:*** Flagyl Comp; Helipak A; Helipak T; Losec Helira†; ***Fr.:*** Birodogyl; Missilor; Rodogyl; Tergynan; ***Hung.:*** Klion-D; ***India:*** Aristogyl Plus; Aristogyl-F; Bacigyl-N†; Dyrade-M; Dysfur-M†; Entamizole; Flagyl-F†; Kaltin MF; Metrogyl-F†; Neocip M; NM Powder; Okaflox M; Powergyl; Qugyl; ***Indon.:*** Fladystin; Flagystatin; Trichostatic; Vagistin; ***Ital.:*** Meclon; ***Malaysia:*** Neo-Penotran; Rodogyl; ***Mex.:*** Acenil; Amebyl; Diodolina; Eskapar Compuesto; Flagenase 400; Flagocil; Flagystatin V; Gynotran; Lambliquin; Madecassol C; Metodine; Metrodiyod; Metrofur; Metroviform†; Norecil; Nysmosons-V; Promibasol-Plus; Rodogyl; Stomffler Plus; Vagitrol-V; ***Philipp.:*** Flagystatin; Neo-Penotran; ***Pol.:*** Gynalgin; ***Rus.:*** Gynalgin (Гиналгин); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Metrogyl Plus (Метрогил Плюс); Neo-Penotran (Нео-Пенотран); ***Singapore:*** Flagystatin; Neo-Penotran; ***Spain:*** Blastoestimulina; Rhodogil; ***Turk.:*** Neo-Penotran; Nidazol-M; ***UK:*** HeliMet†; ***USA:*** Helidac; Pylera.

Monensin *(BAN, USAN, rINN)*

Lilly-67314; Monensina; Monensinum. 4-{2-[2-Ethyl-3′-methyl-5′-(tetrahydro-6-hydroxy-6-hydroxymethyl-3,5-dimethylpyran-2-yl)perhydro-2,2′-bifuran-5-yl]-9-hydroxy-2,8-dimethyl-1,6-dioxaspiro[4.5]dec-7-yl}3-methoxy-2-methylpentanoic acid.

Монензин

$C_{36}H_{62}O_{11}$ = 670.9.
CAS — 17090-79-8.
ATC Vet — QP51AH03.

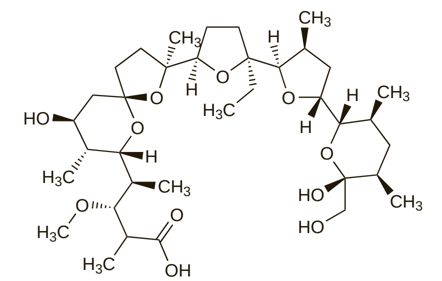

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Monensin). A mixture of antibiotic substances produced by *Streptomyces cinnamonensis*.

Monensin Sodium *(BANM, rINNM)*

Monensin Sodique; Monensina sódica; Natrii Monensinum.

Натрий Монензин

$C_{36}H_{61}NaO_{11}$ = 692.9.
CAS — 22373-78-0.

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Monensin Sodium). An off-white to tan crystalline powder. Slightly soluble in water; soluble in chloroform and in methyl alcohol; practically insoluble in petroleum spirit. Avoid moisture and excessive heat.

Profile

Monensin is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor for cattle.

Narasin *(BAN, USAN, rINN)*

Compound 79891; Lilly-79891; Narasina; Narasine; Narasinum. 2-(6-{5-[2-(5-Ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl}tetrahydro-3,5-dimethylpyran-2-yl)butyric acid.

Наразин

$C_{43}H_{72}O_{11}$ = 765.0.
CAS — 55134-13-9.
ATC Vet — QP51AH04.

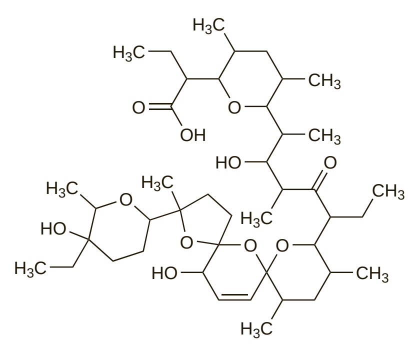

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Narasin Granular). It contains narasin mixed with suitable carriers and inactive ingredients prepared in a granular form that is free-flowing and free of aggregates. Narasin is a white to off-white crystalline powder. Soluble in water and in methyl alcohol.

Profile

Narasin, an antibiotic produced by *Streptomyces aureofaciens*, is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in chickens.

Nicarbazin *(BAN)*

Nicarbazina. An equimolecular complex of 1,3-bis(4-nitrophenyl)urea ($C_{13}H_{10}N_4O_5$) and 4,6-dimethylpyrimidin-2-ol ($C_6H_8N_2O$).

Никарбазин

$C_{19}H_{18}N_6O_6$ = 426.4.
CAS — 330-95-0.
ATC Vet — QP51AE03.

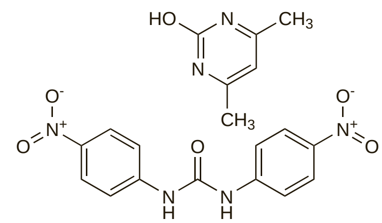

Profile

Nicarbazin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Nifuratel *(BAN, USAN, rINN)*

Methylmercadone; Nifurateeli; Nifuratelum. 5-Methylthiomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidone.

Нифурател

$C_{10}H_{11}N_3O_5S$ = 285.3.
CAS — 4936-47-4.
ATC — G01AX05.
ATC Vet — QG01AX05.

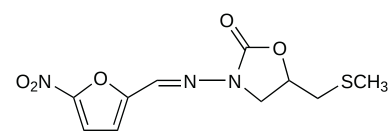

Adverse Effects

Adverse effects associated with nifuratel include gastrointestinal disturbances, peripheral neuropathy, and thrombocytopenic purpura. Allergic reactions, hepatotoxicity, blood dyscrasias, and pulmonary reactions similar to those seen with the structurally related drug nitrofurantoin have been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given nifuratel.

Hypersensitivity. There have been several reports of contact dermatitis associated with nifuratel, including a report after only one application of nifuratel ointment in a man whose wife was undergoing treatment with nifuratel vaginal pessaries.[1]

1. Bedello PG, *et al.* Contact dermatitis from nifuratel. *Contact Dermatitis* 1983; **9:** 166.

Precautions

Nifuratel should not be given to patients with renal impairment, neuropathies, or G6PD deficiency.

Interactions

A disulfiram-like reaction may occur in patients taking alcohol while on nifuratel therapy.

Pharmacokinetics

When taken orally nifuratel is absorbed from the gastrointestinal tract. A metabolite, with activity against bacteria but not against trichomonads, is excreted in the urine.

Uses and Administration

Nifuratel is a nitrofuran derivative with a broad antimicrobial spectrum. It is active against the protozoan *Trichomonas vaginalis* and has an antibacterial spectrum similar to that of nitrofurantoin and some antifungal activity against *Candida albicans*. Although other drugs are preferred, nifuratel has been used to treat susceptible infections of the genito-urinary tract in oral doses of 200 to 400 mg three times daily. It has also been given vaginally.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Macmiror; ***Cz.:*** Macmiror; ***Ger.:*** Inimur; ***Hong Kong:*** Macmiror; ***Ital.:*** Macmiror; ***Mex.:*** Macmiror; ***Pol.:*** Macmiror; ***Rus.:*** Macmiror (Макмирор).

Multi-ingredient: ***Cz.:*** Macmiror Complex; ***Hong Kong:*** Macmiror Complex; ***Ital.:*** Macmiror Complex; ***Mex.:*** Macmiror Complex V; ***Pol.:*** Macmiror Complex; ***Port.:*** Dafnegil; ***Rus.:*** Macmiror Complex (Макмирор Комплекс).

Nifursol *(BAN, USAN, pINN)*

Nifursolum. 3,5-Dinitro-2′-(5-nitrofurfurylidene)salicylohydrazide.

Нифурсол

$C_{12}H_7N_5O_9$ = 365.2.

CAS — 16915-70-1.

ATC Vet — QP51AX05.

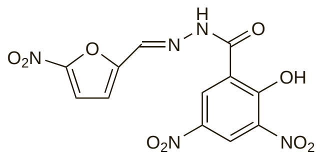

Profile

Nifursol is an antiprotozoal used in veterinary practice for the prevention of blackhead (histomoniasis) in poultry.

Nifurtimox *(BAN, rINN)*

Bayer-2502; Nifurtimoxum. Tetrahydro-3-methyl-4-(5-nitrofurfurylideneamino)-1,4-thiazine 1,1-dioxide.

Нифуртимокс

$C_{10}H_{13}N_3O_5S$ = 287.3.

CAS — 23256-30-6.

ATC — P01CC01.

ATC Vet — QP51AC01.

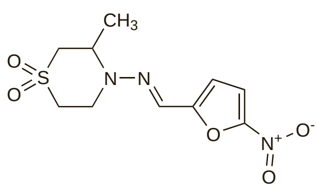

Pharmacopoeias. In *Fr.* and *Int.*

Adverse Effects

Adverse effects are common with nifurtimox and include gastrointestinal effects such as anorexia with loss of weight, abdominal pain, nausea and vomiting, and effects on the nervous system, especially peripheral neuropathy. Psychoses, CNS excitement, insomnia, drowsiness, headache, myalgia, arthralgia, dizziness, and convulsions have also been reported. Skin rashes and other allergic reactions may occur.

Mutagenicity. An increase in chromosomal aberrations has been seen in children given nifurtimox.[1]

1. Gorla NB, *et al.* Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res* 1989; **224:** 263–7.

Pharmacokinetics

Nifurtimox is well absorbed and rapidly metabolised after oral doses.

◊ References.

1. Paulas C, *et al.* Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 454–7.
2. Gonzalez-Martin G, *et al.* The pharmacokinetics of nifurtimox in chronic renal failure. *Eur J Clin Pharmacol* 1992; **42:** 671–3.

Uses and Administration

Nifurtimox is a nitrofuran derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease) due to infection by *Trypanosoma cruzi*, especially the early acute stage of the disease. In African trypanosomiasis it has some activity against *T. brucei gambiense*, the organism responsible for West African sleeping sickness.

Nifurtimox is given orally in 3 to 4 divided doses. It is better tolerated by children than by adults. Treatment for American trypanosomiasis is given for 60 to 120 days (but see below). Doses for adults are 8 to 10 mg/kg daily. Doses for children are: aged 1 to 10 years, 15 to 20 mg/kg daily for 90 days; aged 11 to 16 years, 12.5 to 15 mg/kg daily for 90 days.

Leishmaniasis. Mucocutaneous leishmaniasis of the New World (p.824) is usually treated with pentavalent antimony or, in those who do not respond, with amphotericin B or pentamidine. However, nifurtimox 10 mg/kg daily for a minimum of 4 weeks has been shown to be effective in cases of mucocutaneous leishmaniasis in Colombia and Brazil. Despite this, toxic effects with nifurtimox are common and its role as a second-line drug or with pentavalent antimony has not been established.[1]

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793*, 1990.

African trypanosomiasis. Nifurtimox has been tried as an alternative to melarsoprol or eflornithine in the meningoencephalitic stage of *Trypanosoma brucei gambiense* infection (p.827), but higher doses than those used in American trypanosomiasis are necessary. A good initial response was achieved[1] in 25 patients with nifurtimox 15 mg/kg daily for 60 days, but 3 patients relapsed while still receiving nifurtimox and a further 12 of 19 patients who were followed up relapsed subsequently. An attempt[2] to improve the response by increasing the daily dose even higher to 30 mg/kg for 30 days resulted in substantial toxicity and only a modest improvement in results, with 9 of 25 patients relapsing. However, promising results have been reported[3] from use of oral nifurtimox 15 mg/kg daily for 10 days with eflornithine 400 mg/kg daily intravenously for 7 days.

1. Pepin J, *et al.* An open clinical trial of nifurtimox for arseno-resistant Trypanosoma brucei gambiense sleeping sickness in central Zaire. *Trans R Soc Trop Med Hyg* 1989; **83:** 514–17.
2. Pépin J, *et al.* High-dose nifurtimox for arseno-resistant Trypanosoma brucei gambiense sleeping sickness: an open trial in central Zaire. *Trans R Soc Trop Med Hyg* 1992; **86:** 254–6.
3. Priotto G, *et al.* Nifurtimox-eflornithine combination therapy for second-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Congo. *Clin Infect Dis* 2007; **45:** 1435–42.

American trypanosomiasis. The treatment of American trypanosomiasis (p.827) is generally unsatisfactory, but nifurtimox is of value especially in the acute phase. However, there has been controversy over its ability to cure completely, that is to eradicate all parasites, in chronic disease.[1] Doses recommended by WHO[2,3] are 8 to 10 mg/kg daily in three divided doses for adults, and 15 to 20 mg/kg daily in four divided doses for children. WHO recommends that nifurtimox should be given for 60 or 90 days.[2,3] Some in the USA[4] suggest a 90- to 120-day regimen for adults but nifurtimox is not well tolerated and the experience of other workers[1] suggests that few patients may complete the full course.

1. Gutteridge WE. Existing chemotherapy and its limitations. *Br Med Bull* 1985; **41:** 162–8.
2. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
3. WHO. *WHO model formulary.* Geneva: WHO, 2004.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter, 2007.

Nimorazole *(BAN, rINN)*

Nimorazol; Nimorazolum; Nitrimidazine. 4-[2-(5-Nitroimidazol-1-yl)ethyl]morpholine.

Ниморазол

$C_9H_{14}N_4O_3$ = 226.2.

CAS — 6506-37-2.

ATC — P01AB06.

ATC Vet — QP51AA06.

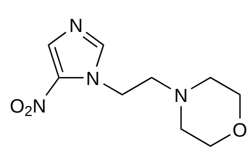

Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for Metronidazole, p.837.

Pharmacokinetics

Nimorazole is readily absorbed from the gastrointestinal tract. Peak blood concentrations are achieved within 2 hours, and high concentrations are reported to occur in salivary and vaginal secretions. Trichomonicidal urinary concentrations may persist for up to 48 hours after a dose. It is excreted in the urine together with 2 active metabolites. Unchanged drug and metabolites also appear in breast milk.

Uses and Administration

Nimorazole is a 5-nitroimidazole derivative. It has antimicrobial actions and uses similar to those of metronidazole (p.839).

In the treatment of trichomoniasis, the usual dose of nimorazole is 2 g orally as a single dose with a main meal. It may alternatively be given in a dose of 1 g every 12 hours for three doses, or 250 mg three times daily for 5 to 7 days. In amoebiasis, nimorazole 1 g is given twice daily, usually for 5 to 10 days and in giardiasis a dose of 500 mg is given twice daily, usually for 5 to 7 days.

Nimorazole may also be used in the treatment of acute ulcerative gingivitis in a dose of 500 mg twice daily for 2 days.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Naxogin; Vagarne†; ***Austria:*** Naxogin; ***Belg.:*** Naxogin; ***Braz.:*** Naxogin; ***Chile:*** Naxogin†; ***Ger.:*** Esclama†; ***Rus.:*** Naxogin (Наксоджин).

Multi-ingredient: ***Arg.:*** Vagarne†; ***Braz.:*** Naxogin Composto; ***Chile:*** Naxogin Compositum; Naxogin Dos†; ***Indon.:*** Gynoxa; Naxogin Complex.

Nitazoxanide *(BAN, USAN, rINN)*

Nitazoxanida; Nitazoxanidum; PH-5776. *N*-(5-Nitro-2-thiazolyl)salicylamide acetate.

Нитазоксанид

$C_{12}H_9N_3O_5S$ = 307.3.

CAS — 55981-09-4.

ATC — P01AX11.

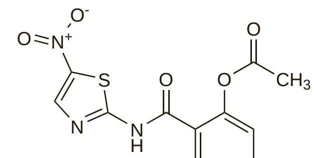

Adverse Effects

The most common adverse effects associated with nitazoxanide are abdominal pain and diarrhoea. Nausea and vomiting, flatulence, and increased appetite have also been reported. Headache may occur. Other reported adverse effects include fever, malaise, pruritus, sweating, dizziness, and rhinitis. Discoloration of urine and of the eyes has been reported rarely. Increased creatinine and liver enzyme values have been noted.

Pharmacokinetics

Nitazoxanide is absorbed from the gastrointestinal tract after oral dosage and is rapidly hydrolysed to an active desacetyl metabolite, tizoxanide. Tizoxanide then partially undergoes conjugation, primarily by glucuronidation. The extent of absorption is enhanced if given with food and peak plasma concentrations of tizoxanide and the glucuronide are seen 1 to 4 hours after an oral dose. The parent drug is not detected in plasma. Tizoxanide is more than 99% bound to plasma proteins. About two-thirds of an oral dose of nitazoxanide is eliminated in the faeces and one-third in the urine; tizoxanide is excreted in the urine, bile, and faeces, while the glucuronide is excreted in only the urine and bile.

Uses and Administration

Nitazoxanide is used for the treatment of cryptosporidiosis and giardiasis in immunocompetent patients. It is given orally and should be taken with food. Doses are 100 mg twice daily for 3 days in those aged 1 to 3 years, 200 mg twice daily for 3 days in those aged 4 to 11 years, and 500 mg twice daily for 3 days in adults. Nitazoxanide has also been tried in a number of other protozoal and helminth infections, particularly in immunocompromised patients, including those with HIV infection. It is also being investigated for the treatment of rotavirus disease and *Clostridium difficile* colitis.

◊ Reviews.

1. Bailey JM, Erramouspe J. Nitazoxanide treatment for giardiasis and cryptosporidiosis in children. *Ann Pharmacother* 2004; **38:** 634–40.
2. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis* 2005; **40:** 1173–80.
3. Musher DM, *et al.* Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006; **43:** 421–7.
4. Anderson VR, Curran MP. Nitazoxanide: a review of its use in the treatment of gastrointestinal infections. *Drugs* 2007; **67:** 1947–67.

Protozoal infections. As well as its established use in cryptosporidiosis (p.823) and giardiasis (p.824), nitazoxanide has been used in other protozoal infections including intestinal amoebiasis (p.822), blastocytosis (p.823), and microsporidiosis (p.826).

Rotavirus diarrhoea. A randomised double-blind placebo-controlled study[1] in 38 young children (median age 11 months) with confirmed rotavirus diarrhoea found that oral nitazoxanide 7.5 mg/kg twice daily for 3 days significantly reduced the duration of rotavirus disease. The median time to resolution of illness after the first dose was 31 hours for those given nitazoxanide compared with 75 hours for those in the placebo group.

1. Rossignol J-F, *et al.* Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet* 2006; **368:** 124–9.

Worm infections. Nitazoxanide has been used in various helminthiases, including ascariasis (p.134), hymenolepiasis (p.136), the liver fluke infection fascioliasis (p.137), and trichuriasis (p.139).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Heliton†; Nixoran; ***Braz.:*** Annita; ***Mex.:*** Bionit; Daxon; Kidonax; Mitafar; NTZ†; Padovan Ton; Paramix; Rosanil; ***USA:*** Alinia; ***Venez.:*** Celectan.

Multi-ingredient: ***Mex.:*** Heliton.

Ornidazole *(USAN, rINN)*

Ornidatsoli; Ornidazol; Ornidazolum; Ro-7-0207. 1-Chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol.

Орнидазол

$C_7H_{10}ClN_3O_3$ = 219.6.

CAS — 16773-42-5.

ATC — G01AF06; J01XD03; P01AB03.

ATC Vet — QG01AF06; QJ01XD03; QP51AA03.

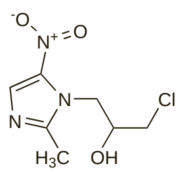

Adverse Effects and Precautions

As for Metronidazole, p.837.

Pharmacokinetics

Ornidazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 3 hours. After repeated oral doses of 500 mg every 12 hours, steady-state peak and trough concentrations are 14 and 6 micrograms/mL respectively.

The plasma elimination half-life of ornidazole is 12 to 14 hours. Less than 15% is bound to plasma proteins. It is widely distributed in body tissues and fluids, including the CSF.

Ornidazole is metabolised in the liver and is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the faeces. Biliary excretion may be important in the elimination of ornidazole and its metabolites.

◊ References.

1. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy* 1976; **22:** 19–29.
2. Matheson I, *et al.* Plasma levels after a single oral dose of 1.5 g ornidazole. *Br J Vener Dis* 1977; **53:** 236–9.
3. Schwartz DE, *et al.* Metabolic studies of ornidazole in the rat, in the dog and in man. *Xenobiotica* 1979; **9:** 571–81.
4. Turcant A, *et al.* Pharmacokinetics of ornidazole in neonates and infants after a single intravenous infusion. *Eur J Clin Pharmacol* 1987; **32:** 111–13.
5. Martin C, *et al.* Pharmacokinetics and tissue penetration of a single dose of ornidazole (1,000 milligrams intravenously) for antibiotic prophylaxis in colorectal surgery. *Antimicrob Agents Chemother* 1990; **34:** 1921–4.
6. Bourget P, *et al.* Disposition of ornidazole and its metabolites during pregnancy. *J Antimicrob Chemother* 1995; **35:** 691–6.

Hepatic impairment. The elimination of ornidazole after a single intravenous dose of 500 mg was impaired in 10 patients with severe liver cirrhosis when compared with 10 healthy subjects; mean half-lives were 21.9 hours and 14.1 hours respectively.[1] These results suggested that the interval between doses of ornidazole should be doubled in patients with marked hepatic impairment. The need for dose adjustment was confirmed in further studies of patients with other forms of liver disease.[2,3]

1. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with severe liver cirrhosis. *Clin Pharmacol Ther* 1986; **40:** 359–64.
2. Bourget P, *et al.* Ornidazole pharmacokinetics in several hepatic diseases. *J Pharmacol Clin* 1988; **7:** 25–32.
3. Taburet AM, *et al.* Pharmacokinetics of ornidazole in patients with acute viral hepatitis, alcoholic cirrhosis, and extrahepatic cholestasis. *Clin Pharmacol Ther* 1989; **45:** 373–9.

Renal impairment. The half-life of intravenous ornidazole was not prolonged in a study in patients with advanced chronic renal failure, including those on continuous ambulatory peritoneal dialysis, although total plasma clearance was halved; modification of the usual dosage is not necessary in such patients. However, the drug was removed by haemodialysis and ornidazole should be given after the dialysis session rather than before.[1] In another study[2] the systemic availability and total body clearance of ornidazole were unaffected in chronic renal failure; it was considered that an additional dose should be given before haemodialysis to compensate for removal during that procedure.

1. Merdjan H, *et al.* Pharmacokinetics of ornidazole in patients with renal insufficiency; influence of haemodialysis and peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 211–17.
2. Horber FF, *et al.* High haemodialysis clearance of ornidazole in the presence of a negligible renal clearance. *Eur J Clin Pharmacol* 1989; **36:** 389–93.

Uses and Administration

Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p.839) in the treatment of susceptible protozoal infections and also in the treatment and prophylaxis of anaerobic bacterial infections.

It is given orally after food, or intravenously. Intravenous solutions of ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes.

In **amoebiasis**, 500 mg of ornidazole is given orally twice daily for 5 to 10 days; children are given 25 mg/kg as a single daily dose for 5 to 10 days. Patients with amoebic dysentery may be given 1.5 g as a single daily dose for 3 days; the children's dose is 40 mg/kg daily. An alternative regimen for adults over 60 kg is 1 g twice daily for 3 days. In severe amoebic dysentery and amoebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days; the children's dose is 20 to 30 mg/kg daily.

In **giardiasis**, 1 or 1.5 g of ornidazole is given orally as a single daily dose for 1 or 2 days; the children's dose is 30 or 40 mg/kg daily.

In **trichomoniasis**, a single oral dose of 1.5 g is given; alternatively, a 5-day oral course of ornidazole 500 mg twice daily may be used. Sexual partners should also be treated. The children's dose is 25 mg/kg as a single dose by mouth.

For the treatment of **anaerobic bacterial infections,** ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 1 g daily as a single dose or in two divided doses for 5 to 10 days; oral therapy with 500 mg every 12 hours should be substituted as soon as possible. Children may be given 10 mg/kg intravenously every 12 hours for 5 to 10 days.

For the prevention of postoperative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery.

Administration in hepatic impairment. In view of the prolonged half-life and reduced clearance of ornidazole reported in patients with hepatic dysfunction (see above), the interval between doses should be doubled in patients with severe hepatic impairment.

Administration in renal impairment. The elimination of ornidazole is reported to be largely unaltered in patients with impaired renal function (see under Pharmacokinetics, above). Dosage adjustment is therefore usually unnecessary, although patients receiving haemodialysis should be given a supplemental dose of ornidazole before dialysis; a supplemental dose of 500 mg should be given if the daily dose is 2 g daily or 250 mg should be given if the daily dose is 1 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mebaxol; ***Belg.:*** Tiberal; ***Chile:*** Invigan; ***Cz.:*** Avrazor; ***Fr.:*** Tiberal; ***Gr.:*** Betiral†; ***India:*** Giro; Oniz; Ornida; Zil; ***Mex.:*** Danubial†; ***NZ:*** Tiberal; ***Rus.:*** Dazolic (Дазолик); Ornisid (Орнисид); ***Spain:*** Tinerol†; ***Switz.:*** Tiberal; ***Turk.:*** Biteral; Borneral; Ornidone; Ornisid; Ornitop; ***Venez.:*** Tiberal†.

Multi-ingredient: ***India:*** Bidoflox-Oz†; Gatiquin Oz Kit; Levoflox Oz Kit; Ocimix; Orflaz Kit; Ornof; Tariflox Plus.

Paromomycin Sulfate *(rINNM)*

Aminosidin Sulphate; Aminosidine Sulphate; Catenulin Sulphate; Crestomycin Sulphate; Estomycin Sulphate; Hydroxymycin Sulphate; Monomycin A Sulphate; Neomycin E Sulphate; Paromomycin Sulphate *(BANM)*; Paromomycine, Sulfate de; Paromomycini Sulfas; Paucimycin Sulphate; Sulfato de paromomicina. *O*-2,6-Diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-*O*-β-D-ribofuranosyl-(1→5)-*O*-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine sulphate.

Паромомицина Сульфат

$C_{23}H_{45}N_5O_{14},xH_2SO_4$.

CAS — 59-04-1 (paromomycin); 7542-37-2 (paromomycin); 1263-89-4 (paromomycin sulfate).

ATC — A07AA06.

ATC Vet — QA07AA06.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, and *US*.
USP 31 (Paromomycin Sulfate). The sulfate salt of an antibiotic substance produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or a mixture of two or more such salts.
A creamy-white to light yellow, odourless or practically odourless, very hygroscopic powder. It loses not more than 5% of its weight on drying. Very soluble in water; insoluble in alcohol, in chloroform, and in ether. pH of a 3% solution in water is between 5.0 and 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Neomycin, p.305.

Effects on the pancreas. Pancreatitis was associated with use of paromomycin during treatment of cryptosporidiosis in a patient with HIV infection.[1]

1. Tan WW, *et al.* Paromomycin-associated pancreatitis in HIV-related cryptosporidiosis. *Ann Pharmacother* 1995; **29:** 22–4.

Interactions

As for Neomycin, p.305.

Antimicrobial Action

Paromomycin is active against various protozoa including *Leishmania* spp., *Entamoeba histolytica*, and *Cryptosporidium* spp. In addition, it has an antibacterial spectrum similar to that of neomycin (p.305). There is cross-resistance between paromomycin and kanamycin, framycetin, neomycin, and streptomycin.

Paromomycin also has anthelmintic properties against tapeworms.

Antimycobacterial activity. References.

1. Kanyok TP, *et al.* Activity of aminosidine (paromomycin) for Mycobacterium tuberculosis and Mycobacterium avium. *J Antimicrob Chemother* 1994; **33:** 323–7.
2. Piersimoni C, *et al.* Bacteriostatic and bactericidal activities of paromomycin against Mycobacterium avium complex isolates. *J Antimicrob Chemother* 1994; **34:** 421–4.
3. Kanyok TP, *et al.* In vivo activity of paromomycin against susceptible and multidrug-resistant Mycobacterium tuberculosis and M. avium complex strains. *Antimicrob Agents Chemother* 1994; **38:** 170–3.

Pharmacokinetics

Paromomycin is poorly absorbed from the gastrointestinal tract and most of the dose is eliminated unchanged in the faeces.

Parenteral administration. References.

1. Kanyok TP, *et al.* Pharmacokinetics of intramuscularly administered aminosidine in healthy subjects. *Antimicrob Agents Chemother* 1997; **41:** 982–6.

Uses and Administration

Paromomycin is an aminoglycoside antibiotic that has been given orally in the treatment of intestinal protozoal infections, including amoebiasis, cryptosporidiosis, and giardiasis. It has also been tried parenterally for visceral, and topically for cutaneous, leishmaniasis. For details of these infections and their treatment, see under Choice of Antiprotozoal, p.822. It has been used in the treatment of tapeworm infection, but it is not the treatment of choice. Like neomycin (p.305), it has been used in the suppression of intestinal flora both pre-operatively and in the management of hepatic encephalopathy.

Paromomycin is given as the sulfate although doses are expressed in terms of the base. In intestinal amoebiasis, the dose for both adults and children is the equivalent of paromomycin 25 to 35 mg/kg daily in 3 divided oral doses with meals for 5 to 10 days. Similar doses have been tried in cryptosporidiosis.

In taeniasis and other tapeworm infections, a dose of 4 g is given orally as a single dose or in divided doses over the course of one hour.

For hepatic coma, 4 g is given daily in divided oral doses at regular intervals for 5 to 6 days.

Leishmaniasis. Topical treatment with paromomycin 15% plus methylbenzethonium chloride 5 or 12% has produced promising results[1-3] in *cutaneous leishmaniasis* (p.824); paromomycin 12 to 15% with urea 10% was better tolerated.[4] However, benefit has not been seen in all studies.[5,6] Treatment with topical paromomycin plus systemic meglumine antimonate was initially promising in patients with New World cutaneous leishmaniasis;[7] however, a subsequent study[8] found no clear advantage over treatment with meglumine antimonate alone. Good responses to parenteral paromomycin 14 mg/kg daily, with sodium stibogluconate 10 mg/kg daily, in cases of *diffuse cutaneous leishmaniasis* have also been reported.[9]

Paromomycin has also been used intramuscularly, either alone[10] or with sodium stibogluconate,[11] in the treatment of *visceral leishmaniasis* in an area of India with increasing resistance to pentavalent antimony compounds. The authors of one study[10] found paromomycin 16 or 20 mg/kg daily for 21 days to be significantly more effective than sodium stibogluconate 20 mg/kg daily for 30 days and suggested that paromomycin be considered as first-line treatment for visceral leishmaniasis in this region. Oral paromomycin plus intravenous pentamidine was reported to be effective in the treatment of amphotericin-resistant visceral leishmaniasis in an HIV-infected patient.[12]

1. El-On J, *et al.* Topical treatment of Old World cutaneous leishmaniasis caused by Leishmania major: a double-blind control study. *J Am Acad Dermatol* 1992; **27:** 227–31.
2. Krause G, Kroeger A. Topical treatment of American cutaneous leishmaniasis with paromomycin and methylbenzethonium chloride: a clinical study under field conditions in Ecuador. *Trans R Soc Trop Med Hyg* 1994; **88:** 92–4.
3. Arana BA, *et al.* Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *Am J Trop Med Hyg* 2001; **65:** 466–70.
4. Bryceson ADM, *et al.* Treatment of Old World cutaneous leishmaniasis with aminosidine ointment: results of an open study in London. *Trans R Soc Trop Med Hyg* 1994; **88:** 226–8.
5. Ben Salah A, *et al.* A randomized, placebo-controlled trial in Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *Am J Trop Med Hyg* 1995; **53:** 162–6.
6. Asilian A, *et al.* A randomized, placebo-controlled trial of a two week regimen of aminosidine (paromomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *Am J Trop Med Hyg* 1995; **53:** 648–51.
7. Soto J, *et al.* Successful treatment of New World cutaneous leishmaniasis with a combination of topical paromomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clin Infect Dis* 1995; **20:** 47–51.
8. Soto J, *et al.* Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment for American cutaneous leishmaniasis: controlled study. *Clin Infect Dis* 1998; **26:** 56–8.
9. Teklemariam S, *et al.* Aminosidine and its combination with sodium stibogluconate in the treatment of diffuse cutaneous leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1994; **88:** 334–9.
10. Jha TK, *et al.* Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *BMJ* 1998; **316:** 1200–5.
11. Thakur CP, *et al.* A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 2000; **94:** 429–31.
12. Manfredi R, *et al.* Diffuse cutaneous dissemination of visceral leishmaniasis during human immunodeficiency virus (HIV) infection, despite negligible immunodeficiency: repeated failure of liposomal amphotericin B administration, followed by successful long-term pentamidine and paromomycin administration. *Int J Antimicrob Agents* 2008; **31:** 590–2.

Trichomoniasis. Local application of a paromomycin cream has been tried in a small number of patients with metronidazole-resistant vaginal trichomoniasis (p.827) with moderate success.[1]

1. Nyirjesy P, *et al.* Difficult-to-treat trichomoniasis: results with paromomycin cream. *Clin Infect Dis* 1998; **26:** 986–8.

Preparations

USP 31: Paromomycin Sulfate Capsules; Paromomycin Sulfate Syrup.

Proprietary Preparations (details are given in Part 3)

Austria: Humatin; ***Belg.:*** Gabbroral; ***Canad.:*** Humatin; ***Ger.:*** Humatin; ***Indon.:*** Gabbryl; ***Ital.:*** Gabbroral; Humatin; Kaman; ***Spain:*** Humatin; ***Switz.:*** Humatin; ***USA:*** Humatin.

Multi-ingredient: ***Israel:*** Leshcutan.

Pentamidine Isetionate *(BANM, rINNM)*

Isetionato de pentamidina; M&B-800; Pentamidiinidi-isetionaatti; Pentamidin Izetiyonat; Pentamidindiisetionat; Pentamidin-diisetionát; Pentamidin-diizetionát; Pentamidine Diisetionate; Pentamidine, diisétionate de; Pentamidine Isethionate *(USAN)*; Pentamidine, Isétionate de; Pentamidini diisetionas; Pentamidini Isethionas; Pentamidini Isetionas; Pentamidino diizetionatas; Pentamidyny diizetionian. 4,4′-(Pentamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

Пентамидина Изетионат

$C_{19}H_{24}N_4O_2,2C_2H_6O_4S = 592.7.$

CAS — 100-33-4 (pentamidine); 140-64-7 (pentamidine isetionate).

ATC — P01CX01.

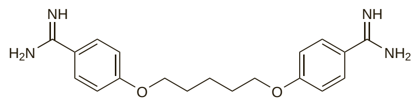

(pentamidine)

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Ph. Eur. 6.2 (Pentamidine Diisetionate; Pentamidine Isetionate BP 2008). A white or almost white powder or colourless crystals; it is hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers.

Incompatibility. Immediate precipitation occurred when a solution of pentamidine isetionate 3 mg/mL in glucose 5% was mixed with each of 5 cephalosporin and 1 cephamycin injections.[1]

Pentamidine isetionate is reported to be incompatible with foscarnet.

1. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Pentamidine Mesilate *(BANM, rINNM)*

Mesilato de pentamidina; Pentamidine Dimethylsulphonate; Pentamidine, Mésilate de; Pentamidine Mesylate; Pentamidine Methanesulphonate; Pentamidini Mesilas; RP-2512. Pentamidine dimethanesulphonate.

Пентамидина Мезилат

$C_{19}H_{24}N_4O_2,2CH_3SO_3H = 532.6.$

CAS — 6823-79-6.

Pharmacopoeias. In *Int.*

Adverse Effects

Pentamidine is a toxic drug and adverse effects are frequent and sometimes severe when given parenterally; fatalities have been reported. Renal impairment is common, usually manifesting as mild and reversible raised blood urea nitrogen and serum creatinine concentrations, but acute renal failure can occur. Raised liver enzyme values and haematological disturbances such as leucopenia, anaemia, and occasionally thrombocytopenia, may develop. Hypoglycaemia, sometimes followed by hyperglycaemia and type 1 diabetes mellitus, is well documented; there have been occasional reports of acute pancreatitis.

The rapid intravenous injection of pentamidine has resulted in sudden hypotension and immediate reactions such as dizziness, headache, vomiting, breathlessness, tachycardia, and fainting. Hypotension may also occur when pentamidine is given intramuscularly or by slow intravenous infusion. Intramuscular pentamidine often causes pain, swelling, sterile abscess formation, and tissue necrosis at the site of injection. Similar damage can follow extravasation during intravenous dosage.

Other adverse effects reported include hypocalcaemia, hyperkalaemia, skin rashes, the Stevens-Johnson syndrome, fever, flushing, gastrointestinal effects such as nausea, vomiting, and taste disturbances, confusion, hallucinations, and cardiac arrhythmias.

Pentamidine is not as toxic when given by inhalation for the prophylaxis of pneumocystis pneumonia. The commonest adverse effects with this route are cough and bronchoconstriction and may be controlled by a bronchodilator. Inhalation may leave a bitter taste. Pneumothorax has been reported, but may be associated with the disease. There have been rare reports of adverse effects such as those seen when pentamidine is given by injection.

Incidence of adverse effects. Adverse effects were seen in 46.8% of 404 patients given pentamidine parenterally for the treatment of pneumocystis pneumonia, according to an analysis from the CDC in the USA.[1] The reactions included impaired renal function (23.5% of patients), abnormal liver function (9.6%), hypoglycaemia (6.2%), haematological disturbances (4.2%), skin rashes (1.5%), and hypocalcaemia (1.2%). Local reactions at injection sites such as pain and abscess occurred in 18.3% and immediate adverse effects such as hypotension in 9.6%.

Retrospective studies[2-4] suggest that adverse reactions occur more commonly in patients with AIDS.

An evaluation of pentamidine in the treatment of 82 patients with visceral leishmaniasis further illustrates its toxicity.[5] Cardiotoxicity (tachycardia, hypotension, and ECG changes of non-specific myocarditis), occurred in about 23% of patients. No hypoglycaemic reaction was noted, but 4 patients developed diabetes mellitus and 3 of them were found to be insulin-dependent. Other adverse reactions included gastrointestinal effects (anorexia, nausea, vomiting, abdominal pain, or diarrhoea) in about 78%, CNS effects (headache associated with flushing, delirium, or sensory disturbances resembling pins and needles) in about 24%, mild reversible albuminuria in about 7%, and allergic manifestations (generalised urticaria, itching, and conjunctival congestion) in about 5%. One patient had severe anaphylaxis.

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. *Am J Med* 1989; **87:** 260–3.
3. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
4. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
5. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistant cases of kala-azar occurring in North Bihar, India. *Trans R Soc Trop Med Hyg* 1983; **77:** 167–70.

Effects on the blood. Haemolytic anaemia has been reported in a 55-year-old man with AIDS being treated with intravenous pentamidine for pneumocystis pneumonia. Symptoms developed after a cumulative dose of 3740 mg of pentamidine had been given and resolved several days after stopping the pentamidine.[1]

1. Taguchi H, *et al.* Pentamidine-induced hemolytic anemia in an AIDS patient. *Ann Pharmacother* 1999; **33:** 503.

Effects on carbohydrate metabolism. As reported under Incidence of Adverse Effects, above, pentamidine can have a range of effects on carbohydrate metabolism. Four patients receiving pentamidine for pneumocystis pneumonia developed severe fasting hypoglycaemia followed later by hyperglycaemia and type 1 diabetes mellitus.[1] It has been suggested that pentamidine has a toxic effect on the β-cells of the pancreatic islets and can induce an early cytolytic release of insulin and hypoglycaemia, followed by β-cell destruction, insulin deficiency, and diabetes mellitus.[1,2] AIDS patients appear to be highly susceptible and have a higher incidence of hypoglycaemia due to pentamidine.[3] The action on the pancreas has led to fatal acute *pancreatitis*;[4-6] fatal hypoglycaemia has also been reported.[7] These reports[1-5,7] involved pentamidine given by injection; pancreatitis[8,9] and diabetes mellitus[10,11] have also been reported in patients given pentamidine by aerosol inhalation.

1. Bouchard P, *et al.* Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes* 1982; **31:** 40–5.
2. Osei K, *et al.* Diabetogenic effect of pentamidine: in vitro and in vivo studies in a patient with malignant insulinoma. *Am J Med* 1984; **77:** 41–6.
3. Stahl-Bayliss CM, *et al.* Pentamidine-induced hypoglycemia in patients with the acquired immune deficiency syndrome. *Clin Pharmacol Ther* 1986; **39:** 271–5.
4. Salmeron S, *et al.* Pentamidine and pancreatitis. *Ann Intern Med* 1986; **105:** 140–1.
5. Zuger A, *et al.* Pentamidine-associated fatal acute pancreatitis. *JAMA* 1986; **256:** 2383–5.
6. Sauleda J, *et al.* Probable pentamidine-induced acute pancreatitis. *Ann Pharmacother* 1994; **28:** 52–3.
7. Sattler FR, Waskin H. Pentamidine and fatal hypoglycemia. *Ann Intern Med* 1987; **107:** 789–90.
8. Herer B, *et al.* Pancreatitis associated with pentamidine by aerosol. *BMJ* 1989; **298:** 605.
9. Hart CC. Aerosolized pentamidine and pancreatitis. *Ann Intern Med* 1989; **111:** 691.
10. Fisch A. Diabetes mellitus in a patient with AIDS after treatment with pentamidine aerosol. *BMJ* 1990; **301:** 875.
11. Chen JP, *et al.* Diabetes after aerosolized pentamidine. *Ann Intern Med* 1991; **114:** 913–14.

Effects on the cardiovascular system. *Hypotension* is a problem with intravenous pentamidine, but can be reduced by infusing the dose over 60 minutes, when the incidence of hypotension appears to be similar to that with the intramuscular route.[1,2] Intravenous pentamidine has also been associated with *torsade de pointes*.[3-5]

1. Navin TR, Fontaine RE. Intravenous versus intramuscular administration of pentamidine. *N Engl J Med* 1984; **311:** 1701.

2. Helmick CG, Green JK. Pentamidine-associated hypotension and route of administration. *Ann Intern Med* 1985; **103:** 480.
3. Harel Y, *et al.* Pentamidine-induced torsade de pointes. *Pediatr Infect Dis J* 1993; **12:** 692–4.
4. Miller HC. Cardiac arrest after intravenous pentamidine in an infant. *Pediatr Infect Dis J* 1993; **12:** 694–6.
5. Zanetti LAF, Oliphant CM. Pentamidine-induced torsade de pointes. *Ann Pharmacother* 1994; **28:** 282–3.

Effects on the kidneys. In an analysis[1] of the adverse effects of parenteral pentamidine (see also under Incidence of Adverse Effects above), *nephrotoxicity* was often the most serious adverse reaction, although it was impossible to attribute it solely to pentamidine. Severe renal impairment occurred in 15 of 404 patients and contributed materially to 12 of 14 ensuing deaths. However, elevation of blood urea nitrogen was usually relatively mild and reversible in those patients who had normal pretreatment renal function and had received no other nephrotoxic agents. In two studies in patients with AIDS,[2,3] severe nephrotoxicity (increase in serum creatinine concentration of 0.5 mg per 100 mL) was reported in about 40% of patients. Analysis of risk factors suggested that the development of adverse reactions to parenteral pentamidine is correlated with the total dose received and the duration of treatment,[2,3] but not with the initial degree of renal function.[2] It has been observed that renal toxicity is more common when pentamidine is given intramuscularly, rather than intravenously, to AIDS patients with diarrhoea, suggesting that fluid status might have an important role.[4] There have been instances of renal failure occurring when pentamidine is inhaled as an aerosol for its local effect.[5,6]

1. Walzer PD, *et al.* Pneumocystis carinii pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80:** 83–93.
2. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. *DICP Ann Pharmacother* 1991; **25:** 1171–4.
3. O'Brien JG, *et al.* A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1997; **24:** 854–9.
4. Stehr-Green JK, Helmick CG. Pentamidine and renal toxicity. *N Engl J Med* 1985; **313:** 694–5.
5. Miller RF, *et al.* Acute renal failure after nebulised pentamidine. *Lancet* 1989; **i:** 1271–2.
6. Chapelon C, *et al.* Renal insufficiency with nebulised pentamidine. *Lancet* 1989; **ii:** 1045–6.

Effects on the nervous system. Paraesthesias have been reported with pentamidine therapy. Perioral numbness occurred in a patient soon after starting the third intravenous infusion of pentamidine for treatment of pneumocystis pneumonia and disappeared after the end of the infusion; numbness recurred with all subsequent pentamidine infusions.[1]

1. Milligan KS, Phillips DL. Perioral numbness associated with intravenous pentamidine administration. *Ann Pharmacother* 2007; **41:** 153–6.

Effects on the respiratory system. Although inhaled pentamidine has produced reactions that are normally associated with the parenteral route, the main problem after inhalation is bronchoconstriction;[1] it can be prevented by prior use of a bronchodilator. Acute eosinophilic pneumonia associated with nebulised pentamidine has been reported in a patient.[2] Concern has also been expressed at the risks to those who are with the patient at the time of inhalation and are exposed to nebulised pentamidine.[3-5]

1. Smith DE, *et al.* Reversible bronchoconstriction with nebulised pentamidine. *Lancet* 1988; **ii:** 905.
2. Dupon M, *et al.* Acute eosinophilic pneumonia induced by inhaled pentamidine isethionate. *BMJ* 1993; **306:** 109.
3. McDiarmid MA, Jacobson-Kram D. Aerosolised pentamidine and public health. *Lancet* 1989; **ii:** 863–4.
4. Thomas SHL, *et al.* Aerosolised pentamidine. *Lancet* 1989; **ii:** 1284.
5. Smaldone GC, *et al.* Detection of inhaled pentamidine in health care workers. *N Engl J Med* 1991; **325:** 891–2.

Precautions

Pentamidine should be used under close supervision and great care is necessary if it is used in patients suffering from any condition likely to be exacerbated by its adverse effects. The CSF should be checked for signs of CNS involvement before giving pentamidine for trypanosomiasis, since it is unlikely to be effective in such cases. Patients should remain supine while it is given and their blood pressure should be monitored. Kidney and liver function, blood-glucose concentrations, blood and platelet counts, and other parameters indicative of developing toxicity, such as serum-calcium concentrations and the ECG, should also be assessed regularly during courses of treatment with pentamidine.

Patients with a history of asthma or smoking may be at increased risk of cough and bronchospasm during inhalation of nebulised pentamidine. Symptoms may be controlled by giving a bronchodilator before pentamidine. Pentamidine solution should not be mixed with other drugs nor should a bronchodilator be given in the same nebuliser. Extrapulmonary *Pneumocystis jirovecii* infections may occur in patients given nebulised pentamidine and should be considered in patients with unexplained signs and symptoms. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to pentamidine.

Interactions

Use of pentamidine with other nephrotoxic drugs such as amphotericin B or foscarnet should preferably be avoided. Extreme caution is also necessary if pentamidine is given with other drugs, such as foscarnet, that can cause hypocalcaemia. There is an increased risk of ventricular arrhythmias if pentamidine is given with drugs which prolong the QT interval such as amiodarone, levacetylmethadol, or terfenadine. There may be an increased risk of pancreatitis when intravenous pentamidine is used with didanosine or zalcitabine and such combinations should be avoided.

Pharmacokinetics

After intravenous doses of the isetionate, pentamidine is rapidly distributed to body tissues and this is followed by a prolonged elimination phase. Elimination half-lives of 6 hours after intravenous infusion and 9 hours after intramuscular injection have been cited, but probably represent an intermediate value, and terminal elimination half-lives of between several days and weeks have been reported. During repeated dosing accumulation is believed to occur, particularly in the liver and kidneys, and only small concentrations of pentamidine are found in the urine.

Distribution to the lung is relatively poor after injection. Systemic absorption after inhalation is reported to result in peak plasma concentrations of 5 to 10% of those after parenteral use, and there have been a few reports of systemic adverse effects. Particle or droplet size appears to be important in achieving adequate pulmonary distribution.

◊ References.

1. O'Doherty MJ, *et al.* Differences in relative efficiency of nebulisers for pentamidine administration. *Lancet* 1988; **ii:** 1283–6.
2. Simonds AK, *et al.* Aerosolised pentamidine. *Lancet* 1989; **i:** 221–2.
3. Baskin MI, *et al.* Regional deposition of aerosolized pentamidine: effects of body position and breathing pattern. *Ann Intern Med* 1990; **113:** 677–83.
4. Bronner U, *et al.* Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense in Côte d'Ivoire. *Trans R Soc Trop Med Hyg* 1991; **85:** 608–11.
5. Lidman C, *et al.* Plasma pentamidine concentrations vary between individuals with Pneumocystis carinii pneumonia and the drug is actively secreted by the kidney. *J Antimicrob Chemother* 1994; **33:** 803–10.
6. Bronner U, *et al.* Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. *Br J Clin Pharmacol* 1995; **39:** 289–95.
7. Conte JE, Golden JA. Intrapulmonary and systemic pharmacokinetics of aerosolized pentamidine used for prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus. *J Clin Pharmacol* 1995; **35:** 1166–73.

Renal impairment. In a study[1] of patients with normal renal function or on haemodialysis, renal clearance of pentamidine during the 24 hours after intravenous use was 2.1% of the plasma clearance in those with normal renal function, suggesting that pentamidine elimination would be largely unaffected by renal impairment. In those with end-stage renal disease on haemodialysis the terminal elimination half-life after a single dose was prolonged to about 75 hours, compared with 30 hours in the patients with normal renal function, but the volumes of distribution and area under the concentration-time curve were not significantly different. In patients with normal or mildly impaired renal function who had received between 12 and 21 doses, the terminal elimination half-life after the final dose was about 12 days and pentamidine was still detectable in the plasma after 6 weeks. There was evidence of accumulation of pentamidine during repeated daily dosing.

1. Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis* 1991; **163:** 169–75.

Uses and Administration

Pentamidine, an aromatic diamidine derivative, is an antiprotozoal used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma brucei gambiense* infections, and in some forms of leishmaniasis. It is also used in the treatment and prophylaxis of pneumocystis pneumonia. It may act by several mechanisms, including interference with protozoal DNA and folate transformation and by inhibition of RNA and protein synthesis.

Pentamidine has been given as the isetionate or mesilate salt, but the isetionate is the only form now available in most countries. There is considerable confusion in the literature regarding the dosage of pentamidine since it is often not clear whether doses are being expressed in terms of pentamidine base, the isetionate salt, or the mesilate salt. In general it would appear that when the isetionate is used doses are expressed in terms of pentamidine isetionate, whereas when the mesilate is used doses are expressed in terms of pentamidine base. Pentamidine isetionate 4 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base; pentamidine mesilate 3.6 mg/kg is equivalent to about 2.3 mg/kg of pentamidine base.

Pentamidine isetionate is given by deep intramuscular injection or by slow intravenous infusion over at least 60 minutes; direct intravenous injection must be avoided. Patients should be lying down. The mesilate has usually been given intramuscularly.

In the treatment of early **African trypanosomiasis** due to *T. b. gambiense*, pentamidine isetionate 4 mg/kg may be given daily or on alternate days by intramuscular injection or intravenous infusion to a total of 7 to 10 doses. Pentamidine is not effective in trypanosomiasis with CNS involvement, but 2 doses of pentamidine may be given in late-stage *T. b. gambiense* infection before starting treatment with melarsoprol or eflornithine.

In the treatment of visceral **leishmaniasis**, and of mucocutaneous leishmaniasis due to *Leishmania braziliensis* or *L. aethiopica* that have not responded to antimonials, pentamidine isetionate 4 mg/kg may be given, preferably intramuscularly three times weekly, for 5 to 25 weeks or longer. An alternative regimen in visceral leishmaniasis is to give 3 to 4 mg/kg on alternate days to a maximum of 10 injections; the course may need to be repeated. In cutaneous leishmaniasis due to *L. aethiopica* or *L. guyanensis*, pentamidine isetionate 3 to 4 mg/kg may be given, preferably intramuscularly once or twice weekly, until the condition resolves. A weekly dose of 3 to 4 mg/kg is also used for diffuse cutaneous leishmaniasis due to *L. aethiopica* and should be continued for at least 4 months after parasites are no longer detectable on skin smears.

In the treatment of **pneumocystis pneumonia**, pentamidine isetionate 4 mg/kg is given once daily for 14 days or longer, by intramuscular injection or preferably slow intravenous infusion. Pentamidine isetionate is given by inhalation through a nebuliser to prevent pneumocystis pneumonia in HIV-positive patients in a dose of 300 mg once every 4 weeks; in those who cannot tolerate this dose 150 mg every 2 weeks may be used. It has also occasionally been used by this route for treating mild to moderate *P. jirovecii* infection in a dose of 600 mg daily for 3 weeks. Nebuliser design can affect the droplet size delivered and hence the amount of pentamidine reaching sites of action within the lungs. The optimal particle size is 1 to 2 μm. Precautions should be taken to minimise atmospheric pollution with pentamidine during nebulisation and to minimise exposure of medical personnel to the drug.

Administration in renal impairment. Since renal clearance accounts for only a small proportion of pentamidine elimination, dosage adjustment is not generally considered necessary for mild to moderate degrees of renal impairment. UK licensed product information recommends dosage reductions in patients with pneumocystis pneumonia who have a creatinine clearance of less than 10 mL/minute. In patients with life-threatening disease the recommended dose of 4 mg/kg daily should be given for 7 to 10 days and then on alternate days for the remainder of the 14-dose course. In less severe disease the suggested dose is 4 mg/kg on alternate days for 14 doses.

Amoebic infections. *ACANTHAMOEBA INFECTIONS.* Pentamidine was used to treat disseminated *Acanthamoeba* infection (p.822) without evidence of CNS involvement in 2 immunocompromised patients.[1,2] It is unlikely that pentamidine would be effective in infections involving the CNS.

1. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.
2. Murakawa GJ, *et al.* Disseminated Acanthamoeba in patients with AIDS: a report of five cases and a review of the literature. *Arch Dermatol* 1995; **131:** 1291–6.

Babesiosis. Pentamidine has been tried for babesiosis (p.823), but while some patients showed clinical improvements,[1-3] the efficacy and safety of pentamidine in this infection has been questioned.[4]

1. Francioli PB, *et al.* Response of babesiosis to pentamidine therapy. *Ann Intern Med* 1981; **94:** 326–30.
2. Raoult D, *et al.* Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; **107:** 944.
3. Clarke CS, *et al.* Babesiosis: under-reporting or case-clustering? *Postgrad Med J* 1989; **65:** 591–3.
4. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; **95:** 241.

Leishmaniasis. Pentamidine has been used in the treatment of visceral leishmaniasis (p.824) both alone and with antimonials in patients who have failed to respond to antimonials alone.[1,2] It has also been tried for long-term secondary prophylaxis in patients with HIV infection.[3] Cutaneous leishmaniasis due to *L. guyanensis* is usually treated with pentamidine to reduce the risk of dissemination;[1] beneficial results in patients infected with *L. infantum*, *L. major*, or *L. tropica* have also been reported.[4] Lesions due to *L. aethiopica* may also respond to pentamidine, but can be left to heal spontaneously since the risk of diffuse cutaneous involvement is small.[1] Diffuse cutaneous or mucocutaneous disease which is unresponsive to antimonials may respond to pentamidine.[1]

For mention of the use of pentamidine with paromomycin to treat visceral leishmaniasis in an HIV-infected patient, see p.844.

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Baily GG, Nandy A. Visceral leishmaniasis: more prevalent and more problematic. *J Infect* 1994; **29:** 241–7.
3. Pérez-Molina JA, *et al.* Pentamidine isethionate as secondary prophylaxis against visceral leishmaniasis in HIV-positive patients. *AIDS* 1996; **10:** 237–8.
4. Hellier I, *et al.* Treatment of Old World cutaneous leishmaniasis by pentamidine isethionate: an open study of 11 patients. *Dermatology* 2000; **200:** 120–3.

Pneumocystis pneumonia. In the treatment of pneumocystis pneumonia (p.521) intravenous pentamidine is generally reserved for patients with moderate to severe disease who do not respond to, or cannot tolerate, co-trimoxazole. Co-trimoxazole with pentamidine is no more effective than pentamidine alone in these patients and is potentially more toxic than either drug.[1] Inhaled pentamidine has occasionally been suggested for mild to moderate infection, but is now generally only used for prophylaxis. However, patients given inhaled pentamidine may be prone to extrapulmonary *Pneumocystis* infections.[2,3]

In both primary and secondary prophylaxis of pneumocystis pneumonia in immunocompromised patients, co-trimoxazole is preferred to inhaled pentamidine. Comparative studies have shown that, in the short term, inhaled pentamidine has been less effective than co-trimoxazole[4,5] and no more effective than another common prophylactic drug, dapsone.[6,7] In addition, both co-trimoxazole and dapsone (given with pyrimethamine) also provide protection against toxoplasmosis and extrapulmonary pneumocystis infections. However, inhaled pentamidine is better tolerated than either of these, and studies have suggested that in the long term the efficacy of the three drugs is comparable,[8,9] at least in patients with CD4+ T lymphocyte counts of more than 100 cells/microlitre. Increasing the dose of pentamidine from 300 mg every four weeks to 300 mg every two weeks[10,11] or 600 mg every week[12] may improve efficacy further. Intermittent parenteral dosage of pentamidine has been used when the more usual drugs cannot be given.[13]

1. Glatt AE, Chirgwin K. Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Arch Intern Med* 1990; **150:** 271–9.
2. Witt K, *et al.* Dissemination of Pneumocystis carinii in patients with AIDS. *Scand J Infect Dis* 1991; **23:** 691–5.
3. Sha BE, *et al.* Pneumocystis carinii choroiditis in patients with AIDS: clinical features, response to therapy, and outcome. *J Acquir Immune Defic Syndr Hum Retrovirol* 1992; **5:** 1051–8.
4. Schneider MME, *et al.* A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 1836–41.
5. Hardy WD, *et al.* A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992; **327:** 1842–8.
6. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
7. Torres RA, *et al.* Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Am J Med* 1993; **95:** 573–83.
8. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
9. Rizzardi GP, *et al.* Risks and benefits of aerosolized pentamidine and cotrimoxazole in primary prophylaxis of Pneumocystis carinii pneumonia in HIV-1-infected patients: a two-year Italian multicentric randomized controlled trial. *J Infect* 1996; **32:** 123–31.
10. Kronawitter U, *et al.* Low incidence of Pneumocystis carinii pneumonia in HIV patients receiving 300 mg pentamidine aerosol every 2 weeks. *Clin Investig* 1992; **70:** 1089–91.
11. Rizzardi GP, *et al.* Better efficacy of twice-monthly than monthly aerosolised pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with AIDS: an Italian multicentric randomised controlled trial. *J Infect* 1995; **31:** 99–105.
12. Ong ELC, *et al.* Efficacy and effects on pulmonary function tests of weekly 600 mg aerosol pentamidine as prophylaxis against Pneumocystis carinii pneumonia. *Infection* 1992; **20:** 136–9.
13. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf (accessed 27/05/05)

African trypanosomiasis. Pentamidine is used for the haemolymphatic phase of African trypanosomiasis caused by *Trypanosoma brucei gambiense* (p.827), and as an adjunct to other treatment for the meningoencephalitic stage of the infection.[1] It is reported to be less effective against *T. b. rhodesiense* and in some areas resistance of *T. b. gambiense* to pentamidine is increasing. Pentamidine has been used with suramin for *T. b. gambiense* infections but this has not been shown to be clinically superior to pentamidine alone.[2]

1. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998.
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90:** 183–6.

Preparations

BP 2008: Pentamidine Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Pentacarinat; ***Belg.:*** Pentacarinat; ***Braz.:*** Pentacarinat; Sideron†; ***Canad.:*** Pentacarinat†; ***Denm.:*** Pentacarinat; ***Fin.:*** Pentacarinat†; ***Fr.:*** Pentacarinat; ***Ger.:*** Pentacarinat; ***Gr.:*** Pentacarinate; Pentam; ***Irl.:*** Pentacarinat; ***Israel:*** Pentacarinat†; ***Ital.:*** Pentacarinat; ***Neth.:*** Pentacarinat; ***NZ:*** Pentacarinat; ***Port.:*** Pentacarinat†; Pentamina; ***Spain:*** Pentacarinat; ***Swed.:*** Pentacarinat; ***Switz.:*** Pentacarinat; ***Thai.:*** Pentacarinat; ***UK:*** Pentacarinat; ***USA:*** NebuPent; Pentacarinat; Pentam.

Quinfamide *(USAN, rINN)*

Quinfamida; Quinfamidum; Win-40014. 1-(Dichloroacetyl)-1,2,3,4-tetrahydroquinolin-6-ol 2-furoic acid ester.

Хинфамид

$C_{16}H_{13}Cl_2NO_4$ = 354.2.
CAS — 62265-68-3.

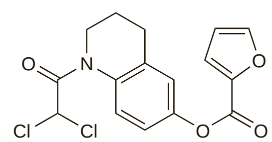

Profile

Quinfamide is a luminal amoebicide. It is given orally for intestinal amoebiasis in a dose of 300 mg, either as a single dose or as three divided doses over 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Amefin; Amefur; Amenox; Amofur; Bisidim; Celemin; Doffler; Falacid; Luminovag; Protosin; Quocel; Serphamida.

Multi-ingredient: *Mex.:* Amibriz†; Amoebriz; Oxal; Vermox-Plus.

Robenidine Hydrochloride *(BANM, USAN, rINNM)*

CL-78116; Hidrocloruro de robenidina; Robénidine, Chlorhydrate de; Robenidini Hydrochloridum; Robenzidene Hydrochloride. 1,3-Bis(4-chlorobenzylideneamino)guanidine hydrochloride.

Робенидина Гидрохлорид

$C_{15}H_{13}Cl_2N_5,HCl$ = 370.7.
CAS — 25875-51-8 (robenidine); 25875-50-7 (robenidine hydrochloride).

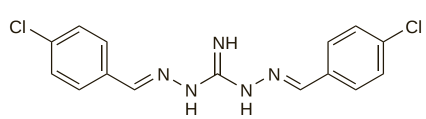

(robenidine)

Profile

Robenidine is an antiprotozoal used as the hydrochloride in veterinary practice for the prevention of coccidiosis in poultry and rabbits.

Ronidazole *(BAN, USAN, pINN)*

Ronidazol; Ronidazolum. (1-Methyl-5-nitroimidazol-2-yl)methyl carbamate.

Ронидазол

$C_6H_8N_4O_4$ = 200.2.
CAS — 7681-76-7.
ATC Vet — QP51AA08.

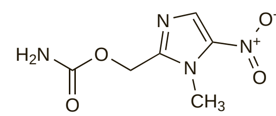

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Ronidazole). A white to yellowish-brown, odourless or almost odourless powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Protect from light.

Profile

Ronidazole is a 5-nitroimidazole antiprotozoal that is used in veterinary practice for the control of trichomoniasis in cage birds and pigeons. It has also been added to turkey feeding stuffs and has been used for the control of swine dysentery.

Salinomycin Sodium *(BANM, rINNM)*

AHR-3096 (salinomycin); K-364 (salinomycin); K-748364A (salinomycin); Natrii Salinomycinum; Salinomicina sódica; Salinomycine Sodique. Sodium (2*R*)-2-{(2*R*,5*S*,6*R*)-6-[(1*S*,2*S*,3*S*,5*R*)-5-{(2*S*,5*S*,7*R*,9*S*,10*S*,12*R*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl]-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl}-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-5-methylpyran-2-yl}butyrate.

Натрий Салиномицин

$C_{42}H_{69}NaO_{11}$ = 773.0.
CAS — 53003-10-4 (salinomycin); 55721-31-8 (salinomycin sodium).

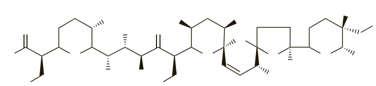

(salinomycin)

Profile

Salinomycin, an antibiotic produced by *Streptomyces albus*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor in pigs.

Secnidazole *(BAN, rINN)*

PM-185184; 14539-RP; RP-14539; Secnidazol; Secnidazolum; Seknidazol. 1-(2-Methyl-5-nitroimidazol-1-yl)propan-2-ol.

Секнидазол

$C_7H_{11}N_3O_3$ = 185.2.
CAS — 3366-95-8.
ATC — P01AB07.

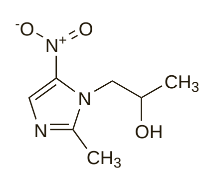

Profile

Secnidazole is a 5-nitroimidazole derivative with properties similar to those of metronidazole (p.837), apart from a much longer plasma half-life of 20 hours or more. It is used in the treatment of amoebiasis, giardiasis, and trichomoniasis.

Secnidazole is given orally, usually as a single dose of 2 g in adults or 30 mg/kg in children. In invasive (hepatic) amoebiasis a dose of 1.5 g daily is given in single or divided doses for 5 days; children may be given 30 mg/kg daily.

◊ References.

1. Gillis JC, Wiseman LR. Secnidazole: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. *Drugs* 1996; **51:** 621–38.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Flagentyl; ***Braz.:*** Decnazol†; Deprozol; Neodazol; Secnaxidol; Secni-Plus; Secnics; Secnidal; Secnidalin; Secnihexal†; Secnitec; Secnitrol†; Secnix; Secnizol†; Tecnid; Unigyn; ***Fr.:*** Secnol; ***India:*** Entosec; Noameba-DS; Secnil; ***Indon.:*** Sentyl; ***Mex.:*** Gisistin; Minovag; Sabima; Secnidal; ***Philipp.:*** Flagentyl; ***Port.:*** Flagentyl; ***Turk.:*** Flagentyl; ***Venez.:*** Ambese; Daksol; Fazol; Secnidal; Secnivax; Seczol; Unidazol.

Multi-ingredient: ***Arg.:*** Gynerium; Gynerium UD; ***Braz.:*** Gynopac; ***India:*** Safkit; ***Mex.:*** Sepia; Sporasec; ***Venez.:*** Sporasec.

Semduramicin *(BAN, USAN, rINN)*

Semduramicina; Semduramicine; Semduramicinum; UK-61689; UK-61689-2 (semduramicin sodium). (2*R*,3*S*,4*S*,5*R*,6*S*)-Tetrahydro-2,4-dihydroxy-6-{(*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-{(2*S*,2′*R*,3′*S*,5′*R*)-octahydro-2-methyl-5′-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-3′-[(2*S*,5*S*,6*R*)-tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yloxy]-2,2′-bifuran-5-yl}-1,6-dioxaspiro[4.5]dec-7-yl]ethyl}-5-methoxy-3-methyl-2*H*-pyran-2-ylacetic acid.

Семдурамицин

$C_{45}H_{76}O_{16}$ = 873.1.

CAS — 113378-31-7 (semduramicin); 119068-77-8 (semduramicin sodium).

Profile

Semduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry. It is also used as the sodium salt.

Suramin Sodium *(rINN)*

Antrypol; Bayer-205; CI-1003; Fourneau-309; Naganinum; Naganol; Suramin Hexasodium *(USAN)*; Suramina sódica; Suramine Sodique; Suraminum Natricum. The symmetrical 3″-urea of the sodium salt of 8-(3-benzamido-4-methylbenzamido)naphthalene-1,3,5-trisulphonic acid; Hexasodium 8,8′-{carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]}bis(1,3,5-naphthalenetrisulfonate).

Сурамин Натрий

$C_{51}H_{34}N_6Na_6O_{23}S_6$ = 1429.2.

CAS — 145-63-1 (suramin); 129-46-4 (suramin sodium).

ATC — P01CX02.

ATC Vet — QP51AE02.

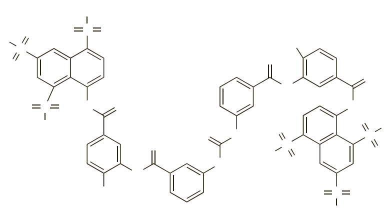

(suramin)

Pharmacopoeias. In *Fr., Int.,* and *It.*

Adverse Effects

An immediate and potentially fatal reaction, with nausea, vomiting, shock, seizures, and loss of consciousness, may follow the injection of suramin sodium in some patients and thus it is usual practice to give a small test dose before starting treatment.

Abdominal pain, mouth ulceration, and skin reactions such as urticaria and pruritus may occur. The risk of hypersensitivity reactions is reported to be greater when onchocerciasis is present.

Other adverse effects include paraesthesia, hyperaesthesia of the palms and soles, skin eruptions, blood dyscrasias, fever, polyuria, increased thirst, raised liver enzyme values, fatigue, and effects on the eye including photophobia and lachrymation. Proteinuria is common; haematuria and casts in the urine may also occur. There have been occasional reports of adrenal insufficiency.

Effects on the blood. Thrombocytopenia has been reported in patients receiving suramin, generally during treatment for AIDS or cancer.[1-4] An immune-mediated mechanism has been proposed[3] although there is evidence that multiple mechanisms may be involved.[4] Other adverse effects on the blood include neutropenia,[1,5] anaemia,[1] deterioration of pre-existing lymphocytopenia,[5] and fatal myelosuppression.[5] Agranulocytosis and haemolytic anaemia have occurred rarely.

1. Levine AM, *et al.* Suramin antiviral therapy in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; **105:** 32–7.
2. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
3. Seidman AD, *et al.* Immune-mediated thrombocytopenia secondary to suramin. *Cancer* 1993; **71:** 851–4.
4. Tisdale JF, *et al.* Severe thrombocytopenia in patients treated with suramin: evidence for an immune mechanism in one. *Am J Hematol* 1996; **51:** 152–7.
5. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14:** 1626–36.

Effects on the eyes. Late effects on the eyes associated with suramin include photophobia, lachrymation, and palpebral oedema. Keratopathy characterised by corneal deposits has been reported in patients receiving suramin. In a study of 114 patients receiving suramin for prostatic cancer, 13 developed corneal deposits similar to those reported with chloroquine therapy after 34 to 98 days of therapy.[1] Symptoms in 10 of the 13 included lachrymation and foreign body sensation. The remaining 3 patients were asymptomatic. Shifts in refractive error were also found. Keratopathy has also been reported in patients with AIDS receiving suramin.[2] In patients treated with suramin for ocular onchocerciasis, the incidence of optic atrophy was higher after 3 years than in untreated patients.[3] A prolonged inflammatory response to dying microfilariae in the optic nerve might be responsible, although a direct toxic or allergic effect could not be ruled out.

1. Hemady RK, *et al.* Ocular symptoms and signs associated with suramin sodium treatment for metastatic cancer of the prostate. *Am J Ophthalmol* 1996; **121:** 291–6.
2. Teich SA, *et al.* Toxic keratopathy associated with suramin therapy. *N Engl J Med* 1986; **314:** 1455–6.
3. Thylefors B, Rolland A. The risk of optic atrophy following suramin treatment of ocular onchocerciasis. *Bull WHO* 1979; **57:** 479–80.

Effects on the kidneys. In addition to the proteinuria commonly seen during suramin therapy, there have been reports of individual cases of renal glycosuria[1] and of acute renal dysfunction.[2]

1. Awadzi K, *et al.* The chemotherapy of onchocerciasis XVIII: aspects of treatment with suramin. *Trop Med Parasitol* 1995; **46:** 19–26.
2. Figg WD, *et al.* Acute renal toxicity associated with suramin in the treatment of prostate cancer. *Cancer* 1994; **74:** 1612–14.

Effects on the nervous system. Neurological disorders reported in patients receiving suramin include paraesthesia and polyneuropathy. Severe polyneuropathy with generalised flaccid paralysis has generally been associated with serum-suramin concentrations greater than 350 micrograms/mL,[1,2] but motor neuropathy was reported in 8 patients with serum concentrations of 275 micrograms/mL.[3]

1. La Rocca RV, *et al.* Suramin-induced polyneuropathy. *Neurology* 1990; **40:** 954–60.
2. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
3. Bitton RJ, *et al.* Pharmacologic variables associated with the development of neurologic toxicity in patients treated with suramin. *J Clin Oncol* 1995; **13:** 2223–9.

Effects on the skin. Pruritus and urticaria may occur as hypersensitivity reactions to suramin. Late skin reactions include erythematous maculopapular rashes.[1] Severe reactions including erythema multiforme,[2] exfoliative dermatitis, and fatal toxic epidermal necrolysis[3,4] have been reported.

1. O'Donnell BP, *et al.* Suramin-induced skin reactions. *Arch Dermatol* 1992; **128:** 75–9.
2. Katz SK, *et al.* Erythema multiforme induced by suramin. *J Am Acad Dermatol* 1995; **32:** 292–3.
3. May E, Allolio B. Fatal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1991; **27:** 1338.
4. Falkson G, Rapoport BL. Lethal toxic epidermal necrolysis during suramin treatment. *Eur J Cancer* 1992; **28A:** 1294.

Precautions

Suramin sodium should be used under close supervision, and the general condition of patients improved as far as possible before treatment starts. Patients who have a severe reaction to the first dose should never receive suramin again. It should not be used in elderly or infirm patients or in the presence of severe hepatic or renal disease. The urine should be tested before treatment starts and weekly during treatment; dosage should be reduced if moderate proteinuria develops and stopped if it becomes severe or if casts appear in the urine.

Pregnancy. Suramin has been reported to be teratogenic in *mice* but not in *rats*.[1] WHO[2] recommends that when necessary suramin should be used in pregnant women with *T. b. rhodesiense* trypanosomiasis, even those with meningoencephalitic disease, because melarsoprol is contra-indicated; in onchocerciasis, suramin treatment should be delayed until after delivery.

1. Mercier-Parot L, Tuchmann-Duplessis H. Action abortive et tératogène d'un trypanocide, la suramine. *C R Soc Biol* 1973; **167:** 1518–22.
2. WHO. *WHO model formulary.* Geneva: WHO, 2004.

Pharmacokinetics

After intravenous injection, suramin becomes bound to plasma proteins and plasma concentrations over 100 micrograms/mL are maintained for several weeks. Unbound suramin is excreted in the urine. Penetration of suramin into the CSF appears to be poor.

◊ The clinical pharmacokinetics of suramin were studied in 4 patients with AIDS given 6.2 g intravenously over 5 weeks.[1] Suramin accumulated during treatment and plasma concentrations exceeded 100 micrograms/mL for several weeks. After the last dose the terminal half-life of suramin ranged from 44 to 54 days. At least 99.7% was bound to plasma proteins. Renal clearance accounted for most of the elimination of suramin from the body. There appeared to be little or no metabolism of suramin.

In another study,[2] ten male patients with onchocerciasis received weekly infusions of suramin for 6 weeks, according to the dose regimen recommended by WHO (see below). In these patients the median elimination half-life was about 92 days, and in each case, the maximum plasma concentration remained below 300 micrograms/mL.

1. Collins JM, *et al.* Clinical pharmacokinetics of suramin in patients with HTLV-III/LAV infection. *J Clin Pharmacol* 1986; **26:** 22–6.
2. Chijioke CP, *et al.* Clinical pharmacokinetics of suramin in patients with onchocerciasis. *Eur J Clin Pharmacol* 1998; **54:** 249–51.

Uses and Administration

Suramin is a trypanocide used in the treatment of African trypanosomiasis and as an anthelmintic in the treatment of onchocerciasis.

Suramin is given as suramin sodium by slow intravenous injection, usually as a 10% solution. Because of the danger of severe reactions it is advisable to give a test dose before starting treatment.

In African trypanosomiasis suramin is used mainly for the early (haematolymphatic) stages of *Trypanosoma brucei rhodesiense* infection; pentamidine may be preferred for early-stage treatment of *T. b. gambiense* infection. Suramin is not used as sole therapy for late-stage infections with CNS involvement. Early-stage trypanosomiasis may be treated with a dose of 5 mg/kg of suramin on day 1, 10 mg/kg on day 3, then 20 mg/kg on days 5, 11, 17, 23, and 30. Another schedule consists of 5 doses of 1 g given over 3 weeks after a test dose of 100 to 200 mg. In late-stage trypanosomiasis injections of suramin are often given before starting treatment with melarsoprol; 5 and 10 mg/kg are given on days 1 and 3 respectively, and in some regimens 20 mg/kg is also given on day 5.

For doses used in onchocerciasis see below.

Malignant neoplasms. Suramin is reported to have antineoplastic activity and has been studied in a number of malignant neoplasms, in particular hormone-resistant prostatic cancer (p.671). However, its clinical usefulness is hindered by dose-limiting toxicity and problems in developing a simple dose schedule. It has also been investigated as a chemosensitiser.

References.

1. Stein CA, *et al.* Suramin: an anticancer drug with a unique mechanism of action. *J Clin Oncol* 1989; **7:** 499–508.
2. Kilbourn RG. Suramin: new therapeutic concepts for an old drug. *Cancer Bull* 1991; **43:** 265–7.
3. Rapoport BL, *et al.* Suramin in combination with mitomycin C in hormone-resistant prostate cancer: a phase II clinical study. *Ann Oncol* 1993; **4:** 567–73.
4. Woll PJ, *et al.* Suramin for breast and prostate cancer: a pilot study of intermittent short infusions without adaptive controls. *Ann Oncol* 1994; **5:** 597–600.
5. Arlt W, *et al.* Suramin in adrenocortical cancer: limited efficacy and serious toxicity. *Clin Endocrinol (Oxf)* 1994; **41:** 299–307.
6. Eisenberger MA, Reyno LM. Suramin. *Cancer Treat Rev* 1994; **20:** 259–73.
7. Rosen PJ, *et al.* Suramin in hormone-refractory metastatic prostate cancer: a drug with limited efficacy. *J Clin Oncol* 1996; **14:** 1626–36.
8. Small EJ, *et al.* Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000; **18:** 1440–50.
9. Chen D, *et al.* Nontoxic suramin as a chemosensitizer in patients: dosing nomogram development. *Pharm Res* 2006; **23:** 1265–74.

Onchocerciasis. Although suramin is the only drug in clinical use for onchocerciasis that is effective against adult worms, its use is restricted because of the frequency of associated compli-

The symbol † denotes a preparation no longer actively marketed

cations and its intrinsic toxicity. Treatment of onchocerciasis (p.137) is currently based on continuous suppression of microfilariae by regular use of ivermectin. WHO[1] advises that suramin should only be considered for the curative treatment of individuals in areas without transmission of onchocerciasis and of individuals leaving an endemic area, and for severe hyperreactive onchodermatitis where symptoms are not adequately controlled with ivermectin. WHO[2] also recommends that it should not be used to treat onchocerciasis in the elderly or infirm, in patients with severe liver or renal disease, in totally blind patients (unless they require relief from intensely itchy lesions), or in pregnant women (who should be treated after delivery).

A total dose of 66.7 mg/kg in six incremental weekly doses is recommended.[1,2] The first (test) dose of suramin sodium 3.3 mg/kg should be given very cautiously by slow intravenous injection; this is followed at weekly intervals by incremental doses of 6.7 mg/kg, 10.0 mg/kg, 13.3 mg/kg, 16.7 mg/kg and 16.7 mg/kg.[2]

1. WHO. Onchocerciasis and its control: report of a WHO expert committee. *WHO Tech Rep Ser 852* 1995.
2. WHO. *WHO model formulary.* Geneva: WHO, 2004.

African trypanosomiasis. Suramin is used in the treatment of the early haematolymphatic phase of African trypanosomiasis (p.827) caused by *Trypanosoma brucei rhodesiense* and for *T. b. gambiense* infections which are resistant to pentamidine.[1] In some regions, suramin is used with pentamidine for *T. b. gambiense* infections but it has not been shown to be clinically superior to pentamidine alone.[2] Although suramin does not reach sufficient concentrations in the CSF to produce a cure in the meningoencephalitic phase, it is used to reduce the number of trypanosomes in the blood and lymph before treatment with melarsoprol.[1] Case reports have suggested that suramin with metronidazole[3] or eflornithine[4] could be useful in *T. b. rhodesiense* infections, although response to suramin plus eflornithine was disappointing in a study involving 6 patients.[5]

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg* 1996; **90:** 183–6.
3. Foulkes JR. Metronidazole and suramin combination in the treatment of arsenical refractory rhodesian sleeping sickness—a case study. *Trans R Soc Trop Med Hyg* 1996; **90:** 422.
4. Taelman H, *et al.* Combination treatment with suramin and eflornithine in late stage rhodesian trypanosomiasis: case report. *Trans R Soc Trop Med Hyg* 1996; **90:** 572–3.
5. Clerinx J, *et al.* Treatment of late stage rhodesiense trypanosomiasis using suramin and eflornithine: report of six cases. *Trans R Soc Trop Med Hyg* 1998; **92:** 449–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Germanin.

Teclozan *(USAN, rINN)*

NSC-107433; Téclozan; Teclozán; Teclozanum; Win-13146. *NN'*-*p*-Phenylenedimethylenebis[2,2-dichloro-*N*-(2-ethoxyethyl)-acetamide].

Теклозан

$C_{20}H_{28}Cl_4N_2O_4$ = 502.3.
CAS — 5560-78-1.
ATC — P01AC04.

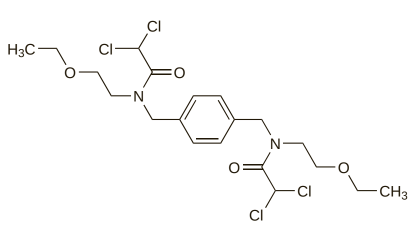

Profile

Teclozan, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p.832). It has been given orally in the treatment of intestinal amoebiasis.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Falmonox; ***Venez.:*** Falmonox.

Tenonitrozole *(rINN)*

TC-109; Tenonitrozol; Ténonitrozole; Tenonitrozolum; Thenitrazole. *N*-(5-Nitrothiazol-2-yl)thiophene-2-carboxamide.

Тенонитрозол

$C_8H_5N_3O_3S_2$ = 255.3.
CAS — 3810-35-3.
ATC — P01AX08.

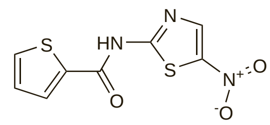

Profile

Tenonitrozole is an antiprotozoal given in the treatment of trichomoniasis (p.827). It is given orally in a dose of 250 mg twice daily with meals, for 4 days.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Atrican; ***Rus.:*** Atrican (Атрикан); ***Venez.:*** Detrican†.

Ternidazole *(rINN)*

Ternidazol; Ternidazolum. 2-Methyl-5-nitroimidazole-1-propanol.

Тернидазол

$C_7H_{11}N_3O_3$ = 185.2.
CAS — 1077-93-6.

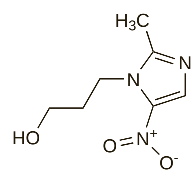

Profile

Ternidazole is a 5-nitroimidazole antiprotozoal with properties similar to those of metronidazole (p.837). It has been an ingredient of preparations used for the treatment of vaginitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Tergynan (Тержинан).

Tilbroquinol *(pINN)*

Tilbroquinolum. 7-Bromo-5-methylquinolin-8-ol.

Тильброхинол

$C_{10}H_8BrNO$ = 238.1.
CAS — 7175-09-9.
ATC — P01AA05.

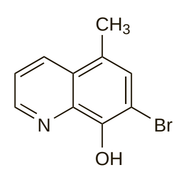

Profile

Tilbroquinol is a halogenated hydroxyquinoline antiprotozoal with properties similar to those of diiodohydroxyquinoline (p.832). It has been used with tiliquinol (below) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Adverse effects. A report of neurotoxicity, considered to be subacute myelo-opticoneuropathy, in a patient who had taken tilbroquinol with tiliquinol for 4 years.[1] Hepatotoxicity has also been reported[2] with this combination.

1. Soffer M, *et al*. Oxyquinoline toxicity. *Lancet* 1983; **i:** 709.
2. Caroli-Bosc F-X, *et al.* Hépatite aiguë due à l'association de tiliquinol et tilbroquinol (Intétrix). *Gastroenterol Clin Biol* 1996; **20:** 605–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Intetrix; ***Rus.:*** Intetrix (Интетрикс).

Tiliquinol *(rINN)*

Tiliquinolum. 5-Methylquinolin-8-ol.

Тилихинол

$C_{10}H_9NO$ = 159.2.
CAS — 5541-67-3.

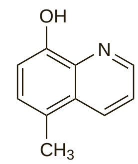

Profile

Tiliquinol has been used with tilbroquinol (above) in the treatment of intestinal infections including amoebiasis but less toxic drugs are preferred.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Intetrix; ***Rus.:*** Intetrix (Интетрикс).

Tinidazole *(BAN, USAN, rINN)*

CP-12574; Tinidatsoli; Tinidazol; Tinidazolas; Tinidazolum; Tynidazol. 1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole.

Тинидазол

$C_8H_{13}N_3O_4S$ = 247.3.
CAS — 19387-91-8.
ATC — J01XD02; P01AB02.
ATC Vet — QJ01XD02; QP51AA02.

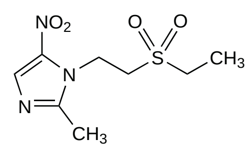

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Tinidazole). An almost white or pale yellow, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.
USP 31 (Tinidazole). An almost white or pale yellow crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Metronidazole, p.837.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of tinidazole by mothers during breast feeding may be of concern, since it is mutagenic *in vitro*. After single-dose therapy, breast feeding may be stopped for 12 to 24 hours to allow excretion of the dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/06/04)

Porphyria. Tinidazole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Shock. An acute severe toxic reaction, considered not to be allergic, occurred in a healthy subject shortly after the intravenous infusion of tinidazole 1.6 g over 80 minutes.[1] He fainted for about 10 seconds and low blood pressure, nausea, and tiredness persisted for several hours. Spasms in the left arm were also experienced but no generalised convulsions. Anaphylactic shock has also been reported,[2] with severe bronchospasm and subsequent development of Stevens-Johnson syndrome, in a patient who had reactions of increasing severity after 3 separate exposures to tinidazole.

1. Aase S, *et al.* Severe toxic reaction to tinidazole. *Eur J Clin Pharmacol* 1983; **24:** 425–7.
2. Singbal SS, Rataboli PV. Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole. *J Postgrad Med* 2005; **51:** 243–4.

Interactions

Tinidazole may, like metronidazole (p.838), produce a disulfiram-like reaction with alcohol.

Pharmacokinetics

The pharmacokinetics of tinidazole resemble those of metronidazole although the half-life is longer.

Tinidazole is rapidly and almost completely absorbed after oral doses and, typically, a peak plasma concentration of about 40 micrograms/mL is achieved 2 hours after a single 2-g dose, falling to about 10 micrograms/mL at 24 hours and 2.5 micrograms/mL at 48 hours; concentrations above 8 micrograms/mL are maintained by daily maintenance doses of 1 g. Comparable concentrations are achieved with equivalent intravenous doses. The plasma elimination half-life of tinidazole is 12 to 14 hours.

Tinidazole is widely distributed and concentrations similar to those in plasma have been achieved in bile, breast milk, CSF, saliva, and a variety of body tissues; it crosses the placenta readily. Only 12% is reported to be bound to plasma proteins. An active hydroxy metabolite has been identified.

Unchanged drug and metabolites are excreted in the urine and, to a lesser extent, in the faeces.

◊ References.

1. Wood BA, *et al*. The pharmacokinetics, metabolism and tissue distribution of tinidazole. *J Antimicrob Chemother* 1982; **10** (suppl A): 43–57.
2. Karhunen M. Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. *Br J Clin Pharmacol* 1984; **18:** 254–7.
3. Evaldson GR, *et al.* Tinidazole milk excretion and pharmacokinetics in lactating women. *Br J Clin Pharmacol* 1985; **19:** 503–7.
4. Wood SG, *et al.* Pharmacokinetics and metabolism of C-tinidazole in humans. *J Antimicrob Chemother* 1986; **17:** 801–9.

Renal impairment. Single-dose studies indicate that the pharmacokinetics of tinidazole in patients with chronic renal failure are not significantly different from those in healthy subjects and that no modification of tinidazole dosage is necessary. However, tinidazole is rapidly removed by haemodialysis.[1,2]

1. Flouvat BL, *et al.* Pharmacokinetics of tinidazole in chronic renal failure and in patients on haemodialysis. *Br J Clin Pharmacol* 1983; **15:** 735–41.
2. Robson RA, *et al.* Tinidazole pharmacokinetics in severe renal failure. *Clin Pharmacokinet* 1984; **9:** 88–94.

Uses and Administration

Tinidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazole and is used similarly (see p.839) in the treatment of susceptible protozoal infections and in the treatment and prophylaxis of anaerobic bacterial infections. It has also been used in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease.

Tinidazole is usually given as a single daily oral dose with or after food; it is also given by intravenous infusion and as vaginal pessaries.

In invasive **amoebiasis**, tinidazole is usually given with a luminal amoebicide. In intestinal amoebiasis, a single daily dose of 2 g is given orally for 2 or 3 days; in hepatic amoebiasis, 1.5 to 2 g as a single daily dose may be given for 3 days or occasionally up to 6 days. Children are given 50 to 60 mg/kg daily for 3 or 5 days respectively.

A single dose of tinidazole 2 g is given orally in the treatment of **giardiasis**, **trichomoniasis**, and acute necrotising **ulcerative gingivitis**; 50 to 75 mg/kg as a single dose is given to children with giardiasis or trichomoniasis. It may sometimes be necessary to repeat this dose once. In trichomoniasis, sexual partners should also be treated.

In **bacterial vaginosis**, a single 2-g dose of tinidazole is usually given orally, although higher cure rates have been achieved with a 2-g dose on 2 successive days or 1 g daily for 5 days.

For the treatment of most **anaerobic bacterial infections**, tinidazole is given orally, usually for 5 or 6 days, in an initial dose of 2 g followed on subsequent days by 1 g daily or 500 mg twice daily. If oral therapy is not possible, tinidazole may be given intravenously, 800 mg being infused as 400 mL of a 2 mg/mL solution at a rate of 10 mL/minute; this initial dose is followed by 800 mg daily or 400 mg twice daily until oral therapy can be substituted. For the *prevention* of postoperative anaerobic bacterial infections, 2 g is given by mouth about 12 hours before surgery. Alternatively 1.6 g is given as a single intravenous infusion before surgery.

In regimens for the treatment of **peptic ulcer disease**, tinidazole 500 mg twice daily has been given with clarithromycin and omeprazole for 7 days.

◊ Reviews.

1. Manes G, Balzano A. Tinidazole: from protozoa to Helicobacter pylori—the past, present and future of a nitroimidazole with peculiarities. *Expert Rev Anti Infect Ther* 2004; **2:** 695–705.
2. Fung HB, Doan TL. Tinidazole: a nitroimidazole antiprotozoal agent. *Clin Ther* 2005; **27:** 1859–84.
3. Nailor MD, Sobel JD. Tinidazole for bacterial vaginosis. *Expert Rev Anti Infect Ther* 2007; **5:** 343–8.

Administration in renal impairment. The elimination of tinidazole is largely unchanged in patients with impaired renal function (see under Pharmacokinetics, above) and dosage adjustment is not generally considered necessary. However tinidazole is removed by haemodialysis, and patients may need additional doses to compensate.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fasigyn; Gynormal; Ladylen Duo; ***Austral.:*** Fasigyn; Simplotan; ***Belg.:*** Fasigyn; ***Braz.:*** Amplium; Facyl; Fasigyn; Ginosutin; Pletil; Tinoral; Trinizol†; ***Chile:*** Fasigyn; Triconidazol†; Troxxil; ***Fr.:*** Fasigyne; ***Ger.:*** Simplotan†; ***Gr.:*** Fasigyn; ***Hong Kong:*** Fasigyn; ***India:*** Amebamagma; Enidazol; Fasigyn; Tiniba; Tinidafyl; Tinidol†; Tinifas; Tinvista; ***Indon.:*** Fasigyn; Flatin; ***Israel:*** Fasigyn; Protocide; ***Ital.:*** Fasigin; Trimonase; ***Malaysia:*** Fasigyn†; Tindol; ***Mex.:*** Amebysol; Ametricid†; Estovyn-T; Fasigyn; Induken†; Trinigyn; Triseptil; ***Neth.:*** Fasigyn†; ***NZ:*** Dyzole; ***Port.:*** Fasigyn; ***Rus.:*** Fasigyn (Фазижин); Tiniba (Тиниба); ***S.Afr.:*** Fasigyn; ***Singapore:*** Fasigyn; ***Spain:*** Tricolam; ***Swed.:*** Fasigyn; ***Switz.:*** Fasigyne; ***Thai.:*** Asiazole-TN; Fasigyn; Funida; Idazole; Sporinex; Tinazole; Tini†; Tonid; Trichonas; Tricogyn; Tricozone; Trigyn†; ***UK:*** Fasigyn; ***USA:*** Tindamax; ***Venez.:*** Cinabel†; Fasigyn; Pangamil.

Multi-ingredient: ***Arg.:*** Aduar; Fasigyn Nistatina; Gynormal; Helmint Compuesto; Ladylen; Mebutar Compuesto; Nistinol; Tru Compuesto; ***Braz.:*** Amplium-G; Anfugine; Cartrax; Colpolase; Duozol; Facyl M; Ginec†; Gino Pletil; Ginometrim Oral†; Ginosutin M; Gynomax; Gynopac; Poliginax; Seczol; Takil; Tizonil M†; Travogyn; Trinizol M†; ***Chile:*** Doxifen; Famidal; Famidal Ad†; Ginecopast; Ginecopast Dual; Ginedazol; Ginedazol Dual; Medidos; Mizonase; ***India:*** Biocip-TZ; Bioflox-TZ; Candizole-T; Cipgen TZ; Ciplox TZ; Ciptini; Citizol; Entrolate†; Forcan TZ; Genflox TZ; Helipac; Nor T; Norflox TZ; Normax TZ; Ofler-TZ; Oflox TZ; Olfi TZ; OTC HP Kit; Parabact; Pylokit; Tinidafyl Plus; Tinvista-CF; Tinvista-NF; Wotinex; ***Indon.:*** Fasigyn-Nystatin; ***Ital.:*** Fasigin N; ***Malaysia:*** Pylobact Combi; ***Mex.:*** Afumix; Fasigyn VT; Mebeciclol; ***Rus.:*** Pylobact (Пилобакт).

Toltrazuril (BAN, USAN, rINN)

Bay-Vi-9142; Toltrazurilo; Toltrazurilum. 1-Methyl-3-(4-{*p*-[(trifluoromethyl)thio]phenoxy}-*m*-tolyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.

Тольтразурил

$C_{18}H_{14}F_3N_3O_4S$ = 425.4.
CAS — 69004-03-1.
ATC Vet — QP51AJ01.

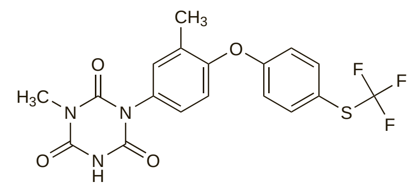

Profile

Toltrazuril is an antiprotozoal used in veterinary practice for the treatment of coccidiosis in poultry and piglets, and for the treatment of isosporiasis in piglets.

Tryparsamide (rINN)

Glyphenarsine; Triparsamida; Tryparsam.; Tryparsamidum; Tryparsone. Sodium hydrogen 4-(carbamoylmethylamino)-phenylarsonate hemihydrate.

Трипарсамид

$C_8H_{10}AsN_2NaO_4,\frac{1}{2}H_2O$ = 305.1.
CAS — 554-72-3 (anhydrous tryparsamide); 6159-29-1 (tryparsamide hemihydrate).

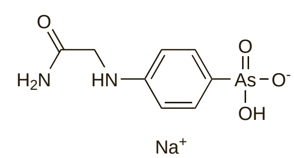

(anhydrous tryparsamide)

Profile

Tryparsamide, a pentavalent arsenical compound, is a trypanocide which penetrates into the CSF and has been used with suramin in the treatment of late-stage African trypanosomiasis due to *Trypanosoma brucei gambiense*, as an alternative to melarsoprol or eflornithine (see p.827). However, because of its toxicity, especially the risk of blindness resulting from damage to the optic nerve, melarsoprol or eflornithine are preferred.

For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p.2260. Like melarsoprol, tryparsamide can cause encephalopathy.

Antivirals

Common cold, p.850
Encephalitis, p.850
Gastro-enteritis, p.850
Haemorrhagic fevers, p.850
Hepatitis, p.851
Herpesvirus infections, p.853
  Cercopithecine herpesvirus 1 infections, p.853
  Cytomegalovirus infections, p.853
  Epstein-Barr virus infections, p.854
  Herpes simplex infections, p.854
  Varicella-zoster infections, p.855
HIV infection and AIDS, p.856
  HIV-associated infections and complications, p.857
  HIV-associated malignancies, p.858
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Influenza, p.859
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Warts, p.861

The drugs described in this chapter are used in the treatment of viral infections; they may also be used to provide protection, usually for a brief period only, against infection. Drug treatment has to be started early in the infection to be effective and inhibit the replicating virus. There is little evidence that antiviral drugs affect latent or nonreplicating viruses. They do not provide an alternative to available immunisation for the long-term prophylaxis of viral infection—for details of such treatment see the chapter on Vaccines Immunoglobulins and Antisera, p.2201.

Choice of Antiviral

Antiviral drugs are effective for the treatment and prophylaxis of a range of viral infections as described below. Non-specific symptomatic and supportive treatments are also important in the management of viral infections. Those viral infections not amenable to antiviral drug therapy include mumps, poliomyelitis, rabies, and rubella.

Common cold

The common cold is a term used for viral upper respiratory tract illness. Rhinoviruses are the commonest cause in all age groups. Adenoviruses, coronaviruses, enteroviruses, and metapneumovirus may also be responsible. Infecting organisms in these groups may be of many different serotypes.

Colds are usually self-limiting and last for 4 to 10 days. Symptoms include nasal discharge and stuffiness, sneezing, sore throat, and cough (see also p.1547); there is little or no malaise, headache, or fever. Colds may predispose to concurrent or subsequent bacterial infection of the upper respiratory tract; exacerbation of asthma or chronic obstructive pulmonary disease may also occur. Acute otitis media or acute sinusitis may result from obstruction of the Eustachian tube and mucosal swelling.

The successful development of a single cure or vaccine is unlikely, given the variety of causative viruses and large number of serotypes. Treatment is symptomatic. Analgesics, cough suppressants, antihistamines, and decongestants relieve symptoms but do not tend to reduce the duration of illness. Antibacterial and antiviral therapy has consistently failed to show any benefit and antibacterials are indicated only if there is secondary bacterial infection.[1] Very large doses of vitamin C have been widely used to prevent and treat colds but a systematic review[2] has concluded that, despite some evidence of benefit in published studies, its failure to reduce the incidence of colds in the normal population indicated that routine high-dose prophylaxis was not justified for community use; it might, however, be of use in persons exposed to brief periods of severe physical exercise or to cold environments. For treatment, no benefit has been found for doses up to 4 g, although one study reported equivocal benefit from a dose of 8 g given at the onset of symptoms.[2] Other drugs[3] tried have included mast-cell stabilisers, interferon alfa-2b, and zinc lozenges. Intranasal interferons have shown some benefit in prophylactic use, but high incidences of unacceptable nasal adverse effects have resulted in interferons failing to fulfill their early promise. Results of studies of zinc treatment have been inconclusive, although 1 study reported benefit from zinc nasal gel.[4] Similarly, there is little consistent evidence to support the use of *Echinacea* for treatment or prevention of colds.[5,6] However, available *Echinacea* products differ greatly and there is some evidence that treatment with those based on the aerial parts of *E. purpurea* might be effective in adults if started early.[5] Pleconaril, a viral capsid binder, has also been studied but there have been concerns with the oral formulation over viral resistance and interactions with oral contraceptives; the intranasal formulation appears more promising.[7]

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Encephalitis

Encephalitis refers to an acute inflammatory process affecting the brain parenchyma; it is distinct from meningitis which is an inflammation of the meninges. Meningoencephalitis involves both the brain parenchyma and meninges. Viral infection is the commonest cause of encephalitis,[1-4] with the herpes simplex virus (p.854) being the commonest organism involved in immunocompetent individuals. Other viruses that may cause encephalitis include enteroviruses (e.g. poliovirus), Epstein-Barr, influenza, Lassa fever, measles and mumps (paramyxoviruses), rabies, rubella, and varicella zoster. CMV and HIV cause encephalitis almost exclusively in immunocompromised individuals. In the 1990s, Hendra virus and Nipah virus, which belong to the paramyxoviridae family, were newly discovered causes of encephalitis. The reservoir for these viruses is *bats*, but transmission to humans can occur via close contact with secondary hosts such as *horses* and *pigs*. A group of viruses known as the arthropod-borne encephalitis viruses (arboviruses) may cause infections in which encephalitis is a major clinical feature. They include:

- bunyaviruses including California encephalitis virus and La Crosse virus (both transmitted by mosquitoes)
- flaviviruses (previously arbovirus Group B) including Japanese encephalitis virus, St Louis encephalitis virus, Murray Valley encephalitis virus, Rocio virus, and West Nile virus (all transmitted by mosquitoes) and the tick-borne viruses of this group, louping ill virus, Powassan virus, and the Eastern and Western subtype viruses
- reoviruses including Colorado tick fever virus (transmitted by ticks)
- togaviruses including Eastern, Western, and Venezuelan equine viruses (transmitted by mosquitoes)

In endemic regions viral encephalitis should be suspected in patients presenting with fever, headache, neck rigidity, altered level of consciousness (which may range from drowsiness to coma), and signs of diffuse cerebral dysfunction (hallucinations, psychosis, personality changes, and agitation). Seizures are common and patients who recover from encephalitis may be left with permanent neurological damage.

Since herpes simplex virus is the commonest cause of viral encephalitis, it is recommended that patients with encephalitis be given intravenous aciclovir empirically until the causative virus has been identified. (Antibacterial treatment for meningitis may also be given empirically until the cause of symptoms has been established.) No specific treatment exists for non-herpetic encephalitis (although investigational treatments, including passive immunisation and the use of inhibitory RNA molecules, are under development[5]), and patients must be managed with vigorous supportive care. Corticosteroids are advocated in some circumstances,[4] but their use is controversial. Pleconaril is under investigation for use in enteroviral encephalitis. Control of mosquito and tick populations in endemic areas and minimising contact with these vectors are important means of preventing infections. Japanese encephalitis vaccine and tick-borne encephalitis vaccine are available for active immunisation of individuals at risk of infection and tick-borne encephalitis immunoglobulins are available in some countries for passive immunisation against infection.

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5. Gould EA, *et al.* Does antiviral therapy have a role in the control of Japanese encephalitis? *Antiviral Res* 2008; **78:** 140–9.

Gastro-enteritis

Gastro-enteritis (inflammation of the stomach and intestines) may be caused by viruses, bacteria, or protozoa.[1-3] Viral gastro-enteritis is an important cause of diarrhoea, especially in children and immunocompromised patients. Viruses causing diarrhoea and other gastrointestinal symptoms include adenovirus, astrovirus, calicivirus (such as norovirus and sapovirus), and rotavirus. Rotavirus infection is recognised as a prominent cause of endemic acute diarrhoea in infants and young children and may occasionally cause acute or chronic diarrhoea in AIDS patients. Infection may be subclinical, although symptomatic rotavirus infection usually presents with fever and vomiting for 2 to 3 days, followed by watery diarrhoea that lasts for 4 to 5 days. Other symptoms include abdominal cramps and headache. Noroviruses (such as the Norwalk virus) are a more common cause of viral gastro-enteritis in older children and adults, but do not appear to cause severe disease in infants. They have been the cause of waterborne outbreaks of gastro-enteritis in nursing homes, military bases, and cruise ships. Sapoviruses (such as the Sapporo virus) are more commonly seen in young children. While illness resulting from these viruses is usually mild and lasts for 24 to 72 hours, the presenting symptoms are usually nausea and abdominal cramps. Other symptoms include diarrhoea, vomiting, headache, myalgias, and low-grade fever. CMV is an important cause of diarrhoea in AIDS (see HIV-associated Wasting, below).

In acute diarrhoea of any cause it is most important to maintain hydration by preventing and replacing fluid and electrolyte loss, especially in infants and the elderly (see p.1694). For further discussion see Oral Rehydration Solutions, p.1672. Antivirals are not used in the management of viral diarrhoeas, except for that caused by CMV, where ganciclovir, valganciclovir, or foscarnet may be beneficial. A 3-day course of oral nitazoxanide was found to significantly reduce the duration of rotavirus disease in young children.[4] Frequent handwashing and good personal hygiene may prevent person-to-person spread of infection. Washing of contaminated clothing and surfaces, and boiling of contaminated water will also assist in preventing infection. Several live oral rotavirus vaccines (p.2236) for use in the prevention of childhood diarrhoea have been developed and some are now licensed.

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4. Rossignol J-F, *et al.* Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. *Lancet* 2006; **368:** 124–9.

Haemorrhagic fevers

The viral haemorrhagic fevers are a group of viral illnesses characterised by a febrile illness that in some patients may be followed by severe bleeding, progressive organ failure, and death. The viruses are typically transmitted by mosquitoes, ticks, or rodents, and are largely geographically restricted. The more important viruses responsible for haemorrhagic fevers in man include:

- arenaviruses causing South American haemorrhagic fever syndromes (including Argentine, Bolivian, Brazilian, and Venezuelan haemorrhagic fever) and Lassa fever (transmitted by rodents)
- filoviruses causing Ebola and Marburg haemorrhagic fever, the natural host for which is unknown

- flaviviruses (previously arbovirus Group B) causing dengue fever and yellow fever (transmitted by mosquitoes), and Kyasanur forest fever and Omsk haemorrhagic fever (transmitted by ticks)
- hantaviruses causing haemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (transmitted by rodents)
- nairovirus causing Crimean Congo haemorrhagic fever (transmitted by ticks)
- phlebovirus causing Rift Valley fever (transmitted by mosquitoes)

Specific symptoms and the incubation time vary according to the infecting virus; in general the incubation time is short (up to 21 days but commonly less than 7 days) and followed by sudden (or, in the case of Lassa fever, more gradual) onset of fever, headache, myalgia, rash, and gastrointestinal disturbances such as abdominal pain, anorexia, diarrhoea, nausea, and vomiting. In patients who develop severe haemorrhagic manifestations (skin or mucosal bleeding, haematemesis, haematuria, or melaena), hepatitis, circulatory, renal, and respiratory failure, and coma are common. Depending on the causative virus, jaundice (yellow fever and Crimean Congo fever), muscle and joint pains (dengue fever), or pulmonary symptoms (hantavirus) may be more pronounced. Mortality is variable and ranges from less than 5% in dengue haemorrhagic fever and Lassa fever with optimal supportive care, to 15 to 30% in yellow fever and Crimean Congo haemorrhagic fever, and 70 to 80% in severe Ebola and Marburg virus infections.

Infection precautions, source isolation, and optimal supportive care are cornerstones of the management of viral haemorrhagic fevers. Vector control and prevention of bites are very important. There is generally no specific drug treatment for haemorrhagic fevers, although ribavirin may reduce mortality in patients with Lassa fever or haemorrhagic fever with renal syndrome, and possibly in Crimean Congo and Bolivian haemorrhagic fevers. Vaccines have been developed for the active immunisation of individuals at risk of Argentine haemorrhagic fever, Rift Valley fever, and yellow fever, and others are being developed for dengue fever and haemorrhagic fever with renal syndrome. Studies are ongoing for a vaccine against Ebola and Marburg viruses. Crimean Congo haemorrhagic fever immunoglobulins are available in some countries for passive immunisation against the disease. Guidelines for the prevention, control, and treatment of dengue and yellow fevers have been produced by WHO[1,2] and related organisations.[3] Guidelines for the management of haemorrhagic fevers have been published for some European countries.[4,5] The Pan American Health Organization[6] and the CDC[7] have also produced guidelines for the management of hantavirus pulmonary syndrome.

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3. Lloyd LS. *Best practices for dengue prevention and control in the Americas*. Washington DC: Environmental Health Project, 2003. Also available at: http://www.ehproject.org/PDF/Strategic_papers/SR7-BestPractice.pdf (accessed 02/04/08)
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Hepatitis

Though hepatitis may have many causes, viral hepatitis describes infections caused by agents that primarily target the liver. Five hepatitis viruses are recognised to be primarily responsible for infection in humans and have been named hepatitis A, B, C, D, and E. Hepatitis may also occur as part of the clinical course of other viral infections, including CMV, Epstein-Barr virus, herpes simplex virus, rubella, varicella-zoster, and yellow fever infections.

Hepatitis A and E are spread via the faecal-oral route. Hepatitis B, C, and D are spread via contaminated blood and blood products, perinatal transmission, or sexual contact. All of these viruses may cause acute and occasionally fulminant hepatitis; hepatitis B, C, and D viruses can also cause chronic hepatitis. The herpesviruses may cause hepatitis during primary infection or during reactivation of a latent infection in immunocompromised persons. (For discussion on the management of herpesvirus infections, see p.853.) Yellow fever virus is transmitted by mosquitoes and may cause fulminant hepatitis in non-immunised persons.

Acute viral hepatitis results in hepatocyte necrosis and inflammation of the liver. Clinical presentation ranges widely from asymptomatic infection to fulminant hepatic failure. Symptomatic acute hepatitis is characterised by abdominal pain, anorexia, fatigue, jaundice, low-grade fever, nausea, vomiting, and raised liver enzymes (AST and ALT). Chronic viral hepatitis is commonly asymptomatic but may result in hepatic fibrosis, cirrhosis, or hepatocellular carcinoma. Acute and chronic hepatitis may be complicated by fulminant hepatitis and liver failure, characterised by hepatic encephalopathy, coma, and death. As HIV and hepatitis B and C share risk factors for transmission, there are a significant number of people co-infected with 2 or all 3 viruses. HIV and hepatitis B or C co-infected patients have been found to have higher rates of hepatitis-related morbidity and mortality, with accelerated progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[1]

Viral hepatitis can be **prevented** by active immunisation against hepatitis A, hepatitis B, and yellow fever. Vaccination against hepatitis A is recommended, for example, for travellers to endemic regions, haemophiliacs, and for those considered to be at high risk due to their occupation or lifestyle (see p.2214). Postexposure prophylaxis with hepatitis A immunoglobulin is recommended in some countries for household and intimate contacts of patients with hepatitis A infection, while others recommend normal immunoglobulins. Vaccination with hepatitis B vaccine is frequently recommended as part of the infant immunisation schedules and for non-immunised infants and adults at risk of infection (see, p.2216). Hepatitis B immunoglobulin is recommended for passive immunisation of individuals exposed to a patient infected with the hepatitis B virus and after liver transplantation in persons infected with the hepatitis B virus, in order to prevent hepatitis B virus induced damage to the grafted liver (see, p.2215). Yellow fever vaccination is recommended for persons at high risk of infection, including travellers to endemic areas and may be considered as part of the standard infant immunisation schedule in countries where the virus is endemic (see, p.2243).

The **treatment of acute hepatitis** infections is largely symptomatic, as no effective antiviral therapy is available. Acute hepatitis B infection resolves without therapy in the majority of immunocompetent adults. A small pilot study[2] reported rapid clinical and biochemical responses to *lamivudine* in 13 of 15 patients with severe acute hepatitis B infection. Acute hepatitis C is more commonly asymptomatic but, if diagnosed, therapy with an *interferon alfa* may be considered[3] as there is some evidence that they may reduce the risk of progression to chronic infection.[4] A study[5] in a small number of patients with acute hepatitis C concluded that if spontaneous clearance has not occurred by 12 weeks, a 6-month course of peginterferon alfa-2b should be given, as response rates to antiviral therapy are higher in patients with acute infection compared to those with established infection. The American Association for the Study of Liver Diseases (AASLD)[4] has stated that either interferon or peginterferon given for a period of at least 6 months should be considered for the treatment of acute hepatitis C if the infection persists 2 to 4 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[6] and by the Scottish Intercollegiate Guidelines Network.[7]

Treatment of chronic hepatitis B aims to achieve seroconversion from e antigen (HBeAg)-positive to e antigen-negative chronic infection (which is associated with lower rates of viral replication and lower rates of disease progression), to suppress viral replication, to delay the progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma, and to treat extrahepatic complications such as glomerulonephritis. Complete suppression of viral replication is important to reduce the risk of viral resistance. Treatment is only recommended in patients with active or advanced liver disease and with high levels of HBV DNA. Drugs used for the treatment of chronic hepatitis B include immune modulators (interferon alfa-2b and peginterferon alfa-2a) and nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir). Emtricitabine is being investigated for use in chronic hepatitis B and clevudine is under development.[8]

Interferon alfa was the first drug approved for the management of chronic hepatitis B. A meta-analysis[9] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HBeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels.[10] Studies have suggested that subcutaneous *peginterferon alfa* is as effective or slightly more effective than interferon alfa given subcutaneously.[10] Results from various studies[11] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[12] and HBeAg-negative patients with chronic hepatitis B,[13] when peginterferon alfa was given subcutaneously once weekly for 48 weeks.

Lamivudine has a similar efficacy to interferon but fewer adverse effects. Studies[14,15] have shown favourable effects on histologic, virologic, and biochemical features of the disease from long-term therapy, including decreased disease progression and progression to hepatocellular carcinoma in patients with cirrhosis or advanced fibrosis. In HBeAg-positive patients, treatment with lamivudine is generally continued for at least 6 months after seroconversion, while HBeAg-negative patients may need indefinite treatment due to high relapse rates when treatment is stopped.[10]

Studies with daily oral *adefovir dipivoxil* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 3.5 logs (factors of 10) in patients with HBeAg-positive chronic hepatitis B[16] and of about 4 logs in patients with HBeAg-negative chronic hepatitis B.[17] When adefovir dipivoxil was continued in HBeAg-negative patients for 144 weeks benefit was maintained whereas viral load rebounded in those patients who stopped treatment at 48 weeks.[17] Hepatitis B virus DNA was undetectable in 71% and 79% of patients after 96 and 144 weeks of treatment respectively.[17] Most HBeAg-positive and HBeAg-negative patients also had improvements in serum-ALT and liver histology.[16,17]

The most recent drugs to be approved for the treatment of chronic hepatitis B, including in patients with lamivudine-resistant disease, are entecavir and telbivudine. Studies with daily oral *entecavir* for 48 weeks have shown a mean drop in hepatitis B viral DNA of about 6.9 logs in patients with HBeAg-positive chronic hepatitis B[18] and of about 5 logs in patients with HBeAg-negative chronic hepatitis B.[19] Entecavir treatment continued through to 96 weeks, in those patients with HBeAg-positive hepatitis B, continued to show benefit.[20] In both these studies entecavir was found to be more potent than oral lamivudine in suppressing hepatitis B virus. *Telbivudine* was reported to be superior to lamivudine in patients with HBeAg-positive chronic hepatitis B and as effective as lamivudine in those with HBeAg-negative disease after 52 weeks of treatment.[21] A small open label study[22] with telbivudine or adefovir for 52 weeks, or adefovir for 24 weeks followed by telbivudine for 28 weeks, in patients with HBeAg-positive hepatitis B, reported greater and more consistent reductions in HBV DNA with telbivudine than with adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients given continuous telbivudine or who switched from adefovir to telbivudine after 24 weeks than in those given adefovir for 52 weeks.

The development of antiviral ***resistance*** is a concern with long-term nucleoside/nucleotide treatment. About 14% of patients who initially respond to lamivudine develop drug resistance within the first year of therapy and resistance increases to about 70% after 5 years of treatment; lamivudine is therefore generally not recommended as first-line treatment.[23] Adefovir dipivoxil showed no resistance after 1 year of treatment, but the rate increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively.[16,17,24,25] Long-term therapy with adefovir dipivoxil resulted in the development of resistance mutations in less than 6% of patients and it was effective in patients who had previously developed resistance to lamivudine.[17] Entecavir showed no resistance up to 2 years of treatment and the resistance rate with telbivudine is reported to be 2 to 4% after 1 year of treatment.[26] Combination therapy with different nucleoside and nucleotide analogues is being investigated in order to prevent drug resistance and improve efficacy.[27] The addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[13,28,29] The combination of lamivudine and adefovir was found to be as effective as lamivudine monotherapy.[30] The combination of lamivudine and telbivudine was less effective than telbivudine alone[31] but emtricitabine and adefovir was more effective than adefovir alone.[30]

While the AASLD[10] states that all the approved treatments may be given as initial therapy, their preferred ***choice*** is peginterferon alfa or the nucleoside analogues adefovir dipivoxil or entecavir, in adults with HBeAg-positive or -negative chronic hepatitis B; interferon alfa or the nucleoside analogues lamivudine and telbivudine may also be used. In children with HBeAg-positive chronic hepatitis B, standard interferon alfa or lamivudine are recommended. In patients who are HBeAg-positive interferon is given for a defined duration (interferon alfa is given for 4 months and peginterferon alfa for 12 months), while a nucleoside/nucleotide analogue is usually given for an additional 6 months after HBeAg seroconversion. Most patients who are HBeAg-negative will relapse after treatment is stopped. In these patients interferon is also given for a defined duration (both interferon and peginterferon alfa are given for 12 months), but treatment with a nucleoside or nucleotide analogue is indefinite. Patients who have not responded to interferon alfa (standard or pegylated) therapy may be re-treated with a nucleoside analogue. Those who fail to respond after 6 months treatment should be switched to an alternative regimen. Adefovir[23,32] or tenofovir[32] may be given with lamivudine in those patients with lamivudine-resistant hepatitis B virus. Interferon alfa is not recommended in patients with compensated cirrhosis as it may cause hepatitis flares and hepatic decompensation. Guidelines are also available for other countries.[33-36]

Hepatitis B patients co-infected with **hepatitis D virus** are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[37] with high-dose interferon alfa (9 million units) given 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[38]

Treatment of chronic hepatitis C aims to decrease viral replication or eradicate hepatitis C virus, delay the progression to cirrhosis, and thereby decrease the frequency of hepatocellular carcinoma, and to treat extrahepatic complications of infection. The first available treatment was *interferon* alfa-2b, and this was followed by interferon alfa-2a, given subcutaneously 3 times a week. Patients treated with these interferons had a 10 to 20% chance of obtaining a sustained virological response (SVR), but had a high relapse rate. The combination of daily oral *ribavirin* with non-pegylated interferon alfa improved the rate of SVR after 48 weeks of treatment to about 40%. Further improvements in the SVR rates to about 60% have been reported since the introduction of weekly subcutaneous peginterferon alfa given with daily oral ribavirin. Studies[39,40] have found peginterferon alfa and ribavirin (SVR of 54 to 56%) to be more effective than interferon alfa and ribavirin (SVR of 44 to 47%). Factors predictive of a poor SVR are viral genotype 1, a high pretreatment viral load, increased body-weight, and the presence of cirrhosis. A study[39] with peginterferon alfa-2b or interferon alfa-2b and ribavirin showed an SVR of 42% in patients with genotype 1, compared with about 80% in patients with genotypes 2 and 3. Furthermore, patients infected with hepatitis C virus genotype 1 require treatment for 48 weeks with the standard dose of ribavirin (1 or 1.2 g daily) compared with 24 weeks of ribavirin 800 mg daily in those infected with genotypes 2 or 3.[41] Other studies[42-46] suggest that SVR can be achieved in some patients infected with genotypes 2 and 3 with a 12 to 16 week course of treatment. This is particularly true for patients in whom hepatitis C virus RNA is undetectable after 4 weeks of treatment. In patients with genotype 1 infection, longer durations of therapy (up to 72 weeks), may be appropriate in slow responders (patients who achieved a 2 log fall in the viral load but in whom viral RNA is still detectable by week 12).[47,48] In one study,[47] a SVR rate of 44% was reported for slow responders who continued treatment for 72 weeks, compared with a SVR rate of 28% in those who received 48 weeks of treatment.

Detailed guidelines have been produced in the UK,[7,49,50] Canada,[51] and in the USA[4,52] for the management of chronic hepatitis C. They all recommend weekly subcutaneous peginterferon alfa plus daily oral ribavirin as the first choice of treatment in patients with moderate to severe chronic hepatitis C. For genotype 2 and 3 infection, 24 weeks of treatment is usually recommended[4,49] but some suggest that 12 or 16 weeks of therapy may be sufficient in patients with genotypes 2 and 3 with undetectable viral RNA at week 4.[7,52] For genotype 1, treatment for 48 weeks is generally recommended. An early prediction of treatment failure in patients with genotype 1 infection is detectable hepatitis C virus RNA with less than a 2-log fall in viral load after 12 weeks of treatment. Some[4,7,50] suggest that stopping treatment in these patients may be considered at this point, while the British Society for Gastroenterology recommends stopping treatment after 24 weeks if hepatitis C virus RNA is still detectable. Some guidelines[4,7] suggest re-treatment (with peginterferon and ribavirin) of nonresponders and relapsers who have significant fibrosis or cirrhosis and who initially received interferon with or without ribavirin. Patients with other genotype infections should be treated with combination therapy for 48 weeks.[50,52]

Thymalfasin is being investigated as an adjunct to conventional therapy for the treatment of chronic hepatitis B and C.

Treatment of chronic hepatitis in HIV co-infected patients. HIV infection reduces the efficacy of current therapies for **hepatitis B**; it decreases response to interferon alfa and increases the incidence of lamivudine-resistant hepatitis B mutations.[1] Guidelines for the management of HIV and hepatitis B co-infection have been developed by various expert groups.[53-55] The British HIV Association guidelines[53] discuss appropriate choice of antivirals and their activity against hepatitis B virus and HIV. In patients not requiring HIV therapy, hepatitis B treatment should be with drugs that have no anti-HIV activity. *Interferon alfa* for 4 to 6 months is considered suitable for non-cirrhotic HBeAg-positive patients but limited evidence suggests that peginterferon alfa may be more effective. Long-term treatment with *adefovir dipivoxil* may be given as an alternative to interferon therapy. Patients who require both HIV and hepatitis B therapy may be given *tenofovir* alone or with either *lamivudine* or *emtricitabine*, as part of, or in addition to, their antiretroviral regimen.[53] Successful treatment of HIV with HAART may result in severe exacerbation of hepatitis B in co-infected patients. Treatment of **hepatitis C** in HIV co-infected patients has been associated with an increased rate of adverse effects and reduced response rates. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[56-58] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[57,58] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[56] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[56,58] The British HIV Association guidelines[59] for the treatment and management of HIV and hepatitis C co-infection recommend combination therapy with *peginterferon alfa* and *ribavirin* for 48 weeks in patients with moderate liver disease and well controlled HIV disease. Similar recommendations have been made by the AASLD.[4] Other guidelines[7,60] recommend reassessment of virologic response at weeks 4 and 12 and that treatment should only be continued in those with an early virologic response. Some experts[60] suggest that shorter periods of treatment (24 weeks) may be considered for patients with genotypes 2 and 3. Patients with genotype 1 and 4 who have no virological response at 4 weeks but response at 12 weeks may be given a longer treatment course of 60 to 72 weeks. Significant haemolytic anaemia may occur with ribavirin, and therefore concurrent use with zidovudine should be avoided and when possible stavudine should be replaced. Didanosine should never be given with ribavirin due to potentially life-threatening complications, such as lactic acidosis, myopathy, neuropathy, pancreatitis, and steatosis.[59-61]

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Herpesvirus infections

Established herpesvirus pathogens discussed below include Cercopithecine herpesvirus 1, CMV, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus. Herpesviruses 6, 7, and 8 have also emerged as potential pathogens and have been associated with a variety of disorders including childhood febrile illnesses, various malignancies including Kaposi's sarcoma (p.675), and multiple sclerosis (p.892).

Cercopithecine herpesvirus 1 infections. *Cercopithecine herpesvirus 1* (herpesvirus simiae, monkey B virus, herpes B virus) is a herpesvirus that usually infects macaque monkeys, but may rarely be transmitted to man by laboratory accidents or bites or scratches from infected monkeys. Initial symptoms and signs may include vesicles at the site of the bite or scratch, fatigue, fever, headache, and myalgia. Lymphadenitis or lymphadenopathy, abdominal pain, nausea, and vomiting may occur. As the infection spreads to the CNS there is increasing neurological involvement that can lead to encephalitis, coma, and death. Those patients who survive usually have serious neurologic impairment.

Initial **treatment**[1,2] should be prompt with thorough cleaning of the wound or exposure site. Intravenous high-dose *aciclovir* or *ganciclovir*, followed by oral therapy, is recommended for symptomatic or culture-confirmed infection. Ganciclovir is recommended in patients who have signs or symptoms of peripheral nervous system or CNS involvement. Routine **prophylactic** use of antivirals is not recommended, although postexposure prophylaxis with oral *valaciclovir* started within a few hours of exposure and given for 14 days may be considered for potential exposures.

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Cytomegalovirus infections. Cytomegalovirus (CMV) is a member of the herpesvirus group. Infection may be by intra-uterine, perinatal, or sexual transmission, by oral contact with the saliva of infected individuals, by blood transfusion, or by transplantation of infected tissue. After infection, viral DNA becomes incorporated into the host cell DNA where it persists, with occasional reactivation, for the life of the individual. Primary infections in immunocompetent adolescents and adults are generally asymptomatic, although they may occasionally present as infectious mononucleosis, lymphocytosis, or lymphadenopathy. Most congenitally infected infants are also asymptomatic, but some may present with intra-uterine growth retardation, jaundice, hepatosplenomegaly, encephalitis, and thrombocytopenia. Conversely, CMV is a major cause of morbidity and mortality in immunocompromised persons, particularly transplant recipients and patients with AIDS where it may present as CMV retinitis, colitis, oesophagitis, hepatitis, pneumonitis, or neurological disease in the form of dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Pneumonitis is more common in transplant recipients while retinitis is most frequent in AIDS patients.

Treatment for CMV disease is usually only given to immunocompromised patients, in whom relapses are likely to occur after treatment is stopped due to the latent nature of the virus. Ganciclovir and its oral prodrug valganciclovir are used in the treatment of severe infections in transplant recipients and patients with AIDS but ganciclovir may cause neutropenia. Foscarnet is an alternative to ganciclovir with similar efficacy and does not produce myelosuppression, although nephrotoxicity and electrolyte disturbances are common. Cidofovir may also be used for the treatment of CMV retinitis, and has the advantage of intermittent use. However, long-term treatment may be limited by renal toxicity.

HIV-infected patients. US guidelines[1] for the **initial treatment** of ***CMV retinitis*** in HIV-infected adults and adolescents recommend, for immediate sight-threatening lesions, intra-ocular ganciclovir implants along with oral valganciclovir. For patients with peripheral retinal lesions, oral valganciclovir alone is recommended. Alternatives are intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, or intravenous cidofovir. For HIV-infected children, intravenous ganciclovir is recommended;[2] intravenous foscarnet is an alternative.

After induction therapy, **maintenance therapy** (secondary prophylaxis) is recommended in AIDS patients with CMV retinitis until immune reconstitution as a result of antiretroviral therapy has been achieved or for life if it is not. The drugs of choice for retinitis are oral valganciclovir or intravenous foscarnet, both of which provide protection for the contralateral eye. Alternatives are intravenous cidofovir or intravitreal injections of fomivirsen.[1] Maintenance therapy may be stopped in patients with inactive CMV disease who have an increase in CD4+ T lymphocyte count to 100 to 150 cells/microlitre sustained for 6 months or more, although continued ophthalmic monitoring should be performed. Maintenance therapy should begin again if the CD4+ T lymphocyte count falls below 100 cells/microlitre.[1]

Relapse of CMV retinitis in patients with persistent immunodeficiency is common and is generally due to poor penetration of drugs into the eye when given systemically, rather than drug resistance. Hence, ganciclovir intra-ocular implants, with re-induction by the same systemic therapy used previously, are recommended in patients who relapse after systemic treatment. An alternative drug should only be considered if drug resistance is suspected or toxicity precludes use of the initial drug. Combined ganciclovir and foscarnet may be considered for patients who are not suitable for other alternatives, but is associated with greater toxicity. In patients who relapse later in therapy due to drug resistance, repeated intravitreal injections of fomivirsen can be given, but should be combined with systemic therapy.[1]

In HIV-infected adults and adolescents, ***CMV colitis*** or ***oesophagitis*** should be treated initially with intravenous ganciclovir or foscarnet, or with oral valganciclovir.[1] Chronic maintenance therapy is not routinely recommended but should be considered if relapse occurs.[1] For ***neurological*** disease, starting therapy promptly is critical for an optimal clinical response. Combination treatment with intravenous ganciclovir and foscarnet is currently favoured. Maintenance therapy should be continued for life.[1] Treatment of CMV ***pneumonitis*** is usually reserved for patients with histological evidence of CMV disease who do not respond to treatment for other pathogens. The role of maintenance in these patients is yet to be established.[1]

In HIV-infected adults and adolescents, ***primary prophylaxis*** with oral ganciclovir can be considered for all patients who are CMV-seropositive and who have a CD4+ T lymphocyte count below 50 cells/microlitre.[3] The US guidelines[3] consider aciclovir and valaciclovir unsuitable for prophylaxis in patients with HIV infection, although preliminary studies have suggested that valaciclovir may be effective in these patients.[4]

Transplant recipients. Primary **prophylaxis** of CMV disease in high-risk patients, particularly transplant recipients, has been reported using intravenous ganciclovir,[5-7] valganciclovir,[8,9] foscarnet,[10] valaciclovir,[11-15] and CMV immunoglobulins.[16,17] Oral ganciclovir has also been used for primary prophylaxis and for *pre-emptive therapy* (treatment when active CMV infection is documented but disease has not yet been evident) in some transplant patients.[18-20] A systematic review[21] found that giving CMV immunoglobulins did not reduce the risk of CMV disease or all-cause mortality in solid organ transplant recipients and adding them to aciclovir or ganciclovir was not more effective than an antiviral given as monotherapy.

The British Transplantation Society has published recommendations for the prevention and management of CMV disease after ***solid organ transplantation***.[22] These recommend that CMV-seronegative recipients of a solid organ transplant from a seropositive donor should be offered primary prophylaxis. The following options are available in the UK and are recommended by the British Transplantation Society:[22]

- oral valganciclovir for 100 days (in heart, kidney, kidney/pancreas, or liver transplant recipients)
- valaciclovir for 90 days (heart, kidney, kidney/pancreas, liver, or lung)
- intravenous ganciclovir for at least 28 days (heart, kidney, kidney/pancreas, liver, or lung)
- high-dose oral aciclovir for 12 weeks (kidney)
- intermittent CMV hyperimmune globulin for 12 weeks (kidney)

Frequent monitoring and possible pre-emptive treatment, usually with intravenous ganciclovir, may also be required.[22]

The above regimens are also used to prevent CMV disease when the donor and recipient are both CMV-seropositive and the patient is being treated with antithymocyte globulin, antilymphocyte immunoglobulin, or muromonab-CD3. If these drugs are not used, no prophylaxis is needed for CMV-seropositive recipients of kidney, kidney and pancreas, liver, or heart transplants from seropositive donors; lung transplant recipients should be given chemoprophylaxis as for seronegative patients above.[22]

The British Transplantation Society also recommended oral ganciclovir for 90 days as an option for prophylaxis after heart, kidney, kidney/pancreas, liver, or lung transplant, but acknowledged in their recommendations that, during their preparation, the UK manufacturer ceased production of oral ganciclovir; it was, however, retained as an option in the recommendations in case of availability in the future.[22]

Recommendations have also been produced for the management of CMV infection in recipients of allogeneic ***stem cell transplantation*** by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation.[23] For treatment of CMV pneumonia, normal immunoglobulin is given with ganciclovir, but normal immunoglobulin is not required in other forms of CMV disease.[23] For prevention of CMV disease, pre-emptive therapy with either intravenous ganciclovir or foscarnet rather than primary prophylaxis, is the recommended approach. Intravenous ganciclovir is, however, effective for primary prophylaxis but should be reserved for patients at high risk of developing disease. Aciclovir or valaciclovir may also be used for primary prophylaxis but their use must be combined with monitoring and pre-emptive therapy with either intravenous ganciclovir or foscarnet. If, however, ganciclovir has been given for primary prophylaxis then foscarnet should be used for first-line pre-emptive therapy. The use of valganciclovir for primary prophylaxis is under investigation, but if it is given then foscarnet should be used subsequently for first-line pre-emptive therapy. Cidofovir may be used as second-line pre-emptive therapy.[23]

CMV vaccines are currently in development.

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Epstein-Barr virus infections. Epstein-Barr virus (EBV) is a DNA virus of the herpesvirus group occurring worldwide. EBV is the causative agent in infectious mononucleosis and many people acquire a non-symptomatic infection, frequently in childhood. After primary exposure the individual becomes a lifelong carrier of the virus. Chronic EBV infection, particularly in immunocompromised individuals, is associated with several malignant diseases including Burkitt's lymphoma, nasopharyngeal carcinoma, lymphoproliferative diseases, Hodgkin's disease, T-cell lymphomas, and some gastric cancers. EBV is also associated with chronic interstitial pneumonitis in infants with AIDS and with oral hairy leucoplakia and CNS lymphomas in older AIDS patients.

Infectious mononucleosis (glandular fever) is an acute, self-limiting, lymphoproliferative infection that is seen when primary infection occurs in adolescents or young adults.[1] Transmission is by intimate oral contact and the incubation period ranges from 30 to 50 days. Illness is characterised by fever, sore throat, and lymphadenopathy. Other signs and symptoms include malaise, myalgias, jaundice, rash, and hepatosplenomegaly. Symptoms may last for about 2 to 3 weeks and most patients recover uneventfully with only supportive treatment, although fatigue may continue for some months. Complications, including encephalitis, anaemias, or cytopenias, may occur in a few patients but are rarely fatal. Very rarely the illness may become chronic. Chronic active EBV is defined as severe illness lasting longer than 6 months, evidence of major organ involvement, and elevated titres of antibody to EBV. Prognosis in these patients is poor and many die due to progressive pancytopenia and hypogammaglobulinaemia, or lymphomatous disease.

There is no specific **treatment** for EBV infections[1] although various experimental approaches have been investigated.[2] Treatment is generally symptomatic: hydration, paracetamol or NSAIDs, and throat lozenges or sprays. A meta-analysis[3] of five randomised controlled studies involving 339 patients with mild, moderate, or severe EBV infection, found that patients who took aciclovir had less oropharyngeal shedding, but clinical benefit was marginal and not sustained on stopping treatment. In a small number of patients with chronic active EBV, ganciclovir[4,5] and interferons[6,7] appeared to have a beneficial effect on symptoms or EBV replication. Corticosteroids are generally not indicated in uncomplicated EBV infection[8] but may be useful in patients with airways obstruction.[1,9] They may also be considered in systemic complications such as autoimmune haemolytic anaemia, aplastic anaemia, and thrombocytopenia and some also consider that they may be used for CNS involvement, myocarditis or pericarditis. However, concern has been expressed that they may impair immunity, resulting in a larger reservoir of latent virus and thereby potentially increasing the risk of developing EBV-related tumours in later years.

Concurrent throat infection with streptococci should not be treated with amoxicillin or ampicillin since they may cause a maculopapular rash in patients with infectious mononucleosis.

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Herpes simplex infections. Herpes simplex virus (HSV, herpesvirus hominis) is a DNA virus belonging to the herpesviridae family and occurs worldwide.[1] HSV can be divided into serotypes HSV-1 and HSV-2. Both viruses establish chronic infection of sensory nerve ganglia from where reactivation may occur by various triggers such as stress, bacterial infection, fever, irradiation (including sunlight), menstruation, and immunosuppression.

Herpes is characterised by an initial, primary infection, which may be followed by recurrent episodes in the same area. **Primary** HSV infection is acquired through direct contact with lesions or mucosal secretions of persons with active HSV lesions or persons shedding virus asymptomatically. Primary HSV-1 infections usually occur in the perioral area, and HSV-2 in the genital area, but infection may be acquired at other sites, including the fingers (whitlow), and rectum (herpes proctitis) after anal intercourse. The incubation period for both viruses ranges from 2 to 12 days and most primary HSV infections are asymptomatic.

- HSV-1 commonly causes symptomatic *oropharyngeal herpes* presenting as acute gingivostomatitis or pharyngitis and characterised by lesions of the buccal and gingival mucosa, fever, and cervical adenopathy.

  HSV-1 infections are common among immunocompromised patients, especially organ transplant recipients and those undergoing chemotherapy. In these patients infection may be more severe with extensive mucocutaneous and disseminated disease.
- *Genital herpes* is characterised by a painful ulcerative rash, and may be accompanied by dysuria, vaginal or urethral discharge, and tender inguinal lymphadenopathy. Genital herpes is most commonly caused by HSV-2 but may also be caused by HSV-1. Genital herpes tends to be more extensive when caused by HSV-2 and may include complications such as aseptic meningitis, disseminated disease, extragenital lesions, and bacterial superinfection.

  Herpes lesions are common among HIV-positive patients and may be severe, painful, and atypical; HSV recurrences and asymptomatic shedding are also increased.
- *Ocular herpes* is generally caused by HSV-1. It usually affects only one eye and most often occurs on the cornea resulting in epithelial or stromal keratitis. Epithelial keratitis usually heals without scarring whereas stromal keratitis infection involves the deeper layers and may lead to scarring, loss of vision, and occasionally blindness. Less commonly, HSV may also cause uveitis, chorioretinitis, or acute necrotising retinitis.
- HSV has been identified as one of the commonest causes of Bell's palsy and acute, sporadic viral *encephalitis*. Both HSV-1 and HSV-2 may cause encephalitis and if left untreated it is often fatal or may result in neurologic sequelae, especially in those over 35 years of age.
- *Neonatal herpes* may result from transmission of HSV-2 (or HSV-1) from mother to child during the perinatal period. Risk of neonatal herpes is highest when the mother develops primary genital herpes near the time of delivery whereas risk is much reduced with recurrent episodes. Neonatal herpes is a severe disseminated infection and often results in CNS disease. Untreated it is often fatal and survivors often have persistent ocular disease.

Recurrent herpes results from **reactivation** of latent infection and is usually milder and the duration is shorter than the primary infection. Reactivation is frequently associated with prodromal signs and symptoms, ranging from a mild tingling sensation to shooting pains. Systemic symptoms and lymphadenopathy are rare. *Herpes labialis*, also known as fever blisters or cold sores, are the most common infection resulting from reactivation of HSV-1. Recurrence of genital herpes is more likely with HSV-2 than HSV-1 infections.

Management. The most widely used antiviral for herpes simplex infections is aciclovir. Alternatives with improved bioavailability include famciclovir and valaciclovir. Antiviral treatment of primary herpes simplex infections, while relieving symptoms and reducing the duration of viral shedding, does not prevent recurrences. Antiviral therapy is generally more effective for primary infections than for recurrences, and should be given as early as possible during the course of an active infection, preferably within 3 days of the onset of symptoms. Resistance to aciclovir is emerging, mainly in immunocompromised patients.[2] Herpes simplex vaccines have also been tried but with generally disappointing results.

- **Orofacial herpes simplex infection.** Primary mucocutaneous HSV infection can be treated with topical, oral, or intravenous aciclovir. Oral famciclovir and valaciclovir have similar efficacy to oral aciclovir and are recommended alternatives.[1] Mucocutaneous HSV in HIV co-infected patients may be treated with intravenous or oral aciclovir, oral famciclovir, or oral valaciclovir. Recurrent episodes of herpes labialis are usually self-limiting and rarely require antiviral therapy. In immunocompetent patients careful hygiene, symptomatic treatment with analgesics, and the use of antiseptics to reduce secondary infection will usually suffice. The use of sunscreens may also reduce the frequency of recurrences. If antivirals are used they should be started early in the prodromal phase. Topical antivirals, including aciclovir, penciclovir, and tromantadine, have been used and are most effective when started during the prodromal phase.[3] Docosanol may be a further alternative for topical use.[4] Oral antivirals (aciclovir, famciclovir, and valaciclovir) may shorten the duration of symptomatic lesions by about 1 day.[3] High-dose oral valaciclovir has also been reported to be effective for suppression of recurrences and may provide the convenience of single-day treatment.[5] In immunocompromised patients with primary symptomatic infection or recurrent episodes of infection, intravenous or oral aciclovir, oral famciclovir, or valaciclovir may be used. An oral antiviral (aciclovir, famciclovir, or valaciclovir) is recommended for patients with herpes labialis and concurrent HIV infection.[6]
- **Genital herpes** is usually treated with oral aciclovir, famciclovir, or valaciclovir.[6-9] Intravenous aciclovir is given for severe disease or neurological complications. A study[10] found that both oral aciclovir and oral valaciclovir were effective in suppressing the frequency of recurrences and amount of HSV shedding. However, treatment of the primary HSV infection appears to have no effect on subsequent recurrences. Symptomatic recurrences in patients with a recognisable prodrome may be aborted or the severity reduced by a 5-day course of oral aciclovir, famciclovir, or valaciclovir begun by the patient.[7-9] Alternative regimens include high oral doses of aciclovir for 2 days,[8,11] famciclovir for 1 day, or valaciclovir for 3 days.[7,8] Symptomatic HSV recurrences in HIV-positive patients respond more slowly to anti-HSV treatment and longer treatment courses and higher doses of antivirals are needed.[8,12]

  In HIV-negative patients without a prodrome, or those with frequent recurrences, continuous suppressive therapy with aciclovir, famciclovir, or valaciclovir should be considered.[7-9] Once-daily suppressive therapy with valaciclovir was found to significantly reduce the risk of transmission of genital herpes among heterosexual, HSV-2-discordant couples.[13] Suppressive therapy should be considered for all HIV-infected persons.[7,12]
- **Ocular herpes simplex infections** usually require treatment with antivirals and/or interferons. Topical antivirals include aciclovir, ganciclovir, trifluridine, and vidarabine; no one drug appears to be more effective than another.[14] Systemic antivirals include aciclovir, famciclovir, and valaciclovir. Other systemic antivirals that have been evaluated are ganciclovir, foscarnet, and cidofovir.[14] HSV epithelial keratitis can be treated with a topical antiviral, a topical interferon (alfa or beta), or a combination of both. Benefit appears to be similar after 7 days of treatment with either an interferon or antiviral monotherapy, but combination therapy with interferon and an antiviral produces faster healing than a topical antiviral alone.[14] Trifluridine eye drops are the treatment of choice for herpes simplex epithelial keratitis in HIV-infected patients.[6]

  Topical corticosteroid monotherapy is contra-indicated for epithelial keratitis as disease severity can be increased; however, the treatment for stromal keratitis does consists of both topical trifluridine and topical corticosteroids. The Herpes Eye Disease Study[15] reported that the addition of topical prednisolone to trifluridine reduced the risk of persistent or progressive stromal kerato-uveitis by 68%, while the further addition of oral aciclovir provided no additional benefit.[16] Stromal keratitis or iritis was not prevented by the addition of oral aciclovir in patients with epithelial keratitis and currently receiving topical trifluridine.[17] Oral aciclovir, however, was effective in reducing the rate of recurrent HSV ocular disease, particularly in patients with prior stromal keratitis,[18] and may be of benefit to patients in uveitis when added to topical corticosteroid and antiviral therapy.[19]
- **Severe or disseminated herpes simplex infections**, particularly in immunocompromised patients, require intravenous therapy. Aciclovir is given for CNS infections and disseminated HSV infections,[1,6,20] with foscarnet or cidofovir as alternatives for infections resistant to aciclovir.[6] Neonates with evidence of herpes infection should be given high-dose intravenous aciclovir.[7,9,20] Immunocompromised patients with frequent or disabling recurrences may benefit from prophylactic oral aciclovir or famciclovir.[6,20,21]

Prevention. Intravenous aciclovir is recommended for all HSV-seropositive patients undergoing allogeneic haematopoietic stem cell transplants to prevent reactivation of latent HSV. Aciclovir may also be considered for HSV-seropositive patients undergoing autologous haematopoietic stem cell transplantation who are at risk of developing severe mucositis from the conditioning chemotherapy.[22] Oral aciclovir, famciclovir, or valaciclovir may be given to patients who can tolerate oral therapy. There is a risk of neonatal herpes in the infants of mothers with genital herpes infection. Prophylactic use of aciclovir in late pregnancy is not routinely recommended[7] but may be considered in HIV-infected mothers with frequent recurrences.[21] Although antivirals reduce viral shedding and recurrence at labour and birth and the use of caesarean section there is no evidence they reduce the occurrence of neonatal herpes.[23]

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Varicella-zoster infections. Varicella-zoster virus (VZV) belongs to the herpesviridae and causes 2 separate diseases: chickenpox (varicella) and herpes zoster (zoster, shingles). Infection may be acquired through the respiratory tract via airborne droplets or by close contact with infected individuals. Primary infection with VZV usually occurs in childhood and results in chickenpox. In immunocompetent persons chickenpox is self-limiting and results in lifelong immunity. However, the virus is not eliminated and remains dormant within sensory nerve ganglia. In later life or in immunocompromised persons, reactivation of the virus from the sensory nerve may occur and give rise to nerve pain and a dermatomal rash (herpes zoster). Immunocompromised patients may develop a second episode of chickenpox.

The incubation period for *chickenpox* is about 14 to 15 days. In children it usually presents with a generalised rash, fever, and malaise. The rash rapidly progresses from macules to papules and then to vesicular lesions before crusting, with successive crops appearing over several days. Chickenpox acquired in childhood is commonly a mild disease lasting 3 to 5 days, with secondary bacterial skin infections the commonest complication. Chickenpox in adults may be more severe, and have a higher incidence of complications. Immunocompromised individuals may develop severe chickenpox with multiple organ involvement, high fever, more extensive vesicular skin eruption, severe pneumonia, and encephalitis.

Primary varicella infection in the first 20 weeks of pregnancy has been associated rarely with congenital varicella syndrome, characterised by skin scarring, local muscular atrophy, chorioretinitis, encephalitis, cortical atrophy, and microcephaly. Maternal infection until at least 5 days before delivery may result in a mild neonatal infection, while maternal infection from 7 days before to 7 days after delivery may result in a severe infection of the neonate with a reported fatality of about 30%.

Herpes zoster is characterised by painful vesicular eruptions in a dermatomal distribution. It may be preceded by a prodromal phase with fever and malaise or pain over the affected dermatome. Lesions continue to form over a period of 3 to 5 days, and disappear, often with a degree of scarring, after 10 to 15 days. Chronic pain that may persist after the rash has healed is termed postherpetic neuralgia (p.9) and occurs in about 10% of patients. Involvement of the trigeminal nerve can lead to sight-threatening ophthalmic herpes zoster. Herpes zoster may be more severe and extensive in immunocompromised patients but is rarely fatal.

Treatment. Recommendations for the treatment of ***chickenpox*** in children,[1] adults,[2] and during pregnancy[3] have been developed. Treatment in otherwise healthy patients is usually symptomatic using antipyretics, analgesics, and antipruritics and is aimed at reducing complications. Antibacterials may be required for secondary skin infections. Antivirals are not recommended for the treatment of uncomplicated chickenpox in otherwise healthy children.[1] However, oral aciclovir may shorten the duration of fever and the number of lesions when given within 24 hours of onset of symptoms.[4] Antivirals do not reduce the incidence of chickenpox-associated complications in otherwise healthy children but may be useful in adults or immunocompromised patients. Intravenous therapy may be used in severe chickenpox.

The place of antivirals in the treatment of ***herpes zoster*** is well established and guidelines on management have been produced.[5-7] Antiviral treatment can reduce the severity and duration of acute pain, minimise complications and propagation of the rash, and reduce viral shedding.[5] Systemic antivirals are recommended for all immunocompetent patients who are over 50 years of age, have moderate to severe pain or rash, or have nontruncal involvement. Treatment should be started within 72 hours of the onset of the rash and is usually continued for 7 to 10 days. Antiviral therapy may also be considered in those presenting 72 hours after the onset of the rash when there are skin, motor, neurological, or ocular complications, when new vesicles are still forming, in the elderly, or in those with severe pain.[7] Topical antivirals are not recommended.

Aciclovir may be given orally or intravenously, depending upon the severity of the infection. Oral famciclovir, valaciclovir, or brivudine are alternatives.[7] Bioavailabilities of these drugs are better than aciclovir and they also appear to be superior in terms of healing lesions and equally or more effective in relieving pain.[7-9]

There has been controversy over the use of oral aciclovir to prevent **postherpetic neuralgia** and ocular complications. A meta-analysis suggested that treatment of herpes zoster with oral aciclovir within 72 hours of the onset of rash could reduce the *incidence* of residual pain at 6 months by 46% in immunocompetent adults.[10] A more recent analysis[11] considered that there was only marginal evidence that aciclovir decreased the incidence of postherpetic neuralgia and that there was no reduction in incidence with either famciclovir or valaciclovir. It is, however, generally agreed that antivirals do reduce the *duration* of postherpetic neuralgia[11] and some experts recommend antivirals in patients at low risk for developing postherpetic neuralgia and other complications.[7] The addition of corticosteroids to antiviral therapy does not reduce the incidence or duration of postherpetic neuralgia, but may improve the rate of resolution of the neuritis or improve pain control.[12,13]

Severely **immunocompromised** patients or others at high risk of severe or disseminated herpes zoster should receive intravenous aciclovir. Oral aciclovir, famciclovir, or valaciclovir may be considered in less severely immunocompromised patients.[7] Sorivudine and brivudine are also effective against zoster infections.[14] Brivudine is as effective, if not more, than aciclovir in immunocompromised patients[15] but is not recommended in such patients because of a potentially fatal interaction with fluorouracil (and related drugs).[7] Sorivudine has been withdrawn from the market after deaths in patients also taking fluorouracil. Foscarnet may be of value in aciclovir-resistant varicella-zoster infections[16-18] although treatment failures have been reported.[19]

Ophthalmic herpes zoster is treated with an oral antiviral, given within 72 hours of the onset of the rash; additional treatment with topical aciclovir to the eye may also be considered. Oral aciclovir, famciclovir, and valaciclovir are all effective in reducing the pain associated with ophthalmic zoster.[20,21]

Prevention. Varicella-zoster immunoglobulins are used for the prevention of chickenpox in patients at high risk of developing complications, such as the immunocompromised, neonates whose mothers developed chickenpox 7 days before to 7 days after delivery, and in susceptible pregnant women after significant exposure. There have been reports of severe chickenpox occurring in patients undergoing corticosteroid therapy. In the UK, use of varicella-zoster immunoglobulins is recommended in persons exposed to the virus who have received high doses of corticosteroids within the previous 3 months[22] (see also Varicella, under Precautions for Corticosteroids, p.1494).

Varicella-zoster vaccines are available in some countries and in the UK vaccination is recommended for active immunisation against chickenpox in persons considered to be at high risk of either infection or complications, including healthy contacts of immunocompromised patients. In the USA, a 2-dose vaccination regimen is recommended as part of the primary immunisation schedule of infants and children. Routine vaccination is also recommended for persons over the age of 13 years without evidence of immunity[23] and a high-potency vaccine against herpes zoster is recommended for persons 60 years of age and older.[24] For further discussion of varicella-zoster vaccines, see p.2242.

Transmission of chickenpox to household contacts is not prevented by giving aciclovir to the primary case but there is evidence to suggest that transmission can be suppressed by giving aciclovir to susceptible contacts during the incubation period.[25,26] Although the need for such prophylaxis has been questioned, especially in otherwise healthy children,[27] prophylaxis or early treatment with antivirals may be useful for household contacts in whom the infection might prove to be more severe.[1,28,29]

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HIV infection and AIDS

The causative agent of AIDS (acquired immunodeficiency syndrome) is the human immunodeficiency virus (HIV; previously known as HTLV-III or LAV), a retrovirus transmitted by sexual contact, blood and blood products, the use of contaminated needles, or vertically from mother to fetus. Two subtypes of HIV have been identified. The most common is HIV-1, which occurs worldwide. HIV-2 is found mainly in West Africa and is associated with a slower progression to AIDS than HIV-1.

HIV uses the CD4 receptor and the CCR5 or CXCR4 co-receptors to enter T lymphocytes and monocytes/macrophages, where viral RNA is reverse transcribed into DNA and inserted into the host genome. Viral replication results in immune activation and progressive depletion of CD4+ T lymphocytes. Primary HIV infection is characterised by the development of non-neutralising HIV antibodies (seroconversion), and in some patients may manifest as a transient rash, sore throat, and lymphadenopathy (seroconversion illness). Primary HIV infection is usually followed by a largely asymptomatic chronic infection, during which persistent generalised lymphadenopathy may be noted. Chronic HIV infection is characterised by gradual depletion of CD4+ T lymphocytes resulting in progressive immunodeficiency. This may become clinically apparent when symptoms such as fatigue, weight loss, recurrent fever, diarrhoea, or thrush occur. Alternatively, patients may develop severe opportunistic infections such as pneumocystis pneumonia, toxoplasma encephalitis, oesophageal candidiasis, cryptococcal meningitis, CMV retinitis, *Mycobacterium avium* complex, recurrent bacterial pneumonia, pulmonary or extrapulmonary tuberculosis, or neoplasms such as Kaposi's sarcoma, cervical carcinoma, and lymphomas; these are collectively referred to as AIDS-defining illnesses. AIDS-defining illnesses generally do not occur until severe immunodeficiency is present (CD4+ T lymphocyte count of less than 200 cells/microlitre or less than 14% of the total lymphocyte count). Most AIDS-defining events can therefore be prevented if effective HIV treatment is started before the CD4+ count has fallen to this level. Since the availability of highly active antiretroviral therapy (HAART), the incidence of AIDS-defining illnesses has markedly declined. However, antiretroviral therapy may result in toxicity or paradoxical worsening of underlying opportunistic infections.

During the course of chronic HIV infection, measurement of the CD4+ count and HIV RNA (viral load) will aid prognosis. The absolute CD4+ count or CD4% reflects the susceptibility to opportunistic infections while a high HIV viral load is associated with a more rapid decline in CD4+ count and more rapid clinical disease progression. The HIV viral load is also used to monitor success of antiretroviral therapy, where the goal is complete suppression of viral replication (resulting in undetectable HIV viral loads). CD4+ counts and viral loads are both taken into consideration in the decision to start antiretroviral therapy.

TREATMENT.

The following discussion relates to the use of antiretrovirals in HIV infection and AIDS. The treatment of secondary and opportunistic infections and other complications is covered under the relevant sections, below.

Treatment strategies for HIV infection are changing rapidly and guidelines for the treatment of HIV infection have been published and frequently updated for the USA,[1-3] for the UK,[4] and by WHO[5-7] for resource-limited settings.

Data from clinical studies in support of treatment of *acute* HIV infection are limited. Treatment of the primary HIV infection may be beneficial in relieving symptoms due to HIV during the seroconversion illness; it may restrict damage to the immune system, reduce the viral load set point once treatment is stopped and reduce the rate of viral mutation and risk of HIV transmission to sexual partners.[8] The UK guidelines do not recommend early treatment of acute HIV infection, but suggest that patients be offered enrolment in clinical studies to evaluate the issue.[4] US guidelines[2] state that treatment of acute infection is optional.

In *chronic* infection, the goal of antiretroviral therapy is to prevent or reverse immunodeficiency, prevent opportunistic infections, and prolong survival. The decision of when to start antiretroviral therapy should be individualised to take into account patient-specific relative risks and benefits of treatment. Guidelines[1,2,4-6] recommend that antiretroviral treatment should be given to patients whose CD4+ counts have fallen below 200 to 350 cells/microlitre or who have symptomatic disease, irrespective of their viral load or CD4+ count. Treatment is generally not indicated for asymptomatic patients with a CD4+ count greater than 350 cells/microlitre but may be considered for patients with a viral load greater than 100 000 copies/mL.

Combination therapy with antiretroviral drugs aims to improve potency, minimise toxicity, and delay drug resistance. The drugs used in combination therapy are:

- nucleoside reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, and zidovudine) or the nucleotide reverse transcriptase inhibitor tenofovir
- HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir)

- non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine, and etravirine)
- the entry inhibitors, including the HIV-fusion inhibitor enfuvirtide, the CCR5-antagonist maraviroc, and the HIV-integrase inhibitors raltegravir and elvitegravir

Although ritonavir inhibits HIV-protease when given in high doses, it is almost exclusively used in low doses for its CYP450 inhibitory properties, to boost the plasma concentrations of co-administered HIV-protease inhibitors. Combination of three antiretrovirals, typically two nucleoside/nucleotide reverse transcriptase inhibitors (NsRTI/NtRTI) plus either a (boosted) HIV-protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), is referred to as ***highly active antiretroviral therapy*** (***HAART***). Such regimens have produced sustained reductions in viral load often to levels below the limit of detection, and have been associated with improvements in CD4+ count, immune function, and clinical well-being. This is reflected by the decline in morbidity and mortality among patients with HIV infection since the availability of HAART. Triple therapy regimens, consisting of at least 2 classes of antiretrovirals, are superior to monotherapy, dual therapy, or triple NRTI therapy. Quadruple therapy regimens may be of benefit in some patients but are likely to increase toxicity. Complete suppression of viral replication minimises the emergence of drug-resistant HIV.[9-11]

When considering combination antiretroviral therapy several factors need to be taken into consideration. Drug combinations should provide additive or synergistic antiviral activity without increased toxicity or pharmacokinetic interactions that may affect the efficacy of co-administered drugs. Drugs with maximal potency should be combined so as to minimise the risk of drug resistance developing. The patient's ability to adhere to a regimen and the likelihood of pregnancy should also be taken into consideration.

In the developed world the availability of co-formulations of zidovudine with lamivudine, abacavir with lamivudine, and tenofovir with emtricitabine, and concerns over the toxicity of stavudine and zalcitabine have resulted in most treatment-naive patients starting with one of these combinations. There has been a shift from zidovudine/lamivudine to abacavir/lamivudine or to tenofovir/emtricitabine because of concern over the adverse effects and long-term toxicity (lipoatrophy) associated with zidovudine. Similarly, among the NNRTIs, delavirdine is now rarely used and a shift from nevirapine to efavirenz has occurred because of the potential of nevirapine to cause severe skin and liver toxicity. HIV-protease inhibitors are almost exclusively used with ritonavir boosting. Giving amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, or tipranavir, with ritonavir, improves the pharmacokinetic properties and clinical efficacy of these HIV-protease inhibitors.

Although HAART regimens are generally most effective in antiretroviral-naive patients, good responses can also be achieved in treatment-experienced patients.[12] In patients who have an inadequate response to therapy, adherence needs to be carefully assessed and reasons for potential non-adherence addressed. If a patient has drug toxicity, intolerance to therapy, or for any other reason is unable to adhere to therapy, a change of drugs should be considered. Change of treatment should also be considered if the patient has a suboptimal virologic response to their current antiretroviral therapy and may be considered in those with limited gains or decreases in their CD4+ count or clinical deterioration while on fully suppressive regimens.

Choice of second-line regimen is essentially empirical, since there is a lack of evidence from controlled studies.[13] When a new regimen is started, 2 to 3 drugs should be included to which the patient has not been exposed or to which the virus is not resistant. A failing regimen of two NRTIs and an NNRTI may be replaced by a boosted HIV-protease inhibitor with one or two different NRTIs. When patients fail on an NRTI and a boosted HIV-protease inhibitor, consideration needs to be given to an increase in the dose of the HIV-protease inhibitor, substitution with a HIV-protease inhibitor with limited cross-resistance, and/or the addition of a drug with a different mechanism of action, such as the HIV-fusion inhibitor enfuvirtide.[1,2,4] Boosted tipranavir[14,15] or darunavir,[16] when used as part of a multi-drug regimen, result in better viral suppression and CD4+ count increases in patients with multidrug resistant HIV-1 infection than standard ritonavir-boosted HIV-protease inhibitors, particularly when given with at least one (preferably two) active agents such as enfuvirtide or etravirine.[17,18] Addition of a single antiretroviral drug to a failing combination regimen is generally not recommended because further resistance may result.[1,2,4]

While HAART maintains plasma viral load at undetectable levels in most patients, viral replication rapidly returns to pretreatment levels once treatment is stopped. Treatment interruption may be associated with a precipitous decline of CD4+ count, clinical disease progression, and the development of drug resistance. Structured treatment interruptions (or planned breaks) are generally not recommended in patients with HIV infection, even if drug-resistance results in chronic non-suppression of HIV RNA.[1,2,4,19] The continued effectiveness of any HAART regimen is dependent on strict adherence to treatment. The improved formulation and co-formulation of several antiretrovirals has reduced the pill burden and newer drugs tend to have fewer adverse effects. However, the cost of treatment is high and access to effective treatment in developing countries with high burdens of disease, although improving, remains limited.[5]

Newer antiretroviral drugs to further reduce pill burden and limit toxicity are in development. In addition, drugs with enhanced activity against resistant isolates, such as HIV-entry inhibitors (that inhibit the three steps of HIV entry: CD4 attachment, chemokine receptor binding, and membrane fusion) and HIV-integrase inhibitors are under investigation.[20,21] Interleukin-2 may improve the CD4+ count in patients with advanced HIV infection, or preserve CD4+ counts in patients with early HIV infection (see p.736). However, it is unclear whether this prevents opportunistic infections and the role of interleukin-2 remains to be defined. A number of vaccines aimed at preventing HIV infection or reducing the HIV viral load are currently under investigation (see AIDS Vaccines, p.2203).

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HIV-associated infections and complications. Infections. Patients with HIV infection and AIDS are at increased risk of specific bacterial, fungal, protozoal, and viral infections largely as a result of impaired cell-mediated immunity. With the introduction of antimicrobial prophylaxis and HAART there has been a significant decrease in the incidence of most AIDS-defining opportunistic infections, especially in the developed world. However, HIV-related opportunistic infections and deaths still occur in patients newly diagnosed with HIV infection, in those in the early course of HAART, in those non-adherent to their HIV treatment, or in those with drug-resistant HIV infection; deaths also result from non-opportunistic infections and chronic viral hepatitis.[1]

- Infections affecting the *lungs* include recurrent bacterial pneumonia (p.186), pneumocystis pneumonia (p.521), and pulmonary tuberculosis (p.196).
- Many pathogens cause *gastrointestinal-tract disease* in HIV-infected patients, including candida oesophagitis (p.518), CMV colitis (p.853), and amoebiasis (p.822), cryptosporidiosis (p.823), giardiasis (p.824), isosporiasis (p.824), or microsporidiosis (p.826).
- AIDS-defining *neurological* infections include AIDS dementia complex (HIV encephalopathy), cryptococcal meningitis (p.519), cerebral toxoplasmosis (p.826), and progressive multifocal leukoencephalopathy (see Infections in Immunocompromised Patients, p.859).
- *Systemic* opportunistic infections in AIDS patients include tuberculosis, coccidioidomycosis (p.518), histoplasmosis (p.519), and *Mycobacterium avium* complex infections (see Nontuberculous Mycobacterial Infections, p.181). CMV retinitis (p.853) may be a cause of blindness, while chronic herpesvirus infections (p.853) may affect the skin and gastrointestinal tract.

Recommendations have been published for both treatment[2,3] and prophylaxis[4] of opportunistic infections in AIDS patients. Recovery of immune function in patients responding to HAART may be sufficient to protect against certain opportunistic infections and to allow primary or secondary prophylaxis to be stopped.[1,5]

Other complications. Non-infectious complications of HIV infection include renal disease, metabolic and skeletal disorders, toxicities of HAART, and malignancies (below).

Black patients with HIV infection may develop chronic or end-stage *renal disease* due to HIV-associated nephropathy (HIVAN) or thrombotic microangiopathy. Acute renal failure is common in hospitalised patients with (opportunistic) infections, malignancies, or hepatitis C co-infection, while proteinuria is common in all HIV patients and may reflect an increased risk of cardiovascular events. Antiretrovirals, in particular tenofovir and indinavir, may cause renal dysfunction.[6-9] Guidelines for the management of chronic kidney disease in HIV-infected patients have been developed by the HIV Medicine Association of the Infectious Diseases Society of America.[6]

Metabolic complications associated with HIV infection and HAART include dyslipidaemia, abnormal glucose metabolism (insulin resistance, impaired glucose tolerance, and diabetes mellitus), and bone disorders (osteopenia, osteoporosis, and osteonecrosis); hepatic steatosis may occur with or without lipodystrophy in the form of lipohypertrophy (fat accumulation) or lipoatrophy (fat loss). HAART may occasionally cause lactic acidosis.[10,11]

Pancytopenia is commonly seen in patients with advanced HIV infection, and *neurological syndromes* such as aseptic meningitis, headache, neuropathy, myopathy, and Guillain-Barré syndrome, may occur at any stage of the infection.

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HIV-associated malignancies. There is an increased incidence of certain malignancies in patients with HIV infection. Malignancies commonly associated with HIV infection are Kaposi's sarcoma (p.675), Hodgkin's disease, non-Hodgkin's lymphoma and primary CNS lymphoma (see AIDS-related Lymphomas, p.657), invasive cervical cancer (p.663), and anal cancer (see Malignant Neoplasms of the Anus, p.666). Some tumours may regress in response to effective antiretroviral therapy. Guidelines for the management of HIV-associated malignancies have been issued by the British HIV association.[1]

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HIV-associated wasting. Severe malnutrition in HIV-infected patients is recognised as wasting syndrome[1-4] and has been defined as an involuntary loss of body-weight of 10% or more (of both lean and fat tissue) and may be associated with fatigue, fever, and diarrhoea (not explained by another cause). However, there is some debate as to whether it should be defined as the loss of 5 or 10% of usual weight and whether changes in body composition, rather than weight alone, better define the syndrome. Wasting is associated with morbidity and mortality in advanced HIV infection and AIDS. Wasting syndrome has been associated with inadequate oral intake, malabsorption syndrome, metabolic disorders, hypogonadism, and increased cytokine production. Weight loss and malnutrition tend to be less severe in patients taking HAART. However, loss of body cell mass may occur in patients given HAART and needs to be differentiated from fat redistribution (lipodystrophy).

Since HIV replication is central to the pathogenesis of wasting syndrome, antiretroviral therapy is indicated. Nutritional intervention, exercise, and drug treatment may be indicated in patients who have an incomplete response to antiretroviral therapy. Drugs that have been tried include growth hormone, the appetite stimulants dronabinol and megestrol, the growth hormone mediator mecasermin, steroid hormones (testosterone and testosterone analogues), synthetic anabolic steroids (nandrolone, oxandrolone, and oxymetholone), and drugs that decrease cytokine production such as pentoxifylline and thalidomide. A suggested initial approach to the management of wasting[3] is to increase dietary intake of protein or total calories. Nutritional supplementation and exercise should always be considered and encouraged before drug treatment is started. Testosterone replacement may be given to HIV-infected men with significant weight loss and low testosterone levels, and megestrol may be given to patients who are unable to voluntarily increase or maintain total energy intake. Other drug treatments such as growth hormone and anabolic steroids may be considered where rapid weight loss is associated with acute infection and in severe cases of continued weight loss refractory to non-drug therapies.

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HIV infection prophylaxis

Non-occupational exposure to HIV. Behavioural changes are the most effective methods of reducing the spread of HIV infection in the general population. These include the promotion of safe sex practices and needle exchange schemes for intravenous drug users. Guidelines have been published in the USA[1] for postexposure prophylaxis (PEP) after sexual activity, intravenous drug use, or other non-occupational exposure to HIV amongst the general population:

- a 28-day course of HAART is recommended for persons who have had non-occupational exposure to potentially infected body fluids of a person known or suspected to have HIV infection when there is a substantial risk of transmission and when the person presents within 72 hours of exposure
- for persons seeking care within 72 hours of non-occupational exposure from a person of unknown HIV status, or when such exposure would represent a substantial risk for transmission if the source were HIV-infected, it is recommended that risks and benefits of PEP be evaluated on an individual case basis
- PEP is generally not recommended for persons seeking care where there is no substantial risk for HIV transmission or for those presenting more than 72 hours after exposure (although it may be considered for persons seeking care after more than 72 hours if the exposure represents a substantial risk for transmission)

Guidelines for non-occupational PEP have also been produced in the UK[2] for exposure outside the healthcare setting and are similar to those for occupational exposures (see below); when given, PEP should be started as soon as possible after exposure.

Occupational exposure to HIV. The risk of seroconversion is estimated at about 0.3 to 0.4% after percutaneous contamination with HIV-infected blood and considerably less for accidents involving contamination of intact skin or mucous membranes. In view of potential toxicity of antiretrovirals, the decision whether to give PEP should balance the risk of infection against the potential drug toxicity and PEP should generally only be offered to intermediate to high-risk cases. Factors associated with increased risk of occupationally-acquired HIV infection include:

- deep injury
- visible blood on the device which caused the injury
- injury with a needle which had been placed in a source patient's artery or vein
- primary HIV infection or terminal HIV-related illness in the source patient

If PEP is given it should be started as soon as possible after the exposure. Zidovudine monotherapy has been extensively used for PEP and reduces seroconversion after percutaneous exposure by 79%. PEP with combination antiretroviral drugs is now preferred as it results in more complete suppression of viral replication and is more likely to afford some protection against drug-resistant HIV strains.

Guidelines for the UK[2] recommend a 4-week course of antiretroviral therapy after occupational percutaneous, mucous membrane, or broken skin site exposure to high-risk body fluids or tissues known to be, or suspected of being, infected with HIV. They advise that PEP emergency starter packs should contain two nucleoside reverse transcriptase inhibitors (NsRTIs) (zidovudine and lamivudine) and a boosted HIV-protease inhibitor (lopinavir-ritonavir). Nelfinavir was the recommended HIV-protease inhibitor of choice but it was recalled from the European market in June 2007. Alternative HIV-protease inhibitors include saquinavir and amprenavir.

Guidelines in the USA[3] recommend selection of PEP regimens based on the level of risk of transmission presented by the exposure and other considerations such as possible antiretroviral drug resistance in the source. Most occupational HIV exposures can be managed with a two-drug regimen, using two NsRTIs or one NsRTI and one nucleotide reverse transcriptase inhibitor (NtRTI). Although there are no definitive data to show increased efficacy of 3-drug PEP regimens over 2-drug regimens, the addition of further drugs may be considered for exposures that pose an increased risk of transmission or if antiretroviral drug resistance is likely. HIV-protease inhibitors are recommended as the preferred drug for inclusion into 3- or 4- drug regimens but the NNRTI, efavirenz, may be considered when resistance to HIV-protease inhibitors in the source person is known or suspected. Due to the higher risk for potentially serious or life-threatening adverse effects abacavir, delavirdine, nevirapine, zalcitabine, and the combination of didanosine and stavudine, are not recommended for PEP.

Measures aimed at reducing **vertical transmission** of HIV from mothers to their infants include antiretroviral therapy to the mother and baby, elective caesarean section, and avoidance of breast feeding when replacement feeding is acceptable, affordable, and safe.[4-8]

The risk of vertical transmission is directly proportional to the maternal plasma HIV viral load at the time of delivery, and very few HIV-infected children are born to mothers whose HIV viral load is undetectable (below 400 copies/mL). The benefit of elective caesarean section is therefore most profound in women with detectable or high HIV viral loads. In contrast, zidovudine monotherapy given during pregnancy and labour, and to the infant postpartum, reduces the rate of vertical transmission by about 70%, irrespective of maternal viral load or CD4+ count.[9,10] However, zidovudine monotherapy is suboptimal for mothers with high viral loads, in whom combination antiretroviral therapy should be used to prevent vertical transmission.

Guidelines for the management of HIV infection in pregnant women and for the prevention of transmission of HIV from mother to child have been developed for the USA[6] and the UK.[8] The US guidelines[6] recommend that zidovudine-based therapy is of proven benefit in preventing perinatal HIV transmission, but combination drug regimens should be considered the standard of care for both treatment of HIV infection in pregnant women and prevention of perinatal HIV transmission. Treatment to prevent the latter should be offered to all women, regardless of CD4 count:

- women who are taking HAART and become pregnant should continue with their regimen, although regimens with potentially teratogenic drugs such as efavirenz should be substituted in the first trimester, as should combinations with known adverse potential for the mother, such as stavudine/didanosine. Nelfinavir should be avoided because of concerns about potentially teratogenic contaminants from manufacturing. Treatment should be continued both during labour (with zidovudine given intravenously and other drugs orally), and postpartum
- women who have not had antiretroviral treatment and have indications for therapy should also begin HAART, subject to the same precautions as above; those who do not require HAART for their own health should be offered it for prevention of perinatal transmission, but treatment may be delayed until after the first trimester, and should be stopped postpartum unless indications for continuing it develop. If the regimen includes a long half-life NNRTI, consideration should be given to continuing NRTIs for 7 days after stopping the former
- women who have previously had antiretrovirals should be offered an HAART regimen based on resistance testing; use of zidovudine as a component of the regimen is recommended when feasible. Need for continuing therapy should be evaluated postpartum
- in all cases above, the *infant* should be treated with zidovudine intravenously or orally for 6 weeks, starting 6 to 12 hours after birth
- in women who have had no antiretroviral therapy before labour, treatment should be offered with:
  - *mother*: continuous infusion of zidovudine during labour; *infant*: zidovudine for 6 weeks started within 6 to 12 hours of birth

    or
  - *mother*: continuous infusion of zidovudine during labour, plus a single dose of nevirapine at onset; consideration should be given to adding lamivudine during labour and zidovudine and lamivudine for 7 days

postpartum, to reduce development of nevirapine resistance; *infant*: single oral dose of nevirapine at 2 to 3 days after birth, plus zidovudine for 6 weeks

- if the mother has no antiretroviral therapy either before or during labour, the infant should still be given zidovudine for 6 weeks, started as soon as possible after birth. The use of other drugs for prophylaxis in infants requires specialist consulation

While similar to those of the USA, the UK guidelines[8] recommend that zidovudine monotherapy combined with elective caesarean section may still be an option for pregnant women in whom HAART is contra-indicated and whose HIV viral load is less than 10 000 copies/mL, or for women not wishing to take HAART during pregnancy. Infants born to HIV-infected mothers should be given zidovudine for 4 weeks after birth. Alternative antiretroviral therapy may be given to infants whose mothers did not take zidovudine in their treatment regimen and triple therapy may be considered for infants whose mothers had no antiretroviral therapy or whose mothers are infected with drug-resistant HIV.

WHO has published guidelines on the use of antiretrovirals in pregnancy and for preventing HIV transmission to infants in resource-limited settings.[4,7] In countries where HAART is available, women with a CD4+ T lymphocyte count below 250 cells/microlitre and those with a CD4+ T lymphocyte count between 250 and 350 cells/microlitre who have other indications for antiretroviral treatment should start HAART during their pregnancy. The preferred regimen is zidovudine plus lamivudine and nevirapine. Women already taking antiretrovirals should continue their therapy; but consideration should be given to switching those who are in the first trimester of pregnancy and taking efavirenz to a nevirapine-containing regimen. Infants born to mothers taking HAART should be given zidovudine for 7 days from birth. Women in whom maternal HAART is not indicated, or those living in countries where HAART is not available, should be given short-course zidovudine starting at 28 weeks of pregnancy or as soon as feasible thereafter and continued into labour. A single dose of nevirapine should be given at the onset of labour to the mother followed by 7 days treatment with zidovudine and lamivudine to reduce the emergence of nevirapine resistance. Infants born to these mothers should be given zidovudine for 7 days from birth and a single dose of nevirapine within 72 hours of birth. Women presenting late in pregnancy and who have not received HAART or completed at least 4 weeks of zidovudine may be given one of the following regimens:

- a single dose of oral nevirapine plus oral zidovudine and lamivudine during delivery followed by 7 days postpartum treatment with oral zidovudine and lamivudine; the newborn should be given a single oral dose of nevirapine plus oral zidovudine for 4 weeks
- oral zidovudine and lamivudine during delivery, followed by 7 days postpartum treatment with oral zidovudine and lamivudine; the newborn should also get 7 days treatment with oral zidovudine and lamivudine
- a single dose of oral nevirapine at the onset of labour; the newborn should also have a single oral dose of nevirapine.

Infants born within 2 hours of the mother taking a single oral dose of nevirapine or to mothers who have taken less than 4 weeks of antiretroviral prophylaxis (or none at all), should be given a single dose of oral nevirapine immediately after birth plus 4 weeks of oral zidovudine.

Other measures necessary to minimise the transmission of infection include the rigorous selection of blood donors, microbiological screening of blood, and, where possible, heat treatment of blood products. Maternal vitamin A deficiency has been identified as a risk factor for vertical transmission in Africa (see p.1974). Nutritional intervention and vaginal cleansing during labour could reduce vertical transmission in regions where zidovudine therapy is not readily available.

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Infections in immunocompromised patients

Most viral infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Among the viral infections that may be a particular problem in immunocompromised patients are hepatitis, herpesvirus infections (including CMV and Epstein-Barr virus infections), measles, and RSV infections. For further information and treatment of these infections, see under the individual diseases. For secondary infections occurring in HIV-infected patients, see p.857.

Persistent infection with human **parvovirus B19** can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients; treatment with immunoglobulin has been reported to be successful.

Infection with a polyomavirus (JC virus)[1,2] can cause **progressive multifocal leukoencephalopathy**. Although no treatment has been consistently successful,[1] prolonged survival has been reported in patients receiving interferon alfa[3] and in those receiving HAART.[4-6] Cidofovir may be of benefit in patients unresponsive to HAART.[7,8]

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Influenza

Influenza is an acute respiratory-tract infection caused by RNA viruses of the family Orthomyxoviridae. Three types of influenza virus, A, B, and C, have been classified. Type A causes most infections in man; type B causes a similar though possibly milder infection than type A; type C generally only causes mild infection. Epidemic influenza is usually caused by the type A influenza virus. Outbreaks of influenza due to the type A virus occur in most years while those due to the type B virus tend to occur at intervals of several years. Influenza viruses are antigenically labile with the principal surface antigens, haemagglutinin and neuraminidase, undergoing frequent changes. Major changes (antigenic shifts) in these surface antigens occur periodically and are responsible for the emergence of the subtypes of virus which may cause pandemic influenza; minor changes (antigenic drift) occur more frequently and are responsible for the annual epidemic outbreaks of influenza.

Influenza is transmitted from person to person in respiratory droplets with an incubation period of 1 to 2 days. Infection with influenza A or B virus usually lasts for about 1 to 2 weeks and is characterised by sudden onset of fever, chills, headache, malaise, myalgia, dry cough, nasal obstruction, and a dry or sore throat. Infections are usually acute but self-limiting and persons with pre-existing immunity, or those who have received influenza vaccine, have less severe symptoms. Complications that may occur in the course of infection include primary viral pneumonia, secondary bacterial pneumonia, croup, exacerbation of asthma or chronic bronchitis, myositis, Reye's syndrome, and the toxic shock syndrome. Patients at high risk of complications include the elderly, those with heart disease or chronic chest disease, and immunocompromised individuals.

Since 1997, infection of humans with avian influenza virus H5N1 (so-called 'bird flu') has been reported, initially in Hong Kong. Avian influenza may cause severe illness and is associated with high mortality. Since then cases have also been reported in other Asian countries and in the near East. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic.[1,2] WHO[3,4] has developed detailed guidelines for the pharmacological management of avian influenza in humans. Similar guidelines for the management of an influenza pandemic have been developed in many countries.[5-7]

The most effective means of **preventing** influenza is to provide seasonal vaccination with *influenza vaccine* adjusted to take account of current antigenic drifts and shifts and to provide protection against both influenza A and B. WHO[8] recommends that elderly individuals and persons of any age who are considered to be at high risk of influenza-related complications should be vaccinated. Similar recommendations have been made in the UK[9] and USA.[10]

In healthy adults living in industrialised countries, protective efficacy of influenza vaccine is about 70 to 90%, and vaccination of the elderly living in the community reduces the number of hospitalisations by 25 to 39% and death by 39 to 75%.[8] No vaccine is currently available for avian influenza.[2,11]

Four antiviral drugs are available for the prevention of influenza: the M2 ion channel inhibitors, amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir. Antivirals appear to act independently of vaccination and provide additional barriers to the virus, but should not be used as a substitute for vaccination. They may be considered for postexposure prophylaxis, for seasonal prophylaxis in unvaccinated individuals at high risk, for persons who take care of those at high risk, and in vaccinated individuals if an influenza outbreak occurs less than 2 weeks after vaccination with an inactivated vaccine, or if circulating influenza strains are thought to be different to the vaccine strain. Prophylaxis with antivirals may also be considered in vaccinated immunocompromised individuals whose antibody response to the vaccine is likely to be incomplete.[11,12]

Amantadine and *rimantadine*, when started before exposure and continued throughout the period of exposure, are effective in preventing influenza A in 60 to 90% of patients. They are ineffective against influenza B and therefore cannot be considered as a substitute for vaccination unless the vaccine is contra-indicated.[11,13] Additional problems with these drugs are the rapid development of viral resistance and subsequent spread of resistant virus to close contacts and the potential to cause serious CNS adverse effects.

Clinical studies in healthy adults indicate that both the neuraminidase inhibitors, *oseltamivir* and *zanamivir* are effective in preventing infection with influenza A and B in about 80% of individuals and both have been reported to prevent illness in persons in close contact with infected household members.[14,15]

In the USA, all 4 antiviral drugs are licensed for prophylaxis of influenza but only oseltamivir and zanamivir are recommended by the Advisory Committee on Immunization Practices[10] and the American Academy of Pediatrics.[16] In the UK, amantadine and oseltamivir are licensed for prophylaxis, but only oseltamivir is recommended by

NICE[17] for postexposure prophylaxis in persons 13 years of age or older at high risk of complications of influenza. Neither drug is recommended for seasonal prophylaxis of influenza.

For most people **treatment** of influenza is largely symptomatic and supportive. However, antivirals may be used for the treatment of vaccinated or unvaccinated individuals who develop symptoms. *Amantadine* and *rimantadine* have been shown to reduce the duration of uncomplicated influenza A infection when given within 48 hours of the onset of symptoms. These drugs may be considered for patients at high risk of complications. Treatment failures may be due to the rapid emergence of drug resistance.[11,13,18] They are not effective against influenza B or the avian influenza H5N1 strain.[11] *Oseltamivir* and *zanamivir* given within 48 hours of the onset of symptoms are active against both influenza A and B viruses and reduce the duration of uncomplicated influenza by about 1 day in healthy adults and adolescents. Data is limited and inconclusive for all 4 drugs in terms of effectiveness when given to individuals at high risk of complications of influenza. Neuraminidase inhibitors have several advantages compared with amantadine, including reduced viral resistance, additional efficacy against influenza B, fewer adverse effects (including CNS effects), and reduction in clinical symptoms. Viral strains resistant to amantadine and rimantadine generally remain susceptible to neuraminidase inhibitors.[14,15,18,19]

In the UK, oseltamivir and zanamivir are recommended[20] for the treatment of adults at risk of complications of influenza who can start treatment within 48 hours of the onset of symptoms. Only oseltamivir is recommended for the treatment of influenza in children. In the UK NICE does not recommend the use of amantadine for the treatment of influenza. In the USA, the Advisory Committee on Immunization Practices[10] and the American Academy of Pediatrics[16] recommend oseltamivir or zanamivir for treatment of acute illness caused by influenza A or B. Neuraminidase inhibitors have also been effective against some strains of avian influenza in animal studies and may be considered for both prophylaxis and treatment of suspected H5N1 disease.[2,11,16]

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Measles

Measles[1] is an acute viral illness caused by an RNA virus of the Morbillivirus genus and of the family Paramyxoviridae. It is a highly contagious disease spread by airborne droplets or direct contact with respiratory secretions of infected persons. Infection confers lifelong immunity.

The incubation period for measles is about 8 to 12 days followed by a prodromal phase lasting several days. This phase is usually characterised by malaise, fever, conjunctivitis, cough, rhinitis, congestion, and later Koplik's spots on the buccal mucosa. An erythematous, maculopapular rash appears towards the end of the prodromal phase, starting on the face and spreading over the trunk and limbs. Measles is generally benign and uncomplicated and recovery usually takes place during the week after the rash's appearance. However, severe disease and complications may develop and are more common in adults and in children who are undernourished or immunocompromised. Most complications occur when the measles virus further suppresses host immune responses, resulting in a reactivation of latent infections or superinfection by bacteria. Respiratory complications include giant cell pneumonia, bronchopneumonia, and laryngotracheobronchitis, while neurological complications include febrile seizures, acute encephalitis, progressive subacute encephalitis, and the more slowly progressive subacute sclerosing panencephalitis (SSPE) which may develop several years after the original measles infection. Other complications include diarrhoea, otitis media, thrombocytopenia with purpura and bleeding, hepatitis, myocarditis, pericarditis, and severe keratitis that may progress to blindness.

Measles can be **prevented** by active immunisation with measles vaccine, and measles immunoglobulins may be used for passive immunisation against measles. Normal immunoglobulins may be used to prevent, or possibly modify, an attack of measles in those at risk of developing severe or fatal disease such as immunocompromised patients.

Measles usually requires only symptomatic and supportive **treatment** such as antipyretics and fluid replacement. *Vitamin A* treatment for children with measles in developing countries has been associated with a significant reduction in mortality (see p.1974). A systematic review of randomised studies concluded that a dose of 200 000 units of vitamin A given on 2 consecutive days reduced mortality in children under 2 years with measles.[2] WHO recommends that supplementary vitamin A be given to all children with measles in developing countries in order to prevent keratitis and blindness. A recent review has suggested that prophylactic antibacterials may be of benefit in preventing complications such as pneumonia, purulent otitis media, and tonsillitis in children with measles but of no benefit for conjunctivitis or gastro-enteritis;[3] evidence from earlier reviews did not support such use.[4,5] However, prompt antibacterial therapy should be given to those patients who develop keratitis, otitis media, or pneumonia. There appears to be no good evidence for the use of antivirals, although there are case reports of ribavirin being used to treat severely affected and immunocompromised adults with acute measles[6] or patients with subacute sclerosing panencephalitis (intravenous ribavirin plus intrathecal high-dose interferon alfa[7] or intraventricular ribavirin[8]). No controlled studies have been conducted and the use of ribavirin should be considered experimental.

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Respiratory syncytial virus infection

Respiratory syncytial virus (RSV) is an RNA virus of the family Paramyxoviridae and occurs worldwide. RSV is a prominent cause of respiratory infections in infants and young children and is generally confined to the respiratory tract. However, disease may occur at any age, and it has been recognised as a cause of morbidity and mortality among the elderly,[1] as well as among children and adults with compromised cardiac, respiratory, or immune systems. RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated environmental surfaces. RSV infection is highly contagious and may result in extensive nosocomial transmission. RSV outbreaks tend to occur annually, usually from late autumn through to early spring.

Primary infection in infants and young children is characterised by fever, cough, runny or congested nose, vomiting, and sometimes wheezing. During the primary infection up to 50% of infants develop lower respiratory-tract disease, most commonly bronchiolitis and pneumonia, and about 1 to 2% of these infants may require hospitalisation. Most infants needing hospitalisation are less than 6 months old or at risk of severe infection, for example because of a history of prematurity, or pre-existing cardiac or respiratory diseases or immunodeficiency. Otitis media and persistent wheezing are common complications of RSV infection in infants and young children. RSV infection may trigger acute respiratory distress syndrome and exacerbate pre-existing, underlying cardiac, renal (nephrotic syndrome), or lung (cystic fibrosis) disease. Acquired immunity does not prevent re-infection, although subsequent infections are typically milder.

The **management** of mild RSV infection in infants and children[2-7] consists of supportive care such as fever control and adequate hydration. Children with more severe lower respiratory-tract disease may require hospitalisation for supplementary oxygen. Measures to limit the spread of infection in hospitals and institutions are important. Pharmacological therapies are of limited benefit. Beta$_2$-agonist *bronchodilators* are often used in the management of bronchiolitis even though systematic reviews and meta-analyses of studies have indicated only modest short-term benefit of clinical symptoms and no reduction in hospital admission rates, length of hospital stay, or improvement in oxygen saturation.[2,4,5,8] A review[9] of the use of the anticholinergic bronchodilator ipratropium bromide reported no proven efficacy. An evaluation of clinical studies[2] using nebulised or intravenous adrenaline to treat RSV infection has reported clinical benefit in some infants, as well as a reduction in hospital admission or stay. However, a systematic review[10] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients. Some recommend that if a trial with a bronchodilator or inhaled adrenaline is considered, treatment should be stopped if no response is evident after 1 or 2 treatments.[2,4,6]

Systemic *corticosteroids* are also widely used despite a lack of documented clear benefit. A systematic review[11] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. Although a later study[12] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms another[13] showed that a single oral dose of dexamethasone was of no benefit in infants with moderate to severe bronchiolitis. Inhaled corticosteroids given during the initial acute phase of bronchiolitis did not prevent post-bronchiolitic wheezing.[14] The routine use of systemic corticosteroids is not recommended by expert groups.[6,7]

Ribavirin is the only antiviral drug that has been licensed for the treatment of infants and children with severe RSV bronchiolitis (and it is only available in some countries). Although some studies with aerosolised ribavirin have shown some clinical benefit in infants with lower respiratory-tract RSV infection, days of hospitalisation and short-term outcomes have not been affected.[2,15] Due to the small number of patients enrolled in these studies, evaluation of the effects has been difficult. Also, there are some difficulties in giving the drug, and concerns about occupational health and safety, and the high cost. Routine use is not recommended;[6,7] but it may be used for selected infants and children at risk of severe disease and complications. If used, ribavirin should be started early in the course of the disease.[2,3,6]

Antibacterials, although often used in the management of bronchiolitis, are not routinely recommended.[6,7] The results from three small studies[16] suggest that *surfactant* may reduce duration of ventilation and length of intensive care stay.

Prevention of RSV infection involves good infection control practices and use of *RSV immunoglobulin* and a human monoclonal antibody to RSV, *palivizumab*. Both RSV immunoglobulin and palivizumab can be given during an RSV outbreak to prevent serious complications of infection in infants and children considered at high risk. The effectiveness of RSV immunoglobulin[17] and palivizumab[18] were tested in randomised, placebo-controlled clinical studies involving high-risk infants and children (history of prematurity or with bronchopulmonary dysplasia). A 41% overall reduction in hospital admissions was reported in those given RSV immunoglobulin prophylaxis. Prophylaxis with palivizumab resulted in a 55% overall reduction in hospitalisation; reduction rates were 39% and 78% in those with and without bronchopulmonary dysplasia respectively. Respiratory severity scores, hospital days, days of oxygen requirement, and the rate of intensive care admission were also significantly lower in the palivizumab group than for the placebo group. Prophylaxis with palivizumab was also found to reduce post-bronchiolitic wheezing in premature infants.[19] It is recommended by some expert groups for prophylaxis in infants and children at high risk of severe RSV infections.[6,7,20] Vaccines to prevent RSV infection are currently under development.

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3. Jafri HS. Treatment of respiratory syncytial virus: antiviral therapies. *Pediatr Infect Dis J* 2003; **22** (suppl): S89–S93.
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12. Csonka P, *et al.* Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. *J Pediatr* 2003; **143:** 725–30.
13. Corneli HM, *et al.* Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN). A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007; **357:** 331–9.
14. Blom D, *et al.* Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 03/04/08).
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SARS

Severe acute respiratory syndrome (SARS)[1,2] is a respiratory illness caused by a newly identified coronavirus (SARS-CoV). SARS presents primarily in previously healthy adults although there have been some cases reported in children. SARS-CoV is transmitted by contact or droplets and transmission mainly occurs during the second week of illness. The incubation period for SARS is usually 2 to 10 days but may be as long as 16 days. The disease manifests initially as flu-like prodromal symptoms, usually characterised by fever, malaise, myalgia, headache, and rigors. Cough (initially dry), dyspnoea, and diarrhoea may be present in the first week but are more commonly present in the second week of illness. Severe cases develop rapidly progressive respiratory distress and hypoxia and up to about 20% of patients may require intubation or mechanical ventilation. About 20% of patients develop large volume, watery diarrhoea. The overall fatality rate during the 2002–2003 SARS outbreak was about 9.5%.

There is currently no consensus on the optimal treatment for SARS and treatment recommendations are based on the experience gained during the 2002–2003 SARS outbreak. Guidelines for the **surveillance and management** of SARS have been developed by WHO.[3] In the UK guidelines[4] have been issued for the hospital management of adults with SARS, and others have also been developed by clinicians involved in the SARS outbreak in Hong Kong.[5] Because SARS is indistinguishable from pneumonia caused by viral and bacterial pathogens, empirical antibacterial treatment in accordance with local guidelines for severe community-acquired pneumonia (p.186) is recommended. Fluids and oxygen therapy should be given as required. Other treatments tried have included corticosteroids, ribavirin, interferons, normal immunoglobulins, and the co-formulated HIV-protease inhibitor ritonavir-boosted lopinavir. Corticosteroids, usually with ribavirin, were widely used and the timely use of high-dose corticosteroids may decrease fever, improve radiographic appearances, and reduce oxygen requirements.[6-8] There is, however, concern that high-dose and long-term use of corticosteroids may suppress the patient's immune system resulting in increased viral replication and possible bacterial or fungal superinfection. The UK guidelines recommend that their use be considered in moderate doses in severely ill patients with increased oxygen requirements.[4] Additionally there is no convincing clinical evidence that the use of ribavirin alters clinical outcome and the UK guidelines state that its routine use is not recommended.[4] Although interferon beta shows greater *in-vitro* antiviral activity against SARS-CoV, most experience during the 2002–2003 outbreak was with interferon alfa with or without normal immunoglobulins.[6] An open study[9] using interferon-alfacon-1 and high-dose pulse methylprednisolone reported more rapid improvement in radiographic appearance and oxygenation than corticosteroids alone. Better clinical improvement was reported in patients treated with daily interferon alfa plus high-dose corticosteroids than in those given interferon plus low-dose or limited corticosteroids.[8] The UK guidelines state that no recommendation can be given regarding the use of interferons.[4] Although normal immunoglobulins have been used in SARS their effectiveness cannot be established as they were usually given with other therapies.[6] A preliminary open study[10] with ritonavir-boosted lopinavir in 41 patients with probable SARS and receiving the local standard treatment of ribavirin and corticosteroids, reported an improved outcome at 21 days and reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

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Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Anogenital warts are known as condylomata acuminata. Treatment generally relies on some form of local tissue destruction (see p.1584). Interferons have also been used (see p.891).

Abacavir *(BAN, rINN)*

Abacavirum; Abakaviiri; Abakavir. {(1*S*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl}methanol.

Абакавир

$C_{14}H_{18}N_6O$ = 286.3.
CAS — 136470-78-5.
ATC — J05AF06.
ATC Vet — QJ05AF06.

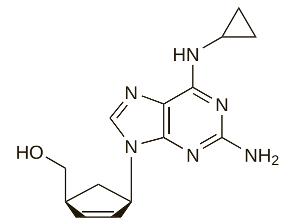

NOTE. The code 1592U89 has been applied to abacavir but is more properly reserved for abacavir sulfate.

Abacavir Succinate *(BANM, USAN, rINNM)*

Abacavir, Succinate d'; Abacaviri Succinas; Succinato de abacavir.

Абакавира Суксинат

$C_{14}H_{18}N_6O,C_4H_6O_4$ = 404.4.
CAS — 168146-84-7.
ATC — J05AF06.
ATC Vet — QJ05AF06.

NOTE. The code 1592U89 has been applied to abacavir succinate but is more properly reserved for abacavir sulfate.

Abacavir Sulfate *(USAN, rINNM)*

Abacavir, Sulfate d'; Abacavir Sulphate *(BANM)*; Abacaviri Sulfas; Sulfato de abacavir; 1592U89.

Абакавира Сульфат

$(C_{14}H_{18}N_6O)_2,H_2SO_4$ = 670.7.
CAS — 188062-50-2.
ATC — J05AF06.
ATC Vet — QJ05AF06.

NOTE. The code 1592U89 and its abbreviated form, 1592, have also been applied to abacavir and abacavir succinate.

Adverse Effects

The most significant adverse effects associated with antiretroviral regimens containing abacavir are severe hypersensitivity reactions, sometimes fatal, that may occur in up to 9% of patients given abacavir, especially (but not exclusively) during the first 6 weeks of treatment, or during intermittent therapy. Symptoms of hypersensitivity often include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has occurred. Caution is needed as hypersensitivity may be misdiagnosed as influenza, respiratory disease, or gastroenteritis. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred rarely. Other adverse effects associated with abacavir include pancreatitis and raised liver enzyme values. Lactic acidosis, sometimes fatal and usually associated with severe hepatomegaly and steatosis, has been reported in patients receiving NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including abacavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including abacavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the heart. For the possible risk of myocardial infarction in patients taking abacavir, see Effects on the Heart under Adverse Effects of Zidovudine, p.914.

Effects on the skin. Stevens-Johnson syndrome occurring in a patient receiving antiretroviral therapy with abacavir, lamivudine, and zidovudine was probably associated with abacavir.[1] Resolution occurred upon stopping antiretroviral therapy and the condition did not recur upon rechallenge with an alternative regimen also containing lamivudine and zidovudine.

1. Bossi P, *et al.* Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; **35:** 902.

Hypersensitivity. Reviews of hypersensitivity associated with abacavir.[1,2]

1. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002; **34:** 1137–42.
2. Hughes CA, *et al.* Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008; **42:** 387–96.

Precautions

Patients considered to be at increased risk for an abacavir hypersensitivity reaction are those that carry the human leucocyte antigen (HLA) HLA-B(*)5701 allele; screening patients for HLA-B(*)5701 allele before starting treatment with abacavir has been shown to reduce the risk of hypersensitivity reactions. Routine screening of all patients before starting treatment with an abacavir-containing product is therefore recommended. Abacavir should be stopped immediately if symptoms associated with hypersensitivity occur and should *never be restarted* in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first 2 months of treatment, although hypersensitivity reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if they have not previously had symptoms of hypersensitivity. Since intermittent therapy may increase the risk of hypersensitivity developing, patients should be advised of the importance of regular dosing.

Abacavir should not be used in patients with moderate to severe hepatic impairment, and should be used with caution and reduced doses in those with lesser degrees of impairment and those with risk factors for liver disease. Treatment should be stopped if liver function deteriorates rapidly or if hepatomegaly or unexplained metabolic acidosis develop.

Abacavir should be avoided in patients with end-stage renal disease.

Interactions

Use of alcohol with abacavir may result in decreased elimination of abacavir and consequent increases in exposure. Abacavir increases the systemic clearance of oral methadone and patients should be monitored for signs of withdrawal symptoms. The dose of methadone may need to be increased in some patients.

Alcohol. References.

1. McDowell JA, *et al.* Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; **44:** 1686–90.

Antiviral Action

Abacavir is converted intracellularly in stages to its active form carbovir triphosphate. This halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

◊ References.

1. Faletto MB, *et al.* Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. *Antimicrob Agents Chemother* 1997; **41:** 1099–1107.

Pharmacokinetics

Abacavir is rapidly absorbed after oral doses with a bioavailability of about 80%. Absorption is delayed slightly by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50% bound to plasma proteins. The elimination half-life is about 1.5 hours after a single dose. Abacavir undergoes intracellular metabolism to the active antiviral metabolite carbovir triphosphate. Elimination is via hepatic metabolism primarily by alcohol dehydrogenase and by glucuronidation and the metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

◊ References.

1. Kumar PN, *et al.* Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother* 1999; **43:** 603–8.
2. Hughes W, *et al.* Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 1999; **43:** 609–15.
3. McDowell JA, *et al.* Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000; **44:** 2061–7.
4. Izzedine H, *et al.* Pharmacokinetics of abacavir in HIV-1-infected patients with impaired renal function. *Nephron* 2001; **89:** 62–7.
5. Jullien V, *et al.* Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. *J Clin Pharmacol* 2005; **45:** 257–64.
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Uses and Administration

Abacavir is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when abacavir is used alone, and it is therefore used with other antiretrovirals.

Abacavir is given orally as the sulfate but doses are expressed in terms of the base; 1.17 g of abacavir sulfate is equivalent to about 1 g of abacavir. The adult dose is 300 mg twice daily or 600 mg once daily. For details of doses in children, see below. Doses should be reduced in patients with hepatic impairment (see below).

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing abacavir in combination with lamivudine and with lamivudine and zidovudine are available in some countries.

◊ Reviews.

1. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 447–79.
2. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.
3. Castillo SA, *et al.* Long-term safety and tolerability of the lamivudine/abacavir combination as components of highly active antiretroviral therapy. *Drug Safety* 2006; **29:** 811–26.

Administration in children. For the treatment of HIV infection in children 3 months of age and older, abacavir may be given orally as a tablet or solution with other antiretroviral drugs. Doses are based on body-weight:

- 14 to 21 kg: 150 mg (half a tablet) twice daily
- 22 to 29 kg: 150 mg (half a tablet) in the morning and 300 mg (1 tablet) in the evening
- 30 kg or more: 300 mg (1 tablet) twice daily

or

- the solution may be given in a dose of 8 mg/kg twice daily to a maximum dose of 300 mg twice daily

Administration in hepatic impairment. Abacavir should not be used in patients with moderate to severe hepatic impairment, although reduced oral doses of 200 mg twice daily may be given to patients with mild impairment (Child-Pugh score 5 to 6).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Filabac; Finecil; Plusabcir; Zepril; Ziagenavir; ***Austral.:*** Ziagen; ***Austria:*** Ziagen; ***Belg.:*** Ziagen; ***Braz.:*** Ziagenavir; ***Canad.:*** Ziagen; ***Chile:*** Ziagen; ***Cz.:*** Ziagen; ***Denm.:*** Ziagen; ***Fin.:*** Ziagen; ***Fr.:*** Ziagen; ***Ger.:*** Kivexa; Ziagen; ***Gr.:*** Ziagen; ***Hong Kong:*** Ziagen; ***Hung.:*** Ziagen; ***India:*** Abamune; ***Irl.:*** Ziagen; ***Israel:*** Ziagen; ***Ital.:*** Ziagen; ***Mex.:*** Ziagenavir; ***Neth.:*** Ziagen; ***Norw.:*** Ziagen; ***NZ:*** Ziagen; ***Pol.:*** Ziagen; ***Port.:*** Ziagen; ***Rus.:*** Ziagen (Зиаген); ***S.Afr.:*** Ziagen; ***Singapore:*** Ziagen; ***Spain:*** Ziagen; ***Swed.:*** Ziagen; ***Switz.:*** Ziagen; ***Thai.:*** Ziagenavir; ***Turk.:*** Ziagen; ***UK:*** Ziagen; ***USA:*** Ziagen; ***Venez.:*** Ziagen.

Multi-ingredient: ***Arg.:*** Kivexa; Tricivir; Trivudin; ***Austral.:*** Kivexa; Trizivir; ***Austria:*** Trizivir; ***Belg.:*** Kivexa; Trizivir; ***Canad.:*** Kivexa; Trizivir; ***Chile:*** Kivexa; Tricivir; ***Cz.:*** Kivexa; Trizivir; ***Denm.:*** Kivexa; Trizivir; ***Fin.:*** Kivexa; Trizivir; ***Fr.:*** Kivexa; Trizivir; ***Ger.:*** Trizivir; ***Gr.:*** Kivexa; Trizivir; ***Hong Kong:*** Trizivir; ***Hung.:*** Kivexa; Trizivir; ***Irl.:*** Kivexa; Trizivir; ***Israel:*** Trizivir; ***Ital.:*** Kivexa; Trizivir; ***Mex.:*** Kivexa; Trizivir; ***Neth.:*** Kivexa; Trizivir; ***Norw.:*** Kivexa; Trizivir; ***NZ:*** Kivexa; Trizivir; ***Pol.:*** Kivexa; Trizivir; ***Port.:*** Kivexa; Trizivir; ***Rus.:*** Trizivir (Тризивир); ***S.Afr.:*** Trizivar; ***Singapore:*** Trizivir†; ***Spain:*** Kivexa; Trizivir; ***Swed.:*** Kivexa; Trizivir; ***Switz.:*** Trizivir; ***UK:*** Kivexa; Trizivir; ***USA:*** Epzicom; Trizivir; ***Venez.:*** Trizivir.

Aciclovir *(BAN, rINN)*

Aciclogunanosina; Aciclovirum; Aciklovír; Aciklovir; Acikloviras; Acycloguanosine; Acyclovir *(USAN)*; Acyklowir; Asikloviiri; Asiklovir; BW-248U. 9-[(2-Hydroxyethoxy)methyl]guanine; 2-Amino-1,9-dihydro-9-(2-hydroxyethoxymethyl)-6*H*-purin-6-one.

Ацикловир

$C_8H_{11}N_5O_3$ = 225.2.

CAS — 59277-89-3.

ATC — D06BB03; J05AB01; S01AD03.

ATC Vet — QD06BB03; QJ05AB01; QS01AD03.

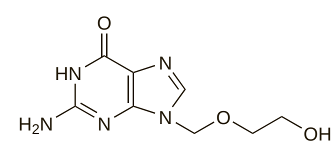

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Aciclovir). A white to almost white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dimethyl sulfoxide; soluble in dilute solutions of alkali hydroxides and mineral acids.

USP 31 (Acyclovir). A white to off-white crystalline powder. Slightly soluble in water; insoluble in alcohol; soluble in dilute hydrochloric acid. Store in airtight containers. Protect from light and moisture.

Aciclovir Sodium *(BANM, rINNM)*

Aciclovir sódico; Aciclovir Sodique; Acyclovir Sodium *(USAN)*; Natrii Aciclovirum.

Натрий Ацикловир

$C_8H_{10}N_5NaO_3$ = 247.2.

CAS — 69657-51-8.

ATC — D06BB03; J05AB01; S01AD03.

ATC Vet — QD06BB03; QJ05AB01; QS01AD03.

Incompatibility. Aciclovir is reported to be incompatible with foscarnet.[1,2]

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.

Stability. A study[1] found that aciclovir sodium solutions prepared with sodium chloride 0.9% and with dextrose 5% were stable for 7 and 21 days respectively when stored at 23°. Solutions stored at 4° were found to be stable for 35 days although subsequent storage at room temperature produced irreversible precipitation. Precipitation may also occur when freshly prepared solutions are refrigerated but the precipitate redissolves at room temperature. US licensed product information recommends that diluted solutions be used within 24 hours of preparation.

1. Zhang Y, *et al.* Stability of acyclovir sodium 1, 7, and 10 mg/mL in 5% dextrose injection and 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1998; **55:** 574–7.

Adverse Effects

Aciclovir is generally well tolerated. When given intravenously as aciclovir sodium it may cause local reactions at the injection site with inflammation and phlebitis; these reactions may be associated with extravasation that can lead to tissue necrosis.

Renal impairment may be associated with systemic use of aciclovir in some patients; it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. The risk of renal toxicity is increased by conditions favouring deposition of aciclovir crystals in the tubules such as when the patient is poorly hydrated, has existing renal impairment, or when the drug is given at a high dosage or by rapid or bolus injection. Some patients taking systemic aciclovir may have transient increases in blood concentrations of urea and creatinine although this is more acute with intravenous dosage.

Occasional adverse effects after systemic use include increased serum bilirubin and liver enzymes, haematological changes, skin rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), fever, headache, dizziness, and gastrointestinal effects such as nausea, vomiting, and diarrhoea. Anaphylaxis has been reported. Hepatitis and jaundice have been reported rarely. Reversible neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions, and coma have been reported in a small number of patients, particularly in those given intravenous aciclovir and with predisposing factors such as renal impairment; these effects may be more marked in older patients. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients given high parenteral doses of aciclovir. Accelerated diffuse hair loss has also been reported.

Topical application of aciclovir may produce transient stinging, burning, itching, or erythema. Eye ointments may occasionally produce transient stinging, superficial punctate keratopathy, blepharitis, or conjunctivitis.

Effects on the blood. There has been no evidence of bone-marrow toxicity in patients given aciclovir after bone marrow transplantation.[1,2] However, megaloblastic haematopoiesis was seen in the bone marrow of 3 patients given aciclovir for suspected or proven herpes simplex encephalitis.[3] There has also been a report of inhibition of human peripheral blood lymphocytes in samples taken from healthy subjects given aciclovir.[4]

1. Serota FT, *et al.* Acyclovir treatment of herpes zoster infections: use in children undergoing bone marrow transplantation. *JAMA* 1982; **247:** 2132–5.
2. Gluckman E, *et al.* Oral acyclovir prophylactic treatment of herpes simplex infection after bone marrow transplantation. *J Antimicrob Chemother* 1983; **12** (suppl B): 161–7.
3. Amos RJ, Amess JAL. Megaloblastic haemopoiesis due to acyclovir. *Lancet* 1983; **i:** 242–3.
4. Tauris P, *et al.* Evaluation of the acyclovir-induced modulation of the plaque-forming cell response of human peripheral blood lymphocytes. *J Antimicrob Chemother* 1984; **13:** 71–7.

Effects on the kidneys. Aciclovir is excreted mostly by the kidney, and reaches high concentrations in the tubular lumen, but is relatively insoluble in urine and may therefore cause intratubular precipitation of crystals in the kidney. High doses, volume depletion, or pre-existing renal impairment increase the risk of aciclovir-associated acute renal failure, which has been reported in 12 to 48% of patients in some series. Although usually asymptomatic there may be nausea, vomiting, and flank pain, together with haematuria and pyuria. Most patients recover on stopping the drug and volume replacement, though some need temporary dialysis; use of a loop diuretic may be helpful in some cases. Slow infusion and adequate hydration can help to prevent crystal precipitation, and doses should be reduced in patients with underlying renal impairment.[1]

There are also occasional reports of renal toxicity apparently unrelated to crystal precipitation.[2-4]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; **106:** 459–65.
2. Giustina A, *et al.* Low-dose acyclovir and acute renal failure. *Ann Intern Med* 1988; **108:** 312.
3. Eck P, *et al.* Acute renal failure and coma after a high dose of oral acyclovir. *N Engl J Med* 1991; **325:** 1178.
4. Johnson GL, *et al.* Acute renal failure and neurotoxicity following oral acyclovir. *Ann Pharmacother* 1994; **28:** 460–3.

Effects on the nervous system. Neurotoxicity, including tremor, confusion, myoclonus, agitation, lethargy, or hallucination, is an uncommon adverse effect of aciclovir, and may be hard to distinguish from progression of the underlying disease state. Renal impairment may increase the risk, although no clear relationship with peak plasma concentrations has been demonstrated; cases are also more common in elderly patients and those taking other neurotoxic drugs.[1] Of 143 patients given aciclovir by intravenous infusion in doses ranging from 0.75 to 3.6 g/m^2 daily for the treatment of herpesvirus infections after bone marrow transplantation, 6 developed reversible neurological symptoms including tremor, agitation, nausea, lethargy, mild disorientation, autonomic instability, hemiparaesthesia, and slurred speech.[2] EEGs were diffusely abnormal in all 6. Symptoms improved in all patients on withdrawing aciclovir; reinstituting aciclovir in 2 produced a recurrence of symptoms. Concomitant therapy included irradiation and methotrexate intrathecally for all 6, interferon alfa for 3, and ciclosporin for 1.

1. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. *Ann Pharmacother* 1998; **32:** 111–13.
2. Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann Intern Med* 1983; **98:** 921–5.

Effects on the skin. A report of vesicular lesions associated with intravenous use of aciclovir in a patient thought to have herpes simplex encephalitis.[1] Careful evaluation is necessary to differentiate the reaction from herpetic lesions.

1. Buck ML, *et al.* Vesicular eruptions following acyclovir administration. *Ann Pharmacother* 1993; **27:** 1458–9.

Vasculitis. Aciclovir has been associated with vasculitis. In one patient[1] it was one of many drugs given that may have caused a necrotising vasculitis. In another report an immunocompromised child with chickenpox given aciclovir by infusion developed a vasculitic rash which diminished on withdrawal of the drug.[2]

For a report of peripheral neuropathy associated with vasculitis due to the prodrug valaciclovir, see Effects on the Nervous System, p.911.

1. von Schulthess GK, Sauter C. Acyclovir and herpes zoster. *N Engl J Med* 1981; **305:** 1349.
2. Platt MPW, Eden OB. Vasculitis in association with chickenpox treatment in childhood acute lymphoblastic leukaemia. *Lancet* 1982; **ii:** 763–4.

Precautions

Systemic aciclovir should be used with caution and in reduced doses in patients with renal impairment. The elderly and patients with existing renal impairment should be closely monitored for neurological adverse effects. Adequate hydration should be maintained in patients given parenteral or high oral doses of aciclovir. Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided. The risk of renal impairment is increased by use with other nephrotoxic drugs. Intravenous aciclovir should also be used with caution in patients with underlying neurological abnormalities, with significant hypoxia, or with serious hepatic or electrolyte abnormalities.

Breast feeding. Aciclovir is distributed into breast milk[1-4] and in some instances higher concentrations are obtained than in maternal serum.[1-3] Licensed product information reports that a maternal oral dose of 200 mg five times daily could expose a breast-fed infant to 300 micrograms/kg daily and advises caution when giving nursing mothers aciclovir. However, no adverse effects have been seen in breast-fed infants whose mothers were taking aciclovir, and the American Academy of Pediatrics considers[5] that it is therefore usually compatible with breast feeding.

1. Lau RJ, *et al.* Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. *Obstet Gynecol* 1987; **69:** 468–71.
2. Meyer LJ, *et al.* Acyclovir in human breast milk. *Am J Obstet Gynecol* 1988; **158:** 586–8.
3. Bork K, Benes P. Concentration and kinetic studies of intravenous acyclovir in serum and breast milk of a patient with eczema herpeticum. *J Am Acad Dermatol* 1995; **32:** 1053–5.
4. Taddio A, *et al.* Acyclovir excretion in human breast milk. *Ann Pharmacother* 1994; **28:** 585–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/04/08)

Pregnancy. The incidence of congenital abnormality and spontaneous fetal loss in 1246 cases of prenatal exposure to aciclovir did not significantly differ from those in the general population.[1]

1. Stone KM, *et al.* Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the International Acyclovir Pregnancy Registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol* 2004; **70:** 201–7.

Sodium content. Each g of aciclovir sodium represents 4.05 mmol of sodium.

Interactions

Probenecid is reported to block the renal clearance of aciclovir. The risk of renal impairment is increased by use with other nephrotoxic drugs.

Antivirals. Use of *zidovudine* with aciclovir is not generally associated with additional toxicity.[1] However, there is a report[2] of a patient who had overwhelming fatigue when given aciclovir and zidovudine together; no such effect occurred when each drug was given alone.

Former product information for *interferon alfa-n1* reported progressive renal failure in patients also given aciclovir.

1. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; **35:** 2225–31.
2. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; **316:** 547.

Xanthines. For reference to evidence that aciclovir inhibits *theophylline* metabolism, resulting in accumulation, see p.1144.

Antiviral Action

Aciclovir is active against herpes simplex virus type 1 and type 2 and against varicella-zoster virus. This activity requires intracellular conversion of aciclovir by viral thymidine kinase to the monophosphate with subsequent conversion by cellular enzymes to the diphosphate and the active triphosphate. This active form inhibits viral DNA synthesis and replication by inhibiting the herpesvirus DNA polymerase enzyme as well as being incorporated into viral DNA. This process is highly selective for infected cells. Studies in *animals* and *in vitro* have found various sensitivities but show that target viruses are inhibited by concentrations of aciclovir that are readily achieved clinically. Herpes simplex virus type 1 appears to be the most susceptible, then type 2, followed by varicella-zoster virus.

The Epstein-Barr virus and CMV are also susceptible to aciclovir to a lesser extent. However, for CMV it does not appear to be activated by thymidine kinase and may act via a different mechanism. Epstein-Barr virus may have reduced thymidine kinase activity but its DNA polymerase is very sensitive to inhibition by aciclovir triphosphate, which may account for the partial activity.

Aciclovir has no activity against latent viruses, but there is some evidence that it inhibits latent herpes simplex virus at an early stage of reactivation.

Resistance

Herpes simplex virus develops resistance to aciclovir *in vitro* and *in vivo* by selection of mutants deficient in thymidine kinase. Other mechanisms of resistance include altered substrate specificity of thymidine kinase and reduced sensitivity of viral DNA polymerase. Resistance has also been reported with varicella-zoster virus, probably by similar mechanisms.

Although occasional treatment failures have been reported, resistance has not yet emerged as a major problem in treating herpes simplex infections. However, resistant viruses are more likely to be a problem in patients with a suppressed immune response; AIDS patients may be particularly prone to aciclovir-resistant mucocutaneous herpes simplex virus infections.

Viruses resistant to aciclovir because of absence of thymidine kinase may be cross-resistant to other antivirals phosphorylated by this enzyme, such as brivudine, idoxuridine, and ganciclovir. Viruses resistant because of altered substrate specificity of thymidine kinase may display cross-resistance to brivudine; those with altered DNA polymerase sensitivity may be resistant to brivudine and vidarabine. However, those viruses with altered enzyme specificity or sensitivity tend to have variable cross-resistance patterns and may be relatively susceptible to the aforementioned antivirals.

◊ References.

1. Bacon TH, *et al.* Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev* 2003; **16:** 114–28.
2. Malvy D, *et al.* A retrospective, case-control study of acyclovir resistance in herpes simplex virus. *Clin Infect Dis* 2005; **41:** 320–6.

Pharmacokinetics

Aciclovir is poorly absorbed from the gastrointestinal tract after oral doses. Bioavailability of oral aciclovir is about 10 to 20%; orally active prodrugs such as valaciclovir (p.911) have been developed to overcome this poor absorption.

After intravenous dosage as aciclovir sodium it is widely distributed to body tissues and fluids including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9 to 33%.

Aciclovir is excreted largely unchanged in the urine, by glomerular filtration and some active tubular secretion, with up to 14% appearing in the urine as the inactive metabolite 9-carboxymethoxymethylguanine. In patients with normal renal function, the half-life is about 2 to 3 hours. In patients with chronic renal failure, this value is increased and may be up to 19.5 hours in anuric patients. During haemodialysis the half-life has been reported to be reduced to 5.7 hours, with 60% of a dose of aciclovir being removed. Faecal excretion may account for about 2% of a dose.

Probenecid increases the half-life and the area under the plasma concentration-time curve of aciclovir.

Aciclovir crosses the placenta and is distributed into breast milk in concentrations about 3 times higher than those in maternal serum.

Absorption of aciclovir is usually slight after topical application to intact skin, although it may be increased by changes in formulation. Aciclovir is absorbed after application of a 3% ointment to the eye giving a relatively high concentration in the aqueous humour but negligible amounts in the blood.

◊ Reviews.

1. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother* 1983; **12** (suppl B): 29–37.
2. Laskin OL. Clinical pharmacokinetics of acyclovir. *Clin Pharmacokinet* 1983; **8:** 187–201.
3. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.

Distribution. The pharmacokinetics of oral aciclovir and its distribution into the eye.[1]

1. Hung SO, *et al.* Pharmacokinetics of oral acyclovir (Zovirax) in the eye. *Br J Ophthalmol* 1984; **68:** 192–5.

Uses and Administration

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. It is used mainly for the treatment and prophylaxis of viral infections due to herpes simplex virus types 1 and 2 (p.854) and varicella-zoster virus (herpes zoster and chickenpox—p.855).

Herpes simplex infections, including herpes keratitis, herpes labialis, and genital herpes, respond to aciclovir by the intravenous, oral, or topical route, given as soon as possible after symptoms appear. Both initial and recurrent infections can be successfully treated. Prolonged treatment can reduce the incidence of recurrence which is particularly important in immunocompromised patients. However, when prolonged treatment is withdrawn, infections may recur.

Aciclovir also improves the healing of herpes zoster lesions and reduces acute pain when given intravenously or by mouth; use to prevent postherpetic neuralgia is controversial (see p.9). Beneficial effects may be more marked in immunocompromised patients.

Aciclovir is given by ***intravenous infusion*** as the sodium salt over 1 hour. Doses are expressed in terms of the base. Aciclovir sodium 1.1 g is equivalent to about 1 g of aciclovir. Solutions for infusion are usually prepared to give a concentration of aciclovir of 25 or 50 mg/mL; this must then be further diluted to a final concentration not greater than about 5 mg/mL (0.5%). Alternatively, a solution containing 25 mg/mL may be given by injection using a controlled-rate infusion pump, over 1 hour. In obese patients the dose should be calculated on the basis of ideal body-weight, to avoid overdosage.

For **herpes simplex infections** in the *immunocompromised*, and for severe initial *genital herpes*, or for *prophylaxis* of herpes simplex infections in *immunocompromised* patients the dose by the intravenous route is 5 mg/kg given every 8 hours, and recommended periods of treatment range from 5 to 7 days. A higher dose of 10 mg/kg every 8 hours is given in the treatment of *herpes simplex encephalitis*, and treatment is usually continued for 10 days.

For **varicella-zoster infections** in immunocompetent patients, a dose of 5 mg/kg every 8 hours may also be given. In *immunocompromised* patients the higher dose of 10 mg/kg every 8 hours should be used.

Oral doses of aciclovir also vary according to indication. In **herpes simplex infections**:

- for treatment of *primary infections*, including genital herpes, the usual oral dose is 200 mg five times daily (usually every 4 hours while awake) for 5 to 10 days
- severely *immunocompromised* patients or those with *impaired absorption* may be given 400 mg five times daily for 5 days
- for *suppression* of recurrent herpes simplex in *immunocompetent* patients, the oral dose is 800 mg daily in two to four divided doses; dosage reduction to 400 to 600 mg daily can be tried. Higher doses of 1 g daily have also been used. Therapy should be interrupted every 6 to 12 months for reassessment of the condition

  Chronic suppressive treatment is not suitable for mild or infrequent recurrences of herpes simplex. In such cases *episodic treatment* of recurrences may be preferred; a dose of 200 mg five times daily for 5 days has been recommended, preferably begun during the prodromal period.
- for *prophylaxis* of herpes simplex in *immunocompromised* patients, the dose is 200 to 400 mg four times daily.

The usual oral dose of aciclovir for treatment of **chickenpox** is 800 mg four or five times daily for 5 to 7 days; for herpes zoster 800 mg five times daily may be given for 7 to 10 days.

In **herpes simplex infections of the skin**, including genital herpes and herpes labialis, ***topical treatment*** with an ointment or cream containing aciclovir 5% may be applied 5 or 6 times daily for periods of 5 to 10 days, preferably beginning in the prodromal period as soon as signs or symptoms occur. In herpes simplex **keratitis** a 3% eye ointment may be applied 5 times daily until 3 days after healing.

Doses should be reduced in *renal impairment* (see below).

For details of doses in children, see Administration in Children, below.

◊ Reviews.

1. Wagstaff AJ, *et al.* Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 153–205.
2. Leflore S, *et al.* A risk-benefit evaluation of aciclovir for the treatment and prophylaxis of herpes simplex virus infections. *Drug Safety* 2000; **23:** 131–42.

Administration in children. Aciclovir is licensed for use in infants and children for the treatment of herpes simplex and varicella-zoster infections, and for the prophylaxis of herpes simplex infections in the immunocompromised. It may be given by slow intravenous infusion over 1 hour, or orally.

Recommended ***intravenous doses*** vary according to country and age of the patient.

In the *UK* the 8-hourly dose for children aged 3 months to 12 years is calculated by body-surface. The usual course of treatment is 5 to 10 days:

- herpes simplex and varicella-zoster infections in immunocompetent patients: 250 mg/m^2
- varicella-zoster infection in immunocompromised children or those with herpes simplex encephalitis: 500 mg/m^2

In the *USA*, the 8-hourly intravenous dose for children aged 3 months to 12 years is calculated by body-weight:

- herpes simplex infections: 10 mg/kg for 7 days
- varicella-zoster infections in immunocompromised children: 20 mg/kg for 7 days
- herpes simplex encephalitis: 20 mg/kg for 10 days

In the *UK* and the *USA* the intravenous dose for neonates and infants up to 3 months of age is calculated by body-weight; an 8-hourly intravenous dose of 10 mg/kg may be given for the treatment of herpes simplex infections. Treatment for neonatal herpes simplex usually continues for 7 or 10 days. Higher intravenous doses of up to 20 mg/kg for at least 7 days have been recommended by the *BNFC* in neonates with varicella-zoster infections. A similar dose given for 14 days (21 days if CNS involvement) is also recommended in the treatment of disseminated herpes simplex in neonates and infants up to 3 months of age.

In the *UK* the following ***oral doses*** are permitted in the treatment of herpes simplex infections, and in the prophylaxis of herpes simplex infections in the immunocompromised:

- 2 years and over: usual adult dose (see above)
- under 2 years: half usual adult dose

In the *UK* and the *USA* the oral doses for the treatment of chickenpox are:

- over 2 years: 20 mg/kg, up to a maximum of 800 mg, four times daily for 5 days

  Alternatively, the following oral doses may be used:
- under 2 years: 200 mg four times daily
- 2 to 5 years: 400 mg four times daily
- 6 years and over: 800 mg four times daily

Administration in renal impairment. Doses of aciclovir should be reduced in renal impairment according to creatinine clearance (CC) and licensed product information gives the following guidance:

intravenous dosage:

- CC between 25 and 50 mL/minute: the interval between infusions may be increased to 12 hours
- CC 10 to 25 mL/minute: the interval between infusions may be increased to 24 hours
- CC less than 10 mL/minute: patients on *peritoneal dialysis* should receive half the usual appropriate dose given once every 24 hours; patients on *haemodialysis* should receive half the usual dose every 24 hours plus an extra half-dose after haemodialysis

oral dosage:

- CC less than 10 mL/minute: *herpes simplex infections*: 200 mg every 12 hours; *varicella-zoster infections*: 800 mg every 12 hours
- CC between 10 and 25 mL/minute: *varicella-zoster infections*: 800 mg three times daily every 8 hours

Erythema multiforme. For patients with recurrent erythema multiforme (p.1580) associated with herpes simplex infection a 5-day course of oral aciclovir at the start of the infection has been proposed to prevent the subsequent skin lesions.[1] If this fails, a 6-month course of oral aciclovir has been found to be of benefit,[2] even if the association with herpes is not obvious. It should be noted, however, that erythema multiforme may occur as an adverse effect of systemic aciclovir.

1. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.
2. Tatnall FM, *et al.* A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995; **132:** 267–70.

Preparations

BP 2008: Aciclovir Cream; Aciclovir Eye Ointment; Aciclovir Intravenous Infusion; Aciclovir Oral Suspension; Aciclovir Tablets; Dispersible Aciclovir Tablets;

USP 31: Acyclovir Capsules; Acyclovir for Injection; Acyclovir Ointment; Acyclovir Oral Suspension; Acyclovir Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acerpes; Aciclo; Aciclotex; Apofarm; Dioxis; Lafevir; Lisovyr; Poviral; Virostatic; Xiclovir; Zovirax; ***Austral.:*** Acihexal; Acyclo-V; Chemists Own Cold Sore; Lovir; Ozvir; Zolaten†; Zovirax; Zyclir; ***Austria:*** Acic; Aciclobene; Aciclostad; Aciclotyrol†; Activir; Acyclox; Exviral; Farocid†; Fibral; Herpomed; Nycovir; Simplex-Fieberblasen; Stadovir; ViroMed; Xorox; Zovirax; ***Belg.:*** Aciclomed; Aciclophar; Docaciclo; Viratop; Zovirax; ***Braz.:*** Aciclomed; Aciclor†; Aciclovan†; Aciveral; Acivirax; Anclomax; Antivirax; Aviral; Ciclavix†; Ciclocris†; Clovir; Ductovirax; Exavir†; Ezopen; Heclivir; Herpesil†; Hervirax; Hpvir; Uni Vir; Ziclovir†; Zovirax; Zoylex†; ***Canad.:*** Avirax†; Zovirax; ***Chile:*** Eurovir; Lisovyr; Oftavir; Vironida; Zovirax; ***Cz.:*** Acyclostad; Herpesin; Herpotern†; Provirsan; Ranvir; Supraviran†; Viro†; Virolex; Xorox†; Zovirax; ***Denm.:*** Aciclodan; Acivir; Avirox; Geavir; Herpavir; Orivir†; Zovir; ***Fin.:*** Aclovir; Acyclostad†; Acyrax; Antix; Geavir†; Herpolips; Zovirax; ***Fr.:*** Aciclovivax; Activir; Kendix; Virucalm; Zovirax; ***Ger.:*** Acerpes; Acic; Acic-Ophtal; Aciclo; Aciclobeta; Aciclostad; Acivir; Dynexan Herpescreme; Herpetad; Juviral†; Mapox†; Supraviran; Virax†; Virupos; Viruseen†; Virzin; Zoliparin; Zovirax; ***Gr.:*** Abduce; Biozirox; Cargosil; Cevinolon; Clovirax; Cyclovir†; Cycloviran; Erpaclovir; Erpizon; Etasisen; Hagevir; Helposol; Herzkur; Neldim; Pulibex; Uniplex†; Verpir; Virusteril; Xorox†; Zeramil; Zidovimm; Zovirax; ***Hong Kong:*** Acilax; Aclovirax; Acyvir; Avorax; Cusiviral; Cyclorax†; Cyclovax; Entir; Euroclovir; Lovir; Medovir; Qualiclovir; Synclovir; Vidaclovir; Virest; Viroclear; Virucid; Wariviron; Zevin; Zoral; Zoraxin; Zovirax; ***Hung.:*** Acyclostad; Herpesin; Telviran; Virokill†; Virolex; Zovirax; ***India:*** Acivir; Cyclovir; Herpex; Ocurax; Zovirax; ***Indon.:*** Acifar; Azovir; Clinovir; Clopes; Danovir; Herax; Herpiclof; Kenrovir; Matrovir; Molavir; Nevirz; Quavir; Scanovir; Viralis; Vircella; Vircovir; Virdam; Vireth; Virpes; Virtaz-200; Virules; Zorel; Zoter; Zovirax; Zumasid; Zyclorax; ***Irl.:*** Acic; Soothelip†; Viralief; Zovirax; ***Israel:*** Acivir; Acyclo-V; Cyclomed; Supra-Vir; Zovirax; ***Ital.:*** Aciclin; ACY; Acyvir; Alovir; Amodivyr; Avirase; Avix; Avyclor; Avyplus; Avysal†; Cevirin†; Citivir; Cycloviran; Dravyr; Efriviral; Esavir; Euclivir; Fuviron; Herpesnil; Iliaclor; Immunovir; Ipaviran; Ipsovir; Neclovir†; Neviran; Rexan; Riduvir; Sanavir; Sifiviral†; Voraclor; Zovirax; ***Jpn:*** Zovirax; ***Malaysia:*** Acylete; Avorax; Cusiviral; Cyclovax†; Declovir; Hepirax; Lovir; Medovir; Vacrax; Virest†; Virless; Zevin; Zoral; Zorax†; Zovirax; ***Mex.:*** Acifur; Akevir; Apo-Vir; Avirex-T; Bioviraz; Brimex; Cicloferon; Clirbest; Clociver; Clovex; Clyvorax; Epsin; Erser; Exaliver†; Firex; Hercivir; Herpilem; Isavir; Jersin; Kerastil; Laciken; Lesaclor; Maclov; Opthavir; Pharcilex†; Seracic; Sinarden; Sophivir; Soviclor; Vicloran; Viclovir; Virestat; Viroxil; Zetavir†; Zirconia; Ziverone; Zovirax; ***Neth.:*** Herpolips; Kruidvat Koortslipcreme; Zovirax; ***Norw.:*** Zovirax; ***NZ:*** Acicvir†; Lovir; Viraban; Zolaten; Zovirax; ***Philipp.:*** Acyhex; Cyclostad; Herpex; Klozivex; Virest; Zovirax; ***Pol.:*** Abbovir; Acix; Antivir; Awirol; Cusiviral; Hascovir; Herpesin; Herpex; Heviran; Virolex; Xorovir; Zovirax; ***Port.:*** Aciclosina; Aciclovax; Cicloviral; Divicil; Faulviral; Hermix-Sofex; Hermocil†; Herpex; Milavir; Vidovir; Zov800; Zovirax; ***Rus.:*** Aciclostad

(Ациклостад)†; Cyclovir (Цикловир); Herpesin (Герпесин); Lovir (Ловир); Medovir (Медовир); Virolex (Виролекс); Vivorax (Виворакс); Zovirax (Зовиракс); ***S.Afr.:*** Acitab DT; Acitop; Activir; Cyclivex; Lovire; Vyrohexal; Zovirax; ***Singapore:*** Avorax; Bearax; Cusiviral; Danovir†; Dravyr; Entir; Erlvirax†; Lovir; Medovir; Vacrax; Virest; Virless; Zoral; Zorax; Zovirax; ***Spain:*** Aciclostad; Bel Labial; Maynar; Milavir; Virherpes; Virmen; Viruderm; Zovirax; ***Swed.:*** Anti; Geavir; Zovirax; ***Switz.:*** Acerpes†; Acivir; Aviral; Helvevir; Virucalm; Zovirax; ***Thai.:*** ACV; Acyvir; Clinovir; Clovin; Clovira; Colsor; Cyclorax; Entir; Herpenon; Herpirax; Lermex; Marvir; Norum; Ranvir; Vermis; Vilerm; Viraxy; Virogon; Virolan; Viromed; Viropox†; Vivax; Vivir; Zevin; Zocovin; Zovirax; ***Turk.:*** Acyl; Aklovir; Asiviral; Hernovir; Herpeks; Klovireks-L; Provir; Silovir; Virosil; Virupos; Xorox; Zovirax; ***UAE:*** Lovrak; ***UK:*** Aviral; Clearsore; Herpetad; Soothelip; Virasorb; Virovir; Zovirax; ***USA:*** Zovirax; ***Venez.:*** Aciclor; Avir; Cloryvil; Clovirex†; Herpiclor†; Herpin; Klovir†; Zovirax.

Adefovir *(BAN, USAN, rINN)*

Adéfovir; Adefovirum; GS-0393; PMEA. {[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl}phosphonic acid; 9-[2-(Phosphonomethoxy)ethyl]adenine.

Адефовир

$C_8H_{12}N_5O_4P$ = 273.2.

CAS — 106941-25-7.

ATC — J05AF08.

ATC Vet — QJ05AF08.

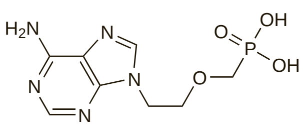

Adefovir Dipivoxil *(BANM, USAN, rINNM)*

Adefovir Dipivoksil; Adéfovir Dipivoxil; Adefovirum Dipivoxilum; Dipivoxilo de adefovir; GS-0840; Piv2PMEA; *Bis*(POM)PMEA. 9-[2-({Bis[(pivaloyloxy)methoxy]phosphinyl}methoxy)ethyl]adenine.

Адефовир Дипивоксил

$C_{20}H_{32}N_5O_8P$ = 501.5.

CAS — 142340-99-6.

ATC — J05AF08.

ATC Vet — QJ05AF08.

Adverse Effects

The most common adverse effects reported from adefovir have been gastrointestinal effects including nausea, flatulence, diarrhoea, dyspepsia, and abdominal pain. Other common adverse effects are headache and asthenia. There have also been reports of pruritus and skin rashes. Increases in serum-creatinine concentrations may occur and there have been instances of renal impairment and acute renal failure; proximal renal tubulopathy, Fanconi syndrome, and hypophosphataemia have also been reported. Raised liver enzyme concentrations may occur and severe acute exacerbation of hepatitis has been reported after stopping treatment with adefovir.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p.914).

Precautions

Adefovir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Adefovir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Careful differentiation should be made between patients whose liver enzyme concentrations become elevated due to response to treatment and those in whom it is indicative of toxicity. Exacerbation of hepatitis has been reported in patients who developed resistance to adefovir and in those who stopped adefovir; patients who stop treatment should be monitored closely for an appropriate period. In order to minimise the risk of resistance in patients with lamivudine-resistant hepatitis B, adefovir should be used with lamivudine and not as monotherapy. Patients taking adefovir should be monitored every 3 months for signs of deteriorating renal function; particular care should be exercised in patients with a creatinine clearance of less than 50 mL/minute, who may require dosage modification, and in those receiving other drugs that may affect renal function.

Use of adefovir to treat chronic hepatitis B infection in patients with undiagnosed or untreated HIV infection may result in the emergence of resistant strains of HIV. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with adefovir.

Breast feeding. It is not known whether adefovir is distributed into breast milk but licensed product information recommends that mothers should not breast feed if taking adefovir.

Pregnancy. Studies in *rodents* given high intravenous doses of adefovir (systemic exposure 38 times that in the human) have found it to be fetotoxic or embryotoxic; those given high oral doses (systemic exposure 23 to 40 times that in the human) or lower intravenous doses (systemic exposure 12 times that in the human) did not show evidence of teratogenicity or embryotoxicity. There are no studies available on the use of adefovir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Caution should be exercised when adefovir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug. Care is required when adefovir is given with other drugs with the potential for nephrotoxicity.

Antiviral Action

Adefovir is converted intracellularly in stages to the diphosphate, which then inhibits the DNA synthesis of hepatitis B virus through competitive inhibition of reverse transcriptase and incorporation into viral DNA. At high doses it has some activity against HIV.

Antiviral resistance. The development of antiviral resistance is a concern with long-term nucleoside or nucleotide treatment for chronic hepatitis B. Studies[1-4] in patients with chronic hepatitis B showed no resistance to adefovir after 1 year of treatment, but resistance rates increased over time to about 11%, 18%, and 29% at year 3, 4, and 5 respectively. Adefovir was found to be effective in patients who had previously developed resistance to lamivudine.[4]

1. Marcellin P, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348:** 808–16. Correction. *ibid.*: 1192.
2. Hadziyannis SJ, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348:** 800–7. Correction. *ibid.*; 1192.
3. Hadziyannis SJ, *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; **352:** 2673–81.
4. Delaney WE. Progress in the treatment of chronic hepatitis B: long-term experience with adefovir dipivoxil. *J Antimicrob Chemother* 2007; **59:** 827–32.

Pharmacokinetics

After oral doses adefovir dipivoxil is rapidly converted to adefovir. Peak plasma concentrations of adefovir occur after about 0.6 to 4 hours. Bioavailability is reported to be 59% after a single oral dose. Absorption is delayed but not reduced when given with food. Adefovir is widely distributed to body tissues, particularly into the kidneys, liver, and intestines. Less than 4% is bound to plasma or serum proteins. Adefovir is excreted renally by glomerular filtration and active tubular secretion; the terminal elimination half-life is reported to be about 7 hours. Adefovir is partially removed by haemodialysis.

Uses and Administration

Adefovir is a nucleotide reverse transcriptase inhibitor, structurally related to adenine, that is given orally as the prodrug adefovir dipivoxil for the treatment of chronic **hepatitis B** (p.851). It is used in adults with decompensated liver disease, or with compensated liver disease with evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of adefovir dipivoxil is 10 mg once daily. For details of dosage modification in patients with renal impairment, see below.

Adefovir was initially investigated for the treatment of **HIV infection**, but its use is limited by nephrotoxicity due to the high doses needed.

◊ References.

1. Dando TM, Plosker GL. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; **63:** 2215–34.
2. Rivkin AM. Adefovir dipivoxil in the treatment of chronic hepatitis B. *Ann Pharmacother* 2004; **38:** 625–33.
3. Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. *Int J Clin Pract* 2004; **58:** 877–86.

Administration in renal impairment. The dosage of adefovir dipivoxil should be reduced in patients with renal impairment. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: usual 10 mg once-daily dosage (above)
- CC 30 to 49 mL/minute: 10 mg every 48 hours
- CC 10 to 29 mL/minute: 10 mg every 72 hours
- haemodialysis patients: 10 mg every 7 days after dialysis

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Biovir; Hepsera; ***Austral.:*** Hepsera; ***Belg.:*** Hepsera; ***Chile:*** Hepsera; ***Cz.:*** Hepsera; ***Denm.:*** Hepsera; ***Fin.:*** Hepsera; ***Ger.:*** Hepsera; ***Gr.:*** Hepsera; ***Hong Kong:*** Hepsera; ***Hung.:*** Hepsera; ***India:*** Adesera; ***Indon.:*** Hepsera; ***Irl.:*** Hepsera; ***Israel:*** Hepsera; ***Ital.:*** Hepsera; ***Malaysia:*** Hepsera; ***Mex.:*** Hepsera; ***Neth.:*** Hepsera; ***Norw.:*** Hepsera; ***NZ:*** Hepsera; ***Philipp.:*** Hepsera; ***Pol.:*** Hepsera; ***Port.:*** Hepsera; ***Singapore:*** Hepsera; ***Spain:*** Hepsera; ***Swed.:*** Hepsera; ***Switz.:*** Hepsera; ***Thai.:*** Hepsera; ***Turk.:*** Hepsera; ***UK:*** Hepsera; ***USA:*** Hepsera; ***Venez.:*** Hepsera.

Multi-ingredient: ***Fr.:*** Hepsera.

Amprenavir *(BAN, USAN, rINN)*

Amprenaviiri; Amprénavir; Amprenavirum; KVX-478; VX-478; 141W94. (3*S*)-Tetrahydro-3-furyl{(*S*)-α-[(1*R*)-1-hydroxy-2-(*N*[1]-isobutylsulfanilamido)ethyl]phenethyl}carbamate.

Ампренавир

$C_{25}H_{35}N_3O_6S$ = 505.6.

CAS — 161814-49-9.

ATC — J05AE05.

ATC Vet — QJ05AE05.

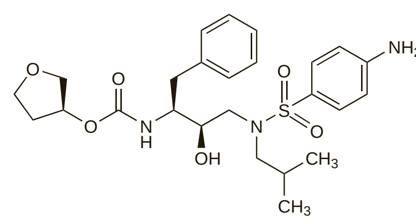

Adverse Effects

Adverse effects associated with antiretroviral regimens containing amprenavir are mostly mild to moderate. The most common adverse effects are gastrointestinal disturbances such as diarrhoea, flatulence, nausea, and vomiting. Other commonly reported adverse effects include fatigue, headache, oral paraesthesia, and taste disorders, while the most frequently reported serious adverse effects include peripheral paraesthesias, skin rash, and mood disorders (including depression). Mild to moderate rashes (usually erythematous or maculopapular and sometimes pruritic), generally occur during the second week of treatment and resolve within 2 weeks. A possible association with Stevens-Johnson syndrome has been reported with amprenavir.

Precautions

Amprenavir (when given with ritonavir) is contra-indicated in patients with severe hepatic impairment, and should be used with caution (and liver enzyme values monitored), in patients with mild to moderate liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Treatment with amprenavir should be permanently stopped in patients who develop a severe or life-threatening skin rash or a skin rash with associated systemic or allergic symptoms or mucosal involvement.

Amprenavir is a sulfonamide and should be used with caution in patients known to be allergic to sulfonamides. The oral solution and capsule formulations (*Agenerase, GlaxoSmithKline*) also provide high daily doses of vitamin E (see p.1993). The oral solution has a high content of propylene glycol, present as an excipient, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p.2374.

Pregnancy. Amprenavir has been associated with teratogenicity in *animals*. The solution is contra-indicated in pregnancy due to the high propylene glycol content.

Interactions

Amprenavir is reported to be metabolised by the cytochrome P450 isoenzyme CYP3A4. It is also a modest inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that affect these isoenzymes may modify amprenavir plasma concentrations and amprenavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system.

Amprenavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam) and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of amprenavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance.

Agenerase oral solution (*GlaxoSmithKline*) is contra-indicated in patients taking disulfiram or other products that reduce alcohol metabolism (such as metronidazole) and in those taking alcohol-containing products (such as ritonavir oral solution) because of the potential risk of toxicity from its propylene glycol content.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Amprenavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance between HIV-protease inhibitors may occur, but cross-resistance between HIV-protease inhibitors and reverse transcriptase inhibitors is considered unlikely. Mechanisms of resistance to amprenavir may differ from those of other HIV-protease inhibitors.

Pharmacokinetics

Amprenavir is rapidly and well absorbed from the gastrointestinal tract after oral doses. Absorption is impaired by ingestion with a high-fat meal. Amprenavir capsules and oral solution are not bioequivalent; oral bioavailability is about 14% lower from the oral solution formulation than from the capsule formulation (*Agenerase, GlaxoSmithKline*). Peak plasma concentrations are attained 1 to 2 hours after a single dose. It is about 90% bound to plasma proteins. Amprenavir is metabolised by hepatic cytochrome P450 isoenzyme CYP3A4. It is excreted mainly in the faeces as metabolites. The plasma elimination half-life is 7.1 to 10.6 hours.

◊ References.

1. Sadler BM, Stein DS. Clinical pharmacology and pharmacokinetics of amprenavir. *Ann Pharmacother* 2002; **36:** 102–18.
2. Stein DS, *et al.* Pharmacokinetic and pharmacodynamic analysis of amprenavir-containing combination therapy in HIV-1-infected children. *J Clin Pharmacol* 2004; **44:** 1301–8.
3. Yogev R, *et al.* Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; **49:** 336–41.

Uses and Administration

Amprenavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when amprenavir is used alone, and it is therefore used with other antiretrovirals.

Amprenavir is given orally as capsules or solution but the bioavailability of these formulations (*Agenerase, GlaxoSmithKline*) differ and their doses are not interchangeable.

- In adults and adolescents (13 to 16 years) weighing 50 kg or more the *capsules* are given in a dose of 1.2 g twice daily; when given with ritonavir (ritonavir-boosted amprenavir) the recommended dose is amprenavir 600 mg with ritonavir 100 mg twice daily or amprenavir 1.2 g with ritonavir 200 mg once daily.
- The *oral solution* is given in a dose of 17 mg/kg three times daily (maximum daily dose 2.8 g) or 1.4 g twice daily.

For details of doses in children and patients weighing less than 50 kg, see below. For dosage in hepatic impairment, also see below.

Amprenavir is also used in the form of the prodrug fosamprenavir (see p.877), which may aid compliance by reducing adverse effects and increasing flexibility of dosing.

◊ Reviews.

1. Noble S, Goa KL. Amprenavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000; **60:** 1383–1410.

Administration in children. For the treatment of HIV infection in children 4 to 12 years of age and in adolescents (13 to 16 years) weighing less than 50 kg, amprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight:

- the *capsules* are given in an oral dose of 20 mg/kg twice daily or 15 mg/kg three times daily, to a maximum daily dose of 2.4 g, or
- the *solution* is given in an oral dose of 22.5 mg/kg twice daily or 17 mg/kg three times daily, to a maximum daily dose of 2.8 g

Administration in hepatic impairment. Amprenavir should be used with caution and in reduced doses in patients with hepatic impairment. Additionally, the oral solution contains propylene glycol and extra restrictions may apply.

The following doses have been recommended in UK licensed product information:

oral solution:
- do not use

capsules:
- moderate impairment: 450 mg twice daily
- severe impairment: 300 mg twice daily

The following doses have been recommended in US product information:

oral solution:
- Child-Pugh score 5 to 8: 513 mg twice daily
- Child-Pugh score 9 to 12: 342 mg twice daily
- hepatic failure: do not use

capsules:
- Child-Pugh score 5 to 8: 450 mg twice daily
- Child-Pugh score 9 to 12: 300 mg twice daily

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Agenerase; ***Austral.:*** Agenerase; ***Austria:*** Agenerase; ***Belg.:*** Agenerase†; ***Braz.:*** Agenerase; ***Canad.:*** Agenerase; ***Chile:*** Agenerase; ***Cz.:*** Agenerase; ***Denm.:*** Agenerase†; ***Fin.:*** Agenerase; ***Fr.:*** Agenerase; ***Ger.:*** Agenerase; ***Gr.:*** Agenerase; ***Irl.:*** Agenerase; ***Israel:*** Agenerase; ***Ital.:*** Agenerase; ***Mex.:*** Agenerase; ***Neth.:*** Agenerase; ***Norw.:*** Agenerase†; ***NZ:*** Agenerase; ***Pol.:*** Agenerase; ***Port.:*** Agenerase; ***Rus.:*** Agenerase (Агенераза); ***Spain:*** Agenerase; ***Swed.:*** Agenerase†; ***Switz.:*** Agenerase; ***Turk.:*** Agenerase; ***UK:*** Agenerase†; ***USA:*** Agenerase†; ***Venez.:*** Agenerase.

Atazanavir Sulfate *(USAN, rINNM)*

Atazanavir, Sulfate d'; Atazanavir Sulphate *(BANM)*; Atazanaviri Sulfas; BMS-232632-05; BMS-232632 (atazanavir); Sulfato de atazanavir. Dimethyl (3*S*,8*S*,9*S*,12*S*)-9-Benzyl-3,12-di-*tert*-butyl-8-hydroxy-4,11-dioxo-6-(*p*-2-pyridylbenzyl)-2,5,6,10,13-pentaazatetradecanedioate sulfate (1:1).

Атазанавира Сульфат

$C_{38}H_{52}N_6O_7,H_2SO_4 = 802.9.$

CAS — 198904-31-3 (atazanavir); 229975-97-7 (atazanavir sulfate).

ATC — J05AE08.

ATC Vet — QJ05AE08.

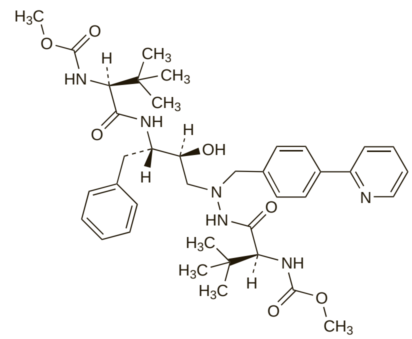

(atazanavir)

Adverse Effects

Commonly reported adverse effects of moderate or greater intensity associated with antiretroviral regimens containing atazanavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, and jaundice), headache, insomnia, and peripheral neurological symptoms, and scleral icterus. Other commonly reported adverse effects are asthenia and fatigue. Mild to moderate rashes (usually maculopapular) generally occurring after 8 weeks of treatment and resolving within 1 to 2 weeks have been reported. Stevens-Johnson syndrome and erythema multiforme have also been reported in patients given atazanavir. Atazanavir may prolong the PR interval of the ECG and asymptomatic first-degree AV block has been reported in some patients. Cases of nephrolithiasis have occurred. Most patients taking atazanavir have asymptomatic elevations in unconjugated bilirubin, which is reversible upon stopping treatment. Other abnormal laboratory results include elevated amylase and lipase, elevated liver enzymes, and low neutrophils.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including atazanavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including atazanavir. Metabolic abnormalities such as insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported; atazanavir does not appear to have a negative effect on lipid levels. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Atazanavir is contra-indicated in patients with severe hepatic impairment and when given with ritonavir is also contra-indicated in more moderate hepatic impairment. It should be used with caution, and liver enzymes values monitored, in patients with mild liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Caution should be exercised in patients with pre-existing cardiac conduction disorders or in those taking drugs that prolong the PR or increase the QT intervals. Patients developing jaundice or scleral icterus associated with hyperbilirubinaemia should be tried on an alternative antiretroviral; dose reductions of atazanavir should not be considered.

Pregnancy. Atazanavir has not been associated with teratogenicity in *animals*. It is not known whether atazanavir given to mothers will exacerbate physiologic hyperbilirubinaemia and lead to kernicterus in neonates and young infants.

Interactions

Atazanavir is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and inhibits CYP3A4, CYP2C8, and UGT1A1. Use with drugs primarily metabolised by these isoenzymes may result in increases in their plasma concentrations, while drugs that inhibit CYP3A4 may increase atazanavir plasma concentrations. When ritonavir-boosted atazanavir is given, the drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

Atazanavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine), antihistamines (astemizole and terfenadine), antineoplastic (irinotecan), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam, triazolam), and statins (simvastatin and lovastatin). Proton pump inhibitors, rifampicin, and St John's wort decrease the concentration of atazanavir; use with the antiretroviral is not recommended due to possible loss of its activity and development of resistance. Atazanavir should also not be given to patients taking indinavir, as indirect hyperbilirubinaemia may result. Atazanavir is also contra-indicated with irinotecan as azatanavir's inhibition of UGT1A1 may increase irinotecan toxicity.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Atazanavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Atazanavir is rapidly absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring after 2 to 2.5 hours. On multiple dosing with a ritonavir-boosted regimen peak plasma concentrations are achieved after 3 hours. Bioavailability (of both ritonavir-boosted and non-boosted regimens) is enhanced if given with food. Atazanavir is reported to be 86% bound to serum proteins. It is distributed into semen and into the CSF. Atazanavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A; the metabolites appear to be inactive. Atazanavir is predominantly excreted in faeces, mainly as metabolites, and to a smaller extent in the urine. The terminal elimination half-life of atazanavir is reported to be about 7 hours and 8.6 hours after a ritonavir-boosted regimen.

◊ Reviews.

1. Le Tiec C, *et al.* Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* 2005; **44:** 1035–50.

Uses and Administration

Atazanavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when atazanavir is used alone, and it is therefore used with other antiretrovirals.

Atazanavir is given orally as the sulfate with food, but doses are expressed in terms of atazanavir; 228 mg of atazanavir sulfate is equivalent to about 200 mg of atazanavir.

The usual adult dose in treatment-naive patients is 400 mg once daily. Ritonavir-boosted atazanavir (atazanavir 300 mg once daily with ritonavir 100 mg once daily) should be used when given with tenofovir, efavirenz, H_2-receptor antagonists, or proton pump inhibitors.

The usual dose in therapy-experienced patients is 300 mg once daily with ritonavir 100 mg once daily. A dose of atazanavir 400 mg once daily with ritonavir 100 mg once daily should be used when given with both tenofovir and an H_2-receptor antagonist.

For details of doses in children and adolescents, see below.

For details of recommended doses of atazanavir in patients with hepatic or renal impairment, see below.

◊ Reviews.

1. Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004; **38:** 1599–1604.
2. Musial BL, *et al.* Atazanavir: a new protease inhibitor to treat HIV infection. *Am J Health-Syst Pharm* 2004; **61:** 1365–74.
3. Orrick JJ, Steinhart CR. Atazanavir. *Ann Pharmacother* 2004; **38:** 1664–74.
4. Swainston Harrison T, Scott LJ. Atazanavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2309–36.

Administration in children. For the treatment of HIV infection in children 6 years of age and older and adolescents, atazanavir is given orally with food. Doses are based on body-weight.

The recommended dosage of atazanavir with ritonavir in *treatment-naive* patients at least 6 years of age is:

- 15 to 24 kg: atazanavir 150 mg once daily with ritonavir 80 mg once daily
- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

For *treatment-naive* patients at least 13 years of age and 39 kg, who are unable to tolerate ritonavir, the recommended dose is atazanavir 400 mg once daily.

The recommended dosage of atazanavir with ritonavir in *treatment-experienced* patients at least 6 years of age is:

- 25 to 31 kg: atazanavir 200 mg once daily with ritonavir 100 mg once daily
- 32 to 38 kg: atazanavir 250 mg once daily with ritonavir 100 mg once daily
- 39 kg or more: atazanavir 300 mg once daily with ritonavir 100 mg once daily

Administration in hepatic impairment. In treatment-naive patients the oral dose of atazanavir should be adjusted in hepatic impairment as follows:

- mild hepatic impairment (Child-Pugh category A): use with caution (no specific reduction recommended)
- moderate impairment (Child-Pugh category B): atazanavir 300 mg daily
- severe hepatic impairment (Child-Pugh category C): not recommended

Ritonavir-boosted atazanavir regimens should be used with caution in patients with mild hepatic impairment and should not be used in those with moderate to severe hepatic impairment.

Administration in renal impairment. Oral dose adjustments are not usually necessary for patients with renal impairment. However, US licensed product information recommends that treatment-naive patients on haemodialysis should be given atazanavir 300 mg once daily with ritonavir 100 mg once daily and that atazanavir should not be used in treatment-experienced patients on haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Reyataz; ***Austral.:*** Reyataz; ***Belg.:*** Reyataz; ***Braz.:*** Reyataz; ***Canad.:*** Reyataz; ***Chile:*** Reyataz; ***Cz.:*** Reyataz; ***Denm.:*** Reyataz; ***Fin.:*** Reyataz; ***Fr.:*** Reyataz; ***Ger.:*** Reyataz; ***Gr.:*** Reyataz; ***Hong Kong:*** Reyataz; ***Hung.:*** Reyataz; ***Indon.:*** Reyataz; ***Irl.:*** Reyataz; ***Ital.:*** Reyataz; ***Jpn:*** Reyataz; ***Malaysia:*** Reyataz; ***Mex.:*** Reyataz; ***Neth.:*** Reyataz; ***Norw.:*** Reyataz; ***NZ:*** Reyataz; ***Pol.:*** Reyataz; ***Port.:*** Reyataz; ***Rus.:*** Reyataz (Реатаз); ***Singapore:*** Reyataz; ***Spain:*** Reyataz; ***Swed.:*** Reyataz; ***Switz.:*** Reyataz; ***Thai.:*** Reyataz; ***UK:*** Reyataz; ***USA:*** Reyataz.

Brivudine *(rINN)*

Brivudin; Brivudina; Brivudinum; BVDU. (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine.

Бривудин

$C_{11}H_{13}BrN_2O_5$ = 333.1.

CAS — 69304-47-8.

ATC — J05AB15.

ATC Vet — QJ05AB15.

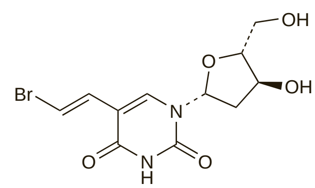

Profile

Brivudine is a nucleoside analogue effective *in vitro* against herpes simplex virus type 1 and varicella-zoster virus; other viruses including herpes simplex virus type 2 have been reported to be sensitive, but only at relatively high concentrations. The activity appears to be due, at least in part, to selective phosphorylation of brivudine by viral deoxythymidine kinase in preference to cellular kinases. There is the possibility of cross-resistance developing between brivudine and aciclovir because of some similar features in their mode of action (see p.863).

Brivudine is given orally in the treatment of herpes zoster (p.855) in a dose of 125 mg daily for 7 days. It has also been given orally for herpes simplex infection and has been used topically.

◊ References.

1. Keam SJ, *et al.* Brivudin (bromovinyl deoxyuridine). *Drugs* 2004; **64:** 2091–7.
2. Wassilew S. Collaborative Brivudin PHN Study Group. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients. A randomized, double-blind, multinational study. *J Eur Acad Dermatol Venereol* 2005; **19:** 47–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Zerpex; ***Cz.:*** Zostevir; ***Ger.:*** Zostex; ***Gr.:*** Brivir; Zostevir; ***Ital.:*** Brivirac; Zecovir; ***Port.:*** Bridic; Zostex; ***Spain:*** Brinix; Nervinex; Nervol; Zostydol†; ***Switz.:*** Brivex; ***Turk.:*** Zostex.

Cidofovir *(BAN, USAN, rINN)*

Cidofovirum; GS-504; GS-0504; HPMPC; Sidofoviiri; Sidofovir. {[(*S*)-2-(4-Amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)-ethoxy]methyl}phosphonic acid; 1-[(*S*)-3-Hydroxy-2-(phosphonomethoxy)propyl]-cytosine.

Цидофовир

$C_8H_{14}N_3O_6P$ = 279.2.

CAS — 113852-37-2 (anhydrous cidofovir); 149394-66-1 (cidofovir dihydrate).

ATC — J05AB12.

ATC Vet — QJ05AB12.

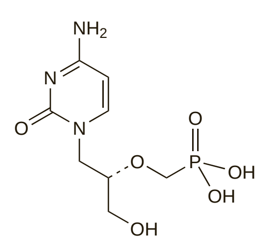

The symbol † denotes a preparation no longer actively marketed

Adverse Effects

The most serious dose-limiting adverse effect of cidofovir is nephrotoxicity, the incidence and severity of which can be reduced by use with probenecid and by ensuring adequate hydration. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Low plasma-bicarbonate concentrations and metabolic acidosis, sometimes associated with proximal tubule injury and renal wasting syndrome (including Fanconi's syndrome) or with liver dysfunction and pancreatitis, have been reported. Reversible neutropenia has also occurred. Other adverse effects include nausea and vomiting, fever, asthenia, skin rash, dyspnoea, alopecia, and ocular hypotony (decreased intra-ocular pressure). Iritis or uveitis has been reported.

Cidofovir is carcinogenic and embryotoxic in *animals* and may have the potential to cause male infertility (see Precautions, below).

Effects on the eyes. Ocular adverse effects associated with intravenous use of cidofovir include iritis,[1] uveitis,[2-4] and ocular hypotony.[4] While development of ocular hypotony is considered to warrant withdrawal of cidofovir,[2] uveitis or iritis alone may respond to topical corticosteroids and cycloplegics thus allowing antiviral therapy to be continued; cidofovir must be stopped if there is no response or worsening of symptoms.

1. Tseng AL, *et al.* Iritis associated with intravenous cidofovir. *Ann Pharmacother* 1999; **33:** 167–71.
2. Ambati J, *et al.* Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. *Br J Ophthalmol* 1999; **83:** 1153–8.
3. Rougier M-B, *et al.* Uvéite antérieure et cidofovir. *J Fr Ophtalmol* 2001; **24:** 491–5.
4. Rapp P, *et al.* Uvéite bilatérale et hypotonie définitive due au cidofovir intraveineux: à propos d'un cas. *J Fr Ophtalmol* 2003; **26:** 717–19.

Effects on the kidneys. Dose-related nephrotoxicity is the most severe adverse effect of cidofovir and marked proteinuria has been reported in up to 50% of patients. There have been instances of acute renal failure after only 1 or 2 doses, and some fatalities. Fanconi's syndrome associated with renal tubular damage has been reported in 2% of patients and, in one such patient, occurred on the third injection of cidofovir and resulted in irreversible renal impairment.[1] Reversible renal impairment with persisting Fanconi syndrome was reported in another.[2] A case of nephrogenic diabetes insipidus without premonitory laboratory abnormalities has also been reported in a patient given cidofovir.[3]

1. Vittecoq D, *et al.* Fanconi syndrome associated with cidofovir therapy. *Antimicrob Agents Chemother* 1997; **41:** 1846.
2. Kazory A, *et al.* Simultaneous development of Fanconi syndrome and acute renal failure associated with cidofovir. *J Antimicrob Chemother* 2007; **60:** 193–4.
3. Schliefer K, *et al.* Nephrogenic diabetes insipidus in a patient taking cidofovir. *Lancet* 1997; **350:** 413–14. Correction. *ibid.*; 1558.

Precautions

Cidofovir is contra-indicated in patients with renal impairment. Renal function should be measured before each dose. In the UK it is recommended that treatment should be interrupted or stopped if renal function deteriorates, but in the USA reduction of the dosage is permitted for increases in serum creatinine up to 300 to 400 micrograms/dL above baseline. Patients should receive oral probenecid and intravenous hydration with each dose of cidofovir. Neutrophil counts should also be monitored and regular ophthalmological follow-up is recommended. Patients with diabetes mellitus are at increased risk of ocular hypotony.

Cidofovir is carcinogenic and embryotoxic in *animals*. Cidofovir should not be given during pregnancy and both sexes should use effective methods of contraception during treatment; in addition, effective contraception should be used, for 1 month by women and for 3 months by men, after the end of treatment. There is also a possibility that cidofovir may cause male infertility.

Cidofovir should be given intravenously only; direct intra-ocular injection has been associated with significant ocular hypotony and visual impairment and is contra-indicated.

Interactions

Additive nephrotoxicity may occur if cidofovir is used with other nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, vancomycin, or NSAIDs. Potentially nephrotoxic drugs should be stopped at least 7 days before starting cidofovir. Probenecid, which is given with cidofovir, may alter the clearance of other drugs (see Interactions under Probenecid, p.558).

Patients with CMV retinitis are at increased risk of adverse inflammatory effects if cidofovir is given within 2 to 4 weeks of intravitreal fomivirsen.

Antiviral Action

Cidofovir undergoes intracellular phosphorylation by cellular kinases to the antiviral metabolite, cidofovir diphosphate, which acts as a competitive inhibitor of viral DNA polymerase. It is active against a range of herpesviruses including CMV, and, since its activity is not reliant on viral enzymes, may retain activity against some aciclovir- and foscarnet-resistant viruses. Cross-resistance with ganciclovir is common.

◊ References.

1. Cherrington JM, *et al.* In vitro antiviral susceptibilities of isolates from cytomegalovirus retinitis patients receiving first- or second-line cidofovir therapy: relationship to clinical outcome. *J Infect Dis* 1998; **178:** 1821–5.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

After intravenous doses of cidofovir, serum concentrations decline with a reported terminal half-life of about 2.2 hours (the intracellular half-life of the active diphosphate may be up to 65 hours). Cidofovir is eliminated mainly by renal excretion, both by glomerular filtration and tubular secretion. About 80 to 100% of a dose is recovered unchanged from the urine within 24 hours. Use with probenecid may reduce the excretion of cidofovir to some extent by blocking tubular secretion, although 70 to 85% has still been reported to be excreted unchanged in the urine within 24 hours.

◊ References.

1. Cundy KC. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovir and adefovir. *Clin Pharmacokinet* 1999; **36:** 127–43.
2. Brody SR, *et al.* Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. *Clin Pharmacol Ther* 1999; **65:** 21–8.
3. Wolf DL, *et al.* Pharmacokinetics and renal effects of cidofovir with a reduced dose of probenecid in HIV-infected patients with cytomegalovirus retinitis. *J Clin Pharmacol* 2003; **43:** 43–51.

Uses and Administration

Cidofovir is a nucleoside analogue that is active against herpesviruses. It is used in the treatment of CMV retinitis (p.853) in patients with AIDS, and is being investigated for ocular herpes simplex and other viral infections.

In the treatment of CMV retinitis, cidofovir is given in a dose of 5 mg/kg by intravenous infusion over 1 hour once a week for 2 consecutive weeks, then once every 2 weeks for maintenance. Probenecid 2 g is given orally 3 hours before each dose of cidofovir and further 1-g doses of probenecid at 2 and 8 hours after completion of the infusion. To ensure adequate hydration, 1 litre of sodium chloride 0.9% is given by intravenous infusion over 1 to 2 hours immediately before each infusion of cidofovir; if the additional fluid load can be tolerated, a further 1 litre of sodium chloride 0.9% may be infused over 1 to 3 hours, starting at the same time as (or immediately after) the cidofovir infusion. For details of modified use of cidofovir in patients with renal impairment, see below.

Cidofovir has also been given experimentally by intravitreal injection but the commercially available formulation is unsuitable for use by this route and licensed product information advises against it (see Precautions, above).

An orally active prodrug of cidofovir known as cyclic-HPMPC (GS-930) is under investigation. Cidofovir has also been investigated for topical use.

◊ Reviews.

1. Lea AP, Bryson HM. Cidofovir. *Drugs* 1996; **52:** 225–30.
2. Kendle JB, Fan-Havard P. Cidofovir in the treatment of cytomegaloviral disease. *Ann Pharmacother* 1998; **32:** 1181–92.
3. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999; **58:** 325–45.
4. De Clercq E. Cidofovir in the treatment of poxvirus infections. *Antiviral Res* 2002; **55:** 1–13.
5. Snoeck R, De Clercq E. Role of cidofovir in the treatment of DNA virus infections, other than CMV infections, in immunocompromised patients. *Curr Opin Investig Drugs* 2002; **3:** 1561–6.

Administration in renal impairment. Cidofovir is contra-indicated in patients with pre-existing renal impairment (serum creatinine more than 1.5 mg/dL) and should be interrupted or stopped if serum creatinine increases by more than 500 micrograms/dL during therapy; in the USA, a reduction in the maintenance dose from 5 to 3 mg/kg is permitted for increases of serum creatinine of up to 300 to 400 micrograms/dL above baseline.

Viral infections. In addition to its use in CMV retinitis, cidofovir has been studied in herpes simplex infections,[1-6] papillomavirus infections,[7-13] molluscum contagiosum,[11,14,15] and progressive multifocal leukoencephalopathy.[16-20]

1. Lalezari JP, *et al.* Treatment with intravenous (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]-cytosine of acyclovir-resistant mucocutaneous infection with herpes simplex virus in a patient with AIDS. *J Infect Dis* 1994; **170:** 570–2.
2. Lalezari J, *et al.* A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis* 1997; **176:** 892–8.
3. Sacks SL, *et al.* A multicenter phase I/II dose escalation study of single-dose cidofovir gel for treatment of recurrent genital herpes. *Antimicrob Agents Chemother* 1998; **42:** 2996–9.
4. Bryant P, *et al.* Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. *Pediatr Infect Dis J* 2001; **20:** 1083–6.
5. Kopp T, *et al.* Successful treatment of an aciclovir-resistant herpes simplex type 2 infection with cidofovir in an AIDS patient. *Br J Dermatol* 2002; **147:** 134–8.
6. Andrei G, *et al.* Dual infection with polyomavirus BK and acyclovir-resistant herpes simplex virus successfully treated with cidofovir in a bone marrow transplant recipient. *Transpl Infect Dis* 2007; **9:** 126–31.
7. Snoeck R, *et al.* Treatment of anogenital papillomavirus infections with an acyclic nucleoside phosphonate analogue. *N Engl J Med* 1995; **333:** 943–4.
8. Davis MDP, *et al.* Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. *J Am Acad Dermatol* 2000; **43:** 340–3.
9. Descamps V, *et al.* Topical cidofovir for bowenoid papulosis in an HIV-infected patient. *Br J Dermatol* 2001; **144:** 642–3.
10. Snoeck R, *et al.* Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis* 2001; **33:** 597–602.
11. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS: a pilot study. *J Eur Acad Dermatol Venereol* 2000; **14:** 484–8.
12. Husak R, *et al.* Refractory human papillomavirus-associated oral warts treated topically with 1-3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol* 2005; **152:** 590–1.
13. Kottke MD, Parker SRS. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; **55:** 533–6.
14. Davies EG, *et al.* Topical cidofovir for severe molluscum contagiosum. *Lancet* 1999; **353:** 2042.
15. Toro JR, *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. *Arch Dermatol* 2000; **136:** 983–5.
16. Segarra-Newnham M, Vodolo KM. Use of cidofovir in progressive multifocal leukoencephalopathy. *Ann Pharmacother* 2001; **35:** 741–4.
17. Razonable RR, *et al.* Cidofovir treatment of progressive multifocal leukoencephalopathy in a patient receiving highly active antiretroviral therapy. *Mayo Clin Proc* 2001; **76:** 1171–5.
18. Marra CM, *et al.* Adult AIDS Clinical Trials Group 363 Team. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002; **16:** 1791–7.
19. Garvey L, *et al.* Progressive multifocal leukoencephalopathy: prolonged survival in patients treated with protease inhibitors and cidofovir: a case series. *AIDS* 2006; **20:** 791–3.
20. Viallard JF, *et al.* Improvement of progressive multifocal leukoencephalopathy after cidofovir therapy in a patient with a destructive polyarthritis. *Infection* 2007; **35:** 33–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Vistide; ***Austria:*** Vistide; ***Belg.:*** Vistide; ***Cz.:*** Vistide; ***Fr.:*** Vistide; ***Ger.:*** Vistide; ***Gr.:*** Vistide†; ***Ital.:*** Vistide; ***Neth.:*** Vistide; ***Port.:*** Vistide; ***Spain:*** Vistide; ***Switz.:*** Vistide; ***UK:*** Vistide; ***USA:*** Vistide.

Darunavir *(USAN, rINN)*

Darunavirum; TMC-114; UIC-94017. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-2-hydroxy-3-(N^1-isobutylsulfanilamido)propyl]carbamate.

Дарунавир

$C_{27}H_{37}N_3O_7S = 547.7$.

CAS — 206361-99-1.

ATC — J05AE10.

ATC Vet — QJ05AE10.

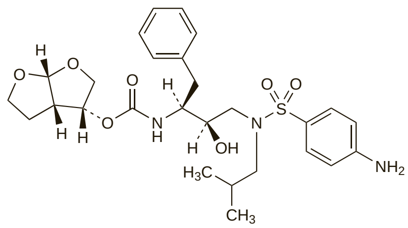

Darunavir Ethanolate *(rINNM)*

Darunavir monoethanolate.

$C_{27}H_{37}N_3O_7S,C_2H_5OH = 593.7$.

ATC — J05AE10.

ATC Vet — QJ05AE10.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing darunavir are gastrointestinal disturbances (abdominal pain, diarrhoea, nausea, and vomiting), nasopharyngitis, and hypertriglyceridaemia. Other reported adverse effects are asthenia, dizziness, fatigue, headache, and insomnia. Less frequently reported adverse effects include folliculitis, myocardial infarction, osteopenia, osteoporosis, polyuria, somnolence, tachycardia, transient ischaemic attacks, and vertigo. Severe cases of skin rashes have been reported, including erythema multiforme and Stevens-Johnson syndrome. Cases of drug-induced hepatitis, including fatalities, have been reported. Abnormal liver and pancreatic function tests and decreases in white blood cell counts have also occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including darunavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including darunavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Patients should undergo liver function tests before starting and during treatment with darunavir. It should not be used in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution (and liver enzymes values monitored), in those with mild to moderate impairment (Child-Pugh A or B) and those with chronic hepatitis B or C co-infection. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. All patients should be instructed to seek medical advice if symptoms suggestive of new or worsening hepatotoxicity occur. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. An association with erythema multiforme and Stevens-Johnson syndrome has been reported and treatment should be stopped in patients who develop skin rashes.

Interactions

Darunavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It may compete with other drugs metabolised by this enzyme, potentially resulting in increased plasma concentrations and toxicity.

Darunavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, quinidine, and systemic lidocaine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Ritonavir-boosted lopinavir, rifampicin, antiepileptics (carbamazepine, phenobarbital, and phenytoin), and St John's wort decrease the concentration of darunavir; use with darunavir is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Darunavir is a selective inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Cross-resistance may develop between some HIV-protease inhibitors, but mechanisms of resistance to darunavir may differ from those to other drugs of the class.

Pharmacokinetics

Darunavir is rapidly absorbed after oral doses, resulting in a bioavailability of 82% when taken with recommended doses of ritonavir; food increases the bioavailability. Peak plasma concentrations are reached within 2.5 to 4 hours. Darunavir is about 95% bound to plasma proteins. It is metabolised by oxidation by the cytochrome P450 system (primarily the isoenzyme CYP3A4), with at least 3 metabolites showing some antiretroviral activity. About 80% of a dose is excreted in the faeces, with 41.2% of this as unchanged drug; 14% is excreted in the urine, with 7.7% being unchanged drug. The mean terminal elimination half-life of darunavir is about 15 hours.

◊ Reviews.

1. Rittweger M, Arastéh K. Clinical pharmacokinetics of darunavir. *Clin Pharmacokinet* 2007; **46:** 739–56.

Uses and Administration

Darunavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when darunavir is used alone, and it is therefore used with other antiretrovirals.

Darunavir is boosted with low-dose ritonavir, which acts as a pharmacokinetic enhancer. It is given orally as the ethanolate, but doses are expressed in terms of the base; 325 mg of darunavir ethanolate is equivalent to about 300 mg of darunavir. The dose is 600 mg (with ritonavir 100 mg) twice daily with food.

◊ References.

1. Clotet B, *et al.* Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369:** 1169–78.
2. Busse KH, Penzak SR. Darunavir: a second-generation protease inhibitor. *Am J Health-Syst Pharm* 2007; **64:** 1593–602.
3. Fenton C, Perry CM. Darunavir: in the treatment of HIV-1 infection. *Drugs* 2007; **67:** 2791–801.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Prezista; ***Cz.:*** Prezista; ***Gr.:*** Prezita; ***Port.:*** Prezista; ***UK:*** Prezista; ***USA:*** Prezista.

Delavirdine Mesilate *(rINNM)*

Délavirdine, Mésilate de; Delavirdine Mesylate *(USAN)*; Delavirdini Mesilas; Mesilato de delavirdina; U-90152S. 1-[3-(Isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)carbonyl]-piperazine monomethanesulfonate.

Делавирдина Мезилат

$C_{22}H_{28}N_6O_3S,CH_4O_3S = 552.7$.

CAS — 136817-59-9 (delavirdine); 147221-93-0 (delavirdine mesilate).

ATC — J05AG02.

ATC Vet — QJ05AG02.

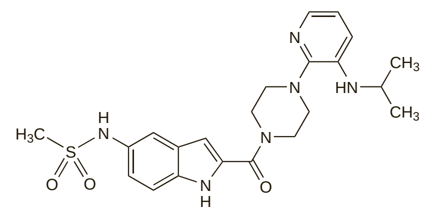

(delavirdine)

Adverse Effects

Adverse effects associated with antiretroviral regimens containing delavirdine are mostly mild to moderate. The most common adverse effect of delavirdine is skin rash, (usually diffuse, maculopapular, erythematous, and often pruritic), generally appearing within the first 3 weeks of starting therapy and resolving in 3 to 14 days. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse effects of moderate to severe intensity include generalised abdominal pain, asthenia, fatigue, fever, flu syndrome, headache, and localised pain. Other reported adverse effects include gastrointestinal disturbances (diarrhoea, nausea, vomiting), increased liver enzyme values, anxiety, depressive symptoms, insomnia, and respiratory effects (bronchitis, cough, pharyngitis, sinusitis, and upper respiratory-tract infections). Liver failure, haemolytic anaemia, rhabdomyolysis, and acute renal failure have been reported during postmarketing use.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including delavirdine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including delavirdine.

Precautions

Delavirdine should be stopped if a severe skin rash develops or if a rash is accompanied by fever, blistering, oral lesions, conjunctivitis, swelling, or muscle or joint aches. Delavirdine should be used with caution in patients with hepatic impairment.

Pregnancy. Delavirdine has been shown to be teratogenic in *animals*. Clinical studies and postmarketing data have identified 10 infants born to mothers who took delavirdine during pregnancy. Eight of the infants were born healthy, 1 infant was born HIV-positive but had no congenital abnormalities, and 1 infant was born prematurely with a small muscular ventricular septal defect that spontaneously resolved.

Interactions

Delavirdine is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Consequently it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of delavirdine. The absorption of delavirdine is reduced by drugs that raise gastric pH such as antacids and histamine H_2-antagonists.

Delavirdine is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life threatening events. These drugs include antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (alprazolam, midazolam, triazolam). The antiepileptics carbamazepine, phenytoin, and phenobarbital, the antimycobacterials rifabutin and rifampicin, and St John's wort decrease the concentration of delavirdine; use with the antiretroviral is not recommended due to the possible loss of antiviral activity and development of resistance. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antibacterials. Plasma concentrations of *dapsone* and *rifabutin* may be increased by delavirdine; *rifabutin* and *rifampicin*[1] may reduce delavirdine plasma concentrations and the use of either of these drugs with delavirdine is not recommended.

1. Borin MT, *et al.* Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. *Clin Pharmacol Ther* 1997; **61:** 544–53.

Antivirals. Use of delavirdine with buffered *didanosine* may result in reduced plasma concentrations of both drugs[1] and they should be given at least 1 hour apart; plasma concentrations of HIV-protease inhibitors including *indinavir* and *saquinavir* may be increased by delavirdine (see Antivirals, under Interactions of Indinavir, p.883) and liver function should be monitored in patients given delavirdine and saquinavir.

1. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Delavirdine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to delavirdine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Delavirdine is rapidly absorbed after oral doses, peak plasma concentrations occurring after about 1 hour. The bioavailability of delavirdine tablets is about 85% of that from an oral solution after a single dose. The bioavailability of the 100-mg tablet can be increased by about 20% by dissolving it in water before use; the 200-mg tablets do not readily disperse in water and should be swallowed intact. Delavirdine is about 98% bound to plasma proteins. It is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzyme CYP3A4 (although CYP2D6 may play some role), to several inactive metabolites. The plasma half-life after usual dosage is about 5.8 hours and ranges from 2 to 11 hours. Delavirdine is excreted as metabolites in the urine and faeces. Less than 5% is excreted in the urine unchanged.

◊ Reviews.

1. Voorman RL, *et al.* Metabolism of delavirdine, a human immunodeficiency virus type-1 reverse transcriptase inhibitor, by microsomal cytochrome P450 in humans, rats, and other species: probable involvement of CYP2D6 and CYP3A. *Drug Metab Dispos* 1998; **26:** 631–9.
2. Tran JQ, *et al.* Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2001; **40:** 207–26.
3. Shelton MJ, *et al.* Pharmacokinetics of ritonavir and delavirdine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2003; **47:** 1694–9.
4. Smith PF, *et al.* Population pharmacokinetics of delavirdine and N-delavirdine in HIV-infected individuals. *Clin Pharmacokinet* 2005; **44:** 99–109.

Uses and Administration

Delavirdine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Viral resistance emerges rapidly when delavirdine is used alone, and it is therefore used with other antiretrovirals for combination therapy of HIV infection and AIDS (p.856).

Delavirdine is given orally as the mesilate in a usual dose of 400 mg three times daily. Some tablet formulations may be dispersed in water before use in order to increase bioavailability (see above).

◊ Reviews.

1. Scott LJ, Perry CM. Delavirdine: a review of its use in HIV infection. *Drugs* 2000; **60:** 1411–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Rescriptor; ***Canad.:*** Rescriptor; ***Mex.:*** Rescriptor†; ***USA:*** Rescriptor.

Denotivir *(pINN)*

Dénotivir; Denotivirum. 5-Benzamido-4′-chloro-3-methyl-4-isothiazolecarboxanilide.

Денотивир

$C_{18}H_{14}ClN_3O_2S$ = 371.8.

CAS — 51287-57-1.

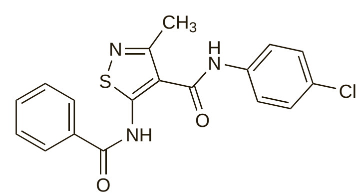

Profile

Denotivir has antiviral, antibacterial, and anti-inflammatory properties. It is used topically as a 3% cream in the treatment of herpes virus infections and in other skin disorders complicated by bacterial infection.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Polvir; Vratizolin.

Didanosine *(BAN, USAN, rINN)*

BMY-40900; ddI; ddIno; Didanocin; Didanosiini; Didanosin; Didanosina; Didanosinum; Didanozin; Didanozinas; Dideoxyinosine; NSC-612049. 2′,3′-Dideoxyinosine.

Диданозин

$C_{10}H_{12}N_4O_3$ = 236.2.

CAS — 69655-05-6.

ATC — J05AF02.

ATC Vet — QJ05AF02.

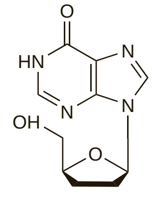

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Didanosine). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in dimethyl sulfoxide.

USP 31 (Didanosine). A white to off-white crystalline powder. Practically insoluble or insoluble in acetone and in methyl alcohol; very soluble in dimethyl sulfoxide. Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects

The most common serious adverse effects of didanosine are peripheral neuropathy and potentially fatal pancreatitis. Other commonly reported adverse effects include abdominal pain, diarrhoea, fatigue, headache, nausea, rash, and vomiting. Abnormal liver function tests may occur and hepatitis or fatal hepatic failure has been reported rarely; fatalities were reported most often in patients taking didanosine with stavudine and hydroxycarbamide. Retinal and optic-nerve changes have been reported in children, particularly in those taking higher than recommended doses; retinal depigmentation has been reported in adult patients. Other adverse effects include alopecia, anaemia, asthenia, dry mouth, fever, flatulence, parotid gland enlargement, leucopenia, hypersensitivity reactions including anaphylaxis, hyperuricaemia, and thrombocytopenia. Lactic acidosis and severe hepatomegaly with steatosis, sometimes fatal, and generally occurring after some months of treatment has been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including didanosine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including didanosine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction such as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the blood. In general, haematological abnormalities are less common in patients taking didanosine than in those taking zidovudine. However, there have been reports of thrombocytopenia associated with didanosine.[1-3]

1. Butler KM, *et al.* Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991; **324:** 137–44.
2. Lor E, Liu YQ. Didanosine-associated eosinophilia with acute thrombocytopenia. *Ann Pharmacother* 1993; **27:** 23–5.
3. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Effects on the eyes. Retinal lesions with atrophy of the retinal pigment epithelium at the periphery of the retina were reported in 4 children receiving didanosine doses of 270 to 540 mg/m^2 daily.[1]

1. Whitcup SM, *et al.* Retinal lesions in children treated with dideoxyinosine. *N Engl J Med* 1992; **326:** 1226–7.

Effects on the heart. For the possible risk of myocardial infarction in patients taking didanosine, see Effects on the Heart under Adverse Effects of Zidovudine, p.914.

Effects on the liver. Fatal fulminant hepatic failure was reported[1] in a patient receiving didanosine. A further 14 cases had been noted by the manufacturer, and elevated liver enzymes have been recorded during clinical studies.[2-5]

1. Lai KK, *et al.* Fulminant hepatic failure associated with 2′,3′-dideoxyinosine (ddI). *Ann Intern Med* 1991; **115:** 283–4.
2. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV type 1 infection and little or no experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
3. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
4. Alpha International Coordinating Committee. The Alpha trial: European/Australian randomized double-blind trial of two doses of didanosine in zidovudine-intolerant patients with symptomatic HIV disease. *AIDS* 1996; **10:** 867–80.
5. Gatell JM, *et al.* Switching from zidovudine to didanosine in patients with symptomatic HIV infection and disease progression. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; **12:** 249–58.

Effects on mental state. Recurrent mania associated with didanosine treatment has been reported in a patient.[1]

1. Brouillette MJ, *et al.* Didanosine-induced mania in HIV infection. *Am J Psychiatry* 1994; **151:** 1839–40.

Effects on metabolism. Hyperuricaemia has been reported to be a common adverse effect during clinical studies of didanosine.[1,2] Hypokalaemia occurred during didanosine therapy in 3 patients, 2 of whom had diarrhoea.[3] There has also been a report of hypertriglyceridaemia occurring on 2 occasions in a patient given didanosine;[4] it was suggested that this hyperlipidaemic effect might be a possible aetiological factor in the development of pancreatitis.

1. Cooley TP, *et al.* Once-daily administration of 2′,3′-dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex: results of a phase I trial. *N Engl J Med* 1990; **322:** 1340–5.
2. Montaner JSG, *et al.* Didanosine compared with continued zidovudine therapy for HIV-infected patients with 200 to 500 CD4 cells/mm : a double-blind, randomized, controlled trial. *Ann Intern Med* 1995; **123:** 561–71.
3. Katlama C, *et al.* Dideoxyinosine-associated hypokalaemia. *Lancet* 1991; **337:** 183.
4. Tal A, Dall L. Didanosine-induced hypertriglyceridemia. *Am J Med* 1993; **95:** 247.

Effects on the mouth. Xerostomia (dry mouth) may be a troublesome effect in patients receiving didanosine.[1,2]

1. Dodd CL, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; **340:** 790.
2. Valentine C, *et al.* Xerostomia associated with didanosine. *Lancet* 1992; **340:** 1542.

Effects on the nervous system. Peripheral neuropathy is a well recognised adverse effect of didanosine and has been the subject of a review.[1]

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; **19:** 481–94.

Effects on the pancreas. Pancreatitis is recognised as being the most serious adverse effect of didanosine and can be fatal.[1-3] It appears to be dose-related, occurring in up to 13% of patients receiving 750 mg of didanosine daily.[2,4] Pancreatitis can resolve if didanosine is withdrawn[5] and cautious reintroduction of didanosine has been possible in some patients.[6] Raised amylase concentrations[3] and glucose intolerance have been reported in patients who subsequently developed pancreatitis.

1. Bouvet E, *et al.* Fatal case of 2′,3′-dideoxyinosine-associated pancreatitis. *Lancet* 1990; **336:** 1515.
2. Kahn JO, *et al.* A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *N Engl J Med* 1992; **327:** 581–7.
3. Dolin R, *et al.* Zidovudine compared with didanosine in patients with advanced HIV-type 1 infection and little or no previous experience with zidovudine. *Arch Intern Med* 1995; **155:** 961–74.
4. Jablonowski H, *et al.* A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995; **9:** 463–9.
5. Nguyen B-Y, *et al.* Five-year follow-up of a phase I study of didanosine in patients with advanced human immunodeficiency virus infection. *J Infect Dis* 1995; **171:** 1180–9.
6. Butler KM, *et al.* Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics* 1993; **91:** 747–51.

Effects on the skin. Didanosine has been implicated in a case of Stevens-Johnson syndrome[1] and of cutaneous vasculitis.[2]

1. Parneix-Spake A, *et al.* Didanosine as probable cause of Stevens-Johnson syndrome. *Lancet* 1992; **340:** 857–8.
2. Herranz P, *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344:** 680.

Precautions

Didanosine should be used with extreme caution in patients with a history of pancreatitis and those with increased triglyceride concentrations should be observed carefully for signs of pancreatitis and treatment with didanosine interrupted in all patients with signs and symptoms of possible pancreatitis, until it has been excluded. Use with other drugs likely to cause pancreatitis or peripheral neuropathy (see Interactions, below) should preferably be avoided; treatment with didanosine should be suspended if possible when use of such drugs is essential.

It may be necessary to interrupt didanosine treatment in patients who develop peripheral neuropathy; on recovery from peripheral neuropathy a reduced dose may be tolerated. Treatment should also be interrupted if uric acid concentrations are elevated.

Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Didanosine should be given with caution to patients with hepatomegaly or other risk factors for liver disease and patients with renal or hepatic impairment; dosage reduction may be necessary. Regular checks of liver function are recommended. If liver enzymes increase to 5 times the upper limit of normal during treatment then didanosine should be stopped. Treatment with didanosine may be associated with lactic acidosis and should also be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, steatosis, or metabolic or lactic acidosis of unknown aetiology.

Children should be monitored for retinal lesions and didanosine withdrawn if they occur. Monitoring should also be considered in adults.

Interactions

Use of didanosine with other drugs known to cause pancreatitis (for example intravenous pentamidine) or with drugs that may cause peripheral neuropathy (for example metronidazole, isoniazid, and vincristine) should be avoided. If co-administration is unavoidable, patients should be monitored carefully for these adverse effects.

An increase in the area under the plasma concentration-time curve for didanosine has been reported when allopurinol or other xanthine oxidase inhibitors are given concurrently.

Plasma concentrations of didanosine may be reduced by methadone and increased by ganciclovir.

Didanosine formulations (chewable or dispersible preparation) contain an antacid and other drugs that could be affected by an increased gastric pH (for example HIV-protease inhibitors, ketoconazole, fluoroquinolone antibacterials, and dapsone) should be given at least 2 hours before didanosine. Didanosine preparations containing magnesium or aluminium antacids should not be given with tetracyclines.

Use of didanosine with tenofovir results in increased plasma concentrations of didanosine and consequently an increased risk of didanosine-related adverse effects such as peripheral neuropathy, pancreatitis, and lactic acidosis. Fatalities have been reported. There have also been reports of virological failure and emergence of resistance at an early stage of treatment when didanosine and tenofovir were given with lamivudine as part of a once daily triple nucleoside regimen. UK licensed product information for both didanosine and tenofovir does not recommend co-administration of these drugs either at standard or reduced doses of didanosine. A 250 mg daily dose of didanosine had been evaluated, but resulted in virological failure and the emergence of resistance. US product information for didanosine, however, recommends that co-administration may be undertaken with caution in patients with normal renal function. For patients weighing greater than 60 kg the dose of didanosine should be reduced to 250 mg daily, while for those weighing less than 60 kg a dose of 200 mg daily is recommended. US product information for tenofovir advises against using didanosine with tenofovir in patients under 60 kg due to a lack of data.

Ribavirin has been shown *in vitro* to increase the intracellular triphosphate levels of didanosine and to potentially increase the risk of adverse effects related to didanosine. UK product information for didanosine recommends that co-administration be undertaken with caution, while the US information does not recommend use of the two drugs together.

See also below for interactions with antivirals.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antivirals. Plasma concentrations of didanosine are roughly doubled when given *ganciclovir.*[1-3] *Valganciclovir,* the prodrug of ganciclovir, inhibits purine nucleoside phosphorylase and increases didanosine concentrations. Significant CD4+ T lymphocyte count decline and symptoms of didanosine toxicity, despite complete viral suppression, occurred in an HIV-positive patient given an antiretroviral regimen containing didanosine plus valganciclovir for the treatment of CMV enteritis. Complete CD4+ count recovery and resolution of symptoms occurred when didanosine was replaced with abacavir.[4]

Changes in the pharmacokinetics of didanosine and *zidovudine* have occurred when these drugs are given together, but results of studies have not been consistent, and the effects have generally been of limited clinical significance. For further details, see under Interactions in Zidovudine, p.915.

Tenofovir has been reported to significantly increase plasma concentrations of didanosine,[5] and may increase the risk of pancreatitis associated with didanosine.[6,7] There has also been a report of acute renal failure and fatal lactic acidosis when tenofovir was added to a regimen containing didanosine.[8]

Use of didanosine with *delavirdine* resulted in reductions in the area under the concentration-time curve for both drugs in a single-dose study.[9] Licensed product information for delavirdine recommends that these two drugs should be given at least 1 hour apart.

Absorption of some *HIV-protease inhibitors* may be reduced by the buffers in some didanosine formulations and doses should be at least 2 hours apart (see p.883).

1. Griffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 227–34.
4. Tseng AL, Salit IE. CD4+ cell count decline despite HIV suppression: a probable didanosine-valganciclovir interaction. *Ann Pharmacother* 2007; **41:** 512–17.
5. Pecora Fulco P, Kirian MA. Effect of tenofovir on didanosine absorption in patients with HIV. *Ann Pharmacother* 2003; **37:** 1325–8.
6. Blanchard JN, *et al.* Pancreatitis with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; **37:** e57–e62. Correction. *ibid.*: 995. [title of paper corrected]
7. Kirian MA, *et al.* Acute onset of pancreatitis with concomitant use of tenofovir and didanosine. *Ann Pharmacother* 2004; **38:** 1660–3.
8. Murphy MD, *et al.* Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis* 2003; **36:** 1082–5.
9. Morse GD, *et al.* Single-dose pharmacokinetics of delavirdine mesylate and didanosine in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 169–74.

Antiviral Action

Didanosine is converted intracellularly to its active form dideoxyadenosine triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

Didanosine-resistant strains of HIV emerge during didanosine therapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. Evidence for the development of didanosine-resistant HIV was reported in 36 of 64 patients with advanced HIV infection within 24 weeks of switching from zidovudine to didanosine monotherapy.[1] Patients with the didanosine resistance mutation for HIV reverse transcriptase showed a greater decline in CD4+ T cell count and increase in viral burden than those without.

Multiple-drug resistant mutations have been found in patients taking long-term combination antiretroviral therapy containing didanosine.[2]

1. Kozal MJ, *et al.* Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. *Ann Intern Med* 1994; **121:** 263–8.
2. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; **98:** 1506–13.

Pharmacokinetics

Didanosine is rapidly hydrolysed in the acid medium of the stomach and is therefore given orally with pH buffers or antacids. Bioavailability is reported to range from 20 to 40% depending on the formulation used; the bioavailability is substantially reduced if taken with or after food. Maximum plasma concentrations are achieved about 1 hour after oral dosage. Binding to plasma proteins is reported to be less than 5%. Didanosine has been reported not to cross the blood brain barrier.

Didanosine is metabolised intracellularly to the active antiviral metabolite dideoxyadenosine triphosphate. The plasma elimination half-life is reported to be about 1.5 hours. Renal clearance is by glomerular filtration and active tubular secretion; about 20% of an oral dose is recovered in the urine. Didanosine is partially cleared by haemodialysis but not by peritoneal dialysis.

◊ References.

1. Balis FM, *et al.* Clinical pharmacology of 2′,3′-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis* 1992; **165:** 99–104.
2. Morse GD, *et al.* Comparative pharmacokinetics of antiviral nucleoside analogues. *Clin Pharmacokinet* 1993; **24:** 101–23.
3. Mueller BU, *et al.* Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics* 1994; **94:** 724–31.

4. Knupp CA, *et al.* Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther* 1996; **60:** 535–42.
5. Wintergerst U, *et al.* Lack of absorption of didanosine after rectal administration in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43:** 699–701.
6. Abreu T, *et al.* Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2000; **44:** 1375–6.

Pregnancy. Fetal blood concentrations of 14 and 19% of the maternal serum-didanosine concentrations have been reported.[1] There is evidence of extensive metabolism in the placenta.[2]

1. Pons JC, *et al.* Fetoplacental passage of 2′,3′-dideoxyinosine. *Lancet* 1991; **337:** 732.
2. Dancis J, *et al.* Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr* 1993; **6:** 2–6.

Uses and Administration

Didanosine is a nucleoside reverse transcriptase inhibitor structurally related to inosine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when didanosine is used alone, and it is therefore used with other antiretrovirals.

Didanosine is given orally, usually as buffered chewable/dispersible tablets or enteric-coated capsules. Doses should be taken at least 30 minutes before, or 2 hours after, a meal. The total daily dose may be given as either a single dose or as two divided doses, the choice being dependent upon both the formulation and the strength used. For adults weighing more than 60 kg the recommended dose is 400 mg daily and for those under 60 kg, 250 mg daily is given.

For details of doses in children, see below.

Doses of didanosine may need to be amended when given with some other antiretrovirals. For further details see under Interactions, above.

Dosage reduction may be necessary in patients with renal (see below) or hepatic impairment, although no specific dose reductions are recommended in patients with hepatic impairment and close monitoring is required.

◊ Reviews.

1. Shelton MJ, *et al.* Didanosine. *Ann Pharmacother* 1992; **26:** 660–70.
2. Lipsky JJ. Zalcitabine and didanosine. *Lancet* 1993; **341:** 30–2.
3. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. *Drugs* 1999; **58:** 1099–1135.
4. Moreno S, *et al.* Didanosine enteric-coated capsule: current role in patients with HIV-1 infection. *Drugs* 2007; **67:** 1441–62.

Administration in children. For the treatment of HIV infection in children, didanosine is given daily with other antiretroviral drugs in doses based on body-surface. Doses are taken on an empty stomach. In the USA an oral solution is available for paediatric use:

- in children aged between 2 weeks and 8 months the recommended dose is 100 mg/m^2 twice daily
- in children over 8 months of age the recommended dose is 120 mg/m^2 twice daily

In the UK chewable or dispersible tablets or enteric-coated capsules are available for use:

- the chewable or dispersible tablets may be given orally to children older than 3 months of age, as either a single dose or as two divided doses, in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine
- enteric-coated capsules may be given orally to children older than 6 years of age in a dose of 240 mg/m^2 daily *or* 180 mg/m^2 daily if given with zidovudine

Administration in renal impairment. Dosage of didanosine should be reduced in patients with renal impairment. The following doses are recommended based on the patient's creatinine clearance (CC):

Adults greater than 60 kg:

- CC more than 60 mL/minute: usual adult doses
- CC 30 to 59 mL/minute: 200 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 150 mg once daily
- CC less than 10 mL/minute: 100 mg once daily

Adults less than 60 kg:

- CC more than 60 mL/minute: usual adult doses
- CC 30 to 59 mL/minute: 150 mg daily as a single dose or in two equally divided doses
- CC 10 to 29 mL/minute: 100 mg once daily
- CC less than 10 mL/minute: 75 mg once daily

Preparations

USP 31: Didanosine for Oral Solution; Didanosine Tablets for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Aso DDI†; Bandotan†; Dibistic†; Megavir†; Ronvir†; Videx; ***Austral.:*** Videx; ***Austria:*** Videx; ***Belg.:*** Videx; ***Braz.:*** Didanox†; Videx; ***Canad.:*** Videx; ***Chile:*** Videx; ***Cz.:*** Videx; ***Denm.:*** Videx; ***Fin.:*** Videx; ***Fr.:*** Videx; ***Ger.:*** Videx; ***Gr.:*** Videx; ***Hong Kong:*** Videx; ***Hung.:*** Videx; ***India:*** Dinex; ***Indon.:*** Videx; ***Irl.:*** Videx; ***Israel:*** Videx†; ***Ital.:*** Videx; ***Malaysia:*** Videx; ***Mex.:*** Apodasi†; Didasten; Videx; ***Neth.:*** Videx; ***Norw.:*** Videx; ***NZ:*** Videx; ***Pol.:*** Videx; ***Port.:*** Videx; ***Rus.:*** Videx (Видекс); ***S.Afr.:*** Videx; ***Singapore:*** Videx; ***Spain:*** Videx; ***Swed.:*** Videx; ***Switz.:*** Videx; ***Thai.:*** Videx; ***Turk.:*** Videx; ***UK:*** Videx; ***USA:*** Videx; ***Venez.:*** Videx.

Multi-ingredient: ***India:*** Odivir Kit.

Docosanol *(USAN)*

Behenyl Alcohol; *n*-Docosanol; Docosyl Alcohol; IK-2. 1-Docosanol.

Докозанол

$C_{22}H_{46}O$ = 326.6.

CAS — 661-19-8.

ATC — D06BB11.

ATC Vet — QD06BB11.

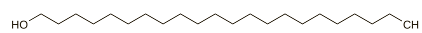

Profile

Docosanol is an antiviral used topically five times daily as a 10% cream in the treatment of recurrent herpes labialis (p.854). Docosanol acts by inhibiting fusion between the cell plasma membrane and the herpes simplex virus, thereby preventing viral entry into cells and subsequent viral replication. It has been investigated for genital herpes.

◊ References.

1. Habbema L, *et al.* n-Docosanol 10% cream in the treatment of recurrent herpes labialis: a randomised, double-blind, placebo-controlled study. *Acta Derm Venereol* 1996; **76:** 479–81.
2. Sacks SL, *et al.* Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; **45:** 222–30.
3. Leung DT, Sacks SL. Docosanol: a topical antiviral for herpes labialis. *Expert Opin Pharmacother* 2004; **5:** 2567–71.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Abreva; ***Cz.:*** Erazaban; ***Gr.:*** Healip; ***Swed.:*** Healip; ***USA:*** Abreva.

Edoxudine *(USAN, rINN)*

Edoxudina; Édoxudine; Edoxudinum; EDU; Ethyl Deoxyuridine; EUDR; ORF-15817; RWJ-15817. 2′-Deoxy-5-ethyluridine.

Эдоксудин

$C_{11}H_{16}N_2O_5$ = 256.3.

CAS — 15176-29-1.

ATC — D06BB09.

ATC Vet — QD06BB09.

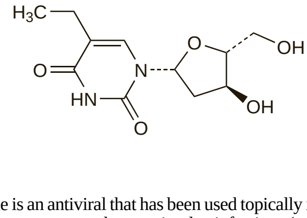

Profile

Edoxudine is an antiviral that has been used topically in the treatment of mucocutaneous herpes simplex infections (p.854); it has also been used as an ophthalmic preparation.

Preparations

Proprietary Preparations (details are given in Part 3)

Switz.: Edurid†.

Efavirenz *(BAN, rINN)*

5B706; DMP-266; Efavirentsi; Éfavirenz; Efavirenzum; L-743; L-743726. (*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

Эфавиренз

$C_{14}H_9ClF_3NO_2$ = 315.7.

CAS — 154598-52-4.

ATC — J05AG03.

ATC Vet — QJ05AG03.

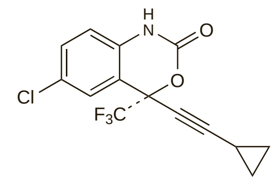

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing efavirenz are skin rashes and psychiatric or CNS disturbances. Mild to moderate rashes (usually maculopapular eruptions) generally appear within the first 2 weeks of starting therapy and may resolve within a month of continued treatment; of severe forms including erythema multiforme and Stevens-Johnson syndrome have been reported occasionally. CNS symptoms include agitation, amnesia, confusion, dizziness, euphoria, headache, insomnia or somnolence, impaired concentration, abnormal thinking or dreaming, convulsions, depersonalisation, and hallucinations. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks; they may occur more frequently when efavirenz is taken with meals, possibly due to increased efavirenz plasma concentrations. Serious psychiatric adverse effects include severe depression, suicidal ideation and attempts, aggressive behaviour, and psychotic reactions including paranoia and mania. Other adverse effects include nausea and vomiting, diarrhoea, fatigue, and pancreatitis. Raised liver enzyme values and raised serum-cholesterol and -triglyceride concentrations have been reported. Hepatic failure and photoallergic dermatitis have occurred.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including efavirenz, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including efavirenz. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported.

◊ References.

1. Clifford DB, *et al.* Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005; **143:** 714–21.

Effects on the mouth. Burning mouth syndrome was diagnosed in a patient 2 weeks after adding efavirenz to her long-standing combination antiretroviral treatment regimen.[1] Efavirenz was stopped and the syndrome resolved within 1 week.

1. Borrás-Blasco J, *et al.* Burning mouth syndrome due to efavirenz therapy. *Ann Pharmacother* 2006; **40:** 1471–2.

Precautions

Efavirenz is contra-indicated in patients with severe hepatic impairment (Child-Pugh class C), and should be used with caution, and liver enzymes values monitored, in patients with mild to moderate liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution should be exercised in patients with a history of seizures or psychiatric disorders including depression. Efavirenz should be stopped if a severe skin rash, associated with blistering, desquamation, mucosal involvement, or fever, develops. Monitoring of serum lipids and blood-glucose may be considered during efavirenz treatment. Food may increase exposure to efavirenz and lead to an increase in the frequency of undesirable effects.

False-positive results in some urinary cannabinoid tests have been reported in subjects receiving efavirenz.

Pregnancy. Licensed product information states that efavirenz has been associated with teratogenicity in *animals*. No specific malformation pattern was noted in more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen. However, retrospective analysis of these pregnancies noted a few cases of neural tube defects, including meningomyelocele. The use of adequate contraceptive measures is recommended during, and for 12 weeks after, treatment with regimens containing efavirenz.

Interactions

Efavirenz is metabolised mainly by cytochrome P450 isoenzymes including CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Enzyme inducers may decrease plasma concentrations of efavirenz; efavirenz itself acts as an enzyme inducer and can reduce plasma concentrations of other drugs. Inhibition of some P450 isoenzymes has also been found *in vitro*.

Efavirenz is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antihistamines (astemizole and terfenadine), calcium-channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam). St John's wort decreases the concentration of efavirenz; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antibacterials. Plasma concentrations of efavirenz may be reduced by *rifampicin* and may necessitate an increase in the dose of efavirenz. A similar interaction might occur with *rifabutin*.

Use of efavirenz with *clarithromycin* has resulted in a decrease in the plasma concentration of clarithromycin and an increase in its active hydroxy metabolite. The combination has been associated with a high incidence of skin rashes.

Antifungals. Giving efavirenz with voriconazole results in a 2-way interaction; efavirenz decreases the concentration of voriconazole and voriconazole increases the concentration of efavirenz. When efavirenz is given with voriconazole, licensed product information for efavirenz suggests the voriconazole maintenance dose should be increased to 400 mg twice daily and the efavirenz dose reduced to 300 mg once daily.

Antivirals. For the effect of efavirenz on *HIV-protease inhibitors*, see p.883.

Grapefruit. The metabolism of efavirenz may be inhibited by concomitant ingestion of grapefruit juice.

Antiviral Action

Efavirenz acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to efavirenz and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Efavirenz is absorbed after oral doses with peak plasma concentrations being achieved after about 3 to 5 hours. Steady-state plasma concentrations are reached in 6 to 7 days after multiple dosing. Bioavailability is increased after a high-fat meal. Efavirenz is more than 99% bound to plasma proteins and is distributed into the CSF. It is metabolised mainly by hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2B6 into inactive hydroxylated, metabolites. Efavirenz acts as an enzyme inducer and induces its own metabolism resulting in a terminal half-life of 40 to 55 hours after multiple doses compared with 52 to 76 hours after a single dose. About 14 to 34% of a dose is excreted in the urine (less than 1% unchanged), and 16 to 61% in the faeces (primarily as unchanged drug).

◊ References.

1. Kappelhoff BS, *et al.* Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2005; **44:** 849–61.
2. Almond LM, *et al.* Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. *J Antimicrob Chemother* 2005; **56:** 738–44.
3. Burger D, *et al.* Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; **61:** 148–54.
4. Back DJ, *et al.* Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2006; **45:** 213–14.

Uses and Administration

Efavirenz is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p.856).

Efavirenz is given orally as *capsules* or *tablets* in a dose of 600 mg once daily; alternatively, it may be given as an *oral solution* in a dose of 720 mg once daily. Efavirenz tablets and capsules should be given on an empty stomach. Dosing at bedtime is recommended during the first 2 to 4 weeks of therapy to improve tolerability. Bioavailability of efavirenz from the oral solution is less than that from the capsule and so proportionately higher doses of the solution are used.

For details of doses in children and adolescents, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing efavirenz in combination with emtricitabine and tenofovir are available in some countries.

◊ References.

1. Adkins JC, Noble S. Efavirenz. *Drugs* 1998; **56:** 1055–64.
2. Gazzard BG. Efavirenz in the management of HIV infection. *Int J Clin Pract* 1999; **53:** 60–4.
3. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. *Drugs* 2006; **66:** 1501–12.

Administration in children. For the treatment of HIV infection in children 3 years of age and older and adolescents efavirenz is given daily with other antiretroviral drugs. In the USA oral *capsules* and *tablets* are available and the dose is based on body-weight:

- 10 to 14 kg: 200 mg once daily
- 15 to 19 kg: 250 mg once daily
- 20 to 24 kg: 300 mg once daily
- 25 to 32.4 kg: 350 mg once daily
- 32.5 to 39 kg: 400 mg once daily
- 40 kg or more: as for adults (above)

Capsules are also available in the UK for use in children and adolescents; doses are similar to those used in the USA.

In the UK an *oral solution* is also available; the dose ranges, which are again calculated in terms of body-weight, also depend on the age range:

- 13 to 14 kg: children less than 5 years, 360 mg daily; children 5 years and older, 270 mg once daily
- 15 to 19 kg: children less than 5 years, 390 mg daily; children 5 years and older, 300 mg once daily
- 20 to 24 kg: children less than 5 years, 450 mg daily; children 5 years and older, 360 mg once daily
- 25 to 32.4 kg: children less than 5 years, 510 mg daily; children 5 years and older, 450 mg once daily
- 32.5 to 39 kg: children 5 years and older, 510 mg once daily
- 40 kg or more: children 5 years and older, as for adults, above

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Efavilea; Filginase; Stocrin; Sulfinav; Virorrever; ***Austral.:*** Stocrin; ***Austria:*** Stocrin; ***Belg.:*** Stocrin; ***Braz.:*** Stocrin; ***Canad.:*** Sustiva; ***Chile:*** Stocrin; ***Cz.:*** Stocrin; Sustiva; ***Denm.:*** Stocrin; ***Fin.:*** Stocrin; ***Fr.:*** Sustiva; ***Ger.:*** Sustiva; ***Gr.:*** Stocrin; ***Hong Kong:*** Stocrin; ***Hung.:*** Stocrin; ***India:*** Efavir; ***Irl.:*** Sustiva; ***Israel:*** Stocrin; ***Ital.:*** Sustiva; ***Malaysia:*** Stocrin; ***Mex.:*** Stocrin; ***Neth.:*** Stocrin; Sustiva; ***Norw.:*** Stocrin; ***NZ:*** Stocrin; ***Pol.:*** Stocrin; ***Port.:*** Stocrin; Sustiva; ***Rus.:*** Stocrin (Стокрин); ***S.Afr.:*** Stocrin; ***Singapore:*** Stocrin; ***Spain:*** Sustiva; ***Swed.:*** Stocrin; ***Switz.:*** Stocrin; ***Thai.:*** Stocrin; ***UK:*** Sustiva; ***USA:*** Sustiva; ***Venez.:*** Efavir; Stocrin.

Multi-ingredient: ***India:*** Odivir Kit; ***UK:*** Atripla; ***USA:*** Atripla.

Elvitegravir *(USAN, rINN)*

Elvitégravir; Elvitegravirum; GS-9137; JTK-303. 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Эльвитегравир

$C_{23}H_{23}ClFNO_5$ = 447.9.

CAS — 697761-98-1.

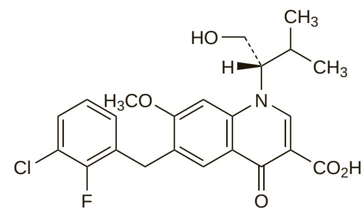

Profile

Elvitegravir is an HIV-integrase inhibitor with antiretroviral activity against HIV-1. It is under investigation for the treatment of HIV infection and AIDS.

◊ References.

1. Ramanathan S, *et al.* Pharmacokinetics of coadministered ritonavir-boosted elvitegravir and zidovudine, didanosine, stavudine, or abacavir. *J Acquir Immune Defic Syndr* 2007; **46:** 160–6.
2. Shimura K, *et al.* Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol* 2008; **82:** 764–74.

Emtricitabine *(USAN, rINN)*

BW-524W91; Emtricitabina; Emtricitabinum; Emtrisitabin; FTC; (−)-FTC; FTC-(−). 5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

Эмтрицитабин

$C_8H_{10}FN_3O_3S$ = 247.2.

CAS — 143491-57-0.

ATC — J05AF09.

ATC Vet — QJ05AF09.

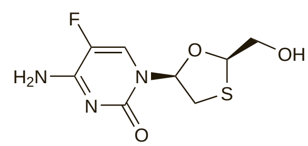

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing emtricitabine are headache, diarrhoea, and nausea; hyperpigmented skin discoloration is very common in children and common in adults. Other common adverse effects include abdominal pain, vomiting, dyspepsia, abnormal dreams, asthenia, dizziness, insomnia, pain, allergic skin reactions, pruritus, rashes, and urticaria. Abnormal laboratory test results associated with emtricitabine-containing regimens include hyperbilirubinaemia, increases in serum lipase and pancreatic amylase, and raised liver enzymes. There have also been reports of neutropenia and anaemia. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including emtricitabine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including emtricitabine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Precautions

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun, and that patients co-infected with HIV and hepatitis B should be monitored for several months after stopping treatment with emtricitabine for signs of exacerbations of hepatitis. Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

Interactions

Caution should be exercised when emtricitabine is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Emtricitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase. Emtricitabine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Emtricitabine is rapidly and extensively absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring after 1 to 2 hours. Bioavailability is reported to be 93% for the capsules. Binding to plasma proteins is reported to be less than 4%. The plasma elimination half-life is about 10 hours. Emtricitabine is metabolised to a limited degree, but is excreted largely unchanged in the urine and to a lesser extent in the faeces. It is partially removed by haemodialysis.

Uses and Administration

Emtricitabine is a nucleoside reverse transcriptase inhibitor related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when emtricitabine is used alone, and it is therefore used with other antiretrovirals.

Emtricitabine is given orally once daily as capsules in a usual adult dose of 200 mg or 240 mg as oral solution.

For details of doses in infants, children, and adolescents, see below.

For details of doses of emtricitabine to be used in patients with renal impairment, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing emtricitabine in combination with tenofovir, and with efavirenz plus tenofovir are available in some countries.

◊ Reviews.

1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
2. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother* 2004; **38:** 1006–14.
3. Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1427–48.
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. *Clin Infect Dis* 2006; **42:** 126–31.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents emtricitabine is given with other antiretroviral drugs. Doses, given once daily, are based on body-weight:

- in infants up to 3 months of age the *oral solution* is given in a dose of 3 mg/kg daily
- in infants, children, and adolescents over 3 months of age the oral solution is given in a dose of 6 mg/kg daily to a maximum daily dose of 240 mg
- the *capsules* may be given to children and adolescents weighing more then 33 kg in the usual adult dose of 200 mg daily.

Administration in renal impairment. Doses of emtricitabine should be reduced in patients with renal impairment, according to the patient's creatinine clearance (CC):

- CC at least 50 mL/minute: usual adult doses (as capsules or solution)
- CC 30 to 49 mL/minute: 200 mg every 48 hours (capsules) or 120 mg every 24 hours (oral solution)
- CC 15 to 29 mL/minute: 200 mg every 72 hours (capsules) or 80 mg every 24 hours (oral solution)
- CC less than 15 mL/minute: 200 mg every 96 hours (capsules) or 60 mg every 24 hours (oral solution)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Emtriva; ***Austral.:*** Emtriva; ***Belg.:*** Emtriva; ***Cz.:*** Emtriva; ***Denm.:*** Emtriva; ***Fin.:*** Emtriva; ***Fr.:*** Emtriva; ***Ger.:*** Emtriva; ***Gr.:*** Emtriva; ***Hung.:*** Emtriva; ***Irl.:*** Emtriva; ***Ital.:*** Emtriva; ***Mex.:*** Emtriva; ***Neth.:*** Emtriva; ***Norw.:*** Emtriva; ***NZ:*** Emtriva; ***Pol.:*** Emtriva; ***Port.:*** Emtriva; ***Spain:*** Emtriva; ***Swed.:*** Emtriva; ***Switz.:*** Emtriva; ***UK:*** Emtriva; ***USA:*** Emtriva.

Multi-ingredient: ***Arg.:*** Truvada; ***Austral.:*** Truvada; ***Cz.:*** Truvada; ***Fin.:*** Truvada; ***Fr.:*** Truvada; ***Ger.:*** Truvada; ***Gr.:*** Truvada; ***Irl.:*** Truvada; ***Ital.:*** Truvada; ***Mex.:*** Truvada; ***Neth.:*** Truvada; ***NZ:*** Truvada; ***Port.:*** Truvada; ***Spain:*** Truvada; ***Swed.:*** Truvada; ***UK:*** Atripla; Truvada; ***USA:*** Atripla; Truvada.

Enfuvirtide *(BAN, USAN, rINN)*

DP-178; Enfuvirtida; Enfuvirtidum; Pentafusida; Pentafuside; T-20.
Энфувиртид
$C_{204}H_{301}N_{51}O_{64}$ = 4491.9.
CAS — 159519-65-0.
ATC — J05AX07.
ATC Vet — QJ05AX07.

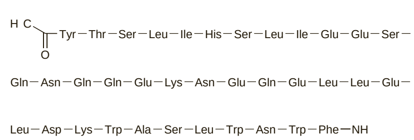

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing enfuvirtide are local injection site reactions with resultant pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis. These reactions have been reported to occur in 98% of patients, but only a small minority needed to stop therapy. Other very common adverse effects include nausea, diarrhoea, weight loss, and peripheral neuropathy. Anorexia, abdominal pain, constipation, pancreatitis, myalgia, weakness or loss of strength, lymphadenopathy, insomnia, depression, 'flu-like' illness, sinusitis, and conjunctivitis are also common. An increased incidence of some bacterial infections, in particular of pneumonia, has occurred in patients receiving enfuvirtide. Hypersensitivity reactions have occurred in about 1% of patients. Other adverse effects have included anxiety, hyperglycaemia, hypertriglyceridaemia, and eosinophilia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV-infected patients with severe immune deficiency. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

◊ References.

1. Maggi P, *et al.* Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; **53:** 678–81.

Precautions

Enfuvirtide should be stopped immediately and should not be restarted in patients who develop signs of a systemic hypersensitivity reaction. An increased incidence of some bacterial infections, in particular of pneumonia, has been seen and patients receiving enfuvirtide should be closely monitored for signs of pneumonia. UK licensed product information recommends that enfuvirtide be used with caution in patients with hepatic impairment and in those with moderate to severe renal impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Antiviral Action

Enfuvirtide is an HIV fusion inhibitor that interferes with entry of HIV into cells by binding to the gp41 subunit of the viral envelope glycoprotein, thereby inhibiting fusion of viral and cellular membranes. Strains of HIV with reduced susceptibility to enfuvirtide have been isolated in patients receiving the drug but, owing to the different mode of action of enfuvirtide and the fact that it does not require intracellular activation for its activity, cross-resistance with other antiretrovirals may occur less frequently.

Resistance. References to the development of resistance to enfuvirtide.

1. Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; **54:** 333–40.

Pharmacokinetics

Enfuvirtide is absorbed after subcutaneous injection with a mean absolute bioavailability of 84%. It is 92% bound to plasma proteins. Enfuvirtide is a peptide and is metabolised by hydrolysis; it does not inhibit cytochrome P450 isoenzymes. The elimination half-life is 3.8 hours after subcutaneous use, although elimination pathways have yet to be identified.

◊ References.

1. Patel IH, *et al.* Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clin Pharmacokinet* 2005; **44:** 175–86.
2. Zhang X, *et al.* Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol* 2007; **47:** 510–17.

Uses and Administration

Enfuvirtide is a synthetic 36-amino acid peptide that blocks HIV cell fusion and viral entry. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS. Enfuvirtide is given by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a usual dose of 90 mg twice daily. Each injection should be given at a different site from the preceding one. For details of doses in children and adolescents, see below.

◊ References.

1. Lalezari JP, *et al.* Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; **348:** 2175–85. Correction. *ibid.*; **349:** 1100.
2. Duffalo ML, James CW. Enfuvirtide: a novel agent for the treatment of HIV-1 infection. *Ann Pharmacother* 2003; **37:** 1448–56.
3. Oldfield V, *et al.* Enfuvirtide: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1139–60.

4. Reynes J, *et al.* TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS* 2007; **21:** 533–43.
5. Wiznia A, *et al.* T20-310 Study Group. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; **26:** 799–805.
6. Rockstroh J, *et al.* Adherence to enfuvirtide and its impact on treatment efficacy. *AIDS Res Hum Retroviruses* 2008; **24:** 141–8.
7. Saberi P, *et al.* Immunologic benefits of enfuvirtide in patients enrolled in a drug assistance program. *Ann Pharmacother* 2008; **42:** 621–6.

Administration in children. For the treatment of HIV infection, enfuvirtide may be given to children 6 to 16 years of age by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a dose of 2 mg/kg twice daily (to a maximum of 90 mg twice daily). Each injection should be given at a different site from the preceding one.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fuzeon; ***Austral.:*** Fuzeon; ***Belg.:*** Fuzeon; ***Braz.:*** Fuzeon; ***Canad.:*** Fuzeon; ***Chile:*** Fuzeon; ***Cz.:*** Fuzeon; ***Denm.:*** Fuzeon; ***Fin.:*** Fuzeon; ***Fr.:*** Fuzeon; ***Ger.:*** Fuzeon; ***Gr.:*** Fuzeon; ***Hung.:*** Fuzeon; ***Irl.:*** Fuzeon; ***Israel:*** Fuzeon; ***Ital.:*** Fuzeon; ***Mex.:*** Fuzeon; ***Neth.:*** Fuzeon; ***Norw.:*** Fuzeon; ***NZ:*** Fuzeon; ***Pol.:*** Fuzeon; ***Port.:*** Fuzeon; ***Spain:*** Fuzeon; ***Swed.:*** Fuzeon; ***Switz.:*** Fuzeon; ***Thai.:*** Fuzeon; ***UK:*** Fuzeon; ***USA:*** Fuzeon.

Entecavir *(USAN, rINN)*

BMS-200475-01; Entécavir; Entecavirum; SQ-34676. 9-[(1S,3R,4S)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine monohydrate.

Энтекавир

$C_{12}H_{15}N_5O_3,H_2O$ = 295.3.

CAS — 142217-69-4 (anhydrous entecavir); 209216-23-9 (entecavir monohydrate).

ATC — J05AF10.

ATC Vet — QJ05AF10.

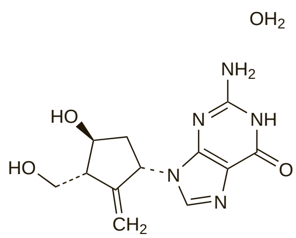

Adverse Effects

The most common adverse effects of entecavir have been headache, fatigue, dizziness, and nausea. Other adverse effects include diarrhoea, dyspepsia, insomnia, somnolence, and vomiting.

Raised liver enzyme concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with entecavir. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p.914).

Entecavir is carcinogenic in *rodents*, but a relationship with human cancer has not been established.

Precautions

Entecavir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Entecavir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Careful differentiation should be made between patients whose liver enzyme concentrations become elevated due to response to treatment and those in whom it is indicative of toxicity. Exacerbation of hepatitis B has been reported both during and after stopping treatment with entecavir. Hepatic function should be monitored closely while on treatment and for several months after treatment is stopped. Dosage reduction may be necessary in patients with renal impairment.

Limited clinical experience suggests there is a potential for HIV to develop resistance to NRTIs if entecavir is used to treat chronic hepatitis B virus infection in patients with undiagnosed or untreated HIV infection. Treatment with entecavir is not recommended for co-infected patients who are not also receiving HAART. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with entecavir.

HIV-infected patients. It was initially thought that entecavir did not inhibit replication of HIV-1 at clinically relevant doses. However, a small consistent decrease in HIV-1 RNA was noted in 3 patients with HIV-1 and hepatitis B virus co-infection being treated with entecavir monotherapy.[1] In 1 of these patients, an HIV variant containing the M184V resistance substitution was found. Subsequent *in vitro* analyses showed that HIV-1 strains containing M184V were resistant to entecavir.

1. McMahon MA, *et al.* The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med* 2007; **356:** 2614–21.

Interactions

Caution should be exercised when entecavir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Entecavir is phosphorylated intracellularly to the active triphosphate form which competes with deoxyguanosine triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby inhibiting every stage of the enzyme's activity.

Although initially thought to be inactive against HIV at clinically relevant doses, entecavir may have sufficient action to result in the selection of resistant HIV variants (see HIV-infected Patients, under Precautions, above).

Pharmacokinetics

Entecavir is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur 30 to 90 minutes after an oral dose and steady state concentrations after 6 to 10 days of treatment. Absorption is both delayed and reduced by food; this is not considered to be clinically relevant in nucleoside treatment-naive patients but may affect efficacy in lamivudine-refractory patients in whom entecavir should be taken on an empty stomach. Bioavailability of the tablet formulation is equal to that of the oral solution and they may be given interchangeably. Binding of entecavir to plasma proteins is about 13% *in vitro*. Entecavir is not metabolised by the cytochrome P450 system. It is mainly eliminated by the kidneys by glomerular filtration and active tubular secretion, with a terminal elimination half-life of 128 to 149 hours. Small amounts of glucuronide and sulfate conjugates are formed. Entecavir is partially removed by haemodialysis.

Uses and Administration

Entecavir is a nucleoside reverse transcriptase inhibitor, structurally related to guanosine with selective antiviral activity against hepatitis B virus. It is used for the treatment of chronic hepatitis B (p.851) in adults with compensated liver disease with evidence of active viral replication, persistently elevated liver enzyme values, and histologically active disease, including those resistant to lamivudine. The usual oral dose of entecavir in nucleoside treatment-naive patients is 500 micrograms once daily, either with or without food. An oral dose of 1 mg once daily on an empty stomach should be used in patients with a history of hepatitis B viraemia during lamivudine therapy or with known resistance to lamivudine. For details of reduced doses to be used in patients with renal impairment, see below.

◊ Reviews.

1. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. *Pharmacotherapy* 2006; **26:** 1745–57.
2. Robinson DM, *et al.* Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2006; **66:** 1605–22.
3. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28:** 184–203.

Administration in renal impairment. Doses of entecavir should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 30 to 49 mL/minute: 250 micrograms once daily or 500 micrograms every 48 hours in nucleoside treatment-naive patients; 500 micrograms once daily in lamivudine-refractory patients
- CC 10 to 29 mL/minute: 150 micrograms once daily or 500 micrograms every 72 hours in nucleoside treatment-naive patients; 300 micrograms once daily or 500 micrograms every 48 hours in lamivudine-refractory patients
- CC less than 10 mL/minute (and patients on haemodialysis or continuous ambulatory peritoneal dialysis): 50 micrograms once daily or 500 micrograms every 5 to 7 days in nucleoside treatment-naive patients; 100 micrograms once daily or 500 micrograms every 72 hours in lamivudine-refractory patients

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Baraclude; ***Austral.:*** Baraclude; ***Cz.:*** Baraclude; ***Fr.:*** Baraclude; ***Gr.:*** Baraclude; ***Hung.:*** Baraclude; ***Indon.:*** Baraclude; ***Malaysia:*** Baraclude; ***NZ:*** Baraclude; ***Philipp.:*** Baraclude; ***Port.:*** Baraclude; ***Singapore:*** Baraclude; ***UK:*** Baraclude; ***USA:*** Baraclude.

Etravirine *(USAN, rINN)*

Etravirina; Étravirine; Etravirinum; R-165335; TMC-125. 4-[6-Amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile.

Этравирин

$C_{20}H_{15}BrN_6O$ = 435.3.

CAS — 269055-15-4.

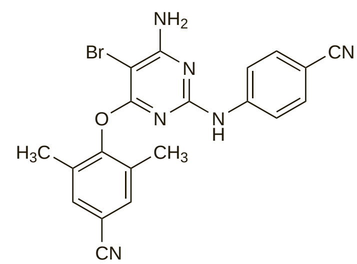

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing etravirine are nausea and skin rash (usually mild to moderate) and generally appearing in the second week of treatment and resolving within 1 to 2 weeks. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse events of moderate to severe intensity reported by at least 2% of patients receiving etravirine in clinical studies included gastrointestinal complaints (abdominal pain, diarrhoea, nausea, and vomiting), fatigue, headache, hypertension, and peripheral neuropathy. Raised liver enzyme values, glucose levels, and serum-cholesterol and -triglyceride concentrations have been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including etravirine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including etravirine.

Precautions

Etravirine should be stopped if a severe skin rash develops. Patients co-infected with chronic hepatitis B or C have experienced worsening of hepatitis-related symptoms when treated with etravirine. Patients who have virologic failure on a NNRTI-containing regimen should not be given etravirine in a regimen containing only NRTIs.

Interactions

Etravirine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19. It is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19. Consequently it may compete with other drugs metabolised by these systems, potentially resulting in mutually altered plasma concentrations and possibly toxicity. Enzyme inducers may decrease plasma concentrations of etravirine.

Etravirine should not be given with other NNRTIs. It should also not be used in regimens with HIV-protease inhibitors given without ritonavir-boosting but use with ritonavir-boosted tipranavir, fosamprenavir, or atazanavir should be avoided. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antiviral Action

Etravirine acts by inhibition of HIV-1 reverse transcriptase and blocks viral RNA- and DNA-dependent DNA polymerase activities. It is a flexible molecule designed to fit in the active pocket of viral reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations. This is considered to reduce the risk of the development of resistance; phase II studies in treatment-experienced patients have shown activity against HIV resistant to other NNRTIs (delavirdine, efavirenz, and nevirapine).

Pharmacokinetics

Etravirine is readily absorbed after oral doses and peak plasma concentrations occur after about 2.5 to 4 hours; absorption is increased by food. It is about 99.9% bound to plasma proteins. Etravirine is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 families, to substantially less active metabolites. The mean plasma half-life after usual dosage is about 41 hours and ranges from 21 to 61 hours. About 93.7% of a dose appears in the faeces (81.2 to 86.4% as unchanged drug), and 1.2% in the urine (unchanged drug was not detected in the urine).

Uses and Administration

Etravirine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is given with other antiretrovirals for the treatment of HIV infection and AIDS (p.856) in treatment-experienced patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretrovirals. Etravirine is given orally in a usual dose of 200 mg twice daily after food.

◊ References.

1. Madruga JV, *et al*. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370:** 29–38.
2. Lazzarin A, *et al*. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370:** 39–48.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Intelence.

Famciclovir *(BAN, USAN, rINN)*

AV-42810; BRL-42810; Famciclovirum; Famciklovir; Famsikloviiri; Famsiklovir. 2[2-(2-Amino-9*H*-purin-9-yl)ethyl]trimethylene diacetate.

Фамцикловир

$C_{14}H_{19}N_5O_4$ = 321.3.
CAS — 104227-87-4.
ATC — J05AB09; S01AD07.
ATC Vet — QJ05AB09; QS01AD07.

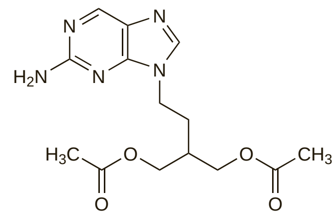

Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

The most common adverse effects of famciclovir are headache and nausea. Other adverse effects rarely reported include jaundice, vomiting, dizziness, skin rash, pruritus, urticaria, somnolence, confusion, and hallucinations. In addition, abdominal pain and fever have been reported in immunocompromised patients given famciclovir.

Dosage should be reduced in patients with renal impairment. Acute renal failure has occurred in patients with renal impairment taking inappropriately high doses of famciclovir.

◊ References.

1. Saltzman R, *et al*. Safety of famciclovir in patients with herpes zoster and genital herpes. *Antimicrob Agents Chemother* 1994; **38:** 2454–7.

Interactions

As for Penciclovir, p.901.

Antiviral Action

As for Penciclovir, p.901.

Pharmacokinetics

Famciclovir is rapidly absorbed after oral doses. Absorption is delayed but not reduced by food. Famciclovir is rapidly converted to penciclovir (see p.901), peak plasma concentrations occurring within about 1 hour of a dose, and virtually no famciclovir is detectable in the plasma or urine. Bioavailability of penciclovir is reported to be 77%. Famciclovir is mainly excreted in the urine (partly by renal tubular secretion) as penciclovir and its 6-deoxy precursor; elimination is reduced in patients with renal impairment.

◊ References.

1. Pue MA, Benet LZ. Pharmacokinetics of famciclovir in man. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 47–55.
2. Boike SC, *et al*. Pharmacokinetics of famciclovir in subjects with varying degrees of renal impairment. *Clin Pharmacol Ther* 1994; **55:** 418–26.
3. Boike SC, *et al*. Pharmacokinetics of famciclovir in subjects with chronic hepatic disease. *J Clin Pharmacol* 1994; **34:** 1199–1207.
4. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. *Clin Pharmacokinet* 1996; **31:** 1–8.

Uses and Administration

Famciclovir is a prodrug of the antiviral penciclovir (p.901). It is given orally in the treatment of herpes zoster (see Varicella-zoster Infections, p.855) and genital and mucocutaneous herpes (see Herpes Simplex Infections, p.854).

For **herpes zoster**, famciclovir is given in a dose of 250 mg three times daily, or 750 mg once daily, for 7 days (in the USA the recommended dose is 500 mg three times daily for 7 days); immunocompromised patients are given 500 mg three times daily for 10 days.

For **herpes simplex infections**, famciclovir is given in a dose of 250 mg three times daily for 5 days for first episodes of genital herpes; immunocompromised patients are given 500 mg twice daily for 7 days. For acute treatment of recurrent episodes of genital herpes, 125 mg is given twice daily for 5 days (in the USA, the recommended dose is 1 g twice daily for 1 day). Treatment should start in the prodromal period as soon as the first signs or symptoms appear. Immunocompromised patients are given 500 mg twice daily for 7 days.

For suppression of recurrent episodes of genital herpes, 250 mg is given twice daily; HIV patients may be given 500 mg twice daily. Such suppressive treatment is interrupted every 6 to 12 months to observe possible changes in the natural history of the disease.

For acute treatment of recurrent mucocutaneous herpes in HIV-infected patients, 500 mg is given twice daily for 7 days.

In the USA, famciclovir may also be given for the treatment of recurrent herpes labialis as a single 1.5 g dose, preferably begun in the prodromal period.

Doses of famciclovir should be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Perry CM, Wagstaff AJ. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1995; **50:** 396–415.
2. Faro S. A review of famciclovir in the management of genital herpes. *Infect Dis Obstet Gynecol* 1998; **6:** 38–43.
3. Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. *Expert Opin Pharmacother* 2006; **7:** 2271–86.
4. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66:** 2397–2416.

Administration in renal impairment. Doses of famciclovir need to be reduced in patients with renal impairment. UK licensed product information recommends the following oral doses based on creatinine clearance (CC):

Immunocompetent patients:

Herpes zoster or an initial episode of genital herpes
- CC 30 to 59 mL/minute per 1.73 m^2: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 250 mg once daily

Acute recurrent genital herpes, treatment
- CC 30 to 59 mL/minute per 1.73 m^2: no dosage adjustment necessary
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg once daily

Recurrent genital herpes, suppression
- CC 30 mL/minute per 1.73 m^2 and over: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg twice daily

Immunocompromised patients:

Herpes zoster
- CC 40 mL/minute per 1.73 m^2 and over: 500 mg three times daily
- CC 30 to 39 mL/minute per 1.73 m^2: 250 mg three times daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg three times daily

Herpes simplex infections
- CC 40 mL/minute per 1.73 m^2 and over: 500 mg twice daily
- CC 30 to 39 mL/minute per 1.73 m^2: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg twice daily

Patients on haemodialysis should be given doses of famciclovir immediately after dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pentavir; Zosvir†; ***Austral.:*** Famvir; ***Austria:*** Famvir; ***Belg.:*** Famvir; ***Braz.:*** Famvir; Fanclomax; Penvir; ***Canad.:*** Famvir; ***Cz.:*** Famvir; ***Denm.:*** Famvir; ***Fin.:*** Famvir; ***Fr.:*** Oravir; ***Ger.:*** Famvir; ***Gr.:*** Famvir; ***Hong Kong:*** Famvir; ***Hung.:*** Famvir; ***India:*** Famtrex; ***Irl.:*** Famvir; ***Israel:*** Famvir†; ***Ital.:*** Famvir; Ziravir; ***Neth.:*** Famvir; ***NZ:*** Famvir†; ***Port.:*** Famvir; Zyvir; ***Rus.:*** Famvir (Фамвир); ***S.Afr.:*** Famvir; ***Singapore:*** Famvir; ***Spain:*** Ancivin; Famvir; ***Swed.:*** Famvir; ***Switz.:*** Famvir; ***Thai.:*** Famvir; ***Turk.:*** Famvir; ***UK:*** Famvir; ***USA:*** Famvir.

Fomivirsen Sodium *(BANM, USAN, rINNM)*

Fomivirseeninatrium; Fomivirsén sódico; Fomivirsen Sodique; Fomivirsennatrium; Fomivirsenum Natricum; Isis-2922; Natrii Fomivirsenum.

Натрий Фомивирсен

$C_{204}H_{243}N_{63}Na_{20}O_{114}P_{20}S_{20}$ = 7122.0.
CAS — 144245-52-3 (fomivirsen); 160369-77-7 (fomivirsen sodium).
ATC — S01AD08.
ATC Vet — QS01AD08.

Adverse Effects and Precautions

Adverse effects after intra-ocular injection of fomivirsen are confined to the treated eye. They include intra-ocular inflammation, transient increases in intra-ocular pressure, retinal detachment and oedema, and visual abnormalities. Other adverse effects associated with the intravitreal injection procedure include vitreal haemorrhage, endophthalmitis, uveitis, and cataract formation.

Patients should be monitored during treatment for changes in intra-ocular pressure and visual field and for extra-ocular CMV disease or disease in the contralateral eye.

Interactions
In order to reduce the risk of inflammation, intra-ocular use of fomivirsen is not recommended within 2 to 4 weeks of cidofovir treatment.

Antiviral Action
Fomivirsen is an antisense oligonucleotide that inhibits human CMV replication. It is active against strains of CMV resistant to ganciclovir, foscarnet, and cidofovir. Resistance to fomivirsen has been induced *in vitro*, but cross-resistance to antivirals with other modes of action is unlikely.

Uses and Administration
Fomivirsen is an antisense oligonucleotide that has been used as the sodium salt for the local treatment of CMV retinitis (p.853) in patients with AIDS. For newly diagnosed disease, a dose of 165 micrograms has been given by intravitreal injection into the affected eye once each week for 3 weeks, then on alternate weeks thereafter. For previously treated disease, 330 micrograms has been injected into the affected eye; this dose may be repeated once after 2 weeks and then once every 4 weeks thereafter.

◊ Reviews.

1. Perry CM, Barman Balfour JA. Fomivirsen. *Drugs* 1999; **57:** 375–80.
2. Geary RS, *et al.* Fomivirsen: clinical pharmacology and potential drug interactions. *Clin Pharmacokinet* 2002; **41:** 255–60.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Vitravene†; ***Switz.:*** Vitravene†; ***USA:*** Vitravene†.

Fosamprenavir Calcium *(USAN, rINNM)*

Calcii Fosamprenavirum; Fosamprenavir cálcico; Fosamprénavir Calcique; GW-433908G. (3*S*)-Tetrahydro-3-furyl{(α*S*)-α-[(1*R*)-1-hydroxy-2-(N^1-isobutylsulfanilamido)ethyl]phenethyl}carbamate calcium phosphate (1:1).

Кальций Фосампренавир

$C_{25}H_{36}CaN_3O_9PS$ = 625.7.

CAS — 226700-79-4 (fosamprenavir); 226700-81-8 (fosamprenavir calcium).

ATC — J05AE07.

ATC Vet — QJ05AE07.

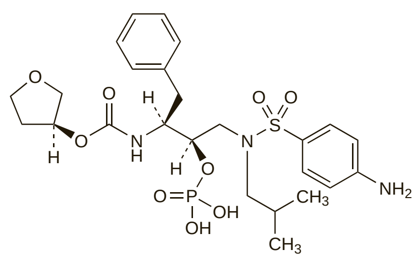

(fosamprenavir)

Adverse Effects and Precautions
As for Amprenavir, p.865.

Interactions
Drugs interacting with amprenavir (p.866) might reasonably also be expected to interact with fosamprenavir.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action
As for Amprenavir (see p.866). Fosamprenavir is a prodrug that is rapidly hydrolysed to amprenavir (p.865) by cellular phosphatases in the gut epithelium as it is absorbed. Fosamprenavir itself has little or no antiviral activity *in vitro*

Pharmacokinetics
After oral doses, fosamprenavir is rapidly hydrolysed to amprenavir in the gastrointestinal epithelium as it is absorbed. Peak plasma concentrations of amprenavir are attained after 1.5 to 4 hours. Fosamprenavir may be given with or without food. For details of the pharmacokinetics of amprenavir, see p.866.

◊ Reviews.

1. Wire MB, *et al.* Fosamprenavir: clinical pharmacokinetics and drug interactions of the amprenavir prodrug. *Clin Pharmacokinet* 2006; **45:** 137–68.

Uses and Administration
Fosamprenavir is a prodrug of amprenavir, which is an HIV-protease inhibitor with antiviral activity against HIV. Fosamprenavir is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when fosamprenavir is used alone, and it is therefore used with other antiretrovirals.

Fosamprenavir may be given with or without food. It is given orally as the calcium salt, but doses are expressed in terms of the base. Fosamprenavir calcium 748 mg is equivalent to about 700 mg of fosamprenavir or to 600 mg of amprenavir and 50 mg of fosamprenavir solution is equivalent to about 43 mg of amprenavir.

In the UK, the recommended dose of ritonavir-boosted fosamprenavir in both treatment-experienced and treatment-naive adult patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

In the USA, recommended doses in treatment-naive adult patients are:
- fosamprenavir 1.4 g twice daily *without ritonavir*, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 200 mg once daily, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 100 mg once daily, or
- fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily

The recommended dose in treatment-experienced patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

For details of doses in children and adolescents, see below.

Doses should be reduced in patients with mild or moderate hepatic impairment (see below).

◊ Reviews.

1. Chapman TM, *et al.* Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs* 2004; **64:** 2101–24.
2. Hester EK, *et al.* Fosamprenavir: drug development for adherence. *Ann Pharmacother* 2006; **40:** 1301–10.

Administration in children. For the treatment of HIV infection in children and adolescents, fosamprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight and should not exceed the adult dose.

In the UK, the recommended dose of fosamprenavir oral solution in children and adolescents weighing 25 to 38 kg is 18 mg/kg twice daily *plus* ritonavir oral solution 3 mg/kg twice daily. Children and adolescents weighing at least 39 kg may be given the adult fosamprenavir tablet dose, see above. It is not licensed for use in children below 25 kg in weight or 6 years of age.

In the USA, the recommended dose of fosamprenavir oral suspension in treatment-naive children 2 to 5 years of age is fosamprenavir 30 mg/kg twice daily. Treatment-naive children 6 years of age or older may be given fosamprenavir 30 mg/kg twice daily or 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily. Treatment-experienced patients 6 years of age or older may be given fosamprenavir 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily.

Ritonavir 100-mg capsules may be given to children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg.

Administration in hepatic impairment. Fosamprenavir should be used with caution in all patients with hepatic impairment.

UK licensed product information recommends:
- in patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily

US licensed product information recommends:
- in treatment-naive patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *without ritonavir*, or *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 700 mg twice daily *without ritonavir*, or fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with severe hepatic impairment (Child-Pugh score 10 to 12): fosamprenavir 350 mg twice daily *without ritonavir*

Fosamprenavir *plus* ritonavir should not be used in patients with severe hepatic impairment.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Telzir; ***Austral.:*** Telzir; ***Belg.:*** Telzir; ***Canad.:*** Telzir; ***Cz.:*** Telzir; ***Denm.:*** Telzir; ***Fin.:*** Telzir; ***Fr.:*** Telzir; ***Ger.:*** Telzir; ***Gr.:*** Telzir; ***Hung.:*** Telzir; ***Irl.:*** Telzir; ***Israel:*** Lexiva; ***Ital.:*** Telzir; ***Mex.:*** Telzer; ***Neth.:*** Telzir; ***Norw.:*** Telzir; ***Pol.:*** Telzir; ***Port.:*** Telzir; ***Spain:*** Telzir; ***Swed.:*** Telzir; ***Switz.:*** Telzir; ***UK:*** Telzir; ***USA:*** Lexiva.

Foscarnet Sodium *(BAN, USAN, rINN)*

A-29622; EHB-776 (anhydrous and hexahydrate); Foscarnet sódico; Foscarnet Sodique; Foscarnet sodique hexahydraté; Foscarnetum Natricum; Foscarnetum natricum hexahydricum; Foskarneettinatriumheksahydraatti; Foskarnet sodná sůl hexahydrát; Foskarnet Sodyum; Foskarnetnatriumhexahydrat; Foskarneto natrio druska heksahidratas; Foszkarnet-nátrium; Phosphonoformate Trisodium; Phosphonoformate Trisodium. Trisodium phosphonatoformate hexahydrate.

Фоскарнет Натрий

$CNa_3O_5P,6H_2O$ = 300.0.

CAS — 63585-09-1 (foscarnet sodium); 34156-56-4 (foscarnet sodium hexahydrate).

ATC — J05AD01.

ATC Vet — QJ05AD01.

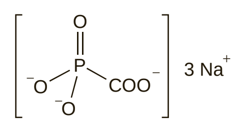

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Foscarnet Sodium Hexahydrate; Foscarnet Sodium BP 2008). A white or almost white crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Protect from light.

Incompatibility. Foscarnet sodium has been found to be visually incompatible with some commonly used injectable drugs including amphotericin B, aciclovir sodium, co-trimoxazole, ganciclovir, and pentamidine isetionate;[1,2] licensed product information also lists incompatibilities with vancomycin, glucose 30% solution, and solutions containing calcium. It is therefore recommended that foscarnet should not be infused via an intravenous line with any other drug.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.

Adverse Effects and Treatment
The most serious common adverse effect of foscarnet sodium is renal impairment, which may be severe. Anaemia may be common and granulocytopenia and thrombocytopenia have been reported. Foscarnet can chelate bivalent metal ions, and may be associated with an acute decrease in ionised calcium in the plasma that is not necessarily reflected by measurements of total calcium; the decrease is proportional to the rate of infusion. Other electrolyte disturbances may occur. Some patients may have convulsions. Excretion of high concentrations in the urine can cause local irritation and genital ulceration. Other adverse effects reported include nausea, vomiting, diarrhoea, malaise, fatigue, fever, headache, dizziness, paraesthesia, tremor, mood disturbances, rash, abnormal liver function tests, blood pressure and ECG changes, and isolated reports of pancreatitis. Intravenous injection may cause phlebitis at the site of injection.

In cases of overdosage it is important to maintain hydration. Foscarnet elimination may be increased by haemodialysis.

Effects on the CNS. Convulsions may occur in up to 10% of AIDS patients receiving foscarnet and have been reported after overdoses. Contributing factors include underlying CNS pathology (HIV-related encephalopathy or other infections) and foscarnet-related electrolyte disturbances. However, seizures have occurred in patients without apparent risk factors.[1]

1. Lor E, Liu YQ. Neurologic sequelae associated with foscarnet therapy. *Ann Pharmacother* 1994; **28:** 1035–7.

Effects on electrolyte balance. Acute hypocalcaemia has been reported to occur in about 30% of AIDS patients receiving foscarnet. Other electrolyte disturbances include hypokalaemia and hypomagnesaemia (each in about 15%), hypophosphataemia (8%), and hyperphosphataemia (6%). Hypocalcaemia may cause paraesthesias and, together with hypomagnesaemia and hypokalaemia, may predispose to seizures and cardiovascular disturbances.

Electrolyte abnormalities (increased calcium, magnesium, phosphate, and potassium requirements, and a reduction in the need for sodium) have been reported to be dramatically accelerated by foscarnet in a patient being given total parenteral nutrition.[1]

1. Matarese LE, *et al.* Foscarnet-induced electrolyte abnormalities in a bone marrow transplant patient receiving parenteral nutrition. *J Parenter Enteral Nutr* 2000; **24:** 170–3.

Effects on the kidneys. The most serious common adverse effect of foscarnet sodium is nephrotoxicity. Clinically significant increases in serum-creatinine concentrations occur in about 30% of patients, and the incidence of nephrotoxicity tends to increase with increasing dose[1] and with duration of therapy.[2] Foscarnet sodium is excreted unchanged in the urine and tubulo-interstitial lesions and deposition of crystals in the glomerular capillary lumen have been implicated.[3] Acute renal failure has occurred and haemodialysis has been reported to have reduced plasma-foscarnet concentrations.[4] The risk of nephrotoxicity can be minimised by ensuring adequate hydration, the use of intermittent dosing schedules,[5] and by adjusting the dose according to serum-creatinine concentrations. Nephrogenic diabetes insipidus and renal tubular acidosis associated with foscarnet have been reported.[6-8]

1. Jacobson MA, *et al.* A dose-ranging study of daily maintenance intravenous foscarnet therapy for cytomegalovirus retinitis in AIDS. *J Infect Dis* 1993; **168:** 444–8.
2. Gaub J, *et al.* The effect of foscarnet (phosphonoformate) on human immunodeficiency virus isolation, T-cell subsets and lymphocyte function in AIDS patients. *AIDS* 1987; **1:** 27–33.
3. Beaufils H, *et al.* Foscarnet and crystals in glomerular capillary lumens. *Lancet* 1990; **336:** 755.
4. Deray G, *et al.* Foscarnet-induced acute renal failure and effectiveness of haemodialysis. *Lancet* 1987; **ii:** 216.
5. Deray G, *et al.* Prevention of foscarnet nephrotoxicity. *Ann Intern Med* 1990; **113:** 332.
6. Farese RV, *et al.* Nephrogenic diabetes insipidus associated with foscarnet treatment of cytomegalovirus retinitis. *Ann Intern Med* 1990; **112:** 955–6.
7. Conn J, *et al.* Nephrogenic diabetes insipidus associated with foscarnet—a case report. *J Antimicrob Chemother* 1996; **37:** 1180–1.
8. Navarro JF, *et al.* Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; **27:** 431–4.

Effects on the skin and mucous membranes. A generalised pruritic macular rash was reported in a patient given foscarnet, which subsided after the drug was withdrawn.[1]

There have been several reports of genital ulceration,[2-7] possibly related to local toxicity arising from high concentrations of foscarnet in the urine. Oral ulceration, usually with genital ulceration, has occurred during foscarnet treatment.[3-5] Uvular and oesophageal ulcerations have also been reported.[4,8]

1. Green ST, *et al.* Generalised cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1990; **21:** 227–8.
2. Van Der Pijl JW, *et al.* Foscarnet and penile ulceration. *Lancet* 1990; **335:** 286.
3. Gilquin J, *et al.* Genital and oral erosions induced by foscarnet. *Lancet* 1990; **335:** 287.
4. Féguex S, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547.
5. Moyle G, *et al.* Penile ulcerations with foscarnet. *Lancet* 1990; **335:** 547–8.
6. Lacey HB, *et al.* Vulval ulceration associated with foscarnet. *Genitourin Med* 1992; **68:** 182.
7. Caumes E, *et al.* Foscarnet-induced vulvar erosion. *J Am Acad Dermatol* 1993; **28:** 799.
8. Saint-Marc T, *et al.* Uvula and oesophageal ulcerations with foscarnet. *Lancet* 1992; **340:** 970–1.

Precautions

Foscarnet sodium should be used with caution in renal impairment and doses should be reduced if serum creatinine is raised. Serum-creatinine concentrations should be measured on alternate days throughout induction treatment; monitoring may be weekly during maintenance therapy. An adequate state of hydration must be maintained during therapy to prevent renal toxicity. Electrolytes, especially calcium and magnesium, should also be monitored and deficiencies corrected before and during foscarnet therapy.

Electrolyte content. Each g of foscarnet sodium (hexahydrate) represents about 10 mmol of sodium and about 3.3 mmol of phosphate.

Interactions

Foscarnet should not be given with other nephrotoxic drugs such as aminoglycosides, amphotericin B, and ciclosporin, or with other drugs that can affect serum-calcium concentrations. Intravenous pentamidine can produce both of these effects and severe additive toxicity may result from its use with foscarnet; fatalities have occurred.

Ciprofloxacin. Tonic-clonic seizures associated with foscarnet use in 2 patients receiving multiple antimicrobial drugs were thought to have been exacerbated by the concurrent use of ciprofloxacin.[1]

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Parenteral nutrition. For mention that foscarnet may exacerbate the need for electrolyte replacement in patients receiving total parenteral nutrition see Effects on Electrolyte Balance, above.

Antiviral Action

Foscarnet inhibits replication of human herpesviruses including CMV, herpes simplex virus types 1 and 2, herpesvirus 6, Epstein-Barr virus, and varicella-zoster virus. Activity is also reported against hepatitis B virus and HIV. Foscarnet acts by inhibition of virus-specific DNA polymerases and reverse transcriptases: unlike the nucleoside reverse transcriptase inhibitors and ganciclovir, foscarnet does not require intracellular conversion to an active triphosphate.

◊ References.

1. Balfour HH, *et al.* Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. *Antimicrob Agents Chemother* 1996; **40:** 2721–6.
2. Jabs DA, *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. *Antimicrob Agents Chemother* 1998; **42:** 2240–4.

Pharmacokinetics

The pharmacokinetics of foscarnet are complicated by the high incidence of renal impairment induced during therapy and by the deposition and subsequent gradual release of foscarnet from bone. Thus the estimation of half-life depends upon the duration of foscarnet therapy and the duration of the observation period. The plasma half-life in patients with normal renal function is about 2 to 4 hours, but terminal half-lives up to about 8 days have been reported when accumulation in bone has taken place. Plasma protein binding is about 14 to 17%. Foscarnet crosses the blood-brain barrier in variable amounts; CSF concentrations ranging from zero to more than 3 times the plasma concentration have been reported. Foscarnet is mostly excreted unchanged in the urine mainly through glomerular filtration.

◊ In 13 HIV-infected male patients with lymphadenopathy or AIDS-related complex[1] foscarnet [sodium] by continuous intravenous infusion (0.14 to 0.19 mg/kg per minute) produced plasma-foscarnet concentrations of about 100 to 500 nanomol/mL. There appeared to be a link between the degree of adverse effects experienced and plasma-foscarnet concentrations above 350 nanomol/mL. Foscarnet was excreted mainly via the kidneys. It was thought that up to 20% of the cumulative intravenous dose may have been deposited in bone 7 days after the end of infusion.

Penetration of foscarnet into the CSF is very variable and in 5 patients[1] CSF concentrations of foscarnet were found to be 13 to 68% of those in the plasma. Subsequent studies showed that CSF concentrations of foscarnet would be virostatic in most patients,[2] attaining a mean concentration of about 25% of plasma concentration after a single infusion[2,3] and 66% under steady state conditions.[3] CSF concentrations ranged from 0 to 340%[2] and 5 to 72%[3] of those in plasma. There was a correlation between the amount of foscarnet in the CSF and inflammation of the meninges in one study,[2] and with the HIV infection stage in another,[3] but neither reported a correlation with plasma concentration.

1. Sjövall J, *et al.* Pharmacokinetics of foscarnet and distribution to cerebrospinal fluid after intravenous infusion in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1989; **33:** 1023–31.
2. Raffi F, *et al.* Penetration of foscarnet into cerebrospinal fluid of AIDS patients. *Antimicrob Agents Chemother* 1993; **37:** 1777–80.
3. Hengge UR, *et al.* Foscarnet penetrates the blood-brain barrier: rationale for therapy of cytomegalovirus encephalitis. *Antimicrob Agents Chemother* 1993; **37:** 1010–14.

Uses and Administration

Foscarnet is a non-nucleoside pyrophosphate analogue active against herpesviruses. It is used as the trisodium salt mainly for the treatment of CMV retinitis in AIDS patients and for aciclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients (see below).

Foscarnet is given by intravenous infusion. A solution containing foscarnet sodium 24 mg/mL may be given via a central vein or diluted with glucose 5% or sodium chloride 0.9% to a concentration of 12 mg/mL and given via a peripheral vein. Hydration with 0.5 to 1 litre of sodium chloride 0.9% is recommended with each infusion to reduce renal toxicity.

For the treatment of **CMV retinitis** in patients with normal renal function, the usual dose is 60 mg/kg infused over at least 1 hour every 8 hours, or 90 mg/kg infused over 1½ to 2 hours every 12 hours, for 2 to 3 weeks; this should then be followed by maintenance therapy with 60 mg/kg daily, increasing to 90 to 120 mg/kg daily infused over 2 hours if tolerated.

For the treatment of aciclovir-resistant mucocutaneous **herpes simplex virus infections** in patients with normal renal function, a dose of 40 mg/kg, infused over at least 1 hour every 8 or 12 hours is given for 2 to 3 weeks or until lesions have healed.

Doses of foscarnet should be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Chrisp P, Clissold SP. Foscarnet: a review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. *Drugs* 1991; **41:** 104–29.
2. Wagstaff AJ, Bryson HM. Foscarnet: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs* 1994; **48:** 199–226.

Administration in renal impairment. Doses of intravenous foscarnet sodium may need to be reduced in patients with renal impairment. The following doses, given every 8 hours, are suggested by the UK licensed product information according to creatinine clearance (CC):

treatment of CMV retinitis:

- CC more than 1.6 mL/kg per minute: 60 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 55 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 49 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 42 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 35 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 28 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 21 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

treatment of aciclovir-resistant mucocutaneous herpes simplex infections:

- CC more than 1.6 mL/kg per minute: 40 mg/kg
- CC 1.6 to 1.4 mL/kg per minute: 37 mg/kg
- CC 1.4 to 1.2 mL/kg per minute: 33 mg/kg
- CC 1.2 to 1.0 mL/kg per minute: 28 mg/kg
- CC 1.0 to 0.8 mL/kg per minute: 24 mg/kg
- CC 0.8 to 0.6 mL/kg per minute: 19 mg/kg
- CC 0.6 to 0.4 mL/kg per minute: 14 mg/kg
- CC less than 0.4 mL/kg per minute: use not recommended

In the USA modification of doses by extending the dose interval has been recommended, resulting in proportional reductions in daily dose similar to those in the UK.

Cytomegalovirus infections. Foscarnet is used in the treatment of severe CMV infections (p.853) in immunocompromised patients and appears to possess similar efficacy to ganciclovir[1] (see also under Ganciclovir, p.880). It has been particularly useful in patients who require antiretroviral therapy for AIDS and are unable to tolerate ganciclovir (because of haematological toxicity). For patients unable to tolerate systemic therapy foscarnet has been tried as an intravitreal injection.[2-4] Beneficial responses have been reported with various regimens including intravitreal injections of foscarnet 1.2 mg every 48 hours for 4 doses[2] or induction with 2.4 mg twice weekly[4] or every 72 hours for 6 doses,[3] then once weekly maintenance thereafter.[3,4] Combined treatment with foscarnet and ganciclovir each given intravitreally has also been reported to be effective;[5] however, although combination systemic therapy has been widely used where resistance to ganciclovir is suspected, the evidence for a synergistic effect against CMV is not very strong.[6]

Foscarnet has also been investigated for primary prophylaxis of CMV infection in bone marrow transplant recipients at high risk of infection.[7,8]

1. Reusser P, *et al.* Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood* 2002; **99:** 1159–64.
2. Lieberman RM, *et al.* Efficacy of intravitreal foscarnet in a patient with AIDS. *N Engl J Med* 1994; **330:** 868–9.

3. Diaz-Llopis M, *et al.* High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. *Br J Ophthalmol* 1994; **78:** 120–4.
4. Ausayakhun S, *et al.* Intravitreal foscarnet for cytomegalovirus retinitis in patients with AIDS. *J Med Assoc Thai* 2005; **88:** 103–7.
5. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
6. Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? *J Clin Virol* 2006; **35:** 485–8.
7. Ippoliti C, *et al.* Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir. *Bone Marrow Transplant* 1997; **20:** 491–5.
8. Bregante S, *et al.* Foscarnet prophylaxis of cytomegalovirus infections in patients undergoing allogeneic bone marrow transplantation (BMT): a dose-finding study. *Bone Marrow Transplant* 2000; **26:** 23–9.

Herpes simplex infections. Although foscarnet is effective in the treatment of herpes simplex infections it is usually reserved for severe or disseminated herpes simplex infections, particularly in immunocompromised patients who have infections resistant to aciclovir (see p.854). A 2% cream applied topically is effective in the treatment of refractory herpes simplex infections of the skin,[1] and is licensed for such use in some countries. Topical use of a 1% foscarnet cream has also been investigated.[2]

1. Gross G, Braun D. Wirksamkeit und Verträglichkeit von topisch appliziertem Foscarnet-Natrium bei der Behandlung von Herpes labialis. Ergebnisse einer Anwendungsbeobachtung. *Hautarzt* 2006; **57:** 40–6.
2. Javaly K, *et al.* Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999; **21:** 301–6.

Varicella-zoster infections. Foscarnet is the recommended treatment for aciclovir-resistant varicella-zoster infections (p.855). In a study[1] of 5 patients with AIDS and aciclovir-resistant zoster infection complete healing was reported for 3 patients after treatment with foscarnet 120 mg/kg daily for 14 to 26 days. Two patients relapsed 7 and 14 days respectively after stopping treatment. In another study[2] 10 of 13 HIV-infected patients with aciclovir-resistant zoster infection had complete healing after treatment with 100 mg/kg twice daily of foscarnet for 12 to 30 days. Five of the patients relapsed after stopping treatment with the median time to relapse being 110 days.

1. Safrin S, *et al.* Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* 1991; **115:** 19–21.
2. Breton G, *et al.* Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998; **27:** 1525–7.

Preparations

BP 2008: Foscarnet Intravenous Infusion.

Proprietary Preparations (details are given in Part 3)

Austral.: Foscavir; ***Austria:*** Foscavir; ***Belg.:*** Foscavir; ***Braz.:*** Foscavir; ***Cz.:*** Foscavir†; ***Fr.:*** Foscavir; ***Ger.:*** Foscavir; Triapten; ***Gr.:*** Foscavir; ***Hung.:*** Foscavir; ***Israel:*** Foscavir; ***Ital.:*** Foscavir; ***Jpn:*** Foscavir; ***Neth.:*** Foscavir; ***Norw.:*** Foscavir; ***NZ:*** Foscavir; ***Port.:*** Foscavir; ***Spain:*** Foscavir; ***Swed.:*** Foscavir; ***Switz.:*** Foscavir; ***UK:*** Foscavir; ***USA:*** Foscavir.

Ganciclovir *(BAN, USAN, rINN)*

BIOLF-62; BN-B759V; BW-759; BWB-759U; BW-759U; DHPG; Dihydroxypropoxymethylguanine; 9-(1,3-Dihydroxy-2-propoxymethyl)guanine; Ganciclovirum; Gancyklovir; Gansikloviiri; Gansiklovir; 2′-NDG; 2′-Nor-2′-deoxyguanosine; RS-21592. 9-[2-Hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine.

Ганцикловир

$C_9H_{13}N_5O_4$ = 255.2.

CAS — 82410-32-0.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

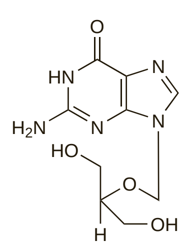

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Ganciclovir). A white to off-white crystalline powder. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Ganciclovir Sodium *(BANM, USAN, rINNM)*

Ganciclovir sódico; Ganciclovir Sodique; Natrii Ganciclovirum.

Натрий Ганцикловир

$C_9H_{12}N_5NaO_4$ = 277.2.

CAS — 107910-75-8.

ATC — J05AB06; S01AD09.

ATC Vet — QJ05AB06; QS01AD09.

Incompatibility. Ganciclovir is reported to be incompatible with foscarnet.

Stability. Ganciclovir sodium solution in sodium chloride 0.9% was found[1] to be stable when stored in polypropylene infusion-pump syringes for 12 hours at 25° and for 10 days at 4°. Little variation was found in ganciclovir concentration after storage of a 2% solution at room temperature, 5°, and –8° for 10 to 24 days.[2]

1. Mulye NV, *et al.* Stability of ganciclovir sodium in an infusion-pump syringe. *Am J Hosp Pharm* 1994; **51:** 1348–9.
2. Morlet N, *et al.* High dose intravitreal ganciclovir for CMV retinitis: a shelf life and cost comparison study. *Br J Ophthalmol* 1995; **79:** 753–5.

Adverse Effects and Treatment

The most common adverse effects of systemic ganciclovir are haematological and include neutropenia and thrombocytopenia; anaemia also occurs. Neutropenia affects up to 50% of patients given ganciclovir, most commonly starting in the first or second week of use. It is usually reversible but may be prolonged or irreversible and can lead to potentially fatal infections. AIDS patients may be at a greater risk of neutropenia than other immunosuppressed patients. Thrombocytopenia occurs in about 20% of patients given ganciclovir. Those with iatrogenic immunosuppression may be more at risk of developing thrombocytopenia than AIDS patients. Other adverse effects occurring in patients given systemic ganciclovir include dyspnoea, headache, fever, rash, pruritus, asthenia, CNS and gastrointestinal disturbances, infection, increased serum-creatinine concentration, and abnormal liver function tests. Less frequent adverse effects reported include anaphylaxis, arrhythmias, hypotension, pancreatitis, haematuria, as well as metabolic, musculoskeletal, urogenital, and cutaneous symptoms. When given intravenously, irritation or phlebitis may occur at the site of injection due to the high pH.

Local adverse effects have been associated with the insertion of ocular implants of ganciclovir.

Animal studies have suggested that there may be a risk of adverse testicular effects with temporary or permanent inhibition of spermatogenesis. Female fertility may also be affected. Such studies also suggest that ganciclovir is a potential mutagen, teratogen, and carcinogen.

Haemodialysis and hydration may be useful in reducing plasma concentrations of ganciclovir. Haematological adverse effects may be reversed in some patients by stopping treatment or reducing dosage; blood cell counts should return to normal within 3 to 7 days.

Colony-stimulating factors have been given with ganciclovir to limit its haematological toxicity.

Effects on the blood. Ganciclovir-induced neutropenia was successfully treated in a patient with CMV retinitis and bone-marrow suppression by intravenous *molgramostim* 5 micrograms/kg.[1] In a multicentre, randomised placebo-controlled study[2] in 69 AIDS patients with CMV infection who developed neutropenia from ganciclovir therapy, *lenograstim* given in a dose of 50 micrograms/m^2 subcutaneously yielded similar positive results.

1. Russo CL, *et al.* Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. *Lancet* 1990; **336:** 751–2.
2. Dubreuil-Lemaire M-L, *et al.* Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol* 2000; **65:** 337–43.

Effects on mental function. Psychosis has been associated with intravenous ganciclovir use in 2 patients with normal renal function.[1,2] In both cases, psychotic symptoms such as agitation, confusion, and hallucination, occurred within 2 to 6 days of starting treatment with ganciclovir; symptoms resolved after ganciclovir was stopped.

1. Hansen BA, *et al.* Ganciclovir-induced psychosis. *N Engl J Med* 1996; **335:** 1397.
2. Southworth MR, Dunlap SH. Psychotic symptoms and confusion associated with intravenous ganciclovir in a heart transplant recipient. *Pharmacotherapy* 2000; **20:** 479–83.

Effects on the skin. An interstitial granulomatous drug reaction was reported[1] in a 57-year old woman after about one month of treatment with intravenous ganciclovir for CMV pneumonia. No other new drugs were given before the onset of the lesions and they resolved spontaneously within 2 weeks of stopping the ganciclovir.

1. Marcollo Pini A, *et al.* Interstitial granulomatous drug reaction following intravenous ganciclovir. *Br J Dermatol* 2008; **158:** 1391–3.

Precautions

Ganciclovir should be used with caution in patients with renal impairment and doses should be adjusted according to creatinine clearance. It should not be given by rapid or bolus injection and adequate hydration should be maintained during intravenous infusion. It should be given with caution to patients with low blood counts or with a history of cytopenic reactions to drugs. Complete blood and platelet counts should be performed every 2 days or daily during the first 14 days of intravenous therapy and once weekly thereafter; ganciclovir should be withdrawn if the neutrophil count falls below 500 cells/microlitre or the platelet count falls below 25 000 cells/microlitre. Patients receiving oral ganciclovir should also be monitored regularly.

Ganciclovir is contra-indicated in pregnancy; contraception is recommended during ganciclovir treatment and, additionally for men, for 90 days thereafter. Adverse effects have occurred in the offspring of *animals* given ganciclovir during pregnancy and lactation.

Because of the risk of carcinogenicity and the high pH of the solution, contact with the skin and eyes should be avoided during the reconstitution of ganciclovir sodium injection.

Sodium content. Each g of ganciclovir sodium represents about 3.6 mmol of sodium.

Interactions

Zidovudine given with ganciclovir may have an additive neutropenic effect and should not normally be given during intravenous ganciclovir induction therapy, although it has been given with caution during oral maintenance therapy. Probenecid and other drugs that inhibit renal tubular secretion and resorption may reduce the renal clearance of ganciclovir, and so increase its serum concentrations. Use of intravenous ganciclovir with oral mycophenolate mofetil may result in increased plasma concentrations of both drugs due to competition for renal tubular secretion. Drugs that inhibit rapid cell division such as amphotericin B, some antineoplastic drugs, co-trimoxazole, dapsone, flucytosine, hydroxycarbamide, nucleoside analogues, and pentamidine may have additive toxic effects if given with ganciclovir. Convulsions have been reported when ganciclovir was given with imipenem and cilastatin.

Antivirals. Additive haematological toxicity, including neutropenia, may occur if ganciclovir is given with *zidovudine* (see Zidovudine, p.915), and there are reports of increased plasma concentrations of *didanosine* when given with ganciclovir (see p.871). There has also been a report[1] of decreased blood concentrations of ganciclovir when didanosine (200 mg every 12 hours) was given orally 2 hours before oral ganciclovir (1 g every 8 hours) but not when the two drugs were given at the same time. However, a later study[2] using twice the dose of oral ganciclovir found no effect irrespective of whether ganciclovir was given 2 hours before or 2 hours after didanosine.

When ganciclovir was given orally with *zalcitabine*, a 22% increase in the area under the concentration-time curve for ganciclovir was noted although it was believed that this did not necessitate any dosage modification.[3] No pharmacokinetic changes were reported when ganciclovir was given orally with *stavudine*.[3]

1. Cimoch PJ, *et al.* Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 227–34.
2. Jung D, *et al.* Effect of high-dose oral ganciclovir on didanosine disposition in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1057–62.
3. Jung D, *et al.* The pharmacokinetics and safety profile of oral ganciclovir combined with zalcitabine or stavudine in asymptomatic HIV- and CMV-seropositive patients. *J Clin Pharmacol* 1999; **39:** 505–12.

The symbol † denotes a preparation no longer actively marketed

Ciclosporin. Reversible acute unilateral or bilateral eye movement disorders typical of sixth cranial nerve palsies[1] occurred in 4 patients who received ciclosporin and ganciclovir after bone marrow transplantation.

1. Openshaw H, *et al.* Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. *Bone Marrow Transpl* 1997; **19:** 503–5.

Antiviral Action

Ganciclovir inhibits replication of human herpesviruses *in vivo* and *in vitro*. It is active against CMV, herpes simplex virus types 1 and 2, Epstein-Barr virus, varicella-zoster virus, and herpesvirus 6, 7, and 8. This activity is due to intracellular conversion of ganciclovir by viral thymidine kinase (in herpes simplex and varicella-zoster infected cells) or possibly by cellular deoxyguanosine kinase (in Epstein-Barr infected cells) to ganciclovir monophosphate with subsequent cellular conversion to the diphosphate and the active triphosphate. Ganciclovir triphosphate inhibits viral DNA synthesis by inhibiting the viral DNA polymerase enzyme as well as being incorporated into the viral DNA. This process is selective for infected cells; the concentration of ganciclovir triphosphate may be up to a hundredfold higher in CMV-infected cells than in uninfected cells.

Ganciclovir has a similar spectrum of activity to aciclovir, herpes simplex virus types 1 and 2 being the most susceptible of the herpesviruses. However, CMV is much more susceptible to ganciclovir than aciclovir.

Resistance

Resistance to ganciclovir has been found *in vitro* in herpes simplex viruses, varicella-zoster virus, and CMV. Possible mechanisms of resistance include a reduction in the phosphorylation of ganciclovir to the active form and reduced sensitivity of viral DNA polymerase. Resistance has been reported in CMV strains isolated from patients receiving ganciclovir for prolonged periods and in those with an initially high viral load. It has also been seen in AIDS patients with CMV retinitis who have never previously received the drug. Cross-resistance with cidofovir is common.

◊ The development of CMV resistance to ganciclovir may be a factor in disease progression in patients receiving prolonged therapy with ganciclovir and the incidence of resistance is reported to increase with duration of therapy.[1] A ganciclovir-resistant isolate of CMV has been detected in about 30% of 95 patients after 9 months of treatment and correlated with dissemination of infection to the contralateral eye.[2] Treatment of unilateral retinitis with systemic ganciclovir (intravenously, or orally together with an implant) was associated with a higher incidence of ganciclovir-resistant CMV infection developing in the contralateral eye, compared with treatment with ganciclovir implant alone.[3]

Ganciclovir-resistant CMV has been reported[4] to be an important cause of late morbidity in seronegative patients who received CMV-seropositive organ transplants; in one study,[5] 5 of 67 seronegative recipients developed ganciclovir-resistant CMV disease compared with none of 173 seropositive subjects.

1. Drew WL. Cytomegalovirus resistance to antiviral therapies. *Am J Health-Syst Pharm* 1996; **53** (suppl 2): S17–S23.
2. Jabs DA, *et al.* Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. *J Infect Dis* 1998; **177:** 770–3.
3. Imai Y, *et al.* Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. *J Infect Dis* 2004; **189:** 611–15.
4. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. *Clin Infect Dis* 2002; **35:** 866–72.
5. Limaye AP, *et al.* Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; **356:** 645–9.

Pharmacokinetics

Ganciclovir is poorly absorbed from the gastrointestinal tract after oral doses and there is minimal systemic absorption after intravitreal injection. Bioavailability of oral ganciclovir is about 5%, and is increased by intake with food to 6 to 9%. After intravenous dosage as ganciclovir sodium it is widely distributed to body tissues and fluids including intra-ocular fluid and CSF. Binding to plasma proteins is reported to be 1 to 2%. Ganciclovir is excreted unchanged in the urine mainly by glomerular filtration and also active tubular secretion. In patients with normal renal function the half-life is about 2.5 to 4.5 hours after intravenous doses and about 4 to 5.7 hours after oral doses. In patients with renal impairment, the renal clearance decreases and the half-life increases; a half-life of 28.5 hours has been reported when the serum-creatinine concentration was greater than 398 micromol/litre.

Haemodialysis has been reported to reduce plasma-ganciclovir concentrations by about 50%.

◊ References.

1. Arevalo JF, *et al.* Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis* 1995; **172:** 951–6.
2. Morlet N, *et al.* High dose intravitreal ganciclovir injection provides a prolonged therapeutic intraocular concentration. *Br J Ophthalmol* 1996; **80:** 214–16.
3. Lavelle J, *et al.* Effect of food on the relative bioavailability of oral ganciclovir. *J Clin Pharmacol* 1996; **36:** 238–41.
4. Zhou X-J, *et al.* Population pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infection. *Antimicrob Agents Chemother* 1996; **40:** 2202–5.
5. Giffy KG. Pharmacokinetics of oral ganciclovir capsules in HIV-infected persons. *AIDS* 1996; **10** (suppl 4): S3–S6.
6. Jung D, *et al.* Steady-state relative bioavailability of three oral ganciclovir dosage regimens delivering 6,000 mg/day in patients with human immunodeficiency virus. *J Clin Pharmacol* 1998; **38:** 1021–4.
7. Jung D, *et al.* Absolute bioavailability and dose proportionality of oral ganciclovir after ascending multiple doses in human immunodeficiency virus (HIV)-positive patients. *J Clin Pharmacol* 1998; **38:** 1122–8.
8. Jung D, *et al.* Effect of food on high-dose oral ganciclovir disposition in HIV-positive subjects. *J Clin Pharmacol* 1999; **39:** 161–5.
9. Snell GI, *et al.* Pharmacokinetic assessment of oral ganciclovir in lung transplant recipients with cystic fibrosis. *J Antimicrob Chemother* 2000; **45:** 511–16.
10. Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44:** 495–507.
11. Asano-Mori Y, *et al.* Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. *J Antimicrob Chemother* 2006; **57:** 1004–7.

Uses and Administration

Ganciclovir is a synthetic nucleoside analogue of guanine closely related to aciclovir (p.862), but has greater activity against CMV. It is used for the treatment and suppression of life-threatening or sight-threatening CMV infections in immunocompromised patients, including those with AIDS and those with iatrogenic immunosuppression associated with organ transplantation or chemotherapy of neoplastic disease (see also below). It has also been used for superficial ocular herpes simplex infections.

Ganciclovir is given by intravenous infusion as the sodium salt but doses are expressed in terms of ganciclovir; 54.3 mg of ganciclovir sodium is equivalent to about 50 mg of ganciclovir. Solutions for infusion are usually prepared to give a concentration of ganciclovir of 50 mg/mL, then further diluted to contain not more than 10 mg/mL. An intravenous solution is given over 1 hour.

In **CMV infections**, the usual initial dose for ***treatment*** is 5 mg/kg by intravenous infusion every 12 hours for 14 to 21 days. This induction period may be followed by *maintenance* therapy to prevent recurrence or progression of the disease. The usual maintenance dosage is 5 mg/kg by intravenous infusion as a single daily dose for 7 days each week or 6 mg/kg daily for 5 days each week. If retinitis recurs or progresses a further induction course of ganciclovir may be given. AIDS patients who have received initial treatment with intravenous ganciclovir, and who have stable CMV retinitis following at least 3 weeks of intravenous therapy, may be given oral valganciclovir. In some countries oral formulations of ganciclovir sodium are available for maintenance; typical dosage is 3 g daily in divided doses.

For ***prevention*** of CMV infection in immunocompromised patients, specifically those receiving immunosuppressive therapy after organ transplantation, ganciclovir may be given in an *initial* dose of 5 mg/kg by intravenous infusion every 12 hours for 7 to 14 days, followed by intravenous *maintenance* therapy as above.

Doses of ganciclovir should be reduced in renal impairment (see below).

Intravitreal implants providing controlled release of ganciclovir are available for those patients with CMV retinitis who are unable to tolerate systemic therapy; the implants are designed to release ganciclovir over a period of 5 to 8 months.

Ganciclovir has been used as a topical ophthalmic 0.15% gel for the treatment of superficial ocular **herpes simplex infections**.

◊ General references.

1. Faulds D, Heel RC. Ganciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs* 1990; **39:** 597–638.
2. Markham A, Faulds D. Ganciclovir: an update of its therapeutic use in cytomegalovirus infection. *Drugs* 1994; **48:** 455–84.
3. Crumpacker CS. Ganciclovir. *N Engl J Med* 1996; **335:** 721–9.
4. McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001; **61:** 1153–83.

Administration in renal impairment. Doses of ganciclovir should be reduced in renal impairment. Licensed product information recommends the following intravenous doses based on creatinine clearance (CC):

- CC 70 mL/minute or more: 5 mg/kg every 12 hours for induction, followed by 5 mg/kg every 24 hours for maintenance
- CC 50 to 69 mL/minute: 2.5 mg/kg every 12 hours for induction, 2.5 mg/kg every 24 hours for maintenance
- CC 25 to 49 mL/minute: 2.5 mg/kg every 24 hours for induction, 1.25 mg/kg every 24 hours for maintenance
- CC 10 to 24 mL/minute: 1.25 mg/kg every 24 hours for induction, 0.625 mg/kg every 24 hours for maintenance
- dialysis patients: on days when dialysis is performed 1.25 mg/kg for induction, or 0.625 mg/kg for maintenance, in each case given shortly after the end of dialysis. In the USA, a maximum of 3 doses each week is recommended

Cytomegalovirus infections. Ganciclovir is used in both the treatment and prophylaxis of CMV infections (p.853) in immunocompromised patients although the prodrug valganciclovir, which is as effective as ganciclovir and has a more convenient oral dosage regimen, may now be preferred.

As with other herpesvirus infections, antiviral treatment tends to be suppressive rather than curative, and long-term maintenance therapy is necessary. Treatment in patients with AIDS is complicated by the additive haematological toxicity of ganciclovir and zidovudine. Clinical studies comparing ganciclovir with foscarnet for AIDS-related CMV retinopathy have shown higher mortality rates in patients given ganciclovir than in those given foscarnet.[1,2] The use of ganciclovir with CMV immunoglobulins[3,4] or normal immunoglobulins,[5] or with foscarnet[6,7] has been reported to improve both efficacy and tolerance.

An alternative is the use of *intravitreal* controlled-release ganciclovir implants[8-11] to avoid systemic adverse effects. Intravitreal ganciclovir used with intravitreal foscarnet has been reported to be effective.[12]

Oral preparations of ganciclovir have been tried for maintenance therapy and may be a useful adjunct to prevent systemic infection in patients treated with the intravitreal implants[13] (but see under Resistance, above). The use of oral ganciclovir in high doses has been investigated;[14] daily doses of up to 6 g have been reported to be of benefit, although a conclusive comparison with standard intravenous doses could not be made. CMV infections at other sites in AIDS patients, including gastrointestinal and pulmonary infections, respond less well to ganciclovir than does retinitis.

Ganciclovir is also valuable for prophylaxis and early treatment of CMV infections in *transplant recipients*.[7,15-22] It is not clear whether pre-emptive therapy in infected patients is a better strategy than prophylaxis.[23] For established infections, ganciclovir is reported to be more effective in solid organ transplant recipients than in bone marrow transplant recipients. Ganciclovir has also been tried for prevention of CMV infection in patients with AIDS, although results are conflicting.[24,25]

Treatment of *congenital infections* has a generally poor outcome. Prolonged treatment periods may improve the response, but the safety of extended treatment with ganciclovir in this age group has not been fully evaluated and there is a need for further randomised controlled studies.[26] There is some recent evidence[27] that a 6-week course started in neonates with clinically apparent disease affecting the CNS prevents hearing deterioration at 6 months and may also prevent deterioration at or beyond 1 year of age.

1. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. *N Engl J Med* 1992; **326:** 213–20.
2. Polis MA, *et al.* Increased survival of a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis who received sodium phosphonoformate (foscarnet). *Am J Med* 1993; **94:** 175–80.

3. D'Alessandro AM, *et al.* Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. *Transplant Proc* 1989; **21:** 3560–1.
4. Salmela K, *et al.* Ganciclovir in the treatment of severe cytomegalovirus disease in liver transplant patients. *Transplant Proc* 1990; **22:** 238–40.
5. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
6. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the Cytomegalovirus Retreatment Trial. *Arch Ophthalmol* 1996; **114:** 23–33.
7. Mylonakis E, *et al.* Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis* 2002; **34:** 1337–41.
8. Anand R, *et al.* Control of cytomegalovirus retinitis using sustained release of intraocular gancyclovir. *Arch Ophthalmol* 1993; **111:** 223–7.
9. Martin DF, *et al.* Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994; **112:** 1531–9.
10. Musch DC, *et al.* Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. *N Engl J Med* 1997; **337:** 83–90.
11. Ausayakhun S, *et al.* Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. *J Med Assoc Thai* 2005; **88** (suppl 9): S15–S20.
12. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
13. Martin DF, *et al.* Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999; **340:** 1063–70.
14. Lalezari JP, *et al.* High dose oral ganciclovir treatment for cytomegalovirus retinitis. *J Clin Virol* 2002; **24:** 67–77.
15. Goodrich JM, *et al.* Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993; **118:** 173–8.
16. Winston DJ, *et al.* Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. *Ann Intern Med* 1993; **118:** 179–84.
17. Hibberd PL, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; **123:** 18–26.
18. Winston DJ, *et al.* Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995; **346:** 69–74.
19. Gane E, *et al.* Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; **350:** 1729–33.
20. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; **32:** 742–51.
21. Paya CV, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; **185:** 854–60.
22. Keven K, *et al.* Cytomegalovirus prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. *Transplant Proc* 2004; **36:** 3107–12.
23. Monforte V, *et al.* Preemptive therapy with intravenous ganciclovir for the prevention of cytomegalovirus disease in lung transplant recipients. *Transplant Proc* 2005; **37:** 4039–42.
24. McCarthy M. Oral ganciclovir fails to prevent CMV in HIV trial. *Lancet* 1995; **346:** 895.
25. Spector SA, *et al.* Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *N Engl J Med* 1996; **334:** 1491–7.
26. Michaels MG, *et al.* Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003; **22:** 504–8.
27. Kimberlin DW, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143:** 16–25.

Epstein-Barr virus infections. There have been anecdotal reports[1-4] of some improvement in patients with Epstein-Barr virus (EBV) infection given ganciclovir, although no antiviral therapy is entirely satisfactory (p.854).

1. Pirsch JD, *et al.* Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *Am J Med* 1989; **86:** 241–4.
2. Ishida Y, *et al.* Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993; **341:** 560–1.
3. MacGinley R, *et al.* Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant* 2001; **16:** 197–8.
4. Adams LA, *et al.* Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol* 2006; **21:** 1758–60.

Herpesvirus infections. Ganciclovir 0.15% gel is licensed in a number of countries for the treatment of superficial ocular infections with herpes simplex. In patients with herpes simplex keratitis it has been reported to be as effective as aciclovir 3% ointment,[1] the drug most commonly used in this infection (see Ocular Herpes Simplex Infections, p.854).

1. Hoh HB, *et al.* Randomised trial of ganciclovir and acyclovir in the treatment of herpes simplex dendritic keratitis: a multicentre study. *Br J Ophthalmol* 1996; **80:** 140–3.

Preparations

USP 31: Ganciclovir for Injection; Ganciclovir Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciganclor; Cymevene; Cytovene†; Gasmilen; Grinevel; Virgan; ***Austral.:*** Cymevene; Vitrasert†; ***Austria:*** Cymevene; ***Belg.:*** Cymevene; Virgan; ***Braz.:*** Cymevene; Gancivir†; Ganvirax; ***Canad.:*** Cytovene; ***Chile:*** Cymevene; ***Cz.:*** Cymevene; Virgan; ***Denm.:*** Cymevene; ***Fin.:*** Cymevene; ***Fr.:*** Cymevan; Virgan; ***Ger.:*** Cymeven; ***Gr.:*** Cymevene; ***Hong Kong:*** Cymevene; ***Hung.:*** Cymevene; ***Indon.:*** Cymevene; ***Irl.:*** Cymevene; ***Israel:*** Cymevene; ***Ital.:*** Citovirax; Cymevene; ***Mex.:*** Cymevene; ***Neth.:*** Cymevene; ***Norw.:*** Cymevene; ***NZ:*** Cymevene; ***Philipp.:*** Cymevene; Virgan; ***Pol.:*** Cymevene; Virgan; ***Port.:*** Cymevene; Virgan; ***S.Afr.:*** Cymevene; ***Singapore:*** Cymevene; ***Spain:*** Cymevene; Vitrasert†; ***Swed.:*** Cymevene; ***Switz.:*** Cymevene; ***Thai.:*** Cymevene; ***Turk.:*** Cymevene; ***UK:*** Cymevene; Virgan†; ***USA:*** Cytovene; Vitrasert; ***Venez.:*** Cymevene.

Ibacitabine *(rINN)*

Ibacitabina; Ibacitabinum; Iododesoxycytidine. 2′-Deoxy-5-iodocytidine.

Ибацитабин

$C_9H_{12}IN_3O_4$ = 353.1.
CAS — 611-53-0.
ATC — D06BB08.
ATC Vet — QD06BB08.

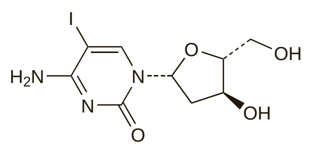

Profile

Ibacitabine is an antiviral used topically as a 1% gel in the treatment of herpes labialis (p.854).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cuterpes.

Idoxuridine *(BAN, USAN, rINN)*

Allergan 211; GF-1115; Idoksuridiini; Idoksuridinas; Idoxuridin; Idoxuridina; Idoxuridinum; IDU; 5-IDUR; 5-IUDR; NSC-39661; SKF-14287. 2′-Deoxy-5-iodouridine.

Идоксуридин

$C_9H_{11}IN_2O_5$ = 354.1.
CAS — 54-42-2.
ATC — D06BB01; J05AB02; S01AD01.
ATC Vet — QD06BB01; QJ05AB02; QS01AD01.

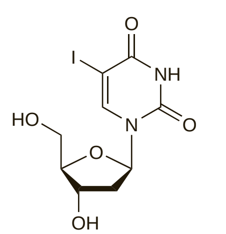

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.*

Ph. Eur. 6.2 (Idoxuridine). A white or almost white crystalline powder. M.p. about 180°, with decomposition. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 31 (Idoxuridine). A white, practically odourless, crystalline powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Iodine vapour is liberated on heating idoxuridine. It has been reported that some decomposition products such as iodouracil are more toxic than idoxuridine and reduce its antiviral activity.

Adverse Effects

Hypersensitivity reactions such as irritation, pain, and pruritus may occur occasionally when idoxuridine is applied to the eyes. Other adverse effects include stinging, conjunctivitis, oedema and inflammation of the eye or eyelids, photophobia, pruritus, and rarely, occlusion of the lachrymal duct. Prolonged or excessive use may damage the cornea.

Idoxuridine applied to the skin may produce irritation, stinging, and hypersensitivity reactions. Taste disturbance may also occur. Excessive application of topical idoxuridine to the skin may cause skin maceration.

Idoxuridine is a potential carcinogen and teratogen.

Carcinogenicity. Squamous carcinoma has been reported in association with topical idoxuridine treatment.[1]

1. Koppang HS, Aas E. Squamous carcinoma induced by topical idoxuridine therapy? *Br J Dermatol* 1983; **108:** 501–3.

Precautions

Idoxuridine should be used with caution in conditions where there is deep ulceration involving the stromal layers of the cornea, as delayed healing has resulted in corneal perforation. Prolonged topical use should be avoided.

The potential teratogenicity of idoxuridine should be taken into account when treating pregnant patients or patients likely to become pregnant. Corticosteroids should be applied with caution in patients also receiving idoxuridine as they may accelerate the spread of viral infection.

Interactions

Preparations containing boric acid should not be applied to the eye in patients also receiving ocular preparations of idoxuridine as irritation ensues.

Antiviral Action

After intracellular phosphorylation to the triphosphate, idoxuridine is incorporated into viral DNA instead of thymidine so inhibiting replication of sensitive viral strains. Idoxuridine is also incorporated into mammalian DNA. Idoxuridine is active against herpes simplex and varicella zoster viruses. It has also been shown to inhibit vaccinia virus, CMV, and adenovirus.

Pharmacokinetics

Penetration of idoxuridine into the cornea and skin is reported to be poor. Idoxuridine is rapidly metabolised in the body to iodouracil, uracil, and iodide, which are excreted in the urine.

Uses and Administration

Idoxuridine is a pyrimidine nucleoside structurally related to thymidine. It is used topically in the treatment of herpes simplex keratitis and cutaneous infections with herpes simplex (p.854) and herpes zoster (see Varicella-zoster Infections, p.855), but has generally been superseded by other antivirals.

In the treatment of herpes simplex keratitis, idoxuridine is applied as a 0.1% ophthalmic solution or a 0.5% eye ointment.

Idoxuridine 5% in dimethyl sulfoxide (to aid absorption) may be painted onto the lesions of cutaneous herpes simplex and herpes zoster four times daily for 4 days.

Preparations

BP 2008: Idoxuridine Eye Drops;
USP 31: Idoxuridine Ophthalmic Ointment; Idoxuridine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Idulea; ***Austral.:*** Herplex-D†; Stoxil; ***Belg.:*** Virexen†; ***Braz.:*** Herpesine; ***Canad.:*** Herplex; ***Ger.:*** Virunguent; Zostrum; ***Hung.:*** Oftan IDU†; ***India:*** Ridinox; ***Indon.:*** Isotic Ixodine; ***Irl.:*** Zostrum†; ***Israel:*** Virusan†; ***Ital.:*** Iducher; Idustatin; ***Malaysia:*** Virunguent†; ***Mex.:*** Idina†; ***Neth.:*** Virexen; ***NZ:*** Virasolve; ***Port.:*** Virexen†; Virunguent†; ***Rus.:*** Oftan IDU (Офтан ИДУ); ***Singapore:*** Virunguent; ***Spain:*** Virexen; ***Switz.:*** Iderpes†; Virunguent; ***UK:*** Herpid; ***Venez.:*** Herpidum†.

Multi-ingredient: ***Arg.:*** Itro†; ***Austral.:*** Virasolve; ***Ger.:*** Virunguent P†; ***Hong Kong:*** Virasolve†.

Imiquimod *(BAN, USAN, rINN)*

Imikimod; Imikimodi; Imiquimodum; R-837; S-26308. 4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline.

Имихимод

$C_{14}H_{16}N_4$ = 240.3.
CAS — 99011-02-6.
ATC — D06BB10.
ATC Vet — QD06BB10.

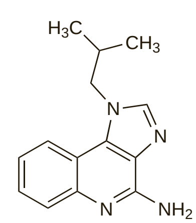

Adverse Effects

Adverse effects after topical application of imiquimod include local skin erosion, erythema, excoriation, flaking, and oedema. There have been reports of localised hypopigmentation and hyperpigmentation. Skin reactions away from the site of application have been reported. Systemic effects after topical application include headache, flu-like symptoms, and myalgia.

Hypotension has occurred after repeated ingestion.

Hypersensitivity. Angioedema, initially of both the hands and feet and later the tongue, occurred in a 61-year-old man 3 weeks after starting treatment with a 5% imiquimod cream for squamous cell carcinoma *in situ* (Bowen's disease).[1]

1. Barton JC. Angioedema associated with imiquimod. *J Am Acad Dermatol* 2004; **51:** 477–8.

Uses and Administration

Imiquimod is an immune response modifier used topically in the treatment of external genital and perianal warts (p.1584), superficial basal cell carcinomas, and actinic keratoses (see below). For the treatment of genital and perianal **warts**, it is applied as a

5% cream three times each week for up to 16 weeks and is left on the skin for 6 to 10 hours. For the management of superficial **basal cell carcinoma**, a 5% cream is applied 5 times each week for 6 weeks and left on the skin for about 8 hours. For the treatment of **actinic keratoses** on the face or scalp, a 5% cream is also used and is again left on the skin for 8 hours. In the UK, this is applied 3 times each week for 4 weeks, repeated after a 4-week break for a further 4 weeks if necessary; in the USA, application twice a week for 16 weeks is recommended.

Imiquimod is also under investigation for the treatment of other squamous cell carcinomas.

◊ Reviews.

1. Tyring S, *et al.* Imiquimod; an international update on therapeutic uses in dermatology. *Int J Dermatol* 2002; **41:** 810–16.
2. Garland SM. Imiquimod. *Curr Opin Infect Dis* 2003; **16:** 85–9.
3. Wagstaff AJ, Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. *Drugs* 2007; **67:** 2187–2210.
4. Schön MP, Schön M. Imiquimod: mode of action. *Br J Dermatol* 2007; **157** (suppl 2): 8–13.

Leishmaniasis. Evidence from small studies[1,2] suggests that topical imiquimod 5 or 7.5% cream, in combination with parenteral meglumine antimonate (p.828) may be of use in the management of cutaneous leishmaniasis (p.824).

1. Miranda-Verástegui C, *et al.* Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clin Infect Dis* 2005; **40:** 1395–1403.
2. Arevalo I, *et al.* Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis* 2007; **44:** 1549–54.

Malignant neoplasms of the skin. Imiquimod is indicated in the treatment of actinic keratosis[1-4] and basal cell carcinoma (p.673).[5-8] It is under investigation for the treatment of Bowen's disease.[9] It has also been tried in lentigo maligna[10] and other forms of localised or *in-situ* melanoma,[11,12] and there are also reports of investigational use in the management of metastatic melanoma.[13,14] and in anal and vulvar intraepithelial neoplasia.[15,16]

1. Lebwohl M, *et al.* Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; **50:** 714–21.
2. Korman N, *et al.* Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol* 2005; **141:** 467–73.
3. Krawtchenko N, *et al.* A randomised study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; **157** (suppl 2): 34–40.
4. Alomar A, *et al.* Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. *Br J Dermatol* 2007; **157:** 133–41.
5. Chen TM, *et al.* Treatment of a large superficial basal cell carcinoma with 5% imiquimod: a case report and review of the literature. *Dermatol Surg* 2002; **28:** 344–6.
6. Drehs MM, *et al.* Successful treatment of multiple superficial basal cell carcinomas with topical imiquimod: case report and review of the literature. *Dermatol Surg* 2002; **28:** 427–9.
7. Schulze HJ, *et al.* Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol* 2005; **152:** 939–47.
8. Bath-Hextall FJ, *et al.* Interventions for basal cell carcinoma of the skin. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
9. Mackenzie-Wood A, *et al.* Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; **44:** 462–70.
10. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155:** 653–6.
11. Lonsdale-Eccles AA, *et al.* Successful treatment of vulval melanoma in situ with topical 5% imiquimod cream. *Br J Dermatol* 2006; **155:** 215–17.
12. Spieth K, *et al.* Topical imiquimod: effectiveness in intraepithelial melanoma of oral mucosa. *Lancet Oncol* 2006; **7:** 1036–7.
13. Zeitouni NC, *et al.* Treatment of cutaneous metastatic melanoma with imiquimod 5% cream and the pulsed-dye laser. *Br J Dermatol* 2005; **152:** 376–7.
14. Utikal J, *et al.* Complete remission of multiple satellite and in-transit melanoma metastases after sequential treatment with isolated limb perfusion and topical imiquimod. *Br J Dermatol* 2006; **155:** 488–91.
15. Wieland U, *et al.* Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006; **142:** 1438–44.
16. van Seters M, *et al.* Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008; **358:** 1465–73.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aldara; Imimore; Miquimod; ***Austral.:*** Aldara; ***Belg.:*** Aldara; ***Braz.:*** Aldara; ***Canad.:*** Aldara; ***Chile:*** Aldara; Imimor; Labimiq; Tocasol; ***Cz.:*** Aldara; ***Denm.:*** Aldara; ***Fin.:*** Aldara; ***Fr.:*** Aldara; ***Ger.:*** Aldara; ***Gr.:*** Aldara; ***Hong Kong:*** Aldara; ***Hung.:*** Aldara; ***Irl.:*** Aldara; ***Israel:*** Aldara; ***Ital.:*** Aldara; ***Malaysia:*** Aldara; ***Mex.:*** Aldara; ***Neth.:*** Aldara; ***Norw.:*** Aldara; ***NZ:*** Aldara; ***Philipp.:*** Aldara; ***Pol.:*** Aldara; ***Port.:*** Aldara; ***S.Afr.:*** Aldara; ***Singapore:*** Aldara; ***Spain:*** Aldara; ***Swed.:*** Aldara; ***Switz.:*** Aldara; ***Thai.:*** Aldara; ***UK:*** Aldara; ***USA:*** Aldara.

Indinavir Sulfate *(USAN, pINNM)*

Indinavir, sulfate d'; Indinavir Sulphate *(BANM)*; Indinaviri sulfas; L-735524; MK-0639; MK-639; Sulfato de indinavir. (αR,γS,2S)-α-Benzyl-2-(*tert*-butylcarbamoyl)-γ-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1).

Индинавира Сульфат

$C_{36}H_{47}N_5O_4,H_2SO_4 = 711.9.$

CAS — 150378-17-9 (indinavir); 157810-81-6 (indinavir sulfate).

ATC — J05AE02.

ATC Vet — QJ05AE02.

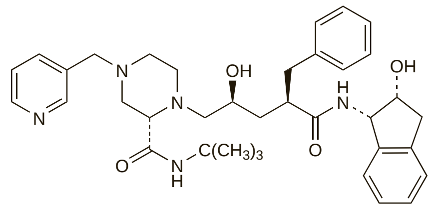

(indinavir)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Indinavir Sulphate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

USP 31 (Indinavir Sulfate). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from moisture.

Adverse Effects

The most commonly reported adverse effects associated with antiretroviral regimens containing indinavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea and vomiting), taste disturbances, headache, and dizziness. Nephrolithiasis, often with flank pain and occurring with or without haematuria, is the most frequently reported serious adverse effect. It appears to be dose-related and is more frequent in patients taking more than 2.4 g daily; it also occurs more often in children. Temporarily stopping treatment and giving fluids often resolve the symptoms, but interstitial nephritis and acute renal failure have been reported. Dry skin and skin rashes occur commonly and may occasionally be severe. Cases of Stevens-Johnson syndrome and erythema multiforme have also been reported. Hypersensitivity reactions, including vasculitis and sometimes anaphylaxis, have been associated with indinavir. Hepatitis, including cases resulting in hepatic failure and death has occurred. Cases of acute haemolytic anaemia have been reported again with some fatalities. Other commonly reported adverse effects are dry mouth, dysuria, fatigue, flatulence, hypoaesthesia, insomnia, paraesthesia, pruritus, and acid regurgitation. Neutrophil counts may be reduced and mean corpuscular volume increased. Abnormal laboratory test results associated with indinavir-containing regimens have included crystalluria, haematuria, proteinuria, raised liver enzymes, and asymptomatic hyperbilirubinaemia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including indinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including indinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

◊ Reviews.

1. Moyle GJ, Gazzard BG. A risk-benefit assessment of HIV protease inhibitors. *Drug Safety* 1999; **20:** 299–321.

Effects on carbohydrate and lipid metabolism. HIV-protease inhibitors have been associated with a lipodystrophy syndrome characterised by peripheral fat wasting, central adiposity and the so called 'buffalo hump', hyperlipidaemia, and insulin resistance.[1]

A survey of 113 HIV-infected patients receiving HIV-protease inhibitors found lipodystrophy in 83% (severe in 11%) and impaired glucose tolerance in 23% (including diabetes mellitus in 7%) after a mean of 21 months of therapy.[2]

A systematic review[3] of published material has concluded that use of HIV-protease inhibitors is associated with increased concentrations of total cholesterol, triglycerides, and low-density lipoprotein; that use is often associated with morphological signs of cardiovascular disease such as increased carotid intima thickness or atherosclerotic lesions; and that there is some evidence of an increased risk of myocardial infarction. Comparison of the effect of specific protease inhibitors showed that ritonavir was consistently associated with elevated lipids and that, although some studies showed that saquinavir was associated with elevated lipids, it was to a lesser degree than other drugs. Guidelines[4] have been published outlining the management, including drug therapy, of antiretroviral-induced lipid disorders in HIV-infected patients.

Impaired glucose tolerance has been linked to reduction in insulin sensitivity[5] and has responded to treatment with sulfonylureas or insulin.[6]

1. Carr A, *et al.* Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; **351:** 1881–3.
2. Carr A, *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353:** 2093–9.
3. Rhew DC, *et al.* Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. *Clin Infect Dis* 2003; **37:** 959–72.
4. Dubé MP, *et al.* Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; **37:** 613–27. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/378131 (accessed 28/08/08)
5. Walli R, *et al.* Impaired glucose tolerance and protease inhibitors. *Ann Intern Med* 1998; **129:** 837–8.
6. Dubé MP, *et al.* Protease inhibitor-associated hyperglycaemia. *Lancet* 1997; **350:** 713–14.

Effects on the cardiovascular system. For adverse effects of HIV-protease inhibitors on carbohydrate and lipid metabolism that increase the risk of coronary vascular disease, see above.

Effects on the kidneys. Nephrolithiasis has been reported in about 10% of patients receiving indinavir, and the incidence may be higher in patients with haemophilia or hepatitis C infection.[1] Both asymptomatic[2] and symptomatic[3,4] crystalluria have been reported in patients receiving indinavir, with symptomatic urinary-tract disease in 8%. Indinavir has been identified as the major constituent of both urinary crystals[2] and calculi.[5] In addition there have been reports of acute interstitial nephritis associated with indinavir[6] and deterioration of renal function associated with both indinavir[7] and ritonavir.[8,9] Renal atrophy was associated with long-term treatment with indinavir.[10,11]

1. Brodie SB, *et al.* Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. *AIDS* 1998; **12:** 2433–7.
2. Kopp JB, *et al.* Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997; **127:** 119–25.
3. Hachey DM, *et al.* Indinavir crystalluria in an HIV-positive man. *Ann Pharmacother* 2000; **34:** 403.
4. Famularo G, *et al.* Symptomatic crystalluria associated with indinavir. *Ann Pharmacother* 2000; **34:** 1414–18.
5. Daudon M, *et al.* Urinary stones in HIV-1-positive patients treated with indinavir. *Lancet* 1997; **349:** 1294–5.
6. Marroni M, *et al.* Acute interstitial nephritis secondary to the administration of indinavir. *Ann Pharmacother* 1998; **32:** 843–4.
7. Boubaker K, *et al.* Changes in renal function associated with indinavir. *AIDS* 1998; **12:** F249–F254.

8. Duong M, *et al.* Renal failure after treatment with ritonavir. *Lancet* 1996; **348:** 693–4.
9. Chugh S, *et al.* Ritonavir and renal failure. *N Engl J Med* 1997; **336:** 138.
10. Hanabusa H, *et al.* Renal atrophy associated with long-term treatment with indinavir. *N Engl J Med* 1999; **340:** 392–3.
11. Cattelan AM, *et al.* Severe hypertension and renal atrophy associated with indinavir. *Clin Infect Dis* 2000; **30:** 619–21.

Effects on the liver. The use of indinavir with other antiretroviral drugs has been associated with the development of severe hepatitis.[1,2]

Hepatic failure was attributed to ritonavir in a patient receiving combination therapy for AIDS.[3]

1. Bräu N, *et al.* Severe hepatitis in three AIDS patients treated with indinavir. *Lancet* 1997; **349:** 924–5.
2. Matsuda J, *et al.* Severe hepatitis in patients with AIDS and haemophilia B treated with indinavir. *Lancet* 1997; **350:** 364.
3. Picard O, *et al.* Hepatotoxicity associated with ritonavir. *Ann Intern Med* 1998; **129:** 670–1.

Effects on the menstrual cycle. Irregular, prolonged, or heavy menstruation[1] in 4 patients receiving ritonavir subsequently returned to normal in the 3 who were transferred to a different HIV-protease inhibitor.

1. Nielsen H. Hypermenorrhoea associated with ritonavir. *Lancet* 1999; **353:** 811–12.

Effects on mental state. Acute paranoid reactions occurred on two occasions in a patient receiving saquinavir.[1]

1. Finlayson JA, Laing RBS. Acute paranoid reaction to saquinavir. *Am J Health-Syst Pharm* 1998; **55:** 2016–17.

Effects on the pancreas. Pancreatitis was associated with use of ritonavir with saquinavir in 1 patient,[1] and with ritonavir (other drugs unspecified) in 2 others,[2] and was believed to be secondary to hyperlipidaemia (see Effects on Carbohydrate and Lipid Metabolism, above).

1. McBride M, *et al.* Lipid lowering therapy in patients with HIV infection. *Lancet* 1998; **352:** 1782–3.
2. Di Perri G, *et al.* HIV-protease inhibitors. *N Engl J Med* 1998; **339:** 773–4.

Effects on sexual function. Sexual dysfunction has been reported in patients given combination therapy with HIV-protease inhibitors and reverse transcriptase inhibitors.[1,2]

1. Martínez E, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 810–11.
2. Colebunders R, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 1802.

Effects on the skin. Skin rashes have been reported in about 20% of patients receiving indinavir and in 3 to 5% of patients receiving nelfinavir or saquinavir. Rash is described as a frequent adverse effect of ritonavir. In patients taking indinavir who reported rashes,[1] the rash commonly appeared within 2 weeks of starting treatment, was frequently accompanied by pruritus, and was usually self-limiting, commonly resolving within 4 weeks.

Paronychia and pyogenic granuloma of the great toes has been reported in patients receiving indinavir.[2]

1. Gajewski LK, *et al.* Characterization of rash with indinavir in a national patient cohort. *Ann Pharmacother* 1999; **33:** 17–21.
2. Bouscarat F, *et al.* Paronychia and pyogenic granuloma of the great toes in patients treated with indinavir. *N Engl J Med* 1998; **338:** 1776–7.

Precautions

Indinavir is primarily metabolised in the liver and therefore caution and possible dosage reduction are required in hepatic impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Although renal excretion is a relatively minor route of elimination, adequate hydration is recommended to reduce the risk of nephrolithiasis; monitoring is advised in the presence of renal impairment. Treatment may need to be temporarily interrupted or stopped completely in patients developing nephrolithiasis. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Mycobacterial infections. Patients with a previously unsuspected *Mycobacterium avium* complex infection experienced a severe febrile syndrome with inflammatory lymphadenitis after starting indinavir treatment.[1] The reaction resolved with appropriate antimycobacterial therapy.

1. Race EM, *et al.* Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998; **351:** 252–5.

Pregnancy. A retrospective survey[1] involving 89 women who received HIV-protease inhibitors during pregnancy indicated that these antivirals appeared generally safe.

1. Morris AB, *et al.* Multicenter review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Syndr* 2000; **25:** 306–11.

Interactions

Indinavir is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. It may compete for the same metabolic pathways with a wide range of drugs that are metabolised similarly, often resulting in mutually increased plasma concentrations. A drug that is a significant inducer of microsomal enzymes, particularly CYP3A4, may reduce plasma concentrations of indinavir. HIV-protease inhibitors may themselves induce metabolism and may reduce plasma concentrations of other drugs.

Indinavir is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These include antiarrhythmics (amiodarone and flecainide), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (alprazolam, midazolam, and triazolam), and statins (lovastatin and simvastatin). Rifampicin and St John's wort decrease the concentration of indinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. Use of indinavir with atazanavir is contra-indicated as both drugs have been associated with indirect hyperbilirubinaemia.

Other HIV-protease inhibitors may have similar interactions. The principal interactions that have been reported as a risk for one or more of the various HIV-protease inhibitors are listed below. For further information on drug interactions of HIV-protease inhibitors see Table 1, p.917.

◊ References to interactions associated with HIV-protease inhibitors.

1. Eagling VA, *et al.* Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol* 1997; **44:** 190–4.
2. von Moltke LL, *et al.* Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *J Clin Pharmacol* 1998; **38:** 106–11.
3. Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Safety* 1999; **20:** 147–69.

Amfetamines. For mention of interactions, including a fatal serotonergic reaction, with *methylenedioxymethamfetamine* (Ecstasy) in patients receiving ritonavir, see p.2159.

Analgesics. Ritonavir and possibly other HIV-protease inhibitors produce complex and potentially serious interactions with some opioids (see p.103). Interactions between ritonavir and *dextropropoxyphene* (p.41) or *pethidine* (p.114) are considered to be especially hazardous. Ritonavir might also prolong *fentanyl*-induced respiratory depression (see p.57). Amprenavir, nelfinavir, ritonavir, and ritonavir-boosted HIV-protease inhibitors may reduce plasma concentrations of *methadone* (see p.84). For the effect of some HIV-protease inhibitors on the pharmacokinetics of *buprenorphine*, see p.30.

Use of ritonavir with *piroxicam* can result in potentially toxic concentrations of piroxicam (see p.118).

Antiarrhythmics. Use of HIV-protease inhibitors with the antiarrhythmics *amiodarone, encainide, flecainide, propafenone*, or *quinidine* may result in potentially toxic plasma concentrations of these drugs with an increased risk of ventricular arrhythmias.

Antibacterials. Plasma concentrations of HIV-protease inhibitors may be reduced to subtherapeutic levels by *rifabutin* or *rifampicin*. In addition, plasma concentrations of rifabutin may be increased, with a consequent risk of uveitis. In general, HIV-protease inhibitors should not be used with rifampicin (p.327) and dosage modifications may be necessary if used with rifabutin; licensed product information for indinavir recommends increasing the dose of the antiretroviral to 1 g every 8 hours and halving the dose of rifabutin. Further information is given in Rifabutin under Interactions, p.324 and Uses, Tuberculosis and HIV Infection, p.325.

HIV-protease inhibitors may inhibit the metabolism of *clarithromycin* (p.249) and possibly other macrolides.

Antidepressants. HIV-protease inhibitors may inhibit the metabolism of *desipramine* and other tricyclic antidepressants (p.380). Interactions may also occur between HIV-protease inhibitors and SSRIs such as *fluoxetine* (p.396), and have also occurred with *bupropion* (p.384).

Plasma concentrations of HIV-protease inhibitors may be reduced by *St John's wort* as a result of induction of cytochrome P450; concomitant use should be avoided.[1]

1. Piscitelli SC, *et al.* Indinavir concentrations and St John's wort. *Lancet* 2000; **355:** 547–8. Correction. *ibid.* 2001; **357:** 1210.

Antiepileptics. Reduced plasma concentrations of HIV-protease inhibitors may be anticipated if the enzyme inducers *carbamazepine, phenobarbital*, or *phenytoin* are given concurrently. Nelfinavir has been reported to reduce the plasma concentration of phenytoin (p.499); a similar effect may occur with ritonavir. In addition, carbamazepine concentrations have been reported to be increased by ritonavir (p.475).

Antifungals. Plasma concentrations of HIV-protease inhibitors may be increased by azole antifungals. Licensed product information recommends that the dose of indinavir should be reduced to 600 mg every 8 hours when given with *itraconazole* 200 mg twice daily. A dose reduction is not considered necessary by the UK licensed product information when indinavir is given with *ketoconazole*, but the US product information recommends a reduction to indinavir 600 mg every 8 hours.

Conversely, plasma concentrations of ketoconazole are increased by ritonavir.

Antihistamines. HIV-protease inhibitors inhibit the metabolism of non-sedating antihistamines such as *astemizole* and *terfenadine* resulting in increased plasma concentrations of these drugs and an increased risk of serious ventricular arrhythmias. Such combinations should be avoided.

Antipsychotics. Ritonavir and possibly other HIV-protease inhibitors may increase plasma concentrations of *clozapine* (but see p.984), *pimozide* (p.1018), and *sertindole* (p.1028) resulting in increased toxicity. Concomitant use should be avoided. Plasma concentrations of *thioridazine* may also be increased when given with some HIV-protease inhibitors.

Antivirals. HIV-protease inhibitors can inhibit metabolism of other drugs from the same class and increases in adverse effects have resulted.

Plasma concentrations of atazanavir, indinavir,[1] and lopinavir-ritonavir may be reduced by *nevirapine*; the UK licensed product information for indinavir recommends a dose increase of indinavir to 1 g every 8 hours be considered.

Plasma concentrations of indinavir[2] and saquinavir may be increased by *delavirdine*; the UK licensed product information for indinavir recommends a dose reduction of indinavir to 400 to 600 mg every 8 hours in patients receiving delavirdine and the UK licensed information for saquinavir recommends that liver function should be monitored if saquinavir is given with delavirdine.

Plasma concentrations of amprenavir, atazanavir, indinavir, *lopinavir*, and saquinavir are decreased when given with *efavirenz*. The use of efavirenz with ritonavir is associated with an increased frequency of adverse effects, presumably due to competitive inhibition of metabolism, and liver enzymes should be monitored in patients receiving this combination. Plasma concentrations of nelfinavir are increased when given with efavirenz, but the combination is usually well tolerated at standard doses.

Although there is no direct interaction between HIV-protease inhibitors and *didanosine*, the buffer included in the didanosine formulation can impair their absorption; doses should be separated by at least 1 to 2 hours from didanosine doses, which should be given on an empty stomach.

For a report of reduced area under the plasma concentration-time curve for *zidovudine* in patients receiving ritonavir, see p.915.

1. Murphy RL, *et al.* Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. *J Infect Dis* 1999; **179:** 1116–23.
2. Ferry JJ, *et al.* Pharmacokinetic drug-drug interaction study of delavirdine and indinavir in healthy subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18:** 252–9.

Benzodiazepines. For the effect of HIV-protease inhibitors on benzodiazepines, see Diazepam, p.990.

Cardiac glycosides. For details of a possible interaction between ritonavir and *digoxin*, see p.1262.

Ciclosporin. Mutual increases in the area under the plasma concentration-time curves for saquinavir and ciclosporin were reported in a kidney transplant recipient.[1] The resultant adverse effects subsided when doses of both drugs were reduced by half. Similar interactions with other HIV-protease inhibitors are possible.

1. Brinkman K, *et al.* Pharmacokinetic interaction between saquinavir and cyclosporine. *Ann Intern Med* 1998; **129:** 914–15.

Corticosteroids. Corticosteroids, in particular *dexamethasone*, may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. For the effect of ritonavir on plasma concentrations of *fluticasone*, see p.1495

Ergot alkaloids. For reports of ergotism in patients receiving HIV-protease inhibitors and ergot alkaloids, see Ergotamine, p.621.

Gastrointestinal drugs. The antidiarrhoeal *loperamide* markedly reduced exposure to saquinavir in 12 healthy subjects given a single dose of both drugs.[1] Exposure was reduced by about 54%, a reduction of the same order of magnitude as seen with enzyme inducers such as rifampicin, although the mechanism in this case was thought likely to be impaired absorption of the antiviral. Prolonged use of loperamide might lead to substantial reductions in saquinavir plasma concentrations, and reduced clinical efficacy. Plasma concentrations of loperamide were also increased, and those of its metabolite desmethylloperamide correspondingly reduced, but this was thought unlikely to be of clinical significance.

Atazanavir and indinavir depend on acid pH in the stomach for adequate absorption, and acid-suppressive therapies such as *histamine H_2-antagonists* and *proton pump inhibitors* may significantly reduce their absorption; if acid-suppressive therapy is necessary, these HIV-protease inhibitors should be boosted with low-dose ritonavir to ensure adequate antiretroviral activity.[2]

For the effect of HIV-protease inhibitors on *cisapride*, see p.1721.

1. Mikus G, *et al.* Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. *Clin Pharmacokinet* 2004; **43:** 1015–24.
2. Fulco PP, *et al.* Acid suppressive therapy and the effects on protease inhibitors. *Ann Pharmacother* 2006; **40:** 1974–83.

Grapefruit. Exposure to saquinavir was increased by 50% when taken with grapefruit juice;[1] however, licensed product information does not recommend any adjustment of dosage of saquinavir.

1. Kupferschmidt HHT, *et al.* Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in men. *Br J Clin Pharmacol* 1998; **45:** 355–9.

Hormonal contraceptives. For the effect of HIV-protease inhibitors on hormonal contraceptives, see p.2068.

Interleukin-2. Plasma concentrations of indinavir were increased[1] during use with interleukin-2.

1. Piscitelli SC, *et al.* Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Pharmacotherapy* 1998; **18:** 1212–16.

Paclitaxel. For the effect of HIV-protease inhibitors on paclitaxel, see Interactions, Antivirals, p.759.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals including indinavir, see Stavudine, p.907.

Sildenafil. For the effect of HIV-protease inhibitors on sildenafil, including a report of fatal myocardial infarction after sildenafil in a patient receiving ritonavir and saquinavir, see p.2194.

Statins. HIV-protease inhibitors may inhibit the metabolism of statins metabolised by CYP3A4 isoenzymes resulting in an increased risk of myopathy. Although those statins less dependent on CYP3A4 for metabolism may be used in certain circumstances to manage HIV-protease inhibitor-induced lipid disorders, use with lovastatin or simvastatin should be avoided, and HIV-protease inhibitors should be given with caution in patients receiving atorvastatin or rosuvastatin.

Tacrolimus. HIV-protease inhibitors may inhibit the metabolism of tacrolimus (see Antivirals, p.1845).

Theophylline. For a potential effect of ritonavir on theophylline, see p.1144.

Warfarin. For the effect of HIV-protease inhibitors on warfarin, see p.1430.

Antiviral Action

Indinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 proteases with a tenfold greater selectivity for HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Indinavir is rapidly absorbed after oral doses producing peak plasma concentrations in 0.8 hours (range 0.5 to 1.1 hours). Bioavailability is about 65% after a single 800-mg dose. Absorption is reduced if given with a meal high in calories, fat, and protein but is less affected by a light meal (for the effect of pH see Gastrointestinal Drugs under Interactions, above). At doses up to 1 g, increases in plasma concentration are proportionately greater than increases in dose. Plasma protein binding is about 60%. Indinavir is reported to cross the blood-brain barrier. It undergoes oxidative metabolism by cytochrome P450 isoenzyme CYP3A4 and glucuronidation. At least seven metabolites (1 glucuronide and 6 oxidative metabolites) have been identified. The elimination half-life is 1.8 hours. Less than 20% of the absorbed dose is excreted in the urine, about half of this as unchanged drug. The remainder is excreted in the faeces.

◊ References.

1. Ståhle L, *et al.* Indinavir in cerebrospinal fluid of HIV-1-infected patients. *Lancet* 1997; **350:** 1823.
2. Bernard L, *et al.* Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. *Lancet* 1998; **352:** 1757–8.
3. Wintergerst U, *et al.* Use of saliva specimens for monitoring indinavir therapy in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000; **44:** 2572–4.
4. Haas DW, *et al.* Steady-state pharmacokinetics of indinavir in cerebrospinal fluid and plasma among adults with human immunodeficiency virus type 1 infection. *Clin Pharmacol Ther* 2000; **68:** 367–74.
5. Burger DM, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; **45:** 701–5.
6. Kappelhoff BS, *et al.* Population pharmacokinetics of indinavir alone and in combination with ritonavir in HIV-1-infected patients. *Br J Clin Pharmacol* 2005; **60:** 276–86.
7. Unadkat JD, *et al.* Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2007; **51:** 783–6.

Uses and Administration

Indinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when indinavir is used alone, and it is therefore used with other antiretrovirals.

Indinavir is given orally as the sulfate, but doses are expressed in terms of the base; 116 mg of indinavir sulfate is equivalent to about 100 mg of indinavir. It is given in a usual adult dose of 800 mg every 8 hours. For the *reduced* doses recommended in patients taking azole antifungals or the NNRTI delavirdine, and *increased* doses in those also taking rifabutin or nevirapine, see Antibacterials, Antifungals, and Antivirals, under Interactions, above. Indinavir should be given either 1 hour before or 2 hours after meals, or with a light, low-fat meal. Adequate hydration should be maintained. Treatment may have to be interrupted if acute episodes of nephrolithiasis occur.

For details of doses in children and adolescents, see below. For details of modified dosage to be used in patients with hepatic impairment, see below.

Administration in children. For the treatment of HIV infection in children 4 years of age and older indinavir is given orally with other antiretroviral drugs. A dose of 500 mg/m² every 8 hours is recommended; doses should not exceed the adult dose (see above).

Administration in hepatic impairment. A reduction in the oral dose of indinavir to 600 mg every 8 hours is recommended for patients with mild to moderate hepatic insufficiency due to cirrhosis.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Avural; Crixivan; Elvenavir; Forli; Indilea; Inhibisam; ***Austral.:*** Crixivan; ***Austria:*** Crixivan; ***Belg.:*** Crixivan; ***Braz.:*** Crixivan; Dinavir†; Indinax; ***Canad.:*** Crixivan; ***Chile:*** Crixivan; ***Cz.:*** Crixivan; ***Denm.:*** Crixivan; ***Fin.:*** Crixivan; ***Fr.:*** Crixivan; ***Ger.:*** Crixivan; ***Gr.:*** Crixivan; ***Hong Kong:*** Crixivan; ***Hung.:*** Crixivan; ***India:*** Indivan; ***Irl.:*** Crixivan; ***Israel:*** Crixivan; ***Ital.:*** Crixivan; ***Jpn:*** Crixivan; ***Malaysia:*** Crixivan; ***Mex.:*** Crixivan; Indilan; ***Neth.:*** Crixivan; ***Norw.:*** Crixivan; ***NZ:*** Crixivan; ***Philipp.:*** Crixivan; ***Pol.:*** Crixivan; ***Port.:*** Crixivan; ***Rus.:*** Crixivan (Криксиван); ***S.Afr.:*** Crixivan; ***Singapore:*** Crixivan; ***Spain:*** Crixivan; ***Swed.:*** Crixivan; ***Switz.:*** Crixivan; ***Thai.:*** Crixivan; ***Turk.:*** Crixivan; ***UK:*** Crixivan; ***USA:*** Crixivan; ***Venez.:*** Crixivan; Indivan.

Inosine Pranobex *(BAN)*

Inosine Dimepranol Acedoben *(pINNM)*; Inosin Pranobeks; Inosina Dimepranol Acedobén; Inosine Acédobène Dimépranol; Inosinum Dimepranolum Acedobenum; Inosinum pranobexum; Inosiplex; Isoprinosine; Methisoprinol; NP-113; NPT-10381. Inosine 2-hydroxypropyldimethylammonium 4-acetamidobenzoate (1:3).

Инозин Димепранол Ацедобен

$C_{10}H_{12}N_4O_5{:}C_{14}H_{22}N_2O_4$ (1:3) = 1115.2.

CAS — 36703-88-5.

ATC — J05AX05.

ATC Vet — QJ05AX05.

NOTE. Dimepranol Acedoben is *pINN* and *USAN*.

Adverse Effects and Precautions

Some patients have had transient nausea, vomiting, headaches, arthralgia, fatigue, vertigo, raised liver enzymes, pruritus, and skin rashes. Metabolism of the inosine content of inosine pranobex leads to increased serum and urine concentrations of uric acid; caution is therefore recommended in treating patients with renal impairment, gout, or hyperuricaemia.

Antiviral Action

Inosine pranobex appears to owe its activity in viral infections more to its capacity to modify or stimulate cell-mediated immune processes than to a direct action on the virus.

Pharmacokinetics

Inosine pranobex is reported to be rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after an oral dose. It is also rapidly metabolised with a plasma half-life of 50 minutes, the inosine portion of the complex yielding uric acid; the other components undergo oxidation and glucuronidation. The metabolites are excreted in the urine.

◊ References.

1. Nielsen P, Beckett AH. The metabolism and excretion in man of NN-dimethylamino-isopropanol and p-acetamido-benzoic acid after administration of isoprinosine. *J Pharm Pharmacol* 1981; **33:** 549–50.

Uses and Administration

Inosine pranobex is a complex of inosine (p.2325) with dimepranol acedoben ((±)-1-(dimethylamino)-2-propanol *p*-acetamidobenzoate). It has been used in the treatment of various viral infections (see below), including herpes simplex, genital warts, and subacute sclerosing panencephalitis, although other treatments or measures are preferred. The oral dose in mucocutaneous herpes simplex is 1 g four times daily for 7 to 14 days. An oral dose of 1 g three times daily is given for 14 to 28 days as an adjunct to standard topical treatment for genital warts. In subacute sclerosing panencephalitis, the oral dose is 50 to 100 mg/kg daily in divided doses given every 4 hours.

◊ Reviews.

1. Campoli-Richards DM, *et al.* Inosine pranobex: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986; **32:** 383–424.

Alopecia. Oral inosine pranobex (50 mg/kg daily in 5 divided doses for 12 weeks) has been investigated[1] with some apparent benefit in the treatment of recalcitrant alopecia areata (p.1577).

1. Georgala S, *et al.* Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. *Acta Derm Venereol* 2006; **86:** 422–4.

Subacute sclerosing panencephalitis. Inosine pranobex has been tried[1,2] in the treatment of subacute sclerosing panencephalitis, a complication of measles (p.860), but the results of clinical studies have been equivocal. Some success has been reported when inosine pranobex has been given with interferons and other antivirals. However, a randomised study involving 121 patients, of whom 67 completed analysis, was unable to show any difference between an oral regimen of inosine pranobex 100 mg/kg daily in 3 divided doses (up to a maximum of 3 g daily) for 6 months, and the same dose combined with intraventricular interferon alfa, although the outcomes, which were considered satisfactory in about 35% of cases, were better than the 10% remission rate in historical controls, implying some benefit with either treatment.[3]

1. Haddad FS, Risk WS. Isoprinosine treatment in 18 patients with subacute sclerosing panencephalitis: a controlled study. *Ann Neurol* 1980; **7:** 185–8.
2. Jones CE, *et al.* Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *Lancet* 1982; **i:** 1034–7.
3. Gascon GG. International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol* 2003; **18:** 819–27. Correction. *ibid.* 2004; **19:** 342.

Warts. Although of no apparent benefit in the treatment of palmar/plantar warts,[1] oral inosine pranobex has been shown to be of value in the treatment of refractory genital warts (p.1584) in the cervix,[2] as well as producing some apparent epithelial morphological improvement in women with subclinical human papillomavirus infection of the vulva.[3]

1. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127:** 262–5.
2. Georgala S, *et al.* Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. *BJOG* 2006; **113:** 1088–91.
3. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS* 1996; **7:** 276–80.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Isoprinosin; ***Belg.:*** Isoprinosine; ***Canad.:*** Imunovir; ***Chile:*** Isoprinosine; ***Cz.:*** Isoprinosine; ***Fr.:*** Isoprinosine; ***Ger.:*** delimmun; Isoprinosine; ***Gr.:*** Isoprinosine; ***Hong Kong:*** Qualiprinol; ***Hung.:*** Isoprinosine; ***Indon.:*** Isprinol; ***Irl.:*** Imunovir; Isoprinosine; ***Ital.:*** Avirin†; Farviran†; Virustop†; Viruxan; ***Mex.:*** Isoprinosine; Pranosine; ***NZ:*** Imunovir; ***Philipp.:*** Immunosin; Isoprinosine; ***Pol.:*** Groprinosin; ***Port.:*** Isovir; ***Rus.:*** Isoprinosine (Изопринозин); ***Singapore:*** Imin; ***UK:*** Imunovir.

Interferon Alfa *(BAN, rINN)*

IFN-α; Interferón-α; Interferon-α; Interferón alfa; Interféron alfa; Interferon alpha; Interferoni alfa; Interferonialfa; Interferonum Alfa; Ro-22-8181 (interferon alfa-2a); Sch-30500 (interferon alfa-2b).

Интерферон Альфа

CAS — 74899-72-2 (interferon alfa); 76543-88-9 (interferon alfa-2a); 99210-65-8 (interferon alfa-2b); 118390-30-0 (interferon alfacon-1); 198153-51-4 (peginterferon alfa-2a); 215647-85-1 (peginterferon alfa-2b).

ATC — L03AB01 (natural); L03AB04 (2a); L03AB05 (2b); L03AB06 (n1); L03AB09 (alfacon-1); L03AB10 (peginterferon alfa-2b); L03AB11 (peginterferon alfa-2a).

ATC Vet — QL03AB01 (natural); QL03AB04 (2a); QL03AB05 (2b); QL03AB06 (n1); QL03AB09 (alfacon-1); QL03AB10 (peginterferon alfa-2b); QL03AB11 (peginterferon alfa-2a).

NOTE. Interferon alfa was previously known as leucocyte interferon or lymphoblastoid interferon.

Interferon alfa-2a, alfa-2b, alfa-n1, and alfa-n3 are *USAN*.

Interferon alfacon-1 (*BAN*, *USAN*, *rINN*) is a recombinant non-naturally occurring alfa interferon. Peginterferon alfa-2a (*BAN*, *USAN*, *rINN*) and peginterferon alfa-2b (*BAN*, *rINN*) are interferons pegylated by conjugation with macrogols.

Pharmacopoeias. *Chin.* includes monographs for recombinant human alfa-2a and alfa-2b. *Eur.* (see p.vii) includes Interferon Alfa-2 Concentrated Solution.

Ph. Eur. 6.2 (Interferon Alfa-2 Concentrated Solution; Interferoni Alfa-2 Solutio Concentrata). It is produced by a method based on recombinant DNA technology using bacteria as host cells. It is a clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of −20° or below. Protect from light.

Nomenclature. Interferon alfa may be derived from leucocytes or lymphoblasts, or produced by recombinant DNA technology. Sub-species of the human alfa gene may produce interferon alfa with protein variants or a mixture of proteins. The protein variants may be designated by a number (as in interferon alfa-2) which may be further qualified by a letter to indicate the amino-acid sequences at positions 23 and 34:

- interferon alfa-2a has lysine at 23 and histidine at 34
- interferon alfa-2b has arginine at 23 and histidine at 34
- interferon alfa-2c has arginine at both positions

In the case of a mixture of proteins an alphanumeric designation is given (as in interferon alfa-n1). Interferon alfacon-1 varies from interferon alfa-2 in 20 of 166 amino acids.

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology; (lns) indicates production from cultured lymphoblasts from the Namalwa cell line that have been stimulated by a Sendai virus; (bls) indicates production from leucocytes from human blood that have been stimulated by a Sendai virus.

References.

1. Finter NB. The naming of cats—and alpha-interferons. *Lancet* 1996; **348:** 348–9.

Adverse Effects and Treatment

The adverse effects of interferon are varied and the natural products appear to be less toxic than the pure synthetic compounds. The frequency and severity of adverse effects of peginterferon alfa appear to be similar to those for interferon alfa although dose-related neutropenia and thrombocytopenia and injection site reactions are more common. Clinical experience suggests that interferons beta and gamma have similar adverse effects.

Adverse effects are generally mild and reversible at doses less than 5 million international units/day. The majority of patients on interferon treatment have 'flu-like' symptoms such as loss of appetite, fever, chills, fatigue, headache, malaise, myalgia, arthralgia, and sweating. These symptoms tend to be dose-related, are most likely to occur at the start of treatment, and mostly respond to paracetamol (but for a possible interaction with paracetamol, see Interactions, below).

Other common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).

Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).

Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, predominantly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported. The reaction is reported frequently with interferon beta, which can produce severe reactions including local necrosis.

Adverse effects of peginterferon alfa (alone or with ribavirin) reported in patients co-infected with hepatitis C virus and HIV, are similar to those reported in patients infected only with hepatitis C virus. Although haematological adverse effects such as neutropenia, thrombocytopenia, and anaemia occurred more often in co-infected patients, most patients could be managed by dose adjustments. Other adverse effects reported in co-infected patients given peginterferon and ribavirin include apathy, raised blood amylase, chapped lips, chromaturia, raised gamma-glutamyltransferase and hepatitis, influenza, lactic acidosis (including hyperlactacidaemia), lipodystrophy, mood alteration, pain in the pharynx, larynx, back, and limbs, pneumonia, and tinnitus. Peginterferon treatment was associated with decreases in CD4+ cell counts within the first 4 weeks that were reversible when the dose was reduced or stopped; no negative impact was noted on the control of HIV viraemia during treatment or follow-up.

Nasal dosage may produce mucosal irritation and damage.

◊ Reviews.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Pardo M, *et al.* Risks and benefits of interferon-α in the treatment of hepatitis. *Drug Safety* 1995; **13:** 304–16.
3. Kirkwood JM, *et al.* Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; **20:** 3703–18.
4. Sleijfer S, *et al.* Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27:** 423–31.

Effects on the blood. Interferon alfa has myelosuppressive effects and the commonest haematological adverse effects associated with its use are dose-related leucopenia, neutropenia, and thrombocytopenia; anaemia is rarely reported. Other reported effects associated with interferon alfa include immune haemolytic anaemia[1] and immune thrombocytopenia.[2,3] Haemorrhage occurred in a patient with immune thrombocytopenic purpura treated with interferon alfa,[4] and it was thought prudent to use interferons with caution, if at all, in this condition.[3,4] Reports of clotting disorders are rare; bleeding associated with induction of factor VIII inhibitor has been seen in a patient given interferon alfa to enhance hydroxycarbamide therapy for chronic myeloid leukaemia.[5] Thrombosis associated with interferon alfa has also been reported.[6]

Restoration of bone-marrow function after marrow transplantation was delayed in 3 patients given a human interferon alfa preparation.[7] Laboratory results showed an inhibition of granulocyte colony growth by human leucocyte interferon alfa. It was considered that interferon alfa was contra-indicated in patients with severe bone-marrow insufficiency and should not be given to marrow transplant patients before the graft was fully functional. However, in another 5 patients recombinant interferon alfa did not affect bone marrow transplants, although 3 patients experienced fever and chills, 4 had more than a 60% reduction in absolute peripheral granulocyte counts, and 4 had a 37 to 80% reduction in absolute platelet counts.[8] Lymphocytes were increased in all patients; blood counts returned to normal when interferon therapy stopped. Interferon alfa produced a decline in CD4+ T-lymphocytes resulting in opportunistic infections in 2 HIV-positive patients treated for chronic hepatitis C.[9]

1. Akard LP, *et al.* Alpha-interferon and immune hemolytic anemia. *Ann Intern Med* 1986; **105:** 306.
2. McLaughlin P, *et al.* Immune thrombocytopenia following α-interferon therapy in patients with cancer. *JAMA* 1985; **254:** 1353–4.
3. Färkkilä M, Iivanainen M. Thrombocytopenia and interferon. *BMJ* 1988; **296:** 642.
4. Matthey F, *et al.* Bleeding in immune thrombocytopenic purpura after alpha-interferon. *Lancet* 1990; **335:** 471–2.
5. English KE, *et al.* Acquired factor VIII inhibitor in a patient with chronic myelogenous leukaemia receiving interferon-alfa therapy. *Ann Pharmacother* 2000; **34:** 737–9.
6. Durand JM, *et al.* Thrombosis and recombinant interferon-α. *Am J Med* 1993; **95:** 115.
7. Nissen C, *et al.* Toxicity of human leucocyte interferon preparations in human bone-marrow cultures. *Lancet* 1977; **i:** 203–4.
8. Winston DJ, *et al.* Safety and tolerance of recombinant leukocyte A interferon in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1983; **23:** 846–51.
9. Pesce A, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; **341:** 1597.

Effects on the cardiovascular system. Hypotension or hypertension, tachycardia, and distal cyanosis are the most commonly reported cardiovascular adverse effects. Other reported cardiac complications include cardiac arrhythmias, atrioventricular block, symptoms of ischaemic heart disease, including myocardial infarction and sudden death, congestive heart failure, acute dyspnoea, pericardial effusion,[1,2] and cardiomyopathy.[1,3,4] Cardiac toxicity was not related to the daily or cumulative total dose, or duration of treatment and is usually reversible on stopping interferon treatment.[1]

Peripheral vascular complications such as Raynaud's syndrome[5-9] have been associated with interferon alfa therapy and other types of interferon.

1. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; **99:** 557–61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
3. Angulo MP, *et al.* Reversible cardiomyopathy secondary to α-interferon in an infant. *Pediatr Cardiol* 1999; **20:** 293–4.
4. Kuwata A, *et al.* A case of reversible dilated cardiomyopathy after α-interferon therapy in a patient with renal cell carcinoma. *Am J Med Sci* 2002; **324:** 331–4.
5. Bachmeyer C, *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; **135:** 481–3.
6. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.
7. Kruit WH, *et al.* Interferon-α induced Raynaud's syndrome. *Ann Oncol* 2000; **11:** 1501–2.
8. Schapira D, *et al.* Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum* 2002; **32:** 157–62.
9. Iorio R, *et al.* Severe Raynaud's phenomenon with chronic hepatitis C disease treated with interferon. *Pediatr Infect Dis J* 2003; **22:** 195–7.

Effects on the endocrine system. Both hypothyroidism[1,2] and hyperthyroidism[2,3] have been associated with interferon alfa therapy. Thyroid disorders are usually minor and regress on stopping the interferon (with or without other specific treatment). However a case of long-lasting ophthalmopathy as a result of interferon alfa-induced Graves' disease has been reported in a patient being treated for hepatitis C.[4]

The development of type 1 diabetes has also been associated with interferon alfa therapy,[5-8] and exacerbation of existing type 2 diabetes has been reported.[9,10] Reversible hypopituitarism has been reported in patients receiving interferon alfa.[11,12] Recombinant interferon gamma was reported not to affect thyroid function.[13]

1. Fentiman IS, *et al.* Primary hypothyroidism associated with interferon therapy of breast cancer. *Lancet* 1985; **i:** 1166.
2. Burman P, *et al.* Autoimmune thyroid disease in interferon-treated patients. *Lancet* 1985; **ii:** 100–1.
3. Schultz M, *et al.* Induction of hyperthyroidism by interferon-α-2b. *Lancet* 1989; **i:** 1452.
4. Binaghi M, *et al.* Ophtalmopathie de Basedow sévère liée à l'interféron alpha. *J Fr Ophtalmol* 2002; **25:** 412–15.
5. Fabris P, *et al.* Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; **340:** 548.
6. Guerci A-P, *et al.* Onset of insulin-dependent diabetes mellitus after interferon-alfa therapy for hairy cell leukaemia. *Lancet* 1994; **343:** 1167–8.
7. Gori A, *et al.* Reversible diabetes in patient with AIDS-related Kaposi's sarcoma treated with interferon α-2a. *Lancet* 1995; **345:** 1438–9.
8. Murakami M, *et al.* Diabetes mellitus and interferon-α therapy. *Ann Intern Med* 1995; **123:** 318.
9. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.
10. Lopes EPA, *et al.* Exacerbation of type 2 diabetes mellitus during interferon-alfa therapy for chronic hepatitis B. *Lancet* 1994; **343:** 244. Correction. *ibid.*: 680.
11. Sakane N, *et al.* Reversible hypopituitarism after interferon-alfa therapy. *Lancet* 1995; **345:** 1305.

12. Concha LB, *et al.* Interferon-induced hypopituitarism. *Am J Med* 2003; **114:** 161–3.
13. Bhakri H, *et al.* Recombinant gamma interferon and autoimmune thyroid disease. *Lancet* 1985; **ii:** 457.

Effects on the eyes. The most typical ocular adverse effect associated with interferon alfa treatment is retinopathy, which is characterised by cotton wool spots and superficial retinal haemorrhages. Reports of interferon-associated retinopathy have been reviewed.[1,2] Reduced vision or complete visual loss is rare or limited and is usually reversible after stopping treatment. In a study of 43 patients with chronic hepatitis given interferon alfa, retinopathy developed in 11 of 37 non-diabetic patients and in 3 of 6 diabetic patients after about 8 to 10 weeks of therapy.[3] None of the patients had had retinopathy before treatment; the condition was reversible in the non-diabetic patients on stopping therapy. Visual acuity remained unchanged. Subconjunctival haemorrhage occurred in a further 3 of the non-diabetic patients. Severe irreversible loss of vision has been reported in a non-diabetic patient given interferon alfa.[4] A prospective study[5] of 156 patients treated with interferon alfa or peginterferon alfa (with or without ribavirin) reported signs of retinopathy in 24% of the patients; 29 patients developed cotton-wool spots, 7 developed retinal haemorrhage, and 2 patients developed both lesions during treatment; none of the patients had retinopathy before starting treatment. The lesions remained asymptomatic and resolved in all the patients. Patient age above 45 years, hypertension, and the use of pegylated alpha-interferon were identified as risk factors for retinopathy. Neurovisual impairment was present in 31 patients before interferon treatment and in 74 patients during treatment. Another study[6] of 19 patients reported that 8 patients developed asymptomatic retinopathy while on treatment with interferon alfa (with or without ribavirin); patients who had previously failed to respond to interferon monotherapy seemed more likely to develop retinopathy when given combined therapy than patients who had responded and then relapsed. The changes were transient and sometimes disappeared while the patients were still on treatment. Retinopathy has been reported in patients being treated with interferon beta for the management of multiple sclerosis.[7,8] Symptoms also resolved after stopping treatment.

Pain in one eyeball leading to exophthalmos and complete visual loss has been reported in a patient given interferon alfa;[9] despite withdrawal of interferon and instigation of antibacterial and corticosteroid treatment, the eyeball subsequently ruptured necessitating ophthalmectomy. Other severe ocular effects reported during interferon alfa treatment include a disorder resembling Vogt-Koyanagi-Harada disease, central retinal vein occlusion, central retinal artery occlusion, and bilateral ischaemic optic neuropathy with severe visual impairment.[10]

1. Hayasaka S, *et al.* Interferon associated retinopathy. *Br J Ophthalmol* 1998; **82:** 323–5.
2. Savant V, Gillow T. Interferon-associated retinopathy. *Eye* 2003; **17:** 534–6.
3. Hayasaka S, *et al.* Retinopathy and subconjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995; **79:** 150–2.
4. Lohmann CP, *et al.* Severe loss of vision during adjuvant interferon alfa-2b treatment for malignant melanoma. *Lancet* 1999; **353:** 1326.
5. d'Alteroche L, *et al.* Ophthalmologic side effects during alpha-interferon therapy for viral hepatitis. *J Hepatol* 2006; **44:** 56–61.
6. Jain K, *et al.* Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001; **85:** 1171–3.
7. Saito H, *et al.* Retinopathy in a multiple sclerosis patient undergoing interferon-therapy. *Multiple Sclerosis* 2007; **13:** 939–40.
8. Longmuir R, *et al.* Cotton wool spots associated with interferon beta-1 alpha therapy. *Semin Ophthalmol* 2007; **22:** 49–53.
9. Yamada H, *et al.* Acute onset of ocular complications with interferon. *Lancet* 1994; **343:** 914.
10. Sène D, *et al.* Intraocular complications of IFN-alpha and ribavirin therapy in patients with chronic viral hepatitis C. *World J Gastroenterol* 2007; **13:** 3137–40.

Effects on the gastrointestinal tract. Mild and transient gastrointestinal adverse effects such as nausea, diarrhoea, vomiting, and anorexia occur in about 30 to 40% of patients being treated with interferon alfa. There have been reports[1-4] of the onset of coeliac disease during treatment of hepatitis C with interferon or peginterferon alfa, in some cases used with ribavirin. Symptoms generally resolved after interferon was stopped and a gluten-free diet started. A case[5] of eosinophilic enteritis has been reported in a patient, with no history of digestive disorders, after 12 weeks of recombinant interferon alfa-2b treatment; symptoms resolved after stopping interferon and on treatment with prednisolone. New[6,7] or exacerbated[8] cases of ulcerative colitis have been reported in patients on interferon or peginterferon alfa treatment (with or without ribavirin). Treatment with interferon was usually stopped[7,8] and symptoms tended to resolve or improve with appropriate therapy (such as mesalazine and/or corticosteroids).[6-8] Cases of ischaemic colitis associated with interferon or peginterferon alpha have been reported rarely.[9]

1. Bardella MT, *et al.* Celiac disease during interferon treatment. *Ann Intern Med* 1999; **131:** 157–8.
2. Cammarota G, *et al.* Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000; **356:** 1494–5.
3. Bourlière M, *et al.* Onset of coeliac disease and interferon treatment. *Lancet* 2001; **357:** 803–4.
4. Martins EV, Gaburri AK. Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arq Gastroenterol* 2004; **41:** 132–3.
5. Kakumitsu S, *et al.* Eosinophilic enteritis observed during alpha-interferon therapy for chronic hepatitis C. *J Gastroenterol* 2000; **35:** 548–51.
6. Mavrogiannis C, *et al.* Ulcerative colitis associated with interferon treatment for chronic hepatitis C. *J Hepatol* 2001; **34:** 964–5.
7. Sprenger R, *et al.* Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. *Gut* 2005; **54:** 438–9.
8. Watanabe T, *et al.* A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. *Gut* 2006; **55:** 1682–3.
9. Leung Y, *et al.* Ischemic colitis during pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Can J Gastroenterol* 2006; **20:** 661–3.

Effects on the hair. Excessive temporary loss of telogen hair causing moderate and reversible alopecia occurs in about 7 to 30% of patients on interferon or peginterferon alfa treatment. Alopecia areata[1-3] and alopecia universalis[4,5] have occasionally been reported; complete regrowth of the hair usually occurs on completing interferon treatment.

A report of marked greying of the hair in a patient beginning after 5 months of treatment with interferon alfa for metastatic malignant melanoma; on completion of interferon therapy the hair regrowth returned to its normal colour.[6] Marked straightening of scalp and body hair has been reported in 2 patients after combined treatment with interferon alfa-2b or peginterferon alfa-2b and ribavirin for chronic hepatitis C.[7] In the first patient, there was also diffuse thinning of scalp hair, change in hair texture, increased greying of the hair, and eyebrow lengthening; the original curly hair began to regrow 6 months after stopping treatment, but the hair abnormalities recurred on rechallenge despite switching from interferon alfa-2b to peginterferon alfa-2b. In the second patient, treatment with peginterferon alfa-2b and ribavirin was associated with straightening of scalp hair, eyebrow hair, and pubic hair.[7] Lengthening and thickening of eyelashes has also been reported with interferon alfa therapy.[8,9] A case of eyelid and eyebrow trichomegaly has also been reported[10] in a patient treated with peginterferon alfa and ribavirin.

1. Radny P, *et al.* Alopecia areata induced by adjuvant treatment with alpha-interferon in malignant melanoma? *Dermatology* 2004; **209:** 249–50.
2. Agesta N, *et al.* Alopecia areata during interferon alpha-2b/ribavirin therapy. *Dermatology* 2002; **205:** 300–1.
3. Kernland KH, Hunziker T. Alopecia areata induced by interferon alpha? *Dermatology* 1999; **198:** 418–19.
4. Taliani G, *et al.* Reversible alopecia universalis during treatment with PEG-interferon and ribavirin for chronic hepatitis C. *J Chemother* 2005; **17:** 212–14.
5. Kartal ED, *et al.* Reversible alopecia universalis secondary to PEG-interferon alpha-2b and ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2007; **19:** 817–20.
6. Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. *Br J Dermatol* 1996; **135:** 337–8.
7. Bessis D, *et al.* Straight hair associated with interferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; **147:** 392–3.
8. Hernández-Núñez A, *et al.* Trichomegaly following treatment with interferon alpha-2b. *Lancet* 2002; **359:** 1107.
9. Dikici B, *et al.* Interferon alpha and hypertrichosis of eyelashes. *Pediatr Infect Dis J* 2002; **21:** 448–9.
10. Howaizi M. Pegylated interferon-induced eyelid and eyebrow trichomegaly during chronic hepatitis C. *J Gastroenterol Hepatol* 2005; **20:** 1945–6.

Effects on hearing. Sensorineural hearing loss, mostly unilateral, has been rarely reported in patients treated with interferon or peginterferon. A prospective study[1] reported sensorineural hearing loss in 18 of 49 patients and tinnitus in 14 of 49 patients given interferons. The authors reported that effects were more common in those given interferon beta than in those given interferon alfa, and resolved in all patients on stopping therapy. A report[2] of 6 patients who experienced sudden hearing loss while on treatment with peginterferon alfa plus ribavirin found that hearing loss did not fully resolve after stopping treatment; but neither did it worsen in those who continued their treatment. A case report[3] of a patient who had acute sensorineural hearing loss 2 months after starting treatment with peginterferon alfa and ribavirin found that when treatment was re-started 4 months after stopping, the patient did not experience further hearing loss and hearing on the left-side was unaffected. In another case report[4] a patient who developed hearing loss 22 weeks after starting treatment with peginterferon alfa, continued with treatment and symptoms did not worsen. Hearing loss resolved within 2 weeks of stopping treatment.

1. Kanda Y, *et al.* Sudden hearing loss associated with interferon. *Lancet* 1994; **343:** 1134–5.
2. Formann E, *et al.* Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am J Gastroenterol* 2004; **99:** 873–7.
3. Wong VK, *et al.* Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J Gastroenterol* 2005; **11:** 5392–3.
4. Elloumi H, *et al.* Sudden hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment. *World J Gastroenterol* 2007; **13:** 5411–12.

Effects on the kidneys. Renal adverse effects associated with interferon alfa are usually limited to mild, asymptomatic proteinuria and moderate increases in serum creatinine in 15 to 20% of patients. Dose-related asymptomatic proteinuria has been reported with interferon gamma treatment.[1] Acute renal failure and nephrotic syndrome associated with interferon alfa treatment is rare and has mostly been reported in patients with underlying renal disease, or malignancies,[2-5] and in those receiving high doses.[6] Cases have also been reported in patients receiving interferon or peginterferon alfa treatment for chronic hepatitis C.[7-9] Nephrotic syndrome has also occurred after use of interferon beta.[10-12] Renal dysfunction usually resolves after stopping treatment, but incomplete resolution and fatalities have been reported.[5,8]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Averbuch SD, *et al.* Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. *N Engl J Med* 1984; **310:** 32–5.
3. Selby P, *et al.* Nephrotic syndrome during treatment with interferon. *BMJ* 1985; **290:** 1180.
4. Herrman J, Gabriel F. Membranoproliferative glomerulonephritis in a patient with hairy-cell leukemia treated with alpha-II interferon. *N Engl J Med* 1987; **316:** 112–13.
5. Colovic M, *et al.* Interferon alpha sensitisation induced fatal renal insufficiency in a patient with chronic myeloid leukaemia: case report and review of literature. *J Clin Pathol* 2006; **59:** 879–81.
6. Kramer P, *et al.* Recombinant leucocyte interferon A induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. *Lancet* 1984; **i:** 989–90.
7. Endo M, *et al.* Appearance of nephrotic syndrome following interferon-α therapy in a patient with hepatitis B virus and hepatitis C virus coinfection. *Am J Nephrol* 1998; **18:** 439–43.
8. Fisher ME, *et al.* A woman with chronic hepatitis C infection and nephrotic syndrome who developed multiple renal lesions after interferon alfa therapy. *Am J Kidney Dis* 2004; **44:** 567–73.
9. Couto CA, *et al.* Life-threatening thrombocytopenia and nephrotic syndrome due to focal segmental glomerulosclerosis associated with pegylated interferon alpha-2b and ribavirin treatment for hepatitis C. *Liver Int* 2006; **26:** 1294–7.
10. Nakao K, *et al.* Minimal change nephrotic syndrome developing during postoperative interferon-beta therapy for malignant melanoma. *Nephron* 2002; **90:** 498–500.
11. Auty A, Saleh A. Nephrotic syndrome in a multiple sclerosis patient treated with interferon beta 1a. *Can J Neurol Sci* 2005; **32:** 366–8.
12. Kumasaka R, *et al.* Nephrotic syndrome associated with interferon-beta-1b therapy for multiple sclerosis. *Clin Exp Nephrol* 2006; **10:** 222–5.

Effects on lipids. Cases[1-3] of reversible hypertriglyceridaemia (with or without elevation of total cholesterol level) have been reported in association with interferon alfa treatment. Hypertriglyceridaemia more often occurs with longer treatment durations and does not appear to be related to pre-existing cardiovascular disorders or baseline dyslipidaemia; frequency and severity are not dose dependent. Lifestyle modifications and drug treatment with a fibrate or statin are usually needed to reduce triglyceride levels. A small study[4] reported that taking omega-3 fatty acid supplements (3 g daily for 6 months) reduced serum triglyceride levels in patients on interferon alfa for the management of chronic hepatitis C.

1. Graessle D, *et al.* Alpha-interferon and reversible hypertriglyceridemia. *Ann Intern Med* 1993; **118:** 316–17.
2. Junghans V, Rünger TM. Hypertriglyceridaemia following adjuvant interferon-α treatment in two patients with malignant melanoma. *Br J Dermatol* 1999; **140:** 183–4.
3. Wong SF, *et al.* Management of hypertriglyceridemia in patients receiving interferon for malignant melanoma. *Ann Pharmacother* 2004; **38:** 1655–9.
4. Malaguarnera M, *et al.* Fish oil treatment of interferon-alpha-induced dyslipidaemia: study in patients with chronic hepatitis C. *BioDrugs* 1999; **11:** 285–91.

Effects on the liver. Mild hepatotoxicity with an asymptomatic and reversible rise in serum aminotransferases has been reported in about 25 to 30% of patients receiving interferon alfa; severe hepatotoxicity is rare[1] but cases of fatal liver failure have been reported,[2-5] sometimes due to severe exacerbation of chronic hepatitis B and/or C infection.[4,5] An analysis of the toxicity of adjuvant high-dose interferon alfa in 40 patients being treated for melanoma reported hepatotoxicity in 39 patients, with 26 patients experiencing grade 3 to 4 hepatotoxicity.[6] Cases[7,8] of peginterferon alfa-induced auto-immune hepatitis have been reported in patients receiving treatment for chronic hepatitis C.

Raised serum-alanine aminotransferase values have been reported in about 37% of patients given interferon beta therapy for the treatment of multiple sclerosis, with grade 3 to 4 hepatotoxicity being reported in about 1.4% of patients.[9]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Durand JM, *et al.* Liver failure due to recombinant alpha interferon. *Lancet* 1991; **338:** 1268–9.
3. Wandl UB, *et al.* Liver failure due to recombinant alpha interferon for chronic myelogenous leukaemia. *Lancet* 1992; **339:** 123–4.
4. Marcellin P, *et al.* Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon. *Lancet* 1991; **338:** 828.
5. Janssen HLA, *et al.* Fatal hepatic decompensation associated with interferon alfa. *BMJ* 1993; **306:** 107–8.
6. Jonasch E, *et al.* Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer J* 2000; **6:** 139–45.
7. Kogure T, *et al.* Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment. *World J Gastroenterol* 2007; **13:** 4394–7.
8. Kontorinis N, *et al.* Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. *Liver Transpl* 2006; **12:** 827–30.
9. Byrnes V, *et al.* Drug induced liver injury secondary to interferon-beta (IFN-beta) in multiple sclerosis. *Ann Hepatol* 2006; **5:** 56–9.

Effects on the nervous system and mental state. Neurological adverse effects have been reported in association with interferon alfa treatment for chronic hepatitis C virus or for malignant diseases;[1-5] notably, an acute confusional state may develop rapidly after starting high-dose interferon alfa treatment and a depressive syndrome may develop more slowly over weeks to months of treatment. Less commonly a manic condition, usually characterised by extreme irritability and agitation but also occasionally by euphoria, may occur.

Acute interferon alfa-induced confusional states are typically characterised by disorientation, lethargy, difficulties with speaking and writing, parkinsonism, psychomotor retardation, psychotic symptoms (such as hallucinations), and somnolence.

Depression[5-9] occurs in about 16 to 58% of patients receiving interferon alfa. Patients considered to be at risk for developing depression are those with pre-existing symptoms of mood and anxiety disorders, those with a history of major depression, and those receiving higher doses of interferon alfa or on long treatment regimens. SSRIs have been used successfully to both treat patients with interferon-associated depression, thus allowing therapy to be continued,[10,11] and as pretreatment to prevent its occurrence.[12]

Should manic symptoms[13] occur, interferon alfa and antidepressant treatment should be stopped and a mood stabiliser given. Interferon alfa-induced mood disorders may also consist of an overlap between depressive and manic symptoms. A prospective study[14] of 93 patients treated with peginterferon alfa plus ribavirin for chronic hepatitis C reported that mood disorders occurred in 30 patients; 3 cases of mania, 15 cases of irritable hypomania, and 12 cases of mixed depressive states. The distinction between the 2 states is important in terms of management as depression-specific symptoms respond well to SSRIs, whereas antidepressants may worsen manic or hypomanic states.

Seizures[15-17] attributed to interferon alfa have been described.

Cases of neurological toxicity have been reported in patients receiving interferon beta,[1,18] although interferon beta is considered to be slightly less neurotoxic.

Chronic hepatitis C virus infection may be complicated by the development of systemic vasculitis caused by mixed cryoglobulinemia or of a non-cryoglobulinemic vasculitis resembling polyarteritis nodosa. Successful treatment of the hepatitis infection with interferon alfa usually results in the improvement of vasculitic symptoms, including neuropathy. However, vasculitis may also be precipitated or exacerbated by treatment with interferon (including peginterferon alfa)[19-21] resulting in development of vasculitic neuropathy; cases of apparently non-vasculitic peripheral neuropathy have also been reported.[20-22] Others[23] have reported no association between peginterferon alfa and peripheral neuropathy. In most cases symptoms improved on treatment with corticosteroids or spontaneously, but fatal exacerbations of vasculitis have occurred despite stopping the interferon treatment and giving immunosuppressants.[21]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Dieperink E, *et al.* Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *Am J Psychiatry* 2000; **157:** 867–76.
3. Malek-Ahmadi P. Mood disorders associated with interferon treatment: theoretical and practical considerations. *Ann Pharmacother* 2001; **35:** 489–95.
4. Van Gool AR, *et al.* Neuropsychiatric side effects of interferon-alfa therapy. *Pharm World Sci* 2003; **25:** 11–20.
5. Raison CL, *et al.* Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* 2005; **19:** 105–23.
6. Janssen HLA, *et al.* Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994; **21:** 241–3.
7. Renault PF, *et al.* Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987; **147:** 1577–80.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Depression with interferon. *Aust Adverse Drug React Bull* 1999; **18:** 6.
9. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alfa therapy by the patient's initial affective state. *N Engl J Med* 1999; **340:** 1370.
10. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon-α. *Am J Gastroenterol* 1993; **88:** 760–1.
11. Schramm TM, *et al.* Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust* 2000; **173:** 359–61.
12. Musselman DL, *et al.* Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; **344:** 961–6.
13. Kingsley D. Interferon-alpha induced 'tertiary mania'. *Hosp Med* 1999; **60:** 381–2.
14. Constant A, *et al.* Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005; **66:** 1050–7.
15. Janssen HLA, *et al.* Seizures associated with low-dose α-interferon. *Lancet* 1990; **336:** 1580.
16. Brouwers PJ, *et al.* Photosensitive seizures associated with interferon alpha-2a. *Ann Pharmacother* 1999; **33:** 113–14.
17. Ameen M, Russell-Jones R. Seizures associated with interferon-α treatment of cutaneous malignancies. *Br J Dermatol* 1999; **141:** 386–7.
18. Goeb JL, *et al.* Psychiatric side effects of interferon-beta in multiple sclerosis. *Eur Psychiatry* 2006; **21:** 186–93.
19. Batisse D, *et al.* Sustained exacerbation of cryoglobulinaemia-related vasculitis following treatment of hepatitis C with peginterferon alfa. *Eur J Gastroenterol Hepatol* 2004; **16:** 701–3.
20. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. *Muscle Nerve* 2002; **25:** 909–13.
21. Beuthien W, *et al.* Vasculitic complications of interferon-alpha treatment for chronic hepatitis C virus infection: case report and review of the literature. *Clin Rheumatol* 2005; **24:** 507–15.
22. Gastineau DA, *et al.* Severe neuropathy associated with low-dose recombinant interferon-alpha. *Am J Med* 1989; **87:** 116.
23. Briani C, *et al.* Peripheral neurotoxicity of pegylated interferon alpha: a prospective study in patients with HCV. *Neurology* 2006; **67:** 781–5.

Effects on the oral mucosa. Painful oral ulcers, necessitating withdrawal of interferon alfa therapy, have occurred in a patient treated for chronic hepatitis.[1] Interferon alfa treatment has been reported to exacerbate pre-existing lichen planus associated with chronic hepatitis C.[2,3] New cases of oral lichen planus have been reported in patients receiving interferon alfa treatment for malignant diseases[4] and chronic hepatitis.[5]

1. Qaseem T, *et al.* A case report of painful oral ulcerations associated with the use of alpha interferon in a patient with chronic hepatitis due to non-A non-B non-C virus. *Mil Med* 1993; **158:** 126–7.
2. Areias J, *et al.* Lichen planus and chronic hepatitis C: exacerbation of the lichen under interferon-alpha-2a therapy. *Eur J Gastroenterol Hepatol* 1996; **8:** 825–8.
3. Nagao Y, *et al.* Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C. *Int J Mol Med* 2005; **15:** 237–41.
4. Kütting B, *et al.* Oropharyngeal lichen planus associated with interferon-α treatment for mycosis fungoides: a rare side-effect in the therapy of cutaneous lymphomas. *Br J Dermatol* 1997; **137:** 836–7.
5. Guijarro Guijarro B, *et al.* Aparición de un liquen plano erosivo durante el tratamiento con interferón alfa-2a por una hepatitis C crónica. *Med Oral* 2001; **6:** 358–63.

Effects on the respiratory system. Pulmonary adverse effects have occasionally been reported in association with interferon or peginterferon alfa treatment. A literature review[1] found that the most commonly reported adverse effect was interstitial pneumonitis, followed by a sarcoid-like reaction with non-caseating granuloma formation. Other, less commonly reported events were asthma exacerbation, pleural effusion, bronchiolitis obliterans with organizing pneumonia, and a case of fatal acute respiratory distress-like syndrome.

1. Midturi J, *et al.* Spectrum of pulmonary toxicity associated with the use of interferon therapy for hepatitis C: case report and review of the literature. *Clin Infect Dis* 2004; **39:** 1724–9.

Effects on skeletal muscle. Myalgia is one of the 'flu-like' symptoms frequently associated with interferons. Rhabdomyolysis[1-3] has occurred in patients being treated with interferon alfa and proved fatal when associated with multiple organ failure in a patient receiving adjuvant high-dose interferon alfa for multiple myeloma.[1] Rhabdomyolysis has also been reported in a patient receiving interferon beta for the treatment of multiple sclerosis.[4]

1. Reinhold U, *et al.* Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high-dose interferon alfa in malignant melanoma. *Lancet* 1997; **349:** 540–1.
2. Gabrielli M, *et al.* Acute reversible rhabdomyolysis during interferon alpha2b therapy for hepatitis C. *Am J Gastroenterol* 2003; **98:** 940.
3. Ozdag F, *et al.* Acute rhabdomyolysis during the treatment of scleromyxedema with interferon alfa. *J Dermatolog Treat* 2001; **12:** 167–9.
4. Lünemann JD, *et al.* Rhabdomyolysis during interferon-beta 1a treatment. *J Neurol Neurosurg Psychiatry* 2002; **72:** 274. Correction. *ibid.*; **73;** 354.

Effects on the skin. Dermatological adverse effects such as dryness, erythema, rash, or urticaria, have been reported in about 5 to 12% of patients given interferon alfa; severe events occur rarely.[1] Exacerbation or development of psoriasis was reported in patients given recombinant interferon alfa[2-4] and peginterferon alfa.[5] However, no such effect was seen in 7 patients given interferon gamma.[6] Both vitiligo and psoriasis developed in a 10-year-old girl with chronic hepatitis B infection given interferon alfa; the skin conditions did not improve on stopping the interferon treatment.[7] A case[8] of vitiligo occurring during the third month of treatment for chronic hepatitis C with peginterferon alfa and ribavirin has been reported; the condition persisted after treatment with peginterferon was completed. Exacerbation of lichen planus has also been reported[9] during interferon alfa treatment (see also Effects on the Oral Mucosa, above). Cases of cutaneous sarcoidosis have been reported in patients with chronic hepatitis C being treated with interferon or pegylated interferon alfa plus ribavirin; skin lesions are usually benign and treatment with interferon alfa may sometimes be continued with resolution of the skin lesions occurring spontaneously or within a few months of completing treatment.[10,11] Cutaneous vascular lesions with punctate telangiectasias were noted in 18 of 44 patients treated with interferon alfa-2a; lesions did not appear at the injection site.[12] Severe necrotising cutaneous lesions were reported at injection sites in a patient given recombinant interferon beta-1b; the lesions healed when interferon alfa-n3 was substituted.[13] However, cutaneous necrosis has also been associated with interferon alfa[14,15] and peginterferon alfa.[16] Five cases[17] of a self-resolving cutaneous lesion at the injection site of interferon, mimicking lupus erythematosus, have been reported; 3 of them involved interferon alfa therapy for malignant melanoma and the other 2 patients were being given interferon beta for multiple sclerosis. Fatal paraneoplastic pemphigus developed in a patient given interferon alfa-2a.[18] Hyperpigmentation of the skin and tongue has been described[19] in 2 dark-skinned patients during treatment with interferon alfa and ribavirin.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet* 1986; **i:** 1466–8.
3. Funk J, *et al.* Psoriasis induced by interferon-α. *Br J Dermatol* 1991; **125:** 463–5.
4. Taylor C, *et al.* Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C. *Postgrad Med J* 2000; **76:** 365–6.
5. Ketikoglou I, *et al.* Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005; **15:** 107–9.
6. Schulze H-J, Mahrle G. Gamma interferon and psoriasis. *Lancet* 1986; **ii:** 926–7.
7. Seçkin D, *et al.* Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. *Pediatr Dermatol* 2004; **21:** 577–9.
8. Tomasiewicz K, *et al.* Vitiligo associated with pegylated interferon and ribavirin treatment of patients with chronic hepatitis C: a case report. *Adv Therapy* 2006; **23:** 139–42.
9. Protzer U, *et al.* Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; **104:** 903–5.
10. Eberlein-König B, *et al.* Cutaneous sarcoid foreign body granulomas developing in sites of previous skin injury after systemic interferon-alpha treatment for chronic hepatitis C. *Br J Dermatol* 1999; **140:** 370–2.
11. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. *Arch Dermatol* 2005; **141:** 865–8.
12. Dreno B, *et al.* Alpha-interferon therapy and cutaneous vascular lesions. *Ann Intern Med* 1989; **111:** 95–6.
13. Sheremata WA, *et al.* Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995; **332:** 1584.
14. Shinohara K. More on interferon-induced cutaneous necrosis. *N Engl J Med* 1995; **333:** 1222.
15. Sasseville D, *et al.* Interferon-induced cutaneous necrosis. *J Cutan Med Surg* 1999; **3:** 320–3.
16. Bessis D, *et al.* Necrotizing cutaneous lesions complicating treatment with pegylated-interferon alfa in an HIV-infected patient. *Eur J Dermatol* 2002; **12:** 99–102.
17. Arrue I, *et al.* Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; **34** (suppl 1): 18–21.
18. Kirsner RS, *et al.* Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. *Br J Dermatol* 1995; **132:** 474–8.
19. Willems M, *et al.* Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149:** 390–4.

Shock. Fatal non-cardiogenic shock occurred after the third dose of interferon alfa-2b in a patient with malignant melanoma.[1] There were similarities to a fatal reaction reported in another patient with malignant melanoma (see under Effects on Skeletal Muscle, above).

1. Carson JJ, *et al.* Fatality and interferon α for malignant melanoma. *Lancet* 1998; **352:** 1443–4.

Precautions

Interferons should be used with caution or avoided altogether in patients with depression or psychiatric disorders, epilepsy or other CNS diseases, severe renal or hepatic impairment, chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver, auto-immune hepatitis, cardiac disorders, myelosuppression, poorly controlled thyroid dysfunction, pulmonary disease, diabetes mellitus, auto-immune diseases, coagulation disorders, or a history of these conditions.

All patients receiving interferons should be closely monitored for any signs or symptoms of psychiatric disorders; if psychiatric symptoms continue or worsen, or suicidal ideation is identified, then interferon therapy should be stopped.

Interferon treatment is not advised for patients whose hypoglycaemia, hyperglycaemia and/or diabetes mellitus is not effectively controlled; patients who develop these conditions during treatment and cannot be controlled with medication should stop interferon treatment. Standard blood and biochemical laboratory tests (including thyroid function) should be done before starting treatment with interferon and then periodically during therapy. Interferon should be used with caution in patients also receiving other potentially myelosuppressive agents.

Assessment of cardiac function is advised before treatment is started in patients with pre-existing cardiac abnormalities and if there is any deterioration of cardiovascular status interferon should be suspended or stopped.

Hepatic and renal function should be monitored during treatment with interferons. Interferon treatment should be stopped in patients who develop evidence of liver decompensation during treatment. Treatment should also be stopped in those patients who despite the dose of interferon being reduced still have progressive and clinically significant increases in serum-alanine aminotransferase.

Patients receiving interferons who have visual disturbances should undergo eye examination. A baseline ocular examination is recommended before treatment, and periodic eye examinations should be performed throughout treatment in patients predisposed to retinopathy, such as those with diabetes mellitus or hypertension; treatment should be stopped in patients who develop new or worsening ophthalmologic disorders.

Patients with psoriasis or sarcoidosis have been reported to experience exacerbations during interferon alfa therapy.

Patients should receive adequate fluids to maintain hydration during treatment with interferon alfa since hypotension related to fluid depletion has been seen in some patients.

Interferons may affect the ability to drive or operate machinery.

Antibodies may develop to exogenous interferon that reduce its activity.

Asthma. For a report of severe exacerbation of asthma in patients receiving interferon alfa, see Effects on the Respiratory System, above.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of interferon alfa by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. It has been suggested that interferons are too large in molecular weight to transfer into breast milk in clinically relevant amounts.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 12/06/08)
2. Kumar AR, *et al.* Transfer of interferon alfa into human breast milk. *J Hum Lact* 2000; **16:** 226–8.

Psychiatric disorders. For comment on the risk of mood disorders in patients with a history of such disorders, see Effects on the Nervous System and Mental State, above.

Interactions

Interactions involving interferons have not been fully evaluated, but it is known that they can inhibit hepatic oxidative metabolism via cytochrome P450 enzymes; the clinical relevance of this interaction is unclear and thus caution should be exercised during use with drugs metabolised in this way. Studies with peginterferon alfa showed increased activity of the cytochrome P450 isoenzymes CYP2C8/9 and CYP2D6; caution is advised when giving peginterferon alfa with drugs that are metabolised by these isoenzymes, such as warfarin, phenytoin, and flecainide. Interferon and peginterferon alfa have been shown to inhibit the metabolism of theophylline which is metabolised via the cytochrome P450 isoenzyme CYP1A2. Drugs likely to exacerbate the haematological effects of interferons, such as ribavirin and zidovudine, should also be used with caution. Interferons may also increase the neurotoxic and cardiotoxic effects of other drugs.

ACE inhibitors. For a report of possible synergistic haematological toxicity in patients receiving interferon alfa and ACE inhibitors, see p.1196.

Anticoagulants. For reference to potentiation of *acenocoumarol* or *warfarin* necessitating dosage reduction in patients also receiving interferon alfa, see p.1430.

Antineoplastics. For reduction in the area under the plasma concentration-time curve for *melphalan* in patients receiving interferon alfa, see p.742.

Antivirals. For a report of synergistic bone-marrow toxicity with interferon alfa and *zidovudine*, see p.915.

Paracetamol. Three patients had increases in liver enzyme values when given paracetamol 1 g two or three times daily on the same three days each week as interferon alfa; vinblastine was also given every third week.[1] Paracetamol has also been found to enhance the antiviral effect of interferon alfa in healthy subjects.[2]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.
2. Hendrix CW, *et al.* Modulation of α-interferon's antiviral and clinical effects by aspirin, acetaminophen, and prednisone in healthy volunteers. *Antiviral Res* 1995; **28:** 121–31.

Thalidomide. For reports of toxicity associated with interferons and thalidomide, see p.2398.

Theophylline. For reference to reduced clearance of theophylline in patients receiving interferon alfa, see p.1144.

Antiviral Action

Interferons are naturally occurring proteins produced by eukaryotic cells in response to viral infection and other biological inducers that confer protection on uninfected cells of the same species. They are cytokines that affect many cell functions and have, in addition to their antiviral activity, antiproliferative and immunoregulatory properties. Three major classes have been identified: alfa, beta and gamma. Interferon alfa and beta are classified as Type I interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities; interferon gamma in particular is a potent macrophage-stimulating factor.

Interferons exert their biological effect by binding to specific receptors on the surface of human cells. After binding, a cascade of intracellular events, including the induction of certain enzymes, occurs. This process is thought to be responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Pegylated interferons have similar, but possibly slightly weaker, actions to the native forms.

Studies have shown interferons to have benefit in infections with hepatitis B virus, hepatitis C virus, herpes simplex viruses, varicella-zoster virus, CMV, rhinoviruses, and papillomaviruses.

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. More than 80% of a subcutaneous or intramuscular dose of interferon alfa is absorbed. After intramuscular injection, interferon alfa produced by recombinant techniques and that from cultured leucocytes produce similar plasma concentrations although there is a large interindividual variation. Plasma concentrations are dose-related; and peak concentrations are usually reached within 4 to 8 hours returning to baseline by 16 to 24 hours. After intravenous doses, serum interferon levels decline at a slightly faster rate than after subcutaneous or intramuscular use and are undetectable 4 hours after infusion. After systemic use low levels of interferon are detected in respiratory secretions, CSF, eye, and brain. The elimination half-life of interferon alfa is about 2 to 7 hours after subcutaneous or intramuscular injections and 2 hours after intravenous infusion. Interferon alfa undergoes renal catabolism and negligible amounts of interferons are excreted in the urine; biliary excretion and liver metabolism are minor pathways of elimination.

The attachment of interferon to large inert macrogol (polyethylene glycol; PEG) molecules, termed pegylation, substantially reduces the rate of absorption and excretion of interferon and increases the plasma concentration. After a subcutaneous dose of peginterferon alfa-2b the maximum serum concentration is attained in about 15 to 44 hours and high concentrations are sustained for 48 to 72 hours; the mean elimination half-life is approximately 40 hours. The maximum serum concentration of peginterferon alfa-2a is attained about 72 to 96 hours after subcutaneous dosing and the mean terminal half-life is approximately 160 hours. The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that of unmodified interferon alfa-2a.

◊ Reviews.

1. Zeuzem S, *et al.* Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; **23** (suppl 1): 23–8.
2. Pedder SC. Pegylation of interferon alfa: structural and pharmacokinetic properties. *Semin Liver Dis* 2003; **23** (suppl 1): 19–22.
3. Caliceti P. Pharmacokinetics of pegylated interferons: what is misleading? *Dig Liver Dis* 2004; **36** (suppl 3): S334–9.

Uses and Administration

The interferons are cytokines that have a range of activities. In addition to their action against viruses they are active against malignant neoplasms and have an immunomodulating effect. Several alfa interferons are available: interferon alfa-2a (rbe), interferon alfa-2b (rbe), alfa-n3 (bls), alfacon-1 (rbe), and the pegylated interferons peginterferon alfa-2a (rbe) and peginterferon alfa-2b (rbe).

Alfa interferons are used in chronic hepatitis B (*alfa-2a and its pegylated form and alfa-2b*) and chronic hepatitis C (*alfa-2a and its pegylated form, alfa-2b and its pegylated form, and alfacon-1*); in several malignant neoplasms including AIDS-related Kaposi's sarcoma (*alfa-2a and alfa-2b*), hairy-cell leukaemia (*alfa-2a and alfa-2b*), chronic myeloid leukaemia (*alfa-2a and alfa-2b*), follicular lymphoma (*alfa-2a and alfa-2b*), cutaneous T-cell lymphoma (*alfa-2a*), carcinoid tumours (*alfa-2b*), melanoma (*alfa-2a and alfa-2b*), multiple myeloma (*alfa-2b*), and renal cell carcinoma (*alfa-2a*); and in condylomata acuminata (*alfa-2b and alfa-n3*).

ADMINISTRATION AND DOSAGE. Dosage regimens for alfa interferons are as follows:

- **Chronic active hepatitis B.** *Interferon alfa-2a* is given in a dose of 2.5 to 5 million units/m^2 three times weekly by subcutaneous injection for 4 to 6 months. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously for 48 weeks. *Interferon alfa-2b* is given in a dose of 5 to 10 million units three times weekly for 4 to 6 months, or 5 million units daily for 16 weeks, by subcutaneous or intramuscular injection.
- **Chronic hepatitis C.** *Interferon alfa-2a* is given in a dose of 3 to 4.5 million units three times weekly by subcutaneous injection for 6 months when it is used with ribavirin. In patients unable to tolerate ribavirin, interferon alfa-2a monotherapy is given either in an initial dose of 3 to 6 million units three times weekly for 6 months followed by 3 million units three times weekly for an additional 6 months, or in a dose of 3 million units three times weekly for 12 months, by subcutaneous injection. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously, with ribavirin or as monotherapy, for 24 to 48 weeks (depending on genotype). *Interferon alfa-2b* is given in a dose of 3 million units three times weekly for 6 to 12 months (depending on genotype) with ribavirin or, when given as monotherapy, for 6 to 18 months, or for up to 24 months (depending on genotype), by subcutaneous or intramuscular injection. *Peginterferon alfa-2b* is given subcutaneously in a dose of 1.5 micrograms/kg once weekly for 24 to 48 weeks with ribavirin, or in a dose of 0.5 or 1 microgram/kg once weekly for 24 to 48 weeks when given as monotherapy. *Interferon alfacon-1* is given in a dose of 9 micrograms three times weekly by subcutaneous injection for 24 weeks followed by 15 micrograms three times weekly for up to 48 weeks if necessary.
- **AIDS-related Kaposi's sarcoma.** *Interferon alfa-2a* is usually given in an escalating dose of 3 million units daily for 3 days, 9 million units daily for 3 days, 18 million units daily for 3 days, and 36 million units daily, if tolerated, on days 10 to 84, by subcutaneous injection; thereafter the maximum tolerated dose (up to 36 million units) may be given three times weekly. *Interferon alfa-2b* is given in a dose of 30 million units/m^2 three times weekly, by subcutaneous or intramuscular injection.
- **Hairy-cell leukaemia.** *Interferon alfa-2a* is given in an initial subcutaneous dose of 3 million units daily for 16 to 24 weeks, then the same dose three times weekly, by subcutaneous injection. Treatment has continued for up to 24 months. *Interferon alfa-2b* is given in a dose of 2 million units/m^2 three times weekly by subcutaneous or intramuscular injection for up to 6 months or more.

- **Chronic myeloid leukaemia.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, 6 million units daily for 3 days, and 9 million units daily thereafter. Patients showing a response after 12 weeks should continue treatment until a complete haematological response is achieved or for a maximum of 18 months; those who achieve a complete haematological response should continue on 9 million units daily (or a minimum of 9 million units three times weekly) in order to achieve a cytogenetic response. *Interferon alfa-2b* is given in a dose of 4 to 5 million units/m^2 daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 5 million units/m^2 daily).
- **Follicular lymphoma.** *Interferon alfa-2a* is given as an adjunct to chemotherapy in a dose of 6 million units/m^2 daily by subcutaneous injection on days 22 to 26 of each 28-day chemotherapy cycle. *Interferon alfa-2b* is given as an adjunct to chemotherapy in a dose of 5 million units three times weekly by subcutaneous injection for 18 months.
- **Cutaneous T-cell lymphoma.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, then 9 million units daily for 3 days, and then 18 million units daily to complete 12 weeks of treatment. The maximum tolerated dose (up to 18 million units) is then given three times weekly for a minimum of 12 months in responding patients.
- **Carcinoid tumours.** *Interferon alfa-2b* is given in a dose of 3 to 9 million units (usually 5 million units) three times weekly by subcutaneous injection. In advanced disease, 5 million units may be given daily.
- **Melanoma.** *Interferon alfa-2a* is given in a dose of 3 million units three times weekly by subcutaneous injection for 18 months. Treatment should start no later than 6 weeks after surgery. *Interferon alfa-2b* is given in an initial dose of 20 million units/m^2 daily on 5 days each week for 4 weeks by intravenous infusion over 20 minutes, and then for maintenance 10 million units/m^2 three times weekly by subcutaneous injection for 48 weeks.
- **Multiple myeloma.** *Interferon alfa-2b* is given as maintenance treatment following chemotherapy induction at a dose of 3 million units/m^2 three times weekly by subcutaneous injection.
- **Renal cell carcinoma.** *Interferon alfa-2a* is given as an adjunct to cytotoxic chemotherapy in an escalating dose of 3 million units three times weekly for one week, then 9 million units three times weekly for one week, then 18 million units three times weekly thereafter for 3 to 12 months, by subcutaneous injection.
- **Condylomata acuminata.** *Interferon alfa-2b* is given in a dose of 1 million units injected into each lesion three times weekly for 3 weeks, and repeated after 12 to 16 weeks if necessary. No more than 5 lesions should be treated in each treatment course. *Interferon alfa-n3* is given in a dose of 0.25 million units per lesion twice weekly for up to 8 weeks, to a maximum of 2.5 million units in each session.

See below for further details of these as well as some other uses of alfa interferons.

◊ General reviews of interferons.

1. Volz MA, Kirkpatrick CH. Interferons 1992: how much of the promise has been realised? *Drugs* 1992; **43:** 285–94.
2. Dorr RT. Interferon-α malignant and viral diseases: a review. *Drugs* 1993; **45:** 177–211.
3. Haria M, Benfield P. Interferon-α-2a: a review of its pharmacological properties and therapeutic use in the management of viral hepatitis. *Drugs* 1995; **50:** 873–96.
4. Ruszczak Z, Schwartz RA. Interferons in dermatology: biology, pharmacology, and clinical applications. *Adv Dermatol* 1997; **13:** 235–88.
5. Edwards L. The interferons. *Dermatol Clin* 2001; **19:** 139–46, ix.
6. Moschos S, *et al.* Interferons in the treatment of solid tumors. *Cancer Treat Res* 2005; **126:** 207–41.
7. Pestka S. The interferons: 50 years after their discovery, there is much more to learn. *J Biol Chem* 2007; **282:** 20047–51.

Age-related macular degeneration. In age-related macular degeneration (senile macular degeneration), a common cause of visual impairment in the elderly, there is a gradual and progressive deterioration of central vision usually affecting both eyes (p.785). Although some encouraging preliminary results[1-4] have been obtained with interferon alfa, controlled data showed no benefit after treatment for one year.[5]

1. Fine SL, *et al.* Age-related macular degeneration. *N Engl J Med* 2000 **342:** 483–92.
2. Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ* 2000 **321:** 741–4.
3. Comer GM, *et al.* Current and future treatment options for nonexudative and exudative age-related macular degeneration. *Drugs Aging* 2004 **21:** 967–92.
4. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 2005 **45:** 115–32.
5. Pharmacological Therapy for Macular Degeneration Study Group. Interferon alfa-2a in ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized placebo-controlled clinical trial. *Arch Ophthalmol* 1997; **115:** 865–72.

Angiomatous disease. Encouraging responses were reported in 4 of 5 children treated with interferon alfa-2a for various angiomatous diseases.[1] Regression of haemangioma size by more than 50% was achieved in 11 of 18 infants and children given interferon alfa-2a for 1 to 5 months,[2] and in 11 of 19 children treated for at least 4 months.[3] Interferon alfa-2b has also been found to cause regression of haemangioma in 27 of 38 children treated for at least 6 months.[4] In addition, there have been reports of the successful use of interferon alfa-2a to treat infantile giant cell angioblastoma[5] and pelvic metastases of adult haemangioendothelioma of the liver.[6]

The use of interferons as anti-angiogenic agents has been reviewed.[7]

1. White CW, *et al.* Treatment of childhood angiomatous diseases with recombinant interferon alfa-2a. *J Pediatr* 1991; **118:** 59–66.
2. Deb G, *et al.* Treatment of hemangiomas of infants and babies with interferon alfa-2a: preliminary results. *Int J Pediatr Hematol/Oncol* 1996; **3:** 109–13.
3. Greinwald JH, *et al.* An update on the treatment of hemangiomas in children with interferon alfa-2a. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 21–7.
4. Garmendía G, *et al.* Regression of infancy hemangiomas with recombinant IFN-α 2b. *J Interferon Cytokine Res* 2001; **21:** 31–8.
5. Marler JJ, *et al.* Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. *Pediatrics* 2002; **109:** e37. Also available at: http://pediatrics.aappublications.org/cgi/content/full/109/2/e37 (accessed 12/06/08)
6. Kayler LK, *et al.* Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation* 2002; **74:** 128–30.
7. Lindner DJ. Interferons as antiangiogenic agents. *Curr Oncol Rep* 2002; **4:** 510–14.

Behçet's syndrome. Behçet's syndrome (p.1499) is a systemic inflammatory disorder characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems. Treatment is essentially symptomatic and empirical. A review of the literature[1] identified 338 patients who had been given interferon alfa (264 patients had received interferon alfa-2a and 74 interferon alfa-2b). Mucocutaneous symptoms improved in 86% of the patients; articular manifestations were present in 90 patients and 95% of them showed a partial or complete response to interferon alfa treatment. Ocular manifestations were present in 182 patients and 94% of them showed a partial or complete response to treatment. Higher doses were reported to be more effective than low-dose regimens. A review[2] on the management of Behçet's syndrome reported that treatment with interferon-alfa during an inflammatory attack improved the duration of and pain associated with oral aphthous ulcers; beneficial effects were also reported in patients with ocular manifestations. Randomised, controlled studies had shown that interferon alfa prevented recurrent attacks and it was considered to be effective in suppressing more severe systemic features, as well as mucocutaneous ones. Open studies with interferon alfa indicated that it might be of benefit in patients with disease resistant to conventional immunosuppressive treatments.

1. Kötter I, *et al.* The use of interferon alpha in Behçet disease: review of the literature. *Semin Arthritis Rheum* 2004; **33:** 320–35.
2. Gul A. Standard and novel therapeutic approaches to Behçet's disease. *Drugs* 2007; **67:** 2013–22.

Blood disorders. Interferon alfa may be used in the management of the myeloproliferative disorders such as *primary (essential) thrombocythaemia*[1-3] (p.654), *polycythaemia vera*,[1-4] (p.654) and *agnogenic myeloid metaplasia*.[2] Benefit has also been reported with interferon alfa in patients with HIV-associated thrombocytopenia,[5] although interferons have been reported to induce immune thrombocytopenia, and there has been a report of bleeding in a patient with idiopathic thrombocytopenic purpura (see Effects on the Blood under Adverse Effects, above).

In addition to case reports of interferon alfa producing improvements in patients with idiopathic *hypereosinophilic syndrome*[6-8] who had not responded to corticosteroids or hydroxycarbamide, studies have also shown beneficial responses to interferon alfa used alone[9] or with corticosteroids or hydroxycarbamide.[10,11]

See also under Malignant Neoplasms, below.

Paradoxically, interferon alfa has also been used with some success in patients with *thrombocytopenia* associated with hepatitis C.[12-14]

1. Elliott MA, Tefferi A. Interferon-alpha therapy in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 1997; **23:** 463–72.
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4. Lengfelder E, *et al.*. Interferon alpha in the treatment of polycythemia vera. *Ann Hematol* 2000; **79:** 103–9.
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12. Uygun A, *et al.* Interferon treatment for thrombocytopenia associated with chronic HCV infection. *Int J Clin Pract* 2000; **54:** 683–4.
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14. Benci A, *et al.* Thrombocytopenia in patients with HCV-positive chronic hepatitis: efficacy of leucocyte interferon-α treatment. *Int J Clin Pract* 2003; **57:** 17–19.

Churg-Strauss syndrome. For reports that interferon alfa may be beneficial in Churg-Strauss syndrome, see p.1501.

Hepatitis. Interferon alfa (including peginterferon alfa) is one of the main drugs used in the treatment of viral hepatitis B and C and chronic hepatitis B and C co-infection with HIV (p.851) and has been the subject of several general reviews.[1-3]

Interferon alfa was the first drug approved for the management of chronic **hepatitis B**. A meta-analysis[4] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HbeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels. Studies have suggested that subcutaneous peginterferon alfa is as effective or slightly more effective than interferon alfa given subcutaneously.[5] Results from various studies[6] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[7] and HBeAg-negative patients with chronic hepatitis B,[8] when peginterferon alfa was given subcutaneously, once weekly for 48 weeks. However, the addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[8,9] Interferon alfa can produce benefit in some patients co-infected with chronic **hepatitis B and D**.[10] However, these co-infected patients are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[10] with high-dose interferon alfa (9 million units) given 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[11]

The first available treatment for **chronic hepatitis C** was interferon alfa-2b, and this was followed by interferon alfa-2a, given subcutaneously 3 times a week. A meta-analysis[12] of studies involving interferon treatment of hepatitis C suggested that treatment with interferon alfa 3 million units three times weekly for at least 12 months had the best risk-benefit ratio for patients with chronic hepatitis C. Studies[13,14] with once-weekly peginterferon alfa showed it to be more effective than interferon alfa given three times weekly in patients with chronic hepatitis C, including those with cirrhosis or extensive fibrosis.[15]

Combination therapy with interferon alfa and oral ribavirin for the treatment of chronic hepatitis C is more effective than either drug alone with sustained responses having been recorded, and is now generally considered to be the treatment of first choice.[16,17] A meta-analysis[18] of randomised studies has concluded that combination therapy is also more effective for chronic hepatitis C in patients who had failed to respond to interferon alone or to any other previous treatment. Studies[19,20] suggest that combination therapy with peginterferon alfa and ribavirin may be more effective and better tolerated than interferon alfa plus ribavirin. One study[19] with peginterferon alfa-2b or interferon alfa-2b and ribavirin showed a sustained virological response (SVR) of around 42% in patients with viral genotype 1, compared with about 80% in patients with genotypes 2 and 3. A review[21] of the use of peginterferon alfa with ribavirin has also concluded that this combination is superior to interferon alfa plus ribavirin or to peginterferon alfa alone. The British Society for Gastroenterology[22] and the American Association for the Study of Liver Diseases (AASLD)[23] recommend weekly subcutaneous peginterferon alfa with daily oral ribavirin as the first choice of treatment for chronic hepatitis C.

Guidelines for the management of **HIV and hepatitis B** co-infection have been developed by various expert groups.[24-26] In patients not requiring HIV therapy interferon alfa for 4 to 6 months is considered suitable for non-cirrhotic HBeAg-positive patients, but limited evidence suggests that peginterferon alfa may be more effective.[24] Treatment of **HIV and hepatitis C** co-infected patients has been associated with a high rate of intolerance and a low rate of response. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[27-29] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[27,29] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[28] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[28,29] The British HIV Association guidelines[30] for the treatment and management of HIV and hepatitis C co-infection recommends combination therapy with peginterferon alfa and ribavirin for 48 weeks in patients with moderate liver disease and well controlled HIV disease. Similar recommendations have been made by the AASLD.[23] For further discussion on the management of chronic hepatitis B and C patients co-infected with HIV, see p.851.

Although antivirals are generally not required in **acute hepatitis**, treatment of acute hepatitis C with interferon alfa has been shown to produce more rapid resolution of viraemia[31] and may decrease the risk of chronic hepatitis developing.[32] Studies[33] with peginterferon alfa-2b, in a small number of patients with acute hepatitis C, have shown similar efficacy. The AASLD[23] recommends that either interferon or peginterferon alfa given for a period of at least 6 months should be considered for the treatment of acute hepatitis C if the infection persists 2 to 4 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[34] and by the Scottish Intercollegiate Guidelines Network.[35]

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7. Lau GKK, *et al.* Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352:** 2682–95.
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14. Perry CM, Jarvis B. Peginterferon-α-2a (40 kD): a review of its use in the management of chronic hepatitis C. *Drugs* 2001; **61:** 2263–88.
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17. Brok J, *et al.* Ribavirin plus interferon versus interferon for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 13/06/08).
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28. Torriani FJ, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351:** 438–50.
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32. Jaeckel E, *et al.* Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345:** 1452–7.
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34. Clinical Effectiveness Group (British Association of Sexual Health and HIV). United Kingdom national guideline on the management of the viral hepatitides A, B & C 2005 [under revision]. Available at: http://www.bashh.org/documents/117/117.pdf (accessed 28/08/08)
35. Scottish Intercollegiate Guidelines Network. Management of hepatitis C: a national clinical guideline (issued December 2006). Available at: http://www.sign.ac.uk/pdf/sign92.pdf (accessed 13/06/08)

Herpes simplex infections. Herpes simplex infections are commonly treated with aciclovir (see p.854), but beneficial responses to topical interferon alfa have been reported in genital herpes, although results are mixed.[1] Interferon alfa has also been reported to have benefit in the treatment of herpes keratitis. A systematic review[2] of interventions for herpes simplex epithelial keratitis found that interferon monotherapy had a slightly beneficial effect on dendritic epithelial keratitis, but no more than that of other antivirals and concluded that the use of an antiviral nucleoside with interferon seemed to speed healing.

1. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. *Drugs* 2000; **60:** 1329–52.
2. Wilhelmus KR. Therapeutic interventions for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 13/06/08).

HIV infection and AIDS. Interferons have been tried with some success in the management of Kaposi's sarcoma and mycobacterial infections in patients with AIDS (see below and under Interferon Gamma, p.894, respectively).

Inflammatory bowel disease. Interferon alfa is one of many drugs that have been tried in inflammatory bowel disease (p.1697). A study[1] found that clinical remission was achieved in 26 of 28 patients with ulcerative colitis after 6 to 12 months of treatment with interferon alfa-2a. Partial remission was reported in 2 of 5 patients with Crohn's disease[2] given interferon alfa, but in another study in 12 patients[3] interferon alfa was of no benefit. Interferon beta has also been found to be of benefit for the treatment of ulcerative colitis unresponsive to corticosteroids.[4]

1. Sümer N, Palabiyikoğlu M. Induction of remission by interferon-α in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995; **7:** 597–602.
2. Davidsen B, *et al.* Tolerability of interferon alpha-2b, a possible new treatment of active Crohn's disease. *Aliment Pharmacol Ther* 1995; **9:** 75–9.
3. Gasché C, *et al.* Prospective evaluation of interferon-α in treatment of chronic active Crohn's disease. *Dig Dis Sci* 1995; **40:** 800–4.
4. Musch E, *et al.* Induction and maintenance of clinical remission by interferon-β in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. *Aliment Pharmacol Ther* 2002; **16:** 1233–9.

Kaposi's sarcoma. The various treatments used for Kaposi's sarcoma, including the role of HAART as first-line therapy in the AIDS-related form, are discussed on p.675. Interferon alfa has been used in AIDS-related Kaposi's sarcoma and in patients with the classical, nonepidemic form. In patients with AIDS-related Kaposi's sarcoma interferon alfa, either as monotherapy or with zidovudine, has shown benefit in HIV-positive patients provided they possess relatively elevated CD4+ T lymphocyte counts (greater than 150 cells/microlitre),[1] although other drugs have generally replaced interferon alfa as treatment for Kaposi's sarcoma.[2] Systemic and local therapy such as interferon alfa and chemotherapy may be combined with HAART.[3]

1. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* 2001; **6:** 34–55.
2. Krown SE. AIDS-associated Kaposi's sarcoma: is there still a role for interferon alfa? *Cytokine Growth Factor Rev* 2007; **18:** 395–402.
3. Aldenhoven M, *et al.* Therapeutic strategies for epidemic Kaposi's sarcoma. *Int J STD AIDS* 2006; 571–8.

Malignant neoplasms. Many reports have been published on the effects of interferons on various neoplasms; most have involved interferon alfa.

Interferons have become established in the treatment of a few malignant disorders, notably hairy-cell leukaemia (but see p.654), Kaposi's sarcoma (see above), and chronic myeloid leukaemia (p.653). Alfa interferons may improve the duration of remission in multiple myeloma,[1-4] but not necessarily survival.[2,5] Combination therapy including interferons has also been used in indolent low-grade non-Hodgkin's lymphoma (p.656) and interferon alfa has been used alone to maintain remission. In renal cell carcinoma (p.667) response to interferon alfa used with interleukin-2 has been promising, but toxicity high; interferon alfa alone produces very modest benefit.[6] Beneficial responses have also been reported in a number of other neoplasms including melanoma (p.673); carcinoid tumours[7] (p.643); myelodysplasia; cutaneous T cell lymphomas including mycosis fungoides (p.657); and in meningioma.[8,9] Interferons have been given locally as an adjunct to surgery for superficial bladder tumours (p.659) and intralesionally or perilesionally in basal cell carcinoma[10-12] and also for keloid scars.[13,14] Use of interferon alfa with fluorouracil has been tried in inoperable colorectal cancer but does not appear to be more beneficial than fluorouracil alone.[15] Interferon alfa given with zidovudine has produced encouraging results in adult T-cell leukaemia-lymphoma.[16] Peginterferon alfa has also been shown to be effective in the management of chronic myeloid leukaemia and solid tumours, including metastatic melanoma and renal cell carcinoma.[17]

1. Mandelli F, *et al.* Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990; **322:** 1430–4.
2. Nordic Myeloma Study Group. Interferon-α2b added to melphalan-prednisone for initial and maintenance therapy in multiple myeloma: a randomized, controlled trial. *Ann Intern Med* 1996; **124:** 212–22.
3. Fritz E, Ludwig H. Interferon-α treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol* 2000; **11:** 1427–36.
4. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol* 2001; **113:** 1020–34.
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6. Medical Research Council Renal Cancer Collaborators. Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled study. *Lancet* 1999; **353:** 14–17.
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8. Wöber-Bingöl Ç, *et al.* Interferon-alfa-2b for meningioma. *Lancet* 1995; **345:** 331.
9. Kaba SE, *et al.* The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery* 1997; **40:** 271–5.
10. Kowalzick L, *et al.* Intralesional recombinant interferon beta-1a in the treatment of basal cell carcinoma: results of an open-label multicentre study. *Eur J Dermatol* 2002; **12:** 558–61.
11. Bostanci S, *et al.* Treatment of basal cell carcinoma located in the head and neck region with intralesional interferon alpha-2a: evaluation of long-term follow-up results. *Clin Drug Investig* 2005; **25:** 661–7.
12. Tucker SB, *et al.* Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006; **54:** 1033–8.
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14. Larrabee WF, *et al.* Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg* 1990; **116:** 1159–62.
15. Thirion P, *et al.* Alpha-interferon does not increase the efficacy of 5-fluorouracil in advanced colorectal cancer: Meta-analysis Group in Cancer. *Br J Cancer* 2001; **84:** 611–20.
16. Gill PS, *et al.* Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med* 1995; **332:** 1744–8.
17. Bukowski RM, *et al.* Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. *Cancer* 2002; **95:** 389–96.

Mycobacterial infections. For the use of interferon alfa in mycobacterial infections, see Interferon Gamma, p.894.

Progressive multifocal leukoencephalopathy. Beneficial responses were reported in patients with HIV-associated progressive multifocal leukoencephalopathy (PML) after treatment with interferon alfa.[1] Daily intramuscular interferon alfa therapy for 2 weeks also resulted in some neurologic improvement in a patient identified as an asymptomatic human T-lymphotropic virus type I carrier, who developed PML and pneumocystis pneumonia.[2] However, in a retrospective analysis[3] of the relative value of HAART and interferon alfa in the treatment of PML associated with AIDS, prolonged survival associated with interferon alfa was found to be not independent of the effects of HAART and it was concluded that interferon alfa provided no additional benefit.

1. Huang SS, *et al.* Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol* 1998; **4:** 324–32.
2. Kimura A, *et al.* Progressive multifocal leukoencephalopathy in an HTLV-I carrier. *Clin Neurol Neurosurg* 2006; **108:** 768–71.
3. Geschwind MD, *et al.* The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol* 2001; **7:** 353–7.

Skin disorders. For the use of interferon alfa in skin disorders associated with raised IgE concentrations, see Interferon Gamma, p.894.

Warts. Various interferons have been tried by various routes in the treatment of anogenital warts (condylomata acuminata) (p.1584).

Intralesional injection has been used to ensure relatively high concentrations of interferon in the wart but the occurrence of systemic adverse effects shows that there is absorption from this site. Complete responses were reported[1] in 36% of patients given intralesional interferon alfa-2b compared with 17% given placebo, and a corresponding overall reduction in the affected area of 62.4% compared with 1.2% respectively. However, follow-up was not sufficiently long to comment on relapse rates. Another study[2] found similar responses using interferons alfa-2b, alfa-n1, or beta in patients with refractory warts, with complete responses in 47% of patients given intralesional interferons compared with 22% of patients given placebo. A study[3] evaluating two different doses of intralesional interferon beta given three times weekly for 3 weeks reported complete responses in 63% of lesions injected with 1 million units compared with 38% of lesions injected with 33 000 units. Good responses have also been reported in patients with both refractory and recurrent warts given intralesional interferon alfa-n3.[4] Relapses were delayed and fewer warts recurred in patients who had received interferon rather than placebo. Intralesional interferon alfa-2b used with podophyllum was more effective that podophyllum alone,[5] although about 66% of patients in each group subsequently relapsed. A systematic review concluded that based on limited available evidence intralesional interferons may have a therapeutic effect, but have no significant advantage over simpler and safer treatments.[6]

Topical application of interferon alfa has also been reported to be more effective than podophyllotoxin.[7,8] Interferon beta has also been applied topically after surgical removal of warts.[9]

Theoretically, *systemic* use should have advantages in controlling subclinical infections and reducing relapses. However, responses to subcutaneous interferon alfa have generally been disappointing[10-12] although responses comparable with cauterisation and a reduction in relapse rates with either subcutaneous or intramuscular interferon alfa-2b have been obtained.[13] Information on the use of systemic interferons as an adjunct to conventional therapy is scarce but a study in 97 patients[14] with recurrent warts found no difference in either response or relapse rates in patients given cryotherapy with subcutaneous interferon alfa or cryotherapy alone. A study comparing subcutaneous interferon alfa, beta, and gamma used with cryotherapy found no significant difference in response rate, although patients given interferon beta or gamma developed new warts at a lower frequency.[15]

Intralesional plus subcutaneous interferon alfa has also been tried in treatment of oral warts; 4 HIV-positive patients with recurrent oral warts that had failed to respond to surgery and other treatments responded to interferon alfa treatment.[16]

1. Eron LJ, *et al.* Interferon therapy for condylomata acuminata. *N Engl J Med* 1986; **315:** 1059–64.
2. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferons administered intralesionally: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 675–9.
3. Monsonego J, *et al.* Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin Med* 1996; **72:** 111–14.
4. Friedman-Kien AE, *et al.* Natural interferon alfa for treatment of condylomata acuminata. *JAMA* 1988; **259:** 533–8.
5. Douglas JM, *et al.* A randomized trial of combination therapy with intralesional interferon α and podophyllin versus podophyllin alone for the therapy of anogenital warts. *J Infect Dis* 1990; **162:** 52–9.
6. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
7. Syed TA, *et al.* Human leukocyte interferon-alpha versus podophyllotoxin in cream for the treatment of genital warts in males: a placebo-controlled, double-blind, comparative study. *Dermatology* 1995; **191:** 129–32.
8. Syed TA, *et al.* Management of genital warts in women with human leukocyte interferon-α vs podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* 1995; **73:** 255–8.
9. Gross G, *et al.* Recombinant interferon beta gel as an adjuvant in the treatment of recurrent genital warts: results of a placebo-controlled double-blind study in 120 patients. *Dermatology* 1998; **196:** 330–4.
10. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferon-α preparations administered parenterally: a double-blind, placebo-controlled trial. *J Infect Dis* 1990; **162:** 1270–6.
11. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alfa-2a: a multicenter double-blind placebo-controlled clinical trial. *JAMA* 1991; **265:** 2684–7.
12. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *Acta Derm Venereol (Stockh)* 1993; **73:** 223–6.
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14. Eron LJ, *et al.* Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon. *Genitourin Med* 1993; **69:** 91–3.
15. Bonnez W, *et al.* A randomized, double-blind, placebo-controlled trial of systemically administered interferon-α, -β, or -γ in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* 1995; **171:** 1081–9.
16. Lozada-Nur F, *et al.* Use of intralesional interferon-alpha for the treatment of recalcitrant oral warts in patients with AIDS: a report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92:** 617–22.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Avirostat; Bioferon; INF; Infostat; Inmutag†; Inter 2-B; Intron A Peg†; Intron A†; Pegasys; Roferon-A†; ***Austral.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Austria:*** IntronA; PegIntron; Roferon-A; ***Belg.:*** Infergen†; IntronA; Pegasys; PegIntron; Roferon-A; ***Braz.:*** Beferon; Blauferon; Intron A; Kinnoferon 2A; Pegasys; PegIntron; Roferon-A; ***Canad.:*** Infergen; Intron A; Pegasys; PegIntron†; Roferon-A†; Unitron PEG; ***Chile:*** Intermax-Alpha; Intron A†; IntronA; Pegasys; PegIntron; Roferon-A†; ***Cz.:*** Alfaferone; Infergen†; Interferon Alfanative†; Intron A; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; Wellferon†; ***Denm.:*** IntronA; Pegasys; PegIntron; Roceron-A†; ***Fin.:*** Finnferon-Alpha†; IntronA; Pegasys; PegIntron; Roferon-A; ***Fr.:*** Infergen; IntronA; Pegasys; Roferon-A; Viraferon; ViraferonPeg; ***Ger.:*** Inferax; IntronA; Pegasys; PegIntron; Roferon-A; ***Gr.:*** Infergen; IntronA; Pegasys; PegIntron; Roferon-A; ***Hong Kong:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Hung.:*** Egiferon; Infergen†; Intron A; Pegasys; PegIntron; Roferon-A; ***India:*** Roferon-A; ***Indon.:*** Interferon Alfanative; IntronA; Kalferon; Pegasys; PegIntron; ***Irl.:*** IntronA; Pegasys; PegIntron†; Roferon-A; ViraferonPeg; ***Israel:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Ital.:*** Alfaferone; Alfater; Biaferone; Cilferon-A†; Haimaferone†; Humoferon†; Infergen; IntronA; Isiferone†; Pegasys; PegIntron; Roferon-A; Wellferon†; ***Jpn:*** Canferon; OIF; Pegasys; Roferon-A; Sumiferon; ***Malaysia:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Mex.:*** Alferon; Altemol†; Intron A; Lemeron; Pegasys; Pegtron; Proquiferon; Roferon-A; Urifron; Viraferon†; ***Neth.:*** Infergen; IntronA; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***Norw.:*** IntronA; Pegasys; PegIntron; Roceron; ***NZ:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Philipp.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Pol.:*** Alfaferone; Intron A; Pegasys; PegIntron; Roferon-A; ***Port.:*** Intron A; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***Rus.:*** Interal; Pegasys (Пегасис); PegIntron (Пегинтрон); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Wellferon (Вэллферон); ***S.Afr.:*** Intron A; Multiferon; Pegasys; PegIntron; Roferon-A; ***Singapore:*** Intron A; Pegasys; PegIntron; Roferon-A†; ***Spain:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Swed.:*** IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; ***Switz.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Thai.:*** Bioferon; Intron A; Pegasys; PegIntron; Roferon-A†; Wellferon†; ***Turk.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***UK:*** IntronA; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***USA:*** Alferon N; Infergen; Intron A; Pegasys; PegIntron; Roferon-A†; ***Venez.:*** Intron; Intron A; Pegasys; PegIntron; Roferon-A.

Multi-ingredient: ***Arg.:*** Bioferon Hepakit; Pegatron†; Rebetron†; ***Austral.:*** Pegasys RBV; Pegatron; Rebetron; ***Canad.:*** Pegasys RBV; Pegetron; Rebetron†; ***Mex.:*** Hepatron C; Pegtron Cotronak Kit; ***NZ:*** Pegasys RBV; Pegatron; Rebetron; Roferon-A RBV; ***Philipp.:*** Pegasys RBV; ***S.Afr.:*** Rebetron†; ***Switz.:*** Intron A/Rebetol†; ***USA:*** Rebetron†.

Interferon Beta *(BAN, rINN)*

IFN-β; Interferón-β; Interferon-β; Interferón beta; Interféron bêta; Interferoni beta; Interferonum Beta; SH-Y-579A (interferon beta-1b).

Интерферон Бета

CAS — 74899-71-1 (interferon beta); 145258-61-3 (interferon beta-1a); 145155-23-3 (interferon beta-1b); 90598-63-3 (interferon beta-1b).

ATC — L03AB02 (natural); L03AB07 (1a); L03AB08 (1b).

ATC Vet — QL03AB02 (natural); QL03AB07 (1a); QL03AB08 (1b).

NOTE. Interferon beta was previously known as fibroblast interferon.

Interferon beta-1a and Interferon beta-1b are both *USAN*.

Nomenclature. Interferon beta may be derived from fibroblasts, or produced by recombinant DNA technology. Sub-species of the human beta gene produce interferon beta with protein variants designated by a number (as in interferon beta-1). Interferon beta-1 is further qualified by a letter to indicate the amino-acid sequences at positions 1 and 17, and to indicate whether or not glycosylation is present:

- interferon beta-1a has methionine at position 1 and cysteine at 17 and is glycosylated at position 80
- interferon beta-1b has serine at position 17 and is not glycosylated

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rch) indicates production from genetically engineered Chinese hamster ovary cells; (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology.

Adverse Effects

As for interferons in general (see Interferon Alfa, p.885).

Severe local reactions at injection sites, including tissue necrosis, have been reported. Menstrual irregularities have been associated with interferon beta use. On injection, transient neurological symptoms that may mimic an exacerbation of multiple sclerosis have been reported. In addition transient episodes of hypertonia and/or severe muscular weakness may occur at any time during treatment.

◊ Reviews.

1. Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. *Drug Safety* 2000; **22:** 149–59.

Auto-immune disorders. Reversible subacute cutaneous lupus erythematosus[1] and SLE[2] have been reported in patients given interferon beta. A case[3] of lupus erythematosus profundus has been reported in a patient after 4 years of treatment with interferon beta-1b for multiple sclerosis; the neurological symptoms and subcutaneous nodules resolved after stopping treatment. There have been case reports of patients developing myasthenia gravis while receiving interferon beta; the patients responded to treatment with pyridostigmine.[4]

1. Nousari HC, *et al.* Subacute cutaneous lupus erythematosus associated with interferon beta-1a. *Lancet* 1998; **352:** 1825–6.
2. Crispín JC, Díaz-Jouanen E. Systemic lupus erythematosus induced by therapy with interferon-β in a patient with multiple sclerosis. *Lupus* 2005; **14:** 495–6.
3. Gono T, *et al.* Lupus erythematosus profundus (lupus panniculitis) induced by interferon-β in a multiple sclerosis patient. *J Clin Neurosci* 2007; **14:** 997–1000.
4. Dionisiotis J, *et al.* Development of myasthenia gravis in two patients with multiple sclerosis following interferon β treatment. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1079.

Effects on the blood. Aplastic anaemia occurred[1] in a patient with multiple sclerosis after treatment with interferon beta-1a for about a year. The interferon was stopped and the patient had a good response to immunosuppressant treatment. The haematological effects of subcutaneous interferon beta-1a in multiple sclerosis patients have been reviewed.[2]

1. Aslam AK, Singh T. Aplastic anemia associated with interferon beta-1a. *Am J Ther* 2002; **9:** 522–3.
2. Rieckmann P, *et al.* Haematological effects of interferon-beta-1a (Rebif) therapy in multiple sclerosis. *Drug Safety* 2004; **27:** 745–56.

Effects on the cardiovascular system. Severe Raynaud's syndrome developed in a patient during treatment with interferon beta.[1] Symptoms subsided once interferon beta was stopped.

1. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.

Effects on hearing. For a report of sensorineural hearing loss in patients receiving interferon beta, see Interferon Alfa, p.886.

Effects on the liver. Hepatotoxicity, sometimes severe and in rare cases fatal, has been reported with interferons and its association specifically with the use of interferon beta-1a in multiple sclerosis patients has been reviewed.[1]

1. Francis GS, *et al.* Hepatic reactions during treatment of multiple sclerosis with interferon-β-1a: incidence and clinical significance. *Drug Safety* 2003; **26:** 815–27.

Effects on the skin. Calcified subcutaneous nodules have been reported in a patient after 3 years of treatment with subcutaneous interferon beta-1a for the treatment of multiple sclerosis.[1] For a report of severe necrotising cutaneous lesions at injection sites in a patient receiving interferon beta, see Interferon Alfa, p.887. See also Auto-immune Disorders, above for a report of cutaneous lupus erythematosus associated with interferon beta.

1. Macbeth AE, *et al.* Calcified subcutaneous nodules: a long-term complication of interferon beta-1a therapy. *Br J Dermatol* 2007; **157:** 624–5.

Precautions

As for interferons in general (see Interferon Alfa, p.887).

Interferon beta in high doses is fetotoxic and abortifacient in *primates* and should be avoided during pregnancy.

Interactions

As for interferons in general (see Interferon Alfa, p.888).

Antiviral Action

As for interferons in general (see Interferon Alfa, p.888).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. About 50% of a subcutaneous dose and 40% of an intramuscular dose of interferon beta is absorbed. For some formulations of interferon beta-1a, bioavailability and area under the plasma concentration-time curves are equivalent for subcutaneous and intramuscular dosage, but for others, intramuscular doses produce higher values than subcutaneous doses and subcutaneous doses therefore cannot be substituted for intramuscular doses. Peak serum concentrations of interferon beta-1a have been reported to occur 3 hours after subcutaneous injection and between 3 and 15 hours after intramuscular injection, and those for beta-1b have been reported to occur 1 to 8 hours after subcutaneous injection. The elimination half-life for intramuscular interferon beta-1a is about 10 hours. Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

Uses and Administration

Interferon beta is a cytokine with antiviral and immunomodulating activities. Two forms of interferon beta are available: interferon beta-1a and interferon beta-1b (see Nomenclature, above). Interferon beta is mainly used in the management of relapsing-remitting multiple sclerosis (below), although its mode of action is unclear. In the UK interferon beta-1b is also licensed for use in secondary progressive multiple sclerosis.

Interferon beta-1a is given in relapsing-remitting multiple sclerosis in a dose dependent upon the formulation used:

- *Avonex* (*Biogen*) is given in a dose of 6 million units (30 micrograms) once weekly by intramuscular injection.
- *Rebif* (*Serono*) is given in an escalating dose over 4 weeks, to 12 million units (44 micrograms) three times weekly by subcutaneous injection, or to 6 million units (22 micrograms) three times weekly by subcutaneous injection in patients unable to tolerate the higher dose.

Interferon beta-1b is given in both relapsing-remitting and in secondary progressive multiple sclerosis in an escalating dose over 3 to 6 weeks to a dose of 8 million units (250 micrograms) on alternate days by subcutaneous injection.

In the UK interferon beta-1a (*Avonex*) and interferon beta-1b are also indicated for the treatment of patients who have had a single demyelinating event with an active inflammatory process if it is sufficiently severe to warrant intravenous corticosteroids.

◊ Reviews.

1. Goodkin DE. Interferon beta-1b. *Lancet* 1994; **344:** 1057–60.
2. Etheridge LJ, *et al.* The use of interferon beta in relapsing-remitting multiple sclerosis. *Arch Dis Child* 2004; **89:** 789–91.
3. Markowitz CE. Interferon-beta: mechanism of action and dosing issues. *Neurology* 2007; **68** (suppl 4): S8–S11.

Guillain-Barré syndrome. Rapid improvement in motor function was reported during use of interferon beta-1a in a patient with Guillain-Barré syndrome associated with *Campylobacter jejuni* infection.[1] However, the relative contributions of interferon therapy and a course of plasma exchange that immediately preceded it could not be assessed.[2] Successful treatment of Guillain-Barré syndrome was reported in a patient after interferon beta-1a was added to treatment with intravenous immunoglobulin.[3] A small randomised, placebo-controlled pilot study[4] of subcutaneous interferon beta-1a or placebo, in addition to intravenous immunoglobulin, in patients with Guillain-Barré syndrome reported no significant difference in the rate of improvement.

1. Créange A, *et al.* Treatment of Guillain-Barré syndrome with interferon-β. *Lancet* 1998; **352:** 368.
2. Sawaya RA. Interferon beta for Guillain-Barré syndrome. *Lancet* 1998; **352:** 1550–1.
3. Schaller B, *et al.* Successful treatment of Guillain-Barré syndrome with combined administration of interferon-β-1a and intravenous immunoglobulin. *Eur Neurol* 2001; **46:** 167–8.
4. Pritchard J, *et al.* A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barré syndrome. *Neurology* 2003; **61:** 1282–4.

Multiple sclerosis. Multiple sclerosis (MS)[1-3] is a chronic inflammatory and demyelinating disease affecting the CNS. It is the most common disabling neurological disease among young adults and is most often diagnosed in those between the ages of 20 and 40, with women being almost twice as likely to develop it as men. Although the etiology and pathogenesis of MS is poorly understood, it is thought that the disease has an immunological basis and occurs in genetically susceptible individuals. MS is characterised by multiple areas of inflammation and demyelination; activated T-cells enter the CNS and produce an immune cascade resulting in localised loss of myelin, oligodendrocytes, and axons. The resulting lesions (plaques) accumulate over time, with impairment or less electrical transmission along the nerve fibres (axons).

Patients with MS commonly present with an individual mix of symptoms, which tend to progress over years to decades. The type and number of symptoms may vary according to the areas affected but typically include bowel and bladder dysfunction, changes in cognitive function, dizziness, depression, fatigue, difficulties with walking and balance, paraesthesias, pain, sexual dysfunction, spasticity, problems with speech and swallowing, tremor, and visual impairment, notably from optic neuritis. Most patients improve to some degree after the initial attack but the course and severity of the disease are unpredictable.

People with MS generally follow one of four clinical courses of disease, which in turn may be mild, moderate, or severe. In about 85% of patients the disease follows a relapsing-remitting course (RR-MS) in which there are recurrent exacerbations (flare-ups) followed by clinical improvement and relatively long periods of remission. After about 10 to 15 years up to 50% of patients develop progressive neurological deterioration, categorised as secondary progressive disease (SP-MS). However, about 15% of people with RR-MS will have a mild course with little or no disability after 15 years (benign MS). About 10 to 15% of patients present without relapses but have slow continuous deterioration, classified as primary progressive disease (PP-MS). In about 5% of patients the disease is described as progressive relapsing; people with this type of MS have steadily worsening disease from the onset but also have acute exacerbations.

Choice of treatment.

A wide range of drugs with immunological actions (disease-modifying drugs) have been tried in the treatment of MS itself with the aim of improving recovery from acute attacks, preventing or reducing further attacks (relapses), and halting the progressive stage of the disease. Different therapies are used for patients having acute attacks, for patients who have RR-MS, for patients who have the progressive subtypes, and for symptomatic management.

Corticosteroids are used for their immunomodulatory and anti-inflammatory effects in acute attacks (relapses). Corticosteroid therapy reduces the duration of the episode and accelerates recovery, but it is not known whether it alters the course of the disease in the long term.[4] The drug of choice is methylprednisolone; usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days and sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g daily have been tried.[5] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis,[6] although the effect was not sustained beyond 2 years.[7] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[8] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[9] A small clinical study indicated that the bioavailability attained after large doses of oral prednisone may be similar to that of high dose intravenous methylprednisolone.[10] In patients with PP-MS, the benefits of short-course methylprednisolone lasted no longer than 3 months[11] although, in patients with SP-MS, a preliminary study has suggested that progression may be delayed by intermittent high-dose methylprednisolone therapy.[12]

Interferon beta has become established for treatment of RR-MS selected patients, and is also used in SP-MS. Studies[13-15] in patients with active RR-MS have shown the efficacy of interferon *beta-1b* given subcutaneously and at different doses. Similar results in RR-MS have been obtained with interferon *beta-1a* given by either subcutaneous or intramuscular routes;[16-18] although comparative studies[19,20] have suggested that subcutaneous interferon beta-1a (44 micrograms given three times a week) is more effective than intramuscular interferon beta-1a (30 micrograms weekly). A prospective, randomised, multicentre study[21] comparing the different frequencies of dosing with interferon beta-1a and beta-1b concluded that high-dose interferon beta-1b given on alternate days was more effective in RR-MS than once-weekly interferon beta-1a. Studies[22-24] in patients presenting with a first demyelinating event (clinically isolated syndrome), or other manifestation of early disease, have shown that treatment with interferon beta may reduce the rate of progression to clinical MS, a view confirmed by a recent systematic review.[25] A 3-year follow-up analysis[26] of one study[24] found that early treatment with interferon beta-1b prevented the development of confirmed disability.

Concern has been expressed over the detection of neutralising antibodies against interferon in up to 46% of patients;[27-29] development of neutralising antibodies correlates with reduced treatment efficacy and the possibility for renewed disease activity. The development of neutralising antibodies is greater in patients treated with higher doses of interferon and in those treated with interferon beta-1b.[30]

Encouraging results have also been obtained with interferon beta-1b in patients with SP-MS,[31] but no effect has been found on disability progression from use of interferon beta-1a in SP-MS.[32,33]

Results of studies[34,35] with *glatiramer* in patients with RR-MS have shown that it can reduce the number of relapses and may produce some improvements in neurological disability. Follow-up of these patients for approximately 3 years continued to show a beneficial effect on disease relapse rate. MRI data supported the beneficial clinical results.[36] These benefits are produced in a different way from those gained with interferon beta leading to expectations of possible treatment with both drugs.

Natalizumab is a humanised monoclonal antibody that has been found to decrease the frequency of exacerbations in RR-MS. A 2-year randomised, placebo-controlled study[37] to assess the safety and efficacy of intravenous natalizumab reported a 68% likelihood of remaining relapse-free and a 83% reduction in the number of new or enlarging brain lesions on MRI; the cumulative probability of sustained disability progression was 17% in the natalizumab patient group compared to 29% in the placebo group. Another 2-year study[38] reported that natalizumab plus intramuscular interferon beta-1a was more effective than interferon beta-1a monotherapy. Patients receiving combination therapy were 55% less likely to relapse and had a 83% reduction in the number of new or enlarging brain lesions on MRI compared with monotherapy. A 23% probability of progression of disability was reported for the combination treatment group compared with 29% for interferon alone. Natalizumab has, however, been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore limited to patients with highly active RR-MS who have had an inadequate response to, or are unable to tolerate, other therapies.

Although some studies have shown modest benefits with *immunosuppressants*, the general conclusions of large controlled studies have tended to be that any slight benefits of existing therapies with immunosuppressants such as azathioprine, ciclosporin, cyclophosphamide, and methotrexate are outweighed by the toxicity of the doses required to have an effect.[39-46] However, a systematic review[47] concluded that azathioprine reduced the number of patients who had relapses and the number who progressed during the first 2 to 3 years of treatment. It considered that azathioprine might be given as an alternative to interferon beta for maintenance treatment for patients who frequently relapse and require corticosteroids. Long-term toxicity (including the risk of malignancy) may be related to cumulative doses above 600 g and treatment for longer than 10 years. Mitoxantrone (given by intravenous infusion) has been studied in patients with RR-, PR-, and SP-MS and found to be moderately effective in reducing disease progression and the frequency of relapses.[48,49] Its use may, however, be limited by dose-related cardiotoxicity and it is suggested that mitoxantrone be used to treat patients with rapidly progressive disease or those not responding to high-dose interferon. A review[50] of cladribine indicated that it reduced the number of enhancing lesions but also had significantly more adverse effects (including myelosuppression) than placebo. The authors suggested that cladribine might have a role in the treatment of refractory patients with SP-MS.

Other immunological approaches evaluated have included the use of monoclonal antibodies such as alemtuzumab, daclizumab, and rituximab, and immunosuppressants such as mycophenolate mofetil. HMG-CoA reductase inhibitors (statins) have immunomodulatory effects and a small study[51] reported that simvastatin significantly decreases the number and volume of new MRI lesions in patients with RR-MS.

A systematic review[52] on the use of intermittent intravenous normal immunoglobulins in patients with RR-MS concluded that there was a reduction in relapse rate and an increased time to relapse, but no evidence that immunoglobulin treatment reduces the progression of MS or reverses existing damage. Intravenous normal immunoglobulins are not effective in SP-MS.[53] Autologous haematopoietic stem cell transplantation has shown benefit in some patients with progressive MS.[54,55]

Guidelines for the management of multiple sclerosis have been produced in the UK,[56,57] the USA,[58] and other countries.[59,60]

Symptomatic treatment.

MS can produce a wide range of symptoms, many of which are manageable; symptomatic treatment is aimed at the management of spasticity, ataxia, tremor, paroxysmal symptoms, pain, fatigue, and bladder dysfunction. Baclofen, dantrolene, diazepam, and tizanidine are the usual drugs given for spasticity (see p.1887). There is also some anecdotal evidence to suggest that cannabis and individual cannabinoids, including synthetic cannabinoids such as nabilone, may improve pain and spasticity;[61] a review[62] considered evidence of effectiveness to be lacking. Patients with MS can suffer from a number of different types of pain, including pain from spasticity, and therapy must be individualised for each specific pain syndrome (see Choice of Analgesic, p.2). Pain, spasms, and spasticity have responded to gabapentin in preliminary studies.[63-68] A review has noted, however, that the absolute and comparative efficacy and tolerability of anti-spasticity drugs is poorly documented.[69] Paraesthesia and dysaesthesia, which can be common, may respond to tricyclic antidepressants or antiepileptics. Amantadine, modafinil, pemoline, and fampridine have all been investigated for the management of fatigue associated with MS.[70] Treatment of bladder dysfunction may include an alpha blocker such as phenoxybenzamine and appropriate parasympathomimetic or antimuscarinic (such as oxybutynin) therapy to control bladder contractions (see Urinary Incontinence and Retention, p.2180). Fampridine and amifampridine have been reported to produce beneficial symptomatic responses such as improvement in walking, dexterity, and vision, possibly as a result of potassium-channel blocking activity but a systematic review[71] was unable to come to a conclusion about safety and efficacy, noting that publication bias posed a problem.

Conventional treatments are only partially effective and may produce adverse effects, and many patients with MS try alternative therapies. The most common *dietary interventions* are supplementation with polyunsaturated fatty acids (such as omega-3 and omega-6 fatty acids, often as fish, evening primrose, or sunflower oils), allergen-free diets, vitamins, and micronutrients and antioxidants (such as selenium, ginkgo biloba extracts, and coenzyme Q10). A review of the relationship between these dietary interventions and MS concluded that there was insufficient evidence to determine their benefits or risks.[72] Polyunsaturated fatty acids seem to have no major effect on disease progression and recurrence of exacerbations over 2 years. Research into the value of vitamin D is ongoing after findings that higher levels of serum vitamin D are associated with a lower risk of MS.[73]

The use of *hyperbaric oxygen* therapy in MS was a matter of debate for many years. Some workers reported benefit, especially in bladder and bowel function or in cerebellar function whereas others were unable to substantiate any long-term benefit and reviews have concluded that there is no convincing evidence that hyperbaric oxygen therapy is useful.[74,75]

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2. Sorensen PS. Early-stage multiple sclerosis: what are the treatment options? *Drugs* 2004; **64:** 2021–9.
3. Murray TJ. Diagnosis and treatment of multiple sclerosis. *BMJ* 2006; **332:** 525–7.
4. Filippini G, *et al.* Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 13/06/08).
5. Oliveri RL, *et al.* Randomized trial comparing two different high doses of methylprednisolone in MS: a clinical and MRI study. *Neurology* 1998; **50:** 1833–6.
6. Beck RW, *et al.* The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 1993; **329:** 1764–9.
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9. Barnes D, *et al.* Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. *Lancet* 1997; **349:** 902–6.
10. Morrow SA, *et al.* The bioavailability of iv methylprednisolone and oral prednisone in multiple sclerosis. *Neurology* 2004; **63:** 1079–80.
11. Cazzato G, *et al.* Double-blind, placebo-controlled, randomized, crossover trial of high-dose methylprednisolone in patients with chronic progressive form of multiple sclerosis. *Eur Neurol* 1995; **35:** 193–8.
12. Goodkin DE, *et al.* A phase II study of IV methylprednisolone in secondary-progressive multiple sclerosis. *Neurology* 1998; **51:** 239–45.
13. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis I: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43:** 655–61.
14. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995; **45:** 1277–85.
15. Paty DW, *et al.* Interferon beta-1b is effective in relapsing-remitting multiple sclerosis II: MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43:** 662–7.
16. Jacobs LD, *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39:** 285–94.
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18. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; **352:** 1498–1504.
19. Panitch H, *et al.* Randomized, comparative study of interferon β-1a treatment regimens in MS: the EVIDENCE trial. *Neurology* 2002; **59:** 1496–1506.
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63. Mueller ME, *et al.* Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; **78:** 521–4.
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Rheumatoid arthritis. Preliminary studies suggested that interferon beta might have a beneficial effect on rheumatoid arthritis,[1] the conventional management of which is described on p.11. However, a subsequent randomised, double-blind study[2] found that adding subcutaneous interferon beta to methotrexate treatment in patients with rheumatoid arthritis had no clinical or radiological benefit over adding placebo.

1. van Holten J, *et al.* Interferon-β for treatment of rheumatoid arthritis? *Arthritis Res* 2002; **4:** 346–52.
2. van Holten J, *et al.* A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; **64:** 64–9.

Warts. For the use of interferon beta in the management of warts, see Interferon Alfa, p.891.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avonex; Betaferon; Blastoferon; Rebif; ***Austral.:*** Avonex; Betaferon; Rebif; ***Austria:*** Avonex; Betaferon; Rebif; ***Belg.:*** Avonex; Betaferon; Rebif; ***Braz.:*** Avonex; Betaferon; Rebif; Serobif; ***Canad.:*** Avonex; Betaseron; Rebif; ***Chile:*** Avonex; Betaferon; Rebif†; ***Cz.:*** Avonex; Betaferon; Rebif; ***Denm.:*** Avonex; Betaferon; Rebif; ***Fin.:*** Avonex; Betaferon; Rebif; ***Fr.:*** Avonex; Betaferon; Rebif; ***Ger.:*** Avonex; Betaferon; Fiblaferon; Rebif; ***Gr.:*** Avonex; Betaferon; Rebif; ***Hong Kong:*** Betaferon; Rebif; ***Hung.:*** Avonex; Betaferon; Rebif; ***India:*** Betaferon; Rebif; ***Indon.:*** Rebif; ***Irl.:*** Avonex; Betaferon; Rebif; ***Israel:*** Avonex; Betaferon; Rebif; ***Ital.:*** Avonex; Betaferon; Betron R†; Rebif; Serobif; ***Jpn:*** Feron; ***Malaysia:*** Betaferon; Rebif; ***Mex.:*** Avonex; Betaferon; Rebif; Uribeta; ***Neth.:*** Avonex; Betaferon; Rebif; ***Norw.:*** Avonex; Betaferon; Rebif; ***NZ:*** Avonex; Betaferon; Rebif; ***Philipp.:*** Betaferon; Rebif; ***Pol.:*** Avonex†; Betaferon; Rebif; ***Port.:*** Avonex; Betaferon; Rebif; ***Rus.:*** Avonex (Авонекс); Betaferon (Бетаферон); Rebif (Ребиф); ***S.Afr.:*** Avonex; Betaferon; Rebif; ***Singapore:*** Betaferon; Rebif; ***Spain:*** Avonex; Betaferon; Rebif; ***Swed.:*** Avonex; Betaferon; Rebif; ***Switz.:*** Avonex; Betaferon; Rebif; ***Thai.:*** Betaferon; Rebif; ***Turk.:*** Avonex; Betaferon; Rebif; ***UK:*** Avonex; Betaferon; Rebif; ***USA:*** Avonex; Betaseron; Rebif; ***Venez.:*** Avonex; Rebif.

Interferon Gamma *(BAN, rINN)*

IFN-γ; Interferón-γ; Interferon-γ; Interféron gamma; Interferón gamma; Interferoni gamma; Interferonigamma; Interferonum Gamma.

Интерферон Гамма

CAS — 98059-18-8 (interferon gamma-1a); 98059-61-1 (interferon gamma-1b).
ATC — L03AB03.
ATC Vet — QL03AB03.

NOTE. Interferon gamma was previously known as immune interferon.
Interferon gamma-1b is *USAN* and was previously known as interferon gamma-2a.

Pharmacopoeias. *Eur.* (see p.vii) includes Interferon Gamma-1b Concentrated Solution.

Ph. Eur. 6.2 (Interferon Gamma-1b Concentrated Solution; Interferoni Gamma-1b Solutio Concentrata). It is a solution of the *N*-terminal methionyl form of interferon gamma. It is produced by a method based on recombinant DNA technology using bacteria as host cells. It is a clear, colourless or slightly yellowish liquid. The pH of the solution is 4.5 to 5.5. Store in airtight containers at a temperature of −70°. Protect from light.

Nomenclature. Interferon gamma may be derived from immunologically stimulated T-lymphocytes (hence its former name of immune interferon) or produced by recombinant DNA technology. Similarly to interferon alfa, protein variants of interferon gamma are designated by a number and further qualified by a letter to indicate the amino-acid sequences at terminal positions 1 and 139:

- interferon gamma-1a has at position 1 hydrogen, cysteine, tyrosine, and cysteine and at position 139 arginine, alanine, serine, glutamine, and a hydroxyl group
- interferon gamma-1b, formerly known as interferon gamma-2a, has at position 1 hydrogen and methionine and at position 139 a hydroxyl group

Interferon gamma derived through recombinant DNA technology is labelled (rbe).

Adverse Effects

As for interferons in general (see Interferon Alfa, p.885)

Precautions

As for interferons in general (see Interferon Alfa, p.887). Interferon gamma in high doses has been shown to increase the incidence of abortions in *primates* and should be avoided during pregnancy.

Interactions

As for interferons in general (see Interferon Alfa, p.888).

Antiviral Action

As for interferons in general (see Interferon Alfa, p.888).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. Peak plasma concentrations of interferon gamma-1b occur about 4 hours after intramuscular injection and about 7 to 8 hours after subcutaneous injection. Half-lives of 38 minutes (intravenous dosage), 2.9 hours (intramuscular dosage), and 4.9 to 5.9 hours (subcutaneous dosage) have been reported.

Uses and Administration

Interferon gamma is a cytokine with antiviral and immunomodulating effects. Interferon gamma-1b is used for its action as a macrophage-stimulating factor as an adjunct to antimicrobial therapy in chronic granulomatous disease. It is also used to delay time to disease progression and reduce the frequency of serious infections in patients with severe malignant osteopetrosis.

Interferon gamma-1b is given in a dose of 50 micrograms/m^2 body-surface (1 million units/m^2) three times weekly by subcutaneous injection. Patients with a body-surface less than 0.5 m^2 should receive 1.5 micrograms/kg body-weight three times weekly.

Interferon gamma-1b is also under investigation for the treatment of cryptogenic fibrosing alveolitis (see below).

Interferon gamma-n1 has also been used for the treatment of cutaneous T-cell lymphomas.

◊ Reviews.

1. Marciano BE, *et al.* Long-term interferon-γ therapy for patients with chronic granulomatous disease. *Clin Infect Dis* 2004; **39:** 692–9.

Bacterial infections. In addition to its use to control infections in chronic granulomatous disease, interferon gamma was used with some success as an adjunct to antibacterials in a patient with Whipple's disease[1] but was of no benefit in a study in burn-related infections.[2] For the conventional management of these infections, see Whipple's Disease, p.200 and Skin Infections, p.194.

1. Schneider T, *et al.* Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998; **129:** 875–7.
2. Wasserman D, *et al.* Interferon-γ in the prevention of severe burn-related infections: a European phase III multicenter trial. *Crit Care Med* 1998; **26:** 434–9.

MYCOBACTERIAL INFECTIONS. Experience with interferons for *nontuberculous mycobacterial infections* in patients with AIDS is limited. Interferon gamma given with antimycobacterials produced beneficial responses in 3 patients with *Mycobacterium avium* complex infections, but produced no response or only a transient response in 3 others given interferon gamma alone.[1,2]

Beneficial responses have also been reported after use of interferon alfa[3] or gamma[4] as an adjunct to antimycobacterial therapy in HIV-negative patients with mycobacterial infections unresponsive to conventional therapy. Interferon alfa has been tried as an adjunct to conventional therapy in *multibacillary leprosy*.[5]

Inhaled interferon alfa[6] or gamma[7] may be a useful adjunct to conventional antimycobacterial treatment for *pulmonary tuberculosis*.

For discussion of these infections and their standard treatment, see Leprosy, p.176, Nontuberculous Mycobacterial Infections, p.181, and Tuberculosis, p.196.

1. Squires KE, *et al.* Interferon-γ and Mycobacterium avium-intracellular infection. *J Infect Dis* 1989; **159:** 599–600.
2. Squires KE, *et al.* Interferon-γ treatment for Mycobacterium avium-intracellulare complex bacillemia in patients with AIDS. *J Infect Dis* 1992; **166:** 686–7.
3. Maziarz RT, *et al.* Reversal of infection with Mycobacterium avium intracellulare by treatment with alpha-interferon in a patient with hairy cell leukemia. *Ann Intern Med* 1988; **109:** 292–4.
4. Holland SM, *et al.* Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma: a preliminary report. *N Engl J Med* 1994; **330:** 1348–55.
5. Ganapati R, *et al.* A multicenter study of recombinant interferon-alpha2b in the treatment of multibacillary leprosy. *Int J Lepr* 1997; **65:** 495–7.
6. Giosuè S, *et al.* Effects of aerosolized interferon-α in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 1998; **158:** 1156–62.
7. Condos R, *et al.* Treatment of multidrug-resistant pulmonary tuberculosis with interferon-γ via aerosol. *Lancet* 1997; **349:** 1513–15.

Cryptogenic fibrosing alveolitis. In a preliminary study[1] in patients with cryptogenic fibrosing alveolitis (CFA; idiopathic pulmonary fibrosis—see Diffuse Parenchymal Lung Disease, p.1502) who had not responded to treatment with corticosteroids or to other immunosuppressive therapy, lung capacity increased in 9 patients given interferon gamma-1b with prednisolone for 12 months, but deteriorated in 9 who were treated with prednisolone alone for the same period. The study was, however, criticised for its methodology and the statistical significance of its findings questioned.[2] A later study[3] involving 330 patients with CFA found that interferon gamma 1-b did not affect progression-free survival or pulmonary function; however, a trend toward lower mortality was seen in patients who received interferon gamma-1b compared with those given placebo. A subsequent study[4] to characterise the molecular effects of subcutaneous interferon gamma-1b versus placebo reported that interferon gamma-1b affected CFA through multiple pathways and could be of potential benefit. A randomised, prospective study[5] comparing interferon gamma-1b and colchicine (given for 24 months) in patients with mild-to-moderate CFA reported that 15.6% of patients treated with interferon gamma-1b and 38.8% of those given colchicine died. Patients treated with interferon gamma-1b also showed a higher forced vital capacity after 24 months of treatment. A review[6] of the use of interferon gamma-1b in the management of CFA found that efficacy of interferon gamma-1b was inconsistent with regard to changes in pulmonary function and mortality, although studies suggested that interferon gamma-1b may be of benefit in earlier-stage disease. A meta-analysis[7] of randomised controlled studies evaluating the use of interferon gamma-1b in the treatment of CFA concluded that interferon gamma-1b therapy was associated with reduced mortality.

1. Ziesche R, *et al.* A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 1999; **341:** 1264–9.
2. King TE. Interferon gamma-1b for the treatment of idiopathic pulmonary fibrosis. *N Engl J Med* 2000; **342:** 974–5.
3. Raghu G, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; **350:** 125–33.
4. Strieter RM, *et al.* Effects of interferon-γ 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; **170:** 133–40.
5. Antoniou KM, *et al.* Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; **28:** 496–504.
6. Pacanowski MA, Amsden GW. Interferon gamma-1b in the treatment of idiopathic pulmonary fibrosis. *Ann Pharmacother* 2005; **39:** 1678–86.
7. Bajwa EK, *et al.* Interferon-γ1b therapy in idiopathic pulmonary fibrosis: a metaanalysis. *Chest* 2005; **128:** 203–6.

Leishmaniasis. Interferon gamma has been tried both systemically and locally as an adjunct to standard treatment of leishmaniasis (p.824) with encouraging results. A review[1] of the use of interferon gamma in non-viral infections concluded that interferon gamma was effective when combined with antimony compounds for treatment failures in visceral leishmaniasis and could enhance the response to initial therapy in untreated patients. However, the response to adjunctive interferon gamma was limited in patients with a high degree of resistance to antimony compounds.[2] For cutaneous infections, intralesional interferon gamma has been shown to be effective[3] but less so than intralesional antimony compounds.[4] Subcutaneous interferon gamma (with antimony given intravenously) was no more effective than antimony alone when given as a short course over 10 days.[5] However, encouraging responses have been reported in patients who have failed to respond to antimony compounds alone.[6]

1. Murray HW. Interferon-gamma and host antimicrobial defense: current and future clinical applications. *Am J Med* 1994; **97:** 459–67.
2. Sundar S, *et al.* Response to interferon-γ plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; **176:** 1117–19.
3. Harms G, *et al.* Effects of intradermal gamma-interferon in cutaneous leishmaniasis. *Lancet* 1989; **i:** 1287–92.
4. Harms G, *et al.* A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-γ in the local treatment of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1991; **85:** 214–16.
5. Arana BA, *et al.* Efficacy of a short course (10 days) of high-dose meglumine antimonate with or without interferon-γ in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis* 1994; **18:** 381–4.
6. Falcoff E, *et al.* Clinical healing of antimony-resistant cutaneous or mucocutaneous leishmaniasis following the combined administration of interferon-γ and pentavalent antimonial compounds. *Trans R Soc Trop Med Hyg* 1994; **88:** 95–7.

Osteopetrosis. Interferon gamma has been tried in the treatment of malignant osteopetrosis (p.1509). A study[1] in 14 patients found that interferon gamma-1b increased bone resorption. In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

1. Key LL, *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995; **332:** 1594–9.

Skin disorders. Interferons have been tried in skin disorders in which IgE levels are raised. Subcutaneous interferon gamma improved *eczema* and reduced serum-IgE concentration in one patient, but the condition gradually returned within a week of stopping treatment.[1] In two studies[2,3] subcutaneous interferon gamma given to patients with severe atopic dermatitis and raised serum-IgE concentrations resulted in improvement of the skin condition; IgE concentrations were reduced in one study[2] but remained high in the other.[3] Subcutaneous interferon alfa, however, was unsuccessful in 2 patients with very severe atopic dermatitis; serum-IgE concentrations and severity of the skin condition remained unaffected.[4] Interferon alfa has been tried in subacute *cutaneous lupus erythematosus*[5,6] and *discoid lupus erythematosus*.[6] Although marked improvement generally occurred, the condition tended to recur within several weeks of stopping treatment. For discussion of the conventional treatment of eczema, see p.1579 and of lupus erythematosus, see Systemic Lupus Erythematosus, p.1513.

There have been reports[7,8] of the successful use of interferon alfa to control the symptoms of *urticaria* associated with mastocytosis (p.1138).

Interferons have also been proposed for antifibrotic therapy in the management of diffuse *scleroderma* (see p.1817). A multicentre study of interferon gamma in scleroderma[9] found that cutaneous symptoms might be improved but that treatment was associated with an unacceptable incidence of adverse effects. Interferon gamma has also been tried in *eosinophilic pustular folliculitis*.[10]

Interferons have also been used for the treatment of warts (see under Interferon Alfa, p.891).

1. Souillet G, *et al.* Alpha-interferon treatment of patient with hyper IgE syndrome. *Lancet* 1989; **i:** 1384.
2. Reinhold U, *et al.* Recombinant interferon-γ in severe atopic dermatitis. *Lancet* 1990; **335:** 1282.
3. Boguniewicz M, *et al.* Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990; **88:** 365–70.
4. MacKie RM. Interferon-α for atopic dermatitis. *Lancet* 1990; **335:** 1282–3.
5. Nicolas J-F, Thivolet J. Interferon alfa therapy in severe unresponsive subacute cutaneous lupus erythematosus. *N Engl J Med* 1989; **321:** 1550–1.
6. Thivolet J, *et al.* Recombinant interferon α2a is effective in the treatment of discoid and subacute cutaneous lupus erythematosus. *Br J Dermatol* 1990; **122:** 405–9.
7. Kolde G, *et al.* Treatment of urticaria pigmentosa using interferon alpha. *Br J Dermatol* 1995; **133:** 91–4.
8. Lippert U, Henz BM. Long-term effect of interferon alpha treatment in mastocytosis. *Br J Dermatol* 1996; **134:** 1164–5.
9. Polisson RP, *et al.* A multicenter trial of recombinant human interferon gamma in patients with systemic sclerosis: effects on cutaneous fibrosis and interleukin 2 receptor levels. *J Rheumatol* 1996; **23:** 654–8.
10. Fushimi M, *et al.* Eosinophilic pustular folliculitis effectively treated with recombinant interferon-γ: suppression of mRNA expression of interleukin 5 in peripheral blood mononuclear cells. *Br J Dermatol* 1996; **134:** 766–72.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Imufor†; Imukin; ***Austral.:*** Imukin; ***Austria:*** Imukin; ***Belg.:*** Immukine; ***Cz.:*** Imukin; ***Denm.:*** Imukin; ***Fin.:*** Imukin; ***Fr.:*** Imukin; ***Ger.:*** Imukin; ***Gr.:*** Imukin; ***Hong Kong:*** Immukin; ***Irl.:*** Immukin; ***Ital.:*** Gammakine†; Imukin; ***Jpn:*** Biogamma; Ogamma†; ***Neth.:*** Immukine; ***Norw.:*** Imukin; ***NZ:*** Imukin; ***Port.:*** Imukin; ***Spain:*** Imukin; ***Swed.:*** Imukin; ***Switz.:*** Imukin; ***UK:*** Immukin; ***USA:*** Actimmune.

Lamivudine *(BAN, USAN, rINN)*

3TC; (−)-2′-Deoxy-3′-thiacytidine; GR-109714X; Lamivudiini; Lamivudin; Lamivudina; Lamivudinum; Lamiwudyna; Lavmivudin. (−)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

Ламивудин

$C_8H_{11}N_3O_3S$ = 229.3.

CAS — 131086-21-0; 134678-17-4.

ATC — J05AF05.

ATC Vet — QJ05AF05.

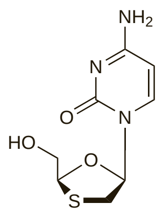

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Lamivudine). A white or almost white powder. It exhibits polymorphism. Soluble in water, slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Lamivudine). A white to off-white solid. Soluble in water. Protect from light.

Adverse Effects

Adverse effects commonly associated with lamivudine either as monotherapy or with other antiretrovirals for the treatment of HIV include abdominal pain, nausea, vomiting, diarrhoea, headache, fever, rash, alopecia, malaise, insomnia, cough, nasal symptoms, arthralgia, and musculoskeletal pain. There have also been reports of pancreatitis, anaemia, neutropenia, and thrombocytopenia. Increases in liver enzymes and serum amylase may occur. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been reported during treatment with nucleoside reverse transcriptase inhibitors.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lamivudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lamivudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Patients taking a lower dose of lamivudine for the treatment of chronic hepatitis B often have abdominal discomfort and pain, diarrhoea, fatigue, headache, nausea, malaise, respiratory-tract infections, and vomiting. The most frequently reported laboratory abnormalities are elevated creatine phosphokinase, increases in serum lipase, and raised liver enzymes, in particular alanine aminotransferase. There have been rare reports of lactic acidosis, pancreatitis, and muscle disorders such as cramps, myalgia, and rhabdomyolysis.

Effects on the blood. Although anaemia associated with lamivudine usually occurs when it is used with zidovudine, there has been a report[1] of severe anaemia in a 62-year-old HIV-infected man given lamivudine alone.

1. Weitzel T, *et al.* Severe anaemia as a newly recognized side-effect caused by lamivudine. *AIDS* 1999; **13:** 2309–11.

Effects on the hair. Hair loss was associated with lamivudine treatment in 5 patients.[1]

1. Fong IW. Hair loss associated with lamivudine. *Lancet* 1994; **344:** 1702.

Effects on the nervous system. Exacerbation of peripheral neuropathy has been reported in a patient after substitution of lamivudine for zalcitabine.[1]

1. Cupler EJ, Dalakas MC. Exacerbation of peripheral neuropathy by lamivudine. *Lancet* 1995; **345:** 460–1.

Hypersensitivity. Angioedema, urticaria, and anaphylactoid reaction occurred in a patient 30 minutes after receiving the first dose of lamivudine.[1]

1. Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. *Lancet* 1996; **348:** 1519.

Precautions

Lamivudine therapy should be stopped in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded.

Treatment with lamivudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, or metabolic or lactic acidosis of unknown aetiology. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Patients co-infected with HIV and chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In patients with chronic hepatitis B, there is a risk of rebound hepatitis when lamivudine is stopped, and liver function should be monitored in such patients. The possibility of HIV infection should be excluded before beginning lamivudine therapy for hepatitis B, since the lower doses used to treat the latter may permit the development of lamivudine-resistant strains of HIV.

Dosage reduction may be necessary in patients with impaired renal function.

Interactions

The renal excretion of lamivudine may be inhibited by other drugs mainly eliminated by active renal secretion, for example trimethoprim. Usual prophylactic doses of trimethoprim are unlikely to necessitate reductions in lamivudine dosage unless the patient has renal impairment, but the co-administration of lamivudine with the high doses of trimethoprim (as co-trimoxazole) used in pneumocystis pneumonia and toxoplasmosis should be avoided. Although there is usually no clinically significant interaction with zidovudine, severe anaemia has occasionally been reported in patients given lamivudine with zidovudine (see Zidovudine, Interactions, p.915). Lamivudine may antagonise the antiviral action of zalcitabine and the two drugs should not be used together. Once daily triple nucleoside regimens of lamivudine and tenofovir with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided.

Phenylpropanolamine. For a possible interaction between phenylpropanolamine and antiretrovirals, see Stavudine, p.907.

Antiviral Action

Lamivudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Lamivudine is also active against hepatitis B virus. Resistance to lamivudine has been reported in isolates of HIV and hepatitis B virus.

Pharmacokinetics

Lamivudine is rapidly absorbed after oral doses and peak plasma concentrations are achieved in about 1 hour. Absorption is delayed, but not reduced, by ingestion with food. Bioavailability is between 80 and 87%. Binding to plasma protein is reported to be up to 36%. Lamivudine crosses the blood-brain barrier with a ratio of CSF to serum concentrations of about 0.12. It crosses the placenta and is distributed into breast milk.

Lamivudine is metabolised intracellularly to the active antiviral triphosphate. Hepatic metabolism is low and it is cleared mainly unchanged by active renal excretion. An elimination half-life of 5 to 7 hours has been reported after a single dose.

◊ References.

1. Mueller BU, *et al.* Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1998; **42:** 3187–92.
2. Johnson MA, *et al.* Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 1999; **36:** 41–66.
3. Bruno R, *et al.* Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily administration in patients with HIV. *Clin Pharmacokinet* 2001; **40:** 695–700.
4. Asari A, *et al.* Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. *Br J Clin Pharmacol* 2007; **64:** 738–44.
5. Burger DM, *et al.* Age-dependent pharmacokinetics of lamivudine in HIV-infected children. *Clin Pharmacol Ther* 2007; **81:** 517–20.
6. Tremoulet AH, *et al.* Pediatric AIDS Clinical Trials Group. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; **51:** 4297–4302.

Uses and Administration

Lamivudine is a nucleoside reverse transcriptase inhibitor structurally related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS, (p.856) and chronic hepatitis B infection (p.851). Viral resistance emerges rapidly when lamivudine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

For HIV infection, the dose of lamivudine for adults is 300 mg by mouth daily as a single dose or in two divided doses.

For chronic hepatitis B, the adult dose is 100 mg once daily by mouth. In patients with concomitant HIV and hepatitis B infection the dosage regimen appropriate for HIV should be used.

For details of doses in infants, children, and adolescents see below.

Reduction of dosage is recommended for patients with renal impairment (see below).

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing lamivudine in combination with zidovudine or abacavir and with abacavir plus zidovudine are available in some countries.

◊ Reviews.

1. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.

Administration in children. For the treatment of HIV infection in infants and children lamivudine is given orally either as tablets or a solution, together with other antiretroviral drugs. Doses are based on body-weight:

- in infants and children over 3 months of age and weighing less than 14 kg or in those unable to swallow tablets the oral solution may be given in a dose of 4 mg/kg twice daily to a maximum daily dose of 300 mg
- in children weighing 14 to 21 kg the tablet formulation may be given in a dose of 75 mg twice daily
- in children weighing 21 to 30 kg the tablet formulation may be given in a dose of 75 mg in the morning and 150 mg at night
- in children weighing over 30 kg the tablet formulation may be given in a dose of 150 mg twice daily

Dosage of lamivudine should be reduced in HIV-infected patients (at least 3 months of age and weighing less than 30 kg) with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute):

- CC 30 to 49 mL/minute: 4 mg/kg for the first dose then 4 mg/kg once daily
- CC 15 to 29 mL/minute: 4 mg/kg for the first dose then 2.6 mg/kg once daily

- CC 5 to 14 mL/minute: 4 mg/kg for the first dose then 1.3 mg/kg once daily
- CC less than 5 mL/minute: 1.3 mg/kg for the first dose then 0.7 mg/kg once daily

For the treatment of chronic hepatitis B infection in children and adolescents aged between 2 and 17 years, US licensed product information recommends an oral dose of lamivudine of 3 mg/kg once daily to a maximum daily dose of 100 mg. Dosage reduction would need to be considered in those with renal impairment. UK licensed product information does not recommend the use of lamivudine for the treatment of chronic hepatitis B in those under 17 years of age.

Administration in renal impairment. Dosage of lamivudine should be reduced in patients with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute).

adults: HIV infection:

- CC 30 to 49 mL/minute: 150 mg for the first dose then 150 mg once daily
- CC 15 to 29 mL/minute: 150 mg for the first dose then 100 mg once daily
- CC 5 to 14 mL/minute: 150 mg for the first dose then 50 mg once daily
- CC less than 5 mL/minute: 50 mg for the first dose then 25 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

adults: chronic hepatitis B infection:

- CC 30 to 49 mL/minute: 100 mg for the first dose then 50 mg once daily
- CC 15 to 29 mL/minute: 100 mg for the first dose then 25 mg once daily
- CC 5 to 14 mL/minute: 35 mg for the first dose then 15 mg once daily
- CC less than 5 mL/minute: 35 mg for the first dose then 10 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

children:

- see Administration in Children, above

Hepatitis. Lamivudine is one of the antivirals being used as an alternative to interferon alfa in the treatment of chronic hepatitis B (p.851).[1-3] In a preliminary study, lamivudine 100 or 300 mg daily reduced hepatitis B virus DNA to low or undetectable levels.[4] In a 1-year double-blind study involving about 350 patients with chronic hepatitis B, lamivudine 100 mg daily was associated with substantial histological improvement in many patients; a dose of 25 mg daily was less effective.[5] Relapses have been reported once treatment with lamivudine is stopped, and a case of reactivation of hepatitis B infection has been observed.[6] Lamivudine may also be effective in preventing re-infection with hepatitis B in patients during chemotherapy[7-9] and in those who have had liver transplants,[10,11] and beneficial responses have been seen in transplant patients with acute hepatitis B infection treated with lamivudine 100 mg daily for prolonged periods.[12]

1. Dienstag JL, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341:** 1256–63.
2. Hagmeyer KO, Pan Y-Y. Role of lamivudine in the treatment of chronic hepatitis B virus infection. *Ann Pharmacother* 1999; **33:** 1104–12.
3. Jonas MM, *et al.* Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346:** 1706–13. Correction. *ibid.*; **347:** 955.
4. Dienstag JL, *et al.* A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995; **333:** 1657–61.
5. Lai C-L, *et al.* A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998; **339:** 61–8.
6. Honkoop P, *et al.* Hepatitis B reactivation after lamivudine. *Lancet* 1995; **346:** 1156–7.
7. Yeo W, *et al.* Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; **22:** 927–34.
8. Idilman R. Lamivudine prophylaxis in HBV carriers with haemato-oncological malignancies who receive chemotherapy. *J Antimicrob Chemother* 2005; **55:** 828–31.
9. Loomba R, *et al.* Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148:** 519–28.
10. Grellier L, *et al.* Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996; **348:** 1212–15. Correction. *ibid.* 1997; **349:** 364.
11. Perrillo RP, *et al.* A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; **33:** 424–32.
12. Andreone P, *et al.* Lamivudine treatment for acute hepatitis B after liver transplantation. *J Hepatol* 1998; **29:** 985–9.

HIV infection and AIDS. Lamivudine is a potent inhibitor of HIV-1 and HIV-2 *in vitro*, including variants resistant to zidovudine.[1] Resistance emerges rapidly when lamivudine is given alone to patients with HIV infections,[2] although sustained responses have been reported despite the emergence of resistance.[3] Combination therapy with lamivudine delays, and may even reverse, the emergence of zidovudine resistance and produces a sustained synergistic antiretroviral effect,[4] but HIV strains resistant to both lamivudine and zidovudine may arise.[5] As discussed on p.856, combination therapy, typically with two nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or an HIV-protease inhibitor, is standard therapy for HIV infection. Treatment with lamivudine plus zidovudine has produced better responses than either drug alone in antiretroviral-naive patients,[6,7] and has produced additional responses in antiretroviral-experienced patients,[8,9] with little additional toxicity. The addition of lamivudine to existing antiretroviral therapy was reported to slow the progression of the disease and improve survival,[10] and treatment with lamivudine, indinavir, and nevirapine produced beneficial responses in patients who had previously failed on combined nucleoside analogue therapy.[11] Clinically useful CNS concentrations of lamivudine were achieved in patients with HIV infection given combination therapy with lamivudine and zidovudine or stavudine.[12]

Lamivudine is also used in prophylactic regimens after occupational exposure to HIV infection (see p.858) and has been tried for reducing vertical transmission from mother to neonate.[13,14]

1. Anonymous. Lamivudine: impressive benefits in combination with zidovudine. *WHO Drug Inf* 1996; **10:** 5–7.
2. Wainberg MA, *et al.* Development of HIV-1 resistance to (–)2′-deoxy-3′-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 1995; **9:** 351–7.
3. Ingrand D, *et al.* Phase I/II study of 3TC (lamivudine) in HIV-positive, asymptomatic or mild AIDS-related complex patients: sustained reduction in viral markers. *AIDS* 1995; **9:** 1323–9.
4. Larder BA, *et al.* Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 1995; **269:** 696–9.
5. Miller V, *et al.* Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapeutic failure. *J Infect Dis* 1998; **177:** 1521–32.
6. Eron JJ, *et al.* Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *N Engl J Med* 1995; **333:** 1662–9.
7. Katlama C, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:** 118–25.
8. Staszewski S, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:** 111–17.
9. Bartlett JA, *et al.* Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 161–72.
10. CAESAR Coordinating Committee. Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. *Lancet* 1997; **349:** 1413–21.
11. Harris M, *et al.* A pilot study of nevirapine, indinavir, and lamivudine among patients with advanced human immunodeficiency virus disease who have had failure of combination nucleoside therapy. *J Infect Dis* 1998; **177:** 1514–20.
12. Foudraine NA, *et al.* Cerebrospinal-fluid HIV-1 RNA and drug concentrations after treatment with lamivudine plus zidovudine or stavudine. *Lancet* 1998; **351:** 1547–51.
13. Mandelbrot L, *et al.* Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; **285:** 2083–93.
14. The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; **359:** 1178–86.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: 3TC; Amilitrap; Birvac†; Ganvirel; Heptodine; Hivirux†; Imunoxa; Kess; Lamibergen; Lamilea; Oralmuv; Ultraviral; Vuclodir; Zeffix†; ***Austral.:*** 3TC; Zeffix; ***Austria:*** Epivir; Zeffix; ***Belg.:*** Epivir; Zeffix; ***Braz.:*** Epivir; Lami; Vudirax; Zeffix†; ***Canad.:*** 3TC; Heptovir; ***Chile:*** 3TC/Epivir; ***Cz.:*** Epivir; Zeffix; ***Denm.:*** Epivir; Zeffix; ***Fin.:*** Epivir; Zeffix; ***Fr.:*** Epivir; Zeffix; ***Ger.:*** Epivir; Kivexa; Zeffix; ***Gr.:*** Epivir; Zeffix; ***Hong Kong:*** 3TC; Zeffix; ***Hung.:*** Epivir; Zeffix; ***India:*** Ladiwin; Lamda; Lamidac; Lamirex†; Lamivir; ***Indon.:*** 3TC; 3TC-HBV; ***Irl.:*** Epivir; Zeffix; ***Israel:*** Epivir; Zeffix; ***Ital.:*** Epivir; Zeffix; ***Jpn:*** Epivir†; ***Malaysia:*** 3TC; Zeffix; ***Mex.:*** 3TC; ***Neth.:*** Epivir; Zeffix; ***Norw.:*** Epivir; Zeffix; ***NZ:*** 3TC; Zeffix; ***Philipp.:*** Zeffix; ***Pol.:*** Epivir; Zeffix; ***Port.:*** Epivir; Zeffix; ***Rus.:*** Epivir (Эпивир); Zeffix (Зеффикс); ***S.Afr.:*** 3TC; ***Singapore:*** Epivir; Zeffix; ***Spain:*** Epivir; Zeffix; ***Swed.:*** Epivir; Zeffix; ***Switz.:*** 3TC; Zeffix; ***Thai.:*** Epivir; Zeffix; ***Turk.:*** Epivir; Zeffix; ***UK:*** Epivir; Zeffix; ***USA:*** Epivir; ***Venez.:*** Epivir; Heptodine†; Lamivir.

Multi-ingredient: ***Arg.:*** 3TC Complex; 3TC/AZT; Ganvirel Duo; Hivirux Complex†; Imunoxa Complex; Kess Complex; Kivexa; Muvidina; Tricivir; Trivudin; Ultraviral Duo; Zetavudin; ***Austral.:*** Combivir; Kivexa; Trizivir; ***Austria:*** Combivir; Trizivir; ***Belg.:*** Combivir; Kivexa; Trizivir; ***Braz.:*** Biovir; Duovir†; Vir-Complex†; Zidolam; ***Canad.:*** Combivir; Kivexa; Trizivir; ***Chile:*** Combivir; Kivexa; Tricivir; ***Cz.:*** Combivir; Kivexa; Trizivir; ***Denm.:*** Combivir; Kivexa; Trizivir; ***Fin.:*** Combivir; Kivexa; Trizivir; ***Fr.:*** Combivir; Kivexa; Trizivir; ***Ger.:*** Combivir; Trizivir; ***Gr.:*** Combivir; Kivexa; Trizivir; ***Hong Kong:*** Combivir; Trizivir; ***Hung.:*** Combivir; Kivexa; Trizivir; ***India:*** Combirex†; Duovir; Duovir N; Lamda-Z; Lamivir S; Lamuzid; Odivir Kit; Triomune; ***Irl.:*** Combivir; Kivexa; Trizivir; ***Israel:*** Combivir; Trizivir; ***Ital.:*** Combivir; Kivexa; Trizivir; ***Malaysia:*** Combivir; ***Mex.:*** Combivir; Kivexa; Trizivir; ***Neth.:*** Combivir; Kivexa; Trizivir; ***Norw.:*** Combivir; Kivexa; Trizivir; ***NZ:*** Combivir; Kivexa; Trizivir; ***Philipp.:*** Combivir; ***Pol.:*** Combivir; Kivexa; Trizivir; ***Port.:*** Combivir; Kivexa; Trizivir; ***Rus.:*** Combivir (Комбивир); Trizivir (Тризивир); ***S.Afr.:*** Combivir; Duovir; Lamzid; Retrovir/3TC Post-HIV Exposure†; Triomune; Trizivar; ***Singapore:*** Combivir; Trizivir†; ***Spain:*** Combivir; Kivexa; Trizivir; ***Swed.:*** Combivir; Kivexa; Trizivir; ***Switz.:*** Combivir; Trizivir; ***Thai.:*** Combid; ***Turk.:*** Combivir; ***UK:*** Combivir; Kivexa; Trizivir; ***USA:*** Combivir; Epzicom; Trizivir; ***Venez.:*** Combivir; Duovir; Triomune; Trizivir.

Lopinavir *(BAN, USAN, rINN)*

A-157378.0; ABT-378; Lopinaviiri; Lopinavirum. (αS)-Tetrahydro-N-((αS)-α-{(2S,3S)-2-hydroxy-4-phenyl-3-[2-(2,6-xylyloxy)acetamido]butyl}phenethyl)-α-isopropyl-2-oxo-1(2H)-pyrimidineacetamide.

Лопинавир

$C_{37}H_{48}N_4O_5$ = 628.8.

CAS — 192725-17-0.

ATC — J05AE06.

ATC Vet — QJ05AE06.

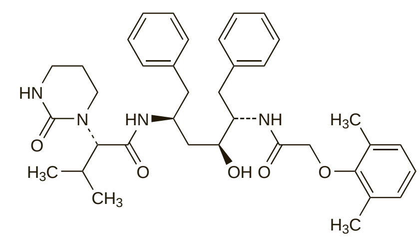

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing lopinavir (formulated with ritonavir) is diarrhoea of mild to moderate severity. Pancreatitis has been seen in patients receiving lopinavir, including those who developed marked triglyceride elevations; in some cases fatalities have occurred. Other commonly reported adverse effects include asthenia, headache, insomnia, pain, paraesthesia, gastrointestinal disturbances, acne, and rash. Abnormal laboratory test results associated with lopinavir-containing regimens include increases in serum cholesterol and triglycerides and raised liver enzymes.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including lopinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including lopinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during treatment with ritonavir-boosted lopinavir. Such therapy should be stopped if symptoms of pancreatitis occur.

The oral solution (*Kaletra*, *Abbott*) has a high content of alcohol and propylene glycol, present as excipients, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p.2374.

Pregnancy. Licensed product information notes that in *rats* given toxic doses of ritonavir-boosted lopinavir, there was early resorption, decreased fetal viability and body weight, and an increased incidence of skeletal variation and delayed skeletal ossification in the offspring.

Interactions

Lopinavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It is formulated with low-dose ritonavir, which inhibits this enzyme and thus increases exposure. The combination is an inhibitor of CYP3A4 and increases plasma concentration of drugs mainly metabolised by this isoenzyme. It has also been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 isoenzymes and by glucuronidation. Drugs that strongly induce CYP3A4 may result in decreased plasma concentrations of the combination.

Ritonavir-boosted lopinavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of lopinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. UK licensed product information contra-indicates the use of vardenafil and amiodarone with ritonavir-boosted lopinavir.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Lopinavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Lopinavir is rapidly absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring after 4 hours. Bioavailability is enhanced when given with a high fat meal. Lopinavir is reported to be 98 to 99% bound to serum proteins. Lopinavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A4; 13 metabolites have been identified with some, such as 4-oxylopinavir and 4-hydroxylopinavir, having antiviral activity. Lopinavir is predominantly excreted in faeces and to a smaller extent in the urine; unchanged lopinavir accounts for about 2.2% of a dose excreted in the urine and 19.8% in the faeces. After multiple dosing, less than 3% of the absorbed lopinavir dose is excreted unchanged in the urine. The terminal elimination half-life of lopinavir is reported to be about 5 to 6 hours.

◊ References.

1. Jullien V, *et al.* Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother* 2006; **50:** 3548–55.

Uses and Administration

Lopinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is formulated with low-dose ritonavir, which acts as a pharmacokinetic enhancer. The combination is used in the treatment of HIV infection and AIDS (p.856). Ritonavir-boosted lopinavir is also recommended for HIV postexposure prophylaxis (p.858). Viral resistance emerges rapidly when ritonavir-boosted lopinavir is used alone, and it is therefore used with other antiretrovirals.

The dose in treatment-naive and -experienced adults is lopinavir 400 mg (with ritonavir 100 mg) twice daily. Alternatively, treatment-naive patients may take a once-daily dose of lopinavir 800 mg (with ritonavir 200 mg).

US licensed product information recommends that if the tablets are given in a treatment regimen with either *amprenavir, fosamprenavir, nelfinavir, efavirenz*, or *nevirapine* in treatment-experienced patients consideration be given to increasing the dose of lopinavir to 600 mg (with ritonavir 150 mg) twice daily. For patients taking the oral solution in such regimens the dose should be increased to lopinavir 533 mg (with ritonavir 133 mg) twice daily.

Lopinavir film-coated tablets may be taken with or without food; the soft capsules and solution should be taken with food.

For details of doses in children, see below.

◊ Reviews.

1. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2006; **66:** 1275–99.

Administration in children. For the treatment of HIV infection in children, ritonavir-boosted lopinavir is given daily with other antiretroviral drugs. The US licensed product information permits use in infants as young as 14 days old, whereas in the UK the age is 2 years. The dose given should not exceed the maximum adult dose (see above).

In the UK the use of the oral solution is preferred to the soft capsules as a more accurate dose may be given. Doses are based on body-surface.

- In children 2 years of age or more the recommended dose of the *oral solution* is lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily with food. The dose should be increased to 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily with food when given with *efavirenz* or *nevirapine*
- The recommended dose of the *oral soft capsules* in children is according to body-surface as follows:
  - 0.40 to 0.75 m^2: lopinavir 133.3 mg (with ritonavir 33.3 mg) twice daily
  - 0.80 to 1.3 m^2: lopinavir 266.6 mg (with ritonavir 66.6 mg) twice daily
  - 1.4 to 1.75 m^2: lopinavir 400 mg (with ritonavir 100 mg) twice daily

In the USA the dose is based on body-weight or body-surface as follows:

- given without interacting antiretrovirals
  - 14 days to 6 months of age: lopinavir 16 mg/kg (with ritonavir 4 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 6 months or older and less than 15 kg: lopinavir 12 mg/kg (with ritonavir 3 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - 15 to 40 kg: lopinavir 10 mg/kg (with ritonavir 2.5 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - over 40 kg: normal adult dose
- given in a treatment regimen with either *amprenavir, fosamprenavir, efavirenz, nelfinavir,* or *nevirapine* (requiring the dose of lopinavir/ritonavir to be increased):
  - 6 months or older and less than 15 kg: lopinavir 13 mg/kg (with ritonavir 3.25 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 15 to 45 kg: lopinavir 11 mg/kg (with ritonavir 2.75 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - over 45 kg: as for adults, above

SARS. In a preliminary open study[1] 41 patients with probable SARS were given ritonavir-boosted lopinavir as well as the local standard treatment of ribavirin and corticosteroids. At 21 days there was improved outcome with reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

1. Chu CM, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Kaletra; ***Austral.:*** Kaletra; ***Austria:*** Kaletra; ***Belg.:*** Kaletra; ***Braz.:*** Kaletra; ***Canad.:*** Kaletra; ***Chile:*** Kaletra; ***Cz.:*** Kaletra; ***Denm.:*** Kaletra; ***Fin.:*** Kaletra; ***Fr.:*** Kaletra; ***Ger.:*** Kaletra; ***Gr.:*** Kaletra; ***Hong Kong:*** Kaletra; ***Hung.:*** Kaletra; ***India:*** Ritomax-L; ***Israel:*** Kaletra; ***Ital.:*** Kaletra; ***Malaysia:*** Kaletra; ***Mex.:*** Kaletra; ***Neth.:*** Kaletra; ***Norw.:*** Kaletra; ***NZ:*** Kaletra; ***Pol.:*** Kaletra; ***Port.:*** Kaletra; ***Rus.:*** Kaletra (Калетра); ***S.Afr.:*** Kaletra; ***Singapore:*** Kaletra; ***Spain:*** Kaletra; ***Swed.:*** Kaletra; ***Switz.:*** Kaletra; ***Thai.:*** Kaletra; ***Turk.:*** Kaletra; ***UK:*** Kaletra; ***USA:*** Kaletra; ***Venez.:*** Kaletra.

Maraviroc *(USAN, rINN)*

Maravirocum; UK-427857. 4,4-Difluoro-*N*-((1*S*)-3-{(1*R*,3*s*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl}-1-phenylpropyl)cyclohexanecarboxamide.

Маравирок

$C_{29}H_{41}F_2N_5O$ = 513.7.

CAS — 376348-65-1.

ATC — J05AX09.

ATC Vet — QJ05AX09.

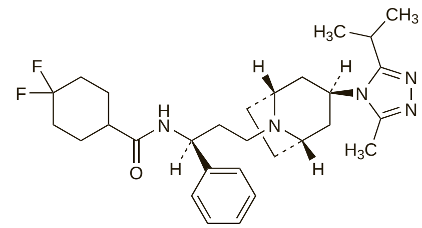

Adverse Effects and Precautions

On the basis of limited data, maraviroc appears to be well tolerated; non-specific adverse effects associated with maraviroc-based regimens include asthenia, cough and upper respiratory-tract infections, dizziness, abdominal pain and distension, constipation, diarrhoea, dyspepsia, nausea, vomiting, fever, headache, insomnia, somnolence, muscle spasms and back pain, pruritus, and rash. Less frequently reported adverse effects include osteonecrosis and cardiovascular effects such as myocardial ischaemia and myocardial infarction; cardiac adverse effects were reported mainly for patients with pre-existing cardiac disease or risk factors.

Hepatotoxicity has occurred; raised liver enzyme values and bilirubin have also been reported and caution is advised in patients with pre-existing liver dysfunction or co-infection with hepatitis B or C. Although renal clearance normally accounts for only a small portion of the dose, maraviroc should be used with caution in patients with renal impairment (creatinine clearance less than 80 mL/minute) who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 as concentrations of maraviroc may be significantly increased.

Interactions

Maraviroc is a substrate for the cytochrome P450 isoenzyme CYP3A4 and for P-glycoprotein, and may therefore have a number of clinically significant interactions. Inhibitors of CYP3A4, such as HIV-protease inhibitors (other than tipranavir), increase the serum concentration of maraviroc. Inducers of CYP3A4 such as efavirenz may decrease serum maraviroc concentrations. No clinically significant interaction is expected between maraviroc and NRTIs, nevirapine, or boosted fosamprenavir or tipranavir.

Non-antiretroviral medications that significantly alter maraviroc metabolism include the CYP3A4 inhibitors ketoconazole, itraconazole, clarithromycin, and nefazodone and the CYP3A4 inducers rifampicin and St John's wort. Maraviroc does not appear to cause clinically significant changes in concentrations of other medications.

Antiviral Action

Maraviroc is an antagonist of the CCR5 chemokine receptor. During infection, HIV binds to the CD4 receptor on the surface of host cells, and then interacts with one of two co-receptors, CCR5 or CXCR4, to allow cell membrane fusion and entry to the cell. By binding to CCR5, maraviroc inhibits this process and prevents strains of HIV-1 that use CCR5 (CCR5-tropic viruses), which appear to be more common in early infection, from entering the cell. It is not active against CXCR4-tropic strains or those with dual or mixed tropism.

Pharmacokinetics
Maraviroc is absorbed after oral doses, and peak concentrations occur in 0.5 to 4 hours. There is considerable interindividual variation in the pharmacokinetics. It is 76% bound to plasma proteins. Maraviroc is metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to inactive metabolites. It is excreted in both urine (20%) and faeces (76%) as unchanged drug and metabolites.

Uses and Administration
Maraviroc is an antagonist of the CCR5 chemokine receptor (see Antiviral Action, above). It is used, with other antiretrovirals, for the treatment of HIV infection and AIDS (p.856) in treatment-experienced adult patients with exclusively CCR5-tropic HIV-1 infection. Co-receptor tropism should be determined by specific testing before maraviroc is used.

Maraviroc is given orally in a dose of 300 mg twice daily, although dose adjustments may be needed depending on interactions with other medicines.

- For patients also taking CYP3A4 inhibitors such as HIV-protease inhibitors (other than fosamprenavir or tipranavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin, the recommended dose is 150 mg twice daily.
- In those whose therapy includes CYP3A4 inducers (without a CYP3A4 inhibitor) such as efavirenz, rifampicin, carbamazepine, phenobarbital, and phenytoin, the recommended dose is 600 mg twice daily.

Patients taking other antiretrovirals (including fosamprenavir or tipranavir), or other drugs, may be given the standard dose of 300 mg twice daily.

◊ References.

1. Carter NJ, Keating GM. Maraviroc. *Drugs* 2007; **67:** 2277–88.
2. Vandekerckhove L, *et al.* Maraviroc: integration of a new antiretroviral drug class into clinical practice. *J Antimicrob Chemother* 2008; **61:** 1187–90.

Administration in renal impairment. UK licensed product information recommends that the oral dose of maraviroc be adjusted in patients with renal impairment who are also taking potent inhibitors of cytochrome P450 isoenzyme CYP3A4. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- For patients also taking CYP3A4 inhibitors such as ritonavir-boosted HIV-protease inhibitors (other than fosamprenavir, tipranavir, or saquinavir), ketoconazole, itraconazole, clarithromycin, and telithromycin and who have a CC less than 80 mL/minute: 150 mg every 24 hours
- For patients also taking ritonavir-boosted saquinavir:
  - CC 50 to 80 mL/minute: 150 mg every 24 hours
  - CC 30 to 49 mL/minute: 150 mg every 48 hours
  - CC 29 mL/minute or less: 150 mg every 72 hours

No adjustment is necessary when maraviroc is given without potent CYP3A4 inhibitors or with fosamprenavir or tipranavir

Preparations
Proprietary Preparations (details are given in Part 3)

Canad.: Celsentri; ***Cz.:*** Celsentri; ***Fr.:*** Celsentri; ***UK:*** Celsentri; ***USA:*** Selzentry.

Moroxydine *(BAN, rINN)*
Moroksidiini; Moroxidin; Moroxidina; Moroxydinum.

Мороксидин

$C_6H_{13}N_5O$ = 171.2.

CAS — 3731-59-7.

ATC — J05AX01.

ATC Vet — QJ05AX01.

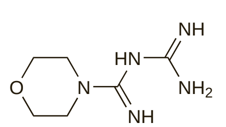

Moroxydine Hydrochloride *(BANM, rINNM)*
Abitilguanide Hydrochloride; ABOB; Hidrocloruro de moroxidina; Moroxydine, Chlorhydrate de; Moroxydini Hydrochloridum. 1-(Morpholinoformimidoyl)guanidine hydrochloride.

Мороксидина Гидрохлорид

$C_6H_{13}N_5O,HCl$ = 207.7.

CAS — 3160-91-6.

ATC — J05AX01.

ATC Vet — QJ05AX01.

Profile
Moroxydine hydrochloride has been given orally in the treatment of herpes simplex and varicella-zoster infections. It has also been used topically. It is included as an ingredient in preparations for the treatment of cold and influenza symptoms.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Virulex Forte; ***Mex.:*** Amgrip; Clorfriol†; Flepin X-3†; Friral†; Singril; Singrilen; ***S.Afr.:*** Corenza C; Virobis†.

Nelfinavir Mesilate *(BANM, rINNM)*
AG-1343 (nelfinavir or nelfinavir mesilate); Mesilato de nelfinavir; Nelfinavir, Mésilate de; Nelfinavir Mesylate *(USAN)*; Nelfinaviri Mesilas. 3*S*[2(2*S**,3*S**),3α,4aβ,8aβ]-*N*-(1,1-Dimethylethyl)decahydro-2-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl-3-isoquinolinecarboxamide monomethanesulphonate; (3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyldecahydro-2-[(2*R*,3*R*)-3-(3-hydroxy-*o*-toluamido)-2-hydroxy-4-(phenylthio)butyl]isoquinoline-3-carboxamide monomethanesulphonate.

Нелфинавира Мезилат

$C_{32}H_{45}N_3O_4S,CH_4O_3S$ = 663.9.

CAS — 159989-64-7 (nelfinavir); 159989-65-8 (nelfinavir mesilate).

ATC — J05AE04.

ATC Vet — QJ05AE04.

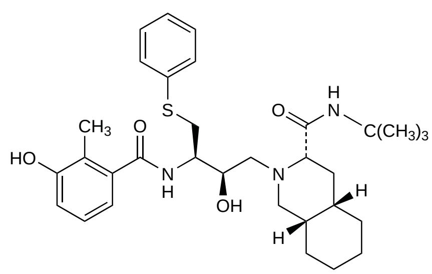

(nelfinavir)

NOTE. Nelfinavir should not be confused with nevirapine (below).

Pharmacopoeias. In *Int.*

Adverse Effects
The most common adverse effects associated with antiretroviral regimens containing nelfinavir are diarrhoea, flatulence, nausea, and rash. Raised liver enzymes and decreases in white blood cell counts have also been reported.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nelfinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including nelfinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Contamination. In June 2007, high levels of ethyl mesilate (ethyl methanesulfonate; EMS) were detected in European-made nelfinavir (*Viracept; Roche*). EMS may cause cancer in humans and has caused birth defects and cancer in *animals*. Nelfinavir was subsequently recalled from the European market in August 2007.[1] The manufacturer later identified and rectified the source of contamination and in September 2007 the EMEA recommended the lifting of the drug's suspension.[2] The US manufacturer (*Pfizer, USA*) notified doctors in September 2007 that EMS had been detected in nelfinavir manufactured in the USA but in much lower amounts than in European-made nelfinavir.[3] The FDA considered the risk of stopping nelfinavir therapy resulting from a drug recall to be greater than the risk of taking US-made nelfinavir but advised that children and pregnant women starting treatment with antiretrovirals for the first time not be given nelfinavir-containing regimens. Pregnant women taking nelfinavir as part of an HIV treatment regimen should be given alternative therapy. All other HIV-infected patients taking nelfinavir-containing regimens could continue to do so.

1. EMEA. European Medicines Agency agrees on action plan following the recall of Viracept and recommends suspension of the marketing authorisation (issued 21 June, 2007). Available at: http://www.emea.europa.eu/pdfs/general/direct/pr/27536707en.pdf (accessed 13/06/08).
2. EMEA. European medicines agency recommends lifing of suspension for Viracept (issued 20 September, 2007). Available at: http://www.emea.europa.eu/pdfs/general/direct/pr/41816807en.pdf (accessed 13/06/08).
3. Pfizer, USA. Viracept (nelfinavir mesylate) 250 mg, 625 mg tablets, and powder for oral suspension: important information for prescribers (issued 10 September 2007). Available at: http://www.fda.gov/medwatch/safety/2007/VIRACEPT_HCPLetter_9_10_07.pdf (accessed 13/06/08).

Precautions
Nelfinavir should be used with caution, and liver enzyme values monitored, in patients with moderate liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

For cautions concerning use in children and in pregnancy see under Contamination, above

Interactions
Nelfinavir is reported to be metabolised in part by cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that induce these isoenzymes may reduce the plasma concentration of nelfinavir. Conversely, when nelfinavir is given with drugs that inhibit CYP3A4 plasma concentrations, nelfinavir concentrations may be increased. It may also alter the pharmacokinetics of drugs metabolised by this isoenzyme system and possibly cause serious adverse effects.

Nelfinavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal motility agents (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Omeprazole, rifampicin, and St John's wort decrease the concentration of nelfinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action
Nelfinavir is a selective, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-pro-

tease inhibitors are given alone and therefore they are used with other antiretrovirals. Mechanisms of resistance to nelfinavir may differ sufficiently from those to other HIV-protease inhibitors to reduce the occurrence of cross-resistance between nelfinavir and other HIV-protease inhibitors. Cross-resistance between nelfinavir and NNRTIs is unlikely because they target different enzymes.

Pharmacokinetics

Nelfinavir is absorbed from the gastrointestinal tract and peak plasma concentrations occur in 2 to 4 hours. Absorption is enhanced when given with food. Nelfinavir is extensively bound to plasma proteins (more than 98%). It is metabolised by oxidation by cytochrome P450 isoenzymes including CYP3A4 and CYP2C19. The major oxidative metabolite has *in-vitro* antiviral activity equal to that of nelfinavir. In patients 13 years of age and older the plasma terminal half-life is 3.5 to 5 hours; in children 2 to 13 years of age, clearance is two to three times greater than in adults. Nelfinavir is excreted mainly in the faeces both as unchanged drug (22%) and as metabolites (78%). Only about 1 to 2% is excreted in the urine, mainly as unchanged drug.

Uses and Administration

Nelfinavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when nelfinavir is used alone, and it is therefore used with other antiretrovirals.

Nelfinavir is given orally as the mesilate, but doses are expressed in terms of the base. Nelfinavir mesilate 292 mg is equivalent to about 250 mg of nelfinavir. Nelfinavir is available as tablets and oral powder. The oral powder should not be taken with acidic foods or drinks as this may result in a bitter taste. Nelfinavir is given in an adult dose of 1.25 g twice daily or 0.75 g three times daily with food.

For details of doses in children, see below.

◊ Reviews.

1. Pai VB, Nahata MC. Nelfinavir mesylate: a protease inhibitor. *Ann Pharmacother* 1999; **33:** 325–39.
2. Perry CM, *et al.* Nelfinavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2209–44.

Administration in children. For the treatment of HIV infection in children nelfinavir is given orally with other antiretroviral drugs. The US licensed product information permits the use of nelfinavir in children 2 years of age and older, whereas UK licensed product information permits use from 3 years of age.

In the UK, the recommended dose of nelfinavir is 50 to 55 mg/kg twice daily or 25 to 30 mg/kg three times daily with food. In the USA, the recommended dose is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily with food.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Filosfil; Nalvir; Nelfilea; Retroinhi; Viracept†; ***Austral.:*** Viracept; ***Austria:*** Viracept; ***Belg.:*** Viracept; ***Braz.:*** Viracept; ***Canad.:*** Viracept; ***Chile:*** Viracept; ***Cz.:*** Viracept; ***Denm.:*** Viracept; ***Fin.:*** Viracept; ***Fr.:*** Viracept; ***Ger.:*** Viracept; ***Gr.:*** Viracept; ***Hong Kong:*** Viracept; ***Hung.:*** Viracept; ***India:*** Nelvir; ***Irl.:*** Viracept; ***Israel:*** Viracept; ***Ital.:*** Viracept; ***Jpn:*** Viracept; ***Mex.:*** Viracept; ***Neth.:*** Viracept; ***Norw.:*** Viracept; ***NZ:*** Viracept; ***Philipp.:*** Viracept; ***Pol.:*** Viracept; ***Port.:*** Viracept; ***S.Afr.:*** Viracept; ***Singapore:*** Viracept†; ***Spain:*** Viracept; ***Swed.:*** Viracept; ***Switz.:*** Viracept; ***Thai.:*** Viracept; ***UK:*** Viracept; ***USA:*** Viracept; ***Venez.:*** Nelvir; Viracept.

Nevirapine *(BAN, USAN, rINN)*

BI-RG-587; BIRG-0587; Nevirapiini; Nevirapiini, vedetön; Nevirapin; Nevirapin bezvodý; Nevirapin, vattenfritt; Nevirapina; Névirapine; Névirapine anhydre; Nevirapinum; Nevirapinum anhydricum; Newirapina bezwodna. 11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-e]-[1,4]diazepin-6-one.

Невирапин

$C_{15}H_{14}N_4O$ = 266.3.

CAS — 129618-40-2.

ATC — J05AG01.

ATC Vet — QJ05AG01.

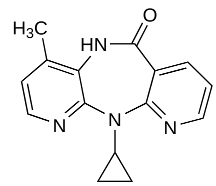

NOTE. Nevirapine should not be confused with nelfinavir (above).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Int. permits anhydrous or the hemihydrate.

Ph. Eur. 6.2 (Nevirapine, Anhydrous). A white or almost white powder. Practically insoluble in water; sparingly soluble or slightly soluble in dichloromethane; slightly soluble in methyl alcohol.

USP 31 (Nevirapine). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white, odourless to nearly odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. The hydrous form is also slightly insoluble in propylene glycol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing nevirapine is skin rash (usually mild to moderate, maculopapular, erythematous, and sometimes pruritic), generally occurring within 6 weeks of starting therapy. Severe and life-threatening skin reactions (with some fatalities) have occurred, including Stevens-Johnson syndrome and, more rarely, toxic epidermal necrolysis. Hypersensitivity reactions including angioedema, urticaria, and anaphylaxis have been reported. Rashes may occur alone or in the context of hypersensitivity reactions when they may be accompanied by other symptoms such as fever, arthralgia, myalgia, lymphadenopathy, eosinophilia, granulocytopenia, or renal dysfunction. Granulocytopenia occurs more commonly in children than in adults. Severe hepatotoxicity, including hepatitis and hepatic necrosis, occasionally fatal, has occurred and may be more prevalent in women and patients with high CD4+ cell counts at the start of treatment. Serious hepatotoxicity has also been reported in HIV-uninfected persons taking multiple doses of nevirapine for HIV postexposure-prophylaxis. Rhabdomyolysis has occurred in patients with skin and/or liver reactions. Other common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, drowsiness, fever, myalgia, and headache.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including nevirapine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including nevirapine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the liver. References.

1. Martinez E, *et al.* Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001; **15:** 1261–8.
2. Committee on Safety of Medicines/Medicines Control Agency. Nevirapine (Viramune): serious adverse reactions when used in HIV post exposure prophylaxis. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
3. Gonzalez de Requena D, *et al.* Liver toxicity caused by nevirapine. *AIDS* 2002; **16:** 290–1.
4. De Maat MM, *et al.* Hepatotoxicity following nevirapine-containing regimens in HIV-1-infected individuals. *Pharmacol Res* 2002; **46:** 295–300.
5. Patel SM, *et al.* Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr* 2004; **35:** 120–5.
6. Torti C, *et al.* BHCC Study Group. Analysis of severe hepatic events associated with nevirapine-containing regimens: CD4+ T-cell count and gender in hepatitis C seropositive and seronegative patients. *Drug Safety* 2007; **30:** 1161–9.

Effects on the skin. References.

1. Warren KJ, *et al.* Nevirapine-associated Stevens-Johnson syndrome. *Lancet* 1998; **351:** 567.
2. Wetterwald E, *et al.* Nevirapine-induced overlap Stevens-Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; **140:** 980–2.
3. Committee on Safety of Medicines/Medicines Control Agency. Nevirapine (Viramune): serious adverse reactions when used in HIV post exposure prophylaxis. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
4. Antinori A, *et al.* Female sex and the use of anti-allergic agents increase the risk of developing cutaneous rash associated with nevirapine therapy. *AIDS* 2001; **15:** 1579–81.
5. de Maat MM, *et al.* Incidence and risk factors for nevirapine-associated rash. *Eur J Clin Pharmacol* 2003; **59:** 457–62.
6. Manosuthi W, *et al.* Incidence and risk factors of nevirapine-associated skin rashes among HIV-infected patients with CD4 cell counts <250 cells/microL. *Int J STD AIDS* 2007; **18:** 782–6.
7. Wit FW, *et al.* Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis* 2008; **46:** 933–40.
8. Kiertiburanakul S, *et al.* Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. *Curr HIV Res* 2008; **6:** 65–9.

Precautions

Patients taking nevirapine should be closely monitored for adverse skin reactions and hepatotoxicity during the first 18 weeks of treatment; extra vigilance is advised during the first 6 weeks of treatment. Nevirapine should be used with extreme caution in patients with moderate hepatic impairment (Child-Pugh class B); it is contra-indicated in those with severe hepatic impairment (Child-Pugh class C). Patients with high CD4+ cell counts (greater than 250 cells/microlitre in women or 400 cells/microlitre in men), as well as patients co-infected with chronic hepatitis B or C are at increased risk of hepatotoxicity. The UK licensed product information suggests that liver function should be monitored every 2 weeks during the first 2 months of treatment, again at 3 months, and then regularly thereafter.

Treatment should be permanently stopped in patients who suffer a severe rash, rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), hypersensitivity reactions, or clinical hepatitis. Transaminase levels should be checked for all patients who develop a rash in the first 18 weeks of treatment and nevirapine should be temporarily stopped if liver enzyme levels increase to greater than 5 times the upper limit of normal or the patient has symptoms suggestive of hepatitis. In some patients treatment may be restarted at the initial dose if liver function returns to baseline values and the patient has no clinical symptoms of hepatitis or signs of a rash (although permanent stoppage is necessary if abnormalities recur). In some cases hepatic injury progresses despite stopping the drug. Dose escalation should not be attempted in patients developing any rash during the first 14 days of treatment until the rash has resolved. Patients or their carers should be counselled on how to recognise hypersensitivity reactions and instructed to seek immediate medical attention if they occur. Doses may need to be modified in patients on renal dialysis.

Pregnancy. Nevirapine has not been associated with teratogenicity in *animals*. Licensed product information states that the Antiretroviral Pregnancy Registry has not found an increased risk of birth defects after first trimester exposures to nevirapine and the prevalence of birth defects after exposure in any trimester was comparable to the prevalence in the general population.

Interactions

Nevirapine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6. Consequently it may compete with other drugs metabolised by this system, possibly resulting in mutually increased plasma concentrations and toxicity. Alternatively, enzyme inducers may decrease plasma concentrations of nevirapine; nevirapine itself acts as a mild to moderate enzyme inducer and may thus reduce plasma concentrations of other drugs.

Rifampicin and St John's wort decrease the concentration of nevirapine; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antivirals. For the effect of nevirapine on *HIV-protease inhibitors*, see p.883.

Methadone. Nevirapine may induce the metabolism of methadone (p.84) resulting in reduced plasma-methadone concentrations.

Antiviral Action

Nevirapine acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to nevirapine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Nevirapine is readily absorbed after oral doses and absorption is not affected by food or antacids. Bioavailability is greater than 90%. Nevirapine tablets and oral suspension are comparably bioavailable and interchangeable at doses up to 200 mg. Peak plasma concentrations occur 4 hours after a single dose. Nevirapine is about 60% bound to plasma proteins. Concentrations in the CSF are about 45% of those in plasma. Nevirapine crosses the placenta and is distributed into breast milk. It is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, to several hydroxylated metabolites. Autoinduction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks at usual dosage, and a decrease in terminal half-life from 45 hours to 25 to 30 hours over the same period. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood; values in children under 8 years are about twice those in adults.

◊ References.

1. Mirochnick M, *et al.* Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet* 2000; **39:** 281–93.
2. Almond LM, *et al.* Intracellular and plasma pharmacokinetics of nevirapine in human immunodeficiency virus-infected individuals. *Clin Pharmacol Ther* 2005; **78:** 132–42.
3. von Hentig N, *et al.* A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *Br J Clin Pharmacol* 2006; **62:** 552–9.

Uses and Administration

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when nevirapine is used alone, and it is therefore used with other antiretrovirals.

Nevirapine is given orally in an adult dose of 200 mg once daily for the first 14 days, then increased to 200 mg twice daily provided that no rash is present (see Precautions, above).

If treatment is interrupted for more than 7 days, it should be reintroduced using the lower dose for the first 14 days as for new treatment.

For details of doses in infants, children, and adolescents, see below.

Nevirapine is often used in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection. In women in whom HAART is not indicated, or where it is not available, a single oral dose of nevirapine 200 mg may be given at the onset of labour, together with a course of zidovudine and lamivudine, for perinatal cover (see HIV Infection Prophylaxis, p.858).

◊ References.

1. Floridia M, *et al.* A randomized, double-blind trial on the use of a triple combination including nevirapine, a nonnucleoside reverse transcriptase HIV inhibitor, in antiretroviral-naive patients with advanced disease. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; **20:** 11–19.
2. Guay LA, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; **354:** 795–802.
3. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000; **2:** 373–407.
4. Dorenbaum A, *et al.* Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002; **288:** 189–98.
5. Moodley D, *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; **187:** 725–35.
6. Taha TE, *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; **362:** 1171–7.
7. Lallemant M, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; **351:** 217–28.
8. Shapiro RL, *et al.* Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS* 2006; **20:** 1281–8.
9. Lockman S, *et al.* Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007; **356:** 135–47.
10. Parienti JJ, *et al.* SIROCCO study team. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *Clin Infect Dis* 2007; **45:** 263–6.
11. Dart Trial Team. Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA). *Trop Med Int Health* 2008; **13:** 6–16.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents nevirapine is given orally with other antiretroviral drugs. The following doses by body-weight have been suggested according to age:

- from 15 days to 8 years: 4 mg/kg once daily for 14 days and then, if no rash is present, 7 mg/kg twice daily
- 8 to 16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily thereafter

Alternatively, the dose may be calculated according to body-surface; an oral dose of 150 mg/m^2 once daily for two weeks is given followed by 150 mg/m^2 twice daily thereafter. A total dose of 400 mg daily should not be exceeded.

For information on the use of nevirapine in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection see HIV Infection Prophylaxis, p.858.

Administration in renal impairment. Dose adjustments are not required for patients with a creatinine clearance more than 20 mL/min. Patients on dialysis should receive an additional 200 mg of nevirapine after each dialysis session.

Preparations

USP 31: Nevirapine Oral Suspension; Nevirapine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Filide; Nerapin; Neviralea†; Protease; Ritvir; Virainhi; Viramune; ***Austral.:*** Viramune; ***Austria:*** Viramune; ***Belg.:*** Viramune; ***Braz.:*** Viramune; ***Canad.:*** Viramune; ***Chile:*** Viramune; ***Cz.:*** Viramune; ***Denm.:*** Viramune; ***Fin.:*** Viramune; ***Fr.:*** Viramune; ***Ger.:*** Viramune; ***Gr.:*** Viramune; ***Hong Kong:*** Viramune; ***Hung.:*** Viramune; ***India:*** Neve; Nevimune; ***Indon.:*** Viramune; ***Irl.:*** Viramune; ***Israel:*** Viramune; ***Ital.:*** Viramune; ***Jpn:*** Viramune; ***Malaysia:*** Nevipan; Viramune; ***Mex.:*** Viramune; ***Neth.:*** Viramune; ***Norw.:*** Viramune; ***NZ:*** Viramune; ***Pol.:*** Viramune; ***Port.:*** Viramune; ***Rus.:*** Viramune (Вирамун); ***S.Afr.:*** Viramune; ***Singapore:*** Viramune; ***Spain:*** Viramune; ***Swed.:*** Viramune; ***Switz.:*** Viramune; ***Thai.:*** Viramune; ***Turk.:*** Viramune; ***UK:*** Viramune; ***USA:*** Viramune; ***Venez.:*** Nevimune; Viramune.

Multi-ingredient: ***India:*** Duovir N; Triomune; ***S.Afr.:*** Triomune; ***Venez.:*** Triomune.

Oseltamivir Phosphate

(BANM, USAN, rINNM)

Fosfato de oseltamivir; GS-4104/002; Oséltamivir, Phosphate d'; Oseltamiviri Phosphas; Ro-64-0796/002. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1).

Осельтамивира Фосфат

$C_{16}H_{28}N_2O_4,H_3PO_4 = 410.4.$

CAS — 196618-13-0 (oseltamivir); 204255-11-8 (oseltamivir phosphate).

ATC — J05AH02.

ATC Vet — QJ05AH02.

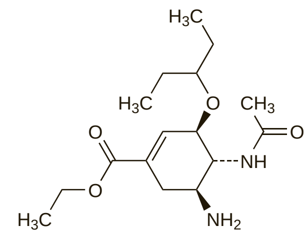

(oseltamivir)

Adverse Effects

The most commonly reported adverse effects associated with oseltamivir treatment or prophylaxis in adults are nausea and vomiting, abdominal pain, bronchitis, insomnia, and vertigo. Diarrhoea, dizziness, headache, cough, and fatigue may occur, but many adverse effects may be difficult to distinguish from the symptoms of influenza. Other adverse effects occurring less commonly have included unstable angina, anaemia, pseudomembranous colitis, pneumonia, pyrexia, and peritonsillar abscess. There have been occasional reports of anaphylaxis and skin rashes, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Elevated liver enzymes and hepatitis have been reported rarely. Prophylaxis in adults has also been associated with aches and pains, dyspepsia, rhinorrhoea, and upper respiratory-tract infections.

The most commonly reported adverse effects in children receiving treatment or prophylaxis with oseltamivir are vomiting and other gastrointestinal problems. Other commonly occurring adverse events include asthma, bronchitis, conjunctivitis, dermatitis, epistaxis, ear disorders and otitis media, lymphadenopathy, pneumonia, and sinusitis.

There have been postmarketing reports (mainly in Japanese children and adolescents) of neuropsychiatric adverse effects (see below).

Neuropsychiatric effects. A FDA review of the Adverse Event Reporting System (AERS) database from March 2004 to April 2005 reported 75 cases of serious adverse effects linked to the use of oseltamivir in children; 69 from Japan, 5 from USA, and 1 from Canada. Thirty-two cases of neuropsychiatric adverse effects including cases of delirium, abnormal behaviour, hallucinations, convulsions, and encephalitis, were reported, with 31 of these cases being reported from Japan. Twelve deaths were reported; 4 from sudden death, 4 due to cardiopulmonary arrest, and others due to disturbance of consciousness (without falling), pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest. All deaths were reported from Japan.[1] The Japanese Ministry of Health Labour and Welfare reported that from 2001 to May 2007 they received 1377 adverse effects reports associated with the use of oseltamivir, including 567 reports of serious neuropsychiatric adverse effects and 211 cases of abnormal behaviour. Death was reported in 71 cases.[2] After the suicides of 2 adolescents, the Japanese authorities advised against the use of oseltamivir in adolescents aged 10 to 19 years.[3] However, given that influenza itself may have neuropsychiatric sequelae, any causal relationship with the drug remains unproven.[1,3]

1. FDA, Center for Drug Evaluation and Research. Pediatric safety update for Tamiflu: Pediatric Advisory Committee meeting (issued 18 November 2005). Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_06_summary.pdf (accessed 13/06/08).
2. Hama R. Oseltamivir's adverse reactions: Fifty sudden deaths may be related to central suppression. *BMJ* 2007; **335:** 59.
3. Maxwell SRJ. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007; **334:** 1232–3.

Precautions

Oseltamivir is not recommended in patients with severe renal impairment and it should be given with caution and dosage should be reduced in patients with moderate renal impairment.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Breast feeding. Oseltamivir and its active metabolite are distributed into breast milk in *rodents*. Licensed product information recommends that it should only be given to breast-feeding mothers if the potential benefit justifies the potential risk.

Pregnancy. Studies in *rodents* given high doses of oseltamivir have not found it to be fetotoxic or embryotoxic. There is little data available on the use of oseltamivir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Oseltamivir may potentially inhibit replication of the influenza virus in live influenza virus vaccines. Therefore, US licensed product information states that live influenza virus vaccines should not be given until 48 hours after stopping oseltamivir and that oseltamivir should not be given for 2 weeks after live influenza virus vaccines have been given. Inactivated (split virion or surface antigen) vaccines are not expected to be affected by oseltamivir.

Antiviral Action

Oseltamivir has antiviral activity similar to that of zanamivir (p.913). Its active metabolite, oseltamivir carboxylate, selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells. Oseltamivir is active against influenza A and B viral neuraminidase.

Resistance. Oseltamivir-resistant type A virus, including H5N1 subtypes, have been reported in patients being treated for influenza.[1-3] A study[1] in Japan found that 9 of 50 (18%) children with influenza A (H3N2) virus infection who had been treated with oseltamivir had a virus with a drug-resistance mutation in the neuraminidase gene (predominantly R292K). Another study[4] in Japan reported resistant influenza A (H1N1) viruses with the H274Y mutation in 7 of 43 (16%) oseltamivir-treated children. In both these studies the children were given an oral dose of 2 mg/kg twice daily. However, a larger study[5] in the US reported no resistance in children who received age- and weight-tailored (and therefore sometimes substantially higher) doses than those used in the Japanese studies. No viruses resistant to zanamivir have been isolated from immunocompetent people,[6] although there is a case of resistance in an immunocompromised child.[7]

1. Kiso M, *et al.* Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004; **364:** 759–65.
2. de Jong MD, *et al.* Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; **353:** 2667–72.
3. Le QM, *et al.* Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 2005; **437:** 1108. Correction. *ibid.*; **438:** 754.
4. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; **55** (suppl 1): i5–i21.
5. Hayden FG, *et al.* Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004; **189:** 440–9.
6. Moscona A. Oseltamivir-resistant influenza? *Lancet* 2004; **364:** 733–4.
7. Gubareva LV, *et al.* Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998; **178:** 1257–62.

Pharmacokinetics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral doses and is extensively metabolised in the liver to the active entity, oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as the carboxylate. Binding to plasma proteins is about 3% for the carboxylate and 42% for the parent drug. Oseltamivir has a plasma half-life of 1 to 3 hours and the carboxylate a plasma half-life of 6 to 10 hours. The carboxylate is not metabolised further and is eliminated in the urine.

◊ Reviews.

1. Abe M, *et al.* Pharmacokinetics of oseltamivir in young and very elderly subjects. *Ann Pharmacother* 2006; **40:** 1724–30.

Uses and Administration

Oseltamivir is a prodrug of oseltamivir carboxylate, an inhibitor of the enzyme neuraminidase (sialidase), which has a role in the infectivity and replication of influenza A and B viruses. It is used in adults and children over 1 year of age for the treatment and postexposure prophylaxis of influenza A and B (below).

Oseltamivir is given orally as the phosphate, but doses are expressed in terms of the base. Oseltamivir phosphate 98.5 mg is equivalent to about 75 mg of oseltamivir. For the *treatment* of adults a dose of 75 mg is given twice daily for 5 days, beginning as soon as possible (within 48 hours) after the onset of symptoms. For *postexposure prophylaxis* the usual dose is 75 mg given once daily for at least 10 days and for up to 6 weeks during an epidemic; therapy should begin within 48 hours of exposure.

For details of doses in children, see below.

Dosage should be reduced in patients with moderate renal impairment (see below).

Oseltamivir has been tried both for prophylaxis and treatment of H5N1 disease (avian influenza) and many countries are stockpiling the drug in order to contain any potential pandemic until an effective vaccine can be developed.

Administration in children. Oseltamivir is given orally in the treatment and prophylaxis of influenza A and B in children aged 1 year and over. Doses determined by body-weight may be given twice daily for treatment, or once daily for prophylaxis, of influenza A and B as follows:

- children over 40 kg: 75 mg
- more than 23 kg to 40 kg: 60 mg
- more than 15 kg to 23 kg: 45 mg
- 15 kg or less: 30 mg

Therapy should begin within 48 hours of exposure.

Administration in renal impairment. Dosage of oseltamivir should be reduced in patients with moderate renal impairment, according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: *treatment of influenza*: 75 mg once daily or 30 mg twice daily; *prevention*: 75 mg on alternate days or 30 mg daily
- CC less than 10 mL/minute: not recommended
- dialysis patients: not recommended

Influenza. Reviews[1-8] of oseltamivir and other neuraminidase inhibitors in the treatment and prophylaxis of influenza (p.859). There is some evidence[9] that zanamivir is more effective than oseltamivir for influenza B.

1. Gubareva LV, *et al.* Influenza virus neuraminidase inhibitors. *Lancet* 2000; **355:** 827–35.
2. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs* 2001; **61:** 263–83.
3. Jefferson TO, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
4. Matheson NJ, *et al.* Neuraminidase inhibitors for preventing and treating influenza in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
5. Cooper NJ, *et al.* Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; **326:** 1235–9.
6. Dutkowski R, *et al.* Safety and pharmacology of oseltamivir in clinical use. *Drug Safety* 2003; **26:** 787–801.
7. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; **55** (suppl 1): i5–i21.
8. Democratis J, *et al.* Use of neuraminidase inhibitors to combat pandemic influenza. *J Antimicrob Chemother* 2006; **58:** 911–15.
9. Kawai N, *et al.* A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect* 2008; **56:** 51–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Agucort; Tamiflu; ***Austral.:*** Tamiflu; ***Austria:*** Tamiflu; ***Belg.:*** Tamiflu; ***Braz.:*** Tamiflu; ***Canad.:*** Tamiflu; ***Chile:*** Rimivat; Tamiflu; Virobin; ***Cz.:*** Tamiflu; ***Denm.:*** Tamiflu; ***Fin.:*** Tamiflu; ***Fr.:*** Tamiflu; ***Ger.:*** Tamiflu; ***Gr.:*** Tamiflu; ***Hong Kong:*** Tamiflu; ***Hung.:*** Tamiflu; ***Irl.:*** Tamiflu; ***Israel:*** Tamiflu; ***Ital.:*** Tamiflu; ***Jpn:*** Tamiflu; ***Malaysia:*** Fluhalt; Tamiflu; ***Neth.:*** Tamiflu; ***Norw.:*** Tamiflu; ***NZ:*** Tamiflu; ***Philipp.:*** Tamiflu; ***Pol.:*** Tamiflu; ***Port.:*** Tamiflu; ***S.Afr.:*** Tamiflu; ***Singapore:*** Tamiflu; ***Swed.:*** Tamiflu; ***Switz.:*** Tamiflu; ***Thai.:*** Tamiflu; ***Turk.:*** Tamiflu; ***UK:*** Tamiflu; ***USA:*** Tamiflu.

Penciclovir *(BAN, USAN, rINN)*

BRL-39123; BRL-39123-D (penciclovir sodium); Penciclovirum; Penciklovir; Pensikloviiri; Pensiklovir. 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.

Пенцикловир

$C_{10}H_{15}N_5O_3 = 253.3.$

CAS — 39809-25-1 (penciclovir); 97845-62-0 (penciclovir sodium).

ATC — D06BB06; J05AB13.

ATC Vet — QD06BB06; QJ05AB13.

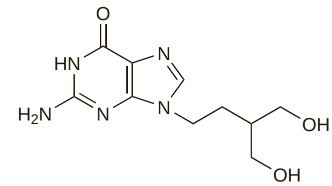

Adverse Effects and Precautions

Penciclovir applied topically may cause transient stinging, burning, and numbness.

For adverse effects of penciclovir after systemic use of famciclovir, see p.876.

Interactions

Plasma concentrations of penciclovir may be increased in patients receiving *probenecid* with the prodrug famciclovir.

Antiviral Action

Penciclovir has antiviral activity similar to that of aciclovir (p.863). It is active *in vitro* and *in vivo* against herpes simplex virus types 1 and 2 and against varicella-zoster virus. This activity is due to intracellular conversion by virus-induced thymidine kinase into penciclovir triphosphate, which inhibits replication of viral DNA and persists in infected cells for more than 12 hours. It also has activity against Epstein-Barr virus and hepatitis B virus.

◊ References.

1. Vere-Hodge RA. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. *Antiviral Chem Chemother* 1993; **4:** 67–84.
2. Boyd MR, *et al.* Penciclovir: a review of its spectrum of activity, selectivity, and cross-resistance pattern. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 3–11.
3. Bacon TH, Boyd MR. Activity of penciclovir against Epstein-Barr virus. *Antimicrob Agents Chemother* 1995; **39:** 1599–1602.

Pharmacokinetics

Penciclovir is poorly absorbed from the gastrointestinal tract. For systemic use it is usually given orally as the prodrug famciclovir, which is rapidly converted to penciclovir. Peak plasma concentrations proportional to the dose (over the range 125 to 750 mg) are achieved after 45 minutes to 1 hour. The plasma elimination half-life is about 2 hours. The intracellular half-life of the active triphosphate metabolite is longer. Penciclovir is less than 20% bound to plasma proteins. Penciclovir is mainly excreted unchanged in the urine.

Uses and Administration

Penciclovir is a nucleoside analogue structurally related to guanine, which is active against herpesviruses. It is applied topically as a 1% cream every 2 hours during waking hours for 4 days in the treatment of herpes labialis (see Herpes Simplex Infections, p.854).

For systemic use, penciclovir is given orally as the prodrug famciclovir (see p.876). Intravenous dosage of penciclovir has been investigated.

◊ References.

1. Spruance SL, *et al.* Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *JAMA* 1997; **277:** 1374–9.
2. Lazarus HM, *et al.* Intravenous penciclovir for treatment of herpes simplex infections in immunocompromised patients: results of a multicenter, acyclovir-controlled trial. *Antimicrob Agents Chemother* 1999; **43:** 1192–7.
3. Boon R, *et al.* Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2000; **22:** 76–90.
4. Raborn GW, *et al.* Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002; **133:** 303–9.
5. Lin L, *et al.* Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatol Treat* 2002; **13:** 67–72.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pentavir; ***Austral.:*** Vectavir; ***Austria:*** Famvir; Vectavir; ***Belg.:*** Vectavir; ***Braz.:*** Penvir Labia; Vectavir; ***Cz.:*** Vectavir; ***Denm.:*** Vectavir; ***Fin.:*** Vectavir; ***Ger.:*** Fenistil Pencivir; Vectavir†; ***Gr.:*** Fenivir; Vectavir; ***Hong Kong:*** Vectavir†; ***Hung.:*** Fenivir; Vectavir†; ***Israel:*** Vectavir†; ***Ital.:*** Vectavir;

Zilip; ***Neth.:*** Famvir; Vectavir; ***Norw.:*** Vectavir; ***NZ:*** Vectavir†; ***Port.:*** Denovir; Fenivir; ***Rus.:*** Fenistil Pencivir (Фенистил Пенцивир); ***Spain:*** Vectavir; ***Swed.:*** Vectavir; ***Switz.:*** Famvir; ***Turk.:*** Vectavir; ***UK:*** Fenistil; Vectavir; ***USA:*** Denavir.

Peptide T

D-Ala-peptide-T-amide; Péptido T.

Пептид Т

Profile

Peptide T is an octapeptide segment of the envelope glycoprotein of HIV. It has been investigated for the treatment of HIV infection and HIV-associated neurological disorders. Peptide T has also been tried in the treatment of psoriasis.

Pleconaril *(USAN, rINN)*

Pléconaril; Pleconarilo; Pleconarilum; VP-63843; Win-63843. 3-{4-[3-(3-Methyl-5-isoxazolyl)propoxy]-3,5-xylyl}-5-(trifluoromethyl)-1,2,4-oxadizole.

Плеконарил

$C_{18}H_{18}F_3N_3O_3$ = 381.3.

CAS — 153168-05-9.

ATC — J05AX06.

ATC Vet — QJ05AX06.

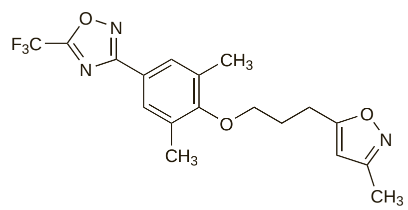

Profile

Pleconaril is an antiviral with activity against a range of picornaviruses. It has been investigated for the oral treatment of viral meningitis and encephalitis, upper respiratory-tract viral infections, and other enteroviral infections. However, there have been concerns over efficacy, viral resistance, and interactions with oral contraceptives. Development of an intranasal formulation for the common cold has also been investigated.

◊ References.

1. Nowak-Wegrzyn A, *et al.* Successful treatment of enterovirus infection with the use of pleconaril in 2 infants with severe combined immunodeficiency. *Clin Infect Dis* 2001; **32:** E13–E14.
2. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; **32:** 228–35.
3. Aradottir E, *et al.* Severe neonatal enteroviral hepatitis treated with pleconaril. *Pediatr Infect Dis J* 2001; **20:** 457–9.
4. Starlin R, *et al.* Acute flaccid paralysis syndrome associated with echovirus 19, managed with pleconaril and intravenous immunoglobulin. *Clin Infect Dis* 2001; **33:** 730–2.
5. Hayden FG, *et al.* Oral pleconaril treatment of picornavirus-associated viral respiratory illness in adults: efficacy and tolerability in phase II clinical trials. *Antivir Ther* 2002; **7:** 53–65.
6. Abzug MJ, *et al.* Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatr Infect Dis J* 2003; **22:** 335–41.
7. Hayden FG, *et al.* Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin Infect Dis* 2003; **36:** 1523–32.

Poly I.poly C12U

Poli(I)²poli(C_{12}U); Poly(I):poly(C_{12},U).

Поли I.Поли C12U

Profile

Poly I.poly C12U is a synthetic mismatched polymer of double-stranded RNA with antiviral and immunomodulatory activity (see also Poly I. Poly C, p.2370). It is under investigation in the treatment of HIV infection, and also in renal cell carcinoma, chronic fatigue syndrome, invasive melanoma, and hepatitis B and C.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ampligen.

Propagermanium *(rINN)*

Propagermanio. A polymer obtained from 3-(trihydroxygermyl)propionic acid.

Пропагерманий

$(C_3H_5GeO_{3.5})_n$.

CAS — 12758-40-6.

Profile

Propagermanium is an immunomodulator that has been used in chronic hepatitis B infections. Acute exacerbation of hepatitis, including some fatalities, has been reported in patients receiving propagermanium.

◊ References.

1. Hirayama C, *et al.* Propagermanium: a nonspecific immune modulator for chronic hepatitis B. *J Gastroenterol* 2003; **38:** 525–32.

Raltegravir *(USAN, rINN)*

Raltégravir; Raltegravirum. *N*-{2-[4-(4-Fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl}-5-methyl-1,3,4-oxadiazole-2-carboxamide.

Ральтегравир

$C_{20}H_{21}FN_6O_5$ = 444.4.

CAS — 518048-05-0.

ATC — J05AX08.

ATC Vet — QJ05AX08.

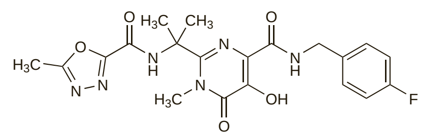

Raltegravir Potassium *(USAN, rINNM)*

Kalii Raltegravirum; MK-0518; Raltegravir potásico; Raltégravir Potassique. Potassium 4-[(4-fluorobenzyl)carbamoyl]-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidin-5-olate.

Калия Ральтегравир

$C_{20}H_{20}FKN_6O_5$ = 482.5.

CAS — 871038-72-1.

Adverse Effects and Precautions

On the basis of limited data, raltegravir appears to be well tolerated; non-specific adverse effects associated with raltegravir-based regimens include headache, abdominal pain, vomiting, asthenia, fatigue, and dizziness. Abnormal creatine phosphokinase values may occur and myopathy and rhabdomyolysis have been reported although a causal relationship has not been established; nonetheless, caution is advised in patients at increased risk of these conditions.

Interactions

Raltegravir is not a substrate for cytochrome P450 isoenzymes, and does not appear to interact with drugs metabolised by this mechanism. However, rifampicin induces the glucuronidase responsible for raltegravir metabolism (UGT1A1) and reduces plasma concentrations of raltegravir.

Antivirals. Plasma concentrations of raltegravir were modestly increased by *atazanavir* and ritonavir-boosted atazanavir in healthy subjects; this increase is not considered to be clinically significant.[1]

1. Iwamoto M, *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin Infect Dis* 2008; **47:** 137–40.

Pharmacokinetics

Raltegravir is absorbed on oral dosage, with peak concentrations achieved about 3 hours after a dose. There is considerable inter-individual variation in the pharmacokinetics. It is metabolised via glucuronidation, catalysed by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and excreted in both urine and faeces as unchanged drug and metabolites.

Uses and Administration

Raltegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is added to treatment with other antiretrovirals for salvage therapy in patients with HIV infection and AIDS (p.856) who have evidence of viral replication and HIV-1 strains resistant to multiple antiretrovirals.

It is given orally as the potassium salt but doses are calculated in terms of the base; 434 mg of raltegravir potassium is equivalent to about 400 mg of raltegravir. The usual dose is the equivalent of 400 mg of raltegravir twice daily, with or without food.

◊ References.

1. Markowitz M, *et al.* Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2006; **43:** 509–15. Correction. *ibid.* 2007; **44:** 492.
2. Grinsztejn B, *et al.* Protocol 005 Team. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet* 2007; **369:** 1261–9.
3. Markowitz M, *et al.* Protocol 004 Part II Study Team. Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007; **46:** 125–33.
4. Iwamoto M, *et al.* Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin Pharmacol Ther* 2008; **83:** 293–9.
5. Croxtall JD, *et al.* Raltegravir. *Drugs* 2008; **68:** 131–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Isentress; ***Fr.:*** Isentress; ***UK:*** Isentress; ***USA:*** Isentress.

Resiquimod *(rINN)*

R-848; Résiquimod; Resiquimodum; S-28463; VML-600. 4-Amino-2-(ethoxymethyl)-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

Резихимод

$C_{17}H_{22}N_4O_2$ = 314.4.

CAS — 144875-48-9.

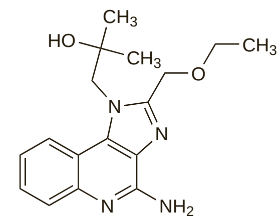

Profile

Resiquimod is an immune response modifier that has been investigated for the topical treatment of genital herpes.

◊ References.

1. Spruance SL, *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; **184:** 196–200.
2. Mark KE, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. *J Infect Dis* 2007; **195:** 1324–31.

Ribavirin *(BAN, USAN, rINN)*

ICN-1229; Ribaviriini; Ribavirina; Ribavirinas; Ribavirine; Ribavirinum; RTCA; Tribavirin. 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

Рибавирин

$C_8H_{12}N_4O_5$ = 244.2.

CAS — 36791-04-5.

ATC — J05AB04.

ATC Vet — QJ05AB04.

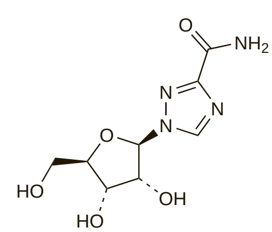

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Ribavirin). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; slightly soluble or very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.5. Protect from light.

USP 31 (Ribavirin). A white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. Store in airtight containers.

Adverse Effects

When given *by inhalation*, ribavirin has sometimes led to worsening of lung function, bacterial pneumonia, and pneumothorax, to cardiovascular effects (including a fall in blood pressure and cardiac arrest), and, rarely, to anaemia, haemolysis, and reticulocytosis. Conjunctivitis and skin rash have also occurred. Precipitation of inhaled ribavirin and consequent accumulation of fluid has occurred in the tubing of ventilating equipment.

The most common adverse effects reported by patients taking *oral* ribavirin, with either interferon alfa or peginterferon alfa, are psychiatric reactions (such as anxiety, depression, insomnia, and irritability) and flu-like symptoms. Life-threatening or fatal adverse effects include severe depression, suicidal ideation, relapse of drug abuse or overdose, and bacterial infection. Severe adverse effects include haemolytic anaemia, leucopenia, thrombocytopenia, aplastic anaemia, diabetes mellitus, auto-immune disorders, gastrointestinal symptoms, pancreatitis, pulmonary embolism, chest pain, liver dysfunction, and interstitial pneumonitis. Lupus erythematosus, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity have also been reported. Growth retardation (including decrease in height and weight) has been reported in children. A wide range of other adverse effects may occur as a result of the use of ribavirin with interferon alfa (see under Adverse Effects in Interferon Alfa, p.885).

Incidence of adverse effects. A review[1] of adverse effects reported in 110 patients with suspected or probable SARS who were treated with ribavirin found that 61% of the patients had evidence of haemolytic anaemia. In a smaller cohort of 76 patients hypocalcaemia and hypomagnesaemia were reported in 58% and 46% of patients, respectively, while 29% had evidence of both hypocalcaemia and hypomagnesaemia. A retrospective cohort study[2] found that the adverse effects strongly associated with the use of ribavirin (mostly high-dose) in 306 patients with confirmed or probable SARS, were progressive anaemia, hypomagnesaemia, and bradycardia.

1. Knowles SR, *et al.* Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis* 2003; **37:** 1139–42.
2. Muller MP, *et al.* Canadian SARS Research Network. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy* 2007; **27:** 494–503.

Precautions

SPECIFIC CAUTIONS FOR INHALED TREATMENT. Standard supportive respiratory and fluid management should be maintained during aerosol treatment with ribavirin and electrolytes should be monitored closely. Equipment should be monitored for precipitation of ribavirin. Precautions should be taken to minimise atmospheric pollution with ribavirin during aerosol inhalation.

SPECIFIC CAUTIONS FOR ORAL TREATMENT. Ribavirin should not be given orally to patients with pre-existing medical conditions that could be exacerbated by ribavirin-induced haemolysis, including significant or unstable cardiac disease or haemoglobinopathies (thalassaemia or sickle-cell anaemia). Blood cell counts and chemistry should be measured at the start of treatment, after 2 and 4 weeks of treatment, and periodically thereafter. Patients with renal impairment and a creatinine clearance of less than 50 mL/minute should not receive oral ribavirin. It should be avoided in patients with severe hepatic impairment or decompensated cirrhosis of the liver (Child-Pugh 6 or more). The potential for development of gout should be considered in predisposed patients. Patients should be monitored for signs and symptoms of psychiatric disorders. Ribavirin therapy is contra-indicated in children and adolescents with a history of, or existing, psychiatric disorders. The growth of children should be monitored and thyroid function should be tested every 3 months. Patients infected with hepatitis C virus and HIV should be carefully monitored for signs of mitochondrial toxicity and lactic acidosis. Dental and periodontal disorders have been reported and regular dental examinations and good oral hygiene are advised.

Contact lenses. Report of damage to a nurse's soft contact lenses after intermittent occupational exposure to aerosolised ribavirin over a period of 1 month.[1]

1. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure. *DICP Ann Pharmacother* 1989; **23:** 428–9.

Pregnancy. Oral ribavirin has been reported to be teratogenic and embryocidal in *rodents* and is contra-indicated in pregnancy or in those who may become pregnant. Ribavirin was not found to be teratogenic in *baboons.* Although there are no case reports of teratogenicity after exposure to aerosolised ribavirin during pregnancy, licensed product information advises that pregnant women and those planning pregnancy should avoid exposure to the aerosol. Pregnancy should also be avoided in partners of male patients taking ribavirin orally. Effective contraception should be used during treatment and for 6 months after the end of treatment. Male patients whose partners are pregnant should use a condom to minimise vaginal exposure to ribavirin.

Interactions

Use of ribavirin with zidovudine is not recommended as patients are at increased risk of anaemia. Increased toxicity has also been seen with didanosine, and the combination should be avoided. Ribavirin inhibits the phosphorylation of NRTIs such as zidovudine, lamivudine, and stavudine, but although UK licensed product information suggests this may reduce their activity against HIV, US product information indicates that no such reduction has been seen in practice.

Anticoagulants. For reference to the effect of ribavirin on the activity of *warfarin*, see under Antivirals, p.1430.

Antiviral Action

Ribavirin inhibits many viruses *in vitro* and in *animal* models. However, this activity has not necessarily correlated with activity against human infections. Ribavirin is phosphorylated but its mode of action is still unclear; it may act at several sites, including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for its antiviral activity. Susceptible DNA viruses include herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, and RSV, and HIV.

Pharmacokinetics

Aerosolised ribavirin is absorbed systemically, but local concentrations in the respiratory tract secretions are much higher than plasma concentrations. Plasma half-life is about 9.5 hours. The bioavailability of aerosolised ribavirin is unknown and may depend on the mode of delivery.

Ribavirin is rapidly absorbed after oral doses and peak plasma concentrations have been reported within 1 to 2 hours. Absorption is extensive but oral bioavailability is about 45 to 65% as a result of first-pass metabolism. Steady state plasma concentrations are achieved after about 4 weeks with twice-daily oral doses resulting in peak plasma concentrations 6 times higher than that after single doses. On stopping dosing the plasma half-life is about 300 hours as a result of slow elimination from non-plasma compartments. Ribavirin does not bind to plasma proteins. Ribavirin is not metabolised by the cytochrome P450 system; it is metabolised by reversible phosphorylation and degradation involving deribosylation and amide hydrolysis to give a triazole carboxyacid metabolite. After a single oral dose the terminal half-life is about 120 to 170 hours. Ribavirin is mainly excreted in the urine as unchanged drug and metabolites. Insignificant amounts of the drug are removed by haemodialysis.

◊ References.

1. Kramer TH, *et al.* Hemodialysis clearance of intravenously administered ribavirin. *Antimicrob Agents Chemother* 1990; **34:** 489–90.
2. Glue P, *et al.* The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *Br J Clin Pharmacol* 2000; **49:** 417–21.
3. Tsubota A, *et al.* Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. *Br J Clin Pharmacol* 2003; **55:** 360–7.
4. Kamar N, *et al.* Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it depends on renal function. *Am J Kidney Dis* 2004; **43:** 140–6.
5. Uchida M, *et al.* Assessment of adverse reactions and pharmacokinetics of ribavirin in combination with interferon alpha-2b in patients with chronic hepatitis C. *Drug Metab Pharmacokinet* 2004; **19:** 438–43.
6. Wade JR, *et al.* Pharmacokinetics of ribavirin in patients with hepatitis C virus. *Br J Clin Pharmacol* 2006; **62:** 710–14.

Uses and Administration

Ribavirin is a synthetic nucleoside analogue structurally related to guanine. It is given by aerosol in the treatment of RSV infections (p.860); this route appears to give better results than the oral route although its efficacy is questionable. It is used orally with an interferon alfa or peginterferon alfa in the treatment of chronic hepatitis C, including HIV co-infection (p.851). Ribavirin has been tried in haemorrhagic fevers (such as haemorrhagic fever with renal syndrome and Lassa fever) and in SARS.

For details of doses in children, see below.

Ribavirin is used, with an interferon alfa or peginterferon alfa, for the treatment of chronic **hepatitis C**. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In those with hepatitis C infection alone (*mono-infection*), patients with viral genotype 1, and probably genotype 4, should generally be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks; data on genotypes 5 or 6 are insufficient to make recommendations. In *co-infection* with HIV, treatment should generally be given for 48 weeks regardless of genotype.

Rebetol (*Schering-Plough*) is used, with interferon alfa-2b or peginterferon alfa-2b for hepatitis C.

The following doses are recommended in the UK:
- adults up to 65 kg: 400 mg both in the morning and in the evening
- 65 to 85 kg: 400 mg in the morning and 600 mg in the evening
- from 85 to 105 kg: 600 mg both in the morning and in the evening
- over 105 kg: 600 mg in the morning and 800 mg in the evening

In the USA, the doses are:
- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

Copegus (*Roche*) is used in the UK with interferon alfa-2a or peginterferon alfa-2a and in the USA with peginterferon alfa-2a.

The following doses are used with peginterferon alfa-2a for mono-infection in genotype 1 or 4:
- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For mono-infection in genotype 2 or 3 (with peginterferon alfa-2a):
- all adults: 400 mg both in the morning and in the evening

The following doses are used with interferon alfa-2a for mono-infection in genotype 1 to 4:
- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For co-infection with HIV:
- all adults: 800 mg daily, irrespective of genotype

Dose reductions of ribavirin may be necessary in patients who develop low haemoglobin concentrations. Ribavirin is contra-indicated in patients with a creatinine clearance less than 50 mL/minute.

◊ Reviews.

1. Plosker GL, Keating GM. Peginterferon-α-2a (40kD) plus ribavirin: a review of its use in hepatitis C virus and HIV co-infection. *Drugs* 2004; **64:** 2823–43.
2. Keating GM, Plosker GL. Peginterferon α-2a (40KD) plus ribavirin: a review of its use in the management of patients with chronic hepatitis C and persistently 'normal' ALT levels. *Drugs* 2005; **65:** 521–36.
3. Gish RG. Treating HCV with ribavirin analogues and ribavirin-like molecules. *J Antimicrob Chemother* 2006; **57:** 8–13.
4. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
5. Keam SJ, Cvetković RS. Peginterferon-α-2a (40 kD) plus ribavirin: a review of its use in the management of chronic hepatitis C mono-infection. *Drugs* 2008; **68:** 1273–1317.

Administration in children. Preparations of ribavirin are available for aerosol administration to infants and children with severe **RSV** infection via a small particle aerosol generator. Solutions containing 20 mg/mL are used; 300 mL, representing 6 g of ribavirin, is delivered over a 12- to 18-hour period by aerosol at an average concentration of 190 micrograms/litre of air. Treatment is given for 3 to 7 days.

Ribavirin is used, with an interferon alfa, for the treatment of chronic **hepatitis C**. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks.

Rebetol (Schering-Plough) is used, with interferon alfa-2b or peginterferon alfa-2b, for hepatitis C.

The following doses are recommended in the UK:

- 47 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 65 kg: 400 mg both in the morning and in the evening
- over 65 kg: the adult dose (above)

In the USA, the doses are:

- 25 to 36 kg: 200 mg both in the morning and in the evening
- 37 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 61 kg: 400 mg both in the morning and in the evening
- over 61 kg: the adult dose

Copegus (Roche) is not licensed for use in those less than 18 years of age.

Encephalitis. A beneficial response to ribavirin was reported in a child with severe La Crosse encephalitis.[1] Ribavirin was given intravenously in a dose of 25 mg/kg over the first 24 hours and then reduced to 15 mg/kg daily for a further 9 days. A small open-label study[2] suggested that ribavirin might also be able to reduce mortality and neurological deficits in acute Nipah encephalitis.

Intraventricular ribavirin (plus intraventricular interferon and oral isoprinosine) was found to be effective in 4 of 5 patients with subacute sclerosing panencephalitis.[3] A concentration of ribavirin in the CSF of 50 to 200 micrograms/mL completely inhibited viral replication; doses of ribavirin given to achieve this concentration ranged from 1 to 9 mg/kg daily.

1. McJunkin JE, *et al.* Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. *Pediatrics* 1997; **99:** 261–7.
2. Chong HT, *et al.* Treatment of acute Nipah encephalitis with ribavirin. *Ann Neurol* 2001; **49:** 810–13.
3. Hosoya M, *et al.* Pharmacokinetics and effects of ribavirin following intraventricular administration for treatment of subacute sclerosing panencephalitis. *Antimicrob Agents Chemother* 2004; **48:** 4631–5.

Haemorrhagic fevers. The treatment of haemorrhagic fevers (p.850) is primarily symptomatic. However, ribavirin has been reported to reduce mortality in patients with Lassa fever,[1] haemorrhagic fever with renal syndrome,[2] and possibly Crimean-Congo haemorrhagic fever[3,4] and Bolivian haemorrhagic fever.[5] Intravenous ribavirin has also been tried in the related hantavirus pulmonary syndrome,[6,7] but a small randomised, double-blind, placebo-controlled study[8] with intravenous ribavirin reported no significant difference in survival between the 2 groups.

For treatment of *Lassa fever*, ribavirin has been given intravenously in a dose of 2 g initially, then 1 g every 6 hours for 4 days, then 500 mg every 8 hours for 6 days.[1] Treatment is most effective if started within 6 days of the onset of fever. Experience has shown that rigors may occur if the drug is given as a bolus injection, but that this can be overcome by giving it as an infusion over 30 minutes.[9] For prophylaxis, an oral dose of ribavirin 600 mg 4 times daily for 10 days has been suggested for adults,[10] although this was considered to be excessive by other commentators[11] who suggested that oral doses of 1 g daily (after an intravenous loading dose for those in whom the start of prophylaxis is delayed) might be suitable.

1. McCormick JB, *et al.* Lassa fever: effective therapy with ribavirin. *N Engl J Med* 1986; **314:** 20–6.
2. Huggins JW, *et al.* Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis* 1991; **164:** 1119–27.
3. Fisher-Hoch SP, *et al.* Crimean Congo-haemorrhagic fever treated with oral ribavirin. *Lancet* 1995; **346:** 472–5.
4. Mardani M, *et al.* The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis* 2003; **36:** 1613–18.
5. Kilgore PE, *et al.* Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997; **24:** 718–22.
6. Anonymous. Hantavirus pulmonary syndrome—northeastern United States, 1994. *JAMA* 1994; **272:** 997–8.
7. Prochoda K, *et al.* Hantavirus-associated acute respiratory failure. *N Engl J Med* 1993; **329:** 1744.
8. Mertz GJ, *et al.* Collaborative Antiviral Study Group. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis* 2004; **39:** 1307–13.
9. Fisher-Hoch SP, *et al.* Unexpected adverse reactions during a clinical trial in rural West Africa. *Antiviral Res* 1992; **19:** 139–47.
10. Holmes GP, *et al.* Lassa fever in the United States: investigation of a case and new guidelines for management. *N Engl J Med* 1990; **323:** 1120–23.
11. Johnson KM, Monath TP. Imported Lassa fever—reexamining the algorithms. *N Engl J Med* 1990; **323:** 1139–41.

Hepatitis. For further discussion on the use of ribavirin with interferon alfa in the management of chronic hepatitis C, see under Interferon Alfa, p.889.

Preparations

BP 2008: Ribavirin Nebuliser Solution;
USP 31: Ribavirin for Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Copegus; Laztie; Vibuzol; Xilopar; ***Austral.:*** Virazide; ***Austria:*** Copegus; Rebetol; ***Belg.:*** Copegus; Rebetol; Virazole; ***Braz.:*** Rebetol†; Ribav; Ribaviron C†; Viramid; Virazole†; ***Canad.:*** Virazole; ***Chile:*** Rebetol; ***Cz.:*** Copegus; Rebetol; ***Denm.:*** Copegus; Rebetol; ***Fin.:*** Copegus; Rebetol; ***Fr.:*** Copegus; Rebetol; ***Ger.:*** Copegus; Rebetol; Virazole; ***Gr.:*** Copegus; Rebetol; ***Hong Kong:*** Copegus; Rebetol; Virazole; ***Hung.:*** Copegus; Rebetol; Virazole†; ***India:*** Ribavin; ***Indon.:*** Rebetol; Virazide; ***Irl.:*** Copegus; Rebetol; ***Israel:*** Copegus; Rebetol; ***Ital.:*** Copegus; Rebetol; Virazole; ***Jpn:*** Copegus; ***Malaysia:*** Rebetol; ***Mex.:*** Copegus; Desiken; Trivorin; Vilona; Virazide; ***Neth.:*** Copegus; Rebetol; Virazole; ***Norw.:*** Copegus; Rebetol; ***NZ:*** Copegus; Rebetol; ***Philipp.:*** Ribazole; ***Pol.:*** Copegus; Rebetol; ***Port.:*** Copegus; Rebetol; ***Rus.:*** Arviron (Арвирон); Rebetol (Ребетол); Ribapeg (Рибапег); Virazole (Виразол); ***S.Afr.:*** Copegus; ***Singapore:*** Copegus; Rebetol; Virazole; ***Spain:*** Copegus; Rebetol; Virazole; ***Swed.:*** Copegus; Rebetol; Virazole; ***Switz.:*** Copegus; Rebetol; Virazole†; ***Thai.:*** Rebetol; ***UK:*** Copegus; Rebetol; Virazole; ***USA:*** Copegus; Rebetol; RibaPak; Ribaspheres; Ribatab; Virazole; ***Venez.:*** Rebetol.

Multi-ingredient: ***Arg.:*** Bioferon Hepakit; Pegatron†; Rebetron†; ***Austral.:*** Pegasys RBV; Pegatron; Rebetron; ***Canad.:*** Pegasys RBV; Pegetron; Rebetron†; ***Mex.:*** Hepatron C; Pegtron Cotronak Kit; ***NZ:*** Pegasys RBV; Pegatron; Rebetron; Roferon-A RBV; ***Philipp.:*** Pegasys RBV; ***S.Afr.:*** Rebetron†; ***Switz.:*** Intron A/Rebetol†; ***USA:*** Rebetron†.

Rimantadine Hydrochloride *(BANM, USAN, rINNM)*

EXP-126; Hidrocloruro de rimantadina; Rimantadine, Chlorhydrate de; Rimantadini Hydrochloridum. (*RS*)-1-(Adamantan-1-yl)ethylamine hydrochloride; α-Methyl-1-adamantanemethylamine hydrochloride.

Римантадина Гидрохлорид

$C_{12}H_{21}N,HCl = 215.8.$

CAS — 13392-28-4 (rimantadine); 1501-84-4 (rimantadine hydrochloride).

ATC — J05AC02.

ATC Vet — QJ05AC02.

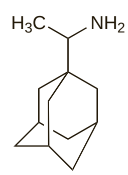

(rimantadine)

Pharmacopoeias. In *US.*

USP 31 (Rimantadine Hydrochloride). Store at a temperature of 15° to 30°.

Adverse Effects and Precautions

The incidence and severity of adverse effects associated with rimantadine appear to be low. Those most commonly reported are gastrointestinal disturbances such as nausea, vomiting, abdominal pain, dry mouth, and anorexia, CNS effects such as headache, insomnia, nervousness, and dizziness, and asthenia. Other less frequently reported adverse effects include ataxia, agitation, concentration difficulties, diarrhoea, dyspepsia, depression, dyspnoea, skin rash, somnolence, and tinnitus.

There have been reports of convulsions, including grand mal convulsions, and rimantadine should be given with caution to patients with epilepsy. Doses are reduced in severe renal or hepatic impairment; reduced doses are also used in the elderly.

◊ A review[1] of clinical studies in adults concluded that rimantadine and amantadine were equally effective for prevention and treatment of influenza A, but rimantadine was significantly better tolerated than amantadine at usual doses. Another systematic review[2] evaluating the safety and efficacy of amantadine and rimantadine in children and the elderly with influenza A concluded that although rimantadine was safe in these groups, its efficacy was unproven and therefore its use could not be recommended.

In a study[3] to evaluate the safety of long-term rimantadine for elderly, chronically ill individuals during an influenza A epidemic, a significantly greater proportion of patients taking rimantadine developed anxiety and/or nausea compared with those taking placebo. There was also a significantly greater number of days in which anxiety, nausea, confusion, depression, or vomiting were reported. Most of these adverse effects lasted less than 9 days and were seldom severe except in 2 patients who withdrew from the study because of insomnia, anxiety, or both and a third who suffered a generalised convulsion. In a larger study[4] the incidence of these symptoms was similar in treatment and placebo groups.

Observations of seizures in 2 patients receiving influenza prophylaxis with rimantadine hydrochloride emphasised that chronically ill and elderly patients prone to seizures (especially those who may have had antiepileptic therapy withdrawn) may be at greater risk of developing seizures.[5] A precautionary measure of reducing the rimantadine hydrochloride dosage to 100 mg daily and temporary re-introduction of antiepileptics was suggested.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 3/10/07).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/02/08).
3. Patriarca PA, *et al.* Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. *Antimicrob Agents Chemother* 1984; **26:** 101–3.
4. Monto AS, *et al.* Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother* 1995; **39:** 2224–8.
5. Bentley DW, *et al.* Rimantadine and seizures. *Ann Intern Med* 1989; **110:** 323–4.

Breast feeding. Rimantadine is distributed into breast milk in *animals* in concentrations about twice those measured in the serum. US licensed product information states that rimantadine should be avoided in breast-feeding mothers.

Pregnancy. Although there is no data available on the use of rimantadine in pregnant women, US licensed product information states that it should only be used if potential benefit justifies the risk to the fetus as embryotoxicity has been reported in *rats* given high doses of rimantadine.

Antiviral Action

Rimantadine is an M2 ion channel inhibitor that inhibits influenza A virus replication mainly by blocking the M2-protein ion channel, thereby preventing fusion of the virus and the host-cell membranes and the release of viral RNA into the cytoplasm of infected cells.

Resistance to rimantadine can occur rapidly and resistant virus may be transmitted to close contacts of patients treated with rimantadine and cause influenza. Rimantadine and amantadine show complete cross-resistance.

Resistance. Resistance of influenza A viruses to the adamantane M2 ion channel inhibitors amantadine and rimantadine can occur spontaneously or emerge rapidly during treatment. A single point mutation in the code sequence for the amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine. The resistant viruses can still replicate and be transmitted.[1-3] A report[4] describing the global prevalence of adamantane-resistant influenza A viruses over a 10 year period shows an increase in drug resistance from 0.4% during the 1994/5 influenza season to 12.3% during the 2003/4 season. During the 2005/6 influenza season, WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories in the United States reported tests on 120 influenza viruses of which 109 (91%) were found to have substitutions in the M2 protein that would confer resistance to amantadine and rimantadine.[3] In the USA, the reported adamantane resistance rate for influenza A increased from 11% for the 2004/5 influenza season to 92% for the 2005/6 influenza season.[5] On the basis of this information, the CDC no longer recommends amantadine or rimantadine for the treatment or prophylaxis of influenza A infections.[3,6]

1. Belshe RB, *et al.* Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* 1988; **62:** 1508–12.
2. Hayden FG, *et al.* Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med* 1989; **321:** 1696–1702.
3. CDC. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005–06 influenza season. *MMWR* 2006; **55:** 44–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5502a7.htm (accessed 13/06/08)
4. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.
5. Bright RA, *et al.* Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. *JAMA* 2006; **295:** 891–4.
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 13/06/08)

Pharmacokinetics

Rimantadine hydrochloride is well, but slowly, absorbed from the gastrointestinal tract and maximum plasma concentrations are reached after about 6 hours. It has a large volume of distribution and long elimination half-life; reported figures for half-life in healthy adults range from 13 to 65 hours (mean 25.4 hours) and from 20 to 65 hours (mean 32 hours) in those over 70 years of age. Protein binding of rimantadine is about 40%. It is extensively metabolised in the liver with less than 25% of a dose being excreted unchanged in the urine; about 75% is excreted as hydroxylated metabolites over 72 hours. In severe renal or hepatic impairment the elimination half-life is about double, necessitating a dosage reduction.

Uses and Administration

Rimantadine hydrochloride is used similarly to amantadine hydrochloride (p.792) in the prophylaxis and treatment of influenza A infections (p.859) in adults and for prophylaxis of influenza A infection in children. It is given orally in usual adult doses of

200 mg daily in divided doses. In elderly patients the usual daily dose is 100 mg. A dosage reduction is also necessary in patients with severe renal or severe hepatic impairment (see below).

For details of doses in children, see below.

◊ Reviews.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/06/08).

Administration in children. For the prophylaxis of influenza A in children from 1 year of age, an oral dose of 5 mg/kg daily, up to a maximum daily dose of 150 mg, may be given. Although not licensed for the treatment of influenza A some experts consider that it may be given to children from 1 year of age.

Administration in hepatic or renal impairment. The usual oral dose of rimantadine in patients with severe renal or severe hepatic impairment and in elderly nursing home patients is 100 mg daily.

Preparations

USP 31: Rimantadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Germic†; Oclovir†; ***Cz.:*** Maridin; ***Mex.:*** Gabirol; ***Rus.:*** Algirem (Альгирем); ***USA:*** Flumadine.

Ritonavir *(BAN, USAN, rINN)*

A-84538; Abbott-84538; ABT-538; Ritonaviiri; Ritonavirum. 5-Thiazolylmethyl {(α*S*)-α-[(1*S*,3*S*)-1-hydroxy-3-((2*S*)-2-{3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido}-3-methylbutyramido)-4-phenylbutyl]phenethyl}carbamate; N^1-[(1*S*,3*S*,4*S*)-1-Benzyl-3-hydroxy-5-phenyl-4-(1,3-thiazol-5-ylmethoxycarbonylamino)pentyl]-N^2-{[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)carbamoyl}-L-valinamide.

Ритонавир

$C_{37}H_{48}N_6O_5S_2$ = 720.9.

CAS — 155213-67-5.

ATC — J05AE03.

ATC Vet — QJ05AE03.

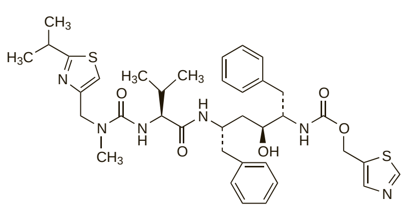

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Ritonavir). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane; very slightly soluble in acetonitrile. It exhibits polymorphism. Protect from light.

USP 31 (Ritonavir). Practically insoluble in water; very soluble in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature between 5° and 30°. Protect from light.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing ritonavir are asthenia, gastrointestinal effects (abdominal pain, anorexia, diarrhoea, nausea, and vomiting), headache, taste disorder, and numbness around the mouth. One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Other commonly reported adverse effects include anxiety, dizziness, insomnia, fever, other gastrointestinal effects (dry mouth, dyspepsia, flatulence, local throat irritation), hyperaesthesia, mouth ulcer, malaise, pharyngitis, pruritus, rash, sweating, vasodilatation, and weight loss. Allergic reactions include urticaria, mild skin eruptions, bronchospasm, angioedema, and rarely anaphylaxis. A possible association with Stevens-Johnson syndrome has been reported with ritonavir. Reported abnormal laboratory results are decreased haemoglobin levels, increased eosinophil counts, raised liver enzymes and uric acid concentrations, and decreased free and total thyroxine concentrations; white blood cell and neutrophil counts may be reduced or increased.

Adverse effects associated with the use of ritonavir as a pharmacokinetic booster are dependent on the other HIV-protease inhibitor.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including ritonavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy including ritonavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Ritonavir (as an antiviral agent or as a pharmacokinetic enhancer) should not be used in patients with decompensated liver disease. Caution is advised in patients with severe hepatic impairment (Child-Pugh Grade C) without decompensation, when ritonavir is used as a pharmacokinetic booster with another HIV-protease inhibitor, although specific recommendations depend on the other drug. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Patients should be monitored for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and increased serum lipase or amylase levels) and ritonavir treatment should be stopped in patients developing pancreatitis.

Interactions

Ritonavir is reported to have a high affinity for several cytochrome P450 isoenzymes with the following ranked order:

CYP3A > CYP2D6 > CYP2C9

Consequently ritonavir may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter; it may also induce glucuronidation and oxidation by CYP1A2 and CYP2C19.

Oral liquid formulations of ritonavir currently contain alcohol and use with disulfiram or metronidazole should be avoided.

Ritonavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include the alpha-adrenergic antagonist alfuzosin, antiarrhythmics (amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine), antifungals (voriconazole), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (clozapine and pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (lovastatin and simvastatin). St John's wort decreases the concentration of ritonavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. UK licensed product information also contra-indicates the use of ritonavir with the analgesics pethidine, piroxicam, and dextropropoxyphene, bupropion, fusidic acid, rifabutin, and some other sedatives and hypnotics (clorazepate, diazepam, estazolam, and flurazepam).

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Ritonavir is also a potent inhibitor of the cytochrome P450 subfamily CYP3A (chiefly the isoenzyme CYP3A4), and low-dose ritonavir is used with other HIV-protease inhibitors to decrease their metabolism and thus increase plasma concentrations of the other protease inhibitor; such use is referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur; in general the greater the number of mutations, the higher the level of resistance. Cross-resistance between HIV-protease inhibitors and NRTIs or NNRTIs is considered unlikely.

Pharmacokinetics

Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults. About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

◊ References.

1. Hsu A, *et al.* Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 1997; **41:** 898–905.
2. Hsu A, *et al.* Ritonavir: clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35:** 275–91.

Uses and Administration

Ritonavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when ritonavir is used alone, and it is therefore given with other antiretrovirals.

Ritonavir is given orally in an adult dose of 600 mg twice daily with food. In order to minimise nausea, ritonavir may be started at a dose of 300 mg twice daily and gradually increased over a period of up to 14 days by 100 mg twice daily to a total of 600 mg twice daily.

For details of doses in children, see below.

When used as a pharmacokinetic enhancer ritonavir is given in doses of 100 to 200 mg once or twice daily with other HIV-protease inhibitors.

◊ Reviews.

1. Lea AP, Faulds D. Ritonavir. *Drugs* 1996; **52:** 541–6.
2. Cooper CL, *et al.* A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; **36:** 1585–92.

Administration. Adjusting the dosage of ritonavir from 600 mg twice daily to 300 mg every 6 hours improved tolerability in 2 patients who would otherwise have stopped the drug.[1]

1. Merry C, *et al.* Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996; **42:** 787.

Administration in children. For the treatment of HIV infection in children, ritonavir is given daily with other antiretroviral drugs. US licensed product information permits the use of oral ritonavir in infants over 1 month of age, whereas in the UK it is recommended from 2 years of age. The dose given should not exceed the maximum adult dose of 600 mg twice daily.

The recommended dose regimen is an initial dose of 250 mg/m^2 twice daily increasing by 50 mg/m^2 twice daily at 2- or 3-day intervals up to 350 to 400 mg/m^2 twice daily.

Molluscum contagiosum. Intractable molluscum contagiosum, a viral skin infection, resolved when a patient was given ritonavir for treatment of HIV infection.[1]

1. Hicks CB, *et al.* Resolution of intractable molluscum contagiosum in a human immunodeficiency virus-infected patient after institution of antiretroviral therapy with ritonavir. *Clin Infect Dis* 1997; **24:** 1023–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rifaxi; ***Austral.:*** Norvir; ***Belg.:*** Norvir; ***Braz.:*** Ritovir†; ***Canad.:*** Norvir; ***Chile:*** Norvir; ***Cz.:*** Norvir; ***Denm.:*** Norvir; ***Fin.:*** Norvir; ***Fr.:*** Norvir; ***Ger.:*** Norvir; ***Gr.:*** Norvir; ***Hong Kong:*** Norvir; ***Hung.:*** Norvir; ***India:*** Ritomune; ***Indon.:*** Norvir; ***Irl.:*** Norvir; ***Israel:*** Norvir; ***Ital.:*** Norvir; ***Jpn:*** Norvir; ***Malaysia:*** Norvir; ***Mex.:*** Norvir; ***Neth.:*** Norvir; ***Norw.:*** Norvir; ***NZ:*** Norvir; ***Pol.:*** Norvir; ***Port.:*** Norvir; ***Rus.:*** Norvir (Норвир)†; ***S.Afr.:*** Norvir; ***Spain:*** Norvir; ***Swed.:*** Norvir; ***Switz.:*** Norvir; ***Thai.:*** Norvir; ***Turk.:*** Norvir; ***UK:*** Norvir; ***USA:*** Norvir; ***Venez.:*** Norvir.

Multi-ingredient: ***Arg.:*** Kaletra; ***Austral.:*** Kaletra; ***Austria:*** Kaletra; ***Belg.:*** Kaletra; ***Braz.:*** Kaletra; ***Canad.:*** Kaletra; ***Chile:*** Kaletra; ***Cz.:*** Kaletra; ***Denm.:*** Kaletra; ***Fin.:*** Kaletra; ***Fr.:*** Kaletra; ***Ger.:*** Kaletra; ***Gr.:*** Kaletra; ***Hong Kong:*** Kaletra; ***Hung.:*** Kaletra; ***India:*** Ritomax-L; ***Israel:*** Kaletra; ***Ital.:*** Kaletra; ***Malaysia:*** Kaletra; ***Mex.:*** Kaletra; ***Neth.:*** Kaletra; ***Norw.:*** Kaletra; ***NZ:*** Kaletra; ***Pol.:*** Kaletra; ***Port.:*** Kaletra; ***Rus.:*** Kaletra (Калетра); ***S.Afr.:*** Kaletra; ***Singapore:*** Kaletra; ***Spain:*** Kaletra; ***Swed.:*** Kaletra; ***Switz.:*** Kaletra; ***Thai.:*** Kaletra; ***Turk.:*** Kaletra; ***UK:*** Kaletra; ***USA:*** Kaletra; ***Venez.:*** Kaletra.

Saquinavir *(BAN, USAN, rINN)*

Ro-31-8959; Sakinavir; Saquinavirum. N^1-{(1*S*,2*R*)-1-Benzyl-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)perhydroisoquinolin-2-yl]-2-hydroxypropyl}-N^2-(2-quinolylcarbonyl)-L-aspartamide; (*S*)-*N*-[(α*S*)-α-{(1*R*)-2-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl}phenethyl]-2-quinaldamidosuccinamide.

Саквинавир

$C_{38}H_{50}N_6O_5$ = 670.8.

CAS — 127779-20-8.

ATC — J05AE01.

ATC Vet — QJ05AE01.

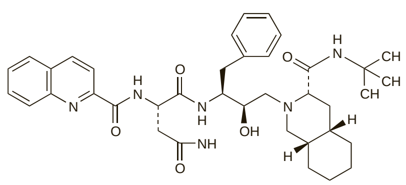

Pharmacopoeias. In *Int.*

Saquinavir Mesilate *(BANM, rINNM)*

Mesilato de saquinavir; Ro-31-8959/003; Sakinaviirimesilaatti; Sakinavirmesilat; Saquinavir, mésilate de; Saquinavir Mesylate *(USAN)*; Saquinaviri mesilas. Saquinavir methanesulfonate.

Саквинавира Мезилат

$C_{38}H_{50}N_6O_5,CH_4O_3S$ = 766.9.

CAS — 149845-06-7.

ATC — J05AE01.

ATC Vet — QJ05AE01.

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Saquinavir Mesylate). Store in airtight containers.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing saquinavir are gastrointestinal disorders (abdominal pain, diarrhoea, flatulence, nausea, vomiting) and fatigue. Other commonly reported adverse effects include alopecia, anaemia, anorexia, increased appetite, asthenia, constipation, dizziness, dry lips, mouth and skin, dyspepsia, dyspnoea, eczema, headache, hypersensitivity, decreased libido, malaise, muscle spasm, paraesthesia, peripheral neuropathy, pruritus, rash, sleep disturbances, and taste disorders. Commonly reported laboratory abnormalities include raised liver enzyme values, increased blood amylase, bilirubin, and creatinine, and lowered haemoglobin and platelet, lymphocyte, and white blood cell count. Rare but serious adverse effects that may be associated with saquinavir include acute myeloid leukaemia, haemolytic anaemia, allergic reactions, ascites, bullous skin eruptions, intestinal obstruction, jaundice, nephrolithiasis, pancreatitis, polyarthritis, portal hypertension, seizures, Stevens-Johnson syndrome, attempted suicide, and thrombocytopenia (occasionally fatal).

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including saquinavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including saquinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Ritonavir-boosted saquinavir should not be used in patients with decompensated liver disease and should be used with caution in patients with moderate hepatic or severe renal impairment. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Interactions

Saquinavir is reported to be metabolised by the cytochrome P450 system, with the specific isoenzyme CYP3A4 responsible for more than 90% of the hepatic metabolism. Saquinavir is also a substrate and an inhibitor of P-glycoprotein. Drugs that affect this isoenzyme and/or P-glycoprotein may modify saquinavir plasma concentrations. Saquinavir may alter the pharmacokinetics of other drugs that are metabolised by this enzyme system or that are substrates for P-glycoprotein.

Saquinavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, propafenone, and quinidine), antihistamines (astemizole and terfenadine), antimycobacterial (rifampicin), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). St John's wort decreases the concentration of saquinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Saquinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. HIV isolates resistant to saquinavir have been reported and variable cross-resistance with other HIV-protease inhibitors has been seen. Cross-resistance between saquinavir and NRTIs or NNRTIs is unlikely because these drugs have different target enzymes.

Pharmacokinetics

Saquinavir is absorbed to a limited extent (about 30%) after oral doses of the mesilate and undergoes extensive first-pass hepatic metabolism, resulting in a bioavailability of 4% when taken with food. Bioavailability was found to be greater from a soft gelatin capsule formulation of saquinavir base in a suitable vehicle (*Fortovase, Roche*) than from a hard capsule formulation (*Invirase, Roche*). Bioavailability is substantially less when saquinavir is taken in the fasting state. Plasma concentrations are reported to be higher in HIV-infected patients than in healthy subjects. Saquinavir is about 98% bound to plasma proteins and extensively distributed into the tissues, although CSF concentrations are reported to be negligible. It is rapidly metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to a number of inactive monohydroxylated and dihydroxylated compounds. It is excreted mainly in the faeces with a reported terminal elimination half-life of 13.2 hours.

◊ References.

1. Regazzi MB, *et al.* Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir (SQV) in HIV-1 infected individuals. *Br J Clin Pharmacol* 1999; **47:** 379–82.
2. Grub S, *et al.* Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2002; **71:** 122–30.
3. Acosta EP, *et al.* Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; **48:** 430–6.

Uses and Administration

Saquinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when saquinavir is used alone, and it is therefore used with other antiretrovirals, including low-dose ritonavir which is given as a pharmacokinetic enhancer (ritonavir-boosted saquinavir).

Saquinavir is given orally as the mesilate but doses are expressed in terms of the base; 229 mg of saquinavir mesilate is equivalent to about 200 mg of saquinavir. The dose is 1 g twice daily given with ritonavir 100 mg twice daily with or after food.

◊ Reviews.

1. Vella S, Floridia M. Saquinavir: clinical pharmacology and efficacy. *Clin Pharmacokinet* 1998; **34:** 189–201.
2. Figgitt DP, Plosker GL. Saquinavir soft-gel capsule: an updated review of its use in the management of HIV infection. *Drugs* 2000; **60:** 481–516.
3. Plosker GL, Scott LJ. Saquinavir: a review of its use in boosted regimens for treating HIV infection. *Drugs* 2003; **63:** 1299–1324.

Preparations

USP 31: Saquinavir Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Fortovase; Proteovir; ***Austral.:*** Fortovase; Invirase; ***Austria:*** Fortovase; Invirase; ***Belg.:*** Fortovase†; Invirase; ***Braz.:*** Fortovase; Invirase; Svir†; ***Canad.:*** Fortovase; Invirase; ***Chile:*** Fortovase†; Invirase; ***Cz.:*** Fortovase†; Invirase; ***Denm.:*** Fortovase; Invirase; ***Fin.:*** Fortovase†; Invirase; ***Fr.:*** Fortovase; Invirase; ***Ger.:*** Fortovase†; Invirase; ***Gr.:*** Fortovase; Invirase; ***Hong Kong:*** Fortovase†; Invirase; ***Hung.:*** Invirase; ***Irl.:*** Fortovase†; Invirase; ***Israel:*** Fortovase; Invirase; ***Ital.:*** Fortovase; Invirase; ***Jpn:*** Fortovase; Invirase; ***Mex.:*** Fortovase; Invirase; ***Neth.:*** Fortovase; Invirase; ***Norw.:*** Fortovase; Invirase; ***NZ:*** Fortovase; Invirase; ***Philipp.:*** Invirase; ***Pol.:*** Invirase; ***Port.:*** Fortovase†; Invirase; ***S.Afr.:*** Fortovase†; Invirase; ***Spain:*** Fortovase; Invirase; ***Swed.:*** Fortovase†; Invirase; ***Switz.:*** Fortovase†; Invirase; ***Thai.:*** Fortovase; ***UK:*** Fortovase†; Invirase; ***USA:*** Fortovase†; Invirase; ***Venez.:*** Fortovase.

Sorivudine *(BAN, USAN, rINN)*

Bravavir; Bromovinylarauracil; Brovavir; BV-araU; BVAU; Sorivudina; Sorivudinum; SQ-32756; YN-72. (*E*)-1-β-D-Arabinofuranosyl-5-(2-bromovinyl)uracil.

Соривудин

$C_{11}H_{13}BrN_2O_6$ = 349.1.

CAS — 77181-69-2.

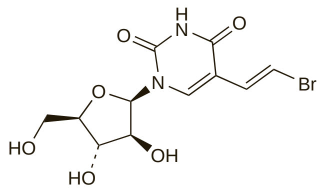

Profile

Sorivudine is a synthetic thymidine derivative with antiviral activity against varicella-zoster virus. It has been investigated for the treatment of herpes zoster but was withdrawn from the market in Japan after deaths in patients also given fluorouracil.

◊ References.

1. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
2. Diasio RB. Sorivudine and 5-fluorouracil: a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.

Stavudine *(BAN, USAN, pINN)*

BMY-27857; d4T; Estavudina; Stavudiini; Stavudin; Stavudinas; Stavudinum. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-thymine.

Ставудин

$C_{10}H_{12}N_2O_4$ = 224.2.

CAS — 3056-17-5.

ATC — J05AF04.

ATC Vet — QJ05AF04.

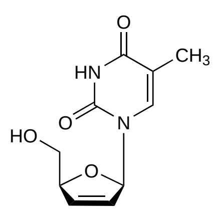

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Stavudine). A white or almost white powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Protect from light and humidity.

USP 31 (Stavudine). A white to off-white, crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in alcohol, in acetonitrile, and in methyl alcohol; slightly soluble in dichloromethane; insoluble in petroleum spirit. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

The most common adverse effect reported with stavudine either as monotherapy or with other antiretrovirals is peripheral neuropathy; it occurs more frequently in patients taking stavudine with didanosine and hydroxycarbamide. Other common adverse effects include abdominal pain, nausea, diarrhoea, dyspepsia, fatigue, dizziness, depression, headache, insomnia, sleep disturbances, pruritus, and rash. Abnormal liver function tests may occur and hepatitis, hepatic failure, and pancreatitis have been reported rarely; fatalities have occurred and were reported most often in patients taking stavudine with didanosine and hydroxycarbamide. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs. There have been reports of motor weakness associated with stavudine, occurring particularly in association with lactic acidosis.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including stavudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including stavudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the nervous system. Peripheral neuropathy is a well recognised adverse effect of stavudine and has been the subject of a review.[1]

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; **19:** 481–94.

Gynaecomastia. Bilateral gynaecomastia was associated with stavudine use in a patient with HIV infection who was also receiving lamivudine and co-trimoxazole.[1] Symptoms resolved when stavudine was stopped. Four other cases of gynaecomastia were reported in HIV-infected patients given HAART regimens containing stavudine.[2]

1. Melbourne KM, *et al.* Gynecomastia with stavudine treatment in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1108.
2. Manfredi R, *et al.* Gynecomastia associated with highly active antiretroviral therapy. *Ann Pharmacother* 2001; **35:** 438–9.

Precautions

Stavudine should be used with caution in patients with a history of peripheral neuropathy and treatment suspended if peripheral neuropathy develops; if symptoms resolve on withdrawal, stavudine may be resumed at half the previous dose. Treatment with stavudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Stavudine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. If liver enzymes increase to 5 times the upper limit of normal during treatment then stavudine should be stopped. Patients co-infected with chronic hepatitis B or C who are being treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. Patients with a history of pancreatitis should also be observed carefully for signs of pancreatitis during stavudine treatment. Use with other drugs likely to cause peripheral neuropathy or pancreatitis should be avoided if possible. Stavudine should be used with caution and doses reduced in patients with renal impairment.

Interactions

The intracellular activation of stavudine and hence its antiviral effect may be inhibited by zidovudine, doxorubicin, and ribavirin.

Use of stavudine with other drugs known to cause pancreatitis or peripheral neuropathy should be avoided if possible. The combination of hydroxycarbamide and didanosine if given with stavudine, may carry a higher risk of adverse effects including hepatotoxicity, peripheral neuropathy, and pancreatitis (fatal and non-fatal).

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antivirals. Reference to *in-vivo* antagonism of the antiretroviral effect of stavudine when used with *zidovudine*.[1]

1. Havlir DV, *et al.* In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000; **182:** 321–5.

Phenylpropanolamine. Hypertensive crisis associated with use of phenylpropanolamine and clemastine occurred in a patient receiving HIV prophylaxis with indinavir, lamivudine, and stavudine.[1] The most likely cause was an interaction between phenylpropanolamine and stavudine, although interactions with the other antiretrovirals could not be ruled out.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Antiviral Action

Stavudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Stavudine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Stavudine is absorbed rapidly after oral doses producing peak plasma concentrations within 1 hour and with a reported bioavailability of about 86%. Giving it with food delays but does not reduce absorption. Stavudine crosses the blood-brain barrier producing a CSF to plasma ratio of about 0.4 after 4 hours. Binding to plasma proteins is negligible. Stavudine is metabolised intracellularly to the active antiviral triphosphate. The elimination half-life is reported to be about 1 to 1.5 hours after single or multiple doses. The intracellular half-life of stavudine triphosphate has been estimated to be 3.5 hours *in vitro*. About 40% of a dose is excreted in the urine by active tubular secretion and glomerular filtration. Stavudine is removed by haemodialysis.

◊ References.

1. Rana KZ, Dudley MN. Clinical pharmacokinetics of stavudine. *Clin Pharmacokinet* 1997; **33:** 276–84.
2. Kaul S, *et al.* Effect of food on bioavailability of stavudine in subjects with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1998; **42:** 2295–8.
3. Grasela DM, *et al.* Pharmacokinetics of single-dose oral stavudine in subjects with renal impairment and in subjects requiring hemodialysis. *Antimicrob Agents Chemother* 2000; **44:** 2149–53.

Uses and Administration

Stavudine is a nucleoside reverse transcriptase inhibitor related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when stavudine is used alone, and it is therefore used with other antiretrovirals. Stavudine is given orally, usually as a capsule or solution. Usual adult doses of stavudine are 40 mg every 12 hours for patients weighing 60 kg or more or 30 mg every 12 hours for patients weighing less than 60 kg.

For details of doses in infants, children, and adolescents, see below.

For details of reduced doses of stavudine to be used in patients with renal impairment, see below.

◊ Reviews.

1. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. *Drugs* 1999; **58:** 919–49.
2. Cheer SM, Goa KL. Stavudine once daily. *Drugs* 2002; **62:** 2667–74.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents stavudine is given orally with other antiretroviral drugs. Doses are based on body-weight:

- in neonates from birth to 13 days old a dose of 500 micrograms/kg every 12 hours may be given
- in infants at least 14 days old and those weighing less than 30 kg the dose is 1 mg/kg every 12 hours
- in children and adolescents weighing 30 kg or more, the adult dose is given (see above)

Administration in renal impairment. Dosage reduction according to creatinine clearance (CC) is recommended for patients receiving oral stavudine who have renal impairment:

- CC 26 to 50 mL/minute: 20 mg every 12 hours (those weighing 60 kg or more) or 15 mg every 12 hours (those weighing less than 60 kg)
- CC below 26 mL/minute: 20 mg every 24 hours (those weighing 60 kg or more) or 15 mg every 24 hours (those weighing less than 60 kg)

Preparations

USP 31: Stavudine Capsules; Stavudine for Oral Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Birac†; Lion; Revixil†; Stamar; Stavubergen; Stelea†; STV; Tonavir; Zerit; ***Austral.:*** Zerit; ***Austria:*** Zerit; ***Belg.:*** Zerit; ***Braz.:*** Svudin†; Zeritavir; ***Canad.:*** Zerit; ***Chile:*** Zerit; ***Cz.:*** Zerit; ***Denm.:*** Zerit; ***Fin.:*** Zerit; ***Fr.:*** Zerit; ***Ger.:*** Zerit; ***Gr.:*** Zerit; ***Hong Kong:*** Zerit; ***Hung.:*** Zerit; ***India:*** Stavir; ***Indon.:*** Zerit; ***Irl.:*** Zerit; ***Israel:*** Zerit†; ***Ital.:*** Zerit; ***Jpn:*** Zerit; ***Malaysia:*** Virostav; Zerit†; ***Mex.:*** Apostavina†; Landstav; Pravidine; Ranstar; Zerit; ***Neth.:*** Zerit; ***Norw.:*** Zerit; ***NZ:*** Zerit; ***Pol.:*** Zerit; ***Port.:*** Zerit; ***Rus.:*** Actastav (Актастав); Zerit (Зерит); ***S.Afr.:*** Stavir; Zerit; ***Singapore:*** Zerit; ***Spain:*** Zerit; ***Swed.:*** Zerit; ***Switz.:*** Zerit; ***Thai.:*** Zerit; ***Turk.:*** Zerit; ***UK:*** Zerit; ***USA:*** Zerit; ***Venez.:*** Stavir; Zerit.

Multi-ingredient: ***India:*** Lamivir S; Triomune; ***S.Afr.:*** Triomune; ***Venez.:*** Triomune.

Telbivudine *(BAN, USAN, rINN)*

L-dT; Epavudine; LDT-600; NV-02B; Telbivudina; Telbivudinum. 2′-Deoxy-L-thymidine; 1-(2-Deoxy-β-L-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

Тельбивудин

$C_{10}H_{14}N_2O_5$ = 242.2.

CAS — 3424-98-4.

ATC — J05AF11.

ATC Vet — QJ05AF11.

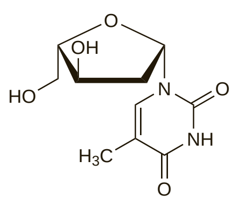

Adverse Effects

The most common adverse effects reported for telbivudine are cough, dizziness, fatigue, gastrointestinal effects including abdominal pain, diarrhoea, and nausea, and rash. There have also been reports of arthralgia, myalgia, myopathy, and malaise. Serum amylase, lipase and creatine phosphokinase levels may be increased. Raised serum alanine aminotransferase concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with telbivudine. There have been occasional reports of peripheral neuropathy, particularly when given with peginterferon alfa-2a.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues (see Zidovudine, p.914).

Precautions

Telbivudine should be given with caution to patients with cirrhosis, hepatomegaly, or other risk factors for liver disease and should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Exacerbation of hepatitis B has been reported both during and after stopping treatment with telbivudine. Liver function should be monitored closely during treatment and for several months after treatment is stopped. Patients taking telbivudine should be monitored for peripheral neuropathy and treatment should be stopped if myopathy or peripheral neuropathy is diagnosed. Dosage reduction may be necessary in patients with renal impairment.

Interactions

Caution should be exercised when telbivudine is given with other drugs that alter renal function; serum concentrations of either drug may be affected. Telbivudine should be given with caution to patients taking other drugs associated with myopathy (such as azole antifungals, ciclosporin, corticosteroids, erythromycin, fibrates, HMG-CoA reductase inhibitors, penicillamine, and zidovudine).

Interferons. For mention of an increased risk of peripheral neuropathy in patients given both telbivudine and *peginterferon alfa-2a*, see Adverse Effects, above.

Antiviral Action

Telbivudine is phosphorylated intracellularly to the active triphosphate form, which competes with thymidine 5'-triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby causing DNA chain termination and inhibiting hepatitis B viral replication.

Telbivudine has no activity against HIV.

Pharmacokinetics

Telbivudine is absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur after about 3 hours. Absorption is not affected when given with food. Binding of telbivudine to plasma proteins is about 3.3% *in vitro*. Telbivudine is not metabolised by the cytochrome P450 system. It is mainly excreted renally by glomerular filtration as unchanged drug, with a terminal elimination half-life of 30 to 53.6 hours. Telbivudine is partially removed by haemodialysis.

Uses and Administration

Telbivudine is an orally bioavailable L-nucleoside analogue with specific activity against the hepatitis B virus. It is given orally for the treatment of chronic hepatitis B (p.851) in patients with compensated liver disease and evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of telbivudine is 600 mg once daily. For details of dosage modification in patients with renal impairment, see below.

◊ References.

1. Lai CL, *et al.* A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. *Hepatology* 2004; **40:** 719–26.
2. Lai CL, *et al.* A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; **129:** 528–36.
3. Kim JW, *et al.* Telbivudine: a novel nucleoside analog for chronic hepatitis B. *Ann Pharmacother* 2006; **40:** 472–8.
4. Jones R, Nelson M. Novel anti-hepatitis B agents: a focus on telbivudine. *Int J Clin Pract* 2006; **60:** 1295–9.
5. Keam SJ. Telbivudine. *Drugs* 2007; **67:** 1917–29.

Administration in renal impairment. The dosage of telbivudine should be reduced in patients with renal impairment by modifying the dosing interval according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: 600 mg once daily
- CC 30 to 49 mL/minute: 600 mg every 48 hours
- CC less than 30 mL/minute (and not on dialysis): 600 mg every 72 hours
- end stage renal disease: 600 mg every 96 hours

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Sebivo; ***Indon.:*** Sebivo; ***Malaysia:*** Sebivo; ***Port.:*** Sebivo; ***UK:*** Sebivo; ***USA:*** Tyzeka.

Tenofovir *(BAN, USAN, rINN)*

GS-1278; PMPA; (*R*)-PMPA; Ténofovir; Tenofovirum. 9-[(*R*)-2-(Phosphonomethoxy)propyl]adenine monohydrate; {[(*R*)-2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}phosphonic acid monohydrate.

Тенофовир

$C_9H_{14}N_5O_4P,H_2O$ = 305.2.

CAS — 147127-20-6 (anhydrous tenofovir); 206184-49-8 (tenofovir monohydrate).

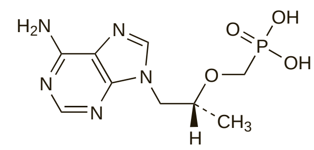

(anhydrous tenofovir)

Tenofovir Disoproxil Fumarate *(BANM, USAN, rINNM)*

Fumarato de disoproxilo de tenofovir; GS-4331/05; Ténofovir Disoproxil, Fumarate de; Tenofovirum Disoproxilum Fumaras. 9-{(*R*)-2-[(Bis{[(isopropoxycarbonyl)oxy]methoxy}phosphinyl)methoxy]propyl}adenine fumarate (1:1).

Тенофовир Дизопроксил Фумарат

$C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$ = 635.5.

CAS — 202138-50-9.

ATC — J05AF07.

ATC Vet — QJ05AF07.

Adverse Effects

Adverse effects commonly associated with tenofovir disoproxil fumarate either as monotherapy for the treatment of chronic hepatitis B or with other antiretrovirals for the treatment of HIV are mild to moderate gastrointestinal events such as anorexia, abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting. Other commonly reported adverse effects are dizziness, fatigue, and headache. Skin rashes may occur. Hypophosphataemia is also common. Serum-amylase concentrations may be raised and pancreatitis has been reported rarely. There have also been reports of raised liver enzymes, hepatitis, nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules, including Fanconi syndrome.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside reverse transcriptase inhibitors.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tenofovir disoproxil fumarate, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tenofovir disoproxil fumarate. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Effects on the kidney. Use of tenofovir in patients with HIV infection has been associated with renal toxicity,[1] including Fanconi syndrome,[2] interstitial nephritis,[3] and acute renal failure.[4,5] The mechanism of acute renal failure appears to be tubular necrosis, which may not resolve on withdrawal of the drug.[6] Some studies have indicated that glomerular filtration rate or creatinine clearance was consistently decreased in patients given tenofovir-containing regimens;[7,8] it has been reported that this is greater if combined with HIV-protease inhibitors than NNRTIs.[8] Other studies have not found renal toxicity to be a significant problem.[9,10]

1. Gitman MD, *et al.* Tenofovir-induced kidney injury. *Expert Opin Drug Saf* 2007; **6:** 155–64.

2. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS* 2008; **22:** 99–103.
3. Schmid S, *et al.* Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. *Virchows Arch* 2007; **450:** 665–70.
4. Hynes P, *et al.* Acute renal failure after initiation of tenofovir disoproxil fumarate. *Ren Fail* 2007; **29:** 1063–6.
5. Kapitsinou PP, Ansari N. Acute renal failure in an AIDS patient on tenofovir: a case report. *J Med Case Reports* 2008; **2:** 94.
6. Zimmermann AE, *et al.* Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006; **42:** 283–90.
7. Fux CA, *et al.* Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther* 2007; **12:** 1165–73.
8. Goicoechea M, *et al.* Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008; **197:** 102–8.
9. Viganò A, *et al.* Renal safety of tenofovir in HIV-infected children: a prospective, 96-week longitudinal study. *Clin Drug Investig* 2007; **27:** 573–81.
10. Madeddu G, *et al.* Tenofovir renal safety in HIV-infected patients: results from the SCOLTA Project. *Biomed Pharmacother* 2008; **62:** 6–11.

Precautions

Treatment with tenofovir disoproxil fumarate should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. It should be given with caution to patients with hepatomegaly or other risk factors for liver disease. In particular, extreme caution should be exercised in patients with co-existing hepatitis C infection who are receiving interferon alfa and ribavirin. In patients co-infected with hepatitis B, there is a risk of severe acute exacerbation of hepatitis when tenofovir is stopped, and liver function should be monitored closely in such patients for at least several months.

Tenofovir should be used with caution, and doses modified, in patients with renal impairment. Renal function and serum phosphates should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months; in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed. If serum-phosphate concentrations fall markedly or if creatinine clearance is below 50 mL/minute, renal function should be evaluated within a week, and the dose interval may need to be adjusted or treatment interrupted. Tenofovir disoproxil fumarate may be associated with reduction in bone density and patients should be observed for evidence of bone abnormalities; bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia.

Interactions

Use of tenofovir disoproxil fumarate with nephrotoxic drugs or with other drugs eliminated by active tubular secretion is not recommended; if such use is unavoidable, renal function should be monitored weekly. Tenofovir increases the plasma concentrations of didanosine (see p.871). Once daily triple nucleoside regimens of tenofovir and lamivudine with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided. Decreased plasma concentrations of atazanavir and increased plasma concentrations of tenofovir occur when tenofovir is given with atazanavir; the effect is significantly reduced when ritonavir is added as a booster. Use of ritonavir-boosted lopinavir with tenofovir modestly increases the plasma concentrations of tenofovir.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antiviral Action

Tenofovir is converted intracellularly to the diphosphate. This diphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Tenofovir-resistant strains of HIV have been identified and cross-resistance to other reverse transcriptase inhibitors may occur.

Pharmacokinetics

Tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir after oral doses, with peak plasma concentrations occurring after 1 to 2 hours. Bioavailability in fasting patients is about 25%, but this is enhanced when tenofovir disoproxil fumarate is taken with a high fat meal. Tenofovir is widely distributed into body tissues, particularly the kidneys and liver. Binding to plasma proteins is less than 1% and that to serum proteins about 7%. The terminal elimination half-life of tenofovir is 12 to 18 hours. Tenofovir is excreted mainly in the urine by both active tubular secretion and glomerular filtration. It is removed by haemodialysis.

◊ Reviews.

1. Kearney BP, *et al.* Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 2004; **43:** 595–612.
2. Kearney BP, *et al.* Pharmacokinetics and dosing recommendations of tenofovir disoproxil fumarate in hepatic or renal impairment. *Clin Pharmacokinet* 2006; **45:** 1115–24.

Uses and Administration

Tenofovir is a nucleotide reverse transcriptase inhibitor with antiviral activity against HIV-1 and hepatitis B. It is used in the treatment of HIV infection and AIDS (p.856) and chronic hepatitis B infection (p.851). Viral resistance emerges rapidly when tenofovir is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

It is given orally as the disoproxil fumarate ester. Tenofovir disoproxil fumarate 300 mg is equivalent to about 245 mg of tenofovir disoproxil and to about 136 mg of tenofovir. For the treatment of either HIV or chronic hepatitis B infection the usual dose is 300 mg of the disoproxil fumarate ester once daily with food.

For details of doses of tenofovir disoproxil fumarate to be used in patients with renal impairment, see below.

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing tenofovir disoproxil fumarate in combination with emtricitabine, and with efavirenz plus emtricitabine are available in some countries.

A gel containing tenofovir is under investigation as a topical microbicide in the prevention of HIV infection.

◊ Reviews.

1. Grim SA, Romanelli F. Tenofovir disoproxil fumarate. *Ann Pharmacother* 2003; **37:** 849–59.
2. Gallant JE, Deresinski S. Tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; **37:** 944–50.
3. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
4. Lyseng-Williamson KA, *et al.* Tenofovir disoproxil fumarate: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 413–32.
5. Wong SN, Lok AS. Tenofovir disoproxil fumarate: role in hepatitis B treatment. *Hepatology* 2006; **44:** 309–13.
6. Reijnders JGP, Janssen HLA. Potency of tenofovir in chronic hepatitis B: mono or combination therapy? *J Hepatol* 2008; **48:** 383–6.
7. Stephan C. Experience with tenofovir disoproxil fumarate for antiretroviral therapy. *Expert Opin Pharmacother* 2008; **9:** 1197–209.
8. Pozniak A. Tenofovir: what have over 1 million years of patient experience taught us? *Int J Clin Pract* 2008; **62:** 1285–93.

Administration in renal impairment. Doses of tenofovir disoproxil fumarate should be modified by adjustment of the dosing interval in patients with renal impairment according to their creatinine clearance (CC):

- CC 50 mL or more per minute: usual once-daily dosage (above)
- CC 30 to 49 mL/minute: every 48 hours
- CC 10 to 29 mL/minute: every 72 to 96 hours
- haemodialysis patients: a dose every 7 days or after a cumulative total of 12 hours of dialysis

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Viread; ***Austral.:*** Viread; ***Austria:*** Viread; ***Belg.:*** Viread; ***Canad.:*** Viread; ***Chile:*** Viread; ***Cz.:*** Viread; ***Denm.:*** Viread; ***Fin.:*** Viread; ***Fr.:*** Viread; ***Ger.:*** Viread; ***Gr.:*** Viread; ***Hung.:*** Viread; ***Irl.:*** Viread; ***Israel:*** Viread; ***Ital.:*** Viread; ***Mex.:*** Viread; ***Neth.:*** Viread; ***Norw.:*** Viread; ***NZ:*** Viread; ***Pol.:*** Viread; ***Spain:*** Viread; ***Swed.:*** Viread; ***Switz.:*** Viread; ***UK:*** Viread; ***USA:*** Viread.

Multi-ingredient: ***Arg.:*** Truvada; ***Austral.:*** Truvada; ***Cz.:*** Truvada; ***Fin.:*** Truvada; ***Fr.:*** Truvada; ***Ger.:*** Truvada; ***Gr.:*** Truvada; ***Irl.:*** Truvada; ***Ital.:*** Truvada; ***Mex.:*** Truvada; ***Neth.:*** Truvada; ***NZ:*** Truvada; ***Port.:*** Truvada; ***Spain:*** Truvada; ***Swed.:*** Truvada; ***UK:*** Atripla; Truvada; ***USA:*** Atripla; Truvada.

Tipranavir *(rINN)*

PNU-140690; Tipranavirum; U-140690. 3′-{(1*R*)-1-[(6*R*)-5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl]propyl}-5-(trifluoromethyl)-2-pyridinesulfonanilide.

Типранавир

$C_{31}H_{33}F_3N_2O_5S$ = 602.7.
CAS — 174484-41-4.
ATC — J05AE09.
ATC Vet — QJ05AE09.

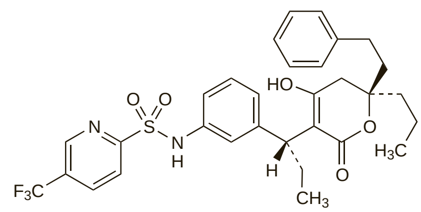

NOTE. Tipranavir Disodium is USAN.

Tipranavir Sodium *(BANM, rINNM)*

Natrii Tipranavirum; PNU-140690E; Tipranavir Disodium *(USAN)*; Tipranavir sodico; Tipranavir Sodique.

Натрий Типранавир

$C_{31}H_{31}F_3N_2Na_2O_5S$ = 646.6.
CAS — 191150-83-1.
ATC — J05AE09.
ATC Vet — QJ05AE09.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing tipranavir are gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting), anorexia, fatigue, and headache. Serious adverse effects reported include increased risk of bleeding, lipid abnormalities (hyperlipidaemia and hypertriglyceridaemia), and severe hepatotoxicity (hepatitis and hepatic decompensation) and intracranial haemorrhage including some fatalities. Rashes, generally occurring after about 2 months of treatment and lasting about 3 weeks have been reported; rashes are sometimes accompanied by joint pain, stiffness, throat tightness, or generalised pruritus.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including tipranavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including tipranavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh class B or C), and should be used with caution in those with mild impairment (Child-Pugh A). Treatment should not be started in patients with pre-treatment liver enzyme values more than 5 times the upper limit of normal. Patients should be closely monitored for clinical signs and symptoms of hepatitis; monitoring of liver enzymes is recommended before and during treatment with tipranavir. In patients with mild hepatic impairment, chronic hepatitis, or other underlying liver disease more frequent monitoring is recommended. Treatment should be interrupted or stopped if liver function deteriorates and should be permanently stopped in those patients with liver enzyme values more than 10 times the upper limit of normal or in those who develop signs or symptoms of clinical hepatitis. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients who are at increased risk of bleeding such as those with haemophilia A and B or who are taking antiplatelet drugs or anticoagulants as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Tipranavir oral solution contains vitamin E and patients given the oral solution should not take high doses of supplemental vitamin E.

Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy.

Interactions

Tipranavir is both an inducer and an inhibitor of the cytochrome P450 isoenzyme CYP3A4 although when given with low-dose ritonavir there is a net inhibition of CYP3A4; there is therefore the potential for complex interactions with other drugs metabolised by this enzyme. Ritonavir-boosted tipranavir is also a net inducer of P-glycoprotein.

Tipranavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, metoprolol, propafenone, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of tipranavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Tipranavir is a non-peptide HIV-protease inhibitor. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. HIV isolates resistant to tipranavir have been reported and viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Tipranavir is absorbed to a limited extent after oral doses. Food improves the tolerability and bioavailability is increased with a high fat meal. Peak plasma concentrations are reached within 1 to 5 hours and steady state is usually reached after 7 to 10 days of treatment. Tipranavir is about 99.9% bound to plasma proteins. It is metabolised by the cytochrome P450 system (predominantly the isoenzyme CYP3A4), although when given with ritonavir metabolism is minimal with the majority of tipranavir being excreted unchanged in the faeces. The mean elimination half-life of tipranavir is 4.8 to 6 hours.

Uses and Administration

Tipranavir is a non-peptide HIV-protease inhibitor with antiviral activity against HIV. It is used for the treatment of HIV infection and AIDS (p.856) in treatment-experienced patients or in those with multidrug-resistant HIV infection. Viral resistance emerges rapidly when tipranavir is used alone, and it is therefore used with other antiretrovirals.

It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer (ritonavir-boosted tipranavir). The dose is tipranavir 500 mg (with ritonavir 200 mg) twice daily with food.

For details of doses in children see below.

No dose adjustment is required for patients with renal impairment or mild liver disease. Tipranavir should not be given to patients with moderate to severe liver disease.

◊ Reviews.

1. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; **65:** 1669–77.
2. Dong BJ, Cocohoba JM. Tipranavir: a protease inhibitor for HIV salvage therapy. *Ann Pharmacother* 2006; **40:** 1311–21.
3. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. *Clin Pharmacokinet* 2006; **45:** 665–82.
4. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of drug-resistant HIV infection. *Clin Infect Dis* 2007; **45:** 761–9.
5. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. *Drugs* 2008; **68:** 1435–63.

Administration in children. For the treatment of HIV infection in children, tipranavir is given orally with other antiretroviral drugs. It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer. US licensed product information permits the use of oral tipranavir in children from 2 years of age. Doses are based on body-weight or body-surface and should not exceed the maximum adult dose (see above).

- The usual recommended dose in children is: tipranavir 14 mg/kg (with ritonavir 6 mg/kg) twice daily *or* tipranavir 375 mg/m^2 (with ritonavir 150 mg/m^2) twice daily
- children who are intolerant or develop toxicities to the usual dose may take a reduced dose: tipranavir 12 mg/kg (with ritonavir 5 mg/kg) twice daily *or* tipranavir 290 mg/m^2 (with ritonavir 115 mg/m^2) twice daily

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aptivus; ***Belg.:*** Aptivus; ***Cz.:*** Aptivus; ***Fin.:*** Aptivus; ***Fr.:*** Aptivus; ***Gr.:*** Aptivus; ***Hung.:*** Aptivus; ***Irl.:*** Aptivus; ***Ital.:*** Aptivus; ***Mex.:*** Aptivus; ***Pol.:*** Aptivus; ***Port.:*** Aptivus; ***Swed.:*** Aptivus; ***UK:*** Aptivus; ***USA:*** Aptivus.

Trichosanthin

Compound Q; GLQ-223 (a purified form of trichosanthin); Tricosantina.

CAS — 60318-52-7 (trichosanthins); 116899-30-0 (Trichosanthes kirilowii); 160185-58-0 (Trichosanthes kirilowii root); 120947-28-6 (GLQ-223).

Profile

Trichosanthin is a polypeptide extracted from the tuber of the Chinese cucumber, *Trichosanthes kirilowii* (Cucurbitaceae). It has been investigated in the treatment of HIV infection and is used in China as an abortifacient.

HIV infection and AIDS. Trichosanthin has been given to patients with AIDS, AIDS-related complex, or HIV infection.[1,2] It has generally been given by intravenous injection, the use of the intramuscular route having been abandoned due to the occurrence of pain and necrosis at the injection site.[1] A common adverse effect with intravenous use was a flu-like syndrome with headache, myalgias, fever, and arthralgia and was generally mild to moderate,[3] although neurological effects progressing to coma with fatalities have been reported.[1,2] Improvements in surrogate markers for HIV infection have been reported including increases in CD4+ T lymphocyte counts in patients with moderate disease[3] and in patients failing to respond to reverse transcriptase inhibitors.[4]

1. Byers VS, *et al.* A phase I/II study of trichosanthin treatment of HIV disease. *AIDS* 1990; **4:** 1189–96.
2. Kahn JO, *et al.* The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. *AIDS* 1990; **4:** 1197–1204.
3. Kahn JO, *et al.* Safety, activity, and pharmacokinetics of GLQ223 in patients with AIDS and AIDS-related complex. *Antimicrob Agents Chemother* 1994; **38:** 260–7.
4. Byers VS, *et al.* A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. *AIDS Res Hum Retroviruses* 1994; **10:** 413–20.

Trifluridine *(USAN, rINN)*

F_3T; F_3TDR; NSC-75520; Trifluorothymidine; Trifluorothymidinum; Trifluorotymidiini; Trifluorotymidin; Trifluridiini; Trifluridin; Trifluridina; Trifluridinum. ααα-Trifluorothymidine; 2′-Deoxy-5-trifluoromethyluridine.

Трифлуридин

$C_{10}H_{11}F_3N_2O_5$ = 296.2.
CAS — 70-00-8.
ATC — S01AD02.
ATC Vet — QS01AD02.

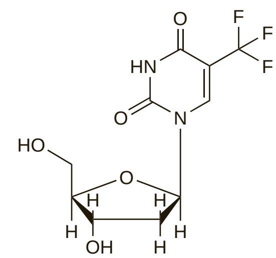

Pharmacopoeias. In *US.*

USP 31 (Trifluridine). A white, odourless powder, appearing under the microscope as rod-like crystals. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects occurring after the use of trifluridine in the eyes are similar to those for idoxuridine (p.881) but have been reported to occur less frequently.

◊ References.

1. Udell IJ. Trifluridine-associated conjunctival cicatrization. *Am J Ophthalmol* 1985; **99:** 363–4.

Antiviral Action

Trifluridine acts similarly to idoxuridine to interfere with viral DNA synthesis after phosphorylation. It is reported to be active against herpes simplex viruses, some adenoviruses, vaccinia viruses, and CMV. Like idoxuridine it is incorporated into mammalian DNA.

Pharmacokinetics

Trifluridine is absorbed through the cornea after application to the eye and penetration may be increased in the presence of damage or inflammation. Systemic absorption does not appear to follow ocular administration.

Uses and Administration

Trifluridine is a pyrimidine nucleoside structurally related to thymidine. It is used in the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses (p.854). One drop of a 1% ophthalmic solution is instilled into the eye every 2 hours up to a maximum of 9 times daily until complete re-epithelialisation has occurred. Treatment is then reduced to one drop every 4 hours to a minimum of 5 drops daily for a further 7 days. Treatment should not be continued for more than a total of 21 days.

Trifluridine, alone or as a combined formulation with a thymidine phosphorylase inhibitor to reduce its metabolism (TAS-102), has been investigated in the treatment of malignant neoplasms.

◊ Reviews.

1. Heidelberger C, King DH. Trifluorothymidine. *Pharmacol Ther* 1979; **6:** 427–42.
2. Carmine AA, *et al.* Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. *Drugs* 1982; **23:** 329–53.
3. Temmink OH, *et al.* Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. *Cancer Sci* 2007; **98:** 779–89.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Viroptic; ***Cz.:*** Triherpine†; ***Fr.:*** Virophta; ***Ger.:*** Triflumann; ***Gr.:*** Thilol; ***Hong Kong:*** Triherpine†; ***Hung.:*** Triherpine†; ***Ital.:*** Triherpine; ***Neth.:*** TFT Ophtiole; ***Port.:*** Adrocil†; Viridin; ***S.Afr.:*** TFT; ***Spain:*** Viromidin; ***Switz.:*** Triherpine†; ***Thai.:*** Triherpine; ***Turk.:*** TFT-Thilo; ***USA:*** Viroptic.

Tromantadine Hydrochloride *(rINNM)*

D-41; Hidrocloruro de tromantadina; Tromantadine, Chlorhydrate de; Tromantadini Hydrochloridum. *N*-1-Adamantyl-2-(2-dimethylaminoethoxy)acetamide hydrochloride; 2-(2-Dimethylaminoethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)acetamide hydrochloride.

Тромантадина Гидрохлорид

$C_{16}H_{28}N_2O_2$,HCl = 316.9.

CAS — 53783-83-8 (tromantadine); 41544-24-5 (tromantadine hydrochloride).

ATC — D06BB02; J05AC03.

ATC Vet — QD06BB02; QJ05AC03.

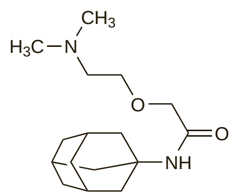

(tromantadine)

Profile

Tromantadine hydrochloride is a derivative of amantadine (p.792) used for its antiviral activity. It is applied topically at a concentration of 1% in the treatment of herpes simplex infections of the skin and mucous membranes (p.854).

Contact dermatitis has been reported after the topical use of tromantadine hydrochloride.

Effects on the skin. References to contact dermatitis associated with the use of tromantadine.

1. Fanta D, Mischer P. Contact dermatitis from tromantadine hydrochloride. *Contact Dermatitis* 1976; **2:** 282–4.
2. Lembo G, *et al.* Allergic dermatitis from Viruserol ointment probably due to tromantadine hydrochloride. *Contact Dermatitis* 1984; **10:** 317.
3. Jauregui I, *et al.* Allergic contact dermatitis from tromantadine. *J Investig Allergol Clin Immunol* 1997; **7:** 260–1.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Viru-Merz Serol; ***Belg.:*** Viru-Merz†; ***Braz.:*** Herpex; ***Chile:*** Viru-Merz†; ***Cz.:*** Viru-Merz; ***Ger.:*** Viru-Merz Serol; ***Gr.:*** Viru-Merz Serol; ***Hong Kong:*** Viru-Merz; ***Hung.:*** Viru-Merz; ***Indon.:*** Viru-Merz; ***Israel:*** Viru-Merz; ***Ital.:*** Viruserol†; ***Malaysia:*** Viru-Merz; ***Mex.:*** Viru-Serol; ***Neth.:*** Viru-Merz†; ***Philipp.:*** Viru-Merz; ***Pol.:*** Viru-Merz; ***Port.:*** Viru-Merz; ***Rus.:*** Viru-Merz Serol (Виру-Мерц Серол); ***Singapore:*** Viru-Merz†; ***Spain:*** Viru-Serol; ***Switz.:*** Viru-Merz Serol.

Valaciclovir Hydrochloride

(BANM, rINNM)

Hidrocloruro de valaciclovir; 256U87 (valaciclovir); Valaciclovir, chlorhydrate de; Valacicloviri hydrochloridum; Valacyclovir Hydrochloride *(USAN)*. L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine hydrochloride.

Валацикловира Гидрохлорид

$C_{13}H_{20}N_6O_4$,HCl = 360.8.

CAS — 124832-26-4 (valaciclovir); 124832-27-5 (valaciclovir hydrochloride);.

ATC — J05AB11.

ATC Vet — QJ05AB11.

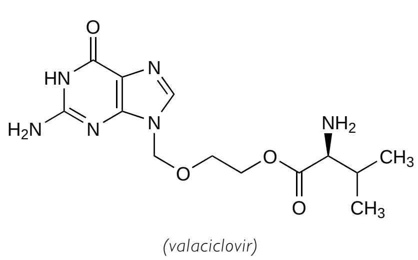

(valaciclovir)

Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

As for Aciclovir, p.863.

Breast feeding. In a study in 5 women who took oral valaciclovir 500 mg twice daily for 7 days, concentrations of the active metabolite aciclovir in breast milk were 3.4 times those in maternal serum at 4 hours after the initial dose, although the ratio declined to 1.85 at steady-state concentrations. Nonetheless, it was calculated that the amount ingested by an infant would be negligible (about 2% of a standard neonatal dose of intravenous aciclovir, with exposure further reduced by the poor oral bioavailability of the drug), and valaciclovir was thus considered compatible with breast feeding.[1]

1. Sheffield JS, *et al.* Acyclovir concentrations in human breast milk after valaciclovir administration. *Am J Obstet Gynecol* 2002; **186:** 100–102.

Effects on the nervous system. Mononeuritis multiplex due to vasculitis has been reported[1] in a woman a week after a one-day course of valaciclovir for the treatment of herpes labialis. Symptoms improved within 10 days of treatment with oral prednisolone but reoccurred upon rechallenge with valaciclovir.

1. Pary LF, *et al.* Vasculitic mononeuritis multiplex induced by valacyclovir. *Neurology* 2004; **62:** 1906–7.

Interactions

As for Aciclovir, p.863.

Antiviral Action

As for Aciclovir, p.863.

Pharmacokinetics

As for Aciclovir, p.863.

Valaciclovir is readily absorbed from the gastrointestinal tract after oral doses, and is rapidly converted to aciclovir and valine by first-pass intestinal or hepatic metabolism. The bioavailability of aciclovir after dosage with valaciclovir is reported to be 54% and peak plasma concentrations of aciclovir are achieved after 1.5 hours. Valaciclovir is eliminated mainly as aciclovir and its metabolite 9-carboxymethoxymethylguanine; less than 1% of a dose of valaciclovir is excreted unchanged in the urine.

◊ References.

1. Steingrimsdottir H, *et al.* Bioavailability of aciclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. *Antimicrob Agents Chemother* 2000; **44:** 207–9.
2. Höglund M, *et al.* Comparable aciclovir exposures produced by oral valaciclovir and intravenous aciclovir in immunocompromised cancer patients. *J Antimicrob Chemother* 2001; **47:** 855–61.
3. Bras AP, *et al.* Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol* 2001; **8:** 207–11.
4. Nadal D, *et al.* An investigation of the steady-state pharmacokinetics of oral valacyclovir in immunocompromised children. *J Infect Dis* 2002; **186** (suppl 1): S123–S130.
5. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. *J Antimicrob Chemother* 2004; **53:** 899–901.

Uses and Administration

Valaciclovir is a prodrug of the antiviral aciclovir (p.864). It is used in the treatment of herpes zoster (p.855) and herpes simplex infections (p.854) of the skin and mucous membranes, including genital herpes. Treatment should be started as soon as symptoms occur. Valaciclovir is used for the suppression of recurrent herpes simplex infections and can reduce the risk of transmission of genital herpes to susceptible partners when used as suppressive therapy and as part of safer sex practices. It is also used for the prophylaxis of CMV infection after renal transplantation. Valaciclovir is given orally as the hydrochloride; doses are expressed in terms of the base. Valaciclovir hydrochloride 1.11 g is equivalent to about 1 g of valaciclovir.

For **herpes zoster**, the dose is 1 g three times daily for 7 days. For treatment of **herpes simplex infections**, 500 mg is given twice daily for 5 days (3 days in the USA) for recurrent episodes or for up to 10 days for a first episode; in the USA, the recommended dose for a first episode of genital herpes is 1 g twice daily for 10 days. For the treatment of herpes labialis, a dose of 4 g in two divided doses 12 hours apart is recommended. For the *suppression* of herpes simplex infection in immunocompetent patients, a dose of 500 mg daily as a single dose or in two divided doses, is recommended; in the USA, a dose of 1 g daily as a single dose is recommended for suppression of recurrent genital herpes. A dose of 500 mg twice daily may be used in immunocompromised patients. To *reduce transmission* of genital herpes a dose of 500 mg daily is taken by the infected partner.

A dose of 2 g four times daily is recommended for prophylaxis of **CMV infection** in renal transplant recipients; prophylaxis should begin within 72 hours and is usually continued for 90 days.

Doses of valaciclovir may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Ormrod D, *et al.* Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000; **59:** 839–63.
2. Ormrod D, Goa K. Valaciclovir: a review of its use in the management of herpes zoster. *Drugs* 2000; **59:** 1317–40.
3. Tyring SK, *et al.* Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; **186** (suppl 1): S40–S46.
4. Corey L, *et al.* Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350:** 11–20.
5. Brantley JS, *et al.* Valacyclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4:** 367–76.
6. Fife KH, *et al.* Effect of valacyclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81:** 1321–7.

Administration in renal impairment. Oral doses of valaciclovir may need to be reduced in patients with renal impairment. The following dosage reductions are suggested by the UK licensed product information according to creatinine clearance (CC):

herpes zoster:
- CC 15 to 30 mL/minute: 1 g twice daily
- CC less than 15 mL/minute: 1 g daily
- patients on haemodialysis: 1 g daily after haemodialysis

herpes simplex infections:
- CC less than 15 mL/minute: 500 mg daily
- patients on haemodialysis: 500 mg daily after haemodialysis

suppression of herpes simplex:
- CC less than 15 mL/minute: *immunocompetent patients*: 250 mg once daily; *immunocompromised patients*: 500 mg once daily
- patients on haemodialysis: *immunocompetent patients*: 250 mg once daily after haemodialysis; *immunocompromised patients*: 500 mg once daily after haemodialysis

reduction of transmission of genital herpes:
- CC less than 15 mL/minute: 250 mg daily
- patients on haemodialysis: 250 mg daily after haemodialysis

prophylaxis of CMV:
- CC 50 to 74 mL/minute: 1.5 g four times daily
- CC 25 to 49 mL/minute: 1.5 g three times daily
- CC 10 to 24 mL/minute: 1.5 g twice daily
- CC less than 10 mL/minute: 1.5 g once daily
- patients on haemodialysis: 1.5 g once daily after haemodialysis

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Valtrex; Viramixal; Viranet; ***Austral.:*** Valtrex; ***Austria:*** Valtrex; ***Belg.:*** Zelitrex; ***Braz.:*** Valtrex; ***Canad.:*** Valtrex; ***Chile:*** Pervioral; Vadiral; Valtrex; Virmax†; ***Cz.:*** Valtrex; ***Denm.:*** Zelitrex; ***Fin.:*** Valavir; Valtrex; ***Fr.:*** Zelitrex; ***Ger.:*** Valtrex; ***Gr.:*** Valtrex; ***Hong Kong:*** Valtrex; ***India:*** Valcivir; ***Indon.:*** Herclov; Valtrex; Valvir; ***Irl.:*** Valtrex; ***Israel:*** Valtrex; ***Ital.:*** Talavir; Zelitrex; ***Malaysia:*** Valtrex; ***Mex.:*** Rapivir; ***Neth.:*** Zelitrex; ***Norw.:*** Valtrex; ***Philipp.:*** Valtrex; ***Port.:*** Valavir; Valtrex; ***Rus.:*** Valtrex (Валтрекс); ***S.Afr.:*** Zelitrex; ***Singapore:*** Valtrex; ***Spain:*** Valherpes; Valtrex; Virval; ***Swed.:*** Valtrex; ***Switz.:*** Valtrex; ***Thai.:*** Valtrex; ***Turk.:*** Valtrex; ***UK:*** Valtrex; ***USA:*** Valtrex; ***Venez.:*** Valtrex.

Valganciclovir Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de valganciclovir; Ro-107-9070/194; RS-079070-194; Valganciclovir, Chlorhydrate de; Valganciclovir Hydrochloridum. L-Valine, ester with 9-{[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl} guanine hydrochloride .

Вальганцикловира Гидрохлорид

$C_{14}H_{22}N_6O_5$,HCl = 390.8.

CAS — 175865-60-8 (valganciclovir); 175865-59-5 (valganciclovir hydrochloride).

ATC — J05AB14.

ATC Vet — QJ05AB14.

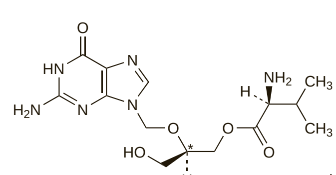

and epimer at C*

(valganciclovir)

Pharmacopoeias. In *US.*

USP 31 (Valganciclovir Hydrochloride). A white to off-white powder. Freely soluble in alcohol; practically insoluble in acetone or in ethyl acetate; slightly soluble in hexane; very soluble in isopropyl alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. References.

1. Anaizi NH, *et al.* Stability of valganciclovir in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59:** 1267–70.
2. Henkin CC, *et al.* Stability of valganciclovir in extemporaneously compounded liquid formulations. *Am J Health-Syst Pharm* 2003; **60:** 687–90.

Adverse Effects, Treatment, and Precautions

As for Ganciclovir, p.879.

In the USA, valganciclovir is not indicated for use in liver transplant recipients, because of reports of a higher incidence of tissue-invasive CMV infection compared with patients treated with ganciclovir (although see Cytomegalovirus Infections, below). In the UK, valganciclovir is licensed for use in the prevention of CMV disease in all solid organ graft recipients.

Interactions

As for Ganciclovir, p.879.

Antiviral Action

As for Ganciclovir, p.880.

Pharmacokinetics

Valganciclovir is well absorbed from the gastrointestinal tract after oral doses and is rapidly converted to ganciclovir by first-pass intestinal or hepatic metabolism. The bioavailability of ganciclovir after an oral dose with food is reported to be about 60% and peak plasma concentrations of ganciclovir are achieved after 1 to 3 hours. Valganciclovir is eliminated in the urine as ganciclovir (see p.880).

◊ References.

1. Brown F, *et al.* Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet* 1999; **37:** 167–76.
2. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. *J Clin Pharmacol* 1999; **39:** 800–4.
3. Pescovitz MD, *et al.* Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; **44:** 2811–15.
4. Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44:** 495–507.
5. Winston DJ, *et al.* Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. *Biol Blood Marrow Transplant* 2006; **12:** 635–40.

Uses and Administration

Valganciclovir is a prodrug of the antiviral ganciclovir (p.880) that is used for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in transplant recipients who have received an organ from a CMV-positive donor (see below).

Valganciclovir is given orally with food as the hydrochloride; doses are expressed in terms of the base. Valganciclovir hydrochloride 1.1 g is equivalent to about 1 g of valganciclovir.

For *induction* in patients with active CMV retinitis, the dose is 900 mg twice daily for 21 days. For *maintenance* following induction, or in patients with inactive CMV retinitis, the dose is 900 mg daily. Patients whose retinitis deteriorates during maintenance may repeat induction but the possibility of viral resistance should be considered. For *prevention* of CMV disease in organ transplant recipients, the dose is 900 mg daily starting within 10 days and continuing until 100 days after transplantation.

Doses of valganciclovir should be reduced in renal impairment (see Administration in Renal Impairment, below).

◊ Reviews.

1. Freeman RB. Valganciclovir: oral prevention and treatment of cytomegalovirus in the immunocompromised host. *Expert Opin Pharmacother* 2004; **5:** 2007–16.
2. Cvetković RS, Wellington K. Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. *Drugs* 2005; **65:** 859–78.

Administration in renal impairment. Doses of oral valganciclovir should be reduced in renal impairment according to creatinine clearance (CC). Licensed product information recommends the following doses:

- CC 40 to 59 mL/minute: 450 mg twice daily for *induction* and 450 mg daily for *maintenance* or *prevention*
- CC 25 to 39 mL/minute: 450 mg daily for *induction* and 450 mg every two days for *maintenance* or *prevention*
- CC 10 to 24 mL/minute: 450 mg every two days for *induction* and 450 mg twice weekly for *maintenance* or *prevention*
- haemodialysis patients: not recommended

Cytomegalovirus infections. Valganciclovir produces high systemic concentrations of ganciclovir after oral doses; exposure may be higher than with intravenous ganciclovir regimens.[1] It is therefore active against CMV infections (p.853). It has been shown to be of benefit for both induction therapy and maintenance treatment of CMV retinitis in patients with AIDS,[2,3] and although this has become less widespread in the developed world with the advent of HAART, it continues to be a problem in resource-poor settings in particular; there have been calls for valganciclovir to be made more widely available for treatment in preference to less effective and convenient drugs.[3]

Valganciclovir is also used in the prophylaxis and preemptive treatment of CMV infections in transplant recipients,[4-8] and many centres consider it to be the standard of care for this indication (including in liver transplantation although it is contra-indicated for such use in the USA—see Adverse Effects, Treatment, and Precautions, above).[9]

1. Einsele H, *et al.* Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood* 2006; **107:** 3002–8.
2. Martin DF, *et al.* Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 2002; **346:** 1119–26. Correction. *ibid.*; **347:** 862.
3. Heiden D, *et al.* Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med* 2007; **4:** e334. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/12/pdf/10.1371_journal.pmed.0040334-S.pdf (accessed 28/08/08)
4. Paya C, *et al.* Valganciclovir Solid Organ Transplant Study Group. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4:** 611–20.
5. Khoury JA, *et al.* Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant* 2006; **6:** 2134–43.
6. Said T, *et al.* Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplant Proc* 2007; **39:** 997–9.
7. Asberg A, *et al.* VICTOR Study Group. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; **7:** 2106–13.
8. Len O, *et al.* RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46:** 20–7.
9. Snydman DR. Use of valganciclovir for prevention and treatment of cytomegalovirus disease. *Clin Infect Dis* 2008; **46:** 28–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Valixa; ***Austral.:*** Valcyte; ***Austria:*** Valcyte; ***Belg.:*** Valcyte; ***Braz.:*** Valcyte; ***Canad.:*** Valcyte; ***Chile:*** Valixa; ***Cz.:*** Valcyte; ***Denm.:*** Valcyte; ***Fin.:*** Valcyte; ***Fr.:*** Rovalcyte; ***Ger.:*** Valcyte; ***Gr.:*** Valcyte; ***Hong Kong:*** Valcyte; ***Hung.:*** Valcyte; ***Indon.:*** Valcyte; ***Irl.:*** Valcyte; ***Israel:*** Valcyte; ***Ital.:*** Darilin; Valcyte; ***Mex.:*** Valcyte; ***Neth.:*** Valcyte; Valixa; ***Norw.:*** Valcyte; ***NZ:*** Valcyte; ***Philipp.:*** Valcyte; ***Pol.:*** Valcyte; ***Port.:*** Rovalcyte; ***S.Afr.:*** Valcyte; ***Singapore:*** Valcyte; ***Spain:*** Valcyte; ***Swed.:*** Valcyte; ***Switz.:*** Valcyte; ***Thai.:*** Valcyte; ***UK:*** Valcyte; ***USA:*** Valcyte; ***Venez.:*** Valixa.

Vidarabine *(BAN, USAN, rINN)*

Adenine Arabinoside; Ara-A; CI-673; Vidarabiini; Vidarabin; Vidarabina; Vidarabinum. 9-β-D-Arabinofuranosyladenine monohydrate.

Видарабин

$C_{10}H_{13}N_5O_4,H_2O$ = 285.3.

CAS — 5536-17-4 (anhydrous vidarabine); 24356-66-9 (vidarabine monohydrate).

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

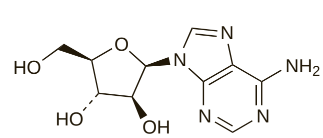

(anhydrous vidarabine)

Pharmacopoeias. In *US.*

USP 31 (Vidarabine). A white to off-white powder. Very slightly soluble in water; slightly soluble in dimethylformamide. Store in airtight containers.

Vidarabine Phosphate *(BANM, USAN, rINNM)*

Ara-AMP; Arabinosyladenine Monophosphate; CI-808; Fosfato de vidarabina; Vidarabine 5′-Monophosphate; Vidarabine, Phosphate de; Vidarabini Phosphas. 9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate).

Видарабина Фосфат

$C_{10}H_{14}N_5O_7P$ = 347.2.

CAS — 29984-33-6.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

Vidarabine Sodium Phosphate *(BANM, USAN, rINNM)*

CI-808 Sodium; Fosfato sódico de vidarabina; Natrii Vidarabini Phosphas; Vidarabine, Phosphate Sodique de. 9-β-D-Arabinofuranosyladenine 5′-(dihydrogen phosphate) disodium.

Натрия Видарабина Фосфат

$C_{10}H_{12}N_5Na_2O_7P$ = 391.2.

CAS — 71002-10-3.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

Adverse Effects

Adverse effects that may occur when vidarabine is applied to the eyes include irritation, pain, superficial punctate keratitis, photophobia, lachrymation, and occlusion of the lachrymal duct.

Pharmacokinetics

Systemic absorption does not occur after application of vidarabine to the eye; trace amounts of its principal metabolite hypoxanthine arabinoside (arabinosyl hypoxanthine), and vidarabine, if the cornea is damaged, may be found in the aqueous humour.

Uses and Administration

Vidarabine is a purine nucleoside obtained from *Streptomyces antibioticus*. It has been used in the treatment of herpes simplex and varicella-zoster infections (p.854 and p.855), although aciclovir and related drugs are generally preferred.

Vidarabine has been used topically in the treatment of herpes simplex keratitis and keratoconjunctivitis as a 3% ophthalmic ointment.

It has also been used as the sodium phosphate as a 10% gel for the treatment of genital herpes.

Vidarabine was formerly used intravenously in the treatment of severe and disseminated herpes simplex infections and herpes zoster but aciclovir is preferred.

Preparations

USP 31: Vidarabine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)

Gr.: Erpimycin; Tekarin; Virerpin; ***Jpn:*** Arasena-A.

Zalcitabine *(BAN, USAN, rINN)*

ddC; ddCyd; Dideoxycytidine; NSC-606170; Ro-24-2027; Ro-24-2027/000; Tsalsitabiini; Zalcitabin; Zalcitabina; Zalcitabinum; Zalsitabin. 2′,3′-Dideoxycytidine.

Зальцитабин

$C_9H_{13}N_3O_3$ = 211.2.

CAS — 7481-89-2.

ATC — J05AF03.

ATC Vet — QJ05AF03.

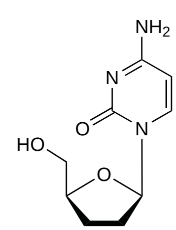

Pharmacopoeias. In *US.*

USP 31 (Zalcitabine). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol, in acetonitrile, in chloroform, and in dichloromethane; slightly soluble in cyclohexane. Store in airtight containers. Protect from light.

Adverse Effects

The most serious adverse effects of zalcitabine are peripheral neuropathy, which can affect up to one-third of patients, and pancreatitis which is rare, affecting up to about 1% of patients, but which can be fatal. Other severe adverse effects include oral and oesophageal ulceration, hypersensitivity reactions including anaphylaxis, cardiomyopathy and heart failure, lactic acidosis and severe hepatomegaly with steatosis (both potentially life-threatening), and hepatic failure.

Precautions

Zalcitabine should be interrupted or stopped if peripheral neuropathy develops. Neuropathy is usually slowly reversible if treatment is stopped promptly but may be irreversible if treatment is continued after symptoms develop. Zalcitabine should be avoided in patients who already have peripheral neuropathy and used with caution in patients at risk of developing it (especially those with a low CD4+ cell count) or taking other drugs that may cause it (see Interactions, below).

Treatment should be interrupted in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded. Zalcitabine should be permanently withdrawn if pancreatitis develops. Patients with a history of pancreatitis or of raised serum amylase should be monitored closely. Zalcitabine should not be used with other drugs known to cause pancreatitis (see Interactions, below).

Zalcitabine should be used with caution in patients with hepatic impairment and treatment interrupted or stopped if hepatic function deteriorates or there are signs of hepatic damage or lactic acidosis. It should be used with caution in patients with renal impairment, and dosage reductions may be necessary. It should also be used with caution in patients with cardiomyopathy or heart failure.

Complete blood count and biochemical tests should be carried out before treatment starts and at regular intervals throughout therapy.

Handling. Exposure of the skin to zalcitabine and inhalation of zalcitabine powder should be avoided.

Interactions

Zalcitabine should not be used with other drugs known to cause pancreatitis (for example intravenous pentamidine). Caution is necessary when zalcitabine is given with other drugs that may cause peripheral neuropathy, such as other nucleoside reverse transcriptase inhibitors, chloramphenicol, dapsone, ethionamide, isoniazid (the clearance of which may also be affected—see p.290), metronidazole, nitrofurantoin, ribavirin, and vincristine. Use of zalcitabine with didanosine is not recommended.

The absorption of zalcitabine is reduced by about 25% when given with aluminium- or magnesium-containing antacids.

Cimetidine, probenecid, or trimethoprim can reduce the renal excretion of zalcitabine, resulting in elevated plasma concentrations. Renal excretion of zalcitabine may also be reduced by amphotericin B, aminoglycosides, or foscarnet, potentially increasing its toxicity.

The antiviral action of zalcitabine may be antagonised by lamivudine and the two drugs should not be used together.

Antiviral Action

Zalcitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

The emergence of zalcitabine-resistant strains of HIV has been reported.

◊ References.

1. Jeffries DJ. The antiviral activity of dideoxycytidine. *J Antimicrob Chemother* 1989; **23** (suppl A): 29–34.

Pharmacokinetics

Zalcitabine is absorbed from the gastrointestinal tract with a bioavailability of greater than 80%. The rate of absorption is reduced if given with food. Peak plasma concentrations in the fasting state are achieved within about 1 hour. Zalcitabine crosses the blood-brain barrier producing CSF concentrations ranging from 9 to 37% of those in plasma. Binding to plasma proteins is negligible. The plasma elimination half-life is about 2 hours.

Zalcitabine is metabolised intracellularly to the active antiviral triphosphate. It does not appear to undergo any substantial hepatic metabolism and is excreted mainly in the urine, in part by active tubular secretion.

Uses and Administration

Zalcitabine is a nucleoside reverse transcriptase inhibitor derived from cytidine with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when zalcitabine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Zalcitabine is given orally in a dose of 750 micrograms every 8 hours. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Doses of zalcitabine should be reduced for patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 40 mL/minute: 750 micrograms every 12 hours
- CC less than 10 mL/minute: 750 micrograms every 24 hours

Preparations

USP 31: Zalcitabine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hivid†; Inxibir†; ***Austral.:*** Hivid; ***Austria:*** Hivid; ***Belg.:*** Hivid; ***Braz.:*** Hivid†; ***Canad.:*** Hivid; ***Chile:*** Hivid†; ***Cz.:*** Hivid†; ***Denm.:*** Hivid†; ***Fin.:*** Hivid; ***Fr.:*** Hivid†; ***Ger.:*** Hivid; ***Gr.:*** Hivid; ***Hong Kong:*** Hivid†; ***Irl.:*** Hivid†; ***Israel:*** Hivid; ***Ital.:*** Hivid; ***Jpn:*** Hivid; ***Mex.:*** Arlevid; Hivid; ***Neth.:*** Hivid; ***Port.:*** Hivid†; ***S.Afr.:*** Hivid†; ***Singapore:*** Hivid†; ***Spain:*** Hivid; ***Swed.:*** Hivid†; ***Switz.:*** Hivid†; ***Thai.:*** Hivid; ***Turk.:*** Hivid; ***UK:*** Hivid†; ***USA:*** Hivid†; ***Venez.:*** Hivid.

Zanamivir *(BAN, USAN, rINN)*

GG-167; GR-121167X; 4-Guanidino-2,4-dideoxy-2,3-dehydro-*N*-acetylneuraminic Acid; Tsanamiviiri; Zanamivirum. 5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enonic acid.

Занамивир

$C_{12}H_{20}N_4O_7$ = 332.3.
CAS — 139110-80-8.
ATC — J05AH01.
ATC Vet — QJ05AH01.

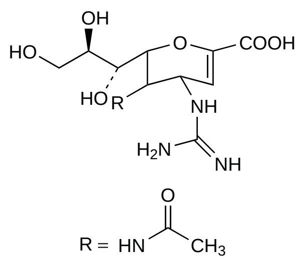

Adverse Effects

Inhaled zanamivir has generally been well tolerated. Acute bronchospasm or decline in respiratory function, with some fatalities, has been reported rarely in patients with a history of respiratory disease and very rarely in those with no such history. Other effects that have been noted include nasal symptoms, headache, gastrointestinal symptoms, cough, and bronchitis, but they may be difficult to distinguish from the symptoms of influenza. There have also been rare reports of hypersensitivity reactions, including oropharyngeal oedema and severe skin rashes.

There have been postmarketing reports (mostly from Japan) of neuropsychiatric adverse effects, such as delirium and abnormal behaviour, in patients taking neuraminidase inhibitors such as zanamivir.

◊ Reviews.

1. Freund B, *et al.* Zanamivir: a review of clinical safety. *Drug Safety* 1999; **21:** 267–81.
2. Gravenstein S, *et al.* Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Safety* 2001; **24:** 1113–25.

Precautions

Zanamivir should be used with caution in patients with chronic respiratory diseases as they may be at increased risk of bronchospasm; if zanamivir use is considered appropriate, patients with asthma or chronic obstructive pulmonary disease should have a fast-acting bronchodilator available during treatment. Patients on maintenance therapy with inhaled bronchodilators should inhale the bronchodilator before zanamivir. Patients experiencing bronchospasm should be advised to stop zanamivir and seek medical attention.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Antiviral Action

Zanamivir inhibits the viral surface enzyme neuraminidase (sialidase) which is essential for the release of newly formed viral particles from infected cells, and may facilitate access of virus through mucus to the cell surface. Zanamivir is active against influenza A and B virus replication.

Resistance. For information on the development of resistance to zanamivir and other neuramidase inhibitors, see under Oseltamivir, p.901.

Pharmacokinetics

Zanamivir is poorly absorbed after oral doses with a bioavailability of about 2%. Inhaled doses produce high local concentrations in the respiratory tract. About 4 to 20% of the inhaled dose is absorbed producing peak serum concentrations at about 1 to 2 hours. Zanamivir is less than 10% bound to plasma protein. It is not metabolized and the absorbed portion is excreted unchanged in the urine with a serum half-life of 2.6 to 5 hours; unabsorbed drug is excreted in the faeces.

◊ References.

1. Aoki FY, Hayden FG (eds.). The pharmacokinetics of zanamivir: a new inhaled antiviral for influenza. *Clin Pharmacokinet* 1999; **36** (suppl 1): 1–58.

Uses and Administration

Zanamivir is a neuraminidase inhibitor used by inhalation for the treatment and prophylaxis (postexposure and seasonal) of influenza A and B (p.859). For *treatment*, it is given to adults in a dose of 10 mg twice daily for 5 days, starting as soon as possible (within 48 hours) after the onset of symptoms.

Zanamivir is given by inhalation for *postexposure prophylaxis* of influenza A and B in household or close contacts and should be started within 36 hours of exposure. The dose for adults is 10 mg once daily for 10 days. For *seasonal prophylaxis* in a community setting 10 mg once daily may be given to adults and adolescents for 28 days and treatment should start within 5 days of an outbreak.

For details of doses in children, see below.

Administration in children. Zanamivir is given by inhalation for the treatment and postexposure prophylaxis of influenza A and B. For *treatment*, children may be given the same dose as adults (10 mg twice daily for 5 days), starting within 36 to 48 hours after the onset of symptoms. In the USA it is approved for those from 7 years of age whereas UK licensed product information permits use from 5 years of age.

Postexposure prophylaxis after close contact with infected patients should be started within 36 hours of exposure. Children from 5 years of age may be given the same dose as adults (10 mg once daily for 10 days).

Influenza. Reviews.[1,2] For further reviews on neuraminidase inhibitors (including zanamivir), see Influenza, under Oseltamivir, p.901.

1. Cheer SM, Wagstaff AJ. Zanamivir: an update of its use in influenza. *Drugs* 2002; **62:** 71–106.
2. Fleming DM. Zanamivir in the treatment of influenza. *Expert Opin Pharmacother* 2003; **4:** 799–805.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Relenza†; ***Austral.:*** Relenza; ***Austria:*** Relenza; ***Belg.:*** Relenza; ***Braz.:*** Relenza; ***Canad.:*** Relenza; ***Chile:*** Relenza†; ***Cz.:*** Relenza; ***Denm.:*** Relenza†; ***Fin.:*** Relenza; ***Fr.:*** Relenza; ***Ger.:*** Relenza; ***Gr.:*** Relenza; ***Hong Kong:*** Relenza; ***Hung.:*** Relenza; ***Irl.:*** Relenza†; ***Israel:*** Relenza†; ***Ital.:*** Relenza; ***Malaysia:*** Relenza; ***Mex.:*** Relenza; ***Neth.:*** Relenza; ***Norw.:*** Relenza; ***NZ:*** Relenza; ***Port.:*** Relenza; ***S.Afr.:*** Relenza; ***Singapore:*** Relenza; ***Spain:*** Relenza; ***Swed.:*** Relenza; ***Switz.:*** Relenza; ***Turk.:*** Relenza; ***UK:*** Relenza; ***USA:*** Relenza.

Zidovudine *(BAN, USAN, rINN)*

Azidodeoxythymidine; Azidothymidine; AZT; BW-A509U; BW-509U; Compound-S; Tsidovudiini; Zidovudin; Zidovudina; Zidovudinas; Zidovudinum; Zydowudyna. 3′-Azido-3′-deoxythymidine.

Зидовудин

$C_{10}H_{13}N_5O_4$ = 267.2.
CAS — 30516-87-1.
ATC — J05AF01.
ATC Vet — QJ05AF01.

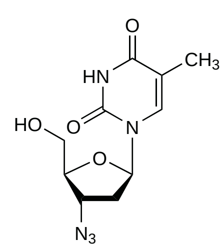

NOTE. The abbreviation AZT has also been used for azathioprine.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Zidovudine). A white or brownish powder. It shows polymorphism. Sparingly soluble in water; soluble in dehydrated alcohol. Protect from light.

USP 31 (Zidovudine). A white to yellowish powder. Exhibits polymorphism. Sparingly soluble in water; soluble in alcohol.

Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

The commonest serious adverse effects reported with zidovudine are haematological toxicities such as anaemia, leucopenia, and neutropenia. They occur most commonly when higher doses are used (1.2 to 1.5 g daily) and in patients with advanced HIV disease and a low CD4+ cell count (less than 100 cells/mm^3). These haematological toxicities are usually reversed by interrupting treatment or reducing dosage but the anaemia may be severe enough to require blood transfusion. Aplastic anaemia, pure red cell aplasia, pancytopenia, and thrombocytopenia have been rarely reported.

Other commonly reported adverse effects include dizziness, headache, malaise, myalgia, and gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea, and vomiting. Long-term use of zidovudine has been associated with myopathy. Raised liver enzymes, hyperbilirubinaemia, lactic acidosis, and severe hepatomegaly with steatosis have been reported as rare, but potentially fatal, occurrences in patients taking zidovudine alone or with other antiretrovirals. Other rare but potentially serious adverse effects include cardiomyopathy, convulsions, and pancreatitis.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including zidovudine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy, including zidovudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the blood. Adverse haematological effects reported with zidovudine may be severe and include anaemia with erythroid aplasia or hypoplasia, and neutropenia.[1-5] Although these effects may be reversed by withdrawal,[5] they may persist for weeks afterwards[2,3] and blood transfusions may be required in some patients.[1-4] A study indicated that zidovudine-induced neutropenia only significantly increased the risk of bacterial infection in patients whose polymorphonuclear cell count fell below 500/microlitre.[6] The effects of zidovudine on the platelet count are considered to be complex, but patients with thrombocytopenia appeared not to be at risk during treatment.[7]

Recombinant erythropoietin has been used in an attempt to reduce blood-transfusion requirements in zidovudine-induced anaemia,[8,9] although the proportion of patients who derive benefit may be limited and some have reported it to have no effect.[10] Similarly granulocyte-macrophage colony-stimulating factor has been reported to improve the neutrophil count in some but not all patients.[11]

1. Forester G. Profound cytopenia secondary to azidothymidine. *N Engl J Med* 1987; **317:** 772.
2. Gill PS, *et al.* Azidothymidine associated with bone marrow failure in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1987; **107:** 502–5.
3. Mir N, Costello C. Zidovudine and bone marrow. *Lancet* 1988; **ii:** 1195–6.
4. Walker RE, *et al.* Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine. *Ann Intern Med* 1988; **108:** 372–6.
5. Cohen H, *et al.* Reversible zidovudine-induced pure red-cell aplasia. *AIDS* 1989; **3:** 177–8.
6. Shaunak S, Bartlett JA. Zidovudine-induced neutropenia: are we too cautious? *Lancet* 1989; **ii:** 91–2.
7. Flegg PJ, *et al.* Effect of zidovudine on platelet count. *BMJ* 1989; **298:** 1074–5.
8. Fischl M, *et al.* Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *N Engl J Med* 1990; **322:** 1488–93.
9. Henry DH, *et al.* Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med* 1992; **117:** 739–48.
10. Shepp DH, *et al.* Erythropoietin for zidovudine-induced anemia. *N Engl J Med* 1990; **323:** 1069–70.
11. Hewitt RG, *et al.* Pharmacokinetics and pharmacodynamics of granulocyte-macrophage colony-stimulating factor and zidovudine in patients with AIDS and severe AIDS-related complex. *Antimicrob Agents Chemother* 1993; **37:** 512–22.

Effects on the CNS. Reports of adverse effects on the CNS associated with zidovudine include mania,[1,2] seizures[3,4] (following an overdose in one patient[5]), psychogenic panic,[6] and Wernicke's encephalopathy,[7] mostly involving one or two patients in each case. CNS toxicity, thought to be zidovudine-related, contributed to the death of an AIDS patient.[8]

For reports of neurological symptoms associated with mitochondrial dysfunction in infants whose mothers received perinatal zidovudine, see Effects on Mitochondria, below.

1. Maxwell S, *et al.* Manic syndrome associated with zidovudine treatment. *JAMA* 1988; **259:** 3406–7.
2. Wright JM, *et al.* Zidovudine-related mania. *Med J Aust* 1989; **150:** 339–40.
3. Harris PJ, Caceres CA. Azidothymidine in the treatment of AIDS. *N Engl J Med* 1988; **318:** 250.
4. D'Silva M, *et al.* Seizure associated with zidovudine. *Lancet* 1995; **346:** 452.
5. Routy JP, *et al.* Seizure after zidovudine overdose. *Lancet* 1989; **i:** 384–5.
6. Levitt AJ, Lippert GP. Psychogenic panic after zidovudine therapy—the therapeutic benefit of an N of 1 trial. *Can Med Assoc J* 1990; **142:** 341–2.
7. Davtyan DG, Vinters HV. Wernicke's encephalopathy in AIDS patient treated with zidovudine. *Lancet* 1987; **i:** 919–20.
8. Hagler DN, Frame PT. Azidothymidine neurotoxicity. *Lancet* 1986; **ii:** 1392–3.

Effects on the heart. An observational study[1] evaluated whether NRTIs increase the risk of myocardial infarction in HIV-infected individuals. Of 33 347 patients enrolled in the D:A:D study, myocardial infarction was reported in 517. Recent use of abacavir or didanosine (but not cumulative use) was associated with an increased rate of myocardial infarction (relative risk 1.90 and 1.49 respectively) compared with those with no recent use of the drugs. The excess risk could not be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after stopping the drug. No associations were found between the rate of myocardial infarction and use of zidovudine, stavudine, or lamivudine.

1. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371:** 1417–26. Correction. *ibid.*; **372:** 292.

Effects on the liver. The development of acute cholestatic hepatitis necessitated stopping zidovudine in a patient who was later unable to tolerate its re-institution.[1] Zidovudine also had to be withdrawn in 3 patients after abnormal liver-function values occurred;[2] it was reinstated in 2 patients without further liver changes. Reversible increases in liver enzymes and rashes were also reported in 2 patients receiving prophylaxis with zidovudine and zalcitabine after exposure to HIV.[3] There has been a report of iron deposition in the liver of patients receiving blood transfusions for zidovudine-related anaemia.[4]

Fatal hepatic dysfunction associated with steatosis in the liver was reported in 6 patients with HIV infection, who were either receiving zidovudine or had previously done so.[5] Five of these patients also developed metabolic acidosis. Cases of fatal lactic acidosis and hepatic failure or steatosis have been reported in patients receiving zidovudine and other nucleoside analogues.[6,7]

1. Dubin G, Braffman MN. Zidovudine-induced hepatotoxicity. *Ann Intern Med* 1989; **110:** 85–6.
2. Melamed AJ, *et al.* Possible zidovudine-induced hepatotoxicity. *JAMA* 1987; **258:** 2063.
3. Henry K, *et al.* Hepatotoxicity and rash associated with zidovudine and zalcitabine chemoprophylaxis. *Ann Intern Med* 1996; **124:** 855.
4. Lindley R, *et al.* Iron deposition in liver in zidovudine-related transfusion-dependent anaemia. *Lancet* 1989; **ii:** 681.
5. Freiman JP, *et al.* Hepatomegaly with severe steatosis in HIV-seropositive patients. *AIDS* 1993; **7:** 379–85.
6. Sundar K, *et al.* Zidovudine-induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: report of two patients and review of the literature. *Crit Care Med* 1997; **25:** 1425–30. Correction. *ibid.*: 1762.
7. Acosta BS, Grimsley EW. Zidovudine-associated type B lactic acidosis and hepatic steatosis in an HIV-infected patient. *South Med J* 1999; **92:** 421–3.

Effects on the metabolism. Lactic acidosis, sometimes in association with myopathy or hepatotoxicity (see above) and in some instances fatal, has been reported after zidovudine treatment.[1-6] However, lactic acidosis with no apparent cause[7] has also been reported in 7 patients with HIV infection: 4 patients were receiving zidovudine, 1 ganciclovir, and 1 clofazimine. The disorder in these patients resembled Reye's syndrome and it was not clear whether the acidosis was induced by zidovudine or the HIV infection.

Lactic acidosis associated with nucleoside reverse transcriptase inhibitors responded to treatment with riboflavin in 4 patients.[8,9]

1. Olano JP, *et al.* Massive hepatic steatosis and lactic acidosis in a patient with AIDS who was receiving zidovudine. *Clin Infect Dis* 1995; **21:** 973–6.
2. Sundar K, *et al.* Zidovudine-induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: report of two patients and review of the literature. *Crit Care Med* 1997; **25:** 1425–30. Correction. *ibid.*: 1762.
3. Scalfaro P, *et al.* Severe transient neonatal lactic acidosis during prophylactic zidovudine treatment. *Intensive Care Med* 1998; **24:** 247–50.
4. Chariot P, *et al.* Zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis, and mitochondrial DNA depletion. *J Hepatol* 1999; **30:** 156–60.
5. Acosta BS, Grimsley EW. Zidovudine-associated type B lactic acidosis and hepatic steatosis in an HIV-infected patient. *South Med J* 1999; **92:** 421–3.
6. Roy P-M, *et al.* Severe lactic acidosis induced by nucleoside analogues in an HIV-infected man. *Ann Emerg Med* 1999; **34:** 282–4.
7. Chattha G, *et al.* Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; **118:** 37–9.
8. Fouty B, *et al.* Riboflavin to treat nucleoside analogue-induced lactic acidosis. *Lancet* 1998; **352:** 291–2.
9. Luzzati R, *et al.* Riboflavine and severe lactic acidosis. *Lancet* 1999; **353:** 901–2.

Effects on mitochondria. Concern has been expressed[1] over the effects of nucleoside reverse transcriptase inhibitors on mitochondria after reports in France[2] of mitochondrial dysfunction in 8 infants whose mothers had received zidovudine alone, or with lamivudine, to prevent vertical transmission of HIV infection during pregnancy. The effects manifested themselves as severe demyelinating neurological disorder in 2 of the 8, both of whom died after about one year of life. Three other infants experienced seizures, 1 with severe cardiomyopathy and 1 with spastic diplegia, while the remaining 3 were asymptomatic. None were infected with HIV. A study[3] involving echocardiograms performed from birth to 5 years of age in 382 infants without HIV infection (36 with zidovudine exposure) and 58 infants with HIV infection (12 with zidovudine exposure), all of whom were born to HIV-infected women, found, however, that there was no evidence of abnormality in left ventricular structure or function associated with perinatal zidovudine. While it was considered that further assessment of this toxicity was required, it was emphasised that current recommendations for zidovudine monotherapy during pregnancy should be maintained.[1,2]

1. Committee on Safety of Medicines. Antiretroviral drugs in pregnancy and mitochondrial cytopathy in infants. *Current Problems* 1999; **25:** 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 22/05/06)
2. Blanche S, *et al.* Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; **354:** 1084–9.
3. Lipshultz SE, *et al.* Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med* 2000; **343:** 759–66.

Effects on the musculoskeletal system. Myalgia and other adverse effects on the muscle can occur in patients taking zidovudine, although it has sometimes been difficult to determine whether the effects were caused by the drug or by the underlying HIV infection.[1-4] Zidovudine-induced myopathy has been considered to be a distinct condition characterised by the presence of abnormal mitochondria in muscle-biopsy specimens;[2] this view is supported by the fact that the myopathy readily responds to the withdrawal of zidovudine or to treatment with corticosteroids or other anti-inflammatory drugs.[1-3] For further discussion of the effects of zidovudine on mitochondria, see above.

Arthralgia involving the knees, elbows, ankles, and wrists has been reported in a patient receiving zidovudine.[5]

1. Gertner E, *et al.* Zidovudine-associated myopathy. *Am J Med* 1989; **86:** 814–18.
2. Dalakas MC, *et al.* Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med* 1990; **322:** 1098–1105.
3. Till M, MacDonell KB. Myopathy with human immunodeficiency virus type 1 (HIV-1) infection: HIV-1 or zidovudine? *Ann Intern Med* 1990; **113:** 492–4.
4. Simpson DM, *et al.* Myopathies associated with human immunodeficiency virus and zidovudine: can their effects be distinguished? *Neurology* 1993; **43:** 971–6.
5. Murphy D, *et al.* Zidovudine related arthropathy. *BMJ* 1994; **309:** 97.

Effects on the nails. Bluish or brownish discoloration of fingernails and/or toenails has been reported in a number of patients receiving zidovudine.[1-5] Dark-skinned patients appear to be most commonly affected.[2,4] Occasionally the abnormal pigmentation also involves the skin.[3,5] It has been pointed out that discoloration of nails has occurred in HIV-infected patients without exposure to zidovudine.[6] Painless periungual pyogenic granulomata has been reported in a patient 3 months after starting treatment with a combined antiretroviral regimen of zidovudine, lamivudine, plus efavirenz; one month after the zidovudine and the lamivudine was stopped the lesions had nearly resolved.[7] Paronychia was reported in 12 HIV-infected patients taking lamivudine.[8] In a further report, 6 patients developed paronychia while taking lamivudine with indinavir.[9]

1. Furth PA, Kazakis AM. Nail pigmentation changes associated with azidothymidine (zidovudine). *N Engl J Med* 1987; **107:** 350.
2. Vaiopoulos G, *et al.* Nail pigmentation and azidothymidine. *Ann Intern Med* 1988; **108:** 777.
3. Merenich JA, *et al.* Azidothymidine-induced hyperpigmentation mimicking primary adrenal insufficiency. *Am J Med* 1989; **86:** 469–70.
4. Don PC, *et al.* Nail dyschromia associated with zidovudine. *Ann Intern Med* 1990; **112:** 145–6.

5. Bendick C, *et al.* Azidothymidine-induced hyperpigmentation of skin and nails. *Arch Dermatol* 1989; **125:** 1285–6.
6. Chandrasekar PH. Nail discoloration and human immunodeficiency virus infection. *Am J Med* 1989; **86:** 506–7.
7. Williams LH, Fleckman P. Painless periungual pyogenic granulomata associated with reverse transcriptase inhibitor therapy in a patient with human immunodeficiency virus infection. *Br J Dermatol* 2007; **156:** 163–4.
8. Zerboni R, *et al.* Lamivudine-induced paronychia. *Lancet* 1998; **351:** 1256.
9. Tosti A, *et al.* Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; **140:** 1165–8.

Precautions

Zidovudine should be used with care in patients with anaemia or bone-marrow suppression. The incidence of neutropenia is greater in patients with low vitamin B_{12} concentrations. Dosage adjustments or treatment interruptions may be necessary and it has been recommended that zidovudine should not be used if the neutrophil count or haemoglobin value is abnormally low. In patients with advanced symptomatic HIV disease taking oral zidovudine, blood tests should be carried out at least every 2 weeks for the first 3 months of treatment and at least monthly thereafter; blood tests should be performed at least every week in those receiving intravenous zidovudine. In patients with early HIV infection blood tests may be performed less frequently (e.g. every 1 to 3 months).

Care is also required in the elderly and in patients with reduced renal or hepatic function who may require reductions in dose. Patients with risk factors for liver disease should be monitored during treatment. Zidovudine is not recommended in patients with moderate to severe liver disease (Child-Pugh scores 7 to 15). Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Patients with hepatitis C receiving interferon alfa and ribavirin may be at special risk and particular care may be necessary in obese patients and in women. Treatment with zidovudine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology.

Zidovudine should not be given to neonates with hyperbilirubinaemia severe enough to need treatment other than phototherapy or with markedly increased aminotransferase concentrations.

Interference with laboratory tests. Raised urinary thymine concentrations in neonates, due to maternal zidovudine treatment, could produce erroneous results in screening tests for inborn errors of metabolism.[1]

1. Sewell AC. Zidovudine and confusion in urinary metabolic screening. *Lancet* 1998; **352:** 1227.

Pregnancy. Giving zidovudine to pregnant women with HIV infection from 14 weeks of gestation until delivery, and subsequently to the neonate, has been shown to reduce vertical transmission of the infection (see Uses and Administration, below). However, studies have shown that zidovudine can be fetotoxic in *animals* when given early in pregnancy, and the long-term consequences for the infant are as yet unknown although no adverse effects were seen in a group of infants followed for up to 5.6 years.[1] Licensed product information therefore recommends that zidovudine should not generally be given before 14 weeks of gestation.

1. Culnane M, *et al.* Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA* 1999; **281:** 151–7.

Interactions

Care should be taken when using zidovudine with drugs that are myelosuppressive (such as amphotericin B, co-trimoxazole, dapsone, doxorubicin, flucytosine, ganciclovir, interferon, systemic pentamidine, pyrimethamine, and vinca alkaloids) or nephrotoxic. Drugs that undergo glucuronidation may delay the metabolism of zidovudine but few of these appear to produce clinically important increases in zidovudine plasma concentrations. Increased toxicity and decreased antiretroviral activity has been reported when zidovudine is given with some other antiviral drugs, and pharmacokinetic interactions have been reported with a number of anti-infective drugs used commonly in patients with HIV infection.

Analgesics. There may be an increased risk of haematotoxicity during use of zidovudine with *NSAIDs*.

Decreased zidovudine clearance[1] and increased area under the zidovudine plasma concentration-time curve[2] has been seen in patients receiving *methadone*.

Severe hepatotoxicity has occurred after use of *paracetamol* in a patient taking zidovudine and co-trimoxazole.[3] However, neither short-term[4] nor long-term[5] studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.

1. Burger DM, *et al.* Pharmacokinetic variability of zidovudine in HIV-infected individuals: subgroup analysis and drug interactions. *AIDS* 1994; **8:** 1683–9.
2. Schwartz EL, *et al.* Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection. *J Acquir Immune Defic Syndr* 1992; **5:** 619–26.
3. Shriner K, Goetz MB. Severe hepatotoxicity in a patient receiving both acetaminophen and zidovudine. *Am J Med* 1992; **93:** 94–6.
4. Sattler FR, *et al.* Acetaminophen does not impair clearance of zidovudine. *Ann Intern Med* 1991; **114:** 937–40.
5. Burger DM, *et al.* Pharmacokinetics of zidovudine and acetaminophen in a patient on chronic acetaminophen therapy. *Ann Pharmacother* 1994; **28:** 327–30.

Antibacterials. Studies have indicated that the absorption of zidovudine could be reduced by *clarithromycin*.[1] Licensed product information recommends giving zidovudine and clarithromycin at least 2 hours apart since this has been shown to have no overall effect on the bioavailability of zidovudine.[2] Use of *rifampicin* by patients taking zidovudine has been reported to reduce exposure to zidovudine, probably by inducing glucuronidation and amination. Licensed product information for zidovudine has warned that this may result in a partial, or total, loss of efficacy of the drug.[3,4] *Rifabutin* has not been shown to have a marked effect on zidovudine clearance.[5] *Trimethoprim* has been reported[6,7] to decrease the renal clearance of zidovudine by up to 60% with a consequent increase in plasma concentrations, although it was only thought likely to be of clinical significance in patients with hepatic impairment.[7]

For a report of reduced *pyrazinamide* concentrations in patients receiving zidovudine, see p.321.

1. Polis MA, *et al.* Clarithromycin lowers plasma zidovudine levels in persons with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1997; **41:** 1709–14.
2. Vance E, *et al.* Pharmacokinetics of clarithromycin and zidovudine in patients with AIDS. *Antimicrob Agents Chemother* 1995; **39:** 1355–60.
3. Burger DM, *et al.* Pharmacokinetic interaction between rifampin and zidovudine. *Antimicrob Agents Chemother* 1993; **37:** 1426–31.
4. Gallicano KD, *et al.* Induction of zidovudine glucuronidation and amination pathways by rifampicin in HIV-infected patients. *Br J Clin Pharmacol* 1999; **48:** 168–79.
5. Gallicano K, *et al.* Effect of rifabutin on the pharmacokinetics of zidovudine in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1995; **21:** 1008–11.
6. Chatton JY, *et al.* Trimethoprim, alone or in combination with sulphamethoxazole, decreases the renal excretion of zidovudine and its glucuronide. *Br J Clin Pharmacol* 1992; **34:** 551–4.
7. Lee BL, *et al.* Zidovudine, trimethoprim, and dapsone pharmacokinetic interactions in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1996; **40:** 1231–6.

Antiepileptics. Giving *valproic acid* to 6 patients taking zidovudine produced increases in plasma-zidovudine concentrations and the area under the plasma concentration-time curve.[1] The evidence suggested that this was due to reduced glucuronidation of zidovudine. Zidovudine may possibly reduce or increase plasma concentrations of *phenytoin*.

1. Lertora JJL, *et al.* Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* 1994; **56:** 272–8.

Antifungals. Use of *fluconazole* with zidovudine produced higher serum-zidovudine concentrations, increased the area under the serum concentration-time curve, and prolonged terminal half-life compared with zidovudine alone in a study in 12 patients.[1] Studies *in vitro* suggested that fluconazole could inhibit the glucuronidation of zidovudine; inhibition was also seen with *amphotericin B*, *ketoconazole*, and *miconazole*, but not with *flucytosine* or *itraconazole*.[2]

1. Sahai J, *et al.* Effect of fluconazole on zidovudine pharmacokinetics in patients infected with human immunodeficiency virus. *J Infect Dis* 1994; **169:** 103–7.
2. Sampol E, *et al.* Comparative effects of antifungal agents on zidovudine glucuronidation by human liver microsomes. *Br J Clin Pharmacol* 1995; **40:** 83–6.

Antiprotozoals. Use of *atovaquone* with zidovudine produced moderate increases in the zidovudine plasma concentration and area under the plasma concentration-time curve, probably by inhibition of glucuronidation.[1]

1. Lee BL, *et al.* Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. *Clin Pharmacol Ther* 1996; **59:** 14–21.

Antivirals. Although there is some evidence from studies *in vitro* that *ribavirin* inhibits phosphorylation of zidovudine, and might therefore reduce its antiviral activity, it is unclear whether an interaction of clinical significance occurs; licensed product information for zidovudine does not recommend the combination, but product information for ribavirin varies, with the US product indicating that no clinical effect was seen. However, the combination may increase the risk of anaemia. Zidovudine product information also recommends that the use of zidovudine with *stavudine* be avoided since similar antagonism has been shown *in vitro*.[1] *Interferon alfa* and zidovudine had a synergistic cytotoxicity to bone-marrow progenitor cells.[2] Severe haematological toxicity occurred when zidovudine was added to *ganciclovir* therapy in AIDS patients with CMV retinitis, necessitating substantial dosage reductions or withdrawal of zidovudine in the majority of patients;[3,4] this additive toxicity with ganciclovir may be one reason why patients given zidovudine and ganciclovir do less well than those given zidovudine and foscarnet. Combined therapy with zidovudine and *aciclovir* is not generally associated with additional toxicity[5] but severe fatigue and lethargy were reported in a patient given aciclovir with zidovudine; this did not occur when either drug was given alone.[6] Evidence of a pharmacokinetic interaction between zidovudine and *didanosine* has been conflicting, with reports of no effect,[7] increased,[8] and decreased[9] plasma concentrations of zidovudine. Small reductions in didanosine plasma concentrations have been reported in patients also receiving zidovudine.[10] However, all changes have generally been small and are likely to be of limited clinical significance. Exposure to zidovudine (as measured by peak plasma concentrations and area under the concentration-time curve) was reduced in HIV patients also given *ritonavir*, whereas the pharmacokinetics of ritonavir were not affected by zidovudine;[11] the clinical relevance of this was not known. Modest increases in plasma-zidovudine concentrations occur on use with *lamivudine*. Although this interaction is usually clinically insignificant, profound anaemia has been reported rarely in patients given this combination.[12,13]

1. Havlir DV, *et al.* In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000; **182:** 321–5.
2. Berman E, *et al.* Synergistic cytotoxic effect of azidothymidine and recombinant interferon alpha on normal human bone marrow progenitor cells. *Blood* 1989; **74:** 1281–6.
3. Millar AB, *et al.* Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity. *Genitourin Med* 1990; **66:** 156–8.
4. Hochster H, *et al.* Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS: an AIDS Clinical Trials Group study. *Ann Intern Med* 1990; **113:** 111–17.
5. Tartaglione TA, *et al.* Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1991; **35:** 2225–31.
6. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* 1987; **316:** 547.
7. Collier AC, *et al.* Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Ann Intern Med* 1993; **119:** 786–93.
8. Barry M, *et al.* Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in patients with the acquired immunodeficiency syndrome. *Br J Clin Pharmacol* 1994; **37:** 421–6.
9. Burger DM, *et al.* Pharmacokinetic interaction study of zidovudine and didanosine. *J Drug Dev* 1994; **6:** 187–94.
10. Gibb D, *et al.* Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection. *Br J Clin Pharmacol* 1995; **39:** 527–30.
11. Cato A, *et al.* Multidose pharmacokinetics of ritonavir and zidovudine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1998; **42:** 1788–93.
12. Hester EK, Peacock JE. Profound and unanticipated anemia with lamivudine-zidovudine combination therapy in zidovudine-experienced patients with HIV infection. *AIDS* 1998; **12:** 439–40.
13. Tseng A, *et al.* Precipitous declines in hemoglobin levels associated with combination zidovudine and lamivudine therapy. *Clin Infect Dis* 1998; **27:** 908–9.

Probenecid. Use of probenecid with zidovudine results in increased plasma concentrations and area under the plasma concentration-time curve of zidovudine, probably due to inhibition of glucuronidation;[1] tubular secretion of the glucuronide metabolite is also reduced. A high incidence of adverse effects has been reported in some patients receiving this combination.[2]

1. de Miranda P, *et al.* Alteration of zidovudine pharmacokinetics by probenecid in patients with AIDS or AIDS-related complex. *Clin Pharmacol Ther* 1989; **46:** 494–500.
2. Petty BG, *et al.* Zidovudine with probenecid: a warning. *Lancet* 1990; **335:** 1044–5.

Antiviral Action

Zidovudine is converted intracellularly in stages to the triphosphate via thymidine kinase and other kinases. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It has also been shown to possess activity against Epstein-Barr virus and Gram-negative bacteria *in vitro*.

Zidovudine-resistant strains of HIV emerge rapidly during zidovudine therapy and are responsible for the lack of benefit with long-term monotherapy. Cross-resistance to other nucleoside reverse transcriptase inhibitors has been recognised.

Resistance. The emergence of zidovudine-resistant HIV strains in patients receiving long-term therapy with zidovudine has been recognised since 1989.[1,2] The emergence of drug resistance is associated with the duration[3] of treatment with zidovudine, but not the dose,[4] and is attributed to a high frequency of mutations in the

HIV reverse transcriptase gene.[3,5] Development of high-level resistance to zidovudine in patients with advanced HIV infection has been associated with rapid disease progression and death.[6] Primary infection with zidovudine-resistant HIV strains has been recorded,[7] as has zidovudine resistance in patients receiving other nucleoside reverse transcriptase inhibitors,[8,9] although it is possible that these patients had unrecorded exposure to zidovudine.[8] Cross-resistance with other reverse transcriptase inhibitors has been recorded and, although the use of zidovudine with lamivudine has been reported to delay or reverse the emergence of some mutations conferring zidovudine resistance, dual resistance to zidovudine and lamivudine has occurred.[10] Analysis of the Delta trial[11] found no delay in the emergence of zidovudine resistance when used with didanosine or zalcitabine, although circulating concentrations of resistant virus were lower during combination therapy and antiviral activity was apparently not impaired. Nevertheless, it could be anticipated that the use of zidovudine with other antiretrovirals, and particularly the highly active regimens which suppress viral replication to a high degree, could delay the emergence of resistance. The clinical response of patients with previous exposure to a number of regimens could be compromised by the presence of multidrug resistance.[12,13]

1. Larder BA, *et al.* HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 1989; **243:** 1731–4.
2. Rooke R, *et al.* Isolation of drug-resistant variants of HIV-1 from patients on long-term zidovudine therapy. *AIDS* 1989; **3:** 411–15.
3. Japour AJ, *et al.* Prevalence and clinical significance of zidovudine resistance mutations in human immunodeficiency virus isolated from patients after long-term zidovudine treatment. *J Infect Dis* 1995; **171:** 1172–9.
4. Richman DD, *et al.* Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1990; **3:** 743–6.
5. Loveday C, *et al.* HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy. *Lancet* 1995; **345:** 820–4.
6. D'Aquila RT, *et al.* Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. *Ann Intern Med* 1995; **122:** 401–8.
7. Erice A, *et al.* Brief report: primary infection with zidovudine-resistant human immunodeficiency virus type 1. *N Engl J Med* 1993; **328:** 1163–5.
8. Lin P-F, *et al.* Genotypic and phenotypic analysis of human immunodeficiency virus type 1 isolates from patients on prolonged stavudine therapy. *J Infect Dis* 1994; **170:** 1157–64.
9. Demeter LM, *et al.* Development of zidovudine resistance mutations in patients receiving prolonged didanosine monotherapy. *J Infect Dis* 1995; **172:** 1480–5.
10. Miller V, *et al.* Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapy failure. *J Infect Dis* 1998; **177:** 1521–32.
11. Brun-Vézinet F, *et al.* HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial. *Lancet* 1997; **350:** 983–90.
12. Kavlick MF, *et al.* Emergence of multi-dideoxynucleoside-resistant human immunodeficiency virus type 1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J Infect Dis* 1998; **177:** 1506–13.
13. Shafer RW, *et al.* Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. *Ann Intern Med* 1998; **128:** 906–11.

Pharmacokinetics

Zidovudine is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism with a bioavailability of about 60 to 70%. Peak plasma concentrations occur after about 1 hour. Absorption is delayed when given with food, but bioavailability is probably unaffected. Zidovudine crosses the blood-brain barrier producing CSF to plasma ratios of about 0.5. It crosses the placenta and is distributed into breast milk. It has been detected in semen. Plasma protein binding is reported to be 34 to 38%. The plasma half-life is about 1 hour.

Zidovudine is metabolised intracellularly to the antiviral triphosphate. It is also metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine as unchanged drug and metabolite.

◊ Reviews.

1. Acosta EP, *et al.* Clinical pharmacokinetics of zidovudine: an update. *Clin Pharmacokinet* 1996; **30:** 251–62.

Neonates. The pharmacokinetics of zidovudine in infants more than 14 days old are reported to be similar to those in adults. After maternal doses the half-life of zidovudine in 7 neonates has been reported to be extended to a mean of 13 hours.[1] In infants given zidovudine, those under 14 days of age had lower total clearance, longer terminal half-life (about 3 hours), and higher bioavailability than older infants.[2] Zidovudine clearance was low and the half-life prolonged to about 7 hours in premature infants.[3]

1. O'Sullivan MJ, *et al.* The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase 1 Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; **168:** 1510–16.
2. Boucher FD, *et al.* Phase 1 evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr* 1993; **122:** 137–44.
3. Mirochnick M, *et al.* Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. *Antimicrob Agents Chemother* 1998; **42:** 808–12.

Pregnancy. In a study in 3 pregnant women with HIV infection,[1] the area under the concentration-time curve for zidovudine was reduced and the clearance of an oral dose increased during pregnancy when compared with up to 4 weeks postpartum. These results differed from those reported from another study which reported no differences during or after pregnancy.[2] This latter study, however, used values obtained no later than 48 hours postpartum for comparison, at which time it is unlikely that physiological functions would have returned to the nonpregnant state. Zidovudine and its glucuronide metabolite cross the placenta reaching concentrations in the fetal blood similar to those in maternal blood.[3,4] However, concentrations of zidovudine in the fetal CNS have been reported to be below those required to exert an anti-HIV effect.[5]

1. Watts DH, *et al.* Pharmacokinetic disposition of zidovudine during pregnancy. *J Infect Dis* 1991; **163:** 226–32.
2. O'Sullivan MJ, *et al.* The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase 1 Acquired Immunodeficiency Syndrome Clinical Trials Group Study (protocol 082). *Am J Obstet Gynecol* 1993; **168:** 1510–16.
3. Gillet JY, *et al.* Fetoplacental passage of zidovudine. *Lancet* 1989; **ii:** 269–70.
4. Chavanet P, *et al.* Perinatal pharmacokinetics of zidovudine. *N Engl J Med* 1989; **321:** 1548–9.
5. Lyman WD, *et al.* Zidovudine concentrations in human fetal tissue: implications for perinatal AIDS. *Lancet* 1990; **335:** 1280–1.

Uses and Administration

Zidovudine is a nucleoside reverse transcriptase inhibitor structurally related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when zidovudine is used alone, and it is therefore usually used with other antiretrovirals. It may be used alone to prevent vertical transmission from mother to infant if combination antiretroviral therapy is not available.

Zidovudine is given orally in doses of 500 to 600 mg daily in 2 or 3 divided doses. Zidovudine may be given by intravenous infusion of a solution containing 2 to 4 mg/mL over 1 hour for short-term management of patients unable to take it orally. The dose is 1 to 2 mg/kg every 4 hours (equivalent to an oral dose of 1.5 to 3 mg/kg every 4 hours).

For the *prevention of maternal-fetal HIV transmission*, zidovudine may be given orally to **mothers** after the fourteenth week of pregnancy until the beginning of labour in a dose of 100 mg five times daily. During labour and delivery, zidovudine is given by intravenous infusion in a dose of 2 mg/kg over 1 hour, then 1 mg/kg per hour until the umbilical cord is clamped. When a caesarean section is planned the intravenous infusion is started 4 hours before the operation.

For details of doses in **infants and children**, including the prevention of maternal-fetal HIV transmission, see below.

Blood tests should be carried out regularly as described under Precautions, above. If the white cell count or haemoglobin level fall, the dose should be reduced or, alternatively, treatment interrupted briefly, until there is evidence of recovery. Treatment should be stopped if toxicity is severe and cautiously reintroduced once the bone marrow has recovered. Dosage adjustments may also be necessary in patients with renal (see below) or hepatic impairment.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing zidovudine in combination with lamivudine or with abacavir plus lamivudine are available in some countries.

Administration in children. For the **treatment of HIV infection** in infants and children zidovudine is given orally or intravenously with other antiretroviral drugs. Doses are based on body-surface:

- *oral* zidovudine is given in a dose of 360 to 480 mg/m^2 daily in 3 or 4 divided doses; the maximum dose should not exceed 200 mg every 6 to 8 hours
- *intravenous* zidovudine is given in a dose of 80 to 160 mg/m^2 every 6 hours. An intravenous dose of 120 mg/m^2 every 6 hours is equivalent to an oral dose of about 180 mg/m^2 every 6 hours

There are slight discrepancies between countries in the age ranges for which the above doses are licensed. The UK licenses these oral and intravenous doses from 3 months of age; the USA permits oral use from 6 weeks of age, but does not include intravenous doses for treatment in children, although it does have intravenous doses for prevention of transmission (below).

For the **prevention of maternal-fetal HIV transmission** the newborn infant is given zidovudine 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing for 6 weeks. Neonates unable to receive oral doses are given 1.5 mg/kg by intravenous infusion over 30 minutes every 6 hours. (For doses to be given to the mother for the prevention of maternal-fetal transmission see above.)

Administration in renal impairment. Oral doses of zidovudine should be reduced in patients with severe renal impairment (creatinine clearance less than 10 to 15 mL/minute) and in those on haemodialysis or peritoneal dialysis. Licensed product information gives the following guidance:

- *oral* administration: 100 mg every 6 to 8 hours
- *intravenous* administration: 1 mg/kg every 6 to 8 hours

HIV infection and AIDS. As discussed on p.856, the use of antiretroviral drugs in HIV infection changed after studies indicated that combination therapy could improve response.

A combination of zidovudine and other antiretroviral drugs improves efficacy, minimises toxicity, and delays drug resistance. Results from the Delta study[1] and the US AIDS Clinical Trial Group 175 (ACTG 175) study[2] showed combination therapy to be more effective than monotherapy in antiretroviral-naive patients and have led to profound changes in clinical practice. Both studies showed substantial reductions in mortality at 30 months in antiretroviral-naive patients treated with zidovudine plus either didanosine or zalcitabine compared with those receiving zidovudine alone. Triple therapy, with zidovudine used with another nucleoside reverse transcriptase inhibitor and either an HIV-protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (HAART regimens), has been found to reduce viral loads more effectively than monotherapy or two-drug combination therapy and such regimens are currently regarded as standard.

1. Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348:** 283–91.
2. Hammer SM, *et al.* A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med* 1996; **335:** 1081–90.

HIV infection prophylaxis. Antiretroviral drugs are used for chemoprophylaxis after *occupational and non-occupational exposure* to HIV infection. Zidovudine is commonly used with other antiretroviral drugs after exposure with a risk of infection (see p.858).

Zidovudine has been shown to be of value in *reducing vertical transmission*. For further information on the use of zidovudine in preventing HIV transmission from mother to child, see HIV Infection Prophylaxis, p.858.

Preparations

USP 31: Zidovudine Capsules; Zidovudine Injection; Zidovudine Oral Solution; Zidovudine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Azoazol†; Azotine†; Crisazet; Enper; Exovir†; Iduvo†; Retrovir; Zetrotax; ***Austral.:*** Retrovir; ***Austria:*** Retrovir; ***Belg.:*** Retrovir; ***Braz.:*** Produvir; Retrovir; Revirax; Virozid†; Zidovir†; Zidovusan†; ***Canad.:*** Novo-AZT†; Retrovir; ***Chile:*** Retrovir; ***Cz.:*** Retrovir; ***Denm.:*** Retrovir; ***Fin.:*** Retrovir; ***Fr.:*** Retrovir; ***Ger.:*** Retrovir; ***Gr.:*** Retrovir; Viroclon; Zidrevir; ***Hong Kong:*** Retrovir; ***Hung.:*** Retrovir; ***India:*** Retrovir; Zidorex†; Zidovir; Zilion; Zydowin; ***Indon.:*** Retrovir; ***Irl.:*** Retrovir; ***Israel:*** Retrovir; ***Ital.:*** Retrovir; ***Malaysia:*** Retrovir; ***Mex.:*** Azetavir; Novavir; Pranadox; Retrovir; Timivudin; Zidic-C; Zidovir†; ***Neth.:*** Retrovir; ***Norw.:*** Retrovir; ***NZ:*** Retrovir; ***Philipp.:*** Retrovir; ***Pol.:*** Azovir; Retrovir; ***Port.:*** Ambrodil; Azidina; Hivalase; Retrovir; Virotec; ***Rus.:*** Retrovir (Ретровир); ***S.Afr.:*** Retrovir; ***Singapore:*** Retrovir; ***Spain:*** Retrovir; ***Swed.:*** Retrovir; ***Switz.:*** Retrovir; ***Thai.:*** Retrovir; T-ZA; T.O.Vir; Zidis†; ***Turk.:*** Retrovir; ***UK:*** Retrovir; ***USA:*** Retrovir; ***Venez.:*** Retrovir; Zidovir.

Multi-ingredient: ***Arg.:*** 3TC Complex; 3TC/AZT; Ganvirel Duo; Hivirux Complex†; Imunoxa Complex; Kess Complex; Muvidina; Tricivir; Trivudin; Ultraviral Duo; Zetavudin; ***Austral.:*** Combivir; Trizivir; ***Austria:*** Combivir; Trizivir; ***Belg.:*** Combivir; Trizivir; ***Braz.:*** Biovir; Duovir†; Vir-Complex†; Zidolam; ***Canad.:*** Combivir; Trizivir; ***Chile:*** Combivir; Tricivir; ***Cz.:*** Combivir; Trizivir; ***Denm.:*** Combivir; Trizivir; ***Fin.:*** Combivir; Trizivir; ***Fr.:*** Combivir; Trizivir; ***Ger.:*** Combivir; Trizivir; ***Gr.:*** Combivir; Trizivir; ***Hong Kong:*** Combivir; Trizivir; ***Hung.:*** Combivir; Trizivir; ***India:*** Combirex†; Duovir; Duovir N; Lamda-Z; Lamuzid; ***Irl.:*** Combivir; Trizivir; ***Israel:*** Combivir; Trizivir; ***Ital.:*** Combivir; Trizivir; ***Malaysia:*** Combivir; ***Mex.:*** Combivir; Trizivir; ***Neth.:*** Combivir; Trizivir; ***Norw.:*** Combivir; Trizivir; ***NZ:*** Combivir; Trizivir; ***Philipp.:*** Combivir; ***Pol.:*** Combivir; Trizivir; ***Port.:*** Combivir; Trizivir; ***Rus.:*** Combivir (Комбивир); Trizivir (Тризивир); ***S.Afr.:*** Combivir; Duovir; Lamzid; Retrovir/3TC Post-HIV Exposure†; Trizivar; ***Singapore:*** Combivir; Trizivir†; ***Spain:*** Combivir; Trizivir; ***Swed.:*** Combivir; Trizivir; ***Switz.:*** Combivir; Trizivir; ***Thai.:*** Combid; ***Turk.:*** Combivir; ***UK:*** Combivir; Trizivir; ***USA:*** Combivir; Trizivir; ***Venez.:*** Combivir; Duovir; Trizivir.

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		**Atazanavir**		**Darunavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antivirals: Antiretrovirals						
Protease Inhibitors						
Amprenavir	N/A	N/A	Boosted atazanavir expected to increase concentration of amprenavir	Co-administration not recommended	Potential interaction	Dual therapy with protease inhibitors generally not recommended
Atazanavir	Boosted atazanavir expected to increase concentration of amprenavir	Co-administration not recommended	N/A	N/A	No clinically significant interaction	No dose adjustment required
Darunavir	Potential interaction	Dual therapy with protease inhibitors generally not recommended	No clinically significant interaction	No dose adjustment required	N/A	N/A
Indinavir	May increase concentration of amprenavir and decrease concentration of indinavir	Close monitoring – appropriate alteration of dose not established	Unspecified clinically significant interaction	Not recommended – both drugs have been associated with hyperbilirubinaemia	Increases concentration of both boosted darunavir and indinavir	Close monitoring; may need to decrease dose of indinavir
Lopinavir/Ritonavir	Increases concentrations of amprenavir and decreases concentration of lopinavir	Close monitoring; may need to alter the dose of ritonavir-boosted lopinavir but do not give as a single daily dose	Boosted atazanavir expected to increase concentration of lopinavir	Co-administration not recommended	Decreases concentration of boosted darunavir	Co-administration not recommended
Nelfinavir	No clinically significant interaction	Alteration of dose not usually needed	Boosted atazanavir expected to increase concentration of nelfinavir	Co-administration not recommended	Potential interaction	Dual therapy with protease inhibitors generally not recommended
Ritonavir	Increases concentration of amprenavir; (solution contains propylene glycol - potential of toxicity)	Dose of amprenavir should be reduced (co-administration of amprenavir and ritonavir solution - contraindicated)	Increases concentration of atazanavir	Co-administered as ritonavir-boosted atazanavir	Increases concentration of darunavir	Co-administered as ritonavir-boosted darunavir
Saquinavir	May decrease concentrations of amprenavir and saquinavir	Close monitoring - appropriate alteration of dose not established	Increases concentration of saquinavir	Close monitoring - appropriate alteration of dose not established	Decreases concentration of boosted darunavir	Dual therapy with protease inhibitors generally not recommended
Tipranavir	Boosted: decreases concentration of amprenavir	Close monitoring or alteration of dose; co-administration not recommended	Boosted: decreases concentration of atazanavir and increases concentration of tipranavir	Co-administration not recommended	Potential interaction	Dual therapy with protease inhibitors generally not recommended
NNRTIs						
Delavirdine	Decreases concentration of delavirdine and increases concentration of amprenavir	Appropriate doses not established; co-administration not recommended	Potential interaction	No established dose adjustment	Potential interaction	Close monitoring or alteration of dose
Efavirenz	May decrease concentration of amprenavir	Unboosted: no established dose adjustment; dose of amprenavir may need to be increased. Boosted: no dose adjustment needed	Decreases concentration of atazanavir	In treatment-naïve patients - give with atazanavir 300mg and ritonavir 100mg; treatment experienced patients - no established dose adjustments	Decreases concentration of boosted darunavir and increases concentration of efavirenz	Close monitoring - combination may be associated with CNS toxicity
Etravirine	Boosted and unboosted amprenavir increases concentration of amprenavir	Contraindicated	Unboosted atazanavir decreases concentration of atazanavir; boosted atazanavir decreases concentration of atazanavir and increases concentration of etravirine	Contraindicated	Boosted darunavir decreases concentration of etravirine	No dose adjustment required
Nevirapine	May decrease concentration of amprenavir	No established dose adjustment	Decreases concentration of atazanavir	No established dose adjustment; co-administration not recommended	Boosted darunavir increases concentration of nevirapine	Not a clinically significant interaction; co-administration without dose adjustments
NsRTIs/NtRTIs						
Abacavir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Didanosine	Decreases concentration of amprenavir (only with buffered didanosine formulation)	Doses of didanosine and amprenavir should be separated by at least 1 hour	Decreases concentration of atazanavir (only with buffered didanosine formulation)	Doses of didanosine and atazanavir should be separated by at least 2 hours	Potential interaction	Close monitoring; separate doses - give didanosine 1 hour before or 2 hours after boosted darunavir
Emtricitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamivudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stavudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Tenofovir	Potential interaction	Close monitoring or alteration of dose	Unboosted - decreases concentration of atazanavir; boosted - increases concentration of tenofovir	Always use boosted atazanavir; close monitoring for tenofovir associated adverse effects	Boosted darunavir increases concentration of tenofovir	Close monitoring for tenofovir associated adverse effects; particularly in patients with renal patients
Zalcitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Zidovudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		**Lopinavir (ritonavir-boosted)**		**Nelfinavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antivirals: Antiretrovirals						
Protease Inhibitors						
Amprenavir	May increase concentration of amprenavir and decrease concentration of indinavir	Close monitoring – appropriate alteration of dose not established	Increases concentration of amprenavir and decreases concentration of lopinavir	Close monitoring; may need to alter the dose of ritonavir-boosted lopinavir but do not give as a single daily dose	No clinically significant interaction	Alteration of dose not usually needed
Atazanavir	Unspecified clinically significant interaction	Contraindicated – both drugs have been associated with hyperbilirubinaemia	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Darunavir	Increases concentration of both boosted darunavir and indinavir	Close monitoring - may need to decrease dose of indinavir	Decreases concentration of boosted darunavir	Co-administration not recommended	Potential interaction	Dual therapy with protease inhibitors generally not recommended
Indinavir	N/A	N/A	Increases concentration of indinavir	Close monitoring; decrease dose of indinavir to 600 mg twice daily when given with ritonavir-boosted lopinavir 400/100 mg twice daily	Increases concentrations of nelfinavir and indinavir	Close monitoring – appropriate alteration of dose not established
Lopinavir/Ritonavir	Increases concentration of indinavir	Close monitoring; decrease dose of indinavir to 600mg twice daily when given with ritonavir-boosted lopinavir 400/100mg twice daily	N/A	N/A	Increases concentration of nelfinavir and decreases concentration of lopinavir	Close monitoring; may need to alter the dose of ritonavir-boosted lopinavir
Nelfinavir	Increases concentration of indinavir and nelfinavir	Close monitoring – appropriate alteration of dose not established	Increases concentration of nelfinavir and decreases concentration of lopinavir	Close monitoring; may need to alter the dose of ritonavir-boosted lopinavir	N/A	N/A
Ritonavir	Increases concentrations of both indinavir and ritonavir	Close monitoring - appropriate alteration of dose not established; combination associated with nephrolithiasis	Unboosted: increases concentration of lopinavir	Close monitoring – appropriate alteration of dose not established	Increases concentration of nelfinavir	Close monitoring – appropriate alteration of dose not established
Saquinavir	Unboosted: increases concentration of saquinavir Boosted: increases concentration of indinavir	Close monitoring – appropriate alteration of dose not established	Increases concentration of saquinavir	Close monitoring - dose of saquinavir is 1g twice daily when given with ritonavir-boosted lopinavir 400/100mg twice daily	Increases concentrations of saquinavir and nelfinavir	Close monitoring – appropriate alteration of dose not established
Tipranavir	Potential interaction	Close monitoring or alteration of dose; co-administration not recommended	Boosted: decreases concentration of lopinavir	Co-administration not recommended	Potential interaction	Close monitoring or alteration of dose; co-administration not recommended
NNRTIs						
Delavirdine	May increase concentration of indinavir	Close monitoring, may need to decrease dose of indinavir to 400 to 600mg every 8 hours	May increase concentrations of lopinavir	Close monitoring - appropriate alteration of dose not established	Increases concentration of nelfinavir and decreases concentration of delavirdine	Close monitoring – appropriate alteration of dose not established
Efavirenz	Decreases concentration of indinavir	Close monitoring, may need to increase dose of indinavir although appropriate alteration of dose not established	May decrease concentrations of lopinavir	Do not give as a once daily dose; in treatment-experienced patients increase dose of ritonavir-boosted lopinavir by about 33%	No clinically significant interaction	No dose adjustment required
Etravirine	Decreases concentration of indinavir	Contraindicated	Increases concentration of etravirine	Use with caution	Increases concentration of nelfinavir	Contraindicated
Nevirapine	Decreases concentration of indinavir	Close monitoring, may need to increase dose of indinavir to 1g every 8 hours	May decrease concentrations of lopinavir	Close monitoring - consider increasing dose of ritonavir-boosted lopinavir by about 33% (do not give as a once daily dose)	Decreases concentration of nelfinavir; not expected to be clinically significant	Close monitoring – alteration of dose not usually needed
NsRTIs/NtRTIs						
Abacavir	No clinically significant interaction	No dose adjustment required	May decrease concentrations of abacavir	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Didanosine	Potential interaction	Close monitoring; separate doses of didanosine and indinavir by 1 hour	Potential interaction	Close monitoring; separate doses – give didanosine 1 hour before or 2 hours after lopinavir/ ritonavir solution	Potential interaction due to formulation of didanosine	Close monitoring; separate doses – give nelfinavir 1 hour before or 2 hours after didanosine (or vice versa)
Emtricitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamivudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stavudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Tenofovir	Increases concentration of indinavir	No dose adjustment required	Modest increase in concentration of tenofovir	Close monitoring for tenofovir associated adverse effects	Potential interaction	Close monitoring or alteration of dose
Zalcitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Zidovudine	No clinically significant interaction	No dose adjustment required	May decrease concentration of zidovudine	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		**Saquinavir**		**Tipranavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antivirals: Antiretrovirals						
Protease Inhibitors						
Amprenavir	Increases concentration of amprenavir; (solution contains propylene glycol – potential of toxicity)	Dose of amprenavir should be reduced (co-administration of amprenavir and ritonavir solution – contraindicated)	May decrease concentrations of amprenavir and saquinavir	Close monitoring – appropriate alteration of dose not established	Boosted: decreases concentration of amprenavir	Close monitoring or alteration of dose; co-administration not recommended
Atazanavir	Increases concentration of atazanavir	Co-administered as ritonavir-boosted atazanavir	Boosted: increases concentration of saquinavir and ritonavir	Close monitoring – appropriate alteration of dose not established	Boosted: decreases concentration of atazanavir and increases concentration of tipranavir	Close monitoring or alteration of dose; co-administration not recommended
Darunavir	Increases concentration of darunavir	Co-administered as ritonavir-boosted darunavir	Decreases concentration of ritonavir-boosted darunavir	Dual therapy with protease inhibitors generally not recommended	Potential interaction	Dual therapy with protease inhibitors generally not recommended
Indinavir	Increases concentrations of indinavir	Close monitoring – appropriate alteration of dose not established; combination associated with nephrolithiasis	Unboosted: increases concentration of saquinavir; Boosted: increases concentration of indinavir	Close monitoring - appropriate alteration of dose not established; Boosted regimens may cause nephrolithiasis	Potential interaction	Close monitoring or alteration of dose; co-administration not recommended
Lopinavir/Ritonavir	Unboosted: increases concentration of lopinavir	Close monitoring – appropriate alteration of dose not established	Unboosted: potential interaction	Close monitoring - dose of saquinavir is 1g twice daily when given with lopinavir/ritonavir 400/100mg twice daily	Boosted: decreases concentration of lopinavir	Close monitoring or alteration of dose; co-administration not recommended
Nelfinavir	Increases concentration of nelfinavir	Close monitoring – appropriate alteration of dose not established	Unboosted: increases concentration of nelfinavir and saquinavir; Boosted: not evaluated	No initial adjustment required; monitor	Potential interaction	Close monitoring or alteration of dose; co-administration not recommended
Ritonavir	N/A	N/A	Increases concentration of saquinavir	Close monitoring or alteration of dose (used clinically as a boosted combination)	Increases concentration of tipranavir	Co-administered as ritonavir-boosted tipranavir
Saquinavir	Increases concentration of saquinavir	Co-administered as ritonavir-boosted saquinavir	N/A	N/A	Boosted: decreases concentration of saquinavir	Close monitoring or alteration of dose; co-administration not recommended
Tipranavir	Increases concentration of tipranavir	Co-administered as ritonavir-boosted tipranavir	Boosted: decreases concentration of saquinavir	Not recommended	N/A	N/A
NNRTIs						
Delavirdine	Increases concentration of ritonavir; may increase concentration of delavirdine	Close monitoring; may need to decrease dose of ritonavir	Unboosted: increases concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose may be required	Potential interaction	Close monitoring or alteration of dose
Efavirenz	Increases concentrations of efavirenz and ritonavir	Close monitoring or alteration of dose; high frequency of adverse effects reported	Unboosted: decreases concentration of saquinavir and efavirenz; Boosted: no relevant interaction	Close monitoring or alteration of dose may be required; boost with ritonavir	Boosted: limited data indicates no significant interactions	Use with caution until more data available
Etravirine	Decreases concentration of etravirine	Contraindicated	Boosted saquinavir decreases concentration of etravirine	No dose adjustment required	Boosted tipranavir decreases concentration of etravirine	Contraindicated
Nevirapine	No clinically significant interaction	No dose adjustment required	Unboosted: decreases concentration of saquinavir; Boosted: not evaluated	Monitor – although not considered clinically relevant	Boosted: limited data indicates no significant interactions	Use with caution until more data available
NsRTIs/NtRTIs						
Abacavir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Boosted: decreases concentration of abacavir	No established dose adjustments; use an alternative NRTI
Didanosine	Potential interaction due to formulation of didanosine	Close monitoring; separate doses of didanosine and ritonavir by 2.5 hours	Boosted: potential interaction	Close monitoring or alteration of dose may be required	Boosted: decreases concentration of didanosine	Administration should be separated by at least 2 hours
Emtricitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamivudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stavudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Tenofovir	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Zalcitabine	No clinically significant interaction	No dose adjustment required	Unboosted: no clinically significant interaction; Boosted: no studies	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Zidovudine	No clinically significant interaction	No dose adjustment required	Unboosted: no clinically significant interaction; Boosted: no studies	No dose adjustment required	Boosted: decreases concentration of zidovudine	No established dose adjustments; use an alternative NRTI

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antiretrovirals						
Enfuvirtide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Maraviroc	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Raltegravir	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Antivirals						
Aciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Adefovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Cidofovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Famciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Foscarnet	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ganciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ribavirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Valaciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Other Drugs						
Analgesics, Anti-inflammatory Drugs and Antipyretics						
Alfentanil	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Aspirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Buprenorphine	Potential Interaction	Close monitoring or alteration of dose	Increases concentration of buprenorphine	Close monitoring; may need to decrease dose of buprenorphine	Potential Interaction	Close monitoring or alteration of dose
Dextropropoxyphene	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Diamorphine	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Fentanyl	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Ibuprofen	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Methadone	Decreases concentrations of methadone and amprenavir	May need to increase dose of methadone; monitor for symptoms of withdrawal; consider an alternative antiretroviral	Boosted atazanavir - no clinically significant interaction	No dose adjustment required	Decreases concentrations of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal
Morphine	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Paracetamol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pethidine	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Piroxicam	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose
Tramadol	Potential Interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential Interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		Lopinavir (ritonavir-boosted)		Nelfinavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antiretrovirals						
Enfuvirtide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Maraviroc	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Raltegravir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antivirals						
Aciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Adefovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Cidofovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Famciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Foscarnet	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ganciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ribavirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Valaciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Other Drugs						
Analgesics, Anti-inflammatory Drugs and Antipyretics						
Alfentanil	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Aspirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Buprenorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Dextropropoxyphene	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diamorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fentanyl	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ibuprofen	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Methadone	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal	Decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal although rare with nelfinavir
Morphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Paracetamol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pethidine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Piroxicam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Tramadol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antiretrovirals						
Enfuvirtide	No clinically significant interaction	No dose adjustment required	Boosted: no clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Maraviroc	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Raltegravir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Antivirals						
Aciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Adefovir	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Cidofovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Famciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Foscarnet	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ganciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ribavirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Valaciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Other Drugs						
Analgesics, Anti-inflammatory Drugs and Antipyretics						
Alfentanil	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Aspirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Buprenorphine	Increase in concentration of buprenorphine; not expected to be clinically significant	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Dextropropoxyphene	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diamorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fentanyl	May increase concentration of fentanyl	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ibuprofen	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Methadone	Decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal	Boosted: decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal	Boosted: decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal
Morphine	May decrease concentration of morphine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Paracetamol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pethidine	Decreases concentration of pethidine and increases concentration of its metabolite	Dose increases and long term use not recommended due to potential for serious CNS related reactions	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of pethidine and increases concentration of its metabolite	Long term use not recommended; close monitoring or alteration of dose
Piroxicam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Tramadol	May increase concentration of tramadol	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antibacterials						
Antimycobacterials						
Ethambutol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Isoniazid	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrazinamide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rifabutin	Increases concentration of rifabutin and its metabolite	Decrease the dose of rifabutin	Increases concentration of rifabutin	Decrease the dose of rifabutin	Increases concentration of rifabutin; decreases concentration of darunavir	Decrease the dose of rifabutin
Rifampicin	Decreases concentration of amprenavir	Contraindicated - loss of antiretroviral activity	Decreases concentration of atazanavir	Contraindicated – loss of antiretroviral activity	Decreases concentration of darunavir	Contraindicated - loss of antiretroviral activity
Streptomycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Macrolides						
Azithromycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential Interaction	Close monitoring or alteration of dose
Clarithromycin	Unboosted: no clinically significant interaction Boosted: may increase concentration of clarithromycin	Unboosted - no dose adjustment required; boosted decrease dose of clarithromycin in patients with renal impairment	Increases concentration of both atazanavir and clarithromycin and decreases concentration of clarithromycin metabolite	Decrease dose of clarithromycin by about 50% or consider alternatives except for *Mycobacterium avium* complex	Increases concentration of clarithromycin; concentration of clarithromycin metabolite not detectable	Normal renal function - caution and monitor; impaired renal function - decrease dose of clarithromycin
Erythromycin	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential Interaction	Close monitoring or alteration of dose
Quinolones						
Ciprofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Others						
Clindamycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Co-trimoxazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Dapsone	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Metronidazole	Potential risk of toxicity due to propylene glycol	Contraindicated - due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Quinupristin/Dalfopristin	—	—	—	—	—	—
Tetracyclines	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antidepressants						
Tricyclics						
Amitriptyline	Increases concentrations of tricyclics	Close monitoring or alteration of dose	Increases concentrations of tricyclics	Caution – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose
Desipramine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Doxepin	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nortriptyline	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
SSRIs						
Citalopram	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluoxetine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Paroxetine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of paroxetine	Start with lowest dose of paroxetine and monitor
Sertraline	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of sertraline	Start with lowest dose of sertraline and monitor

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		Lopinavir (ritonavir-boosted)		Nelfinavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antibacterials						
Antimycobacterials						
Ethambutol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Isoniazid	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrazinamide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rifabutin	Increases concentration of rifabutin; decreases concentration of indinavir	Decrease dose of rifabutin and increase the dose of indinavir	Increases concentration of rifabutin and its metabolite	Decrease dose of rifabutin	Increases concentration of rifabutin; decreases concentration of nelfinavir	Decrease dose of rifabutin
Rifampicin	Decreases concentration of indinavir	Contraindicated – loss of antiretroviral activity	Decreases concentration of lopinavir	Contraindicated – loss of antiretroviral activity	Decreases concentration of nelfinavir	Contraindicated – loss of antiretroviral activity
Streptomycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Macrolides						
Azithromycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Increases concentration of azithromycin	No adjustment required, but monitor liver enzymes and hearing
Clarithromycin	Increases concentrations of clarithromycin and indinavir	Appropriate alteration of dose not established	Increases concentrations of clarithromycin	Normal renal function - no dose adjustments needed; Impaired renal function - decrease dose of clarithromycin	No clinically significant interaction	No dose adjustment required
Erythromycin	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Quinolones						
Ciprofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Others						
Clindamycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Co-trimoxazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Dapsone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Metronidazole	No clinically significant interaction	No dose adjustment required	Lopinavir/ ritonavir formulations contain alcohol	May cause disulfiram reaction	No clinically significant interaction	No dose adjustment required
Quinupristin/Dalfopristin	—	—	—	—	—	—
Tetracyclines	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antidepressants						
Tricyclics						
Amitriptyline	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Desipramine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Doxepin	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nortriptyline	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
SSRIs						
Citalopram	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluoxetine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Paroxetine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Sertraline	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		**Saquinavir**		**Tipranavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antibacterials						
Antimycobacterials						
Ethambutol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Isoniazid	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrazinamide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rifabutin	Increases concentration of rifabutin and its metabolite	Decrease the dose of rifabutin	Unboosted: increases concentration of rifabutin and decreases concentration of saquinavir; Boosted: not evaluated	Decrease the dose of rifabutin	Boosted: increases concentration of rifabutin and metabolites	Decrease dose of rifabutin
Rifampicin	Decreases concentration of ritonavir	Contraindicated – loss of antiretroviral activity	Unboosted: decreases concentration of saquinavir; Boosted: caused hepatocellular toxicity	Both boosted and unboosted saquinavir contraindicated with rifampicin	Boosted: decreases concentration of tipranavir	Contraindicated - loss of antiretroviral activity and possible resistance
Streptomycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Macrolides						
Azithromycin	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Clarithromycin	Increases concentrations of clarithromycin	Normal renal function - no dose adjustments needed; impaired renal function - decrease dose of clarithromycin	Unboosted: increases concentration of clarithromycin and saquinavir; Boosted: not evaluated	Normal renal function - no dose adjustments needed; Impaired renal function - decrease dose of clarithromycin by 50 to 75%	Boosted: increases concentration of tipranavir and clarithromycin; decreases concentration of clarithromycin metabolite	Normal renal function – no dose adjustments needed; impaired renal function – decrease dose of clarithromycin
Erythromycin	May increase concentration of erythromycin	Close monitoring or alteration of dose	Unboosted: no clinically significant interaction; Boosted: not evaluated	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Quinolones						
Ciprofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Others						
Clindamycin	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Co-trimoxazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Dapsone	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metronidazole	Ritonavir formulations contain alcohol	May cause disulfiram reaction	No clinically significant interaction	No dose adjustment required	Tipranavir capsules contain alcohol	May cause disulfiram reaction
Quinupristin/Dalfopristin	—	—	Unboosted: potential to increase concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	—	—
Tetracyclines	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antidepressants						
Tricyclics						
Amitriptyline	May increase concentrations of tricyclics	Close monitoring or alteration of dose	Boosted: potential to decrease concentration of tricyclics	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Desipramine	Increases concentration of desipramine	Low starting dose of desipramine	Potential interaction	Close monitoring or alteration of dose	Boosted: may increase concentration of desipramine	May need to reduce dose of desipramine
Doxepin	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nortriptyline	May increase concentrations of tricyclics	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
SSRIs						
Citalopram	May increase concentration of citalopram	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluoxetine	May increase concentration of fluoxetine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No studies but potential to increase concentration of fluoxetine	Close monitoring or alteration of dose
Paroxetine	May increase concentration of paroxetine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No studies but potential to increase concentration of paroxetine	Close monitoring or alteration of dose
Sertraline	May increase concentration of sertraline	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No studies but potential to increase concentration of sertraline	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antidepressants						
Bupropion	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Mirtazapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nefazodone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
St Johns Wort	Decreases concentration of amprenavir	Contraindicated - loss of antiretroviral activity and possible resistance to amprenavir	Decreases concentration of atazanavir	Contraindicated - loss of antiretroviral activity and possible resistance to atazanavir	Decreases concentration of darunavir	Contraindicated - loss of antiretroviral activity
Trazodone	Increases concentration of trazodone	Caution; may need to decrease dose of trazodone	Increases concentration of trazodone	Caution; may need to decrease dose of trazodone	Increases concentration of trazodone	Caution; may need to decrease dose of trazodone
Venlafaxine	—	—	—	—	—	—
Antidiabetics (Oral)						
Glimepiride	—	—	—	—	—	—
Glipizide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Glyburide	—	—	—	—	—	—
Metformin	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Pioglitazone	—	—	—	—	—	—
Rosiglitazone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Repaglinide	—	—	—	—	—	—
Tolbutamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antiepileptics						
Carbamazepine	Decreases concentration of amprenavir	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of darunavir	Contraindicated - loss of antiretroviral activity
Clonazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ethosuximide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Gabapentin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamotrigine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Phenobarbital	Decreases concentration of amprenavir	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of darunavir	Contraindicated - loss of antiretroviral activity
Phenytoin	Decreases concentration of amprenavir	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of darunavir	Contraindicated - loss of antiretroviral activity
Valproate	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Vigabatrin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antifungals						
Amphotericin B	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Caspofungin	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluconazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Flucytosine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Itraconazole	May increase concentration of itraconazole	Caution – dose adjustment may be needed for patients taking more than 400mg itraconazole daily	May increase concentration of itraconazole	Caution – dose adjustment may be needed for patients taking more than 200mg itraconazole daily	No studies - may increase concentration of itraconazole and darunavir	Caution - dose of itraconazole should not exceed 200mg daily
Ketoconazole	May increase concentration of ketoconazole	Caution – dose adjustment may be needed for patients taking more than 400mg ketoconazole daily	May increase concentration of ketoconazole	Caution – dose adjustment may be needed for patients taking more than 200mg ketoconazole daily	Increases concentration of ketoconazole and darunavir	Caution - dose of ketoconazole should not exceed 200mg daily
Miconazole	—	—	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Terbinafine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Voriconazole	Potential for bi-directional inhibition	Close monitoring or alteration of dose	Potential for bi-directional inhibition	Not recommended unless benefit outweighs risks	No studies - may decrease the concentration of voriconazole	Co-administration generally not recommended

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		**Lopinavir (ritonavir-boosted)**		**Nelfinavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antidepressants						
Bupropion	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Mirtazapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nefazodone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
St Johns Wort	Decreases concentration of indinavir	Contraindicated – loss of antiretroviral activity and possible resistance to indinavir	Decreases concentration of ritonavir-boosted lopinavir	Contraindicated – loss of antiretroviral activity and possible resistance to lopinavir	Decreases concentration of nelfinavir	Contraindicated – loss of antiretroviral activity and possible resistance to nelfinavir
Trazodone	Increases concentration of trazodone	Caution; may need to decrease dose of trazodone	Increases concentration of trazodone	Use with caution, consider a lower dose of trazodone	Increases concentration of trazodone	Use with caution, consider a lower dose of trazodone
Venlafaxine	Decreases concentration of indinavir	Unknown clinical significance	—	—	—	—
Antidiabetics (Oral)						
Glimepiride	—	—	—	—	—	—
Glipizide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Glyburide	—	—	—	—	—	—
Metformin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pioglitazone	—	—	—	—	—	—
Rosiglitazone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Repaglinide	—	—	—	—	—	—
Tolbutamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antiepileptics						
Carbamazepine	Decreases concentration of indinavir	Close monitoring or alteration of dose	Decreases concentration of lopinavir	Close monitoring or alteration of dose	May decrease concentration of nelfinavir	Close monitoring or alteration of dose
Clonazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ethosuximide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Gabapentin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamotrigine	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Phenobarbital	Decreases concentration of indinavir	Close monitoring or alteration of dose	May decrease concentration of lopinavir	Close monitoring or alteration of dose	May decrease concentration of nelfinavir	Close monitoring or alteration of dose
Phenytoin	Decreases concentration of indinavir	Close monitoring or alteration of dose	May decrease concentrations of lopinavir and phenytoin	Close monitoring or alteration of dose	Decreases concentration of phenytoin	Close monitoring or alteration of dose
Valproate	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vigabatrin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antifungals						
Amphotericin B	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Caspofungin	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Fluconazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Modest increase in concentration of nelfinavir; not expected to be clinically significant	No dose adjustment required
Flucytosine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Itraconazole	Increases concentrations of indinavir	Caution – dose adjustment may be needed for patients taking more than 200mg itraconazole daily; consider reducing indinavir to 600mg every 8 hours	Increases concentration of itraconazole	Caution – dose adjustment may be needed for patients taking more than 200mg itraconazole daily	Potential for bi-directional inhibition; not expected to be clinically significant	No dose adjustment required; monitor for toxicities
Ketoconazole	May increase concentration of indinavir	Close monitoring – appropriate alteration of dose not established; consider reducing indinavir to 600mg every 8 hours	Increases concentration of ketoconazole	Close monitoring or alteration of dose; do not exceed 200mg ketoconazole daily	Increase in concentration of nelfinavir; not expected to be clinically significant	No dose adjustment required
Miconazole	No Data	No Data	Potential interaction	Close monitoring or alteration of dose	—	—
Terbinafine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Voriconazole	Unboosted - no clinically significant interaction; boosted - potential interaction	Boosted - close monitoring or alteration of dose	May decrease concentration of voriconazole	Contraindicated	Potential for bi-directional inhibition	Monitor for toxicities

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Other Antidepressants						
Bupropion	Increases concentration of bupropion	Caution – consider decreasing the dose of bupropion	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Mirtazapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nefazodone	May increase concentration of nefazodone	Close monitoring or alteration of dose	Unboosted: increases concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
St Johns Wort	Decreases concentration of ritonavir	Contraindicated – loss of antiretroviral activity and possible resistance to ritonavir	Unboosted: decreases concentration of saquinavir; Boosted: interaction not evaluated	Contraindicated – loss of antiretroviral activity and possible resistance to saquinavir	Decreases concentration of tipranavir	Contraindicated – loss of antiretroviral activity and possible resistance to tipranavir
Trazodone	Increases concentration of trazodone	Use with caution, consider a lower dose of trazodone	Boosted: increases concentration of trazodone	Use with caution, consider a lower dose of trazodone	Boosted: increases concentration of trazodone	Caution – consider a lower dose of trazodone
Venlafaxine	—	—	—	—	—	—
Antidiabetics (Oral)						
Glimepiride	—	—	—	—	No studies but potential for interactions	Caution and glucose monitoring
Glipizide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No studies but potential for interactions	Caution and glucose monitoring
Glyburide	—	—	—	—	No studies but potential for interactions	Caution and glucose monitoring
Metformin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pioglitazone	—	—	—	—	No studies but potential for interactions	Caution and glucose monitoring
Rosiglitazone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Repaglinide	—	—	—	—	No studies but potential for interactions	Caution and glucose monitoring
Tolbutamide	May increase concentration of tolbutamide	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No studies but potential for interactions	Caution and glucose monitoring
Antiepileptics						
Carbamazepine	May increase concentration of carbamazepine	Close monitoring or alteration of dose	Unboosted: potential to decrease concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	Boosted: decreases concentration of tipranavir	Monitoring of antiepileptic concentration advised
Clonazepam	May increase concentration of clonazepam	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ethosuximide	May increase concentration of ethosuximide	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Gabapentin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamotrigine	May decrease concentration of lamotrigine	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Phenobarbital	Potential interaction	Close monitoring or alteration of dose	Unboosted: potential to decrease concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	Boosted: decreases concentration of tipranavir	Monitoring of antiepileptic concentration advised
Phenytoin	May decrease concentration of phenytoin	Close monitoring or alteration of dose	Unboosted: potential to decrease concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	Boosted: decreases concentration of tipranavir	Monitoring of antiepileptic concentration advised
Valproate	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Decreases concentration of valproate	Monitoring of antiepileptic concentration advised
Vigabatrin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antifungals						
Amphotericin B	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Caspofungin	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Fluconazole	No clinically significant interaction	No dose adjustment required	Modest increase in concentration of saquinavir	No dose adjustment required	Boosted: increases concentration of tipranavir	No dose adjustment needed for tipranavir; maximum dose for fluconazole is 200mg daily
Flucytosine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Itraconazole	Increases level of itraconazole	Close monitoring or alteration of dose; do not exceed 200mg itraconazole daily	Unboosted: potential for bi-directional inhibition; Boosted: not evaluated	Close monitoring or alteration of dose	Boosted: potential to increase concentration of itraconazole	Use with caution; do not exceed 200mg itraconazole daily
Ketoconazole	Increases concentration of ketoconazole	Close monitoring or alteration of dose; do not exceed 200mg ketoconazole daily	Unboosted: potential for bi-directional inhibition; Boosted: not evaluated	No dose adjustment required	Boosted: potential to increase concentration of ketoconazole	Use with caution; do not exceed 200mg ketoconazole daily
Miconazole	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Terbinafine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Voriconazole	High dose ritonavir decreases concentration of voriconazole; low dose ritonavir decreases concentration of voriconazole and ritonavir	High dose - contraindicated; low dose - avoid unless benefit outweighs risk	Potential for bi-directional inhibition	Monitor for toxicities	No studies but potential for interactions with boosted tipranavir	Not recommended unless benefit outweighs risk

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antihistamines						
Astemizole	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Cetirizine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fexofenadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Loratadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Terfenadine	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Antimalarials/Antiprotozoals						
Artemisinins	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Atovaquone	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Chloroquine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halofantrine	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated
Lumefantrine	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated
Mefloquine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Pentamidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Proguanil	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine-Sulfadoxine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Quinine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antimigraine Drugs						
Ergot derivatives	Increased risk of ergot toxicity	Contraindicated – due to potential for serious or life-threatening reactions	Increased risk of ergot toxicity	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated - due to potential for serious or life-threatening reactions
Sumatriptan	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antineoplastics						
Cyclophosphamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Doxorubicin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Irinotecan	—	—	Increased toxicity of irinotecan	Contraindicated	—	—
Paclitaxel	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vinca alkaloids	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Anxiolytic Sedatives Hypnotics and Antipsychotics						
Antipsychotics						
Chlorpromazine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clozapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Haloperidol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Olanzapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Perphenazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pimozide	Increased risk of cardiac arrhythmias	Contraindicated – due to potential for serious or life-threatening reactions	Increased risk of cardiac arrhythmias	Contraindicated – due to potential for serious or life-threatening reactions	Increased risk of cardiac arrhythmias	Contraindicated - due to potential for serious or life-threatening reactions
Resperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Thioridazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		Lopinavir (ritonavir-boosted)		Nelfinavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antihistamines						
Astemizole	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Cetirizine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fexofenadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Loratadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Terfenadine	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Antimalarials/Antiprotozoals						
Artemisinins	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Atovaquone	No clinically significant interaction	No dose adjustment required	Decreases concentration of atovaquone	Unknown clinical significance; may need to increase dose of atovaquone	No clinically significant interaction	No dose adjustment required
Chloroquine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halofantrine	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated
Lumefantrine	These drugs should not be co-administered	Contraindicated	Potential interaction	Close monitoring or alteration of dose	These drugs should not be co-administered	Contraindicated
Mefloquine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Pentamidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Proguanil	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine-Sulfadoxine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Quinine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antimigraine Drugs						
Ergot derivatives	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Sumatriptan	No clinically significant interaction	No adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antineoplastics						
Cyclophosphamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Doxorubicin	No clinically significant interaction	No adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Irinotecan	—	—	—	—	—	—
Paclitaxel	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vinca alkaloids	Potential interaction	Close monitoring or alteration of dose	May increase concentration of vinca alkaloids	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Anxiolytic Sedatives Hypnotics and Antipsychotics						
Antipsychotics						
Chlorpromazine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clozapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Haloperidol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Olanzapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Perphenazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pimozide	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Resperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Thioridazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antihistamines						
Astemizole	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unboosted and boosted: thought to increase concentration of astemizole	Contraindicated – results in prolongation of QTc intervals	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Cetirizine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fexofenadine	May increase concentration of fexofenadine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Loratadine	May increase concentration of loratadine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Terfenadine	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unboosted and boosted: increases concentration of terfenadine	Contraindicated – results in prolongation of QTc intervals	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Antimalarials/Antiprotozoals						
Artemisinins	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Atovaquone	May decrease concentration of atovaquone	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Chloroquine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halofantrine	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	Unspecified clinically significant interaction	Contraindicated
Lumefantrine	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	Unspecified clinically significant interaction	Contraindicated
Mefloquine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Pentamidine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Proguanil	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pyrimethamine-Sulfadoxine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Quinine	May increase concentration of quinine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antimigraine Drugs						
Ergot derivatives	Increases concentration of ergot alkaloids	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of ergot alkaloids	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Sumatriptan	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antineoplastics						
Cyclophosphamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Doxorubicin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Irinotecan	—	—	—	—	—	—
Paclitaxel	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vinca alkaloids	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Anxiolytic Sedatives Hypnotics and Antipsychotics						
Antipsychotics						
Chlorpromazine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clozapine	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Haloperidol	May increase concentration of haloperidol	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Olanzapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Perphenazine	May increase concentration of perphenazine	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pimozide	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of pimozide	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Resperidone	May increase concentration of resperidone	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Thioridazine	May increase concentration of thioridazine	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		**Atazanavir**		**Darunavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Anxiolytics						
Buspirone	—	—	—	—	—	—
Benzodiazepines						
Alprazolam	Increases concentration of alprazolam	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clorazepate	Increases concentration of clorazepate	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diazepam	Increases concentration of diazepam	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Flurazepam	Increases concentration of flurazepam	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Lorazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Midazolam	Increases concentration of midazolam	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Triazolam	Increases concentration of triazolam	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Hypnotics						
Zolpidem	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bronchodilators						
Theophylline	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Cardiovascular Drugs						
Digoxin	—	—	—	—	Increases concentration of digoxin	Start with the lowest possible dose of digoxin, then monitor
Anticoagulants						
Warfarin/Acenocoumarol	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary
Antiarrhythmics						
Amiodarone	Increases concentration of amiodarone	Use with caution	May increase concentration of amiodarone	Caution – due to potential for serious or life-threatening reactions	Increases concentration of amiodarone	Contraindicated - due to potential for serious or life-threatening reactions
Disopyramide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Encainide	—	—	—	—	—	—
Flecainide	Unspecified clinically significant interaction	Contraindicated with ritonavir-boosted amprenavir	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated
Lidocaine (systemic)	Increases concentration of lidocaine	Use with caution	May increase concentration of lidocaine	Caution – due to potential for serious or life-threatening reactions	Increases concentration of lidocaine	Contraindicated - due to potential for serious or life-threatening reactions
Mexiletine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Propafenone	Unspecified clinically significant interaction	Contraindicated with ritonavir-boosted amprenavir	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated
Quinidine	Increases concentration of quinidine	Use with caution	May increase concentration of quinidine	Contraindicated – due to potential for serious or life-threatening reactions	Increases concentration of quinidine	Contraindicated – due to potential for serious or life-threatening reactions
Beta Blockers						
Atenolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bisoprolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Carvedilol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metoprolol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Propranolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Timolol	—	—	—	—	—	—

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		**Lopinavir (ritonavir-boosted)**		**Nelfinavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Anxiolytics						
Buspirone	—	—	—	—	—	—
Benzodiazepines						
Alprazolam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clorazepate	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Flurazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Lorazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Midazolam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Triazolam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Hypnotics						
Zolpidem	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bronchodilators						
Theophylline	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Cardiovascular Drugs						
Digoxin	—	—	May increase concentration of digoxin	Caution - close monitoring	—	—
Anticoagulants						
Warfarin/Acenocoumarol	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary	Potential to alter acenocoumarol concentration	Monitor INR and alter dose if necessary
Antiarrhythmics						
Amiodarone	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	May increase concentration of amiodarone	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Disopyramide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Encainide	—	—	—	—	—	—
Flecainide	These drugs should not be co-administered	Contraindicated	These drugs should not be co-administered	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Lidocaine (systemic)	May increase concentration of lidocaine	Close monitoring or alteration of dose	May increase concentration of lidocaine	Caution - close monitoring	Potential interaction	Close monitoring or alteration of dose
Mexiletine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Propafenone	Potential interaction	Close monitoring or alteration of dose	These drugs should not be co-administered	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Quinidine	May increase concentration of quinidine	Close monitoring or alteration of dose	May increase concentration of quinidine	Caution - close monitoring	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Beta Blockers						
Atenolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Bisoprolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Carvedilol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metoprolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Propranolol	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Timolol	—	—	—	—	—	—

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Anxiolytics						
Buspirone	May increase concentration of buspirone	Close monitoring or alteration of dose	—	—	—	—
Benzodiazepines						
Alprazolam	May increase concentration of alprazolam	Close monitoring or alteration of dose	Boosted: increases concentration of alprazolam	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Clorazepate	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of clorazepate	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diazepam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of diazepam	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Flurazepam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of flurazepam	Close monitoring or alteration of dose	—	—
Lorazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No adjustment required	No clinically significant interaction	No dose adjustment required
Midazolam	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unboosted: increases concentration of midazolam; Boosted: not evaluated	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Triazolam	Increases concentration of triazolam	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: potential to increase concentration of triazolam	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Hypnotics						
Zolpidem	Increases concentration of zolpidem	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bronchodilators						
Theophylline	Decreases concentration of theophylline	Close monitoring; may need to increase dose of theophylline	No clinically significant interaction	No dose adjustment required	Potential to decrease concentration of theophylline with boosted tipranavir	Close monitoring; may need to increase dose of theophylline
Cardiovascular Drugs						
Digoxin	May increase concentration of digoxin	Close monitoring or alteration of dose	Boosted: increases concentration of digoxin	Close monitoring or alteration of dose	Boosted: may double exposure to digoxin after 1st dose but at steady state concentration of digoxin may be decreased	Close monitoring or alteration of dose until steady state is reached
Anticoagulants						
Warfarin/Acenocoumarol	Decreases concentration of warfarin	Monitor INR and alter dose if necessary	Potential to alter warfarin concentration	Monitor INR and alter dose if necessary	No studies but potential for interactions	Monitor INR and alter dose if necessary
Antiarrhythmics						
Amiodarone	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of amiodarone	Contraindicated – due to potential for serious or life-threatening cardiac arrhythmias	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Disopyramide	May increase concentration of disopyramide	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Encainide	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	—	—	—	—
Flecainide	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of flecainide	Contraindicated – due to potential for serious or life-threatening cardiac arrhythmias	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Lidocaine (systemic)	May increase concentration of lidocaine	Close monitoring or alteration of dose	Boosted: increases concentration of lidocaine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Mexiletine	May increase concentration of mexiletine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Propafenone	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of propafenone	Contraindicated - due to potential for serious or life-threatening cardiac arrhythmias	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Quinidine	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of quinidine	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Beta Blockers						
Atenolol	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Bisoprolol	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Carvedilol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metoprolol	May increase concentration of metoprolol	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Propranolol	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Timolol	May increase concentration of timolol	Close monitoring or alteration of dose	—	—	—	—

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Calcium Channel Blockers (CCB)						
Amlodipine	May increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bepridil	Increases concentration of CCB	Contraindicated – due to potential for serious or life-threatening reactions	May increase concentration of bepridil	Caution – due to potential for serious or life-threatening reactions	Increases concentration of CCB	Contraindicated - due to potential for serious or life-threatening reactions
Diltiazem	May increase concentration of CCB	Close monitoring or alteration of dose	Increases concentration of diltiazem	Caution - may need to reduce dose of diltiazem	Potential interaction	Close monitoring or alteration of dose
Felodipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose
Isradipine	May increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	—	—
Nicardipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose
Nifedipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose
Nimodipine	May increase concentration of CCB	Close monitoring or alteration of dose	—	—	—	—
Nisoldipine	May increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Verapamil	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Lipid Regulating Drugs						
Atorvastatin	Increases concentration of atorvastatin	Use lowest possible dose of atorvastatin or change to pravastatin or fluvastatin	Increases concentration of atorvastatin	Caution – possible risk of myopathy; use lowest possible dose of atorvastatin	Increases concentration of atorvastatin	Start with lowest dose of atorvastatin and monitor
Cerivastatin	—	—	—	—	—	—
Clofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fenofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fluvastatin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Gemfibrozil	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lovastatin	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy	Potential for increased concentration of lovastatin	Contraindicated - increases risk of myopathy
Pravastatin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	May increase concentration of pravastatin in small numbers of patients	Start with lowest dose of pravastatin and monitor
Rosuvastatin	Potential interaction	Close monitoring or alteration of dose	Increases concentration of rosuvastatin	Caution - possible risk of myopathy; use lowest possible dose of rosuvastatin	Increases concentration of rosuvastatin	Start with lowest dose of rosuvastatin and monitor
Simvastatin	Potential for increased concentration of simvastatin	Not advised – increases risk of myopathy	Potential for increased concentration of simvastatin	Not advised – increases risk of myopathy	Potential for increased concentration of simvastatin	Contraindicated - increases risk of myopathy
Corticosteroids						
Budesonide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Dexamethasone	Decreases concentration of amprenavir	Caution - loss of antiretroviral activity	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of darunavir	Caution - loss of antiretroviral activity
Fluticasone	Increases concentration of fluticasone	Unboosted – consider an alternative for long term use; Boosted – contraindicated	Increases concentration of fluticasone	Unboosted – consider an alternative for long term use; Boosted – not recommended	Increases concentration of fluticasone	Consider an alternative for long term use
Prednisolone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		Lopinavir (ritonavir-boosted)		Nelfinavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Calcium Channel Blockers (CCB)						
Amlodipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Bepridil	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of bepridil	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Diltiazem	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Felodipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of felodipine	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Isradipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Nicardipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of nicardipine	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Nifedipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of nifedipine	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Nimodipine	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Nisoldipine	Potential interaction	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Verapamil	May increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of CCB	Caution - close monitoring	May increase concentration of CCB	Close monitoring or alteration of dose
Lipid Regulating Drugs						
Atorvastatin	Increases concentration of atorvastatin	Caution – possible risk of myopathy; use lowest possible dose of atorvastatin	Increases concentration of atorvastatin	Caution – possible risk of myopathy; use lowest possible dose of atorvastatin	Increases concentration of atorvastatin	Caution – possible risk of myopathy; use lowest possible dose of atorvastatin
Cerivastatin	—	—	—	—	—	—
Clofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fenofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fluvastatin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Gemfibrozil	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lovastatin	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy
Pravastatin	No clinically significant interaction	No dose adjustment required	Increases concentration of pravastatin	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rosuvastatin	Increases concentration of rosuvastatin	Caution - possible risk of myopathy; use lowest possible dose of rosuvastatin	Increases concentration of rosuvastatin	Caution - possible risk of myopathy; use lowest possible dose of rosuvastatin	Increases concentration of rosuvastatin	Caution - possible risk of myopathy; use lowest possible dose of rosuvastatin
Simvastatin	Potential for increased concentration of simvastatin	Not advised – increases risk of myopathy	Potential for increased concentration of simvastatin	Not advised – increases risk of myopathy	Increases concentration of simvastatin	Not advised – increases risk of myopathy
Corticosteroids						
Budesonide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Dexamethasone	Decreases concentration of indinavir	Close monitoring or alteration of dose	May decrease concentration of lopinavir	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluticasone	Increases concentration of fluticasone	Unboosted - consider an alternative for long term use; Boosted - not recommended	Ritonavir component increases concentration of fluticasone	Not recommended unless benefit outweighs risk of corticosteroid-related adverse effects	Increases concentration of fluticasone	Caution - consider an alternative for long term use
Prednisolone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Calcium Channel Blockers (CCB)						
Amlodipine	May increase concentration of amlodipine	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bepridil	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Boosted: increases concentration of CCB	Contraindicated - due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Diltiazem	May increase concentration of diltiazem	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	No studies but potential for interactions	Close monitoring or alteration of dose
Felodipine	—	—	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	May increase concentration of felodipine	Close monitoring or alteration of dose
Isradipine	May increase concentration of CCB	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nicardipine	May increase concentration of CCB	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	No studies but potential for interactions	Close monitoring or alteration of dose
Nifedipine	May increase concentration of nifedipine	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nimodipine	May increase concentration of CCB	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nisoldipine	Potential interaction	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	No studies but potential for interactions	Close monitoring or alteration of dose
Verapamil	May increase concentration of verapamil	Close monitoring or alteration of dose	Boosted: potential to increase concentration of CCB	Close monitoring or alteration of dose	No studies but potential for interactions	Close monitoring or alteration of dose
Lipid Regulating Drugs						
Atorvastatin	Increases concentration of atorvastatin	Caution – possible risk of myopathy; use lowest possible dose of atorvastatin	Boosted: increased concentration of atorvastatin	Start with lowest dose of atorvastatin and monitor ***or*** consider alternative statin	Boosted: increases concentration of atorvastatin; decreases concentration of atorvastatin metabolite	Start with lowest dose of atorvastatin and monitor ***or*** consider alternative statin
Cerivastatin	—	—	—	—	—	—
Clofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fenofibrate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fluvastatin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Gemfibrozil	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lovastatin	Potential for increased concentration of lovastatin	Not advised – increases risk of myopathy	Boosted: increases concentration of lovastatin	Not advised – increases risk of myopathy	Boosted: increased concentration of lovastatin	Not advised – increases risk of myopathy
Pravastatin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rosuvastatin	Increases concentration of rosuvastatin	Caution - possible risk of myopathy; use lowest possible dose of rosuvastatin	Boosted: increased concentration of rosuvastatin	Start with lowest dose of rosuvastatin and monitor *or* consider alternative statin	Boosted: increases concentration of rosuvastatin	Start with lowest dose of rosuvastatin and monitor *or* consider alternative statin
Simvastatin	Increases concentration of simvastatin	Not advised – increases risk of myopathy	Boosted: increases concentration of simvastatin	Not advised – increases risk of myopathy	Boosted: increased concentration of simvastatin	Not advised – increases risk of myopathy
Corticosteroids						
Budesonide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Dexamethasone	May increase concentration of dexamethasone	Close monitoring or alteration of dose	Unboosted: decreases concentration of saquinavir; Boosted: not evaluated	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluticasone	Increases concentration of fluticasone	Contraindicated unless benefit outweighs risk of corticosteroid-related adverse effects	Boosted: increases concentration of fluticasone	Contraindicated unless benefit outweighs risk of corticosteroid-related adverse effects	Boosted: increases concentration of fluticasone	Contraindicated unless benefit outweighs risk of corticosteroid-related adverse effects
Prednisolone	May increase concentration of prednisolone	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Gastro-intestinal Drugs						
Antacids	Decreases concentration of amprenavir	Doses of the antacid and amprenavir should be separated by at least 1 hour	Decreases concentration of atazanavir	Doses of the antacid and atazanavir should be separated by at least 1 to 2 hours	No clinically significant interaction	No dose adjustment required
GI Motility Agents						
Cisapride	Increased risk of cardiac arrhythmias	Contraindicated – due to potential for serious or life-threatening reactions	Increased risk of cardiac arrhythmias	Contraindicated – due to potential for serious or life-threatening reactions	Increased risk of cardiac arrhythmias	Contraindicated - due to potential for serious or life-threatening reactions
Domperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Loperamide	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metoclopramide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
H_2 Antagonists						
Cimetidine	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of atazanavir – class effect	Administer 2 hours before or 10 hours after an H_2 antagonist	No clinically significant interaction	No dose adjustment required
Famotidine	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of atazanavir – class effect	Administer 2 hours before or 10 hours after an H_2 antagonist	No clinically significant interaction	No dose adjustment required
Nizatidine	—	—	Decreases concentration of atazanavir – class effect	Administer 2 hours before or 10 hours after an H_2 antagonist	No clinically significant interaction	No dose adjustment required
Ranitidine	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of atazanavir – class effect	Administer 2 hours before or 10 hours after an H_2 antagonist	No clinically significant interaction	No dose adjustment required
Proton Pump Inhibitors						
Lansoprazole	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of atazanavir – class effect	Contraindicated in treatment-experienced patients; in treatment-naïve patients give 12 hours before atazanavir	No clinically significant interaction	No dose adjustment required
Omeprazole	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of atazanavir – class effect	Contraindicated in treatment-experienced patients; in treatment-naïve patients give 12 hours before atazanavir	No clinically significant interaction	No dose adjustment required
General Anaesthetics						
Enflurane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halothane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ketamine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Immunosuppressants						
Ciclosporin	Increases concentration of ciclosporin	Close monitoring or alteration of dose	May increase concentration of ciclosporin	Close monitoring or alteration of dose	Increases concentration of ciclosporin	Close monitoring or alteration of dose
Sirolimus	Increases concentration of sirolimus	Close monitoring or alteration of dose	May increase concentration of sirolimus	Close monitoring or alteration of dose	Increases concentration of sirolimus	Close monitoring or alteration of dose
Tacrolimus	Increases concentration of tacrolimus	Close monitoring or alteration of dose	May increase concentration of tacrolimus	Close monitoring or alteration of dose	Increases concentration of tacrolimus	Close monitoring or alteration of dose
Oral Contraceptives						
Ethinylestradiol	Increases concentration of ethinylestradiol; decreases concentration of amprenavir	Unboosted and boosted: alternative or additional contraception is recommended	Increases concentration of ethinylestradiol	Alternative or additional contraception recommended	Decreases concentration of ethinylestradiol	Alternative or additional contraception is recommended; HRT - monitor for oestrogen deficiency
Norethindrone	Increases concentration of norethindrone; decreases concentration of amprenavir	Unboosted and boosted: alternative or additional contraception is recommended	Increases concentration of norethindrone	Alternative or additional contraception recommended	Decreases concentration of norethindrone	Alternative or additional contraception is recommended; HRT - monitor for oestrogen deficiency
Progestogens	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sex Hormones						
Megestrol Acetate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nandrolone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stanozolol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Testosterone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		**Lopinavir (ritonavir-boosted)**		**Nelfinavir**	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Gastro-intestinal Drugs						
Antacids	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	—	—
GI Motility Agents						
Cisapride	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions
Domperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Loperamide	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Metoclopramide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
H_2 Antagonists						
Cimetidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Famotidine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nizatidine	—	—	—	—	—	—
Ranitidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Proton Pump Inhibitors						
Lansoprazole	Potential to decrease concentration of indinavir	Close monitoring or alteration of dose; use with boosted indinavir	No clinically significant interaction	No dose adjustment required	Potential to decrease concentration of nelfinavir (class effect)	Not recommended
Omeprazole	Decreases concentration of indinavir	Close monitoring or alteration of dose; use with boosted indinavir	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of nelfinavir	Contraindicated - loss of antiretroviral activity
General Anaesthetics						
Enflurane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halothane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ketamine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Immunosuppressants						
Ciclosporin	May increase concentration of ciclosporin	Close monitoring or alteration of dose	May increase concentration of ciclosporin	Close monitoring or alteration of dose	May increase concentration of ciclosporin	Close monitoring or alteration of dose
Sirolimus	May increase concentration of sirolimus	Close monitoring or alteration of dose	May increase concentration of sirolimus	Close monitoring or alteration of dose	May increase concentration of sirolimus	Close monitoring or alteration of dose
Tacrolimus	May increase concentration of tacrolimus	Close monitoring or alteration of dose	May increase concentration of tacrolimus	Close monitoring or alteration of dose	May increase concentration of tacrolimus	Close monitoring or alteration of dose
Oral Contraceptives						
Ethinylestradiol	Increases concentration of ethinylestradiol	Close monitoring or alteration of dose	Decreases concentration of ethinylestradiol	Alternative or additional contraception is recommended	Decreases concentration of ethinylestradiol	Alternative or additional contraception is recommended
Norethindrone	Increases concentration of norethindrone	Close monitoring or alteration of dose	—	—	Decreases concentration of norethindrone	Alternative or additional contraception is recommended
Progestogens	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sex Hormones						
Megestrol Acetate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nandrolone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stanozolol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Testosterone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Gastro-intestinal Drugs						
Antacids	—	—	No clinically significant interaction	No dose adjustment required	Boosted: decreases concentration of tipranavir	Doses of the antacid and tipranavir should be separated by at least 2 hours
GI Motility Agents						
Cisapride	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction with boosted tipranavir	Contraindicated – due to potential for serious or life-threatening reactions
Domperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Loperamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Boosted: decreases concentration of loperamide	Clinical relevance is not known
Metoclopramide	No clinically significant interaction	No dose adjustment required	—	—	No clinically significant interaction	No dose adjustment required
H_2 Antagonists						
Cimetidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No data but potential for interaction due to increased gastric pH	Close monitoring or alteration of dose
Famotidine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No data but potential for interaction due to increased gastric pH	Close monitoring or alteration of dose
Nizatidine	—	—	—	—	No data but potential for interaction due to increased gastric pH	Close monitoring or alteration of dose
Ranitidine	No clinically significant interaction	No dose adjustment required	Unboosted: increases concentration of saquinavir; boosted: not evaluated	Close monitoring - appropriate alteration of dose not established	No data but potential for interaction due to increased gastric pH	Close monitoring or alteration of dose
Proton Pump Inhibitors						
Lansoprazole	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No data but potential for interaction due to increased gastric pH	Close monitoring or alteration of dose
Omeprazole	No clinically significant interaction	No dose adjustment required	Boosted: increases concentration of saquinavir	Close monitoring or alteration of dose	No data but potential for interaction due to increased gastric pH; may decrease concentration of omeprazole	Close monitoring or alteration of dose
General Anaesthetics						
Enflurane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halothane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ketamine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Immunosuppressants						
Ciclosporin	May increase concentration of ciclosporin	Close monitoring or alteration of dose	Boosted: potential to increase concentration of ciclosporin	Close monitoring or alteration of dose	No studies but potential for interactions with boosted tipranavir	Frequent monitoring of immunosuppressant concentration
Sirolimus	May increase concentration of sirolimus	Close monitoring or alteration of dose	Boosted: potential to increase concentration of sirolimus	Close monitoring or alteration of dose	No studies but potential for interactions with boosted tipranavir	Frequent monitoring of immunosuppressant concentration
Tacrolimus	May increase concentration of tacrolimus	Close monitoring or alteration of dose	Boosted: potential to increase concentration of tacrolimus	Close monitoring or alteration of dose	No studies but potential for interactions with boosted tipranavir	Frequent monitoring of immunosuppressant concentration
Oral Contraceptives						
Ethinylestradiol	Decreases concentration of ethinylestradiol	Close monitoring; alternative or additional contraception recommended	Boosted: decreased concentration of ethinylestradiol	Close monitoring; alternative or additional contraception recommended	Boosted: decreases concentration of ethinylestradiol	Alternative or additional contraception is recommended; HRT – monitor for oestrogen deficiency
Norethindrone	—	—	—	—	No significant clinical effect	Alternative or additional contraception is recommended; HRT - monitor for oestrogen deficiency
Progestogens	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sex Hormones						
Megestrol Acetate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nandrolone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stanozolol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Testosterone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Amprenavir		Atazanavir		Darunavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Urological Drugs						
Alfusozin	—	—	—	—	—	—
Apomorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sildenafil	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours
Tadalafil	Potential interaction	Caution – dose of tadalafil should not exceed 10mg every 72 hours	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours
Vardenafil	Potential interaction	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours	Increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours	Increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours
Miscellaneous						
Amphetamines	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Disulfiram	Potential risk of toxicity due to propylene glycol	Contraindicated – due to potential for serious or life-threatening reactions	Unspecified clinically significant interaction	Contraindicated – due to potential for serious or life-threatening reactions	—	—
Herbals etc.						
Echinacea	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Garlic (capsules)	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Grapefruit Juice	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Milk Thistle (Silymarin)	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vitamin E	Unspecified clinically significant interaction	Supplementary vitamin E contraindicated	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Indinavir		Lopinavir (ritonavir-boosted)		Nelfinavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Urological Drugs						
Alfusozin	—	—	—	—	—	—
Apomorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sildenafil	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours
Tadalafil	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours
Vardenafil	Increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 24 hours	Increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours	Increase concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours
Miscellaneous						
Amphetamines	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Disulfiram	—	—	Lopinavir/ritonavir formulations contain alcohol	May cause disulfiram reaction	—	—
Herbals etc.						
Echinacea	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Garlic (capsules)	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Grapefruit Juice	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Milk Thistle (Silymarin)	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vitamin E	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 1. Interactions: drugs used in the treatment of HIV. The HIV-Protease Inhibitors.

	Ritonavir		Saquinavir		Tipranavir	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Urological Drugs						
Alfuzosin	May increase concentration of alfuzosin	Contraindicated – due to potential for serious or life-threatening reactions	—	—	—	—
Apomorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sildenafil	Increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours	Unboosted: increases concentration of sildenafil	Caution – dose of sildenafil should not exceed 25mg every 48 hours with boosted regimens	No studies but potential to increase concentration of sildenafil with boosted tipranavir	Caution – dose of sildenafil should not exceed 25mg every 48 hours
Tadalafil	Increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours	Boosted: increases concentration of tadalafil	Caution – dose of tadalafil should not exceed 10mg every 72 hours with boosted regimens	Potential to increase concentration of tadalafil with boosted tipranavir	Caution – dose of tadalafil should not exceed 10mg every 72 hours
Vardenafil	Increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours	Boosted: increases concentration of vardenafil	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours with boosted regimens	No studies but potential to increase concentration of vardenafil with boosted tipranavir	Caution – dose of vardenafil should not exceed 2.5mg every 72 hours
Miscellaneous						
Amphetamines	May increase concentration of amphetamines	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Disulfiram	Ritonavir formulations contain alcohol	May cause disulfiram reaction	—	—	Tipranavir capsules contain alcohol	May cause disulfiram reaction
Herbals etc.						
Echinacea	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Garlic (capsules)	Potential interaction	Close monitoring or alteration of dose	Unboosted: decreased concentration of saquinavir; Boosted: interaction not evaluated	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Grapefruit Juice	No clinically significant interaction	No dose adjustment required	Unboosted: no clinically significant interaction; Boosted: not evaluated	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Milk Thistle (Silymarin)	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vitamin E	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs.

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Antivirals: Antiretrovirals								
Protease Inhibitors								
Amprenavir	Decreases concentration of delavirdine and increases concentration of amprenavir	Appropriate doses not established; Co-administration not recommended	May decrease concentration of amprenavir	No established dose adjustment; no dose adjustment needed if used in boosted regimens	Boosted and unboosted amprenavir increases concentration of amprenavir	Contraindicated	May decrease concentration of amprenavir	No established dose adjustment; dose of amprenavir may need to be increased
Atazanavir	Potential interaction	No established dose adjustment	Decreases concentration of atazanavir	In treatment naïve patients - give with atazanavir 300mg and ritonavir 100mg; treatment experienced patients - no established dose adjustments	Unboosted atazanavir decreases concentration of atazanavir; boosted atazanavir decreases concentration of atazanavir and increases concentration of etravirine	Contraindicated	Decreases concentration of atazanavir	No established dose adjustment; co-administration not recommended
Darunavir	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of darunavir and increases concentration of efavirenz	Close monitoring - combination may be associated with CNS toxicity	Boosted darunavir decreases concentration of etravirine	No dose adjustment required	Boosted darunavir increases concentration of nevirapine	Not a clinically significant interaction; co-administration without dose adjustments
Indinavir	Increases concentration of indinavir	Dose reduction of indinavir to 400 to 600mg every 8 hours may be appropriate	Decreases concentration of indinavir	Close monitoring, may need to increase dose of indinavir although appropriate alteration of dose not established	Decreases concentration of indinavir	Contraindicated	Decreases concentration of indinavir	Increased dose of indinavir to 1g every 8 hours may be required
Indinavir/Ritonavir	—	—	No clinically significant interaction	No dose adjustment required	—	—	—	—
Lopinavir/Ritonavir	Increases concentration of both ritonavir & lopinavir	No established dose adjustment	Decreases concentration of lopinavir	Do not give as a once daily dose; in treatment experienced patients increase dose of ritonavir-boosted lopinavir by about 33%	Increases concentration of etravirine	Use with caution	Decreases concentration of lopinavir	Close monitoring - consider increasing dose of ritonavir-boosted lopinavir by about 33% (do not give as a once daily dose)
Nelfinavir	Decreases concentration of delavirdine and increases concentration of nelfinavir	No established dose adjustment	No clinically significant interaction	No dose adjustment required	Increases concentration of nelfinavir	Contraindicated	Decreases concentration of nelfinavir	No established dose adjustment
Ritonavir	Increases concentration of ritonavir	No established dose adjustment	Increases concentration of both ritonavir and efavirenz	Increased adverse effects; monitor liver enzymes	Decreases concentration of etravirine	Contraindicated	No clinically significant interaction	No dose adjustment required
Saquinavir	Unboosted: increases concentration of saquinavir; Boosted: not evaluated	May need to decrease dose of saquinavir	Decreases concentration of saquinavir	Should not be used as the sole protease inhibitor	Boosted saquinavir decreases concentration of etravirine	No dose adjustment required	Unboosted saquinavir decreases concentration of saquinavir; boosted - no clinically significant interaction	May need to increase dose of saquinavir (hard capsule formulation)
Tipranavir	Potential interaction	Close monitoring or alteration of dose	Boosted: limited data indicates no significant interactions	Use with caution until more data available	Boosted tipranavir decreases concentration of etravirine	Contraindicated	Boosted: limited data indicates no significant interactions	Use with caution until more data available
NNRTIs								
Delavirdine	N/A	N/A	Potential interaction	Close monitoring or alteration of dose	Increases concentration of etravirine	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Efavirenz	Potential interaction	Close monitoring or alteration of dose	N/A	N/A	Decreases concentration of etravirine	Contraindicated	Decreases concentration of efavirenz	Contraindicated
Etravirine	Increases concentration of etravirine	Contraindicated	Decreases concentration of etravirine	Contraindicated	N/A	N/A	Decreases concentration of etravirine	Contraindicated
Nevirapine	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of efavirenz	Co-administration not recommended	Decreases concentration of etravirine	Contraindicated	N/A	N/A

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
NsRTIs/NtRTIs								
Abacavir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Didanosine	For buffered tablets – concentration of delavirdine and didanosine decreased	Administration of the two tablets should be separated by at least 1 hour	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Emtricitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamivudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stavudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Tenofovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Zalcitabine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	—	—	No clinically significant interaction	No dose adjustment required
Zidovudine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Decreases concentration of zidovudine	No dose adjustment required
Other Antiretrovirals								
Enfuvirtide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Maraviroc	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Raltegravir	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Antivirals								
Aciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Adefovir	Potential Interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Cidofovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Famciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Foscarnet	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ganciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ribavirin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Valaciclovir	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Other Drugs								
Analgesics, Anti-inflammatory Drugs and Antipyretics								
Buprenorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fentanyl	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of fentanyl	Close monitoring or alteration of dose
Methadone	Increases concentrations of methadone	May need to decrease dose of methadone	Decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal	Potential interaction	May need to adjust dose of methadone; monitor for symptoms of withdrawal	Decreases concentration of methadone	May need to increase dose of methadone; monitor for symptoms of withdrawal
Antibacterials								
Antimycobacterials								
Ethambutol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Isoniazid	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Pyrazinamide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rifabutin	Decreases concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	Decreases concentration of rifabutin	Increase daily dose of rifabutin by 50%	Decreases concentration of etravirine and rifabutin	Contraindicated when given with boosted darunavir or saquinavir; if not given with a boosted protease inhibitor give usual daily dose of rifabutin	Increases concentration of rifabutin	Caution and close monitoring
Rifampicin	Decreases concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	Decreases concentration of efavirenz	Increase dose of efavirenz to 800mg daily	Decreases concentration of etravirine	Contraindicated	Decreases concentration of nevirapine	Contraindicated - use rifabutin as an alternative
Rifapentine	Potential interaction	Co-administration not recommended; higher rate of tuberculosis relapse	Potential interaction	Co-administration not recommended; higher rate of tuberculosis relapse	Decreases concentration of etravirine	Contraindicated	Potential interaction	Co-administration not recommended; higher rate of tuberculosis relapse
Streptomycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Macrolides								
Azithromycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Clarithromycin	Increases concentration of clarithromycin	Reduce clarithromycin dose in patients with renal failure	Decreases concentration of clarithromycin	Alternatives to clarithromycin should be considered	Increases concentration of etravirine and decreases concentration of clarithromycin	Alternatives to clarithromycin should be considered	Significantly decreases concentration of clarithromycin	Alternatives should be considered
Erythromycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Quinolones								
Ciprofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ofloxacin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Others								
Clindamycin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Co-trimoxazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Dapsone	Potential interaction	May need to increase dose of dapsone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Metronidazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Tetracyclines	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antidepressants								
Tricyclics								
Doxepin	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
SSRIs								
Citalopram	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluoxetine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Paroxetine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Sertraline	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of sertraline	Sertraline dose may need to be increased	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Other Antidepressants								
Bupropion	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Mirtazapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nefazodone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Trazodone	Increases concentration of trazodone	Caution; may need to decrease dose of trazodone	—	—	—	—	—	—
St Johns Wort	Potential to decrease concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	May decreases concentration of efavirenz	Contraindicated	Decreases concentration of etravirine	Contraindicated	May decrease concentration of nevirapine	Contraindicated
Antidiabetics (Oral)								
Glipizide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Metformin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Rosiglitazone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Tolbutamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antiepileptics								
Carbamazepine	Decreases concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	May decrease concentration of carbamazepine and/or efavirenz	Caution and monitor antiepileptic concentration	Decreases concentration of etravirine	Contraindicated	May decrease concentration of carbamazepine	Close monitoring or alteration of dose
Clonazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of clonazepam	Close monitoring or alteration of dose
Ethosuximide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of ethosuximide	Close monitoring or alteration of dose
Gabapentin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Lamotrigine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Phenobarbital	Decreases concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	Potential to decrease or increase concentrations of phenobarbital and/or efavirenz	Caution and monitor antiepileptic concentration	Decreases concentration of etravirine	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Phenytoin	Decreases concentration of delavirdine	Co-administration not recommended; possible loss of virologic response	Potential to decrease or increase concentration of phenytoin and/or efavirenz	Caution and monitor antiepileptic concentration	Decreases concentration of etravirine	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Valproate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Vigabatrin	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antifungals								
Amphotericin B	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Caspofungin	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Fluconazole	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	Increases concentration of etravirine	Close monitoring	Increases concentration of nevirapine	Caution and close monitoring – consider alternatives
Itraconazole	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of itraconazole	Clinical implication unknown; consider an alternative antifungal	Increases concentration of etravirine and decreases concentration of itraconazole	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Ketoconazole	Increases concentration of delavirdine	Close monitoring or alteration of dose	May decrease concentration of ketoconazole	Clinical implication unknown	Increases concentration of etravirine and decreases concentration of ketoconazole	Close monitoring or alteration of dose	Decreases concentration of ketoconazole and increases concentration of nevirapine	Contraindicated - consider alternatives
Posaconazole	—	—	Decreases concentration of posaconazole	Not recommended - consider an alternative antifungal	Increases concentration of etravirine	Close monitoring	—	—
Terbinafine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Voriconazole	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of voriconazole and increases concentration of efavirenz	Contraindicated	Increases concentration of etravirine and voriconazole	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antihistamines								
Astemizole	Increased risk of cardiac arrhythmias	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Unspecified clinical interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Cetirizine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Fexofenadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Loratadine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Terfenadine	Increased risk of cardiac arrhythmias	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Unspecified clinical interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose
Antimalarials/Antiprotozoals								
Amodiaquine	—	—	Unspecified clinically significant interaction	Contraindicated	—	—	—	—
Artemisinins	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Halofantrine	Contraindicated	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Lumefantrine	Contraindicated	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Quinine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Antimigraine Drugs								
Ergot derivatives	Increased risk of ergot toxicity	Contraindicated with ergot derivatives	Increased risk of ergot toxicity	Contraindicated with ergot derivatives	Unspecified clinical interaction	Contraindicated	May decrease concentration of ergotamine	Dose adjustments may be needed
Sumatriptan	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Antineoplastics								
Cyclophosphamide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of cyclophosphamide	Close monitoring or alteration of dose
Paclitaxel	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vinca alkaloids	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Anxiolytic Sedatives Hypnotics and Antipsychotics								
Antipsychotics								
Chlorpromazine	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Clozapine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Haloperidol	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Olanzapine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Perphenazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Pimozide	Increased risk of cardiac arrhythmias	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Resperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Thioridazine	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Benzodiazepines								
Alprazolam	Unspecified clinically significant interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diazepam	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Increases concentration of diazepam	May need to increase dose of diazepam	Potential interaction	Close monitoring or alteration of dose

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Lorazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Midazolam	Unspecified clinically significant interaction	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Oxazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Temazepam	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Triazolam	Unspecified clinically significant interaction	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Hypnotics								
Zolpidem	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Cardiovascular Drugs								
Anticoagulants								
Warfarin	Potential to alter coagulation times; increases warfarin concentration	Monitor anticoagulation levels (INR)	Potential to alter coagulation times; can both increase or decrease warfarin concentration	Monitor anticoagulation levels (INR)	Potential to alter coagulation times; increases warfarin concentration	Monitor anticoagulation levels (INR)	Potential to alter coagulation times; can both increase or decrease warfarin concentration	Monitor anticoagulation levels (INR)
Antiarrhythmics								
Amiodarone	Increases concentration of amiodarone	Use with caution	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of amiodarone	Close monitoring or alteration of dose	May decrease concentration of amiodarone	Dose adjustments may be needed
Disopyramide	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of disopyramide	Close monitoring or alteration of dose	May decrease concentration of disopyramide	Dose adjustments may be needed
Flecainide	Potential interaction	Use with caution	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of flecainide	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Lidocaine (systemic)	Increases concentration of lidocaine	Use with caution	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of lidocaine	Close monitoring or alteration of dose	May increase concentration of lidocaine	Dose adjustments may be needed
Mexiletine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of mexiletine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Propafenone	Potential interaction	Use with caution	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of propafenone	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Quinidine	Potential interaction	Use with caution	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of quinidine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Beta Blockers								
Carvedilol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Calcium Channel Blockers (CCB)								
Amlodipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Bepridil	Increases concentration of CCBs	Use with caution	Unspecified clinically significant interaction	Contraindicated	May decrease concentration of bepridil	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Diltiazem	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Decreases concentration of diltiazem	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of diltiazem	Close monitoring or alteration of dose
Felodipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Potential to decrease concentration of felodipine	Close monitoring or alteration of dose	—	—	—	—
Isradipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	—	—	—	—	—	—
Nicardipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Potential to decrease concentration of nicardipine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Nifedipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Potential to decrease concentration of nifedipine	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of nifedipine	Close monitoring or alteration of dose

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Nimodipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	—	—	—	—	—	—
Nisoldipine	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	—	—	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Verapamil	Increases concentration of dihydropyridine CCBs	Caution – for all dihydropyridine CCBs	Potential to decrease concentration of verapamil	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of verapamil	Close monitoring or alteration of dose
Lipid Regulating Drugs								
Atorvastatin	Increases concentration of atorvastatin	Use lowest possible dose of statin	Decreases concentration of atorvastatin	Adjust atorvastatin dose but do not exceed maximum	Decreases concentration of atorvastatin	Dose adjustment of atorvastatin may be needed	Potential interaction	Close monitoring or alteration of dose
Cerivastatin	Increases concentration of cerivastatin	Use lowest possible dose of statin	—	—	—	—	—	—
Fluvastatin	Increases concentration of fluvastatin	Use lowest possible dose of statin	Potential interaction	Close monitoring or alteration of dose	Increases concentration of fluvastatin	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose
Lovastatin	Unspecified clinically significant interaction	Not advised – increases risk of myopathy	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of lovastatin	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose
Pravastatin	No clinically significant interaction	No dose adjustment required	Decreases concentration of pravastatin	Close monitoring or alteration of pravastatin dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Simvastatin	Unspecified clinically significant interaction	Not advised – increases risk of myopathy	Decreases concentration of simvastatin	Adjust simvastatin dose but do not exceed maximum	Decreases concentration of simvastatin	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose
Corticosteroids								
Budesonide	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Dexamethasone	Decreases concentration of delavirdine	Use with caution	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of etravirine	For long term use consider alternatives	Potential interaction	Close monitoring or alteration of dose
Fluticasone	Increases concentration of fluticasone	Use with caution or consider an alternative	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Prednisolone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Gastro-intestinal Drugs								
Antacids	Decreases concentration of delavirdine	Doses of the antacid and delavirdine should be separated by at least 1 hour	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
GI Motility Agents								
Cisapride	Increased risk of cardiac arrhythmias	Contraindicated	Unspecified clinically significant interaction	Contraindicated	Potential interaction	Close monitoring or alteration of dose	May decrease concentration of cisapride	Close monitoring or alteration of dose
Domperidone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Loperamide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Metoclopramide	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
H_2 Antagonists								
Cimetidine	Absorption of delavirdine may be reduced	Chronic use is not recommended	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required
Famotidine	Absorption of delavirdine may be reduced	Chronic use is not recommended	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nizatidine	Absorption of delavirdine may be reduced	Chronic use is not recommended	—	—	—	—	—	—
Ranitidine	Absorption of delavirdine may be reduced	Chronic use is not recommended	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required

Table 2. Interactions: drugs used in the treatment of HIV. NNRTIs. *(Continued)*

	Delavirdine		Efavirenz		Etravirine		Nevirapine	
	Effect	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*	*Effect*	*Clinical Comment*
Proton Pump Inhibitors								
Lansoprazole	Absorption of delavirdine may be reduced	Chronic use is not recommended	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Omeprazole	Absorption of delavirdine may be reduced	Chronic use is not recommended	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
General Anaesthetics								
Enflurane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Halothane	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Ketamine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Immunosuppressants								
Ciclosporin	Increases concentration of ciclosporin	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of ciclosporin	Close monitoring or alteration of dose	May decrease concentration of ciclosporin	Dose adjustments may be needed
Sirolimus	Increases concentration of sirolimus	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of sirolimus	Close monitoring or alteration of dose	May decrease concentration of sirolimus	Dose adjustments may be needed
Tacrolimus	Increases concentration of tacrolimus	Dose adjustments may be needed	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of tacrolimus	Close monitoring or alteration of dose	May decrease concentration of tacrolimus	Dose adjustments may be needed
Oral Contraceptives								
Ethinylestradiol	Increases concentration of ethinylestradiol	Clinical significance unknown; alternative or additional contraception is recommended	Increases concentration of ethinylestradiol	Alternative or additional contraception is recommended	No clinically significant interaction	No dose adjustment required	Decreases concentration of ethinylestradiol	Alternative or additional contraception recommended
Norethindrone	—	—	—	—	No clinically significant interaction	No dose adjustment required	Decreases concentration of norethindrone	Alternative or additional contraception recommended
Progestogens	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	No clinically significant interaction	No dose adjustment required	Potential interaction	Close monitoring or alteration of dose
Sex Hormones								
Megestrol Acetate	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Nandrolone	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Stanozolol	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Testosterone	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Urological Drugs								
Apomorphine	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Sildenafil	Increases concentration of sildenafil	Caution – increased risk of side effects. Do not exceed single dose sildenafil 25mg in 48 hours	Potential interaction	Close monitoring or alteration of dose	Decreases concentration of sildenafil	Close monitoring; may need to adjust dose of sildenafil	Potential interaction	Close monitoring or alteration of dose
Tadalafil	Potential interaction	Do not exceed 10mg every 72 hours	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Vardenafil	Potential interaction	Do not exceed 2.5mg ever 24 hours	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Miscellaneous								
Amphetamines	Increases concentration of amphetamine	Use with caution	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required	No clinically significant interaction	No dose adjustment required
Herbals etc.								
Echinacea	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Garlic	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose
Milk Thistle (Silymarin)	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose	Potential interaction	Close monitoring or alteration of dose

Anxiolytic Sedatives Hypnotics and Antipsychotics

Anxiety disorders, p.952
Obsessive-compulsive disorder, p.952
Panic disorder, p.952
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Post-traumatic stress disorder, p.953
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The drugs in this chapter include:

- anxiolytic sedatives, formerly called minor tranquillisers, which have been used in the management of anxiety disorders
- drugs used to produce sleep (hypnotics)
- drugs used in the treatment of psychoses (antipsychotics, formerly called major tranquillisers). The term neuroleptic is sometimes used to describe those antipsychotics that have effects on the extrapyramidal system

The difference in action between anxiolytics and hypnotics is mainly one of degree and the same drug or group of drugs can have both effects, larger doses being necessary to produce a state of sleep.

The benzodiazepines (typified by Diazepam, p.986) replaced the barbiturates (typified by Amobarbital, p.961) and related sedatives as the major group of drugs used as anxiolytics and hypnotics. Some benzodiazepines are also used for their muscle relaxant and anticonvulsant properties. Newer anxiolytics include buspirone (p.965), a drug that affects serotonin neurotransmission.

The classical antipsychotics (typified by Chlorpromazine, p.969) include the butyrophenones, the diphenylbutylpiperidines, the indole derivatives, the phenothiazines, and the thioxanthenes. Some newer antipsychotics such as clozapine (p.981), risperidone (p.1024), olanzapine (p.1012), quetiapine (p.1022), and amisulpride (p.961) are often referred to as atypical antipsychotics because of their reduced tendency to cause the extrapyramidal effects typical of classical antipsychotics.

◊ General references.

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Anxiety disorders

Anxiety is an emotional condition characterised by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating, and tremor. It can be a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are difficult to define and various classifications exist:

- in **acute stress disorder** anxiety is associated with a recent extremely stressful event such as bereavement, and is likely to resolve within a few weeks
- in **generalised anxiety disorder** there is persistent pervasive anxiety and worry, usually lasting 6 months or more, resulting in distress or marked difficulty in performing daily tasks. Symptoms include fatigue and disturbed sleep, motor tension, autonomic hyperactivity, irritability, and loss of concentration

The first step in the **management** of anxiety that cannot be attributed to an underlying disease is the use of psychological treatments such as cognitive therapy. Such therapy can be effective in most types of anxiety. If unsuccessful, short-term treatment with a benzodiazepine may be considered.[1] Benzodiazepines exert an effect very rapidly, possibly even after the first dose, and this makes them suitable for treating an acute reaction.[2] However, their use in chronic conditions such as generalised anxiety disorder is limited by serious problems of dependence (see under Diazepam, p.987). Tolerance may develop to the anxiolytic effects of benzodiazepines although this appears to be less likely than tolerance to the psychomotor effects. No one benzodiazepine appears more effective than the others in the treatment of anxiety disorders.[3] However, adverse effects and pharmacokinetic parameters may influence choice.

Buspirone, an azaspirodecanedione, appears to have broadly similar efficacy to the benzodiazepines but a slower onset of action; it may cause less sedation and dependence. It is reported to lack euphoriant effect. Its efficacy is reduced in patients who have had previous extensive use of benzodiazepines.[4,5]

Increasingly, antidepressants are considered preferable to benzodiazepines for the treatment of generalised anxiety disorder;[1,2,4,6-10] they are particularly appropriate when medium or long-term therapy is necessary or when depression is also present. They may take several weeks to have an effect, so combined therapy with benzodiazepines may be required initially. Tricyclic antidepressants such as imipramine have a proven benefit in the treatment of generalised anxiety disorder.[2-4,6-8] More recently, SSRIs have been used as alternatives;[3,11,12] paroxetine has been the most extensively studied.[8] The noradrenaline and serotonin reuptake inhibitor venlafaxine may also be used.[1,8] These relatively newer drugs are safer in overdose and are associated with less severe adverse effects than the tricyclics and in the UK NICE[1] and others[9] consider SSRIs to be the antidepressants of choice in generalised anxiety disorder.

Beta blockers may be useful for the control of the physical symptoms of anxiety.[12] There is little evidence to support the efficacy of antihistamines such as hydroxyzine in anxious patients,[2] and the use of antihistamines solely for their sedative effect in anxiety is not considered appropriate. Antipsychotics have been used by some in severe anxiety for their sedative effects; long-term use should be avoided because of the risk of tardive dyskinesia. In a few studies, antiepileptics such as pregabalin and tiagabine have been found to be effective for the treatment of generalised anxiety disorder.[13]

Anxiety may be present with other disorders such as depression in **mixed anxiety and depressive disorders**, the management of which is discussed under Depression on p.373.

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Obsessive-compulsive disorder. Obsessive-compulsive disorder is associated with intrusive, recurrent, obsessional thoughts and/or repetitive compulsive behaviour (e.g. hand washing) performed in a ritualistic manner. A combination of pharmacological, behavioural, and psychosocial methods appears to have the most successful long-term outcome in its treatment. **Drug therapy** is based on antidepressants that inhibit reuptake of serotonin.[1-9] These include clomipramine, the SSRIs, and the serotonin and noradrenaline reuptake inhibitor venlafaxine. There is some evidence that clomipramine is more effective than the SSRIs but its adverse effects are more problematic.[3,5,10] In the UK NICE considers SSRIs to be the antidepressants of choice in obsessive-compulsive disorder.[8] It may take 4 to 6 weeks before any response is obtained and up to about 12 weeks to achieve an optimal effect.[2,11] If one serotonin reuptake inhibitor fails then another can be tried;[2-5,8] for example, it has been suggested that patients who fail to respond to trials with two SSRIs might then try switching to a drug from a different class (e.g. clomipramine or venlafaxine).[6] Treatment should be continued for at least 12 months in those who respond.[8] However, about 40 to 60% of patients do not respond to these drugs and of those who do, many do not experience complete remission.[3] Also of those who do respond, many relapse when drug therapy is withdrawn and prolonged or even life-long therapy may be necessary;[7,11] however, long-term efficacy and tolerability of serotonin reuptake inhibitors in obsessive-compulsive disorder has yet to be established.[12] It has been suggested that patients may be maintained on reduced dosage[13] but the optimum dosage remains uncertain.[7] Gradual withdrawal over several months may be more successful if patients are also receiving behavioural therapy.[5]

Drugs such as buspirone, lithium, pindolol, and some antipsychotics including the atypicals have been tried as **adjuncts** when patients are refractory to serotonin reuptake inhibitors and behavioural therapy but results of such augmentation therapy have been variable.[2-7] NICE recommends adding an antipsychotic to an SSRI or clomipramine, or using clomipramine with citalopram in such patients.[8] Intravenous clomipramine has been tried in patients refractory to augmentation therapy.[6]

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Panic disorder. Panic disorder is characterised by severe, sudden, unexpected, recurrent exacerbations of anxiety (panic attacks). During an attack there is a feeling of fear, terror, and impending doom or even death accompanied by autonomic symptoms. Attacks are followed by persistent worry (for at least 1 month) about further attacks and their consequences.

If behavioural or cognitive therapy fails in the management of panic disorder, drug therapy can then be tried but it may need to be prolonged as there is a high rate of relapse on withdrawal.[1] Antidepressants are the drugs of choice in the treatment of panic disorder. While some also consider the combination of psychotherapy with antidepressant therapy to be first-line treatment for panic disorder[2] others consider that a clear benefit of using cognitive behavioural therapy with drug treatment has not yet been shown.[3] Tricyclic antidepressants or SSRIs can reduce the frequency of panic attacks and can often prevent them completely.[4-7] Efficacy is broadly comparable, although SSRIs may be associated with a lower incidence of serious adverse effects;[7-12] in the UK NICE considers SSRIs to be the drugs of first choice in panic disorder.[13] MAOIs such as phenelzine are also effective but dietary restrictions and serious adverse effects limit their use to patients unresponsive to tricyclics and SSRIs.[6,8] Other antidepressants such as the serotonin and noradrenaline reuptake inhibitor venlafaxine are being evaluated in panic disorder.

It may take several weeks before the effects of antidepressants are seen and initially there may be an increase in anxiety and the frequency of panic attacks. Benzodiazepines are sometimes used as adjuncts until antidepressants exert their full effect.[6-10,12] Short courses of benzodiazepines may also be of use in patients who cannot tolerate, or who are refractory to, antidepressants.[4] However, any benefit may be outweighed by the risk of dependence[5] and NICE does not recommend their use in the treatment of panic disorder.[13] There is little evidence to support the use of beta blockers, but they may control physical symptoms. Other drugs that may produce beneficial effects in some patients include valproate[4,6,9,14] and possibly clonidine.[15]

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Phobic disorders. Phobic disorders consist of an irrational or exaggerated fear of, and a wish to avoid, specific objects, activities, or situations. As there is a strong link between **agoraphobia** and panic disorder (see above) it is treated similarly. Simple or specific phobias are usually unresponsive to pharmacotherapy and respond better to behavioural therapy, although paroxetine or benzodiazepines may be considered for disabling phobias unresponsive to such measures.[1]

SSRIs, particularly paroxetine, are considered to be the drugs of choice for the treatment of **social anxiety disorder** (social phobia).[1-6] The serotonin and noradrenaline reuptake inhibitor venlafaxine is also used.[1] MAOIs such as phenelzine are effective in social anxiety disorder and can improve anticipatory anxiety and functional disability;[7,8] however, a systematic review found them to be less consistently effective than the SSRIs,[9] and their use is limited by dietary restrictions and serious adverse effects. Results with the reversible inhibitor of monoamine oxidase moclobemide have been variable.[2-5,9] The benzodiazepines bromazepam and clonazepam have been reported to be of some benefit,[1,2,4,5,7,10] although benzodiazepines should be used with caution because of the risk of dependence and abuse. Other drugs being investigated for the treatment of social anxiety disorder include gabapentin and pregabalin.[1,11]

Beta blockers may help to reduce the physical symptoms in **performance-related anxiety.**[4,7,10]

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Post-traumatic stress disorder. In post-traumatic stress disorder (PSTD), anxiety is precipitated by persistent recall of a traumatic experience that was exceptionally threatening or catastrophic in nature. Patients may also suffer from negative symptoms such as avoidance, alienation, emotional numbness, and social withdrawal. The main treatment is psychotherapy.[1-5] Drug therapy is largely aimed at accompanying symptoms of anxiety or depression.[6] The combination of both methods of therapy is preferred for severe cases.[7] Negative symptoms are usually resistant to pharmacotherapy. Some 8 to 12 weeks of treatment is generally thought necessary to judge the efficacy of treatment.[2,3]

SSRIs are the drugs of choice for most of the symptoms of PTSD.[1-3,7-10] Tricyclic antidepressants or, in refractory patients, MAOIs, may be used as alternatives to SSRIs to help reduce traumatic recollections and nightmares, and to repress flashbacks.[1-3,8] The newer antidepressants nefazodone and venlafaxine have also been tried,[1-3,8] generally in patients refractory to SSRIs, and some consider these drugs to be more suitable alternatives than tricyclics or MAOIs, which may have serious adverse effects.[9] Atypical antipsychotics have been studied as monotherapy and as adjuncts when patients are refractory to SSRIs; they may also be considered where paranoia or flashbacks are prominent.[9]

In the UK NICE[5] recommends the use of paroxetine, mirtazapine, amitriptyline, or phenelzine in patients who refuse psychotherapy, where psychotherapy is inappropriate or ineffective, or as adjunctive therapy in those with significant comorbid depression or severe hyperarousal. In patients who do not respond, further drug therapy may be considered with a different class of antidepressant or adjunctive olanzapine. Drug therapy should be continued for at least 12 months in responders before gradual withdrawal.

It has been suggested that antiepileptics should be considered in those with comorbid bipolar disorder, and where impulsivity and anger predominate.[9] Carbamazepine and valproate appear to improve symptoms of hyper-reactivity, violent behaviour, and angry outbursts but only a small number of patients have been studied.[8,9,11] Lamotrigine may also relieve avoidance and intrusive symptoms although, again, patient numbers are small.[8,11]

Benzodiazepines may be helpful for short-term management of anxiety and sleep disturbances (although some studies have failed to show benefit[6]) but they must be used with caution because of the risk of dependence and abuse,[1,9,10] and the possibility of worsening PTSD;[10] some do not favour their use, even short-term.[3] In several small studies, prazosin has been found to be a promising and fairly well-tolerated drug in the management of sleep-related symptoms.[12]

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Extrapyramidal disorders

Extrapyramidal disorders are movement disorders involving the brain's motor systems outside the pyramidal tract. They are usually characterised by akinesia (a loss of movement) or bradykinesia (abnormal slowness of movement) accompanied by an increase in muscle tone (typified by parkinsonism, p.791); or by dyskinesias (abnormal involuntary movements), often accompanied by a reduction in muscle tone (see below for some examples). Drug-induced extrapyramidal disorders are discussed under Chlorpromazine, p.971.

Ballism. Ballism, sometimes called hemiballism or hemiballismus because it is usually unilateral, consists of involuntary flinging movements of the extremities and most often results from acute vascular infarction or haemorrhage of the subthalamic nucleus. It often improves spontaneously but dopamine-blocking antipsychotics such as haloperidol or dopamine-depleting drugs such as tetrabenazine may be needed to control severe symptoms. Surgery may be necessary in severe cases.

Chorea. Chorea is characterised by brief involuntary muscle contractions and an inability to sustain voluntary contractions. It may be related to neurological abnormalities in the caudate nucleus and putamen of the striatum as well as other basal ganglia structures. Overactivity of dopaminergic nigrostriatal pathways and depletion of gamma-aminobutyric acid (GABA) and acetylcholine may also play a part. Chorea may be an adverse effect of some drugs, including antipsychotics, levodopa, and oral contraceptives; it may also be a symptom of an underlying disorder such as SLE.

Huntington's chorea (Huntington's disease, progressive hereditary chorea) is a hereditary autosomal dominant disease characterised by chorea, behavioural disturbances, and a progressive decline in cognitive function culminating in dementia and death. The identification of a gene marker for Huntington's chorea now makes it possible to identify carriers of the abnormal gene.[1-3] Symptoms usually appear in mid-life, with death following after about 15 years, although there are also juvenile-onset forms. Westphal variant, a form commonest in children, tends to be characterised more by rigidity than by chorea.[1]

Sydenham's chorea (St Vitus' dance; chorea minor) is an acute, usually self-limiting, disorder with an auto-immune basis, characterised by chorea and behavioural disturbances. It commonly occurs about 6 months after rheumatic fever but is now rare since the incidence of rheumatic fever has declined. It may also arise during pregnancy (chorea gravidarum).

Treatment of chorea is symptomatic only and does not alter the progressive decline of Huntington's chorea;[1-3] Sydenham's chorea resolves spontaneously within weeks or months but antibacterial prophylaxis to prevent recurrence of rheumatic fever (p.189) has been recommended. Other forms of chorea may resolve with treatment of the underlying disorder or withdrawal of any causative drug.

Tetrabenazine has been used effectively in chorea, although not all patients respond, and it may produce depression.[1-3] The mode of action is thought to involve depletion of striatal dopamine.[2] Reserpine, which has a similar action and effects, has also been used but is limited by its adverse effects.[2]

Phenothiazines such as fluphenazine[2] have dopamine-receptor blocking activity and have also been used to treat chorea. Other antipsychotics with a similar mode of action that have been used include haloperidol,[1,2] pimozide,[2] and sulpiride.[1,2] Some atypical antipsychotics[2] such as olanzapine, quetiapine, risperidone, and zotepine have also been tried. Adverse effects such as tardive dyskinesias may limit the use of antipsychotics,[1,2] and doses should be kept as low as possible;[2] attempts to control choreiform movements completely are not recommended. In addition to improving chorea, antipsychotics may also be of value in controlling the behavioural symptoms associated with Huntington's chorea; anxiolytics and antidepressants may also be of use.[1,2]

Carbamazepine[1] has been tried with some degree of success in a limited number of patients. The use of drugs to increase GABA activity has been of little value.[2] Other drugs being investigated include amantadine,[3] minocycline,[2,3] and ubidecarenone.[1-3] Implantation of human and porcine fetal neural cells is being studied,[1] as are various forms of gene therapy.

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Tics. Tics may manifest as sudden, involuntary, brief, isolated, repetitive movements, both simple (e.g. eye blinking, nose twitching, or head jerking) and complex (e.g. touching, jumping, or kicking); they may also be sensory in nature or may present in a vocal or phonic way and can range from simple clearing of the throat to more complex symptoms such as echolalia (involuntary repetition of others speech) or coprolalia (involuntary and inappropriate swearing). Symptoms can usually be suppressed voluntarily and may increase with stress and decrease with distraction.[1-3] Some tics persist during sleep.[2,3] The most common cause is **Tourette's syndrome** (Gilles de la Tourette's syndrome), in which behavioural disturbances usually accompany the tics.[1-5] It is a genetic disorder with an onset during childhood and is characterised by recurrent multiple motor and vocal tics that are not due to the direct physiological effects of a substance or a medical condition, with a duration of at least 1 year.

Most patients' symptoms wax and wane and behavioural therapy and reassurance may be sufficient to resolve mild tics.[1,5] Drug treatment may be necessary if tics are severe enough to cause discomfort or embarrassment.[1,2,4,6] Clonidine[1,5-7] or guanfacine[1,5-7] are increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects. For more severe cases the classical antipsychotics pimozide or haloperidol have been widely tried[3,8] to decrease the frequency and severity of tics, and may improve any accompanying behavioural disturbances. Superiority of either drug in terms of efficacy or adverse effects has not been clearly demonstrated,[8] and the risk of developing serious adverse effects such as tardive dyskinesia should be balanced against the perceived benefits of treatment.[8] Other antipsychotics such as fluphenazine, sulpiride, or tiapride have also been tried;[4,6,8] increasingly, atypical antipsychotics, notably risperidone but also including olanzapine, quetiapine, and ziprasidone, are preferred because their adverse effect profile is seen as more acceptable.[7] Doses should be as low as possible, bearing in mind that optimum treatment does not necessarily lead to the complete control of symptoms.[2,4]

Other drugs[1-4,6,8] that may be used in the management of tics and/or behavioural aspects of Tourette's syndrome include baclofen, botulinum toxin, clonazepam, levodopa, pergolide, and tetrabenazine. Nicotine has been reported to produce benefit when used alone or with haloperidol in patients whose symptoms were not satisfactorily controlled with haloperidol alone.[7,9]

For drugs used in the treatment of comorbid disorders commonly associated with Tourette's syndrome, such as obsessive-compulsive disorder and attention deficit hyperactivity disorder, see above and p.2148, respectively.

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Hypochondriasis

Hypochondriasis (hypochondriacal neurosis) is a morbid preoccupation with one's health characterised by a fear or belief that normal bodily sensations are indicative of serious disease. It persists despite medical reassurance and management is difficult. If hypochondriasis is secondary to a psychiatric disorder, particularly depression and some anxiety disorders, treatment aimed at the primary condition may also lead to resolution of the hypochondriacal symptoms.[1-3]

Cognitive and behavioural therapies may be useful in the treatment of hypochondriasis; drug treatment of primary hypochondriasis has been less well studied although antidepressants such as the SSRIs may be effective.[1-4] Pimozide is used in the management of hypochondriacal psychoses such as delusions of parasitic infestation.[5] Atypical antipsychotics such as quetiapine and risperidone have been used as alternatives to pimozide in the treatment of delusional parasitosis.[6]

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Psychoses

Psychoses and psychotic disorders are terms that have been used to describe a collection of severe psychiatric disorders in which the patient has disordered thinking and loses contact with reality due to delusions and/or hallucinations. There may be accompanying mood or behavioural disturbances. *Organic psychoses* arise from organic brain disease produced by toxic insults, metabolic disturbances, infections, or structural abnormalities and may be acute (delirium) or chronic (dementia) in nature.

Disturbed behaviour. Drug therapy is sometimes indicated for the immediate control of severely disturbed, agitated, or violent behaviour associated with a variety of conditions such as toxic delirium, brain damage, mania (see Bipolar Disorder, p.372), or other psychotic disorders. In the UK NICE has issued guidelines on the short-term management of disturbed or violent behaviour in adults.[1] Antipsychotics and benzodiazepines, either alone or in combination, are commonly used for disturbed behaviour. There is little agreement on the best antipsychotic for these indications, selection depending mainly on the condition of the patient and the adverse effect profile of the drug.[2-6] Oral therapy should be tried first and parenteral therapy only given if this is ineffective or refused. The high-potency butyrophenone haloperidol is commonly used for **acutely disturbed behaviour** although it lacks any sedative effects and may be associated with severe extrapyramidal adverse effects. The atypical antipsychotics such as olanzapine and risperidone are increasingly used in acute situations. A systematic review,[7] albeit of 3 small studies, concluded tentatively that there was no difference in efficacy and incidence of adverse effects between low-dose haloperidol and olanzapine or risperidone in the management of delirium; high-dose haloperidol was associated with a greater incidence of extrapyramidal effects. Benzodiazepines such as diazepam and lorazepam are valuable sedatives for the disturbed or delirious patient. A combination of an antipsychotic and a benzodiazepine allows the use of lower doses of each drug. However, a systematic review[8] considered that there were insufficient data to support or refute the use of benzodiazepines, either alone or with an antipsychotic, in the treatment of acute psychosis. Another systematic review[9] found the combination of haloperidol and the antihistamine promethazine, both given intramuscularly, to be effective.

Other drugs that have had some success in the control of symptoms such as agitation, aggression, rage, or violent behaviour include beta blockers, lithium, carbamazepine, and valproate. Buspirone and antidepressants such as the SSRIs and trazodone may also be useful.

Antipsychotics appear to be modestly effective for the control of disturbed behaviour associated with the **dementia** of chronic conditions such as Alzheimer's disease (p.362).[10-15] However, antipsychotics can themselves precipitate confusion or exacerbate dementia and may hasten cognitive decline, increase the risk of falls, incontinence, and drowsiness, and interfere with the performance of motor skills.[16] Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotics and the reaction can be life-threatening. Antipsychotics are used only after careful consideration of the causes of disturbed behaviour and the benefits and risks of antipsychotic treatment. Very low doses are given at first and increased gradually according to clinical response and development of adverse effects; the necessity for continued use is reviewed periodically. Again, there is no agreement over the choice of antipsychotic. A systematic review noted that while there was limited evidence to support the routine use of haloperidol for agitation in dementia, it appeared to reduce aggression.[17] Atypical antipsychotics such as olanzapine, quetiapine, and risperidone have been used and although they may be less likely to produce extrapyramidal effects, cerebrovascular adverse effects are a problem. The UK CSM recommended[18] in 2004 that risperidone and olanzapine should not be used to treat behavioural problems in elderly patients with dementia after analysis of placebo-controlled clinical studies revealed an increased risk of stroke with these 2 atypical antipsychotics. Guidelines for the management of behavioural and psychiatric symptoms in patients with dementia and a history of stroke or transient ischaemic attacks issued in the UK[19] state that consideration should be given to the withdrawal of existing olanzapine and risperidone therapy, and starting treatment with a classical antipsychotic or an atypical that has not been associated with an increased risk of cerebrovascular adverse effects. Further placebo-controlled studies have shown an increased risk of mortality with the use of the atypical antipsychotics aripiprazole, olanzapine, quetiapine, and risperidone in these patients; most of the deaths appeared due to cardiovascular events or infection. Consequently, in 2005 the FDA issued advice against the use of all atypicals, including clozapine and ziprasidone in patients with dementia-related psychosis[20] (for further details, see Dementia, under Risperidone, p.1024). Furthermore, a large multicentre study[21] concluded that adverse effects of atypical antipsychotics (olanzapine, quetiapine, and risperidone) outweigh their benefits in treating behavioural disturbances in patients with Alzheimer's disease. A long-term placebo-controlled study[22] in patients with Alzheimer's disease given antipsychotics (chlorpromazine, haloperidol, risperidone, thioridazine, or trifluoperazine) also concluded that, for most patients, stopping antipsychotic therapy had no overall detrimental effect on functional and cognitive status. The authors suggested that although antipsychotics may have some value in the maintenance treatment of more severe behavioural disturbances, any potential benefits must be weighed against the risk of serious adverse effects. In addition, in 2008, the FDA extended its advice against the use of antipsychotics in elderly patients with dementia-related psychosis to include classical antipsychotics;[23] the FDA were aware of 2 observational studies showing that the risk of death in such patients taking classical antipsychotics was similar to that seen in those taking atypical antipsychotics. Methodological limitations precluded any conclusion that classical antipsychotics have a greater mortality risk than atypical antipsychotics.

The sedative drug, clomethiazole, may be a useful alternative to antipsychotics for the control of agitated behaviour in elderly patients, generally causing fewer adverse effects; respiratory depression, excessive sedation, and dependence may, however, be a problem. Benzodiazepines are not generally indicated for the management of elderly demented patients because of the risks of dependence with continued use, disinhibiting effects, and the particular problems of these drugs in old people (see the Elderly, under Diazepam, p.989). They are not as effective as antipsychotics in reducing behavioural problems, but may be useful in short courses for the management of severe anxiety disorders, or given as required for patients who only have rare episodes of agitation.

The use of antipsychotics in the control of **disturbed behaviour in children** is controversial and can probably be justified only in severe cases resistant to non-pharmacological therapy.[24-26] Aggression in children (with autism, conduct disorder, and mental retardation) has been treated with antipsychotics on a short-term basis. High-potency classical antipsychotics such as haloperidol may be less likely to cause sedation or impair arousal, cognitive function, and learning. Atypical antipsychotics such as olanzapine and risperidone have been used for the control of aggression in children with autism and conduct disorder but are associated with weight gain.[25,26] Nonetheless, in some countries, including the USA, risperidone is licensed for the treatment of irritability associated with autistic disorder in children and adolescents. Aripiprazole, quetiapine, and ziprasidone have also been tried in the treatment of behavioural disturbances associated with autistic disorder.[27] The tendency of antipsychotics to lower the seizure threshold is an important consideration in autistic children who are at an increased risk of seizure disorders. Other drugs that have been tried include clonidine, lithium, and the SSRIs.[25,26] Guidance on the management of autism spectrum disorders has been issued by the American Academy of Pediatrics.[28]

Antipsychotics have been used to control the symptoms of **drug-induced psychosis** in patients with Parkinson's disease.[29-31] Initially, other possible causes such as infections or metabolic and endocrine changes should be eliminated.[30] If psychotic symptoms persist, antiparkinsonian drugs should be gradually stopped or used at the lowest effective dose. Treatment of sleep disturbances in these patients may reduce psychosis; low doses of sedating antidepressants, such as mirtazapine, nortriptyline, or trazodone, are preferable to benzodiazepines or antihistamines which may contribute to confusion and psychosis.[31] Psychosis may be particularly difficult to treat, since the extrapyramidal effects of classical antipsychotics can exacerbate the movement disorder. Benefit has been reported with the atypical antipsychotic clozapine (which must be used with caution because of the risk of agranulocytosis) but results with other atypical antipsychotics such as risperidone and olanzapine have been mixed; quetiapine appears to be reasonably well tolerated. Other drugs that have been tried include anticholinesterases such as donepezil and rivastigmine; ECT may be considered in patients refractory to drug treatment.[30,31]

Antipsychotics have been used for palliative treatment of agitation and restlessness in patients with **terminal restlessness**.[32,33] Although antipsychotics may exacerbate the existing tendency to myoclonus and convulsions in these patients and may not produce adequate sedation in the terminal phase, haloperidol can be used where sedation is not required. Some[32,33] even consider haloperidol to be the drug of choice; chlorpromazine[32,33] and olanzapine have been used as alternatives. Benzodiazepines (such as lorazepam or midazolam), levomepromazine, and propofol have also been used.[32]

Paraphilias and other **deviant sexual behaviour** are rare in women so treatment is focused largely towards men; it consists mainly of psychotherapy and the use of libido-suppressing drugs such as the anti-androgens.[34-36] The use of such pharmacotherapy is controversial and involves not only medical but legal issues. Drugs used for their anti-androgenic action include cyproterone and medroxyprogesterone. Gonadorelin analogues have also been tried for suppression of libido.[35] Medroxyprogesterone has also been used for the control of intrusive disinhibited sexual behaviour in elderly men with dementia. SSRIs may be used in less severe cases, especially in the control of fantasies associated with various paraphilias; they may also be used together with an antihormonal drug if the latter provides inadequate improvement alone.[36] The antipsychotic benperidol is used in some countries for the management of sexual deviations but its value is not established. In general, few well-controlled blinded studies have been conducted into the pharmacological treatment of sexual offenders and there is no evidence that drug treatment reduces the rate of re-offending.

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Mania. Mania usually occurs as part of bipolar disorder. The treatment of acute attacks of mania including mention of the role of antipsychotics is described under Bipolar Disorder, p.372.

Schizophrenia. Schizophrenia is a complex disorder associated with a high morbidity; it may be a group of related syndromes rather than a single disorder. Schizophrenia begins most commonly in late adolescence to the early twenties and many patients develop a chronic illness with repeated relapses. The estimated prevalence is between 0.2 to 1% in the general population. The main clinical features of acute schizophrenia syndrome can be divided into psychotic features such as delusions and hallucinations, and disorganised features involving speech, thought, and behaviour (together often known as 'positive' symptoms). The main features of the chronic syndrome are apathy, lack of drive, and social withdrawal (so-called 'negative' symptoms). Positive symptoms tend to respond better to drug therapy than negative symptoms. The pathophysiological mechanism of schizophrenia is unclear. Since classical antipsychotics used in the treatment of schizophrenia block dopamine D_2 receptors in the midbrain it has been suggested that dopaminergic system overactivity may be involved. However, the efficacy of atypical antipsychotics such as clozapine (see below), which is a relatively weak dopamine D_2 inhibitor, has raised the possibility that an imbalance of other neurotransmitters such as serotonin and adenosine may also be involved (see also Action, under Chlorpromazine, p.975).

The **treatment** of schizophrenia consists mainly of a combination of social therapy and antipsychotics.[1-17] Drug treatment must be started as soon as possible for best outcome. There is little difference in the efficacy of classical antipsychotics such as chlorpromazine and haloperidol. The atypical antipsychotic clozapine appears to be more effective than classical antipsychotics in the management of both positive and negative symptoms, but its use is restricted because it can cause potentially fatal agranulocytosis. Comparative studies have shown that other atypical antipsychotics are at least as effective on positive symptoms as the classical antipsychotics, although claims of greater effects on negative symptoms remain to be proven.

Choice of therapy depends on the risk of adverse effects (which vary between the different groups of antipsychotics), any past treatment, and, unfortunately, cost. UK guidelines issued by NICE[18] recommend that the oral atypical antipsychotics amisulpride, olanzapine, quetiapine, risperidone, and zotepine are considered as first-line treatments for patients with newly-diagnosed schizophrenia. These atypical antipsychotics should also be considered in patients responding to classical antipsychotics but experiencing unacceptable extrapyramidal or other adverse effects and in those who have relapsed and who experienced poorly-controlled symptoms or unacceptable adverse effects with their previous therapy. However, classical antipsychotics are still widely used, since the diversity of their preparations (tablets, oral liquids, injections, and depot injections) and lower cost offer advantages over the atypical antipsychotics. NICE therefore does not recommend changing to an atypical in patients who are already adequately controlled by classical antipsychotic treatment without unacceptable adverse effects. Because risperidone and olanzapine have been associated with an increased risk of stroke when used in elderly patients with dementia (see p.1024), UK guidelines[19] have recommended that other antipsychotics should be considered for patients with a history of stroke, transient ischaemic attacks, or other cere-brovascular disease even in the absence of dementia. However, there is little evidence to guide prescribing in older patients.[20]

There is great interindividual variation in response to antipsychotics, and choosing the most appropriate one may require a trial of antipsychotics from different chemical groups and careful adjustment of dosage. The Royal College of Psychiatrists in the UK has issued advice for those considering the use of higher than normally recommended doses of antipsychotics (see under Administration in the Uses and Administration of Chlorpromazine, p.976). However, in recent years there has been a trend in favour of lower doses of antipsychotics, often with adjunctive benzodiazepines (see below). The use of more than one antipsychotic at the same time is not usually recommended.

About 30% of patients may have little or no response to classical antipsychotics while many others have only a partial response. Such **resistant schizophrenia** may be due to poor patient compliance, which is a major problem in schizophrenic patients; lack of compliance may be a result of adverse effects (see below for possible treatments) or because the patient experiences a relapse while on medication and is unable to maintain treatment.[21] A patient should not be considered resistant to therapy until at least 2 different antipsychotics (NICE also recommends that at least one of these should have been an atypical[11]) have each been given for an adequate trial period (at least 6 to 8 weeks). If other drugs are still ineffective, clozapine may be tried; it should be given for at least 3 months before resorting to measures such as ECT or the use of adjunctive drugs (see below).

After the initial control of schizophrenia with antipsychotics, relapse rates are high in those who stop treatment, therefore **maintenance** therapy is probably warranted. Some recommend the use of lower doses of antipsychotics during maintenance to reduce adverse effects, although this may increase the risk of relapse. The decision to withdraw an antipsychotic completely in a stabilised patient is complex and depends on the number of previous psychotic episodes. In some cases maintenance therapy may need to be indefinite. Regular injections of long-acting depot antipsychotics are sometimes used for maintenance therapy especially if compliance is a problem.[22] They are particularly useful for patients living in the community, and may also be advantageous for those who respond poorly to therapy because of increased first-pass metabolism or intestinal malabsorption. Concern over the possibility of increased extrapyramidal effects and other adverse effects with depot antipsychotics has not been substantiated.

Adjunctive drugs have been used in schizophrenia either to augment antipsychotics or reduce their adverse effects.[23] The short-term addition of a *benzodiazepine* to the initial treatment of acute episodes of schizophrenia can provide a useful extra sedative and anxiolytic effect. It may also allow a smaller dose of antipsychotic to be used and thereby reduce the likelihood of extrapyramidal effects. However, a systematic review[24] concluded that the available evidence for such use is poor and inconclusive.

The use of *antimuscarinic antiparkinsonian drugs* for the treatment or prophylaxis of antipsychotic-induced extrapyramidal adverse effects is controversial (see Extrapyramidal Disorders on p.971, *et seq.*). They are particularly effective in the management of acute dystonic reactions but efficacy in drug-induced parkinsonism itself may be minimal and little benefit has been found in akathisia. Fears that the long-term use of antimuscarinics increases the risk of tardive dyskinesia appear to be unfounded, although they may worsen the condition and should be stopped if it develops. However, the adverse effects of antimuscarinics can be troublesome and may compound the antimuscarinic actions of the antipsychotic. Antimuscarinics also have euphoric effects. Routine use of prophylactic antimuscarinics is therefore not indicated with the possible exception of short-term use in patients at high risk of developing dystonias, or in patients with a previous history of drug-induced dystonias. Antimuscarinics may be given on a short-term basis to treat dystonias.

Addition of *lithium* to antipsychotic treatment may be worthwhile in some patients who fail to respond to an antipsychotic alone, although there is the danger of an interaction (see p.405).

The value of treatment of depressive symptoms of schizophrenia with *antidepressants* is not established but the addition of antidepressants such as the tricyclics is considered worth a trial for depression occurring during the recovery phase after an acute episode of psychosis.

Carbamazepine has produced modest benefit in some patients with refractory schizophrenia, the main effect being a reduction in accompanying symptoms such as excitement, impulsivity, and aggression, but use of carbamazepine with haloperidol has also resulted in reduced haloperidol concentrations and clinical deterioration in a few patients. A systematic review[25] found no significant benefit of adjunctive carbamazepine therapy. *Valproate* has also been tried.

Propranolol in high doses has been reported to be beneficial in refractory schizophrenia but several controlled studies of adjunctive use have found slight or no benefit. However, it may be of use as an adjunct in patients who develop akathisia unresponsive to antimuscarinics.

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Sedation

Since sedatives reduce excitement and anxiety, they may be used before or during various medical procedures to alleviate fear and produce a state of calmness in the patient. A practical aim for situations requiring **conscious sedation**, for example in *dentistry* or during investigative procedures such as *endoscopy*, may be the reduction or abolition of physiological and psychological responses to the stress without loss of consciousness, cooperation, or protective reflexes. A greater degree of sedation may be required for patients in *intensive care* and some consider that patients should be maintained asleep but easily rousable. The difference between sedatives and hypnotics is mainly dose related. The same drug or group of drugs can have both effects, larger doses being necessary for a hypnotic effect, that is to produce a state of sleep.

Some specific situations where sedation may be required are discussed below. The use of sedatives in premedication for anaesthesia is discussed on p.1780.

Dental sedation. Intravenous midazolam has largely superseded diazepam for sedation in dental procedures. However, midazolam needs to be given slowly in small increments as its sedative end-point is reached much more abruptly than with diazepam. Midazolam has a more rapid onset of action and recovery, and produces a greater degree of amnesia than diazepam, but it can cause hallucinations in children.[1] There is insufficient evidence to support the routine use of intravenous sedation for dental procedures in children under the age of 16 years and it is recommended that such use, along with the use of general anaesthetics, combination regimens, and non-standard routes, should be restricted to specialist centres or hospital settings.[2]

Inhaled nitrous oxide (usually 20 to 40% with oxygen[3]) is a widely used analgesic and sedative for conscious sedation of patients with mild to moderate anxiety about dental procedures.[3,4] It is relatively safe and simple to use although there is some concern over its long-term effect on dental staff.[3,4] Nitrous oxide inhalation is well tolerated by children and remains the preferred technique in the management of anxiety in such patients although a certain amount of patient cooperation is required[1,2,5] and supplementary local analgesia is recommended in potentially painful procedures.[2]

Oral sedatives may also be used to provide conscious sedation[4] and are particularly useful to ensure that the patient has a restful night before the procedure; hypnotics may be used for 1 to 3 nights before. Those drugs used include the benzodiazepines diazepam, nitrazepam, and temazepam; temazepam is preferred when it is important to minimise any residual effects. The antihistamines hydroxyzine and promethazine have been used in children.[1,4,5] Oral sedatives have no analgesic effects and appropriate analgesia should be given.[5] It has been suggested that the efficacy of the oral sedative in adult patients can be enhanced by the careful addition of inhaled nitrous oxide; the depth of sedation can be changed as necessary by varying the titration of the latter.[4]

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Endoscopy. The practice of giving sedation routinely before endoscopy varies widely between and within countries.[1-3] It is unclear whether sedation improves patient comfort and the ease of performing the procedure;[1] there may be a failure to distinguish between the need for sedation and the need for analgesia in such procedures. Ultimately the acceptability of unsedated endoscopy differs from patient to patient and procedure to procedure,[2] and it may be appropriate to offer patients the choice.[4]

Intravenous benzodiazepines are commonly used for sedation during endoscopy.[1,2,5,6] Midazolam is generally preferred to diazepam because of its shorter duration of action and greater amnestic effects.[5] Since hypoventilation and oxygen desaturation may occur with benzodiazepines and the procedure itself can lower oxygen saturation, some recommend the use of prophylactic nasal oxygen with oxygen saturation monitoring.[2,3,5,6]

Intravenous opioid analgesics such as morphine and pethidine have also been given but they have largely been replaced by the newer shorter-acting opioids, for example fentanyl, which have faster recovery times.[3,5] Benzodiazepines have often been given with opioids, including pethidine, since such combinations may reduce gagging and increase patient tolerance.[2] They can be used together to achieve deep sedation at higher doses than those used for conscious sedation.[7] However, there is an increased risk of cardiorespiratory effects and, possibly, fatalities with such combinations.[2,5,6] Therefore, the use of the lowest effective doses has been recommended[3,6] and opioids should be given before benzodiazepines, where possible, and their effects monitored before proceeding.[6]

Low-dose intravenous propofol has also been used for conscious sedation as an alternative to, or with, midazolam and opioids.[4] It potentiates the effects of benzodiazepines and opioids, thus reducing the doses required for sedation and analgesia.[7] Propofol has been used alone for deep sedation especially in prolonged or complex procedures; benefit has not been shown conclusively for shorter procedures.[7] The risk of adverse effects may limit its use and the presence of an anaesthetist is usually required.[6,7]

Continuous monitoring of the sedated patient's haemodynamic and ventilatory status, and level of consciousness is recommended.[2-10]

The use of topical anaesthetics such as lidocaine should probably be reserved for those who prefer to undergo endoscopy without sedation as topical anaesthesia appears to serve little useful function in patients premedicated with benzodiazepines or opioids.[4,5,11] There appears to be no practical difference between individual topical anaesthetics. Sprays are safer and may be more effective than lozenges, but even when using a spray it is difficult to anaesthetise the oropharyngeal region effectively.

There is great variation in the methods of sedation and analgesia used for **children** undergoing endoscopy.[8-10] The choice between general anaesthesia and sedation in these patients is subject to debate.[8] Many of the regimens used appear to be similar to those used in adults; drugs commonly used include midazolam, opioids such as fentanyl or pethidine, and propofol.[8] However, the use of propofol is generally not recommended in children (see Incidence of Adverse Effects, under Propofol, p.1791). In the UK, general anaesthesia is the favoured method for younger children; premedication with oral midazolam has also been used.[9]

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Intensive care. Not all patients in intensive care units require sedatives if sufficient analgesia is achieved, particularly after the first 24 to 48 hours, but most will require a balanced combination of analgesics and sedatives to relieve pain and anxiety.[1-9] It is inappropriate to use high doses of analgesics to achieve deep sedation and it is also inappropriate to use sedatives alone for patients who are in pain. Adequate analgesia is recommended before giving sedatives in order to avoid over-sedation.[6,7] The required level of sedation may vary but, in general, many consider patients should be maintained asleep but easily rousable.

Most sedatives and analgesics are given parenterally. Continuous intravenous infusion avoids the peaks and troughs of analgesia and sedation associated with intermittent intramuscular or intravenous dosage, but to what extent it improves patient outcomes is unclear: sedation produced in this way may prolong the need for mechanical ventilation and increase pulmonary complications.

Opioid analgesics have both sedative and analgesic properties and are appropriate for sedation when pain is anticipated, although special care is required in those not artificially ventilated. The antitussive action of the opioids may also help ventilated patients to tolerate a tracheal tube. The choice of opioid may vary between centres, as well as with patient characteristics. Morphine is a suitable opioid in many situations in intensive care[6] but has a slow onset of action. If prolonged sedation is required, analgesia can be obtained by a loading dose followed by a continuous infusion. Many centres now favour the use of one of the phenylpiperidine derivatives, fentanyl, alfentanil, sufentanil, or remifentanil.[5-9]

Propofol is widely used for short-term sedation (up to 72 hours) in intensive care units,[4-9] although concerns have been raised about its safety, particularly in children (in whom use is generally not recommended), or with prolonged use or higher rates of infusion (see also Incidence of Adverse Effects, under Propofol, p.1791). It may be particularly useful in neurosurgical patients to reduce raised intracranial pressure,[6,8] or when rapid awakening is important.[6]

Benzodiazepines induce sleep and reduce anxiety and muscle tone as well as providing profound amnesia; however, they do not provide analgesia. Midazolam has a rapid onset and short duration of action following single doses, and has largely replaced diazepam as the benzodiazepine of choice for sedation. It is particularly favoured for longer-term sedation (more than 72 hours).[5,9] The half-life of midazolam can be substantially increased when given as a continuous intravenous infusion for long-term sedation in patients in intensive care. Lorazepam has also been used[1,6] particularly in the USA,[6] and may be associated with less variability in awakening times, although onset of action may be slower than midazolam. All benzodiazepines tend to produce cardiovascular and respiratory depression and care is required if they are used with opioids as is usually the case in this setting.

Flumazenil is a specific benzodiazepine antagonist and some suggest that it may be of use to assist the return of spontaneous respiration and consciousness in patients receiving benzodiazepines. Multiple doses may be required as it has a short duration of action.[1] However, its routine use after prolonged benzodiazepine treatment is not usually recommended because of the risk of inducing withdrawal symptoms.[6]

Dexmedetomidine is also approved for use in intensive care as a sedative; it is stated to have analgesic-sparing properties.[6]

Ketamine has been investigated for sedation in the intensive care setting[4] and appears to be effective; it may be used as an adjuvant.[8,9] Clonidine is also used as an adjuvant to other drugs.[3,6,8,9] In agitated or delirious patients haloperidol may be used.[4,6]

Stopping treatment with sedatives such as benzodiazepines, opioids, and propofol too rapidly may lead to withdrawal symptoms,[6,7] especially after high doses or prolonged sedation (more than 1 week). Doses should be tapered to prevent such symptoms. Tolerance to benzodiazepines can develop and may be related to long-term sedation (2 days or more); tolerance to opioids has also been reported.[7]

Methods of sedation and analgesia for **children** in intensive care are subject to debate. Many of the regimens used appear to be similar to those used in adults or modifications of existing regimens for paediatric sedation. Drugs commonly used include midazolam and opioids such as fentanyl or, in particular, morphine.[3] However, there has been some concern over a report of encephalopathy associated with the prolonged use of midazolam with fentanyl for sedation in infants under intensive care (see Encephalopathy, under Effects on the Nervous System, p.988). As mentioned above, propofol is not recommended for children in intensive care.

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Sleep disorders

The exact function of sleep is uncertain but it is believed to be involved in energy conservation, total body restoration and recuperation, and development and growth. There are two states of sleep: non-rapid-eye-movement (non-REM) sleep, which is subdivided into 4 stages, and rapid-eye-movement (REM) sleep, sometimes called stage 5. Initially there is a period of light sleep (stages 1 and 2) followed by deep sleep (stages 3 and 4); this latter period is also known as slow-wave sleep. After stage 4, which occurs about 90 minutes after first falling asleep, there is a period of REM sleep (stage 5) during which most dreams occur and EEG traces show high-frequency waves. During a period of sleep there are several cycles of stages 1 to 4 followed by REM sleep, with periods of non-REM sleep becoming shorter and periods of REM sleep longer. It is the slow-wave sleep that is considered to be the more restorative. Most healthy adults sleep for single periods of between 7 to 8 hours a day, although there is a wide range of normal sleeping time (from 4 to 11 hours). In old age there is less slow-wave sleep and sleep becomes more fragmented.

Sleep disorders include insomnia (see below), hypersomnia such as narcolepsy, p.2148, in which the timing, length, and quality of sleep is altered, and the parasomnias (see Sleep-associated Movement Disorders, below) in which abnormal events occur during sleep.

Insomnia. Insomnia is the inability to achieve or maintain sleep and is the most common of the sleep disorders.[1-14] It often leaves sufferers feeling unrefreshed by sleep and may lead to impaired daytime performance.

- Transient insomnia may occur in those who normally sleep well and may be due to an alteration in the conditions that surround sleep, for example noise, or to an unusual pattern of rest as in shift work or travelling between time zones (jet lag). It may also be associated with acute disorders.
- Short-term insomnia is often related to an emotional problem or more serious medical illness such as acute pain. It may last for a few weeks and may recur.
- Chronic insomnia may be attributed to an underlying psychiatric disorder, especially depression or anxiety, to alcohol or drug abuse, to certain drug treatments, to excessive caffeine intake, to daytime napping, or to physical causes such as pain, pruritus, or dyspnoea.

Management of insomnia requires resolution of any stressful precipitant or identification and treatment of any underlying causes, with an emphasis on non-pharmacological measures such as counselling, behavioural therapy, development of relaxation techniques, and avoidance of stimulant substances. Hypnotic drugs should ideally be reserved for short courses in the acutely distressed patient; they should be avoided in the elderly, and their use is rarely justified in children. Generally, hypnotics should be given at the lowest effective dose for as short a period as possible. In transient insomnia one or two doses of a short-acting hypnotic may be indicated, whereas in short-term insomnia intermittent doses of a short-acting hypnotic given for no more than 3 weeks (preferably only 1 week) may be appropriate. Chronic insomnia rarely benefits from hypnotics and routine use of hypnotics is undesirable. Tolerance can develop rapidly (in 3 to 14 days with continuous use) and withdrawal after long-term use can lead to rebound insomnia and a withdrawal syndrome.

Benzodiazepines are generally regarded as the hypnotics of choice. They hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time, and often impart a sense of deep and refreshing sleep. Slow-wave sleep and REM sleep are, however, reduced and the extra sleeping time is largely made up of relatively light sleep. A short-acting benzodiazepine such as temazepam is generally used when residual sedation is undesirable, if falling asleep is a problem, or, when necessary, in elderly patients. However, a withdrawal syndrome is more common with the short-acting benzodiazepines. Longer-acting benzodiazepines such as nitrazepam are indicated when early waking is a problem and possibly when an anxiolytic effect is needed during the day or when some impairment of psychomotor function is acceptable.

Because of the hazard of dependence with benzodiazepines (see p.987), the UK CSM[15] has issued certain recommendations:

- they should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress
- they should be given in the lowest dose which controls symptoms (if possible, intermittently)
- they should not be continued beyond 4 weeks
- they should be withdrawn by gradual tapering of the dose to zero

Subsequently, the EU Committee on Proprietary Medicinal Products (CPMP) has recommended that the treatment period should be limited to 2 weeks when brotizolam, midazolam, or triazolam are used.[16]

Tolerance to the hypnotic effects of benzodiazepines develops rapidly, with sleep latency and pattern returning to pretreatment levels within a few weeks of starting treatment.

A number of other drugs have been used as alternatives to the benzodiazepines. Zaleplon, zopiclone, and zolpidem act on the same receptors or receptor subtypes as the benzodiazepines although structurally they are unrelated. Their short duration of action makes them more suitable for patients who have trouble falling asleep. The CPMP has recommended that treatment with zolpidem should be limited to a maximum of 4 weeks.[16] It remains to be proven whether these drugs offer any advantages over the benzodiazepines. Indeed, the CSM considers that zopiclone has the same potential for adverse psychiatric reactions, including dependence, as benzodiazepines.[17] NICE[18] in the UK found no compelling evidence of any clinically useful differences between these drugs and the shorter-acting benzodiazepines in terms of effectiveness, adverse effects, or potential for dependence or abuse, and recommends that patients who do not respond to zaleplon, zopiclone, zolpidem, or benzodiazepines should not be switched between these hypnotics; patients may be switched if adverse effects directly related to a specific drug occur.

The use of cloral hydrate and its derivatives as hypnotics is now very limited. They have been used as alternatives to benzodiazepines in the elderly, although there is no convincing evidence of any special value in these patients. They used to be considered useful hypnotics for children but such use is rarely justified.

Clomethiazole has also been used as an alternative to benzodiazepines in the elderly. Nasal and conjunctival irritation may be troublesome, and the danger of overdosage and risk of dependence should be considered.

Some antihistamines have hypnotic properties and a number, including alimemazine, diphenhydramine, doxylamine, and promethazine, are marketed for insomnia. They may cause troublesome antimuscarinic effects and those with longer half-lives may cause hangover effects. Promethazine is also popular for use in children, but such use is not usually justified (see Sudden Infant Death Syndrome under Adverse Effects of Promethazine, p.588, for further details).

Barbiturates are no longer recommended as hypnotics because of their adverse effects. The CSM[19] has advised that barbiturates should only be used for insomnia that is severe and intractable when there are compelling reasons to, and then only in patients already taking barbiturates. It was also advised that attempts should be made to wean patients off barbiturate hypnotics. Similarly, compounds such as ethchlorvynol, glutethimide, and methaqualone are not recommended.

Alcohol is not recommended because it has a short weak hypnotic action, and rebound excitation can result in early morning insomnia. Its diuretic effects can interrupt sleep and chronic use can lead to rapid development of tolerance and addiction.

Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity in the treatment of insomnia. Its efficacy is difficult to substantiate and, since the publication of reports linking tryptophan with the eosinophilic-myalgia syndrome, preparations indicated for insomnia have been withdrawn from the market in many countries.

Melatonin, a hormone believed to be involved in the maintenance of circadian rhythms, may be useful in the treatment of insomnias such as those due to **jet lag**[20] or other disorders (where it might act by resetting the body clock), and in the elderly. However, its benefits have been questioned,[21] and certainly evidence for a direct hypnotic effect is less conclusive; its sleep-inducing properties are usually only seen after very high, supraphysiological concentrations have been attained.[5,6] Ramelteon, a melatonin receptor agonist, is used as a hypnotic in some countries.

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2. Mendelson WB, Jain B. An assessment of short-acting hypnotics. *Drug Safety* 1995; **13:** 257–70.
3. NIH Technology Assessment Panel. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. *JAMA* 1996; **276:** 313–18.
4. Ashton CH. Management of insomnia. *Prescribers' J* 1997; **37:** 1–10.
5. Wagner J, *et al.* Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia. *Ann Pharmacother* 1998; **32:** 680–91.
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9. Lavie P. Sleep disturbances in the wake of traumatic events. *N Engl J Med* 2001; **345:** 1825–32.
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11. Sateia MJ, Nowell PD. Insomnia. *Lancet* 2004; **364:** 1959–73.
12. Silber MH. Chronic insomnia. *N Engl J Med* 2005; **353:** 803–10. Correction. *ibid.*; 2827.
13. Kamel NS, Gammack JK. Insomnia in the elderly: cause, approach, and treatment. *Am J Med* 2006; **119:** 463–9.
14. Summers MO, *et al.* Recent developments in the classification, evaluation, and treatment of insomnia. *Chest* 2006; **130:** 276–86.
15. CSM. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems 21* 1988. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 15/08/08)
16. Anonymous. Short-acting hypnotics: a comparative assessment. *WHO Drug Inf* 1993; **7:** 125–6.
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18. NICE. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia: Technology Appraisal 77 (issued April 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/TA077fullguidance.pdf (accessed 15/08/08)
19. CSM/MCA. Barbiturate hypnotics: avoid whenever possible. *Current Problems* 1996; **22:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
20. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 22/09/05).
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Sleep-associated movement disorders. Parasomnias are motor disorders, with or without autonomic features, that occur during sleep or are exaggerated by sleep. Some of the main parasomnias include nightmares, night terrors, sleepwalking (somnambulism), nocturnal enuresis (p.2180), bruxism (teeth grinding), head banging, and aggression during sleep. Other common movement disorders associated with sleep are restless legs syndrome and periodic limb movements in sleep. Parasomnias are common but rarely require treatment with drugs other than the symptomatic treatment of sleep-related medical problems. The management of some of these conditions is discussed briefly below.

The **restless legs syndrome** is characterised by an unpleasant creeping sensation deep in the legs with an irresistible urge to move them. Symptoms begin during relaxation in the evenings and in bed, and interfere with the ability to fall asleep. The aetiology of this condition is obscure and treatment has been largely empirical.[1-11] Drug treatment may not always be necessary and non-pharmacological methods such as good sleep hygiene should be tried initially.[1,3,7,8,12] There have been reports of efficacy with a wide range of treatments, although few have been well studied. Dopaminergic therapy has emerged as a common first-line treatment, a long-acting agonist, such as cabergoline, pergolide, pramipexole, or ropinirole, being preferred in order to avoid the complications associated with levodopa.[5,6,8-12] Anticonvulsants, such as carbamazepine, clonazepam, and gabapentin may be of use in those intolerant of dopamine agonists or in those who require additional medication.[5,8-11] Other drugs that have been reported to be of benefit include some opioids, clonidine, and the benzodiazepines.[5,7-12] Iron supplementation may be effective if the syndrome is associated with iron deficiency.[2-4,7-12] Many patients with restless legs syndrome exhibit **periodic limb movements in sleep**,[2,3] characterised by repetitive periodic leg and foot jerking during sleep. Treatments tried are similar to those for the restless legs syndrome; clonazepam and levodopa are amongst the drugs shown to be of benefit.

Some **parasomnias** have responded to treatment with benzodiazepines.[13,14] These include bruxism, head banging, aggression during sleep, night terrors, and sleepwalking.

1. Clark MM. Restless legs syndrome *J Am Board Fam Pract* 2001; **14:** 368–74.
2. Odin P, *et al.* Restless legs syndrome. *Eur J Neurol* 2002; **9** (suppl 3): 59–67.
3. Stiasny K, *et al.* Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder. *Sleep Med Rev* 2002; **6:** 253–65.
4. Earley CJ. Restless legs syndrome. *N Engl J Med* 2003; **348:** 2103–9.
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9. Ryan M, Slevin JT. Restless legs syndrome. *Am J Health-Syst Pharm* 2006; **63:** 1599–1612.
10. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest* 2006; **130:** 1596–1604.
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12. Trenkwalder C, *et al.* The restless legs syndrome. *Lancet Neurol* 2005; **4:** 465–75.
13. Stores G. Dramatic parasomnias. *J R Soc Med* 2001; **94:** 173–6.
14. Wills L, Garcia J. Parasomnias: epidemiology and management. *CNS Drugs* 2002; **16:** 803–10.

Abecarnil *(rINN)*

Abécarnil; Abecarnilo; Abecarnilum; ZK-112119. Isopropyl 6-(benzyloxy)-4-(methoxymethyl)-9*H*-pyrido(3,4-*b*)indole-3-carboxylate.

Абекарнил

$C_{24}H_{24}N_2O_4$ = 404.5.

CAS — 111841-85-1.

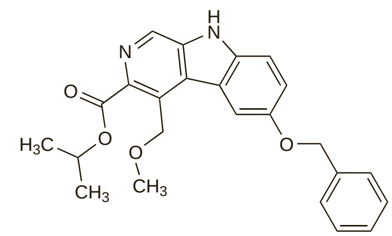

Profile

Abecarnil is a beta-carboline compound reported to be a partial agonist at benzodiazepine receptors. It has been studied for its anxiolytic and anticonvulsant actions in anxiety disorders and alcohol withdrawal syndrome.

◊ References.

1. Krause W, *et al.* Pharmacokinetics and acute toleration of the β-carboline derivative abecarnil in man. *Arzneimittelforschung* 1990; **40:** 529–32.
2. Karara AH, *et al.* Pharmacokinetics of abecarnil in patients with renal insufficiency. *Clin Pharmacol Ther* 1996; **59:** 520–8.
3. Lydiard RB, *et al.* Abecarnil Work Group. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 1997; **58** (suppl 11): 11–18.
4. Pollack MH, *et al.* Abecarnil for the treatment of generalized anxiety disorder: a placebo-controlled comparison of two dosage ranges of abecarnil and buspirone. *J Clin Psychiatry* 1997; **58** (suppl 11): 19–23.
5. Anton RF, *et al.* A double-blind comparison of abecarnil and diazepam in the treatment of uncomplicated alcohol withdrawal. *Psychopharmacology (Berl)* 1997; **131:** 123–9.
6. Rickels K, *et al.* A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2000; **20:** 12–8.

Acamprosate Calcium *(BANM, USAN, rINNM)*

Acamprosate calcique; Acamprosate de Calcium; Acamprosato de calcio; Acamprosatum calcicum; Akamprosaattikalsium; Akamprosát vápenatá sůl; Akamprosatkalcium; Akamprosato kalcio druska; Akamprozát-kalcium; Calcii Acamprosatum; Calcium Acetylhomotaurinate. Calcium 3-acetamido-1-propanesulphate.

Кальций Акампрозат

$C_{10}H_{20}CaN_2O_8S_2$ = 400.5.

CAS — 77337-76-9 (acamprosate); 77337-73-6 (acamprosate calcium).

ATC — N07BB03.

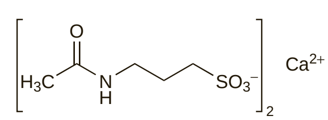

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Acamprosate Calcium). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 5.5 to 7.0.

Adverse Effects

The main adverse effect of acamprosate is dosage-related diarrhoea; nausea, vomiting, and abdominal pain occur less frequently. Other adverse effects have included pruritus, and occasionally a maculopapular rash; bullous skin reactions have occurred rarely. Depression and fluctuations in libido have also been reported. Hypersensitivity reactions including urticaria, angioedema, and anaphylaxis have been reported very rarely.

Effects on the skin. A case of erythema multiforme in a woman with cirrhosis of the liver has been attributed to use of acamprosate[1] although both the diagnosis and any association with acamprosate have been seriously challenged.[2]

1. Fortier-Beaulieu M, *et al*. Possible association of erythema multiforme with acamprosate. *Lancet* 1992; **339:** 991.
2. Potgieter AS, Opsomer L. Acamprosate as cause of erythema multiforme contested. *Lancet* 1992; **340:** 856–7.

Precautions

In the UK, acamprosate is contra-indicated in patients with severe hepatic impairment (Child-Pugh Class C). US licensed product information states that acamprosate is not metabolised via the liver and its pharmacokinetics are not altered in those with mild to moderate hepatic impairment (Child-Pugh Classes A and B); no change in dose is required in such patients. (No advice is given regarding use in those with more severe impairment.) For precautions regarding the use of acamprosate in patients with renal impairment, see under Uses and Administration, below.

Pharmacokinetics

Absorption of acamprosate from the gastrointestinal tract is slow but sustained and is subject to considerable interindividual variation. Steady-state concentrations are achieved after dosage for 7 days. Bioavailability is reduced if given with food. Acamprosate is not protein bound and although it is hydrophilic it is reported to cross the blood-brain barrier. Acamprosate does not appear to be metabolised and is excreted unchanged in the urine. The elimination half-life after oral doses has been reported to be about 33 hours.

◊ References.

1. Saivin S, *et al*. Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet* 1998; **35:** 331–45.

Uses and Administration

Acamprosate has a chemical structure similar to that of the endogenous amino acid, homotaurine, which is a structural analogue of gamma-aminobutyric acid (GABA—p.2308) and taurine (p.2395). It is given as the calcium salt to prevent relapse in alcoholics who have been weaned off alcohol. The usual oral dose is 666 mg of acamprosate calcium given three times daily. UK licensed product information also recommends that patients weighing less than 60 kg should be given a dose of 666 mg at breakfast followed by 333 mg at midday and 333 mg at night. For doses in patients with renal impairment, see below. Treatment should be started as soon as possible after alcohol withdrawal and maintained, even if the patient relapses, for the recommended period of 1 year.

Administration in renal impairment. It is considered[1] likely that accumulation of acamprosate would occur with prolonged use of therapeutic doses in patients with renal impairment. It has been reported that the mean maximum concentration of acamprosate after a single 666-mg dose was 813 nanograms/mL in 12 patients with moderate or severe renal impairment compared with 198 nanograms/mL in 6 healthy subjects; values for the plasma elimination half-life were 47 and 18 hours, respectively.

Licensed product information in the UK does not recommend the use of acamprosate in patients with renal impairment (serum creatinine greater than 120 micromoles/litre).

In the USA the use of acamprosate is contra-indicated in those with severe renal impairment (creatinine clearance (CC) less than 30 mL/minute). However, in those with moderate impairment (CC 30 to 50 mL/minute), a starting dose of 333 mg three times daily may be given.

1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; **53:** 1038–53.

Alcohol dependence. Acamprosate is considered to be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p.1626). Reviews[1-4] of placebo-controlled studies conclude that acamprosate helps to prevent relapse and increase the number of drink-free days during a 1-year course of treatment and possibly for up to one year thereafter. Efficacy appears to be dose related but its effects in promoting abstinence may wane during treatment. Use with disulfiram or naltrexone may improve results but a large multicentre study in the USA found that adding acamprosate to naltrexone or behavioural therapy did not produce any additional benefit, and that the drug was ineffective when used alone.[5] Several mechanisms have been proposed to account for acamprosate's action including inhibition of neuronal hyperexcitability by antagonising excitatory amino acids such as glutamate.

1. Wilde MI, Wagstaff AJ. Acamprosate: a review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 1997; **53:** 1038–53.
2. Anonymous. Acamprosate for alcohol dependence? *Drug Ther Bull* 1997; **35:** 70–2.
3. Mason BJ. Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. *J Clin Psychiatry* 2001; **62** (suppl 20): 42–8.
4. Overman GP, *et al.* Acamprosate for the adjunctive treatment of alcohol dependence. *Ann Pharmacother* 2003; **37:** 1090–9.
5. Anton RF, *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE study: a randomized controlled trial. *JAMA* 2006; **295:** 2003–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Campral†; ***Austral.:*** Campral; ***Austria:*** Campral; ***Belg.:*** Campral; ***Braz.:*** Campral†; ***Chile:*** Campral; ***Cz.:*** Campral; ***Denm.:*** Campral; ***Fr.:*** Aotal; ***Ger.:*** Campral; ***Hong Kong:*** Campral; ***Hung.:*** Campral; ***Irl.:*** Campral; ***Mex.:*** Campral; ***Neth.:*** Campral; ***Norw.:*** Campral; ***Pol.:*** Campral; ***Port.:*** Campral; ***S.Afr.:*** Besobrial; Sobrial†; ***Singapore:*** Campral†; ***Spain:*** Campral; Zulex; ***Swed.:*** Campral; ***Switz.:*** Campral; ***Turk.:*** Campral; ***UK:*** Campral; ***USA:*** Campral.

Acecarbromal *(rINN)*

Acécarbromal; Acecarbromalum; Acetcarbromal; Acetylcarbromal. *N*-Acetyl-*N*′-(2-bromo-2-ethylbutyryl)urea.

Ацекарбромал

$C_9H_{15}BrN_2O_3$ = 279.1.
CAS — 77-66-7.

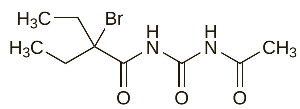

Profile

Acecarbromal is a bromureide with similar actions to those of carbromal (p.967). It has been used for its sedative properties but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Cz.:*** Afrodor; ***Ger.:*** Afrodor; ***Hung.:*** Afrodor†; ***Rus.:*** Afrodor (Афродор).

Acepromazine *(BAN, rINN)*

Acepromazin; Acepromazina; Acépromazine; Acepromazinum; Asepromatsiini. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

Ацепромазин

$C_{19}H_{22}N_2OS$ = 326.5.
CAS — 61-00-7.
ATC — N05AA04.
ATC Vet — QN05AA04.

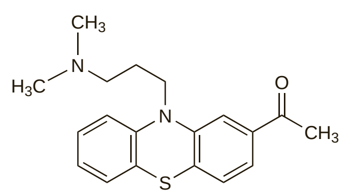

Acepromazine Maleate *(BANM, USAN, rINNM)*

Acépromazine, Maléate d'; Acepromazini Maleas; Acetylpromazine Maleate; Asepromazin Maleat; Maleato de acepromazina. 10-(3-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone hydrogen maleate.

Ацепромазина Малеат

$C_{19}H_{22}N_2OS,C_4H_4O_4$ = 442.5.
CAS — 3598-37-6.
ATC — N05AA04.
ATC Vet — QN05AA04.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.

BP(Vet) 2008 (Acepromazine Maleate). A yellow crystalline powder. Soluble in water and in alcohol; freely soluble in chloroform; slightly soluble in ether. A 1% solution in water has a pH of 4.0 to 4.5.

USP 31 (Acepromazine Maleate). pH of a 1% solution is between 4.0 and 5.5. Protect from light.

Profile

Acepromazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been given orally as the maleate in the treatment of anxiety disorders, hiccups, and nausea and vomiting. Acepromazine, as the base, has also been given in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Plegicil; ***Turk.:*** Plegicil.
Multi-ingredient: ***Fr.:*** Noctran.

Aceprometazine *(rINN)*

16-64 CB; Aceprometazina; Acéprométazine; Aceprometazinum. 10-(2-Dimethylaminopropyl)phenothiazin-2-yl methyl ketone.

Ацепрометазин

$C_{19}H_{22}N_2OS$ = 326.5.
CAS — 13461-01-3.

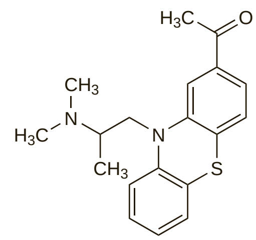

Profile

Aceprometazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is available usually as the maleate in preparations for the management of insomnia.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Mepronizine; Noctran.

Afobazol

Afobazole; Aphobazole; CM-346; SM-346. 5-Ethoxy-2-{[2-(4-morpholinyl)ethyl]thio}-1*H*-benzimidazole Monohydrochloride.

Афобазол

$C_{15}H_{21}N_3O_2S.HCl$ = 343.9.
CAS — 173352-39-1.

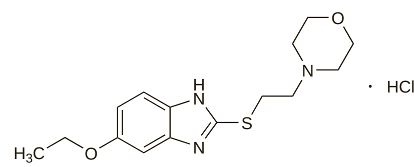

NOTE. Afobazol has also been described as the dihydrochloride.

Profile

Afobazol is a non-benzodiazepine anxiolytic used in the treatment of anxiety disorders. It has been given orally in a usual dose of 10 mg three times daily. A maximum of 60 mg may be given daily.

◊ References.

1. Neznamov GG, *et al.* Aphobazol—new selective anxyolytic drug. *Zh Nevrol Psikhiatr Im S S Korsakova* 2005; **105:** 35–40.

Allobarbital *(USAN, rINN)*

Allobarbitaali; Allobarbitalum; Allobarbitone; Alobarbital; Diallylbarbitone; Diallylbarbituric Acid; Diallylmalonylurea; Diallymalum; NSC-9324. 5,5-Diallylbarbituric acid.

Аллобарбитал

$C_{10}H_{12}N_2O_3$ = 208.2.
CAS — 52-43-7.
ATC — N05CA21.
ATC Vet — QN05CA21.

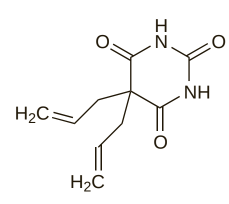

Profile

Allobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used in combination preparations for the treatment of sleep disorders and pain but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Dinyl†; Eunalgit†; ***Hung.:*** Demalgonil; ***Pol.:*** Krople Zoladkowe; Pabialgin P; ***Turk.:*** Spasmo-Panalgine.

Alprazolam *(BAN, USAN, rINN)*

Alpratsolaami; Alprazolám; Alprazolamas; Alprazolamum; U-31889. 8-Chloro-1-methyl-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*]-[1,4]benzodiazepine.

Алпразолам

$C_{17}H_{13}ClN_4$ = 308.8.

CAS — 28981-97-7 (alprazolam).

ATC — N05BA12.

ATC Vet — QN05BA12.

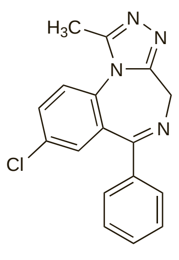

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of alprazolam:

Benzo; Coffins; Dogbones; Fo' Bars; Fo's; Footballs; Forgetful Pills; Four Bars; French Fries; Gold Bars; Green Bars; Quad bar; School Buses; Sticks; Totem Poles; White Bars; X-Boxes; Xan-Bars; Xannies; Xanny; Zanny; Z-Bars; Zan-Bars; Zannies; Zanny-Bars.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Alprazolam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Alprazolam). A white to off-white crystalline powder. Insoluble in water; soluble in alcohol; sparingly soluble in acetone; freely soluble in chloroform; slightly soluble in ethyl acetate.

Dependence and Withdrawal

As for Diazepam, p.987. Dependence may be a particular problem at the high doses used in the treatment of panic attacks.

Adverse Effects and Treatment

As for Diazepam, p.987.

Effects on the liver. A patient receiving phenelzine for depression developed abnormal liver enzyme values on 2 occasions when alprazolam was added to the treatment.[1] It was not possible to say if this was due to alprazolam alone or a synergistic effect with phenelzine.

1. Roy-Byrne P, *et al.* Alprazolam-related hepatotoxicity. *Lancet* 1983; **ii:** 786–7.

Effects on the skin. There have been some reports of alprazolam-induced photosensitivity.[1,2]

1. Kanwar AJ, *et al.* Photosensitivity due to alprazolam. *Dermatologica* 1990; **181:** 75.
2. Watanabe Y, *et al.* Photosensitivity due to alprazolam with positive oral photochallenge test after 17 days administration. *J Am Acad Dermatol* 1999; **40:** 832–3.

Overdosage. A retrospective analysis[1] of 2063 hospital admissions for benzodiazepine overdosage in one region of Australia between January 1987 and October 2002 found that patients who took an overdose of alprazolam were about twice as likely to require admission to intensive care. Flumazenil was required in 14% of the 131 alprazolam overdoses, and ventilation in 16%, which was significantly more than for other benzodiazepines. Given the apparently greater toxicity of alprazolam in overdosage, its increasing prescription to groups at risk of self-poisoning was of concern.

1. Isbister GK, *et al.* Alprazolam is relatively more toxic than other benzodiazepines in overdose. *Br J Clin Pharmacol* 2004; **58:** 88–95.

Precautions

As for Diazepam, p.988.

Abuse. High doses of alprazolam taken after maintenance doses of methadone produced a 'high' without pronounced sedation; the drug was also misused by nonopioid-drug abusers.[1] The usual urine toxicology screens for benzodiazepines often give false-negative results for alprazolam because of the extremely low concentrations of metabolites excreted, making abuse difficult to detect. A subsequent review[2] considered that the literature did not support the widely held belief that alprazolam had a greater liability for abuse than other benzodiazepines, but the possibility could not be discounted.

1. Weddington WW, Carney AC. Alprazolam abuse during methadone maintenance therapy. *JAMA* 1987; **257:** 3363.
2. Rush CR, *et al.* Abuse liability of alprazolam relative to other commonly used benzodiazepines: a review. *Neurosci Biobehav Rev* 1993; **17:** 277–85.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of alprazolam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

From a study[2] of the distribution of alprazolam into breast milk in 8 lactating women it was estimated that the average daily dose of alprazolam ingested by a breast-fed infant would range from 0.3 to 5 micrograms/kg or about 3% of a maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Oo CY, *et al.* Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. *Br J Clin Pharmacol* 1995; **40:** 231–6.

Handling. Care should be taken to prevent inhaling particles of alprazolam and exposing the skin to it.

Hepatic impairment. Alprazolam 1 mg by mouth was absorbed more slowly in 17 patients with alcoholic cirrhosis with no ascites than in 17 healthy subjects.[1] Mean peak alprazolam concentrations were achieved after 3.34 hours in the cirrhosis patients and 1.47 hours in the healthy subjects. Mean elimination half-life for cirrhosis patients was 19.7 hours compared with 11.4 hours for subjects from the healthy group. However, there were no significant differences in the maximum plasma concentrations achieved. The results indicate that alprazolam, in common with other benzodiazepines that undergo oxidative metabolism, would accumulate to a greater extent in patients with alcoholic liver disease than in healthy subjects; the daily dose of alprazolam may need to be reduced by half in this population. See also Administration in Hepatic or Renal Impairment, below.

1. Juhl RP, *et al.* Alprazolam pharmacokinetics in alcoholic liver disease. *J Clin Pharmacol* 1984; **24:** 113–19.

Porphyria. Alprazolam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Alprazolam is well absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being achieved within 1 to 2 hours of a dose. The mean plasma half-life is 11 to 15 hours. Alprazolam is 70 to 80% bound to plasma proteins, mainly albumin. It is metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4. Metabolites include α-hydroxyalprazolam, which is reported to be about half as active as the parent compound, 4-hydroxyalprazolam, and an inactive benzophenone. Plasma concentrations of metabolites are very low. Alprazolam is excreted in urine as unchanged drug and metabolites.

◊ References.

1. Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam: therapeutic implications. *Clin Pharmacokinet* 1993; **24:** 453–71.
2. Wright CE, *et al.* Pharmacokinetics and psychomotor performance of alprazolam: concentration-effect relationship. *J Clin Pharmacol* 1997; **37:** 321–9.
3. Kaplan GB, *et al.* Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin Pharmacol* 1998; **38:** 14–21.
4. Park J-Y, *et al.* Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. *Clin Pharmacol Ther* 2006; **79:** 590–9.

Uses and Administration

Alprazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders in oral doses of 250 to 500 micrograms three times daily, increased where necessary to a total daily dose of 3 or 4 mg. In elderly or debilitated patients, an initial dose of 250 micrograms two or three times daily has been suggested. For doses in patients with hepatic or renal impairment, see below.

Doses of up to 10 mg of alprazolam daily have been used in the treatment of panic attacks. A modified-release preparation of alprazolam is also available for once-daily dosing.

Administration in hepatic or renal impairment. UK licensed product information advises caution when using alprazolam in patients with hepatic or renal impairment; it is contraindicated in those with severe hepatic impairment. In the USA, licensed product information states that patients with advanced liver disease may be given an initial dose of 250 micrograms two or three times daily.

Anxiety disorders. The management of anxiety disorders, including the use of benzodiazepines, is discussed on p.952.

References.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160:** 191–202.
2. Lepola UM, *et al.* Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8:** 115–18.
3. Pollack MH, *et al.* Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 1993; **13:** 257–63.
4. Woodman CL, *et al.* Predictors of response to alprazolam and placebo in patients with panic disorder. *J Affect Disord* 1994; **30:** 5–13.
5. Spiegel DA. Efficacy studies of alprazolam in panic disorder. *Psychopharmacol Bull* 1998; **34:** 191–5.

Depression. Although they may be useful for associated anxiety, benzodiazepines are not usually considered appropriate for treatment of depression (p.373); however, some drugs such as alprazolam have been tried for this indication.[1]

1. Kravitz HM, *et al.* Alprazolam and depression: a review of risks and benefits. *J Clin Psychiatry* 1993; **54:** (suppl.): 78–84.

Premenstrual syndrome. Alprazolam has been reported[1-3] to have produced a marginal to good response in the premenstrual syndrome (p.2099) but others have not found it to be of benefit,[4] and the role of benzodiazepines is limited by their adverse effects. If benzodiazepines are selected it is recommended that in order to reduce the risk of dependence and withdrawal symptoms they should be carefully restricted to the luteal phase in selected patients.[5] Withdrawal symptoms may be more severe after short-acting drugs such as alprazolam. Antidepressant drugs such as SSRIs may be preferred.

1. Smith S, *et al.* Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987; **70:** 37–43.
2. Harrison WM, *et al.* Treatment of premenstrual dysphoria with alprazolam: a controlled study. *Arch Gen Psychiatry* 1990; **47:** 270–5.
3. Freeman EW, *et al.* A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995; **274:** 51–7.
4. Evans SM, *et al.* Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. *Neuropsychopharmacology* 1998; **19:** 499–516.
5. Mortola JF. A risk-benefit appraisal of drugs used in the management of premenstrual syndrome. *Drug Safety* 1994; **10:** 160–9.

Tinnitus. Alprazolam has been tried in the management of tinnitus (p.1866).

References.

1. Johnson RM, *et al.* Use of alprazolam for relief of tinnitus: a double-blind study. *Arch Otolaryngol Head Neck Surg* 1993; **119:** 842–5.
2. Huynh L, Fields S. Alprazolam for tinnitus. *Ann Pharmacother* 1995; **29:** 311–12.
3. Vernon JA, Meikle MB. Masking devices and alprazolam treatment for tinnitus. *Otolaryngol Clin North Am* 2003; **36:** 307–20.

Preparations

USP 31: Alprazolam Oral Suspension; Alprazolam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Alplax; Alprazol; Amziax; Ansielix; Aplacaina; Bayzolam; Becede; Bestrol; Calmol; Emeral; Isoproxal; Krama; Medronal; Nivelan N; Prenadona; Prinox; Psicosedol; PTA; Relaxten; Retan†; Rilow; Tensium; Thiprasolan; Tranquinal; Xanax; ***Austral.:*** Alprax; Kalma; Xanax; ***Austria:*** Alprastad; Alpratyrol†; Xanor; ***Belg.:*** Alpraz; Alprazomed; Docalprazo; Topazolam; Xanax; ***Braz.:*** Alfron; Altrox; Apraz; Constante; Frontal; Neozolam; Tranquinal; ***Canad.:*** Apo-Alpraz; Novo-Alprazol; Nu-Alpraz; Xanax; ***Chile:*** Adax; Grifoalpram; Prazam; Sanerva; Tricalma; Zotran; ***Cz.:*** Frontin; Helex; Neurol; Xanax; ***Denm.:*** Alprox; Tafil; ***Fin.:*** Alprox; Xanor; ***Fr.:*** Xanax; ***Ger.:*** Cassadan; Tafil; Xanax; ***Gr.:*** Antanax†; Saturnil; Xanax; ***Hong Kong:*** Alprax; Nalion; Renax; Xanax; ***Hung.:*** Frontin; Xanax; ***India:*** Alprax; Alprocontin; Anzilum†; Pacyl; Restyl; Tranax; Xycalm; Zolam; ***Indon.:*** Alganax; Alviz; Atarax; Calmlet; Feprax; Frixitas; Soxietas; Xanax; Zypraz; ***Irl.:*** Alprox; Calmax; Gerax; Xanax; ***Israel:*** Alpralid; Alprox; Xanagis; Xanax; ***Ital.:*** Alpravecs; Alprazig; Frontal; Ibizolam†; Mialin; Valeans; Xanax; ***Malaysia:*** Alpranax; Apo-Alpraz; Xanax; ***Mex.:*** Alzam; Farmapram; Irizz; Neupax; Tafil; ***Neth.:*** Xanax; ***Norw.:*** Xanor; ***NZ:*** Xanax; ***Philipp.:*** Xanor; ***Pol.:*** Afobam; Alprazomerck; Alprox; Neurol; Xanax; Zomiren; ***Port.:*** Alpronax†; Pazolam; Prazam; Unilan; Xanax; ***Rus.:*** Alzolam (Алзолам); Helex (Хелекс); Neurol (Неурол); Xanax (Ксанакс)†; ***S.Afr.:*** Alzam; Anxirid†; Azor; Drimpam†; Xanolam†; Xanor; Zopax; ***Singapore:*** Apo-Alpraz; Dizolam†; Xanax; Zacetin†; ***Spain:*** Trankimazin; ***Swed.:*** Xanor; ***Switz.:*** Xanax; ***Thai.:*** Alcelam; Alnax; Alprax; Anax; Anpress; Anzion†; Dizolam; Marzolam; Mitranax†; Pharnax; Siampraxol; Xanacine; Xanax; Xiemed; ***Turk.:*** Xanax; ***UK:*** Xanax; ***USA:*** Niravam; Xanax; ***Venez.:*** Abaxon; Alpram; Ansilan; Danox†; Tafil.

Multi-ingredient: ***Arg.:*** Alplax Digest; Alplax Net; Ansielix Digest; Euciton Stress; Novo Vegestabil†; Sidomal; Tensium Gastric; Tranquinal Soma; ***India:*** Fludep Plus; Restyl Forte; Restyl Plus; Stresnil; Zopax Plus.

Amisulpride *(BAN, rINN)*

Amisülprid; Amisulprid; Amisulprida; Amisulpridas; Amisulpridi; Amisulpridum; Amiszulprid; DAN-216. 4-Amino-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulphonyl)-2-methoxybenzamide; (*RS*)-4-Amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-(ethylsulfonyl)-*o*-anisamide.

Амисульприд

$C_{17}H_{27}N_3O_4S$ = 369.5.

CAS — 71675-85-9.

ATC — N05AL05.

ATC Vet — QN05AL05.

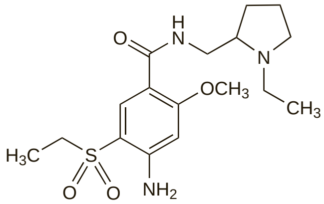

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Amisulpride). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane.

Adverse Effects, Treatment, and Precautions

Although amisulpride may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Insomnia, anxiety, and agitation are common adverse effects with amisulpride. Other less common effects include drowsiness and gastrointestinal disorders such as constipation, nausea, vomiting, and dry mouth. Allergic reactions, abnormal liver function tests, and seizures have been reported rarely.

Hyperprolactinaemia, which may result in galactorrhoea, amenorrhoea, impaired fertility, gynaecomastia, breast pain, and sexual dysfunction, has occurred with amisulpride use. Weight gain has also been noted. Dose-related extrapyramidal dysfunction may occur, but symptoms such as acute dystonia, parkinsonism, and akathisia are generally mild at licensed doses. Tardive dyskinesia has been reported after long-term use and there have been rare cases of neuroleptic malignant syndrome. Hypotension and bradycardia have been reported occasionally; QT prolongation, in rare cases leading to torsade de pointes, has also been noted. The risk of QT prolongation is increased by pre-existing conditions such as bradycardia, hypokalaemia, and congenital or acquired QT prolongation; patients should be reviewed for these conditions before starting amisulpride treatment. Certain medications may also increase the risk (see Interactions, below).

Amisulpride should not be given to patients with phaeochromocytoma or prolactin-dependent tumours. It should be used with caution in patients with severe renal impairment, or a history of epilepsy or Parkinson's disease. The risk of hypotension and sedation is increased in elderly patients.

Amisulpride may affect the performance of skilled tasks including driving.

Withdrawal symptoms have occurred rarely when amisulpride has been stopped abruptly; a gradual dose reduction may be appropriate when stopping amisulpride.

Dementia. The FDA has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class. See under Risperidone, p.1024.

Effects on body-weight. A review[1] has suggested that the risk of weight gain with amisulpride treatment is less than with olanzapine or risperidone, although cases have been reported.[2] The increased risk of weight gain with some atypical antipsychotics is also discussed under Adverse Effects of Clozapine, p.981.

1. McKeage K, Plosker GL. Amisulpride: a review of its use in the management of schizophrenia. *CNS Drugs* 2004; **18:** 933–56.
2. Papadimitriou GN, *et al.* Acute weight gain induced by amisulpride monotherapy in a first-episode schizophrenic patient. *Int Clin Psychopharmacol* 2006; **21:** 181–4.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Overdosage. The effects of overdosage of amisulpride in 2 patients have been reported.[1] The first patient had taken about 3 g of amisulpride and an unknown amount of dosulepin and was found to have had a blood-amisulpride concentration of 9.63 micrograms/mL. Generalised convulsions, which resolved spontaneously, were followed by coma, motor restlessness, tachycardia, and slight prolongation of the QT interval. The patient was treated with gastric lavage and had recovered within 48 hours. The second patient, who had been found dead, had a blood-amisulpride concentration of 41.7 micrograms/mL. Severe cardiotoxicity occurred in 4 further cases of amisulpride overdoses of between about 4 and 32 g reported to Australian poisons information centres;[2] all 4 had marked QT prolongation, with bundle branch block or torsade de pointes, and one, who was thought to have ingested between 16 and 24 g, died after cardiac arrest.

1. Tracqui A, *et al.* Amisulpride poisoning: a report on two cases. *Hum Exp Toxicol* 1995; **14:** 294–8.
2. Isbister GK, *et al.* Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. *Med J Aust* 2006; **184:** 354–6.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

Amisulpride should not be given with drugs that may induce arrhythmias (including torsade de pointes); such drugs include some antiarrhythmics, cisapride, thioridazine, erythromycin, and halofantrine. The risk of arrhythmias is also increased with drugs that prolong the QT interval, such as pimozide, haloperidol, and tricyclic antidepressants, and with drugs that produce bradycardia or hypokalaemia, including beta blockers, some calcium-channel blockers, clonidine, digoxin, guanfacine, potassium-depleting diuretics, and lithium; use of these drugs with amisulpride requires caution.

The central effects of other CNS depressants including alcohol may be enhanced by amisulpride. Amisulpride may also enhance the effects of antihypertensive drugs. The dopamine-blocking activity of amisulpride may antagonise the actions of dopaminergics such as levodopa and they should not be given together.

◊ In 7 patients receiving amisulpride, introduction of *lithium* resulted in an average increase of 32% of the dose-corrected plasma concentration of amisulpride.[1] An earlier study had noted that plasma concentrations of amisulpride were raised in patients also taking *clozapine*.[2]

1. Bergemann N, *et al.* Increase in plasma concentrations of amisulpride after receiving co-medication with lithium. *Pharmacopsychiatry* 2005; **38:** 44.
2. Bergemann N, *et al.* Plasma amisulpride levels in schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol* 2004; **14:** 245–50.

Pharmacokinetics

Amisulpride is absorbed from the gastrointestinal tract but bioavailability is reported to be only about 48%. An initial peak in plasma concentration has been reported to occur 1 hour after oral doses and a second higher peak after 3 to 4 hours. Plasma protein binding is reported to be only about 16%. Metabolism is limited, with most of a dose appearing in the urine as unchanged drug. The terminal elimination half-life is about 12 hours.

◊ References.

1. Rosenzweig P, *et al.* A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol* 2002; **17:** 1–13.

Uses and Administration

Amisulpride is a substituted benzamide atypical antipsychotic. It is reported to have a high affinity for dopamine D_2 and D_3 receptors. Amisulpride is used mainly in the management of psychoses such as schizophrenia but in some countries it has also been tried in depression (p.373).

For acute psychotic episodes in adults and adolescents aged 15 years and over a daily dosage of between 400 and 800 mg may be given orally in 2 divided doses, increased if necessary to 1200 mg daily. For patients with mainly negative symptoms, daily doses between 50 and 300 mg are recommended. Daily doses of up to 300 mg may be given as a single dose. Amisulpride has also been given by intramuscular injection in doses of 400 mg daily.

Administration in renal impairment. For patients with renal impairment, the oral dose of amisulpride should be reduced according to creatinine clearance (CC):

- CC between 30 and 60 mL/minute, half the usual dose
- CC between 10 and 30 mL/minute, one-third the usual dose

Similar reductions are also recommended when amisulpride is given intramuscularly.

Schizophrenia. Reviews[1,2] of amisulpride indicate that it may be more effective than classical antipsychotics against general and negative symptoms of schizophrenia (p.955), and has fewer extrapyramidal adverse effects.

1. Leucht S, *et al.* Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; **159:** 180–90.
2. Mota Neto JIS, *et al.* Amisulpride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 24/05/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Enorden; ***Austral.:*** Solian; ***Austria:*** Majorem; Solian; ***Belg.:*** Solian; ***Braz.:*** Socian; ***Chile:*** Socian; ***Cz.:*** Deniban; Solian; ***Denm.:*** Solian; ***Fr.:*** Solian; ***Ger.:*** Amisulid; Solian; ***Gr.:*** Solian; ***Hong Kong:*** Solian; ***Hung.:*** Amiprid; Amitrex; ***Irl.:*** Solian; ***Israel:*** Solian; ***Ital.:*** Deniban; Solian; Sulamid; ***Mex.:*** Solian; ***Norw.:*** Solian; ***NZ:*** Solian; ***Philipp.:*** Solian; ***Pol.:*** Solian; ***Port.:*** Amitrex; Socian; ***Rus.:*** Solian (Солиан); ***S.Afr.:*** Solian; ***Singapore:*** Solian; ***Spain:*** Amilande†; Solian; ***Switz.:*** Solian; ***Turk.:*** Solian; ***UK:*** Solian.

Amobarbital *(BAN, rINN)*

Amobarbitaali; Amobarbitál; Amobarbitalis; Amobarbitalum; Amylobarbitone; Pentymalum. 5-Ethyl-5-isopentylbarbituric acid.

Амобарбитал

$C_{11}H_{18}N_2O_3$ = 226.3.

CAS — 57-43-2.

ATC — N05CA02.

ATC Vet — QN05CA02.

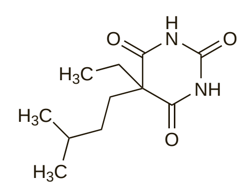

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amobarbital:

Amys; Birds; Blue; Blue angels; Blue birds; Blue bullets; Blue clouds; Blue devils; Blue dolls; Blue heaven; Blue heavens; Blues.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Amobarbital). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; soluble in dichloromethane. Forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Amobarbital Sodium *(BANM, rINNM)*

Amobarbitaalinatrium; Amobarbital sódico; Amobarbital sodique; Amobarbital sodná sůl; Amobarbitalio natrio druska; Amobarbitalnatrium; Amobarbitál-nátrium; Amobarbitalum natricum; Amylobarbitone Sodium; Barbamylum; Natrii Amobarbitalum; Pentymalnatrium; Sodium Amobarbital; Soluble Amylobarbitone. Sodium 5-ethyl-5-isopentylbarbiturate.

Натрий Амобарбитал

$C_{11}H_{17}N_2NaO_3$ = 248.3.

CAS — 64-43-7.

ATC — N05CA02.

ATC Vet — QN05CA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US*.
Jpn includes Amobarbital Sodium for Injection.
Ph. Eur. 6.2 (Amobarbital Sodium). A white or almost white, hygroscopic, granular powder. Very soluble in carbon dioxide-free water (a small fraction may be insoluble); freely soluble in alcohol. A 10% solution in water has a pH of not more than 11.0. Store in airtight containers.
USP 31 (Amobarbital Sodium). A white, odourless, hygroscopic, friable, granular powder. Very soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. Solutions decompose on standing; decomposition is accelerated by heat. pH of a 10% solution in water is not more than 11.0. Store in airtight containers.

Incompatibility. Amobarbital may be precipitated from preparations containing amobarbital sodium, depending on the concentration and pH. Amobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Dependence and Withdrawal of Barbiturates

The development of dependence is a high risk with amobarbital and other barbiturates and may occur after regular use even in therapeutic doses for short periods. Barbiturates should not therefore be stopped abruptly, but should be withdrawn by gradual reduction of the dose over a period of days or weeks. A long-acting barbiturate such as phenobarbital may be substituted for a short- or intermediate-acting one, followed by gradual reduction of the phenobarbital dose.

Withdrawal symptoms are similar to those of alcohol withdrawal and are characterised after several hours by apprehension and weakness, followed by anxiety, headache, dizziness, irritability, tremors, nausea and vomiting, abdominal cramps, insomnia, distortion in visual perception, muscle twitching, and tachycardia. Orthostatic hypotension and convulsions may develop after a day or two, sometimes leading to status epilepticus. Hallucinations and delirium tremens may develop after several days followed by coma before the symptoms disappear or death occurs.

Adverse Effects

Drowsiness, sedation, and ataxia are the most frequent adverse effects of amobarbital and other barbiturates and are a consequence of dose-related CNS depression. Other adverse effects include respiratory depression, headache, gastrointestinal disturbances, skin reactions, confusion, and memory defects. Paradoxical excitement and irritability may occur, particularly in children, the elderly, and patients in acute pain. Hypersensitivity reactions occur rarely and include skin rashes (erythema multiforme and exfoliative dermatitis, sometimes fatal, have been reported), hepatitis and cholestasis, and photosensitivity. Blood disorders, including megaloblastic anaemia after chronic use of barbiturates, have also occurred occasionally.

Neonatal intoxication, drug dependence, and symptoms resembling vitamin-K deficiency have been reported in infants born to mothers who received barbiturates during pregnancy. Congenital malformations have been reported in children of women who took barbiturates during pregnancy, but the causal role is a matter of some debate.

Nystagmus, miosis, slurred speech, and ataxia may occur with excessive doses of barbiturates. The toxic effects of overdosage result from profound central depression and include coma, respiratory and cardiovascular depression, with hypotension and shock leading to renal failure and death. Hypothermia may occur with subsequent pyrexia on recovery. Erythematous or haemorrhagic blisters reportedly occur in about 6% of patients, but are not characteristic solely of barbiturate poisoning.

Solutions of the sodium salts of barbiturates are extremely alkaline, and necrosis has followed subcutaneous injection. Intravenous injection may be hazardous; hypotension, shock, laryngospasm, and apnoea have occurred particularly after rapid injection. Gangrene has resulted from intra-arterial injection into an extremity.

Overdosage. A detailed review of drug-induced stupor and coma, including that caused by barbiturates.[1]

1. Ashton CH, *et al*. Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; **8:** 1–59.

Treatment of Adverse Effects

After an overdose of a barbiturate, endotracheal intubation may be necessary if the patient is unconscious. Giving activated charcoal by mouth or nasogastric tube is recommended in patients who have ingested more than 10 mg/kg and present within 1 hour of ingestion; repeat doses may be necessary. Patients should be managed with intensive supportive therapy, with particular attention being paid to the maintenance of cardiovascular, respiratory, and renal functions, and to the maintenance of the electrolyte balance. Charcoal haemoperfusion can be life-saving in the most severe cases and should be considered if there is no improvement after 24 hours of supportive care. The value of other measures aimed at the active removal of barbiturates is questionable.

Precautions

Amobarbital and other barbiturates are best avoided in elderly and debilitated patients, in young adults, in children, and in those with depression.

Amobarbital is contra-indicated in patients with pulmonary insufficiency, sleep apnoea, pre-existing CNS depression or coma, and severe hepatic impairment, and should be given with caution to those with renal impairment. Barbiturates given to patients in pain may provoke a paradoxical excitatory reaction, unless an analgesic is also given. With continued use, tolerance develops to the sedative or hypnotic effects of the barbiturates to a greater extent than to their lethal effects. Barbiturates may cause drowsiness which may persist the next day; affected patients should not drive or operate machinery.

See Adverse Effects, above, for the hazards of giving barbiturates during pregnancy and Breast Feeding, below, for cautions on their use in nursing mothers.

Dependence readily develops after use of barbiturates with a **withdrawal syndrome** if stopped abruptly (see Dependence and Withdrawal, above).

Barbiturates are abused for their euphoriant effects.

Breast feeding. Small amounts of barbiturates are distributed into breast milk, and most authorities, such as the *BNF*, consider that they should not be taken while breast feeding. The American Academy of Pediatrics notes[1] that the long-acting antiepileptic barbiturate, phenobarbital, has been associated with significant effects on some nursing infants, although it suggests that some other barbiturates may be compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Porphyria. Barbiturates including amobarbital have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Interactions

Sedation or respiratory depression may be enhanced by drugs with CNS-depressant properties; in particular alcohol should be avoided. Barbiturates generally induce liver enzymes, and thus increase the rate of metabolism (and decrease the activity) of many other drugs as well as endogenous substances. Continued use may result in induction of their own metabolism. MAOIs may prolong the CNS depressant effects of some barbiturates, probably by inhibition of their metabolism. However, MAOIs, like other antidepressants, also reduce the convulsive threshold and thereby antagonise the anticonvulsant action of barbiturates.

For some further interactions involving barbiturates, see under Phenobarbital, p.493.

Pharmacokinetics

Amobarbital is readily absorbed from the gastrointestinal tract. It is about 60% bound to plasma proteins. It has a half-life of about 20 to 25 hours which is considerably extended in neonates. It crosses the placenta and small amounts are distributed into breast milk. Amobarbital is metabolised in the liver; up to about 50% is excreted in the urine as 3′-hydroxyamylobarbital and up to about 30% as *N*-hydroxyamylobarbital, less than 1% appearing unchanged; up to about 5% is excreted in the faeces.

Uses and Administration

Amobarbital is a barbiturate that has been used as a hypnotic and sedative. Its use can no longer be recommended because of its adverse effects and risk of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p.957) in patients already taking it. The usual oral dose was 100 to 200 mg of the base or 60 to 200 mg of the sodium salt, taken at bedtime. A more rapid onset of effect was obtained with the sodium salt.

Barbiturates with a longer action such as phenobarbital (p.492) are still used in epilepsy and those with a shorter action such as methohexital (p.1788) or thiopental (p.1795) for anaesthesia.

Cerebrovascular disorders. For reference to the use of barbiturate-induced coma in the management of patients with cerebral ischaemia, see p.1796.

Epilepsy. Amobarbital is used for specialised procedures in expert epilepsy centres only. It is given by deep intramuscular or slow intravenous injection as the sodium salt.

Preparations

USP 31: Amobarbital Sodium for Injection; Secobarbital Sodium and Amobarbital Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Amytal†; Neur-Amyl†; ***Canad.:*** Amytal†; ***Hung.:*** Dorlotyn†; ***UK:*** Amytal; ***USA:*** Amytal.
Multi-ingredient: ***Arg.:*** Cuait N; ***Hung.:*** Tardyl†; ***S.Afr.:*** Repasma; ***Thai.:*** Ama; ***UK:*** Tuinal; ***USA:*** Tuinal.

Amperozide *(BAN, rINN)*

Amperozida; Ampérozide; Amperozidum; FG-5606. 4-[4,4-Bis(4-fluorophenyl)butyl]-*N*-ethylpiperazine-1-carboxamide.
Амперозид
$C_{23}H_{29}F_2N_3O = 401.5.$
CAS — 75558-90-6 (amperozide); 75529-73-6 (amperozide hydrochloride).
ATC Vet — QN05AX90.

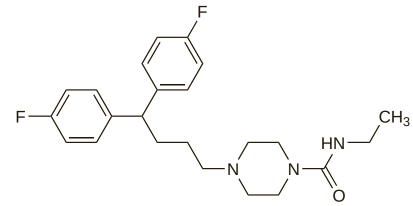

Profile

Amperozide is an antipsychotic that has been used in veterinary medicine.

Aripiprazole *(BAN, USAN, rINN)*

Aripiprazol; Aripiprazolum; OPC-31; OPC-14597. 7-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1*H*)-one.
Арипипразол
$C_{23}H_{27}Cl_2N_3O_2 = 448.4.$
CAS — 129722-12-9.
ATC — N05AX12.
ATC Vet — QN05AX12.

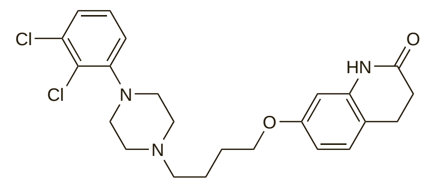

Adverse Effects, Treatment, and Precautions

Although aripiprazole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Common adverse effects with aripiprazole include gastrointestinal disorders such as constipation, dyspepsia, nausea, and vomiting, headache, anxiety, insomnia, lightheadedness, and drowsiness. Weight gain has been reported; however, this appears to be slight. The incidence of extrapyramidal effects with aripiprazole is low with akathisia being most commonly reported. Tardive dyskinesia has been reported infrequently and there have been a few cases of neuroleptic malignant syndrome.

Tachycardia and orthostatic hypotension are uncommon with aripiprazole treatment; bradycardia, ventricular arrhythmias, cardiac arrest, and sudden unexplained death have been reported very rarely as have QT prolongation and torsade de pointes. Nonetheless aripiprazole should be used with caution in patients with cardiovascular or cerebrovascular disease, or in those with conditions that would predispose to hypotension.

Seizures are rare with aripiprazole but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

When aripiprazole is used as an adjunct in depression, patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373.

Aripiprazole may affect the performance of skilled tasks including driving.

◊ References.

1. Marder SR, *et al*. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res* 2003; **61:** 123–36.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class, including aripiprazole; most of the deaths appeared due to cardiovascular events or infection. See also under Risperidone, p.1024.

The manufacturer subsequently also included a warning in the licensed product information for aripiprazole about evidence of a dose-response relationship between cerebrovascular adverse events and the use of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 24/05/05)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. McQuade RD, *et al.* A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry* 2004; **65** (suppl 18): 47–56.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Overdosage. The manufacturer has reported that patients have taken estimated overdoses of up to 1080 mg of aripiprazole with no fatalities. Signs and symptoms have included nausea, vomiting, asthenia, diarrhoea, and somnolence. In one report a 27-year-old woman who ingested 330 mg of aripiprazole with cyclobenzaprine 10 mg and quetiapine 25 mg was found to be drowsy but easily rousable 50 minutes later.[1] Initial treatment consisted of oral activated charcoal; recovery was subsequently uneventful. Serum concentrations of aripiprazole and its main metabolite dehydro-aripiprazole, measured 195 minutes after ingestion, were 596 nanograms/mL and 120 nanograms/mL respectively. In another report[2] a 2⁄-year-old child vomited and became lethargic within 1 hour of taking 195 mg of aripiprazole (17.1 mg/kg). Activated charcoal was given 3 hours after ingestion but she subsequently became unconscious. However, respiratory support was not required and the child gradually regained consciousness over the next 24 hours. Symptoms of somnolence, ataxia and tremulousness resolved over 7 days. The serum concentration of aripiprazole plus dehydro-aripiprazole was found to be 1873 nanograms/mL 10 hours after ingestion.

1. Carstairs SD, Williams SR. Overdose of aripiprazole, a new type of antipsychotic. *J Emerg Med* 2005; **28:** 311–13.
2. Seifert SA. Aripiprazole (Abilify) overdose in a 2.5 year-old. *J Toxicol Clin Toxicol* 2003; **41:** 647–8.

Pregnancy. For comments on the use of some atypical antipsychotics, including aripiprazole, during pregnancy, see under Precautions of Clozapine, p.983.

Licensed product information states that aripiprazole showed possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Aripiprazole should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

The central effects of other CNS depressants including alcohol may be enhanced by aripiprazole. Aripiprazole may also enhance the effects of antihypertensive drugs. It should be used with caution in patients also receiving drugs that prolong the QT interval or cause electrolyte imbalance.

Aripiprazole is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Ketoconazole, a potent CYP3A4 inhibitor, can increase aripiprazole plasma concentrations by about 60%; licensed product information states that the dose of aripiprazole should be reduced by half when given with ketoconazole. Similarly, the dose of aripiprazole should be halved when given with quinidine, a potent inhibitor of CYP2D6. Conversely, plasma concentrations of aripiprazole may decrease by about 70% when given with carbamazepine, a potent CYP3A4 inducer; the dose of aripiprazole should be doubled if carbamazepine is added to aripiprazole treatment. Similar effects may occur with other potent inhibitors or inducers of these isoenzymes and a reduced or increased dose of aripiprazole, respectively, in such combinations is recommended.

Antiepileptics. For a report of Stevens-Johnson syndrome occurring on use of aripiprazole with *lamotrigine*, see p.486.

Pharmacokinetics

Aripiprazole is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations reached in about 3 to 5 hours. Following intramuscular injection, peak plasma concentrations are reached between 1 to 3 hours. The absolute bioavailability is reported to be 87% with tablet formulations and 100% with the intramuscular injection; it is widely distributed. Aripiprazole is metabolised mainly in the liver and pathways involved include dehydrogenation and hydroxylation, via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and *N*-dealkylation, via CYP3A4. The major metabolite, dehydro-aripiprazole, is also active and represents about 40% of the plasma levels of aripiprazole. The mean elimination half-lives of aripiprazole and dehydro-aripiprazole are about 75 and 95 hours, respectively; in a minority of poor metabolisers the half-life of aripiprazole may be extended to about 146 hours. Protein binding of aripiprazole and its major metabolite is about 99%, mainly to albumin. Elimination is mostly in the faeces (about 55%), with about 25% of a dose appearing in the urine, mainly in the form of metabolites. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

◊ References.

1. Mallikaarjun S, *et al.* Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol* 2004; **44:** 179–87.

Uses and Administration

Aripiprazole is an atypical antipsychotic that has serotonin 5-HT_{1A}-receptor partial agonist and 5-HT_{2A}-receptor antagonist properties as well as being a partial agonist at dopamine D_2 receptors. It is used in the management of schizophrenia and in acute manic or mixed episodes associated with bipolar disorder. Aripiprazole is also used as an adjunct in the treatment of depression.

For the treatment of **schizophrenia**, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The usual maintenance dose is 15 mg once daily although the dose may be adjusted at intervals of not less than 2 weeks up to a maximum of 30 mg daily.

Aripiprazole is also used for the treatment of **mania** associated with bipolar disorder. In the USA, it is given in an initial oral dose of 30 mg once daily, this may subsequently be decreased to 15 mg once daily according to tolerance. Similar doses are licensed in the UK although licensed product information recommends an initial dose of 15 mg once daily.

Aripiprazole may be given by deep intramuscular injection for acute agitation in patients with schizophrenia or bipolar mania. The recommended initial dose is 9.75 mg although some patients may only need 5.25 mg and others up to 15 mg. If necessary, further doses may be given after at least 2 hours, up to a maximum total daily dose of 30 mg. Patients should be switched to oral therapy as soon as possible if ongoing treatment is required.

Aripiprazole is used as adjunctive therapy in **depression**. US licensed product information recommends an initial oral dose of 2 to 5 mg once daily, which may be adjusted in increments of up to 5 mg at intervals of not less than 1 week to a maximum of 15 mg daily. The usual recommended dose is 5 to 10 mg once daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, above for further details.

For details of uses and associated doses in children, see below.

Administration in children. In the USA, aripiprazole may be used for the treatment of schizophrenia in adolescents aged 13 to 17 years and for the treatment of acute manic or mixed episodes associated with bipolar disorder in those aged 10 to 17 years. For both indications, the recommended initial oral dose is 2 mg daily increased to 5 mg daily after 2 days and then to the target dose of 10 mg daily after another 2 days; subsequent dose increases should be made in 5-mg increments up to a total maximum dose of 30 mg daily.

Dose adjustments of aripiprazole may be necessary in patients also taking potent inhibitors or inducers of cytochrome P450 isoenzymes. See Interactions, above for further details.

Psychiatric disorders. Aripiprazole is used in the management of *schizophrenia* (p.955) and *bipolar disorder* (p.372).[1-9] Although data are scanty, systematic reviews[8,9] have concluded that aripiprazole does not have significant advantages over other atypical and classical antipsychotics in the treatment of schizophrenia. However, it was found to have a lower risk for hyperprolactinaemia and QT interval prolongation compared with other atypical antipsychotics, and a higher risk for insomnia compared with classical antipsychotics. Aripiprazole is also used as an adjunct in the treatment of *depression*.[10,11]

1. McGavin JK, Goa KL. Aripiprazole. *CNS Drugs* 2002; **16:** 779–86.
2. Goodnick PJ, Jerry JM. Aripiprazole: profile on efficacy and safety. *Expert Opin Pharmacother* 2002; **3:** 1773–81.
3. Taylor DM. Aripiprazole: a review of its pharmacology and clinical use. *Int J Clin Pract* 2003; **57:** 49–54.
4. Keck PE, McElroy SL. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. *Expert Opin Invest Drugs* 2003; **12:** 655–62.
5. Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. *Ann Pharmacother* 2003; **37:** 687–94.
6. Keck PE, *et al.* A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry* 2003; **160:** 1651–8.
7. Harrison TS, Perry CM. Aripiprazole: a review of its use in schizophrenia and schizoaffective disorder. *Drugs* 2004; **64:** 1715–36.
8. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 15/05/06).
9. Bhattacharjee J, El-Sayeh HGG. Aripiprazole versus typicals for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/04/08).
10. Berman RM, *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007; **68:** 843–53.
11. Marcus RN, *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008; **28:** 156–65.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Arlemide; Groven; Irazem; Siblix; ***Austral.:*** Abilify; ***Belg.:*** Abilify; ***Braz.:*** Abilify; ***Chile:*** Abilify; Azymol; Viza; ***Cz.:*** Abilify; ***Denm.:*** Abilify; ***Fin.:*** Abilify; ***Fr.:*** Abilify; ***Ger.:*** Abilify; ***Gr.:*** Abilify; ***Hong Kong:*** Abilify; ***Hung.:*** Abilify; ***India:*** Real One; ***Indon.:*** Abilify; ***Irl.:*** Abilify; ***Ital.:*** Abilify; ***Malaysia:*** Abilify; ***Mex.:*** Abilify; ***Neth.:*** Abilify; ***Norw.:*** Abilify; ***NZ:*** Abilify; ***Philipp.:*** Abilify; ***Port.:*** Abilify; ***S.Afr.:*** Abilify; ***Singapore:*** Abilify; ***Spain:*** Abilify; ***Swed.:*** Abilify; ***Switz.:*** Abilify; ***Thai.:*** Abilify; ***UK:*** Abilify; ***USA:*** Abilify; ***Venez.:*** Abilify.

Avizafone *(BAN, rINN)*

Avizafona; Avizafonum; Prodiazepam; Ro-03-7355; Ro-03-7355/000; Ro-03-7355/002 (avizafone hydrochloride). L-Lysyl-(2′-benzoyl-4′-chloro-*N*′-methyl)glycinanilide.

Авизафон

$C_{22}H_{27}ClN_4O_3$ = 430.9.

CAS — 65617-86-9 (avizafone); 60067-16-5 (avizafone hydrochloride).

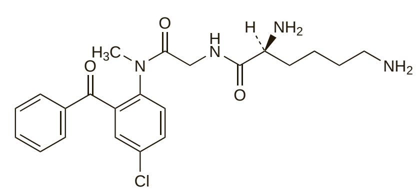

Profile

Avizafone is rapidly metabolised in the body to diazepam (p.986) and is included as the anticonvulsant component of an intramuscular injection used by military personnel as an antidote to nerve agents. The usual dose of avizafone given in this preparation is 10 mg, repeated every 15 minutes if necessary up to a total dose of 30 mg.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Nerve Agent Antidote L4A1.

Azaperone *(BAN, USAN, rINN)*

Atsaperoni; Azaperon; Azaperona; Azapérone; Azaperonum; R-1929. 4′-Fluoro-4-[4-(2-pyridyl)piperazin-1-yl]butyrophenone.

Азаперон

$C_{19}H_{22}FN_3O$ = 327.4.
CAS — 1649-18-9.
ATC Vet — QN01AX91; QN05AD90.

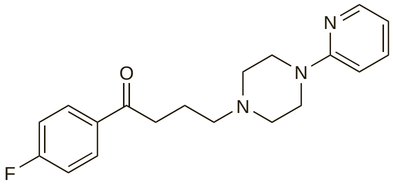

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.
Ph. Eur. 6.2 (Azaperone for Veterinary Use; Azaperone BP(Vet) 2008). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.
USP 31 (Azaperone). M.p. 92° to 95°. Protect from light.

Profile

Azaperone is a butyrophenone antipsychotic used as a tranquilliser in veterinary medicine.

Barbital *(BAN, rINN)*

Barbitaali; Barbitál; Barbitalis; Barbitalum; Barbitone; Diemalum; Diethylmalonylurea. 5,5-Diethylbarbituric acid.

Барбитал

$C_8H_{12}N_2O_3$ = 184.2.
CAS — 57-44-3.
ATC — N05CA04.
ATC Vet — QN05CA04.

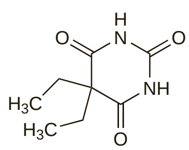

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Barbital). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; soluble in boiling water and in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Barbital Sodium *(BANM, rINN)*

Barbital de sodio; Barbital sódico; Barbital sodique; Barbital sodowy; Barbitalum Natricum; Barbitone Sodium; Diemalnatrium; Soluble Barbitone. Sodium 5,5-diethylbarbiturate.

Барбитал Натрий

$C_8H_{11}N_2NaO_3$ = 206.2.
CAS — 144-02-5.
ATC — N05CA04.
ATC Vet — QN05CA04.

Profile

Barbital is a barbiturate with general properties similar to those of amobarbital (p.961). It was formerly used for its hypnotic and sedative properties but barbiturates are no longer considered appropriate for such purposes.

Benperidol *(BAN, USAN, rINN)*

Benpéridol; Benperidoli; Benperidolis; Benperidolum; Benzperidol; CB-8089; McN-JR-4584; R-4584. 1-{1-[3-(4-Fluorobenzoyl)propyl]-4-piperidyl}benzimidazolin-2-one.

Бенперидол

$C_{22}H_{24}FN_3O_2$ = 381.4.
CAS — 2062-84-2.
ATC — N05AD07.
ATC Vet — QN05AD07.

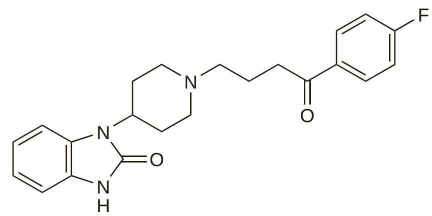

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Benperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Benperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000). Doses of 0.25 to 1.5 mg daily in divided doses are given orally in the management of deviant sexual behaviour. Elderly or debilitated patients may require reduced doses and half the usual dose may be sufficient.

In some countries benperidol is given by mouth or parenterally for the treatment of psychotic conditions (p.954).

Deviant sexual behaviour. Results of a double-blind placebo-controlled crossover study found no difference between the effect of benperidol 1.25 mg daily, chlorpromazine 125 mg daily, or placebo on sexual drive and arousal in 12 paedophilic sexual offenders, except for a lower frequency of sexual thoughts with benperidol.[1] The effects of benperidol are unlikely to be sufficient to control severe forms of antisocial sexually deviant behaviour. The management of deviant sexual behaviour is discussed under Disturbed Behaviour on p.954.

1. Tennent G, *et al*. The control of deviant sexual behaviour by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. *Arch Sex Behav* 1974; **3:** 261–71.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Frenactil; ***Ger.:*** Glianimon; ***Gr.:*** Glianimon; ***Irl.:*** Anquil†; ***Neth.:*** Frenactil; ***UK:*** Anquil; Benquil†.

Bentazepam *(USAN, rINN)*

Bentazépam; Bentazepamum; CI-718; QM-6008. 1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-e]-1,4-diazepin-2-one.

Бентазепам

$C_{17}H_{16}N_2OS$ = 296.4.
CAS — 29462-18-8.

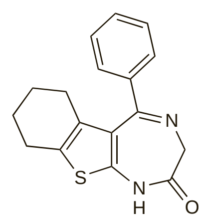

Profile

Bentazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given, in usual oral doses of 25 mg every 8 hours, in the short-term treatment of anxiety disorders; it has also been used in insomnia.

Effects on the liver. Severe chronic active hepatitis has been reported in a 65-year-old man who had received long-term treatment with bentazepam.[1]

1. Andrade RJ, *et al*. Bentazepam-associated chronic liver disease. *Lancet* 1994; **343:** 860.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Tiadipona.

Blonanserin *(rINN)*

AD-5423; Blonanserina; Blonansérine; Blonanserinum. 2-(4-Ethyl-1-piperazinyl)-4-(*p*-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclo-octa[*b*]pyridine.

Блонансерин

$C_{23}H_{30}FN_3$ = 367.5.
CAS — 132810-10-7.

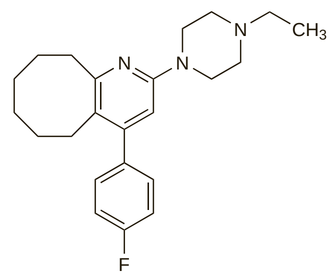

Profile

Blonanserin is an antipsychotic reported to be an antagonist at dopamine D_2 and serotonin ($5\text{-}HT_2$) receptors. It is given orally for the treatment of schizophrenia in an initial dose of 4 mg twice daily, increased gradually according to response thereafter. The usual maintenance dose is 8 to 16 mg daily; the maximum daily dose is 24 mg.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lonasen.

Brallobarbital *(rINN)*

Brallobarbitaali; Brallobarbitalum; Bralobarbital; UCB-5033. 5-Allyl-5-(2-bromoallyl)barbituric acid.

Браллобарбитал

$C_{10}H_{11}BrN_2O_3$ = 287.1.
CAS — 561-86-4.

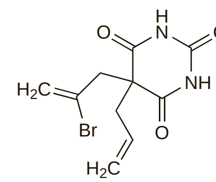

Profile

Brallobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used in preparations for the management of insomnia but barbiturates are no longer considered appropriate for such purposes. Brallobarbital calcium has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Port.:*** Vesparax†.

Bromazepam *(BAN, USAN, rINN)*

Bromatsepaami; Brómazepám; Bromazépam; Bromazepamas; Bromazepamum; Ro-5-3350. 7-Bromo-1,3-dihydro-5-(2-pyridyl)-1,4-benzodiazepin-2-one.

Бромазепам

$C_{14}H_{10}BrN_3O$ = 316.2.
CAS — 1812-30-2.
ATC — N05BA08.
ATC Vet — QN05BA08.

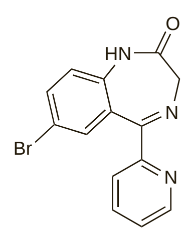

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Bromazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble or sparingly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Bromazepam is a benzodiazepine with general properties similar to those of diazepam (p.992). It has been used in the short-term treatment of anxiety disorders (p.952) occurring alone or associated with insomnia. A usual initial oral dose for anxiety is 6 to 18 mg daily in divided doses. Higher doses up to 60 mg daily have occasionally been given. Initial doses for elderly and debilitated patients should not exceed 3 mg daily in divided doses.

◊ References.

1. Kaplan SA, *et al.* Biopharmaceutical and clinical pharmacokinetic profile of bromazepam. *J Pharmacokinet Biopharm* 1976; **4:** 1–16.
2. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
3. Erb T, *et al.* Preoperative anxiolysis with minimal sedation in elderly patients: bromazepam or clorazepate-dipotassium? *Acta Anaesthesiol Scand* 1998; **42:** 97–101.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Angular†; Atemperator; Benedorm; Bromatanil; Butecam; Creosedin; Equisedin; Estomina; Fabozepam; Finaten; Gasmol; Lexotanil; Molival†; Neurozepam; Nulastres; Octanyl; Sedatus†; Sipcar; Tritopan; ***Austral.:*** Lexotan; ***Austria:*** Lexotanil; ***Belg.:*** Bromatop; Bromidem; Docbromaze; Kelalexan; Lexotan; ***Braz.:*** Bromazepan†; Bromoxon; Brozepax†; Deptran†; Lexotan; Lezepan; Nervium; Neurilan; Novazepam†; Relaxil; Somalium; Uni Bromazepax; ***Canad.:*** Lectopam; ***Chile:*** Lexotanil; Totasedan; ***Cz.:*** Lexaurin; ***Denm.:*** Bromam; Lexotan; ***Fr.:*** Anxyrex†; Lexomil; Quietiline; ***Ger.:*** BromaLich†; Bromaz†; Bromazanil; Bromazep; durazanil; Gityl; Lexostad; Lexotanil; neo OPT; Normoc; ***Gr.:*** Anconevron†; Evagelin; Lexotanil; Libronil-R; Notorium; Pascalium; ***Hong Kong:*** Akamon; Lexilium; Lexotan; ***Indon.:*** Lexotan; ***Irl.:*** Lexotan; ***Israel:*** Lenitin; ***Ital.:*** Brixopan; Compendium; Lexotan; ***Malaysia:*** Akamon; Lexotan; ***Mex.:*** Bropamil†; Lexotan; Otedram; ***Neth.:*** Lexotanil; ***Philipp.:*** Lexotan; ***Pol.:*** Lexotan; Sedam; ***Port.:*** Bromalex; Lexotan; Ultramidol; ***S.Afr.:*** Brazepam; Bromaze; Lexotan; ***Singapore:*** Lexotan; ***Spain:*** Lexatin; ***Switz.:*** Lexotanil; ***Thai.:*** Lexotan; ***Venez.:*** Lexotanil; Nervan.

Multi-ingredient: *Arg.:* Biorgan B; Colixane B; Debridat B; Eudon; Eumotil-T; Faradil Novo; Fenatrop-A; Miopropan-T; Somasedan; Vegestabil Digest; Veralipral T; ***Braz.:*** Bromopirin; Sulpan; ***Ital.:*** Lexil.

Bromisoval *(rINN)*

Bromisovaali; Bromisovalerylurea; Bromisovalum; Bromsoval; Bromvalerylurea; Bromvaletone; Bromylum. *N*-(2-Bromo-3-methylbutyryl)urea.

Бромизовал

$C_6H_{11}BrN_2O_2$ = 223.1.

CAS — 496-67-3.

ATC — N05CM03.

ATC Vet — QN05CM03.

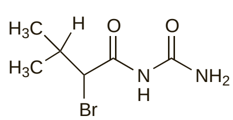

Pharmacopoeias. In *Jpn.*

Profile

Bromisoval has actions and uses similar to those of carbromal (p.967) but the use of bromides is generally deprecated.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Pol.:* Milocardin.

Bromperidol *(BAN, USAN, rINN)*

Bromiperidoli; Brómperidol; Brompéridol; Bromperidoli; Bromperidolis; Bromperidolum; R-11333. 4-[4-(*p*-Bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

Бромперидол

$C_{21}H_{23}BrFNO_2$ = 420.3.

CAS — 10457-90-6.

ATC — N05AD06.

ATC Vet — QN05AD06.

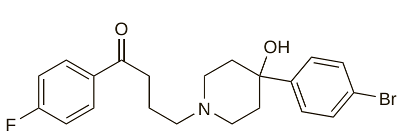

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Bromperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

Bromperidol Decanoate *(BANM, USAN, rINNM)*

Brompéridol, décanoate de; Bromperidoldekanoat; Brómperidol-dekanoát; Bromperidol-dekanoát; Bromperidoli decanoas; Bromperidolidekanoaatti; Bromperidolio dekanoatas; Decanoato de bromperidol; R-46541.

Бромперидола Деканоат

$C_{31}H_{41}BrFNO_3$ = 574.6.

CAS — 75067-66-2.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Bromperidol Decanoate). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane. It melts at about 60°. Store at a temperature below 25°. Protect from light.

Profile

Bromperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000). It is given in the treatment of schizophrenia (p.955) and other psychoses. Some bromperidol preparations are prepared with the aid of lactic acid and may be stated to contain bromperidol lactate. However, doses are expressed in terms of the equivalent amount of bromperidol. A usual oral dose is 1 to 15 mg daily, although up to 50 mg daily has been given. Elderly patients may require reduced doses of bromperidol. Bromperidol has also been given by intramuscular or intravenous injection.

The long-acting decanoate ester may be used for patients requiring long-term therapy with bromperidol. Doses are expressed in terms of the base; bromperidol decanoate 68.4 mg is equivalent to about 50 mg of bromperidol. Doses equivalent to up to 300 mg of bromperidol every 4 weeks have been given by deep intramuscular injection.

◊ References.

1. Benfield P, *et al.* Bromperidol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in psychoses. *Drugs* 1988; **35:** 670–84.

Schizophrenia. A systematic review[1] suggested that depot bromperidol had some benefits in schizophrenia but was less effective than depot haloperidol or fluphenazine.

1. Wong D, *et al.* Depot bromperidol decanoate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bromodol; Erodium; ***Belg.:*** Impromen; ***Ger.:*** Impromen; Tesoprel; ***Ital.:*** Impromen; ***Neth.:*** Impromen; ***Port.:*** Impromen†; ***Thai.:*** Brofed; Impromen†.

Brotizolam *(BAN, USAN, rINN)*

Brotitsolaami; Brotizolamum; Brotyzolam; We-941; We-941-BS. 2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.

Бротизолам

$C_{15}H_{10}BrClN_4S$ = 393.7.

CAS — 57801-81-7.

ATC — N05CD09.

ATC Vet — QN05CD09.

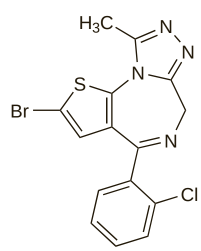

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Brotizolam). A white or yellowish powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble or slightly soluble in methyl alcohol.

Profile

Brotizolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.986). It is given for the short-term (up to 2 weeks) management of insomnia (p.957) in usual oral doses of 250 micrograms at night. The suggested dose for elderly and debilitated patients is 125 micrograms.

Abuse. Reference to abuse of brotizolam in Germany and Hong Kong.[1]

1. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.

Pharmacokinetics. References.

1. Bechtel WD. Pharmacokinetics and metabolism of brotizolam in humans. *Br J Clin Pharmacol* 1983; **16:** 279S–283S.
2. Jochemsen R, *et al.* Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. *Br J Clin Pharmacol* 1983; **16:** 285S–290S.
3. Tokairin T, *et al.* Inhibition of the metabolism of brotizolam by erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; **60:** 172–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Lendorm; ***Belg.:*** Lendormin; ***Chile:*** Dormex; Noctilan; ***Denm.:*** Lendorm†; ***Ger.:*** Lendormin; ***Hung.:*** Lendormin; ***Israel:*** Bondormin; ***Ital.:*** Lendormin; Nimbisan; ***Jpn:*** Lendormin; ***Mex.:*** Lindormin; ***Neth.:*** Lendormin; ***Port.:*** Lendormin; ***S.Afr.:*** Lendormin; ***Spain:*** Sintonal; ***Switz.:*** Lendormine†; ***Venez.:*** Lendormin.

Buspirone Hydrochloride

(BANM, USAN, rINNM)

Buspiron Hidroklorür; Buspirone, chlorhydrate de; Buspironhydrochlorid; Buspironhydroklorid; Buspironi hydrochloridum; Buspironihydrokloridi; Buspironu chlorowodorek; Hidrocloruro de buspirona; MJ-9022-1. 8-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)-butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

Буспирона Гидрохлорид

$C_{21}H_{31}N_5O_2$,HCl = 422.0.

CAS — 36505-84-7 (buspirone); 33386-08-2 (buspirone hydrochloride).

ATC — N05BE01.

ATC Vet — QN05BE01.

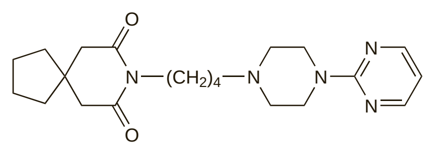

(buspirone)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Buspirone Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 31 (Buspirone Hydrochloride). A white crystalline powder. Very soluble in water; sparingly soluble in alcohol and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol; very slightly soluble in ethyl acetate; practically insoluble in hexanes. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Dependence and Adverse Effects

Dizziness, nausea, headache, nervousness, light-headedness, excitement, paraesthesias, sleep disturbances, chest pain, tinnitus, sore throat, and nasal congestion are amongst the most frequent adverse effects reported after the use of buspirone hydrochloride. Other adverse effects have included tachycardia, palpitations, drowsiness, confusion, seizures, dry mouth, fatigue, and sweating. A syndrome of restlessness appearing shortly after the start of treatment has been reported in a small number of patients given buspirone. Buspirone is reported to produce less sedation, and to have a lower potential for dependence, than the benzodiazepines.

Effects on the nervous system. Mild acute hypertension and panic were reported on two occasions after the addition of single 10-mg doses of buspirone to therapy with tricyclic antidepressants in a 40-year-old man with panic disorder. Adrenergic or serotonin dysfunction were postulated as possible mechanisms for the reaction.[1,2] Psychotic reactions associated with buspirone treatment have also been reported in a few patients.[3] There have also been isolated reports of mania,[4] and seizures have been reported, primarily in overdosage.[5]

1. Chignon JM, Lepine JP. Panic and hypertension associated with single dose of buspirone. *Lancet* 1989; **ii:** 46–7.
2. Norman TR, Judd FK. Panic attacks, buspirone, and serotonin function. *Lancet* 1989; **ii:** 615.
3. Friedman R. Possible induction of psychosis by buspirone. *Am J Psychiatry* 1991; **148:** 1606.
4. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol* 1989; **9:** 150–1.
5. Catalano G, *et al.* Seizures associated with buspirone overdose: case report and literature review. *Clin Neuropharmacol* 1998; **21:** 347–50.

EXTRAPYRAMIDAL DISORDERS. There have been isolated reports of exacerbation or precipitation of movement disorders[1-4] associated with the use of buspirone. However, buspirone has also been reported to have been of benefit in some patients with tardive dyskinesia (see Extrapyramidal Disorders under Uses and Administration, below).

1. Hammerstad JP, *et al.* Buspirone in Parkinson's disease. *Clin Neuropharmacol* 1986; **9:** 556–60.

2. Ritchie EC, *et al.* Acute generalized myoclonus following buspirone administration. *J Clin Psychiatry* 1988; **49:** 242–3.
3. Strauss A. Oral dyskinesia associated with buspirone use in an elderly woman. *J Clin Psychiatry* 1988; **49:** 322–3.
4. LeWitt PA, *et al.* Persistent movement disorders induced by buspirone. *Mov Disord* 1993; **8:** 331–4.

Precautions

Buspirone hydrochloride should be used with caution in patients with renal or hepatic impairment and is contra-indicated if the impairment is severe. It should not be used in patients with epilepsy or a history of such disorders. It does not exhibit cross-tolerance with benzodiazepines or other common sedatives or hypnotics and will not block symptoms of their withdrawal; they should, therefore, be gradually withdrawn before starting treatment with buspirone. Buspirone may impair the patient's ability to drive or operate machinery.

Diagnosis and testing. Buspirone may interfere with diagnostic assays of urinary catecholamines.[1]

1. Cook FJ, *et al.* Effect of buspirone on urinary catecholamine assays. *N Engl J Med* 1995; **332:** 401.

Hepatic impairment. Caution has been advised when using buspirone in patients with liver disease. The mean peak plasma-buspirone concentration after an oral dose was about 16 times higher in cirrhotic patients than in controls[1] and the elimination half-life was prolonged about twofold. A secondary peak concentration was seen in some subjects, occurring between 4 and 24 hours after a dose in the cirrhotics and after between 2 and 8 hours in controls. Data from a multiple-dose study[2] suggested that there was accumulation of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine in hepatic impairment, but that plasma concentrations appeared to reach steady state after 3 days regardless of the state of liver function. The area under the curve and mean peak concentration for buspirone were both higher in patients with hepatic impairment than in healthy subjects, but there were no significant differences for its metabolites. Specific dosing recommendations could not be made for patients with hepatic impairment because of the high intra- and inter-subject variations in plasma-buspirone concentrations.

1. Dalhoff K, *et al.* Buspirone pharmacokinetics in patients with cirrhosis. *Br J Clin Pharmacol* 1987; **24:** 547–50.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Pregnancy and breast feeding. In some *animal* studies, large doses of buspirone during pregnancy had adverse effects on survival and on birth and weanling weight. Recommendations in licensed product information for use during pregnancy or breast feeding vary from avoid, if possible, to contra-indicated.

Renal impairment. Caution has been advised when giving buspirone to patients with renal impairment.[1,2] There is evidence of accumulation of buspirone and its metabolite after repeated doses but plasma concentrations appeared to reach steady state after 3 days regardless of the degree of renal function. At steady state both the area under the curve and maximum concentrations for buspirone and its metabolite were greater in patients with renal failure than in healthy subjects. The metabolite, but not the parent drug, was removed by haemodialysis. Specific dosing recommendations could not be made for patients with renal impairment because of the high intra- and inter-subject variations in buspirone plasma concentrations on repeated dosage.

1. Caccia S, *et al.* Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. *Clin Pharmacokinet* 1988; **14:** 171–7.
2. Barbhaiya RH, *et al.* Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. *Eur J Clin Pharmacol* 1994; **46:** 41–7.

Interactions

The sedative effects of buspirone may be enhanced if taken with alcohol or other CNS depressants. Because of reports of increased blood pressure in patients receiving buspirone hydrochloride with an MAOI, licensed product information for buspirone recommends that it should not be given with an MAOI.

The metabolism of buspirone is mediated by the cytochrome P450 isoenzyme CYP3A4 and therefore there is the potential for interactions between buspirone and other drugs that inhibit or act as a substrate for this isoenzyme. The dose of buspirone may need to be reduced if given at the same time as potent inhibitors of CYP3A4. Plasma concentrations of buspirone may be reduced by enzyme-inducing drugs such as rifampicin.

Antibacterials. Pretreatment with *erythromycin* in healthy subjects given buspirone resulted in mild to moderate adverse effects associated with increased plasma concentrations of buspirone.[1]

Pretreatment with *rifampicin* greatly reduced plasma concentrations of buspirone in healthy subjects.[2] A reduced anxiolytic effect could be expected if buspirone is used with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4.

1. Kivistö KT, *et al.* Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; **62:** 348–54.
2. Lamberg TS, *et al.* Concentrations and effects of buspirone are considerably reduced by rifampicin. *Br J Clin Pharmacol* 1998; **45:** 381–5.

Antidepressants. Use of buspirone with *nefazodone* can raise plasma concentrations of buspirone. US licensed product information for nefazodone recommends that the initial dose of buspirone be lowered (e.g. 2.5 mg daily) and subsequent dose adjustments of either drug should be based on clinical assessment. A possible serotonin syndrome (p.416) has been reported[1] in a patient using buspirone with *fluoxetine*.

1. Manos GH. Possible serotonin syndrome associated with buspirone added to fluoxetine. *Ann Pharmacother* 2000; **34:** 871–4.

Antifungals. Pretreatment with *itraconazole* in healthy subjects given buspirone resulted in mild to moderate adverse effects associated with increased plasma concentrations of buspirone.[1]

1. Kivistö KT, *et al.* Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; **62:** 348–54.

Antipsychotics. For the effect of buspirone on serum concentrations of *haloperidol*, see under Chlorpromazine, p.974. For a report of potentially fatal gastrointestinal bleeding and marked hyperglycaemia after use of buspirone with *clozapine*, see under Clozapine, p.984.

Antivirals. Parkinson-like symptoms developed in a 54-year-old man taking a drug regimen that included buspirone, *indinavir*, and *ritonavir*.[1] It was suspected that ritonavir inhibited the metabolism of buspirone, which is mediated by the cytochrome P450 isoenzyme CYP3A4, leading to increased plasma concentrations of the latter. The inhibitory effect of indinavir on CYP3A4 was considered to be less than that of ritonavir. Symptoms resolved after a change in antiviral regimen and reduction in the dose of buspirone.

1. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. *Ann Pharmacother* 2003; **37:** 202–5.

Calcium-channel blockers. Increases in buspirone plasma concentrations have been seen in healthy subjects pretreated with *diltiazem* or *verapamil*.[1]

1. Lamberg TS, *et al.* Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. *Clin Pharmacol Ther* 1998; **63:** 640–5.

Grapefruit juice. Grapefruit juice increased the plasma concentrations of buspirone in healthy subjects.[1]

1. Lilja JJ, *et al.* Grapefruit juice substantially increases plasma concentrations of buspirone. *Clin Pharmacol Ther* 1998; **64:** 655–60.

Pharmacokinetics

Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 40 to 90 minutes after an oral dose. Systemic bioavailability is low because of extensive first-pass metabolism, but may be increased if given with food as this delays absorption from the gastrointestinal tract and thereby reduces presystemic clearance. Buspirone is about 95% bound to plasma proteins. Metabolism in the liver is extensive via the cytochrome P450 isoenzyme CYP3A4; hydroxylation yields several inactive metabolites and oxidative dealkylation produces 1-(2-pyrimidinyl)-piperazine, which is reported to be about 25% as potent as the parent drug in one model of anxiolytic activity. The elimination half-life of buspirone is usually about 2 to 4 hours but half-lives of up to 11 hours have been reported. Buspirone is excreted mainly as metabolites in the urine, and also in the faeces.

◊ References.

1. Mahmood I, Sahajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet* 1999; **36:** 277–87.

Uses and Administration

Buspirone hydrochloride is an azaspirodecanedione (azapirone) anxiolytic. It is reported to be largely lacking in sedative, anticonvulsant, and muscle relaxant actions.

Buspirone hydrochloride is given, in initial oral doses of 5 mg two or three times daily, in the short-term management of anxiety disorders. The dose may be increased in increments of 5 mg at 2- to 3-day intervals if required. The recommended maximum daily dose, to be given in divided doses, is 45 mg in the UK and 60 mg in the USA.

◊ General reviews.

1. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; **7:** 68–88.
2. Apter JT, Allen LA. Buspirone: future directions. *J Clin Psychopharmacol* 1999; **19:** 86–93.

Action. Buspirone has dopaminergic, noradrenergic, and serotonin-modulating properties[1] and its anxiolytic effects appear to be related to its action on serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. Buspirone, and the related drugs gepirone (p.999) and ipsapirone (p.1002), are partial agonists at 5-HT_{1A} receptors.[1,2] While such drugs may inhibit serotonin neurotransmission (most likely via 5-HT_{1A} autoreceptor stimulation), they may also have postsynaptic 5-HT_{1A} agonist activity and thus facilitate serotonin neurotransmission.[1] To complicate matters further, 5-HT_{1A} partial agonists have shown both anxiolytic and anxiogenic properties in *animal* models of anxiety. Clinical studies have, however, shown that buspirone is effective in the treatment of generalised anxiety.[1,2]

Clinical studies with buspirone and gepirone suggest that 5-HT_{1A} partial agonists may be useful in the treatment of depression, possibly by downregulation of either 5-HT_{1A} or 5-HT_2 receptors or both.[1] There is some suggestion that buspirone has an anti-aggressive action in humans; it is unclear whether this is mediated via dopaminergic or serotonergic mechanisms.

Buspirone also has characteristics of both a dopamine agonist and antagonist; this may result in stimulation of both growth hormone and prolactin secretion.[3]

1. Glitz DA, Pohl R. 5-HT partial agonists: what is their future? *Drugs* 1991; **41:** 11–18.
2. Marsden CA. The pharmacology of new anxiolytics acting on 5-HT neurones. *Postgrad Med J* 1990; **66** (suppl 2): S2–S6.
3. Meltzer HY, *et al.* The effect of buspirone on prolactin and growth hormone secretion in man. *Arch Gen Psychiatry* 1983; **40:** 1099–1102.

Administration in hepatic or renal impairment. For cautions on the use of buspirone in patients with impaired liver or kidney function see under Precautions, above.

Anxiety disorders. Buspirone has been shown to be as effective as the benzodiazepines in the short-term treatment of generalised anxiety disorder (p.952) and to be less likely to cause sedation or psychomotor and cognitive impairment. It also appears to have a lower propensity for interaction with alcohol and a lower risk of abuse and dependence. However, its usefulness may be limited by a relatively slow response to treatment, which may take up to 2 to 4 weeks to appear. Its efficacy may be reduced in patients who have recently taken benzodiazepines. It appears to be ineffective in panic disorder and convincing evidence of efficacy in other anxiety disorders is lacking.

References.

1. Deakin JFW. A review of clinical efficacy of 5-HT agonists in anxiety and depression. *J Psychopharmacol* 1993; **7:** 283–9.
2. Pecknold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Safety* 1997; **16:** 118–32.
3. Fulton B, Brogden RN. Buspirone: an updated review of its clinical pharmacology and therapeutic applications. *CNS Drugs* 1997; **7:** 68–88.
4. Chessick CA, *et al.* Azapirones for generalized anxiety disorder. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/04/08).

Bruxism. SSRI-induced bruxism has been successfully controlled by adjunctive therapy with buspirone.[1,2]

1. Romanelli F, *et al.* Possible paroxetine-induced bruxism. *Ann Pharmacother* 1996; **30:** 1246–7.
2. Bostwick JM, Jaffee MS. Buspirone as an antidote to SSRI-induced bruxism in 4 cases. *J Clin Psychiatry* 1999; **60:** 857–60.

Cerebellar ataxias. In general the management of cerebellar ataxias is mainly supportive; buspirone improved some symptoms of ataxia in a small study of patients with cerebellar cortical activity.[1]

1. Trouillas P, *et al.* Buspirone, a 5-hydroxytryptamine agonist, is active in cerebellar ataxia: results of a double-blind drug placebo study in patients with cerebellar cortical atrophy. *Arch Neurol* 1997; **54:** 749–52.

Depression. Buspirone has been investigated for augmentation of therapy with antidepressants with serotonin reuptake inhibiting activity in patients with refractory depression (p.373), but results have been variable.

References.

1. Fischer P, *et al.* Weak antidepressant response after buspirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *Int Clin Psychopharmacol* 1998; **13:** 83–6.
2. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol* 1998; **18:** 465–9.
3. Landen M, *et al.* A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 1998; **59:** 664–8.
4. Appelberg BG, *et al.* Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001; **62:** 448–52.
5. Önder E, Tural Ü. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. *J Affect Disord* 2003; **76:** 223–7.

Disturbed behaviour. Buspirone has been tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see Disturbed Behaviour, p.954) but evidence of efficacy is limited. Nonetheless, in the management of dementia, some[1] consider that it might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant or unresponsive to antipsychotics.

1. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)

Extrapyramidal disorders. Although there have been reports[1,2] that buspirone may improve symptoms of drug-induced dyskinesia (p.971), drugs with dopaminergic actions have mostly exacerbated symptoms and there are a few reports of extrapyramidal disorders with buspirone (see under Adverse Effects, above).

1. Moss LE, *et al.* Buspirone in the treatment of tardive dyskinesia. *J Clin Psychopharmacol* 1993; **13:** 204–9.
2. Bonifati V, *et al.* Buspirone in levodopa-induced dyskinesias. *Clin Neuropharmacol* 1994; **17:** 73–82.

Substance dependence. ***ALCOHOL.*** Despite an early study[1] suggesting that buspirone could reduce alcohol craving in alcohol dependent patients, later studies[2-4] have overall failed to confirm that buspirone improves abstinence or reduces alcohol consumption. Although some studies[4,5] have found that buspirone may improve certain psychopathological symptoms in these patients, others[2] have found no such benefit; a meta-analysis[6] of 5 studies favoured the former interpretation.

The management of alcohol withdrawal and abstinence is discussed on p.1626.

1. Bruno F. Buspirone in the treatment of alcoholic patients. *Psychopathology* 1989; **22** (suppl 1): 49–59.
2. Malcolm R, *et al.* A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcohol Clin Exp Res* 1992; **16:** 1007–13.
3. George DT, *et al.* Buspirone does not promote long term abstinence in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
4. Malec E, *et al.* Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. *Alcohol Clin Exp Res* 1996; **20:** 307–12.
5. Kranzler HR, *et al.* Buspirone treatment of anxious alcoholics: a placebo-controlled trial. *Arch Gen Psychiatry* 1994; **51:** 720–31.
6. Malec TS, *et al.* Efficacy of buspirone in alcohol dependence: a review. *Alcohol Clin Exp Res* 1996; **20:** 853–8.

NICOTINE. Buspirone has produced conflicting results[1-5] in the management of smoking cessation (p.2354). Although some studies suggest that in the short-term buspirone can increase the numbers of patients who are able to cease smoking, it does not necessarily decrease withdrawal symptoms.

1. West R, *et al.* Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. *Psychopharmacology (Berl)* 1991; **104:** 91–6.
2. Hilleman DE, *et al.* Effect of buspirone on withdrawal symptoms associated with smoking cessation. *Arch Intern Med* 1992; **152:** 350–2.
3. Hilleman DE, *et al.* Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *J Clin Pharmacol* 1994; **34:** 222–4.
4. Schneider NG, *et al.* Efficacy of buspirone in smoking cessation: a placebo-controlled trial. *Clin Pharmacol Ther* 1996; **60:** 568–75.
5. Farid P, Abate MA. Buspirone use for smoking cessation. *Ann Pharmacother* 1998; **32:** 1362–4.

OPIOIDS. Buspirone has been investigated in the management of opioid withdrawal (p.101) in dependent patients.[1,2]

1. Rose JS, *et al.* Effects of buspirone in withdrawal from opiates. *Am J Addict* 2003; **12:** 253–9.
2. Buydens-Branchey L, *et al.* Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol* 2005; **25:** 230–6.

Preparations

USP 31: Buspirone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ansial†; ***Austral.:*** Buspar; ***Austria:*** Buspar; ***Belg.:*** Buspar; ***Braz.:*** Ansienon†; Ansitec; Buspanil†; Buspar; ***Canad.:*** Buspar; Buspirex†; ***Chile:*** Paxon; ***Cz.:*** Anxiron†; Buspar†; ***Denm.:*** Buspar; Stesiron†; ***Fin.:*** Buspar; Stesiron†; ***Fr.:*** Buspar; ***Ger.:*** Anxut; Bespar; Busp; ***Gr.:*** Anchocalm; Antipsichos; Bergamol; Bespar; Boronex; Epsilat; Hiremon; Hobatstress; Komasin; Lanamont; Lebilon; Ledion; Loxapin; Nadrifor; Nervostal; Nevrorestol; Norbal; Pendium; Stressigal; Svitalark; Tendan†; Tensispes; Trafuril†; Umolit; ***Hong Kong:*** Buspar; Kalmiren; ***Hung.:*** Anxiron; Spitomin; ***India:*** Buscalm; ***Indon.:*** Tran-Q; Xiety; ***Irl.:*** Buspar; ***Israel:*** Buspirol†; Sorbon; ***Ital.:*** Axoren†; Buspar; Buspimen†; ***Mex.:*** Buspar; ***Norw.:*** Buspar; Stesiron†; ***NZ:*** Biron; Buspar; ***Pol.:*** Mabuson; Spamilan; ***Port.:*** Ansiten; Busansil; Buscalma; Buspar; Buspium; Establix†; Itagil; Psibeter; ***S.Afr.:*** Buspar; Pasrin; ***Spain:*** Buspar; Effiplen†; ***Swed.:*** Buspar; ***Switz.:*** Buspar; ***Thai.:*** Anxiolan; ***Turk.:*** Buspon; ***UK:*** Buspar; ***USA:*** Buspar; ***Venez.:*** Dalpas.

Butalbital *(USAN, rINN)*

Alisobumalum; Allylbarbital; Allylbarbituric Acid; Butalbitaali; Butalbitalum; Itobarbital; Tetrallobarbital. 5-Allyl-5-isobutylbarbituric acid.

Буталбитал

$C_{11}H_{16}N_2O_3$ = 224.3.

CAS — 77-26-9.

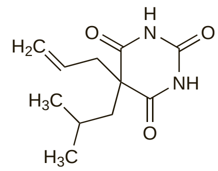

NOTE. The name Butalbital has also been applied to talbutal, the *S*-butyl analogue, which was formerly used as a hypnotic and sedative.

Compounded preparations of butalbital may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine

Pharmacopoeias. In *US.*

USP 31 (Butalbital). A white odourless crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in alcohol, in chloroform, and in ether; soluble in solutions of fixed alkalis and alkali carbonates. A saturated solution is acid to litmus.

Profile

Butalbital is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used mainly in combination preparations with analgesics in the treatment of occasional tension-type headaches, but other treatments are generally preferred.

Preparations

USP 31: Butalbital and Aspirin Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Fiorinal; Fiorinal C; ratio-Tecnal; ratio-Tecnal C; Trianal; Trianal C; ***Chile:*** Cafergot-PB†; ***Denm.:*** Gynergen Comp; ***Ital.:*** Optalidon; ***S.Afr.:*** Cafergot-PB†; ***Spain:*** Cafergot-PB†; ***Switz.:*** Cafergot-PB; ***USA:*** Amaphen with Codeine; Americet; Anolor; Ascomp with Codeine; Bupap; Butex; Dolgic; Dolgic LQ; Dolgic Plus; Endolor; Esgic; Esgic-Plus; Fioricet; Fioricet with Codeine; Fiorinal; Fiorinal with Codeine; Margesic; Marten-Tab; Medigesic; Pacaps; Phrenilin; Phrenilin w Caffeine and Codeine; Promacet; Prominol; Pyridium Plus; Repan; Repan CF†; Sedapap; Tencet; Tencon; Trellium Plus; Triad.

Butobarbital *(BAN)*

Butethal; Butobarbitaali; Butobarbitalum; Butobarbitone. 5-Butyl-5-ethylbarbituric acid.

$C_{10}H_{16}N_2O_3$ = 212.2.

CAS — 77-28-1.

ATC — N05CA03.

ATC Vet — QN05CA03.

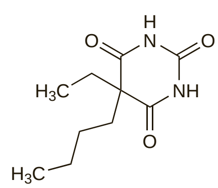

NOTE. Butobarbital should be distinguished from Butabarbital, which is Secbutabarbital (p.1027).

Dependence and Withdrawal

As for Amobarbital, p.962.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p.962.

Interactions

As for Amobarbital, p.962.

Antibacterials. The metabolism of butobarbital may be altered by *metronidazole.*[1]

1. Al Sharifi MA, *et al.* The effect of anti-amoebic drug therapy on the metabolism of butobarbitone. *J Pharm Pharmacol* 1982; **34:** 126–7.

Pharmacokinetics

Butobarbital is metabolised in the liver mainly by hydroxylation; small amounts are excreted in the urine as unchanged drug. It has been reported to have a half-life of about 40 to 55 hours and to be about 26% bound to plasma proteins.

Uses and Administration

Butobarbital is a barbiturate with general properties similar to those of amobarbital (p.962). Its use can no longer be recommended because of the risk of its adverse effects and of dependence, although continued use may occasionally be considered necessary for severe intractable insomnia (p.957) in patients already taking it. It is given in usual oral doses of 100 to 200 mg at night.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Soneryl.

Multi-ingredient: ***Cz.:*** Dinyl†; ***Fr.:*** Hypnasmine†.

Calcium Bromolactobionate

Bromolactobionato de calcio; Calcium Galactogluconate Bromide. Calcium bromide lactobionate hexahydrate.

$Ca(C_{12}H_{21}O_{12})_2,CaBr_2,6H_2O$ = 1062.6.

CAS — 33659-28-8 (anhydrous calcium bromolactobionate).

Profile

Calcium bromolactobionate has sedative properties and has been given orally in the treatment of insomnia and anxiety disorders. The use of bromides is generally deprecated.

Overdosage. Bromide intoxication has been reported[1] in a patient after overdosage with calcium bromolactobionate tablets.

1. Danel VC, *et al.* Bromide intoxication and pseudohyperchloremia. *Ann Pharmacother* 2001; **35:** 386–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Bromocalcio; Nervolta; Sedofantil; ***Cz.:*** Calabron†; ***Ital.:*** Calcibronat; ***Mex.:*** Calcibronat†; ***Mon.:*** Calcibronat; ***Venez.:*** Sedabron†.

Captodiame Hydrochloride *(BANM, pINNM)*

Captodiame, Chlorhydrate de; Captodiami Hydrochloridum; Captodiamine Hydrochloride; Hidrocloruro de captodiamo. 2-(4-Butylthiobenzhydrylthio)ethyldimethylamine hydrochloride.

Каптодиама Гидрохлорид

$C_{21}H_{29}NS_2,HCl$ = 396.1.

CAS — 486-17-9 (captodiame); 904-04-1 (captodiame hydrochloride).

ATC — N05BB02.

ATC Vet — QN05BB02.

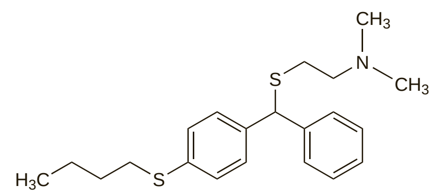

(captodiame)

Profile

Captodiame hydrochloride has been given in oral doses of 50 mg three times daily for the treatment of anxiety disorders (p.952).

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Covatine.

Carbromal *(BAN, rINN)*

Bromodiethylacetylurea; Carbromalum; Karbromaali; Karbromal. *N*-(2-Bromo-2-ethylbutyryl)urea.

Карбромал

$C_7H_{13}BrN_2O_2$ = 237.1.

CAS — 77-65-6.

ATC — N05CM04.

ATC Vet — QN05CM04.

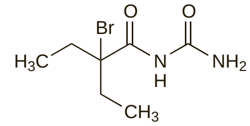

Profile

Carbromal is a bromureide with general properties similar to those of the barbiturates (see Amobarbital, p.961). It was formerly used for its hypnotic and sedative properties. Chronic use of carbromal could result in bromide accumulation and symptoms resembling bromism (see Bromides, p.2269). The use of bromides is generally deprecated.

Porphyria. Carbromal has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Hung.:*** Demalgon.

Carpipramine Hydrochloride *(rINNM)*

Carpipramine, Chlorhydrate de; Carpipramini Hydrochloridum; Hidrocloruro de carpipramina; PZ-1511. 1-[3-(10,11-Dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl]-4-piperidinopiperidine-4-carboxamide dihydrochloride monohydrate.

Карпипрамина Гидрохлорид

$C_{28}H_{38}N_4O,2HCl,H_2O$ = 537.6.
CAS — 5942-95-0 (carpipramine); 7075-03-8 (anhydrous carpipramine hydrochloride).

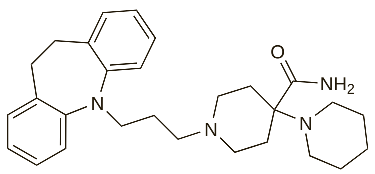

(carpipramine)

Profile

Carpipramine is structurally related both to imipramine (p.400) and to butyrophenones such as haloperidol (p.1000). It has been used in the management of anxiety disorders (p.952) and psychoses such as schizophrenia (p.955). Carpipramine is given as the hydrochloride although doses are expressed in terms of the base; carpipramine hydrochloride 60.2 mg is equivalent to about 50 mg of carpipramine. A usual oral dose is equivalent to 150 mg of the base daily in 2 or 3 divided doses, with a range of 50 to 400 mg daily.

Porphyria. Carpipramine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Prazinil.

Chlordiazepoxide *(BAN, rINN)*

Chlordiazepoksidas; Chlordiazepoxid; Chlordiazépoxide; Chlordiazepoxidum; Chlorodiazepoksyd; Clordiazepóxido; Klooridiatsepoksidi; Klordiazepoksit; Klórdiazepoxid; Klordiazepoxid; Methaminodiazepoxide. 7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide.

Хлордиазепоксид

$C_{16}H_{14}ClN_3O$ = 299.8.
CAS — 58-25-3.
ATC — N05BA02.
ATC Vet — QN05BA02.

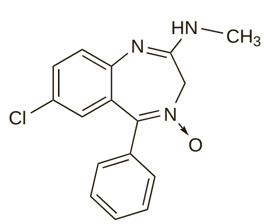

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of chlordiazepoxide: Lib.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Chlordiazepoxide). An almost white or light yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.
USP 31 (Chlordiazepoxide). A yellow, practically odourless, crystalline powder. Insoluble in water; soluble 1 in 50 of alcohol, 1 in 6250 of chloroform, and 1 in 130 of ether. Store in airtight containers. Protect from light.

Chlordiazepoxide Hydrochloride *(BANM, USAN, rINNM)*

Chlordiazepoksido hidrochloridas; Chlordiazepoksydu chlorowodorek; Chlordiazépoxide, chlorhydrate de; Chlordiazepoxid-hydrochlorid; Chlordiazepoxidi hydrochloridum; Hidrocloruro de clordiazepóxido; Klooridiatsepoksidihydrokloridi; Klordiazepoksit Hidroklorür; Klórdiazepoxid-hidroklorid; Klordiazepoxidhydroklorid; Methaminodiazepoxide Hydrochloride; NSC-115748; Ro-5-0690.

Хлордиазепоксида Гидрохлорид

$C_{16}H_{14}ClN_3O,HCl$ = 336.2.
CAS — 438-41-5.
ATC — N05BA02.
ATC Vet — QN05BA02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Chlordiazepoxide Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol. Protect from light.
USP 31 (Chlordiazepoxide Hydrochloride). A white or practically white, odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; insoluble in petroleum spirit. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 15 mg of chlordiazepoxide is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Hepatic impairment. Progressive drowsiness began after 20 days of treatment with chlordiazepoxide in a woman with cirrhosis and hepatitis.[1] One week after stopping the drug the patient could not be roused, and full consciousness was not regained for another week. Accumulation of active metabolites of chlordiazepoxide may have been responsible for the prolonged stupor.

1. Barton K, *et al.* Chlordiazepoxide metabolite accumulation in liver disease. *Med Toxicol* 1989; **4:** 73–6.

Porphyria. Chlordiazepoxide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Absorption of chlordiazepoxide is almost complete after oral doses; peak plasma concentrations are achieved after 1 to 2 hours. Absorption after intramuscular injection may be slow and erratic depending on the site of injection. Chlordiazepoxide is about 96% bound to plasma proteins. Reported values for the elimination half-life of chlordiazepoxide have ranged from about 5 to 30 hours, but its main active metabolite desmethyldiazepam (nordazepam, p.1012) has a half-life of several days. Other pharmacologically active metabolites of chlordiazepoxide include desmethylchlordiazepoxide, demoxepam, and oxazepam (p.1014). Chlordiazepoxide passes into the CSF and breast milk, and crosses the placenta. Unchanged drug and metabolites are excreted in the urine, mainly as conjugated metabolites.

◊ References.

1. Greenblatt DJ, *et al*. Clinical pharmacokinetics of chlordiazepoxide. *Clin Pharmacokinet* 1978; **3:** 381–94.

Uses and Administration

Chlordiazepoxide is a benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders (p.952) and insomnia (p.957). Chlordiazepoxide is also used in muscle spasm (p.1887), in alcohol withdrawal syndrome (p.1626), and for premedication (p.1780).

Chlordiazepoxide is given orally as the hydrochloride or the base; the doses given refer equally to both. It may also be given by deep intramuscular or slow intravenous injection as the hydrochloride. Preparations formulated for intramuscular use are considered unsuitable for intravenous injection due to the formation of air bubbles in the solvent.

Elderly and debilitated patients should be given one-half or less of the usual adult dose.

The usual oral dose for the treatment of **anxiety** is up to 30 mg daily in divided doses; in severe conditions up to 100 mg daily has been given. For acute or severe anxiety an initial dose of 50 to 100 mg of the hydrochloride has been given by injection, followed if necessary by 25 to 50 mg three or four times daily.

For relief of **muscle spasm** a dose of 10 to 30 mg daily orally in divided doses is recommended, and 10 to 30 mg orally may be given before bedtime for insomnia associated with anxiety.

For the control of the acute symptoms of **alcohol withdrawal** chlordiazepoxide or chlordiazepoxide hydrochloride may be given in an oral dose of 25 to 100 mg repeated as needed up to a maximum of 300 mg daily. For severe symptoms treatment may be begun by injection of 50 to 100 mg, repeated if necessary after 2 to 4 hours.

Chlordiazepoxide hydrochloride has also been given for anaesthetic **premedication** in a dose of 50 to 100 mg intramuscularly one hour before surgery.

Preparations

BP 2008: Chlordiazepoxide Capsules; Chlordiazepoxide Hydrochloride Tablets;
USP 31: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules; Chlordiazepoxide Hydrochloride Capsules; Chlordiazepoxide Hydrochloride for Injection; Chlordiazepoxide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: OCM; ***Braz.:*** Psicosedin; ***Cz.:*** Defobin†; Elenium; ***Denm.:*** Klopoxid; Risolid; ***Fin.:*** Risolid; ***Ger.:*** Librium; Multum; Radepur; ***Gr.:*** Oasil; ***Hong Kong:*** Librium; ***Hung.:*** Elenium; Librium; ***India:*** Equilibrium; Librium; ***Indon.:*** Cetabrium; Librium; ***Irl.:*** Librium; ***Ital.:*** Librium; Reliberan†; ***Malaysia:*** Benpine; Klorpo†; ***Mex.:*** Kalmocaps†; ***NZ:*** Novapam; ***Pol.:*** Elenium; ***Port.:*** Paxium; ***Rus.:*** Elenium (Элениум); ***S.Afr.:*** Librium; ***Singapore:*** Benpine; Klorpo; ***Spain:*** Huberplex; Omnalio; ***Thai.:*** Benpine; Cozep; Epoxide†; ***UK:*** Librium; Tropium; ***USA:*** Libritabs†; Librium; Mitran†; Reposans†; ***Venez.:*** Eposal.

Multi-ingredient: ***Arg.:*** Libraxin; Plafonyl†; ***Austria:*** Limbitrol; ***Braz.:*** Limbitrol; Menotensil; ***Canad.:*** Apo-Chlorax; Librax; ***Chile:*** Aero Itan; Aerogastrol; Antalin; Garceptol; Gaseofin†; Gastrolen; Lerogin; Libraxin; Limbatrilin; Lironex†; Morelin; No-Ref; Profisin; Sedogastrol†; Tensoliv; Tiperin; Tranvagal†; ***Fin.:*** Klotriptyl; Librax; Limbitrol; ***Fr.:*** Librax; ***Gr.:*** Librax; ***Hong Kong:*** Bralix; Epilon; Librax; Medocalum†; ***India:*** Emotrip; Equirex; Normaxin; Spasrax; ***Indon.:*** Braxidin; Cliad; Klidibrax; Librax; Limbritol; Melidox; Neurogen; Renagas; Sanmag; Spasmium; ***Israel:*** Nirvaxal; ***Ital.:*** Diapatol; Librax; Limbitryl; Sedans; ***Malaysia:*** Apo-Chlorax†; Liblan; ***Port.:*** Librax; ***Rus.:*** Amixide (Амиксид); ***S.Afr.:*** Librax; Limbitrol; ***Singapore:*** Apo-Chlorax; Chlobax; Librax; Medocalum; ***Spain:*** Psico Blocan; ***Switz.:*** Librax; Librocol; Limbitrol; ***Thai.:*** Kenspa; Librax; Pobrax†; Tumax; Zepobrax†; ***Turk.:*** Klipaks; Libkol; Librax; ***USA:*** Clindex; Librax; Limbitrol; ***Venez.:*** Librax.

Chlormezanone *(BAN, rINN)*

Chlormethazanone; Chlormézanone; Chlormezanonum; Clormezanona; Kloormetsanoni; Klormezanon. 2-(4-Chlorophenyl)-3-methylperhydro-1,3-thiazin-4-one 1,1-dioxide.

Хлормезанон

$C_{11}H_{12}ClNO_3S$ = 273.7.
CAS — 80-77-3.
ATC — M03BB02.
ATC Vet — QM03BB02.

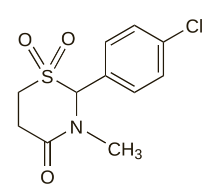

Profile

Chlormezanone has been used in the treatment of anxiety disorders and insomnia. It was also used in conditions associated with painful muscle spasm, often in compound preparations with analgesics; its mechanism of action is not clear but is probably related to its sedative effect. Chlormezanone was withdrawn from use in many countries after reports of serious skin reactions (see below).

Effects on the skin. Chlormezanone was responsible for 5 of 86 cases of fixed drug eruption detected in a Finnish hospital from 1971 to 1980.[1] In the period from 1981 to 1985 chlormezanone was responsible for 1 out of 77 such eruptions.[2] In a case control study[3] comparing drug use in 245 patients hospitalised because of toxic epidermal necrolysis or Stevens-Johnson syndrome and 1147 controls, 13 patients and one control were found to have taken chlormezanone. From these figures a high crude relative risk of 62 was calculated; the excess risk was estimated to be 1.7 cases per million users per week.

1. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; **112:** 575–8.

2. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.
3. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

Porphyria. Chlormezanone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardiosedantol; Restoril†.

Multi-ingredient: ***Chile:*** Adalgen†; Calmosedan; Diapam; Dioran†; Dolnix; Dolonase; Dolorelax†; Fibrorelax; Mesolona†; Multisedil; Neo Butartrol; Promidan; Sedantol; Sedilit; Silrelax†; Sin-Algin; ***Hong Kong:*** Parazone; ***S.Afr.:*** Myoflex.

Chlorproethazine Hydrochloride *(rINNM)*

Chlorproéthazine, Chlorhydrate de; Chlorproethazini Hydrochloridum; Hidrocloruro de clorproetazina; RP-4909 (chlorproethazine). 3-(2-Chlorophenothiazin-10-yl)-*NN*-diethylpropylamine hydrochloride.

Хлорпроэтазина Гидрохлорид

$C_{19}H_{23}ClN_2S,HCl = 383.4.$

CAS — 84-01-5 (chlorproethazine); 4611-02-3 (chlorproethazine hydrochloride).

ATC — N05AA07.

ATC Vet — QN05AA07.

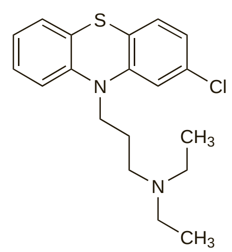

(chlorproethazine)

Profile

Chlorproethazine is a phenothiazine derivative differing chemically from chlorpromazine by the substitution of a diethyl for a dimethyl group. It has general properties similar to those of chlorpromazine (below) but has been used mainly as a muscle relaxant in the management of muscle spasm (p.1887). Although exposure of the skin to phenothiazines has been associated with sensitivity reactions, chlorproethazine hydrochloride has been applied topically with the warning to avoid direct exposure to sunlight. It has also been given orally or by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Neuriplege†.

Chlorpromazine *(BAN, rINN)*

Chlorpromazinum; Clorpromazina; Klooripromatsiini; Klorpromazin. 3-(2-Chlorophenothiazin-10-yl)propyldimethylamine.

Хлорпромазин

$C_{17}H_{19}ClN_2S = 318.9.$

CAS — 50-53-3.

ATC — N05AA01.

ATC Vet — QN05AA01.

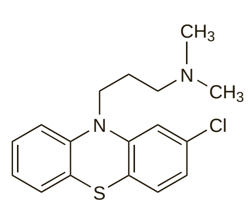

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Chlorpromazine). A white or creamy-white powder or waxy solid; odourless or almost odourless. M.p. 56° to 58°. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform. Protect from light.

USP 31 (Chlorpromazine). A white crystalline solid with an amine-like odour. It darkens on prolonged exposure to light. Practically insoluble in water; soluble 1 in 3 of alcohol, 1 in 2 of chloroform, 1 in 3 of ether, and 1 in 2 of benzene; freely soluble in dilute mineral acids; practically insoluble in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Chlorpromazine Embonate *(BANM, rINNM)*

Chlorpromazine, Embonate de; Chlorpromazine Pamoate; Chlorpromazini Embonas; Embonato de clorpromazina.

Хлорпромазина Эмбонат

$(C_{17}H_{19}ClN_2S)_2,C_{23}H_{16}O_6 = 1026.1.$

ATC — N05AA01.

ATC Vet — QN05AA01.

Chlorpromazine Hydrochloride *(BANM, rINNM)*

Aminazine; Chloropromazyny chlorowodorek; Chlorpromazin hydrochlorid; Chlorpromazine, chlorhydrate de; Chlorpromazini hydrochloridum; Chlorpromazino hidrochloridas; Hidrocloruro de clorpromazina; Klooripromatsiinihydrokloridi; Klorpromazin Hidroklorür; Klórpromazin-hidroklorid; Klorpromazinhydroklorid.

Хлорпромазина Гидрохлорид

$C_{17}H_{19}ClN_2S,HCl = 355.3.$

CAS — 69-09-0.

ATC — N05AA01.

ATC Vet — QN05AA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Chlorpromazine Hydrochloride). A white or almost white crystalline powder. It decomposes on exposure to air and light. Very soluble in water; freely soluble in alcohol. A freshly prepared 10% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Chlorpromazine Hydrochloride). A white or slightly creamy-white odourless crystalline powder. It darkens on prolonged exposure to light. Soluble 1 in 1 of water, 1 in 1.5 of alcohol, and 1 in 1.5 of chloroform; insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Dilution. Solutions containing 2.5% of chlorpromazine hydrochloride may be diluted to 100 mL with 0.9% sodium chloride solution provided the pH of the saline solution is such that the pH of the dilution does not exceed the critical range of pH 6.7 to 6.8.[1] With saline of pH 7.0 or 7.2, the final solution had a pH of 6.4.

1. D'Arcy PF, Thompson KM. Stability of chlorpromazine hydrochloride added to intravenous infusion fluids. *Pharm J* 1973; **210:** 28.

Incompatibility. Incompatibility has been reported between chlorpromazine hydrochloride injection and several other compounds; precipitation of chlorpromazine base from solution is particularly likely if the final pH is increased. Compounds reported to be incompatible with chlorpromazine hydrochloride include aminophylline, amphotericin B, aztreonam, some barbiturates, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, morphine sulfate (when preserved with chlorocresol), some penicillins, and remifentanil.

For a warning about incompatibility between chlorpromazine solution (*Thorazine*; *GSK, USA*) and carbamazepine suspension (*Tegretol*; *Novartis, USA*), see p.471.

Sorption. There was a 41% loss of chlorpromazine hydrochloride from solution when infused for 7 hours via a plastic infusion set (cellulose propionate burette with PVC tubing), and a 79% loss after infusion for 1 hour from a glass syringe through silastic tubing.[1] Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Adverse Effects

Chlorpromazine generally produces less central depression than the barbiturates or benzodiazepines, and tolerance to its initial sedative effects develops fairly quickly in most patients. It has antimuscarinic properties and may cause adverse effects such as dry mouth, constipation, difficulty with micturition, blurred vision, and mydriasis. Tachycardia, ECG changes (particularly Q- and T-wave abnormalities), and, rarely, cardiac arrhythmias may occur; hypotension (usually orthostatic) is common. Other adverse effects include delirium, agitation and, rarely, catatonic-like states, insomnia or drowsiness, nightmares, depression, miosis, EEG changes and convulsions, nasal congestion, minor abnormalities in liver function tests, inhibition of ejaculation, impotence, and priapism.

Hypersensitivity reactions include urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity. A syndrome resembling SLE has been reported. Jaundice has occurred, and probably has an immunological origin. Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes; corneal and lens opacities have occurred. Pigmentary retinopathy has occurred only rarely with chlorpromazine. Photosensitivity reactions are more common with chlorpromazine than with other antipsychotics.

Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis have occasionally been reported; they may be manifestations of a hypersensitivity reaction. Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment, and symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear. Mild leucopenia has been stated to occur in up to 30% of patients on prolonged high dosage.

Extrapyramidal dysfunction and resultant disorders include acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor. The neuroleptic malignant syndrome may also occur.

Chlorpromazine alters endocrine and metabolic functions. Patients have experienced amenorrhoea, galactorrhoea, and gynaecomastia due to hyperprolactinaemia, weight gain, and hyperglycaemia and altered glucose tolerance. Body temperature regulation is impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

There have been isolated reports of sudden death with chlorpromazine; possible causes include cardiac arrhythmias or aspiration and asphyxia due to suppression of the cough and gag reflexes.

Pain and irritation at the injection site may occur on injection. Nodule formation may occur after intramuscular injection.

Phenothiazines do not cause dependence of the type encountered with barbiturates or benzodiazepines. However, withdrawal symptoms have been seen on abrupt withdrawal in patients receiving prolonged and/or high-dose maintenance therapy.

Although the adverse effects of **other phenothiazines** are broadly similar in nature to those of chlorpromazine, their frequency and pattern tend to fall into 3 groups:

- group 1 (e.g. chlorpromazine, levomepromazine, and promazine) are generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects
- group 2 (e.g. pericyazine, pipotiazine, and thioridazine) are generally characterised by moderate sedative effects, marked antimuscarinic effects, and fewer extrapyramidal effects than groups 1 or 3
- group 3 (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine) are generally characterised by fewer sedative and antimuscarinic effects but more pronounced extrapyramidal effects than groups 1 or 2

Classical antipsychotics of **other chemical groups** tend to resemble the phenothiazines of group 3. They include the butyrophenones (e.g. benperidol and haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); substituted benzamides (e.g. sulpiride); oxypertine; and loxapine.

Carcinogenicity. See Effects on Endocrine Function, below.

Convulsions. Treatment with antipsychotics can result in EEG abnormalities and lowered seizure threshold.[1] Seizures can be induced particularly in patients with a history of epilepsy or drug-induced seizures, abnormal EEG, previous electroconvulsive therapy, or pre-existing CNS abnormalities. The risk appears to be greatest at the start of antipsychotic therapy, or with high doses, or abrupt increases of dose, or with the use of more than one antipsychotic. The incidence of antipsychotic-induced convulsions is, however, probably less than 1%.

In general, the epileptic potential has been correlated with the propensity of the antipsychotic to cause sedation. Phenothiazines with marked sedative effects [group 1] such as chlorpromazine appear to present a higher risk than those with strong extrapyramidal effects [group 3]. Haloperidol appears to carry a relatively low risk of seizures. The following drugs have been suggested when classical antipsychotic therapy is considered necessary in patients at risk of seizures or being treated for epilepsy: fluphenazine, haloperidol, pimozide, or trifluoperazine. Antipsychotic dosage should be increased slowly and the possibility of interactions with antiepileptic therapy considered (see under Interactions, below).

The atypical antipsychotic clozapine appears to be associated with a particularly high risk of seizures (see Effects on the Nervous System, under Clozapine, p.982). Risperidone may be preferred if an atypical antipsychotic is to be used in patients at risk of seizures.

1. Pisani F, *et al.* Effects of psychotropic drugs on seizure threshold. *Drug Safety* 2002; **25:** 91–110.

Effects on the blood. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them phenothiazines for which there were 87 reports of agranulocytosis (42 fatal) and 33 of neutropenia (22 fatal). The most frequently implicated phenothiazines were chlorpromazine with 51 reports of agranulocytosis (26 fatal) and 12 of neutropenia (2 fatal) and thioridazine with 20 reports of agranulocytosis (9 fatal) and 10 of neutropenia (none fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 18/07/08)

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. For further details, see Effects on Body-weight, in Clozapine, p.981.

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.

Effects on the cardiovascular system. Orthostatic hypotension is a common problem in patients taking psychotropic drugs and is particularly pronounced with low-potency antipsychotics.[1]

Various **EEG changes** or frank **arrhythmias** have occurred in patients receiving antipsychotics. T-wave changes have been reported with low-potency antipsychotics; they are usually benign and reversible, and subject to diurnal fluctuations. Low-potency antipsychotics, particularly *thioridazine* and *mesoridazine*, and the high-potency drug *pimozide*, prolong the QT interval in a similar manner to class I antiarrhythmics such as quinidine or procainamide; their use is therefore contra-indicated in patients taking such antiarrhythmics. *Droperidol*, another high-potency drug, has also been reported to prolong the QT interval.[2] Thioridazine is most frequently discussed in case reports of psychotropic drug-induced torsade de pointes,[2] which has led to restrictions on its use (see Precautions, and Uses and Administration of Thioridazine, p.1031); *chlorpromazine* and *pimozide* have also been implicated. Torsade de pointes has also been reported after overdosage[3-5] with, or high intravenous[6] doses of, the high-potency antipsychotic *haloperidol*. There are also isolated reports of cardiac arrhythmias after attempts at rapid control with high doses of haloperidol.[7,8] *Melperone*, a butyrophenone antipsychotic related to haloperidol, has been reported to have class III electrophysiologic and antiarrhythmic activity.[9,10]

In the UK, the risk of arrhythmias with antipsychotic treatment has been considered by an expert working group of the CSM;[11] the following recommendations were made regarding ECG monitoring:

- the need for an ECG should be based on a patient's relevant medical history, family history, and clinical examination; the elderly and those with a personal or family history of heart disease or any cardiac abnormalities would benefit the most from a baseline ECG
- during treatment an ECG should be performed in patients who experience palpitations or other symptoms suggestive of cardiac disease; if the QT interval is prolonged then a reduction in dose may be required, if it exceeds 500 milliseconds treatment may need to be stopped
- an ECG should be considered during dose increases
- potassium levels should be monitored before and during treatment and in particular during periods of acute illnesses

Sudden unexpected deaths have long been reported in patients receiving antipsychotics.[12] Whether this is due to the disease being treated or to the treatment is still unclear. However, in a retrospective cohort study[13] involving about 482 000 patients, analysis of 1487 sudden cardiac deaths indicated that patients receiving antipsychotics in doses of more than 100 mg of thioridazine or its equivalent had a 2.4-fold increase in the rate of sudden cardiac death, rising to a 3.53-fold increase in those patients with pre-existing severe cardiovascular disease. A later case-control study[14] in 5 UK psychiatric hospitals found that sudden unexplained death in psychiatric patients was associated with hypertension, ischaemic heart disease, and current treatment with thioridazine. Although several mechanisms have been suggested for the effect, prolongation of the QT interval has been implicated in a proportion of the cases.[12]

Results from a case-control study[15] have suggested that use of classical antipsychotics may be associated with an increased risk of idiopathic **venous thromboembolism.** The risk was most pronounced during the first 3 months of treatment, and was higher for low potency than high potency antipsychotics. This study did not examine the risk of venous thromboembolism with atypical antipsychotics, but see under Clozapine, p.982.

1. DiGiacomo J. Cardiovascular effects of psychotropic drugs. *Cardiovasc Rev Rep* 1989; **10:** 31–2, 39–41, and 47.
2. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
3. Zee-Cheng C-S, *et al.* Haloperidol and torsades de pointes. *Ann Intern Med* 1985; **102:** 418.
4. Henderson RA, *et al.* Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. *Hum Exp Toxicol* 1991; **10:** 59–62.
5. Wilt JL, *et al.* Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med* 1993; **119:** 391–4.
6. O'Brien JM, *et al.* Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; **33:** 1046–50.
7. Mehta D, *et al.* Cardiac arrhythmia and haloperidol. *Am J Psychiatry* 1979; **136:** 1468–9.
8. Bett JHN, Holt GW. Malignant ventricular tachyarrhythmia and haloperidol. *BMJ* 1983; **287:** 1264.
9. Møgelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208:** 61–4.
10. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15:** 144–9.
11. CSM/MHRA. Cardiac arrhythmias associated with antipsychotic drugs. *Current Problems* 2006; **31:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
12. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; **62:** 1649–71.
13. Ray WA, *et al.* Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58:** 1161–7.
14. Reilly JG, *et al.* Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 2002; **180:** 515–22.
15. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000; **356:** 1219–23.

Effects on endocrine function. Antipsychotics can alter the secretion of prolactin, growth hormone, and thyrotrophin from the anterior pituitary via their ability to block central dopamine-D_2 receptors. Therapeutic doses of classical antipsychotics (and some atypical antipsychotics such as amisulpride and risperidone) increase serum-prolactin concentrations; this effect occurs at lower doses and after shorter latent periods than the antipsychotic effects. However, partial tolerance to the hyperprolactinaemic effect may develop on long-term use.[1] Serum prolactin declines to normal values within 3 weeks of stopping oral antipsychotic therapy but may remain raised for 6 months after an intramuscular depot injection.[1]

The long-term consequences of gonadal hormone deficiency, secondary to raised prolactin concentrations, have caused concern. There is evidence[2] that patients taking long-term prolactin-raising antipsychotics are at high risk of osteoporosis associated with hypogonadism. Long-term antipsychotic treatment has also been shown to increase the incidence of mammary tumours in the *rat*. Although early studies[3,4] found little or no evidence that chronic use in humans alters the risk of breast cancer among women with schizophrenia, a later retrospective cohort study[5] found a modest dose-related increase in the risk of breast cancer in women using antipsychotic dopamine antagonists. A similar increase was seen in women receiving antiemetic dopamine antagonists. Fears that pituitary abnormalities, including pituitary tumours,[6] might develop in patients on long-term phenothiazine therapy have not been confirmed.[7,8]

Antipsychotics can in some circumstances reduce both basal and stimulated growth-hormone secretion but attempts to use them to treat dysfunctions in growth-hormone regulation have not been successful.[9] Although a number of clinical studies show that acute dosage of antipsychotics increased both basal and stimulated thyrotrophin secretion, the majority of studies find either no change or only a small increase in thyrotrophin secretion following long-term use.

A small study[10] has suggested that thioridazine may be more likely than other antipsychotics to decrease serum concentrations of testosterone or luteinising hormone in men. However, concentrations were within the normal range in most patients taking antipsychotics.

See also Effects on Fluid and Electrolyte Homoeostasis, below and Effects on Sexual Function, below.

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; **64:** 2291–2314.
2. Meaney AM, *et al.* Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *Br J Psychiatry* 2004; **184:** 503–8.
3. Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health* 1989; **43:** 43–7.
4. Mortensen PB. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res* 1994; **12:** 185–94.
5. Wang PS, *et al.* Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002; **59:** 1147–54.
6. Asplund K, *et al.* Phenothiazine drugs and pituitary tumors. *Ann Intern Med* 1982; **96:** 533.
7. Rosenblatt S, *et al.* Chronic phenothiazine therapy does not increase sellar size. *Lancet* 1978; **ii:** 319–20.
8. Lilford VA, *et al.* Long-term phenothiazine treatment does not cause pituitary tumours. *Br J Psychiatry* 1984; **144:** 421–4.
9. Gunnet JW, Moore KE. Neuroleptics and neuroendocrine function. *Ann Rev Pharmacol Toxicol* 1988; **28:** 347–66.
10. Brown WA, *et al.* Differential effects of neuroleptic agents on the pituitary-gonadal axis in men. *Arch Gen Psychiatry* 1981; **38:** 1270–2.

Effects on the eyes. Phenothiazines may induce a pigmentary retinopathy which is dependent on both the dose and the duration of treatment.[1] Those phenothiazine derivatives with piperidine side-chains such as thioridazine have a higher risk of inducing retinal toxicity than other phenothiazine derivatives, with relatively few cases reported for those with aliphatic side-chains such as chlorpromazine; the piperazine group does not appear to exert direct ocular toxicity.[2] The retinopathy may present either acutely, (sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc), or chronically, (a fine pigment scatter appearing in the central area of the fundus, extending peripherally but sparing the macula). Chronic paracentral and pericentral scotomas may be found. Although pigmentary disturbances may progress after withdrawal of thioridazine, they are not always paralleled by deterioration in visual function; nonetheless, some cases have led to progressive chorioretinopathy.[3] The critical ocular toxic dose of thioridazine is reported to be 800 mg daily[1] and UK licensed product information has recommended that a daily dose of 600 mg should not usually be exceeded. However, there is a report[4] of pigmentary retinopathy in a patient who received long-term thioridazine in daily doses not exceeding 400 mg; the total dose was 752 g.

Pigmentation may also occur in the cornea, lens, and conjunctiva following use of phenothiazines. It may occur in association with pigmentary changes in the skin and is dose-related. In a study of 100 Malaysian patients, ocular pigmentation was observed in slightly more than half of those who had received a total dose of chlorpromazine of 100 to 299 g and in 13 of 15 who had received 300 to 599 g.[5] All those who had received more than 600 g of chlorpromazine or thioridazine had ocular pigmentation. Cataract formation, mainly of an anterior polar variety, has been observed rarely, mainly in patients on chlorpromazine. It does not appear to be dose-related.[2]

A patient who had received fortnightly injections of fluphenazine 12.5 mg for 10 years (total dose 3.25 g) developed bilateral maculopathy following unprotected exposure of less than 2-minute's duration to a welding arc.[6] It was postulated that accumulation of phenothiazine in the retinal epithelium sensitised the patient to photic damage. However, another patient who had received fortnightly injections of fluphenazine 25 mg for 25 years (total dose 16.25 g) developed bilateral maculopathy without exposure to any extreme photochemical sources.[7] The authors concluded that this was due to a direct effect of fluphenazine secondary to its accumulation in the retinal epithelium.

1. Spiteri MA, James DG. Adverse ocular reactions to drugs. *Postgrad Med J* 1983; **59:** 343–9.
2. Crombie AL. Drugs causing eye problems. *Prescribers' J* 1981; **21:** 222–7.
3. Marmor MF. Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function. *Br J Ophthalmol* 1990; **74:** 739–42.
4. Lam RW, Remick RA. Pigmentary retinopathy associated with low-dose thioridazine treatment. *Can Med Assoc J* 1985; **132:** 737.
5. Ngen CC, Singh P. Long-term phenothiazine administration and the eye in 100 Malaysians. *Br J Psychiatry* 1988; **152:** 278–81.
6. Power WJ, *et al.* Welding arc maculopathy and fluphenazine. *Br J Ophthalmol* 1991; **75:** 433–5.
7. Lee MS, Fern AI. Fluphenazine and its toxic maculopathy. *Ophthalmic Res* 2004; **36:** 237–9.

Effects on fluid and electrolyte homoeostasis. There have been occasional reports of water intoxication in patients taking antipsychotics. A review[1] of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion associated with psychotropics summarised 20 such reports for antipsychotics in the literature. The drugs implicated were thioridazine (8 reports), haloperidol (3 reports), chlorpromazine, trifluoperazine, and fluphenazine (2 reports each), and flupentixol, tiotixene, and clozapine (1 report each). The majority of reports did not permit clear conclusions and, particularly in the cases of prolonged treatment, the role of the medication was unclear. However, at least 3 of the cases were well documented and supported the view that antipsychotics could cause hyponatraemia.

A report not considered by the above review described water retention and peripheral oedema associated with chlorpromazine.[2] A small controlled study[3] found that 5 of 10 evaluated patients receiving haloperidol decanoate had impaired fluid homoeostasis.

1. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
2. Witz L, *et al.* Chlorpromazine induced fluid retention masquerading as idiopathic oedema. *BMJ* 1987; **294:** 807–8.
3. Rider JM, *et al.* Water handling in patients receiving haloperidol decanoate. *Ann Pharmacother* 1995; **29:** 663–6.

Effects on lipid metabolism. Most antipsychotics are associated with hyperlipidaemia. A review[1] found evidence of a higher risk of hyperlipidaemia in patients receiving low-potency classical antipsychotics, such as chlorpromazine and thioridazine, or the atypical antipsychotics, clozapine, olanzapine, and quetiapine. High-potency classical antipsychotics, such as haloperidol, and the atypical antipsychotics aripiprazole, risperidone, and ziprasidone, appeared to be associated with a lower risk of hyperlipidaemia. Possible mechanisms for dyslipidaemia associated with antipsychotic therapy include the development of glucose intolerance, weight gain, and dietary changes. For further details, see Effects on Body-weight under Adverse Effects of Clozapine, p.981 and Effects on Body-weight, above.

1. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 2004; **70:** 1–17.

Effects on the liver. Chlorpromazine and other phenothiazines may cause hepatocanalicular cholestasis often with hepatocyte damage suggestive of immunological liver injury.[1] Only a small number of patients taking the drug are affected and the onset is usually in the first 4 weeks of therapy. The drug or one of its metabolites may induce alteration in the liver-cell membrane so that it becomes antigenic; there is also good evidence for direct hepatotoxicity related to the production of free drug radical. There may be an individual idiosyncrasy in the metabolism of chlorpromazine and in the production of these radicals. A study has suggested that patients who have poor sulfoxidation status combined with unimpaired hydroxylation capacity may be most likely to develop jaundice with chlorpromazine.[2]

A preliminary study[3] showing a high incidence of gallstones in psychiatric inpatients in Japan found a correlation between the presence of gallstones and the duration of illness and use of antipsychotics. It was speculated that gallstones could be a consequence of phenothiazine-induced cholestasis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Watson RGP, *et al.* A proposed mechanism for chlorpromazine jaundice—defective hepatic sulphoxidation combined with rapid hydroxylation. *J Hepatol* 1988; **7:** 72–8.
3. Fukuzako H, *et al.* Ultrasonography detected a higher incidence of gallstones in psychiatric inpatients. *Acta Psychiatr Scand* 1991; **84:** 83–5.

Effects on sexual function. The phenothiazines can cause both impotence and ejaculatory dysfunction.[1] Thioridazine has been frequently implicated, and in an early report 60% of 57 male patients taking the drug reported sexual dysfunction compared with 25% of 64 men taking other antipsychotics.[2] There are also several reports of priapism with phenothiazines;[1,3-5] alpha-adrenoceptor blocking properties of these compounds may be partly responsible. Male sexual dysfunction, including priapism, has been reported only rarely with other classical antipsychotics such as the butyrophenones, diphenylbutylpiperidines, and thioxanthenes.[6] Priapism has also been reported with clozapine[7] and other atypical antipsychotics. The effects of antipsychotics on female sexual function are less well studied. Orgasmic dysfunction has been reported with thioridazine, trifluoperazine, and fluphenazine.[8]

The effects of hyperprolactinaemia (see Effects on Endocrine Function, above) on sexual function are described on p.2079.

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Kotin J, *et al.* Thioridazine and sexual dysfunction. *Am J Psychiatry* 1976; **133:** 82–5.
3. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
4. Chan J, *et al.* Perphenazine-induced priapism. *DICP Ann Pharmacother* 1990; **24:** 246–9.
5. Salado J, *et al.* Priapism associated with zuclopenthixol. *Ann Pharmacother* 2002; **36:** 1016–18.
6. Fabian J-L. Psychotropic medications and priapism. *Am J Psychiatry* 1993, **150:** 349–50.
7. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
8. Segraves RT. Psychiatric drugs and inhibited female orgasm. *J Sex Marital Ther* 1988; **14:** 202–7.

Effects on the skin. *DEPOT INJECTION.* Of 217 patients who received a combined total of 2354 depot antipsychotic injections 42 (19.4%) had local problems at the site of injection; 18 (8.3%) experienced chronic complications and 30 (13.8%) acute reactions.[1] Acute problems reported included 31 episodes of unusual pain, 21 of bleeding or haematoma, 19 of clinically important leakage of drug from injection site, 11 of acute inflammatory indurations, and 2 of transient nodules. Complications were more common in patients receiving concentrated preparations, higher doses, weekly injections, haloperidol decanoate or zuclopenthixol decanoate, and injection volumes greater than 1 mL and in those treated for more than 5 years. Chronic reactions were more common in patients aged over 50 years.

1. Hay J. Complications at site of injection of depot neuroleptics. *BMJ* 1995; **311:** 421.

PHOTOSENSITIVITY. Testing in 7 subjects taking chlorpromazine revealed that photosensitivity reactions manifested primarily as immediate erythema and that sensitivity was primarily to light in the long ultraviolet (UVA) and visible wavebands. Sensitivity to UVB was normal.[1] The incidence of photosensitivity reactions to chlorpromazine has been given as 3%. However, a higher incidence of 16-25% has also been reported.[2]

See also Effects on the Eyes, above.

1. Ferguson J, *et al.* Further clinical and investigative studies of chlorpromazine phototoxicity. *Br J Dermatol* 1986; **115** (suppl 30): 35.
2. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.

PIGMENTATION. The pigment found in the skin of patients treated with chlorpromazine was considered[1] to be a chlorpromazine-melanin polymer formed in a light-catalysed anaerobic reaction. Hydrogen chloride liberated during the reaction could account for the skin irritation. Intracutaneous injection of a preparation of the polymer into 2 volunteers produced a bluish-purple discoloration which faded in 3 days.

1. Huang CL, Sands FL. Effect of ultraviolet irradiation on chlorpromazine II: anaerobic condition. *J Pharm Sci* 1967; **56:** 259–64.

Extrapyramidal disorders. Antipsychotics and a number of other drugs, including antiemetics such as metoclopramide and some antidepressants, can produce a range of dyskinesias or involuntary movement disorders involving the extrapyramidal motor system, including parkinsonism, akathisia, acute dystonia, and chronic tardive dyskinesia.[1-4] Such reactions are a major problem in the clinical management of patients receiving antipsychotics. Reactions of this type can occur with any antipsychotic, but (excluding tardive dyskinesia) are particularly prominent during treatment with high-potency drugs such as the tricyclic piperazines and butyrophenones. Antipsychotics such as clozapine carry a low risk of extrapyramidal effects and are therefore described as atypical antipsychotics. The incidence of tardive dyskinesia does appear to be minimal with clozapine, although there is less evidence for other atypical antipsychotics (p.982; but see also below).

Of 2811 patients studied[5] in the first few months of therapy with prochlorperazine (a drug with a high propensity to cause extrapyramidal reactions), 57 reported adverse effects, 16 of which involved the extrapyramidal system. There were 4 dystonic-dyskinesic reactions (an incidence of 1 in 464 and 1 in 707 for patients aged under and over 30 years respectively), 9 reports of parkinsonism (under 60 years, 1 in 1555; over 60 years, 1 in 159), and 3 reports of akathisia (1 in 562).

One explanation of extrapyramidal disorders is an imbalance between dopaminergic and cholinergic systems in the brain. However, this simple model fails to explain the co-existence of a variety of extrapyramidal effects, and several alternative mechanisms have been proposed.[2,6] Hypotheses based on interactions between different dopamine receptor types may help to explain the decreased tendency of some antipsychotic drugs to induce these reactions (see Action under Uses and Administration, below).

1. CSM/MCA. Drug-induced extrapyramidal reactions. *Current Problems* 1994; **20:** 15–16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
2. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
3. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Health-Syst Pharm* 1997; **54:** 2461–77.
4. Jiménez-Jiménez FJ, *et al.* Drug-induced movement disorders. *Drug Safety* 1997; **16:** 180–204.
5. Bateman DN, *et al.* Extrapyramidal reactions to metoclopramide and prochlorperazine. *Q J Med* 1989; **71:** 307–11.
6. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.

AKATHISIA. Akathisia is a condition of mental and motor restlessness in which there is an urge to move about constantly and an inability to sit or stand still. It is the most common motor adverse effect of treatment with antipsychotics.[1] Acute akathisia is dose-dependent, usually develops within a few days of beginning treatment or after a rapid increase in dose, and usually improves if the drug is stopped or the dose reduced. *Antimuscarinic antiparkinsonian drugs* appear to provide only limited benefit, although success may be more likely in patients with concomitant parkinsonism. A low dose of a *beta blocker* such as *propranolol* (although good evidence is lacking[2]) or a *benzodiazepine*[3] may be helpful. Improvement has also been reported with *clonidine* and *amantadine* but the usefulness of these drugs may be limited by adverse effects or development of tolerance, respectively. The tardive form, like tardive dyskinesia (see below), which appears after several months of treatment, does not respond to antimuscarinics and is difficult to treat.

1. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Safety* 2000; **22:** 73–81.
2. Barnes TRE, *et al.* Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).
3. Soares-Weiser K, *et al.* Benzodiazepines for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 21/08/08).

DYSTONIA. Acute dystonic reactions, which mainly affect the muscles of the face, neck, and trunk and include jaw clenching (trismus), torticollis, and oculogyric crisis are reported to occur in up to 10% of patients taking antipsychotics. Laryngeal dystonia is rare, but potentially fatal.[1] Dystonias usually occur within the first few days of treatment or after a dosage increase but may also develop on withdrawal. They are transitory, and are most common in children and young adults. Dystonic reactions may be controlled by *antimuscarinics* such as *biperiden* or *procyclidine*, or *antihistamines* such as *diphenhydramine* or *promethazine*.[2] *Benzodiazepines* such as *diazepam* can also be used. Prophylactic antimuscarinics can prevent the development of dystonias, but routine use is not recommended as not all patients require them and tardive dyskinesia may be unmasked or worsened (see below); such a strategy should probably be reserved for short-term use in those at high risk of developing dystonic reactions, such as young adults starting treatment with high-potency antipsychotics or in patients with a history of drug-induced dystonias.[3,4] Some patients may develop tardive dystonia. A range of drugs has been tried in this condition but without consistent benefit.[5]

1. Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. *Psychosomatics* 1989; **30:** 359–64.
2. van Harten PN, *et al.* Acute dystonia induced by drug treatment. *BMJ* 1999; **319:** 623–6.
3. WHO. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment: a consensus statement. *Br J Psychiatry* 1990; **156:** 412.
4. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
5. Raja M. Managing antipsychotic-induced acute and tardive dystonia. *Drug Safety* 1998; **19:** 57–72.

PARKINSONISM. Parkinsonism, often indistinguishable from idiopathic Parkinson's disease (p.791), may develop during therapy with antipsychotics, usually after the first few weeks or months of treatment. It is generally stated to be more common in adults and the elderly, although a retrospective study with haloperidol found an inverse relationship between drug-induced parkinsonism and age.[1] This parkinsonism is generally reversible on drug withdrawal or dose reduction, and may sometimes disappear gradually despite continued drug therapy. *Antimuscarinic antiparkinsonian* drugs are used to suppress the symptoms of parkinsonism.[2] However, they are often minimally effective and commonly cause adverse effects. Routine use for prophylaxis is not recommended because of the risk of unmasking or exacerbating tardive dyskinesia (see below). *Amantadine* is an alternative to the antimuscarinics.[2]

1. Moleman P, *et al.* Relationship between age and incidence of parkinsonism in psychiatric patients treated with haloperidol. *Am J Psychiatry* 1986; **143:** 232–4.
2. Mamo DC, *et al.* Managing antipsychotic-induced parkinsonism. *Drug Safety* 1999; **20:** 269–75.

TARDIVE DYSKINESIA. The central feature of tardive dyskinesia is orofacial dyskinesia characterised by protrusion of the tongue ('fly catching'), lipsmacking, sucking, lateral chewing, and pouting of the lips and cheeks. The trunk and limbs also become involved with choreiform movements such as repetitive 'piano-playing' hand movements, shoulder shrugging, foot tapping, or rocking movements. The prevalence of tardive dyskinesia among those receiving antipsychotics varies widely but up to 60% of patients may develop symptoms. In most cases the condition is mild and not progressive and tends to wax and wane. Although tardive dyskinesia usually develops after many years of antipsychotic therapy no clear correlation has been shown between development of the condition and the length of drug treatment or the type and class of drug. However, *clozapine* does not appear to be associated with the condition and in some cases use has resulted in improvement of established tardive dyskinesia (see Schizophrenia under Clozapine, p.985). Whether other atypical antipsychotics also have a lower incidence of tardive dyskinesia remains to be established, although there are some data to suggest that this may be the case.[1-3] Symptoms of tardive dyskinesia often develop after stopping the antipsychotic or after dose reduction. Risk factors include old age, female sex, affective disorder, schizophrenia characterised by negative symptoms, and organic brain damage.

Suggested causes of tardive dyskinesia include dopaminergic overactivity, imbalance between dopaminergic and cholinergic activity, supersensitivity of postsynaptic dopamine receptors, presynaptic catecholaminergic hyperfunction, and alterations of the gamma-aminobutyric acid (GABA) system.

Options in the management of tardive dyskinesia include attempts at treatment while maintaining antipsychotic therapy, or withdrawal of antimuscarinic therapy, and either withdrawal of the antipsychotic or reduction of the dosage to the minimum required or transfer to an atypical antipsychotic.

Although many drugs have been tried in the **treatment** of tardive dyskinesia there have been relatively few double-blind studies. Reviews of tardive dyskinesia[1,4-6] have concluded that there appeared to be no reliable or safe treatment. Overall, classical antipsychotics appeared to be the most effective in masking symptoms of tardive dyskinesia but tolerance may develop and a worsening of the underlying pathophysiology by antipsychotics had to be assumed on theoretical grounds. Other drugs with antidopaminergic actions which were probably of comparable efficacy included *reserpine*, *oxypertine*, *tetrabenazine*, and *metirosine*. The next most effective drugs were considered to be noradrenergic antagonists such as *clonidine*. Some encouraging results had also been obtained with GABAergic drugs such as the *benzodiazepines*, *baclofen*, *progabide*, *valproate*, and *vigabatrin*, although systematic reviews of studies of some GABAergic drugs[7] including benzodiazepines[8] found the evidence inconclusive and/or unconvincing. The efficacy of cholinergics could not be confirmed.[9,10] Dopaminergics and antimuscarinics mostly exacerbated symptoms but others[11] had commented that there was no convincing evidence that long-term use of antimuscarinics increased the risk of developing the condition. Other drugs whose value is unclear include *vitamin E*[12] and some calcium-channel blockers.[13]

Withdrawal of the causative drug usually worsens the condition although symptoms often diminish or disappear over a period of weeks or sometimes a year or so. Success is most likely in younger patients. During withdrawal, drugs such as *diazepam* or *clonazepam* may be given to alleviate symptoms. Although classical antipsychotics are effective, their routine use to suppress symptoms is not recommended but they may be required for acute distressing or life-threatening reactions or in chronic tardive dyskinesia unresponsive to other treatment. In extremely severe resistant cases some have used an antipsychotic with *valproate* or *carbamazepine* or *reserpine* with *metirosine*.

In view of the unsatisfactory management of tardive dyskinesia, emphasis is placed on its **prevention**. Antipsychotics should be prescribed only when clearly indicated, should be given in the minimum dose, and continued only when there is evidence of benefit. Although drug holidays have been suggested for reducing the risk of tardive dyskinesia, the limited evidence indicates that interruptions in drug treatment may increase the risk of both persistent dyskinesia and psychotic relapse.[14] Increasing the dose of antipsychotic generally improves the condition, but only temporarily.

1. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 1999; **35** (suppl): S61–S66.
2. Kane JM. Tardive dyskinesia in affective disorders. *J Clin Psychiatry* 1999; **60** (suppl 5): 43–7.
3. Llorca P-M, *et al.* Tardive dyskinesias and antipsychotics: a review. *Eur Psychiatry* 2002; **17:** 129–38.
4. Haag H, *et al.*, eds. Tardive Dyskinesia. *WHO Expert Series on Biological Psychiatry Volume 1.* Seattle: Hogrefe & Huber, 1992.
5. Egan MF, *et al.* Treatment of tardive dyskinesia. *Schizophr Bull* 1997; **23:** 583–609.
6. Najib J. Tardive dyskinesia: a review and current treatment options. *Am J Ther* 1999; **6:** 51–60.
7. Rathbone J, *et al.* Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/08/08).
8. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
9. McGrath J, Soares-Weiser K. Cholinergic medication for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/08/08).
10. Tammenmaa IA, *et al.* Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 1099–1107.
11. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
12. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/08/08).
13. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/05).
14. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 12/05/06).

Neuroleptic malignant syndrome. The neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to a number of drugs including antipsychotics and other dopamine antagonists such as metoclopramide. The clinical **features** of the classic syndrome are usually considered to include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction, and altered levels of consciousness. Skeletal muscle damage may occur and the resulting myoglobinuria may lead to renal failure. However, there appear to be no universal criteria for diagnosis. Some believe the classic syndrome to be the extreme of a range of effects associated with antipsychotics and have introduced the concept of milder variants or incomplete forms. Others consider it to be a rare idiosyncratic reaction and suggest that the term neuroleptic malignant syndrome should be reserved for the full-blown reaction. Consequently, estimates of the **incidence** vary greatly and recent estimates have ranged from 0.02 to 2.5%. The mortality rate has been substantial; although it has decreased over the years with improved diagnosis and management, this may also be due to the detection and inclusion of the milder or incomplete variants. Possible risk factors include dehydration, pre-existing organic brain disease, and a history of a previous episode; young males have also been reported to be particularly susceptible.

The **pathogenesis** of NMS is still unclear. Blockade of dopaminergic receptors in the corpus striatum is thought to cause muscular contraction and rigidity generating heat while blockade of dopaminergic receptors in the hypothalamus leads to impaired heat dissipation. Peripheral mechanisms such as vasomotor paralysis may also play a role. Also a syndrome resembling NMS has been seen after withdrawal of treatment with dopamine agonists such as levodopa (see p.806). Symptoms develop rapidly over 24 to 72 hours and may occur days to months after starting antipsychotic medication or increase in dosage, but no consistent correlation with dosage or length of therapy has been found. Symptoms may last for up to 14 days after stopping oral antipsychotics, or for up to 4 weeks after stopping depot preparations. All antipsychotics are capable of inducing NMS; depot preparations may, however, be associated with prolonged recovery once it develops, and hence a higher mortality rate. Use with lithium carbonate or antimuscarinics may increase the likelihood of developing the syndrome.

Antipsychotic medication should be withdrawn immediately once the diagnosis of the classic syndrome is made; this should be followed by symptomatic and supportive **therapy** including cooling measures, correction of dehydration, and treatment of cardiovascular, respiratory, and renal complications. Whether antipsychotics should be withdrawn from patients with mild attacks and how they should be managed is a matter of debate.

The efficacy of specific drug therapy remains to be proven, and justification for use is based mainly on case reports.

- *Dantrolene* was first used because of its effectiveness in malignant hyperthermia. It has a direct action on skeletal muscle and may be particularly effective for the reversal of hyperthermia of muscle origin.
- In contrast, dopaminergic agonists may resolve hyperthermia of central origin, restoring dopaminergic transmission and hence alleviating extrapyramidal symptoms. There have been isolated reports of success with *amantadine* and *levodopa* but *bromocriptine* is generally preferred. Any underlying psychosis may, however, be aggravated by dopaminergic drugs.
- Since dantrolene and dopaminergics act in different ways a combination of the two might be useful, but any advantage remains to be demonstrated.
- *Antimuscarinics* are generally considered to be of little use and may aggravate the associated hyperthermia.
- *Benzodiazepines* may be used for sedation in agitated patients and may be of use against concomitant catatonia. ECT may be an alternative in refractory cases of NMS or when catatonic symptoms are present.

Re-introduction of antipsychotic therapy may be possible but is not always successful and extreme caution is advised. It has been recommended that a gap of at least 5 to 14 days should be left after resolution of the symptoms before attempting re-introduction.

References.

1. Wells AJ, *et al.* Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intell Clin Pharm* 1988; **22:** 475–80.
2. Bristow MF, Kohen D. How "malignant" is the neuroleptic malignant syndrome? *BMJ* 1993; **307:** 1223–4.
3. Kornhuber J, Weller M. Neuroleptic malignant syndrome. *Curr Opin Neurol* 1994; **7:** 353–7.
4. Velamoor VR, *et al.* Management of suspected neuroleptic malignant syndrome. *Can J Psychiatry* 1995; **40:** 545–50.
5. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
6. Bristow MF, Kohen D. Neuroleptic malignant syndrome. *Br J Hosp Med* 1996; **55:** 517–20.
7. Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. *Drug Safety* 1998; **19:** 73–82.
8. Adnet P, *et al.* Neuroleptic malignant syndrome. *Br J Anaesth* 2000; **85:** 129–35.

Withdrawal. Stopping treatment with an antipsychotic abruptly may produce withdrawal symptoms, the most common of which are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation.[1] Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days. They are more severe and frequent when antimuscarinics are stopped simultaneously.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.

Treatment of Adverse Effects

After an overdose of chlorpromazine, patients should be managed with intensive symptomatic and supportive therapy. Activated charcoal should be given by mouth if a substantial amount of the phenothiazine has been taken within 1 hour of presentation, provided that the airway can be protected; emptying the stomach by gastric lavage has sometimes been recommended. Dialysis is of little or no value in poisoning by phenothiazines.

Hypotension should be corrected by raising the patient's legs, or in severe cases by intravascular volume expansion. An inotrope such as dopamine may be considered in refractory cases. If a vasoconstrictor is considered necessary in the management of phenothiazine-induced hypotension the use of adrenaline or other sympathomimetics with high beta-adrenergic agonist properties should be avoided since the alpha-blocking effects of phenothiazines may impair the usual alpha-mediated vasoconstriction of these drugs, resulting in unopposed beta-adrenergic stimulation and increased hypotension.

The treatment of neuroleptic malignant syndrome and the difficulties of treating extrapyramidal adverse effects, especially tardive dyskinesia, are discussed above.

Precautions

Chlorpromazine and other phenothiazines are contra-indicated in patients with pre-existing CNS depression or coma, bone-marrow suppression, phaeochromocytoma, or prolactin-dependent tumours. They should be used with caution or not at all in patients with impaired liver, kidney, cardiovascular, cerebrovascular, and respiratory function and in those with angle-closure glaucoma, a history of jaundice, parkinsonism, diabetes mellitus, hypothyroidism, myasthenia gravis, paralytic ileus, prostatic hyperplasia, or urinary retention. Care is required in patients with epilepsy or a history of seizures as phenothiazines may lower the seizure threshold. Debilitated patients may be more prone to the adverse effects of phenothiazines as may the elderly, especially those with dementia. For precautions of phenothiazines in pregnancy, see below.

The sedative effects of phenothiazines are most marked in the first few days of treatment; affected patients should not drive or operate machinery.

The effects of phenothiazines on the vomiting centre may mask the symptoms of overdosage of other drugs, or of disorders such as gastrointestinal obstruction. Use at extremes of temperature may be hazardous since body temperature regulation is impaired by phenothiazines.

Regular eye examinations are advisable for patients receiving long-term phenothiazine therapy and avoidance of undue exposure to direct sunlight is recommended. Phenothiazines should be used with caution in the presence of acute infection or leucopenia. Blood counts are advised if the patient develops an unexplained infection or fever.

Patients should remain supine for at least 30 minutes after parenteral doses of chlorpromazine; blood pressure should be monitored.

Abrupt withdrawal of phenothiazine therapy is best avoided.

AIDS. Isolated reports[1,2] have suggested that patients with AIDS may be particularly susceptible to antipsychotic-induced extrapyramidal effects.

1. Hollander H, *et al.* Extrapyramidal symptoms in AIDS patients given low-dose metoclopramide or chlorpromazine. *Lancet* 1985; **ii:** 1186.
2. Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. *Lancet* 1987; **ii:** 341–2.

Asthma. Findings of a retrospective case-control study[1] appeared to indicate that asthmatic patients given antipsychotics were at an increased risk of death or near death from asthma.

1. Joseph KS, *et al.* Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ* 1996; **312:** 79–82.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of chlorpromazine by mothers during breast feeding may be of concern, since there have been reports of galactorrhoea in the mother and of drowsiness, lethargy, and declines in developmental scores in the infant. The *BNF* considers that the use of antipsychotics such as chlorpromazine should be avoided by breast-feeding mothers unless absolutely necessary.

Chlorpromazine was detected[2] in all milk samples from 4 women at concentrations ranging from 7 to 98 nanograms/mL. Two of the women breast-fed their infants, but one infant showed no effects while the other was noted to be drowsy and lethargic;

milk-chlorpromazine concentrations were 7 and 92 nanograms/mL, respectively.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/10/04)
2. Wiles DH, *et al.* Chlorpromazine levels in plasma and milk of nursing mothers. *Br J Clin Pharmacol* 1978; **5:** 272–3.

Children. Few phenothiazines are recommended for use in children; in particular there have been concerns about the use of phenothiazine derivatives in infants (see Sudden Infant Death Syndrome, p.588). For reference to the use of chlorpromazine in infants suffering neonatal abstinence syndrome see Substance Dependence, Opioids, under Uses and Administration, below.

References.

1. Dyer KS, Woolf AD. Use of phenothiazines as sedatives in children: what are the risks? *Drug Safety* 1999; **21:** 81–90.

Contact sensitisation. The *BNF* warns that because of the risk of contact sensitisation, health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

The elderly. The risk of *hip fracture* has been reported to be increased in elderly patients given antipsychotics. A large case-control study in patients over 65 found that current users of antipsychotics had a twofold increase in the risk of hip fractures.[1] The effect was dose-related and the increased risk was similar for chlorpromazine, haloperidol, and thioridazine. It was suggested that antipsychotic-induced sedation or orthostatic hypotension could increase the risk of falls in elderly persons. A study in 12 schizophrenic patients receiving antipsychotics plus other drugs such as antimuscarinics or benzodiazepines has suggested that long-term treatment with antipsychotics may decrease bone mineralisation.[2] A later study suggested that any increased risk of falls might be due to an effect of antipsychotics on balance as thioridazine was found to increase sway in elderly but not young subjects.[3] A meta-analysis of 40 studies[4] concluded that there was a small, but consistent, association between the use of most classes of psychotropic drugs, including antipsychotics, and falls. However, the evidence from these studies was based solely on observational data, with minimal adjustment for confounders, dosage, or duration of therapy.

There is some evidence[5,6] to suggest that the use of antipsychotics to manage behavioural complications of *dementia* may increase the rate of cognitive decline. Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotic drugs,[7,8] and the reaction can be extremely serious, even fatal. If these drugs are to be used in elderly patients with dementia, then very low doses should be used, and special care should be taken if the dementia is suspected to be of the Lewy-body type since sudden life-threatening deterioration may occur.[9] Depot preparations should not be used and, since dopamine D_2 receptors may be involved, it has been suggested that consideration could be given to using an antipsychotic such as clozapine that does not principally antagonise those receptors;[8] however, the FDA now recommends that atypical antipsychotics should not be used in such patients because of evidence of an increased death rate (see Dementia, p.1024).

An *increased risk of death* has also been noted in elderly patients given classical antipsychotics. A retrospective cohort study,[10] involving nearly 23 000 patients given atypical or classical antipsychotics, found that classical antipsychotics were at least as likely as the atypicals to increase the risk of death in the elderly. The authors also suggested that the greatest increase in risk occurred soon after starting therapy and with higher doses of classical antipsychotics. A similar increase in risk with use of classical antipsychotics was also seen in a large retrospective population-based study[11] in elderly patients with dementia when compared with that seen with use of atypicals in this patient group.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p.954.

1. Ray WA, *et al.* Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987; **316:** 363–9.
2. Higuchi T, *et al.* Certain neuroleptics reduce bone mineralization in schizophrenic patients. *Neuropsychobiology* 1987; **18:** 185–8.
3. Liu Y, *et al.* Comparative clinical effects of thioridazine (THD) on fall risk on young and elderly subjects. *Clin Pharmacol Ther* 1995; **57:** 200.
4. Leipzig RM, *et al.* Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999; **47:** 30–9.
5. McShane R, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* 1997; **314:** 266–70.
6. Holmes C, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Carriers of apolipoprotein E ε4 allele seem particularly susceptible to their effects. *BMJ* 1997; **314:** 1411.
7. McKeith I, *et al.* Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992; **305:** 673–8.
8. Piggott MA, *et al.* DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 1994; **343:** 1044–5. Correction. *ibid.*; 1170. [Title: Dopamine D2 receptors in demented patients with severe neuroleptic sensitivity.]
9. CSM/MCA. Neuroleptic sensitivity in patients with dementia. *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
10. Wang PS, *et al.* Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; **353:** 2335–41.
11. Gill SS, *et al.* Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; **146:** 775–86.

Epilepsy. See Convulsions under Adverse Effects, above.

Folic acid deficiency. Concentrations of folate in serum and erythrocytes were reduced in 15 patients receiving long-term treatment with chlorpromazine or thioridazine.[1] All the patients had significant induction of hepatic microsomal enzymes. It was suggested that folate deficiency due to the induction of microsomal enzymes might subsequently limit enzyme induction and hence reduce drug metabolism, which could lead to symptoms of toxicity in patients apparently stabilised for a number of years. The dietary intake of patients on long-term treatment with enzyme-inducing drugs might be inadequate.

1. Labadarios D, *et al*. The effects of chronic drug administration on hepatic enzyme induction and folate metabolism. *Br J Clin Pharmacol* 1978; **5:** 167–73.

Hypoparathyroidism. There have been rare reports[1,2] of acute dystonic reactions associated with the use of phenothiazines in patients with untreated hypoparathyroidism. Caution was recommended in giving phenothiazine derivatives to patients with hypoparathyroidism and it was suggested that any acute reaction to such a drug should prompt investigation for some form of latent tetany.

1. Schaaf M, Payne CA. Dystonic reactions to prochlorperazine in hypoparathyroidism. *N Engl J Med* 1966; **275:** 991–5.
2. Gur H, *et al.* Acute dystonic reaction to methotrimeprazine in hypoparathyroidism. *Ann Pharmacother* 1996; **30:** 957–9.

Pregnancy. Licensed product information generally does not recommend the use of phenothiazines in late pregnancy; such use may be associated with intoxication of the neonate. Chlorpromazine may prolong labour and should be withheld until the cervix is dilated 3 to 4 cm. Overall, however, it has been suggested[1] that the criteria for the selection of an antipsychotic for use in pregnant women do not differ from those used in non-pregnant women. It was also concluded that the benefits of continuing antipsychotic treatment at the minimum effective dose would usually outweigh any risks to the fetus.

A review[2] of the use of phenothiazines in pregnancy concluded that there was no clear evidence that these drugs caused a significant increase in fetal malformations. Nevertheless it was considered advisable that if pregnant patients required such treatment, then a single phenothiazine should be used and that it should be one of the established drugs.

A subsequent review[3] of the literature reported that women with schizophrenia are generally at increased risk for poor obstetric outcomes including preterm delivery, low birth-weight, and neonates who are small for their gestational age. It was also considered that there was an increased risk of congenital malformation when the fetus was exposed to phenothiazines during weeks 4 to 10 of gestation but this conclusion and the methods used to select the data to review have been criticised.[4]

See also p.563 for the use of phenothiazines as antiemetics during pregnancy.

1. Trixler M, Tényi T. Antipsychotic use in pregnancy: what are the best treatment options? *Drug Safety* 1997; **16:** 403–10.
2. McElhatton PR. The use of phenothiazines during pregnancy and lactation. *Reprod Toxicol* 1992; **6:** 475–90.
3. Patton SW, *et al.* Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; **47:** 959–65.
4. Levinson A. Review: women with schizophrenia have poorer pregnancy outcomes than other women, but it is unclear whether antipsychotic medications affect their infants. *Evid Based Ment Health* 2003; **6:** 89.

Renal impairment. Although there do not seem to be specific indications for dosage adjustment of phenothiazines in renal impairment, the *BNF* considers that cerebral sensitivity to antipsychotics may be increased in severe renal impairment. Phenothiazine-induced toxic psychosis occurred in 4 patients with chronic renal failure who had been given chlorpromazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

The most common interactions encountered with phenothiazines such as chlorpromazine result from use with drugs that have similar pharmacological actions. Symptoms of CNS depression may be enhanced by other drugs with CNS-depressant properties including alcohol, general anaesthetics, hypnotics, anxiolytics, and opioids. When given with other drugs that produce orthostatic hypotension, dosage adjustments may be necessary. However, it should be noted that phenothiazines have been reported to reduce the antihypertensive action of guanethidine and other adrenergic neurone blockers. As many phenothiazines possess antimuscarinic actions they can potentiate the adverse effects of other drugs with antimuscarinic actions, including tricyclic antidepressants and the antimuscarinic antiparkinsonian drugs that may be given to treat phenothiazine-induced extrapyramidal effects. In theory, antipsychotics with dopamine-blocking activity and dopaminergic drugs such as those used to treat parkinsonism may be mutually antagonistic. Use with metoclopramide may increase the risk of antipsychotic-induced extrapyramidal effects.

There is an increased risk of arrhythmias when antipsychotics are used with drugs that prolong the QT interval, including certain antiarrhythmics, other antipsychotics, some non-sedating antihistamines, antimalarials, and cisapride; use with diuretics that cause electrolyte imbalance (particularly hypokalaemia) may also have the same effect. There is also an increased risk of arrhythmias when tricyclic antidepressants are used with antipsychotics that prolong the QT interval.

Because of an increased risk of seizures US licensed product information for chlorpromazine recommends withdrawal before the use of metrizamide for radiographic procedures.

◊ Most interactions with antipsychotics are as a result of additive pharmacological effects.[1] Since tolerance develops to many of these adverse effects, interactions are likely to be most important in the early stages of combination therapy.

1. Livingston MG. Interactions that matter: 11 antipsychotic drugs. *Prescribers' J* 1987; **27** (Dec): 26–9.

Alcohol. Phenothiazines may increase the CNS depressant effects of alcohol. There has been a report of akathisia and dystonia after consumption of alcohol by patients taking antipsychotics;[1] alcohol might lower the threshold of resistance to neurotoxic adverse effects.

1. Lutz EG. Neuroleptic-induced akathisia and dystonia triggered by alcohol. *JAMA* 1976; **236:** 2422–3.

Antacids. Studies in 6 patients showed that chlorpromazine plasma concentrations were significantly lower after giving chlorpromazine with an *aluminium hydroxide* and *magnesium trisilicate* antacid gel (*Gelusil*) than after chlorpromazine alone.[1] *In-vitro* studies indicated that chlorpromazine was highly bound to the gel.

1. Fann WE, *et al*. Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* 1973; **13:** 388–90.

Antiarrhythmics. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with antiarrhythmics (especially *amiodarone*, *disopyramide*, *procainamide*, and *quinidine*) should be avoided. Use of haloperidol with amiodarone is also not recommended. A study[1] in healthy subjects has suggested that quinidine might increase plasma concentrations of haloperidol.

1. Young D, *et al.* Effect of quinidine on the interconversion kinetics between haloperidol and reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. *Eur J Clin Pharmacol* 1993; **44:** 433–8.

Antibacterials. Seven schizophrenic patients whose antitubercular therapy included *rifampicin* (in addition to isoniazid, and in some cases also ethambutol) had lower serum concentrations of haloperidol compared with tuberculotic schizophrenic patients receiving no antimycobacterials and with non-tuberculotic schizophrenics.[1] Pharmacokinetic studies involving some of these patients indicated accelerated haloperidol clearance in the presence of rifampicin. Abnormally high serum-haloperidol concentrations were observed in 3 of 18 patients treated with *isoniazid* alone.

Black galactorrhoea occurred in a patient receiving *minocycline*, perphenazine, amitriptyline hydrochloride, and diphenhydramine hydrochloride.[2] Simultaneous occurrence of phenothiazine-induced galactorrhoea and tetracycline-induced pigmentation was considered responsible.

Sudden cardiac deaths have been reported[3] in patients given *clarithromycin* and pimozide. Elevated pimozide plasma concentrations were recorded after pretreatment with clarithromycin.[4] The manufacturer of pimozide has recommended that pimozide should not be used with macrolide antibacterials.

1. Takeda M, *et al.* Serum haloperidol levels of schizophrenics receiving treatment for tuberculosis. *Clin Neuropharmacol* 1986; **9:** 386–97.
2. Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121:** 417–18.
3. Flockhart DA, *et al.* A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. *Clin Pharmacol Ther* 1996; **59:** 189.
4. Desta Z, *et al.* Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolisers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; **65:** 10–20.

Anticoagulants. For reference to the effects of some antipsychotics on the activity of anticoagulants, see under Warfarin, p.1430.

Antidepressants. Interactions between antipsychotics and *tricyclic antidepressants* are generally of two forms: additive pharmacological effects such as antimuscarinic effects or hypotension; or pharmacokinetic interactions. Although not commonly reported in the literature, additive antimuscarinic activity may be a significant risk especially in the elderly. Careful drug selection might help to prevent the development of serious adverse effects. Mutual inhibition of liver enzymes involved in the metabolism of both the antipsychotic and the tricyclic antidepressant might result in increased plasma concentrations of either drug. In one study,[1] addition of *nortriptyline* to chlorpromazine therapy produced an increase in plasma concentrations of chlorpromazine but this resulted in a paradoxical increase in agitation and tension.

There is an increased risk of arrhythmias when tricyclic antidepressants are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with tricyclic antidepressants should be avoided.

Increased serum concentrations of haloperidol have occurred when patients were also given *fluoxetine*,[2] *fluvoxamine*,[3] or *nefazodone*. Isolated reports[4-9] of extrapyramidal symptoms, psychoneuromotor syndrome, stupor, bradycardia, and urinary retention associated with use of fluoxetine with antipsychotics suggest that fluoxetine might exacerbate the adverse effects of antipsychotics or produce additive toxicity. Similar CNS effects have been noted in subjects given perphenazine and *paroxetine*.[10] There has also been an isolated report of a patient who complained of amenorrhoea and galactorrhoea after fluvoxamine was added to loxapine therapy.[11] Significant increases in the plasma concentrations of thioridazine have occurred after use with fluvoxamine.[12] Paroxetine may also inhibit the metabolism of thioridazine, resulting in increased thioridazine plasma concentrations; UK licensed product information for paroxetine contra-indicates their concomitant use. The US licensed product information for paroxetine states that giving paroxetine with pimozide was associated with a mean increase of 151% in the area under the concentration-time curve of pimozide and 62% in its mean maximum plasma concentration. Due to the narrow therapeutic index of pimozide concomitant use of these 2 drugs is contra-indicated.

Combinations of antipsychotics and *lithium* should be used with care. Lithium can reduce plasma-chlorpromazine concentrations and there is a report of ventricular fibrillation on withdrawal of lithium from a patient also taking chlorpromazine. Chlorpromazine has also been reported to enhance the excretion of lithium. Neurotoxic or extrapyramidal symptoms have been reported rarely in patients taking antipsychotics and lithium; these may be atypical cases of lithium toxicity or neuroleptic malignant syndrome. The above issues are discussed in detail, and references given, on p.405.

A patient on long-term trifluoperazine treatment developed neuroleptic malignant syndrome after a single dose of *venlafaxine*.[13] The authors noted that the manufacturers of venlafaxine have received a small number of similar reports after introduction of venlafaxine in patients receiving antipsychotics including molindone.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with phenothiazines.

1. Loga S, *et al.* Interaction of chlorpromazine and nortriptyline in patients with schizophrenia. *Clin Pharmacokinet* 1981; **6:** 454–62.
2. Goff DC, *et al.* Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* 1991; **148:** 790–2.
3. Daniel DG, *et al.* Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 1994; **14:** 340–3.
4. Tate JL. Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine. *Am J Psychiatry* 1989; **146:** 399–400.
5. Ahmed I, *et al.* Possible interaction between fluoxetine and pimozide causing sinus bradycardia. *Can J Psychiatry* 1993; **38:** 62–3.
6. Ketai R. Interaction between fluoxetine and neuroleptics. *Am J Psychiatry* 1993; **150:** 836–7.
7. Hansen-Grant S, *et al.* Fluoxetine-pimozide interaction. *Am J Psychiatry* 1993; **150:** 1751–2.
8. D'Souza DC, *et al.* Precipitation of a psychoneuromotor syndrome by fluoxetine in a haloperidol-treated schizophrenic patient. *J Clin Psychopharmacol* 1994; **14:** 361–3.
9. Benazzi F. Urinary retention with fluoxetine-haloperidol combination in a young patient. *Can J Psychiatry* 1996; **41:** 606–7.
10. Özdemir V, *et al.* Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* 1997; **62:** 334–47.
11. Jeffries J, *et al.* Amenorrhea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* 1992; **12:** 296–7.
12. Carrillo JA, *et al.* Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *J Clin Psychopharmacol* 1999; **19:** 494–9.
13. Nimmagadda SR, *et al.* Neuroleptic malignant syndrome after venlafaxine. *Lancet* 2000; **354:** 289–90.

Antidiabetic drugs. Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of *oral hypoglycaemics* or of *insulin* may need to be increased in diabetics.

Antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* are potent enzyme inducers and use may decrease plasma concentrations of antipsychotics or their active metabolites.[1-5] The clinical effect of any interaction has not been consistent; worsening, improvement, or no change in psychotic symptoms have all been noted. Delirium has been reported in a patient given haloperidol and carbamazepine.[6] Phenytoin might also exacerbate antipsychotic-induced dyskinesia.[7] Care should be taken when withdrawing enzyme-inducing antiepileptics as this may result in a rise in antipsychotic serum concentrations.[8]

The effect of antipsychotics on antiepileptic concentrations is discussed on p.475 (carbamazepine) and p.499 (phenytoin). It should also be remembered that antipsychotics may lower the seizure threshold.

1. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.
2. Linnoila M, *et al.* Effect of anticonvulsants on plasma haloperidol and thioridazine levels. *Am J Psychiatry* 1980; **137:** 819–21.
3. Jann MW, *et al.* Effects of carbamazepine on plasma haloperidol levels. *J Clin Psychopharmacol* 1985; **5:** 106–9.
4. Arana GW, *et al.* Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? *Am J Psychiatry* 1986; **143:** 650–1.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Kanter GL, *et al.* Case report of a possible interaction between neuroleptics and carbamazepine. *Am J Psychiatry* 1984; **141:** 1101–2.
7. DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. *N Engl J Med* 1978; **298:** 457–8.
8. Jann MW, *et al.* Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 1989; **28:** 153–9.

Antihistamines. For the effect of a preparation containing *chlorphenamine maleate* and phenylpropanolamine hydrochloride on thioridazine, see Sympathomimetics (below). There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with antihistamines such as *astemizole* or *terfenadine* should be avoided.

Antihypertensives. For discussion of the interaction between phenothiazines and drugs with hypotensive properties, see Interactions, above. For a report of chlorpromazine enhancing the hyperglycaemic effect of *diazoxide*, see p.1258. For reports of hypertension or dementia in patients given *methyldopa* and antipsychotics, see p.1335.

Antimalarials. Pretreatment with single doses of *chloroquine sulfate*, *amodiaquine hydrochloride*, or *sulfadoxine with pyrimethamine* increased the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, but not of chlorpromazine sulfoxide, in schizophrenic patients maintained on chlorpromazine.[1] The raised plasma concentrations appeared to be associated with a greater level of sedation.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of antipsychotics, and pimozide in particular, with antimalarials such as *halofantrine*, *mefloquine*, or *quinine* should be avoided. For the possible effects of the use of *quinidine* with antipsychotics see Antiarrhythmics, above.

1. Makanjuola ROA, *et al.* Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop Geogr Med* 1988; **40:** 31–3.

Antimigraine drugs. A report[1] of a patient receiving loxapine who had a dystonic reaction within 15 minutes of subcutaneous *sumatriptan* suggests that these two drugs might interact or potentiate each other's adverse effects. However, the patient had a previous history of dystonic reactions associated with haloperidol and was receiving benzatropine prophylactically. Furthermore, the dose of loxapine had been increased 2 days before the event and this may have predisposed the patient to dystonia.

1. Garcia G, *et al.* Dystonic reaction associated with sumatriptan. *Ann Pharmacother* 1994; **28:** 1199.

Antiparkinsonian drugs. Antiparkinsonian drugs are sometimes given with antipsychotics for the management of antipsychotic-induced adverse effects including extrapyramidal disorders (see under Adverse Effects, above). Theoretically, dopaminergics such as *levodopa* and *bromocriptine* might induce or exacerbate psychotic symptoms. A study in 18 subjects and review of the literature suggested that bromocriptine can be used safely in patients at risk of psychotic illness provided they are clinically stable and maintained on antipsychotics.[1] Conversely, antipsychotics might antagonise the effects of dopaminergics; diminished therapeutic effects of levodopa have been noted with several antipsychotics (see p.808) and thioridazine has been reported to oppose the prolactin-lowering action of bromocriptine (see p.800).

Additive antimuscarinic adverse effects are obviously a risk when antimuscarinic antiparkinsonian drugs are given with antipsychotics. Although these are generally mild, serious reactions have occurred. *Trihexyphenidyl*[2] and *orphenadrine*[3] have both been reported to decrease plasma concentrations of chlorpromazine, possibly by interfering with absorption from the gastrointestinal tract. Reports suggesting that antimuscarinics may antagonise the antipsychotic effects of antipsychotics at the neurotransmitter level require substantiating.

1. Perovich RM, *et al.* The behavioral toxicity of bromocriptine in patients with psychiatric illness. *J Clin Psychopharmacol* 1989; **9:** 417–22.
2. Rivera-Calimlim L, *et al.* Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin Pharmacol Ther* 1973; **14:** 978–86.
3. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.

Antipsychotics. Elevated plasma levels of haloperidol were reported[1] in a patient being treated for schizophrenia when *chlorpromazine* or *clozapine* were also given.

1. Allen SA. Effect of chlorpromazine and clozapine on plasma concentrations of haloperidol in a patient with schizophrenia. *J Clin Pharmacol* 2000; **40:** 1296–7.

Antivirals. *Ritonavir* may increase the plasma concentration of some antipsychotics. The increases expected for pimozide were considered in licensed product information for ritonavir to be large enough to recommend that these drugs should not be used together. Other classical antipsychotics predicted to have increases include haloperidol, perphenazine, and thioridazine; it was recommended that monitoring of drug concentrations and/or adverse effects were required when used with ritonavir.

Beta blockers. Chlorpromazine and *propranolol* may mutually inhibit each other's hepatic metabolism. Propranolol has been reported to increase plasma concentrations of chlorpromazine[1] and thioridazine,[2,3] and *pindolol* to increase plasma-thioridazine concentrations.[4] Neither beta blocker tested had a significant effect on haloperidol concentrations,[3,4] although there is a report of severe hypotension or cardiopulmonary arrest occurring on 3 occasions in a schizophrenic patient given haloperidol with propranolol.[5] The clinical significance of antipsychotic-beta blocker interactions is unclear.

For the effect of chlorpromazine on propranolol, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p.1228.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. The use of antipsychotics, and pimozide in particular, with *sotalol* should be avoided.

1. Peet M, *et al.* Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet* 1980; **ii:** 978.
2. Silver JM, *et al.* Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry* 1986; **143:** 1290–2.
3. Greendyke RM, Kanter DR. Plasma propranolol levels and their effect on plasma thioridazine and haloperidol concentrations. *J Clin Psychopharmacol* 1987; **7:** 178–82.
4. Greendyke RM, Gulya A. Effect of pindolol administration on serum levels of thioridazine, haloperidol, phenytoin, and phenobarbital. *J Clin Psychiatry* 1988; **49:** 105–7.
5. Alexander HE, *et al.* Hypotension and cardiopulmonary arrest associated with concurrent haloperidol and propranolol therapy. *JAMA* 1984; **252:** 87–8.

Buspirone. The use of haloperidol with buspirone has resulted in increased serum haloperidol concentrations. However, while some[1] found the mean rise in serum-haloperidol concentrations to be 26%, that observed by others[2] was not statistically significant.

1. Goff DC, *et al.* An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 1991; **11:** 193–7.
2. Huang HF, *et al.* Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. *J Clin Pharmacol* 1996; **36:** 963–9.

Cimetidine. Despite expectations that cimetidine might reduce the metabolism of chlorpromazine, mean steady-state plasma concentrations of chlorpromazine fell rather than rose in 8 patients given cimetidine for 7 days in addition to regular chlorpromazine therapy.[1] The explanation was probably that cimetidine interfered with chlorpromazine absorption. Excessive sedation, necessitating a reduction in chlorpromazine dosage, has been reported[2] after addition of cimetidine to the drug therapy of 2 chronic schizophrenics.

1. Howes CA, *et al.* Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur J Clin Pharmacol* 1983; **24:** 99–102.
2. Byrne A, O'Shea B. Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *Br J Psychiatry* 1989; **155:** 413–15.

Cocaine. The risk of antipsychotic-induced dystonic reactions may be increased in cocaine abusers. Dystonia occurred in 6 of 7 cocaine abusers treated with haloperidol.[1]

1. Kumor K, *et al.* Haloperidol-induced dystonia in cocaine addicts. *Lancet* 1986; **ii:** 1341–2.

Desferrioxamine. Loss of consciousness lasting 48 to 72 hours occurred in 2 patients given prochlorperazine during desferrioxamine therapy.[1] Prochlorperazine may enhance the removal of transition metals from brain cells by desferrioxamine.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Disulfiram. A psychotic patient, previously maintained with plasma-perphenazine concentrations of 2 to 3 nanomol/mL on a dose of 8 mg twice daily by mouth, was readmitted with subtherapeutic plasma-perphenazine concentrations of less than 1 nanomol/mL, despite unchanged dosage, after disulfiram therapy.[1] The concentration of the sulfoxide metabolite of perphenazine was much increased. After a change from oral to intramuscular perphenazine therapy there was a substantial clinical improvement associated with a return to therapeutic plasma concentrations of perphenazine and a fall in concentration of the metabolite. Disulfiram appears to greatly enhance biotransformation of oral perphenazine to inactive metabolites, but parenteral administration avoids the 'first-pass' effect in the liver.

1. Hansen LB, Larsen N-E. Metabolic interaction between perphenazine and disulfiram. *Lancet* 1982; **ii:** 1472.

General anaesthetics. A schizophrenic patient without a history of epilepsy who was receiving oral chlorpromazine and flupentixol depot injection had a convulsive seizure when given *enflurane* anaesthesia.[1]

1. Vohra SB. Convulsions after enflurane in a schizophrenic patient receiving neuroleptics. *Can J Anaesth* 1994; **41:** 420–2.

Naltrexone. Two patients maintained on thioridazine experienced intense sleepiness and lethargy after receiving 2 doses of naltrexone.[1]

1. Maany I, *et al.* Interaction between thioridazine and naltrexone. *Am J Psychiatry* 1987; **144:** 966.

NSAIDs. A report of severe drowsiness and confusion in patients given haloperidol with *indometacin*.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Opioid analgesics. For reference to the effects of phenothiazines on *pethidine*, see p.114.

Piperazine. There has been an isolated report[1] of convulsions associated with the use of chlorpromazine in a child who had received piperazine several days earlier. Subsequent *animal*[1-3] studies produced conflicting evidence for an interaction and it was suggested[3] that an interaction would only be clinically significant when high concentrations of piperazine were reached in the body.

1. Boulos BM, Davis LE. Hazard of simultaneous administration of phenothiazine and piperazine. *N Engl J Med* 1969; **280:** 1245–6.
2. Armbrecht BH. Reaction between piperazine and chlorpromazine. *N Engl J Med* 1970; **282:** 1490–1.
3. Sturman G. Interaction between piperazine and chlorpromazine. *Br J Pharmacol* 1974; **50:** 153–5.

Sympathomimetics. For reference to the possible interaction between phenothiazines and *adrenaline*, see Treatment of Adverse Effects, above.

A 27-year-old woman with schizophrenia and T-wave abnormality of the heart,[1] receiving thioridazine 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of also taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with *phenylpropanolamine hydrochloride* 50 mg (*Contac C*).

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Tobacco smoking. Smoking has been shown to decrease the incidence of chlorpromazine-induced sedation[1,2] and orthostatic hypotension.[2] Studies indicate that the clearance of chlorpromazine,[3] fluphenazine,[4] tiotixene,[5] haloperidol,[6] and thioridazine[7] may be increased in patients who smoke. It has been suggested that some of the components of smoke may act as liver-enzyme inducers. The clinical significance of this effect is unclear but the possible need to use increased doses in smokers should be borne in mind.

1. Swett C. Drowsiness due to chlorpromazine in relation to cigarette smoking: a report from the Boston Collaborative Drug Surveillance Program. *Arch Gen Psychiatry* 1974; **31:** 211–13.
2. Pantuck EJ, *et al.* Cigarette smoking and chlorpromazine disposition and actions. *Clin Pharmacol Ther* 1982; **31:** 533–8.
3. Chetty M, *et al.* Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* 1994; **46:** 523–6.
4. Ereshefsky L, *et al.* Effects of smoking on fluphenazine clearance in psychiatric inpatients. *Biol Psychiatry* 1985; **20:** 329–32.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Jann MW, *et al.* Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology (Berl)* 1986; **90:** 468–70.
7. Berecz R, *et al.* Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. *Eur J Clin Pharmacol* 2003; **59:** 45–50.

Vitamins. Giving *ascorbic acid*, for vitamin C deficiency, to a patient receiving fluphenazine for bipolar disorder was associated with a fall in serum concentrations of fluphenazine and a deterioration of behaviour.[1]

1. Dysken MW, *et al.* Drug interaction between ascorbic acid and fluphenazine. *JAMA* 1979; **241:** 2008.

Xanthine-containing beverages. Studies *in vitro* have shown precipitation of some antipsychotics from solution by addition of coffee and tea.[1,2] However, in a study of 16 patients taking antipsychotics no correlation could be found between plasma-antipsychotic concentrations or behaviour and tea or coffee consumption.[3]

1. Kulhanek F, *et al.* Precipitation of antipsychotic drugs in interaction with coffee or tea. *Lancet* 1979; **ii:** 1130.
2. Lasswell WL, *et al.* In vitro interaction of neuroleptics and tricyclic antidepressants with coffee, tea, and gallotannic acid. *J Pharm Sci* 1984; **73:** 1056–8.
3. Bowen S, *et al.* Effect of coffee and tea on blood levels and efficacy of antipsychotic drugs. *Lancet* 1981; **i:** 1217–18.

Pharmacokinetics

Chlorpromazine is readily, although sometimes erratically, absorbed from the gastrointestinal tract; peak plasma concentrations are attained 2 to 4 hours after ingestion. It is subject to considerable first-pass metabolism in the gut wall and is also extensively metabolised in the liver and is excreted in the urine and bile in the form of numerous active and inactive metabolites; there is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after intramuscular doses. Moreover, there is very wide intersubject variation in plasma concentrations of chlorpromazine; no simple correlation has been found between plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect (see Administration under Uses and Administration, below). Paths of metabolism of chlorpromazine include hydroxylation and conjugation with glucuronic acid, *N*-oxidation, oxidation of a sulfur atom, and dealkylation. Although the plasma half-life of chlorpromazine itself has been reported to be about 30 hours, elimination of the metabolites may be very prolonged. There is limited evidence that chlorpromazine induces its own metabolism.

Chlorpromazine is about 95 to 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placenta and are distributed into breast milk.

Uses and Administration

Chlorpromazine is a phenothiazine antipsychotic. It has a wide range of activity arising from its depressant actions on the CNS and its alpha-adrenergic blocking and antimuscarinic activities. Chlorpromazine is a dopamine inhibitor; the turnover of dopamine in the brain is also increased. There is some evidence that the antagonism of central dopaminergic function, especially at the D_2-dopaminergic receptor, is related to therapeutic effect in psychotic conditions. Chlorpromazine possesses sedative properties but patients usually develop tolerance rapidly to the sedation. It has antiemetic, serotonin-blocking, and weak antihistaminic properties and slight ganglion-blocking activity. It inhibits the heat-regulating centre so that the patient tends to acquire the temperature of the surroundings (poikilothermy). Chlorpromazine can relax skeletal muscle.

Chlorpromazine is widely used in the management of psychotic conditions as well as in some non-psychotic disorders, such as:

- acute and chronic schizophrenia (p.955) in adults and children
- to reduce acute mania, as in bipolar disorder (p.372)
- control of severely disturbed, agitated, or violent behaviour in adults and children (p.954) and sometimes other psychiatric conditions
- in autistic children
- as an adjunct for the short-term treatment of severe anxiety (but see also p.952), and to reduce pre-operative anxiety in adults and children
- as an antiemetic in some forms of nausea and vomiting (p.1700) in adults and children; it is ineffective in motion sickness
- in the alleviation of intractable hiccup (below)
- as an adjunct in the treatment of tetanus in adults and children (p.196 and p.1901) and to control symptoms in acute intermittent porphyria (p.1448)
- for induction of hypothermia

Chlorpromazine is given orally as the hydrochloride and the embonate. For both salts, the doses are expressed as the hydrochloride; chlorpromazine embonate 144 mg is equivalent to about 100 mg of chlorpromazine hydrochloride. Chlorpromazine is also given by injection as the hydrochloride and doses are expressed in terms of this salt. The base is given rectally as suppositories; doses are in terms of the base.

Dosage varies both with the individual and with the purpose for which the drug is being used. In most patients with **psychiatric conditions** *oral treatment* may be used from the start, typically commencing with a dosage of 25 mg of the hydrochloride, or its equivalent as the embonate, three times daily and increasing as necessary; daily doses of 75 mg may be given as a single dose at night. In some patients doses of 10 mg three times daily may be adequate. Maintenance doses, when required, usually range from 25 to 100 mg three times daily, although psychotic patients may require daily doses of up to 1 g or more.

For *parenteral use*, deep intramuscular injection is preferable, but diluted solutions have sometimes been given by slow intravenous infusion for indications such as tetanus, severe intractable hiccup, or nausea and vomiting associated with surgery. Subcutaneous injection is contra-indicated. After injection of chlorpromazine, patients should remain in the supine position for at least 30 minutes; blood pressure should be monitored. The usual dose by intramuscular injection is 25 to 50 mg repeated every 6 to 8 hours if required, although oral therapy should be substituted as soon as possible.

If the oral and parenteral routes are not suitable chlorpromazine may be given *rectally* as suppositories containing 100 mg of chlorpromazine base; this is stated to have an effect comparable with 40 to 50 mg of the hydrochloride orally or 20 to 25 mg intramuscularly. The usual rectal dose is 100 mg every 6 to 8 hours.

Initial oral doses of chlorpromazine of one-third to one-half the usual adult dose have been recommended for *elderly* or *debilitated patients*; doses should be increased more gradually. Intramuscular doses in the elderly may need to be reduced to up to one-quarter of the usual dose.

Chlorpromazine hydrochloride may be given to *children* aged 1 to 12 years in a dose of 500 micrograms/kg every 4 to 6 hours orally or every 6 to 8 hours by intramuscular injection. However, for psychiatric indications the oral dose for children aged over 5 years is usually one-third to one-half the adult dose; alternatively, the *BNFC* suggests a dose of 10 mg 3 times daily. Daily doses should not normally exceed 40 mg of chlorpromazine hydrochloride for children aged 1 to 5 years or 75 mg for children over 5 years of age. Chlorpromazine may be given to infants under 1 year of age if considered to be life-saving. Suppositories containing 25 mg of chlorpromazine base are available in some countries for use in children.

Doses of 10 to 25 mg every 4 to 6 hours orally are recommended for control of **nausea and vomiting**. If necessary, an initial dose of 25 mg may be given by intramuscular injection, followed by 25 to 50 mg every 3 to 4 hours until vomiting stops.

If **intractable hiccup** does not respond to an oral dose of 25 to 50 mg three or four times daily for 2 to 3 days then 25 to 50 mg may be given intramuscularly; if this fails 25 to 50 mg in 500 to 1000 mL of 0.9% sodium chloride should be given by slow intravenous infusion, with the patient supine, and careful monitoring of the blood pressure.

Action. The therapeutic effects of antipsychotics appear to be mediated, at least in part, by interference with dopamine transmission in the brain. Chlorpromazine, thioridazine, and thioxanthene derivatives have relatively equal affinity for D_1 or D_2 receptors, although their metabolites tend to be more potent as D_2 blockers.[1] Butyrophenones (such as haloperidol) and diphenylbutylpiperidines (such as pimozide) are relatively selective for D_2 receptors, and the substituted benzamides (such as sulpiride) are highly D_2-specific. Clozapine has complex actions: it is a relatively weak inhibitor of D_2 receptors but has a high affinity for a number of other receptors including D_1, D_4, and serotonin$_2$ (5-HT_2) receptors.[2] Other atypicals mostly share this profile of greater 5-HT_2 than D_2 antagonism.[2]

The traditional hypothesis of the action of antipsychotics has been that blockade of D_2 receptors in the limbic and cortical regions is responsible for the antipsychotic effects, and that adverse extrapyramidal motor effects result from blockade of D_2 receptors in the striatum (a typical motor region of the basal ganglia).[3] Modification of prolactin secretion results from blockade of D_2

receptors in the anterior pituitary. However, this hypothesis cannot satisfactorily account for the pharmacological profiles of atypical antipsychotics and the debate concerning their mechanism of action continues. It has been suggested that the balance between 5-HT_2 and D_2 antagonism is important in determining 'atypicality' (but the atypical antipsychotic amisulpride lacks marked 5-HT_2 antagonism), or that rapid dissociation from the D_2 receptor may be the determining factor (but it is not clear that some atypicals such as risperidone meet this criterion).[2] Other systems, such as glutamate, may play a role in modulating effectiveness against negative versus positive symptoms;[2] it has been suggested that the calcium antagonist actions of the diphenylbutylpiperidines may also be important in this respect.[4]

Division of antipsychotics into low- and high-potency drugs is discussed in Administration, below. For reference to the actions of antipsychotics on neuroendocrine function, see Effects on Endocrine Function under Adverse Effects, above.

1. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.
2. Remington G. Understanding antipsychotic 'atypicality': a clinical and pharmacological moving target. *J Psychiatry Neurosci* 2003; **28:** 275–84.
3. Anonymous. Now we understand antipsychotics? *Lancet* 1990; **336:** 1222–3.
4. Snyder SH. Drug and neurotransmitter receptors: new perspectives with clinical relevance. *JAMA* 1989; **261:** 3126–9.

Administration. The classical antipsychotics are often divided into:

- **low-potency** drugs (phenothiazines with an aliphatic or piperidine side-chain or thioxanthenes with an aliphatic side-chain)
- **high-potency** drugs (butyrophenones, diphenylbutylpiperidines, and phenothiazines or thioxanthenes with a piperazine side-chain)

At doses with equipotent antipsychotic activity, the low-potency drugs are more prone to cause sedation and antimuscarinic or α-adrenergic-blocking effects than the high-potency drugs. However, they are associated with a lower incidence of extrapyramidal effects, with the exception of tardive dyskinesia which is likely to occur to the same extent with all classical antipsychotics.

Equivalent doses of antipsychotics quoted in the literature have varied considerably. In the UK the following daily doses of oral antipsychotics have been suggested to have approximately equipotent antipsychotic activity for doses up to the maximum licensed doses:

- chlorpromazine hydrochloride 100 mg
- clozapine 50 mg
- haloperidol 2 to 3 mg
- pimozide 2 mg
- risperidone 0.5 to 1 mg
- sulpiride 200 mg
- thioridazine 100 mg
- trifluoperazine 5 mg

It should be noted that all patients receiving pimozide require an annual ECG and all those receiving more than 16 mg of pimozide daily require periodic ECGs (see p.1018). Thioridazine also requires specialist supervision (p.1032).

Suggested equipotent doses of intramuscular depot antipsychotics are:

- flupentixol decanoate 40 mg every 2 weeks
- fluphenazine decanoate 25 mg every 2 weeks
- haloperidol (as the decanoate) 100 mg every 4 weeks
- pipotiazine palmitate 50 mg every 4 weeks
- zuclopenthixol decanoate 200 mg every 2 weeks

It has been noted[1] that *high doses* of antipsychotics (greater than the equivalent of 600 mg of chlorpromazine daily) are generally not necessary for the treatment (both initial and maintenance) of psychotic disorders, and may be associated with an increased risk of adverse effects as well as with a diminished clinical response. However, if high doses of antipsychotics have to be used, then doses should be increased gradually with caution and under the supervision of a specialist with facilities for emergency resuscitation available. The Royal College of Psychiatrists in the UK (which defines high-dose therapy as that involving a total daily dose greater than the upper limit recommended in the *BNF*) has issued recommendations concerning the use of high-dose antipsychotic medication.[2] It considers:

- current evidence does not justify the routine use of high-dose therapy with antipsychotics
- if high-dose therapy is used, this should only be after evidence-based strategies have failed, and as a carefully-monitored therapeutic trial
- the decision to use high-dose therapy, and the expected outcome, should be fully documented, after expert assessment of the patient
- the possible contra-indications to therapy, and the risk of drug interactions, should be assessed beforehand
- an ECG should be carried out before starting high-dose therapy and should be repeated after a few days, and then every 1 to 3 months in the early stages of treatment, or as clinically indicated
- doses should be increased in relatively small increments, with time to assess response before a further increase
- the use of 'as-required' antipsychotic medication, and of drug combinations, should be carefully monitored to avoid the inadvertent increase of total doses above high-dose thresholds

The existence of a *therapeutic range* (or therapeutic window) has not been demonstrated for most antipsychotics (with the possible exception of haloperidol[3]), and plasma concentrations of these drugs must be interpreted with caution.[1,3] Many factors make it difficult to establish a meaningful correlation between dose, plasma concentrations, and clinical improvement. These include incomplete absorption, first-pass effect, enzyme induction, the presence of active and inactive metabolites, ethnicity, smoking, and factors occurring at the receptor level.[3]

1. Baldessarini RJ, *et al.* Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; **45:** 77–91.
2. The Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. *Council Report CR138*; London: Royal College of Psychiatrists, May 2006. Available at: http://www.rcpsych.ac.uk/files/pdfversion/CR138.pdf (accessed 30/05/06)
3. Sramek JJ, *et al.* Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22:** 373–80.

Administration in children. For reference to the use of lytic cocktails containing chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see Lytic Cocktails, under Sedation, p.115.

Bipolar disorder. Patients with bipolar disorder (p.372) suffering from acute mania with coexisting psychotic features, agitation, or disruptive behaviour are usually treated with antipsychotics as they produce rapid control of symptoms. Classical antipsychotics such as chlorpromazine or haloperidol have been widely used, although use of atypical antipsychotics, such as clozapine or olanzapine, is growing.

Chorea. For a discussion of the management of various choreas, including mention of the use of phenothiazines such as chlorpromazine, see p.953.

Dyspnoea. It has been shown that in healthy subjects an oral dose of 25 mg of chlorpromazine hydrochloride can reduce exercise-induced breathlessness without affecting ventilation or causing sedation.[1] Although other drugs may be preferred in patients with advanced cancer and dyspnoea (p.104), chlorpromazine may relieve air hunger unresponsive to usual measures,[2] and, if required, can be used to sedate dying patients who have unrelieved distress. It is recommended that initial doses should be small: 12.5 mg by slow intravenous injection or 25 mg by suppository may be given.

1. O'Neill PA, *et al.* Chlorpromazine—a specific effect on breathlessness? *Br J Clin Pharmacol* 1985; **19:** 793–7.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to other drugs.[1] However, they often act non-specifically, damping down excessive movements by causing a degree of drug-induced parkinsonism and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects, above).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Eclampsia and pre-eclampsia. Drug combinations known as lytic cocktails have been used in many countries for the management of pre-eclampsia and imminent eclampsia. The cocktail has usually consisted of a combination of chlorpromazine, pethidine, and/or promethazine. In general, however, phenothiazines are not recommended in late pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p.1171); the management of eclampsia, which is the convulsive phase, is discussed on p.470.

Headache. Some phenothiazines such as chlorpromazine, levomepromazine, and prochlorperazine have been used in migraine to control severe nausea and vomiting unresponsive to antiemetics such as metoclopramide and domperidone (see p.616), and to relieve the pain of severe migraine attacks unresponsive to parenteral dihydroergotamine or sumatriptan.

References.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20:** 1201–5.
2. Jones EB, *et al.* Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med* 1994; **24:** 237–41.
3. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
4. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
5. Kelly AM, *et al.* Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. *J Accid Emerg Med* 1997; **14:** 209–11.
6. Bigal ME, *et al.* Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med* 2002; **23:** 141–8.

Hiccup. A hiccup is an involuntary spasmodic contraction of the diaphragm that causes a sudden inspiration of air which is then checked abruptly by closure of the glottis. Hiccups often have a simple cause such as gastric distension and usually resolve spontaneously or respond to simple measures. Intractable hiccups may stem from a serious underlying cause such as brain disorders, metabolic or endocrine disturbances, CNS infections, and oesophageal or other gastrointestinal disorders. Other precipitants include anaesthesia or drug therapy.

Treatment of intractable hiccups should initially be aimed at controlling or removing the underlying cause including the relief of gastric distension or oesophageal obstruction.[1-5] Measures that raise carbon dioxide pressure such as breath holding, rebreathing, or alteration of normal respiratory rhythm can be effective. Stimulation of the pharynx can also interrupt hiccups and may explain the action of a host of remedies such as sipping iced water, gargling, and swallowing granulated sugar. Many drugs have been tried in the treatment of hiccups but evidence of efficacy is largely from anecdotal reports or uncontrolled studies. An early treatment protocol[6] for intractable hiccups (based on a review of the literature and the authors' experience) suggested stepwise management until an effective measure was found, as follows:

- correction of any metabolic abnormality
- swallowing dry granulated sugar
- decompressing the stomach via nasogastric tube, then irritation of the pharynx
- intravenous chlorpromazine 25 to 50 mg, repeated up to 3 times if necessary; if parenteral therapy is effective maintain on chlorpromazine by mouth for 10 days (licensed information recommends the use of oral therapy first —see Uses and Administration, above)
- metoclopramide 10 mg intravenously; if successful maintain on metoclopramide by mouth for 10 days
- quinidine 200 mg by mouth 4 times daily
- if this fails, consider left phrenic nerve block and crush

In later discussions,[1,3] chlorpromazine still emerged as the most consistently effective drug treatment; metoclopramide appeared to be an acceptable second choice and nifedipine an appropriate third choice,[3] although haloperidol was also considered to be of value.[1,4] Other phenothiazines that have been used for intractable hiccup include perphenazine and promazine. It was also considered that clonazepam, carbamazepine, phenytoin, and valproic acid might be of value, especially in neuropathic hiccups.[1] Some beneficial results have been reported with amitriptyline and amantadine; other drugs being tried in the treatment of hiccups include baclofen and gabapentin. The *BNF* recommends that in palliative care patients, a preparation combining an antacid with an antiflatulent be given for hiccups due to gastric distension. If this fails, metoclopramide (orally or by subcutaneous or intramuscular injection) should be added; baclofen, nifedipine, or chlorpromazine should be reserved for those patients in whom metoclopramide is also ineffective.

1. Howard RS. Persistent hiccups: if excluding or treating any underlying pathology fails try chlorpromazine. *BMJ* 1992; **305:** 1237–8.
2. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.
3. Friedman NL. Hiccups: a treatment review. *Pharmacotherapy* 1996; **16:** 986–95.
4. WHO. Hiccup. In: *Symptom relief in terminal illness.* Geneva: WHO, 1998.
5. Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. *Am J Hosp Palliat Care* 2003; **20:** 149–54.
6. Williamson BWA, Macintyre IMC. Management of intractable hiccup. *BMJ* 1977; **2:** 501–3.

Lesch-Nyhan syndrome. The Lesch-Nyhan syndrome is an inherited disorder caused by a complete deficiency of hypoxanthine-guanine phosphoribosyl transferase, an enzyme involved in purine metabolism. It is characterised by hyperuricaemia, spasticity, choreoathetosis, self-mutilation, and mental retardation. The hyperuricaemia (see p.552) can be controlled by drugs such as allopurinol but there appears to be no effective treatment for the neurological deficits. It has been suggested that the behavioural problems might be associated with alterations in the brain's dopamine system. There have been rare reports of improvement in self-mutilation in patients given antipsychotics or antiepileptics such as carbamazepine and gabapentin.

References.

1. Nyhan WL, Wong DF. New approaches to understanding Lesch-Nyhan disease. *N Engl J Med* 1996; **334:** 1602–4.

Migraine. See under Headache, above.

Nausea and vomiting. Many antipsychotics, with the notable exception of thioridazine, have antiemetic properties and have been used in the prevention and treatment of nausea and vomiting (p.1700) arising from a variety of causes such as radiation sickness, malignancy, and emesis caused by drugs, including antineoplastics and opioid analgesics. Reference to the risk to the fetus of therapy with phenothiazines during pregnancy can be found under Precautions, above and on p.563.

Schizophrenia. Classical antipsychotics such as chlorpromazine, haloperidol, and thioridazine have been the traditional drug treatment of choice for patients with schizophrenia (p.955); however, atypical antipsychotics may now be preferred as first-line therapy. There is little difference in efficacy between the classical antipsychotics, but the use of thioridazine is now restricted in the treatment of schizophrenia because of the risk of cardiotoxicity.

Substance dependence. ***ALCOHOL.*** For advice against the use of antipsychotics for alcohol withdrawal, see p.1626.

OPIOIDS. In a discussion of neonatal abstinence syndrome (p.102), it was observed in 1986 that, although opioids, diazepam, and phenobarbital were widely used in the USA for the management of this condition, chlorpromazine had tended to be the preferred treatment in the UK.[1] This was still true as late as the mid-1990s, although practice varied widely.[2] However, a systematic review[3] found insufficient evidence to support the use of chlorpromazine in the management of neonatal abstinence syndrome. The following dosage schedule has been suggested:[1] chlorpromazine is begun with a loading dose of 3 mg/kg, followed by a total oral maintenance dose of 3 mg/kg daily, divided into 4 or 6 doses. The authors suggested that this dose might be increased by 3 mg/kg daily if withdrawal symptoms were particularly severe. Once stabilised a reduction in the dose of chlorpromazine by 2 mg/kg every third day is attempted.[1] Complications of phenothiazine usage have been notably absent, although rarely seizures may occur.

1. Rivers RPA. Neonatal opiate withdrawal. *Arch Dis Child* 1986; **61:** 1236–9.
2. Morrison CL, Siney C. A survey of the management of neonatal opiate withdrawal in England and Wales. *Eur J Pediatr* 1996; **155:** 323–6.
3. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 02/10/07).

Taste disorders. Disturbances of the sense of taste may be broadly divided into either loss or distortion of taste. Loss of taste may be either complete (ageusia) or partial (hypogeusia). Distortion of taste (dysgeusia) may occur as aliageusia in which stimuli such as food or drink produce an inappropriate taste or as phantogeusia in which an unpleasant taste is not associated with an external stimuli and is sometimes referred to as a gustatory hallucination. Taste disturbances have many causes including infections, metabolic or nutritional disturbances, radiation, CNS disorders, neoplasms, drug therapy, or may occur as a consequence of normal ageing.[1] Management primarily consists of treatment of any underlying disorder. Withdrawal of offending drug therapy is commonly associated with resolution but occasionally effects persist and may require treatment.[2] Zinc or vitamin therapy has been used but there is insufficient evidence to indicate efficacy[1,3] for taste disturbances secondary to drug therapy or medical conditions that do not involve low zinc or vitamin concentrations. Phantogeusia might be linked to excessive activity of dopaminergic receptors as it has been reported[4] to respond to short-term treatment with small doses of antipsychotic drugs such as haloperidol or pimozide.

1. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997; **278:** 1357–62.
2. Henkin RI. Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Safety* 1994; **11:** 318–77.
3. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
4. Henkin RI. Salty and bitter taste. *JAMA* 1991; **265:** 2253.

Preparations

BP 2008: Chlorpromazine Injection; Chlorpromazine Oral Solution; Chlorpromazine Suppositories; Chlorpromazine Tablets;
USP 31: Chlorpromazine Hydrochloride Injection; Chlorpromazine Hydrochloride Oral Concentrate; Chlorpromazine Hydrochloride Syrup; Chlorpromazine Hydrochloride Tablets; Chlorpromazine Suppositories.

Proprietary Preparations (details are given in Part 3)

Arg.: Ampliactil; Conrax; ***Austral.:*** Largactil; ***Braz.:*** Amplictil; Clorpromaz; Longactil; ***Canad.:*** Chlorpromanyl†; Largactil; ***Chile:*** Largactil; ***Cz.:*** Plegomazin; ***Denm.:*** Largactil; ***Fin.:*** Klorproman; ***Fr.:*** Largactil; ***Ger.:*** Propaphenin; ***Gr.:*** Largactil; Solidon; Zuledin; ***Hong Kong:*** Largactil†; ***Hung.:*** Hibernal; ***Indon.:*** Cepezet; Meprosetil; Promactil; ***Irl.:*** Clonazine; Largactil†; ***Israel:*** Taroctyl; ***Ital.:*** Largactil; Prozin; ***Malaysia:*** Matcine; ***Mex.:*** Largactil; ***Neth.:*** Largactil; ***Norw.:*** Largactil; ***NZ:*** Largactil; ***Philipp.:*** Laractyl; Psynor; Thorazine; ***Pol.:*** Fenactil; ***Port.:*** Largactil; Largatrex; ***Rus.:*** Aminazin (Аминазин); ***S.Afr.:*** Largactil; ***Singapore:*** Largo; Matcine; ***Spain:*** Largactil; ***Swed.:*** Hibernal; ***Switz.:*** Chlorazin; ***Thai.:*** Chlormazine†; Chlorpromasit; Chlorpromed; Duncan; Matcine; Pogetol; Prozine; ***Turk.:*** Largactil; ***UK:*** Largactil; ***USA:*** Thorazine†; ***Venez.:*** Largactil†.

Multi-ingredient: ***Arg.:*** 6 Copin; ***India:*** Trinicalm Forte; ***Spain:*** Largatrex†; ***Thai.:*** Ama.

Chlorprothixene *(BAN, USAN, rINN)*

Chlorprothixène; Chlorprothixenum; Clorprotixeno; Klooriprotikseeni; Klorprotixen; N-714; Ro-4-0403. (*Z*)-3-(2-Chlorothioxanthen-9-ylidene)-*NN*-dimethylpropylamine.

Хлорпротиксен

$C_{18}H_{18}ClNS$ = 315.9.
CAS — 113-59-7.
ATC — N05AF03.
ATC Vet — QN05AF03.

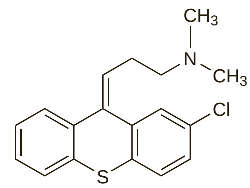

Pharmacopoeias. In *Chin.*

Chlorprothixene Hydrochloride *(BANM, rINNM)*

Chloroprotyksenu chlorowodorek; Chlorprothixène, chlorhydrate de; Chlorprothixen-hydrochlorid; Chlorprothixeni hydrochloridum; Chlorprotikseno hidrochloridas; Hidrocloruro de clorprotixeno; Klooriprotikseenihydrokloridi; Klórprotixen-hidroklorid; Klorprotixenhydroklorid.

Хлорпротиксена Гидрохлорид

$C_{18}H_{19}Cl_2NS$ = 352.3.
ATC — N05AF03.
ATC Vet — QN05AF03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Chlorprothixene Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.4 to 5.2. Protect from light.

Chlorprothixene Mesilate *(BANM, rINNM)*

Chlorprothixène, Mésilate de; Chlorprothixene Mesylate; Chlorprothixeni Mesilas; Chlorprothixenium Mesylicum; Mesilato de clorprotixeno.

Хлорпротиксена Мезилат

$C_{19}H_{22}ClNO_3S_2,H_2O$ = 430.0.
ATC — N05AF03.
ATC Vet — QN05AF03.

Profile

Chlorprothixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.969). It is used mainly in the treatment of psychoses (p.954). Chlorprothixene is given as the acetate and the hydrochloride. Preparations of chlorprothixene prepared with the aid of lactic acid have been stated to contain chlorprothixene lactate. The citrate and the mesilate have also been used.

Chlorprothixene is usually given orally as the hydrochloride and doses are expressed in terms of this salt. The acetate is given by injection with doses expressed in terms of the base. A usual oral initial dose for the treatment of psychoses is 15 to 50 mg three or four times daily, increased according to response; doses of up to 600 mg or more daily have been given in severe or resistant cases. It may also be given intramuscularly or intravenously in single doses of up to 100 mg. Chlorprothixene should be used in reduced dosage for elderly or debilitated patients.

Adverse effects. A 59-year-old man receiving chlorprothixene (for the second time) for acute mania developed severe obstructive jaundice within a few days; he was also taking chlorpropamide, digoxin, and diuretics.[1] Chlorprothixene was considered the most likely cause of the jaundice, though chlorpropamide could not be excluded.

1. Ruddock DGS, Hoenig J. Chlorprothixene and obstructive jaundice. *BMJ* 1973; **1:** 231.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of chlorprothixene on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Chlorprothixene and its sulfoxide metabolite were concentrated in the breast milk of 2 mothers given chlorprothixene 200 mg daily but it was calculated that the amount ingested by the nursing infant was only 0.1% of the maternal dose per kg bodyweight.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Presence of chlorprothixene and its metabolites in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 611–13.

Metabolism. Results from studies on the metabolism of chlorprothixene in *animals* and man[1] indicated that in addition to the major metabolite chlorprothixene-sulfoxide, 2 further urinary metabolites were identified, namely *N*-desmethylchlorprothixene-sulfoxide and chlorprothixene-sulfoxide-*N*-oxide.

1. Raaflaub J. Zum Metabolismus des Chlorprothixen. *Arzneimittelforschung* 1967; **17:** 1393–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Truxal; Truxaletten; ***Denm.:*** Truxal; ***Fin.:*** Cloxan†; Truxal; ***Ger.:*** Truxal; ***Hung.:*** Truxal; ***Neth.:*** Truxal; ***Norw.:*** Truxal; ***Rus.:*** Truxal (Труксал); ***Swed.:*** Truxal; ***Switz.:*** Truxal; Truxaletten.

Cinolazepam *(rINN)*

Cinolazépam; Cinolazepamum; OX-373. 7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo-1*H*-1,4-benzodiazepine-1-propionitrile.

Цинолазепам

$C_{18}H_{13}ClFN_3O_2$ = 357.8.
CAS — 75696-02-5.
ATC — N05CD13.
ATC Vet — QN05CD13.

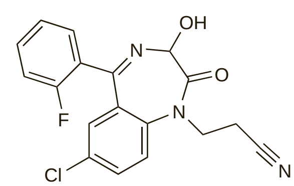

Profile

Cinolazepam is a benzodiazepine derivative with general properties similar to those of diazepam (p.986) that has been used in the short-term management of sleep disorders in usual oral doses of 40 mg at night.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Gerodorm; ***Cz.:*** Gerodorm; ***Hung.:*** Gerodorm.

Clocapramine Hydrochloride *(rINNM)*

Chlorcarpipramine Hydrochloride; Clocapramine, Chlorhydrate de; Clocapramini Hydrochloridum; Hidrocloruro de clocapramina; Y-4153. 1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl][1,4′-bipiperidine]-4′-carboxamide dihydrochloride monohydrate.

Клокапрамина Гидрохлорид

$C_{28}H_{37}ClN_4O,2HCl,H_2O$ = 572.0.
CAS — 47739-98-0 (clocapramine); 28058-62-0 (clocapramine hydrochloride).

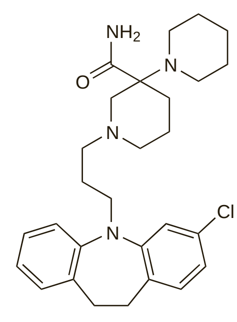

(clocapramine)

Pharmacopoeias. In *Jpn.*

Profile

Clocapramine is a chlorinated derivative of carpipramine (p.968). The hydrochloride has been given orally in the treatment of schizophrenia.

Clomethiazole *(BAN, rINN)*

Chlormethiazole; Clométhiazole; Clomethiazolum; Clometiazol; Klometiatsoli; Klometiazol. 5-(2-Chloroethyl)-4-methyl-1,3-thiazole.

Клометиазол

C_6H_8ClNS = 161.7.

CAS — 533-45-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

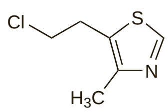

Pharmacopoeias. In *Br.*

BP 2008 (Clomethiazole). A colourless to slightly yellowish-brown liquid with a characteristic odour. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. A 0.5% solution in water has a pH of 5.5 to 7.0. Store at a temperature of 2° to 8°.

Clomethiazole Edisilate *(BANM, rINNM)*

Chlormethiazole Edisylate; Chlormethiazole Ethanedisulphonate; Clométhiazole, Edisilate de; Clomethiazole Edisylate *(USAN)*; Clomethiazoli Edisilas; Edisilato de clometiazol; Klometiazolu edysylan; NEX-002. 5-(2-Chloroethyl)-4-methylthiazole ethane-1,2-disulphonate.

Клометиазола Эдизилат

$(C_6H_8ClNS)_2,C_2H_6O_6S_2$ = 513.5.

CAS — 1867-58-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Clomethiazole Edisilate). A white crystalline powder with a characteristic odour. Freely soluble in water; soluble in alcohol; practically insoluble in ether.

Incompatibility. Several studies have shown that clomethiazole edisilate may permeate through or be sorbed onto plastics used in intravenous infusion bags or giving sets.[1-4] The drug may also react with and soften the plastic.[1] The manufacturers of clomethiazole edisilate have suggested that thrombophlebitis, fever, and headache reported in young children during prolonged infusions may have been due to reaction with plastic giving sets and silastic cannulae. Recommendations for intravenous use have therefore included the use of a motor-driven glass syringe in preference to a plastic drip set in small children, changing plastic drip sets at least every 24 hours when used in older patients, and use of teflon intravenous cannulas.

1. Lingam S, *et al.* Problems with intravenous chlormethiazole (Heminevrin) in status epilepticus. *BMJ* 1980; **280:** 155–6.
2. Tsuei SE, *et al.* Sorption of chlormethiazole by intravenous infusion giving sets. *Eur J Clin Pharmacol* 1980; **18:** 333–8.
3. Kowaluk EA, *et al.* Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J Pharm Sci* 1984; **73:** 43–7.
4. Lee MG. Sorption of four drugs to polyvinyl chloride and polybutadiene intravenous administration sets. *Am J Hosp Pharm* 1986; **43:** 1945–50.

Dependence and Withdrawal

Dependence may develop, particularly with prolonged use of higher than recommended doses of clomethiazole. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Adverse Effects, Treatment, and Precautions

Clomethiazole may produce nasal congestion and irritation, sneezing, and conjunctival irritation sometimes associated with a headache. Nasopharyngeal or bronchial secretions may be increased. Skin rashes and urticaria have also occurred and in rare cases bullous eruptions have been reported. Gastrointestinal disturbances including nausea and vomiting, have been reported after oral doses. Reversible increases in liver enzyme values and blood-bilirubin concentrations have also been noted. Clomethiazole can cause excessive drowsiness, particularly in high doses; drowsiness may persist the next day, and patients affected should not drive or operate machinery. Paradoxical excitation or confusion may occur rarely. Anaphylaxis has also been reported rarely.

Excessive doses may produce coma, respiratory depression, hypotension, and hypothermia; pneumonia may follow increased respiratory secretion. Treatment is as for barbiturate overdose (see Amobarbital, p.962).

Clomethiazole is contra-indicated in patients with acute pulmonary insufficiency, and should be given with care to patients with sleep apnoea syndrome, chronic pulmonary insufficiency, or renal, liver, cerebral, or cardiac disease. Clomethiazole should be given with caution to elderly patients as there may be increased bioavailability and delayed elimination. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome.

Administration by intravenous infusion. Severe adverse effects have followed the intravenous use of clomethiazole, and intravenous preparations are no longer generally available. Facilities for intubation and resuscitation were required when clomethiazole was given intravenously, with care taken to ensure that the patient's airway was maintained since there is a risk of mechanical obstruction during deep sedation. At too high a rate of infusion, sleep induced with clomethiazole could lapse into deep unconsciousness and patients required close and constant observation. Rapid infusion has also caused transient apnoea and hypotension, and special care was needed in patients susceptible to cerebral or cardiac complications, including the elderly. With prolonged infusion there was also a risk of electrolyte imbalance due to the water load involved with the glucose vehicle. Recovery has been considerably delayed after prolonged infusion.

Effects on the heart. Cardiac arrest in 2 chronic alcoholics might have been associated with clomethiazole infusion.[1]

1. McInnes GT, *et al.* Cardiac arrest following chlormethiazole infusion in chronic alcoholics. *Postgrad Med J* 1980; **56:** 742–3.

Overdosage. A report of clomethiazole poisoning on 16 occasions in 13 patients, some of whom had also taken other drugs and alcohol.[1] There was increased salivation on 7 occasions; otherwise the clinical features were those of barbiturate poisoning (see Adverse Effects of Amobarbital, p.962). The highest plasma-clomethiazole concentration was 36 micrograms/mL, with the highest value in a conscious patient 11.5 micrograms/mL. All the patients survived following intensive supportive treatment as for barbiturate poisoning.

1. Illingworth RN, *et al.* Severe poisoning with chlormethiazole. *BMJ* 1979; **2:** 902–3.

Parotitis. Acute bilateral parotitis has been reported in a patient given clomethiazole.[1] The swelling disappeared after withdrawal of clomethiazole and recurred on rechallenge.

1. Bosch X, *et al.* Parotitis induced by chlormethiazole. *BMJ* 1994; **309:** 1620.

Pregnancy. There have been reports of neonates being adversely affected by clomethiazole given to their mothers for toxaemia of pregnancy.[1,2] Effects included sedation, hypotonia, and apnoea. In a report[1] it was suggested that the effects might have been due to a synergistic interaction between clomethiazole and diazoxide as these drugs were given to most of the mothers with affected infants.

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* 1976; **1:** 943.
2. Wood C, Renou P. Sleepy and hypotonic neonates. *Med J Aust* 1978; **2:** 73.

Interactions

The sedative effects of clomethiazole are enhanced by CNS depressants such as alcohol, barbiturates, other hypnotics and sedatives, and antipsychotics.

Alcohol. Although clomethiazole has been a popular choice for the treatment of alcohol withdrawal symptoms (p.1626), if it is given long-term, patients readily transfer dependency to it; if they also continue to abuse alcohol this may lead to severe self-poisoning with deep coma and potentially fatal respiratory depression.[1]

1. McInnes GT. Chlormethiazole and alcohol: a lethal cocktail. *BMJ* 1987; **294:** 592.

Beta blockers. Sinus bradycardia developed in an 84-year-old woman taking *propranolol* for hypertension 3 hours after she took a second dose of clomethiazole 192 mg.[1] Her pulse rate increased on stopping propranolol and clomethiazole and later stabilised when she took propranolol with haloperidol.

1. Adverse Drug Reactions Advisory Committee (Australia). *Med J Aust* 1979; **2:** 553.

Diazoxide. For a report of adverse reactions in neonates born to mothers given clomethiazole and diazoxide, see Pregnancy under Adverse Effects, Treatment, and Precautions, above.

Histamine H_2-antagonists. A study of the pharmacokinetics of clomethiazole edisilate 1 g orally in 8 healthy subjects, before and after doses of *cimetidine* 1 g daily for 1 week, showed that mean clearance of clomethiazole was reduced by 31% by cimetidine.[1] This was associated with an increase in the mean peak plasma concentration of the hypnotic from 2.664 to 4.507 micrograms/mL and an increase in the mean elimination half-life from 2.33 to 3.63 hours. After the original dose of clomethiazole subjects slept for 30 to 60 minutes, whereas after cimetidine, most slept for at least 2 hours.

Ranitidine did not significantly affect the pharmacokinetics of clomethiazole in a study in 7 healthy subjects.[2]

1. Shaw G, *et al.* Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* 1981; **21:** 83–5.
2. Mashford ML, *et al.* Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* 1983; **34:** 231–3.

Pharmacokinetics

Clomethiazole is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 15 to 90 minutes after oral doses depending on the formulation used. It is widely distributed in the body and is reported to be 65% bound to plasma proteins. Clomethiazole is extensively metabolised, probably by first-pass metabolism in the liver with only small amounts appearing unchanged in the urine. The elimination half-life has been reported to be about 4 hours but this may be increased to 8 hours or longer in the elderly or in patients with hepatic impairment. Clomethiazole crosses the placenta and is distributed into breast milk.

Hepatic impairment. Studies in 8 patients with advanced cirrhosis of the liver and in 6 healthy men showed that the amount of unmetabolised clomethiazole reaching the circulation after an oral dose was about 10 times higher in the patients than in the controls.[1] Low concentrations in the controls were related to extensive first-pass metabolism in the liver.

1. Pentikäinen PJ, *et al.* Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. *Eur J Clin Pharmacol* 1980; **17:** 275–84.

Uses and Administration

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is used orally in the treatment of agitation and restlessness (see Disturbed Behaviour, p.954) in elderly patients, in the short-term management of severe insomnia (p.957) in the elderly, and in the treatment of acute alcohol withdrawal symptoms (p.1626). It was also given as an intravenous infusion in the management of status epilepticus (p.469) and impending or actual eclampsia (p.470); however, a parenteral formulation of clomethiazole no longer appears to be available.

In the UK, clomethiazole (as *Heminevrin*; *AstraZeneca*) is available as capsules containing 192 mg of clomethiazole base and as syrup containing 250 mg of the edisilate in 5 mL. As a result of differences in the bioavailability of these preparations, 192 mg of the base in the capsules is considered therapeutically equivalent to 250 mg (5 mL) of the edisilate in the syrup, i.e. one capsule or 5 mL of syrup are equivalent in their effects.

The usual hypnotic dose of clomethiazole for **insomnia** is 1 or 2 capsules (192 or 384 mg of the base) or the equivalent. For **restlessness and agitation** in the elderly 1 capsule (192 mg of the base), or the equivalent dose as one of the other dosage forms, may be given 3 times daily.

Various clomethiazole regimens have been suggested for the treatment of **alcohol withdrawal**, usually starting with 9 to 12 capsules, or the equivalent, divided into 3 or 4 doses, on the first day, and gradually reducing the dosage over the next 5 days. Treatment should be carried out in hospital or in specialist centres, and use for longer than 9 days is not recommended because of the risk of dependence (see above).

Porphyria. Clomethiazole is one of the drugs that has been used for seizure prophylaxis in patients with porphyria (p.471) who continue to experience convulsions while in remission.

Stroke. Clomethiazole has been studied[1,2] as a neuroprotective drug in the acute management of patients with stroke, but no beneficial effect on long-term outcome was found.

1. Wahlgren NG, *et al.* CLASS Study Group. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke* 1999; **30:** 21–8.
2. Lyden P, *et al.* Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke* 2002; **33:** 122–8.

Substance dependence. For a discussion of the management of *opioid* withdrawal symptoms, including mention of the use of clomethiazole, see p.101.

Preparations

BP 2008: Clomethiazole Capsules; Clomethiazole Intravenous Infusion; Clomethiazole Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Hemineurin; ***Belg.:*** Distraneurine†; ***Cz.:*** Heminevrin; ***Denm.:*** Heminevrin; ***Fin.:*** Heminevrin†; ***Ger.:*** Distraneurin; ***Gr.:*** Distraneurine; Heminevrin; ***Hong Kong:*** Heminevrin†; ***Hung.:*** Heminevrin; ***Irl.:*** Heminevrin; ***Norw.:*** Heminevrin; ***Pol.:*** Heminevrin; ***Spain:*** Distraneurine; ***Swed.:*** Heminevrin; ***Switz.:*** Distraneurin; ***UK:*** Heminevrin.

Cloral Betaine *(BAN, rINN)*

Chloral Betaine *(USAN)*; Cloral betaína; Cloral Bétaïne; Cloralum Betainum; Compound 5107. An adduct of cloral hydrate and betaine.

Хлораль Бетаин

$C_7H_{12}Cl_3NO_3,H_2O$ = 282.5.
CAS — 2218-68-0.

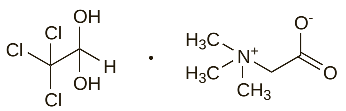

Profile

Cloral betaine rapidly dissociates in the stomach to release cloral hydrate and has actions and uses similar to those of cloral hydrate (below). It is given orally in the short-term management of insomnia (p.957), as tablets containing 707 mg (equivalent to about 414 mg of cloral hydrate). The usual hypnotic dose is one or two tablets taken at night with water or milk. The maximum daily dose is five tablets (equivalent to about 2 g of cloral hydrate). A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Somnwell; Welldorm.

Cloral Hydrate

Chloral Hydrate *(BAN)*; Chloral, hydrate de; Chloralhydrát; Chlorali hydras; Chloralio hidratas; Chloralu wodzian; Cloral, hidrato de; Kloraalihydraatti; Kloral Hidrat; Klorál-hidrát; Kloralhydrat.
2,2,2-Trichloroethane-1,1-diol.

$C_2H_3Cl_3O_2$ = 165.4.
CAS — 302-17-0.
ATC — N05CC01.
ATC Vet — QN05CC01.

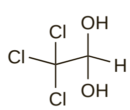

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cloral hydrate:
Jellies; Jelly beans; Joy Juice; Knockout Drops; Knock out drops; Mickey; Mickeys; Mickey Finn; Mickey Finns; Peter; Torpedo.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Chloral Hydrate). Colourless, transparent crystals. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Chloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid odour. It volatilises slowly on exposure to air and melts at about 55°. Soluble 1 in 0.25 of water, 1 in 1.3 of alcohol, 1 in 2 of chloroform, and 1 in 1.5 of ether; very soluble in olive oil. Store in airtight containers.

Incompatibility. Cloral hydrate is reported to be incompatible with alkalis, alkaline earths, alkali carbonates, soluble barbiturates, borax, tannin, iodides, oxidising agents, permanganates, and alcohol (cloral alcoholate may crystallise out). It forms a liquid mixture when triturated with many organic compounds, such as camphor, menthol, phenazone, phenol, thymol, and quinine salts.

Dependence and Withdrawal, Adverse Effects, and Treatment

Cloral hydrate has an unpleasant taste and is corrosive to skin and mucous membranes unless well diluted. The most frequent adverse effect is gastric irritation; abdominal distension and flatulence may also occur. CNS effects such as drowsiness, lightheadedness, ataxia, headache, and paradoxical excitement, hallucinations, nightmares, delirium, and confusion (sometimes with paranoia) occur occasionally. Hypersensitivity reactions include skin rashes (erythema multiforme and Stevens-Johnson syndrome have been reported with the related compound triclofos). Ketonuria may occur.

The effects of acute overdosage resemble acute barbiturate intoxication (see Amobarbital, p.962 and below), and are managed similarly. In addition the irritant effect may cause initial vomiting, and gastric necrosis leading to strictures. Cardiac arrhythmias have been reported. Jaundice may follow liver damage, and albuminuria may follow kidney damage.

Tolerance may develop and dependence may occur. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Incidence of adverse effects. In a drug surveillance programme,[1] adverse effects of cloral hydrate, which were reversible, occurred in 2.3% of 1130 patients evaluated and included gastrointestinal symptoms (10 patients), CNS depression (20), and skin rash (5). In 1 patient the prothrombin time was increased; in 1 patient hepatic encephalopathy seemed to worsen; and bradycardia developed in 1 patient. In another such programme, adverse effects occurred in about 2% of 5435 patients given cloral hydrate.[2] Three reactions were described as life-threatening.

1. Shapiro S, *et al*. Clinical effects of hypnotics II: an epidemiologic study. *JAMA* 1969; **209:** 2016–20.
2. Miller RR, Greenblatt DJ. Clinical effects of chloral hydrate in hospitalized medical patients. *J Clin Pharmacol* 1979; **19:** 669–74.

Carcinogenicity. Cloral hydrate has been widely used as a sedative, especially in children. Concern over warnings that cloral hydrate was carcinogenic in *rodents*[1] has prompted some experts, including the American Academy of Pediatrics, to review the relative risks of the medical use of this drug.[2,3] The original warnings appear to have been based, in part, on the assumption that cloral hydrate was a reactive metabolite of trichloroethylene and was responsible for its carcinogenicity, but there is evidence to suggest that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite. Studies *in vitro* indicate that cloral hydrate can damage chromosomes in some mammalian test systems but there have been no studies of the carcinogenicity of cloral hydrate in humans. Some long-term studies in *mice* have linked cloral hydrate with the development of hepatic adenomas or carcinomas. However, it was noted that cloral hydrate was not the only sedative that had been shown to be a carcinogen in experimental *animals*. The American Academy of Pediatrics considered cloral hydrate to be an effective sedative with a low incidence of acute toxicity when given short-term as recommended and, although the information on carcinogenicity was of concern, it was not sufficient to justify the risk associated with the use of less familiar sedatives. There was no evidence in infants or children showing that any of the available alternatives were safer or more effective. However, the use of repetitive dosing with cloral hydrate to maintain prolonged sedation in neonates and other children was of concern because of the potential for accumulation of drug metabolites and resultant toxicity. A recent cohort study[4] found no persuasive evidence to support a relationship between the use of cloral hydrate and the development of cancer. However, the statistical power was low for weak associations, particularly for some individual cancer sites.

1. Smith MT. Chloral hydrate warning. *Science* 1990; **250:** 359.
2. Steinberg AD. Should chloral hydrate be banned? *Pediatrics* 1993; **92:** 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993; **92:** 471–3.
4. Haselkorn T, *et al*. Short-term chloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29:** 67–77.

Effects on the CNS. A 2-year-old child[1] had the first of 2 seizures 60 minutes after receiving cloral hydrate 70 mg/kg for sedation.

1. Muñoz M, *et al*. Seizures caused by chloral hydrate sedative doses. *J Pediatr* 1997; **131:** 787–8.

Hyperbilirubinaemia. Small retrospective studies[1] have suggested that prolonged use of cloral hydrate in neonates may be associated with the development of hyperbilirubinaemia. This may possibly be related to the prolonged half-life of the metabolite trichloroethanol in neonates.

1. Lambert GH, *et al*. Direct hyperbilirubinemia associated with chloral hydrate administration in the newborn. *Pediatrics* 1990; **86:** 277–81.

Overdosage. The general management of poisoning with cloral hydrate resembles that for barbiturates (see Treatment of Adverse Effects, under Amobarbital, p.962). Activated charcoal may be given orally to adults and children within 1 hour of ingestion of more than 30 mg/kg, provided that the airway can be protected; the value of gastric decontamination for overdose is uncertain. Of 76 cases of cloral hydrate poisoning reported to the UK National Poisons Information Service (NPIS), 47 were severe.[1] Of 39 adults, 12 had cardiac arrhythmias including 5 with cardiac arrest. Antiarrhythmic drugs were recommended unless obviously contra-indicated. Haemoperfusion through charcoal or haemodialysis was recommended for patients in prolonged coma. Cardiac arrhythmias and CNS depression were also major features of 12 cases of cloral hydrate overdosage reported from Australia.[2] Lidocaine was not always successful in controlling arrhythmias, but propranolol was successful in all 7 patients in whom it was used. It was noted that resistant arrhythmias, particularly ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, were the usual cause of death in patients who had taken an overdosage of cloral hydrate. Although there had been no controlled studies of antiarrhythmic therapy in overdosage with cloral hydrate, the successful use of beta blockers appeared to be a recurring feature in reports in the literature. Indeed, the UK NPIS notes that tachyarrhythmias usually respond readily to an intravenous beta blocker such as esmolol or propranolol.

Giving flumazenil produced an increased level of consciousness, pupillary dilatation, and return of respiratory rate and blood pressure towards normal in a patient who had taken an overdosage of cloral hydrate.[3]

1. Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *BMJ* 1978; **2:** 960.
2. Graham SR, *et al*. Overdose with chloral hydrate: a pharmacological and therapeutic review. *Med J Aust* 1988; **149:** 686–8.
3. Donovan KL, Fisher DJ. Reversal of chloral hydrate overdose with flumazenil. *BMJ* 1989; **298:** 1253.

Precautions

Cloral hydrate should not be used in patients with marked hepatic or renal impairment or severe cardiac disease, and oral dosage is best avoided in the presence of gastritis. As with all sedatives, it should be used with caution in those with respiratory insufficiency.

Cloral hydrate can cause drowsiness that may persist the next day; affected patients should not drive or operate machinery. Prolonged use and abrupt withdrawal of cloral hydrate should be avoided to prevent precipitation of withdrawal symptoms. Repeated doses in infants and children may lead to accumulation of metabolites and thereby increase the risk of adverse effects. Use is best avoided during pregnancy.

Cloral hydrate may interfere with some tests for urinary glucose or 17-hydroxycorticosteroids.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of cloral hydrate by breast-feeding mothers has been reported to cause sleepiness in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Neonates. The half-life of trichloroethanol, an active metabolite of cloral hydrate, is prolonged in neonates;[1] values of up to 66 hours have been reported in some studies. Short-term sedation in the neonate with single oral doses of 25 to 50 mg/kg of cloral hydrate is considered[1] to be probably relatively safe, but repeated dosage carries the risk of accumulation of metabolites which may result in serious toxicity. Toxic reactions may occur even after the drug has been stopped since the metabolites may accumulate for several days.

1. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.

Obstructive sleep apnoea. Children with obstructive sleep apnoea could be at risk from life-threatening respiratory obstruction if cloral hydrate is used for sedation. Details of 2 such children who suffered respiratory failure after sedation with cloral hydrate for lung function studies have been reported.[1]

1. Biban P, *et al*. Adverse effect of chloral hydrate in two young children with obstructive sleep apnea. *Pediatrics* 1993; **92:** 461–3.

Porphyria. UK licensed product information recommends that cloral hydrate should not be used in patients with porphyria, although some[1] consider it safe; caution would seem appropriate.

1. Welsh Medicines Information Centre. Drugs that are considered to be safe for use in acute porphyrias. Available at: http://www.wmic.wales.nhs.uk/pdfs/porphyria/PorphyriaSafeList.pdf (accessed 24/06/08)

Interactions

The sedative effects of cloral hydrate are enhanced by other CNS depressants such as alcohol (the 'Mickey Finn' of detective fiction), barbiturates, and other sedatives.

Cloral hydrate may alter the effects of coumarin anticoagulants (see Warfarin, p.1430). A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given an intravenous dose of furosemide subsequent to cloral hydrate.

Pharmacokinetics

Cloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral doses. It is widely distributed throughout the body. It is rapidly metabolised to trichloroethanol and trichloroacetic acid (p.1620) in the erythrocytes, liver, and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide (urochloralic acid) and as trichloroacetic acid. Some is also excreted in the bile.

Trichloroethanol is the active metabolite, and passes into the CSF, into breast milk, and across the placenta. The half-life of trichloroethanol in plasma is reported to range from about 7 to 11 hours but is considerably prolonged in the neonate. Trichloroacetic acid has a plasma half-life of several days.

Uses and Administration

Cloral hydrate is a hypnotic and sedative with properties similar to those of the barbiturates. It is used in the short-term management of insomnia (p.957) and has been used for sedation and as a sedative for premedication (p.1780); its use as a hypnotic, particularly in children, is now limited. It has been widely used for sedation of children before diagnostic, dental, or medical procedures (but see under Carcinogenicity above).

Externally, cloral hydrate has a rubefacient action and has been used as a counter-irritant.

Cloral hydrate is given by mouth as an oral liquid or as gelatin capsules with cloral hydrate dissolved in a suitable vehicle. It has also been dissolved in a bland fixed oil and given by enema or as suppositories.

It should not be given as tablets because of the risk of damage to the mucous membrane of the alimentary tract.

The usual oral hypnotic dose in adults is 0.5 to 2 g given as a single dose at night; as a sedative 250 mg can be given three times daily to a maximum daily dose of 2 g. Oral dosage forms should be taken well diluted or with plenty of water or milk. The *BNFC* suggests that children aged 1 month to 12 years be given 30 to 50 mg/kg to a maximum single dose of 1 g by mouth as a hypnotic (but see above); those aged 12 to 18 years may be given 0.5 to 1 g. Although not licensed in the UK for sedation of children before a painless procedure, the *BNFC* suggests the following oral doses, given 45 to 60 minutes beforehand: 1 month to 12 years, 30 to 50 mg/kg (maximum of 1 g), although up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring; 12 to 18 years, 1 to 2 g. The *BNFC* states that the doses above may be given rectally if the oral route is unavailable. In the USA, a suggested oral or rectal sedative dose for children is 8.3 mg/kg three times daily to a maximum daily dose of 1.5 g; a dose of 20 to 25 mg/kg has been given as a premedicant prior to EEG evaluation.

A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Derivatives of cloral hydrate, such as cloral betaine (above), chloralose (p.2037), and dichloralphenazone (p.994), which break down in the body to yield cloral hydrate, have been used similarly.

◊ References.

1. McCarver-May DG, *et al.* Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996; **128:** 573–6.
2. Napoli KL, *et al.* Safety and efficacy of chloral hydrate sedation in children undergoing echocardiography. *J Pediatr* 1996; **129:** 287–91.

Preparations

USP 31: Chloral Hydrate Capsules; Chloral Hydrate Syrup.

Proprietary Preparations (details are given in Part 3)
Ger.: Chloraldurat; ***Switz.:*** Chloraldurat; Medianox; Nervifene; ***UK:*** Welldorm; ***USA:*** Aquachloral; Somnote.

Multi-ingredient: ***Belg.:*** Dentophar; Sedemol; Sulfa-Sedemol; Synthol; ***Fr.:*** Bain de Bouche Lipha; ***Rus.:*** Efcamon (Эфкамон); ***Spain:*** Dentol Topico; ***Turk.:*** Dilan.

Clorazepic Acid *(BAN)*

Clorazépico, ácido. 7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid.

$C_{16}H_{11}ClN_2O_3$ = 314.7.
CAS — 23887-31-2; 20432-69-3.

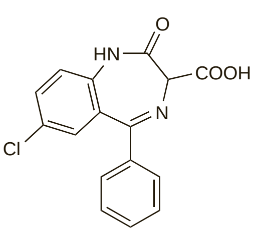

Clorazepate Monopotassium *(USAN)*

Abbott-39083; 4311-CB; Clorazepato monopotásico. Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate.

$C_{16}H_{10}ClKN_2O_3$ = 352.8.
CAS — 5991-71-9.

Dipotassium Clorazepate *(BANM, rINN)*

Abbott-35616; AH-3232; 4306-CB; Clorazépate dipotassique; Clorazepate Dipotassium *(USAN)*; Clorazepato de dipotasio; Dikalii clorazepas; Dikalio klorazepatas; Dikaliumkloratsepaatti; Dikaliumklorazepat; Dikálium-klórazepát; Kalii Clorazepas; Kaliumkloratsepaatti; Klaiumklorazepat; Klorazepát didraselná sůl; Klorazepat Dipotasyum; Potassium Clorazepate. Compound of Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate with potassium hydroxide.

Дикалия Клоразепат

$C_{16}H_{11}ClK_2N_2O_4$ = 408.9.
CAS — 57109-90-7.
ATC — N05BA05.
ATC Vet — QN05BA05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dipotassium Clorazepate). A white or light yellow, crystalline powder. Solutions in water and in alcohol are unstable and should be used immediately. Freely soluble or very soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Clorazepate Dipotassium). A light yellow, crystalline powder which darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in chloroform, in dichloromethane, in ether, and in benzene. Store under nitrogen in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Effects on the liver. Jaundice and hepatic necrosis has been associated with clorazepate.[1]

1. Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. *Postgrad Med J* 1979; **55:** 908–910.

Effects on the nervous system. For reference to extrapyramidal disorders associated with the use of benzodiazepines, including clorazepate, see Diazepam, p.988.

Porphyria. Clorazepate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Clorazepate is decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam (nordazepam, see p.1012), which is quickly absorbed.

◊ References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24:** 446–51.
2. Bertler Å, *et al.* Intramuscular bioavailability of chlorazepate as compared to diazepam. *Eur J Clin Pharmacol* 1985; **28:** 229–30.

Uses and Administration

Clorazepate is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is mainly used in the short-term treatment of anxiety disorders (p.952), as an adjunct in the management of epilepsy, and in the alcohol withdrawal syndrome (p.1626).

Dipotassium clorazepate is usually given orally but preparations for intravenous or intramuscular use are also available in some countries. Modified-release preparations given once daily are available in some countries for maintenance therapy.

In the UK, an oral dose of 7.5 mg of dipotassium clorazepate was given up to three times daily for the treatment of anxiety. In the USA rather higher doses have been recommended; 15 to 60 mg of dipotassium clorazepate may be given daily, in divided doses or as a single dose at night.

Up to 90 mg has been given daily in divided doses in the management of **epilepsy** or the **alcohol withdrawal syndrome**. Children aged between 9 and 12 years may be given a maximum of 60 mg daily in the management of epilepsy.

Reduced doses should be given to elderly or debilitated patients.

Preparations

USP 31: Clorazepate Dipotassium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Justum; Tencilan; Tranxilium; ***Austria:*** Tranxilium; ***Belg.:*** Tranxene; Uni-Tranxene; ***Braz.:*** Tranxilene; ***Canad.:*** Novo-Clopate; Tranxene†; ***Chile:*** Calner; Modival†; Tranxilium; ***Cz.:*** Tranxene†; ***Fr.:*** Tranxene; ***Ger.:*** Tranxilium; ***Gr.:*** Tranxene; ***Hong Kong:*** Tranxene; ***Irl.:*** Tranxene†; ***Israel:*** Tranxal; ***Ital.:*** Transene; ***Malaysia:*** Sanor†; ***Mex.:*** Tranxene; ***Neth.:*** Tranxene; Tranxilium; ***Philipp.:*** Tranxene; ***Pol.:*** Cloranxen; Tranxene; ***Port.:*** Medipax; Tranxene; ***S.Afr.:*** Tranxene; ***Singapore:*** Tranxene; ***Spain:*** Tranxilium; ***Switz.:*** Tranxilium; ***Thai.:*** Anxielax; Cloramed; Cloraxene; Diposef†; Dipot; Flulium; Manotran; Polizep; Pomadom; Posene; Sanor†; Serene; Trancap; Tranclor; Trancon; Tranxene; Zetran; ***Turk.:*** Anksen; Tranxilene; ***UK:*** Tranxene†; ***USA:*** Gen-Xene†; Tranxene; ***Venez.:*** Tranxen.

Multi-ingredient: ***Arg.:*** Euciton Complex; Maxitratobes; Tranxilium Digest; Vegestabil; ***Fr.:*** Noctran; ***Spain:*** Dorken.

Clotiapine *(BAN, rINN)*

Clothiapine *(USAN)*; Clotiapina; Clotiapinum; HF-2159. 2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.

Клотиапин

$C_{18}H_{18}ClN_3S$ = 343.9.
CAS — 2058-52-8.
ATC — N05AX09.
ATC Vet — QN05AX09.

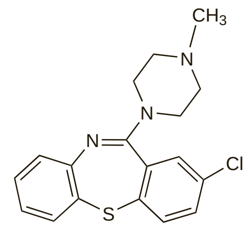

Profile

Clotiapine is a dibenzothiazepine antipsychotic with general properties similar to those of the phenothiazines (see Chlorpromazine, p.969). It is used in a variety of psychiatric disorders including schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and anxiety (p.952). It is given orally in doses ranging from 10 to 200 mg daily in divided doses; up to 360 mg daily has been given in severe or resistant psychoses. It may also be given by slow intravenous or deep intramuscular injection.

Psychoses. A systematic review[1] found that good evidence to support the use of clotiapine over other treatments in acute psychotic illness was lacking.

1. Berk M, *et al.* Clotiapine for acute psychotic illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Etumina; ***Belg.:*** Etumine; ***Israel:*** Entumin; ***Ital.:*** Entumin; ***S.Afr.:*** Etomine; ***Spain:*** Etumina; ***Switz.:*** Entumine.

Clotiazepam *(rINN)*

Clotiazépam; Clotiazepamum; Y-6047. 5-(2-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-2*H*-thieno[2,3-e]-1,4-diazepin-2-one.

Клотиазепам

$C_{16}H_{15}ClN_2OS$ = 318.8.
CAS — 33671-46-4.
ATC — N05BA21.
ATC Vet — QN05BA21.

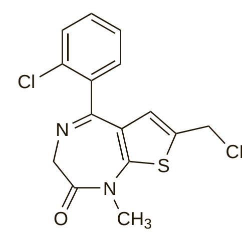

Pharmacopoeias. In *Jpn.*

Profile

Clotiazepam is a short-acting thienodiazepine with general properties similar to those of diazepam (p.986). A usual oral daily dose for the short-term management of anxiety disorders (p.952) is 5 to 15 mg given in divided doses but up to 60 mg daily has been used. For sleep disorders (p.957) 10 mg has been given as a single dose at night. An oral dose of 10 to 15 mg has been given for premedication (see Anaesthesia, p.1780). Reduced doses may be required in elderly or debilitated patients.

◊ References.

1. Jibiki I, *et al.* Beneficial effect of high-dose clotiazepam on intractable auditory hallucinations in chronic schizophrenic patients. *Eur J Clin Pharmacol* 1994; **46:** 367–9.

Effects on the liver. Development of hepatitis in a 65-year-old woman was attributed to clotiazepam begun 7 months earlier.[1] The patient took triazolam and lorazepam without any apparent effect on the liver, and it was speculated that the hepatotoxic effect of clotiazepam was related to the thiophene ring present in the chemical structure.

1. Habersetzer F, *et al.* Clotiazepam-induced acute hepatitis. *J Hepatol* 1989; **9:** 256–9.

Porphyria. Clotiazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Clozan; ***Chile:*** Rize; ***Fr.:*** Veratran; ***Ital.:*** Rizen; Tienor; ***Jpn:*** Rize; ***Spain:*** Distensan.

Cloxazolam *(rINN)*

Cloxazolamum; CS-370; Kloksatsolaami; Kloxazolam. 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Клоксазолам

$C_{17}H_{14}Cl_2N_2O_2$ = 349.2.

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.

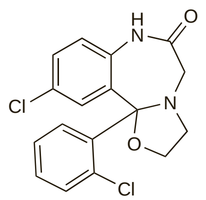

Pharmacopoeias. In *Jpn.*

Profile

Cloxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been given in oral doses of up to 12 mg daily in divided doses for the short-term treatment of anxiety disorders (p.952). A dose of 100 micrograms/kg may be used for premedication (p.1780).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tolestan; ***Belg.:*** Akton; ***Braz.:*** Anoxolan; Clozal; Elum; Eutonis; Olcadil; ***Port.:*** Cloxam; Olcadil; ***Switz.:*** Lubalix†.

Clozapine *(BAN, USAN, rINN)*

Clozapina; Clozapinum; HF-1854; Klotsapiini; Klozapin; Klozapina; Klozapinas. 8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo-[*b,e*][1,4]diazepine.

Клозапин

$C_{18}H_{19}ClN_4$ = 326.8.

CAS — 5786-21-0.

ATC — N05AH02.

ATC Vet — QN05AH02.

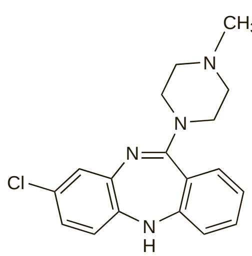

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Clozapine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. It dissolves in dilute acetic acid.

USP 31 (Clozapine). A yellow crystalline powder. Insoluble in water; soluble in alcohol, in acetone, and in chloroform; sparingly soluble in acetonitrile.

Stability. A suspension of clozapine 100 mg in 5 mL, made by crushing clozapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for at least 18 days after preparation.[1]

1. Ramuth S, *et al.* A liquid clozapine preparation for oral administration in hospital. *Pharm J* 1996; **257:** 190–1.

Adverse Effects and Treatment

Although clozapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential (see Precautions, below). Eosinophilia may also occur. Anaemia, thrombocytopenia, and thrombocythaemia have been reported rarely.

Extrapyramidal disorders, including tardive dyskinesia, appear to be rare with clozapine. Clozapine has little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases, circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk of developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional adverse effects of clozapine include dizziness, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, faecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis. There have also been rare reports of dysphagia, parotid gland enlargement, confusion, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose homoeostasis and the onset of diabetes mellitus occur uncommonly; severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, has been reported very rarely. There have also been rare reports of hypercholesterolaemia and hypertriglyceridaemia. Many of the adverse effects of clozapine are most common at the start of therapy and may be minimised by gradual increase in dosage.

Effects on the blood. Clozapine can cause reversible neutropenia which, if the drug is not withdrawn immediately, may progress to a potentially fatal **agranulocytosis**. Particular concern over this adverse effect dates from 1975 when 17 cases of neutropenia or agranulocytosis, 8 of them fatal, were reported in Finland;[1] the calculated incidence[2] of agranulocytosis or severe granulocytopenia during this Finnish epidemic was 7.1 per 1000. These reports led to the withdrawal of clozapine in some countries or to restrictions in its use and intense haematological monitoring in others. After studies showing the efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[3] Clozapine was one of the individual drugs most frequently implicated, with 14 reports of agranulocytosis (1 fatal) and 119 of neutropenia (none fatal). Various estimates of the **incidence** of clozapine-associated agranulocytosis have been made; analysis of data from 11 555 patients given clozapine in the USA[4] showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1 ⁄ years with the risk being increased in elderly patients. The majority of cases of agranulocytosis occurred within 3 months of the start of treatment with the risk peaking in the third month. The manufacturers report a lower incidence of agranulocytosis of 4.8 per 1000 patients for the first 6 months[5] and an annual rate of 0.8 per 1000 patients during the next 2 ⁄ years. These figures were based on data on 56 000 patients in the USA given clozapine up to the end of March 1993. Analysis of data[6] on 6316 patients registered in the UK and Ireland between January 1990 and July 1994 to receive (although not necessarily given) clozapine produced a cumulative incidence of agranulocytosis of 0.7% during the first year and 0.8% over the whole study period. Most cases of agranulocytosis and neutropenia occurred during the first 6 to 18 weeks of treatment. The incidence of agranulocytosis (0.07%) and neutropenia (0.7%) seen during the second year of therapy was of the same order of magnitude noted for some phenothiazine antipsychotics.

These data[6] and comparable data from the USA[7] were considered to indicate that mandatory haematological monitoring (see Precautions, below) helped to reduce the risks of clozapine-induced neutropenia and agranulocytosis and associated deaths.

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune response.[8,9] **Predisposing factors** for development of agranulocytosis have not been identified, apart from a possible excess of cases in female patients and an increased risk with increasing age. Furthermore, both agranulocytosis and neutropenia do not appear to be dose-related effects with clozapine. A postulated higher incidence of agranulocytosis in patients of Jewish background may be related to genetic factors.[10] Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia[6] and it has been noted[11] that many patients from these ethnic groups are currently already excluded from treatment with clozapine because their normal white blood cell and neutrophil counts are below the recommended range for treatment (see Precautions, below). However, UK licensed product information recommends that patients who have low white blood cell counts due to benign ethnic neutropenia may begin clozapine treatment with the agreement of a haematologist.

Evidence would suggest that development of clozapine-induced leucopenia or granulocytopenia precludes **retreatment** with clozapine at any future date; in a series of 9 re-treated patients, all developed leucopenia or agranulocytosis again.[12] In the USA, patients who have had clozapine withdrawn because of moderate leucopenia (judged to be when counts fall to 2000 to 3000 cells/mm^3) are considered eligible for a return to clozapine treatment when this count returns to normal; such patients are considered to have a five- or sixfold greater risk of agranulocytosis.[5]

1. Idänpään-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11:** 193–8.
2. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11:** 199–201.
3. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329:** 162–7.
5. Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346:** 849.
6. Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169:** 483–8.
7. Honigfeld G, *et al.* Reducing clozapine-related morbidity and mortality: 5 years experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59** (suppl 3): 3–7.
8. Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338:** 262–3.
9. Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1–60.
10. Leiberman JA, *et al.* HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47:** 945–8.
11. Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313:** 1262.
12. Safferman AZ, *et al.* Rechallenge in clozapine-induced agranulocytosis. *Lancet* 1992; **339:** 1296–7.

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. However, a later review considered that there was overwhelming evidence that atypical antipsychotics induced more weight gain than classical antipsychotics.[2]

A separate review[3] calculated the average monthly weight gain associated with atypical antipsychotics to be:

- olanzapine (2.28 kg)
- zotepine (2.28 kg)
- quetiapine (1.76 kg)
- clozapine (1.72 kg)
- risperidone (0.96 kg)
- ziprasidone (0.80 kg)

Weight gain occurred most frequently during the first 6 to 12 months of treatment. It was recommended that if weight gain was more than 2 kg during the first 2 weeks, a strict dietary regimen should be started immediately. However, more recent opinion is that a change of antipsychotic may be necessary. Anti-obesity drugs have been tried although their routine use is not generally recommended.[2,4]

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.
2. Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16:** 75–85.
3. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24:** 59–73.
4. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (suppl 7): 22–31.

Effects on carbohydrate metabolism. Treatment with clozapine may be associated with an increased risk of glucose intolerance and diabetes mellitus; a similar association has also been noted for some other atypical antipsychotics.[1]

Data received by WHO indicated that up to December 2000, there had been 480 reports of glucose intolerance with clozapine, 253 with olanzapine, and 138 with risperidone.[2] In some cases weight gain was also reported, which may predispose to development of glucose intolerance. Other risk factors identified included an underlying diabetic condition, male gender, and use with some other medications including valproate, SSRIs, and buspirone. Regular monitoring of weight, blood glucose, and blood lipids was recommended in patients receiving clozapine, olanzapine, and risperidone.

Glucose intolerance has also been reported for the atypical antipsychotic quetiapine.[3,4]

Other reviewers have also found similar evidence of an increased risk of diabetes with atypical antipsychotics.[5] In September 2003 the FDA therefore requested labelling changes for all atypical antipsychotics to include the following recommendations and warnings:

- patients with diabetes mellitus receiving atypical antipsychotics should be monitored regularly for worsening glucose control
- patients with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the start of, and during, treatment with atypical antipsychotics
- all patients given atypical antipsychotics should be monitored during treatment and those who develop hyperglycaemia should undergo fasting blood glucose testing
- in some cases hyperglycaemia resolved on withdrawal but some patients needed to continue antidiabetic therapy despite withdrawal

However, the American Diabetes Association and several other American medical associations[6] consider that the risks vary between atypical antipsychotics and have recommended that this should be taken into account when prescribing. The risk of weight gain, diabetes, and dyslipidaemia was considered to be greatest for clozapine and olanzapine, with risperidone and quetiapine having intermediate effects, and aripiprazole and ziprasidone having little effect (see also Effects on Body-Weight, above). They recommended that *baseline monitoring* should include:

- personal and family history of obesity, diabetes, dyslipidaemia, hypertension, or cardiovascular disease
- weight, height, and waist circumference
- blood pressure
- fasting blood glucose
- fasting lipid profile

Patients at risk for diabetes should receive an atypical drug with a lower propensity for weight gain and glucose intolerance. *Follow-up monitoring* should consist of reassessment of weight at 4, 8, and 12 weeks, and it was recommended that a change of antipsychotic should be considered for any patient who gained more than 5% of their original weight during treatment. Fasting plasma glucose and blood pressure should be assessed at 3 months and annually or more frequently thereafter according to risk. Lipid levels should also be assessed after 3 months and, if normal, at 5-year intervals thereafter. Any patient with worsening glycaemia or dyslipidaemia should be changed to an antipsychotic that has not been associated with significant weight gain or diabetes.

1. Melkersson K, Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs* 2004; **64:** 701–23.
2. Hedenmalm K, *et al.* Glucose intolerance with atypical antipsychotics. *Drug Safety* 2002; **25:** 1107–16.
3. Griffiths J, Springuel P. Atypical antipsychotics: impaired glucose metabolism. *Can Adverse Drug React News* 2001; **11** (4): 3–6. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v11n4-eng.pdf (accessed 21/08/08)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Atypical antipsychotics and hyperglycaemia. *Aust Adverse Drug React Bull* 2004; **23:** 11–12. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0406.htm (accessed 25/05/05)
5. Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of diabetes mellitus. *Ann Pharmacother* 2003; **37:** 1849–57.
6. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27:** 596–601. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/2/596.pdf (accessed 24/05/05)

Effects on the cardiovascular system. The UK CSM[1] issued a warning in November 1993 of the risk of **myocarditis** with clozapine. Three patients who died while taking clozapine had evidence of myocarditis. The CSM had also received one other report of myocarditis and one of cardiomyopathy associated with clozapine. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) subsequently reported[2] another 5 cases of clozapine-associated myocarditis in November 1994. A later report[3] from Australia identified 15 cases of myocarditis, including 5 fatalities, between January 1993 and March 1999 (these figures were established using both data from ADRAC and the Australian manufacturers). Between September 1989 and December 1999 the FDA had received reports of 28 cases of myocarditis (18 fatal) and 41 of cardiomyopathy (10 fatal) temporally associated with clozapine use.[4] A review[5] by the pharmacovigilance authorities in New Zealand stated that by November 1999 the manufacturers (*Novartis*) had analysed 125 reports of myocarditis received worldwide including 35 fatalities; 53% had occurred during the first month of treatment but about 5% occurred more than 2 years after starting treatment. A more recent review[6] of reports submitted to ADRAC between 1993 and 2003 identified 116 cases of myocarditis; of these, 60 patients were known to have recovered and 12 died. Myocarditis developed within a median of 17 days of starting clozapine therapy. In a reminder article,[7] the CSM has also commented that myocarditis occurs most commonly in the first 2 months whereas cardiomyopathy generally develops later in therapy. Pericarditis and pericardial effusions have also been reported. As myocarditis can be difficult to diagnose and confirmation is not always possible, the CSM recommended that if there was a high clinical suspicion of myocarditis, antipsychotic medication should be stopped. Presenting features might include persistent tachycardia at rest, heart failure, arrhythmia, or symptoms mimicking myocardial infarction or pericarditis. Patients who have developed clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

There is also evidence that clozapine may be associated with fatal **thromboembolism**. Between February 1990 and December 1999, the FDA[8] had received 99 reports of venous thromboembolism associated with clozapine treatment. Of these reports, 83 mentioned pulmonary embolism with or without deep-vein thrombosis and 16 mentioned deep-vein thrombosis alone; 63 deaths were due to pulmonary embolism. The Swedish Adverse Reactions Advisory Committee had received reports[9] on 6 cases (5 fatal) of pulmonary embolism and 6 of venous thrombosis associated with clozapine treatment as of March 2000. The effect seemed to occur mainly in the first 3 months of treatment, and the majority of the cases involved men. However, analysis of data[10] from Germany and Switzerland suggests that the incidence of clozapine-associated thromboembolism is no different from that in psychiatric patients treated with classical antipsychotics or no antipsychotics at all.

There have been isolated reports[11,12] of **paradoxical hypertension** in patients receiving clozapine. Use with atenolol has controlled the hypertension and allowed clozapine therapy to be continued.

Some studies[13] have suggested that serious cardiovascular effects might occur more frequently and might be more severe in healthy subjects given clozapine than in patients with schizophrenia. The manufacturers had therefore requested that pharmacokinetic studies of clozapine should be performed in patients with treatment-resistant schizophrenia rather than in healthy subjects.

For further details of effects of clozapine on the cardiovascular system, see Benzodiazepines under Interactions, below.

1. CSM/MCA. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). *Current Problems* 1993; **19:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Clozapine and myocarditis. *Aust Adverse Drug React Bull* 1994; **13** (Nov): 14–15.
3. Kilian JG, *et al.* Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; **354:** 1841–5.
4. La Grenade L, *et al.* Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med* 2001; **345:** 224–5.
5. New Zealand Medicines and Medical Devices Safety Authority. Potentially fatal complications of clozapine therapy: myocarditis, venous thromboembolism and constipation. Available at: http://www.medsafe.govt.nz/profs/puarticles/cloz1.htm (accessed 24/05/05)
6. Haas SJ, *et al.* Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety* 2007; **30:** 47–57.
7. CSM/MCA. Clozapine and cardiac safety: updated advice for prescribers. *Current Problems* 2002; **28:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
8. Knudson JF, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252–3.
9. Hägg S, *et al.* Association of venous thromboembolism and clozapine. *Lancet* 2000; **355:** 1155–6.
10. Wolstein J, *et al.* Antipsychotic drugs and venous thromboembolism. *Lancet* 2000; **356:** 252.
11. Gupta S. Paradoxical hypertension associated with clozapine. *Am J Psychiatry* 1994; **151:** 148.
12. Ennis LM, Parker RM. Paradoxical hypertension associated with clozapine. *Med J Aust* 1997; **166:** 278.
13. Pokorny R, *et al.* Normal volunteers should not be used for bioavailability or bioequivalence studies of clozapine. *Pharm Res* 1994; **11:** 1221.

Effects on fluid and electrolyte homoeostasis. Hyponatraemia has been reported to be associated with clozapine,[1] as with other antipsychotics (p.970). It was emphasised that hyponatraemia should be excluded as a possible trigger when considering the epileptogenic potential of clozapine.

1. Ogilvie AD, Croy MF. Clozapine and hyponatraemia. *Lancet* 1992; **340:** 672.

Effects on the gastrointestinal tract. The UK CSM had received 20 reports of serious gastrointestinal reactions resembling obstruction associated with clozapine treatment as of March 1999, of which 3 were fatal.[1] These reactions were thought to be due to the antimuscarinic actions of clozapine and, therefore, more likely to occur when clozapine was taken with other drugs with antimuscarinic actions such as tricyclic antidepressants, some antiparkinsonian drugs, and other antipsychotics; care was also warranted in those patients with a history of colonic disease or previous bowel surgery. It was also important to recognise and treat constipation in patients receiving clozapine to prevent the development of more serious complications such as obstruction and paralytic ileus.

1. CSM/MCA. Clozapine (Clozaril) and gastrointestinal obstruction. *Current Problems* 1999; **25:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Effects on the kidneys. There have been reports[1-3] of acute interstitial nephritis associated with clozapine treatment. All 3 patients had acute renal failure which resolved when the drug was stopped. The authors of 1 report noted that the UK CSM had received 7 reports of acute renal failure associated with clozapine treatment, including 1 death, between December 1989 and February 1999.[2]

1. Elias TJ, *et al.* Clozapine-induced acute interstitial nephritis. *Lancet* 1999; **354:** 1180–1.
2. Fraser D, Jibani M. An unexpected and serious complication of treatment with the atypical antipsychotic drug clozapine. *Clin Nephrol* 2000; **54:** 78–80.
3. Au AF, *et al.* Clozapine-induced acute interstitial nephritis. *Am J Psychiatry* 2004; **161:** 1501.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism, above.

Effects on the nervous system. As with other antipsychotics (see Convulsions, p.969), clozapine can lower the seizure threshold and cause EEG abnormalities, although treatment with clozapine appears to be associated with a higher frequency of seizures. A review[1] of 1418 patients treated with clozapine in the USA between 1972 and 1988 found that 41 had experienced generalised tonic-clonic seizures. It was considered that the risk of clozapine-induced seizures was dose-related. The seizure frequency was calculated to be:

- 1% at a dosage less than 300 mg daily
- 2.7% at 300 to 599 mg daily
- 4.4% with a dosage of 600 mg or more daily

Six of the patients had been taking other drugs reported to lower the seizure threshold. Therapy with clozapine was continued in 31 of the 41 patients by reducing the total daily dose of clozapine; antiepileptic drug therapy was begun in about half of the patients.

The UK CSM[2] considered that, although the epileptogenic effect of clozapine was claimed to be dose-related, the metabolism and plasma concentrations of clozapine were highly variable, and data from 8 cases reported to the CSM suggested that convulsions might possibly be related to high plasma concentrations in susceptible individuals. A low initial dosage followed by careful increases according to response and downward titration thereafter to a maintenance dose was recommended to avoid convulsions in susceptible individuals.

1. Devinsky O, *et al.* Clozapine-related seizures. *Neurology* 1991; **41:** 369–71.
2. CSM. Convulsions may occur in patients receiving clozapine (Clozaril , Sandoz). *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

Effects on the pancreas. There have been isolated reports of pancreatitis associated with clozapine therapy[1-3] and overdosage.[4] A systematic review[5] of the FDA's surveillance database and published case reports up to February 2002 found 192 patients who had pancreatitis (22 fatalities) after treatment with one or more antipsychotics. This included monotherapy with clozapine (72 patients), olanzapine (62), risperidone (31), and haloperidol (12). Most cases occurred within 6 months of starting therapy.

1. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry* 1992; **149:** 714.
2. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis. *Lancet* 1992; **340:** 251.
3. Garlipp P, *et al.* The development of a clinical syndrome of asymptomatic pancreatitis and eosinophilia after treatment with clozapine in schizophrenia: implications for clinical care, recognition and management. *J Psychopharmacol* 2002; **16:** 399–400.
4. Jubert P, *et al.* Clozapine-related pancreatitis. *Ann Intern Med* 1994; **121:** 722–3.
5. Koller EA, *et al.* Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. *Pharmacotherapy* 2003; **23:** 1123–30.

Extrapyramidal disorders. Clozapine retains a place in therapy, despite its propensity to cause agranulocytosis, because, in part, of its reduced rate of extrapyramidal effects (see also p.971). Other drugs in the class have since been developed. However, although atypical antipsychotics carry a lower risk of causing extrapyramidal disorders, the risk is not zero; acute effects and tardive syndromes have been reported with these drugs, and the developing tendency to use them for high-dose therapy may perhaps narrow the margin of advantage.[1]

1. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Safety* 2005; **28:** 191–208.

Hypersalivation. Hypersalivation has been reported[1] to occur in up to 54% of patients receiving clozapine. The pathophysiology for this effect is unclear, but proposed mechanisms include action at muscarinic (M_3 and M_4) receptors, blockade of

α_2-adrenoceptors, or distortion of the swallowing reflex. Management strategies have included chewing gum to increase frequency of swallowing or reduction of clozapine dosage in stabilised patients; antimuscarinics or α_2-agonists have been tried when other methods have failed. However, antimuscarinics could potentially exacerbate the antimuscarinic adverse effects of clozapine, and intranasal ipratropium bromide has been tried as an alternative with beneficial results in one small uncontrolled study.[2]

1. Davydov L, Botts SR. Clozapine-induced hypersalivation. *Ann Pharmacother* 2000; **34:** 662–5.
2. Calderon J, *et al.* Potential use of ipatropium [sic] bromide for the treatment of clozapine-induced hypersalivation: a preliminary report. *Int Clin Psychopharmacol* 2000; **15:** 49–52.

Neuroleptic malignant syndrome. A review of the literature[1] suggested that clozapine may produce fewer extrapyramidal effects and a lower rise in creatine kinase concentrations than classical antipsychotics. The incidence of neuroleptic malignant syndrome (NMS— p.972) with clozapine appeared to be similar to that with classical antipsychotics;[1] however, its presentation may differ, with fever and rigidity less frequent, and possibly less severe, but diaphoresis more common.[2] Nevertheless, a later review[3] concluded that manifestations of NMS associated with the atypical antipsychotics clozapine, olanzapine, quetiapine, and risperidone were of similar nature and severity to those associated with classical antipsychotics. NMS has also been reported[4] with the use of amisulpride and aripiprazole.

1. Sachdev P, *et al.* Clozapine-induced neuroleptic malignant syndrome: a review and report of new cases. *J Clin Psychopharmacol* 1995; **15:** 365–71.
2. Karagianis JL, *et al.* Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. *Ann Pharmacother* 1999; **33:** 623–30. Correction. *ibid.*; 1011.
3. Ananth J, *et al.* Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; **65:** 464–70.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Aripiprazole and neuroleptic malignant syndrome. *Aust Adverse Drug React Bull* 2007; **26:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0704.pdf (accessed 03/04/08)

Withdrawal. Abrupt withdrawal of clozapine may be associated with symptoms that have been described as 'cholinergic rebound' although the manifestations, which may include headache, profuse sweating, hypersalivation, bronchoconstriction, agitation, enuresis, and diarrhoea also have some common features with the serotonin syndrome (p.416); motor disorders and exacerbation of extrapyramidal disorders have also occurred. In addition, as with other antipsychotics, abrupt withdrawal of clozapine may be associated with rapid relapse of the original psychosis. In a retrospective case-note study of 29 schizophrenic patients whose clozapine treatment was withdrawn, abrupt withdrawal in 20 resulted in a marked, immediate deterioration in their mental state.[1] Of 3 further patients who experienced delirium with psychotic symptoms shortly after stopping clozapine, symptoms developed in 1 within 24 hours despite gradual withdrawal of clozapine over a 2-week period.[2] All the patients responded rapidly to resumption of low doses of clozapine.

1. Baker M, White T. Life after clozapine. *Med Sci Law* 2004; **44:** 217–21.
2. Stanilla JK, *et al.* Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry* 1997; **58:** 252–5.

Precautions

Clozapine should not be given to patients with uncontrolled epilepsy, alcoholic or toxic psychoses, drug intoxication, or a history of circulatory collapse. It should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. It is contra-indicated in patients with bone-marrow suppression, myeloproliferative disorders, or any abnormalities of white blood cell count or differential blood count. It is also contra-indicated in patients with a history of drug-induced neutropenia or agranulocytosis with the exception of that due to chemotherapy. It should not be used with drugs that carry a high risk of bone-marrow suppression (see Interactions, below).

Clozapine is contra-indicated in patients with severe renal impairment; caution is required in mild to moderate renal impairment. It should be used with caution in hepatic impairment and avoided in symptomatic or progressive liver disease or hepatic failure. Patients with a history of cardiac impairment or abnormal cardiac findings on examination should be referred to a specialist for further evaluation, which may include an ECG; treatment with clozapine should only then be started if the potential benefits clearly outweigh any risk. Clozapine should not be used in severe heart failure.

Clozapine possesses antimuscarinic properties and consequently it is contra-indicated in patients with paralytic ileus; it should also be used with caution in benign prostatic hyperplasia and angle-closure glaucoma.

Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes (see Effects on Carbohydrate Metabolism, above).

Monitoring the white blood cell and absolute neutrophil counts is mandatory during clozapine treatment and should be carried out in accordance with official recommendations; these may vary between countries (see Monitoring, below for further details). Patients or their carers should report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

Patients who develop tachycardia at rest, dyspnoea, arrhythmias, chest pain, or other signs and symptoms of heart failure should be investigated immediately and clozapine treatment stopped if a diagnosis of myocarditis or cardiomyopathy is suspected.

Because of an increased risk of collapse due to orthostatic hypotension associated with rapid dose escalation during initial titration of clozapine dosage, it is recommended that treatment should be begun under close medical supervision. In addition, patients with Parkinson's disease should have their blood pressure monitored for the first weeks of treatment.

On planned withdrawal, the dose of clozapine should be reduced gradually over at least a 1- to 2-week period in order to avoid the risk of rebound psychosis and other withdrawal symptoms (see above). If abrupt withdrawal is necessary then patients should be observed carefully.

Clozapine may affect the performance of skilled tasks such as driving.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of clozapine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Clozapine appears to be distributed into breast milk in relatively high concentrations.[2] Concentrations in a patient given 50 mg daily were 63.5 nanograms/mL in breast milk and 14.7 nanograms/mL in plasma; at 100 mg daily they were 115.6 nanograms/mL and 41.4 nanograms/mL, respectively.

The manufacturers have also stated that studies in *animals* suggest that clozapine is excreted into breast milk and has an effect on nursing infants; they recommend that mothers receiving clozapine should not breast feed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/05)
2. Barnas C, *et al.* Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. *Am J Psychiatry* 1994; **151:** 945.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics, including clozapine, in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs in this class. See under Risperidone, p.1024.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 24/05/05)

Monitoring. *WHITE CELL COUNTS.* A white blood cell count and a differential blood count must be performed before starting clozapine therapy and regularly throughout treatment. Treatment should not be started if the white blood cell count is less than 3500 cells/mm^3 and the absolute neutrophil count (ANC) is less than 2000 cells/mm^3, or if there is an abnormal differential count. Monitoring should continue throughout therapy and for 4 weeks after withdrawal.

In the EU, including the UK, monitoring is performed at weekly intervals for the first 18 weeks and then at least every 2 weeks between weeks 18 and 52; after 1 year of treatment with stable neutrophil counts, patients may be monitored at least every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 or the ANC falls to between 1500 and 2000 cells/mm^3 then monitoring should be performed **twice weekly** until values stabilise or increase.
- Clozapine should be **withdrawn** immediately if the white blood cell count falls below 3000 cells/mm^3 or the ANC drops below 1500 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In the USA, white blood cell and ANC are monitored weekly for the first 6 months and then every 2 weeks thereafter; after 1 year of therapy, patients may be monitored every 4 weeks.

- If during therapy the white blood cell count falls to between 3000 and 3500 cells/mm^3 and the ANC is above 1500 cells/mm^3 then monitoring should be performed **twice weekly**.
- If the white blood cell count falls below 3000 cells/mm^3 or the ANC is below 1500 cells/mm^3 then clozapine treatment should be **interrupted** and counts performed daily. Clozapine may be restarted if the white blood cell count recovers to above 3500 cells/mm^3 and the ANC to above 2000 cells/mm^3. After recovery, weekly monitoring is recommended for the next 12 months before reducing to every 2 weeks for 6 months, and then every 4 weeks thereafter.
- Clozapine should be **withdrawn** if the white blood cell count falls below 2000 cells/mm^3 or the ANC drops below 1000 cells/mm^3; counts should be monitored daily until they return to normal. Clozapine should not be restarted in these patients.

In patients with decreased white blood cell or ANC it is especially important that they or their carers report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.

EOSINOPHIL COUNT. In the EU, clozapine should be withdrawn if the eosinophil count is greater than 3000 cells/mm^3; it should only be restarted once the count has fallen to below 1000 cells/mm^3.

Similar advice is given in the USA although the values differ: clozapine should be withdrawn if the eosinophil count is above 4000 cells/mm^3 and restarted once the count has fallen to below 3000 cells/mm^3.

PLATELET COUNT. European licensing information states that clozapine should be stopped if the platelet count falls below 50 000 cells/mm^3.

TREATMENT BREAK. If treatment with clozapine is interrupted for reasons other than abnormal haematological values then more frequent monitoring may be required following resumption of therapy.

In the EU, patients who have taken clozapine for at least 18 weeks and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 4 weeks if the counts are stable; a break of 4 weeks or more would require weekly monitoring for the next 18 weeks.

US licensed product information recommends resuming weekly monitoring for 6 months in patients whose therapy has been interrupted for more than 1 month; frequency of monitoring is then reduced as described in White Cell Counts, see above. Those who have taken clozapine for at least 6 months and stopped therapy for more than 3 days but less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 2 weeks for 6 months if the counts are stable; those on clozapine for over 1 year may be monitored every 4 weeks after initial weekly monitoring for 6 weeks.

Pregnancy. A review of the literature[1] between 1993 and April 2004 suggested that clozapine and olanzapine do not appear to increase the risk of fetal teratogenicity; literature regarding aripiprazole, quetiapine, risperidone, and ziprasidone was incomplete or not available. The rate of spontaneous abortions in pregnant women exposed to clozapine or olanzapine was not found to be higher than that of the general population; however, these 2 drugs increased the risk of hyperglycaemia in pregnant women. A prospective comparative study[2] of pregnancy outcomes in women taking clozapine, olanzapine, quetiapine, and risperidone also concluded that atypicals do not appear to be associated with an increased risk for major malformations when compared to the baseline risk in the general population. The authors recommended that benefits and risks be weighed carefully in each case and optimal control of the psychiatric disorder be maintained throughout pregnancy and postpartum together with careful monitoring.

1. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. *Ann Pharmacother* 2004; **38:** 1265–71.
2. McKenna K, *et al.* Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 2005; **66:** 444–9.

Interactions

Clozapine may enhance the central effects of MAOIs and CNS depressants including alcohol, antihistamines, benzodiazepines, and opioid analgesics.

Clozapine should not be used with drugs that carry a high risk of bone-marrow suppression including carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulfonamides, antineoplastics, or pyrazolone analgesics such as azapropazone. Long-acting depot antipsychotics have myelosuppressive potential and should not be used with clozapine as they cannot be withdrawn rapidly should neutropenia occur. Additive effects may occur when clozapine is given with drugs that possess antimuscarinic, hypotensive, or respiratory depressant effects. Clozapine may reduce the effects of alpha-adrenoceptor agonists such as noradrenaline.

The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit or act as a substrate to this isoenzyme may affect plasma concentrations of clozapine and the dose of clozapine may need to be altered. Increased plasma-clozapine concentrations, with an increased risk of adverse effects, may be seen in patients who suddenly stop smoking. Use with phenytoin or other enzyme-inducing drugs may accelerate the metabolism of clozapine and reduce its plasma concentrations.

◊ References.

1. Taylor D. Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 1997; **171:** 109–12.

Antibacterials. A patient with schizophrenia controlled with clozapine therapy had a tonic-clonic seizure 7 days after starting treatment with *erythromycin*.[1] It appeared that erythromycin had inhibited the metabolism of clozapine and raised its serum concentrations. Increased drowsiness and hypersalivation have been seen in a patient receiving clozapine and *ampicillin*; he recovered when ampicillin was replaced with doxycycline.[2]

Giving clozapine with *rifampicin* has resulted in decreased clozapine concentrations with consequent return of paranoid thoughts in a patient with a complicated history of schizophrenia.[3] An improvement was seen after rifampicin was replaced with ciprofloxacin. The interaction was thought to be due to the induction of cytochrome P450 isoenzymes, particularly CYP1A2, by rifampicin, resulting in the accelerated metabolism of clozapine.

1. Funderburg LG, *et al.* Seizure following addition of erythromycin to clozapine treatment. *Am J Psychiatry* 1994; **151:** 1840–1.
2. Csík V, Molnár J. Possible adverse interaction between clozapine and ampicillin in an adolescent with schizophrenia. *J Child Adolesc Psychopharmacol* 1994; **4:** 123–8.
3. Joos AAB, *et al.* Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with atypical mycobacterial infection. *J Clin Psychopharmacol* 1998; **18:** 83–5.

Antidepressants. Rises in serum concentrations of clozapine have been found in patients receiving clozapine after addition of *fluoxetine*[1] or *fluvoxamine*[2] to therapy. Increased serum concentrations of clozapine have also been reported when *paroxetine* or *sertraline* was added to therapy.[3] A possible serotonin syndrome (p.416) has been reported[4] in a patient receiving *clomipramine* after clozapine was gradually withdrawn from the treatment regimen, although the symptoms were also similar to those of clozapine withdrawal (see above). There has been an isolated report[5] of a patient who developed myoclonic jerks 79 days after fluoxetine was added to treatment with clozapine and lorazepam, although some[6] doubt whether the effects were entirely due to an interaction. Giving clozapine with *lithium* may increase the risk of neuroleptic malignant syndrome. For reference to neurological reactions in patients receiving lithium with clozapine, see p.405.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Jerling M, *et al.* Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994; **16:** 368–74.
3. Centorrino F, *et al.* Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996; **153:** 820–2.
4. Zerjav-Lacombe S, Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. *Ann Pharmacother* 2001; **35:** 180–2.
5. Kingsbury SJ, Puckett KM. Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473.
6. Baldessarini RJ, *et al.* Effects of fluoxetine on serum clozapine levels. *Am J Psychiatry* 1995; **152:** 473–4.

Antiepileptics. Use of *phenytoin* or other *enzyme-inducing antiepileptics* may accelerate the metabolism of clozapine and reduce its plasma concentrations. Studies have found that addition of *sodium valproate* to clozapine therapy may increase[1] or decrease[2] plasma concentrations of clozapine. Although no increase in clozapine-related adverse effects or loss of control of psychotic symptoms were reported in these studies, there has been a report[3] of a patient who experienced sedation, confusion, slurring of speech and other functional impairment after valproate was given with clozapine.

See also under Benzodiazepines, below.

1. Centorrino F, *et al.* Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994; **151:** 123–5.
2. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* 1994; **36:** 487–8.
3. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* 1995; **15:** 139–41.

Antipsychotics. Giving *risperidone* to a patient with schizoaffective disorder partially controlled by clozapine produced clinical improvement but was associated with a 74% rise in serum-clozapine concentrations over a 2-week period.[1] Although no adverse effects occurred in this patient, the potential for serious adverse effects requires caution if these drugs are used together. Neuroleptic malignant syndrome associated with use of clozapine with *haloperidol* has been reported.[2]

See also under Chlorpromazine, p.974.

1. Tyson SC, *et al.* Pharmacokinetic interaction between risperidone and clozapine. *Am J Psychiatry* 1995; **152:** 1401–2.
2. Garcia G, *et al.* Neuroleptic malignant syndrome with antidepressant/antipsychotic drug combination. *Ann Pharmacother* 2001; **35:** 784–5.

Antivirals. Although the UK manufacturers of *ritonavir* have stated that it may increase plasma concentrations of clozapine with a resultant increase in the risk of toxicity, there is evidence to suggest that, in fact, ritonavir may decrease the plasma concentrations of clozapine.[1] Ritonavir has been noted to induce the cytochrome P450 isoenzyme CYP1A2 and hence, as clozapine is primarily metabolised via this isoenzyme, an acceleration of the metabolism of clozapine would be expected. US prescribing information has been amended accordingly.

1. Penzak SR, *et al.* Comment: significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999; **33:** 1372–3.

Benzodiazepines. Concern has been expressed over reports of cardiorespiratory collapse in patients taking both clozapine and benzodiazepines.[1,2] In response, the manufacturers of clozapine outlined[3] similar cases reported to them in the USA. Of 7 cases of respiratory arrest or depression only 2 involved recent use of a benzodiazepine; among 26 cases of orthostatic hypotension with syncope reported during the first year the drug was marketed, only 8 included recent benzodiazepine use. The manufacturers concluded that an increased risk of such reactions in patients taking both drugs simultaneously was possible but not established, and advised caution when starting clozapine therapy in patients taking benzodiazepines.

Hypersalivation associated with clozapine and benzodiazepines may be exacerbated when these drugs are used together. A patient[4] experienced increased hypersalivation, salivary thickening, and distension of the parotid glands when *clonazepam* was added to treatment with clozapine. Adverse effects reported in 5 other patients given clozapine and benzodiazepines together included hypersalivation, sedation, ataxia, and symptoms of delirium.[5,6]

1. Sassim N, Grohmann R. Adverse drug reactions with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry* 1988; **21:** 306–7.
2. Friedman LJ, *et al.* Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518.
3. Finkel MJ, Schwimmer JL. Clozapine—a novel antipsychotic agent. *N Engl J Med* 1991; **325:** 518–19.
4. Martin SD. Drug-induced parotid swelling. *Br J Hosp Med* 1993; **50:** 426.
5. Cobb CD, *et al.* Possible interaction between clozapine and lorazepam. *Am J Psychiatry* 1991; **148:** 1606–7.
6. Jackson CW, *et al.* Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry* 1995; **7:** 139–41.

Buspirone. Potentially fatal gastrointestinal bleeding, accompanied by severe acidosis and hyperglycaemia, developed in a patient given buspirone with clozapine.[1] The patient had previously been taking clozapine for over a year without adverse effect, and was subsequently maintained on clozapine alone without a recurrence of symptoms.

1. Good MI. Lethal interaction of clozapine and buspirone? *Am J Psychiatry* 1997; **154:** 1472–3.

Gastrointestinal drugs. A patient stabilised on clozapine developed increased serum clozapine concentrations and signs of clozapine toxicity after starting treatment with *cimetidine*.[1] Cimetidine was withdrawn and ranitidine substituted without recurrence of toxicity.

A marked reduction in plasma-clozapine concentrations was seen in 2 smokers stabilised on the antipsychotic who began treatment with *omeprazole*,[2] which is a known inducer of the cytochrome P450 isoenzyme CYP1A2. However, a small retrospective analysis of the effect of stopping omeprazole in 13 patients taking both drugs suggested that the effect of omeprazole was only significant in non-smokers, and the clozapine dose did not need to be adjusted in any of these patients.[3]

1. Szymanski S, *et al.* A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 1991; **52:** 21–2.
2. Frick A, *et al.* Omeprazole reduces clozapine plasma concentrations: a case report. *Pharmacopsychiatry* 2003; **36:** 121–3.
3. Mookhoek EJ, Loonen AJ. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm World Sci* 2004; **26:** 180–2.

Xanthines. *Caffeine* may inhibit the metabolism of clozapine.[1,2] Care should be taken before stopping or starting caffeine-containing beverages in patients stabilised on clozapine treatment.

1. Carrillo JA, *et al.* Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998; **18:** 311–16.
2. Hägg S, *et al.* Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000; **49:** 59–63.

Pharmacokinetics

Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by first-pass metabolism. Peak plasma concentrations are achieved, on average, about 2.5 hours after oral doses. Clozapine is about 95% bound to plasma proteins and has a mean terminal elimination half-life of about 12 hours at steady state. It is almost completely metabolised and routes of metabolism include *N*-demethylation, hydroxylation, and *N*-oxidation; the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect. It is distributed into breast milk.

◊ References.

1. Jann MW, *et al.* Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993; **24:** 161–76.
2. Lin S-K, *et al.* Disposition of clozapine and desmethylclozapine in schizophrenic patients. *J Clin Pharmacol* 1994; **34:** 318–24.
3. Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? *Clin Pharmacokinet* 1997; **32:** 93–100.
4. Olesen OV. Therapeutic drug monitoring of clozapine treatment: therapeutic threshold value for serum clozapine concentrations. *Clin Pharmacokinet* 1998; **34:** 497–502.
5. Guitton C, *et al.* Clozapine and metabolite concentrations during treatment of patients with chronic schizophrenia. *J Clin Pharmacol* 1999; **39:** 721–8.
6. Dettling M, *et al.* Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. *Psychopharmacology (Berl)* 2000; **152:** 80–6.
7. Renwick AC, *et al.* Monitoring of clozapine and norclozapine plasma concentration-time curves in acute overdose. *J Toxicol Clin Toxicol* 2000; **38:** 325–8.
8. Frazier JA, *et al.* Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. *J Clin Psychopharmacol* 2003; **23:** 87–91.
9. Tang Y-L, *et al.* Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *Br J Clin Pharmacol* 2007; **64:** 49–56.

Bioavailability. Mean plasma concentration of clozapine increased from 329 to 629 nanograms/mL in 10 patients when switched from an extemporaneous liquid formulation to conventional tablets.[1]

1. Coker-Adeyemi F, Taylor D. Clozapine plasma levels in patients switched from clozapine liquid to tablets. *Pharm J* 2002; **269:** 650–2.

Uses and Administration

Clozapine is a dibenzodiazepine derivative and the prototype of the atypical antipsychotics. It has relatively weak dopamine receptor-blocking activity at D_1, D_2, D_3, and D_5 receptors but has a high affinity for the D_4 receptor. Clozapine possesses alpha-adrenergic blocking, antimuscarinic, antihistaminic, antiserotonergic, and sedative properties.

Clozapine is used for the management of schizophrenia; however, because of the risk of agranulocytosis, it is reserved for patients who fail to respond to other antipsychotics, including other atypicals, or who experience severe neurological effects with such drugs. In the USA, it may also be used for reducing the risk of recurrent suicidal behaviour in those with schizophrenia or schizoaffective disorder who are at chronic risk for suicidal behaviour. In the UK, it is also used in the management of treatment-resistant psychoses associated with Parkinson's disease.

Clozapine use must be accompanied by strict procedures for the monitoring of white blood cell counts (see Precautions, above). To minimise the incidence of adverse effects, clozapine therapy should be introduced gradually, beginning with low doses and increasing according to response.

In the treatment of **schizophrenia**, including reducing the risk of suicidal behaviour, the usual oral dose is 12.5 mg once or twice on the first day followed by 25 mg once or twice on the second day. Thereafter the daily dosage may be increased gradually in steps of 25 to 50 mg to achieve a daily dose of up to 300 mg within 14 to 21 days (in the USA, up to 450 mg daily is permitted by the end of 2 weeks). Subsequent increases in steps of 50 to 100 mg may be made once or twice weekly; a daily dosage of 900 mg should not be exceeded. Once a therapeutic response has been obtained, a gradual reduction of dosage to a suitable maintenance dose is recommended; most patients respond to 200 to 450 mg daily. The total daily dose is given in divided doses; a larger portion may be given at night. Daily maintenance doses of 200 mg or less may be given as a single dose in the evening. If clozapine is to be withdrawn, this should be done gradually over a 1- to 2-week period. However, immediate withdrawal with careful observation is essential if neutropenia develops or if myocarditis or cardiomyopathy is suspected (see Precautions, above).

Elderly patients may require lower doses of clozapine and it is recommended that treatment should start with a dose of 12.5 mg on the first day and that subsequent dose increments should be restricted to 25 mg.

For patients who are restarting treatment after an interval of more than 2 days, 12.5 mg may be given once or twice on the first day. If this dose is well tolerated it may be possible to increase the dosage more quickly than when first starting. However, patients who have had respiratory or cardiac arrest with initial dosing, but were then successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after a break of even 24 hours. Additional monitoring of blood cell counts may also be required if treatment is interrupted, see Treatment Break, under Monitoring, above.

It is recommended that oral therapy with other antipsychotics should be withdrawn gradually before treatment with clozapine is started.

Clozapine has also been given by intramuscular injection.

In the management of treatment-resistant **psychoses in Parkinson's disease**, the initial oral dose of clozapine is no more than 12.5 mg once daily in the evening. Thereafter, the daily dosage may be increased in increments of 12.5 mg up to twice a week; a dose of 50 mg daily should not be reached before the end of the second week. The usual dose ranges from 25 to 37.5 mg daily. Increases in the daily dose above 50 mg should only be made in exceptional cases in increments of 12.5 mg at weekly intervals up to a maximum of 100 mg daily. The total daily dose should preferably be given as a single dose in the evening. Dosage of antiparkinsonian drugs may be increased when there has been complete remission of psychotic symptoms after at least 2 weeks of clozapine therapy. If psychotic symptoms recur after increases in antiparkinsonian therapy, the dose of clozapine may need to be increased in line with the above guidance. As in patients with schizophrenia, planned withdrawal of clozapine in patients with Parkinson's disease should also be gradual in decrements of 12.5 mg over 1 to 2 weeks.

Action. Antipsychotics are thought to work through inhibition of dopamine D_2-receptors (see p.975), but this hypothesis fails to explain the activity of the atypical antipsychotics such as clozapine. How clozapine produces its antipsychotic activity is not clear; it has a high affinity for a number of different receptors.[1]

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164:** 141–8.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of clozapine. Although some reports indicate that it is perfectly possible to switch from branded to generic clozapine,[1-4] the need for monitoring and concerns about any requirement for retitration of doses (because of potential lack of bioequivalence[5]) have to be taken into account. There have been a few reports of exacerbation of psychotic symptoms in patients who were switched to a generic formulation.[6,7]

1. Sajbel TA, *et al.* Converting patients from brand-name clozapine to generic clozapine. *Ann Pharmacother* 2001; **35:** 281–4.
2. Makela EH, *et al.* Branded versus generic clozapine for treatment of schizophrenia. *Ann Pharmacother* 2003; **37:** 350–3.
3. Stoner SC, *et al.* A program to convert patients from trade-name to generic clozapine. *Pharmacotherapy* 2003; **23:** 806–10.
4. Bazire S, Burton V. Generic clozapine in schizophrenia: what is all the fuss about? *Pharm J* 2004; **273:** 720–1.
5. Lam YW, *et al.* Branded versus generic clozapine: bioavailability comparison and interchangeability issues. *J Clin Psychiatry* 2001; **62** (suppl 5): 18–22.
6. Kluznik JC, *et al.* Clinical effects of a randomized switch of patients from clozaril to generic clozapine. *J Clin Psychiatry* 2001; **62** (suppl 5): 14–17.
7. Mofsen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. *Clin Ther* 2001; **23:** 1720–31.

Bipolar disorder. Clozapine is of benefit for the treatment of mania in patients with bipolar disorder (p.372), and the use of atypical antipsychotics in the management of such patients is increasing. However, the adverse effects of clozapine may restrict its use.

Dementia. Although atypical antipsychotics such as clozapine have been tried in elderly patients with dementia, the licensing authorities in the USA now recommend against such use, see under Precautions, above. For further discussion of the management of disturbed behaviour, see p.954.

Parkinsonism. Clozapine is used as an alternative to classical antipsychotics in the management of **treatment-resistant psychoses** in patients with Parkinson's disease (p.791). Some neurologists even consider clozapine to be the antipsychotic of choice in these patients,[1] although this remains to be determined. A review[2] in 1994 considered that there was little evidence to support clozapine as first choice given the quality of the available studies and the need for extensive monitoring. However a subsequent double-blind, placebo-controlled study[3] showed that low-dose clozapine treatment (up to 50 mg daily) significantly improved drug-induced psychosis without worsening parkinsonism. Adverse effects noted in this study were generally mild, although in the clozapine group of 30 patients, there was 1 report of leucopenia. A similar study also reported benefit,[4] although 7 of 32 patients noted some aggravation of parkinsonism, usually mild and transient, while receiving clozapine. Adverse effects reported from other individuals have also included a patient with parkinsonism who had worsening of psychotic symptoms when her dose of clozapine was increased,[5] and the sudden return of psychosis in another patient with parkinsonism whose psychosis was successfully treated with clozapine for 5 years.[6]

Low-dose clozapine (about 40 mg daily) also appears to be of benefit in the management of **levodopa-induced dyskinesias** in patients with severe Parkinson's disease.[7]

1. Klein C, *et al.* Clozapine in Parkinson's disease psychosis: 5-year follow-up review. *Clin Neuropharmacol* 2003; **26:** 8–11.
2. Pfeiffer C, Wagner ML. Clozapine therapy for Parkinson's disease and other movement disorders. *Am J Hosp Pharm* 1994; **51:** 3047–53.
3. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340:** 757–63.
4. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; **353:** 2041–2.
5. Auzou P, *et al.* Worsening of psychotic symptoms by clozapine in Parkinson's disease. *Lancet* 1994; **344:** 955.
6. Greene P. Clozapine therapeutic plunge in patient with Parkinson's disease. *Lancet* 1995; **345:** 1172–3.
7. Durif F, *et al.* Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* 2004; **62:** 381–8.

Schizophrenia. Clozapine is an effective antipsychotic for the management of schizophrenia (p.955) but its use is limited by its blood toxicity. Its effectiveness and superiority over classical antipsychotics was shown in a multicentre study.[1] Patients refractory to at least 3 different antipsychotics and who failed to improve after a single-blind trial of haloperidol, were randomised, double-blind, to treatment for 6 weeks with either clozapine up to 900 mg daily, or chlorpromazine hydrochloride up to 1800 mg daily with benzatropine mesilate up to 6 mg daily. Of the 267 patients included in the evaluation, 5 of 141 (4%) improved with chlorpromazine and benzatropine, and 38 of 126 (30%) improved with clozapine. Clozapine was superior to chlorpromazine in the treatment of negative as well as positive symptoms. Reviews[2,3] of clozapine indicate that these findings have been well replicated both in subsequent studies and in clinical practice. It is, however, unclear for how long clozapine should be tried: although 1 study[4] identified new responses up to 12 months after starting therapy, others have indicated that if improvement was not seen within the first 6 to 24 weeks, it was unlikely to occur.[2,5]

Clozapine is also used to reduce suicide risk in patients with refractory chronic schizophrenia.[6] The reported suicide rate of 0.05% per year in 6300 patients in the UK given clozapine since 1990 was considered to be tenfold less than expected.[7] A subsequent study[8] found it to be more effective than olanzapine in preventing suicide attempts in patients with schizophrenia or schizoaffective disorder at high risk.

Clozapine has shown consistent clinical benefit in schizophrenic patients with persistent aggressive or violent behaviour.[2,9] Whether this is due to a sedative effect, a specific antiaggressive action, or just reflects an overall improvement in psychosis is unknown.

Clozapine has been advocated for use in schizophrenic patients with moderate to severe tardive dyskinesia. It is still unclear whether clozapine can itself cause tardive dyskinesia but some patients with established tardive dyskinesia have experienced improvement in their symptoms when using clozapine.[10,11]

1. Kane J, *et al.* Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45:** 789–96.
2. Buckley PF. New dimensions in the pharmacologic treatment of schizophrenia and related psychoses. *J Clin Pharmacol* 1997; **37:** 363–78. Correction. *ibid.* 1998; **38:** 27.
3. Wahlbeck K, *et al.* Clozapine versus typical neuroleptic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 24/05/05).
4. Meltzer HY, *et al.* A prospective study of clozapine in treatment-resistant schizophrenic patients I: preliminary report. *Psychopharmacology (Berl)* 1989; **99:** S68–S72.
5. Conley RR, *et al.* Time to clozapine response in a standardized trial. *Am J Psychiatry* 1997; **154:** 1243–7.
6. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry* 1995; **152:** 183–90.
7. Kerwin RW. Clozapine: back to the future for schizophrenia research. *Lancet* 1995; **345:** 1063–4.
8. Meltzer HY, *et al.* Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60:** 82–91. Correction. *ibid.* 735.
9. Volavka J, *et al.* Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol* 2004; **24:** 225–8.
10. Tamminga CA, *et al.* Clozapine in tardive dyskinesia: observations from human and animal model studies. *J Clin Psychiatry* 1994; **55** (suppl B): 102–6.
11. Nair C, *et al.* Dose-related effects of clozapine on tardive dyskinesia among "treatment-refractory" patients with schizophrenia. *Biol Psychiatry* 1996; **39:** 529–30.

Preparations

USP 31: Clozapine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lapenax; Sequax; ***Austral.:*** Clopine; Clozaril; ***Austria:*** Lanolept; Leponex; ***Belg.:*** Leponex; ***Braz.:*** Leponex; Zolapin†; ***Canad.:*** Clozaril; ***Chile:*** Leponex; ***Cz.:*** Leponex; ***Denm.:*** Leponex; ***Fin.:*** Froidir; Leponex; ***Fr.:*** Leponex; ***Ger.:*** Elcrit; Leponex; ***Gr.:*** Leponex; ***Hong Kong:*** Clozaril; ***Hung.:*** Leponex; ***India:*** Lozapin; Sizopin; ***Indon.:*** Clozaril; Sizoril; ***Irl.:*** Clozaril; ***Israel:*** Leponex; Lozapine; ***Ital.:*** Leponex; ***Malaysia:*** Clozaril; Zapine; ***Mex.:*** Clopsine; Leponex; ***Neth.:*** Leponex; ***Norw.:*** Leponex; ***NZ:*** Clopine; Clozaril; ***Philipp.:*** Leponex; ***Pol.:*** Klozapol; Leponex; ***Port.:*** Leponex; Ozapim; ***Rus.:*** Leponex (Лепонекс); ***S.Afr.:*** Cloment; Leponex; ***Singapore:*** Clozaril; ***Spain:*** Leponex; ***Swed.:*** Leponex; ***Switz.:*** Clopin; Leponex; ***Thai.:*** Cloril; Clozaril; ***Turk.:*** Leponex; ***UK:*** Clozaril; Denzapine; Zaponex; ***USA:*** Clozaril; FazaClo; Fazalco†; ***Venez.:*** Leponex.

Cyamemazine *(rINN)*

Ciamemazina; Cyamémazine; Cyamemazinum; Cyamepromazine; RP-7204. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile.

Циамемазин

$C_{19}H_{21}N_3S$ = 323.5.
CAS — 3546-03-0 (cyamemazine); 93841-82-8 (cyamemazine tartrate).
ATC — N05AA06.
ATC Vet — QN05AA06.

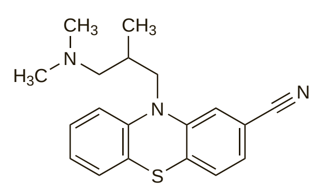

Profile

Cyamemazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is used in the management of a variety of psychiatric disorders including anxiety disorders (p.952) and aggressive behaviour (p.954).

Cyamemazine has been given orally as the base or the tartrate and by injection as the base. Doses are expressed in terms of the base; cyamemazine tartrate 36.6 mg is equivalent to about 25 mg of cyamemazine. Oral doses have ranged from 25 to 600 mg daily, depending on the individual and the condition being treated; the daily dosage is given in 2 or 3 divided doses. Doses given by intramuscular injection have ranged from 25 to 200 mg daily.

Cyamemazine should be given in reduced dosage to elderly patients; the parenteral route is not recommended for the elderly.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Tercian; ***Port.:*** Tercian.

Cyclobarbital *(BAN, rINN)*

Ciclobarbital; Cyclobarbitalum; Cyclobarbitone; Cyklobarbital; Ethylhexabital; Hexemalum; Syklobarbitaali. 5-(Cyclohex-1-enyl)-5-ethylbarbituric acid.

Циклобарбитал

$C_{12}H_{16}N_2O_3$ = 236.3.
CAS — 52-31-3.
ATC — N05CA10.
ATC Vet — QN05CA10.

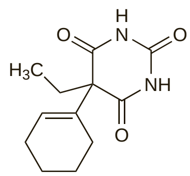

NOTE. The name ciclobarbital has sometimes been applied to hexobarbital.

Cyclobarbital Calcium *(BANM, rINNM)*

Calcii Cyclobarbitalum; Ciclobarbital cálcico; Ciclobarbital Calcium; Cyclobarbital Calcique; Cyclobarbitalum Calcicum; Cyclobarbitone Calcium; Cyklobarbital wapniowy; Hexemalcalcium. Calcium 5-(cyclohex-1-enyl)-5-ethylbarbiturate.

Кальций Циклобарбитал

$(C_{12}H_{15}N_2O_3)_2Ca$ = 510.6.
CAS — 5897-20-1.
ATC — N05CA10.
ATC Vet — QN05CA10.

Pharmacopoeias. In *Pol.*

Profile

Cyclobarbital is a barbiturate with general properties similar to those of amobarbital (p.961). The calcium salt has been used as a hypnotic but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Reladorm (Реладорм).

Delorazepam *(pINN)*

Chlordesmethyldiazepam; Clordesmethyldiazepam; Délorazépam; Delorazepamum. 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Делоразепам

$C_{15}H_{10}Cl_2N_2O$ = 305.2.
CAS — 2894-67-9.

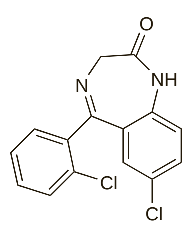

Profile

Delorazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been used in the short-term treatment of anxiety disorders, insomnia, and epilepsy, and for premedication.

Administration in hepatic or renal impairment. The pharmacokinetics of total delorazepam were unchanged in patients with renal failure undergoing haemodialysis compared with controls.[1] However, the apparent volume of distribution of unbound drug was smaller and the clearance slower. The volume of distribution and clearance of unchanged drug was also reduced in patients with liver disease.[2]

1. Sennesael J, *et al.* Pharmacokinetics of intravenous and oral chlordesmethyldiazepam in patients on regular haemodialysis. *Eur J Clin Pharmacol* 1991; **41:** 65–8.
2. Bareggi SR, *et al.* Effects of liver disease on the pharmacokinetics of intravenous and oral chlordesmethyldiazepam. *Eur J Clin Pharmacol* 1995; **48:** 265–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Dadumir; En.

Detomidine Hydrochloride *(BANM, USAN, rINNM)*

Demotidini Hydrochloridum; Detomidiinihydrokloridi; Detomidin hydrochlorid; Détomidine, chlorhydrate de; Detomidin-hidroklorid; Detomidinhydroklorid; Detomidini hydrochloridum; Hidrocloruro de detomidina; MPV-253-AII. 4-(2,3-Dimethylbenzyl)imidazole hydrochloride.

Детомидина Гидрохлорид

$C_{12}H_{14}N_2$,HCl = 222.7.
CAS — 76631-46-4 (detomidine); 90038-01-0 (detomidine hydrochloride).

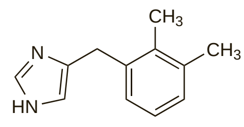

(detomidine)

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.
Ph. Eur. 6.2 (Detomidine Hydrochloride for Veterinary Use; Detomide Hydrochloride BP(Vet) 2008). A white or almost white, hygroscopic, crystalline powder. Soluble in water; freely soluble in alcohol; practically insoluble in acetone; very slightly soluble in dichloromethane. Protect from moisture.

Profile

Detomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Dexmedetomidine Hydrochloride

(BANM, USAN, rINNM)

Deksmedetomidin Hidroklorür; Dexmédétomidine, Chlorhydrate de; Dexmedetomidini Hydrochloridum; Hidrocloruro de dexmedetomidina; MPV-1440 (dexmedetomidine). (*S*)-4-[1-(2,3-Xylyl)ethyl]imidazole hydrochloride.

Дексмедетомидина Гидрохлорид

$C_{13}H_{16}N_2$,HCl = 236.7.
CAS — 113775-47-6 (dexmedetomidine); 145108-58-3 (dexmedetomidine hydrochloride).
ATC — N05CM18.
ATC Vet — QN05CM18.

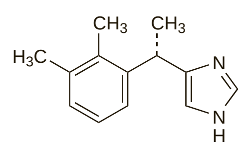

(dexmedetomidine)

Adverse Effects and Precautions

The most frequently observed adverse effect with dexmedetomidine is hypotension. Other common adverse effects include hypertension, nausea and vomiting, bradycardia, tachycardia, fever, hypoxia, and anaemia. Patients should be continuously monitored during use. Dexmedetomidine should be used with caution in patients with advanced heart block, or hepatic or renal impairment, or in the elderly.

Interactions

The effects of other CNS depressants may be enhanced by dexmedetomidine. Dexmedetomidine may also increase the effects of other vasodilators or drugs such as cardiac glycosides, that have negative chronotropic effects.

Pharmacokinetics

Dexmedetomidine is about 94% protein bound, but this has been reported to be significantly decreased in patients with hepatic impairment. Dexmedetomidine is almost completely metabolised by direct glucuronidation or by cytochrome P450 isoenzymes. It is excreted mainly as metabolites in the urine and faeces. The terminal elimination half-life is about 2 hours.

◊ References.

1. Scheinin H, *et al.* Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. *Clin Pharmacol Ther* 1992; **52:** 537–46.
2. Kivistö KT, *et al.* Pharmacokinetics and pharmacodynamics of transdermal dexmedetomidine. *Eur J Clin Pharmacol* 1994; **46:** 345–9.
3. De Wolf AM, *et al.* The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001; **93:** 1205–9.
4. Anttila M, *et al.* Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 2003; **56:** 691–3.

Uses and Administration

Dexmedetomidine is a selective alpha$_2$-adrenergic receptor agonist with anxiolytic, analgesic, and sedative properties. It is used for the sedation of mechanically ventilated patients in intensive care. Dexmedetomidine is given as the hydrochloride, but doses are expressed in terms of the base. Dexmedetomidine hydrochloride 118 micrograms is equivalent to about 100 micrograms of dexmedetomidine.

It is given in sodium chloride 0.9% by intravenous infusion in a loading dose equivalent to 1 microgram/kg of dexmedetomidine over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 micrograms/kg per hour for up to 24 hours. Reduced doses may be necessary in patients with hepatic or renal impairment, or in the elderly.

The racemate, medetomidine (p.1006), is used as the hydrochloride in veterinary medicine.

◊ References.

1. Venn RM, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54:** 1136–42.
2. Bhana N, *et al.* Dexmedetomidine. *Drugs* 2000; **59:** 263–8.
3. Coursin DB, *et al.* Dexmedetomidine. *Curr Opin Crit Care* 2001; **7:** 221–6.
4. Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. *Neurosurgery* 2005; **57** (suppl): 1–10.
5. Szumita PM, *et al.* Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health-Syst Pharm* 2007; **64:** 37–44.
6. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. *Ann Pharmacother* 2007; **41:** 245–53. Correction. *ibid.*; 530–1.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Precedex; ***Austral.:*** Precedex; ***Braz.:*** Precedex; ***Cz.:*** Precedex; ***Hong Kong:*** Precedex; ***Israel:*** Precedex; ***Malaysia:*** Precedex; ***Mex.:*** Precedex; ***NZ:*** Precedex; ***Pol.:*** Precedex; ***Singapore:*** Precedex†; ***Thai.:*** Precedex; ***Turk.:*** Precedex; ***USA:*** Precedex; ***Venez.:*** Precedex†.

Diazepam *(BAN, USAN, rINN)*

Diatsepaami; Diazépam; Diazepám; Diazepamas; Diazepamum; LA-III; NSC-77518; Ro-5-2807; Wy-3467. 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

Диазепам

$C_{16}H_{13}ClN_2O$ = 284.7.
CAS — 439-14-5.
ATC — N05BA01.
ATC Vet — QN05BA01.

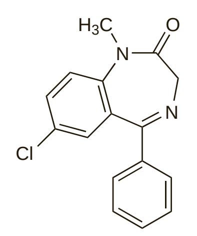

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diazepam:
Benzo; Blue; Blues; Drunk pills; La Roche; Ludes; Mother's little helper; Mother's little helpers; Pami; Roaches; Roachies; Roche; V; V's blues; Vallies; Vals.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Diazepam). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol. Protect from light.
USP 31 (Diazepam). An off-white to yellow, practically odourless, crystalline powder. Soluble 1 in 333 of water, 1 in 16 of alcohol, 1 in 2 of chloroform, and 1 in 39 of ether. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between diazepam and several other drugs. Manufacturers of diazepam injection (*Roche* and others) have advised against its admixture with other drugs.

Sorption. Substantial adsorption of diazepam onto some plastics may cause problems when giving the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should, therefore, be avoided. Giving sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and giving sets for diazepam include glass, polyolefin, polypropylene, and polyethylene.

References.

1. Cloyd JC, *et al.* Availability of diazepam from plastic containers. *Am J Hosp Pharm* 1980; **37:** 492–6.
2. Parker WA, MacCara ME. Compatibility of diazepam with intravenous fluid containers and administration sets. *Am J Hosp Pharm* 1980; **37:** 496–500.

3. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
4. Kowaluk EA, *et al.* Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am J Hosp Pharm* 1983; **40:** 417–23.
5. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Stability. Care should be observed when diluting diazepam injections for infusion because of problems of precipitation. The manufacturer's directions should be followed regarding diluent and concentration of diazepam and all solutions should be freshly prepared.

Dependence and Withdrawal

The development of dependence is common after regular use of benzodiazepines, even in therapeutic doses for short periods. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in those with marked personality disorders. Benzodiazepines should therefore be withdrawn by gradual reduction of the dose after regular use for even a few weeks; the time needed for withdrawal can vary from about 4 weeks to a year or more. The extent to which tolerance occurs has been debated but appears to involve psychomotor performance more often than anxiolytic effects. Drug-seeking behaviour is uncommon with therapeutic doses of benzodiazepines. High doses of diazepam and other benzodiazepines, injected intravenously, have been abused for their euphoriant effects.

Benzodiazepine withdrawal syndrome. Development of dependence to benzodiazepines cannot be predicted but risk factors include high dosage, regular continuous use, the use of benzodiazepines with a short half-life, use in patients with dependent personality characteristics or a history of drug or alcohol dependence, and the development of tolerance. The mechanism of dependence is unclear but may involve reduced gamma-aminobutyric acid (GABA) activity resulting from down-regulation of GABA receptors.

Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Symptoms typical of withdrawal have occurred despite continued use of benzodiazepines and have been attributed either to the development of tolerance or, as in the case of very short-acting drugs such as triazolam, to rapid benzodiazepine elimination. Pseudowithdrawal has been reported in patients who believed incorrectly that their dose of benzodiazepine was being reduced. Benzodiazepine withdrawal syndrome can theoretically be distinguished from these reactions and from rebound phenomena (return of original symptoms at greater than pretreatment severity) by the differing **time course**. A withdrawal syndrome is characterised by its onset, by the development of new symptoms, and by a peak in intensity followed by resolution. Onset of withdrawal symptoms depends on the half-life of the drug and its active metabolites. Symptoms can begin within a few hours after withdrawal of a short-acting benzodiazepine, but may not develop for up to 3 weeks after stopping a longer-acting benzodiazepine. Resolution of symptoms may take several days or months. The dependence induced by short- and long-acting benzodiazepines appears to be qualitatively similar although withdrawal symptoms may be more severe with short-acting benzodiazepines. Rebound effects are also more likely with short-acting benzodiazepines. Rebound and withdrawal symptoms develop particularly rapidly with the very short-acting drug triazolam.

With increased awareness of the problems of benzodiazepine dependence, emphasis has been placed on **prevention** by proper use and careful patient selection. For example, the UK CSM has recommended that benzodiazepines should be reserved for the short-term relief (2 to 4 weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress and is occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness. These recommendations are similar to those of the UK Royal College of Psychiatrists.

Withdrawal from long-term benzodiazepine use should generally be encouraged. Established dependence can be difficult to treat; the patient should have professional and family support and behavioural therapy may be helpful. Withdrawal in a specialist centre may be required for some patients. Since abrupt withdrawal of benzodiazepines may result in severe withdrawal symptoms dosage should be tapered. The *BNF* considers that benzodiazepines can be withdrawn in steps of about one-eighth of the daily dose every fortnight (range one-tenth to one-quarter). There are no comparative studies of the efficacy of various withdrawal schedules and in practice the protocol should be titrated against the response of the patient. Clinicians often favour transferring the patient to an equivalent dose of diazepam given at night and the following rough dosage equivalents to *diazepam 5 mg* have been recommended in the UK:

- chlordiazepoxide 15 mg
- loprazolam 0.5 to 1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5 to 1 mg
- nitrazepam 5 mg
- oxazepam 15 mg
- temazepam 10 mg

The daily dosage of diazepam can then be reduced in steps of 0.5 to 2.5 mg at fortnightly intervals. If troublesome abstinence effects occur the dose should be held level for a longer period before further reduction; increased dosage should be avoided if possible. It is better to reduce too slowly than too quickly. Time required for withdrawal can vary from about 4 weeks to a year or longer. In many cases the rate of withdrawal is best decided by the patient.

Adjuvant therapy should generally be avoided. Although a beta blocker may be given for prominent sympathetic overactivity the *BNF* recommends that this be tried only if other measures fail; antidepressants should be used only for clinical depression or panic attacks. Antipsychotic drugs should be avoided as they may aggravate symptoms.

Symptoms gradually improve after withdrawal but postwithdrawal syndromes lasting for several weeks or months have been described. Continued support may be required for the first year after withdrawal to prevent relapse.

References.

1. CSM. Benzodiazepines, dependence and withdrawal symptoms. *Current Problems 21* 1988. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
2. Marriott S, Tyrer P. Benzodiazepine dependence: avoidance and withdrawal. *Drug Safety* 1993; **9:** 93–103.
3. Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction* 1994; **89:** 1455–59.
4. Ashton H. The treatment of benzodiazepine dependence. *Addiction* 1994; **89:** 1535–41.
5. The Royal College of Psychiatrists. Benzodiazepines: risks, benefits or dependence—a re-evaluation. *Council Report CR59*; London: January, 1997 [under review]. Available at: http://www.rcpsych.ac.uk/publications/collegereports/cr/cr59.aspx (accessed 31/05/06)
6. DoH. *Drug misuse and dependence: guidelines on clinical management*. London: The Stationery Office, 1999. Available at: http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf (accessed 28/04/04)
7. Denis C, *et al.* Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).

Adverse Effects

Drowsiness, sedation, muscle weakness, and ataxia are the most frequent adverse effects of diazepam use. They generally decrease on continued dosage and are a consequence of CNS depression. Less frequent effects include vertigo, headache, confusion, depression (but see Effects on Mental Function, below), slurred speech or dysarthria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, changes in salivation, and amnesia. Some patients may experience a paradoxical excitation which may lead to hostility, aggression, and disinhibition. Jaundice, blood disorders, and hypersensitivity reactions have been reported rarely. Respiratory depression and hypotension occasionally occur with high dosage and parenteral use.

Pain and thrombophlebitis may occur with some intravenous formulations of diazepam; raised liver enzyme values have occurred.

Overdosage can produce CNS depression and coma or paradoxical excitation. However, fatalities are rare when taken alone.

Use of diazepam in the first trimester of pregnancy has occasionally been associated with congenital malformations in the infant but no clear relationship has been established. This topic is reviewed under Pregnancy below. Use of diazepam in late pregnancy has been associated with intoxication of the neonate.

Carcinogenicity. The International Agency for Research on Cancer concluded[1] that there was sufficient evidence from human studies that diazepam did not produce breast cancer, and that there was inadequate data to support its potential carcinogenicity at other sites. For most other benzodiazepines the lack of human studies meant that the carcinogenic risk to humans was not classifiable. However, there appeared to be sufficient evidence of carcinogenicity in *animal* studies for oxazepam to be classified as possibly carcinogenic in humans.

1. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 66* 1996. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol66/volume66.pdf (accessed 15/05/06)

Effects on body temperature. Studies in healthy subjects[1,2] indicate that benzodiazepines can reduce body temperature. After a single dose of diazepam 10 mg by mouth in 11 subjects, body temperature on exposure to cold fell to a mean of 36.93° compared with 37.08° on exposure without the drug.[1] An 86-year-old woman developed hypothermia[3] after being given nitrazepam 5 mg. After recovery she was mistakenly given another 5-mg dose of nitrazepam and again developed hypothermia. Midazolam (given as anaesthetic premedication) also produces modest decreases in core body temperature, which can be abolished by atropine,[4] but its effects are negligible compared with other elements of the anaesthetic regimen.[5]

Hypothermia has been reported in the neonates of mothers given benzodiazepines during the late stages of pregnancy.

1. Martin SM. The effect of diazepam on body temperature change in humans during cold exposure. *J Clin Pharmacol* 1985; **25:** 611–13.
2. Matsukawa T, *et al.* I.M. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; **78:** 396–9.
3. Impallomeni M, Ezzat R. Hypothermia associated with nitrazepam administration. *BMJ* 1976; **1:** 223–4.
4. Matsukawa T, *et al.* Atropine prevents midazolam-induced core hypothermia in elderly patients. *J Clin Anesth* 2001; **13:** 504–8.
5. Kurz A, *et al.* Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; **81:** 393–8.

Effects on endocrine function. Galactorrhoea with normal serum-prolactin concentrations has been noted in 4 women taking benzodiazepines.[1] Gynaecomastia has been reported in a man taking up to 140 mg diazepam daily[2] and in 5 men taking diazepam in doses of up to 30 mg daily.[3] Serum-oestradiol concentrations were raised in the latter group. However, raised plasma-testosterone concentrations have also been observed in men taking diazepam 10 to 20 mg daily for 2 weeks.[4]

1. Kleinberg DL, *et al.* Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977; **296:** 589–600.
2. Moerck HJ, Magelund G. Gynaecomastia and diazepam abuse. *Lancet* 1979; **i:** 1344–5.
3. Bergman D, *et al.* Increased oestradiol in diazepam related gynaecomastia. *Lancet* 1981; **ii:** 1225–6.
4. Argüelles AE, Rosner J. Diazepam and plasma-testosterone levels. *Lancet* 1975; **ii:** 607.

Effects on the eyes. Brown opacification of the lens occurred in 2 patients who took diazepam 5 mg or more daily by mouth over several years.[1] Severe visual field loss associated with very high doses (100 mg) of diazepam has also been described.[2]

1. Pau H. Braune scheibenförmige Einlagerungen in die Linse nach Langzeitgabe von Diazepam (Valium). *Klin Monatsbl Augenheilkd* 1985; **187:** 219–20.
2. Elder MJ. Diazepam and its effects on visual fields. *Aust N Z J Ophthalmol* 1992; **20:** 267–70.

Effects on the liver. Cholestatic jaundice[1] and focal hepatic necrosis with intracellular cholestasis[2] have been associated with the use of diazepam.

1. Jick H, *et al.* Drug-induced liver disease. *J Clin Pharmacol* 1981; **21:** 359–64.
2. Tedesco FJ, Mills LR. Diazepam (Valium) hepatitis. *Dig Dis Sci* 1982; **27:** 470–2.

Effects on mental function. The effects of benzodiazepines on psychomotor performance in laboratory tests[1] are not easily extrapolated to the clinical situation. For example postoperative cognitive dysfunction in the elderly does not seem to be related to benzodiazepine concentration in the blood.[2]

Concern has been expressed over the possible effects of long-term benzodiazepine use on the brain. A detailed study[3] found that performance of tasks involving visual-spatial ability and sustained attention was poor in patients taking high doses of benzodiazepines for long periods of time. There was no evidence of impairment in global measures of intellectual functioning such as memory, flexibility, and simple reaction time. The authors could draw no conclusions about the effect of benzodiazepine withdrawal on these changes. A study of 17 long-term users of benzodiazepines has indicated a dose-dependent increase in cerebral ventricle size.[4]

Sexual fantasies have been reported in women sedated with intravenous diazepam or midazolam.[5] These appear to be dose-related.[6]

The view that benzodiazepines can cause depression, albeit infrequently, has been queried.[7]

Adverse effects of alprazolam on behaviour have also been reviewed.[8]

1. Woods JH, *et al.* Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; **39:** 251–413.
2. Rasmussen LS, *et al.* Benzodiazepines and postoperative cognitive dysfunction in the elderly. *Br J Anaesth* 1999; **83:** 585–9.
3. Golombok S, *et al.* Cognitive impairment in long-term benzodiazepine users. *Psychol Med* 1988; **18:** 365–74.
4. Schmauss C, Krieg J-C. Enlargement of cerebrospinal fluid spaces in long-term benzodiazepine abusers. *Psychol Med* 1987; **17:** 869–73.

5. Dundee JW. Fantasies during sedation with intravenous midazolam or diazepam. *Med Leg J* 1990; **58:** 29–34.
6. Brahams D. Benzodiazepine sedation and allegations of sexual assault. *Lancet* 1989; **i:** 1339–40.
7. Patten SB, Love EJ. Drug-induced depression: incidence, avoidance and management. *Drug Safety* 1994; **10:** 203–19.
8. Cole JO, Kando JC. Adverse behavioral events reported in patients taking alprazolam and other benzodiazepines. *J Clin Psychiatry* 1993; **54** (suppl): 49–61.

Effects on the nervous system. There are a few isolated reports of extrapyramidal symptoms in patients taking benzodiazepines.[1-4] Benzodiazepines have been used to treat such symptoms induced by antipsychotics (see Extrapyramidal Disorders under Chlorpromazine, p.971).

1. Rosenbaum AH, De La Fuente JR. Benzodiazepines and tardive dyskinesia. *Lancet* 1979; **ii:** 900.
2. Sandyk R. Orofacial dyskinesias associated with lorazepam therapy. *Clin Pharm* 1986; **5:** 419–21.
3. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. *BMJ* 1990; **300:** 614.
4. Joseph AB, Wroblewski BA. Paradoxical akathisia caused by clonazepam, clorazepate and lorazepam in patients with traumatic encephalopathy and seizure disorders: a subtype of benzodiazepine-induced disinhibition? *Behav Neurol* 1993; **6:** 221–3.

Encephalopathy. Prolonged use of midazolam with fentanyl has been associated with encephalopathy in infants sedated under intensive care.[1]

1. Bergman I, *et al.* Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991; **119:** 644–9.

Effects on sexual function. The sedative effects of benzodiazepines may reduce sexual arousal and lead to impotence in some patients. Conversely sexual performance may be improved by therapy if it was previously impaired by anxiety.

Increased libido and orgasmic function has been reported in 2 women after withdrawal of long-term benzodiazepine use.[1]

1. Nutt D, *et al.* Increased sexual function in benzodiazepine withdrawal. *Lancet* 1986; **ii:** 1101–2.

Effects on skeletal muscle. In a report[1] of 2 patients who developed rhabdomyolysis secondary to hyponatraemia it was suggested that the use of benzodiazepines might have contributed to the rhabdomyolysis. Of 8 reported cases of rhabdomyolysis associated with hyponatraemia, 5 had received benzodiazepines. Rhabdomyolysis associated with intravenous drug abuse of oral temazepam formulations has also been reported.[2]

1. Fernández-Real JM, *et al.* Hyponatremia and benzodiazepines result in rhabdomyolysis. *Ann Pharmacother* 1994; **28:** 1200–1.
2. Deighan CJ, *et al.* Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. *Q J Med* 2000; **93:** 29–33.

Effects on the skin. There have been rare reports of cutaneous reactions to benzodiazepines, including contact dermatitis, fixed drug eruptions, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Analysis by the Boston Collaborative Drug Surveillance Program of data on 15 438 patients hospitalised between 1975 and 1982 detected 2 allergic skin reactions attributed to diazepam among 4707 recipients of the drug.[1] A reaction rate of 0.4 per 1000 recipients was calculated from these figures.

1. Bigby M, *et al.* Drug-induced cutaneous reactions. *JAMA* 1986; **256:** 3358–63.

Hypersensitivity. Hypersensitivity reactions including anaphylaxis are very rare after use of diazepam. Reactions have been attributed to the polyoxyl castor oil (p.1918) vehicle used for some parenteral formulations.[1] There is also a report of a type I hypersensitivity reaction to a lipid emulsion formulation of diazepam.[2]

See also under Effects on the Skin, above.

1. Hüttel MS, *et al.* Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR). *Br J Anaesth* 1980; **52:** 77–9.
2. Deardon DJ, Bird GLA. Acute (type 1) hypersensitivity to iv Diazemuls. *Br J Anaesth* 1987; **59:** 391.

Local reactions. Ischaemia and gangrene have been reported after accidental intra-arterial injection of diazepam.[1,2] Clinical signs may not occur until several days after the event. Pain and thrombophlebitis after intravenous use may be similarly delayed. Local reactions after intravenous injection have been attributed to the vehicle, and have been observed more often when diazepam is given as a solution in propylene glycol than in polyethoxylated castor oil.[3] An emulsion of diazepam in soya oil and water has been associated with a lower incidence of local reactions.[3] Pain and phlebitis may also be caused by precipitation of diazepam at the site of infusion.[4] Arterial spasm experienced by a patient given diazepam intravenously was probably due to pressure from a cuff on the arm being inflated causing extravasation of diazepam out of the vein and into the radial artery.[5]

Local irritation has also occurred after rectal use of diazepam.[6]

For a report of the exacerbation of diazepam-induced thrombophlebitis by penicillamine, see p.991.

1. Gould JDM, Lingam S. Hazards of intra-arterial diazepam. *BMJ* 1977; **2:** 298–9.
2. Rees M, Dormandy J. Accidental intra-arterial injection of diazepam. *BMJ* 1980; **281:** 289–90.
3. Olesen AS, Hüttel MS. Local reactions to iv diazepam in three different formulations. *Br J Anaesth* 1980; **52:** 609–11.
4. Hussey EK, *et al.* Correlation of delayed peak concentration with infusion-site irritation following diazepam administration. *DICP Ann Pharmacother* 1990; **24:** 678–80.
5. Ng Wing Tin L, *et al.* Arterial spasm after administration of diazepam. *Br J Anaesth* 1994; **72:** 139.
6. Hansen HC, *et al.* Local irritation after administration of diazepam in a rectal solution. *Br J Anaesth* 1989; **63:** 287–9.

Overdosage. Impairment of consciousness is fairly rapid in poisoning by benzodiazepines.[1] Deep coma or other manifestations of severe depression of brainstem vital functions are rare; more common is a sleep-like state from which the patient can be temporarily roused by appropriate stimuli. There is usually little or no respiratory depression, and cardiac rate and rhythm remain normal in the absence of anoxia or severe hypotension. Since tolerance to benzodiazepines develops rapidly, consciousness is often regained while concentrations of drug in the blood are higher than those which induced coma. Anxiety and insomnia can occur during recovery from acute overdosage, while a full-blown withdrawal syndrome, possibly with major convulsions, can occur in patients who have previously been chronic users.

During the years 1980 to 1989, 1576 fatal poisonings in Britain were attributed to benzodiazepines.[2] Of these, 891 were linked to overdosage with benzodiazepines alone and another 591 to overdosage combined with alcohol. A comparison of these mortality statistics with prescribing data for the same period, to calculate a toxicity index of deaths per million prescriptions, suggested that there were differences between the relative toxicities of individual benzodiazepines in overdosage. A later study of another 303 cases of benzodiazepine poisoning[3] supported these findings of differences in toxicity as well as pointing to the relative safety of the benzodiazepines in overdosage.

1. Ashton CH, *et al.* Drug-induced stupor and coma: some physical signs and their pharmacological basis. *Adverse Drug React Acute Poisoning Rev* 1989; **8:** 1–59.
2. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry* 1993; **163:** 386–93.
3. Buckley NA, *et al.* Relative toxicity of benzodiazepines in overdose. *BMJ* 1995; **310:** 219–21.

Treatment of Adverse Effects

The treatment of benzodiazepine overdosage is generally symptomatic and supportive. Activated charcoal may be given orally within one hour of ingestion of more than 100 mg of diazepam (or its equivalent) by adults, or 1 mg/kg by children, provided they are not too drowsy. Gastric lavage is generally not advocated in overdoses of benzodiazepines alone. The specific benzodiazepine antagonist, flumazenil, is rarely required and can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients (see p.1446); the UK Poisons Information Service, contra-indicates its use in mixed overdoses. The *BNF* recommends that flumazenil should be used on expert advice only.

Precautions

Diazepam should be avoided in patients with pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, or sleep apnoea, and used with care in those with chronic pulmonary insufficiency. Diazepam should be given with care to elderly or debilitated patients who may be more prone to adverse effects. Caution is required in patients with muscle weakness, or those with hepatic or renal impairment, who may require reduced doses; its use should be avoided in severe hepatic impairment. The sedative effects of diazepam are most marked during the first few days of use; affected patients should not drive or operate machinery (see also Driving, below). Monitoring of cardiorespiratory function is generally recommended when benzodiazepines are used for deep sedation.

Diazepam is not appropriate for the treatment of chronic psychosis or for phobic or obsessional states. Diazepam-induced disinhibition may precipitate suicide or aggressive behaviour and it should not, therefore, be used alone to treat depression or anxiety associated with depression; it should also be used with care in patients with personality disorders. Caution is required in patients with organic brain changes particularly arteriosclerosis. In cases of bereavement, psychological adjustment may be inhibited by diazepam.

Many manufacturers of diazepam and other benzodiazepines advise against their use in patients with glaucoma, but the rationale for this contra-indication is unclear.

For warnings on benzodiazepines during pregnancy and breast feeding, see below.

Dependence characterised by a withdrawal syndrome may develop after regular use of diazepam, even in therapeutic doses for short periods (see above); because of the risk of dependence, diazepam should be used with caution in patients with a history of alcohol or drug addiction.

Since hypotension and apnoea may occur when benzodiazepines are given intravenously it has been recommended that this route should only be used when facilities for reversing respiratory depression with mechanical ventilation are available. Patients should remain supine and under medical supervision for at least one hour after intravenous injection. Intravenous infusion is best undertaken in specialist centres with intensive care facilities where close and constant supervision can be undertaken.

Administration. ***Intravenous.*** Prolonged use of high-dose intravenous infusions of diazepam preparations containing benzyl alcohol can result in benzyl alcohol poisoning.[1] (Such preparations should never be used in neonates—see p.1632.)

1. López-Herce J, *et al.* Benzyl alcohol poisoning following diazepam intravenous infusion. *Ann Pharmacother* 1995; **29:** 632.

Breast feeding. The American Academy of Pediatrics considers that benzodiazepine use by nursing mothers for long periods was a cause for concern; anxiolytic drugs appear in breast milk and could conceivably alter CNS function in the infant both in the short and long term.[1] Similarly, in the UK the CSM has recommended[2] that benzodiazepines should not be given to breast-feeding mothers. In one reviewer's opinion[3] the limited distribution into breast milk did not constitute a hazard to the breast-fed infant but the infant should be monitored for sedation and the inability to suckle. Another group has also reported a low incidence of toxicity and adverse effects in the breast-fed infants of mothers taking psychotropic drugs including benzodiazepines.[4] It has been suggested[5] that if a benzodiazepine must be used during breast feeding it would be preferable to use a short-acting drug with minimal distribution into breast milk and inactive metabolites; oxazepam, lorazepam, alprazolam, or midazolam might be suitable.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Committee on Safety of Medicines/Medicines Control Agency. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)
3. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
4. Birnbaum CS, *et al.* Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Abstract: *Pediatrics* 1999; **104:** 104. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e11 (accessed 28/04/04)
5. Chisholm CA, Kuller JA. A guide to the safety of CNS-active agents during breastfeeding. *Drug Safety* 1997; **17:** 127–42.

Cardiovascular disorders. See under Respiratory System Disorders, below.

Driving. Most benzodiazepines can adversely affect parameters of driving performance in healthy subjects.[1] It is not entirely clear to what extent benzodiazepines contribute to the risk of driving accidents. A large case-control cohort study[2] in elderly drivers suggested that the risk of accidents was increased in those who took longer-acting benzodiazepines. However, younger drivers are more susceptible to the effects of benzodiazepines or zopiclone as a group;[3,4] the risk is increased by alcohol consumption.[3] Patients affected by drowsiness while taking benzodiazepines should not drive or operate machinery. In the UK, it is an offence to drive while unfit due to the influence of any drug, and benzodiazepines are considered to be the most likely psychotropic medication to impair driving performance, particularly the long-acting compounds.[5] However, it is also noted that drivers with psychiatric illnesses may be safer when well controlled with regular medication than when ill. Drowsiness often becomes less troublesome with continued use of these drugs.

1. Woods JH, *et al.* Abuse liability of benzodiazepines. *Pharmacol Rev* 1987; **39:** 251–413.
2. Hemmelgarn B, *et al.* Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 1997; **278:** 27–31.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
4. Vanakoski J, *et al.* Driving under light and dark conditions: effects of alcohol and diazepam in young and older subjects. *Eur J Clin Pharmacol* 2000; **56:** 453–8.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

The elderly. Old age may alter the distribution, elimination, and clearance of benzodiazepines.[1,2] Metabolic clearance of benzodiazepines metabolised principally by oxidation appears to be reduced but not clearance of those biotransformed by glucuronide conjugation or nitroreduction. Prolonged half-life in the elderly may be a result of such a decrease in clearance or of an increase in the volume of distribution. The clinical consequence of these changes depends on factors such as dosage schedule and extent of first-pass extraction by the liver.

Irrespective of pharmacokinetic changes, the elderly may exhibit increased sensitivity to acute doses of benzodiazepines.[1-3] Impairment of memory, cognitive function, and psychomotor performance and behaviour disinhibition may be more common than with younger patients.[4] Long-term use commonly exacerbates underlying dementia in elderly patients.[4]

The upshot of the pharmacokinetic and pharmacodynamic changes of benzodiazepines in the elderly is that adverse effects may be more frequent in these patients and lower doses are commonly required. An epidemiological study of persons 65 years and older found an increased rate of hip fracture among current users of long-acting benzodiazepines (*chlordiazepoxide*, *clorazepate*, *diazepam*, and *flurazepam*), but not among users of short-acting drugs (*alprazolam*, *bromazepam*, *lorazepam*, *oxazepam*, and *triazolam*).[5] A case-control study[6] of patients with falls leading to femur fractures suggested that the most important factor in increasing risk was the dose of benzodiazepine. However, another case-control study[7] found no correlation between hip fracture and benzodiazepines either as a group or according to half-life or to characterisation as an anxiolytic or a hypnotic; there might, though, be an increase in risk with lorazepam. There was also an increased risk associated with use of two or more benzodiazepines. Nonetheless, if use of a benzodiazepine is considered necessary in elderly patients, a short-acting drug is to be preferred. It should also be remembered that the elderly are at increased risk of sleep-related breathing disorders, such as sleep apnoea and the use of hypnotics such as benzodiazepines should be avoided in these patients (see Respiratory System Disorders, below).

1. Greenblatt DJ, *et al.* Implications of altered drug disposition in elderly: studies of benzodiazepines. *J Clin Pharmacol* 1989; **29:** 866–72.
2. Greenblatt DJ, *et al.* Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations. *Clin Pharmacokinet* 1991; **21:** 165–77 and 262–73.
3. Swift CG. Pharmacodynamics: changes in homeostatic mechanisms, receptor and target organ sensitivity in the elderly. *Br Med Bull* 1990; **46:** 36–52.
4. Juergens SM. Problems with benzodiazepines in elderly patients. *Mayo Clin Proc* 1993; **68:** 818–20.
5. Ray WA, *et al.* Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA* 1989; **262:** 3303–7.
6. Herings RMC, *et al.* Benzodiazepines and the risk of falling leading to femur fractures: dosage more important than elimination half-life. *Arch Intern Med* 1995; **155:** 1801–7.
7. Pierfitte C, *et al.* Benzodiazepines and hip fractures in elderly people: case-control study. *BMJ* 2001; **322:** 704–8.

Hangover effects. Long-acting benzodiazepines accumulate in the body to a greater extent than ones with a shorter half-life. Although this might be expected to increase the frequency of daytime sedation and impairment of performance (so-called hangover effects) after a hypnotic dose, such a straightforward relationship has not always been observed in practice.[1]

Anterograde amnesia is more common with short-acting drugs such as triazolam; 'traveller's amnesia' has been used to describe amnesia in persons taking benzodiazepines for sleep disturbances resulting from jet lag.[2]

1. Greenblatt DJ, *et al.* Neurochemical and pharmacokinetic correlates of the clinical action of benzodiazepine hypnotic drugs. *Am J Med* 1990; **88** (suppl 3A): 18S–24S.
2. Meyboom RHB. Benzodiazepines and pilot error. *BMJ* 1991; **302:** 1274–5.

High-altitude disorders. Sleep may be impaired at high altitude due to frequent arousals associated with pronounced oxygen desaturation and periodic breathing. Traditional advice has been that sedatives should not be given at high altitude.[1] Caution may also be warranted at moderate altitudes especially in nonacclimatised climbers.[2] It has been argued that since diazepam, and possibly other sedatives, blunt the hypoxic ventilatory response, sleep hypoxaemia might be exacerbated. A small study[3] has suggested that small doses of a short-acting benzodiazepine, such as temazepam, might actually improve the subjective quality of sleep and reduce episodes of arterial desaturation without changing mean oxygen saturation. However the possibility of an interaction between acetazolamide taken for prophylaxis or treatment of acute mountain sickness and the benzodiazepine should be borne in mind; ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of triazolam by acetazolamide.[4]

1. Sutton JR, *et al.* Insomnia, sedation, and high altitude cerebral oedema. *Lancet* 1979; **i:** 165.
2. Röggla G, *et al.* Effect of temazepam on ventilatory response at moderate altitude. *BMJ* 2000; **320:** 56.
3. Dubowitz G. Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial. *BMJ* 1998; **316:** 587–9.
4. Masuyama S, *et al.* 'Ondine's curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Neonates. A retrospective review of records from 63 infants given lorazepam or midazolam in a neonatal intensive-care unit indicated that there were 14 cases of adverse effects associated with benzodiazepine use (seizures in 6 cases, hypotension in 5, and respiratory depression in 3).[1] Seven of these were associated with intravenous bolus doses of lorazepam and the remainder with continuous midazolam infusions. Despite the limitations of the study, the incidence of adverse effects in this group seemed high, and the authors recommended that benzodiazepine use in neonates be accompanied by close monitoring.

1. Ng E, *et al.* Safety of benzodiazepines in newborns. *Ann Pharmacother* 2002; **36:** 1150–5.

Nervous system disorders. Benzodiazepines can reduce cerebral perfusion pressure and blood oxygenation to an extent that results in irreversible neurological damage in patients with head injuries. Consequently, they should be given with great care to such patients.[1,2] Their use should be avoided for the control of seizures in patients with head injuries or other acute neurological lesions as these patients can be managed effectively with phenytoin.

1. Eldridge PR, Punt JAG. Risks associated with giving benzodiazepines to patients with acute neurological injuries. *BMJ* 1990; **300:** 1189–90.
2. Papazian L, *et al.* Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. *Br J Anaesth* 1993; **71:** 267–71.

EPILEPSY. As with other antiepileptic drugs,[1] there have been rare reports of benzodiazepines producing paradoxical exacerbation of seizures in patients with epilepsy.[2-5]

1. Guerrini R, *et al.* Antiepileptic drug-induced worsening of seizures in children. *Epilepsia* 1998; **39** (suppl 3): S2–S10.
2. Prior PF, *et al.* Intravenous diazepam. *Lancet* 1971; **2:** 434–5.
3. Tassinari CA, *et al.* A paradoxical effect: status epilepticus induced by benzodiazepines (Valium and Mogadon). *Electroencephalogr Clin Neurophysiol* 1971; **31:** 182.
4. Di Mario FJ, Clancy RR. Paradoxical precipitation of tonic seizures by lorazepam in a child with atypical absence seizures. *Pediatr Neurol* 1988; **4:** 249–51.
5. Borusiak P, *et al.* Seizure-inducing paradoxical reaction to antiepileptic drugs. *Brain Dev* 2000; **22:** 243–5.

Porphyria. Diazepam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Intravenous diazepam has been used successfully, however, to control status epilepticus occurring after the acute porphyric attack. For a discussion of the management of seizures associated with acute porphyric attacks, see p.471.

Pregnancy. Benzodiazepines have been widely used in pregnant patients.[1] Use of benzodiazepines in the *third trimester* and during *labour* seems to be associated in some infants with neonatal withdrawal symptoms or the floppy infant syndrome. Also a small number exposed *in utero* to benzodiazepines have shown slow development in the early years but by 4 years of age most had developed normally, and for those that had not it was not possible to prove a cause-effect relationship with benzodiazepine exposure. In a meta-analysis[2] of live births after benzodiazepine use during the *first trimester* of pregnancy, pooled data from cohort studies showed no apparent association between benzodiazepine use and the risk of major malformations or oral cleft alone. There was, however, a small but significantly increased risk of oral cleft according to data from case-control studies. Although benzodiazepines did not appear to be a major human teratogen, use of ultrasonography was advised to rule out visible forms of cleft lip. The UK CSM has recommended[3] that women of child-bearing potential prescribed benzodiazepines should be advised to contact the physician about stopping the drug if they intend to become, or suspect that they are, pregnant.

1. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8:** 461–75.
2. Dolovich LR, *et al.* Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; **317:** 839–43.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: avoid benzodiazepines in pregnancy and lactation. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 15/05/06)

Respiratory system disorders. Benzodiazepines may affect the control of ventilation during sleep and may worsen sleep apnoea or other sleep-related breathing disorders especially in patients with chronic obstructive pulmonary disease or cardiac failure.[1] Risk factors for sleep apnoea, which often goes undiagnosed, include old age, obesity, male sex, postmenopausal status in women, and a history of heavy snoring. Although benzodiazepines may reduce sleep fragmentation, their long-term use may result in conversion from partial to complete obstructive sleep apnoea in heavy snorers or in short repetitive central sleep apnoea in patients with recent myocardial infarction.

1. Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990; **88** (suppl 3A): 25S–28S.

Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam or other benzodiazepines are given with other drugs that have CNS-depressant properties; these include alcohol, antidepressants, sedative antihistamines, antipsychotics, general anaesthetics, other hypnotics or sedatives, and opioid analgesics. The sedative effect of benzodiazepines may also be enhanced by cisapride. Adverse effects may also be produced by use with drugs that interfere with the metabolism of benzodiazepines. Drugs that have been reported to alter the pharmacokinetics of benzodiazepines are discussed in detail below but few of these interactions are likely to be of clinical significance. Benzodiazepines such as diazepam that are metabolised primarily by hepatic microsomal oxidation may be more susceptible to pharmacokinetic changes than those eliminated primarily by glucuronide conjugation.

Analgesics. The peak plasma concentration of oxazepam was significantly decreased when *diflunisal* was given to 6 healthy subjects, while the renal clearance of the glucuronide metabolite was reduced and its mean elimination half-life increased from 10 to 13 hours.[1] Diflunisal also displaced oxazepam from plasma protein binding sites *in vitro*. *Aspirin* shortened the time to induce anaesthesia with midazolam in 78 patients also possibly due to competition for plasma protein binding sites.[2] *Paracetamol* produced no significant change in plasma concentrations of diazepam or its major metabolite and only marginal changes in urine concentrations in 4 healthy subjects.[3]

Benzodiazepines such as diazepam, lorazepam, and midazolam may be used with opioid analgesics in anaesthetic or analgesic regimens. An additive sedative effect is to be expected[4] but there are also reports of severe respiratory depression with midazolam and *fentanyl*[5] or sudden hypotension with midazolam and fentanyl[6] or *sufentanil*.[7] The clearance of midazolam appears to be reduced by fentanyl,[8] possibly as a result of competitive inhibition of metabolism by the cytochrome P450 isoenzyme CYP3A. Careful monitoring is therefore required during use of midazolam with these opioids and the dose of both drugs may need to be reduced. Synergistic potentiation of the induction of anaesthesia has been reported between midazolam and fentanyl,[9] but one study has suggested that midazolam can reduce the analgesic effects of sufentanil.[10] Pretreatment with *morphine* or *pethidine* has decreased the rate of oral absorption of diazepam. This has been attributed to the effect of opioid analgesics on gastrointestinal motility.[11]

Dextropropoxyphene prolonged the half-life and reduced the clearance of alprazolam but not diazepam or lorazepam in healthy subjects.[12]

1. Van Hecken AM, *et al.* The influence of diflunisal on the pharmacokinetics of oxazepam. *Br J Clin Pharmacol* 1985; **20:** 225–34.
2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Mulley BA, *et al.* Interactions between diazepam and paracetamol. *J Clin Pharm* 1978; **3:** 25–35.
4. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; **68:** 282–5.
5. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
6. Burtin P, *et al.* Hypotension with midazolam and fentanyl in the newborn. *Lancet* 1991; **337:** 1545–6.
7. West JM, *et al.* Sudden hypotension associated with midazolam and sufentanil. *Anesth Analg* 1987; **66:** 693–4.
8. Hase I, *et al.* I.V. fentanyl decreases the clearance of midazolam. *Br J Anaesth* 1997; **79:** 740–3.
9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; **64:** 45–7.
10. Luger TJ, Morawetz RF. Clinical evidence for a midazolam-sufentanil interaction in patients with major trauma. *Clin Pharmacol Ther* 1991; **49:** 133.
11. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
12. Abernethy DR, *et al.* Interaction of propoxyphene with diazepam, alprazolam and lorazepam. *Br J Clin Pharmacol* 1985; **19:** 51–7.

Antiarrhythmics. An interaction between clonazepam and existing therapy with *amiodarone* was suspected in a 78-year-old man who experienced symptoms of benzodiazepine toxicity 2 months after starting with clonazepam 500 micrograms given at bedtime for restless leg syndrome;[1] symptoms resolved on withdrawal of clonazepam.

1. Witt DM, *et al.* Amiodarone-clonazepam interaction. *Ann Pharmacother* 1993; **27:** 1463–4.

Antibacterials. Both *erythromycin*[1] and *troleandomycin*[2] have been reported to inhibit the hepatic metabolism of triazolam in healthy subjects. Peak plasma-triazolam concentrations were increased, half-life prolonged, and clearance reduced. Troleandomycin prolonged the psychomotor impairment and amnesia produced by triazolam.[2] Loss of consciousness after erythromycin infusion in a child premedicated with midazolam was attributed to a similar interaction,[3] and increases in peak plasma concentrations of midazolam with profound and prolonged sedation have been reported after use of erythromycin.[4] Use of midazolam with erythromycin should be avoided or the dose of midazolam reduced by 50 to 75%. The clearance of midazolam is also reduced by *clarithromycin*, with an approximate doubling of the benzodiazepine's oral bioavailability.[5] The manufacturers of *quinupristin/dalfopristin* state that it too may increase plasma concentrations of midazolam. *Roxithromycin* has been reported[6] to have some effects on the pharmacokinetics and pharmacodynamics of midazolam but these changes were not thought clinically relevant. However, it was recommended that as a precaution the lowest possible effective dose of midazolam should be used when given with roxithromycin. In another study[7] *azithromycin* did not appear to have any effect on the metabolism or psychomotor effects of midazolam.

There is an isolated report of significant rises in steady-state blood-midazolam concentration coinciding with dosage of *ciprofloxacin*.[8] Also ciprofloxacin has been reported to reduce diazepam clearance and prolong its terminal half-life,[9] although psychometric tests did not show any changes in diazepam's pharmacodynamics. However, ciprofloxacin appears to have no effect on the pharmacokinetics or pharmacodynamics of temazepam.[10]

Isoniazid has been reported to increase the half-life of a single dose of diazepam[11] and triazolam[12] but not of oxazepam[12] in healthy subjects. In contrast, *rifampicin* has decreased the half-life of alprazolam,[13] diazepam,[14] midazolam,[15] and nitrazepam[16] and more or less abolishes the effects of triazolam,[17] while *ethambutol* has no effect on diazepam pharmacokinetics.[11] In patients receiving therapy for tuberculosis with isoniazid, rifampicin, and ethambutol the half-life of a single diazepam dose was shortened and its clearance increased.[11] Thus the enzyme-inducing effect of rifampicin appears to predominate over the enzyme-inhibiting effect of isoniazid.

1. Phillips JP, *et al.* A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; **6:** 297–9.
2. Warot D, *et al.* Troleandomycin-triazolam interaction in healthy volunteers: pharmacokinetic and psychometric evaluation. *Eur J Clin Pharmacol* 1987; **32:** 389–93.
3. Hiller A, *et al.* Unconsciousness associated with midazolam and erythromycin. *Br J Anaesth* 1990; **65:** 826–8.
4. Olkkola KT, *et al.* A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; **53:** 298–305.
5. Gorski JC, *et al.* The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther* 1998; **64:** 133–43.
6. Backman JT, *et al.* A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; **46:** 551–5.
7. Mattila MJ, *et al.* Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; **47:** 49–52.
8. Orko R, *et al.* Intravenous infusion of midazolam, propofol and vecuronium in a patient with severe tetanus. *Acta Anaesthesiol Scand* 1988; **32:** 590–2.
9. Kamali F, *et al.* The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 365–7.
10. Kamali F, *et al.* The influence of ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of temazepam in the young and elderly. *J Clin Pharm Ther* 1994; **19:** 105–9.
11. Ochs HR, *et al.* Diazepam interaction with antituberculous drugs. *Clin Pharmacol Ther* 1981; **29:** 671–8.
12. Ochs HR, *et al.* Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. *Br J Clin Pharmacol* 1983; **16:** 743–6.
13. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
14. Ohnhaus EE, *et al.* The effect of antipyrine and rifampin on the metabolism of diazepam. *Clin Pharmacol Ther* 1987; **42:** 148–56.
15. Backman JT, *et al.* Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther* 1996; **59:** 7–13.
16. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.
17. Villikka K, *et al.* Triazolam is ineffective in patients taking rifampicin. *Clin Pharmacol Ther* 1997; **61:** 8–14.

Anticoagulants. Plasma binding of diazepam and desmethyldiazepam was reduced, and free concentrations increased, immediately following *heparin* intravenously.[1]

Benzodiazepines do not usually interact with oral anticoagulants although there have been rare reports of altered anticoagulant activity.

1. Routledge PA, *et al.* Diazepam and N-desmethyldiazepam redistribution after heparin. *Clin Pharmacol Ther* 1980; **27:** 528–32.

Antidepressants. It has been recommended that the dosage of alprazolam should be reduced when given with *fluvoxamine*, as concomitant use has resulted in doubling of plasma-alprazolam concentrations.[1] Since plasma concentrations of bromazepam[2] and of diazepam[3] also appear to be affected by fluvoxamine, it has been suggested that patients taking fluvoxamine who require a benzodiazepine should preferentially receive one such as lorazepam, which has a different metabolic pathway.[3] Small studies suggest that *fluoxetine* can also increase plasma concentrations of alprazolam.[4,5] Fluoxetine appears to have a similar effect on diazepam but plasma concentrations of diazepam's active metabolite desmethyldiazepam are reduced and it is considered that the overall effect is likely to be minor.[6] The potential for a clinically significant interaction with *sertraline*, *paroxetine*, or *citalopram* is considered to be less.[7]

The US manufacturers have reported that alprazolam may increase the steady-state plasma concentrations of *imipramine* and *desipramine*, although the clinical significance of such changes is unknown. For a suggestion that benzodiazepines may increase the oxidation of *amineptine* to a toxic metabolite, see Effects on the Liver under Adverse Effects of Amitriptyline, p.377.

Nefazodone has been reported to raise concentrations of alprazolam and triazolam, resulting in increased sedation, and impairment of psychomotor performance.[8,9] Nefazodone may inhibit the oxidative metabolism of alprazolam and triazolam. Raised concentrations of midazolam have similarly been seen when given by mouth with nefazodone.[10] No interaction was reported with lorazepam, which is primarily eliminated by conjugation.

For reference to an isolated report of hypothermia after administration of diazepam and *lithium*, see p.405.

There have been occasional reports of sexual disinhibition in patients taking *tryptophan* with benzodiazepines.

1. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994; **46:** 35–9.
2. Van Harten J, *et al.* Influence of multiple-dose administration of fluvoxamine on the pharmacokinetics of the benzodiazepines bromazepam and lorazepam: a randomized crossover study. *Eur Neuropsychopharmacol* 1992; **2:** 381.
3. Perucca E, *et al.* Inhibition of diazepam metabolism by fluvoxamine: a pharmacokinetic study in normal volunteers. *Clin Pharmacol Ther* 1994; **56:** 471–6.
4. Lasher TA, *et al.* Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology (Berl)* 1991; **104:** 323–7.
5. Greenblatt DJ, *et al.* Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 1992; **52:** 479–86.
6. Lemberger L, *et al.* The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. *Clin Pharmacol Ther* 1988; **43:** 412–19.
7. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
8. Greene DS, *et al.* Coadministration of nefazodone (NEF) and benzodiazepines I: pharmacokinetic assessment. *Clin Pharmacol Ther* 1994; **55:** 141.
9. Kroboth P, *et al.* Coadministration of nefazodone and benzodiazepines II: pharmacodynamic assessment. *Clin Pharmacol Ther* 1994; **55:** 142.
10. Lam YWF, *et al.* Effect of antidepressants and ketoconazole on oral midazolam pharmacokinetics. *Clin Pharmacol Ther* 1998; **63:** 229.

Antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* are all inducers of hepatic drug-metabolising enzymes. Therefore, in patients receiving long-term therapy with these drugs the metabolism of benzodiazepines may be enhanced. For oral midazolam the effects of carbamazepine or phenytoin may be sufficient to virtually abolish the effects of a standard dose, with a more than 90% reduction in peak serum concentrations of the benzodiazepine.[1] Interactions between benzodiazepines and these antiepileptics are further discussed on p.475 (carbamazepine) and p.499 (phenytoin).

Results from a study[2] involving 66 children and adults receiving clobazam as adjunctive therapy for epilepsy showed a significant increase in clobazam clearance, leading to accumulation of its principal active metabolite *N*-desmethylclobazam, in the 16 patients also taking *felbamate*. The metabolism of clobazam and *N*-desmethylclobazam was reduced by *stiripentol*, a potent hepatic enzyme inhibitor, resulting in a threefold increase in the plasma concentrations of this metabolite.[3]

Serum-clonazepam concentrations fell markedly in 4 of 8 children who had *lamotrigine* added to their therapy.[4]

Sodium valproate has been reported to displace diazepam from plasma-protein binding sites.[5] Sporadic reports exist of adverse effects when valproate is given with clonazepam[6,7] with the development of drowsiness and, more seriously, absence status epilepticus, but the existence of an interaction is considered to be unproven.[8] Drowsiness has also been reported when valproate was given with nitrazepam.[9] Use of valproate semisodium with lorazepam has resulted in raised concentrations of lorazepam due to inhibition of glucuronidation of lorazepam.[10]

1. Backman JT, *et al.* Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 1996; **37:** 253–7.
2. Contin M, *et al.* Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. *Ther Drug Monit* 1999; **21:** 604–8.
3. Giraud C, *et al.* In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. *Drug Metab Dispos* 2006; **34:** 608–11.
4. Eriksson A-S, *et al.* Pharmacokinetic interactions between lamotrigine and other antiepileptic drugs in children with intractable epilepsy. *Epilepsia* 1996; **37:** 769–73.
5. Dhillon S, Richens A. Valproic acid and diazepam interaction in vivo. *Br J Clin Pharmacol* 1982; **13:** 553–60.
6. Watson WA. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 678.
7. Browne TR. Interaction between clonazepam and sodium valproate. *N Engl J Med* 1979; **300:** 679.
8. Levy RH, Koch KM. Drug interactions with valproic acid. *Drugs* 1982; **24:** 543–56.
9. Jeavons PM, *et al.* Treatment of generalized epilepsies of childhood and adolescence with sodium valproate (Epilim). *Dev Med Child Neurol* 1977; **19:** 9–25.
10. Samara EE, *et al.* Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol* 1997; **37:** 442–50.

Antifungals. Both a single dose and multiple doses of *ketoconazole* decreased the clearance of a single intravenous injection of chlordiazepoxide.[1] Studies[2-4] have shown that ketoconazole and *itraconazole* can produce marked pharmacokinetic interactions with midazolam or triazolam and greatly increase the intensity and duration of action of these benzodiazepines. The area under the plasma concentration-time curve for midazolam was increased by 15 times by ketoconazole and by 10 times by itraconazole while peak plasma concentrations of midazolam were increased fourfold and threefold, respectively.[2] The area under the curve for triazolam was increased by 22 times by ketoconazole and by 27 times by itraconazole;[3] peak plasma concentrations of triazolam were increased about threefold by both antifungals. Ketoconazole has also been reported to have a similar effect on alprazolam.[5] One study[6] indicated that the risk of interaction persists for several days after cessation of itraconazole therapy. It is recommended that the use of these antifungals with benzodiazepines should be avoided or that the dose of the benzodiazepine should be greatly reduced. A similar but less pronounced interaction occurs between *fluconazole* and midazolam[7] or triazolam;[8] nonetheless the dosage of the benzodiazepine should be reduced during use together.

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Olkkola KT, *et al.* Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **55:** 481–5.
3. Varhe A, *et al.* Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **56:** 601–7.
4. Greenblatt DJ, *et al.* Interaction of triazolam and ketoconazole. *Lancet* 1995; **345:** 191.
5. Schmider J, *et al.* Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics* 1999; **9:** 725–34.
6. Neuvonen PJ, *et al.* The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther* 1996; **60:** 326–31.
7. Ahonen J, *et al.* Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. *Eur J Clin Pharmacol* 1997; **51:** 415–19.
8. Varhe A, *et al.* Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. *Br J Clin Pharmacol* 1996; **42:** 465–70.

Antihistamines. A suggestion[1] that a reduction in temazepam metabolism caused by *diphenhydramine* may have contributed to perinatal death after ingestion of these drugs by the mother.

1. Kargas GA, *et al.* Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; **313:** 1417–18.

Antivirals. The NNRTIs *delavirdine* and *efavirenz*,[1] and HIV-protease inhibitors such as *indinavir*, *nelfinavir*, *ritonavir*,[1-3] and *saquinavir*[1,4] may inhibit the hepatic microsomal systems involved in the metabolism of some benzodiazepines. Prolonged use of protease inhibitors may also *induce* these metabolic systems; interactions may therefore be complex and difficult to predict. Monitoring and dosage adjustments for the benzodiazepine may be needed, or the combination should be avoided. Benzodiazepines which should **not** be used with HIV-protease inhibitors include alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, and triazolam.

1. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; **36:** 1598–1613.
2. Greenblatt DJ, *et al.* Extensive impairment of triazolam and alprazolam clearance by short-term low-dose ritonavir: the clinical dilemma of concurrent inhibition and induction *J Clin Psychopharmacol* 1999; **19:** 293–6.
3. Greenblatt DJ, *et al.* Alprazolam-ritonavir interaction: implications for product labeling. *Clin Pharmacol Ther* 2000; **67:** 335–41.
4. Palkama VJ, *et al.* Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. *Clin Pharmacol Ther* 1999; **66:** 33–9.

Beta blockers. A clear pattern of interactions between benzodiazepines and beta blockers has not emerged. *Propranolol* may inhibit the metabolism of diazepam[1,2] and bromazepam,[3] and *metoprolol* may inhibit the metabolism of diazepam[1,4] or bromazepam[5] to some extent, although in many cases the effect on pharmacokinetics and pharmacodynamics is unlikely to be of clinical significance. No significant pharmacokinetic interaction has been seen between propranolol and alprazolam,[2] lorazepam,[2] or oxazepam,[6] although the rate of alprazolam absorption may be decreased.[2] Similarly no pharmacokinetic interaction has been seen between *atenolol* and diazepam,[1] *labetalol* and oxazepam,[6] or metoprolol and lorazepam.[5]

1. Hawksworth G, *et al.* Diazepam/β-adrenoceptor antagonist interactions. *Br J Clin Pharmacol* 1984; **17:** 69S–76S.
2. Ochs HR, *et al.* Propranolol interactions with diazepam, lorazepam, and alprazolam. *Clin Pharmacol Ther* 1984; **36:** 451–5.
3. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
4. Klotz U, Reimann IW. Pharmacokinetic and pharmacodynamic interaction study of diazepam and metoprolol. *Eur J Clin Pharmacol* 1984; **26:** 223–6.
5. Scott AK, *et al.* Interaction of metoprolol with lorazepam and bromazepam. *Eur J Clin Pharmacol* 1991; **40:** 405–9.
6. Sonne J, *et al.* Single dose pharmacokinetics and pharmacodynamics of oral oxazepam during concomitant administration of propranolol and labetalol. *Br J Clin Pharmacol* 1990; **29:** 33–7.

Calcium-channel blockers. Peak plasma concentrations of midazolam were doubled and the elimination half-life of midazolam prolonged when given to healthy subjects receiving *diltiazem* or *verapamil*.[1] A similar interaction has been found between diltiazem and triazolam.[2,3] Concomitant use should be avoided or the dose of these benzodiazepines reduced in such use.

1. Backman JT, *et al.* Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol* 1994; **37:** 221–5.
2. Varhe A, *et al.* Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin Pharmacol Ther* 1996; **59:** 369–75.
3. Kosuge K, *et al.* Enhanced effect of triazolam with diltiazem. *Br J Clin Pharmacol* 1997; **43:** 367–72.

Ciclosporin. *In-vitro* studies suggested that ciclosporin could inhibit the metabolism of midazolam.[1] However, blood-ciclosporin concentrations in patients given ciclosporin to prevent graft rejection were considered too low to result in such an interaction.

1. Li G, *et al.* Is cyclosporin A an inhibitor of drug metabolism? *Br J Clin Pharmacol* 1990; **30:** 71–7.

Clonidine. Anxiety was reduced and sedation was enhanced when clonidine was given with flunitrazepam for premedication.[1]

1. Kulka PJ, *et al.* Sedative and anxiolytic interactions of clonidine and benzodiazepines. *Br J Anaesth* 1994; **72** (suppl 1): 81.

Clozapine. For reports of cardiorespiratory collapse and other adverse effects in patients taking benzodiazepines and clozapine, see p.984.

Corticosteroids. The metabolism of midazolam was increased in chronic users of *glucocorticoids*,[1] perhaps due to the induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. The changes were not considered clinically relevant if midazolam was given intravenously, but might be so if it was given orally.

1. Nakajima M, *et al.* Effects of chronic administration of glucocorticoid on midazolam pharmacokinetics in humans. *Ther Drug Monit* 1999; **21:** 507–13.

Digoxin. For the effects of alprazolam and diazepam on digoxin pharmacokinetics, see p.1262.

Disulfiram. Evidence from healthy and alcoholic subjects suggests that chronic use of disulfiram can inhibit the metabolism of chlordiazepoxide and diazepam leading to a prolonged half-life and reduced clearance; there was little effect on the disposition of oxazepam.[1] No significant pharmacokinetic interaction was observed between disulfiram and alprazolam in alcoholic patients.[2] Temazepam toxicity, attributed to use of disulfiram with temazepam, has been reported.[3]

See also under Disulfiram, p.2297.

1. MacLeod SM, *et al.* Interaction of disulfiram with benzodiazepines. *Clin Pharmacol Ther* 1978; **24:** 583–9.
2. Diquet B, *et al.* Lack of interaction between disulfiram and alprazolam in alcoholic patients. *Eur J Clin Pharmacol* 1990; **38:** 157–60.
3. Hardman M, *et al.* Temazepam toxicity precipitated by disulfiram. *Lancet* 1994; **344:** 1231–2.

Gastrointestinal drugs. *Antacids* have variable effects on the absorption of benzodiazepines[1-6] but any resulting interaction is unlikely to be of major clinical significance.

Several studies, usually involving single doses of diazepam given to healthy subjects, have shown that *cimetidine* can inhibit the hepatic metabolism of diazepam.[7-10] The clearance of diazepam has generally been decreased and the half-life prolonged. Some studies have also shown impaired metabolic clearance of the major metabolite, desmethyldiazepam (nordazepam). Cimetidine has also been reported to inhibit the metabolism of other benzodiazepines (generally those metabolised by oxidation) including alprazolam,[11,12] bromazepam,[13] chlordiazepoxide,[14] clobazam,[15,16] flurazepam,[17] midazolam,[18] nitrazepam,[19] and triazolam.[11,12] Cimetidine does not appear to inhibit the hepatic metabolism of lorazepam,[17] oxazepam,[17] or temazepam.[20] The clinical significance of these interactions between cimetidine and benzodiazepines remains dubious, and little effect on cognitive function or degree of sedation has been shown.

Most studies have failed to find an effect of *ranitidine* on the hepatic metabolism of diazepam,[21-24] although one study[25] reported an increase in the bioavailability of a single oral dose of midazolam, and considered that an effect on hepatic clearance was more likely than an effect on absorption. These results were consistent with those of another study which showed an enhanced sedative effect of midazolam in patients pretreated with ranitidine.[26] Ranitidine has been reported to have no effect on the pharmacokinetics of lorazepam[22] or on the sedative effect of temazepam[26] but has increased the bioavailability of triazolam.[27] *Famotidine*[10] or *nizatidine*[24] do not appear to inhibit the hepatic metabolism of diazepam.

Oral diazepam was absorbed more rapidly after intravenous *metoclopramide*.[28] Enhanced motility of the gastrointestinal tract was implicated. *Cisapride* may also accelerate the absorption of diazepam.[29]

Studies of continuous *omeprazole* dosage on the pharmacokinetics of a single intravenous dose of diazepam in healthy subjects indicate inhibition of diazepam metabolism in a similar manner to cimetidine.[30,31] Omeprazole decreases the clearance and prolongs the elimination half-life of diazepam; in addition both the formation and elimination of desmethyldiazepam appear to be decreased. The effects may be greater in rapid than in slow metabolisers of omeprazole[32] and vary between ethnic groups.[33] The clinical significance of the interaction remains to be established. *Lansoprazole*[34] and *pantoprazole*[35] have been reported not to affect the pharmacokinetics of diazepam.

1. Nair SG, *et al.* The influence of three antacids on the absorption and clinical action of oral diazepam. *Br J Anaesth* 1976; **48:** 1175–80.
2. Greenblatt DJ, *et al.* Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin Pharmacol Ther* 1976; **19:** 234–9.
3. Chun AHC, *et al.* Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* 1977; **22:** 329–35.
4. Shader RI, *et al.* Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* 1978; **24:** 308–15.
5. Greenblatt DJ, *et al.* Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* 1978; **24:** 600–9.
6. Shader RI, *et al.* Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. *Clin Pharmacol Ther* 1982; **31:** 180–3.
7. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. *N Engl J Med* 1980; **302:** 1012–14.
8. Gough PA, *et al.* Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. *Br J Clin Pharmacol* 1982; **14:** 739–42.
9. Greenblatt DJ, *et al.* Clinical importance of the interaction of diazepam and cimetidine. *N Engl J Med* 1984; **310:** 1639–43.
10. Locniskar A, *et al.* Interaction of diazepam with famotidine and cimetidine, two H -receptor antagonists. *J Clin Pharmacol* 1986; **26:** 299–303.
11. Abernethy DR, *et al.* Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacology (Berl)* 1983; **80:** 275–8.
12. Pourbaix S, *et al.* Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985; **23:** 447–51.
13. Ochs HR, *et al.* Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine, and propranolol. *Clin Pharmacol Ther* 1987; **41:** 562–70.
14. Desmond PV, *et al.* Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann Intern Med* 1980; **93:** 266–8.
15. Grigoleit H-G, *et al.* Pharmacokinetic aspects of the interaction between clobazam and cimetidine. *Eur J Clin Pharmacol* 1983; **25:** 139–42.
16. Pullar T, *et al.* The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and N-desmethylclobazam. *Br J Clin Pharmacol* 1987; **23:** 317–21.
17. Greenblatt DJ, *et al.* Interaction of cimetidine with oxazepam, lorazepam, and flurazepam. *J Clin Pharmacol* 1984; **24:** 187–93.
18. Sanders LD, *et al.* Interaction of H2-receptor antagonists and benzodiazepine sedation: a double-blind placebo-controlled investigation of the effects of cimetidine and ranitidine on recovery after intravenous midazolam. *Anaesthesia* 1993; **48:** 286–92.
19. Ochs HR, *et al.* Cimetidine impairs nitrazepam clearance. *Clin Pharmacol Ther* 1983; **34:** 227–30.
20. Greenblatt DJ, *et al.* Noninteraction of temazepam and cimetidine. *J Pharm Sci* 1984; **73:** 399–401.
21. Klotz U, *et al.* Effect of ranitidine on the steady state pharmacokinetics of diazepam. *Eur J Clin Pharmacol* 1983; **24:** 357–60.
22. Abernethy DR, *et al.* Ranitidine does not impair oxidative or conjugative metabolism: noninteraction with antipyrine, diazepam, and lorazepam. *Clin Pharmacol Ther* 1984; **35:** 188–92.
23. Fee JPH, *et al.* Diazepam disposition following cimetidine or ranitidine. *Br J Clin Pharmacol* 1984; **17:** 617P–18P.
24. Klotz U, *et al.* Nocturnal doses of ranitidine and nizatidine do not affect the disposition of diazepam. *J Clin Pharmacol* 1987; **27:** 210–12.
25. Fee JPH, *et al.* Cimetidine and ranitidine increase midazolam bioavailability. *Clin Pharmacol Ther* 1987; **41:** 80–4.
26. Wilson CM, *et al.* Effect of pretreatment with ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone. *Br J Anaesth* 1986; **58:** 483–6.
27. Vanderveen RP, *et al.* Effect of ranitidine on the disposition of orally and intravenously administered triazolam. *Clin Pharm* 1991; **10:** 539–43.
28. Gamble JAS, *et al.* Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* 1976; **48:** 1181–5.
29. Bateman DN. The action of cisapride on gastric emptying and the pharmacokinetics of oral diazepam. *Eur J Clin Pharmacol* 1986; **30:** 205–8.
30. Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. *Lancet* 1984; **i:** 969.
31. Andersson T, *et al.* Effect of omeprazole and cimetidine on plasma diazepam levels. *Eur J Clin Pharmacol* 1990; **39:** 51–4.
32. Andersson T, *et al.* Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin Pharmacol Ther* 1990; **47:** 79–85.
33. Caraco Y, *et al.* Interethnic difference in omeprazole's inhibition of diazepam metabolism. *Clin Pharmacol Ther* 1995; **58:** 62–72.
34. Lefebvre RA, *et al.* Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992; **52:** 458–63.
35. Gugler R, *et al.* Lack of pharmacokinetic interaction of pantoprazole with diazepam in man. *Br J Clin Pharmacol* 1996; **42:** 249–52.

General anaesthetics. A synergistic interaction has been found for the hypnotic effects of midazolam and *thiopental*.[1] Although midazolam failed to produce anaesthesia at the doses used, the drug caused a twofold increase in the anaesthetic potency of thiopental. Similar synergistic interactions have been seen between midazolam and both *methohexital*[2] and *propofol*.[3,4] The interaction between midazolam and propofol could not be explained solely by alteration in free-plasma concentration of either drug,[5] although a later study[6] does suggest that propofol reduces the clearance of midazolam via its inhibitory effects on the metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4. It has been reported that midazolam can produce a marked reduction in the concentration of *halothane* required for anaesthesia.[7]

1. Short TG, *et al.* Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; **66:** 13–19.
2. Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth* 1989; **63:** 109–12.
3. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
4. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
5. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.
6. Hamaoka N, *et al.* Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an in vivo and in vitro study. *Clin Pharmacol Ther* 1999; **66:** 110–7.
7. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–7.

Grapefruit juice. Grapefruit juice has been reported to be able to increase the bioavailability of oral midazolam[1] or triazolam[2] and to raise peak plasma concentrations. However, these results have been contradicted by another study,[3] which found no evidence for an interaction.

1. Kupferschmidt HHT, *et al.* Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther* 1995; **58:** 20–8.
2. Hukkinen SK, *et al.* Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. *Clin Pharmacol Ther* 1995; **58:** 127–31.
3. Vanakoski J, *et al.* Grapefruit juice does not enhance the effects of midazolam and triazolam in man. *Eur J Clin Pharmacol* 1996; **50:** 501–8.

Kava. A patient whose medication included alprazolam, cimetidine, and terazosin became lethargic and disoriented after starting to take kava.[1] An interaction between kava and the benzodiazepine was suspected.

1. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; **125:** 940–1.

Levodopa. For reference to the effects of benzodiazepines on levodopa, see Anxiolytics, p.808.

Neuromuscular blockers. For reference to the effect of diazepam on neuromuscular blockade, see p.1904.

Oral contraceptives. Some studies with alprazolam,[1] chlordiazepoxide,[2] and diazepam[3] have supported suggestions that oral contraceptives may inhibit the biotransformation of benzodiazepines metabolised by oxidation, although no significant pharmacokinetic alterations have been observed with clotiazepam,[4] or triazolam.[1] The biotransformation of benzodiazepines metabolised by conjugation, such as lorazepam, oxazepam, or temazepam, may be enhanced[1,2] or unchanged.[5] No consistent correlation has been observed between the above pharmacokinetic changes and clinical effects. It has been observed[6] that psychomotor impairment due to oral diazepam was greater during the menstrual pause than during the 21-daily oral contraceptive cycle. This may have been due to an effect of oral contraceptives on diazepam absorption. Another study[7] noted that women taking oral contraceptives appeared to be more sensitive to psychomotor impairment after single oral doses of alprazolam, lorazepam, or triazolam, than controls. The effects of temazepam were minimal in both groups. Alterations in sedative or amnesic effect could not be established with any certainty.

1. Stoehr GP, *et al.* Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; **36:** 683–90.
2. Patwardhan RV, *et al.* Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. *Hepatology* 1983; **3:** 248–53.
3. Abernethy DR, *et al.* Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids. *N Engl J Med* 1982; **306:** 791–2.
4. Ochs HR, *et al.* Disposition of clotiazepam: influence of age, sex, oral contraceptives, cimetidine, isoniazid and ethanol. *Eur J Clin Pharmacol* 1984; **26:** 55–9.
5. Abernethy DR, *et al.* Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; **33:** 628–32.
6. Ellinwood EH, *et al.* Effects of oral contraceptives on diazepam-induced psychomotor impairment. *Clin Pharmacol Ther* 1984; **35:** 360–6.
7. Kroboth PD, *et al.* Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. *Clin Pharmacol Ther* 1985; **38:** 525–32.

Penicillamine. Phlebitis associated with intravenous diazepam resolved with local heat but recurred on two separate occasions after oral penicillamine.[1]

1. Brandstetter RD, *et al.* Exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine. *BMJ* 1981; **283:** 525.

Probenecid. Probenecid increased the half-life of intravenous lorazepam in 9 healthy subjects.[1] Probenecid was considered to impair glucuronide formation selectively and thus the clearance of drugs like lorazepam. Probenecid has also shortened the time to induce anaesthesia with midazolam in 46 patients.[2] The effect was considered to be due to competition for plasma protein binding sites. Probenecid has also been reported[3] to reduce the clearance of nitrazepam but not of temazepam.

1. Abernethy DR, *et al.* Probenecid inhibition of acetaminophen and lorazepam glucuronidation. *Clin Pharmacol Ther* 1984; **35:** 224.

2. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.
3. Brockmeyer NH, *et al.* Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* 1990; **28:** 387–93.

Smooth muscle relaxants. Intracavernosal *papaverine* produced prolonged erection in 2 patients who had been given intravenous diazepam as an anxiolytic before the papaverine.[1]

1. Vale JA, *et al.* Papaverine, benzodiazepines, and prolonged erections. *Lancet* 1991; **337:** 1552.

Tobacco smoking. The Boston Collaborative Drug Surveillance Program reported drowsiness as an adverse effect of diazepam or chlordiazepoxide less frequently in smokers than non smokers.[1] Pharmacokinetic studies have, however, been divided between those indicating that smoking induces the hepatic metabolism of benzodiazepines and those showing no effect on benzodiazepine pharmacokinetics.[2] Hence, diminished end-organ responsiveness may in part account for the observed clinical effects. Taking large amounts of xanthine-containing beverages as well may decrease any enzyme-inducing effects of smoking.[3]

1. Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* 1973; **288:** 277–80.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
3. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.

Xanthines. There are reports of *aminophylline* given intravenously reversing the sedation from intravenous diazepam,[1-3] although not always completely[2] nor as effectively as flumazenil.[4] Blockade of adenosine receptors by aminophylline has been postulated as the mechanism of this interaction.[3,5]

Xanthine-containing beverages may be expected to decrease the incidence of benzodiazepine-induced drowsiness because of their CNS-stimulating effects and their ability to induce hepatic drug-metabolising enzymes. However, decreased drowsiness has only sometimes been seen and the actions of xanthines may themselves be decreased by heavy tobacco smoking.[6,7]

1. Arvidsson SB, *et al.* Aminophylline antagonises diazepam sedation. *Lancet* 1982; **ii:** 1467.
2. Kleindienst G, Usinger P. Diazepam sedation is not antagonised completely by aminophylline. *Lancet* 1984; **i:** 113.
3. Niemand D, *et al.* Aminophylline inhibition of diazepam sedation: is adenosine blockade of GABA-receptors the mechanism? *Lancet* 1984: **i:** 463–4.
4. Sibai AN, *et al.* Comparison of flumazenil with aminophylline to antagonise midazolam in elderly patients. *Br J Anaesth* 1991; **66:** 591–5.
5. Henauer SA, *et al.* Theophylline antagonises diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; **25:** 743–7.
6. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* 1981; **64:** 398–408.
7. Ghoneim MM, *et al.* Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. *J Clin Psychopharmacol* 1986; **6:** 75–80.

Pharmacokinetics

Diazepam is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes of oral doses. Diazepam is rapidly absorbed when given as a rectal solution; peak plasma concentrations are achieved after about 10 to 30 minutes. Absorption may be erratic after intramuscular injection and lower peak plasma concentrations may be obtained compared with those after oral doses. Diazepam is highly lipid soluble and crosses the blood-brain barrier; it acts promptly on the brain, and its initial effects decrease rapidly as it is redistributed into fat depots and tissues.

Diazepam has a biphasic half-life with an initial rapid distribution phase and a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (nordazepam). Diazepam and desmethyldiazepam accumulate on repeated dosage and the relative proportion of desmethyldiazepam in the body increases with long-term use. No simple correlation has been found between plasma concentrations of diazepam or its metabolites and their therapeutic effect.

Diazepam is extensively metabolised in the liver, notably via the cytochrome P450 isoenzyme CYP2C19; in addition to desmethyldiazepam, its active metabolites include oxazepam, and temazepam. It is excreted in the urine, mainly in the form of free or conjugated metabolites. Diazepam is 98 to 99% bound to plasma proteins.

The plasma elimination half-life of diazepam and/or its metabolites is prolonged in neonates, in the elderly, and in patients with liver disease. In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and are distributed into breast milk.

◊ Reviews.

1. Bailey L, *et al.* Clinical pharmacokinetics of benzodiazepines. *J Clin Pharmacol* 1994; **34:** 804–11.

Absorption and plasma concentrations. *CHRONIC ORAL ADMINISTRATION.* In 36 patients who had received diazepam 2 to 30 mg daily for periods from one month to 10 years, plasma-diazepam concentrations were directly related to dose and inversely related to age.[1] There was a close association between the plasma concentrations of diazepam and its metabolite desmethyldiazepam and both concentrations were independent of the duration of therapy. Plasma-diazepam concentration ranges were 0.02 to 1.01 micrograms/mL, and plasma-desmethyldiazepam concentration ranges were 0.055 to 1.765 micrograms/mL. A similar study[2] reached the same general conclusions.

1. Rutherford DM, *et al.* Plasma concentrations of diazepam and desmethyldiazepam during chronic diazepam therapy. *Br J Clin Pharmacol* 1978; **6:** 69–73.
2. Greenblatt DJ, *et al.* Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br J Clin Pharmacol* 1981; **1:** 35–40.

RECTAL. In 6 *adults* given diazepam 10 mg by mouth or as a solution (*Valium injection*) by rectum, mean bioavailability was 76 and 81%, respectively compared with the same dose by intravenous injection.[1] Bioavailability was lower with suppositories than with the solution given rectally. Studies support the use of rectal solution rather than suppositories in children.[2,3]

1. Dhillon S, *et al.* Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. *Br J Clin Pharmacol* 1982; **13:** 427–32.
2. Dhillon S, *et al.* Rectal absorption of diazepam in epileptic children. *Arch Dis Child* 1982; **57:** 264–7.
3. Sonander H, *et al.* Effects of the rectal administration of diazepam. *Br J Anaesth* 1985; **57:** 578–80.

Distribution into breast milk. Concentrations of diazepam and desmethyldiazepam transferred from mother to infant via breast milk have been measured.[1,2]

See also under Precautions, above.

1. Erkkola R, Kanto J. Diazepam and breast-feeding. *Lancet* 1972; **i:** 1235–6.
2. Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneimittelforschung* 1976; **26:** 454–7.

The elderly. For mention of pharmacokinetics in the elderly, see under Precautions, above.

Hepatic impairment. For reference to the altered pharmacokinetics of diazepam in patients with hepatic impairment see Administration in Hepatic Impairment, below.

Metabolism. Most benzodiazepines are highly lipophilic compounds requiring biotransformation before excretion from the body, and many form active metabolites that affect the duration of action. The benzodiazepines may be classified as long-, intermediate-, or short-acting compounds.[1]

- **Long-acting** benzodiazepines are either N_1-desalkyl derivatives (*delorazepam* and *nordazepam*) or are oxidised in the liver to N_1-desalkyl derivatives (benzodiazepines so oxidised include *chlordiazepoxide*, *clobazam*, *clorazepate*, *cloxazolam*, *diazepam*, *flurazepam*, *halazepam*, *ketazolam*, *medazepam*, *oxazolam*, *pinazepam*, *prazepam*, and *quazepam*). Clorazepate and prazepam may be considered as prodrugs since the metabolite is the expected active principle. Both parent drug and metabolites contribute to the activity of the other long-acting drugs. Further biotransformation of N_1-desalkylated metabolites proceeds much more slowly than for the parent drug, and they therefore accumulate in the body after a few days of treatment. The rate-limiting step of their metabolism (with the exception of the 1,5-derivatives) is C3-hydroxylation to the pharmacologically active oxazepam or its 2′-halogenated analogues.
- **Intermediate-acting** benzodiazepines are 7-nitrobenzodiazepines such as *clonazepam*, *flunitrazepam*, and *nitrazepam* which are metabolised by nitroreduction with no important known active metabolites. The metabolites of long- and intermediate-acting benzodiazepines require conjugation before excretion in the urine.
- **Short-acting** benzodiazepines include the C3-hydroxylated benzodiazepines such as *lorazepam*, *lormetazepam*, *oxazepam*, and *temazepam* which undergo rapid conjugation with glucuronic acid to water-soluble inactive metabolites that are excreted in the urine, and drugs such as *alprazolam*, *brotizolam*, *estazolam*, *etizolam*, *midazolam*, *tofisopam*, and *triazolam* which require oxidation involving aliphatic hydroxylation before subsequent conjugation. Although these hydroxylated metabolites may retain pharmacological activity, they are unlikely to contribute significantly to clinical activity because of their negligible plasma concentrations and rapid inactivation by glucuronidation.

Drug-metabolising capacity is influenced by many factors including genetics, age, sex, endocrine and nutritional status, smoking, disease, and concurrent drug therapy. This results in wide interindividual variation in both parent drug concentrations and metabolite-to-parent drug ratios.

1. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.

Pregnancy. The passage of diazepam across the placenta depends in part on the relative degrees of protein binding in mother and fetus. This in turn is influenced by factors such as stage of pregnancy and plasma concentrations of free fatty acids in mother and fetus.[1-6] Adverse effects may persist in the neonate for several days after birth because of immature drug-metabolising enzymes. Competition between diazepam and bilirubin for protein binding sites could result in hyperbilirubinaemia in the neonate.[7]

For further adverse effects associated with the use of benzodiazepines during pregnancy, see under Precautions, above.

1. Lee JN, *et al.* Serum protein binding of diazepam in maternal and foetal serum during pregnancy. *Br J Clin Pharmacol* 1982; **14:** 551–4.
2. Kuhnz W, Nau H. Differences in in vitro binding of diazepam and N-desmethyldiazepam to maternal and fetal plasma proteins at birth: relation to free fatty acid concentration and other parameters. *Clin Pharmacol Ther* 1983; **34:** 220–6.
3. Kanto J, *et al.* Accumulation of diazepam and N-demethyldiazepam in the fetal blood during the labour. *Ann Clin Res* 1973; **5:** 375–9.
4. Nau H, *et al.* Decreased serum protein binding of diazepam and its major metabolite in the neonate during the first postnatal week related to increased free fatty acid levels. *Br J Clin Pharmacol* 1984; **17:** 92–8.
5. Ridd MJ, *et al.* The disposition and placental transfer of diazepam in cesarean section. *Clin Pharmacol Ther* 1989; **45:** 506–12.
6. Idänpään-Heikkilä J, *et al.* Placental transfer and fetal metabolism of diazepam-C in early human pregnancy. *Clin Pharmacol Ther* 1971; **12:** 293.
7. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. *Clin Pharmacokinet* 1990; **18:** 20–36.

Uses and Administration

Diazepam is a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnestic properties. Its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Diazepam is used in the short-term treatment of severe anxiety disorders (p.952), as a hypnotic in the short-term management of insomnia (p.957), as a sedative (p.956) and premedicant (p.1780), as an anticonvulsant (particularly in the management of status epilepticus and febrile convulsions), in the control of muscle spasm, and in the management of withdrawal symptoms (see also the references below).

Diazepam is **administered** orally, rectally, and parenterally with the risk of dependence very much influencing the dose and duration of treatment. Doses should be the lowest that can control symptoms and courses of treatment should be short, not normally exceeding 4 weeks, with diazepam being withdrawn gradually (see above). Elderly and debilitated patients should be given not more than one-half the usual adult dose. Dosage reduction may also be required in patients with hepatic or renal impairment.

Oral use is appropriate for many indications and modified-release formulations are available in some countries. *Rectal* use may be by suppository or rectal solution or gel. Diazepam is also given by deep intramuscular or slow intravenous injection, although absorption after *intramuscular injection* may be erratic and provides lower blood concentrations than those after oral doses. *Intravenous injection* should be carried out slowly into a large vein of the antecubital fossa at a recommended rate of no more than 1 mL of a 0.5% solution (5 mg) per minute. It is advisable to keep the patient in the supine position and under medical supervision for at least an hour after the dose. Diazepam may be given by continuous *intravenous infusion*; because of the risk of precipitation of diazepam, solutions should be freshly prepared following the manufacturer's directions regarding diluent and concentration of diazepam. Diazepam is substantially adsorbed onto some plastics (see Sorption, above). Facilities for resuscitation should always be available when diazepam is given intravenously.

Diazepam may be given for **severe anxiety** in *oral* doses of 2 mg three times daily to a maximum of 30 mg daily. A wider dose range of 4 to 40 mg daily in divided doses is used in the USA with children over 6 months of age receiving up to 10 mg daily. Diazepam may be given as a *rectal solution* in a dose of 500 micrograms/kg repeated after 12 hours if necessary or as *suppositories* in a dose of 10 to 30 mg. Diazepam may sometimes have to be given by intramuscular or intravenous *injection* when a dose of up to 10 mg may be used, repeated if necessary after 4 hours.

The benzodiazepines have a limited role in **insomnia** and diazepam is used for the short-term management of insomnia associated with anxiety. The *BNF* recommends an *oral* dose of 5 to 15 mg at bedtime, although doses up to 30 mg are licensed. Doses of 1 to 5 mg at bedtime have been used in children and adolescents aged from 12 to 18 years to control **night terrors** and **sleepwalking**.

Diazepam may be given for **premedication** before general anaesthesia or to provide sedative cover for minor surgical or investigative procedures. In adults, *oral* doses are in the range of 5 to 20 mg and when given by intravenous *injection* the dose is usually 100 to 200 micrograms/kg. Diazepam may also be given for **sedation** during minor surgical and medical procedures; in adults doses of 10 to 20 mg, given by intravenous injection over 2 to 4 minutes, are recommended. Diazepam 500 micrograms/kg may also be given as a rectal solution. For premedication and sedation in children and adolescents aged from 1 month to 18 years, the *BNFC* suggests that an oral dose of 200 to 300 micrograms/kg may be given 45 to 60 minutes beforehand; the maximum dose is 10 mg for those aged up to 12 years and 20 mg for adolescents aged up to 18 years. Diazepam 100 to 200 micrograms/kg may be given by intravenous injection over 2 to 4 minutes, immediately before the procedure, to those aged 1 month and older; the maximum dose is 5 mg for children aged up to 12 years and 20 mg for adolescents aged up to 18 years. When given as a rectal solution, the *BNFC* suggests the following doses based on age: 1 to 3 years, 5 mg; 3 to 12 years, 5 to 10 mg; 12 to 18 years, 10 mg. Some regard the perioperative use of diazepam in children undesirable since its effect and onset of action are unreliable and paradoxical effects may occur.

Diazepam is used in a variety of **seizures**. It is given *orally* as an adjunct in some types of epilepsy; for this purpose, 2 to 60 mg may be given daily in divided doses. A *rectal gel* formulation is also available for adjunctive use in the management of episodes of increased seizure activity in adults and children aged 2 years and over with refractory epilepsy; doses range from 200 to 500 micrograms/kg, depending on age, repeated after 4 to 12 hours if necessary. For febrile convulsions, status epilepticus, and convulsions due to poisoning, giving a *rectal solution* may be appropriate; suppositories are not suitable because absorption is too slow. Recommended doses for the rectal solution differ but a typical dose is 500 micrograms/kg for adults and children over 10 kg, repeated every 12 hours if necessary; if convulsions are not controlled by the first dose the use of other anticonvulsive measures is recommended. Rectal solutions are not licensed for such use in children under 1 year of age in the UK, but the *BNFC* suggests giving the following doses, repeated after 10 minutes if necessary, based on age: neonates, 1.25 to 2.5 mg; 1 month to 2 years, 5 mg. For older children it recommends: 2 to 12 years, 5 to 10 mg; 12 to 18 years, 10 mg. Alternatively, diazepam may be given *intravenously* to adults in a dose of 10 to 20 mg given at a rate of 5 mg/minute and repeated if necessary after 30 to 60 minutes. Other schedules involve giving smaller amounts more frequently or giving diazepam *intramuscularly*, though again absorption may be too slow. Once the seizures have been controlled, a slow intravenous infusion providing up to 3 mg/kg over 24 hours has been used to protect against recurrence. Doses by intravenous injection in children are within the range of 200 to 300 micrograms/kg; alternatively 1 mg may be given for each year of age. The *BNFC* has suggested that neonates and children aged from 1 month to 12 years may be given doses of 300 to 400 micrograms/kg by intravenous injection over 3 to 5 minutes, repeated after 10 minutes if necessary.

Diazepam may be given *orally* in daily divided doses of 2 to 15 mg to alleviate **muscle spasm**. The dose may be increased in severe spastic disorders, such as cerebral palsy, to up to 60 mg daily in adults. The *BNFC* suggests initial oral doses in children and adolescents, based on age and given twice daily, as follows: 1 to 12 months, 250 micrograms/kg; 1 to 5 years, 2.5 mg; 5 to 12 years, 5 mg; 12 to 18 years, 10 mg (maximum of 40 mg daily). If given by intramuscular or slow intravenous *injection* the dose is 10 mg repeated if necessary after 4 hours. Larger doses are used in tetanus in adults and children aged 1 month and over with 100 to 300 micrograms/kg being given every 1 to 4 hours by intravenous injection. Alternatively 3 to 10 mg/kg may be given over 24 hours by continuous intravenous infusion or by nasoduodenal tube using a suitable liquid oral dose form. Diazepam may also be given by the rectal route as a *rectal solution* in a dose of 500 micrograms/kg for adults and children over 10 kg in weight, repeated every 12 hours if necessary.

Symptoms of the **alcohol withdrawal syndrome** may be controlled by diazepam given *orally* in a dose of 5 to 20 mg, repeated if required after 2 to 4 hours; another approach is to give 10 mg three or four times on the first day reducing to 5 mg three or four times daily as required. Diazepam may need to be given by *injection* if the symptoms are severe and if delirium tremens has developed; 10 to 20 mg by intramuscular or intravenous injection may be adequate, although some patients may require higher doses.

◊ Reviews.

1. Ashton H. Guidelines for the rational use of benzodiazepines: when and what to use. *Drugs* 1994; **48:** 25–40.

Administration in hepatic impairment. Oxidative metabolism of diazepam is apparently reduced in patients with hepatic impairment, resulting in a prolonged half-life and reduced clearance.[1-3] A reduction in dosage was generally required in these studies, but no specific advice is given in licensed information for the UK or USA.

1. Branch RA, *et al.* Intravenous administration of diazepam in patients with chronic liver disease. *Gut* 1976; **17:** 975–83.
2. Klotz U, *et al.* Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. *Clin Pharmacol Ther* 1977; **21:** 430–6.
3. Ochs HR, *et al.* Repeated diazepam dosing in cirrhotic patients: cumulation and sedation. *Clin Pharmacol Ther* 1983; **33:** 471–6.

Administration in renal impairment. Diazepam and its metabolites are excreted in urine, and licensed drug information suggests that dosage reduction may be required in patients with renal impairment, but gives no specific advice on how to do this.

Cardiac arrhythmias. Although not considered to be an antiarrhythmic, diazepam has been tried with good effect in treating the cardiotoxicity of chloroquine poisoning (see p.601). However, diazepam has been reported to possess both antiarrhythmic and pro-arrhythmic properties, possibly depending on the dose.[1]

1. Kumagai K, *et al.* Antiarrhythmic and proarrhythmic properties of diazepam demonstrated by electrophysiological study in humans. *Clin Cardiol* 1991; **14:** 397–401.

Chloroquine poisoning. For reference to the possible use of diazepam to decrease the cardiotoxic effects of chloroquine, see p.601.

Conversion and dissociative disorders. Conversion and dissociative disorders (formerly known as hysteria) are characterised by physical symptoms that occur in the absence of organic disease. Medication has no part to play in the treatment of these disorders unless they are secondary to conditions such as depression or anxiety disorders requiring treatment in their own right.

There have been suggestions that sedatives such as diazepam or midazolam may be used to confirm the diagnosis of hysterical paralysis.[1,2] The test tends to exacerbate organic disease while psychiatric dysfunction may improve.

1. Ellis SJ. Diazepam as a truth drug. *Lancet* 1990; **336:** 752–3.
2. Keating JJ, *et al.* Hysterical paralysis. *Lancet* 1990; **336:** 1506–7.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders, and the value of benzodiazepines, see p.954. Benzodiazepines may sometimes be useful in palliative care for the relief of terminal restlessness. Midazolam is often used although other benzodiazepines such as diazepam have also been tried.[1] A suggested dose for diazepam is 5 to 10 mg given slowly as a rectal solution and repeated every 8 to 12 hours. In practice, however, haloperidol may be preferred; a review suggested that benzodiazepines used alone might exacerbate the problem. If agitation was severe haloperidol or risperidone could be combined with lorazepam, reserving subcutaneous midazolam for refractory cases.[2]

1. Burke AL. Palliative care: an update on "terminal restlessness." *Med J Aust* 1997; **166:** 39–42.
2. Jakobsson M, Strang P. Midazolam (Dormicum) vid terminal oro och agitation: sistahandsalternativ i palliativ vård. *Lakartidningen* 1999; **96:** 2079–81.

Dyspnoea. Despite the hazards of use in patients with any form of respiratory depression or pulmonary insufficiency (see Respiratory System Disorders under Precautions, above) benzodiazepines such as diazepam have been tried in the treatment of dyspnoea (p.104), in the belief that reduction of an elevated respiratory drive may alleviate respiratory distress. However, benefits have not been confirmed. Benzodiazepines may be of use in patients with advanced cancer who have rapid shallow respiration. A daily dose of 5 to 10 mg has been suggested for diazepam.

Eclampsia and pre-eclampsia. Diazepam has been used for the initial control of impending or actual eclampsia (p.470), but magnesium sulfate is now generally the preferred treatment.

Epilepsy and other convulsive disorders. Some benzodiazepines such as diazepam are used for the control of status epilepticus (p.469), including status epilepticus in patients with porphyria (p.471—but see also Porphyria under Precautions, above), and for febrile convulsions (p.470); diazepam has also been used in eclampsia (see above) and for neonatal seizures (p.471). Benzodiazepines such as clobazam and clonazepam may be used in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Diazepam has been used as an adjunct in the management of some types of epilepsy including myoclonus.

References.

1. Rosman NP, *et al.* A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993; **329:** 79–84.
2. Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. *Med J Aust* 1995; **163:** 268–9.
3. Uhari M, *et al.* Effect of acetaminophen and low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126:** 991–5.
4. Akinbi MS, Welty TE. Benzodiazepines in the home treatment of acute seizures. *Ann Pharmacother* 1999; **33:** 99–102.
5. Rey E, *et al.* Pharmacokinetic optimisation of benzodiazepine therapy for acute seizures: focus on delivery routes. *Clin Pharmacokinet* 1999; **36:** 409–24.
6. Ogutu BR, *et al.* Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions. *Br J Clin Pharmacol* 2002; **53:** 49–57.

Extrapyramidal disorders. For reference to the use of benzodiazepines in the treatment of antipsychotic-induced extrapyramidal disorders, see Chlorpromazine, p.971.

Irritable bowel syndrome. Although some benzodiazepines have been used in the management of irritable bowel syndrome (p.1699) there is no evidence to support their use in this condition. The related compound dextofisopam is under investigation.

Mania. Benzodiazepines have been used as short-term adjuncts in the initial control of manic episodes in patients with bipolar disorder (p.372) until lithium has achieved its full effect.

Muscle spasm. Diazepam and other benzodiazepines may be used for the relief of muscle spasm (p.1887) of various aetiologies including that secondary to muscle or joint inflammation or trauma, such as in acute **low back pain** (p.7), or resulting from **spasticity** (p.1887), **dystonias** (p.809), **stiff-man syndrome** (see below), **cerebral palsy**, **poisoning**, or **tetanus** (p.1901). High doses are often required and treatment may be limited by adverse effects or by risk of dependence.

STIFF-MAN SYNDROME. Stiff-man syndrome is a rare condition characterised by painful intermittent spasms and rigidity of the axial and limb muscles. Its exact cause is unknown but there is some evidence to implicate autoantibodies against one of the enzymes involved in the synthesis of the neurotransmitter gamma-aminobutyric acid. It is frequently associated with auto-immune diseases and type 1 diabetes mellitus. Patients typically respond to benzodiazepines and this may be of use in the differential diagnosis of the syndrome. Diazepam has been the mainstay of treatment but clonazepam may also be of use, especially in familial startle disease, a rare congenital form of stiff-man syndrome. Although rigidity and spasms in stiff-man syndrome are not completely resolved by diazepam the degree of improvement can be sufficient to restore the functional level to near normal. However, large doses are often required and sedation might be a limiting factor in some patients. Other drugs that have been used when diazepam is ineffective or poorly tolerated include baclofen or sodium valproate but benefit may be less evident. There have been isolated anecdotal reports of improvement with vigabatrin, tiagabine, and gabapentin. Antiepileptics or baclofen may sometimes be combined with benzodiazepines. Cortico-steroids may be of benefit, although any response may take several weeks, and the chronic nature of the disorder and the high incidence of type 1 diabetes mellitus may make their use problematic. Other attempts at immunomodulation such as plasmapheresis have yielded variable results; there is some evidence of the efficacy of immunoglobulins.

References.

1. Toro C, *et al.* Stiff-man syndrome. *Semin Neurol* 1994; **14:** 154–8.
2. Gerhardt CL. Stiff-man syndrome revisited. *South Med J* 1995; **88:** 805–808.
3. Stayer C, Meinck H-M. Stiff-man syndrome: an overview. *Neurologia* 1998; **13:** 83–8.
4. Levy LM, *et al.* The stiff-person syndrome - an autoimmune disorder affecting neurotransmission of γ-aminobutyric acid. *Ann Intern Med* 1999; **131:** 522–30.
5. Meinck H-M. Stiff man syndrome. *CNS Drugs* 2001; **15:** 515–26.
6. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
7. Vasconcelos OM, Dalakas MC. Stiff-person syndrome. *Curr Treat Options Neurol* 2003; **5:** 79–90.

Nausea and vomiting. Benzodiazepines, particularly lorazepam, are used as adjuncts in the management of nausea and vomiting induced by cancer chemotherapy (p.1700), particularly anticipatory emesis.

Premenstrual syndrome. For mention of the limited role of benzodiazepines in the management of premenstrual syndrome, see p.2099.

Schizophrenia. Benzodiazepines may be useful adjuncts to antipsychotics in the initial management of schizophrenia (p.955).

Sleep-associated movement disorders. Sleep-associated movement disorders (p.958) rarely require treatment other than the symptomatic treatment of sleep-related medical problems. A number of such conditions, including restless legs syndrome, sleepwalking, and night terrors, have been reported to respond to benzodiazepines. Although the muscle relaxant and anxiolytic action of a benzodiazepine can be helpful in bruxism (teeth grinding) it has been recommended that they should only be prescribed on a short-term basis during the acute phase.

References.

1. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. *Am J Med* 1996; **100:** 333–7.

Substance dependence. The benzodiazepines are used in the management of symptoms of *alcohol* withdrawal (p.1626), of *opioid* withdrawal (p.101), and of *cocaine* withdrawal (p.1860).

Vertigo. Although intravenous diazepam has been used to abort acute attacks of vertigo of peripheral origin (p.565), it can prolong compensation and recovery from vestibular lesions.[1]

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; **50:** 777–91.

Preparations

BP 2008: Diazepam Injection; Diazepam Oral Solution; Diazepam Rectal Solution; Diazepam Tablets;
USP 31: Diazepam Capsules; Diazepam Extended-release Capsules; Diazepam Injection; Diazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cuadel; Daiv; Dezepan; Diactal; Dipezona; Fabotranil; Glutasedan†; Lembrol; Plidan; Plidex T; Rupediz†; Saromet; Timab; Valium; ***Austral.:*** Antenex; Ducene; Valium; Valpam; ***Austria:*** Gewacalm; Psychopax; Stesolid; Umbrium; Valium; ***Belg.:*** Valium; ***Braz.:*** Ansilive; Calmociteno; Compaz; Diazefast; Diazepan†; Dienpax; Kiatrium; Letansil; Menostress; Noan; Pazolini; Relapax; Somaplus; Uni Diazepax; Valium; Valix†; Vetansil; ***Canad.:*** Diastat; Diazemuls; Novo-Dipam; Valium; ***Chile:*** Cardiosedantol; Elongal†; Pacinax; ***Cz.:*** Apaurin; Seduxen†; Stesolid; ***Denm.:*** Apozepam; Hexalid; Stesolid; Valaxona; Valium; ***Fin.:*** Diapam; Medipam; Stesolid; ***Fr.:*** Novazam†; Valium; ***Ger.:*** Diazep; Faustan; Lamra; Stesolid; Tranquase†; Valiquid; Valium; Valocordin-Diazepam; ***Gr.:*** Apollonset; Atarviton; Stedon; Stesolid; ***Hong Kong:*** Diazemuls; Kratium; Stesolid; Valpam; ***Hung.:*** Seduxen; Stesolid; ***India:*** Anxol; Calmpose; Elcion; Paxum; Placidox; Rec-DZ; Valium; Zepose; ***Indon.:*** Mentalium; Stesolid; Trazep; Valdimex; Valisanbe; Valium; ***Irl.:*** Anxicalm; Diazemuls; Stesolid; Valium; ***Israel:*** Assival; Diaz; Stesolid; ***Ital.:*** Aliseum; Ansiolin; Diazemuls; Micronoan; Noan; Tranquirit; Valium; Vatran; ***Malaysia:*** Diapine; Diapo; Valium; ***Mex.:*** Alboral; Arzepam; AT-V†; Benzyme; Diacepam†; Diapanil†; Diatex†; Freudal†; Ifa-Fonal; Laxyl; Onapan; Ortopsique; Prizem†; Relazepam; Tandial†; Valium; Zepan; Zeprat†; ***Neth.:*** Diazemuls; Stesolid; Valium; ***Norw.:*** Stesolid; Valium; Vival; ***NZ:*** D-Pam; Diazemuls; Propam; Stesolid; ***Philipp.:*** Nixtensyn; Trankil; Valium; ***Pol.:*** Relanium; Relsed; ***Port.:*** Bialzepam; Metamidol; Stesolid; Unisedil; Valium; ***Rus.:*** Apaurin (Апаурин); Relanium (Реланиум); Relium (Релиум); Seduxen (Седуксен); ***S.Afr.:*** Benzopin; Betapam; Calmpose; Doval; Pax; Tranject; Valium; ***Singapore:*** Diapine; Diapo; Stesolid; ***Spain:*** Aneurol; Ansaserine B6 Tranq†; Complutine; Gobanal; Pacium; Sico Relax†; Stesolid; Valium; Vincosedan; ***Swed.:*** Apozepam†; Stesolid; ***Switz.:*** Paceum; Psychopax; Stesolid; Valium; ***Thai.:*** Azepam; Diano; Diapam; Diapine; Dizan; Dizepam†; Sipam; Stesolid†; V Day Zepam†; Valenium†; Valium; Zopam; ***Turk.:*** Diapam; Diazem; Lizan; Nervium; ***UK:*** Dialar; Diazemuls; Rimapam; Stesolid; Tensium; Valclair; ***USA:*** Diastat; Valium; ***Venez.:*** Talema; Telsomet†; Valium†.

Multi-ingredient: ***Arg.:*** Arnol; Dafne; Dislembral†; Faradil; Pasminox Somatico; Plidex†; Tratobes; ***Austria:*** Betamed; Harmomed; ***Braz.:*** Dialudon; Dobesix†; Moderine; ***Chile:*** Calmosedan; Diapam; Mesolona†; Multisedil; Promidan; Sedantol; Sedilit; ***Cz.:*** Seduxen RG†; ***Fin.:*** Gastrodyn comp; Relapamil; Vertipam; ***Gr.:*** Distedon; ***India:*** Depsonil-DZ; Dericip Plus; ***Indon.:*** Analsik; Cetalgin; Danalgin; Hedix; Neurodial; Neuroval; Opineuron; Proneuron; ***Ital.:*** Gamibetal Plus; Spasen Somatico; Spasmeridan; Spasmomen Somatico; Valpinax; Valtrax; ***Mex.:*** Adepsique; Esbelcaps; Numencial; Qual; Redotex; ***Port.:*** Gamibetal Compositum†; ***Rus.:*** Reladorm (Реладорм); ***Spain:*** Ansium; Tepazepan; Tropargal; ***Turk.:*** Spazmo-Valibrin; ***USA:*** Emergent-Ez; ***Venez.:*** Tepazepam†.

Dichloralphenazone *(BAN)*

Dicloralfenazona; Dikloraalifenatsoni; Dikloralfenazon.

$C_{15}H_{18}Cl_6N_2O_5$ = 519.0.
CAS — 480-30-8.
ATC — N05CC04.
ATC Vet — QN05CC04.

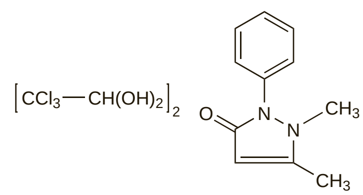

Pharmacopoeias. In *US.*

USP 31 (Dichloralphenazone). A white microcrystalline powder with a slight odour characteristic of cloral hydrate. Freely soluble in water, in alcohol, and in chloroform; soluble in dilute acids. It is decomposed by dilute alkalis liberating chloroform.

Profile

Dichloralphenazone dissociates when given, to form cloral hydrate and phenazone. It has the general properties of cloral hydrate (p.979), although it is less likely to cause gastric irritation after oral doses. Phenazone-induced skin eruptions may, however, occur (see p.116). Dichloralphenazone is used in some countries in combination preparations mainly for the treatment of tension and vascular headaches.

Porphyria. Dichloralphenazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

USP 31: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Duradrin†; Midrin; Migratine†.

Difebarbamate *(rINN)*

Difébarbamate; Difebarbamato; Difebarbamatum. 1,3-Bis(3-butoxy-2-hydroxypropyl)-5-ethyl-5-phenylbarbituric acid dicarbamate ester.

Дифебарбамат

$C_{28}H_{42}N_4O_9$ = 578.7.
CAS — 15687-09-9.

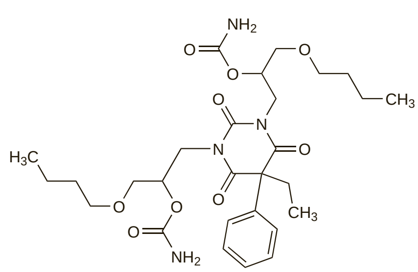

Profile

Difebarbamate is a barbiturate with general properties similar to those of amobarbital (p.961). Tetrabamate, a complex of difebarbamate, febarbamate, and phenobarbital, has been used in the management of anxiety disorders and alcohol withdrawal syndrome but was also associated with the development of hepatitis. Furthermore barbiturates are not considered appropriate in the management of these conditions.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hung.:*** Atrium†.

Dixyrazine

Diksyratsiini; Dixirazina; Dixyrazin; Dixyrazinum; UCB-3412. 2-(2-{4-[2-Methyl-3-(phenothiazin-10-yl)propyl]piperazin-1-yl}ethoxy)ethanol.

$C_{24}H_{33}N_3O_2S$ = 427.6.
CAS — 2470-73-7.
ATC — N05AB01.
ATC Vet — QN05AB01.

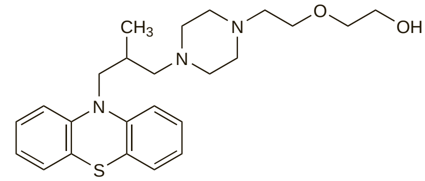

Profile

Dixyrazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has a piperazine side-chain. It is given for its antipsychotic, antiemetic, and sedative properties in oral doses ranging from 20 to 75 mg daily. Dixyrazine has also been given by injection.

◊ References.

1. Larsson S, *et al.* Premedication with intramuscular dixyrazine (Esucos): a controlled double-blind comparison with morphine-scopolamine and placebo. *Acta Anaesthesiol Scand* 1988; **32:** 131–4.
2. Karlsson E, *et al.* The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiol Scand* 1993; **37:** 45–8.
3. Oikkonen M, *et al.* Dixyrazine premedication for cataract surgery: a comparison with diazepam. *Acta Anaesthesiol Scand* 1994; **38:** 214–17.
4. Feet PO, Götestam KG. Increased antipanic efficacy in combined treatment with clomipramine and dixyrazine. *Acta Psychiatr Scand* 1994; **89:** 230–4.
5. Kokinsky E, *et al.* Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. *Acta Anaesthesiol Scand* 1999; **43:** 191–5.
6. Glaser C, *et al.* Dixyrazine for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2004; **48:** 1287–91.

Porphyria. Dixyrazine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Esucos; ***Fin.:*** Esucos; ***Ital.:*** Esucos; ***Norw.:*** Esucos; ***Swed.:*** Esucos.

Droperidol *(BAN, USAN, rINN)*

Dropéridol; Droperidoli; Droperidolis; Droperidolum; McN-JR-4749; R-4749. 1-{1-[3-(4-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl}-benzimidazolin-2-one.

Дроперидол

$C_{22}H_{22}FN_3O_2$ = 379.4.
CAS — 548-73-2.
ATC — N01AX01; N05AD08.
ATC Vet — QN01AX01; QN05AD08.

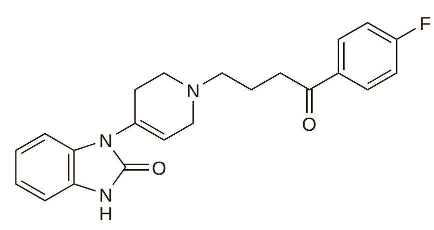

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Droperidol). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dimethylformamide. Protect from light.

USP 31 (Droperidol). A white to light tan amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 140 of alcohol, 1 in 4 of chloroform, and 1 in 500 of ether. Store under nitrogen in airtight containers at a temperature of 8° to 15°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. There is an increased risk of cardiotoxicity and prolongation of the QT interval (see p.970) with droperidol. Droperidol should not be used in patients with known or suspected QT prolongation; it should also be used with extreme caution in patients at risk of arrhythmias, including those with impairment of cardiac function, hypokalaemia, or other electrolyte imbalance. It is recommended that a baseline ECG is performed in all patients before use of droperidol.

Uses and Administration

Droperidol is a butyrophenone with general properties similar to those of haloperidol (p.1001). The duration of action of droperidol has been reported to last about 2 to 4 hours although alteration of alertness may last for up to 12 hours.

One manufacturer of droperidol (*Janssen-Cilag*) voluntarily withdrew it from the market worldwide in March 2001 after reports of QT prolongation, serious ventricular arrhythmias, or sudden death in association with its use. However, in the USA, droperidol remained available from other manufacturers although its use was restricted to the management of nausea and vomiting after surgical or diagnostic procedures in patients who fail to show an adequate response to other treatments. It is also still available, in some other countries, for use as a premedicant, as an adjunct in anaesthesia, and for the control of agitated patients in acute psychoses and in mania. Droperidol has been used in the management of chemotherapy-induced nausea and vomiting. It has also been used with an opioid analgesic such as fentanyl citrate to maintain patients in a state of neuroleptanalgesia in which they are calm and indifferent to the surroundings and able to cooperate with the surgeon. The longer duration of action of droperidol must be kept in mind when using it with such opioid analgesics.

For the prevention of postoperative **nausea and vomiting** a maximum initial dose of 2.5 mg intramuscularly or intravenously has been given; additional doses of 1.25 mg may be given if necessary. Children aged 2 years and over have been given a maximum initial dose of 100 micrograms/kg intramuscularly or intravenously.

◊ References.

1. McKeage K, *et al.* Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. *Drugs* 2006; **66:** 2123–47.

Preparations

BP 2008: Droperidol Injection; Droperidol Tablets;
USP 31: Droperidol Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Droleptan; ***Belg.:*** Dehydrobenzperidol; ***Braz.:*** Droperdal; ***Cz.:*** Dehydrobenzperidol†; Xomolix; ***Denm.:*** Dehydrobenzperidol; ***Fin.:*** Dehydrobenzperidol; ***Fr.:*** Droleptan; ***Gr.:*** Dehydrobenzperidol†; Droleptan; ***India:*** Droperol; ***Ital.:*** Sintodian†; ***Neth.:*** Dehydrobenzperidol; ***NZ:*** Droleptan; ***Port.:*** Dehidrobenzperidol; Xomolix; ***S.Afr.:*** Paxical; ***Spain:*** Dehidrobenzperidol†; ***Swed.:*** Dridol; ***Thai.:*** Dehydrobenzperidol†; ***USA:*** Inapsine.

Multi-ingredient: ***Arg.:*** Disifelit; ***Braz.:*** Nilperidol; ***Ital.:*** Leptofen.

Estazolam *(USAN, rINN)*

Abbott-47631; D-40TA; Estatsolaami; Estazolamum. 8-Chloro-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*]-1,4-benzodiazepine.

Эстазолам

$C_{16}H_{11}ClN_4$ = 294.7.
CAS — 29975-16-4.
ATC — N05CD04.
ATC Vet — QN05CD04.

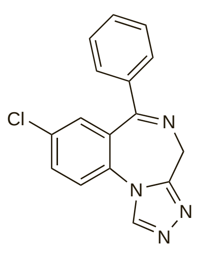

Pharmacopoeias. In *Chin.* and *Jpn.*

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Peak plasma concentrations of estazolam are reached on average within 2 hours of oral doses. Estazolam is about 93% protein bound. Reported mean elimination half-lives have generally been in the range of 10 to 24 hours. Estazolam is extensively metabolised, mainly to 4-hydroxyestazolam and 1-oxoestazolam, which are considered inactive. These metabolites are excreted, either free or conjugated, in the urine with small amounts detected in the faeces. Only a small proportion of a dose is excreted as unchanged drug.

Uses and Administration

Estazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is given as a hypnotic in the short-term management of insomnia (p.957) in usual oral doses of 1 to 2 mg at night. Small or debilitated elderly patients may be given an initial dose of 0.5 mg.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Somnatrol†; ***Braz.:*** Noctal; ***Denm.:*** Domnamid†; ***Fr.:*** Nuctalon; ***Indon.:*** Esilgan; ***Ital.:*** Esilgan; ***Jpn:*** Eurodin; ***Mex.:*** Tasedan; ***Philipp.:*** Esilgan; ***Port.:*** Kainever; ***USA:*** Prosom†.

Eszopiclone *(USAN, rINN)*

Eszopiclona; Eszopiclonum; (*S*)-Zopiclone; (+)-Zopiclone. (+)-(5*S*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

Эсзопиклон

$C_{17}H_{17}ClN_6O_3$ = 388.8.
CAS — 138729-47-2.

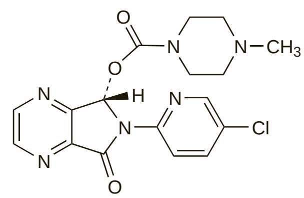

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of eszopiclone:
Sleepeasy.

Profile

Eszopiclone is the (+)-isomer of zopiclone (p.1039) and is used similarly as a hypnotic in the short-term management of insomnia.

The usual oral dose is 2 mg immediately before bedtime; if appropriate, the dose may be started at or increased to 3 mg. In elderly patients who have difficulty falling asleep, the initial dose is 1 mg; this may be increased to 2 mg. For elderly patients who have difficulty staying asleep, the starting dose is 2 mg.

The starting dose should be reduced in patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4; a dose not exceeding 1 mg is recommended which may then be increased to 2 mg. For doses in patients with hepatic impairment, see below.

◊ Reviews.

1. Melton ST, *et al.* Eszopiclone for insomnia. *Ann Pharmacother* 2005; **39:** 1659–66.
2. Halas CJ. Eszopiclone. *Am J Health-Syst Pharm* 2006; **63:** 41–8.

Administration in hepatic impairment. The starting oral dose of eszopiclone should be reduced to 1 mg at bedtime in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild to moderate impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Inductal; ***USA:*** Lunesta.

Ethchlorvynol *(BAN, rINN)*

β-Chlorovinyl Ethyl Ethynyl Carbinol; Etclorvinol; Éthchlorvynol; *E*-Ethchlorvynol; Ethchlorvynolum; Etkloorivinoli; Etklorvinol. 1-Chloro-3-ethylpent-1-en-4-yn-3-ol.

Этхлорвинол

C_7H_9ClO = 144.6.
CAS — 113-18-8.
ATC — N05CM08.
ATC Vet — QN05CM08.

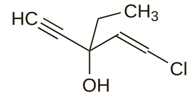

Pharmacopoeias. In *US.*

USP 31 (Ethchlorvynol). A colourless to yellow, slightly viscous liquid having a characteristic pungent odour. It darkens on exposure to air and light. Immiscible with water; miscible with most organic solvents. Store in airtight containers of glass or polyethylene, using polyethylene-lined closures. Protect from light.

Dependence and Withdrawal

Prolonged use of ethchlorvynol may lead to dependence similar to that with barbiturates (see Amobarbital, p.962).

Adverse Effects

Adverse effects of ethchlorvynol include gastrointestinal disturbances, dizziness, headache, unwanted sedation and other symptoms of CNS depression such as ataxia, facial numbness, blurred vision, and hypotension. Hypersensitivity reactions include skin rashes, urticaria, and occasionally, thrombocytopenia and cholestatic jaundice. Idiosyncratic reactions include excitement, severe muscular weakness, and syncope without marked hypotension.

Acute overdosage is characterised by prolonged deep coma, respiratory depression, hypothermia, hypotension, and relative bradycardia. Pancytopenia and nystagmus have occurred.

Pulmonary oedema has followed abuse by intravenous injection.

Treatment of Adverse Effects

Treatment is as for barbiturate overdose (see Amobarbital, p.962). Haemoperfusion may be of value in the treatment of severe poisoning with ethchlorvynol.

Precautions

Ethchlorvynol should be used with caution in patients with hepatic or renal impairment or with depression, in patients with severe uncontrolled pain, and, as with all sedatives, in those with impaired respiratory function. It may cause drowsiness; affected patients should not drive or operate machinery.

Excessively rapid absorption of ethchlorvynol in some patients has been reported to produce giddiness and ataxia; this may be reduced by giving it with food.

Porphyria. Ethchlorvynol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The effect of ethchlorvynol may be enhanced by alcohol, barbiturates, and other CNS depressants. Ethchlorvynol has been reported to decrease the effects of coumarin anticoagulants.

Tricyclic antidepressants. Transient delirium has been reported from the use of ethchlorvynol with *amitriptyline* but details of such an interaction do not appear to have been published in the literature.

Pharmacokinetics

Ethchlorvynol is readily absorbed from the gastrointestinal tract, peak plasma concentrations usually occurring within 2 hours of ingestion. It is widely distributed in body tissues and is extensively metabolised in the liver, and possibly to some extent in the kidneys. It has a biphasic plasma half-life with a rapid initial phase and a terminal phase reported to last from 10 to 20 hours. Ethchlorvynol is excreted mainly in the urine as metabolites and their conjugates. Ethchlorvynol crosses the placenta.

Uses and Administration

Ethchlorvynol is a hypnotic and sedative with some anticonvulsant and muscle relaxant properties. It is given for the short-term management of insomnia (p.957) but has been largely superseded by other drugs. Use for periods greater than one week is not recommended. The usual oral hypnotic dose is 500 mg at night but doses ranging from 200 mg to 1 g have been given. Taking doses with food has been recommended—see Precautions, above.

Preparations

USP 31: Ethchlorvynol Capsules.

Ethyl Loflazepate *(rINN)*

CM-6912; Éthyle, Loflazépate d'; Ethylis Loflazepas; Loflazepato de etilo. Ethyl 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylate.

Этил Лофлазепат

$C_{18}H_{14}ClFN_2O_3$ = 360.8.
CAS — 29177-84-2.
ATC — N05BA18.
ATC Vet — QN05BA18.

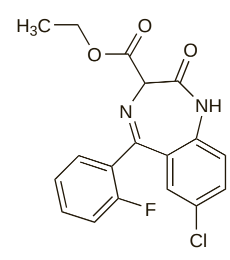

Profile

Ethyl loflazepate is a long-acting benzodiazepine derivative with general properties similar to those of diazepam (p.986). It is used in the short-term treatment of anxiety disorders (p.952) in usual oral doses of 1 to 3 mg daily in a single dose or in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Victan†; ***Belg.:*** Victan; ***Fr.:*** Victan; ***Jpn:*** Meilax; ***Mex.:*** Victan; ***Port.:*** Victan; ***Thai.:*** Victan.

Etifoxine Hydrochloride *(BANM, rINNM)*

Etifoxin Hydrochloride; Étifoxine, Chlorhydrate d'; Etifoxini Hydrochloridum; Hidrocloruro de etifoxina; Hoe-36801. 6-Chloro-4-methyl-4-phenyl-3,1-benzoxazin-2-yl(ethyl)amine hydrochloride.

Этифоксина Гидрохлорид

$C_{17}H_{17}ClN_2O,HCl$ = 337.2.
CAS — 21715-46-8 (etifoxine); 56776-32-0 (etifoxine hydrochloride).
ATC — N05BX03.
ATC Vet — QN05BX03.

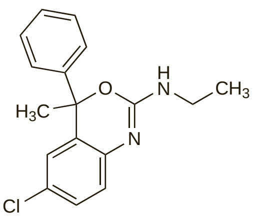

(etifoxine)

Profile

Etifoxine hydrochloride is an anxiolytic used for the short-term treatment of anxiety (p.952). It is given in usual oral doses of 150 or 200 mg daily in 2 or 3 divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Stresam.

Etizolam *(rINN)*

AHR-3219; Étizolam; Etizolamum; Y-7131. 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*]-s-triazolo[4,3-*a*][1,4]diazepine.

Этизолам

$C_{17}H_{15}ClN_4S$ = 342.8.
CAS — 40054-69-1.
ATC — N05BA19.
ATC Vet — QN05BA19.

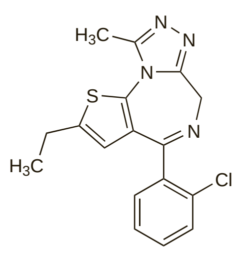

Pharmacopoeias. In *Jpn.*

Profile

Etizolam is a short-acting benzodiazepine derivative with general properties similar to those of diazepam (p.986). It is given for the short-term treatment of insomnia (p.957) and anxiety disorders (p.952) in oral doses of up to 3 mg daily in divided doses or as a single dose at night.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Depas; Pasaden; ***Jpn:*** Depas.

Febarbamate *(rINN)*

Fébarbamate; Febarbamato; Febarbamatum; Go-560. 1-(3-Butoxy-2-carbamoyloxypropyl)-5-ethyl-5-phenylbarbituric acid.

Фебарбамат

$C_{20}H_{27}N_3O_6$ = 405.4.
CAS — 13246-02-1.
ATC — M03BA05.
ATC Vet — QM03BA05.

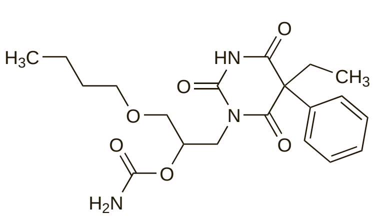

Profile

Febarbamate is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used in the management of anxiety, insomnia, and alcohol withdrawal symptoms. However, barbiturates are no longer considered appropriate in the management of these conditions.

Tetrabamate, a complex of febarbamate, difebarbamate, and phenobarbital, has been used similarly but was associated with the development of hepatitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Hung.:*** Atrium†.

Fluanisone *(BAN, rINN)*

Fluanison; Fluanisona; Fluanisoni; Fluanisonum; Haloanisone; MD-2028; R-2028; R-2167. 4′-Fluoro-4-[4-(2-methoxyphenyl)piperazin-1-yl]butyrophenone.

Флуанизон

$C_{21}H_{25}FN_2O_2$ = 356.4.
CAS — 1480-19-9.
ATC — N05AD09.
ATC Vet — QN05AD09.

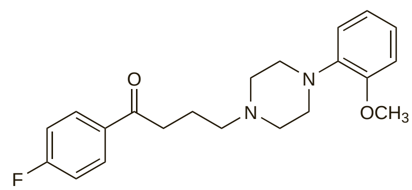

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Fluanisone). White or almost white to buff-coloured, odourless or almost odourless crystals or powder. It exhibits polymorphism. M.p. 72° to 76°. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, and in dilute solutions of organic acids. Protect from light.

Profile

Fluanisone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It has been used in the management of agitated states in psychiatric patients and as anaesthetic premedication.

Fluanisone is used in veterinary medicine for neuroleptanalgesia.

Fludiazepam *(rINN)*

Fludiazépam; Fludiazepamum; ID-540. 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.

Флудиазепам

$C_{16}H_{12}ClFN_2O$ = 302.7.
CAS — 3900-31-0.
ATC — N05BA17.
ATC Vet — QN05BA17.

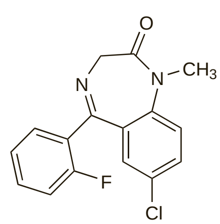

Pharmacopoeias. In *Jpn.*

Profile

Fludiazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been used in the short-term treatment of anxiety disorders.

Flunitrazepam *(BAN, USAN, rINN)*

Flunitratsepaami; Flunitrazépam; Flunitrazepám; Flunitrazepamas; Flunitrazepamum; Ro-5-4200. 5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-1,4-benzodiazepin-2-one.

Флунитразепам

$C_{16}H_{12}FN_3O_3$ = 313.3.
CAS — 1622-62-4.
ATC — N05CD03.
ATC Vet — QN05CD03.

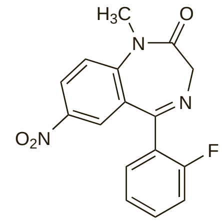

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of flunitrazepam:

Benzo; Circles; Date rape drug; Forget me drug; Forget pill; Forget-me pill; Forget-Me-Pill; Getting roached; La Rocha; La Roche; Lunch money drug; Mexican valium; Pingus; R2; R-2; Reynolds; Rib; Rick James Biatch; Roach 2; Roach-2; Roaches; Roachies; Roapies; Robutal; Rochas dos; Roche; Roches; Rolpes; Roofie; Roofies; Roopies; Rope; Rophies; Rophy; Ropies; Roples; Ropples; Row-shay; Ruffies; Ruffles; Sedexes; Wolfies.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Flunitrazepam). A white or yellowish crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Abuse. A WHO review[1] concluded that flunitrazepam had a moderate abuse potential that might be higher than that of other benzodiazepines. It was reported that there was current evidence of widespread abuse of flunitrazepam among drug abusers, particularly among those who used opioids or cocaine.

Flunitrazepam is tasteless and odourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults[2] and drug-facilitated rape ('date rape').[3] A 1-mg dose may produce impairment for 8 to 12 hours.[4] Some manufacturers have incorporated a blue dye into flunitrazepam tablets to increase visibility when placed into drinks but caution is still necessary as it has been reported that blue tropical drinks and punches are being used to overcome this.[3]

1. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_856.pdf (accessed 21/08/08)
2. Simmons MM, Cupp MJ. Use and abuse of flunitrazepam. *Ann Pharmacother* 1998; **32:** 117–19.
3. National Institute on Drug Abuse. Rohypnol and GHB (issued May 2006). Available at: http://www.nida.nih.gov/PDF/Infofacts/Rohypnol06.pdf (accessed 21/08/08)
4. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.

Breast feeding. Concentrations in breast milk the morning after a single evening 2-mg dose of flunitrazepam were considered to be too low to produce clinical effects in breast-fed infants, although accumulation in the milk might occur after repeated use.[1]

1. Kanto J, *et al*. Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26:** 539–46.

Local reactions. Of 43 patients given a single intravenous dose of flunitrazepam 1 to 2 mg, two had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution]. However, there was little difference in the incidence of local reactions after intravenous use of flunitrazepam and diazepam in another study.[2]

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2:** 1384–5.
2. Mikkelsen H, *et al.* Local reactions after iv injections of diazepam, flunitrazepam and isotonic saline. *Br J Anaesth* 1980; **52:** 817–19.

Porphyria. Flunitrazepam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Flunitrazepam is readily absorbed from the gastrointestinal tract. About 77 to 80% is bound to plasma proteins. It is extensively metabolised in the liver and excreted mainly in the urine as metabolites (free or conjugated). Its principal metabolites are 7-aminoflunitrazepam and *N*-desmethylflunitrazepam; *N*-desmethylflunitrazepam is reported to be pharmacologically active. The elimination half-life of flunitrazepam is reported to be between 16 and 35 hours. Flunitrazepam crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
2. Pariente-Khayat A, *et al.* Pharmacokinetics and tolerance of flunitrazepam in neonates and in infants. *Clin Pharmacol Ther* 1999; **66:** 136–9.

Pregnancy. Concentrations of flunitrazepam in umbilical-vein and umbilical-artery plasma were lower than those in maternal venous plasma about 11 to 15 hours after a dose of flunitrazepam 1 mg in 14 pregnant women; concentrations in amniotic fluid were lower still.[1]

1. Kanto J, *et al.* Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26:** 539–46.

Uses and Administration

Flunitrazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term management of insomnia (p.957), as a premedicant in surgical procedures, and for induction of anaesthesia (p.1780).

A usual oral dose for **insomnia** is 0.5 to 1 mg at night; up to 2 mg may be given if necessary. In elderly or debilitated patients the initial dose should not exceed 0.5 mg at night; up to 1 mg may be given if necessary.

A dose of 1 to 2 mg (15 to 30 micrograms/kg) has been given intramuscularly or orally for **premedication** or by slow intravenous injection for **induction** of general anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nervocuril; Parsimonil†; Primum; Rohypnol; ***Austral.:*** Hypnodorm; ***Austria:*** Guttanotte; Rohypnol; Somnubene; ***Belg.:*** Rohypnol; ***Braz.:*** Rohydorm; Rohypnol; ***Chile:*** Ipnopen; Rohypnol†; ***Cz.:*** Rohypnol†; ***Denm.:*** Flunipam; Rohypnol†; Ronal; ***Fr.:*** Narcozep; Rohypnol; ***Ger.:*** Fluni†; Flunibeta; Flunimerck†; Fluninoc; Rohypnol; ***Gr.:*** Hipnosedon; Ilman; Neo Nifalium; Nilium†; Vulbegal; ***Hong Kong:*** Absint†; Flunita; Rohypnol; ***Irl.:*** Rohypnol; ***Israel:*** Hypnodorm; ***Ital.:*** Darkene; Roipnol; Valsera; ***Mex.:*** Rohypnol; ***Neth.:*** Rohypnol; ***Norw.:*** Flunipam; Rohypnol†; ***Pol.:*** Rohypnol; ***Port.:*** Rohypnol; Sedex†; ***S.Afr.:*** Hypnor†; Insom; Rohypnol; ***Spain:*** Rohipnol; ***Swed.:*** Fluscand; Rohypnol†; ***Switz.:*** Rohypnol; ***Thai.:*** Rohypnol; ***UK:*** Rohypnol†.

Flupentixol *(BAN, rINN)*

Flupenthixol; Flupentiksoli; Flupentixolum; LC-44; N-7009. (*Z*)-2-{4-[3-(2-Trifluoromethylthioxanthen-9-ylidene)propyl]piperazin-1-yl}ethanol.

Флупентиксол

$C_{23}H_{25}F_3N_2OS = 434.5$.

CAS — 2709-56-0.

ATC — N05AF01.

ATC Vet — QN05AF01.

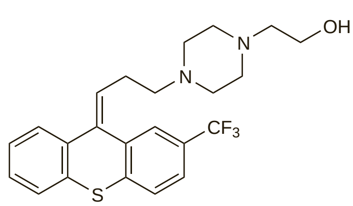

cis-form

Flupentixol Decanoate *(BANM, rINNM)*

Decanoato de flupentixol; Flupenthixol Decanoate; (*Z*)-Flupenthixol Decanoate; *cis*-Flupenthixol Decanoate; Flupentiksol Dekanoat; Flupentixol, Décanoate de; Flupentixoli Decanoas.

Флупентиксола Деканоат

$C_{33}H_{43}F_3N_2O_2S = 588.8$.

CAS — 30909-51-4.

ATC — N05AF01.

ATC Vet — QN05AF01.

Pharmacopoeias. In *Br.*

BP 2008 (Flupentixol Decanoate). A yellow viscous oil. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Store at a temperature below −15° and protect from light.

Flupentixol Hydrochloride *(BANM, rINNM)*

Flupenthixol Dihydrochloride; Flupenthixol Hydrochloride; Flupentiksol Dihidroklorür; Flupentiksolidihydrokloridi; Flupentiksolio dihidrochloridas; Flupentixol, Chlorhydrate de; Flupentixol, dichlorhydrate de; Flupentixol-dihidroklorid; Flupentixol-dihydrochlorid; Flupentixoldihydroklorid; Flupentixoli dihydrochloridum; Flupentixoli Hydrochloridum; Hidrocloruro de flupentixol.

Флупентиксола Гидрохлорид

$C_{23}H_{25}F_3N_2OS,2HCl = 507.4$.

CAS — 2413-38-9.

ATC — N05AF01.

ATC Vet — QN05AF01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flupentixol Dihydrochloride; Flupentixol Hydrochloride BP 2008). A white or almost white powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Enever RP, *et al.* Flupenthixol dihydrochloride decomposition in aqueous solution. *J Pharm Sci* 1979; **68:** 169–71.
2. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Adverse Effects and Treatment

As for Chlorpromazine, p.969. Flupentixol is less likely to cause sedation, but extrapyramidal effects are more frequent.

Sudden death. There has been a report of sudden death in 3 patients given depot injections of flupentixol decanoate.[1]

1. Turbott J, Smeeton WMI. Sudden death and flupenthixol decanoate. *Aust N Z J Psychiatry* 1984; **18:** 91–4.

Precautions

As for Chlorpromazine, p.972. Flupentixol is not recommended in states of excitement or overactivity, including mania.

Porphyria. Flupentixol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Flupentixol is readily absorbed from the gastrointestinal tract and is probably subject to first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous metabolites; there is evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after estimated equivalent doses of the intramuscular depot preparation. Moreover, there is very wide intersubject variation in plasma concentrations of flupentixol, but, in practice, no simple correlation has been found between the therapeutic effect and plasma concentrations of flupentixol and its metabolites. After oral doses, peak plasma concentrations occur in about 4 hours and the biological half-life is about 35 hours. Paths of metabolism of flupentixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. Flupentixol is more than 95% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Flupentixol crosses the placental barrier and small amounts have been detected in breast milk.

The decanoate ester of flupentixol is very slowly absorbed from the site of intramuscular injection and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to flupentixol.

Uses and Administration

Flupentixol is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain. Flupentixol is used mainly in the treatment of schizophrenia (p.955) and other psychoses. Unlike chlorpromazine, an activating effect has been ascribed to flupentixol, and it is not indicated in overactive or manic patients. Flupentixol has also been used for its antidepressant properties.

Flupentixol is given orally as the hydrochloride although doses are expressed in terms of the base; flupentixol hydrochloride 3.5 mg is equivalent to about 3 mg of flupentixol. Flupentixol is also given as the longer-acting decanoate ester by deep intramuscular injection. The long-acting preparation available in the UK contains flupentixol decanoate as the *cis(Z)*-isomer (see Action, below) and doses are expressed in terms of the amount of *cis(Z)*-flupentixol decanoate.

The usual initial *oral* dose for the treatment of **psychoses** is the equivalent of 3 to 9 mg of flupentixol twice daily adjusted according to response; the maximum recommended daily dose is 18 mg. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If given by *deep intramuscular* injection, an initial test dose of 20 mg of the decanoate, as 1 mL of a 2% oily solution, is used. Then after at least 7 days and according to response, this may be followed by doses of 20 to 40 mg every 2 to 4 weeks. Shorter dosage intervals or greater amounts may be required according to the patient's response. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If doses greater than 40 mg (2 mL) are considered necessary they should be divided between 2 separate injection sites. Another means of reducing the volume of fluid to be injected in patients requiring high-dose therapy with flupentixol decanoate is to give an injection containing 100 or 200 mg/mL of the decanoate (10 or 20%). The usual maintenance dose is between 50 mg every 4 weeks and 300 mg every 2 weeks but doses of up to 400 mg weekly have been given in severe or resistant cases.

Flupentixol has also been given as the hydrochloride for the treatment of mild to moderate **depression**, with or without anxiety (p.373). The usual initial *oral* dose, expressed in terms of the equivalent amount of flupentixol, is 1 mg (0.5 mg in the elderly) daily, increased after 1 week to 2 mg (1 mg in the elderly) and then to a maximum of 3 mg (2 mg in the elderly) daily. Doses above 2 mg (1 mg in the elderly) should be given in 2 divided doses. The last dose of the day should be given no later than 4 p.m. and if no effect has been noted within 1 week of reaching the maximum dose, treatment should be withdrawn.

Action. Patients with acute schizophrenic illnesses taking α-flupentixol [(*Z*)-flupentixol or *cis*-flupentixol] improved more after 3 weeks than patients who were taking equal doses of β-flupentixol [(*E*)-flupentixol or *trans*-flupentixol] or a placebo.[1] The α-isomer had more effect on the positive symptoms of the disease; this difference was less apparent for the negative symptoms. The difference in activity between the isomers was attributed to the greater dopamine-receptor blocking activity of the α-isomer rather than to differences in distribution.[2]

1. Johnstone EC, *et al.* Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1978; **i:** 848–51.
2. Crow TJ, Johnstone EC. Mechanism of action of neuroleptic drugs. *Lancet* 1978; **i:** 1050.

Preparations

BP 2008: Flupentixol Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Fluanxol; ***Austria:*** Fluanxol; ***Belg.:*** Fluanxol; ***Canad.:*** Fluanxol; ***Chile:*** Fluanxol; ***Cz.:*** Fluanxol; ***Denm.:*** Fluanxol; ***Fin.:*** Fluanxol; ***Fr.:*** Fluanxol; ***Ger.:*** Fluanxol; Flupendura; ***Hong Kong:*** Fluanxol; ***Hung.:*** Fluanxol; ***India:*** Fluanxol; ***Irl.:*** Depixol; Fluanxol; ***Israel:*** Fluanxol; ***Malaysia:*** Fluanxol; ***Mex.:*** Fluanxol; ***Neth.:*** Fluanxol; ***Norw.:*** Fluanxol; ***NZ:*** Fluanxol; Psytixol†; ***Philipp.:*** Fluanxol; ***Pol.:*** Fluanxol; ***Port.:*** Fluanxol; ***Rus.:*** Fluanxol (Флюанксол); ***S.Afr.:*** Fluanxol; ***Singapore:*** Fluanxol; ***Swed.:*** Fluanxol; ***Switz.:*** Fluanxol; ***Thai.:*** Fluanxol; ***Turk.:*** Fluanxol; ***UK:*** Depixol; Fluanxol.

Multi-ingredient: ***Austria:*** Deanxit; ***Belg.:*** Deanxit; ***Hong Kong:*** Anfree; Deanxit; ***Ital.:*** Deanxit†; ***Singapore:*** Deanxit; ***Spain:*** Deanxit; ***Switz.:*** Deanxit; ***Thai.:*** Deanxit.

Fluphenazine *(BAN, rINN)*

Flufenatsiini; Flufenazin; Flufenazina; Fluphénazine; Fluphenazinum. 2-{4-[3-(2-Trifluoromethylphenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

Флуфеназин

$C_{22}H_{26}F_3N_3OS$ = 437.5.

CAS — 69-23-8.

ATC — N05AB02.

ATC Vet — QN05AB02.

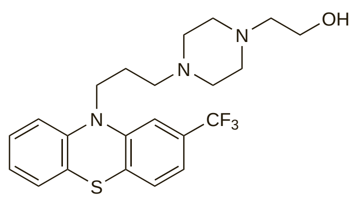

Fluphenazine Decanoate *(BANM, rINNM)*

Decanoato de flufenazina; Flufenatsiinidekanoaatti; Flufenazin Dekanoat; Flufenazindekanoat; Flufenazin-dekanoát; Flufenazine-dekanoát; Flufenazino dekanoatas; Fluphénazine, décanoate de; Fluphenazini decanoas.

Флуфеназина Деканоат

$C_{32}H_{44}F_3N_3O_2S$ = 591.8.

CAS — 5002-47-1.

ATC — N05AB02.

ATC Vet — QN05AB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Fluphenazine Decanoate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Fluphenazine Decanoate). Store in airtight containers. Protect from light.

Fluphenazine Enantate *(BANM, rINNM)*

Enantato de flufenazina; Flufenatsiinienantaatti; Flufenazinenantat; Flufenazin-enantát; Flufenazino enantatas; Fluphénazine, enantate de; Fluphenazine Enanthate; Fluphenazine Heptanoate; Fluphenazini enantas.

Флуфеназина Энантат

$C_{29}H_{38}F_3N_3O_2S$ = 549.7.

CAS — 2746-81-8.

ATC — N05AB02.

ATC Vet — QN05AB02.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Fluphenazine Enantate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Fluphenazine Enanthate). A pale yellow to yellow-orange, clear to slightly turbid, viscous liquid having a characteristic odour. Insoluble in water; soluble 1 in less than 1 of alcohol and of chloroform and 1 in 2 of ether. Stable in air at room temperature but unstable in strong light. Store in airtight containers. Protect from light.

Fluphenazine Hydrochloride *(BANM, rINNM)*

Flufenatsiinihydrokloridi; Flufenazin-dihydrochlorid; Flufenazin-hidroklorid; Flufenazinhydroklorid; Flufenazino hidrochloridas; Flufenazyny chlorowodorek; Fluphénazine, chlorhydrate de; Fluphenazine Dihydrochloride; Fluphenazini Dihydrochloridum; Fluphenazini hydrochloridum; Hidrocloruro de flufenazina.

Флуфеназина Гидрохлорид

$C_{22}H_{26}F_3N_3OS,2HCl$ = 510.4.

CAS — 146-56-5.

ATC — N05AB02.

ATC Vet — QN05AB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Fluphenazine Dihydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 1.9 to 2.4. Protect from light.

USP 31 (Fluphenazine Hydrochloride). A white or nearly white, odourless crystalline powder. Soluble 1 in 1.4 of water and 1 in 6.7 of alcohol; slightly soluble in acetone and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Chlorpromazine, p.969. Fluphenazine is less likely to cause sedation, hypotension, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects.

Convulsions. For mention of fluphenazine as one of the antipsychotics suitable for patients at risk of seizures, see p.969.

Effects on the liver. A patient developed jaundice 17 days after the first of 3 injections of a depot antipsychotic containing fluphenazine decanoate given over a 2-week period.[1] The patient developed indicators of severe liver toxicity, with extreme hyperbilirubinaemia and raised liver enzyme values, and remained very ill for the next 4 months. The patient showed cross-sensitivity to haloperidol but not to flupentixol.

See also under Chlorpromazine, p.971.

1. Kennedy P. Liver cross-sensitivity to antipsychotic drugs. *Br J Psychiatry* 1983; **143:** 312.

Overdosage. A patient who took about 30 fluphenazine hydrochloride 2.5-mg tablets was treated with gastric lavage.[1] Twenty hours after hospital admission he had difficulty in breathing due to spasm of the respiratory muscles; other very severe extrapyramidal adverse effects were also present. Muscle spasm was controlled by diazepam.

There were few adverse effects in a patient given intramuscular fluphenazine decanoate 50 mg every 4 hours, instead of the intended 4 weeks, to a total of 1050 mg.[2] About 3 weeks after the period of overdosage the patient had some degree of hypothermia and tachycardia, and after a further week parkinsonian signs appeared. No specific treatment was given.

1. Ladhani FM. Severe extrapyramidal manifestations following fluphenazine overdose. *Med J Aust* 1974; **2:** 26.
2. Cheung HK, Yu ECS. Effect of 1050 mg fluphenazine decanoate given intramuscularly over six days. *BMJ* 1983; **286:** 1016–17.

Precautions

As for Chlorpromazine, p.972. Fluphenazine may exacerbate depression and therefore it is contra-indicated in severely depressed patients.

Pregnancy. A neonate delivered to a mother who had received fluphenazine hydrochloride 10 to 20 mg daily throughout pregnancy had nasal congestion with severe rhinorrhoea, respiratory distress, vomiting, and extrapyramidal symptoms. Respiratory symptoms appeared to respond to pseudoephedrine.

1. Nath SP, *et al.* Severe rhinorrhea and respiratory distress in a neonate exposed to fluphenazine hydrochloride prenatally. *Ann Pharmacother* 1996; **30:** 35–7.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Fluphenazine hydrochloride is absorbed after oral doses, and has a reported plasma half-life of 14.7 hours after oral doses. Fluphenazine decanoate and fluphenazine enantate are very slowly absorbed from the site of subcutaneous or intramuscular injection. They both gradually release fluphenazine into the body and are therefore suitable for use as depot injections. The plasma half-life of fluphenazine decanoate has been reported to be 6 to 9 days after intramuscular injection.

◊ References[1-4] to the pharmacokinetics of fluphenazine.

The plasma half-life of fluphenazine after a single dose was 14.7 hours in 1 patient given the hydrochloride orally and 14.9 and 15.3 hours in 2 patients given the hydrochloride by intramuscular injection.[1] The half-life was 3.6 and 3.7 days in 2 patients given the enantate intramuscularly and 9.6 and 6.8 days in 2 patients given the decanoate intramuscularly. Peak plasma-fluphenazine concentrations occurred earlier in patients given fluphenazine decanoate compared with those who received the enantate. Fluphenazine sulfoxide and 7-hydroxyfluphenazine were identified in the urine and faeces.

1. Curry SH, *et al.* Kinetics of fluphenazine after fluphenazine dihydrochloride, enanthate and decanoate administration to man. *Br J Clin Pharmacol* 1979; **7:** 325–31.
2. Wistedt B, *et al*. Slow decline of plasma drug and prolactin levels after discontinuation of chronic treatment with depot neuroleptics. *Lancet* 1981; **i:** 1163.
3. Midha KK, *et al.* Kinetics of oral fluphenazine disposition in humans by GC-MS. *Eur J Clin Pharmacol* 1983; **25:** 709–11.
4. Marder SR, *et al.* Plasma levels of parent drug and metabolites in patients receiving oral and depot fluphenazine. *Psychopharmacol Bull* 1989; **25:** 479–82.

Uses and Administration

Fluphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. Fluphenazine is used in the treatment of psychiatric disorders including schizophrenia (p.955), mania (see Bipolar Disorder, p.372), severe anxiety (p.952), and behavioural disturbances (p.954). Fluphenazine is given as the hydrochloride by mouth or sometimes by intramuscular injection; for both routes, doses are expressed in terms of fluphenazine hydrochloride. The longer-acting decanoate or enantate esters of fluphenazine are given by intramuscular or sometimes subcutaneous injection; for both esters, doses are expressed in terms of the ester.

The usual initial *oral* dose of the hydrochloride for the treatment of schizophrenia, mania, and other **psychoses** is 2.5 to 10 mg daily in two or three divided doses; the dose is then increased according to response up to a usual maximum of 20 mg daily, although higher doses have occasionally been given. Dosage may subsequently be reduced to a usual maintenance dose of 1 to 5 mg daily. A lower initial dose of 1 to 2.5 mg daily, increased according to response up to a maximum of 10 mg daily, is recommended in the elderly. Treatment is sometimes started with an initial *intramuscular* injection of 1.25 mg of the hydrochloride adjusted thereafter according to response. The usual initial intramuscular daily dose is 2.5 to 10 mg given in divided doses every 6 to 8 hours. In general the required parenteral doses of fluphenazine hydrochloride have been found to be about one-third to one-half of those given orally. When symptoms are controlled, oral maintenance therapy may be substituted.

The long-acting decanoate or enantate esters of fluphenazine are usually given by deep intramuscular injection and are used mainly for the *maintenance* treatment of patients with schizophrenia or other chronic psychoses. The onset of action is usually within 1 to 3 days of injection and significant effects on psychosis are usually evident within 2 to 4 days. An initial dose of fluphenazine decanoate 12.5 mg (6.25 mg in the elderly) is given intramuscularly. Subsequent adjustments in the amounts and the dosage interval should be made according to the patient's response; the amounts required may range from 12.5 to 100 mg and the intervals required may range from 2 weeks to 5 or 6 weeks. Lower doses may be possible in some patients (see Schizophrenia, below). If doses greater than 50 mg are considered necessary, cautious increments should be made in steps of 12.5 mg. The enantate ester of fluphenazine has been given in a similar dose range at intervals of 1 to 3 weeks.

Fluphenazine hydrochloride has also been given *orally* in initial doses of 1 mg twice daily, increased if necessary to 2 mg twice daily, for the short-term adjunctive management of severe **anxiety** or **behavioural disturbances**.

Schizophrenia. References[1-3] to fluphenazine decanoate in schizophrenia (p.955) indicating that low doses (10 mg or less every 2 weeks) may be effective in some patients. Use of standard doses at greater intervals (6 weeks) has also been tried.[4] A systematic review of the use of depot fluphenazine in schizophrenia found little advantage over oral use in terms of compliance.[5] Another systematic review[6] considered that although oral fluphenazine is inexpensive and widely available, other drugs may be preferable because of its adverse effects.

1. Kane JM, *et al.* Low-dose neuroleptic treatment of outpatient schizophrenics: I preliminary results for relapse rates. *Arch Gen Psychiatry* 1983; **40:** 893–6.
2. Marder SR, *et al.* Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. *Arch Gen Psychiatry* 1987; **44:** 581–21.
3. Hogarty GE, *et al.* Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia: results of a two-year controlled study. *Arch Gen Psychiatry* 1988; **45:** 797–805.
4. Carpenter WT, *et al.* Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry* 1999; **156:** 412–18.
5. David A, *et al.* Depot fluphenazine decanoate and enanthate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/04/05).
6. Matar HE, AlMerie MQ. Oral fluphenazine versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Tourette's syndrome. Fluphenazine has been tried[1] as an alternative to standard dopamine antagonists such as haloperidol or pimozide in the symptomatic management of Tourette's syndrome (p.954).

1. Singer HS, *et al.* Haloperidol, fluphenazine and clonidine in tourette syndrome: controversies in treatment. *Pediatr Neurosci* 1985–86; **12:** 71–4.

Preparations

BP 2008: Fluphenazine Decanoate Injection; Fluphenazine Tablets;
USP 31: Fluphenazine Decanoate Injection; Fluphenazine Enanthate Injection; Fluphenazine Hydrochloride Elixir; Fluphenazine Hydrochloride Injec-

tion; Fluphenazine Hydrochloride Oral Solution; Fluphenazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Anatensol†; Modecate; ***Austria:*** Dapotum; ***Belg.:*** Sevinol†; ***Braz.:*** Flufenan; ***Canad.:*** Modecate; Moditen†; ***Chile:*** Modecate; ***Cz.:*** Moditen; ***Denm.:*** Pacinol†; Siqualone; ***Fin.:*** Pacinol†; Siqualone; ***Fr.:*** Modecate; Moditen; ***Ger.:*** Dapotum; Lyogen; Lyorodin; Omca; ***Hong Kong:*** Modecate; ***Hung.:*** Moditen; ***India:*** Anatensol; Fludecan; ***Indon.:*** Anatensol; Modecate; ***Irl.:*** Modecate; ***Israel:*** Fludecate; ***Ital.:*** Anatensol; Moditen; ***Malaysia:*** Deca; ***Mex.:*** Siqualine; ***Neth.:*** Anatensol; Moditen; ***Norw.:*** Siqualone; ***NZ:*** Anatensol; Modecate; ***Philipp.:*** Modezine; Shrizine; Sydepres; ***Port.:*** Anatensol; Cenilene†; Phenazin; ***Rus.:*** Moditen (Модитен); ***S.Afr.:*** Fludecate; Modecate; ***Singapore:*** Modecate; ***Spain:*** Modecate; ***Swed.:*** Pacinol†; Siqualone; ***Switz.:*** Dapotum; ***Thai.:*** Deca; Fluzine†; Pharnazine; Phenazine†; Potensone†; ***Turk.:*** Prolixin; ***UK:*** Modecate; Moditen†; ***USA:*** Prolixin†; ***Venez.:*** Moditen.

Multi-ingredient: ***Braz.:*** Diserim; ***Chile:*** Motitrel; ***Indon.:*** Motival; ***Irl.:*** Motival; ***Ital.:*** Dominans; ***Mex.:*** Motival; ***S.Afr.:*** Motival; ***Thai.:*** Cetavol; ***UK:*** Motival†.

Flurazepam *(BAN, rINN)*

Fluratsepaami; Flurazépam; Flurazepamum. 7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one.

Флуразепам

$C_{21}H_{23}ClFN_3O$ = 387.9.
CAS — 17617-23-1.
ATC — N05CD01.
ATC Vet — QN05CD01.

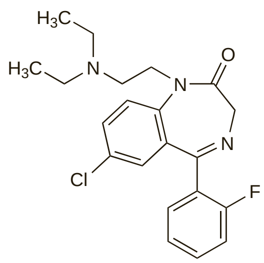

Pharmacopoeias. In *Jpn.*

Flurazepam Monohydrochloride *(BANM, rINNM)*

Fluratsepaamimonohydrokloridi; Flurazepam hydrochlorid; Flurazépam, monochlorhydrate de; Flurazepami Hydrochloridum; Flurazepami monohydrochloridum; Flurazepám-monohidroklorid; Flurazepammonohydroklorid; Flurazepamo monohidrochloridas; Monochidrocloruro de flurazepam.

Флуразепама Моногидрохлорид

$C_{21}H_{23}ClFN_3O,HCl$ = 424.3.
CAS — 36105-20-1.
ATC — N05CD01.
ATC Vet — QN05CD01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Flurazepam Monohydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.0. Protect from light.

Flurazepam Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de flurazepam; Flurazépam, Dichlorhydrate de; Flurazepam Hydrochloride *(USAN)*; Flurazepami Dihydrochloridum; NSC-78559; Ro-5-6901.

Флуразепама Дигидрохлорид

$C_{21}H_{23}ClFN_3O,2HCl$ = 460.8.
CAS — 1172-18-5.
ATC — N05CD01.
ATC Vet — QN05CD01.

Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Flurazepam Hydrochloride). An off-white to yellow crystalline powder. Is odourless or has a slight odour. Soluble 1 in 2 of water, 1 in 4 of alcohol, 1 in 90 of chloroform, 1 in 3 of methyl alcohol, 1 in 69 of isopropyl alcohol, 1 in 5000 of ether and of petroleum spirit, and 1 in 2500 of benzene. A solution in water is acid to litmus. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Effects on the liver. Reports of cholestatic jaundice after the use of flurazepam.[1,2]

1. Fang MH, *et al.* Cholestatic jaundice associated with flurazepam hydrochloride. *Ann Intern Med* 1978; **89:** 363–4.
2. Reynolds R, *et al.* Cholestatic jaundice induced by flurazepam hydrochloride. *Can Med Assoc J* 1981; **124:** 893–4.

Effects on taste. Flurazepam had been reported to cause dysgeusia.[1]

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983 (June): 368–71.

Porphyria. Flurazepam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Renal impairment. Five patients on maintenance haemodialysis developed encephalopathy attributed to flurazepam and diazepam.[1]

1. Taclob L, Needle M. Drug-induced encephalopathy in patients on maintenance haemodialysis. *Lancet* 1976; **ii:** 704–5.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Flurazepam is readily absorbed from the gastrointestinal tract. It undergoes extensive first-pass metabolism and is excreted in the urine, chiefly as conjugated metabolites. The major active metabolite is *N*-desalkylflurazepam, which is reported to have a half-life ranging from 47 to 100 hours or more.

Metabolism. The metabolism of flurazepam was studied in 4 healthy male subjects given 30 mg daily for 2 weeks.[1] A hydroxyethyl metabolite was present in the blood shortly after a dose. The *N*-desalkyl metabolite, the major metabolite in the blood, had a half-life ranging from 47 to 100 hours. Steady-state concentrations were reached after 7 to 10 days and were about 5 to 6 times greater than those observed on day 1. Results from a study in 3 patients indicated that some metabolism of flurazepam may occur in the small bowel mucosa.[2]

1. Kaplan SA, *et al.* Blood level profile in man following chronic oral administration of flurazepam hydrochloride. *J Pharm Sci* 1973; **62:** 1932–5.
2. Mahon WA, *et al.* Metabolism of flurazepam by the small intestine. *Clin Pharmacol Ther* 1977; **22:** 228–33.

Uses and Administration

Flurazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957). In the USA flurazepam is given as the dihydrochloride and doses are expressed in terms of this salt. Flurazepam dihydrochloride 30 mg is equivalent to about 25.3 mg of flurazepam. Doses of 15 to 30 mg orally at night are given. In the UK flurazepam is given as the monohydrochloride although doses are expressed in terms of the base; flurazepam monohydrochloride 32.8 mg is equivalent to about 30 mg of flurazepam. Doses equivalent to 15 to 30 mg of flurazepam at night are given. A maximum initial dose of 15 mg has been suggested in the UK and the USA for elderly or debilitated patients.

Preparations

BP 2008: Flurazepam Capsules;
USP 31: Flurazepam Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Fordrim†; ***Austria:*** Staurodorm; ***Belg.:*** Staurodorm; ***Braz.:*** Dalmadorm; ***Canad.:*** Dalmane†; ***Ger.:*** Dalmadorm; Staurodorm Neu; ***Hong Kong:*** Dalmadorm; ***India:*** Fluraz; ***Indon.:*** Dalmadorm; ***Irl.:*** Dalmane; ***Ital.:*** Dalmadorm; Felison; Flunox; Remdue; Valdorm; ***Neth.:*** Dalmadorm; ***Port.:*** Dalmadorm; Morfex; ***S.Afr.:*** Dalmadorm; ***Singapore:*** Dalmadorm; ***Spain:*** Dormodor; ***Switz.:*** Dalmadorm; ***Thai.:*** Dalmadorm; ***UK:*** Dalmane; ***USA:*** Dalmane†; ***Venez.:*** Fluralema.

Fluspirilene *(BAN, USAN, rINN)*

Fluspirileeni; Fluspirilen; Fluspirilenas; Fluspirilène; Fluspirileno; Fluspirilenum; McN-JR-6218; R-6218. 8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.

Флуспирилен

$C_{29}H_{31}F_2N_3O$ = 475.6.
CAS — 1841-19-6.
ATC — N05AG01.
ATC Vet — QN05AG01.

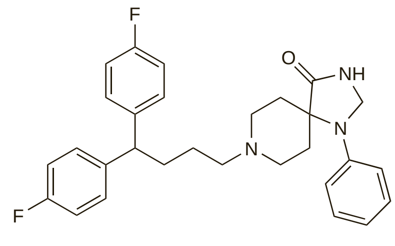

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fluspirilene). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Profile

Fluspirilene is a diphenylbutylpiperidine antipsychotic and has general properties similar to those of the phenothiazine, chlorpromazine (p.969). It is less likely to cause sedation. Fluspirilene has been given by deep intramuscular injection for the treatment of psychoses including schizophrenia (p.955). A usual initial dose is up to 2 mg weekly by deep intramuscular injection, increased according to response. Usual maintenance doses have ranged from 1 to 10 mg weekly although higher doses have been used in exceptional cases.

Adverse effects. References.

1. McCreadie RG, *et al.* Probable toxic necrosis after prolonged fluspirilene administration. *BMJ* 1979; **1:** 523–4.

Schizophrenia. A systematic review[1] found that evidence to support the use of depot fluspirilene over oral chlorpromazine or other depot antipsychotics in the treatment of schizophrenia was lacking.

1. Abhijnhan A, *et al.* Depot fluspirilene for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Imap; ***Belg.:*** Imap; ***Cz.:*** Imap†; ***Ger.:*** Fluspi; Imap; kivat†; ***Irl.:*** Redeptin†; ***Neth.:*** Imap.

Gepirone Hydrochloride *(USAN, rINNM)*

BMY-13805-1; Gépirone, Chlorhydrate de; Gepironi Hydrochloridum; Hidrocloruro de gepirona; MJ-13805-1; Org-33062 (gepirone). 3,3-Dimethyl-*N*-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}glutarimide hydrochloride.

Гепирона Гидрохлорид

$C_{19}H_{29}N_5O_2,HCl$ = 395.9.
CAS — 83928-76-1 (gepirone); 83928-66-9 (gepirone hydrochloride).
ATC — N06AX19.
ATC Vet — QN06AX19.

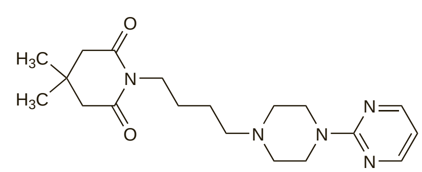

(gepirone)

Profile

Gepirone is structurally related to buspirone (p.965). It has been investigated as the hydrochloride for the treatment of depression and anxiety disorders.

Action. Gepirone is a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the 5-HT_{1A} subtype. For reference to the actions and potential uses of such drugs, see Buspirone, p.966.

References.

1. Feiger AD. A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. *Psychopharmacol Bull* 1996; **32:** 659–65.
2. Rickels K, *et al.* Gepirone and diazepam in generalized anxiety disorder: a placebo-controlled trial. *J Clin Psychopharmacol* 1997; **17:** 272–7.
3. Dogterom PP, *et al.* Pharmacokinetics of gepirone (Org 33062) in subjects with normal renal function and in patients with chronic renal dysfunction. *Clin Pharmacol Ther* 2002; **71:** P95.
4. Feiger AD, *et al.* Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J Clin Psychiatry* 2003; **64:** 243–9.
5. Robinson DS, *et al.* A review of the efficacy and tolerability of immediate-release and extended-release formulations of gepirone. *Clin Ther* 2003; **25:** 1618–33.

6. Timmer CJ, Sitsen JM. Pharmacokinetic evaluation of gepirone immediate-release capsules and gepirone extended-release tablets in healthy volunteers. *J Pharm Sci* 2003; **92:** 1773–8.
7. Amsterdam JD, *et al.* Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. *J Psychiatr Res* 2004; **38:** 259–65.
8. Alpert JE, *et al.* Gepirone extended-release treatment of anxious depression: evidence from a retrospective subgroup analysis in patients with major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1069–75.
9. Keller MB, *et al.* Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol* 2005; **25:** 79–84.

Glutethimide *(BAN, rINN)*

Glutéthimide; Glutethimidum; Glutetimid; Glutetimida; Glutetimide; Glutetimidi. 2-Ethyl-2-phenylglutarimide; 3-Ethyl-3-phenylpiperidine-2,6-dione.

Глутетимид

$C_{13}H_{15}NO_2$ = 217.3.
CAS — 77-21-4.
ATC — N05CE01.
ATC Vet — QN05CE01.

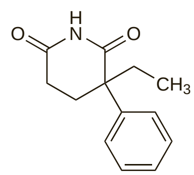

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of glutethimide:
CIBAs; D; Doors; Goofers.

Profile

Glutethimide is a piperidinedione hypnotic and sedative with effects broadly similar to those of the barbiturates (see Amobarbital, p.961). It also has antimuscarinic properties. It has been given for the short-term management of insomnia but it has been superseded by other drugs.

Abuse. A warning of the hazards associated with the abuse of glutethimide in a combination with codeine termed 'loads'.[1]

1. Sramek JJ, Khajawall A. "Loads". *N Engl J Med* 1981; **305:** 231.

Porphyria. Glutethimide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hung.:*** Tardyl†.

Halazepam *(BAN, USAN, rINN)*

Halatsepaami; Halazépam; Halazepamum; Sch-12041. 7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepin-2-one.

Галазепам

$C_{17}H_{12}ClF_3N_2O$ = 352.7.
CAS — 23092-17-3.
ATC — N05BA13.
ATC Vet — QN05BA13.

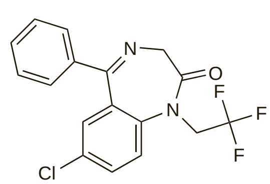

Profile

Halazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given for the short-term treatment of anxiety disorders (p.952) in usual oral doses of 20 to 40 mg every 6 to 8 hours.

Preparations

Proprietary Preparations (details are given in Part 3)

Port.: Pacinone; ***Spain:*** Alapryl.

Haloperidol *(BAN, USAN, rINN)*

Aloperidolo; Halopéridol; Haloperidoli; Haloperidolis; Haloperidolum; McN-JR-1625; R-1625. 4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

Галоперидол

$C_{21}H_{23}ClFNO_2$ = 375.9.
CAS — 52-86-8.
ATC — N05AD01.
ATC Vet — QN05AD01.

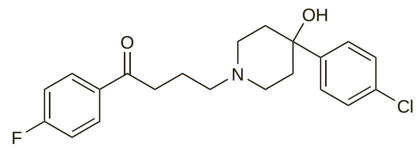

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Haloperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol, in dichloromethane, and in methyl alcohol. Protect from light.

USP 31 (Haloperidol). A white to faintly yellowish amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 15 of chloroform, and 1 in 200 of ether. A saturated solution is neutral to litmus. Store in airtight containers. Protect from light.

Dilution. See Incompatibility, below.

Incompatibility. A precipitate formed after dilution of haloperidol (as the lactate) in sodium chloride 0.9% injection when the final haloperidol concentration was 1 mg/mL or higher.[1]

Undiluted haloperidol (5 mg/mL) injection has been reported to be incompatible with heparin sodium (diluted in sodium chloride 0.9% or glucose 5% injection),[2] sodium nitroprusside (diluted in glucose 5%),[1] cefmetazole sodium,[3] and diphenhydramine.[4] A mixture of equal volumes of sargramostim 10 micrograms/mL and haloperidol (as the lactate) 200 micrograms/mL resulted in a precipitate at 4 hours.[5]

1. Outman WR, Monolakis J. Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 1539–41.
2. Solomon DA, Nasinnyk KK. Compatibility of haloperidol lactate and heparin sodium. *Am J Hosp Pharm* 1982; **39:** 843–4.
3. Hutchings SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
4. Ukhun IA. Compatibility of haloperidol and diphenhydramine in a hypodermic syringe. *Ann Pharmacother* 1995; **29:** 1168–9.
5. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49:** 402–6.

Stability. A combination of the stabilisers benzyl alcohol and vanillin could protect haloperidol from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilisation of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Haloperidol Decanoate *(BANM, USAN, rINNM)*

Decanoato de haloperidol; Halopéridol, décanoate d'; Haloperidoldekanoat; Haloperidol-dekanoát; Haloperidoli decanoas; Haloperidolidekanoaatti; Haloperidolio dekanoatas; R-13672.

Галоперидола Деканоат

$C_{31}H_{41}ClFNO_3$ = 530.1.
CAS — 74050-97-8.
ATC — N05AD01.
ATC Vet — QN05AD01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Haloperidol Decanoate). A white or almost white powder. It melts at about 42°. Practically insoluble in water; very soluble in alcohol, in dichloromethane, and in methyl alcohol. Store at a temperature below 25°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Haloperidol is less likely to cause sedation, hypotension, or antimuscarinic effects, but is associated with a higher incidence of extrapyramidal effects. Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions; patients with hyperthyroidism may also be at increased risk.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of haloperidol by mothers during breast feeding may be of concern, since there have been reports of decline in developmental scores in breast-fed infants. Licensed product information also reports that there have been isolated cases of extrapyramidal effects in breast-fed infants.

The concentration of haloperidol in breast milk of one mother given a mean daily dose of about 30 mg for 6 days was reported to be 5 nanograms/mL; on day 12 the concentration 9 hours after a 12-mg dose was 2 nanograms/mL.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Stewart RB, *et al.* Haloperidol excretion in human milk. *Am J Psychiatry* 1980; **137:** 849–50.

Convulsions. For mention of haloperidol as one of the antipsychotics suitable for patients at risk of seizures, see p.969.

Effects on the liver. Liver dysfunction with jaundice and eosinophilia developed in a 15-year-old male 4 weeks after starting haloperidol and benzatropine mesilate.[1] The drugs were stopped 2 weeks later but some symptoms lasted for 28 months. The reaction was suggestive of a drug-induced hypersensitivity reaction and haloperidol was the most likely cause. Haloperidol-induced liver injury was considered to be rare.

1. Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. *Gastroenterology* 1982; **83:** 694–700.

Overdosage. Symptoms of haloperidol overdosage in children have ranged from the expected, such as drowsiness, restlessness, confusion, marked extrapyramidal symptoms, and hypothermia,[1,2] to unexpected reactions such as bradycardia (possibly secondary to hypothermia)[1] and an episode of severe, delayed hypertension.[3]

Torsade de pointes has followed overdosage in adults (for references, see Effects on the Cardiovascular System under Chlorpromazine, p.970).

1. Scialli JVK, Thornton WE. Toxic reactions from a haloperidol overdose in two children: thermal and cardiac manifestations. *JAMA* 1978; **239:** 48–9.
2. Sinaniotis CA, *et al.* Acute haloperidol poisoning in children. *J Pediatr* 1978; **93:** 1038–9.
3. Cummingham DG, Challapalli M. Hypertension in acute haloperidol poisoning. *J Pediatr* 1979; **95:** 489–90.

Porphyria. Haloperidol is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Retroperitoneal fibrosis. Obstructive uropathy was noted in a 45-year-old woman given haloperidol 5 to 15 mg daily for 8 years.[1] Benzatropine was also taken during that time, and in the previous 5 years she had taken chlorpromazine and fluphenazine. A diagnosis of retroperitoneal fibrosis was made and was tentatively associated with long-term antipsychotic therapy.

1. Jeffries JJ, *et al.* Retroperitoneal fibrosis and haloperidol. *Am J Psychiatry* 1982; **139:** 1524–5.

Toxic encephalopathy. A report[1] of possible toxic encephalopathy after use of high intravenous doses of haloperidol. The patient, who had a history of bipolar disorder and cerebrovascular accident, had been given increasing intravenous doses of haloperidol (up to 270 mg daily) to control post-surgical agitation. The encephalopathy had resolved 8 days after stopping haloperidol.

1. Maxa JL, *et al.* Possible toxic encephalopathy following high-dose intravenous haloperidol. *Ann Pharmacother* 1997; **31:** 736–7.

Interactions

As for Chlorpromazine, p.973.

Haloperidol must be used with extreme caution in patients receiving lithium; an encephalopathic syndrome has been reported after their use together (see p.405).

Pharmacokinetics

Haloperidol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and is excreted in the urine and, via the bile, in the faeces; there is evidence of enterohepatic recycling. Owing to first-pass metabolism in the liver, plasma concentrations after oral doses are lower than those after intramuscular injection. Moreover, there is wide intersubject variation in plasma concentrations of haloperidol. In practice, however, no strong correlation has been found between plasma concentrations of haloperidol and its therapeutic effect. Paths of metabolism of haloperidol include oxidative *N*-dealkylation and reduction of the ketone group to form an alcohol known as reduced haloperidol. Haloperidol has been reported to have a plasma elimination half-life ranging from about 12 to 38 hours after oral doses. Haloperidol is about 92% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Haloperidol is distributed into breast milk.

The decanoate ester of haloperidol is very slowly absorbed from the site of injection and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to haloperidol.

◊ References.

1. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999 **37:** 435–56.

Metabolites. The clinical significance of the reduced metabolite of haloperidol has been much debated.[1,2] Its activity appears to be substantially less than that of the parent drug but there is some evidence for re-oxidation of reduced haloperidol to haloperidol.[1-3] Some studies suggest that nonresponders to haloperidol have elevated ratios of reduced haloperidol to haloperidol in the plasma, although other workers have reported contrary findings.[2] Pyridinium metabolites resulting from oxidation of haloperidol have been detected in the urine and there is concern that they may be neurotoxic in a manner similar to MPTP (see Parkinsonism, p.791), a compound which can induce irreversible parkinsonism.[4]

1. Sramek JJ, *et al.* Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22:** 373–80.
2. Froemming JS, *et al.* Pharmacokinetics of haloperidol. *Clin Pharmacokinet* 1989; **17:** 396–423.
3. Chakraborty BS, *et al.* Interconversion between haloperidol and reduced haloperidol in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 45–8.
4. Eyles DW, *et al.* Quantitative analysis of two pyridinium metabolites of haloperidol in patients with schizophrenia. *Clin Pharmacol Ther* 1994; **56:** 512–20.

Therapeutic drug monitoring. Measurement of concentrations of haloperidol or reduced haloperidol in scalp hair has been suggested as a useful means of monitoring compliance.[1,2] Evidence for the existence of any relationship between plasma concentrations of haloperidol and therapeutic effect in schizophrenia has been discussed.[3]

1. Uematsu T, *et al.* Human scalp hair as evidence of individual dosage history of haloperidol: method and retrospective study. *Eur J Clin Pharmacol* 1989; **37:** 239–44.
2. Matsuno H, *et al.* The measurement of haloperidol and reduced haloperidol in hair as an index of dosage history. *Br J Clin Pharmacol* 1990; **29:** 187–94.
3. Ulrich S, *et al.* The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. *Clin Pharmacokinet* 1998; **34:** 227–63.

Uses and Administration

Haloperidol is a butyrophenone with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It is an antipsychotic with actions most closely resembling those of phenothiazines with a piperazine side-chain.

Haloperidol is used in the treatment of various psychoses including schizophrenia (p.955) and mania (see Bipolar Disorder, p.372), and in behaviour disturbances (p.954), in Tourette's syndrome and severe tics (p.954), in intractable hiccups (p.976), and in severe anxiety (p.952), including for the sedation of patients in intensive care (p.957) or palliative care. Haloperidol has also been used for its antiemetic effect in the management of nausea and vomiting of various causes (p.1700).

Haloperidol is usually given orally or by injection as the base or intramuscularly as the long-acting decanoate ester. Some haloperidol preparations are prepared with the aid of lactic acid and may be stated to contain haloperidol lactate. Doses are expressed in terms of the equivalent amount of haloperidol. Haloperidol decanoate 141 mg is equivalent to about 100 mg of haloperidol. Dosages should be reduced in elderly or debilitated patients; a usual starting dose is half the normal adult dose. Doses at the lower end of the scale are also advised for adolescents.

The usual initial *oral* dose for the treatment of **psychoses** and associated behavioural disorders is 0.5 to 5 mg two or three times daily. In severe or resistant psychoses up to 30 mg daily is recommended in the UK, whereas in the USA doses of up to 100 mg daily are allowed; doses above 100 mg daily have rarely been used. The dose should be reduced gradually according to response. Maintenance doses as low as 3 to 10 mg daily may be sufficient. A suitable initial oral dose for children is 25 to 50 micrograms/kg daily in 2 divided doses, increased cautiously, if necessary. A maximum daily dose of 10 mg has been recommended in the UK but in the USA the suggested maximum daily dose is 150 micrograms/kg as the manufacturer has stated that there is little evidence of behaviour improvement with daily doses of more than 6 mg.

For the control of acute psychotic conditions, haloperidol may be given *intramuscularly* in doses of 2 to 10 mg; subsequent doses may be given hourly, until symptoms are controlled, although dosage intervals of 4 to 8 hours may be adequate, up to a maximum of 18 mg daily. For the emergency control of very severely disturbed patients, an initial intramuscular dose of no more than 18 mg is recommended. The *intravenous* route may also be used.

In patients already stabilised on an oral dose of haloperidol and requiring long-term therapy the long-acting decanoate ester may be given by *deep intramuscular* injection. The usual initial dose is the equivalent of 10 to 20 times the total daily oral dose of haloperidol, up to a maximum of 100 mg; if more than 100 mg is required for an initial dose the excess should be given after 3 to 7 days. Subsequent doses, usually given every 4 weeks, may be increased in steps of 50 mg to up to 300 mg or more, according to the patient's requirements, both dose and dose interval being adjusted as required.

In the management of **nausea and vomiting** haloperidol has been given in a dose of 0.5 to 2 mg by *intramuscular* injection; alternatively, an *oral* dose of 1 mg daily may be given. In palliative care haloperidol 1.5 mg may be given orally once or twice daily, increased if necessary to 5 to 10 mg daily given in divided doses; alternatively, it may be given by *subcutaneous* infusion (via a syringe driver) in doses of 2.5 to 10 mg over 24 hours. The *intravenous* route has also been used.

A starting *oral* dose of 0.5 to 1.5 mg three times daily has been suggested for the management of **Tourette's syndrome** and severe **tics**. Up to about 30 mg daily may be needed in Tourette's syndrome, although requirements vary considerably and the dose must be very carefully adjusted to obtain the optimum response; a maintenance dose of 4 mg daily is effective for most patients.

For intractable **hiccups** a suggested *oral* dose is 1.5 mg given 3 times daily adjusted according to response.

An *oral* dose of 500 micrograms twice daily has been used as adjunctive treatment in the short-term management of severe **anxiety disorders**.

In palliative care, haloperidol has been given in an *oral* dose of 1 to 3 mg every 8 hours for the treatment of **restlessness and confusion**. It may also be given as a *subcutaneous* infusion in a dose of 5 to 15 mg over 24 hours.

Ballism. Dopamine-blocking antipsychotics such as haloperidol may sometimes be needed for the management of patients with ballism (p.953) when symptoms are severe.

Chorea. For a discussion of the management of various choreas, including mention of the use of haloperidol, see p.953.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to other drugs. However, they often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p.971).

Schizophrenia. Systematic reviews[1,2] of the use of haloperidol for schizophrenia (p.955) concluded that it appears to be of similar efficacy to chlorpromazine although it is associated with a high incidence of extrapyramidal adverse effects. An earlier systematic review[3] considered that the limited evidence did not indicate any advantages of giving haloperidol in doses greater than 7.5 mg daily to patients with uncomplicated acute schizophrenia.

1. Joy CB, *et al.* Haloperidol versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 19/03/08).
2. Leucht C, *et al.* Haloperidol versus chlorpromazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).
3. Waraich PS, *et al.* Haloperidol dose for the acute phase of schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 19/03/08).

Sneezing. Report[1] of a patient whose intractable sneezing was controlled by haloperidol given in doses of up to 5 mg twice daily. Symptoms recurred when treatment was stopped after 5 weeks but responded again to 5 mg three times daily. On gradual reduction of dosage over 6 months the patient had no recurrence and had remained symptom-free after 6 months without medication.

1. Davison K. Pharmacological treatment for intractable sneezing. *BMJ* 1982; **284:** 1163–4.

Stuttering. Stuttering (stammering) is a disorder that affects the fluency of speech. Developmental stuttering usually occurs in early childhood and is more common in boys than girls. While stuttering may cease in some children after only a few months, it may become a chronic condition in others. Stuttering that starts during adulthood is rarer and may be the result of a neurological insult. It should also be remembered that stuttering may be drug induced. While stuttering may be greatly improved with intensive speech training the effectiveness of other forms of management such as hypnosis, psychotherapy, counselling, and drug therapy has been largely unconvincing.[1] Although many drugs have been used to treat stuttering a review of the literature[2] indicated that there were few adequate studies of their efficacy. Haloperidol was considered to be the most well studied drug and its efficacy had been shown by several double-blind placebo-controlled studies. However, most patients needed to continue taking haloperidol to maintain improvement but few did so because of its adverse effects. Double-blind studies have on the whole failed to confirm reports of benefit for drugs such as bethanechol, beta blockers, and calcium-channel blockers although isolated patients may have marked improvement. Other drugs that have been studied and which might be of benefit include clomipramine,[3] SSRIs,[4] and atypical antipsychotics[4] such as olanzapine and risperidone; local anaesthetics and injections of botulinum toxin have also been tried.

1. Andrews G, *et al.* Stuttering. *JAMA* 1988; **260:** 1445.
2. Brady JP, *et al.* The pharmacology of stuttering: a critical review. *Am J Psychiatry* 1991; **148:** 1309–16.
3. Gordon CT, *et al.* A double-blind comparison of clomipramine and desipramine in the treatment of developmental stuttering. *J Clin Psychiatry* 1995; **56:** 238–42.
4. Costa D, Kroll R. Stuttering: an update for physicians. *Can Med Assoc J* 2000; **162:** 1849–55.

Taste disorders. For reference to the use of haloperidol in the treatment of taste disorders, see Chlorpromazine, p.977.

Tourette's syndrome. Many patients with Tourette's syndrome (p.954) do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. However, superiority of either drug in terms of efficacy or adverse effects has not been clearly demonstrated.[1,2] Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to be as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al.* Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46:** 722–30.
2. Sallee FR, *et al.* Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154:** 1057–62.

Preparations

BP 2008: Haloperidol Capsules; Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets; Strong Haloperidol Oral Solution;
USP 31: Haloperidol Injection; Haloperidol Oral Solution; Haloperidol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Enabran; Halopidol; Halozen; Limerix; Neupram; Zetoridal†; ***Austral.:*** Haldol; Serenace; ***Austria:*** Haldol; ***Belg.:*** Haldol; ***Braz.:*** Decan Haloper; Haldol; Halo; Haloper; Loperidol; Uni Haloper; ***Canad.:*** Haldol†; Novo-Peridol; Peridol†; ***Chile:*** Alternus; Haldol; ***Denm.:*** Serenase; ***Fin.:*** Serenase; ***Fr.:*** Haldol; ***Ger.:*** Haldol; Haloneural†; Haloper; Sigaperidol†; ***Gr.:*** Aloperidin; Sevium; ***Hong Kong:*** Haldol; Serenace; ***India:*** Cizoren†; Serenace; ***Indon.:*** Dores; Govotil; Haldol; Lodomer; Serenace; ***Irl.:*** Haldol; Serenace; ***Israel:*** Haldol; Haloper; Pericate; Peridor; ***Ital.:*** Haldol; Serenase; ***Malaysia:*** Avant†; Manace; Serenace†; ***Mex.:*** Haldol; Haloperil; Hispadol; Kepsidol; Pulsit; ***Neth.:*** Haldol; ***Norw.:*** Haldol; ***NZ:*** Haldol; Serenace; ***Philipp.:*** Haldol; Seredol; Serenace; ***Pol.:*** Decaldol; ***Port.:*** Haldol; Serenelfi†; ***Rus.:*** Haloper (Галопр)†; Senorm (Сенорм); ***S.Afr.:*** Serenace; ***Singapore:*** Serenace†; ***Swed.:*** Haldol; ***Switz.:*** Haldol; Sigaperidol†; ***Thai.:*** H-Tab; Haldol; Halo-P†; Halomed; Halopol; Haricon; Haridol; Perida; Polyhadon; Schizopol†; Tensidol†; ***Turk.:*** Norodol; Sedaperidol; ***UK:*** Dozic; Haldol; Serenace; ***USA:*** Haldol; ***Venez.:*** Haldol; Tiplac.

Multi-ingredient: ***Fr.:*** Vesadol†.

Haloxazolam *(rINN)*

Haloxazolamum. 10-Bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Галоксазолам

$C_{17}H_{14}BrFN_2O_2$ = 377.2.

CAS — 59128-97-1.

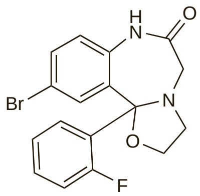

Pharmacopoeias. In *Jpn.*

Profile

Haloxazolam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given orally as a hypnotic in the short-term management of insomnia.

Hexobarbital *(BAN, rINN)*

Enhexymalum; Enimal; Heksobarbitaali; Heksobarbitalis; Hexobarbitál; Hexobarbitalum; Hexobarbitone; Methexenyl; Methylcyclohexenylmethyl-barbitursäure; Methylhexabarbital. 5-(Cyclohex-1-enyl)-1,5-dimethylbarbituric acid.

Гексобарбитал

$C_{12}H_{16}N_2O_3$ = 236.3.

CAS — 56-29-1.

ATC — N01AF02; N05CA16.

ATC Vet — QN01AF02; QN05CA16.

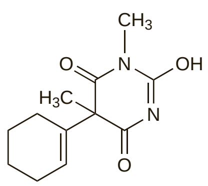

NOTE. The name ciclobarbital (see Cyclobarbital, p.986) has sometimes been applied to hexobarbital.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hexobarbital). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Hexobarbital Sodium *(BANM, rINNM)*

Enhexymalnatrium; Hexenalum; Hexobarbital sódico; Hexobarbital Sodique; Hexobarbitalum Natricum; Hexobarbitone Sodium; Natrii Hexobarbitalum; Sodium Hexobarbital; Soluble Hexobarbitone. Sodium 5-(cyclohex-1-enyl)-1,5-dimethylbarbiturate.

Натрий Гексобарбитал

$C_{12}H_{15}N_2NaO_3$ = 258.2.

CAS — 50-09-9.

ATC — N01AF02; N05CA16.

ATC Vet — QN01AF02; QN05CA16.

Profile

Hexobarbital is a barbiturate with the general properties of amobarbital (p.961). It has been used as a hypnotic and sedative but barbiturates are no longer considered appropriate for such purposes.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Novopan†.

Homofenazine Hydrochloride *(rINNM)*

D-775 (homofenazine); HFZ (homofenazine); Hidrocloruro de homofenazina; Homofénazine, Chlorhydrate d'; Homofenazini Hydrochloridum. 2-{Hexahydro-4-[3-(2-trifluoromethylphenothiazin-10-yl)propyl]-1,4-diazepin-1-yl}ethanol dihydrochloride.

Гомофеназина Гидрохлорид

$C_{23}H_{28}F_3N_3OS,2HCl$ = 524.5.

CAS — 3833-99-6 (homofenazine); 1256-01-5 (homofenazine hydrochloride).

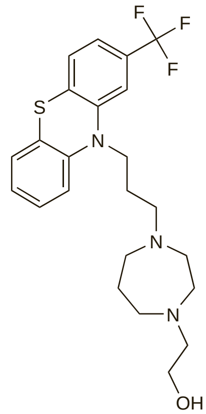

(homofenazine)

Profile

Homofenazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been used in the management of neuropsychiatric disorders.

Ipsapirone Hydrochloride *(BANM, USAN, rINNM)*

Bay-q-7821; Hidrocloruro de ipsapirona; Ipsapirone, Chlorhydrate d'; Ipsapironi Hydrochloridum; TVX-Q-7821. 2-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide hydrochloride.

Ипсапирона Гидрохлорид

$C_{19}H_{23}N_5O_3S,HCl$ = 437.9.

CAS — 95847-70-4 (ipsapirone); 92589-98-5 (ipsapirone hydrochloride).

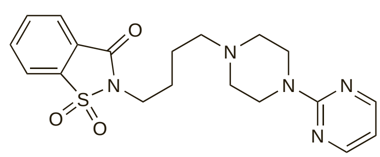

(ipsapirone)

Profile

Ipsapirone is structurally related to buspirone (p.965). It has been investigated as the hydrochloride for the treatment of anxiety disorders and depression.

Action. Ipsapirone is a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the $5\text{-}HT_{1A}$ subtype. For reference to the actions and potential uses of such drugs, see Buspirone, p.966.

References.

1. Cutler NR, *et al.* A double-blind, placebo-controlled study comparing the efficacy and safety of ipsapirone versus lorazepam in patients with generalized anxiety disorder: a prospective multicenter trial. *J Clin Psychopharmacol* 1993; **13:** 429–37.
2. Fuhr U, *et al.* Absorption of ipsapirone along the human gastrointestinal tract. *Br J Clin Pharmacol* 1994; **38:** 83–6.
3. Mandos LA, *et al.* Placebo-controlled comparison of the clinical effects of rapid discontinuation of ipsapirone and lorazepam after 8 weeks of treatment for generalized anxiety disorder. *Int Clin Psychopharmacol* 1995; **10:** 251–6.
4. Lapierre YD, *et al.* A Canadian multicenter study of three fixed doses of controlled-release ipsapirone in outpatients with moderate to severe major depression. *J Clin Psychopharmacol* 1998; **18:** 268–73.

Ketazolam *(BAN, USAN, rINN)*

Ketatsolaami; Kétazolam; Ketazolamum; U-28774. 11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-*d*][1,4]benzodiazepine-4,7(6*H*)-dione.

Кетазолам

$C_{20}H_{17}ClN_2O_3$ = 368.8.

CAS — 27223-35-4.

ATC — N05BA10.

ATC Vet — QN05BA10.

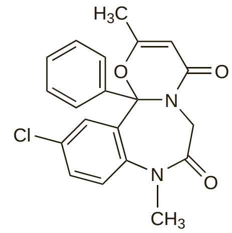

Profile

Ketazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It is given in the short-term treatment of anxiety (p.952) in usual oral doses of 15 to 60 mg daily, either in divided doses or as a single dose at night. Reduced doses may be required in elderly or debilitated patients.

◊ References.

1. Angelini G, *et al.* Ketazolam, a new long-acting benzodiazepine, in the treatment of anxious patients: a multicenter study of 2,056 patients. *Curr Ther Res* 1989; **45:** 294–304.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ansieten; ***Belg.:*** Solatran†; ***Chile:*** Ansietil; Sedatival; ***Ital.:*** Anseren; ***Port.:*** Unakalm; ***S.Afr.:*** Solatran; ***Spain:*** Marcen; Sedotime; ***Switz.:*** Solatran.

Levomepromazine *(BAN, USAN, rINN)*

CL-36467; CL-39743; Levomepromatsiini; Levomepromazin; Levomepromazina; Lévomépromazine; Levomepromazinum; Methotrimeprazine; RP-7044; SKF-5116; XP-03. (−)-*NN*-Dimethyl-3-(2-methoxyphenothiazin-10-yl)-2-methylpropylamine; 3-(2-Methoxyphenothiazin-10-yl)-2-methylpropyldimethylamine.

Левомепромазин

$C_{19}H_{24}N_2OS$ = 328.5.

CAS — 60-99-1.

ATC — N05AA02.

ATC Vet — QN05AA02.

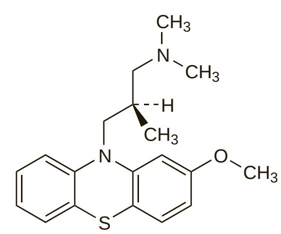

Pharmacopoeias. In *US.* Also in *BP(Vet).*

BP(Vet) 2008 (Levomepromazine). A white or slightly cream-coloured crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in ether. Protect from light.

USP 31 (Methotrimeprazine). A fine white, practically odourless, crystalline powder. Soluble 1 in 10 of water, of alcohol, and of methyl alcohol, and 1 in 2 of chloroform; freely soluble in ether; sparingly soluble in alcohol at 25° but freely soluble in boiling alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Levomepromazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levomepromazina; Levomepromatsiinihydrokloridi; Levomepromazin hydrochlorid; Lévomépromazine, chlorhydrate de; Levomepromazin-hidroklorid; Levomepromazinhydroklorid; Levomepromazini hydrochloridum; Levomepromazino hidrochloridas; Lewomepromazyny chlorowodorek; Methotrimeprazine Hydrochloride.

Левомепромазина Гидрохлорид

$C_{19}H_{24}N_2OS,HCl$ = 364.9.

CAS — 4185-80-2; 1236-99-3.

ATC — N05AA02.

ATC Vet — QN05AA02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Levomepromazine Hydrochloride). A white or very slightly yellow, slightly hygroscopic crystalline powder. It deteriorates on exposure to air and light. Freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Incompatibility. Levomepromazine hydrochloride is reported to be incompatible with alkaline solutions.

Levomepromazine Maleate *(BANM, USAN, rINNM)*

Levomepromatsiinimaleaatti; Levomepromazin maleinát; Lévomépromazine, maléate de; Levomepromazini maleas; Levomepromazinmaleat; Levomepromazin-maleát; Levomepromazino maleatas; Lewomepromazyny maleinian; Maleato de levomepromazina; Methotrimeprazine Hydrogen Maleate; Methotrimeprazine Maleate.

Левомепромазина Малеат

$C_{19}H_{24}N_2OS,C_4H_4O_4$ = 444.5.

CAS — 7104-38-3.

ATC — N05AA02.

ATC Vet — QN05AA02.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Levomepromazine Maleate). A white or slightly yellowish crystalline powder. It deteriorates when exposed to air and light. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. The supernatant of a 2% dispersion in water has a pH of 3.5 to 5.5. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969, although it may be more sedating. See also Adverse Effects of Antihistamines, p.561.

Levomepromazine may cause severe orthostatic hypotension, and patients taking large initial doses, patients over 50 years of age, or those given injections, should be lying down. Children are very susceptible to the hypotensive and sedative effects of levomepromazine.

Interactions

As for Chlorpromazine, p.973.

Antidepressants. Although *MAOIs* have been used with phenothiazines without untoward effects, the use of levomepromazine with MAOIs should probably be avoided as this combination has been implicated in 2 fatalities.[1,2]

1. Barsa JA, Saunders JC. A comparative study of tranylcypromine and pargyline. *Psychopharmacologia* 1964; **6:** 295–8.
2. McQueen EG. New Zealand committee on adverse drug reactions: fourteenth annual report 1979. *N Z Med J* 1980; **91:** 226–9.

Pharmacokinetics

◊ In a study involving 5 psychiatric patients peak plasma concentrations of levomepromazine were noted 1 to 4 hours after oral doses and 30 to 90 minutes after injection into the gluteal muscle.[1] About 50% of an oral dose reached the systemic circulation. Although the metabolite levomepromazine sulfoxide could not be detected after a single intramuscular injection, it was found in concentrations higher than unmetabolised levomepromazine after single and multiple oral dosage, both substances reaching a steady state in the plasma within 7 days of starting multiple-dose oral therapy. Fluctuations in plasma concentration during multiple-dose oral therapy indicated that until the correlation between acute adverse effects and peak plasma concentration of levomepromazine had been further studied the total daily dose should be divided into 2 or 3 portions when larger oral doses of levomepromazine are used.

1. Dahl SG. Pharmacokinetics of methotrimeprazine after single and multiple doses. *Clin Pharmacol Ther* 1976; **19:** 435–42.

Half-life. In 8 psychiatric patients given levomepromazine 50 to 350 mg daily the plasma half-life showed wide variation, from 16.5 to 77.8 hours, and did not correlate with the dose given.[1]

1. Dahl SG, *et al*. Pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. *Eur J Clin Pharmacol* 1977; **11:** 305–310.

Uses and Administration

Levomepromazine is a phenothiazine with pharmacological activity similar to that of both chlorpromazine (p.975) and promethazine (p.589). It has antihistaminic actions (p.561) as well as CNS effects resembling those of chlorpromazine. It is also reported to have analgesic activity. It is used in the treatment of various psychoses including schizophrenia (p.955), as an analgesic for moderate to severe pain usually in non-ambulatory patients, and for premedication (p.1780). It is also used in palliative care for the control of symptoms such as restlessness, agitation, and as an adjunct to opioid analgesia, as well as being an effective broad-spectrum antiemetic in nausea and vomiting (p.1700).

Levomepromazine is also used in veterinary medicine.

Levomepromazine is given orally as the maleate or the hydrochloride or by injection as the hydrochloride. In the UK, doses such as those given below are expressed in terms of the appropriate salt. However, in some countries, the dose of levomepromazine may be expressed in terms of the base. The embonate has also been used. Care is required in elderly patients because of the risk of severe hypotension; if levomepromazine is given to such patients reduced doses may be necessary.

The usual initial oral dose of levomepromazine maleate for the treatment of **schizophrenia** is 25 to 50 mg daily; the daily dosage is usually divided into 3 portions with a larger portion taken at night. Doses of 100 to 200 mg have been given to non-ambulant patients increased gradually up to 1 g daily if necessary. Children are very susceptible to the hypotensive and sedative effects of levomepromazine: a suggested oral dose for a 10-year-old is 12.5 to 25 mg of the maleate daily in divided doses; a dose of 37.5 mg daily should not be exceeded.

When used in **palliative care** as an adjunct to analgesics in the management of severe terminal **pain** and for the control of **nausea and vomiting**, levomepromazine maleate may be given orally in a dose of 12.5 to 50 mg every 4 to 8 hours. The *BNF* also includes an oral dose of levomepromazine maleate 6 to 25 mg daily given in 1 or 2 divided doses for the management of nausea and vomiting where first-line antiemetics have proved inadequate. Alternatively 12.5 to 25 mg of levomepromazine hydrochloride may be given intramuscularly every 6 to 8 hours but patients should remain in bed for at least the first few doses; doses of up to 50 mg have been given for severe agitation. Levomepromazine hydrochloride may also be given intravenously in similar doses after dilution with an equal volume of sodium chloride 0.9% injection. Alternatively it may be given, suitably diluted with sodium chloride 0.9% injection, by continuous subcutaneous infusion via a syringe driver; doses range from a total of 25 to 200 mg daily although lower doses of 5 to 25 mg daily may also be effective against nausea and vomiting. Experience with parenteral use of levomepromazine hydrochloride in children is limited but a dose of 100 to 400 micrograms/kg daily by continuous intravenous or subcutaneous infusion has been suggested for children aged 1 month and over in the management of nausea and vomiting in palliative care; it has also been used in the treatment of restlessness and confusion in palliative care in a dose of 0.35 to 3 mg/kg daily by continuous subcutaneous infusion in those aged 1 year and over.

Levomepromazine hydrochloride given intramuscularly has been used in some countries for the control of acute pain, as a **premedicant**, and for postoperative analgesia. In some countries levomepromazine is also licensed for use as an **anxiolytic** and **sedative**, and in the management of other types of pain, including **labour pain**.

Pain. As levomepromazine appears to possess intrinsic analgesic activity in addition to its antiemetic and antipsychotic actions it has been used for the symptomatic control of restlessness and vomiting and as an adjunct to opioid analgesics in pain control (see Choice of Analgesic, p.2) in terminally ill patients.

References.

1. Oliver DJ. The use of methotrimeprazine in terminal care. *Br J Clin Pract* 1985; **39:** 339–40.
2. Patt RB, *et al.* The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994; **9:** 446–53.
3. O'Neill J, Fountain A. Levomepromazine (methotrimeprazine) and the last 48 hours. *Hosp Med* 1999; **60:** 564–7.
4. Skinner J, Skinner A. Levomepromazine for nausea and vomiting in advanced cancer. *Hosp Med* 1999; **60:** 568–70.

HEADACHE. Levomepromazine is one of those phenothiazines (see p.976) that has been effective[1] in relieving the pain of severe migraine attacks.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20:** 1201–5.

Preparations

BP 2008: Levomepromazine Injection; Levomepromazine Tablets;
USP 31: Methotrimeprazine Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Detenler; Levolam; Nozinan; Togrel; ***Austria:*** Nozinan; ***Belg.:*** Nozinan; ***Braz.:*** Levozine; Neozine; ***Canad.:*** Apo-Methoprazine; Novo-Meprazine†; Nozinan; ***Chile:*** Sinogan; ***Cz.:*** Tisercin; ***Denm.:*** Nozinan; ***Fin.:*** Levozin; Nozinan; ***Fr.:*** Nozinan; ***Ger.:*** Levium; Neurocil; ***Gr.:*** Nozinan; Prazine†; Sinogan; ***Hung.:*** Tisercin; ***Irl.:*** Nozinan; ***Israel:*** Methozane; Nozinan; Ronexine; ***Ital.:*** Nozinan; ***Mex.:*** Levocina; Sinogan; ***Neth.:*** Nozinan; ***Norw.:*** Nozinan; ***NZ:*** Nozinan; ***Philipp.:*** Nozinan; ***Pol.:*** Tisercin; ***Port.:*** Nozinan; ***Rus.:*** Tisercin (Тизерцин); ***Spain:*** Sinogan; ***Swed.:*** Nozinan; ***Switz.:*** Nozinan; ***UK:*** Levinan; Nozinan; ***Venez.:*** Sinogan.

Loprazolam Mesilate *(BANM, rINNM)*

HR-158; Loprazolam, Mésilate de; Loprazolam Mesylate; Loprazolam Methanesulphonate; Loprazolami Mesilas; Mesilato de loprazolam; RU-31158. 6-(2-Chlorophenyl)-2,4-dihydro-2-(4-methylpiperazin-1-ylmethylene)-8-nitroimidazo[1,2-*a*][1,4]benzodiazepin-1-one methanesulphonate monohydrate.

Лопразолама Мезилат

$C_{23}H_{21}ClN_6O_3,CH_4O_3S,H_2O$ = 579.0.

CAS — 61197-73-7 (loprazolam); 70111-54-5 (anhydrous loprazolam mesilate).

ATC — N05CD11.

ATC Vet — QN05CD11.

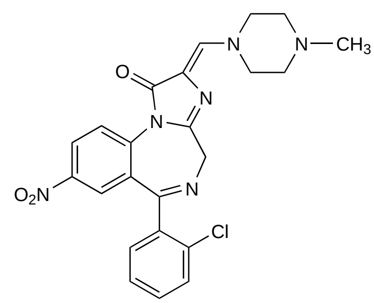

(loprazolam)

Pharmacopoeias. In *Br.*

BP 2008 (Loprazolam Mesilate). A yellow crystalline powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 0.5 to 1 mg of loprazolam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Porphyria. Loprazolam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Dorling MC, Hindmarch I. Pharmacokinetic profile of loprazolam in 12 young and 12 elderly healthy volunteers. *Drugs Exp Clin Res* 2001; **27:** 151–9.

Uses and Administration

Loprazolam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p.992).

Loprazolam mesilate is usually used for its hypnotic properties in the short-term management of insomnia (p.957), in usual oral doses equivalent to 1 mg of loprazolam at night. Dosage may be increased to up to 2 mg if necessary. A starting dose of 0.5 mg increased to a maximum of 1 mg may be appropriate for elderly or debilitated patients.

Preparations

BP 2008: Loprazolam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dormonoct; ***Belg.:*** Dormonoct; ***Fr.:*** Havlane; ***Ger.:*** Sonin; ***Neth.:*** Dormonoct; ***Port.:*** Dormonoct; ***S.Afr.:*** Dormonoct; ***Spain:*** Somnovit.

Lorazepam *(BAN, USAN, rINN)*

Loratsepaami; Lorazépam; Lorazepám; Lorazepamas; Lorazepamum; Wy-4036. 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepin-2-one.

Лоразепам

$C_{15}H_{10}Cl_2N_2O_2$ = 321.2.

CAS — 846-49-1.

ATC — N05BA06.

ATC Vet — QN05BA06.

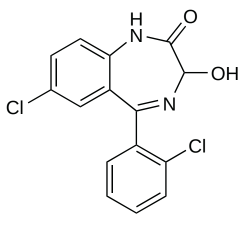

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of lorazepam:
Benzo; Somnios.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Lorazepam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; sparingly or slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Lorazepam). A white or practically white, practically odourless powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Visual incompatibility has been noted with lorazepam and sargramostim[1] or aztreonam.[2]

1. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49:** 402–6.
2. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 1086–90.

Solubility. The solubility of lorazepam in fluids for intravenous use (water, glucose injection, lactated Ringer's injection, and sodium chloride injection) was greatest in glucose injection (5%) at 62 micrograms/mL and lowest in sodium chloride injection (0.9%) at 27 micrograms/mL;[1] these differences in solubility appeared to be pH related. Commercial injections are reported to contain polyethylene glycol in propylene glycol to overcome this poor solubility. However, precipitation has been noted[2] in solutions prepared by dilution of lorazepam injection with sodium chloride injection (0.9%) to a concentration of 500 micrograms/mL. One group of workers[3] have reported that they had overcome such problems with precipitation by using glucose injection (5%) as a diluent and by avoiding final concentrations of lorazepam between 0.08 mg/mL and 1 mg/mL. It was suggested that the propylene glycol in the mixture might account for the unusual concentration effect. Such recommendations have been adopted by another group[4] although they observed that precipitation occurred if a formulation of lorazepam containing 4 mg/mL was used to prepare the injection; no precipitation was noted when a formulation containing 2 mg/mL was used. The group also commented that, in the USA, licensed product information for lorazepam injection advises that admixtures should be prepared with the 2 mg/mL formulation only.

1. Newton DW, *et al.* Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* 1983; **40:** 424–7.
2. Boullata JI, *et al.* Precipitation of lorazepam infusion. *Ann Pharmacother* 1996; **30:** 1037–8.
3. Volles DF, *et al.* More on usability of lorazepam admixtures for continuous infusion. *Am J Health-Syst Pharm* 1996; **53:** 2753–4.
4. Levanda M. Noticeable difference in admixtures prepared from lorazepam 2 and 4 mg/ml. *Am J Health-Syst Pharm* 1998; **55:** 2305.

Sorption. Significant loss of lorazepam has been reported from solutions stored in PVC[1] or polypropylene[2] giving equipment; polyolefin[3-5] or glass[6] equipment appears to be more suitable.

1. Hoey LL, *et al.* Lorazepam stability in parenteral solutions for continuous intravenous administration. *Ann Pharmacother* 1996; **30:** 343–6.
2. Stiles ML, *et al.* Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. *Am J Health-Syst Pharm* 1996; **53:** 1583–8.
3. Trissel LA, Pearson SD. Storage of lorazepam in three injectable solutions in polyvinyl chloride and polyolefin bags. *Am J Hosp Pharm* 1994; **51:** 368–72.
4. Norenberg JP, *et al.* Stability of lorazepam in 0.9% sodium chloride stored in polyolefin bags. *Am J Health-Syst Pharm* 2004; **61:** 1039–41.
5. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
6. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 500 micrograms of lorazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. Pain and a sensation of burning have occurred following injection of lorazepam.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of lorazepam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Free lorazepam concentrations in the breast milk of 4 mothers ranged from 8 to 9 nanograms/mL four hours after receiving a 3.5-mg oral dose.[2] This represented about 15 to 26% of the concentration in plasma, and was probably sufficiently low to cause no adverse effects in breast-fed infants.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; **57:** 1042–3.

Effects on the blood. A case of pancytopenia associated with oral lorazepam was reported[1] in 1988; only 5 instances of thrombocytopenia and none of leucopenia had been reported to the UK CSM or the UK manufacturers over the previous 13 years.

1. El-Sayed S, Symonds RP. Lorazepam induced pancytopenia. *BMJ* 1988; **296:** 1332.

Effects on fluid and electrolyte homoeostasis. Inappropriate secretion of antidiuretic hormone related to ingestion of lorazepam was considered to be the cause of hyponatraemia in an 81-year-old woman.[1]

1. Engel WR, Grau A. Inappropriate secretion of antidiuretic hormone associated with lorazepam. *BMJ* 1988; **297:** 858.

Effects on the nervous system. For reference to extrapyramidal disorders associated with use of lorazepam, see Diazepam, p.988.

The elderly. For discussion of the need for reduced dosage of benzodiazepines in elderly patients, including mention of lorazepam, see Diazepam, p.989.

Formulation. There have been reports of toxicity, presumed to be due to polyethylene glycol[1,2] or propylene glycol,[3] after prolonged parenteral use of lorazepam; polyethylene glycol in propylene glycol is included as a solubiliser in lorazepam solutions. Diarrhoea in an infant given large enteral doses of lorazepam or diazepam solutions may have been due to the combined osmotic effect of polyethylene glycol and propylene glycol in these preparations.[4]

1. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; **29:** 1110–4.
2. Tayar J *et al.* Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002; **346:** 1253–4.
3. Seay RE, *et al.* Possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; **31:** 647–8. Woycik CL, Walker PC. Correction and comment: possible toxicity from propylene glycol in injectable drug preparations. *ibid.*: 1413.
4. Marshall JD, *et al.* Diarrhea associated with enteral benzodiazepine solutions. *J Pediatr* 1995; **126:** 657–9.

Hepatic impairment. Lorazepam is contra-indicated in severe hepatic impairment; patients with mild to moderate impairment may require reduced doses. Although the elimination half-life of lorazepam was increased in 13 patients with alcoholic cirrhosis compared with 11 control subjects, this was not associated with an impairment in systemic plasma clearance.[1] With the exception of a modest decrease in the extent of plasma protein binding, acute viral hepatitis had no effect on the disposition kinetics of lorazepam.

1. Kraus JW, *et al.* Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; **24:** 411–19.

Local reactions. Of 40 patients given a single intravenous dose of lorazepam 4 mg three had local thrombosis 2 to 3 days later and 6 had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution].

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2:** 1384–5.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Lorazepam is readily absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 90%; peak plasma concentrations are reported to occur about 2 hours after an oral dose. The absorption profile after intramuscular injection is similar to that after oral dosage.

Lorazepam is about 85% bound to plasma proteins. It crosses the blood-brain barrier and the placenta; it is also distributed into breast milk. Lorazepam is metabolised in the liver to the inactive glucuronide, and excreted in urine. The elimination half-life has been reported to range from about 10 to 20 hours.

◊ References.

1. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; **6:** 89–105.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

Children. References to the pharmacokinetics of lorazepam in children.

1. Relling MV, *et al.* Lorazepam pharmacodynamics and pharmacokinetics in children. *J Pediatr* 1989; **114:** 641–6.

NEONATES. References to slow elimination of lorazepam by neonates.

1. Cummings AJ, Whitelaw AGL. A study of conjugation and drug elimination in the human neonate. *Br J Clin Pharmacol* 1981; **12:** 511–15.
2. McDermott CA, *et al.* Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992; **120:** 479–83.
3. Reiter PD, Stiles AD. Lorazepam toxicity in a premature infant. *Ann Pharmacother* 1993; **27:** 727–9.

Distribution. Evidence that lorazepam undergoes enterohepatic recirculation with possible first-pass metabolism.[1]

1. Herman RJ, *et al.* Disposition of lorazepam in human beings: enterohepatic recirculation and first-pass effect. *Clin Pharmacol Ther* 1989; **46:** 18–25.

CNS. In a study involving 6 healthy subjects, peak plasma-lorazepam concentrations were reached 5 minutes after the end of a one-minute intravenous injection.[1] CNS effects, as measured by EEG activity, were not maximal until 30 minutes after injection; they declined to baseline values slowly over 5 to 8 hours in a similar manner to plasma concentrations. In contrast, CNS effects of diazepam were maximal immediately after the injection. They also declined more rapidly than lorazepam, but again in a similar way to plasma concentrations. Studies in *mice* suggested that the slow onset of action of lorazepam that has been reported by some is at least partly explained by a delay in passage from systemic blood into brain tissue.

1. Greenblatt DJ, *et al.* Kinetic and dynamic study of intravenous lorazepam; comparison with intravenous diazepam. *J Pharmacol Exp Ther* 1989; **250:** 134–40.

Uses and Administration

Lorazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders (p.952), as a hypnotic in the short-term management of insomnia (p.957), and as an anticonvulsant in the management of status epilepticus (p.469). When used in the treatment of status epilepticus lorazepam has a prolonged antiepileptic action and may be the preferred initial treatment if intravenous access is available. It is also used for its sedative and amnestic properties in premedication and as an adjunct in regimens for the control of nausea and vomiting associated with cancer chemotherapy (p.1700).

Lorazepam is usually given orally or by injection as the base although the pivalate is available for oral use in some countries. Sublingual tablets are used in some countries in doses similar to those for standard tablets. The intramuscular route is usually only used when oral or intravenous dosage is not possible. Injections should usually be diluted before use; intravenous injections should be given at a rate of not more than 2 mg/minute into a large vein. Lorazepam should be given in reduced dosage to elderly or debilitated patients; half the usual adult dose, or less, may be sufficient.

The usual oral dose of lorazepam for the treatment of **anxiety disorders** is 1 to 6 mg daily in 2 or 3 divided doses with the largest dose taken at night; up to 10 mg daily has been given. A dose of 25 to

30 micrograms/kg may be given by injection every 6 hours for acute anxiety. Lorazepam has also been used for **panic attacks**. A suggested dose in the *BNF* is 3 to 5 mg daily. A single oral dose of 1 to 4 mg at bedtime may be given for **insomnia** associated with anxiety. However, the MHRA in the UK advises against the use of oral daily doses of lorazepam above 4 mg for anxiety and phobia, and 2 mg for insomnia.

For **premedication** an oral dose of 2 to 3 mg may be given the night before the operation; the *BNF* suggests that this may be followed if necessary the next morning by a smaller dose. Alternatively, 2 to 4 mg may be given 1 to 2 hours before an operation. In the UK, although lorazepam tablets are not licensed for premedication of *children* under 5 years of age, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given orally at least 1 hour before an operation to those aged 1 month to 12 years; the same dose may also be given the night before, in addition to, or to replace the dose before, the operation. Lorazepam may also be given parenterally for premedication; a dose of 50 micrograms/kg may be given 30 to 45 minutes before the operation if given intravenously or 1 to 1½ hours before if given intramuscularly. Again, although unlicensed in the UK for premedication of children under 12 years of age, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given by slow intravenous injection to those aged 1 month to 18 years.

In the management of **status epilepticus** 4 mg may be given as a single intravenous dose; the *BNF* suggests that this may be repeated once after 10 minutes if seizures recur. A dose of 2 mg has been suggested for *children* by one manufacturer (*Wyeth*). Alternatively, the *BNFC* suggests that neonates and children up to 12 years of age may be given 100 micrograms/kg (maximum of 4 mg) as a single dose sublingually, rectally, or by slow intravenous injection; this may be repeated once after 10 minutes if necessary.

In patients receiving modestly emetogenic chemotherapy, lorazepam 1 to 2 mg orally may be added to antiemetic therapy with domperidone or metoclopramide, for the prophylaxis of **nausea and vomiting**. The addition of lorazepam may be helpful in the prevention of anticipatory symptoms because of its sedative and amnestic effects.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders and the value of benzodiazepines, see p.954.

References.

1. Bieniek SA, *et al*. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; **18:** 57–62.

Nausea and vomiting. References.

1. Malik IA, *et al*. Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin: a prospective randomized trial. *Am J Clin Oncol* 1995; **18:** 170–5.

Premedication and sedation. Lorazepam is used as a premedicant (p.1780) and as a sedative for therapeutic and investigative procedures such as dental treatment (p.956) and endoscopy (p.956), and also in intensive care (p.957).

References.

1. Maltais F, *et al*. A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; **109:** 1195–8.

Substance dependence. Lorazepam has been used in the management of symptoms of alcohol withdrawal (p.1626).

References.

1. D'Onofrio G, *et al*. Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; **340:** 915–9.

Preparations

BP 2008: Lorazepam Injection; Lorazepam Tablets;
USP 31: Lorazepam Injection; Lorazepam Oral Concentrate; Lorazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aplacasse; Calmatron; Emotival; Kalmalin; Lorezan; Microzepam; Nervistop; Sedatival†; Sidenar; Trapax; Tratenamin†; ***Austral.:*** Ativan; ***Austria:*** Merlit; Temesta; ***Belg.:*** Docloraze; Lauracalm; Lorazemed; Lorazetop; Loridem; Optisedine; Serenase; Temesta; Vigiten†; ***Braz.:*** Calmogenol†; Lorapan; Lorax; Lorazefast; Lorazepan†; Max-Pax; Mesmerin; ***Canad.:*** Ativan; Novo-Lorazem; Nu-Loraz; ***Chile:*** Abinol; Amparax; ***Cz.:*** Loram†; Tavor†; ***Denm.:*** Lorabenz; Temesta; ***Fin.:*** Temesta; ***Fr.:*** Equitam†; Temesta; ***Ger.:*** duralozam†; Laubeel; Somagerol; Tavor; Tolid; ***Gr.:*** Aripax; Ativan; Cicletan†; Dorm; Modium; Nifalin; Novhepar; Proneurit†; Tavor; Titus; Trankilium; ***Hong Kong:*** Ativan†; LAtiwen; Lorans; Lorivan; Silence; ***India:*** Ativan; Calmese; Larpose; ***Indon.:*** Ativan; Merlopam; Renaquil; ***Irl.:*** Ativan; ***Israel:*** Lorivan; ***Ital.:*** Control; Loralin; Lorans; Tavor; Zeloram; ***Malaysia:*** Ativan; Lorans; ***Mex.:*** Ativan; Sinestron†; ***Neth.:*** Temesta; ***NZ:*** Ativan; Lorapam†; ***Pol.:*** Lorafen; ***Port.:*** Ansilor; Lorenin; Lorsedal; Rialam; ***Rus.:*** Lorafen (Лорафен); ***S.Afr.:*** Ativan; Tranqipam; ***Singapore:*** Ativan; Lorans; ***Spain:*** Donix; Idalprem; Orfidal; Placinoral; Sedicepan; ***Swed.:*** Temesta; ***Switz.:*** Lorasifar; Sedazin; Temesta; ***Thai.:*** Anta; Anxira; Ativan†; Lonza; Lora; Loramed; Lorapam; Lorazene†; Lorazep; Ora; Razepam†; Tranavan†; ***Turk.:*** Ativan; ***UK:*** Ativan; ***USA:*** Ativan; ***Venez.:*** Ativan.

Multi-ingredient: ***Austria:*** Somnium†; ***Switz.:*** Somnium.

Lormetazepam *(BAN, USAN, rINN)*

Lormetatsepaami; Lormétazépam; Lormetazepamum; Wy-4082. (*RS*)-7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-1,4-benzodiazepin-2-one.

Лорметазепам

$C_{16}H_{12}Cl_2N_2O_2$ = 335.2.
CAS — 848-75-9.
ATC — N05CD06.
ATC Vet — QN05CD06.

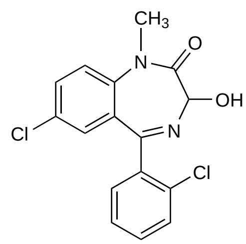

Pharmacopoeias. In *Br.*
BP 2008 (Lormetazepam). A white crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 0.5 to 1 mg of lormetazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Lormetazepam is rapidly absorbed from the gastrointestinal tract and metabolised to the inactive glucuronide. The terminal half-life is reported to be about 11 hours.

◊ A brief review of the pharmacokinetics of lormetazepam.[1]

1. Greenblatt DJ, *et al*. Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.

Uses and Administration

Lormetazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is mainly used as a hypnotic in the short-term management of insomnia (p.957) in usual oral doses of 0.5 to 1.5 mg at night. A dose of 500 micrograms is recommended for elderly or debilitated patients. Lormetazepam is also used in some countries for premedication (p.1780).

Preparations

BP 2008: Lormetazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dilamet†; ***Austria:*** Noctamid; ***Belg.:*** Doclormeta; Keladormet; Loramet; Loranka; Lormetamed; Metatop; Noctacalm; Noctamid; Octonox; Sedaben; Stilaze; ***Chile:*** Nocton; ***Denm.:*** Pronoctan; ***Fr.:*** Noctamide; ***Ger.:*** Ergocalm; Loretam; Noctamid; ***Gr.:*** Loramet; ***Hong Kong:*** Loramet†; ***Irl.:*** Noctamid; ***Ital.:*** Axilium; Ipnolor; Luzul; Mexylor; Minias; ***Neth.:*** Loramet†; Noctamid; ***NZ:*** Noctamid; ***Pol.:*** Noctofer; ***Port.:*** Noctamid†; ***S.Afr.:*** Loramet; Noctamid; ***Singapore:*** Loramet; ***Spain:*** Aldosomnil; Loramet; Noctamid; ***Switz.:*** Loramet; Noctamid; ***Thai.:*** Loramet†.

Loxapine *(BAN, USAN, rINN)*

CL-62362; Loksapiini; Loxapin; Loxapina; Loxapinum; Oxilapine; SUM-3170. 2-Chloro-11-(4-methylpiperazin-1-yl)dibenz[*b,f*]-[1,4]oxazepine.

Локсапин

$C_{18}H_{18}ClN_3O$ = 327.8.
CAS — 1977-10-2.
ATC — N05AH01.
ATC Vet — QN05AH01.

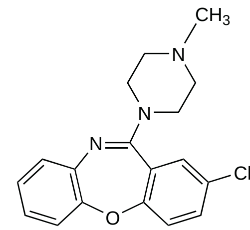

Loxapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de loxapina; Loxapine, Chlorhydrate de; Loxapini Hydrochloridum.

Локсапина Гидрохлорид

$C_{18}H_{18}ClN_3O,HCl$ = 364.3.
ATC — N05AH01.
ATC Vet — QN05AH01.

Loxapine Succinate *(BANM, USAN, rINNM)*

CL-71563; Loxapine, Succinate de; Loxapini Succinas; Succinato de loxapina.

Локсапина Суксинат

$C_{18}H_{18}ClN_3O,C_4H_6O_4$ = 445.9.
CAS — 27833-64-3.
ATC — N05AH01.
ATC Vet — QN05AH01.

Pharmacopoeias. In *US.*
USP 31 (Loxapine Succinate). A white to yellowish, odourless, crystalline powder. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Other adverse effects reported include nausea and vomiting, seborrhoea, dyspnoea, ptosis, headache, paraesthesia, facial flush, weight gain or loss, and polydipsia.

Abuse. There has been a report of 3 cases of loxapine succinate abuse.[1]

1. Sperry L, *et al*. Loxapine abuse. *N Engl J Med* 1984; **310:** 598.

Effects on carbohydrate metabolism. Reversible nonketotic hyperglycaemia, coma, and delirium developed in a patient receiving loxapine 150 mg daily in addition to lithium therapy.[1] Symptoms improved on stopping loxapine, but subsequently recurred when the patient was given amoxapine. The causative agent may have been 7-hydroxyamoxapine, a common metabolite of both amoxapine and loxapine.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Mania. A patient, initially diagnosed as having schizophrenia, developed manic symptoms after receiving loxapine.[1] The diagnosis was revised to schizoaffective disorder but it was suspected that loxapine had a role in the emergence of the affective symptoms. As loxapine shares common metabolites with the antidepressant amoxapine it was suggested that an antidepressant effect might have precipitated the manic symptoms.

1. Gojer JAC. Possible manic side-effects of loxapine. *Can J Psychiatry* 1992; **37:** 669–70.

Overdosage. An 8-year-old child was treated with activated charcoal within 30 minutes of being given 375 mg of loxapine by accident.[1] The child became drowsy and was asleep but arousable 1 hour after ingestion. The degree of sedation appeared to peak after 3.75 hours and the child was discharged about 20 hours after ingestion.

1. Tarricone NW. Loxitane overdose. *Pediatrics* 1998; **101:** 496.

Porphyria. Loxapine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Loxapine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 2 hours. It is very rapidly and extensively metabolised and there is evidence for a first-pass effect. It is mainly excreted in the urine, in the form of its conjugated metabolites, with smaller amounts appearing in the faeces as unconjugated metabolites; a substantial proportion of a dose is excreted in the first 24 hours. The major metabolites of loxapine are the active 7- and 8-hydroxyloxapine, which are conjugated to the glucuronide or sulfate; other metabolites include hydroxyloxapine-*N*-oxide, loxapine-*N*-oxide, and hydroxydesmethylloxapine (hydroxyamoxapine). Loxapine is widely distributed and is thought, on the basis of *animal* studies, to cross the placenta and be distributed into breast milk.

Uses and Administration

Loxapine is a dibenzoxazepine with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It is given orally as the succinate and by intramuscular injection as the base in the treatment of psychoses including schizophrenia. Doses are expressed in terms of the base; loxapine succinate 34 mg is equivalent to about 25 mg of loxapine.

The usual oral dose is 20 to 50 mg daily initially, in 2 divided doses, increased according to response over the next 7 to 10 days to 60 to 100 mg daily or more, in 2 to 4 divided doses; the maximum recommended dose is 250 mg daily. Maintenance doses are usually in the range of 20 to 60 mg daily, in divided doses. For the control of acute conditions it is given by intramuscular injection in daily doses of up to 300 mg in 2 or 3 divided doses. Reduced dosage may be required in elderly patients.

Loxapine has also been given orally and by intramuscular injection as the hydrochloride.

Disturbed behaviour. For a discussion of the use and limitations of antipsychotics such as loxapine in patients with disturbed behaviour, see p.954.

References.

1. Carlyle W, *et al*. Aggression in the demented patient: a double-blind study of loxapine versus haloperidol. *Int J Clin Psychopharmacol* 1993; **8:** 103–8.

Schizophrenia. A brief review of loxapine[1] found no conclusive evidence that it was particularly effective in patients with paranoid schizophrenia (p.955). A subsequent systematic review considered that the limited evidence did not indicate a clear difference in its effects from other antipsychotics.[2]

1. Anonymous. Clozapine and loxapine for schizophrenia. *Drug Ther Bull* 1991; **29:** 41–2.
2. Chakrabarti A, *et al*. Loxapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 19/03/08).

Preparations

USP 31: Loxapine Capsules.

Proprietary Preparations (details are given in Part 3)
Canad.: Loxapac; ***Fr.:*** Loxapac; ***Gr.:*** Loxapac†; ***India:*** Loxapac; ***Spain:*** Desconex†; ***UK:*** Loxapac†; ***USA:*** Loxitane.

Medazepam *(BAN, rINN)*

Medatsepaami; Médazépam; Medazepamum. 7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine.

Медазепам

$C_{16}H_{15}ClN_2$ = 270.8.
CAS — 2898-12-6.
ATC — N05BA03.
ATC Vet — QN05BA03.

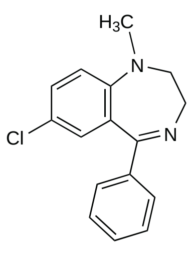

Pharmacopoeias. In *Jpn.*

Medazepam Hydrochloride *(USAN)*

Medazepam, hidrocloruro de; Ro-5-4556.

$C_{16}H_{15}ClN_2,HCl$ = 307.2.
CAS — 2898-11-5.
ATC — N05BA03.
ATC Vet — QN05BA03.

Profile

Medazepam is a long-acting benzodiazepine with properties similar to those of diazepam (p.986). It has been given for the short-term treatment of anxiety disorders (p.952). A usual oral dose is 10 to 30 mg daily in divided doses; in severe conditions up to 60 mg daily has been given. Reduced doses should be given to elderly or debilitated patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ansilan; Rusedal†; ***Ger.:*** Rudotel; Rusedal; ***Hung.:*** Nobrium; Rudotel; Rusedal; ***Pol.:*** Rudotel; ***Rus.:*** Rudotel (Рудотель).

Multi-ingredient: ***Ital.:*** Debrum; ***Spain:*** Nobritol; ***Turk.:*** Tanko-Buskas; Tranko-Buskas.

Medetomidine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de medetomidina; Medetomidiinihydrokloridi; Médétomidine, Chlorhydrate de; Medetomidinhydroklorid; Medetomidini Hydrochloridum; MPV-785. (±)-4-[1-(2,3-Xylyl)ethyl]imidazole monohydrochloride.

Медетомидина Гидрохлорид

$C_{13}H_{16}N_2,HCl$ = 236.7.
CAS — 86347-15-1 (medetomidine hydrochloride); 86347-14-0 (medetomidine).

Profile

Medetomidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties. It is used as the hydrochloride in veterinary medicine.

Its isomer dexmedetomidine (p.986) is used as the hydrochloride in intensive care.

Melperone Hydrochloride *(BANM, rINNM)*

FG-5111; Flubuperone Hydrochloride; Hidrocloruro de melperona; Melperon Hidroklorür; Melpérone, Chlorhydrate de; Melperoni Hydrochloridum; Methylperone Hydrochloride. 4′-Fluoro-4-(4-methylpiperidino)butyrophenone hydrochloride.

Мелперона Гидрохлорид

$C_{16}H_{22}FNO,HCl$ = 299.8.
CAS — 3575-80-2 (melperone); 1622-79-3 (melperone hydrochloride).
ATC — N05AD03.
ATC Vet — QN05AD03.

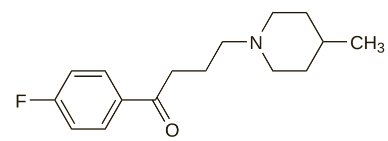

(melperone)

Profile

Melperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It is given as the hydrochloride by mouth or by intramuscular injection for the management of psychoses such as schizophrenia (p.955) and in disturbed behaviour (p.954); doses are expressed as the hydrochloride. A usual oral dose is up to 400 mg daily in divided doses. In acute conditions it may be given intramuscularly in doses of 25 to 100 mg repeated to a usual maximum of 200 mg daily.

Cardiac arrhythmias. Melperone has been reported to have class III electrophysiologic and antiarrhythmic activity[1,2] but its clinical use as an antiarrhythmic would be limited by a high incidence of adverse effects.[2] For a discussion of the cardiovascular effects of antipsychotics in general, see under Chlorpromazine, p.970.

1. Møgelvang JC, *et al*. Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208:** 61–4.
2. Hui WKK, *et al*. Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15:** 144–9.

Pharmacokinetics. References.

1. Köppel C, *et al*. Gas chromatographic-mass spectrometric study of urinary metabolism of melperone. *J Chromatogr Biomed Appl* 1988; **427:** 144–50.

Schizophrenia. References[1-3] to the use of melperone in schizophrenia. It has been suggested that melperone should be considered as an atypical antipsychotic in view of the low incidence of extrapyramidal effects associated with its use.

1. Meltzer HY, *et al*. Melperone in the treatment of neuroleptic-resistant schizophrenia. *Psychiatry Res* 2001; **105:** 201–9.
2. Sumiyoshi T, *et al*. The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. *Schizophr Res* 2003; **59:** 7–16.
3. Sumiyoshi T, *et al*. A comparison of two doses of melperone, an atypical antipsychotic drug, in the treatment of schizophrenia. *Schizophr Res* 2003; **62:** 65–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Buronil; Neuril†; ***Belg.:*** Buronil; ***Cz.:*** Buronil; ***Denm.:*** Buronil; ***Fin.:*** Buronil†; Melpax; ***Ger.:*** Eunerpan; Harmosin; Mel-Puren; Melneurin; Melperomerck; ***Port.:*** Bunil; ***Swed.:*** Buronil; ***Turk.:*** Buronon.

Meprobamate *(BAN, rINN)*

Meprobamaatti; Meprobamát; Meprobamat; Meprobamatas; Méprobamate; Meprobamato; Meprobamatum; Meprotanum. 2-Methyl-2-propyltrimethylene dicarbamate.

Мепробамат

$C_9H_{18}N_2O_4$ = 218.3.
CAS — 57-53-4.
ATC — N05BC01.
ATC Vet — QN05BC01.

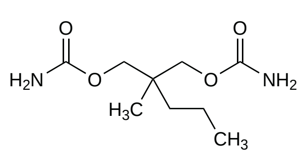

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of meprobamate: Miltown; Mother's little helper; Uncle Miltie.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*

Ph. Eur. 6.2 (Meprobamate). A white or almost white, crystalline or amorphous powder. Slightly soluble in water; freely soluble in alcohol.

USP 31 (Meprobamate). A white powder having a characteristic odour. Slightly soluble in water; freely soluble in alcohol and in acetone; practically insoluble or insoluble in ether. Store in airtight containers.

Dependence and Withdrawal

As for the barbiturates (see Amobarbital, p.962).

Adverse Effects and Treatment

Drowsiness is the most frequent adverse effect of meprobamate. Other effects include nausea, vomiting, diarrhoea, paraesthesia, weakness, and CNS effects such as headache, paradoxical excitement, dizziness, ataxia, and disturbances of vision. There may be hypotension, tachycardia, and cardiac arrhythmias. Hypersensitivity reactions occur occasionally. These may be limited to skin rashes, urticaria, and purpura or may be more severe with angioedema, bronchospasm, or anuria. Erythema multiforme or Stevens-Johnson syndrome, and exfoliative or bullous dermatitis have been reported.

Blood disorders including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia have occasionally been reported.

Overdosage with meprobamate produces symptoms similar to those of barbiturate overdosage (see Amobarbital, p.962), and is managed similarly.

Overdosage. Two children aged 2 and 2.5 years recovered with conservative management alone after overdosage of meprobamate with bendroflumethiazide despite measured plasma-meprobamate concentrations of 170 and 158 micrograms/mL, respectively.[1] Although it had been recommended that haemoperfusion should be considered at plasma-meprobamate concentrations above 100 micrograms/mL, the authors considered that experience with adults suggested haemoperfusion should normally only be considered at plasma concentrations above 200 micrograms/mL.

1. Dennison J, *et al*. Meprobamate overdosage. *Hum Toxicol* 1985; **4:** 215–17.

Precautions

Meprobamate should be used with caution in patients with hepatic or renal impairment, depression, muscle weakness, and, as with all sedatives, in patients with impaired respiratory function. Meprobamate should be given with care to elderly or debilitated patients. Meprobamate may induce seizures in patients with a history of epilepsy.

Meprobamate may cause drowsiness; affected patients should not drive or operate machinery.

Breast feeding. The *BNF* considers that the use of meprobamate should be avoided in breast feeding mothers as concentrations in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in the infant.

Porphyria. Meprobamate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Studies on the use of meprobamate during pregnancy.

1. Milkovich L, van den Berg BJ. Effects of prenatal meprobamate and chlordiazepoxide hydrochloride on human embryonic and fetal development. *N Engl J Med* 1974; **291:** 1268–71.
2. Crombie DL, *et al*. Fetal effects of tranquilizers in pregnancy. *N Engl J Med* 1975; **293:** 198–9.
3. Hartz SC, *et al*. Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. *N Engl J Med* 1975; **292:** 726–8.

Interactions

The sedative effects of meprobamate are enhanced by CNS depressants including alcohol. Meprobamate is capable of inducing hepatic microsomal enzyme systems involved in drug metabolism: the metabolism of other drugs may be enhanced if given concurrently.

Pharmacokinetics

Meprobamate is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after ingestion. Meprobamate is widely distributed. It is extensively metabolised in the liver and is excreted in the urine mainly as an inactive hydroxylated metabolite and its glucuronide conjugate. About 10% of a dose is excreted unchanged. Meprobamate has a half-life reported to range from about 6 to 17 hours, although this may be prolonged after chronic use.

It diffuses across the placenta and appears in breast milk at concentrations of up to 4 times those in the maternal plasma.

Uses and Administration

Meprobamate is a carbamate with hypnotic, sedative, and some muscle relaxant properties, although in therapeutic doses its sedative effect rather than a direct action may be responsible for muscle relaxation. It has been used in the short-term treatment of anxiety disorders (p.952) and also for the short-term management of insomnia (p.957) but has largely been superseded by other drugs. Meprobamate has sometimes been used, alone or with an analgesic, in the management of muscle spasm (p.1887) and painful musculoskeletal disorders but such use is no longer considered appropriate.

The usual anxiolytic dose is 400 mg orally three or four times daily to a maximum of 2.4 g daily. In elderly patients, no more than half the usual adult dose has been suggested.

Preparations

USP 31: Meprobamate Oral Suspension; Meprobamate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Cyrpon; Epikur; Microbamat; Miltaun; ***Belg.:*** Pertranquil†; Reposo-Mono†; ***Fr.:*** Equanil; ***Ger.:*** Visano N†; Visano-mini N†; ***Hung.:*** Andaxin; ***Israel:*** Mepro; ***Ital.:*** Quanil; ***S.Afr.:*** Equanil; ***Switz.:*** Meprodil; ***USA:*** Miltown†; Neuramate†.

Multi-ingredient: ***Arg.:*** Hidromens†; ***Canad.:*** 282 Mep†; ***Chile:*** Butartrol; ***Fin.:*** Anervan; Crampiton; Potentol†; ***Fr.:*** Kaologeais; Mepronizine; Palpipax†; Precyclan; ***Indon.:*** Deparon; ***Mex.:*** Artrilan; ***Norw.:*** Anervan; ***Port.:*** Vitasma†; ***S.Afr.:*** Adco-Payne; Antipyn Forte; Ban Pain; Briscopyn; Equagesic; Fevapar; Go-Pain; Medipyn; Megapyn; Meprogesic; Mepromol; Micro-Gesic; Nopyn†; Noralget†; Painagon; Painrite; Pynmed; Salterpyn; Spectrapain Forte; Stilpane; Stopayne; Supragesic; Synaleve; Tenston; Trinagesic; Vacudol Forte; Xeramax†; Xerogesic†; ***Swed.:*** Anervan; ***UK:*** Paxidal; ***USA:*** Equagesic; Micrainin†.

Mesoridazine *(BAN, USAN, rINN)*

Mesoridatsiini; Mesoridazin; Mesoridazina; Mésoridazine; Mesoridazinum; Mesuridazine; Mezoridazin; NC-123; TPS-23. 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylsulphinyl)phenothiazine.

Мезоридазин

$C_{21}H_{26}N_2OS_2$ = 386.6.
CAS — 5588-33-0.
ATC — N05AC03.
ATC Vet — QN05AC03.

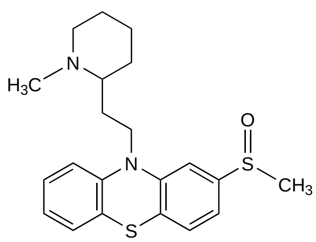

Mesoridazine Besilate *(BANM, rINNM)*

Bencenosulfonato de mesoridazina; Mesoridazine Benzenesulphonate; Mésoridazine, Bésilate de; Mesoridazine Besylate; Mesoridazini Besilas; Mesuridazine Benzenesulphonate.

Мезоридазина Безилат

$C_{21}H_{26}N_2OS_2,C_6H_6O_3S$ = 544.7.
CAS — 32672-69-8 (mesoridazine besilate).
ATC — N05AC03.
ATC Vet — QN05AC03.

Pharmacopoeias. In *US.*

USP 31 (Mesoridazine Besylate). A white to pale yellowish powder having not more than a faint odour. Soluble 1 in 1 of water, 1 in 11 of alcohol, 1 in 3 of chloroform, and 1 in 6300 of ether; freely soluble in methyl alcohol. pH of a freshly prepared 1 in 100 solution is between 4.2 and 5.7. Store in airtight containers. Protect from light.

Profile

Mesoridazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain and is a metabolite of thioridazine (p.1031). Mesoridazine has usually been given as the besilate, orally or by intramuscular injection.

Mesoridazine has been shown to prolong the QT interval in a dose-related manner which increases the risk of life-threatening arrhythmias such as torsade de pointes and sudden death; consequently its use in schizophrenia has been restricted. Details of these restrictions are given under Precautions of Thioridazine, the parent drug of mesoridazine (see p.1031). Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential, and it is no longer available in many countries.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of mesoridazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Preparations

USP 31: Mesoridazine Besylate Injection; Mesoridazine Besylate Oral Solution; Mesoridazine Besylate Tablets.

Proprietary Preparations (details are given in Part 3)
Turk.: Lidanil; ***USA:*** Serentil†.

Methaqualone *(BAN, USAN, rINN)*

CI-705; CN-38703; Metacualona; Metakvalon; Metakvalonas; Metakvaloni; Methachalonum; Methakvalon; Méthaqualone; Methaqualonum; QZ-2; R-148; TR-495. 2-Methyl-3-*o*-tolylquinazolin-4-(3*H*)-one.

Метахалон

$C_{16}H_{14}N_2O$ = 250.3.
CAS — 72-44-6 (methaqualone); 340-56-7 (methaqualone hydrochloride).
ATC — N05CM01.
ATC Vet — QN05CM01.

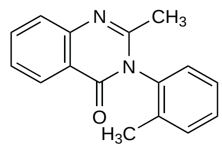

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methaqualone:
300's; 714; 714s; Bandits; Beiruts; Blou Bulle; Blue Balls; Blue bulls; Disco biscuits; Down and dirtys; Drunfos; Drunken Monkey; Ewings; Flamingos; Flowers; Four-strokes; Fuckers; Genuines; Germans; Golfsticks; Gorilla Biscuits; Humbles; Joe Fridays; Knoppies; Lemmon 714; Lemons; Lennons; Lewds; Lizards; Loss-of-memory; Love drug; Lovers; Ludes; Luds; Lula; Magwheels; Pressouts; Pupumala; Q; Qua; Quaa; Quaalude; Quaaludes; Quaass; Quack; Quad; Quads; Quas; Seven fourteens; Shiny Tops; Soaper; Sopor; Sopors; Sporos; Strawberries; Super Sopors; Supers; Supper; Three hundreds; Vitamin Q; Wagon Wheels; Wallbangers; Whore pills.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Methaqualone). A white or almost white, crystalline powder. Very slightly soluble in water; soluble in alcohol; dissolves in dilute sulfuric acid. Protect from light.

Profile

Methaqualone is a quinazoline derivative with hypnotic and sedative properties. It has been given orally in the short-term management of insomnia but the use of methaqualone for this purpose is no longer considered appropriate. It has also been given with diphenhydramine for an enhanced effect.

Methaqualone has been withdrawn from the market in many countries because of problems with abuse.

Adverse effects and symptoms of overdosage are similar to those of barbiturates (see Amobarbital, p.962) although cardiac and respiratory depression reportedly occur less frequently.

Abuse. Although oral abuse of methaqualone has greatly declined in developed countries after the widespread withdrawal of the tablets, smoking of (usually illicitly manufactured) methaqualone, generally in combination with cannabis and tobacco, is a major public health problem in South Africa, and some other parts of Africa and India. Although diazepam has been used to manage dependence, controlled studies to inform the management of the condition are lacking.[1]

1. McCarthy G, *et al.* Treatment for methaqualone dependence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 11/05/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Switz.:*** Toquilone compositum†.

Mexazolam *(rINN)*

CS-386; Methylcloxazolam; Mexazolamum. 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-3-methyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Мексазолам

$C_{18}H_{16}Cl_2N_2O_2$ = 363.2.
CAS — 31868-18-5.

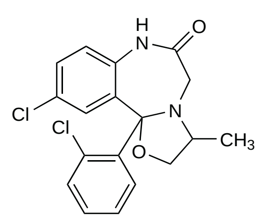

Profile

Mexazolam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given by mouth for its anxiolytic and sedative properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Sedoxil.

Midazolam *(BAN, rINN)*

Midatsolaami; Midazolám; Midazolamas; Midazolamum; Ro-21-3971. 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine.

Мидазолам

$C_{18}H_{13}ClFN_3$ = 325.8.
CAS — 59467-70-8.
ATC — N05CD08.
ATC Vet — QN05CD08.

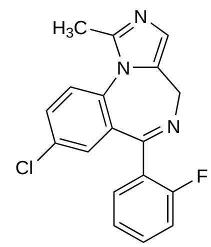

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Midazolam). A white or yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in methyl alcohol.

Midazolam Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de midazolam; Midazolam, Chlorhydrate de; Midazolami Hydrochloridum; Ro-21-3981/003.

Мидазолама Гидрохлорид

$C_{18}H_{13}ClFN_3,HCl$ = 362.2.
CAS — 59467-96-8.
ATC — N05CD08.
ATC Vet — QN05CD08.

Incompatibility. The visual compatibility of midazolam hydrochloride with a range of drugs was studied over a period of 4 hours.[1] A white precipitate was formed immediately with dimenhydrinate, pentobarbital sodium, perphenazine, prochlorperazine edisilate, and ranitidine hydrochloride. Similar incompatibility has been reported[2,3] with furosemide, thiopental, and parenteral nutrition solutions. Other workers[4] have reported that a precipitate is formed with midazolam hydrochloride if the resultant mixture has a pH of 5 or more.

1. Forman JK, Souney PF. Visual compatibility of midazolam hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1987; **44:** 2298–9.
2. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
3. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–300.
4. Swart EL, *et al.* Compatibility of midazolam hydrochloride and lorazepam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2020–2.

Stability. Licensed product information states that solutions of midazolam hydrochloride in sodium chloride 0.9%, glucose 5%, or glucose 4% with sodium chloride 0.18% are stable at room temperature for up to 24 hours, and similar solutions containing the equivalent of 0.5 mg/mL of the base were stable for 36 days[1] when stored in glass bottles at temperatures of 4° to 6°, 24° to 26°, and 39° to 41°. Other workers[2] found that a solution containing midazolam hydrochloride equivalent to 1 mg/mL of the base in sodium chloride 0.9% was stable for at least 10 days when stored in PVC bags. The product information advises against admixture with Compound Sodium Lactate Intravenous Infusion (Hartmann's solution) as the potency of midazolam is reduced.

1. Pramar YV, *et al.* Stability of midazolam hydrochloride in syringes and i.v. fluids. *Am J Health-Syst Pharm* 1997; **54:** 913–15.
2. McMullin ST, *et al.* Stability of midazolam hydrochloride in polyvinyl chloride bags under fluorescent light. *Am J Health-Syst Pharm* 1995; **52:** 2018–20.

Midazolam Maleate *(BANM, USAN, rINNM)*

Maleato de midazolam; Midazolam, Maléate de; Midazolami Maleas; Ro-21-3981/001.

Мидазолама Малеат

$C_{18}H_{13}ClFN_3,C_4H_4O_4$ = 441.8.
CAS — 59467-94-6.
ATC — N05CD08.
ATC Vet — QN05CD08.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ Withdrawal symptoms occurred[1] in 2 children after stopping midazolam, which had been used for sedation during mechanical ventilation.

1. van Engelen BGM, *et al.* Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. *Ann Pharmacother* 1993; **27:** 579–81.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. There have been reports of life-threatening adverse respiratory and cardiovascular events occurring after use of midazolam; when giving midazolam the precautions given below should be observed to lessen the risk of such reactions. Pain, tenderness, and thrombophlebitis have occurred after injection of midazolam. Hiccups have been reported.

Incidence of adverse effects. Death due to respiratory depression, hypotension, or cardiac arrest has been reported in patients given intravenous midazolam for conscious sedation.[1] Within about 6 months of its introduction in the USA in May 1986, 13 fatalities due to cardiorespiratory depression had been reported (higher doses were used initially in the USA than those in the UK). By January 1988, 66 deaths had been reported, although in November 1987 the adult dosage recommendation had been reduced to 70 micrograms/kg and to 50 micrograms/kg for elderly patients. Fatalities have also occurred in the UK [where the dose is 70 micrograms/kg, reduced in the elderly] with 4 deaths reported to the UK CSM by November 1987.

While it appears that midazolam and diazepam produce very similar degrees of hypoventilation and oxygen desaturation when used in equivalent doses,[2] the sedative end-point does appear to be reached more abruptly with midazolam.[3] Appropriate precautions should therefore be taken:

- facilities for resuscitation should always be available when intravenous midazolam is used
- respiratory and cardiac function should be monitored continuously
- the dose of midazolam should be carefully titrated against the response of the patient and the product recommendations concerning dosage rate be observed
- particular care, including a reduction in midazolam dosage, is required in patients also receiving opioid analgesics, in the elderly and children, and in patients with compromised cardiorespiratory function
- similar warnings apply to the use of oral midazolam where it is available

The availability of the benzodiazepine antagonist, flumazenil, should not be an encouragement to use larger doses of midazolam.[1]

Since endoscopy of the upper gastrointestinal tract can itself reduce oxygen saturation, some workers have advocated the prophylactic use of nasal oxygen during this procedure for those patients at particular risk as outlined above.

1. Anonymous. Midazolam—is antagonism justified? *Lancet* 1988; **ii:** 140–2.
2. Bell GD. Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. *Aliment Pharmacol Ther* 1990; **4:** 103–22.
3. Ryder W, Wright PA. Dental sedation: a review. *Br Dent J* 1988; **165:** 207–16.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of midazolam on breast-fed infants is unknown its use by mothers during breast feeding may be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Midazolam could not be detected in breast milk from 11 mothers the morning after either the first or the fifth nightly 15-mg oral dose.[2] Additional study of 2 mothers found that midazolam and its hydroxy-metabolite disappeared rapidly from milk with undetectable concentrations at 4 hours. The mean milk to plasma ratio for midazolam was 0.15 in 6 paired samples.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30:** 787–93.

Children. An intravenous bolus injection of midazolam in children already receiving intravenous morphine after cardiac surgery produced an undesirable transient fall in cardiac output.[1] It was suggested that for patients already receiving other drugs that provide sedation the use of midazolam in the early postoperative period should be limited to a continuous infusion. Similarly, it has been recommended[2] that bolus intravenous doses of midazolam should be avoided in neonates due to the occurrence of hypotension.

The initial dosage of midazolam used for continuous intravenous sedation may need to be reduced in critically ill children under 3 years of age since the plasma clearance of midazolam appears to be reduced in these patients.[3]

1. Shekerdemian L, *et al.* Cardiovascular effects of intravenous midazolam after open heart surgery. *Arch Dis Child* 1997; **76:** 57–61.
2. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
3. Hughes J, *et al.* Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996; **30:** 27–30.

Effects on mental function. For discussion of the adverse effects of benzodiazepines on mental function, including reports of sexual fantasies in women sedated with intravenous midazolam, see Diazepam, p.987.

Effects on the nervous system. For reference to acute dystonia associated with use of midazolam, see Diazepam, p.988.

ENCEPHALOPATHY. For a report of prolonged use of midazolam with fentanyl being associated with encephalopathy in infants sedated under intensive care, see Diazepam, p.988.

MYOCLONUS. Myoclonic twitching of all four limbs was noted[1] in 6 of 102 neonates who received a continuous intravenous infusion of midazolam at a rate of 30 to 60 micrograms/kg per hour. Myoclonus ceased a few hours after stopping the infusion and never recurred. No ictal activity was detected in EEGs recorded during the myoclonus.

1. Magny JF, *et al.* Midazolam and myoclonus in neonate. *Eur J Pediatr* 1994; **153:** 389–90.

The elderly. Sedation with midazolam in elderly subjects needed only about half the dose necessary to produce comparable effects in younger subjects.[1] Pharmacodynamic differences due to age suggested an increase in sensitivity of the CNS to midazolam in the elderly subjects.

1. Albrecht S, *et al.* The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther* 1999; **65:** 630–9.

Hepatic impairment. For the precautions to be observed in patients with impaired liver function, see under Pharmacokinetics, below.

Renal impairment. Five patients with severe renal impairment experienced prolonged sedation when given midazolam; this was attributed to accumulation of conjugated metabolites.[1]

1. Bauer TM, *et al.* Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; **346:** 145–7.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Absorption of midazolam is rapid, peak plasma concentrations being achieved within 20 to 60 minutes of a dose, depending on the route. Extensive first-pass metabolism results in a low systemic bioavailability after oral doses. Bioavailability is higher, but variable, after intramuscular injection; figures of more than 90% are often cited.

Midazolam is lipophilic at physiological pH. It crosses the placenta and is distributed into breast milk (but see above). Midazolam is about 96% bound to plasma proteins.

Midazolam usually has a short elimination half-life of about 2 hours although half-lives longer than 7 hours have been reported in some patients. The half-life of midazolam is also prolonged in neonates, in the elderly, and in patients with liver disorders.

Midazolam is metabolised in the liver via the cytochrome P450 isoenzyme CYP3A4. The major metabolite, 1-hydroxymidazolam (alpha-hydroxymidazolam) has some activity; its half-life is less than 1 hour. Midazolam metabolites are excreted in the urine, mainly as glucuronide conjugates.

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

Children. In a study[1] of the pharmacokinetics of midazolam in children the bioavailability of a dose of 0.15 mg/kg was 100, 87, 27, and 18% when given by the intravenous, intramuscular, oral, and rectal routes, respectively. The oral bioavailability was reduced to 16 and 15% after increasing the dose to 0.45 and 1 mg/kg, respectively. There was bioequivalence between the 0.15 mg/kg intramuscular dose and the 0.45 mg/kg oral dose from 45 to 120 minutes after dosage. Absorption from the rectal route gave lower serum-midazolam concentrations than the oral route at the 0.15 mg/kg dose.

Midazolam appears to be absorbed rapidly when given intranasally to children with mean maximum plasma concentrations being achieved within about 12 minutes;[2-4] values of 30% and 55% have been reported for the bioavailability[3,4] but methods to optimise nasal delivery have resulted in higher bioavailability in studies in adults (see below). A study comparing intranasal, intravenous, and rectal dosage of midazolam in children found that plasma concentrations from 45 minutes after intranasal and intravenous doses were similar; those after rectal doses were consistently less than after these other 2 routes.[2] Possible reasons suggested by the authors for this included the effect that the wide interindividual variations in rectal pH may have had on the absorption of midazolam.

Another study has investigated the relationship between intravenous dose and plasma-midazolam concentrations in children.[5]

See also Children under Precautions, above.

1. Payne K, *et al.* The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; **37:** 267–72.
2. Malinovsky J-M, *et al.* Plasma concentrations of midazolam after iv, nasal or rectal administration in children. *Br J Anaesth* 1993; **70:** 617–20.
3. Rey E, *et al.* Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; **41:** 355–7.
4. Kauffman RE, *et al.* Intranasal absorption of midazolam. *Clin Pharmacol Ther* 1995; **57:** 209.
5. Tolia V, *et al.* Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *J Pediatr* 1991; **119:** 467–71.

NEONATES. References to the pharmacokinetics of midazolam in neonates. See also Children under Precautions, above.

1. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam in critically ill neonates. *Eur J Clin Pharmacol* 1990; **39:** 191–2.
2. Jacqz-Aigrain E, *et al.* Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992; **42:** 329–32.
3. Burtin P, *et al.* Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994; **56:** 615–25.
4. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.
5. Harte GJ, *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997 **33:** 335–8.
6. Lee TC, *et al.* Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology* 1999; **90:** 451–7.
7. de Wildt SN, *et al.* Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 2001; **70:** 525–31.

Half-life. Data collected from 7 studies involving 90 subjects has suggested that the prolonged midazolam half-lives reported in a small number of patients are secondary to increases in the volume of distribution and not a result of alterations in clearance and metabolism.[1] Prolongation of the half-life of midazolam has been reported[2] in 2 patients after sustained infusion for status epilepticus.

1. Wills RJ, *et al.* Increased volume of distribution prolongs midazolam half-life. *Br J Clin Pharmacol* 1990; **29:** 269–72.
2. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology* 2000 **54:** 1366–8.

Intranasal administration. Plasma concentrations of midazolam sufficient to induce conscious sedation are rapidly attained after intranasal doses.[1] Although bioavailability of up to 55% had previously been obtained in children after intranasal use (see above), slow administration and other methods to optimise nasal delivery had resulted in a bioavailability of 83% in adults.[2,3]

1. Burstein AH, *et al.* Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. *J Clin Pharmacol* 1997; **37:** 711–18.
2. Björkman S, *et al.* Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. *Br J Anaesth* 1997; **79:** 575–80.
3. Knoester PD, *et al.* Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray: a study in healthy volunteers. *Br J Clin Pharmacol* 2002; **53:** 501–7.

Liver disorders. The pharmacokinetics of midazolam in patients with advanced cirrhosis of the liver were characterised by an increase in oral systemic bioavailability[1] and by a decrease in clearance with consequent prolongation of elimination half-life.[1,2] Dosage may need to be reduced. However, metabolism of midazolam has been found in the anhepatic period of liver transplantation indicating extrahepatic metabolism (see below).

1. Pentikäinen PJ, *et al.* Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989; **29:** 272–7.
2. MacGilchrist AJ, *et al.* Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut* 1986; **27:** 190–5.

Metabolism. For a discussion of the metabolism of benzodiazepines, see Diazepam, p.992. Midazolam appears to be metabolised by at least 3 different cytochrome P450 isoenzymes found in the liver and in the kidney.[1] Variations in the activity of these enzymes might account for some of the interindividual differences in pharmacokinetics and pharmacodynamics seen with midazolam.[2] However, a study[3] in patients undergoing liver transplantation has indicated that the small intestine is a significant site for the first-pass metabolism of midazolam, metabolism presumably being catalysed by the cytochrome P450 isoenzyme CYP3A4 found in intestinal mucosa.

1. Wandel C, *et al.* Midazolam is metabolized by at least three different cytochrome P450 enzymes. *Br J Anaesth* 1994; **73:** 658–61.
2. Lown KS, *et al.* The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther* 1995; **57:** 16–24.
3. Paine MF, *et al.* First-pass metabolism of midazolam by the human intestine. *Clin Pharmacol Ther* 1996; **60:** 14–24.

Sublingual administration. High bioavailability (about 75%) and reliable plasma concentrations have been achieved after sublingual doses of midazolam.[1]

1. Schwagmeier R, *et al.* Midazolam pharmacokinetics following intravenous and buccal administration. *Br J Clin Pharmacol* 1998; **46:** 203–6.

Uses and Administration

Midazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992), except that it has a more potent amnestic action. It is mainly used for sedation (p.956) in minor surgical or investigative procedures and in intensive care, for premedication, and for induction of general anaesthesia. It is also used as a hypnotic in the short-term management of insomnia. When midazolam is used as a premedicant or for conscious sedation, onset of sedation occurs at about 15 minutes after intramuscular injection reaching a peak at 30 to 60 minutes, and within about 3 to 5 minutes after intravenous injection. When given intravenously as an anaesthetic induction agent, anaesthesia is induced in about 2 to 2.5 minutes; onset of action is more rapid when premedication with an opioid analgesic has been given.

Since the sedative end-point is reached abruptly with midazolam, dosage must be titrated carefully against the response of the patient; lower doses of midazolam are required when it is used with opioid analgesics. Respiratory and cardiac function should be monitored continuously, and facilities for resuscitation should always be available. It is advisable to keep the patient supine during intravenous use and throughout the procedure. The doses given below are, except where specified, the usual adult doses: midazolam should be given in reduced doses to **elderly** or **debilitated patients**.

Midazolam is used as the hydrochloride for oral, parenteral, and rectal dosage; the maleate may also be given orally. All doses are given in terms of the base; midazolam hydrochloride 8.3 mg or midazolam maleate 10.2 mg are both equivalent to about 7.5 mg of midazolam.

A usual total **sedative** dose for dental and minor surgical and other procedures ranges from 2.5 to 7.5 mg (about 70 micrograms/kg) *intravenously*; an initial dose of 2 mg over 30 seconds has been suggested, with further incremental doses of 0.5 to 1 mg at intervals of 2 minutes if required until the desired end-point is reached. In the USA a suggested initial dose of up to 2.5 mg is given intravenously over at least 2 minutes and repeated if necessary after an additional 2 minutes or more to a usual maximum total dose of 5 mg.

Sedation in children aged 6 months and over may be achieved orally. A single *oral* dose of 250 to 500 micrograms/kg, up to a maximum of 20 mg, is recommended although younger patients (6 months to less than 6 years) may require up to 1 mg/kg. If the *intravenous* route is more suitable, doses of 50 to 100 micrograms/kg up to a total dose of 600 micrograms/kg (but not exceeding 6 mg) are recommended in children aged 6 months to 5 years; children aged 6 to 12 years may be given 25 to 50 micrograms/kg up to a total dose of 400 micrograms/kg (or a maximum of 10 mg). Initial doses should be given over 2 to 3 minutes and an additional interval of at least 2 minutes is recommended before giving further doses. In some countries including the UK, the injection may be used *rectally* for sedation in children over 6 months of age; doses range from 300 to 500 micrograms/kg as a single dose. The injection solution may be diluted with Water for Injections up to a total volume of 10 mL if the volume is too small. The *intramuscular* route should only be used in children in exceptional cases as such injections are painful; usual doses ranging from 50 to 150 micrograms/kg have been suggested for intramuscular use in children aged 1 to 15 years. In the UK, although midazolam is not licensed for sedation of children under 6 months of age, the *BNFC* suggests that it may be given orally or intravenously to those aged 1 month and over in doses similar to those used in children aged 6 months and over (see above). Although also unlicensed, it further suggests that midazolam may be given *buccally* to children 6 months to 10 years of age in doses of 200 to 300 micrograms/kg (maximum of 5 mg); those aged 10 to 18 years may be given 6 to 7 mg (maximum of 8 mg if weighing 70 kg or over). The injection solution has been given *intranasally* to children aged 1 month and over; however, severe irritation of the nasal mucosa may occur (see Administration, below) and use of this route is not recommended in the *BNFC*.

Patients in **intensive care** who require continuous sedation (p.957) can be given midazolam by *intravenous infusion*. An initial loading dose of 30 to 300 micrograms/kg may be given by intravenous infusion over 5 minutes to induce sedation; in the USA a lower dose of 10 to 50 micrograms/kg is recommended. The maintenance dose required varies considerably but a dose of between 20 and 200 micrograms/kg per hour has been suggested. The loading dose should be reduced or omitted, and the maintenance dose reduced, for patients with hypovolaemia, vasoconstriction, or hypothermia. The need for continuous infusion should be reassessed on a daily basis to reduce the risk of accumulation and prolonged recovery. Sedation can also be achieved by giving intermittent *intravenous bolus injections* of midazolam; doses of 1 to 2 mg may be given, and repeated, until the desired level of sedation has been reached.

Midazolam is also used in children in intensive care who require sedation. In those aged over 6 months, an initial loading dose of 50 to 200 micrograms/kg is given by *slow intravenous injection*; maintenance doses are given as an intravenous infusion and range from 60 to 120 micrograms/kg per hour. Neonates with a gestational age of greater than 32 weeks and infants aged up to 6 months may be given midazolam by intravenous infusion in a dose of 60 micrograms/kg per hour; neonates with a gestational age of less than 32 weeks should be started on 30 micrograms/kg per hour. Loading doses are not recommended in infants aged under 6 months.

Abrupt withdrawal should be avoided after prolonged use.

Midazolam is given *intramuscularly* as a **premedicant** about 20 to 60 minutes before surgery. The usual dose is about 5 mg; doses range from 70 to 100 micrograms/kg. Children aged 6 months and over may be premedicated with *oral* midazolam in similar doses to those used for sedation (see above). The *rectal* route is used for premedication in some countries; total doses recommended in the UK in children aged over 6 months range from 300 to 500 micrograms/kg. The *intramuscular* route is also licensed in children aged 1 to 15 years in doses of 80 to 200 micrograms/kg; however, as before, this route should only be used in exceptional circumstances.

The usual dose of midazolam for **induction of anaesthesia** (p.1780) is about 150 to 200 micrograms/kg by slow *intravenous injection* in premedicated patients and at least 300 micrograms/kg in those who have not received a premedicant. Additional doses may be needed to complete induction; up to 600 micrograms/kg has been used in resistant cases. Further incremental doses of midazolam of about 25% of the induction dose have also been given as a component of the regimens used for the maintenance of anaesthesia during short surgical procedures. A dose of 150 micrograms/kg has been recommended for the induction of anaesthesia in children over 7 years of age; however, the *BNFC* notes that such use is rare and suggests a maximum total dose of 500 micrograms/kg (not exceeding 25 mg) in those aged up to 18 years.

Midazolam is also given for sedation in **combined anaesthesia** by *intravenous injection* in a dose of 30 to 100 micrograms/kg repeated as required or by *intravenous infusion* in a dose of 30 to 100 micrograms/kg every hour.

Midazolam maleate is also given *orally* for the short-term management of **insomnia**; the usual dose is the equivalent of midazolam 7.5 to 15 mg at night.

◊ References.

1. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; **35:** 37–47.
2. Marshall J, *et al.* Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol* 2000; **40:** 578–89.

Administration. The rectal,[1] intranasal,[1-5] buccal,[6-8] and sublingual[1,9] routes have all been proposed as alternatives to parenteral use of midazolam.

Intranasal midazolam has caused intense burning, irritation, and lachrymation on instillation, and use of a lidocaine nasal spray has been advocated before giving midazolam to children.[10] The use of midazolam spray intranasally in adults would be impractical and uncomfortable because of the large volume required. It has therefore been tried as a nebulised solution.[11]

1. Wong L, McQueen KD. Midazolam routes of administration. *DICP Ann Pharmacother* 1991; **25:** 476–7.
2. Theroux MC, *et al.* Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. *Pediatrics* 1993; **91:** 624–7.
3. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
4. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; **24:** 646–51.
5. Ljungman G, *et al.* Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics* 2000; **105:** 73–8.
6. Body R, Ijaz M. Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence. *Emerg Med J* 2005; **22:** 364–5.
7. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.
8. Baysun S, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005; **44:** 771–6.
9. Karl HW, *et al.* Transmucosal administration of midazolam for premedication of pediatric patients: comparison of the nasal and sublingual routes. *Anesthesiology* 1993; **78:** 885–91.
10. Lugo RA, *et al.* Complication of intranasal midazolam. *Pediatrics* 1993; **92:** 638.
11. Hodgson PE, *et al.* Administration of nebulized intranasal midazolam to healthy adult volunteers: a pilot study. *Br J Anaesth* 1994; **73:** 719P.

INTRATHECAL. See Pain, below.

Conversion and dissociative disorders. For reference to the use of midazolam in the diagnosis of conversion disorders, such as hysterical paralysis, see p.993.

Convulsions. Benzodiazepines such as diazepam or lorazepam given parenterally are often tried first to control status epilepticus (p.469). Midazolam has been used as an alternative.[1] It may be of value when intravenous access is difficult as effective concentrations of midazolam can be obtained after intramuscular injection.[2,3] The *BNF* considers it to be the benzodiazepine of choice when a continuous subcutaneous infusion is required for the control of convulsions, such as in palliative care, and states that it may be given in an initial dose of 20 to 40 mg every 24 hours. Intravenous midazolam has been used in some centres[4] for status epilepticus refractory to diazepam, lorazepam, or phenytoin but reviews of the literature[5] reveal that evidence of efficacy is limited mainly to uncontrolled studies and anecdotal reports.

The intranasal[6,7] and buccal[8] routes have also been used for the management of seizures, and UK guidelines[9] consider buccal midazolam an alternative to rectal diazepam for initial management of status epilepticus in the home setting or where intravenous access is not possible. In addition, a recent study[10] found that buccal midazolam was more effective than rectal diazepam for treatment of children with seizures in the hospital setting and did not appear to increase the risk of respiratory depression. The *BNF* states that a dose of midazolam 10 mg, repeated once if necessary, may be given by the buccal route to adults and children aged over 10 years.

The *BNFC* suggests giving a single buccal dose of 300 micrograms/kg to neonates. It suggests giving the following buccal doses, which may be repeated once if necessary, according to age: 1 to 6 months, 300 micrograms/kg (maximum of 2.5 mg); 6 months to 1 year, 2.5 mg; 1 to 5 years, 5 mg; 5 to 10 years, 7.5 mg. Alternatively, 1 microgram/kg per minute by continuous intravenous infusion may be given to neonates, children, and adolescents after an initial loading dose of 150 to 200 micrograms/kg. This may be increased by 1 microgram/kg per minute every 15 minutes until the seizure is controlled or until a maximum of 5 micrograms/kg per minute is reached.

1. Hanley DF, *et al.* Use of midazolam in the treatment of refractory status epilepticus. *Clin Ther* 1998; **20:** 1093–1105.

2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
3. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. *J Emerg Med* 1999; **17:** 323–8.
4. Bebin M, Bleck TP. New anticonvulsant drugs: focus on flunarizine, fosphenytoin, midazolam and stiripentol. *Drugs* 1994; **48:** 153–71.
5. Denzel D, Burstein AH. Midazolam in refractory status epilepticus. *Ann Pharmacother* 1996; **30:** 1481–3.
6. Wallace SJ. Nasal benzodiazepines for management of acute childhood seizures? *Lancet* 1997; **349:** 222.
7. Lahat E, *et al.* Intranasal midazolam for childhood seizures. *Lancet* 1998; **352:** 620.
8. Scott RC, *et al.* Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; **353:** 623–6.
9. NICE. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (issued October 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CG020NICEguideline.pdf (accessed 21/08/08)
10. McIntyre J, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005; **366:** 205–10.

Disturbed behaviour. For a discussion of the palliative treatment of terminal restlessness with benzodiazepines such as midazolam, see p.954.

Dyspnoea. Midazolam has been suggested[1] as an alternative to chlorpromazine in patients with advanced cancer and intractable dyspnoea (p.104) to relieve air hunger and to sedate dying patients who have unrelieved distress. Suggested[2] initial doses are 2.5 to 5 mg subcutaneously or 10 mg given by infusion over a period of 24 hours, increased as necessary. It may be combined successfully with morphine.[3]

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.
2. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
3. Navigante AH, *et al.* Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage* 2006; **31:** 38–47.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Midazolam given intravenously or subcutaneously has been reported[1] to have been effective in 2 patients with metastatic cancer who had hiccups unresponsive to conventional treatment. However, it has been noted[1,2] that benzodiazepines such as midazolam may exacerbate or precipitate hiccups.

1. Wilcock A, Twycross R. Midazolam for intractable hiccup. *J Pain Symptom Manage* 1996; **12:** 59–61.
2. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.

Insomnia. For discussion of the management of insomnia including limitations on the use of benzodiazepines and a recommendation that the period of treatment with midazolam should be limited to 2 weeks, see p.957.

References.

1. Monti JM, *et al.* The effect of midazolam on transient insomnia. *Eur J Clin Pharmacol* 1993; **44:** 525–7.

Pain. The conventional use of benzodiazepines in pain management is as muscle relaxants to relieve pain associated with skeletal muscle spasm (see under Choice of Analgesic, p.2). Midazolam has been studied[1-5] for use as an intrathecal analgesic but efficacy has been inconsistent.

1. Cripps TP, Goodchild CS. Intrathecal midazolam and the stress response to upper abdominal surgery. *Clin J Pain* 1988; **4:** 125–8.
2. Serrao JM, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. *Pain* 1992; **48:** 5–12.
3. Baaijens PFJ, *et al.* Intrathecal midazolam for the treatment of chronic mechanical low back pain: a randomized double-blind placebo-controlled study. *Br J Anaesth* 1995; **74** (suppl 1): 143.
4. Valentine JMJ, *et al.* The effect of intrathecal midazolam on post-operative pain. *Eur J Anaesthesiol* 1996; **13:** 589–93.
5. Batra YK, *et al.* Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. *Int J Clin Pharmacol Ther* 1999; **37:** 519–23.

Premedication and sedation. Midazolam is used as a premedicant (p.1780) and as a sedative for therapeutic and investigative procedures such as dental treatment (p.956) and endoscopy (see below). It is also used to provide continuous sedation in patients in intensive care (p.957) although a systematic review has raised concerns about such use in neonates.

References.

1. Sandler ES, *et al.* Midazolam versus fentanyl as premedication for painful procedures in children with cancer. *Pediatrics* 1992; **89:** 631–4.
2. Stenhammar L, *et al.* Intravenous midazolam in small bowel biopsy. *Arch Dis Child* 1994; **71:** 558.
3. Jacqz-Aigrain E, *et al.* Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994; **344:** 646–50.
4. Mitchell V, *et al.* Comparison of midazolam with trimeprazine as an oral premedicant for paediatric anaesthesia. *Br J Anaesth* 1995; **74** (suppl 1): 94–5.
5. McCarver-May DG, *et al.* Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996; **128:** 573–6.
6. Zedie N, *et al.* Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; **59:** 341–8.
7. McErlean M, *et al.* Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. *J Pediatr* 2003; **142:** 429–30.
8. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *BMJ* 2003; **327:** 708–11.
9. Ng E, *et al.* Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/03/06).
10. Averley PA, *et al.* An RCT pilot study to test the effects of intravenous midazolam as a conscious sedation technique for anxious children requiring dental treatment: an alternative to general anaesthesia. *Br Dent J* 2004; **197:** 553–8.

ENDOSCOPY. Intravenous benzodiazepines such as diazepam or midazolam are often the preferred drugs for sedation in patients undergoing endoscopy (p.956). They are sometimes used with opioid analgesics for sedation.[1]

A reduced dose of midazolam was required for endoscopy when it was given as a bolus intravenous injection rather than as a slow intravenous titration. A study in 788 patients undergoing endoscopy found that a mean dose of 4.65 mg of midazolam given as a bolus intravenous injection was safe and effective in patients under 70 years of age whereas a mean dose of 1.89 mg was sufficient for patients over 70 years of age.[2] Furthermore, topical pharyngeal anaesthesia was not required with these doses of midazolam. Intravenous boluses were also easier to give and associated with less oxygen desaturation than titrating the dose.[3] Another study found that even lower doses of midazolam (35 micrograms/kg) were effective as premedication before gastroscopy, and were associated with fewer complications than higher doses (70 micrograms/kg).[4]

Intranasal[5] and oral[6] midazolam have also been tried for sedation before endoscopy, particularly in children.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; **47:** 319–23.
2. Smith MR, *et al.* Small bolus injections of intravenous midazolam for upper gastrointestinal endoscopy: a study of 788 consecutive cases. *Br J Clin Pharmacol* 1993; **36:** 573–8.
3. Morrow JB, *et al.* Sedation for colonoscopy using a single bolus is safe, effective, and efficient: a prospective, randomized, double-blind trial. *Am J Gastroenterol* 2000; **95:** 2242–7.
4. Campo R, *et al.* Efficacy of low and standard midazolam doses for gastroscopy: a randomized, double-blind study. *Eur J Gastroenterol Hepatol* 2000; **12:** 187–90.
5. Fishbein M, *et al.* Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. *J Pediatr Gastroenterol Nutr* 1997; **25:** 261–6.
6. Martinez JL, *et al.* A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy. *J Pediatr Gastroenterol Nutr* 2002; **35:** 51–8.

Preparations

BP 2008: Midazolam Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Dalam; Dormicum; Dormid; Drimnorth; Gobbizolam; Ormir†; Rem; Ukel; ***Austral.:*** Hypnovel; ***Austria:*** Dormicum; ***Belg.:*** Dormicum; ***Braz.:*** Dormire; Dormium; Dormonid; Hipnazolam; Zolidan†; ***Canad.:*** Versed†; ***Chile:*** Dormonid; Noctura; Terap; Zolmid; ***Cz.:*** Dormicum; Fulsed; ***Denm.:*** Dormicum; ***Fin.:*** Dormicum; ***Fr.:*** Hypnovel; Versed; ***Ger.:*** Dormicum; Midaselect†; ***Gr.:*** Damizol; Dormicum; Dormixal; ***Hong Kong:*** Dormicum; ***Hung.:*** Dormicum; ***India:*** Fulsed; ***Indon.:*** Dormicum; Fortanest; Miloz; ***Irl.:*** Hypnovel; ***Israel:*** Dormicum; Midazol; Midolam; ***Ital.:*** Ipnovel; ***Malaysia:*** Dormicum; Fulsed†; Mizolam; ***Mex.:*** Dormicum; ***Neth.:*** Dormicum; ***Norw.:*** Dormicum; ***NZ:*** Hypnovel; ***Philipp.:*** Dormicum; ***Pol.:*** Dormicum; Midanium; Sopodorm; ***Port.:*** Dormicum; Zolamid; ***S.Afr.:*** Dormicum; Midacum; Midanium; ***Singapore:*** Dormicum; Fulsed; ***Spain:*** Dormicum; ***Swed.:*** Dormicum; ***Switz.:*** Dormicum; ***Thai.:*** Dormicum; Midazol†; ***Turk.:*** Dormicum; ***UK:*** Hypnovel; ***USA:*** Versed†; ***Venez.:*** Benzosed; Doricum; Midazepin.

Molindone Hydrochloride *(BANM, USAN, rINNM)*

EN-1733A; Hidrocloruro de molindona; Molindone, Chlorhydrate de; Molindoni Hydrochloridum. 3-Ethyl-1,5,6,7-tetrahydro-2-methyl-5-(morpholinomethyl)indol-4-one hydrochloride.

Молиндона Гидрохлорид

$C_{16}H_{24}N_2O_2,HCl = 312.8.$

CAS — 7416-34-4 (molindone); 15622-65-8 (molindone hydrochloride).

ATC — N05AE02.

ATC Vet — QN05AE02.

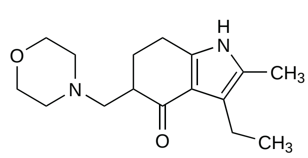

(molindone)

Pharmacopoeias. In *US.*

USP 31 (Molindone Hydrochloride). pH of a 1% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Molindone hydrochloride is less likely to cause hypotension than chlorpromazine, and extrapyramidal effects may be frequent but less severe. The incidence of sedation is intermediate between that of chlorpromazine and of phenothiazines with a piperazine side-chain. Weight gain or loss may occur, but weight loss appears to be more prominent (see p.970).

Effects on the liver. A report of hepatotoxicity, associated with a flu-like syndrome, in a patient given molindone.[1] Symptoms and liver-enzyme values returned to normal on stopping the drug and recurred on rechallenge with low doses. The effect was probably due to a hypersensitivity reaction.

1. Bhatia SC, *et al.* Molindone and hepatotoxicity. *Drug Intell Clin Pharm* 1985; **19:** 744–6.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Molindone is readily absorbed after oral doses, with peak concentrations of unchanged molindone occurring within about 1.5 hours. It is rapidly and extensively metabolised and a large number of metabolites have been identified. It is excreted in the urine and faeces mainly as metabolites and less than 2 to 3% as unchanged drug. The pharmacological effect from a single oral dose is reported to last for 24 to 36 hours.

◊ References.

1. Zetin M, *et al.* Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. *Clin Ther* 1985; **7:** 169–75.

Uses and Administration

Molindone is an indole derivative with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It is given as the hydrochloride for the treatment of psychoses including schizophrenia (p.955).

The usual oral dose of molindone hydrochloride is 50 to 75 mg daily initially, increased in 3 or 4 days to 100 mg daily; in severe or resistant conditions doses of up to 225 mg daily may be required. The maintenance dose can range from 15 to 225 mg daily according to severity of symptoms. The daily dose is usually divided into 3 or 4 portions.

Molindone should be given in reduced dosage to elderly or debilitated patients.

Psychiatric disorders. A systematic review[1] found that, based on limited data, molindone appeared to be effective in schizophrenia and other severe psychoses but evidence of differences from other classical antipsychotics was lacking.

1. Bagnall A, *et al.* Molindone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/03/08).

Preparations

USP 31: Molindone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Moban.

Moperone Hydrochloride *(rINNM)*

Hidrocloruro de moperona; Methylperidol Hydrochloride; Mopérone, Chlorhydrate de; Moperoni Hydrochloridum; R-1658 (moperone). 4′-Fluoro-4-(4-hydroxy-4-*p*-tolylpiperidino)butyrophenone hydrochloride.

Моперона Гидрохлорид

$C_{22}H_{26}FNO_2,HCl = 391.9.$

CAS — 1050-79-9 (moperone); 3871-82-7 (moperone hydrochloride).

ATC — N05AD04.

ATC Vet — QN05AD04.

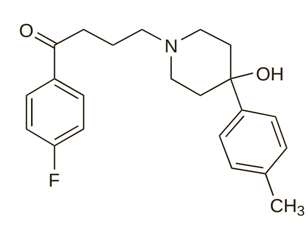

(moperone)

Profile

Moperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It has been given orally for the treatment of psychoses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Luvatren.

Mosapramine *(rINN)*

Clospipramine; Mosapramina; Mosapraminum; Y-516. (±)-1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl]hexahydrospiro[imidazo[1,2-*a*]pyridine-3(2*H*),4′-piperidin]-2-one.

Мозапрамин

$C_{28}H_{35}ClN_4O$ = 479.1.
CAS — 89419-40-9.
ATC — N05AX10.
ATC Vet — QN05AX10.

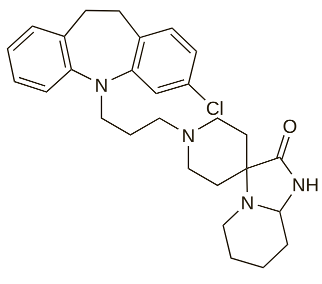

Profile

Mosapramine is an antipsychotic that has been tried in the treatment of schizophrenia.

◊ References.

1. Ishigooka J, *et al.* Pilot study of plasma concentrations of mosapramine, a new iminodibenzyl antipsychotic agent, after multiple oral administration in schizophrenic patients. *Curr Ther Res* 1994; **55:** 331–42.
2. Takahashi N, *et al.* Comparison of risperidone and mosapramine addition to neuroleptic treatment in chronic schizophrenia. *Neuropsychobiology* 1999; **39:** 81–5.

Nemonapride *(rINN)*

Emonapride; Nemonaprida; Némonapride; Nemonapridum; YM-09151-2. (±)-*cis*-*N*-(1-Benzyl-2-methyl-3-pyrrolidinyl)-5-chloro-4-(methylamino)-*o*-anisamide.

Немонаприд

$C_{21}H_{26}ClN_3O_2$ = 387.9.
CAS — 93664-94-9.

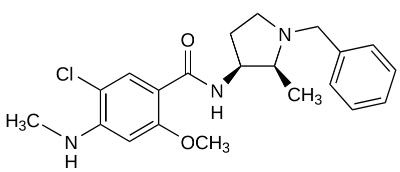

Profile

Nemonapride is a substituted benzamide antipsychotic with general properties similar to those of sulpiride (p.1028). It is given orally in the treatment of schizophrenia in usual doses of 9 to 36 mg daily in divided doses; up to 60 mg daily may be given if necessary.

◊ References.

1. Satoh K, *et al.* Effects of nemonapride on positive and negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 1996; **11:** 279–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Emilace.

Nimetazepam *(rINN)*

Menifazepam; Nimétazépam; Nimetazepamum; S-1530. 1,3-Dihydro-1-methyl-7-nitro-5-phenyl-1,4-benzodiazepin-2-one.

Ниметазепам

$C_{16}H_{13}N_3O_3$ = 295.3.
CAS — 2011-67-8.

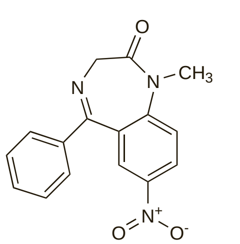

Profile

Nimetazepam is a benzodiazepine with the general properties of diazepam (p.986). It has been given orally for the short-term management of insomnia. It appears to have been subject to abuse, especially in South East Asia.

Nitrazepam *(BAN, USAN, rINN)*

Nitratsepaami; Nitrazépam; Nitrazepám; Nitrazepamas; Nitrazepamum; NSC-58775; Ro-4-5360; Ro-5-3059. 1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

Нитразепам

$C_{15}H_{11}N_3O_3$ = 281.3.
CAS — 146-22-5.
ATC — N05CD02.
ATC Vet — QN05CD02.

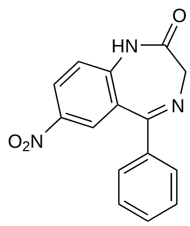

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nitrazepam:
Don; Moggies; Moogles; Nitro's; The Don.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.*

Ph. Eur. 6.2 (Nitrazepam). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 5 mg of nitrazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Effects on the digestive system. Two children given nitrazepam as part of their antiepileptic therapy developed drooling, eating difficulty, and aspiration pneumonia; symptoms improved in one patient when the dosage of nitrazepam was reduced.[1] Manometric studies indicated that the onset of normal cricopharyngeal relaxation in swallowing was delayed in these patients until after hypopharyngeal contraction, resulting in impaired swallowing and spillover of material into the trachea. Other workers[2] have found similar effects on swallowing and cricopharyngeal relaxation in children given nitrazepam. The deaths of 6 epileptic children under 5 years of age who were treated with nitrazepam have been reported.[3] Three of the deaths were unexpected, and in view of the previous reports of swallowing difficulties and aspiration, it was recommended that the use of nitrazepam in young children be restricted to those in whom seizure control fails to improve with other antiepileptics. Another study[4] also found an apparently increased risk of death, especially in young patients with intractable epilepsy, associated with nitrazepam therapy.

1. Wyllie E. *et al.* The mechanism of nitrazepam-induced drooling and aspiration. *N Engl J Med* 1986; **314:** 35–8.
2. Lim HCN, *et al.* Nitrazepam-induced cricopharyngeal dysphagia, abnormal esophageal peristalsis and associated bronchospasm: probable cause of nitrazepam-related sudden death. *Brain Dev* 1992; **14:** 309–14.
3. Murphy JV, *et al.* Deaths in young children receiving nitrazepam. *J Pediatr* 1987; **111:** 145–7.
4. Rintahaka PJ, *et al.* Incidence of death in patients with intractable epilepsy during nitrazepam treatment. *Epilepsia* 1999; **40:** 492–6.

Porphyria. Nitrazepam has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Nitrazepam is fairly readily absorbed from the gastrointestinal tract, although there is some individual variation. It is about 87% bound to plasma proteins. It crosses the blood-brain and the placental barriers and traces are found in breast milk. Nitrazepam is metabolised in the liver, mainly by nitroreduction followed by acetylation; none of the metabolites possess significant activity. It is excreted in the urine in the form of its metabolites (free or conjugated) with only small amounts of a dose appearing unchanged. Up to about 20% of an oral dose is found in the faeces. Mean elimination half-lives of 24 to 30 hours have been reported.

Distribution into breast milk. A mean milk-to-plasma ratio of 0.27 was obtained after giving nitrazepam 5 mg for 5 nights to 9 puerperal women.[1] The accumulation of nitrazepam in milk over the study period was similar to that in plasma.

1. Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30:** 787–93.

Hepatic impairment. The pharmacokinetics of intravenous nitrazepam in 12 patients with cirrhosis of the liver has been compared with 9 healthy subjects aged 22 to 49 years and 8 healthy elderly subjects aged 67 to 76 years.[1] The mean elimination half-life of nitrazepam was 26 hours in young and 38 hours in elderly subjects, the difference, which was not significant, being chiefly due to the greater volume of distribution in elderly subjects. Although there was also no significant difference between young and elderly subjects in percentage of unbound nitrazepam (13.0 and 13.9% respectively) there was a substantially higher unbound fraction in the patients with cirrhosis, the mean value being 18.9%, and clearance of unbound nitrazepam was reduced relative to healthy subjects.

1. Jochemsen R, *et al.* Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. *Br J Clin Pharmacol* 1983; **15:** 295–302.

Metabolism. Although the acetylation of the reduced metabolite of nitrazepam has been reported to be controlled by acetylator phenotype,[1] no significant differences between either half-life or residual effects of nitrazepam were observed in slow and fast acetylators.[2]

1. Karim AKMB, Price Evans DA. Polymorphic acetylation of nitrazepam. *J Med Genet* 1976; **13:** 17–19.
2. Swift CG, *et al.* Acetylator phenotype, nitrazepam plasma concentrations and residual effects. *Br J Clin Pharmacol* 1980; **9:** 312P–313P.

Uses and Administration

Nitrazepam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957) and is reported to act in 30 to 60 minutes to produce sleep lasting for 6 to 8 hours. Nitrazepam has also been used in epilepsy, notably for infantile spasms (see below).

The usual oral dose for insomnia is 5 mg at night, although 10 mg may be required in some patients. Elderly or debilitated patients should not be given more than half of the normal adult dose.

Epilepsy. Benzodiazepines are sometimes employed in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Nitrazepam has perhaps been most useful in the treatment of infantile spasms (as for example in West's syndrome) and the so-called infantile myoclonic seizures. The *BNFC* suggests that those aged from 1 month to 2 years may be given initial oral doses of 125 micrograms/kg twice daily, adjusted according to response over 2 to 3 weeks to 250 micrograms/kg twice daily (maximum 500 micrograms/kg, but not exceeding 5 mg, twice daily); the same total daily dose may also be given in 3 divided doses. There has been concern, however, over swallowing difficulties with subsequent aspiration and reports of unexpected death associated with the use of nitrazepam in young children (see Effects on the Digestive System under Adverse Effects, above).

Preparations

BP 2008: Nitrazepam Oral Suspension; Nitrazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Alodorm; Mogadon; ***Austria:*** Mogadon; ***Belg.:*** Mogadon; ***Braz.:*** Nitrapan; Nitrazepol; Sonebon; ***Canad.:*** Mogadon; Nitrazadon; ***Denm.:*** Apodorm; Mogadon; Pacisyn; ***Fin.:*** Insomin; ***Fr.:*** Mogadon; ***Ger.:*** Dormalon; Dormo-Puren; Eatan N; Imeson; Mogadan; Novanox; Radedorm; ***Hong Kong:*** Mogadon; ***Hung.:*** Eunoctin; ***India:*** Hypnotex; Nitavan; Nitravet; ***Indon.:*** Dumolid; ***Irl.:*** Mogadon; Somnite†; ***Israel:*** Numbon; ***Ital.:*** Mogadon; ***Malaysia:*** Mogadon†; ***Neth.:*** Mogadon; ***Norw.:*** Apodorm; Mogadon; ***NZ:*** Insoma; Nitrados; ***Rus.:*** Eunoctin (Эуноктин); Nitrosun (Нитросан); Radedorm (Радедорм); ***S.Afr.:*** Arem; Mogadon; Ormodon; Paxadorm; ***Singapore:*** Dima; Nitrados; ***Swed.:*** Apodorm; Mogadon; ***Switz.:*** Mogadon; ***Thai.:*** Alodorm†; Nitrados†; ***UK:*** Mogadon; Remnos; Somnite; ***Venez.:*** Onirema.

Multi-ingredient: ***Arg.:*** Cavodan†.

Nordazepam (rINN)

A-101; Demethyldiazepam; Desmethyldiazepam; *N*-Desmethyldiazepam; Nordazépam; Nordazepamum; Nordiazepam; Ro-5-2180. 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

Нордазепам

$C_{15}H_{11}ClN_2O$ = 270.7.
CAS — 1088-11-5.
ATC — N05BA16.
ATC Vet — QN05BA16.

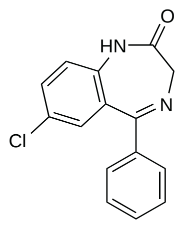

Profile

Nordazepam is a long-acting benzodiazepine with the general properties of diazepam (p.986). It is the principal active metabolite of a number of benzodiazepines and has a half-life of 2 to 5 days. It is given in oral doses of up to 15 mg daily for the short-term treatment of anxiety disorders (p.952) and insomnia (p.957).

Porphyria. Nordazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Calmday; ***Fr.:*** Nordaz; ***Ger.:*** Tranxilium N; ***Ital.:*** Madar; ***Port.:*** Sopax; ***Singapore:*** Nordaz.

Olanzapine (BAN, USAN, rINN)

LY-170053; Olantsapiini; Olanzapin; Olanzapina; Olanzapinum. 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

Оланзапин

$C_{17}H_{20}N_4S$ = 312.4.
CAS — 132539-06-1.
ATC — N05AH03.
ATC Vet — QN05AH03.

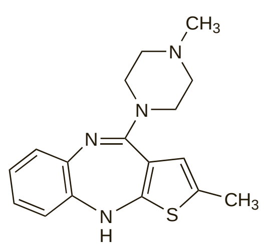

Stability. A suspension of olanzapine 1 mg/mL, made by crushing olanzapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for 2 weeks when stored in a refrigerator.[1]

1. Harvey EJ, *et al.* The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. *Pharm J* 2000; **265:** 275–6.

Adverse Effects, Treatment, and Precautions

Although olanzapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. The most frequent adverse effects with olanzapine are somnolence and weight gain; hyperprolactinaemia is also common, but usually asymptomatic. Increased appetite, dizziness, fatigue, elevated plasma glucose, triglyceride, and liver enzyme values, eosinophilia, oedema, orthostatic hypotension, and mild transient antimuscarinic effects such as constipation and dry mouth are also relatively common. More severe abnormalities of glucose homoeostasis are uncommon; severe hyperglycaemia, or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis, coma, or death, has occurred. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Clinical monitoring of plasma lipids and weight have also been recommended.

Olanzapine is associated with a low incidence of extrapyramidal effects, including tardive dyskinesia, although these effects may be more likely at high doses and in the elderly; the risk of tardive dyskinesia also increases with long-term use. Neuroleptic malignant syndrome has been reported rarely.

Patients receiving olanzapine intramuscularly should be closely observed for 2 to 4 hours for hypotension, bradyarrhythmia, and hypoventilation. Olanzapine should not be given intramuscularly to patients with a history of cardiovascular disease or following heart surgery; caution is recommended when giving olanzapine by mouth to such patients and to those with cerebrovascular disease or conditions predisposing to hypotension. It is recommended that blood pressure is periodically assessed in elderly patients.

The antimuscarinic effects of olanzapine contra-indicate its use in patients with angle-closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus. Olanzapine is also not recommended in Parkinson's disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations. It should be used with caution in patients with hepatic impairment, or a history of blood dyscrasias, bone marrow depression, or myeloproliferative disease. Seizures are rare with olanzapine but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

Olanzapine may affect the performance of skilled tasks such as driving.

Withdrawal symptoms, including sweating, tremor, anxiety, and nausea and vomiting, have occurred rarely when olanzapine has been stopped abruptly; a gradual dose reduction may be appropriate when stopping olanzapine.

◊ References.

1. Beasley CM, *et al.* Safety of olanzapine. *J Clin Psychiatry* 1997; **58** (suppl 10): 13–17.
2. Biswasl PN, *et al.* The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *J Psychopharmacol* 2001; **15:** 265–71.

Breast feeding. From a study[1] of the distribution of olanzapine into breast milk in 7 breast feeding women taking a median dose of 7.5 mg daily, it was estimated that the weight-adjusted median dose ingested by the breast-fed infants was 1.02% of the maternal dose. Olanzapine was not detected in the plasma of the 6 infants from whom a sample was taken; no adverse effects were observed in all 7 infants. However, UK licensed product information states that at steady state the estimated mean exposure of breast-fed infants of mothers taking olanzapine would be 1.8% of the maternal dose and recommends that patients should not breast feed if they are taking olanzapine.

1. Gardiner SJ, *et al.* Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *Am J Psychiatry* 2003; **160:** 1428–31.

Dementia. For details of a possibly increased risk of mortality in elderly patients with dementia given olanzapine and other atypical antipsychotics, see under Risperidone, p.1024.

Effects on the blood. A review[1] has described 11 reports of olanzapine-associated haematotoxicity that included 3 cases of agranulocytosis, 6 of neutropenia, and 2 of leucopenia. In most cases, the haematotoxicity developed within the first month of treatment and patients recovered after olanzapine withdrawal. There was a history of clozapine-associated haematotoxicity in 5 patients. It was suggested that white blood cell counts should be monitored periodically during olanzapine treatment.

Olanzapine has also apparently delayed recovery of granulocyte counts in patients with clozapine-induced granulocytopenia who were switched to olanzapine before blood counts had returned to the normal range.[2]

There have been case reports[3,4] of thrombocytopenia associated with olanzapine treatment. In one report,[3] the patient improved on stopping olanzapine but subsequently had a similar episode associated with benzatropine therapy. In another report,[4] an elderly patient with pre-existing idiopathic thrombocytopenic purpura died from bleeding complications due to thrombocytopenia associated with olanzapine treatment; the patient's plasma concentration of olanzapine was reported to be 10 times the usual mean therapeutic value.

1. Tolosa-Vilella C, *et al.* Olanzapine-induced agranulocytosis: a case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 411–4.
2. Flynn SW, *et al.* Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997; **17:** 494–5.
3. Bogunovic O, Viswanathan R. Thrombocytopenia possibly associated with olanzapine and subsequently with benztropine mesylate. *Psychosomatics* 2000; **41:** 277–88.
4. Carrillo JA, *et al.* Thrombocytopenia and fatality associated with olanzapine. *Eur J Clin Pharmacol* 2004; **60:** 295–6.

Effects on body temperature. Olanzapine has been associated with occasional reports of hypothermia. In one report[1] body temperature fell as low as 33.4° over several days in a woman receiving olanzapine for bipolar disorder. The patient, who also had subclinical hypothyroidism, was asymptomatic, and body temperature returned to normal once olanzapine was stopped; it was unclear whether the endocrine abnormalities had contributed to the condition.

1. Blass DM, Chuen M. Olanzapine-associated hypothermia. *Psychosomatics* 2004; **45:** 135–9.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. Haberfellner EM, Rittmannsberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004; **19:** 251–3.
2. Hennen J, *et al.* Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry* 2004; **65:** 1679–87.
3. Hester EK, Thrower MR. Current options in the management of olanzapine-associated weight gain. *Ann Pharmacother* 2005; **39:** 302–10.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Further references for such effects associated with olanzapine use are given below; in some cases the outcome was fatal.

1. Bettinger TL, *et al.* Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; **34:** 865–7.
2. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketonic coma. *Ann Pharmacother* 2001: **35:** 300–302.
3. Bonanno DG, *et al.* Olanzapine-induced diabetes mellitus. *Ann Pharmacother* 2001; **35:** 563–5.
4. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001; **35:** 1556–8.
5. Koller E, *et al.* Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 2001; **286:** 2547–8.
6. CSM. Olanzapine (Zyprexa) and diabetes. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
7. Koro CE, *et al.* Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; **325:** 243–5.
8. Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; **30:** 589–99.

Effects on the cardiovascular system. Two of 3 elderly patients who developed venous thromboembolism shortly after starting treatment with olanzapine also had symptoms of pulmonary embolism.[1] There have been 2 further isolated cases[2,3] of pulmonary embolism associated with olanzapine therapy; it had been reported in a 28-year-old man[2] and in a 22-year-old man[3] after 10 weeks and after 6 months of olanzapine therapy, respectively. Both patients recovered and were switched to another atypical antipsychotic.

1. Hägg S, *et al.* Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol* 2003; **18:** 299–300.
2. Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ* 2003; **327:** 1384.
3. Health Canada. Olanzapine (Zyprexa): suspected association with pulmonary embolism. *Can Adverse React News* 2005; **15** (1): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Further references.

1. Osser DN, *et al.* Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 1999; **60:** 767–70.

Effects on the liver. A report[1] of acute hepatocellular cholestatic jaundice that developed in a 78-year-old woman 13 days after starting treatment with olanzapine.

1. Jadallah KA, *et al.* Acute hepatocellular-cholestatic liver injury after olanzapine therapy. *Ann Intern Med* 2003; **138:** 357–8.

Effects on the nervous system. A 31-year-old woman with a complicated medical history suffered three generalised tonic-clonic seizures after 13 days of therapy with olanzapine.[1] She recovered after treatment with phenytoin. Another patient with Huntington's disease also suffered a severe generalised tonic-clonic seizure following treatment with olanzapine 30 mg daily for 1 month.[2] Olanzapine was continued but carbamazepine was added; there was no recurrence of the seizure.

1. Lee JW, *et al.* Seizure associated with olanzapine. *Ann Pharmacother* 1999; **33:** 554–6.
2. Bonelli RM. Olanzapine-associated seizure. *Ann Pharmacother* 2003; **37:** 149–50.

Effects on the pancreas. There have been isolated reports of pancreatitis associated with olanzapine.[1-3] See also under Clozapine, p.982.

1. Doucette DE, *et al.* Olanzapine-induced acute pancreatitis. *Ann Pharmacother* 2000; **34:** 1128–31.
2. Hagger R, *et al.* Olanzapine and pancreatitis. *Br J Psychiatry* 2000; **177:** 567.
3. Waage C, *et al.* Olanzapine-induced pancreatitis: a case report. *JOP* 2004; **5:** 388–91.

Effects on sexual function. Priapism has been reported[1,2] in 2 patients receiving olanzapine.

1. Deirmenjian JM, *et al.* Olanzapine-induced reversible priapism: a case report. *J Clin Psychopharmacol* 1998; **18:** 351–3.
2. Songer DA, Barclay JC. Olanzapine-induced priapism. *Am J Psychiatry* 2001; **158:** 2087–8.

Extrapyramidal disorders. There have been isolated reports[1,2] of tardive dyskinesia associated with olanzapine treatment. However, the incidence of extrapyramidal effects (p.971) is generally lower with atypical than classical antipsychotics.

1. Herrán A, Vázquez-Barquero JL. Tardive dyskinesia associated with olanzapine. *Ann Intern Med* 1999; **131:** 72.
2. Bella VL, Piccoli F. Olanzepine-induced tardive dyskinesia. *Br J Psychiatry* 2003; **182:** 81–2.

Mania. Although olanzapine is used in the treatment of bipolar disorder, it has been associated with reports of mania in both schizophrenic and bipolar patients.[1-4] A report sponsored by the manufacturers noted that no association was seen in pooled data from 2 placebo-controlled studies involving 254 bipolar patients.[5]

1. Lindenmayer J-P, Klebanov R. Olanzapine-induced manic-like syndrome. *J Clin Psychiatry* 1998; **59:** 318–19.
2. Fitz-Gerald MJ, *et al.* Olanzapine-induced mania. *Am J Psychiatry* 1999; **156:** 1114.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; **61:** 649–55.
4. Henry C, Demotes-Mainard J. Olanzapine-induced mania in bipolar disorders. *J Psychiatry Neurosci* 2002; **27:** 200–201.
5. Baker RW, *et al.* Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord* 2003; **73:** 147–53.

Neuroleptic malignant syndrome. Cases of neuroleptic malignant syndrome (p.972) have been associated with olanzapine therapy.[1-4]

1. Filice GA, *et al.* Neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 1998; **32:** 1158–9.
2. Nyfort-Hansen K, Alderman CP. Possible neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 2000; **34:** 667.
3. Suh H, *et al.* Neuroleptic malignant syndrome and low-dose olanzapine. *Am J Psychiatry* 2003; **160:** 796.
4. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome–a case review. *Hum Psychopharmacol* 2003; **18:** 301–9.

Overdosage. A 2⁄-year-old boy was found sleeping and difficult to arouse after taking one or two 7.5-mg olanzapine tablets.[1] His reported symptoms included agitation, aggressive behaviour, miosis, hypersalivation, tachycardia, and ataxia; he recovered after 24 hours. Symptoms suggestive of diabetes insipidus, together with mild CNS depression, have also been reported,[2] in an adolescent who took 75 mg of olanzapine with a small quantity of prazepam. The polyuria responded to desmopressin. A review[3] identified 29 fatalities associated with olanzapine overdose, but evidence of a direct causative relationship was limited.

1. Yip L, *et al.* Olanzapine toxicity in a toddler. *Pediatrics* 1998; **102:** 1494.
2. Etienne L, *et al.* Polyuria after olanzapine overdose. *Am J Psychiatry* 2004; **161:** 1130.
3. Chue P, Singer P. A review of olanzapine-associated toxicity and fatality in overdose. *J Psychiatry Neurosci* 2003; **28:** 253–61.

Parkinsonism. Worsening of motor function has been reported[1-4] in patients with parkinsonism after use of olanzapine.

1. Graham JM, *et al.* Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. *J Neurol Neurosurg Psychiatry* 1998 **65:** 774–7.
2. Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* 1999; **14:** 1014–16.
3. Goetz CG, *et al.* Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 2000; **55:** 789–94.
4. Manson AJ, *et al.* Low-dose olanzapine for levodopa induced dyskinesias. *Neurology* 2000; **55:** 795–9.

Pregnancy. The manufacturer has reviewed both prospective and retrospective cases of pregnancies that have been exposed to olanzapine treatment.[1] Of the 37 prospective pregnancies, there were 14 therapeutic abortions (with no reported abnormality in the fetus), 3 spontaneous abortions (again with no reported abnormality in the fetus), and 1 still-birth. The remaining 19 pregnancies included 16 normal births without complications and 1 premature birth; the 2 other births were complicated by post-term deliveries. Eleven retrospective cases were also identified and included 2 cases of major malformation (dysplastic kidney and Down's syndrome), 1 case of fetal death following an overdose by the mother, and 1 case each of neonatal convulsion and sudden infant death. For comments on the use of some atypical antipsychotics, including olanzapine, during pregnancy, see under Precautions of Clozapine, p.983.

1. Goldstein DJ, *et al.* Olanzapine-exposed pregnancies and lactation: early experience. *J Clin Psychopharmacol* 2000; **20:** 399–403.

Speech disorders. Although olanzapine may be used in the treatment of stuttering, it has also been associated with reports of the development of the disorder, see under Uses and Administration, below.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by olanzapine. Olanzapine may antagonise the effects of dopaminergics. Neutropenia may be more common when olanzapine is given with valproate. Use with valproate or lithium has also been associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain.There is a theoretical risk of QT prolongation when olanzapine is given with other drugs that are known to cause this effect.

Drugs that induce hypotension, bradycardia, or respiratory depression should be used with caution in patients given intramuscular olanzapine. Parenteral benzodiazepine treatment should be given at least 1 hour after intramuscular olanzapine as it is recommended that they are not given together.

The metabolism of olanzapine is mediated to some extent by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit, induce, or act as a substrate to this isoenzyme may affect plasma concentrations of olanzapine and a dose adjustment of olanzapine may be required. The CYP1A2 inhibitor fluvoxamine significantly inhibits the metabolism of olanzapine. The clearance of olanzapine is increased by tobacco smoking and carbamazepine.

Valproate. In a study of 4 patients, valproate reduced plasma concentrations of olanzapine by 32.3 to 78.8% (mean 53.6%).[1]

1. Bergemann N, *et al.* Valproate lowers plasma concentrations of olanzapine. *Pharmacopsychiatry* 2005; **38:** 44.

Pharmacokinetics

Olanzapine is well absorbed from the gastrointestinal tract after oral doses but undergoes considerable first-pass metabolism. Peak plasma concentrations are achieved about 5 to 8 hours after oral doses and about 15 to 45 minutes after an intramuscular dose. Olanzapine is about 93% bound to plasma proteins. It is extensively metabolised in the liver, primarily by direct glucuronidation and by oxidation mediated through the cytochrome P450 isoenzymes CYP1A2, and, to a lesser extent, CYP2D6. The 2 major metabolites 10-*N*-glucuronide and 4′-*N*-desmethyl olanzapine appear to be inactive. About 57% of a dose is excreted in the urine, mainly as metabolites, and about 30% appears in the faeces. The mean plasma elimination half-life has been variously reported to be about 30 to 38 hours; half-lives tend to be longer in female than in male patients. Olanzapine is distributed into breast milk.

◊ References.

1. Callaghan JT, *et al.* Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; **37:** 177–93.
2. Markowitz JS, *et al.* Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 2006; **46:** 164–71.

Uses and Administration

Olanzapine is a thienobenzodiazepine atypical antipsychotic. It has affinity for serotonin, muscarinic, histamine (H_1), and adrenergic (α_1) receptors as well as various dopamine receptors.

Olanzapine is used for the management of schizophrenia and for the treatment of moderate to severe mania associated with bipolar disorder.

In the UK, the usual initial oral dose for **schizophrenia** is 10 mg daily as a single dose; thereafter dosage adjustments may be made according to response at intervals of not less than 24 hours to within the range of 5 to 20 mg daily. In the USA, the starting dose is 5 to 10 mg daily and it is recommended that dosage adjustments beyond 10 mg daily are made at intervals of not less than 1 week; the daily dosage should be adjusted in steps of 5 mg. However, it is recommended that doses above 10 mg daily should be given only after clinical reassessment.

For the treatment of **acute mixed or manic episodes** in bipolar disorder, a recommended initial oral dose is 10 or 15 mg daily as monotherapy or 10 mg if given as part of combination therapy; the daily dosage may be adjusted in steps of 5 mg if necessary, at intervals of not less than 24 hours to a dose of between 5 and 20 mg daily. If a response is achieved, therapy may continue at the same dosage to prevent recurrence. For **prevention of recurrence** in patients whose manic episodes have responded previously to olanzapine, the recommended starting dose is 10 mg daily.

For the **rapid control of agitation and disturbed behaviour** in patients with schizophrenia or mania, olanzapine may be given intramuscularly in an initial dose of 5 to 10 mg followed by 5 to 10 mg as required after 2 hours. Not more than 3 injections should be given in any 24-hour period and the maximum daily dose, including olanzapine given orally, should not exceed 20 mg. Injections may be given for up to a maximum of 3 days but transfer to oral therapy should be started as soon as possible.

The metabolism of olanzapine might be slower in female, elderly, or non-smoking patients; if more than one of these factors is present, a lower initial dose (e.g. 5 mg daily if given orally) and a more gradual dose escalation should be considered. The intramuscular dose should be reduced by half in the elderly. See below for doses in patients with hepatic or renal impairment.

Administration in hepatic or renal impairment. A starting dose of 5 mg daily of olanzapine orally or by intramuscular injection may be necessary for patients with renal or hepatic impairment; for patients with moderate hepatic insufficiency, the starting dose should only be increased with caution.

Bipolar disorder. Olanzapine is of benefit for the treatment of mania, with or without psychosis, in patients with bipolar disorder (p.372), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of olanzapine-induced mania (see above).

There is also increasing interest in the use of olanzapine for the depressive phase of bipolar disorder, and for other forms of resistant depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine for use in the former condition.

References.

1. Shelton RC, *et al.* A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001; **158:** 131–4.
2. Rendell JM, *et al.* Olanzapine alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/05/05).
3. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar I disorder. *Drugs* 2004; **64:** 2709–26.
4. Shelton RC. Olanzapine/fluoxetine combination for bipolar depression. *Expert Rev Neurother* 2006; **6:** 33–9.

Nausea and vomiting. For mention of the use of olanzapine as a second-line drug to control nausea and vomiting in palliative care see p.1700.

Parkinsonism. Olanzapine is associated with a relatively low incidence of extrapyramidal disorders and has been studied[1] for use in the treatment of psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p.954). However, there have been a number of reports of adverse effects including exacerbation of the movement disorder (see Parkinsonism, under Precautions, above).

1. Wolters EC, *et al.* Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. *Neurology* 1996; **47:** 1085–7.

Psychiatric disorders. The main treatment for *post-traumatic stress disorder* (p.953) is psychotherapy but adjunctive olanzapine may be used in patients refractory to psychotherapy and/or drug treatment with antidepressants. Olanzapine has also been tried for the control of *aggression* in children with autism and conduct disorder (see Disturbed Behaviour, p.954).

Schizophrenia. Studies suggest that olanzapine is as effective as haloperidol against positive symptoms of schizophrenia (p.955) and more effective against negative symptoms in the short-term and possibly in the long-term,[1-5] although a systematic review considered the evidence equivocal.[6] Quality of life has also been judged to be greater in patients treated with olanzapine.[7] In comparative studies, extrapyramidal adverse effects have been less frequent with olanzapine than haloperidol and fewer patients have discontinued treatment with olanzapine. There are relatively few published comparisons with other atypical antipsychotics, but one systematic review[8] concluded that there was little to differentiate between olanzapine and risperidone apart from their adverse effects; risperidone was particularly associated with movement disorders and sexual dysfunction while olanzapine induced rapid weight gain. Another study has suggested that olanzapine is not inferior to clozapine.[9] Olanzapine's efficacy in the treatment of patients with refractory schizophrenia remains to be determined; a small, randomised study found it to be no more effective than haloperidol.[10]

1. Beasley CM, *et al.* Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996; **14:** 111–23.
2. Beasley C, *et al.* Olanzapine versus haloperidol: long-term results of the multi-center international trial. *Eur Neuropsychopharmacol* 1996; **6** (suppl 3): 59.
3. Beasley CM, *et al.* Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 1997; **7:** 125–37.
4. Tollefson GD, *et al.* Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997; **154:** 457–65.
5. Bhana N, *et al.* Olanzapine: an updated review of its use in the management of schizophrenia. *Drugs* 2001; **61:** 111–61.
6. Duggan L, *et al.* Olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 24/05/05).
7. Hamilton SH, *et al.* Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 1998; **18:** 41–9.
8. Jayaram MB, *et al.* Risperidone versus olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/01/07).
9. Naber D, *et al.* Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatr Scand* 2005; **111:** 106–15.
10. Buchanan RW, *et al.* Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry* 2005; **162:** 124–9.

Stuttering. Although olanzapine may be of benefit in the treatment of stuttering (p.1001),[1,2] it has been associated with reports of stuttering in 6 adult patients with schizophrenia or depression.[3]

1. Lavid N, *et al.* Management of child and adolescent stuttering with olanzapine: three case reports. *Ann Clin Psychiatry* 1999; **11:** 233–6.
2. Maguire GA, *et al.* Olanzapine in the treatment of developmental stuttering: a double-blind, placebo-controlled trial. *Ann Clin Psychiatry* 2004; **16:** 63–7.
3. Bär KJ, *et al.* Olanzapine- and clozapine-induced stuttering: a case series. *Pharmacopsychiatry* 2004; **37:** 131–4.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p.954) haloperidol or pimozide are commonly used but atypical antipsychotics, including olanzapine, are increasingly being tried.[1-4]

1. Stamenkovic M, *et al.* Effective open-label treatment of tourette's disorder with olanzapine. *Int Clin Psychopharmacol* 2000; **15:** 23–8.
2. Onofrj M, *et al.* Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. *J Neurol* 2000; **247:** 443–6.
3. Budman CL, *et al.* An open-label study of the treatment efficacy of olanzapine for Tourette's disorder. *J Clin Psychiatry* 2001; **62:** 290–4.
4. Stephens RJ, *et al.* Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome: a pilot study. *J Child Adolesc Psychopharmacol* 2004; **14:** 255–66.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Midax; Zyprexa; ***Austral.:*** Zyprexa; ***Austria:*** Zyprexa; ***Belg.:*** Zyprexa; ***Braz.:*** Zyprexa; ***Canad.:*** Zyprexa; ***Chile:*** Olivin; Zyprexa; ***Cz.:*** Zalasta; Zyprexa; ***Denm.:*** Zyprexa; ***Fin.:*** Zyprexa; ***Fr.:*** Zyprexa; ***Ger.:*** Zyprexa; ***Gr.:*** Zyprexa; ***Hong Kong:*** Zyprexa; ***Hung.:*** Zyprexa; ***India:*** Joyzol; Olexar; Ozapin; Psycholanz; ***Indon.:*** Zyprexa; ***Irl.:*** Zyprexa; ***Israel:*** Zyprexa; ***Ital.:*** Zyprexa; ***Malaysia:*** Zyprexa; ***Mex.:*** Zyprexa; ***Neth.:*** Zyprexa; ***Norw.:*** Zyprexa; ***NZ:*** Zyprexa; ***Philipp.:*** Zyprexa; ***Pol.:*** Olzapin; Zalasta; Zolafren; Zyprexa; ***Port.:*** Olapin; Zalasta; Zolafren; Zyprexa; ***Rus.:*** Zyprexa (Зипрекса); ***S.Afr.:*** Zyprexa; ***Singapore:*** Zyprexa; ***Spain:*** Zyprexa; ***Swed.:*** Zyprexa; ***Switz.:*** Zyprexa; ***Thai.:*** Zyprexa; ***Turk.:*** Zyprexa; ***UK:*** Zyprexa; ***USA:*** Zyprexa; ***Venez.:*** Zyprexa.

Multi-ingredient: ***Arg.:*** Combined†; Symbyax†; ***Chile:*** Symbyax; ***Mex.:*** Symbyax; ***USA:*** Symbyax.

Oxazepam *(BAN, USAN, rINN)*

Oksatsepaami; Oksazeoam; Oksazepam; Oksazepamas; Oxazépam; Oxazepám; Oxazepamum; Wy-3498. 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one.

Оксазепам

$C_{15}H_{11}ClN_2O_2$ = 286.7.

CAS — 604-75-1.

ATC — N05BA04.

ATC Vet — QN05BA04.

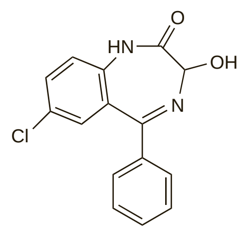

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Oxazepam). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Oxazepam). A creamy-white to pale yellow, practically odourless powder. Practically insoluble in water; soluble 1 in 220 of alcohol, 1 in 270 of chloroform, and 1 in 2200 of ether. pH of a 2% suspension in water is between 4.8 and 7.0.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 15 mg of oxazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, but short-acting ones such as oxazepam may be preferred.

Seven patients with acute viral hepatitis, 6 with cirrhosis of the liver, and 16 age-matched healthy control subjects took a single dose of oxazepam 15 or 45 mg orally.[1] Urinary excretion rates and plasma elimination patterns were unaltered in patients with acute and chronic parenchymal liver disease. Oxazepam 15 mg orally was also given three times daily for 2 weeks to 2 healthy subjects and to 2 patients with cirrhosis and did not appear to accumulate in any of the four.

1. Shull HJ, *et al.* Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; **84:** 420–5.

Porphyria. Oxazepam is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Renal impairment. Pharmacokinetic studies suggest that, in general, the dosage of oxazepam does not need adjusting in patients with renal impairment.[1-3]

1. Murray TG, *et al.* Renal disease, age, and oxazepam kinetics. *Clin Pharmacol Ther* 1981; **30:** 805–9.
2. Busch U, *et al.* Pharmacokinetics of oxazepam following multiple administration in volunteers and patients with chronic renal disease. *Arzneimittelforschung* 1981; **31:** 1507–11.
3. Greenblatt DJ, *et al.* Multiple-dose kinetics and dialyzability of oxazepam in renal insufficiency. *Nephron* 1983; **34:** 234–8.

Thyroid disorders. There was a reduction in half-life and an increase in the apparent oral clearance of oxazepam in 7 hyperthyroid patients.[1] In 6 hypothyroid patients there was no overall change in oxazepam elimination, although 5 of the 6 complained of drowsiness despite a relatively low dose (15 mg).

1. Scott AK, *et al.* Oxazepam pharmacokinetics in thyroid disease. *Br J Clin Pharmacol* 1984; **17:** 49–53.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Oxazepam is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations about 2 hours after ingestion. It crosses the placenta and has been detected in breast milk. Oxazepam is about 85 to 97% bound to plasma proteins and has been reported to have an elimination half-life ranging from about 3 to 21 hours. It is largely metabolised to the inactive glucuronide which is excreted in the urine.

Pregnancy. The placental passage of oxazepam and its metabolism in 12 women given a single dose of oxazepam 25 mg during labour has been studied.[1] Oxazepam was readily absorbed and peak plasma concentrations were in the same range as those reported in healthy males and non-pregnant females given the same dose, although the plasma half-life (range 5.3 to 7.8 hours in 8 subjects studied) was shorter than that reported for non-pregnant subjects. Oxazepam was detected in the umbilical vein of all 12 patients with the ratio between umbilical to maternal vein concentration of oxazepam reaching a value of about 1.35 and remaining constant beyond a dose-delivery time of 3 hours. All of the babies had a normal Apgar score value. The oxazepam plasma half-life in the newborns was about 3 to 4 times that of the mothers, although in 3 the plasma concentration of oxazepam conjugate rose during the first 6 to 10 hours after delivery indicating the ability of the neonate to conjugate oxazepam.

1. Tomson G, *et al*. Placental passage of oxazepam and its metabolism in mother and newborn. *Clin Pharmacol Ther* 1979; **25:** 74–81.

Uses and Administration

Oxazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term management of anxiety disorders (p.952) and insomnia (p.957) associated with anxiety. Oxazepam is also used for the control of symptoms associated with alcohol withdrawal (p.1626). Oxazepam is usually given as the base but the hemisuccinate has been used in some multi-ingredient preparations.

The usual oral dose of oxazepam for the treatment of anxiety or for control of symptoms of alcohol withdrawal is 15 to 30 mg three or four times daily. A suggested initial dose for elderly or debilitated patients is 10 mg three times daily increased if necessary up to 10 to 20 mg three or four times daily. For the treatment of insomnia associated with anxiety oxazepam 15 to 25 mg may be given one hour before retiring; up to 50 mg may occasionally be necessary.

Administration in renal impairment. For a suggestion that dosage adjustment of oxazepam may not be necessary in patients with renal impairment, see Renal Impairment, above.

Preparations

BP 2008: Oxazepam Tablets;
USP 31: Oxazepam Capsules; Oxazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Pausafren T; ***Austral.:*** Alepam; Murelax; Serepax; ***Austria:*** Adumbran; Anxiolit; Oxahexal; Praxiten; ***Belg.:*** Seresta; Tranquo; ***Chile:*** Serepax†; ***Denm.:*** Alopam; Oxabenz; Oxapax; Serepax; ***Fin.:*** Alopam†; Opamox; Oxamin; Oxepam†; ***Fr.:*** Seresta; ***Ger.:*** Adumbran; Azutranquil†; durazepam; Mirfudorm; Noctazepam†; Oxa; Praxiten; Sigacalm†; Uskan; ***India:*** Serepax; ***Israel:*** Vaben; ***Ital.:*** Limbial; Serpax; ***Neth.:*** Seresta; ***Norw.:*** Alopam; Sobril; ***NZ:*** Ox-Pam; ***Pol.:*** Oxam; ***Port.:*** Serenal; ***Rus.:*** Tazepam (Тазепам); ***S.Afr.:*** Medopam; Noripam; Purata; Serepax; ***Spain:*** Adumbran†; ***Swed.:*** Oxascand; Sobril; ***Switz.:*** Anxiolit; Seresta; ***USA:*** Serax; ***Venez.:*** Anastil†.

Multi-ingredient: ***Arg.:*** Cavodan†; Pankreoflat Sedante†; ***Austria:*** Anxiolit plus; ***Chile:*** Novalona; ***Port.:*** Sedioton†; ***Spain:*** Novo Aerofil Sedante†; Suxidina; ***Venez.:*** Vuscobras.

Oxazolam *(rINN)*

Oxazolamum; Oxazolazepam. 10-Chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Оксазолам

$C_{18}H_{17}ClN_2O_2$ = 328.8.

CAS — 24143-17-7.

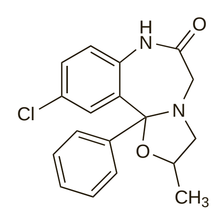

Pharmacopoeias. In *Jpn.*

Profile

Oxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been given by mouth for the short-term treatment of anxiety disorders.

Oxazolam has also been used as a premedicant in general anaesthesia.

Oxypertine (BAN, USAN, rINN)

Oksipertiini; Oxipertin; Oxipertina; Oxypertinum; Win-18501-2. 5,6-Dimethoxy-2-methyl-3-[2-(4-phenylpiperazin-1-yl)ethyl]-indole.

Оксипертин

$C_{23}H_{29}N_3O_2$ = 379.5.

CAS — 153-87-7 (oxypertine); 40523-01-1 (oxypertine hydrochloride).

ATC — N05AE01.

ATC Vet — QN05AE01.

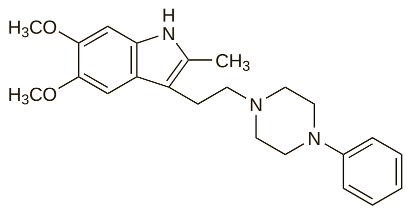

Profile

Oxypertine is an indole derivative with general properties similar to those of the phenothiazine, chlorpromazine (p.969). It has been given orally in the treatment of psychoses including schizophrenia, mania, and disturbed behaviour, and in severe anxiety.

Paliperidone (USAN, rINN)

9-Hydroxyrisperidone; Paliperidona; Palipéridone; Paliperidonum; RO-76477. (±)-3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl}-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Палиперидон

$C_{23}H_{27}FN_4O_3$ = 426.5.

CAS — 144598-75-4.

ATC — N05AX13.

ATC Vet — QN05AX13.

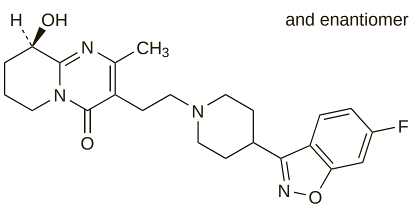

and enantiomer

Paliperidone Palmitate (USAN, rINNM)

Palipéridone, Palmitate de; Paliperidoni Palmitas; Palmitato de paliperidona; RO-92670. (9*RS*)-3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.

Палиперидона Палмитат

$C_{39}H_{57}FN_4O_4$ = 664.9.

CAS — 199739-10-1.

Profile

Paliperidone is a benzisoxazole derivative and is the major active metabolite of the atypical antipsychotic risperidone (p.1024). It is reported to be an antagonist at dopamine D_2, serotonin (5-HT_2), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is used in the treatment of schizophrenia.

The recommended oral dose of paliperidone is 6 mg once daily as a modified-release preparation; doses may range from 3 to 12 mg daily. US licensed product information recommends that dose increases are made in small steps of 3 mg at intervals of more than 5 days.

For details of dose reductions in patients with renal impairment, see below.

Paliperidone palmitate is being developed as a long-acting intramuscular formulation.

Administration in renal impairment. The plasma concentrations of paliperidone are increased in patients with renal impairment. The usual oral daily dosage (see above) should therefore be adjusted according to creatinine clearance (CC).

In the UK, licensed product information recommends the following doses:

- CC 50 to 80 mL/minute: initially 3 mg once daily, may be increased thereafter according to response and tolerance
- CC 30 to 50 mL/minute: 3 mg once daily
- CC 10 to 30 mL/minute: initially 3 mg on alternate days which may be increased thereafter to 3 mg once daily after clinical reassessment

However, US licensed product information recommends the following maximum doses:

- CC 50 to 80 mL/minute: 6 mg once daily
- CC 10 to 50 mL/minute: 3 mg once daily

Paliperidone has not been studied in patients with a CC of less than 10 mL/minute; UK product information does not recommend its use in such patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Invega; ***Fr.:*** Invega; ***Port.:*** Invega; ***UK:*** Invega; ***USA:*** Invega.

Paraldehyde

Paracetaldehyde; Paraldehid; Paraldehidas; Paraldehído; Paraldehit; Paraldehyd; Paraldéhyde; Paraldehydi; Paraldehydum. The trimer of acetaldehyde; 2,4,6-Trimethyl-1,3,5-trioxane.

$(C_2H_4O)_3$ = 132.2.

CAS — 123-63-7.

ATC — N05CC05.

ATC Vet — QN05CC05.

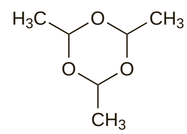

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Paraldehyde). A colourless or slightly yellow, transparent liquid. It solidifies on cooling to form a crystalline mass. It may contain a suitable amount of an antoxidant. Relative density 0.991 to 0.996. F.p. is 10° to 13°; not more than 10% distils below 123° and not less than 95% below 126°. Soluble in water but less soluble in boiling water; miscible with alcohol and with volatile oils. Store in small well-filled airtight containers. Protect from light.

USP 31 (Paraldehyde). A colourless transparent liquid with a strong characteristic, but not unpleasant or pungent, odour. It is subject to oxidation to form acetic acid. It may contain a suitable stabiliser. Specific gravity is about 0.99. It has a congealing temperature of not lower than 11° and distils completely between 120° and 126°. Soluble 1 in 10 of water v/v, but only 1 in 17 of boiling water v/v; miscible with alcohol, with chloroform, with ether, and with volatile oils. Store in well-filled airtight containers of not more than 30 mL at a temperature not exceeding 25°. Protect from light. It must not be used more than 24 hours after opening the container.

Incompatibility. Paraldehyde exerts a solvent action upon rubber, polystyrene, and styrene-acrylonitrile copolymer and should not be given in plastic syringes made with these materials.

An evaluation of the compatibility of paraldehyde with plastic syringes and needle hubs concluded that, if possible, all-glass syringes should be used with paraldehyde.[1] Needles with plastic hubs could be used. Polypropylene syringes with rubber-tipped plastic plungers (*Plastipak*), or glass syringes with natural rubber-tipped plastic plungers (*Glaspak*) were acceptable only for the immediate administration or measurement of paraldehyde doses.

1. Johnson CE, Vigoreaux JA. Compatibility of paraldehyde with plastic syringes and needle hubs. *Am J Hosp Pharm* 1984; **41:** 306–8.

Stability. Paraldehyde decomposes on storage, particularly after the container has been opened. Partly decomposed paraldehyde is **dangerous** if given. It must not be used if it has a brownish colour or a sharp penetrating odour of acetic acid.

Dependence and Withdrawal

Prolonged use of paraldehyde may lead to dependence, especially in alcoholics. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Adverse Effects and Treatment

Paraldehyde decomposes on storage and deaths from corrosive poisoning have followed the use of such material. Paraldehyde has an unpleasant taste and imparts a smell to the breath; it may cause skin rashes.

Oral or rectal use of paraldehyde may cause gastric or rectal irritation. Intramuscular injection is painful and associated with tissue necrosis, sterile abscesses, and nerve damage. Intravenous use is extremely hazardous since it may cause pulmonary oedema and haemorrhage, hypotension and cardiac dilatation, and circulatory collapse; thrombophlebitis is also associated with intravenous use.

Overdosage results in rapid laboured breathing owing to damage to the lungs and to acidosis. Nausea and vomiting may follow an overdose by mouth. Respiratory depression and coma as well as hepatic and renal damage may occur. Treatment is as for barbiturate overdose (see Amobarbital, p.962).

Precautions

Paraldehyde should not be given to patients with gastric disorders and it should be used with caution, if at all, in patients with bronchopulmonary disease or hepatic impairment. It should not be given rectally in the presence of colitis. Old paraldehyde must never be used.

Paraldehyde must be well diluted before oral or rectal use; if it is deemed essential to give paraldehyde intravenously it must be well diluted and given very slowly with extreme caution (see also Adverse Effects, above and Uses, below). Intramuscular injections may be given undiluted but care should be taken to avoid nerve damage. Plastic syringes should be avoided (see Incompatibility, above).

Interactions

The sedative effects of paraldehyde are enhanced by CNS depressants such as alcohol, barbiturates, and other sedatives. A few case reports suggest that disulfiram may enhance the toxicity of paraldehyde; use together is not recommended.

Pharmacokinetics

Paraldehyde is generally absorbed readily, although absorption is reported to be slower after rectal than after oral or intramuscular doses. It is widely distributed and has a reported half-life of 4 to 10 hours. About 80% of a dose is metabolised in the liver probably to acetaldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid. Unmetabolised drug is largely excreted unchanged through the lungs; only small amounts appear in the urine. It crosses the placental barrier and is distributed into breast milk.

Uses and Administration

Paraldehyde is a hypnotic and sedative with antiepileptic effects. However, because of the hazards associated with its use, its tendency to react with plastic, and the risks associated with its deterioration, it has largely been superseded by other drugs. It is still occasionally used to control status epilepticus (p.469) resistant to conventional treatment. Given rectally or intramuscularly it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

At low temperature it solidifies to form a crystalline mass. If it solidifies, the whole should be liquefied before use.

A usual dose for adults is 10 to 20 mL given rectally as a 10% solution in sodium chloride 0.9% solution or diluted with 1 or 2 parts of oil. Doses of 5 to 10 mL are also occasionally given intramuscularly up to a maximum of 20 mL daily with not more than 5 mL being given at any one site. In the UK it is licensed for intramuscular use in children; however, the *BNFC* advocates use of the rectal route instead, diluted as above. Recommended single daily doses by either route are:

- up to 3 months, 0.5 mL (the *BNFC* suggests a single rectal dose of 0.4 mL/kg (maximum of 0.5 mL) in those under 1 month)
- 3 to 6 months, 1 mL
- 6 to 12 months, 1.5 mL
- 1 to 2 years, 2 mL
- 3 to 5 years, 3 to 4 mL
- 6 to 12 years, 5 to 6 mL

Paraldehyde has been given by slow intravenous infusion in specialist centres with intensive care facilities but this route is not usually recommended; it must be diluted in sodium chloride 0.9% before use.

Paraldehyde has been given orally; it should always be well diluted to avoid gastric irritation.

Preparations

BP 2008: Paraldehyde Injection.

Proprietary Preparations (details are given in Part 3)
USA: Paral.

Penfluridol (BAN, USAN, rINN)

McN-JR-16341; Penfluridoli; Penfluridolum; R-16341. 4-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(*p,p'*-difluorobenzhydryl)propyl]piperidin-4-ol.

Пенфлуридол

$C_{28}H_{27}ClF_5NO$ = 524.0.

CAS — 26864-56-2.

ATC — N05AG03.

ATC Vet — QN05AG03.

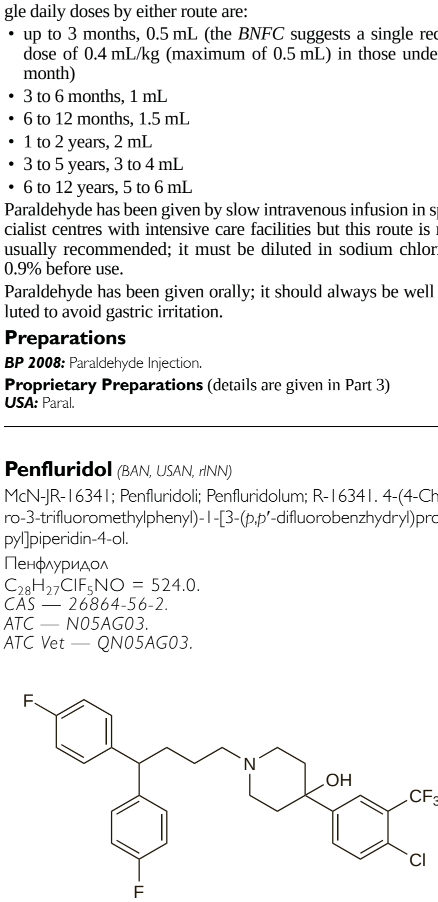

Pharmacopoeias. In *Chin.*

Profile

Penfluridol is a diphenylbutylpiperidine antipsychotic and shares the general properties of the phenothiazine, chlorpromazine (p.969). After oral doses it has a prolonged duration of action that lasts for about a week. It is used in the treatment of psychoses including schizophrenia (p.955).

The usual oral dose of penfluridol for the treatment of chronic psychoses is 20 to 60 mg once a week. Doses of up to 250 mg once a week may be required in severe or resistant conditions.

Schizophrenia. A systematic review[1] concluded that penfluridol appears to have a similar efficacy and adverse effects profile to other classical antipsychotics used in the treatment of schizophrenia (p.955). The authors also suggested that penfluridol, in a weekly oral dose of 40 to 80 mg, is a suitable alternative, particularly for patients who do not respond to daily oral medication or adapt well to depot drugs.

1. Soares BGO, Lima MS. Penfluridol for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/03/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Semap; ***Belg.:*** Semap; ***Braz.:*** Semap; ***Cz.:*** Semap†; ***Denm.:*** Semap; ***Fr.:*** Semap†; ***Gr.:*** Flupidol; ***Israel:*** Semap; ***Mex.:*** Semap; ***Neth.:*** Semap; ***Switz.:*** Semap.

Pentobarbital *(BAN, rINN)*

Aethaminalum; Mebubarbital; Mebumal; Pentobarbitaali; Pentobarbitál; Pentobarbitalis; Pentobarbitalum; Pentobarbitone. 5-Ethyl-5-(1-methylbutyl)barbituric acid.

Пентобарбитал

$C_{11}H_{18}N_2O_3$ = 226.3.

CAS — 76-74-4.

ATC — N05CA01.

ATC Vet — QN05CA01; QN51AA01.

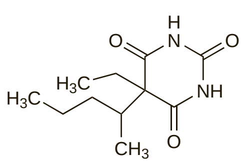

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of pentobarbital: Blockbuster; Menish; Nebbies; Nembies; Nemish; Nemmies; Nimbies; Nimby; Yellow; Yellow bullets; Yellow dolls; Yellow jackets; Yellow submarines; Yellows.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pentobarbital). Colourless crystals or a white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in dehydrated alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates, and with ammonia.

USP 31 (Pentobarbital). A white or practically white, practically odourless, fine powder. Very slightly soluble in water and in carbon tetrachloride; soluble 1 in 4.5 of alcohol, 1 in 4 of chloroform, and 1 in 10 of ether; very soluble in acetone and in methyl alcohol; soluble in benzene. Store in airtight containers.

Pentobarbital Calcium *(BANM, rINNM)*

Calcii Pentobarbitalum; Pentobarbital cálcico; Pentobarbital Calcique; Pentobarbitone Calcium. Calcium 5-ethyl-5-(1-methylbutyl)barbiturate.

Кальций Пентобарбитал

$(C_{11}H_{17}N_2O_3)_2Ca$ = 490.6.

ATC — N05CA01.

ATC Vet — QN05CA01.

Pharmacopoeias. In *Jpn.*

Pentobarbital Sodium *(BANM, rINNM)*

Aethaminalum-Natrium; Ethaminal Sodium; Mebumalnatrium; Natrii Pentobarbitalum; Pentobarbitaalinatrium; Pentobarbital sódico; Pentobarbital sodique; Pentobarbital sodná sůl; Pentobarbitalio natrio druska; Pentobarbitalnatrium; Pentobarbitál-nátrium; Pentobarbitalum natricum; Pentobarbitone Sodium; Sodium Pentobarbital; Soluble Pentobarbitone. Sodium 5-ethyl-5-(1-methylbutyl)barbiturate.

Натрий Пентобарбитал

$C_{11}H_{17}N_2NaO_3$ = 248.3.

CAS — 57-33-0.

ATC — N05CA01.

ATC Vet — QN05CA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pentobarbital Sodium). A white or almost white, hygroscopic, crystalline powder. Very soluble in water. A 10% solution in water has a pH of 9.6 to 11.0 when freshly prepared. Store in airtight containers.

USP 31 (Pentobarbital Sodium). White, crystalline granules or white powder. Is odourless or has a slight characteristic odour. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.8 and 11.0. Solutions decompose on standing, the decomposition being accelerated at higher temperatures. Store in airtight containers.

Incompatibility. Pentobarbital may be precipitated from preparations containing pentobarbital sodium, depending on the concentration and pH. Pentobarbital sodium has, therefore, been reported to be incompatible with many other drugs particularly acids and acidic salts.

Dependence and Withdrawal

As for Amobarbital, p.962.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p.962.

Interactions

As for Amobarbital, p.962.

Pharmacokinetics

Pentobarbital is well absorbed from the gastrointestinal tract after oral or rectal doses, and is reported to be about 60 to 70% bound to plasma proteins. The elimination half-life appears to be dose-dependent and reported values have ranged from 15 to 50 hours. Pentobarbital is metabolised in the liver, mainly by hydroxylation, and excreted in the urine mainly as metabolites.

Uses and Administration

Pentobarbital is a barbiturate that has been used as a hypnotic and sedative. It has general properties and uses similar to those of amobarbital (p.962). It has been used as a sedative and in the short-term management of insomnia (p.957) but barbiturates are not considered appropriate for such purposes. Pentobarbital sodium has also been used for premedication in anaesthetic procedures (p.1780), but barbiturates for pre-operative sedation have been replaced by other drugs. Pentobarbital is usually given as the sodium salt, although pentobarbital itself and its calcium salt have both been used.

A usual oral dose of pentobarbital sodium for insomnia was 100 to 200 mg, given at bedtime. Usual parenteral doses for other indications were 150 to 200 mg as a single intramuscular dose or 100 mg by slow intravenous injection.

Cerebrovascular disorders. For reference to the use of barbiturate-induced coma in the management of patients with cerebral ischaemia, see under Thiopental, p.1796. See also p.1181 for reference to the use of barbiturates in the management of raised intracranial pressure.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used, but pentobarbital has been used similarly.

Preparations

BP 2008: Pentobarbital Tablets;
USP 31: Pentobarbital Elixir; Pentobarbital Sodium Capsules; Pentobarbital Sodium Injection.

Proprietary Preparations (details are given in Part 3)

Canad.: Nembutal†; ***Denm.:*** Mebumal; ***Hong Kong:*** Nembutal†; ***S.Afr.:*** Sopental; ***Thai.:*** Nembutal†; ***USA:*** Nembutal.

Multi-ingredient: ***Arg.:*** Dimaval; ***Canad.:*** Cafergot-PB†; ***USA:*** Cafatine-PB.

Perazine Dimalonate

P-725 (perazine); Pemazine Dimalonate; Perazina, dimalonato de. 10-[3-(4-Methylpiperazin-1-yl)propyl]phenothiazine dimalonate.

$C_{20}H_{25}N_3S,2C_3H_4O_4$ = 547.6.

CAS — 84-97-9 (perazine); 14777-25-4 (perazine dimalonate).

ATC — N05AB10.

ATC Vet — QN05AB10.

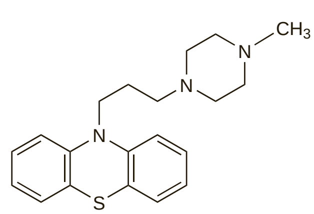

(perazine)

Pharmacopoeias. *Pol.* includes only an injection of the dimalonate. It also includes a monograph for Perazine Dimaleate.

Profile

Perazine dimalonate is a phenothiazine with general properties similar to those of chlorpromazine (p.969) and is used for the treatment of psychotic conditions. It has a piperazine side-chain. It is given orally as the dimalonate although doses are expressed in terms of the base; perazine dimalonate 40.3 mg is equivalent to about 25 mg of perazine. Usual doses are the equivalent of 50 to 600 mg of the base daily; up to 1000 mg daily has been given in resistant cases. It has also been given intramuscularly.

Perazine dimaleate given orally has been used similarly.

Adverse effects. A report of 5 patients receiving perazine dimalonate who developed acute axonal neuropathies of superficial nerve fibres after exposure to sunlight.[1]

1. Roelcke U, *et al.* Acute neuropathy in perazine-treated patients after sun exposure. *Lancet* 1992; **340:** 729–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Taxilan; ***Pol.:*** Perazin; Perazyna; Pernazinum.

Pericyazine *(BAN)*

Periciazine *(pINN)*; Periciazin; Periciazina; Périciazine; Periciazinum; Perisiatsiini; Propericiazine; RP-8909; SKF-20716. 10-[3-(4-Hydroxypiperidino)propyl]phenothiazine-2-carbonitrile; 1-[3-(2-Cyanophenothiazin-10-yl)propyl]piperidin-4-ol.

Перициазин

$C_{21}H_{23}N_3OS$ = 365.5.

CAS — 2622-26-6.

ATC — N05AC01.

ATC Vet — QN05AC01.

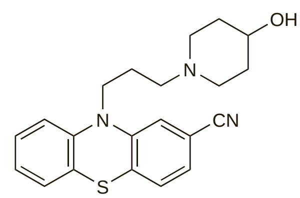

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Sedation and orthostatic hypotension may be marked.

Interactions

As for Chlorpromazine, p.973.

Uses and Administration

Pericyazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain. It is used in the treatment of psychoses including schizophrenia (p.955) and disturbed behaviour (p.954), and in the short-term management of severe anxiety (p.952).

Pericyazine is usually given as the base but the mesilate and tartrate have also been used.

The usual oral dose for the treatment of severe anxiety, agitation, aggression, or impulsive behaviour is 15 to 30 mg daily given in 2 divided doses, the larger amount in the evening. In schizophrenia and severe psychoses initial doses of 75 mg daily may be given in divided doses, increased if necessary, at weekly intervals by increments of 25 mg, to a maximum of 300 mg daily.

A recommended initial oral dose in children aged over 1 year is 500 micrograms daily for a child weighing 10 kg; for heavier children this initial dose may be increased by 1 mg for each additional 5 kg, to a maximum total of 10 mg daily. Thereafter the dose may be gradually increased according to response but the daily maintenance dose should not exceed twice the initial dose.

Elderly patients should be given reduced doses: a recommended initial dose is 5 to 10 mg daily for anxiety or disturbed behaviour and 15 to 30 mg daily for schizophrenia or psychosis, both in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Neuleptil; ***Austral.:*** Neulactil; ***Austria:*** Neuleptil; ***Braz.:*** Neuleptil; ***Canad.:*** Neuleptil; ***Chile:*** Neuleptil; ***Cz.:*** Neuleptil†; ***Denm.:*** Neulactil; ***Fin.:*** Neulactil; ***Fr.:*** Neuleptil; ***Gr.:*** Neuleptil; ***Hong Kong:*** Neulactil; ***Irl.:*** Neulactil†; ***Israel:*** Neuleptil; ***Ital.:*** Neuleptil; ***Neth.:*** Neuleptil; ***NZ:*** Neulactil; ***Rus.:*** Neuleptil (Неулептил); ***S.Afr.:*** Neulactil†; ***Spain:*** Nemactil; ***UK:*** Neulactil; ***Venez.:*** Neuleptil.

Perospirone Hydrochloride *(rINNM)*

Hidrocloruro de perospirona; Pérospirone, Chlorhydrate de; Perospironi Hydrochloridum; SM-9018. *cis-N*-{4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl}-1,2-cyclohexanedicarboximide hydrochloride.

Пероспирона Гидрохлорид

$C_{23}H_{30}N_4O_2S,HCl = 463.0.$

CAS — 150915-41-6 (perospirone); 129273-38-7 (perospirone hydrochloride).

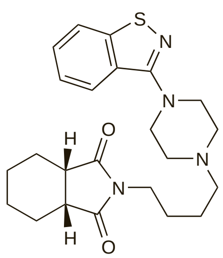

(perospirone)

Profile

Perospirone is an antipsychotic used in the treatment of schizophrenia. Although it has been described as an atypical antipsychotic, the incidence of extrapyramidal effects may be rather higher than is usually seen with atypical drugs such as clozapine (p.981). Perospirone hydrochloride is given in usual oral doses of 12 to 48 mg daily in 3 divided doses.

◊ References.

1. Onrust SV, McClellan K. Perospirone. *CNS Drugs.* 2001; **15:** 329–37.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lullan.

Perphenazine *(BAN, rINN)*

Perfenatsiini; Perfenazin; Perfenazina; Perfenazinas; Perfenazyna; Perphénazine; Perphenazinum. 2-{4-[3-(2-Chlorophenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

Перфеназин

$C_{21}H_{26}ClN_3OS = 404.0.$

CAS — 58-39-9.
ATC — N05AB03.
ATC Vet — QN05AB03.

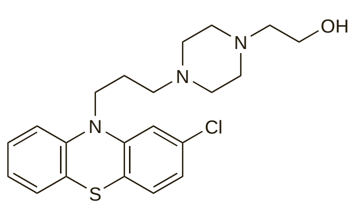

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*
Jpn also includes the maleate.

Ph. Eur. 6.2 (Perphenazine). A white or yellowish-white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute solutions of hydrochloric acid. Protect from light.

USP 31 (Perphenazine). A white to creamy-white odourless powder. M.p. 94° to 100°. Practically insoluble in water; soluble 1 in 7 of alcohol and 1 in 13 of acetone; freely soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Perphenazine has been reported to be incompatible with cefoperazone sodium[1] and with midazolam hydrochloride (see p.1007).

1. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.

Perphenazine Decanoate *(BANM, rINNM)*

Decanoato de perfenazina; Perphénazine, Décanoate de; Perphenazini Decanoas.

Перфеназина Деканоат

$C_{31}H_{44}ClN_3O_2S = 558.2.$

ATC — N05AB03.
ATC Vet — QN05AB03.

Perphenazine Enantate *(BANM, rINNM)*

Enantato de perfenazina; Perphénazine, Enantate de; Perphenazine Enanthate; Perphenazine Heptanoate; Perphenazini Enantas.

Перфеназина Энантат

$C_{28}H_{38}ClN_3O_2S = 516.1.$

CAS — 17528-28-8.
ATC — N05AB03.
ATC Vet — QN05AB03.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Perphenazine has been associated with a lower frequency of sedation, but a higher incidence of extrapyramidal effects.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of perphenazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The distribution of perphenazine into breast milk was studied[2] in a mother who was receiving oral perphenazine 24 mg daily, later reduced to 16 mg daily. Breast feeding was started after it was estimated that a breast-fed infant would ingest about 0.1% of a maternal dose. Treatment with perphenazine lasted for 3.5 months and during this period the child thrived normally and no drug-induced symptoms were seen.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Olesen OV, *et al.* Perphenazine in breast milk and serum. *Am J Psychiatry* 1990; **147:** 1378–9.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Perphenazine is well absorbed after oral doses and undergoes some first-pass metabolism, resulting in a relative bioavailability of about 60 to 80%. Peak plasma concentrations are achieved between 1 to 3 hours after ingestion. It is widely distributed and crosses the placenta. Perphenazine is extensively metabolised; up to 70% is excreted in the urine mainly as metabolites, with about 5% being excreted in the faeces. The plasma elimination half-life of perphenazine is between 9 and 12 hours. Perphenazine decanoate and perphenazine enantate are slowly absorbed from the site of intramuscular injection. They gradually release perphenazine into the body and are therefore suitable for use as depot injections.

◊ Perphenazine 5 or 6 mg given intravenously had a plasma half-life from 8.4 to 12.3 hours in a study of 4 schizophrenic patients and 4 healthy subjects.[1] Plasma-perphenazine concentrations varied considerably 3 to 5 hours after dosing; this was followed by an exponential elimination phase. Plasma concentrations were undetectable after a 6-mg oral dose in 4 healthy subjects and only low plasma concentrations of its sulfoxide metabolite could be detected; this was attributed to a marked first-pass effect. Systemic availability was also variable and poor in 4 schizophrenic patients given perphenazine 12 mg three times daily. However, it was considered that oral therapy should be given at 8-hour intervals. Intramuscular injection of perphenazine enantate 50 or 100 mg every 2 weeks gave plasma-perphenazine concentrations similar to those after continuous oral dosage, but high initial absorption in the first 2 to 3 days was associated with serious CNS adverse effects.

1. Hansen CE, *et al.* Clinical pharmacokinetic studies of perphenazine. *Br J Clin Pharmacol* 1976; **3:** 915–23.

Metabolism. In a study in 12 healthy subjects there was a clear difference in the disposition of a single oral dose of perphenazine between poor and extensive hydroxylators of debrisoquine.[1]

1. Dahl-Puustinen M-L, *et al.* Disposition of perphenazine is related to polymorphic debrisoquin hydroxylation in human beings. *Clin Pharmacol Ther* 1989; **46:** 78–81.

Uses and Administration

Perphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. It is used in the treatment of various psychoses including schizophrenia (p.955) and mania (see Bipolar Disorder, p.372) as well as disturbed behaviour (p.954) and in the short-term, adjunctive management of severe anxiety (p.952). Perphenazine is also used for the management of postoperative or chemotherapy-induced nausea and vomiting (p.1700) and for the treatment of intractable hiccup (p.976).

Perphenazine is usually given orally and sometimes by intramuscular or intravenous injection as the base. Long-acting decanoate or enantate esters of perphenazine, available in some countries, are given by intramuscular injection.

The usual initial oral dose for the treatment of **schizophrenia, mania, and other psychoses** is 4 mg three times daily. The dose is adjusted according to response up to a usual maximum of 24 mg daily, although up to 64 mg daily has occasionally been used in hospitalised patients. Similar doses have been used for the management of **severe agitated or violent behaviour** or in **severe anxiety**. Perphenazine has sometimes been used in preparations with tricyclic antidepressants such as amitriptyline in the treatment of anxiety with depression.

For the **control of nausea and vomiting** the usual oral dose is 4 mg three times daily but up to 8 mg three times daily may be required.

Perphenazine may be given by deep *intramuscular* injection for control of acute psychotic symptoms or for severe nausea and vomiting. An initial dose of 5 or 10 mg is followed, if necessary, by 5 mg every 6 hours to a maximum of 15 to 30 mg daily.

Perphenazine, diluted to a concentration of 500 micrograms/mL in sodium chloride 0.9%, is occasionally given by *intravenous* injection in divided doses, not more than 1 mg being given every 1 to 2 minutes; the maximum intravenous dose is 5 mg. The intravenous route is usually reserved for the control of severe vomiting or intractable hiccup. Perphenazine has also been given by slow infusion.

The long-acting decanoate or enantate esters of perphenazine are given by deep intramuscular injection in doses ranging from about 50 to 300 mg of ester given at intervals of 2 to 4 weeks.

Perphenazine and its esters should be given in reduced doses to the elderly but it should be noted that they are not indicated for the management of agitation and restlessness in these patients.

◊ References.

1. Hartung B, *et al.* Perphenazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 14/04/05).

Preparations

BP 2008: Perphenazine Tablets;
USP 31: Perphenazine and Amitriptyline Hydrochloride Tablets; Perphenazine Injection; Perphenazine Oral Solution; Perphenazine Syrup; Perphenazine Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Decentan; ***Belg.:*** Trilafon†; ***Canad.:*** Trilafon; ***Denm.:*** Trilafon; ***Fin.:*** Peratsin; ***Fr.:*** Trilifan; ***Ger.:*** Decentan; ***Indon.:*** Trilafon; ***Israel:*** Perphenan; ***Ital.:*** Trilafon; ***Mex.:*** Leptopsique; Trilafon†; ***Neth.:*** Trilafon; ***Norw.:*** Trilafon; ***Philipp.:*** Trilafon; ***Pol.:*** Trilafon; ***S.Afr.:*** Trilafon†; ***Spain:*** Decentan; ***Swed.:*** Trilafon; ***Switz.:*** Trilafon; ***Thai.:*** Conazine; Pernamed; Pernazine; Perzine†; Porazine; ***UK:*** Fentazin; ***USA:*** Trilafon†.

Multi-ingredient: ***Arg.:*** Karile; Mutabon D†; ***Canad.:*** PMS-Levazine; Triavil†; ***Chile:*** Mutabon D†; ***Fin.:*** Pertriptyl; ***Gr.:*** Minitran; ***Indon.:*** Mutabon-D; Mutabon-M; ***Ital.:*** Mutabon; ***Mex.:*** Adepsique; ***Port.:*** Mutabon; ***S.Afr.:*** Etrafon†; ***Spain:*** Mutabase; ***Thai.:*** Anxipress-D†; Neuragon; Polybon; ***UK:*** Triptafen; ***USA:*** Etrafon; Triavil†.

Phenazepam

Fenazepam. 7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{10}BrClN_2O = 349.6.$

CAS — 51753-57-2.

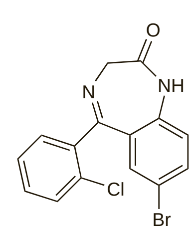

Profile

Phenazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It is used in the short-term treatment of anxiety disorders and as an anticonvulsant.

Phenprobamate *(BAN, rINN)*

Fenprobamaatti; Fenprobamat; Fenprobamato; MH-532; Phenprobamatum; Proformiphen. 3-Phenylpropyl carbamate.

Фенпробамат

$C_{10}H_{13}NO_2$ = 179.2.
CAS — 673-31-4.
ATC — M03BA01.
ATC Vet — QM03BA01.

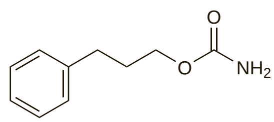

Profile

Phenprobamate is a carbamate with general properties similar to those of meprobamate (p.1006). It has been used for its anxiolytic and muscle relaxant actions.

Preparations

Proprietary Preparations (details are given in Part 3)
Turk.: Gamaflex; Gamakuil.
Multi-ingredient: *Turk.:* Kuiflex; Kuilil.

Pimozide *(BAN, USAN, rINN)*

McN-JR-6238; Pimotsidi; Pimozid; Pimozida; Pimozidas; Pimozidum; Pimozyd; R-6238. 1-{1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidyl}benzimidazolin-2-one; 1-{1-[3-(4,4′-Difluorobenzhydryl)propyl]-4-piperidyl}benzimidazolin-2-one.

Пимозид

$C_{28}H_{29}F_2N_3O$ = 461.5.
CAS — 2062-78-4.
ATC — N05AG02.
ATC Vet — QN05AG02.

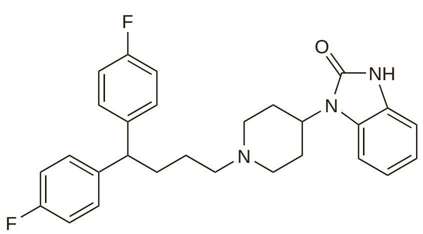

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pimozide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Pimozide). A white crystalline powder. Insoluble in water; soluble 1 in 1000 of alcohol, of ether, and of methyl alcohol, 1 in 100 of acetone, 1 in 10 of chloroform, and 1 in more than 1000 of 0.1N hydrochloric acid. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Extrapyramidal effects may be more common than with chlorpromazine but pimozide may be less likely to cause sedation, hypotension, or antimuscarinic effects.

Ventricular arrhythmias and other ECG abnormalities, such as prolongation of the QT interval and T-wave changes, have been associated with the use of pimozide; an ECG should therefore be performed before, and repeated periodically during, treatment. If repolarisation changes appear or arrhythmias develop, the need for continuing treatment should be reviewed; the dose of pimozide should be reduced or, if the QT interval exceeds 500 milliseconds, therapy should be withdrawn. Pimozide is contra-indicated in patients with pre-existing prolongation of the QT interval, or a family history of congenital QT prolongation, and in patients with a history of cardiac arrhythmias. Electrolyte disturbances such as hypokalaemia or hypomagnesaemia in patients receiving pimozide may lead to cardiotoxicity.

Effects on the cardiovascular system. The UK CSM has received reports of ventricular arrhythmias and other ECG abnormalities such as prolongation of the QT interval and T-wave changes associated with the use of pimozide.[1,2] In August 1990 they had received 13 reports of sudden unexpected death since 1971; many of these patients had no evidence of pre-existing cardiac disease, and 7 were under 30 years of age. Five of the 13 were also taking other antipsychotics. Most cases were associated with doses greater than 20 mg daily and many had had the dose increased rapidly, possibly resulting in substantial tissue accumulation. By February 1995 the CSM had received a total of 40 reports (16 fatal) of serious cardiac reactions most of which involved arrhythmias.

See also under Chlorpromazine, p.970.

1. CSM. Cardiotoxic effects of pimozide. *Current Problems 29* 1990. Also available at: http://www.mhra.gov.uk/idcplg?IdcService=GET_FILE&dDocName=CON2024447&RevisionSelectionMethod=LatestReleased (accessed 07/08/08)
2. CSM/MCA. Cardiac arrhythmias with pimozide (Orap). *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Interactions

As for Chlorpromazine, p.973. The risk of arrhythmias with pimozide may be increased by other drugs that prolong the QT interval including some antiarrhythmics, other antipsychotics (including depot preparations), tricyclic antidepressants, the antihistamines terfenadine and astemizole, antimalarials, and cisapride; use together should be avoided. Use with drugs that induce electrolyte disturbances, such as diuretics, should also be avoided.

The use of pimozide with drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 is contra-indicated; the resultant decrease in the metabolism of pimozide may lead to increased plasma concentrations and hence greater risk of cardiac arrhythmias. CYP3A4 inhibitors include the macrolide antibacterials such as clarithromycin, erythromycin, and troleandomycin; the azole antifungals including itraconazole and ketoconazole; the HIV-protease inhibitors; the NNRTIs; nefazodone, and zileuton. The metabolism of pimozide may also be inhibited by grapefruit juice and use together should be avoided.

Pimozide is also metabolised by CYP2D6, albeit to a lesser extent, and *in vitro* data indicate that the CYP2D6 inhibitor quinidine may reduce the metabolism of pimozide; UK licensed product information contra-indicates the use of such inhibitors with pimozide. The isoenzyme CYP1A2 may also be involved in the metabolism of pimozide and consequently there is a theoretical possibility of interactions with CYP1A2 inhibitors.

Pimozide should also not be used with SSRIs such as citalopram, escitalopram, paroxetine, and sertraline.

Antibacterials. Sudden deaths have occurred in patients given pimozide and *clarithromycin*, see p.973.

Pharmacokinetics

More than half of an oral dose of pimozide is reported to be absorbed. It undergoes significant first-pass metabolism. Peak plasma concentrations have been reported after 4 to 12 hours and there is a considerable interindividual variation in the concentrations achieved. Pimozide is metabolised in the liver mainly by *N*-dealkylation and excreted in the urine and faeces in the form of metabolites and unchanged drug. Metabolism is mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2D6; CYP1A2 may also be involved. Pimozide has a mean elimination half-life of about 55 hours, although half-lives of up to 150 hours have been noted in some patients.

Uses and Administration

Pimozide is a diphenylbutylpiperidine antipsychotic and is structurally similar to the butyrophenones. It is a long-acting antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975), although it also has some calcium-blocking activity. Pimozide is given orally in the management of psychoses including schizophrenia, paranoid states, and monosymptomatic hypochondria (p.954) and in Tourette's syndrome. An ECG should be performed in all patients before starting treatment with pimozide (see Adverse Effects, Treatment, and Precautions, above).

In **schizophrenia**, treatment is usually begun with a dose of 2 mg daily (the *BNFC* suggests 1 mg in those aged 12 to 18 years), adjusted thereafter according to response in increments of 2 to 4 mg at intervals of not less than 1 week. A maximum daily dose of 20 mg should not be exceeded. It is usually given as a single daily dose.

In **monosymptomatic hypochondria** and **paranoid psychoses**, the initial dose is 4 mg daily adjusted as above to a maximum daily dose of 16 mg.

Pimozide treatment should start at half the usual initial dosage in elderly patients.

In the USA, pimozide is used for the treatment of **Tourette's syndrome** in an initial dose of 1 to 2 mg daily in divided doses; children may be given 50 micrograms/kg daily initially. Dosage may be increased gradually to a maximum of 10 mg daily or 200 micrograms/kg daily; data are limited in children under 12 years of age. Although not licensed in the UK for the treatment of Tourette's syndrome, the *BNFC* suggests that children aged from 2 to 12 years may be given 1 to 4 mg daily and those aged from 12 to 18 years, 2 to 10 mg daily.

Chorea. Antipsychotics such as pimozide have some action against choreiform movements (p.953) as well as being of use to control the behavioural disturbances of Huntington's chorea.

References.

1. Shannon KM, Fenichel GM. Pimozide treatment of Sydenham's chorea. *Neurology* 1990; **40:** 186.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to other drugs.[1] In very severe dystonia combination therapy may be required. Pimozide in gradually increasing doses up to 12 mg daily with tetrabenazine and trihexyphenidyl is sometimes effective. However, antipsychotics often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p.971).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Schizophrenia. A systematic review[1] concluded that pimozide appears to be of similar efficacy to other classical antipsychotics in the treatment of schizophrenia (p.955). There was no evidence that it was particularly useful for those with delusional disorders or with mainly negative symptoms.

1. Rathbone J, McMonagle T. Pimozide for schizophrenia or related psychoses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 20/03/08).

Taste disorders. For reference to the use of pimozide in the treatment of taste disorders, see Chlorpromazine, p.977.

Tourette's syndrome. Tourette's syndrome (see Tics, p.954) is a disorder characterised by motor and vocal tics and behavioural disturbances. Many patients with Tourette's syndrome do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide[1,2] have been most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. However, superiority of either drug in terms of efficacy or adverse effects has not been clearly demonstrated. Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al.* Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46:** 722–30.
2. Sallee FR, *et al.* Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154:** 1057–62.

Preparations

BP 2008: Pimozide Tablets;
USP 31: Pimozide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Orap; ***Austral.:*** Orap; ***Austria:*** Orap; ***Belg.:*** Orap; ***Braz.:*** Orap; ***Canad.:*** Orap; ***Chile:*** Orap; ***Cz.:*** Orap†; ***Denm.:*** Orap; ***Fr.:*** Orap; ***Ger.:*** Orap; ***Gr.:*** Pirium; ***Hong Kong:*** Orap; ***India:*** Orap; ***Indon.:*** Orap; ***Irl.:*** Orap; ***Israel:*** Orap; ***Ital.:*** Orap; ***Jpn:*** Orap; ***Neth.:*** Orap; ***NZ:*** Orap; ***Port.:*** Orap; ***S.Afr.:*** Orap; ***Spain:*** Orap; ***Thai.:*** Orap; Pizide; ***Turk.:*** Norofren; ***UK:*** Orap; ***USA:*** Orap; ***Venez.:*** Orap.

Pinazepam *(rINN)*

Pinazépam; Pinazepamum. 7-Chloro-1,3-dihydro-5-phenyl-1-(prop-2-ynyl)-2*H*-1,4-benzodiazepin-2-one.

Пиназепам

$C_{18}H_{13}ClN_2O$ = 308.8.

CAS — 52463-83-9.

ATC — N05BA14.

ATC Vet — QN05BA14.

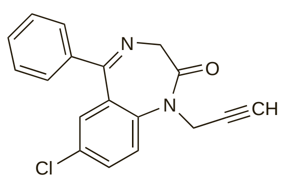

Profile

Pinazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It is given in oral doses of 5 to 20 mg daily in divided doses for the short-term treatment of anxiety disorders (p.952). Doses of 2.5 to 5 mg at night have been used in the treatment of insomnia (p.957).

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Domar; ***Ital.:*** Domar; ***Mex.:*** Yunir; ***Singapore:*** Domar; ***Spain:*** Duna; ***Thai.:*** Domar.

Pipamperone *(BAN, USAN, rINN)*

Floropipamide; McN-JR-3345; Pipamperon; Pipamperona; Pipampérone; Pipamperoni; Pipamperonum; R-3345. 1-[3-(4-Fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide.

Пипамперон

$C_{21}H_{30}FN_3O_2$ = 375.5.

CAS — 1893-33-0.

ATC — N05AD05.

ATC Vet — QN05AD05.

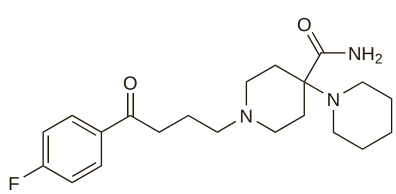

Pipamperone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipamperona; Pipampérone, Chlorhydrate de; Pipamperoni Hydrochloridum.

Пипамперона Гидрохлорид

$C_{21}H_{30}FN_3O_2,2HCl$ = 448.4.

CAS — 2448-68-2.

ATC — N05AD05.

ATC Vet — QN05AD05.

Profile

Pipamperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It is given orally as the hydrochloride for the treatment of psychoses. Doses are expressed in terms of the base; pipamperone hydrochloride 47.8 mg is equivalent to about 40 mg of pipamperone. Usual initial doses equivalent to 40 mg of the base have been given 2 or 3 times daily, increased gradually thereafter according to response; doses of 360 mg or more have been given daily in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Dipiperon; ***Denm.:*** Dipiperon; ***Fr.:*** Dipiperon; ***Ger.:*** Dipiperon; ***Gr.:*** Dipiperon; ***Ital.:*** Piperonil†; ***Neth.:*** Dipiperon; ***Switz.:*** Dipiperon.

Pipotiazine *(BAN, rINN)*

Pipothiazine; Pipotiatsiini; Pipotiazin; Pipotiazina; Pipotiazinum; RP-19366. 10-{3-[4-(2-Hydroxyethyl)piperidino]propyl}-*NN*-dimethylphenothiazine-2-sulphonamide; 2-{4-[3-(2-Dimethylsulphamoylphenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

Пипотиазин

$C_{24}H_{33}N_3O_3S_2$ = 475.7.

CAS — 39860-99-6.

ATC — N05AC04.

ATC Vet — QN05AC04.

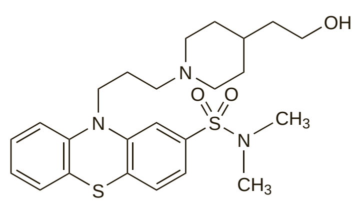

Pipotiazine Palmitate *(BANM, USAN, rINNM)*

IL-19552; Palmitato de pipotiazina; Pipothiazine Palmitate; Pipotiazine, Palmitate de; Pipotiazini Palmitas; RP-19552.

Пипотиазина Пальмитат

$C_{40}H_{63}N_3O_4S_2$ = 714.1.

CAS — 37517-26-3.

ATC — N05AC04.

ATC Vet — QN05AC04.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Effects on mental function. Manic symptoms developed in a schizophrenic patient given pipotiazine palmitate. Symptoms recurred on rechallenge.[1]

1. Singh AN, Maguire J. Pipothiazine palmitate induced mania. *BMJ* 1984; **289:** 734.

Pharmacokinetics

Pipotiazine palmitate is very slowly absorbed from the site of intramuscular injection. It gradually releases pipotiazine into the body and is therefore suitable for use as a depot injection.

Uses and Administration

Pipotiazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain. It is used in the treatment of schizophrenia (p.955) and other psychoses. Pipotiazine is given orally as the base and by deep intramuscular injection as the palmitate ester; oral doses are expressed as the base and parenteral doses are expressed as the ester.

A usual oral dose of pipotiazine for the treatment of psychoses is 5 to 20 mg daily in a single dose; in severe psychoses higher doses have been given for brief periods, up to 60 mg daily being permitted in some countries.

The long-acting palmitate ester of pipotiazine is given by deep intramuscular injection. An initial test dose of 25 mg is followed by a further 25 to 50 mg after 4 to 7 days. The dosage is then adjusted in increments of 25 to 50 mg according to response every 4 weeks. Usual maintenance doses of 50 to 100 mg are given at average intervals of 4 weeks; the maximum recommended dose in the UK is 200 mg every 4 weeks.

Pipotiazine should be given in reduced dosage to elderly patients; a starting dose of 5 to 10 mg has been suggested for pipotiazine palmitate intramuscular injections.

Schizophrenia. A systematic review[1] concluded that depot pipotiazine palmitate appeared to be no different in terms of efficacy or adverse effects to other antipsychotics given orally or by depot injection.

1. Dinesh M, *et al.* Depot pipotiazine palmitate and undecylenate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Piportyl L4; ***Braz.:*** Piportil; ***Canad.:*** Piportil L4; ***Chile:*** Piportyl; ***Fr.:*** Piportil; ***Hung.:*** Piportil; ***Irl.:*** Piportil; ***Mex.:*** Piportil L4; ***Neth.:*** Piportil†; ***NZ:*** Piportil; ***Rus.:*** Piportil (Пипортил); ***Singapore:*** Piportil†; ***Spain:*** Lonseren; ***UK:*** Piportil.

Prazepam *(BAN, USAN, rINN)*

Pratsepaami; Prazépam; Prazepám; Prazepamas; Prazepamum; W-4020. 7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

Празепам

$C_{19}H_{17}ClN_2O$ = 324.8.

CAS — 2955-38-6.

ATC — N05BA11.

ATC Vet — QN05BA11.

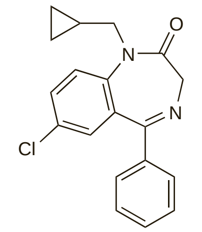

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Prazepam). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

Profile

Prazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). After oral doses, prazepam undergoes extensive first-pass metabolism in the liver to oxazepam (p.1014) and desmethyldiazepam (nordazepam, p.1012). Desmethyldiazepam is largely responsible for the pharmacological activity of prazepam. The usual oral dose for the short-term treatment of anxiety disorders (p.952) is 30 mg daily as a single nightly dose or in divided doses; in severe conditions up to 60 mg daily has been given. In elderly or debilitated patients, treatment should start with a daily dose of no more than 15 mg.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of prazepam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The ratio of desmethyldiazepam in plasma to that in breast milk of 5 women given prazepam 20 mg three times daily for 3 days was 9.6 from measurements 12 hours after the last dose.[2] It was estimated that a breast-fed infant of a mother on continuous prazepam therapy would ingest the equivalent of about 4% of the daily maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Brodie RR, *et al.* Concentrations of N-descyclopropylmethylprazepam in whole-blood, plasma, and milk after administration of prazepam to humans. *Biopharm Drug Dispos* 1981; **2:** 59–68.

Pharmacokinetics. References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24:** 446–51.

Porphyria. Prazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Demetrin; ***Belg.:*** Lysanxia; ***Fr.:*** Lysanxia; ***Ger.:*** Demetrin; Mono Demetrin; ***Gr.:*** Centrac; ***Irl.:*** Centrax; ***Ital.:*** Prazene; Trepidan; ***Neth.:*** Reapam; ***Port.:*** Demetrin; ***S.Afr.:*** Demetrin; ***Switz.:*** Demetrin; ***Thai.:*** Pozapam; Prasepine.

Prochlorperazine (BAN, rINN)

Chlormeprazine; Prochlorpemazine; Prochlorpérazine; Prochlorperazinum; Proclorperazina; Proklooriperatsiini; Proklorperazin. 2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine.

Прохлорперазин

$C_{20}H_{24}ClN_3S$ = 373.9.

CAS — 58-38-8.

ATC — N05AB04.

ATC Vet — QN05AB04.

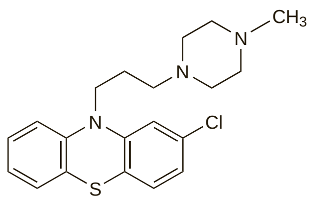

Pharmacopoeias. In *US.*

USP 31 (Prochlorperazine). A clear, pale yellow, viscous liquid, sensitive to light. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in ether. Store in airtight containers. Protect from light.

Prochlorperazine Edisilate (BANM, rINNM)

Chlormeprazine Edisylate; Edisilato de proclorperazina; Prochlorpemazine Edisylate; Prochlorpérazine, Edisilate de; Prochlorperazine Edisylate; Prochlorperazine Ethanedisulphonate; Prochlorperazini Edisilas.

Прохлорперазина Эдизилат

$C_{20}H_{24}ClN_3S,C_2H_6O_6S_2$ = 564.1.

CAS — 1257-78-9.

ATC — N05AB04.

ATC Vet — QN05AB04.

Pharmacopoeias. In *US.*

USP 31 (Prochlorperazine Edisylate). A white to very light yellow odourless crystalline powder. Soluble 1 in 2 of water and 1 in 1500 of alcohol; insoluble in chloroform and in ether. Solutions in water are acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. See under Prochlorperazine Mesilate, below.

Prochlorperazine Maleate (BANM, rINNM)

Chlormeprazine Maleate; Maleato de proclorperazina; Prochloroperazyny maleinian; Prochlorpemazine Maleate; Prochlorperazine Dihydrogen Maleate; Prochlorperazine Dimaleate; Prochlorpérazine, Maléate de; Prochlorperazini maleas; Prochlorperazin-maleinát; Prochlorperazino maleatas; Proklooriperatsiinimaleaatti; Proklorperazinmaleat; Proklórperazin-maleát.

Прохлорперазина Малеат

$C_{20}H_{24}ClN_3S,2C_4H_4O_4$ = 606.1.

CAS — 84-02-6.

ATC — N05AB04.

ATC Vet — QN05AB04.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Prochlorperazine Maleate). A white or pale yellow, crystalline powder. Very slightly soluble in water and in alcohol. A freshly prepared saturated solution in water has a pH of 3.0 to 4.0. Protect from light.

USP 31 (Prochlorperazine Maleate). A white or pale yellow, practically odourless, crystalline powder. Practically insoluble in water; soluble 1 in 1200 of alcohol; slightly soluble in warm chloroform. Its saturated solution is acid to litmus. Store in airtight containers. Protect from light.

Prochlorperazine Mesilate (BANM, rINNM)

Chlormeprazine Mesylate; Mesilato de proclorperazina; Prochlorpemazine Mesylate; Prochlorperazine Dimethanesulphonate; Prochlorpérazine, mésilate de; Prochlorperazine Mesylate; Prochlorperazine Methanesulphonate; Prochlorperazini mesilas; Prochlorperazini Mesylas.

Прохлорперазина Мезилат

$C_{20}H_{24}ClN_3S,2CH_3SO_3H$ = 566.2.

CAS — 5132-55-8.

ATC — N05AB04.

ATC Vet — QN05AB04.

Pharmacopoeias. In *Br.*

BP 2008 (Prochlorperazine Mesilate). A white or almost white, odourless or almost odourless powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 2.0 to 3.0. Protect from light.

Incompatibility. Incompatibility has been reported between the edisilate or mesilate salts of prochlorperazine and several other compounds: these include aminophylline, amphotericin B, ampicillin sodium, aztreonam, some barbiturates, benzylpenicillin salts, calcium gluconate, cefalotin sodium, cefmetazole sodium, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, midazolam hydrochloride, and some sulfonamides. Incompatibility between prochlorperazine edisilate and morphine sulfate has been attributed to phenol present in some formulations of the opioid.[1,2] Incompatibility has been reported on dilution of prochlorperazine edisilate injection with sodium chloride injection containing methyl hydroxybenzoate and propyl hydroxybenzoate as preservatives.[3] The problem did not occur with unpreserved sodium chloride or when benzyl alcohol was used as preservative. Prochlorperazine mesilate syrup has been reported to be incompatible with magnesium trisilicate mixture.[4]

1. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; **42:** 2651.
2. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
3. Jett S, *et al.* Prochlorperazine edisylate incompatibility. *Am J Hosp Pharm* 1983; **40:** 210.
4. Greig JR. Stemetil syrup and magnesium trisilicate. *Pharm J* 1986; **237:** 504.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Prochlorperazine may cause less sedation and fewer antimuscarinic effects but extrapyramidal effects may be more frequent.

Severe dystonic reactions have followed the use of prochlorperazine, particularly in children and adolescents. It should therefore be used with extreme care in children. In addition, in the UK, parenteral use in children is not recommended.

Local irritation has occurred after the use of buccal tablets of prochlorperazine maleate.

Effects on the cardiovascular system. Hypertension has been reported[1] in a few patients given prochlorperazine intravenously for prophylaxis of cisplatin-induced nausea and vomiting.

1. Roche H, *et al.* Hypertension and intravenous antidopaminergic drugs. *N Engl J Med* 1985; **312:** 1125–6.

Effects on the mouth. Reports of ulceration and soreness of the lip and tongue have been associated with use of prochlorperazine maleate oral tablets.[1,2] The erosive cheilitis resolved after withdrawal of prochlorperazine and recurred on rechallenge.

1. Duxbury AJ, *et al.* Erosive cheilitis related to prochlorperazine maleate. *Br Dent J* 1982; **153:** 271–2.
2. Reilly GD, Wood ML. Prochlorperazine—an unusual cause of lip ulceration. *Acta Derm Venereol (Stockh)* 1984; **64:** 270–1.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

◊ The pharmacokinetics of prochlorperazine were studied in 8 healthy subjects after doses of 6.25 and 12.5 mg intravenously, and 25 mg by mouth.[1] There was a marked interindividual variation in pharmacokinetics after intravenous doses but no evidence of dose-dependent pharmacokinetics; mean terminal half-lives were 6.8 hours for the higher and 6.9 hours for the lower dose. The apparent volume of distribution was very high and plasma clearance values were apparently greater than liver plasma flow, suggesting that the liver may not be the only site of metabolism. After oral doses, prochlorperazine concentrations were detectable in only 4 of the 8 subjects, due in part to a low bioavailability but also to the lack of sensitivity of the high-pressure liquid chromatographic assay used. The time to peak plasma concentration varied from 1.5 to 5 hours, and the peak concentrations varied from 1.6 to 7.6 nanograms/mL. Bioavailability was estimated to range from 0 to 16%. A low bioavailability due to high first-pass metabolism would be expected because of the high plasma clearance of prochlorperazine.

1. Taylor WB, Bateman DN. Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers. *Br J Clin Pharmacol* 1987; **23:** 137–42.

Buccal route. Both single- and multiple-dose studies indicated that bioavailability of prochlorperazine maleate was greater after buccal doses than when given orally.[1,2] Doses of 3 mg twice daily by the buccal route and 5 mg three times daily by mouth produced similar steady-state plasma-prochlorperazine concentrations.[1]

1. Hessell PG, *et al.* A comparison of the availability of prochlorperazine following im buccal and oral administration. *Int J Pharmaceutics* 1989; **52:** 159–64.
2. Finn A, *et al.* Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. *J Clin Pharmacol* 2005; **45:** 1383–90.

Uses and Administration

Prochlorperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. Prochlorperazine and its salts are widely used in the prevention and treatment of nausea and vomiting (p.1700) including that associated with migraine or drug-induced emesis. They are also used for the short-term symptomatic relief of vertigo (p.565) as occurs in Ménière's disease (p.564) or labyrinthitis, and in the management of schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and other psychoses. Prochlorperazine has been used as an adjunct in the short-term management of severe anxiety (p.952).

Prochlorperazine maleate is generally administered by the oral or buccal routes, while prochlorperazine edisilate and mesilate are given orally or parenterally. The base has been given rectally.

Depending on the country or the manufacturer, doses of prochlorperazine are expressed either as the base or the salt. Prochlorperazine edisilate 7.5 mg, prochlorperazine maleate 8.1 mg, or prochlorperazine mesilate 7.6 mg are equivalent to about 5 mg of prochlorperazine. Most doses in the UK are expressed in terms of the maleate or mesilate, while most doses in the USA are expressed in terms of the base. As a result there is a disparity in the dosage recommendations for these countries, with the doses in the USA tending to be higher.

Reduced dosage may be required in elderly patients.

For **nausea and vomiting** doses are as follows:

- in the UK, the usual *oral* dose for prevention is 5 to 10 mg of the maleate or mesilate (roughly equivalent to about 3 to 6.5 mg of the base) 2 or 3 times daily
- for the treatment of nausea and vomiting, recommended UK doses are 20 mg of the maleate or mesilate *orally* or 12.5 mg of the mesilate by deep *intramuscular* injection; further doses, preferably orally, are given if necessary. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily
- in the USA, the *oral* dose for the control of nausea and vomiting is the equivalent of 5 or 10 mg of the base (as edisilate or maleate) given 3 or 4 times daily; alternatively the equivalent of 10 mg of the base twice daily or 15 mg once daily of the base (both as the maleate) may be taken as modified-release capsules. The recommended *intramuscular* dosage is the equivalent of 5 to 10 mg of the base (as edisilate) given every 3 to 4 hours if necessary, up to a total of 40 mg of the base daily. The *rectal* dose is 25 mg of the base given twice daily. In the management of severe nausea and vomiting the equivalent of 2.5 to 10 mg of prochlorperazine (as the edisilate) may be given by slow *intravenous* injection or infusion at a rate not exceeding 5 mg/minute; doses should not exceed 40 mg daily

For treatment of **psychoses** the following doses have been given:

- in the UK, prochlorperazine maleate or mesilate may be given in an *oral* dose of 12.5 mg twice daily for 7 days adjusted gradually to 75 to 100 mg daily according to response; some patients may be maintained on doses of 25 to 50 mg daily. The equivalent of prochlorperazine mesilate 12.5 to 25 mg two or three times daily may be given by deep *intramuscular* injection
- in the USA, prochlorperazine is given as the maleate or edisilate in usual initial *oral* doses equivalent to 5 or 10 mg of the base 3 or 4 times daily adjusted according to response up to a maximum of 150 mg of base daily. In acute disturbances it may be given by deep *intramuscular* injection as the edisilate in doses equivalent to 10 to 20 mg of the base and repeated every 2 to 6 hours if necessary

There are similar discrepancies with **children's doses**. Owing to the risk of severe extrapyramidal reactions, prochlorperazine should be used with extreme caution in children; it is not recommended for very young children or those weighing less than 10 kg. Where use in children is unavoidable, UK licensed product information has suggested that 250 micrograms/kg of the maleate or mesilate may be given orally 2 or 3 times daily to children aged 1 year and over for the prevention and treatment of nausea and vomiting; the intramuscular route is considered unsuitable. However, the *BNFC* suggests giving intramuscular doses, repeated up to 3 times daily if necessary, according to age as follows: 2 to 5 years, 1.25 to 2.5 mg; 5 to 12 years, 5 to 6.25 mg.

In the USA oral, rectal, and intramuscular routes have all been advocated for children aged 2 years and over. The usual oral or rectal antiemetic dose ranges up to 7.5 mg of the base or its equivalent daily in children weighing 10 to 13 kg; in children 14 to 17 kg, up to 10 mg daily; from 18 to 39 kg, up to 15 mg daily. Higher doses have been given for psychoses. The suggested intramuscular dose for children in the USA is the equivalent of about 130 micrograms/kg of base given as a single deep intramuscular injection of the edisilate.

Oral doses of 5 to 10 mg of the maleate or mesilate (or, in the USA, the equivalent of 5 mg of the base) up to 3 or 4 times daily have been used for short-term adjunctive management of **severe anxiety disorders**. A modified-release preparation may be given in doses similar to those used in nausea and vomiting.

Prochlorperazine is also used in the UK in the treatment of **vertigo** including that due to Ménière's disease. It is given *orally* in doses of 15 to 30 mg of the maleate or mesilate daily in divided doses; after several weeks the dose may be gradually reduced to 5 to 10 mg daily. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily.

Headache. Some phenothiazines such as prochlorperazine have been used in the control of the symptoms of severe migraine (see p.976). In comparative studies[1,2] prochlorperazine appears to have been more effective in relieving migraine headache and nausea and vomiting than metoclopramide when these drugs were given parenterally. Intravenous prochlorperazine was shown to be effective in aborting intractable migraine in children in a small uncontrolled study.[3]

1. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
2. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
3. Kabbouche MA, *et al.* Tolerability and effectiveness of prochlorperazine for intractable migraine in children. *Pediatrics* 2001; **107:** 767. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e62 (accessed 28/04/04)

Preparations

BP 2008: Prochlorperazine Buccal Tablets; Prochlorperazine Injection; Prochlorperazine Oral Solution; Prochlorperazine Tablets;
USP 31: Prochlorperazine Edisylate Injection; Prochlorperazine Maleate Tablets; Prochlorperazine Oral Solution; Prochlorperazine Suppositories.

Proprietary Preparations (details are given in Part 3)

Austral.: Stemetil; Stemzine; ***Canad.:*** Apo-Prochlorazine; Nu-Prochlor; Stemetil; ***Denm.:*** Stemetil; ***Fin.:*** Stemetil; ***Hong Kong:*** Dhaperazine; Seratil; Stemetil; ***India:*** Bukatel†; Emidoxyn; Stemetil; Vometil; ***Irl.:*** Buccastem; Stemetil; ***Ital.:*** Stemetil; ***Malaysia:*** Dhaperazine; Nautisol; Prochlor; Stemetil†; ***Neth.:*** Stemetil; ***Norw.:*** Stemetil; ***NZ:*** Antinaus; Buccastem; Stemetil; ***Pol.:*** Chloropernazinum; ***S.Afr.:*** Mitil; Scripto-Metic; Stemetil; ***Singapore:*** Dhaperazine; Prochlor; Stemetil; ***Swed.:*** Stemetil; ***Thai.:*** Proclozine; Stemetil; ***UK:*** Buccastem; Proziere†; Stemetil; ***USA:*** Compazine; Compro.

Multi-ingredient: ***Ital.:*** Difmetre.

Promazine *(BAN, rINN)*

A-145; NSC-31447; Promatsiini; Promazin; Promazina; Promazinum; Propazinum; 3276-RP; RP-3276; WY-1094. *NN*-Dimethyl-3-phenothiazin-10-ylpropylamine.

Промазин

$C_{17}H_{20}N_2S$ = 284.4.
CAS — 58-40-2.
ATC — N05AA03.
ATC Vet — QN05AA03.

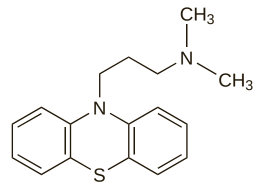

NOTE. The code A-145 has also been used for *N*-ethylcarbaminomethyl-*L*-isoleucine, a compound investigated as an antineoplastic

Promazine Embonate *(BANM, rINNM)*

Embonato de promazina; Promazine, Embonate de; Promazine Pamoate; Promazini Embonas.

Промазина Эмбонат

$(C_{17}H_{20}N_2S)_2,C_{23}H_{16}O_6$ = 957.2.
ATC — N05AA03.
ATC Vet — QN05AA03.

Promazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de promazina; Promatsiinihydrokloridi; Promazine, chlorhydrate de; Promazin-hidroklorid; Promazin-hydrochlorid; Promazinhydroklorid; Promazini hydrochloridum; Promazino hidrochloridas; Promazyny chlorowodorek.

Промазина Гидрохлорид

$C_{17}H_{20}N_2S,HCl$ = 320.9.
CAS — 53-60-1.
ATC — N05AA03.
ATC Vet — QN05AA03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Promazine Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Very soluble in water, in alcohol, and in dichloromethane. A freshly prepared 5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 31 (Promazine Hydrochloride). A white or slightly yellow, practically odourless, crystalline powder. It oxidises upon prolonged exposure to air and acquires a pink or blue colour. Soluble 1 in 3 of water; freely soluble in chloroform. pH of a 1 in 20 solution is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between promazine hydrochloride and several other compounds: these include aminophylline, some barbiturates, benzylpenicillin potassium, chlortetracycline, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, phenytoin sodium, prednisolone sodium phosphate, and sodium bicarbonate.

Sorption. A study[1] of drug loss from intravenous delivery systems reported an 11% loss of promazine hydrochloride from solution when infused for 7 hours via a plastic infusion set, and a 59% loss after infusion for one hour from a glass syringe through silastic tubing. Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Stability. A study of the stability of promazine diluted to a 0.1% infusion in sodium chloride 0.9% or glucose 5% found that solutions in glucose 5% remained stable for up to 6 days at 4°, and at room temperature, provided they were stored in the dark.[1] However, with sodium chloride 0.9% as the diluent, deterioration of promazine was observed 24 hours after preparation, even when stored in the dark, and after 8 hours when exposed to light. Temperature had no effect on degradation rate.

1. Tebbett IR, *et al.* Stability of promazine as an intravenous infusion. *Pharm J* 1986; **237:** 172–4.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Pregnancy. An increased incidence of neonatal jaundice coincided with the increased use of promazine.[1] A decrease in the incidence of jaundice was noted 3 months after the total withdrawal of the drug from the hospital although restriction of its use during labour had no impact.

1. John E. Promazine and neonatal hyperbilirubinaemia. *Med J Aust* 1975; **2:** 342–4.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

The pharmacokinetics of promazine appear to be generally similar to those of chlorpromazine (p.975).

Uses and Administration

Promazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has relatively weak antipsychotic activity and is not generally used for the management of psychoses. It is mainly used for the short-term management of agitated or disturbed behaviour (p.954). It has also been given for the alleviation of nausea and vomiting (p.1700). Promazine is given as the hydrochloride by mouth, intramuscularly, or by slow intravenous injection. Promazine has also been given by mouth as the embonate.

For the treatment of **agitated behaviour**, promazine is given in doses equivalent to 100 to 200 mg of the hydrochloride 4 times daily by mouth or 50 mg by intramuscular injection repeated if necessary after 6 to 8 hours. It has also been given by slow intravenous injection in concentrations not exceeding 25 mg/mL, for severely agitated hospitalised patients.

An oral dose of 25 to 50 mg every 4 to 6 hours has been given for the control of **nausea and vomiting**; it has also been given by intramuscular injection for this indication.

Promazine should be given in reduced dosage to elderly or debilitated patients; 25 mg orally of the hydrochloride initially, increasing, if necessary, to 50 mg four times daily has been suggested for the control of agitation and restlessness; for intramuscular injection, a dose of 25 mg may be sufficient.

Hiccup. Promazine hydrochloride has been used in some countries for the treatment of intractable hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p.976.

Preparations

BP 2008: Promazine Injection; Promazine Tablets;
USP 31: Promazine Hydrochloride Injection; Promazine Hydrochloride Oral Solution; Promazine Hydrochloride Syrup; Promazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Prazine†; ***Denm.:*** Sparine†; ***Fin.:*** Sparine†; ***Ger.:*** Protactyl†; Sinophenin†; ***Gr.:*** Sinophenin; Sparine†; ***Ital.:*** Talofen; ***S.Afr.:*** Sparine; ***Switz.:*** Prazine; ***USA:*** Prozine.

Propionylpromazine

Dipropimazine; Propionilpromazina; Propiopromazine.
CAS — 3568-24-9.

Profile

Propionylpromazine is a phenothiazine antipsychotic that has been used for sedation and premedication in veterinary medicine.

Prothipendyl Hydrochloride *(BANM, rINNM)*

D-206; Hidrocloruro de protipendilo; Phrenotropin; Prothipendyl, Chlorhydrate de; Prothipendyli Hydrochloridum. *NN*-Dimethyl-3-(pyrido[3,2-*b*][1,4]benzothiazin-10-yl)propylamine hydrochloride monohydrate.

Протипендила Гидрохлорид

$C_{16}H_{19}N_3S,HCl,H_2O$ = 339.9.
CAS — 303-69-5 (prothipendyl); 1225-65-6 (anhydrous prothipendyl hydrochloride).
ATC — N05AX07.
ATC Vet — QN05AX07.

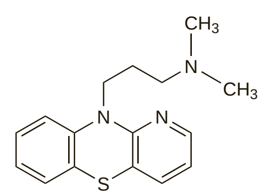

(prothipendyl)

Profile

Prothipendyl is an azaphenothiazine with general properties similar to those of chlorpromazine (p.969). It is given as the hydrochloride in oral doses of 40 to 80 mg two to four times daily for the treatment of psychoses and agitation, and as an adjunct to analgesics in the treatment of severe pain. Prothipendyl hydrochloride may also be given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Dominal; ***Belg.:*** Dominal; ***Ger.:*** Dominal.

Proxibarbal *(rINN)*

HH-184; Proksybarbal; Proxibarbalum; Proxibarbital. 5-Allyl-5-(2-hydroxypropyl)barbituric acid.

Проксибарбал

$C_{10}H_{14}N_2O_4$ = 226.2.
CAS — 2537-29-3.
ATC — N05CA22.
ATC Vet — QN05CA22.

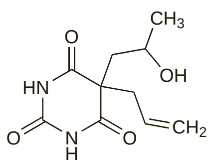

Pharmacopoeias. In *Pol.*

Profile

Proxibarbal is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used as a sedative in the management of anxiety disorders. It has also been used in the treatment of headache. However, barbiturates are not considered appropriate in the management of these conditions. Proxibarbal has been associated with severe hypersensitivity-induced thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Vasalgin.

Pyrithyldione *(rINN)*

Didropyridinum; NU-903; Piritildiona; Pyrithyldionum; Pyrityldion; Pyrityylidioni. 3,3-Diethylpyridine-2,4(1*H*,3*H*)-dione.

Пиритильдион

$C_9H_{13}NO_2$ = 167.2.
CAS — 77-04-3.
ATC — N05CE03.
ATC Vet — QN05CE03.

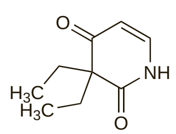

Profile

Pyrithyldione has been given in preparations with diphenhydramine in the short-term management of insomnia but there have been reports of agranulocytosis associated with the use of this combination.

Quazepam *(BAN, USAN, rINN)*

Kvatsepaami; Kvazepam; Quazépam; Quazepamum; Sch-16134. 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepine-2-thione.

Квазепам

$C_{17}H_{11}ClF_4N_2S$ = 386.8.
CAS — 36735-22-5.
ATC — N05CD10.
ATC Vet — QN05CD10.

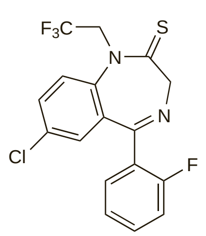

Pharmacopoeias. In *US.*
USP 31 (Quazepam). Off-white to yellowish powder.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of quazepam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

However, a study in 4 women given a single 15-mg dose of quazepam found that only about 0.1% of the dose was excreted over 48 hours in breast milk, as quazepam and its 2 major metabolites.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Hilbert JM, *et al.* Excretion of quazepam into human breast milk. *J Clin Pharmacol* 1984; **24:** 457–62.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Quazepam is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached in about 2 hours. It is metabolised extensively in the liver. The principal active metabolites are 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam (*N*-desalkylflurazepam) which have elimination half-lives of about 39 and 73 hours respectively, compared with a half-life of 39 hours for quazepam. Further hydroxylation occurs and quazepam is excreted in urine and faeces mainly as conjugated metabolites.

Quazepam and its two active metabolites are more than 95% bound to plasma proteins. Quazepam and its metabolites are distributed into breast milk.

Uses and Administration

Quazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is given as a hypnotic in the short-term management of insomnia (p.957), in an initial oral dose of 15 mg at night; in elderly or debilitated patients and some other patients this can be reduced to 7.5 mg.

Preparations

USP 31: Quazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Ital.: Quazium†; ***Jpn:*** Doral; ***Port.:*** Prosedar†; ***S.Afr.:*** Dorme†; ***Spain:*** Quiedorm; ***USA:*** Doral.

Quetiapine Fumarate

(BANM, USAN, pINNM)

Fumarato de quetiapina; ICI-204636; Quétiapine, Fumarate de; Quetiapini Fumaras; ZD-5077; ZM-204636. 2-[2-(4-Dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol fumarate (2:1) salt.

Кветиапина Фумарат

$(C_{21}H_{25}N_3O_2S)_2,C_4H_4O_4$ = 883.1.
CAS — 111974-69-7 (quetiapine); 111974-72-2 (quetiapine fumarate).
ATC — N05AH04.
ATC Vet — QN05AH04.

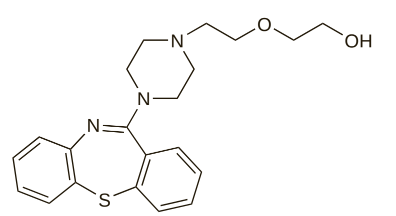

(quetiapine)

Adverse Effects, Treatment, and Precautions

Although quetiapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Quetiapine has been associated with a low incidence of extrapyramidal symptoms but tardive dyskinesia may occur after long-term treatment. Rises in prolactin concentrations may be less than with chlorpromazine.

The most frequent adverse effects with quetiapine are somnolence and dizziness. Mild asthenia, anxiety, fever, rhinitis, peripheral oedema, constipation, dyspepsia, dry mouth, and raised liver enzyme values are also relatively common. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has been reported, particularly during initial dose-titration. Prolongation of QT interval is rarely significant with quetiapine. Hyperglycaemia and exacerbation of pre-existing diabetes have been reported rarely. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of developing, diabetes. Weight gain, particularly during early treatment, has also been noted. Neuroleptic malignant syndrome is rare with quetiapine. Leucopenia, neutropenia, and eosinophilia have also been reported. Other adverse effects have included rises in plasma-triglyceride and cholesterol concentrations, and reduced plasma-thyroid hormone concentrations. There have been rare reports of seizures, hypersensitivity reactions including angioedema, and priapism.

Asymptomatic changes in the lens of the eye have occurred in patients during long-term treatment with quetiapine; cataracts have developed in *dogs* during chronic dosing studies. In the USA, it is recommended that patients should have an eye examination to detect cataract formation when starting therapy with quetiapine and every 6 months during treatment.

Quetiapine should be used with caution in patients with hepatic or renal impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

When quetiapine is used for the depressive phase in bipolar disorder, patients should be closely monitored during early therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Bipolar Disorder, p.372.

Quetiapine may affect the performance of skilled tasks including driving.

Gradual withdrawal of quetiapine is recommended because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses, with abrupt cessation.

Breast feeding. In a case report[1] of a mother receiving quetiapine 200 mg daily by mouth, the maximum concentration of the drug in breast milk an hour after the dose was reported to be 62 micrograms/litre; the mean concentration over 6 hours was 13 micrograms/litre. The authors concluded that the breast-fed infant would ingest, at maximum, the daily equivalent of 0.43% of the weight-adjusted maternal dose. Follow-up at 4.5 months reported no adverse effects in the infant, who had been breast fed from 8 weeks of age.

Licensed product information recommends that patients receiving quetiapine should not breast feed.

1. Lee A, *et al.* Excretion of quetiapine in breast milk. *Am J Psychiatry* 2004; **161:** 1715–16.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class, including quetiapine; most of the deaths appeared due to cardiovascular events or infection. See also under Risperidone, p.1024.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 30/05/05)

Effects on the blood. There have been reports of leucopenia,[1] neutropenia,[2] and pancytopenia[3] associated with quetiapine therapy; all 3 patients improved when the drug was stopped. Thrombotic thrombocytopenic purpura has also been reported in a patient who received quetiapine on 2 separate occasions 2 years apart.[4] From December 1997 to October 2006, Health Canada[5] had received 11 reports of thrombocytopenia associated with quetiapine, 6 of which were associated with quetiapine alone. In one of these 6 cases, thrombocytopenia recurred 3 months after restarting quetiapine, which had stopped for 1 month.

1. Clark N, *et al.* Quetiapine and leukopenia. *Am J Psychiatry* 2001; **158:** 817–18.
2. Croarkin P, Rayner T. Acute neutropenia in a patient treated with quetiapine. *Psychosomatics* 2001; **42:** 368.
3. Iraqi A. A case report of pancytopenia with quetiapine use. *Am J Geriatr Psychiatry* 2003; **11:** 694.
4. Huynh M, *et al.* Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother* 2005; **39:** 1346–8.
5. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. Brecher M, *et al.* Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* 2007; **68:** 597–603.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including quetiapine, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Further references for such effects associated with quetiapine use are given below.

1. Koller EA, *et al.* A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. *J Clin Psychiatry* 2004; **65:** 857–63.
2. Takahashi M, *et al.* Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry* 2005; **38:** 183–4.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Effects on the pancreas. From December 1997 to October 2006, Health Canada[1] had received 9 reports of pancreatitis associated with quetiapine, 5 of which were associated with quetiapine alone. One patient was reported to have developed severe haemorrhagic pancreatitis, and another, necrotising pancreatitis. One report described pancreatitis occurring on two separate occasions in the patient.

1. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on the respiratory system. Hyperventilation and respiratory alkalosis have been reported with quetiapine use.[1] Acute respiratory failure developed[2] in a 92-year-old woman with a history of chronic obstructive pulmonary disease who was given a single 50-mg dose of quetiapine.

1. Shelton PS, *et al.* Hyperventilation associated with quetiapine. *Ann Pharmacother* 2000; **34:** 335–7.
2. Jabeen S, *et al.* Acute respiratory failure with a single dose of quetiapine fumarate. *Ann Pharmacother* 2006; **40:** 559–62.

Mania. Although it is used in the treatment of bipolar disorder, quetiapine has been associated with mania. In one report, a 26-year-old man with schizophrenia developed manic symptoms after starting treatment with quetiapine; the symptoms resolved when quetiapine was withdrawn.[1]

1. Lykouras L, *et al.* Manic symptoms associated with quetiapine treatment. *Eur Neuropsychopharmacol* 2003; **13:** 135–6.

Overdosage. Hypotension, tachycardia, and somnolence were the main clinical events seen in a patient who had taken an overdose of 3 g of quetiapine.[1] Tachycardia of an unexpectedly long duration was also noted. Management was symptomatic, including maintenance of fluids. Asymptomatic prolongation of the QT interval was seen in another patient who had taken a 2-g overdose of quetiapine.[2] Her treatment regimen also included risperidone, and the authors warned that considerable QT interval prolongation may occur when patients overdose on quetiapine while taking therapeutic doses of risperidone.

A subsequent report[3] has described a case series of 18 patients who took from 500 mg to 24 g of quetiapine either alone (6 patients) or with other drugs (12). Quetiapine overdosage was primarily associated with CNS and respiratory depression and sinus tachycardia. Four of the 18 patients required mechanical ventilation but no deaths occurred. The corrected QT interval, but not the QT interval, was prolonged, but apart from sinus tachycardia no patient had a dysrhythmia. Seizures occurred in 2 patients and delirium in 3. The patient who took 24 g of quetiapine was found to have had a peak blood concentration of 20.48 micrograms/mL. She had presented 1.5 hours after ingestion and was intubated and treated with gastric lavage followed by activated charcoal. About 2.5 hours later she had a generalised tonic-clonic seizure. The patient was discharged after 40 hours without sequelae. Another analysis[4] considered 14 cases of overdose, the amounts varying from 1.2 to 18 g; there appeared to be no correlation between the amount taken and the serum concentration, nor was severity of intoxication necessarily correlated with greater intake. Toxicity was generally mild, with tachycardia and somnolence as the main presenting symptoms; there were no fatalities.

1. Beelen AP, *et al.* Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. *Hum Exp Toxicol* 2001; **20:** 215–19.
2. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. *Clin Pharmacol Ther* 2000; **68:** 92–7.
3. Balit CR, *et al.* Quetiapine poisoning: a case series. *Ann Emerg Med* 2003; **42:** 751–8.
4. Hunfeld NG, *et al.* Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. *Ther Drug Monit* 2006; **28:** 185–9.

Pregnancy. For comments on the use of some atypical antipsychotics, including quetiapine, during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by quetiapine. Quetiapine should be used with caution in patients also receiving antihypertensives or drugs that prolong the QT interval. Quetiapine may antagonise the actions of dopaminergics such as levodopa.

CYP3A4 is the main isoenzyme responsible for cytochrome P450-mediated metabolism of quetiapine and caution is advised when quetiapine is used with potent inhibitors of CYP3A4 such as erythromycin, fluconazole, itraconazole, and ketoconazole; lower doses of quetiapine should be used when given with such drugs. Conversely, enzyme inducers such as carbamazepine and phenytoin may decrease the plasma concentrations of quetiapine, and higher doses of quetiapine may be necessary. Thioridazine has also been reported to increase the clearance of quetiapine.

Antibacterials. In a study involving 19 Chinese patients with schizophrenia taking quetiapine 200 mg twice daily, adding *erythromycin* 500 mg three times daily increased the maximum plasma concentration, area under the concentration-time curve, and terminal elimination half-life of quetiapine by 68, 129, and 92%, respectively. Reductions in plasma concentrations of the metabolites of quetiapine suggested that erythromycin had probably inhibited quetiapine's metabolism by the cytochrome P450 isoenzyme CYP3A4. Modification of dosage was recommended in this patient group taking these two drugs together.[1]

1. Li K-Y, *et al.* Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; **60:** 791–5.

Antipsychotics. For a report of asymptomatic QT prolongation associated with quetiapine in a patient also receiving *risperidone*, see under Overdosage, above.

Pharmacokinetics

Quetiapine is well absorbed after oral doses and widely distributed throughout the body. Peak plasma concentrations are reached in about 1.5 hours. It is about 83% bound to plasma proteins. Quetiapine is extensively metabolised in the liver by sulfoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation. It is excreted mainly as inactive metabolites with about 73% of a dose appearing in the urine and about 20% in the faeces. The elimination half-life has been reported to be about 6 to 7 hours.

It is distributed into breast milk.

◊ References.

1. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001; **40:** 509–22.
2. Jaskiw GE, *et al.* Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. *Clin Pharmacokinet* 2004; **43:** 1025–35. Correction. *ibid.*; 1178.

Uses and Administration

Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic. It is reported to have affinity for serotonin ($5\text{-}HT_2$), histamine (H_1), and adrenergic (α_1 and α_2) receptors as well as dopamine D_1 and D_2 receptors. Quetiapine is used in the treatment of schizophrenia and of bipolar disorder.

Quetiapine is given orally as the fumarate although doses are expressed in terms of the base; 28.8 mg of quetiapine fumarate is equivalent to about 25 mg of quetiapine.

The usual initial daily dose in **schizophrenia** is the equivalent of 50 mg of the base on day one. In the UK, 100 mg is given on day two, 200 mg on day three, and 300 mg on day four; daily doses are given in 2 divided doses. The dosage is then adjusted according to response to a usual range of 300 to 450 mg daily, although 150 mg daily may be adequate for some patients; the maximum recommended dose is 750 mg daily. In the USA, the usual initial daily dose is increased on days two and three in increments of 50 to 150 mg, as tolerated, to a target of 300 to 400 mg daily by day four. The daily dose on the first day is given in 2 divided doses, but may be given in 3 divided doses thereafter. The daily dosage may be further adjusted as necessary in steps of 50 to 100 mg at intervals of not less than 2 days to a usual range similar to that in the UK. A modified-release preparation of quetiapine is also available in some countries for once-daily dosing up to the equivalent of 800 mg daily of the base.

In the treatment of acute manic episodes associated with **bipolar disorder**, the initial dose is 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, and 200 mg twice daily on day four. The dose may then be adjusted according to response to a usual range of 400 to 800 mg daily, although, in some patients, 200 mg daily may be adequate. Increments in dosage should be no greater than 200 mg daily. Quetiapine is also licensed in the USA for use in the depressive phase of bipolar disorder. The initial dose is 50 mg once daily at bedtime increased to 100 mg on day two, 200 mg on day three, and 300 mg on day four. The dose may be further increased to 400 mg on day five and 600 mg on day eight, if necessary. In the USA, quetiapine is also licensed for the maintenance treatment of bipolar disorder as an adjunct to lithium or valproate; patients should be continued on the dose that controlled their initial symptoms.

Quetiapine should be given in reduced doses to the elderly; a recommended starting dose is 25 mg daily, which may be increased every day in increments of 25 to 50 mg according to response; the effective dose range is likely to be lower than in younger adults. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. Quetiapine should be given in reduced doses to patients with hepatic impairment; a recommended initial oral dose is 25 mg daily, increased in steps of 25 to 50 mg daily according to response. UK licensed product information also recommends a similar dose reduction in patients with renal impairment.

Bipolar disorder. Quetiapine is of benefit for the treatment of mania in patients with bipolar disorder (p.372) and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of quetiapine-induced mania (see above). In some countries, quetiapine is also licensed for use in the depressive phase of bipolar disorder.

References.

1. Sajatovic M, *et al.* Quetiapine alone and added to a mood stabilizer for serious mood disorders. *J Clin Psychiatry* 2001; **62:** 728–32.
2. Vieta E, *et al.* Quetiapine in the treatment of rapid cycling bipolar disorder. *Bipolar Disord* 2002; **4:** 335–40.
3. Delbello MP, *et al.* A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1216–23.
4. Altamura AC, *et al.* Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study. *J Affect Disord* 2003; **76:** 267–71.
5. Yatham LN, *et al.* Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol* 2004; **24:** 599–606. Correction. *ibid.* 2005; **25:** 103.
6. Bowden CL, *et al.* A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 2005; **66:** 111–21.
7. Dando TM, Keating GM. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. *Drugs* 2005; **65:** 2533–51.
8. Pini S, *et al.* The role of quetiapine in the treatment of bipolar disorder. *Expert Opin Pharmacother* 2006; **7:** 929–40.
9. Khouzam HR, Singh F. Bipolar disorder: historic perspective, current pharmacologic treatment options and a review of quetiapine. *Expert Rev Neurother* 2006; **6:** 131–44.
10. Keating GM, Robinson DM. Quetiapine: a review of its use in the treatment of bipolar depression. *Drugs* 2007; **67:** 1077–94.
11. Brahm NC, *et al.* Quetiapine for acute mania in bipolar disorder. *Am J Health-Syst Pharm* 2007; **64:** 1045–53.

Parkinsonism. Quetiapine has been tried as an antipsychotic[1-3] in patients with parkinsonism (p.791).

1. Fernandez HH, *et al.* Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. *Mov Disord* 2003; **18:** 510–14.
2. Juncos JL, *et al.* Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Mov Disord* 2004; **19:** 29–35.
3. Morgante L, *et al.* Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol* 2004; **27:** 153–6. Correction. *ibid.*; 256.

Schizophrenia. A systematic review[1] noted that, although quetiapine is effective for the treatment of schizophrenia, it appeared comparable with classical antipsychotics and risperidone.

The incidence of extrapyramidal effects was lower with quetiapine therapy but the risk of dry mouth and somnolence was higher. Quetiapine was not found to benefit negative symptoms.

1. Srisurapanont M, *et al.* Quetiapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 30/05/05).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p.954) haloperidol or pimozide are commonly used but atypical antipsychotics, including quetiapine, are increasingly being tried.[1-3]

1. Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 2003; **13:** 295–9.
2. Little AE, *et al.* Quetiapine in the treatment of tic disorder. *Ann Pharmacother* 2006; **40:** 1472.
3. de Jonge JL, *et al.* Quetiapine in patients with Tourette's disorder: an open-label, flexible-dose study. *J Clin Psychiatry* 2007; **68:** 1148–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Quetiazic; Seroquel; Vesparax; ***Austral.:*** Seroquel; ***Austria:*** Seroquel; ***Belg.:*** Seroquel; ***Braz.:*** Seroquel; ***Canad.:*** Seroquel; ***Chile:*** Norsic; Quetidin; Seroquel; ***Cz.:*** Ketilept; Kventiax; Nantarid; Quepita; Questax; Quetin; Seroquel; Stadaquel; ***Denm.:*** Seroquel; ***Fin.:*** Seroquel; ***Ger.:*** Seroquel; ***Gr.:*** Seroquel; ***Hong Kong:*** Seroquel; ***Hung.:*** Ketilept; Seroquel; ***India:*** Quel; Seroquin; Socalm; ***Indon.:*** Seroquel; ***Irl.:*** Seroquel; ***Israel:*** Seroquel; ***Ital.:*** Seroquel; ***Jpn:*** Seroquel; ***Malaysia:*** Seroquel; ***Mex.:*** Seroquel; ***Neth.:*** Seroquel; ***Norw.:*** Seroquel; ***NZ:*** Quetapel; Seroquel; ***Philipp.:*** Seroquel; ***Pol.:*** Ketrel; Seroquel; ***Port.:*** Alzen; Seroquel; ***Rus.:*** Seroquel (Сероквель); ***S.Afr.:*** Seroquel; ***Singapore:*** Seroquel; ***Spain:*** Seroquel; ***Swed.:*** Seroquel; ***Switz.:*** Seroquel; ***Thai.:*** Seroquel; ***Turk.:*** Seroquel; ***UK:*** Seroquel; ***USA:*** Seroquel; ***Venez.:*** Seroquel.

Raclopride *(BAN, rINN)*

A-40664 (raclopride tartrate); FLA-870; Racloprida; Raclopridium; Raclopridum; Raklöprid; Raklopridi. (*S*)-3,5-Dichloro-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide.

Раклоприд

$C_{15}H_{20}Cl_2N_2O_3$ = 347.2.

CAS — 84225-95-6 (raclopride); 98185-20-7 (raclopride tartrate).

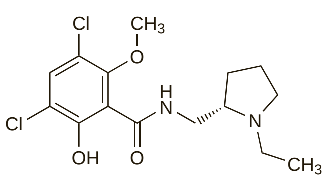

Profile

Raclopride is a substituted benzamide related to sulpiride (p.1028). It has been investigated for the treatment of psychoses. Since it binds selectively and with high affinity to D_2 dopaminergic receptors, raclopride labelled with carbon-11 has been tried as a tracer in computerised tomographic studies of neurological disorders associated with dysfunction of brain D_2 dopaminergic receptors.

Ramelteon *(BAN, USAN, rINN)*

Ramelteón; Rameltéon; Ramelteonum; TAK-375. (-)-*N*-{2-[(8*S*)-1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl]ethyl}propanamide.

Рамельтеон

$C_{16}H_{21}NO_2$ = 259.3.

CAS — 196597-26-9.

ATC — N05CH02.

ATC Vet — QN05CH02.

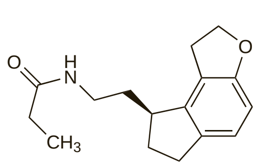

Profile

Ramelteon is a melatonin receptor agonist used as a hypnotic in the management of insomnia (p.957), particularly in patients who have difficulty falling asleep. The usual oral dose is 8 mg taken within 30 minutes of bedtime; it should not be taken with or immediately after a high-fat meal. Ramelteon is not recommended for patients with severe hepatic impairment; it should be used with caution in those with moderate impairment.

Ramelteon is metabolised mainly via the cytochrome P450 isoenzyme CYP1A2 and consequently, it should not be used with fluvoxamine, a potent inhibitor of this isoenzyme; it should also be used with caution in patients taking other drugs that inhibit this isoenzyme.

◊ References.

1. Karim A, *et al.* Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT and MT melatonin receptor agonist indicated for treatment of insomnia. *J Clin Pharmacol* 2006; **46:** 140–8.
2. Greenblatt DJ, *et al.* Age and gender effects on the pharmacokinetics and pharmacodynamics of ramelteon, a hypnotic agent acting via melatonin receptors MT and MT . *J Clin Pharmacol* 2007; **47:** 485–96.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Rozerem; ***Jpn:*** Rozerem; ***USA:*** Rozerem.

Rilmazafone Hydrochloride *(rINNM)*

Hidrocloruro de rilmazafona; Rilmazafone, Chlorhydrate de; Rilmazafoni Hydrochloridum; 450191-S. 5-[(2-Aminoacetamido)methyl]-1-[4-chloro-2-(*o*-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide hydrochloride dihydrate.

Рильмазафона Гидрохлорид

$C_{21}H_{20}Cl_2N_6O_3,HCl,2H_2O$ = 547.8.

CAS — 99593-25-6 (rilmazafone); 85815-37-8 (anhydrous rilmazafone hydrochloride).

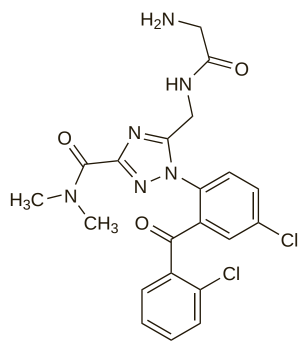

(rilmazafone)

Profile

Rilmazafone hydrochloride is a hypnotic and sedative used in the short-term treatment of insomnia in usual oral doses of 1 to 2 mg at bedtime; it is also used in similar doses as a premedicant.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rhythmy.

Risperidone *(BAN, USAN, rINN)*

R-64766; Risperidon; Risperidona; Risperidonas; Rispéridone; Risperidoni; Risperidonum; Riszperidon; Rysperydon. 3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl}-6,7,8,9-tetrahydro-2-methylpyrido[1,2-*a*]pyrimidin-4-one.

Рисперидон

$C_{23}H_{27}FN_4O_2$ = 410.5.

CAS — 106266-06-2.

ATC — N05AX08.

ATC Vet — QN05AX08.

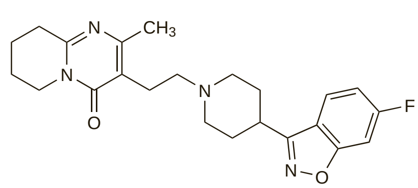

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Risperidone). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute acid solutions. Protect from light.

USP 31 (Risperidone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in dichloromethane.

Adverse Effects, Treatment, and Precautions

Although risperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Risperidone is reported to be less likely to cause sedation or extrapyramidal effects (see also Uses and Administration, below) but agitation may occur more frequently. Other common adverse effects include insomnia, anxiety, and headache. Dyspepsia, nausea and vomiting, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, rash and other allergic reactions, drowsiness, concentration difficulties, dizziness, fatigue, and rhinitis have been reported less commonly. In addition to orthostatic hypotension, hypertension has been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, increased liver enzyme values, and decreases in neutrophil or thrombocyte counts. Risperidone may cause dose-dependent increases in prolactin levels. In rare cases, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have also been reported. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Other rare effects include seizures, body temperature dysregulation, hyponatraemia, neuroleptic malignant syndrome, and tardive dyskinesia.

Risperidone should be used with caution in patients with cardiovascular disease, including conditions associated with QT prolongation, or conditions predisposing to hypotension. Caution is also recommended in patients with a history of or at risk of developing cerebrovascular disease, in patients with Parkinson's disease or epilepsy, and in patients with hepatic or renal impairment.

Risperidone may affect the performance of skilled tasks such as driving.

Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms, including sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Breast feeding. From the study of concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, in the breast milk of a mother receiving 6 mg daily by mouth, it was estimated that a breast-fed infant would ingest the daily equivalent of 4.3% (as risperidone equivalents) of the weight-adjusted maternal dose.[1] Later case reports[2] of 3 women receiving risperidone 3 mg daily, 4 mg daily, and 1.5 mg daily, by mouth, estimated that a breast-fed infant would receive the daily equivalent of 2.3%, 2.8%, and 4.7%, respectively, of the weight-adjusted maternal dose. Where breast feeding occurred, in the latter 2 cases, no adverse effects were reported in the breast-fed infants; risperidone and 9-hydroxyrisperidone were not detected in the plasma of either infant.

Licensed product information states that patients receiving risperidone should not breast feed; the US information also recommends that patients should not breast feed for at least 12 weeks after intramuscular injection.

1. Hill RC, *et al.* Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 2000; **20:** 285–6.
2. Ilett KF, *et al.* Transfer of risperidone and 9-hydroxyrisperidone into human milk. *Ann Pharmacother* 2004; **38:** 273–6.

Dementia. After analysis of data from controlled studies there was evidence that the use of risperidone in elderly patients with dementia appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. In 4 studies, involving 764 such patients treated with risperidone, there were 29 cases of cerebrovascular adverse events (4 fatal) versus 7 cases (1 fatal) in 466 patients given placebo. Postmarketing data for elderly dementia patients, representing over 2.4 million patient-years of exposure, included 37 cases, of which 16 were fatal.[1]

The UK CSM[2] have therefore recommended that risperidone should not be used to treat behavioural problems in elderly patients with dementia. Similarly, the CSM[2] and the EMEA[3] have recommended that olanzapine should not be used to treat behavioural problems or dementia-related psychosis in elderly patients with dementia after analysis of placebo-controlled studies revealed a threefold increase in cerebrovascular adverse effects including stroke and a twofold increase in all-cause mortality. It was considered[2] that the risk may not be confined to use in dementia and should be considered relevant to any patient with a history of stroke or transient ischaemic attack or other risk factors for cerebrovascular disease, including hypertension, diabetes, current smoking, or atrial fibrillation. The FDA[4] has also issued advice against the use of all atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia. Their advice was based on an unpublished analysis of 17 placebo-controlled studies involving aripiprazole, olanzapine, quetiapine, or risperidone use in elderly demented patients with behavioral disorders: the analysis found that 15 studies showed an increase in the mortality rate in the drug-treated group compared to the placebo-treated patients. A total of 5106 patients were included in these studies, and a 1.6- to 1.7-fold increase in mortality was seen; most of the deaths appeared due to cardiovascular events or infection. Another published meta-analysis[5] of placebo-controlled studies also had similar findings.

However, 2 large retrospective population-based studies in the elderly (1 involving 10 385 patients given atypicals and 1015 given classical antipsychotics,[6] the other involving 17 845 given atypicals and 14 865 given classical antipsychotics[7]), suggested that use of atypical antipsychotics was not associated with a statistically significant increased risk of stroke compared with the classical drugs.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p.954.

1. Janssen-Ortho Inc./Health Canada. Important drug safety information: Risperdal (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials (issued 11/10/02). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/risperdal_hpc-cps-eng.pdf (accessed 21/08/08)
2. Duff G. Atypical antipsychotic drugs and stroke: message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 09/03/04). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019488.pdf (accessed 21/08/08)
3. EMEA. EMEA public statement on the safety of olanzapine (Zyprexa, Zyprexa Velotab): cerebrovascular adverse events and increased mortality in elderly patients with dementia (issued 09/03/04). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/085604en.pdf (accessed 21/08/08)
4. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 30/05/05)
5. Schneider LS, *et al.* Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; **294:** 1934–43.
6. Herrmann N, *et al.* Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004; **161:** 1113–15.
7. Gill SS, *et al.* Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 2005; **330:** 445–8.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. Safer DJ. A comparison of risperidone-induced weight gain across the age span. *J Clin Psychopharmacol* 2004; **24:** 429–36.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including risperidone, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. Koller EA, *et al.* Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy* 2003; **23:** 735–44.
2. Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; **30:** 589–99.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Effects on the liver. There has been a report of 2 cases of hepatotoxicity associated with risperidone.[1] An idiosyncratic reaction to risperidone was suspected in another patient who developed hepatotoxicity after receiving only 2 doses of risperidone.[2]

1. Fuller MA, *et al.* Risperidone-associated hepatotoxicity. *J Clin Psychopharmacol* 1996; **16:** 84–5.
2. Phillips EJ, *et al.* Rapid onset of risperidone-induced hepatotoxicity. *Ann Pharmacother* 1998; **32:** 843.

Effects on the skin. A patient developed facial and periorbital oedema 2 weeks after her dose of risperidone reached 6 mg daily.[1] The oedema subsided when the dose was halved but recurred shortly after it was again increased to 6 mg. She had previously had a similar reaction to lithium and there was also a family history of angioedema.

1. Cooney C, Nagy A. Angio-oedema associated with risperidone. *BMJ* 1995; **311:** 1204.

Extrapyramidal disorders. In reports of 3 cases of tardive dystonia associated with oral risperidone therapy,[1,2] onset ranged from 3 to 8 months after starting the drug. Dyskinesia has also been reported 5 days after the withdrawal of oral risperidone and citalopram therapy.[3] In another report,[4] three patients receiving risperidone orally developed early-onset tardive dyskinesia despite the addition of antimuscarinic therapy with biperiden or trihexyphenidyl. Extrapyramidal adverse effects have also been reported within 24 hours of intramuscular risperidone injection.[5] However, the incidence of extrapyramidal effects (p.971) is generally lower with atypical than classical antipsychotics.

1. Vercueil L, Foucher J. Risperidone-induced tardive dystonia and psychosis. *Lancet* 1999; **353:** 981.
2. Krebs MO, Olie JP. Tardive dystonia induced by risperidone. *Can J Psychiatry* 1999; **44:** 507–508.
3. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; **34:** 269.
4. Suzuki E, *et al.* Tardive dyskinesia with risperidone and anticholinergics. *Am J Psychiatry* 2002; **159:** 1948.
5. Adamou M, Hale AS. Extrapyramidal syndrome and long-acting injectable risperidone. *Am J Psychiatry* 2004; **161:** 756–7.

Mania. Although it is used in the treatment of bipolar disorder, risperidone has been associated with reports of mania in both schizophrenic and bipolar patients.[1-3]

1. Dwight MM, *et al.* Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. *Lancet* 1994; **344:** 554–5.
2. Zolezzi M, Badr MG. Risperidone-induced mania. *Ann Pharmacother* 1999; **33:** 380–1.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; **61:** 649–55.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (p.972) has occasionally been associated with risperidone.[1-5]

1. Sharma R, *et al.* Risperidone-induced neuroleptic malignant syndrome. *Ann Pharmacother* 1996; **30:** 775–8.
2. Tarsy D. Risperidone and neuroleptic malignant syndrome. *JAMA* 1996; **275:** 446.
3. Reeves RR, *et al.* Neuroleptic malignant syndrome during a change from haloperidol to risperidone. *Ann Pharmacother* 2001; **35:** 698–701.
4. Gerritsen AA, *et al.* Het maligne neurolepticasyndroom bij gebruik van risperidon. *Ned Tijdschr Geneeskd* 2004; **148:** 1801–4.
5. Norris B, *et al.* Neuroleptic malignant syndrome with delayed onset of fever following risperidone administration. *Ann Pharmacother* 2006; **40:** 2260–4.

Overdosage. A 3⁄-year-old child developed extrapyramidal symptoms after accidental ingestion of a single 4-mg tablet of risperidone.[1] The child was initially treated with gastric lavage, activated charcoal, and sorbitol; extrapyramidal symptoms responded to treatment with diphenhydramine and the child recovered completely. The need to monitor for and treat hypotension after overdosage with risperidone was highlighted in a report[2] of a 15-year-old girl who took 40 mg of risperidone. A 72-year-old woman receiving risperidone 6 mg daily was found unconscious, hypotensive, and hypothermic.[3] Other reported symptoms include first-degree heart block, prolonged QT interval, and respiratory arrest; she recovered after supportive treatment.

1. Cheslik TA, Erramouspe J. Extrapyramidal symptoms following accidental ingestion of risperidone in a child. *Ann Pharmacother* 1996; **30:** 360–3.
2. Himstreet JE, Daya M. Hypotension and orthostasis following a risperidone overdose. *Ann Pharmacother* 1998; **32:** 267.
3. Rassam S, Srinivasa R. Respiratory depression after accidental risperidone overdose. *Am J Emerg Med* 2002; **20:** 570.

Pregnancy. For comments on the use of some atypical antipsychotics, including risperidone, during pregnancy, see under Precautions of Clozapine, p.983.

Further references.

1. Coppola D, *et al.* Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. *Drug Safety* 2007; **30:** 247–64.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by risperidone. Risperidone may also enhance the effects of antihypertensives. There may be an increased risk of QT prolongation when risperidone is given with other drugs that are known to cause this effect. Risperidone may antagonise the actions of levodopa and other dopaminergics.

Carbamazepine has been shown to decrease the antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) of risperidone and a similar effect may be seen with other enzyme inducers. Fluoxetine may increase the plasma concentrations of the antipsychotic fraction by raising the concentration of risperidone. Dose adjustment of risperidone may be necessary in such situations.

Antiepileptics. For the effect of risperidone on *valproate*, see p.511.

Antipsychotics. For a report suggesting that risperidone might increase plasma concentrations of *clozapine*, see p.984. For a report of asymptomatic QT prolongation associated with *quetiapine* in a patient also receiving risperidone, see under Overdosage of Quetiapine, p.1023.

Antivirals. Dystonia and worsening of tremors were reported 1 week after adding *indinavir* and *ritonavir* to treatment with risperidone in a patient with AIDS;[1] he recovered once all 3 drugs were withdrawn and following treatment with clonazepam. An early exposure to risperidone, indinavir, and ritonavir had not resulted in any extrapyramidal adverse effects. The authors considered this to reflect the patient's relatively short exposure to risperidone at the time.

1. Kelly DV, *et al.* Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. *Ann Pharmacother* 2002; **36:** 827–30.

Pharmacokinetics

Risperidone is readily absorbed after oral doses, peak plasma concentrations being reached within 1 to 2 hours. It is extensively metabolised in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone (paliperidone, p.1015); oxidative *N*-dealkylation is a minor metabolic pathway. Hydroxylation is mediated by the cytochrome P450 isoenzyme CYP2D6 and is the subject of genetic polymorphism. Excretion is mainly in the urine and, to a lesser extent, in the faeces. Risperidone and 9-hydroxyrisperidone are about 90% and 77% bound to plasma proteins, respectively. Both are distributed into breast milk.

Metabolism. Although the hydroxylation of risperidone is subject to genetic polymorphism, the pharmacokinetics and effects of the active antipsychotic fraction (risperidone plus 9-hydroxyrisperidone) have been reported to vary little between extensive and poor metabolisers.[1] A mean value of 19.5 hours has been reported for the terminal elimination half-life of the active fraction following oral doses of risperidone.[1]

1. Huang M-L, *et al.* Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 1993; **54:** 257–68.

Uses and Administration

Risperidone is a benzisoxazole atypical antipsychotic, reported to be an antagonist at dopamine D_2, serotonin ($5\text{-}HT_2$), adrenergic (α_1 and α_2), and histamine (H_1) receptors. It is given orally for the treatment of schizophrenia and other psychoses and in the short-term treatment of acute manic or mixed episodes associated with bipolar disorder. In the USA, risperidone is used similarly in children and also for the treatment of irritability associated with autistic disorder; for further details see Administration in Children and Disturbed Behaviour, below. Risperidone may also be given by deep intramuscular injection for maintenance therapy in patients with schizophrenia or other psychoses tolerant to oral antipsychotics.

For **schizophrenia**, the usual initial oral dose of risperidone is 2 mg daily; this may be increased to 4 mg daily on the second day, and subsequently adjusted as required in steps of 1 or 2 mg according to tolerance, at intervals of not less than 24 hours. Most patients benefit from doses of 4 to 6 mg daily. Risperidone may be given once daily or in 2 divided doses. Extrapyramidal symptoms may be more likely with doses above 10 mg daily; US licensed product information does not recommend daily doses above 6 mg if divided into 2 doses, although higher doses are permitted if given as a single dose. The maximum recommended dose is 16 mg daily.

An initial oral dose of 500 micrograms twice daily slowly increased in steps of 500 micrograms twice daily, if necessary, to a dose of 1 to 2 mg twice daily is recommended for elderly or debilitated patients. Above doses of 1.5 mg twice daily, increases should be made at intervals of at least 1 week.

The long-acting formulation of risperidone should be given by deep intramuscular injection every 2 weeks. Patients with no history of risperidone use should be given risperidone orally for several days to assess tolerability. Treatment may then be started as follows:

- patients not stabilised on oral risperidone: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses of 4 mg daily or less: 25 mg every 2 weeks
- patients stabilised on oral risperidone for at least 2 weeks in doses above 4 mg daily: 37.5 mg every 2 weeks
- elderly patients should be given a maximum of 25 mg every 2 weeks

Oral risperidone should be continued for the first 3 weeks after the first injection.

Dose increases of 12.5 mg may be considered at least 4 weeks after the previous adjustment up to a maximum of 50 mg every 2 weeks; the clinical effects of a dose adjustment may not be seen for at least 3 weeks after the change.

For the treatment of **mania** in bipolar disorder, a recommended initial oral dose is 2 to 3 mg once daily. Dosage adjustments of 1 mg daily may be made at intervals of not less than 24 hours up to a total of 6 mg daily. The initial dosage regimen in elderly or debilitated patients should be reduced as for schizophrenia (see above).

Reduced doses are recommended in patients with hepatic or renal impairment, see below.

Action. Risperidone is described as an atypical antipsychotic; although it has a lower propensity to produce parkinsonism, dystonias and akathisias have been reported.[1] (See also Extrapyramidal Disorders, above.) The traditional hypothesis is that antipsychotics work through inhibition of dopamine D_2 receptors and that extrapyramidal adverse effects result from blockade of D_2 receptors in the striatum (see p.975). Like clozapine, risperidone has a high affinity for 5-HT_2 receptors and, like haloperidol, it has a high affinity for dopamine D_2 receptors. Risperidone also binds to alpha-adrenergic and histamine H_1 sites. It is unclear whether risperidone's antipsychotic effect is due to activity at dopamine D_2 receptors or at another site. It has been suggested[1] that other potent effects of risperidone may be counterbalancing the D_2 activity to produce its atypicality.

1. Kerwin RW. The new atypical antipsychotics: a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994; **164:** 141–8.

Administration in children. In the USA, risperidone is licensed for the treatment of schizophrenia in adolescents aged 13 to 17 years, for the short-term treatment of acute manic or mixed episodes associated with bipolar disorder in children and adolescents aged 10 to 17 years, and for the treatment of irritability associated with autistic disorder in those aged 5 to 16 years.

For **schizophrenia** or **mania**, an initial oral dose of 500 micrograms is given once daily in the morning or in the evening. This may be increased in steps of 0.5 or 1 mg according to tolerance, at intervals of not less than 24 hours, to a dose of 3 mg daily for schizophrenia or 2.5 mg daily for mania. The maximum recommended dose for both indications is 6 mg daily. The total daily dose may be given in 2 divided doses to those who experience persistent somnolence.

For the treatment of **irritability associated with autistic disorder**, the following oral doses are given once daily or in 2 divided doses according to body-weight:

- under 20 kg: the usual initial daily dose is 250 micrograms; this may be increased to 500 micrograms daily after at least 4 days and subsequently adjusted as required in steps of 250 micrograms, generally at intervals of no less than 2 weeks. The maximum recommended dose is 1 mg daily. Caution should be exercised with dosage for children who weigh less than 15 kg
- 20 kg and over: the usual initial daily dose is 500 micrograms; this may be increased to 1 mg daily after at least 4 days and subsequently adjusted as required in steps of 500 micrograms, generally at intervals of no less than 2 weeks. The maximum recommended dose is 2.5 mg daily in those weighing over 20 kg and 3 mg daily in those over 45 kg
- For those who experience persistent somnolence, the total daily dose may be given as a single dose at bedtime, or in 2 divided doses, or in a reduced dose

For further details on the use of risperidone in children with autism see Disturbed Behaviour, below.

Risperidone is not licensed in the UK for use in children aged under 15 years; however, the *BNFC* suggests that it may be used in those aged 12 years and over for the oral treatment of acute and chronic psychoses. Doses are similar to those used in the treatment of schizophrenia in adults (see above). The *BNFC* also suggests that risperidone may be used, under specialist supervision, in children over 5 years of age for the short-term treatment of severe aggression in autism; doses are similar to those licensed for autistic disorders in the USA.

Administration in hepatic or renal impairment. The recommended initial oral dose of risperidone in patients with renal or hepatic impairment is 500 micrograms twice daily; this may be slowly increased in steps of 500 micrograms twice daily, if necessary, to a dose of 1 to 2 mg twice daily. Above doses of 1.5 mg twice daily, increases should be made at intervals of at least 1 week.

Patients with schizophrenia who tolerate an oral dose of risperidone of at least 2 mg daily may be switched to the long-acting formulation of risperidone; a dose of 25 mg by deep intramuscular injection every 2 weeks is recommended. Alternatively, an initial dose of 12.5 mg by deep intramuscular injection may be given.

AIDS. Risperidone was used successfully to control HIV- or AIDS-related psychosis in 21 patients, some of whom also had manic symptoms.[1] No extrapyramidal symptoms were reported during treatment. However, for reports suggesting that risperidone can induce or exacerbate manic symptoms in patients with schizoaffective disorders, see under Mania in Adverse Effects, above. For an interaction between risperidone and antiretroviral therapy in a patient with AIDS, see under Interactions, above.

1. Singh AN, *et al.* Treatment of HIV-related psychotic disorders with risperidone: a series of 21 cases. *J Psychosom Res* 1997; **42:** 489–93.

Anxiety disorders. Although there have been anecdotal reports[1,2] of improvement after the addition of risperidone to treatment in patients with obsessive-compulsive disorder refractory to conventional treatment, there has also been a report[3] of a patient whose obsessive-compulsive behaviour recurred when he was treated with risperidone for tardive dyskinesia.

1. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry* 1995; **56:** 423–9.
2. McDougle CJ, *et al.* Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. *J Clin Psychiatry* 1995; **56:** 526–8.
3. Remington G, Adams M. Risperidone and obsessive-compulsive symptoms. *J Clin Psychopharmacol* 1994; **14:** 358–9.

Bipolar disorder. Risperidone is of benefit for the treatment of mania, including in patients with bipolar disorder (p.372), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of risperidone-induced mania (see above).

References.

1. Segal J, *et al.* Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol* 1998; **21:** 176–80.
2. Sachs GS, *et al.* Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry* 2002; **159:** 1146–54.
3. Yatham LN, *et al.* Mood stabilisers plus risperidone or placebo in the treatment of acute mania: international, double-blind, randomised controlled trial. *Br J Psychiatry* 2003; **182:** 141–7. Correction. *ibid.*; 369.
4. Hirschfeld RM, *et al.* Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry* 2004; **161:** 1057–65.
5. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. *Ann Pharmacother* 2006; **40:** 674–82.
6. Rendell JM, *et al.* Risperidone alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
7. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. *Ann Pharmacother* 2006; **40:** 674–82.

Disturbed behaviour. Although risperidone has been used for the management of behavioural disturbances[1,2] in **elderly patients with dementia** (p.954), such use is no longer recommended, see Dementia, under Adverse Effects, above. Furthermore, despite anecdotal reports[3] of efficacy in patients with Lewy-body dementia, other reports[4] suggest that these patients are likely to be just as sensitive to risperidone as to classical antipsychotics (see the Elderly in Precautions for Chlorpromazine, p.973).

There is evidence[5-10] that risperidone may be effective in reducing behavioural disturbances in **children with autism** (see Disturbed Behaviour, p.954), but it appears to have little effect on core symptoms, and it has been pointed out that the marked hyperprolactinaemia induced by risperidone could lead to hypogonadism, and deleterious effects on adolescent bones.[11] A systematic review[12] concluded that risperidone may be of some benefit for symptoms such as hyperactivity, irritability, repetition, and social withdrawal although this must be weighed against the risk of adverse effects, notably weight gain. The authors noted that only 3 studies were analysed, including 1 that was carried out in adults, and the data available were limited; further studies were considered warranted. Nonetheless, in some countries, including the USA, risperidone is licensed for the treatment of irritability associated with autistic disorder in children and adolescents aged 5 to 16 years; for details of doses see Administration in Children, above.

1. De Deyn PP, *et al.* A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999; **53:** 946–55.
2. Falsetti AE. Risperidone for control of agitation in dementia patients. *Am J Health-Syst Pharm* 2000; **57:** 862–70.
3. Allen RL, *et al.* Risperidone for psychotic and behavioural symptoms in Lewy body dementia. *Lancet* 1995; **346:** 185.
4. McKeith IG, *et al.* Neuroleptic sensitivity to risperidone in Lewy body dementia. *Lancet* 1995; **346:** 699.
5. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 314–21.
6. Shea S, *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Abstract: *Pediatrics* 2004; **114:** 1329. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/5/e634 (accessed 15/01/07)
7. Reyes M, *et al.* A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry* 2006; **163:** 402–10.
8. Reyes M, *et al.* Long-term safety and efficacy of risperidone in children with disruptive behaviour disorders: results of a 2-year extension study. *Eur Child Adolesc Psychiatry* 2006; **15:** 97–104.
9. Chavez B, *et al.* Role of risperidone in children with autism spectrum disorder. *Ann Pharmacother* 2006; **40:** 909–16.
10. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Pediatr Drugs* 2007; **9:** 343–54.
11. Valiquette G. Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; **347:** 1890–1.
12. Jesner OS, *et al.* Risperidone for autism spectrum disorder. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 10/04/08).

Dystonias. Antipsychotics are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to treatment with levodopa or antimuscarinics, but, as with classical antipsychotics, there is the risk of adding drug-induced extrapyramidal effects to the dystonia. Risperidone has been reported to be of benefit in a few patients with idiopathic segmental dystonia partly insensitive to haloperidol.[1]

1. Zuddas A, Cianchetti C. Efficacy of risperidone in idiopathic segmental dystonia. *Lancet* 1996; **347:** 127–8.

Parkinsonism. There have been conflicting reports of the use of risperidone as an antipsychotic in a small number of patients with Parkinson's disease (see also Disturbed Behaviour, p.954). While some patients found that risperidone ameliorated levodopa-induced hallucinations without worsening extrapyramidal symptoms,[1,2] others reported that risperidone produced a substantial worsening of symptoms.[2,3]

1. Meco G, *et al.* Risperidone for hallucinations in levodopa-treated Parkinson's disease patients. *Lancet* 1994; **343:** 1370–1.
2. Leopold NA. Risperidone treatment of drug-related psychosis in patients with parkinsonism. *Mov Disord* 2000; **15:** 301–4.
3. Ford B, *et al.* Risperidone in Parkinson's disease. *Lancet* 1994; **344:** 681.

Schizophrenia. Risperidone is claimed to produce a relatively low incidence of extrapyramidal effects and to have efficacy against both positive and negative symptoms of schizophrenia. Most of the earlier studies compared risperidone with haloperidol but, of these, some of the major studies[1-3] were criticised for potential methodological flaws[4,5] and it was difficult to determine any difference in efficacy including effect on negative symptoms. A later systematic review[6] suggested that risperidone's benefits over haloperidol or other classical antipsychotics were marginal; although it did appear to reduce the risk of extrapyramidal effects compared with haloperidol, the latter produces a relatively high incidence of such effects. Furthermore, the risk of extrapyramidal effects with risperidone appears to be dose-dependent:[7] although similar to that for placebo overall, at doses of more than 10 mg the risk appears to approach that associated with haloperidol. In a more recent double-blind randomised study[8] the relapse rate after at least 2 years of treatment in patients with first-episode psychosis, who had initially responded to relatively small daily doses of risperidone (mean modal 3.3 mg) or haloperidol (2.9 mg), was 42% (82 of 197 patients) and 55% (111 of 203), respectively. The median time to relapse was also longer for risperidone (466 days) when compared with haloperidol (205 days). In the few comparative studies with other atypical antipsychotics, risperidone has appeared to be of similar efficacy to clozapine.[9] However, another systematic review[10] concluded that such equivalence with clozapine cannot be assumed. For a systematic review of studies comparing risperidone with olanzapine, see p.1013. There is insufficient evidence to indicate whether risperidone is effective for treatment-resistant or poorly responsive patients but there is some evidence that patients stabilised on risperidone may be less likely to relapse.[11] A systematic review[12] of the use of the long-acting injectable formulation of risperidone in schizophrenia considered that, although it might offer the advantage of better compliance, there was little evidence of benefit over oral use.

1. Chouinard G, *et al.* A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; **13:** 25–40.
2. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; **151:** 825–35.
3. Peuskens J, *et al.* Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995; **166:** 712–26.
4. Livingston MG. Risperidone. *Lancet* 1994; **343:** 457–60.
5. Musser WS, Kirisci L. Critique of the Canadian multicenter placebo-controlled study of risperidone and haloperidol. *J Clin Psychopharmacol* 1995; **15:** 226–8.
6. Hunter RH, *et al.* Risperidone versus typical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 30/05/05).
7. Owens DGC. Extrapyramidal side effects and tolerability of risperidone: a review. *J Clin Psychiatry* 1994; **55** (suppl 5): 29–35.
8. Schooler N, *et al.* Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; **162:** 947–53.

9. Klieser E, *et al.* Randomized, double-blind, controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995; **15** (suppl 1): 45S–51S.
10. Gilbody SM, *et al.* Risperidone versus other atypical antipsychotic medication for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 30/05/05).
11. Csernansky JG, *et al.* A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002; **346:** 16–22.
12. Hosalli P, Davis JM. Depot risperidone for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 30/05/05).

Stuttering. Risperidone 0.5 to 2 mg daily was found to be of benefit in the management of stuttering in a placebo-controlled study[1] involving 16 patients but there has also been a case report[2] of a patient whose stuttering returned during treatment with risperidone.

1. Maguire GA, *et al.* Risperidone for the treatment of stuttering. *J Clin Psychopharmacol* 2000; **20:** 479–82.
2. Lee H-J, *et al.* A case of risperidone-induced stuttering. *J Clin Psychopharmacol* 2001; **21:** 115–16.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p.954) haloperidol or pimozide are commonly used but atypical antipsychotics, especially risperidone, are being increasingly tried.[1-3]

1. Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. *J Clin Psychiatry* 1996; **57:** 29–31.
2. Bruggeman R, *et al.* Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry* 2001; **62:** 50–6.
3. Scahill L, *et al.* A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003; **60:** 1130–5.

Preparations

USP 31: Risperidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dozic; Dropicine; Edalen; Restelea; Riatul; Risper; Risperdal; Risperin; Rispex; Sequinan; ***Austral.:*** Risperdal; ***Austria:*** Belivon†; Risperdal; Rispolin; ***Belg.:*** Risperdal; ***Braz.:*** Respidon; Risperdal; Viverdal; Zargus; ***Canad.:*** Risperdal; ***Chile:*** Dagotil; Goval; Radigen; Risperdal; Spiron; ***Cz.:*** Apo-Risper; Medorisper; Ridoner; Rigenin; Rileptid; Ripetomar; Risepro; Rispadim; Rispedep; Rispedolet; Rispedospes; Rispemar; Rispen; Rispera; Risperdal; Risperinin; Risperit; Rispimed; Rispolux; Risset; Rorendo; ***Denm.:*** Risperdal; ***Fin.:*** Risperdal; ***Fr.:*** Risperdal; ***Ger.:*** Risperdal; ***Gr.:*** Adovia; Axelabron; Depolan; Depredon; Dixine; Helposper; Isipredon; Lassen; Luciperal; Nerve; Novoris; Preridon; Rifocus; Ripepral; Risenar; Risgal; Risidral; Rispalm; Rispefar; Risperascol; Risperdal; Risperom; Risperoprol; Rispogen; Wisperdon; Zafitral; ***Hong Kong:*** Risperdal; ***Hung.:*** Hunperdal; Perdox; Ripedon; Risperdal; Rispolux; Rispons; Ronkal; Rosipin; Torendo; Ziperid; ***India:*** Respidon; Risnia; Risperdal; Rispid†; Rozidal; Sizorisp†; ***Indon.:*** Neripros; Persidal; Risperdal; Rizodal; Zofredal; ***Irl.:*** Risperdal; ***Israel:*** Risperdal; ***Ital.:*** Belivon; Risperdal; ***Jpn:*** Risperdal; ***Malaysia:*** Risperdal; ***Mex.:*** Risperdal; ***Neth.:*** Belivon; Risperdal; Rispimed; Rispimedica; ***Norw.:*** Risperdal; ***NZ:*** Ridal; Risperdal; ***Philipp.:*** Risperdal; ***Pol.:*** Lioxam; Mepharis; Rispen; Risperatio; Risperiwin; Risperon; Rispolept; Rispolux; Risset; Ryspolit; Speridan; Ziperid; ***Port.:*** Belivon†; Perdin; Risperdal; ***Rus.:*** Rileptid (Рилептид); Risdonal (Рисдонал); Rispolept (Рисполепт); Risset (Риссет); Speridan (Споридан); ***S.Afr.:*** Risperdal; ***Singapore:*** Risperdal; ***Spain:*** Arketin; Diaforin; Risfarmal; Risperdal; ***Swed.:*** Risperdal; ***Switz.:*** Risperdal; ***Thai.:*** Risperdal; ***Turk.:*** Risperdal; ***UK:*** Risperdal; ***USA:*** Risperdal; ***Venez.:*** Ridal; Risperdal; Risperid.

Ritanserin *(BAN, USAN, rINN)*

R-55667; Ritanserina; Ritansérine; Ritanserinum. 6-{2-[4-(4,4′-Difluorobenzhydrylidene)piperidino]ethyl}-7-methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-one.

Ритансерин

$C_{27}H_{25}F_2N_3OS = 477.6.$
CAS — 87051-43-2.

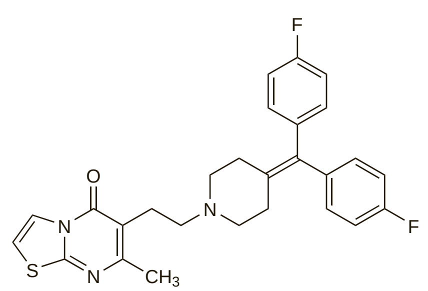

Profile

Ritanserin is a serotonin antagonist that has been studied in a variety of disorders including anxiety disorders, depression, and schizophrenia. It is reported to have little sedative action.

Action. Ritanserin is a relatively selective antagonist at serotonin (5-hydroxytryptamine, 5-HT) receptors of the 5-HT_2 subtype, although it also has appreciable affinity for 5-HT_{1C} receptors.[1] Unlike ketanserin (p.1320), it does not block α_1-adrenergic receptors. Ritanserin has anxiolytic activity; it also hastens the onset of slow-wave sleep although sleep may be impaired on withdrawal.

Ritanserin may interfere with platelet function[2,3] but has been reported to have no significant effect on blood pressure, blood flow, or heart rate in patients with hypertension.[2,4] Features characteristic of class III antiarrhythmic activity have also been noted.[2]

1. Marsden CA. The pharmacology of new anxiolytics acting on 5-HT neurones. *Postgrad Med J* 1990; **66** (suppl 2): S2–S6.
2. Stott DJ, *et al.* The effects of the 5HT antagonist ritanserin on blood pressure and serotonin-induced platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1988; **35:** 123–9.
3. Wagner B, *et al.* Effect of ritanserin, a 5-hydroxytryptamine -receptor antagonist, on platelet function and thrombin generation at the site of plug formation in vivo. *Clin Pharmacol Ther* 1990; **48:** 419–23.
4. Chau NP, *et al.* Comparative haemodynamic effects of ketanserin and ritanserin in the proximal and distal upper limb circulations of hypertensive patients. *Eur J Clin Pharmacol* 1989; **37:** 215–20.

Substance dependence. Despite some encouraging preliminary data[1] suggesting that ritanserin might influence the desire to drink alcohol, subsequent studies[2,3] have failed to support a role for ritanserin in patients with *alcohol* dependence (p.1626).

1. Meert TF. Ritanserin and alcohol abuse and dependence. *Alcohol Alcohol* 1994; **2** (suppl): 523–30.
2. Johnson BA, *et al.* Ritanserin Study Group. Ritanserin in the treatment of alcohol dependence—a multi-center clinical trial. *Psychopharmacology (Berl)* 1996; **128:** 206–15.
3. Wiesbeck GA, *et al.* The effects of ritanserin on mood, sleep, vigilance, clinical impression, and social functioning in alcohol-dependent individuals. *Alcohol Alcohol* 2000; **35:** 384–9.

Romifidine *(BAN, rINN)*

Romifidiini; Romifidin; Romifidina; Romifidinum; STH-2130. 2-Bromo-6-fluoro-*N*-(1-imidazolin-2-yl)aniline.

Ромифидин

$C_9H_9BrFN_3 = 258.1.$
CAS — 65896-16-4.
ATC Vet — QN05CM93.

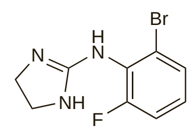

Profile

Romifidine is an α_2-adrenoceptor agonist with sedative, muscle relaxant, and analgesic properties and is used in veterinary medicine.

Secbutabarbital *(rINN)*

Butabarbital; Butabarbitone; Secbutabarbitalum; Secbutobarbital *(BAN)*; Secbutobarbitone. 5-*sec*-Butyl-5-ethylbarbituric acid.

Секбутабарбитал

$C_{10}H_{16}N_2O_3 = 212.2.$
CAS — 125-40-6.

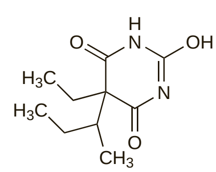

NOTE. Butabarbital should be distinguished from Butobarbital (p.967).

Pharmacopoeias. In *US.*

USP 31 (Butabarbital). A white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol, in chloroform, in ether, and in aqueous solutions of alkali hydroxides and carbonates. Store in airtight containers.

Secbutabarbital Sodium *(rINNM)*

Butabarbital Sodium; Natrii Secbutabarbitalum; Secbutabarbital sódico; Secbutabarbital Sodique; Secbutobarbital Sodium *(BANM)*; Secbutobarbitone Sodium; Secumalnatrium; Sodium Butabarbital. Sodium 5-*sec*-butyl-5-ethylbarbiturate.

Натрий Секбутабарбитал

$C_{10}H_{15}N_2NaO_3 = 234.2.$
CAS — 143-81-7.

Pharmacopoeias. In *US.*

USP 31 (Butabarbital Sodium). A white powder. Soluble 1 in 2 of water, 1 in 7 of alcohol, and 1 in 7000 of chloroform; practically insoluble in absolute ether. pH of a 10% solution in water is between 10.0 and 11.2. Store in airtight containers.

Profile

Secbutabarbital is a barbiturate with general properties similar to those of amobarbital (p.961). It was used as a hypnotic and sedative although barbiturates are no longer considered appropriate for such purposes. For the short-term management of insomnia (p.957) it was usually given as the sodium salt in oral doses of 50 to 100 mg at night; as a sedative 15 to 30 mg has been given 3 or 4 times daily. Secbutabarbital base has also been given.

Preparations

USP 31: Butabarbital Sodium Elixir; Butabarbital Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Butisol.

Multi-ingredient: *USA:* Butibel; Phenazopyridine Plus; Urelief Plus; ***Venez.:*** Butropina; Eumidral.

Secobarbital *(rINN)*

Meballymal; Quinalbarbitone; Sécobarbital; Secobarbitalum; Secobarbitone; Sekobarbitaali. 5-Allyl-5-(1-methylbutyl)barbituric acid.

Секобарбитал

$C_{12}H_{18}N_2O_3 = 238.3.$
CAS — 76-73-3.
ATC — N05CA06.
ATC Vet — QN05CA06; QN51AA02.

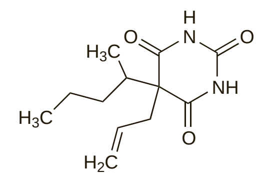

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of secobarbital:
F-40s; Marshmallow reds; M&Ms; Mexican reds; Pink ladies; Pink lady; Pinks; RDs; Red birds; Red bullets; Red devil; Red devils; Red dolls; Red lillies; Reds; Seccies; Seccy; Seco; Seggy.

Pharmacopoeias. In *US.*

USP 31 (Secobarbital). A white amorphous or crystalline odourless powder. Very slightly soluble in water; freely soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates; soluble in chloroform; soluble 1 in 8.5 of 0.5N sodium hydroxide. A saturated solution in water has a pH of about 5.6. Store in airtight containers.

Secobarbital Sodium *(BAN, rINNM)*

Meballymalnatrium; Natrii Secobarbitalum; Quinalbarbitone Sodium; Secobarbital sódico; Sécobarbital Sodique; Secobarbitalum Natricum; Secobarbitone Sodium. Sodium 5-allyl-5-(1-methylbutyl)barbiturate.

Натрий Секобарбитал

$C_{12}H_{17}N_2NaO_3 = 260.3.$
CAS — 309-43-3.
ATC — N05CA06.
ATC Vet — QN05CA06.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Secobarbital Sodium). A white odourless hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. pH of a 10% solution in water is between 9.7 and 10.5. Solutions decompose on standing, heat accelerating the decomposition. Store in airtight containers.

Incompatibility. Secobarbital may be precipitated from preparations containing secobarbital sodium depending on the concentration and pH. Secobarbital sodium has, therefore, been reported to be incompatible with many other drugs, particularly acids and acidic salts.

Dependence and Withdrawal

As for Amobarbital, p.962.

Adverse Effects, Treatment, and Precautions

As for Amobarbital, p.962.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving secobarbital, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, for the view that barbiturates should not be used in women who are breast feeding, see under Amobarbital, p.962.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)

Industrial exposure. Exposure to secobarbital sodium among 6 workers in the pharmaceutical industry resulted in absorption of substantial amounts of the drug, with blood concentrations approaching those expected after a therapeutic dose.[1] There continued to be evidence of absorption, despite protective masks to reduce inhalation, and it appeared that substantial absorption was taking place through the skin.

1. Baxter PJ, *et al.* Exposure to quinalbarbitone sodium in pharmaceutical workers. *BMJ* 1986; **292:** 660–1.

Porphyria. Secobarbital has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Amobarbital, p.962.

Pharmacokinetics

Secobarbital is well absorbed from the gastrointestinal tract after oral doses and is reported to be about 46 to 70% bound to plasma proteins. The mean elimination half-life is reported to be 28 hours. It is metabolised in the liver, mainly by hydroxylation, and excreted in urine as metabolites and a small amount of unchanged drug.

Uses and Administration

Secobarbital is a barbiturate that has been used as a hypnotic and sedative. It has general properties similar to those of amobarbital (p.962). As a hypnotic in the short-term management of insomnia (p.957) it was usually given in an oral dose of 100 mg of the sodium salt at night, but barbiturates are no longer considered appropriate for such use.

Secobarbital sodium has also been given orally or by intramuscular or intravenous injection for premedication in anaesthetic procedures (p.1780) but barbiturates for pre-operative sedation have been replaced by other drugs.

Preparations

USP 31: Secobarbital Elixir; Secobarbital Sodium and Amobarbital Sodium Capsules; Secobarbital Sodium Capsules; Secobarbital Sodium for Injection; Secobarbital Sodium Injection.

Proprietary Preparations (details are given in Part 3)
UK: Seconal; ***USA:*** Seconal.

Multi-ingredient: ***Port.:*** Vesparax†; ***UK:*** Tuinal; ***USA:*** Tuinal.

Sertindole *(BAN, USAN, rINN)*

Lu-23-174; Sertindol; Sertindoli; Sertindolum. 1-(2-{4-[5-Chloro-1-(*p*-fluorophenyl)indol-3-yl]piperidino}ethyl)-2-imidazolidinone.

Сертиндол

$C_{24}H_{26}ClFN_4O$ = 440.9.
CAS — 106516-24-9.
ATC — N05AE03.
ATC Vet — QN05AE03.

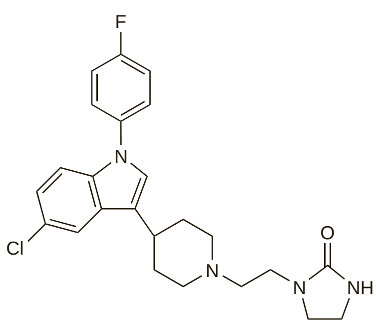

Adverse Effects, Treatment, and Precautions

Although sertindole may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Sertindole is associated with a low incidence of extrapyramidal adverse effects and does not appear to cause sedation. Prolactin elevation may be less frequent. The most common adverse effects with sertindole are peripheral oedema, rhinitis, dyspnoea, sexual dysfunction, dizziness, dry mouth, orthostatic hypotension, weight gain, and paraesthesia. Hyperglycaemia, convulsions, and tardive dyskinesia are uncommon.

Marketing of sertindole has been restricted because of cardiac arrhythmias and sudden cardiac deaths associated with its use (see below). Since sertindole has been associated with prolongation of the QT interval, usually during the first 3 to 6 weeks of treatment, it is recommended that patients should have an ECG before the start of therapy and periodically during treatment. Patients with pre-existing prolongation of the QT interval or a family history of congenital QT prolongation should not be given sertindole and sertindole should be stopped if such prolongation occurs during treatment. In addition, sertindole is contra-indicated in patients with a history of cardiovascular disease, heart failure, cardiac hypertrophy, arrhythmias, or bradycardia. Certain medications may also increase the risk (see Interactions, below).

Sertindole should not be given to patients with uncorrected hypokalaemia or hypomagnesaemia. Baseline serum potassium and magnesium screening should be performed before starting sertindole therapy in patients who are at risk of significant electrolyte disturbances. Serum potassium should be monitored in patients with electrolyte disturbances, vomiting or diarrhoea, or receiving diuretics during sertindole treatment. It is also recommended that blood pressure should be monitored during dose titration and in early maintenance therapy.

Sertindole is contra-indicated in patients with severe hepatic impairment. It should be used with caution in the elderly and in patients with Parkinson's disease, mild to moderate hepatic impairment, or a history of seizures.

Sertindole may affect the performance of skilled tasks including driving.

Gradual withdrawal of sertindole is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Dementia. The FDA has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs in this class. See under Risperidone, p.1024.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on the cardiovascular system. Prolongation of the QT interval is said by the manufacturer to be common in patients given sertindole, with the effect being greater at the upper end of the dose range. In addition, the QT interval is prolonged to a greater extent than that seen with some other antipsychotics. QT interval prolongation is a known risk factor for the development of serious arrhythmias such as torsade de pointes although such arrhythmias are uncommon with sertindole.

In evidence presented to the FDA it was reported that as of 1st June 1996 there had been 27 deaths, 16 due to adverse cardiac events, among the 2194 patients given sertindole in clinical studies.[1] By the end of November 1998, the UK CSM was aware of 36 suspected adverse drug reactions with a fatal outcome, 9 of which originated in the UK.[2] There had also been 13 reports of serious but non-fatal cardiac arrhythmias in the UK. Although not all the fatalities were related to sudden cardiac events, at the time the CSM considered that, given the number of serious arrhythmias and sudden cardiac deaths, the risk-benefit ratio of sertindole was no longer favourable. The drug was withdrawn from the market in the UK and subsequently in a number of other countries, although it remained available on a named-patient basis. However, in 2001, the issue was re-evaluated by the CSM and the European advisory body, the Committee on Proprietary Medicinal Products, and it was recommended that sertindole could be reintroduced in Europe under certain restrictions.[3] Initially sertindole should only be prescribed to patients enrolled in clinical studies to ensure that they are carefully selected and monitored. In the UK, sertindole was remarketed in September 2002.

1. Barnett AA. Safety concerns over antipsychotic drug, sertindole. *Lancet* 1996; **348:** 256.
2. CSM/MCA. Suspension of availability of sertindole (Serdolect). *Current Problems* 1999; **25:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
3. CSM/MCA. Restricted re-introduction of the atypical antipsychotic sertindole (Serdolect) (issued 10th September, 2002). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019523 (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

The risk of arrhythmias with sertindole may be increased by other drugs that prolong the QT interval and use together should be avoided. Sertindole should be given with caution with drugs that produce electrolyte disturbances; monitoring of serum potassium is recommended if given with potassium-depleting diuretics.

Sertindole may antagonise the effects of dopaminergics.

Sertindole is extensively metabolised by the cytochrome P450 isoenzymes of the group CYP3A and by CYP2D6. The use of potent inhibitors of CYP3A such as indinavir, itraconazole, and ketoconazole with sertindole is contra-indicated. Minor increases in sertindole plasma concentrations have been noted in patients also given macrolide antibacterials or calcium-channel blockers which also inhibit CYP3A; however, despite the small increase, the use of these CYP3A4 inhibitors with sertindole is not recommended. Fluoxetine and paroxetine, potent inhibitors of CYP2D6, have increased plasma concentrations of sertindole by a factor of 2 to 3 and lower maintenance doses of sertindole may be required. In contrast, enzyme inducers such as rifampicin, carbamazepine, phenytoin, and phenobarbital may decrease sertindole plasma levels by a factor of 2 to 3; in such cases, higher doses of sertindole may be required.

Pharmacokinetics

Sertindole is slowly absorbed with peak concentrations occurring about 10 hours after oral doses. It is about 99.5% bound to plasma proteins and readily crosses the placenta. Sertindole is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A. There is moderate interindividual variation in the pharmacokinetics of sertindole due to polymorphism in the isoenzyme CYP2D6. Poor metabolisers, deficient in this isoenzyme, may have plasma concentrations of sertindole 2 to 3 times higher than other patients. The two major metabolites, dehydrosertindole and norsertindole, appear to be inactive. Sertindole and its metabolites are excreted slowly, mainly in the faeces with a minor amount appearing in the urine. The mean terminal half-life is about 3 days.

Uses and Administration

Sertindole is an atypical antipsychotic that is an antagonist at central dopamine (D_2), serotonin (5-HT_2), and adrenergic (α_1) receptors. It is used in the treatment of schizophrenia (p.955) in patients who are unable to tolerate at least one other antipsychotic. In addition, sertindole should only be prescribed to patients enrolled in clinical studies to ensure adequate monitoring, especially regular ECG measurements (see Adverse Effects, above).

Sertindole is given in an initial oral dose of 4 mg once daily, increased gradually in steps of 4 mg every 4 or 5 days to a usual maintenance dose of 12 to 20 mg once daily. The maximum dose is 24 mg daily. Slower dose titration and lower maintenance doses are advisable for the elderly and patients with mild to moderate hepatic impairment.

If therapy is interrupted for 1 week or more, the dose of sertindole should be re-titrated. An ECG should also be undertaken before re-starting sertindole.

◊ References.

1. Lewis R. *et al.* Sertindole for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/05/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Serdolect; ***Cz.:*** Serdolect; ***Fr.:*** Serdolect; ***Gr.:*** Serdolect; ***Hung.:*** Serdolect; ***Neth.:*** Serdolect; ***Port.:*** Serdolect; ***Rus.:*** Serdolect (Сердолект); ***Switz.:*** Serdolect; ***UK:*** Serdolect.

Sulpiride *(BAN, USAN, rINN)*

Sulpirid; Sulpirida; Sulpiridas; Sulpiridi; Sulpiridum; Sülprid; Szulpirid. *N*-(1-Ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulphamoylbenzamide.

Сульпирид

$C_{15}H_{23}N_3O_4S$ = 341.4.
CAS — 15676-16-1 (sulpiride).
ATC — N05AL01.
ATC Vet — QN05AL01.

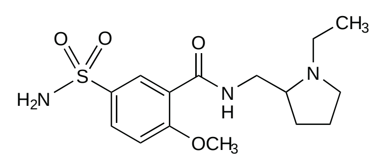

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*
Ph. Eur. 6.2 (Sulpiride). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. It dissolves in dilute solutions of mineral acids and in alkali hydroxides.

Levosulpiride *(rINN)*

Levosulpirida; Lévosulpiride; Levosulpiridum; Levosulpride; L-Sulpiride.

Левосульпирид

$C_{15}H_{23}N_3O_4S$ = 341.4.
CAS — 23672-07-3.
ATC — N05AL07.
ATC Vet — QN05AL07.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Sleep disturbances, overstimulation, and agitation may occur. Extrapyramidal effects appear to be as frequent as with chlorpromazine but have usually been mild. It has been suggested that sulpiride is less likely to cause tardive dyskinesia but good evidence of any important difference is lacking. Sulpiride is less likely to cause sedation than chlorpromazine and antimuscarinic effects are minimal. Cardiovascular effects such as hypotension are generally rare although they may occur with overdosage.

Sulpiride should be given with care to manic or hypomanic patients in whom it may exacerbate symptoms.

Breast feeding. Sulpiride may be distributed into breast milk and the *BNF* recommends that its use should be avoided in mothers wishing to breast feed.

On the fifth day after starting D-sulpiride, DL-sulpiride, or L-sulpiride in a dose of 50 mg twice daily, mean concentrations of sulpiride in breast milk from 45 women were 840, 850, and 810 nanograms/mL respectively.[1]

1. Polatti F. Sulpiride isomers and milk secretion in puerperium. *Clin Exp Obstet Gynecol* 1982; **9:** 144–7.

Effects on the cardiovascular system. Sulpiride 100 mg by mouth caused an attack of hypertension in 6 of 26 hypertensive patients; in 4 it induced a rise in urinary excretion of vanillylmandelic acid and catecholamines.[1] A transient rise in blood pressure and catecholamines after sulpiride occurred in 3 patients who were found to have a phaeochromocytoma; another patient probably had a phaeochromocytoma. The means by which sulpiride provoked hypertension were not known but appeared to be due to a noradrenergic effect. Sulpiride should be avoided during the treatment of phaeochromocytoma, and prescribed with great care in hypertensive patients.

1. Corvol P, *et al*. Poussées hypertensives déclenchées par le sulpiride. *Sem Hop Paris* 1974; **50:** 1265–9.

Porphyria. Sulpiride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Renal impairment. For the precautions to be observed in patients with impaired renal function, see under Uses and Administration, below.

Interactions

As for Chlorpromazine, p.973

Gastrointestinal drugs. Giving sulpiride with therapeutic doses of *sucralfate* or an *antacid* containing aluminium and magnesium hydroxides to 6 healthy subjects reduced the mean oral bioavailability of sulpiride by 40 and 32%, respectively.[1] When sulpiride was given 2 hours after the antacid or sucralfate (each in 2 subjects), bioavailability was reduced by about 25%. This interaction was expected to be clinically significant, and it was recommended that sulpiride should be given before, rather than with or after, sucralfate or antacids.

1. Gouda MW, *et al*. Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. *Int J Pharmaceutics* 1984; **22:** 257–63.

Pharmacokinetics

Sulpiride is slowly absorbed from the gastrointestinal tract; peak plasma concentrations are attained 3 to 6 hours after ingestion. Bioavailability is low and subject to interindividual variation. It is rapidly distributed to the tissues but passage across the blood-brain barrier is poor. Sulpiride is about 40% bound to plasma proteins and is reported to have a plasma half-life of about 8 to 9 hours. It is excreted in the urine and faeces, mainly as unchanged drug. Sulpiride is distributed into breast milk.

◊ References.

1. Wiesel F-A, *et al*. The pharmacokinetics of intravenous and oral sulpiride in healthy human subjects. *Eur J Clin Pharmacol* 1980; **17:** 385–91.
2. Bressolle F, *et al.* Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci* 1984; **73:** 1128–36.
3. Bressolle F, *et al.* Absolute bioavailability, rate of absorption, and dose proportionality of sulpiride in humans. *J Pharm Sci* 1992; **81:** 26–32.
4. Mauri MC, *et al.* L-sulpiride in young and elderly negative schizophrenics: clinical and pharmacokinetic variables. *Prog Neuropsychopharmacol Biol Psychiatry* 1994; **18:** 355–6.
5. Muller MJ, *et al*. Serum levels of sulpiride enantiomers after oral treatment with racemic sulpiride in psychiatric patients: a pilot study. *Pharmacopsychiatry* 2001; **34:** 27–32.

Uses and Administration

Sulpiride is a substituted benzamide antipsychotic that is reported to be a selective antagonist of central dopamine (D_2, D_3, and D_4) receptors. It is also claimed to have mood elevating properties.

Sulpiride is mainly used in the treatment of psychoses such as schizophrenia (below). It has also been given in the management of Tourette's syndrome (below), anxiety disorders (p.952), depression (p.373), vertigo (p.565), and benign peptic ulceration (below). Levosulpiride, the L-isomer of sulpiride, has been used similarly to sulpiride.

In the treatment of **schizophrenia** in adults and children aged 14 years and over, initial oral doses of 200 to 400 mg of sulpiride are given twice daily, increased if necessary up to a maximum of 1.2 g twice daily in patients with mainly positive symptoms or up to a total of 800 mg daily in patients with mainly negative symptoms. Patients with mixed positive and negative symptoms, with neither predominating, are given usual doses of 400 to 600 mg twice daily. Lower initial doses have been recommended in elderly patients, subsequently adjusted as required.

Sulpiride is also given in some countries by intramuscular injection, in usual doses ranging from 200 to 800 mg daily.

Dosage adjustment is advised in patients with renal impairment (see below).

Administration in renal impairment. A single intravenous dose of sulpiride 100 mg was given to 6 healthy subjects with normal renal function (creatinine clearance greater than 90 mL/minute) and to 3 groups of 6 patients each with creatinine clearances (CC) in the ranges of 30 to 60, 10 to 30, and less than 10 mL/minute.[1] There was a progressive diminution in the rate of elimination and an increase in half-life with decreasing renal function. The mean plasma elimination half-lives were 5.90, 11.02, 19.27, and 25.96 hours in the 4 groups, respectively.

In the UK it has been recommended that the oral dose be reduced according to CC as follows:

- CC 30 to 60 mL/minute: two-thirds of the usual dose, or prolong dosage interval by a factor of 1.5
- CC 10 to 30 mL/minute: half the usual dose, or double dosage interval
- CC less than 10 mL/minute: one-third of the usual dose, or triple dosage interval

However, the *BNF* suggests that sulpiride should be avoided if CC is less than 10 mL/minute.

1. Bressolle F, *et al.* Pharmacokinetics of sulpiride after intravenous administration in patients with impaired renal function. *Clin Pharmacokinet* 1989; **17:** 367–73.

Chorea. Antipsychotics have some action against choreiform movements (p.953) as well as being of use to control the behavioural disturbances of Huntington's chorea. Although sulpiride was found to have produced an overall reduction in abnormal movements in 11 patients with Huntington's chorea when compared with placebo in a double-blind study[1] there was generally no accompanying functional improvement and patients with mild disease tended to worsen when taking sulpiride.

1. Quinn N, Marsden CD. A double blind trial of sulpiride in Huntington's disease and tardive dyskinesia. *J Neurol Neurosurg Psychiatry* 1984; **47:** 844–7.

Gastrointestinal disorders. Although sulpiride is used in some countries as an adjunct in the treatment of peptic ulcer disease (p.1702) it is not among the more usual drugs used for this indication. Efficacy has also been claimed for sulpiride or levosulpiride in a variety of other gastrointestinal disorders, including irritable bowel disease (p.1699), decreased gastrointestinal motility (p.1694), and nausea and vomiting (p.1700), but again they are not among the drugs usually considered for use in these conditions.

Lactation induction. Drug therapy has been used occasionally to stimulate lactation in breast-feeding mothers, although mechanical stimulation of the nipple remains the primary method. Dopamine antagonists such as sulpiride can produce modest increases in breast milk production[1-3] although metoclopramide has been more widely used (see p.2003). However, there is concern about the adverse effects of these drugs. As sulpiride appears in breast milk and may be associated with adverse effects in the infant it has been recommended that it should not be used to enhance milk production.[4,5]

1. Aono T, *et al*. Effect of sulpiride on poor puerperal lactation. *Am J Obstet Gynecol* 1982; **143:** 927–32.
2. Ylikorkala O, *et al.* Sulpiride improves inadequate lactation. *BMJ* 1982; **285:** 249–51.
3. Ylikorkala O, *et al.* Treatment of inadequate lactation with oral sulpiride and buccal oxytocin. *Obstet Gynecol* 1984; **63:** 57–60.
4. Pons G, *et al.* Excretion of psychoactive drugs into breast milk: pharmacokinetic principles and recommendations. *Clin Pharmacokinet* 1994; **27:** 270–89.
5. Lasich AJ. Sulpiride and breastfeeding. *S Afr Med J* 2005; **95:** 624–6.

Schizophrenia. A systematic review[1] of the use of sulpiride for schizophrenia (p.955) or serious mental illness concluded that while sulpiride might be as effective as the classical antipsychotics for schizophrenia and appeared to produce few adverse effects, evidence of its value for treating negative symptoms was lacking. Comparisons with the atypical antipsychotic drugs were also lacking.

1. Soares B, *et al.* Sulpiride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 21/08/08).

Tourette's syndrome. When drug treatment is needed for tics and behavioural disturbances in Tourette's syndrome (p.954) dopamine antagonists such as the antipsychotics haloperidol or pimozide are most commonly used but sulpiride has also been tried.[1] Although unlicensed in the UK for the treatment of Tourette's syndrome, the *BNFC* has suggested that oral doses of sulpiride 50 to 400 mg twice daily may be given to those aged from 2 to 12 years, and 100 to 400 mg twice daily to adolescents aged from 12 to 18 years.

1. Robertson MM, *et al.* Management of Gilles de la Tourette syndrome using sulpiride. *Clin Neuropharmacol* 1990; **13:** 229–35.

Preparations

BP 2008: Sulpiride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dislep; Nivelan†; Vipral; ***Austria:*** Dogmatil; Meresa; ***Belg.:*** Docsulpiri; Dogmatil; Levopraid; ***Braz.:*** Dogmatil; Equilid; ***Chile:*** Aplacid; Dislep; Sanblex; Sedusen; Sulpilan; ***Cz.:*** Dogmatil; Eglonyl†; Prosulpin; Sulpirol; ***Denm.:*** Dogmatil; ***Fin.:*** Suprium; ***Fr.:*** Aiglonyl†; Dogmatil; Synedil; ***Ger.:*** Arminol; Dogmatil; Meresa; neogama; neogama D novo†; Sulp†; Sulpivert; Vertigo-Meresa; vertigo-neogama; ***Gr.:*** Calmoflorine; Darleton; Dogmatyl; Eclorion†; Noneston†; Nufarol; Nylipark†; Restful; Stamonevrol; Valirem; ***Hong Kong:*** Dogmatil; ***Hung.:*** Depral; ***Indon.:*** Dogmatil; ***Irl.:*** Dolmatil; ***Israel:*** Modal; ***Ital.:*** Championyl; Dobren; Equilid; Levobren; Levopraid; ***Jpn:*** Dogmatyl; ***Malaysia:*** Dogmatil; ***Mex.:*** Dislep; Ekilid; Pontiride; Rimastine; ***Neth.:*** Dogmatil; ***Philipp.:*** Dogmatil; ***Port.:*** Dogmatil; Gustamax†; Lisopride†; ***Rus.:*** Betamaks (Бетамакс); Eglek (Эглек); Eglonil (Эвитол); Prosulpin (Просульпин); ***S.Afr.:*** Eglonyl; Espiride; ***Singapore:*** Dogmatil†; ***Spain:*** Digton; Dogmatil; Guastil; Lebopride; Levogastrol; Pausedal; Psicocen; Sulkine†; Tepavil; ***Switz.:*** Dogmatil; ***Turk.:*** Dogmatil; Meresa; Sulpir; Zeprid; ***UK:*** Dolmatil; Sulpitil†; Sulpor; ***Venez.:*** Dislep; Guven†.

Multi-ingredient: ***Arg.:*** Alplax Digest; Novo Vegestabil†; Tranquinal Soma; Tranxilium Digest; Vegestabil; ***Braz.:*** Bromopirin; Sulpan; ***Mex.:*** Numencial; ***Spain:*** Ansium; Sirodina†; Tepazepan; ***Venez.:*** Tepazepam†.

Sultopride Hydrochloride *(rINNM)*

Hidrocloruro de sultoprida; LIN-1418; Sultopride, Chlorhydrate de; Sultopridi Hydrochloridum. *N*-(1-Ethylpyrrolidin-2-ylmethyl)-5-ethylsulphonyl-2-methoxybenzamide hydrochloride.

Сультоприда Гидрохлорид

$C_{17}H_{26}N_2O_4S,HCl = 390.9.$

CAS — 53583-79-2 (sultopride); 23694-17-9 (sultopride hydrochloride).

ATC — N05AL02.

ATC Vet — QN05AL02.

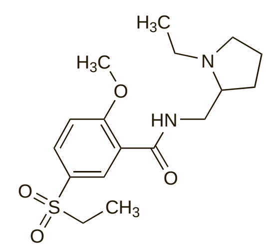

(sultopride)

Profile

Sultopride is a substituted benzamide with general properties similar to those of sulpiride (above). It is used in psychoses such as schizophrenia (p.955). It has also been used in the emergency management of agitation in psychotic or aggressive patients. It is given as the hydrochloride but doses are expressed in terms of the base; sultopride hydrochloride 441 mg is equivalent to about 400 mg of sultopride.

For acute and chronic psychoses it may be given in oral doses of 400 to 800 mg daily; it may also be given intramuscularly.

Ventricular arrhythmias, including torsade de pointes, have been reported. It has been recommended that sultopride should not be used in patients with bradycardia.

Porphyria. Sultopride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Barnetil†; ***Fr.:*** Barnetil†; ***Ital.:*** Barnotil†; ***Port.:*** Barnetil†.

Tandospirone Citrate *(BANM, USAN, rINNM)*

Citrato de tandospirona; Metanopirone Citrate; SM-3997 (tandospirone or tandospirone citrate); Tandospirone, Citrate de; Tandospironi Citras. (1R*,2S*,3R*,4S*)-*N*-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl}-2,3-norbornanedicarboximide citrate.

Тандоспирона Цитрат

$C_{21}H_{29}N_5O_2,C_6H_8O_7$ = 575.6.

CAS — 87760-53-0 (tandospirone); 112457-95-1 (tandospirone citrate).

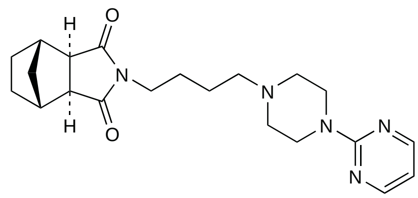

(tandospirone)

Profile

Tandospirone, a partial agonist at serotonin (5-HT) receptors of the 5-HT_{1A} subtype, is an anxiolytic structurally related to buspirone (p.965). It also has antidepressant actions. Tandospirone citrate is given in usual oral doses of 30 mg daily in 3 divided doses up to a maximum of 60 mg daily.

◊ References.

1. Sumiyoshi T, *et al.* The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. *Biol Psychiatry* 2001; **49:** 861–8.
2. Yamada K, *et al.* Clinical efficacy of tandospirone augmentation in patients with major depressive disorder: a randomized controlled trial. *Psychiatry Clin Neurosci* 2003; **57:** 183–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Sediel.

Temazepam *(BAN, USAN, rINN)*

ER-115; 3-Hydroxydiazepam; K-3917; Ro-5-5345; Tematsepaami; Témazépam; Temazepám; Temazepamas; Temazepamum; Wy-3917. 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-1,4-benzodiazepin-2-one.

Темазепам

$C_{16}H_{13}ClN_2O_2$ = 300.7.

CAS — 846-50-4.

ATC — N05CD07.

ATC Vet — QN05CD07.

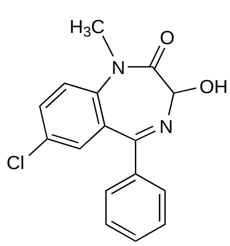

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of temazepam:
Beans; Egg; Eggs; Jellies; Knockout Pills; Mazzies; Oranges; Rugby Balls; Temazies; Temmies; Terms; Wobbly jellies.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Temazepam). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Temazepam). A white or nearly white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 10 mg of temazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Abuse. Liquid-filled temazepam *capsules* (known on the street as 'eggs') were widely abused on the illicit drugs market, the liquid gel lending itself to intravenous injection.[1] This formulation was, therefore, replaced in a number of countries by tablets or by semi-solid gel-filled capsules, which were intended to be difficult to inject even after heating or diluting the gel in various solvents.[2] In spite of this there is evidence of intravenous or intra-arterial abuse of these capsules,[3-5] and there are reports of ischaemia, in some cases necessitating amputation.[6-8] The *tablets* may also be liable to abuse; there has been a report of death after intravenous injection of a solution containing crushed temazepam tablets.[9] The manufacturers of a temazepam *elixir* considered that, because of its viscosity and its low strength relative to the liquid in the capsules, it had a low potential for intravenous abuse.[10] Nonetheless, there have been reports[3] of some drug abusers injecting large quantities of diluted elixir.

For mention of rhabdomyolysis associated with abuse of temazepam, see Effects on Skeletal Muscle, under Diazepam, p.988.

1. Farrell M, Strang J. Misuse of temazepam. *BMJ* 1988; **297:** 1402.
2. Launchbury AP. Temazepam abuse. *Pharm J* 1990; **244:** 749.
3. Ruben SM, Morrison CL. Temazepam misuse in a group of injecting drug users. *Br J Addict* 1992; **87:** 1387–92.
4. Scott RN, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
5. Adiseshiah M, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
6. Blair SD, *et al.* Leg ischaemia secondary to non-medical injection of temazepam. *Lancet* 1991; **338:** 1393–4.
7. Fox R, *et al.* Misuse of temazepam. *BMJ* 1992; **305:** 253.
8. Feeney GFX, Gibbs HH. Digit loss following misuse of temazepam. *Med J Aust* 2002; **176:** 380.
9. Vella EJ, Edwards CW. Death from pulmonary microembolization after intravenous injection of temazepam. *BMJ* 1993; **307:** 26.
10. Drake J, Ballard R. Misuse of temazepam. *BMJ* 1988; **297:** 1402.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of temazepam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Temazepam was detected in breast milk in only one of 10 mothers given temazepam as a bedtime sedative;[2] temazepam was given in a dose of 10 to 20 mg and milk concentrations were measured about 15 hours after a dose. The authors considered that breast-fed neonates would ingest negligible amounts of temazepam.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Lebedevs TH, *et al.* Excretion of temazepam in breast milk. *Br J Clin Pharmacol* 1992; **33:** 204–6.

Effects on the skin. Generalised lichenoid drug eruption that had persisted for 5 months in an elderly patient receiving therapy including temazepam resolved within 10 days of stopping the benzodiazepine.[1] Bullous eruptions associated with temazepam overdose have also been reported.[2]

1. Norris P, Sounex TS. Generalised lichenoid drug eruption associated with temazepam. *BMJ* 1986; **293:** 510.
2. Verghese J, Merino J. Temazepam overdose associated with bullous eruptions. *Acad Emerg Med* 1999; **6:** 1071.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, and licensed product information in the UK advises that temazepam should be avoided in severe cases. However, short-acting benzodiazepines such as temazepam may pose less risk in patients with hepatic impairment; in a study of 15 patients with cirrhosis and 16 healthy subjects, liver disease had no significant effect on the pharmacokinetic parameters or pattern of elimination of temazepam.[1]

1. Ghabrial H, *et al.* The effects of age and chronic liver disease on the elimination of temazepam. *Eur J Clin Pharmacol* 1986; **30:** 93–7.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Temazepam is fairly readily absorbed from the gastrointestinal tract, although the exact rate of absorption depends on the formulation. It is about 96% bound to plasma proteins. Mean elimination half-lives of about 8 to 15 hours or longer have been reported. It is excreted mainly in the urine in the form of its inactive glucuronide conjugate together with small amounts of the demethylated derivative, oxazepam, also in conjugated form.

Absorption and plasma concentration. Various oral temazepam formulations have been available worldwide. These included powder-filled hard gelatin capsules, liquid-filled soft gelatin capsules, semi-solid gel-filled soft gelatin capsules, and an elixir. There has been considerable debate over the comparative absorption profiles of temazepam from these formulations which have, in some cases, been modified over the years. It should be noted that pharmacokinetic studies of temazepam do not always clearly state the formulation used.

Temazepam 30 mg was given as a premedicant to 80 patients undergoing surgery in the form of capsules [type not stated] or elixir.[1] Mean peak plasma concentrations of about 800 nanograms/mL occurred 30 minutes after a dose of either formulation although there was wide interindividual variation in plasma concentrations. The evidence corresponded with previous suggestions that a plasma concentration of about 250 nanograms/mL or more was required to ensure sedation. The presence or absence of anxiety did not influence the absorption of the preparations.

1. Hosie HE, Nimmo WS. Temazepam absorption in patients before surgery. *Br J Anaesth* 1991; **66:** 20–4.

Distribution into CSF. A study in 13 male patients showed a correlation between the unbound concentration of temazepam in plasma and the amount of temazepam detected in CSF.[1] The mean CSF to total plasma temazepam concentration ratio was 5.2.

1. Badcock NR. Plasma and cerebrospinal fluid concentrations of temazepam following oral drug administration. *Eur J Clin Pharmacol* 1990; **38:** 153–5.

Metabolism. References.

1. Locniskar A, Greenblatt DJ. Oxidative versus conjugative biotransformation of temazepam. *Biopharm Drug Dispos* 1990; **11:** 499–506.

Sex differences. The elimination half-life was significantly longer at 16.8 hours among 17 women given temazepam 30 mg compared with 12.3 hours among 15 men.[1] The total clearance was also lower among women. After correction for differences in protein binding, unbound clearance was still lower in women than men but there was no significant effect of age on this parameter. Time to peak plasma concentration and volume of distribution were not affected by the age or sex of the subjects.

1. Divoll M, *et al.* Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981; **70:** 1104–7.

Uses and Administration

Temazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957) and for premedication before surgical or investigative procedures (p.1780).

A usual oral dose for insomnia is 10 to 20 mg at night; exceptionally, doses up to 40 mg may be required. For premedication the usual oral dose is 20 to 40 mg given half to one hour beforehand. The *BNFC* states that children aged 1 year and over may be given 1 mg/kg orally for premedication, to a maximum total dose of 30 mg.

Temazepam should be given in reduced dosage to elderly or debilitated patients; one-half the usual adult dose, or less, may be sufficient.

Administration. For reference to the various formulations of oral temazepam that have been used, see Abuse under Adverse Effects, Treatment, and Precautions, above.

Administration in the elderly. In a small study[1] a 7.5-mg dose of temazepam was found to be adequate for the short-term management of insomnia in elderly patients.

1. Vgontzas AN, *et al.* Temazepam 7.5 mg: effects on sleep in elderly insomniacs. *Eur J Clin Pharmacol* 1994; **46:** 209–13.

Preparations

BP 2008: Temazepam Oral Solution; Temazepam Tablets;
USP 31: Temazepam Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Euhypnos†; Nocturne†; Normison; Temaze; Temtabs; ***Austria:*** Levanxol; Remestan†; ***Belg.:*** Euhypnos†; Normison†; ***Canad.:*** Restoril; ***Fin.:*** Normison; Tenox; ***Fr.:*** Normison; ***Ger.:*** Norkotral Tema; Planum; Pronervon T; Remestan; Temazep; ***Gr.:*** Normison; ***Hung.:*** Signopam; ***Irl.:*** Euhypnos†; Insomniger; Normison†; Nortem; Tenox; ***Ital.:*** Euipnos; Normison; ***Neth.:*** Normison; ***NZ:*** Euhypnos; Normison; Somapam†; ***Pol.:*** Signopam; ***Port.:*** Normison; ***Rus.:*** Signopam (Сигнопам); ***S.Afr.:*** Normison; ***Switz.:*** Normison; ***Thai.:*** Euhypnos; ***USA:*** Restoril.

Tetrazepam *(BAN, pINN)*

CB-4261; Tetratsepaami; Tétrazépam; Tetrazepám; Tetrazepamas; Tetrazepamum. 7-Chloro-5-(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.

Тетразепам

$C_{16}H_{17}ClN_2O$ = 288.8.

CAS — 10379-14-3.

ATC — M03BX07.

ATC Vet — QM03BX07.

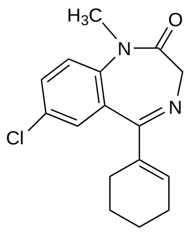

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tetrazepam). A light yellow or yellow crystalline powder. Practically insoluble in water; soluble in acetonitrile; freely soluble in dichloromethane. Protect from light.

Profile

Tetrazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It is used for its muscle relaxant properties in the treatment of muscle spasm (p.1887). The usual initial dose is 25 to 50 mg orally increased, if necessary, to 150 mg or more daily.

Pharmacokinetics. References.

1. Bun H, *et al.* Plasma levels and pharmacokinetics of single and multiple dose of tetrazepam in healthy volunteers. *Arzneimittelforschung* 1987; **37:** 199–202.

Porphyria. Tetrazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Myolastan; ***Belg.:*** Epsipam; Myolastan; ***Cz.:*** Myolastan; ***Fr.:*** Megavix; Myolastan; Panos; ***Ger.:*** Mobiforton; Musapam; Musaril; Muskelat†; Myospasmal; Rilex; Spasmorelax; Tethexal†; Tetra-saar; Tetramdura; Tetrazep; ***Mex.:*** Miolastan; ***Pol.:*** Miozepam; Myolastan; Myopam; Tetratio; ***Spain:*** Myolastan.

Thioproperazine Mesilate *(BANM, rINNM)*

Mesilato de tioproperazina; RP-7843; SKF-5883; Thioproperazine Dimethanesulphonate; Thiopropérazine, Mésilate de; Thioproperazine Mesylate; Thioproperazine Methanesulphonate; Thioproperazini Mesilas. *NN*-Dimethyl-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine-2-sulphonamide dimethanesulphonate.

Тиопроперазина Мезилат

$C_{22}H_{30}N_4O_2S_2,2CH_4O_3S$ = 638.8.

CAS — 316-81-4 (thioproperazine); 2347-80-0 (thioproperazine mesilate).

ATC — N05AB08.

ATC Vet — QN05AB08.

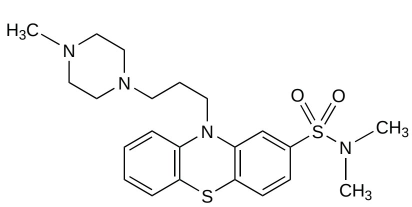

(thioproperazine)

Pharmacopoeias. In *Fr.*

Profile

Thioproperazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has a piperazine side-chain. It is used in the treatment of schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and other psychoses. Thioproperazine is given as the mesilate although doses are expressed in terms of the base; thioproperazine mesilate 7.2 mg is equivalent to about 5 mg of thioproperazine. Initial daily doses of 5 mg are given orally, increased as necessary; the usual effective dosage is 30 to 40 mg daily. In severe or resistant cases daily doses of 90 mg or more have been given.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Majeptil; ***Gr.:*** Majeptil; ***Mex.:*** Majeptil†; ***Rus.:*** Majeptil (Мажептил); ***Spain:*** Majeptil; ***Venez.:*** Majeptil†.

Thioridazine *(BAN, USAN, rINN)*

Thioridazin; Thioridazinum; Tioridatsiini; Tioridazin; Tioridazina; Tioridazinas; TP-21. 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-methylthiophenothiazine.

Тиоридазин

$C_{21}H_{26}N_2S_2$ = 370.6.

CAS — 50-52-2.

ATC — N05AC02.

ATC Vet — QN05AC02.

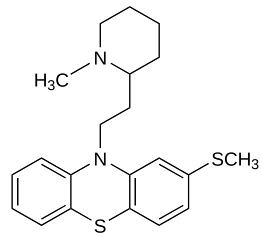

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Thioridazine). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Thioridazine). A white to slightly yellow crystalline or micronised powder; odourless or having a faint odour. Practically insoluble in water; freely soluble in dehydrated alcohol and in ether; very soluble in chloroform. Protect from light.

Thioridazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tioridazina; Thioridazin hydrochlorid; Thioridazine, chlorhydrate de; Thioridazini hydrochloridum; Tioridatsiinihydrokloridi; Tioridazinhidroklorid; Tioridazinhydroklorid; Tioridazino hidrochloridas; Tiorydazny chlorowodorek; Tiorydazyny chlorowodorek.

Тиоридазина Гидрохлорид

$C_{21}H_{26}N_2S_2,HCl$ = 407.0.

CAS — 130-61-0.

ATC — N05AC02.

ATC Vet — QN05AC02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Thioridazine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 31 (Thioridazine Hydrochloride). A white to slightly yellow granular powder having a slight odour. Freely soluble in water, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. For a warning about incompatibility between thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p.471.

Adverse Effects and Treatment

As for Chlorpromazine, p.969.

Thioridazine has been associated with a higher incidence of antimuscarinic effects, but lower incidence of extrapyramidal effects than chlorpromazine. It may also be less sedating. However, it is more likely to induce hypotension and there is an increased risk of cardiotoxicity and dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use has been restricted (see Precautions, and Uses and Administration, below). Sexual dysfunction also appears to be more frequent with thioridazine.

Pigmentary retinopathy characterised by reduced visual acuity, brownish colouring of vision, and impairment of night vision has been seen particularly in patients taking large doses.

Effects on the cardiovascular system. Between 1964 and 2001, the UK CSM received 42 reports of suspected heart rate and rhythm disorders associated with thioridazine.[1] There were 21 fatalities reported out of 39 cases where the outcome was known.

See also under Chlorpromazine, p.970.

1. Committee on Safety of Medicines/Medicines Control Agency. QT interval prolongation with antipsychotics. *Current Problems* 2001; **27:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 12/05/06)

Hypersensitivity. Pruritus and erythematous rash on the genitals of a woman after sexual intercourse were found to be due to thioridazine present in the seminal fluid of her husband, who was taking 100 mg daily at night.[1]

1. Sell MB. Sensitization to thioridazine through sexual intercourse. *Am J Psychiatry* 1985; **142:** 271–2.

Overdosage. Rhabdomyolysis has been reported in a patient after overdosage with thioridazine.[1] Twenty-four hours after taking 9.4 g of thioridazine the patient presented with difficulty in moving and speaking. On examination he had swelling and tenderness over his upper arms, thighs, and calves. Ataxia and transient dysarthria were attributed to generalised muscle weakness. Other effects were consistent with antimuscarinic effects of thioridazine. He had no signs of neuroleptic malignant syndrome but his urine contained myoglobin. The patient was treated with gastric lavage, activated charcoal, and rehydration. Serum biochemistry returned to normal over 1 week and the muscle tenderness and weakness disappeared.

1. Nankivell BJ, *et al.* Rhabdomyolysis induced by thioridazine. *BMJ* 1994; **309:** 378.

Precautions

As for Chlorpromazine, p.972. Thioridazine should not be used in patients with clinically significant cardiac disorders, uncorrected hypokalaemia or other electrolyte imbalance, with known or suspected QT prolongation or a family history of QT prolongation, or with a history of ventricular arrhythmias including torsade de pointes. Use is also contra-indicated in patients known to have reduced activity of the cytochrome P450 isoenzyme CYP2D6, which is responsible for thioridazine metabolism. Use with drugs liable to interfere with the metabolism of thioridazine, with other drugs known to prolong the QT interval, and with drugs likely to cause electrolyte imbalance should also be avoided (see under Interactions, below).

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Porphyria. Thioridazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Chlorpromazine, p.973. The metabolism of thioridazine is mediated by the cytochrome P450 isoenzyme CYP2D6; thioridazine itself is also an inhibitor of CYP2D6. Therefore, there is the potential for interactions between thioridazine and other drugs that inhibit or act as a substrate for this enzyme; such drugs should not be given with thioridazine. Some examples include antiarrhythmics, certain antidepressants including the SSRIs and tricyclics, certain antipsychotics, beta blockers, HIV-protease inhibitors, and opioids.

Use with other drugs known to prolong the QT interval such as class IA and class III antiarrhythmics, tricyclic antidepressants, and some other antipsychotics should also be avoided, as should use with those drugs known to cause electrolyte imbalance.

Pharmacokinetics

The pharmacokinetics of thioridazine appear to be generally similar to those of chlorpromazine (p.975). Thioridazine is metabolised by the cytochrome P450 isoenzyme CYP2D6. Its main active metabolite is mesoridazine (p.1007); another metabolite, sulforidazine, also has some activity. Thioridazine and its active metabolites are reported to be highly bound to plasma proteins (more than 95%). The plasma half-life of thioridazine has been estimated to be about 4 to 10 hours. It also crosses the placenta and is distributed into breast milk.

◊ References.

1. Mårtensson E, Roos B-E. Serum levels of thioridazine in psychiatric patients and healthy volunteers. *Eur J Clin Pharmacol* 1973; **6:** 181–6.
2. Axelsson R, Mårtensson E. Serum concentration and elimination from serum of thioridazine in psychiatric patients. *Curr Ther Res* 1976; **19:** 242–65.

Metabolism. In 10 psychiatric patients stabilised on thioridazine, therapy was replaced by equipotent doses of the side-chain sulfoxide (mesoridazine) and side-chain sulfone (sulforidazine) metabolites of thioridazine.[1] Both metabolites were shown to have an antipsychotic effect, the dose of each required being about two-thirds that of thioridazine. The serum half-lives were thioridazine 21 hours, mesoridazine 16 hours, and sulforidazine 13 hours. Apathy, depression, and restlessness gradually developed during treatment with the 2 metabolites and they could not be used for any length of time. Extrapyramidal symptoms, hypersalivation, and drowsiness were more common with the metabolites; 2 patients had epileptic seizures, and 1 receiving sulforidazine developed probable cholestatic jaundice.

There is some evidence that the metabolism of thioridazine is influenced by debrisoquine hydroxylation phenotype.[2] A single-dose study in 19 healthy male subjects demonstrated slower formation of mesoridazine, and hence higher serum-thioridazine concentrations in poor debrisoquine hydroxylators compared with extensive hydroxylators. Formation of thioridazine ring-sulfoxide appeared to be compensatorily increased in slow hydroxylators.

1. Axelsson R. On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients. *Curr Ther Res* 1977; **21:** 587–605.
2. von Bahr C, *et al.* Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. *Clin Pharmacol Ther* 1991; **49:** 234–40.

Uses and Administration

Thioridazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperidine side-chain and, unlike chlorpromazine, has little antiemetic activity.

The use of thioridazine has been restricted to the treatment of schizophrenia (p.955) in patients who fail to show an adequate response to treatment with other antipsychotics. Its use in other psychiatric disorders was abandoned after it was felt that there was an unacceptable balance of risks and benefits as a result of its cardiotoxic potential; it has been withdrawn in some countries, including the UK.

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Thioridazine is given orally as the hydrochloride or the base, and doses may be expressed in terms of either. In some countries, doses of oral liquid preparations have been given in terms of the base, whereas those of the tablets have been given as the hydrochloride. In the USA, all doses are given in terms of the hydrochloride. Thioridazine 22.8 mg is equivalent to about 25 mg of thioridazine hydrochloride.

In the treatment of schizophrenia thioridazine hydrochloride should be started at the usual dose of 50 to 100 mg three times daily and slowly titrated upwards to a maximum of 800 mg daily if necessary; doses should be reduced once effective control is achieved. The daily dosage range is 200 to 800 mg, which may be given in 2 to 4 divided doses. It has been recommended that increases in doses should be no more than 100 mg weekly.

Thioridazine should be given in lower initial doses to patients with a low body-mass or those with hepatic or renal impairment; dosage increases should also be more gradual.

In those patients who require withdrawal of thioridazine, the dose should be gradually reduced over 1 to 2 weeks to avoid symptoms such as gastrointestinal disorders, dizziness, anxiety, and insomnia that are sometimes seen after abruptly stopping high-dose or long-term treatment.

◊ References.

1. Fenton M, *et al.* Thioridazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/03/08).

Preparations

USP 31: Thioridazine Hydrochloride Oral Solution; Thioridazine Hydrochloride Tablets; Thioridazine Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Meleril†; ***Austral.:*** Aldazine; Melleril†; ***Austria:*** Melleril†; ***Belg.:*** Melleril†; ***Braz.:*** Melleril†; Unitidazin; ***Chile:*** Meleril†; Nervosan†; Simultan; Tinsenol†; ***Denm.:*** Melleril†; ***Fin.:*** Melleril†; Orsanil†; ***Fr.:*** Melleril†; ***Ger.:*** Melleretten†; Melleril†; ***Gr.:*** Melleril†; ***Hong Kong:*** Melleril†; ***Hung.:*** Melleril†; ***India:*** Thioril; ***Indon.:*** Melleril; ***Irl.:*** Melleril†; Melzine†; Thiozine†; ***Israel:*** Ridazin; ***Ital.:*** Melleril†; ***Malaysia:*** Aldazine†; Melleril†; ***Mex.:*** Dazithin; Melleril†; ***Neth.:*** Melleril†; ***Norw.:*** Melleril†; ***NZ:*** Aldazine; Melleril†; ***Port.:*** Melleril†; ***Rus.:*** Sonapax (Сонапакс); Thiodazine (Тиодазин); Thioril (Тиорил); Tison (Тисон); ***S.Afr.:*** Melleril†; ***Spain:*** Meleril†; ***Swed.:*** Mallorol†; ***Switz.:*** Mellerettes†; Melleril†; ***Thai.:*** Calmaril†; Dazine†; Ridazine; Thiomed; Thiosia; ***Turk.:*** Mellerettes†; Melleril†; ***UK:*** Melleril†; Rideril†; ***USA:*** Mellaril†; ***Venez.:*** Meleril†.

Tiapride Hydrochloride *(BANM, rINNM)*

FLO-1347; Hidrocloruro de tiaprida; Tiapride, chlorhydrate de; Tiaprid-hidroklorid; Tiaprid-hydrochlorid; Tiapridhydroklorid; Tiapridi hydrochloridum; Tiapridihydrokloridi; Tiaprido hidrochloridas. *N*-(2-Diethylaminoethyl)-2-methoxy-5-methylsulphonylbenzamide hydrochloride.

Тиаприда Гидрохлорид

$C_{15}H_{24}N_2O_4S,HCl = 364.9.$

CAS — 51012-32-9 (tiapride); 51012-33-0 (tiapride hydrochloride).

ATC — N05AL03.

ATC Vet — QN05AL03.

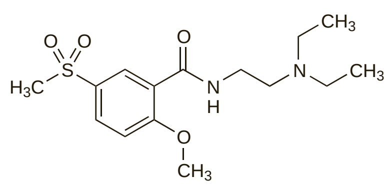

(tiapride)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tiapride Hydrochloride). A white or almost white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. A 5% solution in water has a pH of 4.0 to 6.0.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Effects on the cardiovascular system. Torsade de pointes developed after a single dose of tiapride in an elderly patient with cardiac disease, a known risk factor for such arrhythmias.[1]

1. Iglesias E, *et al.* Tiapride-induced torsade de pointes. *Am J Med* 2000; **109:** 509.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Tiapride is rapidly absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is excreted largely unchanged in the urine. The plasma half-life is reported to range from 3 to 4 hours. It is thought to be distributed into breast milk on the basis of *animal* studies.

◊ The steady-state pharmacokinetics of tiapride have been studied in 5 elderly patients with tardive dyskinesia, and in 2 patients with Huntington's chorea.[1] All patients received tiapride 100 mg three times daily by mouth for 7 days. The mean peak plasma concentration of tiapride was 1.47 micrograms/mL, achieved a mean of 1.4 hours after dosing, and the mean elimination half-life was 3.8 hours. These values did not differ significantly from those previously reported in younger healthy subjects, although renal clearance was slightly lower in these patients. About half of the dose of tiapride was excreted unchanged by the kidneys; a metabolite, probably *N*-monodesethyltiapride was detected in the urine but its identity was not confirmed.

1. Roos RAC, *et al*. Pharmacokinetics of tiapride in patients with tardive dyskinesia and Huntington's disease. *Eur J Clin Pharmacol* 1986; **31:** 191–4.

Uses and Administration

Tiapride is a substituted benzamide with general properties similar to those of sulpiride (p.1028).

It is usually given as the hydrochloride in the management of behavioural disorders and to treat dyskinesias. Doses are expressed in terms of the equivalent amount of base; tiapride hydrochloride 222.2 mg is equivalent to about 200 mg of tiapride. Oral doses of 200 to 400 mg daily are usually given, although higher daily doses have been used, particularly in the management of dyskinesias. Tiapride hydrochloride has also been given by intramuscular or intravenous injection.

Disturbed behaviour. For a discussion of the management of disturbed behaviour including limitations on the use of antipsychotics, see p.954.

References.

1. Gutzmann H, *et al.* Measuring the efficacy of psychopharmacological treatment of psychomotoric restlessness in dementia: clinical evaluation of tiapride. *Pharmacopsychiatry* 1997; **30:** 6–11.
2. Allain H, *et al.* Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. *Psychopharmacology (Berl)* 2000; **148:** 361–6.

Extrapyramidal disorders. Tiapride has been tried in the treatment of antipsychotic-induced tardive dyskinesia (p.971), but, as with all antipsychotics, improvement may only be short-term.

Tiapride has also been tried in the treatment of Tourette's syndrome (p.954).

For reference to the use of tiapride in suppressing the adverse effects of levodopa on respiration, see p.806.

CHOREA. Antipsychotics have some action against choreiform movements as well as being of use to control the behavioural disturbances of Huntington's chorea, and tiapride has been quite widely used for this purpose. For a discussion of the management of various choreas, see p.953.

References.

1. Roos RAC, *et al*. Tiapride in the treatment of Huntington's chorea. *Acta Neurol Scand* 1982; **65:** 45–50.
2. Deroover J, *et al.* Tiapride versus placebo: a double-blind comparative study in the management of Huntington's chorea. *Curr Med Res Opin* 1984; **9:** 329–38.

Substance dependence. An early review[1] concluded that the role of tiapride in acute *alcohol* withdrawal (p.1626) was likely to be limited as patients at risk of severe reactions would still require adjunctive therapy for the control of hallucinations and seizures. Following detoxification, tiapride appeared to help, to some degree, to alleviate distress, improve abstinence and drinking behaviour, and facilitate reintegration within society.[2] Interest in its use with carbamazepine continues.[3-5]

1. Peters DH, Faulds D. Tiapride: a review of its pharmacology and therapeutic potential in the management of alcohol dependence syndrome. *Drugs* 1994; **47:** 1010–32.
2. Shaw GK, *et al.* Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 1994; **165:** 515–23.
3. Franz M, *et al.* Treatment of alcohol withdrawal: tiapride and carbamazepine versus clomethiazole: a pilot study. *Eur Arch Psychiatry Clin Neurosci* 2001; **251:** 185–92.
4. Lucht M, *et al.* Alcohol withdrawal treatment in intoxicated vs non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. *Alcohol Alcohol* 2003; **38:** 168–75.
5. Soyka M, *et al.* Efficacy and safety of outpatient alcohol detoxification with a combination of tiapride/carbamazepine: additional evidence. *Pharmacopsychiatry* 2006; **39:** 30–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Etiles†; ***Austria:*** Delpral; ***Belg.:*** Tiapridal; ***Braz.:*** Tiapridal; ***Chile:*** Sereprid; ***Cz.:*** Tiapra; Tiapridal; ***Fr.:*** Clemental†; Equilium†; Tiapridal; ***Ger.:*** Tiapridex; ***Gr.:*** Tiapridal; ***Hong Kong:*** Tiapridal†; ***Hung.:*** Tiapridal; ***Israel:*** Doparid; ***Ital.:*** Italprid; Sereprile; ***Jpn:*** Gramalil; ***Neth.:*** Betaprid; Elbaprid; Tiacob; Tiajac; Tiapridal; Tiastad; Tiazet; ***Pol.:*** Tiapridal; ***Port.:*** Normagit†; Tiapridal; ***Rus.:*** Tiapridal (Тиапридал); ***Spain:*** Tiaprizal; ***Switz.:*** Tiapridal.

Timiperone *(rINN)*

DD-3480; Timiperona; Timipérone; Timiperonum. 4′-Fluoro-4-[4-(2-thioxo-1-benzimidazolinyl)piperidino]butyrophenone.

Тимиперон

$C_{22}H_{24}FN_3OS = 397.5.$

CAS — 57648-21-2.

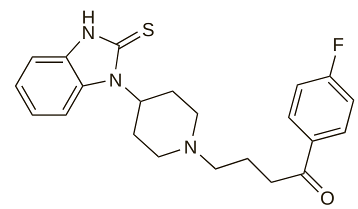

Profile

Timiperone is a butyrophenone with general properties similar to those of haloperidol (p.1000). It has been used by mouth in the treatment of schizophrenia. Timiperone has also been given by injection.

Tiotixene *(BAN, rINN)*

NSC-108165; P-4657B; Thiothixene *(USAN)*; Tiotikseeni; Tiotixen; Tiotixène; Tiotixeno; Tiotixenum. (*Z*)-*NN*-Dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]thioxanthene-2-sulphonamide.

Тиотиксен

$C_{23}H_{29}N_3O_2S_2 = 443.6.$

CAS — 5591-45-7; 3313-26-6 (tiotixene Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

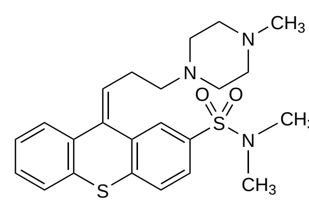

cis-form

Pharmacopoeias. In *US.*

USP 31 (Thiothixene). White to tan, practically odourless, crystals. Practically insoluble in water; soluble 1 in 110 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 120 of ether; slightly soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Tiotixene Hydrochloride *(BANM, rINNM)*

CP-12252-1; Hidrocloruro de tiotixeno; Thiothixene Hydrochloride *(USAN)*; Tiotixène, Chlorhydrate de; Tiotixeni Hydrochloridum.

Тиотиксена Гидрохлорид

$C_{23}H_{29}N_3O_2S_2,2HCl,2H_2O = 552.6.$

CAS — 58513-59-0 (anhydrous tiotixene hydrochloride); 49746-04-5 (anhydrous tiotixene hydrochloride, Z-isomer); 22189-31-7 (tiotixene hydrochloride dihydrate); 49746-09-0 (tiotixene hydrochloride dihydrate, Z-isomer).

ATC — N05AF04.

ATC Vet — QN05AF04.

Pharmacopoeias. In *US*, which permits both the dihydrate and the anhydrous form.

USP 31 (Thiothixene Hydrochloride). It is anhydrous ($C_{23}H_{29}N_3O_2S_2,2HCl = 516.5$) or contains two molecules of water of hydration. A white or practically white crystalline powder having a slight odour. Soluble 1 in 8 of water, 1 in 270 of dehydrated alcohol, and 1 in 280 of chloroform; practically insoluble in acetone, in ether, and in benzene. Store in airtight containers. Protect from light.

Stability. A combination of the stabilisers hydroxyquinoline sulfate and vanillin could protect tiotixene from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Tiotixene is less likely to cause sedation but extrapyramidal effects are more frequent.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

◊ In 15 adequately controlled schizophrenic patients receiving oral tiotixene 15 to 60 mg daily in 2, 3, or 4 divided doses, plasma concentrations were found to be in the relatively narrow range of 10 to 22.5 nanograms/mL 126 to 150 minutes after the last daily dose despite the fourfold difference in dosage.[1] Investigations in a further 5 patients indicated that peak plasma concentrations were obtained about 1 to 3 hours after a dose, indicating rapid absorption with an absorption half-time of about 30 minutes. There was an early plasma half-life of about 210 minutes and a late half-life of about 34 hours; resurgence of drug concentrations in some subjects might have been due to enterohepatic recycling.

1. Hobbs DC, *et al*. Pharmacokinetics of thiothixene in man. *Clin Pharmacol Ther* 1974; **16:** 473–8.

Metabolism. There has been a study[1] indicating that tiotixene may induce its own metabolism.

1. Bergling R, *et al*. Plasma levels and clinical effects of thioridazine and thiothixene. *J Clin Pharmacol* 1975; **15:** 178–86.

Uses and Administration

Tiotixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain. It is used in the treatment of psychoses including schizophrenia (p.955). Tiotixene is given orally as the base or hydrochloride and by intramuscular injection as the hydrochloride. Doses are expressed in terms of the base. Tiotixene 1 mg is equivalent to about 1.2 mg of tiotixene hydrochloride.

The usual initial oral dose is 2 mg three times daily (or 5 mg twice daily in more severe conditions) gradually increasing to 20 to 30 mg daily if necessary; once-daily dosage may be adequate. In severe or resistant psychoses doses of up to 60 mg daily may be given. The usual initial intramuscular dose is 4 mg two to four times daily increased if necessary to a maximum of 30 mg daily.

Tiotixene should be given in reduced dosage to elderly or debilitated patients.

Preparations

USP 31: Thiothixene Capsules; Thiothixene Hydrochloride for Injection; Thiothixene Hydrochloride Injection; Thiothixene Hydrochloride Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Navane; ***Canad.:*** Navane; ***Hong Kong:*** Navane; ***Neth.:*** Navane†; ***NZ:*** Thixit; ***USA:*** Navane.

Tofisopam *(rINN)*

EGYT-341; Tofisopaami; Tofisopamum; Tofizopam. 1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine.

Тофизопам

$C_{22}H_{26}N_2O_4$ = 382.5.
CAS — 22345-47-7.
ATC — N05BA23.
ATC Vet — QN05BA23.

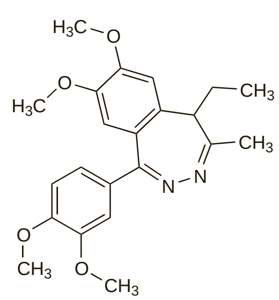

Pharmacopoeias. In *Jpn.*

Profile

Tofisopam is a 2,3-benzodiazepine related structurally to the 1,4-benzodiazepines such as diazepam (p.986) and sharing some of the same actions. It is reported, however, to be largely lacking in the sedative, anticonvulsant, and muscle relaxant properties of the conventional benzodiazepines. Tofisopam has been given orally in the short-term treatment of anxiety disorders. The *R*-(+)-isomer, dextofisopam, is under investigation in the treatment of irritable bowel syndrome.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Grandaxin; ***Hung.:*** Grandaxin; ***Jpn:*** Grandaxin; ***Rus.:*** Grandaxin (Грандаксин); ***Thai.:*** Grandaxin.

Triacetonamine Tosilate

Tempidon. 2,2,6,6-Tetramethyl-4-piperidone-toluenesulfonate.

Триацетонамина Тозилат

$C_{16}H_{25}NO_4S$ = 327.4.
CAS — 826-36-8 (triacetonamine); 29334-13-2 (triacetonamine tosilate).

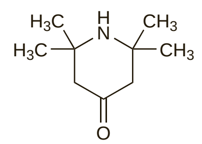

(triacetonamine)

Profile

Triacetonamine tosilate has anxiolytic actions and is used in combination preparations with analgesics.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Tempalgin (Темпалгин); Tempanginol (Темпангинол).

Triazolam *(BAN, USAN, rINN)*

Clorazolam; Triatsolaami; Triazolamum; U-33030. 8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

Триазолам

$C_{17}H_{12}Cl_2N_4$ = 343.2.
CAS — 28911-01-5.
ATC — N05CD05.
ATC Vet — QN05CD05.

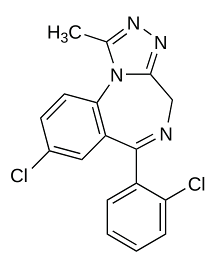

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Triazolam). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 1000 of alcohol, 1 in 25 of chloroform, and 1 in 600 of 0.1N hydrochloric acid.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects and Treatment

As for Diazepam, p.987.

Effects on the liver. A 44-year-old man developed severe pruritus with jaundice which subsequently proved fatal. Liver histology showed intense cholestasis. Triazolam was considered to be the most likely cause.[1]

1. Cobden I, *et al*. Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981; **57:** 730–1.

Effects on mental function. The effects of triazolam on mental function have been controversial since van der Kroef first described in 1979 a range of symptoms including anxiety, amnesia, depersonalisation and derealisation, depression, paranoia, and severe suicidal tendencies that he had seen in 25 patients and attributed to triazolam.[1] This led to suspension of triazolam in the Netherlands (re-approved in 1990) and removal of the 1-mg tablet from other markets. Continued reporting of similar symptoms of cognitive impairment with triazolam resulted in withdrawal of the 500-microgram dosage form in several countries in 1987 and 1988 and in a gradual reduction of recommended dosage from 1 mg at night down to 125 to 250 micrograms at night. Triazolam was withdrawn from the UK[2] and some other markets in 1991. Opinion still remains divided over the adverse effects of triazolam, the main issues being its propensity to cause adverse effects relative to other benzodiazepines and whether its risk-benefit ratio is acceptable to justify its continued use.[3,4]

Others[5] have reviewed spontaneous adverse effects reported to the FDA in the USA for triazolam, temazepam, and flurazepam. Daytime sedation was noted with all three, but triazolam caused more agitation, confusion, hallucinations, and amnesia. Such effects occurred frequently with the 250-microgram dose as well as with the 500-microgram dose. Similar results were obtained after analysis of reports for triazolam and temazepam in the first 7 years of marketing, although the possibility that selection factors were producing higher reporting rates for triazolam could not be entirely excluded.[6] A study[7] gave triazolam 500 micrograms, lormetazepam 2 mg, or placebo, to groups of 40 patients for 25 nights and observed the greatest frequency of daytime anxiety, panic, derealisation, and paranoia with triazolam. Another[8] found a greater total number of reports of memory impairment or amnesia after nightly doses of triazolam 500 micrograms compared with temazepam 30 mg. Triazolam also impaired delayed, but not immediate, memory recall. Similar cases of memory impairment occurring with triazolam at doses of 125 and 250 micrograms have reportedly been submitted to the UK CSM.[2] The emergence of daytime symptoms after more than a few days' treatment with triazolam could be attributed to rebound or withdrawal phenomena occurring as a result of rapid elimination of the drug.

As regards the risk-benefit ratio of triazolam some workers have questioned the hypnotic efficacy of the drug at a dose of 250 micrograms and consider that reduction of the dose has decreased efficacy more than adverse effects.[3]

In defence of triazolam, the FDA and the manufacturers (*Upjohn*) have considered epidemiological studies which, unlike the FDA spontaneous reporting scheme, have been unable to demonstrate a substantial difference in its adverse effects compared with other benzodiazepines except, perhaps, in the incidence of amnesia.[9] Retrospective studies[10,11] claiming similar findings have been the subject of criticism.[12-14] Other workers have cited studies indicating benefit of triazolam 250 micrograms for the treatment of insomnia.[15] A review by the US Institute of Medicine found that triazolam was safe when given in a dose of 250 micrograms daily for 7 to 10 days but called for studies of lower doses and of long-term use.[16]

1. Van der Kroef C. Reactions to triazolam. *Lancet* 1979; **ii:** 526.
2. Anonymous. The sudden withdrawal of triazolam—reasons and consequences. *Drug Ther Bull* 1991; **29:** 89–90.
3. O'Donovan MC, McGuffin P. Short acting benzodiazepines. *BMJ* 1993; **306:** 945–6.
4. Ghaeli P, *et al*. Triazolam treatment controversy. *Ann Pharmacother* 1994; **28:** 1038–40.
5. Bixler EO, *et al*. Adverse reactions to benzodiazepine hypnotics: spontaneous reporting system. *Pharmacology* 1987; **35:** 286–300.
6. Wysowski DK, Barash D. Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's spontaneous reporting system. *Arch Intern Med* 1991; **151:** 2003–8.
7. Adam K, Oswald I. Can a rapidly-eliminated hypnotic cause daytime anxiety? *Pharmacopsychiatry* 1989; **22:** 115–19.
8. Bixler EO, *et al*. Next-day memory impairment with triazolam use. *Lancet* 1991; **337:** 827–31.
9. Drucker RF, MacLeod N. Benzodiazepines. *Pharm J* 1989; **243:** 508.
10. Hindmarch I, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 55.
11. Rothschild AJ, *et al*. Triazolam and disinhibition. *Lancet* 1993; **341:** 186.
12. Hawley CJ, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
13. Vela-Bueno A. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
14. Kales A, *et al*. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567–8.
15. Gillin JC, Byerley WF. Diagnosis and management of insomnia. *N Engl J Med* 1990; **323:** 487.
16. Ault A. FDA advisers find no major Halcion dangers. *Lancet* 1997; **350:** 1760.

Precautions

As for Diazepam, p.988.

Hepatic impairment. Cirrhosis decreased the apparent oral clearance of triazolam to an extent depending on the severity of the liver disease.[1] An initial dose of 125 micrograms was suggested for patients with severe liver dysfunction. It was suggested that the relative lack of effect that mild to moderate cirrhosis had on the metabolism of oral triazolam might be due to some first-pass metabolism occurring in the intestinal wall.[2]

1. Kroboth PD, *et al*. Nighttime dosing of triazolam in patients with liver disease and normal subjects: kinetics and daytime effects. *J Clin Pharmacol* 1987; **27:** 555–60.
2. Robin DW, *et al*. Triazolam in cirrhosis: pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1993; **54:** 630–7.

Renal impairment. Peak plasma-triazolam concentrations were lower in 11 dialysis patients compared with 11 controls.[1] It was postulated that a relatively high basal gastric acid secretion in dialysis patients could result in hydrolysis and opening of the ring structure of triazolam effectively reducing its systemic availability. Giving an antacid could reverse this effect. Renal failure had no other effect on the pharmacokinetics of triazolam which could probably be given in usual doses.

1. Kroboth PD, *et al.* Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. *Br J Clin Pharmacol* 1985; **19:** 839–42.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Triazolam is rapidly and nearly completely absorbed from the gastrointestinal tract, peak plasma concentrations being achieved within 2 hours of an oral dose. Triazolam has a plasma elimination half-life ranging from 1.5 to 5.5 hours. It is reported to be about 89% bound to plasma proteins. Hydroxylation of triazolam in the liver is mediated by the cytochrome P450 isoenzyme CYP3A4. Triazolam is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged.

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Greenblatt DJ, *et al.* Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther* 2004; **76:** 467–79.

Uses and Administration

Triazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957) in oral doses of 125 to 250 micrograms at night for no more than 2 weeks; doses of up to 500 micrograms at night have been used for resistant cases but these may be associated with an increased risk of severe adverse effects (see Effects on Mental Function, above). Initial doses of 125 micrograms at night have been suggested for elderly or debilitated subjects, increased up to a maximum of 250 micrograms only if necessary.

Administration in hepatic or renal impairment. See under Precautions, above.

Preparations

USP 31: Triazolam Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Halcion; ***Austria:*** Halcion; ***Belg.:*** Halcion; ***Braz.:*** Halcion†; ***Canad.:*** Apo-Triazo; Halcion; ***Chile:*** Balidon; Somese; ***Cz.:*** Halcion†; ***Denm.:*** Halcion; Rilamir; ***Fin.:*** Halcion; ***Fr.:*** Halcion†; ***Ger.:*** Halcion; ***Gr.:*** Halcion; ***Hong Kong:*** Halcion; ***Irl.:*** Halcion; Trilam; ***Israel:*** Halcion; ***Ital.:*** Halcion; Songar; ***Malaysia:*** Somese; ***Mex.:*** Halcion; ***Neth.:*** Halcion†; ***NZ:*** Halcion; Hypam; ***Port.:*** Halcion; ***S.Afr.:*** Halcion; ***Spain:*** Halcion; ***Swed.:*** Halcion; ***Switz.:*** Halcion; ***Thai.:*** Halcion; Trycam†; ***USA:*** Halcion; ***Venez.:*** Somese.

Triclofos Sodium *(BANM, USAN, rINNM)*

Natrii Triclofosum; Sch-10159; Sodium Triclofos; Triclofós sódico; Triclofos Sodique. Sodium 2,2,2-trichloroethyl hydrogen orthophosphate.

Натрий Триклофос

$C_2H_3Cl_3NaO_4P$ = 251.4.

CAS — 306-52-5 (triclofos); 7246-20-0 (triclofos sodium).

ATC — N05CM07.

ATC Vet — QN05CM07.

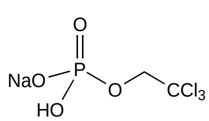

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2008 (Triclofos Sodium). A white or almost white, odourless or almost odourless, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 3.0 to 4.5.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Cloral Hydrate, p.979 but causes fewer gastrointestinal disturbances. Also, triclofos sodium is not corrosive to skin and mucous membranes.

Interactions

As for Cloral Hydrate, p.979.

Pharmacokinetics

Triclofos sodium is rapidly hydrolysed to trichloroethanol, peak serum concentrations being achieved within about one hour after oral dosage. For the pharmacokinetics of trichloroethanol, see Cloral Hydrate, p.979.

Uses and Administration

Triclofos sodium has hypnotic and sedative actions similar to those of cloral hydrate (p.979) but it is more palatable and causes less gastric irritation. It is used similarly in the short-term management of insomnia (p.957) and for sedation of children before painless procedures; however, its use as a hypnotic, particularly in children, is now limited.

The usual adult dose as a hypnotic is 1 to 2 g orally at night. A suggested hypnotic dose for children 1 month to 1 year of age is 25 to 30 mg/kg; children aged 1 to 5 years may be given single doses of 250 to 500 mg, and children aged 6 to 12 years may be given single doses of 0.5 to 1 g. Although not licensed in the UK for sedation of children before painless procedures, the *BNFC* suggests that those aged 1 month to 18 years may be given 30 to 50 mg/kg (maximum of 2 g) 45 to 60 minutes before the procedure; up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring.

Preparations

BP 2008: Triclofos Oral Solution.

Proprietary Preparations (details are given in Part 3)
India: Tricloryl; ***Irl.:*** Tricloryl†; ***Israel:*** Triclonam.

Trifluoperazine Hydrochloride

(BANM, rINNM)

Hidrocloruro de trifluoperazina; Trifluoperazin Hidroklorür; Trifluoperazin hydrochlorid; Trifluopérazine, chlorhydrate de; Trifluoperazinhidroklorid; Trifluoperazinhydroklorid; Trifluoperazini hydrochloridum; Trifluoperazino hidrochloridas; Trifluoperazyny chlorowodorek; Trifluoriperatsiinihydrokloridi; Triphthazinum. 10-[3-(4-Methylpiperazin-1-yl)propyl]-2-trifluoromethylphenothiazine dihydrochloride.

Трифлуоперазина Гидрохлорид

$C_{21}H_{24}F_3N_3S,2HCl$ = 480.4.

CAS — 117-89-5 (trifluoperazine); 440-17-5 (trifluoperazine hydrochloride).

ATC — N05AB06.

ATC Vet — QN05AB06.

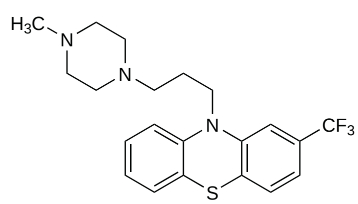

(trifluoperazine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Trifluoperazine Hydrochloride). A white to pale yellow, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in ether. A 10% solution in water has a pH of 1.6 to 2.5. Protect from light.

USP 31 (Trifluoperazine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. Soluble 1 in 3.5 of water, 1 in 11 of alcohol, and 1 in 100 of chloroform; insoluble in ether and in benzene. pH of a 1 in 20 solution is between 1.7 and 2.6. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Trifluoperazine is less likely to cause sedation, hypotension, hypothermia, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects particularly when the daily dose exceeds 6 mg.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trifluoperazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Trifluoperazine hydrochloride is readily absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations are attained 1.5 to 6 hours after ingestion and bioavailability is subject to interindividual variation. It is highly bound to plasma proteins. The elimination of trifluoperazine is multiphasic and the terminal half-life is about 22 hours. The major metabolite is the possibly active *N*-oxide. Other metabolites include the sulfoxide and the 7-hydroxy derivative. Trifluoperazine is distributed into breast milk.

Uses and Administration

Trifluoperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain.

Trifluoperazine is used in the treatment of a variety of psychiatric disorders including schizophrenia (p.955), severe anxiety (p.952), and disturbed behaviour (p.954). It is also used for the control of nausea and vomiting (p.1700).

Trifluoperazine is given as the hydrochloride but doses are expressed in terms of the base. Trifluoperazine 1 mg is equivalent to about 1.2 mg of trifluoperazine hydrochloride. A modified-release preparation is also available in some countries. Trifluoperazine should be given in reduced dosage to elderly or debilitated patients.

The usual initial *oral* dose for the treatment of schizophrenia and other **psychoses** is 2 to 5 mg twice daily, gradually increased to a usual range of 15 to 20 mg daily; in severe or resistant psychoses daily doses of 40 mg or more have been given. For the control of acute psychotic symptoms it may be given by deep *intramuscular* injection in a dose of 1 to 2 mg, repeated if necessary every 4 to 6 hours; more than 6 mg daily is rarely required. The initial oral dose for use in *children* is up to 5 mg daily in divided doses adjusted according to age, body-weight, and response, or 1 mg given once or twice daily by intramuscular injection.

For the control of **nausea and vomiting** the usual adult *oral* dose is 1 or 2 mg twice daily; up to 6 mg daily may be given in divided doses. *Children* aged 3 to 5 years may be given up to 1 mg daily in divided doses; this may be increased to a maximum of 4 mg daily in children aged 6 to 12 years.

When used as an adjunct in the short-term management of **severe anxiety disorders** doses are similar to those used for the control of nausea and vomiting.

Schizophrenia. A systematic review[1] of the use of trifluoperazine for schizophrenia (p.955) concluded that it appeared to be of similar efficacy to other commonly used classical antipsychotics with a similar profile of adverse effects. However, there did not appear to be good evidence for claims that it was effective for schizophrenia at low doses.

1. Marques LO, *et al.* Trifluoperazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 17/05/05).

Preparations

BP 2008: Trifluoperazine Tablets;
USP 31: Trifluoperazine Hydrochloride Injection; Trifluoperazine Hydrochloride Syrup; Trifluoperazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Stelazine; ***Austral.:*** Stelazine; ***Braz.:*** Stelazine; ***Gr.:*** Stelazine; Stelium; ***India:*** Trinicalm; ***Indon.:*** Stelazine; ***Irl.:*** Stelazine; ***Ital.:*** Modalina; ***Mex.:*** Flupazine; Stelazine; ***NZ:*** Stelazine; ***S.Afr.:*** Stelazine; Terflurazine; ***Spain:*** Eskazine; ***Thai.:*** Psyrazine; Triflumed; Triozine; Triplex; ***Turk.:*** Stilizan; ***UK:*** Stelazine; ***Venez.:*** Leptazine; Taclorpil†.

Multi-ingredient: ***Arg.:*** Cuait D; Cuait N; Stelapar; ***Braz.:*** Stelapar†; ***Canad.:*** Stelabid†; ***India:*** Sycot; Trinicalm Forte; Trinicalm Plus; ***Ital.:*** Parmodalin; ***Mex.:*** Stelabid.

Trifluperidol (BAN, USAN, rINN)

McN-JR-2498; R-2498; Triflupéridol; Trifluperidoli; Trifluperidolum. 4′-Fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone.

Трифлуперидол

$C_{22}H_{23}F_4NO_2$ = 409.4.
CAS — 749-13-3.
ATC — N05AD02.
ATC Vet — QN05AD02.

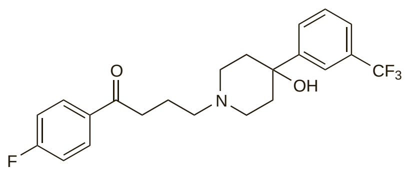

Trifluperidol Hydrochloride (BANM, rINNM)

Hidrocloruro de trifluperidol; Triflupéridol, Chlorhydrate de; Trifluperidoli Hydrochloridum.

Трифлуперидола Гидрохлорид

$C_{22}H_{23}F_4NO_2$,HCl = 445.9.
CAS — 2062-77-3.
ATC — N05AD02.
ATC Vet — QN05AD02.

Profile

Trifluperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000), and has been used as the hydrochloride in the treatment of psychoses including schizophrenia.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Triperidol.

Triflupromazine (BAN, rINN)

Fluopromazine; Triflupromazina; Triflupromazinum. *NN*-Dimethyl-3-(2-trifluoromethylphenothiazin-10-yl)propylamine.

Трифлупромазин

$C_{18}H_{19}F_3N_2S$ = 352.4.
CAS — 146-54-3.
ATC — N05AA05.
ATC Vet — QN05AA05.

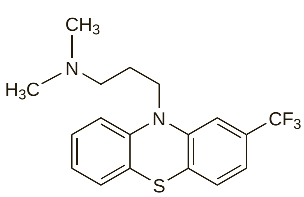

Pharmacopoeias. In *US.*

USP 31 (Triflupromazine). A light amber viscous oily liquid that crystallises into large irregular crystals during prolonged storage. Practically insoluble in water. Store in airtight containers. Protect from light.

Triflupromazine Hydrochloride (BANM, rINNM)

Fluopromazine Hydrochloride; Hidrocloruro de triflupromazina; Triflupromazine, Chlorhydrate de; Triflupromazini Hydrochloridum.

Трифлупромазина Гидрохлорид

$C_{18}H_{19}F_3N_2S$,HCl = 388.9.
CAS — 1098-60-8.
ATC — N05AA05.
ATC Vet — QN05AA05.

Pharmacopoeias. In *US.*

USP 31 (Triflupromazine Hydrochloride). A white to pale tan crystalline powder having a slight characteristic odour. Soluble 1 in less than 1 of water and of alcohol and 1 in 1.7 of chloroform; soluble in acetone; insoluble in ether. Store in glass containers. Protect from light.

Profile

Triflupromazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is used mainly in the management of psychoses (p.954) and the control of nausea and vomiting (p.1700). Triflupromazine hydrochloride is usually given by injection but in some countries oral preparations are available.

In the management of psychosis, the usual dose is 60 to 150 mg daily by intramuscular injection. For the control of nausea and vomiting 5 to 15 mg is given intramuscularly and repeated after 4 hours if necessary up to a maximum of 60 mg daily; a dose of 1 mg to a maximum total daily dose of 3 mg may be given intravenously.

A suggested intramuscular dose for children over 2⁄ years of age is 200 to 250 micrograms/kg daily up to a maximum of 10 mg daily.

Reduced doses should be used in elderly or debilitated patients.

Preparations

USP 31: Triflupromazine Hydrochloride Injection; Triflupromazine Hydrochloride Tablets; Triflupromazine Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austria: Psyquil; ***Ger.:*** Psyquil†; ***India:*** Siquil.

Trimetozine (USAN, rINN)

Abbott-22370; NSC-62939; PS-2383; Trimetozina; Trimétozine; Trimetozinum. 4-(3,4,5-Trimethoxybenzoyl)morpholine.

Триметоцин

$C_{14}H_{19}NO_5$ = 281.3.
CAS — 635-41-6.

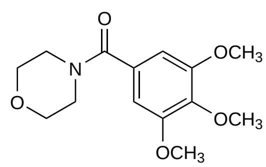

Profile

Trimetozine has been used for its sedative properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Trioxazin.

Valnoctamide (USAN, rINN)

McN-X-181; NSC-32363; Valnoctamida; Valnoctamidum. 2-Ethyl-3-methylvaleramide.

Вальноктамид

$C_8H_{17}NO$ = 143.2.
CAS — 4171-13-5.
ATC — N05CM13.
ATC Vet — QN05CM13.

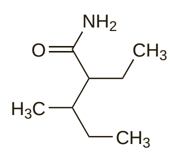

Profile

Valnoctamide, an isomer of valpromide (p.508), has been given orally in the treatment of anxiety disorders.

◊ References.

1. Bialer M, *et al.* Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 289–91.
2. Barel S, *et al.* Stereoselective pharmacokinetic analysis of valnoctamide in healthy subjects and in patients with epilepsy. *Clin Pharmacol Ther* 1997; **61:** 442–9.

Interactions. For a discussion of the potential interaction between carbamazepine and valnoctamide, see Antiepileptics, p.474.

Veralipride (rINN)

Veraliprida; Véralipride; Veralipridum. *N*-[(1-Allyl-2-pyrrolidinyl)methyl]-5-sulphamoyl-2-veratramide.

Вералиприд

$C_{17}H_{25}N_3O_5S$ = 383.5.
CAS — 66644-81-3.
ATC — N05AL06.
ATC Vet — QN05AL06.

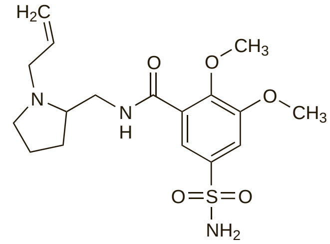

Profile

Veralipride is a substituted benzamide antipsychotic. It has been used in the treatment of cardiovascular and psychological symptoms associated with the menopause; the usual oral dose is 100 mg daily for 20 days repeated at intervals of 7 to 10 days. Preparations of veralipride have now been withdrawn from the market in some countries because of the opinion that there is an unacceptable balance of risks and benefits; adverse effects such as anxiety, depression, and tardive dyskinesia have been associated with veralipride, both during and after treatment.

Menopausal disorders. HRT with oestrogens is the mainstay of treatment for acute symptoms associated with the menopause (see p.2077) but when it is considered to be unsuitable a variety of other drugs including veralipride have been tried.[1] It has also been tried with raloxifene in postmenopausal women.[2] However, treatment with veralipride has been associated with extrapyramidal adverse effects.[3,4]

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40:** 220–30.
2. Morgante G, *et al.* Veralipride administered in combination with raloxifene decreases hot flushes and improves bone density in early postmenopausal women. *Gynecol Endocrinol* 2004; **18:** 194–8.
3. Masmoudi K, *et al.* Troubles extrapyramidaux sous véralipride (Agréal), traitement symptomatique des bouffées de chaleur: à propos de 17 cas. *Rev Med Interne* 2005; **26:** 453–7.
4. Raja M, Azzoni A. Tardive dyskinesia after long-term veralipride treatment. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 252–3.

Porphyria. Veralipride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Veralipral; ***Belg.:*** Agreal†; ***Braz.:*** Agreal; ***Chile:*** Agreal; ***Fr.:*** Agreal†; ***Ital.:*** Agradil; Veralipril†; ***Mex.:*** Aclimafel; Veraligral; ***Port.:*** Agreal†; ***Spain:*** Agreal†.

Multi-ingredient: ***Arg.:*** Veralipral T.

Zaleplon (BAN, USAN, rINN)

CL-284846; L-846; LJC-10846; Tsaleploni; ZAL-846; Zaleplón; Zaléplone; Zaleplonum. 3′-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide.

Залеплон

$C_{17}H_{15}N_5O$ = 305.3.
CAS — 151319-34-5.
ATC — N05CF03.
ATC Vet — QN05CF03.

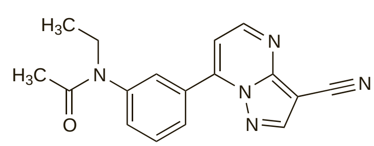

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. Zaleplon should be used with caution and in reduced doses in patients with hepatic impairment, and should be avoided where this is severe.

Treatment of overdose is largely supportive. Activated charcoal may be given orally to patients who present within one hour of ingestion of more than 50 mg zaleplon by adults, or 1 mg/kg by children, provided that the airway can be protected. Flumazenil may be considered in cases of severe CNS depression.

◊ References.

1. Israel AG, Kramer JA. Safety of zaleplon in the treatment of insomnia. *Ann Pharmacother* 2002; **36:** 852–9.

Abuse. In a controlled study in healthy patients with a history of drug abuse, zaleplon was shown to have a comparable abuse potential to that of the benzodiazepine, triazolam.[1]

1. Rush CR, *et al.* Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. *Psychopharmacology (Berl)* 1999; **145:** 39–51.

Breast feeding. Licensed product information for zaleplon advises that it should not be given to breast-feeding mothers since, although only a small amount is excreted into breast milk, the effect on the nursing infant is not known.

Zaleplon was detected in the breast milk of 5 women who had been given a 10-mg dose.[1] The milk-to-plasma concentration ratio for zaleplon was about 0.5.

1. Darwish M, *et al.* Rapid disappearance of zaleplon from breast milk after oral administration to lactating women. *J Clin Pharmacol* 1999; **39:** 670–4.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zaleplon, see under Zolpidem, below.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zaleplon, see under Zolpidem, below.

Interactions

As for Diazepam, p.989. Zaleplon is primarily metabolised by aldehyde oxidase and use with inhibitors of this enzyme, such as cimetidine, may result in increased plasma concentrations of zaleplon (see Uses and Administration, below). Zaleplon is also partly metabolised by the cytochrome P450 isoenzyme CYP3A4 and, consequently, caution is advised when zaleplon is given with drugs that are substrates for, or potent inhibitors of, this isoenzyme. Cimetidine is also an inhibitor of CYP3A4 and thus inhibits both the primary and secondary metabolic pathways of zaleplon.

Use with rifampicin or other potent enzyme-inducing drugs may accelerate the metabolism of zaleplon and reduce its plasma concentrations.

Pharmacokinetics

Zaleplon is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in about one hour after oral dosage. A heavy meal or one with a high-fat content delays absorption and reduces peak concentrations. Bioavailability is about 30% due to significant first-pass hepatic metabolism. Zaleplon is metabolised primarily by aldehyde oxidase to form 5-oxo-zaleplon and, to a lesser extent, by the cytochrome P450 isoenzyme CYP3A4 to desethylzaleplon, which is further metabolised by aldehyde oxidase to 5-oxo-desethylzaleplon. The plasma-elimination half-life of zaleplon is about 1 hour. About 70% of a dose is excreted in the urine as these inactive metabolites or their glucuronides; less than 1% is excreted unchanged. About 17% of a dose is eliminated in the faeces, mainly as 5-oxo-zaleplon. Zaleplon is distributed into breast milk.

◊ References.

1. Greenblatt DJ, *et al.* Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin Pharmacol Ther* 1998; **64:** 553–61.
2. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
3. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Uses and Administration

Zaleplon is a pyrazolopyrimidine with similar sedative properties to the benzodiazepines (see Diazepam, p.992). It is used as a hypnotic in the short-term management of insomnia. Zaleplon has a rapid onset and short duration of action. The usual oral dose is 10 mg at bedtime although US product information notes that occasional patients may require 20 mg. Elderly or debilitated patients or those also taking cimetidine should be given 5 mg. For dosages in patients with hepatic impairment, see below.

Administration in hepatic impairment. The oral dose of zaleplon should be reduced to 5 mg at bedtime in patients with mild to moderate hepatic impairment; it should not be given to those with severe impairment.

Insomnia. Zaleplon is a pyrazolopyrimidine hypnotic. Although not related structurally to the benzodiazepines it appears to act by binding selectively to the benzodiazepine type I receptor (BZ1- or ω_1-receptors) on the GABA subtype A complex. Zaleplon reduces sleep latency but has little effect on sleep duration; it is rapidly absorbed and eliminated and consequently residual effects the next day are said to be minimal. These characteristics make it best suited for the treatment of patients with insomnia (p.957) who have difficulty falling asleep; zaleplon can either be taken at bedtime or during the night if a patient has trouble falling back to sleep, provided they are assured of at least 4 hours uninterrupted sleep.

References.

1. Anonymous. Zaleplon for insomnia. *Med Lett Drugs Ther* 1999; **41:** 93–4.
2. Danjou P, *et al.* A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. *Br J Clin Pharmacol* 1999; **48:** 367–74.
3. Elie R, *et al.* Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry* 1999; **60:** 536–44.
4. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. *Drugs* 2000; **60:** 413–45.
5. George CFP. Pyrazolopyrimidines. *Lancet* 2001; **358:** 1623–6.
6. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.
7. Barbera J, Shaprio [sic] C. Benefit-risk assessment of zaleplon in the treatment of insomnia. *Drug Safety* 2005; **28:** 301–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Hegon; Hipnodem; ***Austria:*** Sonata; ***Belg.:*** Sonata; ***Braz.:*** Sonata; ***Canad.:*** Starnoc; ***Chile:*** Noctiplon†; Plenidon; Rhem†; Sedartryl; Somnipax†; ***Cz.:*** Sonata; Zerene; ***Denm.:*** Sonata; ***Fin.:*** Sonata; ***Ger.:*** Sonata; ***Gr.:*** Sonata; ***Hung.:*** Sonata; ***India:*** Zalep; Zaplon†; Zaso; ***Irl.:*** Sonata; ***Ital.:*** Sonata; Zerene; ***Mex.:*** Sonata†; ***Neth.:*** Sonata; Zerene; ***Pol.:*** Selofen; ***Port.:*** Sonata; Zerene; ***Rus.:*** Andante (Анданте); ***Spain:*** Sonata; ***Swed.:*** Sonata; ***Switz.:*** Sonata; ***UK:*** Sonata†; ***USA:*** Sonata.

Ziprasidone *(BAN, rINN)*

Ziprasidona; Ziprasidonum. 5-{2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-2-indolinone.
Зипрасидон
$C_{21}H_{21}ClN_4OS = 412.9.$
CAS — 146939-27-7 (ziprasidone).
ATC — N05AE04.
ATC Vet — QN05AE04.

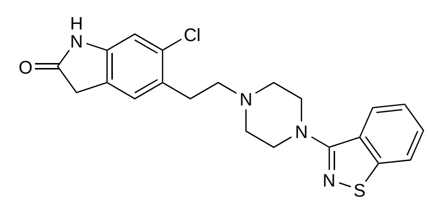

Ziprasidone Hydrochloride *(BANM, USAN, rINNM)*

CP-88059; CP-88059-1; Hidrocloruro de ziprasidona; Ziprasidone, chlorhydrate de; Ziprasidoni hydrochloridum.
Зипрасидона Гидрохлорид
$C_{21}H_{21}ClN_4OS,HCl,H_2O = 467.4.$
CAS — 138982-67-9.
ATC — N05AE04.
ATC Vet — QN05AE04.

Ziprasidone Mesilate *(BANM, rINNM)*

CP-88059/27; Mesilato de ziprasidona; Ziprasidone, Mésilate de; Ziprasidone Mesylate *(USAN)*; Ziprasidoni Mesilas.
Зипрасидона Мезилат
$C_{21}H_{21}ClN_4OS,CH_4O_3S,3H_2O = 563.1.$
CAS — 199191-69-0.
ATC — N05AE04.
ATC Vet — QN05AE04.

Adverse Effects, Treatment, and Precautions

Although ziprasidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Frequent adverse effects with ziprasidone include somnolence, rash or urticaria, gastrointestinal disturbances, dizziness, flu-like symptoms, hypertension, headache, agitation, confusion, and dyspnoea. Orthostatic hypotension may be a problem, particularly when starting treatment. Ziprasidone may increase prolactin levels and weight gain has also been noted. Sexual dysfunction has been reported infrequently. Extrapyramidal symptoms may occur, and tardive dyskinesia may develop with prolonged use. There have also been infrequent or rare cases of cholestatic jaundice, hepatitis, seizures, blood dyscrasias including leucopenia and thrombocytopenia, and hyperlipidaemia. Hyperglycaemia occurs uncommonly with ziprasidone. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of, developing diabetes.

Ziprasidone has been associated with dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use is contra-indicated in patients with a history of QT prolongation or cardiac arrhythmias, with recent acute myocardial infarction, or with decompensated heart failure. Certain medications may also increase the risk (see Interactions, below). Baseline serum potassium and magnesium screening should be performed in patients who are at risk of significant electrolyte disturbances and hypokalaemia or hypomagnesaemia should be corrected before starting ziprasidone therapy. Serum electrolytes should be monitored in patients who start diuretic therapy during ziprasidone treatment. Patients receiving ziprasidone who have symptoms that might indicate torsade de pointes (e.g. dizziness, palpitations, or syncope) should be further evaluated.

Ziprasidone should be used with caution in patients with a history of seizures or in conditions that lower the seizure threshold, cardiovascular or cerebrovascular disease, or conditions which predispose to hypotension. Since intramuscular injections are formulated with cyclodextrin, which is cleared by renal filtration, the manufacturer recommends caution in patients with renal impairment.

Ziprasidone may affect the performance of skilled tasks including driving.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics, including ziprasidone, in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class. See under Risperidone, p.1024.

1. Food and Drug Administration. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11/04/05). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 30/05/05)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Extrapyramidal disorders. There have been reports[1-3] of tardive dyskinesia associated with ziprasidone therapy; onset ranged from 2 to 34 months after starting the drug. Acute dystonia has also been reported[4,5] with ziprasidone. However, the incidence of extrapyramidal adverse effects (p.971) is generally lower with atypical than classical antipsychotics.

1. Rosenquist KJ, *et al.* Tardive dyskinesia and ziprasidone. *Am J Psychiatry* 2002; **159:** 1436.
2. Keck ME, *et al.* Ziprasidone-related tardive dyskinesia. *Am J Psychiatry* 2004; **161:** 175–6.
3. Ananth J, *et al.* Tardive dyskinesia in 2 patients treated with ziprasidone. *J Psychiatry Neurosci* 2004; **29:** 467–9.
4. Ziegenbein M, *et al.* Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatr Clin Neurosci* 2003; **15:** 458–9.
5. Mason MN, *et al.* Ziprasidone-induced acute dystonia. *Am J Psychiatry* 2005; **162:** 625–6.

Mania. Although it is used in the treatment of bipolar disorder, ziprasidone has been associated with reports of mania in bipolar patients, see under Uses and Administration, below.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS— p.972) has been associated with ziprasidone;[1] however, the patient had also received lithium, a drug that has been associated with NMS.

1. Borovicka MC, *et al.* Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* 2006; **40:** 139–42.

Pregnancy. For comments on the use of some atypical antipsychotics, including ziprasidone, during pregnancy, see under Precautions of Clozapine, p.983.

US licensed drug information states that ziprasidone demonstrated possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Ziprasidone should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

Use of ziprasidone with other drugs known to prolong the QT interval is contra-indicated because of the increased risk of arrhythmias. Monitoring of serum electrolytes is recommended if ziprasidone is given with diuretics.

The metabolism of ziprasidone is mediated by the cytochrome P450 isoenzyme CYP3A4. Therefore, there is the potential for interactions between ziprasidone and other drugs that induce, inhibit, or act as a substrate for this enzyme.

Ziprasidone may enhance the effects of other CNS depressants and certain antihypertensives; it may antagonise the effects of levodopa and dopaminergics.

Pharmacokinetics

Ziprasidone is well absorbed from the gastrointestinal tract with peak plasma concentrations being reached 6 to 8 hours after oral doses. The presence of food may double the absorption. Following intramuscular injection, peak plasma concentrations are reached within 1 hour. Plasma protein binding is about 99%. Ziprasidone is extensively metabolised by aldehyde oxidase (about 66% of a dose) and by the cytochrome P450 isoenzyme CYP3A4. The mean terminal elimination half-life has been reported to be about 7 hours after oral dosage and about 2 to 5 hours after intramuscular dosage. Ziprasidone is excreted mainly as metabolites in the faeces (about 66%) and urine (about 20%); less than 5% of a dose appears as unchanged drug.

◊ References.

1. Various. The pharmacokinetics of ziprasidone. *Br J Clin Pharmacol* 2000; **49** (suppl 1): 1S–76S.
2. Miceli JJ, *et al.* Pharmacokinetics, safety, and tolerability of intramuscular ziprasidone in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 620–30.
3. Preskorn SH. Pharmacokinetics and therapeutics of acute intramuscular ziprasidone. *Clin Pharmacokinet* 2005; **44:** 1117–33.

Uses and Administration

Ziprasidone is an atypical antipsychotic reported to have affinity for adrenergic (α_1), histamine (H_1), and serotonin (5-HT_2) receptors as well as dopamine (D_2) receptors. It is used for the treatment of schizophrenia and in acute manic or mixed episodes associated with bipolar disorder. Ziprasidone is given by mouth usually as the hydrochloride; it is also given parenterally as the mesilate. Doses are expressed in terms of the base; ziprasidone hydrochloride 11.3 mg or ziprasidone mesilate 13.6 mg are each equivalent to about 10 mg of ziprasidone.

For the treatment of **schizophrenia**, ziprasidone hydrochloride is given in an initial oral dose of 20 mg twice daily with food. Doses may be increased if necessary at intervals of not less than 2 days up to 80 mg twice daily. For maintenance, doses as low as 20 mg twice daily may be effective.

For acute agitation in patients with schizophrenia, ziprasidone may be given as the mesilate by intramuscular injection. The recommended dose is 10 to 20 mg as required, up to a maximum of 40 mg daily for 3 consecutive days. Doses of 10 mg may be given every 2 hours and doses of 20 mg may be given every 4 hours. Patients should be switched to oral therapy as soon as possible.

For the treatment of **mania**, ziprasidone hydrochloride is given in an initial oral dose of 40 mg twice daily with food. The dose should be increased to 60 or 80 mg twice daily on the second day of treatment and subsequently adjusted according to tolerance.

Bipolar disorder. Ziprasidone is effective in the management of acute mania in patients with bipolar disorder[1] but it may also be associated with the induction of mania or hypomania in such patients.[2]

1. Keck PE, *et al.* Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003; **160:** 741–8.
2. Baldassano CF, *et al.* Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disord* 2003; **5:** 72–5.

Schizophrenia. A systematic review[1] of the effectiveness and safety of ziprasidone in patients with schizophrenia (p.955) found that from the limited data available ziprasidone was as effective as haloperidol; it was less likely to provoke extrapyramidal disorders but appeared to cause more nausea and vomiting, and pain at the site of injection. Comparisons with other atypical antipsychotics were lacking. A comparative study[2] of intramuscular ziprasidone with intramuscular haloperidol also found a favourable outcome in patients with acute psychoses.

1. Bagnall A, *et al.* Ziprasidone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 20/10/05).
2. Brook S, *et al.* Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; **61:** 933–41.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (p.954), haloperidol or pimozide are commonly used but atypical antipsychotics such as ziprasidone are increasingly being tried.[1]

1. Sallee FR, *et al.* Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 292–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Zeldox; ***Austral.:*** Zeldox; ***Austria:*** Zeldox; ***Braz.:*** Geodon; ***Chile:*** Zeldox; ***Cz.:*** Zeldox; ***Denm.:*** Zeldox; ***Fin.:*** Zeldox; ***Ger.:*** Zeldox; ***Gr.:*** Geodon; ***Hong Kong:*** Zeldox; ***Hung.:*** Zeldox; ***India:*** Zipsydon; ***Irl.:*** Geodon; ***Israel:*** Geodon; ***Malaysia:*** Zeldox; ***Mex.:*** Geodon; ***Norw.:*** Zeldox; ***NZ:*** Zeldox; ***Philipp.:*** Zeldox; ***Pol.:*** Zeldox; ***Port.:*** Zeldox; ***Rus.:*** Zeldox (Зелдокс); ***S.Afr.:*** Geodon; ***Singapore:*** Zeldox; ***Spain:*** Geodon; Zeldox; ***Swed.:*** Zeldox; ***Thai.:*** Zeldox; ***USA:*** Geodon; ***Venez.:*** Geodon.

Zolazepam Hydrochloride *(BANM, USAN, rINNM)*

CI-716; Hidrocloruro de zolazepam; Zolazépam, Chlorhydrate de; Zolazepami Hydrochloridum. 4-(*o*-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpirazole[3,4-e][1,4]diazepin-7(1*H*)-one monohydrochloride.

Золазепама Гидрохлорид

$C_{15}H_{15}FN_4O,HCl$ = 322.8.

CAS — 31352-82-6 (zolazepam); 33754-49-3 (zolazepam hydrochloride).

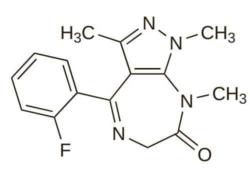

(zolazepam)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Zolazepam Hydrochloride). A white to off-white crystalline powder. Freely soluble in water and in 0.1N hydrochloric acid; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. pH of a 10% solution in water is between 1.5 and 3.5. Store in airtight containers.

Profile

Zolazepam hydrochloride is a benzodiazepine with general properties similar to those of diazepam (p.992). It is used with tiletamine (p.1796) for general anaesthesia in veterinary medicine.

Zolpidem Tartrate *(BANM, USAN, rINNM)*

SL-80.0750 (zolpidem); SL-80.0750-23N; Tartrato de zolpidem; Tsolpideemitartraatti; Zolpidem Hemitartrate; Zolpidem, tartrate de; Zolpidemi tartras; Zolpidemo tartratas; Zolpidem-tartarát; Zolpidemtartrat; Zolpidemu winian. *N,N*-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide hemitartrate.

Золпидема Тартрат

$(C_{19}H_{21}N_3O)_2,C_4H_6O_6$ = 764.9.

CAS — 82626-48-0 (zolpidem); 99294-93-6 (zolpidem tartrate).

ATC — N05CF02.

ATC Vet — QN05CF02.

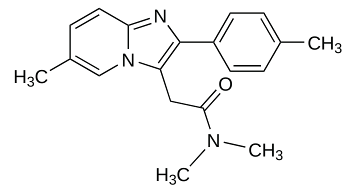

(zolpidem)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of zolpidem tartrate: Sleepeasy; Tic-Tacs.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zolpidem Tartrate). A white or almost white hygroscopic crystalline powder. Slightly soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Withdrawal symptoms. A 37-year-old man, who increased his dose from 10 mg to 130 mg daily over 2 months, had a generalised tonic-clonic seizure after zolpidem was abruptly stopped.[1] The patient recovered after being started on a benzodiazepine dosage tapering programme. Symptoms attributed to daytime abstinence after excessive night-time doses have been reported[2] in 2 patients and included anxiety, tremor, sweating, nausea, gastric and abdominal pain, swallowing difficulties, tachycardia, and tachypnoea. The patients had increased their doses because of the development of tolerance to the hypnotic effect but had begun to experience muscle twitches and myoclonic jerks.

1. Gilbert DL, Staats PS. Seizure after withdrawal from supratherapeutic doses of zolpidem tartrate, a selective omega I benzodiazepine receptor agonist. *J Pain Symptom Manage* 1997; **14:** 118–20.
2. Cavallaro R, *et al.* Tolerance and withdrawal with zolpidem. *Lancet* 1993; **342:** 374–5.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Treatment of overdose is largely supportive. Activated charcoal may be given orally within one hour of ingestion of 100 mg zolpidem or more by adults, or more than 5 mg by children. Alternatively, gastric lavage may be considered in adults if they present within 1 hour of a potentially life-threatening overdose. Flumazenil may be considered in cases of severe CNS depression (see also Overdosage, below).

◊ Reviews.

1. Darcourt G, *et al.* The safety and tolerability of zolpidem—an update. *J Psychopharmacol* 1999; **13:** 81–93.

Abuse. Zolpidem abuse has been reported;[1,2] effects noted include a paradoxical stimulant effect when taking large doses of zolpidem. Tolerance may also develop. Intravenous abuse has also been reported.[3]

See also under Dependence and Withdrawal, above.

1. Gericke CA, Ludolph AC. Chronic abuse of zolpidem. *JAMA* 1994; **272:** 1721–2.
2. Victorri-Vigneau C, *et al.* Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol* 2007; **64:** 198–209.
3. Brunelle E, *et al.* Zolpidem: intravenous misuse in drug abusers. *Addiction* 2005; **100:** 1377–8.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving zolpidem, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In 5 women given a 20-mg dose of zolpidem, the amount of drug excreted in breast milk after 3 hours ranged between 0.76 and

3.88 micrograms, which represented 0.004 to 0.019% of the dose.[2] No detectable (below 0.5 nanograms/mL) zolpidem was found in subsequent milk samples.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)
2. Pons G, *et al.* Zolpidem excretion in breast milk. *Eur J Clin Pharmacol* 1989; **37:** 245–8.

Effects on the liver. Hepatitis developed on 2 separate occasions in a 53-year-old woman after the use of zolpidem for insomnia.[1]

1. Karsenti D, *et al.* Hepatotoxicity associated with zolpidem treatment. *BMJ* 1999; **318:** 1179.

Effects on mental function. Psychotic reactions, which may not subsequently be recalled, have been reported in patients taking therapeutic doses of zolpidem.[1-4] Somnambulism has also been reported with zolpidem.[5,6] Other complex sleep-related behaviours, such as eating or driving while asleep, have been reported with zaleplon,[7] zolpidem,[6,7] and zopiclone. Such behaviour is more likely to occur when these drugs are taken with alcohol or other CNS depressants, or when taken in doses exceeding the recommended maximum. It is not clear if there are differences in risk with individual drugs; however, as a precautionary measure, the FDA[8] had requested for labelling changes that highlight these adverse effects to be made to all hypnotics marketed in the USA.

1. Ansseau M, *et al.* Psychotic reactions to zolpidem. *Lancet* 1992; **339:** 809.
2. Iruela LM, *et al.* Zolpidem-induced macropsia in anorexic woman. *Lancet* 1993; **342:** 443–4.
3. Brodeur MR, Stirling AL. Delirium associated with zolpidem. *Ann Pharmacother* 2001; **35:** 1562–4.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Seeing things with zolpidem. *Aust Adverse Drug React Bull* 2002; **21:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0202.pdf (accessed 21/08/08)
5. Yang W, *et al.* One rare side effect of zolpidem—sleepwalking: a case report. *Arch Phys Med Rehabil* 2005; **86:** 1265–6.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Zolpidem and bizarre sleep related effects. *Aust Adverse Drug React Bull* 2007; **26:** 2–3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0702.pdf (accessed 10/03/08)
7. Southworth MR, *et al.* FDA. Nonbenzodiazepine hypnotic use and cases of "sleep driving". *Ann Intern Med* 2008; **148:** 486–7.
8. FDA. FDA news: FDA requests label change for all sleep disorder drug products (issued 14th March, 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html (accessed 07/08/08)

Hypersensitivity. Rare cases of angioedema involving the tongue, glottis, or larynx have been reported after the first or subsequent doses of hypnotics such as eszopiclone, zaleplon, zolpidem, and zopiclone; additional symptoms suggestive of anaphylaxis have also developed in some patients.

Overdosage. A retrospective analysis of 344 cases of acute overdosage with zolpidem reported to the Paris Poison Center and the manufacturers *Synthelabo* has been published.[1] The ingested dose, where known, ranged from 10 to 1400 mg, and the most common adverse effect was drowsiness (in 89 patients). Other adverse effects probably associated with the overdosage included coma in 4 patients and vomiting in 7. Recovery was usually rapid when overdosage involved only zolpidem. It was recommended that patients who had ingested more than 100 mg of zolpidem should undergo gastric lavage and should be monitored for at least 12 hours (see also above). Although it has been shown that flumazenil[2] can effectively antagonise the CNS effects of zolpidem the authors of this analysis[1] found that in general it was not required.

1. Garnier R, *et al.* Acute zolpidem poisoning—analysis of 344 cases. *J Toxicol Clin Toxicol* 1994; **32:** 391–404.
2. Patat A, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther* 1994; **56:** 430–6.

Interactions

As for Diazepam, p.989.

Antidepressants. A 16-year-old girl who had been taking *paroxetine* 20 mg daily for 3 days began to hallucinate and became disorientated one hour after taking zolpidem 10 mg at night. The delirium cleared spontaneously 4 hours later without treatment.[1] When questioned, at least one other of the author's patients receiving this combination reported transient visual hallucinations. Other isolated cases of visual hallucinations have been reported in patients taking zolpidem with antidepressants including *bupropion*, *desipramine*, *fluoxetine*, *sertraline*, and *venlafaxine*.[2]

1. Katz SE. Possible paroxetine-zolpidem interaction. *Am J Psychiatry* 1995; **152:** 1689.
2. Elko CJ, *et al.* Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *J Toxicol Clin Toxicol* 1998; **36:** 195–203.

Antiepileptics. A 47-year-old man with a history of bipolar disorder, who was receiving citalopram and zolpidem, had episodes of somnambulism after he was also given *valproic acid* for treatment of manic symptoms.[1] The episodes stopped on withdrawal of valproic acid and returned on rechallenge. An interaction between zolpidem and valproic acid was suspected (but somnambulism has also been associated with zolpidem alone, see Effects on Mental Function, above).

For the suggestion that *carbamazepine* and *phenytoin* may interact with zolpidem, see Rifampicin, below.

1. Sattar SP, *et al.* Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003; **37:** 1429–33.

Antifungals. Use of *ketoconazole* with zolpidem has resulted in increased plasma concentrations, and an enhanced sedative effect, of zolpidem, albeit only modest.[1] The use of zolpidem with *fluconazole*[1] or *itraconazole*[1,2] has resulted in small, non-significant changes in the pharmacokinetics and sedative effects of zolpidem.

1. Greenblatt DJ, *et al.* Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. *Clin Pharmacol Ther* 1998; **64:** 661–71.
2. Luurila H, *et al.* Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. *Eur J Clin Pharmacol* 1998; **54:** 163–6.

Antivirals. HIV-protease inhibitors such as *ritonavir* may increase plasma concentrations of zolpidem with a risk of extreme sedation and respiratory depression; use together is possible provided the patient is carefully monitored for excessive sedative effects.

Rifampicin. Rifampicin reduced the hypnotic effect of zolpidem in a study in 8 healthy female subjects.[1] The area under the curve for zolpidem was reduced by 73% after rifampicin and the peak plasma concentration by 58%. The elimination half-life of zolpidem was reduced from 2.5 to 1.6 hours. Similar effects could be expected with other potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as carbamazepine and phenytoin.

1. Villikka K, *et al.* Rifampin reduces plasma concentrations and effects of zolpidem. *Clin Pharmacol Ther* 1997; **62:** 629–34.

Pharmacokinetics

Zolpidem is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached within 3 hours. Zolpidem undergoes first-pass metabolism and an absolute bioavailability of about 70% has been reported. Zolpidem has an elimination half-life of about 2.5 hours and is about 92% bound to plasma proteins. It is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4; the inactive metabolites of zolpidem are excreted in the urine and faeces. Zolpidem is distributed into breast milk.

◊ References.

1. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. *Clin Pharmacokinet* 1995; **29:** 142–53.
2. von Moltke LL, *et al.* Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and vivo correlations. *Br J Clin Pharmacol* 1999; **48:** 89–97.
3. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
4. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.
5. Greenblatt DJ, *et al.* Dynamics and kinetics of a modified-release formulation of zolpidem: comparison with immediate-release standard zolpidem and placebo. *J Clin Pharmacol* 2006; **46:** 1469–80.

Uses and Administration

Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines (see Diazepam, p.992), but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia. The usual oral dose is 10 mg taken immediately before retiring. In elderly or debilitated patients, treatment should be limited to a dose of 5 mg at night. Doses should also be reduced in patients with hepatic impairment, see below. A modified-release formulation of zolpidem tartrate is also available.

Administration in hepatic impairment. In patients with hepatic impairment, treatment with immediate-release formulations of zolpidem tartrate should be started with a dose of 5 mg at night; the dose may be increased to 10 mg, if necessary, in those under 65 years. UK licensed product information contraindicates the use of zolpidem in patients with severe impairment.

Catatonia. Anecdotal reports[1,2] suggesting that zolpidem may be a useful test in the diagnosis of catatonia.

1. Thomas P, *et al.* Test for catatonia with zolpidem. *Lancet* 1997; **349:** 702.
2. Zaw ZF, Bates GDL. Replication of zolpidem test for catatonia in an adolescent. *Lancet* 1997; **349:** 1914.

Insomnia. Zolpidem is an imidazopyridine with strong sedative actions, but only minor anxiolytic, muscle relaxant, or anticonvulsant properties. Some degree of amnesia has been reported. Zolpidem appears to act by binding to the benzodiazepine receptor component of the GABA receptor complex. It has, however, a selective affinity for the subtype of benzodiazepine receptors prevalent in the cerebellum (BZ1- or ω_1-receptors) as opposed to those more commonly found in the spinal cord (BZ2- or ω_2-receptors) or in the peripheral tissues (BZ3- or ω_3-receptors). Zolpidem has a rapid onset and short duration of hypnotic action and at usual doses decreases time to sleep onset and increases duration of sleep with little apparent effect on sleep stages (see Insomnia, p.957). Reviews agree that clinical studies have shown zolpidem to have hypnotic activity superior to placebo and generally similar to comparative benzodiazepines. Although it does not appear to produce rebound insomnia to any great extent, there appears to be little evidence that zolpidem offers any advantage over short-acting benzodiazepines in terms of residual effects the next day, or its potential to induce tolerance or withdrawal symptoms or dependence (see also under Dependence and Withdrawal, above).

References.

1. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; **40:** 291–313.
2. Lobo BL, Greene WL. Zolpidem: distinct from triazolam? *Ann Pharmacother* 1997; **31:** 625–32.
3. Nowell PD, *et al.* Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997; **278:** 2170–7.
4. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; **59:** 865–89.
5. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.
6. Harrison TS, Keating GM. Zolpidem: a review of its use in the management of insomnia. *CNS Drugs* 2005; **19:** 65–89.

Parkinsonism. Although preliminary findings[1] in 10 patients suggested that zolpidem might improve symptoms of Parkinson's disease concern has been expressed[2] over the risk of falls associated with zolpidem-induced drowsiness and the serious consequences for these patients. Benefit has also been reported[3] in the treatment of antipsychotic-induced parkinsonism in one patient with symptoms of repetitive persistent gross tremors of the hands.

1. Daniele A, *et al.* Zolpidem in Parkinson's disease. *Lancet* 1997; **349:** 1222–3.
2. Lavoisy J, Marsac J. Zolpidem in Parkinson's disease. *Lancet* 1997; **350:** 74.
3. Farver DK, Khan MH. Zolpidem for antipsychotic-induced parkinsonism. *Ann Pharmacother* 2001; **35:** 435–7.

Permanent vegetative state. Zolpidem in a single dose of 10 mg has produced temporary arousal in 3 patients thought to be in permanent vegetative state.[1] Effects lasted for about 4 hours.

1. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation* 2006; **21:** 23–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Balidorm†; Dormilan; Durnit; Nocte; Somit; Sumenan; Zolodorm; ***Austral.:*** Dormizol; Somidem; Stildem; Stilnox; Zolpibell; ***Austria:*** Ivadal; Mondeal; Zoldem; Zolpidohexal; ***Belg.:*** Stilnoct; ***Braz.:*** Lioram; Stilnox; ***Chile:*** Adormix; Damixan; Dormilam; Dormosol; Somnil; Somnipron; Somno; Sucedal; ***Cz.:*** Eanox; Hypnogen; Stilnoct; Stilnox; Zolpimerck; Zolpinox; Zolsana; Zonadin; ***Denm.:*** Eanox†; Nimadorm; Stilnoct; Zonoct; ***Fin.:*** Somnor; Stella; Stilnoct; ***Fr.:*** Stilnox; ***Ger.:*** Bikalm; Stilnox; Zodormdura; Zoldem; Zolpi-Lich; Zolpi-Q; Zolpinox; ***Gr.:*** Alespan; Hypnoforin; Stilnox; ***Hong Kong:*** Stilnox; Stilpidem; ***Hung.:*** Ambien; Hypnogen; Pidezol; Sanval; Stilnox; ***India:*** Ambiz; Sove; Zleep; Zoldem; ***Indon.:*** Stilnox; Zolmia; ***Irl.:*** Nytamel; Stilnoct; Zoldem; Zolnod; ***Israel:*** Stilnox; Zodorm; ***Ital.:*** Niotal; Nottem; Stilnox; ***Jpn:*** Myslee; ***Malaysia:*** Sobrium; Somidem; Stilnox; ***Mex.:*** Nocte; Stilnox; ***Neth.:*** Stilnoct; Zolpidol; ***Norw.:*** Stilnoct; ***Philipp.:*** Stilnox; Ziohex; ***Pol.:*** Hypnogen; Nasen; Polsen; Sanval; Stilnox; Xentic; Zolpic; ZolpiGen; Zolsana; Zoratio; ***Port.:*** Cymerion; Stilnox; ***Rus.:*** Hypnogen (Гипноген); Nitrest (Нитрест); Sanval (Санвал); Snovitel (Сновител); ***S.Afr.:*** Ivedal; Noxidem; Stilnox; Zolnoxs; Zolpihexal; ***Singapore:*** Stilnox; ***Spain:*** Dalparan; Stilnox; ***Swed.:*** Stilnoct; ***Switz.:*** Sedovalin; Stilnox; Zoldorm; Zolpi-Med; ***Thai.:*** Stilnox; ***UK:*** Stilnoct; ***USA:*** Ambien; Tovalt; ***Venez.:*** Atrimon; Stilnox; Zolpidex.

Zopiclone *(BAN, rINN)*

27267-RP; Tsopikloni; Zopiclona; Zopiclonum; Zopiklon; Zopiklonas. 6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

Зопиклон

$C_{17}H_{17}ClN_6O_3$ = 388.8.

CAS — 43200-80-2.

ATC — N05CF01.

ATC Vet — QN05CF01.

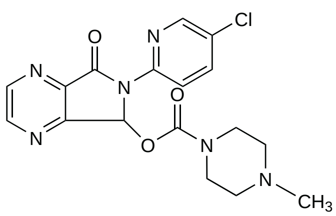

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of zopiclone: Zoppies.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zopiclone). A white or slightly yellowish powder. Practically insoluble in water and in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ There have been reports[1,2] of zopiclone dependence and associated withdrawal symptoms on dosage reduction or cessation of use. However, a 67-year-old man who increased his dosage of zopiclone up to 337.5 mg daily to treat insomnia without apparent adverse effects, had his zopiclone withdrawn without severe complications over 4 weeks using drug and cognitive therapy.[3] A WHO expert committee[4] considered in 2006 that the likelihood of zopiclone abuse was low and not great enough to warrant international control.

1. Jones IR, Sullivan G. Physical dependence on zopiclone: case reports. *BMJ* 1998; **316:** 117.
2. Sikdar S. Physical dependence on zopiclone. *BMJ* 1998; **317:** 146.
3. Kuntze MF, *et al.* Excessive use of zopiclone: a case report. *Swiss Med Wkly* 2002; **132:** 523.
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. A bitter or metallic taste in the mouth has been the most frequently reported adverse effect with zopiclone.

Treatment of overdose is largely supportive. Activated charcoal may be given orally within one hour of ingestion of more than 150 mg zopiclone by adults, or 1.5 mg/kg by children. Alternatively gastric lavage may be considered in adults if they present within 1 hour of a potentially life-threatening overdose. Flumazenil has been used in cases of severe CNS depression (see also Overdosage, below).

Incidence of adverse effects. In a French postmarketing survey[1] of 20 513 patients treated with zopiclone the most commonly reported adverse events were bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%) and nightmares (0.5%). The UK CSM[2] had received 122 reports of adverse reactions to zopiclone over a period of about one year since the product's introduction in November 1989. A fifth of these were neuropsychiatric reactions, a proportion similar to that found with other hypnotics. Many of these reactions were potentially serious and involved hallucinations (3 auditory and 2 visual), amnesia (4 cases), and behavioural disturbances (10, including 3 cases of aggression). Most reactions started immediately or shortly after the first dose and improved rapidly on stopping the drug. Three patients had difficulty in stopping treatment, 2 because of withdrawal symptoms and one due to repeated rebound insomnia. The CSM considered that, although differing structurally from the benzodiazepines, zopiclone has the same potential for adverse psychiatric reactions, including dependence. As with the benzodiazepines it should be reserved for patients with severe sleep disturbance and its duration of use limited to 28 days; care should also be taken in the elderly, those who have a history of previous psychiatric illness, or who are prone to drug abuse.

1. Allain H, *et al.* Postmarketing surveillance of zopiclone in insomnia: analysis of 20,513 cases. *Sleep* 1991; **14:** 408–13.
2. Committee on Safety of Medicines. Zopiclone (Zimovane) and neuro-psychiatric reactions. *Current Problems 30* 1990.

Abuse. For a report of zopiclone abuse see under Dependence and Withdrawal, above.

Administration. Results in 9 healthy subjects given zopiclone indicated a significant delay in onset of action when the drug was taken in the supine, as opposed to the standing, position; this was associated with a prolongation of more than 20 minutes in the lag time before absorption began.[1] In order to obtain a rapid and complete hypnotic effect from zopiclone the tablet should be swallowed in the standing position.

1. Channer KS, *et al.* The effect of posture at the time of administration on the central depressant effects of the new hypnotic zopiclone. *Br J Clin Pharmacol* 1984; **18:** 879–86.

Driving. For reference to the increased risk of road-traffic accidents for drivers taking zopiclone, see p.988.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zopiclone, see under Zolpidem, above.

Hepatic impairment. Zopiclone was given in a dose of 7.5 mg to 7 cirrhotic patients and 8 healthy subjects; a further 2 cirrhotic patients received 3.75 mg.[1] Mean peak plasma concentrations were similar in healthy subjects and those with hepatic impairment following equivalent doses but time to peak plasma concentration was 4 hours in the latter as compared with 2 hours in the healthy subjects. Elimination was greatly prolonged in cirrhotic patients, in whom the mean plasma half-life was 8.53 hours compared with 3.5 hours. The CNS-depressant effects of zopiclone were delayed in the cirrhotic patients in a way consistent with the pharmacokinetic changes. There was also some evidence of an increased response in these patients. The authors recommended caution when giving zopiclone to patients with severe hepatic disease; licensed product information contra-indicates the use of zopiclone in such patients.

1. Parker G, Roberts CJC. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; **16:** 259–65.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zopiclone, see under Zolpidem, above.

Overdosage. Consciousness was rapidly regained after intravenous flumazenil was given to a patient who had taken an overdosage of zopiclone.[1] However, fatalities after zopiclone overdose have also been reported.[2,3]

1. Ahmad Z, *et al.* Diagnostic utility of flumazenil in coma with suspected poisoning. *BMJ* 1991; **302:** 292.
2. Boniface PJ, Russell SGG. Two cases of fatal zopiclone overdose. *J Anal Toxicol* 1996; **20:** 131–3.
3. Meatherall RC. Zopiclone fatality in a hospitalized patient. *J Forensic Sci* 1997; **42:** 340–3.

Interactions

As for Diazepam, p.989. Use with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4, such as carbamazepine or phenytoin, is likely to reduce the effects of zopiclone.

Antibacterials. In a study in healthy subjects *erythromycin* increased the rate of absorption of zopiclone and prolonged its elimination.[1] In another study[2] in 8 healthy subjects *rifampicin* was associated with an 82% reduction in the area under the curve for zopiclone. The peak plasma concentration of zopiclone was reduced from 76.9 to 22.5 nanograms/mL and the elimination half-life from 3.8 to 2.3 hours.

1. Aranko K, *et al.* The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; **38:** 363–7.
2. Villikka K, *et al.* Concentrations and effects of zopiclone are greatly reduced by rifampicin. *Br J Clin Pharmacol* 1997; **43:** 471–4.

Pharmacokinetics

Zopiclone is rapidly absorbed and widely distributed after oral doses. It has an elimination half-life of 3.5 to 6.5 hours and is reported to be about 45 to 80% bound to plasma proteins. Zopiclone is extensively metabolised in the liver; the 2 major metabolites, the less active zopiclone *N*-oxide and the inactive *N*-desmethylzopiclone, are excreted mainly in the urine. About 50% of a dose is converted by decarboxylation to inactive metabolites, which are partly eliminated via the lungs as carbon dioxide. Only about 5% of a dose appears unchanged in the urine and about 16% appears in the faeces. Excretion of zopiclone in the saliva may explain reports of a bitter taste. It is also distributed into breast milk.

◊ Reviews.

1. Fernandez C, *et al.* Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet* 1995; **29:** 431–41.
2. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Distribution into breast milk. Zopiclone was distributed into breast milk in 12 women in concentrations about half those in plasma.[1] The calculated dose that would be received by a neonate was 1.5 micrograms/kg, corresponding to 1.2% of the maternal dose.

1. Matheson I, *et al.* The excretion of zopiclone into breast milk. *Br J Clin Pharmacol* 1990; **30:** 267–71.

Uses and Administration

Zopiclone is a cyclopyrrolone with similar sedative, anxiolytic, muscle relaxant, amnestic, and anticonvulsant properties to those of the benzodiazepines (see Diazepam, p.992). Like diazepam, its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA) in the brain. Zopiclone is reported to bind to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. It has a short duration of action.

Zopiclone is used as a hypnotic in the short-term management of insomnia. The usual oral dose is 7.5 mg before bed. In elderly patients, treatment should start with a dose of 3.75 mg before bed. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Eszopiclone, the (+)-isomer of zopiclone, is used similarly (see p.995).

Administration in hepatic or renal impairment. In those with renal impairment or mild to moderate hepatic impairment, treatment with zopiclone should start with an oral dose of 3.75 mg before bed. It should not be given to patients with severe hepatic impairment.

Insomnia. Zopiclone has a similar pharmacological and pharmacokinetic profile to the short-acting benzodiazepines. It is claimed to initiate sleep rapidly, without reduction of total rapid-eye-movement (REM) sleep, and then sustain it with preservation of normal slow-wave sleep (see Insomnia, p.957). It is generally considered to be as effective as a hypnotic as the benzodiazepines. Rebound insomnia has occurred but does not appear to be common. Residual effects the next day may be less pronounced after zopiclone than after short-acting benzodiazepines but there appears to be little evidence that zopiclone offers any clinical advantage in terms of its potential to induce tolerance, withdrawal symptoms, or dependence. For recommendations of the UK CSM concerning its use as a hypnotic, see Incidence of Adverse Effects, above.

References.

1. Noble S, *et al.* Zopiclone: an update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; **55:** 277–302.
2. Hajak G. A comparative assessment of the risks and benefits of zopiclone: a review of 15 years' clinical experience. *Drug Safety* 1999; **21:** 457–69.
3. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Foltran; Imovane; Insomnium; ***Austral.:*** Imovane; Imrest; ***Austria:*** Sedolox; Somnal; ***Belg.:*** Imovane; ***Braz.:*** Imovane; Neurolil†; ***Canad.:*** Imovane; Rhovane; ***Chile:*** Alpaz; Imovane; Losopil; Nuctane†; Zedax†; Zetix; Zometic; Zonix; ***Cz.:*** Imovane†; Zopitin; ***Denm.:*** Imoclone; Imovane; Imozop; ***Fin.:*** Imovane; Zopinox; ***Fr.:*** Imovane; ***Ger.:*** espa-dorm†; Optidorm; Somnosan; Ximovan; Zodurat; Zop; Zopi-Puren; Zopicalm; Zopiclodura; ***Gr.:*** Imovane; ***Hong Kong:*** Amvey; Dopareel; Eurovan; Imovane; Zolief; Zomni; ***Hung.:*** Imovane; Somnol; Zopigen; ***India:*** Zonap†; Zopicon; ***Irl.:*** Zileze; Zimoclone; Zimovane; Zopitan; Zorclone; ***Israel:*** Imovane; Nocturno; ***Ital.:*** Imovane; Nenia†; ***Malaysia:*** Imovane; ***Mex.:*** Imovane; ***Neth.:*** Imovane; ***Norw.:*** Imovane; ***NZ:*** Imovane; ***Pol.:*** Dobroson; Imovane; Zopiratio; ***Rus.:*** Imovane (Имован); Piclodorm (Пиклодорм); Relaxon (Релаксон)†; Somnol (Сомнол); ***S.Afr.:*** Alchera; Imovane; Z-Dorm; Zopigen; Zopimed; Zopivane; ***Singapore:*** Imovane; ***Spain:*** Datolan; Limovan; Siaten; Zopicalma; ***Swed.:*** Imovane; ***Switz.:*** Imovane; ***Turk.:*** Imovane; ***UK:*** Zileze†; Zimovane; ***Venez.:*** Imovane†.

Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum. 2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.

Зотепин

$C_{18}H_{18}ClNOS = 331.9$.

CAS — 26615-21-4.

ATC — N05AX11.

ATC Vet — QN05AX11.

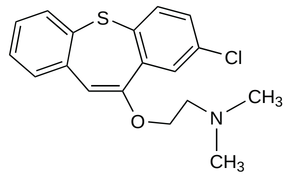

Adverse Effects, Treatment, and Precautions

Although zotepine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Common adverse effects include asthenia, headache, hypotension and, less commonly, orthostatic hypotension, tachycardia, gastrointestinal disturbances, elevated liver enzyme values, leucopenia, agitation, anxiety, dizziness, insomnia, somnolence, rhinitis, sweating, and blurred vision. Other less common adverse effects include thrombocytopenia, hyperglycaemia, hyperlipidaemia, convulsions, sexual dysfunction, and urinary incontinence. Extrapyramidal symptoms have been reported and tardive dyskinesia may occur with prolonged therapy. Neuroleptic malignant syndrome has been reported rarely. Prolactin levels may be increased and weight gain has been noted.

Zotepine can prolong the QT interval and patients with pre-existing prolongation of the QT interval should not be given the drug. It should be used with caution in patients at risk of developing arrhythmias; in such patients an ECG should be performed before starting treatment. Electrolytes should also be measured and any imbalance corrected. Monitoring of ECG and electrolytes should be continued during treatment especially at each dose increase. Zotepine may also increase the heart rate and, consequently, it should be used with care in patients with angina pectoris due to coronary artery disease. Caution is also recommended in patients with other cardiovascular disorders such as severe hypertension.

Zotepine has uricosuric properties and should not be given to patients with acute gout or a history of nephrolithiasis; it should be used with caution in patients with a history of gout or hyperuricaemia. Zotepine lowers the seizure threshold and should not be used in patients with a personal or family history of epilepsy unless the potential benefit outweighs the risk of convulsions. It has antimuscarinic actions and should be used with caution in patients with disorders such as benign prostatic hyperplasia, urinary retention, angle-closure glaucoma, and paralytic ileus. It should also be used with caution in patients with hepatic impairment; in such patients, weekly monitoring of liver function is recommended for at least the first 3 months of therapy. Zotepine may exacerbate the symptoms of Parkinson's disease. It should be used with caution in patients with tumours of the adrenal medulla such as phaeochromocytoma or neuroblastoma.

Zotepine may affect the performance of skilled tasks including driving.

Gradual withdrawal of zotepine is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Dementia. The FDA has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class. See under Risperidone, p.1024.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also under Adverse Effects of Clozapine, p.981.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

Zotepine may enhance the effects of other CNS depressants and antimuscarinics. The risk of seizures is particularly increased when zotepine is given with high doses of other antipsychotics and the combination is not recommended. Additive hypotensive effects may theoretically occur with antihypertensives and some anaesthetic drugs; however its α-blocking actions might reduce the effects of methyldopa or clonidine.

The risk of arrhythmias with zotepine may be increased by use with other drugs that prolong the QT interval or cause hypokalaemia. Use of zotepine with fluoxetine or diazepam may lead to increased plasma concentrations of zotepine.

Pharmacokinetics

Zotepine is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations being achieved 2 to 3 hours later. It undergoes extensive first-pass metabolism to the equipotent metabolite norzotepine and inactive metabolites. CYP1A2 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of zotepine. Plasma protein binding of zotepine and norzotepine is 97%. Zotepine is excreted mainly in the urine and faeces as inactive metabolites and has an elimination half-life of about 14 hours. It is thought to be distributed into breast milk on the basis of studies in *rats*.

Uses and Administration

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin ($5\text{-}HT_2$), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It is given in the treatment of schizophrenia in an initial oral dose of 25 mg three times daily; this is increased according to response, at intervals of 4 days, to a maximum of 100 mg three times daily. There is an appreciable increase in the incidence of seizures at total daily doses above the recommended maximum of 300 mg. For elderly patients, the recommended starting dose is 25 mg given twice daily, increased gradually up to a maximum of 75 mg twice daily. Doses should also be reduced in patients with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, the recommended initial oral dose of zotepine is 25 mg given twice daily increased gradually up to a maximum of 75 mg twice daily.

Schizophrenia. A systematic review[1] of short-term studies of zotepine for schizophrenia (p.955) concluded tentatively that it was as effective as classical antipsychotics and might be of benefit in patients with negative symptoms; in addition, it seemed less likely to provoke extrapyramidal disorders. Comparisons with atypical antipsychotics were too scanty for a meaningful comparison to be drawn.

1. DeSilva P, *et al.* Zotepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews ; Issue 4. Chichester: John Wiley; 2006 (accessed 10/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Nipolept; ***Cz.:*** Zoleptil; ***Ger.:*** Nipolept; ***Indon.:*** Lodopin; ***Jpn:*** Lodopin; ***Port.:*** Zoleptil; ***UK:*** Zoleptil.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *Z*-Clopenthixol; *cis*-Clopenthixol; α-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol. (*Z*)-2-{4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl}ethanol.

Зуклопентиксол

$C_{22}H_{25}ClN_2OS = 401.0$.

CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).

ATC — N05AF05.

ATC Vet — QN05AF05.

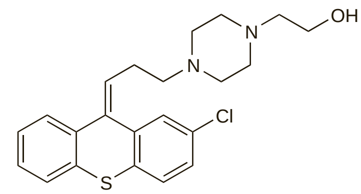

NOTE. Clopenthixol (*BAN, INN, USAN*) is the racemic mixture.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuklopentiksol Asetat.

Зуклопентиксола Ацетат

$C_{24}H_{27}ClN_2O_2S = 443.0$.

CAS — 85721-05-7.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Acetate). A yellowish, viscous oil. Very slightly soluble in water; very soluble in alcohol, in dichloromethane, and in ether. Store at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, décanoate de; Zuclopenthixoli decanoas; Zuklopenthixol-dekanoát; Zuklopentiksol Dekanoat; Zuklopentiksolio dekanoatas; Zuklopentixoldekanoat; Zuklopentyksolu dekanonian.

Зуклопентиксола Деканоат

$C_{32}H_{43}ClN_2O_2S = 555.2$.

CAS — 64053-00-5.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zuclopenthixol Decanoate). A yellow viscous oily liquid. Very slightly soluble in water; very soluble in alcohol and in dichloromethane. Store under an inert gas in airtight containers at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuklopentiksol Dihidroklorür.

Зуклопентиксола Гидрохлорид

$C_{22}H_{25}ClN_2OS,2HCl = 473.9$.

CAS — 58045-23-1.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Hydrochloride). An off-white granular powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. Zuclopenthixol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Zuclopenthixol is absorbed after oral doses with peak plasma concentrations occurring 3 to 6 hours later. The biological half-life after oral doses is reported to be about 1 day. Paths of metabolism of zuclopenthixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. It is mainly excreted in the faeces as unchanged drug and its *N*-dealkylated metabolite. Zuclopenthixol is about 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Small amounts of drug or metabolites cross the placenta and are distributed into breast milk.

On intramuscular injection the acetate and decanoate esters of zuclopenthixol are hydrolysed to release zuclopenthixol. Zuclopenthixol acetate has a relatively quick onset of action after injection and a duration of action of 2 to 3 days. It is therefore useful for the control of acute psychotic symptoms while avoiding repeated injections. The decanoate has a much longer duration of action and is a suitable depot preparation for maintenance treatment.

Metabolism. Determination of metaboliser phenotype with regard to cytochrome P450 isoenzyme CYP2D6 appeared to be of limited value in patients receiving zuclopenthixol as interindividual variation appeared to be the main factor affecting dose to serum concentration ratios.[1]

1. Linnet K, Wiborg O. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. *Ther Drug Monit* 1996; **18:** 629–34.

Uses and Administration

Zuclopenthixol is a thioxanthene of high potency with general properties similar to the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain.

Zuclopenthixol is used for the treatment of schizophrenia (see below), mania (see Bipolar Disorder, p.372), and other psychoses. It may be particularly suitable for agitated or aggressive patients who may become overexcited with flupentixol. Zuclopenthixol hydrochloride is usually given orally with doses expressed in terms of the base; zuclopenthixol hydrochloride 11.8 mg is equivalent to about 10 mg of zuclopenthixol. Zuclopenthixol hydrochloride has also been given intramuscularly. Zuclopenthixol acetate and zuclopenthixol decanoate are given by deep intramuscular injection; doses are expressed in terms of the ester. The acetate ester has a rapid onset of action and a duration of action of 2 to 3 days; it is used as a 5% oily solution for the initial treatment of acute psychoses and for exacerbations of chronic psychoses. The longer-acting decanoate ester is used as a 20% oily solution for the maintenance treatment of chronic psychoses; a 50% solution is available for those requiring high doses.

- The usual initial *oral* dose of the hydrochloride for the treatment of **psychoses** is the equivalent of 20 to 30 mg of the base daily in divided doses; in severe or resistant cases up to 150 mg daily has been given. The usual maintenance dose is 20 to 50 mg daily.
- The usual dose of zuclopenthixol acetate is 50 to 150 mg by deep *intramuscular* injection repeated, if necessary, after 2 or 3 days. Some patients may need an additional injection between 1 and 2 days after the first dose.

  Zuclopenthixol acetate is not intended for maintenance treatment; no more than 4 injections should be given in a maximum course of 2 weeks and the total dose should not exceed 400 mg. When maintenance treatment is required, *oral* zuclopenthixol hydrochloride may be introduced 2 to 3 days after the last injection of zuclopenthixol acetate, or *intramuscular* injections of the decanoate (see below) begun with the last injection of the acetate.
- The long-acting decanoate should be given by deep *intramuscular* injection; treatment is usually started with a test dose of 100 mg. This may be followed after at least 1 week by a dose of 200 to 500 mg or more, every 1 to 4 weeks, adjusted according to response. Injection volumes greater than 2 mL should be divided between 2 separate injection sites. The maximum recommended dose of zuclopenthixol decanoate is 600 mg weekly.

Elderly or debilitated patients should be given reduced doses of zuclopenthixol. Licensed product information states that the dose of the hydrochloride or the decanoate may need to be reduced to one-quarter or one-half of the usual initial dose; in addition, the maximum single dose of the acetate should be limited to 100 mg.

Administration in hepatic or renal impairment. Licensed product information recommends that for zuclopenthixol acetate, half the normal recommended intramuscular dose should be used for patients with hepatic impairment; a dosage reduction is considered to be unnecessary in patients with renal impairment but where there is renal failure half the normal intramuscular dosage is recommended.

Schizophrenia. A systematic review[1] comparing zuclopenthixol decanoate with other depot antipsychotics considered that although it may induce more adverse effects, limited data suggested it might offer advantages such as lower relapse rates and increased acceptability in the treatment of schizophrenia (p.955) and similar serious mental illnesses. Similar reviews of the use of the acetate[2] or hydrochloride[3] found, however, that evidence of additional benefit over other antipsychotics was lacking.

1. Coutinho E, *et al*. Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 14/04/05).
2. Gibson RC, *et al*. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).
3. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).

Preparations

BP 2008: Zuclopenthixol Acetate Injection; Zuclopenthixol Decanoate Injection; Zuclopenthixol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Clopixol; ***Austral.:*** Clopixol; ***Austria:*** Cisordinol; ***Belg.:*** Clopixol; ***Braz.:*** Clopixol; ***Canad.:*** Clopixol; ***Chile:*** Cisordinol; ***Cz.:*** Cisordinol; ***Denm.:*** Cisordinol; ***Fin.:*** Cisordinol; ***Fr.:*** Clopixol; ***Ger.:*** Ciatyl-Z; ***Gr.:*** Clopixol; ***Hong Kong:*** Clopixol; ***Hung.:*** Cisordinol; ***India:*** Clopixol; ***Irl.:*** Clopixol; ***Israel:*** Clopixol; ***Ital.:*** Clopixol; ***Malaysia:*** Clopixol; ***Mex.:*** Clopixol; ***Neth.:*** Cisordinol; Clopixol; ***Norw.:*** Cisordinol; ***NZ:*** Clopixol; ***Philipp.:*** Clopixol; ***Pol.:*** Clopixol; ***Port.:*** Cisordinol; ***Rus.:*** Clopixol (Клопиксол); ***S.Afr.:*** Clopixol; Colpixol; ***Singapore:*** Clopixol; ***Spain:*** Cisordinol; Clopixol; ***Swed.:*** Cisordinol; ***Switz.:*** Clopixol; ***Thai.:*** Clopixol; ***Turk.:*** Clopixol; ***UK:*** Clopixol.

Blood Products Plasma Expanders and Haemostatics

Haematopoiesis, p.1042
Anaemias, p.1042
Aplastic anaemia, p.1042
Haemolytic anaemia, p.1043
Iron-deficiency anaemia, p.1044
Megaloblastic anaemia, p.1044
Normocytic-normochromic anaemia, p.1044
Sideroblastic anaemia, p.1044
Haemoglobinopathies, p.1044
Sickle-cell disease, p.1044
β-Thalassaemia, p.1045
Haemostasis and Fibrinolysis, p.1045
Acquired haemorrhagic disorders, p.1047
Disseminated intravascular coagulation, p.1048
Haemophilias, p.1048
Inherited haemorrhagic disorders, p.1050
Neonatal intraventricular haemorrhage, p.1050
Thrombocytopenia, p.1051
von Willebrand's disease, p.1051
Neutropenia, p.1051

This chapter describes the management of blood disorders including some anaemias, haemorrhagic disorders, and neutropenia. It covers blood, blood products and substitutes, and colloid plasma expanders; crystalloid plasma expanders are generally solutions of sodium chloride (p.1686) or glucose (p.1945) or both. Also included in the chapter are haemostatic drugs and erythropoietin and other colony-stimulating factors. The management of haematological malignancies is covered in the Antineoplastics chapter, p.635.

Haematopoiesis

In the embryo and fetus, the formation and development of blood cells occurs at various sites including the liver, spleen, thymus, lymph nodes, and bone marrow; from birth throughout the rest of life it occurs mainly in the bone marrow with a small amount occurring in the lymph nodes. The bone marrow contains pluripotent stem cells that differentiate into different types of progenitor cells (committed stem cells); these then mature into various types of blood cells under the influence of growth factors and hormones. The main cellular components of blood are red blood cells (erythrocytes), white blood cells (leucocytes), and platelets.

Erythrocyte production is stimulated by erythropoietin, a hormone released by the kidney in response to anaemia or hypoxia.

The leucocytes are classified according to their morphological appearance into granulocytes, lymphocytes, and monocytes. The granulocytes are further classified as neutrophils, eosinophils, and basophils, according to the characteristics of their cytoplasmic granules. The term polymorphonuclear leucocytes can be applied to granulocytes in general but applies in particular to neutrophils. Most lymphocytes are matured in the lymph nodes, thymus, and spleen, from bone marrow lymphocyte precursors. Lymphocytes enter the bloodstream via the lymphatics, but only a small proportion are present in the blood. Monocytes are released into the blood but then enter the tissues to become fixed tissue macrophages. The maturation of leucocytes is stimulated by granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF).

Platelet maturation is stimulated by thrombopoietin.

Other growth factors involved at various stages of blood cell development include stem cell factor and interleukins-1, -3, -4, -5, -6, and -11.

The average blood cell counts in adults are:

- erythrocytes (men): 5.0×10^{12} cells/litre
- erythrocytes (women): 4.3×10^{12} cells/litre
- leucocytes: 7.0×10^{9} cells/litre (7000 cells/mm^3) but the value can vary markedly, even in the same individual at different times, from 4 to 11×10^{9} cells/litre. This total is made up of:
  - neutrophils (40 to 80%)
  - lymphocytes (20 to 40%)
  - monocytes (2 to 10%)
  - eosinophils (1 to 6%)
  - basophils (<1 to 2%)
- platelets: 150 to 450×10^{9} cells/litre (150 000 to 450 000 cells/mm^3)

Anaemias

Anaemia is usually understood to mean a lowering of haemoglobin concentration, red cell count, or packed cell volume to below 'normal' values, but the criteria for normality are difficult to establish. WHO's suggested definition of anaemia in populations living at around sea level is a haemoglobin concentration below:

- 13 g per 100 mL in men
- 12 g per 100 mL in women
- 11 g per 100 mL in pregnant women
- 12 g per 100 mL in children aged 12 to 14 years
- 11.5 g per 100 mL in children aged 5 to 11 years
- 11 g per 100 mL in children aged 6 to 59 months

However, because of individual variation, some apparently normal individuals have blood haemoglobin concentrations below these values, while others may be above these values and still be effectively anaemic.

Reduction in overall haemoglobin concentrations may be due to fewer red cells, with the cells retaining normal amounts of haemoglobin (normochromic anaemia), or the amount of haemoglobin in the cells may be reduced (hypochromic anaemia). Red cells themselves may be reduced in size (microcytic), enlarged (macrocytic), or normal in size (normocytic).

The immediate cause of anaemia may be decreased red cell production (due to defective proliferation and/or maturation of red cells from their precursors in bone marrow), increased red cell destruction (i.e. haemolysis), or loss of red cells from the circulation due to haemorrhage, either occult or overt. These conditions may occur due to underlying disease, nutritional deficiency, congenital disorders, or toxicity due to drugs or other substances and the cause must always be sought before an appropriate treatment can be determined.

The symptoms of anaemia are as variable as its causes but may include fatigue, pallor, dyspnoea, palpitations, headache, faintness or lightheadedness, tinnitus, anorexia and gastrointestinal disturbances, and loss of libido; tachycardia, heart failure, and retinal haemorrhage may occur in severe anaemia.

The treatment of anaemia depends upon its type and cause. Some of the principal types are classified in Table 1, below, and their management is discussed in more detail under the relevant headings. Sickle-cell disease and β-thalassaemia are discussed under Haemoglobinopathies.

Table 1. Types of anaemias.

Classification	Anaemia	Mean cell volume	Haemoglobin	Associated with
Microcytic	Iron-deficiency anaemia	Decreased (or normal in early stages)	Hypochromic	Blood loss, malabsorption, inadequate iron intake
	Hereditary sideroblastic anaemia	Decreased	Hypochromic	
	Thalassaemias	Decreased	Hypochromic	
Macrocytic	Megaloblastic anaemia	Increased	Normochromic	Vitamin B_{12} deficiency, folate deficiency (including drug induced)
	Acquired sideroblastic anaemia	Increased	Hypochromic	Alcoholism, drug or other toxicity
Normocytic	Normocytic-normochromic anaemia	Normal	Normochromic	Anaemia of chronic disorders, bone-marrow disorders (including aplastic anaemia), malignancy, renal failure, endocrine disorders, prematurity
Haemolytic	Haemolytic anaemia	Increased		Immune disorders, drug toxicity, hereditary disorders
	Sickle-cell anaemia			

◊ Reviews.

1. Spivak JL. The blood in systemic disorders. *Lancet* 2000; **355:** 1707–12.
2. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. *Mayo Clin Proc* 2003; **78:** 1274–80.
3. Tefferi A. Practical algorithms in anemia diagnosis. *Mayo Clin Proc* 2004; **79:** 955–6.

Aplastic anaemia

Aplastic anaemia is characterised by pancytopenia (a deficiency of all cellular elements of the blood) and hypoplasia of the bone marrow, with less than 25% of the marrow occupied by haematopoietic cells but without evident fibrosis or malignant infiltration. It is relatively rare, although it may be somewhat more common in the Far East, and is mainly seen in younger adults. Some forms, such as Fanconi's anaemia, are inherited but most are induced, for example by the effects of cytotoxic drugs or radiation, idiosyncratic reactions to other drugs, seronegative fulminant hepatitis, or auto-immune reactions. Since all cell lines are affected patients develop thrombocytopenia and neutropenia as well as anaemia, and symptoms include bleeding syndromes and infections as well as typical symptoms of anaemia. Paroxysmal nocturnal haemoglobinuria (see Haemolytic Anaemia, below), in which genetic mutation causes the production of abnormal blood cells and results in haemolysis, can be associated with aplastic anaemia.

Although spontaneous recovery has occurred, untreated aplastic anaemia is usually fatal. Management may be divided into supportive care and attempts to restore bone-marrow function with bone marrow transplantation or immunosuppression, and has been the subject of guidelines and reviews.[1-4]

Supportive care involves the prevention and treatment of infection (see Infections in Immunocompromised Patients, p.174), the control of haemorrhage with platelet concentrates, and where necessary, infusions of red blood cells (with platelets to prevent haemorrhage) for anaemia. Transfusions should be minimised in candidates for bone marrow transplant (see below).

In patients aged under 40 years with severe disease and with a suitable HLA-matched donor, **bone marrow transplantation** offers the prospect of long-term cure, and is considered the treatment of choice.[1-5] Ideally this should be performed early before the patient has received too many transfusions, which increase the risk of rejection, and before infection develops. Transfusion of cord blood from an HLA-identical sibling can also produce permanent engraftment, and may be associated with less acute graft-versus-host disease than bone marrow transplantation.[2] However, recent results have suggested that chronic graft-versus-host disease and overall survival may be worse when peripheral blood stem cells are used rather than bone marrow.[3]

In patients unsuitable for bone marrow transplantation, or where a suitable donor is not available, treatment with **immunosuppressants** may be tried. About 50% of patients are reported to respond to a course of antilymphocyte immunoglobulin within 3 months, and the addition of ciclosporin further improves response rates to between 60 and 80% and 5-year survival to between 75 and 90%.[1,2] However, one long-term study[6] providing follow-up data for 11 years has found no significant difference in survival between regimens of antilymphocyte immunoglobulin with or without ciclosporin.[6] Ciclosporin has been used alone but is less effective than antilymphocyte immunoglobulin.[1,3]

Despite these good rates of response with the addition of ciclosporin, relapse is not uncommon.[7] A second course of antilymphocyte immunoglobulin is recommended if there is no response, or there is relapse, after 3 months.[2] Ciclosporin is continued after a response has occurred and until the blood count has been stable for at least 6 months; it may then be slowly withdrawn, usually over many months and depending on blood counts.[2] Some patients may require continued therapy.[3,4]

Good response rates have been reported from combined regimens including a granulocyte colony-stimulating factor.[8] However, there are concerns about long-term use and the role of these factors is still under investigation.[2,3,9] There has been interest in the use of other haematopoietic growth factors including granulocyte-macrophage colony-stimulating factor, ancestim (stem cell factor), epoetin, interleukin-1, interleukin-3, and interleukin-6, either alone or with immunosuppression, but results have generally been poor or trials stopped because of toxicity, and so the use of these factors is not recommended.[2,9] However, short courses of granulocyte colony-stimulating factor may be considered for supportive therapy in neutropenic patients with severe systemic infections that are not responding to antibacterial or antifungal therapy.[2]

Oxymetholone was used extensively before the availability of antilymphocyte immunoglobulin and ciclosporin. It can increase the response to antilymphocyte immunoglobulin alone, but it can be hepatotoxic and causes virilisation, and is generally used for patients who have failed several courses of antilymphocyte immunoglobulin with ciclosporin, or where this regimen cannot be used.[2] Mycophenolate mofetil is under investigation in patients who are ineligible for bone marrow transplantation and refractory to standard immunosuppressive therapy.[2] Cyclophosphamide is commonly used in preparation for bone marrow transplantation and complete remission has also been reported with high-dose cyclophosphamide alone.[10,11] However, a randomised trial[12] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was observed in those receiving cyclophosphamide. Further follow-up[13] also found that relapse rates were no different. Nonetheless, cyclophosphamide continues to be of investigational interest.[4]

Responses to immunosuppressants are often partial, but this may be sufficient to free the patient from dependency on transfusions and intensive antibacterial cover, and is considered well worth achieving.[1,2] Nevertheless, the procedure is not curative; patients appear to retain some underlying defect in marrow function, and in the long term about 15% of them develop leukaemias or myelodysplasias.[1]

Children with severe aplastic anaemia are treated similarly to adults.[14] Although some reports have suggested that the response to immunosuppressant therapy may be lower in children under 5 years of age, others have shown the opposite. The choice of treatment in children may also need to take into account the potential long-term adverse effects of treatment, particularly with immunosuppressants or irradiation, on endocrine function, growth, fertility, and the development of secondary malignancies.

Older patients tend to be treated with immunosuppressant therapy rather than bone marrow transplantation.[2] A retrospective cohort study[15] that compared patients older than 50 years with younger patients found that more older patients had received ciclosporin alone, that the response to immunosuppression was independent of age at the time of treatment, and that although survival decreased with age deaths were similar to those in a general population and were not related to the type of treatment or the number of courses of treatment.

The outcome of **pregnancy** in women who had previously been treated for aplastic anaemia with an immunosuppressant regimen has been described.[16] Of 36 pregnancies, 22 were uncomplicated and 7 were complicated by relapse of aplastic anaemia; complications appeared to be more likely in women with low platelet counts and paroxysmal nocturnal haemoglobinuria. Rarely, aplastic anaemia can develop during pregnancy, and although the disease may remit spontaneously after termination or delivery, this does not occur in all cases.[17,18] Supportive care is the mainstay for management of aplastic anaemia during pregnancy, although the use of ciclosporin may be considered if transfusions are required.[2]

Patients with **non-severe aplastic anaemia** may require supportive therapy only. For those who do require immunosuppression there is less evidence on which to base treatment, but one prospective study[19] of patients with non-severe disease who had become transfusion-dependent reported that the combination of antilymphocyte immunoglobulin and ciclosporin produced a higher response rate with an earlier onset than ciclosporin alone. Although survival was no different between the groups, combination therapy was associated with less disease progression and a higher probability of disease-free survival.

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Haemolytic anaemia

The normal life span of an erythrocyte is about 120 days; a haemolytic state is defined as a reduction in this mean life span due to premature destruction of red cells, either intravascularly, or more commonly after sequestration by the spleen or liver. Healthy bone marrow can compensate for even quite severe haemolysis by increased erythropoiesis; however, if the red cell survival-time is less than 15 days, or if the bone marrow is abnormal, or there is a deficiency of folate, iron, or other necessary nutrients, then compensation will be inadequate and haemolytic anaemia will result. In addition to typical symptoms of anaemia (above) patients frequently exhibit jaundice and splenomegaly, while the increased erythropoiesis results in reticulocytosis (elevated counts of immature red cells).

Haemolytic anaemias may be either congenital or acquired. The **congenital** disorders include:

- those due to membrane defects in the erythrocyte, such as spherocytosis or elliptocytosis
- those due to enzyme defects (including the various forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency)
- those due to haemoglobin defects (haemoglobinopathies), including sickle-cell disease and β-thalassaemia (below)

The **acquired** haemolytic anaemias arise from numerous causes but may be divided into immune and non-immune types. The immune types include:

- some drug-induced haemolytic anaemias (including those produced by penicillins, rifampicin, and methyldopa)
- auto-immune haemolytic anaemia (further classified into warm or cold depending on the temperature at which the red cell antibodies are most active)
- paroxysmal nocturnal haemoglobinuria, resulting from complement-mediated red cell lysis
- haemolytic disease of the newborn (see p.2204)

The non-immune types include:

- haemolysis due to infections such as malaria
- chemically-induced haemolysis (due to a direct effect on the red cell rather than an immunologically-mediated one, and including the effects of toxins such as copper and arsenic as well as some snake venoms, and drugs such as amphotericin B, dapsone, and sulfasalazine)
- the effects of mechanical trauma

Treatment of haemolytic anaemia depends on the underlying cause, although general supportive measures (bed rest, transfusion if haemodynamic abnormalities make it necessary, and supplementation with folate) will be similar in all poorly-compensated patients. Well compensated haemolysis may require no treatment at all, although clearly elucidation and, where possible, removal of the cause is desirable.

Hereditary haemolytic disorders such as spherocytosis[1] mostly respond well to splenectomy, although milder forms may not require treatment. In patients with G6PD deficiency, treatment consists essentially of avoidance of drugs or foodstuffs likely to provoke haemolysis.

Acquired haemolytic anaemia is best treated by identification and where possible elimination of any underlying cause. Most drug-induced haemolytic anaemias respond rapidly to withdrawal of the offending substance.

Auto-immune haemolytic anaemias require treatment aimed at maintaining the patient and controlling haemolysis. Although treatment may need to be prolonged, in many patients with idiopathic disease antibodies eventually disappear or decrease to insignificant titres after months or years. The auto-immune haemolytic anaemias may be secondary to other disorders including leukaemias, lymphomas, and SLE; correction of the underlying disease often results in marked improvement of accompanying haemolysis.

In patients with warm auto-immune haemolytic anaemia treatment starts with corticosteroids.[2] A typical initial dose is prednisone or prednisolone 1 to 1.5 mg/kg by mouth daily. The onset of response is usually rapid and most patients demonstrate benefit within 10 to 14 days. The initial effective dose of corticosteroid should be continued until a satisfactory response has been obtained, and once there is haematologic stabilisation the dose may be gradually reduced. Many patients will require low-dose maintenance therapy. If symptoms do not respond to tolerable doses of corticosteroids splenectomy should be considered. Immunosuppressants such as azathioprine or cyclophosphamide may be considered in patients refractory to other therapy;

responses are reportedly variable, but they sometimes permit reduction of corticosteroid maintenance doses. There are some reports of benefit from the use of danazol and some cases have responded to rituximab. High-dose intravenous normal immunoglobulin may be used in some patients if the adverse effects of long-term corticosteroid or immunosuppressant therapy are severe. Plasma exchange may be useful for acute management of severe haemolysis while other therapies are taking effect.[2] Transfusion is problematic in these patients because of the difficulty in establishing compatibility between patient and donor.[3] Nonetheless, transfusion may be life-saving in acute disease, and the least incompatible blood should be used.

In patients with cold auto-immune haemolytic anaemias such as cold haemagglutinin disease it is additionally important to keep the patient warm.[2] Corticosteroids and splenectomy are generally of no benefit in these patients (although there may be a responsive subgroup), but treatment with chlorambucil 2 to 4 mg daily by mouth may produce a response. Blood transfusion should be avoided if possible, and if given it should be preferably via a warming coil and infused slowly. Rituximab has also been tried with some success in cold auto-immune haemolytic anaemia.

In paroxysmal nocturnal haemoglobinuria, red cells are more sensitive to complement-mediated lysis because of a deficiency in protective membrane proteins on the cell surface. Haemolysis may be accompanied by neutropenia, thrombocytopenia, and venous thrombosis, and in some patients there may be some overlap with aplastic anaemia, see above. Curative therapy for paroxysmal nocturnal haemoglobinuria is possible with allogeneic haematopoietic stem cell transplantation. More recently, eculizumab has become available; a monoclonal antibody directed at the complement protein C5, it inhibits terminal complement activation to reduce haemolysis and transfusion requirements.[4]

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Iron-deficiency anaemia

For a discussion of iron deficiency anaemia and its management, see under Iron, p.1951.

Megaloblastic anaemia

For a discussion of megaloblastic anaemia and its management, see under Vitamin B_{12}, p.1982.

Normocytic-normochromic anaemia

Anaemias in which red cell size and cellular haemoglobin are not significantly different from normal (normocytic-normochromic anaemias) form a substantial proportion of all cases. Such anaemias are usually secondary to another disease and include:

- anaemia of chronic disorders (associated with chronic infection such as tuberculosis, malignancy, inflammatory disorders such as inflammatory bowel disease, polymyalgia rheumatica, rheumatoid arthritis, and SLE)
- anaemia of renal failure
- anaemia of prematurity
- anaemia associated with endocrine disorders such as hypothyroidism or hypopituitarism
- anaemias associated with primary bone-marrow failure (including aplastic anaemia, above, pure red cell aplasia, marrow fibrosis or infiltration as in myelodysplasia or leukaemia, and marrow failure associated with AIDS).

Iron-deficiency anaemia (p.1951), which is usually classified as microcytic and hypochromic may in fact be neither, particularly in the early stages, and should be differentiated from anaemia of chronic disease. The latter is also accompanied by changes in iron metabolism, notably sequestration of iron in reticuloendothelial cells: plasma iron is low but in contrast to iron deficiency the total iron binding capacity is reduced and serum ferritin is often increased.

The **treatment** of most of these anaemias is essentially that of the underlying disease. Blood transfusion has been given when anaemia is severe. In patients with anaemia of renal failure, which is due at least in part to decreased erythropoietin production by the damaged kidney, regular subcutaneous or intravenous injection of recombinant human erythropoietins (epoetins) can completely reverse the anaemia. Epoetins may also have a role in anaemia of prematurity and some drug-induced anaemias, and have been investigated in patients with the anaemia of chronic disease and some other normocytic-normochromic anaemias.

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Sideroblastic anaemia

The sideroblastic anaemias are characterised by a population of hypochromic red cells in the presence of increased serum-iron concentrations, and abnormal erythroid precursors, known as ring sideroblasts, in the bone marrow. They are associated with abnormalities in porphyrin biosynthesis leading to diminished production of haem, and increased mitochondrial iron uptake. Sideroblastic anaemias may be of various types, and are classified as acquired or hereditary.

Acquired sideroblastic anaemia. Acquired sideroblastic anaemia may either be idiopathic, or secondary to either a drug or toxin (such as alcohol, isoniazid, chloramphenicol, or lead) or to a disease (including hypothyroidism, rheumatoid arthritis, haemolytic or megaloblastic anaemias, leukaemias, and lymphomas). The treatment of the secondary forms is essentially the treatment of the underlying disease or removal of the precipitating cause. The anaemia is usually mild and often macrocytic.

Patients with idiopathic disease usually have only mild anaemia, and most require no treatment. Although rarely suffering from vitamin B_6 deficiency a few patients will respond at least partially to high doses of pyridoxine by mouth, up to 400 mg daily, and a trial is considered worthwhile in all patients. If patients become symptomatic, transfusion may be required, but should be kept to a minimum because of the problems of iron overload. All patients with sideroblastic anaemia must have their serum-iron and -ferritin concentrations regularly monitored, and be given desferrioxamine by regular bolus injection when there is evidence of iron overload. The use of epoetins and granulocyte colony-stimulating factor is under investigation.

Hereditary sideroblastic anaemia. The hereditary forms of the disease appear to be sex-linked, and almost always manifest themselves in males. The anaemia may be more severe than in acquired sideroblastic anaemia, and is usually microcytic.

A trial of pyridoxine is considered worthwhile as some forms are responsive, but in many cases there is no benefit. Some patients develop gradually increasing iron loads, and may eventually develop haemosiderosis; to prevent this, regular venesection or the use of desferrioxamine are indicated if there is evidence of iron accumulation. Allogeneic bone marrow or haematopoietic stem cell transplantation is under investigation.

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Haemoglobinopathies

Haemoglobinopathies are clinical abnormalities due to altered structure, function, or production of haemoglobin. Human haemoglobins are tetramers, constructed of 4 globin chains each enfolding an iron-containing haem moiety: two of these globins are of the 'α-like' types (globins α or ζ) and two are 'non-α' (types β, γ, δ, or ε). The normal major adult haemoglobin, haemoglobin A, comprises two α and two β chains, while the predominant fetal haemoglobin, haemoglobin F (also present in minute amounts in normal adults), is composed of two α and two γ globins. The erythroblast inherits two genes for the production of α globin and one for β globin production from each parent, and a mutation in a single α gene will therefore affect only 25% of the haemoglobin produced, whereas a single β mutation will affect 50%: the β-haemoglobinopathies, due to defective β globin production, are therefore more likely to produce symptoms, and the most widespread forms are the β-thalassaemias and sickle-cell disease, which are discussed below.

Sickle-cell disease

Sickle-cell disease is a haemoglobinopathy (see above) in which a structural abnormality in the β globin chain results in the formation of an abnormal haemoglobin, haemoglobin S. In the deoxygenated state haemoglobin S is less soluble and polymerises into rod-like fibres, and cells containing high concentrations of haemoglobin S subsequently become deformed into a sickle shape. Normal haemoglobins can be incorporated into the polymer but some, such as fetal haemoglobin (haemoglobin F), are not; increasing concentrations of these in the red cell reduce the rate of sickling.

The heterozygous form, sickle-cell trait, is generally asymptomatic except in conditions of extreme anoxia, although characteristic abnormalities of renal function (inadequate concentration of the urine) may be present. As with thalassaemia trait (see below) it is more common in populations of tropical origin, and has been postulated to offer a degree of protection against malaria. In the homozygous form a varying degree of haemolytic anaemia is present, accompanied by increased erythropoiesis. In addition to shortened survival, the decreased flexibility of the deformed erythrocytes can lead to occlusion of the microvasculature, and sickle-cell crisis. The latter may manifest as excruciating pain due to infarction of the blood supply to the bones, or infarction of other organs including lung, liver, kidney, penis (leading to priapism), and brain (stroke). An acute chest syndrome occurs in many patients, and may be fatal. It is a form of acute lung injury associated with infarction, fat embolism, and infection, and may progress to acute respiratory distress syndrome. Occasionally a large proportion of red cell mass may become trapped in the spleen or liver (sequestration crisis) with death due to gross anaemia. Chronic complications include skin ulceration, renal failure, retinal detachment, and increased susceptibility to infection.

Treatment of sickle-cell disease is essentially symptomatic.[1-5] Young children should receive prophylactic penicillin and pneumococcal vaccine, to reduce the risk of infection (see Spleen Disorders, p.194). Infection should be treated early, and folate supplementation given if necessary since the increased erythropoiesis resulting from chronic haemolysis may increase folate requirements.

Sickle-cell crisis requires hospitalisation, with the use of large volumes of intravenous fluids for dehydration, analgesia including opioids for pain (see p.9), and treatment of any concurrent infection. Oxygen should be given if the patient is hypoxaemic. Where crisis affects a vital organ with life-threatening or potentially disabling consequences partial exchange transfusion should be carried out promptly, as no other therapy exists. Where rapid enlargement of spleen or liver indicates a sequestration crisis, transfusion is also important to avoid fatal anaemia.

Maintenance transfusion is rarely indicated, although it may be given to patients who have already had a stroke; measures to avoid iron overload such as phlebotomy or desferrioxamine chelation are necessary in patients receiving regular transfusions. Prophylactic transfusions in children at high risk have been reported[6] to reduce the incidence of first stroke but the risks and benefits of treatment must be carefully considered. A further study[7] investigated whether prophylactic transfusions could be safely stopped after 30 months in children who had not had an overt stroke and who had reverted to low stroke risk. The study was stopped early when it was found that in those who stopped transfusions there was a significant return to high risk and that some patients had subsequently suffered a stroke. Splenectomy may be recommended in the management of recurrent splenic sequestration.

Research into specific therapy for sickling has produced some promising results. Because haemoglobin F is known to protect against sickling, considerable interest has centred on attempts to stimulate fetal haemoglobin production. Most studies have used hydroxycarbamide. Initial trials showed some elevation in mean fetal haemoglobin concentrations, but responses were very variable. However, a subsequent randomised controlled study in 299 patients[8] reported that therapy with hydroxycarbamide caused a 44% reduction in the median annual rate of painful crises. The beneficial effects did not become evident for several months. Observational follow-up of 233 patients in this group,[9] for up to 9 years, suggested that hydroxycarbamide also reduced mortality. Beneficial effects have also been reported in initial studies in children[10-12] and sustained benefits have been reported in longer-term cohort studies.[13,14] Results from a small study[15] in children suggested that hydroxycarbamide, with serial phlebotomy to reduce iron overload, may be an effective replacement for secondary stroke prophylaxis in patients who are unable to continue with long-term maintenance transfusions. Although one study,[14] in which some children had received hydroxycarbamide for up to 8 years, found no evidence of mutagenic changes or cases of malignancy, the potential toxicity of long-term therapy remains a concern. A short-chain fatty acid, butyric acid, which has a low order of toxicity, has been reported to stimulate fetal haemoglobin in patients with sickle-cell disease when given by infusion as arginine butyrate.[16] Promising results have also been reported in small studies[17] using oral sodium phenylbutyrate. Other drugs under investigation include clotrimazole, decitabine, inhaled nitric oxide, and the nonionic surfactant poloxamer 188. There is also some investigation into gene therapy.

As in thalassaemia (see below), bone marrow transplantation is potentially curative in a small minority of patients, but the indications for transplantation are much less well established.[18]

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β-Thalassaemia

β-Thalassaemia is a haemoglobinopathy (above) that is due to a deficiency in β globin production accompanied by normal production of α globin chains that, in the absence of sufficient partner chains, are insoluble and precipitate out in erythrocytes and erythroid precursors as large cellular inclusions. These interfere with red cell maturation resulting in ineffective haematopoiesis, retard the passage of red cells from the bone marrow, and create a tendency for those red cells that do mature to be trapped and destroyed in the spleen. The condition is therefore characterised by a hypochromic, microcytic anaemia accompanied by haemolysis. In the heterozygous form, where only one of the β globin genes is affected (known as thalassaemia trait or thalassaemia minor) the anaemia is mild and clinically insignificant. There is some evidence that patients with this form of the disease experience a degree of protection from malaria, which may account for the more frequent distribution of the trait in the populations of areas such as the Mediterranean, parts of Africa, and Asia.

The more severe forms of the disease (known as thalassaemia intermedia if haemoglobin levels are high enough not to require regular transfusion, or thalassaemia major in transfusion-dependent patients) occur in homozygous patients who inherit a defective β globin gene from both parents. Severe anaemia develops in the first year of life as fetal haemoglobin production (which does not involve a β globin) is replaced by the production of adult haemoglobin. The anaemia stimulates erythropoietin production, and if not corrected massive proliferation of red cell precursors develops within, and eventually beyond, the bone marrow, resulting in recurrent bone fractures, deformity of the skull due to expansion of the marrow spaces, and compression of vital structures such as the spinal cord with consequent paresis. Other symptoms include splenomegaly and hypersplenism (resulting in neutropenia and thrombocytopenia), increased susceptibility to infection, and hypermetabolism which may lead to folate deficiency because of the increased folate requirement. If untreated, death in patients with thalassaemia major usually occurs by the 2nd or 3rd year.

Treatment. The mainstay of treatment for severe β-thalassaemia is regular blood transfusion to correct the anaemia. Transfusions should be started as early as possible in life once it is clear that anaemia is severe enough to warrant them. Various transfusion regimens have been used based on different pretransfusion haemoglobin concentrations.[1] The Thalassaemia International Federation[2] recommends regular blood transfusions, usually every 2 to 5 weeks, to maintain a pretransfusion haemoglobin concentration of 9 to 10.5 g per 100 mL. The post-transfusion concentration should not exceed 15 g per 100 mL. It is also recommended that patients should receive leucocyte-depleted packed red cells in order to minimise adverse reactions and platelet allo-immunisation (an immune response to donor platelets). Washed red cells may be used in patients who have repeated severe allergic transfusion reactions. The use of leucocyte-depleted red cells is also desirable in patients who are candidates for haematopoietic stem cell transplantation to reduce the risk of graft rejection and CMV reactivation.[1] An increase in transfusion requirements is a sign of hypersplenism, and splenectomy may be indicated depending on the state of iron overload. However, splenectomy should be avoided if possible below the age of 5 years because of the increased risk of infection.[2] For a discussion of antibacterial prophylaxis in splenectomised patients, see Spleen Disorders, p.194.

If anaemia is corrected by transfusion, growth and development proceed fairly normally in thalassaemic children. However, because the body lacks a mechanism for the excretion of excess iron, repeated transfusion invariably results in iron overload (p.1442), leading eventually to haemochromatosis. The consequences of haemochromatosis include liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and particularly heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up usually leads to death (mainly through heart failure or arrhythmia) by the time patients reach their mid-20s. The accumulation of iron can be retarded by the chelator desferrioxamine and regular systemic use has been shown to improve survival in thalassaemic children,[2,3] and to protect against the cardiac complications of iron overload.[2-4] The greatest increase in iron excretion may be seen in patients given the drug by continuous subcutaneous infusion rather than intramuscular bolus. Continuous intravenous infusion may be considered in patients with severe iron overload or cardiac complications.[2] There is some suggestion that intensive desferrioxamine therapy can improve impaired organ function,[3] but it is considered preferable to begin chelation therapy as early as possible to try to prevent organ damage developing in the first place. In practice, desferrioxamine therapy is started after the first 10 to 20 transfusions or when the ferritin concentration rises above 1 mg/litre, usually at about 3 years of age.[2,5] If therapy is started before this age, careful monitoring of growth and bone development is recommended[2] and liver biopsy has been advocated.[3] Better iron excretion is achieved if patients are given ascorbic acid 100 to 200 mg daily in addition to desferrioxamine (but see under Interactions for Desferrioxamine, p.1440). Patients with thalassaemia may have increased folate requirements and folate supplementation may also be necessary. Although it is not yet certain how much chelation therapy will prolong survival the fact that a nearly normal iron balance can be achieved long term seems hopeful. Deferiprone has been used as an oral alternative to desferrioxamine,[6] but there are conflicting reports regarding its efficacy and safety in the longer term.[7,8] It may have a role in patients for whom desferrioxamine therapy is unsuitable.[2] Investigation of combination therapy using desferrioxamine with deferiprone is underway, as is the development of other oral chelators.[5]

In addition to the essentially symptomatic treatment of thalassaemia a very few patients may be candidates for bone marrow transplantation where suitable facilities and compatible donors exist; if transplantation is carried out before organ damage is marked, successfully transplanted patients are apparently cured and can lead a normal life.[9,10] Gene therapy is also under investigation.

An alternative approach using hydroxycarbamide in an attempt to stimulate fetal haemoglobin production and 'mop up' some of the excess α globin chains has been tried experimentally but results have been mixed. Results of an initial study in patients given butyric acid (as an arginine butyrate infusion) for the same purpose appeared more promising[11] although a subsequent study failed to show any benefit.[12] Mixed results have also been reported with the use of oral butyrate derivatives such as sodium phenylbutyrate[13] and isobutyramide.[14]

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Haemostasis and Fibrinolysis

Haemostasis is the physiological response that occurs when blood vessels are damaged. It results in coagulation (formation of a blood clot) and thus arrests bleeding. The initial response is the formation of a plug of platelets, which adhere both to the injured tissue and to each other. The vessel injury, with factors released by the platelets, trigger a series of reactions (the coagulation 'cascade') mediated by proteins circulating in the plasma (blood clotting factors). This results in formation of an insoluble fibrin clot that reinforces the initial platelet plug. Regulatory mechanisms come into operation to prevent widespread coagulation. Lysis of the clot (fibrinolysis) then occurs when wound healing and tissue repair are underway.

Platelet aggregation. Platelets usually circulate in plasma in an inactive form. Contact with damaged endothelium causes them to become activated and to adhere to the site of injury. This adhesion is partly mediated by binding of von Willebrand factor, a plasma protein that also acts as a carrier for factor VIII, to a glycoprotein (termed GPIb) on the platelet membrane surface. Substances are secreted by the activated platelets which cause further platelet aggregation (adenosine diphosphate and thromboxane A_2) and vasoconstriction (serotonin and thromboxane A_2). Thromboxane A_2 secreted by platelets is derived from arachidonic acid.

- The enzyme cyclo-oxygenase is required for the synthesis of thromboxane A_2 and this enzyme is inhibited by the **antiplatelet drugs** aspirin and sulfinpyrazone. Aspirin binds irreversibly to the enzyme and therefore the antiplatelet effect lasts for the lifetime of the platelet. Sulfinpyrazone is a reversible inhibitor of the enzyme.

Platelet aggregation involves interaction of fibrinogen with a receptor, glycoprotein IIb/IIIa, on the platelet surface.

- Antiplatelet drugs such as abciximab act by blocking this receptor.

In addition to their action in forming the initial haemostatic plug, platelets are also involved in coagulation by providing a surface on which interactions between clotting factors take place, resulting in more efficient coagulation.

Coagulation. The series of reactions that results in formation of a fibrin clot may be conveniently considered as two pathways, the *intrinsic* pathway (triggered within the blood) and the *extrinsic* pathway (triggered by substances extraneous to the blood). While this distinction is useful for understanding *in-vitro* coagulation and is the basis for tests that are specific for each pathway (see below), the mechanism of *in-vivo* coagulation is not so segregated and factors appearing in one pathway are also necessary for reactions in the other pathway. The intrinsic and extrinsic pathways of coagulation and the *in-vivo* pathways are discussed further below and are represented in summary form in Figure 1, p.1047 and Figure 2, p.1048 respectively. Factors circulate in the blood in an inactive form and are activated by cleavage of peptide bonds. The numerals attached to the factors reflect the order in which they were discovered and not their importance or position in the chain of reaction. The letter 'a' after a factor name or number denotes the activated form. Factors involved in blood coagulation are listed in Table 2, below. Once the coagulation cascade is started, activated factors act in positive feedback mechanisms to amplify the activation steps thus producing rapid coagulation. Cofactors are necessary as they increase the speed of the reactions. Other components necessary for coagulation are calcium ions and a membrane surface. Calcium ions are required for nearly all the reactions. Many of the activation steps, notably those involving factors VII, IX, and X, take place on a membrane surface expressing tissue factor, or platelets. Factors bind to phospholipids on the membrane surface.

The *extrinsic* pathway begins when *tissue factor* (factor III) is released from damaged tissue. This forms a complex with *factor VII* and factor VIIa and directly activates *factor X*. The *intrinsic* pathway begins when blood comes into contact with a negatively charged surface. *Factor XII* interacts with high molecular weight kininogen (Fitzgerald factor) and prekallikrein (Fletcher factor) to produce *kallikrein*, which activates factor XII. The active factor XIIa then activates *factor XI*, which in turn activates *factor IX*. *Factor VIII* is activated by thrombin to factor VIIIa to act as a cofactor for factor IXa, which converts *factor X* to factor Xa. The extrinsic and intrinsic pathways therefore converge with the activation of factor X. *Factor V* is activated by thrombin to factor Va to be a cofactor for factor Xa, which converts prothrombin (*factor II*) to thrombin with the subsequent formation of a *fibrin* gel. *Factor XIII* is also activated by thrombin to factor XIIIa, which stabilises the fibrin gel to form a stable clot.

The dependence of many steps in the coagulation cascade on calcium ions allows coagulation *in vitro* to be blocked by the addition of calcium chelators, such as sodium citrate, to collected blood. When collected blood is tested for coagulation function, addition of calcium ions allows clotting to proceed. Tests of coagulation function include activated partial thromboplastin time (APTT), which is a measure of the activity of the intrinsic system, prothrombin time (PT), a measure of the activity of the extrinsic system, and thrombin clotting time, which measures the conversion of fibrinogen to fibrin.

The factors involved in triggering the *in-vitro intrinsic* pathway, that is prekallikrein, factor XII, and possibly factor XI, are probably not important in *in-vivo* blood coagulation as deficiency of any of these factors is not associated with a serious bleeding disorder. The important step in the clotting cascade *in vivo* is release of *tissue factor* (factor III) from damaged tissue. As has already been mentioned, tissue factor forms a complex with *factor VII* and factor VIIa that activates *factor X*. Factor Xa activates *prothrombin* resulting in formation of a *fibrin clot* which occurs as described above under the *in-vitro* systems. To enhance coagulation, various positive feedback mechanisms and other clotting factors operate to increase production of activated factors VII and X. For example, formation of factor VIIa is amplified by factor VIIa itself and by factor Xa. Formation of factor Xa is amplified by factor IXa produced by the action of thrombin on factor XI.

Regulation of coagulation. The process of blood coagulation is regulated to ensure that it remains localised at the site of injury and does not result in more widespread clotting. This is achieved by dilution of clotting factors in flowing blood, by rapid hepatic clearance of many activated factors or products, and by natural anticoagulant mechanisms, which include antithrombin III, protein C, and protein S (see Figure 2). *Antithrombin III* inhibits the serine protease clotting factors, that is, thrombin, IXa, Xa, XIa, and XIIa. Antithrombin III is activated by binding to glycosaminoglycans, such as heparan glycosaminoglycan and dermatan sulfate, present in vascular endothelium.

- Heparin and low-molecular-weight heparins act as **anticoagulants** by binding antithrombin III at a specific binding site and enhancing its inhibitory effect on the serine protease clotting factors. At therapeutic doses of heparin the factors inhibited are thrombin and factor Xa. Low-dose heparin, such as that given for the prophylaxis of thromboembolism, inhibits factor Xa. Very high doses of heparin have a direct inhibitory effect on antithrombin III. Heparinoids which lack the specific binding site for antithrombin III do not have the anticoagulant properties of heparin. Low-molecular-weight heparins have a higher ratio of anti-factor-Xa to antithrombin activity than heparin and therefore mainly inhibit factor Xa.

Proteins C and S are both vitamin K-dependent plasma proteins. Protein C circulates in plasma in an inactive form. It is activated by contact with thrombin that is bound to thrombomodulin, a receptor located on the surface of endothelial cells. Activated protein C inhibits factors Va and VIIIa and therefore slows blood clotting. Protein S acts as a cofactor in this inhibition.

Vitamin K is essential for the activities of factors II, VII, IX, and X. It is also essential for the activity of proteins C and S. These factors contain glutamic acid residues that undergo carboxylation in the liver, a reaction requiring reduced vitamin K as a cofactor. This carboxylation step allows the factors to bind calcium, a reaction necessary for their function in the clotting cascade.

- Deficiency of vitamin K or the use of **oral anticoagulants** (which are vitamin K antagonists) therefore impairs the function of these clotting factors. Oral anticoagulants have no effect on circulating clotting factors and thus the time required before the anticoagulant effect is seen depends on the individual clearance rate of the factor.

Fibrinolysis is the mechanism of clot dissolution. It is mediated by *plasminogen*, which circulates in plasma in an inactive form; conversion to its active form, *plasmin*, occurs when plasminogen binds to fibrin in the presence of a *plasminogen activator* (see Figure 2). Plasmin, a *proteolytic enzyme*, digests fibrin clots and hydrolyses other proteins, including factors II, V, VIII, and XII. As fibrin is lysed, plasmin is released which is inhibited by α_2-antiplasmin to prevent a systemic lytic state developing. There are two types of plasminogen activator, *tissue plasminogen activator* (tPA), which originates from the endothelium, and *urokinase*, which

Table 2. Proteins involved in blood coagulation and in fibrinolysis.

	Proteins	Synonyms
Blood coagulation	Factor I	Fibrinogen
	Factor II*	Prothrombin
	Factor III	Tissue thromboplastin; tissue factor
	Factor IV	Calcium ion
	Factor V	Ac-globulin; labile factor; proaccelerin
	Factor VI (unassigned)	
	Factor VII*	Proconvertin; SPCA; stable factor
	Factor VIII	Antihaemophilic factor; AHF
	Factor IX*	Christmas factor; plasma thromboplastin component; PTC
	Factor X*	Stuart factor; Stuart-Prower factor
	Factor XI	Plasma thromboplastin antecedent; PTA
	Factor XII	Hageman factor
	Factor XIII	Fibrin stabilising factor; FSF
	von Willebrand factor	Factor VIII-related antigen; vWF
	High molecular weight kininogen	HMWK; Fitzgerald factor
	Prekallikrein	Fletcher factor
Fibrinolysis	Plasminogen	
	Prourokinase	
	Tissue plasminogen activator	tPA
	Antithrombin III	Major antithrombin; AT-III; Heparin cofactor
	Protein C*	Autoprothrombin IIA; Factor XIV
	Protein S*	
	α_2-Antiplasmin	

* denotes vitamin K-dependent factor

Figure 1. Simplified representation of in-vitro coagulation.

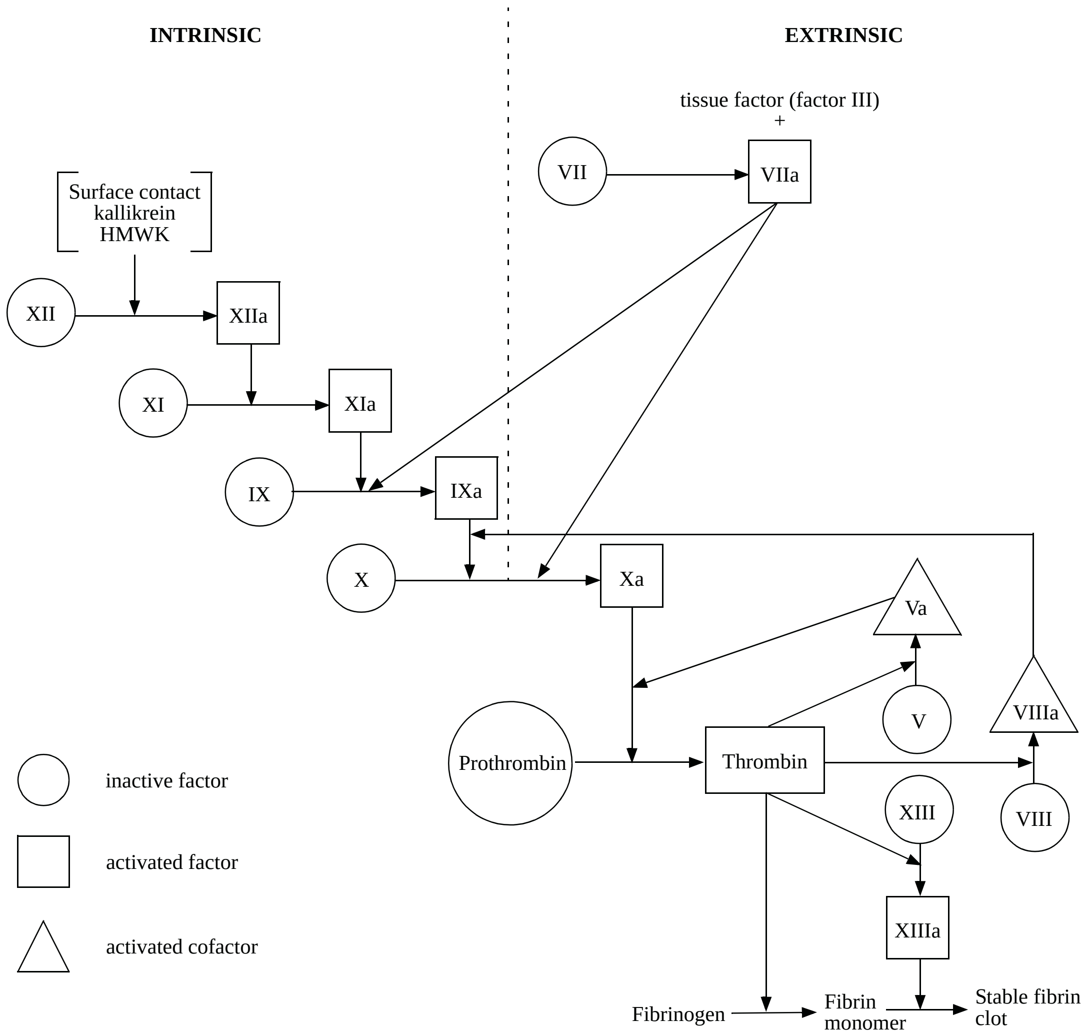

is activated from prourokinase. Activators of prourokinase include plasmin. Tissue plasminogen activator binds to fibrin and thus activates plasminogen bound to fibrin much more rapidly than circulating plasminogen; therefore the fibrinolytic action of tissue plasminogen activator is fibrin specific. Urokinase does not bind to fibrin, and therefore its fibrinolytic action is not fibrin specific, although it is activated by plasmin that is bound to fibrin. *In vivo*, fibrinolysis is almost entirely due to the activity of tissue plasminogen activator.

- The two types of plasminogen activator with their different modes of action provide the basis for the specificity of **thrombolytics** (the so-called 'clot specific' effect), which act by promoting the conversion of plasminogen to plasmin. The tissue plasminogen activators alteplase and tenecteplase are fibrin-specific thrombolytics, and streptokinase and urokinase are fibrin-nonspecific.
- The **antifibrinolytic drugs** aminocaproic acid and tranexamic acid act primarily by blocking the binding of plasminogen and plasmin to fibrin, thereby preventing the breakdown of fibrin clots.
- Aprotinin, an inhibitor of proteolytic enzymes, acts as a **haemostatic** by inhibiting the action of plasmin and therefore preventing the breakdown of fibrin clots. Other drugs acting as haemostatics include batroxobin, which is reported to promote the production of fibrin from fibrinogen, and etamsylate, which has a stabilising effect on the capillary wall. Drugs such as oxidised cellulose, calcium alginate, collagen, and gelatin act by providing a physical meshwork within which clotting can occur. Adrenaline, adrenalone, and noradrenaline produce haemostasis by causing vasoconstriction. Drugs with astringent properties such as alum and ferric chloride are also used for haemostasis.

The use of haemostatics may be considered when bleeding cannot be controlled by direct measures such as the application of pressure, suture or ligation, or electrocoagulation.

Dysfunction of the haemostatic mechanisms or the systems regulating haemostasis produces haemorrhagic disorders (acquired and inherited, see below) or thromboembolic (p.1187) disorders.

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Acquired haemorrhagic disorders

Bleeding disorders sometimes arise due to disturbances in either clotting factors or platelets, or to vascular wall defects occurring as a result of a disease or a medical or surgical procedure. Disturbances and defects may also be drug-induced. In some conditions, including renal and liver disease, cardiopulmonary bypass procedures, or following massive blood transfusion, disturbances in many of the homoeostatic mechanisms occur simultaneously producing complex haemorrhagic disorders, sometimes referred to as complex acquired coagulopathies.

One of the commoner causes of haemorrhagic disorder caused by *disturbance of clotting factors* is overdose with heparin, oral anticoagulants, or thrombolytics. Different approaches are used in the management of overdose with these drugs, as discussed in Treatment of Adverse Effects under Heparin (p.1302), Warfarin Sodium (p.1426), and Streptokinase (p.1404).

Deficiencies in clotting factors may occur in several diseases. Vitamin K is essential for the activity of a number of clotting factors and plasma proteins (see Haemostasis and Fibrinolysis, above), and disorders that cause a deficiency of vitamin K can lead to impairment of these. Diseases of the small bowel and biliary tract can impair absorption of vitamin K, and liver disease reduces the production of clotting factors. Deficiency is generally treated by giving vitamin K, although this is not always effective in patients with liver diseases. Vitamin K is widely used for the prevention and treatment of neonatal vitamin K deficiency bleeding (p.1997). Examples of other acquired disorders that affect clotting factors but occur rarely include acquired haemophilia affecting factor VIII (see Haemophilias, below) and von Willebrand syndrome (see von Willebrand's Disease, below).

Low platelet concentrations can be associated with many other illnesses and increase the risk of bleeding; management is discussed in Thrombocytopenia, below.

Various drugs are used, or are under investigation, for their effect on *perioperative blood loss*.[1,2] Topical treatments such as fibrin glue, gelatin-based films and sponges, oxidised cellulose, and thrombin are used for a local haemostatic effect in surgical procedures. The antifibrinolytic drugs aprotinin, aminocaproic acid, and tranexamic acid are used to reduce bleeding and transfusion requirements in procedures such as liver transplantation and cardiac sur-

Figure 2. Simplified representation of *in-vivo* coagulation and fibrinolysis

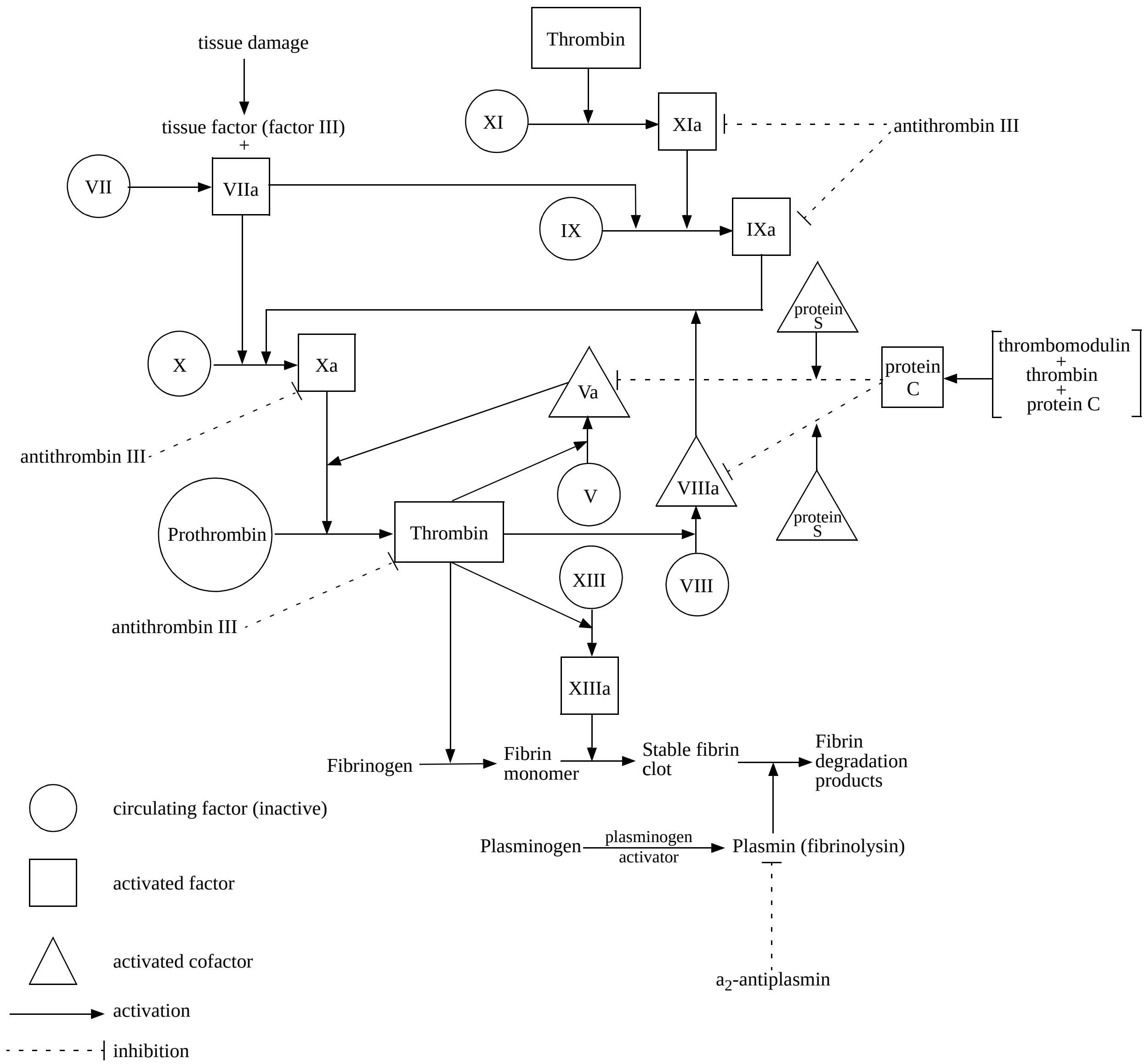

gery involving cardiopulmonary bypass. Desmopressin is used in surgical patients with some congenital and acquired bleeding disorders, but in patients without pre-existing bleeding disorders it has not consistently been shown to be of benefit. Recombinant activated factor VII (eptacog alfa) is used in the management of bleeding in patients with haemophilia, but it is also under investigation in surgical patients with normal haemostasis.

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Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is an acute or chronic syndrome resulting from an underlying condition that causes pathological stimulation of coagulation at some point in the coagulation pathway (above); thrombin generation triggered by uncontrolled tissue factor is probably the main factor in most cases. Causes include obstetric emergencies (placental abruption, amniotic fluid embolism), infection (bacterial septicaemia, viraemia), neoplasms, trauma (head injury, burns), venomous snake bites, transfusion of incompatible blood, liver disease, and various vascular causes.

Stimulation of coagulation leads to microvascular thrombosis that produces widespread tissue ischaemia and may lead to ischaemia of major organs. Simultaneously, secondary activation of the fibrinolytic system and consumption of coagulation factors produces bleeding, which is often the predominant manifestation. Symptoms are therefore very variable and include those of bleeding, such as spontaneous bruising, prolonged bleeding from intravenous puncture sites, and gastrointestinal and pulmonary haemorrhage, and those of thrombosis, such as acute renal failure, venous thromboembolism, skin necrosis, liver failure, cerebral infarction, acute respiratory distress, and coma. Some cases may be asymptomatic.

Treatment of DIC is aimed primarily at the underlying cause since the condition will not resolve until the underlying trigger is removed. Recovery is often fairly rapid once treatment is started. Supportive therapy to ensure adequate hydration and tissue oxygenation is also vital. These measures may be sufficient in patients with asymptomatic DIC. Most patients with symptomatic DIC also require therapy with plasma and platelets to replace coagulation factors and arrest bleeding. Coagulation factor concentrates such as fibrinogen concentrate or cryoprecipitate are not favoured, as they do not contain all coagulation factors and they may be contaminated with traces of activated coagulation factors, which can exacerbate the coagulation disorder in these patients. Heparin has been used in the management of DIC with the aim of switching off the coagulatory mechanisms. Although benefit has been shown with some underlying causes, heparin may worsen bleeding and its use in DIC is considered by some to be controversial. Where the risk of bleeding is relatively minor and thrombosis predominates, heparin may be appropriate. Other measures that have been tried in limited numbers of patients include use of a low-molecular-weight heparin. Concentrates of activated protein C, and more recently the recombinant form drotrecogin alfa (activated), have been used in DIC associated with severe sepsis and have improved coagulation abnormalities and mortality. Antithrombin III has also been used, but despite beneficial reports of use in sepsis-related DIC a large study found no benefit.

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Haemophilias

The haemophilias are bleeding disorders caused by low concentrations of specific coagulation factors. Acquired haemophilia is rare and most patients have inherited forms. The most well known are haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency). Factor XI deficiency, originally called haemophilia C, is mentioned under Inherited Haemorrhagic Disorders, below.

Haemophilia A (classical haemophilia, factor VIII deficiency) is the most common of the serious hereditary bleeding disorders.[1] It is an X-linked recessive disorder and therefore, with rare exceptions, males are affected and females are carriers. The condition is due to deficiency of factor VIII and severity of bleeding is related to the residual factor level. The condition is severe when there is less than 1% of normal factor VIII activity, moderate when the factor VIII concentration is 1 to 5% of normal, and mild when the factor concentration is greater than 5%. Clots are slow to form and break up easily, and bleeding after trauma or surgery may be prolonged. In moderate and severe haemophilia A bleeding may occur into major joints producing long-term joint destruction, a major cause of morbidity in haemophilia. Other frequent sites of bleeding are large muscles, and renal and intestinal tracts. CNS haemorrhage may also occur, especially after trauma.

Treatment of bleeding episodes depends on the severity of the haemophilia.[1-4] Patients with moderate to mild haemophilia A can be satisfactorily treated with desmopressin,[5,6] which produces an increase in factor VIII and von Willebrand factor, and increases platelet adhesion and expression of tissue factor. Desmopressin also transiently stimulates plasma fibrinolytic activity, and it has been suggested that use with an antifibrinolytic, such as tranexamic acid, may inhibit this effect. However, there is no evidence for haemostatic improvement with this combination, although tranexamic acid itself is effective in the management of mucosal bleeding and during dental surgery.[5] Desmopressin is usually given intravenously. The subcutaneous route is an alternative but the maximum effect is slower. It can also be given intranasally, and this route is used by patients to treat themselves outside hospital. In patients with more severe haemophilia A, desmopressin is ineffective and treatment of bleeding episodes requires replacement of factor VIII. The amount given depends on the severity of bleeding.

Desmopressin and factor VIII preparations are also used for the *prevention of bleeding episodes* in situations where haemorrhage may be anticipated, for example before surgery or dental treatment;[7,8] patients with haemophilia A should also not be given intramuscular injections (because of potential muscle damage and bleeding into muscle) unless they are given during a period when the patient is covered by replacement factor. Prophylactic cover with an antifibrinolytic, such as tranexamic acid given orally (or, in dentistry, also topically as a mouthwash), may also be used and should be continued for 5 to 7 days after the procedure. Fibrin glue can also be useful in the control of local bleeding.[8]

An alternative method of management has been practised in Sweden since 1958 where *continuous prophylaxis* with factor VIII is given to patients with severe haemophilia A with the aim of preventing arthropathy. Therapy is started at 1 to 2 years of age and the factor VIII concentration is maintained at a level of at least 1% of normal. Patients who began receiving prophylaxis before the age of 2 have had almost no bleeding episodes and joints have remained normal for up to 16 years of follow-up.[9,10] This approach has subsequently been adopted in a number of other countries, although questions remain about the best age at which to start therapy, when to stop, the optimum dose, and effects on quality of life.[1,2,11]

There are various factor VIII preparations available that vary in activity and source.[4] Most products were previously derived from pooled donor plasma and were associated with transmission of viruses including HIV (leading to the subsequent development of AIDS), hepatitis B, and other hepatitis viruses. The introduction of products treated with heat or chemicals, and efforts to screen the donor material from which factor VIII is obtained, seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses such as human parvovirus B19 and hepatitis A may still be transmitted. It is recommended that patients not already immune should be vaccinated against hepatitis A and B. There is some concern that variant Creutzfeldt-Jakob disease (vCJD) may be transmitted by plasma-derived clotting factor products, but there is no proof as yet that this has occurred. Factor VIII produced by recombinant DNA technology may avoid the dangers of possible viral transmission and is therefore the factor VIII preparation of choice (but see also Transmission of Infections under Factor VIII, p.1067). It has been suggested that high-purity plasma-derived factor VIII preparations slow the decline in CD4 count in haemophiliac patients who are HIV-positive, but this was based on the measurement of surrogate markers and the purity of clotting factor preparations has been found not to affect the development of AIDS. Factor VIII preparations are usually given by bolus injection, but there is increasing interest in the use of continuous infusion[2,11] because it can maintain a steady state of clotting factor concentrations and reduce the amount of concentrate used. Evidence from controlled studies is needed to confirm the perceived benefits of this method.

A serious complication of replacement therapy in haemophilia A is the development of *antibodies to factor VIII* (often called inhibitors). The reported incidence varies widely, up to about 30%. Antibodies are more likely to develop in young patients with severe haemophilia who receive continuous prophylaxis, but can also arise in patients with mild haemophilia, typically after intensive replacement therapy; some patients appear to have a genetic predisposition.[12] Antibody concentrations can be measured and may be classified as either low-titre or high-titre; patients are further described as low or high responders according to the increase in antibody production when given factor VIII.[13]

The management of acute bleeding episodes can be problematic in these patients, and depends on the characteristics of the antibodies.[12-14] Patients with low-titre low-responding antibodies are generally treated with high-dose factor VIII. Porcine factor VIII may be useful in high-titre or highly-responding patients at least in the short term, although with longer use antibodies to the porcine material can develop in turn. Otherwise, when high-titre highly-responding antibodies are present, bleeding episodes are managed with factor VIII inhibitor bypassing fraction, or recombinant factor VIIa, which bypass the factor VIII-dependent step in the coagulation cascade. The removal of antibodies by plasmapheresis, with or without extracorporeal immunoadsorption, followed by high-dose factor VIII, has been used in high-titre patients when other measures have failed.[14]

Attempts have been made to induce tolerance and eradicate the antibodies.[12,13,15] Regimens have used regular doses of factor VIII over prolonged periods, sometimes with immunosuppression by cyclophosphamide, immunomodulation by normal immunoglobulin, or extracorporeal immunoadsorption. The treatment of bleeding episodes during immune tolerance induction therapy can be difficult, requiring the use of factor VIII inhibitor bypassing fraction or recombinant factor VIIa.

A future development that may provide a clinical cure for haemophilia is *gene therapy*.[1,16] However, despite successful treatment in *animal* models, initial human trials for haemophilia A and B have shown no sustained responses.

Haemophilia B (factor IX deficiency; Christmas disease) is less common than haemophilia A. The classification and clinical features of this form are the same as for haemophilia A, but are related to a deficiency of factor IX. Treatment follows the same principles as for haemophilia A,[1-4] except that desmopressin does not affect factor IX concentrations and is therefore ineffective in haemophilia B. Bleeding episodes are treated with factor IX replacement, preferably using recombinant factor IX or plasma-derived highly purified factor IX preparations that do not contain other clotting factors. Low-purity factor IX preparations derived from plasma that contain other clotting factors in addition to factor IX (prothrombin complex concentrates) are associated with thromboembolic complications, particularly in patients with liver disease and others at increased risk of thromboembolism or disseminated intravascular coagulation. Fresh frozen plasma may be used in emergencies if specific factor IX products are unavailable. Antifibrinolytic drugs may be used in patients treated with purified factor IX preparations, but should be avoided in those given prothrombin complex concentrates because of the increased risk of thrombosis.[3] Continuous prophylaxis using factor IX preparations has also been used in haemophilia B.[9,10] As in patients with haemophilia A, vaccination against hepatitis A and hepatitis B is recommended for all haemophiliacs not already immune.

Antibody inhibitors of factor IX can be produced although the incidence of antibody formation is lower than that seen in haemophilia A. Acute bleeding episodes in these patients may be managed using recombinant factor VIIa.[1] Induction of tolerance has also been used for antibodies in haemophilia B, but the response is not as good as for haemophilia A and these patients appear to be at risk of anaphylaxis and nephrotic syndrome.[1,12]

As mentioned under haemophilia A, gene therapy is under investigation as a possible clinical cure.

Acquired haemophilia is a rare disease in which autoantibodies form against factor VIII.[17] In about 50% of cases, factor VIII autoantibodies are idiopathic; the rest are associated with other conditions including the postpartum period, malignancies, auto-immune diseases, and adverse drug reactions. The bleeding pattern is different to congenital haemophilia and usually occurs as bleeding in the skin or muscles, haematuria, haematemesis or melaena, and prolonged postpartum or postoperative bleeding; haemarthroses are relatively uncommon.

Treatment for acute episodes depends on the severity of bleeding and the antibody titre. Desmopressin is only effective in patients with low inhibitor titres. Large doses of plasma-derived or recombinant factor VIII may be effective, but the dose required to saturate the autoantibodies can be difficult to predict and therapy must be closely monitored to adjust dosage according to factor VIII concentrations. The use of porcine factor VIII concentrate is an alternative. A small number of patients have been managed with factor VIII inhibitor bypassing fraction or recombinant factor VIIa, and these may be used when the titre is very high or bleeding persists despite the use of factor VIII concentrates.

Up to a third of patients with acquired haemophilia have a spontaneous resolution of their autoantibodies. For other patients, treatment to eradicate or suppress the autoantibodies is often based on a corticosteroid, such as prednisone, given alone or combined with cyclophosphamide; evidence for the efficacy of such treatment is largely anecdotal however. Other combinations that have also been tried include a corticosteroid with azathioprine, or a corticosteroid with cyclophosphamide plus vincristine. Ciclosporin, alone or with a corticosteroid, has been used as a salvage therapy. Intravenous immunoglobulin has been tried, but any benefit is questionable. Similarly, plasmapheresis and immunoadsorption have been used, but their contribution to the success of treatment is difficult to assess because they are usually combined with immunosuppressive drug therapy. Factor VIII immune tolerance regimens are rarely, if ever, used in acquired haemophilia.

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Inherited haemorrhagic disorders

Inherited disorders that lead to abnormal bleeding include platelet disorders and disturbances in clotting factors.

Inherited platelet disorders can affect platelet function, size, and number. Platelet function disorders include abnormalities in platelet receptors (such as Glanzmann's thrombasthenia), platelet granules (storage pool deficiencies), signal transduction pathways and granule release, and membrane phospholipids.[1,2] Treatment depends on the disorder, but in some conditions desmopressin or platelet transfusions are useful in the management of bleeding.[1] Inherited thrombocytopenias are discussed under Thrombocytopenia, below.

Inherited disorders that result in deficiencies or abnormalities of clotting factors can cause variable degrees of bleeding. The most common inherited disorders of clotting factors are haemophilias A and B (above) and von Willebrand disease (below). Other inherited disorders are rare[3] but include abnormalities of fibrinogen, deficiencies of the individual factors II, V, VII, X, XI (haemophilia C), XIII, and combined deficiencies of factors V and VIII, or of factors II, VII, IX, and X. Management depends on the clotting factors affected and the degree or risk of bleeding. In general, antifibrinolytics such as tranexamic acid may be adequate for control of mucosal bleeding and menorrhagia, and fibrin glue may be useful for local haemostasis. Severe bleeding requires the replacement of clotting factors, preferably using specific factor concentrates or recombinant factor products; fresh frozen plasma may be a suitable alternative when more specific products are not available. Vitamin K treatment may be considered in patients with deficiencies of vitamin K-dependent clotting factors (II, VII, IX, and X).

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Neonatal intraventricular haemorrhage

Intraventricular haemorrhage, also referred to as periventricular or periventricular-intraventricular haemorrhage, is bleeding from vessels in or around the ventricles of the brain. It is the major cause of death in very low birth-weight neonates and can affect up to 60% of neonates weighing less than 1500 g. Intraventricular haemorrhage is rare in neonates over 32 weeks of gestation, since the vessels that bleed involute early in the third trimester. Intraventricular haemorrhage usually develops within the first 3 days of life. The haemorrhage may be graded from 1 to 4 according to severity, the higher numbered grades being the most severe and most likely to produce the long-term consequences of impaired motor and mental function. The aetiology is probably multifactorial and may include fluctuations in cerebral blood flow due to failure of autoregulatory mechanisms and tissue damage caused by oxygen free-radicals.

Once intraventricular haemorrhage has occurred **treatment** is supportive and includes correction of anaemia, hypotension, and acidaemia, and management of raised intracranial pressure.

As intraventricular haemorrhage is a major risk factor for impaired motor and mental development **prevention** is very important. Numerous interventions aim to reduce its incidence and include prevention of premature births, avoidance of hypercapnia, correction of major haemodynamic disturbances, and correction of coagulation abnormalities. Various drugs have also been tried including corticosteroids, etamsylate, indometacin, pancuronium, phenobarbital, vitamin E, and vitamin K. Some of these drugs have been given to the mother antenatally since the development of intraventricular haemorrhage may be related to perinatal events.

• Giving corticosteroids to pregnant women at risk of preterm delivery is recommended to prevent neonatal respiratory distress syndrome (p.1508) and may also reduce the incidence of intraventricular haemorrhage.[1] A review of data from 12 controlled studies involving antenatal corticosteroid use (primarily to prevent respiratory distress syndrome)[2] suggested that the risk of intraventricular haemorrhage was also reduced but this was based on limited data. Further studies[3-6] have supported this finding, although few have involved randomised doses of corticosteroids. The mechanism for the beneficial effect of corticosteroids is not clear but avoidance of neonatal hypotension has been suggested.[3]

• Etamsylate limits capillary bleeding through its action on hyaluronic acid and initial studies showed a reduction in intraventricular haemorrhage. A subsequent study[7] showed little evidence of benefit on short-term follow-up, although confidence intervals were wide. Follow-up[8] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Follow-up of another study[9] also found that despite a reported reduction in intraventricular haemorrhage with etamsylate, developmental outcome assessments at about 4 years of age showed that it had not reduced cerebral palsy compared with the control group.

• Indometacin may reduce cerebral blood flow as a result of vasoconstriction, reduce oxygen free-radical damage, and accelerate maturation of blood vessels around the ventricles. Early studies produced conflicting results but a later larger multicentre study[10] showed a reduction in both incidence and severity although there was an unusually large number of neonates with severe intraventricular haemorrhage in the control group.[11] A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps.[11] However, follow-up of the infants included in the multicentre study at the ages of 3 years,[12] 4.5 years,[13] and 8 years,[14] reported no adverse effects on cognitive or motor development. Further analysis of the data from this cohort has suggested that indometacin may reduce intraventricular haemorrhage in boys but have little effect in girls;[15] a true difference in effect between the sexes remains to be confirmed however. Another large multicentre study[16] also found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[17] concluded that although indometacin prophylaxis reduced the rate of severe intraventricular haemorrhage, it did not improve the rate of survival free of neurosensory disability.

• Neuromuscular blockers, such as pancuronium, abolish non-synchronous respiration and therefore stabilise both cerebral and arterial blood flow velocity and some studies have shown a reduction in intraventricular haemorrhage in mechanically ventilated neonates (see Intensive Care, p.1901). However, other studies have produced conflicting results and routine use in all ventilated neonates is not recommended.

• Phenobarbital was also suggested to act by stabilising fluctuations in cerebral blood flow, and studies of use in neonates show similarly inconsistent results with many showing no benefit. A meta-analysis[18] concluded that postnatal phenobarbital could not be recommended as prophylaxis, and was associated with an increased need for mechanical ventilation. Initial studies of antenatal phenobarbital were more promising with a decrease in severity of haemorrhage being reported.[19] However, a larger randomised study[20] in 610 women failed to show any effect of antenatal phenobarbital on incidence or severity of intraventricular haemorrhage. An assessment of surviving infants who could be traced at about 20 months of age also found that antenatal phenobarbital had no apparent effect on neurodevelopmental outcome.[21] A concern with the use of phenobarbital in the perinatal period is that it may lower Apgar scores and produce respiratory depression. A meta-analysis[22] did not support the maternal use of phenobarbital.

• Vitamin E protects polyunsaturated fatty acids, and thus membranes, from oxidation. As oxygen free-radical damage may contribute to the development of intraventricular haemorrhage, vitamin E may have a role in its prevention. Results have been conflicting. A systematic review[23] of studies in preterm infants (gestational age less than 37 weeks or birth-weight less than 2500 g) found that vitamin E reduced the risk of intraventricular haemorrhage overall, but only reduced the risk of severe haemorrhage in surviving very low birth-weight infants (less than 1000 g). There was also a suggestion that intravenous vitamin E may have no effect compared with other dosage routes. However, the strength of these findings is limited and there was an increased risk of sepsis associated with vitamin E use, such that the role of supplementation with this vitamin has not been established in preterm infants.

• The activity of vitamin K-dependent coagulation factors is reduced in neonates and antenatal vitamin K in mothers has been tried as a means of preventing intraventricular haemorrhage. However, results of studies have not been promising. Most trials have been too small to produce conclusive results and a larger randomised controlled study[24] in 139 mothers failed to find any benefit from vitamin K prophylaxis. A subsequent systematic review[25] of 5 trials, including this one, also concluded that antenatal vitamin K use did not prevent intraventricular haemorrhage in preterm infants.

Plasma volume expansion using fresh frozen plasma or a plasma substitute has also been thought to reduce intraventricular haemorrhage by stabilising the circulation, but a prospective multicentre study found no evidence of reduction in haemorrhage[26] or subsequent death and disability[27] after the use of plasma or gelatin as volume expanders.

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Thrombocytopenia

Platelet concentrations in healthy individuals range from 150×10^9 cells/litre to 450×10^9 cells/litre, and thrombocytopenia is often **defined** as a reduction in the number of circulating platelets to less than 150×10^9 cells/litre (150 000 cells/mm^3). As the platelet count falls the risk of bleeding increases, although spontaneous bleeding is uncommon unless the count falls below 10×10^9 cells/litre to 20×10^9 cells/litre, or there is an abnormality in platelet function. Thrombocytopenia can result from decreased production, increased destruction, or abnormal splenic sequestration of platelets.

There are a number of **congenital forms** of thrombocytopenia that can affect platelet size, number, and function. They range across a wide clinical spectrum from mild forms, which may only be discovered incidentally and do not require specific treatment, to severe forms that are associated with a high risk of bleeding and may ultimately require haematopoietic stem cell transplantation.[1]

Secondary thrombocytopenia can be associated with many other illnesses.[2] Decreased platelet production may occur in bone marrow diseases such as leukaemias and aplastic anaemia, some viral illnesses, chronic alcohol toxicity, and liver disease. Increased destruction of platelets occurs in many disorders including idiopathic thrombocytopenic purpura (p.1505), sepsis, disseminated intravascular coagulation (above), and thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p.1076). Gestational thrombocytopenia[3] is a mild form that usually occurs in late pregnancy, in which platelet concentrations return to normal within 12 weeks after delivery. More severe thrombocytopenia may be caused by obstetric conditions including pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. Neonatal thrombocytopenia[4] that is mild and of early onset (in the first 72 hours of life) may be secondary to placental insufficiency and reduced platelet production. More severe thrombocytopenia of later onset may result from platelet destruction associated with sepsis or necrotising enterocolitis. In neonatal allo-immune thrombocytopenia, maternal antibodies against fetal platelet antigens cross the placenta to cause disease ranging from mild self-limiting thrombocytopenia to neonatal intracranial haemorrhage. In neonatal auto-immune thrombocytopenia there is placental transfer of maternal platelet autoantibodies in mothers with conditions such as idiopathic thrombocytopenic purpura or SLE.

Drug-induced thrombocytopenia has been reported with many drugs.[5-9] Decreased platelet production can be caused by drugs that have a toxic effect on bone marrow, including many antineoplastics. Drugs that are often implicated in immune-mediated platelet destruction include anticonvulsants, cinchona alkaloid derivatives (quinine, quinidine), diuretics, disease-modifying antirheumatic drugs (penicillamine, gold salts), NSAIDs, and sulfonamides. The 2 types of heparin-induced thrombocytopenia have been well documented (see p.1302).

Treatment of thrombocytopenia is based on management of the underlying disorder where appropriate, or stopping the offending drug. Platelet infusions are used in the treatment of active bleeding or in thrombocytopenic patients who are at risk of bleeding. They should not be used when there is a thrombotic process such as in thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia. The platelet count at which infusion may be considered depends on various factors including the cause of thrombocytopenia, the presence of additional risk factors such as sepsis, the degree of bleeding, and whether the risk is related to surgery. For example, if there is active bleeding or invasive procedures are contemplated, platelet infusion may be used when the count is less than 50×10^9 cells/litre. In patients with no bleeding and no additional risk factors, a lower threshold of 5×10^9 cells/litre may be adequate.[2,10] Patients requiring long-term treatment may develop antibodies to HLA with repeated transfusions from random donors, which results in impaired responsiveness to subsequent transfusion; these patients should receive platelets obtained from a single donor for each transfusion, preferably HLA-matched.[2,10] In platelet refractoriness, when thrombocytopenia is a result of non-immune platelet destruction, treatment is problematic and although prophylactic platelet infusions may be given, it is not known whether this is effective.[10]

Oprelvekin (recombinant human interleukin-11) is a platelet growth factor that has recently been introduced for the prevention of severe antineoplastic-induced thrombocytopenia. Recombinant human thrombopoietin and the non-peptide thrombopoietin receptor agonist, eltrombopag, are also under investigation.

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von Willebrand's disease

von Willebrand's disease (vWD)[1,2] is a congenital bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor (vWF), a plasma protein that stimulates platelet aggregation and acts as a carrier for factor VIII to protect it from premature destruction. There is also a secondary deficiency of factor VIII, because of its dependence on vWF. There are 3 main phenotypes of vWD:

- type 1 is the most common and is characterised by mild to moderate deficiencies of vWF and factor VIII
- type 2 results in qualitative abnormalities of vWF, and is further divided into subtypes according to the defect
- type 3 is rare but is a severe bleeding disorder due to very low or undetectable plasma levels of vWF, with low but usually detectable concentrations of factor VIII.

The clinical presentation of vWD includes easy bruising and bleeding from mucosal surfaces, such as epistaxis; severely affected patients may suffer spontaneous soft-tissue bleeding resulting in haematomas and haemarthroses. Excessive and prolonged bleeding can occur after surgery, and women may experience excessive bleeding during menstruation and childbirth.[1,2]

Patients are usually only treated at the time of spontaneous bleeding or given prophylaxis before invasive procedures. Desmopressin transiently increases both vWF and factor VIII levels and is used in patients with type 1 disease. It is less likely to be effective in type 2 disease where vWF is dysfunctional, and it is generally contra-indicated in type 2B disease because the abnormal vWF that is released may induce platelet aggregation and thrombocytopenia. Type 3 disease does not respond to desmopressin because of the lack of vWF stores.[1,2]

Plasma concentrates that contain both vWF and factor VIII are used when desmopressin is not suitable. A concentrate that contains highly purified vWF, with very little factor VIII, is available in some countries. Very highly purified factor VIII preparations, or recombinant forms, should not be used; they do not contain appreciable amounts of vWF so the factor VIII therefore has a very short half-life, making it ineffective (but see also below, about the management of patients with alloantibodies). When haemorrhage is not controlled despite adequate factor VIII levels, platelet concentrates may be required.[1,2] Cryoprecipitate may be used as a source of clotting factors and vWF when other measures have failed, but it does not consistently correct bleeding time and has a higher risk of transfusion-transmitted infection.[2]

Some patients with type 3 disease who have received multiple transfusions develop alloantibodies that inactivate vWF and form circulating immune complexes. Further use of concentrates that contain vWF is contra-indicated because of the risk of anaphylaxis. There are a few reports of successful control of surgical bleeding in such patients by continuous infusion of recombinant forms of factor VIII and activated factor VII, which contain no vWF.[1,2]

Antifibrinolytic drugs, such as tranexamic acid or aminocaproic acid, may be sufficient in the management of less severe forms of mucosal bleeding, and are used as adjuncts to desmopressin or plasma concentrates in patients undergoing surgery.[1,2] Hormonal contraceptives can reduce bleeding in women with vWD and menorrhagia.[1,2]

Acquired von Willebrand syndrome is rare, and is usually associated with conditions such as lymphoproliferative and myeloproliferative diseases, cancers, auto-immune diseases, and hypothyroidism. Some drugs have been reported to cause an acquired von Willebrand syndrome, including ciprofloxacin and valproic acid. Depending on the underlying cause, vWF activity may be affected by accelerated clearance, reduced synthesis, or an inhibition of function. Management is based on treatment of the underlying cause, but specific options for treatment of bleeding include desmopressin, factor concentrates, and intravenous immunoglobulin.[1-3] Plasma exchange and extracorporeal immunoadsorption have also been used successfully.[2,3]

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Neutropenia

A circulating neutrophil count below 1.5×10^9 cells/litre (1500 cells/mm^3) is usually regarded as abnormal and neutrophil counts below 0.5×10^9 cells/litre are associated with increased risk of infections. Neutropenia may be a result of reduced production, increased peripheral destruction, or increased peripheral pooling of neutrophils, and can be inherited or acquired.

Inherited forms of neutropenia are rare and include congenital agranulocytosis (Kostmann's syndrome: severe persistent neutropenia with frequent and severe infections that start in infancy) and cyclic neutropenia (fluctuating periods of neutropenia accompanied by fever, mouth ulceration, and serious infection).

Granulocyte colony-stimulating factors have been shown to reduce the incidence of severe infections and have improved substantially the quality of life of patients with congenital neutropenias although there are some concerns over their safety. As patients survive longer with such treatment they show an increased risk of developing myelodysplastic syndrome and leukaemia. However, it is unclear whether prolonged survival unmasks the natural course of the disease or whether granulocyte colony-stimulating factor further increases the risk of leukaemic transformation. Haematopoietic stem cell transplantation may be indicated for patients whose disease is refractory to colony-stimulating therapy or has transformed into myelodysplastic syndrome or leukaemia. Cyclic neutropenia is also managed with granulocyte colony-stimulating factor, but leukaemic transformation does not seem to occur in these patients.

There are many causes of **acquired** neutropenia. Drugs are a common cause, either by direct toxicity to the bone marrow, or by immune-mediated marrow suppression or peripheral destruction. Drugs that cause dose-related direct toxicity include cytotoxic and immunosuppressive drugs, flucytosine, ganciclovir, and zidovudine. Drugs that appear to cause neutropenia by immune-mediated mechanisms include sulfur-containing drugs (such as captopril, co-trimoxazole, and some antithyroid drugs), clozapine, penicillins, and cephalosporins. Patients with drug-induced neutropenia usually present with fever of sudden onset, sore throat, mouth ulcers, headache, and malaise. This condition is also known as **agranulocytosis**. Other causes of acquired neutropenia include serious bacterial and viral infections, radiotherapy, neoplasms that invade bone marrow, and some auto-immune disorders.

The management of acquired neutropenia includes the treatment of any contributory condition. Drug-induced neutropenia is usually managed by withdrawal of the offending drug. After an idiosyncratic reaction the implicated drug should not be given again, since abrupt neutropenia will usually be precipitated. Colony-stimulating factors can be used to manage drug-induced neutropenia.

In all neutropenic patients onset of fever is indicative of serious infection and is treated immediately with empirical antibacterial therapy as described on p.174.

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Albumin ⊗

Albümin; Albúmina; Albumine; Albuminum.

ATC — B05AA01.

ATC Vet — QB05AA01; QV08DA01 (microspheres of human albumin).

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Human Albumin Solution; Albumini Humani Solutio). An aqueous solution of protein obtained from the plasma of healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. It is prepared as a concentrated solution containing 15 to 25% of total protein or as an isotonic solution containing 3.5 to 5% of total protein; not less than 95% of the total protein is albumin. A suitable stabiliser, such as sodium octanoate or *N*-acetyltryptophan or a combination of the two, may be added but no antimicrobial preservative is added. It contains not more than 160 mmol of sodium per litre and not more than 200 micrograms of aluminium per litre. The solution is sterilised by filtration and distributed aseptically into containers which are sealed to prevent contamination and maintained at 59° to 61° for not less than 10 hours. Finally, the containers are incubated for not less than 14 days at 30° to 32° or for not less than 4 weeks at 20° to 25° and examined visually for signs of microbial contamination. It should be stored in a colourless glass container and protected from light.

A clear, almost colourless, yellow, amber, or green slightly viscous liquid. A solution in sodium chloride 0.9% containing 1% protein has a pH of 6.7 to 7.3.

The BP 2008 gives Albumin and Human Albumin as approved synonyms.

USP 31 (Albumin Human). A sterile, nonpyrogenic, preparation of serum albumin obtained by fractionating material (blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product that is safe for intravenous use. It contains 4, 5, 20, or 25% of serum albumin and not less than 96% of the total protein is albumin. It may contain sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent; it contains no added antimicrobial agent. It contains 130 to 160 mmol of sodium per litre. It is a practically odourless, moderately viscous, clear, brownish fluid. It should be stored in airtight containers.

Adverse Effects and Precautions

Adverse reactions to albumin infusion occur rarely and include nausea and vomiting, increased salivation, flushing, urticaria, hypotension, tachycardia, and febrile reactions. These effects usually respond to slowing or stopping the infusion. Allergic reactions, including severe anaphylactic shock, are possible. Rapid increases in circulatory volume can cause vascular overload, hypertension, haemodilution, and pulmonary oedema. Solutions containing albumin 20 or 25% are hyperosmotic and draw fluid from the extravascular compartment.

Infusion of albumin solutions is contra-indicated in patients with severe anaemia or heart failure. They should be given with caution to patients with hypertension or low cardiac reserve. Dehydrated patients may require additional fluids. Injured or postoperative patients should be observed carefully when given albumin as the rise in blood pressure may result in bleeding from previously undetected sites.

Human albumin preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60°, have reduced the risk of transmitting some viral infections.

Aluminium toxicity. Albumin solutions may contain appreciable amounts of aluminium. Marked increases in plasma-aluminium concentrations have been demonstrated in patients receiving large volumes by infusion and accumulation of aluminium may occur in patients with renal impairment.[1-3] In the UK albumin solutions with an aluminium content of less than 200 micrograms/litre are available for use in premature infants and patients undergoing dialysis.

1. Milliner DS, *et al.* Inadvertent aluminum administration during plasma exchange due to aluminum contamination of albumin-replacement solutions. *N Engl J Med* 1985; **312:** 165–7.
2. Maher ER, *et al.* Accumulation of aluminium in chronic renal failure due to administration of albumin replacement solutions. *BMJ* 1986; **292:** 306.
3. Maharaj D, *et al.* Aluminium bone disease in patients receiving plasma exchange with contaminated albumin. *BMJ* 1987; **295:** 693–6.

Critically ill patients. Volume expansion with albumin (a colloid) has been widely used in critically ill patients, although its use had never been formally tested in large controlled studies. A systematic review based on available studies up to March 1998 (relatively small, old trials that recorded only a small number of deaths) suggested that albumin was of no benefit in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia, and that it might be linked to increased mortality.[1] The authors of the review stressed that these results should be treated with caution but nevertheless called for an urgent reconsideration of the use of albumin in critically ill patients.

The review was severely criticised[2] and while it was recognised that albumin had probably been overused in the past it was considered that more studies were required to define the effect of albumin on mortality.[3-5] Another review[6] found that the use of albumin did not significantly affect mortality; this meta-analysis had broader criteria and included studies that were considered to be relevant but that had been excluded by the other review.

In response to this debate, albumin 4% was compared with sodium chloride 0.9% for resuscitation in a study of 6997 hypovolaemic patients in intensive care (the SAFE study).[7] This large, randomised, double-blind study found equivalent rates of death from any cause during the 28-day study period. Survival-time during the 28 days, length of stay in the intensive care unit and in hospital, time on mechanical inhalation or renal replacement therapy, and development of organ failure were also similar. Although these two fluids seem clinically equivalent in a heterogeneous population of patients in intensive care, further study of selected groups, such as those with trauma or severe sepsis, is required.

An update to the original 1998 review included the results of SAFE. The authors maintained that patients with burns (a group excluded from the large trial) or hypoproteinaemia might still be at risk of increased mortality, and although no longer suggesting a generally increased risk, concluded that there was no evidence that albumin reduced mortality in patients with hypovolaemia. Whether highly selected groups of critically ill patients might benefit is as yet unclear.[8]

Pharmacovigilance data reported to albumin suppliers over 3 years (1998 to 2000) has also been analysed.[9] During this period of heightened awareness about possible adverse effects of albumin, due to the publication of the 1998 review, a total of 1.62×10^7 doses of 40 g had been distributed. Serious adverse effects possibly or probably related to albumin were found to be rare, and no death was classified as probably related to albumin use.

On a broader level, debate continues about the relative merits and risks of such colloid solutions, compared with those of crystalloids such as glucose or sodium chloride solutions, in the management of hypovolaemia and shock (p.1183).

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317:** 235–40.
2. Various. Human albumin administration in critically ill patients. *BMJ* 1998; **317:** 882–6. [Letters.]
3. Tomlin M. Albumin usage in the critically ill. *Pharm J* 1998; **261:** 193.
4. McClelland B. Albumin: don't confuse us with the facts. *BMJ* 1998; **317:** 829–30.
5. Committee on Safety of Medicines/Medicines Control Agency. The safety of human albumin. *Current Problems* 1999; **25:** 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
6. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; **135:** 149–64.
7. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350:** 2247–56.
8. The Albumin Reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/10/05).
9. Vincent J-L, *et al.* Safety of human albumin—serious adverse events reported worldwide in 1998–2000. *Br J Anaesth* 2003; **91:** 625–30.

Dilution. If concentrated albumin solutions are to be diluted before use, a suitable solution such as sodium chloride 0.9% or glucose 5% must be used. Albumin 25% that was erroneously diluted with water to produce a hypo-osmolar albumin 5% solution has produced severe haemolysis and renal failure in patients undergoing plasmapheresis,[1,2] including a fatality in one patient.[3]

1. Steinmuller DR. A dangerous error in the dilution of 25 percent albumin. *N Engl J Med* 1998; **338:** 1226.
2. Pierce LR, *et al.* Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health-Syst Pharm* 1998; **55:** 1057,1062, 1070.
3. Anonymous. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. *MMWR* 1999; **48:** 157–9.

Transmission of infections. There has been concern that albumin preparations may carry a potential risk of transmission of viral and subviral particles, notably Creutzfeldt-Jakob disease. In 1993, *Pasteur-Mérieux* (one of the largest producers of blood products) withdrew all products containing albumin derived from placental blood[1] due to uncertainty regarding the adequacy of screening procedures for placentas as a source. It was considered that the agent responsible for Creutzfeldt-Jakob disease might be contained in placentas from women who have been treated with growth hormone derived from cadaver pituitaries. More recently, the production of blood products (including albumin) using plasma from UK donors has been phased out due to the possible risk of transmission of new variant Creutzfeldt-Jakob disease.

1. Anonymous. Placental-derived albumin preparations withdrawn. *WHO Drug Inf* 1994; **8:** 29–30.

Uses and Administration

Albumin is the major protein involved in maintaining colloid osmotic pressure in the blood. It also binds a number of endogenous and exogenous substances including bilirubin, steroid hormones, and many, mainly acidic, drugs.

Albumin solutions are used for plasma volume replacement and to restore colloid osmotic pressure. They have been used in conditions such as burns, severe acute albumin loss, and acute hypovolaemic shock (p.1183). They are also used as an exchange fluid in therapeutic plasmapheresis. Concentrated albumin solutions are used in neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn (p.2204). They have also been suggested for short-term management of hypoproteinaemia in hepatic disease and in diuretic-resistant patients with nephrotic syndrome but are of little value in chronic hypoproteinaemias.

Albumin may be included in diagnostic preparations such as those labelled with technetium-99m (p.2055) for use as radiopharmaceuticals in scanning of the heart, lung, liver, spleen, bone marrow, veins, and lymphatic system. Albumin labelled with iodine-125 (p.2054) is used to measure blood and plasma volumes, blood circulation, and cardiac output. A suspension of albumin microspheres with perflutren (p.1488) is available for enhancing cardiac ultrasound imaging.

Recombinant forms of human albumin have been developed as excipients for vaccines and other drug products, and for the treatment of hypoalbuminaemia and hypovolaemic shock.

Albumin solutions are usually available as 4.5% or 5% solutions, which are iso-osmotic with plasma, and as 20% or 25% solutions which are hyperosmotic with respect to plasma, and cause a movement of fluid from the extravascular to the intravascular compartment. These concentrated solutions may be used undiluted or may be diluted with a suitable solution, commonly sodium chloride 0.9% or glucose 5%. Adequate hydration should be maintained and electrolytes monitored in patients receiving hyperosmotic solutions of albumin.

The amount of albumin solution given will depend upon the clinical condition of the patient and the response to treatment. The following doses have been suggested:

- acute hypovolaemic shock: an initial dose of 25 g for adults (for example, 500 mL of a 5% solution or 100 mL of a 25% solution) and up to about 1 g/kg for children
- hypoproteinaemia: a maximum of 2 g/kg daily
- neonatal hyperbilirubinaemia: 1 g/kg before exchange transfusion

The rate of infusion should be adjusted according to the indication and patient response, but in general, suggested rates of infusion are up to 5 mL/minute (5% solution) or 1 to 2 mL/minute (20% solution). In plasmapheresis the albumin infusion rate should be adjusted according to the rate of removal.

Albumin solutions should not be used for parenteral nutrition.

◊ References.

1. Nicholson JP, *et al.* The role of albumin in critical illness. *Br J Anaesth* 2000; **85:** 599–610.
2. Matejtschuk P, *et al.* Production of human albumin solution: a continually developing colloid. *Br J Anaesth* 2000; **85:** 887–95.
3. Haynes GR, *et al.* Albumin administration–what is the evidence of clinical benefit? A systematic review of randomized controlled trials. *Eur J Anaesthesiol* 2003; **20:** 771–93.
4. Mendez CM, *et al.* Albumin therapy in clinical practice. *Nutr Clin Pract* 2005; **20:** 314–20.
5. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19:** 157–67.
6. Kobayashi K. Summary of recombinant human serum albumin development. *Biologicals* 2006; **34:** 55–9.

Preparations

Ph. Eur.: Human Albumin Solution;
USP 31: Albumin Human.

Proprietary Preparations (details are given in Part 3)

Arg.: Buminate; Zenalb†; ***Austral.:*** Albumex; ***Austria:*** Albuminativ; ***Braz.:*** Albumax†; Albuminar; Beribumin; Blaubimax; Blaubumin†; Plasbumin; Zenalb†; ***Canad.:*** Plasbumin; ***Chile:*** Plasbumin; ***Cz.:*** Flexbumin; ***Denm.:*** Octalbin; ***Fin.:*** Albuminativ; Octalbin; ***Fr.:*** Octalbine; Vialebex; ***Ger.:*** Humanalbin; ***Gr.:*** Zenalb; ***Hong Kong:*** Albuminar; Albutein; Biseko; Buminate; Kamapharm; Plasbumin; ***Indon.:*** Albapure; Alburaas; Albutein; Farmin; Fimalbumin; Octalbin; Plasbumin; ***Israel:*** Albuminar; Egg Plus; Plasbumin†; ***Ital.:*** Albital; Albuman†; Alburex; Albutein; Plasbumin; ***Jpn:*** Medway; ***Malaysia:*** Albutein; Buminate; Plasbumin†; Zenalb; ***Mex.:*** Albital†; Albumar†; Albumyn†; Biomina†; Buminate†; Hi-Bumin†; Octalbin; Probialbumin†; Seralbumin†; Vanderbumin; ***Neth.:*** Albuminativ†; Cealb; Octalbine; ***NZ:*** Albumex; ***Philipp.:*** Albumax; Albuminar; Albutein; Plasbumin; ***Pol.:*** Biseko; ***Port.:*** Flexbumin; ***Rus.:*** Plasbumin (Плазбумин); ***S.Afr.:*** Albusol; ***Singapore:*** Albutein; Plasbumin†; Zenalb; ***Spain:*** Octalbin; Plasbumin; ***Swed.:*** Albuminativ; ***Switz.:*** Albuman; ***Thai.:*** Alburaas; Albutein; Buminate; Zenalb; ***Turk.:*** Alba; Albuman; Albuminar; Cealb; Plasbumin; Zenalb; ***UK:*** Alba†; Albutein; Zenalb; ***USA:*** Albumarc; Albuminar; Albutein; Buminate; Plasbumin.

Multi-ingredient: ***Denm.:*** Pharmalgen Albumin; ***Swed.:*** Tisseel Duo Quick.

Aminaphthone

Aminaftona; Aminaftone; Aminaphtone; Aminonaphthone. 2-Hydroxy-3-methylnaphtho-1,4-hydroquinone 2-(4-aminobenzoate); 3-Methylnaphthalene-1,2,4-triol 2-(4-aminobenzoate).

$C_{18}H_{15}NO_4$ = 309.3.
CAS — 14748-94-8.

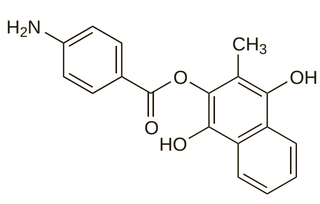

Profile

Aminaphthone is a haemostatic. Daily doses of 150 to 225 mg orally have been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Capilarema; ***Ital.:*** Capillarema; ***Port.:*** Capilarema; ***Spain:*** Capilarema†.

Aminocaproic Acid *(BAN, USAN, rINN)*

Acide aminocaproïque; Ácido aminocapróico; Ácido aminocaproico; Acidum aminocaproicum; Aminokapronihappo; Aminokaprono rūgštis; Aminokapronsav; Aminokapronsyra; CL-10304; CY-116; EACA; Epsilon Aminocaproic Acid; JD-177; Kwas ε-aminokapronowy; Kyselina aminokapronová; NSC-26154. 6-Aminohexanoic acid.

Аминокапроновая Кислота

$C_6H_{13}NO_2$ = 131.2.
CAS — 60-32-2.
ATC — B02AA01.
ATC Vet — QB02AA01.

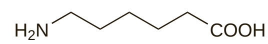

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Aminocaproic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 20% solution in water has a pH of 7.5 to 8.0.

USP 31 (Aminocaproic Acid). A fine, white, odourless or practically odourless, crystalline powder. Soluble 1 in 3 of water and 1 in 450 of methyl alcohol; slightly soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in acids and in alkalis. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects

Adverse effects associated with aminocaproic acid include dose-related gastrointestinal disturbances, dizziness, tinnitus, headache, nasal and conjunctival congestion, and skin rashes. Aminocaproic acid may cause muscle damage. This has usually occurred with high doses given for prolonged periods; renal failure may develop. Thrombotic complications have been reported, although they are usually a consequence of inappropriate use. If aminocaproic acid is given by rapid intravenous injection it can produce hypotension, bradycardia, and arrhythmias. There have been reports of a few patients suffering from convulsions, dry ejaculation, or cardiac and hepatic damage.

Effects on the blood. Very high doses of aminocaproic acid (36 g or more daily) have been given intravenously in the management of subarachnoid haemorrhage (see Stroke, p.1185). One study[1] reported rebleeding and excessive intra-operative bleeding and suggested that this was due to an antiplatelet effect of the aminocaproic acid. However, a comment on this report[2] pointed out that any antiplatelet effect was independent of its antifibrinolytic action and that this effect could only aggravate rebleeding, if it occurs, rather than causing it. However, early surgical intervention is now used to manage subarachnoid haemorrhage, and in a series of 307 patients treated with high-dose short-term aminocaproic acid before early surgery it was found that, compared with older reports in the literature, there was a low rate of rebleeding without an apparent increase in adverse effects.[3]

1. Glick R, *et al.* High dose ε-aminocaproic acid prolongs the bleeding time and increases rebleeding and intraoperative hemorrhage in patients with subarachnoid hemorrhage. *Neurosurgery* 1981; **9:** 398–401.
2. Kassell NF. Comment. *Neurosurgery* 1981; **9:** 401.
3. Leipzig TJ, *et al.* Reducing the risk of rebleeding before early aneurysm surgery: a possible role for antifibrinolytic therapy. *J Neurosurg* 1997; **86:** 220–5.

Effects on the kidneys. Adverse renal effects of aminocaproic acid are rare but have included renal arterial thrombosis, glomerular capillary thrombosis, and renal pelvic or ureteral obstruction caused by upper urinary tract thrombosis.[1] Cases of acute renal failure associated with myopathy are described under Effects on the Muscles, below.

1. Manjunath G, *et al.* Epsilon-aminocaproic acid and renal complications: case report and review of the literature. *Clin Nephrol* 2002; **58:** 63–7.

Effects on the muscles. There have been cases of reversible myopathy,[1-4] associated with daily doses of aminocaproic acid ranging from 10 to 49 g and treatment durations of about 1 to 3 months. In some patients myoglobinuria or acute tubular necrosis also occurred. Suggested mechanisms for the reaction have included a direct dose-related effect on the muscle fibre[2] or a defect in aerobic energy provision induced by aminocaproic acid.[3]

1. Brown JA, *et al.* Myopathy induced by epsilon-aminocaproic acid. *J Neurosurg* 1982; **57:** 130–4.
2. Vanneste JAL, van Wijngaarden GK. Epsilon-aminocaproic acid myopathy. *Eur Neurol* 1982; **21:** 242–8.
3. Van Renterghem D, *et al.* Epsilon amino caproic acid myopathy: additional features. *Clin Neurol Neurosurg* 1984; **86:** 153–7.
4. Seymour BD, Rubinger M. Rhabdomyolysis induced by epsilon-aminocaproic acid. *Ann Pharmacother* 1997; **31:** 56–8.

Precautions

As for Tranexamic Acid, p.1081.

The range of adverse effects that have been noted with aminocaproic acid indicates that caution is required in patients with renal or cardiac disorders. Should treatment be prolonged, it is advisable to monitor creatine phosphokinase values for signs of muscle damage.

Renal impairment. High anion gap metabolic acidosis developed in a 65-year-old woman with sepsis and acute renal failure who received aminocaproic acid for a haemorrhagic coagulopathy.[1] The acidosis improved temporarily after haemodialysis and resolved on withdrawal of aminocaproic acid and systemic alkalinisation. Although the dose of aminocaproic acid had been reduced because of renal impairment, it was suggested that more conservative dosing and close monitoring may be indicated in such patients. Hyperkalaemia has been attributed to the use of aminocaproic acid in a few patients with chronic renal failure.[2]

1. Budris WA, *et al.* High anion gap metabolic acidosis associated with aminocaproic acid. *Ann Pharmacother* 1999; **33:** 308–11.
2. Nzerue CM, Falana B. Refractory hyperkalaemia associated with use of epsilon-aminocaproic acid during coronary bypass in a dialysis patient. *Nephrol Dial Transplant* 2002; **17:** 1150–1.

Interactions

Retinoids. Aminocaproic acid should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p.1619).

Pharmacokinetics

Aminocaproic acid is readily absorbed when given orally and peak plasma concentrations are reached within 2 hours. It is widely distributed and is rapidly excreted in the urine, mainly unchanged, with a terminal elimination half-life of about 2 hours.

Uses and Administration

Aminocaproic acid is an antifibrinolytic used similarly to tranexamic acid (p.1081) in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It has also been used in the prophylaxis of hereditary angioedema (below).

A plasma concentration of about 130 micrograms/mL is considered to be necessary for effective inhibition of fibrinolysis and the recommended dosage schedules are aimed at producing and maintaining this concentration for as long as is necessary. For the treatment and prophylaxis of **haemorrhage**, aminocaproic acid may be given orally in an initial dose of 4 to 5 g, followed by 1 to 1.25 g every hour. Alternatively, the same dose may be given intravenously as a 2% solution; the initial dose (4 to 5 g) should be given over one hour followed by a continuous infusion of 1 g/hour. Up to 8 hours of treatment is often sufficient. Should treatment need to be extended, then the maximum dose over 24 hours should not normally exceed 24 g.

In patients with **haemophilia** (p.1048) who undergo dental extraction, aminocaproic acid has been given in an initial dose of 6 g orally immediately after the procedure, followed by 6 g orally every 6 hours for up to 10 days.

Care is required when aminocaproic acid is used in patients with renal impairment and dosage should be reduced.

Hereditary angioedema. In the management of hereditary angioedema (p.1081), antifibrinolytic drugs may be used as an alternative to androgens for the prophylaxis of attacks. The usual oral dose of aminocaproic acid in such patients is 1 g three or four times daily. It has also been used intravenously for acute attacks, and anecdotal reports suggest it may be modestly helpful, but there is no published evidence suggesting significant benefit.[1]

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.

Preparations

USP 31: Aminocaproic Acid Injection; Aminocaproic Acid Syrup; Aminocaproic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ipsilon; ***Austral.:*** Amicar†; ***Braz.:*** Ipsilon; ***Canad.:*** Amicar†; ***Fr.:*** Hexalense†; ***Hung.:*** Acepramin; ***India:*** Hemocid; ***Ital.:*** Caprolisin; ***Mex.:*** Amicar†; ***NZ:*** Amicar†; ***Port.:*** Episcaprom; ***Spain:*** Caproamin; ***USA:*** Amicar; ***Venez.:*** Caproamin.

Multi-ingredient: ***Braz.:*** Eaca Balsamico; Expectovac†; Ginurovac†; ***Spain:*** Caprofides Hemostatico.

Aminomethylbenzoic Acid

Aminometilbenzoico, ácido; PAMBA. 4-Aminomethylbenzoic acid.

$C_8H_9NO_2$ = 151.2.
CAS — 56-91-7.
ATC — B02AA03.
ATC Vet — QB02AA03.

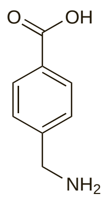

Profile

Aminomethylbenzoic acid is an antifibrinolytic with actions and uses similar to those of tranexamic acid (p.1080). It is given orally in typical doses of 300 mg to 1 g daily, in 3 or 4 divided doses; it is also given by intramuscular injection, or intravenously by slow injection or infusion.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gumbix†; ***Cz.:*** Gumbix†; Pamba; ***Ger.:*** Gumbix; Pamba.

Ancestim *(USAN, rINN)*

Ancestimum; r-metHuSCF; SCF; Stem Cell Factor. *N*-L-Methionyl-1–165-haematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer.

Анцестим
CAS — 163545-26-4.
ATC — L03AA12.
ATC Vet — QL03AA12.

Adverse Effects and Precautions

Injection site reactions commonly occur with the use of ancestim. Other skin reactions, including pruritus, rash, and urticaria, are less frequent. Systemic hypersensitivity reactions are also common and may be life-threatening. Premedication with antihistamines (both H_1- and H_2-antagonists) and an inhaled beta$_2$ agonist bronchodilator should be used, and the patient observed for at least an hour after ancestim is given. Tachycardia and respiratory symptoms including pharyngitis, dyspnoea, and cough, have also been reported.

Ancestim should not be given in the period from 24 hours before to 24 hours after a dose of cytotoxic chemotherapy or radiotherapy.

Uses and Administration

Ancestim is a recombinant human stem cell factor. It is used with filgrastim (p.1070) to mobilise peripheral blood progenitor cells that are to be collected by apheresis harvest and used for autologous transplantation. The dose of ancestim is 20 micrograms/kg daily by subcutaneous injection; the injections of ancestim and filgrastim must be given at separate sites.

◊ References.

1. Chin-Yee IH, *et al.* Optimising parameters for peripheral blood leukapheresis after r-metHuG-CSF (filgrastim) and r-metHuSCF (ancestim) in patients with multiple myeloma: a temporal analysis of CD34(+) absolute counts and subsets. *Bone Marrow Transplant* 2002; **30:** 851–60.
2. Prosper F, *et al.* Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy. *Leukemia* 2003; **17:** 437–41.
3. To LB, *et al.* Successful mobilization of peripheral blood stem cells after addition of ancestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte colony-stimulating factor) alone or with chemotherapy plus filgrastim. *Bone Marrow Transplant* 2003; **31:** 371–8.
4. da Silva MG, *et al.* Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection. *Bone Marrow Transplant* 2004; **34:** 683–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Stemgen; ***Canad.:*** Stemgen; ***NZ:*** Stemgen.

Antithrombin III *(BAN, rINN)*

Antithrombin III Human; Antithrombine III; Antithrombinum III; Antitrombiini III; Antitrombin III; Antitrombina III; Antitrombina III humana; Antytrombina III; AT-III; Cofactor I de la heparina; Heparin Cofactor; Heparin Cofactor I; Major Antithrombin.

Антитромбин III
CAS — 52014-67-2.
ATC — B01AB02.
ATC Vet — QB01AB02.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Human Antithrombin III Concentrate; Antithrombinum III Humanum Densatum). A preparation of a glycoprotein fraction obtained from human plasma that inactivates thrombin in the presence of an excess of heparin. The plasma is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, distributed into sterile containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or in an atmosphere of inert gas. No antimicrobial preservative is added but a suitable stabiliser (such as albumin) is permitted. When reconstituted in the volume of solvent stated on the label, the resulting solution contains not less than 25 international units of antithrombin III per mL.

A white or almost white, hygroscopic, friable solid or powder. Store in airtight containers. Protect from light.

USP 31 (Antithrombin III Human). A glycoprotein, which is the major inhibitor of thrombin and other activated clotting factors, including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. When reconstituted in the recommended volume of diluent, the pH is between 6.0 and 7.5, and the potency is not less than 25 USP units of antithrombin III per mL.

Store at a temperature of 2° to 8°, excursions permitted up to 25°. Protect from light.

Antithrombin Alfa *(USAN, rINN)*

Antithrombine Alfa; Antithrombinum Alfa; Antitrombina alfa; Human Antithrombin III from the milk of transgenic goats (glycoform alfa); Recombinant Human Antithrombin.

Антитромбин Альфа
CAS — 84720-88-7.

Units

The potency of antithrombin III is expressed in international units and preparations may be assayed using the second International Standard for antithrombin concentrate (1997); each ampoule contains 4.7 international units of functional activity and 5.1 international units of antigenic activity.

One USP unit is described as the amount of antithrombin III that forms a complex with 1 unit of thrombin at 25° in the presence of heparin at a pH of 8.4. Since assays of antithrombin III are carried out at 37°, it is unclear whether USP units and international units are precisely equivalent, but in practice US preparations, like those elsewhere, appear to have their potency defined in international units.

The potency of antithrombin alfa is also expressed in international units.

Adverse Effects and Precautions

Adverse effects of antithrombin III include flushing, headache, dizziness, chest tightness, nausea, a foul taste in the mouth, chills, and cramps. These can be controlled by slowing or stopping the infusion. Allergic reactions occur rarely.

Human plasma-derived antithrombin III preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60°, have reduced the risk of transmitting some viral infections. Antithrombin alfa is produced in the milk of transgenic goats, and should not be used in patients who are hypersensitive to goat proteins or goat milk components.

Uses and Administration

Antithrombin III is a protein in plasma; it is the major endogenous inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII (p.1045), and is the cofactor through which heparin (p.1303) exerts its effect. Genetic and acquired deficiency of antithrombin III occurs and is associated with susceptibility to thromboembolic disorders.

Human plasma-derived antithrombin III is given intravenously to patients with antithrombin III deficiency in the treatment of thromboembolism and for prophylaxis associated with surgical and obstetric procedures. The aim of therapy is to restore plasma-antithrombin III concentrations to at least 80% of normal. The dose, frequency, and duration of therapy are individualised for each patient taking into account the patient's pretreatment concentration and presence of active coagulation. A usual initial dose is about 30 to 50 international units/kg.

Antithrombin alfa is used similarly in the prophylaxis of venous thromboembolism in surgical patients with congenital antithrombin III deficiency. The dose is individualised, but a usual initial dose is about 20 to 25 international units/kg given as an intravenous infusion over 15 minutes, followed by a maintenance infusion of about 4 to 5 international units/kg per hour.

◊ References.

1. Bucur SZ, *et al.* Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion* 1998; **38:** 481–98.
2. Roemisch J, *et al.* Antithrombin: a new look at the actions of a serine protease inhibitor. *Blood Coag Fibrinol* 2002; **13:** 657–70.
3. Konkle BA, *et al.* Use of recombinant human antithrombin in patients with congenital antithrombin deficiency undergoing surgical procedures. *Transfusion* 2003; **43:** 390–4.

Septicaemia. Antithrombin III has been used in septicaemia (p.190) in an attempt to manage the pro-coagulant state that occurs. Initial small studies reported a reduction in mortality[1] but a large controlled study[2] (KyberSept) found that treatment with antithrombin III had no effect on 28-day mortality. A further small observational study and meta-analysis also found no benefit from the use of antithrombin III in septicaemia.[3] These studies had used antithrombin III for less than 7 days, and a small study[4] in surgical patients with septicaemia found that 14 days of treatment with antithrombin III did improve measures of coagulation and fibrinolysis, the changes being most evident in the second week of therapy. However, the study was not large enough to test effects on mortality. Subsequent analysis of data from the KyberSept study appeared to show that 28-day mortality was in fact reduced in patients who had not been given heparin as well as antithrombin III;[5] combined use increased the risk of bleeding and apparently decreased the benefits of treatment with antithrombin III.

1. Eisele B, *et al.* Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; **24:** 663–72.
2. Warren BL, *et al.* KyberSept Trial Study Group. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286:** 1869–78. Correction. *ibid.* 2002; **287:** 192.
3. Messori A, *et al.* Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care* 2002; **6:** 447–51.
4. Hoffmann JN, *et al.* Effect of long-term and high-dose antithrombin supplementation on coagulation and fibrinolysis in patients with severe sepsis. *Crit Care Med* 2004; **32:** 1851–9.
5. Hoffmann JN, *et al.* The KyberSept Investigators. Benefit/risk profile of high-dose antithrombin in patients with severe sepsis treated with and without concomitant heparin. *Thromb Haemost* 2006; **95:** 850–6.

Veno-occlusive disease. There is some evidence[1] from case reports and small studies that antithrombin III may have a beneficial effect on veno-occlusive disease associated with haematopoietic stem cell transplantation (p.1811).

1. Ibrahim RB, *et al.* Anti-thrombin III in the management of hematopoietic stem-cell transplantation–associated toxicity. *Ann Pharmacother* 2004; **38:** 1053–9.

Preparations

Ph. Eur.: Human Antithrombin III Concentrate;
USP 31: Antithrombin III Human.

Proprietary Preparations (details are given in Part 3)
Arg.: Kybernin P; ***Austral.:*** Thrombotrol-VF; ***Austria:*** Atenativ; Kybernin P; Thrombhibin; ***Braz.:*** Kybernin P; ***Canad.:*** Thrombate; ***Cz.:*** Anbinex; ATryn; Kybernin P; ***Denm.:*** Atenativ; ***Fin.:*** Atenativ; ***Fr.:*** Aclotine; ***Ger.:*** Anbinex; AT III; Atenativ; Kybernin; ***Gr.:*** Atenativ; Kybernin P; ***Hung.:*** Atenativ; Kybernin P; ***Indon.:*** Kybernin P; ***Ital.:*** Anbin; Atenativ; Kybernin P; ***Jpn:*** Neuart; ***Mex.:*** Atend; Octatit; ***Neth.:*** Atenativ; ***Norw.:*** Atenativ; ***NZ:*** Thrombotrol-VF; ***Port.:*** Atenativ; ATryn; ***Spain:*** Anbinex; Atenativ; Kybernin P; ***Swed.:*** Atenativ; ***Switz.:*** Atenativ; Kybernin; ***Turk.:*** Kybernin P; ***UK:*** ATryn; ***USA:*** Thrombate III.

Aprotinin *(BAN, USAN, rINN)*

Aprotiniini; Aprotinina; Aprotininas; Aprotinine; Aprotininum; Aprotynina; Bayer A-128; Riker 52G; RP-9921.

Апротинин

CAS — 9087-70-1.
ATC — B02AB01.
ATC Vet — QB02AB01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Aprotinin). A polypeptide consisting of 58 amino acids that inhibits the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It contains not less than 3 Ph. Eur. units/mg calculated with reference to the dried substance. An almost white, hygroscopic powder. Soluble in water and in isotonic solutions; practically insoluble in organic solvents. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Aprotinin Concentrated Solution). A solution of aprotinin containing not less than 15 Ph. Eur. units/mL. A clear colourless solution. Store in airtight containers. Protect from light.

USP 31 (Aprotinin). A polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilised powder. Its potency is not less than 3 USP units/mg calculated with reference to the dried substance.

The lyophilised powder should be stored in airtight containers at a temperature between 8° and 15°. Protect from light. The bulk solution should be stored in airtight containers at a temperature not exceeding 25°. Do not allow to freeze.

Incompatibility. Aprotinin is reported to be incompatible with corticosteroids, heparin, tetracyclines, and nutrient solutions containing amino acids or fat emulsions.

Units

The potency of aprotinin is expressed in terms of kallikrein (kallidinogenase) inactivator units (KIU) or of trypsin inactivation (Ph. Eur. units). One KIU is contained in 140 nanograms of aprotinin. One Ph. Eur. and one USP unit is equivalent to about 1800 KIU.

Potency has also been expressed in terms of plasmin inactivation (antiplasmin units).

Adverse Effects and Precautions

Aprotinin is usually well tolerated. Local thrombophlebitis can occur. Adverse effects including bronchospasm, hypotension, cardiac arrhythmias, gastrointestinal disturbances, and skin rashes are considered to be hypersensitivity reactions; anaphylaxis, including fatalities, has occurred. Licensed UK product information warns that the risk of anaphylactic reaction increases when re-exposure occurs within 6 months, but product information in the US extends this warning to contra-indicate the use of aprotinin for 12 months after a previous exposure. A test dose is recommended for all patients and the use of prophylactic histamine antagonists may be considered; a hypersensitivity reaction to the therapeutic dose of aprotinin can still occur even after an uneventful test dose. There have been reports of renal dysfunction and reversible renal failure in patients given aprotinin during open-heart surgery with extracorporeal circulation; the risk may be increased in patients with pre-existing renal impairment or risk factors for altered renal function. For further details of an increased risk of cardiovascular and cerebrovascular events, renal failure, and death in patients undergoing surgery, see Haemorrhagic Disorders under Uses and Administration, below.

Disseminated intravascular coagulation. Fatal disseminated intravascular coagulation has been reported in a patient after the use of intraoperative autotransfusion and aprotinin during surgery.[1] Activation of the clotting system occurs during autotransfusion although this usually causes no systemic adverse effects. While there were other possible causes, it was suggested that aprotinin could have contributed to deposition of fibrin microthrombi in the microvasculature and prevented subsequent fibrinolysis.

1. Milne AA, *et al.* Disseminated intravascular coagulation after aortic aneurysm repair, intraoperative salvage autotransfusion, and aprotinin. *Lancet* 1994; **344:** 470–1.

Effects on coagulation tests. In patients receiving heparin, aprotinin may prolong the activated clotting time when measured by some methods, but this may not represent increased anticoagulation. It has been recommended that an alternative to the activated clotting time should be used to monitor heparin therapy when aprotinin is used concurrently.

It should also be noted that aprotinin injection and heparin injection are pharmaceutically incompatible.

Effects on the respiratory system. Acute respiratory distress syndrome developed in a 24-year-old male 2 hours after the start of an intravenous infusion of aprotinin for bleeding after tonsillectomy.[1] Mechanical ventilation was required for 4 days.

1. Vucicevic Z, Suskovic T. Acute respiratory distress syndrome after aprotinin infusion. *Ann Pharmacother* 1997; **31:** 429–32.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, can occur with the use of aprotinin both on primary and secondary exposure. In a study[1] of 248 re-exposures to aprotinin in 240 patients undergoing cardiac surgery, there were 7 cases of anaphylactic reactions ranging from mild to severe with a higher incidence of reactions occurring in those patients re-exposed within 6 months of the previous dose. A review[2] of 124 reported reactions in 122 patients also found that reactions ranged from mild to severe, and that about half were life-threatening and 11 were fatal. The risk of reaction was greatest with re-exposure to aprotinin as this had been the situation in 80% of the cases, although there were 19 cases associated with the first use of aprotinin. The average risk of anaphylaxis was estimated to be 2.8% in re-exposed patients. Most reactions occurred within 6 months of previous exposure, and the risk was greatest in the first 3 months. Various diagnostic tests have been tried in an attempt to predict hypersensitivity risk. Aprotinin-specific serum-IgG was reported to be detectable in about 50% of patients who had received only one aprotinin treatment, but other tests such as preoperative skin testing were not found to be reliable.

A number of measures have been suggested in order to reduce the risk of hypersensitivity reactions to aprotinin, including the use of an intravenous test dose in all patients, but it must be noted that these also have the potential to trigger a reaction.[1] For patients who have previously received aprotinin it has been recommended that re-exposure should be avoided for at least 6 months,[1,2] that aprotinin-specific antibody screening should be done,[2] and that prophylactic histamine H_1- and H_2-antagonists should be given to ameliorate severe anaphylactic reactions[1] although there are reports of reactions occurring despite antihistamine and corticosteroid prophylaxis.[2] It has also been suggested that in cardiac surgery, aprotinin should only be given when cardiopulmonary bypass is available to assist resuscitation.[1,2]

There have also been rare reports of hypersensitivity reactions on re-exposure to aprotinin used locally as a component of fibrin sealant.[3,4] In one fatal case[4] the previous exposure to fibrin sealant had been 5 years before.

1. Dietrich W, *et al.* Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997: **113:** 194–201.
2. Beierlein W, *et al.* Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; **79:** 741–8.
3. Beierlein W, *et al.* An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; **40:** 302–5.
4. Oswald A-M, *et al.* Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99:** 762–3.

Interactions

Heparin. For comment on the use of aprotinin with heparin, see Effects on Coagulation Tests, above.

Neuromuscular blockers. For reports of apnoea when aprotinin was used with neuromuscular blockers, see p.1904.

Retinoids. Aprotinin should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p.1619).

Pharmacokinetics

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. After intravenous use, it is excreted in the urine as inactive degradation products. The terminal elimination half-life is about 5 to 10 hours.

Renal impairment. The terminal elimination half-life of aprotinin was reported as 13.3 and 14.9 hours, respectively, in two patients with chronic renal impairment given aprotinin by intravenous infusion over 30 minutes.[1] A study[2] of cardiac surgical patients undergoing cardiopulmonary bypass also found that aprotinin clearance was reduced in those with renal impairment. The elimination half-life was about 20 hours in patients with end stage renal disease compared with about 8 hours in those with creatinine clearance greater than 50 mL/min.

1. Müller FO, *et al.* Pharmacokinetics of aprotinin in two patients with chronic renal impairment. *Br J Clin Pharmacol* 1996; **41:** 619–20.
2. O'Connor CJ, *et al.* The impact of renal dysfunction on aprotinin pharmacokinetics during cardiopulmonary bypass. *Anesth Analg* 1999; **89:** 1101–7.

Uses and Administration

Aprotinin is a haemostatic. It is an inhibitor of proteolytic enzymes including chymotrypsin, kallikrein (kallidinogenase), plasmin, and trypsin.

Aprotinin has been used to reduce blood loss and transfusion requirements in patients at increased risk of major blood loss during coronary artery bypass graft surgery with cardiopulmonary bypass. However, the marketing of aprotinin injection has been suspended worldwide because of a possible increased risk of death associated with its use in cardiac surgery (see Haemorrhagic Disorders, below). Nevertheless, it may be available in some countries, such as the USA, using a special access protocol. It has also been used in the treatment of hyperfibrinolytic haemorrhage associated with raised plasma concentrations of plasmin. Aprotinin is applied topically as a component of fibrin glues (p.1069).

It is recommended that because of the risk of hypersensitivity reactions an intravenous test dose of 10 000 KIU should be given to all patients at least 10 minutes before the therapeutic dose. All intravenous doses of aprotinin should be given through a central venous line.

In **coronary artery bypass graft surgery**, the test dose is followed by a loading dose given with the patient in a supine position, after induction of anaesthesia but before incision; 2 000 000 KIU is given intravenously over 20 to 30 minutes. The loading dose is followed by a continuous infusion of 500 000 KIU/hour until the end of the operation. An additional dose of 2 000 000 KIU is added to the prime volume of the extracorporeal circuit. In patients with septic endocarditis, a dose of 3 000 000 KIU is added to the prime volume of the circuit and the continuous infusion may be continued into the early postoperative period. The total amount of aprotinin used is usually no more than 7 000 000 KIU. A regimen using half the dose for loading, maintenance, and to prime the circuit, may be used in low-risk patients.

Haemorrhagic disorders. Aprotinin has been used in the treatment of life-threatening haemorrhage caused by raised plasma concentrations of plasmin. It has also been used in the treatment of severe bleeding arising from overdosage with thrombolytics (see Treatment of Adverse Effects under Streptokinase, p.1404).

Aprotinin has been used to reduce blood loss in patients undergoing surgery, particularly cardiac surgery involving cardiopulmonary bypass. This bypass procedure is complicated by a postperfusion syndrome that includes impairment of haemostasis and pulmonary dysfunction. Contributing factors include ischaemia reperfusion, surgical trauma, endotoxaemia, and blood contact with the artificial surfaces of the bypass apparatus. This syndrome has been interpreted as a 'whole body inflammatory response', and the beneficial effect of aprotinin has been attributed to an attenuation of this response. As well as its inhibitory effect on fibrinolysis, aprotinin is thought to have effects on the complement system, cytokines, neutrophil activation, and platelet function.[1,2] Aprotinin has reduced blood loss and transfusion requirements in patients undergoing both primary and repeat cardiac surgery.[1,3-6] The usual dosage regimen (as given in Uses and Administration, above) and low-dosage regimens (50% of the usual dose) appear to be equally effective, but regimens that use aprotinin only as a pump prime dose appear to be less effective.[1,5]

The safety of aprotinin in cardiac surgery has been questioned, however, because of the results of two observational studies. One analysis[7] of patient outcome after the use of aminocaproic acid, aprotinin, tranexamic acid, or no treatment, found that although the three drugs had reduced blood loss to a similar extent, aprotinin was associated with an increased risk of cardiovascular and cerebrovascular events (myocardial infarction, heart failure, stroke, or encephalopathy) and renal failure. Observational follow-up also found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death in the 5 years after surgery.[8] In another study[9] that compared data from patients who had received either aprotinin or tranexamic acid, there was an increased risk of renal dysfunction associated with aprotinin, particularly in patients with abnormal pre-operative renal function. In response to these studies, the FDA recommended[10] that patients receiving aprotinin should be carefully monitored, and that physicians should consider limiting its use to situations where the clinical benefit of reduced blood loss is essential and outweighs the potential risks. The concerns raised by these studies and the FDA's recommendation prompted further analysis of data relating to the effects of aprotinin. A meta-analysis[5] that included studies in different types of surgery, although the majority were in cardiac surgery, found no increased risk of death, cardiovascular events, or renal failure. However, because the reporting of renal function was lacking for many studies, and therefore a potential for bias, the authors were not confident that a modest increase in risk could be ruled out. Another meta-analysis[11] that was limited to studies in cardiac surgery also found no increased risk of death or cardiovascular events with aprotinin. There was also no increase in the risk of dialysis-dependent renal failure, but high-dose aprotinin did increase the risk of renal dysfunction, compared with placebo. Two large retrospective studies, which attempted to account for confounding variables, were also undertaken in cohorts of patients who had undergone coronary artery bypass graft surgery. One study found that, compared with aminocaproic acid, aprotinin increased the risk of in-hospital death.[12] The other found increased in-patient renal dysfunction, and death at 30 days and 1 year, in patients given aprotinin compared with aminocaproic acid or no antifibrinolytic therapy. Survival estimates also found an association between aprotinin use and reduced survival for up to 10 years after surgery.[13] Preliminary data analysis from a randomised study (BART) also found an increased risk of death with aprotinin, compared with aminocaproic acid or tranexamic acid, and in November 2007, authorities such as the FDA[14] and EMEA[15] recommended that marketing of aprotinin injection be suspended.

Aprotinin has been used to reduce transfusion requirements during liver transplantation, by its effect on intra-operative hyperfibrinolysis.[16,17] However, concerns about an increased risk of thromboembolism in these patients has been raised.[18] A systematic review[19] of 23 studies using antifibrinolytic drugs, 18 of which used aprotinin, found no evidence of an increased risk of thromboembolic complications in liver transplant patients, but noted that the studies were underpowered and that identification of subgroups of patients at risk may have been missed. Aprotinin has also been used to reduce transfusion requirements during orthopaedic surgery.[20]

1. Peters DC, Noble S. Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. *Drugs* 1999; **57** 233–60.
2. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg* 2001; **71:** 745–54.
3. Bidstrup BP, *et al.* Aprotinin cardiac centers in the United Kingdom. *Ann Thorac Surg* 1993; **55:** 971–6.
4. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997; **85:** 1258–67.
5. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).
6. Sedrakyan A, *et al.* Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; **128:** 442–8.
7. Mangano DT, *et al.* The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; **354:** 353–65.
8. Mangano DT, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007; **297:** 471–9.
9. Karkouti K, *et al.* A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; **46:** 327–38.
10. FDA. Aprotinin injection (marketed as Trasylol) (issued 8th February, 2006). Available at: http://www.fda.gov/cder/drug/advisory/aprotinin.htm (accessed 26/11/07)
11. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; **115:** 2801–13.
12. Schneeweiss S, *et al.* Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008; **358:** 771–83.
13. Shaw AD, *et al.* The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med* 2008; **358:** 784–93.
14. FDA. FDA requests marketing suspension of Trasylol (issued 5th November, 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01738.html (accessed 26/11/07)
15. EMEA. European Medicines Agency recommends suspension of marketing authorisation of aprotinin-containing medicines for systemic use (issued 21st November, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/53467807en.pdf (accessed 26/11/07)
16. Porte RJ, *et al.* Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet* 2000; **355:** 1303–9.
17. Rentoul TM, *et al.* The effect of aprotinin on transfusion requirements in pediatric orthotopic liver transplantation. *Pediatr Transplant* 2003; **7:** 142–8.
18. Lentschener C, *et al.* A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; **100:** 1248–55.
19. Molenaar IQ, *et al.* Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; **7:** 185–94.
20. Kokoszka A, *et al.* Evidence-based review of the role of aprotinin in blood conservation during orthopaedic surgery. *J Bone Joint Surg Am* 2005; **87-A:** 1129–36.

Pancreatitis. Aprotinin has been tried in the management of pancreatitis (p.2361) because of the postulated role of proteolytic enzymes in this condition. However, results have been largely disappointing.

Preparations

BP 2008: Aprotinin Injection;
USP 31: Aprotinin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Quagu-Test; Rivilina; ***Austral.:*** Trasylol†; ***Austria:*** Pantinol†; Trasylol†; ***Belg.:*** Trasylol†; ***Braz.:*** Trasylol†; ***Canad.:*** Trasylol†; ***Chile:*** Trasylol†; ***Cz.:*** Antilysin†; Gordox†; Trasylol†; ***Denm.:*** Trasylol†; ***Fin.:*** Trasylol†; ***Fr.:*** Trasylol†; ***Ger.:*** Trasylol†; ***Gr.:*** Trasylol†; ***Hong Kong:*** Trasylol†; ***Hung.:*** Gordox†; Trasylol†; ***Indon.:*** Trasylol; ***Israel:*** Protosol; ***Malaysia:*** Trasylol†; ***Mex.:*** Protinin†; Trasylol†; ***Neth.:*** Trasylol†; ***NZ:*** Trasylol†; ***Pol.:*** Traskolan†; Trasylol†; ***Rus.:*** Aprotex (Апротекс); Contrykal (Контрикал); Gordox (Гордокс); Trasylol (Трасилол)†; ***S.Afr.:*** Trasylol†; ***Singapore:*** Trasylol†; ***Spain:*** Trasylol†; ***Swed.:*** Trasylol†; ***Switz.:*** Trasylol†; ***Thai.:*** Trasylol†; ***Turk.:*** Trasylol†; ***UK:*** Trasylol†; ***USA:*** Trasylol†; ***Venez.:*** Trasylol†.

Multi-ingredient: ***Arg.:*** Beriplast P; Lacrimax; Maxus; Optilac; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Beriplast; Tissucol; ***Ger.:*** Beriplast; TachoComb†; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Tissucol; Tissucol Duo; ***Pol.:*** Beriplast; ***Port.:*** Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Beriplast P; Tissucol; Tissucol Duo S; ***Thai.:*** TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** Tisseel.

Batroxobin *(rINN)*

Batroxobina; Batroxobine; Batroxobinum.

Батроксобин

CAS — 9039-61-6 (batroxobin); 9001-13-2 (haemocoagulase).
ATC — B02BX03.
ATC Vet — QB02BX03.

Profile

Batroxobin is an enzyme obtained from the venom of the viper *Bothrops atrox*. It has also been obtained from *Bothrops moojeni* and a similar preparation is derived from *Bothrops jararaca*.

Batroxobin is reported to act on fibrinogen to produce a fibrin monomer that can be converted by thrombin to a fibrin clot. It is used both as a haemostatic and, in larger doses, to induce a hypofibrinogen state in the management of thromboembolic disorders. When used as a haemostatic it is usually given with a factor-X activator; such a combined preparation is known as haemocoagulase (hemocoagulase). Batroxobin has been given parenterally or by local application.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Defibrase; Reptilase; ***Fr.:*** Reptilase†; ***India:*** Reptilase; ***Ital.:*** Botropase†; ***Port.:*** Reptilase†.

Blood ⊗

Sangre.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US.*

USP 31 (Whole Blood). It is blood that has been collected from suitable human donors under rigid aseptic precautions for transfusion or for further processing into one or more of its components for transfusion. It contains a citrate-based anticoagulant (Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or Anticoagulant Citrate Phosphate Dextrose Adenine Solution).

Whole blood must be tested for syphilis, hepatitis B virus, human T-cell lymphotropic virus (HTLV) type I and type II, hepatitis C, and HIV. It should also be tested for blood group and rhesus factors, and for unexpected antibodies to red cell antigens.

One unit (dose) of whole blood contains a minimum of 50 g of haemoglobin. One unit of whole blood filtered for removal of leucocytes (Whole Blood, Leukocytes Reduced), contains less than 5×10^6 residual leucocytes.

Whole blood is stored in the original container or transferred to an equivalent one using a technique that does not compromise sterility. It should be stored at 1° to 6°, unless platelets are to be prepared, in which case the blood is stored for no longer than 8 hours after collection at room temperature.

Whole blood collected in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at 1° to 6° after the blood has been drawn. Whole blood collected in Anticoagulant Citrate Phosphate Dextrose Adenine Solution may be stored for up to 35 days at 1° to 6°. If the hermetic seal of the container is broken during collection, preparation, or further processing, the expiry date is not later than 24 hours after the seal is broken (when blood is stored at 1° to 6°), but not to exceed the original expiry date of the unit.

It is a deep red, opaque liquid from which the corpuscles readily settle upon standing for 24 to 48 hours, leaving a clear, yellowish or pinkish supernatant layer of plasma.

The USP 31 gives the names ACD Whole Blood, CPD Whole Blood, CPDA-1 Whole Blood, and Heparin Whole Blood, which specify the anticoagulant used.

Adverse Effects

The rapid transfusion of large volumes of whole blood may overload the circulation and cause pulmonary oedema. Transfusion of very large volumes of citrated blood can lead to hypocalcaemia, although this is not usually a problem unless there is hepatic impairment or hypothermia. Hyperkalaemia may occur but on its own is rarely clinically significant. Hypothermia may result from rapid transfusion of large volumes of cooled blood and may, combined with hypocalcaemia, hyperkalaemia, and resultant acidosis, lead to cardiac toxicity. Disseminated intravascular coagulation may also occur in patients receiving large-volume transfusions. Repeated transfusions of blood, as in thalassaemia, may lead to iron overload.

The transfusion of incompatible blood causes haemolysis, possibly with renal failure. Pyrexia, rigors, and urticaria may be due to antibodies towards a number of blood components. Severe allergic reactions and anaphylaxis can occur. Delayed reactions may occur more than 24 hours after transfusion in patients in whom previous transfusion or pregnancy has induced sensitisation; these reactions are usually mild and manifest as fever, chills, fall in haemoglobin concentration, and haemoglobinuria.

Transmission of infections. The use of blood, blood components, or blood products has been associated with the transmission of viruses, most notably hepatitis B virus and HIV; other reports of transmission include CMV, hepatitis C and possibly other hepatitis viruses, HTLV-I and -II, and the agent causing Creutzfeldt-Jakob disease. Transmission of bacterial and parasitic diseases is also possible including syphilis, Chagas' disease, and malaria.

The main methods of minimising the risk of transmission of infection are by rigorous selection of blood donors and by microbiological screening tests. Contamination during collection and processing is minimised by using closed systems and by strict aseptic technique. Treatment of blood products with heat or chemicals can inactivate some organisms including some viruses, in particular HIV-1, but blood and blood components cannot be treated in either of these ways. Patients receiving multiple transfusions of pooled plasma products are at increased risk of contracting infections and can be offered immunological protection, for example hepatitis B vaccine.

◊ Reviews.

1. Contreras M, Mollison PL. Immunological complications of transfusion. In: Contreras M, ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 53–7.
2. Barbara JAJ, Contreras M. Infectious complications of blood transfusion: bacteria and parasites. In: Contreras M. ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 58–61.
3. Barbara JAJ, Contreras M. Infectious complications of blood transfusion: viruses. In: Contreras M. ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 62–6.
4. Regan F, Taylor C. Blood transfusion medicine. *BMJ* 2002; **325:** 143–7.
5. Goodnough LT. Risks of blood transfusion. *Crit Care Med* 2003; **31** (suppl): S678–S686.
6. Pomper GJ, *et al.* Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol* 2003; **10:** 412–18.
7. Hardy J-F, *et al.* Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anesth* 2004; **51:** 293–310.
8. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007.
Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 15/02/07)

Creutzfeldt-Jakob disease. While there is no proof that transmission of Creutzfeldt-Jakob disease by blood or blood products has occurred,[1] 3 cases have been reported of possible transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion.[2-4] It is recognised that there is a need for further assessment of the potential risk of transmission of vCJD by such products.

A number of precautionary measures have been implemented in the UK to minimise transmission of vCJD by blood or tissues:[5]

- plasma is imported from outside the UK for fractionation to manufacture plasma derivatives
- leucocytes are removed from donated blood (leucodepletion) as it was thought that this would remove infectivity. However, *animal* studies have shown that this is not the case and that prion concentration in the blood is likely to be reduced by only about 40%[6]
- plasma is imported for clinical use in patients born after January 1996 (this date was chosen because it was considered that foods infected with bovine spongiform encephalopathy had been largely eliminated from the diet by this time[6])
- donations of blood, platelets, and live bone are not accepted from donors who themselves have received blood components since 1 January 1980, or from any donors who have received intravenous immunoglobulin prepared from UK plasma or who have undergone plasma exchange anywhere in the world

Concern at the risk of transmitting Creutzfeldt-Jakob disease by albumin prepared from placental blood has led to restriction on this source of albumin (see Transmission of Infections under Albumin, p.1052).

1. Wilson K, *et al.* Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *BMJ* 2000; **321:** 17–19.
2. Llewelyn CA, *et al.* Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; **363:** 417–21.
3. Peden AH, *et al.* Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; **364:** 527–9.
4. Wroe SJ, *et al.* Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006; **368:** 2061–7.
5. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services.* 4th ed. London: The Stationery Office, 2007.
Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 15/02/07)
6. Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol* 2005; **132:** 13–24.

Effects on leucocytes. A study of 50 patients in an intensive care unit found that 45 of them developed leucocytosis after transfusion of packed red blood cells.[1] The leucocytosis, which was accounted for by neutrophils, occurred immediately after transfusion and persisted for 12 hours. A further study[2] of 96 critically ill patients found that leucocytosis commonly occurred in those who were not septic and had received unfiltered packed red cells. Mean white cell counts were increased significantly 2 hours after infusion, remained elevated for about 12 hours, and returned to baseline by 24 hours. In 11 patients who required more than one transfusion, the use of filtered packed red cells was not associated with leucocytosis. Concentrations of interleukin-8 were found to be raised in unfiltered blood after 4 weeks of storage, and were higher in the transfused blood that caused leucocytosis. The authors suggested that cytokines produced by leucocytes in stored blood might be responsible for leucocytosis in recipients of unfiltered packed red cells.

1. Fenwick JC, *et al.* Blood transfusion as a cause of leucocytosis in critically ill patients. *Lancet* 1994; **344:** 855–6.
2. Izbicki G, *et al.* Transfusion-related leukocytosis in critically ill patients. *Crit Care Med* 2004; **32:** 439–42.

Effects on the lungs. A rare but life-threatening complication of transfusion of blood or other plasma-containing products is acute lung injury, often termed transfusion-related acute lung injury (TRALI). Symptoms develop during or within 6 hours of infusion and are those of acute respiratory distress syndrome[1-3] (p.1498). Treatment is the same as for acute respiratory distress of any cause but oxygen exchange usually begins to improve between 24 and 48 hours; if the patient survives there appear to be no long-term sequelae.[1] The presence of HLA-specific antileucocyte antibodies in plasma from multiparous female donors appears to play a role in starting the reaction;[1,3] such antibodies have also been identified in some implicated male donors.[2] Another mechanism, the neutrophil priming hypothesis, proposes that TRALI results from 2 independent events. The first event causes the recipient's neutrophils to be primed and is related to the recipient's condition; in the second event the infused blood product activates the primed neutrophils in the lung, which causes endothelial damage.[2,3]

1. Wallis JP. Transfusion-related acute lung injury (TRALI)—under-diagnosed and under-reported. *Br J Anaesth* 2003; **90:** 573–6.
2. Holness L, *et al.* Fatalities caused by TRALI. *Transfus Med Rev* 2004; **18:** 184–8.
3. Kleinman S, *et al.* Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004; **44:** 1774–89.

Graft-versus-host disease. Acute graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p.1811) has been reported in both immunocompromised and immunocompetent patients after blood transfusion.[1] Symptoms include fever, rash, abnormal liver function tests, diarrhoea, and pronounced leucopenia and pancytopenia. The reaction can be severe and fatal.

High-risk immunocompromised groups include bone marrow transplant recipients, patients with congenital immunodeficiencies, fetuses receiving intra-uterine transfusions, patients with Hodgkin's disease, and patients treated with purine analogue drugs such as fludarabine. Patients at less risk include those with acute leukaemia, non-Hodgkin's lymphoma, solid tumours treated with intensive chemotherapy or radiotherapy, premature infants and those undergoing exchange transfusion, and solid organ transplant recipients.

Immunocompetent patients who share an HLA haplotype with HLA-homozygous blood donors also appear to be at increased risk. Such cases have been reported particularly in Japan, where practices have included the use of transfusions from blood relatives. There is also a high incidence of shared haplotype in the population.

Infusion of products containing viable lymphocytes appears to be responsible. Treatment of graft-versus-host disease associated with transfusion is largely ineffective and patients considered to be at risk should be given products depleted of viable lymphocytes by irradiation. Blood products depleted of leucocytes by filtration still contain a small percentage of viable leucocytes, and this should not be used as the sole method to prevent graft-versus-host disease.

1. Schroeder ML. Transfusion-associated graft-versus-host disease. *Br J Haematol* 2002; **117:** 275–87.

Malignant neoplasms. It has been suggested that perioperative allogeneic blood transfusion is associated with an increase in the risk of recurrence, and decreased long-term survival, after resection of malignancy. This suggestion was based on retrospective observational studies, and was attributed to immunosuppressant effects of allogeneic blood. Randomised controlled trials have produced conflicting results, but a 1996 review[1] did not find a detrimental effect on the risk of cancer recurrence, and suggested that the findings of the observational studies probably resulted from the confounding effect of factors associated with the need for transfusion. A later meta-analysis[2] of 32 studies of perioperative transfusion in patients undergoing colorectal surgery concluded that the cancer recurrence rate was increased (odds ratio 1.68) in patients given transfusions. Risk factors associated with this increase were rectal disease, more advanced disease, and an increased number of transfused units. However, many of the included studies had small sample sizes, there was significant heterogeneity, and other possible surgery-related risk factors could not be evaluated, such that a causal association between the increased risk of cancer recurrence and transfusion could not be established. Other systematic reviews have come to different conclusions. A meta-analysis[3] of studies in patients undergoing resection of any type of solid tumour included only studies that used an active comparator (leucocyte-depleted or autologous blood). Only 8 studies met the inclusion criteria and the analysis provided no evidence of an increased risk of death or cancer recurrence in patients given allogeneic blood. The proposed detrimental immunosuppressive effect of perioperative allogeneic blood transfusion was studied in colorectal cancer patients given either allogeneic packed red cells (buffy coat removed) or leucocyte-depleted red cells.[4] Although the leucocyte count is reduced when the buffy coat is removed, more leucocytes are removed from leucocyte-depleted red cells, which should reduce any immunosuppressive effect. However, after 5 years there was no difference in survival or recurrence rates between the two groups. Survival was better for a third group of non-transfused patients, but this may be explained by a higher incidence of rectal cancer in the transfused groups, and the better clinical status of patients not requiring transfusion. A review[5] of individual studies and meta-analyses concluded that a causal relationship between allogeneic blood transfusion and solid cancer recurrence had not been proven. There was some evidence for transfusion-associated immunomodulation, but the mechanisms of effect and the specific constituents of allogeneic blood that mediate the effect remain unclear.

Epidemiological studies have reported an increase in the incidence of non-Hodgkin's lymphoma coinciding with the increase in the use of allogeneic blood transfusions since the 1950s. Proposed mechanisms have included transfusion-associated immunosuppression, transmission of oncogenic viruses, and blood donation by prelymphomatous donors.[6,7] Although some case-control studies have reported no association between blood transfusion and the development of non-Hodgkin's lymphoma,[8,9] others have reported a positive association, particularly for some subtypes of lymphoma.[10] Reviews[6,7] of these and other studies have found considerable disagreement between reports. This may result from biases in study design, confounding factors such as HIV infection, and lack of consensus on lymphoma classification.

1. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. *Transfusion* 1996; **36:** 175–86.
2. Amato AC, Pescatori M. Effect of perioperative blood transfusions on recurrence of colorectal cancer: meta-analysis stratified on risk factors. *Dis Colon Rectum* 1998; **41:** 570–85.
3. McAlister FA, *et al.* Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies. *Br J Surg* 1998; **85:** 171–8.
4. van de Watering LMG, *et al.* Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. *Br J Surg* 2001; **88:** 267–72.
5. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? *Blood* 2001; **97:** 1180–95.
6. Vamvakas EC. Allogeneic blood transfusion as a risk factor for the subsequent development of non-Hodgkin's lymphoma. *Transfus Med Rev* 2000; **14:** 258–68.
7. Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. *Epidemiol Rev* 2002; **24:** 269–79.
8. Maguire-Boston EK, *et al.* Blood transfusion and risk of non-Hodgkin's lymphoma. *Am J Epidemiol* 1999; **149:** 1113–18.
9. Chow EJ, Holly EA. Blood transfusions as a risk factor for non-Hodgkin's lymphoma in the San Francisco Bay Area: a population-based study. *Am J Epidemiol* 2002; **155:** 725–31.
10. Cerhan JR, *et al.* Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. *Cancer Epidemiol Biomarkers Prev* 2001; **10:** 361–8.

Precautions

Whole blood should generally not be transfused unless the ABO and Rh groups of the patient's and the donor's blood have been verified and a compatibility check made between the patient's serum and the donor's red cells (see under Blood Groups, below).

The Rh group of the recipient should always be determined and ideally all patients should be transfused with blood of homologous Rh groups.

To reduce the possibility of cardiac arrest from cardiac hypothermia when large volumes are used or the blood is transfused rapidly, and to minimise postoperative shivering, stored blood should be carefully warmed to about 37° before transfusion.

Whole blood should not be given to patients with chronic anaemia who have a normal or elevated plasma volume.

Drugs should *not* be added to blood.

Transfusion of blood from donors who have recently been receiving drug treatment may be hazardous to the recipient.

◊ Guidelines[1-4] for accepting blood from donors who have been receiving drugs have been published.

1. Ferner RE, *et al.* Drugs in donated blood. *Lancet* 1989; **ii:** 93–4.
2. Stichtenoth DO, *et al.* Blood donors on medication: are deferral periods necessary? *Eur J Clin Pharmacol* 2001; **57:** 433–40.
3. UK Blood Transfusion Services. Whole blood and components donor selection guidelines: drug index (revised 23/04/08). Available at: http://www.transfusionguidelines.org.uk/index.asp?Publication=DI&Section=4 (accessed 29/08/08)
4. American Red Cross. Blood donation eligibility guidelines (revised 08/05/08). Available at: http://www.redcross.org/services/biomed/0,1082,0_557_,00.html#med (accessed 29/08/08)

Abuse. References to the infusion of whole blood or packed red blood cells to enhance athletic performance.[1,2]

1. Ekblom BT. Blood boosting and sport. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000; **14:** 89–98.
2. Leigh-Smith S. Blood boosting. *Br J Sports Med* 2004; **38:** 99–101.

Blood groups. The chief blood group systems are the ABO system and the Rhesus system.

In simple terms red blood cells carry on their surface genetically determined antigens. A person with antigen A, B, A plus B, or neither is classified as group A, B, AB, or O respectively. Such persons will have, in their serum, antibodies to B, A, neither, or both respectively—anti-B (β), anti-A (α), or anti-B plus anti-A ($\alpha + \beta$). Giving blood containing red cells from a person of group A to a person with anti-A results in agglutination or possibly haemolysis. For the determination of the ABO group the agglutinogens of the red cells and the agglutinins of the serum are determined by testing against known standards.

In the Rhesus system many persons carry an antigen (Rh-positive) which stimulates antibody formation in Rh-negative persons; subsequent exposure to Rh-positive blood causes haemolysis.

Many variants of these and other systems, are recognised.

Uses and Administration

Blood is a complex fluid with many functions including the maintenance of hydration of the tissues, maintenance of body temperature, and the transport within the body of gases, ions, nutrients, hormones, enzymes, antibodies, waste products of metabolism, and drugs.

The main components of blood are plasma, red blood cells (erythrocytes), white blood cells (leucocytes), and platelets (for further information on different blood cells and their formation, and average counts in adults, see Haematopoiesis, p.1042). Serum is the fluid which remains once blood or plasma has clotted; it is, in effect, plasma with fibrinogen removed.

Whole blood is used as a source of red cell concentrates, clotting factors, platelets, plasma and plasma fractions, and immunoglobulins, each of which has specific indications for use. Because of the risks involved in transfusing whole blood and the need for economy in its use, the appropriate blood component should be used whenever possible.

Whole blood may be used where replacement of plasma proteins as well as red blood cells is needed, for example after acute blood loss during surgery or severe haemorrhage. It may also be used to supplement the circulation during cardiac bypass surgery.

The amount of whole blood transfused and the rate at which it is given depend upon the patient's age and general condition, upon the state of their circulatory system, and upon the therapeutic indication for transfusion.

The expression 'unit of blood' generally represents a volume of about 510 mL, including anticoagulant. For blood preparations a unit generally refers to the quantity of a blood component obtained from 1 unit of whole blood. Specific units of activity are used for some blood components.

The haemoglobin concentration of the blood of the average adult is raised by about 1 g per 100 mL by the transfusion of 1 unit of whole blood.

◊ Reviews and guidelines for the use of blood and blood components.

1. Contreras M, ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998.
2. Goodnough LT, *et al.* Transfusion medicine: blood transfusion. *N Engl J Med* 1999; **340:** 438–47.
3. World Health Organization. *The clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns*. Geneva: World Health Organization, 2001. Also

available as *The clinical use of blood handbook* at: http://whqlibdoc.who.int/publications/2001/9241545399.pdf (accessed 27/10/05)

4. Cable R, *et al.* American Red Cross practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature (May 2002). Available at: http://www.newenglandblood.org/professional/pgbtscreen.pdf (accessed 27/10/05)
5. Australian Red Cross Blood Service. *Transfusion medicine manual*. Available at: http://www.manual.transfusion.com.au/Home.aspx (accessed 29/08/08)
6. British Committee for Standards in Haematology Transfusion Task Force. Transfusion guidelines for neonates and older children. *Br J Haematol* 2004; **124:** 433–53. Correction. *ibid.* 2007; **136:** 514–16. Also available at: http://www.bcshguidelines.com/pdf/Neonates_124_4_2004.pdf (accessed 27/10/05)
7. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services*. 4th ed. London: The Stationery Office, 2007. Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 15/02/07)
8. British Committee for Standards in Haematology. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; **135:** 634–41.
9. Klein HG, *et al.* Red blood cell transfusion in clinical practice. *Lancet* 2007; **370:** 415–26.
10. Council of Europe. *Guide to the preparation, use and quality assurance of blood components.* 13th ed. Strasbourg: Council of Europe Publishing, 2007.

Autologous blood transfusion. Reviews and guidelines have been published on autologous blood transfusion, a procedure where a patient acts as their own blood donor, the blood usually being collected shortly before elective surgery or salvaged during the surgical procedure.[1-6]

1. British Committee for Standards in Haematology Blood Transfusion Task Force. Guidelines for autologous transfusion II: perioperative haemodilution and cell salvage. *Br J Anaesth* 1997; **78:** 768–71. Also available at: http://www.bcshguidelines.com/pdf/bja768.pdf (accessed 27/10/05)
2. Gillon J, Thomas DW. Autologous transfusion. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998: 23–8.
3. Goodnough LT, *et al.* Transfusion medicine: blood conservation. *N Engl J Med* 1999; **340:** 525–33.
4. Vanderlinde ES, *et al.* Autologous transfusion. *BMJ* 2002; **324:** 772–5.
5. Carless P, *et al.* Autologous transfusion techniques: a systematic review of their efficacy. *Transfus Med* 2004; **14:** 123–44.
6. British Committee for Standards in Haematology, Transfusion Task Force. Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion. *Transfus Med* 2007; **17:** 354–65. Also available at: http://www.bcshguidelines.com/pdf/alt_allogeneic_blood_transfusion.pdf (accessed 09/06/08)

Preparations

USP 31: Whole Blood.

Calcium Alginate

Alginato cálcico; E404.

CAS — 9005-35-0.
ATC — B02BC08.
ATC Vet — QB02BC08.

Profile

Calcium alginate is the calcium salt of alginic acid, a polyuronic acid composed of residues of D-mannuronic and L-guluronic acids. It may be obtained from seaweeds, mainly species of *Laminaria*. Calcium alginate is used as an absorbable haemostatic and for the promotion of wound healing (p.1585); it is also used in the form of a mixed calcium-sodium salt of alginic acid as a fibre made into a dressing or packing material. Calcium ions in the calcium alginate fibres are exchanged for sodium ions in the blood and exudate to form a hydrophilic gel.

Alginic acid and its calcium and sodium salts are widely used in the food industry.

◊ References.

1. Thomas S. Alginate dressings in surgery and wound management–part 1. *J Wound Care* 2000; **9:** 56–60.
2. Thomas S. Alginate dressings in surgery and wound management: part 2. *J Wound Care* 2000; **9:** 115–19.
3. Thomas S. Alginate dressings in surgery and wound management: part 3. *J Wound Care* 2000; **9:** 163–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kaltostat; Nu-Derm Alginato; Tegagen†; ***Austral.:*** Kaltostat†; Melgisorb; Sorbsan†; ***Canad.:*** Algisite†; Kaltostat; Melgisorb; Restore Calcicare; Tegagen†; ***Fr.:*** Algosteril; Coalgan; Sorbalgon; Stop Hemo; ***Ger.:*** Algosteril†; Urgosorb; ***Gr.:*** Stop Hemo†; ***Irl.:*** Kaltostat; Sorbsan; ***Ital.:*** Algosteril; Cutinova Alginate; Kaltostat; Sorbsan†; ***Port.:*** Sorbsan†; ***S.Afr.:*** Kaltostat; ***UK:*** Algosteril; Comfeel SeaSorb; Kaltostat; Sorbsan; ***USA:*** Calalgin.

Multi-ingredient: ***Arg.:*** Comfeel Plus; Comfeel Purilon†; Comfeel SeaSorb†; Fibracol Plus; Mylanta Reflux; Purilon; Seasorb; ***Canad.:*** Carboflex†; ***Fr.:*** Amivia†; Askina Sorb†; Clip Hemo; Melgisorb; Purilon; Seasorb; Urgosorb; ***Ger.:*** Algosteril Trionic†; Comfeel Plus; Purilon; SeaSorb Soft; ***Israel:*** Kaltocarb; Kaltostat; ***Port.:*** Askina Sorb†; Carboflex†; Kaltostat; ***UK:*** Comfeel Plus; SeaSorb Soft; ***Venez.:*** Mylanta Plus†.

Carbazochrome *(rINN)*

AC-17; Adrenochrome Monosemicarbazone; Carbazochromum; Carbazocromo. 3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone.

Карбазохром

$C_{10}H_{12}N_4O_3$ = 236.2.

CAS — 69-81-8 (carbazochrome); 13051-01-9 (carbazochrome salicylate); 51460-26-5 (carbazochrome sodium sulfonate).
ATC — B02BX02.
ATC Vet — QB02BX02.

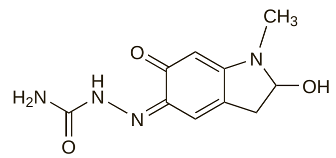

Pharmacopoeias. *Jpn* includes Carbazochrome Sodium Sulfonate ($C_{10}H_{11}N_4NaO_5S,3H_2O$ = 376.3).

Profile

Carbazochrome, an oxidation product of adrenaline, has been given as a haemostatic. Carbazochrome sodium sulfonate may be given orally in doses ranging from 30 to 150 mg daily, in at least 3 divided doses. Parenteral doses of 10 mg may be given subcutaneously or intramuscularly, and up to 100 mg may be given intravenously. It has also been given as the dihydrate and as the salicylate.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Adrenoplasma†; Adrenoxil†; ***Ger.:*** Adrenoxyl†; ***Hong Kong:*** Adona; ***India:*** Sigmachrome; Siochrome; Styptocid; ***Indon.:*** Adona; Adrome; ***Ital.:*** Adona; ***Jpn:*** Adona; ***Port.:*** Adrenoxil; ***Thai.:*** Neo-Hesna.

Multi-ingredient: ***India:*** Cadisper C; CKP; Siochrome; Styptocid; Styptocip†; ***Ital.:*** Fleboside; ***Mex.:*** Hemosin-K; ***Spain:*** Cromoxin K†; Flebeside†; Perfus Multivitaminico; ***Venez.:*** Dremo-K†.

Darbepoetin Alfa *(BAN, USAN, rINN)* ⊗

Darbepoetiinialfa; Darbepoetina alfa; Darbépoétine Alfa; Darbepoetinum Alfa; NESP; Novel Erythropoiesis Stimulating Protein. 30-L-Asparagine-32-L-threonine-87-L-valine-88-L-asparagine-90-L-threonineerythropoietin (human).

Дарбепоетин Альфа

CAS — 209810-58-2.
ATC — B03XA02.
ATC Vet — QB03XA02.

Adverse Effects and Precautions

As for Epoetins, p.1061.

Pharmacokinetics

On subcutaneous injection the bioavailability of darbepoetin alfa is about 37% and absorption is slow. It undergoes extensive metabolism, with terminal half-lives of 21 and 49 hours after intravenous and subcutaneous use respectively.

◊ References.

1. Heatherington AC, *et al.* Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) in cancer patients: preliminary report. *Br J Cancer* 2001; **84** (suppl): 11–16.
2. Allon M, *et al.* Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther* 2002; **72:** 546–55.
3. Lerner G, *et al.* Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. *Pediatr Nephrol* 2002; **17:** 933–7.
4. Heatherington AC, *et al.* Pharmacokinetics of darbepoetin alfa after intravenous or subcutaneous administration in patients with non-myeloid malignancies undergoing chemotherapy. *Clin Pharmacokinet* 2006; **45:** 199–211.

Uses and Administration

Darbepoetin alfa is an analogue of the endogenous protein hormone erythropoietin with similar properties to the epoetins (p.1062). It is used in the management of anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p.1044) and for anaemia caused by chemotherapy in patients with non-myeloid malignancies.

For **anaemia associated with chronic renal failure** in adults and children aged 11 years and older, the aim of treatment is to increase the haemoglobin concentration to 10 to 12 g per 100 mL. The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 2 g per 100 mL per month is suggested. Darbepoetin alfa is given by subcutaneous or intravenous injection in an initial dose of 450 nanograms/kg once weekly, as a single injection. In patients on haemodialysis, the intravenous route is recommended to reduce the risk of developing neutralising antibodies and pure red cell aplasia (see Effects on the Blood under Epoetins, p.1061). The dose should be adjusted at intervals of not less than 4 weeks, according to response, until the target haemoglobin concentration is achieved. In general, adjustments are made by increasing or decreasing the dose by about 25%. Maintenance doses may then be continued once weekly. Patients may be converted from weekly doses to once every 2 weeks, and should receive a dose that is equal to twice the dose that had been given once weekly. Alternatively, for patients who are not on dialysis, an initial dose of 750 nanograms/kg subcutaneously once every 2 weeks may be used, followed by dose adjustment. When the target haemoglobin concentration is achieved, a maintenance dose may be given once a month; this is equal to twice the dose that had been given once every 2 weeks.

For **anaemia in chemotherapy patients** with non-myeloid malignancies, darbepoetin alfa is given subcutaneously in an initial dose of 500 micrograms (6.75 micrograms/kg) once every 3 weeks; if the response is inadequate after 9 weeks, further therapy with darbepoetin alfa may not be effective. Alternatively, it may be given in an initial dose of 2.25 micrograms/kg once weekly. If the response is inadequate after 6 weeks, the dose may be increased to 4.5 micrograms/kg once weekly. Darbepoetin alfa should be stopped after the course of chemotherapy has finished, but it may be continued for up to 4 weeks in the UK. The rate of rise in haemoglobin should be gradual; a rate not exceeding 2 g per 100 mL per month, and a target haemoglobin of not more than 12 g per 100 mL, are suggested. Once the desired haemoglobin target has been reached, the dose should be reduced by 25 to 50% to maintain that level.

◊ Reviews.

1. Ibbotson T, Goa KL. Darbepoetin alfa. *Drugs* 2001; **61:** 2097–2104.
2. The NESP Usage Guidelines Group. Practical guidelines for the use of NESP in treating renal anaemia. *Nephrol Dial Transplant* 2001; **16** (suppl 3): 22–8.
3. Overbay DK, Manley HJ. Darbepoetin-α: a review of the literature. *Pharmacotherapy* 2002; **22:** 889–97.
4. Joy MS. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. *Ann Pharmacother* 2002; **36:** 1183–92.
5. Cvetkovic RS, Goa KL. Darbepoetin alfa in patients with chemotherapy-related anaemia. *Drugs* 2003; **63:** 1067–74.
6. Siddiqui MAA, Keating GM. Darbepoetin alfa: a review of its use in the treatment of anaemia in patients with cancer receiving chemotherapy. *Drugs* 2006; **66:** 997–1012.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Aranesp; ***Austria:*** Aranesp; ***Belg.:*** Aranesp; ***Canad.:*** Aranesp; ***Cz.:*** Aranesp; Nespo; ***Denm.:*** Aranesp; ***Fin.:*** Aranesp; ***Fr.:*** Aranesp; ***Ger.:*** Aranesp; ***Gr.:*** Aranesp; ***Hong Kong:*** Aranesp; ***Hung.:*** Aranesp; ***Irl.:*** Aranesp; ***Israel:*** Aranesp; ***Ital.:*** Aranesp; Nespo; ***Neth.:*** Aranesp; Nespo; ***Norw.:*** Aranesp; ***Pol.:*** Aranesp; ***Port.:*** Aranesp; Nespo; ***Spain:*** Aranesp; ***Swed.:*** Aranesp; ***Switz.:*** Aranesp; ***Turk.:*** Aranesp; ***UK:*** Aranesp; ***USA:*** Aranesp.

Dextran 1 *(BAN, rINN)* ⊗

Dekstraani 1; Dekstranas 1; Dextrán 1; Dextranum 1.

Декстран 1

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dextran 1 for Injection). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 1000.

A white or almost white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol.

USP 31 (Dextran 1). A low-molecular-weight fraction of dextran, consisting of a mixture of isomalto-oligosaccharides. It is obtained by controlled hydrolysis and fractionation of dextrans produced by fermentation of certain strains of *Leuconostoc mesenteroides*, in the presence of sucrose. It is a glucose polymer in

which the linkages between glucose units are almost exclusively α-1,6. Its weight average molecular weight is about 1000.
A white to off-white, hygroscopic powder. Very soluble in water; sparingly soluble in alcohol. pH of a 15% solution in water is between 4.5 and 7.0. Store at a temperature between 4° and 30°.

Profile

Dextran 1 is used to prevent severe anaphylactic reactions to infusions of dextran. It is reported to occupy the binding sites of dextran-reactive antibodies and so prevent the formation of large immune complexes with higher molecular weight dextrans.

Dextran 1 is given in usual doses of 20 mL of a solution containing 150 mg/mL by intravenous injection about 1 to 2 minutes before the infusion of the higher molecular weight dextran; the interval should not exceed 15 minutes. A suggested dose for children is 0.3 mL/kg. The dose of dextran 1 should be repeated if further infusions of dextran are required more than 48 hours after the initial dose.

Use. Two large multicentre studies (involving about 29 200 and 34 950 patients) have suggested that dextran 1 prevented anaphylactic reactions by hapten inhibition in a dose-dependent way.[1,2] It did not reduce the incidence of mild reactions, which are not generally mediated by antibodies. Another large study[3] comparing the effects of giving dextran 1 either 2 minutes before injection of dextran 40 or 70 or mixed with the injection, was stopped after the occurrence of 2 severe reactions in the admixture group. A comparison[4] of severe anaphylactic reactions to dextran infusion during the period 1983 to 1992 (when prophylaxis with dextran 1 was used) with reactions reported during the period 1975 to 1979 (no prophylaxis) found that the use of dextran 1 was associated with a 35-fold reduction in severe anaphylactic reactions to dextran infusion.

There were 21, 20, and 2 adverse reactions to dextran 1 in the first 3 studies respectively, including nausea, skin reactions, bradycardia, and hypotension. Apart from one patient, reactions to dextran 1 were mild and were considered to be of minor clinical importance. In the fourth study, adverse effects to dextran 1 were reported in about one case per 100 000 doses.

1. Ljungström K-G, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition I: a Scandinavian multicenter study on the effects of 10 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 341–8.
2. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition III: Scandinavian multicenter study on the effects of 20 mL dextran 1, 15% administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 355–60.
3. Renck H, *et al.* Prevention of dextran-induced anaphylactic reactions by hapten inhibition II: a comparison of the effects of 20 mL dextran 1, 15% administered either admixed to or before dextran 70 or dextran 40. *Acta Chir Scand* 1983; **149:** 349–53.
4. Ljungström K-G. Safety of dextran in relation to other colloids - ten years experience with hapten inhibition. *Infusionsther Transfusionsmed* 1993; **20:** 206–10.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Promit; ***Austria:*** Praedex; Promit; ***Denm.:*** Promiten; ***Ger.:*** Promit†; ***Hung.:*** Promit; ***Neth.:*** Promiten; ***Norw.:*** Promiten; ***S.Afr.:*** Promit; ***Swed.:*** Promiten; ***Switz.:*** Promit†; ***USA:*** Promit.

Dextran 40 *(BAN, USAN, rINN)* ⊗

Dekstraani 40; Dekstran 40; Dekstranas 40; Dextrán 40; Dextranum 40; LMD; LMWD; Low-molecular-weight Dextran; LVD.

Декстран 40
CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*
Eur. (see p.vii) and *Jpn* describe Dextran 40 for Injection.
Ph. Eur. 6.2 (Dextran 40 for Injection). A mixture of polysaccharides, principally of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 40 000.
A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.
USP 31 (Dextran 40). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 35 000 to 45 000 range. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 40 preparations.

Adverse Effects, Treatment, and Precautions

As for Dextran 70, p.1059.

Rapid renal excretion of dextran 40 in patients with reduced urine flow can result in high urinary concentrations which increase urinary viscosity and may cause oliguria or acute renal failure. Therefore, infusions of dextran 40 are contra-indicated in renal disease with oliguria; should anuria or oliguria occur during treatment dextran 40 should be withdrawn. Dehydration should preferably be corrected before giving dextran 40. Dextran 40 can cause capillary oozing of wound surfaces.

Effects on the kidneys. Acute renal failure has been associated with dextran 40[1-4] and less frequently with dextran 70.[1] The mechanism of the effect is unclear but suggestions include an increase in plasma oncotic pressure that decreases filtration pressure in the glomerulus and hence decreases glomerular filtration rate,[2] obstruction within the tubules,[2,4] or a direct toxic effect on renal cells.[4] Plasmapheresis has been used successfully to remove dextran from the circulation.[2-4]

1. Feest TG. Low molecular weight dextran: a continuing cause of acute renal failure. *BMJ* 1976; **2:** 1300.
2. Tsang RKY, *et al.* Acute renal failure in a healthy young adult after dextran 40 infusion for external-ear reattachment surgery. *Br J Plast Surg* 2000; **53:** 701–3.
3. Kato A, *et al.* Complication of oliguric acute renal failure in patients treated with low-molecular weight dextran. *Ren Fail* 2001; **23:** 679–84.
4. Vos SCB, *et al.* Acute renal failure during dextran-40 antithrombotic prophylaxis: report of two microsurgical cases. *Ann Plast Surg* 2002; **48:** 193–6.

Hypersensitivity. For reports of anaphylactic reactions associated with use of dextran 40, see Dextran 70, below, and Dextran 1, above.

Pharmacokinetics

After intravenous infusion dextran 40 is slowly metabolised to glucose. About 70% of a dose is excreted unchanged in the urine within 24 hours. A small amount is excreted into the gastrointestinal tract and eliminated in the faeces.

Uses and Administration

Dextran 40 is a plasma volume expander used in the management of hypovolaemic shock (p.1183). As a 10% solution, dextran 40 exerts a slightly higher colloidal osmotic pressure than plasma proteins and thus produces a greater expansion of plasma volume than dextrans of a higher molecular weight, although the expansion may have a shorter duration because of more rapid renal excretion. Dextran 40 also reduces blood viscosity and inhibits sludging or aggregation of red blood cells. It is used in the prophylaxis and treatment of postoperative thromboembolic disorders, in conditions where improved circulatory flow is required, and as a priming solution during extracorporeal circulation.

Dextran 40 is given by intravenous infusion as a 10% solution in sodium chloride 0.9% or glucose 5%. Doses depend on the clinical condition of the patient.

In **shock**, a maximum of 20 mL/kg during the first 24 hours has been recommended; the first 10 mL/kg may be given by rapid intravenous infusion. Doses of up to 10 mL/kg may be given daily thereafter for up to 5 days. Dehydration should preferably be corrected before dextran 40 is given.

In the treatment of **thromboembolic disorders** a suggested regimen is 500 to 1000 mL over 4 to 6 hours on the first day, then 500 mL over 4 to 6 hours on the next and subsequent alternate days for not more than 10 days.

For prophylaxis of postoperative thromboembolic disorders, 500 mL over 4 to 6 hours may be given during or at the end of surgery and the dose repeated on the next day; treatment may be continued in high risk patients on alternate days for up to 10 days.

Infants may be given up to 5 mL/kg and children up to 10 mL/kg.

A dose of 10 to 20 mL/kg has been added to extracorporeal perfusion fluids.

Dextran 40 is also an ingredient of artificial tears.

Post-dural puncture headache. Dextran 40 has been used in the treatment of post-dural puncture headache (p.1851) when other measures, including epidural autologous blood patch, have been ineffective. Reports[1-3] have described dextran 40 given in an epidural bolus dose of 20 mL. Sometimes this has been followed by a continuous epidural infusion of 3 to 4 mL/hour, and in these cases headache was relieved within 20 hours of starting the infusion.[1,2]

1. Aldrete JA. Persistent post-dural-puncture headache treated with epidural infusion of dextran. *Headache* 1994; **34:** 265–7.
2. Reynvoet MEJ, *et al.* Epidural dextran 40 patch for postdural puncture headache. *Anaesthesia* 1997; **52:** 886–8.
3. Souron V, Hamza J. Treatment of postdural puncture headaches with colloid solutions: an alternative to epidural blood patch. *Anesth Analg* 1999; **89:** 1333–4.

Thromboembolic disorders. Dextran 40 is only one of a variety of drugs that have been used for the prophylaxis of venous thromboembolism (p.1189) resulting from surgical operations such as hip replacement surgery. Dextran 40 may be used to prevent thromboembolic complications in some types of vascular surgery including carotid endarterectomy.[1]

1. Abir F, *et al.* Efficacy of dextran solutions in vascular surgery. *Vasc Endovascular Surg* 2004; **38:** 483–91.

Preparations

BP 2008: Dextran 40 Intravenous Infusion;
USP 31: Dextran 40 in Dextrose Injection; Dextran 40 in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Elorheo; Rheofusin†; Rheomacrodex; ***Braz.:*** Volumax D 40†; ***Canad.:*** Gentran 40; ***Cz.:*** Rheodextran†; ***Denm.:*** Rheomacrodex; ***Ger.:*** Infukoll M 40†; Longasteril 40†; Rheomacrodex†; ***Gr.:*** Rheomacrodex†; ***Hung.:*** Rheomacrodex; ***Israel:*** Rheomacrodex; ***Ital.:*** Eudextran; Plander R; Solplex 40†; ***Mex.:*** Rheomacrodex; ***Norw.:*** Rheomacrodex; ***Philipp.:*** LM Dextran; ***Port.:*** Neodextril 40; ***Rus.:*** Rheomacrodex (Реомакродекс); Rheopolydex (Реополидекс); Rheopolyglukin with Glucose (Реополиглюкин С Глюкозой); ***S.Afr.:*** Rheomacrodex; ***Spain:*** Rheomacrodex; ***Swed.:*** Perfadex; Rheomacrodex; ***Switz.:*** Rheomacrodex†; ***Thai.:*** Onkovertin; ***Turk.:*** Rheomacrodex; ***UK:*** Gentran 40; ***USA:*** Gentran 40; Rheomacrodex.

Multi-ingredient: ***Indon.:*** Otsutran; ***Port.:*** Bas-Dextrano; ***Rus.:*** Rheogluman (Реоглюман).

Dextran 60 *(BAN, rINN)* ⊗

Dekstraani 60; Dekstranas 60; Dextrán 60; Dextranum 60.

Декстран 60
CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Pharmacopoeias. *Eur.* (see p.vii) describes Dextran 60 for Injection.
Ph. Eur. 6.2 (Dextran 60 for Injection). A mixture of polysaccharides, principally of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 60 000.
A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 60 preparations.

Profile

Dextran 60 is a plasma volume expander with actions and uses similar to those of dextran 70 (below). It is given by intravenous infusion as a 3 or 6% solution in sodium chloride 0.9% or a mixture of electrolytes.

Dextran 60 is also used topically for dry eyes.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Macrodex; ***Ger.:*** Macrodex†; ***Hung.:*** Macrodex; ***Mex.:*** Rescuesol†; ***Norw.:*** Plasmodex; ***Swed.:*** Plasmodex.

Dextran 70 *(BAN, USAN, rINN)* ⊗

Dekstraani 70; Dekstran 70; Dekstranas 70; Dextrán 70; Dextranum 70; Polyglucin (dextran).

Декстран 70
CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*
Eur. (see p.vii) describes Dextran 70 for Injection.
Ph. Eur. 6.2 (Dextran 70 for Injection). A mixture of polysaccharides, principally of the α-1,6-glucan type, obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using a certain strain or substrains of *Leuconostoc mesenteroides*. The average relative molecular mass is about 70 000.
A white or almost white powder. Very soluble in water; very slightly soluble in alcohol.
USP 31 (Dextran 70). It is derived by controlled hydrolysis and fractionation of polysaccharides elaborated by the fermentative action of certain appropriate strains of *Leuconostoc mesenteroides* on a sucrose substrate. It is a glucose polymer in which the linkages between glucose units are almost entirely of the α-1:6 type. Its weight average molecular weight is in the 63 000 to 77 000 range. A 6% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Incompatibilities may arise from the slightly acid pH of dextran 70 preparations.

Storage. Crystals may form in solutions of dextran if they are stored at low temperatures. These may be redissolved by warming for a short time.

Adverse Effects and Treatment

Infusions of dextrans may occasionally produce hypersensitivity reactions such as fever, nasal congestion, joint pains, urticaria, hypotension, and bronchospasm. Severe anaphylactic reactions occur rarely and may be fatal. Dextran-reactive antibodies have been detected in patients who have not previously received dextran. This may possibly be in response to dietary or bacterial polysaccharides. Nausea and vomiting have also been reported. These reactions are treated symptomatically after withdrawal of the dextran.

Dextran 1 (p.1058) may be used to block the formation of dextran-reactive antibodies and hence the hypersensitivity reactions.

Effects on the blood. A syndrome of acute hypotension, pulmonary oedema, coagulopathy, and anaemia, has occurred after the intra-uterine instillation of 32% solution of dextran 70 for hysteroscopy.[1] The volumes of solution that were used in 10 reported cases ranged from 300 to 1200 mL, and these large volumes may have contributed to the intravascular absorption of dextran. The pathogenesis and role of dextran in this syndrome are unclear but suggestions have included acute volume overload, direct alveolar endothelial damage, and release of tissue factors that promote fibrinolysis and a consumptive coagulopathy.

1. Ellingson TL, Aboulafia DM. Dextran syndrome: acute hypotension, noncardiogenic pulmonary edema, anemia, and coagulopathy following hysteroscopic surgery using 32% dextran 70. *Chest* 1997; **111:** 513–18.

Effects on the kidneys. For a report of acute renal failure associated with use of dextran 70, see Dextran 40, above.

Hypersensitivity. In a retrospective study of allergic reactions to dextran 40 and dextran 70 reported in Sweden from 1970 to 1979,[1] there were 478 reports of reactions, 458 of which were considered to be due to dextran, out of 1 365 266 infusions given. There was a male to female ratio of 1.5 to 1 for all reactions and a ratio of 3 to 1 for the most severe reactions. The mean age of the patients was higher in those with severe reactions. Of the 28 fatal reactions, 27 occurred within 5 minutes of the start of the infusion and 25 when less than 25 mL had been infused. Three of the fatal reactions occurred after a test dose of only 0.5 to 1 mL and it was strongly recommended that such test doses should not be used.

An anaphylactic reaction has also been reported[2] more than 75 minutes after intraperitoneal instillation. After successful symptomatic treatment symptoms recurred 20 minutes later, due to slow absorption of dextran from the peritoneal cavity. No further reaction occurred after removal of 200 mL of intraperitoneal fluid by culdocentesis.

Anaphylactoid reactions after BCG vaccination have been attributed to hypersensitivity to dextran in the formulation.[3]

The use of dextran 1 for the prevention of hypersensitivity reactions is discussed under that monograph (p.1058).

1. Ljungström K-G, *et al.* Adverse reactions to dextran in Sweden 1970–1979. *Acta Chir Scand* 1983; **149:** 253–62.
2. Borten M, *et al.* Recurrent anaphylactic reaction to intraperitoneal dextran 75 used for prevention of postsurgical adhesions. *Obstet Gynecol* 1983; **61:** 755–7.
3. Rudin C, *et al.* Anaphylactoid reaction to BCG vaccine containing high molecular weight dextran. *Eur J Pediatr* 1995; **154:** 941–2.

Precautions

Dextran infusions produce a progressive dilution of oxygen-carrying capacity, coagulation factors, and plasma proteins and may overload the circulation. They are therefore contra-indicated in patients with severe heart failure, bleeding disorders such as hypofibrinogenaemia or thrombocytopenia, or renal failure and should be used with caution in patients with renal impairment, haemorrhage, chronic liver disease, or those at risk of developing pulmonary oedema or heart failure. Central venous pressure should be monitored during the initial period of infusion to detect fluid overload. Also patients should be watched closely during the early part of the infusion period, and the infusion stopped immediately if signs of anaphylactic reactions appear. Infusions should also be stopped if there are signs of oliguria or renal failure. The haematocrit should not be allowed to fall below 30% and all patients should be observed for early signs of bleeding complications. The bleeding time may be increased especially in patients receiving large volumes of dextrans. Deficiency of coagulation factors should be corrected and fluid and electrolyte balance maintained. Dehydration should be corrected before or at least during dextran infusions, in order to maintain an adequate urine flow.

The anticoagulant effect of heparin may be enhanced by dextran.

The higher molecular weight dextrans may interfere with blood grouping and cross-matching of blood, while the lower molecular weight dextrans may interfere with some methods. Therefore, whenever possible, a sample of blood should be collected before giving the dextran infusion and kept frozen in case such tests become necessary.

The presence of dextran may interfere with the determination of glucose, bilirubin, or protein in blood.

Pharmacokinetics

After intravenous infusion dextrans with a molecular weight of less than 50 000 are excreted unchanged by the kidney. Dextrans with a molecular weight greater than 50 000 are slowly metabolised to glucose. Small amounts of dextrans are excreted into the gastrointestinal tract and eliminated in the faeces.

About 50% of dextran 70 is excreted unchanged in the urine within 24 hours.

Uses and Administration

Dextran 70 is a plasma volume expander used in the management of hypovolaemic shock (p.1183). As a 6% solution dextran 70 exerts a colloidal osmotic pressure similar to that of plasma proteins and thus produces less expansion of plasma volume than dextrans of a lower molecular weight, although the expansion may have a longer duration because of less rapid renal excretion. Dextran 70 also reduces blood viscosity, interferes with fibrin polymerisation, has an antiplatelet effect, and inhibits sludging or aggregation of red blood cells. It may be used in the prophylaxis of postoperative thromboembolic disorders (p.1189).

Dextran 70 is given by intravenous infusion as a 6% solution, usually in sodium chloride 0.9% or glucose 5%.

Doses depend on the severity of the plasma loss and on the degree of haemoconcentration.

In **shock**, the usual initial dose for rapid expansion of plasma volume is 500 to 1000 mL infused at a rate of 20 to 40 mL/minute. A suggested maximum dose is 20 mL/kg during the first 24-hour period and 10 mL/kg per day thereafter; treatment should not continue for longer than 3 days. Patients may also require blood, coagulation factors, and electrolytes. A hypertonic solution of 6% dextran 70 in sodium chloride 7.5% is also available for use as a plasma expander, given in a single intravenous dose of 250 mL over 2 to 5 minutes, followed by isotonic fluids as required.

For the prophylaxis of pulmonary embolism or venous **thrombosis** in moderate- to high-risk patients undergoing surgery, a dose of 500 to 1000 mL may be given over 4 to 6 hours either during or immediately after surgery. A dose of 500 mL should be given on the next day and in high-risk patients on subsequent alternate days for up to 2 weeks after the operation.

A 32% solution of dextran 70 has been instilled into the uterus in a dose of 50 to 100 mL as a rinsing and dilatation fluid to aid **hysteroscopy**.

Dextran 70 is also an ingredient of artificial tears.

Hypertonic solutions. There is some evidence to suggest that hypertonic solutions of dextran 70 in sodium chloride 7.5% may be an effective treatment option for hypovolaemic shock resulting from trauma.[1,2]

1. Wade CE, *et al.* Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery* 1997; **122:** 609–16.
2. Alpar EK, Killampalli VV. Effects of hypertonic dextran in hypovolaemic shock: a prospective clinical trial. *Injury* 2004; **35:** 500–506.

Preparations

BP 2008: Dextran 70 Intravenous Infusion;
USP 31: Dextran 70 in Dextrose Injection; Dextran 70 in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Hyskon; ***Braz.:*** Volumax D 70†; ***Canad.:*** Gentran 70; ***Cz.:*** Tensiton†; ***Denm.:*** Macrodex; RescueFlow; ***Fin.:*** RescueFlow; ***Ger.:*** Longasteril 70†; RescueFlow†; ***Israel:*** Macrodex; ***Ital.:*** Plander; Solplex 70†; ***Mex.:*** Macrodex†; ***Neth.:*** RescueFlow; ***Norw.:*** Macrodex; RescueFlow; ***Port.:*** Neodextril 70; RescueFlow; ***S.Afr.:*** Macrodex; RescueFlow; ***Swed.:*** Macrodex; RescueFlow; ***Switz.:*** Dialens; Macrodex†; ***Turk.:*** Macrodex; ***UK:*** Gentran 70; RescueFlow; ***USA:*** Gentran 70; Hyskon; Macrodex; ***Venez.:*** Lacridos; Lacrimart; Lagrimas Artificiales.

Multi-ingredient: ***Arg.:*** Alcon Lagrimas; Kalopsis Lagrimas; Phoenix Lagrimas; Tears Naturale; Visine Plus; ***Austral.:*** Bion Tears; Opti-Free Comfort†; Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Belg.:*** Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.:*** Lacribell; Lacrima Plus; Lacrima†; Trisorb; ***Canad.:*** Artificial Tears; Bion Tears; Tears Naturale; Tears Naturale Forte; Visine Advance Triple Action; ***Chile:*** Lagrimas Artificiales; Naphtears; Nico Drops; Nicotears; Tears Naturale; ***Cz.:*** Tears Naturale; ***Denm.:*** Dacriosol; ***Ger.:*** Isopto Naturale; ***Gr.:*** Tears Naturale; ***Hong Kong:*** Bion Tears; Tears Naturale Forte; ***Hung.:*** Dacrolux; Tears Naturale; ***Indon.:*** Isotic Tearin; Tears; Tears Naturale II; ***Irl.:*** Tears Naturale; ***Israel:*** Tears Naturale; ***Ital.:*** Dacriosol; ***Malaysia:*** Bion Tears; Dacrolux; Tears Naturale; ***Mex.:*** Lacrima Plus; Naphtears; Naturalag; Tears Naturale; Visine Extra; ***Neth.:*** Duratears; ***Norw.:*** Tears Naturale; ***NZ:*** Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Philipp.:*** Gentle Tears; Tears Naturale; ***Pol.:*** Tears Naturale; ***Port.:*** Tears Naturale†; ***Rus.:*** Tears Naturale (Слеза Натуральная); ***S.Afr.:*** Tears Naturale; ***Singapore:*** Bion Tears; Dacrolux†; Tears Naturale; ***Spain:*** Dacrolux; Tears Humectante; ***Swed.:*** Bion Tears; ***Switz.:*** Tears Naturale; ***Thai.:*** Bion Tears; Tears Naturale; ***Turk.:*** Dacrolux; Tears Naturale; ***UK:*** Tears Naturale; ***USA:*** Advanced Relief Visine; Aquasite†; Bion Tears; Lacri-Tears; LubriTears; Moisture Drops; Nature's Tears; Ocucoat; Tears Naturale; Tears Renewed.

Dextran 75 *(BAN, USAN, rINN)* ⊗

Dextrán 75; Dextranum 75.

Декстран 75

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Profile

Dextran 75 consists of dextrans (glucose polymers) of weight average molecular weight about 75 000 that are derived from the dextrans produced by the fermentation of sucrose by means of a certain strain of *Leuconostoc mesenteroides*.

Dextran 75 is a plasma volume expander with actions and uses similar to dextran 70 (p.1059). It is given by intravenous infusion as a 6% solution in sodium chloride 0.9% or glucose 5%.

Ecallantide *(USAN, rINN)*

DX-88; Ecalantida; Écallantide; Ecallantidum. Human plasma kallikrein-inhibitor (synthetic protein).

Экальлантид

CAS — 460738-38-9.

Profile

Ecallantide is a recombinant inhibitor of human plasma kallikrein. It is under investigation in the management of hereditary angioedema (p.1081).

◊ Reviews.

1. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Invest Drugs* 2006; **15:** 1077–90.

Eltrombopag *(rINN)*

Eltrombopagum. 3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid.

Элтромбопаг

$C_{25}H_{22}N_4O_4$ = 442.5.
CAS — 496775-61-2.

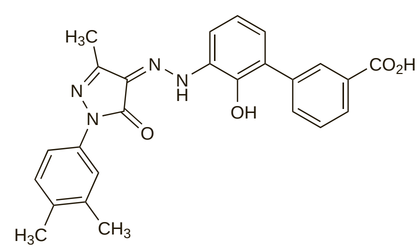

Eltrombopag Olamine *(USAN, rINNM)*

Eltrombopag olamina; Eltrombopagum Olaminum; SB-497115-GR. 3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3- methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid compound with 2-aminoethanol (1:2).

Элтромбопаг Оламин

$C_{25}H_{22}N_4O_4,2(C_2H_7NO)$ = 564.6.
CAS — 496775-62-3.

Profile

Eltrombopag is a non-peptide thrombopoietin receptor agonist. It is under investigation as a platelet growth factor given orally for the management of thrombocytopenia in patients with hepatitis C infection, and in idiopathic thrombocytopenic purpura.

◊ References.

1. McHutchison JG, *et al.* Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; **357:** 2227–36.
2. Bussel JB, *et al.* Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; **357:** 2237–47.

Epoetins ⊗

Epoetinas.
ATC — B03XA01.
ATC Vet — QB03XA01.

Description. Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor produced primarily in the kidneys.

Erythropoietin for clinical use is produced by recombinant DNA technology and the name epoetin is often applied to such material. Epoetin alfa, epoetin beta, epoetin gamma, epoetin omega, and epoetin zeta are recombinant human erythropoietins derived from a cloned human erythropoietin gene. All have the same 165 amino acid sequence but differ in the glycosylation pattern. Epoetin delta is a recombinant human erythropoietin derived from a genetically engineered continuous human cell line. It has the same amino acid sequence and glycosylation pattern as human erythropoietin.

Pharmacopoeias. *Eur.* (see p.vii) includes Erythropoietin Concentrated Solution.

Ph. Eur. 6.2 (Erythropoietin Concentrated Solution). A clear or slightly turbid colourless solution, containing 0.05 to 1% of glycoproteins indistinguishable from naturally occurring human erythropoietin in terms of amino acid sequence and glycosylation pattern. It has a potency of not less than 100 000 units per mg of active substance. Store in airtight containers below −20° and avoid repeated freezing and thawing.

Epoetin Alfa *(BAN, USAN, rINN)* ⊗

EPO; Epoetina alfa; Époétine Alfa; Epoetinum Alfa. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α.

Эпоэтин Альфа
CAS — 113427-24-0.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Beta *(BAN, USAN, rINN)* ⊗

BM-06.019; EPOCH; Epoetina beta; Époétine Bêta; Epoetinum Beta. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β.

Эпоэтин Бета
CAS — 122312-54-3.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Delta *(USAN, rINN)* ⊗

Epoetina delta; Époétine Delta; Epoetinum Delta; GA-EPO; HMR-4396. 1–165-Erythropoietin (human HMR4396), glycoform δ.

Эпоэтин Дельта
CAS — 261356-80-3.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Gamma *(BAN, rINN)* ⊗

BI-71.052; Epoetina gamma; Époétine Gamma; Epoetinum Gamma. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform γ.

Эпоэтин Гамма
CAS — 130455-76-4.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Omega *(rINN)* ⊗

Epoetina omega; Époétine Oméga; Epoetinum Omega. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ω.

Эпоэтин Омега
CAS — 148363-16-0.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Zeta *(rINN)* ⊗

Epoetina Dseta; Époétine Zêta; Epoetinum Zeta. 1–165-Erythropoietin (human clone B03XA01), glycoform ζ.

Эпоэтин Цета
CAS — 604802-70-2.
ATC — B03XA01.
ATC Vet — QB03XA01.

Stability. Proprietary preparations of recombinant human erythropoietin may contain albumin or amino acids for stability. Use in neonates may necessitate making very dilute solutions. A study of the stability of epoetin alfa in various intravenous fluids[1] found that a minimum of 0.05% protein was required to prevent loss of drug from solutions containing epoetin alfa 0.1 units/mL. In another study,[2] 0.0125% albumin was sufficient to prevent loss of drug from a solution containing epoetin alfa 100 units/mL. Epoetin alfa was stable for up to 24 hours in a solution for enteral use in neonates, formulated to mimic amniotic fluid, which also contained filgrastim and electrolytes.[3] Epoetin alfa and filgrastim were stable for at least 24 hours when refrigerated and for at least 3 weeks when frozen. At room temperature epoetin alfa was stable for 24 hours and filgrastim was stable for 18 hours. Lowered epoetin alfa concentrations were thought to be due to adsorption to the plastic infusion bag or tubing, and this was overcome by priming the tubing.

1. Ohls RK, Christensen RD. Stability of human recombinant epoetin alfa in commonly used neonatal intravenous solutions. *Ann Pharmacother* 1996; **30:** 466–8.
2. Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. *Ann Pharmacother* 1996; **30:** 1501–2.
3. Calhoun DA, *et al.* Stability of filgrastim and epoetin alfa in a system designed for enteral administration in neonates. *Ann Pharmacother* 2000; **34:** 1257–61.

Adverse Effects and Treatment

Adverse effects of epoetins include flu-like symptoms such as fever, chills, headache, arthralgias, myalgias, asthenia, dizziness, and tiredness, which occur especially at the start of treatment. Other effects include rashes, urticaria, nausea and vomiting, diarrhoea, hyperkalaemia, and reactions at the injection site. Severe hypersensitivity reactions have been reported rarely. Pure red cell aplasia associated with neutralising antibodies has also been reported rarely in patients with chronic renal failure. Modest increases in the platelet count within the normal range may occur during epoetin therapy.

Hypertension is common with the use of epoetins, particularly in patients with renal failure, and is associated with a rapid rise in haematocrit. Hypertensive crisis with encephalopathy and seizures has been reported, even in patients with initially normal or low blood pressure.

Reports of thromboembolism include myocardial ischaemia and infarction, transient ischaemic attacks and cerebrovascular accidents, deep-vein thrombosis, and pulmonary embolism. Shunt thromboses may occur in the arteriovenous fistulae of dialysis patients, and occlusion of the dialysis system is possible, due to an increased haematocrit.

◊ General references.

1. Sowade B, *et al.* The safety of treatment with recombinant human erythropoietin in clinical use: a review of controlled studies. *Int J Mol Med* 1998; **1:** 303–14.
2. Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis* 1999; **33:** 821–8.
3. Smith KJ, *et al.* The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59:** 538–48.

Effects on the blood. The use of recombinant human erythropoietin has been associated with an increase in **thrombotic events**, including vascular access thrombosis in haemodialysis patients. A number of mechanisms have been proposed for this increase such as increased blood viscosity, effects on proteins involved in coagulation, activation of platelets and the endothelium, and a vasoconstrictor effect on vascular smooth muscle.[1]

Pure red cell aplasia has been reported rarely in patients with chronic renal failure after months to years of treatment with epoetin alfa; most patients have been found to have antibodies to epoetins.[2] There have also been a few cases in patients treated with epoetin beta.[3-5] A review[5] of cases reported between January 1988 and April 2004 found that the number peaked in 2001 and 2002, and decreased rapidly when changes were made to recommendations for storage, handling, and use of epoetin alfa preparations. The effect appeared to be brand specific[6-8] and associated particularly with the subcutaneous use of preparations containing polysorbate 80 as a stabiliser.[9] Other possible causes have been proposed including contamination with silicone lubricant used in pre-filled syringes or release of organic compounds from rubber plungers.[10] Subsequently, manufacturers have reported that cases of red cell aplasia with neutralising antibodies have also occurred in chronic renal failure patients treated with subcutaneous darbepoetin alfa.[11] They also warn that because of cross-reactivity, patients who develop antibody-mediated anaemia with either an epoetin or darbepoetin alfa should not be swapped to another erythropoietic protein.

Epoetin-induced red cell aplasia has been managed with withdrawal of the epoetin and treatment with immunosuppressants including corticosteroids, cyclophosphamide, and ciclosporin. Intravenous normal immunoglobulin has also been used. Kidney transplantation is reported to bring about a rapid recovery.[10,12]

1. Smith KJ, *et al.* The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59:** 538–48.
2. Casadevall N, *et al.* Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; **346:** 469–75.
3. Krüger A, *et al.* PRCA in a patient treated with epoetin beta. *Nephrol Dial Transplant* 2003; **18:** 1033–4.
4. Tolman C, *et al.* Four cases of pure red cell aplasia secondary to epoetin β, with strong temporal relationships. *Nephrol Dial Transplant* 2004; **19:** 2133–6.
5. Bennett CL, *et al.* Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004; **351:** 1403–8.
6. Gershon SK, *et al.* Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346:** 1584–5.
7. Casadevall N, Mayeux P. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346:** 1585. Correction. *ibid.*; **347:** 458.
8. Macdougall IC. Pure red cell aplasia with anti-erythropoietin antibodies occurs more commonly with one formulation of epoetin alfa than another. *Curr Med Res Opin* 2004; **20:** 83–6.
9. Janssen-Ortho. Important drug safety information: Eprex (epoetin alfa) sterile solution revised prescribing information for patients with chronic renal failure (January 13, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/eprex_3_hpc-cps-eng.pdf (accessed 29/08/08)
10. Rossert J, *et al.* Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004; **15:** 398–406.
11. Amgen USA. Aranesp (darbepoetin alfa), November 2005. Available at: http://www.fda.gov/medwatch/safety/2005/Aranesp_DHCP.pdf (accessed 11/04/06)
12. Verhelst D, *et al.* Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet* 2004; **363:** 1768–71.

Effects on electrolytes. Hyperkalaemia and hyperphosphataemia may occur in patients receiving recombinant human erythropoietin. However, hypophosphataemia has also been reported in cirrhotic patients given erythropoietin before autologous blood donation.[1]

1. Kajikawa M, *et al.* Recombinant human erythropoietin and hypophosphatemia in patients with cirrhosis. *Lancet* 1993; **341:** 503–4.

Effects on mental function. Visual hallucinations occurred in 4 patients during treatment with recombinant human erythropoietin, stopped when treatment was withdrawn, and recurred in 2 patients when erythropoietin was reinstituted.[1] Commenting on these and a further 7 cases,[2] the manufacturers considered the reaction to be extremely rare and that the contribution of concurrent medication could not be discounted. In two groups of dialysis patients treated with recombinant human erythropoietin, 15 of 134 and 2 of 103 experienced visual hallucinations.[3] Increasing age appeared to be a risk factor. Hallucination, associated with hypertension, has occurred during epoetin therapy in a patient with a history of bone marrow transplantation.[4]

1. Steinberg H. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
2. Stead RB. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
3. Steinberg H, *et al.* Erythropoietin and visual hallucinations in patients on dialysis. *Psychosomatics* 1996; **37:** 556–63.
4. van den Bent MJ, *et al.* Erythropoietin induced visual hallucinations after bone marrow transplantation. *J Neurol* 1999; **246:** 614–16.

Effects on the skin. Skin rashes may occur during treatment with recombinant human erythropoietin.

Pseudoporphyria cutanea tarda, a photosensitivity disorder, has been reported in 2 children undergoing peritoneal dialysis and receiving erythropoietin.[1] However, it was pointed out that this disorder has occurred in adults undergoing dialysis and the children were also receiving other potential photosensitisers.

1. Harvey E, *et al.* Pseudoporphyria cutanea tarda: two case reports on children receiving peritoneal dialysis and erythropoietin therapy. *J Pediatr* 1992; **121:** 749–52.

Effects on the spleen. Aggravation of splenomegaly was reported in 2 patients with myeloproliferative disorders after use of recombinant human erythropoietin.[1] Splenic infarction has been reported in a patient with aplastic anaemia given erythropoietin,[2] and peliosis of the spleen was discovered at autopsy in a patient with end-stage renal failure who had been receiving erythropoietin.[3]

1. Iki S, *et al.* Adverse effect of erythropoietin in myeloproliferative disorders. *Lancet* 1991; **337:** 187–8.
2. Imashuku S, *et al.* Splenic infarction after erythropoietin therapy. *Lancet* 1993; **342:** 182–3.
3. Lam KY, *et al.* Peliosis of the spleen: possible association with chronic renal failure and erythropoietin therapy. *Postgrad Med J* 1995; **71:** 493–6.

Effects of subcutaneous injection. Localised pain can occur on subcutaneous injection of human recombinant erythropoietin. In comparisons of preparations it has been suggested that different excipients may affect this.[1-5] It has generally been reported that epoetin alfa preparations containing citrate buffer are more painful than those with phosphate buffer, and that epoetin beta preparations are less painful than epoetin alfa preparations.

1. Frenken LAM, *et al.* Assessment of pain after subcutaneous injection of erythropoietin in patients receiving haemodialysis. *BMJ* 1991; **303:** 288.
2. Lui SF, *et al.* Pain after subcutaneous injection of erythropoietin. *BMJ* 1991; **303:** 856.
3. Yu AW, *et al.* Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alfa. *Int J Artif Organs* 1998; **21:** 341–3.
4. Veys N, *et al.* Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. *Clin Nephrol* 1998; **49:** 41–4.
5. Cumming MN, *et al.* Subcutaneous erythropoietin alpha (Eprex) is more painful than erythropoietin beta (Recormon). *Nephrol Dial Transplant* 1998; **13:** 817.

Treatment of adverse effects. Venesection[1] and erythropheresis[2] have been used to treat raised haematocrit and haemoglobin concentrations caused by recombinant human erythropoietin overdose. Venesection also successfully reduced the blood pressure in 4 patients with life-threatening hypertension associated with recombinant human erythropoietin treatment.[3] None of the patients had a raised haematocrit and the hypertension had been unresponsive to antihypertensive therapy.

1. Brown KR, *et al.* Recombinant erythropoietin overdose. *Am J Emerg Med* 1993; **11:** 619–21.
2. Hoffman RS, *et al.* Erythropoietin overdose treated with emergent erythropheresis. *Vet Hum Toxicol* 2002; **44:** 157–9.
3. Fahal IH, *et al.* Phlebotomy for erythropoietin-associated malignant hypertension. *Lancet* 1991; **337:** 1227.

Precautions

Epoetins should be used with caution in patients with hypertension, a history of seizures, thrombocytosis, chronic hepatic impairment, ischaemic vascular disease, or in patients with malignant tumours. Hypertension should be well controlled before treatment is started and blood pressure monitored during treatment.

Response to epoetins may be diminished by iron deficiency, infection or inflammatory disorders, haemolysis, or aluminium intoxication. Anaemia due to folic acid and vitamin B_{12} deficiencies should also be excluded, since these may also reduce the response. Patients developing sudden lack of efficacy should be investigated. If pure red cell aplasia is diagnosed treatment should be stopped and testing for epoetin antibodies considered; patients should not be transferred to another epoetin.

Patients undergoing dialysis may require increased doses of heparin in view of the increase in packed cell volume.

Platelet counts, haemoglobin concentrations, and serum-potassium concentrations should be monitored regularly.

Dosage must be carefully controlled to avoid too fast an increase in haematocrit and haemoglobin, and recommended values should not be exceeded because of the increased risks of hypertension and thrombotic events.

For reference to the uncertainty of the effect of epoetins on tumour progression and progression-free survival when used in patients with cancer, see under Anaemias in Uses and Administration, p.1063.

Abuse. The potential dangers from abuse of recombinant human erythropoietin by athletes have been reviewed.[1] Normally, optimal athletic conditioning leads to little change in red cell volume but a significant increase in plasma volume and total blood volume. In contrast, the artificial increase in the red cell mass induced by epoetin is usually accompanied by a decrease in plasma volume and no change in total blood volume. Lack of medical supervision and fluid loss during endurance events increase the risk of serious adverse consequences of these changes in blood viscosity produced by such misuse of epoetin. In one case,[2] cerebral sinus thrombosis in a cyclist was attributed to the combined use of epoetin, human growth hormone, and high doses of vitamins A and E.

1. Spivak JL. Erythropoietin use and abuse: when physiology and pharmacology collide. *Adv Exp Med Biol* 2001; **502:** 207–24.
2. Lage JMM, *et al.* Cyclist's doping associated with cerebral sinus thrombosis. *Neurology* 2002; **58:** 665.

Haematocrit and haemoglobin. A study[1] involving 1233 patients undergoing haemodialysis and suffering from heart failure or ischaemic heart disease found that erythropoietin in doses sufficient to increase haematocrit to 42% (within the normal range) was associated with lack of benefit and a trend towards increased mortality when compared with doses sufficient to maintain a lower haematocrit of around 30%. However, these results are difficult to interpret, since within each group, increased haematocrit was associated with lower mortality, despite the between-group differences. The possibility that intravenous iron supplementation might have contributed to these adverse results was considered, but commentators suggested that until further data were available aiming for a haematocrit of 33 to 36%, and using intravenous iron supplementation where necessary, was still appropriate.[2]

Two studies have looked at the effects of adjusting haemoglobin to different concentrations in patients with chronic renal impairment who did not yet need dialysis. In the CHOIR study[3] of 1432 patients, epoetin alfa was used to adjust haemoglobin to either 11.3 or 13.5 g per 100 mL. The risk of cardiovascular complications, particularly death and hospitalisation for congestive heart failure, was increased in the group with the higher haemoglobin target, without any additional improvement in quality of life. The CREATE study[4] included 603 patients who were treated with epoetin beta to adjust haemoglobin to either 13.0 to 15.0 g per 100 mL or 10.5 to 11.5 g per 100 mL. Although the measures for quality of life were better in the group adjusted to the higher target and there was no statistically significant difference between the groups in the risk of cardiovascular complications, there was a trend towards a more favourable outcome in the low-target group. The FDA subsequently issued a reminder[5] that in patients receiving epoetins or darbepoetin alfa, a target haemoglobin range of 10 to 12 g per 100 mL is recommended, and that haemoglobin concentrations and blood pressure should be monitored.

1. Besarab A, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.
2. Adamson JW, Eschbach JW. Erythropoietin for end-stage renal disease. *N Engl J Med* 1998; **339:** 625–7.
3. Singh AK, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085–98.
4. Drüeke TB, *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355:** 2071–84.
5. FDA. Information for healthcare professionals: erythropoiesis stimulating agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)] (issued 16/11/06). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE_HCP.htm (accessed 20/11/06)

Resistance. Many factors may contribute to a poor response to recombinant human erythropoietin (see Precautions, above). A study in patients with anaemia of end-stage renal disease[1] found that inadequate dialysis was associated with a reduced response to erythropoietin treatment. The dialysis time and mode of dialysis may also influence response to erythropoietin therapy.[2] Antibodies to recombinant human erythropoietin have also been reported.[3,4] Delayed clinical response to recombinant human erythropoietin in a patient[5] could have been due to an inherited subclinical pyruvate kinase deficiency.

1. Ifudu O, *et al.* The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996; **334:** 420–5.
2. Locatelli F, *et al.* The modality of dialysis treatment: does it influence the response to erythropoietin treatment? *Nephrol Dial Transplant* 2001; **16:** 1971–4.
3. Peces R, *et al.* Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; **335:** 523–4.
4. Viron B, *et al.* Anticorps anti-érythropoïétine humaine recombinante: une cause exceptionnelle de résistance à l'érythropoïétine. *Nephrologie* 2002; **23:** 19–22.
5. Zachée P, *et al.* Pyruvate kinase deficiency and delayed clinical response to recombinant human erythropoietin treatment. *Lancet* 1989; **i:** 1327–8.

Pharmacokinetics

Epoetins exhibit some differences in their pharmacokinetics, possibly due to differences in glycosylation and in the formulation of the commercial preparations.

Epoetin alfa is slowly and incompletely absorbed after subcutaneous injection, and a relative bioavailability of about 10 to 20% has been reported. Peak concentrations after epoetin alfa intravenously are attained within 15 minutes, and within 5 to 24 hours after subcutaneous injection.

The elimination half-life of epoetin alfa after intravenous doses has been reported to be 4 to 13 hours in patients with chronic renal failure; the half-life is generally less in patients with normal renal function. An estimated elimination half-life of about 24 hours has been reported for epoetin alfa given subcutaneously.

Epoetin beta is similarly slowly and incompletely absorbed after subcutaneous injection, and its absolute bioavailability has been reported to be 23 to 42%. Peak serum concentrations are attained within 12 to 28 hours of subcutaneous doses. An elimination half-life of 4 to 12 hours has been reported after intravenous doses and a terminal half-life of 13 to 28 hours after subcutaneous doses.

Epoetin delta has a bioavailability after subcutaneous injection of between 26 and 36%, the peak serum concentration occurs after 8 to 36 hours, and the half-life in patients is about 27 to 33 hours. After intravenous injection, it has an elimination half-life of about 4 to 13 hours in patients with chronic renal failure, which is about double that measured in healthy subjects.

Epoetin zeta has a bioavailability of about 20% after subcutaneous injection, and peak serum concentrations occur after about 12 to 18 hours. The half-life after subcutaneous injection has been estimated to be about 24 hours. After intravenous injection, a half-life of about 4 hours has been measured in healthy subjects, and about 5 hours in patients with chronic renal failure; the half-life in children is about 6 hours.

◊ References.

1. Macdougall IC, *et al.* Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). *Clin Pharmacokinet* 1991; **20:** 99–113.
2. Halstenson CE, *et al.* Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991; **50:** 702–12.
3. Gladziwa U, *et al.* Pharmacokinetics of epoetin (recombinant human erythropoietin) after long term therapy in patients undergoing haemodialysis and haemofiltration. *Clin Pharmacokinet* 1993; **25:** 145–53.
4. Montini G, *et al.* Pharmacokinetics and hematologic response to subcutaneous administration of recombinant human erythropoietin in children undergoing long-term peritoneal dialysis: a multicenter study. *J Pediatr* 1993; **122:** 297–302.
5. Brown MS, *et al.* Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. *J Pediatr* 1993; **122:** 655–7.
6. Reddingius RE, *et al.* Pharmacokinetics of recombinant human erythropoietin in children treated with continuous ambulatory peritoneal dialysis. *Eur J Pediatr* 1994; **153:** 850–4.
7. Chakraborty A, *et al.* Population pharmacokinetics of erythropoietin in critically ill subjects. *J Clin Pharmacol* 2005; **45:** 193–202.

Uses and Administration

Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor. It is secreted primarily by the kidneys, although a small amount is produced in extrarenal sites such as the liver. Erythropoietin regulates erythropoiesis by stimulating the differentiation and proliferation of erythroid precursors, the release of reticulocytes into the circulation, and the synthesis of cellular haemoglobin. The release of erythropoietin is promoted by hypoxia or anaemia, and up to 1000 times the normal serum-erythropoietin concentration may be reached under these conditions; this response may be impaired in some disease states such as chronic renal failure. The haematological response to erythropoietin is reduced if there is an inadequate supply of iron. For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p.1042.

Epoetins alfa, beta, delta, and zeta are recombinant human erythropoietins available for clinical use that have the same pharmacological actions as endogenous erythropoietin. They are used in the management of anaemia associated with chronic renal failure in dialysis and predialysis patients; they may reduce or obviate the need for blood transfusions in these patients. Epoetins alfa, beta, and zeta are also used in the management of chemotherapy-induced anaemia in patients with non-myeloid malignant disease. Epoetin alfa is used in zidovudine-related anaemia in HIV-positive patients. Epoetin beta is used in the management of anaemia of prematurity. Recombinant human erythropoietin is also being evaluated in the management of other types of normocytic-normochromic anaemias, including that associated with inflammatory disorders such as rheumatoid arthritis. In all patients, iron status should be monitored and supplementation provided if necessary.

Epoetins alfa, beta, and zeta may also be used in patients with moderate anaemia (but no iron deficiency) before elective surgery to increase the yield of blood collected for autologous blood transfusion. Epoetin alfa may also be used in such patients to reduce the need for allogeneic blood transfusion.

In the management of **anaemia of chronic renal failure** epoetin alfa, beta, or delta may be given intravenously or subcutaneously; epoetin zeta may only be given intravenously. For haemodialysis patients the dose of epoetin should be given intravenously because of the risk of pure red cell aplasia reported with subcutaneous use (see Effects on the Blood, above); it may be given during or at the end of the dialysis session using the dialysis vascular access. For predialysis and peritoneal dialysis patients, in whom intravenous access is not readily available, doses should be given subcutaneously. The aim of treatment in adults is to increase the haemoglobin concentration to 10 to 12 g per 100 mL or to increase the haematocrit to 30 to 36%. The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 2 g per 100 mL per month is suggested.

Epoetin alfa may be given subcutaneously or by intravenous injection over at least 1 minute; slow intravenous injection over 5 minutes may be used in patients who experience flu-like symptoms as adverse effects. ***Epoetin zeta*** may be given intravenously.

- In predialysis and haemodialysis patients, a recommended initial dose of epoetin alfa or zeta is 50 international units/kg three times weekly. For epoetin alfa, a higher initial dose of 50 to 100 units/kg three times weekly has been suggested in the USA.
- Doses may be increased at 4-week intervals in increments of 25 units/kg three times weekly until the target is reached.
- In patients on peritoneal dialysis an initial dose of 50 units/kg given twice weekly may be used.

Once the target is reached doses may need to be adjusted for maintenance therapy.

- The usual total weekly maintenance dose of epoetin alfa or zeta in predialysis patients is 50 to 100 units/kg given in three divided doses, and in haemodialysis patients it is about 75 to 300 units/kg given in three divided doses. In predialysis patients a total weekly dose of 600 units/kg should not be exceeded. In patients on peritoneal dialysis, the usual total weekly maintenance dose is 50 to 100 units/kg given in two divided doses.

In children, epoetin alfa or zeta may be given intravenously to those on haemodialysis.

- The initial dose is 50 units/kg three times weekly. The dose may be increased at 4-week intervals in increments of 25 units/kg three times weekly until a target haemoglobin concentration of 9.5 to 11 g per 100 mL is reached.

The usual total weekly maintenance dose given in three divided doses is:

- 225 to 450 units/kg for those weighing less than 10 kg
- 180 to 450 units/kg for those weighing 10 to 30 kg
- 90 to 300 units/kg for those weighing over 30 kg

Epoetin beta is used similarly in the management of anaemia of chronic renal failure in dialysis and predialysis patients. It may be given subcutaneously or by intravenous injection over 2 minutes. The following dosages may be used in adults and children:

- For subcutaneous injection the initial dose is 60 units/kg weekly for 4 weeks; the total weekly dose may be divided to be given in daily doses or three times a week
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased to 80 units/kg three times weekly
- Thereafter the dose of epoetin beta may be increased at 4-week intervals, for both subcutaneous and intravenous injection, in increments of 60 units/kg weekly in divided doses, until the target haemoglobin concentration or haematocrit is reached. A total weekly dose of 720 units/kg of epoetin beta should not be exceeded

For maintenance, the dose is halved initially and then adjusted every 1 to 2 weeks according to response. The weekly subcutaneous maintenance dose may be divided into 1, 3, or 7 doses; in patients stabilised on a once-weekly dose, it may be possible to adjust to a single dose every 2 weeks.

Epoetin delta is also used in the management of anaemia of chronic renal failure in dialysis and predialysis patients.

- For subcutaneous injection, the initial dose is 50 units/kg twice weekly.
- For intravenous injection, the initial dose is 50 units/kg three times weekly.
- Dosage may be adjusted by 25 to 50%, at intervals of at least 4 weeks, as required.

In adults receiving chemotherapy for **non-myeloid malignant disease**, epoetin alfa, beta, or zeta may be given by subcutaneous injection for symptomatic anaemia, usually when the haemoglobin concentration has fallen to 10 g or lower per 100 mL. The rise in haemoglobin should be gradual; a rate not exceeding 2 g per 100 mL per month, and a target haemoglobin concentration of not more than 12 g per 100 mL, are suggested.

- Epoetin alfa or zeta may be given in an initial dose of 150 units/kg three times weekly or 450 units/kg once weekly. The dose may be increased after 4 or 8 weeks, if necessary, to 300 units/kg three times weekly. If the response is still inadequate after 4 weeks at this higher dose, treatment should be stopped. Epoetin alfa may also be given in a once-weekly dose of 40 000 units, which may be increased to 60 000 units after 4 weeks if necessary.
- Epoetin beta may be given in an initial dose of 30 000 units (about 450 units/kg) weekly, as a single dose or divided into 3 to 7 doses. The dose may be doubled after 4 weeks if necessary, but treatment should be stopped if the response is still inadequate after 4 weeks at the higher dose. The total weekly dose should not exceed 60 000 units. Once the desired haemoglobin concentration has been reached, the dose should be reduced by 25 to 50% for maintenance therapy, and adjusted as necessary.

Epoetins should be stopped after the end of chemotherapy, but epoetin alfa, beta, or zeta may be continued for up to one month in the UK.

In children, epoetin alfa may be given intravenously in a single weekly dose of 600 units/kg (to a maximum of 40 000 units). The dose may be increased if necessary after 4 weeks to 900 units/kg (maximum 60 000 units).

In adult **HIV-positive patients** on zidovudine therapy, epoetin alfa may be beneficial if the endogenous serum-erythropoietin concentration is 500 milliunits/mL or less. Epoetin alfa is given by subcutaneous or intravenous injection in an initial dose of 100 units/kg three times weekly for 8 weeks. The dose may then be increased every 4 to 8 weeks by 50 to 100 units/kg three times weekly according to response. However, patients are unlikely to benefit from doses above 300 units/kg three times weekly if this dose has failed to elicit a satisfactory response.

In the management of **anaemia of prematurity** epoetin beta is given subcutaneously in a dose of 250 units/kg three times weekly. Treatment should be started as early as possible and continued for 6 weeks.

To increase the yield of **autologous blood** in adults, epoetin alfa, beta, or zeta may be used with iron supplementation. The dose depends on the volume of blood required for collection and on factors such as the patient's whole blood volume and haematocrit. Suggested regimens are:

- epoetin alfa or zeta 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- up to 800 units/kg of epoetin beta intravenously, or up to 600 units/kg subcutaneously, twice weekly for 4 weeks before surgery

To reduce the need for allogeneic blood transfusion in adults, epoetin alfa may be given in a dose of 600 units/kg subcutaneously once weekly starting 3 weeks before surgery, with a fourth dose given on the day of surgery. Alternatively, when the time before surgery is short, 300 units/kg subcutaneously daily may be given for 10 days before surgery, on the day of surgery, and for 4 days after.

◊ Reviews.

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2. Dunn CJ, Markham A. Epoetin beta: a review of its pharmacological properties and clinical use in the management of anaemia associated with chronic renal failure. *Drugs* 1996; **51:** 299–318.
3. Beguin Y. A risk-benefit assessment of epoetin in the management of anaemia associated with cancer. *Drug Safety* 1998; **19:** 269–82.
4. Cheer SM, Wagstaff AJ. Epoetin beta: a review of its clinical use in the treatment of anaemia in patients with cancer. *Drugs* 2004; **64:** 323–46.
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6. Corwin HL. The role of erythropoietin therapy in the critically ill. *Transfus Med Rev* 2006; **20:** 27–33.
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Administration in neonates. Recombinant human erythropoietin may be given to neonates for anaemia of prematurity (see Anaemias, below). It is usually given by subcutaneous injection. Intravenous infusion in total parenteral nutrition solutions produced satisfactory results in a group of 20 neonates.[1] Enteral dosage in one small study[2] increased plasma-erythropoietin concentrations and peak reticulocyte counts, but in another larger study[3] it had no effect.

For a warning about diluting recombinant human erythropoietin solutions, see Stability, above.

1. Ohls RK, *et al.* Pharmacokinetics and effectiveness of recombinant erythropoietin administered to preterm infants by continuous infusion in total parenteral nutrition solution. *J Pediatr* 1996; **128:** 518–23.
2. Ballin A, *et al.* Erythropoietin, given enterally, stimulates erythropoiesis in premature infants. *Lancet* 1999; **353:** 1849.
3. Juul SE. Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. *J Pediatr* 2003; **143:** 321–6.

Anaemias. Epoetins are used in normocytic-normochromic anaemias (p.1044) associated with low endogenous erythropoietin concentrations.

Anaemia associated with *chronic renal disease* is primarily a result of inadequate production of erythropoietin in the kidney. Other factors that can contribute to the anaemia include iron deficiency, blood loss associated with dialysis, and severe hyperparathyroidism. The use of epoetins in the management of renal anaemia is well established,[1,2] as consistently good results have been obtained not only for correction of anaemia but also for improvement in quality of life.[1,3] In predialysis patients, epoetins also correct anaemia, reduce the requirement for blood transfusions, and improve quality of life and exercise capacity, but there may be increased hypertension[2,4] and it is not known whether the need for dialysis is delayed.[4] Over 90% of patients with renal anaemia respond to treatment with epoetins.[1] Many factors can contribute to a poor response (see Precautions, above) and the patient should always be investigated and the cause corrected where possible. Common causes of inadequate response are iron deficiency, inflammatory disorders, chronic blood loss, hyperparathyroidism, and aluminium toxicity.[1,5]

Epoetins may be given intravenously or subcutaneously. Epoetin given subcutaneously produces lower but more sustained plasma concentrations and total weekly maintenance doses are reduced.[1,2,6] The subcutaneous route is generally used in predialysis patients and those on peritoneal dialysis,[1,2] partly because of the need to avoid venepuncture of veins that are likely to be needed for future haemodialysis access. While subcutaneous injection can also be used for haemodialysis patients, the intravenous route is preferred because of the rare risk of pure red cell aplasia reported with subcutaneous use[1] (see Effects on the Blood, above) and the ready availability of intravenous access. The dosage frequency may also be important in maximising the response to treatment, but may be influenced by the epoetin being used, route of administration, treatment phase, and patient preference. For example, giving epoetins 2 or 3 times a week may allow for a lower total weekly dose than once weekly, and may be more effective, but dosing once weekly may be more convenient for maintenance therapy.[1,2] A systematic review[7] concluded that there was no evidence to support one frequency over another in terms of maintaining target haemoglobin. See Uses and Administration, above, for examples of licensed doses, routes, and dose frequency for epoetins. Darbepoetin alfa (p.1058) is given at longer dosage intervals than epoetins and there is no difference in weekly dosage requirements between subcutaneous and intravenous routes.[2,6]

Intraperitoneal use of epoetins has also been proposed and investigated.[8,9] However, this route is rarely used because the doses must be given into a dry abdomen,[1] dose requirements are generally higher than those for intravenous or subcutaneous use, and there is the potential for more frequent episodes of peritonitis.[1,2]

Blood transfusions are often used to treat *anaemia of prematurity*, and epoetins have been investigated as a means of reducing transfusion requirements. A systematic review[10] found that although epoetin reduced transfusion needs, the effect was only modest and there was considerable variation between studies. More selective reviews of very-low-birth-weight infants (less than 1500 g) also found modest reductions in transfusion requirements, whether epoetin was started within the first week of life[11] or after one week,[12] although transfusion requirements were unlikely to be eliminated completely. Response to the late use of epoetin was also found to be dose-dependent.[12]

Factors contributing to *cancer-related anaemia* include chemotherapy, radiotherapy, and the malignancy itself. Epoetin therapy can reduce the need for blood transfusions in cancer patients[13,14] and may improve quality of life.[14,15] Guidelines for the use of epoetins in chemotherapy-induced anaemia have been issued (see Anaemia, under Bone-marrow Depression, p.639). There has, however, been some concern raised about the effect of epoetin therapy on patient survival. A placebo-controlled study of epoetin alfa to maintain normal haemoglobin concentrations (12 to 14 g per 100 mL) in patients receiving chemotherapy for metastatic breast cancer was terminated early when an increase in death was found in the epoetin group.[16] In another placebo-controlled study[17] of patients with head and neck cancer undergoing radiotherapy, epoetin beta was associated with correction of anaemia but poorer locoregional progression-free survival. In contrast, analysis of a study[18] in patients with lymphoproliferative malignancies found no effect of epoetin beta on patient survival. Two meta-analyses[14,19] found no conclusive evidence that epoetins affected tumour response or survival, but pointed out that few studies were primarily designed to assess these outcomes. Subsequently, a study of the quality of life in anaemic patients with advanced non-small cell lung cancer was stopped early, when an unplanned safety analysis suggested a reduced overall survival in patients given epoetin alfa.[20] However, two later studies did aim to investigate whether epoetin therapy influenced cancer treatment outcome and survival. One study in women treated with radiochemotherapy for advanced cervical cancer reported no positive correlation between haemoglobin increase and improvement in clinical outcomes, and could not draw a definite conclusion as to whether epoetin beta had an effect on disease progression or survival.[21] Another study, in women given chemotherapy for metastatic breast cancer, found that epoetin beta had no significant effect on overall survival.[22] Nevertheless, a further meta-analysis[23] of studies in cancer patients found that epoetin or darbepoetin alfa therapy was associated with increased risks of venous thromboembolism and death. Studies to date have generally used haemoglobin targets of 12 g and above per 100 mL, and further information is needed on the benefits and risks associated with the lower targets now advised (see Uses and Administration, above). In response to these concerns, authorities have strengthened warnings in licensed product information regarding the use of epoetins and related products in patients with cancer. The MHRA has also advised[24] that blood transfusion should be the preferred option for the management of anaemia in patients with cancer, particularly in those receiving adjuvant chemotherapy or who are being treated with curative intent. They also suggest that transfusion may be preferable in patients with advanced or metastatic cancer who have a good survival prognosis.

Epoetins are sometimes used to treat *anaemias from other causes*. Potential applications include zidovudine-induced anaemia in AIDS patients (see Effects on the Blood under Zidovudine, p.914), postpartum anaemia,[25,26] anaemia in critically ill patients,[27-29] and anaemia of chronic diseases such as rheumatoid arthritis,[30,31] inflammatory bowel disease,[32-34] and chronic heart failure.[35]

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Cardiovascular diseases. There is some interest in the non-haematopoietic effects of erythropoietin, including protection from apoptosis, antoxidant activity, and pro-angiogenic effects. A possible role in the management of ischaemic stroke and myocardial infarction is under investigation.[1]

1. van der Meer P, *et al.* Erythropoietin in cardiovascular diseases. *Eur Heart J* 2004; **25:** 285–91.

Surgery. Concern over the safety of blood transfusions and the need to conserve blood supplies has led to interest in methods of reducing blood use in surgery. Recombinant human erythropoietin has been used to increase the number of units harvested for autologous transfusion[1] and to reduce transfusion requirements.[2-4] It has also been used as an alternative to blood transfusions in Jehovah's Witnesses.[5-8]

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Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Epogen; Eprex; Eritrogen; Hemax; Hypercrit; Pronivel; Recormon; ***Austral.:*** Eprex; NeoRecormon; ***Austria:*** Culat; Erypo; NeoRecormon; Recormon; ***Belg.:*** Eprex; NeoRecormon; ***Braz.:*** Eprex; Eritina; Eritromax; Hemax-Eritron; Hemoprex; Mepotin†; Recormon; Tinax; ***Canad.:*** Eprex; ***Chile:*** Epokine; Eprex; Hypercrit; Recormon; ***Cz.:*** Binocrit; Dynepo; Epomax†; Eprex; NeoRecormon; Recormon†; Retacrit; Silapo; ***Denm.:*** Eprex; NeoRecormon; ***Fin.:*** Eprex; NeoRecormon; ***Fr.:*** Eprex; NeoRecormon; ***Ger.:*** Eprex; Erypo; NeoRecormon; ***Gr.:*** Eprex; NeoRecormon; ***Hong Kong:*** Eprex; Recormon; ***Hung.:*** Eprex; NeoRecormon; ***India:*** Wepox; ***Indon.:*** Epotrex-NP; Eprex; Hemapo; Recormon; ***Irl.:*** Eprex; NeoRecormon; ***Israel:*** Eprex; Recormon; ***Ital.:*** Epoxitin†; Eprex; Globuren†; NeoRecormon; ***Jpn:*** Epogin; Espo; ***Malaysia:*** Eprex; Recormon; ***Mex.:*** Bioyetin; Epomax; Eprex; Erlan; Exetin-A; Hypercrit; Negortire; Recormon; Yepotin; ***Neth.:*** Dynepo; Eprex; NeoRecormon; ***Norw.:*** Eprex; NeoRecormon; ***NZ:*** Eprex; Recormon; ***Philipp.:*** Epokine; Eposino; Eprex; Recormon; Renogen; ***Pol.:*** Eprex; NeoRecormon; ***Port.:*** Dynepo; Eprex; NeoRecormon; Recormon†; Retacrit; Silapo; ***Rus.:*** Epocrin (Эпокрин); Eprex (Эпрекс); Erythrostim (Эритростим); Recormon (Рекормон); ***S.Afr.:*** Eprex; Recormon; Repotin; ***Singapore:*** Eprex; Recormon; ***Spain:*** Epopen; Eprex; NeoRecormon; ***Swed.:*** Eprex; NeoRecormon; ***Switz.:*** Eprex; Recormon; ***Thai.:*** Epokine; Eprex; Espogen; Hemax; Recormon; ***Turk.:*** Eprex; NeoRecormon; ***UAE:*** Epotin; ***UK:*** Binocrit; Dynepo; Eprex; NeoRecormon; Retacrit; ***USA:*** Epogen; Procrit; ***Venez.:*** Eprex; Hypercrit; Recormon.

Etamsylate *(BAN, rINN)*

Cyclonamine; E-141; Etamsilat; Etamsilatas; Etamsilato; Etamsylaatti; Etamsylát; Etamsylat; Étamsylate; Etamsylatum; Etamszilát; Ethamsylate *(USAN)*; MD-141. Diethylammonium 2,5-dihydroxybenzenesulphonate.

Этамзилат

$C_{10}H_{17}NO_5S = 263.3.$

CAS — 2624-44-4.

ATC — B02BX01.

ATC Vet — QB02BX01.

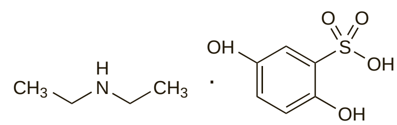

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Etamsylate). A white or almost white, crystalline powder. It shows polymorphism. Very soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 10% solution in water has a pH of 4.5 to 5.6. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Nausea, vomiting, diarrhoea, fever, headache, and skin rash have occurred after use of etamsylate. Headache and skin rashes may disappear on reduced dosage, and gastrointestinal disturbances are reduced by giving etamsylate after food. Transient hypotension has been reported following intravenous injection.

Porphyria. Etamsylate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pharmacokinetics

Etamsylate is absorbed from the gastrointestinal tract. It is excreted unchanged, mainly in the urine. Etamsylate is distributed into breast milk.

Uses and Administration

Etamsylate is a haemostatic that appears to maintain the stability of the capillary wall and correct abnormal platelet adhesion. It is given for the prophylaxis and control of haemorrhages from small blood vessels.

For short-term blood loss in menorrhagia a dose of 500 mg is given orally four times daily during menstruation. For the prophylaxis and treatment of periventricular haemorrhage in low birth-weight neonates 12.5 mg/kg is given by intramuscular or intravenous injection every 6 hours. For the control of haemorrhage after surgery etamsylate may be given orally to adults, or by intramuscular or intravenous injection in a dose of 250 to 500 mg; this dose may be repeated every 4 to 6 hours as necessary.

Menorrhagia. When given during menstruation to women with idiopathic menorrhagia (p.2126), etamsylate was as effective as mefenamic acid in reducing uterine blood loss in 1 study,[1] but was ineffective in another.[2] A review, which included published and unpublished results from these and 2 earlier studies, reported that etamsylate produced about a 10 to 15% reduction in menstrual blood loss.[3] Etamsylate is now considered to be less effective than other treatments for menorrhagia, and is no longer recommended.[4]

1. Chamberlain G, *et al.* A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1991; **98:** 707–11.
2. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
3. Coulter A, *et al.* Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care* 1995; **11:** 456–71.
4. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 06/03/08)

Neonatal intraventricular haemorrhage. Etamsylate is one of several drugs that have been tried in the prevention of intraventricular haemorrhage in very low birth-weight infants (p.1050). In a multicentre, placebo-controlled, double-blind study,[1] etamsylate was given in an initial dose of 12.5 mg/kg intravenously or intramuscularly within 1 hour of delivery, followed by the same dose intravenously every 6 hours for 4 days to a total dose of 200 mg/kg. Of 330 infants who had had no evidence of haemorrhage soon after delivery, the subsequent incidence of haemorrhage in the 162 who received etamsylate was reduced, particularly the more extensive grades when compared with the 168 who received placebo. Of a further 30 infants with evidence of periventricular haemorrhage before treatment, 21 were given etamsylate and 9 placebo; treatment with etamsylate limited the extension of bleeding. There was also a reduction in patent ductus arteriosus in the treated infants. However, a subsequent study using the same dosage regimen,[2] showed little benefit on short-term follow-up. It was considered that the study size may have been too small and the drug given too late; the initial dose was given within 4 hours of birth whereas, in the previous study, treatment was started within 1 hour of birth. Follow-up[3] of these infants at 2 years of age found that etamsylate had not reduced the risk of death, impairment, or disability. Developmental outcome assessments at about 4 years of age in patients from the first study[4] also found that despite the original reduction in intraventricular haemorrhage with etamsylate, it had not reduced cerebral palsy compared with the control group.

1. Benson JWT, *et al.* Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986; **ii:** 1297–1300.
2. The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child* 1994; **70:** F201–F205.
3. Elbourne D, *et al.* Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F183–F187.
4. Schulte J, *et al.* Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F31–F35.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Impedil; ***Belg.:*** Dicynone; ***Braz.:*** Dicinone; ***Chile:*** Om-Dicynone†; ***Cz.:*** Dicynone; ***Fr.:*** Dicynone; ***Hung.:*** Dicynone; ***India:*** Alstat; Ethacid; Ethamcip; Ethasyl; Hemsyl; Revici-E; ***Indon.:*** Dicynone; ***Irl.:*** Dicynene; ***Ital.:*** Dicynone; Eselin; ***Mex.:*** Dicynone; ***Rus.:*** Dicynone (Дицинон); ***Singapore:*** Dicynone†; ***Spain:*** Dicinone; Hemo 141; ***Switz.:*** Dicynone; ***UK:*** Dicynene; ***Venez.:*** Dicynone.

Etherified Starches ⊗

Almidón, éteres de; HES; Hydroxyethyl Starch; Hydroxyéthylamidon; Hydroxyethylamylum. 2-Hydroxyethyl ether starch.

CAS — 9005-27-0.

ATC — B05AA07.

ATC Vet — QB05AA07.

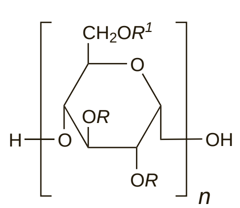

in which either *R* or *R*[1] may be either H or CH_2CH_2OH

(hetastarch)

Description. Etherified starches are starches that are composed of more than 90% of amylopectin and that have been etherified to varying extents.

- hetastarch (*BAN*, *USAN*): an average of 7 to 8 of the hydroxy groups in each 10 D-glucopyranose units of starch polymer have been converted into OCH_2CH_2OH groups
- pentastarch (*BAN*, *USAN*): an average of 4 to 5 of the hydroxy groups in each 10 D-glucopyranose units of the starch polymer have been converted to OCH_2CH_2OH groups

Etherified starches also vary in terms of average molecular weight and the position of etherification within the glucopyranose unit.

Incompatibility. Hetastarch is incompatible with many compounds including a number of injectable antibacterials.

References.

1. Wohlford JG, Fowler MD. Visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1989; **46:** 995–6.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.

Adverse Effects and Precautions

Hypersensitivity reactions including anaphylactic reactions have occurred after infusion of etherified starches. Pruritus can occur after long-term use of high doses of etherified starches; the onset may be delayed until weeks after the last infusion. Serum-amylase concentrations may appear to increase during infusion of etherified starches due to formation of an enzyme-substrate complex that is only eliminated slowly.

Precautions that should be observed with plasma expanders are described under Dextran 70, p.1060, and these should be considered when etherified starches are used. There may be some interference with blood grouping and cross-matching of blood.

◊ Reviews.

1. Wiedermann CJ. Hydroxyethyl starch - can the safety problems be ignored? *Wien Klin Wochenschr* 2004; **116:** 583–94.

Effects on the blood. Use of plasma expanders causes dilution of clotting factors and may also have direct effects on coagulation. Effects of etherified starches on the coagulation system include[1,2] a decrease in clotting factor VIII and von Willebrand factor that results in an acquired type I von Willebrand disease (see p.1051), a prolongation of the activated partial thromboplastin time, and a reduction in platelet volume. The extent of these effects appears to depend on the molecular weight and the rate of degradation *in vivo* of the starch. Etherified starches of high molecular weight that are more slowly degraded (due to a high degree of substitution or a high ratio of hydroxyethylation at the C2:C6 positions) have a greater effect on blood coagulation than medium and low molecular weight, easily degraded, etherified starches. Coagulopathy and haemorrhage have been reported with the use of solutions of etherified starches.[1,3] Serious complications such as intracranial bleeding and cerebral oedema have been reported in studies of patients with ischaemic stroke and other brain injuries who have been treated with etherified starches of various molecular weights and degrees of substitution, and several trials have been stopped prematurely as a result.[4]

1. Treib J, *et al.* Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78:** 974–83.
2. de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29:** 1261–7.
3. Jonville-Béra A-P, *et al.* Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. *N Engl J Med* 2001; **345:** 622–3.
4. Wiedermann CJ. Complications of hydroxyethyl starch in acute ischemic stroke and other brain injuries. *Pathophysiol Haemost Thromb* 2003; **33:** 225–8.

Effects on the kidneys. Osmotic-nephrosis-like lesions found at biopsy in some transplanted kidneys have been attributed to use of solutions of etherified starches in the donor patient.[1] Such use has also been reported to impair immediate graft function.[2] However, another study[3] found no association between the use of these solutions in the donor patient and osmotic-nephrosis-like lesions or delayed graft function. Oliguric acute renal failure and osmotic-nephrosis-like lesions occurred in a patient who was given an etherified starch infusion during surgery for carcinoma of the tonsils.[4]

Etherified starches should be used with caution in patients with renal impairment.[5]

1. Legendre CH, *et al.* Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342:** 248–9.
2. Cittanova ML, *et al.* Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348:** 1620–22.
3. Coronel B, *et al.* Hydroxyethylstarch and renal function in kidney transplant recipients. *Lancet* 1997; **349:** 884.
4. De Labarthe A, *et al.* Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. *Am J Med* 2001; **111:** 417–18.
5. Boldt J. Hydroxyethylstarch as a risk factor for acute renal failure: is a change of clinical practice indicated? *Drug Safety* 2002; **25:** 837–46.

Effects on the skin. Pruritus has been reported after infusion of etherified starches.[1] It appears to be associated with tissue deposition of the starch although the actual mechanism by which this provokes pruritus is unresolved. The effect appears to be dose-related, which may explain the differences in reported incidences that have ranged from less than 10% to more than 60% of patients being affected. The molecular weight and degree of substitution of the etherified starch do not appear to be risk factors. The pruritus is usually generalised, but there are reports of localised pruritus affecting the trunk, extremities, anogenital area, and head and neck. It is frequently severe, persistent, and refractory to treatment, causing sleep disturbances and adversely affecting quality of life. Attacks of pruritus may be precipitated by heat, sweating, exercise, bathing, mechanical pressure, and mental stress. It typically has a delayed onset of 1 to 6 weeks after exposure to the etherified starch. Average durations of 9 to 15 weeks have been reported, but in some cases pruritus has continued for up to 2 years. The condition is generally unresponsive to treatment, although there have been reports of relief with topical capsaicin, ultraviolet therapy, or oral naltrexone.

Marked and persistent periocular swelling developed in a patient after 15 daily infusions of hetastarch.[2] Abnormal accumulation of hetastarch was found in the periocular tissues.

1. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. *Br J Dermatol* 2005; **152:** 3–12.
2. Kiehl P, *et al.* Decreased activity of acid α-glucosidase in a patient with persistent periocular swelling after infusions of hydroxyethyl starch. *Br J Dermatol* 1998; **138:** 672–77.

Pharmacokinetics

Etherified starches consist of mixtures of molecules with a range of molecular weights and with varying degrees of etherification. After intravenous infusion the molecules with a molecular weight of less than 50 000 are readily excreted unchanged by the kidney; larger molecules are metabolised and eliminated more slowly. The rate of metabolism depends upon the size of the molecule and the degree and position of etherification, with a high molecular weight, high degree of etherification, and etherification predominantly at the C2 position leading to a slower rate of metabolism and hence a longer duration of action. About 33% of a dose of high-molecular-weight hetastarch (weight average molecular weight 450 000) and about 70% of a dose of medium-molecular-weight pentastarch (weight average molecular weight 250 000) is excreted in the urine in 24 hours. Etherified starches may be distributed to various tissues; a small proportion of the dose may persist in the body for several years.

◊ References.

1. Mishler JM, *et al.* Changes in the molecular composition of circulating hydroxyethyl starch following consecutive daily infusions in man. *Br J Clin Pharmacol* 1979; **7:** 505–9.
2. Mishler JM, *et al.* Post-transfusion survival of hydroxyethyl starch 450/0.70 in man: a long-term study. *J Clin Pathol* 1980; **33:** 155–9.
3. Yacobi A, *et al.* Pharmacokinetics of hydroxyethyl starch in normal subjects. *J Clin Pharmacol* 1982; **22:** 206–12.
4. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinet* 2005; **44:** 681–99.

Uses and Administration

Etherified starches are plasma volume expanders used in the management of hypovolaemic shock (p.1183). Those most commonly used include high-molecular-weight hetastarch (weight average molecular weight 450 000 to 480 000) and medium-molecular-weight pentastarch (weight average molecular weight 200 000 to 250 000). Other etherified starches that are used include low-molecular-weight pentastarch and medium-molecular-weight hexastarch, which has a degree of etherification between that of pentastarch and hetastarch. A higher molecular weight hetastarch is also available. Iso-oncotic solutions of etherified starches, for example, 6% hetastarch or 6% medium-molecular-weight pentastarch, exert a similar colloidal osmotic pressure to human albumin, and when given by intravenous infusion produce an expansion of plasma volume slightly in excess of the infused volume. Hyperoncotic solutions, for example 10% medium-molecular-weight pentastarch, produce an expansion of plasma volume of about 1.5 times the infused volume. The duration of effect depends on the characteristics of the starch used; for 6% hetastarch the effect lasts for 24 to 36 hours.

Etherified starches are given intravenously as solutions in sodium chloride 0.9% or other electrolytes; concentrations used are usually 6 or 10%, although 3% solutions are also available for some. The dose and rate of infusion depend on the amount of fluid lost and degree of haemoconcentration; usual doses are in the range of 500 to 2500 mL daily, depending on the preparation used, and the infusion rate may be up to about 20 mL/kg per hour if necessary.

Hetastarch and pentastarch increase the erythrocyte sedimentation rate when added to whole blood. They are therefore used in leucapheresis procedures to increase the yield of granulocytes. Doses of 250 to 700 mL may be added to venous blood in the ratio 1 part to at least 8 parts of whole blood in such procedures. Up to 2 such procedures per week and a total of 7 to 10 have been reported to be safe.

Hetastarch and hexastarch have also been used in extracorporeal perfusion fluids.

◊ References.

1. Treib J, *et al.* An international view of hydroxyethyl starches. *Intensive Care Med* 1999; **25:** 258–68.

Administration in children. Etherified starches of various degrees of substitution and molecular weights have been used as plasma expanders in children.[1-4]

1. Boldt J, *et al.* Volume replacement with hydroxyethyl starch solutions in children. *Br J Anaesth* 1993; **70:** 661–5.
2. Brutocao D, *et al.* Comparison of hetastarch with albumin for postoperative volume expansion in children after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1996; **10:** 348–51.
3. Paul M, *et al.* A randomized, controlled study of fluid management in infants and toddlers during surgery: hydroxyethyl starch 6% (HES 70/0.5) vs lactated Ringer's solution. *Paediatr Anaesth* 2003; **13:** 603–8.
4. Liet J-M, *et al.* Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003; **4:** 305–7.

Stroke. Haemodilution with pentastarch has been tried in patients with acute ischaemic stroke (p.1185) in an attempt to improve reperfusion of the brain by lowering blood viscosity. However, one study was terminated early when an excess mortality was noted in the haemodilution group.[1] The early fatalities occurred almost exclusively in patients with severe strokes; cerebral oedema was the main cause of death within one week of the onset of symptoms. Among the survivors neurological recovery was better among those who received haemodilution. A systematic review[2] of 18 haemodilution studies, which included 5 using etherified starches, found no benefit in terms of fatality or functional outcome with haemodilution. See also Effects on the Blood, above

1. Hemodilution in Stroke Study Group. Hypervolemic hemodilution treatment of stroke: results of a randomized multicenter trial using pentastarch. *Stroke* 1989; **20:** 317–23.
2. Asplund K. Haemodilution for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 27/10/05).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Hemohes†; Hessico; Infukoll HES; Venofundin; Voluven; ***Austria:*** Elohast; Expafusin; Expahes; HAES-steril; Hyperhes; Isohes; Osmohes; Plasmasteril; Varihes; Voluven; ***Braz.:*** Pentaspan†; ***Canad.:*** Hextend; Pentaspan; ***Chile:*** HAES-steril; Hemohes; Voluven; ***Cz.:*** Elohast†; HAES-steril; Hemohes; HyperHAES; Serag-HAES; Tetraspan; Voluven; ***Denm.:*** HAES-steril; HyperHAES; Venofundin; Voluven; ***Fin.:*** HAES-steril; Hemohes; HyperHAES; Plasmafusin†; Venofundin; Voluven; ***Fr.:*** Heafusine†; Hesteril; Hyperhes; Voluven; ***Ger.:*** Expafusin; Haemofusin; HAES-Rheopond; HAES-steril; Hemohes; HyperHAES; Infukoll HES; Plasmafusin†; Plasmasteril†; Rheohes; Serag-HAES; Venofundin; Vitafusal; VitaHES; Voluven; ***Gr.:*** HAES-steril; Hemohes; Venofundin; Voluven; ***Hong Kong:*** Voluven; ***Hung.:*** HAES-steril; Hemohes; HyperHAES; Isohes†; Osmohes†; Tetraspan; Voluven; ***Indon.:*** Expafusin; Fima HES; HAES-steril; Hemohes; Voluven; WIDAHES; ***Israel:*** HAES-sterile; ***Ital.:*** Amidolite; HAES-steril; HyperHAES; Voluven; ***Jpn:*** Hespander; ***Malaysia:*** HAES-steril†; Voluven; ***Mex.:*** HAES-steril; Hestar; Pentaspan†; Voluven; ***Neth.:*** Elohaes; HAES-steril; Hemohes; HyperHAES; Venofundin; Voluven; ***Norw.:*** HAES-steril†; Hemohes; HyperHAES; Voluven; ***NZ:*** Hemohes; Pentaspan†; ***Philipp.:*** HAES-steril; Voluven; ***Pol.:*** HAES-steril; Hemohes; Voluven; ***Port.:*** HAES-steril; Hemohes; HyperHAES; Tetraspan; Venofundin; Voluven; ***Rus.:*** HAES-steril (ХАЕС-стерил); HyperHAES (ГиперХАЕС); Infukoll HES (Инфукол ГЭК); Refortan (Рефортан); Stabisol (Стабизол); Voluven (Волювен); ***S.Afr.:*** HAES-steril; Voluven; ***Singapore:*** HAES-steril; Hemohes†; ***Spain:*** Elohes; HAES Esteril; Hemohes; Hes Grifols; Hesteril; Voluven; ***Swed.:*** HAES-steril; Hemohes†; HyperHAES; Venofundin; Voluven; ***Switz.:*** Expahes†; HAES-steril; Hemohes; HyperHAES; Isohes†; Plasmasteril†; Varihes†; Venofundin; Voluven; ***Thai.:*** HAES-steril; Hemohes; Hespander†; Voluven; ***Turk.:*** Biohes; Bioplazma; Expahes; HAES-steril; Hemohes; Isohes; Plasmasteril; Varihes; Voluven; ***UK:*** Elohaes†; HAES-steril; Hemohes; HyperHAES; Infukoll; Venofundin; Volulyte; Voluven; ***USA:*** Hespan; Pentaspan; Voluven; ***Venez.:*** HAES-steril†.

Factor VII

Facteur VII; Proconvertin; SPCA; Stable Factor.

ATC — B02BD05.

ATC Vet — QB02BD05.

Description. Factor VII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Eptacog Alfa (Activated) is in use for a recombinant factor VIIa.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human Coagulation Factor VII; Factor VII Coagulationis Humanus; Dried Factor VII Fraction BP 2008). A plasma protein fraction that contains the single-chain glycoprotein factor VII and may also contain small amounts of the activated form, the two-chain derivative factor VIIa, as well as coagulation factors II, IX, and X, and protein C and protein S. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VII fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. No antimicrobial preservative is added. The specific activity is not less than 2 international units of factor VII per mg of protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 15 international units/mL.

A white or almost white, pale yellow, green, or blue hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Eptacog Alfa (Activated) *(BAN, rINN)*

Eptacog alfa (activado); Eptacog Alfa (activé); Eptacogum Alfa (activatum). Blood-coagulation factor VII (human clone λHVII2463 protein moiety).

Эптаког Альфа (Активированный)

CAS — 102786-52-7; 102786-61-8.

ATC — B02BD08.

ATC Vet — QB02BD08.

Units

The potency of factor VII is expressed in international units and preparations may be assayed using the International Standard for blood coagulation factor VII concentrate, human (1998).

The potency of factor VIIa (activated factor VII) is expressed in international units and preparations may be assayed using the first International Standard for blood coagulation factor VIIa concentrate (1993).

Adverse Effects and Precautions

Use of eptacog alfa (activated) may be associated with minor skin reactions, fever, headache, and changes in blood pressure. Eptacog alfa (activated) should be used with caution in patients with conditions associated with circulating tissue factor, such as advanced atherosclerosis, crush injury, or septicaemia, since there is a risk of precipitating thrombosis or disseminated intravascular coagulation.

Effects on the cardiovascular system. Reports of 185 serious thromboembolic events associated with eptacog alfa (activated), that had been received by the FDA up to the end of 2004, have been reviewed.[1] Data were collected from both clinical trials and spontaneous reports. Various forms of arterial and venous thrombosis had been described, and most events were found to have occurred after its use for unlicensed indications in patients without haemophilia.

1. O'Connell KA, *et al.* Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; **295:** 293–8.

Uses and Administration

Factor VII may be used as replacement therapy in patients with rare genetic deficiencies of factor VII.

Factor VIIa (activated factor VII) is used to treat bleeding episodes and to prevent bleeding associated with surgery in patients with haemophilia A or haemophilia B who have developed antibodies to factor VIII or factor IX, respectively, and in acquired haemophilia (see Haemophilias, p.1048). It may also be used in congenital factor VII deficiency and Glanzmann's thrombasthenia (see Inherited Haemorrhagic Disorders, p.1050). Factor VIIa may also be useful in patients with von Willebrand's disease (p.1051). Factor VIIa is given as the recombinant form, eptacog alfa (activated). Eptacog alfa (activated) 100 micrograms is equivalent to 5000 international units.

In the treatment of bleeding episodes in patients with **haemophilia**, an initial dose of eptacog alfa (activated) 90 micrograms/kg is given by intravenous bolus injection over 2 to 5 minutes. Further doses may be given as required to achieve and maintain haemostasis, initially every 2 to 3 hours. The dose may then be adjusted (effective doses have ranged from 35 to 120 micrograms/kg), or the dosing interval increased, according to response. Treatment may need to be continued for up to 3 weeks or more following serious bleeding episodes. A similar regimen may be used in patients with haemophilia when they undergo an invasive procedure or surgery, in which case the initial dose should be given immediately before the intervention.

In **factor VII deficiency**, the usual dose of eptacog alfa (activated) for treating bleeding episodes due to surgery or invasive procedures is 15 to 30 micrograms/kg every 4 to 6 hours until haemostasis is achieved.

In **Glanzmann's thrombasthenia** that is refractory to platelet transfusions, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 90 micrograms/kg every 2 hours; at least 3 doses should be given.

◊ Reviews.

1. Poon M-C. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol* 2001; **8:** 312–18.
2. Midathada MV, *et al.* Recombinant factor VIIa in the treatment of bleeding. *Am J Clin Pathol* 2004; **121:** 124–37.
3. Anonymous. Novoseven for non-hemophilia hemostasis. *Med Lett Drugs Ther* 2004; **46:** 33–4.
4. Mathew P. The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics: a systematic review. *Thromb Haemost* 2004; **92:** 738–46.
5. Parameswaran R, *et al.* Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11:** 100–106.
6. Siddiqui MAA, Scott LJ. Recombinant factor VIIa (eptacog alfa): a review of its use in congenital or acquired haemophilia and other congenital bleeding disorders. *Drugs* 2005; **65:** 1161–77.
7. Mariani G, *et al.* Congenital factor VII deficiency: therapy with recombinant activated factor VII—a critical appraisal. *Haemophilia* 2006; **12:** 19–27.

Administration. Recombinant factor VIIa is usually given by bolus intravenous injection. The successful use of continuous infusion has been described in a few small studies and case reports.[1]

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.

Haemorrhagic disorders. As well as being used in patients with haemophilia, recombinant factor VIIa has been tried or investigated in patients with bleeding of various other causes.[1] There have been reports of recombinant factor VIIa used to manage or prevent bleeding in patients receiving warfarin[2-4] or a low-molecular-weight heparin.[5] There are also a few reports of it successfully controlling bleeding associated with diffuse alveolar haemorrhage[6-8] or dengue haemorrhagic fever;[9] it has also been studied in the management of acute variceal bleeding (p.2346). In the management of massive postpartum haemorrhage (p.2003), recombinant factor VIIa is increasingly being used when standard medical and surgical therapies are inadequate. There are suggestions that it may reduce the need for blood products, control bleeding sufficiently to allow transfer of the patient to a facility where angiography and embolisation can be performed, and reduce the need for hysterectomy.[10] However, evidence consists largely of case reports and case series. Although advice has been published, based on this evidence and expert opinion,[11] the place of recombinant factor VIIa in the treatment of postpartum haemorrhage remains to be confirmed. Initial investigation of recombinant factor VIIa in the acute management of intracerebral haemorrhage was promising,[12] but a phase 3 study found that it did not reduce the rates of death or severe disability, compared with placebo.[13] Recombinant factor VIIa is also under investigation in the management of serious bleeding after surgery or trauma.[14,15]

1. Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. *Ann Pharmacother* 2005; **39:** 885–91.
2. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002; **137:** 884–8.

3. Freeman WD, *et al.* Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc* 2004; **79:** 1495–1500.
4. Talkad A, *et al.* Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke. *Neurology* 2005; **64:** 1480–1.
5. Hu Q, Brady JO. Recombinant activated factor VII for treatment of enoxaparin-induced bleeding. *Mayo Clin Proc* 2004; **79:** 827.
6. Betensley AD, Yankaskas JR. Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. *Am J Respir Crit Care Med* 2002; **166:** 1291–2.
7. Pastores SM, *et al.* Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest* 2003; **124:** 2400–2403.
8. Henke D, *et al.* Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med* 2004; **140:** 493–4.
9. Chuansumrit A, *et al.* The use of recombinant activated factor VII for controlling life-threatening bleeding in dengue shock syndrome. *Blood Coag Fibrinol* 2004; **15:** 335–42.
10. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth* 2007; **16:** 29–34.
11. Welsh A, *et al.* Guidelines for the use of recombinant activated factor VII in massive obstetric haemorrhage. *Aust N Z J Obstet Gynaecol* 2008; **48:** 12–16.
12. Mayer SA, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352:** 777–85.
13. Mayer SA, *et al.* FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; **358:** 2127–37.
14. Dutton RP, *et al.* Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; **57:** 709–18.
15. Levi M, *et al.* Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med* 2005; **33:** 883–90.

Preparations

Ph. Eur.: Human Coagulation Factor VII.

Proprietary Preparations (details are given in Part 3)
Arg.: NovoSeven; ***Austral.:*** NovoSeven; ***Austria:*** NovoSeven; ***Belg.:*** NovoSeven; ***Braz.:*** NovoSeven; ***Canad.:*** NiaStase; ***Chile:*** NovoSeven; ***Cz.:*** NovoSeven; ***Denm.:*** NovoSeven; ***Fin.:*** NovoSeven; ***Fr.:*** NovoSeven; ***Ger.:*** NovoSeven; ***Gr.:*** NovoSeven; ***Hong Kong:*** NovoSeven; ***Hung.:*** NovoSeven; ***Irl.:*** NovoSeven; ***Israel:*** NovoSeven; ***Ital.:*** NovoSeven; Provertin-UM TIM 3; ***Jpn:*** NovoSeven; ***Malaysia:*** NovoSeven; ***Mex.:*** NovoSeven; ***Neth.:*** NovoSeven; ***Norw.:*** NovoSeven; ***NZ:*** NovoSeven; ***Philipp.:*** NovoSeven; ***Pol.:*** NovoSeven; ***Port.:*** NovoSeven; ***Rus.:*** NovoSeven (НовоСэвен); ***S.Afr.:*** NovoSeven; ***Singapore:*** NovoSeven; ***Spain:*** NovoSeven; ***Swed.:*** NovoSeven; ***Switz.:*** NovoSeven; ***Thai.:*** NovoSeven; ***Turk.:*** NovoSeven; ***UK:*** NovoSeven; ***USA:*** NovoSeven.

Factor VIII

AHF; Antihaemophilic Factor; Facteur VIII.
ATC — B02BD02.
ATC Vet — QB02BD02.

Description. Factor VIII is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The names Moroctocog Alfa (see below) and Octocog Alfa (see below) are in use for recombinant factor VIII.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Human Coagulation Factor VIII; Factor VIII Coagulationis Humanus; Dried Factor VIII Fraction BP 2008). A plasma protein fraction that contains the glycoprotein coagulation factor VIII with varying amounts of von Willebrand factor, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor VIII fraction is dissolved in an appropriate liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under an inert gas. Auxiliary substances such as a stabiliser may be added. No antimicrobial preservative is added. The specific activity is not less than 1 international unit of factor VIII:C per mg of total protein before the addition of any protein stabiliser. When reconstituted as stated on the label the resulting solution contains not less than 20 international units of factor VIII:C per mL.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Human Coagulation Factor VIII (rDNA); Factor VIII Coagulationis Humanus (ADNr)Dried Factor VIII (rDNA) BP 2008). A freeze-dried preparation of glycoproteins having the same activity as coagulation factor VIII in human plasma. It is prepared as full-length factor VIII (octocog alfa), or as a shortened two-chain structure (relative molecular mass 90 000 and 80 000), in which the B-domain has been deleted from the heavy chain (moroctocog alfa). Full-length human rDNA coagulation factor VIII contains 25 potential *N*-glycosylation sites, 19 in the B-domain of the heavy chain, 3 in the remaining part of the heavy chain (relative molecular mass 90 000) and 3 in the light chain (relative molecular mass 80 000).

Human coagulation factor VIII (rDNA) is produced by recombinant DNA technology in mammalian cell culture. Auxiliary substances such as a stabiliser may be added. A white or slightly yellow powder or friable mass. pH of the reconstituted preparation is 6.5 to 7.5. Protect from light.

USP 31 (Antihemophilic Factor). A sterile freeze-dried powder containing the factor VIII fraction prepared from units of human venous plasma that have been tested for the absence of hepatitis B surface antigen, obtained from whole-blood donors and pooled; it may contain heparin sodium or sodium citrate. It contains not less than 100 units per g of protein. Unless otherwise specified it should be stored at 2° to 8° in hermetically-sealed containers. It should be used within 4 hours of reconstitution and should be administered with equipment that includes a filter.

A white or yellowish powder. On reconstitution it is opalescent with a slight blue tinge or is a yellowish liquid.

USP 31 (Cryoprecipitated Antihemophilic Factor). A sterile frozen concentrate of human antihaemophilic factor prepared from the cryoprotein fraction, rich in factor VIII, of human venous plasma obtained from suitable whole-blood donors from a single unit of plasma derived from whole blood or by plasmapheresis, collected and processed in a closed system. It contains no preservative. It has an average potency of not less than 80 units per container. It should be stored at or below −18° in hermetically-sealed containers. It should be thawed to 20° to 37° before use; this liquid should be stored at room temperature and used within 6 hours of thawing; it should also be used within 4 hours of opening the container and administered with equipment that includes a filter.

A yellowish frozen solid. On thawing it becomes a very viscous, yellow, gummy liquid.

Moroctocog Alfa *(BAN, rINN)*

Moroctocogum Alfa; Moroktokog Alfa; Moroktokogialfa. (1—742)–(1637—1648)-Blood-coagulation factor VIII (human reduced) complex with 1649—2332-blood-coagulation factor VIII (human reduced).

Мороктоког Альфа

CAS — 284036-24-4.

Pharmacopoeias. *Eur.* (see p.vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Octocog Alfa *(BAN, rINN)*

Bay-w-6240; Factor VIII (rDNA); Octocogum Alfa. Blood-coagulation factor VIII (human), glycoform α.

Октоког Альфа

CAS — 139076-62-3;.

Pharmacopoeias. *Eur.* (see p.vii) includes under the title Human Coagulation Factor VIII (rDNA) (see above).

Units

The potency of factor VIII is expressed in international units and preparations may be assayed using the sixth International Standard for blood coagulation factor VIII concentrate, human (1998).

Adverse Effects and Precautions

Allergic reactions may sometimes follow the use of factor VIII preparations; the chills, urticaria, and headache experienced by some patients may be allergic manifestations. There is the possibility of intravascular haemolysis in patients with blood groups A, B, or AB receiving high doses or frequently repeated doses of factor VIII preparations due to the content of blood group isoagglutinins; also massive doses of some preparations may produce hyperfibrinogenaemia. Such risks should be reduced with more highly purified preparations.

Factor VIII preparations have been associated with the transmission of some viral infections, including hepatitis B and C, and more notably transmission of HIV. Strenuous efforts are now undertaken to screen the donor material from which factor VIII material is obtained and new methods of manufacture have also been introduced with the aim of inactivating any viruses present. Vaccination against hepatitis A and B is recommended for patients not already immune. Recombinant preparations are also available.

Some patients develop antibodies to factor VIII (see Resistance, below).

Effects on blood platelets. There have been case reports of thrombocytopenia associated with use of porcine factor VIII.[1] A retrospective study[2] of patients treated with porcine factor VIII found that the platelet count fell in 61% of 175 infusions given to 57 patients. The fall was generally clinically insignificant and platelet count appeared to recover within an hour. The effect was, however, dose-related, and larger reductions in platelet count were usually associated with intensive replacement over several days for surgery or trauma.

1. Green D, Tuite GF. Declining platelet counts and platelet aggregation during porcine VIII:C infusions. *Am J Med* 1989; **86:** 222–4.
2. Hay CRM, *et al.* Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost* 1996; **75:** 25–9.

Resistance. Some patients with haemophilia A develop inhibitory antibodies to factor VIII (see Haemophilias, p.1048). The risk is highest within the first 20 to 100 treatments. Low-titre antibodies are usually transient and overcome by increased or continuing treatment with factor VIII. With high-titre highly responding antibodies, however, bleeding episodes may need to be managed with factor VIII inhibitor bypassing fraction (activated prothrombin complex concentrate), or recombinant factor VIIa. Highly responding antibodies can be eradicated by immune tolerance regimens, using regular infusion of factor concentrates over long periods, with additional immunosuppression and immuno-adsorption in some cases.[1] Postmarketing monitoring in Europe has revealed a higher number of cases of inhibitory antibodies associated with recombinant factor VIII preparations than would be expected from experience with plasma-derived products.[2] However, a review[3] by the EMEA found that, on the basis of available data, it was not possible to estimate and compare the incidence of inhibitors between different recombinant factor VIII products. They warned that recurrence of low-titre antibodies had occurred after switching from one product to another in previously treated patients with more than 100 exposure days who had a history of inhibitor development. They also requested that further investigation be undertaken by companies that market recombinant factor VIII products.

There have also been reports of lack of effect with the use of the recombinant factor VIII, moroctocog alfa, for prophylaxis, in patients who have no evidence of antibodies to factor VIII.[4]

1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. *Lancet* 2003; **361:** 1801–9.
2. EMEA. EMEA public statement: review of recombinant factor VIII (FVIII) products and inhibitor development: Advate, Kogenate Bayer/Helixate NexGen, Kogenate/Helixate, Recombinate, ReFacto (issued 18 October 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/33131605en.pdf (accessed 13/06/08)
3. EMEA. Public statement: EMEA completes the review of recombinant factor VIII products and inhibitor development (issued 31 July 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/31022507en.pdf (accessed 13/06/08)
4. Wyeth Canada. Important safety information about Refacto (moroctocog alfa), antihemophilic factor (recombinant) [BDDrFVIII] (issued September 15, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/refacto_hpc-cps-eng.pdf (accessed 29/08/08)

Transmission of infections. Treatment with heat or chemicals and efforts to screen the donor material from which factor VIII and other clotting factors are obtained seem to have overcome problems with transmission of HIV and hepatitis B and C, although there is concern that non-lipid-enveloped viruses, such as human parvovirus B19 and hepatitis A, may still be transmitted. Vaccination against hepatitis A and B has been recommended for all patients who receive or may require blood products. Plasma-derived clotting factor preparations, or recombinant preparations containing added albumin, may carry a risk of transmission of variant Creutzfeldt-Jakob disease (see under Blood, p.1056). There has also been some concern about the use of human and animal products in the culture media used to manufacture recombinant clotting factor preparations, because of the theoretical risk of viral transmission from infected cell lines. Recombinant manufacturing techniques and formulations have changed over time and human and animal products are no longer used in some preparations.[1]

1. Keeling D, *et al.* United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO). Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2008; **14:** 671–84. Also available at: http://www.robsoft.plus.com/ukhcdo/docs/guidelines/2008_guideline_on_the_selection_and_use_of_therapeutic_products.pdf (accessed 13/08/08)

Pharmacokinetics

In patients with haemophilia A, factor VIII preparations have a terminal half-life of about 12 hours, whether human-derived or of recombinant origin.

◊ References.

1. Messori A, *et al.* Clinical pharmacokinetics of factor VIII in patients with classic haemophilia. *Clin Pharmacokinet* 1987; **13:** 365–80.
2. Björkman S, *et al.* Pharmacokinetics of factor VIII in humans: obtaining clinically relevant data from comparative studies. *Clin Pharmacokinet* 1992; **22:** 385–95.

Uses and Administration

Factor VIII is used as replacement therapy in patients with haemophilia A, a genetic deficiency of factor VIII; it may also be used in acquired haemophilia (see Haemophilias, p.1048).

Preparations of factor VIII may be derived from human plasma or recombinant sources. They are used to control bleeding episodes in the treatment of patients with haemophilia A and to prevent bleeding episodes in such patients undergoing dental and surgical procedures. They may also be used for long-term prophylaxis in patients with severe haemophilia A.

Preparations of factor VIII are given by slow intravenous injection or short infusion, and some octocog alfa preparations may also be given by continuous infusion. The dosage of factor VIII should be determined for each patient and will vary with the circumstances involving bleeding or type of surgery to be performed. In adults, a dose of 1 international unit/kg has been reported to raise the plasma concentration of factor VIII by about 2% (of normal). The response may be lower in children. A suggested formula to calculate, approximately, the dose required for a given effect is:

units = wt (kg) × 0.5 × % desired increase (of normal)

Recommended doses vary depending on the preparation used, but the following increments in plasma concentration of factor VIII have been suggested:

- for mild to moderate haemorrhage an increase to 20 to 30% of normal, usually with a single dose of 10 to 15 units/kg
- for more serious haemorrhage or minor surgery an increase to 30 to 50% of normal, by a usual initial dose of 15 to 25 units/kg followed by 10 to 15 units/kg every 8 to 12 hours if required
- for severe haemorrhage or major surgery an increase to 80 to 100% of normal may be necessary, the usual initial dose being 40 to 50 units/kg followed by 20 to 25 units/kg every 8 to 12 hours. Some octocog alfa preparations may also be given for major surgery as an initial pre-operative bolus followed by a continuous infusion, adjusted postoperatively to daily clearance and desired factor VIII concentrations

For long-term prophylaxis in severe haemophilia A, doses of 10 to 50 units/kg every 2 or 3 days, as required, may be used.

In patients with inhibitory antibodies to human factor VIII, a porcine factor VIII preparation may be used in doses of 25 to 150 units/kg depending upon the severity of the haemorrhage.

Some factor VIII concentrates also contain von Willebrand factor and these preparations may be used in the management of von Willebrand's disease (p.1051). Commercial very highly purified and recombinant factor VIII preparations do not contain appreciable amounts of von Willebrand factor and are thus ineffective.

Cryoprecipitate is an alternative source of clotting factors and contains factor VIII, factor XIII, von Willebrand factor, fibrinogen, and fibronectin. It has been used in the treatment of haemophilia A and von Willebrand's disease but safer more specific clotting factor alternatives are now available and preferred.

◊ Reviews.

1. McCormack PL, Plosker GL. Octocog alfa, plasma/albumin-free method. *Drugs* 2005; **65:** 2613–20.
2. Frampton JE, Wagstaff AJ. Sucrose-formulated octocog alfa: a review of its use in patients with haemophilia A. *Drugs* 2008; **68:** 839–53.

Administration. Surgical prophylaxis or significant haemorrhage in patients with haemophilia A is usually managed with injections of factor VIII given intravenously every 8 to 12 hours. However, continuous intravenous infusion has been used as an alternative.[1,2] It prevents wide fluctuations in factor VIII plasma concentrations and there is a progressive decrease in clearance associated with steady state. Studies have suggested that continuous infusion is as effective as bolus injection, but with a lower concentrate requirement. Concerns about continuous infusion include factor VIII stability, bacterial contamination, local irritation and thrombophlebitis, and inhibitor formation.

1. Stachnik JM, Gabay MP. Continuous infusion of coagulation factor products. *Ann Pharmacother* 2002; **36:** 882–91.
2. Schulman S. Continuous infusion. *Haemophilia* 2003; **9:** 368–75.

Preparations

Ph. Eur.: Human Coagulation Factor VIII; Human Coagulation Factor VIII (rDNA);
USP 31: Antihemophilic Factor; Cryoprecipitated Antihemophilic Factor.

Proprietary Preparations (details are given in Part 3)
Arg.: Beriate P; Emoclot; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Immunate; Koate-DVI†; Monarc-M†; Monoclate-P; Octanate; Recombinate; ReFacto†; ***Austral.:*** AHF†; Biostate; Kogenate; Recombinate; ReFacto; ***Austria:*** Advate; Beriate; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Belg.:*** Advate; Factane; Haemate; Helixate; Kogenate; Recombinate; ReFacto; ***Braz.:*** Beriate P; Fatori 8Y†; Haemate; Immunate†; Koate†; Kryobulin†; Monoclate-P; Octavi†; Vueffe†; ***Canad.:*** Helixate; Humate-P; Kogenate; Recombinate; ReFacto; ***Chile:*** Emoclot; Fanhdi; Koate-DVI; Octanate†; ***Cz.:*** Advate; Emoclot†; Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil M†; Immunate; Kogenate; Metoda M†; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Denm.:*** Advate; Haemate; Helixate; Kogenate; Monoclate-P†; Recombinate; ReFacto; ***Fin.:*** Advate; Amofil; Kogenate; Recombinate; ReFacto; ***Fr.:*** Advate; Factane; Helixate; Hemofil M†; Kogenate; Monoclate-P†; Recombinate; ReFacto; ***Ger.:*** Advate; Beriate P; Fanhdi; Haemate; Haemoctin SDH; Helixate; Hemofil†; Immunate; Kogenate; Monoclate-P†; Octanate; Profilate†; Recombinate; ReFacto; Wilate; ***Gr.:*** 8Y; Advate; Fanhdi; Fibrogammin P; Haemoctin; Helixate; Hemofil M; Immunate; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Hong Kong:*** Alphanate; Haemate; Hemofil M; Koate-DVI; Recombinate; ***Hung.:*** Beriate P; Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Humafactor-8; Immunate; Koate†; Kogenate; Octanate; Recombinate; ReFacto; ***Indon.:*** Koate; ***Irl.:*** Haemate†; Kogenate; Monoclate-P†; ReFacto; ***Israel:*** Fanhdi; Haemate; Haemoctin SDH; Hemofil M; Hyate:C; Koate; Monarc-M; Monoclate-P; Omrixate; Profilate; Recombinate; ***Ital.:*** Advate; Alphanate; Beriate P; Emoclot; Fanhdi; Haemate; Helixate; Hemofil M; Immunate; Kogenate; Recombinate; ReFacto; Uman-Cry DI†; Vueffe†; ***Jpn:*** Advate; Recombinate; ***Malaysia:*** Alphanate; Fanhdi; Hemofil; Koate-DVI†; ***Mex.:*** Emoclot†; Hemofil M†; Immunate†; Koate-DVI†; Monoclate-P; Octanate; ***Neth.:*** Advate; Alphanate; Haemate; Helixate; Hemofil; Immunate; Kogenate; Recombinate; ReFacto; ***Norw.:*** Helixate; Kogenate; Recombinate; ReFacto; ***NZ:*** Advate; AHF; Biostate; Kogenate; Octanate; Recombinate; ReFacto; ***Philipp.:*** Alphanate; Hemofil M; Koate-DVI; ***Pol.:*** Czynnik VIII (Metoda M); Haemoctin; Hemofil; Immunate; ***Port.:*** Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; Wilate; ***Rus.:*** Emoclot (Эмоклот); Koate (Коэйт-ДВИ); Octanate (Октанат); ***S.Afr.:*** Haemosolvate; ***Singapore:*** Alphanate; Fanhdi; Haemoctin SDH; Hemofil M†; Koate-DVI†; Optivate; ***Spain:*** Advate; Beriate P; Fanhdi; Haemate; Helixate; Hemofil M; Kogenate; Monoclate-P†; Octanate; Recombinate; ReFacto; ***Swed.:*** Advate; Beriate P†; Haemate; Helixate; Hemofil M†; Immunate; Kogenate; Monoclate-P†; Octonativ-M; Recombinate; ReFacto; ***Switz.:*** Advate; Beriate P; Haemate; Helixate; Immunate; Kogenate; Octanate; Recombinate; ReFacto; ***Thai.:*** Alphanate; Fanhdi; Haemoctin SDH; Hemoraas; Method M†; Octanate; ***Turk.:*** Beriate P; Emoclot; Factane; Fanhdi; Haemate; Haemoctin SDH; Haemoetin; Hemofil M; Immunate; Koate-DVI; Liberate; Monarc-M; Octanate; ***UK:*** Advate; Alphanate; Beriate P; Fanhdi; Haemate; Helixate; Hemofil M†; Hyate:C; Kogenate; Liberate†; Monoclate-P; Optivate; Recombinate; ReFacto; Replenate; ***USA:*** Advate; Alphanate; Bioclate†; Helixate; Hemofil M; Humate-P; Hyate:C†; Koate-DVI; Kogenate; Monarc-M; Monoclate-P; Recombinate; ReFacto; Xyntha; ***Venez.:*** Fandhi; Hemofil M†; Immunate†.

Multi-ingredient: ***Fr.:*** Innobranduo†.

Factor VIII Inhibitor Bypassing Fraction

Activated Prothrombin Complex Concentrate; Anti-inhibitor Coagulant Complex; Complejo coagulante antiinhibidor del factor VIII; Faktör VIII İnhibitör Baypaslayan Fraksiyonu.

ATC — B02BD03.
ATC Vet — QB02BD03.

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of preparations with factor VIII inhibitor bypassing activity. Rapid infusion may cause headache, flushing, and changes in blood pressure and pulse rate.

It should not be given if disseminated intravascular coagulation is suspected or if there are signs of fibrinolysis. It should be used with caution in patients with liver disease. The risk of thromboembolism may be increased with the use of high doses or in patients with thrombotic risk factors.

As with other plasma-derived products, there is a risk of transmission of infection.

Safety. References.

1. Ehrlich HJ, *et al.* Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002; **8:** 83–90.
2. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. *Haemophilia* 2004; **10** (suppl): 10–16.

Uses and Administration

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma and contain factors II, IX, and X, and activated factor VII; small amounts of factor VIII and factors of the kallikrein-kinin system are also present. They are used in patients with haemophilia A who have antibodies to factor VIII and in patients with acquired antibodies to factor VIII (see Haemophilias, p.1048). The dose is given intravenously and depends on the preparation used.

◊ References.

1. White GC. Seventeen years' experience with Autoplex/Autoplex T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. *Haemophilia* 2000; **6:** 508–12.
2. Wilde JT. Evidence for the use of activated prothrombin complex concentrates (aPCCs) in the treatment of patients with haemophilia and inhibitors. *Pathophysiol Haemost Thromb* 2002; **32** (suppl): 9–12.
3. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004; **10:** 169–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Feiba; ***Austria:*** Feiba; ***Belg.:*** Feiba; ***Braz.:*** Feiba†; ***Canad.:*** Feiba; ***Cz.:*** Feiba; Ocplex; ***Denm.:*** Feiba; ***Fin.:*** Feiba; ***Fr.:*** Feiba; ***Ger.:*** Autoplex†; Feiba; ***Hong Kong:*** Feiba†; ***Hung.:*** Feiba; ***Israel:*** Feiba; ***Ital.:*** Feiba; ***Malaysia:*** Autoplex T†; Feiba; ***Mex.:*** Feiba†; ***Neth.:*** Cofact; Feiba; ***NZ:*** Feiba; ***Pol.:*** Feiba; ***Port.:*** Feiba; ***S.Afr.:*** Feiba; ***Spain:*** Feiba; ***Swed.:*** Autoplex†; Feiba; Ocplex; ***Switz.:*** Feiba; ***Turk.:*** Feiba; ***UK:*** Feiba; ***USA:*** Autoplex T†; Feiba.

Factor IX

Christmas Factor; Facteur IX; Plasma Thromboplastin Component; PTC.

ATC — B02BD04.
ATC Vet — QB02BD04.

Description. Factor IX is a plasma protein involved in blood coagulation. It may be obtained from human plasma or produced by recombinant DNA technology. The name Nonacog Alfa is in use for recombinant factor IX.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Human Coagulation Factor IX; Factor IX Coagulationis Humanus; Dried Factor IX Fraction BP 2008). A plasma protein fraction containing coagulation factor IX, prepared by a method that effectively separates it from other prothrombin complex factors (factors II, VII, and X). It is prepared from human plasma obtained from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed to maintain functional integrity of factor IX, to minimise activation of any coagulation factor, and includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor IX fraction is dissolved in a suitable liquid, passed through a bacteria-retentive filter, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. Heparin, antithrombin, or other auxiliary substances such as a stabiliser may be included. No antimicrobial preservative is added. The specific activity is not less than 50 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

Ph. Eur. 6.2 (Human Prothrombin Complex; Prothrombinum Multiplex Humanum; Dried Prothrombin Complex BP 2008). It contains factor IX with variable amounts of coagulation factors II, VII, and X. It is prepared by fractionation of human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation is designed in particular to minimise thrombogenicity and includes a step or steps that have been shown to remove or inactivate known agents of infection. The prothrombin complex fraction is dissolved in a suitable liquid, sterilised by filtration, distributed aseptically into final containers, and immediately frozen. The preparation is freeze-dried and the containers are sealed under vacuum or under an inert gas. No antimicrobial preservative is added. Heparin, antithrombin, and other auxiliary substances such as a stabiliser may be added. The potency of the preparation is not less than 0.6 international units of factor IX per mg of total protein before the addition of any protein stabiliser. The dried product is a white or slightly coloured, very hygroscopic, powder or friable solid. Store in airtight containers. Protect from light. When reconstituted as stated on the label the resulting solution contains not less than 20 international units/mL.

USP 31 (Factor IX Complex). A sterile freeze-dried powder consisting of partially purified factor IX fraction, as well as concentrated factor II, VII, and X fractions of venous plasma obtained from healthy human donors. It contains no preservatives. It should be stored at 2° to 8° in hermetically-sealed containers. It should be used within 4 hours after reconstitution and administered with equipment that includes a filter.

Nonacog Alfa *(BAN, USAN, rINN)*

Nonacogum Alfa; Nonakog Alfa; Nonakogialfa. Blood-coagulation factor IX (human), glycoform α; Blood-coagulation factor IX (synthetic human); .

Нонаког Альфа

CAS — 113478-33-4; 181054-95-5;.
ATC — B02BD09.
ATC Vet — QB02BD09.

Units

The activity of factor IX is expressed in terms of international units and preparations may be assayed using the third International Standard for blood coagulation factor IX concentrate, human (1996).

Adverse Effects and Precautions

Hypersensitivity reactions may follow the use of factor IX preparations and there may be chills and urticaria. Other adverse effects include nausea and vomiting, headache, and flushing particularly after rapid infusion. Intravascular coagulation and thrombosis have been reported, mainly in patients with liver disease, and factor IX should be used with care in patients at risk of thromboembolism or disseminated intravascular coagulation. The risk should be less with more highly purified preparations.

As with other plasma derivatives there is a possibility of transmitting viral infection, although selection of donors and heat or chemical treatments of products are used to minimise the risk. Vaccination against hepatitis A and B is recommended for patients not already immune.

Antibodies to factor IX may develop rarely.

Effects on the cardiovascular system. Some factor IX preparations derived from plasma contain other clotting factors in addition to factor IX (prothrombin complex concentrates), and some preparations have also contained activated clotting factors. Such preparations have the potential to produce thromboembolic complications.[1,2] Reported complications include arterial and venous thrombosis, pulmonary embolism, acute myocardial infarction, and disseminated intravascular coagulation. Risk factors in haemophiliacs include liver disease, severe muscle haemorrhages, crush injuries, immobilisation, and orthopaedic surgery. Rapid infusion of factor IX concentrates, or repeated large doses, may also increase the risk of thromboembolism. The risks of thromboembolism have been reduced with the development of more purified prothrombin complex concentrates, and highly purified factor IX preparations that do not contain other clotting factors.[1,3]

1. Köhler M. Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999; **95** (suppl): S13–S17.
2. Najaf SM, *et al.* Myocardial infarction during factor IX infusion in hemophilia B: case report and review of the literature. *Ann Hematol* 2004; **83:** 604–7.
3. Santagostino E, *et al.* Markers of hypercoagulability in patients with hemophilia B given repeated, large doses of factor IX concentrates during and after surgery. *Thromb Haemost* 1994; **71:** 737–40.

Uses and Administration

Factor IX is used as replacement therapy in patients with haemophilia B (Christmas disease), a genetic deficiency of factor IX (see Haemophilias, p.1048).

There are two forms of factor IX preparation derived from plasma; one is of high purity, the other is rich in other clotting factors (prothrombin complex concentrates). A recombinant factor IX preparation, nonacog alfa, is also available. Preparations that contain other factors as well as factor IX may sometimes be useful for the treatment of bleeding due to deficiencies of factors II, VII, and X, as well as IX, and in the preparation of such patients for surgery; they may also be used for immediate reversal of coumarin anticoagulants and in the management of patients with haemophilia A who have antibodies to factor VIII.

Factor IX is given by slow intravenous infusion. In patients with factor IX deficiency the dosage should be determined for each patient and will vary with the preparation used and the circumstances of bleeding or type of surgery to be performed. Suggested target factor IX concentrations for patients with haemophilia B vary, but the following have been suggested:

- for mild to moderate haemorrhage the plasma concentration of factor IX should be raised to 20 to 30% of normal
- for more serious haemorrhage or minor surgery it should be raised to 30 to 60% of normal
- for severe haemorrhage or major surgery an increase to 60 to 100% of normal may be necessary

Calculation of the appropriate dose varies according to the manufacturers' recommendations.

For long-term prophylaxis in severe haemophilia B, doses of 20 to 40 international units/kg every 3 or 4 days, as required, may be used.

Preparations

Ph. Eur.: Human Coagulation Factor IX; Human Prothrombin Complex; ***USP 31:*** Factor IX Complex.

Proprietary Preparations (details are given in Part 3)
Arg.: Aimafix; Benefix; Berinin P; Immunine; Mononine; Octanine; Protromplex; Replenine†; ***Austral.:*** Benefix; Monofix-VF; ***Austria:*** Benefix; Beriplex; Immunine; Octanine; Octaplex; Prothromplex S-TIM 4; ***Belg.:*** Benefix; Mononine; Octanine; PPSB Conc SD; ***Braz.:*** Bebulin†; Benefix†; Berinin; Beriplex PN; Immunine†; Mononine; Octanyne†; Prothromplex-T†; Replenine†; ***Canad.:*** Benefix; Immunine; Mononine; ***Chile:*** Aimafix; Benefix†; Octanyne†; ***Cz.:*** Benefix; Immunine; Mononine; Nonafact; Octanine; Prothromplex; ***Denm.:*** Benefix; Immunine†; Mononine†; ***Fin.:*** Bemofil†; Benefix; Nonafact; ***Fr.:*** Benefix; Betafact; Kaskadil; Mononine; Octafix; ***Ger.:*** Alphanine; Benefix; Berinin; Beriplex PN; Immunine; Mononine; Octanine; Octaplex; PPSB Konzentrat S-TIM; Prothrombinkomplex BaWu†; ***Gr.:*** Benefix; Betafact; Mononine; Replenine; ***Hong Kong:*** Alphanine; Profilnine; Proplex T†; ***Hung.:*** Berinin P; Beriplex PN; Humafactor-9; Immunine; Octanine F; Prothromplex; ***Irl.:*** Mononine†; ***Israel:*** Betafact; Profilnine; Proplex; Replenine; ***Ital.:*** Aimafix; Alphanine; Benefix; Immunine; Mononine; Protromplex TIM 3; Uman-Complex DI; ***Malaysia:*** Alphanine; Profilnine; Proplex T†; Replenine; ***Mex.:*** Benefix†; Berinin P; Immunine†; Konyne†; Octanine F; Replenine; ***Neth.:*** Alphanine; Benefix; Betafact; Immunonine; Mononine; Nonafact; ***Norw.:*** Benefix; ***NZ:*** Benefix; Monofix; Prothrombinex; ***Philipp.:*** Alphanine; Profilnine; ***Pol.:*** Immunine; Prothromplex; ***Port.:*** Benefix; Betafact; Immunine; Mononine; Nanotiv; Nonafact; Octaninef; Octaplex; ***Rus.:*** Aimafix (Аимафикс); Octanine (Октанайн Ф); ***S.Afr.:*** Haemosolvex; Prothromplex-T TIM 4; ***Singapore:*** Alphanine; Profilnine; Replenine; ***Spain:*** Benefix; Berinin P; Immunine; Mononine; Nanotiv; Prothromplex; ***Swed.:*** Benefix; Immunine; Mononine; Nanotiv; ***Switz.:*** Benefix; Berinin HS; Beriplex; Immunine; Octanine F; Prothromplex Total S-TIM 4; ***Thai.:*** Alphanine; Octanine; Profilnine; ***Turk.:*** Aimafix; Berinin P; Betafact; Immunine; Kaskadil; Konyne; Octanine F; Octanyne; Replenine; ***UK:*** Alphanine; Benefix; Beriplex PN; Defix†; Hipfix†; Mononine; Replenine; ***USA:*** Alphanine; Bebulin VH; Benefix; Mononine; Profilnine; Proplex T; ***Venez.:*** Inmunine†; Proplex†.

Multi-ingredient: ***Arg.:*** Beriplex PN.

Factor XI

Facteur XI; Plasma Thromboplastin Antecedent; PTA.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human Coagulation Factor XI; Factor XI Coagulationis Humanus; Dried Factor XI Fraction BP 2008). A plasma protein fraction that contains coagulation factor XI. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The factor XI fraction is dissolved in a suitable liquid, distributed aseptically into the final containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or under nitrogen. Heparin, C_1-esterase inhibitor, and antithrombin III, may be added. No antimicrobial preservative is added. When reconstituted as stated on the label the resulting solution contains not less than 50 units/mL.

A white or almost white powder or friable solid. pH of the reconstituted preparation is 6.8 to 7.4. Store at a temperature of 2° to 8°. Protect from light.

Profile

Factor XI is used as replacement therapy in patients with congenital factor XI deficiency (haemophilia C; see Inherited Haemorrhagic Disorders, p.1050) for the prevention and treatment of haemorrhage. The dose is based on the degree of factor XI deficiency and the condition of the patient.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Hemoleven.

Factor XIII

Fibrin-stabilising Factor; FSF.

ATC — B02BD07.
ATC Vet — QB02BD07.

Profile

Factor XIII is used as replacement therapy in patients with a genetic deficiency of factor XIII (see Inherited Haemorrhagic Disorders, p.1050). It may also be used in patients with acquired deficiency of factor XIII (see Acquired Haemorrhagic Disorders, p.1047), and for supportive therapy in postoperative wound healing. Dosage of factor XIII is based on the degree of deficiency and the condition of the patient. For prophylaxis of haemorrhage in patients with genetic deficiency about 10 units/kg may be given intravenously once a month. The interval between doses may be shortened if spontaneous haemorrhage occurs. For pre-operative use, a dose of up to 35 units/kg may be given immediately before the operation and followed by adequate doses to maintain efficacy until the wound is healed. For the treatment of severe bleeding episodes 10 to 20 units/kg should be given daily, until bleeding stops. In acute bleeding, especially intracranial bleeding, doses of up to 50 units/kg may be needed to raise factor XIII to normal levels. Doses of at least 15 to 20 units/kg may be required for the treatment of haemorrhage in acquired factor XIII deficiency. In the promotion of postoperative wound healing, a dose of 10 units/kg may be given on the day of the operation and on each of the next 3 days. Like other clotting factor preparations (see Factor VIII, p.1067), the use of factor XIII may be associated with risks of hypersensitivity reactions, thrombosis, and viral infection transmission; inhibitors of factor XIII may occur very rarely.

Cryoprecipitate is also used as a source of factor XIII.

Factor XIII is also a component of fibrin glues (see Fibrin, p.1069).

Inflammatory bowel disease. Some patients with inflammatory bowel disease (p.1697) may be deficient in factor XIII, possibly due to increased intestinal blood loss seen in severe ulcerative colitis or increased mucosal deposition of factor XIII in Crohn's disease. Factor XIII concentrate given intravenously has produced beneficial results in 12 patients with active ulcerative colitis resistant to conventional therapy with corticosteroids and mesalazine[1] and has also been associated with healing of intractable fistulae in 3 of 4 patients with Crohn's disease.[2] However, a controlled study[3] found no benefit from factor XIII in active corticosteroid-refractory ulcerative colitis.

1. Lorenz R, *et al.* Factor XIII substitution in ulcerative colitis. *Lancet* 1995; **345:** 449–50.
2. Oshitani N, *et al.* Treatment of Crohn's disease fistulas with coagulation factor XIII. *Lancet* 1996: **347:** 119–20.
3. Bregenzer N, *et al.* Lack of clinical efficacy of additional factor XIII treatment in patients with steroid refractory colitis. *Z Gastroenterol* 1999; **37:** 999–1004.

Wounds and ulcers. Topical factor XIII has been reported to promote wound healing in patients with refractory leg ulcers.[1-3]

1. Wozniak G, *et al.* Factor XIII in ulcerative leg disease: background and preliminary clinical results. *Semin Thromb Hemost* 1996; **22:** 445–50.
2. Herouy Y, *et al.* Factor XIII-mediated inhibition of fibrinolysis and venous leg ulcers. *Lancet* 2000; **355:** 1970–1.
3. Hildenbrand T, *et al.* Treatment of nonhealing leg ulcers with fibrin-stabilizing factor XIII: a case report. *Dermatol Surg* 2002; **28:** 1098–9.

Preparations

Ph. Eur.: Fibrin Sealant Kit.

Proprietary Preparations (details are given in Part 3)
Arg.: Fibrogammin P; ***Austria:*** Fibrogammin; ***Belg.:*** Fibrogammin; ***Braz.:*** Fibrogammin; ***Cz.:*** Fibrogammin P†; ***Ger.:*** Fibrogammin; ***Hong Kong:*** Fibrogammin P; ***Israel:*** Fibrogammin P; ***Switz.:*** Fibrogammin; ***UK:*** Fibrogammin P.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Beriplast; Tissucol; ***Ger.:*** Beriplast; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; Tisseel; ***Hung.:*** Beriplast P; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Tissucol; Tissucol Duo; ***Pol.:*** Beriplast; ***Port.:*** Tissucol Duo; ***Spain:*** Beriplast P Combi; Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Beriplast P; Tissucol; Tissucol Duo S; ***Turk.:*** Beriplast P; ***UK:*** Tisseel.

Fibrin *(rINN)*

Fibrina; Fibrine; Fibrinum.

Фибрин

Pharmacopoeias. Many pharmacopoeias have monographs for fibrin preparations, including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fibrin Sealant Kit; Fibrini Glutinum). It is composed of two components, a fibrinogen concentrate containing human fibrinogen (component 1), and a human thrombin preparation (component 2). The kit may also contain other ingredients, such as human factor XIII, a fibrinolysis inhibitor, or calcium ions. Stabilisers such as human albumin may be added. The human constituents are obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. The constituents are passed through a bacteria-retentive filter and distributed aseptically into sterile containers. Containers of freeze-dried constituents are sealed under vacuum or filled with oxygen-free nitrogen or other suitable inert gas before sealing. No antimicrobial preservative is added. When thawed or reconstituted as stated on the label, the fibrinogen concentrate contains not less than 40 g/litre of clottable protein; the activity of the thrombin preparation varies over a wide range (about 4 to 1000 international units/mL). Protect from light.

Profile

Fibrin glue is prepared by mixing solutions containing fibrinogen, thrombin, and calcium ions, with the addition of aprotinin to inhibit fibrinolysis. It may also include factor XIII and other clotting components. Fibrin glue is used as a haemostatic to control haemorrhage during surgical procedures or as a spray to bleeding surfaces.

A dry artificial sponge of human fibrin, known as human fibrin foam, has been used similarly; it is prepared by clotting human thrombin with a foam of human fibrinogen solution. A collagen sponge coated with thrombin and fibrinogen is also available.

Adverse effects. Fatal neurotoxicity has been reported[1] after the use of a fibrin sealant during neurosurgical procedures. The toxicity may have been due to the presence of tranexamic acid as a stabiliser in the formulation, and such formulations should not be used in surgical operations where contact with the CSF or dura mater could occur.[2]

For rare reports of hypersensitivity reactions to aprotinin used locally as a component of fibrin sealant, see p.1055.

1. Committee on Safety of Medicines/Medicines Control Agency. Quixil human surgical sealant: reports of fatal reactions. *Current Problems* 1999; **25:** 19. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)
2. Committee on Safety of Medicines/Medicines Control Agency. Quixil human surgical sealant: update on fatal neurotoxic reactions. *Current Problems* 2000; **26:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 31/05/06)

Use. Reviews.

1. Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. *Drugs* 1999; **58:** 863–86.

2. Carless PA, *et al.* Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/06/05).
3. MacGillivray TE. Fibrin sealants and glues. *J Card Surg* 2003; **18:** 480–5.
4. Fattahi T, *et al.* Clinical applications of fibrin sealants. *J Oral Maxillofac Surg* 2004; **62:** 218–24.
5. Schexneider KI. Fibrin sealants in surgical or traumatic hemorrhage. *Curr Opin Hematol* 2004; **11:** 323–6.

Preparations

Ph. Eur.: Fibrin Sealant Kit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; TachoSil; Tissucol; ***Ger.:*** Beriplast; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; Tisseel; ***Hung.:*** Beriplast P; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; TachoSil; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** TachoSil; Tissucol Duo; ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Turk.:*** Beriplast P; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Fibrinogen

Factor I; Fibrinogène; Fibrinógeno; Fibrinogenum; Fibrinojen; Fibrynogen.

ATC — B02BB01; B02BC10.
ATC Vet — QB02BB01.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human Fibrinogen; Fibrinogenum Humanum). It contains the soluble constituent of human plasma that is transformed to fibrin on addition of thrombin. It is obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Stabilisers, including protein such as human albumin, salts, and buffers may be added. No antimicrobial preservative is added. When dissolved in the volume of solvent stated on the label, the solution contains not less than 10 g/litre of fibrinogen.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

Fibrinogen has been used to control haemorrhage associated with low blood-fibrinogen concentration in afibrinogenaemia or hypofibrinogenaemia although plasma or cryoprecipitate is usually preferred. Fibrinogen has also been used in disseminated intravascular coagulation (p.1048). It is a component of fibrin glue (see Fibrin, above). Recombinant human fibrinogen is under investigation.

Fibrinogen labelled with radionuclides has also been used in diagnostic procedures.

Preparations

Ph. Eur.: Fibrin Sealant Kit; Human Fibrinogen.

Proprietary Preparations (details are given in Part 3)

Austria: Haemocomplettan; ***Cz.:*** Haemocomplettan; ***Ger.:*** Haemocomplettan; ***Gr.:*** Haemocomplettan; ***Hung.:*** Haemocomplettan; ***Neth.:*** Haemocomplettan; ***Port.:*** Haemocomplettan; ***Switz.:*** Haemocomplettan; ***Thai.:*** Fibroraas.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; TachoSil; Tissucol; ***Ger.:*** Beriplast; Quixil; TachoComb†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; Quixil; TachoSil; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Quixil; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** TachoSil; Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Thai.:*** Fibrin Glue†; TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Filgrastim *(BAN, USAN, rINN)*

Filgrastiimi; Filgrastimum; r-metHuG-CSF. A recombinant human granulocyte colony-stimulating factor.

Филграстим
CAS — 121181-53-1.
ATC — L03AA02.
ATC Vet — QL03AA02.

Pegfilgrastim *(BAN, rINN)*

Pegfilgrastiimi; Pegfilgrastimum; Pegfilgrastimun. Filgrastim conjugated with monomethoxy polyethylene glycol.

Пэгфильграстим
CAS — 208265-92-3.
ATC — L03AA13.
ATC Vet — QL03AA13.

Incompatibility. References.

1. Trissel LA, Martinez JF. Compatibility of filgrastim with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1907–13.

Stability. Solutions of filgrastim must not be diluted with sodium chloride solutions as precipitation will occur. Glucose 5% solution may be used if dilution is necessary. However, filgrastim in diluted solution may be adsorbed onto glass or plastic materials and so it should not be diluted below the recommended minimum concentration (2 micrograms/mL). Also, to protect from adsorption, solutions that are diluted to concentrations of filgrastim below 15 micrograms/mL must have albumin added to give a final concentration of 2 mg/mL. For mention of the stability of filgrastim in a solution intended for enteral use in neonates, see Stability under Epoetins, p.1061.

Adverse Effects

The main adverse effects of granulocyte colony-stimulating factors such as filgrastim during short-term treatment are musculoskeletal pain and dysuria. Hypersensitivity reactions have been reported rarely. In patients receiving long-term treatment the most frequent adverse effects are bone pain and musculoskeletal pain. Other adverse effects include splenic enlargement, thrombocytopenia, anaemia, epistaxis, headache, diarrhoea, and cutaneous vasculitis. There have been reports of pulmonary infiltrates leading to respiratory failure or acute respiratory distress syndrome, and rare reports of splenic rupture. Rises in lactate dehydrogenase, alkaline phosphatase, and uric acid, are usually mild to moderate, dose-dependent, and reversible.

Colony-stimulating factors are fetotoxic in *animal* studies.

◊ General references.

1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13:** 371–406.
2. Gutierrez-Delgado F, Bensinger W. Safety of granulocyte colony-stimulating factor in normal donors. *Curr Opin Hematol* 2001; **8:** 155–60.
3. Cottle TE, *et al.* Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. *Semin Hematol* 2002; **39:** 134–40.
4. Crawford J. Safety and efficacy of pegfilgrastim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2003; **23** (suppl): 15S–19S.

Disseminated intravascular coagulation. Long-term treatment with granulocyte colony-stimulating factor in a 7-year-old boy with HIV infection and zidovudine-induced neutropenia produced evidence of disseminated intravascular coagulation on 2 occasions.[1]

1. Mueller BU, *et al.* Disseminated intravascular coagulation associated with granulocyte colony-stimulating factor therapy in a child with human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 749–52.

Effects on the bones. Bone mineral loss and osteoporosis have been reported in children with severe congenital neutropenia receiving granulocyte colony-stimulating factor for long periods.[1-3] However, the role of granulocyte colony-stimulating factor in producing this effect is uncertain since bone mineral loss may be a feature of the underlying disease.

1. Bishop NJ, *et al.* Osteoporosis in severe congenital neutropenia treated with granulocyte colony-stimulating factor. *Br J Haematol* 1995; **89:** 927–8.
2. Yakisan E, *et al.* High incidence of significant bone loss in patients with severe congenital neutropenia (Kostmann's syndrome). *J Pediatr* 1997; **131:** 592–7.
3. Sekhar RV, *et al.* Severe osteopenia in a young boy with Kostmann's congenital neutropenia treated with granulocyte colony-stimulating factor: suggested therapeutic approach. Abstract: *Pediatrics* 2001; **108:** 756–7. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e54 (accessed 27/10/05)

Effects on the eyes. Subretinal haemorrhage resulting in irreversible loss of vision in one eye occurred in a 4-year-old girl who received filgrastim and nartograstim for chemotherapy-induced neutropenia and for mobilising peripheral blood stem cells.[1] It was postulated that the colony-stimulating factor reactivated a primary ocular inflammation probably caused by an infection. Bilateral peripapillary and macular retinal haemorrhage occurred in an adult being treated for mantle cell lymphoma.[2] It was attributed to retinal leucostasis secondary to hyperleucocytosis resulting from the use of filgrastim for stem cell mobilisation. Vision improved after cessation of filgrastim and the use of leucapheresis.

1. Matsumura T, *et al.* Subretinal haemorrhage after granulocyte colony-stimulating factor. *Lancet* 1997; **350:** 336. Correction. *ibid.*; 1406.
2. Salloum E, *et al.* Hyperleukocytosis and retinal hemorrhages after chemotherapy and filgrastim administration for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 1998; **21:** 835–7.

Effects on the lungs. There have been reports of exacerbation of chemotherapy-induced pulmonary toxicity in patients receiving granulocyte colony-stimulating factor (G-CSF) with bleomycin, cyclophosphamide, or methotrexate. A systematic review[1] of 73 cases noted that the doses of the antineoplastics were below the usual toxic cumulative dose, suggesting that G-CSF may have lowered the threshold for pulmonary toxicity of these drugs. It has been proposed that G-CSF has an activating effect on neutrophils that makes them toxic to the alveolar capillary wall. The review also included 2 cases of pulmonary toxicity in non-neutropenic patients treated with G-CSF alone. The circumstances of 9 other cases suggested that neutropenic patients with a recent history of pulmonary infiltrates may be at increased risk of acute respiratory distress syndrome during neutropenia recovery. The true role of G-CSF in these cases of pulmonary toxicity remains unclear, however.

1. Azoulay E, *et al.* Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001; **120:** 1695–1701.

Effects on the skin. Skin reactions may occur in patients given colony-stimulating factors. In a study in women with inflammatory breast cancer, a pruritic skin reaction developed at the subcutaneous injection site in all 7 given granulocyte-macrophage colony-stimulating factor.[1] A review[2] of 8 cases of generalised pruritic maculopapular rash associated with granulocyte or granulocyte-macrophage colony-stimulating factor found that in 6 of them the rash resolved in 4 to 17 days even though therapy was continued and half the patients did not receive any treatment for the rash. A localised lichenoid reaction has been described for granulocyte colony-stimulating factor.[3] Exacerbation of psoriasis[4] and precipitation or exacerbation of neutrophilic dermatoses including Sweet's syndrome,[5-7] pyoderma gangrenosum,[8] and neutrophilic eccrine hidradenitis[9] have been reported following use of granulocyte colony-stimulating factor.

1. Steger GG, *et al.* Cutaneous reactions to GM-CSF in inflammatory breast cancer. *N Engl J Med* 1992; **327**: 286.
2. Álvarez-Ruiz S, *et al.* Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol Venereol* 2004; **18:** 310–13.
3. Viallard AM, *et al.* Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (filgrastim). *Dermatology* 1999; **198:** 301–3.
4. Kavanaugh A. Flare of psoriasis and psoriatic arthritis following treatment with granulocyte colony-stimulating factor. *Am J Med* 1996; **101:** 567.
5. Petit T, *et al.* Lymphoedema-area-restricted Sweet syndrome during G-CSF treatment. *Lancet* 1996; **347:** 690.
6. Garty BZ, *et al.* Sweet syndrome associated with G-CSF treatment in a child with glycogen storage disease type Ib. *Pediatrics* 1996; **97:** 401–3.
7. Hasegawa M, *et al.* Sweet's syndrome associated with granulocyte colony-stimulating factor. *Eur J Dermatol* 1998; **8:** 503–5.
8. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors: a review of associated neutrophilic dermatoses and vasculitides. *Arch Dermatol* 1994; **130:** 77–81.
9. Bachmeyer C, *et al.* Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol* 1998; **139:** 354–5.

Effects on the thyroid. Reversible thyroid dysfunction has been reported in patients with pre-existing thyroid antibodies during treatment with granulocyte-macrophage colony-stimulating factor,[1] but not with granulocyte colony-stimulating factor.[2] However, clinical hypothyroidism has been reported in a patient with no history of thyroid dysfunction or thyroid antibodies during treatment with granulocyte colony-stimulating factor.[3]

1. Hoekman K, *et al.* Reversible thyroid dysfunction during treatment with GM-CSF. *Lancet* 1991; **338**: 541–2.
2. van Hoef MEHM, Howell A. Risk of thyroid dysfunction during treatment with G-CSF. *Lancet* 1992; **340:** 1169–70.
3. de Luis DA, Romero E. Reversible thyroid dysfunction with filgrastim. *Lancet* 1996; **348:** 1595–6.

Inflammatory disorders. Reactivation of various inflammatory disorders including rheumatoid arthritis[1] and pseudogout[2,3] has been reported after use of granulocyte colony-stimulating factors. For further reports of reactivation of sites of inflammation, see under Effects on the Eyes and Effects on the Skin, above.

1. Vildarsson B, *et al.* Reactivation of rheumatoid arthritis and development of leukocytoclastic vasculitis in a patient receiving granulocyte colony-stimulating factor for Felty's syndrome. *Am J Med* 1995; **98:** 589–91.
2. Sandor V, *et al.* Exacerbation of pseudogout by granulocyte colony-stimulating factor. *Ann Intern Med* 1996; **125:** 781.
3. Teramoto S, *et al.* Increased synovial interleukin-8 and interleukin-6 levels in pseudogout associated with granulocyte colony-stimulating factor. *Ann Intern Med* 1998; **129:** 424–5.

Precautions

Since granulocyte colony-stimulating factors such as filgrastim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. Filgrastim and lenograstim should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy because of the sensitivity of rapidly dividing myeloid cells. Pegfilgrastim should not be used from 14 days before until 24 hours after chemotherapy. The safety and efficacy of granulocyte colony-stimulating factor therapy has not been established in patients receiving chemoradiotherapy, and concomitant use is generally avoided.

Granulocyte colony-stimulating factors should be used with caution in patients with sickle-cell disease. Preparations of filgrastim may contain sorbitol as an excipient; care is advisable in patients with hereditary fructose intolerance.

The complete blood count should be monitored regularly during therapy with granulocyte colony-stimulating factors. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Transient positive changes in bone imaging findings have occurred with growth factor therapy, and should be considered when interpreting results. Bone density should be monitored in patients with osteoporosis who are receiving long-term treatment with filgrastim.

Sickle-cell disease. Granulocytosis occurs during sickle-cell crisis (p.1044) although the role of granulocytes in vaso-occlusion has not been established. Sickle-cell crisis has occurred in patients with sickle-cell disease who have been given granulocyte colony-stimulating factor.[1-3]

1. Abboud M, *et al.* Granulocytosis causing sickle-cell crisis. *Lancet* 1998; **351:** 959.
2. Adler BK, *et al.* Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. *Blood* 2001; **97:** 3313–14.
3. Wei A, Grigg A. Granulocyte colony-stimulating factor–induced sickle cell crisis and multiorgan dysfunction in a patient with compound heterozygous sickle cell/β thalassemia. *Blood* 2001; **97:** 3998–9.

Pharmacokinetics

After subcutaneous injection, peak serum concentrations of filgrastim occur within about 8 hours. The serum elimination half-life of filgrastim after intravenous or subcutaneous injection is about 3.5 hours. Pegfilgrastim peak concentrations occur later, at 16 to 120 hours after subcutaneous doses. Elimination of pegfilgrastim is non-linear and clearance becomes saturated and decreases with increasing dose. It is mainly eliminated by neutrophil-mediated clearance, such that the serum concentration of pegfilgrastim declines rapidly with neutrophil recovery. It has a half-life of 15 to 80 hours after subcutaneous injection.

◊ Reviews.

1. Zamboni WC. Pharmacokinetics of pegfilgrastim. *Pharmacotherapy* 2003; **23** (suppl): 9S–14S.

Uses and Administration

Filgrastim is a granulocyte colony-stimulating factor (G-CSF), a haematopoietic growth factor that stimulates the development of granulocytes (see Haematopoiesis, p.1042). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation. It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Filgrastim is also used in the management of chronic neutropenia (congenital, cyclic, or idiopathic), and for persistent neutropenia in patients with advanced HIV infection.

Filgrastim may be given intravenously or subcutaneously. Doses may be expressed in micrograms or in units; 10 micrograms is equivalent to 1 million units.

As an **adjunct to antineoplastic therapy**, filgrastim is given in a dose of 5 micrograms/kg daily starting not less than 24 hours after the last dose of antineoplastic. It can be given as a single daily subcutaneous injection, as a continuous intravenous or subcutaneous infusion, or as a daily intravenous infusion over 15 to 30 minutes. Treatment is continued until the neutrophil count has stabilised within the normal range which may take up to 14 days or more. A formulation of filgrastim conjugated with monomethoxy polyethylene glycol (pegfilgrastim) may also be used to reduce the incidence of neutropenia associated with antineoplastic therapy; it is given by subcutaneous injection in a single dose of 6 mg, given not less than 24 hours after the last dose of antineoplastic.

The initial dose of filgrastim following **bone marrow transplantation** is 10 micrograms/kg daily, adjusted according to response. This may be given by intravenous infusion over 30 minutes or 4 hours, or by continuous intravenous or subcutaneous infusion over 24 hours.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 10 micrograms/kg daily of filgrastim may be given subcutaneously as a single daily injection or by continuous infusion for 4 to 7 days until the last leucapheresis procedure (usually performed on days 5 to 7 as required). If filgrastim is given after myelosuppressive chemotherapy, the dose is halved to 5 micrograms/kg daily by subcutaneous injection. It is given from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 4 or 5 days until leucapheresis (usually started on day 5).

In patients with **congenital neutropenia** the initial dose is 12 micrograms/kg daily and in patients with idiopathic or cyclic neutropenia the initial dose is 5 micrograms/kg daily. In these forms of neutropenia the dose is given subcutaneously in single or divided doses and should be adjusted according to response.

In patients with **HIV infection** and persistent neutropenia the initial dose is 1 microgram/kg daily by subcutaneous injection. The dose may be titrated up to a maximum of 4 micrograms/kg daily until a normal neutrophil count is achieved and then adjusted for maintenance according to response. Maintenance doses of 300 micrograms daily on 1 to 7 days a week have been used.

The filgrastim doses described above for patients receiving antineoplastic therapy and for chronic neutropenias may also be given to **children**. Pegfilgrastim should not be used in children or adolescents weighing less than 45 kg.

◊ Some reviews of filgrastim and pegfilgrastim.

1. Dale DC, ed. Filgrastim anniversary supplement: reviewing 10 years of clinical experience, a seminar-in-print. *Drugs* 2002; **62** (suppl 1): 1–98.
2. Curran MP, Goa KL. Pegfilgrastim. *Drugs* 2002; **62:** 1207–13.
3. Willis F, Pettengell R. Pegfilgrastim. *Expert Opin Biol Ther* 2002; **2:** 985–92.

Aplastic anaemia. Colony-stimulating factors, including granulocyte colony-stimulating factors, have been tried in patients with aplastic anaemia (p.1042).

Infections. As well as stimulating the development and maturation of haematopoietic precursors, granulocyte and granulocyte-macrophage colony-stimulating factors have been found to enhance neutrophil chemotaxis and phagocytosis, enhance oxidative activity, increase microbicidal activity and antibody-mediated cellular cytotoxicity, and delay neutrophil apoptosis. Granulocyte-macrophage colony-stimulating factor also modifies macrophage and monocyte functions in inflammation and cellular immune response.[1] It has therefore been suggested that colony-stimulating factors might be useful adjuncts in the treatment of infections in non-neutropenic patients, but their clinical role is yet to be established.

The use of granulocyte colony-stimulating factor was reported[2] to reduce mortality rates in patients with septic shock due to the bacterial infection melioidosis (p.178). In small placebo-controlled studies of patients with the protozoal infection cutaneous leishmaniasis (p.824), ulcers healed faster in those treated with granulocyte-macrophage colony-stimulating factor, as an adjunct to antimony therapy, by intralesional injection[3] and topical application.[4]

However, granulocyte colony-stimulating factor does not appear to be of benefit as an adjunct in the management of pneumonia[5] (p.186). In diabetic foot infections (see Diabetic Complications, p.433) granulocyte colony-stimulating factor does not appear to affect wound healing, although there is some suggestion that it may reduce the likelihood of surgical intervention.[6]

In HIV infection (p.856), granulocyte-macrophage colony-stimulating factor has been reported to improve CD4+ cell counts.[7]

Granulocyte-macrophage colony-stimulating factor has been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[8]

1. Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in non-neutropenic patients. *J Infect Dis* 1999; **179** (suppl): S342–S352.
2. Cheng AC, *et al.* Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004; **38:** 32–7.
3. Almeida R, *et al.* Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony-stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. *J Infect Dis* 1999; **180:** 1735–7.
4. Santos JB, *et al.* Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *J Infect Dis* 2004; **190:** 1793–6.
5. Cheng AC, *et al.* Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 16/06/08).
6. Cruciani M, *et al.* Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* 2005; **28:** 454–60.
7. Deresinski SC. Granulocyte-macrophage colony-stimulating factor: potential therapeutic, immunological and antiretroviral effects in HIV infection. *AIDS* 1999; **13:** 633–43.
8. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.

Ischaemia. Colony-stimulating factors have been investigated for their ability to mobilise stem cells and modulate inflammation in cardiovascular disorders characterised by ischaemia. In patients with atherosclerotic coronary artery disease (p.1159) filgrastim[1] and molgramostim[2] have been tried in an attempt to promote neovascularisation; there was no cardiac benefit with the former, and although the latter promoted collateral artery growth the balance of benefit to risk was questionable, since 2 of 7 actively treated patients developed an acute coronary syndrome. Benefit has been reported in 7 patients with acute ischaemic stroke (p.1185) given filgrastim 15 micrograms/kg subcutaneously daily for 5 days in addition to the usual care given to 3 controls.[3] There was a greater improvement in neurological function in filgrastim-treated patients on 12 months of follow-up, but larger studies are required to confirm the benefit.

1. Hill JM, *et al.* Outcomes and risks of granulocyte colony-stimulating factor in patients with coronary artery disease. *J Am Coll Cardiol* 2005; **46:** 1643–8.
2. Zbinden S, *et al.* Safety and efficacy of subcutaneous-only granulocyte-macrophage colony-stimulating factor for collateral growth promotion in patients with coronary artery disease. *J Am Coll Cardiol* 2005; **46:** 1636–42.
3. Shyu W-C, *et al.* Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial. *Can Med Assoc J* 2006; **174:** 927–33.

Neutropenia. Granulocyte colony-stimulating factors are used in the management of neutropenia. They may be used[1] long-term in the management of inherited forms of neutropenia (p.1051). They are used short-term[2-5] to treat or prevent antineoplastic-induced neutropenia (p.640) and have also been used in patients with neutropenia induced by a wide range of other drugs.[6-11] The use of colony-stimulating factors has been investigated[12] in the management of neutropenia in patients with HIV-associated infection (p.857). A controlled study[13] in 258 patients with advanced HIV infection found that prophylactic use of granulocyte colony-stimulating factor reduced the incidence of severe neutropenia and also suggested that the incidence and duration of bacterial infections was reduced.

Due to immature neutrophil production and function, neonates are susceptible to infection and preterm neonates are at particular risk. The use of colony-stimulating factors for prophylaxis or as adjuncts in the treatment of septicaemia (p.190) in neonates has been investigated in a few small trials but there is insufficient evidence of benefit to recommend the use of granulocyte or granulocyte-macrophage colony-stimulating factors in these patients. Although there is limited evidence to suggest that they may reduce mortality as adjuncts to treatment in patients with sepsis and severe neutropenia, further study is needed.[14,15] Granulocyte colony-stimulating factors have also been tried with mixed results in neonates with the rare condition of alloimmune neutropenia.[16,17]

1. Zeidler C, *et al.* Management of Kostmann syndrome in the G-CSF era. *Br J Haematol* 2000; **109:** 490–5.
2. Repetto L, *et al.* EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 2003; **39:** 2264–72.
3. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22:** 3350–6.
4. Clark OAC, *et al.* Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2005; **23:** 4198–4214.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://www.jco.org/cgi/reprint/24/19/3187 (accessed 20/09/06)

6. Wickramanayake PD, *et al.* Use of granulocyte colony-stimulating factor (filgrastim) in the treatment of non-cytotoxic drug-induced agranulocytosis. *Eur J Med Res* 1995; **1:** 153–6.
7. Murphy PT, Casey MC. Sulphasalazine induced agranulocytosis revisited. *Ir Med J* 1998; **91:** 216.
8. Bhidayasiri R, *et al.* Correction of mesalazine-induced neutropenia with high dose G-CSF. *Am J Gastroenterol* 2000; **95:** 3321–2.
9. Andrès E, *et al.* Nonchemotherapy drug-induced agranulocytosis in elderly patients: the effects of granulocyte colony-stimulating factor. *Am J Med* 2002; **112:** 460–4.
10. Andrès E, *et al.* Modern management of non-chemotherapy drug-induced agranulocytosis: a monocentric cohort study of 90 cases and review of the literature. *Eur J Intern Med* 2002; **13:** 324–8.
11. Hägg S, *et al.* Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol* 2003; **18:** 173–4.
12. Kuritzkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis* 2000; **30:** 256–60.
13. Kuritzkes DP, *et al.* Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. *AIDS* 1998; **12:** 65–74.
14. Banerjea MC, Speer CP. The current role of colony-stimulating factors in prevention and treatment of neonatal sepsis. *Semin Neonatol* 2002; **7:** 335–49.
15. Carr R, *et al.* G-CSF and GM-CSF for treating or preventing neonatal infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/10/05).
16. Felix JK, Calhoun DA. Neonatal alloimmune neutropenia in premature monozygous twins. *Pediatrics* 2000; **106:** 340–2.
17. Maheshwari A, *et al.* Resistance to recombinant human granulocyte colony-stimulating factor in neonatal alloimmune neutropenia associated with anti-human neutrophil antigen-2a (NB1) antibodies. Abstract: *Pediatrics* 2002; **109:** 698. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/4/e64 (accessed 27/10/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Filgen; Neupogen; Neutrofil; Neutromax; ***Austral.:*** Neulasta; Neupogen; ***Austria:*** Neulasta; Neupogen; ***Belg.:*** Neulasta; Neupogen; ***Braz.:*** Filgrastine; Granulen; Granulokine; Leucin; Neulastim; ***Canad.:*** Neulasta; Neupogen; ***Chile:*** Neupogen; Neutromax; ***Cz.:*** Neulasta; Neupogen; Neupopeg; ***Denm.:*** Neulasta; Neupogen; ***Fin.:*** Neulasta; Neupogen; ***Fr.:*** Neulasta; Neupogen; ***Ger.:*** Neulasta; Neupogen; ***Gr.:*** Granulokine; Neulasta; ***Hong Kong:*** Neupogen; ***Hung.:*** Neulasta; Neupogen; ***India:*** Neupogen; ***Indon.:*** Neulastim; Neupogen; ***Irl.:*** Neulasta; Neupogen; ***Israel:*** Neupogen; ***Ital.:*** Granulokine; Neulasta; Neupogen; Neupopeg; ***Jpn:*** Gran; ***Malaysia:*** Neupogen; Peglasta; ***Mex.:*** Filatil; Neulastim; Neupogen; ***Neth.:*** Neulasta; Neupogen; Neupopeg; ***Norw.:*** Neulasta; Neupogen; ***NZ:*** Neupogen; ***Philipp.:*** Granulokine; ***Pol.:*** Neulasta; Neupogen; ***Port.:*** Neulasta; Neupogen; Neupopeg; ***Rus.:*** Neupogen (Нейпоген); ***S.Afr.:*** Neupogen; ***Singapore:*** Neulastim; Neupogen; ***Spain:*** Neulasta; Neupogen; ***Swed.:*** Neulasta; Neupogen; ***Switz.:*** Neulasta; Neupogen; ***Thai.:*** Neupogen; Neutromax; ***Turk.:*** Neupogen; ***UK:*** Neulasta; Neupogen; ***USA:*** Neulasta; Neupogen; ***Venez.:*** Neupogen.

Gelatin ⊗

Gelatina; Gélatine; Liivate; Modifiye Jelatin; Želatina; Żelatyna; Zselatin.

ATC — B02BC01 (absorbable gelatin sponge); B05AA06 (gelatin).

ATC Vet — QB02BC01 (absorbable gelatin sponge); QB05AA06 (gelatin).

Grades. Gelling grades of gelatin are usually graded by gel strength, expressed as 'Bloom value', 'Bloom strength', or 'Bloom rating'.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF.*

The gelatin described in some pharmacopoeias is not necessarily suitable for preparations for parenteral use or for other special purposes.

Ph. Eur. 6.2 (Gelatin). A purified protein obtained either by partial acid hydrolysis (type A), by partial alkaline hydrolysis (type B), or by enzymatic hydrolysis of collagen from animals (including fish and poultry); it may also be a mixture of different types. The hydrolysis leads to gelling and non-gelling product grades. Gelling grades are characterised by the gel strength (Bloom value). It is not suitable for parenteral use or for other special purposes.

A faintly yellow or light yellowish-brown solid, usually occurring as translucent sheets, shreds, powder, or granules.

Gelling grades of gelatin swell in cold water and on heating give a colloidal solution which on subsequent cooling forms a more or less firm gel. Gelatin is practically insoluble in common organic solvents. Different gelatins form aqueous solutions that vary in clarity and colour. A 1% solution in water at about 55° has a pH of 3.8 to 7.6. Protect from heat and moisture.

USNF 26 (Gelatin). It is obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A, and gelatin derived from an alkali-treated precursor is known as Type B.

Faintly yellow or amber sheets, flakes, or shreds, or a coarse to fine powder, the colour varying in depth according to the particle size. A solution has a slight, characteristic, bouillon-like odour. It is stable in air when dry, but is subject to microbial decomposition when moist or in solution. Gelatin swells and softens when immersed in cold water, gradually absorbing 5 to 10 times its weight of water. Soluble in hot water, in 6N acetic acid, and in a hot mixture of glycerol and water; insoluble in alcohol, in chloroform, in ether, and in fixed and volatile oils.

Incompatibility. A white precipitate was formed immediately when vancomycin injection was infused through a giving set containing modified fluid gelatin solution.[1]

1. Taylor A, Hornbrey P. Incompatibility of vancomycin and gelatin plasma expanders. *Pharm J* 1991; **246:** 466.

Adverse Effects

Hypersensitivity reactions including anaphylactic reactions have occurred after the infusion of gelatin or its derivatives. Rapid infusion of gelatin derivatives may directly stimulate the release of histamine and other vasoactive substances.

For adverse reactions associated with the topical use of gelatin, see Haemostasis under Uses and Administration, below.

Hypersensitivity. Severe anaphylactoid reactions have been reported with infusion of modified fluid gelatin solutions.[1,2] As of June 2006, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[3] had also received 70 reports of hypotension or hypersensitivity reactions associated with succinylated gelatin. Although severe hypersensitivity reactions to gelatin-based plasma expanders appear to be rare, they may be under-reported and fatalities have occurred.[2] The possibility of cross reactivity between succinylated gelatin and polygeline has also been considered; there are a few reports of patients who, after a reaction during clinical use with one plasma expander, have shown a positive skin test result to the other.[4,5] Some hypersensitivity reactions have been attributed to the use of gelatin as an excipient in vaccines[6-8] and other injectable drug products.[9] A haemostatic gelatin sponge put into place at the end of spinal surgery for a disc hernia was thought to be responsible for a delayed hypersensitivity reaction that caused oedema of the soft tissues and subsequent tingling and paresis of the lower limbs; removal of the sponge produced improvement.[10]

For reports of fatal reactions in asthmatic patients given gelatin derivatives, see Polygeline, p.1077.

1. Blanloeil Y, *et al.* Accidents anaphylactoïdes sévères après perfusion d'une gélatine fluide modifiée en solution équilibrée *Therapie* 1983; **38:** 539–46.
2. Walker SR, MacSweeney ST. Plasma expanders used to treat or prevent hypotension can themselves cause hypotension. *Postgrad Med J* 1998; **74:** 492–4.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Problems with colloids in fluid resuscitation. *Aust Adverse Drug React Bull* 2006; **25:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0606.pdf (accessed 07/12/06)
4. Russell WJ, Fenwick DG. Anaphylaxis to Haemaccel and cross reactivity to Gelofusin . *Anaesth Intensive Care* 2002; **30:** 481–3.
5. Russell WJ, Fenwick DG. Cross-reactivity between Gelofusin and Haemaccel. *Anaesth Intensive Care* 2003; **31:** 121–2.
6. Kelso JM. The gelatin story. *J Allergy Clin Immunol* 1999; **103:** 200–202.
7. Patja A, *et al.* Allergic reactions to measles-mumps-rubella vaccination. Abstract: *Pediatrics* 2001; **107:** 398. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/2/e27 (accessed 27/10/05)
8. Pool V, *et al.* Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. Abstract: *Pediatrics* 2002; **110:** 1241. Full version: http://pediatrics.aappublications.org/cgi/content/full/110/6/e71 (accessed 27/10/05)
9. Sakaguchi M, *et al.* A case of anaphylaxis to gelatin included in erythropoietin products. *J Allergy Clin Immunol* 1999; **103:** 349–50.
10. Purello-D'Ambrosio F, *et al.* Allergy to gelatin. *Allergy* 2000; **55:** 414–15.

Precautions

When gelatin or its derivatives are used as plasma expanders the precautions under Dextran 70 (p.1060) should be considered. There does not appear to be any interference with blood grouping and cross-matching of blood.

When gelatin is used as an absorbable haemostatic the precautions under Oxidised Cellulose (p.1075) should be considered.

Pharmacokinetics

After infusion of modified fluid gelatin (succinylated gelatin), 75% of the dose is excreted in the urine in 24 hours. The half-life is about 4 hours.

Uses and Administration

Gelatin is a protein that has both clinical and pharmaceutical uses.

Gelatin is used as a haemostatic in surgical procedures as an absorbable film or sponge and can absorb many times its weight of blood. It is also employed as a plasma volume expander similarly to the dextrans in hypovolaemic shock (p.1183). A 4% solution of a modified fluid gelatin (succinylated gelatin) has been infused in doses of 500 to 1000 mL. It may also be used in the form of a gelatin-derived polymer, see Polygeline, p.1077.

Gelatin rods may be employed to temporarily block tear outflow in the diagnosis of dry eye (p.2140).

Gelatin is used in the preparation of pastes, pastilles, suppositories, tablets, and hard and soft capsule shells. It is also used for the microencapsulation of drugs and other industrial materials. It has been used as a vehicle for injections: Pitkin's Menstruum, which consists of gelatin, glucose, and acetic acid, has been used in a modified form for heparin while hydrolysed gelatin has been used for corticotropin. Gelatin is an ingredient of preparations used for the protection of stomas and lesions.

Haemostasis. Gelatin acts as a haemostatic (p.1045) by providing a physical meshwork within which clotting can occur.

Gelatin powder may be applied dry to wound beds and may be most useful when mixed with saline or thrombin and applied to bone. Gelatin sponge can be applied dry or soaked in saline or thrombin solutions. When applied to skin wounds the gelatin liquefies within 2 to 5 days; when implanted into tissues it is absorbed within 4 to 6 weeks. Adverse reactions include an increased incidence of infection, compression of surrounding tissue due to fluid absorption, granuloma formation, and fibrosis. Generally, gelatin sponges cause little tissue reaction and can be applied to bone, dura, and pleural tissue (but see also Hypersensitivity, above).

References.

1. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14:** 623–32.
2. Schonauer C, *et al.* The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *Eur Spine J* 2004; **13** (suppl): S89–S96.
3. Gabay M. Absorbable hemostatic agents. *Am J Health-Syst Pharm* 2006; **63:** 1244–53.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p.1050). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155:** 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348:** 229–32.

Preparations

USP 31: Absorbable Gelatin Film; Absorbable Gelatin Sponge.

Proprietary Preparations (details are given in Part 3)
Arg.: Gelafundin; Geloplasma; Infukoll; ***Austral.:*** Gelfilm†; Gelfoam; Gelofusine; ***Austria:*** Gelofusin; ***Belg.:*** Gelfoam†; Gelofusine†; ***Braz.:*** Colagenan; Gelfoam; ***Canad.:*** Gelfilm; Gelfoam; ***Chile:*** Gelfoam; Gelofusine; Geloplasma; ***Cz.:*** Gelofusine; Geloplasma; ***Fin.:*** Gelofusine; ***Fr.:*** Bloxang; Gel-Phan; Gelodiet; Gelofusine†; Hydrocoll; ***Ger.:*** Gelafundin; Gelafusal; Gelaspon; Gelastypt; Spongostan; stypro; Thomaegelin†; ***Gr.:*** Gelofusine; ***Hong Kong:*** Gelfoam†; Gelofusine; ***Hung.:*** Gelaspon†; Gelofusine; ***India:*** Seraccel†; ***Indon.:*** Gelafundin; ***Israel:*** Gelfoam; ***Ital.:*** Cutanplast; Eufusin; Gelofusine; Spongostan; ***Malaysia:*** Gelfoam; ***Neth.:*** Gelfilm†; Gelfoam†; Gelofusine; Geloplasma; Willospon†; ***NZ:*** Gelfilm; Gelfoam; Gelofusine; ***Philipp.:*** Gelfoam; ***Pol.:*** Gelofusine; ***Port.:*** Gelafundina; Gelofusine; ***S.Afr.:*** Gelofusine; ***Singapore:*** Gelfoam; Gelofusine†; ***Switz.:*** Physiogel; ***Thai.:*** Gelafundin; Gelofusine; ***Turk.:*** Gelofusin; ***UK:*** Gelofusine; Geloplasma; Volplex; ***USA:*** Gelfilm; Gelfoam; ***Venez.:*** Gelfoam; Gelofusine.

Multi-ingredient: ***Arg.:*** Megaplus; Mucobase; ***Austral.:*** Orabase; Orahesive†; Stomahesive†; ***Austria:*** Gelacet; ***Canad.:*** Orabase†; Orahesive†; Tegasorb; ***Fr.:*** Plasmion; Rectopanbiline; ***Ger.:*** Gelacet N†; ***Irl.:*** Orabase; ***Israel:*** Orabase†; ***Ital.:*** Solecin; ***Mex.:*** Gelafundin; ***NZ:*** Orabase; Stomahesive; ***Port.:*** Dagragel; Varihesive†; ***S.Afr.:*** Granuflex; Orabase; ***Switz.:*** Gelacet†; ***UK:*** Orabase; Orahesive; Stomahesive; ***USA:*** Dome-Paste.

Haemoglobin ⊗

Hemoglobina.

Hemoglobin Glutamer *(rINN)* ⊗

Haemoglobin Glutamer; Hemoglobina glutámero; Hémoglobine Glutamère; Hemoglobinum Glutamerum.

Гемоглобин Глутамер

ATC — B05AA10 (bovine).

ATC Vet — QB05AA10 (bovine); QB05AA90.

NOTE. The species of origin and average molecular mass should be indicated (e.g. hemoglobin glutamer-250 (bovine) indicates a polymerised haemoglobin of bovine origin with an average mass of 250 kD).

Profile

Haemoglobin has the property of reversible oxygenation and is the respiratory pigment of blood. Solutions of haemoglobin or modified haemoglobin are being investigated as blood substitutes.

Hemoglobin glutamer-250 (bovine) (HBOC-201; haemoglobin-based oxygen carrier-201) is a polymerised bovine haemoglobin that is used for the treatment of anaemia in surgical patients.

Hemoglobin glutamer-200 (bovine) (HBOC-301) is used in veterinary medicine for the treatment of anaemia in *dogs*.

Use. The structure of haemoglobin gives a non-linear oxygen dissociation curve; almost maximum oxygen saturation occurs in normal arterial blood without the need for oxygen-enriched air. Thus the use of haemoglobin solutions for emergencies appears logical. Initial *animal* experiments with haemoglobin from haemolysed erythrocytes resulted in serious renal damage but haemoglobin is not itself nephrotoxic and the development of stroma-free haemoglobin solutions reduced this toxicity. However, once released from the erythrocytes, haemoglobin loses its ability to hold 2,3-diphosphoglycerate, which is essential for the delivery of oxygen, and haemoglobin, being a small molecule, is rapidly excreted by the kidneys. Various methods have been tried to overcome these problems; formation of crosslinked haemoglobin restores the oxygen affinity to that of whole blood and conjugation, polymerisation, or microencapsulation in a lipid membrane extend the half-life. Although there is ongoing development of these preparations there are reservations concerning haemoglobin solutions as blood substitutes. Bovine blood is one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability. There is also concern about impairment of immune mechanisms. The development of recombinant human haemoglobin may overcome these problems and may allow further modification of the haemoglobin molecule.

References.

1. Farrar D, Grocott M. Intravenous artificial oxygen carriers. *Hosp Med* 2003; **64:** 352–6.
2. Creteur J, Vincent J-L. Hemoglobin solutions. *Crit Care Med* 2003; **31** (suppl): S698–S707.
3. Chang TMS. Hemoglobin-based red blood cell substitutes. *Artif Organs* 2004; **28:** 789–94.
4. Mackenzie CF, Bucci C. Artificial oxygen carriers for trauma: myth or reality. *Hosp Med* 2004; **65:** 582–8.
5. Awasthi V. Pharmaceutical aspects of hemoglobin-based oxygen carriers. *Curr Drug Deliv* 2005; **2:** 133–42.
6. Stowell CP. What happened to blood substitutes? *Transfus Clin Biol* 2005; **12:** 374–9.
7. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11:** 4099–4114.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Hemopure.

Multi-ingredient: *India:* Blosyn; Haem Up.

Interleukin-3

IL-3; Interleucina 3.

Profile

Interleukin-3 is a cytokine that acts as a colony-stimulating factor. It is under investigation in the management of myelosuppression associated with cancer chemotherapy and after bone marrow transplantation. A fusion molecule with granulocyte-macrophage colony-stimulating factor, known as milodistim (PIXY-321), has also been investigated but results have been disappointing.

Lenograstim *(BAN, USAN, rINN)*

Lenograstiimi; Lénograstim; Lenograstimum; rG-CSF. A recombinant human granulocyte colony-stimulating factor.

Ленограстим

CAS — 135968-09-1.
ATC — L03AA10.
ATC Vet — QL03AA10.

Stability. Solutions of colony-stimulating factors may be adsorbed onto glass or plastic materials. Solutions of lenograstim should not be diluted below the minimum recommended concentration for the formulation used.

Adverse Effects and Precautions

As for Filgrastim, p.1070.

Uses and Administration

Lenograstim is a granulocyte colony-stimulating factor with actions and uses similar to those of filgrastim (p.1071). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p.640). It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation.

Lenograstim may be given for **neutropenia** in a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily to patients after bone marrow transplantation and also to patients established on antineoplastic therapy; in post-transplant patients it is given by intravenous infusion over 30 minutes or by subcutaneous injection, and in patients on antineoplastics it is given subcutaneously. Treatment is given until the neutrophil count has stabilised within the normal range, but a maximum treatment period of 28 consecutive days should not be exceeded.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily may be given by subcutaneous injection. It is started the day after completion of chemotherapy and given until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. When used alone, a lenograstim dose of 10 micrograms/kg (1.28 million international units/kg) daily is given subcutaneously for 4 to 6 days, with leucapheresis usually performed between days 5 and 7. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 5 or 6 days before leucapheresis.

◊ References.

1. Frampton JE, *et al.* Lenograstim: a review of its pharmacological properties and therapeutic efficacy in neutropenia and related clinical settings. *Drugs* 1995; **49:** 767–93.
2. Dunn CJ, Goa KL. Lenograstim: an update of its pharmacological properties and use in chemotherapy-induced neutropenia and related clinical settings. *Drugs* 2000; **59:** 681–717.
3. Martino M, *et al.* Harvesting peripheral blood progenitor cells from healthy donors: retrospective comparison of filgrastim and lenograstim. *J Clin Apher* 2005; **20:** 129–36.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Granocyte†; Lenobio; Leumostin†; ***Austral.:*** Granocyte; ***Austria:*** Granocyte; ***Belg.:*** Granocyte; ***Braz.:*** Granocyte; ***Chile:*** Granocyte; ***Cz.:*** Granocyte†; ***Denm.:*** Granocyte; ***Fin.:*** Granocyte; ***Fr.:*** Granocyte; ***Ger.:*** Granocyte; ***Gr.:*** Granocyte; ***Hung.:*** Granocyte; ***Indon.:*** Granocyte; ***Irl.:*** Granocyte; ***Israel:*** Granocyte; ***Ital.:*** Granocyte; Myelostim; ***Jpn:*** Neutrogin; ***Malaysia:*** Granocyte; ***Neth.:*** Granocyte; ***Norw.:*** Granocyte; ***NZ:*** Granocyte; ***Philipp.:*** Granocyte; ***Pol.:*** Granocyte; ***Port.:*** Granocyte; ***Rus.:*** Granocyte (Граноцит); ***S.Afr.:*** Granocyte; ***Singapore:*** Granocyte; ***Spain:*** Euprotin; Granocyte; ***Swed.:*** Granocyte; ***Switz.:*** Granocyte; ***Thai.:*** Granocyte; ***UK:*** Granocyte; ***Venez.:*** Granocyte.

Leucocytes

Leucocitos.

Description. Preparations of leucocytes contain granulocytes with a variable content of red blood cells, lymphocytes, and platelets. Depending on the method of collection they may also contain dextran or hetastarch.

Adverse Effects and Precautions

Leucocyte transfusions may cause severe transfusion reactions and fever. As with other blood products, there is a risk of transmission of infection. Severe lung reactions, including fluid overload with pulmonary oedema, are a particular problem in patients with active pulmonary infections.

Red blood cell compatibility testing is necessary because of the content of red blood cells. Graft-versus-host disease may occur in immunosuppressed recipients, and can be avoided by irradiating the product before it is given.

Uses and Administration

Transfusion of leucocytes has been used in patients with severe granulocytopenia and infection which has not been controlled by treatment with appropriate antimicrobials. Transfusion of 1×10^{10} granulocytes once or twice daily has been suggested as an effective dose. Daily transfusions for at least 3 to 4 days are usually advised. Hydrocortisone and chlorphenamine may be given intravenously before transfusion to reduce the severity of adverse reactions.

◊ References.

1. Brozović B, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 17–22.
2. Yeghen T, Devereux S. Granulocyte transfusion: a review. *Vox Sang* 2001; **81:** 87–92.
3. Hubel K, Engert A. Granulocyte transfusion therapy for treatment of infections after cytotoxic chemotherapy. *Onkologie* 2003; **26:** 73–9.
4. Briones MA, *et al.* Granulocyte transfusion: revisited. *Curr Hematol Rep* 2003; **2:** 522–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Immodin; ***Ger.:*** LeukoNorm.

Mirimostim *(rINN)*

Mirimostimum. A macrophage colony-stimulating factor; 1–214-Colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer.

Миримостим

CAS — 121547-04-4.

Profile

Mirimostim is a macrophage colony-stimulating factor (M-CSF). It promotes the differentiation and proliferation of monocytes and macrophage precursors, and stimulates secretion of granulocyte and granulocyte-macrophage colony-stimulating factors (see Haematopoiesis, p.1042). Mirimostim is used in the management of neutropenia in patients receiving myelosuppressive cancer chemotherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Leukoprol.

Molgramostim *(BAN, USAN, rINN)*

Molgramostiimi; Molgramostimum; Sch-39300. A recombinant human granulocyte-macrophage colony-stimulating factor; Colony-stimulating factor 2 (human clone pHG_{25} protein moiety reduced).

Молграмостим

CAS — 99283-10-0.
ATC — L03AA03.
ATC Vet — QL03AA03.

Pharmacopoeias. *Eur.* (see p.vii) includes a concentrated solution.

Ph. Eur. 6.2 (Molgramostim Concentrated Solution; Molgramostimi Solutio Concentrata). A solution of a protein having the structure of the granulocyte-macrophage colony-stimulating factor which is produced and secreted by various human blood cell types. It contains not less than 2.0 mg of protein per mL. A clear, colourless liquid. Store in airtight containers at a temperature below −65°. Protect from light.

Stability. Solutions of molgramostim may be adsorbed onto glass and plastic materials and therefore should not be diluted below the recommended minimum concentration of 7 micrograms/mL.

Adverse Effects

Granulocyte-macrophage colony-stimulating factors such as molgramostim may cause transient hypotension and flushing, bone pain and musculoskeletal pain, fever and chills, dyspnoea, rash, fatigue, and gastrointestinal effects. Antibodies have been detected. Anaphylactic reactions, pleural and pericardial effusion, and cardiac arrhythmias have been reported rarely.

Colony-stimulating factors are fetotoxic in *animal* studies.

◊ General references.

1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13:** 371–406.
2. Moleski RJ. Comparison of G-CSF and GM-CSF adverse event profiles in office-based practices: preliminary study results. *Pharmacotherapy* 2000; **20** (suppl): 112S–117S.
3. Milkovich G, *et al.* Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2000; **20:** 1432–40.

Antibodies. Antibodies can develop in patients given recombinant granulocyte-macrophage colony-stimulating factors. The antibodies have been reported to occur more commonly, and in higher titres, in patients who are not immunocompromised compared with those who are.[1,2] Although some binding antibodies are non-neutralising and have no apparent clinical effect,[3] neutralising antibodies can reduce the efficacy of the colony-stimulating factor in repeated treatment cycles.[1,2] However, antibodies have been reported to become undetectable after a number of weeks[2] and do not appear to have long-term effects.[1] Cross-reactivity between different granulocyte-macrophage colony-stimulating factors has been reported,[1-3] and antibody formation may also be product dependent.[2]

1. Ragnhammar P, *et al.* Induction of anti-recombinant human granulocyte-macrophage colony-stimulating factor (Escherichia coli-derived) antibodies and clinical effects in nonimmunocompromised patients. *Blood* 1994; **84:** 4078–87.
2. Wadhwa M, *et al.* Immunogenicity of granulocyte-macrophage colony-stimulating factor (GM-CSF) products in patients undergoing combination therapy with GM-CSF. *Clin Cancer Res* 1999; **5:** 1353–61.
3. Ullenhag G, *et al.* Incidence of GM-CSF antibodies in cancer patients receiving GM-CSF for immunostimulation. *Clin Immunol* 2001; **99:** 65–74.

Effects on the skin. See under Filgrastim, p.1070.

Effects on the thyroid. See under Filgrastim, p.1070.

Precautions

Since granulocyte-macrophage colony-stimulating factors such as molgramostim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. They should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy or radiotherapy because of the sensitivity of rapidly dividing myeloid cells.

Granulocyte-macrophage colony-stimulating factors should be used with caution in patients with pulmonary disease as they may be predisposed to dyspnoea. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Caution is also necessary in patients with fluid retention or heart failure as fluid retention may be aggravated.

The complete blood count should be monitored regularly during therapy.

Uses and Administration

Molgramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF), a haematopoietic growth factor that stimulates the development of white blood cells, particularly granulocytes, macrophages, and monocytes (see Haematopoiesis, p.1042). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p.640). It has also been used to reduce ganciclovir-induced neutropenia (see Effects on the Blood, p.879).

As an **adjunct to antineoplastic therapy**, molgramostim is given by subcutaneous injection, starting 24 hours after the last dose of antineoplastic, in a dose of 5 to 10 micrograms/kg (60 000 to 110 000 international units/kg) daily. Treatment should be continued for 7 to 10 days.

Following **bone marrow transplantation**, molgramostim may be given by intravenous infusion over 4 to 6 hours in a dose of 10 micrograms/kg (110 000 international units/kg) daily. Treatment should be begun the day after bone marrow transplantation and continued for up to 30 days depending on the neutrophil count.

For the management of **ganciclovir-induced neutropenia**, molgramostim has been given by subcutaneous injection in a dose of 5 micrograms/kg (60 000 international units/kg) daily. After 5 doses have been given the dose of molgramostim should be adjusted according to the neutrophil count.

The maximum dose for any indication should not exceed 10 micrograms/kg (110 000 international units/kg) daily.

Granulocyte colony-stimulating factors such as filgrastim (p.1070) and macrophage colony-stimulating factors such as mirimostim (p.1073) are also used.

◊ General references.

1. Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998; **92:** 4491–4508.
2. Mangi MH, Newland AC. Febrile neutropenia: prophylactic and therapeutic use of GM-CSF. *Eur J Cancer* 1999; **35** (suppl): S4–S7.
3. Croockewit S. GM-CSF in haematopoietic stem cell transplantation. *Eur J Cancer* 1999; **35** (suppl): S11–S13.
4. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22:** 3350–6.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://www.jco.org/cgi/reprint/24/19/3187 (accessed 20/09/06)

Infections. See under Filgrastim, p.1071, and under HIV Infection and AIDS in Sargramostim, p.1079.

Ischaemia. For mention of the use of molgramostim in patients with atherosclerotic coronary artery disease see under Filgrastim, p.1071.

Respiratory disorders. Pulmonary alveolar proteinosis is a rare diffuse lung disease that may result from impaired alveolar macrophage function caused by neutralising autoantibodies. It is characterised by excessive surfactant accumulation, and is usually managed with whole-lung lavage. Several months of therapy with subcutaneous granulocyte-macrophage colony-stimulating factor, typically in doses of 5 or 6 micrograms/kg daily, has been reported to induce remission in a number of these patients.[1-6] There has also been a case report[7] of the effective use of inhaled granulocyte-macrophage colony-stimulating factor.

1. Barraclough RM, Gillies AJ. Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy. *Thorax* 2001; **56:** 664–5.
2. Seymour JF, *et al.* Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am J Respir Crit Care Med* 2001; **163:** 524–31.
3. Schoch OD, *et al.* BAL findings in a patient with pulmonary alveolar proteinosis successfully treated with GM-CSF. *Thorax* 2002; **57:** 277–80.
4. Romero A, *et al.* GM-CSF therapy in pulmonary alveolar proteinosis. *Thorax* 2002; **57:** 837.
5. Khanjari F, *et al.* GM-CSF and proteinosis. *Thorax* 2003; **58:** 645.
6. Abdul Rahman JA, *et al.* Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage. *Respirology* 2004; **9:** 419–22.
7. Arai T, *et al.* Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. *Respir Med* 2004; **98:** 1227–30.

Wounds and ulcers. Macrophages and granulocyte-macrophage colony-stimulating factors play important roles in several mechanisms essential to wound healing.[1] Recombinant granulocyte-macrophage colony-stimulating factors are being tried in non-healing wounds and ulcers (p.1585), particularly chronic venous leg ulcers. They have been given by perilesional subcutaneous injection and topical application in a few small studies and case reports with apparent promotion of wound healing.[1] In a study[2] of patients with pressure ulcers, healing was better during a 35-day period of treatment with granulocyte-macrophage colony-stimulating factor compared with placebo. However, a year after the treatment period there was no difference.[3] In a group of 3 patients with inherited disorders of neutrophil function, topical sargramostim was reported to be of benefit in wound healing.[4] In 1 case sargramostim was also given by continuous subcutaneous infusion for 72 hours into the surgical site of a gastrostomy closure. Topical molgramostim has also been used to promote healing of sickle-cell leg ulcers.[5] Molgramostim has been used as a mouthwash to relieve severe recurrent aphthous mouth ulcers in a small number of patients with AIDS.[6] There has also been some investigation of the use of granulocyte-macrophage colony-stimulating factor for oral mucositis in cancer patients, particularly those undergoing radiotherapy for head and neck cancers. Small studies of subcutaneous injection or topical application as a mouthwash have provided some optimistic results.[7,8] Comparative studies, however, have found molgramostim to be no better than hydrocortisone mouthwash[9] and perhaps only slightly better than sucralfate mouthwash.[10]

1. Groves RW, Schmidt-Lucke JA. Recombinant human GM-CSF in the treatment of poorly healing wounds. *Adv Skin Wound Care* 2000; **13:** 107–12.
2. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–611.
3. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
4. De Ugarte DA, *et al.* Treatment of chronic wounds by local delivery of granulocyte-macrophage colony-stimulating factor in patients with neutrophil dysfunction. *Pediatr Surg Int* 2002; **18:** 517–20.
5. Méry L, *et al.* Topical effectiveness of molgramostim (GM-CSF) in sickle cell leg ulcers. *Dermatology* 2004; **208:** 135–7.
6. Herranz P, *et al.* Successful treatment of aphthous ulcerations in AIDS patients using topical granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2000; **142:** 171–6.
7. Fung SM, Ferrill MJ. Granulocyte macrophage-colony stimulating factor and oral mucositis. *Ann Pharmacother* 2002; **36:** 517–20.
8. Mantovani G, *et al.* Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy- and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: an evaluation of effectiveness, safety and costs. *Oncol Rep* 2003; **10:** 197–206.
9. Sprinzl GM, *et al.* Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *Eur J Cancer* 2001; **37:** 2003–9.
10. Saarilahti K, *et al.* Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *Int J Radiat Oncol Biol Phys* 2002; **54:** 479–85.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Growgen-GM; Leucomax†; Molcass; ***Austria:*** Leucomax†; ***Belg.:*** Leucomax†; ***Braz.:*** Gramostim†; Leucocitim; Leucomax†; ***Chile:*** Leucomax†; ***Cz.:*** Leucomax†; ***Denm.:*** Leucomax†; ***Fin.:*** Leucomax†; ***Ger.:*** Leucomax†; ***Gr.:*** Leucomax; Mielogen; ***Hong Kong:*** Leucomax†; ***Hung.:*** Leucomax†; ***India:*** Leucomax; ***Irl.:*** Leucomax; ***Israel:*** Leucomax; ***Ital.:*** Leucomax†; Mielogen†; ***Malaysia:*** Leucomax†; ***Mex.:*** Gramal; Leucomax†; ***Neth.:*** Leucomax†; ***Norw.:*** Leucomax†; ***NZ:*** Leucomax; ***S.Afr.:*** Leucomax†; ***Spain:*** Leucomax†; ***Swed.:*** Leucomax†; ***Switz.:*** Leucomax†; ***Thai.:*** Leucomax†; ***UK:*** Leucomax†; ***Venez.:*** Leucomax†.

Naftazone *(BAN, rINN)*

Naftazona; Naftazonum. 1,2-Naphthoquinone 2-semicarbazone.

Нафтазон

$C_{11}H_9N_3O_2$ = 215.2.
CAS — 15687-37-3.

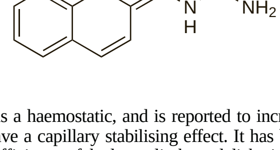

Profile

Naftazone is a haemostatic, and is reported to increase venous tone and have a capillary stabilising effect. It has been used in venous insufficiency of the lower limbs and diabetic retinopathy, in oral doses of 30 mg daily. It was formerly given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mediaven; ***Fr.:*** Etioven; ***Switz.:*** Mediaven.

Nartograstim *(rINN)*

Nartograstimum. A recombinant human granulocyte colony-stimulating factor; *N*-L-Methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine colony-stimulating factor (human clone 1034).

Нартограстим

CAS — 134088-74-7.

Profile

Nartograstim is a granulocyte colony-stimulating factor with properties similar to those of filgrastim (p.1070). It has been given by intravenous or subcutaneous injection in the management of neutropenia.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Neu-Up.

Oprelvekin *(USAN, rINN)*

Oprelvekina; Oprelvékine; Oprelvekinum. 2-178-Interleukin 11 (human clone pXM/IL-11).

Опрельвекин

$C_{854}H_{1411}N_{253}O_{235}S_2$ = 19047.0.
CAS — 145941-26-0.
ATC — L03AC02.
ATC Vet — QL03AC02.

Adverse Effects and Precautions

Fluid retention may occur and lead to peripheral oedema, dyspnoea and pulmonary oedema, capillary leak syndrome, and exacerbation of pre-existing pleural effusions; caution is required when giving oprelvekin to patients with a history or signs of heart failure. Dilutional anaemia may occur. Fluid balance and electrolytes should be monitored in patients receiving long-term diuretic therapy. Transient atrial arrhythmias commonly occur; there have also been some reports of ventricular arrhythmias occurring within 2 to 7 days of starting oprelvekin. Other adverse effects include exfoliative dermatitis, blurred vision, and conjunctival injection. Hypersensitivity reactions, including anaphylaxis, have been reported with the use of oprelvekin. Papilloedema has been reported, and oprelvekin should be used with caution in patients with pre-existing papilloedema or tumours involving the CNS.

Use of oprelvekin after myeloablative chemotherapy and bone marrow transplantation is considered to be contra-indicated because of an increased incidence of adverse effects.

Fetotoxicity has been reported in *animals.*

◊ Reviews.

1. Smith JW. Tolerability and side-effect profile of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 41–7.

Effects on the eyes. Papilloedema has been reported in patients treated with oprelvekin,[1] and was found to be a dose-limiting adverse effect in a study of safety and pharmacokinetics in children.[2]

1. Peterson DC, *et al.* Oprelvekin-associated bilateral optic disk edema. *Am J Ophthalmol* 2005; **139:** 367–8.
2. Cairo MS, *et al.* Phase I/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. *Br J Haematol* 2005; **128:** 49–58.

Pharmacokinetics

The bioavailability of oprelvekin after subcutaneous injection is about 80%, peak serum concentrations are reached after about 3 hours, and it has a terminal half-life of about 7 hours. Oprelvekin is metabolised before excretion by the kidneys, and its clearance is reduced in renal impairment.

Uses and Administration

Oprelvekin, a recombinant human interleukin-11, is a platelet growth factor that stimulates the proliferation and maturation of megakaryocytes and thus increases the production of platelets. Oprelvekin is given by subcutaneous injection in a dose of 50 micrograms/kg daily to prevent severe thrombocytopenia and reduce the need for platelet transfusions in high-risk patients after myelosuppressive, but not myeloablative, chemotherapy for non-myeloid malignancies (see Thrombocytopenia under Treatment of Adverse Effects in Antineoplastics, p.640). The dose should be reduced in severe renal impairment (see below). The initial dose should be given 6 to 24 hours after the last dose of antineoplastic, and continued up to a maximum of 21 days. Treatment with oprelvekin should be stopped at least 2 days before starting the next planned cycle of chemotherapy.

Oprelvekin is under investigation for the treatment of Crohn's disease, rheumatoid arthritis, and chronic hepatitis C.

Administration in renal impairment. In severe renal impairment (creatinine clearance less than 30 mL/min) the recommended dose of oprelvekin is 25 micrograms/kg daily by subcutaneous injection.

Thrombocytopenia. References.

1. Tepler I, *et al.* A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood* 1996; **87:** 3607–14.
2. Isaacs C, *et al.* Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; **15:** 3368–77.
3. Reynolds CH. Clinical efficacy of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 32–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Neumega†; ***Braz.:*** Neumega; ***Chile:*** Neumega†; ***Mex.:*** Neumega†; ***USA:*** Neumega; ***Venez.:*** Neumega.

Oxidised Cellulose

Cellulosic Acid; Celulosa oxidada; Oxidized Cellulose.

CAS — 9032-53-5.

ATC — B02BC02.

ATC Vet — QB02BC02.

Description. Oxidised cellulose is a sterile polyanhydroglucuronic acid, prepared by the oxidation of a suitable form of cellulose.

Pharmacopoeias. In *US* which also includes Oxidized Regenerated Cellulose.

USP 31 (Oxidized Cellulose). It contains not less than 16% and not more than 24% of carboxyl groups, calculated on the dried basis. It is a slightly off-white gauze or lint with a slight, charred odour. Insoluble in water and in acids; soluble in dilute alkalis. Store at a temperature not exceeding 8°. Protect from direct sunlight.

USP 31 (Oxidized Regenerated Cellulose). It contains 18 to 24% of carboxyl groups calculated on the dried basis. It is a slightly off-white knit fabric, with a slight odour. Insoluble in water and in dilute acids; soluble in dilute alkalis. Store at a temperature between 15° and 30°. Protect from direct sunlight.

Adverse Effects and Precautions

Foreign body reactions may occur after the use of oxidised cellulose or oxidised regenerated cellulose. Headache, burning, and stinging have been reported and sneezing has been noted after use in epistaxis. Oxidised cellulose swells on contact with a bleeding surface; this could result in tissue necrosis, nerve damage, obstruction, or vascular stenosis if packed closely, especially into bony cavities, or if wrapped tightly around blood vessels. To minimise such complications the removal of excess material should be considered after haemostasis is achieved, and oxidised cellulose should always be removed after use near the spinal cord or optic nerve. Oxidised cellulose should not be used in packing or implantation for fractures since it may interfere with bone regeneration or cause cyst formation. It should not be used as a surface dressing, except for immediate control of haemorrhage, as it inhibits epithelialisation.

Oxidised cellulose should be used as the dry material since moistening will reduce its ability to absorb blood. Silver nitrate or other escharotic chemicals should not be applied before use as cauterisation might inhibit absorption of oxidised cellulose. Thrombin is inactivated by the low pH of oxidised cellulose; it is recommended that oxidised cellulose should not be impregnated with other haemostatics or antibacterials.

Uses and Administration

Oxidised cellulose and oxidised regenerated cellulose are absorbable haemostatics (p.1045). When applied to a bleeding surface, they swell to form a gelatinous mass which aids in the formation of a clot. It is gradually absorbed by the tissues, usually within 7 to 14 days. These materials also have a weak bactericidal action. They are used in surgery as adjuncts in the control of moderate bleeding where suturing or ligation is impracticable or ineffective; they should not be used to control haemorrhage from large arteries. The gauze, lint, or knitted material should be laid on the bleeding surface or held firmly against the tissues until haemostasis is achieved; removal should then be considered (see Adverse Effects and Precautions, above). Oxidised cellulose should be used as the dry material as moistening will reduce its ability to absorb blood.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Surgicel; ***Ger.:*** Tabotamp; ***Hong Kong:*** Seal On†; ***Irl.:*** Alltracel P†; Premdoc†; Seal-On; Traumacel P; ***Ital.:*** Tabotamp; ***UK:*** Oxycel; StopBleed; ***USA:*** Oxycel; Surgicel.

Multi-ingredient: ***Fr.:*** Promogran; ***Irl.:*** Alltracel S†; ***Ital.:*** Promogran; ***UK:*** Seal-On.

Oxypolygelatin ⊗

Oxipoligelatina.

Profile

Oxypolygelatin is a polymer derived from gelatin (p.1072). It is used as a 5.5% solution as a plasma volume expander. There have been reports of anaphylaxis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gelifundol†; ***Austria:*** Gelifundol; ***Cz.:*** Gelifundol†; ***Ger.:*** Gelifundol†; ***Hong Kong:*** Gelifundol†; ***Hung.:*** Gelifundol†; ***S.Afr.:*** Gelifundol†; ***Thai.:*** Gelifundol.

Pegzerepoetin Alfa ⊗

Methoxy Polyethylene Glycol-Epoetin Beta; Pegserepoetin Alfa; R-744; Ro-50-3821. 1-165-Erythropoietin (human) monoamide with α-(3-carboxypropyl)-ω-methoxypoly(oxy-1,2-ethanediyl).

CAS — 677324-53-7.

ATC — B03XA03.

ATC Vet — QB03XA03.

Adverse Effects and Precautions

As for Epoetins, p.1061.

Pharmacokinetics

In patients with chronic renal impairment, pegzerepoetin alfa is absorbed after subcutaneous injection with an absolute bioavailability of about 60%. It has a terminal elimination half-life of about 134 hours after intravenous injection and about 140 hours when given subcutaneously. Haemodialysis does not affect the pharmacokinetics of pegzerepoetin alfa.

Uses and Administration

Pegzerepoetin alfa is described as a continuous erythropoietin receptor activator (CERA). It has similar properties to the epoetins (p.1062), but a longer duration of action. Pegzerepoetin alfa is used in the treatment of anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p.1044). A starting dose of 600 nanograms/kg is given once every 2 weeks as a single intravenous or subcutaneous injection. The dose may be adjusted by about 25%, at monthly intervals, so that the rate of rise of haemoglobin is between 1 and 2 g per 100 mL each month. When the target haemoglobin concentration of between 11 and 12 g per 100 mL has been achieved, a maintenance dose of pegzerepoetin alfa may be given once monthly; this is equal to twice the dose that had been given once every 2 weeks.

Pegzerepoetin alfa is also under investigation in the treatment of anaemia in patients with non-myeloid malignant disease receiving chemotherapy.

◊ References.

1. de Francisco ALM, *et al.* BA16260 Study Investigators. Continuous Erythropoietin Receptor Activator (C.E.R.A.) administered at extended administration intervals corrects anaemia in patients with chronic kidney disease on dialysis: a randomised, multicentre, multiple-dose, phase II study. *Int J Clin Pract* 2006; **60:** 1687–96.
2. Sulowicz W, *et al.* PROTOS Study Investigators. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007; **2:** 637–46.
3. Levin NW, *et al.* MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet* 2007; **370:** 1415–21.
4. Österborg A, *et al.* Phase II study of three dose levels of continuous erythropoietin receptor activator (C.E.R.A.) in anaemic patients with aggressive non-Hodgkin's lymphoma receiving combination chemotherapy. *Br J Haematol* 2007; **136:** 736–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mircera; ***Fr.:*** Mircera; ***Port.:*** Mircera; ***UK:*** Mircera; ***USA:*** Mircera.

Plasma

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human Plasma for Fractionation; Plasma Humanum ad Separationem). The liquid part of human blood remaining after separation of the cellular elements from whole blood or collected in an apheresis procedure; it is intended for the manufacture of plasma-derived products. It is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

A light yellow to green, clear or slightly turbid liquid, without visible signs of haemolysis. Frozen plasma should be stored at or below −20°; it may still be used for fractionation if the temperature is between −20° and −15° for not more than a total of 72 hours without exceeding −15° on more than one occasion as long as the temperature is at all times −5° or lower.

Ph. Eur. 6.2 (Human Plasma (Pooled and Treated for Virus Inactivation); Plasma Humanum Coagmentum Conditumque ad Exstinguendum Virum). A frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The plasma used complies with the requirements for Human Plasma for Fractionation (above). The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to inactivate known agents of infection.

The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles. The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Adverse Effects and Precautions

As for Blood, p.1056, though with a low risk of transmitting cell-associated viruses. However, the production of blood products using plasma from UK donors has been phased out due to the possible risk of transmission of Creutzfeldt-Jakob disease.

Uses and Administration

Fresh frozen plasma contains useful amounts of clotting factors. It should be reserved for patients with proven abnormalities in blood coagulation. Indications include congenital deficiencies in clotting factors for which specific concentrates are unavailable, severe multiple clotting factor deficiencies (for example in patients with liver disease), rapid reversal of the action of coumarin anticoagulants, and disseminated intravascular coagulation. It may be used after massive blood transfusion when there is evidence of coagulation deficiency but its value for routine prophylaxis against abnormal bleeding tendencies in patients receiving massive blood transfusions is contentious except where clotting abnormalities have been confirmed. It has also been used in the treatment of thrombotic thrombocytopenic purpura and as a source of plasma proteins.

The amount of fresh frozen plasma transfused depends on the required level of clotting factors. A unit of fresh frozen plasma refers to the quantity of plasma obtained from 1 unit of whole blood; this generally represents a volume of about 250 mL, including anticoagulant.

Fresh frozen plasma should not be used as a volume expander or as a nutritional source.

Therapeutic plasma exchange or plasmapheresis (see below) are used in a wide variety of disorders.

Plasma is used to prepare blood products including albumin, antithrombin III, blood clotting factors, immunoglobulins, and platelets. Other preparations include cryoprecipitate depleted plasma, which is deficient in fibrinogen, factor VIII, von Willebrand factor, cryoglobulin, and fibronectin, and single donor plasma, which is not frozen. A solvent-detergent-treated plasma preparation is available.

Guidelines and reviews. General references to the use of plasma.

1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. Cohen H, *et al.* Plasma, plasma products, and indications for their use. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London; BMJ Books, 1998: 40–44.
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126:** 11–28. Also available at: http://www.bcshguidelines.com/pdf/freshfrozen_280604.pdf (accessed 27/10/05) Addenda, amendments, and corrections (4 sets) at http://www.bcshguidelines.com/pdf/Amendments_FFP_091205.pdf (issued 07/12/05), *ibid.* 2007; **136:** 514–16, at http://www.bcshguidelines.com/pdf/FFPAmendment_1_17_Oct_2007.pdf (issued 17/10/07), at http://www.bcshguidelines.com/pdf/FFPAmendment_2_17_Oct_2007.pdf (issued 17/10/07) (accessed 19/06/08)
4. Stanworth SJ, *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126:** 139–52.

Hereditary angioedema. For a mention of fresh frozen plasma being used in hereditary angioedema, see p.1081.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p.1050). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155:** 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348:** 229–32.

Plasma exchange. Therapeutic plasma exchange or plasmapheresis are procedures in which plasma is selectively removed from the body while the cellular constituents of blood are retained. Although the two terms are commonly used synonymously, plasmapheresis generally involves the removal of small volumes of plasma, whereas plasma exchange removes larger volumes which must be replaced with a suitable fluid.

They have been tried in a number of disorders, including many with an immunological basis, when conventional treatment has not been successful. The aim is removal or reduction of those constituents of plasma causing or aggravating a disease or replacement of deficient plasma factors if the deficiency is the cause of the disorder.

Volume and frequency of plasma exchange is determined by the pathophysiology of the undesirable plasma constituent. For example, removal of antibody usually requires exchange of 1.5 times the estimated plasma volume (3 to 4 litres) repeated daily or on alternate days until the desired reduction is obtained. The replacement fluid used depends on the volume and the condition being treated; albumin solutions, plasma expanders, or sodium chloride 0.9% are frequently used, whereas in conditions where there is deficiency of a plasma factor replacement of blood components such as immunoglobulins may be required. Fresh frozen plasma has been used as a replacement fluid but is associated with a high incidence of adverse effects and is generally reserved for the management of thrombotic thrombocytopenic purpura.

Technological developments, such as the use of specific adsorbents and the use of multiple filters with different pore sizes, may enable removal of only the desired constituent and avoid removal and subsequent replacement of total plasma.

References.

1. Urbaniak SJ, Robinson EA. Therapeutic apheresis. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998: 67–70.
2. Michaud D, *et al.* Therapeutic plasma exchange. *Dynamics* 2001; **12:** 18–24.
3. Madore F. Plasmapheresis: technical aspects and indications. *Crit Care Clin* 2002; **18:** 375–92.
4. McLeod BC. Therapeutic apheresis: use of human serum albumin, fresh frozen plasma and cryosupernatant plasma in therapeutic plasma exchange. *Best Pract Res Clin Haematol* 2006; **19:** 157–67.

Thrombotic microangiopathies. Thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome are both syndromes characterised by intravascular platelet clumping.[1-6] Thrombocytopenia also occurs and fragmentation of erythrocytes, partly caused by the red cells passing through areas of the microvasculature occluded by the platelet aggregation, leads to microvascular haemolytic anaemia. In **thrombotic thrombocytopenic purpura** (TTP) the platelet aggregation is extensive and obstructs the vessels of various organs producing ischaemia or even infarction. The CNS, notably the brain, is often the area predominantly affected although some degree of renal involvement may occur. It is an uncommon disorder; adult women, in whom the condition presents as a chronic relapsing illness, are slightly more frequently affected. It may be associated with abnormalities of von Willebrand factor due to deficiency or impaired activity of a protease, ADAMTS-13.[5,6]

In **haemolytic-uraemic syndrome** (HUS) the platelet aggregation is relatively less widespread and less severe and mainly affects the renal microvasculature although extra-renal manifestations may also occur. The primary consequences are hypertension and acute renal insufficiency or ultimately, if untreated, renal failure. Most cases of HUS occur in early childhood and follow a diarrhoeal illness caused by *Shigella dysenteriae* or *Escherichia coli*. However, the condition is becoming increasingly recognised in adults, particularly the elderly. Some cases may be drug induced. With appropriate symptomatic therapy HUS is typically a self-limiting disease with spontaneous recovery although fatalities have been known.

The supportive **management** of both syndromes follows similar lines.[1,3,4] In HUS, or TTP with renal symptoms, special attention needs to be directed towards the prevention of renal failure. Hypovolaemia should be corrected, with careful control of fluid and electrolyte balance and hypertension. Haemodialysis will be needed if renal failure develops. Severe anaemia requires blood transfusion, but platelet transfusion should be avoided.

Plasma exchange (see above) is considered to be the mainstay of therapy for TTP.[1-6] The optimal regimen has not been determined, but it is usually performed daily. There is also some debate about the preferred fluid replacement; plasma exchange using cryosupernatant (the plasma remaining after cryoprecipitate is prepared, and which is depleted of von Willebrand factor) may be more efficacious than fresh frozen plasma.[3] When plasma exchange is not available, infusion of fresh frozen plasma may be used.[1,3] In HUS, there is some debate over the use of plasma exchange or infusion. Some consider that these have no proven benefit in HUS[2,3] but others[1] have challenged this belief.

Antiplatelet therapy and corticosteroids are often given, although neither has been adequately investigated and antiplatelets such as ticlopidine and clopidogrel have been reported to cause TTP (see p.1411). Aspirin and dipyridamole have been used, but are not recommended when profound thrombocytopenia is present because of the potential bleeding risk, without proven benefit. However, low-dose aspirin may be used when platelet counts have recovered after plasma exchange in TTP.[1,3] Some reports have described improved outcome in both syndromes with corticosteroids.[7] They are often used with plasma exchange in TTP.[1,3,4] However, a randomised, double-blind trial[8] in children with HUS failed to show any difference between oral corticosteroids and placebo in terms of haematological or neurological recovery, although renal function appeared to improve more rapidly in those receiving corticosteroids.

Other drugs may also be tried, particularly in refractory TTP. Some treatments that have been reported to be beneficial in case reports or small series include normal immunoglobulin,[1,4] azathioprine,[1] ciclosporin,[1,3] cyclophosphamide,[3] and vincristine.[1-4] The monoclonal antibody, rituximab, is under investigation.[2] The use of a protein-A immuno-adsorption column may be considered in the management of TTP associated with malignancy or bone marrow transplantation.[3] Epoprostenol may be tried in order to inhibit platelet-endothelial interactions but again has not been subject to controlled studies; anecdotal evidence presents both favourable and negative results.[9] Alteplase has been used successfully in one patient with HUS.[10] Splenectomy may also be considered.[1,3,4]

1. Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Mayo Clin Proc* 2001; **76:** 1154–62.
2. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; **347:** 589–600.
3. British Society for Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; **120:** 556–73. Also available at: http://www.bcshguidelines.com/pdf/BJH556.pdf (accessed 27/10/05)
4. Nabhan C, Kwaan HC. Current concepts in the diagnosis and management of thrombotic thrombocytopenic purpura. *Hematol Oncol Clin North Am* 2003; **17:** 177–99.
5. Mayer SA, Aledort LM. Thrombotic microangiopathy: differential diagnosis, pathophysiology and therapeutic strategies. *Mt Sinai J Med* 2005; **72:** 166–75.
6. George JN. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; **354:** 1927–35.
7. Bell WR, *et al.* Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med* 1991; **325:** 398–403.
8. Perez N, *et al.* Steroids in the hemolytic uremic syndrome. *Pediatr Nephrol* 1998; **12:** 101–4.
9. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
10. Kruez W, *et al.* Successful treatment of haemolytic-uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Octaplas; ***Cz.:*** Octaplas; ***Fin.:*** Octaplas; ***Ger.:*** Octaplas; ***Ital.:*** Octaplas; Plasmasafe; ***Mex.:*** Octaplas; ***Neth.:*** Octaplas; ***Norw.:*** Octaplas; ***NZ:*** Octaplas; ***Port.:*** Novoplas; Octaplas; ***Swed.:*** Octaplas; ***Switz.:*** Octaplas; ***UK:*** Octaplas.

Multi-ingredient: ***Port.:*** Quixil.

Plasma Protein Fraction ⊗

Fracción proteica del plasma.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US.*

USP 31 (Plasma Protein Fraction). A sterile preparation of serum albumin and globulin obtained by fractionating material (blood, plasma, or serum) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It contains 5% of protein; not less than 83% of the total protein is albumin; not more than 17% is alpha and beta globulins; not more than 1% has the electrophoretic properties of gamma globulin. It contains sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent but no antimicrobial preservative. It contains 130 to 160 mmol/litre of sodium, and not more than 2 mmol/litre of potassium. A solution in 0.15M sodium chloride containing 1% protein has a pH between 6.7 and 7.3. It should be used within 4 hours of opening the container.

Profile

Plasma protein fraction consists mainly of albumin with a small proportion of globulins; it does not contain blood-clotting factors. It has properties and uses similar to those of other albumin solutions (p.1052). It is given intravenously as a solution containing 5% of total protein. The amount of plasma protein fraction given will depend upon the clinical condition of the patient. For hypovolaemic shock an initial infusion of up to 500 mL for adults has been suggested at a rate not normally exceeding 10 mL/minute. A suggested dose in infants and small children for shock with dehydration is up to 33 mL/kg given at a rate of up to 5 to 10 mL/minute. In hypoproteinaemia, 1 to 1.5 litres of a 5% solution will provide 50 to 75 g of protein. Patients with normal blood volume may require slow infusion to prevent excessive volume expansion.

As with other albumin solutions, plasma protein fraction should not be used for parenteral nutrition.

Preparations

USP 31: Plasma Protein Fraction.

Proprietary Preparations (details are given in Part 3)
Austria: Biseko; ***Cz.:*** Biseko†; ***Ger.:*** Biseko; ***Gr.:*** Alburex; ***Hung.:*** Biseko; ***Indon.:*** Plasmanate; ***Israel:*** Plasmanate; ***Ital.:*** Haimaserum†; PPS; Uman-Serum; ***Malaysia:*** Plasmanate†; ***Philipp.:*** Plasmanate; ***S.Afr.:*** Bioplasma FDP; ***Thai.:*** Biseko; ***USA:*** Plasma-Plex; Plasmanate; Protenate.

Multi-ingredient: ***Fin.:*** Tisseel Duo Quick; ***Ger.:*** Tissucol Duo S; Tissucol-Kit; ***Hung.:*** Tissucol-Kit; ***Ital.:*** Tissucol; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Tissucol Duo S.

Platelets

Plaquetas.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US.*

USP 31 (Platelets). The portion of blood that contains platelet cells derived from human whole blood from which red blood cells and a portion of the plasma are removed by centrifugation, sedimentation, or apheresis. Platelets derived from whole blood may be pooled from multiple donors to form one dose of platelets. The source blood for platelets must be tested for syphilis, hepatitis B, human T-cell lymphotropic virus (HTLV) Type I and Type II, hepatitis C, and HIV Type 1 and Type 2.

Platelets derived from whole blood should have a minimum of 5.5×10^{10} platelet cells suspended in a volume of 40 to 70 mL of original plasma. Platelets produced by apheresis should have a minimum of 3.0×10^{11} platelet cells suspended in 100 to 500 mL of original plasma or in an approved additive solution.

Platelets derived from whole blood or by apheresis may be further processed by filtration for removal of leucocytes, or by irradiation to inactivate lymphocytes.

The names of the different platelet preparations are:

- Platelets—prepared from a single unit of whole human blood within 8 hours of collection
- Platelets, Pooled—individual platelet units derived from whole human blood and pooled by aseptic techniques, labelled with a unique identifying number related to the number of individual units pooled, and with an expiry date of 4 hours after pooling of the individual units
- Platelets, Pheresis—prepared by apheresis from a single donor
- Platelets, Leukocyte Reduced—prepared from whole blood, either by centrifugation or by sedimentation, and filtered to yield less than 8.3×10^5 white blood cells in the final container
- Platelets, Pheresis, Leukocyte Reduced—contains less than 5×10^6 white blood cells, prepared by apheresis, with or without a filter

Platelets may be stored in plasma or in an approved additive solution at 20° to 24° with continuous gentle agitation for no more than 5 days after date of preparation. The pH must be greater than 6.2 throughout the storage period.

USP 31 (Platelet Concentrate). It contains the platelets taken from plasma obtained, in a single procedure, by whole blood collection, plasmapheresis, or plateletpheresis from a single suitable human donor. The platelets are suspended in a specified volume (20 to 30 mL, or 30 to 50 mL) of the original plasma. The suspension contains not less than 5.5×10^{10} platelets per unit in not less than 75% of the units tested. It should be stored in hermetically-sealed sterile containers at 20° to 24° (30 to 50 mL volume), or at 1° to 6° (20 to 30 mL volume) except during transport when the temperature may be 1° to 10°. The expiration time is not more than 72 hours from the time of collection of the source material. Continuous gentle agitation must be maintained if stored at 20° to 24°. The suspension must be used within 4 hours of opening the container and should be administered with equipment that contains a filter.

Adverse Effects and Precautions

Transmission of infection has been associated with the transfusion of blood products including platelets (p.1056). Since platelets are stored at room temperature there is increased risk of bacterial infection after transfusion. Transfusion reactions including fever and urticaria are not uncommon. Recipients of multiple transfusions of platelet concentrates from random donors may develop antibodies to HLA which result in impaired responsiveness to subsequent transfusions.

Use of leucocyte-depleted platelet concentrates reduces the incidence of transfusion reactions and of HLA sensitisation. Platelet concentrates prepared from Rh(D)-positive donors should generally not be given to Rh(D)-negative women of child-bearing potential. Ideally platelet concentrates should also be ABO-compatible with the recipient.

ABO compatibility. Platelets express the ABO blood group antigens and the plasma component of platelet concentrates may contain alloantibodies from the donor (see Blood Groups, p.1057). Ideally, ABO-identical platelet concentrates should be used, but ABO-compatible concentrates are often used and incompatible concentrates may be used in an emergency. However, the use of ABO-mismatched platelets can reduce the efficacy of the platelet transfusion. Also, acute haemolytic reactions can occur after infusion of mismatched platelets if the infused plasma contains high antibody titres or the volume of plasma infused is large. Some have suggested that screening donors for high antibody titres should be routine in order to avoid this, but there is no consensus as to the definition of critical titre. There have been mixed reports on whether the use of ABO-mismatched platelets has an effect on the recipient's long-term clinical course.

Reviews.

1. Lozano M, Cid J. The clinical implications of platelet transfusions associated with ABO or Rh(D) incompatibility. *Transfus Med Rev* 2003; **17:** 57–68.

HLA antibodies. Platelets obtained from single donors have been used in patients receiving multiple transfusions of platelet concentrates to reduce the formation of antibodies to HLA. Some practitioners suggest[1] that patients who are likely to need long-term platelet support should be typed for HLA A and B antigens and screened for HLA antibodies. Leucocyte-depleted platelets and UVB-irradiated platelets have also been tried. A study[2] in 530 patients found that the incidence of platelet refractoriness was reduced from 13% of those patients receiving pooled platelet concentrates to 3% and 5% of those receiving leucocyte-depleted and UVB-irradiated platelets, respectively. A meta-analysis[3] of this and earlier small studies also concluded that leucocyte depletion reduced the risk of alloimmunisation and platelet refractoriness. Some guidelines[4] have nonetheless considered that there is no convincing evidence of clinical benefit from routine use.

1. Dan ME, Schiffer CA. Strategies for managing refractoriness to platelet transfusions. *Curr Hematol Rep* 2003; **2:** 158–64.
2. The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 1997; **337:** 1861–9.
3. Vamvakas EC. Meta-analysis of randomized controlled trials of the efficacy of white cell reduction in preventing HLA-alloimmunization and refractoriness to random-donor platelet transfusions. *Transfus Med Rev* 1998; **12:** 258–70.
4. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; **8:** 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)

Uses and Administration

Blood platelets assist in the haemostatic process (p.1045) by aggregating to form a platelet thrombus, and by releasing factors involved in initiating coagulation.

Transfusions of platelet concentrates are given to patients with thrombocytopenic haemorrhage (see p.1051). They are also given prophylactically to reduce the frequency of haemorrhage in thrombocytopenia associated with the chemotherapy of neoplastic disease (see p.640).

◊ References.

1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. Brozović B, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 17–22.
3. Schiffer CA, *et al.* Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; **19:** 1519–38. Also available at: http://www.jco.org/cgi/reprint/19/5/1519.pdf (accessed 27/10/05)
4. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; **122:** 10–23. Also available at: http://www.bcshguidelines.com/pdf/platelettrans040703.pdf (accessed 27/10/05)
5. Heal JM, Blumberg N. Optimizing platelet transfusion therapy. *Blood Rev* 2004; **18:** 149–65.
6. Stroncek DF, Rebulla P. Platelet transfusions. *Lancet* 2007; **370:** 427–38.

Preparations

USP 31: Platelet Concentrate; Platelets.

Plerixafor *(USAN, rINN)*

AMD-3100; JM-3100; Plérixafor; Plerixaforum; SDZ-SID-791; SID-791. 1,1′-(1,4-Phenylenebismethylene)bis(1,4,8,11-tetraazacyclotetradecane).

Плериксафор

$C_{28}H_{54}N_8$ = 502.8.

CAS — 110078-46-1 (plerixafor); 155148-31-5 (plerixafor hydrochloride).

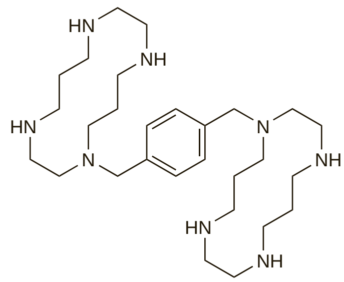

Profile

Plerixafor is a CXCR4 receptor antagonist. It is under investigation for the mobilisation of haematopoietic stem cells for collection and subsequent autologous or allogeneic transplantation.

Policresulen *(rINN)*

Acidum Metacresolsulfonicum c. Formaldehydo; *m*-Cresolsulphonic acid-formaldehyde condensation product; Dicresulene polymer; Dihydroxydimethyldiphenylmethanedisulphonic acid polymer; Formaldehydhaltig Metakresolsulfonsyra; Formaldehydipitoinen Metakresolisulfonihappo; Metacresolsulfonic Acid-Formaldehyde; Metacresolsulphonic Acid-Formaldehyde; Methylenebis(hydroxytoluenesulphonic acid) polymer; Policrésulène; Policresuleno; Policresulenum; Polikresuleeni; Polikresulen; Polímero de dicresuleno; Polycresolsulfonate. α-(4-Hydroxy-2-methyl-5-sulfobenzyl)-ω-(4-hydroxy-5-sulfo-*o*-tolyl)poly[(4-hydroxy-2-methyl-5-sulfo-*m*-phenylene)methylene]; 2-Hydroxy-*p*-toluenesulfonic acid, polymer with formaldehyde.

Поликрезулен

$(C_8H_9O_4S)(C_8H_8O_4S)_n(C_7H_7O_4S)$.

CAS — 9011-02-3; 101418-00-2.

ATC — D08AE02; G01AX03.

ATC Vet — QD08AE02; QG01AX03; QG51AD02.

Profile

Policresulen is used as a topical haemostatic and antiseptic. It is also used similarly in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Albocresil; ***Braz.:*** Albocresil; ***Chile:*** Albocresil†; ***Cz.:*** Vagothyl; ***Fr.:*** Negatol†; ***Ger.:*** Albothyl; ***Hong Kong:*** Albothyl; ***Hung.:*** Vagothyl; ***Indon.:*** Albothyl; ***Ital.:*** Emaftol; Negatol; ***Malaysia:*** Albothyl; ***Mex.:*** Albothyl; ***Philipp.:*** Albothyl; ***Pol.:*** Albothyl; Vagothyl; ***Port.:*** Nelex; ***Rus.:*** Vagothyl (Ваготил); ***S.Afr.:*** Nelex†; ***Singapore:*** Albothyl; ***Switz.:*** Negatol; Negatol Dental.

Multi-ingredient: ***Arg.:*** Proctyl; ***Braz.:*** Proctyl; ***Cz.:*** Faktu; ***Fin.:*** Faktu†; ***Ger.:*** Faktu; ***Hong Kong:*** Faktu; ***Indon.:*** Faktu; ***Mex.:*** Proctoacid; ***Philipp.:*** Faktu; ***Port.:*** Faktu; ***Singapore:*** Faktu†; ***Switz.:*** Faktu.

Polygeline *(BAN, pINN)* ⊗

Poligelina; Polygéline; Polygelinum.

Полигелин

CAS — 9015-56-9.

ATC — B05AA10.

Description. Polygeline is a polymer prepared by cross-linking polypeptides derived from denatured gelatin with a di-isocyanate to form urea bridges.

Incompatibility. Intravenous preparations of polygeline contain calcium ions and are incompatible with citrated blood.

Adverse Effects

As for Gelatin, p.1072.

Hypersensitivity. Fatal reactions after polygeline infusion have been reported in 2 patients with bronchial asthma.[1,2] Both patients were undergoing epidural analgesia with bupivacaine and polygeline was given to correct hypotension that had not responded to infusion of crystalloids. One patient developed focal seizures.[2] Both patients developed refractory bronchospasm and cardiac arrhythmias and died despite intensive resuscitation attempts.

Licensed drug information recommends that prophylaxis with histamine H_1- and H_2-antagonists should be given to patients with known allergic conditions such as asthma. Similar advice has been offered[3] for patients undergoing anaesthesia and receiving polygeline following findings of an increased incidence of severe histamine-related reactions in such patients. Nevertheless, severe respiratory distress developed in an asthmatic patient given polygeline under spinal anaesthesia despite premedication with bronchodilators and antihistamines.[4]

There is a possibility of cross reactivity between polygeline and succinylated gelatin (see Gelatin, p.1072).

1. Freeman MK. Fatal reaction to haemaccel. *Anaesthesia* 1979; **34:** 341–3.
2. Barratt S, Purcell GJ. Refractory bronchospasm following "Haemaccel" infusion and bupivacaine epidural anaesthesia. *Anaesth Intensive Care* 1988; **16:** 208–11.
3. Lorenz W, *et al.* Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Lancet* 1994; **343:** 933–40.
4. Kathirvel S, *et al.* Severe life threatening reaction to Haemaccel in a patient with bronchial asthma. *Eur J Anaesthesiol* 2001; **18:** 122–3.

Precautions

Precautions that should be observed with plasma expanders are described under Dextran 70, p.1060, and should be considered when polygeline is used for this purpose.

Polygeline preparations contain calcium ions and therefore should be used with caution in patients being treated with cardiac glycosides.

Pharmacokinetics

Like gelatin, polygeline is excreted mainly in the urine. The half-life is about 5 to 8 hours.

Renal impairment. In a study[1] in 52 patients with normal or impaired renal function given 500 mL of polygeline 3.5% about 50% of the dose was excreted in the urine within 48 hours in those with normal renal function. Excretion of polygeline in those with renal impairment, based on the patient's glomerular filtration rate (GFR), was found to be:

- GFR 31 to 90 mL/minute: unimpaired
- GFR 11 to 30 mL/minute: slightly reduced
- GFR 2 to 10 mL/minute: reduced to 27% in 48 hours
- GFR 0.5 to 2 mL/minute: reduced to 9.3% in 48 hours

The mean half-life of the elimination phase was 505 minutes in those with adequate renal function, increasing to 985 minutes in those with end-stage renal failure. Polygeline 500 mL of 3.5% solution could be given twice weekly for 1 to 2 months even in patients with total anuria.

1. Köhler H, *et al.* Elimination of hexamethylene diisocyanate cross-linked polypeptides in patients with normal or impaired renal function. *Eur J Clin Pharmacol* 1978; **14:** 405–12.

Uses and Administration

Polygeline is a plasma volume expander used as a 3.5% solution with electrolytes in the management of hypovolaemic shock (p.1183). The rate of infusion depends on the condition of the patient and does not normally exceed 500 mL in 60 minutes although it may be greater in emergencies. Initial doses for hypovolaemic shock usually consist of 500 to 1000 mL; up to 1500 mL of blood loss can be replaced by polygeline alone. Patients losing greater volumes of blood will require blood transfusion as well as plasma expanders.

Polygeline is also used in extracorporeal perfusion fluids, as a perfusion fluid for isolated organs, as fluid replacement in plasma exchange, and as a carrier solution for insulin. For plasma exchange, up to 2 litres of polygeline may be given as sole replacement fluid.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Haemaccel†; ***Austral.:*** Haemaccel; ***Austria:*** Haemaccel; ***Belg.:*** Haemaccel†; ***Braz.:*** Haemaccel; ***Chile:*** Haemaccel†; ***Cz.:*** Haemaccel†; ***Ger.:*** Haemaccel; ***Gr.:*** Haemaccel†; ***Hong Kong:*** Haemaccel†; ***India:*** Haemaccel; ***Indon.:*** Haemaccel; ***Irl.:*** Haemaccel†; ***Israel:*** Haemaccel†; ***Ital.:*** Emagel; Gelplex; ***Malaysia:*** Haemaccel†; ***Mex.:*** Haemaccel; Phygelin; ***Neth.:*** Haemaccel; ***Norw.:*** Haemaccel†; ***NZ:*** Haemaccel; ***Port.:*** Haemaccel; ***S.Afr.:*** Haemaccel; ***Singapore:*** Haemaccel; ***Switz.:*** Haemaccel†; ***Thai.:*** Haemaccel; Plasmax; ***UK:*** Haemaccel.

Protein C

Autoprothrombin IIA; Factor XIV; Proteína C.

ATC — B01AD12.

ATC Vet — QB01AD12.

Drotrecogin Alfa (Activated) *(BAN, rINN)*

Drotrecogina alfa (activada); Drotrécogine Alfa (activé); Drotrecoginum Alfa; Drotrecoginum Alfa (activatum); Drotrekogiini-alfa; Drotrekogin Alfa; LY-203638.

Дротрекогин Альфа (activated)

CAS — 98530-76-8.
ATC — B01AD10.
ATC Vet — QB01AD10.

Incompatibility. In a simulated Y-site study,[1] only 6 of 34 drugs were found to be both physically and chemically compatible with drotrecogin alfa (activated); these were ceftriaxone, cisatracurium, fluconazole, glyceryl trinitrate, potassium chloride, and vasopressin. Drugs found to be incompatible were adrenaline hydrochloride, albumin, amiodarone hydrochloride, ampicillin with sulbactam, ceftazidime, ciclosporin, ciprofloxacin, clindamycin, dobutamine hydrochloride, dopamine hydrochloride, fosphenytoin, furosemide, gentamicin sulfate, heparin sodium, imipenem with cilastatin, insulin, levofloxacin, magnesium sulfate, metronidazole, midazolam hydrochloride, nitroprusside sodium, noradrenaline acid tartrate, piperacillin with tazobactam, potassium phosphate, ranitidine hydrochloride, ticarcillin with clavulanic acid, tobramycin sulfate, and vancomycin hydrochloride.

1. Mann HJ, *et al.* Physical and chemical compatibility of drotrecogin alfa (activated) with 34 drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; **61:** 2664–71. Correction. *ibid.* 2005; **62:** 1134.

Adverse Effects and Precautions

As with other plasma-derived products, protein C preparations carry a risk of transmission of infection. Hypersensitivity reactions have been reported infrequently. Antibodies to protein C may develop in patients treated for congenital protein C deficiency.

Drotrecogin alfa (activated) may increase the risk of severe bleeding episodes. When used in patients with severe sepsis, it is therefore contra-indicated in those who are at low risk for death, such as those with single-organ failure, especially after surgery. It is also contra-indicated in patients with active internal bleeding and in those in which bleeding could be associated with a high risk of death or significant morbidity. Drotrecogin alfa (activated) should be used with caution when there is any other increased risk of bleeding. Drotrecogin alfa (activated) should be stopped 2 hours before any invasive surgery or procedure with an inherent risk of bleeding; it may be restarted 12 hours after major invasive procedures or surgery, or immediately after uncomplicated less invasive procedures, if adequate haemostasis has been achieved.

Effects on the blood. The safety data from early clinical studies and spontaneous reports during clinical use of drotrecogin alfa (activated) have been reviewed.[1] The overall rate of serious bleeding events was 5.3% during the 28-day study period. Serious bleeding events that were considered to be probably related to the use of drotrecogin alfa (activated) occurred in between 2.1% and 2.8% of patients, and often during the infusion period. Risks associated with serious bleeding events were invasive procedures and severe thrombocytopenia; meningitis may also be a risk factor for intracranial haemorrhage. It was recommended that drotrecogin alfa (activated) should not be used when the platelet count is less than 30 000/mm^3.

A subsequent large, multicentre randomised study in patients with severe sepsis, but a low risk of death (the ADDRESS study), confirmed the increased incidence of bleeding in patients with single organ failure who had undergone recent surgery (within 30 days); these patients also had an increased death rate (see Severe Sepsis, below).

1. Bernard GR, *et al.* Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. *Crit Care* 2003; **7:** 155–63.

Interactions

When oral anticoagulants such as warfarin are started in patients receiving protein C replacement therapy, a transient hypercoagulable state may occur because of the rapid suppression of vitamin K-dependent protein C activity. An initial low dose of the oral anticoagulant should be increased gradually, and protein C replacement continued, until anticoagulation is stabilised. The risk of bleeding may be increased if tissue plasminogen activator and protein C are used together.

The risk of bleeding with drotrecogin alfa (activated) may be increased if it is used with other drugs that affect haemostasis, such as thrombolytics, oral anticoagulants, antiplatelet drugs, glycoprotein IIb/IIIa-receptor antagonists, and prostacyclins. Low doses of heparin for venous thromboembolism prophylaxis may be used with drotrecogin alfa (activated) without increased risk of serious bleeding. However, in a study of patients with severe sepsis who were already receiving prophylactic heparin, the risks of death and serious adverse events were increased if heparin was stopped when drotrecogin alfa (activated) was started; the reason for this was unclear.

Pharmacokinetics

During continuous infusion for the management of severe sepsis, steady-state plasma concentrations of drotrecogin alfa (activated) are reached in about 2 hours. It is inactivated by plasma protease inhibitors and rapidly cleared from the circulation, falling to below measurable limits within about 2 hours of stopping the infusion.

◊ References.

1. Macias WL, *et al.* Pharmacokinetic-pharmacodynamic analysis of drotrecogin alfa (activated) in patients with severe sepsis. *Clin Pharmacol Ther* 2002; **72:** 391–402.
2. Levy H, *et al.* Obesity does not alter the pharmacokinetics of drotrecogin alfa (activated) in severe sepsis. *Ann Pharmacother* 2005; **39:** 262–7.

Uses and Administration

Protein C is an endogenous inhibitor of blood coagulation (see Haemostasis and Fibrinolysis, p.1045). A preparation of protein C purified from human plasma is used in the management of thromboembolic disorders in patients with congenital deficiency of protein C. The dose should be adjusted according to response in protein C activity. Licensed UK product information suggests an initial dose of 60 to 80 international units/kg. In the USA, an initial dose of 100 to 120 international units/kg is suggested for acute episodes and short-term prophylaxis of thromboembolism, followed by 3 doses of 60 to 80 units/kg every 6 hours, then maintenance doses of 45 to 60 units/kg every 6 or 12 hours. Doses of 45 to 60 units/kg every 12 hours are suggested for long-term prophylaxis. As a solution of 100 international units/mL it is given by intravenous injection at a maximum rate of 2 mL/minute.

Drotrecogin alfa (activated) is a recombinant activated protein C that is used in the management of severe sepsis in high-risk patients with multiple organ failure. It is given by intravenous infusion in a dose of 24 micrograms/kg per hour for 96 hours. Treatment should be started within 48 hours, and preferably within 24 hours, of the onset of sepsis-induced organ dysfunction.

For the use of protein C and drotrecogin alfa (activated) in children, see below.

Administration in children. Dosage regimens of protein C used for children and neonates with protein C deficiency are the same as those used in adults (see above). However, for children weighing less than 10 kg the rate of injection should not exceed 0.2 mL/kg per minute.

Drotrecogin alfa (activated) is not licensed for use in children under 18 years of age (see also Severe Sepsis, below).

Severe sepsis. Severe sepsis (sepsis associated with acute organ dysfunction; see Septicaemia, p.190) involves a systemic inflammatory response, inappropriate coagulation, and impaired fibrinolysis. These contribute to the development of disseminated intravascular coagulation (DIC) and microvascular thrombosis (p.1048). Endogenous protein C becomes depleted as it is activated in an attempt to restore homoeostasis. In the small number of cases that have been reported,[1-3] protein C replacement appeared to improve rate of survival and clinical outcome in the management of purpura fulminans and DIC in severe meningococcaemia. Protein C has also been used in a few patients with purpura fulminans associated with sepsis caused by other organisms such as *Streptococcus pneumoniae*.[4]

Drotrecogin alfa (activated) has been studied in the management of severe sepsis and found to reduce morbidity and mortality, but with an increased risk of serious bleeding events[5-9] (see also Effects on the Blood, above). Pooled study data suggested that earlier treatment (within 24 hours of first organ dysfunction) was associated with more benefit than later treatment,[10] and subgroup analysis suggested that the benefits were greatest in those at greater risk of death.[11] A subsequent large, multicentre randomised study[12] (the ADDRESS trial) examined the effects of drotrecogin alfa (activated) in patients with severe sepsis but a low risk of death (APACHE II score less than 25, or single organ failure). The study was terminated early, as interim analysis indicated that there was no benefit from active therapy, and in the subgroup of patients with single organ failure who had undergone surgery within the last 30 days, those given the drug appeared to have a higher mortality rate than those assigned to placebo. Various regulatory bodies have issued guidance restricting the use of drotrecogin alfa (activated) to high-risk patients under specialist care.[13-15]

Similar results to those in adults have been reported in initial studies of drotrecogin alfa (activated) in children.[16,17] However, a large placebo-controlled study was stopped early when an interim analysis found that drotrecogin alfa (activated) was highly unlikely to show an improvement over placebo in the primary end-point of composite time to complete organ failure resolution over 14 days.[18] The analysis also found an increase in the rate of CNS bleeding in the drotrecogin alfa (activated) group. The efficacy of drotrecogin alfa (activated) does not appear to depend on the identity of the infective organism.[19]

1. Rintala E, *et al.* Protein C in the treatment of coagulopathy in meningococcal disease. *Lancet* 1996; **347:** 1767.
2. Smith OP, *et al.* Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. *Lancet* 1997; **350:** 1590–3.
3. Alberio L, *et al.* Protein C replacement in severe meningococcemia: rationale and clinical experience. *Clin Infect Dis* 2001; **32:** 1338–46. Correction. *ibid.*; 1803.
4. Rintala E, *et al.* Protein C substitution in sepsis-associated purpura fulminans. *Crit Care Med* 2000; **28:** 2373–8.
5. Bernard GR, *et al.* The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344:** 699–709.
6. Lyseng-Williamson KA, Perry CM. Drotrecogin alfa (activated). *Drugs* 2002; **62:** 617–30.
7. Vincent J-L, *et al.* Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003; **31:** 834–40.
8. Bernard GR, *et al.* Extended evaluation of recombinant human activated protein C United States Trial (ENHANCE US): a single-arm, phase 3B, multicenter study of drotrecogin alfa (activated) in severe sepsis. *Chest* 2004; **125:** 2206–16.
9. Vincent J-L, *et al.* Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; **33:** 2266–77.
10. Vincent J-L, *et al.* Use of an integrated clinical trial database to evaluate the effect of timing of drotrecogin alfa (activated) treatment in severe sepsis. *Crit Care* 2006; **10:** R74.
11. Ely EW, *et al.* Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003; **31:** 12–19.
12. Abraham E, *et al.* Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; **353:** 1332–41.
13. NICE. Drotrecogin alfa (activated) for severe sepsis: Technology Appraisal 84 (September 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/TA084guidance.pdf (accessed 01/09/08)
14. European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use. Press release (issued 21st April 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/13844405en.pdf (accessed 01/09/08)
15. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Drotrecogin alfa (activated) (Xigris): risk-benefit in the management of sepsis. *Current Problems* 2006; **31:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/05/07)
16. Barton P, *et al.* Safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis. *Pediatrics* 2004; **113:** 7–17.
17. Goldstein B, *et al.* ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr Crit Care Med* 2006; **7:** 200–211.
18. Nadel S, *et al.* REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007; **369:** 836–43.
19. Opal SM, *et al.* Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated). *Clin Infect Dis* 2003; **37:** 50–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Xigris; ***Austral.:*** Xigris; ***Austria:*** Ceprotin; Xigris; ***Belg.:*** Ceprotin; Xigris; ***Braz.:*** Xigris; ***Canad.:*** Xigris; ***Chile:*** Xigris; ***Cz.:*** Ceprotin; Xigris; ***Denm.:*** Ceprotin; Xigris; ***Fin.:*** Ceprotin; Xigris; ***Fr.:*** Ceprotin; Protexel; Xigris; ***Ger.:*** Ceprotin; Xigris; ***Gr.:*** Ceprotin; Xigris; ***Hong Kong:*** Xigris; ***Hung.:*** Xigris; ***India:*** Xigris; ***Irl.:*** Xigris; ***Israel:*** Xigris; ***Ital.:*** Ceprotin; Xigris; ***Malaysia:*** Xigris; ***Mex.:*** Xigris; ***Neth.:*** Ceprotin; Xigris; ***Norw.:*** Ceprotin; Xigris; ***NZ:*** Xigris; ***Pol.:*** Ceprotin; Xigris; ***Port.:*** Ceprotin; Xigris; ***Rus.:*** Xigris (Зигрис); ***S.Afr.:*** Xigris; ***Singapore:*** Xigris; ***Spain:*** Ceprotin; Xigris; ***Swed.:*** Ceprotin; Xigris; ***Switz.:*** Ceprotin; Xigris; ***Turk.:*** Xigris; ***UK:*** Ceprotin; Xigris; ***USA:*** Ceprotin; Xigris; ***Venez.:*** Xigris.

Red Blood Cells ⊗

Eritrocitos.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US.*

USP 31 (Red Blood Cells). It is the portion of blood that contains haemoglobin and is derived from human whole blood (from which plasma and platelets are removed by centrifugation, sedimentation) or by apheresis. Red blood cells may be further processed by addition of red cell preservatives, irradiation to inactivate lymphocytes, filtration for removal of leucocytes, washing to remove proteins, freezing and thawing, or rejuvenation using validated and approved procedures.

For preparations derived from whole blood, one unit (dose) of Red Blood Cells contains a minimum of 50 g of haemoglobin. One unit of Red Blood Cells, Leukocytes Reduced contains a minimum of 42.5 g of haemoglobin and has a residual leucocyte count of less than 5×10^6. One unit of Red Blood Cells, Deglycerolized contains a minimum of 40 g of haemoglobin. One unit of Red Blood Cells, Leukocytes Reduced and Deglycerolized contains a minimum of 34 g of haemoglobin and has a residual leucocyte count of less than 5×10^6.

For preparations derived by apheresis, one unit (dose) of Red Blood Cells, Pheresis contains a mean haemoglobin content of 60 g of haemoglobin. One unit of Red Blood Cells, Pheresis, Leukocytes Reduced contains a mean haemoglobin content of 51 g of haemoglobin and has a residual leucocyte count of less than 5×10^6.

Red blood cells should be stored in the original container, or transferred to an equivalent container using a technique that does not compromise sterility. An approved additive solution may be added after removal of the plasma. Liquid red blood cells is stored at 1° to 6°. Frozen red blood cells is stored at or below −65°.

Red blood cells in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at 1° to 6° after the blood has been drawn. Red blood cells in Anticoagulant Citrate Dextrose Phosphate Adenine Solution may be stored for up to 35 days at 1° to 6°. Red blood cells may be stored in an approved additive solution for up to 42 days at 1° to 6°.

Frozen red blood cells prepared with low glycerol content (20%) may be stored at or below −120° for not later than 10 years from years from the date of collection. Frozen red blood cells prepared with high glycerol content (40%) may be stored at or below −65° for not later than 10 years from years from the date of collection. If the frozen red blood cells is processed for freezing or for thawing, in an open system, the expiry date for the thawed red blood cells is 24 hours after removal from −65° storage, provided it is then stored at the temperature of unfrozen red blood cells.

Dark red in colour when packed and may show a slight creamy layer on the surface and a small supernatant layer of yellow or opalescent plasma.

Adverse Effects and Precautions

As for Blood, p.1056.

Antibody formation. Patients with sickle-cell anaemia frequently require repeated transfusions of red blood cells. Alloimmunisation is a common problem in these patients, and has the potential to cause haemolytic transfusion reactions.[1] Alloantibodies were detected in 32 of 107 black patients with sickle-cell anaemia who had received red cell transfusions compared with 1 of 19 non-black patients who had received transfusions for other chronic anaemias.[2] The incidence of antibody formation was related to the number of transfusions received. An analysis of the red cell phenotypes suggested that the high rate of alloimmunisation among patients with sickle-cell anaemia could be due to racial differences between donors and recipients. Alloimmunisation can also occur in thalassaemia patients who are given transfusions,[3] and the incidence in these patients may also be affected by racial differences between donors and recipients.[4] Erythrocyte autoantibody formation has also been reported.[1,3]

1. Aygun B, *et al.* Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion* 2002; **42:** 37–43.
2. Vichinsky EP, *et al.* Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990; **322:** 1617–21.
3. Singer ST, *et al.* Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. *Blood* 2000; **96:** 3369–73.
4. Ho H-K, *et al.* Alloimmunization in Hong Kong southern Chinese transfusion-dependent thalassemia patients. *Blood* 2001; **97:** 3999–4000.

Uses and Administration

Transfusions of red blood cells are given for the treatment of severe anaemia without hypovolaemia (p.1042).

Red blood cells are also used for exchange transfusion in babies with haemolytic disease of the newborn (p.2204). Red cells may be used with volume expanders for acute blood loss of less than half of the blood volume; if more than half of the blood volume has been lost, whole blood should be used.

Other red blood cell products are available. Concentrated red cells in an optimal additive solution containing sodium chloride, adenine, glucose, and mannitol has reduced viscosity and an extended shelf-life. Leucocyte-depleted red cells may be used in patients who have developed antibodies to previous transfusions or in whom development of antibodies is undesirable. Frozen, thawed, and washed red cell concentrates in which plasma proteins are removed in addition to leucocytes and platelets may be used in patients with rare antibodies.

◊ Reviews and guidelines.

1. Davies SC, Williamson LM. Transfusion of red cells. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998: 10–16.
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; **8:** 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; **113:** 24–31. Also available at: http://www.bcshguidelines.com/pdf/bjh2701.pdf (accessed 27/10/05)
4. Hill SR, *et al.* Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 16/06/05).

Preparations

USP 31: Red Blood Cells.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Arg.:* Vulnofilin Compuesto†.

Romiplostim *(USAN, rINN)*

AMG-531; Romiplostimum. L-Methionyl[human immunoglobulin heavy constant gamma 1-(227 *C*-terminal residues)-peptide (Fc fragment)] fusion protein with 41 amino acids peptide, (7-7′:10,10′)-bisdisulfide dimer.

Ромиплостим

CAS — 267639-76-9.

Profile

Romiplostim is a protein that acts as an agonist at the thrombopoietin receptor to stimulate platelet production, although it has no sequence homology with endogenous thrombopoietin. It is under investigation in the treatment of chronic idiopathic thrombocytopenic purpura.

◊ References.

1. Bussel JB, *et al.* AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; **355:** 1672–81. Correction. *ibid.*; 2054.
2. Kuter DJ, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; **371:** 395–403.

Sargramostim *(BAN, USAN, rINN)*

BI-61.012; rhu GM-CSF; Sargramostimum. A recombinant human granulocyte-macrophage colony-stimulating factor; 23-L-Leucinecolony-stimulating factor 2 (human clone pHG_{25} protein moiety).

Сарграмостим

CAS — 123774-72-1.

ATC — L03AA09.

ATC Vet — QL03AA09.

Pharmacopoeias. In *US.*

USP 31 (Sargramostim). A single chain, glycosylated polypeptide of 127 amino acid residues expressed from *Saccharomyces cerevisiae*. The glycoprotein primarily consists of three molecular species having relative molecular weights of about 19 500, 16 800, and 15 500 due to different levels of glycosylation. Sargramostim has the property of generating granulocyte, macrophage, and mixed granulocyte macrophage colonies from haematopoietic progenitor cells found in bone marrow. Store in sealed containers at a temperature of −20° or below.

Stability. Solutions of sargramostim may be adsorbed onto glass or plastic materials and so albumin must be added to give a final concentration of 1 mg/mL to solutions that are diluted to concentrations of sargramostim below 10 micrograms/mL.

Adverse Effects and Precautions

As for Molgramostim, p.1073.

Uses and Administration

Sargramostim is a granulocyte-macrophage colony-stimulating factor with actions and uses similar to those of molgramostim (p.1074). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p.640). It is also used after bone marrow transplantation when engraftment is delayed or has failed. Sargramostim may be used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous peripheral blood stem cell transplantation, as well as after transplantation to improve engraftment.

As an **adjunct to antineoplastic therapy**, sargramostim is given by intravenous infusion over 4 hours in a dose of 250 micrograms/m^2 daily for up to 42 days as required.

After **bone marrow transplantation**, sargramostim may be given in a dose of 250 micrograms/m^2 daily by intravenous infusion over 2 hours. When engraftment is delayed or has failed, a course of sargramostim 250 micrograms/m^2 daily for 14 days may be used. The dose can be repeated after a 7-day interval if engraftment has not occurred. A third course of 500 micrograms/m^2 daily for 14 days may be tried after another 7-day interval if needed, but further dose escalation is unlikely to be of benefit.

For **mobilisation** of peripheral blood progenitor cells a dose of 250 micrograms/m^2 daily is given by continuous intravenous infusion over 24 hours or by subcutaneous injection, with leucapheresis usually starting on day 5. The same dosing regimen may be used after peripheral blood stem cell transplantation, until neutrophil recovery.

HIV infection and AIDS. Sargramostim has been evaluated in the management of HIV infection (p.856). There is some evidence to suggest that it might help to decrease and suppress viral load, and increase CD4+ cell counts, by enhancing the activity of antiretroviral drugs and increasing the resistance of monocytes to HIV infection.[1-3] However, in a study[4] of patients who were medically stable but had incompletely controlled HIV replication, sargramostim did not have a significant antiviral effect and there was only a trend towards increased CD4+ counts. The effect of molgramostim has been studied in a small trial[5] in which it was found to blunt viral rebound following interruption of HAART.

1. Skowron G, *et al.* The safety and efficacy of granulocyte-macrophage colony-stimulating factor (sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. *J Infect Dis* 1999; **180:** 1064–71.
2. Brites C, *et al.* A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. *J Infect Dis* 2000; **182:** 1531–5.
3. Angel JB, *et al.* Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. *AIDS* 2000; **14:** 387–95.
4. Jacobson JM, *et al.* Granulocyte-macrophage colony-stimulating factor induces modest increases in plasma human immunodeficiency virus (HIV) type 1 RNA levels and CD4+ lymphocyte counts in patients with uncontrolled HIV infection. *J Infect Dis* 2003; **188:** 1804–14.
5. Fagard C, *et al.* A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART. *AIDS* 2003; **17:** 1487–92.

Inflammatory bowel disease. A small dose-escalating study[1] reported a beneficial effect from the use of sargramostim in Crohn's disease (see Inflammatory Bowel Disease, p.1697). A subsequent larger placebo-controlled study[2] in moderate to severe active disease found that the rate of response to sargramostim was not significantly different from that of placebo. Although disease severity and quality of life improved in the sargramostim group, later unpublished study results were said to be disappointing, and in June 2007 the manufacturer declared that it would not be investigating sargramostim any further in Crohn's disease.

1. Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; **360:** 1478–80.
2. Korzenik JR, *et al.* Sargramostim for active Crohn's disease. *N Engl J Med* 2005; **352:** 2193–2201.

Malignant neoplasms. It has been suggested that granulocyte-macrophage colony-stimulating factor may be able to increase antitumour immune activity. Sargramostim, given by nebuliser to stimulate a local response, has been investigated in patients with lung metastases.[1,2]

1. Anderson PM, *et al.* Aerosol granulocyte macrophage-colony stimulating factor: a low toxicity, lung-specific biological therapy in patients with lung metastases. *Clin Cancer Res* 1999; **5:** 2316–23.
2. Rao RD, *et al.* Aerosolized granulocyte macrophage colony-stimulating factor (GM-CSF) therapy in metastatic cancer. *Am J Clin Oncol* 2003; **26:** 493–8.

Wounds and ulcers. See under Molgramostim (p.1074) for mention of the use of sargramostim in the promotion of wound healing.

Preparations

USP 31: Sargramostim for Injection.

Proprietary Preparations (details are given in Part 3)
USA: Leukine.

Thrombin *(rINN)*

Factor IIa; Thrombine; Thrombinum; Trombin; Trombina.

Тромбин

CAS — 9002-04-4.
ATC — B02BC06; B02BD30.
ATC Vet — QB02BC06; QB02BD30.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US.*

USP 31 (Thrombin). A sterile, freeze-dried powder derived from bovine plasma containing the protein substance prepared from prothrombin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma, or a solution of fibrinogen. It should be stored at 2° to 8°. Once reconstituted, solutions should be used within a few hours of preparation. The label should state that the prepared solution should not be injected into or otherwise allowed to enter large blood vessels.

A white to greyish, amorphous substance dried from the frozen state.

Thrombin Alfa *(USAN, rINN)*

Human thrombin (recombinant, glycosylated); Thrombine Alfa; Thrombinum Alfa; Trombina Alfa. Human thrombin (recombinant, glycofrom α).

Тромбин Альфа

CAS — 869858-13-9.

Adverse Effects and Precautions

Hypersensitivity reactions, including anaphylaxis, have occurred rarely. Thrombin solutions must not be injected into blood vessels.

Antibody formation. Exposure to thrombin preparations of bovine origin has led to the development of antibodies to bovine thrombin and factor V with cross-reactivity, in some cases, to human factors. The presence of inhibitors to human factors may produce bleeding abnormalities and interfere with clotting measurements. Platelet infusions, fresh frozen plasma, and activated prothrombin complex concentrates have been used in the management of acute haemorrhagic complications, though often with limited success. Treatments that have been tried, in order to reduce the antibody titre, have included corticosteroids, ciclosporin, antineoplastics, intravenous immunoglobulin, and plasmapheresis.[1,2] Despite the availability of preparations containing virus-inactivated human fibrinogen the use of bovine thrombin is reported to be widespread and cases of acquired factor V inhibitor continue to occur.[3]

1. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999; **133:** 326–34.
2. Streiff MB, Ness PM. Acquired FV inhibitors: a needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; **42:** 18–26.
3. Kirkeby KM, Aronowitz P. Acquired factor V inhibitor: a common and avoidable complication of topical bovine thrombin application. *Am J Med* 2005; **118:** 805.

Uses and Administration

Thrombin is a protein substance produced *in vivo* from prothrombin that converts soluble fibrinogen into insoluble fibrin thus producing coagulation.

Thrombin of either human or bovine origin is applied topically to control bleeding from capillaries and small venules. It is applied directly to the bleeding surface either as a solution or dry powder. It may also be used with absorbable gelatin sponge during surgical procedures. Thrombin alfa, a recombinant human thrombin, is used similarly.

Thrombin is a component of fibrin glue (p.1069).

General references. Reviews.

1. Lundblad RL, *et al.* A review of the therapeutic uses of thrombin. *Thromb Haemost* 2004; **91:** 851–60.

Pseudoaneurysm. An acute pseudoaneurysm is an arterial rupture, contained by fibromuscular tissue, that communicates with the artery via a narrow neck. Insertion-site femoral pseudoaneurysm can occur as a result of procedures such as cardiac catheterisation and peripheral angiography. It is usually treated with ultrasound-guided compression, but this time-consuming technique causes discomfort for both the patient and the staff carrying out the procedure, and may be of limited success for large pseudoaneurysms and patients receiving anticoagulation. Surgical repair may be required in some patients. As an alternative to pressure or surgery, thrombin has been given by ultrasound-guided percutaneous injection. In reported series,[1-4] complete thrombosis of the pseudoaneurysm sac occurred in more than 90% of patients with one injection of bovine thrombin. Bovine thrombin has also been used when compression has failed,[4,5] and a comparative study[6] in 30 patients found thrombin to be more successful than compression. Human thrombin has also been used successfully.[7] A retrospective review[8] concluded that bovine and human thrombin were equally effective. The successful use of autologous thrombin in a few patients has also been described.[9]

1. La Perna L, *et al.* Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000; **102:** 2391–5.
2. Mohler ER, *et al.* Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001; **6:** 241–4.
3. Olsen DM, *et al.* A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002; **36:** 779–82.
4. Stone P, *et al.* Iatrogenic pseudoaneurysms: comparison of treatment modalities, including duplex-guided thrombin injection. *W V Med J* 2003; **99:** 230–2.
5. Lönn L, *et al.* Treatment of femoral pseudoaneurysms: percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002; **43:** 396–400.
6. Lönn L, *et al.* Prospective randomized study comparing ultrasound-guided thrombin injection to compression in the treatment of femoral pseudoaneurysms. *J Endovasc Ther* 2004; **11:** 570–6.
7. Maleux G, *et al.* Percutaneous injection of human thrombin to treat iatrogenic femoral pseudoaneurysms: short- and midterm ultrasound follow-up. *Eur Radiol* 2003; **13:** 209–12.
8. Vázquez V, *et al.* Human thrombin for treatment of pseudoaneurysms: comparison of bovine and human thrombin sonogram-guided injection. *Am J Roentg* 2005; **184:** 1665–71.
9. Quarmby JW, *et al.* Autologous thrombin for treatment of pseudoaneurysms. *Lancet* 2002; **359:** 946–7.

Preparations

Ph. Eur.: Fibrin Sealant Kit;
USP 31: Thrombin.

Proprietary Preparations (details are given in Part 3)
Austral.: Thrombostat†; ***Canad.:*** Thrombostat†; ***NZ:*** Thrombostat; ***Pol.:*** Gastrotrombina; ***S.Afr.:*** Tisseel; ***USA:*** Evithrom; Recothrom; Thrombinar; Thrombogen†; Thrombostat.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Ger.:*** Beriplast; Quixil; TachoComb†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Quixil; Tisseel; ***Ital.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Quixil; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** Quixil; TachoSil; Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Thai.:*** Fibrin Glue†; TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Thrombomodulin Alfa *(rINN)*

ART-123; Thrombomoduline Alfa; Thrombomodulinum Alfa; Trombomodulina alfa. 1–498-Thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced).

Тромбомодулин Альфа

CAS — 120313-91-9.

Profile

Endogenous thrombomodulin is a transmembrane protein found on the surface of endothelial cells, which acts as a thrombin receptor. Thrombomodulin-bound thrombin activates protein C, which then inactivates clotting factors and so limits coagulation.

Thrombomodulin alfa, a recombinant form of thrombomodulin, is under investigation in the prophylaxis of venous thromboembolism and the treatment of disseminated intravascular coagulation.

◊ References.

1. Kearon C, *et al.* Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2005; **3:** 962–8.
2. Saito H, *et al.* Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; **5:** 31–41.

Thromboplastin

Cytozyme; Thrombokinase; Tromboplastina; Tromboplastyna.

Profile

Tissue thromboplastin (tissue factor; factor III) is a membrane glycoprotein that is released from damaged tissue and initiates coagulation. The term thromboplastin may also be applied to other related substances with similar activity. Commercial preparations may contain tissue extracts comprising a variety of such substances.

Preparations of thromboplastin have been used as haemostatics.

A preparation of thromboplastin derived from rabbit brain is used in the determination of the prothrombin time for the control of anticoagulant therapy (for further details see Uses and Administration of Warfarin Sodium, p.1432).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Clauden.

Multi-ingredient: ***Braz.:*** Claudemor; ***Port.:*** Claudemor†; ***Venez.:*** Claudemor†.

Thrombopoietin

Trombopoyetina.

Profile

Thrombopoietin is a naturally occurring colony-stimulating factor that regulates thrombopoiesis (see Haematopoiesis, p.1042). Recombinant thrombopoietin, and a form of recombinant thrombopoietin conjugated with polyethylene glycol (pegacaristim, PEG-megakaryocyte growth and development factor, PEG-rHuMGDF), are under investigation. They have been studied in the management of thrombocytopenia (p.1051) in patients receiving myelosuppressive or myeloablative chemotherapy, and in patients with myelodysplastic syndrome or HIV-associated thrombocytopenia. There is also some interest in the use of recombinant forms of thrombopoietin in stem cell mobilisation regimens and to increase platelet counts in healthy apheresis donors. However, some results have been disappointing and there are reports of neutralising antibody development.

General references. Studies and reviews.

1. Vadhan-Raj S, *et al.* Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. *Lancet* 2002; **359:** 2145–52.
2. Nomura S, *et al.* Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 2002; **100:** 728–30.
3. Schuster MW, *et al.* The effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. *Exp Hematol* 2002; **30:** 1044–50.
4. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002; **100:** 3457–69.
5. Linker C, *et al.* Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003; **9:** 405–13.
6. Vadhan-Raj S, *et al.* Importance of predosing of recombinant human thrombopoietin to reduce chemotherapy-induced early thrombocytopenia. *J Clin Oncol* 2003; **21:** 3158–67.
7. Geissler K, *et al.* Prior and concurrent administration of recombinant human megakaryocyte growth and development factor in patients receiving consolidation chemotherapy for de novo acute myeloid leukemia—a randomized, placebo-controlled, double-blind safety and efficacy study. *Ann Hematol* 2003; **82:** 677–83.

Tranexamic Acid *(BAN, USAN, rINN)*

Acide tranexamique; Ácido tranexámico; Acidum tranexamicum; AMCA; *trans*-AMCHA; CL-65336; Kyselina tranexamová; Traneksaamihappo; Traneksamik Asit; Traneksamo rūgštis; Tranexámsav; Tranexamsyra. *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid.

Транексамовая Кислота

$C_8H_{15}NO_2$ = 157.2.

CAS — 1197-18-8.
ATC — B02AA02.
ATC Vet — QB02AA02.

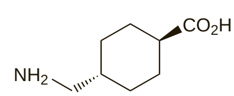

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Tranexamic Acid). A white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 7.0 to 8.0.

Incompatibility. Solutions of tranexamic acid are incompatible with benzylpenicillin.

Adverse Effects

Tranexamic acid appears to be well tolerated. It can produce dose-related gastrointestinal disturbances. Hypotension has occurred, particularly after rapid intravenous dosage. Thrombotic complications have been reported in patients receiving tranexamic acid, but these are usually a consequence of its inappropriate use (see Precautions, below). There have been a few instances of transient disturbance of colour vision associated with use of tranexamic acid; in such cases the drug should be stopped. Hypersensitivity skin reactions have also been reported.

Effects on the eyes. Tranexamic acid has been associated with retinopathy[1] and visual impairment.[2] A haemodialysis patient developed almost total loss of vision within 2 weeks of starting daily tranexamic acid injections after emergency surgery for a bleeding peptic ulcer. Vision was largely restored within a few days of stopping tranexamic acid,[2] although some impairment persisted in conditions of poor light. The patient had experienced visual impairment previously when given tranexamic acid. The authors noted that doses of tranexamic acid should be reduced in patients with renal impairment undergoing dialysis.

A patient undergoing regular peritoneal dialysis for Epstein's syndrome developed ligneous conjunctivitis, gingival hyperplasia, and peritoneal protein loss associated with the use of tranexamic acid.[3]

1. Snir M, *et al*. Central venous stasis retinopathy following the use of tranexamic acid. *Retina* 1990; **10:** 181–4.
2. Kitamura H, *et al.* Tranexamic acid-induced visual impairment in a hemodialysis patient. *Clin Exp Nephrol* 2003; **7:** 311–14.
3. Diamond JP, *et al.* Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions. *Br J Ophthalmol* 1991; **75**: 753–4.

Effects on the skin. A widespread, patchy rash with associated blisters, considered on skin biopsy to be a fixed-drug eruption, occurred in a 33-year-old woman.[1] Tranexamic acid, which she had taken for 8 years and which had been well tolerated, was identified as the cause. Desensitisation was unsuccessful. Tranexamic acid was also suspected as being the cause of a fixed-drug eruption in a 36-year-old woman.[2] Pruritic, vesicle-bullous lesions appeared within a few hours of starting tranexamic acid and the lesions resolved completely 3 days after stopping therapy even though other drug treatment was continued.

1. Kavanagh GM, *et al*. Tranexamic acid (Cyklokapron)-induced fixed-drug eruption. *Br J Dermatol* 1993; **128:** 229–30.
2. Carrión-Carrión C, *et al.* Bullous eruption induced by tranexamic acid. *Ann Pharmacother* 1994; **28:** 1305–6.

Precautions

Tranexamic acid should not be used in patients with active intravascular clotting because of the risk of thrombosis. Patients with a predisposition to thrombosis are also at risk if given antifibrinolytic therapy. Haemorrhage due to disseminated intravascular coagulation should therefore not be treated with antifibrinolytic compounds unless the condition is predominantly due to disturbances in fibrinolytic mechanisms; tranexamic acid has been used when the latter conditions are met, but with careful monitoring and anticoagulant cover.

Lysis of existing extravascular clots may be inhibited in patients receiving tranexamic acid. Clots in the renal system can lead to intrarenal obstruction, so caution is required in patients with haematuria. Doses of tranexamic acid should be reduced in patients with renal impairment. Licensed product information recommends that regular eye examinations and liver function tests should be performed if tranexamic acid is used long term.

Some studies have suggested that tranexamic acid when given to patients after a subarachnoid haemorrhage increases the incidence of cerebral ischaemic complications (see Haemorrhagic Disorders under Uses, below).

Rapid intravenous dosage may be associated with adverse effects (see above).

Interactions

Drugs with actions on haemostasis should be given with caution to patients on antifibrinolytic therapy. The potential for thrombus formation may be increased by oestrogens, for example, or the action of the antifibrinolytic antagonised by compounds such as thrombolytics.

Retinoids. Antifibrinolytics should be used with caution in patients receiving oral *tretinoin* as thrombotic events have been reported in patients being treated with tranexamic acid and tretinoin (see Antifibrinolytics, p.1619).

Pharmacokinetics

Tranexamic acid is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 3 hours. Bioavailability is about 30 to 50%. Tranexamic acid is widely distributed throughout the body and has very low protein binding. It diffuses across the placenta and is distributed into breast milk. Tranexamic acid has a plasma elimination half-life of about 2 hours. It is excreted in the urine mainly as unchanged drug.

◊ References.

1. Andersson L, *et al*. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci* 1968; **146:** 642–56.
2. Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; **49:** 241–2.
3. Pilbrant Å, *et al.* Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol* 1981; **20:** 65–72.

Uses and Administration

Tranexamic acid is an antifibrinolytic drug that inhibits breakdown of fibrin clots. It acts primarily by blocking the binding of plasminogen and plasmin to fibrin; direct inhibition of plasmin occurs only to a limited degree. Tranexamic acid is used in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It is also used in the prophylaxis of hereditary angioedema.

Tranexamic acid is given by mouth and by slow intravenous injection or continuous infusion. Parenteral dosage is usually changed to oral after a few days. Alternatively, an initial intravenous injection may be followed by continuous infusion.

For short-term use in **haemorrhage**, oral doses are 1 to 1.5 g (or 15 to 25 mg/kg) 2 to 4 times daily. When given by slow intravenous injection doses are 0.5 to 1 g (or 10 mg/kg) 3 times daily. Tranexamic acid is given by continuous infusion at a rate of 25 to 50 mg/kg daily.

Tranexamic acid is given for prolonged periods in **hereditary angioedema** in doses of 1 to 1.5 g by mouth 2 or 3 times daily.

Children may be given doses of 25 mg/kg orally or 10 mg/kg intravenously, usually 2 or 3 times daily, depending on the indication.

Reduced doses are recommended for patients with renal impairment (see below).

Solutions of tranexamic acid have been applied topically, for example as a bladder irrigation or mouthwash.

Administration in renal impairment. Licensed drug information recommends reduced doses of tranexamic acid for patients with renal impairment, based on the serum-creatinine concentration (SCC):

- SCC 120 to 250 micromoles/litre: 15 mg/kg twice daily orally, or 10 mg/kg twice daily intravenously
- SCC 250 to 500 micromoles/litre: 15 mg/kg once daily orally, or 10 mg/kg once daily intravenously
- SCC higher than 500 micromoles/litre: 7.5 mg/kg once daily or 15 mg/kg once every 48 hours orally, or 5 mg/kg once daily or 10 mg/kg once every 48 hours intravenously (some products contra-indicate use in severe renal impairment)

Haemorrhagic disorders. Tranexamic acid and aminocaproic acid are structurally related synthetic antifibrinolytic drugs that block the binding of plasminogen and plasmin to fibrin, thereby preventing dissolution of the haemostatic plug.[1,2] A plasma concentration of tranexamic acid of 5 to 10 micrograms/mL has been considered necessary for effective inhibition of fibrinolysis.[2]

Antifibrinolytics are used to control haemorrhage that is considered to be caused by excessive fibrinolysis. Antifibrinolytic therapy may also be indicated in the prevention of rebleeding in some haemorrhagic conditions, the rationale being to retard dissolution of the haemostatic plug formed in response to vascular injury.

In haemorrhage caused by a congenital or acquired deficiency of blood coagulation factors, haemostatic drugs have a secondary role and may be useful in reducing requirements of factor concentrates. In patients with haemophilias (p.1048) antifibrinolytics may be added to coagulation factor replacement before dental surgery, and used in the prevention and treatment of mucosal bleeding after the procedure. The route depends on the severity of the coagulation factor deficiency and the procedure to be undertaken; for example, tooth extraction will probably require more prophylactic cover than dental scaling. Regimens therefore vary,[3-7] but an initial oral or intravenous dose of tranexamic acid may be followed by oral use, or topical 5% mouthwash continued for up to 7 days after dental procedures. Tranexamic acid has been used similarly in patients with von Willebrand's disease[4] (p.1051). An approach using tranexamic acid mouthwashes has also been used to reduce the risk of bleeding after oral surgery in patients on anticoagulant therapy.[8,9] Tranexamic acid may prove beneficial in patients with other congenital bleeding disorders such as α_2-antiplasmin deficiency.[10] Aminocaproic acid has been tried in a few patients with hereditary haemorrhagic telangiectasia with mixed results.[11] Tranexamic acid has been reported to be effective in the control of epistaxis in these patients; reports generally describe oral use,[12,13] but tranexamic acid has also been applied directly as nasal drops.[14]

Tranexamic acid and aminocaproic acid have each been used in an attempt to prevent rebleeding in patients with subarachnoid haemorrhage (see Stroke, p.1185), particularly if surgery is to be delayed. However, while rebleeding may be reduced, there can be an increase in the incidence of cerebral ischaemic complications resulting in little overall improvement in outcome.[15] Paradoxically, rebleeding has been noted in patients given high doses of aminocaproic acid after subarachnoid haemorrhage (see Effects on the Blood under Aminocaproic Acid, p.1053).

Tranexamic acid has been used to control gastrointestinal haemorrhage, e.g. due to peptic ulcer disease (p.1702) or oesophageal varices (see Variceal Haemorrhage under Monoethanolamine, p.2346). In a meta-analysis[16] of 6 studies, involving a total of 1267 patients given tranexamic acid for acute upper gastrointestinal haemorrhage, treatment with tranexamic acid was associated with a 20 to 30% decrease in the rate of rebleeding, a 30 to 40% decrease in the need for surgery, and a 40% decrease in mortality. However, the validity of one study included in the analysis has been disputed,[17,18] and it is not the usual treatment in these patients.

Tranexamic acid or aminocaproic acid have been suggested to control bleeding in many other conditions. These include haemorrhage after surgical or other procedures including prostatectomy, bladder surgery, and cervical conisation. They may be used to reduce perioperative blood loss and allogeneic transfusion requirements.[19-23] They may also be effective in other conditions associated with excessive fibrinolysis such as menorrhagia (see below), epistaxis, and placental abruption.

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Hereditary angioedema. Hereditary angioedema, formerly known as hereditary angioneurotic oedema, is a rare autosomal dominant disease caused by either a deficiency of complement C1 esterase inhibitor or, more rarely, a lack of functioning inhibitor.[1-6] The disease presents as episodic attacks of oedema, usually of the extremities and face, and often involving the gastrointestinal mucosa producing abdominal pain. A non-pruritic rash may also occur. A few patients develop life-threatening laryngeal oedema. Attacks generally last about 1 to 3 days and may occur as frequently as weekly or there may be years between attacks. The first attack may occur at any age although initial presentation in childhood is most common. Trauma, especially dental surgery, illness, and emotional stress may provoke an attack although often there is no precipitating factor.

Treatment of the acute attack is essentially supportive. If laryngeal oedema is present adrenaline, antihistamines, and corticosteroids may be given (as for Anaphylaxis, p.1205) even though patients with hereditary angioedema often fail to respond adequately to them. The mainstay of treatment of an acute attack is replacement therapy with complement C1 esterase inhibitor. Fresh frozen plasma has been used although there is a risk of initially exacerbating the oedema due to the presence of other complements in the plasma. Tracheostomy or tracheal intubation may be necessary.

Once the acute attack has subsided most patients will not require further treatment, but those who experience life-threatening attacks, repeated episodes of swelling around the face or neck, or incapacitating attacks require long-term **prophylactic therapy**. A synthetic androgen (danazol or stanozolol) or an antifibrinolytic (aminocaproic acid or tranexamic acid) is effective for long-term prophylaxis.[1,2,4,6] Danazol and stanozolol raise serum concentrations of C1 esterase inhibitor possibly by enhancing its synthesis in the liver.[2,6] Aminocaproic acid and tranexamic acid may act by inhibiting plasmin activation.[7] A synthetic androgen is often preferred because these seem to be more effective than antifibrinolytics. In children, however, androgens are generally avoided because of their adverse effects. Nevertheless, they have been used in children, with close monitoring, when antifibrinolytics have been ineffective.[3] In exceptional circumstances, long-term prophylaxis with twice weekly C1 esterase inhibitor may be indicated for adults when antifibrinolytics and androgens are ineffective, not tolerated, or contra-indicated.[6]

Short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental work. Complement C1 esterase inhibitor is given within 24 hours before the procedure, or fresh frozen plasma may be used if this is not available. Alternatively, a synthetic androgen or antifibrinolytic may be used, but these must be started several days before the procedure and continued for 2 days after.

Investigational therapies for the management of hereditary angioedema include a recombinant complement C1 esterase inhibitor, icatibant acetate (a bradykinin receptor antagonist), and ecallantide (an inhibitor of human plasma kallikrein).

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Menorrhagia. Tranexamic acid is used in women with menorrhagia (p.2126) who do not require contraception or hormonal therapy. It reduces uterine blood loss in such women when used during menstruation.[1-3] A comparative trial[1] found tranexamic acid 1 g by mouth every 6 hours to be more effective than the NSAID mefenamic acid, a commonly used treatment for the condition, and etamsylate. It is also more effective than cyclical norethisterone[2] (although less so than a progesterone-releasing intra-uterine device[3]). A review,[4] which included these and some other studies, reported that tranexamic acid reduces menstrual blood loss by about 34 to 59% over 2 to 3 cycles.

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Preparations

BP 2008: Tranexamic Acid Injection; Tranexamic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Cyklokapron; ***Austria:*** Cyklokapron; ***Belg.:*** Exacyl; ***Braz.:*** Hemoblock; Transamin; ***Canad.:*** Cyklokapron; ***Chile:*** Espercil; ***Cz.:*** Cyklokapron†; Exacyl; ***Denm.:*** Cyklokapron; ***Fin.:*** Caprilon; Cyklokapron; ***Fr.:*** Exacyl; Spotof; ***Ger.:*** Anvitoff†; Cyklokapron; ***Gr.:*** Transamin; ***Hong Kong:*** CP-Tran; Cyklokapron; Qualixamin; Transamin; ***Hung.:*** Exacyl; ***India:*** Tranarest; Tranfib; Traxamic†; ***Indon.:*** Asamnex; Clonex; Ditranex; Intermic; Kalnex; Lunex; Nexa; Plasminex; Pytramic; Ronex; Theranex; Tranexid; Transamin; ***Irl.:*** Cyklokapron; ***Israel:*** Hexakapron; ***Ital.:*** Tranex; Ugurol; ***Jpn:*** Transamin; ***Malaysia:*** Transamin; Tren; ***Neth.:*** Cyklokapron; ***Norw.:*** Cyklokapron; ***NZ:*** Cyklokapron; ***Philipp.:*** Cyclotrax; Cyklokapron; Dostan; Fibrinon; Fimoplas; Hemoclot; Hemostan; Hemotrex; Micranex; Proklot; Trenaxin; ***Pol.:*** Exacyl; ***S.Afr.:*** Cyklokapron; ***Singapore:*** Cyklokapron; ***Spain:*** Amchafibrin; ***Swed.:*** Cyklo-F; Cyklokapron; Tranon; ***Switz.:*** Anvitoff†; Cyklokapron; ***Thai.:*** Tramic; Transamin; ***Turk.:*** Transamine; ***UK:*** Cyklokapron; ***USA:*** Cyklokapron; ***Venez.:*** Ciclokapron.

Multi-ingredient: ***Fr.:*** Quixil; ***Ger.:*** Quixil; ***India:*** Tranfib MF; ***Ital.:*** Quixil; ***Jpn:*** Sin Colgen Kowa Kaze; ***Neth.:*** Quixil; ***Port.:*** Quixil.

von Willebrand Factor

Facteur Willebrand humain (human von Willebrand factor); Factor humanus von Willebrandi (human von Willebrand factor); Factor VIII-related Antigen; vWF.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human von Willebrand Factor). A preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors: the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

When reconstituted as stated on the label, the potency is not less than 20 international units of von Willebrand factor per mL. It is a white or pale yellow, hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

von Willebrand factor is used in the treatment and prophylaxis of bleeding in von Willebrand's disease (p.1051), usually when desmopressin is ineffective or contra-indicated. It is generally contained in plasma concentrate preparations with factor VIII, but highly purified preparations that contain very little factor VIII are also available in some countries. Dosage depends on the extent and source of bleeding. Hypersensitivity reactions may occur rarely, and as for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

◊ References.

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Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Wilfactin; Wilstart; ***Gr.:*** Wilfactin.

Bone Modulating Drugs

Bone and Bone Disease, p.1083
Hypercalcaemia of malignancy, p.1083
Malignant neoplasms, p.1083
Osteogenesis imperfecta, p.1083
Osteomalacia and rickets, p.1084
Osteoporosis, p.1084
Paget's disease of bone, p.1086
Renal osteodystrophy, p.1086
Rickets, p.1087
Parathyroid Disorders, p.1087
Hyperparathyroidism, p.1087
Hypoparathyroidism, p.1087

The processes of bone turnover, and the regulation of body calcium, are intimately connected. The concentration of calcium in plasma is normally kept within a narrow range (p.1667). It is regulated by the absorption and excretion of calcium, and also by modulation of the normal resorption and formation of bone and hence the movement of calcium to and from the skeletal reservoir. The endogenous substances parathyroid hormone, calcitonin, and vitamin D, are involved in the regulation of calcium homoeostasis.

Drugs described in this chapter affect bone resorption or formation, with effects on serum calcium. They include:

- bisphosphonates
- bone morphogenetic proteins
- calcitonins
- cinacalcet hydrochloride
- gallium nitrate
- parathyroid hormone
- strontium ranelate
- teriparatide

The inorganic fluoride salts, which can promote bone formation when given in appropriate doses, are discussed in the chapter on Nutritional Agents (see Sodium Fluoride, p.1962).

Bone and Bone Disease

The skeleton acts as mechanical support and protection to softer tissues and organs. It is also important in electrolyte homoeostasis, acting as a reservoir of certain ions and minerals such as calcium, phosphorus, and magnesium.

Bone has two components: an organic matrix, called **osteoid**, consisting mainly of collagen, and a mineral phase deposited through that matrix; the latter, comprising about 70% of the skeletal mass, is composed chiefly of hydroxyapatite (a complex crystalline salt of calcium and phosphate). There are two structural forms known in mature bone, namely cortical (lamellar) bone, which has a dense, continuous structure, and trabecular (cancellous) bone, which has a 'spongy' structure of linked plates and is associated with high bone turnover and growth. The peripheral or appendicular parts of the skeleton are mainly cortical bone, while the axial or central parts, such as the spine and pelvis, contain substantial amounts of trabecular bone.

Bone is a dynamic tissue: once new bone has been laid down it is subject to a continual process of formation and resorption called **remodelling**. Remodelling takes place along bone surfaces and is carried out by bone cells (osteoclasts and osteoblasts) that originate in the marrow and share common origins with blood cells. Stimulated by physical or chemical signals, **osteoclasts** dig a cavity into the bone (bone resorption); they are then replaced by **osteoblasts** that synthesise new osteoid to fill the cavity (bone formation) and may help to promote its subsequent mineralisation. The actions of these two types of bone cell are closely linked, and agents that suppress resorption ultimately decrease bone formation too. However, at any given time there is a deficit in potential bone mass, the **remodelling space**, which represents sites of bone resorption that have not yet been filled in. Any stimulus that affects bone turnover by altering the recruitment of osteoblasts and osteoclasts to remodelling will result in an increase or decrease in the remodelling space, until a new steady state is achieved, and this will be seen as a decrease or increase in bone mass. Lifelong accumulation of remodelling deficits leads to age-related bone loss.

Bone also contains **osteocytes**, which are cells derived from osteoblasts thought to be involved in the movement of minerals.

Bone cells are controlled by systemic hormones including parathyroid hormone, 1,25-dihydroxycholecalciferol (calcitriol), calcitonin, and local regulators such as bone morphogenetic proteins and cytokines. A local signalling system involving the protein RANKL (receptor activator of nuclear factor-kappa B ligand), which induces osteoclast differentiation and activation and promotes bone resorption, and the protein osteoprotegerin, which inhibits osteoclast formation and prevents bone resorption, is mediated via the receptor RANK found on osteoclasts and their precursors.

Bone diseases may be due to defects in the production of osteoid or its mineralisation, or to an imbalance in resorption and formation of bone. Bone balance can be affected by diverse stimuli such as dietary insufficiency, hormones, including sex hormones, and drugs such as corticosteroids.

Hypercalcaemia of malignancy

About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive.[1,2] The condition is thought to be mediated usually by parathyroid hormone-related protein released from tumour tissue, which acts both locally and systemically to enhance osteoclastic bone resorption and increase renal tubular calcium reabsorption. Increased levels of parathyroid hormone-related protein have been found in hypercalcaemic patients, especially those with solid tumours, regardless of the existence of bone metastases.[3,4] Other causes of hypercalcaemia of malignancy include the activation of osteoclasts by the local release of bone-resorbing cytokines such as interleukin-1, interleukin-6, tumour necrosis factors, and growth factors;[3,4] this mechanism occurs particularly in those with myeloma.[4] The RANKL signalling system may play an important role.[5] Some lymphomas secrete active vitamin D, enhancing osteoclastic bone resorption and intestinal calcium absorption. Rarely, ectopic secretion of parathyroid hormone may cause hypercalcaemia.[6]

Bisphosphonates are the preferred drugs for **treating** hypercalcaemia once the patient has been adequately rehydrated with intravenous sodium chloride 0.9% (see Hypercalcaemia, p.1668). It has been recommended[6] that therapy be begun as soon as possible, since a response is only seen after 2 to 4 days; in about 60 to 90% of patients serum calcium concentrations normalise within 4 to 7 days, and responses last for up to 3 weeks.[6] There is some evidence that bisphosphonates may be less effective in patients with high initial levels of parathyroid hormone-related protein; in addition, they have no effect on the renal tubular resorption of calcium.[2] There is no consensus as to the best bisphosphonate to choose. Pamidronate has been widely used and is considered by many to be the drug of choice.[7] A systematic review,[2] which noted that aminobisphosphonates were most effective in this condition, considered low-dose clodronate less effective than pamidronate although no difference was seen at higher doses. Others have queried the existence of a dose response for clodronate;[1] the fact it can be given subcutaneously, or orally (after intravenous therapy) may be useful.[1,4] Etidronate, which can also be given orally, is also less effective than pamidronate,[7,8] and prolonged therapy may cause osteomalacia. Alendronate has been found to be as effective as clodronate, and superior to etidronate.[2] Studies with neridronate, olpadronate, and risedronate have been more limited;[1] incadronate has also been used.[2] However, newer aminobisphosphonates such as ibandronate and zoledronate may be the most effective option, with longer durations of response and more convenient dosage than pamidronate.[1,4] In patients unresponsive to low initial doses of bisphosphonates, some recommend larger doses;[6] alternatively, other drugs may be considered.

Calcitonin has a rapid onset of action, and is particularly useful in life-threatening hypercalcaemia.[1,7] This effect, however, is short-lived, and calcitonin is generally used as adjunctive therapy.[1] When given with bisphosphonates, calcitonin reduces serum calcium more rapidly than bisphosphonates given alone.[4]

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, has been used to obtain a rapid (within 24 hours) and sustained reduction in plasma-calcium concentrations in severe hypercalcaemia. However, it is highly toxic and its use no longer recommended.[1,5] Gallium nitrate also inhibits bone resorption; initial studies in patients with hypercalcaemia associated with malignancy have indicated beneficial effects,[3] but bisphosphonates are still likely to be preferred.[4,5]

Corticosteroids are useful in hypercalcaemia associated with corticosteroid-sensitive haematological malignancies such as lymphoma or myeloma.[1,4,6] In addition they may be useful to overcome renal tubular resistance to calcitonin[9] but otherwise are not usually effective.[10] There have been individual reports of beneficial results using somatostatin analogues such as octreotide for the treatment of hypercalcaemia of malignancy.

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Malignant neoplasms

The bisphosphonates and calcitonins are used to control the hypercalcaemia that often accompanies malignant disease (see above). Bisphosphonates are also used in metastatic bone disease (p.660) to control bone pain and to reduce skeletal complications such as fractures. Evidence of the ability of bisphosphonates to prevent the development of bone metastases is conflicting. Bisphosphonates have been found to be effective in reducing the skeletal complications of multiple myeloma (p.658) and are recommended in those patients with bone disease.

Osteogenesis imperfecta

Osteogenesis imperfecta (brittle bone syndrome) is a heterogeneous inherited disorder of connective tissue characterised by bone fragility, osteopenia, short stature, joint laxity, teeth defects, and hearing abnormalities.[1,2] It is often classified into 4 forms, I-IV, which vary in clinical severity, and radiological and genetic aspects;[1] some distinguish 3 further forms, V, VI, and VII.[2]

Orthopaedic treatment and physical activity programmes form the basis of therapy: at present there is no curative drug therapy.[1-3] Calcitonins were commonly used in management, but their use has declined.[1] Beneficial effects have been reported with growth hormone, especially in moderate forms of the disease.[1] Bisphosphonates have yielded substantial improvements in chronic pain, bone mineral density, fracture rate and mobility,[3,4] without significant adverse effects, and may be especially beneficial in severe osteogenesis imperfecta.[1] Cyclic intravenous pamidronate has been the most widely used bisphosphonate, but benefit has also been reported with intermittent intravenous neridronate,[5,6] as well as daily oral clodronate,[7] and daily oral olpadronate.[8] Alendronate and zoledronate are under investigation.[4] Bisphosphonates may also be useful for associated immobilisation hypercalcaemia.[9] Immobilisation can also result in calcium and vitamin D deficiency, and prophylactic supplementation may be useful.[3] Bone marrow transplantation and the potential of antisense gene therapy are being investigated.[1,2]

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Osteomalacia and rickets

Osteomalacia occurs in adults when there is impaired mineralisation of the bone matrix, and rickets occurs in children due to defective mineralisation of the cartilaginous growth plate.[1-3] Generally the inadequate bone mineralisation results from deficiency or abnormal metabolism of vitamin D,[1,2,4] calcium deficiency,[1,5] or phosphate deficiency or depletion.[1-3] Several hereditary disorders are associated with the development of rickets including vitamin D-pseudodeficiency rickets (vitamin D-dependent rickets), in which there is impaired synthesis of 1,25-dihydroxycholecalciferol (Type I) or receptor resistance to 1,25-dihydroxycholecalciferol (Type II), and X-linked hypophosphataemic rickets.[2,6] Osteomalacia also occurs in renal osteodystrophy[2] associated with chronic renal failure (see below). Oncogenic osteomalacia is a rare form characterised by hypophosphataemia and renal phosphate wasting caused by a tumour, usually mesenchymal.[2,3] Some drugs including various antiepileptics (p.496), etidronate, and aluminium salts, can interfere with bone mineralisation and cause osteomalacia. Osteomalacia may present with generalised or local bone pain, polyarthralgias, or muscle weakness.[2] Rickets characteristically causes skeletal deformities, epiphyseal enlargement, muscle hypotonia, and teeth defects.[1-4,6]

Treatment of osteomalacia and rickets is mainly aimed at correcting any underlying deficiency.[2] Vitamin D substances, calcium, or phosphate supplements can be given orally as appropriate but doses require careful individual adjustment to maintain calcium and phosphate concentrations within normal limits.[2,5] Vitamin D requirements are probably greater in those with reduced calcium intake, and calcium requirements greater in those with limited sunlight exposure and dietary vitamin D intake.[5] A variety of forms or analogues of vitamin D are available (see p.1986). For the treatment of simple vitamin D deficiency colecalciferol or ergocalciferol are generally preferred.[4] If malabsorption is suspected, larger doses or parenteral use may be necessary, but where large doses are required it may be preferable to use one of the more potent forms of vitamin D such as calcitriol.[2] Simple calcium deficiency may be a more important cause of rickets than vitamin D deficiency in some populations. A study in African children with rickets found that their calcium intake was low and that they responded better to calcium supplementation, with or without vitamin D, than to vitamin D alone.[5]

Type I vitamin D-pseudodeficiency rickets requires replacement therapy with calcitriol. In Type II disease, resistance to calcitriol treatment may be so extreme that only very large supplements of calcium may be effective. X-linked hypophosphataemic rickets is considered to be best treated with combined phosphate supplementation and calcitriol.[3] There has also been some interest in the use of growth hormone in children with hypophosphataemic rickets.[7] A form of hypophosphataemic rickets, rickets of prematurity (see under Osteomalacia, p.1684), may occur in small, premature infants fed exclusively on breast milk, and phosphate supplementation plus calcium and vitamin D has been suggested in such cases. Prophylaxis of calcium or vitamin D deficiencies through adequate dietary intake or supplementation is controversial given difficulties in definitive requirements (see Human Requirements under Calcium, p.1677, and Human Requirements, p.1988, and Osteomalacia, p.1990, under vitamin D).

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Osteoporosis

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and risk of fracture, particularly of the long bones (distal forearm and neck of the femur) and the vertebrae.[1-9] Although bone formation outstrips resorption in youth, accumulated small deficits from remodelling (see Bone and Bone Disease, above) result in a gradual loss of bone mass after the third or fourth decades.[2-4,6,10] Primary osteoporosis is therefore usually an age-related disease. It can affect both sexes, though women are at greater risk because bone loss is accelerated, to a variable degree, after the menopause.[1-3,5,6,10,11] Osteoporosis can also be secondary to chronic endocrine or metabolic conditions[1,5,6,10-12] such as hyperparathyroidism (p.1087), hyperthyroidism (p.2165), diabetes mellitus (p.431), Cushing's syndrome (p.2344), malabsorption syndromes, anorexia nervosa, or inflammatory bowel disease (p.1697) affecting calcium and vitamin D absorption. Other conditions associated with bone loss and osteoporosis include osteogenesis imperfecta (p.1083), rheumatoid arthritis (p.11), complex regional pain syndrome (p.6), chronic renal disease, and multiple myeloma (p.658); osteoporosis may also follow organ and tissue transplantation or prolonged immobilisation. Other secondary causes include the use of drugs[1,5,6,10,11] such as corticosteroids (p.1491), thyroid hormones, anticonvulsants, gonadorelin analogues (p.2106), and heparin (p.1302).

Risk factors for osteoporosis include non-modifiable predictors of low bone mineral density (BMD), such as female sex, increased age, Caucasian or Asian race, while other factors are potentially modifiable but may be independent of BMD, such as cigarette smoking, alcohol consumption, low body-weight, and physical inactivity. Other factors include early menopause, prolonged amenorrhoea, high caffeine intake, and nutritional deficiencies such as low calcium intake and vitamin D deficiency.[1,3,6,10,13] The most important risk factors for osteoporosis-related fracture are a previous history of low-trauma fracture as an adult (40 years of age or older) and low BMD.[1,3,4]

Patients are usually asymptomatic until fractures occur,[6,13] and up to two-thirds of vertebral fractures may also be asymptomatic.[1,6] Fractures can result in pain, deformity (kyphosis, loss of height), and disability.[1] Currently, the most reliable method of assessing osteoporosis and fracture risk is measurement of BMD, usually by dual energy X-ray absorptiometry.[1,3,4,6,14] WHO have defined osteoporosis as a BMD 2.5 standard deviations or more below the young adult mean, and severe or established osteoporosis as this BMD in the presence of one or more fragility fractures.[3] There is no universally agreed policy on screening for osteoporosis, but measurement of BMD should be considered in those thought to be at risk of osteoporosis if the result is likely to affect treatment decisions.[2,3,7,10,15,16]

Since osteoporosis is defined in terms of BMD, the distinction between clinical consequences, such as fractures, and risk, is blurred. Thus, differences between prevention and treatment are increasingly difficult to define; objectives are similar and interventions the same.[3] Goals in management are to prevent fractures, optimise skeletal development to maximise peak BMD at skeletal maturity, stabilise BMD and prevent bone loss, preserve structural skeletal integrity, and to decrease morbidity and mortality from fractures.[1,4] Secondary causes of osteoporosis should be identified and treated as appropriate.[4]

General **non-pharmacological** measures include:

- ensuring adequate dietary calcium and vitamin D intake (see under Human Requirements, p.1677 and p.1988), especially during growth.[1,3,4,17] Supplementation may be necessary, see below.
- regular weight-bearing exercise; during growth this optimises peak bone mass,[3,4,16,17] but is also beneficial in pre- and postmenopausal women in terms of increasing BMD and reducing the risk of fractures.[1,4,16,18] However, exercise does not appear to prevent fractures in postmenopausal women during the first 2 years of exercise.[19]
- lifestyle modifications such as smoking cessation (p.2354) and moderation of caffeine and alcohol intake.[1,3,9,18,20]
- interventions to reduce or prevent falls and injuries; measures to protect the patient should falls occur may also be considered.[1,16,18,20]
- Supportive therapy in the acute phase of a fracture, including pain relief, surgery or appropriate orthopaedic management.[17]

Pharmacological treatment aims to increase bone mass, either by inhibiting bone resorption, or by stimulating bone formation through anabolic effects.[1,21] While many drugs are used, not all have been well evaluated for their effect on fracture rates, and there is little comparative data.[22] Furthermore, many studies have been conducted in postmenopausal osteoporotic women, and evaluation in postmenopausal women with normal BMD, osteopenic women with no fracture, or men, is limited.[3,16]

- Calcium and vitamin D supplementation is accepted baseline adjunctive treatment for osteoporosis and may also be used as a prophylactic measure.[4,7,17,21] Calcium supplementation has a small but positive effect on BMD and tends to reduce the incidence of vertebral fractures. Low vitamin D status has been associated with reduced BMD, and increased risk of falls and hip fracture in elderly people; however, differences in baseline vitamin D concentrations make comparison of studies difficult.[8] Vitamin D supplementation appears to reduce the risk of hip and non-vertebral fractures,[7,8] especially in those with vitamin D deficiency. Excessive vitamin D should be avoided, as this may decrease BMD.[2] Studies of supplementation with calcium plus vitamin D show equivocal results on fracture rates.[8] However, daily calcium with vitamin D supplementation is recommended for elderly institutionalised people with limited exposure to sunlight.[15,16,18]
- Bisphosphonates are antiresorptive drugs that are used first-line for the treatment and prevention of osteoporosis.[4,15,16,20] While aminobisphosphonates and non-nitrogen-containing bisphosphonates differ in their effect on BMD,[14,23] no comparative studies have been done and BMD changes do not necessarily correlate with fracture reduction;[23] some consider effect on fracture rates to be similar.[14]

  There is good evidence that alendronate or risedronate, given orally, can prevent bone loss,[4,11] improve BMD,[1,4,6] and reduce the risk of both vertebral and non-vertebral fractures.[1,2,8,9,13,21] These effects are seen within 1 year of starting treatment,[24] and effects on BMD persist for some while after stopping the drug, particularly with alendronate.[14] Evidence for other bisphosphonates is more patchy: oral or intravenous ibandronate,[11] and intravenous pamidronate[6] or zoledronate[1,11] have all been shown to increase BMD at the spine and hip. Oral ibandronate has been shown to decrease vertebral fracture risk in women with osteoporosis, as well as non-vertebral fracture risk in those with severe disease.[11,25] Intravenous ibandronate has been associated with a reduction in the incidence of new fractures.[11] In a controlled study,[26] a once-yearly infusion of zoledronate given over a 3-year period significantly reduced the risk of vertebral, hip, and other fractures. BMD at the hip, femoral neck, and lumbar spine also increased significantly compared with placebo. Oral cyclical etidronate has been shown to decrease the risk of vertebral fractures,[1,3] (as has oral clodronate[17]), but evidence for an effect on non-vertebral fractures is less clear.[17] In the UK, NICE[27] recommends the use of bisphosphonates for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Alendronate, etidronate, or risedronate may be given to all women aged 75 years and older, to women aged between 65 and 74 years with confirmed osteoporosis, and to postmenopausal women younger than 65 with very low BMD or with confirmed osteoporosis and one or more additional age-independent risk factors.
- Calcitonins are antiresorptive agents with an adjunctive or second-line role in the treatment of osteoporosis; calcitonin (salmon) is given by subcutaneous injection or intranasally as a spray. Both routes have been found to increase spinal BMD;[1,4,5] decreases in vertebral[4,28] fracture risk have been seen with the nasal spray, although

the beneficial effect on nonvertebral fracture may be less than with bisphosphonates.[29] It has been suggested that the analgesic effects of calcitonins may be valuable in patients with acute pain due to osteoporotic fractures,[2,3,15,21] the analgesia being achieved within 2 weeks.[6]

- In postmenopausal women, HRT (p.2077) was initially considered first-line,[28] as its antiresorptive action has been shown to preserve BMD and decrease hip and vertebral fracture risk.[1,2,21] However, results from the Women's Health Initiative and Million Women studies suggested that long-term use of HRT could increase the risk of breast and some other cancers (see p.2071), while not reducing cardiovascular risk or improving cognitive function. The UK CSM has thus recommended that HRT no longer be considered as a first-line therapy for the prevention of osteoporosis in women aged over 50 years and at increased risk of fractures;[30] it remains an option for those intolerant of or refractory to other therapies, and for prevention of osteoporosis in women with premature menopause until the age of 50. It has been suggested that treatment not exceed 5 years,[21] although others suggest treatment of 7 to 10 years in order to maximise effect in those women considered at greater benefit than risk with HRT.[2] A large study found that women who had stopped using HRT more than 5 years previously had similar hip fracture risk to those who had never used HRT. However, those who had stopped using HRT within the previous 5 years had a higher risk of hip fracture than in those who had never taken HRT.[31]
- Raloxifene is a selective oestrogen receptor modulator (SERM) that partially mimics the effects of oestrogen in bone and the cardiovascular system, but without the stimulatory effects on the endometrium and breast.[3] Raloxifene significantly increases BMD in postmenopausal women and reduces vertebral fracture risk in those women with osteoporosis,[32] although it may exacerbate cardiovascular problems.[11,15] Risk of non-vertebral fracture is not affected,[3,15] and some consider SERMs less effective than the bisphosphonates.[6] NICE recommends raloxifene[27] for the secondary prevention of osteoporotic fragility fractures in women unable to take bisphosphonates or who have had an unsatisfactory response to bisphosphonate treatment.
- Combination therapy of HRT or raloxifene with bisphosphonates has increased BMD but with no effects on fracture reduction.[17]
- Tibolone is a synthetic steroid with combined oestrogenic, progestogenic, and androgenic properties, that increases BMD comparably to HRT, relieves vasomotor symptoms, and does not cause endometrial proliferation.[3] However, there are limited data on fracture prevention, and some do not recommend its use for treatment of osteoporosis.[21] A large study[33,34] of the treatment of osteoporosis in postmenopausal women was stopped early when it was found that although tibolone reduced the risk of fracture there was an increased risk of stroke. However, the full results of this study are yet to be published.
- Fluoride has a direct anabolic effect on the osteoblast, stimulating bone formation; it has been given as sodium fluoride or sodium monofluorophosphate in the treatment of osteoporosis.[3,35] However, increases in lumbar BMD with fluoride have not resulted in decreased vertebral fracture rate, and may even be associated with increased bone fragility and an increase in non-vertebral fractures.[3,36] Thus fluoride is not widely recommended for osteoporosis management; fluoride water concentrations should be taken into account if it is used.[3]
- Parathyroid hormone and its analogue teriparatide also have anabolic effects on bone, and increase BMD at the spine.[20,21] Daily subcutaneous injections of teriparatide reduced the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis.[4,35] Teriparatide has also been shown to increase lumbar and femoral BMD, and reduce non-vertebral fractures to a greater extent than alendronate.[5] The response to parathyroid hormone may be modified by previous or concurrent treatment with antiresorptive drugs.[8] Combination therapy with alendronate offered no advantage over parathyroid hormone (or teriparatide) monotherapy in terms of changes in BMD. However, after 1 year of parathyroid hormone monotherapy, BMD gains were maintained or increased when followed with alendronate therapy, but lost if followed by placebo.[37] NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates or who are intolerant to bisphosphonates, and who have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3 standard deviations or more) plus one or more additional risk factors.[27]
- Strontium ranelate has both anabolic and resorptive properties.[17] It has been found to increase BMD at the spine and hip, and reduce new vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis.[9,11]
- Anabolic steroids such as nandrolone have been found to increase BMD similarly to HRT, but adverse effects and limited data on fracture reduction efficacy have limited their use.[3,16]
- There is some suggestion that HMG-CoA reductase inhibitors (statins) can stimulate bone formation and have the potential to reduce fracture risk, but data are conflicting, and further trials are needed.[35,38,39]
- Thiazide diuretics reduce urinary calcium excretion and observational studies have found patients to have a higher BMD and fewer hip fractures;[3] however, effects are small and therapy is likely to be restricted to an adjunctive preventative role.[1,3,5]
- Ipriflavone is a synthetic isoflavone that may inhibit bone resorption; results on BMD from trials are conflicting, and data on fracture reduction lacking.[1,3]
- Vitamin K plays a role in bone metabolism, and is licensed in some countries in the management of osteoporosis; it has been suggested that vitamin K substances should be given to patients at risk of reduced bone mineralisation.[40] A systematic review and meta-analysis found that vitamin K supplementation was associated with increased BMD and a reduced fracture incidence, especially of the hip;[41] however, routine supplementation is not considered justified until these results are confirmed in a large randomised study with fractures as primary outcome.
- Potential anabolic agents in the management of osteoporosis include growth hormone and insulin-like growth factor I.[5,35] Novel antiresorptive agents under investigation include cathepsin K inhibitors, cytokine inhibitors,[5,21] the RANKL monoclonal antibody denosumab,[42] and osteoprotegerin.[5,43]

There is less evidence to guide decisions on the management of osteoporosis in **men**[3,44] than in postmenopausal women. Calcium and vitamin D intake or supplementation, nutritional and lifestyle advice are similar to that for women.[44-46] In hypogonadal men with osteoporosis, testosterone replacement therapy should be used.[3,44,45] In eugonadal men, there are concerns regarding the potential long-term adverse effects of exogenous testosterone.[44,46] Therefore, in men with idiopathic osteoporosis, bisphosphonates may be the treatment of choice.[45] Alendronate has been found to increase BMD at all sites and decrease vertebral fracture rates in men with osteoporosis,[45] and there have been some reports of beneficial effects on lumbar BMD have been reported with cyclical etidronate. Preliminary results with risedronate indicate favourable increases in lumbar BMD and a decrease in vertebral fracture risk.[44]

Beneficial effects on both lumbar and femoral BMD have been reported with teriparatide; its effect on BMD when used alone was found to be greater than when used with alendronate, or that of alendronate alone.[45] While efficacy in fracture prevention is lacking, it may be considered second-line for patients unable to take bisphosphonates.[44] Nasal calcitonin (salmon) has been found to increase lumbar BMD in men with idiopathic osteoporosis,[45] but most similarly reserve its use for those who cannot tolerate bisphosphonates.[44,46]

Of the other available drugs, fluoride has increased BMD and decreased vertebral but not non-vertebral fractures.[45] Thiazide diuretics have been reported to be of benefit, but data on BMD and fracture risk are conflicting; they may be given as adjunctive therapy in men with hypercalciuria.[44] Use of growth hormone in men with idiopathic osteoporosis has led to gains in BMD in a small uncontrolled study.[46]

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Paget's disease of bone

Paget's disease of bone (osteitis deformans) is a progressive bone disease of unknown aetiology, characterised by excessive and disorganised bone resorption and formation.[1-4] It may affect single (monostotic) or multiple bones (polyostotic);[1,2,5] the most commonly affected bones include the pelvis, femur, lumbar spine, skull, and tibia.[2,4,5] Although its prevalence appears to be decreasing,[1,2,4,6] Paget's disease occurs in about 3% of the population over 40 years of age[1] and its frequency increases with age.[1,2] Patients may be asymptomatic, but some present with musculoskeletal and bone pain, or with bone weakness and deformity that can result in fractures.[2-4,7] Other complications include hearing loss, osteoarthritis, spinal stenosis, nerve compression (especially of the spinal cord), cranial nerve palsies, and rarely, hydrocephalus or brainstem compression. Cardiac output increases due to increased skeletal vascularity, but high-output heart failure is rare, as is malignant transformation to osteosarcoma.[2-4]

Patients who are asymptomatic may require no treatment;[5,8] however treatment is warranted, in those patients with biochemical markers of active disease or in whom the sites of disease are associated with a risk of progression and future complications.[4,8] Drug therapy is guided by monitoring biochemical improvement in disease activity.[2,6]

Bone pain may be treated with analgesics or NSAIDs, or with drugs that reduce bone resorption, such as the calcitonins and bisphosphonates.[2,4,5]

Bisphosphonates are indicated for persistent bone pain, or to prevent further progression of the disease, especially if complications such as spinal-cord compression are present or there is a risk of such complications.[3,8] Disease activity may be reduced for several months, or years, after bisphosphonate therapy has ceased.[8] However, while bone turnover is suppressed, and osteolytic lesions may be healed, the underlying disorder is not cured; data on long-term effects of bisphosphonates on fractures, bone deformity, or osteoarthritis are limited and they may theoretically exacerbate hearing loss.[2]

Initial experience was with etidronate,[1,6,8] but it is less effective than the newer drugs, and with high doses or prolonged treatment can affect bone mineralisation;[4,6,8] while some still consider it effective,[8] others consider it to have little place in the management of Paget's disease.[3,6,9] Clodronate appears to provide a higher and more sustained response than etidronate.[8] Pamidronate, more effective at healing lesions than etidronate, also gives a prolonged response, although its effects may diminish due to resistance.[8] Alendronate or risedronate both reduce biochemical markers of disease activity with sustained remission,[4,8,9] are more effective than etidronate,[9] and overcome resistance to pamidronate;[3] risedronate may be useful after incomplete response to etidronate.[8] Tiludronate is also more effective than etidronate, with no effect on bone mineralisation, no reported resistance,[1,8] and may be a viable option for those patients unable to tolerate other bisphosphonates.[4] Neridronate has been reported to be beneficial in those patients with resistance to etidronate and clodronate.[8] Preliminary studies indicate suppression of disease activity with ibandronate.[6] Olpadronate and zoledronate have shown benefit in refractory disease, and some suggest zoledronate should be a first-line option.[7]

Bisphosphonates have superseded calcitonins,[1,3,5,6,8] which have a short-lived effect and which generally are less effective in suppressing bone turnover and improving bone pain.[2] Calcitonins may still have a role in those patients for whom bisphosphonates are intolerable or ineffective;[5,6] however, resistance to both bisphosphonates and calcitonins may occur.[1,4]

Plicamycin, a cytotoxic antibiotic with particular activity against osteoclasts, is highly effective in the treatment of Paget's disease of bone.[8] However, it is associated with severe toxicity and is therefore now avoided or reserved for patients refractory to other drugs.[4,6,8]

Studies with gallium nitrate, another inhibitor of bone resorption, have indicated beneficial effects in the treatment of Paget's disease of bone, but long-term haematological safety has not been established,[1,8] and routine use is not recommended.[6] Ipriflavone has also been reported to be of benefit, but remains investigational for Paget's disease.[8]

In selected patients, orthopaedic surgery for a fracture, knee or hip replacement, spinal stenosis, or correction of a bone deformity may be appropriate.[4,6,8] A calcitonin or bisphosphonate may be given for up to 3 months before surgery in order to reduce bone vascularity and minimise blood loss during the operation,[2,4,8] although this effect has not been verified in studies.[6] Such treatment also helps to prevent development of hypercalcaemia due to prolonged immobilisation.[4]

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Renal osteodystrophy

Patients with chronic renal failure (p.1672) may develop complex changes to bone known as renal osteodystrophy[1-6] as part of the wider metabolic derangement know as chronic kidney disease-mineral and bone disorder (CKD-MBD).[7,8] These are often classified according to the state of bone turnover[1,3,5] and bone biopsy is the gold standard for diagnosis and classification.[2-6] Progressive renal failure is associated with hypocalcaemia, hyperphosphataemia, and some decrease in vitamin D metabolism, which increase the production of parathyroid hormone. This leads to secondary hyperparathyroidism (see below) and **high bone turnover** disease.[1,3-5] This manifests as *osteitis fibrosa*,[1,3-5] a condition characterised by increased osteoclastic and osteoblastic activity, woven and irregular osteoid, and bone marrow fibrosis.[2-6] **Low bone turnover** disease includes *osteomalacia* (see above) and *adynamic bone disease*.[1-5] These are characterised by defective mineralisation, decreased bone formation, and an absence of osteoclasts and osteoblasts; osteoid seams are wider or increased in osteomalacia, but normal or decreased in adynamic bone disease.[1-4,9] Osteomalacia, associated with vitamin D deficiency or aluminium toxicity (which has adverse effects on bone, see p.1706), is decreasing in incidence with the removal of aluminium from dialysate solutions and decreasing use of aluminium-containing phosphate binders.[1-3,5,10] The pathogenesis of adynamic bone disease is not fully understood; its increasing incidence is thought to be due to suppression of parathyroid hormone secretion caused by increased exposure to calcium salts, as phosphate binders or in dialysate fluid, and vitamin D analogues.[1-6,9,10] Risk factors for its development include elderly age, diabetes mellitus, and peritoneal dialysis.[1-3,5,9] **Mixed uraemic osteodystrophy** has features of both high bone turnover with hyperparathyroidism, and defective bone mineralisation or osteomalacia.[1-6]

Patients with renal osteodystrophy may develop **osteopenia** or **osteoporosis**.[11]

Treatment is aimed at preventing bone disease by controlling the plasma concentrations of phosphate, calcium, parathyroid hormone, and correcting vitamin D deficiency; it should therefore be begun early in the course of renal impairment.[1,2,4,5]

- *Hyperphosphataemia* (p.1669) is initially controlled with a low-phosphate diet but many patients, especially those on dialysis, also need an oral phosphate binder to complex with dietary phosphate in the gastrointestinal tract and reduce its absorption.[1,4]

  Calcium salts such as the carbonate or acetate are effective phosphate binders and have been found to suppress parathyroid hormone concentrations.[1,2,4,12] Calcium citrate is not recommended, because it increases intestinal aluminium absorption.[3,4,12] Calcium salts also raise plasma-calcium concentrations but hypercalcaemia can occur.[4,9] The use of dialysis fluids with a lower calcium content has been suggested for these patients.[4] Use of calcium can also contribute to the development of adynamic bone disease[1,9] and precipitate exogenous calcium deposition in the soft tissues;[1,9,12] coronary artery calcification is a particular problem contributing to cardiac mortality in patients with chronic renal failure.[2-4,13] Hyperphosphataemia or use of vitamin D can exacerbate calcification.[4,12,13]

  Aluminium-based phosphate binders have been given but relatively large doses are required and, as mentioned above, aluminium accumulation can lead to osteomalacia and adynamic bone disease in patients with impaired renal function; their use is no longer generally recommended.[2,3,12] Magnesium carbonate also binds phosphate, but may cause hypermagnesaemia and interfere with bone mineralisation.[2] Dialysate magnesium content may need to be reduced.[4]

  Other phosphate binders that do not contain calcium or aluminium have been tried. Sevelamer is a cationic polymer capable of binding phosphate[2,3] without affecting serum calcium.[4] It has been shown to be equivalent to calcium-based binders,[2,3,12] and is effective in dialysis patients.[1] It has been reported to reduce calcium scores in the coronary artery when compared with calcium salts.[4] Lanthanum carbonate is a cation with a high affinity for phosphate and similar efficacy to calcium carbonate.[3] It has been used effectively in dialysis patients but long-term potential toxic effects are as yet undetermined.[4]

- Vitamin D compounds that do not require renal hydroxylation, such as calcitriol or its synthetic analogue, alfacalcidol, are used to correct *hypocalcaemia* and to contribute to the control of *secondary hyperparathyroidism*;[1,4] calcium supplements may also occasionally be required. Oversuppression of parathyroid hormone concentration should be avoided to deter the development of adynamic bone disease.[1] Calcitriol is given orally at first, but may also be given intravenously or intraperitoneally to patients on dialysis;[2,4-6] doses are adjusted according to response but the effect should be carefully monitored as hypercalcaemia and hyperphosphataemia may develop.[1,4,5] Use of alfacalcidol in the early stages of renal failure, before dialysis is required, has been reported to improve subclinical bone disease.[1] Newer vitamin D analogues suppress parathyroid activity but with potentially less effect on serum calcium and phosphate;[2-4,13] these include doxercalciferol, maxacalcitol, paricalcitol, and falecalcitriol (see Hyperparathyroidism, p.1989).

  Calcimimetics increase the sensitivity of the calcium-sensing receptor of the parathyroid cells.[3] Cinacalcet has reduced parathyroid hormone concentrations[2] without inducing hypercalcaemia or hyperphosphataemia[13] in dialysis patients.

  Patients with hyperparathyroidism unresponsive to drug therapy, or who develop hypercalcaemia (which may itself further aggravate the decline in renal function), may require sub-total or total parathyroidectomy.[2-4] There is a risk of inducing a low turnover bone state; hyperparathyroidism can also recur after surgery.[4] Bone mineral density improves after surgery.[2]

  Bisphosphonates can be used in the acute management of hypercalcaemia,[2] but seem to be of little use in the long-term treatment of hyperparathyroidism. They may be effective in increasing bone mineral density in haemodialysis patients.[3] Some, however, consider their use is unjustified, even in those with documented osteopenia or osteoporosis, and that they may exacerbate adynamic bone disease due to their effects on bone mineralisation.[11]

- *Adynamic bone disease* is treated by stimulating parathyroid hormone-driven bone turnover and mineralisation.[2,3] Calcium and vitamin D supplementation may need to be reduced or stopped, and dialysate calcium concentrations reduced.[2,9] Aluminium deposition needs to be excluded; the use of aluminium-based phosphate binders is clearly undesirable in these patients.[2,9] On bone biopsy, if aluminium accumulation is evident, chelation with desferrioxamine may be considered.[2,4]
- *Osteomalacia* may respond to vitamin D treatment.[2]
- Treatment of mixed uraemic osteodystrophy involves management of both hyperparathyroidism and mineralisation defects.[2]

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Rickets

See Osteomalacia and Rickets, above.

Parathyroid Disorders

Parathyroid hormone, secreted by the parathyroid gland, maintains concentrations of ionised calcium in extracellular fluid within normal limits. It acts directly on the kidney to enhance renal reabsorption of calcium, to increase phosphate excretion, and to promote the conversion of vitamin D to its active metabolite, 1,25-dihydroxycholecalciferol, which in turn, enhances calcium absorption from the gastrointestinal tract. Parathyroid hormone also acts on bone, to accelerate bone resorption and the release of calcium and phosphate into the extracellular fluid. Secretion of parathyroid hormone is primarily regulated by the extracellular concentration of ionised calcium; hypocalcaemia stimulates secretion whereas hypercalcaemia has an inhibitory effect. 1,25-Dihydroxycholecalciferol can also suppress parathyroid hormone secretion.

Disorders of parathyroid hormone secretion cause a disruption of calcium homoeostasis and in the long-term, may result in bone disease.

Hyperparathyroidism

Primary hyperparathyroidism is a disorder of parathyroid hormone hypersecretion usually caused by adenomas or hyperplasia of the parathyroid glands; parathyroid carcinoma is a rare cause.[1-4] Patients are often asymptomatic, or have non-specific constitutional symptoms such as fatigue, weakness, anorexia, or bone pain.[3-6] About 20% of patients present with nephrolithiasis, overt bone disease, or neuromuscular weakness.[5] Symptoms and signs of hypercalcaemia (p.1668) may occur;[3,5] hypercalcaemia is usually mild or even intermittent, and severe hypercalcaemia is rare.[7]

Secondary hyperparathyroidism is common in chronic renal failure (p.1672). Other causes of hypocalcaemia or vitamin D deficiency resulting in increased parathyroid hormone secretion include dietary deficiencies or malabsorption, or lack of exposure to sunlight.[1,3] While patients may also be asymptomatic, manifestations can include arthritis, bone pain, myopathy, tendon rupture, or complications such as coronary artery calcification and calciphylaxis; symptoms of the underlying cause can occur.[3]

Tertiary hyperparathyroidism results from autonomous hypersecretion by the parathyroid gland in patients with long-standing secondary hyperparathyroidism, and often occurs after kidney transplantation.[1,3]

Surgical parathyroidectomy is the treatment of choice for symptomatic primary hyperparathyroidism.[1-4,6,8] In patients with asymptomatic primary hyperparathyroidism, no treatment may be necessary, and patients are monitored for serum calcium, serum creatinine, and bone mineral density;[3,5,6,9] the timing of any surgical intervention has been subject to debate.[1,2,4]

In patients for whom surgery is not an option, hypercalcaemia must be controlled. Restriction of dietary calcium is not generally recommended, as this may raise parathyroid hormone levels further.[3,5,6,9,10] While vitamin D supplementation may be reasonable in patients with low concentrations of 1,25-dihydroxycholecalciferol, high doses can worsen hypercalcaemia and cause hypercalciuria.[5] Oral phosphate supplements have been given in the short-term to alleviate hypercalciuria and hypercalcaemia; intravenous use is no longer recommended.[9] The more potent bisphosphonates can be used in the acute management of hypercalcaemia,[9] but seem to be of little benefit in the long-term treatment of hyperparathyroidism.[1,9] However, bisphosphonates such as alendronate may be of use in those patients with low bone mineral density.[3,5,8-12] Although calcitonins have a rapid hypocalcaemic effect it is usually short-lived;[9] they are therefore generally given as adjunctive therapy with a bisphosphonate.[2] Oestrogens have been reported to increase bone mineral density in postmenopausal women with primary hyperparathyroidism, and to have a small effect on calcium concentrations;[5] however, the high doses needed, and the risks associated with HRT, generally preclude their use.[3,5,6] Raloxifene, a selective oestrogen receptor modulator, may be an alternative, having been found to decrease serum calcium and bone turnover in a small, short-term trial.[13] Calcium receptor agonists (calcimimetics) may be of benefit in primary hyperparathyroidism by increasing the sensitivity of the calcium-sensing receptor.[5,8-10] In a small dose-finding study,[14] cinacalcet decreased serum calcium and lowered parathyroid hormone concentrations without increasing urinary calcium excretion in all dose groups. A larger, placebo-controlled trial by the same group found that cinacalcet rapidly normalised serum calcium and modestly decreased parathyroid hormone concentrations; this effect was sustained over 52 weeks.[15] Use of parathyroid hormone peptides to induce autoantibodies against parathyroid hormone resulted in improvement in hypercalcaemia in a woman with parathyroid carcinoma.[16]

Treatment of secondary hyperparathyroidism is usually aimed at the underlying cause of the hypocalcaemia;[1] early treatment of patients with chronic renal failure can prevent or delay its onset. Treatment is based on appropriate vitamin D replacement and reduction of hyperphosphataemia.[1,3] Oral phosphate binders bind dietary phosphate in the gastrointestinal tract reducing its absorption.[1,3] These have included calcium salts such as the carbonate and acetate, which raise serum calcium but carry the risk of inducing hypercalcaemia. Aluminium hydroxide also binds phosphate, but can cause osteomalacia (p.1084) and adynamic bone disease (see Renal Osteodystrophy, above). Sevelamer is a polymer that does not contain calcium or aluminium, and is capable of binding phosphate.[3] Vitamin D compounds that do not require renal hydroxylation for activation, such as calcitriol or its analogue alfacalcidol, are used to lower parathyroid hormone, but the high doses required can induce hypercalcaemia and hyperphosphataemia;[3] newer analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol (see p.1989). Cinacalcet is also given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and on haemodialysis. In a placebo-controlled study,[17] cinacalcet lowered parathyroid hormone levels and reduced serum calcium and phosphate concentrations.

In patients refractory to medical therapy for secondary hyperparathyroidism, parathyroidectomy may be an option; percutaneous ethanol injection has been used as an alternative.[3,10] Kidney transplantation (p.1813) may cause regression of secondary hyperparathyroidism in some patients, but the condition recurs in about a third of renal graft recipients.[1] Tertiary hyperparathyroidism is usually treated with surgery.[1,3]

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12. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.
13. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 1174–8.
14. Shoback DM, *et al.* The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 5644–9.
15. Peacock M, *et al.* Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.
16. Bradwell AR, *et al.* Control of hypercalcaemia of parathyroid carcinoma by immunisation. *Lancet* 1999; **353:** 370–3.
17. Block GA, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; **350:** 1516–25.

Hypoparathyroidism

Hypoparathyroidism occurs when there is a deficiency of parathyroid hormone secretion. This may be due to damage or destruction of the glands, e.g. by surgery[1] or disease.[2] Hypoparathyroidism can also arise from auto-immune disease, agenesis of the parathyroid glands (DiGeorge syndrome), defective synthesis of parathyroid hormone (familial hypoparathyroidism), or mutations of the parathyroid and renal calcium-sensing receptors (autosomal dominant hypocalcaemic hypercalciuria) leading to defective regulation of parathyroid hormone secretion.[1,2] Other factors that may lead to a deficiency in parathyroid hormone include hypomagnesaemia and parathyroid adenomas. Where the deficiency results from resistance to parathyroid hormone the condition is termed **pseudohypoparathyroidism**.[1] Parathyroid hormone, as teriparatide, is used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism leads to hypocalcaemia and hyperphosphataemia,[1,3] although in some patients these may not become significant until there is an increased calcium demand, as in pregnancy. Vitamin D deficiency also develops.[1,3] Clinical features reflect the underlying cause of the hypoparathyroidism, but if it occurs rapidly, hypocalcaemia can be acute, with consequent paraesthesia, tetany, and seizures.[1] In chronic hypoparathyroidism, chronic hypocalcaemia may cause cataracts and visual impairment.[1] Hypomagnesaemia and metabolic alkalosis may also occur.[3]

Treatment is aimed at correcting the hypocalcaemia (p.1668) that results mainly from decreased renal tubular calcium resorption.[3] In patients with acute hypocalcaemic tetany parenteral doses of calcium salts, along with either oral or parenteral calcitriol, may be necessary.[1,3] In those with chronic hypocalcaemia treatment is usually with oral calcium, such as calcium carbonate (which has the advantage of binding phosphate), and vitamin D compounds such as calcitriol (which increase the intestinal absorption of calcium).[1,3] Calcium concentrations and renal function require careful monitoring as resultant hypercalcaemia can cause hypercalciuria, nephrolithiasis, and renal damage.[1] Thiazide diuretics may also minimise renal calcium losses.[3] Efficacy of treatment may vary depending on the underlying cause.[1,2]

Teriparatide has been shown to be effective in the treatment of chronic hypoparathyroidism. In 2 studies comparing it with calcium and calcitriol treatment,[4,5] teriparatide maintained serum calcium in the normal range, and decreased urine calcium excretion.

Parathyroid tissue transplantation is rarely possible as allografts require immunosuppression. Autografting may result in recurrence of pre-parathyroidectomy hyperparathyroidism.[1] However, good results have been reported after transplantation of parathyroid cells, depleted of antigen-bearing cells, in a few patients with postsurgical hypoparathyroidism.[6,7]

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6. Decker GAG, *et al.* Allotransplantation of parathyroid cells. *Lancet* 1995; **345:** 124. Correction. *ibid.*; 464.
7. Hasse C, *et al.* Parathyroid allotransplantation without immunosuppression. *Lancet* 1997; **350:** 1296–7.

Alendronate

ATC — M05BA04.
ATC Vet — QM05BA04.

Alendronic Acid *(BAN, rINN)*

Acide Alendronique; Ácido alendrónico; Acidum Alendronicum; AHButBP; Alendronihappo; Alendronik Asit; Alendronsyra; Aminohydroxybutylidene Diphosphonic Acid. 4-Amino-1-hydroxybutane-1,1-diylbis(phosphonic acid).

Алендроновая Кислота

$C_4H_{13}NO_7P_2$ = 249.1.
CAS — 66376-36-1.
ATC — M05BA04.
ATC Vet — QM05BA04.

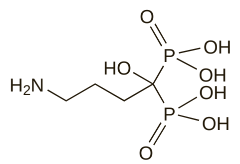

Alendronate Sodium *(USAN, rINNM)*

Alendronat Sodyum; Alendronate de Sodium; Alendronato sódico; G-704650; L-670452; MK-0217; MK-217; Monosodium alendronate; Natrii alendronas; Natrii Alendronas Trihydricus; Natrio alendronatas; Natriumalendronaatti; Natriumalendronat; Nátrium-alendronát; Nátrium-alendronát trihydrát; Sodium Alendronate *(BANM)*; Sodium, alendronate de. Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate trihydrate.

Натрий Алендронат

$C_4H_{12}NNaO_7P_2,3H_2O$ = 325.1.
CAS — 121268-17-5.
ATC — M05BA04.
ATC Vet — QM05BA04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Sodium Alendronate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dichloromethane; very slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0.

USP 31 (Alendronate Sodium). A white, free-flowing powder. Soluble in water; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in isopropyl alcohol; very slightly soluble in dimethyl sulfoxide, in methyl alcohol, and in propylene glycol.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Gastrointestinal symptoms such as abdominal pain, dyspepsia, diarrhoea or constipation are the most frequent adverse effects with alendronate. Severe oesophageal reactions such as oesophagitis, erosions, ulceration, and stricture have occurred (see below); patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as dysphagia, new or worsening heartburn, pain on swallowing, or retrosternal pain. Peptic ulceration has also been reported.

Alendronate should not be given to patients with abnormalities of the oesophagus or other factors that might delay oesophageal emptying, or those unable to stand or sit upright for at least 30 minutes. It should be used with caution in patients with upper gastrointestinal abnormalities. To minimise the risk of oesophageal reactions:

- patients should be instructed to swallow alendronate tablets whole with plenty of water (not less than 200 mL), in an upright position (standing or sitting). Mineral water with a high concentration of calcium should be avoided
- tablets should be taken on rising for the day, on an empty stomach, at least 30 minutes before breakfast and any other oral medication
- patients should remain upright after taking the tablets (the *BNF* recommends standing or sitting upright for at least 30 minutes), and should not lie down before eating the first meal of the day
- alendronate should not be taken at bedtime, or before getting up for the day

Hypocalcaemia should be corrected before starting alendronate therapy, and other disorders affecting mineral metabolism such as vitamin D deficiency or hypoparathyroidism should also be treated; serum calcium in these patients should be monitored during therapy.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including alendronate, see under Bisphosphonates, p.1090.

Effects on the heart. For a report of a possible association between alendronate and atrial fibrillation, see Effects on the Heart, under Bisphosphonates, p.1090.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including alendronate, see under Bisphosphonates, p.1091.

Effects on the liver. Hepatitis[1,2] and hepatocellular damage with raised liver enzyme concentrations[3,4] have been reported after therapy with alendronate.

1. Lieverse RJ. Hepatitis after alendronate. *Neth J Med* 1998; **53:** 271–2.
2. Carrère C, *et al.* Hépatite aiguë sévère imputable á l'alendronate. *Gastroenterol Clin Biol* 2002; **26:** 179–80.
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4. de la Serna Higuera C, *et al.* Lesión hepatocelular inducida por alendronato. *Gastroenterol Hepatol* 2001; **24:** 244–6.

Effects on mental state. Auditory hallucinations and red-coloured visual disturbances were reported[1] in a patient taking alendronate for osteoporosis.

1. Coleman CI, *et al.* Alendronate-induced auditory hallucinations and visual disturbances. *Pharmacotherapy* 2004; **24:** 799–802.

Effects on the musculoskeletal system. A 63-year old woman given alendronate 70 mg once weekly for osteoporosis developed diffuse severe myalgia and transient acute symmetrical polyarthritis 12 hours after ingestion. Symptoms did not recur after stopping the drug.[1] From the initial marketing of alendronate up until November 2002, the FDA had received reports of severe bone, joint, and/or muscle pain in 118 patients, including a child given the drug in error. Of 83 patients for whom information was available, 55 improved after stopping alendronate; in most of these improvement was gradual, although some experienced immediate relief. Nine of these 83 patients had recurrence of pain when given alendronate again. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[2] As of May 2006, 7 cases of synovitis linked to alendronate use had been reported in New Zealand; in one case, severe synovitis caused carpal tunnel syndrome that required urgent decompression.[3]

Concerns have been raised about potential oversuppression of bone turnover during long-term therapy with alendronate. In a report on 9 patients who developed spontaneous non-spinal fractures while taking alendronate, fracture healing was absent or incomplete in 6 patients who continued therapy for between 3 months and 2 years after fracture onset. When alendronate was stopped, fracture healing was still incomplete in 4 patients after 8 to 12 months. Use of estrogen (in 3 cases) or the presence of glucocorticoid-induced osteoporosis (in 2) may have contributed to the development of bone turnover suppression in some, but 4 patients had received alendronate as monotherapy; duration of therapy was also considered to be a factor as bone suppression might be cumulative.[4]

Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including alendronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

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2. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.
3. Savage R. Alendronate and inflammatory adverse reactions (issued May 2006). Available at: http://www.medsafe.govt.nz/profs/puarticles/alendinflam.htm#Myalgia (accessed 15/04/08)
4. Odvina CV, *et al.* Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005; **90:** 1294–1301.

Effects on the oesophagus. Between September 1995 and March 1996 the UK CSM had received 10 reports of adverse effects on the oesophagus in patients receiving alendronate sodium.[1] Of these, 4 were of oesophageal reflux, 4 of oesophagitis, and 2 of oesophageal ulceration. As of March 1996, worldwide an estimated 475 000 patients had received alendronate and 199 patients had oesophageal reactions reported to the manufacturer, of which 51 were serious or severe.[2] Endoscopic findings included erosions, ulcerations, exudative inflammation, and thickening of the oesophagus. Bleeding was rare, and oesophageal perforation was not reported. Most oesophageal reactions occurred within 1 week to 2 months of starting alendronate therapy. Recovery occurred when alendronate was stopped; however, it was considered important that patients be followed up for the possible development of strictures.[2] In about 60% of the cases where the information was available, alendronate had not been taken in accordance with the precautions for use (see above).

The CSM subsequently noted[3] that it had continued to receive reports of reactions; by July 1998 there had been 97 reports in the UK, in 1 case associated with a fatality. It was estimated that 1 to 2% of patients might experience oesophageal reactions even when following the precautions for use. Some have reported a much higher incidence of unacceptable upper gastrointestinal symptoms in clinical practice.[4] However, a large placebo-controlled trial of alendronate did not find any increase in upper gastrointestinal events in patients taking alendronate.[5]

1. Committee on Safety of Medicines/Medicines Control Agency. Oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1996; **22:** 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. de Groen PC, *et al.* Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; **335:** 1016–21.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: severe oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)
4. Kelly R, Taggart H. Incidence of gastrointestinal side effects due to alendronate is high in clinical practice. *BMJ* 1997; **315:** 1235.
5. Bauer DC, *et al.* Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med* 2000; **160:** 517–25.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare, see p.1091.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Like other bisphosphonates, alendronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is about 0.4% when taken half an hour before food, reduced from 0.7% in the fasting state; absorption is negligible when taken up to 2 hours after a meal. Plasma protein binding is about 78%. Bisphosphonates do not appear to be metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

◊ References.

1. Gertz BJ, *et al.* Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 1995; **58:** 288–98.
2. Cocquyt V, *et al.* Pharmacokinetics of intravenous alendronate. *J Clin Pharmacol* 1999; **39:** 385–93.
3. Porras AG, *et al.* Pharmacokinetics of alendronate. *Clin Pharmacokinet* 1999; **36:** 315–28.

Uses and Administration

Alendronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It is a potent inhibitor of bone resorption and is given in the management of osteoporosis either alone or with vitamin D. Alendronate is used for the treatment of Paget's disease of bone. It has also been given in the treatment of bone metastases and hypercalcaemia of malignancy.

Alendronate is given orally as the sodium salt, but doses are expressed in terms of alendronic acid; alendronate sodium 1.3 mg is equivalent to about 1 mg of alendronic acid. The specific instructions given in Adverse Effects and Precautions, above should be followed to minimise adverse effects and permit adequate absorption.

The usual dosage for the treatment of **osteoporosis** in men and women is 10 mg daily. Postmenopausal women may be given 5 mg daily for prophylaxis. It may also be given once weekly to postmenopausal women in a dose of 70 mg for treatment of osteoporosis, or 35 mg for prophylaxis. Men with osteoporosis may be treated with 70 mg once weekly.

For the treatment and prevention of corticosteroid-induced osteoporosis a dose of 5 mg daily is given; postmenopausal women who do not take HRT should be given 10 mg daily.

In adults with **Paget's disease** of bone the usual dose is 40 mg daily for 6 months; treatment may be repeated if necessary after an interval of a further 6 months.

Alendronate has also been given by intravenous infusion.

Administration. Alendronate once-weekly was considered to be therapeutically equivalent to once-daily dosing in both the treatment[1,2] and prevention[3] of osteoporosis, although the treatment study[1] was considered[4,5] to lack information about other drugs being taken and reasons for withdrawal, and studied bone mineral density, not fracture. Tolerability of a once-weekly regimen was comparable to placebo in one study[6] and to once-daily dosing in another;[7] a review[5] concluded that weekly dosage carried a lower risk of upper gastrointestinal symptoms.

1. Schnitzer T, *et al.* Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000; **12:** 1–12.
2. The Alendronate Once-Weekly Study Group. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002; **17:** 1988–96.
3. Luckey MM, *et al.* Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. *Obstet Gynecol* 2003; **101:** 711–21.
4. Tsun EC, Heck AM. Intermittent dosing of alendronate. *Ann Pharmacother* 2001; **35:** 1471–5.
5. Sambrook P. Once weekly alendronate. *Drugs Today* 2003; **39:** 339–46.
6. Greenspan S, *et al.* Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2002; **77:** 1044–52.
7. Simon JA, *et al.* Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002; **24:** 1871–86.

Administration in renal impairment. Elimination of alendronate is reduced in *rats* with kidney failure and is likely to be reduced in patients with renal impairment. Licensed product information makes the following recommendations for oral dosage based on creatinine clearance (CC):

- mild to moderate renal impairment (CC greater than 35 mL/minute): no dose adjustment needed
- severe renal impairment (CC less than 35 mL/minute): use is not recommended due to lack of experience with alendronate in this population

Charcot neuroarthropathy. Six months of treatment with once-weekly alendronate has been reported[1] to improve signs and symptoms of Charcot neuroarthropathy (a sometimes painful deformity in limbs that have lost sensory innervation).

1. Pitocco D, *et al.* Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial. *Diabetes Care* 2005; **28:** 1214–15.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous alendronate 7.5 mg daily for 3 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Adami S, *et al.* Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; **56:** 201–4.

Gaucher disease. In a placebo-controlled study of patients with Gaucher disease (p.2249), the addition of oral alendronate 40 mg daily to enzyme therapy increased lumbar bone mineral density, but had no effect on focal lesions;[1] the authors concluded that alendronate may be useful adjunctive therapy especially in those patients at risk of osteopenic fracture.

1. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; **104:** 1253–7.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. A randomised dose-response study[1] found that single intravenous doses of alendronate 5 mg or more effectively lowered serum-calcium concentrations in patients with tumour-induced hypercalcaemia. Alendronate has also been used to treat hypercalcaemia associated with vitamin D intoxication in children.[2,3]

1. Nussbaum SR, *et al.* Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. *J Clin Oncol* 1993; **11:** 1618–23.
2. Orbak Z, *et al.* Vitamin D intoxication and therapy with alendronate (case report and review of literature). *Eur J Pediatr* 2006; **165:** 583–4.
3. Doneray H, *et al.* Intragastric alendronate therapy in two infants with vitamin D intoxication: a new method. *Clin Toxicol* 2008; **46:** 300–2.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p.1087), but seem to be of little benefit for long-term treatment. In patients with primary hyperparathyroidism, oral alendronate significantly increased bone mineral density, especially at the lumbar spine; virtually all of this gain appeared to occur within the first year of treatment. Alendronate is considered to be useful in those patients for whom parathyroidectomy is not possible.[1-4]

1. Rossini M, *et al.* Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 113–19.
2. Parker CR, *et al.* Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 2002; **87:** 4482–9.
3. Chow CC, *et al.* Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 581–7.
4. Khan AA, *et al.* Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Alendronate significantly increases bone mineral density (BMD) of the lumbar spine and femoral neck in **postmenopausal women** with osteoporosis;[1,2] it increases vertebral BMD in postmenopausal women without osteoporosis, but not quite to the same extent as HRT.[1]

Continuous long-term therapy appears to be more effective than short-term treatment in terms of skeletal benefits,[1-4] but a residual effect on BMD remains for several years after stopping treatment,[3-5] despite resumption of bone loss after withdrawal of alendronate.[4-6] Studies[7,8] in early postmenopausal women suggested that a *higher initial dosage* might be more effective in terms of BMD gain and residual effect.

The effect of alendronate on fracture risk may depend on *baseline bone mineral density*.[2] Treatment reduced the incidence of new vertebral and nonvertebral fractures in women with prior fractures; in women without prior fractures, alendronate reduced the incidence of clinical fractures in those with osteoporosis,[9] but not in those with higher BMD.[10] A systematic review[11] found that alendronate showed a clinically important benefit in the secondary prevention of all osteoporotic fractures; statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were seen. No significant reductions were found for primary prevention of osteoporotic fractures, but the reduction in vertebral fractures with alendronate was deemed to be clinically important.

Alendronate is also used in **men** with osteoporosis; in a 2-year randomised study, 10 mg daily by mouth was found to increase vertebral and nonvertebral BMD and help prevent vertebral fractures.[12] Alendronate at 70 mg weekly by mouth also increased BMD significantly in osteoporotic men after 1 year when compared to placebo; fracture incidence, not a primary end-point, was similar in both groups.[13]

Alendronate also increases bone mass density in men and women receiving oral **corticosteroids** at doses equivalent to at least 7.5 mg prednisone daily,[14,15] and may be of some benefit in reducing bone loss after heart[16] and liver[17] **transplantation**.

In men with prostate cancer given androgen deprivation therapy, BMD of the spine and hip significantly improved in those given once-weekly alendronate compared with those given calcium and vitamin D supplementation alone.[18]

Limited available data suggest that alendronate may be safe and effective for patients with HIV who have decreased BMD.[19]

1. Sharpe M, *et al.* Alendronate: an update of its use in osteoporosis. *Drugs* 2001; **61:** 999–1039.
2. Pérez-López FR. Postmenopausal osteoporosis and alendronate. *Maturitas* 2004; **48:** 179–92.
3. Tonino RP, *et al.* Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000; **85:** 3109–15.
4. Bone HG, *et al.* Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; **350:** 1189–99.
5. Black DM, *et al.* FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; **296:** 2927–38.
6. Ravn P, *et al.* Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab* 2000; **85:** 1492–7.
7. Sambrook PN, *et al.* Alendronate in the prevention of osteoporosis: 7-year follow-up. *Osteoporosis Int* 2004; **15:** 483–8.
8. McClung MR, *et al.* Early Postmenopausal Intervention Cohort (EPIC) Group Study. Prevention of postmenopausal bone loss: six-year results from the Early Postmenopausal Intervention Cohort Study. *J Clin Endocrinol Metab* 2004; **89:** 4879–85.
9. Black DM, *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. *J Clin Endocrinol Metab* 2000; **85:** 4118–24.
10. Cummings SR, *et al.* Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; **280:** 2077–82.
11. Wells GA, *et al.* Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
12. Orwoll E, *et al.* Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000; **343:** 604–10.
13. Miller PD, *et al.* Weekly oral alendronic acid in male osteoporosis. *Clin Drug Invest* 2004; **24:** 333–41.
14. Saag KG, *et al.* Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998; **339:** 292–9.
15. de Nijs RNJ, *et al.* STOP Investigators. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. *N Engl J Med* 2006; **355:** 675–84.
16. Shane E, *et al.* Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. *N Engl J Med* 2004; **350:** 767–76.
17. Atamaz F, *et al.* The prevention of bone fractures after liver transplantation: experience with alendronate treatment. *Transplant Proc* 2006; **38:** 1448–52.
18. Greenspan SL, *et al.* Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. *Ann Intern Med* 2007; **146:** 416–24.
19. Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 15/04/08).

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Alendronate, at oral doses of 40 mg daily for 6 months, has been shown to be more effective than both etidronate and placebo in the treatment of Paget's disease,[1] although an earlier study[2] found a more sustained reduction in biochemical markers with an oral dose of 80 mg daily.

1. Reid IR, Siris E. Alendronate in the treatment of Paget's disease of bone. *Int J Clin Pract* 1999; **101** (suppl): 62–6.
2. Khan SA, *et al.* Alendronate in the treatment of Paget's disease of bone. *Bone* 1997; **20:** 263–71.

Polymyositis and dermatomyositis. Alendronate has been reported to be effective in the treatment of calcinosis[1] associated with juvenile dermatomyositis (p.1510).

1. Mukamel M, *et al.* New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. *J Pediatr* 2001; **138:** 763–6.

Preparations

USP 31: Alendronate Sodium Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Actimax; Alenato; Arendal; Berlex; Brek; Dronat; Elandur†; Filxine; Findeclin; Findeclin Combi; Fosamax; Lafedam†; Lendronal; Marvil; Maxtral†; Oseotenk; Osteobon; Osteofene; Osteonate; Phostarac†; Regenesis; Silidral; Tilios; ***Austral.:*** Adronat; Alendro; Fosamax; Ossmax; ***Austria:*** AlendronHexal; Fosamax; ***Belg.:*** Fosamax; ***Braz.:*** Alendil; Bonalen; Cleveron; Endronax; Fosamax; Minusorb†; Ossomax†; Ostenan; Osteofar; Osteoform; Osteoral; Osteotrat†; Recalfe†; Terost; ***Canad.:*** Fosamax; ***Chile:*** Aldrox; Arendal; Fosamax; Fosval; Holadren; Leodrin; Osdren; Oseotal; Osteofem†; Osteosan; Pasodron; ***Cz.:*** Alendrogen; Alenwin; Bonalen; Fosamax; Fosteofos; Gendron; Lindron; Ralenost; Siranin; ***Denm.:*** Fosamax; ***Fin.:*** Fosamax; ***Fr.:*** Fosamax; ***Ger.:*** Alendro-Q; Fosamax; Tevanate; ***Gr.:*** Aldromax; Alefos; Alendo; Alendral; Ampine; Aurodren; Bestalen; Bonedron; Caltera; Dargol; Debenal; Deparex; Difonate; Discozal; Dronalent; Fosalen; Fosamax; Fosazom; Jamax-S; Osaston; Ostalert; Ostomax; Promax; Ridon; Riledron; Tevanate; Tivarun; ***Hong Kong:*** Fosamax; Osteofos; ***Hung.:*** Alendromax; Alendron; Epolar; Fortimax; Fosamax; Massidron; Sedron; Trabecan; ***India:*** Bifosa; Osteofos; ***Indon.:*** Alexonal; Alovell; Fosamax; Nichospor; Osteofar; Voroste; ***Irl.:*** Fosamax; Osteomel; ***Israel:*** Fosalan; Maxibone; ***Ital.:*** Adronat; Alendros; Dronal; Fosamax; Genalen; ***Jpn:*** Bonalon; Onclast†; ***Malaysia:*** Fosamax; ***Mex.:*** Apodrolen; Blindafe; Dronadil; Drovitan; Fosamax; Fosfacid; Landrolen; Sinfract; Synostep; Zondra; ***Neth.:*** Fosamax; ***Norw.:*** Fosamax; ***NZ:*** Fosamax; ***Philipp.:*** Fosamax; ***Pol.:*** Alenato; Fosamax; Lindron; Osalen; Ostemax; Ostenil; Ostolek; Rekostin; ***Port.:*** Adronat; Fosamax; ***Rus.:*** Fosamax (Фосамакс); Tevanate (Теванат); ***S.Afr.:*** Fosagen; Fosamax; Osteobon; ***Singapore:*** Fosamax; ***Spain:*** Fosamax; ***Swed.:*** Alenat; Fosamax; ***Switz.:*** Fosamax; ***Thai.:*** Fosamax; ***Turk.:*** Andante; Bonemax; Fosamax; Osteomax; ***UK:*** Fosamax; ***USA:*** Fosamax; ***Venez.:*** Aldronac; Aliot; Defixal; Denfos†; Fixopan; Fosamax; Genalmen†; Osteodur; Osteomax; Porosal.

Multi-ingredient: ***Arg.:*** Fosamax Plus; Regenesis Max; Silidral Plus; ***Austral.:*** Fosamax Plus; ***Belg.:*** Fosavance; ***Braz.:*** Alendil Calcio D; ***Cz.:*** Adrovance; Fosavance; ***Fin.:*** Fosavance; ***Fr.:*** Adrovance; Fosavance; ***Ger.:*** Fosavance; ***Gr.:*** Adrovance; Fosavance; ***Hong Kong:*** Fosamax Plus; ***Hung.:*** Calcisedron-D; Fosavance; ***Indon.:*** Fosamax Plus; ***Irl.:*** Fosavance; ***Ital.:*** Fosavance; ***Malaysia:*** Fosamax Plus; ***Mex.:*** Fosamax Plus; ***NZ:*** Fosamax Plus; ***Philipp.:*** Fosavance; ***Port.:*** Fosavance; ***Singapore:*** Fosamax Plus; ***Spain:*** Fosavance; ***UK:*** Fosavance; ***USA:*** Fosamax Plus.

Bisphosphonates

Bifosfonatos; Biphosphonates; Diphosphonates.

Bisphosphonates are analogues of pyrophosphate, in which the central oxygen atom is replaced by a carbon atom with two further substituents—see Figure 1, p.1090. Like pyrophosphate they have a strong affinity for bone. The bisphosphonates are used chiefly for their antiresorptive and hypocalcaemic properties (see Uses and Administration, below).

Adverse Effects, Treatment, and Precautions

Bisphosphonates may cause gastrointestinal disturbances including abdominal pain, nausea and vomiting, and diarrhoea or constipation. Peptic ulceration has been reported. Existing gastrointestinal problems may be exacerbated, and oral bisphosphonates should generally be given with care or avoided if acute upper gastrointestinal inflammation is present. Gastrointestinal disturbances may be more frequent with aminobisphosphonates such as alendronate, ibandronate, and risedronate; oesophagitis has also occurred. General

The symbol † denotes a preparation no longer actively marketed

Figure 1. Comparative structures of the bisphosphonates.

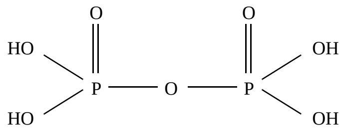

Pyrophosphate

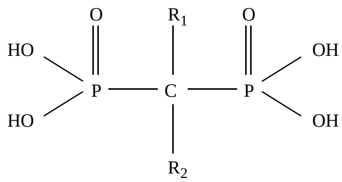

Generic structure of a bisphosphonate

R_1	R_2	Name
$C_3H_6.NH_2$	OH	Alendronic Acid
Cl	Cl	Clodronic Acid
CH_3	OH	Etidronic Acid
$C_2H_4.NCH_3.C_5H_{11}$	OH	Ibandronic Acid
$C_7H_{13}.NH$	H	Incadronic Acid
H	H	Medronic Acid
$CH_2.C_7H_5N_2$	OH	Minodronic Acid
$C_5H_{10}.NH_2$	OH	Neridronic Acid
$C_2H_4.N(CH_3)_2$	OH	Olpadronic Acid
H	OH	Oxidronic Acid
$C_2H_4.NH_2$	OH	Pamidronic Acid
$CH_2.C_5H_4N$	OH	Risedronic Acid
$S.C_6H_4Cl$	H	Tiludronic Acid
$CH_2.C_3H_3N_2$	OH	Zoledronic Acid

precautions to minimise the risk of oesophageal reactions, (see under Alendronate, p.1088) should be observed.

Disturbances in serum electrolytes may occur, most commonly hypocalcaemia and hypophosphataemia. Existing hypocalcaemia or other disturbances of bone and mineral metabolism should be effectively treated before starting bisphosphonate therapy. Adequate intake of calcium and vitamin D is important, and supplementation may be needed if dietary intake is insufficient. Bisphosphonates may cause musculoskeletal pain (which can be severe and incapacitating), osteonecrosis of the jaw (see also Dental Care, below), ocular disturbances, and headache. Hypersensitivity reactions have occurred rarely; angioedema, rashes, urticaria, and pruritus have been reported. Other rare adverse effects include blood disorders such as anaemia, thrombocytopenia, leucopenia and disturbances in liver enzyme values.

Transient fever and flu-like symptoms have been reported, usually at the start of treatment, and are common with infusions of ibandronate, pamidronate, and zoledronate. There may be local reactions, including thrombophlebitis, after parenteral doses. Dizziness, vertigo, asthenia, peripheral oedema, paraesthesia, taste disturbances, and joint disorders have also occurred.

Impairment of renal function has been reported with bisphosphonates, particularly when given parenterally. As a result their use should generally be avoided in patients with moderate to severe renal impairment and they should be used with care in those with lesser degrees of renal impairment.

Etidronate interferes with bone mineralisation, especially at higher doses, which can result in osteomalacia and an increased incidence of fracture. Etidronate should be stopped if a fracture occurs, until healing is complete. It has also been associated with a flare in bone pain in some patients with Paget's disease. Impaired mineralisation is much less marked at usual doses of other bisphosphonates.

Overdosage with bisphosphonates would be likely to result in symptoms of hypocalcaemia; if necessary, parenteral infusion of a calcium salt could be given. Giving milk or antacids, to bind the bisphosphonate and minimise absorption, has been suggested for oral overdosage.

There is little clinical experience with bisphosphonates in pregnancy and they are generally contra-indicated; bisphosphonates have been associated with skeletal abnormalities in the fetus when given to pregnant *animals.*

◊ Reviews.

1. Adami S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. *Drug Safety* 1996; **14:** 158–70.
2. Body J-J. Dosing regimens and main adverse events of bisphosphonates. *Semin Oncol* 2001; **28** (suppl): 49–53.
3. Kherani RB, *et al.* Long-term tolerability of the bisphosphonates in postmenopausal osteoporosis: a comparative review. *Drug Safety* 2002; **25:** 781–90.
4. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; **17:** 897–907.
5. Bobba RS, *et al.* Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. *Drug Safety* 2006; **29:** 1133–52.
6. Strampel W, *et al.* Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Safety* 2007; **30:** 755–63.

Dental care. Osteonecrosis of the jaw has been reported in patients given bisphosphonates (see Effects on the Musculoskeletal System, below). Of the published cases most were associated with intravenous therapy in cancer patients, although some have followed oral therapy in patients with osteoporosis. In many cases the effect followed dental surgery. The Adverse Drug Reactions Advisory Committee in Australia has recommended that all patients scheduled to receive intravenous bisphosphonates should have a dental review,[1] and that any dental procedures be completed before beginning the drug.[1,2] Furthermore, health professionals should be aware of the presenting clinical features of osteonecrosis.[2] In the UK, the Commission on Human Medicines has recommended that a dental review should be considered before bisphosphonate treatment in patients with risk factors such as cancer, chemotherapy, corticosteroid therapy, or poor oral hygiene.[3] Licensed information for some bisphosphonates has been amended in a number of countries to include similar warnings.[4]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and osteonecrosis of the jaw. *Aust Adverse Drug React Bull* 2005; **24:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.pdf (accessed 30/11/06)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; **25:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 30/11/06)
3. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Osteonecrosis of the jaw with bisphosphonates. *Current Problems* 2006; **31:** 4–5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
4. Tarassoff P, Hei Y-J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 101–102. Correction. *ibid.*; 2728.

Effects on the ears. For mention of ototoxicity associated with the use of etidronate in 2 patients with pre-existing otosclerosis, and a recommendation that such patients be monitored when given bisphosphonates, see p.1097. For similar effects with pamidronate, see p.1101.

Effects on the eyes. Ocular effects have been associated with bisphosphonates and although reactions to pamidronate appeared to be rare, the manufacturers were aware of 23 cases up to September 1993 that were possibly associated with the drug.[1] The reactions included anterior uveitis in 7 patients and unilateral episcleritis or scleritis in 3. In one previously reported case,[2] bilateral iritis was associated with risedronate and subsequently pamidronate in a patient who had earlier received etidronate without ill-effect. There have been subsequent reports of unilateral and bilateral scleritis with pamidronate, requiring the drug to be stopped.[3] Anterior[3,4] and posterior[5] uveitis have continued to be reported, and more recently, diplopia with conjunctival swelling and eyelid oedema.[6,7] Similarly, alendronate[8-11] and zoledronate[12] have been associated with scleritis and anterior uveitis. Scleritis,[13] episcleritis,[14] and uveitis[15] have also been reported with risedronate, and bilateral anterior uveitis with clodronate.[16] Non-specific conjunctivitis and abnormal or blurred vision have occurred with most of the bisphosphonates, including etidronate.[13] Dry eye, sore eye, and conjunctivitis were the most frequently reported ophthalmological events assessed as related to risedronate therapy in a prescription-event monitoring study in England.[17] The Australian Adverse Drug Reactions Advisory Committee was aware of 38 reports of serious ocular reactions to bisphosphonates as of April 2004; these were associated with pamidronate or alendronate in 18 cases each, and risedronate or zoledronate in 1 case each.[15] Most reports were of inflammatory reactions such as uveitis, iritis, scleritis, episcleritis, or optic neuritis, and occurred a median of 3 weeks after starting therapy. The risk might be higher with intravenous bisphosphonates, but the frequency of reports was thought to relate mostly to usage.[15] Acute retinal pigment epitheliitis has been reported after an intravenous infusion of zoledronate.[18] Patients who have ocular pain or vision loss while taking bisphosphonates should have the drug stopped and be referred to an ophthalmologist.[13]

1. Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994; **118:** 220–4.
2. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; **341:** 436–7.
3. Fraunfelder FW, *et al.* Scleritis and other ocular side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003; **135:** 219–22.
4. Rey J, *et al.* Uveitis, an under-recognized adverse effect of pamidronate: case report and literature review. *Joint Bone Spine* 2000; **67:** 337–40.
5. Haverbeke G, *et al.* Posterior uveitis: an under-recognized adverse effect of pamidronate: 2 case reports. *Bull Soc Belge Ophtalmol* 2003; **290:** 71–6.
6. Meaney TPJ, *et al.* Diplopia following intravenous administration of pamidronate. *Eye* 2004; **18:** 103–4.
7. Ryan PJ, Sampath R. Idiopathic orbital inflammation following intravenous pamidronate. *Rheumatology (Oxford)* 2001; **40:** 956–7.
8. Mbekeani JN, *et al.* Ocular inflammation associated with alendronate therapy. *Arch Ophthalmol* 1999; **117:** 837–8.
9. Malik AR, *et al.* Bilateral acute anterior uveitis after alendronate. *Br J Ophthalmol* 2002; **86:** 1443.
10. Salmen S, *et al.* Nongranulomatous anterior uveitis associated with alendronate therapy. *Invest Clin* 2002; **43:** 49–52.
11. Asensio Sánchez VM, *et al.* Bifosfonatos e inflamación intraocular. *Arch Soc Esp Oftalmol* 2004; **79:** 85–8.
12. Moore MM, Beith JM. Acute unilateral anterior uveitis and scleritis following a single infusion of zoledronate for metastatic breast cancer. *Med J Aust* 2008; **188:** 370–1.
13. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003; **348:** 1187–8.
14. Viñas G, *et al.* Epiescleritis secundaria a risedronato. *Med Clin (Barc)* 2002; **118:** 598–9.
15. Adverse Drug Reactions Advisory Committee (ADRAC). Bisphosphonates and ocular inflammation. *Aust Adverse Drug React Bull* 2004; **23:** 7–8. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0404.htm (accessed 22/02/05)
16. Fietta P, *et al.* Clodronate induced uveitis. *Ann Rheum Dis* 2003; **62:** 378.
17. Aurich-Barrera B, *et al.* Ophthalmological events in patients receiving risedronate: summary of information gained through follow-up in a prescription-event monitoring study in England. *Drug Safety* 2006; **29:** 151–60.
18. Gilhotra JS, *et al.* Acute retinal pigment epitheliitis associated with intravenous bisphosphonate. *Br J Ophthalmol* 2006; **90:** 798–9.

Effects on the heart. In a study of once-yearly zoledronate for the treatment of postmenopausal osteoporosis, the number of patients who had arrhythmia in the zoledronate group was significantly higher than that in the placebo group.[1] An increased incidence of serious atrial fibrillation was also seen in the zoledronate group. Fifty patients in the zoledronate group had serious atrial fibrillation, compared with 20 patients in the placebo group. Among the 50 patients, the events occurred more than 30 days after infusion in 47 patients, by which time zoledronate would be undetectable in the circulation. The mechanism by which bisphosphonates might cause arrhythmia or atrial fibrillation is unclear; little or no effect on serum calcium concentrations was seen when measured 9 to 11 days after zoledronate infusion. In an analysis[2] of a randomised study of alendronate in postmenopausal women with osteoporosis, 47 serious atrial fibrillation adverse events were reported in the alendronate group, compared with 31 events among those receiving placebo. There was no increased risk of all atrial fibrillation adverse events.

Although the observed association might have been due to chance,[1] it was felt that the possibility of an increased risk of atrial fibrillation with bisphosphonates should be explored.[2] Two case-control studies examining the association[3,4] came to opposite conclusions as to whether bisphosphonate treatment increased the risk of atrial fibrillation. In the UK, the MHRA stated in July 2008 that any risk appeared low and the balance of risk and benefit for bisphosphonates remained favourable.[5] The FDA in the USA, which came to similar preliminary conclusions, was said to be seeking additional data for a more detailed analysis.

1. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
2. Cummings SR, *et al.* Alendronate and atrial fibrillation. *N Engl J Med* 2007; **356:** 1895–6.
3. Heckbert SR, *et al.* Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med* 2008; **168:** 826–31.
4. Sørensen HT, *et al.* Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ* 2008; **336:** 813–16.
5. MHRA/CHM. Bisphosphonates: atrial fibrillation. *Drug Safety Update* 2008; **1** (12): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 16/07/08)

Effects on the kidneys. Renal failure was associated with the intravenous use of etidronate in 2 patients with hypercalcaemia of malignancy.[1] One had been given a high dose (1 g) by short intravenous infusion on two successive days and the other had an elevated serum-creatinine concentration before treatment. A third patient given clodronate, who also developed renal failure, also had a slightly raised serum-creatinine concentration beforehand. Others[2] commented that with smaller doses of etidronate or clodronate (up to 300 mg daily) by intravenous infusion over 2 to 3 hours, renal impairment had not been seen in more than 40 patients treated. They noted a trend towards raised creatinine concentrations which was reversed when etidronate infusions were stopped. Another group[3] found increased serum-creatinine concentrations after the first infusion of etidronate when compared with placebo, but not after subsequent infusions. An overdose of parenteral etidronate led to acute renal failure in one patient.[4] Pamidronate has been associated with nephrotoxicity,[5] proteinuria,[6] acute tubular necrosis,[7,8] and collapsing focal segmental glomerulosclerosis.[9] Over a period of 2 years, 72 cases of renal failure associated with intravenous zoledronate were reported to the FDA.[10] Of 7 cases reported over the course of 3.5 years in France, 3 patients recovered completely, and 1 partially, after stopping zoledronate. Two fatalities were reported, but comorbidities prohibited a direct causal link to zoledronate; the outcome in the remaining case was unknown.[11] Six cases of acute tubular necrosis have been reported with zoledronate;[12] all patients had received pamidronate on previous occasions, and most had mildly raised baseline serum creatinine. While pamidronate may have potentiated the renal toxicity seen with zoledronate, the authors noted that the patterns of nephrotoxicity differ between the 2 drugs. Reports to the Australian Adverse Drug Reactions Advisory Committee have suggested that renal failure or renal impairment may occur more often with zoledronate than with other bisphosphonates. While the deterioration in renal function with zoledronate was acute, in many cases it appeared to be unrelated to the infusion rate; patients may also have been predisposed to renal impairment.[13] There has also been a report of acute renal failure with alendronate treatment in a patient with myeloma,[14] and with tiludronate in a patient treated for hypercalcaemia of malignancy.[15]

1. Bounameaux HM, *et al.* Renal failure associated with intravenous diphosphonates. *Lancet* 1983; **i:** 471.
2. Kanis JA, *et al.* Effects of intravenous diphosphonates on renal function. *Lancet* 1983; **i:** 1328.
3. Hasling C, *et al.* Etidronate disodium for treating hypercalcaemia of malignancy: a double blind placebo-controlled study. *Eur J Clin Invest* 1986; **16:** 433–7.
4. O'Sullivan TL, *et al.* Acute renal failure associated with the administration of parenteral etidronate. *Ren Fail* 1994; **16:** 767–73.
5. Lockridge L, *et al.* Pamidronate-associated nephrotoxicity in a patient with Langerhans' histiocytosis. *Am J Kidney Dis* 2002; **40:** E2.
6. Desikan R, *et al.* Nephrotic proteinuria associated with high-dose pamidronate in multiple myeloma. *Br J Haematol* 2002; **119:** 496–9.
7. Banerjee D, *et al.* Short-term, high-dose pamidronate-induced acute tubular necrosis: the postulated mechanisms of bisphosphonate nephrotoxicity. *Am J Kidney Dis* 2003; **41:** E18.
8. Smetana S, *et al.* Pamidronate-induced nephrotoxic tubular necrosis—a case report. *Clin Nephrol* 2004; **61:** 63–7.
9. Markowitz GS, *et al.* Nephrotic syndrome after treatment with pamidronate. *Am J Kidney Dis* 2002; **39:** 1118–22.
10. Chang JT, *et al.* Renal failure with the use of zoledronic acid. *N Engl J Med* 2003; **349:** 1676–8.
11. Munier A, *et al.* Zoledronic acid and renal toxicity: data from French Adverse Effect Reporting Database. *Ann Pharmacother* 2005; **39:** 1194–7.
12. Markowitz GS, *et al.* Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003; **64:** 281–9.
13. Adverse Drug Reactions Advisory Committee (ADRAC). Renal impairment with zoledronic acid. *Aust Adverse Drug React Bull* 2007; **26:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.htm (accessed 06/11/07)
14. Zazgornik J, *et al.* Acute renal failure and alendronate. *Nephrol Dial Transplant* 1997; **12:** 2797–8.
15. Dumon JC, *et al.* Efficacy and safety of the bisphosphonate tiludronate for the treatment of tumor-associated hypercalcemia. *Bone Miner* 1991; **15:** 257–66.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported with the use of some bisphosphonates.[1-8] The majority of reports have been in cancer patients treated with intravenous bisphosphonates who were also receiving chemotherapy and corticosteroids. However, osteonecrosis has also been reported in patients receiving oral bisphosphonates for osteoporosis or Paget's disease. Most cases have been associated with dental procedures such as tooth extraction, and many patients had local infection including osteomyelitis.[6,7,9,10] Presenting features may include altered local sensation, maxillofacial pain, toothache, denture sore spots, loose teeth, exposed bone or impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour.[7] A history of underlying dental problems, such as infection, dental extraction, or maxillofacial surgery may exacerbate the problem.[1] Other predisposing factors include oral trauma, periodontitis, and poor dental hygiene.[11] For recommendations on dental care in patients prescribed intravenous bisphosphonates see above.

Length of exposure was found to correlate with development of osteonecrosis,[9,12,13] although some cases have occurred only a few months after bisphosphonate use.[9] There is also some evidence for a dose-response relationship.[8] Furthermore, the type of bisphosphonate used may affect the risk; intravenous use of bisphosphonates containing an aminoterminal group of a nitrogen-containing side-chain appear to present the highest risk,[9] and there is some suggestion that the risk may be higher with zoledronate than with pamidronate.[1,12] The incidence appears to be higher in patients with multiple myeloma,[1,9,12] and elderly myeloma patients may be at increased risk.[9,13]

The mechanism by which bisphosphonates induce osteonecrosis has not been fully elucidated. Avascular necrosis of the hip has been reported; it is possible that osteonecrosis may be a systemic bone disease with initial manifestation in the jaw.[13] A case of osteonecrosis of the auditory canal has been reported;[14] the patient had concurrent osteonecrosis of the jaw.

No effective treatment is known and there is no consensus on management. Stopping bisphosphonate therapy does not necessarily promote healing of the necrotic process;[8,9,13] recovery of normal osteoclast function and bone turnover may be too gradual for this measure to have clinical significance.[10] However, there have been anecdotal reports of healing and complete resolution of lesions several months after cessation of therapy.[10] Treatment is directed towards control of pain and infection and careful local debridement of necrotic bone, but not wide excision of lesions.[8,10]

1. Durie BGM, *et al.* Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 99–100.
2. Migliorati CA. Bisphosphanates [sic] and oral cavity avascular bone necrosis. *J Clin Oncol* 2003; **21:** 4253–4.
3. Ruggiero SL, *et al.* Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; **62:** 527–34.
4. Carter G, *et al.* Bisphosphonates and avascular necrosis of the jaw: a possible association. *Med J Aust* 2005; **182:** 413–15.
5. Gibbs SDJ, *et al.* Bisphosphonate-induced osteonecrosis of the jaw requires early detection and intervention. *Med J Aust* 2005; **183:** 549–50.
6. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Osteonecrosis of the jaw with bisphosphonates. *Current Problems* 2006; **31:** 4–5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Osteonecrosis of the jaw (ONJ) with bisphosphonates. *Aust Adverse Drug React Bull* 2006; **25:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0608.pdf (accessed 28/11/06)
8. Krueger CD, *et al.* Bisphosphonate-induced osteonecrosis of the jaw. *Ann Pharmacother* 2007; **41:** 276–84.
9. Migliorati CA, *et al.* Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006; **7:** 508–14.
10. Woo S-B, *et al.* Narrative review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; **144:** 753–61. Correction. *ibid.*; **145:** 235. [title]
11. Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? *N Engl J Med* 2006; **355:** 2278–81.
12. Bamias A, *et al.* Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005; **23:** 8580–7.
13. Badros A, *et al.* Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 2006; **24:** 945–52.
14. Polizzotto MN, *et al.* Bisphosphonate-associated osteonecrosis of the auditory canal. *Br J Haematol* 2006; **132:** 114.

Effects on the respiratory system. Bronchospasm induced by bisphosphonates has been reported in 2 patients who were aspirin-sensitive asthmatics. The first patient complained of shortness of breath and wheezing 10 minutes after the start of an infusion of clodronate while the second developed similar symptoms 2 days after the start of cyclical therapy with etidronate by mouth. Oral rechallenge in both patients resulted in a fall in the forced expiratory values at 1 second.[1] The reaction in these 2 patients was not considered to be immune-mediated. Risedronate reportedly induced bronchiolitis obliterans organising pneumonia in a patient with sarcoidosis.[2]

For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, under Etidronate, p.1097.

1. Rolla G, *et al.* Bisphosphonate-induced bronchoconstriction in aspirin-sensitive asthma. *Lancet* 1994; **343:** 426–7.
2. Arai T, *et al.* Risedronate induced BOOP complicated with sarcoidosis. *Thorax* 2005; **60:** 613–14.

Hypersensitivity. Bisphosphonates may rarely cause hypersensitivity reactions such as angioedema, urticaria, and pruritus. Reports include a severe allergic reaction to medronate disodium when given as a radiopharmaceutical,[1] and mild skin rashes in 2 patients given oral pamidronate.[2] There has also been a report of erythroderma with lesions of the mucous membranes associated with use of clodronate in one patient,[3] and severe epidermal necrosis may have been associated with tiludronate in another.[4] A possibly drug-related rash has also been reported in a patient receiving alendronate.[5] Other cutaneous reactions reported with alendronate include urticaria,[6] erythematous papules and petechiae,[7] gyrate erythema,[8] and drug-induced lichen planus;[9] licensed product information states that Stevens-Johnson syndrome has been reported. Two patients with cutaneous reactions to pamidronate or clodronate were able to continue oral clodronate after desensitisation.[10] Licensed product information states that zoledronate has been associated with rare reports of hypersensitivity, including angioedema and bronchoconstriction, and very rarely, with anaphylaxis.

1. Elliott AT, *et al.* Severe reaction to diphosphonate: implications for treatment of Paget's disease. *BMJ* 1988; **297:** 592–3.
2. Mautalen CA, *et al.* Side effects of disodium aminohydroxypropylidenediphosphonate (APD) during treatment of bone diseases. *BMJ* 1984; **288:** 828–9.
3. Pajus I, *et al.* Erythroderma after clodronate treatment. *BMJ* 1993; **307:** 484.
4. Roux C, *et al.* Long-lasting dermatological lesions after tiludronate therapy. *Calcif Tissue Int* 1992; **50:** 378–80.
5. Chesnut CH, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995; **99:** 144–52.
6. Kontoleon P, *et al.* Urticaria after administration of alendronate. *Acta Derm Venereol* 2000; **80:** 398.
7. Kimura M, *et al.* Drug eruption due to alendronate sodium hydrate. *Contact Dermatitis* 2003; **48:** 116.
8. High WA, *et al.* Superficial gyrate erythema as a cutaneous reaction to alendronate for osteoporosis. *J Am Acad Dermatol* 2003; **48:** 945–6.
9. Lazarov A, *et al.* Alendronate-induced lichen planus. *Isr Med Assoc J* 2002; **4:** 389–90.
10. Phillips EJ, *et al.* Allergic reactions to bisphosphonates: a report of three cases and an approach to management. *J Clin Pharmacol* 1998; **38:** 842–86.

Interactions

The bisphosphonates are not well absorbed from the gastrointestinal tract, and dosage with food further impairs their absorption.

Compounds containing aluminium, calcium, iron, or magnesium, including antacids and mineral supplements and some osmotic laxatives, can also impair the absorption of bisphosphonates given by mouth.

It has been suggested that the use of certain bisphosphonates with NSAIDs may result in an increased incidence of gastrointestinal or renal adverse effects.

There may be additive hypocalcaemic effects with aminoglycosides.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*,[1] or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; **4:** 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; **302:** 295. Correction. *ibid.*; 791.

Pharmacokinetics

The bisphosphonates are poorly absorbed after oral doses, with bioavailabilities in the fasting state ranging from about 0.7% (alendronate; risedronate) to up to 6% (etidronate; tiludronate). Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. They have a high affinity for bone, with about 50% of an absorbed dose sequestered to ossified tissues and retained in the body for prolonged periods. Excretion is in the urine, as unchanged drug; they do not appear to be metabolised.

◊ References.

1. Cremers SCLM, *et al.* Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. *Clin Pharmacokinet* 2005; **44:** 551–70.

Uses and Administration

The bisphosphonates inhibit bone resorption and thus have a hypocalcaemic effect. They are pyrophosphate analogues that have a high affinity for the hydroxyapatite of bone, and that inhibit bone resorption by osteoclasts; because of the coupling of resorption and formation this results in an overall reduction in remodelling and bone turnover (see Bone and Bone Disease, p.1083). Their antiresorptive potency varies widely. The bisphosphonates also inhibit the formation and dissolution of hydroxyapatite crystals and thus have the potential to interfere with bone mineralisation. The degree to which the bisphosphonates inhibit mineralisation in clinical practice varies; etidronate is the most potent inhibitor of those now in general clinical use.

Because bone resorption increases plasma-calcium concentrations, the bisphosphonates are used as adjuncts to the treatment of severe hypercalcaemia, especially when associated with malignancy. They are also used in disorders associated with excessive bone resorption and turnover, such as Paget's disease of bone and osteoporosis, as well as in the management of bone metastases. Etidronate has been used in the prevention and treatment of ectopic ossification.

The affinity of bisphosphonates for bone allows complexes labelled with radioactive technetium-99m (see p.2055) to be used diagnostically as bone scanning agents.

Bisphosphonates have been given by intravenous infusion or orally. In the latter case food should be avoided for a suitable period before and after a dose, especially foods with a high calcium content such as milk.

◊ References.

1. Brown DL, Robbins R. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999; **39:** 651–60.
2. Shoemaker LR. Expanding role of bisphosphonate therapy in children. *J Pediatr* 1999; **134:** 264–7.
3. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des* 2003; **9:** 2643–58.
4. Cohen SB. An update on bisphosphonates. *Curr Rheumatol Rep* 2004; **6:** 59–65.
5. Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother* 2005; **39:** 668–77.
6. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics* 2007; **119** (suppl 2): S150–S162.
7. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. *J Dent Res* 2007; **86:** 1022–33.
8. Russell RG, *et al.* Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci* 2007; **1117:** 209–57.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients.

Ectopic ossification. Bisphosphonates that are potent inhibitors of mineralisation such as etidronate have been advocated for prevention of ectopic ossification (p.100), but they do not prevent the formation of the osteoid matrix, and delayed mineralisation may occur once they are withdrawn.

Hypercalcaemia. In patients with severe symptomatic hypercalcaemia restoration and maintenance of adequate hydration and urine flow is essential, and helps to reduce plasma-calcium concentrations by promoting calcium diuresis. In hypercalcaemia of malignancy (p.1083) therapy with inhibitors of bone resorption such as the bisphosphonates is used. Although sustained, the action of bisphosphonates is not particularly rapid; they may be used with a calcitonin where both rapid and prolonged diminution of plasma-calcium concentration is desired.

Hyperparathyroidism. Bisphosphonates have been used to inhibit bone resorption in the treatment of hypercalcaemia associated with hyperparathyroidism (p.1087), but seem to be of little benefit for long-term treatment.

Juvenile idiopathic arthritis. Bisphosphonates may have a role[1] in preventing low bone mineral density and fragility fractures in children with juvenile idiopathic arthritis (p.10).

1. Thornton J, *et al.* Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; **91:** 753–61.

Malignant neoplasms of the bone. There is good evidence that some bisphosphonates are of benefit in **treatment** of patients with metastatic bone disease (p.660) not only to control bone pain[1,2] and to manage the attendant hypercalcaemia, but also to reduce skeletal complications such as fractures.[2-8] Maximum benefit in terms of skeletal events occurs only after 6 months of treatment.[9] It has been suggested that given the strength of the evidence, treatment with bisphosphonates should be begun at first diagnosis of bone metastases, and continued until no longer clinically relevant.[2,10] While some continue treatment despite disease progression, others advocate changing to a more potent bisphosphonate, or stopping treatment altogether.[9] Starting bisphosphonates in women with breast cancer without evidence of bone metastases is not recommended.[11]

There are concerns over the development of osteonecrosis of the jaw with bisphosphonate treatment (see Effects on the Musculoskeletal System, under Adverse Effects, above), and a possibly increased incidence in patients with multiple myeloma. Some have recommended[12,13] that monthly intravenous bisphosphonate therapy continue for 2 years in myeloma patients. After 2 years, therapy can be stopped in those who have achieved a complete response or who are in a stable plateau phase. If disease is still active, frequency of infusion can be decreased to once every 3 months. However, others recommend stopping therapy after 1 year in those with a complete response or very good partial response. For those with a poorer response and ongoing active bone disease, bisphosphonates may be continued for up to 2 years.[14] In newly diagnosed patients, pamidronate is favoured over zoledronate as data suggest the risk of osteonecrosis may be higher with the latter.[12-14] However, routinely switching patients from zoledronate to pamidronate is not recommended, as no data suggest that this will prevent osteonecrosis. Multiple myeloma patients without evidence of skeletal involvement should not routinely be given bisphosphonates.[12]

There is also much interest in the use of bisphosphonates to **prevent** the development of bone metastases;[2,4,5,8] however, preliminary evidence of their efficacy is conflicting. Specific references may be found under the individual drugs.

1. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 30/11/06).
2. Aapro M, *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008; **19:** 420–32.
3. Rule S. Managing cancer-related skeletal events with bisphosphonates. *Hosp Med* 2004; **65:** 355–60.
4. Brown JE, *et al.* The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer* 2004; **11:** 207–24.
5. Pavlakis N, *et al.* Bisphosphonates for breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 30/11/06).
6. Saad F, Schulman CC. Role of bisphosphonates in prostate cancer. *Eur Urol* 2004; **45:** 26–34.
7. Djulbegovic B, *et al.* Bisphosphonates in multiple myeloma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/11/06).
8. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005; **23:** 8219–24.
9. Gainford MC, *et al.* Recent developments in bisphosphonates for patients with metastatic breast cancer. *BMJ* 2005; **330:** 769–73.
10. Ross JR, *et al.* Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003; **327:** 469–72. Correction. *ibid.* 2004; **328:** 384.
11. Hillner BE, *et al.* American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003; **21:** 4042–57. Correction. *ibid.* 2004; **22:** 1351.
12. Lacy MQ, *et al.* Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; **81:** 1047–53.
13. Kyle RA, *et al.* American Society of Clinical Oncology. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; **25:** 2464–72.
14. Durie BGM, *et al.*. International Myeloma Working Group. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic consensus statement. *Mayo Clin Proc* 2007; **82:** 516–7; author reply 517–18.

Osteogenesis imperfecta. Bisphosphonates have been tried in osteogenesis imperfecta (p.1083), but orthopaedic treatment and physical activity programmes form the basis of therapy.

Osteoporosis. Bisphosphonates are used first-line in the prevention and treatment of osteoporosis (p.1084). Alendronate, risedronate and cyclical etidronate are used orally; clodronate and ibandronate have been used both orally and parenterally, and ibandronate, pamidronate, and zoledronate by intermittent intravenous infusion. Generally, in the management of **postmenopausal** osteoporosis, bisphosphonates increase bone mineral density (BMD) at both the spine and hip and reduce vertebral fractures; effect on non-vertebral fractures varies.[1,2] Treatment in women at highest risk, with prevalent fractures or low BMD, is considered most effective.[2] In the UK, NICE[3] recommends the use of bisphosphonates for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Alendronate, etidronate, or risedronate may be given to all women aged 75 years and older, to women aged between 65 and 74 years with confirmed osteoporosis, and to postmenopausal women younger than 65 with very low BMD or with confirmed osteoporosis and one or more additional age-independent risk factors. Data also suggest that the more severe the osteoporosis, the greater the benefit, and since bone density continues to decline with age, and vertebral fracture incidence rises after age 75, some consider it more beneficial in older women.[4] However, others have expressed concern about a possible increase in brittleness of bones with long-term bisphosphonate treatment.[5]

Although there is less evidence for the efficacy of bisphosphonates for the treatment of idiopathic osteoporosis in **men**, some consider them the treatment of choice. A systematic review[6] stated that, while further evaluation of bisphosphonate therapy in **children** with secondary osteoporosis is warranted, evidence does not support their use as standard therapy.

Bisphosphonates are also considered effective at prevention and treatment of **corticosteroid-induced** osteoporosis.[7] Fracture risk (see p.1491) may also be reduced although a systematic review was inconclusive in this respect.[7]

A meta-analysis of bisphosphonate use in the early **post-transplant** period found that they were effective in reducing BMD decline at the lumbar spine; however, prolonged and more intensive treatment may increase the risk of adynamic or low bone turnover disease.[8]

1. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med* 2003; **19:** 395–414.
2. Masud T, Giannini S. Preventing osteoporotic fractures with bisphosphonates: a review of the efficacy and tolerability. *Aging Clin Exp Res* 2003; **15:** 89–98.
3. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 87 (issued January 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/TA087guidance.pdf (accessed 23/07/08)
4. Dhesi JK, *et al.* The implications of a growing evidence base for drug use in elderly patients. Part 4: vitamin D and bisphosphonates for fractures and osteoporosis. *Br J Clin Pharmacol* 2006; **61:** 521–8.
5. Ott S. New treatments for brittle bones. *Ann Intern Med* 2004; **141:** 406–7.
6. Ward L, *et al.* Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 18/04/08).
7. Homik J, *et al.* Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 22/02/05).
8. Mitterbauer C, *et al.* Effects of bisphosphonates on bone loss in the first year after renal transplantation—a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21:** 2275–81.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease.

Bone Morphogenetic Proteins

BMP; Proteínas morfogenéticamente óseas.

Костные Морфогенетические Белки

ATC — M05BC01 (BMP-2); M05BC02 (BMP-7).

Dibotermin Alfa *(BAN, USAN, rINN)*

Dibotermina alfa; Dibotermine Alfa; Diboterminum Alfa; hrBMP-2; rhBMP-2. Human recombinant bone morphogenetic protein 2.

Диботермин Альфа

CAS — 246539-15-1.

ATC Vet — QM05BC01.

Eptotermin Alfa *(rINN)*

Eptotermina alfa; Eptotermine Alfa; Eptoterminum Alfa; hrBMP-7; OP-1; Osteogenic Protein-1. Human recombinant bone morphogenetic protein 7.

Эптотермин Альфа

CAS — 129805-33-0.

ATC Vet — QM05BC02.

Profile

Bone morphogenetic proteins (BMPs) are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix. Several have been identified and developed for use in orthopaedic and reconstructive surgery; some have been produced by recombinant technology.

Eptotermin alfa is a recombinant form used in adults for the treatment of non-union of tibia of at least 9 months duration in cases where autograft has failed or is unfeasible. Dibotermin alfa, another recombinant form, is used as an adjunct to standard care for the treatment of acute tibia fractures in adults, as an implant containing 12 mg. The implant is also indicated for anterior lumbar spine fusion, as a substitute for bone grafting, in adults with degenerative disc disease who have had at least 6 months of non-operative treatment. Dibotermin alfa is also used as an alternative to bone grafting for sinus augmentation, and for localised alveolar ridge augmentations for defects associated with extraction sockets. Osteogenin (BMP-3) is under investigation.

◊ References.

1. Croteau S, *et al.* Bone morphogenetic proteins in orthopedics: from basic science to clinical practice. *Orthopedics* 1999; **22:** 686–95.
2. Groeneveld EH, Burger EH. Bone morphogenetic proteins in human bone regeneration. *Eur J Endocrinol* 2000; **142:** 9–21.
3. Valentin-Opran A, *et al.* Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Orthop* 2002; **395:** 110–20.
4. Govender S, *et al.* Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am* 2002; **84:** 2123–34.
5. Johnsson R, *et al.* Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion. *Spine* 2002; **27:** 2654–61.
6. Khan SN, Lane JM. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in orthopaedic applications. *Expert Opin Biol Ther* 2004; **4:** 741–8.
7. Westerhuis RJ, *et al.* Use of bone morphogenetic proteins in traumatology. *Injury* 2005; **36:** 1405–12.
8. Giannoudis PV, Tzioupis C. Clinical applications of BMP-7: the UK perspective. *Injury* 2005; **36** (suppl 3): S47–S50.
9. Wikesjö UM, *et al.* Tissue engineering with recombinant human bone morphogenetic protein-2 for alveolar augmentation and oral implant osseointegration: experimental observations and clinical perspectives. *Clin Implant Dent Relat Res* 2005; **7:** 112–19.
10. Granjeiro JM, *et al.* Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res* 2005; **38:** 1463–73.
11. Garrison KR, *et al.* Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess* 2007; **11:** 1–150.
12. Mussano F, *et al.* Bone morphogenetic proteins and bone defects: a systematic review. *Spine* 2007; **32:** 824–30.

Adverse effects. The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products in cervical spine fusion had been associated with at least 38 reports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrollment in approved clinical studies was recommended when treating cervical spine problems.[1]

1. FDA. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. Available at: http://www.fda.gov/cdrh/safety/070108-rhbmp.html (accessed 17/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: InductOs; ***Cz.:*** InductOs; Osigraft; ***Denm.:*** InductOs; Osigraft; ***Fin.:*** InductOs; ***Gr.:*** InductOs; Osigraft; ***Irl.:*** InductOs; ***Ital.:*** InductOs; Osigraft; ***Neth.:*** Osigraft; ***Norw.:*** InductOs; ***Port.:*** Osigraft; ***Spain:*** InductOs; Osigraft; ***Swed.:*** InductOs; ***UK:*** InductOs; ***USA:*** Infuse Bone Graft.

Calcitonins

Calcitoninas.

ATC — H05BA01 (salmon synthetic); H05BA02 (pork natural); H05BA03 (human synthetic).

ATC Vet — QH05BA01 (salmon synthetic); QH05BA02 (pork natural); QH05BA03 (human synthetic).

Calcitonin (Human)

Calcitonina (humana); Calcitonin-human; Human Calcitonin.

$C_{151}H_{226}N_{40}O_{45}S_3$ = 3417.8.
CAS — 21215-62-3.
ATC — H05BA03 (human synthetic).
ATC Vet — QH05BA03 (human synthetic).

Description. Calcitonin (human) is a synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) *(BANM)*

Calcitonina (cerdo).
CAS — 12321-44-7.
ATC — H05BA02 (pork natural).
ATC Vet — QH05BA02 (pork natural).

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.
Description. Calcitonin (pork) is a polypeptide hormone obtained from pork thyroid.

Calcitonin (Salmon) *(BAN)*

Calcitonina (salmón); Calcitonin-salmon; Calcitoninum salmonis; Kalcitonin lososí; Kalcytonina łososiowa; Kalsitoniini (lohi); Kalsitonin (Somon); Lašišų kalcitoninas; Laxkalcitonin; Lazac-kalcitonin; Salcatonin; Salkatonin; Salmon Calcitonin; SCT-1; SMC-20-051.

$C_{145}H_{240}N_{44}O_{48}S_2$ = 3431.9.
CAS — 47931-85-1.
ATC — H05BA01 (salmon synthetic).
ATC Vet — QH05BA01 (salmon synthetic).

NOTE. There may be some confusion between the terms Salcatonin and Calcitonin (Salmon) (Salmon Calcitonin; Calcitonin-salmon) although in practice these names appear to be used for the same substance.

- The Ph. Eur. 6.2 defines Calcitonin (Salmon) as a polypeptide having the structure determined for salmon calcitonin I. It is available as an acetate.
- Calcitonin (Salmon)/Salcatonin (*BAN*) is defined as a *component* of natural salmon calcitonin. The BP 2008 defines Calcitonin (Salmon)/Salcatonin as a synthetic polypeptide having the structure determined for salmon calcitonin I.
- In the USA, Calcitonin (*USAN*) includes calcitonin (human) and calcitonin (salmon) and there Salcatonin is understood to be a synthetic polypeptide structurally similar to natural salmon calcitonin (Calcitonin Salmon (Synthesis)). The US manufacturers use Calcitonin-salmon for a synthetic polypeptide with the same structure as calcitonin of salmon origin.

Pharmacopoeias. In *Chin, Eur.* (see p.vii), and *US..*
Ph. Eur. 6.2 (Calcitonin (Salmon)). A white or almost white powder. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. Freely soluble in water. Store at 2° to 8°. If the substance is sterile store in a sterile, airtight, tamper-proof container. Protect from light.
USP 31 (Calcitonin Salmon). It is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. One mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP units. Store in airtight containers at a temperature of 2° to 8°, or maintain in a frozen state. Protect from light.

Elcatonin *(rINN)*

[Aminosuberic Acid 1,7]-eel Calcitonin; [Asu^{1,7}]-E-CT; Carbocalcitonin; Elcatonina; Elcatonine; Elcatoninum. 1-Butyric acid-7-(L-2-aminobutyric acid)-26-L-aspartic acid-27-L-valine-29-L-alanine-calcitonin (salmon).

Элькатонин

$C_{148}H_{244}N_{42}O_{47}$ = 3363.8.
CAS — 60731-46-6.
ATC — H05BA04.
ATC Vet — QH05BA04.

Description. Elcatonin is a synthetic analogue of eel calcitonin.

Pharmacopoeias. In *Jpn.*

Incompatibility. Like some other peptide drugs, calcitonin may be adsorbed onto the plastic of intravenous giving sets; it has been suggested that solutions for intravenous infusion should contain some protein to prevent the sorption and consequent loss of potency (see under Administration, below).

Units

0.8 units of calcitonin, porcine, are contained in one ampoule of the second International Standard Preparation (1991).

128 units of calcitonin, salmon, are contained in approximately 20 micrograms of freeze-dried purified synthetic salmon calcitonin, with mannitol 2 mg in one ampoule of the second International Standard Preparation (1989).

17.5 units of calcitonin, human, are contained in one ampoule of the second International Standard Preparation (1991).

88 units of calcitonin, eel, are contained in one ampoule of the first International Standard Preparation (1989).

Potency of calcitonins is estimated by comparing the hypocalcaemic effect, in *rats*, with that of the standard preparation, and is expressed in international or MRC units which are considered to be equivalent. One manufacturer states that 100 international units by this assay is equivalent to 1 mg of porcine or human calcitonin, and to 25 micrograms of salmon calcitonin although other, slightly different, equivalencies have been cited for other preparations. However, although 1 unit of pork calcitonin, 1 unit of salmon calcitonin, and 1 unit of human calcitonin should give the same response in humans this is not necessarily the case. Doses of calcitonin that have been considered approximately equivalent in practice are:

- 80 units of pork calcitonin
- 50 units of salmon calcitonin
- 500 micrograms of human calcitonin

Clinically, doses of pork and salmon calcitonin are expressed in units whereas those of human calcitonin can be expressed by weight, probably a reflection of its purity.

Adverse Effects, Treatment, and Precautions

Calcitonins may cause nausea, vomiting, diarrhoea, dizziness, flushing, and tingling of the hands. These reactions are dose dependent, usually transient, and occur more often with intravenous doses. Other adverse effects have included skin rash, an unpleasant taste, abdominal pain, urinary frequency, and tremor. A diabetogenic effect has been reported rarely. Inflammatory reactions at the injection site have been reported with some calcitonins, and rhinitis and other local reactions have been reported with nasal formulations. Transient hypocalcaemia may occur after injections of calcitonin, and use is contra-indicated in patients with hypocalcaemia.

Calcitonins should be given with care to patients with renal impairment (see below) or heart failure. If children receive calcitonin it should preferably be for short periods and bone growth should be monitored.

Circulating antibodies may develop after several months of use but resistance does not necessarily follow (see also below). In patients with suspected sensitivity, a skin test has been advised before use as hypersensitivity reactions, including anaphylaxis, have occurred.

Calcitonin has inhibited lactation in *animals*.

Nausea and vomiting may be reduced by giving doses at bedtime or by giving an antiemetic beforehand.

Calcitonin (pork) may contain trace amounts of thyroid hormones, but clinical effects are unlikely in most patients.

Antibody formation. Long-term treatment with heterologous calcitonins may lead to the formation of neutralising antibodies. This appears to be common in patients given calcitonin (pork) or, to a lesser extent, calcitonin (salmon). Calcitonin (human) is less immunogenic than pork or salmon, but a study[1] has also detected antibodies to human calcitonin in 1 of 33 women with postmenopausal osteoporosis after 6 months of therapy.

The degree to which such antibodies affect therapeutic activity is uncertain. Some studies have suggested a significant loss of therapeutic activity in patients who developed neutralising antibodies to calcitonin (salmon),[2] or a restoration in activity after a switch from salmon to human calcitonin in such patients;[3] equally, others have presented evidence that the activity of calcitonin (salmon) was not reduced by the development of antibodies to the drug.[4]

1. Grauer A, *et al.* Formation of neutralizing antibodies after treatment with human calcitonin. *Am J Med* 1993; **95:** 439–42.
2. Grauer A, *et al.* In vitro detection of neutralizing antibodies after treatment of Paget's disease of bone with nasal salmon calcitonin. *J Bone Miner Res* 1990; **5:** 387–91.
3. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; **89:** 181–4.
4. Reginster JY, *et al.* Influence of specific anti-salmon calcitonin antibodies on biological effectiveness of nasal salmon calcitonin in Paget's disease of bone. *Scand J Rheumatol* 1990; **19:** 83–6.

Effect on glucose metabolism. A single subcutaneous injection of calcitonin (salmon) has been reported to increase blood-glucose concentrations,[1] but long-term treatment with calcitonins was considered unlikely to cause diabetes.[2] Nevertheless, deterioration in diabetic control has been noted in a patient given calcitonin (pork)[3] and postprandial release of insulin was abolished by intravenous salmon calcitonin in 8 patients with duodenal ulcers.[4]

1. Gattereau A, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1977; **ii:** 1076–7.
2. Evans IMA, *et al.* Hyperglycaemic effect of synthetic salmon calcitonin. *Lancet* 1978; **i:** 280.
3. Thomas DW, *et al.* Deterioration in diabetic control during calcitonin therapy. *Med J Aust* 1979; **2:** 699–70.
4. Jonderko K. Effect of calcitonin on gastric emptying in patients with an active duodenal ulcer. *Gut* 1989; **30:** 430–5.

Gynaecomastia. A 62-year-old man developed painful gynaecomastia on two occasions after treatment with calcitonin (salmon) given by subcutaneous injection.[1]

1. Vankrunkelsven PJ, Thijs MM. Salcatonin and gynaecomastia. *Lancet* 1994; **344:** 482.

Interactions

There is a theoretical possibility that dosage adjustments of cardiac glycosides or calcium-channel blockers may be required in patients who are given injections of calcitonin, because of the effects of the latter on serum calcium.

Pharmacokinetics

Calcitonins are rapidly inactivated when given orally. After injection, calcitonins are quickly metabolised, primarily in the kidneys but also in blood and peripheral tissues. Bioavailability has been reported to be about 70%; plasma protein binding is about 30 to 40%. The inactive metabolites and a small proportion of unchanged drug are excreted in the urine. The elimination half-life after injection of calcitonin (human) is stated to be 60 minutes and that of calcitonin (salmon) about 70 to 90 minutes.

Calcitonins are also absorbed through the nasal and rectal mucosa. Although figures have varied widely, about 3% of an intranasal dose of calcitonin (salmon) is reported to be bioavailable compared with the same dose given by intramuscular injection, with peak plasma concentrations occurring after about 30 to 40 minutes compared with 15 to 25 minutes after the parenteral dose. Elimination half-life has been reported to be about 16 to 43 minutes.

◊ After the *subcutaneous injection* of 19.9 micrograms of synthetic calcitonin (salmon) in 16 healthy subjects,[1] absorption was rapid with an absorption half-life of 23.4 minutes. The maximum mean plasma concentration was 384 picograms/mL at 60 minutes after which excretion was fairly rapid with an elimination half-life of 87 minutes. These results and those from previously reported investigations of salmon, human, and porcine calcitonin could not easily be compared, especially since different assay methods had been used. Nevertheless it was concluded that bioavailability from subcutaneous and intramuscular injection sites was good; that dosage may need to be adjusted in renal insufficiency because of low metabolic clearance rate; and that the higher potency of calcitonin (salmon) is due to higher intrinsic activity at the receptor site rather than to pharmacokinetic differences. The US manufacturers have cited a half-life of 1.02 hours after a single subcutaneous injection of calcitonin (human) 500 micrograms. The plasma elimination half-life of elcatonin was about 4.8 hours after *intramuscular injection* in healthy subjects.[2]

Calcitonins are absorbed on *intranasal* or *rectal* dosage. Peak plasma concentrations of calcitonin (salmon) were achieved after 20 to 60 minutes when given by nasal spray in doses ranging from 200 to 400 units.[3] In another study[4] calcitonin (salmon) 200 units, repeated once after 3 hours, was given by nasal spray or suppository to healthy subjects. Absorption was prompt and the total amount absorbed was similar with either route. However, whereas intranasal dosage produced low peaks with calcitonin (salmon) still detectable in the blood after 3 to 5 hours, rectal dosage produced peak plasma concentrations about 6 to 8 times higher but the drug was undetectable within 2 hours; plasma concentrations were lower than those found after injection. Another group[5] found calcitonin (human) to be poorly absorbed when given intranasally to healthy subjects. Absorption from nasal powder or spray solutions was improved by the presence of the surfactants dihydrofusinate or glycocholate.

Investigations carried out in 4 osteoporotic patients[6] suggested that the rectal calcitonin (salmon) could provide 65% of the bioavailability of intramuscular doses.

A study of an *oral* formulation of calcitonin (salmon) in healthy subjects evaluated different oral doses in comparison to intravenous dosing, and found 1.2 mg orally to be comparable to 10 micrograms intravenously, in terms of bioavailability and efficacy.[7]

1. Nüesch E, Schmidt R. Comparative pharmacokinetics of calcitonins. In: Pecile A, ed. *Calcitonin international congress series no. 540*. Amsterdam: Excerpta Medica, 1980: 352–64.
2. Segre G, *et al.* Pharmacokinetics of carbocalcitonin in humans. *Clin Trials J* 1986; **23** (suppl 1): 23–8.
3. Kurose H, *et al.* Intranasal absorption of salmon calcitonin. *Calcif Tissue Int* 1987; **41:** 249–51.
4. Buclin T, *et al.* The effect of rectal and nasal administration of salmon calcitonin in normal subjects. *Calcif Tissue Int* 1987; **41:** 252–8.
5. Pontiroli AE, *et al.* Nasal administration of glucagon and human calcitonin to healthy subjects: a comparison of powders and spray solutions and of different enhancing agents. *Eur J Clin Pharmacol* 1989; **37:** 427–30.
6. Gennari C, *et al.* Pharmacodynamic activity of synthetic salmon calcitonin in osteoporotic patients: comparison between rectal and intramuscular administration: pilot study. *Curr Ther Res* 1993; **53:** 301–8.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.

Uses and Administration

Calcitonin is a hormone produced by mammalian thyroid parafollicular cells or the ultimobranchial gland in non-mammalian vertebrates. In man its secretion and biosynthesis are regulated by the plasma-calcium concentration. It has a hypocalcaemic action that is due primarily to inhibition of osteoclastic bone resorption; of less importance is a direct effect on the kidneys resulting in increased urinary excretion of calcium and phosphorus. Calcitonin contains 32 amino acids; the sequence varies according to the species. Synthetic calcitonin (salmon) and synthetic calcitonin (human) are in clinical use; calcitonin (salmon) is the most potent. Naturally occurring calcitonin (pork) has been used and elcatonin, a synthetic derivative of eel calcitonin, is available in some countries.

Calcitonins are used in the treatment of diseases characterised by high bone turnover such as Paget's disease of bone. They are also given as an adjunct in the treatment of severe hypercalcaemia, especially that associated with malignancy. Some calcitonins are used in the management of osteoporosis.

Calcitonins are generally given by subcutaneous or intramuscular injection; some have been given intranasally, rectally, or by intravenous infusion or slow intravenous injection.

In **Paget's disease of bone** the usual dose range for calcitonin (salmon) is 50 units three times weekly to 100 units daily in single or divided doses by subcutaneous or intramuscular injection. Calcitonin (human) is usually given by subcutaneous or intramuscular injection; doses range from 500 micrograms two to three times weekly, to 250 or 500 micrograms daily; severe cases may require up to 1 mg daily in divided doses.

As an adjunct to the treatment of **hypercalcaemia**, calcitonins have a rapid effect which is greatest in patients with an increased bone turnover. Calcitonin (salmon) may be given by subcutaneous or intramuscular injection in a dose of 4 units/kg every 12 hours, increased if necessary after one or two days to 8 units/kg every 12 hours, up to a maximum of 8 units/kg every 6 hours after a further two days. Alternatively, 100 units every 6 to 8 hours may be given, increased after one or two days to a maximum of 400 units every 6 to 8 hours. Doses greater than 8 units/kg every 6 hours are considered to have no additional benefit. In the emergency treatment of hypercalcaemic crisis, calcitonin (salmon) has also been given intravenously: a suggested dose is up to 10 units/kg diluted in 500 mL of sodium chloride 0.9% and given by slow intravenous infusion over at least 6 hours (see also under Administration below for the problems of intravenous dosage). Calcitonin (human) 500 micrograms every 6 hours has also been given by slow intravenous injection for hypercalcaemia of malignancy.

Calcitonin (salmon) is used in the treatment of **postmenopausal osteoporosis** in a dose of 200 units daily intranasally by nasal spray, alternating nostrils each day. In some countries it has also been given in a dose of 100 units daily or every other day by subcutaneous or intramuscular injection. Supplementary calcium (equivalent to at least 600 mg of elemental calcium daily) and, if necessary, vitamin D (400 units daily) should also be given.

Calcitonin (salmon) is also used for the prevention of acute bone loss due to sudden **immobilisation** such as in patients with recent osteoporotic fractures. The recommended dose is 100 units daily (or 50 units twice daily) by subcutaneous or intramuscular injection, for 2 to 4 weeks. The dose may be reduced to 50 units daily at the start of remobilisation; treatment is maintained until patients are fully mobilised.

Calcitonin (salmon) has also been used for the control of **bone pain due to malignant neoplasms** although in the EU such use is no longer considered appropriate.

Oral formulations of calcitonin (salmon) are being studied.

Administration. Calcitonins have poor oral bioavailability and are usually given by subcutaneous or intramuscular injection. To improve patient acceptability, especially in diseases requiring long-term drug therapy, alternative routes have been investigated:[1]

- calcitonin (salmon) has proved effective when given **intranasally** in usual doses of 50 to 200 units daily (for references, see Osteoporosis below), and intranasal products for osteoporosis are available.
- suppositories containing 300 units of calcitonin (salmon) have been used **rectally** in the management of hypercalcaemia; one suppository being given three times daily (total daily dose of 900 units).[2,3] Daily doses of 100 units of calcitonin (salmon) by suppository have been tried in postmenopausal osteoporosis[4] and in patients with bone pain.[5]
- calcitonins have been given by **intravenous infusion**, but this is rarely necessary and may cause more adverse effects. If intravenous use is essential, it has been suggested[6] that some protein must be present in the solution to prevent adsorption onto the plastic of the giving set. However, in practice this does not seem to be the case; in the UK, manufacturer's recommendations are for dilution with normal saline, while acknowledging that such dilution results in a loss of potency, and dosage is adjusted accordingly. Presumably dilution with a protein-containing solution would allow lower doses to be used. The manufacturers do specify that solutions for infusion should be prepared immediately before use and that glass or hard plastic containers should not be used.

Novel formulations of an orally active calcitonin have been investigated; one such formulation using a low-molecular-weight carrier, was considered effective and well-tolerated in a Phase I study.[7]

1. Inzerillo AM, *et al.* Calcitonin: physiological actions and clinical applications. *J Pediatr Endocrinol Metab* 2004; **17:** 931–40.
2. Thiébaud D, *et al.* Effectiveness of salmon calcitonin administered as suppositories in tumor-induced hypercalcemia. *Am J Med* 1987; **82:** 745–50.
3. Thiébaud D, *et al.* Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; **150:** 2125–8.
4. Gonnelli S, *et al.* Effect of rectal salmon calcitonin treatment on bone mass and bone turnover in patients with established postmenopausal osteoporosis: a 1-year crossover study. *Curr Ther Res* 1993; **54:** 458–65.
5. Mannarini M, *et al.* Analgesic effect of salmon calcitonin suppositories in patients with bone pain. *Curr Ther Res* 1994; **55:** 1079–83.
6. Stevenson JC. Current management of malignant hypercalcaemia. *Drugs* 1988; **36:** 229–38.
7. Buclin T, *et al.* Bioavailability and biological efficacy of a new oral formulation of salmon calcitonin in healthy volunteers. *J Bone Miner Res* 2002; **17:** 1478–85.

Administration in renal impairment. Calcitonins are metabolised mainly in the kidneys and pharmacokinetic studies (see above) have indicated that the dosage of calcitonins may need to be reduced in patients with renal insufficiency, but there have been no specific guidelines.

Charcot neuroarthropathy. In a small study in patients with acute Charcot neuroarthropathy, intranasal calcitonin with calcium supplementation significantly reduced bone turnover compared with calcium supplementation alone.[1]

1. Bem R, *et al.* Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes Care* 2006; **29:** 1392–4.

Hypercalcaemia. Calcitonins can be used in addition to rehydration and diuresis in the management of moderate to severe symptomatic hypercalcaemia (p.1668), including that of malignancy (p.1083). Because of their rapid effect, they may be particularly useful in life-threatening hypercalcaemia. However, although they have a rapid effect it is usually short-lived; calcitonins are therefore generally given as an adjunct with other therapy such as a bisphosphonate.

Malignant neoplasms of the bone. Calcitonins may be useful adjuvants in the treatment of malignant disease involving the bone (p.660), not only to correct hypercalcaemia of malignancy (p.1083), but perhaps to relieve bone pain and osteolysis. A systematic review[1] concluded however that available evidence did not support the use of calcitonin for metastatic bone pain; the review was limited to only a few studies. Other therapeutic measures were recommended until further studies are done. In the EU, the use of injectable calcitonins for metastatic bone pain is no longer recommended.

1. Martinez-Zapata MJ, *et al.* Calcitonin for metastatic bone pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/04/08).

Osteogenesis imperfecta. There have been reports[1,2] of beneficial effects with calcitonins in the treatment of osteogenesis imperfecta (p.1083), but their use has declined in favour of bisphosphonates.

1. Castells S, *et al.* Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. *J Pediatr* 1979; **95:** 807–11.
2. Nishi Y, *et al.* Effect of long-term calcitonin therapy by injection and nasal spray on the incidence of fractures in osteogenesis imperfecta. *J Pediatr* 1992; **121:** 477–80.

Osteoporosis. Calcitonins may be used in the prevention and treatment of osteoporosis (p.1084). In the treatment of **postmenopausal** osteoporosis they are usually second-line agents; however, because of their analgesic effect, they may be useful for the initial treatment of those with bone pain due to vertebral crush fractures.[1] Calcitonin (salmon) nasal spray has been shown to significantly reduce the risk of vertebral fractures in women with established osteoporosis,[2] although the study has been criticised[3] for a high drop-out rate. Any effect on hip fracture is unestablished.[1,2] In the management of **corticosteroid**-induced osteoporosis, calcitonin appears to maintain bone mineral density (BMD) at the lumbar spine, but not at the femoral neck. Effects on prevention of fractures have not been established.[1,4] Nasal calcitonin (salmon) has been found to increase lumbar spine BMD in **men** with idiopathic osteoporosis.[1]

1. Silverman SL. Calcitonin. *Endocrinol Metab Clin North Am* 2003; **32:** 273–84.
2. Chesnut CH, *et al.* A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med* 2000; **109:** 267–76.
3. Cummings SR, Chapurlat RD. What PROOF proves about calcitonin and clinical trials. *Am J Med* 2000; **109:** 330–1.
4. Cranney A, *et al.* Calcitonin for preventing and treating corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 22/02/05).

Paget's disease of bone. Calcitonins may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. However, the bisphosphonates have largely superseded the calcitonins in this role.

Pain. In addition to bone pain associated with malignancy and with bone disorders such as Paget's disease, calcitonins may also have other analgesic properties. Beneficial results have been seen in various painful conditions, including complex regional pain syndrome (p.6), and particularly with intranasal salmon calcitonin.[1] Salmon calcitonin 100 or 200 units intravenously has also provided relief[2] from phantom limb pain (p.9) after amputation. A small double-blind crossover study of intravenous calcitonin in amputee patients with phantom limb pain found it was ineffective, however, in contrast to ketamine.[3] Intranasal calcitonin at a dose of 200 units also provided only transient relief of phantom limb sensation after spinal cord injury in a patient refractory to clomipramine;[4] the authors speculated that optimal dosage may not have been used and noted that all previous studies were in amputees.

For a discussion on pain and its management, see p.2.

1. Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. *Bone* 2002; **30** (suppl): 84S–86S.
2. Wall GC, Heyneman CA. Calcitonin in phantom limb pain. *Ann Pharmacother* 1999; **33:** 499–501.
3. Eichenberger U, *et al.* Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; **106:** 1265–73.
4. Shapiro S, *et al.* Calcitonin treatment for phantom limb pain. *Can J Psychiatry* 2004; **49:** 499.

Preparations

BP 2008: Calcitonin (Salmon) Injection;
USP 31: Calcitonin Salmon Injection; Calcitonin Salmon Nasal Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Anguilcet†; Calsynar†; Citonina†; Osmil†; Salmocalcin†; ***Austral.:*** Miacalcic; ***Austria:*** Calcitonin; Calco; Casalm; Cibacalcin; Elcimen†; Miacalcic†; Ucecal; ***Belg.:*** Calsynar; Miacalcic; Steocalcin; ***Braz.:*** Acticalcin; Calsynar; Cibacalcina†; Miacalcic; Seacalcit; Serocalcin; ***Canad.:*** Calcimar; Caltine; Miacalcin; ***Chile:*** Calfosina†; Calnisan; Miacalcic; ***Cz.:*** Calsynar†; Caltine†; Fixocal†; Miacalcic; Osteodon; Ostostabil†; Tonocalcin; Ucecal†; ***Denm.:*** Miacalcic; ***Fin.:*** Miacalcic; ***Fr.:*** Cadens; Calsyn; Cibacalcine; Miacalcic; ***Ger.:*** Azucalcit†; Calci; Calsynar†; Casalm†; Cibacalcin†; Karil; Osteos; Ostostabil; ***Gr.:*** Alciton; Arsipor; Assocals; Aurocalcin; Brosidon; Calci-10; Calcicontrol; Calcideron; Calciphar; Calciplus; Calcispren; Calcitherapy; Calciton; Calco; Calsal; Calsynar; Caltec; Crocalcin; Doctadryle; Farmicalcine; Galcin; Genecalcin; Iamacalcin; Iricalcin; Latonina; Lixocam; Miacalcic; Miadenil; Mioser; Neostesin; Nopremin; Norcalcin; Nylex; Osanit; Osivan; Osteonorm; Osticalcin†; Ostifix; Ostoplus; Ostosalm; Pluston; Rafacalcin; Redicalcin; Rothrin; Sal-Cal; Salmocalcin; Salmofar†; Salmoten; Sanopor; Steocin; Tendolon; Tonocalcin; Tosicalcin; Transcalcium; Velkacalcin; ***Hong Kong:*** Miacalcic; Osteocalcin†; ***Hung.:*** Biostin; Calco; Miacalcic; ***India:*** Miacalcic; Zycalcit; ***Indon.:*** Miacalcic; Tonocalcin; ***Israel:*** Cibacalcin; Miacalcic; Salco; ***Ital.:*** Biocalcin; Calciben†; Calciosint†; Calcioton†; Calcitonina; Calco†; Carbicalcin†; Catonin†; Ipocalcin†; Miacalcic†; Miadenil†; Osteocalcin†; Osteotonina†; Osteovis; Rulicalcin†; Salmofar; Steocin†; Tonocalcin†; Turbocalcin†; ***Jpn:*** Calcitoran; Elcitonin; ***Malaysia:*** Menocal†; Miacalcic; Osteocalcin†; ***Mex.:*** Endocal†; Miacalcic; Oseum; Tonocalcin†; ***Norw.:*** Miacalcic; ***NZ:*** Miacalcic; ***Philipp.:*** Miacalcic; ***Pol.:*** Calcihexal; Calcitonin; Miacalcic; Tonocalcin; ***Port.:*** Calcimon†; Calcitar; Calogen†; Calsyn; Cibacalcina†; Forcaltonin; Miacalcic; Osseocalcina; Osteodon; Ostinate; Ostosalm†; Salcat; Tonocaltin; ***Rus.:*** Miacalcic (Миакальцик); ***S.Afr.:*** Miacalcic; ***Singapore:*** Calco†; Menocal†; Miacalcic; ***Spain:*** Calogen; Calsynar; Carbicalcin; Diatin; Miacalcic; Oseototal; Ospor; Osteobion; Ostetan; Sical†; Tonocaltin; Ucecal†; ***Swed.:*** Miacalcic; ***Switz.:*** Miacalcic; ***Thai.:*** Calco; Miacalcic; Osteocalcin†; Tonocalcin; ***Turk.:*** Calcitonina; Miacalcic; Salmocalcin; Tonocalcin; Ucecal; ***UK:*** Calsynar†; Miacalcic; ***USA:*** Calcimar; Fortical; Miacalcin; Osteocalcin; ***Venez.:*** Calnisan†; Caltanid†; Miacalcic†; Serocalcin†.

Cinacalcet Hydrochloride *(BANM, USAN, rINNM)*

AMG-073 (cinacalcet); Cinacalcet, Chlorhydrate de; Cinacalceti Hydrochloridum; Hidrocloruro de cinacalcet; KRN-1493. *N*-[(1*R*)-1-(Naphthalen-1-yl)ethyl]-3-[3-(trifluoromethyl)phenyl]-propan-1-amine hydrochloride.

Цинакальцета Гидрохлорид

$C_{22}H_{22}F_3N,HCl$ = 393.9.
CAS — 364782-34-3.
ATC — H05BX01.
ATC Vet — QH05BX01.

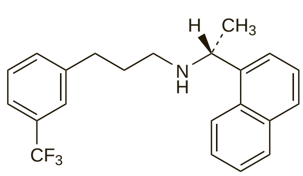

(cinacalcet)

Adverse Effects and Precautions

Hypocalcaemia and adynamic bone disease can occur; serum calcium and intact parathyroid hormone concentrations should be monitored regularly, especially in patients with a history of seizure disorders or hepatic impairment. Other adverse effects of cinacalcet include gastrointestinal disturbances, myalgia, dizziness, paraesthesia, hypertension, asthenia, anorexia, rashes, and non-cardiac chest pain. There have been isolated reports of hypotension, worsening heart failure, or both, in patients with impaired cardiac function. Hypersensitivity reactions have been reported rarely.

Interactions

Cinacalcet is partly metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Concentrations of cinacalcet have almost doubled when given with the CYP3A4 inhibitor ketoconazole. Dose adjustments of cinacalcet may be required if therapy with strong inhibitors or inducers of CYP3A4 is started, or stopped. Plasma levels of cinacalcet may be lower in smokers due to induction of CYP1A2-mediated metabolism, and dose adjustments may be necessary if patients start or stop smoking. Cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme CYP2D6; exposure to amitriptyline, desipramine, and nortriptyline has been increased when given with cinacalcet.

Pharmacokinetics

Peak plasma concentrations are obtained 2 to 6 hours after an oral dose of cinacalcet, and are substantially increased if given with food. Clearance from plasma is biphasic, with a terminal half-life of about 30 to 40 hours. Cinacalcet is approximately 93 to 97% bound to plasma proteins. It is rapidly and extensively metabolised by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Metabolites are renally excreted, with 80% of the dose recovered in the urine, and 15% in the faeces.

◊ References.

1. Kumar GN, *et al.* Metabolism and disposition of calcimimetic agent cinacalcet HCl in humans and animal models. *Drug Metab Dispos* 2004; **32:** 1491–1500.
2. Padhi D, *et al.* No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar /Mimpara). *Clin Pharmacokinet* 2005; **44:** 509–16.

Uses and Administration

Cinacalcet is a calcimimetic agent that increases the sensitivity to extracellular calcium of the calcium-sensing receptors of the parathyroid gland, which regulate parathyroid hormone secretion; this results in a reduction in parathyroid hormone secretion as well as a decrease in serum calcium. Cinacalcet hydrochloride is given orally in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, as well as for the reduction of hypercalcaemia in patients with parathyroid carcinoma or primary hyperparathyroidism (where parathyroidectomy is not an option). Doses are expressed in terms of the base; cinacalcet hydrochloride 33 mg is equivalent to about 30 mg of cinacalcet.

In the treatment of **secondary hyperparathyroidism**, the initial dose is 30 mg once daily, increased at intervals of 2 to 4 weeks by 30 mg to a maximum of 180 mg daily.

For the treatment of **hypercalcaemia** in patients with parathyroid carcinoma or primary hyperparathyroidism, cinacalcet is given in an initial dose of 30 mg twice daily, increased sequentially at intervals of 2 to 4 weeks to a maximum of 90 mg three or four times daily.

◊ References.

1. Franceschini N, *et al.* Cinacalcet HCl: a calcimimetic agent for the management of primary and secondary hyperparathyroidism. *Expert Opin Invest Drugs* 2003; **12:** 1413–21.
2. Shoback DM, *et al.* The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 5644–9.
3. Block GA, *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; **350:** 1516–25.
4. Joy MS, *et al.* Calcimimetics and the treatment of primary and secondary hyperparathyroidism. *Ann Pharmacother* 2004; **38:** 1871–80.
5. Peacock M, *et al.* Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.
6. Barman Balfour JA, Scott LJ. Cinacalcet hydrochloride. *Drugs* 2005; **65:** 271–81.
7. Cunningham J, *et al.* Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68:** 1793–1800.
8. Dong BJ. Cinacalcet: an oral calcimimetic agent for the management of hyperparathyroidism. *Clin Ther* 2005; **27:** 1725–51.
9. NICE. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: Technology Appraisal Guidance 117 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA117guidance.pdf (accessed 18/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Sensipar; ***Canad.:*** Sensipar; ***Cz.:*** Mimpara; Parareg; ***Denm.:*** Mimpara; ***Fin.:*** Mimpara; ***Fr.:*** Mimpara; ***Ger.:*** Mimpara; ***Gr.:*** Mimpara; ***Hung.:*** Mimpara; ***Irl.:*** Mimpara; ***Ital.:*** Mimpara; Parareg; ***Neth.:*** Mimpara; Parareg; ***Norw.:*** Mimpara; ***NZ:*** Sensipar; ***Pol.:*** Mimpara; ***Port.:*** Mimpara; Parareg; ***Spain:*** Mimpara; ***Swed.:*** Mimpara; ***Switz.:*** Mimpara; ***UK:*** Mimpara; ***USA:*** Sensipar.

Clodronate

ATC — M05BA02.
ATC Vet — QM05BA02.

Clodronic Acid *(BAN, USAN, rINN)*

Acide clodronique; Ácido clodrónico; Acidum clodronicum; Cl_2MBP; Cl_2MDP; DkhMDF; Klodronihappo; Klodronsyra. (Dichloromethylene)diphosphonic acid.

Клодроновая Кислота

$CH_4Cl_2O_6P_2$ = 244.9.
CAS — 10596-23-3.
ATC — M05BA02.
ATC Vet — QM05BA02.

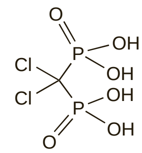

Clodronate Disodium *(USAN, rINNM)*

177501; BM-06.011; Clodronas Dinatricum; Clodronate disodique; Clodronate Sodium; Clodronato disódico; Dichloromethane Diphosphonate Disodium; Dichloromethylene Diphosphonate Disodium; Dinatrii clodronas; Dinatriumklodronaatti; Dinatriumklodronat; Disodium Clodronate; Sodium Clodronate *(BANM)*; Sodyum Klodronat; ZK-00091106. Disodium (dichloromethylene)diphosphonate tetrahydrate.

Динатрий Клодронат

$CH_2Cl_2Na_2O_6P_2,4H_2O$ = 360.9.
CAS — 22560-50-5.
ATC — M05BA02.
ATC Vet — QM05BA02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clodronate Disodium Tetrahydrate). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. A 5% solution in water has a pH of 3.0 to 4.5.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Gastrointestinal symptoms with oral clodronate may be reduced by giving it in divided doses rather than as a single daily dose. Reversible increases in liver enzyme values and serum parathyroid hormone have occurred; transient moderate leucopenia has been reported. Monitoring of hepatic and renal function, white cell counts, and serum calcium and phosphate is advised. Clodronate has precipitated bronchospasm, even in patients with no history of asthma. Transient proteinuria has been reported immediately after intravenous infusion.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including clodronate, see under Bisphosphonates, p.1090.

Effects on the kidneys. For mention of renal failure developing in a patient with slightly raised serum-creatinine concentrations who subsequently received an intravenous infusion of clodronate, see under Bisphosphonates, p.1091.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including clodronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

Effects on the respiratory system. For a report of bronchospasm in an aspirin-sensitive asthmatic, induced by an infusion of clodronate, see p.1091.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. For published reports of cutaneous reactions associated with clodronate, see p.1091.

Interactions

As for the bisphosphonates in general, p.1091.

Aminoglycosides. Severe hypocalcaemia has been reported after treatment with *amikacin*[1], or *netilmicin*[2] in patients who had previously received clodronate. In both cases, signs of aminoglycoside toxicity were evident; clodronate had been withdrawn in one patient upon starting the aminoglycoside,[1] and in the other several weeks before.[2] Bisphosphonates and aminoglycosides can induce hypocalcaemia by different mechanisms and the effects of both drugs may persist for several weeks; care should be taken when giving them together.[1,2]

1. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* 1993; **4:** 432–3.
2. Pedersen-Bjergaard U, Myhre J. Severe hypocalcaemia after treatment with diphosphonate and aminoglycoside. *BMJ* 1991; **302:** 295. Correction. *ibid.*; 791.

Pharmacokinetics

Like other bisphosphonates, clodronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is only 1 to 4%, and may differ appreciably between different oral formulations. On absorption or intravenous dosage it is cleared rapidly from the blood with a reported plasma half-life of only about 2 hours, but has a high affinity for bone. Binding to serum plasma proteins is low. Clodronate is not metabolised. Over 70% of an intravenous dose is excreted unchanged in the urine within 24 hours, the remainder being sequestered to bone tissue.

◊ References.

1. Conrad KA, Lee SM. Clodronate kinetics and dynamics. *Clin Pharmacol Ther* 1981; **30:** 114–20.
2. Yakatan GJ, *et al.* Clodronate kinetics and bioavailability. *Clin Pharmacol Ther* 1982; **31:** 402–10.
3. Ylitalo P, *et al.* Comparison of pharmacokinetics of clodronate after single and repeated doses. *Int J Clin Pharmacol Ther* 1999; **37:** 294–300.

Bioavailability. Enhanced bioavailability tablets of clodronate disodium are available in some countries, the licensed dose of which is less than the dose of the standard formulations (see below). However, an open, randomised, crossover study in 88 subjects found that a 1040-mg dose of the enhanced tablet formulation provided only 52% of the bioavailable dose of 1600 mg of the standard capsule formulation.[1]

1. Lapham G, *et al.* Bioavailability of two clodronate formulations. *Br J Hosp Med* 1996; **56:** 231–3.

Uses and Administration

Clodronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses. Clodronate is used, generally as the disodium salt, as an adjunct in the treatment of severe hypercalcaemia associated with malignancy. In addition, it is used in the management of osteolytic lesions and bone pain associated with skeletal metastases. Doses are expressed in terms of anhydrous clodronate disodium; 125 mg of clodronate disodium tetrahydrate is equivalent to about 100 mg of anhydrous substance.

Clodronate is given by slow intravenous infusion, diluted in sodium chloride 0.9% or glucose 5%, or orally, as a single daily dose or in 2 divided doses; food should be avoided for at least 1 hour before or 1 hour after an oral dose. Clodronate disodium is available in capsules of 400 mg and standard tablets of 800 mg. Tablets of clodronate disodium 520 mg are also available in some countries, and have a greater bioavailability than the capsules or standard tablets; one such tablet of clodronate disodium 520 mg is equivalent to about two capsules each containing clodronate disodium 400 mg or one 800-mg standard tablet (but see Bioavailability, above).

In the management of osteolytic lesions, hypercalcaemia, and bone pain associated with **skeletal metastases** in patients with breast cancer or multiple myeloma, clodronate disodium 1.6 g daily (4 capsules or 2 standard tablets) is given orally, and may be increased if necessary to a maximum of 3.2 g daily. Alternatively a dose of 1.04 g (2 tablets) daily, increased if necessary up to 2.08 g daily, may be given as enhanced bioavailability tablets.

In **hypercalcaemia of malignancy** clodronate disodium is given by intravenous infusion over not less than 2 hours in a dose of 300 mg in 500 mL of infusion solution daily on successive days until normocalcaemia is achieved (usually within 5 days); duration of treatment should not exceed 10 days. Alternatively, it may be given as a single intravenous infusion of 1.5 g in 500 mL of infusion solution over a period of 4 hours. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy may be given orally in similar doses to those used for initial oral treatment of metastases. If hypercalcaemia recurs, the intravenous dose may be repeated.

◊ General references.

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Kanis JA, McCloskey EV. Clodronate. *Cancer* 1997; **80** (suppl): 1691–5.
3. Brandi ML. Impiego del clodronato nei disordini del metabolismo minerale: stato dell'arte nell'anno 2000. *Minerva Med* 2001; **92:** 251–68.
4. Dando TM, Wiseman LR. Clodronate: a review of its use in the prevention of bone metastases and the management of skeletal complications associated with bone metastases in patients with breast cancer. *Drugs Aging* 2004; **21:** 949–62.

Administration. In Italy, clodronate is also used *intramuscularly*.[1,2] The usual dose for maintenance therapy of hypercalcaemia is 100 mg daily for 2 to 3 weeks; in the prevention and treatment of postmenopausal osteoporosis, 100 mg is given every 7 to 14 days. However, injection into the gluteal muscle caused local hardening; severe pain at the injection site may limit prolonged use of this route.[1] In Canada, clodronate has been given *subcutaneously* in doses of 1500 mg in 50 to 250 mL of infusion solution over 2 to 3 hours, to treat hypercalcaemia associated with malignancy. The chest and abdomen were the sites most frequently used; pain was the most common adverse effect.[3]

1. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
2. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
3. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

Administration in renal impairment. A pharmacokinetic study[1] found that renal clearance of intravenous clodronate was highly dependent on renal function. While recommending caution in interpreting these results for patients with malignancy or severe bone disease, the authors recommended the following dose adjustments based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: up to 25% reduction in dose
- CC 12 to 49 mL/minute: 25 to 50% dose reduction
- CC less than 12 mL/minute: 50% dose reduction

However, some manufacturers recommend that *intravenous* infusion of clodronate should be avoided in patients with moderate to severe renal impairment (serum creatinine greater than 440 micromoles/litre). Others recommend, where multiple infusions are given, adjustment according to creatinine clearance (CC) as follows:

- mild renal impairment (CC 50 to 80 mL/minute): 25% reduction in dose
- moderate renal impairment (CC 10 to 50 mL/minute): 25 to 50% dose reduction
- severe impairment (CC below 10 mL/minute): contra-indicated

For the *oral* route the following adjustments may be made:

- CC between 10 and 30 mL/minute: 50% dose reduction
- CC below 10 mL/minute (or serum creatinine greater than 440 micromoles/litre): contra-indicated

1. Saha H, *et al.* Pharmacokinetics of clodronate in renal failure. *J Bone Miner Res* 1994; **9:** 1953–8.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients. In a small study,[1] intravenous clodronate 300 mg daily for 10 days significantly improved pain, tenderness, swelling, and motion compared with placebo.

1. Varenna M, *et al.* Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome: a randomized, double blind, placebo controlled study. *J Rheumatol* 2000; **27:** 1477–83.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. Clodronate has been shown to be effective[1-4] in the treatment of malignant hypercalcaemia. A small dose-response study[3] found low-dose clodronate for mild cases to be as effective as high-dose clodronate for moderate to severe cases of tumour-induced hypercalcaemia.

1. O'Rourke NP, *et al.* Effective treatment of malignant hypercalcaemia with a single intravenous infusion of clodronate. *Br J Cancer* 1993; **67:** 560–3.
2. Elomaa I, Blomqvist C. Clodronate and other bisphosphonates as supportive therapy in osteolysis due to malignancy. *Acta Oncol* 1995; **34:** 629–36.
3. Shah S, *et al.* Is there a dose response relationship for clodronate in the treatment of tumour induced hypercalcaemia? *Br J Cancer* 2002; **86:** 1235–7.
4. Roemer-Bécuwe C, *et al.* Safety of subcutaneous clodronate and efficacy in hypercalcaemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003; **26:** 843–8.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Clodronate is licensed for such use in many countries. Studies in breast cancer patients with bone metastases found that clodronate reduced the incidence of fractures,[1,2] and delayed the time to onset of new bone events.[2,3] Whether bisphosphonates can prevent the development of new skeletal metastases is unclear. Results of studies using clodronate to reduce skeletal metastases in women with breast cancer have been conflicting,[1,4-6] and one study in women with node-positive disease actually suggested an increase in concomitant visceral metastases.[5] Overall, the studies appeared limited by duration, and further data are needed.[7] In a trial of patients with multiple myeloma,[8] oral clodronate was found to slow the progression of skeletal disease, especially in those patients with less overt disease at diagnosis; the authors suggested starting clodronate early in the course of the disease.

1. Kanis JA, *et al.* Clodronate decreases the frequency of skeletal metastases in women with breast cancer. *Bone* 1996; **19:** 663–7.
2. Kristensen B, *et al.* Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999; **246:** 67–74.
3. Tubiana-Hulin M, *et al.* Essai comparatif randomisé en double aveugle clodronate oral 1600 mg/j versus placebo chez des patientes avec métastases osseuses de cancer du sein: double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. *Bull Cancer* 2001; **88:** 701–7.
4. Diel IJ, *et al.* Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998; **339:** 357–63.
5. Saarto T, *et al.* Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001; **19:** 10–17.
6. Powles T, *et al.* Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002; **20:** 3219–24.
7. Hurst M, Noble S. Clodronate: a review of its use in breast cancer. *Drugs Aging* 1999; **15:** 143–67.
8. McCloskey EV, *et al.* A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. *Br J Haematol* 1998; **100:** 317–25.

Osteogenesis imperfecta. Clodronate has been reported to be of benefit in a boy with osteogenesis imperfecta (p.1083) type I. Starting at 13⁄ years old he was given oral clodronate 400 mg daily for 5 years, and sustained no new low-trauma fractures during this time. Treatment was stopped for 8 months, but bone mineral density remained below normal limits. Clodronate was restarted at 800 mg daily and given with no untoward effects, until the patient was 22 years old, 8 years after initial referral.[1]

1. Ashford RU, *et al.* Oral clodronate as treatment of osteogenesis imperfecta. *Arch Dis Child* 2003; **88:** 945.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Clodronate is licensed for this use in some countries. Studies of its use in daily oral doses, or intermittent intravenous infusions,[1] or intramuscular injections (at 7-, 10- or 14-day intervals)[1,2] found increases in bone mineral density at various sites in postmenopausal women with osteoporosis or low bone mass. A large study[3] in postmenopausal women with vertebral osteopenia found that oral clodronate 800 mg daily prevented bone loss in the lumbar spine and femoral trochanter, but not the femoral neck; this dose has been shown to reduce vertebral fracture risk in women with postmenopausal or secondary osteoporosis.[4] The risk of vertebral fractures was also reduced in patients with arthritis receiving corticosteroids, who were given intramuscular clodronate once weekly.[5] Oral clodronate may be of benefit in reducing bone loss after heart transplantation,[6] but the benefits of intravenous clodronate in a small prospective study in patients receiving parenteral nutrition (who are at high risk of osteoporosis) were uncertain.[7]

1. Filipponi P, *et al.* Intermittent versus continuous clodronate administration in postmenopausal women with low bone mass. *Bone* 2000; **26:** 269–74.
2. Rossini M, *et al.* Intramuscular clodronate therapy in postmenopausal osteoporosis. *Bone* 1999; **24:** 125–9.
3. Välimäki MJ, *et al.* Prevention of bone loss by clodronate in early postmenopausal women with vertebral osteopenia: a dose-finding study. *Osteoporosis Int* 2002; **13:** 937–47.
4. McCloskey E, *et al.* Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004; **19:** 728–36.
5. Frediani B, *et al.* Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone* 2003; **33:** 575–81.
6. Ippoliti G, *et al.* Clodronate treatment of established bone loss in cardiac recipients: a randomized study. *Transplantation* 2003; **75:** 330–4.
7. Haderslev KV, *et al.* Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. *Am J Clin Nutr* 2002; **76:** 482–8.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. A review[1] of clodronate stated that oral doses of 800 to 1600 mg daily were effective in reducing bone turnover in patients with Paget's disease, and that remission after stopping was longer with the higher dose. Duration of therapy also appears to affect response;[1] longer treatment was associated with a longer time to relapse.[2] Short-term intravenous clodronate (300 mg daily for 5 to 10 days) has also been found to reduce biochemical markers of bone turnover, and sustain remission for up to 1 year.[1,3]

1. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1994; **47:** 945–82.
2. Khan SA, *et al.* Duration of response with oral clodronate in Paget's disease of bone. *Bone* 1996; **18:** 185–90.
3. Broggini M, *et al.* Short courses of intravenous clodronate in the treatment of Paget's disease of bone: a long-term follow-up trial. *Int J Clin Pharmacol Res* 1993; **13:** 301–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Bonefos; ***Austria:*** Ascredar; Bonefos; Lodronat; ***Belg.:*** Bonefos; Ostac†; ***Braz.:*** Bonefos; Ostac; ***Canad.:*** Bonefos; Ostac; ***Chile:*** Lodronat†; ***Cz.:*** Bonefos; Lodronat; ***Denm.:*** Bonefos; ***Fin.:*** Bonefos; ***Fr.:*** Clastoban; Lytos; ***Ger.:*** Bonefos; Clodron; Clodron beta; Ostac; ***Gr.:*** Bonefos; Ostac; ***Hong Kong:*** Bonefos; Ostac; ***Hung.:*** Bonefos; Lodronat†; ***Indon.:*** Bonefos; ***Irl.:*** Bonefos; Loron; ***Israel:*** Bonefos; Ostac; ***Ital.:*** Clasteon; Climaclod; Clodeosten; Clodron; Clody; Difosfonal; Dolkin†; Moticlod; Niklod; Ossiten;

Osteonorm; Osteostab; ***Malaysia:*** Bonefos; ***Mex.:*** Bonefos; ***Neth.:*** Bonefos; Ostac; ***Norw.:*** Bonefos; ***Philipp.:*** Bonefos; ***Pol.:*** Bonefos; Sindronat; ***Port.:*** Bonefos; Ostac; ***Rus.:*** Bonefos (Бонефос); ***S.Afr.:*** Bonephos; Ostac†; ***Singapore:*** Bonefos; ***Spain:*** Bonefos; Hemocalcin†; Mebonat†; ***Swed.:*** Bonefos; Ostac; ***Switz.:*** Bonefos; Ostac; ***Thai.:*** Bonefos; ***Turk.:*** Bonefos; ***UK:*** Bonefos; Clasteon; Loron.

Denosumab *(USAN, rINN)*

AMG-162; Dénosumab; Denosumabum.

Деносумаб

CAS — 615258-40-7.

Profile

Denosumab is a human monoclonal antibody that specifically targets the receptor activator of nuclear factor-kappa B ligand (RANKL), a mediator of the resorptive phase of bone remodelling. Denosumab is under investigation for various conditions, including osteoporosis, treatment-induced bone loss, rheumatoid arthritis, bone metastases, and multiple myeloma.

◊ References.

1. Lewiecki EM. RANK ligand inhibition with denosumab for the management of osteoporosis. *Expert Opin Biol Ther* 2006; **6:** 1041–50.
2. Body J-J, *et al.* A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006; **12:** 1221–8.
3. McClung MR, *et al.* Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006; **354:** 821–31.
4. Hamdy NA. Targeting the RANK/RANKL/OPG signaling pathway: a novel approach in the management of osteoporosis. *Curr Opin Investig Drugs* 2007; **8:** 299–303.
5. Lewiecki EM, *et al.* AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res* 2007; **22:** 1832–41.
6. Lipton A, *et al.* Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007; **25:** 4431–7.
7. Bone HG, *et al.* Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008; **93:** 2149–57.
8. Cohen SB, *et al.* Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum* 2008; **58:** 1299–1309.
9. Miller PD, *et al.* Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008; **43:** 222–9.

Etidronate

ATC — M05BA01.

ATC Vet — QM05BA01.

Etidronic Acid *(BAN, USAN, rINN)*

Acide Étidronique; Ácido etidrónico; Acidum Etidronicum; Etidronihappo; Etidronsyra. 1-Hydroxyethylidenedi(phosphonic acid).

Этидроновая Кислота

$C_2H_8O_7P_2$ = 206.0.

CAS — 2809-21-4.

ATC — M05BA01.

ATC Vet — QM05BA01.

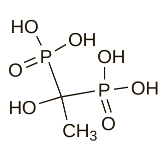

Etidronate Disodium *(USAN, rINNM)*

Dinatrii etidronas; Dinatriumetidronaatti; Dinatriumetidronat; Dinatrium-etidronát; Disodium Etidronate *(BANM)*; Disodu etydronian; Disodyum Etidronat; EHDP; Etidronas Dinatricum; Étidronate disodique; Etidronate Disodique; Etidronato disódico. Disodium dihydrogen (1-hydroxyethylidene)diphosphonate.

Динатрий Этидронат

$C_2H_6Na_2O_7P_2$ = 250.0.

CAS — 7414-83-7.

ATC — M05BA01.

ATC Vet — QM05BA01.

NOTE. Other etidronic acid sodium salts are designated as etidronate monosodium, etidronate trisodium, and etidronate tetrasodium. The name etidronate sodium is used only in *Martindale* where the salt cannot be identified more precisely.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Etidronate Disodium). A white or yellowish, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.2 to 5.2. Store in airtight containers.

USP 31 (Etidronate Disodium). A white powder that may contain lumps. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. pH of a 1% solution in water is between 4.2 and 5.2.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Unlike the newer bisphosphonates etidronate produces marked impairment of bone mineralisation at high therapeutic doses. An increase in bone pain may occur in patients with Paget's disease. Impairment of bone mineralisation may result in osteomalacia, and fractures have been reported. If a fracture occurs etidronate should be stopped until healing is complete. Hyperphosphataemia may occur, usually at high doses, but generally resolves 2 to 4 weeks after the end of therapy. There have been reports of paraesthesias, peripheral neuropathy, and confusion. Burning of the tongue, alopecia, erythema multiforme, and exacerbation of asthma have occurred rarely. Transient loss or alteration of taste has been reported mainly during and after intravenous infusion.

Effects on the blood. For a report of pancytopenia caused by etidronate therapy, see Effects on the Skin, below.

Effects on the ears. Ototoxicity, manifest as tinnitus and hearing loss, has been reported[1] in 2 patients given etidronate for osteoporosis; both patients had pre-existing otosclerosis and the authors recommended that those with ear pathology be monitored audiometrically when given bisphosphonates.

1. Yeşil S, *et al.* Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J* 1998; **74:** 363–4.

Effects on the eyes. For reports of ocular effects associated with the bisphosphonates, including etidronate, see under Bisphosphonates, p.1090.

Effects on the gastrointestinal tract. Oral etidronate was not associated with an increased incidence of upper gastrointestinal problems in a retrospective cohort study.[1] There was also no evidence of an increased incidence of gastrointestinal effects when given with NSAIDs or corticosteroids. Similarly, another large cohort study found no increased risk of peptic ulcer disease associated with the use of cyclical etidronate.[2] However, oesophageal ulceration has been reported with daily etidronate;[3,4] in one case possibly associated with incorrect use,[3] and in another, complicated by prior use of diclofenac, and a history of gastro-oesophageal reflux disease.[4]

1. van Staa T, *et al.* Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997; **103:** 462–7.
2. Burger H, *et al.* Cyclical etidronate use is not associated with symptoms of peptic ulcer disease. *Eur J Clin Pharmacol* 2000; **56:** 319–22.
3. Macedo G, *et al.* Ulcerative esophagitis caused by etidronate. *Gastrointest Endosc* 2001; **53:** 250–1.
4. Maroy B. Ulcère géant de l'œsophage probablement dû à la prise d'étidronate. *Gastroenterol Clin Biol* 2001; **25:** 917–18.

Effects on the kidneys. Bisphosphonates are excreted by the kidneys, thus caution is advised in patients with renal impairment. When given by intravenous infusion for the treatment of hypercalcaemia of malignancy they have been reported to affect renal function adversely; hypercalcaemia or malignancy may also have contributed. For reports of renal failure associated with etidronate see under Bisphosphonates, p.1091.

Effects on mental state. Sensory hallucinations and confusion were reported in an elderly woman given daily etidronate for a week. Symptoms resolved on stopping the drug and recurred on rechallenge.[1] Mood disturbances, lack of concentration, and memory impairment were also reported in 3 patients receiving longer-term cyclical treatment; symptoms again diminished on stopping etidronate and reappeared after rechallenge.[2]

1. Burnet SP, Petrie JP. 'Wake up and smell the roses'—a drug reaction to etidronate. *Aust N Z J Med* 1999; **29:** 93.
2. Wolffenbuttel BHR, van der Klauw MM. Psychische bijwerkingen van behandeling met bisfosfonaten. *Ned Tijdschr Geneeskd* 2003; **147:** 35–7.

Effects on the respiratory system. For a report of bronchospasm induced by etidronate in an aspirin-sensitive asthmatic, see p.1091. For a report of fatal cardiorespiratory failure secondary to acute respiratory distress syndrome caused by etidronate, see Effects on the Skin, below.

Effects on the skin. A 47-year old woman with a history of auto-immune rheumatic disease developed toxic epidermal necrolysis, pancytopenia, and acute respiratory distress syndrome 7 days after starting etidronate for osteoporosis; she died of cardiorespiratory failure, secondary to the acute respiratory distress syndrome, despite aggressive supportive measures.[1]

1. Coakley G, Isenberg DA. Toxic epidermal necrolysis, pancytopenia and adult respiratory syndrome. *Br J Rheumatol* 1995; **34:** 798.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare (see p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Anti-inflammatory drugs. For a lack of apparent interaction between cyclical etidronate and corticosteroids or NSAIDs see under Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

After oral doses of etidronate, absorption is variable and appears to be dose dependent. At usual doses about 1 to 6% of a dose is absorbed. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. Etidronate is rapidly cleared from the blood and has been reported to have a plasma half-life of 1 to 6 hours. It is not metabolised. About 50% is excreted in the urine within 24 hours, the remainder being sequestered to bone and slowly eliminated. The half-life of etidronate in bone exceeds 90 days. Unabsorbed etidronate appears in the faeces.

Uses and Administration

Etidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits the growth and dissolution of hydroxyapatite crystals in bone and may also directly impair osteoclast activity. It diminishes bone resorption and thus reduces bone turnover.

Etidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also given in bone disorders in which excessive bone resorption is a problem, such as Paget's disease of bone and osteoporosis. In addition, it may be used for the prevention and treatment of ectopic (heterotopic) ossification. A chelate of etidronate with radioactive technetium-99m (p.2055) is used diagnostically as a bone scanning agent and a similar compound with rhenium-186 for the palliation of bone metastases in prostate cancer (see below).

Etidronate is given as the disodium salt, by intravenous infusion over at least 2 hours, or orally, usually as a single daily dose. Food should be avoided for 2 hours before and after oral doses.

In the treatment of **Paget's disease**, etidronate disodium is given orally in a usual initial dose of 5 mg/kg daily for not more than 6 months. Doses above 10 mg/kg daily should be reserved for severe disease and should not be given for more than 3 months at a time. The maximum dose is 20 mg/kg daily. The response to etidronate may be slow in onset and may continue for several months after stopping therapy. Therefore, further treatment should only be given after a drug-free interval of at least 3 months and after evidence of relapse; it should not be given for longer than the initial treatment.

In the treatment of **hypercalcaemia of malignancy** the recommended dose of etidronate disodium by slow intravenous infusion is 7.5 mg/kg daily for 3 successive days, although infusions may be continued for up to 7 days if necessary. This daily dose should be diluted in at least 250 mL of sodium chloride 0.9% and infused over at least 2 hours. There should be at least a 7-day interval between courses of treatment. Once serum-calcium concentrations have been reduced to an acceptable level, maintenance therapy with oral etidronate disodium 20 mg/kg daily for 30 days may be started on the day after the last intravenous dose; treatment may be extended to a maximum of 90 days.

For the prevention and treatment of **ectopic ossification** complicating hip replacement etidronate disodium has been given orally in a dose of 20 mg/kg daily for 1 month before and 3 months after the operation. For ectopic ossification due to spinal cord injury it has been given in a dose of 20 mg/kg daily for 2 weeks followed by 10 mg/kg daily for 10 weeks.

For the treatment of **osteoporosis**, the prevention of bone loss in postmenopausal women, and the prevention and treatment of corticosteroid-induced osteoporosis, etidronate is given in an intermittent or cyclical regimen with a calcium salt; oral etidronate disodium 400 mg is given daily for 14 days followed by the equivalent of 500 mg of elemental calcium orally for 76 days. Treatment has continued for 3 years in most patients; a small number of patients have been successfully treated for up to 7 years. The optimum duration of treatment has not been established.

Administration in renal impairment. Some manufacturers have recommended that etidronate disodium should not be given *intravenously* to patients with serum-creatinine concentrations greater than 50 mg/litre, and that doses may need to be reduced in those with concentrations between 25 and 49 mg/litre. Reduced *oral* doses are similarly recommended in mild renal impairment, and avoidance in moderate to severe impairment.

Ectopic ossification. Bisphosphonates that inhibit bone mineralisation such as etidronate have been used to prevent ectopic ossification (p.100). Some studies, using higher and more prolonged dosage (20 mg/kg daily by mouth for 6 months) than is generally recommended for treatment after spinal cord injury, have suggested that this may improve effectiveness.[1,2] Etidronate has also been used to treat calciphylaxis and vascular and soft-tissue calcification associated with haemodialysis.[3-5]

1. Banovac K, *et al.* Treatment of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 1997; **20:** 60–65.
2. Banovac K. The effect of etidronate on late development of heterotopic ossification after spinal cord injury. *J Spinal Cord Med* 2000; **23:** 40–4.
3. Hashiba H, *et al.* Inhibition of the progression of aortic calcification by etidronate treatment in hemodialysis patients: long-term effects. *Ther Apher Dial* 2006; **10:** 59–64.
4. Shiraishi N, *et al.* Successful treatment of a patient with severe calcific uremic arteriolopathy (calciphylaxis) by etidronate disodium. *Am J Kidney Dis* 2006; **48:** 151–4.
5. Mori H, *et al.* Etidronate for the treatment of progressive tumoral calcinosis in hemodialysis patients. *Intern Med* 2007; **46:** 1485–6.

Hypercalcaemia. Bisphosphonates (including etidronate although other bisphosphonates may be more suitable) are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated.

There are reports of response[1-3] to etidronate 5 mg/kg twice daily by mouth in the treatment of hypercalcaemia associated with subcutaneous fat necrosis of the newborn refractory to standard treatment.

1. Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatr* 1999; **134:** 349–51.
2. Wiadrowski TP, Marshman G. Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. *Australas J Dermatol* 2001; **42:** 207–10.
3. Trullemans B, *et al.* Etidronate per os dans le cadre d'une hypercalcémie secondaire à une cytostéatonécrose compliquée de néphrocalcinose. *Arch Pediatr* 2007; **14:** 170–2.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660). Etidronate, labelled with rhenium-186 or its isotope rhenium-188, is used for the palliation of painful bone metastases of prostate,[1,2] breast,[3,4] lung,[4,5] and various other cancers.[4]

1. Han SH, *et al.* The Placorhen study: a double-blind, placebo-controlled, randomized radionuclide study with Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. *J Nucl Med* 2002; **43:** 1150–6.
2. Liepe K, *et al.* Therapeutic efficiency of rhenium-188-HEDP in human prostate cancer skeletal metastases. *Br J Cancer* 2003; **89:** 625–9.
3. Sciuto R, *et al.* Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. *Breast Cancer Res Treat* 2001; **66:** 101–9.
4. Li S, *et al.* Rhenium-188 HEDP to treat painful bone metastases. *Clin Nucl Med* 2001; **26:** 919–22.
5. Zhang H, *et al.* Rhenium-188-HEDP therapy for the palliation of pain due to osseous metastases in lung cancer patients. *Cancer Biother Radiopharm* 2003; **18:** 719–26.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p.1084). Etidronate is used in a cyclical regimen for both the treatment and prevention of **postmenopausal** osteoporosis. It increases bone mineral density (BMD), largely in the lumbar spine and femoral neck, and reduces the risk of vertebral fractures,[1,2] but not non-vertebral fractures.[2] Additive effects on BMD have been found when etidronate was used with oestrogen.[1] Etidronate also prevents bone loss and maintains or increases BMD in **corticosteroid-induced** osteoporosis,[1,3] and has shown some benefit in reducing bone loss after organ transplantation.[1] In an uncontrolled study[4] in **men** with idiopathic vertebral osteoporosis, cyclical etidronate increased BMD at the lumbar spine.

1. Hanley DA, *et al.* Etidronate therapy in the treatment and prevention of osteoporosis. *J Clin Densitom* 2000; **3:** 79–95.
2. Wells GA, *et al.* Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/08).
3. Adachi JD, *et al.* A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol* 2000; **27:** 2424–31.
4. Anderson FH, *et al.* Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures. *Age Ageing* 1997; **26:** 359–65.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Initial experience was with etidronate, but bisphosphonates that have less effect on bone mineralisation may be preferred. In studies, alendronate[1] and risedronate[2] were found to be more effective than etidronate.

1. Siris E, *et al.* Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. *J Clin Endocrinol Metab* 1996; **81:** 961–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; **106:** 513–20.

Preparations

USP 31: Etidronate Disodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Difosfen; ***Austral.:*** Didronel; ***Austria:*** Detidron; Didronel; ***Belg.:*** Didronel†; Osteodidronel; ***Canad.:*** Didronel; ***Chile:*** Osteotop†; ***Denm.:*** Didronate; ***Fin.:*** Didronate; ***Fr.:*** Didronel; ***Ger.:*** Didronel; Diphos; Etidron; ***Gr.:*** Anfozan; Biotredine†; Dralen†; Etidron; Etiplus; Feminoflex; Maxibral; Oflocin; Osfo; Ostedron; Osteodrug; Osteoton; Ostogene; Ostopor; Somaflex†; Sterodome†; Sviroxit; Tilferan†; ***Hong Kong:*** Didronel†; ***India:*** Dronate-OS; ***Irl.:*** Didronel; ***Israel:*** Didronel; ***Ital.:*** Didronel†; Etidron; ***Jpn:*** Didronel; ***Neth.:*** Didronel; ***NZ:*** Didronel; Etidrate; ***Pol.:*** Ostedron; ***Port.:*** Didronel†; ***Singapore:*** Difosfen; ***Spain:*** Difosfen; Osteum; ***Swed.:*** Didronate; Etidrel; ***Switz.:*** Didronel; ***Thai.:*** Difosfen; ***Turk.:*** Didronat; ***UK:*** Didronel; ***USA:*** Didronel.

Multi-ingredient: ***Arg.:*** Emoform Total; Squam; ***Austral.:*** Didrocal; ***Canad.:*** Didrocal; ***Denm.:*** Didronate Calcium; ***Fin.:*** Didronate + Calcium; ***Ger.:*** Didronel Kit; Etidron Kombi; ***Irl.:*** Didronel PMO; ***Neth.:*** Didrokit; ***Norw.:*** Didronate + Calsium; ***Swed.:*** Didronate + Calcium; Etidrel Kit; ***UK:*** Didronel PMO; Tiloetca Combi.

Gallium Nitrate *(USAN)*

Galio, nitrato de; NSC-15200; WR-135675.

$Ga(NO_3)_3,9H_2O = 417.9.$

CAS — 13494-90-1 (anhydrous gallium nitrate); 135886-70-3 (gallium nitrate nonahydrate).

Adverse Effects, Treatment, and Precautions

Gallium nitrate may produce serious nephrotoxicity, especially when given as a brief intravenous infusion; continuous infusion, with adequate hydration, may reduce the incidence of renal damage. Serum creatinine should be monitored during therapy and treatment stopped if it exceeds 25 mg/litre. Gallium nitrate should be given with great care and in reduced doses, if at all, to patients with existing renal impairment.

Gastrointestinal disturbances, rashes, metallic taste, visual and auditory disturbances, anaemia, hypophosphataemia, and hypocalcaemia have also been reported.

Effects on the nervous system. Although it has been suggested, given the chemical similarity of gallium to aluminium, that repeated doses, particularly in the presence of renal impairment, might lead to severe neurotoxicity,[1] studies in *rats* do not provide any evidence of central neurological abnormalities.[2]

1. Altmann P, Cunningham J. Hazards of gallium for the treatment of Paget's disease of bone. *Lancet* 1990; **335:** 477.
2. Matkovic V, *et al.* Hazards of gallium for Paget's disease of bone. *Lancet* 1990; **335:** 1099. Correction. *ibid.*; 1352.

Uses and Administration

Gallium nitrate is an inorganic metallic salt with hypocalcaemic properties. It acts to decrease bone resorption by osteoclasts, with a lesser and probably indirect increase in bone formation, and a consequent decline in serum calcium.

Gallium nitrate is used in the treatment of hypercalcaemia associated with malignant neoplasms. It has been investigated in other disorders associated with abnormally enhanced bone turnover, such as Paget's disease of bone, and is under investigation in refractory non-Hodgkin's lymphoma. For the treatment of hypercalcaemia of malignancy doses of 100 to 200 mg/m^2 may be given daily for up to 5 days, diluted in 1 litre of sodium chloride 0.9% or glucose 5% and infused intravenously over 24 hours. Treatment may be repeated after 2 to 4 weeks, if necessary. Adequate hydration before and during treatment is essential: a urinary output of at least 2 litres daily should be maintained, and renal function should be regularly monitored.

Hypercalcaemia. Gallium nitrate is used in the treatment of hypercalcaemia of malignancy (p.1083). It appears to be effective in patients with solid tumours and increased levels of parathyroid-related protein.[1,2]

1. Chitambar CR. Gallium nitrate revisited. *Semin Oncol* 2003; **30** (suppl): 1–4.
2. Leyland-Jones B. Treatment of cancer-related hypercalcemia: the role of gallium nitrate. *Semin Oncol* 2003; **30** (suppl); 13–19.

Paget's disease of bone. Beneficial results[1] were reported when gallium nitrate was given subcutaneously in doses of 250 or 500 micrograms/kg daily for 14 days to patients with advanced Paget's disease of bone (p.1086). In this pilot multicentre study 14 days of gallium nitrate injections were followed by 4 weeks off medication and the cycle repeated once.

1. Bockman RS, *et al.* A multicenter trial of low dose gallium nitrate in patients with advanced Paget's disease of bone. *J Clin Endocrinol Metab* 1995; **80:** 595–602.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ganite.

Ibandronate

ATC — M05BA06.
ATC Vet — QM05BA06.

Ibandronic Acid *(BAN, rINN)*

Acide Ibandronique; Ácido ibandrónico; Acidum Ibandronicum; BM-21.0955; Ibandronik Asit. [1-Hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid.

Ибандроновая Кислота

$C_9H_{23}NO_7P_2 = 319.2.$
CAS — 114084-78-5.
ATC — M05BA06.
ATC Vet — QM05BA06.

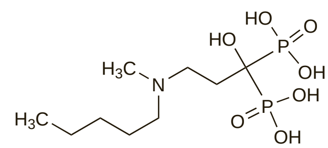

Ibandronate Sodium *(USAN)*

Sodium Ibandronate *(BANM, rINNM)*; Ibandronate de Sodium; Ibandronato sódico; Natrii Ibandronas; Natriumibandronaatti; Natriumibandronat.

Натрий Ибандронат

$C_9H_{22}NNaO_7P_2,H_2O = 359.2.$
CAS — 138926-19-9.
ATC — M05BA06.
ATC Vet — QM05BA06.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Gastrointestinal symptoms such as abdominal pain, dyspepsia, and nausea are the most frequent adverse effects with oral ibandronate. Severe oesophageal reactions such as oesophagitis, and ulceration have occurred; patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn. Gastric ulceration has been reported. To minimise the risk of oesophageal reactions, precautions similar to those for alendronate (see p.1088) should be observed. Anaemia and bronchospasm have occurred rarely, as has taste disturbance, paraesthesia, and uraemia. Serum calcium, magnesium, and phosphate should be monitored. Hypocalcaemia should be corrected before starting ibandronate therapy; adequate intake of calcium and vitamin D is important. Transient fever after parenteral use is common. Flu-like symptoms have been reported after both parenteral and intermittent oral use, typically after the first dose.

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including ibandronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Like other bisphosphonates, ibandronate is poorly absorbed after oral doses; absolute bioavailability is less than 1%. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is reduced by about 90% when given with food, by about 30% when given half an hour before food, and by about 75% when given

2 hours after food. About half of the absorbed portion is sequestered to bone; the remainder is excreted in urine. Plasma protein binding is about 87%. Bisphosphonates do not appear to be metabolised, and the unabsorbed fraction of ibandronate is excreted unchanged in the faeces.

◊ References.

1. Bergner R, *et al.* Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. *J Clin Pharmacol* 2007; **47:** 942–50.

Uses and Administration

Ibandronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. It is used as the sodium salt in hypercalcaemia of malignancy, for the prevention of fracture and bone complications in patients with breast cancer and bone metastases, and for the treatment and prevention of postmenopausal osteoporosis.

Ibandronate sodium is given by intravenous infusion or orally, the dose being expressed in terms of ibandronic acid; ibandronate sodium 1.13 mg is equivalent to about 1 mg of ibandronic acid. Specific instructions for oral use (see Precautions in Alendronate, p.1088) should be followed to minimise adverse effects and permit adequate absorption.

For **hypercalcaemia of malignancy**, a single intravenous dose of the equivalent of 2 to 4 mg ibandronic acid is given, up to a maximum of 6 mg; it is diluted in 500 mL of sodium chloride 0.9% or glucose 5%, and infused over 2 hours.

For the prevention of skeletal events in patients with breast cancer and **bone metastases**, the equivalent of 6 mg ibandronic acid is given intravenously, diluted in 100 mL of sodium chloride 0.9% or glucose 5%, and infused over at least 15 minutes. The dose is repeated every 3 to 4 weeks. Alternatively, ibandronic acid 50 mg daily may be given orally.

For the prevention and treatment of postmenopausal **osteoporosis**, ibandronate is given orally in a usual dose equivalent to 150 mg of ibandronic acid once monthly on the same date each month; alternatively, 2.5 mg daily by mouth may be given. If the once-monthly dose is missed, and the next scheduled dose is more than 7 days away, the dose should be taken the next morning, and the patient should then return to the original schedule. However, if the next dose is less than 7 days away, then the patient should wait until that next scheduled dose; 2 tablets must not be taken within the same week. Alternatively, treatment may be given intravenously, in a dose equivalent to 3 mg of ibandronic acid once every 3 months; the injection is given over 15 to 30 seconds. If the dose is missed, the injection should be given as soon as possible; the next injection should then be rescheduled 3 months from this injection, as it should not be given more frequently than once every 3 months.

◊ General references.

1. Dooley M, Balfour JA. Ibandronate. *Drugs* 1999; **57:** 101–108.
2. Barrett J, *et al.* Ibandronate: a clinical pharmacological and pharmacokinetic update. *J Clin Pharmacol* 2004; **44:** 951–65.
3. Anonymous. Ibandronate (Boniva): a new oral bisphosphonate. *Med Lett Drugs Ther* 2005; **47:** 35.
4. Guay DR. Ibandronate, an experimental intravenous bisphosphonate for osteoporosis, bone metastases, and hypercalcemia of malignancy. *Pharmacotherapy* 2006; **26:** 655–73.
5. Zaidi M, *et al.* Progression of efficacy with ibandronate: a paradigm for the development of new bisphosphonates. *Ann N Y Acad Sci* 2007; **1117:** 273–82.
6. Reginster JY, *et al.* Ibandronate in profile: drug characteristics and clinical efficacy. *Expert Opin Drug Metab Toxicol* 2008; **4:** 941–51.

Administration in renal impairment. UK and US licensed product information for ibandronate states that the dose should be adjusted on the basis of creatinine clearance (CC).

When used for the prevention of skeletal events in patients with breast cancer and **bone metastases**, the following *oral* doses are recommended:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: 50 mg once weekly

Since a 15-minute infusion time has not been studied in cancer patients with a CC less than 50 mL/minute, the following *intravenous* doses are recommended, to be given every 3 to 4 weeks in a solution of sodium chloride 0.9% or glucose 5%:

- CC equal to or greater than 50 mL/minute: no adjustment necessary
- CC less than 50 mL/minute, but equal to or greater than 30 mL/minute: 6 mg in 500 mL of infusion solution, infused over 1 hour
- CC less than 30 mL/minute: 2 mg in 500 mL of infusion solution, infused over 1 hour

In patients with **osteoporosis**, the following recommendations are given, for *oral* or *intravenous* use:

- mild or moderate renal impairment (CC equal to or greater than 30 mL/minute): no adjustment necessary
- CC below 30 mL/minute: not recommended

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. In a dose-response study,[1] 2 mg of ibandronate was found to be significantly less effective than 4 or 6 mg in correcting hypercalcaemia, and response was better in those patients with breast cancer or haematological tumours. In comparison to pamidronate,[2] ibandronate was reported to be more effective in those patients with higher initial baseline serum calcium; duration of response was also longer with ibandronate. In a series of case reports, intravenous ibandronate rapidly corrected hypercalcaemia and restored renal function in multiple myeloma patients. The authors suggested that, although unlicensed for this use, ibandronate should be considered in this patient population.[3]

1. Ralston SH, *et al.* Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. *Br J Cancer* 1997; **75:** 295–300.
2. Pecherstorfer M, *et al.* Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003; **11:** 539–47.
3. Henrich D, *et al.* Ibandronate for the treatment of hypercalcemia or nephrocalcinosis in patients with multiple myeloma and acute renal failure: case reports. *Acta Haematol (Basel)* 2006; **116:** 165–72.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Ibandronate is licensed for such use in many countries. In patients with bone metastases from breast cancer, both oral[1] and intravenous[2] ibandronate reduced the skeletal morbidity period rate (the number of 12-week periods with new bone complications). A pilot study[3] in 18 patients with skeletal metastases from various tumours, and with bone pain insufficiently controlled with opioid analgesics, found short-term intensive intravenous ibandronate (4 mg for 4 consecutive days) to significantly reduce bone pain scores; this analgesic effect was obtained within 7 days, and sustained for a further 5 weeks. A review[4] concluded that once-monthly intravenous dosing could aid compliance, since it can be given simultaneously with cancer therapy; the absence of any apparent renal toxicity associated with ibandronate was a further advantage in its use in cancer patients.

Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Tripathy D, *et al.* Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. *Ann Oncol* 2004; **15:** 743–50.
2. Body J-J, *et al.* Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003; **14:** 1399–1405.
3. Mancini I, *et al.* Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004; **22:** 3587–92.
4. McCormack PL, Plosker GL. Ibandronic acid: a review of its use in the treatment of bone metastases of breast cancer. *Drugs* 2006; **66:** 711–28.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). In the treatment of **postmenopausal** osteoporosis, *oral* ibandronate in intermittent regimens of 20 mg every alternate day,[1] or 20 mg weekly[2] has been found to have equivalent effects on bone mineral density (BMD) to 2.5 mg daily. Intermittent oral ibandronate (20 mg every alternate day for 12 doses every 3 months) was also as effective as the lower daily dose in reducing the incidence of osteoporotic fractures in postmenopausal women.[3] In the prevention of postmenopausal bone osteoporosis, both 2.5 mg daily[4] and 20 mg weekly[5] prevented bone loss at the spine and hip. A large study comparing three different monthly regimens with the 2.5 mg daily regimen found them to be of similar efficacy in terms of improvement in lumbar BMD after 1 year; 150 mg given once monthly was considered to be superior to the low-dose daily regimen.[6] A review[7] concluded that this unique once-monthly regime could benefit patients by improving compliance.

Intravenous ibandronate 2 mg given every 3 months has also proven effective in increasing BMD in the treatment[8] and prevention[9] of postmenopausal osteoporosis. A large, randomised, double-blind study compared 2 intravenous regimens (2 mg every 2 months and 3 mg every 3 months) with oral ibandronate 2.5 mg daily in postmenopausal women with osteoporosis. After 1 year, both intravenous regimens increased lumbar BMD scores significantly more than the oral regimen. Similar results were obtained for proximal femoral BMD scores, except that for femoral neck BMD, the 2-monthly regimen and daily oral regimen were not significantly different.[10] After 2 years, these results were reported to have been maintained.[11] In **corticosteroid-induced** osteoporosis, intravenous ibandronate 2 mg every 3 months was better than daily oral alfacalcidol at reducing vertebral fractures.[12,13] Intravenous ibandronate has also shown to be of benefit in reducing bone loss after kidney **transplantation**.[14] A pilot study[15] of intermittent ibandronate given intravenously to **men** with severe osteoporosis significantly increased BMD at the lumbar spine, trochanter, and femoral neck.

1. Riis BJ, *et al.* Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. *J Bone Miner Res* 2001; **16:** 1871–8.
2. Cooper C, *et al.* Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 4609–15.
3. Chesnut CH, *et al.* Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; **19:** 1241–9.
4. McClung MR, *et al.* Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res* 2004; **19:** 11–18.
5. Tankó LB, *et al.* Oral weekly ibandronate prevents bone loss in postmenopausal women. *J Intern Med* 2003; **254:** 159–67.
6. Miller PD, *et al.* Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005; **20:** 1315–22.
7. Chesnut CH. Treating osteoporosis with bisphosphonates and addressing adherence: a review of oral ibandronate. *Drugs* 2006; **66:** 1351–9.
8. Adami S, *et al.* Efficacy and safety of ibandronate given by intravenous injection once every 3 months. *Bone* 2004; **34:** 881–9.
9. Stakkestad JA, *et al.* Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. *Ann Rheum Dis* 2003; **62:** 969–75.
10. Delmas PD, *et al.* Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006; **54:** 1838–46.
11. Croom KF, Scott LJ. Intravenous ibandronate: in the treatment of osteoporosis. *Drugs* 2006; **66:** 1593–1601.
12. Ringe JD, *et al.* Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. *Osteoporosis Int* 2003; **14:** 801–7.
13. Ringe JD, *et al.* Three-month ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. *Rheumatology (Oxford)* 2003; **42:** 743–9.
14. Grotz W, *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12:** 1530–7.
15. Lamy O, *et al.* Intravenous ibandronate in men with osteoporosis: an open pilot study over 2 years. *J Endocrinol Invest* 2003; **26:** 728–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Bandrobon; Bonviva; Elasterin; Femorel; Idena; Modifical; ***Austria:*** Bondronat; ***Belg.:*** Bondronat; ***Chile:*** Bondronat; Bonviva; ***Cz.:*** Bondenza; Bondronat; Bonviva; ***Denm.:*** Bondronat; ***Fin.:*** Bondronat; Bonviva; ***Fr.:*** Bondronat; Bonviva; ***Ger.:*** Bondronat; Bonviva; ***Gr.:*** Bondronat; Bonviva; ***Hong Kong:*** Bondronat; ***Hung.:*** Bondronat; Bonviva; ***Indon.:*** Bonviva; ***Irl.:*** Bondronat; Bonviva; ***Israel:*** Bonat; ***Ital.:*** Bondronat; Bonviva; ***Malaysia:*** Bonviva; ***Mex.:*** Bondronat; ***Neth.:*** Bondenza; Bondronat; Bonviva; Destara; ***Norw.:*** Bondronat; ***Philipp.:*** Bondronat; Bonviva; ***Pol.:*** Bondronat; Bonviva†; ***Port.:*** Bondenza; Bondronat; Bonviva; ***Rus.:*** Bondronat (Бондронат); ***S.Afr.:*** Bondronat; ***Singapore:*** Bondronat; Bonviva; ***Spain:*** Bondronat; ***Swed.:*** Bondronat; Bonviva; ***Switz.:*** Bondronat; ***Thai.:*** Bondronat; ***UK:*** Bondronat; Bonviva; ***USA:*** Boniva.

Multi-ingredient: ***Arg.:*** Femorel Max.

Incadronate

Incadronic Acid *(rINN)*

Acide Incadronique; Ácido incadrónico; Acidum Incadronicum; Cimadronic Acid; YM-175. [(Cycloheptylamino)methylene]diphosphonic acid.

Инкадроновая Кислота

$C_8H_{19}NO_6P_2$ = 287.2.
CAS — 124351-85-5.

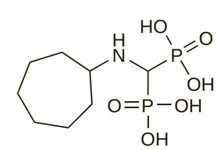

Incadronate Disodium

Disodium Incadronate *(rINNM)*; Incadronas Dinatricum; Incadronate Disodique; Incadronato disódico. Disodium [(cycloheptylamino)methylene]diphosphonate.

Динатрий Инкадронат

$C_8H_{17}NNa_2O_6P_2$ = 331.2.
CAS — 138330-18-4.

Profile

Incadronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. It is given by intravenous infusion as incadronate disodium for hypercalcaemia of malignancy in a dose of 10 mg over 2 to 4 hours; if necessary this dose may be repeated at intervals of no less than 1 week. Hypocalcaemia and hypotension may occur. Incadronate is under investigation for the treatment of bone metastases in patients with breast cancer.

◊ References.

1. Usui T, *et al.* Pharmacokinetics of incadronate, a new bisphosphonate, in healthy volunteers and patients with malignancy-associated hypercalcemia. *Int J Clin Pharmacol Ther* 1997; **35:** 239–44.
2. Matsumoto T, *et al.* Comparative study of incadronate and elcatonin in patients with malignancy-associated hypercalcaemia. *J Int Med Res* 2002; **30:** 230–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Bisphonal; ***Philipp.:*** Bisphonal; ***Thai.:*** Bisphonal.

Ipriflavone *(rINN)*

FL-113; Ipriflavona; Ipriflavonum. 7-Isopropoxyisoflavone.

Иприфлавон

$C_{18}H_{16}O_3$ = 280.3.
CAS — 35212-22-7.
ATC — M05BX01.
ATC Vet — QM05BX01.

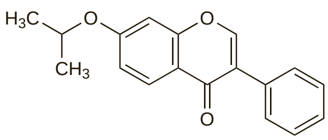

Profile

Ipriflavone is a synthetic isoflavonoid that inhibits resorption of bone and is available in some countries for the treatment of osteoporosis (p.1084). It is given orally in a dose of 200 mg three times daily.

Osteoporosis. Despite an earlier favourable report,[1] a prospective randomised controlled study in postmenopausal women with low bone mass failed to show prevention of bone loss or improvements in markers of bone metabolism with ipriflavone.[2] There was also a significant incidence of lymphopenia with the drug.

1. Agnusdei D, *et al.* Effects of ipriflavone on bone mass and bone remodeling in patients with established postmenopausal osteoporosis. *Curr Ther Res* 1992; **51:** 82–91.
2. Alexandersen P, *et al.* Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; **285:** 1482–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ipriosten†; ***Braz.:*** Osteoplus; Rebone; ***Ital.:*** Iprosten†; Osteofix; ***Jpn:*** Osten.

Multi-ingredient: ***Indon.:*** Vosteon; ***UK:*** Osteopro.

Medronate

Medronic Acid *(BAN, USAN, pINN)*

Acid medronique; Acide Médronique; Ácido medrónico; Acidum medronicum. Methylenebis(phosphonic acid).

Медроновая Кислота

$CH_6O_6P_2$ = 176.0.
CAS — 1984-15-2.

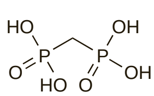

Medronate Disodium *(USAN, pINNM)*

Disodium Medronate *(BANM)*; Disodium Methylene Diphosphonate; MDP; Medronas Dinatricum; Médronate Disodique; Medronato disódico. Disodium dihydrogen methylenediphosphonate.

Динатрий Медронат

$CH_4Na_2O_6P_2$ = 220.0.
CAS — 25681-89-4.

Profile

Medronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1089). It has a strong affinity for bone. Complexes of medronate disodium and stannous chloride or fluoride, or medronic acid, stannous chloride dihydrate, and ascorbic acid, are labelled with radioactive technetium-99m (p.2055) and used diagnostically as bone scanning agents; they are given intravenously.

Hypersensitivity. For reference to a severe allergic reaction attributed to the medronate component of a radiopharmaceutical, see under Adverse Effects and Precautions of Bisphosphonates, p.1091.

Minodronate

Minodronic Acid *(rINN)*

Acide Minodronique; Ácido minodrónico; Acidum minodronicum; YH-529; YM-529. (1-Hydroxy-2-imidazo[1,2-*a*]pyridin-3-ylethylidene)diphosphonic acid.

Минодроновая Кислота

$C_9H_{12}N_2O_7P_2$ = 322.1.
CAS — 127657-42-5.

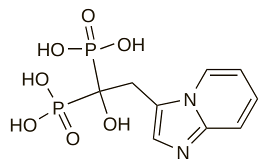

Profile

Minodronate is a bisphosphonate under investigation for osteoporosis, multiple myeloma, and bone metastases.

Neridronate

Neridronic Acid *(rINN)*

Acide Néridronique; Ácido neridrónico; Acidum neridronicum; AHDP; AHHexBP; Aminohexane Diphosphonate. (6-Amino-1-hydroxyhexylidene)diphosphonic acid.

Нéридроновая Кислота

$C_6H_{17}NO_7P_2$ = 277.1.
CAS — 79778-41-9.

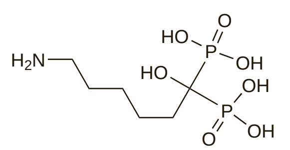

Neridronate Sodium *(rINNM)*

Natrii Neridronas; Néridronate de Sodium; Neridronato sódico.

Натрий Неридронат

Profile

Neridronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1089). It inhibits bone resorption and is given intravenously as the sodium salt in the management of osteogenesis imperfecta (p.1083); it has been used in the treatment of malignant hypercalcaemia (p.1083) and diseases associated with excessive bone turnover such as Paget's disease of bone (p.1086) and osteoporosis (p.1084).

◊ References.

1. O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; **69:** 914–17.
2. Filipponi P, *et al.* Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. *Bone* 1998; **23:** 543–8.
3. Adami S, *et al.* Short-term intravenous therapy with neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; **20:** 55–8.
4. Adami S, *et al.* Intravenous neridronate in adults with osteogenesis imperfecta. *J Bone Miner Res* 2003; **18:** 126–30.
5. Braga V, *et al.* Intravenous intermittent neridronate in the treatment of postmenopausal osteoporosis. *Bone* 2003; **33:** 342–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Nerixia.

Olpadronate

Olpadronic Acid *(rINN)*

Acide Olpadronique; Ácido olpadrónico; Acidum olpadronicum; Alpudronic Acid. [3-(Dimethylamino)-1-hydroxypropylidene]diphosphonic acid.

Олпадроновая Кислота

$C_5H_{15}NO_7P_2$ = 263.1.
CAS — 63132-39-8.

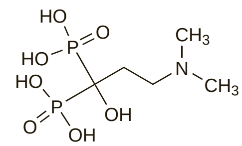

Olpadronate Disodium

IG-8801; Sodium Olpadronate.

$C_5H_{13}NNa_2O_7P_2$ = 307.1.
CAS — 121368-58-9.

Profile

Olpadronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1089). It has been investigated for the treatment of Paget's disease of bone and osteogenesis imperfecta.

◊ References.

1. González DC, Mautalen CA. Short-term therapy with oral olpadronate in active Paget's disease of bone. *J Bone Miner Res* 1999; **14:** 2042–7.
2. Soerdjbalie-Maikoe V, *et al.* Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton. *Eur J Nucl Med Mol Imaging* 2002; **29:** 494–8.
3. Cremers SCLM, *et al.* Relationships between pharmacokinetics and rate of bone turnover after intravenous bisphosphonate (olpadronate) in patients with Paget's disease of bone. *J Bone Miner Res* 2003; **18:** 868–75.
4. Eekhoff MEMW, *et al.* Determinants of induction and duration of remission of Paget's disease of bone after bisphosphonate (olpadronate) therapy. *Bone* 2003; **33:** 831–8.
5. Sakkers R, *et al.* Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. *Lancet* 2004; **363:** 1427–31.

Oxidronate

Oxidronic Acid *(BAN, USAN, pINN)*

Acide Oxidronique; Ácido oxidrónico; Acidum Oxidronicum. (Hydroxymethylene)diphosphonic acid.

Оксидроновая Кислота

$CH_6O_7P_2$ = 192.0.
CAS — 15468-10-7.

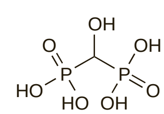

Oxidronate Disodium *(pINNM)*

Disodium Oxidronate; HMDP; Oxidronas Dinatricum; Oxidronate Disodique; Oxidronate Sodium; Oxidronato disódico; Sodium Oxidronate *(BANM)*. Disodium (hydroxymethylene)diphosphonate.

Динатрий Оксидронат

$CH_4Na_2O_7P_2$ = 236.0.
CAS — 14255-61-9.

Profile

Oxidronate is a bisphosphonate with general properties similar to those of the other bisphosphonates (p.1089). It has a strong affinity for bone. A chelate of oxidronate disodium with radioactive technetium-99m (p.2055) is used diagnostically as a bone scanning agent; it is given intravenously.

Pamidronate

ATC — M05BA03.
ATC Vet — QM05BA03.

Pamidronic Acid *(BAN, rINN)*

Acide Pamidronique; Ácido pamidrónico; Acidum Pamidronicum; Aminohydroxypropylidenebisphosphonate; APD; Pamidronihappo; Pamidronsyra. 3-Amino-1-hydroxypropylidene-bis(phosphonic acid).

Памидроновая Кислота

$C_3H_{11}NO_7P_2$ = 235.1.
CAS — 40391-99-9.
ATC — M05BA03.
ATC Vet — QM05BA03.

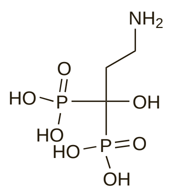

Pamidronate Disodium *(USAN, rINNM)*

Aminohydroxypropylidenebisphosphonate Disodium; CGP-23339A; CGP-23339AE; Dinatrii pamidronas pentahydricus; Dinatriumpamidronaattipentahydraatti; Dinatrium-pamidronát pentahydrát; Disodium Aminohydroxypropylidenediphosphonate; Disodium Pamidronate *(BANM)*; Disodu pamidronian pięciowodny; Disodyum Pamidronat; Pamidronaattidinatrium; Pamidronas Dinatricum; Pamidronatdinatrium; Pamidronatdinatriumpentahydrat; Pamidronate Disodique; Pamidronate disodique pentahydraté; Pamidronato disódico; Pamidronatum Dinatricum. Disodium 3-amino-1-hydroxypropylidenebisphosphonate pentahydrate.

Динатрий Памидронат

$C_3H_9NNa_2O_7P_2,5H_2O$ = 369.1.
CAS — 109552-15-0 (pamidronate disodium pentahydrate); 57248-88-1 (anhydrous pamidronate disodium).
ATC — M05BA03.
ATC Vet — QM05BA03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pamidronate Disodium Pentahydrate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in dichloromethane. It is sparingly soluble in dilute mineral acids and dissolves in dilute alkaline solutions. A 1.0% solution in water has a pH of 7.8 to 8.8.

USP 31 (Pamidronate Disodium). A white crystalline powder. Soluble in water and in 2N sodium hydroxide; sparingly soluble 0.1N acetic acid and in 0.1N hydrochloric acid; practically insoluble in organic solvents. pH of a 1% solution in water is between 7.8 and 8.8. Store in airtight containers at a temperature not exceeding 30°.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089.

Fever and flu-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes) are common during intravenous infusion of pamidronate but generally resolve spontaneously. Pamidronate should not be given by bolus injection, as severe local reactions and thrombophlebitis have occurred. CNS effects include agitation, confusion, dizziness, lethargy, insomnia, and somnolence. There have been isolated cases of seizures, and visual hallucinations. In addition to hypocalcaemia and hypophosphataemia, which are common, hypomagnesaemia or hypokalaemia may occur, and rarely, hypernatraemia, or hyperkalaemia. Both hypotension and hypertension have been reported. Anaemia, thrombocytopenia, and lymphocytopenia may occur. Bronchospasm and interstitial pneumonitis have occurred rarely.

Pamidronate should be used with caution in those with cardiac disease, because of the potential for fluid overload, and in those who have had thyroid surgery, because of the increased risk of hypocalcaemia due to relative hypoparathyroidism. Serum electrolytes, calcium and phosphate should be monitored during therapy, along with renal function. Patients should be warned against driving or operating machinery after treatment if somnolence or dizziness occur.

Effects on the ears. Ototoxicity, manifest as tinnitus and sudden hearing loss, has been reported[1] in 2 patients given both intravenous and oral pamidronate for pre-existing otosclerosis.[1] A patient given 5 pamidronate infusions for Paget's disease developed tinnitus, vertigo, and hearing loss; the latter two symptoms resolved over 9 months, but tinnitus persisted.[2]

1. Boumans LJJM, Poublon RML. The detrimental effect of aminohydroxypropylidene bisphosphonate (APD) in otospongiosis. *Eur Arch Otorhinolaryngol* 1991; **248:** 218–21.
2. Reid IR, *et al.* Ototoxicity associated with intravenous bisphosphonate administration. *Calcif Tissue Int* 1995; **56:** 584–5.

Effect on electrolytes. Pamidronate has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in 2 patients. In each case, other conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including pamidronate, see under Bisphosphonates, p.1090.

Effects on the gastrointestinal tract. The tolerability of pamidronate given *orally* may depend to some extent on the particular formulation. Gastrointestinal disturbances (in 21.8%) and haematological abnormalities (in 9.4%) were the main adverse effects associated with oral pamidronate in an open study of elderly patients.[1] Oesophagitis, noted earlier[2] in 4 of 49 patients given a different formulation, was not reported in this study.[1]

1. Spivacow FR, *et al.* Tolerability of oral pamidronate in elderly patients with osteoporosis and other metabolic bone diseases. *Curr Ther Res* 1996; **57:** 123–30.
2. Lufkin EG, *et al.* Pamidronate: an unrecognised problem in gastrointestinal tolerability. *Osteoporosis Int* 1994; **4:** 320–2.

Effects on the kidneys. Like other bisphosphonates (see p.1091), pamidronate may cause adverse renal effects. UK licensed product information notes that there have been isolated cases of haematuria, acute renal failure, and deterioration of pre-existing renal disease. Renal function should be monitored during long-term pamidronate therapy, especially in patients with pre-existing renal disease or a predisposition to renal impairment. Longer infusion times may reduce the risk of renal toxicity, and various infusion rates have been recommended, see Uses and Administration, below.

Effects on mental state. Palpitations, followed by visual hallucinations, suicidal ideation, and clinical depression were reported in an elderly man after a single infusion of pamidronate for Paget's disease; he had no previous psychiatric history. Treatment with thioridazine reduced the frequency and effect of the hallucinations.[1]

1. Foley-Nolan D, *et al.* Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; **51:** 927–8.

Effects on the musculoskeletal system. Although pamidronate appears to be a less potent inhibitor of bone mineralisation than etidronate, mineralisation defects have been reported in patients with Paget's disease of bone receiving pamidronate.[1] The resultant osteomalacia was not associated with any adverse clinical effects. Pamidronate-induced osteopetrosis has also been reported.[2] Acute pseudogout arthritis in a woman treated with pamidronate for acute hypercalcaemia was possibly due to deposition of calcium in the joints.[3] Severe bone pain occurred in more patients than expected when pamidronate was used for treatment of low bone density in cystic fibrosis;[4] an increase in proinflammatory cytokines was postulated as a mechanism for this effect.[5]

Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including pamidronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

1. Adamson BB, *et al.* Mineralisation defects with pamidronate therapy for Paget's disease. *Lancet* 1993; **342:** 1459–60.
2. Whyte MP, *et al.* Bisphosphonate-induced osteopetrosis. *N Engl J Med* 2003; **349:** 457–63.
3. Malnick SDH *et al.* Acute pseudogout as a complication of pamidronate. *Ann Pharmacother* 1997; **31:** 499–500.
4. Haworth CS, *et al.* Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet* 1998; **352:** 1753–4.
5. Teramoto S, *et al.* Increased cytokines and pamidronate-induced bone pain in adults with cystic fibrosis. *Lancet* 1999; **353:** 750.

Hypersensitivity. Allergic reactions to bisphosphonates are rare. Rash and pruritus occasionally follow pamidronate infusion. Mild skin rashes have also been reported in some patients taking oral pamidronate (see also under Bisphosphonates, p.1091).

Pregnancy. Bisphosphonates cross the placenta in animals and humans. These drugs also persist in mineralised bone for many years. Thus, in theory, even if use were to be avoided during pregnancy, the fetus might still be exposed to bisphosphonates from prior therapy released from the maternal skeleton. Furthermore, suppressed bone turnover caused by residual bisphosphonate might cause maternal complications during pregnancy.[1] However, no adverse effects were seen during pregnancy in 2 women with osteogenesis imperfecta given intravenous pamidronate before conception. One infant had transient asymptomatic hypocalcaemia, and one had bilateral talipes equinovarus (a congenital deformity in which the foot turns downwards and inwards). No other skeletal abnormalities were noted. The authors advised monitoring of neonatal calcium concentrations in infants born to mothers treated with pamidronate.[1] In another report of 3 women given long-term pamidronate before conception, 4 healthy infants were born with no evidence of biochemical or skeletal abnormalities.[2]

1. Munns CFJ, *et al.* Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. *J Bone Miner Res* 2004; **19:** 1742–5.
2. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. *J Clin Endocrinol Metab* 2006; **91:** 2017–20.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Plasma concentrations of pamidronate rise rapidly after the start of an intravenous infusion; the apparent plasma half-life is 0.8 hours. Plasma protein binding is about 54%. Pamidronate is not metabolised, and about 20 to 55% of the dose is excreted in the urine unchanged within 72 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment and infusion rates may need to be reduced (see below).

Like all bisphosphonates, oral pamidronate is poorly absorbed from the gastrointestinal tract; bioavailability is about 1 to 3%.

Uses and Administration

Pamidronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It inhibits bone resorption, but appears to have less effect on bone mineralisation than etidronate at comparable doses.

Pamidronate is used as an adjunct in the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic lesions and bone pain in multiple myeloma or bone metastases associated with breast cancer. It may also be of benefit in bone disorders associated with excessive bone resorption, including Paget's disease of bone.

Pamidronate disodium is given by slow intravenous infusion. UK licensed product information recommends infusion at a rate not exceeding 60 mg/hour (or not exceeding 20 mg/hour in patients with established or suspected renal impairment) and at a concentration not exceeding 60 mg per 250 mL of infusion solution (sodium chloride 0.9% or glucose 5%). In the USA, the recommended concentration of infusion and rate vary depending on the indication.

In **hypercalcaemia of malignancy** pamidronate disodium is given by slow intravenous infusion in a total dose of 15 to 90 mg according to the initial plasma-calcium concentration. In the UK, the total dose is given as a single infusion or in divided doses over 2 to 4 days. In the USA, the total dose is given as a single infusion, doses of 60 mg to 90 mg being given over 2 to 24 hours. Plasma-calcium concentrations generally start declining 24 to 48 hours after a dose of pamidronate with normalisation within 3 to 7 days. Treatment may be repeated if normocalcaemia is not achieved within this time or if hypercalcaemia recurs.

In patients with **osteolytic lesions and bone pain** of multiple myeloma or bone metastases associated with breast cancer, pamidronate disodium may be given in doses of 90 mg by intravenous infusion every 3 to 4 weeks.

In the treatment of **Paget's disease** the dosage regimen in the UK is 30 mg by slow infusion once a week for 6 weeks (total dose 180 mg), or 30 mg in the first week then 60 mg every other week for 6 weeks (total dose 210 mg). These courses may be repeated every 6 months, and the total dose increased if necessary up to

The symbol † denotes a preparation no longer actively marketed

a maximum of 360 mg. Alternatively, the dose used in the USA is 30 mg by infusion over 4 hours, repeated on consecutive days to a total dose of 90 mg. This course is repeated when clinically indicated.

Pamidronate has also been given orally.

◊ General references.

1. Coukell AJ, Markham A. Pamidronate: a review of its use in the management of osteolytic bone metastases, tumour-induced hypercalcaemia and Paget's disease of bone. *Drugs Aging* 1998; **12:** 149–68.

Administration in renal impairment. Pharmacokinetic studies suggest that no dosage reduction of pamidronate disodium is required in patients with any degree of renal impairment.[1] However, UK product information currently recommends that the rate of infusion be reduced to a maximum of 20 mg/hour for patients with established or suspected renal impairment; use in those with severe renal impairment (creatinine clearance less than 30 mL/minute) is not advised as clinical experience is limited.

1. Berenson JR, *et al.* Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol* 1997; **37:** 285–90.

Complex regional pain syndrome. Osteoporosis is one of the features of complex regional pain syndrome (p.6). Bisphosphonates may be of benefit in controlling associated pain in some patients. In small studies, intravenous pamidronate 30 mg daily for 3 days, or at 1 mg/kg daily for 1 or 3 days,[1] or 60 mg daily for 3 days,[2] significantly improved pain and range of movement in cases refractory to previous treatment.

1. Maillefert JF, *et al.* Pooled results from 2 trials evaluating bisphosphonates in reflex sympathetic dystrophy. *J Rheumatol* 1999; **26:** 1856–7.
2. Kubalek I, *et al.* Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. *Rheumatology (Oxford)* 2001; **40:** 1394–7.

Gaucher disease. Treatment with oral pamidronate disodium in doses of 600 mg daily in adults,[1] and 150 to 300 mg daily in children,[2] or intravenous pamidronate disodium in doses of 45 mg every 3 weeks,[3] has been reported to improve bone lesions of Gaucher disease (p.2249) in a few patients.

1. Harinck HIJ, *et al.* Regression of bone lesions in Gaucher's disease during treatment with aminohydroxypropylidene bisphosphonate. *Lancet* 1984; **ii:** 513.
2. Samuel R, *et al.* Aminohydroxy propylidine bisphosphonate (APD) treatment improves the clinical skeletal manifestations of Gaucher's disease. *Pediatrics* 1994; **94:** 385–9.
3. Ciana G, *et al.* Short-term effects of pamidronate in patients with Gaucher's disease and severe skeletal involvement. *N Engl J Med* 1997; **337:** 712.

Hypercalcaemia. Bisphosphonates, of which pamidronate is one of the most effective, are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Pamidronate is licensed for such use in many countries. A literature review[1] of phase II and III studies concluded that pamidronate was effective in the treatment of pain and skeletal complications from metastatic disease, particularly in patients with breast cancer or multiple myeloma, but that its efficacy in those with other neoplasms needed confirmation. A long-term follow-up[2] of 2 randomised trials of pamidronate in women with breast cancer confirmed its efficacy over placebo. However, a pooled analysis[3] of its use for palliation of bone pain in men with metastatic prostate cancer found no treatment benefit with pamidronate over placebo. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Ripamonti C, *et al.* Role of pamidronate disodium in the treatment of metastatic bone disease. *Tumori* 1998; **84:** 442–55.
2. Lipton A, *et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; **88:** 1082–90.
3. Small EJ, *et al.* Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; **21:** 4277–84.

Osteogenesis imperfecta. Pamidronate has produced benefit in patients with osteogenesis imperfecta (p.1083). Although the dosage and timing varied between centres and age groups, all patients were given cyclical intravenous pamidronate;[1-5] bone mineral density increased, fracture incidence decreased, and patients reported improvements in mobility, pain and chronic fatigue. Treated infants achieved motor milestones earlier than untreated controls; vertebral height was also improved.[5] While bone size and density also increased in patients given pamidronate, especially in those with larger baseline deficits in bone mass,[6] serum calcium decreased markedly, and bone turnover was suppressed;[7] clinical problems were not evident if calcium intake was sufficient, but consequences of a chronically low bone turnover are unknown. A study in young patients found that bone metabolism is still suppressed, and that bone mass gains continue, for 2 years after stopping therapy.[8]

1. Glorieux FH, *et al.* Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998; **339:** 947–52.
2. Plotkin H, *et al.* Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000; **85:** 1846–50.
3. Åström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002; **86:** 356–64.
4. Falk MJ, *et al.* Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics* 2003; **111:** 573–8.
5. Åström E, *et al.* Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Arch Dis Child* 2007; **92:** 332–8.
6. Rauch F, *et al.* Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res* 2003; **18:** 610–14.
7. Rauch F, *et al.* Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab* 2003; **88:** 986–92.
8. Rauch F, *et al.* Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006; **91:** 1268–74.

Osteoporosis. Bisphosphonates are used in the prevention and treatment of osteoporosis (p.1084). A placebo-controlled trial of oral pamidronate 150 mg daily found it to be effective in increasing bone mineral density (BMD) of the lumbar spine and femoral neck in both **men** and **women**.[1] Intravenous pamidronate at 30 mg every 3 months, or 60 mg every 6 months, also increased BMD in the lumbar spine, femoral neck, and trochanter in an observational, retrospective study.[2] Single intravenous infusions of pamidronate given every 3 months have also been reported to increase BMD and reduce fracture rates in **children** with osteoporosis;[3,4] annual doses were in the region of 4 mg/kg.

An open study[5] in men with prostate cancer (but no bone metastases) and receiving leuprolide, found that addition of pamidronate 60 mg intravenously every 12 weeks prevented **therapy-induced** bone loss in the hip and lumbar spine. Acute bone loss from the femur and pelvis after hip arthroplasty was also reduced by a single infusion of 90 mg pamidronate in a small prospective study.[6] Similarly, in premenopausal women with chemotherapy-induced bone loss, pamidronate 60 mg intravenously every 3 months prevented bone loss at the spine and hip compared with placebo.[7]

In a small study[8] of patients receiving **corticosteroids**, pamidronate given intravenously either as a single infusion of 90 mg, or as 90 mg followed by 30 mg every 3 months for 1 year, significantly increased BMD at the lumbar spine, femoral neck, and total hip. In lymphoma patients receiving corticosteroids as part of chemotherapy regimens, pamidronate 30 mg intravenously every 3 months reduced bone loss when compared with placebo.[9] Pamidronate has shown beneficial increases in or preservation of BMD in patients after heart,[10,11] liver,[11] lung,[12] or stem cell[13] transplantation.

1. Brumsen C, *et al.* Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 2002; **17:** 1057–64.
2. Chan SSY, *et al.* Intravenous pamidronate in the treatment and prevention of osteoporosis. *Intern Med J* 2004; **34:** 162–6.
3. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr* 2003; **142:** 417–23.
4. Gandrud LM, *et al.* Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. *J Pediatr Endocrinol Metab* 2003; **16:** 887–92.
5. Smith MR, *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2001; **345:** 948–55.
6. Wilkinson JM, *et al.* Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. *J Bone Miner Res* 2001; **16:** 556–64.
7. Fuleihan GE-H, *et al.* Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 3209–14.
8. Boutsen Y, *et al.* Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001; **16:** 104–12.
9. Kim SH, *et al.* Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *Am J Med* 2004; **116:** 524–8.
10. Krieg MA, *et al.* Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. *Osteoporosis Int* 2001; **12:** 112–16.
11. Dodidou P, *et al.* Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporosis Int* 2003; **14:** 82–9.
12. Cahill BC, *et al.* Prevention of bone loss and fracture after lung transplantation: a pilot study. *Transplantation* 2001; **72:** 1251–5.
13. Grigg AP, *et al.* Pamidronate reduces bone loss after allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2006; **91:** 3835–43.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Pamidronate was initially used orally for Paget's disease, but intravenous therapy has been preferred because of a lower incidence of adverse effects.[1,2] With the usual total dose of 180 mg, remission is considered likely in most patients with mild to moderate disease, but unlikely if disease is severe.[2] However, higher doses (about 340 mg) were found to be effective in those with very active disease, and also associated with a longer remission.[1] In a 2-year study[3] of 3 different doses, pamidronate increased bone mineral density in pagetic bone of the lumbar spine, femoral neck, and total hip, but lacked this effect on non-pagetic bone in the same areas; loss of density was apparent in non-pagetic forearm bone in the group given the highest dose (240 mg). Patients with co-existent osteoarthritis or arthropathy responded less well to pamidronate in terms of pain perception, than those patients without joint disease.[4] While hearing loss may or may not improve with pamidronate,[5,6] there has been a report of successful treatment of optic neuropathy due to Paget's disease with pamidronate and dexamethasone.[7] Bisphosphonates have also been given in other bone diseases with a similar pathology, particularly increased osteoclastic resorption. For example, pamidronate has had beneficial effects in patients with fibrous dysplasia of bone, a rare congenital disease leading to osteolytic lesions.[8-10]

1. Selby PL. Pamidronate in the treatment of Paget's disease. *Bone* 1999; **24:** 57S–58S.
2. Tucci JR, Bontha S. Intravenously administered pamidronate in the treatment of Paget's disease of bone. *Endocr Pract* 2001; **7:** 423–9. Correction. *ibid.* 2002; **8:** 78.
3. Gutteridge DH, *et al.* Bone density changes in Paget's disease 2 years after iv pamidronate: profound, sustained increases in pagetic bone with severity-related loss in forearm nonpagetic cortical bone. *Bone* 2003; **32:** 56–61.
4. Vasireddy S, *et al.* Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. *Clin Rheumatol* 2003; **22:** 376–80.
5. Donáth J, *et al.* Effect of bisphosphonate treatment in patients with Paget's disease of the skull. *Rheumatology (Oxford)* 2004; **43:** 89–94.
6. Murdin L, Yeoh LH. Hearing loss treated with pamidronate. *J R Soc Med* 2005; **98:** 272–4.
7. Isasi C, *et al.* Successful treatment of optic neuropathy in osteitis deformans. *Rheumatology (Oxford)* 2002; **41:** 948–50.
8. Liens D, *et al.* Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; **343:** 953–4.
9. Zacharin M, O'Sullivan M. Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome. *J Pediatr* 2000; **137:** 403–9.
10. Plotkin H, *et al.* Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab* 2003; **88:** 4569–75.

Rheumatoid arthritis and spondyloarthropathies. Intravenous[1] and oral[2] use of pamidronate has reportedly produced some modification of disease in a few patients with rheumatoid arthritis (p.11). Continuous oral pamidronate therapy was shown to be effective in preserving and increasing bone mass in a 3-year randomised controlled trial involving 105 patients with rheumatoid arthritis.[3] In contrast, a small controlled study[4] in 26 patients found no significant effect on rheumatoid arthritis disease activity with intravenous pamidronate. There are reports of an analgesic response to pamidronate in patients with acute rheumatic pain of various aetiologies, including arthritis and ankylosing spondylitis, and a trial[5] in patients with ankylosing spondylitis found a dose-dependent therapeutic effect with pamidronate.[6] Use of intravenous pamidronate and methylprednisolone has also been investigated as part of the management of patients with NSAID-unresponsive ankylosing spondylitis.[7]

1. Eggelmeijer F, *et al.* Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J Rheumatol* 1994: **21:** 2016–20.
2. Maccagno A, *et al.* Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994; **23:** 211–14.
3. Eggelmeijer F, *et al.* Increased bone mass with pamidronate treatment in rheumatoid arthritis: results of a three-year randomized, double-blind trial. *Arthritis Rheum* 1996; **39:** 396–402.
4. Lodder MC, *et al.* Effects of high dose intravenous pamidronate on disease activity and bone metabolism in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2003; **30:** 2080–1.
5. El-Shafei A, *et al.* Is pamidronate effective for acute rheumatic pain? *Ann Rheum Dis* 2002; **61:** 183.
6. Maksymowych WP, *et al.* A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; **46:** 766–73.
7. Malaviya AN, *et al.* A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. *J Assoc Physicians India* 2007; **55:** 193–7.

Preparations

BP 2008: Pamidronate Disodium Intravenous Infusion;
USP 31: Pamidronate Disodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aminomux; Pamdosa; Pandrat; ***Austral.:*** Aredia; Pamisol; ***Austria:*** Aredia; Pamitor; ***Belg.:*** Aredia; Pamidrin; ***Braz.:*** Aredia; Pamidrom; ***Canad.:*** Aredia; ***Chile:*** Aminomux; Aredia†; ***Cz.:*** Aredia; Pamitor; ***Denm.:*** Aredia; Pamifos; ***Fin.:*** Aredia; Pamifos; ***Fr.:*** Aredia; Ostepam; ***Ger.:*** Aredia; Pamidro-cell; Pamidron; Pamifos; Ribodronat; ***Gr.:*** Aredia; Pamerit; ***Hong Kong:*** Aredia; Pamisol; ***Hung.:*** Aredia; Pamifos; Pamitor; ***India:*** Aredronet†; Pamidria; Pamifos; ***Indon.:*** Aredia; ***Irl.:*** Aredia; ***Israel:*** Aredia; ***Ital.:*** Amidrox; Aredia; ***Malaysia:*** Aredia; Pamired; Pamisol; ***Mex.:*** Aredia; Pamisol; ***Neth.:*** Aredia; Pamipro; ***Norw.:*** Aredia†; ***NZ:*** Aredia†; Pamisol;

Philipp.: Aredia; ***Pol.:*** Aredia; Pamifos; Pamitor; ***Port.:*** Aredia†; Pamidran; ***Rus.:*** Aredia (Аредиа); ***S.Afr.:*** Aredia; ***Singapore:*** Aredia†; Pamisol; ***Spain:*** Aredia; Linoten; Pamifos; Xinsidona; ***Swed.:*** Aredia; Pamifos; ***Switz.:*** Aredia; ***Thai.:*** Aredia; Pamisol; ***Turk.:*** Aredia; ***UK:*** Aredia; ***USA:*** Aredia; ***Venez.:*** Aminomux; Aredia†.

Parathyroid Hormone *(BAN, USAN, rINN)*

1-84 Parathormone; ALX1-11 (human recombinant parathyroid hormone); Hormona paratiroidea; Hormone Parathyroïde; Hormonum Parathyroidum; Parathormone; Parathyrin; Parathyroid hormone (1-84); PTH; PTH (1-84).

Паратироид Гормон

CAS — 9002-64-6; 68893-82-3 (human parathyroid hormone); 345663-45-8 (human recombinant parathyroid hormone).
ATC — H05AA03.
ATC Vet — QH05AA03.

Adverse Effects, Treatment, and Precautions

Transient hypercalcaemia and hypercalciuria are very common with parathyroid hormone treatment; persistent hypercalcaemia may necessitate dose reduction or withdrawal of therapy (see Uses and Administration, below). Patients should be monitored at months 1, 3, and 6 for elevated concentrations of serum or urinary calcium; monitoring beyond 6 months is not considered necessary for those whose serum calcium is within normal limits at 6 months. On injection, serum calcium concentrations reach a maximum after 6 to 8 hours, returning to baseline after 20 to 24 hours; blood samples for monitoring should thus be taken at least 20 hours after the most recent dose. Gastrointestinal disturbances, especially nausea, also occur commonly, as do headache, dizziness, fatigue, palpitations, muscle cramps, extremity or back pain, and injection site erythema. Hyperuricaemia has also been reported.

Pharmacokinetics

Subcutaneous parathyroid hormone produces peak plasma concentrations 1 to 2 hours after injection. The average half-life is about 1.5 hours and the absolute bioavailability is about 55%. Parathyroid hormone is removed from the blood by a receptor-mediated process in the liver and broken down into smaller peptide fragments, which either undergo further degradation within the cell or are released back into the blood and renally cleared.

Uses and Administration

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first (N-terminal) 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations through its actions on bone, kidney, and indirectly on the gastrointestinal tract (see also under Parathyroid Disorders, p.1087).

Exogenous parathyroid hormone was formerly used in acute hypoparathyroidism with tetany. It has also been used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism. A human recombinant form is under investigation for the treatment of hypoparathyroidism.

The human recombinant form is used for the treatment of osteoporosis in postmenopausal women at high risk of fractures. The recommended dose is 100 micrograms once daily, given by subcutaneous injection into the abdomen; treatment may be continued for up to 24 months. Supplemental calcium and vitamin D may be needed if dietary intake is inadequate. However, if serum calcium becomes persistently raised, and there is no underlying disease, calcium and vitamin D should be withdrawn, and parathyroid hormone dosing changed to 100 micrograms on every other day. If elevated concentrations persist, parathyroid hormone therapy should be stopped until values return to normal.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones are now used for diagnostic purposes, and for the treatment of osteoporosis (see Teriparatide, p.1105).

◊ References.

1. Rittmaster RS, *et al.* Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000; **85:** 2129–34.
2. Hodsman AB, *et al.* Efficacy and safety of human parathyroid hormone-(1–84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003; **88:** 5212–20.
3. Anonymous. ALX 111: ALX1-11, parathyroid hormone (1-84)–NPS Allelix, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs R D* 2003; **4:** 231–5.
4. White H, Ahmad A. PREOS NPS (Allelix/Nycomed). *Curr Opin Investig Drugs* 2005; **6:** 1057–66.
5. Shrader SP, Ragucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother* 2005; **39:** 1511–16.
6. Moen MD, Scott LJ. Recombinant full-length parathyroid hormone (1-84). *Drugs* 2006; **66:** 2371–81; discussion 2382–5.
7. Greenspan SL, *et al.* Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007; **146:** 326–39.

Administration in renal or hepatic impairment. UK licensed product information states that no dose adjustment is necessary for parathyroid hormone when it is used in patients with mild to moderate renal or hepatic impairment, defined as those with a creatinine clearance of 30 to 80 mL/minute, and a total score of 7 to 9 on the Child-Pugh scale, respectively. Use in severe renal or hepatic impairment is not recommended due to lack of data.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Preotact; ***Gr.:*** Preotact; ***UK:*** Preotact.

Plicamycin *(BAN, USAN, rINN)*

A-2371; Aureolic Acid; Mithramycin; Mithramycinum; Mitramycin; Mitramysiini; NSC-24559; PA-144; Plicamicina; Plicamycine; Plicamycinum.

Пликамицин

$C_{52}H_{76}O_{24}$ = 1085.1.
CAS — 18378-89-7.
ATC — L01DC02.
ATC Vet — QL01DC02.

Description. Plicamycin is an antineoplastic antibiotic produced by the growth of *Streptomyces argillaceus*, *S. plicatus* and *S. tanashiensis.*

Pharmacopoeias. In *US.*

USP 31 (Plicamycin). A yellow, odourless, hygroscopic, crystalline powder, with a potency of not less than 900 micrograms/mg, calculated on the dry basis. It loses not more than 8% of its weight when dried. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in ethyl acetate. A 0.05% solution in water has a pH of 4.5 to 5.5. Store at 2° to 8° in airtight containers. Protect from light.

Profile

Plicamycin is a highly toxic antibiotic with antineoplastic and hypocalcaemic properties. It may act by complexing with DNA in the presence of divalent cations and inhibiting synthesis of ribonucleic acid. Lowering of serum calcium concentrations has been suggested to result from antagonism of the effects of vitamin D and parathyroid hormone on osteoclasts.

Plicamycin has been used in the symptomatic management of hypercalcaemia and hypercalciuria associated with malignancy if it cannot be managed by other means (see below). It has also been used in the treatment of malignant neoplasms of the testis not susceptible to surgery or radiotherapy; however, other agents are preferred (p.673).

The major adverse effect of plicamycin is a dose-related bleeding syndrome, manifest initially as epistaxis, which may progress to haematemesis and potentially fatal haemorrhage. Severe thrombocytopenia may also occur due to bone-marrow depression. Gastrointestinal effects are common and other adverse effects include fever, malaise, drowsiness, lethargy and weakness, headache, depression, skin rashes, facial flushing, and reduced serum concentrations of calcium, phosphorus, and potassium. There may also be reversible impairment of renal and hepatic function.

Extravasation of plicamycin solutions may cause local irritation, cellulitis, and phlebitis.

Hypercalcaemia. Where treatment is required for hypercalcaemia it is aimed at increasing urinary excretion of calcium and maintaining adequate hydration. Drugs that inhibit bone resorption may also be used if hypercalcaemia is severe, particularly when it is associated with malignancy (see p.1083). Plicamycin is highly toxic, and the bisphosphonates and calcitonins are generally preferred; however, it has been given in a dose of 25 micrograms/kg intravenously over 4 to 6 hours.[1,2] Although a single dose might be sufficient to normalise the serum calcium concentration, the dose can be repeated several times at intervals of 24 to 72 hours.

1. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–1203.
2. Hall TG, Schaiff RAB. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm* 1993; **12:** 117–25.

Paget's disease of bone. Plicamycin has been used as a second- or third-line drug in the therapy of Paget's disease of bone (p.1086), reserved for patients refractory to other treatment. Nonetheless, occasional successes are reported: one patient with refractory Paget's disease had apparent cure of her symptoms after treatment with plicamycin 25 micrograms/kg daily for 15 doses, followed by 1500 micrograms weekly for about 2 months and every 2 weeks for 6 weeks.[1] She had remained asymptomatic for 18 years after treatment. However, similar regimens have been used in other patients without this degree of success.[1] Another patient, who was refractory to calcitonin and pamidronate therapy, showed a considerable improvement in pain relief and biochemical parameters when treated with 30 micrograms/kg plicamycin daily for 3 days.[2]

1. Ryan WG, *et al.* Apparent cure of Paget's disease of bone. *Am J Med* 1990; **89:** 825–6.
2. Wimalawansa SJ. Dramatic response to plicamycin in a patient with severe Paget's disease refractory to calcitonin and pamidronate. *Semin Arthritis Rheum* 1994; **23:** 267.

Preparations

USP 31: Plicamycin for Injection.

Proprietary Preparations (details are given in Part 3)
Gr.: Mithracin†.

Risedronate

Risedronaatti; Risedronat; Risedronatum.
ATC — M05BA07.
ATC Vet — QM05BA07.

Risedronic Acid *(BAN, rINN)*

Acide Risédronique; Ácido risedrónico; Acidum Risedronicum. [1-Hydroxy-2-(3-pyridinyl)ethylidene]diphosphonic acid.

Ризедроновая Кислота

$C_7H_{11}NO_7P_2$ = 283.1.
CAS — 105462-24-6.
ATC — M05BA07.
ATC Vet — QM05BA07.

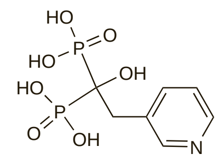

Risedronate Sodium *(BANM, USAN, rINNM)*

Monosodium Risedronate; Natrii Risedronas; NE-58095; Risedronat Sodyum; Risédronate de Sodium; Risedronato sódico; Sodium Risedronate. Sodium trihydrogen [1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate.

Натрий Ризедронат

$C_7H_{10}NNaO_7P_2$ = 305.1.
CAS — 115436-72-1.
ATC — M05BA07.
ATC Vet — QM05BA07.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. The most frequent adverse effects during risedronate therapy are arthralgia and gastrointestinal disturbances. To minimise the risk of gastrointestinal effects precautions similar to those for alendronate should be observed (see p.1088), although UK licensed product information allows for the tablets to be taken other than on rising (but not at bedtime or within 2 hours of food or drink). Hypocalcaemia should be corrected before beginning risedronate therapy.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including risedronate, see under Bisphosphonates, p.1090.

Effects on the gastrointestinal tract. Although, like other oral bisphosphonates, it is recommended that risedronate be taken with care (see above) to avoid gastrointestinal effects, pooled analysis of 9 studies involving 10 068 patients receiving risedronate 5 mg daily indicated that the drug was not associated with an increased frequency of upper gastrointestinal effects, even among patients at increased risk due to active gastrointestinal disease or treatment with aspirin or NSAIDs as well.[1] However, it was noted that comprehensive postmarketing data would be required to see how these results would be reflected in clinical practice. Studies in women previously intolerant to alendronate found that risedronate 5 mg daily[2] and 30 mg once weekly[3] were well tolerated.

In 2 large trials, male and female patients with mild to moderate osteoarthritis of the knee were given risedronate 5 mg once daily, 15 mg once daily, 35 mg once weekly, 50 mg once weekly, or placebo. Patients were allowed continued use of aspirin or NSAIDs. Again, pooled analysis found no increased frequency of upper gastrointestinal adverse events in those given risedronate, even in those patients considered at increased risk for such events.[4]

1. Taggart H, *et al.* Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002; **77:** 262–70. Correction. *ibid.*; 601.
2. Adachi JD, *et al.* Tolerability of risedronate in postmenopausal women intolerant of alendronate. *Aging (Milano)* 2001; **13:** 347–54.
3. Delaney MF, *et al.* Bone density changes with once weekly risedronate in postmenopausal women. *J Clin Densitom* 2003; **6:** 45–50.
4. Adami S, *et al.* Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 1278–85.

Effects on the musculoskeletal system. From the initial marketing of risedronate until June 2003, the FDA had received 6 reports of severe bone, joint, or muscle pain. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[1]

Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including risedronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

1. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.

Effects on the respiratory system. For a report of bronchiolitis obliterans organising pneumonia induced by risedronate, see p.1091.

Hypersensitivity. Allergic reactions to bisphosphonates are rare, see p.1091. Angioedema, generalised rashes, and bullous skin reactions, some severe, have been reported with risedronate.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Like other bisphosphonates, risedronate is poorly absorbed orally. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The mean bioavailability is 0.63% in the fasting state, and is reduced by 30% when given 1 hour before breakfast, and by 55% when given half an hour before breakfast. Plasma protein binding is about 24%. Risedronate is not metabolised. About half of the absorbed portion is excreted in the urine within 24 hours; the remainder is sequestered to bone for a prolonged period. Unabsorbed drug is eliminated unchanged in the faeces.

Absorption. Absorption of a single dose of risedronate was comparable when given 0.5 to 1 hour before breakfast or 2 hours after an evening meal in a study in healthy subjects.[1] The pharmacokinetics of risedronate are dose-proportional after a single oral dose.[2]

1. Mitchell DY, *et al.* The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol* 1999; **48:** 536–42.
2. Mitchell DY, *et al.* Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol* 2000; **40:** 258–65.

Uses and Administration

Risedronate is an aminobisphosphonate with similar properties to those of the bisphosphonates in general (p.1091). It inhibits bone resorption and is used either alone or with calcium, or with calcium and vitamin D for the prevention and treatment of postmenopausal osteoporosis. It is also used for the treatment of osteoporosis in men. Risedronate is also used for prevention and treatment of corticosteroid-induced osteoporosis, and for the treatment of Paget's disease of bone.

Risedronate is given orally as the sodium salt. The specific instructions given in Adverse Effects and Precautions, above should be followed to minimise gastrointestinal adverse effects and permit adequate absorption. The recommended dosage for **Paget's disease** of bone is 30 mg of risedronate sodium once daily for 2 months. Treatment may be repeated once if necessary after an interval of a further 2 months. The recommended dosage for the treatment or prevention of postmenopausal or corticosteroid-induced **osteoporosis** is 5 mg daily. Alternatively, for postmenopausal osteoporosis, 35 mg may be taken once weekly, 75 mg may be taken on 2 consecutive days of each month, or 150 mg may be taken once a month. For men with osteoporosis, the recommended dose is 35 mg once weekly.

◊ General references.

1. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
2. Dunn CJ, Goa KL. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 2001; **61:** 685–712.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. White NJ, Perry CM. Risedronate once a week. *Treat Endocrinol* 2003; **2:** 415–20.

Administration. A procedure for the extemporaneous preparation of an oral solution from risedronate tablets has been proposed,[1] for use in patients who cannot swallow whole tablets or require feeding tubes.

1. Dansereau RJ, Crail DJ. Extemporaneous procedures for dissolving risedronate tablets for oral administration and for feeding tubes. *Ann Pharmacother* 2005; **39:** 63–7.

Administration in renal impairment. Renal clearance of risedronate significantly correlated to renal function in a pharmacokinetic study,[1] although the authors concluded that generally no dosage adjustment appears necessary for patients with mild to moderate renal impairment (creatinine clearance (CC) greater than 20 mL/minute). Licensed product information states that no dosage adjustment is necessary when CC is greater than 30 mL/minute; however, use of risedronate is contra-indicated in patients with severe renal impairment (CC less than 30 mL/minute), due to a lack of clinical data.

1. Mitchell DY, *et al.* Effect of renal function on risedronate pharmacokinetics after a single oral dose. *Br J Clin Pharmacol* 2000; **49:** 215–22.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Risedronate improves bone mineral density (BMD) and reduces the risk of both vertebral and non-vertebral fractures in **postmenopausal** osteoporosis;[1-4] effects are maintained for at least 5 years.[5] In **corticosteroid-induced** osteoporosis, risedronate increases BMD at the lumbar spine, femoral neck, and trochanter.[3,6] Risedronate is also used to treat **men** with osteoporosis. In a controlled study in elderly men after a stroke, those given risedronate had increased BMD and a decreased risk of hip fracture.[7] In a prospective controlled study, 12 months of daily risedronate significantly increased BMD at the lumbar spine, femoral neck, and hip, and significantly reduced the incidence of new vertebral fractures in men with primary or secondary osteoporosis.[8]

A once-monthly regimen of risedronate was found to be similar in efficacy and safety to the once-daily regimen.[9]

1. Sickels JM, Nip C-S. Risedronate for the prevention of fractures in postmenopausal osteoporosis. *Ann Pharmacother* 2002; **36:** 664–70.
2. Crandall C. Risedronate: a clinical review. *Arch Intern Med* 2001; **161:** 353–60.
3. Umland EM, Boyce EG. Risedronate: a new oral bisphosphonate. *Clin Ther* 2001; **23:** 1409–21.
4. Wells G, *et al.* Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
5. Sorensen OH, *et al.* Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; **32:** 120–6.
6. Dougherty JA. Risedronate for the prevention and treatment of corticosteroid-induced osteoporosis. *Ann Pharmacother* 2002; **36:** 512–16.
7. Sato Y, *et al.* Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med* 2005; **165:** 1743–8.
8. Ringe JD, *et al.* Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 2006; **26:** 427–31.
9. Delmas PD, *et al.* Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008; **42:** 36–42.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Risedronate has been found to improve pagetic bone lesions,[1] and to be more effective than etidronate.[2]

1. Brown JP, *et al.* Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. *Bone* 2000; **26:** 263–7.
2. Miller PD, *et al.* A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med* 1999; **106:** 513–20.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Actonel; Ductonar; Rentop; Ribastamin; Ridron; Risedon; ***Austral.:*** Actonel; ***Austria:*** Actonel; ***Belg.:*** Actonel; ***Braz.:*** Actonel; Risedross; ***Canad.:*** Actonel; ***Chile:*** Actonel; ***Cz.:*** Actonel; Norsed; Risendros; ***Fin.:*** Optinate; ***Fr.:*** Actonel; ***Ger.:*** Actonel; ***Gr.:*** Actonel; ***Hong Kong:*** Actonel; ***Hung.:*** Actonel; ***India:*** Actonel; Risofos; ***Indon.:*** Actonel; Osteonate; ***Irl.:*** Actonel; ***Israel:*** Actonel; ***Ital.:*** Actonel; Optinate; ***Jpn:*** Benet; ***Malaysia:*** Actonel; ***Mex.:*** Actonel; Seralis; ***Neth.:*** Actonel; ***Norw.:*** Optinate; ***Philipp.:*** Actonel; ***Pol.:*** Actonel; ***Port.:*** Actonel; Norsed; ***S.Afr.:*** Actonel; ***Singapore:*** Actonel; ***Spain:*** Acrel; Actonel; ***Swed.:*** Optinate; Optinate Septimum; ***Switz.:*** Actonel; ***Thai.:*** Actonel; ***Turk.:*** Actonel; ***UK:*** Actonel; ***USA:*** Actonel; ***Venez.:*** Actonel.

Multi-ingredient: ***Arg.:*** Ribastamin Duo; Ridron Pack; ***Austral.:*** Actonel Combi; ***Fr.:*** Actonelcombi; ***Hung.:*** Actonel Trio; ***Irl.:*** Actonel Combi; ***Neth.:*** Actokit; ***Swed.:*** Optinate Combi; ***UK:*** Actonel Combi; ***USA:*** Actonel with Calcium.

Strontium Ranelate *(rINNM)*

FK-481; Ranelate de Strontium; Ranelato de estroncio; S-12911; Strontii Ranelas. 2-(2-Carboxy-4-cyano-5-[*N*,*N*-di(carboxymethyl)amino]thiophen-3-yl) acetic acid distrontium salt.

Стронций Ранелат

$C_{12}H_6N_2O_8SSr_2$ = 513.5.
CAS — 135459-87-9.
ATC — M05BX03.
ATC Vet — QM05BX03.

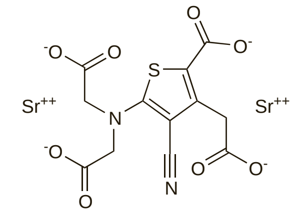

Adverse Effects and Precautions

Common adverse effects of strontium ranelate include gastrointestinal disturbances, headache, dermatitis, and eczema. Disturbances in consciousness, memory loss, and seizures may occur. Treatment with strontium ranelate has been associated with an increased incidence in venous thromboembolism including pulmonary embolism, and should be given with caution to those patients considered at risk or with a history of thromboembolic disorders. Transient reversible increases in creatine kinase activity have been reported. Hypersensitivity reactions, including rash, pruritus, urticaria, angioedema, and Stevens-Johnson syndrome have occurred. Drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, has also been reported. Strontium may interfere with certain methods used for the determination of serum and urinary calcium.

Strontium ranelate should not be given with food or antacids—see Interactions, below.

Hypersensitivity. As of November 2007, the EMEA had received reports of 16 cases of drug rash with eosinophilia and systemic symptoms (DRESS), a serious and life-threatening condition, in patients treated with strontium ranelate. Two fatalities were reported. Reactions appeared within 3 to 6 weeks of starting therapy, with skin rash, accompanied by fever, swollen glands, eosinophilia, and effects on the liver, kidneys, and lungs. Patients are advised to stop treatment with strontium ranelate if a rash occurs and to seek medical advice; treatment should not be restarted.[1] Similar advice, and a reminder that the drug should also be used with caution in patients with risk factors for venous thromboembolism, was issued in June 2008 by the Australian regulatory authorities; although there had been no fatalities, they had seen 16 reports of rash, one accompanied by fever and one by eosinophilia.[2]

1. EMEA. EMEA recommends changes in the product information for Protelos/Osseor due to the risk of severe hypersensitivity reactions (issued 16th November 2007). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf (accessed 21/01/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Severe skin reactions and venous thromboembolism with strontium ranelate (Protos). *Aust Adverse Drug React Bull* 2008; **27:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0806.pdf (accessed 17/07/08)

Interactions

Food, milk, and calcium-containing compounds may reduce the bioavailability of strontium ranelate; antacids containing aluminium or magnesium may reduce its absorption. Such products should be given at least 2 hours apart from, and, in the case of antacids, preferably after, strontium ranelate. Because of possible complex formation, strontium ranelate should not be given with oral tetracyclines or quinolones.

Pharmacokinetics

Strontium ranelate has an absolute bioavailability of about 25% after an oral dose; calcium or food reduces the bioavailability by about 60 to 70%. Peak plasma concentrations are achieved 3 to 5 hours after an oral dose. Plasma protein binding is low. Strontium ranelate has a high affinity for bone tissue. It is not metabolised, and has a half-life of about 60 hours. Excretion occurs via the kidneys and gastrointestinal tract.

Uses and Administration

Strontium ranelate is claimed to stimulate bone formation as well as reduce bone resorption. It is given orally in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. The recommended dose is 2 g daily by mouth, given preferably at night and at least 2 hours after food.

◊ References.

1. Marie PJ. Strontium ranelate: new insights into its dual mode of action. *Bone* 2007; **40** (suppl 1): S5–S8.
2. Fonseca JE. Rebalancing bone turnover in favour of formation with strontium ranelate: implications for bone strength. *Rheumatology (Oxford)* 2008; **47** (suppl 4): iv17–iv19.

Administration in renal impairment. Strontium excretion occurs via the kidneys and clearance decreases as creatinine clearance (CC) decreases. UK licensed product information states that no dosage adjustment of strontium ranelate is required in patients with mild to moderate renal impairment (CC 30 to 70 mL/minute). However, it is not recommended for those with severe renal impairment (CC below 30 mL/minute) because of a lack of pharmacokinetic data in these patients; continuation of treatment in patients developing severe renal impairment should be considered on an individual basis.

Osteoporosis. Strontium ranelate, given orally with calcium and vitamin D supplements, has been found to reduce the risk of vertebral[1] and non-vertebral[2] fractures in postmenopausal women with osteoporosis. A pooled analysis of data from these 2 studies concluded that strontium ranelate reduced both vertebral and non-vertebral fractures in patients aged 80 years or older.[3] Protection against fractures was detected within 12 months, and sustained throughout 3 years of treatment. Hip fractures were also reduced over 3 years, but this did not reach statistical significance; the authors concluded that the analysis may not have been sufficiently powered in this respect. A systematic review[4] concluded that while strontium ranelate reduces vertebral fractures, there is less of a reduction with non-vertebral fractures, and the effect on hip fracture remains unclear. Some have cautioned about the interpretation of bone mineral density (BMD) changes with strontium ranelate, since stronger X-ray attenuation by strontium compared with calcium must be corrected for to avoid overestimating the effect. However, increases in BMD could be useful clinically in gauging long-term compliance.[5]

A review[6] of the place of strontium ranelate in therapy considered that although it might be an alternative in patients who could not tolerate a bisphosphonate there was no convincing published evidence to support claims that it stimulated bone formation as well as reducing resorption. Further reviews[4,7] concluded that additional research to confirm its mechanism of action is required and that long-term fracture data are needed, along with comparative trials evaluating the efficacy of strontium ranelate relative to other therapies such as bisphosphonates.

1. Meunier PJ, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; **350:** 459–68.
2. Reginster JY, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005; **90:** 2816–22.
3. Seeman E, *et al.* Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; **21:** 1113–20.
4. O'Donnell S, *et al.* Strontium ranelate for preventing and treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis: is useful, but changes in bone mineral density need careful interpretation. *BMJ* 2005; **330:** 1400–1.
6. Anonymous. Strontium ranelate for osteoporosis? *Drug Ther Bull* 2006; **44:** 29–32.
7. Stevenson M, *et al.* The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007; **11:** 1–134.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Osteovital; Protos; ***Austral.:*** Protos; ***Belg.:*** Protelos; ***Braz.:*** Protos; ***Cz.:*** Osseor; Protelos; ***Denm.:*** Protelos; ***Fr.:*** Protelos; ***Ger.:*** Protelos; ***Gr.:*** Protelos; ***Hong Kong:*** Protos; ***Hung.:*** Protelos; ***Indon.:*** Protos; ***Irl.:*** Protelos; ***Ital.:*** Osseor; Protelos; ***Malaysia:*** Protaxos; ***Neth.:*** Osseor; Protelos; ***NZ:*** Protos; ***Philipp.:*** Protos; ***Pol.:*** Protelos; ***Port.:*** Osseor; Protelos; ***Rus.:*** Bivalos (Бивалос); ***S.Afr.:*** Protos; ***Singapore:*** Protos; ***Spain:*** Osseor; Protelos; ***Swed.:*** Protelos; ***UK:*** Protelos.

Teriparatide *(USAN, rINN)*

(1-34) Human parathormone; (1-34) Human parathyroid hormone; 1-34 Parathormone (human); hPTH 1-34; Human parathormone (1-34); Human parathyroid hormone (1-34); Human PTH (1-34); LY-333334; Parathyroid hormone peptide (1-34); Teriparatid; Teriparatida; Tériparatide; Teriparatidum.

Терипаратид

$C_{181}H_{291}N_{55}O_{51}S_2$.
CAS — 52232-67-4.
ATC — H05AA02.
ATC Vet — QH05AA02.

Teriparatide Acetate *(USAN, rINNM)*

Acetato de teriparatida; Tériparatide, Acétate de; Teriparatidi Acetas.

Терипаратида Ацетат

$C_{181}H_{291}N_{55}O_{51}S_2,xH_2O,yC_2H_4O_2$.
CAS — 99294-94-7 (teriparatide acetate).
ATC — H05AA02.
ATC Vet — QH05AA02.

Adverse Effects and Precautions

Gastrointestinal disturbances, pain in the limb of injection, headache, and dizziness are the most common adverse effects in patients treated with subcutaneous teriparatide. Dizziness, vertigo, and syncope may be associated with transient orthostatic hypotension in some patients, particularly when beginning treatment. Those so affected should not drive or operate potentially hazardous machinery. Asthenia, arthralgia, and rhinitis may occur. Angina pectoris, depression, dyspnoea, leg cramps, pneumonia, urinary disorders, and sciatica have also been reported. A metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate. It is a peptide and the possibility of systemic hypersensitivity reactions should be borne in mind. Hypercalcaemia may develop with teriparatide or the acetate and it is therefore contra-indicated in patients with pre-existing hypercalcaemia.

Teriparatide is contra-indicated in patients with severe renal impairment and should be used with caution with those with moderate impairment.

There have been reports of osteosarcoma in *rats* given teriparatide and patients who may be at increased risk, including those with a history of skeletal metastases or previous radiotherapy to the skeleton, should not receive it. It is also contra-indicated in those with metabolic bone disease including Paget's disease and hyperparathyroidism, or unexplained elevations of serum alkaline phosphatase. Use in children or those with open epiphyses is also contra-indicated. In the UK treatment is also limited to a maximum of 18 months.

Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%. The serum half-life is 5 minutes after intravenous use, and approximately 1 hour after subcutaneous injection (reflecting time needed for absorption from the injection site). No studies have been done on the metabolism or excretion of teriparatide; parathyroid hormone is believed to be enzymatically metabolised in the liver and excreted by the kidneys.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid biologically active N-terminal region of human parathyroid hormone (p.1103). It is used in the treatment of established postmenopausal osteoporosis, especially in those with a high fracture risk, and in men with primary or hypogonadal osteoporosis who are at increased risk of fracture. The usual dose is 20 micrograms subcutaneously daily into the thigh or abdominal wall. Treatment is limited to a maximum of 18 months in the UK, although it has been used for up to 2 years in the USA. Teriparatide acetate has been given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Hypoparathyroidism. Hypoparathyroidism is characterised by a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism is characterised by resistance to the effects of parathyroid hormone (see p.1087). Teriparatide acetate is used *diagnostically* to distinguish between these 2 conditions.[1] A synthetic 1-38 fragment of human parathyroid hormone (hPTH 1-38) has been used similarly.[2] Teriparatide has also been used to *treat* hypoparathyroidism.[3-5]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; **109:** 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; **146:** 373–7.
3. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* 1996; **276:** 631–6.
4. Winer KK, *et al.* A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998; **83:** 3480–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.

Osteoporosis. Parathyroid hormone is capable of stimulating both formation and resorption of bone. Continuous infusion of teriparatide leads to a persistent elevation of parathyroid hormone and greater bone resorption by stimulating osteoclasts, with a net decrease in bone volume, and resultant hypercalcaemia; in contrast, daily (intermittent) injections increase bone volume by increasing osteoblastic proliferation.[1-3] Teriparatide appears to have less effect on cortical than trabecular bone,[3] suggesting that, although it may be helpful in preventing vertebral fractures, its impact on fractures of the proximal femur may be more limited. However, while treatment with teriparatide substantially increases lumbar spine bone mineral density (BMD), beneficial increases are also seen at the hip,[1] and in a pivotal study (the Fracture Prevention Trial)[4] in **postmenopausal** women with osteoporosis (p.1084), it decreased the risk of both vertebral and non-vertebral fracture. In a follow-up study, the reduction in vertebral fracture risk in patients treated with teriparatide for a mean of 19 months persisted for at least an additional 18 months after daily treatment was stopped.[5] Teriparatide appears to improve bone geometry, with no detrimental effect on cortical bone.[6] In the UK, NICE recommends teriparatide as an option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates, or who are intolerant to bisphosphonates, and who have an extremely low BMD (4 standard deviations or more below the mean) or a very low BMD (3 standard deviations or more) plus one or more additional risk factors.[7] It has been pointed out that evidence of reduction in teriparatide's effect with current or recent alendronate therapy (see below) might make its use as a second-line agent problematic.[8]

Data on combination therapy are limited, but some studies suggest that teriparatide with HRT is more effective than HRT alone.[9] The effect of teriparatide with the antiresorptive bisphosphonates has yet to be determined.[2,6,9,10] Although there is some suggestion that teriparatide still increases bone formation after treatment with alendronate,[9] a study in men found that, when given together, alendronate impaired the anabolic effects of teriparatide.[11] For this reason, some consider that teriparatide be started immediately after stopping bisphosphonates.[10] It has been suggested that the degree of suppression of bone turnover before treatment may dictate the response to teriparatide.[6] A study of daily or cyclical teriparatide in women with osteoporosis found that although the teriparatide-induced increase in BMD may be slightly lower in women who had previously taken alendronate than in those who had never received it, the increase in spinal BMD was still impressive. Intermittent cyclical treatment with teriparatide was found to have similar effects on BMD to those induced by daily dosage.[12]

In postmenopausal women with osteoporosis taking HRT and **corticosteroids**,[13] the addition of teriparatide significantly increased BMD of the lumbar spine; modest changes in hip bone mass were not significant.

In **men** with osteoporosis, teriparatide increased BMD in the lumbar spine and at the femoral neck;[9] risk of fracture was also reduced.[1]

1. Cappuzzo KA, Delafuente JC. Teriparatide for severe osteoporosis. *Ann Pharmacother* 2004; **38:** 294–302.
2. Madore GR, *et al.* Parathyroid hormone. *J Am Acad Orthop Surg* 2004; **12:** 67–71.
3. Brixen KT, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol* 2004; **94:** 260–70.
4. Neer RM, *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344:** 1434–41.
5. Lindsay R,*et al.* Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med* 2004; **164:** 2024–30.
6. Rubin MR, Bilezikian JP. Parathyroid hormone as an anabolic skeletal therapy. *Drugs* 2005; **65:** 2481–98.
7. NICE. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: Technology Appraisal 87 (issued January 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/TA087guidance.pdf (accessed 23/07/08)
8. Anonymous. Teriparatide for postmenopausal osteoporosis. *Drug Ther Bull* 2004; **42:** 93–5.
9. Quattrocchi E, Kourlas H. Teriparatide: a review. *Clin Ther* 2004; **26:** 841–54.
10. Deal C. The use of intermittent human parathyroid hormone as a treatment for osteoporosis. *Curr Rheumatol Rep* 2004; **6:** 49–58.
11. Finkelstein JS, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; **349:** 1216–26.
12. Cosman F, *et al.* Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; **353:** 566–75.
13. Lane NE, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. *J Clin Invest* 1998; **102:** 1627–33.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Forteo; ***Austral.:*** Forteo; ***Belg.:*** Forsteo; ***Braz.:*** Forteo; ***Canad.:*** Forteo; ***Chile:*** Forteo; ***Cz.:*** Forsteo; ***Denm.:*** Forsteo; ***Fin.:*** Forsteo; ***Fr.:*** Forsteo; ***Ger.:*** Forsteo; ***Gr.:*** Forsteo; ***Hong Kong:*** Forteo; ***Hung.:*** Forsteo; ***Irl.:*** Forsteo; ***Israel:*** Forteo; ***Ital.:*** Forsteo; ***Malaysia:*** Forteo; ***Mex.:*** Forteo; ***Norw.:*** Forsteo; ***NZ:*** Forteo; ***Philipp.:*** Forteo; ***Port.:*** Forsteo; ***S.Afr.:*** Forteo; ***Singapore:*** Forteo; ***Spain:*** Forsteo; ***Swed.:*** Forsteo; ***Switz.:*** Forsteo; ***Thai.:*** Forteo; ***UK:*** Forsteo; ***USA:*** Forteo; ***Venez.:*** Forteo.

Tiludronate

ATC — M05BA05.
ATC Vet — QM05BA05.

Tiludronic Acid *(BAN, rINN)*

Acide Tiludronique; Ácido tiludrónico; Acidum Tiludronicum; ME-3737; SR-41319; Tiludronihappo; Tiludronik Asit; Tiludronsyra. {[(*p*-Chlorophenyl)thio]methylene}diphosphonic acid.

Тилудроновая Кислота

$C_7H_9ClO_6P_2S = 318.6$.
CAS — 89987-06-4.
ATC — M05BA05.
ATC Vet — QM05BA05.

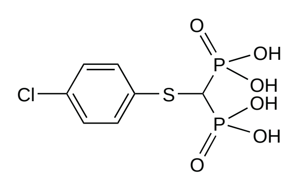

Tiludronate Disodium *(USAN)*

Tiludronate Sodium *(BANM, rINNM)*; Disodium Tiludronate; Natrii Tiludronas; Sodium Tiludronate; SR-41319B; Tiludronate de Sodium; Tiludronato sódico. Disodium dihydrogen {[(*p*-chlorophenyl)thio]methylene}diphosphonate hemihydrate.

Натрий Тилудронат

$C_7H_7ClNa_2O_6P_2S,\frac{1}{2}H_2O$ = 371.6.

CAS — 149845-07-8 (anhydrous disodium tiludronate); 155453-10-4 (tiludronate disodium hemihydrate).

ATC — M05BA05.

ATC Vet — QM05BA05.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Asthenia and dizziness have been reported rarely.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including tiludronate, see under Bisphosphonates, p.1091.

Effects on the skin. As with other bisphosphonates, tiludronate has been associated with rash and pruritus. For reference to a case of massive epidermal necrosis possibly associated with tiludronate, see Hypersensitivity, under Bisphosphonates, p.1091.

Interactions

As for the bisphosphonates in general, p.1091. Indometacin may increase the bioavailability of tiludronate two to fourfold; diclofenac does not appear to have this effect. Aspirin may decrease the bioavailability of tiludronate by 50%.

Pharmacokinetics

Like other bisphosphonates tiludronate is poorly absorbed after oral doses. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations. The oral bioavailability of tiludronate is about 6% in the fasting state, and is reduced by about 90% when given within 2 hours of food. Plasma protein binding is about 90%, mostly to albumin. Tiludronate is not metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

Uses and Administration

Tiludronate is a bisphosphonate with similar properties to those of the bisphosphonates in general (p.1091). It inhibits bone resorption and is used for Paget's disease of bone.

It is given orally as tiludronate disodium, but doses are expressed in terms of the equivalent amount of tiludronic acid; 117 mg of tiludronate disodium is equivalent to about 100 mg of tiludronic acid. To ensure adequate absorption doses should be taken with plenty of water (at least 200 mL), at least 2 hours before or after meals. In Paget's disease of bone the usual dose is 400 mg once daily for 3 months, and this may be repeated if necessary after an interval of at least 3 to 6 months.

Tiludronate has been tried in postmenopausal osteoporosis, but results were disappointing.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Skelid; ***Austria:*** Skelid; ***Belg.:*** Skelid; ***Fin.:*** Skelid†; ***Fr.:*** Skelid; ***Ger.:*** Skelid; ***Hung.:*** Skelid; ***Neth.:*** Skelid; ***Port.:*** Skelid; ***Spain:*** Skelid; ***Swed.:*** Skelid†; ***Switz.:*** Skelid; ***UK:*** Skelid; ***USA:*** Skelid.

Zoledronate

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronic Acid *(BAN, USAN, rINN)*

Acide Zolédronique; Ácido zoledrónico; Acidum Zoledronicum; CGP-42446; Tsoledronihappo; Zoledronik Asit; Zoledronsyra. (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid.

Золедроновая Кислота

$C_5H_{10}N_2O_7P_2$ = 272.1.

CAS — 118072-93-8 (anhydrous zoledronic acid); 165800-06-6 (zoledronic acid monohydrate).

ATC — M05BA08.

ATC Vet — QM05BA08.

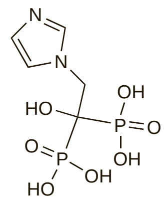

Zoledronate Disodium *(BANM, USAN, rINNM)*

CGP-42446A; ZOL-446; Zoledronas Dinatricum; Zolédronate Disodique; Zoledronato disódico. Disodium dihydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate tetrahydrate.

Динатрий Золедронат

$C_5H_8N_2Na_2O_7P_2,4H_2O$ = 388.1.

CAS — 165800-07-7.

ATC — M05BA08.

ATC Vet — QM05BA08.

Zoledronate Trisodium *(BANM, USAN, rINNM)*

CGP-42446B; Zoledronas Trinatricum; Zolédronate Trisodique; Zoledronato trisódico. Trisodium hydrogen (1-hydroxy-2-imidazol-1-ylethylidene)diphosphonate hydrate (5:2).

Тринатрий Золедронат

$C_5H_7N_2Na_3O_7P_2,2\frac{1}{2}H_2O$ = 383.1.

CAS — 165800-08-8.

ATC — M05BA08.

ATC Vet — QM05BA08.

Adverse Effects and Precautions

As for Pamidronate, p.1101. It is important to ensure adequate hydration before and after doses of zoledronic acid as dehydration predisposes to deterioration in renal function.

Effect on electrolytes. Zoledronate has more potent effects on calcium than some of the other bisphosphonates, and has precipitated severe hypocalcaemia, resulting in tetany and paraesthesia, in some patients.[1,2] In most cases, pre-existing conditions interfered with the expected compensatory physiological response to the hypocalcaemia.[1] Vitamin D deficiency should be treated before starting zoledronate.[1,2]

1. Peter R, *et al.* Severe hypocalcaemia after being given intravenous bisphosphonate. *BMJ* 2004; **328:** 335–6.
2. Breen TL, Shane E. Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency. *J Clin Oncol* 2004; **22:** 1531–2.

Effects on the eyes. For reports of ocular effects with bisphosphonates, including zoledronate, see p.1090.

Effects on the heart. For a report of a possible association between zoledronate and serious atrial fibrillation, see Effects on the Heart, under Bisphosphonates, p.1090.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, see under Bisphosphonates, p.1091. Doses may need adjusting in some patients with renal impairment (see Administration in Renal Impairment, below).

Effects on the musculoskeletal system. Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including zoledronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been variously reported as 22 or 56%. Zoledronate is not metabolised, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment (see Administration in Renal Impairment, below).

◊ References.

1. Chen T, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42:** 1228–36.

Uses and Administration

Zoledronate is an aminobisphosphonate (p.1089) that is a potent inhibitor of bone resorption. Zoledronic acid is given as an intravenous infusion over not less than 15 minutes.

It is used for **hypercalcaemia of malignancy**, in a single dose of 4 mg, diluted with 100 mL of sodium chloride 0.9% or glucose 5%. The treatment may be repeated if necessary after at least 7 days, at a dose of 4 mg. Individual doses should not exceed 4 mg, as there is an increased risk of adverse renal effects, including renal failure.

Zoledronic acid is given for the prevention of skeletal events in patients with advanced **bone malignancies** (p.660) at a dose of 4 mg, diluted as above, every 3 to 4 weeks.

For the treatment of **Paget's disease** of bone, zoledronic acid is given as a single intravenous infusion of 5 mg.

Zoledronic acid is also used for the treatment of **osteoporosis** in postmenopausal women; the recommended dose is a single intravenous infusion of 5 mg given once a year.

◊ Reviews.

1. Cheer SM, Noble S. Zoledronic acid. *Drugs* 2001; **61:** 799–805.
2. Theriault RL. Zoledronic acid (Zometa) use in bone disease. *Expert Rev Anticancer Ther* 2003; **3:** 157–66.
3. Neville-Webbe H, Coleman RE. The use of zoledronic acid in the management of metastatic bone disease and hypercalcaemia. *Palliat Med* 2003; **17:** 539–53.
4. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003; **25:** 2669–2708.
5. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
6. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.
7. Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; **34:** 183–92.

Administration in renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study[1] concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

Licensed product information also states that no adjustment is necessary in mild to moderate renal impairment for patients with *hypercalcaemia of malignancy*, but defines this degree of impairment in terms of serum creatinine less than 400 micromoles/litre or less than 4.5 mg per 100 mL.

However, for patients with *advanced bone malignancies*, the intravenous dose of zoledronic acid should be adjusted on the basis of creatinine clearance (CC) as follows:

- CC greater than 60 mL/minute: 4 mg (no adjustment necessary)
- CC 50 to 60 mL/minute: 3.5 mg
- CC 40 to 49 mL/minute: 3.3 mg
- CC 30 to 39 mL/minute: 3 mg
- CC below 30 mL/minute: treatment not recommended

Serum creatinine should be measured before each dose and treatment withheld if renal function has deteriorated. Renal deterioration is defined as an increase of 44 micromoles/litre or 0.5 mg per 100 mL for those patients with normal baseline creatinine, and an increase of 88 micromoles/litre or 1 mg per 100 mL for those with abnormal baseline creatinine. Treatment may be restarted at the dose used before treatment interruption once the creatinine returns to within 10% of the baseline value.

For patients with *Paget's disease* or *osteoporosis*, UK licensed product information states that no dose adjustment is considered necessary for those with CC of 40 mL/minute or more; due to a lack of clinical data, treatment is not recommended for those with CC of less than 40 mL/minute.

1. Skerjanec A, *et al.* The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003; **43:** 154–62.

Hypercalcaemia. Bisphosphonates are the preferred drugs for treating hypercalcaemia of malignancy (p.1083) once the patient has been adequately rehydrated. Zoledronate has been shown to have a faster onset, higher response rate, and longer duration of action than pamidronate.[1] It also has a shorter infusion time than pamidronate,[1] and some consider it the treatment of choice for hypercalcaemia of malignancy.[2-4] However, zoledronate has caused severe hypocalcaemia in some patients, see Effects on Electrolytes, above.

1. Major P, *et al.* Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; **19:** 558–67.
2. Major P. The use of zoledronic acid, a novel, highly potent bisphosphonate, for the treatment of hypercalcemia of malignancy. *Oncologist* 2002; **7:** 481–91.
3. Wellington K, Goa KL. Zoledronic acid: a review of its use in the management of bone metastases and hypercalcaemia of malignancy. *Drugs* 2003; **63:** 417–37.
4. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs* 2004; **64:** 1197–1211.

Malignant neoplasms of the bone. Bisphosphonates are of benefit in some patients with metastatic bone disease (p.660) not only to manage bone pain and hypercalcaemia, but to reduce skeletal complications such as fractures. Zoledronate is licensed for such use in many countries.[1]

In the treatment of skeletal complications from bone metastases secondary to multiple myeloma or breast cancer, zoledronate was more effective than pamidronate in reducing the risk of complications from breast cancer; it was of similar efficacy in those with multiple myeloma.[2] In a placebo-controlled study in patients with prostate cancer,[3] zoledronate reduced the number of skeletal-related events, and increased the median time to events. In patients with bone metastases arising from lung cancer and other solid tumours (excluding breast or prostate cancer), zoledronate reduced skeletal morbidity; the primary end-point, which excluded hypercalcaemia as a skeletal-related event, did not reach statistical significance.[4] However, the authors noted that the patient groups had a shorter-than-expected survival-time. A longer term follow-up of this study[5] confirmed a sustained reduction in risk of developing skeletal events with zoledronate. Whether bisphosphonates can prevent the development of new skeletal metastases is unclear.

1. Dhillon S, Lyseng-Williamson KA. Zoledronic Acid: a review of its use in the management of bone metastases of malignancy. *Drugs* 2008; **68:** 507–34.
2. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; **98:** 1735–44.
3. Saad F, *et al.* Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004; **96:** 879–82.
4. Rosen LS, *et al.* Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; **21:** 3150–7.
5. Rosen LS, *et al.* Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004; **100:** 2613–21.

Osteoporosis. Bisphosphonates are used for the prevention and treatment of osteoporosis (p.1084). Five different dosage regimens of zoledronate all increased bone mineral density (BMD) in **postmenopausal** women when given intermittently over the course of 1 year in a placebo-controlled study.[1] Compared with placebo, a once-yearly infusion of zoledronate over a 3-year period significantly reduced the risk of vertebral, hip, and other fractures in postmenopausal women with osteoporosis.[2] BMD was also significantly increased. Adverse events were similar in both groups, including renal function changes; however, serious atrial fibrillation occurred more frequently in the zoledronate group (see Effects on the Heart, under Bisphosphonates, p.1090). Once-yearly infusion of zoledronate beginning within 90 days after surgical repair of a low-trauma hip fracture was associated with a reduction in the rate of new vertebral and nonvertebral fractures, although the reduction in the risk of new hip fractures was non-significant.[3]

Preliminary results from a study evaluating zoledronate for the prevention of cancer **treatment-induced** bone loss, in postmenopausal women with early breast cancer treated with letrozole, suggest that adding zoledronate to the regimen from the start is more effective than delaying treatment until there is evidence of bone loss.[4] In a small study,[5] zoledronate also improved the calcium content of cancellous bone, maintained femoral neck BMD, and increased lumbar spine BMD after kidney transplantation. In a similar study of liver transplant recipients, zoledronate also had favourable effects on BMD. This effect tended to diminish at 12 months when compared with placebo; the authors considered this to be due to improved general health, mobility, muscle mass, and nutrition as a consequence of improved liver function.[6]

1. Reid IR, *et al.* Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002; **346:** 653–61.
2. Black DM, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356:** 1809–22.
3. Lyles KW, *et al.* HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; **357:** 1799–1809.
4. Brufsky A, *et al.* Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007; **25:** 829–36.
5. Haas M, *et al.* Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003; **63:** 1130–6.
6. Crawford BAL, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144:** 239–48.

Paget's disease of bone. Bisphosphonates may be indicated for patients with Paget's disease of bone (p.1086) if bone pain is persistent, or to prevent further progression of the disease. Zoledronate is highly effective in Paget's disease. Single infusions of up to 400 micrograms have been shown to inhibit bone resorption in patients with active Paget's disease.[1,2] In a patient[3] with disease refractory to other bisphosphonates, a single infusion of 4 mg improved symptoms and improved biochemical markers of disease activity. A placebo-controlled study compared a single infusion of 5 mg zoledronic acid with a 60-day course of oral risedronate 30 mg daily. Patients receiving zoledronic acid had significantly more rapid and marked reduction in serum alkaline phosphatase concentrations, higher response rates, and shorter median times to response than those on risedronate. During an open extension study, patients on risedronate had a significantly larger loss of therapeutic response than those given zoledronic acid.[4] A review[5] concluded that zoledronic acid was an important first-line treatment for Paget's disease.

1. Arden-Cordone M, *et al.* Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; **60:** 415–18.
2. Buckler H, *et al.* Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; **24** (suppl): 81S–85S.
3. Chung G, Keen RW. Zoledronate treatment in active Paget's disease. *Ann Rheum Dis* 2003; **62:** 275–6.
4. Reid IR, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005; **353:** 898–908.
5. Keating GM, Scott LJ. Zoledronic acid: a review of its use in the treatment of Paget's disease of bone. *Drugs* 2007; **67:** 793–804.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aclasta; Rionit; Zometa; ***Austral.:*** Zometa; ***Austria:*** Zometa; ***Belg.:*** Aclasta; Zometa; ***Braz.:*** Zometa; ***Canad.:*** Aclasta; Zometa; ***Chile:*** Zometa; ***Cz.:*** Aclasta; Zometa; ***Denm.:*** Aclasta; Zometa; ***Fin.:*** Aclasta; Zometa; ***Fr.:*** Aclasta; Zometa; ***Ger.:*** Aclasta; Zometa; ***Gr.:*** Aclasta; Zometa; ***Hong Kong:*** Zometa; ***Hung.:*** Aclasta; Zometa; ***India:*** Zoldria; Zometa; ***Indon.:*** Zometa; ***Irl.:*** Aclasta; Zometa; ***Israel:*** Zomera; ***Ital.:*** Zometa; ***Malaysia:*** Zometa; ***Mex.:*** Zometa; ***Neth.:*** Zometa; ***Norw.:*** Aclasta; Zometa; ***NZ:*** Zometa; ***Philipp.:*** Zometa; ***Pol.:*** Zometa; ***Port.:*** Zometa; ***Rus.:*** Zometa (Зомета); ***S.Afr.:*** Zometa; ***Singapore:*** Zometa; ***Spain:*** Aclasta; Zometa; ***Swed.:*** Aclasta; Zometa; ***Switz.:*** Zometa; ***Thai.:*** Zometa; ***Turk.:*** Zometa; ***UK:*** Aclasta; Zometa; ***USA:*** Reclast; Zometa; ***Venez.:*** Zoldria; Zometa.

Bronchodilators and Anti-asthma Drugs

This chapter includes many of those drugs used for their bronchodilator or anti-inflammatory properties in the management of reversible airways obstruction, such as asthma and chronic obstructive pulmonary disease.

The main bronchodilators discussed in this chapter are the sympathomimetic beta agonists (stimulants of beta-adrenoceptors), and the xanthines (mainly theophylline). The antimuscarinic bronchodilators ipratropium, oxitropium, and tiotropium are also included. The major class of anti-inflammatory drugs, the corticosteroids, are discussed separately, on p.1490; other drugs considered to act on the processes of airway inflammation and which are included in this section include sodium cromoglicate and its analogues, and the various drugs that act on leukotriene synthesis and receptor binding, on platelet-activating factor (PAF), or on other aspects of the inflammatory cascade.

Anti-asthma Drug Groups

Antimuscarinics. The parasympathetic nervous system plays a role in the regulation of bronchomotor tone, and antimuscarinic drugs have bronchodilator properties. The quaternary ammonium compounds ipratropium bromide, oxitropium bromide, and tiotropium bromide are the main antimuscarinic (anticholinergic) bronchodilators in current use; as well as reduced CNS effects they have less effect on mucociliary clearance than drugs such as atropine, which can produce accumulation of viscid lower airway secretions and a risk of mucus plugging in these patients. An antimuscarinic may be the bronchodilator of choice in the management of chronic obstructive pulmonary disease. In patients with asthma they are usually reserved for use in life-threatening acute asthma exacerbations.

Described in this chapter are

Ipratropium, p.1124	Tiotropium, p.1148
Oxitropium, p.1129	

Beta agonists. The sympathetic nervous system plays a role in the regulation of bronchomotor tone and beta$_2$-adrenoceptors in bronchial smooth muscle produce bronchodilatation when stimulated. Short-acting selective agonists of beta$_2$-adrenoceptors (beta$_2$ agonists; beta$_2$ stimulants), of which salbutamol is the paradigmatic example, are therefore first-line drugs for the relief of asthma symptoms. They are also widely used in the management of chronic obstructive pulmonary disease, although antimuscarinic bronchodilators may be preferred or used in addition. Long-acting beta$_2$ agonists are used in asthma in patients also requiring anti-inflammatory therapy.

Described in this chapter are

Arformoterol, p.1115	Orciprenaline, p.1129
Bambuterol, p.1115	Pirbuterol, p.1130
Bitolterol, p.1116	Procaterol, p.1130
Clenbuterol, p.1120	Reproterol, p.1131
Fenoterol, p.1121	Salbutamol, p.1131
Formoterol, p.1122	Salmeterol, p.1135
Hexoprenaline, p.1123	Terbutaline, p.1138
Indacaterol, p.1123	Tretoquinol, p.1149
Isoetarine, p.1125	Tulobuterol, p.1150
Levosalbutamol, p.1125	

Corticosteroids. Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) properties in the management of asthma, and may be beneficial in some patients with chronic obstructive pulmonary disease. Because of the potential adverse effects associated with prolonged systemic corticosteroid therapy, inhalation of corticosteroids with reduced systemic activity is preferred; oral corticosteroids are generally only used in short courses, and at relatively low doses, to gain control of the disease. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p.1490.

Leukotriene inhibitors and antagonists. Leukotrienes appear to play an important role in the inflammatory process of asthma, and some drugs may modify or inhibit this action. Leukotriene synthesis may be prevented by blockade of the enzyme 5-lipoxygenase with inhibitors such as zileuton. Alternatively, leukotriene receptor antagonists such as zafirlukast may be used to block specific receptors (usually those of leukotriene D$_4$) and prevent their activation. These anti-leukotriene drugs have a role in the prophylactic management of asthma as an alternative when inhaled corticosteroids cannot be used in mild asthma, and as add-on therapy in more severe asthma.

Described in this chapter are

Amlexanox, p.1115	Pranlukast, p.1130
Ibudilast, p.1123	Tipelukast, p.1149
Montelukast, p.1126	Zafirlukast, p.1150
Pemirolast,p.1129	Zileuton, p.1151

Mast cell stabilisers. The role of the mast cell in starting an inflammatory cascade has long been recognised as important, and the best established of the mast cell stabilisers are sodium cromoglicate and nedocromil sodium. These compounds inhibit mast cell degranulation in response to antigens or other stimuli, and hence prevent the release of histamine, leukotrienes, and other inflammatory mediators. They are usually well tolerated and guidelines for the treatment of asthma mention their use for prophylactic therapy as an alternative, or a supplement, to corticosteroids, particularly in children. However, it is generally considered that the corticosteroids are more effective.

Described in this chapter are

Amlexanox, p.1115	Repirinast, p.1131
Nedocromil, p.1127	Sodium Cromoglicate, p.1136
Pemirolast, p.1129	Tranilast, p.1149

Xanthines. Xanthines are drugs with complex actions that include, in varying degrees, relaxation of bronchial smooth muscle and relief of bronchospasm, stimulant effects on respiration, and anti-inflammatory effects. Theophylline and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease, but the narrow therapeutic range and the propensity for interactions with other drugs make theophylline a difficult drug to use, and it tends to be reserved for combination therapy in patients who cannot be managed with other bronchodilators (such as the beta$_2$ agonists) plus inhaled corticosteroids.

Described in this chapter are

Acefylline piperazine, p.1114	Doxofylline, p.1120
Ambroxol acefyllinate, p.1114	Etamiphylline Camsilate, p.1120
Aminophylline, p.1114	Etofylline, p.1121
Bamifylline, p.1116	Heptaminol Acefyllinate, p.1123
Bufylline, p.1116	Proxyphylline, p.1130
Caffeine, p.1116	Theobromine, p.1140
Choline Theophyllinate, p.1119	Theophylline, p.1140
Diprophylline, p.1120	

Management of Reversible Airways Obstruction

Asthma

Asthma is a chronic inflammatory disease in which the patient has episodes of reversible airways obstruction due to bronchial hyperresponsiveness. It is a common disorder, the prevalence of which has increased sharply over the last 40 years, particularly in children, with prevalence greater than 30% in some areas. More than 10% of the population in developed countries are affected. Rates are increasing in developing countries as they become more westernised,[1] and global differences in prevalence appear to be lessening.[2] It has been suggested that asthma is probably not one illness, but a collection of different phenotypes which meet the criteria for clinical diagnosis of asthma.[3,4] Although there is no clear definition of the asthma phenotype, 3 categories have been suggested: clinical phenotypes such as severity-defined or defined by age at onset, trigger-related phenotypes such as allergy- or aspirin-induced asthma, and inflammatory phenotypes such as eosinophilic asthma.[4] Current guidelines classify by severity according to the clinical features present before treatment.[5-7] Asthma may be described as extrinsic when it is associated with exposure to a specific allergen such as pollen or house-dust mite, or to a non-specific stimulus such as a chemical irritant or exercise. It may be described as intrinsic when no external precipitating factor is identifiable.

The aetiology of asthma is poorly understood, but both genetic and environmental factors are believed to contribute to development and progression of the disease.[1,8,9] Resistance to airflow in asthma is increased by a number of abnormalities, including contraction of the airway smooth muscle, the presence of excessive secretions within the airway lumen, and inflammatory cell infiltration. The inflammation in chronic asthma causes remodelling, found as shedding and thickening of the airway epithelium, and hypertrophy and hyperplasia of smooth muscle.[8,9] Airway remodelling or thickening may be important in more severe disease and can result in relatively irreversible narrowing of the airways.[7]

The principal symptoms of asthma are wheezing, dyspnoea (breathlessness), chest tightness, and cough, and these symptoms tend to be variable, intermittent, worse at night or early morning, and provoked by particular triggers. In an acute attack, the respiratory rate is rapid and tachycardia is common.[5-7] The peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV$_1$) are decreased in asthma, and in a severe asthmatic attack the PEF is generally less than 50% of predicted values. Life-threatening features include exhaustion, cyanosis, bradycardia, hypotension, confusion, and coma.[5-7]

Management of asthma. As asthma is a chronic disease, management involves prophylactic measures to reduce inflammation and airway resistance and to maintain airflow, as well as specific regimens for the treatment of acute attacks. **Measurements** of lung function play an important part in determining treatment and patients are encouraged to monitor their own disease by using a simple peak flow meter to measure PEF and adjust their therapy accordingly.[5-7] Spirometry is used to measure airflow limitation and reversibility in hospitals and surgeries.[5-7] Use of exhaled nitric oxide has been investigated to monitor disease control with corticosteroids;[10] however, an asthma treatment strategy using exhaled nitric oxide did not result in a large reduction in exacerbations or less use of inhaled corticosteroids.[11]

Drug therapy is preferably given by **inhalation** to deliver the drugs directly to the desired site of action. This produces higher local concentrations and permits smaller doses than would be required orally, with a consequent reduction in adverse effects. Systematic reviews[12-14] have found that hand-held inhaler devices including pressurised metered-dose inhalers (MDIs), dry powder inhalers, and breath actuated pressurised MDIs, are generally equally effective for the delivery of short-acting beta$_2$ agonists and corticosteroids in stable asthma. Choice of inhaler should be individualised, especially in children, taking into account ease of use, safety, and convenience.[6,7,14] Differences in drug delivery exist between inhaler devices and this should be considered when substituting one device for another.[7]

Spacer devices can be fitted to some MDIs to act as reservoirs for the drug to make it easier for the patient to inhale each dose correctly. Use of MDIs with spacer devices produce outcomes which are at least equivalent to nebuliser therapy.[14,15] Nebulisers tend to be reserved for patients who are unable or unwilling to use these devices, although the choice of spacer and method of use may substantially affect drug delivery.[5,16] A large volume spacer device is recommended for the inhalation of high doses of corticosteroids to reduce oropharyngeal deposition and systemic absorption.[5,7] Specially adapted or modified inhalation devices, as well as spacer devices, are also available to enable children to achieve a correct technique when using inhaled drug therapy, but alternative routes of delivery such as oral dosage or nebulisation may be necessary for some infants and small children.[16] Frequent intermittent or continuous nebulisation of short-acting beta$_2$ agonists are both effective in patients with severe bronchoconstriction.[14]

The standard **drugs** used in the management of asthma are the beta$_2$ agonists and corticosteroids.[5-7]

Beta$_2$ agonists relax the bronchial smooth muscle to produce bronchodilatation by selectively stimulating beta$_2$-adrenergic receptors. Short-acting selective beta$_2$ agonists such as salbutamol or terbutaline are the initial drugs of choice for use as required to relieve acute bronchospasm; if inhaled, they can have an almost immediate bronchodilating effect. Regular use of beta$_2$ agonists is mainly restricted to long-acting beta$_2$ agonists such as salmeterol xinafoate in patients also requiring anti-inflammatory prophylactic treatment; a short-acting beta$_2$ agonist should still be used as required.[5-7]

Corticosteroids are the most effective preventer therapy available for the management of asthma.[17] They are used for their anti-inflammatory properties and to reduce bronchial hyperresponsiveness; they must be taken regularly to achieve maximum benefit. Corticosteroid therapy is recommended both for acute attacks and chronic asthma prophylaxis. Meta-analysis suggests that systemic corticosteroids speed the resolution of exacerbations and reduce the rate of relapse.[18,19] It has also been suggested that inhaled corticosteroids may be of benefit in acute asthma if multiple doses are inhaled at intervals of less than 30 minutes, over a 90 to 120 minute period.[20] In chronic asthma, regular inhaled corticosteroids are one of the cornerstones of management. Combining inhaled corticosteroids with long-acting beta$_2$ agonists may have synergistic benefits;[17,21,22] such a combination is more effective than combining inhaled corticosteroids with anti-leukotriene drugs.[23] The use of an inhaled corticosteroid, budesonide, and a rapid and long-acting beta$_2$ agonist, formoterol, in a combined inhaler as both regular maintenance therapy and as a reliever when required, has been studied. Giving additional corticosteroid with each reliever inhalation in response to symptoms could be expected to provide improved control of airway inflammation,[24] and reductions in the rate of exacerbations have been reported[25,26] with relatively lower doses of inhaled corticosteroid in patients with uncontrolled persistent asthma, compared with more conventional treatment regimens using a $beta_2$ agonist as a reliever. While the place of budesonide/formoterol maintenance and reliever therapy in the management of asthma is not yet clearly defined,[24] some guidelines[6,7] include this regimen (referred to by the manufacturer, *AstraZeneca*, as Symbicort® Maintenance and Reliever Therapy, or SMART®) as an option for adults at Step 3 (see below).

Exercise-induced bronchoconstriction is also reduced in both adults and children by regular use of inhaled corticosteroids.[27]

Various studies have examined the role that inhaled corticosteroids might play in modifying the development of asthma in symptomatic children.[28-30] Although the short-term therapeutic efficacy varied between studies, possibly due to the differing lengths of treatment and study populations used, in all 3 studies the long-term clinical and functional outcomes did not differ in children treated with inhaled corticosteroids compared with placebo.

Xanthines such as aminophylline or theophylline may be given for their bronchodilating properties although there is evidence that the long-acting $beta_2$ agonist salmeterol produces a greater improvement in lung function, reduces the need for rescue short-acting $beta_2$ agonists, and has fewer adverse effects compared with theophylline.[31] There is disagreement about adding xanthine treatment to $beta_2$ agonists for the management of acute severe asthma (see below).

Inhaled *antimuscarinics* such as ipratropium bromide or oxitropium bromide, used with $beta_2$ agonists, are given in acute asthma; a systematic review[32] found that inhaled multiple doses of antimuscarinic reduced hospital admissions and improved lung function tests compared with $beta_2$ agonists alone.

Cromoglicate or nedocromil may be used as an alternative to corticosteroids for the prophylaxis of less severe asthma or combined with other therapy. *Anti-leukotrienes* such as the leukotriene receptor antagonist zafirlukast and the leukotriene inhibitor zileuton are another alternative or adjunct to inhaled corticosteroids. When used with inhaled corticosteroids, anti-leukotrienes bring modest improvements in lung function compared with inhaled corticosteroids alone.[33] They may also be useful in exercise-induced bronchoconstriction in some patients.[5-7] The anti-IgE monoclonal antibody *omalizumab*[17,34] is available for use in selected patients with allergen-induced asthma. A systematic review of omalizumab,[35] as adjunctive therapy to corticosteroids, found that treatment led to a reduction, and in some cases, withdrawal of regular inhaled corticosteroid, as well as a reduction in asthma exacerbations; longer term evaluation of adverse effects, direct comparison with inhaled corticosteroids, and assessment in children is needed.

CHRONIC ASTHMA

Advice for patients with chronic asthma includes avoidance of smoking, of allergens such as pollen, and of bronchoconstricting drugs such as beta blockers. Patients who have had asthma induced by aspirin and NSAIDs should also avoid these drugs. Skin testing to determine allergen sensitivity may be advisable.[5-7] US guidelines[5] suggest consideration of immunotherapy to desensitise patients with poorly controlled disease unavoidably exposed to a precipitating allergen. Although there is increasing evidence of benefit from such treatment[36] the size of the benefit overall remains somewhat uncertain, and the potential adverse effects make it controversial (see under Allergen Immunotherapy, p.2251). UK guidelines[6] consider that although there is evidence of benefit from immunotherapy when compared with placebo, comparative studies with other asthma treatments are needed.

Gastro-oesophageal reflux has been suggested as another exacerbating factor;[37] symptoms of gastro-oesophageal reflux disease are about one and a half times more common among individuals with asthma than the general population,[38] although the exact nature of the association remains unclear. A 2003 systematic review of acid suppressive therapy concluded that it did not benefit asthma in most patients;[39] more recent studies on the subject support this view,[40,41] although one did note reduced exacerbations and an improvement in the asthma quality of life in patients given lansoprazole compared with placebo.[41]

Guidelines for drug therapy of chronic asthma have been issued in many countries including Australia,[42] Canada,[43,44] and the UK,[6] and the USA,[5] and by the Global Initiative for Asthma (GINA),[7] and are broadly similar, providing a stepwise approach. Guidelines specifically for the management of childhood asthma have recently been issued by The European Pediatric Asthma Group.[45] Initial control is achieved with the early use of anti-inflammatory drugs at doses most appropriate for the severity of disease. In mild to moderate asthma, starting inhaled corticosteroids at very high doses and stepping down confers no benefit,[46,47] and relatively low initial doses are recommended.[5-7]

Guidelines vary slightly in their definition of low, moderate and high inhaled **corticosteroid doses**—for the definitions of these terms in UK, US, and global asthma guidelines see Asthma, under Choice of Corticosteroid, p.1499.

In adults and older children

The ***UK*** recommendations for adults and children over 5 years of age with chronic asthma are as follows:

- Step 1; mild intermittent asthma

  Patients requiring only occasional relief from symptoms may be adequately managed with an inhaled short-acting $beta_2$ agonist such as salbutamol or terbutaline taken when needed.

- Step 2; regular preventer therapy

  Regular inhaled corticosteroids may be added at an appropriate starting dose for the severity of the disease, if symptoms are present or an inhaled $beta_2$agonist is required three times a week or more, or if symptoms wake the patient from sleep one night a week. Patients who have had an exacerbation of asthma requiring oral corticosteroids in the last 2 years should also be considered for regular inhaled corticosteroids. *Alternatives* are cromoglicate or nedocromil, leukotriene receptor antagonists, or modified-release oral theophylline, but these are less effective.

- Step 3; initial add-on therapy

  If adequate control is not achieved, the preferred treatment is to supplement low-dose inhaled corticosteroids with a long-acting inhaled $beta_2$ agonist such as salmeterol xinafoate. If there is only suboptimal response, the long-acting $beta_2$ agonist is continued and inhaled corticosteroid increased to a moderate dose. If there is no response to a long-acting $beta_2$ agonist, it should be stopped and inhaled corticosteroid increased to a moderate dose; if control is still inadequate addition of either a leukotriene receptor antagonist or modified-release oral theophylline should be considered.

- Step 4; persistent poor control

  For patients with persistent poor control of asthma despite use of inhaled moderate-dose corticosteroids and an additional drug (usually a long-acting inhaled $beta_2$ agonist), increasing the inhaled corticosteroid to a high dose should be considered. Patients over 12 years of age may alternatively benefit from addition of either a leukotriene receptor antagonist, modified-release oral theophylline, or an oral modified-release $beta_2$ agonist. If a trial of a particular treatment option is ineffective, the drug is stopped (or in the case of an increased dose of inhaled corticosteroid, reduced).

- Step 5; continuous or frequent use of oral corticosteroids

  If further control is needed, then an oral corticosteroid such as prednisolone may also be given in single daily doses at the lowest dose providing adequate control. High-dose inhaled corticosteroids should also be maintained. Other treatments may be considered to minimise the use of corticosteroid tablets, such as a 6 week trial of treatment with long-acting $beta_2$ agonists, leukotriene receptor antagonists, or theophylline. If a trial of a particular treatment option is not effective, the drug is stopped. When other treatments have proved unsuccessful in patients over 12 years of age, a 3 month trial of immunomodulators such as methotrexate, ciclosporin, and gold may be considered for their anti-inflammatory, immunosuppressant, and corticosteroid-sparing properties: their use must be balanced against their potentially serious adverse effects. Referral for specialist care is advised for all patients at this step.

The ***US*** recommendations for chronic asthma management in adults and children over 5 years are:

- Step 1

  A short-acting inhaled $beta_2$ agonist is recommended, taken as required to relieve symptoms.

- Step 2

  As in UK guidelines, if regular controller therapy is needed, then a low-dose inhaled corticosteroid is the preferred treatment. Other alternatives include cromoglicate, nedocromil, a leukotriene receptor antagonist, and theophylline.

- Step 3

  The preferred treatment for patients over 12 years who are not controlled with low-dose inhaled corticosteroids, is either addition of a long-acting inhaled $beta_2$ agonist or increasing the inhaled corticosteroid to a moderate dose. In children aged 5 to 12 years either a leukotriene receptor antagonist or modified-release oral theophylline are equally acceptable treatment options in place of a long-acting inhaled $beta_2$ agonist; however, they are secondary options for patients 12 years and over long with the leukotriene inhibitor zileuton.

- Step 4

  An increase in the inhaled corticosteroid to a moderate dose is recommended in patients not controlled by Step 3. A long-acting inhaled $beta_2$ agonist is the preferred addition to this; alternatives include either a leukotriene receptor antagonist or modified-release theophylline, or in patients 12 years and over, the leukotriene inhibitor zileuton.

- Step 5

  High-dose inhaled corticosteroid in addition to a long-acting inhaled $beta_2$ agonist is the preferred treatment for patients on Step 5. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting inhaled $beta_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.

- Step 6

  As in Step 5 of the UK guidelines above, an oral corticosteroid may be added to the inhaled high-dose corticosteroid and long-acting $beta_2$ agonist. Alternatively, children aged 5 to 11 years may benefit from either a leukotriene receptor antagonist or modified-release theophylline in place of a long-acting $beta_2$ agonist. Omalizumab may be considered for patients 12 years and over who have allergies.

Consultation with an asthma specialist is recommended from Step 4.

Global guidelines for the management of asthma in adults and children aged over 5 years recommend:

- Step 1, as for UK guidelines, a short-acting inhaled $beta_2$ agonist is the recommended reliever treatment. An inhaled antimuscarinic such as ipratropium, a short-acting oral $beta_2$ agonist, or immediate-release theophylline may be considered as alternatives.

- Step 2; reliever medication plus single controller

  Similar to UK guidelines, but an anti-leukotriene is the only alternative recommended to the preferred treatment with a low-dose inhaled corticosteroid.

- Step 3; reliever medication plus one or two controllers

  A low-dose inhaled corticosteroid with a long-acting inhaled $beta_2$ agonist (the preferred option in adolescents and adults), or else increasing the inhaled corticosteroid to a moderate (the preferred option in children over 5 years) or high dose should be considered. Alternative treatment options for all ages are a combination of low-dose inhaled corticosteroid with either an anti-leukotriene or modified-release theophylline.

- Step 4; reliever medication plus two or more controllers

  The preferred treatment at Step 4 is to combine a moderate or high dose of an inhaled corticosteroid with a long-acting inhaled $beta_2$ agonist. Addition of either an anti-leukotriene or modified-release theophylline may also provide benefit. High-dose inhaled corticosteroids should be reserved for patients who are not controlled by moderate doses combined with a long-acting inhaled $beta_2$ agonist and/or an additional controller; they are recommended only on a trial basis for 3 to 6 months.

- Step 5

  As in Step 5 of UK guidelines and Step 6 of US guidelines, an oral corticosteroid may be considered in addition to another controller medication. Omalizumab is an option for patients with allergic asthma who remain uncontrolled on combinations of other controllers including a high dose of inhaled or oral corticosteroids.

Referral to an asthma specialist is recommended from Step 4.

A short 'rescue' course of oral prednisolone 30 to 60 mg daily may also be needed at any time and at any step for an acute exacerbation.

In children under 5 years of age

Recommendations for the management of chronic asthma in children under 5 years of age have also been issued in the UK[6] and USA.[5] There is limited information available for this age group, however, and some recommendations are based on extrapolations from studies in older children and adults. These guidelines also provide a stepwise approach to management. UK recommendations for management of chronic asthma in children under 5 years of age are as follows:

- Step 1; mild intermittent asthma

  Inhaled short-acting $beta_2$ agonist as required.
- Step 2; regular preventer therapy

  A low-dose inhaled corticosteroid may be added if control is poor. If a corticosteroid cannot be used, an alternative to be considered is a leukotriene receptor antagonist.
- Step 3; initial add-on therapy

  In children aged 2 to 5 years, addition of a leukotriene receptor antagonist may be considered if control is poor in those already taking inhaled corticosteroids. In those taking a leukotriene receptor antagonist alone, addition of a low-dose inhaled corticosteroid should be reconsidered. Children under 2 years and those who have persistent poor control on Step 3, may be referred to a respiratory paediatrician (Step 4).

The US makes the following recommendations for the management of chronic asthma in children under 5 years of age:

- Step 1, as for UK guidelines above.
- Step 2

  As in UK guidelines, addition of a low-dose inhaled corticosteroid is recommended. Alternative, but less preferable, treatments include the leukotriene receptor antagonist montelukast, and cromoglicate.
- Step 3

  An increase in the inhaled corticosteroid to moderate-dose should be considered.
- Step 4

  In addition to moderate-dose inhaled corticosteroid, consider either a long-acting inhaled $beta_2$ agonist or montelukast.
- Step 5

  The inhaled corticosteroid is increased to high-dose, in addition to either a long-acting $beta_2$ agonist or montelukast.
- Step 6

  In patients who remain uncontrolled, an oral corticosteroid may be added.

Consultation with an asthma specialist is recommended from step 4 onwards.

As in adults and older children, a short course of oral prednisolone (1 to 2 mg/kg daily) may be needed for acute exacerbations of asthma.

For all ages, treatment should be regularly **reviewed** and **reduced** in a stepwise manner if asthma is well controlled. Patients should be maintained on the lowest possible dose of inhaled corticosteroid; a reduction in dose every 3 months should be considered, decreasing the dose by about 25 to 50% each time.

ACUTE SEVERE ASTHMA

An acute attack of severe asthma (status asthmaticus) is potentially life-threatening and treatment should be instituted as soon as possible. UK guidelines[6] provide guidance on the assessment and initial treatment of exacerbations of asthma in general practice and in the accident and emergency department. Patients with any features of a life-threatening attack, or a severe attack persisting after initial treatment with high-dose short-acting $beta_2$ agonist and an oral corticosteroid, require admission to hospital.

In adults.

Guidelines suggest the following regimen for the hospital management of adults:[6]

- Initially, oxygen should be given at the highest concentration available (40 to 60%) with a high flow rate.
- High doses of inhaled short-acting $beta_2$ agonists (salbutamol 5 mg or terbutaline 10 mg) and antimuscarinic (ipratropium bromide 500 micrograms) should be given via a nebuliser with oxygen, or compressed air if oxygen is not available; if neither of these is available, multiple actuations of a MDI into a large volume spacer device may be used.
- High doses of systemic corticosteroids are also required: for example, prednisolone 40 to 50 mg by mouth or hydrocortisone 100 mg intravenously, or both.
- A single intravenous dose of magnesium sulfate (1.2 to 2 g infused over 20 minutes) may be considered at this stage if life-threatening features are still present. The role of magnesium sulfate has not been fully established, however, and results of clinical studies have been conflicting. A meta-analysis concluded that its routine use was not justified, but that it appears to be safe and beneficial in some patients with severe exacerbations.[48]
- Subsequently, oxygen therapy should be continued as should corticosteroid treatment (oral prednisolone 40 to 50 mg daily or hydrocortisone 100 mg every 6 hours intravenously).
- Nebulised $beta_2$ agonists and ipratropium bromide may be given every 4 to 6 hours. If the patient's condition has not improved after 15 to 30 minutes, the nebulised $beta_2$ agonist should be given more frequently (up to every 15 minutes, or in a continuous regimen such as salbutamol 10 mg hourly).
- If progress is still unsatisfactory, then an infusion of aminophylline (5 mg/kg over 20 minutes then 500 to 700 micrograms/kg per hour, monitoring blood concentrations if continued for more than 24 hours; the loading dose should not be given to patients already on maintenance oral therapy), or a parenteral $beta_2$ agonist may be considered, although there is limited evidence to support the routine use of either of these drugs.
- Patients who deteriorate further with drowsiness, unconsciousness, or respiratory arrest need transferral to an intensive care unit and intermittent positive-pressure ventilation.

Once lung function is stabilised the patient can be discharged taking inhaled corticosteroids and bronchodilators, and a short course of oral corticosteroid, which has been shown to reduce the chance of relapse and use of short-acting $beta_2$ agonists.[49]

In children.

UK guidelines suggest the following regimen for **children aged 2 years and over**:

- Severe acute attacks in children are initially treated with oxygen given via either a face mask or nasal cannula. High-dose short-acting $beta_2$ agonists are also given, either via a nebuliser (salbutamol 2.5 mg or terbutaline 5 mg in children aged 2 to 5 years; up to 5 mg of salbutamol and up to 10 mg of terbutaline may be given in children over 5 years) using oxygen as the driving gas, or as multiple actuations of a MDI into a large volume spacer device.[6] There is some evidence that in children with acute asthma, use of spacers rather than nebulisers improves oxygenation, and reduces adverse effects and time spent in the emergency department.[15]
- A systemic corticosteroid at a high dose is also required, either oral prednisolone (20 mg daily in children aged 2 to 5 years, and 30 to 40 mg daily in those over 5 years of age: children already receiving maintenance oral corticosteroids should receive 2 mg/kg up to a maximum of 60 mg daily), or intravenous hydrocortisone (4 mg/kg every 4 hours in more severely affected children).
- If life-threatening features are present, or response to $beta_2$ agonists is poor, nebulised ipratropium bromide (250 micrograms) may be added. Bronchodilators may be repeated every 20 to 30 minutes.
- If no improvement is seen, transferral to a paediatric intensive care unit is recommended. Further treatment options to consider are intravenous salbutamol (15 micrograms/kg over 10 minutes followed by an infusion of 1 to 5 micrograms/kg per minute of a 200 microgram/mL solution); intravenous aminophylline (5 mg/kg over 20 minutes then 1 mg/kg per hour; the loading dose should not be given in children already receiving oral theophylline); and, for children over 5 years of age, a single intravenous dose of magnesium sulfate (40 mg/kg to a maximum of 2 g over 20 minutes).

Subsequent management follows a similar routine to that in adults.

For **children under 2 years of age** with acute asthma UK guidelines recommend beginning with oxygen and a trial of short-acting $beta_2$ agonist given by multiple actuations of an MDI into a large volume spacer, and repeated every 1 to 4 hours if responding. If a poor response is seen, nebulised ipratropium is added, and a short course of a high-dose oral corticosteroid (prednisolone 10 mg daily for up to 3 days) may be considered.

Global guidelines for acute severe asthma are similar to those in the UK; however, US guidelines for acute severe asthma in adults and children are slightly different.[5] Although subcutaneous adrenaline or terbutaline has been used in the management of acute severe asthma in the USA, the guidelines suggest that the parenteral use of $beta_2$ agonists is of unproven value. Moreover, in contrast to the UK the intravenous use of xanthines is not recommended. In compiling the UK guidelines the British Thoracic Society has taken the view that although most patients on maximal doses of nebulised $beta_2$ agonists and corticosteroids derive no additional benefit from intravenous aminophylline, some could obtain additional bronchodilatation; intravenous aminophylline was therefore recommended for patients with life-threatening unresponsive acute asthma attacks;[6] some evidence in children,[50] although not in adults,[51] supports this. In contrast, the most recent US guidelines issued by the National Asthma Education and Prevention Program do not recommend the use of xanthines as they are considered to offer no benefit over the optimal use of inhaled short-acting $beta_2$ agonists and increases the frequency of adverse effects.[5] In consequence, in the US guidelines, adult patients whose asthma cannot be managed with oxygen, inhaled short-acting $beta_2$ agonists and antimuscarinics, and systemic corticosteroids may be considered for treatment with intravenous magnesium sulfate or nebulisation with a mixture of helium and oxygen (heliox) in order to avoid intubation and mechanical ventilation. UK guidelines consider there is no evidence to support the use of heliox; a meta-analysis[52] concluded that the existing evidence on heliox failed to show a clear benefit, and although lung function might be improved in the most severe acute asthma patients, the number and size of studies available for analysis was small and the quality variable.

OTHER ASPECTS OF ASTHMA MANAGEMENT

Other therapeutic approaches for the management of asthma are currently under investigation. Ultra-long-acting $beta_2$ agonists under development such as carmoterol, GSK-159797 (TD-3327), and indacaterol are suitable for once daily use, leading to increased convenience for patients.[53] Carbamazepine has shown potential as a treatment for asthma in addition to regular asthma therapy;[54] improved lung function and fewer exacerbations have been reported. The recombinant human B-type natriuretic peptide (BNP), nesiritide, has been reported to be an effective bronchodilator when given intravenously;[55] its clinical role, if any, remains to be determined. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases. However, a systematic review[1] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further studies were warranted. Ketolides also appear to have immunomodulatory effects: a 10-day course of oral telithromycin started with standard treatment for acute asthma in adults was reported to improve asthma symptoms, regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[56] The mechanism of this effect is unclear, however, and further studies are needed.[57]

Interestingly, furosemide given by inhalation has been found to protect against bronchoconstriction induced by exercise[58] and external stimuli,[59,60] but was not effective in improving bronchial hyperresponsiveness in a 4-week study,[61] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[62] Any clinical application has yet to be determined.[63] There has been some interest in heparin given by inhalation,[63-65] and nebulised lidocaine may be of some benefit;[63,66,67] intravenous lidocaine or oral mexiletine have been shown to block reflex bronchoconstriction.[68] Inhaled magnesium sulfate may also be of some adjunctive benefit to $beta_2$ agonists in the management of acute episodes.[69]

There is increasing study of the cellular mechanisms of inflammation in asthma and ways of controlling them.[70] Phosphodiesterase type-4 is an enzyme that hydrolyses cyclic adenosine monophosphate (cyclic AMP), stimulating the release of acute inflammatory mediators and immune responses; it is found in airways smooth muscle, pulmonary nerves, and inflammatory and immune cells relevant to the pathogenesis of asthma. Phosphodiesterase type-4 inhibitors such as cilomilast and roflumilast are under investigation for their anti-inflammatory and bronchodilator activity.[70,71] The thromboxane A_2 antagonist, seratrodast, is being tried for its effects on pulmonary function and mucus secretion. Asthma-relevant cytokines or chemokines have been targeted in a number of ways. Interleukin-4 (IL-4) stimulates a range of inflammatory processes in asthma, and soluble recombinant interleukin-4 receptor (IL-4R; rhuIL-4R) is being investigated[72,73] as an antagonist to bind and neutralise interleukin-4. Investigation into the recombinant human IL-4 variant, pitrakinra, is showing promising results in late phase asthmatic responses to allergen challenge.[74] The anti-CD25 interleukin-2 antagonist daclizumab has also been investigated with some reported benefit. An anti-interleukin-5 antibody, mepolizumab, has also been investigated;[70,73] although reductions in airway and bone-marrow eosinophils were observed, no clinical benefits were noted. Cytokines which have a potential anti-inflammatory effect are interleukin-10,[70] interleukin-12, and interferon gamma.[70,73] TNF-α may also play a role in severe asthma. The anti-TNF antibody infliximab, and the TNF receptor blocker etanercept have been shown to be effective in other inflammatory diseases.[70] Small studies using parenteral etanercept have shown some benefit on lung function and symptoms;[75,76] promising results have also been reported with intravenous infliximab.[77]

The effects of diet and dietary supplements on asthma have also been of interest. Modification of dietary fatty acids in the first 5 years of life,[78] did not reduce the risk of asthma or allergic disease in children considered to be at high risk for developing asthma. Dietary ascorbic acid supplementation has been investigated in a small group of adult patients with asthma and exercise-induced bronchoconstriction;[79] an improvement in post-exercise lung function and symptoms were noted compared with placebo. Maternal diet during pregnancy has also been examined; Vitamin D deficiency has been suggested as playing a possible role in immune-mediated disorders such as asthma.[80]

Exercise-induced asthma. For most patients exercise-induced asthma is an expression of poorly controlled asthma and regular treatment with inhaled corticosteroids should be reviewed.[6] Immediately before exercise, short-acting beta_2 agonists are the drugs of choice.[6,7] If exercise is a specific problem in patients taking inhaled corticosteroids, consideration may be given to leukotriene receptor antagonists, long-acting beta_2 agonists (although some tolerance may occur), cromoglicate, oral beta_2 agonists or theophylline.[6]

Pregnancy. It is particularly important that asthma should be well controlled during pregnancy; where this is achieved asthma has no important effects on pregnancy, labour, or the fetus.[5-7,81-84]

Inhalation has particular advantages as a means of giving drugs during pregnancy because the therapeutic action can be achieved without the need for plasma drug concentrations liable to have a pharmacological effect on the fetus. Systemic treatment should not be withheld if indicated, although there is insufficient information to support the use of anti-leukotrienes, except as continued treatment in women who were taking these before pregnancy for asthma not controlled by other medications.[6,82,83]

Severe exacerbations can have an adverse effect on pregnancy and should be treated promptly with conventional therapy, including oral or parenteral corticosteroids, oxygen, and nebulisation of a beta_2 agonist.[6,83] Prednisolone is a suitable corticosteroid for oral use since very little of the drug reaches the fetus.[82]

Occupational asthma. More than 10% of adult-onset asthma cases can be attributed to occupational exposure to pulmonary irritants.[85] Reduction or avoidance of exposure to the trigger is ideally an important component of management.[6,7,85] Symptoms may still persist; however, the prognosis for workers with occupational asthma is worse for those who remain exposed for more than one year after symptoms develop, compared with those removed earlier.[6]

Rhinitis and asthma. There is a significant association between allergic rhinitis and asthma.[7,86] It has been proposed that they are both manifestations of a single inflammatory process within the respiratory tract.[87] Asthma outcomes may be improved by following a combined therapeutic approach to comorbid allergic rhinitis and asthma.[86] Intranasal corticosteroids, an effective treatment for allergic rhinitis, have produced conflicting results in studies which assessed their effects on asthma symptoms.[86] Leukotriene receptor antagonists have produced benefits for patients with both allergic rhinitis and asthma and the anti-IgE antibody omalizumab may have a role in more severe cases.[86,88]

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Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD, chronic obstructive lung disease, chronic obstructive airways disease) is a common disorder characterised by airflow obstruction which is more or less continuous and not fully reversible, unlike asthma. The airflow limitation is usually progressive and is associated with chronic inflammation which is mainly caused by cigarette smoking;[1,2] passive smoking exposure[3] genetic factors, infections, environmental pollution, and occupational dust and chemical exposure[4] may also have an aetiological role. Symptoms of COPD include chronic and progressive dyspnoea, wheeze, frequent respiratory-tract infections, cough, and sputum production.[1,2] COPD may affect central or proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature to varying degrees in individuals with the disease[1,5]

- **Central airways.** Hypertrophy of the mucous glands and an increase in the number of goblet cells within the bronchial mucosa leads to an increase in mucus production (*chronic bronchitis*). Patients suffer from a chronic productive cough with excessive sputum production, and have been described as 'blue bloaters'. Airway wall changes include squamous metaplasia of the airway epithelium, loss of cilia and ciliary dysfunction, and increased smooth muscle and connective tissue.
- **Peripheral airways.** *Bronchiolitis* is present in the small airways. Goblet cell hyperplasia, squamous cell metaplasia, inflammatory cell infiltration, and fibrosis are all seen, leading to irreversible narrowing of the airways.
- **Lung parenchyma.** *Emphysema* occurs in the lung parenchyma in COPD. An abnormal permanent enlargement of air spaces distal to the terminal bronchioles is accompanied by destruction of the alveolar wall without obvious fibrosis. There is excessive airway collapse upon expiration and irreversible airways obstruction. Dyspnoea is a prominent symptom; a marked loss of weight may also be noted. Patients may hyperventilate to maintain oxygen levels in the blood and have been called 'pink puffers' in contrast to the 'blue bloaters' of the classic bronchitic presentation. Emphysema can sometimes be caused by a hereditary deficiency of alpha$_1$-proteinase inhibitor (alpha$_1$ antitrypsin), see p.2253. Microscopic lesions can progress to form bullae, which are defined as an emphysematous space greater than 1 cm in diameter.
- **Pulmonary vasculature.** Initially these changes are characterised by thickening of the vessel wall and endothelial dysfunction. These are followed by increased vascular smooth muscle and inflammatory cell infiltration. In advanced stages of the disease there is collagen deposition and emphysematous destruction of the capillary bed.
- **Extrapulmonary changes.** Patients with severe COPD with hypoxaemia and hypercapnia can develop *cor pulmonale* (heart disease secondary to disease of the lungs and respiratory system) marked by pulmonary hypertension, right ventricular hypertrophy, and right heart failure.[5,6] COPD is also associated with systemic inflammation and skeletal muscle wasting.[5]

Management of COPD. Although there is less consensus than for asthma, guidelines for the treatment of COPD have been issued in a number of countries,[1,2,5,7-9] and some clinicians have developed clinical algorithms for management.[10] The most important therapeutic intervention is encouraging those patients who smoke to stop; this is the only intervention clearly shown to reduce disease progression.[1,11] Psychological support and adjunctive drug therapy may be required (see Smoking Cessation, p.2354). Prevention of respiratory infection should be considered; influenza vaccination is recommended[1,2,5,7,8] and can reduce serious illness and death in patients with COPD by about 50%.[1,5,7,8] Compared with influenza vaccination, there is less well-defined benefit from pneumococcal vaccination in patients with COPD.[7,8] It is generally recommended however,[1,2,7] and a study found most benefit in younger patients and those with more severe disease.[12]

Drug treatment is primarily symptomatic and palliative using bronchodilators, corticosteroids, and oxygen therapy.

First-line drug therapy for the treatment of COPD consists of bronchodilators to alleviate bronchospasm and any reversible component of the airways obstruction. Either an inhaled short-acting *antimuscarinic*, such as ipratropium bromide, or a short-acting *beta$_2$ agonist*, is suggested as the initial bronchodilator.[1,2,7] Short-acting beta$_2$ agonists, have a more rapid action, but there is some suggestion that short-acting antimuscarinics have a more prolonged effect.[7] Nevertheless, patients vary in their responsiveness and a beta$_2$ agonist should be tried in those who do not respond well to an antimuscarinic, and vice versa.[1] In mild disease inhaled bronchodilators can be used on an as-needed basis.[1,2,7,8] In moderate and more severe disease, therapeutic options include the regular use of these bronchodilators either alone[7] or in combination,[1,2,7,8] or the addition of long-acting bronchodilators such as the beta$_2$ agonists salmeterol and formoterol or the antimuscarinic tiotropium.[1,2,5,8] A review[13] of the role of long-acting bronchodilators in COPD found that they effectively improved lung function; however, they differed in their effects on other outcomes. Only tiotropium had consistent superiority to the short-acting bronchodilator ipratropium. A reduction in COPD exacerbations and related hospitalisations and improved symptoms and quality of life have been reported in two systematic reviews[14,15] of tiotropium compared with either placebo or ipratropium; improvements in lung function compared with either placebo, ipratropium, or a long-acting beta$_2$ agonist were also noted. A treatment algorithm for the introduction of long-acting bronchodilators has been proposed.[13] Regular treatment with long-acting bronchodilators is more effective and convenient than with shorter acting drugs.[1,2,7] Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilatation while avoiding the need for high doses and the associated adverse effects.[1,2] Ipratropium given with salmeterol has been associated with beneficial effects on quality of life and lung function compared with salmeterol alone.[16] Beneficial effects on lung function have also been reported with tiotropium plus formoterol compared with either treatment alone.[17,18] A *xanthine* such as an oral modified-release preparation of theophylline may also be considered, usually where short and long-acting bronchodilators are ineffective, or in patients unable to use inhaled therapy, as there is an increased risk of adverse effects and drug interactions as well as a need for monitoring.[1,2,7,8,19] Low-dose theophylline has been reported to reduce exacerbations in patients with COPD but does not increase post-bronchodilator lung function;[1] it may have positive cardiac inotropic effects which could be of value in cor pulmonale, see under Chronic Obstructive Pulmonary Disease, p.1148.

Guidelines recommend regular treatment with an *inhaled corticosteroid* combined with a long-acting beta$_2$ agonist for symptomatic patients with moderate to severe COPD and repeated exacerbations;[1,2,5] inhaled corticosteroids have been reported to reduce the rate of exacerbations.[20-22] Whether inhaled corticosteroids improve the long-term outcomes of COPD is less clear. There has been some suggestion that inhaled corticosteroids reduce mortality,[23,24] although a subsequent systematic review[22] did not find any significant effect. The effect, if any, that inhaled corticosteroids have on the rate of decline in lung function seen in COPD patients has also been studied. A pooled analysis[25] found that, although small but significant improvements in FEV$_1$ were recorded in the first 6 months of treatment with inhaled corticosteroid compared with placebo (particularly in ex-smokers and women), the rate of decline was not affected after the first 6 months. A systematic review[22] came to similar conclusions regarding lung function decline, but reported a slowing in the rate of decline in quality of life.

Although some guidelines[7] still recommend that patients requiring frequent bronchodilator therapy should receive a trial of oral prednisolone to assess whether inhaled corticosteroids are indicated, a large study[26] found that the response to a trial of oral prednisolone was unrelated to the change in FEV$_1$ and health status over the next 3 years of treatment with either inhaled fluticasone or placebo. A subsequent systematic review[22] also found that bronchodilator reversibility and bronchial hyper-responsiveness did not predict response to inhaled corticosteroids. Other guidelines[1,2] have therefore concluded that a short course of oral corticosteroid is a poor predictor of long-term response to inhaled therapy, and do not recommend this assessment.

Combined therapy with an inhaled corticosteroid and a long-acting beta$_2$ agonist is recommended for patients with more severe disease;[1,2,5,8] combination treatment should be stopped if there is no benefit after 4 weeks.[2] A study[27] designed to assess the effect of a combination inhaler containing an inhaled corticosteroid (fluticasone) and the long-acting beta$_2$ agonist salmeterol on survival in COPD patients did not show a significant reduction in all-cause mortality, but benefits were seen in the rate of exacerbations, lung function, and health status compared with placebo. Unexpectedly, the study investigators also reported a higher probability of pneumonia being reported as an adverse effect amongst patients given medications containing fluticasone. A later case-control study[28] examining the association between inhaled corticosteroids and pneumonia, also found an excess risk in patients with COPD which increased with higher doses of inhaled corticosteroids. Neither of these studies was able to confirm the diagnosis of pneumonia radiographically. Subsequent meta-analyses compared combined inhaled corticosteroid and long-acting beta$_2$ agonist in one inhaler with either placebo,[29] long-acting beta$_2$ agonist,[30] or inhaled corticosteroid.[31] Combination therapy led to a significant reduction in exacerbation rates compared with placebo, long-acting beta$_2$ agonist, and inhaled corticosteroid. All-cause mortality was reduced with combination therapy compared with either placebo or inhaled corticosteroid, but no impact was seen in comparison with long-acting beta$_2$ agonists. Again, the increased incidence of pneumonia in the inhaled corticosteroid groups was a cause of concern. Recently the UK MHRA has warned[32] of the need to be vigilant for the development of pneumonia and other infections in those with COPD who are receiving inhaled corticosteroids as the symptoms of infection often overlap with those of exacerbation of COPD; the use of corticosteroids should be reconsidered if such infections develop.

Long-term maintenance use of *oral* corticosteroids is not generally recommended,[1,2,5,7,8] although they have a place in the short-term management of exacerbations (see below), and withdrawal after an exacerbation may be difficult in some patients with advanced disease.[2]

In patients with severe COPD and persistent hypoxaemia, supplemental *oxygen* provided on an almost continuous long-term basis at home has been found to improve survival and alleviate complications such as cor pulmonale, polycythaemia and neuropsychological impairment.[33,34] Guidelines recommend starting oxygen therapy in patients whose resting PaO_2 is less than 55 mmHg (about 7.3 kPa), or whose arterial-oxygen saturation is less than about 88%.[1,2,5,7,8] It may also be considered when PaO_2 is between 55 and 60 mmHg (7.3 to 8 kPa) or arterial-oxygen saturation is less than 90%, or if there is evidence of polycythaemia, pulmonary hypertension, or right heart failure.[1,2,5,7,8] Nocturnal oxygen therapy may benefit some patients who suffer from nocturnal hypoxaemia,[2,5,7] but not all guidelines recommend it, as evidence for clinical benefits and improvement in survival is lacking.[5,8] Evidence of benefit from short-term, 'as-needed' oxygen inhalation after exertion is also lacking,[35] although a review of studies using ambulatory oxygen during an exercise test reported an improvement in exercise performance versus placebo;[36] selected patients might gain some benefits.[2,37]

A meta-analysis[38] of the use of *mucolytics* suggested a small reduction in exacerbations and in the total number of days of disability; benefit may be greater in patients with frequent or prolonged exacerbations. Although most guidelines do not recommend widespread use,[1,2,7] patients with chronic productive cough may be considered for treatment.[1,2] Patients who are not prescribed inhaled corticosteroids may also gain some benefit.[38] Improved pulmonary function has been reported in patients given aerosolised surfactant.[39]

There is some evidence that treatment with *cardiovascular drugs* can produce improvements in some pulmonary measures. Cohort and case control studies have reported a reduced COPD and pneumonia/influenza mortality risk in association with the use of statins.[40] Another case control study[41] also reported a reduction in pulmonary as well as cardiovascular outcomes with statins, ACE inhibitors, and angiotensin II receptor inhibitors, the largest benefits occurring with the combination of statins and either ACE inhibitors or angiotensin II receptor inhibitors. This combination was associated with a reduction in COPD hospitalisations, total mortality in both high- and low-risk groups, and myocardial infarction in the high-risk group.

A systematic review[42] to assess the effects of cardioselective beta blockers on respiratory function of patients with COPD found no adverse effects on lung function or respiratory symptoms compared with placebo, and concluded that they should not be routinely withheld from patients with COPD and cor pulmonale. Additionally, a retrospective study[43] noted a reduced mortality associated with beta blocker use in patients hospitalised for acute exacerbations of COPD.

Surgery may be used in selected patients with end-stage disease who remain symptomatic despite optimal medical treatment. Bullectomy may be used to remove a large bulla that does not contribute to gas exchange.[1,2,5,7,8,44] Lung transplantation (p.1815) may be used in very advanced COPD,[1,2,5,7,8] particularly in patients with idiopathic emphysema or $alpha_1$ antitrypsin deficiency.[44] In severe COPD with hyperinflation and obvious target areas, lung volume reduction surgery may be considered; it may be a better option than medical therapy to reduce mortality in patients with predominantly upper-lobe emphysema and low exercise capacity.[1,2,5,7,8,45]

Much *investigational therapy* has focussed, with variable results, on three key processes in COPD: oxidative tissue damage, protease-mediated tissue destruction, and leucocyte-driven chronic inflammation.[46,47] Oxidative stress has been targeted with antoxidants, particularly acetylcysteine.[1,48] Various mediators of the inflammatory processes have also been targeted, for example, inhibitors of interleukin-8[48,49] and phosphodiesterase type 4.[48,50,51] Other therapies which have been considered include inhibitors of cell signalling, TNF, and adhesion molecules and chemokines.[48] Retinoids have been studied in emphysema for potential positive effects on lung repair.[52] An inhaled formulation of trospium chloride is under development for the treatment of COPD. There is also evidence that oral therapy with polyunsaturated fatty acids (including omega-3 and omega-6 fatty acids) may improve exercise capacity.[53] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases; however, their role in COPD remains to be determined.

Exacerbations. Patients with COPD frequently suffer acute exacerbations of their symptoms, and may require hospitalisation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase inflammation.[54] Treatment options include maximal bronchodilators, antibacterials, systemic corticosteroids, and oxygen as necessary, with appropriate management of any associated cardiovascular disorder.[1,2,5,7,8,55]

For *bronchodilator* therapy a short-acting $beta_2$ agonist may be combined with a short-acting antimuscarinic such as ipratropium,[1,5,7,8] although evidence for the effectiveness of this combination is lacking.[56] Some guidelines[1,2] further advocate use of a xanthine such as intravenous theophylline in unresponsive patients, although evidence of a clear benefit with systemic xanthines is inconsistent.[57]

Systemic *corticosteroids* are beneficial in acute exacerbations of COPD.[1,2,5,7,8] Studies[58,59] of severe acute exacerbation requiring hospitalisation have found systemic corticosteroids to improve lung function and reduce the length of hospital stay, and a later meta-analysis confirmed that early treatment with oral or parenteral corticosteroids reduced treatment failure and the need for additional treatment, although it was also associated with an increased risk of adverse effects.[60] Some consider that the most effective dose and duration of treatment is yet to be established,[60,61] although one study[58] found that a 2-week course was as effective as a longer course of 8 weeks. Guidelines suggest oral doses of prednisolone 30 to 50 mg daily, or equivalent, for 7 to 14 days.[1,2,5,7,8] There is also no evidence of long-term benefit.[58,59] Nebulised budesonide may be an alternative to oral corticosteroids in the treatment of non-acidotic exacerbations.[1]

The use of *antibacterials* for acute exacerbations has long been controversial. Meta-analysis[62] has suggested a decrease in mortality, treatment failure, and sputum purulence compared with placebo in moderately to severely ill patients, although the analysis included only a small number of studies, with important differences in design (see also Bronchitis, p.165). Guidelines recommend their use on an empirical basis where signs of infection are present[1,2,5,7,8] but do not support prophylactic antibacterial cover for those with recurrent acute exacerbations.[1,2,5,7] Short courses of antibacterial therapy (5 days or less) are as effective as longer courses in mild to moderate exacerbations.[63]

Oxygen therapy is required in patients with hypoxia; the goal is to maintain oxygen saturation above 90% but prevent increasing CO_2 retention.[1,2,5,7] The initial concentration of oxygen to give in COPD exacerbations is controversial. During the transfer to hospital, UK guidelines[2] recommend starting at 40% and titrating upwards if the oxygen saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93 to 94%. Special care is needed for patients with known type II respiratory failure, especially if they require a long ambulance journey or receive oxygen at home for a prolonged period before an ambulance arrives, as uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis, and respiratory arrest. In hospital, arterial blood gases should be used to guide treatment. Other guidelines[7] consider that lower initial oxygen concentrations of 24 to 28% are usually sufficient. A 2006 systematic review[64] found a lack of evidence on the safest way to provide initial oxygen treatment in COPD exacerbations.

Respiratory stimulants such as doxapram[65] are of limited use but may be considered when non-invasive ventilation is unavailable or inappropriate.[1,2]

Despite intensive therapy, some patients progress to respiratory muscle fatigue and require ventilatory support.

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62. Ram FSF, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/04/08).
63. El Moussaoui R, *et al.* Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax* 2008; **63:** 415–22.
64. Austin M, Wood-Baker R. Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 16/04/08).
65. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/04/08).

Acefylline Piperazine *(BAN, rINN)*

Acefilina piperazina; Acéfylline Pipérazine; Acefyllinum Piperazinum; Acepifylline; Piperazine Theophylline Ethanoate. Piperazine bis(theophyllin-7-ylacetate) (1:1).

Ацефиллин Пиперазин

$(C_9H_{10}N_4O_4)_2,C_4H_{10}N_2 = 562.5.$

CAS — 18833-13-1; 18428-63-2.

ATC — R03DA09.

ATC Vet — QR03DA09.

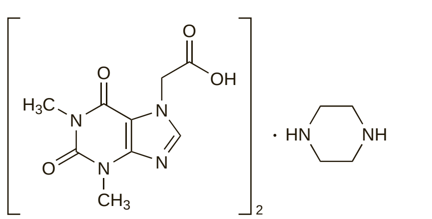

Profile

Acefylline piperazine is a derivative of theophylline (p.1140) that has been used for its bronchodilator effects. It is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Etophylate†; ***Indon.:*** Etaphylline.

Multi-ingredient: ***India:*** Cadiphylate.

Ambroxol Acefyllinate *(BANM, rINNM)*

Acebrofylline; Acebrophylline; Acefilinato de ambroxol; Ambroxol Acéfylline; Ambroxoli Acefyllinas.

Амброксола Ацефиллинат

$C_{13}H_{18}Br_2N_2O,C_9H_{10}N_4O_4 = 616.3.$

CAS — 96989-76-3.

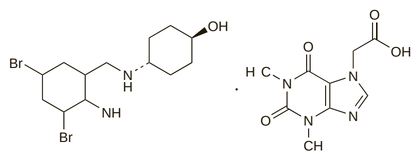

Profile

Ambroxol acefyllinate is a xanthine derivative that is used as a bronchodilator. It is given in an oral dose of 100 mg twice daily. For doses in children see below.

Administration in children. Ambroxol acefyllinate can be used as a bronchodilator in children. Children from 1 to 6 years of age may be given an oral dose of 25 mg twice daily, and children from 6 to 12 years, 50 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dogistin†; Mucomex†; ***Braz.:*** Brismucol; Brondilat; Bronfilil; Cebronfilina; Expecdilat; Filinar; Teomuc; ***Ital.:*** Ambromucil; Broncomnes; Surfolase; ***Mex.:*** Brismucol; ***Port.:*** Surfolase†; Tusolven†; ***Venez.:*** Brixilon; Bronilis.

Aminophylline *(BAN, pINN)*

Aminofilin; Aminofilina; Aminofylin; Aminofylliini; Aminofyllin; Aminophyllinum; Euphyllinum; Metaphyllin; Teofilinas-etilendiaminas; Teofillinetiléndiamin; Teofylliinietyleenidiamiini; Teofyllinetylendiamin; Theophyllaminum; Theophylline and Ethylenediamine; Theophylline Ethylenediamine Compound; Théophylline-éthylènediamine; Theophyllinum et ethylenediaminum. A mixture of theophylline and ethylenediamine (2:1), its composition approximately corresponding to the formula below.

Аминофиллин

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2 = 420.4.$

CAS — 317-34-0 (anhydrous aminophylline).

ATC — R03DA05.

ATC Vet — QR03DA05.

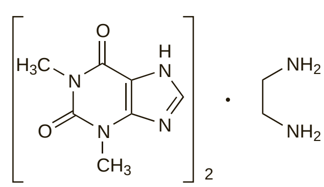

Pharmacopoeias. In *Eur.* (see p.vii), *Int., US,* and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 6.2 (Theophylline-ethylenediamine; Aminophylline BP 2008). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 31 (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Aminophylline Hydrate *(BANM, pINNM)*

Aminofilina dwuwodna; Aminofilina hidratada; Aminofylin hydratovaný; Aminophylline, Hydrate d'; Aminophyllini Hydratum; Aminophyllinum Dihydricum; Aminophyllinum Hydricum; Teofylliinietyleenidiamiinihydraatti; Teofyllinetylendiaminhydrat; Théophylline-éthylènediamine hydratée; Theophyllinum et ethylenediaminum hydricum.

Аминофиллина Гидрат

$(C_7H_8N_4O_2)_2,C_2H_4(NH_2)_2,2H_2O = 456.5.$

CAS — 49746-06-7 (aminophylline dihydrate).

ATC — R03DA05.

ATC Vet — QR03DA05.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.* Some pharmacopoeias include anhydrous and hydrated aminophylline in one monograph. Some pharmacopoeias do not specify the hydration state.

Ph. Eur. 6.2 (Theophylline-ethylenediamine Hydrate; Aminophylline Hydrate BP 2008). It contains 84.0 to 87.4% of anhydrous theophylline and 13.5 to 15.0% of anhydrous ethylenediamine. A white or slightly yellowish powder, sometimes granular. Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide); practically insoluble in dehydrated alcohol. Store in well-filled airtight containers. Protect from light.

USP 31 (Aminophylline). It is anhydrous or contains not more than two molecules of water of hydration. It contains not less than 84.0 and not more than 87.4% of anhydrous theophylline. It consists of white or slightly yellowish granules or powder, having a slight ammoniacal odour. Upon exposure to air it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallises upon standing, but redissolves when a small amount of ethylenediamine is added; insoluble in alcohol and in ether. Its solutions are alkaline to litmus. Store in airtight containers.

Incompatibility. Aminophylline solutions should not be allowed to come into contact with metals.

Solutions of aminophylline are alkaline and if the pH falls below 8, crystals of theophylline will deposit.[1] Drugs known to be unstable in alkaline solutions, or that would lower the pH below the critical value, should not be mixed with aminophylline.

1. Edward M. pH—an important factor in the compatibility of additives in intravenous therapy. *Am J Hosp Pharm* 1967; **24:** 440–9.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140. Hypersensitivity has been associated with the ethylenediamine content.

Porphyria. Aminophylline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

As for Theophylline, p.1142.

Pharmacokinetics

Aminophylline, a complex of theophylline with ethylenediamine, readily liberates theophylline in the body. The pharmacokinetics of theophylline are discussed on p.1145.

◊ Studies in healthy subjects suggested that ethylenediamine does not affect the pharmacokinetics of theophylline after oral or intravenous dosage.[1,2]

1. Aslaksen A, *et al.* Comparative pharmacokinetics of theophylline and aminophylline in man. *Br J Clin Pharmacol* 1981; **11:** 269–73.
2. Caldwell J, *et al.* Theophylline pharmacokinetics after intravenous infusion with ethylenediamine or sodium glycinate. *Br J Clin Pharmacol* 1986; **22:** 351–5.

Uses and Administration

Aminophylline has the actions and uses of theophylline (see p.1146) and is used similarly as a bronchodilator in the management of asthma (p.1108) and chronic obstructive pulmonary disease (p.1112). Aminophylline is also used to relieve neonatal apnoea (p.1118). It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease. Aminophylline is usually preferred to theophylline when greater solubility in water is required, particularly in intravenous formulations.

Aminophylline may be given in the anhydrous form or as the hydrate, and doses may be expressed as either; aminophylline hydrate 1.09 mg is equivalent to about

1 mg of aminophylline. The USP 31 specifies that aminophylline preparations should be labelled with respect to their anhydrous *theophylline* content. As the pharmacokinetics of theophylline are affected by a number of factors including age, smoking, disease, diet, and drug interactions, the dose of aminophylline must be carefully individualised and serum-theophylline concentrations monitored (see Uses and Administration of Theophylline, p.1146).

In the management of **acute severe bronchospasm**, aminophylline may be given intravenously by slow injection or infusion. To reduce adverse effects, intravenous aminophylline should not be given at a rate greater than 25 mg/minute. In adults who have not been taking aminophylline, theophylline, or other xanthine-containing medication, a loading dose of 5 mg/kg ideal (lean) body-weight or 250 to 500 mg of aminophylline may be given intravenously over 20 to 30 minutes by slow injection or infusion, followed by a maintenance infusion dose of 500 micrograms/kg per hour. Older patients and those with cor pulmonale, heart failure, or liver disease may require lower maintenance doses; smokers often need higher maintenance doses. A loading dose may not be considered necessary unless the patient's condition is deteriorating.

Intravenous aminophylline is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, the serum-theophylline concentration should first be assessed and the initial loading dose should be calculated on the basis that each 600 micrograms/kg of aminophylline (equivalent to 500 micrograms/kg theophylline) will increase serum-theophylline concentration by 1 microgram/mL.

In the management of **chronic bronchospasm** aminophylline may be given orally as modified-release preparations; a usual dose is aminophylline hydrate 225 to 450 mg twice daily. Therapy should start with the lower dose and be increased as appropriate. Retitration of the dosage is required if the patient is changed from one modified-release preparation to another as the bioavailability of modified-release aminophylline preparations may vary.

For doses of aminophylline used in children, see Administration in Children, below.

Intramuscular injection of aminophylline causes intense local pain and is not recommended.

Aminophylline has also been used as the hydrochloride.

Administration. RECTAL ADMINISTRATION. Absorption from aminophylline suppositories is erratic and this dose form has been associated with toxicity, hence the warnings that suppositories should not be used, especially in children. In the UK suppositories are no longer readily available and one hospital wishing to use the rectal route for apnoea in premature infants (see Neonatal Apnoea, p.1118) achieved therapeutic plasma-theophylline concentrations with a specially formulated rectal gel.[1]

1. Cooney S, *et al*. Rectal aminophylline gel in treatment of apnoea in premature newborn babies. *Lancet* 1991; **337:** 1351.

Administration in children. Aminophylline may be given intravenously, by slow injection or infusion, to manage **acute severe bronchospasm** in children. Doses should be calculated using ideal or lean body-weight. In children who have not been taking aminophylline, theophylline or other xanthine-containing medicine, UK licensed product information recommends a loading dose of 5 mg/kg given by slow injection or infusion over 20 to 30 minutes. Initial maintenance dose ranges are:

- 6 months up to 10 years of age: 1 mg/kg per hour
- 10 to 16 years of age: 800 micrograms/kg per hour

Although unlicensed in the UK for use in children under 6 months, the *BNFC* allows a dose of 1 mg/kg per hour from 1 month of age. Children aged from 16 years and above may be given adult doses, see Uses and Administration, above. Serum-theophylline concentrations should be used to guide further dose adjustments.

Children who are already receiving theophylline, aminophylline or other xanthine-containing medicines, should not normally receive intravenous aminophylline unless serum-theophylline concentration is available to guide dosage. Loading doses are based on the expectation that each 500 micrograms/kg lean body-weight of theophylline will result in a 1-microgram/mL increase in serum-theophylline concentration.

Oral modified-release preparations are given to children with a body-weight over 40 kg in the long-term management of **chronic bronchospasm**. An initial dose of 225 mg twice daily may be given if the child has not previously received xanthine preparations, increased after 1 week to 450 mg twice daily according to serum-theophylline concentrations. Different modified-release preparations are not considered interchangeable.

Aminophylline may also be used in the management of **neonatal apnoea** (see p.1118). Although the injection is unlicensed in the UK in children under 6 months of age, the *BNFC* recommends an initial dose of 6 mg/kg by intravenous injection over 20 minutes. This is followed by 2.5 mg/kg every 12 hours, increased if necessary to 3.5 mg/kg every 12 hours. The plasma theophylline concentration for optimum response in neonatal apnoea is 8 to 12 mg/litre. For further information on the dosage of theophylline itself in neonates, see Administration in Infants, p.1147.

Erectile dysfunction. For reference to the use of a cream containing aminophylline, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p.747.

Motor neurone disease. A study[1] in 25 patients with amyotrophic lateral sclerosis (see p.2380) found that aminophylline improved the endurance of respiratory muscles and increased the handgrip strength of skeletal muscles; it may have some potential therapeutic benefit in such patients.

1. Berto MC, *et al*. Acute action of aminophylline in patients with amyotrophic lateral sclerosis. *Acta Neurol Scand* 2007; **115:** 301–5.

Reduction of body fat. Cosmetic aminophylline cream has been promoted for its supposed ability to remove fat ('cellulite') from the thighs.[1] Concern has been raised about the potential for topical sensitisation.[2]

1. Dickinson BI, Gora-Harper ML. Aminophylline for cellulite removal. *Ann Pharmacother* 1996; **30:** 292–3.
2. Simon PA. Comment: aminophylline-containing cream. *Ann Pharmacother* 1996; **30:** 1341.

Preparations

BP 2008: Aminophylline Injection; Aminophylline Tablets;
USP 31: Aminophylline Delayed-release Tablets; Aminophylline Injection; Aminophylline Oral Solution; Aminophylline Rectal Solution; Aminophylline Suppositories; Aminophylline Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardirenal†; Fadafilina; Larjanfilina; ***Austria:*** Euphyllin; Mundiphyllin†; ***Braz.:*** Aminoima; Aminoliv; Asmafin; Asmapen; Asmodrin; Asmoquinol; Minoton; Unifilin; ***Canad.:*** Phyllocontin; ***Chile:*** Cardiomin†; ***Cz.:*** Pharophyllin†; Syntophyllin; ***Denm.:*** Teofylamin; ***Fin.:*** Aminocont; ***Ger.:*** Phyllotemp†; ***Hung.:*** Diaphyllin; ***Indon.:*** Phyllocontin; ***Irl.:*** Phyllocontin; ***Ital.:*** Aminomal; Tefamin; ***Jpn:*** Neophyllin; ***Mex.:*** Amofilin; Drafilyn-Z; ***Neth.:*** Euphyllin†; ***Port.:*** Filotempo; ***S.Afr.:*** Peterphyllin; Phyllocontin; ***Swed.:*** Teofyllamin; ***Switz.:*** Escophylline†; Phyllotemp†; ***Thai.:*** Asmalia; Fileen†; ***Turk.:*** Aminocardol; Asmafilin; Carena; ***UK:*** Amnivent†; Phyllocontin; ***USA:*** Truphylline†; ***Venez.:*** Broncophilina.

Multi-ingredient: Austria: Asthma-Hilfe; Limptar; Myocardon; ***Braz.:*** Alergo Filinal; Alergotox Expectorante†; Alergotox†; Dispneitrat; ***Ger.:*** Limptar†; ***Hong Kong:*** Asmeton; ***Mex.:*** Isobutil†; Paliatil; ***Port.:*** Anti-Asmatico; ***S.Afr.:*** Diphenamill†; Genasma; Lotussin Expectorant†; Natrophylline Compound; Repasma; ***Thai.:*** Asmeton†; ***USA:*** Emergent-Ez; ***Venez.:*** Fedratal†.

Amlexanox *(BAN, USAN, rINN)*

AA-673; Amlexanoxo; Amlexanoxum; Amoxanox; CHX-3673. 2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid.

Амлексанокс

$C_{16}H_{14}N_2O_4$ = 298.3.
CAS — 68302-57-8.
ATC — A01AD07; R03DX01.
ATC Vet — QA01AD07; QR03DX01.

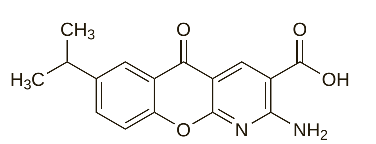

Profile

Amlexanox has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1136) and also acts as a leukotriene inhibitor. It is given orally in the management of asthma (p.1108) and for allergic rhinitis (p.565); a dose of 25 or 50 mg three times daily has been suggested. Amlexanox is also given as a metered-dose nasal spray for allergic rhinitis.

Amlexanox is also applied as a 5% oral paste four times daily in the management of aphthous ulcers (see Mouth Ulceration, p.1700). A 2-mg biodegradable oral disc designed to deliver amlexanox locally is also available.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Solfa; ***Neth.:*** Miraftil; ***USA:*** Aphthasol.

Arformoterol Tartrate *(USAN, rINNM)* ⊗

Arformotérol, Tartrate d'; Arformoteroli Tartras; *R,R*-Formoterol Tartrate; Tartrato de arformoterol. (-)-*N*-[2-Hydroxy-5-((1*R*)-1-hydroxy-2-{[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino}ethyl)phenyl]formamide hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Арформотерола Тартрат

$C_{19}H_{24}N_2O_4,C_4H_6O_6$ = 494.5.
CAS — 67346-49-0 (arformoterol); 200815-49-2 (arformoterol tartrate).

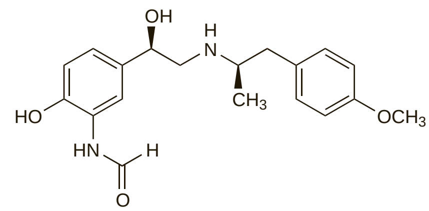

(arformoterol)

Profile

Arformoterol is the *R,R*-enantiomer of the beta$_2$-adrenoceptor agonist formoterol (p.1122) and has similar properties. Arformoterol is a long-acting selective beta$_2$ agonist which is used as a bronchodilator in the management of chronic obstructive pulmonary disease (p.1112). It is given as the tartrate, but doses are described in terms of the base; 22 micrograms of arformoterol tartrate is equivalent to about 15 micrograms of arformoterol. Given as a nebulised solution, a usual inhaled dose of arformoterol is 15 micrograms given every 12 hours.

◊ References.

1. Lötvall J, *et al*. The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
2. Anonymous. Arformoterol (Brovana) for COPD. *Med Lett Drugs Ther* 2007; **49:** 53–5.
3. Baumgartner RA, *et al*. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther* 2007; **29:** 261–78.
4. Matera MG, Cazzola M. Ultra-long-acting β -adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? *Drugs* 2007; **67:** 503–15.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Brovana.

Bambuterol Hydrochloride *(BANM, rINNM)* ⊗

Bambutérol, chlorhydrate de; Bambuterol-hidroklorid; Bambuterol-hydrochlorid; Bambuterolhydroklorid; Bambuteroli hydrochloridum; Bambuterolihydrokloridi; Bambuterolio hidrochloridas; Hidrocloruro de bambuterol; KWD-2183. (*RS*)-5-(2-*tert*-Butylamino-1-hydroxyethyl)-*m*-phenylene bis(dimethylcarbamate) hydrochloride.

Бамбутерола Гидрохлорид

$C_{18}H_{29}N_3O_5,HCl$ = 403.9.
CAS — 81732-65-2 (bambuterol); 81732-46-9 (bambuterol monohydrochloride).
ATC — R03CC12.
ATC Vet — QR03CC12.

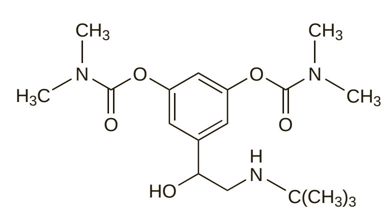

(bambuterol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Bambuterol Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; soluble in alcohol.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Bambuterol is not recommended for patients with severe hepatic impairment as its metabolism would be unpredictable. The dose of bambuterol should be reduced in renal impairment (see below). It is unsuitable for the relief of acute bronchospasm or in patients with unstable respiratory disease.

Effects on the heart. A prescription event monitoring study found an excess risk of non-fatal heart failure in elderly patients receiving bambuterol, particularly in the first month of treatment.[1] See also under Salbutamol, p.1131.

1. Martin RM, *et al.* Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β agonists. *Thorax* 1998; **53:** 558–62.

Interactions

As for Salbutamol, p.1132. Bambuterol inhibits plasma cholinesterases and can prolong the action of drugs such as suxamethonium (see Sympathomimetics, under Suxamethonium, p.1912) that are inactivated by these enzymes.

Pharmacokinetics

Nearly 20% of a dose of bambuterol is absorbed from the gastrointestinal tract after oral doses. It is slowly metabolised in the body to its active metabolite, terbutaline; peak terbutaline concentrations are reported to occur about 4 to 7 hours after a dose of bambuterol as tablets. The slow rate at which metabolism occurs determines the prolonged duration of action of bambuterol of at least 24 hours. Hydrolysis of bambuterol is catalysed by plasma cholinesterase; however, bambuterol also inhibits plasma cholinesterase and therefore partly inhibits its own metabolism. For the metabolism and excretion of terbutaline, see p.1139.

◊ References.

1. Sitar DS. Clinical pharmacokinetics of bambuterol. *Clin Pharmacokinet* 1996; **31:** 246–56.
2. Nyberg L, *et al.* Pharmacokinetics of bambuterol in healthy subjects. *Br J Clin Pharmacol* 1998; **45:** 471–8.
3. Bang U, *et al.* Pharmacokinetics of bambuterol in subjects homozygous for the atypical gene for plasma cholinesterase. *Br J Clin Pharmacol* 1998; **45:** 479–84.
4. Ahlström H, *et al.* Pharmacokinetics of bambuterol during oral administration to asthmatic children. *Br J Clin Pharmacol* 1999; **48:** 299–308.
5. Rosenborg J, *et al.* Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. *Br J Clin Pharmacol* 2000; **49:** 199–206.

Uses and Administration

Bambuterol is an inactive prodrug of terbutaline (p.1138), a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has similar actions to those of salbutamol (p.1133) except that it has a more prolonged duration of action (at least 24 hours). Bambuterol hydrochloride is used as a long-acting bronchodilator for persistent reversible airways obstruction in conditions such as asthma (p.1108). The usual dose is 10 to 20 mg orally once daily at bedtime. Doses may need to be reduced in renal impairment (see below).

Administration in renal impairment. Licensed product information recommends that the initial dose of bambuterol hydrochloride should be halved in patients with renal impairment (glomerular filtration rate less than 50 mL/minute). Further doses should be adjusted according to response.

Asthma. References.

1. Fugleholm AM, *et al.* Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. *Eur Respir J* 1993; **6:** 1474–8.
2. Gunn SD, *et al.* Comparison of the efficacy, tolerability and patient acceptability of once-daily bambuterol tablets against twice-daily controlled release salbutamol in nocturnal asthma. *Eur J Clin Pharmacol* 1995; **48:** 23–8.
3. Zarkovic JP, *et al.* The Bambuterol Multicentre Study Group. One-year safety study with bambuterol once daily and terbutaline three times daily in 2-12-year-old children with asthma. *Pediatr Pulmonol* 2000; **29:** 424–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Bambec; ***Braz.:*** Bambec; ***Cz.:*** Bambec†; ***Denm.:*** Bambec; ***Fr.:*** Oxeol; ***Ger.:*** Bambec; ***Hong Kong:*** Bambec†; ***Hung.:*** Bambec†; ***India:*** Bambudil; ***Ital.:*** Bambec†; ***Malaysia:*** Bambec†; ***Norw.:*** Bambec; ***NZ:*** Bambec; ***Philipp.:*** Bambec; ***Singapore:*** Bambec; ***Spain:*** Bambec; ***Swed.:*** Bambec; ***Thai.:*** Bambec; ***UK:*** Bambec.

Multi-ingredient: ***India:*** Montair Plus.

Bamifylline Hydrochloride *(BANM, USAN, rINNM)*

AC-3810; Bamifylline, Chlorhydrate de; Bamifyllini Hydrochloridum; BAX-2739Z; 8102-CB; CB-8102; Hidrocloruro de bamifilina. 8-Benzyl-7-[2-(*N*-ethyl-*N*-2-hydroxyethylamino)ethyl]theophylline hydrochloride.

Бамифиллина Гидрохлорид

$C_{20}H_{27}N_5O_3,HCl = 421.9.$

CAS — 2016-63-9 (bamifylline); 20684-06-4 (bamifylline hydrochloride).

ATC — R03DA08.

ATC Vet — QR03DA08.

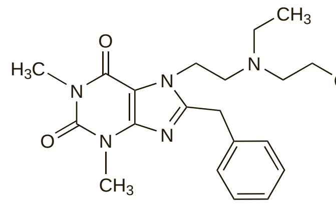

(bamifylline)

Profile

Bamifylline hydrochloride is a theophylline derivative (p.1140) that is used for its bronchodilator properties in reversible airways obstruction. It is not converted to theophylline in the body. It is given in usual oral doses of 600 or 900 mg daily in 2 or 3 divided doses. It is also given rectally as suppositories, and by slow intravenous infusion.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Trentadil; ***Braz.:*** Bamifix; ***Fr.:*** Trentadil; ***Ital.:*** Airest†; Bamifix; Bamixol†; Briofil.

Bitolterol Mesilate *(BANM, rINNM)* ⊗

Bitoltérol, Mésilate de; Bitolterol Mesylate *(USAN)*; Bitolteroli Mesilas; Mesilato de bitolterol; Win-32784. 4-[2-(*tert*-Butylamino)-1-hydroxyethyl]-*o*-phenylene di-*p*-toluate methanesulphonate.

Битолтерола Мезилат

$C_{28}H_{31}NO_5,CH_4O_3S = 557.7.$

CAS — 30392-40-6 (bitolterol); 30392-41-7 (bitolterol mesilate).

ATC — R03AC17.

ATC Vet — QR03AC17.

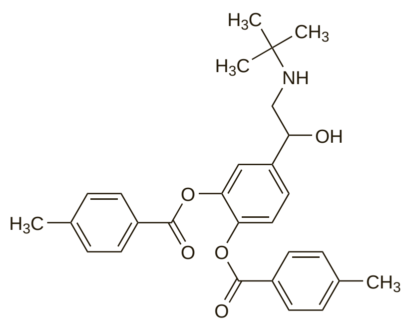

(bitolterol)

Profile

Bitolterol is an inactive prodrug that is hydrolysed in the body to colterol, a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has similar properties to those of salbutamol (p.1131).

It has been used as a bronchodilator in the management of diseases with reversible airways obstruction such as asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112); inhalation results in the rapid onset of bronchodilatation (2 to 4 minutes) with a duration of action of 5 or more hours.

Bitolterol has been given by inhalation via a metered-dose aerosol supplying 370 micrograms of bitolterol mesilate per inhalation. For the *relief* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) followed by a third inhalation (370 micrograms) if required. For the *prevention* of bronchospasm the usual adult dose is 2 inhalations (740 micrograms) every 8 hours. Maximum doses have been stated to be 3 inhalations (1110 micrograms) every 6 hours or 2 inhalations (740 micrograms) every 4 hours. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, bitolterol indicates deterioration of asthma control and the need for review of therapy.

Alternatively, a 0.2% inhalation solution of bitolterol mesilate has been given by nebulisation. Using *continuous flow* nebulisation, the usual adult dose is from 1.5 to 3.5 mg three or four times daily as required, to a maximum daily dose of 14 mg. Using *intermittent flow* nebulisation, the usual adult dose is 0.5 to 2 mg three or four times daily as required, up to a maximum daily dose of 8 mg. In all cases dosage intervals should be greater than or equal to 4 hours.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Tornalate.

Bufylline *(BAN)*

Ambuphylline *(USAN)*; Bufilina; Theophylline-aminoisobutanol. 2-Amino-2-methylpropan-1-ol theophyllinate.

Буфиллин

$C_{11}H_{19}N_5O_3 = 269.3.$

CAS — 5634-34-4.

ATC — R03DA10.

ATC Vet — QR03DA10.

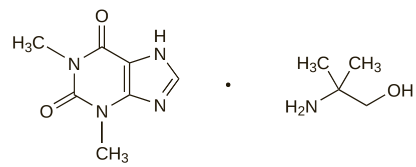

Profile

Bufylline is a theophylline derivative (p.1140) that has been used for its bronchodilator effects as an ingredient of preparations promoted for coughs and other respiratory-tract disorders. The ethiodide has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Broncolex†; EMS Expectorante; Revenil; Revenil Dospan; Revenil Expectorante; ***S.Afr.:*** Nethaprin Dospan; Nethaprin Expectorant.

Caffeine *(BAN)*

Anhydrous Caffeine; Cafeína; Caféine; Coffeinum; Guaranine; Kofeiini; Kofein; Kofeina; Kofeinas; Koffein; Methyltheobromine; Théine. 1,3,7-Trimethylpurine-2,6(3*H*,1*H*)-dione; 1,3,7-Trimethylxanthine; 7-Methyltheophylline.

Кофеин

$C_8H_{10}N_4O_2 = 194.2.$

CAS — 58-08-2.

ATC — N06BC01.

ATC Vet — QN06BC01.

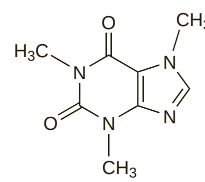

NOTE. Compounded preparations of caffeine may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Caffeine Citrate *(BANM)*

Cafeína, citrato de; Citrated Caffeine; Coffeinum Citricum.

Кофеина Цитрат

$C_8H_{10}N_4O_2,C_6H_8O_7 = 386.3.$

CAS — 69-22-7.

ATC — N06BC01.

ATC Vet — QN06BC01.

Caffeine Hydrate *(BANM)*

Cafeína monohidrato; Caféine monohydratée; Caffeine Monohydrate; Coffeinum monohydricum; Kofeiinimonohydraatti; Kofein monohydrát; Kofeinas monohidratas; Koffein-monohidrát; Koffeinmonohydrat.

Кофеин Моногидрат

$C_8H_{10}N_4O_2,H_2O$ = 212.2.

CAS — 5743-12-4.

ATC — N06BC01.

ATC Vet — QN06BC01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine Monohydrate; Caffeine Hydrate BP 2008). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; **41:** 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; **23:** 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; **12:** 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; **51:** 512–14.
5. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. *Am J Health-Syst Pharm* 1997; **54:** 1106, 1108.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140.

Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly.

◊ General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; **252:** 822–4.
2. Fredholm BB, *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; **51:** 83–133.

Breast feeding. Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern have been reported.[1-4]

The American Academy of Pediatrics[5] states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 to 3 cups daily) and caffeine is usually compatible with breast feeding.

1. Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979; **54:** 787–800.
2. Hildebrandt R, *et al.* Transfer of caffeine to breast milk. *Br J Clin Pharmacol* 1983; **15:** 612P.
3. Sagraves R, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. *Drug Intell Clin Pharm* 1984; **18:** 507.
4. Berlin CM, *et al.* Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984; **73:** 59–63.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

Effects on the cardiovascular system. An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine consumption may be a factor contributing to essential hypertension in young people.

High dose caffeine (25 mg/kg) used as a loading dose in the prevention and treatment of neonatal apnoea (see p.1118) resulted in a marked reduction of cerebral and intestinal blood flow velocity in preterm infants;[2] no changes were noted in left ventricular output, blood pressure, or heart rate. The authors attributed the effect on blood flow velocity to vasoconstriction, and suggested a smaller caffeine loading dose, repeated several hours later. A later study, also in preterm infants, which examined the effect of a divided loading dose of caffeine (12.5 mg/kg repeated after 4 hours), found that cerebral blood flow velocity was decreased after the second dose; intestinal blood flow velocity and left ventricular output remained unchanged.[3] The authors concluded that the 20% reduction in cerebral blood flow velocity observed was probably not meaningful for infants with adequate cerebral oxygen supply; however, an infant's ability to respond to hypoxaemia by vasodilatation may be compromised.

For a discussion of the effects of caffeine-containing beverages on cardiovascular risk factors, see p.2415.

1. Savoca MR, *et al.* Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; **18:** 116–20.
2. Hoecker C, *et al.* Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002; **109:** 784–7.
3. Hoecker C, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F61–F64.

Effects on mental function. A report of 6 cases of excessive daytime sleepiness associated with high caffeine intake.[1]

1. Regestein QR. Pathologic sleepiness induced by caffeine. *Am J Med* 1989; **87:** 586–8.

Headache. Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[1] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[2-4] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[5] A prospective study suggested that a prophylactic intravenous dose of caffeine on the day of surgery reduced the likelihood of postoperative headache in patients at risk of caffeine withdrawal.[6]

In a case-control study,[7] investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. Patients suffering from CDH were more likely overall to have been high caffeine consumers before the onset of CDH; no association was found with current caffeine consumption.

1. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ* 1990; **300:** 1558–9.
2. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; **i:** 1335.
3. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; **68:** 842–5.
4. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; **72:** 295–7.
5. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; **336:** 632.
6. Weber JG, *et al.* Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc* 1997; **72:** 621–6.
7. Scher AI, *et al.* Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004; **63:** 2022–7.

Overdosage. Reports and reviews of caffeine toxicity.

1. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; **14:** 1227–9.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; **28:** 144–50.
3. Rivenes SM, *et al.* Intentional caffeine poisoning in an infant. *Pediatrics* 1997; **99:** 736–8.
4. Anderson BJ, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999; **27:** 307–11.
5. Ergenekon E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001; **11:** 737–9.
6. Holstege CP, *et al.* Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003; **41:** 1003–7.

Pregnancy. In the USA, the FDA has advised pregnant women to limit their intake of caffeine and caffeine-containing beverages to a minimum, but this recommendation was based largely on *animal* studies and the effect of caffeine on the human fetus and fetal loss during pregnancy is controversial.[1] Although some studies found no evidence that moderate caffeine use increased the risk of spontaneous abortion,[2,3] others have reported conflicting results.[4,5] There is some evidence for an effect on fetal growth, but again it is not clear that this applies generally: a prospective population-based study in the UK found that a decreased birth-weight with increased caffeine intake was only significant in smokers.[6] The authors of this study concurred that a reduction in caffeine intake during pregnancy would be prudent, together with stopping smoking. An association between high maternal caffeine intake during pregnancy and an increased risk of the sudden infant death syndrome has also been reported,[7] although another study found no such association.[8]

1. Eskenazi B. Caffeine during pregnancy: grounds for concern? *JAMA* 1993; **270;** 2973–4.
2. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; **269:** 593–7.
3. Klebanoff MA, *et al.* Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999; **341:** 1639–44.
4. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; **270:** 2940–3.
5. Cnattingius S, *et al.* Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; **343:** 1839–45.
6. Cook DG, *et al.* Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ* 1996; **313:** 1358–62.
7. Ford RPK, *et al.* Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998; **78:** 9–13.
8. Alm B, *et al.* Caffeine and alcohol as risk factors for sudden infant death syndrome. *Arch Dis Child* 1999; **81:** 107–11.

Interactions

Like theophylline (see p.1142) caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to numerous interactions with other drugs and substances which enhance or reduce its metabolic clearance.

◊ Reviews.

1. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; **39:** 127–53.

Alcohol. In a study of 8 healthy subjects given an oral dose of alcohol of 2.2 mL/kg, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1] Another study[2] found that some antagonism of the central effects of alcohol was produced by caffeine, although there was no reversal of subjective sensations of drunkenness; however the dose of caffeine in this study (400 mg) was considerably higher.

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; **54:** 528–34.
2. Azcona O, *et al.* Evaluation of the central effects of alcohol and caffeine interaction. *Br J Clin Pharmacol* 1995; **40:** 393–400.

Antiarrhythmics. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lidocaine*, *flecainide*, and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; **317:** 117.

Antibacterials. Caffeine elimination half-life has been reported to be increased and clearance decreased when given with *ciprofloxacin*,[1-3] *enoxacin*,[2,3] and *pipemidic acid*,[2,3] whereas *lomefloxacin*,[4] *norfloxacin*,[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; **33:** 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; **87** (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; **39:** 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; **35:** 660–4.

Antidepressants. Fluvoxamine has been reported to significantly reduce the clearance and prolong the elimination half-life of caffeine.[1] The clinical importance of this interaction, attributed to inhibition of cytochrome P450 isoenzyme CYP1A2 by fluvoxamine, remains to be established.

1. Culm-Merdek KE, *et al.* Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* 2005; **60:** 486–93.

Antiepileptics. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; **36:** 401–6.

Antifungals. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg/kg given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 279–83.

Antigout drugs. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days of treatment with *allopurinol* 300 mg or 600 mg daily by mouth. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; **21:** 454–8.

Gastrointestinal drugs. *Cimetidine* 1 g daily by mouth reduced the systemic clearance of caffeine and prolonged its elimination half-life in 5 healthy subjects. Although the steady-state plasma-caffeine concentration would increase by about 70%, it was thought unlikely that this would produce adverse clinical effects.[1] However, in contrast a study in 11 children given cimetidine in doses of 11 to 36 mg/kg daily for gastritis found no evidence that it altered the metabolism of a dose of ^{13}C-labelled caffeine.[2]

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* 1981; **12:** 155–9.
2. Parker AC, *et al.* Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. *Br J Clin Pharmacol* 1997; **43:** 467–70.

Lithium. For mention of the effect of caffeine on serum-lithium concentrations, see Xanthines, p.405.

Methoxsalen. Single oral doses of 1.2 mg/kg methoxsalen have reduced the clearance of caffeine in patients with psoriasis,[1,2] consistent with a cytochrome P450 isoenzyme CYP1A2-dependent inhibition of caffeine demethylation.[2]

1. Mays DC, *et al.* Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* 1987; **42:** 621–6.
2. Bendriss EK, *et al.* Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. *Br J Clin Pharmacol* 1996; **41:** 421–4.

Sex hormones. The clearance of caffeine has been reported to be reduced and its elimination half-life increased in women taking *oral contraceptives*.[1-3] This interaction was thought to be due to impairment of hepatic metabolism of caffeine by sex hormones and could result in increased accumulation of caffeine. Similar results have been reported[4] in a study of postmenopausal women given oestrogens for *hormone replacement therapy* and caffeine.

1. Patwardhan RV, *et al.* Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* 1980; **95:** 603–8.
2. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985; **28:** 425–8.
3. Balogh A, *et al.* Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. *Eur J Clin Pharmacol* 1995; **48:** 161–6.
4. Pollock BG, *et al.* Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. *J Clin Pharmacol* 1999; **39:** 936–40.

Sympathomimetics. Use of caffeine 400 mg with *phenylpropanolamine* 75 mg, both given orally as modified-release preparations, produced greater plasma-caffeine concentrations in healthy subjects than caffeine alone. Greater increases in blood pressure and more reports of physical adverse effects occurred after the combination than after either drug alone.[1]

Giving caffeine with *ephedrine* has been reported to produce significant cardiovascular, metabolic, and hormonal responses, including increased systolic blood pressure and heart rate, and raised fasting glucose and insulin.[2] These enhanced effects appear to be the result of a pharmacodynamic rather than a pharmacokinetic interaction, and led to the issue of a warning by Health Canada in 2006 not to use weight loss products containing both caffeine and ephedrine, since the combination had caused reported adverse effects ranging from dizziness, tremors, headaches, and irregularities in heart rate to seizures, psychosis, heart attacks, and stroke.[3] Those particularly at risk include individuals suffering from ischaemic heart disease, hypertension, and diabetes.[2,3]

1. Lake CR, *et al.* Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990; **47:** 675–85.
2. Haller CA, *et al.* Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* 2004; **75:** 259–73.
3. Health Canada. Health Canada advises consumers not to use weight loss products containing ephedrine and caffeine (issued 23rd May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_33-eng.php (accessed 09/07/08)

Theophylline. For the effect of caffeine on the metabolism and elimination of theophylline, see p.1144.

Pharmacokinetics

Caffeine is absorbed readily after oral doses and is widely distributed throughout the body. It is also absorbed through the skin. Absorption when given rectally by suppository may be slow and erratic. Absorption after intramuscular injection may be slower than after oral doses. Caffeine passes readily into the CNS and into saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged. Hepatic cytochrome P450 isoenzyme CYP1A2 is involved in caffeine enzymatic metabolism. Neonates have a greatly reduced capacity to metabolise caffeine, due to their immature hepatic enzyme systems, and it is largely excreted unchanged in the urine. By 9 months of age, urinary excretion is similar to that seen in adults. Elimination half-lives are about 3 to 7 hours in adults but may be about 3 to 4 days in neonates.

Metabolism and excretion. The metabolism of caffeine has been shown to be dose dependent[1,2] with clearance decreasing as the dose is increased suggesting saturable metabolism. Four- to fivefold differences in plasma half-lives of caffeine are common among healthy people. The plasma half-life of caffeine is decreased by smoking[3] and by exercise,[4] and is increased by liver disease such as cirrhosis and viral hepatitis,[3,5] and in pregnancy.[3] The plasma half-life of caffeine is not affected by old age[6] or obesity.[7] Drug interactions also affect the pharmacokinetics of caffeine (see above).

1. Cheng WSC, *et al.* Dose-dependent pharmacokinetics of caffeine in humans: relevance as a test of quantitative liver function. *Clin Pharmacol Ther* 1990; **47:** 516–24.
2. Denaro CP, *et al.* Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther* 1990; **48:** 277–85.
3. Kalow W. Variability of caffeine metabolism in humans. *Arzneimittelforschung* 1985; **35:** 319–24.
4. Collomp K, *et al.* Effects of moderate exercise on the pharmacokinetics of caffeine. *Eur J Clin Pharmacol* 1991; **40:** 279–82.
5. Scott NR, *et al.* The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. *Br J Clin Pharmacol* 1989; **27:** 205–13.
6. Blanchard J, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm* 1983; **11:** 109–26.
7. Abernethy DR, *et al.* Caffeine disposition in obesity. *Br J Clin Pharmacol* 1985; **20:** 61–6.

Uses and Administration

Caffeine is a methylxanthine that, like theophylline (p.1146), inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. It is a stimulant of the CNS, particularly the higher centres, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Its bronchodilating properties are weaker than those of theophylline. Caffeine facilitates the performance of muscular work and increases the total work that can be performed by a muscle. The diuretic action of caffeine is weaker than that of theophylline.

Caffeine is used as a mild CNS stimulant in usual oral doses of 50 to 100 mg, although doses of up to 200 mg may be used. Doses should not be taken more often than every 3 hours. It is also frequently included in oral analgesic preparations with aspirin, paracetamol, or codeine in unit doses of about 15 to 65 mg but its clinical benefit is debated (see Pain, below). Caffeine is sometimes given with ergotamine in preparations for the treatment of migraine, usually in unit doses of 100 mg. Caffeine citrate has been used similarly. For details of doses in children, see Administration in Children, below.

Caffeine and sodium benzoate and caffeine and sodium salicylate are readily soluble in water and have been used when caffeine is to be given by injection.

Beverages of coffee, tea, and cola provide active doses of caffeine (see p.2415).

◊ General references.

1. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.

Administration in children. Caffeine is used in the short-term treatment of neonatal apnoea of prematurity (below). An initial loading dose of caffeine citrate is 20 mg/kg (equivalent to 10 mg/kg caffeine), followed by a maintenance dose of caffeine citrate 5 mg/kg daily. These doses may be given either orally or by intravenous infusion. Serum concentrations of caffeine should be measured before starting treatment in infants who have already been treated with theophylline (which is metabolised to caffeine in infants) or whose mothers consumed caffeine before delivery; serious toxicity has been associated with serum concentrations greater than 50 micrograms/mL.

Asthma. Caffeine's bronchodilating activity is about 40% that of theophylline[1] and oral doses of 5 or 10 mg/kg have been shown to produce an effect.[2,3] Because of its weak action other xanthines are generally recommended in asthma (p.1108), but it may need to be avoided before tests of lung function.[4]

1. Gong H, *et al.* Bronchodilator effects of caffeine in coffee: a dose-response study of asthmatic subjects. *Chest* 1986; **89:** 335–42.
2. Becker AB, *et al.* The bronchodilator effects and pharmacokinetics of caffeine in asthma. *N Engl J Med* 1984; **310:** 743–6.
3. Bukowskyj M, Nakatsu K. The bronchodilator effect of caffeine in adult asthmatics. *Am Rev Respir Dis* 1987; **135:** 173–5.
4. Bara AI, Barley EA. Caffeine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 19/03/08).

Dementia. A cohort study in 7017 patients aged 65 years and over examined the association between caffeine intake, cognitive decline, and incident dementia.[1] Caffeine consumption itself was found to be significantly associated with a wide range of variables also associated with cognitive decline, such as age, gender, depressive symptoms, and cardiovascular disease. Although no relationship was found between baseline caffeine intake and incident dementia in a 4-year follow-up period, caffeine consumption appeared to reduce cognitive decline in women without dementia. The authors concluded that further studies are required to ascertain whether caffeine may be of value in prolonging the period of mild cognitive impairment in women before a diagnosis of dementia.

1. Ritchie K, *et al.* The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology* 2007; **69:** 536–45.

Diabetes mellitus. A single dose of caffeine 250 mg proved beneficial in augmenting warning symptoms and physiological responses to experimentally-induced hypoglycaemia in diabetic patients,[1] and was suggested as a potentially useful adjunct for diabetics who have difficulty in recognising the onset of hypoglycaemia (see Diabetic Emergencies, p.435). In a subsequent placebo-controlled crossover study oral caffeine 200 mg twice daily appeared to enhance the intensity of hypoglycaemic warning symptoms in patients with type 1 diabetes on a low-caffeine diet.[2] A later study[3] reported an association between caffeine and a reduction in the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes, which the authors suggested may explain the increase in warning symptoms and hormonal responses previously reported in daytime hypoglycaemia. Caffeine has also been seen to impair postprandial glucose metabolism in patients with type 2 diabetes,[4] raising concern about the potential hazards of caffeine in these patients for whom decreases in insulin sensitivity might increase average glucose levels and the risk of diabetic complications.

1. Debrah K, *et al.* Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; **347:** 19–24.
2. Watson JM, *et al.* Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; **23:** 455–9.
3. Richardson T, *et al.* Influence of caffeine on frequency of hypoglycaemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. *Diabetes Care* 2005; **28:** 1316–20.
4. Lane JD, *et al.* Caffeine impairs glucose metabolism in type 2 diabetes. *Diabetes Care* 2004; **27:** 2047–8.

Diagnosis and testing. Caffeine excretion assessed by measuring its urinary metabolites or by the exhalation of labelled CO_2 in breath after doses of ^{13}C- or ^{14}C-labelled caffeine has been used to develop liver function tests and to determine the activity of specific enzymes such as xanthine oxidase, P450 cytochromes, and polymorphic *N*-acetyltransferase.[1]

Caffeine given orally has been used to assess acetylator status by determining the metabolic ratio of the metabolites 5-acetylamino-6-formylamino-1-methyluracil (AFMU) to 1-methylxanthine in urine,[2] but some have questioned its value.[3]

Caffeine has also been investigated in the diagnosis of susceptibility to malignant hyperthermia.[4] Intramuscular injection induced a temporary hypermetabolic reaction in subjects susceptible to malignant hyperthermia, but not in non-susceptible subjects or healthy controls. The authors suggested that monitoring of carbon dioxide, produced by hypermetabolism, might offer a minimally invasive test for such susceptibility.

1. Kalow W, Tang B-K. The use of caffeine for enzyme assays: a critical appraisal. *Clin Pharmacol Ther* 1993; **53:** 503–14.
2. Hildebrand M, Seifert W. Determination of acetylator phenotype in caucasians with caffeine. *Eur J Clin Pharmacol* 1989; **37:** 525–6.
3. Notarianni LJ, *et al.* Caffeine as a metabolic probe: NAT2 phenotyping. *Br J Clin Pharmacol* 1996; **41:** 169–73.
4. Anetseder M, *et al.* Diagnosis of susceptibility to malignant hyperthermia by use of a metabolic test. *Lancet* 2002; **359:** 1579–80.

ECT. In patients whose seizure duration is declining despite maximal ECT stimulation, pretreatment with high-dose intravenous caffeine increases seizure duration without affecting seizure threshold. Theophylline has been used similarly, see p.1142.

References.

1. Hinkle PE, *et al.* Use of caffeine to lengthen seizures in ECT. *Am J Psychiatry* 1987; **144:** 1143–8.
2. Coffey CE, *et al.* Caffeine augmentation of ECT. *Am J Psychiatry* 1990; **147:** 579–85.
3. Kelsey MC, Grossberg GT. Safety and efficacy of caffeine-augmented ECT in elderly depressives: a retrospective study. *J Geriatr Psychiatry Neurol* 1995; **8:** 168–72.

Neonatal apnoea. Apnoea of infancy has been defined as cessation of breathing either lasting 20 seconds or more or associated with bradycardia, cyanosis, pallor, and marked hypotonia, for which no specific cause can be identified.[1] Premature infants (less than 37 weeks of gestation) can exhibit periodic breathing with pathological apnoea (apnoea of prematurity); this usually resolves as the infant approaches term and the neurological systems controlling ventilation mature.[1,2]

The management of neonatal apnoea for which no underlying disorder can be found may involve supportive measures such as cardiorespiratory monitoring;[1] continuous positive airways pressure and drug therapy may be required.[3]

The methylxanthines, aminophylline, theophylline, and caffeine, reduce the frequency of apnoea and the need for mechanical ventilation in preterm infants during the first seven days of therapy.[4] In preterm infants given intermittent positive airway pressure, prophylactic methylxanthine treatment increases the chances of successful extubation within one week.[5] There is evidence to suggest that this benefit might be more helpful in infants of extremely low birth-weight extubated in the first week. High doses of caffeine, 20 mg/kg daily, have been used around the time of extubation in neonates born at less than 30 weeks of gestation. Short term benefits were noted,[6] and no evidence of harm in the first year of life. Caffeine has also been reported to reduce the incidence of bronchopulmonary dysplasia in infants with very low birth-weight,[3] so that positive airways pressure could be stopped earlier in infants given caffeine compared with those given placebo. A later evaluation of these infants found that caffeine therapy improved the rate of survival without neurodevelopmental disability at 18 to 21 months.[7] The incidence of cerebral palsy and cognitive delay were also reduced. Earlier stopping of positive airway pressure in the infants assigned to caffeine explained almost half of the beneficial long-term effect of caffeine, but further studies are required to ascertain other potential mechanisms of action. Caffeine has a wider therapeutic index, fewer peripheral adverse effects than theophylline, and a longer half-life enabling once-daily dosage, and is therefore preferred.[4,8] Caffeine is given as the citrate salt. It is well absorbed when given orally; intravenous treatment is rarely necessary. For details of doses, see Administration in Children, above. The *BNFC* considers appropriate serum concentrations in neonatal apnoea to be 8 to 12 micrograms/mL for theophylline and 10 to 20 micrograms/mL for caffeine. Higher caffeine concentrations of 25 to 35 micrograms/mL may sometimes be required. Previous treatment with theophylline, infants born to mothers who consumed caffeine before delivery, infants showing signs of toxicity, or infants who require higher doses will require monitoring of plasma caffeine concentrations; however, routine monitoring of plasma concentrations is not always considered necessary.[9] During the first year of life, the elimination half-life of both caffeine and theophylline decreases significantly as the infant matures; regular monitoring of serum concentrations and constant dosage adjustments are therefore required if therapy is prolonged.[1]

For details of the adverse effects on the cardiovascular system associated with caffeine during treatment of neonatal apnoea, see Effects on the Cardiovascular System, above.

Use of doxapram may be considered for apnoea that does not respond to xanthine therapy.[1,2,10] It is reported to be similar in effect to the methylxanthines, and may also be of benefit as an addition to xanthine therapy.[11,12] Doxapram is poorly absorbed orally and adverse effects such as hypertension, CNS stimulation, and heart block have been reported.[13]

1. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
2. Ruggins NR. Pathophysiology of apnoea in preterm infants. *Arch Dis Child* 1991; **66:** 70–73.
3. Schmidt B, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354:** 2112–21.
4. Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 19/03/08).
5. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for extubation in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 19/03/08).
6. Steer P, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F499–F503.
7. Schmidt B, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; **357:** 1893–1902.
8. Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 19/03/08).
9. Natarajan G, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007; **119:** 936–40.
10. Hascoet J-M, *et al.* Risks and benefits of therapies for apnoea in premature infants. *Drug Safety* 2000; **23:** 363–79.
11. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
12. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
13. Henderson-Smart DJ, Steer P. Doxapram versus methylxanthine for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Obesity. A 1999 review[1] of non-prescription weight loss supplements concluded that controlled studies have not shown fat loss in overweight individuals using caffeine without an energy-restricted diet. A later study[2] examined a herbal combination product, containing amongst its active ingredients caffeine (from kola nut) and ephedrine (from ephedra), in the treatment of overweight and obesity without other lifestyle modifications. Some beneficial effects on body-weight were reported after 12 weeks of treatment compared with placebo; however, although no serious adverse effects were seen in the healthy subjects enrolled in this study, the herbal product used contained relatively low amounts of active ingredients compared with preparations used in other similar studies. The FDA has since banned the sale of dietary supplements containing ephedra as they present an unreasonable risk to health (see Ephedra, p.1558), and concerns have been raised about potential additive stimulant effects of preparations containing both caffeine and ephedrine, see Sympathomimetics under Interactions, above.

1. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; **171:** 604–8.
2. Coffey CS, *et al.* A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disord* 2004; **28:** 1411–19.

Orthostatic hypotension. Caffeine has been of benefit in the treatment of orthostatic hypotension (p.1530) due to autonomic failure in some patients, especially for postprandial hypotension.[1-3] However, efficacy has only been shown in mild cases and it is usually ineffective in severe cases.[4]

1. Onrot J, *et al.* Hemodynamic and humoral effects of caffeine in autonomic failure. *N Engl J Med* 1985; **313:** 549–54.
2. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with dihydroergotamine and caffeine. *Ann Intern Med* 1986; **105:** 168–73.
3. Tonkin AL. Postural hypotension. *Med J Aust* 1995; **162:** 436–8.
4. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.

Pain. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit (see under Choice of Analgesic, p.2). Some investigators have failed to show that caffeine offers any benefit[1,2] but others have shown that the adjuvant use of caffeine can increase analgesic activity.[3-8] A meta-analysis of 10 studies comparing paracetamol plus caffeine with paracetamol alone in women with postpartum uterine cramp found any benefit of the combination to be minimal.[9] A literature review[10] concluded that there was some evidence that caffeine may be useful as an analgesic adjuvant in relieving headache, but that the dose may need to be at least 65 mg and that these higher doses increase the risk of nervousness and dizziness. Evidence for the effects of caffeine in other types of pain, such as postpartum, postoperative, dental, rheumatic, and cancer pain, was inconclusive.

In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache.

Whether caffeine enhances the gastrointestinal absorption of ergotamine in preparations for the relief of migraine is not clear.

1. Winter L, *et al.* A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with post-operative oral surgery pain. *Curr Ther Res* 1983; **33:** 115–22.
2. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.
3. Laska EM, *et al.* Caffeine as an analgesic adjuvant. *JAMA* 1984; **251:** 1711–18.
4. Rubin A, Winter L. A double-blind randomized study of an aspirin/caffeine combination versus acetaminophen/aspirin combination versus acetaminophen versus placebo in patients with moderate to severe post-partum pain. *J Int Med Res* 1984; **12:** 338–45.
5. Schachtel BP, *et al.* Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991; **151:** 733–7.
6. Migliardi JR, *et al.* Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* 1994; **56:** 576–86.
7. Kraetsch HG, *et al.* Analgesic effects of propyphenazone in comparison to its combination with caffeine. *Eur J Clin Pharmacol* 1996; **49:** 377–82.
8. Diener HC, *et al.* The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25:** 776–87.
9. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain—a meta-analysis. *J Clin Pharm Ther* 1996; **21:** 261–82.
10. Zhang W-Y. A benefit-risk assessment of caffeine as an analgesic adjuvant. *Drug Safety* 2001; **24:** 1127–42.

POST-DURAL PUNCTURE HEADACHE. Intravenous caffeine sodium benzoate may relieve post-dural puncture headache (p.1851) that persists despite conservative therapy.

Psoriasis. The efficacy of a 10% formulation of topical caffeine in the treatment of psoriasis has been investigated in a group of 39 patients with stable plaque psoriasis.[1] Improvements were seen at each 2-week follow-up stage, but the difference only became significant after 8 weeks. The only adverse effect noted during the study was mild itching, reported by 2 of the caffeine recipients.

1. Vali A, *et al.* Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *J Dermatol Treat* 2005; **16:** 234–7.

Preparations

BP 2008: Aspirin and Caffeine Tablets; Caffeine Citrate Injection; Caffeine Citrate Oral Solution;
USP 31: Acetaminophen and Caffeine Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Caffeine and Sodium Benzoate Injection; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Guarana; Percutafeine; ***Austria:*** Coffekapton; ***Braz.:*** Percutafeine†; ***Canad.:*** Wake-Up Tablets; ***Chile:*** Asafen Nueva Formula†; Jaquedryl; ***Cz.:*** Kinedryl; ***Fin.:*** Cofi-Tabs; ***Fr.:*** Percutafeine; ***Ger.:*** Percoffedrinol N†; ***Gr.:*** Cafcit; ***Irl.:*** Pro-Plus; ***Mex.:*** Ifa Kafen†; Kafen†; ***Pol.:*** Kofex; ***Port.:*** Bioregime SlimKit†; ***Rus.:*** Vasobral (Вазобрал); ***Spain:*** Durvitan; ***UK:*** Pro-Plus; ***USA:*** Cafcit; Caffedrine; Enerjets; Keep Alert; Lucidex; NoDoz; Stay Alert; Vivarin.

Multi-ingredient: numerous preparations are listed in Part 3.

Choline Theophyllinate *(BAN, rINN)*

Choline, Théophyllinate de; Cholini Theophyllinas; Koliiniteofyllinaatti; Kolinteofyllinat; Oxtriphylline; Teofilinato de colina; Theophylline Cholinate.

Холина Теофиллинат

$C_{12}H_{21}N_5O_3$ = 283.3.
CAS — 4499-40-5.
ATC — R03DA02.
ATC Vet — QR03DA02.

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2008 (Choline Theophyllinate). A white crystalline powder, odourless or with a faint amine-like odour. It contains between 41.9% and 43.6% of choline and between 61.7% and 65.5% of theophylline, each calculated with reference to the dried substance. Very soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. Store at a temperature not exceeding 25°. Protect from light.

USP 31 (Oxtriphylline). A white crystalline powder, having an amine-like odour. It contains not less than 61.7% and not more than 65.5% of anhydrous theophylline. Soluble 1 in 1 of water; freely soluble in alcohol; very slightly soluble in chloroform. A 1% solution in water has a pH of about 10.3. Store in airtight containers.

Profile

Choline theophyllinate is a theophylline salt that liberates theophylline (p.1140) in the body; choline theophyllinate 1.57 mg is equivalent in theophylline content to about 1 mg of anhydrous theophylline. It is used as a bronchodilator for reversible airways obstruction. The usual oral maintenance dose for adults is 800 mg daily, in 4 divided doses. The daily dose should be adjusted according to clinical response and serum-theophylline concentrations (see Uses and Administration of Theophylline, p.1146). For details of doses in children see Administration in children, below.

Administration in children. Choline theophyllinate can be given to children in oral doses of 10 to 20 mg/kg daily, in 3 or 4 divided doses.

Preparations

BP 2008: Choline Theophyllinate Tablets;
USP 31: Oxtriphylline Delayed-release Tablets; Oxtriphylline Extended-release Tablets; Oxtriphylline Oral Solution; Oxtriphylline Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Brondecon Elixir; ***Canad.:*** Choledyl; ***Ger.:*** Euspirax†; ***Gr.:*** Choledyl; ***Swed.:*** Teovent; ***USA:*** Choledyl†.

Multi-ingredient: ***Austral.:*** Brondecon Expectorant; ***Canad.:*** Choledyl Expectorant; ***NZ:*** Broncelix; Brondecon; Pharmacycare Cough Expectorant†; ***Port.:*** Vitasma†.

Cilomilast *(USAN, rINN)*

Cilomilastum; SB-207499. *cis*-4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanecarboxylic acid.

Циломиласт

$C_{20}H_{25}NO_4$ = 343.4.
CAS — 153259-65-5.

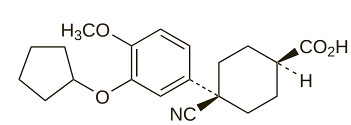

Profile

Cilomilast is a phosphodiesterase type-4 inhibitor that has been investigated in the treatment of chronic obstructive pulmonary disease.

Clenbuterol Hydrochloride *(BANM, rINNM)* ⊗

Clenbutérol, chlorhydrate de; Clenbuteroli hydrochloridum; Hidrocloruro de clenbuterol; Klenbuterol hydrochlorid; Klenbuterolhidroklorid; Klenbuterolhydroklorid; Klenbuterolihydrokloridi; Klenbuterolio hidrochloridas; NAB-365 (clenbuterol). 1-(4-Amino-3,5-dichlorophenyl)-2-*tert*-butylaminoethanol hydrochloride.

Кленбутерола Гидрохлорид

$C_{12}H_{18}Cl_2N_2O,HCl$ = 313.7.

CAS — 37148-27-9 (clenbuterol); 21898-19-1 (clenbuterol hydrochloride).

ATC — R03AC14; R03CC13.

ATC Vet — QR03AC14; QR03CC13.

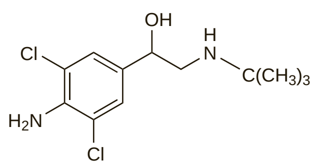

(clenbuterol)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of clenbuterol:

Angel Dust;
Clen.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clenbuterol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 7.0.

Profile

Clenbuterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131). It is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in certain patients with chronic obstructive pulmonary disease (p.1112). A usual oral dose is 20 micrograms twice daily; doses of up to 40 micrograms twice daily have occasionally been given. Clenbuterol hydrochloride has also been given by inhalation. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, clenbuterol indicates deterioration of asthma control and the need for review of therapy.

Abuse. Clenbuterol has been used illicitly in animal feeds in an attempt to promote weight gain and to increase muscle to lipid mass. Adverse effects typical of sympathomimetic activity have been attributed to such misuse both in farmers perpetrating such acts[1] and in innocent persons consuming meat products from affected animals.[2-5] Clenbuterol has been abused by sportsmen for its anabolic effects,[6] although it is doubtful as to whether it enhances performance.[7] Myocardial infarction was described in an otherwise healthy 17-year-old bodybuilder after abuse of clenbuterol.[8] Coronary artery spasm and/or temporary thrombosis were suggested as possible explanations for this adverse effect. Contamination of illicit heroin with clenbuterol has also been reported.[9]

1. Dawson J. β Agonists put meat in the limelight again. *BMJ* 1990; **301:** 1238–9.
2. Martínez-Navarro JF. Food poisoning related to consumption of illicit β-agonist in liver. *Lancet* 1990; **336:** 1311.
3. Maistro S, *et al.* Beta blockers to prevent clenbuterol poisoning. *Lancet* 1995; **346:** 180.
4. Brambilla G, *et al.* Food poisoning following consumption of clenbuterol-treated veal in Italy. *JAMA* 1997; **278:** 635.
5. Ramos F, *et al.* Proposed guidelines for clenbuterol food poisoning. *Am J Med* 2004; **117:** 362.
6. Anonymous. Muscling in on clenbuterol. *Lancet* 1992; **340:** 403.
7. Spann C, Winter ME. Effect of clenbuterol on athletic performance. *Ann Pharmacother* 1995; **29:** 75–7.
8. Kierzkowska B, *et al.* Myocardial infarction in a 17-year-old body builder using clenbuterol. *Circ J* 2005; **69:** 1144–6.
9. CDC. Atypical reactions associated with heroin use: five states, January-April 2005. *MMWR* 2005; **54:** 793–6. Correction. *ibid.*; 852.

Urinary incontinence. A systematic review of the use of adrenergic agonists, including clenbuterol, in urinary incontinence, found that there was weak evidence to suggest that their use was better than placebo.[1] Although only minor adverse effects were reported, the authors noted that there was still potential for rare but serious adverse effects reported elsewhere in the literature.

1. Alhasso A, *et al.* Adrenergic drugs for urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 15/01/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bronq-C; Clembumar; Oxibron; ***Austria:*** Spiropent; ***Chile:*** Airum; Asmeren; Broncotosil†; ***Cz.:*** Spiropent; ***Ger.:*** Contraspasmin†; Spiropent; ***Gr.:*** Spiropent; ***Hong Kong:*** Clenasma†; ***Hung.:*** Spiropent; ***Indon.:*** Spiropent; ***Ital.:*** Clenasma†; Monores; Prontovent†; Spiropent; ***Jpn:*** Spiropent; ***Mex.:*** Novegam; Oxyflux; Spiropent; ***Philipp.:*** Spiropent; ***Port.:*** Broncoterol; Cesbron; ***Spain:*** Spiropent†; Ventolase; ***Venez.:*** Brodilan; Brodilin; Buclen; Clenbunal; Risopent.

Multi-ingredient: ***Arg.:*** Mucosolvon Compositum; Oxibron NF; ***Austria:*** Mucospas; ***Ger.:*** Spasmo-Mucosolvan; ***Mex.:*** Ambodil-C; Balsibron-C; Brogal Compositum; Bronolban-M; Brosolan C; Broxofar Compuesto; Broxol Plus; Broxolim-C; Ebromin P; Fludexol-CL; Loxorol; Mucosolvan Compositum; Mucovibrol C; Sekretovit Ex; Septacin Ex; Seraxol; Serbol; ***Port.:*** Clembroxol; Mucospas; Ventoliber; ***Venez.:*** Ambromuco Compositum; Arbixil; Clenbuxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Diprophylline *(BAN, rINN)*

Dihydroxypropyltheophyllinum; Diprofilina; Diprofilinas; Diprofillin; Diprofylin; Diprofylliini; Diprofyllin; Diprophyllinum; Dyphylline; Glyphyllinum; Hyphylline. 7-(2,3-Dihydroxypropyl)-1,3-dimethylxanthine; 7-(2,3-Dihydroxypropyl)theophylline.

Дипрофиллин

$C_{10}H_{14}N_4O_4$ = 254.2.

CAS — 479-18-5.

ATC — R03DA01.

ATC Vet — QR03DA01.

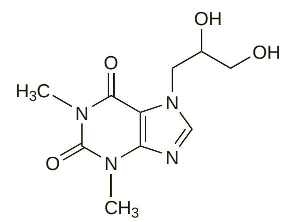

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Diprophylline). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Dyphylline). A white, odourless, amorphous or crystalline solid. Freely soluble in water; sparingly soluble in alcohol and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140. Diprophylline is primarily excreted unchanged in the urine and should therefore be used with caution in patients with renal impairment; dose adjustments may be required. However, unlike theophylline, plasma concentrations of diprophylline are not greatly affected by changes in liver function or hepatic enzyme activity such as those produced by smoking or age.

Breast feeding. In a study of 20 women given diprophylline by intramuscular injection,[1] diprophylline was found to concentrate in breast milk, with a milk to serum concentration ratio of about 2. However, it was felt that the quantity of diprophylline a breast-fed infant would ingest was unlikely to produce any pharmacological action unless the child was very sensitive. The American Academy of Pediatrics[2] also considers that the use of diprophylline is usually compatible with breast feeding.

1. Jarboe CH, *et al.* Dyphylline elimination kinetics in lactating women: blood to milk transfer. *J Clin Pharmacol* 1981; **21:** 405–10.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

Interactions

Since diprophylline does not undergo metabolism by hepatic microsomal cytochrome P450 it does not exhibit the numerous interactions seen with theophylline (p.1142). However, the possibility of synergistic effects should be borne in mind if it is prescribed with other xanthines.

Probenecid. Probenecid has been reported to decrease the clearance of diprophylline thus prolonging its half-life.[1-3]

1. May DC, Jarboe CH. Inhibition of clearance of dyphylline by probenecid. *N Engl J Med* 1981; **304:** 791.
2. May DC, Jarboe CH. Effect of probenecid on dyphylline elimination. *Clin Pharmacol Ther* 1983; **33:** 822–5.
3. Acara M, *et al.* Probenecid inhibition of the renal excretion of dyphylline in chicken, rat and man. *J Pharm Pharmacol* 1987; **39:** 526–30.

Pharmacokinetics

Diprophylline is rapidly absorbed from the gastrointestinal tract and from the site of intramuscular injections. Diprophylline is not converted to theophylline in the body. It is largely excreted unchanged in the urine with an elimination half-life of about 2 hours. Diprophylline is distributed into breast milk.

Uses and Administration

Diprophylline is a theophylline derivative which is used similarly to theophylline (p.1146) as a bronchodilator in reversible airways obstruction.

The usual oral dose of diprophylline is up to 15 mg/kg every 6 hours. It has also been given intramuscularly. Diprophylline is also an ingredient of preparations that have been promoted for coughs.

Action. Improvements in measurements of lung function after diprophylline in oral doses of 15 and 20 mg/kg were only one-third to one-half those obtained after oral theophylline 6 mg/kg.[1]

1. Furukawa CT, *et al.* Diphylline versus theophylline: a double-blind comparative evaluation. *J Clin Pharmacol* 1983; **23:** 414–18.

Preparations

USP 31: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Dyphylline Elixir; Dyphylline Injection; Dyphylline Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Astrophyllin†; ***Gr.:*** Silbephylline†; ***Hong Kong:*** Syneophylline; ***Ital.:*** Katasma; ***Port.:*** Neufil; ***Turk.:*** Difilin; ***USA:*** Dilor†; Dylix; Lufyllin.

Multi-ingredient: ***Fr.:*** Ozothine a la Diprophylline; ***Israel:*** Philinal; Philinet; ***Ital.:*** Cort-Inal; ***Spain:*** Alergical Expect; Bronsal; Novofilin†; ***UK:*** Noradran; ***USA:*** Difil-G; Dilex-G; Dy-G; Dyflex-G; Dyline GG†; Dyphylline-GG; Jay-Phyl; Lufyllin-EPG†; Lufyllin-GG; Panfil G.

Doxofylline *(USAN, rINN)*

ABC 12/3; Doxofilina; Doxofyllinum. 7-(1,3-Dioxolan-2-ylmethyl)theophylline.

Доксофиллин

$C_{11}H_{14}N_4O_4$ = 266.3.

CAS — 69975-86-6.

ATC — R03DA11.

ATC Vet — QR03DA11.

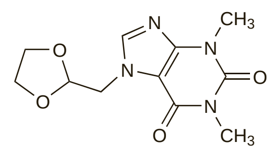

Profile

Doxofylline is a theophylline derivative (p.1140) which is used as a bronchodilator in reversible airways obstruction. It is given in oral doses of up to 1200 mg daily. It may also be given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Ansimar; ***Mex.:*** Axofin; ***Philipp.:*** Ansimar; ***Thai.:*** Puroxan.

Etamiphylline Camsilate *(BANM, rINNM)*

Camsilato de etamifilina; Diétamiphylline Camphosulfonate; Étamiphylline, Camsilate d'; Etamiphylline Camsylate; Etamiphyllini Camsilas; Etamphyllin Camsylate. 7-(2-Diethylaminoethyl)-1,3-dimethylxanthine camphor-10-sulphonate; 7-(2-Diethylaminoethyl)theophylline camphor-10-sulphonate.

Этамифиллина Камзилат

$C_{23}H_{37}N_5O_6S$ = 511.6.

CAS — 314-35-2 (etamiphylline); 19326-29-5 (etamiphylline camsilate).

ATC — R03DA06.

ATC Vet — QR03DA06.

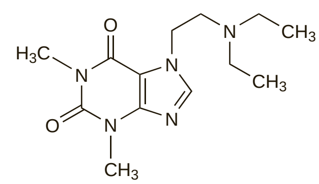

(etamiphylline)

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Etamiphylline Camsilate). A white or almost white powder. Very soluble in water; soluble in alcohol and in chloroform; very slightly soluble in ether. A 10% solution in water has a pH of 3.9 to 5.4.

Profile

Etamiphylline camsilate is a derivative of theophylline (p.1140) and has been used as a bronchodilator in reversible airways obstruction. Etamiphylline does not liberate theophylline in the body. Etamiphylline camsilate is used in veterinary medicine.

The hydrochloride salt has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Solufilina.

Etofylline *(BAN, rINN)*

Aethophyllinum; Etofilina; Etofilinas; Etofillin; Etofylin; Etofylliini; Etofylliin; Étofylline; Etofyllinum; Hydroxyaethyltheophyllinum; Hydroxyéthylthéophylline; Oxyetophylline. 7-(2-Hydroxyethyl)-1,3-dimethylxanthine; 3,7-Dihydro-7-(2-hydroxyethyl)-1,3-dimethyl-1*H*-purine-2,6-dione; 7-(2-Hydroxyethyl)theophylline.

Этофиллин

$C_9H_{12}N_4O_3$ = 224.2.
CAS — 519-37-9.
ATC — C04AD04.
ATC Vet — QC04AD04.

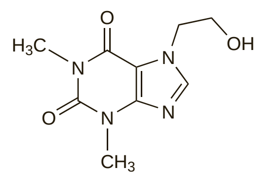

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Etofylline). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol. Protect from light.

Profile

Etofylline is a derivative of theophylline (p.1140) that is an ingredient of preparations promoted for respiratory and cardiovascular disorders. It is not converted to theophylline in the body.

Etofylline nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Oxyphyllin.

Multi-ingredient: ***Austria:*** Instenon; ***Cz.:*** Ersilan; Oxantil; ***Hong Kong:*** Instenon; ***India:*** Albutamol; Bronchilet†; Dericip; Deriphyllin; Etyofil†; Terphylin; ***Rus.:*** Instenon (Инстенон); ***S.Afr.:*** Actophlem; Alcophyllex; Dilinct; Solphyllex; Solphyllin; Theophen; Theophen Comp; ***Thai.:*** Instenon†.

Fenoterol *(BAN, USAN, rINN)* ⊗

Fénotérol; Fenoteroli; Fenoterolum. 1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol.

Фенотерол

$C_{17}H_{21}NO_4$ = 303.4.
CAS — 13392-18-2.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.

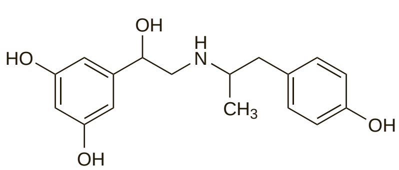

Fenoterol Hydrobromide *(BANM, rINNM)* ⊗

Fénotérol, bromhydrate de; Fenoterol-hidrobromid; Fenoterol-hydrobromid; Fenoterol-hydrobromid; Fenoteroli hydrobromidum; Fenoterolihydrobromidi; Fenoterolio hidrobromidas; Fenoterolu bromowodorek; Hidrobromuro de fenoterol; TH-1165a. 1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol hydrobromide.

Фенотерола Гидробромид

$C_{17}H_{21}NO_4,HBr$ = 384.3.
CAS — 1944-12-3.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fenoterol Hydrobromide). A white or almost white, crystalline powder. Soluble in water and in alcohol. A 4% solution in water has a pH of 4.2 to 5.2. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131.

Increased mortality. Since the introduction of metered-dose aerosols of beta agonists there have been two reported epidemics of increased morbidity and mortality in asthmatic patients associated with their use. The first occurred in the 1960s and was linked with the use of high-dose isoprenaline inhalers.[1] The use of isoprenaline was subsequently largely stopped in favour of more selective beta$_2$ agonists.

The second epidemic occurred in New Zealand in the late 1970s and 1980s and was associated with the use of fenoterol.[1-5] When use of fenoterol fell in New Zealand, so too did the asthma mortality rate.[5] Heavy or regular use of fenoterol was implicated.[6,7] Fenoterol was also implicated in increased asthma morbidity and mortality in a study in Canada,[7] as was salbutamol, and results from Japan also suggested a relation between asthma deaths and excessive use of beta agonists, particularly fenoterol.[8] However, an analysis of the New Zealand deaths could not identify such a risk with beta agonists other than fenoterol.[5]

There is still debate about this second epidemic. The individual case control studies, including the one from Canada,[7] showed an increased morbidity and mortality in patients taking fenoterol, but a meta-analysis of the accumulated data to 1992 suggested that the increase in mortality in the patients taking beta$_2$ agonists was slight and only significant when they were given by nebulisation.[9] Also a working party of the UK CSM considered[10] that a causal link between asthma mortality and beta-agonist use could neither be confirmed nor refuted.

Not surprisingly there are different views on the cause of the increased asthma mortality. The cardiotoxicity of the beta agonist might have to be considered, although evidence for such an effect is felt by some to be slight.[11] The severity of the asthma might have been a factor in two different ways. One hypothesis is that patients used more fenoterol because they had severe asthma and were already at increased risk of dying.[12] Another proposes that heavy beta-agonist use led to an increase in asthma severity[13] which could be explained by a down regulation of beta receptors.[14]

This may appear to be only of historical interest since mortality rates have fallen and current recommendations for the use of short-acting beta$_2$ agonists, which are generally more selective than fenoterol, are for them to be taken as required rather than on a regular basis; indeed increasing use of such drugs is seen as an indication to amend the treatment schedule. Moreover, the dose of fenoterol has been reduced in recent years. However, controversy over regular use of short-acting beta$_2$ agonists continues to be fed by conflicting studies of their benefit. More recently 2 further observational studies have reported an association between use of short-acting beta$_2$ agonists and adverse effects on mortality.[15,16] A cohort study,[15] designed to evaluate the effect of respiratory medications on asthma death, found an association between the excessive use of short-acting beta$_2$ agonists and an increased risk of asthma death; no additional risk was found with fenoterol beyond the risk associated with beta$_2$ agonists as a class. It was unknown whether excessive use was a symptom or a cause of worsening asthma. A case-control study[16] similarly found a modestly increased risk of mortality associated with use of short-acting beta$_2$ agonists in the previous 1 to 5 years. However, the study had insufficient power to come to any conclusions regarding the effects of fenoterol, which was rarely prescribed alone, and concluded that evidence for a direct adverse effect of beta$_2$ agonists was inconclusive; other explanations might include lack of more appropriate asthma care, more severe disease or increasing severity of disease, or a tendency for patients whose disease was not responding to receive a wider range of treatments.

For discussion of similar concerns about the use of *long-acting* beta$_2$ agonists in asthma, see Salmeterol, p.1135.

1. Pearce N, *et al.* Beta agonists and asthma mortality: déjà vu. *Clin Exp Allergy* 1991; **21:** 401–10.
2. Crane J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* 1989; **i:** 917–22.
3. Pearce N, *et al.* Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990; **45:** 170–5.
4. Grainger J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981–7: a further case-control study. *Thorax* 1991; **46:** 105–111.
5. Pearce N, *et al.* End of the New Zealand asthma mortality epidemic. *Lancet* 1995; **345:** 41–4.
6. Sears MR, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; **336:** 1391–6.
7. Spitzer WO, *et al.* The use of β-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; **326:** 501–6.
8. Beasley R, *et al.* β-agonist therapy and asthma mortality in Japan. *Lancet* 1998; **351:** 1406–7.
9. Mullen M, *et al.* The association between β-agonist use and death from asthma: a meta-analytic integration of case control studies. *JAMA* 1993; **270:** 1842–5.
10. Committee on Safety of Medicines. Beta-agonist use in asthma: report from the CSM Working Party. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)
11. Sears MR, Taylor DR. The β -agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994; **11:** 259–83.
12. Fuller RW. Use of β agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 795–6.
13. Sears MR. Asthma deaths in New Zealand. *Lancet* 1995; **345:** 655–6.
14. Tattersfield AE. Use of β agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 794–5.
15. Lanes SF, *et al.* Respiratory medications and risk of asthma death. *Thorax* 2002; **57:** 683–6.
16. Anderson HR, *et al.* Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; **330:** 117. Full version: http://www.bmj.com/cgi/reprint/330/7483/117 (accessed 15/01/08)

Pulmonary oedema. Pulmonary oedema has occurred in women given beta agonists, including fenoterol,[1] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, on p.1132.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

Fenoterol is incompletely absorbed from the gastrointestinal tract and is also subject to extensive first-pass metabolism by sulfate conjugation. It is excreted in the urine and bile almost entirely as the inactive sulfate conjugate. Fenoterol is distributed into breast milk.

◊ References.

1. Warnke K, *et al.* The pharmacokinetics of the beta 2-adrenoceptor agonist fenoterol in healthy women. *Eur J Clin Pharmacol* 1992; **43:** 663–5.
2. Hochhaus G, Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. *Int J Clin Pharmacol Ther Toxicol* 1992; **30:** 342–62.
3. Hildebrandt R, *et al.* Pharmacokinetics of fenoterol in pregnant and nonpregnant women. *Eur J Clin Pharmacol* 1993; **45:** 275–7.

Uses and Administration

Fenoterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity largely selective for beta$_2$ receptors (a beta$_2$ agonist). It has actions and uses similar to those of salbutamol (p.1133) and is used as a bronchodilator in the management of reversible airways obstruction, as occurs in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). On inhalation, fenoterol acts rapidly (5 minutes) and has a duration of action of about 6 to 8 hours.

In the management of **reversible airways obstruction,** fenoterol hydrobromide may be given from a *metered-dose aerosol* in a dose of 1 or 2 inhalations of 100 micrograms up to 3 or 4 times daily, to a maximum of 800 micrograms daily. Current asthma guidelines recommend that inhaled short-acting beta$_2$ agonists such as fenoterol be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of fenoterol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, fenoterol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

Fenoterol hydrobromide may be given as a *nebulised solution*; the usual dose for inhalation by this route is 0.5 to 1 mg. In more refractory cases up to 2.5 mg may be given. Treatment may be repeated every 6 hours as required.

Fenoterol hydrobromide may also be given *orally* for the relief of bronchospasm at a dose of 2.5 to 5 mg three times daily.

For doses in children, see Administration in Children, below.

Fenoterol hydrobromide has also been used similarly to salbutamol, in the management of **premature labour** (see p.2003). A suggested dose, by intravenous infusion, has been 1 to 3 micrograms/minute, up to a maximum of 5 micrograms/minute, followed by oral doses of 5 mg every 3 to 6 hours.

Administration in children. In some countries fenoterol has been given via a metered-dose inhaler to children over 6 years of age, at the same doses used in adults (see Uses and Administration, above).

Fenoterol hydrobromide is also given orally to children for the relief of bronchospasm in the following doses:

- children aged 1 to 3 years, 1.25 mg three times daily
- children aged 4 to 10 years, 2.5 mg three times daily
- children aged over 10 years, as for adults (see Uses and Administration, above)

Preparations

BP 2008: Fenoterol Pressurised Inhalation.

Proprietary Preparations (details are given in Part 3)
Arg.: Alveofen; Asmopul; Berotec; ***Austral.:*** Berotec†; ***Austria:*** Berotec; ***Belg.:*** Berotec; ***Braz.:*** Berotec; Bromifen; Bromotec; Febiotec†; Fenozan; ***Canad.:*** Berotec; ***Chile:*** Berotec†; Parsistene†; ***Cz.:*** Berotec; Partusisten†; ***Denm.:*** Berotec; ***Fin.:*** Berotec†; ***Ger.:*** Berotec; Partusisten; ***Hong Kong:*** Berotec†; ***Hung.:*** Berotec; ***Indon.:*** Berotec; ***Ital.:*** Dosberotec; ***Jpn:*** Berotec; ***Malaysia:*** Berotec; Feno; ***Mex.:*** Berotec†; Partusisten; ***Neth.:*** Berotec; Partusisten; ***Norw.:*** Berotec; ***Philipp.:*** Berotec; ***Pol.:*** Berotec; ***Port.:*** Berotec; ***Rus.:*** Berotec (Беротек); Partusisten (Партусистен); ***S.Afr.:*** Berotec; ***Singapore:*** Berotec; ***Spain:*** Berotec†; ***Swed.:*** Berotec†; ***Switz.:*** Berotec; ***Thai.:*** Berotec; ***Venez.:*** Berotec†; Segamol.

Multi-ingredient: ***Arg.:*** Berodual; Duotec†; Ipradual; ***Austria:*** Berodual; Berodualin; Ditec; ***Belg.:*** Duovent; ***Braz.:*** Duovent; Fymnal†; ***Canad.:*** Duovent; ***Chile:*** Berodual; ***Cz.:*** Berodual; Ditec†; ***Denm.:*** Berodual; ***Fin.:*** Atrovent Comp; ***Fr.:*** Bronchodual; ***Ger.:*** Berodual; Ditec†; ***Gr.:*** Berodual; ***Hong Kong:*** Berodual†; ***Hung.:*** Berodual; Duotec†; ***India:*** Fenovent; ***Indon.:*** Berodual; ***Irl.:*** Duovent; ***Ital.:*** Duovent; Iprafen; ***Malaysia:*** Berodual; Duovent; ***Mex.:*** Berodual; Berosolvon; ***Neth.:*** Berodual; ***Philipp.:*** Berodual; ***Pol.:*** Berodual; ***Port.:*** Berodual; ***Rus.:*** Berodual (Беродуал); Ditec (Дитек); ***S.Afr.:*** Atrovent Beta; Berodual; Duovent; Sabax Nebrafen; ***Singapore:*** Berodual; Duovent; ***Spain:*** Berodual†; ***Switz.:*** Berodual; ***Thai.:*** Berodual; Inhalex; Punol; ***UK:*** Duovent; ***Venez.:*** Berodual; Berosolvon†; Duovent; Respidual.

Fenspiride Hydrochloride *(USAN, rINNM)*

Decaspiride; Fenspiride, Chlorhydrate de; Fenspiridi Hydrochloridum; Hidrocloruro de fenspirida; JP-428; NAT-333; NDR-5998A. 8-Phenethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride.

Фенспирида Гидрохлорид

$C_{15}H_{20}N_2O_2,HCl = 296.8.$

CAS — 5053-06-5 (fenspiride); 5053-08-7 (fenspiride hydrochloride).

ATC — R03BX01; R03DX03.

ATC Vet — QR03BX01; QR03DX03.

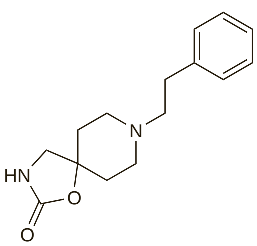

(fenspiride)

Profile

Fenspiride is reported to have bronchodilator and anti-inflammatory properties. It is given as the hydrochloride in asthma (p.1108) and other respiratory disorders in usual oral doses of 160 to 240 mg daily in divided doses before meals. It has also been given rectally and by intramuscular or intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Pneumorel; ***Hong Kong:*** Pneumorel; ***Ital.:*** Pneumorel; ***Pol.:*** Eurespal; ***Port.:*** Fenspin†; Pneumorel; ***Rus.:*** Eurespal (Эреспал).

Formoterol Fumarate *(BANM, USAN, rINNM)* ⊗

BD-40A; CGP-25827A; Eformoterol Fumarat; Eformoterol Fumarate; Formoterol Fumarat; Formotérol, fumarate de; Formoterolfumarat; Formoterol-fumarát; Formoteroli fumaras; Formoterolifumaraatti; Formoterolio fumaratas; Formoterolu fumaran; Fumarato de formoterol; YM-08316. (±)-2′-Hydroxy-5′-[(*RS*)-1-hydroxy-2-{[(*RS*)-*p*-methoxy-α-methylphenethyl]amino}ethyl]formanilide fumarate.

Формотерола Фумарат

$(C_{19}H_{24}N_2O_4)_2,C_4H_4O_4 = 804.9.$

CAS — 73573-87-2 (formoterol); 43229-80-7 (formoterol fumarate).

ATC — R03AC13.

ATC Vet — QR03AC13.

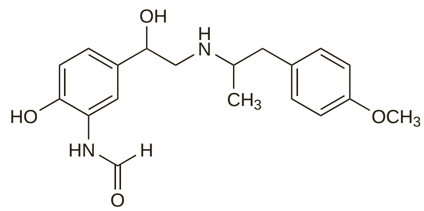

(formoterol)

Pharmacopoeias. In *Jpn. Eur.* (see p.vii) includes the dihydrate.

Ph. Eur. 6.2 (Formoterol Fumarate Dihydrate; Formoteroli Fumaras Dihydricus). A white or almost white or slightly yellow powder. Slightly soluble in water and in isopropyl alcohol; practically insoluble in acetonitrile; soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Inhalation of formoterol may be associated with paradoxical bronchospasm, and high doses have been associated with an increase in severe exacerbations of asthma. It should not be used in patients who are not also receiving an inhaled corticosteroid.

Long-acting $beta_2$ agonists such as formoterol are not appropriate for the treatment of acute bronchospasm.

Conjunctival irritation and eyelid oedema have been reported in isolated cases.

◊ References.

1. Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. *Drug Safety* 2002; **25:** 213–23.
2. Pauwels RA, *et al.* Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003; **22:** 787–94.

Asthma. A review of 3 controlled studies comparing inhaled formoterol with placebo, concluded that regular use of high-dose formoterol (48 micrograms daily) may be associated with more frequent serious asthma exacerbations.[1] The concomitant use of inhaled corticosteroids was allowed but not mandatory, and was not reported in the review, which led to debate on whether the results of the study would be applicable when current prescribing guidelines for asthma were followed.[2,3]

In contrast to this, a subsequent study,[4] designed to test the hypothesis of a dose-related increase in serious asthma exacerbations with formoterol therapy, did not show any increase in serious asthma exacerbations between different formoterol doses and placebo. Again, inhaled corticosteroid use was allowed but not mandatory, with 62.4% of patients reported as receiving regular anti-inflammatory therapy.

A systematic review[5] firmly concluded that the addition of a long-acting $beta_2$ agonist (such as formoterol) to low or high doses of inhaled corticosteroids reduced the risk of asthma exacerbations compared with ongoing treatment with similar doses of inhaled corticosteroids alone. The addition of a long-acting $beta_2$ agonist reduced by 19% the relative risk and by 5% the absolute risk of patients requiring systemic corticosteroids for an asthma exacerbation, over 4 to 54 weeks.

For discussion of serious adverse effects associated with long-acting $beta_2$ agonists in asthma, see Increased Mortality, under Salmeterol p.1135.

1. Mann M, *et al.* Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003; **124:** 70–4.
2. Rissmiller RW, *et al.* Asthma exacerbations and formoterol. *Chest* 2004; **125:** 1590–1.
3. van der Molen T. Formoterol and asthma exacerbations. *Chest* 2004; **125:** 1591.
4. Wolfe J, *et al.* Formoterol, 24μg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12μg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006; **129:** 27–38.
5. Ni Chroinin M, *et al.* Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).

Effects on skeletal muscle. Myalgia and muscle weakness associated with elevated creatine kinase has been reported during formoterol therapy.[1] Subsequent muscle biopsy suggested mitochondrial dysfunction. No inflammatory changes were seen and symptoms resolved on withdrawal of formoterol.

1. Kiernan MC, *et al.* Mitochondrial dysfunction and rod-like lesions associated with administration of β2 adrenoceptor agonist formoterol. *Neuromuscul Disord* 2004; **14:** 375–7.

Tolerance. Regular use of formoterol produced bronchodilator desensitisation,[1-3] and tachyphylaxis to bronchoprotection against methacholine, effects that have been noted with other long-acting $beta_2$ agonists (see Salmeterol, p.1135) and short-acting $beta_2$ agonists (see Salbutamol, p.1132).

1. van der Woude HJ, *et al.* Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting β agonists. *Thorax* 2001; **56:** 529–35.
2. Jones SL, *et al.* Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. *Eur Respir J* 2001; **17:** 368–73.
3. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. *Respir Res* 2005; **6:** 107. Also available at: http://respiratory-research.com/content/pdf/1465-9921-6-107.pdf (accessed 15/01/08)

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

Inhaled formoterol is rapidly absorbed. It is largely metabolised by glucuronidation and *O*-demethylation, with about 10% being excreted in the urine as unchanged drug. The mean terminal elimination half-life after inhalation is estimated to be 10 hours.

Stereoselectivity. Formoterol occurs as a racemic mixture, of which arformoterol (p.1115) is the *R,R*-enantiomer. Only the *R,R*-enantiomer is active.[1,2] It has been suggested that stereoselective metabolism and excretion may account for the individual variation in duration of effect seen with formoterol, although the exact mechanism remains unclear.[1,3]

1. Zhang M, *et al.* Stereoselective glucuronidation of formoterol by human liver microsomes. *Br J Clin Pharmacol* 2000; **49:** 152–7.
2. Lötvall J, *et al.* The effect of formoterol over 24 h in patients with asthma: the role of enantiomers. *Pulm Pharmacol Ther* 2005; **18:** 109–13.
3. Zhang M, *et al.* Stereoselective urinary excretion of formoterol and its glucuronide conjugate in human. *Br J Clin Pharmacol* 2002; **54:** 246–50.

Uses and Administration

Formoterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity specific to $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1133), but like salmeterol (p.1135) it has a prolonged duration of action of up to 12 hours; it is therefore not considered suitable for the symptomatic relief of acute attacks of bronchospasm. It is used when the regular use of a long-acting $beta_2$ agonist is needed for management of reversible airways obstruction, as in chronic asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112).

Formoterol is given by inhalation as the fumarate but how the dose is expressed may depend on the formulation.

- A usual dose is 12 micrograms of formoterol fumarate twice daily from inhalational capsules, increased to 24 micrograms twice daily if necessary in severe disease.
- Metered doses from a dry powder inhaler may be expressed as the amount delivered *into* the mouthpiece (multiples of 6 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to multiples of 4.5 micrograms per inhalation). Usual doses, expressed as the amount delivered *into* the mouthpiece, are 6 or 12 micrograms once or twice daily, increased if necessary in severe disease to 24 micrograms twice daily.
- Metered doses from an aerosol inhaler may also be expressed as the amount delivered *into* the mouthpiece (12 micrograms per inhalation) or the amount delivered *from* the mouthpiece (corresponding to 10.1 micrograms per inhalation). Usual doses are 1 or 2 inhalations twice daily.

Treatment should be reassessed if this proves inadequate; in the UK, some preparations are licensed for additional short-term symptom relief, but such use is contrary to current asthma guidelines (see p.1108).

Formoterol fumarate may also be inhaled via a nebuliser in a dose of 20 micrograms twice daily. Oral doses of 80 micrograms have been given twice daily in adults.

For doses of formoterol fumarate used in children, see Administration in Children, below.

◊ Reviews.

1. Faulds D, *et al.* Formoterol: a review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991; **42:** 115–37.
2. Bartow RA, Brogden RN. Formoterol: an update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998; **55:** 303–22.
3. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β -agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. Doses of formoterol fumarate inhaled from inhalational capsules in children aged 5 years or older are the same as those for adults, see Uses and Administration, above.

Formoterol fumarate may be given by metered-dose dry powder inhaler to children 6 years of age and over. The usual dose, expressed as the amount delivered *into* the mouthpiece, is 6 to 12 micrograms once or twice daily. Occasionally up to 48 micrograms daily may be required (maximum single dose should not exceed 12 micrograms).

In some countries, such as Japan, formoterol fumarate has been given orally to children from the age of 6 months at a dose of 4 micrograms/kg daily, in 2 or 3 divided doses.

Asthma. Formoterol is a long-acting beta$_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p.1108, generally recommend that the use of long-acting beta$_2$ agonists be reserved for patients with chronic asthma who have already progressed to inhaled corticosteroids; it is not a substitute for corticosteroids. The exact dose of inhaled corticosteroid at which to add additional therapy, such as a long-acting beta$_2$ agonist, has yet to be determined. There is some evidence to suggest that, apart from in severe exacerbations, adding a long-acting beta$_2$ agonist to standard dose inhaled corticosteroid therapy may be more effective than increasing the dose of corticosteroid, or than combining a corticosteroid and an anti-leukotriene drug. Combinations of formoterol with an inhaled corticosteroid, used as both maintenance and reliever therapy, have also been studied. Results are seemingly encouraging, although what role such combinations should play in therapy is not yet clearly defined. Some asthma guidelines include this regimen as an option for adults at treatment step 3, see p.1108. Formoterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, protection against bronchoconstriction is reduced (see Tolerance, above), and high-dose therapy may be associated with an increased rate of severe exacerbations (see Asthma under Adverse Effects and Precautions, above).

References.

1. van der Molen T, *et al.* Effects of the long acting β agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1996; **52:** 535–9.
2. Pauwels RA, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997; **337:** 1405–11. Correction. *ibid.*; 1998; **338:** 139.
3. O'Byrne PM, *et al.* Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; **164:** 1392–7.
4. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; **64:** 1597–1618.
5. Rabe KF, *et al.* Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; **368:** 707–8.
6. Pedersen S. Budesonide plus formoterol for reliever therapy in asthma. *Lancet* 2006; **368:** 707–8.
7. Pohunek P, *et al.* Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatr Allergy Immunol* 2006; **17:** 458–65. Correction. *ibid.*; 551.
8. Berger WE. The use of inhaled formoterol in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 24–33. Correction. *ibid.*; 562. [dosage error in text]
9. Hermansen MN, *et al.* Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006; **129:** 1203–9.
10. Bateman ED, *et al.* Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res* 2006; **7:** 13.
11. O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006; **368:** 794–803.
12. O'Byrne PM, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; **171:** 129–36.

Stuttering. Inhaled formoterol 12 micrograms daily was reported to improve stuttering (p.1001) in 3 children between 14 and 20 years old. In 2 males, the onset of effect was about 6 weeks, but long-term follow-up was not possible. In the female patient there was early improvement that persisted during 45 weeks of treatment.[1]

1. Pešák J. Preliminary experience with formoterol for the treatment of stuttering. *Ann Pharmacother* 2004; **38:** 1323.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fordilen; Oxis; Xanol; ***Austral.:*** Foradile; Oxis; ***Austria:*** Foradil; Oxis; ***Belg.:*** Foradil; Oxis; ***Braz.:*** Fluir; Foradil; Formocaps; Oxis; ***Canad.:*** Foradil; Oxeze; ***Cz.:*** Atimos; Foradil; Forair; Formano; Formovent; Oxis; ***Denm.:*** Delnil; Foradil; Oxis; ***Fin.:*** Foradil; Oxis; ***Fr.:*** Foradil; ***Ger.:*** Foradil; Forair; Formatris; FormoLich; Formotop; Oxis; ***Gr.:*** Broncoteril; Foradil; Forair; Forcap; Formopen; Formotil; Imotec; Oxez; ***Hong Kong:*** Foradil†; Oxis; ***Hung.:*** Atimos; Diffumax; Foradil; Fortofan; Oxis; ***India:*** Foratec; ***Irl.:*** Foradil; Oxis; ***Israel:*** Foradil; Oxis; ***Ital.:*** Atimos; Eolus; Foradil; Liferol; Oxis; ***Jpn:*** Atock; ***Malaysia:*** Foradil†; Oxis; ***Mex.:*** Foradil; Oxis; ***Neth.:*** Foradil; Oxis; ***Norw.:*** Foradil; Oxis; ***NZ:*** Foradil; Oxis; ***Philipp.:*** Atock; Foradil; Oxis; ***Pol.:*** Atimos; Diffumax; Foradil; Forastmin; Oxis; Oxodil; Zafiron; ***Port.:*** Asmatec; Atimos; Eformax; Foradil; Forair; Formaxa; Oxis; ***Rus.:*** Atimos (Атимос); Foradil (Форадил); Oxis (Оксис); ***S.Afr.:*** Foradil; Foratec; Oxis; ***Singapore:*** Foradil; Oxis; ***Spain:*** Broncoral; Foradil; Neblik; Oxis; ***Swed.:*** Foradil; Oxis; ***Switz.:*** Foradil; Oxis; ***Thai.:*** Oxis†; ***Turk.:*** Foradil; Oxis; ***UK:*** Atimos Modulite; Foradil; Oxis; ***USA:*** Foradil; Perforomist; ***Venez.:*** Fluir; Foradil; Formotec; Oxis†.

Multi-ingredient: ***Arg.:*** Neumoterol; Symbicort; ***Austral.:*** Symbicort; ***Austria:*** Symbicort; ***Belg.:*** Symbicort; ***Braz.:*** Alenia; Foraseq; Symbicort; ***Canad.:*** Symbicort; ***Chile:*** Symbicort; ***Cz.:*** Combair; Formodual; Symbicort; ***Denm.:*** Symbicort; ***Fin.:*** Symbicort; ***Fr.:*** Innovair; Symbicort; ***Ger.:*** Symbicort; ***Gr.:*** Symbicort; ***Hong Kong:*** Symbicort; ***Hung.:*** Symbicort; ***India:*** Duova; Foracort; ***Indon.:*** Symbicort; ***Irl.:*** Symbicort; ***Israel:*** Symbicort; ***Ital.:*** Assieme; Sinestic; Symbicort; ***Malaysia:*** Foracort; Symbicort; ***Mex.:*** Symbicort; ***Neth.:*** Assieme; Sinestic; Symbicort; ***Norw.:*** Symbicort; ***NZ:*** Symbicort; ***Philipp.:*** Symbicort; ***Pol.:*** Symbicort; ***Port.:*** Assieme; Formodual; Foster; Symbicort; ***Rus.:*** Simbicort (Симбикорт); ***S.Afr.:*** Symbicord; ***Singapore:*** Symbicort; ***Spain:*** Rilast; Symbicort; ***Swed.:*** Symbicort; ***Switz.:*** Symbicort; ***Thai.:*** Symbicort; ***Turk.:*** Symbicort; ***UK:*** Fostair; Symbicort; ***USA:*** Symbicort; ***Venez.:*** Foraseq; Symbicort.

Heptaminol Acefyllinate *(rINNM)*

Acefilinato de heptaminol; Acéfyllinate d'Heptaminol; Acefyllinum Heptaminolum; Heptaminol Acéfylline; Heptaminol Acephyllinate; Heptaminol Theophylline Ethanoate; Heptaminol Theophylline-7-acetate; Heptaminoli Acefyllinas. The 6-amino-2-methylheptan-2-ol salt of theophyllin-7-ylacetic acid .

Гептаминола Ацефиллинат

$C_8H_{19}NO,C_9H_{10}N_4O_4$ = 383.4.
CAS — 5152-72-7; 10075-18-0.
ATC — C01DX08.
ATC Vet — QC01DX08.

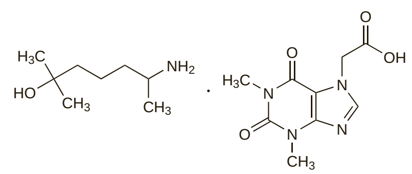

Profile

Heptaminol acefyllinate is a derivative of theophylline (p.1140) that has been used for its bronchodilator and cardiovascular effects.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Cariamyl.

Multi-ingredient: ***Braz.:*** Sureptil; ***Spain:*** Clinadil Compositum; Diclamina.

Hexoprenaline Hydrochloride *(BANM, rINNM)* ⊗

Hexoprénaline, Chlorhydrate d'; Hexoprenalini Hydrochloridum; Hidrocloruro de hexoprenalina; ST-1512. *N,N'*-Hexamethylenebis[4-(2-amino-1-hydroxyethyl)pyrocatechol] dihydrochloride; *N,N'*-Hexamethylenebis[2-amino-1-(3,4-dihydroxyphenyl)ethanol] dihydrochloride.

Гексопреналина Гидрохлорид

$C_{22}H_{32}N_2O_6,2HCl$ = 493.4.
CAS — 3215-70-1 (hexoprenaline); 4323-43-7 (hexoprenaline dihydrochloride).
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.

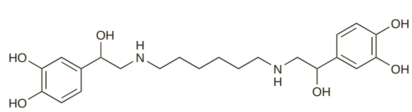

(hexoprenaline)

Hexoprenaline Sulfate *(USAN, rINNM)* ⊗

Hexoprénaline, Sulfate d'; Hexoprenaline Sulphate *(BANM)*; Hexoprenalini Sulfas; Sulfato de hexoprenalina. (±)-α,α'-[Hexamethylenebis(iminomethylene)]-bis[3,4-dihydroxybenzyl alcohol] sulfate (1:1).

Гексопреналина Сульфат

$C_{22}H_{32}N_2O_6,H_2SO_4$ = 518.6.
CAS — 32266-10-7.
ATC — R03AC06; R03CC05.
ATC Vet — QR03AC06; QR03CC05.

Profile

Hexoprenaline is a direct-acting sympathomimetic with mainly beta-adrenergic activity selective to beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p.1131) and has been used as a bronchodilator in the treatment of reversible airways obstruction as occurs with asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). It has sometimes been used similarly to salbutamol in the management of premature labour (p.2003).

Hexoprenaline is usually given as the hydrochloride or sulfate.

For the relief of **bronchoconstriction**, a typical adult oral dose of the salts has been 0.5 to 1 mg three times daily. By inhalation, hexoprenaline sulfate has been given by aerosol inhaler in doses of 100 to 200 micrograms up to 6 times daily, and the hydrochloride has been given by nebulisation in doses of 250 to 500 micrograms every 4 to 6 hours to a maximum of 3 mg daily. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, hexoprenaline indicates deterioration of asthma control and the need for review of therapy.

In the management of **premature labour** an intravenous infusion of hexoprenaline sulfate, diluted in glucose 5% or sodium chloride 0.9%, can be given at an initial rate of about 300 nanograms/minute. Infusion may be preceded by slow intravenous injection of 10 micrograms as a loading dose over 5 to 10 minutes. A prolonged infusion of 75 nanograms/minute has been used when there is no cervical change. Therapy may be changed from intravenous to oral once suppression of labour has been achieved for at least 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Argocian; ***Austria:*** Gynipral; Ipradol; ***Chile:*** Gynipral†; ***Cz.:*** Gynipral; ***Hong Kong:*** Ipradol; ***Hung.:*** Gynipral†; Ipradol†; ***Rus.:*** Gynipral (Гинипрал); ***S.Afr.:*** Ipradol; ***Switz.:*** Gynipral; ***Thai.:*** Ipradol†.

Ibudilast *(rINN)*

AV-411; Ibudilastum; KC-404; MN-166. 1-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-2-methyl-1-propanone.

Ибудиласт

$C_{14}H_{18}N_2O$ = 230.3.
CAS — 50847-11-5.
ATC — R03DC04.
ATC Vet — QR03DC04.

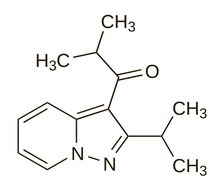

Profile

Ibudilast is an orally active leukotriene antagonist (p.1108), phosphodiesterase inhibitor, and platelet-activating factor antagonist. It is given orally in the management of asthma (p.1108) in a dose of 10 mg twice daily.

Ibudilast is also promoted for the management of dizziness secondary to impaired cerebral circulation following cerebral infarction, in doses of 10 mg three times daily.

Ibudilast is also under investigation for the treatment of multiple sclerosis and for chronic neuropathic pain.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Ketas.

Indacaterol *(rINN)* ⊗

Indacatérol; Indacaterolum; QAB-149. 5-{(1*R*)-2-[(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1*H*)-one.

Индакатерол

$C_{24}H_{28}N_2O_3$ = 392.5.
CAS — 312753-06-3.

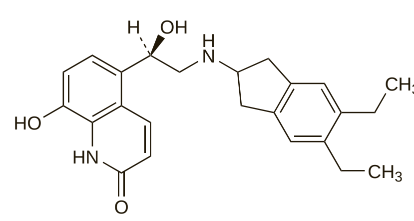

Profile

Indacaterol is a long-acting beta$_2$ agonist under investigation in asthma and chronic obstructive pulmonary disease.

Ipratropium Bromide *(BAN, USAN, rINN)*

Bromuro de ipratropio; Ipratropii bromidum; Ipratropii Bromidum Monohydricum; Ipratropio bromidas; Ipratropiowy bromek; Ipratropium bromid monohydrát; Ipratropium, bromure d'; Ipratropiumbromid; Ipratropium-bromid; Ipratropiumbromidi; Ipratropyum Bromür; Sch-1000; Sch-1000-Br-monohydrate. (1*R*,3*r*,5*S*,8*r*)-8-Isopropyl-3-[(±)-tropoyloxy]tropanium bromide monohydrate.

Ипратропия Бромид

$C_{20}H_{30}BrNO_3,H_2O$ = 430.4.

CAS — 22254-24-6 (anhydrous ipratropium bromide); 66985-17-9 (ipratropium bromide monohydrate).

ATC — R01AX03; R03BB01.

ATC Vet — QR01AX03; QR03BB01.

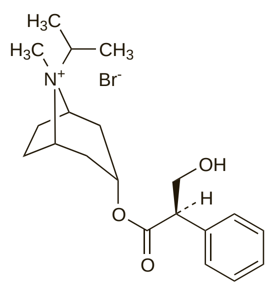

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ipratropium Bromide). White or almost white crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. The pH of a 1% solution in water is 5.0 to 7.5.

USP 31 (Ipratropium Bromide). A white to off-white, crystalline powder. Soluble in water; slightly soluble in alcohol; freely soluble in methyl alcohol. A 10% solution has a pH of 5 to 7. Store in airtight containers.

Stability. In a study[1] of the stability of admixtures of ipratropium and salbutamol nebuliser solutions equal ratio mixtures were found to retain more than 90% of their initial concentrations after storage for 5 days at 4° or 22° in the dark or at 22° under continuous fluorescent lighting.

1. Jacobson GA, Peterson GM. Stability of ipratropium bromide and salbutamol nebuliser admixtures. *Int J Pharm Pract* 1995; **3:** 169–73.

Adverse Effects and Precautions

Ipratropium and other inhaled antimuscarinic bronchodilators commonly cause dry mouth and constipation, and rarely, urinary retention. They should be used with care in prostatic hyperplasia. Acute angle-closure glaucoma has been reported; the mist or solution should not be allowed to enter the eyes, particularly in patients susceptible to glaucoma. As with other bronchodilators, paradoxical bronchospasm has occurred. Tachycardia, palpitations, and arrhythmias have been reported with ipratropium. Hypersensitivity reactions, including urticaria, angioedema, rash, and anaphylaxis have occurred rarely. Nausea and vomiting, dyspepsia, headaches, and dizziness have also been reported.

Intranasal ipratropium has been associated with nasal dryness, irritation, and epistaxis.

For details of the adverse effects of, and precautions for, antimuscarinics in general, see Atropine, p.1219.

Buccal ulceration. A report[1] of inflammation and ulceration of the buccal mucosa associated with the use of an ipratropium bromide inhaler.

1. Spencer PA. Buccal ulceration with ipratropium bromide. *BMJ* 1986; **292:** 380.

Effects on the eyes. Ocular complications have been reported with the use of aerosolised ipratropium. A patient with a history of glaucoma developed angle-closure glaucoma after use of ipratropium from a metered dose inhaler (MDI) with nebulised salbutamol.[1] Pupillary dilatation[2] and blurred vision[3] have been reported in association with ipratropium given through a spacer device in patients also given salbutamol therapy, and a 4-year-old child who attempted to self-administer an ipratropium MDI developed anisocoria (unequal dilatation of the pupils) and ataxia.[4] Angle-closure glaucoma,[5-7] pupillary dilatation,[7-10] and anisocoria[11,12] have been reported in patients given *nebulised* ipratropium, usually with salbutamol, through a poorly fitting face mask. The antimuscarinic effects of ipratropium can lead to impaired drainage of aqueous humour in the eyes of patients predisposed to angle-closure glaucoma; use with salbutamol may intensify this problem by increasing the production of aqueous humour.[6] Studies[13,14] suggest that patients with a history of angle-closure glaucoma might be at an increased risk of developing glaucoma when nebulised ipratropium and salbutamol are used together.

1. Hall SK. Acute angle-closure glaucoma as a complication of combined β-agonist and ipratropium bromide therapy in the emergency department. *Ann Emerg Med* 1994; **23:** 884–7.
2. Weir REP, *et al.* Pupil blown by a puffer. *Lancet* 2004; **363:** 1853.
3. Kizer KM, *et al.* Blurred vision from ipratropium bromide inhalation. *Am J Health-Syst Pharm* 2000; **57:** 996–7.
4. Bond DW, *et al.* Mydriasis due to self-administered inhaled ipratropium bromide. *Eur J Pediatr* 2002; **161:** 178.
5. Packe GE, *et al.* Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet* 1984; **ii:** 691.
6. Shah P, *et al.* Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. *BMJ* 1992; **304:** 40–1.
7. Mulpeter KM, *et al.* Ocular hazards of nebulized bronchodilators. *Postgrad Med J* 1992; **68:** 132–3.
8. Roberts TE, Pearson DJ. Wide eyed and breathless. *BMJ* 1989; **299:** 1348.
9. Woelfle J, *et al.* Unilateral fixed dilated pupil in an infant after inhalation of nebulized ipratropium bromide. *J Pediatr* 2000; **136:** 423–4.
10. Openshaw H. Unilateral mydriasis from ipratropium in transplant patients. *Neurology* 2006; **67:** 914–15.
11. Lust K, Livingstone I. Nebulizer-induced anisocoria. *Ann Intern Med* 1998; **128:** 327.
12. Iosson N. Nebulizer-associated anisocoria. *N Engl J Med* 2006; **354:** e8.
13. Watson WTA, *et al.* Effect of nebulized ipratropium bromide on intraocular pressures in children. *Chest* 1994; **105:** 1439–41.
14. Kalra L, Bone MF. The effect of nebulized bronchodilator therapy on intraocular pressures in patients with glaucoma. *Chest* 1988; **93:** 739–41.

Effects on the gastrointestinal tract. Paralytic ileus developed shortly after starting ipratropium therapy in 2 patients, apparently due to the inadvertent swallowing of the drug during inhalation.[1,2] Both patients also had other predisposing factors for paralytic ileus (cystic fibrosis,[1] spastic diplegia[2]).

1. Mulherin D, FitzGerald MX. Meconium ileus equivalent in association with nebulised ipratropium bromide in cystic fibrosis. *Lancet* 1990; **355:** 552.
2. Markus HS. Paralytic ileus associated with ipratropium. *Lancet* 1990; **355:** 1224.

Effects on the respiratory tract. Antimuscarinics typically inhibit mucociliary clearance and inhibit secretions of the nose, mouth, pharynx, and bronchi. However, inhaled ipratropium bromide has virtually no effect on sputum viscosity or volume and, in contrast to atropine, it does not affect mucociliary function in the respiratory tract.[1,2]

1. Gross NJ. Ipratropium bromide. *N Engl J Med* 1988; **319:** 486–94.
2. Mann KV, *et al.* Use of ipratropium bromide in obstructive lung disease. *Clin Pharm* 1988; **7:** 670–80.

BRONCHOSPASM. Paradoxical bronchoconstriction occurring after the use of ipratropium was reported in 3 patients.[1] A further report[2] of paradoxical bronchoconstriction after nebulised salbutamol and ipratropium suggested that this adverse effect might have been caused by benzalkonium chloride present in the nebuliser solutions. Nebuliser solutions of ipratropium in some countries contain benzalkonium chloride as a preservative. Solutions available in the UK are preservative-free but licensed product information still recommends that the first doses of ipratropium nebuliser solution should be inhaled under medical supervision.

1. Connolly CK. Adverse reaction to ipratropium bromide. *BMJ* 1982; **285:** 934–5.
2. Boucher M, *et al.* Possible associations of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; **26:** 772–4.

Effects on the urinary tract. Treatment with nebulised ipratropium bromide has resulted in urinary retention in elderly men especially those with prostatic hyperplasia.[1,2]

1. Lozewicz S. Bladder outflow obstruction induced by ipratropium bromide. *Postgrad Med J* 1989; **65:** 260–1.
2. Pras E, *et al.* Urinary retention associated with ipratropium bromide. *DICP Ann Pharmacother* 1991; **25:** 939–40.

Increased mortality. A case-control study found an unexpected association between death from asthma and treatment with ipratropium, which was not explained by co-morbidity due to chronic obstructive airways disease.[1] A retrospective cohort study[2] of elderly patients found no increase in all-cause mortality associated with the use of ipratropium for chronic obstructive pulmonary disease (COPD). In patients with asthma there was a slight increase in the risk of death, but this may have been due to the confounding effect of disease severity. A later longitudinal cohort study of 1100 patients with obstructive lung disease found an increased risk of premature death associated with ipratropium in both asthma and COPD patients.[3] After adjusting for confounding factors such as forced expiratory volume, smoking status, BMI, and presence of cor pulmonale, ipratropium was associated with a mortality risk ratio (RR) of 2.4 in asthmatic patients and 1.6 in COPD patients. Again, residual confounding by disease severity could not be ruled out.

1. Guite HF, *et al.* Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999; **54:** 301–7.
2. Sin DD, Tu JV. Lack of association between ipratropium bromide and mortality in elderly patients with chronic obstructive airway disease. *Thorax* 2000; **55:** 194–7.
3. Ringbæk T, Viskum K. Is there any association between inhaled ipratropium and mortality in patients with COPD and asthma? *Respir Med* 2003; **97:** 264–72.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p.1220. However, these interactions are not usually seen with antimuscarinics, such as ipratropium, given by inhalation.

Salbutamol. For reference to nebulised salbutamol exacerbating the adverse effects of nebulised ipratropium in patients predisposed to angle-closure glaucoma, see under Effects on the Eyes, above.

Pharmacokinetics

After inhalation, around 10 to 30% of a dose is deposited in the lungs where it exerts its therapeutic effect. Only a small amount of ipratropium reaches the systemic circulation. The majority of a dose is swallowed but is poorly absorbed from the gastrointestinal tract. Ipratropium and its metabolites are eliminated in the urine and faeces.

◊ References.

1. Ensing K, *et al.* Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. *Eur J Clin Pharmacol* 1989; **36:** 189–94.

Uses and Administration

Ipratropium bromide is a quaternary ammonium antimuscarinic (p.1108). It is used by inhalation as a bronchodilator in the treatment of reversible airways obstruction, as in asthma and chronic obstructive pulmonary disease (see below).

In the UK the dose of ipratropium bromide from the metered-dose aerosol is expressed in terms of the amount of drug released from the valve into the mouthpiece (20 micrograms) whereas in the USA it is expressed in terms of the dose emitted from the mouthpiece (17 micrograms, equivalent to 21 micrograms released from the valve); recommended doses may therefore appear lower in the USA. For **reversible airways obstruction**, the usual UK dose from a metered-dose aerosol is 1 or 2 inhalations (20 or 40 micrograms) three or four times daily; single doses of up to 4 inhalations may be required. Comparable doses are used in the USA, but it is recommended that the daily dose should not exceed 12 inhalations.

Dry powder inhalation capsules are also available; the usual dose is 40 micrograms three or four times daily, to a maximum of 320 micrograms daily.

Ipratropium bromide may be given by inhalation as a nebulised solution in doses of 250 to 500 micrograms up to 4 times daily.

Ipratropium bromide, given intranasally, is also used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms is given into each nostril by metered-dose nasal spray 2 or 3 times daily. US licensing also permits higher doses of 84 micrograms into each nostril 3 or 4 times daily, for up to 4 days when rhinorrhoea is associated with the common cold; doses of 84 micrograms may be given into each nostril 4 times daily, for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis.

For details of doses in children, see Administration in Children, below.

Administration in children. Children may be given ipratropium bromide via a metered dose aerosol in the treatment of **reversible airways obstruction**. UK licensed product information recommends doses by age as follows:

- under 6 years: 1 inhalation of 20 micrograms three times daily
- 6 to 12 years: 1 or 2 inhalations of 20 micrograms three times daily
- 12 years and over: adult doses, see above

Dry powder inhalation capsules are also available, and are licensed for use in children from 12 years of age using the adult dose, see above.

Ipratropium bromide may also be given by inhalation as a nebulised solution. UK licensed product information recommends the following doses:

- under 6 years, for the treatment of acute asthma only: 125 to 250 micrograms, given no more often than every 6 hours up to a total daily dose of 1 mg
- 6 to 12 years, for the treatment of acute or chronic asthma: 250 micrograms, repeated if necessary up to a total daily dose of 1 mg
- 12 years and over: adult doses, see above.

Ipratropium bromide is used in the management of rhinorrhoea associated with **rhinitis**. A dose of 42 micrograms may be given into both nostrils two or three times daily. In the UK this dose may be given to children from 12 years of age, but in the USA this dose is licensed in children from 6 years of age.

US licensing also permits higher doses for up to 4 days when rhinorrhoea is associated with the common cold:

- 5 to 11 years: 84 micrograms into each nostril three times daily
- 12 years and over: adult doses, see above

Higher doses are also permitted in the USA for up to 3 weeks when rhinorrhoea is associated with seasonal allergic rhinitis. Children 5 years of age and over may be given the same dose as adults, see above.

Asthma. Ipratropium bromide is currently recommended as an adjunct to beta$_2$ agonists in the management of acute severe asthma, see p.1108. Antimuscarinic drugs, mainly ipratropium but also including oxitropium (p.1129), glycopyrronium and atropine, have been reviewed in the treatment of both acute and chronic asthma. A systematic review and meta-analysis[1] of the effectiveness of antimuscarinics in the treatment of acute asthma in children and adults, found they produced significant reductions in hospital admissions. Combined treatment with an inhaled beta$_2$ agonist also produced a significant increase in respiratory function.

Systematic reviews of antimuscarinic drugs have concluded that there is currently insufficient evidence to justify their routine use in adults[2] or children[3] with chronic asthma.

1. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; **60:** 740–6.
2. Westby M, *et al.* Anticholinergic agents for chronic asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 18/02/08).
3. McDonald NJ, *et al.* Anticholinergic therapy for chronic asthma in children over 2 years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 18/02/08).

Chronic obstructive pulmonary disease. Inhaled antimuscarinics, such as ipratropium bromide, are currently recommended as bronchodilators in chronic obstructive pulmonary disease (COPD) guidelines, see p.1112. A systematic review compared regular treatment with ipratropium (given for at least 4 weeks) with treatment using regular short-acting beta$_2$ agonists in stable COPD;[1] it found small benefits on lung function outcomes and quality of life with ipratropium compared with a short-acting beta$_2$ agonist; a reduction in the requirements for oral corticosteroids was also seen. Combination therapy with ipratropium and a short-acting beta$_2$ agonist was associated with some clinically meaningful lung function outcomes compared with the beta$_2$ agonist alone, but these were not reflected in subjective improvements or symptom scores.

A systematic review comparing ipratropium with a long-acting beta$_2$ agonist in stable COPD,[2] found that salmeterol had more effect than ipratropium on lung function, but no major differences were seen between symptom responses to ipratropium and salmeterol. Combination treatment with these two drugs was better than salmeterol alone in terms of quality of life.

1. Appleton S, *et al.* Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
2. Appleton S, *et al.* Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/02/08).

Rhinitis. Ipratropium bromide is used intranasally for the treatment of rhinorrhoea in allergic and non-allergic rhinitis (p.565). It has also relieved rhinorrhoea and sneezing associated with the common cold.

References.

1. Georgitis JW, *et al.* Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. *Clin Exp Allergy* 1994; **24:** 1049–55.
2. Hayden FG, *et al.* Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 89–97.
3. Dockhorn R, *et al.* Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 1999; **82:** 349–59.
4. Bonadonna P, *et al.* Cold-induced rhinitis in skiers—clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol* 2001; **15:** 297–301.
5. Kim KT, *et al.* Pediatric Atrovent Nasal Spray Study Group. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005; **94:** 73–9.

Preparations

BP 2008: Ipratropium Nebuliser Solution; Ipratropium Powder for Inhalation; Ipratropium Pressurised Inhalation.

Proprietary Preparations (details are given in Part 3)

Arg.: Aerotrop; Atrovent; Iprabron; ***Austral.:*** Aeron; Apoven; Atrovent; Ipratrin; Ipravent; ***Austria:*** Atrovent; Itrop; ***Belg.:*** Atronase; Atrovent; ***Braz.:*** Alvent†; Ares; Atrovent; Bromovent; Iprabon; Ipraneo; ***Canad.:*** Apo-Ipravent; Atrovent; Novo-Ipramide; ***Chile:*** Atrovent; Neorinol†; ***Cz.:*** Atrovent; Itrop†; ***Denm.:*** Atrovent; ***Fin.:*** Atrovent; ***Fr.:*** Atrovent; ***Ger.:*** Atrovent; Itrop; ***Gr.:*** Atrovent; ***Hong Kong:*** Atrovent; Cyclovent; Ipravent†; ***Hung.:*** Atrovent; ***India:*** Ipranase; Ipravent; ***Indon.:*** Atrovent; ***Irl.:*** Atrovent; Rinatec; ***Israel:*** Aerovent; Apovent; Atrovent; ***Ital.:*** Atem; Rinovagos; ***Jpn:*** Atrovent; ***Malaysia:*** Atrovent; ***Mex.:*** Atrovent; ***Neth.:*** Atrovent; Ipraxa; ***Norw.:*** Atrovent; Respontin†; ***NZ:*** Apo-Ipravent; Atrovent; Ipra†; ***Philipp.:*** Atrovent; ***Pol.:*** Atrovent; ***Port.:*** Atrovent; ***Rus.:*** Atrovent (Атровент); ***S.Afr.:*** Atrovent; Ipvent; ***Singapore:*** Atrovent; ***Spain:*** Atrovent; ***Swed.:*** Atrovent; ***Switz.:*** Atrovent; Rhinovent; ***Thai.:*** Atrovent; ***Turk.:*** Atrovent; ***UAE:*** Atropulm; ***UK:*** Atrovent; Respontin; Rinatec; ***USA:*** Atrovent; ***Venez.:*** Alovent.

Multi-ingredient: ***Arg.:*** Berodual; Combivent; Ipradual; Iprasalb; Salbutral AC; Salbutrop†; ***Austral.:*** Combivent; ***Austria:*** Berodual; Berodualin; Combivent; Di-Promal; ***Belg.:*** Combivent; Duovent; ***Braz.:*** Combivent; Duovent; ***Canad.:*** Combivent; Duovent; ratio-Ipra Sal UDV; ***Chile:*** Berodual; Combivent; Salbutral AC; ***Cz.:*** Berodual; Combivent†; ***Denm.:*** Berodual; Combivent; ***Fin.:*** Atrodual; Atrovent Comp; ***Fr.:*** Bronchodual; Combivent; ***Ger.:*** Berodual; ***Gr.:*** Berodual; Berovent; ***Hong Kong:*** Berodual†; Combivent; ***Hung.:*** Berodual; ***India:*** Duolin; Fenovent; ***Indon.:*** Berodual; Combivent; ***Irl.:*** Combivent; Duovent; Ipramol; ***Ital.:*** Breva; Duovent; Iprafen; ***Malaysia:*** Berodual; Combivent; Duovent; Ipramol; ***Mex.:*** Berodual; Combivent; ***Neth.:*** Berodual; Combivent; ***NZ:*** Combivent; Duolin; ***Philipp.:*** Berodual; Combipul; Combivent; Duavent; ***Pol.:*** Berodual; ***Port.:*** Berodual; Combivent; ***Rus.:*** Berodual (Беродуал); ***S.Afr.:*** Atrovent Beta; Berodual; Combivent; Duolin; Duovent; Sabax Combineb; Sabax Nebrafen; ***Singapore:*** Berodual; Combivent; Duovent; ***Spain:*** Berodual†; Combivent; Legis†; ***Swed.:*** Combivent; ***Switz.:*** Berodual; Dospir; ***Thai.:*** Berodual; Combivent; Inhalex; Punol; ***Turk.:*** Combivent; ***UK:*** Combivent; Duovent; Ipramol; ***USA:*** Combivent; DuoNeb; ***Venez.:*** Berodual; Combivent; Duolin; Duovent; Ipralin; Respidual.

Isoetarine *(BAN, rINN)* ⊗

Isoetariini; Isoetarin; Isoetarina; Isoétarine; Isoetarinum; Isoetharine *(USAN)*; Win-3406. 1-(3,4-Dihydroxyphenyl)-2-isopropylaminobutan-1-ol.

Изоэтарин

$C_{13}H_{21}NO_3 = 239.3.$

CAS — 530-08-5.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

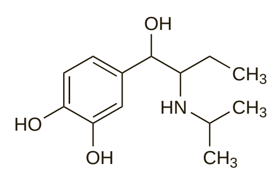

Isoetarine Hydrochloride *(BANM, rINNM)* ⊗

Etyprenaline Hydrochloride; Hidrocloruro de isoetarina; Isoétarine, Chlorhydrate d'; Isoetarini Hydrochloridum; Isoetharine Hydrochloride; *N*-Isopropylethylnoradrenaline Hydrochloride.

Изоэтарина Гидрохлорид

$C_{13}H_{21}NO_3,HCl = 275.8.$

CAS — 50-96-4; 2576-92-3.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

Pharmacopoeias. In *US.*

USP 31 (Isoetharine Hydrochloride). A white to off-white, odourless, crystalline solid. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 4.0 to 5.6. Store in airtight containers.

Isoetarine Mesilate *(BANM, rINNM)* ⊗

Isoétarine, Mésilate d'; Isoetarini Mesilas; Isoetharine Mesylate; Isoetharine Methanesulphonate; *N*-Isopropylethylnoradrenaline Mesylate; Mesilato de isoetarina.

Изоэтарина Мезилат

$C_{13}H_{21}NO_3,CH_4O_3S = 335.4.$

CAS — 7279-75-6.

ATC — R03AC07; R03CC06.

ATC Vet — QR03AC07; QR03CC06.

Pharmacopoeias. In *US.*

USP 31 (Isoetharine Mesylate). White or practically white, odourless, crystals. Freely soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 5.5. Store in airtight containers.

Profile

Isoetarine is a sympathomimetic with mainly beta-adrenergic activity. It has actions similar to those of salbutamol (p.1131) but is less selective for beta$_2$ adrenoceptors. Isoetarine has been used as a bronchodilator in the management of reversible airways obstruction.

Isoetarine is given by inhalation, as a nebulised solution of the hydrochloride in strengths up to 0.25%; a 1% solution can be given by a hand nebuliser.

Preparations

USP 31: Isoetharine Inhalation Solution; Isoetharine Mesylate Inhalation Aerosol.

Levosalbutamol *(rINN)* ⊗

Levalbuterol; Lévosalbutamol; Levosalbutamolum. (*R*)-α[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol.

Левосальбутамол

$C_{13}H_{21}NO_3 = 239.3.$

CAS — 34391-04-3.

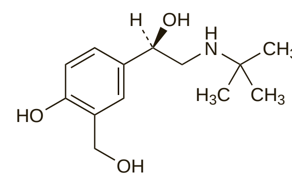

Levosalbutamol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levosalbutamol; Levalbuterol Hydrochloride *(USAN)*; Lévosalbutamol, Chlorhydrate de; Levosalbutamoli Hydrochloridum. (*R*)-α[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol hydrochloride.

Левосальбутамола Гидрохлорид

$C_{13}H_{21}NO_3,HCl = 275.8.$

CAS — 50293-90-8.

Pharmacopoeias. In *US.*

USP 31 (Levalbuterol Hydrochloride). A 1% solution has a pH of 4.5 to 5.5. Store in airtight containers at 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Levosalbutamol Sulfate *(rINNM)* ⊗

Levalbuterol Sulfate *(USAN)*; Lévosalbutamol, Sulfate de; Levosalbutamol Sulphate; Levosalbutamoli Sulfas; Sulfato de levosalbutamol. (*R*)-α[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-αα′-diol sulfate (2:1).

Левосальбутамола Сульфат

$(C_{13}H_{21}NO_3)_2,H_2SO_4 = 576.7.$

CAS — 148563-16-0.

Levosalbutamol Tartrate *(rINNM)* ⊗

Levalbuterol Tartrate *(USAN)*; Lévosalbutamol, Tartrate de; Levosalbutamoli Tartras; Tartrato de levosalbutamol. (α[1]*R*)-α[1]-{[(1,1-Dimethylethyl)amino]methyl}-4-hydroxy-1,3-benzenedimethanol (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1).

Левосальбутамола Тартрат

$2(C_{13}H_{21}NO_3),C_4H_6O_6 = 628.7.$

CAS — 661464-94-4.

Adverse Effects and Precautions

As for Salbutamol, p.1131.

Incidence of adverse effects. Some studies have reported that beta-adrenergic adverse effects (e.g. nervousness and increased heart rate) are less frequent with inhaled levosalbutamol than with racemic salbutamol.[1-3] Despite preliminary evidence that the increased airway hyperresponsiveness occasionally seen with long-term racemic salbutamol (see Tolerance, p.1132) may be due to the *S*(+)-enantiomer, and therefore might not occur with levosalbutamol,[4] a small study was unable to find any favourable protective effect.[5]

1. Nelson HS, *et al.* Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998; **102:** 943–52.
2. Milgrom H, *et al.* Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol* 2001; **108:** 938–45.
3. Handley DA, *et al.* Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. *J Asthma* 2000; **37:** 319–27.
4. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
5. Sjöswärd KN, *et al.* Single-isomer R-salbutamol is not superior to racemate regarding protection for bronchial hyperresponsiveness. *Respir Med* 2004; **98:** 990–9.

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

There is some systemic absorption of inhaled levosalbutamol. After a single dose levosalbutamol has a half-life of 3.3 hours. For details of the metabolism and excretion of salbutamol enantiomers, see Stereoselectivity, under Salbutamol p.1133.

Metabolism. There is evidence that levosalbutamol is metabolised faster than *S*(+)-salbutamol.

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41:** 35–40.
2. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; **52:** 849–52.
3. Gumbhir-Shah K, *et al.* Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 1096–1106.
4. Boulton DW, Fawcett JP. The pharmacokinetics of levosalbutamol: what are the clinical implications? *Clin Pharmacokinet* 2001; **40:** 23–40.

Uses and Administration

Levosalbutamol, the *R*(−)-enantiomer of salbutamol (p.1131), may be used as an alternative to racemic salbutamol for the management of asthma (p.1108). It is given as the hydrochloride, sulfate, or tartrate but doses are usually expressed in terms of the base; 1.15 mg of levosalbutamol hydrochloride, 2.4 mg of levosalbutamol sulfate, and 2.63 mg of levosalbutamol tartrate are equivalent to about 1 mg of levosalbutamol. For the relief of acute bronchospasm, 1 or 2 inhalations of the equivalent of 45 micrograms of levosalbutamol can be given from a metered-dose aerosol, repeated every 4 to 6 hours as required.

Levosalbutamol may also be inhaled via a nebuliser; usual doses equivalent to levosalbutamol 630 micrograms are inhaled three times daily, increased if necessary to 1.25 mg three times daily. For children's doses, see Administration in Children below. In patients with asthma, as-required beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, levosalbutamol indicates deterioration of asthma control and the need for review of therapy.

Levosalbutamol is also under investigation in a topical formulation for the treatment of cutaneous lupus erythematosus.

◊ General reviews.

1. Jenne JW. The debate on S-enantiomers of β-agonists: tempest in a teapot or gathering storm? *J Allergy Clin Immunol* 1998; **102:** 893–5.
2. Nowak R. Single-isomer levalbuterol: a review of the acute data. *Curr Allergy Asthma Rep* 2003; **3:** 172–8.
3. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol* 2003; **90:** 583–91.
4. Datta D, *et al.* An evaluation of nebulized levalbuterol in stable COPD. *Chest* 2003; **124:** 844–9.
5. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Action. *In vitro*, levosalbutamol had slightly higher affinity than racemic salbutamol for beta$_1$ and beta$_2$ adrenoceptors.[1] The *S*(+)-enantiomer had low affinity for these receptors. All 3 were mildly selective for beta$_2$ adrenoceptors.

1. Penn RB, *et al.* Comparison of R-, S-, and RS-albuterol interaction with human β - and β -adrenergic receptors. *Clin Rev Allergy Immunol* 1996; **14:** 37–45.

Administration in children. Children aged 4 years and older may be given levosalbutamol via a metered-dose aerosol at the same dose as that used for adults, see Uses and Administration, above.

Children aged from 6 to 11 years of age may be given levosalbutamol via a nebuliser in doses from 310 to 630 micrograms three times daily.

Asthma. Controlled studies comparing levosalbutamol with racemic salbutamol for the treatment of asthma have produced variable results. Levosalbutamol provided greater bronchodilatation than the equivalent amount of the racemate in some studies.[1,2] A decrease in hospital admissions and an increase in patient-discharge rates have also been reported.[3-5] Two controlled studies comparing levosalbutamol with racemic salbutamol in children with acute asthma failed to show any clinical benefit over the racemate.[6,7] A review concluded that, although current studies did not provide evidence of a substantial advantage for levosalbutamol over racemic salbutamol, the data were insufficient to determine whether subsets of the patient population might benefit from single isomer therapy.[8]

1. Pleskow WW, *et al.* Pairwise comparison of levalbuterol versus racemic albuterol in the treatment of moderate-to-severe asthma. *Allergy Asthma Proc* 2004; **25:** 429–36.
2. Nowak R, *et al.* A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. *Am J Emerg Med* 2006; **24:** 259–67.
3. Carl JC, *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. *J Pediatr* 2003; **143:** 731–6.
4. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. *Am J Emerg Med* 2005; **23:** 842–7.
5. Truitt T, *et al.* Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest* 2003; **123:** 128–35.
6. Qureshi F, *et al.* Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; **46:** 29–36.
7. Hardasmalani MD, *et al.* Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; **21:** 415–19.
8. Kelly HW. Levalbuterol for asthma: a better treatment? *Curr Allergy Asthma Rep* 2007; **7:** 310–14.

Preparations

USP 31: Levalbuterol Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Albulair; Ventoplus; ***India:*** Levolin; ***USA:*** Xopenex.

Montelukast Sodium *(BANM, USAN, rINNM)*

L-706631; MK-476; Montelukast sódico; Montélukast Sodique; Natrii Montelukastum. Sodium 1-[({(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]-benzyl}thio)methyl] cyclopropaneacetate.

Натрий Монтелукаст

$C_{35}H_{35}ClNNaO_3S$ = 608.2.

CAS — 158966-92-8 (montelukast); 151767-02-1 (montelukast sodium).

ATC — R03DC03.

ATC Vet — QR03DC03.

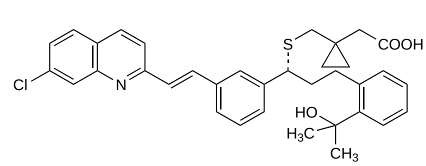

(montelukast)

Adverse Effects and Precautions

As for Zafirlukast, p.1150.

◊ Suspected adverse effects reported to the UK CSM after the launch of montelukast included oedema, agitation and restlessness, allergy (including anaphylaxis, angioedema, and urticaria), chest pain, tremor, dry mouth, vertigo, and arthralgia.[1] Further suspected adverse effects included nightmares, sedation, palpitations, and increased sweating.[2] In March 2008 the FDA announced[3] that it was investigating a possible association between the use of montelukast and behaviour/mood changes, suicidality, and suicide. Other postmarketing adverse events that had been incorporated into the US licensed product information in the previous year had included: tremor, depression, suicidality, and anxiousness.

1. Committee on Safety of Medicines/Medicines Control Agency. Leukotriene antagonists: a new class of asthma treatment. *Current Problems* 1998; **24:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/04/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Leukotriene receptor antagonists: update on adverse reaction profiles. *Current Problems* 1999; **25:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 14/04/08)
3. FDA. Early communication about an ongoing safety review of montelukast (Singulair) (issued 27th March 2008). Available at: http://www.fda.gov/cder/drug/early_comm/montelukast.htm (accessed 22/05/08)

Churg-Strauss syndrome. Churg-Strauss syndrome has been reported with the use of montelukast.[1-5] Relapse has occurred in a patient with Churg-Strauss syndrome who was in complete remission when montelukast therapy was started.[5] For discussion of the unresolved role of leukotriene antagonists in this disorder and precautions to be observed, see under Zafirlukast, p.1150.

1. Franco J, Artés MJ. Pulmonary eosinophilia associated with montelukast. *Thorax* 1999; **54:** 558–60.
2. Tuggey JM, Hosker HSR. Churg-Strauss syndrome associated with montelukast therapy. *Thorax* 2000; **55:** 805–6.
3. Meghjee SPL, White JS. Montelukast and Churg-Strauss syndrome. *Thorax* 2001; **56:** 244.
4. Gal AA, *et al.* Cutaneous lesions of Churg-Strauss syndrome associated with montelukast therapy. *Br J Dermatol* 2002; **147:** 618–19.
5. Solans R, *et al.* Montelukast and Churg-Strauss syndrome. *Thorax* 2002; **57:** 183–5.

Hepatic impairment. Although there is evidence of effects on the liver in patients receiving montelukast, and although it is largely eliminated by hepatic metabolism, montelukast (unlike zafirlukast) is not considered by UK licensed product information to be contra-indicated in hepatic impairment, and no dose adjustment is considered necessary in mild to moderate hepatic impairment.

Interactions

Licensed product information recommends caution when potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as phenytoin, phenobarbital, or rifampicin are given with montelukast.

Corticosteroids. For a report of peripheral oedema in a patient given montelukast and *prednisone*, see Leukotriene Antagonists, p.1495.

Phenobarbital. Peak serum concentrations after a single dose of montelukast 10 mg were reduced by 20% in 14 healthy subjects who took phenobarbital 100 mg daily for 14 days, and area under the serum concentration-time curve was reduced by 38%. However, it was not thought that montelukast doses would need adjustment if given with phenobarbital.[1]

1. Holland S, *et al.* Metabolism of montelukast (M) is increased by multiple doses of phenobarbital (P). *Clin Pharmacol Ther* 1998; **63:** 231.

Pharmacokinetics

Peak plasma concentrations of montelukast are achieved in 3 to 4 hours after oral doses. The mean oral bioavailability is 64%. Montelukast is more than 99% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP3A4, CYP2A6, and CYP2C9, and is excreted principally in the faeces via the bile.

◊ References.

1. Knorr B, *et al.* Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999; **39:** 786–93.
2. Knorr B, *et al.* Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol* 1999; **41:** 612–19.
3. Migoya E, *et al.* Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol* 2004; **44:** 487–94.
4. Knorr B, *et al.* Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* 2006; **46:** 620–7.
5. Kearns GL, *et al.* Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 2008; **48:** 502–11.

Uses and Administration

Montelukast is a selective leukotriene receptor antagonist with actions and uses similar to those of zafirlukast (p.1150) although it is reported to have a longer duration of action. It is used as the sodium salt, but doses are expressed in terms of the base; montelukast sodium 10.38 mg is equivalent to about 10 mg of montelukast.

In the management of chronic asthma (see below), allergic rhinitis (see below), and as prophylaxis for exercise-induced asthma, montelukast sodium is given in doses equivalent to 10 mg of montelukast once daily in the evening. It should not be used to treat an acute asthma attack.

For details of doses in children, see below.

Administration in children. Montelukast sodium is available as oral granules and chewable tablets for use in children. Oral granules are suitable for infants as they may be given directly into the mouth or mixed with a small amount of soft food. UK licensed oral doses for the management of chronic asthma and as prophylaxis for exercise-induced asthma, expressed as montelukast, are as follows:

- 6 months to 5 years, 4 mg daily taken in the evening
- 6 to 14 years, 5 mg daily taken in the evening
- 15 years and over, use the adult dose, see above

In the USA these doses are licensed from 1 year of age in asthma and from 15 years in exercise-induced asthma. Montelukast is also licensed for use in allergic rhinitis (p.565) in the USA. The above doses can be given from 2 years of age in seasonal allergic rhinitis and from 6 months of age in perennial allergic rhinitis.

Asthma. Use of montelukast in asthma has been reviewed,[1-3] (further general references for leukotriene antagonists can be found under Zafirlukast, p.1151). Montelukast produced modest improvements compared with placebo in chronic asthma and exercise-induced asthma in both adults[4,5] and children.[6-8] In a systematic review[9] of studies in adults and children comparing leukotriene receptor antagonists with inhaled corticosteroids for mild to moderate asthma, in which more than half of the studies used montelukast, leukotriene antagonists were found to be less effective in maintaining asthma control. A more recent study in children came to a similar conclusion,[10] but another 12-month study in children with mild persistent asthma, reported that montelukast was not inferior to an inhaled corticosteroid (fluticasone);[11] similar numbers of days without rescue medication, the primary outcome in this study, were reported with both treatments. However, some of the conclusions drawn from the latter study have been questioned[12] since patients who received inhaled fluticasone achieved better secondary outcomes such as fewer asthma attacks and less requirement for systemic corticosteroids.

Addition of montelukast to an inhaled corticosteroid has significantly improved asthma control in adults[13] and children[14,15] with mild to moderate asthma. Significant improvements in quality of life have also been reported,[16] in association with a fall in the levels of exhaled inflammatory mediators leading the authors of this study to conclude that leukotriene receptor antagonists may provide a complementary effect to inhaled corticosteroids when suppression of inflammation is incomplete. Another study[17] has reported that the use of montelukast did permit reduction in the dose of inhaled corticosteroid; adding montelukast to an inhaled corticosteroid (budesonide) may be as effective as doubling the dose of the corticosteroid.[18]

There is some evidence that montelukast may be more effective than inhaled salmeterol for the chronic treatment of exercise-induced asthma,[19,20] and although a later study[21] found similar effects on lung function with the two drugs, a more favourable effect was seen on gas exchange during moderate exercise with the use of montelukast.

An intravenous form of montelukast is under investigation for the treatment of severe acute asthma.[22,23]

1. Anonymous. Montelukast for persistent asthma. *Med Lett Drugs Ther* 1998; **40:** 71–3.
2. Anonymous. Montelukast and zafirlukast in asthma. *Drug Ther Bull* 1998; **36:** 65–8.
3. Jarvis B, Markham A. Montelukast: a review of its therapeutic potential in persistent asthma. *Drugs* 2000; **59:** 891–928.
4. Leff JA, *et al.* Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; **339:** 147–52.
5. Reiss TF, *et al.* Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Arch Intern Med* 1998; **158:** 1213–20.
6. Knorr B, *et al.* Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA* 1998; **279:** 1181–6.
7. Kemp JP, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; **133:** 424–8.
8. Knorr B, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Abstract: *Pediatrics* 2001; **108:** 754–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e48 (accessed 14/04/08)
9. Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).
10. Ostrom NK, *et al.* Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005; **147:** 213–20.
11. Garcia Garcia ML, *et al.* Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005; **116:** 360–9.
12. Turkalj M, Plavec D. "Inferiority complex" for a reason. *Pediatrics* 2006; **117:** 588–90.
13. Vaquerizo MJ, *et al.* CASIOPEA (Capacidad de Singulair Oral en la Prevencion de Exacerbaciones Asmaticas) Study Group. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003; **58:** 204–10.
14. Phipatanakul W, *et al.* Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003; **91:** 49–54.
15. Johnston NW, *et al.* Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; **120:** e702–e712.
16. Biernacki WA, *et al.* Effect of montelukast on exhaled leukotrienes and quality of life in asthmatic patients. *Chest* 2005; **128:** 1958–63.
17. Löfdahl C-G, *et al.* Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthma. *BMJ* 1999; **319:** 87–90.
18. Price DB, *et al.* Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003; **58:** 211–16.
19. Villaran C, *et al.* Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 1999; **104:** 547–53.
20. Edelman JM, *et al.* Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. *Ann Intern Med* 2000; **132:** 97–104.
21. Steinshamn S, *et al.* Effects of montelukast and salmeterol on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Chest* 2004; **126:** 1154–60.
22. Dockhorn RJ, *et al.* Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000; **55:** 260–5.
23. Camargo CA, *et al.* A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003; **167:** 528–33.

Bronchiolitis. Bronchiolitis due to RSV infection is often followed by post-bronchiolitic reactive airways disease, characterised by asthma-like wheeze and other symptoms. In a pilot study,[1] montelukast 5 mg orally daily was given for 4 weeks to infants who had been admitted for moderate to severe bronchiolitis. Symptom-free days and nights were increased, daytime cough was reduced, and exacerbations were delayed compared with placebo. The benefit of montelukast over placebo was only apparent after the first 2 weeks of treatment. Although the safety and efficacy of such treatment remains to be properly established,[2] there is some interest in whether montelukast can prevent or modify more persistent asthma that has been associated with RSV.

1. Bisgaard H. Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003; **167:** 379–83.
2. Szefler SJ, Simoes EAF. Montelukast for respiratory syncytial virus bronchiolitis: significant effect or provocative findings? *Am J Respir Crit Care Med* 2003; **167:** 290–1.

Cystic fibrosis. A small study in children with cystic fibrosis (p.166) found that montelukast reduced eosinophilic inflammation.[1] A later study,[2] reported improved lung function and a reduction in coughing and wheezing, and concluded that montelukast may have measurable anti-inflammatory activity in patients with cystic fibrosis. In a small group of adult patients with cystic fibrosis[3] montelukast improved symptoms, in particular exercise tolerance and peak expiratory flow rates. The patients who benefited the most had positive *Aspergillus* serology, and the authors suggested that colonisation of the airways in cystic fibrosis by *Aspergillus* stimulates T helper cell inflammation and leukotriene synthesis. A review of leukotriene receptor antagonists in cystic fibrosis[4] concluded that clinical benefit seemed likely in a subset of patients with cystic fibrosis who experience bronchial hyperresponsiveness similar to that seen in asthma.

A study into the pharmacokinetics of montelukast in cystic fibrosis[5] found that the dose of montelukast and the dosing interval do not need to be modified if the goal of therapy is to achieve similar serum concentrations as for asthma treatment; however the effectiveness of these concentrations for the inflammatory lung disease of patients with cystic fibrosis was unknown.

1. Schmitt-Grohé S, *et al.* Anti-inflammatory effects of montelukast in mild cystic fibrosis. *Ann Allergy Asthma Immunol* 2002; **89:** 599–605.
2. Stelmach I, *et al.* Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. *Ann Allergy Asthma Immunol* 2005; **95:** 372–80.
3. Morice AH, *et al.* Montelukast sodium in cystic fibrosis. *Thorax* 2001; **56:** 244–5.
4. Schmitt-Grohé S, Zielen S. Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. *Pediatr Drugs* 2005; **7:** 353–63.
5. Graff GR, *et al.* Montelukast pharmacokinetics in cystic fibrosis. *J Pediatr* 2003; **142:** 53–6.

Eczema. Despite early indications from some small clinical studies and case reports[1-3] that montelukast might be of benefit in eczema (p.1579) larger, more recent studies have failed to show any improvement compared with placebo.[4,5]

1. Capella GL, *et al.* A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11:** 209–13.
2. Hon KLE, *et al.* Brief case series: montelukast, at doses recommended for asthma treatment, reduces disease severity and increases soluble CD14 in children with atopic dermatitis. *J Dermatolog Treat* 2005; **16:** 15–18.
3. Angelova-Fischer I, Tsankov N. Successful treatment of severe atopic dermatitis with cysteinyl leukotriene receptor antagonist montelukast. *Acta Dermatovenerol Alp Panonica Adriat* 2005; **14:** 115–19.
4. Veien NK, *et al.* Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2005; **53:** 147–9.
5. Friedmann PS, *et al.* A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. *Clin Exp Allergy* 2007; **37:** 1536–40.

Gastrointestinal disorders. Benefit has been reported[1] with the use of montelukast in patients with eosinophilic oesophagitis, a rare condition involving eosinophilic infiltration of the oesophagus with intermittent painful dysphagia. A systematic review with recommendations for the diagnosis and treatment of eosinophilic oesophagitis[2] concluded that although leukotriene receptor antagonists had been shown to induce symptomatic relief at high doses, no significant improvements in histology were noted and their use for the treatment of eosinophilic oesophagitis is not supported by the current literature.

1. Attwood SEA, *et al.* Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut* 2003; **52:** 181–5.
2. Furuta GT, *et al.* American Gastroenterological Association; North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133:** 1342–63. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508507014746.pdf (accessed 14/04/08)

Graft-versus-host disease. A pilot study in refractory, chronic graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (p.1811),[1] saw an improvement in 15 of 19 patients after montelukast was added to their standard immunosuppressive regimens; in 4 patients signs of chronic GVHD were resolved, 2 showed significant improvement, and 9 showed moderate improvement.

1. Or R, *et al.* Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. *Transplantation* 2007; **83:** 577–81.

Mastocytosis. Montelukast has been tried, with some success, in the treatment of systemic mastocytosis (p.1138) in an infant.[1]

1. Tolar J, *et al.* Leukotriene-receptor inhibition for the treatment of systemic mastocytosis. *N Engl J Med* 2004; **350:** 735–6.

Rhinitis. Montelukast is used in allergic rhinitis (p.565), where large placebo-controlled studies have shown it to relieve symptoms in both seasonal allergic rhinitis,[1,2] and perennial allergic rhinitis.[3] However, a meta-analysis[4] of leukotriene antagonists (mainly montelukast) for management of allergic rhinitis concluded that while leukotriene antagonists were modestly more effective than placebo and of similar efficacy to antihistamines, in reducing nasal symptoms and improving rhinoconjunctivitis, they were less effective than corticosteroids even when used with antihistamines. A later systematic review[5] commented that some studies in allergic rhinitis using a combination of montelukast and an antihistamine had produced results comparable with intranasal corticosteroids. Also, in patients with both allergic rhinitis and asthma, montelukast had resulted in significant improvements in both when compared with placebo.

1. Philip G, *et al.* Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; **32:** 1020–8.
2. van Adelsberg J, *et al.* Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **90:** 214–22.
3. Patel P, *et al.* Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **95:** 551–7.
4. Wilson AM, *et al.* Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004; **116:** 338–44.
5. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs* 2007; **67:** 887–901.

Sleep-disordered breathing. Montelukast with an intranasal corticosteroid has been reported to be beneficial in a small study in children with residual sleep-disordered breathing after tonsillectomy and adenoidectomy.[1]

1. Kheirandish L, *et al.* Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* 2006; **117:** e61–e66.

Urticaria. Montelukast has been investigated in the treatment of urticaria (p.1584) with variable results.[1] However, urticaria has also been described as a suspected adverse effect of montelukast therapy (see above).

Montelukast has been reported to be more effective than placebo when used with the antihistamine desloratadine in the treatment of delayed pressure urticaria.[2]

1. McBayne TO, Siddall OM. Montelukast treatment of urticaria. *Ann Pharmacother* 2006; **40:** 939–42.
2. Nettis E, *et al.* Desloratadine in combination with montelukast suppresses the dermagraphometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **155:** 1279–82.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lukair†; Singulair; ***Austral.:*** Singulair; ***Austria:*** Singulair; ***Belg.:*** Singulair; ***Braz.:*** Singulair; ***Canad.:*** Singulair; ***Chile:*** Brondilat; Leukast†; Singulair; ***Cz.:*** Singulair; ***Denm.:*** Singulair; ***Fin.:*** Singulair; ***Fr.:*** Singulair; ***Ger.:*** Singulair; ***Gr.:*** Singulair; ***Hong Kong:*** Singulair; ***Hung.:*** Singulair; ***India:*** Montair; Montelast; ***Irl.:*** Singulair; ***Israel:*** Singulair; ***Ital.:*** Lukasm; Montegen; Singulair; ***Jpn:*** Kipres; ***Malaysia:*** Singulair; ***Mex.:*** Singulair; ***Neth.:*** Singulair; ***Norw.:*** Singulair; ***NZ:*** Singulair; ***Philipp.:*** Singulair; ***Pol.:*** Singulair; ***Port.:*** Lukair; Singulair; Singulergy; Synglarin; ***Rus.:*** Singulair (Сингуляр); ***S.Afr.:*** Singulair; ***Singapore:*** Singulair; ***Spain:*** Singulair; ***Swed.:*** Singulair; ***Switz.:*** Singulair; ***Thai.:*** Singulair; ***Turk.:*** Singulair; ***UK:*** Singulair; ***USA:*** Singulair; ***Venez.:*** Airon; Inuvic; Monukast; Singulair.

Multi-ingredient: ***India:*** Montair Plus.

Nedocromil Sodium *(BANM, USAN, rINNM)*

FPL-59002 (nedocromil); FPL-59002KC (nedocromil calcium); FPL-59002KP (nedocromil sodium); Natrii Nedocromilum; Nédocromil Sodique; Nedocromilo sódico; Nedocromilum Natricum; Nedokromiilinatrium; Nedokromil Sodyum; Nedokromilnatrium. Disodium 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-4*H*-pyrano[3,2-g]quinoline-2,8-dicarboxylate.

Натрий Недокромил

$C_{19}H_{15}NNa_2O_7 = 415.3.$

CAS — 69049-73-6 (nedocromil); 69049-74-7 (nedocromil sodium); 101626-68-0 (nedocromil calcium).

ATC — R01AC07; R03BC03; S01GX04.

ATC Vet — QR01AC07; QR03BC03; QS01GX04.

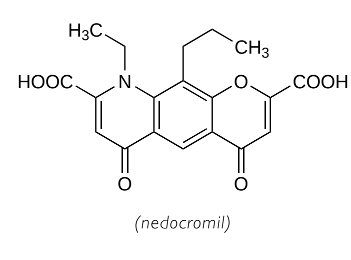

(nedocromil)

NOTE. Nedocromil Calcium is also *USAN*.

Adverse Effects and Precautions

Inhaled nedocromil sodium may cause headache, gastrointestinal disturbances (nausea, vomiting, dyspepsia, and abdominal discomfort). An unusual or unpleasant taste is reported rarely. Paradoxical bronchospasm may occur. Eye drops may cause transient burning and stinging.

It should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (see p.1136) also apply.

Incidence of adverse effects. A review[1] of nedocromil sodium noted that adverse effects were infrequent, mild, and short-lived. The most common effect appeared to be an unpleasant or bitter taste, which was experienced by 12 to 13% of patients, although less than 1% of patients stopped treatment because of it. Other adverse effects included cough (in 7%), headache (6%), sore throat (5.7%), nausea (4%), and vomiting (1.7%).

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; **45:** 693–715.

Pharmacokinetics

Nedocromil sodium is poorly absorbed from the gastrointestinal tract; about 10% of the inhaled dose is absorbed from the lungs. Absorption is also poor after topical ophthalmic use, and occurs mainly through the nasal mucosa. Nedocromil sodium is excreted unchanged in the urine and faeces. The half-life is stated to range from about 1 to 3.3 hours.

◊ The extent of absorption or bioavailability of nedocromil sodium after inhalation in healthy subjects was 7 to 9% of the dose, including 2 to 3% oral absorption and 5 to 6% absorption from the respiratory tract.[1] After inhalation of nedocromil sodium 4 mg the mean peak plasma concentration was 3.3 nanograms/mL in healthy subjects and 2.8 nanograms/mL in asthmatic patients, with peak values being reached at about 20 and 40 minutes respectively. The mean total urinary excretion 24 hours after a single dose was 5.4% of the dose in healthy subjects and 2.3% in asthmatics.

1. Neale MG, *et al.* The pharmacokinetics of nedocromil sodium, a new drug for the treatment of reversible obstructive airways disease, in human volunteers and patients with reversible obstructive airways disease. *Br J Clin Pharmacol* 1987; **24:** 493–501.

Uses and Administration

Nedocromil sodium has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1137) and is used similarly in the management of chronic asthma. It should not be used to treat an acute attack of asthma.

For **asthma**, nedocromil sodium is inhaled from a metered-dose aerosol. The usual dose for adults and children from 6 years of age is 4 mg inhaled four times daily which may be decreased to 4 mg twice daily after control of symptoms is achieved. Clinical improvement may not be obtained for 1 week or longer after beginning therapy.

Nedocromil sodium is also used topically in the treatment of **allergic conjunctivitis** and allergic **rhinitis**. For seasonal and perennial allergic conjunctivitis it is given as a 2% solution, instilled into each eye twice daily. This may be increased to 4 times daily if necessary, which is the usual dose in vernal keratoconjunctivitis. In seasonal allergic conjunctivitis, treatment is usually given for no more than 12 weeks. In allergic rhinitis nedocromil sodium is used as a 1% nasal spray: one spray is given into each nostril 4 times daily. For details of doses in children, see Administration in Children, below.

◊ General references.

1. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993; **45:** 693–715.
2. Parish RC, Miller LJ. Nedocromil sodium. *Ann Pharmacother* 1993; **27:** 599–606.

Administration in children. Nedocromil sodium is given by metered-dose aerosol inhalation for the treatment of asthma in children from 6 years of age at the adult dose, see above. Although unlicensed in the UK for younger children, the *BNFC* recommends the same dose from 5 years of age.

Similarly, for the topical treatment of seasonal allergic conjunctivitis and vernal keratoconjunctivitis, the adult dose may be given to children from 6 years of age, see above. Treatment of perennial allergic conjunctivitis with nedocromil sodium is not licensed in children in the UK, but the *BNFC* recommends adult doses from 6 years of age.

Asthma. Nedocromil sodium is generally considered to be an alternative to sodium cromoglicate in the management of asthma (p.1108). Nedocromil has been shown to improve symptoms and reduce bronchodilator intake in adults[1] and children[2] with chronic asthma. However, a systematic review[3] of nedocromil for chronic asthma in children subsequently found that although a number of small studies have shown that nedocromil improves airflow limitation, reduces symptoms, and reduces bronchial hyperresponsiveness, this has not been confirmed in a larger long-term study of children with milder asthma. Its place in relation to other asthma therapies for children is also unclear. It may be used before exercise to reduce exercise-induced bronchoconstriction,[4] and appears to be as effective as sodium cromoglicate for this indication.[5]

1. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993; **6:** 35–41.
2. Armenio L, *et al.* Double blind, placebo controlled study of nedocromil sodium in asthma. *Arch Dis Child* 1993; **68:** 193–7.
3. Sridhar AV, McKean M. Nedocromil sodium for chronic asthma in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/04/08).
4. Spooner CH, *et al.* Nedocromil sodium for preventing exercise-induced bronchoconstriction. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 14/04/08).
5. Kelly K, *et al.* Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction in asthmatics. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 14/04/08).

Cough. For references indicating a positive response to sodium cromoglicate but not to nedocromil sodium in the management of cough induced by ACE inhibitor therapy, see Cough, p.1137.

Rhinitis and conjunctivitis. Nedocromil has been used in the management of allergic rhinitis (p.565) and conjunctivitis (p.564). In the management of seasonal allergic rhinitis, there is some evidence that prophylactic mometasone furoate (p.1539) reduces symptoms more effectively than nedocromil.[1] In vernal keratoconjunctivitis (see p.1138) nedocromil may be more effective than cromoglicate, but is less effective than fluorometholone.[2]

1. Pitsios C, *et al.* Efficacy and safety of mometasone furoate vs nedocromil sodium as prophylactic treatment for moderate/severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006; **96:** 673–8.
2. Tabbara KF, Al-Kharashi SA. Efficacy of nedocromil 2% versus fluorometholone 0.1%: a randomised, double masked trial comparing the effects on severe vernal keratoconjunctivitis. *Br J Ophthalmol* 1999; **83:** 180–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Tilade; ***Austria:*** Tilade; Tilarin; Tilavist; ***Braz.:*** Tilade; ***Canad.:*** Alocril; Tilade†; ***Cz.:*** Tilade; Tilarin†; Tilavist†; ***Denm.:*** Tilade; Tilavist; ***Fin.:*** Tilade; Tilarin†; Tilavist†; ***Fr.:*** Tilavist; ***Ger.:*** Halamid†; Irtan; Tilade; ***Gr.:*** Tilade; ***Hong Kong:*** Tilade†; ***Hung.:*** Tilade†; ***Irl.:*** Tilade; Tilavist†; ***Israel:*** Tilade; Tilavist; ***Ital.:*** Kovilen; Kovinal; Tilade; Tilarin; Tilavist; ***Mex.:*** Irtan; ***Neth.:*** Tilade; Tilavist; ***Norw.:*** Tilavist; ***NZ:*** Tilade; ***Port.:*** Tilavist; ***Rus.:*** Tilade (Тайлед); ***Spain:*** Brionil; Cetimil; Tilad; Tilavist; ***Swed.:*** Tilavist; ***Switz.:*** Tilade†; Tilarin; Tilavist; ***Turk.:*** Tilade; ***UK:*** Rapitil; Tilade; ***USA:*** Alocril; Tilade.

Multi-ingredient: ***Ital.:*** Zarent†.

Omalizumab *(BAN, USAN, rINN)*

CGP-51901; E-25; IGE-025; Olizumab; Omalizumabum; rhuMAb-E25. Immunoglobulin G, anti-(human immunoglobulin E Fc region)(human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ-chain, dimer.

Омализумаб

CAS — 242138-07-4.

ATC — R03DX05.

ATC Vet — QR03DX05.

Adverse Effects and Precautions

Injection site reactions are common with the use of omalizumab. Other adverse effects that have been reported include generalised pain, fatigue, arthralgia, dizziness, earache, gastrointestinal disturbances, headache, and alopecia. An increased incidence of parasitic infection has been reported in patients at high risk for helminthic infections. Viral infections, upper respiratory-tract infections, sinusitis, pharyngitis, and flu-like illness can also occur. Churg-Strauss syndrome has also been reported. Hypersensitivity reactions such as urticaria, dermatitis, and pruritus can occur. Rarely, systemic reactions, including potentially life-threatening anaphylaxis, have occurred. Anaphylactic reactions may occur up to 4 days after a dose, and as early as the first dose or more than 1 year after beginning regular treatment.

Severe thrombocytopenia has been reported with use of omalizumab.

Licensed product information notes an increased incidence of malignancies in patients given omalizumab.

Omalizumab should not be used for the treatment of acute asthma attacks, and inhaled corticosteroids should not be abruptly withdrawn on starting omalizumab therapy.

Pharmacokinetics

Omalizumab is absorbed after subcutaneous injection with a bioavailability of about 62%, reaching peak serum concentrations after 7 to 8 days. It is removed by IgG and IgE clearance processes in the liver, with a serum elimination half-life of about 26 days. During treatment with omalizumab, the serum concentration of free IgE decreases but that of total IgE increases because the omalizumab-IgE complex has a slower elimination rate than free IgE.

◊ References.

1. Hayashi N, *et al.* A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007; **63:** 548–61.

Uses and Administration

Omalizumab is a recombinant humanised monoclonal antibody that selectively binds to IgE. It inhibits the binding of IgE on the surface of mast cells and basophils, thus reducing the release of mediators of the allergic response. Omalizumab is used in the prophylactic management of moderate to severe, persistent allergic asthma (p.1108). The dose depends on the patient's weight and pre-treatment serum-IgE concentrations; regimens range from 75 to 300 mg every 4 weeks to 225 to 375 mg every 2 weeks. Omalizumab is given by subcutaneous injection, and not more than 150 mg should be given at one injection site. Total IgE concentrations rise during treatment (see Pharmacokinetics, above), remaining elevated for up to 1 year after withdrawal, and cannot be used to determine continued dosage. Dose determination after treatment interruptions lasting up to 1 year should be based on pre-treatment serum-IgE concentrations.

Omalizumab is under investigation in the prophylactic management of seasonal allergic rhinitis.

◊ References.

1. Ädelroth E, *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; **106:** 253–9.
2. Easthope S, Jarvis B. Omalizumab. *Drugs* 2001; **61:** 253–60.
3. Casale TB, *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; **286:** 2956–67.
4. Chervinsky P, *et al.* Omalizumab, an anti-IgE antibody, in treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; **91:** 160–7.
5. Hanf G, *et al.* Omalizumab inhibits allergen challenge-induced nasal response. *Eur Respir J* 2004; **23:** 414–18.
6. Vignola AM, *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; **59:** 709–17.

Aspergillosis. Successful treatment of allergic bronchopulmonary aspergillosis with omalizumab has been reported in children with cystic fibrosis.[1,2] In one such report,[1] repeated improvement in symptoms and normalisation in lung function within 2 to 4 hours of giving omalizumab led to complete withdrawal of corticosteroid treatment in a 12 year old girl. Others[2] have reported similar benefits.

1. van der Ent CK, *et al.* Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax* 2007; **62:** 276–7.
2. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol* 2008; **43:** 607–10.

Asthma. Current guidelines recommend omalizumab as an option for the treatment of severe persistent allergic (IgE mediated) asthma as an add-on therapy to optimised standard therapy in adults (see Asthma, p.1108). It has been shown to reduce exacerbations and corticosteroid requirement compared with placebo in adults with moderate-to-severe allergic asthma.[1] It also reduced exacerbation rates in patients with inadequately controlled, severe persistent asthma,[2] and is considered to be an effective therapy in difficult-to-treat, high-risk adult patients.[3,4]

A systematic review[5] of omalizumab therapy for chronic asthma found that omalizumab was more effective than placebo at reducing exacerbations and improving quality of life. Although omalizumab had an *inhaled*-corticosteroid-sparing effect, the clinical significance of the magnitude of reduction remains open to interpretation, and other factors such as cost-effectiveness and comparative efficacy compared to other add-on therapy should be considered. In patients on *oral* corticosteroids, no significant impact was seen on either exacerbations or oral corticosteroid dose.

Omalizumab has been investigated in the treatment of childhood asthma with encouraging results.[6,7]

1. Solèr M, *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; **18:** 254–61.
2. Humbert M, *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; **60:** 309–16.
3. Hendeles L, Sorkness CA. Anti-immunoglobulin E therapy with omalizumab for asthma. *Ann Pharmacother* 2007; **41:** 1397–1410.
4. Price D. The use of omalizumab in asthma. *Prim Care Respir J* 2008; **17:** 62–72.
5. Walker S, *et al.* Anti-IgE for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
6. Berger W, *et al.* Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; **91:** 182–8.
7. Milgrom H, *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; **108:** E36. Full version: http://pediatrics.aappublications.org/cgi/content/reprint/108/2/e36.pdf (accessed 14/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Xolair; ***Austral.:*** Xolair; ***Belg.:*** Xolair; ***Canad.:*** Xolair; ***Cz.:*** Xolair; ***Fr.:*** Xolair; ***Gr.:*** Xolair; ***Hung.:*** Xolair; ***Israel:*** Xolair; ***Malaysia:*** Xolair; ***NZ:*** Xolair; ***Pol.:*** Xolair; ***Port.:*** Xolair; ***Singapore:*** Xolair; ***Swed.:*** Xolair; ***UK:*** Xolair; ***USA:*** Xolair; ***Venez.:*** Xolair.

Orciprenaline Sulfate *(rINNM)* ⊗

Metaproterenol Sulfate *(USAN)*; Metaproterenol Sulphate; Orciprenalin sulfát; Orciprénaline, sulfate d'; Orciprenaline Sulphate *(BANM)*; Orciprenalini sulfas; Orciprenalino sulfatas; Orciprenalinsulfat; Orciprenalin-szulfát; Orcyprenaliny siarczan; Orsiprenaliinisulfaatti; Orsiprenalin Sülfat; Sulfato de orciprenalina; Th-152. 1-(3,5-Dihydroxyphenyl)-2-isopropylaminoethanol sulphate; *N*-Isopropyl-*N*(β,3,5-trihydroxyphenethyl)ammonium sulphate.

Орципреналина Сульфат

$(C_{11}H_{17}NO_3)_2,H_2SO_4$ = 520.6.

CAS — 586-06-1 (orciprenaline); 5874-97-5 (orciprenaline sulfate).

ATC — R03AB03; R03CB03.

ATC Vet — QR03AB03; QR03CB03.

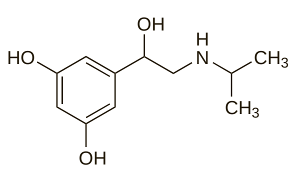

(orciprenaline)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Orciprenaline Sulphate). A white, slightly hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Metaproterenol Sulfate). A white to off-white crystalline powder. Freely soluble in water. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Adverse effects are more common because of the non-selective beta agonist effect of orciprenaline. For the adverse effects and precautions pertaining to non-selective beta agonists see under Sympathomimetics, p.1407.

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

After oral doses orciprenaline is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver; about 40% of an oral dose is reported to reach the circulation unchanged. It is excreted in the urine primarily as metabolites.

Uses and Administration

Orciprenaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity. It has actions and uses similar to those of salbutamol (p.1133) but is less selective for beta$_2$ receptors.

Orciprenaline sulfate is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). However, more selective beta$_2$ agonists such as salbutamol or terbutaline are now preferred. On inhalation, the onset of action is usually within 30 minutes and can last from 1 to 5 hours.

A typical adult dose for the relief of acute **bronchospasm** has been 1 or 2 inhalations of orciprenaline sulfate 750 micrograms from a metered-dose aerosol, repeated as needed up to a maximum of 12 inhalations (9 mg) in 24 hours. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, orciprenaline indicates deterioration of asthma control and the need for review of therapy.

Orciprenaline sulfate has also been inhaled in 5% solution from a hand nebuliser, the usual adult dose being 10 inhalations. If the solution is used with any other nebulising device such as an intermittent positive-pressure breathing (IPPB) apparatus the adult dose is 0.2 to 0.3 mL of a 5% solution diluted up to about 2.5 mL with physiological saline (i.e. dilution to a 0.4 to 0.6% solution) given not more often than every 4 hours. Unit-dose vials containing a prediluted solution of orciprenaline sulfate 0.4 and 0.6% are also available for nebulisation by an IPPB device.

In the chronic management of reversible airways obstruction, orciprenaline sulfate has been given orally in a usual adult dose of 20 mg three or four times daily.

Orciprenaline sulfate has also been used similarly to isoprenaline (see p.1317) for its cardiovascular effects in the treatment of **bradycardia** of various types, notably in AV heart block and sinus bradycardia. In such cases oral doses of up to 240 mg daily in divided doses, or 250 to 500 micrograms by slow intravenous injection have been given; orciprenaline sulfate may also be given by intravenous infusion, or intramuscular or subcutaneous injection. For doses of orciprenaline used in children, see Administration in Children, below.

Administration in children. Although more selective beta agonists are generally preferred, in some countries orciprenaline sulfate is licensed for use in children via a metered-dose inhaler in similar doses to adults; in the USA, use is not recommended under 12 years of age. A metered-dose inhaler was formerly available in the UK and licensed doses in children were:

- under 6 years of age: 1 inhalation of 750 micrograms as necessary; doses should not be repeated within 30 minutes. A maximum of 4 inhalations in 24 hours was suggested
- 6 to 12 years of age: 1 or 2 inhalations of 750 micrograms as necessary; doses should not be repeated within 30 minutes. A maximum of 8 inhalations in 24 hours was suggested

In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use, and chronic oral treatment with orciprenaline would generally be regarded as inappropriate in children. Nonetheless, a syrup is licensed for such use in the UK, licensed oral doses in children being:

- up to 1 year: 5 mg three times daily, increased if necessary to a maximum of 10 mg three times daily
- 1 to 3 years: 5 mg four times daily, increased if necessary to a maximum of 10 mg four times daily
- 3 to 12 years: 10 mg four times daily, increased if necessary to a maximum of 20 mg three times daily
- over 12 years: as for adults (see above)

Preparations

BP 2008: Orciprenaline Tablets;
USP 31: Metaproterenol Sulfate Inhalation Aerosol; Metaproterenol Sulfate Inhalation Solution; Metaproterenol Sulfate Syrup; Metaproterenol Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Alupent†; ***Austria:*** Alupent; ***Canad.:*** Alupent†; ***Ger.:*** Alupent; ***Gr.:*** Alupent; ***India:*** Alupent; ***Indon.:*** Alupent; ***Irl.:*** Alupent†; ***Ital.:*** Alupent; ***Jpn:*** Alotec; ***Mex.:*** Alupent; ***Pol.:*** Astmopent; ***Rus.:*** Astmopent (Астмопент); ***Thai.:*** Alupent†; ***UK:*** Alupent; ***USA:*** Alupent; ***Venez.:*** Alupent†.

Multi-ingredient: ***Chile:*** Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron; Vapoflu; ***Indon.:*** Silomat Compositum; ***Irl.:*** Alupent Expectorant; ***Mex.:*** Bisolpent Ex; ***Philipp.:*** Bisolpent; ***S.Afr.:*** Adco-Linctopent; Benylin Chesty; Bisolvon Linctus DA; Bronkese Compound; Flemeze; Silomat DA†; ***UAE:*** Orcinol; ***Venez.:*** Bisolpent†; Silomat Compositum†.

Oxitropium Bromide *(BAN, rINN)*

Ba-253; Bromuro de oxitropio; Oksitropiumbromidi; Oxitropii bromidum; Oxitropium, bromure d'; Oxitropiumbromid. 6,7-Epoxy-8-ethyl-3-[(*S*)-tropoyloxy]tropanium bromide; (3*s*,6*R*,7*S*,8*r*)-8-Ethyl-3-[(*S*)-tropoyloxy]-6,7-epoxytropanium bromide.

Окситропия Бромид

$C_{19}H_{26}BrNO_4$ = 412.3.

CAS — 30286-75-0.

ATC — R03BB02.

ATC Vet — QR03BB02.

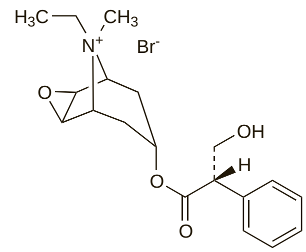

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oxitropium Bromide). A white or almost white, crystalline powder. It exhibits polymorphism. Very soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol; practically insoluble in dichloromethane.

Profile

Oxitropium bromide is a quaternary ammonium antimuscarinic with actions similar to those of ipratropium bromide (p.1124), to which it is structurally related. It is used as a bronchodilator in the treatment of reversible airways obstruction, as in asthma (p.1108) and chronic obstructive pulmonary disease (p.1112). Doses of 100 or 200 micrograms by inhalation from a metered-dose aerosol have been given 2 or 3 times daily. Oxitropium bromide may also be given as a nebulised solution in doses of 1.5 mg inhaled 2 or 3 times daily. *Animal* studies have shown reproductive toxicity with high doses of oxitropium, hence the recommendation that it should not be used during pregnancy.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Oxivent†; ***Fin.:*** Ventox†; ***Fr.:*** Tersigat†; ***Ger.:*** Ventilat†; ***Irl.:*** Oxivent†; ***Ital.:*** Oxivent; ***Jpn:*** Tersigan; ***UK:*** Oxivent†; ***Venez.:*** Tersigat†.

Pemirolast Potassium *(USAN, rINNM)*

BL-5617; BMY-26517; Kalii Pemirolastum; Pemirolast potásico; Pémirolast Potassique. Potassium 9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

Калия Пемироласт

$C_{10}H_7KN_6O$ = 266.3.

CAS — 69372-19-6 (pemirolast); 100299-08-9 (pemirolast potassium).

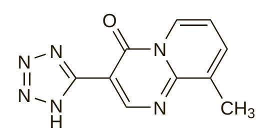

(pemirolast)

Profile

Pemirolast potassium has mast cell stabilising properties like sodium cromoglicate (p.1136) and may also be a leukotriene inhibitor. It has been used in the treatment of chronic asthma (p.1108) and in the prophylaxis of allergic rhinitis (p.565) and conjunctivitis (p.564). Pemirolast potassium has no bronchodilator properties and should not be used for the treatment of acute asthma attacks.

For asthma, the usual dose is 10 mg orally twice daily after food. For allergic rhinitis the dose is halved. Pemirolast potassium 0.1% eye drops are instilled 4 times daily in the prophylactic management of allergic conjunctivitis. For details of doses in children, see below.

Pemirolast has also been investigated for the prevention of restenosis after coronary artery stent placement.

◊ References.

1. Tinkelman DG, Berkowitz RB. A pilot study of pemirolast in patients with seasonal allergic rhinitis. *Ann Allergy* 1991; **66:** 162–5.
2. Hasegawa T, *et al.* Kinetic interaction between theophylline and a newly developed anti-allergic drug, pemirolast potassium. *Eur J Clin Pharmacol* 1994; **46:** 55–8.
3. Anonymous. New drugs for allergic conjunctivitis. *Med Lett Drugs Ther* 2000; **42:** 39–40.
4. Abelson MB, *et al.* Pemirolast potassium 0.1% ophthalmic solution is an effective treatment for allergic conjunctivitis: a pooled analysis of two prospective, randomized, double-masked, placebo-controlled, phase III studies. *J Ocul Pharmacol Ther* 2002; **18:** 475–88.
5. Shulman DG. Two mast cell stabilizers, pemirolast potassium 0.1% and nedocromil sodium 2%, in the treatment of seasonal allergic conjunctivitis: a comparative study. *Adv Therapy* 2003; **20:** 31–40.
6. Ohsawa H, *et al.* Preventive effect of an antiallergic drug, pemirolast potassium, on restenosis after stent placement: quantitative coronary angiography and intravascular ultrasound studies. *J Cardiol* 2003; **42:** 13–22.
7. Gous P, Ropo A. A comparative trial of the safety and efficacy of 0.1 percent pemirolast potassium ophthalmic solution dosed

twice or four times a day in patients with seasonal allergic conjunctivitis. *J Ocul Pharmacol Ther* 2004; **20:** 139–50.
8. Yahata H, *et al.* Prophylactic effect of pemirolast, an antiallergic agent, against hypersensitivity reactions to paclitaxel in patients with ovarian cancer. *Int J Cancer* 2006; **118:** 2636–8.

Administration in children. Pemirolast potassium may be used in the management of asthma in children in the following oral doses:

- 1 to 4 years: 2.5 mg twice daily after food
- 5 to 10 years: 5 mg twice daily after food
- 11 years and above: use adult doses, see above

For allergic rhinitis, the above doses are halved.

Pemirolast potassium 0.1% eye drops can be used four times daily in children over 3 years with allergic conjunctivitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Pemirox; ***Indon.:*** Alegysal; ***Jpn:*** Alegysal; ***Philipp.:*** Alegysal; ***Thai.:*** Pemirox; ***USA:*** Alamast.

Pirbuterol *(BAN, rINN)* ⊗

Pirbutérol; Pirbuteroli; Pirbuterolum; Pyrbuterol. 2-*tert*-Butylamino-1-(5-hydroxy-6-hydroxymethyl-2-pyridyl)ethanol.

Пирбутерол

$C_{12}H_{20}N_2O_3$ = 240.3.
CAS — 38677-81-5.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.

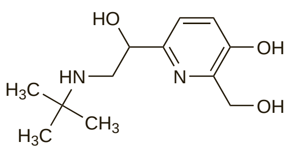

Pirbuterol Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de pirbuterol; CP-24314-14; Pirbutérol, Acétate de; Pirbuteroli Acetas; Pyrbuterol Acetate.

Пирбутерола Ацетат

$C_{12}H_{20}N_2O_3,C_2H_4O_2$ = 300.4.
CAS — 65652-44-0.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.

Pirbuterol Hydrochloride *(BANM, USAN, rINNM)* ⊗

CP-24314-1; Hidrocloruro de pirbuterol; Pirbutérol, Chlorhydrate de; Pirbuteroli Hydrochloridum; Pyrbuterol Hydrochloride.

Пирбутерола Гидрохлорид

$C_{12}H_{20}N_2O_3,2HCl$ = 313.2.
CAS — 38029-10-6.
ATC — R03AC08; R03CC07.
ATC Vet — QR03AC08; QR03CC07.

Profile

Pirbuterol is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131).

Pirbuterol is used for its bronchodilating properties. It is given as the acetate in the management of reversible airways obstruction, as in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). On inhalation, pirbuterol exerts an effect within 10 minutes, which is reported to last at least 5 hours.

Pirbuterol is given by inhalation as the acetate but doses are expressed in terms of the base: pirbuterol acetate 250 micrograms is equivalent to about 200 micrograms of pirbuterol. It is given via a metered-dose aerosol in a usual dose equivalent to pirbuterol 200 to 400 micrograms (1 to 2 inhalations) as required but not more often than every four hours. A total daily dose of 2.4 mg (12 inhalations) should not be exceeded. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, pirbuterol indicates deterioration of asthma control and the need for review of therapy.

Pirbuterol has also been given orally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exirel†; ***Fr.:*** Maxair; ***Switz.:*** Maxair†; ***USA:*** Maxair.

Pitrakinra *(rINN)*

Pitrakinrum. L-Methionyl-[121-aspartic acid,124-aspartic acid]interleukin-4.

Питракинра

```
                                             M
HKCDITLQEI IKTLNSLTEQ KTLCTELTVT DIFAASKNTT
EKETFCRAAT VLRQFYSHHE KDTRCLGATA QQFHRHKQLI
RFLKRLDRNL WGLAGLNSCP VKEANQSTLE NFLERLKTIM
DEKDSKCSS
```

Profile

Pitrakinra is a dual interleukin-4 and -13 receptor antagonist that is under investigation in the treatment of asthma.

Pranlukast *(BAN, rINN)*

ONO-1078; Pranlukastum. *N*-[4-Oxo-2-(1*H*-tetrazol-5-yl)-4*H*-1-benzopyran-8-yl]-*p*-(4-phenylbutoxy)benzamide.

Пранлукаст

$C_{27}H_{23}N_5O_4$ = 481.5.
CAS — 103177-37-3.
ATC — R03DC02.
ATC Vet — QR03DC02.

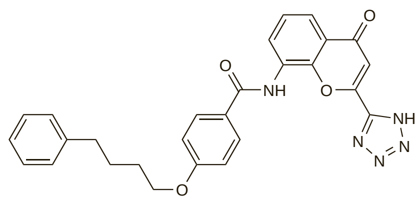

Profile

Pranlukast is a selective antagonist of the leukotriene C_4, D_4, and E_4 receptors with similar properties to zafirlukast (p.1150). It is used in the management of asthma (p.1108) and allergic rhinitis (p.565), at a usual oral dose of pranlukast hydrate 225 mg twice daily. For details of doses in children, see below.

◊ References.

1. Tamaoki J, *et al.* Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. *Am J Respir Crit Care Med* 1997; **155:** 1235–40.
2. Barnes NC, *et al.* Pranlukast, a novel leukotriene receptor antagonist: results of the first European, placebo-controlled, multicentre clinical study in asthma. *Thorax* 1997; **52:** 523–7.
3. Grossman J, *et al.* Results of the first US double-blind, placebo-controlled, multicenter clinical study in asthma with pranlukast, a novel leukotriene receptor antagonist. *J Asthma* 1997; **34:** 321–8.
4. Keam SJ, *et al.* Pranlukast: a review of its use in the management of asthma. *Drugs* 2003; **63:** 991–1019.

Administration in children. Children with asthma may be given 3.5 mg/kg of pranlukast hydrate orally twice daily. The maximum daily dose is 10 mg/kg, not to exceed the usual adult daily dose of 450 mg (see above).

Churg-Strauss syndrome. Churg-Strauss syndrome has been reported with the use of pranlukast.[1-3] For discussion of the unresolved role of leukotriene antagonists in this disorder and precautions to be observed, see under Zafirlukast, p.1150.

1. Kobayashi S, *et al.* Churg-Strauss syndrome (CSS) in a patient receiving pranlukast. *Clin Rheumatol* 2003; **22:** 491–2.
2. Katsura T, *et al.* The Churg-Strauss syndrome after pranlukast treatment in a patient not receiving corticosteroids. *Ann Intern Med* 2003; **139:** 386–7.
3. Shimbo J, *et al.* Churg-Strauss syndrome and the leukotriene receptor antagonist pranlukast. *Clin Rheumatol* 2005; **24:** 661–2.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Onon; ***Mex.:*** Azlaire; ***Venez.:*** Azlaire.

Procaterol Hydrochloride *(BANM, USAN, rINNM)* ⊗

CI-888; Hidrocloruro de procaterol; OPC-2009; Procatérol, Chlorhydrate de; Procateroli Hydrochloridum; Prokaterolhydroklorid; Prokaterolihydrokloridi. (±)-*erythro*-8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)quinolin-2(1*H*)-one hydrochloride; (±)-8-Hydroxy-5-[(1*R**,2*S**)-1-hydroxy-2-isopropylaminobutyl]-2-quinolone hydrochloride.

Прокатерола Гидрохлорид

$C_{16}H_{22}N_2O_3,HCl$ = 326.8.
CAS — 72332-33-3 (procaterol); 59828-07-8 (procaterol hydrochloride).
ATC — R03AC16; R03CC08.
ATC Vet — QR03AC16; QR03CC08.

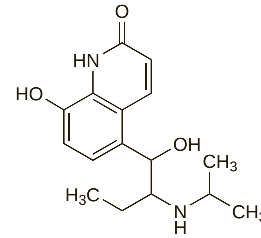

(procaterol)

NOTE. Commercial procaterol hydrochloride is the hemihydrate ($C_{16}H_{22}N_2O_3,HCl,½H_2O$ = 335.8).

Pharmacopoeias. *Chin.* and *Jpn* include the hemihydrate.

Profile

Procaterol hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenoceptor stimulant activity selective to $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131) and it is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112). On inhalation it produces an effect within 5 minutes and the effect can last up to 8 hours.

To relieve acute bronchospasm, a usual dose of 20 micrograms of procaterol hydrochloride is given by inhalation from a metered-dose aerosol or dry powder inhaler up to 4 times daily. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, procaterol indicates deterioration of asthma control and the need for review of therapy. An inhalation solution containing 100 micrograms/mL has been given via a nebuliser in usual doses of 30 to 50 micrograms. Procaterol hydrochloride can also be given orally in doses of 50 micrograms once or twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Lontermin; ***Hong Kong:*** Meptin; ***Hung.:*** Lontermin†; ***Indon.:*** Ataroc; Meptin; ***Ital.:*** Procadil; Propulm; ***Jpn:*** Meptin; ***Malaysia:*** Meptin; ***Philipp.:*** Meptin; ***Port.:*** Onsudil; ***S.Afr.:*** Normalin†; ***Singapore:*** Meptin; ***Spain:*** Onsukil†; ***Thai.:*** Caterol; Meptin.

Proxyphylline *(BAN, rINN)*

Proksifilinas; Proksifylliini; Proxifilina; Proxifillin; Proxifyllin; Proxyfylin; Proxyphyllinum. 7-(2-Hydroxypropyl)-1,3-dimethylxanthine; (*RS*)-1,3-Dimethyl-7-(2-hydroxypropyl)purine-2,6(3*H*,1*H*)-dione; 7-(2-Hydroxypropyl)theophylline.

Проксифиллин

$C_{10}H_{14}N_4O_3$ = 238.2.
CAS — 603-00-9.
ATC — R03DA03.
ATC Vet — QR03DA03.

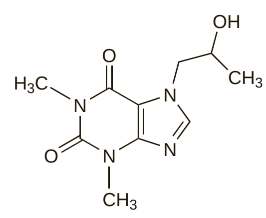

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Proxyphylline). A white or almost white, crystalline powder. Very soluble in water; soluble in alcohol. Protect from light.

Profile

Proxyphylline is a derivative of theophylline (p.1140) which is used as a bronchodilator and for its cardiovascular properties. Proxyphylline is readily absorbed from the gastrointestinal tract and it is not converted to theophylline in the body.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Purofilina†.

Multi-ingredient: ***Austria:*** Asthma Efeum; Omega; ***Braz.:*** Santussal; ***Ger.:*** Antihypertonicum S; ***Spain:*** Novofilin†.

Repirinast *(USAN, rINN)*

MY-5116; Répirinast; Repirinastum. Isopentyl 5,6-dihydro-7,8-dimethyl-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate.

Репиринаст

$C_{20}H_{21}NO_5$ = 355.4.

CAS — 73080-51-0.

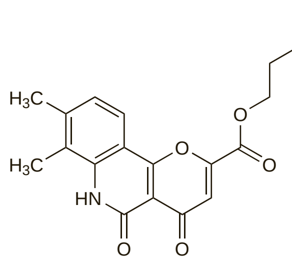

Profile

Repirinast is an orally active anti-allergic with a stabilising action on mast cells resembling that of sodium cromoglicate (p.1136). It has been given orally in the management of asthma (p.1108).

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Romet†.

Reproterol Hydrochloride *(BANM, USAN, rINNM)* ⊗

D-1959 (reproterol); Hidrocloruro de reproterol; Réprotérol, Chlorhydrate de; Reproteroli Hydrochloridum; W-2946M. 7-{3-[(3,5,β-Trihydroxyphenethyl)amino]propyl}theophylline hydrochloride.

Репротерола Гидрохлорид

$C_{18}H_{23}N_5O_5,HCl$ = 425.9.

CAS — 54063-54-6 (reproterol); 13055-82-8 (reproterol hydrochloride).

ATC — R03AC15; R03CC14.

ATC Vet — QR03AC15; QR03CC14.

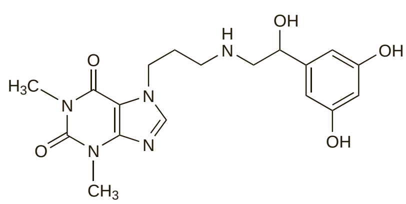

(reproterol)

Profile

Reproterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131).

Reproterol hydrochloride is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112).

For the relief of acute attacks of bronchospasm the usual dose of reproterol hydrochloride is 1 or 2 inhalations of 500 micrograms from a metered-dose aerosol repeated every 3 to 6 hours as required. Reproterol is often used with sodium cromoglicate in combined preparations. In patients with asthma, 'as-required' beta agonist therapy is preferable to regular use. An increased need for, or decreased duration of effect of, reproterol indicates deterioration of asthma control and the need for review of therapy. It has also been given orally: adult doses are 10 to 20 mg three times daily. A slow intravenous injection of 90 micrograms, repeated after 10 minutes if necessary, has been used in the treatment of status asthmaticus.

For doses of reproterol used in children, see Administration in Children, below.

Administration in children. Reproterol hydrochloride has been given via a metered-dose aerosol to relieve bronchospasm in children from 6 years of age at the same dose used in adults (see Uses and Administration, above). Reproterol is often used with sodium cromoglicate in combined preparations.

Reproterol hydrochloride has also been given orally to children from 6 years of age at a dose of 10 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Bronchospasmin; ***Ital.:*** Broncospasmine†.

Multi-ingredient: *Ger.:* Aarane N; Allergospasmin; ***Switz.:*** Aarane†; Allergospasmine†.

Roflumilast *(USAN, rINN)*

APTA-2217; B-9302-107; BY-217; BYK-20869; Roflumilastum. 3-(Cyclopropylmethoxy)-*N*-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide.

Рофлумиласт

$C_{17}H_{14}Cl_2F_2N_2O_3$ = 403.2.

CAS — 162401-32-3.

ATC — R03DX07.

ATC Vet — QR03DX07.

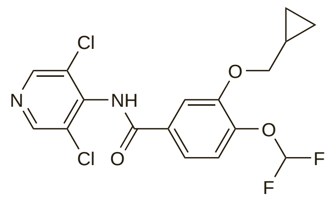

Profile

Roflumilast is a phosphodiesterase type-4 inhibitor. It is under investigation in the treatment of asthma and chronic obstructive pulmonary disease.

◊ References.

1. Spina D. Phosphodiesterase-4 inhibitors in the treatment of inflammatory lung disease. *Drugs* 2003; **63:** 2575–94.
2. Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. *Lancet* 2005; **365:** 167–75.
3. Rabe KF, *et al.* Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2005; **366:** 563–71.
4. Karish SB, Gagnon JM. The potential role of roflumilast: the new phosphodiesterase-4 inhibitor. *Ann Pharmacother* 2006; **40:** 1096–1104.
5. Bateman ED, *et al.* Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 679–86.
6. Calverley PM, *et al.* Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **176:** 154–61.
7. Hermann R, *et al.* Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet* 2007; **46:** 403–16.
8. Bethke TD, *et al.* Dose-proportional intraindividual single- and repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. *J Clin Pharmacol* 2007; **47:** 26–36.
9. Field SK. Roflumilast: an oral, once-daily selective PDE-4 inhibitor for the management of COPD and asthma. *Expert Opin Invest Drugs* 2008; **17:** 811–8.

Salbutamol *(BAN, rINN)* ⊗

AH-3365; Albuterol *(USAN)*; Salbutamoli; Salbutamolis; Salbutamolum; Sch-13949W; Szalbutamol. 2-*tert*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol.

Сальбутамол

$C_{13}H_{21}NO_3$ = 239.3.

CAS — 18559-94-9.

ATC — R03AC02; R03CC02.

ATC Vet — QR03AC02; QR03CC02.

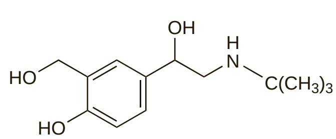

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*
Ph. Eur. 6.2 (Salbutamol). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.
USP 31 (Albuterol). A white crystalline powder. Sparingly soluble in water; soluble in alcohol. Protect from light.

Salbutamol Sulfate *(rINNM)* ⊗

Albuterol Sulfate *(USAN)*; Salbutamol Hemisulphate; Salbutamol, sulfate de; Salbutamol Sulphate *(BANM)*; Salbutamoli sulfas; Salbutamolio sulfatas; Salbutamolisulfaatti; Salbutamolsulfat; Salbutamol-sulfát; Salbutamolu siarczan; Sulfato de salbutamol; Szalbutamol-szulfát.

Сальбутамола Сульфат

$(C_{13}H_{21}NO_3)_2,H_2SO_4$ = 576.7.
CAS — 51022-70-9.
ATC — R03AC02; R03CC02.
ATC Vet — QR03AC02; QR03CC02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*
Ph. Eur. 6.2 (Salbutamol Sulphate). A white or almost white crystalline powder. Freely soluble in water; practically insoluble or very slightly soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Albuterol Sulfate). A white or practically white powder. Freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether. Protect from light.

Stability. For mention of the stability of a 1:1 mixture of salbutamol and ipratropium nebuliser solutions, see under Ipratropium, p.1124.

Adverse Effects

As for Sympathomimetics, p.1407. Salbutamol has mainly beta-agonist effects and, like other beta agonists, may cause fine tremor of skeletal muscle (particularly the hands), palpitations, tachycardia, nervous tension, headaches, peripheral vasodilatation, and rarely muscle cramps. Inhalation causes fewer adverse effects than systemic dosage, and the more selective $beta_2$ agonists cause fewer adverse effects than less selective beta agonists. Potentially serious hypokalaemia has been reported after large doses. Myocardial ischaemia has also been reported. Hypersensitivity reactions have occurred, including paradoxical bronchospasm, angioedema, urticaria, hypotension, and collapse.

The high doses of salbutamol used intravenously to delay premature labour have additionally been associated with nausea and vomiting, and with severe adverse cardiac and metabolic effects and pulmonary oedema.

Effects on the CNS. Visual hallucinations lasting for an hour have been reported[1] after use of nebulised salbutamol in an elderly patient. At the time of the report the manufacturers were aware of 3 cases of hallucinations in children given oral salbutamol but no such reaction had been previously reported in adults given recommended doses.

Hyperactivity and restlessness have been reported with the use of salbutamol; however, a small placebo-controlled study of 19 children,[2] failed to show a statistically significant difference in activity levels after a nebulised dose of salbutamol.

1. Khanna PB, Davies R. Hallucinations associated with the administration of salbutamol via a nebuliser. *BMJ* 1986; **292:** 1430.
2. Hadjikoumi I, *et al.* Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002; **86:** 202–4. Also available at: http://adc.bmj.com/cgi/reprint/86/3/202 (accessed 15/01/08)

Effects on electrolytes and metabolism. Salbutamol, in common with other $beta_2$-agonists, may cause *hypokalaemia* and *hyperglycaemia*. These effects are related to the dose and route of salbutamol used; hypokalaemia is more common after parenteral and nebulised use. Hypokalaemia may be potentiated by therapy with corticosteroids, diuretics, or xanthines, and by hypoxia; potassium concentrations should therefore be monitored in severe asthma.

Effects on the eyes. It has been suggested that salbutamol and to a greater extent ritodrine may contribute to retinopathy in the premature infant when used for premature labour.[1]

A case of acute angle-closure glaucoma was attributed to dilatation of the pupil by stimulation of the sympathetic nervous system secondary to local absorption of nebulised salbutamol in the eye; the patient also had other risk factors for developing glaucoma.[2] For reports of glaucoma precipitated by the combined use of ipratropium bromide and salbutamol via a nebuliser, see Ipratropium Bromide, p.1124.

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71:** F149.
2. Rho DS. Acute angle-closure glaucoma after albuterol nebulizer treatment. *Am J Ophthalmol* 2000; **130:** 123–4.

Effects on the heart. The main adverse cardiac effect of salbutamol is tachycardia due to increased sympathetic effects on the cardiovascular system. Such tachycardia is dose dependent and is more common after systemic than inhaled therapy. A meta-analysis[1] of randomised, placebo-controlled studies in patients with asthma or chronic obstructive pulmonary disease (COPD) confirmed that single doses of $beta_2$ agonists can cause an increase in heart rate and a reduction in potassium concentrations (see also Effects on Electrolytes and Metabolism, above). The longer-term effects of beta$_2$ agonists on the cardiovascular system were also assessed and an increased risk of adverse cardiovascular events due to sinus tachycardia was found. There was also a trend towards an increase in major adverse events including ventricular tachycardia, atrial fibrillation, syncope, heart failure, myocardial infarction, cardiac arrest, and sudden death. Myocardial ischaemia has been reported in association with salbutamol when used to delay premature labour.[2] Eleven of 17 reports were considered serious, including one fatality. Most of these reports involved the use of parenteral formulations; none involved the use of inhaled salbutamol formulations for the relief of bronchospasm. However, there is some evidence that high doses of inhaled salbutamol can decrease coronary flow reserve, and might exacerbate ischaemia in patients with coronary artery disease.[3] Case-control studies[4,5] have also suggested that the use of inhaled beta$_2$ agonists is associated with an increased risk of myocardial infarction, and another case-control study[6] found an increased risk of cardiac arrest in patients with asthma being treated with inhaled short-acting beta$_2$ agonists, but not in those with COPD. In contrast, however, a cohort study[7] of patients with COPD found no increase in the risk of myocardial infarction associated with the use of beta$_2$ agonists given by inhalation, nebulisation, or mouth. Case-control and cohort studies have also suggested that patients with pre-existing heart failure may be at increased risk of hospitalisation from arrhythmias[8] or exacerbation of heart failure[9,10] with the use of beta$_2$ agonists.

A causal relationship cannot necessarily be established from these case-control and cohort studies, however, because of confounding factors such as co-morbidity, and because the extent of beta$_2$ agonist use could only be estimated from prescription record systems.

See also Pregnancy, below.

1. Salpeter SR, *et al.* Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; **125:** 2309–21.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Kochiadakis GE, *et al.* Effect of inhaled salbutamol on coronary circulation in humans. *Int J Cardiol* 2007; **117:** 408–10.
4. Au DH, *et al.* The risk of myocardial infarction associated with inhaled β-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000; **161:** 827–30.
5. Au DH, *et al.* Association between inhaled β-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002; **121:** 846–51.
6. Lemaitre RN, *et al.* Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002; **113:** 711–16.
7. Suissa S, *et al.* Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003; **58:** 43–6.
8. Bouvy ML, *et al.* Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med* 2000; **160:** 2477–80.
9. Au DH, *et al.* Risk of mortality and heart failure exacerbations associated with inhaled β-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003; **123:** 1964–9.
10. Au DH, *et al.* Association between chronic heart failure and inhaled β-2-adrenoceptor agonists. *Am Heart J* 2004; **148:** 915–20.

Effects on the respiratory system. Paradoxical bronchoconstriction has occasionally been reported after bronchodilating therapy. With nebuliser solutions, it has been suggested that the preservatives present could be responsible (see also under Ipratropium, p.1124), or that the pH may contribute if non-neutral. In addition, regular use of beta$_2$ agonists such as salbutamol (as opposed to use on an as-needed basis) has been shown to increase airway hyperresponsiveness to various stimuli and to lead to the possible development of tolerance to the bronchoprotective effect (see below).

The increased risk of pulmonary oedema associated with salbutamol is mentioned under Pulmonary Oedema, below.

Increased mortality. The increased incidence of morbidity and mortality that occurred in asthmatic patients mainly involved fenoterol, but salbutamol has been implicated. The debate on the relevance of beta agonist therapy to this increased morbidity and mortality is discussed under Fenoterol on p.1121.

Overdosage. Reports of overdosage with salbutamol[1-6] have generally only described the features that may be expected with beta$_2$ agonists such as tachycardia, CNS stimulation, tremor, hypokalaemia, and hyperglycaemia. Symptomatic treatment of the adverse effects has proved successful although it is unlikely to be required after repeated inhalation. Activated charcoal may be considered after oral overdose in patients who have taken a potentially toxic amount and present within 1 hour. The plasma-potassium concentration and pulse rate have been found to correlate with the plasma concentration of salbutamol.[7]

1. Morrison GW, Farebrother MJB. Overdose of salbutamol. *Lancet* 1973; **ii:** 681.
2. O'Brien IAD, *et al.* Hypokalaemia due to salbutamol overdosage. *BMJ* 1981; **282:** 1515–16.
3. Prior JG, *et al.* Self-poisoning with oral salbutamol. *BMJ* 1981; **282:** 1932.
4. Connell JMC, *et al.* Metabolic consequences of salbutamol poisoning reversed by propranolol. *BMJ* 1982; **285:** 779.
5. Spiller HA, *et al.* A two-year retrospective study of accidental pediatric albuterol ingestions. *Pediatr Emerg Care* 1993; **9:** 338–40.
6. Leikin JB, *et al.* Hypokalemia after pediatric albuterol overdose: a case series. *Am J Emerg Med* 1994; **12:** 64–6.
7. Lewis LD, *et al.* A study of self poisoning with oral salbutamol—laboratory and clinical features. *Hum Exp Toxicol* 1993; **12:** 397–401. Correction. *ibid.* 1994; **13:** 371.

Pregnancy. Most adverse effects associated with salbutamol in pregnancy relate to the cardiovascular and metabolic effects of the very high doses given by intravenous infusion in attempts to delay premature labour (see also under Pulmonary Oedema, below). Maternal effects include myocardial ischaemia,[1,2] unifocal ventricular ectopics associated with the hypokalaemic response to intravenous salbutamol,[3] and heart failure in a hypertensive woman.[4] Similarly, serious fetal and neonatal cardiovascular complications have also been associated with tocolytic salbutamol.[5]

Metabolic acidosis after salbutamol infusions in diabetic women has also been reported.[6,7]

For reports of retinopathy in the infant see Effects on the Eyes above.

1. Whitehead MI, *et al.* Myocardial ischaemia after withdrawal of salbutamol for pre-term labour. *Lancet* 1979; **ii:** 904.
2. GlaxoSmithKline, Canada. Health Canada endorsed important safety information on Ventolin I.M. injection and Ventolin I.V. infusion solution: for pregnant women & labour and delivery (issued 12th June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ventolin_hpc-cps-eng.pdf (accessed 09/07/08)
3. Chew WC, Lew LC. Ventricular ectopics after salbutamol infusion for preterm labour. *Lancet* 1979; **ii:** 1383–4.
4. Whitehead MI, *et al.* Acute congestive cardiac failure in a hypertensive woman receiving salbutamol for premature labour. *BMJ* 1980; **280:** 1221–2.
5. Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from β-sympathomimetic therapy for tocolysis. *Am J Obstet Gynecol* 1989; **161:** 1–4.
6. Chapman MG. Salbutamol-induced acidosis in pregnant diabetics. *BMJ* 1977; **1:** 639–40.
7. Thomas DJB, *et al.* Salbutamol-induced diabetic ketoacidosis. *BMJ* 1977; **2:** 438.

Pulmonary oedema. Pulmonary oedema has occurred in women given beta$_2$ agonists, including salbutamol,[1-4] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions, below.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110:** 714–18.
3. Chapuis C, *et al.* Œdème aigu du poumon au décours d'une tocolyse par nicardipine et salbutamol lors d'une menace d'accouchement prématuré sur grossesse gémellaire. *J Gynecol Obstet Biol Reprod (Paris)* 2005; **34:** 493–6.
4. Hamel H, *et al.* Œdème pulmonaire et tocolyse par bêta-mimétiques. *Rev Mal Respir* 2002; **19:** 241–4.

Tolerance. Some studies suggest that regular inhalation of a short-acting beta$_2$ agonist, although it continues to produce bronchodilatation, increases airway hyperresponsiveness and may reduce the protective effect against bronchoconstriction provoked by stimuli such as bradykinin, methacholine, or allergen.[1-6] Such tolerance is considered another argument against regular use of short-acting drugs.[1] Reduced bronchoprotective effects have also been demonstrated with long-acting beta$_2$ agonists (see Salmeterol, p.1135).

It has been suggested that reduced benefit with salbutamol may be due to the *S*(+)-enantiomer,[7,8] which unlike the *R*(−)-enantiomer (levosalbutamol, p.1125) does not possess bronchodilating activity. Stereoselective metabolism (see under Pharmacokinetics, below) means that regular use of the racemate could lead to accumulation of the *S*-enantiomer, which provides a possible mechanism for the effect. Genetic polymorphism of the beta$_2$-adrenoceptor has also been proposed as another possible mechanism.[9,10]

1. Cockcroft DW, *et al.* Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; **342:** 833–7.
2. O'Connor BJ, *et al.* Tolerance to the nonbronchodilator effects of inhaled β -agonists in asthma. *N Engl J Med* 1992; **327:** 1204–8.
3. Cockcroft DW, *et al.* Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995; **96:** 44–9.
4. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; **153:** 65–9.
5. Crowther SD, *et al.* Varied effects of regular salbutamol on airway responsiveness to inhaled spasmogens. *Lancet* 1997; **350:** 1450.
6. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.
7. Perrin-Fayolle M. Salbutamol in the treatment of asthma. *Lancet* 1995; **346:** 1101.
8. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of β agonists. *J Allergy Clin Immunol* 1999; **104** (suppl): S69–S76.
9. Israel E, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004; **364:** 1505–12.
10. Broadley KJ. β-Adrenoceptor responses of the airways: for better or worse? *Eur J Pharmacol* 2006; **533:** 15–27.

Precautions

Salbutamol and other beta agonists should be given with caution in hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, and diabetes mellitus (especially on intravenous use—blood glucose should be monitored since ketoacidosis has been reported).

In *severe asthma* particular caution is also required to avoid inducing hypokalaemia as this effect may be potentiated by hypoxia or by the effect of other anti-asthma drugs on potassium (see Interactions, below); plasma-potassium concentrations should be monitored.

Beta$_2$ agonists such as salbutamol are not appropriate for use alone in the treatment of more than mild asthma (see Asthma, p.1108). Increasing need for, or decreased duration of effect of, inhaled salbutamol and other short-acting beta$_2$ agonists indicates deterioration of asthma control and the likely requirement for increased anti-inflammatory therapy.

In *women being treated for premature labour* the risk of pulmonary oedema means that the patient's state of hydration and cardiac and respiratory function should be monitored very carefully; the volume of infusion fluid should be kept to the minimum (normally using glucose 5% as the diluent), and beta$_2$-agonist therapy should be stopped immediately and diuretic therapy started if signs of pulmonary oedema develop. Other risk factors for pulmonary oedema include multiple pregnancy and heart disease. Ischaemic heart disease or significant risk factors for ischaemic heart disease are specific contra-indications; where heart disease is suspected assessment by a physician experienced in cardiology is needed. Eclampsia and severe pre-eclampsia are also contra-indications, with special care needed in mild to moderate pre-eclampsia. Other contra-indications include intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (which requires immediate delivery), placenta praevia, and cord compression; beta$_2$ agonists should not be used for threatened miscarriage. See also Uses and Administration, below.

For details of the precautions to be observed with sympathomimetics in general, see p.1407.

Abuse. Salbutamol inhalers have been subject to abuse, particularly by children and young adults.[1-5] This has occurred in both asthmatic and non-asthmatic individuals and has been thought to be for the effect of sympathetic stimulation and for the effect of the fluorocarbon propellants. The introduction of fluorocarbon-free inhalers should reduce the latter motivation, although not the former.

1. Brennan PO. Inhaled salbutamol: a new form of drug abuse? *Lancet* 1983; **ii:** 1030–1.
2. Thompson PJ, *et al.* Addiction to aerosol treatment: the asthmatic alternative to glue sniffing. *BMJ* 1983; **287:** 1515–16.
3. Brennan PO. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
4. Wickramasinghe H, Liebeschuetz HJ. Addiction to aerosol treatment. *BMJ* 1983; **287:** 1877.
5. O'Callaghan C, Milner AD. Aerosol treatment abuse. *Arch Dis Child* 1988; **63:** 70.

Interactions

Use of salbutamol and other beta$_2$ agonists with corticosteroids, diuretics, or xanthines increases the risk of hypokalaemia, and monitoring of potassium concentrations is recommended in severe asthma, where such combination therapy is common (see also Effects on Electrolytes and Metabolism, above). For an outline of interactions associated with sympathomimetics in general, see p.1407.

Beta$_2$ agonists. Patients receiving *salmeterol* may require salbutamol to control an acute attack of bronchospasm. One study indicated that the effects might be additive,[1] but another showed that patients receiving salmeterol had reduced sensitivity to salbutamol and might need higher doses of the latter for acute relief.[2] However, a study in asthmatics admitted to a hospital emergency department with acute exacerbations of their illness, found that previous salmeterol therapy did not reduce the effectiveness of standard doses of salbutamol.[3] Others have also noted attenuation of the bronchoprotective effects of a beta$_2$ agonist (in this case, *fenoterol*) by salmeterol.[4]

1. Smyth ET, *et al.* Interaction and dose equivalence of salbutamol and salmeterol in patients with asthma. *BMJ* 1993; **306:** 543–5.

2. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995; **346:** 201–6.
3. Korosec M, *et al.* Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999; **107:** 209–13.
4. van Veen A, *et al.* Regular use of long-acting β -adrenoceptor agonists attenuates the bronchoprotective efficacy of short-acting β -adrenoceptor agonists in asthma. *Br J Clin Pharmacol* 2000; **50:** 499P.

Beta blockers. Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators and are contra-indicated in asthmatic patients as they may cause serious bronchoconstriction, even if given as eye drops. No adverse interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers; however, bronchospasm can sometimes occur in asthmatic patients, particularly if high doses are used. In a case-control study in postoperative coronary artery bypass graft patients, use of sotalol with salbutamol led to an increased risk for postoperative atrial fibrillation.[1]

1. Vader C, *et al.* Interaction between sotalol and albuterol after CABG: influence on postoperative arrhythmias and length of stay at an intensive care unit. *Br J Clin Pharmacol* 2002; **53:** 555P–556P.

Cardiac glycosides. Hypokalaemia produced by beta$_2$ agonists may result in an increased susceptibility to digitalis-induced arrhythmias although salbutamol intravenously and by mouth can also decrease serum concentrations of *digoxin* (see Beta$_2$ Agonists, p.1262).

Corticosteroids. Corticosteroids and beta$_2$ agonists may both produce falls in plasma potassium concentrations; there is evidence that such falls can be exacerbated by use together.[1] The possibility of enhanced hyperglycaemic effects from such a combination should also be borne in mind.

It has been suggested that in acute severe asthma, corticosteroids may modify beta receptors, reversing the beta receptor desensitisation and downregulation caused by beta$_2$ agonists and enhancing the bronchodilator response.[2] In chronic asthma there is little evidence to support this theory; however, combination therapy with corticosteroids and beta$_2$ agonists has been found to have beneficial effects on asthma control; the exact mechanism for this remains unclear.

1. Taylor DR, *et al.* Interaction between corticosteroid and beta-agonist drugs: biochemical and cardiovascular effects in normal subjects. *Chest* 1992; **102:** 519–24.
2. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. *Thorax* 2000; **55:** 595–602.

Diuretics. Hypokalaemia is known to be a possible adverse effect during treatment with beta$_2$ agonists such as salbutamol or terbutaline, and this may be enhanced if diuretics are also given;[1,2] in addition the arrhythmogenic potential of this interaction may be clinically important in patients with ischaemic heart disease.[1]

1. Lipworth BJ, *et al.* Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med* 1989; **86:** 653–7.
2. Newnham DM, *et al.* The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* 1991; **32:** 630–2.

Neuromuscular blockers. Salbutamol given intravenously has been reported to enhance the neuromuscular blockade produced by *pancuronium* and by *vecuronium* (see Sympathomimetics, p.1905).

Xanthines. An enhanced hypokalaemic effect may occur when salbutamol is given with *theophylline*.[1,2] See also under Terbutaline, p.1139 and Sympathomimetics, under Theophylline, p.1145 for the potentiation of other effects.

1. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
2. Kolski GB, *et al.* Hypokalemia and respiratory arrest in an infant with status asthmaticus. *J Pediatr* 1988; **112:** 304–7.

Pharmacokinetics

Salbutamol is readily absorbed from the gastrointestinal tract. When given by inhalation, 10 to 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is swallowed and absorbed from the gut.

Salbutamol is subject to first-pass metabolism in the liver and possibly in the gut wall but does not appear to be metabolised in the lung; the main metabolite is the inactive sulfate conjugate.

Salbutamol is rapidly excreted, mainly in the urine, as metabolites and unchanged drug; a smaller proportion is excreted in the faeces.

The plasma half-life of salbutamol has been estimated to range from 4 to 6 hours.

◊ General references.

1. Walker SR, *et al.* The clinical pharmacology of oral and inhaled salbutamol. *Clin Pharmacol Ther* 1972; **13:** 861–7.
2. Hetzel MR, Clark TJH. Comparison of intravenous and aerosol salbutamol. *BMJ* 1976; **2:** 919.
3. Lin C, *et al.* Isolation and identification of the major metabolite of albuterol in human urine. *Drug Metab Dispos* 1977; **5:** 234–8.
4. Morgan DJ, *et al.* Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986; **22:** 587–93.
5. Lipworth BJ, *et al.* Single dose and steady-state pharmacokinetics of 4 mg and 8 mg oral salbutamol controlled-release in patients with bronchial asthma. *Eur J Clin Pharmacol* 1989; **37:** 49–52.
6. Rey E, *et al.* Pharmacokinetics of intravenous salbutamol in renal insufficiency and its biological effects. *Eur J Clin Pharmacol* 1989; **37:** 387–9.
7. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; **34:** 311–15.
8. Milliez JM, *et al.* Pharmacokinetics of salbutamol in the pregnant woman after subcutaneous administration with a portable pump. *Obstet Gynecol* 1992; **80:** 182–5.

Stereoselectivity. The *R*(–)-enantiomer of salbutamol (levosalbutamol—p.1125) is preferentially metabolised and is therefore cleared from the body more rapidly than the *S*(+)-enantiomer, which lacks bronchodilator activity but may be implicated in some of the adverse effects of salbutamol (see Tolerance, under Adverse Effects, above).

References.

1. Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41:** 35–40.
2. Boulton DW, *et al.* Transplacental distribution of salbutamol enantiomers at Caesarian section. *Br J Clin Pharmacol* 1997; **44:** 587–90.
3. Lipworth BJ, *et al.* Pharmacokinetics and extrapulmonary β adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997; **52:** 849–52.
4. Ward JK, *et al.* Enantiomeric disposition of inhaled, intravenous and oral racemic-salbutamol in man — no evidence of enantioselective lung metabolism. *Br J Clin Pharmacol* 2000; **49:** 15–22.

Uses and Administration

Salbutamol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist—p.1108). This results in its bronchodilating action being more prominent than its effect on the heart.

Salbutamol and salbutamol sulfate are used as bronchodilators in the management of reversible airways obstruction, as in asthma and in some patients with chronic obstructive pulmonary disease. Salbutamol also decreases uterine contractility and may be given as the sulfate to arrest premature labour (p.2003).

Inhalation results in the rapid onset (within 5 minutes) of bronchodilatation, which lasts for about 3 to 6 hours. After oral doses, the onset of action is within 30 minutes, with a peak effect between 2 to 3 hours after the dose, and a duration of action of up to 6 hours; modified-release preparations that have a longer duration of action are available.

Salbutamol is used as the base or sulfate in aerosol inhalers and as the sulfate in other preparations. The dosage is expressed in terms of salbutamol base; salbutamol sulfate 1.2 mg is equivalent to about 1 mg of salbutamol.

For the relief of **acute bronchospasm**, 1 or 2 inhalations of salbutamol 100 micrograms may be given from a conventional *metered-dose aerosol* as required, up to 4 times daily. Two inhalations may also be given just before exertion for the prophylaxis of exercise-induced bronchospasm. (In the USA these inhalations may be expressed as supplying 100 micrograms, the amount delivered *into* the mouthpiece, or 90 micrograms, the amount delivered *from* the mouthpiece.) Current asthma guidelines (see p.1108) recommend that inhaled short-acting beta$_2$ agonists such as salbutamol be used on an as-required, not regular, basis. In those patients requiring more than occasional use of salbutamol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, salbutamol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy. Salbutamol sulfate is now available in chlorofluorocarbon (CFC)-free aerosols. Doses for these aerosols (expressed in terms of salbutamol) are the same as for conventional aerosols.

Salbutamol may also be inhaled as the sulfate from dry powder *inhalation capsules* or *discs*, particularly by patients who experience difficulty in using aerosol formulations. Owing to differences in the relative bioavailability to the lungs between these dry powder systems and the inhalation aerosol a 200-microgram dose (expressed in terms of salbutamol) from an inhalation capsule or disc is about equivalent in activity to a 100-microgram dose from a conventional aerosol; usual recommended doses are 200 or 400 micrograms up to four times daily.

When inhalation is ineffective, *oral* salbutamol may be given in a dose of 2 to 4 mg three or four times daily as the sulfate; some patients may require doses of up to 8 mg three or four times daily, but such increased doses are unlikely to be tolerated or to provide much extra benefit. Elderly patients should be given the lower doses initially. Modified-release preparations are also available; a usual adult dose is 8 mg twice daily.

In more severe or unresponsive bronchospasm salbutamol sulfate may be given intermittently via a *nebuliser* in adults and children. Licensed doses are 2.5 to 5 mg of salbutamol repeated up to 4 times daily; continuous use is also possible, usually at a rate of 1 to 2 mg/hour. However, guidelines allow for more frequent use or continuous use at a higher rate in acute severe asthma (see under Asthma, p.1108). Single-dose units of 0.1% or 0.2%, or a concentrated solution of salbutamol 0.5%, are available for nebulisation. Continuous use is usually as a 0.005 to 0.01% solution in sodium chloride 0.9%. Patients with acute severe asthma may require supplemental oxygen.

In acute severe asthma where delivery via nebuliser is not available, 4 to 6 inhalations of salbutamol 100 micrograms from a metered-dose inhaler may be given at intervals of 10 to 20 minutes via a large volume spacer.

In the management of a severe attack of bronchospasm a slow *intravenous injection* of salbutamol 250 micrograms as a solution containing 50 micrograms/mL as the sulfate may be required; alternatively salbutamol may be given by intravenous infusion of a solution containing 5 mg in 500 mL (10 micrograms/mL) at a usual rate of 3 to 20 micrograms/minute according to the patient's need; higher dosages have been used in patients with respiratory failure.

Salbutamol sulfate can also be given for bronchospasm by *subcutaneous* or *intramuscular* injection in doses of salbutamol 500 micrograms every 4 hours as required.

For the arrest of uncomplicated **premature labour** between 24 and 33 weeks of gestation salbutamol sulfate is given by *intravenous infusion*, preferably with the aid of a syringe pump at a concentration of 200 micrograms/mL of salbutamol in glucose 5%. If no syringe pump is available then the infusion should be with a more dilute solution of 20 micrograms/mL in glucose 5%. The same dose is used as with the syringe pump. The recommended initial rate of infusion is 10 micrograms/minute increased at intervals of 10 minutes until there is a response; the rate is then increased slowly until contractions cease. The usual effective dose is 10 to 45 micrograms/minute. The infusion should be maintained at the rate at which contractions cease for 1 hour, then reduced by decrements of 50% at intervals of 6 hours. Prolonged therapy should be avoided as the risks to the mother (see Precautions, above) increase after 48 hours, and there is a lack of evidence of benefit from further treatment.

The maternal pulse should be monitored throughout the infusion and the infusion rate adjusted to avoid a maternal heart rate of more than 140 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema.

Salbutamol may subsequently be given *orally* in a dose of 4 mg three or four times daily but such usage is not recommended by the *BNF*, given the problems with prolonged therapy already mentioned.

For doses of salbutamol used in children, see Administration in Children below.

Administration. Beta$_2$ agonists are used extensively in the management of reversible airways obstruction. A common, effective, and convenient method of dosage is by a pressurised aerosol inhaler. With this route relief is provided rapidly and fewer systemic adverse effects are likely to occur than with oral use. It is important that patients using conventional inhalers employ the correct technique, which involves coordinating actuation of the aerosol with inhalation; if patients have difficulty with this, alternatives are available. Spacer devices may be used with inhalers. These are added on to the inhaler and reduce the velocity of the aerosol; also more propellant may evaporate before inhalation allowing a greater proportion of the drug to reach the lungs, and coordination of actuation of the aerosol and inhalation is less important. Breath-actuated aerosol inhalers and dry powder inhalers are also available and are actuated by the patient's inspiration and thus avoid entirely the need for coordination of actuation and inhalation; however, inhalation of the dry powder has occasionally caused irritation of the throat or coughing.

The oral route can be used although generally a form of inhaled therapy as described above is preferable. Formulations intended for oral use are commercially available, including modified-release formulations. Nebulisation is an alternative method of delivery and this may be used in the management of severe acute attacks as may parenteral therapy.

Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Conventional and breath-actuated HFA preparations are available. HFA aerosols may feel and taste different to CFC aerosols.

Administration in children. For the treatment of reversible airways obstruction, including nocturnal asthma, and prevention of exercise-induced **bronchospasm** in children, the *BNFC* suggests the following doses:

by aerosol inhalation

- 1 month to 18 years of age, 100 or 200 micrograms (1 or 2 inhalations) up to four times daily, for occasional use only

by inhalation of dry powder from inhalation capsules or discs

- 5 to 12 years of age, 200 micrograms up to four times daily, for occasional use only
- over 12 years of age, doses as for adults, see Uses and Administration, above

Inhaled therapy is generally considered first-line treatment, but oral therapy may be necessary if an inhaler device cannot be used. In the UK salbutamol syrup is licensed for children from 2 years of age and modified-release oral preparations from 3 years of age.

by mouth using an immediate-release preparation

- 1 month to 2 years of age, 100 micrograms/kg (up to a maximum dose of 2 mg) three or four times daily
- 2 to 6 years of age, 1 to 2 mg three or four times daily
- 6 to 12 years of age, 2 mg three or four times daily
- over 12 years of age, doses as for adults, see Uses and Administration, above

by mouth using a modified-release preparation

- 3 to 12 years of age, 4 mg twice daily
- over 12 years of age, as for adults, see above

In the management of acute mild to moderate **exacerbations** of asthma, salbutamol may be given using a metered-dose aerosol inhaler via a spacer device. For children of all ages, 1 inhalation (100 micrograms) may be given every 15 to 30 seconds up to a maximum of 10 inhalations. The dose may be repeated after 20 to 30 minutes if required. In more severe exacerbations, salbutamol can be given intermittently via a nebuliser. A dose of 2.5 mg, which can be increased to 5 mg in children over 5 years of age, can be repeated every 20 to 30 minutes if necessary. Immediate transfer to hospital and inhalation of oxygen is also required. Children under 18 months of age often respond poorly to bronchodilators; nebulised beta$_2$ agonists have been associated with mild paradoxical bronchospasm and transient worsening of oxygen saturation.

Although parenteral salbutamol is not licensed in the UK for use in children, the *BNFC* recommends the following doses in the management of **acute severe** or life-threatening acute asthma:

by intravenous injection over 5 minutes

- 1 month to 2 years of age, 5 micrograms/kg as a single dose
- 2 to 18 years of age, 15 micrograms/kg (to a maximum of 250 micrograms) as a single dose

by continuous intravenous infusion

- 1 month to 18 years of age, 60 to 300 micrograms/kg per hour, adjusted according to response and heart rate. Doses above 120 micrograms/kg per hour require close monitoring

Salbutamol can be used to treat severe **hyperkalaemia** in children (see Hyperkalaemia below). The *BNFC* recommends:

by intravenous injection over 5 minutes

- children of all ages, 4 micrograms/kg as a single dose; repeated if necessary

by inhalation of nebulised solution (although intravenous injection is preferred)

- children of all ages, 2.5 or 5 mg as a single dose; repeated if necessary

Asthma. Short-acting beta$_2$ agonists such as salbutamol are used for short-term relief in all patients with symptomatic asthma (p.1108). High doses are used in acute asthma, but current recommendations for chronic asthma are for low doses to be inhaled as required rather than regularly. When patients with mild asthma find that symptomatic relief is needed more than 2 or 3 times a week, then that should be a sign for additional treatment with anti-inflammatory drugs. Increasing need for, or decreased effect of, short-acting beta$_2$ agonists indicates deteriorating asthma and the requirement for stepping up therapy. In one placebo-controlled study,[1] patients with stable asthma receiving regular high doses of a short-acting inhaled beta$_2$ agonist were able to reduce the dose considerably with no change in asthma control, lending further support to the recommendation for 'as-required' rather than regular use of these drugs. The discussion under Fenoterol on p.1121 on the increased mortality that has been observed in asthma patients and the connection with asthma therapy includes a view that regular use might have contributed to the increased mortality. However, a systematic review[2] of studies of short-acting beta$_2$ agonists, most of which used salbutamol, found no clear clinical advantage or detriment from regular use compared with taking them as required.

1. Harrison TW, *et al.* Randomised placebo controlled trial of β agonist dose reduction in asthma. *Thorax* 1999; **54:** 98–102.
2. Walters EH, *et al.* Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/01/08).

Bronchiolitis. Acute bronchiolitis (inflammation of the bronchioles associated with viral respiratory-tract infection, usually due to RSV—see p.860) is a poorly defined respiratory condition seen in infants and young children. The diagnostic criteria, and the usual management, vary considerably from country to country. Beta$_2$ agonists such as salbutamol are widely prescribed in the USA, but not in the UK, and attempts to establish their benefits have produced conflicting results.[1] Modest benefit (but no difference in hospital admission rate) has been reported from a meta-analysis of bronchodilator therapy in general,[2] but a meta-analysis of beta$_2$-agonist therapy in bronchiolitis did not show it to be effective.[3] Some comparative studies have suggested that nebulised adrenaline is more effective than salbutamol.[4,5] However, one study in hospitalised children found no benefit from nebulised salbutamol in terms of improved oxygenation or length of hospital stay,[6] and another[7] found no difference in efficacy between nebulised adrenaline, salbutamol, and sodium chloride 0.9%.

The use of oral salbutamol in infants with acute viral bronchiolitis has been found to be no more effective than placebo and so is not recommended.[8]

1. Everard ML. Acute bronchiolitis—a perennial problem. *Lancet* 1996; **348:** 279–80.
2. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 25/01/08).
3. Flores G, Horwitz RI. Efficacy of β -agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997; **100:** 233–9.
4. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
5. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
6. Dobson JV, *et al.* The use of albuterol in hospitalized infants with bronchiolitis. *Pediatrics* 1998; **101:** 361–8.
7. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
8. Patel H, *et al.* Randomized, double-blind, placebo-controlled trial of oral albuterol in infants with mild-to-moderate acute viral bronchiolitis. *J Pediatr* 2003; **142:** 509–14.

Chronic obstructive pulmonary disease. Salbutamol and other beta$_2$ agonist bronchodilators form part of the first-line treatment of chronic obstructive pulmonary disease (p.1112).

Cough. For studies of inhaled salbutamol in the treatment of cough, see under Beclometasone, p.1518.

Hyperkalaemia. Salbutamol can lower plasma-potassium concentrations by promoting intracellular uptake,[1,2] and this effect has been used in treating mild hyperkalaemia (p.1669) associated with chronic disorders such as renal failure[3,4] and hyperkalaemic periodic paralysis.[5] However, such use is controversial: the effects of salbutamol may be inconsistent[6] and some clinicians prefer to avoid the use of beta$_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7]

Salbutamol has been used to lower plasma-potassium concentrations in children[8] and premature neonates[9] with some success. For doses of salbutamol used to treat severe hyperkalaemia in children, see Administration in Children above.

1. Bushe C. Salbutamol for hyperkalaemia. *Lancet* 1983; **ii:** 797.
2. Anonymous. Hyperkalaemia—silent and deadly. *Lancet* 1989; **i:** 1240.
3. Allon M, *et al.* Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; **110:** 426–9.
4. McClure RJ, *et al.* Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994; **70:** 126–8.
5. Wang P, Clausen T. Treatment of attacks in hyperkalaemic familial periodic paralysis by inhalation of salbutamol. *Lancet* 1976; **i:** 221–3.
6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; **33:** 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.
8. Helfrich E, *et al.* Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001; **90:** 1213–16.
9. Singh BS, *et al.* Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002; **141:** 16–20.

Lymphangioleiomyomatosis. Inhaled beta$_2$ agonists are often helpful in treating the reversible component of airway obstruction in women with pulmonary lymphangioleiomyomatosis, and a trial of treatment is warranted.[1,2] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p.2114.

1. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
2. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.

Muscular dystrophies. There is some evidence that beta$_2$ agonists affect muscle strength and have an anabolic effect. Salbutamol has therefore been investigated in a small number of patients in the management of muscular dystrophies (p.1507). Oral doses of modified-release salbutamol up to 12 mg daily have been used in boys aged between 5 and 11 years with Duchenne or Becker muscular dystrophies,[1,2] and doses of 8 or 16 mg twice daily have been given to adults with facioscapulohumeral dystrophy.[3,4] Although some improvements in muscle strength and muscle mass have been reported, not all muscle groups respond and the long-term effects of treatment are not known.

1. Fowler EG, *et al.* Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. *Neurology* 2004; **62:** 1006–8.
2. Skura CL, *et al.* Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. *Neurology* 2008; **70:** 137–43.
3. Kissel JT, *et al.* Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. *Neurology* 2001; **57:** 1434–40.
4. van der Kooi EL, *et al.* Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology* 2004; **63:** 702–8.

Premature labour. Beta$_2$ agonists such as salbutamol have been used as tocolytics in the management of premature labour (p.2003), and can postpone labour for a few days, but the risk of adverse cardiovascular and metabolic events including pulmonary oedema (see above) means that great care and appropriate monitoring of the patient's heart rate and state of hydration are needed.

Proctalgia fugax. Inhalation of salbutamol from a metered-dose inhaler at the beginning of an attack has been shown to reduce the duration of pain in patients with proctalgia fugax.[1]

1. Eckardt VF, *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol* 1996; **91:** 686–9.

Preparations

BP 2008: Salbutamol Injection; Salbutamol Nebuliser Solution; Salbutamol Oral Solution; Salbutamol Powder for Inhalation; Salbutamol Pressurised Inhalation; Salbutamol Tablets;
USP 31: Albuterol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Airomir†; Airsalbu; Amocasin; Asmatol; Butamol; Duopack; Medihaler†; Microterol; Nebutrax; Respiret; Salbulin; Salbutol; Salbutral; Salbutral + Aeromed; Ventolin; Yontal; Zoom; ***Austral.:*** Airomir; Asmol; Butamol; Epaq; Respax; Ventolin; ***Austria:*** Buventol; Sultanol; ***Belg.:*** Airomir; Docsalbuta; Ventolin; ***Braz.:*** Acobelin†; Aero-Ped†; Aerodini; Aerogreen†; Aerojet; Aerolin; Aerotamol†; Aerotrat; Asmakil; Asmaliv; Bronconal; Bronquil†; Butovent; Dilamol; Oxiterol†; Prodotamol; Pulmoflux; Salburin†; Salbutalin†; Salbutam; Salbutamax; Salbutib†; Salrolin†; Teoden†; Tussiliv; ***Canad.:*** Airomir; Apo-Salvent; Novo-Salmol†; Ventodisk; Ventolin; ***Chile:*** Aero-Sal†; Aerolin; Airomir; Asmavent; Broncoterol†; Bropil; Butotal; Fesema; Respolin; Salbutral; Sinasmal; ***Cz.:*** Apo-Salvent†; Asthalin†; Broncovaleas†; Butovent†; Buventol; Ecosal; Etinoline†; Salamol†; Steri-Neb Salamol†; Ventodisks†; Ventolin; Volmax†; ***Denm.:*** Airomir; Buventol; Salbudan†; Salbuvent; Ventoline; Volmax; ***Fin.:*** Airomir; Buventol; Salbuvent†; Ventoline; ***Fr.:*** Airomir; Asmasal; Buventol; Salbumol; Spreor†; Ventexxair†; Ventilastin; Ventodisks†; Ventoline; ***Ger.:*** Apsomol; Asthmalitan; Broncho Fertiginhalat; Broncho Inhalat; Bronchospray; Epaq; Loftan; Padiamol; Pentamol; Salbu; Salbubreathe; Salbuhexal; Salbulair; Salbulind; Salbupp†; Salmundin†; Salvent†; Sultanol; Ventilastin; Volmac; ***Gr.:*** Aerolin; Asthmotrat; Buventol†; Normobron; Salbunova; ***Hong Kong:*** Airomir; Apo-Salvent†; Azmacon; Buto Asma†; Cybutol; Respolin; Respreve†; Salamol; Salmol; Ventodisks; Ventolin; Ventomol; Volmax; Zenmolin; ***Hung.:*** Ac-Butamol†; Buventol; Ecosal; Huma-Salmol†; Salvuron†; Ventolin; ***India:*** Asthalin; Derihaler; Salbetol; Salmaplon; Salsol; ***Indon.:*** Asmacare; Azmacon; Buventol; Fartolin; Glisend; Hivent; Lasal; Librentin; Pritasma; Salbron; Salbuven; Suprasma; Ventolin; Volmax; ***Irl.:*** Aerolin; Airomir; Asmasal; Gerivent; Salamol; Steri-Neb Salamol; Ventamol; Ventodisks†; Ventolin; ***Israel:*** Ventolin; Volmax†; ***Ital.:*** Aerotec†; Broncovaleas; Salbufax†; Salbutard†; Ventmax; Ventolin; Volmax; ***Malaysia:*** Airomir; Asmovent†; Beatolin; Butahale†; Buventol; Colin†; Respolin†; Salbuterol†; Salmax; Salmol†; Ventamol†; Ventolin; Volmax; ***Mex.:*** Anebron†; Apo-Salvent; Assal; Avedox-FC; Azyrol; Biorenyn; Bolbasalt†; Bonair; Butotal†; Capacit; Cobamol; Dicoterol; Exafil; Oladin; Salamol; Salbulin†; Salbutalan; Salcomed; Unibron; Ventolin; Volmax; Zibil; ***Neth.:*** Airomir; Butovent; Ventolin; ***Norw.:*** Airomir; Buventol; Ventoline; ***NZ:*** Airomir; Apo-Salvent; Asmigen; Asmol†; Buventol; Respigen; Respolin; Salamol; Salapin; Ventolin; Volmax; ***Philipp.:*** Activent; Airomir; Amoltex; Asbunyl; Asfrenon; Asmacaire; Asmalin; Astagen; Asvimol; Axmaxolv; Cletal; Emplusal; Hivent; Librentin; Provexel NS; Prox-S; Resdil; Rhinol; Salbumed; Salvex; Sedalin; Venalax; Ventar; Vento-Broncho; Ventolin; Ventosal; ***Pol.:*** Steri-Neb Salamol; Velaspir; Ventodisk; Ventolin; ***Port.:*** Ventilan; ***Rus.:*** Salamol (Саламол); Salben (Сальбен); Salgim (Сальгим); Saltos (Сальтос); Ventolin (Вентолин); ***S.Afr.:*** Airomir; Asthavent; Breatheze†; Cybutol†;

Salbulin†; Venteze; Ventodisk†; Ventolin; Volmax; ***Singapore:*** Airomir†; Azmasol; Butahale; Buto Asma†; Buventol; Medolin; Respolin†; Sabutol†; Salamol†; Salbuair; Salmol; Venderol; Ventolin; Volmax; ***Spain:*** Aldobronquial; Asmasal†; Buto Air; Buto Asma; Emican†; Respiroma; Ventadur; Ventilastin; Ventolin; ***Swed.:*** Airomir; Buventol; Ventoline; ***Switz.:*** Airomir†; Buventol†; Ecovent; Ventodisk; Ventolin; Volmax; ***Thai.:*** Airomir†; Asmasal; Asthmolin†; Butamol; Buto Asma; Butovent; Buventol; Respolin†; Salbusian; Salbutac; Salda; Salmol; Solia; Venterol; Ventolin; Violin; Volmax†; Zebu; ***Turk.:*** Asthavent; Salbulin; Salbutam; Salbutol; Ven-o-sal; Ventodisks; Ventolin; Volmax; ***UAE:*** Butalin; ***UK:*** Airomir; Asmasal; Kentamol†; Pulvinal Salbutamol; Salamol; Salapin; Salbulin; Ventmax; Ventodisks†; Ventolin; Volmax; ***USA:*** Accuneb; ProAir; Proventil; Ventolin; Volmax†; VoSpire; ***Venez.:*** Asthalin; Butahale†; Butoas; Respolin†; Salbulis; Salbumed; Salburol; Salbutan; Ventolin†.

Multi-ingredient: ***Arg.:*** Beclasma; Butocort; Butosol; Combivent; Fatigan Bronquial†; Iprasalb; Salbutol Beclo; Salbutral AC; Salbutrop†; Ventide; Ventolin Compuesto†; ***Austral.:*** Combivent; ***Austria:*** Combivent; Di-Promal; Ventide; ***Belg.:*** Combivent; ***Braz.:*** Aeroflux; Aerotide; Clenil Compositum; Combivent; ***Canad.:*** Combivent; ratio-Ipra Sal UDV; ***Chile:*** Aero-Plus; Aerosoma; Asmavent-B; Beclasma†; Belomet; Broncoterol-B†; Butotal B; Combivent; Herolan Aerosol; Salbutral AC; Ventide; ***Cz.:*** Combivent†; Intal Plus†; ***Denm.:*** Combivent; ***Fin.:*** Atrodual; Redol Comp; ***Fr.:*** Combivent; ***Gr.:*** Berovent; ***Hong Kong:*** Combivent; Ventide; Ventolin Expectorant; ***India:*** Aerocort; Albutamol; Ambrodil-S; Amcof; Asthacrom; Asthalin AX; Asthalin Expectorant; Axalin-AX; Axalin†; Bronchilet†; Budesal†; Deletus A†; Duolin; Kofarest; Mucolinc; Okaril; Pulmo-Rest; Pulmo-Rest Expectorant; Suprivent; Suprivent-A; Theo-Asthalin; Ventorlin; ***Indon.:*** Combivent; Fartolin Expectorant; Lasal Expectorant; Proventol Expectorant; Salbron Expectorant; Salbuven Expectorant; Teosal; Ventide; Ventolin Expectorant; ***Irl.:*** Combivent; Ipramol; ***Ital.:*** Breva; Clenil Compositum; Plenaer; Ventolin Espettorante†; Ventolin Flogo†; Zarent†; ***Malaysia:*** Beatolin Expectorant†; Combivent; Ipramol; Salbutamol Expectorant; Ventamol Expectorant†; Ventolin Expectorant; ***Mex.:*** Aeroflux; Broxol Air; Combivent; Flamebin; Fluvicil; Fluxol; Fultac; Mucoflux; Musaldox; Neumyn-AS; Removil; Salamflux; Sibilex; Ulax-C; Ventide; ***Neth.:*** Combivent; ***NZ:*** Combivent; Duolin; ***Philipp.:*** Asbunyl Plus; Asfrenon GF; Asmalin Broncho; Broncaire Expectorant; Clarituss Plus; Combipul; Combivent; Duavent; Hicaryl; Histaril; Neovent; Pecof; Pulmovent; Salvex XP; SGX; Solmux-Broncho (Reformulated); Ventar EXP; Vento-Broncho G; Ventolin Expectorant; Venzadril; ***Port.:*** Combivent; Propavente; ***Rus.:*** Ascoril Expectorant (Аскорил Экспекторант); Biasten (Биастен); ***S.Afr.:*** Combivent; Duolin; Sabax Combineb; ***Singapore:*** Clenil Compositum†; Combivent; Ventide†; ***Spain:*** Butosol; Combivent; Legis†; ***Swed.:*** Combivent; ***Switz.:*** Dospir; ***Thai.:*** Almasal; Asmasal Expectorant†; Biovent; Clenil Compositum; Combivent; Royalin; Salmol Expectorant; Ventide†; Ventolin Expectorant; ***Turk.:*** Combivent; Ventide; ***UK:*** Combivent; Ipramol; ***USA:*** Combivent; DuoNeb; ***Venez.:*** Aerocort; Aeroflux; Beclomet Compositum†; Beclosal; Broxodin; Butosol; Combivent; Duolin; Ipralin; Salbomex†; Salbutide†; Venticort; Ventide.

Salmeterol Xinafoate *(BANM, USAN, rINNM)*

⊗

GR-33343G; Salmaterol Xinafoate; Salmeterol 1-Hydroxy-2-naphthoate; Salmeterol Ksinafoat; Salmétérol, xinafoate de; Salmeteroli xinafoas; Salmeteroliksinafoaatti; Salmeterolio ksinafoatas; Salmeterol-xinafoát; Sameterolxinafoat; Xinafoato de Salmeterol. (*RS*)-5-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-salicyl alcohol 1-hydroxy-2-naphthoate.

Салметерола Ксинафоат

$C_{25}H_{37}NO_4,C_{11}H_8O_3$ = 603.7.

CAS — 89365-50-4 (salmeterol); 94749-08-3 (salmeterol xinafoate).

ATC — R03AC12.

ATC Vet — QR03AC12.

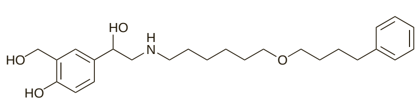

(salmeterol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Salmeterol Xinafoate). A white or almost white powder. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131. Inhalation of salmeterol may be associated with paradoxical bronchospasm, and it should not be used in patients who are not also receiving an inhaled corticosteroid.

Salmeterol is not appropriate for the treatment of acute bronchospasm or for patients whose asthma is deteriorating.

Effects on the cardiovascular system. A pooled analysis[1] of safety data from 7 studies of salmeterol in chronic obstructive pulmonary disease found no evidence of an increased risk of cardiovascular adverse effects. The duration of these studies had ranged from 12 weeks to 1 year.

1. Ferguson GT, *et al.* Cardiovascular safety of salmeterol in COPD. *Chest* 2003; **123:** 1817–24.

Effects on the respiratory system. Transient paradoxical bronchoconstriction with breathlessness, wheeze, or cough has been reported in 6 asthmatic patients after inhalation of salmeterol from a metered-dose aerosol but not after inhalation of the dry powder formulation by diskhaler.[1] The fluorocarbon propellants in the metered-dose aerosol were suspected as the irritants causing bronchoconstriction.

1. Wilkinson JRW, *et al.* Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *BMJ* 1992; **305:** 931–2.

Effects on the skin. Urticarial rash associated with inhaled salmeterol, of which the propellant was not the cause, has been reported. Although many urticarial reactions and a variety of rashes had been attributed to beta-agonist therapy their reproducibility had not always been documented.[1]

1. Hatton MQF, *et al.* Salmeterol rash. *Lancet* 1991; **337:** 1169–70.

Increased mortality. Interim results from a large controlled study (SMART)[1] designed to evaluate the safety of salmeterol compared with placebo, found a small but statistically significant increase in respiratory-related and asthma-related deaths or life-threatening episodes in the total population receiving salmeterol compared with placebo. This imbalance occurred mainly in the African-American subpopulation, and combined with difficulties in enrolment, led to early termination of the study. Various factors may have influenced the differences in outcomes seen with salmeterol; greater disease severity was noted at baseline in the African-American subgroup compared to Caucasian subjects, and nearly half of all participants were not receiving inhaled corticosteroids.

A subsequent meta-analysis[2] of 19 placebo-controlled studies of patients with asthma who were taking the long-acting $beta_2$ agonists salmeterol or formoterol (see p.1122), reported an increased risk of hospitalisation for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. A sub-group analysis that examined studies in which more than 75% of patients were also receiving inhaled corticosteroids also found an increased risk of hospital admission. The applicability of this review to therapy as recommended by current guidelines has been questioned,[3] as many of the studies included in the primary analysis did not require inhaled corticosteroids to be used, and studies which compared different asthma maintenance regimens were excluded because they were not placebo-controlled. Concomitant asthma treatments and adherence to treatment,[4,5] differences in baseline disease severity,[1,4] racial or genetic factors,[1] polymorphism,[6] tolerance,[6,7] and masking of underlying airway inflammation by long-acting $beta_2$ agonists[6] have all been proposed as possible explanations for the increased risk of adverse outcomes reported with long-acting $beta_2$ agonists.

In contrast to the above studies, a case-control study[8] that included 532 patients under age 65 who had died from asthma, matched with 532 controls with a hospital admission for asthma, found no evidence of adverse effects on mortality with medium to long-term use of inhaled long-acting $beta_2$ agonists. An earlier observational cohort study also found no evidence that salmeterol contributed to deaths reported from asthma.[9]

Current guidelines advocate use of a long-acting $beta_2$ agonist in addition to inhaled corticosteroids, and not as monotherapy, see Management of Asthma, p.1108

A recent review[10] by the UK MHRA concluded that:

- epidemiological data indicated that since the introduction of long-acting beta-agonists there had been a reduction in asthma-related hospitalisations in adolescents and a decrease in asthma related-mortality in all ages.
- data from controlled clinical study did not reflect the safety concern from postmarketing studies, possibly due to more consistent use of corticosteroids in controlled settings
- the data supported the use of long-acting beta-agonists with inhaled corticosteroids consistent with the UK guidelines on the management of asthma and that to aid compliance in the concomitant use of a corticosteroid, a combination inhaler should be used when appropriate

1. Nelson HS, *et al.* The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; **129:** 15–26.
2. Salpeter SR, *et al.* Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006; **144:** 904–12.
3. Ernst P, *et al.* Safety and effectiveness of long-acting inhaled β-agonist bronchodilators when taken with inhaled corticosteroids. *Ann Intern Med* 2006; **145:** 692–4.
4. Glassroth J. The role of long-acting β-agonists in the management of asthma: analysis, meta-analysis, and more analysis. *Ann Intern Med* 2006; **144:** 936–7.
5. Nelson HS, Dorinsky PM. Safety of long-acting β-agonists. *Ann Intern Med* 2006; **145:** 706.
6. Currie GP, *et al.* Long-acting β -agonists in asthma: not so SMART? *Drug Safety* 2006; **29:** 647–56.
7. Weinberger M, Abu-Hasan M. Life-threatening asthma during treatment with salmeterol. *N Engl J Med* 2006; **355:** 852–3.
8. Anderson HR, *et al.* Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; **330:** 117. Full version: http://www.bmj.com/cgi/content/full/330/7483/117 (accessed 15/01/08)
9. Mann RD, *et al.* Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996; **49:** 247–50.
10. MHRA/CHM. Long-acting β agonists for asthma: review. *Drug Safety Update* 2008: **1** (6): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)

Tolerance. As with short-acting $beta_2$ agonists (see Salbutamol, p.1132), there is evidence that regular use of long-acting $beta_2$ agonists such as salmeterol produces tachyphylaxis to their protective effect against bronchoconstriction, as provoked by stimuli such as allergen, methacholine, or exercise.[1-4] The authors of a study of the long-term effect of salmeterol on exercise-induced asthma concluded that the decreased bronchoprotective effect over time was due to a decrease in duration of action (to less than 9 hours) rather than tachyphylaxis,[5] but this interpretation was criticised.[6,7]

There is also some evidence to suggest that symptomatic relief by short-acting $beta_2$ agonists is significantly reduced by regular use of long-acting $beta_2$ agonists.[8,9] Receptor downregulation, induced by regular use of a long-acting $beta_2$ agonist, has been suggested as the mechanism for this reduction in response and may lead to patients requiring higher doses of $beta_2$ agonists to attain relief from an acute asthma attack.[9,10] One study suggested that the greater tachyphylaxis to short-acting $beta_2$ agonists seen with salmeterol compared with formoterol might represent the expression of partial antagonism by salmeterol at $beta_2$ receptors.[8] Whatever the mechanism, the reduced bronchoprotective effect is perhaps more of a concern with long-acting $beta_2$ agonists, since, unlike the short-acting $beta_2$ agonists, their use on a regular basis is recommended.[11] See also $Beta_2$ Agonists, under Interactions of Salbutamol, p.1132.

1. Cheung D, *et al.* Long-term effects of a long-acting β -adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; **327:** 1198–1203.
2. Bhagat R, *et al.* Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995; **108:** 1235–9.
3. Booth H, *et al.* Salmeterol tachyphylaxis in steroid treated asthmatic subjects. *Thorax* 1996; **51:** 1100–4.
4. Simons FER, *et al.* Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997; **99:** 655–9.
5. Nelson JA, *et al.* Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998; **339:** 141–6.
6. Aziz I, Lipworth BJ. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783.
7. Dickey BF, Adachi R. Exercise-induced asthma. *N Engl J Med* 1998; **339:** 1783–4.
8. van Veen A, *et al.* A comparison of salmeterol and formoterol in attenuating airway responses to short-acting β -agonists. *Pulm Pharmacol Ther* 2003; **16:** 153–61.
9. Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. Abridged version: *Respir Res* 2005; **6:** 107. Full version: http://respiratory-research.com/content/6/1/107 (accessed 15/01/08)
10. Lipworth BJ. Airway subsensitivity with long-acting β -agonists: is there cause for concern? *Drug Safety* 1997; **16:** 295–308.
11. Abisheganaden J, Boushey HA. Long-acting inhaled β -agonists and the loss of "bronchoprotective" efficacy. *Am J Med* 1998; **104:** 494–7.

Interactions

As for Salbutamol, p.1132.

◊ For a study suggesting a decreased effect of salbutamol in patients receiving salmeterol, as well as a report of additive effects, see $Beta_2$ Agonists under Interactions of Salbutamol, p.1132.

Pharmacokinetics

Plasma concentrations of salmeterol are negligible after inhalation of therapeutic doses.

◊ Reviews.

1. Cazzola M, *et al.* Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002; **41:** 19–30.

Uses and Administration

Salmeterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). When given by inhalation, salmeterol acts as a bronchodilator. The onset of action is about 10 to 20 minutes but the full effect may not be apparent until after several doses. Unlike short-acting $beta_2$ agonists (see Salbutamol, p.1133), salmeterol is therefore not suitable for the symptomatic relief of an acute attack of bronchospasm. However, it is long-acting with a duration of action of about 12 hours and is indicated where the regular use of a long-acting $beta_2$ agonist is required for persistent reversible airways obstruction, as in chronic asthma or in some patients with chronic obstructive pulmonary disease. It may be useful in protecting against nocturnal and exercise-induced asthma attacks. Short-acting beta$_2$ agonists (on an as-required basis) and regular anti-inflammatory therapy should continue to be used.

Salmeterol is used in the form of the xinafoate; doses are expressed in terms of the equivalent amount of salmeterol; salmeterol xinafoate 1.45 micrograms is equivalent to about 1 microgram of salmeterol.

The usual dose is 50 micrograms of salmeterol twice daily from a metered-dose aerosol or dry powder inhaler; if necessary, up to 100 micrograms may be inhaled twice daily. For doses of salmeterol used in children, see Administration in Children, below.

◊ Reviews.

1. Meyer JM, *et al.* Salmeterol: a novel, long-acting beta -agonist. *Ann Pharmacother* 1993; **27:** 1478–87.
2. Bennett J, Tattersfield A. Drugs in focus: 15. Salmeterol. *Prescribers' J* 1995; **35:** 84–8.
3. Adkins JC, McTavish D. Salmeterol: a review of its pharmacological properties and clinical efficacy in the management of children with asthma. *Drugs* 1997; **54:** 331–54.
4. Jackson CM, Lipworth B. Benefit-risk assessment of long-acting β -agonists in asthma. *Drug Safety* 2004; **27:** 243–70.
5. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β -agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. For persistent reversible airways obstruction which requires regular bronchodilatation, including nocturnal asthma and prevention of exercise-induced asthma, children aged 4 to 12 years may be given 50 micrograms of salmeterol twice daily by inhalation.

Asthma. Salmeterol is a long-acting beta$_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p.1108, generally recommend that salmeterol should be reserved for use in patients with chronic asthma who have already progressed to inhaled corticosteroids; it is not a substitute for corticosteroids. Evidence suggests that, apart from in severe exacerbations, adding a long-acting beta$_2$ agonist to standard dose inhaled corticosteroid therapy may be more effective than increasing the dose of corticosteroid, or than combining a corticosteroid and an anti-leukotriene drug. Salmeterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, duration of protection against exercise-induced bronchoconstriction is reduced (see Tolerance, above).

References.

1. Lockey RF, *et al.* Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. *Chest* 1999; **115:** 666–73.
2. Shrewsbury S, *et al.* Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000; **320:** 1368–73.
3. Holimon TD, *et al.* Nocturnal asthma uncontrolled by inhaled corticosteroids: theophylline or long-acting beta2 agonists. *Drugs* 2001; **61:** 391–418.
4. Johansson G, *et al.* Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. *Clin Drug Invest* 2001; **21:** 633–42.
5. Heyneman CA, *et al.* Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. *Ann Pharmacother* 2002; **36:** 1944–9.
6. Bateman ED, *et al.* Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004; **170:** 836–44.
7. Weiler JM, *et al.* Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005; **94:** 65–72.
8. Ni Chroinin M, *et al.* Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
9. Gibson PG, *et al.* Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
10. Masoli M, *et al.* Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005; **60:** 730–4.
11. Ducharme FM, *et al.* Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/01/08).
12. Walters EH, *et al.* Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
13. The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007; **356:** 2027–39.

Chronic obstructive pulmonary disease. Short-acting beta$_2$ agonists are used as bronchodilators in patients with chronic obstructive pulmonary disease (see p.1112), although there is some evidence to suggest that an antimuscarinic might be preferable. Guidelines indicate that long-acting beta$_2$ agonists such as salmeterol may be used for maintenance therapy in moderate and more severe disease. Improvement in lung function and symptoms has been seen in such patients after regular treatment with inhaled salmeterol;[1-3] a reduction in exacerbations has also been seen.[4] Additional benefit has been reported from the use of salmeterol with inhaled corticosteroids.[5-7]

1. Boyd G, *et al.* An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; **10:** 815–21.
2. Mahler DA, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; **115:** 957–65.
3. Stockley RA, *et al.* Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. *Thorax* 2006; **61:** 122–8.
4. Appleton S, *et al.* Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 15/01/08).
5. Calverley P, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; **361:** 449–56. Correction. *ibid.*; 1660.
6. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; **67:** 2383–2405.
7. Kardos P, *et al.* Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **175:** 144–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Abrilar†; Serevent; ***Austral.:*** Serevent; ***Austria:*** Serevent; ***Belg.:*** Serevent; ***Braz.:*** Serevent; ***Canad.:*** Serevent; ***Chile:*** Kolpovent†; Serevent; Xemos; ***Cz.:*** Serevent; ***Denm.:*** Serevent; ***Fin.:*** Serevent; ***Fr.:*** Serevent; ***Ger.:*** Aeromax; Serevent; ***Gr.:*** Serevent; ***Hong Kong:*** Serevent; ***Hung.:*** Serevent; ***India:*** Salmeter; Serobid; ***Indon.:*** Serevent; ***Irl.:*** Serevent; ***Israel:*** Serevent; ***Ital.:*** Arial; Salmetedur; Serevent; ***Jpn:*** Serevent; ***Malaysia:*** Serevent; ***Mex.:*** Serevent; ***Neth.:*** Serevent; ***Norw.:*** Serevent; ***NZ:*** Serevent; ***Philipp.:*** Serevent; ***Pol.:*** Serevent; ***Port.:*** Dilamax; Serevent; Ultrabeta; ***Rus.:*** Seretide (Серетид); Serevent (Серевент); ***S.Afr.:*** Serevent; ***Singapore:*** Serevent; ***Spain:*** Beglan; Betamican; Inaspir; Serevent; ***Swed.:*** Serevent; ***Switz.:*** Serevent; ***Thai.:*** Serevent; ***Turk.:*** Astmerole; Serevent; ***UK:*** Serevent; ***USA:*** Serevent; ***Venez.:*** Salmeter†; Salspray; Serevent.

Multi-ingredient: ***Arg.:*** Flutivent; Neumotide; Seretide; ***Austral.:*** Seretide; ***Austria:*** Seretide; Viani; ***Belg.:*** Seretide; ***Braz.:*** Seretide; ***Canad.:*** Advair; ***Chile:*** Aerometrol Plus; Aurituss; Brexotide; Seretide; ***Cz.:*** Duaspir; Seretide; ***Denm.:*** Seretide; ***Fin.:*** Seretide; ***Fr.:*** Seretide; ***Ger.:*** Atmadisc; Viani; ***Gr.:*** Seretide; Viani†; ***Hong Kong:*** Seretide; ***Hung.:*** Seretide; Thoreus; ***India:*** Forair; Seretide; Seroflo; ***Indon.:*** Seretide; ***Irl.:*** Seretide; ***Israel:*** Seretide; ***Ital.:*** Aliflus; Seretide; ***Malaysia:*** Seretide; ***Mex.:*** Seretide; ***Neth.:*** Seretide; Viani; ***Norw.:*** Seretide; ***NZ:*** Seretide; ***Philipp.:*** Seretide; ***Pol.:*** Seretide; ***Port.:*** Brisomax; Maizar; Seretaide; Veraspir; ***S.Afr.:*** Seretide; ***Singapore:*** Seretide; ***Spain:*** Anasma; Brisair; Inaladuo; Plusvent; Seretide; ***Swed.:*** Seretide; ***Switz.:*** Seretide; ***Thai.:*** Seretide; ***Turk.:*** Seretide; ***UK:*** Seretide; ***USA:*** Advair; ***Venez.:*** Seretide.

Seratrodast *(USAN, rINN)*

A-73001; AA-2414; Abbott-73001; ABT-001; Sératrodast; Seratrodastum. (±)-2,4,5-Trimethyl-3,6-dioxo-ζ-phenyl-1,4-cyclohexadiene-1-heptanoic acid.

Сератродаст

$C_{22}H_{26}O_4$ = 354.4.

CAS — 112665-43-7; 103186-19-2.

ATC — R03DX06.

ATC Vet — QR03DX06.

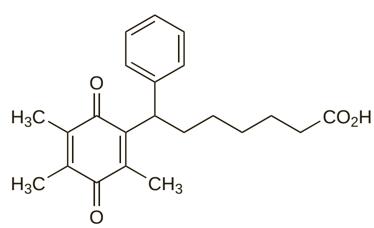

Profile

Seratrodast is a thromboxane A_2 antagonist that is reported to reduce airway hyperresponsiveness. It is given orally in the prophylactic management of asthma (p.1108), in single doses of 80 mg in the evening after food.

Adverse effects include gastrointestinal disturbances, drowsiness, headache, palpitations, and hepatitis. Hepatic function should be monitored and the drug should be withdrawn if hypersensitivity reactions such as rashes and pruritus occur, or if there is elevation of liver enzyme values. Seratrodast should be used with care in patients with pre-existing hepatic impairment. It is not suitable for the treatment of an acute asthmatic attack.

◊ References.

1. Tamaoki J, *et al.* Effect of a thromboxane A antagonist on sputum production and its physicochemical properties in patients with mild to moderate asthma. *Chest* 2000; **118:** 73–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Bronica.

Sodium Cromoglicate *(BANM, rINNM)*

Cromoglicate de Sodium; Cromoglicato de sodio; Cromoglicato disódico; Cromolyn Sodium *(USAN)*; Dinatrii Cromoglicas; Dinatrium-chromoglykát; Disodium Cromoglycate; FPL-670; Natrii cromoglicas; Natrio kromoglikatas; Natriumchromoglicat; Natriumkromoglikaatti; Natriumkromoglikat; Nátrium-kromoglikát; Sodium, cromoglicate de; Sodium Cromoglycate; Sodyum Kromoglikat. Disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4*H*-chromene-2-carboxylate).

Натрий Кромоглициат

$C_{23}H_{14}Na_2O_{11}$ = 512.3.

CAS — 16110-51-3 (cromoglicic acid); 15826-37-6 (sodium cromoglicate).

ATC — A07EB01; D11AX17; R01AC01; R03BC01; S01GX01.

ATC Vet — QA07EB01; QD11AX17; QR01AC01; QR03BC01; QS01GX01.

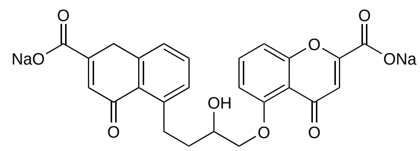

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Sodium Cromoglicate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.
USP 31 (Cromolyn Sodium). A white, odourless, hygroscopic, crystalline powder. Soluble in water; insoluble in alcohol and in chloroform. Store in airtight containers.

Adverse Effects

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe reactions such as marked bronchospasm, laryngeal oedema, angioedema, and anaphylaxis have been reported rarely.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pains have occurred when it is taken orally. Transient burning and stinging have occasionally been reported after use of sodium cromoglicate eye drops.

Formulation. Some of the adverse effects reported with sodium cromoglicate may be due to its formulation: there is a view that some of the irritant effects reported on inhalation may be due to the use of dry powder inhalers. It has also been suggested that in some patients receiving sodium cromoglicate via a nebuliser, hypotonicity of the nebuliser solution may induce bronchospasm,[1] although others consider this debatable.[2] Nausea, bloating, abdominal cramps, and flatulence developed in a 24-year-old lactase-deficient woman 2 hours after the use of sodium cromoglicate (*Intal*) inhalation capsules via a turbo-haler for exercise-induced asthma.[3] These symptoms recurred on rechallenge and were attributed to ingestion of lactose contained within the capsules.

1. Chin TW, Nussbaum E. Detrimental effect of hypotonic cromolyn sodium. *J Pediatr* 1992; **120:** 641–3.
2. Rachelefsky GS, *et al.* Detrimental effects of hypotonic cromolyn sodium. *J Pediatr* 1992; **121:** 992.
3. Brandstetter RD, *et al.* Lactose intolerance associated with Intal capsules. *N Engl J Med* 1986; **315:** 1613–14.

Precautions

Sodium cromoglicate has no role in the treatment of acute asthmatic attacks. Withdrawal of sodium cromoglicate may lead to recurrence of the symptoms of asthma. Should withdrawal be necessary it has been suggested that the dose be reduced gradually over a period of one week; patients in whom sodium cromoglicate therapy has permitted a reduction of corticosteroid dosage may require restoration of full corticosteroid cover.

Systemic corticosteroid therapy that has been reduced or stopped in asthmatic patients may need to be reinstated if symptoms increase, during periods of stress such as infection, illness, trauma, or severe antigen challenge, or where airways obstruction impairs inhalation of sodium cromoglicate.

Pharmacokinetics

Sodium cromoglicate is poorly absorbed from the gastrointestinal tract, with a reported bioavailability of only 1%. It has been reported that on inhalation as a fine powder only about 8% of a dose is deposited in the lungs from where it is rapidly absorbed and excreted unchanged in the urine and bile. Less than 7% of an intranasal dose appears to be absorbed. The majority of an inhaled or an intranasal dose is swallowed and excreted unchanged via the gastrointestinal tract. About 0.03% of an ophthalmic dose is reported to be absorbed. The terminal elimination half-life has been reported to be about 20 minutes after intravenous dosage, but the elimination half-life after oral doses or inhalation is about 80 minutes.

◊ A study[1] in patients with exercise-induced asthma concluded that the plasma concentration of cromoglicate was almost certainly not related directly to its protective effect, although another study in asthmatic children given sodium cromoglicate by dry-powder inhalation, found both blood concentration and clinical response to be correlated with inhalation technique.[2]

1. Patel KR, *et al.* Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. *Br J Clin Pharmacol* 1986; **21:** 231–3.
2. Yahav Y, *et al.* Sodium cromoglycate in asthma: correlation between response and serum concentrations. *Arch Dis Child* 1988; **63:** 592–7.

Uses and Administration

Sodium cromoglicate is used for the prevention of allergic reactions. Although its precise mode of action remains uncertain, it is believed to act primarily by preventing release of mediators of inflammation from sensitised mast cells through stabilisation of mast-cell membranes. It has no direct antihistamine or anti-inflammatory action.

Sodium cromoglicate can prevent the asthmatic response to a variety of allergic and non-allergic stimuli. It is used in the management of chronic asthma that cannot be managed with inhaled $beta_2$ agonists alone; it is not used for acute attacks of asthma.

Sodium cromoglicate is also used in the prophylaxis and treatment of seasonal and perennial allergic rhinitis and allergic conditions of the eye including acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis. It has been given orally, with dietary restriction, for the prevention of food allergies, and is also used in the treatment of mastocytosis.

It is important that the regular use of sodium cromoglicate is maintained, both in the prophylactic control of asthma and in the management of other allergic conditions. Beneficial effects may take several weeks to become established.

In the prophylaxis of **asthma**, sodium cromoglicate is given by inhalation either as a dry powder, or as a nebulised solution, or from a metered-dose aerosol. The usual dose as dry powder or nebulised solution is 20 mg by inhalation 4 times daily increased, if necessary, to 6 or 8 times daily. Once the asthma has been stabilised it may be possible to reduce the dosage. In different countries, sodium cromoglicate is available in different strengths of metered-dose aerosol. Using a metered-dose aerosol providing 5 mg per inhalation, the usual dose is 10 mg four times daily, increased to 6 to 8 times daily if necessary; it may be possible to reduce the dosage to 5 mg four times daily once the asthma has been stabilised. Additional doses as the aerosol or dry powder may be taken before exercise. Metered-dose aerosols providing 1 mg per inhalation are also available. The usual dose is 2 mg four times daily, which can be doubled if necessary. The adequacy of the lower dosage has been questioned (see under Administration, below).

Inhalation of sodium cromoglicate may cause bronchospasm; separate inhalation of a $beta_2$ agonist such as salbutamol a few minutes beforehand should prevent this. Use of a combination product containing a $beta_2$ agonist is not recommended as this is liable to be used inappropriately for relief of bronchospasm rather than for its prophylactic effect.

For the prophylaxis of **allergic rhinitis**, a 2 or 4% sodium cromoglicate solution can be given as a spray into both nostrils. The 2% spray contains about 2.5 mg per actuation and is given 4 to 6 times daily, and the 4% spray contains about 5 mg per actuation and is given 2 to 4 times daily. Prophylactic treatment for seasonal allergic rhinitis should begin 2 to 3 weeks before exposure to the offending allergen and should continue throughout the season. In **allergic conjunctivitis** and **vernal keratoconjunctivitis**, sodium cromoglicate is used as drops of 2 or 4%, applied 4 to 6 times daily.

In **food allergy** and in **mastocytosis**, sodium cromoglicate may be given in oral doses of 200 mg four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled, but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled.

For details of doses in children, see Administration in Children below.

Action. Sodium cromoglicate has a range of actions at cellular level that may be important for its protective effect in asthma. It is known as a mast cell stabiliser that inhibits the release of histamine and other inflammatory mediators from sensitised mast cells. Other reported actions include a direct effect on airway nerves[1,2] and antagonism[3] of substance P, which ties up with its inhibition of the effects of platelet activating factor (PAF).[4,5]

There have been a few reports[6-8] of sodium cromoglicate producing bronchodilatation. However, in practice other drugs with accepted bronchodilating activity are used for this effect in asthma treatment schedules, see p.1108.

1. Barnes PJ. Asthma as an axon reflex. *Lancet* 1986; **i:** 242–5.
2. Dixon M, *et al.* The effects of sodium cromoglycate on lung irritant receptors and left ventricular cardiac receptors in the anaesthetized dog. *Br J Pharmacol* 1979; **67:** 569–74.
3. Page C. Sodium cromoglycate, a tachykinin antagonist? *Lancet* 1994; **343:** 70.
4. Morley J, *et al.* The platelet in asthma. *Lancet* 1984; **ii:** 1142–4.
5. Morley J. PAF and airway hyperreactivity: prospects for novel prophylactic anti-asthma drugs. In: *PAF, Platelets, and Asthma*, Basel, Birkhäuser Verlag, 1987: 87–95.
6. Horn CR, *et al.* Bronchodilator effect of disodium cromoglycate administered as a dry powder in exercise induced asthma. *Br J Clin Pharmacol* 1984; **18:** 798–801.
7. Weiner P, *et al.* Bronchodilating effect of cromolyn sodium in asthmatic patients at rest and following exercise. *Ann Allergy* 1984; **53:** 186–8.
8. Yuksel B, Greenough A. Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely. *Eur Respir J* 1993; **6:** 387–90.

Administration. The effectiveness of sodium cromoglicate 2 mg four times daily by metered-dose aerosol inhaler has been reported by controlled studies in adults and children with asthma.[1-5] However, although sodium cromoglicate 2 mg by inhalation from a metered-dose aerosol was reported[6] to be as effective as 20 mg inhaled as powder, the tenfold difference in dosage has been questioned,[7] and others have reported contrary results.[8,9] It has been suggested that an aerosol supplying 5 mg per metered dose (see Uses and Administration, above) would be preferable.[10] In a comparison of single-dose pretreatment from metered-dose inhalers, sodium cromoglicate 10 mg (2 × 5 mg puffs) was as effective as beclometasone dipropionate 200 micrograms in inhibiting bronchial responsiveness to histamine.[11]

Care is required if inhaled sodium cromoglicate is given via a spacer device; evidence suggests that these may greatly influence the amount of drug delivered, reducing it to one-third of the dose delivered by inhaler actuation in some cases.[12]

1. Geller-Bernstein C, Levin S. Sodium cromoglycate pressurised aerosol in childhood asthma. *Curr Ther Res* 1983; **34:** 345–9.
2. Wheatley D. Sodium cromoglycate in aerosol form in regular users of bronchodilator drugs. *Curr Med Res Opin* 1983; **8:** 333–7.
3. Rubin AE, *et al.* The treatment of asthma in adults using sodium cromoglycate pressurized aerosol: a double-blind controlled trial. *Curr Med Res Opin* 1983; **8:** 553–8.
4. Blumenthal MN, *et al.* A multicenter evaluation of the clinical benefits of cromolyn sodium aerosol by metered-dose inhaler in the treatment of asthma. *J Allergy Clin Immunol* 1988; **81:** 681–7.
5. Selcow JE, *et al.* Clinical benefits of cromolyn sodium aerosol (MDI) in the treatment of asthma in children. *Ann Allergy* 1989; **62:** 195–9.
6. Latimer KM, *et al.* Inhibition by sodium cromoglycate of bronchoconstriction stimulated by respiratory heat loss: comparison of pressurised aerosol and powder. *Thorax* 1984; **39:** 277–81.
7. Anonymous. Sodium cromoglycate aerosol. *Drug Ther Bull* 1982; **20:** 27.
8. Robson RA, *et al.* Sodium cromoglycate: spincaps or metered dose aerosol. *Br J Clin Pharmacol* 1981; **11:** 383–4.
9. Bar-Yishay E, *et al.* Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations. *Arch Dis Child* 1983; **58:** 624–7.
10. Tullett WM, *et al.* Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma. *Thorax* 1985; **40:** 41–4.
11. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987; **79:** 734–40.
12. Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996; **51:** 835–40.

Administration in children. Children may be given sodium cromoglicate for prophylactic management of asthma and allergic rhinitis, and in the prophylaxis and treatment of acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis, using adult doses, see Uses and Administration, above. Different countries may have different licensed lower age limits and some inhalation dosage forms are unsuitable in very young children.

In food allergy and in mastocytosis, sodium cromoglicate may be given orally to children from 2 years of age. A dose of 100 mg is given four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled. For food allergy, adult doses may be given to children from 14 years of age, and from 13 years for mastocytosis, see above.

Asthma. Sodium cromoglicate is used as a prophylactic agent in the management of chronic asthma (p.1108), but in practice inhaled corticosteroids are preferred if regular prophylactic treatment is indicated, i.e. if the condition cannot be managed with occasional use of an inhaled short-acting $beta_2$ agonist alone. Even in children, in whom cromoglicate has tended to be more widely used, inhaled corticosteroids are considered first-line preventers. A systematic review[1] comparing sodium cromoglicate with inhaled corticosteroids found that inhaled corticosteroids were superior in terms of asthma control and lung function for both children and adults with chronic asthma. However, guidelines still specify the use of cromoglicate or nedocromil as a valid alternative to inhaled corticosteroids in some circumstances.

Response to treatment with nebulised sodium cromoglicate was found to be age-related in a study of children under 2 years of age with recurrent or persistent wheezy bronchitis and a history of allergic symptoms.[2] It was effective in children of 12 to 24 months of age but not in those below 12 months. Similarly, nebulised sodium cromoglicate was no more effective than placebo in the treatment of a group of 31 infants with persistent wheezing aged under 1 year,[3] and long-term inhalation therapy was ineffective in children aged 1 to 4 years.[4]

1. Guevara JP, *et al.* Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
2. Geller-Bernstein C, Levin S. Nebulised sodium cromoglycate in the treatment of wheezy bronchitis in infants and young children. *Respiration* 1982; **43:** 294–8.
3. Furfaro S, *et al.* Efficacy of cromoglycate in persistently wheezing infants. *Arch Dis Child* 1994; **71:** 331–4.
4. Tasche MJA, *et al.* Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4-year-old children with moderate asthma. *Lancet* 1997; **350:** 1060–4. Correction. *ibid.* 1998; **351:** 376.

Cogan's syndrome. Sodium cromoglicate eye drops improved blurred vision in a patient who had had Cogan's syndrome (p.1502) for 18 years.[1] Sodium cromoglicate capsules [by mouth] also reduced the frequency of fever attacks in this patient.

1. Carter F, Nabarro J. Cromoglycate for Cogan's syndrome. *Lancet* 1987; **i:** 858.

Cough. Sodium cromoglicate has been used with modest success by aerosol inhalation to suppress the cough associated with ACE inhibitor therapy (p.1194) in some patients.[1,2] However, inhalation of nedocromil sodium was not helpful in the treatment of ACE inhibitor induced cough in 6 diabetic patients.[3] A systematic review[4] considered that there was no good evidence to support the use of inhaled cromoglicate or nedocromil in the treatment of non-specific cough in children.

1. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; **341:** 560.
2. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; **345:** 13–16.
3. Puolijoki H, Rekiaro M. Lack of effect of nedocromil sodium in ACE-inhibitor-induced cough. *Lancet* 1995; **345:** 394.
4. Chang A, *et al.* Inhaled cromones for prolonged non-specific cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).

Eczema. Application of a 4% sodium cromoglicate lotion was found to be of benefit in improving symptoms and reducing topical corticosteroid use in a study[1] in children with moderately severe atopic dermatitis (p.1579).

1. Stainer R, *et al.* Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; **152:** 334–41.

Food allergy. Oral sodium cromoglicate has been used in the prophylaxis of food allergy reactions (p.564). However, efficacy has not been unequivocally established.

Mastocytosis. Mastocytosis is a rare condition characterised by abnormal proliferation of mast cells and their accumulation in body tissues.[1-3] Signs and symptoms of the disease result from the spontaneous or induced release of mast cell mediators. Mastocytosis occurs in cutaneous or systemic forms, which are further subdivided based on clinical presentation and prognosis. Clinical algorithms and recommendations for diagnosis, treatment, and response criteria have been developed.[4]

- *Cutaneous mastocytosis* most often manifests as urticaria pigmentosa (disseminated red-brown macules, papules, or plaques); other symptoms include flushing, pruritus, urticaria, blistering, and dermatographism. Mastocytomas may occur as brownish solitary or multiple nodular accumulations of mast cells. In children with cutaneous mastocytosis, symptoms will resolve in about half by adolescence.
- *Systemic mastocytosis* can involve diverse organs and tissues including the bones, liver, spleen, lymph nodes, haematopoietic system, gastrointestinal tract, and also the skin. General symptoms include fatigue, weight loss, fever, and sweats. Gastrointestinal complaints such as abdominal pain and diarrhoea are common, and some patients may experience malabsorption, steatorrhoea, or peptic ulcer disease. Bone marrow involvement may result in bone pain, osteoporosis, fractures, bone marrow fibrosis, and myeloproliferative and myelodysplastic diseases. Other systemic effects include lymphadenopathy, hepatosplenomegaly, headache and other neuropsychiatric symptoms, syncope, and anaphylactoid reactions.

Avoidance of trigger factors is an important measure in the management of mastocytosis. Such factors include exposure to extremes of cold or heat (hot bath or sunbathing), emotional stress, mechanical irritation (vigorous towel rubbing, massage), infections, alcohol, some drugs (e.g. aspirin, NSAIDs, opioid analgesics, sympathomimetics, polymyxin B, dextran, radiographic dyes), and animal venoms.[1,2,5]

Treatment is aimed at relieving symptoms and does not alter the course of the disease.[1,2,4-6] H_1-antagonist antihistamines such as hydroxyzine and cyproheptadine are used to provide relief of flushing, pruritus, urticaria, blistering, and abdominal pain. Patients at risk of anaphylactoid reactions should carry adrenaline for self-injection, and those who have repeated reactions should be given prophylactic antihistamines. H_2-antagonist antihistamines such as cimetidine, and proton pump inhibitors such as omeprazole, are used to manage gastrointestinal symptoms, particularly gastritis and peptic ulcer disease. Bisphosphonates may be helpful for osteopenia and bone pain. Sodium cromoglicate is given to manage abdominal pain, nausea, and diarrhoea. It may also provide some relief of headache, neuropsychiatric symptoms, and skin symptoms in some patients. Photochemotherapy using an oral psoralen with ultraviolet A irradiation (PUVA—see p.1606) has been used to reduce cutaneous manifestations of mastocytosis, but urticaria pigmentosa usually recurs within several weeks. Topical PUVA appears to be ineffective. Mastocytomas that cause symptoms may be treated with local PUVA or potent topical corticosteroids. Although surgical removal may be considered, the majority of mastocytomas will involute spontaneously.

Other treatments have also been tried in the treatment of small numbers of patients with aggressive systemic mastocytosis. Mixed results have been reported with the use of interferon alfa.[1] There is a report of ciclosporin with methylprednisolone being used successfully.[4] Imatinib has been used successfully in systemic mastocytosis with associated eosinophilia and with a mutation of the platelet-derived growth factor receptor-α gene on chromosome 4q12.[6] Beneficial responses to cladribine have also occurred in a small number of patients with systemic disease.[6,7]

1. Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144:** 682–95.
2. Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002; **86:** 315–19.
3. Castells MC. Mastocytosis: classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 2004; **25:** 33–6.
4. Valent P, *et al.* Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; **37:** 435–53.
5. Almahroos M, Kurban AK. Management of mastocytosis. *Clin Dermatol* 2003; **21:** 274–7.
6. Tefferi A, Pardanani A. Systemic mastocytosis: current concepts and treatment advances. *Curr Hematol Rep* 2004; **3:** 197–202.
7. Kluin-Nelemans HC, *et al.* Cladribine therapy for systemic mastocytosis. *Blood* 2003; **102:** 4270–6.

Rhinitis and conjunctivitis. Many drugs, including sodium cromoglicate, are used in the management of allergic rhinitis (p.565) and conjunctivitis (p.564). There is some evidence that nedocromil[1] or lodoxamide[2] may be more effective than cromoglicate in the management of vernal keratoconjunctivitis.

1. El Hennawi M. A double-blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; **78:** 365–9.
2. Leonardi A, *et al.* Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* 1997; **81:** 23–6.

Preparations

BP 2008: Sodium Cromoglicate Eye Drops; Sodium Cromoglicate Powder for Inhalation;
USP 31: Cromolyn Sodium Inhalation Powder; Cromolyn Sodium Inhalation Solution; Cromolyn Sodium Nasal Solution; Cromolyn Sodium Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Claroftal; Clo-5†; Intal; Klonalcrom; Sificrom†; ***Austral.:*** Cromese; Intal; Opticrom; Rynacrom; ***Austria:*** Acromax; Aeropaxyn†; Allergo-COMOD; Coldacrom; Cromal†; Cromoglin; Cromophtal; Intal; Lomusol; Vividrin; ***Belg.:*** Cromabak; Cromonez-Pos; Cromophta-Pos; Lomudal; Lomusol; Opticrom; ***Braz.:*** Cromabak; Cromocato; Cromolerg; Intal; Maxicrom; Rilan†; ***Canad.:*** Apo-Cromolyn; Cromolyn; Gen-Cromolyn†; Intal; Nalcrom; Opticrom; Solu-Crom; ***Chile:*** Oftacon; ***Cz.:*** Allergo-COMOD; Allergocrom; Cromobene; Cromogen†; Cromohexal; Cromolyn†; Cusicrom; DNCG†; Hay-Crom†; Intal†; Lecrolyn; Nalcrom; Stadaglicin†; Steri-Neb Cromogen†; Vividrin†; ***Denm.:*** Hexacroman†; Lecrolyn; Lomudal; ***Fin.:*** Glinor; Lecrolyn; Lomudal; ***Fr.:*** Allergo-COMOD†; Alloptrex; Cromabak; Cromadoses; Cromoptic; Cromosoft†; Intercron; Lomudal; Lomusol; Multicrom; Nalcron†; Ophtacalm; Opticron; ***Ger.:*** Acecromol†; Alerg†; Allergo-COMOD; Allergocrom; Allergoval; Colimune; Crom-Ophtal; Cromo; Cromoglicin†; Cromohexal; Cromolind; Cromopp; Diffusyl; Dispacromil; DNCG; duracroman†; Fenistil†; Flenid†; Flui-DNCG; Intal; IsoCrom; Lomupren; Opticrom; Otriven H†; Padiacrom; Pentacrom†; Pentatop; Pulbil†; Siozwo Allerg†; Vividrin; ***Gr.:*** Allergojovis; Allergostop; Allergotin; Botastin; Crolidin†; Cromabak; Cromo-POS; Cromodal; Cromolergin UD; Duobetic†; Erystamine-K; Fluvet†; Indoprex†; Iopanchol; Kaosyl; Lomudal; Nalcrom; Spaziron; Ufocollyre; Vekfanol; Vividrin; Zineli; Zulboral; ***Hong Kong:*** Cromabak; Cromal; Intal†; Mitayaku; Opticrom†; Stadaglicin; ***Hung.:*** Cromohexal; Cromolyn†; Cusicrom†; Intal; Lecrolyn; Opticrom; Stadaglicin†; Taleum; ***India:*** Cromal; Fintal†; ***Indon.:*** Crom-Ophtal; ***Irl.:*** Cromogen; Hay-Crom; Intal; Nalcrom; Opticrom; Rynacrom; Vividrin; ***Israel:*** Cromogen†; Cromolyn; Cromoptic; Cronase; Lomudal; Opticrom; Vicrom; ***Ital.:*** Acticrom†; Brunicrom; Cromabak; Cromantal; Cromosan†; Frenal†; Gastrofrenal; Lomudal; Lomuspray†; Nalcrom; Sificrom; ***Jpn:*** Intal; ***Malaysia:*** Allergocrom†; Cusicrom; Intal†; Opticrom; Stadaglicin; Vividrin†; ***Mex.:*** Alercrom; Exaler†; Intal; Livari; Maxicrom; Oftacon†; Opticrom; Rynacrom; Spralyn; ***Mon.:*** Zallyre; ***Neth.:*** Allerg-Abak; Allergo-COMOD; Allergocrom†; Lomudal; Lomusol; Nalcrom; Opticrom; Otrivin hooikoorts†; Prevalin; Vividrin; ***Norw.:*** Lecrolyn; Lomudal; ***NZ:*** Cromolux; Intal; Nalcrom; Opticrom; Optrex Hayfever Allergy; Rynacrom; Vicrom; ***Philipp.:*** Cromabak; Lecrolyn; Vividrin; ***Pol.:*** Allergo-COMOD; Allergocrom; Cromogen; Cromohexal; Cromosol; Cromoxal; Cropoz G; Cusicrom; Lecrolyn; Nalcrom; Polcrom; Vividrin; ***Port.:*** Croglina; Cromabak; Cromex†; Cusicrom†; Davicrome; Fenolip; Intal; Opticrom; Rynacrom†; ***Rus.:*** Cromoglin (Кромоглин); Cromohexal (Кромогексал); Cropoz (Кропоз); Hay-Crom (Хай-кром); Ifiral (Ифирал); Intal (Интал); Lecrolyn (Лекролин); ***S.Afr.:*** Cromabak†; Cromohexal; Stop-Allerg; Vividrin†; ***Singapore:*** Cromabak; Intal; Opticrom; Rynacrom†; Sificrom†; Vividrin; ***Spain:*** Alergocrom; Cromo Asma†; Cusicrom; Farmacrom; Frenal; Gastrofrenal; Intal†; Nebulasma; Nebulcrom; Poledin†; Primover; Renocil; Rinilyn†; Rinofrenal; ***Swed.:*** Lecrolyn; Lomudal; Pollyferm; Rinil†; ***Switz.:*** Allergo-COMOD; Cromabak; Cromodyn; Cromosol ophta; Cromosol UD; Glicinal†; Lomudal; Lomusol; Nalcrom; Opticrom; Vividrin; ***Thai.:*** Intal; Lecrolyn†; Opticrom†; Rynacrom; Vividrin; ***Turk.:*** Allergo-COMOD; Allergocrom; Allersol; Intal; Opticrom; Rynacrom; ***UK:*** Clariteyes; Clarityn; Cromogen†; Hay-Crom; Hayfever Eye Drops; Intal; Nalcrom; Opticrom; Optrex Allergy; Pollenase Allergy; Rynacrom; Vivicrom; Vividrin; ***USA:*** Crolom; Gastrocrom; Intal; Nasalcrom; Opticrom; ***Venez.:*** Alergocrom†; Cromisol; Cromo-Spray†; Cromoftal; Maxicrom†.

Multi-ingredient: ***Arg.:*** Duotec†; Hyalcrom; Rinogel; ***Austria:*** Ditec; ***Cz.:*** Allergocrom Kombi; Ditec†; Intal Plus†; ***Ger.:*** Aarane N; Allergospasmin; Ditec†; Lomupren compositum†; ***Hung.:*** Duotec†; ***India:*** Asthacrom; ***Ital.:*** Cromozil; Rinofrenal; Visuglican; ***Malaysia:*** Rynacrom Compound†; ***Port.:*** Ringoglin†; ***Rus.:*** Ditec (Дитек); ***Spain:*** Frenal Compositum; Rinofrenal Plus; ***Switz.:*** Aarane†; Allergospasmine†; Lomusol-X†; ***Thai.:*** Rynacrom Compound†; ***Turk.:*** Rynacrom Compound; ***UK:*** Rynacrom Compound†.

Suplatast Tosilate *(rINN)*

IPD-1151T; Suplatast, Tosilate de; Suplatast Tosylate; Suplatastum Tosilas; Tosilato de suplatast. (±)-(2-{[*p*-(3-Ethoxy-2-hydroxypropoxy)phenyl]carbamoyl}ethyl)dimethylsulphonium *p*-toluenesulphonate; (3-{[4-(3-Ethoxy-2-hydroxypropoxy)phenyl]amino}-3-oxopropyl)dimethylsulphonium *p*-toluenesulphonate.

Суплатаст Тозилат

$C_{23}H_{33}NO_7S_2$ = 499.6.

CAS — 94055-76-2.

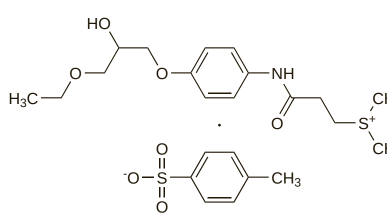

Profile

Suplatast tosilate is an anti-allergic given orally in the prophylactic management of asthma and other allergic conditions.

◊ References.

1. Sano Y, *et al.* Anti-inflammatory effect of suplatast tosilate on mild asthma. *Chest* 1997; **112:** 862–3.
2. Nihei Y, *et al.* Suplatast tosilate (IPD), a new immunoregulator, is effective in vitiligo treatment. *J Dermatol* 1998; **25:** 250–5.
3. Tamaoki J, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 2000; **356:** 273–8.
4. Shioya T, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on cough variant asthma. *Eur J Clin Pharmacol* 2002; **58:** 171–6.
5. Matsuda Y, *et al.* Improvement of alanine aminotransferase by administration of suplatast tosilate plus ursodeoxycholic acid in patients with resistance to ursodeoxycholic acid monotherapy on hepatitis C virus-related chronic liver disease. *Intern Med* 2002; **41:** 774–9.
6. Sakuma-Oyama Y, *et al.* A case of recurrent cutaneous eosinophilic vasculitis: successful adjuvant therapy with suplatast tosilate. *Br J Dermatol* 2003; **149:** 901–3.
7. Sano T, *et al.* Higashishikoku Asthma Research Group. Add-on effects of suplatast tosilate in bronchial asthma patients treated with inhaled corticosteroids. *Lung* 2003; **181:** 227–35.
8. Teraki Y, Fukuda T. Pemphigoid nodularis associated with psoriatic erythroderma: successful treatment with suplatast tosilate. *Br J Dermatol* 2008; **158:** 424–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: IPD.

Terbutaline Sulfate *(USAN, rINNM)* ⊗

KWD-2019; Sulfato de terbutalina; Terbutaliinisulfaatti; Terbutalin Sülfat; Terbutaline, sulfate de; Terbutaline Sulphate *(BANM)*; Terbutalini sulfas; Terbutalinsulfat; Terbutalin-sulfát; Terbutalin-szulfát. 2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate.

Тербуталина Сульфат

$(C_{12}H_{19}NO_3)_2,H_2SO_4$ = 548.6.

CAS — 23031-25-6 (terbutaline); 23031-32-5 (terbutaline sulfate).

ATC — R03AC03; R03CC03.

ATC Vet — QR03AC03; QR03CC03.

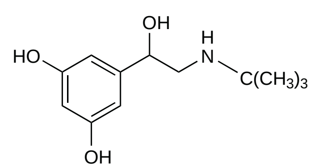

(terbutaline)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Terbutaline Sulphate). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol.

USP 31 (Terbutaline Sulfate). A white to grey-white crystalline powder; odourless or has a faint odour of acetic acid. Soluble in water and in 0.1N hydrochloric acid; insoluble in chloroform; slightly soluble in methyl alcohol. Store at 15° to 30°. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131.

Overdosage. An overdose of terbutaline due to transcutaneous absorption has been reported after inappropriate topical application to skin infected with tinea.[1] Transcutaneous absorption should be considered especially when children with facial eczema or dermatitis are given terbutaline via a nebuliser and mask.

For general effects of $beta_2$ agonists after overdose, see Salbutamol p.1132.

1. Ingrams GJ, Morgan FB. Transcutaneous overdose of terbutaline. *BMJ* 1993; **307:** 484.

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including terbutaline, for premature labour.[1] The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, p.1132.

1. Perry KG, *et al.* Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995; **173:** 1273–7.

Tolerance. As with other $beta_2$ agonists (see p.1132) there is some evidence[1] that tolerance may develop to terbutaline when it is used regularly.

1. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.

Tooth erosion. The pH of some inhaled powder formulations of terbutaline, as well as of some corticosteroids, was found to be below 5.5, and it was suggested that this might contribute to the dissolution of enamel surfaces of teeth.[1] A later cohort study found no association between asthma and tooth erosion; however only about 10% of the medication prescribed for asthma in the cohort had a pH lower than 5.5.[2]

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; **317:** 820.
2. Dugmore CR, Rock WP. Asthma and tooth erosion: is there an association? *Int J Paediatr Dent* 2003; **13:** 417–24.

Interactions

As for Salbutamol, p.1132.

Xanthines. The metabolic and cardiovascular responses to terbutaline infusion were significantly enhanced by *theophylline* in a study in 7 healthy subjects; in particular the fall in serum potassium was greater when both drugs were given.[1] Careful monitoring of serum potassium is recommended in severe asthma where theophylline and beta$_2$-agonists may be given together.

Terbutaline conversely has an effect on theophylline. Terbutaline can reduce serum-theophylline concentrations by increasing its systemic clearance. This may, or may not, have clinical implications, as improved clinical scores have still occurred with combined therapy despite the theophylline concentration being lower than when used alone; if respiratory symptoms persist, an increase in dosage may be contemplated while monitoring theophylline adverse effects and concentration.[2]

1. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
2. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.

Pharmacokinetics

On inhalation of terbutaline, less than 10% of the drug is absorbed from the airways. The remainder is swallowed where it is variably absorbed from the gastrointestinal tract. Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food. Terbutaline undergoes extensive first-pass metabolism by sulfate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces partly as the inactive sulfate conjugate and partly as unchanged terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours. There is some placental transfer. Trace amounts are distributed into breast milk.

Stereoselectivity. Terbutaline, like many other sympathomimetics, exists in two stereoisometric forms but only the (−)-enantiomer of terbutaline is pharmacologically active. Pharmacokinetic studies have been conducted on the two enantiomers and on the racemate.

The oral bioavailability of (−)-terbutaline was 14.8%, which was similar to that of the racemate; the bioavailability of (+)-terbutaline was much lower at 7.5%. The difference in bioavailability between the two enantiomers was mainly due to a difference in absorption (about 75% and 50% respectively) although a small difference in subsequent first-pass metabolism also occurred, with the (+)-isomer undergoing slightly more metabolism. It appeared that the (+)-isomer governed the elimination behaviour, both first-pass metabolism and renal clearance, of the racemate whereas the (−)-isomer determined the absorption.[1]

Other studies have also shown stereoselective sulfate conjugation of terbutaline with sulfation of the (+)-enantiomer being double that of the (−)-enantiomer.[2] The primary site of terbutaline sulfation for both enantiomers appears to be in the gut and is significantly correlated with the activity of catechol sulfotransferase.[3]

1. Borgström L, *et al.* Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989; **27:** 49–56.
2. Walle T, Walle UK. Stereoselective sulphate conjugation of racemic terbutaline by human liver cytosol. *Br J Clin Pharmacol* 1990; **30:** 127–33.
3. Pacifici GM, *et al.* (+) and (−) terbutaline are sulphated at a higher rate in human intestine than in the liver. *Eur J Clin Pharmacol* 1993; **45:** 483–7.

Uses and Administration

Terbutaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has actions and uses similar to those of salbutamol (p.1133).

Terbutaline is given as the sulfate for its bronchodilating properties in reversible airways obstruction, as occurs in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). It also decreases uterine contractility and may be used to arrest premature labour (p.2003).

On inhalation, the bronchodilating effect of terbutaline usually begins within 5 minutes and lasts for up to 6 hours. The onset of action after oral doses is 30 to 45 minutes and its duration is up to 8 hours; the maximum effect occurs 1 to 4 hours after the dose.

Current asthma guidelines (see p.1108) recommend that inhaled short-acting beta$_2$ agonists such as terbutaline be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of terbutaline, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, terbutaline indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

- To relieve **acute bronchospasm** the usual dose is 1 or 2 inhalations of terbutaline sulfate 250 micrograms as required from a *metered-dose aerosol* every 4 to 6 hours, to a maximum of 8 inhalations in 24 hours.
- A breath-actuated metered-dose *powder inhaler* containing terbutaline sulfate is also available; one inhalation of 500 micrograms is taken when required up to a maximum of 6 inhalations in 24 hours.
- When inhalation is ineffective, terbutaline sulfate may be given *orally*; the usual initial dose is 2.5 or 3 mg three times daily increased up to 5 mg three times daily as necessary. Modified-release tablets are also available; the usual adult dose is 7.5 mg twice daily.
- Severe or unresponsive bronchospasm may require the use of terbutaline sulfate intermittently via a *nebuliser.* A usual dose is 5 to 10 mg inhaled 2 to 4 times daily. Single-dose units or a suitable dilution of a concentrated solution containing terbutaline sulfate 1% are used for this purpose.

Guidelines also allow for beta$_2$ agonists to be given more frequently or by continuous dosage at a higher rate in acute severe asthma (see under Asthma, p.1108).

- In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous, intramuscular, or slow intravenous *injection*; a dose of 250 to 500 micrograms may be given up to 4 times daily. Terbutaline sulfate may also be given by *intravenous infusion*, as a solution containing 3 to 5 micrograms/mL at a rate of 0.5 to 1 mL/minute.

Terbutaline sulfate is also used to arrest uncomplicated **premature labour** between 24 and 33 weeks of gestation. It is given by *intravenous infusion* in glucose 5%, preferably by syringe pump when the concentration is 100 micrograms/mL. If no syringe pump is available then the concentration of the infusion should be 10 micrograms/mL. The recommended initial rate of infusion is 5 micrograms/minute increased by 2.5 micrograms/minute at intervals of 20 minutes until contractions stop. Usually, a rate of up to 10 micrograms/minute is sufficient; rates in excess of 20 micrograms/minute should not be used and if that maximum rate does not delay labour then the infusion should be stopped. The maternal pulse should be monitored throughout the infusion which should be adjusted to avoid a maternal heart rate of more than 135 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Once contractions have ceased, the infusion should be given for 1 hour, then the dose may be decreased by 2.5 micrograms/minute at 20-minute intervals to the lowest maintenance dose that produces continued suppression of contractions. After a further 12 hours, *oral* maintenance therapy with 5 mg three times daily may be started. However, such usage is not recommended by the *BNF* as the risks to the mother (see Precautions under Salbutamol, p.1132) increase after 48 hours, and furthermore there is a lack of evidence of benefit from further treatment. *Subcutaneous* doses of 250 micrograms four times daily have been given for a few days before oral treatment was commenced.

For terbutaline sulfate doses used for bronchospasm in children, see Administration in Children, below.

Terbutaline in a bioadhesive vaginal gel is under investigation for the treatment of infertility linked to endometriosis.

Administration in children. To relieve **acute bronchospasm** in children, the *BNFC* recommends a dose of 500 micrograms of terbutaline sulfate, inhaled via a metered-dose *powder inhaler*, up to four times daily in children aged 5 years and over. *Oral* doses, although not recommended and unlicensed in the UK for children under 7 years of age, may be given in doses ranging from:

- 1 month to 7 years of age, 75 micrograms/kg (maximum dose 2.5 mg) three times daily
- 7 to 15 years of age, 2.5 mg two or three times daily
- over 15 years of age, as for adults (see Uses and Administration, above)

Severe or unresponsive bronchospasm may require the use of terbutaline sulfate inhaled via a *nebuliser*. UK licensed product information gives doses based on weight and age:

- under 3 years of age, average body-weight 10 kg, 2 mg given 2 to 4 times daily
- 3 to 5 years of age, average body-weight 15 kg, 3 mg given 2 to 4 times daily
- 6 to 7 years of age, average body-weight 20 kg, 4 mg given 2 to 4 times daily
- 8 years of age and over, body-weight greater than 25 kg, 5 mg given 2 to 4 times daily

In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous or slow intravenous *injection*; in children 2 years of age and over, the *BNFC* recommends a dose of 10 micrograms/kg given every 6 hours as required. A maximum single dose of 300 micrograms is recommended in children from 2 to 15 years of age, and in children over 15 years a maximum single dose of 500 micrograms is recommended.

Terbutaline sulfate may also be given by *intravenous infusion*; the *BNFC* recommends an initial dose of 2 to 4 micrograms/kg, then 1 to 10 micrograms/kg per hour according to response and heart rate. Although the injection is unlicensed in the UK for children under 2 years of age, the *BNFC* allows this dose for children from 1 month of age.

Cardiac disorders. A case report on the use of oral terbutaline for chronotropic support, in the setting of acute rejection after heart transplantation, found it to be effective and without any significant adverse effects.[1]

1. Coons JC, *et al.* Terbutaline for chronotropic support in heart transplantation. *Ann Pharmacother* 2004; **38:** 586–9.

Hypoglycaemia. Giving terbutaline 5 mg orally at night reduced the risk of nocturnal hypoglycaemia in a study in patients with type 1 diabetes.[1] A later study[2] reproduced these results in 21 patients with type 1 diabetes; however, hyperglycaemia was seen the next morning.

1. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
2. Raju B, *et al.* Nocturnal hypoglycaemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 2006; **91:** 2087–92.

Systemic capillary leak syndrome. Systemic capillary leak syndrome is a rare disorder marked by shifts of plasma from the intravascular to the extracellular space, and is often fatal. Acute attacks are treated with intravenous fluid resuscitation, but there is some anecdotal evidence that treatment with terbutaline combined with aminophylline or theophylline, both orally, may be useful in preventing further attacks.[1-3] Infusion of epoprostenol has also been used in acute management.[4]

1. Droder RM, *et al.* Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med* 1992; **92:** 523–6.
2. Amoura Z, *et al.* Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. *Am J Med* 1997; **103:** 514–19.
3. Tahirkheli NK, Greipp PR. Treatment of the systemic capillary leak syndrome with terbutaline and theophylline: a case series. *Ann Intern Med* 1999; **130:** 905–9.
4. Fellows IW, *et al.* Epoprostenol in systemic capillary leak syndrome. *Lancet* 1988; **ii:** 1143.

Urticaria. Patients with various types of urticaria unresponsive to conventional therapy with antihistamines (see p.1584) have obtained benefit from treatment with a combination of terbutaline and ketotifen; the urticarias have included chronic idiopathic urticaria,[1] dermographism,[1] and cold urticaria.[1,2] Terbutaline on its own was relatively ineffective and the mechanism of the combination was believed to be due to a stabilising effect on mast cells.[1]

Treatment of cold urticaria with a combination of terbutaline and aminophylline has also been studied.[3] The effectiveness of this combined therapy was reported to vary considerably between patients, but complete remission of the urticarial response was eventually seen in 37 of the 42 patients. Treatment was stopped in 3 patients in the first week due to cardiac adverse effects.

1. Saihan EM. Ketotifen and terbutaline in urticaria. *Br J Dermatol* 1981; **104:** 205–6.
2. Edge JA, Osborne JP. Terbutaline and ketotifen in cold urticaria in a child. *J R Soc Med* 1989; **82:** 439–40.
3. Husz S, *et al.* Treatment of cold urticaria. *Int J Dermatol* 1994; **33:** 210–13.

Preparations

BP 2008: Terbutaline Tablets;
USP 31: Terbutaline Sulfate Inhalation Aerosol; Terbutaline Sulfate Injection; Terbutaline Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bricanyl; ***Austral.:*** Bricanyl; ***Austria:*** Bricanyl; ***Belg.:*** Bricanyl; ***Braz.:*** Bricanyl; Terbutil; ***Canad.:*** Bricanyl; ***Chile:*** Bricanyl†; ***Cz.:*** Bricanyl; ***Denm.:*** Bricanyl; ***Fin.:*** Bricanyl; ***Fr.:*** Bricanyl; ***Ger.:*** Aerodur; Arubendol†; Asthmoprotect†; Bricanyl; Butaliret†; Butalitab†; Contimit; Terbul; Terbuturmant†; ***Gr.:*** Bricanyl; Dracanyl; ***Hong Kong:*** Ataline; Bricanyl; Butylin†; Dhataline;

Lanterbine; Terbron; Terbuta; Tolbin†; Vida-Butaline; ***Hung.:*** Bricanyl; ***India:*** Bricanyl; ***Indon.:*** Astherin; Brasmatic; Bricasma; Forasma; Lasmalin; Nairet; Pulmobron; Relivan; Sedakter; Tabas; Terasma; Tismalin; Yarisma; ***Irl.:*** Bricanyl; ***Israel:*** Bricalin; Terbulin; ***Ital.:*** Bricanyl; ***Malaysia:*** Ataline; Bricanyl; Bucanil; Butaline; Butanil†; Terbron†; Terbulin†; Tolbin; ***Mex.:*** Bricanyl†; Taziken†; Terbuken; ***Neth.:*** Bricanyl; Terbasmin; ***Norw.:*** Bricanyl; ***NZ:*** Bricanyl; ***Philipp.:*** Alloxygen; Astebron; Bricanyl; Bronchodam; Pulmonyl; Pulmoxcel; Terbulin; ***Port.:*** Bricanyl; ***S.Afr.:*** Bricanyl; ***Singapore:*** Ataline; Bricanyl; Bucanil†; Tolbin†; ***Spain:*** Tedipulmo; Terbasmin; ***Swed.:*** Bricanyl; ***Switz.:*** Bricanyl; ***Thai.:*** Asmaline; Asthmasian; Bricanyl; Broncholine; Bronchonyl; Bronco Asmo; Bucaril; Cencanyl; Med-Broncodil†; Proasma-T; Sulterline; Terbron†; Terbulin; Terbuno; Tolbin; Vacanyl†; ***Turk.:*** Bricanyl; ***UK:*** Bricanyl; Monovent†; ***USA:*** Brethine; Bricanyl†; ***Venez.:*** Bricanil†; Nortol†.

Multi-ingredient: ***Austria:*** Bricanyl comp; ***Braz.:*** Bricanyl Composto; ***Ger.:*** Bricanyl comp†; ***Hong Kong:*** Bricanyl Expectorant†; ***India:*** Ascoril +; Asmotone Plus; Bricarex; Bro-Zedex; Bronchosolvin; Cof QX; Grilinctus-BM; Mucaryl-AX†; Mucosol; Okaril Plus; Tergil; Tergil-T; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; ***Indon.:*** Bricasma Expectorant; Terasma Expectorant; ***Irl.:*** Bricanyl Expectorant; ***Mex.:*** Bricanyl EX; ***Philipp.:*** Bricanyl Expectorant; ***S.Afr.:*** Benylin Bronchospect; Bronchoped; Bronchospect†; ***Spain:*** Terbasmin Expectorante; ***Thai.:*** Bricanyl Expectorant†; Cofbron; Med-Broncodil Expectorant†; Terbosil†; Terbron Expectorant†; Tolbin.

Theobromine *(BAN)*

Santheose; Teobromiini; Teobromin; Teobromina; Teobrominas; Theobromin; Théobromine; Theobrominum. 3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione; 3,7-Dimethylxanthine.

Теобромин

$C_7H_8N_4O_2$ = 180.2.

CAS — 83-67-0.

ATC — C03BD01; R03DA07.

ATC Vet — QC03BD01; QR03DA07.

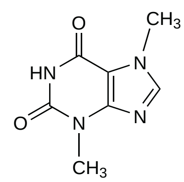

Pharmacopoeias. In *Eur.* (see p.vii)

Ph. Eur. 6.2 (Theobromine). A white or almost white powder. Very slightly soluble in water and in dehydrated alcohol; slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids.

Profile

Theobromine has the general properties of the other xanthines (see Theophylline, p.1140). It has a weaker activity than theophylline or caffeine and has practically no stimulant effect on the CNS. Large doses can cause nausea and vomiting. Theobromine has been used for its bronchodilating properties and in the treatment of cardiovascular disorders. Theobromine and calcium salicylate (theosalicin), theobromine and sodium acetate, and theobromine and sodium salicylate (themisalum, theobromsal) have all been used similarly to theobromine.

Theobromine is the chief xanthine in the beverage cocoa (p.2415). It is also present in chocolate and in small amounts in tea. Theobroma oil may contain up to 2% theobromine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Asthma-Hilfe; ***Braz.:*** Urodonal†.

Theophylline *(BAN)*

Anhydrous Theophylline; Teofilin; Teofilina; Teofilinas; Teofillin; Teofillina; Teofylliini; Teofyllin; Theofylin; Théophylline; Theophyllinum. 3,7-Dihydro-1,3-dimethylpurine-2,6(1*H*)-dione; 1,3-Dimethylxanthine.

Теофиллин

$C_7H_8N_4O_2$ = 180.2.

CAS — 58-55-9.

ATC — R03DA04.

ATC Vet — QR03DA04.

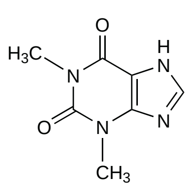

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn, US,* and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 6.2 (Theophylline). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 31 (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Theophylline Hydrate *(BANM)*

Teofilina monohidrato; Teofilinas monohidratas; Teofylliinimonohydraatti; Teofyllinmonohydrat; Theofylin monohydrát; Theophylline Monohydrate; Théophylline monohydratée; Theophyllinum monohydricum.

Теофиллина Гидрат

$C_7H_8N_4O_2,H_2O$ = 198.2.

CAS — 5967-84-0.

ATC — R03DA04.

ATC Vet — QR03DA04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *US,* and *Viet.* Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

Ph. Eur. 6.2 (Theophylline Monohydrate; Theophylline Hydrate BP 2008). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

USP 31 (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

Stability. Alcohol-free theophylline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophylline.[1] However, it was recommended that solutions be protected from light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found[2] to be stable for up to 90 days in amber plastic bottles stored at 23° to 25°.

1. Johnson CE, Drabik BT. Stability of alcohol-free theophylline liquid repackaged in plastic oral syringes. *Am J Hosp Pharm* 1989; **46:** 980–1.
2. Johnson CE, *et al.* Stability of anhydrous theophylline in extemporaneously prepared alcohol-free oral suspensions. *Am J Health-Syst Pharm* 2005; **62:** 2518–20.

Adverse Effects

The adverse effects commonly encountered with theophylline and xanthine derivatives irrespective of the route, are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of theophylline greater than 20 micrograms/mL (110 micromol/litre) are associated with an increased risk of adverse effects (but see below).

Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Convulsions, cardiac arrhythmias, severe hypotension, or cardiac arrest may follow rapid intravenous injection, and fatalities have been reported. The drug is too irritant for intramuscular use. Proctitis may follow repeated use of suppositories.

◊ Adverse effects are uncommon at serum-theophylline concentrations of 5 to 10 micrograms/mL but become more frequent at 15 micrograms/mL or above, and are greatly increased in frequency and severity at concentrations greater than 20 micrograms/mL.[1-3] The severity of toxicity is generally correlated with age, underlying disease, and serum-theophylline concentration, but a distinction has been made between acute and chronic theophylline intoxication; symptoms appear to occur at a lower theophylline concentration in chronic toxicity than after acute ingestion of large amounts.[1,2,4,5] Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.[6,7] Older patients with chronic intoxication may be at greater risk of major toxic effects, such as arrhythmias, seizures, and death, than those with acute intoxication.[5]

Common clinical manifestations of theophylline toxicity after overdosage of aminophylline or theophylline include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur.[1-3] Other toxic effects reported include dementia,[8] toxic psychosis,[9] symptoms of acute pancreatitis,[10] rhabdomyolysis[11-13] with associated renal failure,[11] and acute compartment syndrome.[14]

Serious toxic symptoms may not be preceded by minor symptoms. In acute intoxication with sustained-release preparations the onset of major toxic symptoms may be delayed for up to 24 hours[1] and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL[12,14] but fatalities have occurred with much lower serum concentrations.[10,15,16] Mortality in severe poisoning may be as high as 10%.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
4. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
5. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Arch Intern Med*1999; **159:** 989–94.
6. Shannon M, Lovejoy FH. Effect of acute versus chronic intoxication on clinical features of theophylline poisoning in children. *J Pediatr* 1992; **121:** 125–30.
7. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med* 1993; **119:** 1161–7.
8. Drummond I. Aminophylline toxicity in the elderly. *BMJ* 1982; **285:** 779–80.
9. Wasser WG, *et al.* Theophylline madness. *Ann Intern Med* 1981; **95:** 191.
10. Burgan THS, *et al.* Fatal overdose of theophylline simulating acute pancreatitis. *BMJ* 1982; **284:** 939–40.
11. Macdonald JB, *et al.* Rhabdomyolysis and acute renal failure after theophylline overdose. *Lancet* 1985; **i:** 932–3.
12. Rumpf KW, *et al.* Rhabdomyolysis after theophylline overdose. *Lancet* 1985; **i:** 1451–2.
13. Modi KB, *et al.* Theophylline poisoning and rhabdomyolysis. *Lancet* 1985; **ii:** 160–1.
14. Lloyd DM, *et al.* Acute compartment syndrome secondary to theophylline overdose. *Lancet* 1990; **ii:** 312.
15. Whyte KF, Addis GJ. Toxicity of salbutamol and theophylline together. *Lancet* 1983; **ii:** 618–19.
16. Davies RJ, Hawkey CJ. Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis. *Postgrad Med J* 1989; **65:** 49–50.

Effects on carbohydrate metabolism. Hyperglycaemia is frequent in theophylline intoxication, and is thought to be secondary to theophylline-induced adrenal catecholamine release.[1,2] Whether the effects on blood glucose are significant at more modest serum concentrations of theophylline is unclear, although in 29 preterm infants, mean plasma-glucose concentrations were significantly higher after treatment with intravenous aminophylline and oral theophylline than in those not treated. Two of 15 treated infants developed clinically significant hyperglycaemia and glycosuria. It was recommended that plasma-glucose concentrations be monitored in preterm infants receiving theophylline.[3]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Shannon M. Hypokalemia, hyperglycemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994; **32:** 41–7.
3. Srinivasan G, *et al.* Plasma glucose changes in preterm infants during oral theophylline therapy. *J Pediatr* 1983; **103:** 473–6.

Effects on electrolytes. Hypokalaemia is a common metabolic disturbance in theophylline intoxication, but it has also been reported[1] in patients with plasma-theophylline concentrations within the therapeutic range. It is considered to be secondary to theophylline-induced adrenal catecholamine release, with cellular influx of potassium ions.[2] It is recommended[1] that plasma-potassium is monitored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, below). Hypophosphataemia[1,3] and hyponatraemia[1] can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia[4] and hypercalcaemia[5] have occurred in theophylline overdose.

1. Zantvoort FA, *et al.* Theophylline and serum electrolytes. *Ann Intern Med* 1986; **104:** 134–5.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
3. Laaban J-P, *et al.* Hypophosphatemia complicating management of acute severe asthma. *Ann Intern Med* 1990; **112:** 68–9.
4. Hall KW, *et al.* Metabolic abnormalities associated with intentional theophylline overdose. *Ann Intern Med* 1984; **101:** 457–62.
5. McPherson ML, *et al.* Theophylline-induced hypercalcemia. *Ann Intern Med* 1986; **105:** 52–4.

Effects on the heart. *ARRHYTHMIAS.* Theophylline or aminophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions at therapeutic serum-theophylline concentrations[1] and in overdose.[2,3] Multifocal atrial tachycardia has also been associated with both theophylline overdose[2] and serum-theophylline concentrations within the generally accepted therapeutic range of 10 to 20 micrograms/mL.[4] Use of theophylline with oral beta-adrenoceptor stimulants is associated with a significant increase in the mean heart rate.[5,6]

1. Josephson GW, *et al.* Cardiac dysrhythmias during the treatment of acute asthma: a comparison of two treatment regimens by a double blind protocol. *Chest* 1980; **78:** 429–35.
2. Greenberg A, *et al.* Severe theophylline toxicity: role of conservative measures, antiarrhythmic agents, and charcoal hemoperfusion. *Am J Med* 1984; **76:** 854–60.
3. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15:** 471–81.
4. Levine JH, *et al.* Multifocal atrial tachycardia: a toxic effect of theophylline. *Lancet* 1985; **i:** 12–14.
5. Coleman JJ, *et al.* Cardiac arrhythmias during the combined use of β-adrenergic agonist drugs and theophylline. *Chest* 1986; **90:** 45–51.
6. Conradson T-B, *et al.* Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. *Chest* 1987; **91:** 5–9.

Effects on the kidneys. For a report of rhabdomyolysis-induced acute renal failure occurring after aminophylline overdose, see the general discussion on toxicity, above.

Effects on mental function. As mentioned in the general discussion on toxicityabove, theophylline toxicity has been associated with reports of dementia and toxic psychosis, as well as the more common adverse effects of anxiety and restlessness.

LEARNING AND BEHAVIOUR PROBLEMS. Several small studies[1-3] have suggested that theophylline may be associated with learning and behaviour problems in children, especially those with a low IQ. However, the FDA has concluded[4] that such studies provide insufficient evidence to support an adverse effect of theophylline on learning behaviour or school performance. Other studies have found no marked behavioural adverse effects that could be attributed to theophylline.[5,6] Additionally, academic achievement generally appeared to be unaffected by either asthma or by treatment with appropriate doses of theophylline.[7]

1. Furukawa CT, *et al.* Learning and behaviour problems associated with theophylline therapy. *Lancet* 1984; **i:** 621.
2. Springer C, *et al.* Clinical, physiologic, and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. *J Allergy Clin Immunol* 1985; **76:** 64–9.
3. Schlieper A, *et al.* Effect of therapeutic plasma concentrations of theophylline on behavior, cognitive processing, and affect in children with asthma. *J Pediatr* 1991; **118:** 449–55.
4. Anonymous. Theophylline and school performance. *FDA Drug Bull* 1988; **18:** 32–3.
5. Bender B, Milgrom H. Theophylline-induced behavior change in children: an objective evaluation of parents' perceptions. *JAMA* 1992; **267:** 2621–4.
6. Bender BG, *et al.* Neuropsychological behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998; **101:** 355–60.
7. Lindgren S, *et al.* Does asthma or treatment with theophylline limit children's academic performance? *N Engl J Med* 1992; **327:** 926–30.

Effects on the nervous system. *CONVULSIONS.* The risk of convulsions with acute theophylline toxicity is low at serum theophylline concentrations less than 60 micrograms/mL;[1] seizures are most likely in patients with peak concentrations above 100 micrograms/mL.[2] However, the risk of seizures is much greater after chronic overdosage;[1,2] seizure activity has been reported at serum concentrations just above or even within the therapeutic range.[3] Elderly patients or those with previous brain injury or neurological disease may be at increased risk,[2-4] although some have questioned the association.[1] The outcome of seizures appears to be variable: death and severe neurological deficit have occurred,[2,3] but other series have recorded recovery without serious morbidity.[4]

1. Paloucek FP, Rodvold KA. Evaluation of theophylline overdoses and toxicities. *Ann Emerg Med* 1988; **17:** 135–44.
2. Olson KR, *et al.* Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3:** 386–94.
3. Bahls FH, *et al.* Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: risk factors for serious outcome in adults. *Neurology* 1991; **41:** 1309–12.
4. Covelli HD, *et al.* Predisposing factors to apparent theophylline-induced seizures. *Ann Allergy* 1985; **54:** 411–15.

Effects on the skin. For reports of cutaneous reactions to theophylline and aminophylline, see under Hypersensitivity, below.

Effects on the urinary tract. Although diuresis is more commonly seen, urinary retention has been reported in male patients during therapy with aminophylline[1] or theophylline.[2]

1. Owens GR, Tannenbaum R. Theophylline-induced urinary retention. *Ann Intern Med* 1981; **94:** 212–13.
2. Prakash M, Washburne JD. Theophylline and urinary retention. *Ann Intern Med* 1981; **94:** 823.

Hypersensitivity. Hypersensitivity reactions have been reported after oral or intravenous doses of aminophylline. Reactions include erythematous rash with pruritus,[1,2] erythroderma,[2] and exfoliative dermatitis.[3] Aminophylline can produce both type I (immediate) and type IV (delayed) hypersensitivity reactions, the latter being due to the ethylenediamine component and can be confirmed by skin patch tests.[1-3] If hypersensitivity to ethylenediamine is confirmed it is recommended that aminophylline is avoided and treatment continued with theophylline or another theophylline salt.[1,3,4] Hypersensitivity reactions to theophylline have been reported rarely but type I reactions have occurred.[4] An erythematous, maculopapular rash has been reported[5] during treatment with a modified-release theophylline preparation, which did not occur when another modified-release theophylline product was given.

1. Hardy C, *et al.* Allergy to aminophylline. *BMJ* 1983; **286:** 2051–2.
2. Mohsenifar Z, *et al.* Two cases of allergy to aminophylline. *Ann Allergy* 1982; **49:** 281–2.
3. Nierenberg DW, Glazener FS. Aminophylline-induced exfoliative dermatitis: cause and implications. *West J Med* 1982; **137:** 328–31.
4. Gibb WRG. Delayed-type hypersensitivity to theophylline/aminophylline. *Lancet* 1985; **i:** 49.
5. Mendel S, *et al.* Dermatologic reaction to a sustained-release theophylline product. *Clin Pharm* 1985; **4:** 334–5.

Hyperuricaemia. In a study of 112 asthmatic patients receiving modified-release theophylline 200 to 400 mg 12-hourly, there was a significant correlation of serum-uric acid concentrations and serum-theophylline concentrations.[1] Gout has been reported in a woman receiving theophylline and aminophylline;[2] her serum-uric acid concentration was increased while receiving the xanthines, but subsequently fell when they were stopped, and rose again when treatment was resumed.

1. Morita Y, *et al.* Theophylline increases serum uric acid levels. *J Allergy Clin Immunol* 1984; **74:** 707–12.
2. Toda K, *et al.* Gout due to xanthine derivatives. *Br J Rheumatol* 1997; **36:** 1131–2.

Necrotising enterocolitis. Although there have been reports of neonatal necrotising enterocolitis associated with oral theophylline or aminophylline,[1,2] a study of 275 infants concluded that theophylline did not significantly contribute to its development.[3] It has been suggested that the high osmolality of liquid feeds and drugs including oral theophylline preparations may be involved in the aetiology of necrotising enterocolitis.[4]

1. Robinson MJ, *et al.* Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 494–5.
2. Williams AJ. Xanthines and necrotising enterocolitis. *Arch Dis Child* 1980; **55:** 973–4.
3. Davis JM, *et al.* Role of theophylline in pathogenesis of necrotizing enterocolitis. *J Pediatr* 1986; **109:** 344–7.
4. Watkinson M, *et al.* Hyperosmolar preparations for neonates. *Pharm J* 1987; **241:** 488.

Withdrawal syndromes. Episodes of apnoea beginning 28 hours after birth and increasing in frequency and severity over the next 4 days occurred in a neonate whose mother had taken aminophylline and theophylline throughout pregnancy. Measurement of serum-theophylline concentration showed the increasing apnoea coincided with falling theophylline concentration. The infant's apnoea resolved on giving theophylline; treatment was stopped after 4 months.[1]

Worsening asthma control may occur when theophylline is withdrawn; there is some evidence of a rebound deterioration in lung function due to the development of tolerance.[2]

1. Horowitz DA, *et al.* Apnea associated with theophylline withdrawal in a term neonate. *Am J Dis Child* 1982; **136:** 73–4.
2. Bennett JA, *et al.* The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998; **45:** 402–4.

Treatment of Adverse Effects

After theophylline or aminophylline overdosage, elimination may be enhanced by repeated oral doses of activated charcoal regardless of the route of overdose (see below). An osmotic laxative may also be considered. Treatment is symptomatic and supportive; ECG monitoring is recommended. Serum-theophylline concentrations should be monitored and if modified-release preparations have been taken monitoring should be prolonged. Metabolic abnormalities, particularly hypokalaemia, should be corrected; hypokalaemia may be so severe as to require intravenous infusion of potassium. In the non-asthmatic patient severe tachycardia, hypokalaemia, and hyperglycaemia may be reversed by a non-selective beta blocker (see also below). Patients with asthma or chronic obstructive pulmonary disease (COPD) who, after correction of hypokalaemia, have severe tachycardia, may be treated with intravenous verapamil. Alternatively direct current (DC) cardioversion may be considered. Ventricular arrhythmias causing haemodynamic compromise should also be treated with DC cardioversion. Isolated convulsions may be controlled by intravenous diazepam or a barbiturate; phenytoin may be less effective. In the most refractory cases general anaesthesia, and neuromuscular blockade, with ventilation, may be required.

Charcoal haemoperfusion or haemodialysis may be required.

◊ Reviews.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151:** 689–93.
2. Skinner MH. Adverse reactions and interactions with theophylline. *Drug Safety* 1990; **5:** 275–85.
3. Minton NA, Henry JA. Treatment of theophylline overdose. *Am J Emerg Med* 1996; **14:** 606–12.

Activated charcoal. Multiple-dose oral activated charcoal is considered the cornerstone of treatment for theophylline and xanthine poisoning. It reduces the absorption of oral theophylline, and also enhances the elimination of theophylline from the body even after absorption or intravenous doses of xanthine. Aggressive antiemetic therapy may be required to allow use and retention of activated charcoal, since theophylline toxicity causes protracted vomiting. A cathartic such as sorbitol may be given with the activated charcoal to aid elimination of theophylline, but can cause fluid and electrolyte disturbances. For oral theophylline overdose the use of gastric lavage before oral activated charcoal may not be better than activated charcoal alone.

References.

1. Neuvonen PJ, *et al.* Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur J Clin Pharmacol* 1983; **24:** 557–62.
2. Berlinger WG, *et al.* Enhancement of theophylline clearance by oral activated charcoal. *Clin Pharmacol Ther* 1983; **33:** 351–4.
3. Mahutte CK, *et al.* Increased serum theophylline clearance with orally administered activated charcoal. *Am Rev Respir Dis* 1983; **128:** 820–2.
4. Park GD, *et al.* Effects of size and frequency of oral doses of charcoal on theophylline clearance. *Clin Pharmacol Ther* 1983; **34:** 663–6.
5. Goldberg MJ, *et al.* The effect of sorbitol and activated charcoal on serum theophylline concentrations after slow-release theophylline. *Clin Pharmacol Ther* 1987; **41:** 108–11.
6. Al-Shareef AH, *et al.* The effects of charcoal and sorbitol (alone and in combination) on plasma theophylline concentrations after a sustained-release formulation. *Hum Exp Toxicol* 1990; **9:** 179–82.
7. Minton NA, *et al.* Prevention of drug absorption in simulated theophylline overdose. *Hum Exp Toxicol* 1995; **14:** 170–4.

Beta blockers. Infusion of propranolol after theophylline overdose in 2 patients was associated with improvement in hyperglycaemia, hypokalaemia, tachycardia, and hypotension. Beta-adrenergic blockade may therefore be of benefit in the management of the metabolic changes of theophylline poisoning, especially in the non-asthmatic patient.[1,2] However, in asthmatic patients, beta blockers should be reserved for those with severe hypokalaemia or cardiac arrhythmias when mechanical ventilation is available as beta blockers can cause bronchoconstriction.[1,2] Propranolol reduces the clearance of theophylline (see under Interactions, below) and it has been suggested that a non-interacting beta blocker may be more appropriate.[3] Esmolol has been used successfully to manage cardiovascular symptoms of overdosage.[4]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Amin DN, Henry JA. Propranolol administration in theophylline overdose. *Lancet* 1985; **i:** 520–1.
3. Farrar KT, Dunn AM. Beta-blockers in treatment of theophylline overdose. *Lancet* 1985; **i:** 983.
4. Seneff M, *et al.* Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. *Ann Emerg Med* 1990; **19:** 671–3.

Endoscopy. Absorption is delayed after overdosage with modified-release oral preparations of aminophylline or theophylline and may be further prolonged by the formation of tablet aggregates, or bezoars, in the stomach.[1-3] Of 11 patients admitted with overdosage, one vomited a bezoar, 2 had bezoars removed at gastroscopy, and in one a bezoar was found at necropsy.[3] If bezoar formation occurs gastric lavage and activated charcoal will have little if any effect and the patient may appear to stabilise before experiencing increasing serum-theophylline concentration and clinical deterioration;[1,2] fatalities have been reported.[1] Endoscopy should be considered in cases of modified-release theophylline overdosage in which clinical signs and serial concentration measurements suggest continuing drug absorption.[2]

1. Coupe M. Self-poisoning with sustained-release aminophylline: a mechanism for observed secondary rise in serum theophylline. *Hum Toxicol* 1986; **5:** 341–2.
2. Cereda J-M, *et al.* Endoscopic removal of pharmacobezoar of slow release theophylline. *BMJ* 1986; **293:** 1143.
3. Smith WDF. Endoscopic removal of a pharmacobezoar of slow release theophylline. *BMJ* 1987; **294:** 125.

Haemodialysis and haemoperfusion. Extracorporeal theophylline removal techniques after overdosage of aminophylline or theophylline have been reviewed.[1] Neither peritoneal dialysis nor exchange transfusion produced a significant increase in the total body clearance of theophylline, whereas haemodialysis could be expected to double clearance, and haemoperfusion results in four- to sixfold increases in clearance. Charcoal haemoperfusion should be considered if the plasma-theophylline concentration exceeds 100 micrograms/mL in an acute intoxication, or 60 micrograms/mL in chronic overdose (40 micrograms/mL if there is significant respiratory or heart failure, or liver disease) though plasma concentrations alone should not determine its use (see under Adverse Effects, above). If there is intractable vomiting, arrhythmias, or seizures charcoal haemoperfusion should be started without delay. In most patients a 4-hour haemoperfusion allows significant clinical improvement, but treatment should continue until plasma concentrations are below 15 micrograms/mL. Plasma concentrations should be followed at least every 4 hours for the first 12 hours post-perfusion, as rebound increases have been noted on terminating perfusion.

Haemodialysis may rarely be an alternative if haemoperfusion is not available, or in series with haemoperfusion if significant rhabdomyolysis is present. There has been a case report[2] of continuous venovenous haemofiltration used to treat severe theophylline toxicity.

1. Heath A, Knudsen K. Role of extracorporeal drug extraction in acute theophylline poisoning: a review. *Med Toxicol* 1987; **2:** 294–308.
2. Henderson JH, *et al.* Continuous venovenous haemofiltration for the treatment of theophylline toxicity. *Thorax* 2001; **56:** 242–3.

Precautions

Theophylline or aminophylline should be given with caution to patients with peptic ulceration, porphyria, hyperthyroidism, hypertension, cardiac arrhythmias or other cardiovascular disease, or epilepsy, as these conditions may be exacerbated. They should also be given with caution to patients with heart failure, hepatic dysfunction, acute febrile illness, and to neonates and the elderly, since in all of these circumstances theophylline clearance may be decreased, resulting in increases in serum-theophylline concentrations and serum half-life. Conversely, smoking and alcohol consumption increase theophylline clearance. Many drugs interact with theophylline; for details see Interactions, below.

Intravenous injections of theophylline or aminophylline must be given very slowly to prevent dangerous CNS and cardiovascular adverse effects resulting from the direct stimulant effect.

Dosage requirements of theophylline vary widely between subjects; in view of the many factors affecting theophylline pharmacokinetics, serum concentration monitoring is necessary to ensure concentrations are within the therapeutic range.

Patients should not be transferred from one modified-release theophylline or aminophylline preparation to another without clinical assessment and the measurement of serum-theophylline concentrations because of bioavailability differences.

Acute febrile illness. A reduction in theophylline clearance has been noted in patients presenting with acute respiratory illness[1] and appears to be associated with the severity of the underlying pulmonary disease and the rate of change in the patient's condition.[2] Caution has been advised in giving theophylline to patients with chronic obstructive pulmonary disease with acute exacerbations, since these patients appear most likely to exhibit altered theophylline metabolism.[2]

Similarly, a decrease in theophylline clearance and an increase in the incidence of adverse effects has been reported during acute viral infections such as influenza in children receiving theophylline therapy for chronic asthma.[3,4] Another study in asthmatic children found that acute febrile illness accompanied by increased C-Reactive Protein (CRP) level may affect theophylline metabolism.[5] The authors postulated that cytokines released in the process of acute illness were responsible. Influenza vaccination has also been reported to reduce theophylline clearance (see under Interactions, below). The mechanism by which theophylline metabolism is reduced in these patients may be related to increased interferon production during the acute febrile response. A dosage reduction of one half has been recommended[6] in children receiving chronic theophylline therapy who are febrile for more than 24 hours. Further dose adjustments should be based on serum-theophylline concentrations until the patients have recovered from their acute illness and are restabilised on their usual dosage. However, conflicting results have been reported and in one controlled study RSV infection was found to have no significant effect on theophylline disposition in children.[7]

1. Vozeh S, *et al.* Changes in theophylline clearance during acute illness. *JAMA* 1978; **240:** 1882–4.
2. Richer M, Lam YWF. Hypoxia, arterial pH and theophylline disposition. *Clin Pharmacokinet* 1993; **25:** 283–99.
3. Chang KC, *et al.* Altered theophylline pharmacokinetics during acute respiratory viral illness. *Lancet* 1978; **i:** 1132–3.
4. Kraemer MJ, *et al.* Altered theophylline clearance during an influenza B outbreak. *Pediatrics* 1982; **69:** 476–80.
5. Yamaguchi A, *et al.* Higher incidence of elevated body temperature or increased C-reactive protein level in asthmatic children showing transient reduction of theophylline metabolism. *J Clin Pharmacol* 2000; **40:** 284–9.
6. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
7. Muslow HA, *et al.* Lack of effect of respiratory syncytial virus infection on theophylline disposition in children. *J Pediatr* 1992; **121:** 466–71.

Age. For the effects of age on the metabolism and excretion of theophylline see under Pharmacokinetics, below. Dosage regimens for infants are discussed under Administration in Infants, in Uses and Administration, below.

Breast feeding. From one study of 3 women it was estimated that less than 1% of the total theophylline eliminated was found in breast milk.[1] Another study of 5 women estimated that a breast-fed infant would receive less than 10% of the maternal dose of theophylline.[2] These amounts were considered unlikely to cause toxicity, but it has been reported that irritability in one infant seemed to occur on the intermittent days when the mother took aminophylline. The American Academy of Pediatrics[3] states that theophylline is usually compatible with breast feeding, although it noted that irritability has been reported in infants whose mothers were receiving theophylline.

1. Stec GP, *et al.* Kinetics of theophylline transfer to breast milk. *Clin Pharmacol Ther* 1980; **28:** 404–8.
2. Yurchak AM, Jusko WJ. Theophylline secretion into breast milk. *Pediatrics* 1976; **57:** 518–20.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

ECT. Patients receiving theophylline are at risk of prolonged seizures during ECT, and status epilepticus has been reported.[1,2] The ability of theophylline to prolong seizures has led to it being used as an adjunct in ECT.[3] Caffeine has been used similarly, see p.1118.

1. Peters SG, *et al.* Status epilepticus as a complication of concurrent electroconvulsive and theophylline therapy. *Mayo Clin Proc* 1984; **59:** 568–70.
2. Rasmussen KG, Zorumski CF. Electroconvulsive therapy in patients taking theophylline. *J Clin Psychiatry* 1993; **54:** 427–31.
3. Leentjens AFG, *et al.* Facilitation of ECT by intravenous administration of theophylline. *Convuls Ther* 1996; **12:** 232–7.

Porphyria. Theophylline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. It has been recommended[1] that serum-theophylline concentrations are measured at monthly intervals throughout pregnancy and 1 and 4 weeks after delivery since the pharmacokinetics of theophylline may be altered. An increase in the volume of distribution of theophylline, a decrease in plasma-protein binding, and a continuing decrease in clearance throughout pregnancy have been noted in some patients, especially during the later part of pregnancy,[2-4] but other studies have noted an increase in theophylline clearance during pregnancy.[1,5] Some studies have found that after delivery there is a return of clearance values to those existing before pregnancy,[2] while others have not.[4]

In a study of 12 neonates whose mothers received various theophylline preparations throughout their pregnancies[6] maternal, cord, and neonatal heelstick theophylline concentrations ranged from 2.3 to 19.6 micrograms/mL. Transient jitteriness was seen in 2 neonates and tachycardia in one, at cord theophylline concentrations of 11.7 to 17 micrograms/mL. There were no instances of vomiting, seizure, arrhythmias, diarrhoea, or feeding disturbances, which had been reported previously.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. Carter BL, *et al.* Theophylline clearance during pregnancy. *Obstet Gynecol* 1986; **68:** 555–9.
3. Frederiksen MC, *et al.* Theophylline pharmacokinetics in pregnancy. *Clin Pharmacol Ther* 1986; **40:** 321–8.
4. Gardner MJ, *et al.* Longitudinal effects of pregnancy on the pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1987; **31:** 289–95.
5. Romero R, *et al.* Pharmacokinetics of intravenous theophylline in pregnant patients at term. *Am J Perinatol* 1983; **1:** 31–5.
6. Labovitz E, Spector S. Placental theophylline transfer in pregnant asthmatics. *JAMA* 1982; **247:** 786–8.

Renal impairment. Theophylline is eliminated mainly by hepatic metabolism and usual doses of aminophylline or theophylline can be given to patients with renal impairment. In patients undergoing haemodialysis the clearance of theophylline is increased and its elimination half-life reduced; mean values of 84.8 and 83 mL/minute and 2.5 and 2.3 hours respectively have been reported.[1,2] Haemodialysis removes up to 40% of a dose of theophylline.[1] Peritoneal dialysis has little effect on the pharmacokinetics of theophylline removing about 3.2% of a dose.[1]

1. Lee C-SC, *et al.* Comparative pharmacokinetics of theophylline in peritoneal dialysis and hemodialysis. *J Clin Pharmacol* 1983; **23:** 274–80.
2. Anderson JR, *et al.* Effects of hemodialysis on theophylline kinetics. *J Clin Pharmacol* 1983; **23:** 428–32.

Smoking. Certain components of tobacco smoke, notably aromatic hydrocarbons, induce hepatic drug-metabolising enzymes and cigarette smoking has been reported[1-3] to increase theophylline clearance and shorten its elimination half-life. The effect of smoking may override factors that tend to decrease theophylline clearance, such as old age.[4] The duration of enzyme induction after stopping smoking is uncertain; theophylline clearance decreased by 38% after one week of abstinence from smoking in one study,[5] while others have found changes in clearance persisting for at least 3 months.[1] Tobacco chewing has also been reported to increase theophylline clearance,[6] but nicotine chewing gum appears to have no effect.[5]

1. Hunt SN, *et al.* Effect of smoking on theophylline disposition. *Clin Pharmacol Ther* 1976; **19:** 546–51.
2. Jusko WJ, *et al.* Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin Pharmacol Ther* 1978; **24:** 406–10.
3. Grygiel JJ, Birkett DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther* 1981; **30:** 491–6.
4. Cusack B, *et al.* Theophylline kinetics in relation to age: the importance of smoking. *Br J Clin Pharmacol* 1980; **10:** 109–14.
5. Lee BL, *et al.* Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* 1987; **106:** 553–5.
6. Rockwood R, Henann N. Smokeless tobacco and theophylline clearance. *Drug Intell Clin Pharm* 1986; **20:** 624–5.

Interactions

The toxic effects of theophylline, aminophylline, and other xanthines are additive. Use with other xanthine medications should therefore be avoided; if intravenous aminophylline is to be given for acute bronchospasm in patients who have been taking maintenance theophylline therapy, serum-theophylline concentrations should be measured first and the initial dose reduced as appropriate (see Uses and Administration, below).

Theophylline clearance may be reduced by interaction with other drugs including allopurinol, some antiarrhythmics, cimetidine, disulfiram, fluvoxamine, interferon alfa, macrolide antibacterials and quinolones, oral contraceptives, tiabendazole, and viloxazine, and the dose of theophylline may need to be reduced. Phenytoin and some other antiepileptics, ritonavir, rifampicin, and sulfinpyrazone may increase theophylline clearance, and require an increase in dose or dosing frequency of theophylline.

Xanthines can potentiate hypokalaemia caused by hypoxia or associated with the use of beta$_2$-adrenoceptor stimulants (beta$_2$ agonists), corticosteroids, and diuretics. There is a risk of synergistic toxicity if theophylline is given with halothane or ketamine, and it may antagonise the effects of adenosine and of competitive neuromuscular blockers; lithium elimination may be enhanced with a consequent loss of effect. The interaction between theophylline and beta blockers is complex (see below) but use together tends to be avoided on pharmacological grounds since beta blockers produce bronchospasm.

◊ Theophylline is metabolised by several hepatic cytochrome P450 isoenzymes, of which the most important seems to be CYP1A2.[1] Numerous drugs affect the metabolic clearance of theophylline and aminophylline,[2] but the variability in theophylline pharmacokinetics makes the clinical significance of these interactions difficult to predict. Giving theophylline with drugs that inhibit its metabolism should be avoided but, if unavoidable, the dose of theophylline should be halved.[3] There is some evidence to suggest that less of a dose reduction is required in the presence of severe liver dysfunction,[4] aside from that already required by impaired hepatic metabolism, see Administration in Hepatic Impairment, below. Subsequent doses should be adjusted based on serum-theophylline monitoring.[3] Even when introducing medication for which no interaction is suspected, a check on the serum-theophylline concentration within 24 hours of beginning the new drug has been advised.[3]

Theophylline reduces liver plasma flow[5] and may therefore prolong the half-life and increase steady-state levels of hepatically eliminated drugs but it is claimed to have no effect on antipyrine clearance.[6]

1. Ha HR, *et al.* Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; **39:** 321–6.
2. Upton RA. Pharmacokinetic interactions between theophylline and other medication. *Clin Pharmacokinet* 1991; **20:** 66–80 (part I) and 135–50 (part II).
3. American Academy of Pediatrics Committee on Drugs. Precautions concerning the use of theophylline. *Pediatrics* 1992; **89:** 781–3.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Onrot J, *et al.* Reduction of liver plasma flow by caffeine and theophylline. *Clin Pharmacol Ther* 1986; **40:** 506–10.
6. Døssing M, *et al.* Effect of theophylline and salbutamol on hepatic drug metabolism. *Hum Toxicol* 1989; **8:** 225–8.

Antiarrhythmics. An increase in serum-theophylline concentration from 93.2 to 194.2 micromol/litre with symptoms of tachycardia, nervousness, and tremors occurred in a patient 9 days after starting *amiodarone* therapy.[1] Elevated theophylline concentrations and/or decreased clearance have also been reported following addition of *mexiletine* to theophylline therapy.[2-6] Amiodarone and mexiletine probably interact with theophylline through inhibition of its hepatic metabolism. *Tocainide* has also been found to impair theophylline metabolism resulting in a reduction in theophylline clearance but the effect was substantially smaller than that of mexiletine.[7] In one patient stabilised on theophylline therapy, an increase in the plasma-theophylline concentration with subsequent toxicity was noted after starting treatment with *propafenone*.[8] See also under Calcium-channel Blockers, below.

1. Soto J, *et al.* Possible theophylline-amiodarone interaction. *DICP Ann Pharmacother* 1990; **24:** 1115.
2. Stanley R, *et al.* Mexiletine-theophylline interaction. *Am J Med* 1989; **86:** 733–4.
3. Ueno K, *et al.* Interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1990; **24:** 471–2.
4. Hurwitz A, *et al.* Mexiletine effects on theophylline disposition. *Clin Pharmacol Ther* 1991; **50:** 299–307.
5. Loi C-M, *et al.* Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. *Clin Pharmacol Ther* 1991; **49:** 571–80.
6. Ueno K, *et al.* Mechanism of interaction between theophylline and mexiletine. *DICP Ann Pharmacother* 1991; **25:** 727–30.
7. Loi C-M, *et al.* The effect of tocainide on theophylline metabolism. *Br J Clin Pharmacol* 1993; **35:** 437–40.
8. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. *Clin Pharmacol Ther* 1992; **51:** 353–5.

Antibacterials. ***IMIPENEM.*** Seizures have been reported in 3 patients receiving theophylline who were given imipenem,[1] although serum concentrations of theophylline were not affected.

1. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* 1991; **84:** 465–8.

ISONIAZID. Isoniazid inhibits oxidative enzymes in the liver and has been found to impair the elimination of theophylline. Both clearance and volume of distribution of theophylline were reduced with an increase in serum-theophylline concentrations in healthy subjects after 14 days of pretreatment with isoniazid[1] and theophylline toxicity has been reported[2] in a patient one month after adding theophylline to isoniazid therapy.

1. Samigun, *et al.* Lowering of theophylline clearance by isoniazid in slow and rapid acetylators. *Br J Clin Pharmacol* 1990; **29:** 570–3.
2. Torrent J, *et al.* Theophylline-isoniazid interaction. *DICP Ann Pharmacother* 1989; **23:** 143–5.

MACROLIDES. There are conflicting reports of the effect of *erythromycin* on the pharmacokinetics of theophylline. Significant decreases in the clearance of theophylline and prolonged elimination half-life have been reported[1-3] but other studies have found no interaction.[4,5] It has also been noted that the serum concentrations and bioavailability of erythromycin may be reduced by theophylline[6,7] (see also p.271). The clearance of theophylline is also markedly decreased by *troleandomycin*,[8-10] but there have been reports that for clinical purposes the pharmacokinetics of theophylline do not seem to be significantly altered by *dirithromycin*,[11-13] *josamycin*,[9,14] *midecamycin*,[10,15,16] *rokitamycin*,[17] *roxithromycin*,[18] or *spiramycin*.[19] *Clarithromycin* also seems unlikely to have a significant effect in most patients, but in a few theophylline dosage may need to be adjusted.[20,21] In one case report, serum-theophylline concentrations fell over a few days after the withdrawal of *azithromycin*.[22]

1. Zarowitz BJM, *et al.* Effect of erythromycin base on theophylline kinetics. *Clin Pharmacol Ther* 1981; **29:** 601–5.
2. Renton KW, *et al.* Depression of theophylline elimination by erythromycin. *Clin Pharmacol Ther* 1981; **30:** 422–6.
3. May DC, *et al.* The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; **22:** 125–30.
4. Maddux MS, *et al.* The effect of erythromycin on theophylline pharmacokinetics at steady state. *Chest* 1982; **81:** 563–5.
5. Hildebrandt R, *et al.* Lack of clinically important interaction between erythromycin and theophylline. *Eur J Clin Pharmacol* 1984; **26:** 485–9.
6. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
7. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
8. Weinberger M, *et al.* Inhibition of theophylline clearance by troleandomycin. *J Allergy Clin Immunol* 1977; **59:** 228–31.
9. Brazier JL, *et al.* Retard d'élimination de la théophylline dû à la troléandomycine: absence d'effet de la josamycine. *Therapie* 1980; **35:** 545–9.
10. Lavarenne J, *et al.* Influence d'un nouveau macrolide, la midécamycine, sur les taux sanguins de théophylline. *Therapie* 1981; **36:** 451–6.
11. Bachmann K, *et al.* Changes in the steady-state pharmacokinetics of theophylline during treatment with dirithromycin. *J Clin Pharmacol* 1990; **30:** 1001–5.
12. Bachmann K, *et al.* Steady-state pharmacokinetics of theophylline in COPD patients treated with dirithromycin. *J Clin Pharmacol* 1993; **33:** 861–5.
13. McConnell SA, *et al.* Lack of effect of dirithromycin on theophylline pharmacokinetics in healthy volunteers. *J Antimicrob Chemother* 1999; **43:** 733–6.
14. Ruff F, *et al.* Macrolide et théophylline: absence d'interaction josamycine-théophylline. *Nouv Presse Med* 1981; **10:** 175.
15. Principi N, *et al.* Effect of miocamycin on theophylline kinetics in children. *Eur J Clin Pharmacol* 1987; **31:** 701–4.
16. Couet W, *et al.* Lack of effect of ponsinomycin on the plasma pharmacokinetics of theophylline. *Eur J Clin Pharmacol* 1989; **37:** 101–4.
17. Ishioka T. Effect of a new macrolide antibiotic, 3″-O-propionylleucomycin A (rokitamycin) on serum concentrations of theophylline and digoxin in the elderly. *Acta Ther* 1987; **13:** 17–24.
18. Saint-Salvi B, *et al.* A study of the interaction of roxithromycin with theophylline and carbamazine. *J Antimicrob Chemother* 1987; **20** (suppl B): 121–9.
19. Debruyne D, *et al.* Spiramycin has no effect on serum theophylline in asthmatic patients. *Eur J Clin Pharmacol* 1986; **30:** 505–7.
20. Bachand RT. Comparative study of clarithromycin and ampicillin in the treatment of patients with acute bacterial exacerbations of chronic bronchitis. *J Antimicrob Chemother* 1991; **27** (suppl A): 91–100.
21. Gillum JG, *et al.* Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1996; **40:** 1715–16.
22. Pollak PT, Slayter KL. Reduced serum theophylline concentrations after discontinuation of azithromycin: evidence for an unusual interaction. *Pharmacotherapy* 1997; **17:** 827–9.

QUINOLONES. The fluoroquinolone antibacterials vary in their propensity to interact with theophylline. *Enoxacin* shows the most marked interaction and has been reported[1] to cause serious nausea and vomiting, tachycardia, and headaches, associated with unexpectedly high plasma-theophylline concentrations in patients with respiratory-tract infections. Studies,[2-5] mainly in healthy subjects, have found that enoxacin decreases theophylline clearance by up to 74%[3] with an increase in the elimination half-life and serum-theophylline concentration.

Ciprofloxacin[2,6-8] and *pefloxacin*[2] interact with theophylline to a lesser extent than enoxacin, decreasing theophylline clearance by about 30%. Eight clinically important interactions between ciprofloxacin and theophylline had been reported to the UK CSM[9] including 1 death. A ciprofloxacin-induced seizure has been reported[10] which may have been due to the combined inhibitory effects of the 2 drugs on GABA binding. It has been recommended that ciprofloxacin should not be used in patients treated with theophylline.[9]

Norfloxacin[4,11-13] and *ofloxacin*[4,11,14] have been reported to have minor effects on the pharmacokinetics of theophylline. Although their effects were usually considered not to be clinically significant, the US FDA had received 9 reports of theophylline toxicity associated with use with norfloxacin, including 1 death.[15] *Fleroxacin*,[16] *flumequine*,[17] *lomefloxacin*,[8,18,19] *moxifloxacin*,[20] and *rufloxacin*[21] have been reported to have no significant effect on the pharmacokinetics of theophylline in small studies in healthy subjects.

The mechanism of interaction involves a reduction in the metabolic clearance of theophylline due to inhibition of hepatic microsomal enzymes. However, the exact mechanism is unknown and it is difficult to predict which patients will be at risk. Extreme caution should be used when giving quinolones with theophylline, particularly in the elderly[15] and it may be advisable to use a non-interacting fluoroquinolone, although theophylline concentrations should still be monitored.

Of the non-fluorinated quinolones, *nalidixic acid*[2] has been reported not to affect theophylline clearance whereas *pipemidic acid* has markedly inhibited theophylline clearance.[19]

1. Wijnands WJA, *et al.* Enoxacin raises plasma theophylline concentrations. *Lancet* 1984; **ii:** 108–9.
2. Wijnands WJA, *et al.* The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; **22:** 677–83.
3. Beckmann J, *et al.* Enoxacin—a potent inhibitor of theophylline metabolism. *Eur J Clin Pharmacol* 1987; **33:** 227–30.
4. Sano M, *et al.* Inhibitory effect of enoxacin, ofloxacin and norfloxacin on renal excretion of theophylline in humans. *Eur J Clin Pharmacol* 1989; **36:** 323–4.
5. Koup JR, *et al.* Theophylline dosage adjustment during enoxacin coadministration. *Antimicrob Agents Chemother* 1990; **34:** 803–7.
6. Nix DE, *et al.* Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; **19:** 263–9.
7. Schwartz J, *et al.* Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob Agents Chemother* 1988; **32:** 75–7.
8. Robson RA, *et al.* Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 491–3.
9. Bem JL, Mann RD. Danger of interaction between ciprofloxacin and theophylline. *BMJ* 1988; **296:** 1131.
10. Karki SD, *et al.* Seizure with ciprofloxacin and theophylline combined therapy. *DICP Ann Pharmacother* 1990; **24:** 595–6.
11. Sano M, *et al.* Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. *Eur J Clin Pharmacol* 1987; **32:** 431–2.
12. Ho G, *et al.* Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1988; **44:** 35–8.
13. Davis RL, *et al.* Effect of norfloxacin on theophylline metabolism. *Antimicrob Agents Chemother* 1989; **33:** 212–14.
14. Gregoire SL, *et al.* Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. *Antimicrob Agents Chemother* 1987; **31:** 375–8.
15. Grasela TH, Dreis MW. An evaluation of the quinolone-theophylline interaction using the Food and Drug Administration spontaneous reporting system. *Arch Intern Med* 1992; **152:** 617–21.
16. Parent M, *et al.* Safety of fleroxacin coadministered with theophylline to young and elderly volunteers. *Antimicrob Agents Chemother* 1990; **34:** 1249–53.
17. Lacarelle B, *et al.* The quinolone, flumequine, has no effect on theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1994; **46:** 477–8.
18. LeBel M, *et al.* Influence of lomefloxacin on the pharmacokinetics of theophylline. *Antimicrob Agents Chemother* 1990: **34:** 1254–6.
19. Staib AH, *et al.* Interaction of quinolones with the theophylline metabolism in man: investigations with lomefloxacin and pipemidic acid. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 289–93.
20. Stass H, Kubitza D. Lack of pharmacokinetic interaction between moxifloxacin, a novel 8-methoxyfluoroquinolone, and theophylline. *Clin Pharmacokinet* 2001; **40** (suppl 1): 63–70.
21. Kinzig-Schippers M, *et al.* Absence of effect of rufloxacin on theophylline pharmacokinetics in steady state. *Antimicrob Agents Chemother* 1998; **42:** 2359–64.

RIFAMPICIN. Rifampicin induces hepatic oxidative enzymes and a dose of 600 mg daily by mouth for 6 to 14 days has been shown to increase mean plasma-theophylline clearance by 25 to 82% due to enhancement of hepatic theophylline metabolism. This increase in clearance is sufficient to require dosage adjustment in some patients,[1-4] including children.[5]

1. Straughn AB, *et al.* Effect of rifampin on theophylline disposition. *Ther Drug Monit* 1984; **6:** 153–6.
2. Robson RA, *et al.* Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways. *Br J Clin Pharmacol* 1984; **18:** 445–8.
3. Boyce EG, *et al.* The effect of rifampin on theophylline kinetics. *J Clin Pharmacol* 1986; **26:** 696–9.
4. Adebayo GE, *et al.* Attenuation of rifampicin-induced theophylline metabolism by diltiazem/rifampicin coadministration in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 127–31.
5. Brocks DR, *et al.* Theophylline-rifampin interaction in a pediatric patient. *Clin Pharm* 1986; **5:** 602–4.

TETRACYCLINES. *Tetracycline* weakly inhibited theophylline clearance after 5 days of therapy in 5 non-smoking adults with chronic obstructive airways disease[1] and theophylline toxicity has been reported[2] in a patient given a 10-day course of tetracycline during theophylline therapy. *Doxycycline* has been reported not to have any significant effect on theophylline pharmacokinetics in healthy subjects.[3]

1. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. *Drug Intell Clin Pharm* 1986; **20:** 694–7.
2. McCormack JP, *et al.* Theophylline toxicity induced by tetracycline. *Clin Pharm* 1990; **9:** 546–9.
3. Jonkman JHG, *et al.* No influence of doxycycline on theophylline pharmacokinetics. *Ther Drug Monit* 1985; **7:** 92–4.

Antidepressants. Significantly reduced clearance and increased plasma concentrations of theophylline have been reported when given with *viloxazine*.[1,2] The dosage of theophylline should be decreased and its plasma concentrations monitored when viloxazine is also prescribed.[2] The interaction probably involves competition between the two drugs for hepatic microsomal enzymes.

Fluvoxamine has also been associated with a significant reduction in theophylline clearance[3,4] and theophylline toxicity has been described in patients when fluvoxamine was added to their therapy.[5,6] This interaction which is due to potent liver enzyme inhibition[7] has been the subject of a warning by the UK CSM[8] in which they issued the standard advice of avoiding the two drugs if at all possible and, where they could not be avoided, of giving half the dose of theophylline and monitoring plasma concentrations. A small study evaluating the effect of liver cirrhosis on the interaction between fluvoxamine and theophylline observed a decrease in fluvoxamine-induced inhibition of theophylline clearance as the severity of liver cirrhosis increased.[4] The authors suggest that theophylline may require less of a dose reduction in the presence of severe liver dysfunction, aside from that already required by impaired hepatic metabolism, see Administration in Hepatic Impairment, below.

St John's wort may have decreased theophylline concentrations and increased the theophylline dosage requirement in one case report.[9] However, a study[10] in 12 healthy subjects found that 15 days of treatment with St John's wort did not significantly change theophylline pharmacokinetics.

For a mention of the effect of theophylline on the renal clearance of *lithium*, see Xanthines, under Interactions of Lithium, p.405.

1. Thomson AH, *et al.* Theophylline toxicity following coadministration of viloxazine. *Ther Drug Monit* 1988; **10:** 359–60.
2. Perault MC, *et al.* A study of the interaction of viloxazine with theophylline. *Ther Drug Monit* 1989; **11:** 520–2.
3. Donaldson KM, *et al.* The effect [of] fluvoxamine at steady state on the pharmacokinetics of theophylline after a single dose in healthy male volunteers. *Br J Clin Pharmacol* 1994; **37:** 492P.
4. Orlando R, *et al.* Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2-mediated theophylline metabolism by fluvoxamine. *Clin Pharmacol Ther* 2006; **79:** 489–99.
5. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* 1991; **6:** 460–2.
6. Thomson AH, *et al.* Interaction between fluvoxamine and theophylline. *Pharm J* 1992; **249:** 137.
7. Rasmussen BB, *et al.* Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 1995; **39:** 151–9.
8. Committee on Safety of Medicines/Medicines Control Agency. Fluvoxamine increases plasma theophylline levels. *Current Problems* 1994; **20:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
9. Nebel A, *et al.* Potential metabolic interaction between St John's wort and theophylline. *Ann Pharmacother* 1999; **33:** 502.
10. Morimoto T, *et al.* Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 95–101.

Antiepileptics. *Phenytoin* markedly decreases the elimination half-life and increases the clearance of theophylline, probably due to hepatic enzyme induction, at therapeutic serum-phenytoin concentrations,[1-3] at subtherapeutic phenytoin concentrations,[2,4] and even in heavy smokers.[2] A preliminary report suggested that the serum concentration of phenytoin may be decreased simultaneously,[5] perhaps due to enzyme induction by theophylline[5] or reduced phenytoin absorption.[6] The interaction has been reported to occur within 5 to 14 days of taking phenytoin and theophylline, and theophylline clearance has increased by up to 350%, and reductions in serum half-life have ranged from 25 to 70% of initial values.[3,4]

Carbamazepine has also been seen to increase theophylline elimination. In one patient, theophylline serum half-life was decreased by about 24 to 60%, and clearance was increased by about 35 to 100% when carbamazepine was given.[2] In an 11-year-old girl theophylline-serum half-life was almost halved with loss of asthma control after 3 weeks of concurrent carbamazepine therapy.[7] In turn, theophylline has been reported to reduce serum concentrations of carbamazepine—see p.475.

Although *phenobarbital* was not found to have a significant effect on the pharmacokinetics of a single dose of theophylline given intravenously,[8] enhanced theophylline clearance has been seen in patients after longer periods of treatment with phenobarbital.[9,10] The magnitude of the changes in theophylline elimination appears to be smaller with phenobarbital than phenytoin. *Pentobarbital* in high doses has also been reported to increase theophylline metabolism.[11] A more recent study[12] has also shown that therapeutic doses of pentobarbital (100 mg daily) increase plasma clearance of theophylline by a mean of 40%, although this was subject to marked interindividual variations. Renal clearance was not affected, suggesting hepatic enzyme induction as the probable mechanism.

1. Marquis J-F, *et al.* Phenytoin-theophylline interaction. *N Engl J Med* 1982; **307:** 1189–90.
2. Reed RC, Schwartz HJ. Phenytoin-theophylline-quinidine interaction. *N Engl J Med* 1983; **308:** 724–5.
3. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. *Drug Intell Clin Pharm* 1985; **19:** 34–6.
4. Miller M, *et al.* Influence of phenytoin on theophylline clearance. *Clin Pharmacol Ther* 1984; **35:** 666–9.
5. Taylor JW, *et al.* The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* 1980; **14:** 638.
6. Hendeles L, *et al.* Decreased oral phenytoin absorption following concurrent theophylline administration. *J Allergy Clin Immunol* 1979; **63:** 156.
7. Rosenberry KR, *et al.* Reduced theophylline half-life induced by carbamazepine therapy. *J Pediatr* 1983; **102:** 472–4.
8. Piafsky KM, *et al.* Effect of phenobarbital on the disposition of intravenous theophylline. *Clin Pharmacol Ther* 1977; **22:** 336–9.
9. Jusko WJ, *et al.* Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. *J Pharm Sci* 1979; **68:** 1358–66.
10. Saccar CL, *et al.* The effect of phenobarbital on theophylline disposition in children with asthma. *J Allergy Clin Immunol* 1985; **75:** 716–19.
11. Gibson GA, *et al.* Influence of high-dose phenobarbital on theophylline pharmacokinetics: a case report. *Ther Drug Monit* 1985; **7:** 181–4.
12. Dahlqvist R, *et al.* Induction of theophylline metabolism by pentobarbital. *Ther Drug Monit* 1989; **11:** 408–10.

Antifungals. There have been reports that *ketoconazole* does not appear significantly to alter the pharmacokinetics of theophylline.[1,2] The manufacturer of *fluconazole* has, however, stated that plasma clearance of theophylline may be decreased by fluconazole. A 16% reduction in theophylline clearance has been reported[3] after oral fluconazole but fluconazole was considered to have only a minor inhibitory effect on theophylline metabolism and theophylline disposition was not significantly affected. Theophylline metabolism has been inhibited to a similar degree by *terbinafine*.[4]

1. Brown MW, *et al.* Effect of ketoconazole on hepatic oxidative drug metabolism. *Clin Pharmacol Ther* 1985; **37:** 290–7.
2. Heusner JJ, *et al.* Effect of chronically administered ketoconazole on the elimination of theophylline in man. *Drug Intell Clin Pharm* 1987; **21:** 514–17.
3. Konishi H, *et al.* Effect of fluconazole on theophylline disposition in humans. *Eur J Clin Pharmacol* 1994; **46:** 309–12.
4. Trépanier EF, *et al.* Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* 1998; **42:** 695–7.

Antigout drugs. *Allopurinol* 300 mg by mouth daily for 7 days was found to have no effect on the pharmacokinetics of theophylline after a single intravenous dose of aminophylline[1,2] or after oral theophylline given to steady state.[1] However, oral allopurinol 600 mg daily for 28 days has been found to inhibit the metabolism of theophylline,[3] increasing the mean half-life by 25% after 14 days and 29% after 28 days and there has been a report of allopurinol increasing peak plasma-theophylline concentrations by 38% in one patient within 2 days of use together.[4]

Probenecid has been reported[5] to have no effect on the hepatic metabolism or total body clearance of theophylline in a single-dose study in healthy subjects.

Sulfinpyrazone 800 mg daily for 7 days increased the total plasma clearance of theophylline by 22% in healthy subjects due to selective induction of certain cytochrome P450 isoenzymes.[6]

1. Grygiel JJ, *et al.* Effects of allopurinol on theophylline metabolism and clearance. *Clin Pharmacol Ther* 1979; **26:** 660–7.
2. Vozeh S, *et al.* Influence of allopurinol on theophylline disposition in adults. *Clin Pharmacol Ther* 1980; **27:** 194–7.
3. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin Pharmacol Ther* 1981; **29:** 224–9.
4. Barry M, Feely J. Allopurinol influences aminophenazone elimination. *Clin Pharmacokinet* 1990; **19:** 167–9.
5. Chen TWD, Patton TF. Effect of probenecid on the pharmacokinetics of aminophylline. *Drug Intell Clin Pharm* 1983; **17:** 465–6.
6. Birkett DJ, *et al.* Evidence for a dual action of sulphinpyrazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* 1983; **15:** 567–9.

Antineoplastics. There has been a report of increased clearance of theophylline in 3 patients given *aminoglutethimide*.[1]

The clearance of theophylline (given as theophylline, aminophylline, or choline theophyllinate) was reported to decrease by an average of 19% in 8 patients with severe corticosteroid-dependent asthma given low-dose weekly intramuscular injections of *methotrexate*.[2] A high degree of interpatient variability was seen. Three patients reported nausea; one of whom required a decrease in theophylline dose. The authors reported that the most likely explanation for the change in theophylline clearance was inhibition of microsomal enzyme activity.

For reference to a possible interaction between theophylline and *lomustine*, see Lomustine, p.741.

1. Lønning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.
2. Glynn-Barnhart AM, *et al.* Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol* 1991; **88:** 180–6.

Antivirals. A single injection of recombinant human *interferon alfa* reduced theophylline clearance by 33 to 81% in 8 of 9 subjects, resulting in a 1.5- to sixfold increase in the theophylline elimination half-life.[1] Injection of interferon alfa once daily for 3 days in 11 healthy subjects also reduced theophylline clearance and increased elimination half-life,[2] but the magnitude of the changes were of a similar order to normal intra-individual variation and the interaction was considered of minor clinical significance.

Licensed product information for *ritonavir* states that it substantially increases the clearance of theophylline; theophylline dosage may need to be increased to maintain efficacy.

There is evidence[3] that *aciclovir* inhibits theophylline metabolism, resulting in accumulation.

1. Williams SJ, *et al.* Inhibition of theophylline metabolism by interferon. *Lancet* 1987; **ii:** 939–41.
2. Jonkman JHG, *et al.* Effects of α-interferon on theophylline pharmacokinetics and metabolism. *Br J Clin Pharmacol* 1989; **27:** 795–802.
3. Maeda Y, *et al.* Inhibition of theophylline metabolism by aciclovir. *Biol Pharm Bull* 1996; **19:** 1591–5.

Benzodiazepines. For reference to the antagonism of benzodiazepine sedation by aminophylline, see Xanthines, under Interactions of Diazepam, p.992.

Beta blockers. *Propranolol* reduced theophylline clearance by 36% in healthy subjects given aminophylline intravenously. *Metoprolol* did not reduce clearance in the group as a whole, but a reduction was noted in some smokers whose theophylline clearance was initially high.[1] Propranolol is thought to exert a dose-dependent selective inhibitory effect on the separate cytochrome P450 isoenzymes involved in theophylline demethylation and 8-hydroxylation.[2] The less lipophilic beta blockers *atenolol*[3,4] and *nadolol*[4] had no significant effect on the pharmacokinetics of theophylline.

In general, however, beta blockers should be avoided in patients taking theophylline as they can dangerously exacerbate bronchospasm in patients with a history of asthma or chronic obstructive pulmonary disease.

1. Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 1980; **28:** 463–7.
2. Miners JO, *et al.* Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. *Br J Clin Pharmacol* 1985; **20:** 219–23.
3. Cerasa LA, *et al.* Lack of effect of atenolol on the pharmacokinetics of theophylline. *Br J Clin Pharmacol* 1988; **26:** 800–2.
4. Corsi CM, *et al.* Lack of effect of atenolol and nadolol on the metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29:** 265–8.

Caffeine. Abstention from dietary methylxanthines by healthy subjects has resulted in faster elimination of theophylline.[1] While the addition of extra caffeine to the diet has been reported not to alter theophylline disposition,[2] some studies in healthy subjects have indicated that the ingestion of moderate amounts of caffeine (120 to 900 mg daily), which could be consumed by drinking several cups of coffee daily, can have a pronounced influence on the pharmacokinetics of theophylline.[3,4] In these latter studies the mean theophylline clearance was reduced by 23 and 29% with a corresponding increase in the elimination half-lives.

1. Monks TJ, *et al.* Influence of methylxanthine-containing foods on theophylline metabolism and kinetics. *Clin Pharmacol Ther* 1979; **26:** 513–24.
2. Monks TJ, *et al.* The effect of increased caffeine intake on the metabolism and pharmacokinetics of theophylline in man. *Biopharm Drug Dispos* 1981; **2:** 31–7.
3. Jonkman JHG, *et al.* The influence of caffeine on the steady-state pharmacokinetics of theophylline. *Clin Pharmacol Ther* 1991; **49:** 248–55.
4. Sato J, *et al.* Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. *Eur J Clin Pharmacol* 1993; **44:** 295–8.

Calcium-channel blockers. *Verapamil* has been reported[1] to decrease the clearance of theophylline by a mean of 14% in healthy subjects and although this was not considered to be clinically significant, symptoms of theophylline toxicity, associated with near doubling of the serum-theophylline concentration have occurred in a 76-year-old woman taking theophylline after 6 days of therapy with verapamil.[2] Studies in healthy subjects and asthmatic patients have produced conflicting results of the effect of *nifedipine* on the pharmacokinetics of theophylline. Reduced clearance[1] and an increase in the volume of distribution[3,4] of theophylline have been reported and both decreased[4] and increased[5] serum-theophylline concentrations; theophylline toxicity has been reported.[6,7] However, most studies have concluded that the effects of nifedipine are unlikely to be of clinical importance.[1,4,5,8]

Serum concentrations of theophylline have been reported to be increased by *diltiazem*[5] and reduced by *felodipine*;[9] neither of these effects were considered to be clinically significant.

1. Robson RA, *et al.* Selective inhibitory effects of nifedipine and verapamil on oxidative metabolism: effects on theophylline. *Br J Clin Pharmacol* 1988; **25:** 397–400.
2. Burnakis TG, *et al.* Increased serum theophylline concentrations secondary to oral verapamil. *Clin Pharm* 1983; **2:** 458–61.
3. Jackson SHD, *et al.* The interaction between iv theophylline and chronic oral dosing with slow release nifedipine in volunteers. *Br J Clin Pharmacol* 1986; **21:** 389–92.
4. Adebayo GI, Mabadeje AFB. Effect of nifedipine on antipyrine and theophylline disposition. *Biopharm Drug Dispos* 1990; **11:** 157–64.
5. Smith SR, *et al.* The influence of nifedipine and diltiazem on serum theophylline concentration-time profiles. *J Clin Pharm Ther* 1989; **14:** 403–8.
6. Parrillo SJ, Venditto M. Elevated theophylline blood levels from institution of nifedipine therapy. *Ann Emerg Med* 1984; **13:** 216–17.
7. Harrod CS. Theophylline toxicity and nifedipine. *Ann Intern Med* 1987; **106:** 480.
8. Spedini C, Lombardi C. Long-term treatment with oral nifedipine plus theophylline in the management of chronic bronchial asthma. *Eur J Clin Pharmacol* 1986; **31:** 105–6.
9. Bratel T, *et al.* Felodipine reduces the absorption of theophylline in man. *Eur J Clin Pharmacol* 1989; **36:** 481–5.

Cannabis. A search of the literature[1] revealed 2 studies, both published in the 1970s, that showed that marijuana smoking increased the clearance of theophylline.

1. Brown D. Influence on theophylline clearance. *Pharm J* 1994; **253:** 595.

Corticosteroids. In 3 patients with acute severe asthma given aminophylline intravenously, serum-theophylline concentrations rose rapidly from the therapeutic range to between 40 and 50 micrograms/mL when *hydrocortisone* was given intravenously.[1] In studies in healthy subjects, no significant changes in serum-theophylline concentrations were noted when hydrocortisone, *methylprednisolone*,[2] or *prednisone*[3] were given, although there was a trend towards increased theophylline clearance during corticosteroid therapy.[2,3] In preterm neonates, exposure to *betamethasone in utero* stimulated the hepatic metabolism of theophylline,[4,5] but did not affect dosage requirements.

The possibility that adverse effects such as hypokalaemia may be potentiated by use of theophylline with corticosteroids should be borne in mind.

1. Buchanan N, *et al.* Asthma—a possible interaction between hydrocortisone and theophylline. *S Afr Med J* 1979; 56: 1147–8.
2. Leavengood DC, *et al.* The effect of corticosteroids on theophylline metabolism. *Ann Allergy* 1983; **50:** 249–51.
3. Anderson JL, *et al.* Potential pharmacokinetic interaction between theophylline and prednisone. *Clin Pharm* 1984; **3:** 187–9.
4. Jager-Roman E, *et al.* Increased theophylline metabolism in premature infants after prenatal betamethasone administration. *Dev Pharmacol Ther* 1982; **5:** 127–35.
5. Baird-Lambert J, *et al.* Theophylline metabolism in preterm neonates during the first weeks of life. *Dev Pharmacol Ther* 1984; **7:** 239–44.

Disulfiram. In a study involving 20 recovering alcoholic patients, disulfiram decreased the plasma clearance and prolonged the elimination half-life of theophylline in a dose-dependent manner.[1] It was concluded that disulfiram exerts a dose-dependent inhibitory effect on the hepatic metabolism of theophylline and that, in order to minimise the risk of toxicity, the dosage of theophylline may need to be reduced by up to 50% if given together.

1. Loi C-M, *et al.* Dose-dependent inhibition of theophylline metabolism by disulfiram in recovering alcoholics. *Clin Pharmacol Ther* 1989; **45:** 476–86.

Diuretics. Although increased mean serum-theophylline concentrations were noted in 10 patients given continuous intravenous aminophylline infusions after intravenous injection of *furosemide*,[1] in 8 patients with chronic stable asthma, mean peak serum-theophylline concentrations were reduced from 12.14 micrograms/mL with placebo to 7.16 micrograms/mL when furosemide was given. Reduced concentrations were noted for up to 6 hours after furosemide.[2] Decreased theophylline concentrations were also noted in 4 neonates receiving oral or intravenous theophylline when given furosemide.[3] Serum-theophylline concentrations returned to normal when furosemide and theophylline were given more than 2 hours apart.

The possibility that adverse effects such as hypokalaemia may be potentiated if theophylline is given with diuretics should be borne in mind.

1. Conlon PF, *et al.* Effect of intravenous furosemide on serum theophylline concentration. *Am J Hosp Pharm* 1981; **38:** 1345–7.
2. Carpentiere G, *et al.* Furosemide and theophylline. *Ann Intern Med* 1985; **103:** 957.
3. Toback JW, Gilman ME. Theophylline-furosemide inactivation. *Pediatrics* 1983; **71:** 140–1.

Gastrointestinal drugs. Oral *antacids* do not appear to affect the total absorption of theophylline from the gut.[1-5] However, some studies have shown a reduction in the rate of absorption from both immediate-[1] and modified-release theophylline preparations[2] after antacids. Also an increase in peak serum-theophylline concentrations has been noted with certain modified-release formulations.[3]

Cimetidine inhibits the oxidative metabolism of theophylline reducing its clearance by 20 to 35% and prolonging its serum half-life;[6-8] toxic effects have been reported.[6] It has been recommended that the dose of aminophylline should be reduced by about one-third if given with cimetidine.[6] This inhibition of theophylline metabolism may be enhanced by liver disease,[9] but there is wide interindividual variation. The reduction in clearance may be greater in smokers.[10] Studies have suggested that *ranitidine* does not significantly inhibit theophylline metabolism,[11-14] even at very high doses.[15] However, there have been occasional reports of theophylline toxicity after use with ranitidine.[16-18] *Famotidine*[19] has also been reported to not alter theophylline disposition but one small study found a significant decrease in theophylline clearance in some patients with chronic obstructive pulmonary disease.[20]

Omeprazole, lansoprazole, and *pantoprazole* generally have insignificant or no effect on theophylline clearance.[21,22] In CYP2C19 poor metabolisers there may be an increase in omeprazole concentrations and subsequent induction of CYP1A, a major enzyme of theophylline metabolism. A pharmacokinetic study[23] of this induction in 5 poor metabolisers given omeprazole did find a trend towards an increase in theophylline clearance.

1. Arnold LA, *et al.* Effect of an antacid on gastrointestinal absorption of theophylline. *Am J Hosp Pharm* 1979; **36:** 1059–62.
2. Shargel L, *et al.* Effect of antacid on bioavailability of theophylline from rapid and timed-release drug products. *J Pharm Sci* 1981; **70:** 599–602.
3. Darzentas LJ, *et al.* Effect of antacid on bioavailability of a sustained-release theophylline preparation. *Drug Intell Clin Pharm* 1983; **17:** 555–7.
4. Myhre KI, Walstad RA. The influence of antacid on the absorption of two different sustained-release formulations of theophylline. *Br J Clin Pharmacol* 1983; **15:** 683–7.
5. Muir JF, *et al.* Lack of effect of magnesium-aluminium hydroxide on the absorption of theophylline given as a pH-dependent sustained-release preparation. *Eur J Clin Pharmacol* 1993; **44:** 85–8.
6. Bauman JH, *et al.* Cimetidine-theophylline interaction: report of four patients. *Ann Allergy* 1982; **48:** 100–102.
7. Vestal RE, *et al.* Cimetidine inhibits theophylline clearance in patients with chronic obstructive pulmonary disease: a study using stable isotope methodology during multiple oral dose administration. *Br J Clin Pharmacol* 1983; **15:** 411–18.
8. Roberts RK, *et al.* Cimetidine-theophylline interaction in patients with chronic obstructive airways disease. *Med J Aust* 1984; **140:** 279–80.
9. Gugler R, *et al.* The inhibition of drug metabolism by cimetidine in patients with liver cirrhosis. *Klin Wochenschr* 1984; **62:** 1126–31.
10. Grygiel JJ, *et al.* Differential effects of cimetidine on theophylline metabolic pathways. *Eur J Clin Pharmacol* 1984; **26:** 335–40.
11. Breen KJ, *et al.* Effects of cimetidine and ranitidine on hepatic drug metabolism. *Clin Pharmacol Ther* 1982; **31:** 297–300.
12. Seggev JS, *et al.* No evidence for interaction between ranitidine and theophylline. *Arch Intern Med* 1987; **147:** 179–80.
13. Adebayo GI. Effects of equimolar doses of cimetidine and ranitidine on theophylline elimination. *Biopharm Drug Dispos* 1989; **10:** 77–85.
14. Boehning W. Effect of cimetidine and ranitidine on plasma theophylline in patients with chronic obstructive airways disease treated with theophylline and corticosteroids. *Eur J Clin Pharmacol* 1990; **38:** 43–5.
15. Kelly HW, *et al.* Ranitidine at very large doses does not inhibit theophylline elimination. *Clin Pharmacol Ther* 1986; **39:** 577–81.
16. Fernandes E, Melewicz FM. Ranitidine and theophylline. *Ann Intern Med* 1984; **100:** 459.
17. Gardner ME, Sikorski GW. Ranitidine and theophylline. *Ann Intern Med* 1985; **102:** 559.
18. Hegman GW, Gilbert RP. Ranitidine-theophylline interaction—fact or fiction? *DICP Ann Pharmacother* 1991; **25:** 21–5.
19. Chremos AN, *et al.* Famotidine does not interfere with the disposition of theophylline in man: comparison to cimetidine. *Clin Pharmacol Ther* 1986; **39:** 187.
20. Dal Negro R, *et al.* Famotidine and theophylline pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1993; **24:** 255–8.
21. Kokufu T, *et al.* Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* 1995; **48:** 391–5.
22. Dilger K, *et al.* Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. *Br J Clin Pharmacol* 1999; **48:** 438–44.
23. Cavuto NJ, *et al.* Effect of omeprazole on theophylline clearance in poor metabolizers of omeprazole. *Clin Pharmacol Ther* 1995; **57:** 215.

General anaesthetics. There have been several reports[1,2] of increased cardiotoxicity when patients taking theophylline were anaesthetised with *halothane.* There was also an early report of seizures and tachycardia attributed to an interaction between theophylline and *ketamine.*[3]

1. Barton MD. Anesthetic problems with aspirin-intolerant patients. *Anesth Analg* 1975; **54:** 376–80.
2. Richards W, *et al.* Cardiac arrest associated with halothane anesthesia in a patient receiving theophylline. *Ann Allergy* 1988; **61:** 83–4.
3. Hirschman CA, *et al.* Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* 1982; **56:** 464–7.

Leukotriene inhibitors and antagonists. *Zileuton* prolongs the half-life and reduces the clearance of theophylline;[1] dosage of theophylline should be reduced to avoid toxicity when both drugs are given together, and plasma-theophylline concentrations should be monitored. Use of *zafirlukast* with theophylline decreased zafirlukast plasma concentrations but had no effect on theophylline plasma concentrations in clinical trials. However, toxic serum-theophylline concentrations occurred in one patient when zafirlukast was added to therapy, and recurred on rechallenge.[2] A dose of *montelukast* 10 mg daily did not affect the pharmacokinetics of theophylline, but doses of 200 mg and 600 mg daily reduced the maximum plasma concentration, area under the concentration-time curve, and elimination half-life of theophylline.[3]

1. Granneman GR, *et al.* Effect of zileuton on theophylline pharmacokinetics. *Clin Pharmacokinet* 1995; **29** (suppl 2): 77–83.
2. Katial RK, *et al.* A drug interaction between zafirlukast and theophylline. *Arch Intern Med* 1998; **158:** 1713–15.
3. Malmstrom K, *et al.* Effect of montelukast on single-dose theophylline pharmacokinetics. *Am J Ther* 1998; **5:** 189–95.

Methoxsalen. In a single-dose pharmacokinetic study in 3 healthy subjects, the rate of elimination of theophylline was decreased after a single oral dose of methoxsalen, while urinary excretion of unchanged theophylline increased.[1] Methoxsalen probably inhibits the metabolism of cytochrome P450 isoenzyme CYP1A2,[2] and it has been suggested that theophylline dose reductions are likely to be required when used with systemic methoxsalen but seem unlikely to be necessary with topical PUVA therapy.

1. Apseloff G, *et al.* Inhibition and induction of theophylline metabolism by 8-methoxypsoralen: in vivo study in rats and humans. *Drug Metab Dispos* 1990; **18:** 298–303.
2. Tantcheva-Poór I, *et al.* Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* 2001; **144:** 1127–32.

Neuromuscular blockers. For reference to resistance to neuromuscular block with pancuronium in patients receiving aminophylline, see Xanthines, p.1905.

Oral contraceptives. Oral contraceptives have been reported to decrease the clearance of theophylline by about 30%, and serum concentrations may be increased,[1-3] due to the inhibitory effects of oral contraceptives on hepatic P450 isoenzymes.

1. Tornatore KM, *et al.* Effect of chronic oral contraceptive steroids on theophylline disposition. *Eur J Clin Pharmacol* 1982; **23:** 129–34.
2. Gardner MJ, *et al.* Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol* 1983; **16:** 271–80.
3. Roberts RK, *et al.* Oral contraceptive steroids impair the elimination of theophylline. *J Lab Clin Med* 1983; **101:** 821–5.

Sympathomimetics. The effect of beta-adrenoceptor agonists on the pharmacokinetics of theophylline is unclear. Whereas some studies have found that *orciprenaline*[1] or *terbutaline*[2] had no effect on theophylline disposition, others have shown an increase in theophylline clearance after *isoprenaline*[3,4] or *terbutaline.*[5,6]

Use of theophylline with beta-adrenoceptor agonists can potentiate adverse effects including hypokalaemia,[7,8] hyperglycaemia,[7] tachycardia,[7,8] hypertension,[7] and tremor.[9] Of 9 patients reported to the UK CSM with hypokalaemia during such combined therapy, 4 had clinical sequelae of cardiorespiratory arrest, intestinal pseudo-obstruction, or confusion. Monitoring of serum-potassium concentrations was recommended in patients with severe asthma given both beta-adrenoceptor agonists and xanthine derivatives.[10]

The possibility of an interaction with *phenylpropanolamine* should also be borne in mind, as it has been shown to reduce the clearance of theophylline significantly.[11]

1. Conrad KA, Woodworth JR. Orciprenaline does not alter theophylline elimination. *Br J Clin Pharmacol* 1981; **12:** 756–7.
2. Snidow J, *et al.* Acute effects of short-term subcutaneous terbutaline on theophylline disposition. *Eur J Clin Pharmacol* 1987; **32:** 191–3.
3. Hemstreet MP, *et al.* Effect of intravenous isoproterenol on theophylline kinetics. *J Allergy Clin Immunol* 1982; **69:** 360–4.
4. Griffith JA, Kozloski GD. Isoproterenol-theophylline interaction: possible potentiation by other drugs. *Clin Pharm* 1990; **9:** 54–7.
5. Danziger Y, *et al.* Reduction of serum theophylline levels by terbutaline in children with asthma. *Clin Pharmacol Ther* 1985; **37:** 469–71.
6. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.
7. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
8. Whyte KF, *et al.* Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline. *Br J Clin Pharmacol* 1988; **25:** 571–8.
9. van der Vet APH, *et al.* Pharmacodynamics (lungfunction tests, tremor measurements and cAMP determinations) of a single dose of 0.5 mg terbutaline subcutaneously during sustained-release theophylline medication in patients with asthmatic bronchitis. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 569–73.
10. Committee on Safety of Medicines. β agonists, xanthines and hypokalaemia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 20/05/08)
11. Wilson HA, *et al.* Phenylpropanolamine significantly reduces the clearance of theophylline. *Am Rev Respir Dis* 1991; **143:** A629.

Tacrine. Results of a study in healthy subjects indicated that tacrine reduced theophylline clearance by about 50% and increased plasma-theophylline concentrations. Competitive inhibition by tacrine of theophylline metabolism was proposed.[1]

1. deVries TM, *et al.* Effect of multiple-dose tacrine administration on single-dose pharmacokinetics of digoxin, diazepam, and theophylline. *Pharm Res* 1993; **10** (suppl): S333.

Tiabendazole. Tiabendazole has been reported[1,2] to increase serum-theophylline concentrations and to decrease theophylline clearance. It has been recommended[2] that theophylline dosage should be reduced by 50% when tiabendazole therapy is started.

1. Sugar AM, *et al.* Possible thiabendazole-induced theophylline toxicity. *Am Rev Respir Dis* 1980; **122:** 501–3.
2. Lew G, *et al.* Theophylline-thiabendazole drug interaction. *Clin Pharm* 1989; **8:** 225–7.

Ticlopidine. Theophylline elimination half-life was increased and plasma clearance was decreased in 10 healthy subjects after the use of ticlopidine 500 mg daily by mouth for 10 days.[1]

1. Colli A, *et al.* Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* 1987; **41:** 358–62.

Vaccines. Transient inhibition of the hepatic metabolism of theophylline, possibly secondary to interferon production, resulting in increased theophylline serum half-life and concentration has been reported after BCG vaccination[1] and influenza vaccination.[2,3] Other studies have not been able to confirm the interaction with influenza vaccine.[4-7] The differing findings are probably due to differences in vaccine; modern purified subvirion vaccines which do not induce interferon production do not appear to alter theophylline metabolism.[8,9]

1. Gray JD, *et al.* Depression of theophylline elimination following BCG vaccination. *Br J Clin Pharmacol* 1983; **16:** 735–7.
2. Renton KW, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980; **123:** 288–90.
3. Walker S, *et al.* Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1981; **125:** 243–4.
4. Goldstein RS, *et al.* Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1982; **126:** 470.
5. Fischer RG, *et al.* Influence of trivalent influenza vaccine on serum theophylline levels. *Can Med Assoc J* 1982; **126:** 1312–13.
6. Britton L, Ruben FL. Serum theophylline levels after influenza vaccination. *Can Med Assoc J* 1982; **126:** 1375.
7. Patriarca PA, *et al.* Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* 1983; **308:** 1601–2.
8. Stults BM, Hashisaki PA. Influenza vaccination and theophylline pharmacokinetics in patients with chronic obstructive lung disease. *West J Med* 1983; **139:** 651–4.
9. Winstanley PA, *et al.* Lack of effect of highly purified subunit influenza vaccination on theophylline metabolism. *Br J Clin Pharmacol* 1985; **20:** 47–53.

Pharmacokinetics

Theophylline is rapidly and completely absorbed from liquid preparations, capsules, and uncoated tablets; the rate, but not the extent, of absorption is decreased by food, and food may also affect theophylline clearance. Peak serum-theophylline concentrations occur 1 to 2 hours after ingestion of liquid preparations, capsules, and uncoated tablets. Modified-release preparations exhibit considerable variability in their absorption characteristics and in the effect of food. They are generally not considered to be interchangeable; if a patient needs to be transferred from one such preparation to another then the dose should be retitrated. Rectal absorption is rapid from enemas, but may be slow and erratic from suppositories. Absorption after intramuscular injection is slow and incomplete.

Theophylline is about 40 to 60% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced. Optimum therapeutic serum concentrations for bronchodilatation are generally considered to range from 10 to 20 micrograms/mL (55 to 110 micromol/litre) although some consider a lower range appropriate (see Therapeutic Drug Monitoring, below).

Theophylline is metabolised in the liver to 1,3-dimethyluric acid, 1-methyluric acid (via the intermediate 1-methylxanthine), and 3-methylxanthine. Demethylation to 3-methylxanthine (and possibly to 1-methylxanthine) is catalysed by the cytochrome P450 isoenzyme CYP1A2; hydroxylation to 1, 3-dimethyluric acid is catalysed by CYP2E1 and CYP3A3. Both the demethylation and hydroxylation pathways of theophylline metabolism are capacity-limited, resulting in non-linear elimination. The metabolites are excreted in the urine. In adults, about 10% of a dose of theophylline is excreted unchanged in the urine, but in neonates around 50% is excreted unchanged, and a large proportion is excreted as caffeine. Considerable interindividual differences in the rate of hepatic metabolism of theophylline result in large variations in clearance, serum concentrations, and half-lives. Hepatic metabolism is further affected by factors such as age, smoking, disease, diet, and drug interactions. The serum half-life of theophylline in an otherwise healthy, non-smoking asthmatic adult is 7 to 9 hours, in children 3 to 5 hours, in cigarette smokers 4 to 5 hours, in neonates and premature infants 20 to 30 hours, and in elderly non-smokers 10 hours. The serum half-life of theophylline may be increased in patients with heart failure or liver disease. Steady state is usually achieved within 48 hours with a consistent dosing schedule.

Theophylline crosses the placenta; it is also distributed into breast milk.

Absorption. *FOOD.* Food has substantial but variable effects on the absorption of theophylline from modified-release formulations but it is difficult to predict whether a particular formulation will be affected.[1] Some formulations are not affected by the presence of food but for others increases or decreases in the rate and/or extent of absorption have been reported. The composition and fluid content of the food appears to be important and a rapid release of theophylline ('dose-dumping') has occurred with some formulations after a meal, especially one with a high fat content.

A diet high in protein and low in carbohydrate has been reported to increase theophylline clearance, and a low-protein, high-carbohydrate diet to decrease theophylline clearance.[2-6] The consumption of methylxanthines, particularly caffeine, in the diet may decrease theophylline clearance (see Caffeine, under Interactions, above).

1. Jonkman JHG. Food interactions with sustained-release theophylline preparations: a review. *Clin Pharmacokinet* 1989; **16:** 162–79.
2. Kappas A, *et al.* Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin Pharmacol Ther* 1976; **20:** 643–53.
3. Feldman CH, *et al.* Effect of dietary protein and carbohydrate on theophylline metabolism in children. *Pediatrics* 1980; **66:** 956–62.
4. Feldman CH, *et al.* Interaction between nutrition and theophylline metabolism in children. *Ther Drug Monit* 1982; **4:** 69–76.
5. Juan D, *et al.* Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. *Clin Pharmacol Ther* 1986; **40:** 187–94.
6. Juan D, *et al.* Impairment of theophylline clearance by a hypocaloric low-protein diet in chronic obstructive pulmonary disease. *Ther Drug Monit* 1990; **12:** 111–14.

Metabolism and excretion. *AGE.* From about 1 year of age until adolescence, children have a rapid theophylline clearance.[1] Premature infants and those under 1 year of age have a slower clearance[2,3] due to immature metabolic pathways.[3-5] In neonates the capacity of hepatic cytochrome P450 enzymes is much reduced compared with older children and adults, and *N*-demethylation and oxidation reactions play a minor role in the metabolism of theophylline.[4-6] Neonates are, however, capable of methylating theophylline at the N7 position to form caffeine, which is present at about one-third the concentration of theophylline at steady state.[5,6] The proportion of theophylline excreted unchanged is also increased in premature neonates and decreases with age as hepatic enzyme systems develop.[6] More rapid clearance on the first day of life in premature neonates has been reported.[7]

Some studies have found a progressive decline in clearance throughout adult years[8] whereas others have not.[9] Similarly, some studies have noted a decreased clearance in the elderly[10,11] but others have found no significant change.[12,13]

1. Zaske DE, *et al.* Oral aminophylline therapy: increased dosage requirements in children. *JAMA* 1977; **237:** 1453–5.
2. Aranda JV, *et al.* Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976; **295:** 413–16.
3. Kraus DM, *et al.* Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 1993; **54:** 351–9.
4. Grygiel JJ, Birkett DJ. Effect of age on patterns of theophylline metabolism. *Clin Pharmacol Ther* 1980; **28:** 456–62.
5. Tserng K-Y, *et al.* Theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1981; **29:** 594–600.
6. Tserng K-Y, *et al.* Developmental aspects of theophylline metabolism in premature infants. *Clin Pharmacol Ther* 1983; **33:** 522–8.
7. Stile IL, *et al.* Pharmacokinetics of theophylline in premature infants on the first day of life. *Clin Ther* 1986; **8:** 336–41.
8. Randolph WC, *et al.* The effect of age on theophylline clearance in normal subjects. *Br J Clin Pharmacol* 1986; **22:** 603–5.
9. Wiffen JK, *et al.* Does theophylline clearance alter within the adult age range? *Br J Clin Pharmacol* 1984; **17:** 219P.
10. Antal EJ, *et al.* Theophylline pharmacokinetics in advanced age. *Br J Clin Pharmacol* 1981; **12:** 637–45.
11. Jackson SHD, *et al.* The relationship between theophylline clearance and age in adult life. *Eur J Clin Pharmacol* 1989; **36:** 29–34.
12. Bauer LA, Blouin RA. Influence of age on theophylline clearance in patients with chronic obstructive pulmonary disease. *Clin Pharmacokinet* 1981; **6:** 469–74.
13. Fox RW, *et al.* Theophylline kinetics in a geriatric group. *Clin Pharmacol Ther* 1983; **34:** 60–7.

ELIMINATION KINETICS. There is evidence that the elimination of theophylline is dose-dependent and that at high serum concentrations, a small change in dose of a theophylline preparation could cause a disproportionate increase in serum-theophylline concentration, due to a reduction in clearance.[1-3] However, it is not clear that this effect is clinically significant when serum-theophylline concentrations are within the therapeutic range.[4-8] It has also been suggested that repeated oral dosing of theophylline might result in a decrease of clearance compared with pre-treatment values.[9]

1. Weinberger M, Ginchansky E. Dose-dependent kinetics of theophylline disposition in asthmatic children. *J Pediatr* 1977; **91:** 820–4.
2. Tang-Liu DD-S, *et al.* Nonlinear theophylline elimination. *Clin Pharmacol Ther* 1982; **31:** 358–69.
3. Butcher MA, *et al.* Dose-dependent pharmacokinetics with single daily dose slow release theophylline in patients with chronic lung disease. *Br J Clin Pharmacol* 1982; **13:** 241–3.
4. Koëter GH, *et al.* Pharmacokinetics of sustained release theophylline in low and high multidose regimens. *Br J Clin Pharmacol* 1981; **12:** 647–51.
5. Rovei V, *et al.* Pharmacokinetics of theophylline: a dose-range study. *Br J Clin Pharmacol* 1982; **14:** 769–78.
6. Gundert-Remy U, *et al.* Non-linear elimination processes of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 71–8.
7. Brown PJ, *et al.* Lack of dose dependent kinetics of theophylline. *Eur J Clin Pharmacol* 1983; **24:** 525–7.
8. Milavetz G, *et al.* Dose dependency for absorption and elimination rates of theophylline: implications for studies of bioavailability. *Pharmacotherapy* 1984; **4:** 216–20.
9. Efthimiou H, *et al.* Influence of chronic dosing on theophylline clearance. *Br J Clin Pharmacol* 1984; **17:** 525–30.

GENDER. A higher theophylline clearance and shorter elimination half-life has been reported in healthy premenopausal women than in healthy men, probably due to sex-related differences in hepatic metabolism.[1] Changes in the pharmacokinetics of theophylline in women have also been reported according to the stage of the menstrual cycle;[2,3] another study[4] found no changes.

1. Nafziger AN, Bertino JS. Sex-related differences in theophylline pharmacokinetics. *Eur J Clin Pharmacol* 1989; **37:** 97–100.
2. Bruguerolle B, *et al.* Influence of the menstrual cycle on theophylline pharmacokinetics in asthmatics. *Eur J Clin Pharmacol* 1990; **39:** 59–61.
3. Nagata K, *et al.* Increased theophylline metabolism in the menstrual phase of healthy women. *J Allergy Clin Immunol* 1997; **100:** 39–43.
4. Matsuki S, *et al.* Pharmacokinetic changes of theophylline and amikacin through the menstrual cycle in healthy women. *J Clin Pharmacol* 1999; **39:** 1256–62.

Pregnancy and breast feeding. For mention of the pharmacokinetics of theophylline during pregnancy and breast feeding, see under Precautions, above.

Protein binding. Albumin is the major plasma binding protein for theophylline, binding is pH-dependent, and the percentage of theophylline bound at physiological pH is reported to range from about 35 to 45%.[1,2] Some studies have found the plasma protein binding of theophylline to be concentration dependent,[3] but others have not confirmed this.[1,4] Protein binding has been reported to be slightly but significantly higher in patients with bronchial asthma than in healthy controls.[5] Reduced protein binding occurs in patients with hypoalbuminaemia;[6,7] it has also been found in obese subjects[8] (possibly due to elevated concentrations of free fatty acids, which can displace theophylline from binding sites).

1. Buss D, *et al.* Determinants of the plasma protein binding of theophylline in health. *Br J Clin Pharmacol* 1983; **15:** 399–405.
2. Brørs O, *et al.* Binding of theophylline in human serum determined by ultrafiltration and equilibrium dialysis. *Br J Clin Pharmacol* 1983; **15:** 393–7.
3. Gundert-Remy U, Hildebrandt R. Binding of theophylline and its metabolites to human plasma proteins. *Br J Clin Pharmacol* 1983; **16:** 573–4.
4. Buss DC, *et al.* Protein binding of theophylline. *Br J Clin Pharmacol* 1985; **19:** 529–31.
5. Trnavská Z. Theophylline protein binding. *Arzneimittelforschung* 1990; **40:** 166–9.
6. Leopold D, *et al.* The ex vivo plasma protein binding of theophylline in renal disease. *Br J Clin Pharmacol* 1985; **19:** 823–5.
7. Connelly TJ, *et al.* Characterization of theophylline binding to serum proteins in pregnant and nonpregnant women. *Clin Pharmacol Ther* 1990; **47:** 68–72.
8. Shum L, Jusko WJ. Effects of obesity and ancillary variables (dialysis time, drug, albumin, and fatty acid concentrations) on theophylline serum protein binding. *Biopharm Drug Dispos* 1989; **10:** 549–62.

Therapeutic drug monitoring. Dosage requirements of theophylline preparations vary widely between subjects and even vary with time in individuals, since serum-theophylline concentrations are influenced by factors including disease states, other drugs, diet, smoking, and age. Serious toxicity is related to serum concentration and may not be preceded by minor symptoms. For these reasons it is recommended that serum-theophylline concentrations should be monitored.

The generally accepted optimal serum concentration is between 10 and 20 micrograms/mL,[1-4] but this should be regarded as a guide and not a rigid barrier and clinical decisions should never be based solely on the serum concentration.[1] The therapeutic range in the treatment of neonatal apnoea is usually considered to be 5 to 15 micrograms/mL although some babies may respond at lower concentrations.[5] Some now consider that this is a more appropriate range in asthma (except perhaps acute severe asthma).[6] It has been suggested that pulmonary function tests provide a better guide in long-term therapy with theophylline.[7]

Serum-theophylline concentrations were originally measured by spectrophotometry but this is subject to considerable interference from other drugs. High performance liquid chromatography is now the method of choice when extreme accuracy is important and the enzyme multiplied immunoassay technique (EMIT) has become popular because of its rapidity and adaptability to processing large batches.[2] Devices are also available that provide serum-theophylline measurements within several minutes using monoclonal antibody technology.[2,8]

The use of salivary concentrations for monitoring theophylline dosage requirements has been tried, because it is noninvasive, but poor correlations between salivary- and serum-theophylline concentrations mean it has not gained general usage.

1. Hampson JP. The theophylline "therapeutic window"—fact or fallacy? *Pharm J* 1988; **241:** 722–4.
2. Bierman CW, Williams PV. Therapeutic monitoring of theophylline: rationale and current status. *Clin Pharmacokinet* 1989; **17:** 377–84.
3. Holford N, *et al.* Theophylline target concentration in severe airways obstruction—10 or 20 mg/L. A randomised concentration-controlled trial. *Clin Pharmacokinet* 1993; **25:** 495–505.
4. Pesce AJ, *et al.* Standards of laboratory practice: theophylline and caffeine monitoring. *Clin Chem* 1998; **44:** 1124–8.
5. Edwards C. Theophylline and caffeine. *Pharm J* 1986; **237:** 128–9.
6. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37:** 96–101.
7. Ashutosh K, *et al.* Use of serum theophylline level as a guide to optimum therapy in patients with chronic obstructive lung disease. *J Clin Pharmacol* 1990; **30:** 324–9.
8. Clifton GD, *et al.* Accuracy and time requirements for use of three rapid theophylline assay methods. *Clin Pharm* 1988; **7:** 462–6.

Uses and Administration

Theophylline is a xanthine (p.1108) and relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration. It stimulates the myocardium and CNS, decreases peripheral resistance and venous pressure, and causes diuresis. It is still not clear how theophylline exerts these effects. Inhibition of phosphodiesterase with a resulting increase in intracellular cyclic adenosine monophosphate (cyclic AMP) occurs, and may play a role. Other proposed mechanisms of action include adenosine receptor antagonism, prostaglandin antagonism, and effects on intracellular calcium. In addition, theophylline may also have an anti-inflammatory effect.

Theophylline is used as a bronchodilator in the management of reversible airways obstruction, such as in asthma. Although selective $beta_2$ adrenoceptor stimulants ($beta_2$ agonists) such as salbutamol are generally the preferred bronchodilators for initial treatment, theophylline is commonly used as an adjunct to $beta_2$ agonist and corticosteroid therapy in patients requiring an additional bronchodilating effect. Some patients with chronic obstructive pulmonary disease also have a beneficial response to theophylline therapy. Theophylline is also used to relieve apnoea in neonates. It was formerly used as an adjunct in the treatment of heart failure, and may occasionally have a role in patients with this condition who are also suffering from obstructive airways disease.

Theophylline may be given in the anhydrous form or as the hydrate. Doses of theophylline are usually expressed as anhydrous theophylline; theophylline hydrate 1.1 mg is equivalent to about 1 mg of theophylline.

The pharmacokinetics of theophylline may be altered by factors including age, smoking, disease, diet, and drug interactions (see above under Precautions, Interactions, and Pharmacokinetics). Theophylline doses should therefore be adjusted for each individual patient according to clinical response, adverse effects, and serum-theophylline concentrations.

- Optimum **therapeutic serum concentrations** of theophylline are traditionally considered to range from 10 to 20 micrograms/mL (55 to 110 micromoles/litre) and toxic effects are more common above 20 micrograms/mL. A range of 5 to 15 micrograms/mL may be effective, and associated with fewer adverse effects.

For long-term use, once a maintenance dose has been established, monitoring of serum-theophylline concentrations at 6- to 12-monthly intervals has been recommended.

In the management of **acute severe bronchospasm**, theophylline may be given by *intravenous infusion* where available, though usually aminophylline is preferred (see p.1114). (Anhydrous theophylline 1 mg is equivalent to about 1.18 mg anhydrous aminophylline or 1.28 mg aminophylline hydrate.)

- In patients who have not received theophylline, aminophylline, or other xanthine-containing medications in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes followed by a suggested maintenance dose of 400 to 600 micrograms/kg per hour. Lower doses should be used in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose. Dosage should be calculated in terms of lean or ideal body-weight.
- Intravenous theophylline therapy is best avoided in patients already taking theophylline, aminophylline, or other xanthine-containing medication but, if considered necessary, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in an increase of serum-theophylline concentration of 1 microgram/mL.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* in conventional dosage forms; modified-release preparations are not suitable.

- In adults not currently taking theophylline or xanthine-containing products a suggested loading dose is 5 mg/kg, to produce an average peak serum concentration of 10 micrograms/mL. Doses should again be reduced in the elderly and those with cor pulmonale, heart failure, or liver disease; smokers may require a higher maintenance dose.

In the long-term management of **chronic bronchospasm**, theophylline may be given orally in doses ranging from 300 to 1000 mg daily in divided doses as conventional tablets, capsules, liquid preparations, or modified-release preparations. For conventional dosage forms the divided doses are generally given every 6 to 8 hours. However, modified-release preparations are more commonly used as they reduce adverse effects and the need for frequent dosing, especially in patients with a rapid theophylline clearance.

- A usual dose of modified-release theophylline is 175 to 500 mg every 12 hours, though the bioavailability of different modified-release theophylline preparations may not be comparable and retitration of dosage is required if the patient is changed from one modified-release preparation to another. Larger doses may be given in either the evening or the morning to achieve optimum therapeutic effect when symptoms are most severe. Modified-release preparations which are given once daily are also available; usual doses are 400 or 600 mg daily.
- Initially, low doses of theophylline should be given and they should be gradually adjusted according to clinical response and serum-theophylline measurements. In the USA a preferred approach to initial dosage titration in adults may be to begin with 300 mg daily, in divided doses, for 3 days; if well tolerated, the total daily dose is increased to 400 mg for 3 days, and then, if tolerated and required, to 600 mg. For doses of theophylline used in children, see Administration in Children, below.

Intramuscular injection and dosage by suppository are not recommended due to severe local irritation and slow unreliable absorption.

Theophylline is an ingredient of some preparations promoted for coughs.

There are topical cosmetic preparations containing theophylline derivatives, particularly aminophylline, that have been promoted for the local reduction of body fat (p.1115).

Theophylline monoethanolamine (theophylline olamine), theophylline calcium salicylate, theophylline and sodium acetate (theophylline sodium acetate), theophylline sodium glycinate (theophylline sodium aminoacetate), theophylline calcium glycinate, and theophylline glycinate have all been used similarly to theophylline.

◊ General references.

1. Vasallo R, Lipsky JJ. Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clin Proc* 1998; **73:** 346–54.

Administration. Various methods have been proposed for estimating theophylline pharmacokinetic parameters to enable optimisation of initial dosage but none should be substituted for the subsequent determination of serum-theophylline concentrations and clearance at steady state.[1-3]

It was noted in 1997 that dosage requirements for theophylline had declined relative to those of historical controls, apparently due to a downward shift in theophylline clearance in the US population (perhaps due to environmental changes, such as a decrease in exposure to tobacco smoke).[4] It was suggested that earlier dosage guidelines for theophylline needed to be revised in the light of these data, so that the initial oral dose did not exceed 300 mg daily—for an approach to initial dosage titration consonant with this view, see Uses and Administration, above.

1. Erdman SM, *et al.* An updated comparison of drug dosing methods part II: theophylline. *Clin Pharmacokinet* 1991; **20:** 280–92.
2. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
3. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
4. Asmus MJ, *et al.* Apparent decrease in population clearance of theophylline: implications for dosage. *Clin Pharmacol Ther* 1997; **62:** 483–9.

Administration in children. In the management of **acute severe bronchospasm** in children, theophylline may be given by *intravenous infusion* where available, although aminophylline is preferred (see p.1115). In children who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. Initial maintenance doses are designed to achieve a serum-theophylline concentration of 10 micrograms/mL. The following doses, based on lean or ideal body-weight, have been suggested:

- 1 to 9 years of age, 0.8 to 1 mg/kg per hour
- 9 to 12 years of age, 0.7 to 0.77 mg/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments. See Administration in Infants, below for doses used in children under 1 year of age. Children 12 years of age and over can receive similar doses to adults, see Uses and Administration, above.

If intravenous theophylline therapy is considered necessary in children who are already being given theophylline, aminophylline or other xanthine-containing medicine, serum-theophylline concentrations should be measured to determine a loading dose. Loading doses are based on the expectation that each 500 micrograms of theophylline/kg of lean body-weight will result in a 1-microgram/mL increase in serum-theophylline concentration.

In the treatment of **acute bronchospasm** that has not required intravenous therapy, theophylline has been given *orally* using immediate-release preparations to children aged 1 year old and above, using doses similar to those used in adults, see Uses and Administration, above. For doses used in children under 1 year of age, see Administration in Infants, below.

Oral modified-release preparations of theophylline are given to children from 6 months of age in the long-term management of **chronic bronchospasm**. Dose and dosage frequency depend on the preparation being used, and licensed product information should be consulted; different formulations are not considered interchangeable.

ADMINISTRATION IN INFANTS. Theophylline clearance is reduced in premature neonates and infants under 1 year of age due to an immature hepatic microsomal enzyme system (see under Metabolism and Excretion in Pharmacokinetics, above). Postconceptional age may have a slight influence on theophylline clearance but postnatal age is thought to be more significant.[1]

Theophylline dosage guidelines for infants under 1 year of age were issued by the FDA[2] in 1985, but a number of clinicians considered that higher doses might be necessary.[1,3,4] Subsequent guidelines for *oral* theophylline,[5] issued in 1995, suggested a modified regimen: premature infants should be given initial doses of 1 mg/kg every 12 hours if less than 24 days postnatal age, or 1.5 mg/kg every 12 hours if more than 24 days; in full-term infants up to 1 year of age initial daily dosage (to be given in 3 or 4 divided doses) could be calculated on the basis of the equation:

$$\text{Daily dose (mg/kg)} = (0.2 \times \text{age in weeks}) + 5.0$$

Subsequent dosage should be adjusted based on steady-state serum-theophylline concentrations, which might take as long as 5 days to be achieved in premature neonates if a loading dose is not used.[5] The recommended serum concentrations were 5 to 10 micrograms/mL in neonates and 10 to 15 micrograms/mL in older infants. If a loading dose is considered necessary, 5 mg/kg (or 1 mg/kg for each 2 micrograms/mL increase in serum-theophylline concentration in those already being given theophylline) has been suggested.

Other equations and models of population pharmacokinetics have been proposed for the calculation of appropriate theophylline doses in neonates.[6-8]

Theophylline may be given by *intravenous infusion*, where available, in the management of **acute severe bronchospasm** in infants, although aminophylline is preferred (see p.1115). In infants who have not had theophylline, aminophylline or other xanthine-containing medicine in the previous 24 hours, a suggested loading dose of 4 to 5 mg/kg may be given by intravenous infusion over 20 to 30 minutes. In neonates the following initial maintenance doses have been suggested by the *American Hospital Formulary Service* to achieve a serum-theophylline concentration of 7.5 micrograms/mL :

- neonate, postnatal age 24 days or less, 1 mg/kg every 12 hours
- neonate, postnatal age over 24 days, 1.5 mg/kg every 12 hours

To achieve a serum-theophylline concentration of 10 micrograms/mL the following initial maintenance doses have been suggested by the *Canadian Pharmacists Association*:

- neonate, 170 micrograms/kg per hour
- 6 weeks to 6 months of age, 430 micrograms/kg per hour
- 6 months to 1 year of age, 500 to 600 micrograms/kg per hour

Serum-theophylline concentrations should be used to guide further dose adjustments.

Theophylline may be given prophylactically to reduce some of the adverse renal consequences of perinatal asphyxia (see below).

Theophylline has been used in **neonatal apnoea**, although caffeine is preferred. See Neonatal Apnoea, under Caffeine p.1118.

1. Gilman JT, Gal P. Inadequacy of FDA dosing guidelines for theophylline use in neonates. *Drug Intell Clin Pharm* 1986; **20:** 481–4.
2. Anonymous. Use of theophylline in infants. *FDA Drug Bull* 1985; **15:** 16–17.
3. Murphy JE, *et al.* New FDA guidelines for theophylline dosing in infants. *Clin Pharm* 1986; **5:** 16.
4. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
5. Hendeles L, *et al.* Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy* 1995; **15:** 409–27.
6. Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993; **123:** 651–6.
7. Lee TC, *et al.* Theophylline population pharmacokinetics from routine monitoring data in very premature infants with apnoea. *Br J Clin Pharmacol* 1996; **41:** 191–200.
8. Gagnon AJ. Aminophylline dosing in the treatment of apnea of prematurity—a commentary. *Pharmacotherapy* 1996; **16:** 317–18.

Administration in hepatic impairment. Theophylline clearance is reduced by 50% or more in patients with hepatic insufficiency such as cirrhosis, acute hepatitis, or cholestasis. Careful attention to dose reduction and frequent monitoring of serum-theophylline concentrations are required.

Asthma. Theophylline and its derivatives may be used in the treatment of chronic asthma (p.1108) as an adjunct to beta$_2$ agonists and corticosteroid therapy when an additional bronchodilator is indicated. Modified-release preparations can be useful in the control of nocturnal asthma.

Evidence suggests[1,2] that adding low-dose oral theophylline to inhaled corticosteroids is as effective as increasing the dose of corticosteroid in patients with moderate asthma and persistent symptoms. A systematic review[3] of studies that compared theophylline with long-acting beta$_2$ agonists found that they were both effective for control of nocturnal asthma, but that long-acting beta$_2$ agonists may be more effective in reducing asthma symptoms, including night waking and the need for rescue medication, and are associated with fewer adverse effects.

The use of xanthines in acute asthma attacks is more controversial. UK guidelines permit the use of intravenous aminophylline in patients with severe or life-threatening acute asthma unresponsive to maximal doses of bronchodilators and oral corticosteroids, (a point supported in children[4] but not in adults[5] by systematic review) whereas US guidelines do not consider xanthines have any benefit over the optimal use of beta agonists and consequently do not recommend their use (see p.1108).

1. Wang Y, *et al.* Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. *Respirology* 2005; **10:** 189–95.
2. Lim S, *et al.* Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; **55:** 837–41.
3. Tee AKH, *et al.* Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
4. Mitra A, *et al.* Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 19/03/08).
5. Parameswaran K, *et al.* Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Cardiac arrhythmias. Theophylline has been tried in various bradyarrhythmias, usually when other treatment has failed or is contra-indicated.[1-6] It appears to be of little value in bradyasystolic cardiac arrest.[7,8]

1. Viskin S, *et al.* Aminophylline for bradyasystolic cardiac arrest refractory to atropine and epinephrine. *Ann Intern Med* 1993; **118:** 279–81.
2. Sra JS, *et al.* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; **328:** 1085–90.
3. Bertolet BD, *et al.* Theophylline for the treatment of atrioventricular block after myocardial infarction. *Ann Intern Med* 1995; **123:** 509–11.
4. Alboni P, *et al.* Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. *Circulation* 1997; **96:** 260–6.
5. Ling CA, Crouch MA. Theophylline for chronic symptomatic bradycardia in the elderly. *Ann Pharmacother* 1998; **32:** 837–9.
6. Cawley MJ, *et al.* Intravenous theophylline — an alternative to temporary pacing in the management of bradycardia secondary to AV nodal block. *Ann Pharmacother* 2001; **35:** 303–7.
7. Abu-Laban RB, *et al.* Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. *Lancet* 2006; **367:** 1577–84.
8. Hayward E, *et al.* Aminophylline in bradyasystolic cardiac arrest. *Emerg Med J* 2007; **24:** 582–3.

Cheyne-Stokes respiration. Oral theophylline considerably reduced Cheyne-Stokes respiration (periodic breathing) and episodes of central apnoea in 2 studies in patients with stable heart failure and left ventricular systolic dysfunction.[1,2] This was associated with an improvement in arterial-oxygen saturation during sleep. One study[1] observed no significant change in cardiac function, although pulmonary function did improve. Theophylline was also effective in a patient with Cheyne-Stokes respiration possibly related to diabetic autonomic neuropathy[3] (the use of the term Cheyne-Stokes respiration to describe this patient's respiratory disorder has been questioned[4,5]).

1. Javaheri S, *et al.* Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; **335:** 562–7.
2. Hu K, *et al.* The effect of theophylline on sleep-disordered breathing in patients with stable chronic congestive heart failure. *Chin Med J* 2003; **116:** 1711–16.
3. Pesek CA, *et al.* Theophylline therapy for near-fatal Cheyne-Stokes respiration: a case report. *Ann Intern Med* 1999; **130:** 427–30.
4. Sin DD, Bradley TD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713.
5. Geigel EJ, Chediak AD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713–14.

Chronic obstructive pulmonary disease. In the treatment of chronic obstructive pulmonary disease (p.1112), the bronchodilators of first choice are usually either an antimuscarinic such as ipratropium bromide, or a beta$_2$ agonist such as salbutamol, given by inhalation. However the addition of an oral xanthine such as theophylline may be of value in some patients to maximise respiratory function and for its positive cardiac inotropic effects.

A systematic review[1] of studies comparing oral theophylline with placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD), found that theophylline treatment improved lung function, ventilatory capacity, and arterial blood gas tensions. A decrease in thoracic gas entrapment and hyperinflation, and an increase in respiratory muscle function and diaphragmatic strength could be responsible for the improvement in symptoms. Improvements in arterial blood gas tensions may result from an increased tidal volume caused by either a direct positive inotropic effect on the respiratory muscles, or a central stimulatory action, or both. The authors concluded that theophylline produced an improvement in lung function similar to that reported for long acting beta$_2$ agonists in COPD patients, and that with close monitoring beneficial effects may be obtained from theophylline therapy in those patients who remain symptomatic from COPD despite first-line bronchodilator therapy. Theophylline has been reported to exert an inhibitory effect on airway inflammation in COPD, particularly at plasma concentrations below 10 micrograms/mL.[2] It has also been suggested that low-dose theophylline may restore corticosteroid responsiveness in COPD patients, but further research is required to assess its role.

1. Ram FSF, *et al.* Oral theophylline for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 19/03/08).
2. Barnes PJ. Theophylline for COPD. *Thorax* 2006; **61:** 742–4.

Contrast nephropathy. For mention of theophylline as a potential protectant against kidney damage induced by iodinated contrast media, see Effects on the Kidneys, under Amidotrizoic Acid, p.1476.

ECT. For mention of the use of theophylline as an adjunct to electroconvulsive therapy, see under Precautions, above.

Erythrocytosis. When pharmacological treatment is required for secondary erythrocytosis (p.1198), current UK guidelines[1,2] recommend an ACE inhibitor or an angiotensin II receptor antagonist as the usual drugs of first choice. Although theophylline appears to be less effective than an ACE inhibitor in post-transplantation erythrocytosis[3] an oral daily dose of 8 mg/kg has produced beneficial effects.[4,5] Theophylline may be of use given either alone or with an ACE inhibitor in those who fail to respond to first-line therapy. Theophylline treatment may also reduce erythrocytosis associated with chronic obstructive pulmonary disease.[6]

1. McMullin MF, *et al.* General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 19/03/08)
2. McMullin MF, *et al.* National Cancer Research Institute, Myeloproliferative Disorder Subgroup. British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; **138:** 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 19/03/08)
3. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
4. Bakris GL, *et al.* Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; **323:** 86–90.
5. Ilan Y, *et al.* Erythrocytosis after renal transplantation: the response to theophylline treatment. *Transplantation* 1994; **57:** 661–4.
6. Oren R, *et al.* Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; **157:** 1474–8.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p.747.

Perinatal asphyxia. Perinatal asphyxia frequently results in damage to the kidneys;[1] vasomotor nephropathy or acute renal failure may develop as a result of decreased perfusion to the kidneys.[2] Theophylline has been studied for the prevention of renal dysfunction associated with perinatal asphyxia in both term and preterm neonates.[1-3] Beneficial effects have been observed after early use of intravenous theophylline, including significant decreases in serum creatinine[1-3] and urinary β2-microglobulin (an indicator of tubular performance),[1,3] and a significant increase in creatinine clearance.[1-3] A single dose of 8 mg/kg theophylline, by slow intravenous injection in the first hour of life, was given to neonates at term.[1,3] Lower doses were used for preterm neonates; 1 mg/kg daily for 3 consecutive days.[2]

1. Bhat MA, *et al.* Theophylline for renal function in term neonates with perinatal asphyxia: a randomised, placebo-controlled trial. *J Pediatr* 2006; **149:** 180–4.
2. Cattarelli D, *et al.* A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F80–F84.
3. Jenik AG, *et al.* A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000; **105:** e45. Also available at: http://pediatrics.aappublications.org/cgi/content/full/105/4/e45 (accessed 19/03/08)

Preparations

BP 2008: Prolonged-release Theophylline Tablets;
USP 31: Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution; Theophylline Capsules; Theophylline Extended-release Capsules; Theophylline in Dextrose Injection; Theophylline Oral Solution; Theophylline Sodium Glycinate Elixir; Theophylline Sodium Glycinate Tablets; Theophylline Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aminofilin†; Asmabiol†; Crisasma; Drilyna; Nefoben; Teodosis; Teosona; Teosona Sol; Theo-Dur†; ***Austral.:*** Nuelin; ***Austria:*** Aerodyne†; Afonilum; Euphyllin; Respicur; Theoplus; Theospirex; Unifyl; ***Belg.:*** Euphyllin; Theo-2; Theolair; Xanthium; ***Braz.:*** Bermacia†; Codrinan; Talofilina; Teofilab; Teolong; Teophyl; Teoston; ***Canad.:*** Apo-Theo; Novo-Theophyl; Quibron-T†; Theo-Dur†; Theolair; Uniphyl; ***Chile:*** Elixine; ***Cz.:*** Afonilum; Euphyllin; Euphylong†; Spophyllin; Teotard†; Theo-Dur†; Theophyllard†; Theoplus; Uni-Dur†; Unilair†; ***Denm.:*** Nuelin; Pulmo-Timelets; Theo-Dur; UniXan; Uno-Lin†; ***Fin.:*** Euphyllin†; Nuelin; Retafyllin; Theo-Dur†; Theofol; ***Fr.:*** Euphylline; Theostat; Xanthium†; ***Ger.:*** Aerobin; Afonilum; Afonilum novo; afpred-THEO; Bronchoparat; Bronchoretard; Contiphyllin; Cronasma†; duraphyllin; Euphylong; Pulmidur†; Pulmo-Timelets; Solosin; Theo; Theolair†; Tromphyllin; Unilair; Uniphyllin; ***Gr.:*** Aberten; Mediphyllin Chrono; Novaphylline†; Theo-Bros; Theo-Dur; Theoplus; Uniphyllin; ***Hong Kong:*** CP-Theo; Euphylong; Novo-Theophyl†; Nuelin; Slo-Theo; Theo-Dur†; Theotrim; ***Hung.:*** Egifilin; Euphylong; Retafyllin; Theophtard; Theospirex; ***India:*** Phylobid; Phyloday; Theo PA; Theobid; Theoday; Theoped; Unicontin; ***Indon.:*** Bronchophylin; Brondilex; Bronsolvan; Euphyllin; Quibron-T; Retaphyl; Theobron; ***Irl.:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; Zepholin; ***Israel:*** Glyphyllin; Theotard; Theotrim; ***Ital.:*** Aminomal; Diffumal; Euphyllina; Frivent; Paidomal; Respicur; Tefamin; Theo-24; Theo-Dur; Theolair; ***Jpn:*** Theodur; Theolong; ***Malaysia:*** Apo-Theo; Nuelin; Numalin†; Retafyllin; Theolin†; ***Mex.:*** Apoteoprol†; Elixofilina; Fluidasa; Pharmafil; Slo-Bid†; Teolong†; Uni-Dur†; ***Neth.:*** Euphylong; Theolair; ***Norw.:*** Nuelin; Theo-Dur; ***NZ:*** Nuelin; ***Philipp.:*** Asmasolon; Brondil (Reformulated); Nuelin; Phenedrine; Theo-Dur; ***Pol.:*** Afonilum; Euphyllin; Theoplus; Theospirex; Theovent; ***Port.:*** Eufilina; Lepobron†; Teonibsa†; Teovent†; Unicontin; ***Rus.:*** Teotard (Теотард); ***S.Afr.:*** Alcophyllin; Chronophyllin†; Euphyllin; Microphyllin; Nuelin; Pulmophyllin; Theoplus; Uniphyl; ***Singapore:*** Apo-Theo; Nuelin; Retafyllin†; Theolin; Theoplus†; Xanthium†; ***Spain:*** Chantaline†; Elixifilin; Eufilina; Histafilin; Pulmeno; Teolixir; Teromol; Theo Max†; Theo-Dur; Theolair; Theoplus; Unilong†; Vent Retard†; ***Swed.:*** Euphylong†; Theo-Dur; ***Switz.:*** Euphyllin; Sodip-phylline†; Theolair; Unifyl; ***Thai.:*** Aerobin†; Almarion; Asmasolon; Bronoday; Franol; Med-Phylline†; Nuelin; Retafyllin; Temaco; Theotrim; Xanthium; ***Turk.:*** Bronkolin; Pirasmin; Talotren; Teobag; Teokap; Teosel; Theo-Dur; Xanthium; ***UAE:*** Theophar; ***UK:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; ***USA:*** Accurbron; Aerolate; Aquaphyllin†; Asmalix; Elixomin†; Elixophyllin; Quibron-T†; Respbid†; Slo-Bid; Slo-Phyllin; Sustaire†; T-Phyl; Theo-24; Theo-X†; Theochron; Theoclear†; Theolair; Theovent†; Uniphyl; ***Venez.:*** Nuelin; Teobid.

Multi-ingredient: ***Arg.:*** Airbronal†; Bronkasma†; Dexa Aminofilin; Dexa Teosona; Fatigan Bronquial†; Inastmol†; Sedacris; ***Austria:*** Ambredin; Asthma 23 D; ***Braz.:*** Abacateirol†; Alergotox†; Asmatiron†; Bronquitos; Endotussin; Franol; Marax; ***Canad.:*** ratio-Theo-Bronc; ***Cz.:*** Oxantil; ***Fin.:*** Theofol Comp; ***Fr.:*** Hypnasmine†; ***Ger.:*** Broncho-Euphyllin; ***Gr.:*** Gulamyl; ***India:*** Alergin; Asmapax; Asthmino†; Broncofol-P†; Broncofol†; Dericip; Dericip Plus; Deriphyllin; Etyofil†; Marax; Tergil-T; Theo-Asthalin; Theobric; ***Indon.:*** Asmadex; Asmano; Asmasolon; Asthma Soho; Neo Napacin; Prinasma; Teosal; Theochodil; Tusapres; ***Irl.:*** Franol Expectorant†; ***Malaysia:*** Asthma; Brondal†; Grenin†; Theophylline Expectorant; ***Mex.:*** Aminoefedrison; ***Philipp.:*** Mucophylline; ***Pol.:*** Baladex; ***Port.:*** Cosmaxil†; Prelus†; ***S.Afr.:*** Actophlem; Alcophyllex; Diatussin; Metaxol; Solphyllex; Solphyllin; Theophen; Theophen Comp; ***Spain:*** Novofilin†; Teolixir Compositum; ***Thai.:*** Almasal; Asiabron; Bronchil; Brondil; Mila-Asma; Polyphed; Qualiton; ***UK:*** Do-Do ChestEze; Franol Plus†; Franol†; ***USA:*** Elixophyllin-GG; Elixophyllin-KI; Glyceryl-T; Hydrophed; Marax; Neoasma; Quadrinal; Quibron†; Slo-Phyllin GG†; Tedrigen; Theodrine; Theomax DF; ***Venez.:*** Marax†; Metilfedrin†; Metoxifilin; Teofedril†.

Tiotropium Bromide *(BAN, rINN)*

Ba-679; Ba-679BR; Bromuro de tiotropio; Tiotropii bromidum; Tiotropium, bromure de; Tiotropyum Bromür: 6β,7β-Epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide di-2-thienylglycolate.

Тиотропия Бромид

$C_{19}H_{22}BrNO_4S_2$ = 472.4.

CAS — 186691-13-4 (tiotropium); 139404-48-1 (anhydrous tiotropium bromide or tiotropium bromide hydrate); 136310-93-5 (anhydrous tiotropium bromide); 411207-31-3 (tiotropium bromide monohydrate).

ATC — R03BB04.

ATC Vet — QR03BB04.

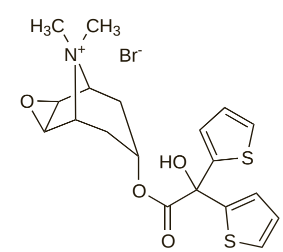

Adverse Effects and Precautions

As for Ipratropium Bromide (p.1124).

Pharyngitis, sinusitis, rhinitis, and epistaxis have also been reported after inhalation.

Patients with moderate to severe renal impairment (creatinine clearance 50 mL/minute or less) should be closely monitored as tiotropium bromide is mainly excreted by the kidneys.

Effects on the cerebrovascular system. In March 2008 the FDA reported[1] that the manufacturer of tiotropium bromide (*Boehringer Ingelheim*) had informed them that they had identified a possible increased risk of stroke in patients taking tiotropium bromide. From pooled analysis of 29 clinical studies in patients with chronic obstructive pulmonary disease preliminary estimates of the risk of stroke were 8 per 1000 patients treated for one year with tiotropium compared with 6 per 1000 patients given placebo for one year. The FDA had not yet confirmed the analyses and urged caution in interpreting these preliminary results.

1. FDA. Early communication about ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 18th March 2008). Available at: http://www.fda.gov/cder/drug/early_comm/tiotropium.htm (accessed 22/05/08)

Effects on the skin. Subacute cutaneous lupus erythematosus has been reported in a patient inhaling tiotropium.[1] Skin lesions developed one week after introduction of the drug, resolved when the drug was stopped, and recurred on rechallenge.

Inhaled tiotropium has also been associated with a photosensitive lichenoid eruption in another patient,[2] 22 months after starting treatment. The lesions resolved when the drug was stopped; patch testing however, gave a negative result. Rechallenge was not attempted.

1. Pham H-C, Saurat J-H. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; **141:** 911–12.
2. Pérez-Pérez L, *et al.* Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology* 2007; **214:** 97–8.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p.1220. However, these interactions are not usually seen with antimuscarinics, such as tiotropium, given by inhalation.

Pharmacokinetics

After inhalation, some tiotropium bromide is absorbed from the lung, with the majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 20% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma proteins. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The terminal elimination half-life is between 5 and 6 days.

Uses and Administration

Tiotropium bromide is a quaternary ammonium antimuscarinic that is structurally related to ipratropium but has a prolonged bronchodilator action. It is used similarly to ipratropium (p.1124) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (below); tiotropium is not suitable for the initial treatment of acute bronchospasm. Tiotropium bromide can be given as inhalation powder in capsules containing 22.5 micrograms of tiotropium bromide monohydrate, equivalent to 18 micrograms of tiotropium, and supplying 10 micrograms of tiotropium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled daily, at the same time each day.

Tiotropium bromide can also be given as inhalation solution via a metered-dose inhaler. Each metered dose contains 3.124 micrograms of tiotropium bromide monohydrate equivalent to 2.5 micrograms of tiotropium. Two doses of 2.5 micrograms are inhaled daily, at the same time each day.

◊ References.

1. Hvizdos KM, Goa KL. Tiotropium bromide. *Drugs* 2002; **62:** 1195–1203.

Chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease (COPD; p.1112) tiotropium bromide has been shown to be effective at improving dyspnoea,[1-3] health-related quality of life,[1,3] symptom-limited exercise tolerance,[2] lung function measurements,[3] and reducing exacerbations[1,3,4] compared with placebo.

Tiotropium has also been found to be more effective than ipratropium at improving dyspnoea, health-related quality of life,[5] and lung function,[5,6] and reducing exacerbations;[5] consideration of tiotropium as first-line maintenance treatment in COPD has been suggested.

Similarly, tiotropium has produced better bronchodilatation, reduced dyspnoea, and improved health-related quality of life scores compared with salmeterol.[7]

Combining tiotropium therapy with an inhaled corticosteroid and a long-acting $beta_2$ agonist did not statistically influence rates of COPD exacerbations but did improve lung function, quality of life, and hospitalisation rates in patients with moderate to severe COPD.[8]

A systematic review[9] and a meta-analysis[10] confirmed that tiotropium reduces exacerbations and related hospitalisations, improves quality of life and symptoms in stable COPD. Tiotropium may also have slowed the decline in forced expiratory volume (FEV) seen in COPD; however, the authors concluded that further studies are required to evaluate the effect of tiotropium on FEV and to clarify its role in relation to long-acting $beta_2$ agonists.

The role of tiotropium in the management of COPD has been extensively reviewed.[11-14]

1. Casaburi R, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; **19:** 217–24.
2. Maltais F, *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; **128:** 1168–78.
3. Brusasco V, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; **58:** 399–404.
4. Niewoehner DE, *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; **143:** 317–26.
5. Vincken W, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; **19:** 209–16.
6. van Noord JA, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 289–94.
7. Donohue JF, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122:** 47–55.
8. Aaron SD, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; **146:** 545–55.
9. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 18/02/08).
10. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; **61:** 854–62. Correction. *ibid.*; **62:** 191.
11. Gross NJ. Tiotropium bromide. *Chest* 2004; **126:** 1946–53.
12. Olin JL. Tiotropium: an inhaled anticholinergic for chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2005; **62:** 1263–9.
13. Somand H, Remington TL. Tiotropium: a bronchodilator for chronic obstructive pulmonary disease. *Ann Pharmacother* 2005; **39:** 1467–75.
14. Burns G, Bianchi S. Chronic obstructive pulmonary disease: the evidence for use of tiotropium. *Br J Hosp Med* 2006; **67:** 85–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Spiriva; ***Austral.:*** Spiriva; ***Austria:*** Spiriva; ***Belg.:*** Spiriva; ***Braz.:*** Spiriva; ***Canad.:*** Spiriva; ***Chile:*** Spiriva; ***Cz.:*** Spiriva; ***Denm.:*** Spiriva; ***Fin.:*** Spiriva; ***Fr.:*** Spiriva; ***Ger.:*** Spiriva; ***Gr.:*** Spiriva; ***Hong Kong:*** Spiriva; ***Hung.:*** Spiriva; ***India:*** Tiova; ***Indon.:*** Spiriva; ***Irl.:*** Spiriva; ***Israel:*** Spiriva; ***Ital.:*** Spiriva; ***Jpn:*** Spiriva; ***Malaysia:*** Spiriva; ***Mex.:*** Spiriva; ***Neth.:*** Spiriva; ***Norw.:*** Spiriva; ***NZ:*** Spiriva; ***Philipp.:*** Spiriva; ***Pol.:*** Spiriva; ***Port.:*** Spiriva; ***Rus.:*** Spiriva (Спирива); ***S.Afr.:*** Spiriva; ***Singapore:*** Spiriva; ***Spain:*** Spiriva; ***Swed.:*** Spiriva; ***Switz.:*** Spiriva; ***Thai.:*** Spiriva; ***Turk.:*** Spiriva; ***UK:*** Spiriva; ***USA:*** Spiriva; ***Venez.:*** Spiriva.

Multi-ingredient: ***India:*** Duova.

Tipelukast *(USAN, rINN)*

KCA-757; MN-001; Tipélukast; Tipelukastum. 4-(6-Acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy}-2-propylphenoxy)butanoic acid.

Типелукаст

$C_{29}H_{38}O_7S$ = 530.7.
CAS — 125961-82-2.

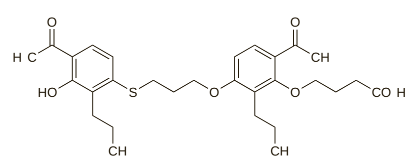

Profile

Tipelukast is a leukotriene receptor antagonist (p.1108), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

Tranilast *(USAN, rINN)*

MK-341; N-5′; Tranilastum. *N*-(3,4-Dimethoxycinnamoyl)anthranilic acid.

Траниласт

$C_{18}H_{17}NO_5$ = 327.3.
CAS — 53902-12-8.

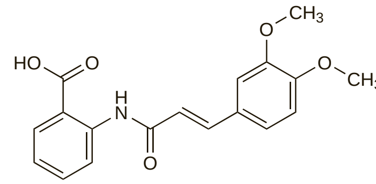

Adverse Effects and Precautions

Adverse effects reported with tranilast have included gastrointestinal disturbances, headache, drowsiness or insomnia, dizziness, malaise, and skin rashes and generalised pruritus. Rarely, liver function disturbance or jaundice, renal dysfunction, cystitis-like symptoms, anaemia, leucopenia, thrombocytopenia, palpitations, oedema, facial flushing, and stomatitis may occur. Tranilast should be used with caution in patients with impaired hepatic or renal function. Haematological monitoring is recommended.

Irritation and blepharitis have been reported after topical application to the eye.

Licensed product information advises against the use of tranilast in pregnancy because of teratogenicity in *animal* studies.

Tranilast should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (p.1136) also apply.

Uses and Administration

Tranilast has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1137). It is also stated to inhibit collagen synthesis in fibroblasts. It is used in the prophylactic management of asthma (p.1108) and in allergic rhinitis (p.565), conjunctivitis (p.564), and eczema (p.1579). It is also used in the management of keloids and hypertrophic scarring. The usual oral adult dose is 100 mg three times daily. For details of doses in children, see below. Eye drops containing tranilast 0.5% are used four times daily for allergic conjunctivitis.

Tranilast has been investigated for the prevention of restenosis after coronary artery revascularisation procedures but was found to be ineffective.

Administration in children. Tranilast is given to children for the prophylactic management of asthma, in allergic rhinitis and eczema, and in the management of keloids and hypertrophic scars. An oral daily dose of 5 mg/kg, given in 3 divided doses, may be used.

Sarcoidosis. For a mention of possible benefit from tranilast in cutaneous sarcoidosis, see p.1512.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rizaben.

Tretoquinol Hydrochloride *(pINNM)* ⊗

AQ-110 (tretoquinol); Hidrocloruro de tretoquinol; Ro-07-5965; Trétoquinol, Chlorhydrate de; Tretoquinoli Hydrochloridum; Trimethoquinol Hydrochloride; Trimetoquinol Hydrochloride. (−)-1,2,3,4-Tetrahydro-1-(3,4,5-trimethoxybenzyl)isoquinoline-6,7-diol hydrochloride monohydrate.

Третохинола Гидрохлорид

$C_{19}H_{23}NO_5,HCl,H_2O$ = 399.9.
CAS — 30418-38-3 (tretoquinol); 18559-59-6 (anhydrous tretoquinol hydrochloride).
ATC — R03AC09; R03CC09.
ATC Vet — QR03AC09; QR03CC09.

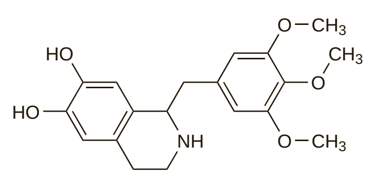

(tretoquinol)

Pharmacopoeias. In *Jpn.*

Profile

Tretoquinol is a direct-acting sympathomimetic reported to have a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131). It is given as the hydrochloride for its bronchodilating properties in the management of reversible airways obstruction, as in asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112).

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Inolin; ***Jpn:*** Inolin†.

Tulobuterol Hydrochloride *(BANM, rINNM)* ⊗

C-78; Hidrocloruro de tulobuterol; HN-078 (tulobuterol); Tulobutérol, Chlorhydrate de; Tulobuterolhydroklorid; Tulobuteroli Hydrochloridum; Tulobuterolihydrokloridi. 2-*tert*-Butylamino-1-*o*-chlorophenylethanol hydrochloride.

Тулобутерола Гидрохлорид

$C_{12}H_{18}ClNO,HCl$ = 264.2.

CAS — 41570-61-0 (tulobuterol); 56776-01-3 (tulobuterol hydrochloride).

ATC — R03AC11; R03CC11.

ATC Vet — QR03AC11; QR03CC11.

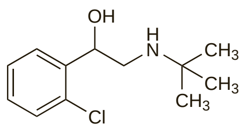

(tulobuterol)

Pharmacopoeias. In *Jpn.*

Profile

Tulobuterol is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has properties similar to those of salbutamol (p.1131).

Tulobuterol is used as a bronchodilator in the management of reversible airways obstruction, as in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). It is given orally as the hydrochloride. The initial oral dose in adults is 1 or 2 mg of tulobuterol hydrochloride twice daily, which can be increased to 3 mg twice daily if necessary. An increased need for, or decreased duration of effect of, tulobuterol indicates deterioration of asthma control and the need for review of therapy. Tulobuterol has also been given as the base by inhalation from a metered-dose inhaler. A transdermal formulation of tulobuterol base is also available; a dose of 2 mg daily is used together with anti-inflammatory therapy.

For doses of tulobuterol used in children aged 14 years and under, see Administration in Children, below.

◊ References to the transdermal formulation of tulobuterol.

1. Uematsu T, *et al.* The pharmacokinetics of the β -adrenoceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol.* 1993; **44:** 361–4.
2. Iikura Y, *et al.* Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy* 1995; **74:** 147–51.
3. Fukuchi Y, *et al.* Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005; **4:** 447–55.
4. Yoshihara S, *et al.* The use of patch formulation of tulobuterol, a long-acting beta2-adrenoceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006; **96:** 879–80.
5. Fujimoto K, *et al.* Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. *J Asthma* 2006; **43:** 501–7.
6. Nishiyama O, *et al.* Comparison of the effects of tulobuterol patch and salmeterol in moderate to severe asthma. *Clin Exp Pharmacol Physiol* 2006; **33:** 1016–21.
7. Kobayashi Y, *et al.* Addition of transdermal or inhaled long-acting β -agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler. *J Asthma* 2007; **44:** 77–81.

Administration in children. Tulobuterol hydrochloride has been used to treat bronchospasm in children in the following *oral* doses:

- 1 to 6 years of age, 0.25 to 0.5 mg twice daily
- 6 to 10 years of age, 0.5 to 1 mg twice daily
- 10 to 14 years of age, 1 to 1.5 mg twice daily

In some countries, children 12 years of age and over may be given the adult dose of tulobuterol, see above.

Transdermal delivery of tulobuterol is also used in children, in the following doses:

- 6 months to 3 years of age, 0.5 mg once daily
- 3 to 9 years of age, 1 mg once daily
- 9 years of age and older, as for adults (see above)

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Bremax; ***Belg.:*** Respacal†; ***Ger.:*** Atenos; Brelomax; ***Jpn:*** Hokunalin; ***Mex.:*** Bremax; ***Philipp.:*** Bremax; ***Port.:*** Atenos†; ***Venez.:*** Bremax†; Bretol.

Zafirlukast *(BAN, USAN, rINN)*

ICI-204219; Tsafirlukasti; Zafirlukastum. Cyclopentyl 3-{2-methoxy-4-[(o-tolylsulfonyl)carbamoyl]benzyl}-1-methylindole-5-carbamate.

Зафирлукаст

$C_{31}H_{33}N_3O_6S$ = 575.7.

CAS — 107753-78-6.

ATC — R03DC01.

ATC Vet — QR03DC01.

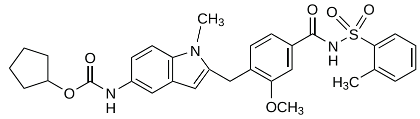

Adverse Effects and Precautions

Headache, an increased incidence of respiratory-tract infection (in the elderly), and gastrointestinal disturbances have been reported with zafirlukast and other leukotriene antagonists. Other adverse effects have included generalised and abdominal pain, arthralgia, myalgia, fever, malaise, insomnia, and dizziness. Elevations in liver enzyme values have occurred, and rarely, symptomatic hepatitis or hyperbilirubinaemia (see also below); fatalities have occurred. Hypersensitivity reactions, including rashes, pruritus, urticaria, and angioedema, have been reported. There have also been rare reports of agranulocytosis, bleeding, bruising and oedema. There have been a few reports of systemic eosinophilia consistent with Churg-Strauss syndrome in patients receiving zafirlukast (see below); treatment should be withdrawn in these patients.

Zafirlukast and other leukotriene antagonists should not be used for the treatment of acute asthma attacks. Zafirlukast is contra-indicated in patients with hepatic impairment or cirrhosis.

Incidence of adverse effects. An observational study[1] of 7976 patients prescribed zafirlukast found it to be generally well tolerated. Similarly to UK licensed product information, the most frequently reported adverse effects (1 to 2% of patients) were headache, rash, abdominal pain, malaise, and gastrointestinal disturbances such as nausea, diarrhoea, and dyspepsia. Dizziness and palpitations were more common in the first month of treatment. An increased incidence of depression was also noted.

1. Twaites BR, *et al.* Safety of zafirlukast: results of a postmarketing surveillance study on 7976 patients in England. *Drug Safety* 2007; **30:** 419–29.

Churg-Strauss syndrome. Pulmonary infiltrates and eosinophilia, resembling the Churg-Strauss syndrome, with dilated cardiomyopathy, were reported after withdrawal of corticosteroid therapy in 8 patients taking zafirlukast.[1] Symptoms responded to withdrawal of zafirlukast and treatment with corticosteroids, with or without cyclophosphamide. It has been suggested that the patients' original asthmatic symptoms had been part of an unrecognised vasculitic syndrome that was unmasked by stopping corticosteroids.[2,3] However, others have reported Churg-Strauss syndrome associated with zafirlukast in those not receiving corticosteroids,[4,5] although these cases were not inconsistent with the view that treatment with leukotriene antagonists was coincidental.[6] It has also been noted that leukotriene receptor antagonists tend to be prescribed for patients with more severe asthma, which may be a precursor to the development of Churg-Strauss syndrome.[3] In addition, eosinophilic syndromes have been reported for other anti-asthma drugs including inhaled fluticasone and sodium cromoglicate, evidence supporting a non-drug-related aetiology.[6] However, the number of reports with zafirlukast and the other leukotriene antagonists, montelukast (see p.1126) and pranlukast,[7] means that a particular class-effect cannot be ruled out.[3,8] It has been suggested that patients should be monitored carefully (e.g. by measuring erythrocyte sedimentation rate, C reactive protein, and eosinophil counts) if the introduction of an anti-asthma drug such as a leukotriene antagonist permits the reduction of oral corticosteroid dosage.[9] In addition, in patients with asthma and features of multisystem disease, the possibility of underlying Churg-Strauss syndrome (p.1501) may be worth considering.

1. Wechsler ME, *et al.* Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998; **279:** 455–7.
2. Churg A, Churg J. Steroids and Churg-Strauss syndrome. *Lancet* 1998; **352:** 32–3.
3. Keogh KA. Leukotriene receptor antagonists and Churg-Strauss syndrome: cause, trigger or merely an association? *Drug Safety* 2007; **30:** 837–43.
4. Katz RS, Papernik M. Zafirlukast and Churg-Strauss syndrome. *JAMA* 1998; **279:** 1949.
5. Green RL, Vayonis AG. Churg-Strauss syndrome after zafirlukast in two patients not receiving systemic steroid treatment. *Lancet* 1999; **353:** 725–6.
6. Wechsler M, Drazen JM. Churg-Strauss syndrome. *Lancet* 1999; **353:** 1970.
7. Kinoshita M, *et al.* Churg-Strauss syndrome after corticosteroid withdrawal in an asthmatic patient treated with pranlukast. *J Allergy Clin Immunol* 1999; **103:** 534–5.
8. Green RL, Vayonis AG. Churg-Strauss syndrome. *Lancet* 1999; **353:** 1971.
9. D'Cruz DP, *et al.* Difficult asthma or Churg-Strauss syndrome? *BMJ* 1999; **318:** 475–6.

Effects on the liver. Severe hepatotoxicity has been associated with zafirlukast.[1-4] The Canadian manufacturer reported[4] in April 2004 that from worldwide postmarketing surveillance of zafirlukast there had been 46 reports of hepatitis, 14 of hepatic failure, 3 of which progressed to fulminant hepatitis, and 59 reports of other clinically significant hepatic dysfunction; 7 fatalities had occurred. In most, but not all, cases symptoms had abated and liver enzymes had returned to normal after stopping zafirlukast. It was important that prescribers, patients and/or their carers were alert to the signs and symptoms of hepatotoxicity. Licensed product information for zafirlukast advises stopping treatment if hepatotoxicity is suspected, and performing liver function tests;

1. Grieco AJ, Burstein-Stein J. Oral montelukast versus inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000; **133:** 392.
2. Reinus JF, *et al.* Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. *Ann Intern Med* 2000; **133:** 964–8.
3. Danese S, *et al.* Severe liver injury associated with zafirlukast. *Ann Intern Med* 2001; **135:** 930.
4. AstraZeneca Canada. Important safety information regarding reports of serious hepatic events in patients receiving Accolate (zafirlukast) (issued 14th April 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/accolate_2_hpc-cps-eng.pdf (accessed 09/07/08)

Lupus. Zafirlukast was thought to be responsible for the development of lupus in a 9-year-old girl.[1]

1. Finkel TH, *et al.* Drug-induced lupus in a child after treatment with zafirlukast (Accolate). *J Allergy Clin Immunol* 1999; **103:** 533–4.

Renal impairment. The UK licensed product information states that zafirlukast should be used with caution in patients with moderate or severe renal impairment because of limited experience in this group. However, the US product information mentions no such caution, and states that the pharmacokinetics of zafirlukast in patients with renal impairment do not appear to differ from those in patients with normal renal function. Only about 10% of a dose is reported to be excreted in the urine.

Interactions

Zafirlukast is metabolised by hepatic cytochrome P450, specifically the CYP2C9 isoenzyme, and has been shown to inhibit the activity of isoenzymes CYP2C9 and CYP3A4. Therefore, use with other drugs that are metabolised by these hepatic enzymes may result in increases in plasma concentrations, and possibly, adverse effects. Patients receiving warfarin may develop prolongation of the prothrombin time and anticoagulant dosage should be adjusted accordingly. Erythromycin, terfenadine, and theophylline may reduce plasma concentrations of zafirlukast; zafirlukast has rarely been reported to increase plasma-theophylline concentrations. Increased plasma concentrations of zafirlukast have been seen when given with high doses of aspirin.

Pharmacokinetics

Peak plasma concentrations of zafirlukast occur about 3 hours after oral doses. The absolute bioavailability is uncertain, but taking it with food reduces both the rate and extent of absorption, decreasing bioavailability by about 40%. Zafirlukast is about 99% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9, and excreted principally in faeces, as unchanged drug and metabolites. About 10% of a dose is excreted in urine as metabolites. The terminal elimination half-life of zafirlukast is about 10 hours. Studies in *animals* suggest that small amounts cross the placenta; it is also distributed into breast milk.

◊ Reviews.

1. Dekhuijzen PNR, Koopmans PP. Pharmacokinetic profile of zafirlukast. *Clin Pharmacokinet* 2002; **41:** 105–14.

Uses and Administration

Zafirlukast is a selective and competitive antagonist of the leukotriene C_4, D_4, and E_4 receptors (p.1108), stimulation of which by circulating leukotrienes is thought to play a role in the pathogenesis of asthma. The drug suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants, but is not suitable for the management of acute attacks of asthma.

Zafirlukast is used in the management of chronic asthma (see below). It is given orally in doses of 20 mg twice daily, taken at least 1 hour before or 2 hours after meals. For details of doses in children, see below.

◊ General references.

1. García-Marcos L, *et al.* Benefit-risk assessment of antileukotrienes in the management of asthma. *Drug Safety* 2003; **26:** 483–518.
2. Anonymous. Leukotriene receptor antagonists—an update. *Drug Ther Bull* 2005; **43:** 85–8.
3. Currie GP, McLaughlin K. The expanding role of leukotriene receptor antagonists in chronic asthma. *Ann Allergy Asthma Immunol* 2006; **97:** 731–41.
4. Riccioni G, *et al.* Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007; **14:** 1966–77.

Administration in children. In the management of chronic asthma, US licensed product information recommends a zafirlukast dose of 10 mg twice daily orally in children aged from 5 to 11 years. Children 12 years of age and over may be given the adult dose, see above. In the UK, zafirlukast is unlicensed in children under 12 years of age.

Asthma. Zafirlukast produces modest improvement in mild-to-moderate asthma,[1,2] which was of a similar order to that seen with inhaled sodium cromoglicate in one study,[3] but less than that of inhaled salmeterol in another.[4] It has also been found to be less effective than inhaled fluticasone in persistent asthma.[5-7] Guidelines for the management of asthma (p.1108) permit the use of zafirlukast as an alternative to inhaled corticosteroids in patients with mild persistent asthma, who cannot be managed with inhaled $beta_2$ agonists on an as-needed basis alone. It can also be considered for use in moderate or severe persistent asthma, usually added to standard therapy of inhaled corticosteroids and long-acting inhaled $beta_2$ agonists. Combination of anti-leukotriene drugs with inhaled corticosteroids alone seems, however, to be less effective than a combination of the latter with long-acting inhaled $beta_2$ agonists. In a study in patients presenting to the emergency room with acute severe asthma, adding zafirlukast to standard therapy in hospital and for 28 days after discharge was associated with a reduced rate of relapse, and a reduction in the need for extended care.[8]

1. Suissa S, *et al.* Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 177–83.
2. Fish JE, *et al.* Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. *Clin Ther* 1997; **19:** 675–90.
3. Nathan RA, *et al.* Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. *Ann Allergy Asthma Immunol* 1999; **82:** 497–503.
4. Busse W, *et al.* Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999; **103:** 1075–80.
5. Busse W, *et al.* Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001; **50:** 595–602.
6. Nathan RA, *et al.* A comparison of short-term treatment with inhaled fluticasone propionate and zafirlukast for patients with persistent asthma. *Am J Med* 2001; **111:** 195–202.
7. Brabson JH, *et al.* Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. *Am J Med* 2002; **113:** 15–21.
8. Silverman RA, *et al.* Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest* 2004; **126:** 1480–9.

Rhinitis. Although it was reported to improve symptoms of seasonal allergic rhinitis (p.565) in one study,[1] zafirlukast 20 mg twice daily was not effective when compared with placebo and intranasal beclometasone in another.[2] Some benefits have been reported in perennial allergic rhinitis, in particular an improvement in nasal obstruction.[3,4] A review of the role of leukotrienes in allergic rhinitis concluded that leukotriene receptor antagonists have modest efficacy given alone but can be usefully added to other treatments.[5]

1. Donnelly AL, *et al.* The leukotriene D -receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995; **151:** 1734–9.
2. Pullerits T, *et al.* Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1999; **159:** 1814–18.
3. Jiang R-S. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. *J Otolaryngol* 2006; **35:** 117–21.
4. Ho C-Y, Tan C-T. Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol* 2007; **21:** 439–43.
5. Peters-Golden M, Henderson WR. The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; **94:** 609–18.

Urticaria. Leukotriene antagonists, such as zafirlukast, are reported to have some benefit in the management of chronic urticaria (p.1584).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Accolate; Vanticon†; Zafirasmal†; ***Austral.:*** Accolate; ***Belg.:*** Accolate; Resma; ***Braz.:*** Accolate; ***Canad.:*** Accolate; ***Chile:*** Accolate; ***Cz.:*** Accolate; ***Fin.:*** Accolate; ***Hong Kong:*** Accolate; ***Hung.:*** Accolate; ***India:*** Zuvair; ***Indon.:*** Accolate; ***Irl.:*** Accolate; ***Ital.:*** Accoleit; Zafirst; ***Mex.:*** Accolate; ***Philipp.:*** Accolate; ***Pol.:*** Accolate; ***Port.:*** Accolate; ***Rus.:*** Accolate (Аколат); ***S.Afr.:*** Accolate; ***Singapore:*** Accolate; ***Spain:*** Accolate; Aeronix; Olmoran; ***Switz.:*** Accolate; ***Thai.:*** Accolate†; ***Turk.:*** Accolate; ***UK:*** Accolate; ***USA:*** Accolate; ***Venez.:*** Accolate.

Zileuton *(BAN, USAN, rINN)*

A-64077; Abbott-64077; Zileutón; Zileutonum. (±)-1-(1-Benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea.

Зилейтон

$C_{11}H_{12}N_2O_2S$ = 236.3.

CAS — 111406-87-2.

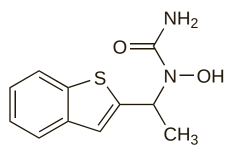

Pharmacopoeias. In *US.*

USP 31 (Zileuton). A white to off-white powder. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

The most commonly reported adverse effects associated with zileuton treatment are headache, pain including pharyngolaryngeal pain, gastrointestinal disturbances, myalgia, and sinusitis. Hypersensitivity, urticaria, rash, and leucopenia have been reported in a few patients. Zileuton has also been associated with raised liver enzyme values and severe hepatic injury.

Zileuton is not suitable for the treatment of acute asthma attacks.

Effects on the liver. Cases of severe hepatotoxicity including fatalities, jaundice, hyperbilirubinaemia, and raised liver enzymes have been reported in patients taking zileuton. US licensed product information therefore contraindicates the use of zileuton in patients with active liver disease or liver transaminase elevations greater than or equal to three times the upper limit of normal. Caution is required in patients with a history of liver disease or who consume substantial quantities of alcohol. Alanine aminotransferase (ALT) is considered the most sensitive indicator of liver injury due to zileuton. Most rises in ALT concentrations occurred in the first 3 months of zileuton therapy,[1] and monitoring is therefore recommended before starting zileuton therapy, once a month for the first 3 months of therapy, every 2 to 3 months for the remainder of the first year of therapy, and periodically thereafter.

1. Watkins PB, *et al.* Clinical pattern of zileuton-associated liver injury: results of a 12-month study in patients with chronic asthma. *Drug Safety* 2007; **30:** 805–15.

Interactions

Zileuton has been reported to impair the metabolism of some drugs metabolised via hepatic cytochrome P450 enzymes, including propranolol, terfenadine, theophylline, and warfarin.

Pharmacokinetics

Zileuton is reported to be well absorbed from the gastrointestinal tract after oral dosage, with peak plasma concentrations of immediate-release preparations occurring within about 2 hours of a dose. It is about 93% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2, CYP2C9, and CYP3A4, and excreted in the urine, largely as glucuronide metabolites. The elimination half-life is reported to be about 2.5 hours for the immediate-release preparation and about 3 hours for the controlled-release preparation.

◊ References.

1. Wong SL, *et al.* The pharmacokinetics of single oral doses of zileuton 200 to 800 mg, its enantiomers, and its metabolites, in normal healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 9–21.
2. Awni WM, *et al.* Pharmacokinetics and pharmacodynamics of zileuton after oral administration of single and multiple dose regimens of zileuton 600 mg in healthy volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 22–33.
3. Braeckman RA, *et al.* The pharmacokinetics of zileuton in healthy young and elderly volunteers. *Clin Pharmacokinet* 1995; **29** (suppl 2): 42–8.
4. Awni WM, *et al.* Population pharmacokinetics of zileuton, a selective 5-lipoxygenase inhibitor, in patients with rheumatoid arthritis. *Eur J Clin Pharmacol* 1995; **48:** 155–60.
5. Awni WM, *et al.* The effect of mild or moderate hepatic impairment (cirrhosis) on the pharmacokinetics of zileuton. *Clin Pharmacokinet* 1995; **29** (suppl 2): 49–61.
6. Awni WM, *et al.* Pharmacokinetics of zileuton and its metabolites in patients with renal impairment. *J Clin Pharmacol* 1997; **37:** 395–404.
7. Dubé LM, *et al.* Zileuton, a leukotriene synthesis inhibitor in the management of chronic asthma: clinical pharmacokinetics and safety. *Clin Rev Allergy Immunol* 1999; **17:** 213–21.

Uses and Administration

Zileuton is an orally active 5-lipoxygenase inhibitor and therefore inhibits leukotriene formation (p.1108). It is used in the management of chronic asthma (see below) but has no bronchodilator properties and is not suitable for the management of acute attacks. Zileuton is given in oral doses of 600 mg 4 times daily as an immediate-release preparation. A controlled-release formulation of zileuton is also available; the usual oral dose is 1.2 g twice daily.

It has also been tried in other disorders including arthritis, allergic rhinitis, and inflammatory bowel disease.

Asthma. Zileuton has been found to be of some benefit in asthma, including that provoked by cold air, exercise, and NSAIDs. US guidelines for the management of asthma (p.1108) permit its use in addition to inhaled corticosteroid therapy in moderate persistent asthma. Combination of anti-leukotriene drugs with inhaled corticosteroids alone seems however to be less effective than a combination of the latter with long-acting inhaled $beta_2$ agonists. Due to a lack of data on efficacy and the need for liver function monitoring, zileuton is also considered a less desirable treatment option for addition to inhaled corticosteroids than the leukotriene receptor antagonists.

An intravenous form of zileuton is under investigation for use in asthma.

References.

1. Israel E, *et al.* The effects of a 5-lipoxygenase inhibitor on asthma induced by cold, dry air. *N Engl J Med* 1990; **323:** 1740–4.
2. Israel E, *et al.* The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993; **119:** 1059–66.
3. McGill KA, Busse WW. Zileuton. *Lancet* 1996; **348:** 519–24.
4. Israel E, *et al.* Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: a randomized controlled trial. *JAMA* 1996; **275:** 931–6.
5. O'Connor BJ, *et al.* Zileuton added to low-dose inhaled beclomethasone for the treatment of moderate to severe persistent asthma. *Respir Med* 2007; **101:** 1088–96.

Inflammatory bowel disease. Despite initial hopes that inhibition of lipoxygenase might prove of benefit in patients with ulcerative colitis,[1] a study in those with mild or moderately active relapsing disease found that the symptomatic benefits of zileuton were confined to those not already receiving sulfasalazine.[2] A subsequent study showed zileuton was not significantly better than placebo in maintaining remission.[3] For a discussion of inflammatory bowel disease and its management, see p.1697.

1. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition in ulcerative colitis. *Lancet* 1990; **335:** 683–5.
2. Laursen LS, *et al.* Selective 5-lipoxygenase inhibition by zileuton in the treatment of relapsing ulcerative colitis: a randomized double-blind placebo-controlled multicentre trial. *Eur J Gastroenterol Hepatol* 1994; **6:** 209–15.
3. Hawkey CJ, *et al.* A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. *Gastroenterology* 1997; **112:** 718–24.

Rhinitis. A study in 8 patients with allergic rhinitis (p.565) found that a single dose of zileuton 800 mg reduced the response to a nasal antigen challenge 3 hours later,[1] including reduced sneezing and nasal congestion.

1. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; **323:** 1745–8.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Zyflo.

Cardiovascular Drugs

The Circulatory System, p.1152
The Heart, p.1152
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- Adrenergic neurone blockers, p.1152
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- Angiotensin II receptor antagonists, p.1153
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- Anticoagulants, p.1153
- Antiplatelet drugs, p.1154
- Beta blockers, p.1154
- Calcium-channel blockers, p.1154
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- Thromboembolic disorders, p.1187
- Valvular heart disease, p.1187
- Vasospastic arterial disorders, p.1188
- Venous thromboembolism, p.1189

This chapter describes drugs used principally in the management of cardiovascular disorders, as well as the choice of treatment for a particular disorder. Blood products, plasma expanders, and haemostatics, which also have a role in cardiovascular disease, are described elsewhere (p.1042).

The Circulatory System

The cardiovascular system consists of the heart and two vascular systems, the pulmonary and systemic circulations. The **heart** (below) pumps blood from the right ventricle through the **pulmonary circulation**, in which gas exchange occurs, and the oxygenated blood then returns to the left side of the heart, where the left ventricle pumps it to the **systemic circulation** which delivers blood to individual organs. Arteries supply blood at high pressure whereas arterioles are smaller vessels with muscular walls which allow direct control of flow through the capillary beds. Capillaries have thin walls, comprising a single layer of endothelial cells, which allow exchange of substances such as nutrients, hormones, and waste products between blood and tissues. Veins return blood from the capillary beds to the heart, and contain about 70% of the circulating blood volume.

Cardiac output is the product of heart rate and stroke volume; typically, in a 70-kg adult, these might be around 70 beats per minute, and 70 mL respectively, giving an output of around 5 litres per minute. Stroke volume in turn is dependent on **preload** (the ventricular volume at the end of diastole, when the ventricle relaxes and fills), **afterload** (the resistance to ventricular ejection, or systemic vascular resistance, determined mainly by the diameter of the arterioles), and **contractility**, or the strength of contraction of the heart muscle, which is influenced by the sympathetic nervous system but also by many other factors, including drugs, acid-base balance, and myocardial oxygen supply. In a healthy individual, cardiac output should adjust to match metabolic demand.

Blood pressure and flow is controlled by complex neurohormonal systems, involving the autonomic nervous system and peptides and regulators released by the kidneys and the circulatory system itself, such as the renin-angiotensin system and the natriuretic peptides. Substances such as nitric oxide and prostacyclin, produced by the endothelium of the vascular system, play an important role in controlling local blood flow.

All these systems can be manipulated by pharmacological therapy with the various drug groups (see below) used in the treatment of cardiovascular disorders (p.1156).

The Heart

The heart acts as a pump, maintaining circulation of blood around the body. It does this by coordinated contraction and relaxation of the cardiac muscle (myocardium). In a normal cardiac cycle the atria contract first (atrial systole), forcing blood into the ventricles, which then contract (ventricular systole), pumping blood out into the blood vessels; atria and ventricles then both relax (diastole), allowing the atria to refill before the cycle begins again. Each cycle corresponds to a heart beat and in a healthy 70-kg person at rest cycles occur regularly at a rate of 70 to 75 beats/minute, although the exact rate varies more widely than this depending on circumstances.

The contraction of myocardial cells is controlled by electrical changes across the cell membrane, which can be represented by the *action potential*. The action potential in cardiac cells has 5 phases, although the exact pattern depends on the type of cell. A typical ventricular action potential is shown in Figure 1 (below).

- phase 0 is the depolarisation phase when there is rapid influx of sodium ions (lasting a few milliseconds) and the cell contracts
- in phase 1, there is a transient rapid efflux of potassium ions and the cell begins to repolarise
- a slow influx of calcium ions then occurs which balances the potassium efflux leading to a plateau stage (phase 2) and maintenance of contraction
- this is followed by an increase in potassium efflux, while calcium influx stops, and repolarisation (phase 3) occurs
- the cell then relaxes and finally returns to the resting membrane potential (phase 4), and ion pumps return the balance of sodium and potassium to the baseline state

Figure 1. The action potential.

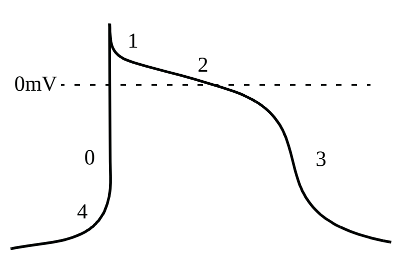

The depolarisation of one cell triggers action potentials in adjacent cells, allowing the electrical impulse to spread rapidly across the myocardium so that in a healthy heart all of the cells contract at the same time in a coordinated fashion.

Certain cells within the heart undergo spontaneous depolarisation during phase 4 and the initial depolarisation depends mainly on calcium ion influx rather than sodium ions. These *pacemaker cells* are able to initiate impulses. Although a number of cells have this property, impulses are normally generated in the *sino-atrial* (SA) or *sinus node*; the resulting heart rhythm is known as *sinus rhythm*, and has been defined as a sinus node rate of 60 to 100 beats/minute. Impulses generated in the SA node spread across the atria, causing them to contract, but normally only pass to the ventricles through the specialised conducting cells of the atrioventricular (AV) node. From the AV node, the impulse passes through the bundle of His and down the Purkinje fibres to the ventricles, which then contract. The delay caused by this selective conduction through the AV node means that the atria contract before the ventricles and ensures the forward movement of the blood.

The movement of electrical impulses can be recorded as an electrocardiogram (ECG). The ECG corresponds to the phases of the action potential in different parts of the heart and depends on the position of the recording leads; a typical ECG trace is shown in Figure 2, below. The P wave corresponds to atrial depolarisation, while the QRS complex corresponds to ventricular depolarisation; the PR interval corresponds to the delay between atrial and ventricular depolarisation. Phases 0 and 1 of the ventricular action potential produce the R and S waves, and phase 2 corresponds to the ST interval. The T wave represents ventricular repolarisation (phase 3).

Figure 2. A normal ECG trace.

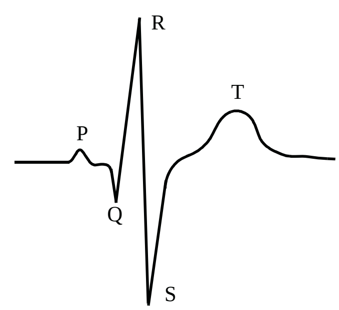

Cardiovascular Drug Groups

Although very diverse, cardiovascular drugs can be broadly classified according to their pharmacological action. Basic details of the major groups follow, together with lists of the drugs described in this chapter.

ACE inhibitors

The main uses of ACE (angiotensin-converting enzyme) inhibitors are in the management of heart failure, hypertension, and myocardial infarction. Their actions and uses are discussed in more detail on p.1193.

Described in this chapter are
- Alacepril, p.1206
- Benazepril, p.1223
- Captopril, p.1239
- Cilazapril, p.1244
- Delapril, p.1256
- Enalapril, p.1276
- Enalaprilat, p.1276
- Fosinopril, p.1291
- Imidapril, p.1313
- Lisinopril, p.1325
- Moexipril, p.1343
- Perindopril, p.1368
- Quinapril, p.1382
- Ramipril, p.1385
- Spirapril, p.1399
- Temocapril, p.1409
- Teprotide, p.1410
- Trandolapril, p.1416
- Zofenopril, p.1434

Adrenergic neurone blockers

Adrenergic neurone blockers are used in hypertension although they have largely been superseded by other drugs less likely to cause orthostatic hypotension. They have also been used in open-angle glaucoma.

Adrenergic neurone blockers act by selectively inhibiting transmission in postganglionic adrenergic nerves. They are believed to act mainly by preventing the release of noradrenaline at nerve endings; they cause the depletion of noradrenaline stores in peripheral sympathetic nerve terminals. They do not prevent the secretion of catecholamines by the adrenal medulla.

Described in this chapter are

Debrisoquine, p.1256	Guanadrel, p.1300
Guabenxan, p.1299	Guanethidine, p.1300

Alpha blockers

Alpha blockers are used mainly in the management of hypertension and to relieve urinary obstruction in benign prostatic hyperplasia.

Alpha blockers are also known as alpha-adrenergic antagonists or alpha-adrenergic receptor antagonists. Some have particular affinities for one of the subtypes of the alpha adrenoceptor. Drugs such as indoramin or prazosin are much more potent in blocking $alpha_1$ than $alpha_2$ adrenoceptors and are often termed selective $alpha_1$ blockers. Blockade of $alpha_1$ adrenoceptors inhibits the vasoconstriction induced by endogenous catecholamines. Both arteriolar and venous vasodilatation may occur resulting in a fall in blood pressure because of decreased peripheral resistance. Blockade of $alpha_2$ adrenoceptors with a selective drug such as yohimbine (p.2200) can conversely lead to a rise in blood pressure. With phenoxybenzamine and phentolamine, which broadly have similar affinities for both the $alpha_1$ and $alpha_2$ subtypes of receptor, any increase in blood pressure due to $alpha_2$ blockade is prevented by the inhibition of vasoconstriction caused by $alpha_1$ blockade. Alpha blockers also act at alpha adrenoceptors in nonvascular smooth muscle, for example in the bladder where alpha blockade produces decreased resistance to urinary outflow; alpha blockers used mainly for urinary disorders are discussed under Urological Drugs, p.2178. Most alpha blockers are reversible or 'competitive' inhibitors of alpha adrenoceptors; phenoxybenzamine is an irreversible or 'non-competitive' alpha blocker and is particularly useful in phaeochromocytoma.

References.

Described in this chapter are

Bunazosin, p.1237	Phentolamine, p.1370
Doxazosin, p.1275	Prazosin, p.1375
Indoramin, p.1315	Terazosin, p.1410
Moxisylyte, p.1344	Tolazoline, p.1415
Phenoxybenzamine, p.1369	Urapidil, p.1419

1. Frishman WH, Kotob F. Alpha-adrenergic blocking drugs in clinical medicine. *J Clin Pharmacol* 1999; **39:** 7–16.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists (angiotensin II receptor blockers) are used in the management of hypertension; they may have a particular role in patients who develop cough with ACE inhibitors. Some are also used in diabetic nephropathy and in the management of heart failure. They act mainly by selective blockade of AT_1 receptors thus reducing the pressor effects of angiotensin II.

References.

Described in this chapter are

Candesartan, p.1238	Olmesartan,p.1361
Eprosartan, p.1281	Telmisartan, p.1409
Irbesartan, p.1316	Valsartan, p.1420
Losartan, p.1326	

1. Schiffrin EL. Vascular and cardiac benefits of angiotensin receptor blockers. *Am J Med* 2002; **113:** 409–18. Correction. *ibid.*; 705.

Antiarrhythmics

Antiarrhythmics (formerly described as cardiac depressants) are a diverse group of drugs that affect the conduction of electrical impulses within the heart (see p.1152). Many of them, such as beta blockers (p.1225), digoxin (p.1259), lidocaine (p.1862), magnesium (p.1678), and phenytoin (p.495) have important actions in addition to their antiarrhythmic properties and thus, have a wide range of other clinical applications.

The most widely used **classification** of antiarrhythmics is that proposed by Vaughan Williams (later modified by Harrison) and is based largely on their *in-vitro* electrophysiological effects. There are 4 main classes:

◊ **Class I** includes drugs that block the fast inward sodium channels and therefore interfere with depolarisation (phase 0 of the action potential); these drugs have been called membrane-stabilising drugs and have both antiarrhythmic and local anaesthetic properties. They have different properties depending on their affinity for different states of the sodium channel (open, closed, or inactivated) and can be further subdivided depending on additional characteristics.

Class Ia drugs slow the rate of change of the depolarisation phase of the action potential, although less so than class Ic drugs. They also prolong the repolarisation phase (phase 3), possibly by an effect on potassium channels. They prolong the PR, QRS, and QT intervals on the ECG.

Described in this chapter are

Ajmaline, p.1206	Pirmenol, p.1373
Disopyramide, p.1269	Procainamide, p.1377
Hydroquinidine, p.1312	Quinidine, p.1383

◊ *Class Ib* drugs have little effect on the rate of change of the depolarisation phase of the action potential in normal cells, but have a more selective effect in ischaemic or diseased tissue; they are also more effective if external potassium concentrations are high. They shorten the repolarisation phase, shorten the QT interval, and elevate the fibrillation threshold. The local anaesthetic lidocaine has class Ib properties.

Described in this chapter are

Aprindine, p.1216	Tocainide, p.1414
Mexiletine, p.1339	

◊ *Class Ic* drugs markedly slow the rate of change of the depolarisation phase of the action potential, but have little effect on the repolarisation phase. They prolong the PR and QRS intervals.

Described in this chapter are

Ethacizine, p.1283	Pilsicainide, p.1371
Flecainide, p.1288	Propafenone, p.1379

◊ **Class II** drugs are characterised by beta-blocking activity; they reduce both heart rate and myocardial contractility, and also slow conduction of impulses through the myocardial conducting system. They reduce the rate of spontaneous depolarisation in cells with pacemaker activity but have little effect on the action potential in most myocardial cells.

Described in this chapter are

Beta blockers (but sotalol has mainly class III activity), p.1225	Bretylium, p.1236

◊ **Class III** drugs slow the repolarisation phase (phase 3) and prolong the action potential duration and the QT interval. Various mechanisms may be involved, but most class III drugs act by potassium channel blockade.

Described in this chapter are

Amiodarone, p.1210	Dofetilide, p.1272
Azimilide, p.1222	Ibutilide, p.1312
Bretylium, p.1236	Nifekalant, p.1357
Cibenzoline, p.1244	Sotalol, p.1398

◊ **Class IV** drugs are calcium-channel blockers (p.1154) that act by blocking the slow inward calcium current and particularly affect the pacemaker cells where calcium influx is relatively more important. However, differences in tissue specificity mean that not all calcium-channel blockers have antiarrhythmic properties.

Described in this chapter are

Cibenzoline, p.1244	Verapamil, p.1421
Diltiazem, p.1265	

◊ A major limitation of the Vaughan Williams classification is that many antiarrhythmics have multiple actions, and may not fit neatly into a single class. Some are assigned to several classes, while others are included in one class although they also have characteristics of another. Bretylium is included in both class II and class III, whereas propafenone is usually considered a class Ic drug despite possessing beta-blocking properties. Beta blockers are traditionally described as class II, although some also have class I actions, while sotalol, despite sharing the properties of beta blockers, has mainly class III activity and is usually described as a class III drug. Drugs such as adenosine and digoxin do not fit into the Vaughan Williams classification at all.

Another problem with the Vaughan Williams classification is that the electrophysiological effects of antiarrhythmics are not clearly related to their effectiveness in treating a particular arrhythmia in an individual patient. Alternative classification systems have therefore been suggested, for example based on the cardiac tissue that the drug affects. Thus drugs that act on the sino-atrial node include beta blockers, class IV antiarrhythmics, and cardiac glycosides such as digoxin; class I and class III antiarrhythmics act on the ventricles; and drugs acting on atrial arrhythmias include class Ia, Ic, and III antiarrhythmics and beta blockers. Class Ia and III antiarrhythmics act on accessory pathways and drugs acting on the AV node include class Ic and IV antiarrhythmics, beta blockers, and cardiac glycosides. A simplification of this scheme is to classify drugs into those that act on both ventricular and supraventricular arrhythmias such as amiodarone, beta blockers, disopyramide, procainamide, and quinidine, those that act mainly on ventricular arrhythmias such as lidocaine, mexiletine, and phenytoin, and those that act mainly on supraventricular arrhythmias such as verapamil. The Sicilian Gambit is another approach based on the mechanisms by which arrhythmias are generated and the ways that drugs could influence them.

References.

1. Vaughan Williams EM. Classification of antidysrhythmic drugs. *Pharmacol Ther* 1975; **1:** 115–38.
2. Harrison DC. Current classification of antiarrhythmic drugs as a guide to their rational clinical use. *Drugs* 1986; **31:** 93–5.
3. Frumin H, *et al.* Classification of antiarrhythmic drugs. *J Clin Pharmacol* 1989; **29:** 387–94.
4. Vaughan Williams EM. Classifying antiarrhythmic actions: by facts or speculation. *J Clin Pharmacol* 1992; **32:** 964–77.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 1991; **84:** 1831–51.
6. Hancox JC, *et al.* Antiarrhythmics—from cell to clinic: past, present, and future. *Heart* 2000; **84:** 14–24.

Anticoagulants

Anticoagulants are used in the treatment and prophylaxis of thromboembolic disorders. They may be divided into direct anticoagulants such as the heparins, low-molecular-weight heparins, heparinoids, and direct thrombin inhibitors, and indirect anticoagulants such as the coumarin and indanedione derivatives.

◊ **Direct anticoagulants**

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on antithrombin III's inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect.

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Like heparin, these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin activity) than heparin. Although the possibility that such selective factor-Xa inhibition would result in antithrombotic activity without anticoagulant, and hence haemorrhagic, effects has not been confirmed by clinical experience, they have more predictable effects and require less monitoring than heparin. Low-molecular-weight heparins also have less effect on platelet aggregation than heparin.

Fondaparinux and idraparinux are synthetic polysaccharides that act as direct inhibitors of factor Xa. Rivaroxaban, an oral factor Xa inhibitor, is under investigation.

Described in this chapter are

Ardeparin, p.1216	Low-molecular-weight Heparins, p.1329
Bemiparin, p.1223	Nadroparin, p.1346
Certoparin, p.1242	Parnaparin, p.1366
Dalteparin, p.1255	Reviparin, p.1388
Enoxaparin, p.1277	Rivaroxaban, p.1389
Fondaparinux, p.1291	Tinzaparin, p.1413
Heparin, p.1301	
Idraparinux, p.1312	

◊ The *direct thrombin inhibitors* bind to the active thrombin site and inhibit both free and clot-bound thrombin. Most are recombinant forms or synthetic analogues of hirudin and need to be given parenterally, but oral thrombin inhibitors have been developed. Dabigatran, given orally as the prodrug dabigatran etexilate, is used in the prophylaxis of venous thromboembolism. Ximelagatran, another synthetic small molecule with oral activity, was withdrawn from the market due to toxicity (as was melagatran, the parenteral form).

References.

Described in this chapter are

Argatroban, p.1217	Hirudin, p.1305
Bivalirudin, p.1234	Lepirudin, p.1323
Dabigatran, p.1254	Melagatran, p.1332
Desirudin, p.1257	Ximelagatran, p.1332

1. Di Nisio M, *et al.* Direct thrombin inhibitors. *N Engl J Med* 2005; **353:** 1028–40. Correction. *ibid.;* 2827.

◊ The term *heparinoid* includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly sulfated polysaccharides of similar structure, such as danaparoid and dermatan sulfate. Some compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans, glycosaminoglycan polysulfate compounds, or sulfated mucopolysaccharides.

Described in this chapter are

Danaparoid, p.1255	Sodium Apolate, p.1397
Dermatan Sulfate, p.1256	Suleparoid, p.1406
Pentosan Polysulfate Sodium, p.1367	Sulodexide, p.1406

◊ **Indirect anticoagulants**

Indirect anticoagulants act by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. Warfarin, a coumarin, is the main drug used; other coumarins (although not all coumarins have anticoagulant activity) and indanediones such as phenindione are also available. Since they act indirectly, they have no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Described in this chapter are

Acenocoumarol, p.1201	Fluindione, p.1290
Anisindione, p.1216	Phenindione, p.1369
Dicoumarol, p.1258	Phenprocoumon, p.1370
Ethyl Biscoumacetate, p.1284	Tioclomarol, p.1413
	Warfarin, p.1425

Antiplatelet drugs

Platelet aggregation is important in haemostasis (p.1045) and is also involved in thrombus formation, particularly in the arterial circulation. Antiplatelet drugs reduce platelet aggregation and are used to prevent further thromboembolic events in patients who have suffered myocardial infarction, ischaemic stroke or transient ischaemic attacks, or unstable angina, and for primary prevention of a thromboembolic event in patients at risk. Some are also used for the prevention of reocclusion or restenosis following angioplasty and bypass procedures.

Antiplatelet drugs act through a wide range of mechanisms. Aspirin (p.20) is the most widely used and studied; it acts by irreversibly inhibiting platelet cyclo-oxygenase and thus preventing synthesis of thromboxane A_2. Reversible cyclo-oxygenase inhibitors such as indobufen are also available, and thromboxane synthase inhibitors and thromboxane receptor antagonists have also been used.

Drugs that interfere with adenosine metabolism have an antiplatelet effect and those used include some prostaglandins, which act by increasing platelet cyclic adenosine monophosphate levels; the thienopyridines clopidogrel and ticlopidine, which interfere with adenosine diphosphate mediated platelet activation; and the adenosine reuptake inhibitor dipyridamole.

Thrombin inhibitors such as heparin and the hirudins have antiplatelet and anticoagulant effects. Glycoprotein IIb/IIIa-receptor antagonists, such as abciximab, eptifibatide, and tirofiban, interfere with the final step in platelet aggregation and are used in unstable angina and as adjuncts in reperfusion and revascularisation procedures.

References.

Described in this chapter are

Abciximab, p.1192	Picotamide, p.1371
Cilostazol, p.1245	Prasugrel, p.1374
Clopidogrel, p.1250	Sarpogrelate, p.1390
Cloricromen, p.1251	Sibrafiban, p.1390
Dipyridamole, p.1268	Ticlopidine, p.1411
Ditazole, p.1271	Tirofiban, p.1414
Eptifibatide, p.1281	Trapidil, p.1416
Indobufen, p.1315	Triflusal, p.1418
Lamifiban, p.1322	Xemilofiban, p.1434
Orbofiban, p.1364	

1. Patrono C, *et al.* Expert consensus document on the use of antiplatelet agents: the task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European Society of Cardiology. *Eur Heart J* 2004; **25:** 166–81. Also available at: http://eurheartj.oxfordjournals.org/cgi/reprint/25/2/166.pdf (accessed 27/08/08)
2. Born G, Patrono C. Antiplatelet drugs. *Br J Pharmacol* 2006; **147** (suppl 1): S241–S251.
3. Clappers N, *et al.* Antiplatelet treatment for coronary heart disease. *Heart* 2007; **93:** 258–65.
4. Kikano GE, Brown MT. Antiplatelet therapy for atherothrombotic disease: an update for the primary care physician. *Mayo Clin Proc* 2007; **82:** 583–93.

Beta blockers

Beta blockers are competitive antagonists at beta-adrenergic receptor sites and are used in the management of cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. They are also given to control symptoms of sympathetic overactivity in alcohol withdrawal, anxiety states, hyperthyroidism, and tremor and in the prophylaxis of migraine and of bleeding associated with portal hypertension. Their actions and uses are discussed in more detail on p.1225.

Beta blockers used mainly as eye drops to reduce raised intra-ocular pressure in glaucoma and ocular hypertension are discussed under Miotics, Mydriatics, and Antiglaucoma Drugs, p.1873.

Described in this chapter are

Acebutolol, p.1200	Indenolol, p.1315
Alprenolol, p.1207	Labetalol, p.1321
Amosulalol, p.1215	Landiolol, p.1323
Arotinolol, p.1217	Mepindolol, p.1333
Atenolol, p.1217	Metoprolol, p.1338
Betaxolol, p.1231	Nadolol, p.1345
Bevantolol, p.1231	Nebivolol, p.1347
Bisoprolol, p.1234	Oxprenolol, p.1365
Bopindolol, p.1235	Penbutolol, p.1366
Bucindolol, p.1236	Pindolol, p.1372
Bupranolol, p.1238	Propranolol, p.1380
Carazolol, p.1240	Sotalol, p.1398
Carteolol, p.1241	Talinolol, p.1409
Carvedilol, p.1241	Tertatolol, p.1411
Celiprolol, p.1242	Tilisolol, p.1412
Esatenolol, p.1282	Timolol, p.1412
Esmolol, p.1282	

Calcium-channel blockers

The main use of calcium-channel blockers is in the management of angina pectoris and hypertension; some are also used in cardiac arrhythmias.

Calcium-channel blockers, (calcium antagonists, calcium-entry blockers, or slow-channel blockers) inhibit the cellular influx of calcium that is responsible for maintenance of the plateau phase of the action potential. Thus calcium-channel blockers primarily affect tissues in which depolarisation is dependent upon calcium rather than sodium influx, such as vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes. The main actions of the calcium-channel blockers include dilatation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs, and therefore their uses, are modified by their selectivity of action at different tissue sites and by baroreceptor reflexes.

Traditionally, calcium-channel blockers have been classified according to their chemical structure; other methods of classification relate to the subtypes of calcium channels which they block, and their effects on heart rate. There are three major groups that are highly specific blockers of calcium channels.

Dihydropyridine calcium-channel blockers (such as nifedipine) act on slow, L-type channels. They have a greater selectivity for vascular smooth muscle than for myocardium and therefore their main effect is vasodilatation. They are non-rate-limiting, with little or no action at the SA or AV nodes, and negative inotropic activity is rarely seen at therapeutic doses. They are used for their antihypertensive and anti-anginal properties. Some dihydropyridine derivatives, for example nimodipine, cross the blood-brain barrier and are used in cerebral ischaemia.

Benzothiazepine calcium-channel blockers (such as diltiazem) and **phenylalkylamine** calcium-channel blockers (such as verapamil) also act on L-type channels but they have less selective vasodilator activity than dihydropyridine derivatives. They are classed as rate-limiting and have a direct effect on myocardium, causing depression of SA and AV nodal conduction. They are used for their antiarrhythmic, anti-anginal, and antihypertensive properties.

Drugs acting principally on the fast T-type calcium channels have also been investigated. Mibefradil, a benzimidazolyl-substituted tetraline derivative, is an example of this class. It is rate-limiting, and causes coronary and peripheral vasodilatation. However, it is no longer used clinically due to serious interactions with a wide range of drugs.

For further discussion of the actions and uses of the three main groups of calcium-channel blockers, see Nifedipine, p.1350, Diltiazem, p.1265, and Verapamil, p.1421, respectively.

References.

Described in this chapter are

Amlodipine, p.1214	Lacidipine, p.1322
Aranidipine, p.1216	Lercanidipine, p.1324
Azelnidipine, p.1222	Lidoflazine, p.1325
Barnidipine, p.1222	Manidipine, p.1330
Benidipine, p.1224	Mibefradil, p.1340
Bepridil, p.1225	Nicardipine, p.1348
Cilnidipine, p.1245	Nifedipine, p.1350
Diltiazem, p.1265	Nilvadipine, p.1357
Efonidipine, p.1276	Nimodipine, p.1357
Felodipine, p.1285	Nisoldipine, p.1358
Gallopamil, p.1295	Nitrendipine, p.1358
Isradipine, p.1319	Verapamil, p.1421

1. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. *N Engl J Med* 1999; **341:** 1447–57.
2. Eisenberg MJ, *et al.* Calcium channel blockers: an update. *Am J Med* 2004; **116:** 35–43.

Cardiac inotropes

Positive cardiac inotropes increase the force of contraction of the myocardium and are therefore used in the management of acute and chronic heart failure. Some inotropes also increase or decrease the heart rate (positive or negative chronotropes), provide vasodilatation (inodilators), or improve myocardial relaxation (positive lusitropes), and these additional properties influence the choice of drug in specific situations. Drugs that are used mainly for their inotropic effects include the cardiac glycosides and phosphodiesterase inhibitors; sympathomimetics have a role as inotropes but also have other important uses.

References.

1. Feldman AM. Classification of positive inotropic agents. *J Am Coll Cardiol* 1993; **22:** 1223–7.
2. Cuthbertson BH, *et al.* Inotropic agents in the critically ill. *Br J Hosp Med* 1996; **56:** 386–91.
3. Lehtonen LA, *et al.* Pharmacokinetics and pharmacodynamics of intravenous inotropic agents. *Clin Pharmacokinet* 2004; **43:** 187–203.

◊ **Cardiac glycosides**, such as digoxin, possess positive inotropic activity, which is mediated by inhibition of sodium-potassium adenosine triphosphatase (Na/K-ATPase). They also reduce conductivity in the heart, particularly through the atrioventricular node, and therefore have a negative chronotropic effect. The cardiac glycosides have very similar pharmacological effects but differ considerably in their speed of onset and duration of action. They are used to slow the heart rate in supraventricular arrhythmias, especially atrial fibrillation, and are also given in chronic heart failure.

Described in this chapter are

Acetyldigoxin, p.1201	Digoxin, p.1259
Deslanoside, p.1257	Lanatoside C, p.1322
Digitalis Lanata Leaf, p.1258	Metildigoxin, p.1336
Digitalis Leaf, p.1258	Ouabain, p.1364
Digitoxin, p.1259	Proscillaridin, p.1382
	Strophanthin-K, p.1406

◊ **Phosphodiesterase inhibitors** are potent inotropes; they also have vasodilator effects. They are used in the short-term treatment of severe heart failure; long-term oral therapy with some phosphodiesterase inhibitors has been associated with increased mortality.

Described in this chapter are

Amrinone, p.1215	Olprinone, p.1361
Enoximone, p.1278	Pimobendan, p.1371
Milrinone, p.1341	Vesnarinone, p.1425

Centrally acting antihypertensives

Centrally acting antihypertensives include $alpha_2$-adrenoceptor agonists such as clonidine and methyldopa. Stimulation of $alpha_2$ adrenoceptors in the CNS results in a reduction in sympathetic tone and a fall in blood pressure. Heart rate is also reduced. They are used in the management of hypertension, although other drugs with fewer adverse effects are generally preferred. Apraclonidine (p.1877) and brimonidine (p.1878) are alpha$_2$-adrenoceptor agonists that are used in the management of glaucoma.

Described in this chapter are

Clonidine, p.1247	Methyldopa, p.1334
Guanabenz, p.1299	Moxonidine, p.1345
Guanfacine, p.1301	Rilmenidine, p.1388

Diuretics

Diuretics promote the excretion of water and electrolytes by the kidneys. They are used in the treatment of heart failure or in hepatic, renal, or pulmonary disease when salt and water retention has resulted in oedema or ascites. Diuretics are also used, either alone, or in association with other drugs, in the treatment of hypertension, although the mechanism for their antihypertensive effect is poorly understood.

The principal groups of diuretics are as follows.

◊ **Carbonic anhydrase inhibitors** such as acetazolamide (p.1875) are weak diuretics and are used mainly to reduce intra-ocular pressure in glaucoma. They are described under Miotics, Mydriatics, and Antiglaucoma Drugs, p.1873.

◊ **'Loop'** or **'high-ceiling' diuretics** produce an intense, dose-dependent diuresis of relatively short duration.

Described in this chapter are

Azosemide, p.1222	Furosemide, p.1292
Bumetanide, p.1237	Piretanide, p.1372
Etacrynic Acid, p.1283	Torasemide, p.1415
Etozolin, p.1284	

◊ **Osmotic diuretics** raise the osmolality of plasma and renal tubular fluid. They are used to reduce or prevent cerebral oedema, to reduce raised intra-ocular pressure, and in acute renal failure.

Described in this chapter are

Isosorbide, p.1317	Mannitol, p.1330

◊ **Potassium-sparing diuretics** have a relatively weak diuretic effect and are normally used in conjunction with thiazide or loop diuretics. Canrenone, eplerenone, potassium canrenoate, and spironolactone are aldosterone antagonists and are particularly used in conditions where aldosterone contributes to the pathophysiology.

Described in this chapter are

Amiloride, p.1209	Spironolactone, p.1400
Canrenone, p.1239	Triamterene, p.1417
Eplerenone, p.1279	
Potassium Canrenoate, p.1374	

◊ **Thiazides** (benzothiadiazines), such as bendroflumethiazide and hydrochlorothiazide, and certain other compounds, such as metolazone, with structural similarities to the thiazides, inhibit sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion.

Described in this chapter are

Altizide, p.1209	Hydroflumethiazide, p.1311
Bemetizide, p.1223	Indapamide, p.1314
Bendroflumethiazide, p.1224	Mebutizide, p.1331
Benzthiazide, p.1225	Mefruside, p.1332
Butizide, p.1238	Methyclothiazide, p.1334
Chlorothiazide, p.1243	Meticrane, p.1336
Chlortalidone, p.1243	Metipamide, p.1336
Clopamide, p.1250	Metolazone, p.1337
Cyclopenthiazide, p.1254	Polythiazide, p.1373
Cyclothiazide, p.1254	Quinethazone, p.1383
Epitizide, p.1279	Teclothiazide, p.1409
Hydrochlorothiazide, p.1307	Trichlormethiazide, p.1418
	Tripamide, p.1419
	Xipamide, p.1434

Endothelin receptor antagonists

Endothelin receptor antagonists act by blocking the effects of endothelin, a potent vasoconstrictor. Bosentan blocks both the endothelin ET$_A$ and ET$_B$ receptors, whereas ambrisentan and sitaxentan are selective for ET$_A$. They are used in the management of pulmonary hypertension. Tezosentan, which blocks both ET$_A$ and ET$_B$, has been investigated in heart failure.

Described in this chapter are

Ambrisentan, p.1209	Sitaxentan, p.1396
Bosentan, p.1235	Tezosentan, p.1411

1. Attinà T, *et al*. Endothelin antagonism in pulmonary hypertension, heart failure, and beyond. *Heart* 2005; **91:** 825–31.

Ganglion blockers

Ganglion blockers are nicotinic antagonists that inhibit the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. Their antihypertensive action is due to sympathetic blockade, which produces peripheral vasodilatation; there is also a direct vasodilator effect on peripheral blood vessels.

Described in this chapter are

Azamethonium, p.1222	Trimetaphan, p.1419
Mecamylamine, p.1331	

Lipid regulating drugs

Lipid regulating drugs are used to modify blood lipid concentrations in the management of hyperlipidaemias and for the reduction of cardiovascular risk. The principal groups of lipid regulating drugs are the statins, fibrates, bile-acid binding resins, nicotinates, and omega-3 triglycerides; ezetimibe, an inhibitor of intestinal cholesterol absorption, is also used.

◊ The **statins** are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme for cholesterol synthesis. They reduce cholesterol by stimulating an increase in low-density-lipoprotein (LDL)-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase high-density-lipoprotein (HDL)-cholesterol. They are generally considered to be the most effective lipid lowering drugs.

Described in this chapter are

Atorvastatin, p.1218	Pitavastatin, p.1373
Fluvastatin, p.1290	Pravastatin, p.1374
Lovastatin, p.1328	Rosuvastatin, p.1389
Mevastatin, p.1339	Simvastatin, p.1390

◊ The **fibrates** include derivatives of fibric acid and related compounds. They are activators of peroxisome proliferator-activated receptor (PPAR)-α and inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of very-low-density lipoproteins (VLDL); they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.

Described in this chapter are

Bezafibrate, p.1232	Fenofibrate, p.1286
Ciprofibrate, p.1246	Gemfibrozil, p.1295
Clinofibrate, p.1246	Pirifibrate, p.1372
Clofibrate, p.1246	
Etofylline Clofibrate, p.1284	

◊ **Bile-acid binding resins** (bile-acid sequestrants) lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol.

Described in this chapter are

Colesevelam, p.1252	Colestyramine, p.1252
Colestilan, p.1252	Colextran, p.1254
Colestipol, p.1252	

◊ **Nicotinates** include nicotinic acid (p.1957) and its derivatives. Nicotinic acid is a member of the vitamin B group and, in high doses, has beneficial effects on blood lipids; it reduces triglycerides and increases HDL-cholesterol, and may also modestly reduce LDL-cholesterol. Nicotinates are mainly used in hypertriglyceridaemia. Compounds derived from both nicotinic acid and clofibrate (nicotinate-fibrate derivatives) are also used.

Described in this chapter are

Acipimox, p.1201	Niceritrol, p.1348
Binifibrate, p.1234	Tocoferil Nicotinate, p.1415
Etofibrate, p.1284	

◊ **Omega-3 fatty acids** are long-chain polyunsaturated fatty acids that primarily reduce triglycerides.

Described in this chapter are

Omega-3 Fatty Acids, p.1362

Nitrates

Nitrates are peripheral and coronary vasodilators used in the management of angina pectoris, heart failure, and myocardial infarction. Some of them may also be used to control blood pressure during surgery. Nitrates are believed to exert their vasodilator effect through release of nitric oxide (p.1358), which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. Nitrates are thus termed nitrovasodilators. In their action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Nitrates also have a coronary vasodilator effect which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Described in this chapter are

Eritrityl Tetranitrate, p.1282	Linsidomine, p.1325
Glyceryl Trinitrate, p.1296	Molsidomine, p.1343
Isosorbide Dinitrate, p.1317	Pentaerithrityl Tetranitrate, p.1366
Isosorbide Mononitrate, p.1318	Propatylnitrate, p.1380
	Sodium Nitroprusside, p.1397
	Tenitramine, p.1410

Potassium-channel openers

Potassium-channel openers (potassium-channel activators) have been used in the management of hypertension; nicorandil is used in angina pectoris. They have a direct relaxant effect on smooth muscle. They act at potassium channels to allow cellular efflux of potassium which hyperpolarises the cell membrane and leads to a reduction in intracellular calcium. The reduction in intracellular calcium produces relaxation of smooth muscle. Activation of potassium channels in blood vessels produces vasodilatation. Potassium-channel openers may also have potential use in other conditions caused by smooth muscle contraction, for example asthma and urinary incontinence.

Described in this chapter are

Nicorandil, p.1349	Pinacidil, p.1371

Prostaglandins

Prostaglandins (p.2374) are endogenous substances with a wide range of actions. Epoprostenol (the synthetic form of prostacyclin or prostaglandin I$_2$) and its analogues have vasodilator and antiplatelet properties and are used in pulmonary hypertension and peripheral vascular disease, and to prevent clotting of blood in extracorporeal circuits. Limaprost, an analogue of alprostadil (prostaglandin E$_1$), has similar properties and is used in peripheral vascular disease.

Described in this chapter are

Beraprost, p.1225	Limaprost, p.1325
Epoprostenol, p.1279	Treprostinil, p.1417
Iloprost, p.1313	

Sympathomimetics

Sympathomimetics produce either direct or indirect stimulation of adrenergic receptors and have various effects depending on the specific receptors involved. Their actions and uses are described in more detail on p.1407. In cardiovascular disorders, they are mainly used for their alpha$_1$ and beta$_1$ properties to provide haemodynamic support in the management of acute heart failure and shock.

Sympathomimetics with primarily non-cardiovascular uses include alpha agonists, such as phenylephrine (p.1568), pseudoephedrine (p.1571), and naphazoline (p.1565), which are used to produce vasoconstriction of the nasal mucosa for the symptomatic relief of nasal congestion. Apraclonidine (p.1877) and brimonidine (p.1878) are examples of sympathomimetics with alpha$_2$-agonist properties that are used to lower intra-ocular pressure and treat glaucoma. Beta$_2$ agonists are used as bronchodilators and in premature labour and are described under Bronchodilators and Anti-asthma Drugs, p.1108.

Described in this chapter are

Adrenaline, p.1203	Mephentermine, p.1332
Amezinium, p.1209	Metaraminol, p.1333
Arbutamine, p.1216	Methoxamine, p.1333
Denopamine, p.1256	Midodrine, p.1341
Dimetofrine, p.1268	Noradrenaline, p.1360
Dobutamine, p.1271	Norfenefrine, p.1361
Docarpamine, p.1272	Octodrine, p.1361
Dopamine, p.1273	Oxedrine, p.1364
Dopexamine, p.1274	Oxilofrine, p.1364
Etilefrine, p.1284	Pholedrine, p.1371
Ibopamine, p.1312	Prenalterol, p.1377
Isoprenaline, p.1316	Xamoterol, p.1433

Thrombolytics

Thrombolytics are used in the treatment of thromboembolic disorders such as myocardial infarction, peripheral arterial thromboembolism, and venous thromboembolism (deep-vein thrombosis and pulmonary embolism), and some may be used in ischaemic stroke. They are also used to clear blocked cannulas and shunts.

Thrombolytics activate plasminogen to form plasmin, a proteolytic enzyme that degrades fibrin and thus produces dissolution of clots. Some thrombolytics, such as alteplase, act only on fibrin-bound plasminogen and have little effect on circulating, unbound plasminogen; these thrombolytics are termed fibrin-specific agents. Thrombolytics, such as streptokinase, that affect circulating, unbound as well as fibrin-bound plasminogen are termed fibrin-nonspecific agents. Although it has been suggested that the degree of fibrin specificity should influence the risk of haemorrhage, the clinical significance of this has not been established (see Haemorrhage under Adverse Effects of Streptokinase, p.1403).

References.

Described in this chapter are

Alteplase, p.1207	Pamiteplase, p.1365
Anistreplase, p.1216	Plasminogen, p.1373
Defibrotide, p.1256	Reteplase, p.1388
Duteplase, p.1275	Saruplase, p.1390
Fibrinolysin, p.1287	Staphylokinase, p.1402
Lanoteplase, p.1323	Streptokinase, p.1402
Monteplase, p.1344	Tenecteplase, p.1410
Nasaruplase, p.1346	Urokinase, p.1420
Nateplase, p.1346	

1. Ross AM. New plasminogen activators: a clinical review. *Clin Cardiol* 1999; **22:** 165–71.
2. Verstraete M. Third-generation thrombolytic drugs. *Am J Med* 2000; **109:** 52–8.

Vasodilators

Vasodilator is a broad term applied to drugs that produce dilatation of blood vessels. The main groups of drugs producing vasodilatation are ACE inhibitors (p.1193), nitrates (above), and direct-acting vasodilators.

◊ **Direct-acting vasodilators** act predominantly on the arterioles reducing peripheral resistance and producing a fall in blood pressure. Their main use is in hypertension, although other drugs are generally preferred. Some of them are used in hypertensive crises.

Described in this chapter are

Cadralazine, p.1238	Hydralazine, p.1305
Diazoxide, p.1257	Minoxidil, p.1342
Dihydralazine, p.1264	Todralazine, p.1415
Endralazine, p.1277	Tolazoline, p.1415

◊ **Other vasodilators** may be used for ischaemic heart disease.

Described in this chapter are

Carbocromen, p.1241	Fendiline, p.1286
Cinepazet, p.1246	Hexobendine, p.1305
Cloridarol, p.1251	Oxyfedrine, p.1365
Dilazep, p.1265	Trapidil, p.1416
Etafenone, p.1283	Trimetazidine, p.1419

◊ Vasodilators are also used for cerebral and peripheral vascular disorders. Some of these are now thought to improve microcirculatory flow disturbances by altering the rheological properties of blood or tissue metabolism, and this may be more important than their vasodilator effects.

Described in this chapter are

Azapetine, p.1222	Ifenprodil, p.1313
Bamethan, p.1222	Inositol Nicotinate, p.1316
Bencyclane, p.1224	Naftidrofuryl, p.1346
Buflomedil, p.1236	Nicotinyl Alcohol, p.1349
Butalamine, p.1238	Pentifylline, p.1366
Calcitonin Gene-related Peptide, p.1238	Pentoxifylline, p.1367
Cetiedil, p.1243	Pipratecol, p.1372
Cinepazide, p.1246	Propentofylline, p.1380
Cyclandelate, p.1254	Raubasine, p.1386
Di-isopropylammonium Dichloroacetate, p.1265	Xantinol Nicotinate, p.1433
Fasudil, p.1285	

Management of Cardiovascular Disorders

Management of the main cardiovascular disorders is discussed below. These overviews focus on pharmacological therapy, but other options are also mentioned where they form an important part of treatment.

Advanced cardiac life support

Cardiac arrest is the cessation of effective cardiac mechanical activity and is usually a result of ischaemic heart disease in adults and respiratory or circulatory failure in children. It may be associated with four arrhythmias, namely **ventricular fibrillation, pulseless ventricular tachycardia, asystole**, and **electromechanical dissociation (pulseless electrical activity)**. Ventricular fibrillation is the commonest in adults and asystole in children. In ventricular fibrillation and pulseless ventricular tachycardia there is chaotic electrical and mechanical activity; in asystole a total absence of both activities; and in electromechanical dissociation an absence of mechanical activity, or undetectable activity, in the presence of some electrical activity.

Cardiac arrest is an emergency situation[1,2] and should be treated with full life support measures.

International recommendations[3] for advanced life support and the immediate period of cardiac arrest have been published, developed by the International Liaison Committee on Resuscitation. American,[4] European,[5] and UK[6] guidelines have also been published; these are based on the international recommendations and, apart from some differences in detail, are broadly similar.

In order to maintain cardiorespiratory function, **basic life support** (cardiopulmonary resuscitation; CPR) consisting of chest compression and ventilation (mouth-to-mouth/mask or mouth-to-nose) should be started immediately and continued during the resuscitation attempt. **Subsequent procedures** will depend to some extent on the type of arrhythmia present. For the commonest, ventricular fibrillation, rapid *defibrillation* is of paramount importance and should not be delayed by other necessary measures such as giving oxygen, intubation, and providing intravenous access. Defibrillation is intended to produce momentary asystole and allow the natural pacemakers to resume normal activity. *Adrenaline* is given principally to increase the efficacy of basic life support rather than as an adjunct to defibrillation although evidence that it improves survival is limited; through its alpha agonist effects it increases myocardial and cerebral blood flow. A dose of 1 mg of adrenaline is regarded as the 'standard' intravenous dose for adults. A higher dose of 5 mg has been used in some clinical trials, but there is no evidence that this dose is associated with an improvement in overall survival rate and it is not generally recommended. For children, the usual initial dose is 10 micrograms/kg; as in adults, higher doses have been used subsequently but again there is no evidence that this is beneficial.[7] *Vasopressin* has been tried as an alternative although it has not been shown to be superior to adrenaline.[8] In the case of asystole, atropine may be given to block excess vagal tone. *Amiodarone* may be considered for ventricular tachycardia or fibrillation; *lidocaine* may be used if amiodarone is not available. A study[9] comparing lidocaine with amiodarone for shock-resistant ventricular fibrillation found that survival to hospital admission was higher in those given amiodarone. Survival to discharge was not increased, however, but the study was not powered to assess this outcome. *Other drugs* that may be given for specific indications during resuscitation attempts include buffering agents such as intravenous sodium bicarbonate for acidosis, calcium, magnesium, or potassium salts for known deficiencies, and aminophylline for refractory bradycardia. Therapeutic *hypothermia* may be beneficial in patients who remain unconscious after resuscitation, and cooling to 32° to 34° has been recommended[3-6] in unconscious adults whose initial rhythm was ventricular fibrillation. Specific guidelines for the different types of arrhythmia are as follows.

Ventricular fibrillation and **pulseless ventricular tachycardia** are treated in the same way. The guidelines for **adults** emphasise that the first defibrillating shock must be given as quickly as possible, although a short period of CPR may be appropriate first if the arrest was not witnessed. In cases of witnessed cardiac arrest a precordial thump, which sometimes aborts the arrhythmia if given within 30 seconds of the loss of cardiac output, may be given before attaching the monitor/defibrillator, but the attachment of the defibrillator must not be delayed. Although a strategy of three initial shocks has been the standard, it is now recommended that a single shock is given, since this appears to be as effective as three shocks while minimising the interruption to chest compressions. Monophasic or biphasic shocks may be given, depending on the equipment available. For monophasic devices, the recommended energy for all shocks is 360J. For biphasic devices the optimum energy varies; in the UK and Europe an initial shock of 150-200J is recommended, with subsequent shocks of 150-360J, but in other countries devices using lower energies may be available.

After the initial shock, CPR should be immediately resumed for 2 minutes before reassessing the rhythm; a further shock should then be given if indicated, followed by immediate resumption of CPR, and this cycle of assessment, shock, and CPR should be continued throughout resuscitation. At the same time, drug therapy may be started. In the UK and Europe, adrenaline 1 mg intravenously is recommended before the third shock, repeated every 3 to 5 minutes (roughly every 2 cycles) while resuscitation continues; in the USA, adrenaline may be started before the second or third shock. If the intravenous route is not available, the same dose may be given by intraosseous injection. Endotracheal dosage is a further alternative; doses 2 to 3 times greater than those given intravenously are suggested, although studies investigating this route have had mixed results.[10,11] A single dose of vasopressin (as argipressin) 40 units intravenously may be given instead of the first or second dose of adrenaline,[4] but this is not universally recommended.[5,6] Amiodarone may be given before the fourth shock (before the third or fourth shock in the USA); lidocaine is an alternative if amiodarone is not available. Other drugs (such as those described above) may be used as appropriate. Cycles of CPR, shocks, and adrenaline should continue for as long as defibrillation is indicated. The total number of cycles is a matter of judgement but a resuscitation attempt may reasonably last for anything from 10 minutes to 1 hour.

Ventricular fibrillation in **children** is unusual; the basic management is the same as in adults, but the energies used for defibrillation and the doses of drugs used are different and a precordial thump is not generally given. The dose of adrenaline is 10 micrograms/kg by intravenous or intraosseous injection. A higher dose of 100 micrograms/kg has been used for the second and subsequent doses but is no longer recommended.[3-6] The endotracheal route is an alternative, but only if intravenous or intraosseous access cannot be obtained; the suggested endotracheal dose is 100 micrograms/kg.

In survivors of ventricular fibrillation and pulseless ventricular tachycardia in whom it is considered there is a high risk of **recurrence**, implantable cardioverter defibrillators may be used. Drug therapy may also be used prophylactically (see Ventricular Tachycardia under Cardiac Arrhythmias, p.1160).

Asystole and **electromechanical dissociation** have a much less favourable prognosis than ventricular fibrillation or pulseless ventricular tachycardia, although there are certain causes such as hypovolaemia, hypoxia, pneumothorax, pulmonary embolism, drug overdose, hypothermia, and electrolyte imbalances that may respond to treatment and these should be considered and the appropriate therapy given promptly once resuscitation has been started. As described above, a precordial thump may be appropriate if the cardiac arrest is witnessed. Once ventricular fibrillation or tachycardia is positively excluded, CPR should begin immediately and adrenaline 1 mg should be given by intravenous or intraosseous injection every 3 to 5 minutes; in the USA, a single dose of vasopressin may be given instead of either the first or second dose of adrenaline if the patient is in asystole.[4] For asystole a single dose of atropine 3 mg intravenously is also given to block vagal activity;[5,6] in the American guidelines[4] atropine is recommended in repeated doses of 1 mg to a total maximum dose of 3 mg. Other drugs (such as buffering agents) may be considered. Cardiac pacing may be started once there is evidence of electrical activity. Resuscitation should generally continue for at least 20 to 30 minutes from the time of collapse; it is not usually prolonged as recovery rarely occurs after 15 to 20 minutes of asystole if there has been no response.

For **children** with asystole or electromechanical dissociation, the initial dose of adrenaline recommended is 10 micrograms/kg given by intravenous or intraosseous injection; as for ventricular fibrillation, higher doses have been used subsequently but are not generally recommended. Alternatively, adrenaline may be given by the endotracheal route in doses of 100 micrograms/kg. Atropine is not generally used and a precordial thump is not recommended.

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Angina pectoris

Angina pectoris is a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischaemia) and is part of the spectrum of coronary or ischaemic heart disease. Myocardial oxygen supply depends upon coronary blood flow, which normally increases to meet increased oxygen demands. Ischaemia occurs when blood flow either cannot be increased, or is reduced; this may be due to a fixed obstruction in the coronary arteries, vasoconstriction, thrombus formation, or platelet aggregation. The main symptom is transient precordial discomfort ranging from a mild ache to severe pain. Some patients may also experience dyspnoea, nausea, sweating, and left arm discomfort.

Three main types of angina have been described: stable angina; unstable angina; and Prinzmetal's angina. Although these are discrete groups, stable angina may become unstable, and Prinzmetal's angina may co-exist with stable or unstable angina.

Stable angina (effort angina) is usually brought on by exertion and relieved by rest. It is often called chronic stable angina and as the name implies the frequency, intensity, and duration of the attacks are stable. The main underlying disorder is coronary atherosclerosis causing a fixed obstruction in one or more coronary arteries. While the restricted coronary blood flow is still adequate for oxygenation of the unstressed heart, it is not capable of being increased to meet the increase in myocardial oxygen demand that may occur during exercise, cold exposure, emotional stress, or after eating.

Unstable angina and the related condition **non-ST elevation myocardial infarction** are acute coronary syndromes intermediate between stable angina pectoris and acute myocardial infarction. There are 3 main presentations:

- angina that presents from the beginning as severe and frequent attacks
- an increase in the frequency, intensity, and/or duration of previously stable angina, often with diminishing responsiveness to sublingual nitrates (crescendo angina)
- recurring or prolonged angina at rest

As in stable angina, the underlying disorder is usually coronary atherosclerosis, but the decreased coronary artery blood flow is usually caused by disruption of an atherosclerotic plaque, which leads to platelet adhesion and aggregation, thrombus formation, and vasoconstriction. This may result in partial occlusion of one or more coronary arteries, and the coronary blood flow can be so restricted that it does not meet the oxygenation demands of the unstressed heart. However, in unstable angina the ischaemia is not severe enough to cause myocardial damage, whereas in non-ST elevation myocardial infarction some degree of myocardial necrosis occurs, although to a lesser extent than in acute myocardial infarction. Patients with the different acute coronary syndromes may present similarly and definitive diagnosis is only possible retrospectively once the results of biochemical measurements such as cardiac troponins or cardiac enzymes are available or the ECG shows evidence of new Q waves. However, patients without ST-elevation on the presenting ECG rarely develop Q waves and are managed as for unstable angina; those with ST-elevation should be treated as for acute myocardial infarction (p.1175). Patients with unstable angina are at an increased risk of sudden death or progression to myocardial infarction, and those with rest pain are at the greatest risk.

Prinzmetal's angina (variant angina) is a rare form of angina caused by coronary vasospasm, although it is often associated with atherosclerosis. It occurs spontaneously at rest and with greater frequency during the night or early hours of the morning. It is associated with transient ST-segment elevation and carries a risk of progression to myocardial infarction. Prolonged vasospasm may also lead to ventricular arrhythmias, heart block, or death.

Patients who have **angina with normal coronary arteries** as shown by angiography may have microvascular dysfunction or altered cardiac pain perception. Prognosis is generally better than in other forms of angina although quality of life may be significantly impaired.[1,2]

In addition to the types of angina described above periods of **silent myocardial ischaemia** (asymptomatic transient myocardial ischaemia) in which there is no anginal pain have been identified during ECG monitoring. In some patients all ischaemic episodes are asymptomatic. However, asymptomatic ischaemic episodes also occur in patients with angina and seem to be more common than symptomatic episodes. It is not clear why some episodes of ischaemia are symptomatic while others are not.

Treatment depends on the type of angina and involves symptomatic management of acute anginal pain, antithrombotic therapy to prevent progression to myocardial infarction, and long-term management both to prevent angina attacks and to reduce the risk of other cardiovascular events. Anti-anginal treatment is used in both stable and unstable angina and is described in more detail below; it includes drug therapy (nitrates, beta blockers, calcium-channel blockers, and potassium-channel openers), and non-pharmacological interventions. Antithrombotics are used in unstable angina and include anticoagulants and antiplatelet drugs (see Treatment of Unstable Angina, below). Long-term measures to reduce cardiovascular risk are important in all patients, even when symptoms are controlled, and include antiplatelet therapy (which should be given to all patients unless contra-indicated), lipid lowering therapy, and lifestyle changes; these interventions are discussed in more detail under Cardiovascular Risk Reduction, p.1164. Patients with ischaemic heart disease who undergo non-cardiac surgery are at risk of complications resulting from perioperative myocardial ischaemia.

Anti-anginal drugs act in a variety of ways. Glyceryl trinitrate and other organic *nitrates* have a vasodilator effect with venodilatation predominating over dilatation of the arterioles. Dilatation of veins decreases venous return as a result of venous pooling and lowers left ventricular diastolic volume and pressure (together termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequence of these effects is a reduction in myocardial oxygen demand. Also the vasodilator effect improves regional coronary blood flow to ischaemic areas, and alleviates coronary spasm. *Beta blockers* cause a slowing of the heart rate and reduction in contractility and therefore reduce myocardial oxygen demand. *Calcium-channel blockers* reduce the work of the heart by dilating peripheral arteries, and diltiazem and verapamil also slow the heart rate. Calcium-channel blockers also act on the coronary circulation preventing spasm. *Potassium-channel openers* act as coronary vasodilators, while nicorandil also has a nitrate component that may contribute to its effect.

The main ***non-pharmacological treatments*** used are *percutaneous coronary interventions* (PCI), such as balloon angioplasty and stenting, and bypass surgery. Balloon angioplasty is a catheter-based technique that mechanically dilates the occluded artery; coronary stents are used to prevent recoil and to reduce the incidence of restenosis. Nitrates and calcium-channel blockers may be given to alleviate coronary spasm due to the procedure. Coronary artery *bypass surgery* uses a vein or artery graft to bypass the occlusion. Both PCI and bypass surgery abolish or reduce episodes of angina in most patients but symptoms commonly recur over a period of time due to restenosis. Adjunctive therapy is therefore needed both to prevent short-term thromboembolic complications and long-term reocclusion (see Reperfusion and Revascularisation Procedures, p.1181). Other non-pharmacological methods that have been tried in refractory angina include enhanced external counterpulsation, transmyocardial revascularisation, and spinal cord stimulation;[3,4] gene- and stem cell-based therapies are also under investigation.[4]

Treatment of stable angina. Management of the patient with stable angina[4-10] mainly involves the use of anti-anginal drugs, antiplatelet therapy, and measures to reduce cardiovascular risk. Any contributory conditions, such as anaemia, should be identified and treated.

Treatment of *infrequent* angina episodes (less than about 2 attacks per week) usually consists of glyceryl trinitrate given when required, generally sublingually; alternatively, a buccal tablet or spray formulation may be used. Isosorbide dinitrate, in the form of sublingual tablets or spray, may be used, although it has a slower onset of action than glyceryl trinitrate. Glyceryl trinitrate in sublingual or buccal forms may also be used before an activity or circumstance that might precipitate an attack.

When episodes occur *more frequently*, sublingual glyceryl trinitrate, at least on its own, may no longer be appropriate, and regular symptomatic treatment has to be considered. Choice depends upon patient characteristics and any concurrent medical conditions.

- Beta blockers are the mainstay of therapy. They are generally considered to be first-line treatment if sublingual glyceryl trinitrate is not adequate since they provide effective symptom control and have also been shown to reduce mortality in certain patients with high cardiovascular risk.[5,6,9] The different beta blockers have similar efficacy in terms of symptom control, but those with $beta_1$-selectivity may be preferred;[9] beta blockers with intrinsic sympathomimetic activity may be less effective for secondary prevention after myocardial infarction and are not recommended.[11]
- Calcium-channel blockers appear to have similar efficacy to beta blockers in terms of symptom control and cardiovascular outcomes[12] and long-acting calcium-channel blockers may be used as alternative first-line therapy,[5,9] particularly in patients unable to tolerate beta blockers. Both dihydropyridines (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) may be used, with choice depending on individual patient characteristics and adverse effects. Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended (see under Adverse Effects of Nifedipine, p.1350).
- Regular nitrate therapy is a further alternative, and includes modified-release forms of glyceryl trinitrate, for example transdermal patches, and the long-acting nitrates such as isosorbide dinitrate or isosorbide mononitrate; it may be particularly suitable in patients with left ventricular dysfunction. Diminished effectiveness or tolerance occurs, particularly with nitrate preparations that produce sustained plasma concentrations, and dosage regimens including a nitrate-free period should be used (see Nitrate Tolerance, p.1297).
- Nicorandil, which is both a potassium-channel opener and a nitrate, is another alternative that can be used for monotherapy.[6,9] Ivabradine, a selective sinus node I_f inhibitor, may be used in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta blockers. Other drugs that are sometimes used include trimetazidine, which has anti-ischaemic effects through a metabolic action and may be of benefit in refractory angina, and the nitrovasodilator molsidomine. Several other vasodilators have also been used (see p.1156) but no longer have an established role.

Where optimal therapy with a single drug fails to control symptoms, *combination therapy* may be used. There is additional benefit from nitrates with beta blockers, since nitrates can moderate the excessive effects that beta blockers may have in increasing left ventricular diastolic volume and pressure and in inducing bradycardia. Calcium-channel blockers may also be used with nitrates; the use of verapamil or diltiazem with a nitrate may be preferrable to nifedipine (or other dihydropyridine derivative) with nitrates as both nifedipine and nitrates cause reflex tachycardia, hypotension, and headaches. Use of beta blockers with calcium-channel blockers may also be of benefit,[13] although adverse effects can be a problem. Combined therapy with beta blockers and dihydropyridines or diltiazem improves exercise tolerance, but caution is needed with dihydropyridines in patients with heart failure (although amlodipine and felodipine appear to be safe) and with diltiazem in patients with conduction disorders. Verapamil should generally be avoided with beta blockers as the risk of conduction disorders is particularly high (see p.1422).

Nicorandil may also be given with other anti-anginals. Ranolazine, which has metabolic effects, is another drug that may be used as an adjunct to standard therapy, although its role is not yet established.

Triple therapy using a nitrate, a beta blocker, and a calcium-channel blocker may sometimes be used although it is likely to be associated with more adverse effects.

If medical treatment does not control the angina the patient should be investigated to determine suitability for *revascularisation*.[9,14] The choice between PCI and coronary artery bypass surgery in patients with coronary artery disease is not entirely clear, and a systematic review[15] found that both procedures had similar effects on mortality, but the need for further revascularisation procedures was lower with bypass surgery. In general, PCI is preferred in patients with single-vessel disease, whereas bypass surgery is usual in patients with triple-vessel disease, disease of the left main coronary artery, or impaired left ventricular function.[16,17] PCI has also been used in patients whose angina is controlled with medical therapy, but its role is not clear. Although symptom control and quality of life may be higher with PCI than medical therapy,[18,19] a meta analysis[20] found no evidence that it improved mortality or reduced the incidence of major cardiovascular events.

Treatment of unstable angina. Unstable angina and non-ST segment elevation myocardial infarction are managed similarly,[21-28] and are generally regarded as an emergency. Patients with a change in the pattern of previously stable angina or with recurring or prolonged angina at rest should therefore be hospitalised and rapidly assessed. Presenting symptoms are similar for all the acute coronary syndromes and a resting ECG should be obtained as a priority. This allows identification of patients with ST elevation, who require treatment for acute myocardial infarction (p.1175), and also allows initial risk stratification. In patients without ST elevation, the immediate priority is to control symptoms and reduce ischaemia; at the same time, the risk of progression to acute myocardial infarction should be assessed, and subsequent treatment planned as appropriate. *Initial treatment* involves antiplatelet drugs, anticoagulants, nitrates, beta blockers, and possibly calcium-channel blockers; additional antiplatelet therapy and urgent revascularisation may then be considered. Once the patient has been stabilised, underlying risk factors should be identified and treated, and long-term anti-anginal therapy may be given.

- Aspirin is routinely included in the initial treatment. It inhibits platelet aggregation and substantially reduces the incidence of myocardial infarction and death, although it has not been shown to reduce the number of ischaemic episodes or to relieve pain during the acute phase.
- Clopidogrel or ticlopidine may be alternatives if aspirin is not tolerated, although clopidogrel has fewer adverse effects and is generally preferred. Dual antiplatelet therapy with clopidogrel and aspirin, both started immediately, may provide additional benefit[29] and has been recommended.[21,23,28]
- Anticoagulants are generally given in addition to aspirin to reduce thrombin generation and fibrin formation, although the optimum choice is unclear.[21]

  Both unfractionated heparin[30,31] and low-molecular-weight heparin[31] reduce the number of ischaemic episodes and major cardiovascular events during the acute phase, and also longer term. There is some evidence that low-molecular-weight heparins may be more effective than unfractionated heparin.[32-34] They may also be easier to use since low-molecular-weight heparins are given subcutaneously, whereas unfractionated heparin is generally given by continuous infusion for at least 48 hours,[22] although it may also be effective subcutaneously.[35] Reactivation of unstable angina may occur when treatment with either unfractionated[36] or low-molecular-weight heparin[37] is stopped; it is less likely in patients who are also taking aspirin,[36] and the risk may be reduced if treatment is stopped gradually. Guidelines[21,23,28] therefore allow the use of either unfractionated or low-molecular-weight heparin; unfractionated heparin may be preferred in patients undergoing bypass surgery[21] but either is suitable for PCI.[38]

  The pentasaccharide fondaparinux may be an alternative; it is at least as effective as enoxaparin[39] and may be the preferred option in patients for whom urgent PCI is not planned;[23] however, the incidence of catheter thrombosis was increased with fondaparinux in patients undergoing PCI[40] and unfractionated heparin should be given at the time of the procedure if PCI is performed.[21,23] For patients in whom early PCI is planned, the direct thrombin inhibitor bivalirudin is another alternative; a study[41,42] in patients scheduled for PCI found that bivalirudin was as effective as heparin (unfractionated or low-molecular-weight) and the risk of bleeding was reduced.
- Nitrates are widely used although evidence from controlled studies is limited.[21,23] The initial treatment may be given intravenously to produce a fast response and to provide better dose control than can be achieved with other routes. Glyceryl trinitrate or isosorbide dinitrate are used. Generally, the intravenous route is only used during the acute phase, and once the patient is stabilised the infusion is withdrawn, usually within about 48 hours. Sublingual glyceryl trinitrate may be tried initially in patients with less severe symptoms.
- Treatment with a beta blocker is started during the acute phase to reduce myocardial oxygen demand. Oral treatment is usually preferred,[21,23] although the intravenous route may be used initially if required. Beta blockers with intrinsic sympathomimetic activity do not reduce resting heart rate and are not recommended.[11,21,22]
- Calcium-channel blockers may be added to therapy although they are generally reserved for patients with angina refractory to treatment with the above drugs, or in whom beta blockers are contra-indicated. However, calcium-channel blockers are the drugs of choice if the angina has a vasospastic aetiology, for example in Prinzmetal's angina. The choice of calcium-channel blocker is described under the treatment of stable angina above.
- Thrombolytics have been tried in unstable angina but do not improve outcome and are associated with an excess of bleeding complications; thrombolytic therapy is therefore not recommended in patients with unstable angina.[21,22]

Once the initial therapy has been started patients at high or intermediate risk of progression to acute myocardial infarction, including those with recurrent ischaemia and those with raised cardiac troponins, should be assessed for *additional treatment*. Patients may be assigned to either an invasive or a conservative strategy. For those in whom an invasive strategy is chosen, early angiography is performed, with urgent revascularisation if appropriate. For those assigned to a conservative strategy and in patients at lower risk, angiography and revascularisation are only performed if medical therapy fails to control symptoms or if indicated by stress testing. Choice between the two remains controversial. Meta-analyses[43-45] have suggested that an invasive strategy is associated with a reduction in recurrent angina; there may also be a reduction in myocardial infarction and mortality in the longer term, although a later review[46] was unable to confirm this. Most benefit appears to be in higher risk patients, and a conservative strategy may be appropriate in those at lower risk.

- Additional antiplatelet therapy with glycoprotein IIb/IIIa inhibitors may have a role in patients treated invasively or conservatively.[47] Benefit has been established in patients undergoing PCI (see Reperfusion and Revascularisation Procedures, p.1181), but results in patients treated medically have been less consistent. A meta-analysis[48] of studies of glycoprotein IIb/IIIa inhibitors in unstable angina or non-ST elevation myocardial infarction found that they reduced the risk of death or myocardial infarction in patients who were not scheduled for early revascularisation, particularly in those at high risk of progression, such as those with raised troponins. However, many of the patients included in the analysis did receive revascularisation and the use of glycoprotein IIb/IIIa inhibitors in patients not undergoing intervention remains questionable.[21] Whether all the glycoprotein IIb/IIIa inhibitors are effective is also unclear. For patients not undergoing PCI, individual studies have reported beneficial results with tirofiban and aspirin, alone[49] or in combination with heparin therapy,[50] and with eptifibatide[51] in addition to standard therapy, but not with abciximab[52] in addition to aspirin and heparin. The benefit of treatment with glycoprotein IIb/IIIa inhibitors in patients already taking aspirin and clopidogrel is also not yet established.[53,54]
- The use of statins early after admission for acute coronary syndromes has been recommended,[23] although meta-analyses have come to differing conclusions regarding their benefit. One analysis[55] found early use of statins had no effect on outcomes at 1 or 4 months after the initial event, but another[56] reported a reduction in cardiovascular events with statin therapy for 6 months or longer; benefit may be increased with high-dose regimens.[57]

After discharge, patients should continue to take aspirin and a beta blocker; clopidogrel should also continue to be added to aspirin for up to 9 to 12 months.[21,23,58] Statins should also be continued, and other measures to reduce cardiovascular risk should be adopted. Anti-ischaemic drugs should be given as required; some patients are given a long-acting nitrate for long-term prophylaxis, although nitrates have not been shown to protect against subsequent cardiovascular events. Long-term oral anticoagulation has been used but is not routine therapy, and studies of warfarin with aspirin have given mixed results.[59,60] Prolonged use of low-molecular-weight heparins has been investigated,[61,62] but benefit has not been confirmed.

Treatment of Prinzmetal's angina. This should be treated like unstable angina with the addition of a calcium-channel blocker; the selection of an appropriate calcium-channel blocker is described above under the treatment of stable angina. Once stabilised, maintenance should include a nitrate, or calcium-channel blocker, or both to protect against further spasm. Surgery may be considered in some patients.

Treatment of angina with normal coronary arteries. Symptomatic treatment with standard anti-anginal drugs is the mainstay in patients with angina but no evidence of coronary artery disease, although response varies. Beta blockers appear to be the most effective treatment and are usually considered first-line.[1,2]

Treatment of silent myocardial ischaemia. Silent myocardial ischaemia has been recognised as a potential risk factor for future cardiovascular morbidity and mortality and research has been undertaken to assess whether suppressing such episodes can improve long-term outcome. Although many of the therapies used in angina reduce the incidence of silent ischaemia it is not yet clear whether complete suppression of ischaemia affects prognosis.[63,64] Other studies have suggested that periods of ischaemia may protect the heart during subsequent myocardial infarction, although the clinical relevance of this is unclear.[65,66]

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Ascites

Ascites is the accumulation of fluid within the peritoneal cavity. Although it is not strictly a cardiovascular disorder, treatment depends mainly on cardiovascular drugs. Alcoholic hepatic cirrhosis is probably the commonest underlying cause in the western world; others include malignant neoplasms, heart failure, and tuberculosis. The following discussion is restricted mainly to **cirrhotic ascites**.

The mechanism of ascites formation in hepatic cirrhosis has been explained by various hypotheses. Whatever the mechanism, ascites formation is linked to renal sodium and water retention partly as a result of increased circulating renin and aldosterone concentrations. Portal hypertension and hypoalbuminaemia may be contributory factors. More details may be found in reviews of the pathophysiology of ascites formation.[1-3]

Small amounts of ascitic fluid may go undetected but as it accumulates abdominal distension becomes apparent, and there is a feeling of discomfort. There may be respiratory distress and cardiac dysfunction in severe cases. Peripheral oedema may, or may not, be present. Renal dysfunction may progress to severe impairment (the hepatorenal syndrome). Patients are at risk of primary (spontaneous) bacterial peritonitis (p.184).

Management[1-10] depends on the severity of ascites but the mainstays are dietary sodium restriction and diuretic treatment. In mild to moderate ascites, sodium restriction alone may sometimes be effective but most patients also require diuretics. Bed rest has been advocated but is no longer generally recommended.[10] Response is monitored by measuring the daily reduction in body-weight. The diuretic of choice is the aldosterone antagonist spironolactone, with the addition of a loop diuretic such as furosemide if necessary. Amiloride or another potassium-sparing diuretic may be used as an alternative to spironolactone if adverse effects are a problem. Spironolactone together with furosemide from the outset has also been used; benefit has also been suggested with combined furosemide and albumin in selected patients.[11] In tense or refractory ascites, large-volume or total paracentesis (removal of ascitic fluid by drainage) is often used initially; patients may then be maintained on diuretics or repeated paracentesis may be used. Plasma volume replacement with albumin or dextrans after paracentesis is usual, particularly if large volumes are removed. Where ascites remains refractory or repeated paracentesis is not tolerated various shunting procedures have been tried, although their role is not established. In severe cases liver transplantation may be necessary.

In **malignant ascites** (ascites due to malignant neoplasms; see Malignant Effusions, p.659), paracentesis is often necessary but spironolactone may be of benefit in some patients.

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Atherosclerosis

Atherosclerosis is a pathological condition affecting medium and large arteries in which lipid-rich lesions (atheromas) develop in the intimal lining, leading to arterial dysfunction, obstruction of blood flow, and ischaemia. **Ischaemic heart disease** (coronary heart or coronary artery disease), which includes angina pectoris (p.1157) and myocardial infarction (p.1175), is the most common manifestation of atherosclerosis and in most industrialised countries ischaemic heart disease is a leading cause of death. Atherosclerosis of peripheral or cerebral arteries leads to peripheral vascular disease (p.1178) or ischaemic stroke (p.1185). Atherosclerotic diseases are thus a major cause of mortality and morbidity and the prevention and treatment of atherosclerosis has an important role in the management of these diseases.

Atherosclerosis is a progressive condition and various stages of atheroma development are recognised.[1-3] Early lesions include fatty streaks, which develop from infancy and are composed of lipid-filled macrophages (foam cells). These progress to fibrous plaques, which consist of a core of lipid and lipid-rich macrophages surrounded by a connective-tissue matrix. Plaques may undergo calcification and may become sufficiently large to obstruct the lumen of the artery. However, acute occlusion more commonly occurs as a result of thrombosis at the site of a plaque, due to endothelial denudation or disruption of the plaque (plaque rupture or fissuring) with exposure of the thrombogenic core. Endothelial dysfunction is an important underlying factor, promoting both the development of atheromas (atherogenesis) and subsequent thrombosis.[4,5]

Although symptoms depend on the site of obstruction, atherosclerosis is essentially a generalised condition and patients with peripheral vascular disease, for example, are also likely to develop, or to have evidence of, ischaemic heart disease.

The management of atherosclerotic diseases involves treatment of the clinical manifestations (as discussed under the specific diseases) and measures to reduce the risk of cardiovascular events occurring (see Cardiovascular Risk Reduction, p.1164). Some of the measures used to reduce risk, such as lipid regulating drugs or antihypertensives, may also reduce the progression of atherosclerosis. Other approaches have been targeted more directly at the atherosclerotic process, and some of these are discussed below.

Oxidation of low-density lipoprotein (LDL) is thought to be a crucial step in atherogenesis[6-8] and a number of studies have investigated the use of dietary antoxidants such as vitamins E and C and betacarotene (see Prophylaxis of Ischaemic Heart Disease, p.1926). Although some studies have found a reduction in the progression of atherosclerosis, others have not confirmed this finding, and several large studies have failed to find any effect on the risk of clinical events. Polyphenol compounds found in various foods, including red wine, have also received much attention for their possible role in the prevention of atherosclerosis.

Hyperhomocysteinaemia has been suggested as a risk factor for atherosclerosis, although its importance is not clear.[9] Interventions to reduce homocysteine, such as the use of folic acid or vitamin B supplements (see Cardiovascular Disease, p.1941), have been tried. Some effects on endothelial function have been noted, but there is as yet no evidence that clinical events are reduced.

Inflammation appears to have an important role in the development and progression of atherosclerosis, and in acute events due to plaque instability.[10,11] Various studies have shown an association between C-reactive protein, a marker of inflammation, and cardiovascular events, although its precise role is unclear.[9] Statins, which lower blood lipids and have an established role in reducing clinical events, have also been shown to reduce the progression of atherosclerosis,[5] possibly through an effect on inflammation, and high doses may induce regression.[12] Other non-lipid effects such as improvement of endothelial dysfunction, or an effect on thrombosis, have also been suggested.

Another possible cause of inflammation that has been investigated is infection,[13] and serological and pathological studies have found an association with a number of organisms. The evidence appears to be strongest for *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), although its precise role in the development or progression of atherosclerosis is unclear.[14] Treatment with antibacterials has been tried in patients with atherosclerotic disorders but any benefit has not yet been confirmed;[13,14] meta-analyses[15,16] of trials using antichlamydial drugs in patients with ischaemic heart disease have found no evidence that they reduced either mortality or further cardiovascular events. Some antibacterials may also have a direct anti-inflammatory action that could contribute to their effects.[14]

Chelation therapy with disodium edetate has been tried, as calcium deposition has been proposed as another factor in the development of atherosclerosis; however, the benefits remain to be established (see Atherosclerosis under Sodium Edetate, p.1464).

Women have a lower risk of atherosclerotic disease than men of a comparable age, although the difference narrows with increasing age postmenopausally, and the use of HRT has therefore been investigated. HRT lowers lipid concentrations and some angiographic or ultrasound studies have shown beneficial effects on the progress of atherosclerosis, although others have failed to confirm these findings. However, controlled studies do not support a role for HRT in the prevention of cardiovascular disease in postmenopausal women (see Effects on the Cardiovascular System, p.2073).

Therapeutic angiogenesis (the development and growth of blood vessels) is also under investigation to improve perfusion in atherosclerotic diseases. Preliminary studies of growth factor proteins, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), and gene therapy to stimulate VEGF production, have shown promise.[17,18] The use of stem cells is also being investigated.[19] However, since neovascularisation of the vessel wall and plaque angiogenesis may play a role in atherosclerosis, anti-angiogenic therapy may also have potential.[20]

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Cardiac arrhythmias

Cardiac arrhythmias are disorders of the rhythm of the heart (p.1152) that may affect its ability to maintain blood circulation. They can be asymptomatic and in some cases benign, but often cause symptoms and may lead to syncope and sudden death; thromboembolic disorders associated with atrial arrhythmias are a common cause of stroke.

Definitions. A *cardiac arrhythmia* can be defined as any abnormality of rate, regularity, or site of origin of the cardiac impulse or as a disturbance in conduction that causes an abnormal sequence of activation. Arrhythmias may therefore occur due to disorders of the SA node, affecting initiation of impulses; disorders of the AV node and conducting system, affecting spread of the impulse to the ventricles; or abnormal conduction through other myocardial cells such as accessory pathways. Impulses may be generated outside the SA node (*ectopic pacemakers*), particularly in the AV node or the His-Purkinje system. The normal rate of impulse generation by these ectopic pacemakers is less than that of the SA node and therefore they do not usually trigger the heart beat, although they may become dominant in some situations. Since the action potential depends on the movement of ions across cell membranes, electrolyte disorders may be an important cause of arrhythmias; congenital disorders affecting the ion channels (channelopathies) are also increasingly being recognised as a cause.

Arrhythmias may be classified as bradyarrhythmias (slow) or tachyarrhythmias (fast), depending on the heart rate, and as supraventricular (atrial or AV junctional) or ventricular, depending on their presumed site of origin. They may also be divided on the basis of the underlying mechanism into those associated with abnormal automaticity, re-entry, or triggered activity (see Tachyarrhythmias, below). Symptoms depend on the arrhythmia but may include fatigue, dyspnoea, dizziness, and syncope; sudden death may occur. *Palpitations*, an unacceptable awareness of the beating heart, may occur normally in circumstances such as emotion, exercise, or stress but can occur in association with arrhythmias.

Bradyarrhythmias are commonly caused by sinus node dysfunction (sick sinus syndrome), which either depresses impulse generation or disturbs the conduction of impulses from the sinus node to the atria.[1] In some patients periods of bradycardia and tachycardia alternate (bradycardia-tachycardia syndrome), making management difficult. *Heart block* (AV block) is another cause of bradycardia, and involves disturbance of conduction of the atrial impulse to the ventricles. First-degree block, in which the impulse is delayed, is usually asymptomatic but may progress to second- or third-degree block, with intermittent (second-degree) or complete (third-degree) failure of atrial impulses to reach the ventricles. This usually causes bradycardia since the intrinsic rate of ventricular contraction is slower than that of the atria, but in AV dissociation ventricular activity is faster than, and independent of, the atrial activity.

Tachyarrhythmias may arise in either the atria or the ventricles. The precise mechanism is often unclear, but for many of the clinically important tachyarrhythmias it involves *re-entry*. Impulses normally spread in a single direction and die out once ventricular contraction occurs, but in re-entry the impulse continues to propagate in a cyclical manner, reactivating the heart. Abnormal automaticity and triggered activity are alternative mechanisms that may be involved.

Ectopic beats, *extrasystoles*, or *premature contractions* can arise in either the atria or the ventricles and, although their precise meaning and definition differs, for practical purposes they can be considered equivalent. Generally, they cause few or no symptoms and usually have no prognostic value although some patients suffer distressing symptoms or palpitations.

Diagnosis. The precise identification of an arrhythmia is not always easy, but is important for correct management since inappropriate use of antiarrhythmics may be not only ineffective but actively harmful. Clinical symptoms may be useful, but the mainstay of diagnosis is the electrocardiogram (ECG), which records the electrical rhythm of the heart. A typical normal ECG trace is shown in Figure 2, p.1152. Many arrhythmias have distinctive ECG patterns, but this is not always the case; an arrhythmia with a narrow QRS complex is always supraventricular in origin whereas a broad QRS complex can indicate either a supraventricular or ventricular origin. Other specialised tests and features relevant to the individual arrhythmias may aid diagnosis.

Management. Treatment of arrhythmias may be indicated to relieve symptoms and/or to improve survival and may involve antiarrhythmic drugs (see p.1153 for an explanation of the classification of antiarrhythmics), electrical cardioversion, or cardiac pacing; surgical or catheter ablation of arrhythmic pathways also has an increasingly important role. Drug therapy is mainly used for tachyarrhythmias and these are the focus of the following discussion. For **bradyarrhythmias**, cardiac pacing is the treatment of choice,[1-3] although atropine[2] or sympathomimetics have been used.

Atrial fibrillation is a supraventricular tachyarrhythmia with an underlying mechanism of re-entry. It is the commonest arrhythmia encountered clinically, and has been the subject of reviews[4-11] and guidelines.[12-14] Atrial fibrillation is usually associated with disorders that predispose the atria to re-entry, although it is now recognised that the arrhythmia may start from an ectopic focus, often in the pulmonary vein. The main underlying cardiovascular disorders are ischaemic or hypertensive heart disease and heart failure, and the incidence increases markedly with age. Rheumatic heart disease is also an important cause, although this is now less common in developed countries. Other causes include hyperthyroidism and acute alcohol intoxication. Atrial fibrillation is also relatively common after cardiothoracic surgery, although this is usually self-limiting. In some patients there is no obvious cause ('lone' atrial fibrillation).

Atrial fibrillation is characterised by an irregular and very rapid atrial rate (usually more than 300 beats/minute) and, although the AV node is incapable of conducting all the impulses adequately, the increased ventricular response results in a rapid and totally irregular ventricular rate. Atrial fibrillation has been classified in several ways, but patients with 2 or more episodes are generally considered to have recurrent atrial fibrillation; this may be classed as paroxysmal (intermittent) if the arrhythmia terminates spontaneously, or persistent (chronic) if it is sustained. Persistent atrial fibrillation that does not respond to cardioversion or where cardioversion is not attempted is classed as permanent.

Although atrial fibrillation can cause distressing symptoms such as severe palpitations and exercise intolerance it is not usually immediately life-threatening; however, it does result in long-term morbidity and mortality. The increased rate may lead to tachycardia-induced cardiomyopathy, while left atrial dilatation and reduced cardiac output lead to stasis of blood in the left atrium, which can result in thrombus formation and subsequent systemic embolisation, notably ischaemic stroke. Thromboembolic events are relatively rare in lone atrial fibrillation but the risk is very much increased if other cardiovascular disease is present, especially rheumatic heart disease.

Management of atrial fibrillation aims to control symptoms and prevent long-term morbidity and mortality, including thromboembolic complications. The available approaches are to restore and maintain sinus rhythm (*rhythm control*), or to control the ventricular rate while allowing atrial fibrillation to continue (*rate control*). Use of anticoagulation depends on the risk of thromboembolic events but may be required with either strategy.

- Rate control may be used for both acute management of symptoms and maintenance therapy and generally involves drugs that act on the AV node to slow conduction.[15] Digoxin has traditionally been used, but has a slow onset of action and is not effective during exercise and is no longer considered first-line in most patients. Beta blockers or rate-limiting calcium-channel blockers such as diltiazem or verapamil are usually the preferred treatment; they provide effective rate control, including during exercise, and may be given intravenously when acute control is needed. Digoxin may be used in sedentary patients, and is also useful in patients with heart failure; it is often given with beta blockers or calcium-channel blockers since many patients require more than one drug to maintain an adequate rate. Amiodarone, which has rate-limiting properties as well as an antifibrillatory effect, may be used if symptoms are not controlled with digoxin and beta blockers or calcium-channel blockers; catheter ablation of AV conduction pathways followed by permanent pacing may be necessary in patients intolerant or unresponsive to drug therapy.
- In a rhythm control approach, restoration of sinus rhythm (cardioversion) may be achieved either by synchronised direct current or by drugs, but both methods must be preceded by anticoagulation unless fibrillation is of recent onset (less than 24 hours). Both methods are effective and choice depends on the duration of atrial fibrillation, availability, and preference; direct current cardioversion restores sinus rhythm more rapidly and is more effective than pharmacological cardioversion if atrial fibrillation is not of recent onset but has the disadvantage that it needs to be performed under sedation or general anaesthesia. Various drugs have been used but evidence of efficacy is limited in some cases[13,14,16] and adverse effects may be a problem. Flecainide and propafenone are most widely recommended as first-line;[12-14] ibutilide and dofetilide are alternatives.[12,14] Amiodarone may also be used;[12-14] it has a slower onset but is equally effective[17] and is particularly useful in patients with structural heart disease.[13] Evidence is more limited for quinidine, procainamide, disopyramide, and sotalol. Adjunctive pharmacological therapy may be started before electrical cardioversion to increase the success of the procedure and to reduce the risk of early recurrence;[13,14] drugs used include amiodarone, flecainide, ibutilide, propafenone, and sotalol.

  Once sinus rhythm has been achieved, long-term maintenance drug therapy needs to be considered since relapse is common. Patients with a first episode of atrial fibrillation are rarely started on maintenance therapy, particularly if a reversible cause has been identified and can be treated.[13,14] However, patients who have troublesome symptoms due to paroxysmal or recurrent atrial fibrillation are usually given long-term antiarrhythmics. Drugs used are similar to those used for cardioversion, and again there is limited evidence to guide choice.[18] Beta blockers may be tried initially,[13] particularly in patients with lone atrial fibrillation,[14] and they have the advantage of providing rate control if relapse occurs, but flecainide, propafenone, or sotalol are often required. Amiodarone and dofetilide may also be used; amiodarone may be more effective than other antiarrhythmics[19] but its use is limited by long-term adverse effects and it is generally only recommended in resistant cases or in patients with heart failure who are unsuitable for alternative therapy. Catheter ablation procedures (for example, isolation of the pulmonary veins[20]) are an alternative to drugs, and surgery or implantable defibrillators may be used in selected cases. Patients with infrequent episodes of paroxysmal atrial fibrillation and good response to drugs may be prescribed single doses of flecainide or propafenone for outpatient use ('pill-in-the-pocket') if symptoms recur.[13,14,21]

The choice between rate and rhythm control has been debated. Rhythm control has theoretical advantages since restoration of sinus rhythm should both alleviate symptoms and reduce thromboembolic risk. However, the adverse effects and limited efficacy of antiarrhythmic drugs in preventing relapse may limit any benefit. A review[22] and meta-analyses[23,24] of studies comparing rate control with rhythm control found little difference between the two strategies in terms of symptom control or clinical events, and choice therefore depends on patient characteristics and preference.[12-14,25] For elderly patients with minimal symptoms rate control is generally the preferred option, whereas younger patients or those who remain symptomatic despite rate control should be considered for rhythm control.

Prophylaxis of atrial fibrillation may have a role in some situations. Although atrial fibrillation after cardiothoracic surgery is usually self-limiting, it may be associated with increased morbidity and mortality, and prophylaxis should be considered. Beta blockers, amiodarone, and sotalol are effective,[13,14,26,27] and some benefit has also been reported with magnesium[28,29] and corticosteroids.[30] Use of statins[31] or omega-3 fatty acids[32] has also been investigated. For non-surgical patients, there is some evidence of a lower incidence of atrial fibrillation in patients taking drugs affecting the renin-angiotensin system,[33] but the benefit of prophylactic use requires confirmation in controlled studies.

Prevention of thromboembolic events, particularly ischaemic stroke, is a major aspect of atrial fibrillation management and has been the subject of several reviews[34-38] as well as being addressed in the general reviews and guidelines quoted above. Patients are at risk both during cardioversion procedures and long-term, and should be given appropriate antithrombotic therapy. If atrial fibrillation has been present for 48 hours or more it is generally recognised that there is a potential risk of causing systemic embolisation once sinus rhythm is restored. In unstable patients who require immediate cardioversion, intravenous heparin should be given. In more stable patients cardioversion should be delayed until the patient has received adequate anticoagulation with warfarin for 3 to 4 weeks, but if more rapid cardioversion is preferred, intravenous heparin may be started, followed by transoesophageal echocardiography to exclude the presence of thrombi. Control of the ventricular rate as outlined above should be undertaken while the patient is waiting for cardioversion, and oral anticoagulants are usually continued for at least 4 weeks after a successful procedure.[39] There is some evidence[40] that subcutaneous low-molecular weight heparin may be an alternative to intravenous heparin followed by oral anticoagulants when transoesophageal echocardiography is used.

Long-term prophylaxis is indicated in selected patients. The risk of stroke is increased about 17 times in atrial fibrillation associated with rheumatic heart disease and the benefits of long-term prophylaxis with warfarin are well-established. For non-rheumatic heart disease the risk is less, but is still increased by about fivefold and affects many more patients; however, the use of warfarin is more controversial. Meta-analyses have clearly shown that warfarin is effective in the primary[41,42] and secondary[41,43] prevention of stroke in patients with non-rheumatic atrial fibrillation, and cohort studies[44,45] have reported similar findings. Oral anticoagulants are therefore recommended in all patients with atrial fibrillation and a history of stroke or transient ischaemic attack,[13,14,39,46] but for primary prevention the relative risks and benefits are less clear and the decision to treat depends on individual patient factors. Oral anticoagulants are recommended for all patients at high risk of thromboembolism, including older patients and those with ischaemic or hypertensive heart disease, heart failure, hyperthyroidism, or history or evidence of thromboembolism.[39,46] In some patients, alternative strategies may be appropriate. Antiplatelet therapy is widely used and there is good evidence that aspirin reduces the risk of stroke.[47,48] However, antiplatelets are generally considered less effective than warfarin for both primary[41] and secondary prevention,[41,49] and are usually only recommended where the risk of stroke is outweighed by the risk of haemorrhage, or in those who are unwilling or unable to take anticoagulants. Use of low-dose warfarin with aspirin has been shown[50,51] to be less effective than adjusted-dose warfarin and is not recommended, although a study[52] using triflusal and moderate-dose phenprocoumon reported beneficial effects. A study[53] using clopidogrel in addition to aspirin found that the combination was less effective than warfarin.

Atrial flutter is an arrhythmia somewhat similar in nature to atrial fibrillation and has been discussed in reviews[54] and guidelines.[55] Like atrial fibrillation it is characterised by a rapid (about 300 beats/minute) atrial rate, although the atrial rhythm is more regular and organised, and by a corresponding increase in the ventricular rate. It is far less common than atrial fibrillation, to which it often degenerates if left untreated; it may revert to normal sinus rhythm in some cases. Unlike atrial fibrillation, atrial flutter has not been considered to carry an increased risk of thromboembolic episodes, but several studies have suggested this may not be the case.[56-58] Anticoagulation may therefore have a role in patients with recurrent or chronic atrial flutter,[39,54,55] and has been recommended prior to cardioversion.[39,55] Management strategies for atrial flutter are broadly similar to those outlined above for atrial fibrillation, namely controlling the increased ventricular response rate and cardioversion. However, in general terms drug therapy for either of these interventions is less successful in flutter than in fibrillation. Cardioversion with drug therapy has a relatively low success rate and cardiac pacing is usually used, which often results in a self-terminating atrial fibrillation. Synchronised direct current cardioversion may be used to restore sinus rhythm if pacing fails. Radiofrequency ablation may also be used,[55] and may be the treatment of choice if long-term therapy is required.[54]

Other atrial arrhythmias include **atrial premature beats** and various types of **atrial tachycardia**. Premature beats are usually asymptomatic but if symptoms are severe (the awareness of a pause between normal beats) beta blockers may be used.[59] Atrial tachycardia may also be treated with beta blockers or rate-limiting calcium-channel blockers,[55,60,61] but if it is due to digoxin toxicity, withdrawal of digoxin may be all that is required.[55]

Paroxysmal supraventricular tachycardia is a re-entry arrhythmia. The term paroxysmal atrial tachycardia was formerly used, but became obsolete when it was realised that many such arrhythmias arise in the atrioventricular junction rather than in atrial muscle. The re-entry circuit can be either due to an accessory pathway between the atria and ventricles (atrioventricular reciprocating tachycardia; AVRT) or re-entry can occur at the site of the node itself (atrioventricular nodal reciprocating tachycardia; AVNRT). It is a relatively common arrhythmia occurring in otherwise healthy individuals. It may resolve spontaneously, or reflex vagal stimulation by respiratory manoeuvres, prompt squatting, or pressure over one carotid sinus may restore normal sinus rhythm. If symptoms associated with the rapid heart rate are severe, treatment will be needed. For termination of paroxysmal supraventricular tachycardia adenosine given intravenously is often the drug of choice;[55,59,60,62,63] intravenous verapamil or diltiazem, or intravenous beta blockers, are alternatives. If there is no response, or in patients with a wide QRS complex and unclear diagnosis, propafenone, flecainide, procainamide, sotalol, amiodarone, or ibutilide may be used.[55,59,60,63] Direct current cardioversion may be necessary in some cases, particularly in those who are unstable. Long-term maintenance therapy to prevent recurrence is required in some patients, but there is limited evidence to guide choice of therapy.[55] For many patients radiofrequency catheter ablation is the preferred treatment, particularly in those with AVRT and an accessory pathway. Alternatively, pharmacological therapy may be used. Drugs that block AV conduction are first-line and include beta blockers, rate-limiting calcium-channel blockers, and digoxin. Flecainide and propafenone, class Ic drugs that act on atrial refractoriness, may be used if first-line drugs are ineffective; amiodarone is generally preferred if patients have structural heart disease. Other drugs that may be used include sotalol, quinidine, procainamide, and dofetilide.

Wolff-Parkinson-White syndrome[64] is a congenital abnormality characterised by an accessory atrioventricular conduction pathway known as a Kent bundle that leads to ventricular pre-excitation. Although many patients remain asymptomatic, there is an increased risk of atrial fibrillation or paroxysmal supraventricular tachycardia with a danger of degeneration into ventricular fibrillation, particularly if AV-blocking drugs are used. Antiarrhythmics should be used with great caution in such patients, and catheter ablation of the accessory pathway is the treatment of choice.[55,63]

Supraventricular tachycardia can occur rarely *in utero* and is associated with hydrops fetalis and perinatal mortality and morbidity. Treatment is with antiarrhythmic drugs such as digoxin, flecainide, sotalol, or amiodarone given to the mother (transplacental therapy).[61,65,66] In resistant cases direct intraperitoneal or intravascular dosage to the fetus may be necessary.

Ventricular tachycardia[67-70] is usually a re-entry arrhythmia and is often associated with underlying cardiovascular disease such as myocardial infarction or cardiomyopathies. It may also be caused by drugs that prolong the QT interval, or by digoxin toxicity. Congenital channelopathies such as Brugada syndrome[71] and long QT syndrome may cause ventricular arrhythmias in patients with structurally normal hearts. The heart rate is about 120 to 250 beats/minute and the tachycardia, which arises in the ventricles below the AV node, can be paroxysmal, consisting of short self-terminating episodes, or can be sustained (lasting 30 seconds or longer). Ventricular tachycardia can be asymptomatic (if the episodes are non-sustained) or cause minimal symptoms such as palpitations, but is potentially a serious condition which may lead to reduced cardiac output, shock, and progression to **ventricular fibrillation** and cardiac arrest. It is one of the most common causes of sudden unexplained cardiac death.[72] The ECG trace of ventricular tachycardia may be confused with that of supraventricular tachycardia but since the treatments differ markedly, every effort should be made to obtain the correct diagnosis; if the diagnosis is unclear the patient should be treated for ventricular tachycardia.[2,55]

The *initial treatment* of ventricular tachycardia depends largely on the haemodynamic status of the patient. Unstable patients with ventricular fibrillation or pulseless ventricular tachycardia, and patients with irregular sustained ventricular tachycardia, should be given defibrillation, as outlined under Advanced Cardiac Life Support (p.1156). More stable patients with regular monomorphic ventricular tachycardia may be treated with intravenous antiarrhythmics or by sedation and direct current cardioversion; pacing may be effective in some patients. Amiodarone is widely recommended;[2,73,74] procainamide is an alternative[2,73] and may be preferred if a rapid effect is required.[74] Sotalol may also be used, and lidocaine (which was previously the drug of choice) may have a role in some patients, although it is generally less effective. Other alternatives that are available in some countries include ajmaline, flecainide, and propafenone. In some patients with non-sustained ventricular tachycardia, beta blockers may be effective; catheter ablation may have a role if termination of the arrhythmia is not urgent.[74]

After restoration of normal sinus rhythm *maintenance therapy* needs to be considered. Long-term treatment is generally not warranted in low risk patients such as those who have experienced asymptomatic non-sustained ventricular tachycardia, but patients with severe symptoms or those at high risk of sudden cardiac death, such as survivors of ventricular fibrillation and pulseless ventricular tachycardia, require treatment. Although antiarrhythmic drugs have been used, studies have shown that implantable cardioverter defibrillators reduce mortality more effectively, and these are now recommended for most patients.[74-76] Beta blockers are also effective and may be used,[74] but there is little evidence to support the use of other drugs, even when electrophysiological testing is used, and this is no longer generally recommended. Sotalol, or amiodarone with a beta blocker, may have a role if implantable cardioverter defibrillators are considered inappropriate, or to prevent frequent device activation in patients with implantable cardioverter defibrillators and recurrent arrhythmias.[74,77] There is also some evidence that drugs that are beneficial for cardiovascular risk reduction may reduce the risk of ventricular arrhythmias, including ACE inhibitors and omega-3 fatty acids, but their role is not yet established.[74]

Myocardial infarction is a particular risk factor for ventricular arrhythmias and prophylactic treatment has therefore been tried. Arrhythmias are particularly common early after acute myocardial infarction and lidocaine has been used prophylactically; however, there is little evidence of benefit and routine use is no longer recommended.[78,79] Implantable cardioverter defibrillators may be used for primary prevention of sudden cardiac death in patients with evidence of sustained ventricular tachycardia more than 48 hours after acute myocardial infarction, particularly in patients who also have heart failure; beta blockers,[80,81] amiodarone,[82] or sotalol, may also be considered. Patients with asymptomatic ventricular arrhythmias may also be at increased risk of sudden death but use of antiarrhythmic drugs increases mortality[80,81,83] and is not advised.

Primary prophylaxis may also have a role in other cardiac disorders that are known to cause ventricular arrhythmias and sudden cardiac death, including heart failure, cardiomyopathies, and Brugada syndrome or similar congenital disorders. Implantable cardioverter defibrillators are recommended in high risk patients; beta blockers and amiodarone may have a role in specific cases.[74]

QT prolongation and drug-induced arrhythmias. Antiarrhythmic drugs also have proarrhythmic properties and may exacerbate or induce arrhythmias of all kinds, and non-cardiac drugs may also have proarrhythmic effects. *Torsade de pointes* is a particularly serious ventricular arrhythmia that is often drug-induced. It is associated with prolongation of the QT interval (prolongation of ventricular repolarisation), which allows afterdepolarisations to trigger a re-entry tachycardia; this is often non-sustained, but may persist for long enough to cause syncope or it may even progress to ventricular fibrillation. Drugs that cause QT prolongation include antiarrhythmics and several non-cardiac drugs[84-89] including phenothiazines, tricyclic antidepressants, antihistamines such as astemizole and terfenadine, antibacterials such as erythromycin, the antimalarial halofantrine, and the lipid lowering drug probucol. Patients with congenital channelopathies may also have QT prolongation and develop torsade de pointes, often in response to stress- or exercise-induced tachycardia; other causes include electrolyte disorders and bradycardia. If torsade de pointes is drug-induced, withdrawal and subsequent avoidance of the offending drug is mandatory. Initial therapy is usually with intravenous magnesium, to correct any contributory magnesium deficiency, with temporary pacing of the atria or ventricles and correction of any other electrolyte disorders as appropriate. Isoprenaline has been given cautiously to increase the heart rate and shorten the QT interval, until pacing is instituted. Congenital long QT syndromes are usually treated with beta blockers and/or pacing.[84,85]

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Cardiomyopathies

Cardiomyopathy is a term used to describe diseases of the heart muscle associated with cardiac dysfunction. Although formerly used to describe conditions with an unknown cause (idiopathic), increased awareness of disease mechanisms and genetic factors has broadened the definition. Cardiomyopathies may develop as a consequence of other cardiovascular or systemic disorders, such as systemic or pulmonary hypertension, ischaemic heart disease, valvular heart disease, congenital abnormalities, metabolic disorders, inflammatory or infectious diseases, and drug-induced conditions. Primary cardiomyopathies (those affecting only or predominantly the heart muscle) have usually been divided into 3 distinct types namely dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy; the dilated and hypertrophic forms are the two major types. Other forms identified more recently, such as arrhythmogenic right ventricular cardiomyopathy, do not fit readily into this classification and differentiation based on genetic or non-genetic origin may now be preferred.[1] The management of the individual forms has been reviewed.[2-15]

In **dilated cardiomyopathy** (previously known as congestive cardiomyopathy) the main finding is systolic dysfunction with dilated and poorly contracting ventricles and a low cardiac output. The right, left, or both ventricles may be affected. Although there may be some ventricular hypertrophy, because of the dilatation there is no overall increase in the thickness of the ventricle walls. Dilated cardiomyopathy may be asymptomatic for some time but the initial manifestations are commonly those of heart failure; chest pain, systemic and pulmonary embolism, and arrhythmias may also occur. Management should generally follow the conventional strategies for heart failure (see p.1165), including ACE inhibitors, diuretics, and beta blockers. Early studies[16-18] with beta blockers in patients with dilated cardiomyopathy found significant improvements in cardiac function and symptoms, together with prevention of clinical deterioration, but failed to show a significant effect on overall mortality. However, a further trial evaluating carvedilol therapy in patients with heart failure, including patients with dilated cardiomyopathy, was terminated early because mortality was significantly reduced in the carvedilol groups[19] and the CIBIS-II trial[20] using bisoprolol was also terminated early because of favourable results. A further long-term study[21] using metoprolol has also reported a significantly higher survival rate in those taking metoprolol for up to 7 years. Although calcium-channel blockers are not usually used in heart failure, symptomatic improvement has also been reported with the calcium-channel blocker diltiazem.[22]

Patients with dilated cardiomyopathy may be at particular risk for systemic or pulmonary thromboembolism, due to blood stasis in the poorly contracting ventricle. Chronic oral anticoagulation has therefore been suggested, although current recommendations generally limit its use to those with atrial fibrillation, previous systemic embolism, or severe left ventricular dysfunction.[2,23] Arrhythmias should be treated as appropriate (see Cardiac Arrhythmias, p.1160); amiodarone may be particularly suitable as it has no negative inotropic effect. Low-dose amiodarone has been tried in patients at high risk of sudden death, but its role has not yet been confirmed.[2,8]

Surgical treatments that restore ventricular shape and function have been tried but cardiac transplantation remains the main method of improving survival in these patients. Other therapies that have been tried include growth hormone, levothyroxine, pentoxifylline, levocarnitine, and immunosuppressants for presumed myocarditis.

In **hypertrophic cardiomyopathy** (previously known as obstructive cardiomyopathy) there is, as the name implies, ventricular hypertrophy but the ventricles are not dilated. This leads to diastolic dysfunction since diastolic filling is impaired by the stiff hypertrophied ventricular walls. It is an inherited condition occurring as an autosomal dominant trait and can occur at any age although presentation during the second decade of life is common. Patients may be asymptomatic or may experience chest pain, syncope, dyspnoea, or arrhythmias. Sudden death associated with emotional stress or exercise is not an uncommon finding and patients should avoid intense exercise. However, overall life expectancy is similar to that of the general population and many patients have little or no disability and do not require treatment.[5,11]

Patients should be investigated for the presence of any arrhythmias and treated appropriately (see Cardiac Arrhythmias, p.1160) although this may not necessarily prevent sudden death. Atrial fibrillation is particularly important and is probably most effectively treated with amiodarone.[4,5,11-13] Anticoagulation should be considered in all patients with sustained atrial fibrillation.[4,5,11-13]

Beta blockers may be used for control of symptoms. They curtail emotion- or exercise-induced tachycardia. Anginal pain is also reduced and syncopal attacks may be prevented. Calcium-channel blockers (usually verapamil) also improve symptoms and exercise tolerance and may be considered in those who continue to have disabling symptoms or who are unable to tolerate beta blockers; however, verapamil may have adverse effects in patients with outflow obstruction and it should be used with caution in such patients.[9-13] In a crossover study,[24] exercise capacity was not improved by either verapamil or nadolol, although most patients preferred one or other of the drugs rather than placebo and quality of life did appear to be improved by verapamil. Other drugs that may provide symptomatic relief include disopyramide, which is used for its negative inotropic effect and is often given with beta blockers. Diuretics may be needed for congestive symptoms but may also reduce cardiac output. Surgery or septal ablation to reduce outflow obstruction may be of benefit in some patients whose symptoms are resistant to drug therapy.[4,5,9-13]

The risk of sudden death is difficult to assess, particularly in asymptomatic patients. Neither beta blockers nor verapamil, as used for possible symptomatic relief, prevent ventricular arrhythmias. However, there is some evidence[25] that high-dose therapy with beta blockers may improve survival in children with hypertrophic cardiomyopathy. Low-dose amiodarone may have a role in high risk patients, but adverse effects may limit its use;[9,11] implantable cardioverter-defibrillators are also used in some patients.[11-13,26]

In **restrictive cardiomyopathy** the filling of the ventricles is impaired, often due to endomyocardial fibrosis, resulting in mostly diastolic dysfunction. Diuretics may improve congestive symptoms but should be used cautiously as they may decrease cardiac output. Arrhythmias should be treated if they are symptomatic and anticoagulation is advised, particularly in patients with atrial fibrillation, valvular disorders, or a low cardiac output.[6]

Management of **arrhythmogenic right ventricular cardiomyopathy** may involve implantation of a defibrillator, the use of antiarrhythmic drugs (notably sotalol), or catheter ablation.[27-30]

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Cardiovascular risk reduction

Atherosclerotic cardiovascular disease includes ischaemic (coronary) heart disease (myocardial infarction and angina pectoris), ischaemic stroke, and peripheral vascular disease. Ischaemic heart disease, in particular, is a major cause of mortality in developed countries, and cardiovascular disease overall is associated with considerable morbidity. The benefits of a number of interventions are well established in patients at high risk of cardiovascular disease, and identification and treatment of such people is therefore an important healthcare strategy.[1-6]

Overall cardiovascular risk depends on a number of factors. Those who are at the highest risk are those with manifestations of atherosclerosis, particularly those who have already had a cardiovascular event such as a myocardial infarction or ischaemic stroke, but also those with symptoms of angina or peripheral vascular disease. The major modifiable risk factors identified through epidemiological studies are tobacco smoking, raised blood pressure, and raised blood-lipid concentrations;[7,8] other established risk factors include age, sex, left ventricular hypertrophy, and family history. Diabetics are also at considerable risk of ischaemic heart disease, even when treated, and aggressive therapy to reduce risk may be appropriate. Obesity, lack of exercise, abnormal blood clotting profile, and hyperhomocysteinaemia have also been associated with increased risk, although their relevance is less established;[9] psychosocial factors may also be involved.[10] Patients with abdominal obesity, hypertension, dyslipidaemia, and glucose intolerance are considered to have the **metabolic syndrome**, and are at increased risk of both cardiovascular disease and diabetes mellitus.[11-13]

The aim of cardiovascular risk reduction is to prevent clinical events occurring by abolishing or reducing any modifiable risk factors that are present. This requires both individual intervention, to identify and treat those at high risk, and also a population approach based on general health promotion and education to reduce the overall levels of risk factors in the general populace. Guidelines[1,3-6] have been published for identification and management at the individual level, including specific guidelines for women[14] and the elderly.[15] Since atheroma development may begin in childhood, approaches to risk reduction should also be considered from an early age,[16] especially in those at high risk.[17]

Lifestyle and dietary modifications are the mainstay of risk reduction, particularly at a population level, and include advice not to smoke, avoidance of obesity, increased exercise, moderation of alcohol intake, and a diet that is low in saturated fat and high in fruit, vegetables, and fish.[1,3-6,18-21] In unselected populations, these efforts probably produce only modest changes in risk factors,[22,23] and while the incidence of ischaemic heart disease is falling in many populations, the WHO MONICA project (Monitoring the Trends and Determinants in Cardiovascular Diseases) found only a weak association between changes in classic risk factors and changes in event rates.[24] In individuals with established modifiable risk factors, drug treatment may also be required. Smoking cessation should be encouraged in all smokers, and specific strategies are discussed on p.2354. Influenza vaccination may reduce the risk of cardiovascular events and has been recommended.[25] Treatment of hypertension and hyperlipidaemias depends on their severity and the patient's overall risk and is discussed under the individual diseases (see p.1171 and p.1169, respectively). Assessment of risk is a complex procedure and risk and treatment tables are available to aid decisions about when to start therapy in patients without established cardiovascular disease.[3,4] Guidelines differ as to the level of risk at which treatment should start; this is a matter of judgement and may depend on economic factors and the balance between benefit and risk of adverse effects in otherwise healthy people. Tight control of blood glucose is important in diabetic patients (see Diabetic Complications, p.433). Other interventions that may be of benefit in some individuals include antiplatelet therapy, reduction of lipids in those with normal lipid concentrations, and ACE inhibitors.

Antiplatelet therapy has been investigated for primary and secondary prevention of various cardiovascular disorders. Numerous studies[26] have established that antiplatelet therapy reduces the risk of subsequent cardiovascular events but that the risk of bleeding is increased, and absolute benefit therefore depends on the individual level of risk. In patients with a previous vascular event, the use of antiplatelet drugs for secondary prevention is well established.[3-6] Aspirin, given in the acute phase and continued long-term, reduces the risk of re-infarction and death after myocardial infarction and should be given indefinitely.[26] Long-term prophylaxis with aspirin also reduces the risk of future serious vascular events, including stroke, in patients who have suffered an ischaemic stroke or transient ischaemic attack,[26-28] regardless of age.[29] A number of studies also support the benefits of antiplatelet drugs for primary prevention of cardiovascular events in individuals at high risk. Aspirin may reduce the risk of first myocardial infarction in patients with stable chronic angina.[30] The Thrombosis Prevention Trial[31] in males at high risk of developing occlusive vascular disease and the Hypertension Optimal Treatment (HOT) trial[32] in hypertensive patients have, more recently, confirmed that aspirin reduces the incidence of myocardial infarction in these at-risk groups, although both studies reported little or no effect on the overall incidence of stroke. The Primary Prevention Project,[33] a study in patients with at least one major risk factor, showed a reduction in cardiovascular mortality and in a composite of cardiovascular events including death, myocardial infarction, and stroke.

Primary prevention in healthy individuals is more controversial, and studies have produced conflicting results. A study in healthy male physicians in the UK[34] found no reduction in the incidence of fatal and non-fatal myocardial infarction in those who had taken aspirin, while a similar study in the US[35] showed a reduction in subjects 50 years of age or older; both showed a slight non-significant increase in the number of disabling strokes which, in the US study, were attributed to cerebral haemorrhage. In women, a large observational study in healthy US nurses[36] indicated that aspirin might reduce the risk of first myocardial infarction, but a randomised trial[37] found no effect on either myocardial infarction or death, although the incidence of stroke was reduced. Meta-analyses[26,38,39] have generally concluded that for most healthy individuals, aspirin therapy is inappropriate.

Aspirin has been the most widely studied antiplatelet drug and appears to be effective over a range of doses (see p.24); however, some patients are resistant to its effects and remain at high risk for cardiovascular events.[40] Other drugs may be used in those intolerant of aspirin, and combination therapy may also be considered. In the CAPRIE study,[41] clopidogrel was shown to be at least as effective as aspirin in reducing cardiovascular events, including myocardial infarction and stroke, in individuals at high risk. In patients with ischaemic stroke, dipyridamole, given alone or with aspirin, is effective for secondary prevention,[42] but use of clopidogrel with aspirin increases the risk of bleeding without reducing the risk of ischaemic events.[43] Clopidogrel with aspirin is of benefit in patients with acute coronary syndromes, but in patients with high cardiovascular risk who do not present acutely the increased bleeding risk appears to outweigh any benefit.[44] ***Oral anticoagulants*** may be more effective than antiplatelet therapy but the risk of bleeding is increased,[31,45] and they are generally only recommended in patients unable to take antiplatelet drugs or in whom they are ineffective. Addition of antiplatelet drugs in patients taking oral anticoagulants for other indications only appears to be beneficial in those with mechanical heart valves.[46]

Lipid lowering therapy has an established role in cardiovascular risk reduction, and the benefits of statins, in particular, have been demonstrated in a wide range of patients. Meta-analyses[47-52] have shown that statins improve outcomes when used for primary or secondary prevention, and that this includes patients with raised or average cholesterol concentrations, women, and older individuals. The absolute benefit depends on the patient's initial cardiovascular risk and the degree of cholesterol reduction achieved,[51] and increased benefit has been reported[53-55] with the use of intensive lipid lowering regimens. Although most recent studies have used statins, fibrates[56] and other lipid lowering drugs may also be effective; beneficial effects for secondary prevention of ischaemic heart disease have been reported for gemfibrozil[57] in men whose primary lipid abnormality was a low HDL-cholesterol level, and for omega-3 marine triglycerides[58] in a Mediterranean population.

There has been concern that there might be an association between low cholesterol concentrations and increased morbidity and mortality from non-cardiac causes including haemorrhagic stroke, cancer, accidents and suicide, and chronic respiratory, liver, and bowel disease.[59-64] Although controlled studies suggest that the risk of haemorrhagic stroke may be increased,[65] meta-analyses have shown that statin therapy reduces both cardiovascular and all-cause mortality,[47,50,51] and that there is no significant increase in non-illness mortality.[66]

The use of ***ACE inhibitors*** has mainly been investigated in individuals with established cardiovascular disease. Studies[67,68] in patients with heart failure suggested that ACE inhibitors also reduced the risk of myocardial infarction, while in the HOPE study,[69] treatment with ramipril significantly reduced the rate of death, myocardial infarction, and stroke in patients at high risk for cardiovascular disease. A reduction in cardiovascular events was also found[70] in patients with stable ischaemic heart disease given perindopril, but not in a trial using trandolapril;[71] the authors suggested that patients in the trandolapril trial may have been at lower risk due to intensive treatment of other risk factors.

The main benefit seen with ACE inhibitors is due to the reduction in blood pressure they cause, but blockade of the renin-angiotensin system may also have other beneficial effects.[72] A study[73] using perindopril, alone or with a diuretic, found that the risk of recurrent stroke was reduced in patients with a history of stroke or transient ischaemic attack, irrespective of whether they had normal or raised blood pressure at study entry. However, a study[74] using enalapril in patients with ischaemic heart disease and normal blood pressure found no significant effect on cardiovascular events and no benefit when compared with amlodipine. ***Angiotensin II receptor antagonists*** have been tried as an alternative to ACE inhibitors; a study[75] comparing losartan with a beta blocker in hypertensive patients with left ventricular hypertrophy found that there was a greater reduction in cardiovascular events with losartan despite a similar effect on blood pressure.

Women have a lower risk of atherosclerotic disease than men of a comparable age, although the difference narrows with increasing age postmenopausally, and the use of ***HRT*** has therefore been investigated. Some epidemiological studies have suggested that HRT lowers the risk of cardiovascular events, although other studies have produced conflicting results (see p.2076). However, randomised trials have failed to confirm a beneficial effect on clinical events[76,77] and HRT is no longer recommended[14] for either the primary or secondary prevention of cardiovascular disease in women.

Specific interventions to reduce the progression of atherosclerosis are discussed on p.1159.

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Cerebrovascular disease

The term 'cerebrovascular disease' may cover disorders of the cerebral circulation such as ischaemic stroke and subarachnoid haemorrhage (see Stroke, p.1185), but is often used to cover the rather vague concept of cerebrovascular insufficiency.

At one time it was believed that the dementia associated with Alzheimer's disease (p.362) was due to cerebrovascular insufficiency and many drugs with vasodilator activity have been tried, but overall there is little convincing evidence of benefit.[1] Ergot derivatives such as codergocrine mesilate and nicergoline have been commonly used; however, any effectiveness is now attributed to their action as metabolic enhancers or nootropic drugs rather than to vasodilatation and their place in therapy has still to be established. The calcium-channel blocker nimodipine has shown benefit in some patients with dementia. Other vasodilators used have included buflomedil, cyclandelate, isoxsuprine, naftidrofuryl, pentoxifylline, and propentofylline.

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Heart failure

Heart failure is a clinical diagnosis made in a patient with a known or suspected cardiac disorder who presents with dyspnoea, fatigue, and oedema (peripheral and/or pulmonary). It may be graded as mild, moderate, or severe depending upon whether symptoms such as dyspnoea and fatigue appear on ordinary physical exertion, on little exertion, or at rest, respectively. Another grading system (that of the New York Heart Association) has four grades (NYHA grades I, II, III, IV), again partly classified on appearance of symptoms in relation to exertion (with grade IV representing the most severe form). The discussion that follows focuses on the chronic form of heart failure; acute heart failure, which may result in cardiogenic shock, is covered under Shock, p.1183.

Heart failure is a common condition[1] and is a consequence of abnormalities in cardiac structure or function. It may result from disorders or diseases of the heart muscle, injury, or cardiovascular stress such as hypertension or valve disorders. Myocardial infarction is one of the leading causes of heart failure, and chronic myocardial ischaemia may also be a contributing factor. Cardiomyopathies, cor pulmonale, infections causing myocardial damage, and cardiotoxicity arising from alcoholism or induced by drugs may also lead to heart failure. The increased demands put on the heart by chronic severe anaemia or hyperthyroidism can also be precipitating factors.

Traditionally, heart failure has been thought of in purely haemodynamic terms, as a condition in which the heart is unable to provide an adequate blood flow to meet the metabolic demands of the body. However, it is now appreciated that compensatory neurohormonal mechanisms play just as important a role in its development.[2-4] Echocardiography, the most useful investigative procedure in patients with heart failure, assesses haemodynamic factors; it allows assessment of ventricular function and ejection fraction, enables structural changes to be observed, and rapidly identifies patients with potentially correctable abnormalities such as valvular disease. Measurement of blood concentrations of brain natriuretic peptide has been suggested as another useful investigation;[5-8] this relates to the neurohormonal mechanisms involved.

Echocardiography may identify dysfunction of either the right or left ventricle (right- or left-sided heart failure), although dysfunction of both ventricles is likely to be present to some extent. In most patients, the predominant finding is that of a dilated and poorly contracting left ventricle, with a reduction in both ventricular ejection fraction and cardiac output. This represents left ventricular systolic dysfunction, and is particularly common in patients with heart failure after myocardial infarction. Patients with symptoms of heart failure but a preserved left ventricular ejection fraction are often described as having diastolic dysfunction or isolated left ventricular diastolic dysfunction;[9-11] cardiac output is usually normal in such patients, but fails to increase in response to exercise. Diastolic dysfunction is more common in the elderly and also occurs in some cardiomyopathies (see p.1163); many patients have both diastolic and systolic dysfunction. Asymptomatic left ventricular dysfunction has been found in some patients, especially those in the early postmyocardial infarction period, and although these patients are not strictly defined as having heart failure, treatment may be given to prevent the development of full symptomatic disease.

Neurohormonal disturbances both result from, and contribute to, the deterioration in ventricular function.[3,4] Myocardial injury or impairment leads to an inability of the ventricles to empty adequately during systole. The resulting ventricular dilatation increases wall tension and initially leads to an increase in contraction while the decrease in cardiac output and blood pressure results in activation of the sympathetic nervous system, leading to an increase in the force and frequency of contraction. Reduced blood flow to the kidney also leads to activation of the renin-angiotensin-aldosterone system, resulting in vasoconstriction and fluid retention. At the same time, an increase in wall stress also occurs in the atria, leading to secretion of atrial natriuretic peptide; this inhibits the release of noradrenaline but also has direct vasodilator and natriuretic actions that lower the haemodynamic load on the heart. Thus, in the short term, compensation for myocardial injury can occur and cardiac output may be maintained. In the long term, these compensatory haemodynamic and neurohormonal mechanisms become ineffective. Ventricular dilatation progresses, the sympathetic nervous system and renin-angiotensin system are persistently activated, ventricular hypertrophy occurs, and ventricular function deteriorates progressively.

Management. Heart failure is a progressively disabling condition associated with considerable morbidity and mortality. Management is aimed therefore not only at providing symptomatic relief, but also at improving prognosis, in terms of both progression and mortality. Reviews[6,12-18] and guidelines[5,7,8] about management have been published; these are generally specific to heart failure due to left ventricular systolic dysfunction. The management of patients with preserved left ventricular ejection fraction, or diastolic dysfunction, is less clear.[8-11,19] In theory, this should differ from systolic dysfunction, but few trials have specifically studied such patients. While many of the early drug trials were based on a clinical diagnosis of heart failure and may have included patients with diastolic dysfunction, therapy for such patients is not established and the following discussion is specific for patients with systolic dysfunction unless stated otherwise.

Treatment involves non-pharmacological and pharmacological interventions. Any underlying cause or exacerbating factors should be corrected, and several general measures may be beneficial. Weight reduction should be attempted in the overweight and moderate salt restriction may be undertaken. In acute heart failure bed rest may become necessary, but in controlled chronic heart failure exercise should be encouraged and specific exercise programmes may be of benefit.[5,8,20,21] Immunisation with influenza and pneumococcal vaccines is advised.[5,7,8,19] Anaemia may be both a cause and a consequence of heart failure and should be treated appropriately (see p.1042). Drug therapy of heart failure is based on the use of diuretics, ACE inhibitors or angiotensin II receptor antagonists, and beta blockers; aldosterone antagonists, cardiac glycosides, and vasodilators may also be used. Surgical interventions and implantable devices may have a role in selected patients.

Diuretics have been the mainstay in the treatment of heart failure, and continue to have an important role. They provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a *thiazide diuretic*, such as *bendroflumethiazide* or *hydrochlorothiazide*, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a *loop diuretic* such as *furosemide* will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade) may be needed in some patients, especially when there is diuretic resistance.[22] A loop diuretic with either a thiazide or *metolazone* is often used,[5,7,19] but severe fluid and electrolyte disturbances may occur, particularly with metolazone; loop diuretics with potassium-sparing diuretics have also been used[7] but should be reserved for patients with hypokalaemia. *Spironolactone* is an aldosterone antagonist and has diuretic and possibly additional effects, as discussed below.

However, diuretics are not a sufficient treatment on their own as clinical stability tends to deteriorate over time. In addition, although a meta-analysis[23] has suggested that diuretics have beneficial effects on symptoms and mortality, there have been no long-term trials assessing the effect of diuretics on prognosis, and drugs that have been shown to have a mortality benefit are also required.

At all stages of chronic heart failure, ***ACE inhibitors*** given orally produce additional clinical benefit to that seen with diuretics. They relieve symptoms such as dyspnoea and improve exercise tolerance. Studies have also shown that ACE inhibitors improve survival and reduce the progression of mild or moderate heart failure to more severe stages.[24] ACE inhibitors may also be beneficial in asymptomatic left ventricular dysfunction.[25] The Studies of Left Ventricular Dysfunction (SOLVD)[26] trials indicated that ACE inhibitors, in this case enalapril, might protect against myocardial infarction, unstable angina, and cardiac death in patients with either symptomatic or asymptomatic heart failure. ACE inhibitors are therefore now recommended[7,8,19] in all patients with symptomatic heart failure due to left ventricular systolic dysfunction, including those whose symptoms are controlled with diuretic therapy. Some guidelines[7,8,19] recommend that ACE inhibitors should be given to all patients with significantly reduced left ventricular ejection fraction, whether or not they have symptoms. Where tolerated, doses should be titrated to those found to be effective in randomised trials, rather than according to symptomatic response.

ACE inhibitors have also been given to patients shortly after suffering myocardial infarction (p.1175) but before the development of symptomatic heart failure and appear to be beneficial. However, it is not yet clear which patients should be given such therapy or when it should be started.

The precise mode of action of ACE inhibitors in heart failure is not completely understood but appears to be a result of both haemodynamic and neurohormonal mechanisms. They are vasodilators and cause both arteriolar and venous dilatation, mainly through reduction of angiotensin II formation. They also attenuate the ventricular dilatation and prevent the ventricular remodelling that develops after a myocardial injury. It has also been suggested that they may protect against the development of arrhythmias,[27] although this has not been confirmed.[28]

Angiotensin II receptor antagonists have been investigated both as alternatives to ACE inhibitors, and also with ACE inhibitors to provide more complete blockade of the renin-angiotensin system. Although an early study[29] suggested that *losartan* improved mortality compared with enalapril, this was not confirmed in the larger ELITE II study,[30] although losartan was found to be better tolerated. Studies with losartan[31] and *valsartan*[32] in patients with heart failure after myocardial infarction also failed to show superiority over ACE inhibitors. However, there were generally fewer adverse effects with angiotensin II receptor antagonists, and a further study[33] found that *candesartan* was of benefit in patients who could not take ACE inhibitors. Guidelines therefore continue to recommend ACE inhibitors as first-line therapy, with angiotensin II receptor antagonists as an alternative, particularly in those unable to tolerate ACE inhibitors.

Dual inhibition of the renin-angiotensin system using ACE inhibitors and angiotensin II receptor antagonists together may be of benefit; both candesartan[34] and valsartan[35] have been shown to reduce hospitalisation for heart failure when added to ACE inhibitors, although the effects on mortality are unclear. Although one study[35] suggested detrimental effects in patients who were also taking beta blockers, this has not been confirmed. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.[7,8,19]

Beta blockers have negative inotropic properties and have generally been contra-indicated in patients with heart failure. However, persistent activation of the sympathetic nervous system is associated with disease progression and the benefit of beta blockers in the long-term management of heart failure is now established.[36-39] It is not clear whether all beta blockers are equally effective.[40] *Bisoprolol*, *carvedilol*, and *metoprolol* have shown positive effects on mortality and morbidity in patients with varying degrees of heart failure and are acceptable therapy, although a meta-analysis[41] in patients with mild to moderate heart failure has suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation. A large study[42] comparing carvedilol with metoprolol also found a greater mortality reduction with carvedilol, although the equivalence of the doses used in the study has been questioned.[43] Another beta blocker with vasodilator properties, *nebivolol*, has shown benefit in elderly patients with heart failure.[44] The role of beta blockers in severe heart failure is less established; a study with *bucindolol*[45] was stopped early because no mortality benefit was found, although carvedilol was found to reduce mortality in a similar study.[46] Beta blockers are now recommended[5,7,8,19] in all patients with clinically stable heart failure due to left ventricular systolic dysfunction and should be given with ACE inhibitors and diuretics. They must be introduced cautiously since symptoms may initially worsen, but if tolerated the doses should then be titrated to those found to be effective in randomised trials. Beta blockers also appear to be of value in heart failure due to idiopathic dilated cardiomyopathy (see Cardiomyopathies, p.1163) and possibly in isolated diastolic dysfunction.

Although the precise neurohormonal mechanisms leading to the development of heart failure are still not clear, there is evidence that raised levels of aldosterone may contribute to the pathophysiology.[47] ACE inhibitor therapy suppresses aldosterone production but this effect is not complete and ***aldosterone antagonists*** have therefore been studied in combination with ACE inhibitors. In patients with severe heart failure, addition of low-dose *spironolactone* to ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation.[48] Another aldosterone antagonist, *eplerenone*, has shown benefit[49] in patients with heart failure after myocardial infarction. Guidelines[7,8,19] therefore recommend that aldosterone antagonists may be added to standard therapy in patients with severe heart failure, and in patients with heart failure after myocardial infarction. In patients with less severe heart failure, their role remains to be established, although a small study[50] has suggested that spironolactone may be of benefit. However, adverse effects may limit use, and all patients taking spironolactone with ACE inhibitors must have their plasma-potassium concentrations closely monitored.

Cardiac glycosides such as *digoxin* or *digitoxin* have an extremely long history in the management of heart failure. They are positive inotropes and increase the contractility of the heart thereby increasing cardiac output. Additional effects in heart failure appear to be due to neuroendocrine suppression such as inhibition of the sympathetic nervous system and indirect arterial vasodilatation.

The benefit of cardiac glycosides in heart failure accompanied by atrial fibrillation is not disputed although beta blockers are generally preferred. However, their role in patients with sinus rhythm has been debated. There is evidence that withdrawal of digoxin from patients taking diuretics (the PROVED trial)[51] or ACE inhibitors (the RADIANCE study)[52] carries a considerable risk of clinical deterioration, and patients stable on such combinations should therefore be continued on them. However, the large DIG study[53] found that, while addition of digoxin to diuretics and ACE inhibitors improved symptoms, there was no effect on mortality, and a systematic review[54] came to a similar conclusion. The role of digoxin therefore appears to be limited, although it may be used in patients who remain symptomatic despite ACE inhibitor, diuretic, and beta-blocker therapy.[5,7,8,19]

Various ***vasodilators*** have been studied in heart failure. There appears to be no specific role for direct-acting vasodilators, but some benefit has been reported with a combination of *isosorbide dinitrate* and *hydralazine*. The rationale for using them together has been that nitrates produce a predominantly venous dilatation whereas hydralazine produces arterial vasodilatation, although other mechanisms may also be involved. Used together, they alleviate peripheral vasoconstriction and produce symptomatic control, including a benefit on exercise tolerance, but are of somewhat limited efficacy in long-term control. A modest improvement in long-term survival has been noted but this effect is less than that seen with ACE inhibitors. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[55] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality. Use of isosorbide dinitrate with hydralazine may be considered in patients with left ventricular dysfunction who are unable to tolerate ACE inhibitors or angiotensin II receptor antagonists;[8] they may also be used as adjuncts in patients who remain symptomatic despite therapy with ACE inhibitors, diuretics, beta blockers, and digoxin.

Calcium-channel blockers, like beta blockers, have generally been contra-indicated in heart failure because of their negative inotropic activity. Despite this, their use as adjuncts has been investigated but studies have failed to show any additional benefit in patients given standard therapy for heart failure. However, in both the PRAISE study[56] (using *amlodipine*) and the V-HeFT III study[57] (using *felodipine*), no adverse effect on morbidity or mortality was found. Amlodipine or felodipine might therefore be suitable as a treatment for angina or hypertension in patients with heart failure, although experience is limited with felodipine in severe heart failure.

Phosphodiesterase inhibitors act as both positive inotropes and vasodilators, a combination of mechanisms that appears particularly attractive in heart failure. Short-term use improves haemodynamic variables, and intravenous *amrinone* or *milrinone* may have a role in patients with severe heart failure unresponsive to other treatment. However, studies with long-term oral phosphodiesterase inhibitors have generally been disappointing. A systematic review[58] found that treatment with oral phosphodiesterase inhibitors was associated with a significant increase in mortality in patients with heart failure, and their use is not therefore recommended.

Antiarrhythmics are not routinely used in heart failure since many have a negative inotropic effect. However, sudden deaths in patients with severe heart failure have been attributed to ventricular arrhythmias,[59] and antiarrhythmics such as *amiodarone*, which is not a negative inotrope, have therefore been tried. A meta-analysis[60] of 5 studies involving 1452 patients with symptomatic compensated heart failure indicated that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality, but a later study[61] in mild to moderate heart failure found no survival benefit. Adverse effects may also limit the use of amiodarone, and it is currently only recommended in patients who also have symptomatic arrhythmias. Implantable devices may be an alternative. A reduction in mortality has been shown[61] with use of implantable cardioverter-defibrillators. Resynchronisation therapy using biventricular pacemakers improves symptoms and reduces mortality from progressive heart failure, although a meta-analysis[62] found that the effect on overall mortality was not significant. Both implantable cardioverter-defibrillators and resynchronisation therapy may therefore be considered in selected patients,[5,7,8,19] and there is evidence that they may be used safely together.[63]

The risk of thromboembolism is increased in heart failure, but the role of routine ***antithrombotic*** therapy is unclear.[64] Anticoagulants should be given to patients who have additional indications, such as atrial fibrillation. The use of *aspirin* in heart failure has been controversial, since there has been some suggestion that it might reduce the benefit of ACE inhibitors. However, such an effect has not been confirmed and guidelines[5,7] therefore recommend that aspirin should be given to heart failure patients with appropriate indications, such as atherosclerosis.

Miscellaneous drugs targeting a number of mechanisms have been tried in heart failure, but in most cases results have been disappointing, and toxicity and increased mortality have also been seen. *Flosequinan*, an arterial and venous vasodilator, and *epoprostenol*, a prostaglandin that causes vasodilatation, have both been associated with increased mortality. Oral sympathomimetic inotropes including *xamoterol*, a partial β_1-adrenoceptor agonist, and *ibopamine*, an oral dopamine agonist, have similarly produced negative effects. Increased mortality has also been reported with long-term intermittent *dobutamine* infusions, although a small study[65] suggested that survival might be increased if patients were also given amiodarone. *Moxonidine*, a centrally-acting antihypertensive, has also been associated with increased mortality. *Endothelin antagonists* such as *bosentan* appear to be ineffective.[66] Disappointing results have also been reported[67] with *tumour necrosis factor antagonists* such as *etanercept* and *infliximab*, and there have been reports[68] of exacerbation of heart failure in some patients.

Other approaches that have been tried include inhibition of neutral endopeptidase, the enzyme that inactivates atrial natriuretic peptide, with drugs such as *candoxatril*. *Omapatrilat*, a dual inhibitor of endopeptidase and angiotensin-converting enzyme, has shown some benefit,[69] but adverse effects may limit its use. *Vasopressin antagonists*, such as *conivaptan* and *tolvaptan*, are also under investigation. Positive haemodynamic effects have been reported with *growth hormone*, although further studies are needed.[70] There is also some evidence that *statins* may be of benefit.[71,72]

Many patients with chronic heart failure have exacerbations of their condition (**decompensated heart failure**) requiring hospitalisation.[73,74] Guidelines for treatment are limited.[75,76] Patients with peripheral or pulmonary oedema due to fluid overload may need intravenous diuretics. Intravenous vasodilators reduce cardiac filling pressure and increase cardiac output and may be needed if symptoms are severe or there is an inadequate response to diuretics. Intravenous nitrates are often used; *nesiritide*, a natriuretic peptide with vasodilator properties, is an alternative, although its effects on mortality are controversial.[77] If cardiac output is low, intravenous inotropes, such as dobutamine or milrinone, may be required. *Levosimendan*, a calcium-sensitiser with both vasodilator and inotropic actions, may also be used. Patients who cannot be weaned from intravenous inotropes may require long-term continuous infusions, either as palliative therapy or as a bridge to transplantation, but regular intermittent infusions may increase mortality and are not generally recommended.[19]

Some patients with **refractory heart failure** may be suitable for ***surgical*** management. Heart transplantation is the optimum surgical therapy but availability is limited and various alternatives have been tried.[78] Left ventricular assist devices may be useful as a bridge to recovery or transplantation, but are not yet established for long-term use. Revascularisation or mitral valve repair may have a role in selected patients, but procedures to augment the heart muscle or reduce ventricular dilatation are not generally recommended since there is limited evidence to support their use.[7]

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High-altitude disorders

Rapid ascent (ascent without time to acclimatise) to high altitudes may produce a spectrum of illness (altitude illness) ranging from the usually benign acute mountain sickness to life-threatening pulmonary oedema and cerebral oedema. Factors influencing the development of altitude illness include rate of ascent, altitude attained, sleeping altitude, and length of stay at altitude. Individual susceptibility is also an important factor. Symptoms of altitude sickness are common at altitudes above 2500 metres (8125 feet), although susceptible individuals may be affected at altitudes as low as 2000 metres (6500 feet).[1-3] Reported incidences at higher altitudes vary, but in general symptoms occur in about 50% of people ascending rapidly to altitudes of over 4000 metres (13 000 feet) and in about 75% of people at 4500 metres (14 625 feet); they are severe (pulmonary oedema or cerebral oedema) in about 4%.

Symptoms of **acute mountain sickness** include headache, which is worse in the supine position, nausea, vomiting, anorexia, lethargy, insomnia, and dizziness. These may develop during ascent, but characteristically occur 6 to 48 hours after arrival at altitude. They are usually short-lived and resolve after a few days at altitude. In a very few people symptoms persist for longer. Chronic mountain sickness, characterised by persistent severe hypoxia and polycythaemia, may develop during prolonged residence at high altitude. The discussion that follows is limited to management of the acute forms. A small proportion of people with acute mountain sickness suddenly deteriorate and develop pulmonary oedema or cerebral oedema, both of which may be life-threatening. Occasionally, pulmonary or cerebral oedema develops without symptoms of acute mountain sickness. Symptoms of **pulmonary oedema** include rapid onset of breathlessness and tachypnoea at rest, and a dry cough which may develop into haemoptysis. Symptoms of **cerebral oedema** include increasing headache, ataxia, mental disturbances, drowsiness and eventually coma. Pulmonary and cerebral oedema frequently occur together.

The **pathogenesis** of altitude illness is not fully understood, and it is not known whether the mechanisms of acute mountain sickness and pulmonary or cerebral oedema differ in nature or merely degree. Hypoxia, a result of the reduced partial pressure of oxygen at high altitudes, is considered the primary stimulus in the development of altitude illness.[1-4] When ascent to high altitudes occurs gradually, the bicarbonate concentration and the pH of extracellular fluid fall progressively. The falling pH increases the sensitivity of chemoreceptors to hypoxia and so permits greater ventilation, thus allowing acclimatisation. Rapid ascent to high altitudes does not allow time for these changes to occur and although the hypoxia stimulates hyperventilation, it produces a respiratory alkalosis which limits the ventilatory response to hypoxia. The hypoxaemia produced leads to neurohumoral and haemodynamic changes that ultimately result in the symptoms of altitude illness.[1] Symptoms are often worse at night when ventilation is reduced leading to a worsening of the hypoxaemia.

Prophylaxis. Altitude illness may be avoided by ascending to high altitudes slowly and thereby allowing time for acclimatisation. This may be achieved by spending several days at 1500 to 3000 metres and avoiding strenuous physical activity, thus allowing the body to adapt to the reduced oxygen pressure and to ascend above 3000 metres without sickness. Acclimatisation may also be achieved when going above 3000 metres by increasing the sleeping altitude by no more than 300 to 600 metres a day and by adding a rest day for every 1000 metres climbed;[1,2,4] slower rates of ascent than this have also been advised.

However, when time for acclimatisation is limited or when abrupt arrival at high altitude (for instance by air) cannot be avoided, drug prophylaxis may be considered. Prophylaxis should also be considered for those individuals who have developed symptoms on ascending to high altitudes on previous occasions.

Acetazolamide is the most frequently used drug[1-4] and has been shown[5,6] to effectively reduce the frequency of symptoms, although the optimum dose is not clear. It produces a mild metabolic acidosis which has the effect of stimulating chemoreceptors to produce an increase in the rate of respiration and tidal volume, and it therefore accelerates the process of acclimatisation. Although acetazolamide has diuretic actions it does not prevent fluid retention or prevent or protect against pulmonary or cerebral oedema. It improves sleep hypoxaemia and quality of sleep, reduces proteinuria, improves exercise performance, and reduces loss of muscle mass, probably by improving oxygen supply to the tissues.[7] Acetazolamide should be taken on the day of ascent or 1 or 2 days before ascent to altitudes above 3000 metres, and continued for several days at the higher altitudes.[1,4] However, there has been concern that the use of acetazolamide to prevent symptoms of acute mountain sickness may encourage too rapid an ascent and perhaps increase the risk of developing pulmonary or cerebral oedema.[7]

Dexamethasone has also been shown[5] to be effective in the prevention of acute mountain sickness. The rationale for its use is to control the mild cerebral oedema thought to contribute to the symptoms of acute mountain sickness, although it has also been shown to prevent the development of pulmonary oedema.[8] However, as the adverse effects associated with dexamethasone are more severe than those associated with acetazolamide, it is not considered suitable for routine prophylaxis; it may have a role if acetazolamide is unavailable or contra-indicated.[1,2,4] If it is used, dexamethasone should be started a few hours before ascent;[4] adverse effects may be fewer if the dose is tapered before stopping.[5]

Nifedipine has been shown to lower pulmonary artery pressure and to protect against pulmonary oedema in people susceptible to the development of pulmonary symptoms at altitude[9] but is not usually recommended for prophylaxis due to the risk of adverse effects.

Other drugs that have shown some benefit in small studies include *spironolactone*,[5] *sildenafil*,[10,11] and sumatriptan.[12] *Ginkgo biloba* has also been used, but a randomised trial[6] found no benefit. A study[13] with inhaled *salmeterol* suggested that it reduced the risk of pulmonary oedema in people considered to be at high risk, while tadalafil reduced the risk of pulmonary oedema but did not prevent acute mountain sickness.[8] *Aspirin* was reported[14] to reduce the incidence of headache in a small study in people with a history of headache at high altitude.

Treatment. Once symptoms of altitude illness develop the course of action should be determined by the severity and nature of the symptoms.

When symptoms are ***mild*** and are not suggestive of pulmonary or cerebral oedema, rest and mild analgesics for headache are usually all that is required; symptoms resolve within a few days and further ascent is possible.[1,2,4] *Acetazolamide* may have some benefit in relieving symptoms[1-3,15] although studies have been small. If mild symptoms of pulmonary oedema are present, such as dyspnoea and cough, rest with supplementary oxygen and further oxygen at night may resolve the symptoms and allow further ascent; however signs and symptoms at altitude may be confusing and it is always safest to descend. The use of hypnotics at altitude is not generally advised since there is a risk that respiratory depression may further reduce oxygen saturation. However, a small study[16] using the short-acting benzodiazepine *temazepam* reported that sleep quality was improved without an alteration in mean oxygen saturation.

When symptoms are ***moderate to severe***, and are progressing or suggestive of cerebral oedema, immediate descent is necessary.[1-4] Descending by as little as 400 to 500 metres is beneficial. Various drugs and therapies have been given to alleviate symptoms and to facilitate descent and should also be used when immediate descent is not possible. For example, *dexamethasone* can reduce the symptoms of acute mountain sickness and might be used in emergencies.[17,18] Portable hyperbaric chambers are available[19] and provide rapid but short-term improvement. They may be useful in combination with dexamethasone, which has a more sustained effect.[20]

If pulmonary oedema is present, oxygen, which relieves hypoxia and reduces pulmonary hypertension, should be given;[1-4] *nifedipine*, which suppresses the exaggerated hypoxic pulmonary vasoconstrictor response seen in people with pulmonary oedema, has provided benefit.[21] Positive-pressure expiration may also be useful;[2] it has the effect of increasing oxygen saturation and partial pressure of carbon dioxide at altitude. Inhalation of nitric oxide has also been reported to improve oxygenation but use may not be feasible at altitude.[22]

People with cerebral oedema should be given *dexamethasone* and oxygen therapy.[3]

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Hyperlipidaemias

Hyperlipidaemia results from a disorder in the synthesis and degradation of plasma lipoproteins. Although the main concern has generally been the overall elevation of plasma lipids (hyperlipidaemia), it is now increasingly recognised that the balance of lipids in the plasma is also important, and the term dyslipidaemia is often used. Dyslipidaemias have genetic and other causes, and are often associated with a high-fat diet. Although patients with hyperlipidaemia may have symptoms that require treatment, the major concern is their increased risk of ischaemic heart disease.

The **lipids** that are of relevance in hyperlipidaemias are cholesterol, an essential component of cell membranes and a precursor of steroid hormone synthesis, and triglyceride, an important energy source. They are transported in the blood as lipoproteins.

Lipoproteins are complex particles[1,2] comprising a hydrophilic coat of phospholipids, free cholesterol, and specific polypeptides termed apolipoproteins (apoproteins) around a core of varying proportions of triglyceride and cholesterol (present as cholesteryl ester). The lipoproteins are characterised by their density, which in general increases as they are metabolised and the proportion of cholesteryl ester to triglyceride increases. Table 1, below, lists the principal lipoproteins and their associated lipids. The lowest density lipoproteins are the **chylomicrons** which transport triglyceride derived from dietary fat, and the **VLDL** (very low-density lipoproteins; pre-β lipoproteins) which transport endogenous triglyceride mainly synthesised in the liver, to peripheral tissues. The triglyceride is hydrolysed in the peripheral tissues by lipoprotein lipase, which is activated by apolipoprotein CII present in the lipoproteins. Both chylomicrons and VLDL are progressively depleted of triglyceride, yielding increasingly dense lipoprotein particles termed 'remnant' particles. Chylomicron remnants are cleared rapidly from plasma by the liver where they are metabolised, releasing free cholesterol. VLDL remnants, which include **IDL** (intermediate-density lipoproteins; broad β-lipoproteins), may also be cleared by the liver or converted to **LDL** (low-density lipoprotein; β-lipoprotein). **HDL** (high-density lipoproteins; α-lipoproteins) are synthesised in the liver and small intestine and have a role in the transport of cholesterol from the peripheral tissues back to the liver, where it is either utilised or excreted in the bile as bile acids and unesterified cholesterol. The majority is reabsorbed from the intestines and a small proportion is excreted in the faeces.

Defining hyperlipidaemia is difficult due to the marked variation in lipid concentrations between different populations. Apparently 'normal' lipid concentrations may still be associated with a significant risk of cardiovascular disease, and this may depend on which lipids are affected. Epidemiological data show a progressive and continuous relationship between plasma-cholesterol concentrations and mortality from ischaemic heart disease. The Framingham Study[3] found a 9% increase in death from cardiovascular disease for each 10 mg/dL (0.26 mmol/litre) rise in total plasma-cholesterol concentration. Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease. The increased risk is due mainly to raised LDL-cholesterol. In contrast, HDL-cholesterol is inversely associated with ischaemic heart disease. Low plasma concentrations of HDL-cholesterol (below 1 mmol/litre or 40 mg/dL) are generally associated with increased risk of ischaemic heart disease, whereas high concentrations are protective.[4] There also appears to be an association between plasma-triglyceride concentrations and risk of ischaemic heart disease.[5] Some triglyceride-rich lipoproteins such as chylomicron remnant particles and IDL are atherogenic and the risk of heart disease increases as triglyceride concentrations increase in patients who also have high total cholesterol and low HDL-cholesterol concentrations. Hypertriglyceridaemia alone (greater than 2.3 mmol/litre or 200 mg/dL) may be an independent risk factor for ischaemic heart disease, but any clinical benefit from intervention to lower triglyceride levels is yet to be established.[6] However, the absolute risk for any individual also depends on other cardiovascular risk factors, including smoking and hypertension, and treatment decisions should in general be based on assessment of overall risk (see Cardiovascular Risk Reduction, p.1164).

Hyperlipidaemias may result from a number of underlying defects and various methods have been used for classification.[7] A simple system is to divide them on the basis of whether raised serum cholesterol (hypercholesterolaemia), triglyceride (hypertriglyceridaemia), or both (mixed or combined hyperlipidaemia) is the predominant abnormality. Alternatively, the Frederickson/WHO method (see Table 2, below) describes them in terms of the lipoprotein abnormality (hyperlipoproteinaemia), although this is less useful clinically. Within these systems, primary hyperlipidaemias are those with an underlying genetic defect, whereas secondary hyperlipidaemias are caused by another disease state or by drug therapy. Primary and secondary causes of hyperlipidaemia may co-exist.

Primary hyperlipidaemias (see Table 3, p.1170) may be monogenic, relating to a single genetic defect, but much more commonly they are due to the interaction of a number of genes with dietary and other factors (polygenic). Individuals with common, polygenic (multifactorial) hypercholesterolaemia tend to have only mild or moderate elevations of plasma-cholesterol, whereas those with monogenic hyperlipidaemias tend to have much higher plasma-lipid concentrations.

Secondary hyperlipidaemias may have various causes. Diseases producing hypertriglyceridaemia include diabetes mellitus, chronic renal failure, and bulimia. Hypercholesterolaemia can occur in hypothyroidism, nephrotic syndrome, biliary obstruction, and anorexia nervosa. Drugs that may produce hypertriglyceridaemia and/or hypercholesterolaemia include thiazide diuretics (in high doses), beta blockers, corticosteroids, and antivirals in patients with HIV infection. Excessive alcohol intake may produce elevated plasma-triglyceride concentrations.

The degree of hyperlipidaemia seen in patients with either primary or secondary hyperlipidaemia is influenced by various factors, including, importantly, diet. A diet rich in saturated fat and cholesterol and poor in fibre can produce hypercholesterolaemia. Obesity further predisposes to hyperlipidaemia. Other factors that may influence lipid concentrations include pregnancy, lack of exercise, and smoking. After myocardial infarction cholesterol levels may be temporarily reduced for several weeks; therefore, to measure the patient's usual level of cholesterol, blood samples should be taken within a few hours of the infarction.

The majority of people with hyperlipidaemia have plasma-lipid concentrations that are only mildly or moderately elevated, and they exhibit no **clinical symptoms**. At the other end of the spectrum, severe hypercholesterolaemia can cause tendon, tuberous, or planar xanthomas, xanthelasma, and arcus corneae; it is also associated with an increased risk of ischaemic stroke. Severe hypertriglyceridaemia can cause acute severe abdominal pain due to pancreatitis; hepatic and splenic enlargement, eruptive xanthomas, and lipaemia retinalis may also occur. However, the main concern in patients with hyperlipidaemias is the increased risk of ischaemic heart disease. In patients with very severe hypercholesterolaemia, such as familial hypercholesterolaemia, this may occur at a very young age; in those with the heterozygous form onset of heart disease during their 20s or 30s is not unusual, and in the rarer homozygous form ischaemic heart disease may develop by the age of 10.

Treatment of hyperlipidaemias. In patients with clinical symptoms, treatment is indicated to promote the regression or non-progression of disfiguring xanthomas, or to prevent attacks of acute pancreatitis in those with severe hypertriglyceridaemia. The main aim of treatment, however, particularly in patients with only mildly elevated lipids, is to reduce the risk of ischaemic heart disease.[1,8-12]

Since the relationship between plasma-cholesterol concentrations and ischaemic heart disease is continuous, the level at which treatment with lipid regulating drugs should be started has been widely debated. Guidelines recommend that the decision to treat should be based on the overall risk profile of the patient and that other risk factors

Table 1. Principal lipoproteins and associated lipids.

Lipoprotein	Lipid
Chylomicron	Triglyceride
VLDL	Triglyceride
IDL	Cholesterol and triglyceride
LDL	Cholesterol
HDL	Cholesterol

Table 2. Classification of hyperlipoproteinaemias.

		Plasma lipids affected	
WHO classification	Lipoproteins elevated	Cholesterol	Triglyceride
I	Chylomicrons	Normal or elevated	Elevated
IIa	LDL	Elevated	Normal
IIb	LDL and VLDL	Elevated	Elevated
III	VLDL with abnormally high cholesterol content	Elevated	Elevated
IV	VLDL	Normal or elevated	Elevated
V	Chylomicrons and VLDL	Elevated	Elevated

Table 3. Primary hyperlipidaemias.

	Lipoprotein Abnormality (WHO type)	Prevalence	Typical lipid concentrations (mmol/L) Cholesterol	Triglyceride	Risk of IHD	Pancreatitis
Common (polygenic) hypercholesterolaemia	IIa or IIb	Very common	6.5 to 9.0	< 2.3	+	–
Familial hypercholesterolaemia	IIa or IIb	Moderately common	7.5 to 16.0	< 2.3	+++	–
Familial hypertriglyceridaemia	IV or V	Common	6.5 to 12.0	10 to 30	?	++
Familial combined hyperlipidaemia	IIa, IIb, IV, or V	Common	6.5 to 10.0	2.3 to 12.0	++	–
Familial dysbetalipoproteinaemia or remnant hyperlipoproteinaemia	III	Uncommon	9.0 to 14.0	9.0 to 14.0	++	+
Abnormal lipoprotein lipase function	I	Rare	< 6.5	10.0 to 30.0	–	+++

+ = elevated risk; – = no risk; ? = uncertain risk; IHD = ischaemic heart disease

should also be treated (see Cardiovascular Risk Reduction, p.1164). Specifically, British guidelines[13] advise that all high-risk patients should have drug therapy, including patients with established cardiovascular disease, most diabetics, patients with a ratio of total plasma cholesterol to HDL-cholesterol 6.0 or higher, and those with familial dyslipidaemias. In all cases, the target for therapy is total cholesterol below 4.0 mmol/litre and LDL-cholesterol below 2.0 mmol/litre; alternatively, a 25% reduction in total cholesterol and a 30% reduction in LDL-cholesterol should be the target if this results in a lower concentration. European guidelines[14] suggest that diabetics and patients with established cardiovascular disease should have a target of total cholesterol below 4.5 mmol/litre (and below 4.0 mmol/litre if feasible) and LDL-cholesterol below 2.5 mmol/litre (and below 2.0 mmol/litre if feasible); patients with total cholesterol above 8 mmol/litre or LDL-cholesterol above 6 mmol/litre should be treated irrespective of their other risk factors. US guidelines[2,15] suggest that drug treatment should be considered if the LDL-cholesterol level is 190 mg/dL or higher. For patients with 2 or more risk factors, drug therapy should be considered if the LDL-cholesterol is 160 mg/dL or higher, and for those with existing cardiovascular disease, diabetes mellitus, or particularly high risk, drug therapy should be considered if LDL-cholesterol is 130 mg/dL or higher. The US guidelines also give target LDL-cholesterol levels of less than 160 mg/dL, less than 130 mg/dL, and less than 100 mg/dL, respectively, for the three risk groups. However, it has been suggested[16] that treatment may be appropriate in some very high risk patients at LDL-cholesterol concentrations below 100 mg/dL and that a goal of below 70 mg/dL may be reasonable; others consider that there is little good clinical evidence to support such targets.[17] Although low HDL-cholesterol is an additional risk factor, the benefits of raising HDL-cholesterol are not established and no target is therefore specified in the current guidelines.

The main methods of treating hyperlipidaemias are dietary and lifestyle changes and the use of lipid regulating drugs.[2,13-15] Some surgical and other procedures may also be used in familial hypercholesterolaemia (see below).

Dietary therapy should be started in all patients with hyperlipidaemia with the aim of weight reduction in the obese and a reduction in total fat intake. Dietary recommendations[13,15] include a reduction in saturated fatty acids, restriction of *trans* fatty acids, increased consumption of fish or other sources of long-chain n-3 polyunsaturated fatty acids, and increased intake of fruit and vegetables; the intake of cholesterol and n-6 polyunsaturated fatty acids should be restricted. Increased physical exercise is also recommended. Moderation of alcohol intake is advised, particularly in patients with hypertriglyceridaemia, in whom alcohol may precipitate pancreatitis. However, more rigorous diet than that often recommended may be necessary for diet alone to be of much value,[18] and most patients will require drug therapy to achieve target lipid concentrations. Patients at low cardiovascular risk should have a trial of dietary therapy before drugs are started, but in those with established cardiovascular disease or major risk factors drug therapy and dietary changes may be started at the same time.

The principal groups of **lipid regulating drugs** (hypolipidaemic drugs) are the statins, fibric acid derivatives and related compounds, bile-acid binding resins, nicotinic acid and its derivatives, the omega-3 marine triglycerides, and ezetimibe.[1,10-12,19,20] *Statins* (HMG-CoA reductase inhibitors) reduce cholesterol by stimulating an increase in LDL-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase HDL-cholesterol. They are generally considered to be the most effective lipid lowering drugs. *Fibrates* inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of VLDL; they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia. *Bile-acid binding resins* lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol. *Nicotinic acid* inhibits production of VLDL in the liver; it lowers LDL-cholesterol and triglycerides and increases HDL-cholesterol, but adverse effects may limit its use. *Omega-3 fatty acids* primarily reduce triglycerides. *Ezetimibe* is a cholesterol absorption inhibitor and reduces intestinal absorption of both dietary and biliary cholesterol.[21] *Dietary supplements* containing soluble fibre, such as guar gum or ispaghula, or plant stanols or sterols, may also be used to reduce cholesterol absorption; garlic preparations and other supplements have also been used, although their role is not established.[22] *Other drugs* that have been tried include cholesteryl ester transfer protein inhibitors, which increase HDL; however, they have not yet been shown to have clinical benefits,[23] and development of torcetrapib was stopped as it was found to increase mortality. In postmenopausal women, oestrogen therapy reduces lipid concentrations, but the adverse effects may outweigh any benefit (see Effects on the Cardiovascular System, p.2073); soya protein may have a similar effect.

Choice of therapy ideally depends upon the lipid profile of the individual patient since the drug groups differ in their effects on the different lipid components. In practice, most patients have common, polygenic hypercholesterolaemia, and can be treated effectively with statins as first-line therapy. Bile-acid binding resins or nicotinic acid may be alternatives, but are generally less well tolerated. Ezetimibe or fibrates may also be used, but are generally only recommended when patients are unable to take statins.[24,25] Combination therapy may be required in some patients to reach target lipid concentrations, but the risk of adverse effects is increased in patients taking statins and fibrates together (see Effects on Skeletal Muscle under Adverse Effects of Simvastatin, p.1391). In patients with hypertriglyceridaemia, statins or fibrates may be used, although fibrates should only be given first-line in severe, isolated hypertriglyceridaemia;[25] resins should not be used alone since they may increase triglyceride concentrations.

Patients with the less common familial dyslipidaemias[26] generally have higher lipid concentrations and require more intensive therapy. Specific treatment strategies are as follows:

- ***FAMILIAL HYPERCHOLESTEROLAEMIA.*** Patients with familial hypercholesterolaemia usually have very high plasma-cholesterol concentrations, which rarely respond adequately to diet alone and drug therapy is therefore often necessary in this high-risk group. Aggressive therapy may lead to regression of atherosclerotic lesions.[27] The first-line drugs are the statins. In severe cases combination therapy is usually required, such as a statin with a bile-acid binding resin, ezetimibe, or nicotinic acid. A low dose of the bile-acid binding resin may be sufficient. In the homozygous form of familial hypercholesterolaemia there may be a complete lack of functional LDL-receptors and drugs that act by increasing LDL-receptors, such as statins and bile-acid binding resins, may be less effective. However, statins may be useful as adjunctive therapy in those patients who have some LDL-receptor function. In some forms of familial hypercholesterolaemia, and where plasma-cholesterol concentrations are very high, plasma-triglyceride concentrations may also be raised. In these cases a fibric acid derivative or nicotinic acid may be effective, and in more severe cases the combination of a bile-acid binding resin together with a fibric acid derivative or a statin may be used. In patients with the homozygous form liver transplantation is the most definitive treatment. Plasma exchange (weekly or fortnightly) or more selective procedures such as LDL apheresis, including the use of heparin to precipitate LDL (the HELP system—Heparin Extracorporeal LDL Precipitation) may also be used in combination with lipid regulating drugs. Gene therapy is under investigation as a treatment for familial hypercholesterolaemia.
- ***FAMILIAL HYPERTRIGLYCERIDAEMIA.*** In patients with familial hypertriglyceridaemia dietary therapy is generally adequate, but drugs may be required if there is a high risk of acute pancreatitis or if there is a family history of atherosclerosis. The risk of acute pancreatitis is high when plasma-triglyceride concentrations are above 20 mmol/litre. Nicotinic acid or the fibric acid derivatives, particularly gemfibrozil, are generally recommended and may be used in combination in severe cases. Omega-3 marine triglycerides may also be of value. In severe intractable hypertriglyceridaemia, particularly type V hyperlipoproteinaemia, norethisterone has been suggested for women or oxandrolone for men.
- ***FAMILIAL COMBINED HYPERLIPIDAEMIA.*** Drug therapy may be used in patients who do not respond to dietary therapy alone. The choice will depend on the predominant lipid abnormality. A statin is the first choice, particularly in cases where hypercholesterolaemia is predominant. A fibric acid derivative may be used when hypertriglyceridaemia predominates, and nicotinic acid is useful where plasma concentrations of triglyceride and cholesterol are raised to a similar degree. Bile-acid binding resins should not be used alone since they can aggravate hypertriglyceridaemia, but they may be useful with a triglyceride-lowering drug in some patients. Treatment with a combination of drugs that lowers both cholesterol and triglyceride concentrations may be required in some patients especially in those with markedly raised plasma concentrations of triglyceride or cholesterol, as treatment of these patients with drugs effective against only the predominant lipid may produce a rise in the plasma-concentrations of the other lipid. The choice of treatment in these cases is largely empirical as responses are not always predictable in individual patients.
- ***FAMILIAL DYSBETALIPOPROTEINAEMIA*** (remnant hyperlipoproteinaemia; remnant particle disease). In this lipid

disorder the degree of hyperlipidaemia is usually severe and, although it may respond remarkably to dietary therapy, drug treatment is usually necessary. Fibric acid derivatives, statins, or nicotinic acid may be used.

- *ABNORMAL LIPOPROTEIN LIPASE FUNCTION* (chylomicronaemia). Drug therapy is largely ineffective, although fibrates and nicotinic acid may have modest effects. The condition is treated with severe restriction of dietary fat; the diet may be supplemented by medium-chain triglycerides to improve tolerability, but their value is controversial.[8]

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Hypertension

Hypertension, particularly essential or primary hypertension, is widespread. Although it is usually asymptomatic, hypertension is a major risk factor for cardiovascular morbidity and mortality, especially that associated with stroke, and control of hypertension is therefore a major aspect of cardiovascular risk reduction. National[1-3] and international[4,5] guidelines on management have been published, but several areas of controversy remain,[6,7] and in many patients hypertension continues to be difficult to treat.[8]

Definitions. The term ***blood pressure*** generally means arterial blood pressure, that is, the pressure of the blood on artery walls. It is usually measured indirectly in the brachial artery just above the elbow using an appropriately calibrated sphygmomanometer[9] and is expressed in mmHg. Two measurements are made:

- *systolic* or maximum blood pressure (achieved during ventricular contraction of the heart)
- *diastolic* or minimum blood pressure (achieved during ventricular dilatation)

Hypertension means a higher than 'normal' blood pressure; it has been defined as the level of blood pressure above which intervention has been shown to reduce the associated cardiovascular risk. Many factors influence blood pressure, resulting in a bell-shaped distribution curve in the general population, and in consequence it is difficult to define an absolute norm.

Classification and subsequent treatment decisions should be based on blood pressure measurements taken on several occasions over a period that varies according to the severity of hypertension. Ambulatory blood pressure monitoring may have advantages in some situations[1,2,5,9,10] and automated devices for home monitoring may also have a role.[1,5,9] However, home and ambulatory blood pressures tend to be lower than those measured in healthcare settings, and different thresholds for normal and abnormal values apply.[1,5,9,10] Guidelines generally use conventional blood pressure measurements to determine treatment decisions since this is the basis of most outcome studies.

Normal adult blood pressure has been arbitrarily defined as a systolic pressure below 130 mmHg together with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg), but more recent studies have suggested that optimal blood pressure, in terms of cardiovascular risk, may be lower than this. US guidelines[2] now define normal blood pressure as below 120/80 mmHg, while European[5] and British[1] guidelines classify this as optimal. Blood pressures of 130–139/85–89 mmHg are regarded as high normal[1,5] or are included in the classification of *pre-hypertension*.[2] Although hypertension was formerly defined in terms of diastolic blood pressure alone, it is now recognised that systolic pressure is also important in determining risk, and current guidelines give equal emphasis to both.

Blood pressure above 140 mmHg systolic, and/or 90 mmHg diastolic is generally considered to represent hypertension. Although classifications of *mild*, *moderate*, and *severe hypertension* have been widely used, these terms may be misleading since absolute cardiovascular risk is more important in determining the need for treatment and depends on other factors in addition to blood pressure. Most guidelines[1,4,5] therefore use a grading system to classify hypertension, as follows:

grade 1: 140–159/90–99 mmHg;

grade 2: 160–179/100–109 mmHg;

grade 3: ≥180/≥110 mmHg.

In the US guidelines,[2] stage 1 hypertension corresponds to grade 1, whereas stage 2 includes both grades 2 and 3.

When systolic and diastolic pressure fall into different categories the higher value is used for classification purposes.

The term *malignant* or *accelerated hypertension* has been used for rapidly progressing severe hypertension associated with retinopathy and often renal impairment, but this is now generally considered part of the spectrum of hypertensive crises (see below).

Isolated systolic hypertension occurs mainly in the elderly and has been defined[1,5] as systolic pressure of 140 mmHg or more and diastolic pressure under 90 mmHg.

Origins. In the majority of cases of hypertension the cause is unknown, and such *primary* or *essential* hypertension is probably multifactorial in origin, with genotype, as well as external factors such as diet and body-weight, playing a role.[11,12] Hypertension may also be associated with surgery or pregnancy and is prevalent in diabetics. In a limited number of cases hypertension is *secondary* to some other condition, such as renal disease, Cushing's syndrome, phaeochromocytoma, or the adverse effects of drugs such as oestrogens, and such causes may be suspected particularly in resistant or malignant hypertension.[13] Although treatment of the underlying condition will generally be desirable, the resultant hypertension will not necessarily be abolished by this.

Management of hypertension. Most of what follows relates to primary or essential hypertension in adults. Hypertensive crises, hypertension in children, and hypertension associated with surgery, diabetes, renal disease, or pregnancy are also discussed below under separate headings.

Hypertension may be discovered because of adverse vascular events, especially in the eyes, brain, kidneys, or heart, but is more often asymptomatic and only discovered on routine measurement of blood pressure. Once diagnosed, decisions have to be made about the need for treatment. It is well-established that hypertension is a risk factor for the development of stroke, heart failure, and renal damage, and to a lesser extent ischaemic heart disease, and a reduction in blood pressure is generally beneficial, although mortality remains higher than in non-hypertensives.[14] However, it is important to assess hypertension in the context of overall cardiovascular risk, including the presence of target-organ disease, such as left ventricular hypertrophy or renal disease, associated conditions such as atherosclerosis or diabetes, and other risk factors such as hyperlipidaemia or smoking. Treatment of hypertension may involve both non-pharmacological and pharmacological interventions to reduce blood pressure, as well as assessment and treatment of any other cardiovascular risk factors (see Cardiovascular Risk Reduction, p.1164); any co-existing diseases should also be treated. Differences in the detail of guidelines on the management of hypertension reflect varying judgements on the justification for intervention and the relative risks and benefits of different treatments.

Non-pharmacological treatment. Adopting a healthy lifestyle is beneficial for all individuals, and any patient with raised blood pressure should be encouraged to make lifestyle changes that will reduce their cardiovascular risk. Some of these changes may also reduce blood pressure,[11,15,16] and in those who are at low overall risk no other treatment may be needed; a trial of non-pharmacological treatment is recommended in most patients before starting drug therapy,[1,2,4,5] but should not unnecessarily delay treatment, especially if the patient is at high risk.[1,5] Interventions that have been shown to reduce blood pressure include:

- reduction in excess weight
- reduction in excess alcohol consumption
- reduction in sodium intake
- adequate exercise
- reduced fat intake
- increased fruit and vegetable consumption

Other interventions that have been tried, but with less evidence of benefit, include:

- increased intake of potassium, magnesium, and calcium
- increased polyunsaturated fat intake with reduced saturated fat intake
- relaxation therapies for stress reduction.

These lifestyle changes may also be promoted in the population as a whole, or in individuals most likely to develop hypertension, in strategies for the *primary prevention* of high blood pressure.[17]

Pharmacological treatment. The main decisions in drug treatment relate to the blood pressure at which therapy should be begun, the target blood pressure, and the most appropriate drug regimen to use. Controversies exist in all these areas.

When to intervene with antihypertensive drugs depends on factors including both the measured blood pressure and the overall cardiovascular risk.

- Patients with grade 3 hypertension (180/110 mmHg or higher) should receive prompt drug treatment.[1,2,5]
- In grade 2 hypertension, drug therapy is indicated if blood pressure remains at 160/100 mmHg or higher after a period of lifestyle modification, which varies depending on the overall level of risk;[1,2,5] prompt drug therapy is advised for those at high or very high risk.[5]
- For patients with grade 1 hypertension, the need for treatment is less well established; those with associated risk factors should be given drug therapy if lifestyle modification is inadequate, but some guidelines suggest that antihypertensives are not indicated in those at lower risk,[1] or state that priority should be given to those at highest risk.[4]
- Lower thresholds may apply in patients with renal disease or diabetes (see below), but whether there is any benefit in treating uncomplicated patients with prehypertension is controversial.[18]

For *elderly patients* (over 60 years) there is evidence[19-22] to support the benefit of treating hypertension, including isolated systolic hypertension,[23] and this applies up to at least 80 years of age, suggesting a strict age limit to drug therapy is inappropriate. Guidelines therefore generally recommend that treatment decisions should not be based on age, although slower titration of drugs has been suggested[5] in older patients since they may be more susceptible to adverse effects. In the very old (those over 80 years) the benefit of starting therapy is less clear,[21,23,24] although a study[25] in patients aged 80 years and over found a reduction in mortality; those already being treated should continue.[1,5]

Target blood pressures are also controversial. There has been concern that over-aggressive reduction of diastolic pressure might increase the risk of ischaemic heart disease,[26] although a meta-analysis[27] suggested that any increased mortality at low blood pressures was not linked to antihypertensive therapy but may have been due to poor health as a cause of low blood pressure. The HOT study[28] found that effective control to maintain the diastolic pressure below 90 mmHg (at about 85 mmHg) reduced the rate of cardiovascular events, but lower pressures (of around 70 mmHg) did not provide any further benefit, while a meta-analysis[29] found no evidence of a threshold for treatment benefit down to a blood pressure of at least 115/75 mmHg. Target blood pressures of below 140/90 mmHg[2,5] or below 140/85 mmHg[1] are now recommended; lower targets may be considered if tolerated by the patient, particularly in patients at high risk.[5] A lower target of below 130/80 mmHg has also been suggested for patients with established ischaemic heart disease,[30] and lower targets may also be appropriate in diabetics and patients with renal disease (see below).

The drug regimen may include drugs with differing pharmacological actions; the antihypertensive mechanism is not fully understood in all cases. Historically, thiazide diuretics and beta blockers have been the mainstay of drug therapy for hypertension, but calcium-channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and alpha blockers are now also widely used.

Choice of initial therapy depends on antihypertensive efficacy, safety, and long term effects on morbidity and mortality.[31,32] Studies such as the TOMHS[33] (comparing chlortalidone, acebutolol, amlodipine, enalapril, and doxazosin), and a similar study[34] (comparing hydrochlorothiazide, atenolol, diltiazem, captopril, prazosin, and clonidine), have shown that the main types of antihypertensive drug reduce blood pressure to a similar extent and in a similar proportion of patients, although the response may also depend on individual factors such as age[35] and race.[36,37] Angiotensin II receptor antagonists also effectively reduce blood pressure. However, it is now generally acknowledged that a single drug is unlikely to control blood pressure adequately and most patients will require more than one drug to reach their treatment target. Tolerance of the drug groups is also similar, although there has been concern about the metabolic effects of thiazides and beta blockers. Alpha blockers (specifically doxazosin[38]) have been associated with an increased risk of heart failure, which may limit their use. The safety of short-acting dihydropyridine calcium-channel blockers has also been questioned, and they are no longer generally recommended for hypertension (see Effects on Mortality under Adverse Effects of Nifedipine, p.1350); long-acting dihydropyridines, however, are of established benefit.[39]

All of the main drug groups are therefore established as effective antihypertensives, but their effects on long-term mortality and morbidity have been less clear. The different drug groups have differing effects on several surrogate outcomes, such as left ventricular hypertrophy[40] and endothelial dysfunction,[41] but the clinical significance of this has not been established, although there is some evidence[42] that regression of left ventricular hypertrophy is associated with a reduction in clinical events. Diuretics (particularly thiazides) and beta blockers were the first drugs to demonstrate an effect on mortality in long-term outcome studies and have therefore been preferred for initial therapy. However, long-term studies with other drug groups have now been performed, and have generally shown comparable effects on mortality and morbidity. A meta-analysis[43] concluded that there was little difference in overall cardiovascular outcomes for regimens based on ACE inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, beta blockers, or diuretics, suggesting the major benefit of treatment related to reduction of blood pressure rather than to specific properties of the individual drugs. However, cause-specific outcomes did differ between the drug groups, and some large studies have also questioned the benefit of certain regimens. A study[44] (ALLHAT) comparing treatment based on a diuretic (chlortalidone), an ACE inhibitor (lisinopril), or a calcium-channel blocker (amlodipine), found no differences in all-cause mortality, but another arm of the study based on an alpha blocker (doxazosin) was stopped early due to an excess of heart failure in this group.[38] Another study[45] (ASCOT-BP-LA) was also stopped early when results suggested that a regimen of amlodipine with addition of perindopril if required, prevented major cardiovascular events more effectively than a regimen of atenolol with addition of a thiazide if required. However, blood pressure reductions were greater in patients receiving the amlodipine-based regimen, making the significance of the results unclear. Subsequent meta-analyses[37,46,47] have, however, found that beta blockers may be less effective than the other major groups of antihypertensives, particularly in older patients,[37] and their role in initial therapy has therefore been questioned.

In general, guidelines acknowledge that lowering blood pressure appears to be more important than which drug is chosen for initial therapy, and that most patients will require a combination of drugs, making the initial choice less important. Thiazide diuretics, ACE inhibitors, angiotensin II receptor antagonists, or calcium-channel blockers may all be used, and choice should take into account individual patient characteristics, including age, ethnicity, contra-indications or compelling indications for specific drugs, adverse effects, and relative cost-effectiveness.[1,2,4,5] Strict guidance is therefore not generally given, although for uncomplicated patients US[2] and international[4] guidelines recommend *thiazide diuretics* as first-line, whereas in the UK[3] diuretics or *calcium-channel blockers* are recommended for older patients (55 years or over) and black patients, while in younger, non-black patients *ACE inhibitors* or *angiotensin II receptor antagonists* are preferred. Compelling indications in all the guidelines include the use of ACE inhibitors or angiotensin II receptor blockers in patients with nephropathy, diuretics or calcium-channel blockers in elderly patients, and beta blockers in patients who have had a myocardial infarction. The use of *beta blockers* as initial therapy in patients who have not had a myocardial infarction remains controversial; UK guidelines[3] issued since the publication of ASCOT-BPLA suggest that they should be avoided except in younger patients who are unable to take ACE inhibitors or angiotensin II receptor antagonists and in women of child-bearing potential, whereas more recent European guidelines[5] allow their use in all patients other than those at risk of metabolic effects.

Having decided what drug to use, treatment is started at the lowest recommended dose. If this is ineffective or only partially effective the dose may be increased (except in the case of thiazide diuretics where there is generally no additional benefit, but more adverse effects); alternatively another first-line drug may either be substituted (*sequential therapy*) or added (*combination therapy*). Two-drug combinations will control blood pressure in a higher proportion of patients and may be necessary in most patients to achieve optimal levels, although the effects of the two drugs may not be fully additive. Combination therapy also allows lower doses of the individual drugs to be used with a consequent reduction in adverse effects. Initial treatment with a low-dose combination may be considered in some patients.[2,5] The most effective combinations involve drugs that act on different physiological systems. Appropriate combinations therefore include:

- diuretic plus beta blocker
- diuretic plus ACE inhibitor
- diuretic plus angiotensin II receptor antagonist
- calcium-channel blocker plus ACE inhibitor
- calcium-channel blocker plus angiotensin II receptor antagonist
- calcium-channel blocker (except verapamil) plus beta blocker

Alpha blockers may be used with any of the other classes but are usually reserved for third-line therapy unless specifically indicated for another reason. A 3-drug combination is often required, especially in severe hypertension. In patients who maintain an elevated diastolic blood pressure despite triple therapy the possibility of secondary hypertension should be considered, although factors such as non-compliance, NSAID use, or alcohol abuse may contribute to resistance.[7,8]

Other classes of antihypertensive drugs that are sometimes used include: centrally acting drugs such as clonidine, methyldopa, and the less sedating moxonidine; direct-acting vasodilators such as hydralazine and minoxidil; the aldosterone antagonist, eplerenone; and the renin inhibitor, aliskiren. Older drugs like the adrenergic neurone blocker guanethidine and the rauwolfia alkaloid reserpine are rarely recommended now. Endopeptidase inhibitors and endothelin antagonists are among various drug groups that are under investigation.

Withdrawal of drug treatment. It has been standard teaching that drug treatment for hypertension is continued indefinitely, but there have been some reports of successful withdrawal in selected patients.[48-50] If this is attempted, blood pressure must be closely monitored and lifestyle measures should be continued indefinitely.[3,5]

Hypertension in children. Hypertension is less common in children than in adults but the incidence may be increasing in parallel with an increase in childhood obesity,[51] and guidelines for diagnosis and management have been published.[52] Lifestyle measures are the mainstay of treatment, particularly in children with less severe hypertension and no evidence of target organ damage, since the benefits of treatment and the risks of long-term drug therapy are not established. However, drug treatment may be required in some cases and should generally be based on individual patient characteristics.

Hypertensive crises. Patients with severe hypertension may be divided into those in whom there is evidence of rapid or progressive CNS, cardiovascular, or renal deterioration (hypertensive *emergencies*) and those with no evidence of target-organ damage (urgent hypertensive crises or hypertensive *urgencies*).[2,53-57] In the former case the goal is a reduction in mean arterial blood pressure by 25%, or a fall in diastolic blood pressure to 100 to 110 mmHg, over a period of several minutes to several hours depending on the clinical situation; intravenous therapy is often required although oral therapy may be adequate. In the latter case a drastic reduction in blood pressure is inappropriate and oral therapy is preferred, with the aim of a reduction in blood pressure over several hours to days. In both situations too rapid a reduction of blood pressure may be detrimental and may lead to cerebral infarction and blindness, to deterioration in renal function, and to myocardial ischaemia.

If *oral treatment* can be given and there is no evidence of ongoing target-organ damage, beginning standard antihypertensive therapy is appropriate, although the patient should be closely monitored. Short-acting drugs with a rapid effect are often used, although caution is required since they may lower blood pressure abruptly. Drugs that have been recommended[2,55,56] include the beta blocker labetalol, the centrally acting drug clonidine, the ACE inhibitor captopril, and the alpha blocker prazosin (especially when there are increased circulating catecholamines); calcium-channel blockers such as amlodipine, felodipine, and isradipine may also be suitable.[56] Diuretics may have a role in volume overload but many patients with hypertensive crises are volume depleted and diuretics may therefore be less appropriate in the initial stages. Nifedipine and captopril have been given sublingually for a faster onset, but there appears to be no clearly defined clinical advantage for this route and it is generally considered that nifedipine should not be used.[2,54,56,58]

In the emergency situation, when *parenteral therapy* is required, choice of therapy depends on concomitant clinical conditions.[53,54,56] Sodium nitroprusside given by intravenous infusion, has most often been the drug of choice, but close monitoring is required as toxicity may be a problem.[2,53,55,56] Intravenous labetalol, nicardipine, or fenoldopam are suitable alternatives in most situations. Other drugs that are used in specific indications include glyceryl trinitrate (in patients with coronary ischaemia), phentolamine (in phaeochromocytoma and other states associated with catecholamine excess such as the MAOI-tyramine interaction), enalaprilat (in acute heart failure), esmolol (particularly in aortic dissection or perioperatively), and hydralazine (in eclampsia, but see Hypertension in Pregnancy, below). Trimetaphan[54] and urapidil[56] have also been used.

Hypertensive emergencies in children are managed similarly to those in adults.[52,59,60]

Hypertension during surgery. Giving antihypertensive drugs to patients about to undergo surgery is not only safe but probably best continued up to and including the morning of surgery.[2,61]

Perioperative hypertension may occur as a result of surgery and often needs to be controlled with parenteral antihypertensives since the oral route may not be available. The parenteral drug of choice is often sodium nitroprusside; others include glyceryl trinitrate (especially after coronary artery bypass), labetalol, enalaprilat, esmolol, fenoldopam, and nicardipine; diazoxide, hydralazine, and methyldopa have also been used.[61-63]

Hypertension in diabetic patients. Hypertension is twice as common in diabetic as in nondiabetic subjects, and up to 50% of patients with type 2 diabetes mellitus become hypertensive.[64,65] The reasons proposed for this increased prevalence are controversial, but insulin resistance has been implicated.[66] In addition to being a major risk factor for atherosclerosis in large blood vessels, hypertension in diabetes appears to contribute to small vessel disease and is a risk factor for diabetic nephropathy and possibly for diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) Group has reported[67] that tight control of blood pressure (with a target of below 150/85 mmHg) reduces the risk of diabetes-related death and diabetic complications, including diabetic retinopathy, in type 2 diabetics.

The threshold for intervention with drug treatment may be lower in diabetic than in non-diabetic hypertensive patients and treatment targets are also lower. An initial target of 140/80 mmHg has been suggested,[1] while a target below 130/80 mmHg may be optimal and is recommended in many guidelines;[1,2,4,5,13,68] the lower target is particularly advised in type 1 diabetics with nephropathy.

All the main groups of antihypertensive drugs can be used in diabetics,[69] and most patients will require at least two drugs to achieve target blood pressure. ACE inhibitors (with angiotensin II receptor antagonists as an alternative) have been particularly recommended, as there is evidence of benefit in preserving renal function in patients with nephropathy. However, a systematic review[70] found limited evidence to support a specific renoprotective action in diabetics, independent of their effect on blood pressure. Diuretics and beta blockers have often been avoided because of their potential adverse effects on glucose and lipid metabolism, but may be used where indicated. In the UKPDS treatment with an ACE inhibitor (captopril) or a beta blocker (atenolol) was equally effective in reducing the risk of diabetic complications, although the ACE inhibitor appeared to be better tolerated.[71] Although there has been concern regarding the safety of calcium-channel blockers, long-acting calcium-channel blockers have been shown to be a suitable choice.[72]

Hypertension and renal disease. Hypertension is closely linked with the kidney—the kidney may have a role in the pathogenesis of hypertension and it may also be a prime target of damage caused by hypertension. Both renal parenchymal disorders and renovascular disorders may be associated with hypertension. In the former, hypertension is often resistant to treatment and a combination of drugs, including vasodilators, may be required. Antihypertensive therapy is also important in these patients since it may slow the decline in renal function in patients with nephropathy.[73] There is some evidence that ACE inhibitors may have a greater protective effect than other antihypertensives,[74,75] although this is not certain,[70] and they have been recommended as the basis of therapy (with angiotensin II receptor antagonists as an alternative), usually with a diuretic.[1,2,5] The effect of blood pressure reduction appears to be related to the degree of proteinuria, and studies have shown that patients with proteinuria higher than 1 g/day benefit from lower blood pressures.[75] Current guidelines[1,2,5] recommend a target blood pressure of below 130/80 mmHg in patients with nephropathy, with a lower target[1] of 125/75 mmHg in those with proteinuria of 1 g/day or over.

Renovascular hypertension has been defined as arterial hypertension resulting from obliteration or compression of one or both renal arteries, the commonest cause being stenosis due to atherosclerosis. Underperfusion of the kidney leads to increased release of renin and a consequent rise in blood pressure. However, the relationship between renovascular hypertension and renal artery stenosis is not clear cut; the two conditions may simply co-exist or hypertension may cause the stenosis rather than the other way round.[76,77]

Renovascular hypertension may be difficult to distinguish clinically, but carries a worse prognosis than essential hypertension, may be less amenable to treatment, carries a higher risk of progression to accelerated or malignant hypertension, and may result in irreversible ischaemic failure of the affected kidney.

Diagnostic methods used to detect renovascular hypertension include imaging studies such as ultrasonography and angiography, and functional tests such as the captopril test (see under ACE inhibitors on p.1198 for further details); renal scintigraphy with and without ACE inhibition is also used.

Although blood pressure in renovascular hypertension can often be controlled by antihypertensive drugs, patients with renal artery stenosis are often treated by angioplasty of the affected artery. There is some evidence that angioplasty lowers blood pressure more effectively than drug therapy, particularly in patients with bilateral stenosis, but the relative effects on other outcomes are less clear.[77,78] Renal function may deteriorate in patients given antihypertensives since blood flow to the kidney is reduced; however, sudden restoration of blood flow by angioplasty may also have deleterious effects. Reduced blood flow is a particular concern with the use of ACE inhibitors or angiotensin II receptor antagonists, since renal perfusion may be dependent on angiotensin II in patients with renal artery stenosis, and renovascular hypertension is often considered a contra-indication to the use of these drugs, particularly in patients with bilateral stenosis or stenosis affecting the only functioning kidney. However, they may be required in patients with resistant hypertension,[79] although they must be used cautiously and in low doses, with careful monitoring of renal function (see Precautions for ACE inhibitors, p.1195).

Hypertension in pregnancy. Hypertension in pregnancy may be life-threatening to both mother and fetus. It may be pre-existing or may develop for the first time during pregnancy. Definitions vary, but hypertension presenting before 20 weeks of gestation generally continues long-term and is considered chronic hypertension. After the twentieth week (gestational hypertension) it may be transient (pregnancy-induced hypertension), chronic, or represent pre-eclampsia. Gestational hypertension is usually defined as a blood pressure of 140/90 mmHg or more on at least two occasions in a previously normotensive woman; it is considered transient hypertension if the blood pressure has returned to normal limits by the twelfth week postpartum. In pre-eclampsia, increased blood pressure occurs with proteinuria; abnormal coagulation, liver dysfunction, and oedema may also be present. Pre-eclampsia may progress to eclampsia, a convulsive phase.

Recommendations about the treatment of ***gestational*** or ***pre-existing hypertension*** during pregnancy have been controversial. Most women with chronic or transient hypertension will have grade 1 or grade 2 hypertension and a low risk of cardiovascular complications during the short period of pregnancy, and the benefits of treatment in such patients are not established. It is usually agreed that blood pressures of 170/110 mmHg or above should be treated as an emergency,[5,80] but recommendations for management of lower blood pressures are less clear. Although treatment of patients with blood pressures of 140/90 mmHg or above has been suggested,[5,80,81] there is little evidence that this improves maternal or neonatal outcomes, although the incidence of severe hypertension is reduced.[82] Some guidelines allow withdrawal of antihypertensives in pregnant women with pre-existing hypertension, with treatment restarted if the blood pressure exceeds specific threshold values.[2,81,83] However, women with mild hypertension are at an increased risk of developing pre-eclampsia, regardless of whether they receive antihypertensives, and should be closely monitored.

For women with *mild to moderate hypertension* in whom the decision is made to give antihypertensives, optimum choice of drug therapy is unclear. Women with pre-existing hypertension usually continue their existing treatment, although ACE inhibitors and angiotensin II receptor antagonists are contra-indicated in pregnancy and should be changed to an alternative. For gestational hypertension, methyldopa or beta blockers have generally been preferred, although there is little evidence that outcomes differ for any of the main drug groups.[82] A systematic review[84] found no evidence of substantive benefits with beta blockers, but another review[82] found that they reduced the risk of severe hypertension more effectively than methyldopa. Methyldopa has the advantage of reassuring long-term safety results in the infant, whereas there have been concerns about fetal growth retardation with beta blockers, particularly with atenolol.[85-87] Nifedipine[81,88] or hydralazine[81] may also be used. Diuretics are not generally recommended for controlling hypertension in pregnancy because of the theoretical risk of exacerbating the volume depletion of pre-eclampsia; however, they appear to be safe in practice and may be used if necessary.[1,83]

For patients with ***pre-eclampsia***[81,89-92] the definitive *treatment* is delivery (although pre-eclampsia may also develop post-partum[92]), but where the maternal condition allows this is usually delayed to allow fetal maturation. Antihypertensive therapy is therefore given to reduce the risk of maternal complications, and prophylactic anticonvulsants, particularly magnesium sulfate, may also be given in those at high risk for eclampsia (see p.470). Evidence to guide choice of antihypertensive in severe hypertension is limited.[93] Oral therapy may be appropriate, in which case methyldopa or beta blockers (preferably labetalol[5,92]) are usually first-line; calcium-channel blockers such as nifedipine are an alternative. However, in acute pre-eclampsia or if delivery is imminent, parenteral antihypertensives are required. Intravenous hydralazine is widely used,[2,92] although there is some evidence that it may be less effective and have more adverse effects than other drugs,[94] and some guidelines recommend that it should be avoided.[5] Intravenous labetalol and oral nifedipine are also used, and sodium nitroprusside may be required in some patients.[2,5] Glyceryl trinitrate may be used if there is pulmonary oedema.[5] Other drugs that have been given include diazoxide and clonidine.

Prevention of pre-eclampsia. It was hoped that prevention of pre-eclampsia might be possible by reducing the local platelet aggregation thought to be responsible for some of its manifestations. Several small studies suggested that low-dose aspirin reduced the risk of pregnancy-induced hypertension and intra-uterine growth retardation in high-risk patients.[95] However, larger studies in women at lower risk generally failed to confirm this benefit[96,97] and in one[97] the risk of placental abruption was higher in those taking aspirin. Findings of the CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) multicentre study[98] involving over 9000 women considered to be at increased risk of pre-eclampsia or intra-uterine growth retardation did not support the routine prophylactic or therapeutic use of antiplatelet therapy in all such women. A further study[99] in high-risk women also failed to show any benefit, although aspirin appeared to be safe for mother and fetus. However, systematic reviews[100,101] have concluded that antiplatelet therapy provides a small to moderate benefit in patients at risk of developing pre-eclampsia, although it is not clear which women are most likely to benefit.[101] Calcium supplementation has also been shown[102] to reduce the risks of pregnancy-induced hypertension and pre-eclampsia, although its role is not yet established. Preliminary evidence suggested that supplementation with vitamins C and E might be beneficial in women at high risk,[103] but further studies[104,105] were unable to confirm this effect.

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Hypotension

As discussed under Hypertension (above) many factors influence blood pressure making it difficult to define an absolute norm. The link between chronically raised blood pressure and cardiovascular risk is well established, and definitions of 'normal' blood pressure are based on estimates of this risk. For adults, a systolic pressure below 130 mmHg, with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg) has generally been considered as normal, although recent guidelines[1,2] have suggested that a blood pressure below 120/80 mmHg may be more desirable. Exactly how far below these values blood pressure can safely be remains uncertain. Although acute hypotension leads to symptoms such as syncope (fainting) or shock, the consequences of chronically low blood pressure are much less clear. Thus, while there are national and international guidelines relating to the diagnosis and treatment of hypertension, there is no accepted definition for low blood pressure or hypotension.

Despite such shortcomings over definition, the existence of several acute and chronic hypotensive disorders is recognised.

Hypotension can occur after haemorrhage or in other forms of shock and the management of this acute and potentially dangerous form of low blood pressure is usually with volume replacement and vasopressors (see Shock, p.1183); sympathomimetics with vasoconstrictor properties, such as noradrenaline and dopamine, are particularly useful when blood pressure is very low. Another situation in which acute hypotension can develop is during anaesthesia and surgery; spinal or epidural block is associated with a greater risk than many other forms of anaesthesia. Hypotension results from venodilatation and decreased cardiac output due to sympathetic block, and the usual treatment is again with sympathomimetics, particularly ephedrine or phenylephrine (see p.1559).

Recurrent forms of acute hypotension may also occur. These include orthostatic (postural) hypotension and neurally mediated hypotension; both are important causes of syncope.[3,4] Orthostatic hypotension may be due to autonomic failure and loss of the reflex vasoconstriction that usually occurs on rising, or may be related to volume depletion. Drug treatment is usually with fludrocortisone (see p.1530). For neurally mediated hypotension, however, choice of therapy is less clear.[3,5-9]

Neurally mediated hypotension (neurocardiogenic syncope, neurally mediated reflex syncope, vasodepressor syncope, or vasovagal syncope) is a common cause of recurrent lightheadedness (presyncope) and syncope in persons with structurally normal hearts. It is characterised by a paradoxical neurocardiogenic reflex; although the mechanism is not entirely clear, reduced cardiac filling appears to stimulate cardiac receptors that normally respond to hypertension, and there is an inappropriate autonomic response leading to vasodilatation, bradycardia, and hypotension. Diagnostic tests may be required to exclude structural or arrhythmic cardiac disorders as a cause of the syncope, and tilt-testing may be necessary to confirm the diagnosis.[3] Treatment primarily involves reassurance and non-pharmacological measures such as avoidance of triggering factors, an increase in dietary salt and fluid intake, and physical manoeuvres such as crossing the legs or tensing the muscles if presyncope occurs.[3,9] Cardiac pacing may be required in some patients, although there is limited evidence of benefit.[10]

Drug treatment for neurally mediated hypotension is more controversial and there is little evidence that any drugs are effective.[4-6,8,9] Fludrocortisone and beta blockers have been widely used, but controlled studies[11,12] with beta blockers have found no evidence that they are superior to placebo; beta blockers may also lead to an increase in adverse effects.[3,8] Disopyramide has also been used, but is not considered first-line.[8] SSRIs have been effective in some cases.[5-7] Benefit has also been reported with vasoconstrictors, including the alpha agonist midodrine.[5,9,13,14] Antimuscarinics, such as propantheline bromide, have also been tried.[6,8]

One contentious issue has been whether general and nonspecific symptoms of ill health such as mental and physical fatigue, depression, and anxiety could be attributed to a chronically low blood pressure (for example, a systolic pressure below 110 mmHg or diastolic pressure below 60 mmHg).[15] In the UK and the USA such an association has not generally been accepted whereas in some European countries (e.g. Germany) a wide range of preparations, usually containing a sympathomimetic, has been available for treatment. There is some evidence that depression[16-18] and reduced general well-being[19] are associated with low blood pressure, and there may also be a link with cognitive impairment.[20] Studies have also suggested an association between chronic fatigue syndrome and either neurally-mediated[21,22] or orthostatic[23] hypotension. However, any implications for treatment are far from clear.

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Kawasaki disease

Cardiac effects including coronary artery abnormalities are the major complications of Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood. Normal immunoglobulin and aspirin are used in its initial management, and antiplatelet therapy, usually with aspirin, may be continued long term to prevent coronary thrombosis. Further details concerning the overall management of Kawasaki disease are provided under Normal Immunoglobulins, p.2228.

Myocardial infarction

Myocardial infarction is an acute coronary syndrome in which necrosis of the heart muscle occurs as a result of acute ischaemia. In the initial stages, clinical symptoms are similar to those of unstable angina, but necrosis results in irreversible damage to the myocardium and long-term complications. The definition of myocardial infarction has changed considerably as the accuracy of detecting myocardial necrosis has improved. It is now considered that any degree of necrosis associated with clinical ischaemia should be defined as myocardial infarction,[1] since it is associated with a worse prognosis, although this definition includes many cases that would formerly have been classified as unstable angina. However, most evidence for treatment is based on earlier classifications, and in practice the diagnosis of acute myocardial infarction is generally made on clinical grounds, determined by characteristic symptoms, ECG changes (ST-segment elevation or bundle branch block), and changes in biochemical markers. The following discussion relates to the management of acute ST-elevation myocardial infarction (STEMI); the management of other acute coronary syndromes is discussed under Angina Pectoris (p.1157).

Although the incidence may be declining, myocardial infarction remains a leading cause of mortality in western societies. The introduction of aspirin and reperfusion techniques has transformed the management of acute STEMI, but a significant number of sudden deaths occur within the first hour and therefore before treatment can be begun. While new therapies for the management of acute STEMI may further reduce in-hospital mortality, earlier recognition and presentation for treatment is important if survival is to be improved further, and primary prophylaxis in patients at risk or at a population level may also have a role (see Cardiovascular Risk Reduction, p.1164). Patients who survive a myocardial infarction are at high risk for further cardiovascular events and often develop complications such as arrhythmias, left ventricular failure, persistent angina, and venous thromboembolism. Management of acute STEMI therefore involves both early treatment of the acute condition, and long-term therapy in survivors to reduce risk and to treat and prevent complications.

Myocardial ischaemia generally occurs as a result of coronary artery occlusion, usually due to thrombosis at the site of a recently ruptured atheromatous plaque; in a few patients coronary embolism or spasm, arteritis, spontaneous thrombosis, or a sudden severe rise in blood pressure, as in phaeochromocytoma, is responsible. The immediate consequence of coronary occlusion is myocardial ischaemia, which leads to impaired contractility, arrhythmias, and eventually myocardial cell death. The lay term 'heart attack' describes both sudden cardiac death and myocardial infarction. Sudden death is usually due to ventricular fibrillation and most patients who are resuscitated from ventricular fibrillation develop features of myocardial infarction or have coronary artery disease. In many cases myocardial infarction is asymptomatic or 'silent' and is only diagnosed due to characteristic changes on the ECG.[2]

Early management. Guidelines,[3-7] recommendations,[8] and reviews[9-11] emphasise the importance of rapid recognition and treatment of patients with acute STEMI. The initial symptoms are usually chest pain, breathlessness, and sweating. The chest pain is typically severe and resembles that of angina pectoris, being precordial with radiation to the neck, lower jaw, and left arm; chest pain lasting more than 20 minutes is generally considered to indicate myocardial infarction, although this is absent in many patients. Other signs and symptoms include nausea and vomiting, bradycardia, hypotension, and apprehension. The characteristic ECG changes confirm the clinical diagnosis and guide initial treatment; elevation of biochemical markers such as troponins and cardiac enzymes develops later and is useful for confirming the diagnosis and determining prognosis.

Those patients with myocardial infarction who develop ventricular fibrillation very quickly have a high mortality and require rapid provision of life support measures. Ventricular fibrillation is treated by defibrillation followed by adrenaline and possibly antiarrhythmics if defibrillation alone is unsuccessful (see Advanced Cardiac Life Support, p.1156, for further details). Paramedic ambulance teams experienced in defibrillation and programmes aimed at educating the public in the basic techniques of cardiopulmonary resuscitation have an important role. Patients with suspected myocardial infarction should be admitted to hospital and where possible managed in a coronary care unit.

The immediate priority in patients with suspected acute STEMI is to give aspirin (as discussed below), to relieve pain and anxiety, and to confirm the diagnosis so that reperfusion can be achieved as rapidly as possible.

Pain should be relieved with an opioid analgesic, usually diamorphine or morphine given intravenously (see Myocardial Infarction Pain, p.8); an antiemetic such as metoclopramide intravenously may also be necessary. Supplemental oxygen should also be given. An inhaled mixture of nitrous oxide and oxygen (Entonox) has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given. A benzodiazepine may be useful for ***anxiety***.

Reperfusion. In patients with confirmed STEMI, the value of rapid reperfusion is well established. The extent of myocardial necrosis or recovery depends on the speed and completeness with which coronary blood flow can be restored,[12] and reperfusion should therefore be achieved as rapidly as possible. Two methods are commonly used: pharmacological reperfusion with intravenous thrombolytics, or mechanical reperfusion with percutaneous coronary intervention (PCI). Combination of the two methods has been tried but benefit has not yet been established.

Thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium. Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and long-term mortality in patients with ECG evidence of ST elevation or new left bundle branch block (for more details see Ischaemic Heart Disease under Uses of Streptokinase, p.1405). The greatest benefit is seen in those given thrombolytics early;[13] mortality is significantly reduced in those receiving treatment within 6 hours of symptom onset, and there is also benefit up to 12 hours. In those presenting later than 12 hours, the benefits are less well established; there has been some evidence of early excess mortality due to cardiac rupture in some patients given late thrombolytics. Evidence of benefit in patients over the age of 75 years is also limited;[13]

there is some evidence of increased short-term mortality, but this may be outweighed by improved longer-term outcomes.[14]

Streptokinase has been the most widely used thrombolytic, although fibrin-specific thrombolytics such as alteplase are increasingly preferred,[7] particularly in patients presenting late after symptom onset.[3] Overall efficacy appears to be similar for all the drugs available and factors such as cost, method of use, and contra-indications help to determine the choice. If streptokinase or anistreplase, so-called antigenic thrombolytics, have been used recently, non-antigenic drugs such as alteplase or urokinase should be given. However, choice of thrombolytic is probably less important than ensuring that one is given as soon as possible; recommendations are for a delay of no more than 90 minutes between calling the medical services and thrombolytic therapy ('call to needle' time),[3] and for no more than 30 minutes between admission to hospital and therapy ('door to needle' time).[3,5] Prehospital thrombolysis is feasible and reduces the time to give a thrombolytic, and short-term mortality.[15] Five-year follow-up of one study[16] has suggested that there is also a beneficial effect on long-term mortality.

Percutaneous coronary interventions include balloon angioplasty, coronary stenting, and similar procedures. They are effective methods for reopening occluded coronary arteries,[17] including in elderly patients,[14] and can be used in acute coronary syndromes (primary PCI) and in stable coronary heart disease. However, specialist facilities are required, and availability may be limited. PCI is also safe and effective in patients in whom thrombolytics have failed to achieve adequate reperfusion (rescue PCI)[18] and appears to be more effective than repeated thrombolytics or conservative therapy.[19] Routine PCI after successful thrombolysis (facilitated PCI) has also been tried but appears to provide no additional benefit and may be detrimental, particularly if a full dose of thrombolytic has been given.[20,21]

Choice of reperfusion strategy is controversial and depends on patient factors and availability.[12,17] PCI is more effective at opening occluded arteries than thrombolysis. Studies have shown that it is associated with lower mortality and re-infarction rates both early and late after STEMI,[22] with benefit maintained up to 5 years,[23] including in patients with cardiogenic shock.[24] However, the advantage of PCI over thrombolysis appears to diminish as the delay to reperfusion increases; although some analyses[25] have found that PCI is superior to thrombolysis irrespective of the time delay, others have suggested[26] that thrombolysis may be preferred if the delay to PCI is 90 minutes or more, although this depends on patient characteristics.[27] Guidelines[3,4,7] therefore recommend that all patients with STEMI presenting within 12 hours should be reperfused. For those with a symptom duration of 3 hours or less, primary PCI is preferred if it can be performed within 90 minutes or the delay to treatment is less than 1 hour longer than for thrombolysis; PCI is also preferred if symptom duration is greater than 3 hours, if the patient has cardiogenic shock or heart failure, or if thrombolytics are contra-indicated. Patients presenting more than 12 hours after symptom onset should generally only receive thrombolysis or PCI if there is evidence of ongoing ischaemia.

The overall effectiveness of reperfusion is limited by persistent coronary occlusion, re-occlusion, and infrequent but serious bleeding complications (including intracranial haemorrhage with thrombolytics), and long-term restenosis after PCI. Antiplatelet and antithrombin drugs are given as **adjuncts** to thrombolytics to improve reperfusion and limit re-occlusion,[28] and have been given in the ambulance as an adjunct to prehospital thrombolysis.[29] Adjunctive therapy is also necessary with PCI to prevent re-occlusion and restenosis but is discussed under Reperfusion and Revascularisation Procedures (p.1181).

Antiplatelet drugs. The value of giving oral aspirin as an antiplatelet drug was shown by the ISIS-2 study,[30] in which aspirin started during the first 24 hours after myocardial infarction reduced mortality and also reduced the incidence of re-infarction and stroke. Use with streptokinase proved to be more effective than either streptokinase or aspirin alone. Aspirin should therefore be taken as soon as possible when myocardial infarction is suspected and the tablet chewed so that some buccal absorption occurs;[4] alternatively, it has been given intravenously..

Additional antiplatelet therapy has been investigated in an attempt to further improve outcomes. There is some evidence that early use of clopidogrel in addition to aspirin and other standard therapies improves short-term outcomes,[31,32] including mortality,[32] and immediate dual antiplatelet therapy with aspirin and clopidogrel is now recommended.[6,7] Glycoprotein IIb/IIIa inhibitors may also add to the effects of aspirin in some patients, and a reduction in mortality has been shown with abciximab in patients receiving primary angioplasty.[33] However, in those given thrombolytics, no mortality benefit has been shown with abciximab,[33,34] although early patency rates may be improved.[35] Similarly disappointing results have been reported with eptifibatide[36] and tirofiban.[37]

Anticoagulants. Heparin was widely used in acute myocardial infarction before thrombolytics were available, but the necessity for adjuvant therapy with heparin in addition to aspirin in patients treated with thrombolytics is not certain. An overview of randomised studies[38] found that in patients receiving aspirin, addition of heparin (either intravenous or subcutaneous) produced a small reduction in mortality but was associated with an excess of major bleeds, while a later meta-analysis[39] found no conclusive benefit with intravenous unfractionated heparin, although most of the studies included were underpowered to show an effect on mortality. In addition, many of the studies supporting the use of thrombolytics included unfractionated heparin, and it continues to be widely used. It has been suggested that heparin may provide benefit by preventing re-occlusion of the artery after thrombolysis, a problem that occurs particularly with fibrin-specific thrombolytics such as alteplase. Heparin, normally given for up to 48 hours, has therefore been suggested when alteplase or similar thrombolytics are used, but may not be necessary with streptokinase;[3,4] however, updated guidelines[6] recommend that anticoagulants should be given irrespective of the thrombolytic used. Low-molecular-weight heparins have also been tried. They appear to be more effective than unfractionated heparin,[39,40] and may therefore be preferred; however, studies have generally compared short-term unfractionated heparin (up to 48 hours) with longer-term low-molecular-weight heparin (4 to 8 days), and any benefit may reflect the longer duration of treatment. Fondaparinux, a direct factor Xa inhibitor, is also effective,[41] and may be used as an alternative.[6,7] Direct thrombin inhibitors have generally proved disappointing (see Ischaemic Heart Disease under Lepirudin, p.1323), although they may have a role in patients with heparin-induced thrombocytopenia.[4] Longer-term use of heparin to prevent systemic embolisation may be considered in patients at risk of developing left ventricular mural thrombosis or in those with complications likely to result in immobility.

Standard early therapy for STEMI therefore consists of antiplatelet drugs, anticoagulants, and immediate pharmacological or mechanical reperfusion. **Other early treatments** that have been tried include beta blockers, nitrates, ACE inhibitors, magnesium, and metabolic support.

Beta blockers. In studies performed before the routine use of thrombolytics, intravenous beta blockers, such as atenolol and metoprolol, given in the early period after myocardial infarction were associated with a reduction in mortality. Contributory mechanisms were considered to be a reduction in size of infarction or number of re-infarctions and an antiarrhythmic effect, although the ISIS-1 study[42] suggested that beta blockers improved early survival by reducing the incidence of cardiac rupture. The role of intravenous beta blockers in the reperfusion era is less clear. A systematic review[43] of randomised studies found that early use of beta blockers provided, at most, a small mortality benefit; most of the studies preceded routine use of reperfusion, although some thrombolytic studies were included. A later randomised study,[44] in which about half of the patients received thrombolytics, found that early intravenous metoprolol followed by oral dosage did not reduce mortality at 28 days; there was a reduction in re-infarction and ventricular fibrillation but this was offset by an increase in deaths due to cardiogenic shock, particularly during the first few days. Current recommendations[6,7] are that intravenous beta blockers should not be used in patients with cardiogenic shock or other contra-indications, and it has been suggested[6] that early use should be reserved for patients with hypertension.

Nitrates. Intravenous nitrates are widely used in acute myocardial infarction, although evidence to support their use in patients undergoing reperfusion is limited. An overview[45] of studies carried out before reperfusion (thrombolysis or PCI) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality, but whether they are of benefit in addition to reperfusion is not clear. However, they appear to be safe[46] and should therefore be given where clinically indicated for ongoing ischaemic pain.[4,7] Nicorandil, which is both a potassium-channel opener and a nitrate, has also been tried in the early stages of myocardial infarction, but results have been mixed.[47,48]

ACE inhibitors. ACE inhibitors have an established role in the long-term management of patients after myocardial infarction, but their use in the early stages is more controversial (see p.1199). A systematic review[49] of studies of ACE inhibitors started within the first 1 to 2 days after acute myocardial infarction found that 30-day mortality and the incidence of heart failure were reduced in those given ACE inhibitors, although the greatest absolute benefit was seen in high-risk patients such as those who had already developed heart failure. Guidelines[3,4] therefore agree that patients with evidence of heart failure should be given early treatment with ACE inhibitors; routine use in all patients may be considered[4,7] but is less well-established.

Magnesium. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium and it has been suggested that use of magnesium in acute myocardial infarction might protect against both arrhythmias and reperfusion injury. Although early studies reported some benefit, larger studies found no effect on mortality, and a systematic review[50] concluded that it was unlikely that magnesium reduced mortality; ventricular arrhythmias were less frequent, but profound hypotension and bradycardia were increased. Routine use of magnesium is therefore not currently recommended.

Metabolic support. Infusions containing glucose, insulin, and potassium have been used in small numbers of patients with the aim of providing metabolic support in the acute phase of myocardial infarction. A meta-analysis of randomised controlled trials that were performed before the widespread use of thrombolytics found that mortality was reduced in recipients of glucose-insulin-potassium,[51] but large randomised studies[52] in patients undergoing reperfusion have found no overall effect on mortality. Intensive glucose control, including insulin-glucose infusions, is however of benefit in diabetics with acute myocardial infarction (see Myocardial Infarction under Insulin, p.452) and short-term outcomes may also be improved in non-diabetics with hyperglycaemia treated with insulin.[53]

Other early treatments that are being investigated[54] include hypothermia, hyperbaric oxygen, calcium modulation, and complement inhibitors such as pexelizumab. Early use of stem cell infusions[55] or colony-stimulating factors[56] to promote myocardial repair has also been tried, but the optimum approach remains unclear.[57]

Long-term management. Patients who survive the immediate post-infarction period remain at high risk for cardiovascular mortality. The main predictors of poor outcome are the extent of left ventricular dysfunction, residual myocardial ischaemia, and ventricular arrhythmias. Follow-up should include cardiac rehabilitation and the identification and modification of risk factors for ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164). Exercise testing, echocardiography, myocardial imaging techniques, and pharmacological stress testing (see Myocardial Imaging under Dipyridamole, p.1268) can be used after myocardial infarction to help identify those at high risk for recurrent ischaemic events and to select patients needing coronary angiography.[3,4] In patients who develop angina soon after myocardial infarction, exercise testing may be unhelpful and potentially hazardous, although many will need angiography to determine whether angioplasty or bypass surgery is required.

Drug therapy is important in the long-term management of patients after myocardial infarction, both for symptom control and for secondary prevention.[3,4,58,59]

- *Aspirin*, given during the acute phase and then continued for one to two years, has been shown to reduce mortality and re-infarction rates. A meta-analysis[60] confirmed the benefit of prolonged antiplatelet treatment in the secondary prevention of myocardial infarction and patients should receive antiplatelet therapy indefinitely. Clopidogrel appears to be as effective as aspirin[61] and should be considered in patients intolerant of, or with contra-indications to, aspirin. Dual antiplatelet therapy with both aspirin and clopidogrel for 2 to 4 weeks may also be considered after acute STEMI,[6,58] and it may be reasonable to continue for longer.[6]

- Routine use of *oral anticoagulation* after acute myocardial infarction in patients without another indication is not usually recommended, although warfarin may be used in patients unable to take antiplatelet drugs.[58] There is some evidence that medium-intensity warfarin anticoagulation (INR 2.0 to 2.5) given with aspirin may be more effective than aspirin alone,[62] but bleeding is increased and the combination is only generally recommended as an alternative in patients requiring dual antiplatelet therapy who are unable to take clopidogrel.[58]
- Long-term prophylactic treatment with oral *beta blockers* (most studies have used propranolol, metoprolol, or timolol) has reduced mortality and the rate of re-infarction.[43] In patients with no contra-indications to beta-blocker therapy (see Precautions, p.1227) they are usually started before hospital discharge and continued for a minimum of one year; indefinite use has been recommended.[3,4,6,58] A survey of 201 752 patients who had a myocardial infarction found that low-risk patients and those with conditions often considered to be contra-indications also benefited from a beta blocker.[63] There is also clear evidence of benefit in the elderly,[64,65] although beta blockers have often been underused in such patients.
- *Calcium-channel blockers* are not routinely used in the long-term management of myocardial infarction, although in selected patients without heart failure verapamil or diltiazem may be of some benefit if beta blockers are contra-indicated.
- *ACE inhibitors* reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Myocardial infarction patients with left ventricular dysfunction benefit from long-term oral ACE inhibitors started early after infarction and continued for at least 4 to 6 weeks.[66,67] Long-term use of ACE inhibitors in patients without left ventricular dysfunction is less established, since less benefit has been found in this group. However, the HOPE study[68] found that treatment with ramipril significantly improved outcome in patients at high risk for cardiovascular disease, including patients with previous myocardial infarction but preserved left ventricular function, and some guidelines[6,58] therefore consider that long-term use of ACE inhibitors is reasonable in all patients after myocardial infarction.
- *Angiotensin II receptor antagonists* may be an alternative; a study[69] comparing valsartan with captopril found that both were equally effective, although another study[70] comparing losartan with captopril suggested that ACE inhibitors should remain first-line.
- *Aldosterone receptor blockade* with a drug such as eplerenone is recommended in patients with evidence of heart failure.[6,7,58]
- *Statins* are effective in the primary and secondary prevention of myocardial infarction in patients with both high and average cholesterol concentrations and their use has been advocated in all patients who have suffered a myocardial infarction (see Cardiovascular Risk Reduction, p.1164).
- *Omega-3 acid ethyl esters* may be considered if dietary intake is inadequate.[58]
- Some patients, for example those with myocardial ischaemia or poor left ventricular function, may require long-term *nitrates*, but there is no evidence to support their routine use in all patients.[3]

Post-infarction problems such as heart failure (left ventricular dysfunction), angina pectoris, and arrhythmias are discussed on p.1165, p.1157, and p.1160, respectively.

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Patent ductus arteriosus

The ductus arteriosus is a vascular channel present in the fetal circulation that connects the pulmonary artery and the descending aorta. In some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. Details of its management are given on p.68.

Peripheral arterial thromboembolism

Occlusion of the peripheral arteries may occur due to embolism or thrombosis (see Thromboembolic Disorders, p.1187). Sudden or acute occlusion causes reduction of blood flow to the distal portions of the limb and may lead to critical limb ischaemia. Emergency treatment with surgery or thrombolytic drugs is often required to restore blood flow and preserve the limb.

Acute peripheral arterial thromboembolism produces pain, pallor, and coldness in the affected limb. Numbness and paraesthesia may occur and if the clot is not removed, gangrene develops. Sudden onset is usually due to occlusion by an embolus. The heart is a frequent source of emboli; atrial fibrillation, cardiomyopathy, myocardial infarction, and valvular heart disease are all associated with peripheral arterial embolism. Peripheral arterial thrombosis often has a more gradual onset due to collateral vessels maintaining some perfusion of the limb. Thrombosis is usually the result of thrombus formation at a site of atheroma in an atherosclerotic artery; thus it may occur in patients with chronic occlusive arterial disease (see Peripheral Vascular Disease, p.1178). Thrombosis is now more common than pure embolism although the two may coexist.

Sudden arterial occlusion requires emergency treatment to restore circulation and to avoid gangrene and possible amputation of the limb. Where there is imminent danger to the limb surgery is necessary to rapidly restore blood flow. In patients with **embolism** in otherwise healthy arteries surgical removal of the embolus by catheter (embolectomy) is used and usually results in restoration of blood flow. Sudden arterial occlusion due to **thrombosis** where gangrene is imminent requires emergency bypass surgery to restore blood flow; surgical removal of a thrombus (thrombectomy) is not usually successful as most arterial thromboses are superimposed on atheromatous plaques, particularly in elderly patients, and thrombectomy adds to the intimal damage.

Where the risk from ischaemia is less acute, angiography may be performed to confirm the type of occlusion, and intra-arterial thrombolysis may be used as initial therapy, particularly if the cause is thrombotic.[1-3] This method is particularly useful for occlusion of smaller vessels, distal occlusions in surgically inaccessible small arteries, or in patients too ill to undergo surgery. However, it is a slower method of restoring blood flow and its use in limb-threatening ischaemia is controversial.[4] The TOPAS study[5] reported no significant difference in outcomes in patients with acute arterial occlusion treated initially with thrombolysis or surgery, although the rate of bleeding complications was higher with thrombolysis. It has therefore been suggested that thrombolysis may be appropriate for initial therapy in acute occlusion, providing this will not lead to an unacceptable delay in reperfusion.[6-8] However, others[9] consider that thrombolysis should not be used as first-line therapy due to the lack of significant benefit and the increased risk of bleeding.

Thrombolytics may be given intravenously, but giving low doses of intra-arterial thrombolytics directly into the clot is often preferred. Despite the use of low doses the risk of major haemorrhage is still about 10%. Continuous intra-arterial infusion, pulse infusion, and different thrombolytics (alteplase, streptokinase, or urokinase) are used; the optimal technique and choice of thrombolytic are unclear. Local treatment with low-dose streptokinase or urokinase infused into the clot is successful in about 50 to 80% of patients and recanalisation is sustained for a year in 50%. Thrombolytic therapy is more likely to be successful if it is begun soon after thrombosis occurs. If no lysis has occurred within the first 12 to 24 hours the procedure is unlikely to be successful, but where thrombolysis is occurring infusion has been continued for several days. There is rather less experience with alteplase; it is claimed to produce more rapid thrombolysis than streptokinase although studies have been too small to provide evidence of reduced limb loss or mortality.[1] On completion of thrombolytic therapy angiography should be repeated to identify the underlying abnormalities that caused the original occlusion. The lesions can then be treated by balloon angioplasty or surgical repair, and this should be done as soon as possible to avoid rethrombosis, which occurs in about 10 to 30% of patients.

Intra-arterial thrombolysis may also be used in conjunction with surgical techniques, particularly when surgery fails to restore blood flow due to distal occlusions.[10-13]

Adjunctive treatment with antithrombotics, such as heparin and aspirin, is often given to patients with peripheral arterial thromboembolism to prevent propagation of the clot and also to prevent postoperative thromboembolic complications. However, there is an increased risk of serious bleeding complications if heparin is used with thrombolytic therapy.[5] Glycoprotein IIb/IIIa-receptor antagonists, such as abciximab, have also been tried.[14] Where the occlusion has been due to embolism, the patient should be investigated for a possible source of emboli and long-term oral anticoagulation should be considered to prevent recurrent embolism.

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Peripheral vascular disease

The term peripheral vascular disease is often used for atherosclerotic or occlusive arterial disease but in its widest sense covers both arterial and venous disorders and may be due to atherosclerosis, vasospasm, or thromboembolism. Peripheral arterial occlusive disorders are the subject of the following discussion; for reviews of vasospastic arterial disorders see p.1188. Venous disorders are covered under Venous Thromboembolism (p.1189); for chronic venous disease see also Varicose Veins (p.2347) and Wounds and Ulcers (p.1585).

The commonest form of **occlusive arterial disease** is caused by atherosclerosis. It may well be only one manifestation of a generalised atherosclerotic process and sufferers also usually experience, or are at increased risk of, ischaemic heart disease. **Thromboangiitis obliterans** (Buerger's disease)[1] is also an occlusive arterial disease, but, rather than being caused by atherosclerosis, it is a result of inflammatory and proliferative lesions in medium and small arteries and veins of the limbs. The lesions are mainly thrombotic in nature. It progresses more rapidly than atherosclerotic disease; severe ulceration and gangrene, necessitating amputation, may often occur. Sufferers are typically heavy smokers. **Intermittent claudication** is a major feature of occlusive arterial disease of the lower limbs and is characterised by pain that develops during exercise and which usually disappears at rest although it may persist in severe forms of disease. The pain is due to ischaemia (insufficient oxygen supply) resulting from the obstruction or vasoconstriction of peripheral arteries. Ischaemia may also result in trophic changes in the skin. In severe or advanced disease, ulceration of skin and tissues can occur and may even progress to gangrene. Although the cause of arterial obstruction is usually atherosclerosis, ischaemia is commonly precipitated by thrombosis. Smoking causes vasoconstriction and is frequently a contributory factor.

Management. Patients with occlusive arterial disease are at high risk of other cardiovascular events such as myocardial infarction and stroke, and treatment is important both to reduce this risk and to improve symptoms.[2-11] Measures to reduce cardiovascular risk (see p.1164) include general lifestyle changes, antiplatelet therapy, treatment of hypertension and hyperlipidaemia, and smoking cessation. In the case of thromboangiitis obliterans, cessation of smoking is essential to halt progression of the disease. These measures do not generally improve symptoms in those with intermittent claudication, although supervised exercise programmes have been shown[12] to improve walking distance and are recommended,[7] and there is also some evidence[13,14] that lipid lowering therapy may do the same.

Many **drugs** have been used for symptom control in occlusive arterial disease, but studies have often been unsatisfactory and their efficacy and/or overall place in management remains to be firmly established.[15,16]

Vasodilators have been the most commonly used drugs in intermittent claudication, although any purported benefit is probably due to mechanisms other than vasodilatation, such as actions on blood cells or changes in blood rheology. Vasodilators do not preferentially dilate the affected arteries, which may in any case be fully dilated already. Dilatation of arteries supplying non-ischaemic tissues elsewhere in the body may actually divert blood away from the affected ischaemic area—the so-called 'steal' phenomenon; this is a known risk with all vasodilators, but especially with powerful arterial vasodilators such as hydralazine and this type of drug is not suitable for use in peripheral arterial disease. *Cilostazol*, which has antiplatelet and vasodilator effects, has been shown to increase walking distance,[17,18] and has been recommended in patients with disabling claudication.[7,19] *Naftidrofuryl* and *pentoxifylline* have been widely used; they may increase the time and distance walked before the onset of pain, but evidence of benefit is limited.[15,20] Pentoxifylline may be considered[7] as second-line therapy to cilostazol. Other vasodilators that have been promoted for the treatment of intermittent claudication include buflomedil, cinnarizine, cyclandelate, and inositol nicotinate; ketanserin, which inhibits vasoconstriction and also changes indices of blood rheology, has also been used.

Prostaglandins such as *alprostadil* (prostaglandin E_1) and *epoprostenol* (prostacyclin) act as vasodilators and have been used in obstructive arterial disease.[2,3] A beneficial effect on rest pain has been noted and some ulcers have either regressed or healed; in selected patients this form of therapy has avoided the need for amputation. However, their role remains unclear. A systematic review[21] concluded that prostaglandin E_1 and its analogues, given intravenously or intra-arterially, were beneficial, but their use may not be practical in most patients.[7] Oral prostaglandins such as *beraprost* have also been tried but do not appear to be effective and are not recommended.[7,9,19] Topical *dinoprostone* has also been used.

Other drugs that have shown positive results in small studies include arginine,[16] ginkgo biloba,[15] glutathione,[16] levocarnitine,[15,22] policosanol,[16] and sulodexide.[23] Growth factors[24] (given locally) and gene therapy[25] have also been tried.

If intermittent claudication is severe, and does not respond to medical treatment, **non-pharmacological** techniques such as bypass surgery, endarterectomy, percutaneous transluminal angioplasty, or intravascular stenting should be considered.[7,9] After these procedures, treatment to prevent postoperative thrombosis and restenosis may be necessary (see Reperfusion and Revascularisation Procedures, p.1181).

Sudden or **acute arterial occlusion** due to emboli or to thrombosis may occur in 10% of patients with atherosclerotic disease, but is rare in thromboangiitis obliterans. The initial approach has been surgical removal; dissolution of the thrombus using local or systemic thrombolytic therapy may be considered. For further details, see Peripheral Arterial Thromboembolism, p.1178.

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Phaeochromocytoma

Phaeochromocytoma is a rare catecholamine-secreting tumour of the adrenal medulla. Patients with phaeochromocytoma are usually hypertensive and suffer headache, palpitations, and excessive sweating; the hypertension may be either episodic or sustained. However, if the tumour is mainly adrenaline-secreting, tachyarrhythmias may be associated with a normal or even decreased arterial pressure and if the tumour secretes mainly noradrenaline, vasoconstriction may lead to contraction of the venous pool and hypovolaemia. If the effects of the release of catecholamines are not controlled a life-threatening crisis ultimately ensues and may range from a shock-like syndrome with multiple organ failure to hypertensive crisis, depending on the predominance of the catecholamine secreted.

For a diagnosis of phaeochromocytoma, history and clinical symptoms are important, but a firm diagnosis requires further investigative techniques. Raised plasma or urinary concentrations of catecholamine metabolites indicate the presence of a tumour; measurement of urinary or plasma concentrations of adrenaline and noradrenaline may be necessary to confirm the diagnosis in some patients. The precise location of the tumour can be established by procedures such as computed tomography, magnetic resonance imaging, or scintigraphy with ^{131}I-iobenguane (^{131}I-*m*-iodobenzylguanidine). Other tests that may be used include use of drugs such as clonidine that suppress catecholamine release in normal patients but not in those with phaeochromocytoma. A glucagon stimulation test may also be used but other provocative tests are generally considered obsolete.

Although surgery to remove the tumour is the ultimate treatment goal, the initial step in management must be the prevention of the pressor and other effects of catecholamines. Alpha blockers, given orally, are the mainstay of therapy; they both reduce the blood pressure and allow the plasma volume to return to normal. Phenoxybenzamine is the alpha blocker of choice since the long-lasting, non-competitive blockade that it produces cannot be overridden by surges of catecholamine release, as may happen with competitive blockers. In patients who are unable to tolerate phenoxybenzamine, a selective alpha$_1$-adrenoceptor blocker such as prazosin may be used; it results in less tachycardia and may be preferable if the tumour is predominantly adrenaline-secreting, but hypotension may be a problem. Phentolamine may be given intravenously in patients with hypertensive crises. The initial dose of alpha blocker should be small and should be increased gradually until all signs of pressor activity are suppressed. Once, but not until, alpha blockade is successfully established, tachycardia can be controlled by the cautious use of a beta blocker. A beta$_1$-selective blocker is preferred so that peripheral beta$_2$-mediated vasodilatation is unaffected. α-Methyltyrosine, which suppresses catecholamine synthesis, may be tried in selected patients such as those resistant to alpha blockade or those in whom the effects of alpha or beta blockade may be undesirable.

Once the pressor effects of catecholamine secretion are controlled, surgery can be undertaken. Drugs used for premedication and anaesthesia should be chosen so as to avoid those which may cause pressor responses or tachycardia and ideally should suppress the adrenergic response to surgical stimuli. This will still not be adequate to prevent catecholamine release when the tumour is handled and potent vasodilators such as sodium nitroprusside or glyceryl trinitrate have been given intravenously to prevent dangerously high arterial pressures; the alpha blocker phentolamine has also been advocated although tachycardia is invariably a problem. Cardioselective beta blockers such as atenolol may be given, often in high dosage, to control tachycardia during surgery.

If it proves impossible to remove all the active tissue of a phaeochromocytoma during surgery, or in patients who are unsuitable for surgery or who have malignant phaeochromocytoma, maintenance therapy with alpha and beta blockade needs to be continued or α-methyltyrosine may be used. Alternatively, ^{131}I-iobenguane has been given in high doses sufficient to cause radionecrosis; antineoplastic therapy has also been used.

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Pulmonary hypertension

Pulmonary hypertension is a disorder in which there is an increase in pulmonary vascular resistance, leading to an increase in pulmonary arterial pressure. Mean pulmonary artery pressure in a resting individual at sea level is normally about 15 mmHg; pulmonary hypertension is usually defined as a pressure above 25 mmHg at rest, or above 30 mmHg during exercise. Pressures will be correspondingly higher at higher altitudes.

Pulmonary hypertension has been classified in a number of ways and the terminology used has changed as the underlying pathophysiology has become clearer. The most common classification used has been to divide pulmonary hypertension into primary and secondary forms, depending on the absence or presence of an underlying cause. However, this classification has little meaning in terms of the pathophysiology or treatment and guidelines[1,2] now recommend against the use of these terms. Pulmonary arterial hypertension is the preferred term where the increased pressure is due to a disorder of the pulmonary arteries themselves. This includes both idiopathic and familial forms (previously classified as primary pulmonary hypertension), as well as forms that were previously classified as secondary, including those associated with connective tissue disorders, infections, drugs and toxins, and a number of other disorders. The discussion that follows relates to the management of these forms. Other types are classified into groups covering pulmonary hypertension associated with cardiac, pulmonary, thromboembolic, or other disorders, for which management primarily involves treatment of the underlying disease.

Pulmonary arterial hypertension[3-8] is a progressive disease with a high mortality rate, and patients appear to be prone to sudden death. Idiopathic pulmonary arterial hypertension occurs in patients of all ages and in both sexes but women in the fourth decade of life are those typically seen. A functional classification system similar to the New York Heart Association grades used for heart failure (see p.1165) may be used to indicate severity.[1,2] Initial complaints include dyspnoea on exertion, fatigue, and chest discomfort or pain. In advanced disease, cor pulmonale (an enlargement of the right ventricle due to either dilatation, hypertrophy, or both) occurs and may progress to right-sided heart failure. The pulmonary arteries may also be affected by thromboembolic disease.

The aim of treatment in pulmonary arterial hypertension has generally been to decrease the pulmonary arterial pressure, preferably in conjunction with an increase in cardiac output, and thus improve symptoms. However, more recent therapies also improve survival and reduce the need for transplantation, and this is reflected in current guidelines[1,9,10] for management. Although most studies have been in patients with idiopathic pulmonary arterial hypertension, there is some evidence that patients with pulmonary arterial hypertension associated with other disorders respond similarly,[1,6,10] and they are usually managed in the same way. Improved understanding of the pathophysiology of pulmonary arterial hypertension has also led to the development of new treatments, although evidence of long-term benefit is limited in most cases.

General treatment for pulmonary arterial hypertension[1,9,10] includes measures to prevent hypoxia, since this causes pulmonary vasoconstriction, and treatment of associated right-sided heart failure. Oxygen therapy may be needed in some patients, and anaemia should be avoided. Pneumococcal and influenza vaccines are recommended to reduce the risk of pulmonary infections. *Diuretics* produce symptomatic benefit in patients with fluid retention, and should be given as appropriate. *Digoxin* has been used, although its role is less clearly established unless patients also have atrial fibrillation. Patients with pulmonary arterial hypertension also appear to be at risk of thromboembolic complications, and *oral anticoagulation* has been advised.

Specific therapy has generally been based on the use of vasodilators. Vasoconstriction is believed to play an important role in the pathophysiology of pulmonary arterial hypertension, and many of the vasodilators used in systemic hypertension have therefore been tried.[11] While most reduce pulmonary artery pressure, they also reduce systemic blood pressure,[12] producing undesirable and sometimes intolerable adverse effects, and this limits their use. Those with an established role in pulmonary arterial hypertension are calcium-channel blockers and prostacyclin analogues.

Calcium-channel blockers improve pulmonary haemodynamics, and there is some evidence of a survival benefit; an observational study[13] over a 5-year period found that survival was improved in patients given high doses. However, only a small proportion of patients respond,[14] and adverse effects may be a concern. Guidelines[1,9,10] therefore recommend that an acute response test should be performed in all patients before starting long-term treatment. Although oral calcium-channel blockers have been used for testing, this has been associated with severe adverse effects and it is now recommended that only short-acting vasodilators such as intravenous epoprostenol, intravenous adenosine, or inhaled nitric oxide, should be used. Those who respond may then be started on oral calcium-channel blockers, with the choice usually being nifedipine in patients with relative bradycardia, and diltiazem in those with relative tachycardia. The dose should be increased gradually, as tolerated, and long-term therapy should only be continued in patients with a sustained response.

Prostacyclin is a potent endogenous vasodilator and there is evidence that it may be deficient in patients with pulmonary arterial hypertension. Epoprostenol, a synthetic form of prostacyclin, was originally used in patients with end-stage pulmonary hypertension to sustain them long enough to have a heart-lung transplant. However, some studies have suggested that long-term therapy with epoprostenol may also have a role as an alternative to transplantation. Sustained clinical improvement and improved survival have been reported[15,16] in some patients given long-term intravenous therapy using portable infusion pumps, and guidelines[1,9,10] now recommend that epoprostenol may be used in patients with pulmonary arterial hypertension who do not respond to calcium-channel blockers and who are in functional class III or class IV. Continuous intravenous iloprost, a more stable analogue, has also shown some benefit,[17] and may be an alternative. Another analogue, treprostinil, can be given by continuous subcutaneous infusion[18,19] and may be used, particularly in patients for whom intravenous treatment is not suitable;[10] a small study[20] has reported the safe transfer of patients from epoprostenol to treprostinil therapy. However, severe pain may occur with subcutaneous treprostinil, and it may be given intravenously if required.[10,21] Prostaglandin analogues have also been given by inhalation. Epoprostenol has been used, but iloprost, which has a longer action, is generally preferred;[10,22] treprostinil has also been used.[23] Another analogue, beraprost sodium, has been given orally,[24-26] but is not widely available. Although primarily thought to act as vasodilators, epoprostenol and its analogues also affect vascular remodelling and platelet aggregation and this may contribute to their beneficial effects.

Endothelin receptor antagonists may also be used. Endothelin-1 is a potent endogenous vasoconstrictor and appears to be overproduced in pulmonary arterial hypertension; it also stimulates vascular remodelling and has pro-inflammatory effects. Bosentan, an oral endothelin receptor antagonist, has been shown[27,28] to improve haemodynamics and exercise capacity, and there is some evidence that survival may also be improved.[29] It may be used as an alternative to prostacyclin analogues in patients in functional class III and a small study[30] has suggested that some patients can be safely transferred from prostacyclin analogues to bosentan. However, in unstable functional class IV patients, epoprostenol is usually preferred.[1,10] Studies with sitaxentan[31] and ambrisentan,[32] which are selective for the endothelin ET_A-receptor, have also demonstrated positive results.

Phosphodiesterase inhibitors such as sildenafil have also shown some benefit in pulmonary arterial hypertension,[33,34] and may have a role, particularly in patients who fail to respond to other therapies.[1,10] Another alternative may be to use a combination of treatments, such as a prostacyclin analogue with an endothelin receptor antagonist, but this suggestion is based on limited evidence and is not yet established.[1,6,10] There have been case reports[35-37] suggesting benefit with imatinib, a platelet-derived growth factor antagonist, but controlled studies are needed.

Surgical intervention, and ultimately lung or heart-lung transplantation may be needed in patients who do not respond to vasodilator therapy.[1,9]

Pulmonary hypertension associated with an established cardiopulmonary disorder is much more common than pulmonary arterial hypertension and the clinical manifestations are dominated by those of the underlying condition. Chronic obstructive pulmonary disease is the commonest respiratory cause, but it may also occur in patients with respiratory distress syndromes, sarcoidosis, or cryptogenic fibrosing alveolitis. Pulmonary arterial pressure may also be raised in thromboembolic disease, and in patients with impaired left ventricular function, for example associated with myocardial infarction or mitral valve disease. Management generally involves appropriate treatment of the underlying disorder. Inhaled nitric oxide has been used in patients with acute pulmonary hypertension following cardiac surgery or associated with respiratory distress syndrome.[38] There have also been reports[39] of long-term use in patients with chronic lung disease.

Persistent pulmonary hypertension of the newborn, sometimes also termed persistent fetal circulation, is a form of pulmonary hypertension specifically affecting neonates. It can be primary in nature (that is, idiopathic, affecting infants with an anatomically normal heart and no pulmonary disease) or secondary, being associated with a number of cardiopulmonary conditions including congenital heart disease, diaphragmatic hernia, meconium aspiration, respiratory distress syndrome, or sepsis. The pulmonary hypertension and altered vasoreactivity lead to a right-to-left shunting of blood across the patent ductus arteriosus or foramen ovale and this often results in critical hypoxaemia.

Management generally involves high-frequency oscillatory ventilation (to achieve optimal lung inflation) and, if necessary, extracorporeal membrane oxygenation. Treatment to reduce pulmonary vascular resistance may also be tried. Mechanical hyperventilation has been used to induce alkalosis, since this reduces pulmonary vasoconstriction; intravenous sodium bicarbonate may be an alternative.[40] Inhaled *nitric oxide* which is a potent, selective pulmonary vasodilator, is also widely used.[41] Studies[42-46] have shown that it can cause marked improvement in oxygenation and a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been found. Although there have been concerns that use of inhaled nitric oxide might adversely affect neurodevelopmental outcome more than conventional therapy, this has not been confirmed in infants followed up for up to 2 years.[47,48] Use of inhaled nitric oxide in combination with high-frequency oscillatory ventilation may have additional benefits.[49]

Nitric oxide is not effective in all patients and alternatives may be required.[50,51] Intravenous vasodilators have been used, although, as discussed above, this is generally limited by their systemic effects. *Tolazoline* has been most commonly used, and may be given intravenously or by the endotracheal route. Intravenous *epoprostenol* is also used; it has also been given by inhalation,[52,53] which may reduce systemic effects. *Phosphodiesterase inhibitors* may have a role; dipyridamole has been used, and there have been reports[54,55] of benefit with sildenafil. Other vasodilators that have been tried include intravenous *adenosine*,[56,57] intravenous *magnesium sulfate*,[58-60] and inhaled *sodium nitroprusside*,[61] but none of these has an established role.

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Raised intracranial pressure

The intracranial compartment consists of brain parenchyma, vascular tissue, and cerebrospinal fluid (CSF). Since the skull is a rigid structure an increase in the volume of any one of these compartments will raise intracranial pressure. This may be due to the formation of cerebral oedema after head injury or around tumours, mass-lesions such as tumours or haemorrhage, CNS infections, or metabolic disorders. Other mechanisms that can raise intracranial pressure include increased dural sinus venous pressure, increased resistance to CSF outflow, and an increased rate of formation of CSF. In idiopathic intracranial hypertension there is no obvious cause. Raised intracranial pressure (intracranial hypertension) can produce irreversible damage to the CNS and is potentially fatal; herniation of brain tissue can occur and reduced cerebral blood flow can lead to cerebral ischaemia. Symptoms of raised intracranial pressure include headache, which is often worse in the morning and may wake the patient from sleep, vomiting, drowsiness, and visual disturbances; most patients have papilloedema on examination.

There are several ways of reducing raised intracranial pressure, the choice of treatment being determined mainly by the underlying cause.[1-8] Whatever the cause, in acutely raised intracranial pressure the initial aim is to reduce the volume of the intracranial contents as quickly as possible to prevent brain damage. For patients with haematoma or tumours the treatment of choice is often surgery but other methods may be used to control intracranial pressure before surgery.

Intracranial pressure monitoring can be helpful in guiding therapy since reducing the intracranial pressure too far is also deleterious. Patients may be sedated to avoid elevations of intracranial pressure due to unnecessary movement but if this is ineffective the use of neuromuscular blockers such as pancuronium or atracurium with artificial ventilation should be considered. Hyperventilation reduces the intracranial pressure by constricting the cerebral blood vessels and controlled hyperventilation has been used; however, it also reduces cerebral blood flow and routine use is not generally advised.[4,5] Raising the patient's head to promote venous drainage may be helpful. Although restriction of fluid intake has been advised, hypotension reduces cerebral blood flow and should be avoided, and intravenous fluids should therefore be given as required.[4] Removal of CSF through a ventricular catheter may also be effective. Controlled hypothermia has been used, but a review[9] of its use in head injury found no evidence that it improves outcome.

The mainstay of pharmacological treatment for acutely raised intracranial pressure is diuretic therapy, usually with an osmotic diuretic. Mannitol is most often used but urea, glycerol, sorbitol, and hypertonic glucose or sodium chloride solutions have also been given.[3] Osmotic diuretics act by increasing the osmolality of plasma and drawing water out of the tissues, as well as by promoting an osmotic diuresis. They should not be given to patients with intracranial bleeding after head injury since they can exacerbate the bleeding,[6] and should also be avoided in patients who are already dehydrated. *Mannitol* decreases intracranial pressure and increases cerebral blood flow both by an osmotic effect and by decreasing blood viscosity.[4,10] It is widely used to reduce intracranial pressure after severe head injury,[4,5,8] although evidence from randomised studies is limited.[11] It is also used to control intracranial pressure before surgery, and has been suggested for cerebral oedema in hepatic failure.[12] Mannitol has also produced beneficial responses in *children* with raised intracranial pressure from birth asphyxia,[13] diabetic ketoacidosis,[14] or Reye's syndrome.[15,16] The use of osmotic diuretics to reduce intracranial pressure in patients with cerebral malaria is not routinely recommended and is controversial in other CNS infections.

In addition to its ability to lower intracranial pressure *glycerol* is reported to be able to increase blood flow to areas of brain ischaemia. It has been used orally or intravenously in an attempt to reduce cerebral oedema and raised intracranial pressure in a variety of conditions including Reye's syndrome[17] and meningitis;[18] it has been reported to be ineffective in hepatic coma.[19] Some patients have experienced severe adverse effects including haemolysis, haemoglobinuria, and renal failure. Strongly *hyperosmotic glucose* solutions (25 to 50%) have been used to reduce raised intracranial pressure and cerebral oedema caused by delirium or acute alcohol intoxication. *Hypertonic sodium chloride* has been shown to reduce intracranial pressure in several studies. It may have a role in resistant cases,[4,20] and has also been suggested in place of mannitol in acute head injury.[21]

If control is required for more than a few hours, repeated doses or continuous administration of osmotic diuretics may be necessary. Mannitol may accumulate with continuous infusion and repeated bolus doses are generally preferred. Fluid and electrolyte balance and plasma osmolality should be closely monitored.

Loop diuretics such as *furosemide* are also effective and may be used as alternatives to osmotic diuretics, particularly where a sustained effect is required. They may increase the effect of osmotic diuretics and may be used as adjuncts, usually given after the osmotic diuretic. Furosemide decreases cerebral water content and possibly also reduces secretion of CSF. It may be preferred to mannitol in patients undergoing neurosurgery.[22]

Corticosteroids have an accepted and important role in the management of raised intracranial pressure associated with tumour-induced cerebral oedema. They may be used intravenously in high doses to control acutely raised intracranial pressure due to a rapidly expanding tumour. Lower doses are given orally for maintenance or where the onset of cerebral oedema is more insidious. Corticosteroids have also been tried in patients with stroke, but results have been disappointing. Although corticosteroids have been widely used in traumatic head injury, a large randomised trial[23] found that they increased the risk of mortality and they are no longer routinely recommended.[24]

The use of barbiturate-induced coma with intravenous *thiopental* or *pentobarbital* for raised intracranial pressure has been controversial but it may be of benefit in patients refractory to conventional therapies.[4,5] In addition to their effect on intracranial pressure barbiturates may be able to protect the brain from ischaemia. *Trometamol* is reported to lower raised intracranial pressure in patients with head injury; it may do this by causing metabolic acidosis leading to vasoconstriction of cerebral vessels.[3]

Idiopathic intracranial hypertension (pseudotumor cerebri) is a rare disorder of unknown cause in which there is a raised intracranial pressure in the absence of an intracranial mass or obstruction to CSF outflow. Although it was previously known as benign intracranial hypertension, since it is not life-threatening and is usually self-limiting, symptoms may be severe or become chronic, and there is a risk of irreversible visual loss.[25,26] Patients are often obese and tend to be young and female. Drug-induced intracranial hypertension may also occur.

Management of mild symptoms usually involves diuretic treatment with furosemide, a thiazide, or acetazolamide. Analgesics, tricyclic antidepressants, or the antiepileptic topiramate may be used to control headache.[25] Corticosteroids can control acute symptoms but long-term adverse effects limit their use. Repeated lumbar puncture to remove CSF may relieve symptoms and has been used every 2 to 5 days to induce remission. In patients who cannot be controlled medically, surgical methods such as lumboperitoneal shunting may be required. There has been an anecdotal report of beneficial effects with *octreotide* in a few patients.[27]

Acetazolamide has also been tried in the treatment of patients with chronically raised intracranial pressure due to cryptococcal meningitis.[28]

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Reperfusion and revascularisation procedures

Ischaemia due to impaired blood flow is a major factor in cardiovascular disorders such as angina pectoris (p.1157), myocardial infarction (p.1175), peripheral vascular disease (p.1178) and ischaemic stroke (p.1185). The underlying cause is usually atherosclerosis (p.1159); this leads to narrowing of arteries with a consequent reduction in blood flow, while rupture of the atherosclerotic plaque may lead to thrombosis and acute occlusion of the artery. Restoration of blood flow is therefore one of the main aims of treatment for atherosclerotic disorders, and may be achieved by pharmacological and non-pharmacological methods. The choice of method depends on the condition being treated and is discussed under the individual diseases. Pharmacological methods such as thrombolysis are usually only used in acute occlusion to break down the blood clot and restore flow. Non-pharmacological methods may be used in acute occlusion or electively in situations where stenosis of the blood vessel restricts but does not totally obstruct flow. The methods used in the coronary circulation include percutaneous coronary interventions (PCI) such as balloon angioplasty and stenting,[1-3] and surgical procedures such as coronary artery bypass grafting (CABG); similar techniques are used for peripheral vascular and cerebrovascular disease. Where non-pharmacological methods are used, adjunctive drug therapy is required to prevent and treat acute and long-term complications, and this is the focus of the following discussion.

Patients undergoing surgery or PCI are at risk of **thrombosis** during and immediately after the procedure due to damage to the arteries at the site of intervention and the use of angioplasty catheters or extracorporeal circulation. Antithrombotic therapy with anticoagulants and antiplatelet drugs therefore has an important role[2-4] at the time of the procedure and may also be needed long-term (see below).

Anticoagulants are used in both surgery and PCI.

- For *surgery* involving cardiopulmonary bypass, high doses of unfractionated heparin are given by intravenous infusion. The dose is usually adjusted according to the activated clotting time (ACT), although monitoring blood-heparin concentrations may be an alternative. A target ACT of 400 to 480 seconds has been suggested,[5] with reversal of anticoagulation at the end of surgery.

Lower doses may be adequate in patients undergoing 'off-pump' or 'beating-heart' surgery (target ACT 250 seconds[5]) and in peripheral bypass surgery, although the optimum degree of anticoagulation is not established.

- Alternatives to heparin have been tried and positive results have been reported with hirudins (bivalirudin[6] and lepirudin[7]) and with the direct thrombin inhibitor argatroban,[8] although they are usually reserved for patients with heparin-induced thrombocytopenia.[5]
- Antifibrinolytics have been given to reduce bleeding complications after surgery, although there is some evidence that use of aprotinin may be detrimental (see Haemorrhagic Disorders under Uses and Administration of Aprotinin, p.1055).
- In *PCI*, unfractionated heparin is generally used since it can be rapidly reversed if emergency surgery is required, but the high doses (target ACT 250 to 350 seconds[2,3]) make bleeding a problem and alternatives have been tried. Lower doses of heparin may be effective and safer, particularly if glycoprotein IIb/IIIa-receptor antagonists are also used, and a target ACT of 200 to 250 seconds has been suggested;[2,3] however, an analysis[9] found no clear relation between heparin dose and outcome.
- Low-molecular-weight heparins have been used, although evidence for their efficacy is limited;[2,3,10,11] a meta-analysis[12] that included mostly non-blinded studies found that low-molecular-weight heparin was as safe and effective as unfractionated heparin, and further studies[13,14] have come to similar conclusions.
- Direct thrombin inhibitors may be another alternative;[2,3,11] bivalirudin appears to be as effective as heparin,[15,16] while a study with desirudin[17] found fewer early ischaemic events but no long term benefit compared with heparin.
- Fondaparinux has also been tried,[18] but the risk of catheter thrombosis may be increased and additional unfractionated heparin is recommended at the time of the procedure.[3,11]

Antiplatelet drugs have an important role in reducing acute thrombotic complications and in long-term treatment.

- In patients undergoing *surgical* bypass, they are not usually started until after the procedure since they increase the risk of bleeding, and patients who are already taking such drugs usually have them withheld for several days before elective surgery.[19] Continuation of antiplatelet therapy pre-operatively increases blood loss and the need for blood products,[20-22] although there is some evidence that use of aspirin pre-operatively may improve outcomes.[23]
- In patients undergoing *PCI*, the use of antiplatelet drugs with anticoagulants during the procedure is of established benefit. Aspirin is considered standard therapy,[2,3,11] and patients who are not already taking aspirin are usually given a loading dose at least 2 hours before the procedure; a thienopyridine such as clopidogrel or ticlopidine may be used in patients unable to tolerate aspirin. However, aspirin does not completely inhibit platelet function and combination therapy and more potent drugs have also been studied.
- Use of clopidogrel with aspirin improves outcomes and is now generally recommended,[2,3,11] although the dose and timing have been debated. Pretreatment with clopidogrel appears to be most effective, but the increased bleeding risk may be of concern if emergency surgery is required. Use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention[2,3] and there is some evidence that it needs to be given at least 15 hours before.[24] A higher dose of 600 mg may be effective if given at least 2 hours before PCI[25,26] and has been recommended,[3] particularly in patients with non-ST elevation acute coronary syndromes.[11] However, in patients with stable angina, routine use of a 600-mg loading dose at least 6 hours before angiography was no more effective than a selective strategy in which the same dose was given immediately after angiography only to those patients proceeding to PCI.[27]
- Glycoprotein IIb/IIIa-receptor antagonists such as abciximab, eptifibatide, and tirofiban given intravenously improve outcomes in a variety of patients undergoing PCI,[28] including those with acute coronary syndromes, those undergoing elective PCI, and patients receiving intracoronary stents. However, recommendations for their use vary,[2,3,11,29] and some guidelines consider them unnecessary in low-risk patients unless complications occur. Evidence for tirofiban is limited to patients with acute coronary syndromes, while abciximab is generally preferred in patients undergoing PCI for acute myocardial infarction.

  In most studies glycoprotein IIb/IIIa-receptor antagonists have been given as adjuncts to heparin and aspirin, and their role in patients also taking clopidogrel is less clear; studies in patients undergoing PCI electively[30] or for acute coronary syndromes[31] have found that abciximab adds no further benefit to clopidogrel pretreatment except in patients with raised troponins. There is also some evidence[32] that use of glycoprotein IIb/IIIa-receptor antagonists (in this case eptifibatide) with both clopidogrel and aspirin may make the routine use of heparin unnecessary.

Other acute complications during PCI include vasospasm, reperfusion injury, and arrhythmias; lack of reflow in the target artery ('no-reflow') may result from vasospasm or distal embolisation. Vasodilators such as nitrates or calcium-channel blockers may be given at the start of the procedure to reduce vasospasm;[2] verapamil, adenosine, or sodium nitroprusside may be used to treat no-reflow,[2] but are not recommended for routine prophylaxis.[33] Various drugs have been tried for cardioprotection,[34] and to protect against myocardial reperfusion injury,[35] but none yet has an established role.

Long-term treatment. Patients undergoing surgical or percutaneous revascularisation remain at risk of thrombosis after the procedure as the endothelium heals, and are also at risk of further cardiovascular events due to generalised atherosclerosis. Antithrombotic therapy should therefore be continued long-term, and patients should also be assessed for their overall cardiovascular risk and treated as appropriate (see Cardiovascular Risk Reduction, p.1164).

Anticoagulants are usually only given intravenously at the time of the procedure and oral anticoagulants such as warfarin are not routinely used. They may have a role in addition to aspirin in patients at high risk of graft occlusion after peripheral artery bypass,[36] although a study[37] comparing oral anticoagulants with aspirin found no difference in reocclusion or mortality, whereas bleeding was higher in patients receiving anticoagulants.

Antiplatelet drugs have an established role in reducing major coronary events after surgical and percutaneous revascularisation procedures,[38,39] and may also reduce reocclusion after peripheral percutaneous interventions.[40] Aspirin is recommended indefinitely in all patients.[11,19,36] Clopidogrel may be used as an alternative in patients unable to take aspirin, but may also be given as additional therapy. There is evidence that it reduces major coronary events when given with aspirin after PCI,[41] and long-term use of the combination has been recommended,[3,11,19] especially in patients with coronary stents.

Coronary artery stents[1,42] were initially developed to treat or prevent acute occlusion of the vessel due to elastic recoil after balloon angioplasty, but are now used routinely in most PCI to reduce the risk of restenosis (see below), although their effect on mortality is unclear.[43] Thrombotic occlusion 2 to 14 days after the procedure (subacute stent thrombosis) is a major complication with stent use, and initially led to the use of intensive anticoagulant/antiplatelet regimens.[42] However, with optimal stent deployment and use of heparin during the procedure, oral antiplatelet drugs alone appear to be adequate, and a combination of aspirin with clopidogrel is now recommended. Aspirin should be continued indefinitely, but the optimum duration for clopidogrel therapy is less clear. For patients with bare metal stents, clopidogrel should be given for at least 2 to 4 weeks,[2] and treatment for 12 months has been recommended.[3,19] For patients with drug-eluting stents, the risk of occlusion persists for longer, and the benefit of continuing clopidogrel is better established.[44,45] Combination therapy is therefore recommended for at least 12 months,[3,19,46] and may be continued indefinitely if tolerated.[19] Cilostazol has also been used, both as an alternative to thienopyridines,[47,48] and as part of a triple platelet regimen.[49] Heparin-coated stents may also have a role.[50]

Restenosis is a specific long-term complication of percutaneous procedures.[1,51,52] Several pathological processes are believed to be responsible, including platelet aggregation and thrombus formation, elastic recoil, vascular remodelling, and neointimal hyperplasia. Symptomatic restenosis often requires a repeat revascularisation procedure and increases the risk for clinical events. Stents reduce restenosis by preventing elastic recoil and vascular remodelling, but are associated with a higher risk of neointimal hyperplasia, and in-stent restenosis is a particular problem.[53,54] This has led to the investigation of drugs to prevent restenosis, but results have generally been disappointing. Greater success has been reported with drug-eluting stents, and these are now widely used, as discussed below; however, they are not without complications, and oral therapies continue to be investigated.

Although **systemic therapy** with antiplatelet drugs and anticoagulants reduces the risk of thrombus formation, there is little evidence that they reduce the degree of restenosis; studies with cilostazol have suggested that it may have some effect,[55,56] but this is not yet established. Lipid-regulating drugs are indicated in most PCI patients for cardiovascular risk reduction, but again their effects on restenosis are unclear;[51] there is weak evidence that omega-3 fatty acids[57] reduce restenosis, while mixed results have been reported with statins[58,59] and with probucol.[60,61] Folate therapy (folic acid, vitamin B6, and vitamin B12) has been tried since it reduces plasma-homocysteine concentrations, a risk factor for atherosclerosis and possibly restenosis, but again results have been mixed.[62]

Antiproliferative drugs have been tried, but early positive results have generally not been confirmed in larger studies.[51,63] Sirolimus, which is widely used in drug-eluting stents, has shown benefit[64-66] when given orally. Other drugs for which positive or mixed results have been reported include angiotensin II receptor antagonists,[67,68] calcium-channel blockers,[69,70] corticosteroids,[71] and thiazolidinediones,[72] but none has an established place in therapy.

The disappointing results with systemic drug treatment may relate to the difficulty in achieving adequate concentrations at the target site and **localised methods** of treatment have therefore been tried. Intracoronary radiotherapy (brachytherapy) has reduced the rates of restenosis after angioplasty,[73] and after stenting,[74] but is complex to perform and availability may be limited. *Drug-eluting stents* are now generally the preferred treatment.

These usually consist of metal stents coated with a polymer containing the drug, which is then released over a period of time, and they allow the localised delivery of high doses of drugs to the site of vessel injury. Heparin-coated stents have been used to reduce periprocedural thrombosis and may reduce long-term stenosis,[50] but stents releasing antiproliferative drugs are most widely used. Both sirolimus- and paclitaxel-eluting stents have been shown[75,76] to reduce neointimal proliferation and clinical events, including the need for repeat revascularisation, and they appear to be more effective than intravascular brachytherapy.[77,78] Outcomes may be better with sirolimus than with paclitaxel,[79] but this does not appear to be clinically important.[80,81] Other drugs that are used include sirolimus analogues such as everolimus and zotarolimus, and dexamethasone; lanreotide, and the sirolimus analogues tacrolimus and biolimus A9 are under investigation. Use of a paclitaxel-coated angioplasty balloon has also been tried,[82] and local gene therapy is also under investigation.

Although drug-eluting stents clearly reduce the incidence of restenosis, late stent thrombosis has been reported[83,84] and appears to occur more frequently than with bare-metal stents;[85] possible mechanisms include delayed endothelialisation due to the drug or hypersensitivity reactions possibly related to the polymer coating.[86] However, analyses using different definitions of late thrombosis have suggested[87] that there is no significant difference between the types of stent, and the clinical relevance of any increase in the incidence of late thrombosis remains unclear. The effect of drug-eluting stents on mortality has also been debated; some analyses[88,89] have reported an increased mortality with drug-eluting stents, whereas others[85,90] have found no significant effect. There is some evidence[91,92] that outcomes with drug-eluting stents are worse in high-risk clinical situations, although observational studies[93,94] suggest they are as safe as bare metal stents in such patients, and it appears that late events may be related to duration of antiplatelet therapy.[84] The FDA has stated[46] that the concerns about thrombosis do not outweigh the benefits of drug-eluting stents when used for their approved indications, but that outcomes may not be the same in other patients.

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Shock

Shock is a complex clinical syndrome in which there is a failure of the circulatory system to maintain cellular perfusion and function. There are many aetiologies, but the underlying defect is either inadequate venous return to the heart due to an absolute or relative reduction in plasma volume, or failure of the pumping action of the heart. A traditional approach has been to place the cause of shock into one of several basic groups:

- *Hypovolaemic shock* results from fluid loss; cardiac output is reduced due to inadequate filling pressure. Haemorrhagic causes include severe gastrointestinal bleeding and traumatic injury, while non-haemorrhagic causes include severe vomiting and diarrhoea, polyuria, and burns. Hypovolaemia can also be present in other forms of shock; in septic or anaphylactic shock fluid loss from the vasculature may occur due to capillary leakage, while peripheral vasodilatation may lead to relative hypovolaemia

- *Cardiogenic shock* usually results from acute cardiac dysfunction or failure, leading to an inadequate stroke volume and reduced cardiac output. It has a number of causes, but is most often associated with acute myocardial infarction. Other cardiac causes include valvular heart disease, cardiomyopathies, and severe cardiac arrhythmias; episodes of acute heart failure may also occur due to decompensation in patients with chronic heart failure. Shock due to circulatory disorders such as massive pulmonary embolism is also sometimes classified as cardiogenic. Other forms of shock may also have a cardiac component
- *Septic shock* occurs as a complication of infectious disease and is described and defined in more detail under Septicaemia, p.190. Hypotension occurs primarily due to peripheral vasodilatation, but fluid loss and direct effects on the heart may also be involved. Cardiac output may be reduced due to hypovolaemia; however, if circulatory volume is adequate, cardiac output is often high
- *Anaphylactic shock* (p.1205) is the result of a hypersensitivity reaction and is similar haemodynamically to septic shock

In the early stages of shock, compensatory mechanisms are usually sufficient to maintain the blood pressure, but these generally become inadequate and patients in decompensated shock classically present with hypotension, tachycardia, and tachypnoea. The skin is often cold, clammy, and cyanotic, due to compensatory peripheral vasoconstriction, while impaired organ perfusion results in dulled mental alertness, which may progress to stupor or coma; oliguria or anuria, due to impaired renal perfusion, are also frequent. Pulmonary oedema may occur as a result of impaired cardiac output in cardiogenic shock. Complications of shock include disseminated intravascular coagulation due to platelet sludging and microvascular insufficiency, acute respiratory distress syndrome (previously termed 'shock lung') (p.1498), and acute renal failure. The terms multiple organ failure syndrome (MOFS) and multiple organ dysfunction syndrome (MODS) are applied to the consequences of shock where several organs or body systems have become hypoperfused and are unable to maintain their normal function.

Management. The initial aim of treatment in all forms of shock is to restore tissue perfusion by correcting hypovolaemia and hypotension, and restoring cardiac output.[1-6] Hypoxaemia should be avoided and supplemental oxygen or mechanical ventilation may be required. Intravenous opioid analgesics may be needed for pain, and an adequate diuresis should be maintained in order to prevent renal failure; diuretics may also be required if there is pulmonary oedema. Impaired tissue perfusion often leads to lactic acidosis, but the need for specific treatment (see Metabolic Acidosis, p.1667) is unclear; sodium bicarbonate may be given for severe acidosis,[1] although some[4] consider that it should not be used. Other electrolyte abnormalities should be corrected as appropriate.

Hypovolaemia. Restoration of the circulating volume is essential, both to replace lost fluids in hypovolaemia and to maintain cardiac filling pressure in other forms of shock; small volumes may be beneficial in cardiogenic shock, but should be given cautiously to prevent pulmonary oedema. Replacement fluids available include blood products and crystalloid or colloid plasma expanders,[7-9] and the choice depends on the clinical situation. Blood products are expensive and not always available, while the relative merits of crystalloids and colloids continue to be debated.

In haemorrhage, volume expansion to maintain organ perfusion is initially the most important consideration,[10] although in trauma patients the optimum timing and quantity of fluid to give is not clear.[8,9,11] Anaemia is generally better tolerated than hypovolaemia, but where blood loss is extensive (usually considered as 40% or more of the total blood volume), red cell replacement is also required.[10,12] This usually takes the form of packed red cells with plasma expanders, and other plasma components as required. Blood substitutes are also under investigation as an alternative to red cell products, but none yet has an established role.[8,9]

In non-haemorrhagic hypovolaemia, plasma expanders alone are used. Crystalloids (solutions containing solutes such as glucose or sodium chloride that can pass a semipermeable membrane) rapidly expand both the intravascular and extravascular compartments, which could be beneficial since both become depleted in hypovolaemia. However, large volumes may be required and the duration of effect is short as fluid is rapidly redistributed. Hypertonic crystalloid solutions may allow smaller volumes to be used. Colloids (solutions containing large molecules such as albumin, dextrans, gelatins, and etherified starches, which do not pass semipermeable membranes) expand the intravascular space more effectively; they have a longer duration of effect and smaller volumes are required. This may be beneficial since it causes less haemodilution, but the exact significance of this has been questioned; the risk of hypersensitivity reactions, including anaphylaxis, may also be a concern.

Studies comparing the use of crystalloids and colloids in hypovolaemia have generally been of poor quality and the results are difficult to interpret. A systematic review[13] of trials in critically ill patients concluded that there was a small increase in mortality associated with the use of colloids, and that since they were more expensive and of no proven benefit they should not be routinely used. A further review,[14] looking specifically at the use of albumin, also suggested an increased mortality with use of the colloid. Both reviews were severely criticised,[15-17] and the relative benefits of the different types of fluid continue to be debated. A large trial[18] comparing the use of albumin and sodium chloride 0.9% in intensive care patients who required fluid resuscitation found no difference in mortality at 28 days. Updates to both reviews[19,20] to include this study found that there was no evidence of any benefit for colloids compared with crystalloids, and the authors continued to state that colloids should not be routinely used. However, there was no clear difference in mortality between patients given colloids or crystalloids, other than a suggestion[20] that albumin might increase mortality in patients with burns or hypoproteinaemia. In practice, a mixture of colloids and crystalloids tends to be given. Choice of the best crystalloid or colloid to give remains unclear; systematic reviews have found no evidence that one colloid is better than another,[21] or that hypertonic solutions are better than isotonic solutions if crystalloids are used.[22]

Hypotension and low cardiac output. Although correction of hypovolaemia may be sufficient to restore blood pressure, hypotension in shock may be profound (sometimes a systolic pressure of less than 70 mmHg) despite fluid replacement, and additional therapy with inotropes and vasopressors is often needed to improve cardiac output and reverse signs of impaired organ function.[1,4] Sympathomimetics are often used since they may have effects on the heart and the vasculature, but alternative vasoconstrictors and inotropes may also have a role. Choice depends on individual patient characteristics and the type of shock,[23] although this is generally based on theoretical considerations; a systematic review[24] of the use of vasopressors in shock found insufficient evidence to make any recommendations.

In cardiogenic or hypovolaemic shock cardiac output is usually low but peripheral resistance is high and drugs that have predominantly inotropic effects, such as dobutamine or dopamine, are often chosen. Dobutamine causes some peripheral vasodilatation and is useful where hypotension is not significant; dopamine similarly causes peripheral vasodilatation at low doses but at higher doses vasoconstriction occurs. Low-dose dopamine has been widely used as an adjunct to other inotropes since it was thought that the vasodilatation would lead to renal protection, but clinical benefit has not been established and such use is no longer recommended (see Surgery and Intensive Care, p.1274). Phosphodiesterase inhibitors such as amrinone and milrinone can also be considered in low cardiac output states; they have positive inotropic activity and produce peripheral vasodilatation, and may be particularly useful in patients with decompensated chronic heart failure who have been taking beta blockers.[2,4,5] Vasodilators such as intravenous glyceryl trinitrate or sodium nitroprusside may also be beneficial for patients in shock with a low cardiac output but adequate blood pressure, as well as in patients with pulmonary oedema.[1,2,5] They act by reducing cardiac afterload but must be used with care as there is a risk of precipitating hypotension.

In septic or anaphylactic shock, where cardiac output is generally high but peripheral resistance is low, vasoconstrictors such as noradrenaline or dopamine are usually preferred;[1,6] they may be given with more potent inotropes such as dobutamine or adrenaline. Adrenaline has also been given alone although renal artery vasoconstriction may limit its use; it has also been reported to cause lactic acidosis,[25] but a study[26] comparing noradrenaline plus dobutamine with adrenaline alone found no difference in outcomes in patients with septic shock. Vasopressin may be an alternative,[6,27,28] particularly in patients with vasodilatation that is resistant to sympathomimetics, but is not recommended for routine use. It may also be used as an adjunct to sympathomimetics, although no clear benefit has been shown compared with sympathomimetics alone.[29].

The opioid antagonist naloxone may also improve blood pressure in shock,[30] but its role is not established.

Specific therapies are indicated in some types of shock. In cardiogenic shock associated with ***myocardial infarction***,[2,31] specific therapy to restore myocardial perfusion is also required (see p.1175).

In ***septic shock*** appropriate antibacterial therapy should be given as outlined under Septicaemia on p.190. Methods of inhibiting endogenous mediators released in response to sepsis that are thought to be responsible for the haemodynamic effects are also under investigation but clinical benefits have not yet been shown.[3,32] However, improved outcomes have been reported[33,34] with the use of low-dose corticosteroids, and in severe sepsis activated protein C may also be used.[6]

Adrenaline is the cornerstone of management in ***anaphylactic shock*** (see p.1205).

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Stroke

Stroke, sometimes called a cerebrovascular accident, is the major consequence of cerebrovascular disease and has been defined as an acute neurological dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas of the brain. If signs and symptoms persist for more than 24 hours or lead to death the event is termed a completed stroke, whereas if they disappear within a few minutes or hours, or at most within 24 hours, the event is termed a transient ischaemic attack.

Strokes may be ischaemic (infarction-related) or haemorrhagic.[1-4] **Ischaemic stroke** is by far the commonest type and generally results from occlusion of cerebral arteries. This may be caused by local thrombosis at sites of atheroma, but more commonly results from thromboemboli arising from outside the brain and lodging in the cerebral vessels; an example of the latter is cardioembolic infarction associated with atrial fibrillation or acute myocardial infarction. Arterial occlusion results in inadequate cerebral perfusion, which leads to ischaemia and subsequently to stroke. About 20% of patients with acute ischaemic stroke experience worsening of symptoms within a few days of onset. This is termed progressing stroke, stroke-in-evolution, or unstable stroke, and may be due to progression of the thrombosis; haemorrhagic conversion, with bleeding into the infarcted area, may also occur. **Transient ischaemic attacks** are acute episodes of focal neurological deficit or monocular visual loss (amaurosis fugax), mainly due to ischaemia associated with atherothrombosis. There is usually complete clinical recovery but a tendency for recurrence, and patients are also at an increased risk of stroke. **Haemorrhagic stroke** is secondary to subarachnoid or to intracerebral haemorrhage. *Subarachnoid haemorrhage* is bleeding into the fluid-filled subarachnoid space between the brain and the skull, and usually occurs after rupture of an aneurysm; other causes include arteriovenous malformations and hypertensive microaneurysms. *Intracerebral haemorrhage* is bleeding into the parenchyma of the brain, and may result from rupture of arteries damaged by chronic hypertension. Haemorrhage produces a focal haematoma causing a local increase in pressure which may lead to further bleeding and enlargement of the haematoma. The increase in pressure in the area of the haematoma may also produce local ischaemia.

Clinical presentation of stroke can vary enormously in severity and combination of signs and symptoms, and depends on the site and extent of infarction or haemorrhage. Haemorrhagic stroke is typically of sudden onset with severe headaches, vomiting, and rapid deterioration of consciousness – all signs of raised intracranial pressure – but mild to moderate haemorrhage may be difficult to distinguish from infarction on the basis of clinical signs alone. Neurological deficits in all forms of stroke may include impairments to speech, balance, vision, touch sensation, and movement. Recovery is variable and patients have been classed as major or minor stroke (reversible ischaemic neurological deficit) victims according to their degree of recovery at a given time after the stroke.

Accurate diagnosis of the type of stroke is important since management is very different and interventions that are beneficial in infarction may be dangerous in patients with haemorrhage. Although clinical presentation may suggest the type of stroke this is not always reliable and imaging is usually required to distinguish between haemorrhagic and ischaemic stroke. Computed tomography (CT) is the preferred technique, but magnetic resonance imaging may also be used.[5,6] Diagnosis of transient ischaemic attacks usually rests on the patient's history as these short attacks are seldom witnessed by a physician and there are no objective confirmatory tests; however, imaging has an important role in determining aetiology and guiding subsequent management.[7,8]

Management of stroke involves immediate treatment of the acute stroke, treatment and prevention of complications such as swallowing disorders or spasticity, rehabilitation, and long-term treatment for secondary prevention. Where possible, patients should be managed within a stroke unit since this has been shown to improve outcome. Primary prevention may be considered in individuals at risk of ischaemic stroke. This includes those with atrial fibrillation, a major risk factor for stroke (see Cardiac Arrhythmias, p.1160), and those with risk factors for atherosclerosis (see Cardiovascular Risk Reduction p.1164); the role of endarterectomy in individuals with carotid artery stenosis is discussed under Long-term Management, below.

Ischaemic stroke. Reviews[9-14] and guidelines[5,6,15] emphasise that, as in myocardial infarction, early recognition of symptoms and prompt evaluation and treatment of stroke are of vital importance. The aim of treatment is to limit or reverse damage to the brain. Ischaemia deprives the cells of oxygen and glucose, leading to infarction, but this appears to be time-dependent. While some tissue may be irreversibly damaged when the patient presents, there is evidence that surrounding tissue (the 'ischaemic penumbra') may be salvageable. Restoration or improvement of blood flow is therefore a logical means to preserve this tissue; strategies to protect the cells from the consequences of ischaemia are an alternative approach.

Acute management involves general supportive measures, and specific treatments to reverse ischaemia and protect the brain tissue. General supportive measures include ensuring adequate oxygenation and fluid and electrolyte balances, avoiding hypercapnia and hyperglycaemia or hypoglycaemia, abolishing seizures, and treating fever; nutritional status should also be assessed. Control of hypertension is controversial since lowering the blood pressure may reduce cerebral perfusion and worsen ischaemia, and hypertension usually resolves spontaneously without treatment.[16] Antihypertensive therapy may be indicated in specific patients, such as those with severe hypertension or those being considered for thrombolytic therapy.

Specific therapy for ischaemic stroke is limited. As in myocardial infarction, the main cause of ischaemic stroke is thromboembolic occlusion, and use of antithrombotic drugs such as antiplatelets, heparin, and thrombolytics, therefore appears logical. However, evidence of benefit is not as clear as it is in myocardial infarction, and the risks may be greater; the presence of haemorrhage must be excluded and the risk of potentiating spontaneous secondary brain haemorrhage (haemorrhagic transformation) must be borne in mind. Other strategies to improve blood flow or to limit the effects of ischaemia using neuroprotectants have also been tried, but results to date have been disappointing.

Antiplatelet drugs. Aspirin has been evaluated in two large studies—the International Stroke Trial (IST)[17] and the Chinese Acute Stroke Trial (CAST).[18] The combined results of these studies[18] found that aspirin 160 mg[18] or 300 mg[17] daily started within 48 hours of symptom onset produced about 9 fewer deaths or non-fatal strokes per 1000 patients in the first few weeks following ischaemic stroke. Aspirin has therefore been recommended for patients with ischaemic stroke who are not receiving thrombolytic or anticoagulant therapy, and should be started within 48 hours of stroke onset.[5,6,19] Other antiplatelet drugs are under investigation, but do not yet have an established role;[5,6] a study with the glycoprotein IIb/IIIa antagonist abciximab was stopped early due to an increased incidence of bleeding.[20]

Anticoagulants are not routinely recommended in the early management of acute ischaemic stroke,[5] although they may have a role in selected patients.[6] Anticoagulation should prevent further thrombus formation and limit the size of the cerebral infarct; however, any benefit may be offset by an increase in intracranial haemorrhage, and a systematic review[21] has suggested there is no evidence to support routine use. The IST,[17] which evaluated two dosages of heparin (5000 units or 12 500 units subcutaneously twice daily), found no benefit from either regimen and the higher dose particularly was associated with haemorrhagic stroke and bleeding. Another study,[22] comparing the low-molecular-weight heparin tinzaparin with aspirin, similarly found no benefit. It had been suggested that patients with cardioembolic stroke were likely to benefit from heparin therapy,[23] even though there is a special risk of haemorrhagic transformation in these patients, which means that early anticoagulation is often hazardous. However, the IST[17] failed to show any benefit in this group, and a study[24] of low-molecular-weight heparin in patients with acute ischaemic stroke and atrial fibrillation also showed no benefit. No improvement in outcome was reported after 3 months in a study of danaparoid given in acute ischaemic stroke.[25] A study[26] with ancrod found an improvement in outcome when given within 3 hours of stroke onset, but a further study was terminated due to lack of benefit.

The risk of venous thromboembolism (deep-vein thrombosis and pulmonary embolism) is increased after stroke, particularly in immobile patients, and prophylaxis with low-dose subcutaneous heparin or low-molecular-weight heparin may be considered in those at high risk.[6,19]

Thrombolytics. Intravenous thrombolytics increase the risk of cerebral haemorrhage and have therefore generally been contra-indicated in both ischaemic and haemorrhagic stroke. However, there is evidence that use of thrombolytics in ischaemic stroke may be of benefit, despite the increased risk of bleeding, and they may have a role in selected patients,[27-29] particularly if they can be given in the early stages.[30] A study[31] with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial) found that clinical outcome was improved, despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[31] and this benefit was maintained at 12 months.[32] However, there was no difference in mortality or rate of recurrence of stroke. On the basis of this study, guidelines[5,6,19] now recommend alteplase for selected patients if it can be given within 3 hours of stroke onset, and this appears to be safe in practice.[33,34] Other thrombolytics, such as streptokinase, have generally produced less favourable results, and none of these are currently recommended. The intra-arterial route has also been tried and may be used in selected patients.[5,6,19] Combined use of intravenous and intra-arterial alteplase,[35] as well as use of adjunctive therapies such as therapeutic ultrasound[36] or antithrombotics, are under investigation but do not yet have an established role.[5]

Other approaches that have been tried include various methods to improve cerebral blood flow. Haemodilution with *dextran* or *pentastarch* has generally been disappointing and is not usually recommended.[5,6] Drug-induced hypertension may also increase cerebral blood flow and appears to be safe,[37] but clinical benefit remains to be established.[5] Hypoxia and hypocapnia may cause cerebral vasoconstriction as well as directly contributing to ischaemic injury, and there have been anecdotal reports and small studies reporting benefit with *hyperbaric oxygen therapy*, although a systematic review[38] suggested that clinical benefit was unlikely. Treatment with *corticosteroids* or hyperosmolar diuretics such as *glycerol* or *mannitol* in an attempt to reduce the cerebral oedema has also been disappointing. There may be some benefit with glycerol, but further evidence is needed.[39]

Neuroprotection. Ischaemia leads to a complex series of biochemical changes, the 'ischaemic cascade', resulting eventually in cell necrosis. The process is incompletely understood, but steps include calcium influx and release of neurotransmitters. Drugs acting at different steps in this ischaemic cascade, sometimes termed neuroprotectants, have been tried in acute ischaemic stroke in the hope of limiting the damage caused by ischaemia. Results of studies so far have been largely disappointing, and no drug has yet been found to be effective. However, research continues,[40] with many trials focusing on starting treatment in the first few hours after ischaemic stroke.[41]

Long-term management. Patients who have had an ischaemic stroke or transient ischaemic attack are at risk of further stroke but are also at increased risk of other cardiovascular events, including myocardial infarction and sudden death. Long-term treatment for secondary prevention therefore has an important role.[6,42-46] All patients should be assessed for standard cardiovascular risk factors, particularly hypertension, and these should be treated as appropriate (see Cardiovascular Risk Reduction, p.1164). There is some evidence that reduction of blood pressure and lipids reduces the risk of stroke irrespective of the presence of hypertension or hyperlipidaemia,[44] and the use of ACE inhibitors or angiotensin II receptor antagonists[47] and statins[6] has been recommended. Atrial fibrillation is a specific risk factor for stroke and should also be treated (see Cardiac Arrhythmias, p.1160). Hypercoagulability may increase the risk of stroke and blood screening for polycythaemia, thrombocytosis, and abnormal coagulation function has been recommended. Carotid endarterectomy is of established benefit for secondary prevention in patients with clinically significant carotid stenosis,[6,48] but its role in primary prevention is less clear.[49,50] Antithrombotic therapy may also have a specific role.

Antiplatelet drugs. Long-term prophylaxis with aspirin reduces the risk of future serious vascular events including stroke in patients who have already suffered an ischaemic stroke or transient ischaemic attack,[19,45,46,51] regardless of age.[52] The optimum dose is unclear; medium doses of 75 to 325 mg of aspirin daily have been most widely studied[51] and an analysis of trials using aspirin over a dose range of 50 to 1500 mg daily found no relationship between dose and the reduction in risk of stroke.[53] In patients undergoing carotid endarterectomy the risk of stroke, myocardial infarction, and death over 3 months may be lower for those taking medium dose aspirin compared with higher doses.[54] Dipyridamole is also effective,[55,56] and has been used in patients unable to tolerate aspirin, but it is more effective when given with aspirin[56,57] and combination therapy is now preferred.[6,19,45] Clopidogrel is another alternative,[58] but should not be given with aspirin since any benefit is offset by an increased risk of bleeding.[59] Ticlopidine has also been used, but adverse effects are a problem and a study[60] in black patients found that it was less effective than aspirin.

Anticoagulants. Oral anticoagulants have an established role in patients with cardioembolic stroke, but in patients with non-cardioembolic stroke or with transient ischaemic attacks they have no clear advantage over antiplatelet drugs,[61,62] and some studies[63,64] comparing warfarin with aspirin have been stopped early due to increased bleeding risks with the anticoagulant. Anticoagulants are therefore not generally recommended for secondary prevention in non-cardioembolic stroke[6,45,46] although they have been used in patients with recurrent symptoms despite antiplatelet therapy and may be considered in other selected patients.[6,19,45]

Subarachnoid haemorrhage. Subarachnoid haemorrhage[65-68] is associated with high morbidity and mortality, early deaths being due to damage from initial bleeding, recurrence of bleeding, and infarction. Infarction is often a result of vasospasm which is one of the pathophysiological mechanisms that contributes to stopping the bleeding; clot formation and increasing intracranial pressure are other processes involved. Up to a quarter of patients with subarachnoid haemorrhage develop delayed cerebral ischaemia mainly between days 5 and 14 after the initial bleed, and again vasospasm may be a contributory factor. Early medical treatment aims to prevent delayed cerebral ischaemia, to prevent rebleeding, and to stabilise the patient. Surgical or endovascular interventions to clip or embolise the aneurysm or correct the arteriovenous malformation are then performed to prevent further haemorrhage. Vasospasm and delayed cerebral ischaemia may be prevented by maintaining or slightly increasing plasma volume and blood pressure, and a fluid intake of 2 to 3 litres daily has been recommended.[65] However, there is no good evidence to support routine volume expansion.[69] Oral nimodipine is of benefit[70] and should be started as soon as possible after diagnosis of subarachnoid haemorrhage. Antiplatelet drugs have also been tried and may improve outcomes, but this remains to be confirmed.[71] Established vasospasm may be treated by angioplasty, or intra-arterial vasodilators may be given. There is some evidence of benefit with intra-arterial papaverine,[72] although adverse effects have also been reported;[73] verapamil has also been used.[74] Use of antifibrinolytics such as aminocaproic acid or tranexamic acid to prevent rebleeding is no longer generally recommended.[65] A systematic review[75] found that any benefits were offset by an increase in poor outcomes due to cerebral ischaemia; paradoxically, rebleeding has been noted in patients given high doses of aminocaproic acid after subarachnoid haemorrhage (see Effects on the Blood, under Adverse Effects of Aminocaproic Acid, p.1053). Headache can be managed with analgesics such as paracetamol, dextropropoxyphene, codeine, or tramadol. Localised haematomas may be amenable to surgical evacuation, and intraventricular thrombolytics have also been used.[76]

Intracerebral haemorrhage. Outcome of intracerebral haemorrhage depends on the location and size of the haematoma (determined by computed tomography), on the level of consciousness, and on the progression of neurological signs, and development of increased intracranial pressure.[77-79] Any known cause of bleeding, such as warfarin anticoagulation, should be reversed. Optimum management of blood pressure is uncertain; it should probably be lowered when it is very high (>200 mmHg systolic[80]), but hypoperfusion should be avoided. Short-acting antihypertensives such as labetalol, esmolol, or sodium nitroprusside are generally used,[80] although theoretically nitroprusside may increase intracranial pressure and should be avoided if this is already raised.[79] Surgical drainage of the haematoma may sometimes be possible, but its role is uncertain;[79,80] routine early surgery has not been shown[81] to improve outcome. Instillation of a thrombolytic to improve aspiration of the haematoma has been reported,[82] but benefit has not been established. Raised intracranial pressure should be controlled[80] (see p.1181). Antiepileptic prophylaxis may be necessary in some patients.[80] Use of activated factor VII to reduce the risk of further bleeding provided some benefit,[83] but has not been shown to improve survival or functional outcome.[84] Long-term management of risk factors, particularly hypertension, should be considered for secondary prevention.

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Thromboembolic disorders

The term thromboembolic disorder has been applied loosely to cardiovascular disorders associated with thrombus and embolus formation in blood vessels. A **thrombus** is a stationary blood clot composed of fibrin and platelets and other cellular elements. **Thrombosis** is occlusion of a vein or artery by a thrombus. An **embolus** is a fragment of blood clot, atheromatous material, or other foreign matter carried along in the bloodstream. Occlusion of a blood vessel by an embolus is termed **embolism** or **thromboembolism**.

Formation of blood clots in the body is the result of a coagulation cascade (see Haemostasis and Fibrinolysis, p.1045). Under normal circumstances systemic coagulation is prevented by natural antithrombotic systems that limit blood clots to sites of vascular injury. Thromboembolic disorders occur when there is an imbalance between these systems. Three factors are involved, namely damage to the endothelial lining of blood vessels, reduced blood flow, or changes in the coagulation mechanisms of the blood. A further factor that increases the risk of clotting is the presence of an artificial surface in contact with the blood, for example mechanical heart valves, intravascular catheters, or during extracorporeal circulation procedures. Thromboembolism can occur in any part of the circulation, including the heart and the capillaries, but the characteristics of the thrombi, the consequences, and the management of thromboembolism depend to a large extent upon whether the arterial or venous system is involved.

The mainstay of management for thromboembolic disorders is antithrombotic drugs. These act at different points in the coagulation cascade and include anticoagulants and antiplatelet drugs, which are used to limit the extent of thrombosis or thromboembolism and to prevent further thromboembolic events occurring, and thrombolytics, which are used to lyse the clot.

Arterial thromboembolism is almost always a consequence of damage to the endothelium due to atherosclerosis (p.1159); the atheroma may block the blood vessel or, more commonly, occlusion is a result of thrombus formation at a site of a recently ruptured atheromatous plaque. Arterial thrombi contain more platelets than venous thrombi and tend to remain fixed, but emboli may break off and occlude distal vessels. Arterial emboli may also result from thrombosis within the heart, for example due to arrhythmias or valvular heart disorders.

Thrombosis or thromboembolism in the arterial circulation produces ischaemia in the tissues perfused by the artery, which may lead to infarction. It may therefore result in myocardial infarction (p.1175) or unstable angina (p.1157) if it occurs in coronary arteries, stroke (p.1185) if it occurs in cerebral arteries, or critical limb ischaemia if it occurs in peripheral arteries (p.1178).

Venous thromboembolism (p.1189) is usually a consequence of stasis of the blood, but other factors such as local trauma or coagulation activation are also required. Reduced venous blood flow occurs in many conditions, including obesity, heart failure, and during prolonged immobilisation. Abnormal clotting may occur in conditions such as malignancy, pregnancy, and the nephrotic syndrome, or during oestrogen therapy; it may also be due to inherited or acquired clotting disorders or thrombophilias (see below). Surgical operations are particularly associated with venous thromboembolism; trauma activates clotting factors and reduced blood flow may occur during the procedure and recovery period.

Venous thrombi have a 'red tail' of fibrin and red cells that may occlude the vein but which often separates to form an embolus; this is most likely during the early stages when the thrombus is only loosely attached. Thrombosis or thromboembolism in the venous circulation produces oedema or inflammation in the tissue drained by the affected vein. The commonest type of venous thrombosis is deep-vein thrombosis, which is associated especially with immobility and the postoperative period. Pulmonary embolism is the most serious complication of deep-vein thrombosis and occurs when part of the thrombus migrates in the circulation and becomes lodged in the pulmonary artery. Hypercoagulable states may result in deep-vein thrombosis or more generalised clotting in microvessels (microvessel thrombosis), such as thrombotic thrombocytopenic purpura or purpura fulminans (see Thrombotic Microangiopathies, p.1076).

Thrombophilias are acquired or inherited disorders of the clotting system in which the antithrombotic mechanisms are impaired. Inherited deficiencies of antithrombin III, protein C and protein S all predispose to thromboembolism. Resistance to activated protein C has been identified as a major cause of inherited thrombophilia and appears to be due to a mutation in the factor V gene (factor V Leiden). A mutation in the prothrombin (factor II) gene is associated with increased concentrations of prothrombin and risk of thrombosis. Acquired thrombophilias may occur secondary to disorders such as malignancy, infection, or collagen-vascular disorders; in many cases antiphospholipid antibodies (such as lupus anticoagulant) are present. Hyperhomocysteinaemia is another risk factor and may have both inherited and acquired causes.

Inherited thrombophilias generally result in venous thromboembolism; this is often recurrent and may occur in unusual sites or at a young age. They often present when some further risk factor is present, such as pregnancy, use of combined oral contraceptives, or surgery, but the value of screening asymptomatic patients remains unclear. Acquired thrombophilias may lead to arterial or venous thromboembolism.

Patients with thrombophilias who develop thromboembolism should be treated conventionally, with anticoagulants or thrombolytics as appropriate. There continues to be debate regarding the duration of therapy, with some authorities recommending life-long anticoagulant therapy after a single episode and others recommending life-long therapy only in those with recurrent thrombosis. The optimum intensity of long-term anticoagulation in patients with thrombophilia is also debated. If anticoagulation is not continued, thromboprophylaxis should be given during high risk situations. Thromboprophylaxis is probably also necessary during pregnancy, particularly in women with antiphospholipid antibodies who are at risk for recurrent fetal loss (see Systemic Lupus Erythematosus, p.1513), but the risks to the fetus from anticoagulant therapy must also be considered (see Venous Thromboembolism, p.1189). Replacement of antithrombotic factors may have a role in some situations.

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Valvular heart disease

Valvular heart disease affects the normal function of the heart and leads to disorders of blood circulation. The principal cause of valvular disease in the developing world is rheumatic heart disease. Other causes are more common in Western countries; they include congenital abnormalities, cardiovascular disorders such as ischaemic heart disease and hypertension, and degenerative disorders. Any of the heart valves may be affected but disorders of the aortic and mitral valves are most significant; more than one valve may be involved in some patients.

The symptoms of valvular heart disease depend upon the valve that is affected, and whether the problem is stenosis or regurgitation. All valve disorders place a haemodynamic burden on the heart and ultimately lead to heart failure. Other consequences include the development of pulmonary hypertension and arrhythmias. Infective endocarditis and thromboembolic disorders, in particular stroke or systemic embolism, are important complications.

The main aims of treatment in patients with valvular heart disease are to reduce symptoms, prevent complications, and reduce mortality.[1-3] Surgical management is usually necessary once symptoms develop and may also be warranted in some patients who are asymptomatic. Medical therapy is generally reserved for pre-operative symptom control and for patients who are unsuitable for surgery.

Medical treatment for **symptomatic patients** is similar to that used in other forms of heart failure (see p.1165). In acute situations sodium nitroprusside and inotropes such as dopamine or dobutamine may be indicated, but for chronic therapy diuretics, digoxin, ACE inhibitors, and beta blockers are used. The choice of drug depends on the valve affected. ACE inhibitors and other vasodilators have generally been avoided in *aortic stenosis* since any reduction in blood pressure cannot be balanced by an increase in cardiac output and there is a theoretical risk of severe hypotension. However, symptomatic improvement has been reported[4] with enalapril in patients with severe aortic stenosis and preserved left ventricular function, although it was not tolerated in those with left ventricular dysfunction, and sodium nitroprusside has been used successfully for acute symptoms.[5] Some guidelines also recommend that beta blockers should be avoided in aortic stenosis.[3] For patients with *aortic regurgitation* who require medical therapy, vasodilators may be of particular value, especially in severe forms.[6] Symptomatic benefit has also been reported[7] with ACE inhibitors in *mitral stenosis*. Arrhythmias should be treated with standard antiarrhythmics (see p.1160).

Drug therapy to prevent the progression of valvular disorders has generally been disappointing. Although similarities have been suggested between aortic stenosis and atherosclerosis, an observational study[8] in asymptomatic patients taking ACE inhibitors for hypertension found no effect on the progression of stenosis, and initial indications of benefit[8] with statins in patients with calcific aortic stenosis were not confirmed in later studies,[9,10] except in a small group of patients with very early disease.[9] The results of an early study[11] indicating that long-term vasodilator therapy with nifedipine improved outcome in asymptomatic patients with severe aortic regurgitation have not been confirmed by a later study of long-term therapy with nifedipine or enalapril.[12] Another study[13] found no benefit with ACE inhibitors in asymptomatic patients with mitral regurgitation.

Surgery is the mainstay of treatment in valvular heart disease and generally involves valve replacement with either bioprosthetic (tissue) or mechanical valves; the latter are longer lasting, but pose a greater risk for thromboembolism. Valve repair may be suitable in some cases, particularly for mitral regurgitation, while balloon valvulotomy may have a role in some patients with stenosis.[2] Valve replacement alleviates symptoms, but patients remain at risk for complications.

In **asymptomatic patients** and in those with **prosthetic valves**, the main aim of therapy is to prevent the complications of bacterial endocarditis and of systemic embolism from thrombus formation within the heart. Antibacterial prophylaxis should be given to patients with valvular heart disease where indicated (see Endocarditis, p.168). Long-term thromboembolism prophylaxis is generally only recommended in patients with another risk factor for embolisation, such as atrial fibrillation, a dilated left atrium, left ventricular dysfunction, a hypercoagulable state, or previous systemic embolism,[2,14,15] and in those with mechanical replacement valves. However, antiplatelet drugs may be considered in other patients.

Long-term treatment with an oral anticoagulant such as warfarin is generally regarded as essential for patients with a *mechanical prosthetic heart valve*,[2,3,15] but the optimum level of anticoagulation is unclear. The risk of thromboembolism depends upon the type and position of the valve and the presence of other risk factors, but must be balanced against bleeding risk. In the UK, specific target INRs are recommended where the valve type and position are known and vary between 2.5 and 3.5 for valves in the aortic position and between 3.0 and 3.5 for valves in the mitral position. If specific information is not available a generic target of 3.0 is recommended for valves in the aortic position and 3.5 for valves in the mitral position.[16] In the USA, the recommended INR range is 2.5 to 3.5, with a lower range of 2.0 to 3.0 suggested as being adequate for most types of valves in the aortic position when there are no other risk factors.[2,15] However, a large study[17] in patients stratified to different target INR ranges found that the risk of moderate to severe thromboembolism and of bleeding complications was comparable for INRs ranging from 2.0 to 4.5; patients had aortic or mitral valve replacement, or both, and all had one particular type of valve. There is evidence that adding an antiplatelet drug (dipyridamole or low-dose aspirin) further reduces the risk of death and thromboembolism although the risk of bleeding is increased.[18] Adjunctive antiplatelet drugs may be considered for patients with additional risk factors such as embolism while on warfarin therapy, or ischaemic heart disease.[2,3,15] Alternatively, or in addition, patients with systemic embolism despite an adequate INR may have their target INR range increased.[15]

For patients with *bioprosthetic heart valves* anticoagulants are recommended for the first 3 months after replacement,[15] although aspirin may be equally effective,[19] and it is often used instead of anticoagulants when only the aortic valve is involved. Longer term oral anticoagulant therapy is generally considered necessary only for patients with additional risk factors (as for asymptomatic patients, above).[2,15] An INR of 2.0 to 3.0 appears adequate for patients with bioprosthetic heart valves. Low-dose aspirin has been recommended[2,15] in patients with bioprosthetic valves who do not require oral anticoagulants, although other guidelines[3] state that there is no evidence to support this.

For patients on long-term anticoagulation, interruption of therapy for surgical procedures or due to bleeding complications exposes patients to the risk of thromboembolism. A study[20] in patients with haemorrhage suggested that it is safe to withhold oral anticoagulants. For patients undergoing surgery, the evidence for either withholding anticoagulants or converting to an alternative form of antithrombotic therapy perioperatively is not conclusive, although recommendations have been made.[2,3] In procedures with a low bleeding risk, anticoagulation can usually be continued. In procedures with a higher bleeding risk, anticoagulants may be withheld if the risk of thromboembolism is low, but otherwise conversion to heparin is recommended. Intravenous unfractionated heparin is preferred;[2,3] low-molecular-weight heparin may be suitable as an alternative, but there have been concerns about its safety and this remains controversial.[21]

The use of anticoagulants is also controversial in patients with infective endocarditis because of the substantial increase in risk of haemorrhage in these patients. Routine anticoagulation is not advised, and patients who are already taking oral anticoagulants should generally stop therapy until it is clear that surgery is not required and the patient is stable.[15]

If obstruction of prosthetic valves by thrombus formation occurs, surgical intervention is usually recommended.[2,3,22] Thrombolytics such as streptokinase or urokinase may be used[15] but are often ineffective and are associated with high risk. They are therefore usually reserved for patients at greatest risk from surgical intervention,[2,3] although a study[23] of patients with left-sided prosthetic valve thrombosis found thrombolytics to be more successful than surgery, especially in the critically ill. Repeated treatments[24] may increase the success rate. Heparin may have a role in non-obstructive thrombosis. Patients who have had a valve thrombosis should have their anticoagulant control optimised;[3] higher target INRs or adjunctive antiplatelet therapy may be considered.[2,15]

The haemodynamic changes that occur during **pregnancy** may complicate the management of women with valvular heart disease.[25-27] In addition, pregnancy is a known risk-factor for thromboembolism and patients with valvular heart disease who become pregnant are therefore at increased risk.[28] However, long-term prophylaxis with an oral anticoagulant such as warfarin presents a problem since warfarin is generally contra-indicated in pregnancy (see Adverse Effects under Warfarin, p.1425). Women with mechanical prosthetic valves must continue anticoagulation but choice of therapy is unclear.[2,29] A systematic review[30] found that continued use of oral anticoagulants increased the risk to the fetus, but that thromboembolic complications were higher with heparin. Most guidelines therefore advise that the choice should be discussed with the patient, balancing the risks for each individual, but specific recommendations vary.[2,3,31] The main risk of embryopathy with warfarin is between weeks 6 and 12 of gestation and heparin therapy is often substituted during this period and also at term (to avoid an anticoagulated neonate). However, satisfactory outcomes have been reported[32] with use of warfarin throughout pregnancy, including the first trimester. The risk of embryopathy appears to be lower with daily warfarin doses of 5 mg or lower, and patients with an adequate INR at this dose may continue warfarin until the 36th week, before switching to heparin.[2,3] If heparin is substituted for warfarin, either during the first trimester or throughout pregnancy, use of an adequate dosage is critical, and strict monitoring is required. Adjusted-dose subcutaneous heparin, with an initial dose of 17 500 to 20 000 units subcutaneously every 12 hours has been suggested;[31] intravenous heparin may be an alternative, but low-dose subcutaneous heparin should not be used as it provides inadequate protection. Low-molecular-weight heparin has also been used, although this is controversial;[2,3,21] if it is used, anti-factor Xa concentrations should be monitored carefully. Low-dose aspirin may be used as an adjunct to subcutaneous heparin or warfarin in women at high risk of thromboembolism.[2,31]

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Vasospastic arterial disorders

Raynaud's syndrome is the most important form of vasospastic peripheral arterial disease and forms part of the spectrum of peripheral vascular disease (see p.1178). Vasospastic arterial disorders represent an inappropriate response to temperature, resulting in vasoconstriction and/or vasospasm; Raynaud's syndrome, acrocyanosis, and chilblains are usually induced by cold, whereas erythromelalgia is caused by heat.

In **Raynaud's syndrome**, paroxysmal attacks of pallor and cyanosis, usually of the digits, occur in response to cold, or sometimes emotional stress. Erythema replaces the cyanosis as the attacks resolve. The cause of primary Raynaud's syndrome (Raynaud's disease) is unknown. Features identified include intense vasoconstriction or vasospasm, disturbance of sympathetic nerve supply, changes in circulating catecholamines, enhanced platelet aggregation, red cell deformability, and fibrinolysis. It is probable that not all cases are due to the same mechanism. It has been suggested that the underlying problem may not be an overreaction to the initial cold insult but a defect in the normal ensuing adaptive response. Secondary Raynaud's syndrome (Raynaud's phenomenon) frequently co-exists with arterial occlusive disease such as thromboangiitis obliterans and connective tissue disorders, in particular scleroderma (systemic sclerosis). Trauma and certain drugs, notably beta blockers and ergotamine, may also be responsible for inducing secondary Raynaud's syndrome.

Management. In mild cases of Raynaud's syndrome, where attacks are infrequent and of limited severity, protective measures to keep warm are the mainstay of treatment; this involves wearing appropriate clothing and the use of appliances such as heated gloves. Smoking should be avoided because of the vasoconstriction caused. Any underlying or co-existing disease or cause in secondary Raynaud's syndrome should be treated. Drug therapy is indicated in more severe cases.[1-7] It is directed towards producing vascular smooth muscle relaxation and vasodilatation in order to improve resting blood flow, thereby reducing the extent of tissue ischaemia. Some drugs may also act by modifying platelet aggregation or blood rheology. Numerous drugs have been tried in Raynaud's syndrome, although only a few have an established role.

- *Calcium-channel blockers* have been of benefit and are widely used in Raynaud's syndrome, but it is not entirely clear which of their pharmacological actions is responsible. Dihydropyridines are usually preferred; the most widely used and studied is *nifedipine*.
- *Moxisylyte*, an alpha blocker with vasodilating activity, is also widely employed. Other alpha blockers, for example, phenoxybenzamine and prazosin, as well as reserpine, have been used although in some cases adverse effects have limited their usefulness.
- *Cinnarizine*, *naftidrofuryl*, *pentoxifylline*, and *nicotinic acid derivatives* such as inositol nicotinate have had widespread use in Raynaud's syndrome but evidence of efficacy is lacking. Topical vasodilators, including glyceryl trinitrate, have also been used.
- In severe Raynaud's syndrome complicated by ulceration and gangrene, *prostaglandins* have been promising. *Alprostadil*, *epoprostenol*, and *iloprost* have been given by intravenous infusion. In some cases the beneficial effects have persisted for a few months after treatment and two or three infusions given at intervals over the winter months have prevented the severe complications of Raynaud's suffered in previous years. Oral iloprost has also been reported to reduce the severity of attacks. Prostaglandins applied topically in ulcerative cases include *dinoprostone*.
- Small studies or anecdotal reports have noted variable effects with many *other drugs* including the ACE inhibitors captopril and enalapril, the serotonin reuptake inhibitors fluoxetine and venlafaxine, ketanserin, piracetam, sodium nitroprusside, calcitonin gene-related peptide, and losartan. None of these therapies appears, however, to have an established role. There is also some evidence[8] that phosphodiesterase type-5 inhibitors such as sildenafil may be of benefit.

Acrocyanosis is characterised by a persistent blue discoloration of the skin. There is an abnormal constriction of arterioles, even at normal environmental conditions and this is potentiated by cold. **Chilblains** are an inflammatory condition (perniosis) affecting the extremities and symptoms include erythema, pruritus, and ulceration; they may be acute or chronic. Chilblains are more common in cold damp conditions. Acrocyanosis and chilblains do not generally require specific treatment; smoking cessation, protection from the cold, or symptomatic antipruritic treatment are often sufficient. However, if severe, the drugs described above under Raynaud's syndrome may be considered.

Erythromelalgia (sometimes also called erythermalgia) is a vasospastic condition usually provoked by heat although it may also be drug-induced or secondary to other conditions. It is characterised by painful, red extremities together with a burning sensation and increased skin temperature of the affected area. Thrombocythaemia (p.654) is the most common underlying cause and, indeed, erythromelalgia may be the presenting feature of this disorder; in thrombocythaemia, arteriolar occlusion may occur as a result of platelet aggregation. Small doses of aspirin have produced considerable relief in some patients, presumably by preventing platelet aggregation. Beta blockers may also be of some help, and there are anecdotal reports of benefit with various other drugs.[9] Attacks should be prevented wherever possible by avoiding exposure to heat.

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Venous thromboembolism

The term venous thromboembolism embraces both deep-vein thrombosis (DVT) and pulmonary embolism;[1] the two often co-exist and should be considered as a single clinical entity. In DVT a thrombus forms, often in the pockets of valves, and blocks the veins of the lower limbs or main pelvic veins. Pulmonary embolism occurs when the thrombus or part of it migrates in the circulation and blocks the pulmonary artery. About 70% of patients with confirmed pulmonary embolism have thrombosis in their deep leg veins and about 40% of patients with confirmed DVT have silent pulmonary embolism. Proximal DVT is associated with a higher risk of pulmonary embolism than distal DVT.

Venous thromboembolism is a common but underdiagnosed condition and causes considerable morbidity and mortality, especially among hospitalised patients. Various factors underlie the development of thrombosis and there are a number of conditions that predispose patients to venous thromboembolism (see Thromboembolic Disorders, p.1187).

Symptoms of *deep-vein thrombosis* include a tender and swollen calf; increased temperature, cyanosis, and engorgement of the superficial veins of the affected limb; fever; and tachycardia. However, about half of all cases may be symptomless. In the longer term chronic venous insufficiency and venous ulceration often occur (post-phlebitic or post-thrombotic syndrome). As most clinical signs of DVT are non-specific, the diagnosis should always be confirmed before committing a patient to long-term anticoagulation treatment. UK guidelines[2] suggest that assessment of clinical probability and measurement of D-dimer concentrations may be used to exclude the diagnosis in symptomatic outpatients, but diagnostic imaging is recommended for patients with a moderate or high clinical probability or with raised D-dimer concentrations, and also for all patients with a history of venous thromboembolism or who are pregnant. It should be noted that D-dimer assays may be affected by heparin use, and where possible should be done on blood taken before heparin is given.[2] Where imaging is required, noninvasive techniques are usually adequate, although venography may be required in some patients.[3,4] Compression ultrasound is the preferred method; impedance plethysmography may also be used,[3] but is less sensitive. *Pulmonary embolism* may present in a number of ways depending on its extent and duration. Acute massive embolism causes serious haemodynamic disturbance with a sudden reduction in cardiac output and circulatory collapse. The most common form of pulmonary embolism seen, however, is acute minor embolism where the patient may present with pleuritic pain, haemoptysis, dyspnoea, tachycardia, and fever. Diagnosis may involve perfusion/ventilation scans, angiography, or computed tomography (CT); echocardiography may also be used.[5,6]

Prophylaxis of venous thromboembolism. Prophylaxis with anticoagulants aims to prevent DVT and hence pulmonary embolism in patients at risk. Ideally all medical and surgical hospital inpatients should be assessed for risk factors and should be given prophylaxis according to their degree of risk at least until discharge or, for those at higher risk, after discharge; however, considerable underuse has been reported.[7] A prophylactic regimen should be chosen for a particular patient after balancing the degree of risk against the potential complications of prophylaxis. Guidelines have been published in the UK[8-10] and the USA.[11]

Patients can be categorised as being at low, medium, or high risk of venous thromboembolism according to the duration and type of operation in those undergoing surgery, to age, and to the presence of other risk factors such as cancer, heart failure, and lung disease.[10,11] Low-risk patients include young patients undergoing short operative procedures. Older age, operations lasting longer than 30 minutes, and a history of thrombophilia or previous thromboembolism indicate medium risk. Orthopaedic surgery is associated with a high risk of venous thromboembolism in all patients. Other patients at high risk include those with multiple risk factors. Non-surgical patients are also at risk of thromboembolism, particularly if they are immobile, or have major trauma or spinal cord injury. Pregnancy is also a risk factor and is discussed in more detail below.

Methods of prophylaxis may be physical or pharmacological. Physical methods act by increasing venous blood flow and include elevation of the legs, early ambulation, graduated compression stockings, and intermittent pneumatic compression devices. Pharmacological methods generally involve anticoagulation with heparin, low-molecular-weight heparins, or an oral anticoagulant. Other therapies that have been used include antiplatelet drugs, dihydroergotamine, dextrans, heparinoids such as danaparoid, and the direct thrombin inhibitor desirudin. Fondaparinux is a more recently introduced alternative. Ancrod and argatroban have been used in patients who have developed heparin-induced thrombocytopenia or thrombosis.

For low-risk surgical patients measures such as early ambulation and the use of graduated compression stockings are generally considered adequate. Moderate- and high-risk patients require pharmacological methods, although physical methods alone may be used in those who are at high risk from bleeding complications. Physical methods are not suitable in patients with significant peripheral vascular disease. In practice, a combination of mechanical and pharmacological methods is often used, and may give better protection than either method alone.[8,10,11]

For moderate-risk patients, such as those undergoing general surgical procedures lasting more than 30 minutes, low-dose subcutaneous heparin has been the most widely used pharmacological method. Alternatively, subcutaneous low-molecular-weight heparins may be used,[8,9,11] and may be preferred.[9,10] Fondaparinux may also be used.[10,11] High-risk patients may require more aggressive prophylaxis with higher doses of low-molecular-weight heparin; higher doses of unfractionated heparin or oral anticoagulants may also be used.

The use of ***unfractionated heparin*** for surgical thromboembolism prophylaxis is well established. It is usually given subcutaneously in a low dose ('standard heparin prophylaxis'); a typical regimen is 5000 units subcutaneously 2 hours pre-operatively, then every 8 or 12 hours postoperatively for 7 days or until the patient is mobile. In an overview[12] of more than 70 randomised studies in 16 000 patients heparin reduced the risk of subclinical DVT by 67% in general surgery, 68% in orthopaedic surgery, and 75% in urological surgery. There was also a 40% reduction in non-fatal cases of pulmonary embolism, a 64% reduction in fatal cases, and a 47% reduction of all cases. Surgical thromboembolism prophylaxis with heparin also decreased total mortality. Adjusted-dose heparin may be more effective in higher risk patients but the need for laboratory monitoring and the risk of bleeding complications limit its use.

Low-molecular-weight heparins have a number of potential advantages over unfractionated heparin, including less frequent dosage and no need for monitoring, and they are widely used. However, they have not been clearly shown to reduce the risk of bleeding and they may increase the risk of spinal haematoma with spinal or epidural anaesthesia, which may limit their use. Generally, studies have shown low-molecular-weight heparins to be as effective as unfractionated or standard heparin, but meta-analyses have come to differing conclusions regarding superiority.

The evidence suggests that low-molecular-weight heparins are better in orthopaedic surgery,[13-16] particularly with regard to proximal DVT;[15] however a systematic review[17] concluded that, in patients having surgery for hip fracture, there was not enough evidence to say whether either is better, or to confirm protection against pulmonary embolism. In general surgery both types of heparin appear to be of equivalent efficacy, although one analysis[14] reported that low-molecular-weight heparins were superior. A large study[18] showed low-molecular-weight heparins to be as effective as heparin for prophylaxis after major abdominal surgery and to be associated with fewer bleeding complications. UK[9] and US[11] guidelines suggest that, in general surgery, either may be used. Two meta-analyses of 45 studies[19] and 56 studies[20] respectively evaluated the efficacy of several prophylactic methods (such as aspirin, dextran, oral anticoagulants, heparin, heparin with dihydroergotamine, low-molecular-weight heparins, and intermittent pneumatic compression) against DVT after major hip surgery and concluded that low-molecular-weight heparins should be the method of choice. A meta-analysis[21] of low-molecular-weight heparins in major orthopaedic surgery found no evidence that giving the first dose pre- rather than postoperatively was more effective; there were similar risks for major bleeds. Either option is therefore acceptable; first dosage close to the time of surgery may be more effective but has been associated with increased risk of major bleeds. Low-molecular-weight heparins may also be more effective than unfractionated heparin in patients with major trauma.[22]

The optimum *duration of prophylaxis* is unclear.[23] Prophylaxis is usually only continued during hospitalisation but extended prophylaxis may have a role, particularly in high-risk patients after orthopaedic surgery,[8,10,11] or in very high-risk general surgical patients.[8,11] After orthopaedic surgery there is an increased risk for DVT detected by venography up to a month after discharge, which may be reduced by low-molecular-weight heparin.[24,25] However, the clinical significance of this finding has been questioned[26] and a systematic review[27] suggested that the benefit of extended prophylaxis may have been overestimated. A meta-analysis[28] of 2 studies in patients having surgery for cancer also found a reduction in thrombosis when enoxaparin or dalteparin was given for 4 weeks.

Oral anticoagulants have not been so widely used as subcutaneous heparin although US guidelines[11] allow the use of adjusted-dose warfarin to give an international normalised ratio (INR) of 2.0 to 3.0 in patients having hip or knee replacement surgery.

Antiplatelet drugs such as aspirin have been considered less effective antithrombotics than anticoagulants in the venous circulation and to be of limited value in preventing venous thromboembolism. An overview[29] of randomised trials of antiplatelet therapy (mainly aspirin) available up to March 1990 and a more recent placebo-controlled trial[30] of aspirin in patients having hip surgery have suggested that antiplatelet drugs reduce the risk of venous thromboembolism and should thus be considered in high-risk patients. However, both reports have been criticised and, while some guidelines recommend the use of aspirin,[8] others suggest it should not be used alone since other methods are generally more effective.[11] Long-term use of low-dose aspirin appears to have little effect on the incidence of venous thromboembolism.[31]

Direct thrombin inhibitors have been tried.[32] *Desirudin* has been shown to be effective and was reported to be superior to both low-dose subcutaneous heparin and to a low-molecular-weight heparin in patients undergoing hip replacement surgery. *Bivalirudin* has also been tried. *Dabigatran*, an oral direct thrombin inhibitor, is effective[33] and may be used in patients having hip or knee replacement.

The ***direct inhibitor of factor Xa***, *fondaparinux*, a synthetic pentasaccharide, has been reported[34] to be more effective than low-molecular-weight heparin for orthopaedic surgery, and may be used as an alternative,[9-11] although bleeding may be increased. Extended prophylaxis may be of benefit.[35] *Rivaroxaban*, an oral factor Xa inhibitor, has also been tried.[36]

Of the ***other drugs*** tried for surgical thromboembolism prophylaxis, *dihydroergotamine* can reduce venous stasis by vasoconstriction of capacitance vessels and has enhanced postoperative prophylaxis when used with low-dose heparin, but there is a risk of peripheral ischaemia and it is no longer widely used. *Dextrans* (dextran 70 or dextran 40) alone, or with dihydroergotamine, have also been used for prophylaxis, but their use involves the infusion of 500 to 1000 mL of fluid, a procedure which is cumbersome and may interfere with fluid balance.

In non-surgical patients, meta-analyses[37,38] have confirmed that anticoagulant prophylaxis reduces the risk of symptomatic venous thromboembolism, but it is less clear which patients require treatment.[39] Use of low-dose subcutaneous heparin or low-molecular-weight heparin should be considered in patients at high risk;[8,11] low-molecular-weight heparin may be preferred.[9] Patients with cancer are at particular risk;[40] one study[41] showed that very-low-dose warfarin (average daily dose of 2.6 mg) was safe and effective in patients given chemotherapy for metastatic breast cancer. Prophylaxis with low-molecular-weight heparin has been shown to be effective in patients with immobilisation of the leg,[42] and in acutely ill medical patients with risk factors for venous thromboembolism.[43,44] Standard unfractionated heparin prophylaxis, however, had no effect on mortality in patients admitted to hospital with infection.[45] A study[46] in older medical patients found that fondaparinux may be effective. Although some studies[47,48] have shown an increased risk of venous thromboembolism after prolonged travel, the role of prophylaxis is unclear. A systematic review[49] suggested that compression stockings were effective in preventing flight-related venous thromboembolism in low- to high-risk patients; compression stockings and low-dose aspirin may be considered, while low-molecular-weight heparin may be needed in those at high risk.[8] Other guidelines[11,50] make similar recommendations but do not support the use of aspirin.

Treatment of venous thromboembolism. Treatment of *deep-vein thrombosis*[3,51,52] aims to prevent the development of pulmonary embolism, to prevent extension of the thrombus, to reduce the risk of recurrence, and to reduce the long-term complications of chronic venous insufficiency and venous ulceration. Non-pharmacological therapy may include bed rest with the foot of the bed raised, limb exercise, and graduated compression stockings.[53] These measures may be adequate in patients with small thrombi confined to the calf veins, although this is controversial. Heparin and oral anticoagulants are the mainstay of treatment; they prevent further thrombosis while allowing natural thrombolytic mechanisms to act on the existing clot. Anticoagulants may be used with non-pharmacological methods; graduated compression stockings may reduce the risk of post-phlebitic symptoms in patients receiving anticoagulants,[54,55] and are recommended for 2 years.[56] Thrombolytics or surgical thrombectomy may sometimes have a role.[57]

Heparin has an immediate effect whereas oral anticoagulants such as warfarin take several days to achieve their full anticoagulant effect. Heparin is therefore used for initial therapy and oral anticoagulants are used for maintenance. Doses of unfractionated heparin and oral anticoagulants must be adjusted according to laboratory monitoring. In the initial treatment of DVT, unfractionated heparin is given intravenously, as a loading dose of 5000 units, and then continuous infusion at a dose of 18 units/kg per hour, adjusted according to response;[9,56] doses are usually in the range of 1000 to 2000 units/hour. Alternatively, the infusion may be replaced with a similar total daily dose given subcutaneously in 2 divided doses;[9] in the USA, an initial dose of 17 500 units subcutaneously every 12 hours is recommended.[56] However, low-molecular-weight heparins have a number of advantages and are now generally preferred.[9,56] A number of meta-analyses[58,59] have shown them to be at least as effective and safe as unfractionated heparin in the treatment of deep-vein thrombosis and pulmonary embolism, and a systematic review[60] has found that once daily treatment may be as safe and effective as twice daily treatment. They are also safe and effective for the outpatient treatment of DVT[61,62] and have been recommended for outpatient treatment in patients with uncomplicated pulmonary embolism.[6]

Fondaparinux has been reported[63] to be an effective alternative to low-molecular-weight heparin in the initial treatment of venous thromboembolism. Ancrod, argatroban, or the recombinant hirudin, lepirudin, may be used as an alternative to heparin in patients who have developed heparin-induced thrombocytopenia or thrombosis. A heparinoid such as danaparoid or a low-molecular-weight heparin may also be suitable, although there may be cross-reactivity.

Treatment with an oral anticoagulant (usually warfarin) should generally be started at the same time as heparin.[56] A standard loading dose is usually given, and dosage is then adjusted to maintain the INR within recommended limits.[56,64] Heparin should be continued until the INR is stable and in the therapeutic range;[56] 5 to 7 days is usually adequate. The optimum duration of oral anticoagulation is unclear. Meta-analyses[65,66] of studies comparing different lengths of treatment have found that recurrence is reduced for as long as anticoagulation is continued; therefore, to prevent recurrence, treatment should ideally be continued for as long as the patient is at risk. This must be assessed for each patient.[23,67] Thromboembolism is most likely to recur in patients with ongoing risk factors or idiopathic thromboembolism, and men may be at higher risk of recurrence than women.[68] However, risk of recurrence needs to be balanced against the risk of haemorrhage. One of the meta-analyses[65] found that, overall, the absolute risk of recurrence decreased with time but the bleeding risk remained the same, suggesting that lifelong treatment was probably not routinely indicated. The other analysis[66] found that clinical benefit was maintained after stopping anticoagulation, although at a reduced level, but that prolonged treatment did not significantly increase bleeding risk. A shorter duration of therapy is therefore generally considered adequate for patients with transient risk factors, while those with ongoing or unknown risk factors may require longer treatment. How long this should be in each case, however, is less clear. Although one study[69] concluded that 1 month of treatment was adequate in patients with postoperative thromboembolism, analysis of other studies[70] has suggested that patients with transient risk factors should be treated for 3 months. Guidelines reflect this uncertainty. Both UK[64] and US[56] guidelines recommend treatment for at least 3 months in patients with transient risk factors, although in the UK treatment for at least 6 weeks is considered appropriate for patients with calf-vein thromboembolism. For patients with idiopathic venous thromboembolism, periods at least of 6 months[64] or at least 3 months[56] are recommended, and lifelong treatment may be considered.[56] Lifelong treatment may also be considered for patients with repeated thromboembolic events or with a continuing risk factor.

The limitations of long-term oral anticoagulation, including bleeding complications and recurrent thromboembolism, have led to the investigation of other approaches. A meta-analysis[71] has shown that low-molecular-weight heparins may be as safe and effective as warfarin when given for 3 months; they may be more effective than continued warfarin in patients with recurrence during warfarin therapy.[72] They may also be more effective than warfarin as initial therapy in patients with cancer,[73] and are recommended[56] for the first 3 to 6 months of long-term anticoagulant therapy in such patients. Use of lower-intensity warfarin regimens has been tried for extended prophylaxis, and may reduce the risk of recurrence compared with no therapy.[74] However, a study[75] comparing low- and high-intensity regimens found that the lower intensity regimen was less effective and did not reduce the risk of bleeding. Subcutaneous idraparinux, a factor Xa inhibitor, has also been tried,[76] but may cause more bleeding than standard therapy when given for extended periods.[77] In patients who have contra-indications to anticoagulation or in whom thrombosis recurs despite anticoagulation, insertion of a vena caval filter may be appropriate. The use of filters with anticoagulation has also been investigated.[78] Although the incidence of pulmonary embolism was reduced during the first 12 days, no effect on mortality was shown at 2 years.

Therapy with thrombolytics such as streptokinase is generally reserved for very extensive thrombosis. A systematic review[79] showed no effect on mortality in patients with DVT and the main advantages are continued venous patency and reduced incidence of post-phlebitic syndrome. There may be a small risk of increased bleeding. Since thrombolytic activity fades when infusion stops, heparin followed by oral anticoagulation is given to prevent re-occlusion.

Minor *pulmonary embolism* is treated with heparin or low-molecular-weight heparin and oral anticoagulants as described for DVT (above).[6,80-85] Fondaparinux may be an alternative to heparin.[83,84,86] For more severe pulmonary embolism the initial bolus dose of heparin may be doubled. An initial dose of unfractionated heparin may also be given before treatment with low-molecular-weight heparins.[6] Acute massive pulmonary embolism with major haemodynamic disturbance may be treated initially with thrombolytic therapy;[5,6,83,84] surgical methods such as embolectomy or percutaneous catheter fragmentation may be preferred in some patients.[83,84,87,88] Streptokinase, urokinase, and alteplase have all been shown to accelerate the lysis of pulmonary emboli and to decrease pulmonary vascular obstruction. However, their effects on mortality are uncertain and bleeding risk is increased;[89] a meta-analysis[90] found benefit only in studies that included patients at high risk, and they are therefore not recommended in non-massive pulmonary embolism.[6] Comparisons between thrombolytics have been difficult because the doses used in different studies have not always been comparable. Probably more important than the choice of thrombolytic is ensuring that treatment starts quickly in patients where it is indicated.[80]

Venous thromboembolism in children. Venous thromboembolism is relatively rare in children and has differing epidemiology to that in adults.[91,92] Although guidelines[93] for its management have been published they generally rely on extrapolation from studies in adults.

Venous thromboembolism in pregnancy. Pregnancy is a known risk factor for venous thromboembolism and, although the absolute risk is low, pulmonary embolism is the commonest cause of maternal death during pregnancy in the UK. Anticoagulation during pregnancy may be necessary either to prevent or treat venous thromboembolism; continued anticoagulation may also be needed in pregnant patients at risk of systemic embolism because of valvular heart disease or prosthetic heart valves (see above).

Oral anticoagulants such as warfarin cross the placenta and may harm the fetus; they are generally contra-indicated during pregnancy. Heparin does not appear to cross the placenta and despite potential maternal complications such as osteoporosis and thrombocytopenia remains the anticoagulant of choice in pregnancy. Low-molecular-weight heparins appear to be as safe as unfractionated heparin during pregnancy[94] and may have advantages, including a lower risk of osteoporosis and thrombocytopenia.[95]

The management of venous thromboembolism in pregnancy has been reviewed[96-100] and guidelines have been published in the UK[101,102] and the US.[95] **Prophylactic anticoagulation** is not necessary in all pregnancies, but should be considered in women at special risk of venous thromboembolism either because of a history of thromboembolism and/or a thrombophilic abnormality such as inherited deficiency of antithrombin III, protein C, or protein S or acquired thrombophilia due to antiphospholipid antibodies in plasma. Patients must be managed individually and current strategies differ. In those women with a history of thromboembolism but without thrombophilic abnormalities some authors recommend prophylactic anticoagulation at delivery and for 6 weeks post partum provided there has been only one episode of thromboembolism and there are no additional risk factors; others advocate prophylaxis with subcutaneous heparin throughout pregnancy. However, a prospective study[103] has suggested that it is safe to withhold anticoagulation until after delivery in such patients, and this approach has been recommended.[95] Although standard low-dose heparin has been recommended, higher doses may be necessary during pregnancy.[95-97] Low-molecular-weight heparins may also be used.[95,97,99,102] Those with inherited or acquired thrombophilic abnormalities but no evidence of thrombosis do not necessarily require anticoagulation, but must be assessed carefully.

If acute venous thromboembolism occurs during pregnancy it should be **treated** with low-molecular-weight heparin or intravenous heparin as in non-pregnant patients (see above). Antenatal patients need to continue anticoagulation for the rest of their pregnancy, usually by substituting adjusted-dose subcutaneous heparin every 12 hours after 6 to 10 days of intravenous therapy; low-molecular-weight heparins may be an alternative,[95,97] and may be preferred.[101] Special care must be taken at delivery. Patients given full therapeutic doses of heparin should have their dose reduced or stopped on the day of delivery; this may not be necessary in those on lower prophylactic doses of heparin. Low-molecular-weight heparins should be stopped 24 hours before planned delivery.[95,101] If possible patients taking warfarin should be changed to heparin 2 or 3 weeks before labour or delivery and not later than 36 weeks' gestation. Anticoagulants should be continued after delivery, but can usually be stopped after 6 weeks; the total duration of treatment should be at least 3 months.[101]

During pregnancy, especially the third trimester, laboratory monitoring of anticoagulation may be less reliable because high procoagulant concentrations particularly of factor VIII and fibrinogen, may result in low activated partial thromboplastin time (APTT) values despite adequate heparin concentrations in plasma.

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Abciximab *(BAN, USAN, rINN)*

Abciximabum; Absiksimab; Absiksimabi; Absiximab; c7E3; c7E3 Fab; 7E3. Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3V$_H$hC 4 Fab fragment anti-human platelet glycoprotein IIb/IIIa complex), disulphide with human-mouse monoclonal c7E3 clone p7E3V hC light chain.

Абциксимаб

$C_{2101}H_{3229}N_{551}O_{673}S_{15}$ = 47455.4.

CAS — 143653-53-6.

ATC — B01AC13.

ATC Vet — QB01AC13.

Adverse Effects

Bleeding during the first 36 hours after a dose is the most common adverse effect of abciximab. Other adverse effects include hypotension, nausea and vomiting, back pain, chest pain, headache, haematoma, bradycardia, fever, cardiac tamponade, and thrombocytopenia. Hypersensitivity reactions (see Precautions, below) have occurred on repeated use.

Effects on the blood. In clinical studies increased bleeding has been the most common adverse effect of abciximab, and this has also been reported[1] during clinical use. Thrombocytopenia is also a well documented adverse effect of abciximab therapy. In a review[2] of the major clinical studies of abciximab, mild thrombocytopenia was reported in 4.2% of patients and severe thrombocytopenia in 1.0%; patients also received heparin. There have also been a number of case reports of patients developing severe thrombocytopenia.[3,4] It is recommended that platelet counts should be monitored before and 2 hours after starting abciximab, and that the drug should be withdrawn if thrombocytopenia occurs.[3] However, pseudothrombocytopenia also occurs in some patients and should be excluded before withdrawing therapy.[5,6] Although there have been case reports, the incidence of thrombocytopenia does not appear to be increased with other glycoprotein IIb/IIIa receptor inhibitors,[2] and there have been reports of the successful use of eptifibatide[7] and tirofiban[8] in patients who developed thrombocytopenia with abciximab.

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Precautions

Abciximab should not be given to patients who are actively bleeding or to patients at increased risk of haemorrhage. Such patients include: those with haemorrhagic disorders, including thrombocytopenia; those with cerebrovascular disorders, including intracerebral neoplasms, aneurysms, or arteriovenous malformation, and those with a history of stroke; those with uncontrolled hypertension; or those who have recently undergone major surgery or severe trauma. Other patients in whom caution is required include those with severe renal impairment, vasculitis, haemorrhagic retinopathy, acute pericarditis, or aortic dissection. Abciximab should be stopped if serious uncontrolled bleeding occurs or emergency surgery is required. Abciximab should not be given to patients with severe renal impairment requiring haemodialysis, or to those with severe hepatic impairment, in whom coagulation may be affected. Platelet counts should be monitored before and after giving abciximab.

Antibodies may develop 2 to 4 weeks after a dose of abciximab and hypersensitivity reactions could occur when other monoclonal antibodies are used or after readministration of abciximab (see below). Hypersensitivity reactions have not been noted after a single dose but the possibility should be considered.

Readministration. Antibodies to abciximab develop in about 5.8% of patients after use and could lead to hypersensitivity reactions or to reduced efficacy if use of abciximab is repeated. In a retrospective study[1] in 164 patients given a second course of therapy with abciximab, efficacy was not affected and no allergic or anaphylactic reactions occurred. However, severe thrombocytopenia was noted in 4% of patients, and the incidence was highest in those receiving abciximab within 2 weeks of the first course. Similar results were reported from a larger registry study;[2] the patients included had received abciximab at least 7 days previously without developing thrombocytopenia, suggesting that platelet counts need to be monitored in patients receiving a first or repeated course of abciximab.

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Interactions

There may be an increased risk of bleeding if abciximab is given with other drugs that affect bleeding, including anticoagulants, other antiplatelet drugs, or thrombolytics.

Pharmacokinetics

After intravenous doses of abciximab free plasma concentrations fall rapidly due to binding to platelet receptors. Platelet function recovers over about 48 hours although abciximab may remain in the circulation for 15 days or more in a platelet-bound state.

Uses and Administration

Abciximab is the Fab fragment of the chimeric monoclonal antibody 7E3. It binds to the glycoprotein IIb/IIIa receptor on the surface of platelets. This prevents binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the receptor sites and inhibits platelet aggregation. It is used as an adjunct to heparin and aspirin therapy for the prevention of acute ischaemic complications in patients undergoing percutaneous transluminal coronary procedures including angioplasty, atherectomy, and stenting. It is also used in patients with unstable angina who are candidates for such procedures. It has been investigated in acute ischaemic stroke.

Abciximab is given intravenously as a bolus injection over 1 minute in a dose of 250 micrograms/kg followed immediately by an infusion of 0.125 micrograms/kg per minute (to a maximum dose of 10 micrograms/minute). For stabilisation in patients with unstable angina the bolus dose followed by the infusion should be started up to 24 hours before the possible intervention and continued for 12 hours after; for other patients the bolus should be given 10 to 60 minutes before the intervention followed by the infusion for 12 hours.

◊ General references.

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Ischaemic heart disease. Antiplatelet drugs have an established role as adjuncts to medical or interventional treatment in patients with ischaemic heart disease (stable angina, unstable angina, or myocardial infarction) and abciximab has been used to provide additional antiplatelet effects during interventional procedures and in patients with acute myocardial infarction.

In patients undergoing acute or elective *percutaneous coronary intervention* (PCI; see Reperfusion and Revascularisation Procedures, p.1181), use of abciximab as an adjunct to heparin and aspirin improves short-term[1-3] and long-term[4,5] outcomes in various groups of patients, including those receiving coronary stents.[6-8] Most benefit has been seen in patients given abciximab as a bolus injection immediately before intervention followed by intravenous infusion for 12 hours,[1,2] and in a study[9] in which abciximab was given for 18 to 24 hours before angioplasty and for 1 hour after, the initial benefit was not maintained at 6 months.

For patients undergoing PCI who are pretreated with both aspirin and clopidogrel, the role of abciximab is less clear. In stable patients undergoing elective PCI, no benefit was found at 30 days,[10] or at 1 year.[11] A study[12] in diabetic patients also found no effect on mortality or risk of myocardial infarction at 1 year, despite their higher risk, although restenosis was reduced. However, in patients undergoing PCI for non-ST elevation acute coronary syndromes, use of abciximab in addition to aspirin and clopidogrel pretreatment improved clinical outcomes at 30 days, although this effect was restricted to patients with raised troponins.[13] Positive results have also been reported[14,15] with abciximab given as a single bolus injection without subsequent infusion in patients undergoing coronary stenting.

In *acute ST-elevation myocardial infarction* (p.1175), abciximab has been used as an adjunct to primary PCI, including coronary stenting, and has been shown to reduce reinfarction rates and mortality,[16] with benefit persisting long-term.[17] There is some evidence that starting treatment as soon as possible rather than immediately before the procedure may provide additional benefit.[18,19] Abciximab has also been used as an adjunct to thrombolysis and some benefit has been shown,[20] but this appears to be offset by an increased bleeding rate, even when reduced doses of thrombolytics are used.[21,22] In patients with *unstable angina* (p.1157) receiving noninterventional treatment, a large study[23] with abciximab failed to show any benefit over placebo, although other glycoprotein IIb/IIIa inhibitors have a role in such patients.

Some promising results have been reported with intracoronary abciximab in patients with acute coronary syndromes,[24] and with abciximab-coated stents in patients with acute myocardial infarction.[25]

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16. De Luca G, *et al.* Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 2005; **293:** 1759–65.
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Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: ReoPro†; ***Austral.:*** ReoPro; ***Austria:*** ReoPro; ***Belg.:*** ReoPro; ***Braz.:*** ReoPro; ***Canad.:*** ReoPro; ***Chile:*** ReoPro; ***Cz.:*** ReoPro; ***Denm.:*** ReoPro; ***Fin.:*** ReoPro; ***Fr.:*** ReoPro; ***Ger.:*** ReoPro; ***Gr.:*** ReoPro; ***Hong Kong:*** ReoPro; ***India:*** ReoPro; ***Irl.:*** ReoPro; ***Israel:*** ReoPro; ***Ital.:*** ReoPro; ***Malaysia:*** ReoPro; ***Mex.:*** ReoPro; ***Neth.:*** ReoPro; ***Norw.:*** ReoPro; ***NZ:*** ReoPro; ***Pol.:*** ReoPro; ***Port.:*** ReoPro; ***Rus.:*** ReoPro (Peonpo); ***S.Afr.:*** ReoPro; ***Singapore:*** ReoPro; ***Spain:*** ReoPro; ***Swed.:*** ReoPro; ***Switz.:*** ReoPro; ***Thai.:*** ReoPro; ***UK:*** ReoPro; ***USA:*** ReoPro.

Acadesine *(BAN, USAN, rINN)*

Acadesina; Acadésine; Acadesinum; AICA Riboside; GP-1-110; GP-1-110-0. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide.

Акадезин

$C_9H_{14}N_4O_5$ = 258.2.
CAS — 2627-69-2.
ATC — C01EB13.
ATC Vet — QC01EB13.

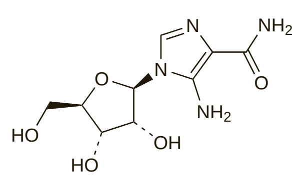

Profile

Acadesine is a purine nucleoside analogue reported to have cardioprotective effects. It is being investigated in the management of myocardial ischaemia, particularly in patients undergoing coronary artery bypass graft surgery. Acadesine may protect against further ischaemia by influencing metabolism in ischaemic cells, enhancing the release of adenosine in preference to inosine after the breakdown of adenosine monophosphate.

Acadesine is also under investigation for chronic lymphocytic leukaemia.

◊ References.

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4. Mangano DT, *et al.* Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Post-reperfusion myocardial infarction: long-term survival improvement using adenosine regulation with acadesine. *J Am Coll Cardiol* 2006; **48:** 206–14.

ACE Inhibitors

Angiotensin-converting Enzyme Inhibitors; Inhibidores de la ECA.

There appear to be few significant differences between ACE inhibitors. They may be distinguished from each other by the presence or absence of a sulfhydryl group, whether they are prodrugs or not, their route of elimination, and their affinity for angiotensin-converting enzyme in vascular and other tissue, although whether these characteristics modify pharmacodynamics and therefore clinical efficacy is uncertain. Differences in these characteristics do however influence onset and duration of action of ACE inhibitors.

Adverse Effects and Treatment

Many of the adverse effects of ACE inhibitors relate to their pharmacological action and all therefore have a similar spectrum of adverse effects. Some effects, such as taste disturbances and skin reactions, were at one time attributed to the presence of a sulfhydryl group (as in captopril) but have now also been reported with other ACE inhibitors; however, they may be more common with captopril.

The most common adverse effects are due to the vascular effects of ACE inhibitors and include hypotension, dizziness, fatigue, headache, and nausea and other gastrointestinal disturbances.

Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume-depleted patients (for example, those given previous diuretic therapy). Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations, and chest pain.

Deterioration in renal function, including increasing blood concentrations of urea and creatinine, may occur, and reversible acute renal failure has been reported. Renal effects are most common in patients with existing renal or renovascular dysfunction or heart failure, in whom vasodilatation reduces renal perfusion pressure; it may be aggravated by hypovolaemia. Proteinuria has also occurred and in some patients has progressed to nephrotic syndrome. Hyperkalaemia and hyponatraemia may develop due to decreased aldosterone secretion.

Other adverse effects include persistent dry cough and other upper respiratory tract symptoms, and angioedema; these may be related to effects on bradykinin or prostaglandin metabolism. Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported.

Blood disorders have been reported with ACE inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia, and anaemias.

Other less common adverse effects reported with ACE inhibitors include stomatitis, abdominal pain, pancreatitis, hepatocellular injury or cholestatic jaundice, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence.

ACE inhibitors have been associated with fetal toxicity (see Pregnancy under Precautions, below).

Most of the adverse effects of ACE inhibitors are reversible on withdrawing therapy. Symptomatic hypotension, including that after overdosage, generally responds to volume expansion with an intravenous infusion of sodium chloride 0.9%.

◊ General reviews.

1. Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme (ACE) inhibitors: an update. *Drug Safety* 1992; **7:** 14–31.
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3. Agusti A, *et al.* Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction : meta-analysis of randomised clinical trials. *Drug Safety* 2003; **26:** 895–908.
4. Adam A, *et al.* Physiopathologie des effets secondaires aigus des inhibiteurs de l'enzyme de conversion de l'angiotensine. *Bull Acad Natl Med* 2007; **191:** 1433–43.

Angioedema. See under Hypersensitivity, below.

Cough. Treatment with ACE inhibitors has been associated with the development of cough in up to 20% of hypertensive patients; cough may be less troublesome in those with heart failure,[1] although the incidence may be higher.[2] The cough is reported to be persistent, paroxysmal, and non-productive; it causes irritation of the throat, may be accompanied by voice changes (hoarseness or huskiness), and is often worse when lying down.[1,3,4] It is more common in women and non-smokers, and may be delayed in onset by weeks or even months.

The majority of reports of this adverse effect concern captopril and enalapril,[3,4] but it has also occurred in patients receiving many of the other ACE inhibitors,[5] suggesting that the effect is common to all drugs of this class.

The mechanism that produces the reaction is uncertain but appears to be related to the non-specific blockade of ACE since angiotensin II receptor antagonists are associated with a much lower incidence of cough.[6] The sensitivity of the cough reflex is increased.[7] Prostaglandins released in the respiratory tract have been proposed as mediators,[3] but other mediators such as bradykinin[8] or substance P,[9] both of which are substrates for ACE, have been suggested. However, attempts to show a link between the effects of ACE inhibitors on cough, and bronchial hyperreactivity of the type found in obstructive airways disease and asthma have produced conflicting evidence, with bronchial hyperreactivity being shown in some studies[10] but not in others.[11]

Where the patient can tolerate the cough, it may be reasonable to continue treatment; in some cases reducing the dose may help. Spontaneous recovery or improvement in the cough has been reported.[12] Changing to an alternative ACE inhibitor is not advised since it is rarely effective.[7] Drugs that inhibit prostaglandin synthesis, including the NSAIDs sulindac[13] and indometacin,[14] have been reported to suppress the cough, but NSAIDs and ACE inhibitors may interact adversely (see under Interactions, below). The calcium-channel blocker nifedipine also reduced cough, although to a lesser extent than indometacin, possibly by a similar mechanism.[14] Inhaled bupivacaine,[15] inhaled sodium cromoglicate,[16,17] oral baclofen,[18] oral picotamide,[19] and oral ferrous sulfate,[20] have also been reported to be of help. However, in many patients there will be no alternative but to withdraw the ACE inhibitor, and this is recommended by some in all patients presenting with ACE-inhibitor induced cough.[21] Angiotensin II receptor antagonists may be a suitable alternative in patients with hypertension.[21]

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2. Ravid D, *et al.* Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and congestive heart failure. *J Clin Pharmacol* 1994; **34:** 1116–20.
3. Coulter DM, Edwards IR. Cough associated with captopril and enalapril. *BMJ* 1987; **294:** 1521–3.
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8. Ferner RE, *et al.* Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. *BMJ* 1987; **294:** 1119–20.
9. Morice AH, *et al.* Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987; **ii:** 1116–18.
10. Bucknall CE, *et al.* Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. *BMJ* 1988; **296:** 86–8.
11. Boulet L-P, *et al.* Pulmonary function and airway responsiveness during long-term therapy with captopril. *JAMA* 1989; **261:** 413–16.
12. Reisin L, Schneeweiss A. Spontaneous disappearance of cough induced by angiotensin-converting enzyme inhibitors (captopril or enalapril). *Am J Cardiol* 1992; **70:** 398–9.
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20. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
21. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl): 169S–173S.

Effects on the blood. Blood disorders have occurred in patients receiving ACE inhibitors, although there have been few reports in the literature. A reduction in haemoglobin concentration and haematocrit may occur but is not usually clinically significant, although an unfavourable effect on recovery from anaemia has been reported;[1] ACE inhibitors have also been used therapeutically to reduce the haematocrit (see Erythrocytosis under Uses, below). Cases of neutropenia and agranulocytosis (particularly in patients with renal or collagen vascular disorders), and thrombocytopenia have been noted. Aplastic anaemia has also occurred[2,3] and may be fatal.[3]

1. Ripamonti V, *et al.* Angiotensin-converting enzyme inhibitors slow recovery from anemia following cardiac surgery. *Chest* 2006; **130:** 79–84.
2. Kim CR, *et al.* Captopril and aplastic anemia. *Ann Intern Med* 1989; **111:** 187–8.
3. Harrison BD, *et al.* Fatal aplastic anaemia associated with lisinopril. *Lancet* 1995; **346:** 247–8.

Effects on the kidneys. ACE inhibitors have complex effects on the kidney;[1,2] they have established renoprotective effects but also cause acute deterioration in renal function in some patients. These apparently contradictory effects are related to the action of ACE inhibitors on the renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system has an important role in maintaining normal renal blood flow and renal function. A reduction in renal perfusion, for example due to hypovolaemia, heart failure, or renal artery stenosis, leads to activation of this system and an increase in angiotensin II release. This results mainly in post-glomerular renal vasoconstriction, which maintains renal glomerular pressure and thus glomerular filtration, despite the fall in renal blood flow.

In normal individuals with unrestricted sodium intake, the renin-angiotensin-aldosterone system is suppressed and ACE inhibitors have little effect on renal function. In patients with essential hypertension ACE inhibitors generally increase renal blood flow despite the reduction in arterial blood pressure, since this is exceeded by the effects of renal vasodilatation. However, filtration fraction falls since the pressure within the glomerulus is reduced, and there are only minor changes in glomerular filtration rate. The increase in renal blood flow is more pronounced during sodium restriction and in younger patients.

These effects are generally beneficial. However, in patients with reduced renal perfusion, glomerular filtration rate may be critically dependent on the renin-angiotensin-aldosterone system and the use of ACE inhibitors may provoke problems. Severe renal function loss or even anuria have been reported in patients with a single transplanted kidney with renal artery stenosis, or patients with bilateral renal artery disease. The stenotic kidney maintains its filtering capacity by preferential vasoconstriction of the efferent arterioles, a mechanism mainly mediated by the renin-angiotensin system; under ACE inhibition, vasodilatation of the efferent arterioles combined with the drop in arterial pressure can result in a critical decrease in filtration pressure. Hypovolaemia or sodium depletion, for example due to diuretics, also leads to activation of the renin-angiotensin-aldosterone system and predisposes patients to renal impairment. Most patients developing renal insufficiency have been using diuretics and sodium repletion can restore renal function despite continuing ACE inhibition.

Patients with heart failure may also be at risk of a decline in renal function on long-term ACE inhibitor therapy. This is because in chronic heart failure, angiotensin-II mediated systemic and renal vasoconstriction is again important in the maintenance of renal perfusion pressure. The decline may be alleviated by reduction of the dosage of diuretics or liberalisation of dietary salt intake, despite continuing the ACE inhibitor. An additional risk factor in elderly patients with heart failure is the high incidence of occult renovascular disease in these patients.[3]

Moderate impairment of renal function either before or during use of ACE inhibitors is not necessarily an indication to stop therapy. The effects of ACE inhibitors on renal function are generally reversible, and the reduction in filtration pressure may result in renoprotection. A review[4] of studies of the use of ACE inhibitors in patients with renal impairment found that those who initially lost renal function had the greatest long-term benefit.

In addition to pathophysiological effects ACE inhibitors may induce membranous glomerulopathy or interstitial nephritis. The former has been associated with captopril use, particularly at high doses, but is rare, and seems less likely to occur at the lower doses favoured today. The proteinuria usually clears without appreciable renal function loss irrespective of whether or not the drug is continued, although persistent proteinuria and renal function loss have been described. Proven interstitial nephritis has also been reported rarely, and may possibly be due to an allergic mechanism.

1. Navis G, *et al.* ACE inhibitors and the kidney: a risk-benefit assessment. *Drug Safety* 1996; **15:** 200–11.
2. Schoolwerth AC, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001; **104:** 1985–91.
3. MacDowall P, *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; **352:** 13–16.
4. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; **160:** 685–93.

Effects on the liver. Hepatotoxicity has been reported with ACE inhibitors, including captopril,[1,2] enalapril,[2] lisinopril,[2] and ramipril.[3] Most reports have been associated with captopril. In a report[1] of 3 cases of liver disease apparently caused or aggravated by captopril, it was noted that jaundice due to captopril is usually mainly cholestatic in nature but acute hepatocellular injury has also been seen. Of 29 cases of liver dysfunction due to captopril and reported to the UK CSM, 9 had hepatocellular jaundice, with 2 deaths; 8 were cholestatic jaundice, with 1 fatality; and 3 patients had hepatorenal syndrome, all of whom died. Worldwide, excluding the UK, 164 cases of hepatic adverse reactions had been notified to the WHO by January 1989. The incidence of such reactions is estimated at 0.09 per 1000 patients but this is likely to be an underestimate. Resolution may take a long time and captopril should be withdrawn immediately at the earliest hint of liver sensitivity.

1. Bellary SV, *et al.* Captopril and the liver. *Lancet* 1989; **ii:** 514.
2. Hagley MT, *et al.* Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1993; **27:** 228–31.
3. Yeung E, *et al.* Ramipril-associated hepatotoxicity. *Arch Pathol Lab Med* 2003; **127:** 1493–7.

Effects on the mouth. Aphthous and tongue ulcers may occur during treatment with ACE inhibitors. There have been a few reports of a 'scalded mouth syndrome', described as similar to being scalded by hot liquids, associated with captopril,[1] enalapril,[1] and lisinopril[2] therapy.

1. Vlasses PH, *et al.* "Scalded mouth" caused by angiotensin-converting enzyme inhibitors. *BMJ* 1982; **284:** 1672–3.
2. Savino LB, Haushalter NM. Lisinopril-induced "scalded mouth syndrome." *Ann Pharmacother* 1992; **26:** 1381–2.

Effects on the nervous system. Encephalopathy and focal neurological signs,[1] and peripheral neuropathy,[2,3] including Guillain-Barré neuropathy,[3] have been reported in patients receiving captopril. Some CNS effects of captopril may be attributable to alterations in cerebral blood flow. In a study in patients with severe heart failure, cerebral blood flow in patients aged under 65 was improved by a single dose of captopril 12.5 mg, but in patients aged over 70 there was a 13% reduction.[4] Two patients in whom captopril 6.25 mg produced impaired consciousness and paraesthesias, and dizziness, blurred vision, and aphasia, were found to have stenosis of the carotid arteries.[5] Agitation, panic, extreme depression, and insomnia was reported in a patient 4 weeks after starting treatment with enalapril; depressive episodes recurred on rechallenge.[6] There have been reports of mania possibly precipitated by captopril,[7] and visual hallucinations have been reported in association with captopril and enalapril therapy.[8]

1. Rapoport S, Zyman P. Captopril and central nervous system effects. *Ann Intern Med* 1983; **98:** 1023.
2. Samanta A, Burden AC. Peripheral neuropathy due to captopril. *BMJ* 1985; **291:** 1172.
3. Chakraborty TK, Ruddell WSJ. Guillain-Barré neuropathy during treatment with captopril. *Postgrad Med J* 1987; **63:** 221–2.
4. Britton KE, *et al.* Angiotensin-converting-enzyme inhibitors and treatment of heart failure. *Lancet* 1985; **ii:** 1236.
5. Jensen H, *et al.* Carotid artery stenosis exposed by an adverse effect of captopril. *BMJ* 1986; **293:** 1073–4.
6. Ahmad S. Enalapril-induced acute psychosis. *DICP Ann Pharmacother* 1991; **25:** 558–9.
7. Peet M, Peters S. Drug-induced mania. *Drug Safety* 1995; **12:** 146–53.
8. Haffner CA, *et al.* Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. *Postgrad Med J* 1993; **69:** 240.

Effects on the pancreas. The manufacturers of captopril, enalapril, and lisinopril have all been reported[1] to have data on file on drug-associated pancreatitis. In 1994 the UK CSM[2] noted that there had been 23 reports of pancreatitis associated with ACE inhibitors (captopril 11, enalapril 10, fosinopril 1, and quinapril 1) although whether or not this was causal was not certain.

1. Dabaghi S. ACE inhibitors and pancreatitis. *Ann Intern Med* 1991; **115:** 330–1.
2. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)

Effects on the respiratory system. Cough is a recognised adverse effect of ACE inhibitors but evidence for a link with bronchial hyperreactivity or airways obstruction is controversial (see Cough, above). In reports of adverse respiratory reactions to ACE inhibitors submitted to the Swedish Adverse Drug Reactions Advisory Committee and to WHO, symptoms of airway obstruction such as dyspnoea, asthma, and bronchospasm occurred rarely, usually within the first few weeks of treatment.[1] However, the evidence for a causal link between ACE inhibitors and these symptoms was questioned.[2]

Severe nasal obstruction was associated with enalapril treatment in a 45-year-old woman with a history of mild rhinorrhoea and sneezing. Symptoms cleared within 2 days of stopping enalapril and recurred on rechallenge.[3] Another woman taking enalapril developed obstructive sleep apnoea,[4] which improved when the enalapril was stopped.

There have been case reports of pneumonitis associated with treatment with captopril[5] and perindopril.[6]

1. Lunde H, *et al.* Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1994; **308:** 18–21.
2. Inman WHW, *et al.* Angiotensin converting enzyme inhibitors and asthma. *BMJ* 1994; **308:** 593–4.
3. Fennerty A, *et al.* Enalapril-induced nasal blockage. *Lancet* 1986; **ii:** 1395–6.

4. Cicolin A, *et al.* Angiotensin-converting enzyme inhibitors and obstructive sleep apnea. *Mayo Clin Proc* 2006; **81:** 53–5.
5. Kidney JC, *et al.* Captopril and lymphocytic alveolitis. *BMJ* 1989; **299:** 981.
6. Benard A, *et al.* Perindopril-associated pneumonitis. *Eur Respir J* 1996; **9:** 1314–16.

Effects on skeletal muscle. Severe muscle pain and weakness, accompanied by morning stiffness, was reported[1] in a patient taking enalapril. Symptoms resolved within a few days of stopping the drug.

1. Leloët X, *et al.* Pseudopolymyalgia rheumatica during treatment with enalapril. *BMJ* 1989; **298:** 325.

Effects on the skin. Skin rashes may occur during treatment with ACE inhibitors; they have been reported in 1 to 6% of patients receiving captopril. Angioedema is also an adverse effect of ACE inhibitors (see Hypersensitivity, below). There have been reports of bullous pemphigoid,[1] hyperhidrosis,[2] Kaposi's sarcoma,[3] lichen planus,[4] onycholysis,[5,6] pemphigus,[7,8] and cutaneous hypersensitivity vasculitis[9] associated with use of captopril. Kaposi's sarcoma has also been reported[10] with lisinopril. Onycholysis has also occurred with enalapril,[11] pemphigus with enalapril[12,13] and ramipril,[14] and bullous pemphigoid with lisinopril.[15] Lichen planus pemphigoides has been reported with ramipril.[16] A severe cutaneous reaction, resembling early mycosis fungoides, and possibly allergic in nature, has been reported after use of captopril or enalapril.[17] Captopril has also been reported to exacerbate psoriasis.[18] Vulvovaginal pruritus with dysuria[19] has been noted in a patient receiving enalapril.

1. Mallet L, *et al.* Bullous pemphigoid associated with captopril. *DICP Ann Pharmacother* 1989; **23:** 63.
2. Morse MH. Hyperhidrosis: a possible side effect of captopril treatment. *BMJ* 1984; **289:** 1272.
3. Puppin D, *et al.* Kaposi's sarcoma associated with captopril. *Lancet* 1990; **336:** 1251–2.
4. Cox NH, *et al.* Lichen planus associated with captopril: a further disorder demonstrating the 'tin-tack' sign. *Br J Dermatol* 1989; **120:** 319–21.
5. Brueggemeyer CD, Ramirez G. Onycholysis associated with captopril. *Lancet* 1984; **i:** 1352–3.
6. Borders JV. Captopril and onycholysis. *Ann Intern Med* 1986; **105:** 305–6.
7. Parfrey PS, *et al.* Captopril-induced pemphigus. *BMJ* 1980; **281:** 194.
8. Butt A, Burge SM. Pemphigus vulgaris induced by captopril. *Br J Dermatol* 1995; **132:** 315–16.
9. Miralles R, *et al.* Captopril and vasculitis. *Ann Intern Med* 1988; **109:** 514.
10. Bilen N, *et al.* Possible causal role of lisinopril in a case of Kaposi's sarcoma. *Br J Dermatol* 2002; **147:** 1042–4.
11. Gupta S, *et al.* Nail changes with enalapril. *BMJ* 1986; **293:** 140.
12. Kuechle MK, *et al.* Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc* 1994; **69:** 1166–71.
13. Frangogiannis NG, *et al.* Pemphigus of the larynx and esophagus. *Ann Intern Med* 1995; **122:** 803–4.
14. Vignes S, *et al.* Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135:** 657–8.
15. Kalińska-Bienias A, *et al.* Can pemphigoid be provoked by lisinopril? *Br J Dermatol* 2006; **155:** 854–5.
16. Ogg GS, *et al.* Ramipril-associated lichen planus pemphigoides. *Br J Dermatol* 1997; **136:** 412–14.
17. Furness PN, *et al.* Severe cutaneous reactions to captopril and enalapril; histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39:** 902–7.
18. Hamlet NW, *et al.* Does captopril exacerbate psoriasis? *BMJ* 1987; **295:** 1352.
19. Heckerling PS. Enalapril and vulvovaginal pruritus. *Ann Intern Med* 1990; **112:** 879–80.

Gynaecomastia. Painful unilateral gynaecomastia was reported in a patient with systemic lupus erythematosus and renal impairment who was given captopril for hypertension.[1] In view of reports of breast enlargement in women given penicillamine it was suggested that the sulfhydryl structure might be responsible; however, gynaecomastia has also been reported in 2 patients receiving enalapril,[2,3] which does not contain the sulfhydryl grouping.

1. Markusse HM, Meyboom RHB. Gynaecomastia associated with captopril. *BMJ* 1988; **296:** 1262–3.
2. Nakamura Y, *et al.* Gynaecomastia induced by angiotensin converting enzyme inhibitor. *BMJ* 1990; **300:** 541.
3. Llop R, *et al.* Gynecomastia associated with enalapril and diazepam. *Ann Pharmacother* 1994; **28:** 671–2.

Hypersensitivity. Some of the adverse effects of ACE inhibitors might be mediated by the immune system, but evidence of specific **hypersensitivity reactions** seems to be limited. The presence of an IgG antibody to captopril was demonstrated in the serum of 2 of 45 patients taking the drug but the clinical significance was unclear.[1] A reaction resembling serum sickness was reported in a patient given captopril, with deposition of immune complexes in the glomerular basement membrane, and symptoms of rash, arthralgia, epidermolysis, fever, and lymphadenopathy.[2] Eosinophilia has also been reported in a number of patients.[3] The formation of antinuclear antibodies and lupus-like reactions have been described.[4,5]

Treatment with ACE inhibitors (enalapril, captopril, or lisinopril) has been associated with the development of **anaphylactoid reactions** in patients undergoing high-flux haemodialysis using polyacrylonitrile membrane (AN69).[6,7] The UK CSM has advised that the combined use of ACE inhibitors and such membranes should be avoided.[8] Similar anaphylactoid reactions have occurred in patients taking ACE inhibitors while being treated for severe hypercholesterolaemia by extracorporeal removal of low-density lipoproteins (LDL-apheresis) with dextran sulfate columns.[9] These reactions are thought to be bradykinin-mediated. Prolonging the interval between the last dose of ACE inhibitor and dextran sulfate apheresis has averted the reaction;[10] successful prevention has also been reported with the bradykinin receptor antagonist icatibant acetate (p.2324).[11] Hypotensive reactions associated with blood transfusion through bedside leucoreduction filters in patients taking ACE inhibitors have also been attributed to bradykinin.[12] There have also been rare reports of severe allergic reactions, including anaphylaxis, occurring in patients taking ACE inhibitors who were stung by insects or during desensitisation with Hymenoptera venom (e.g. bee or wasp venom).[13]

Angioedema, a known adverse effect of ACE inhibitors,[14-17] is reported to occur in 0.1 to 0.2% of patients.[16,17] The incidence may be higher in black American[18] or Afro-Caribbean[19] patients. There is no evidence that it results from an immunological mechanism in these patients and it has been suggested that the effect is due to impaired kinin degradation. However, angioedema has been reported with lisinopril in a patient who had previously tolerated captopril.[20] The onset of angioedema has usually been within hours or at most a week of starting treatment with the ACE inhibitor,[16] but can occur after prolonged therapy for several months or years.[21-24] It may also occur episodically with long symptom-free intervals.[24] Visceral angioedema presenting as abdominal pain with diarrhoea, nausea, and vomiting, has also been reported.[25,26] If angioedema occurs the ACE inhibitor should be withdrawn and if there is swelling affecting the tongue, glottis, or larynx likely to cause airway obstruction, adrenaline should be given (see p.1204). Fatalities have occurred.[27] Angiotensin II receptor antagonists have been suggested as an alternative in patients unable to tolerate ACE inhibitors, but there have also been reports of angioedema associated with their use (see under Losartan Potassium, p.1326). For a report of angioedema occurring after use of alteplase for stroke in patients taking ACE inhibitors, see under Interactions of Alteplase, p.1207.

1. Coleman JW, *et al.* Drug-specific antibodies in patients receiving captopril. *Br J Clin Pharmacol* 1986; **22:** 161–5.
2. Hoorntje SJ, *et al.* Serum-sickness-like syndrome with membranous glomerulopathy in patient on captopril. *Lancet* 1979; **ii:** 1297.
3. Kayanakis JG, *et al.* Eosinophilia during captopril treatment. *Lancet* 1980; **ii:** 923.
4. Schwartz D, *et al.* Enalapril-induced antinuclear antibodies. *Lancet* 1990; **336:** 187.
5. Pelayo M, *et al.* Drug-induced lupus-like reaction and captopril. *Ann Pharmacother* 1993; **27:** 1541–2.
6. Verresen L, *et al.* Angiotensin-converting-enzyme inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1990; **336:** 1360–2.
7. Tielmans C, *et al.* ACE inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1991; **337:** 370–1.
8. Committee on Safety of Medicines. Anaphylactoid reactions to high-flux polyacrylonitrile membranes in combination with ACE inhibitors. *Current Problems 33* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
9. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340:** 908–9.
10. Keller C, *et al.* LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. *Lancet* 1993; **341:** 60–1.
11. Davidson DC, *et al.* Prevention with icatibant of anaphylactoid reactions to ACE inhibitor during LDL apheresis. *Lancet* 1994; **343:** 1575.
12. Quillen K. Hypotensive transfusion reactions in patients taking angiotensin-converting-enzyme inhibitors. *N Engl J Med* 2000; **343:** 1422–3.
13. Stumpf JL, *et al.* Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* 2006; **40:** 699–703.
14. Wood SM, *et al.* Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *BMJ* 1987; **294:** 91–2.
15. Hedner T, *et al.* Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1992; **304:** 941–6.
16. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. *Ann Intern Med* 1992; **117:** 234–42.
17. Vleeming W, *et al.* ACE inhibitor-induced angioedema. *Drug Safety* 1998; **18:** 171–88.
18. Brown NJ, *et al.* Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996; **60:** 8–13.
19. Gibbs CR, *et al.* Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Clin Pharmacol* 1999; **48:** 861–5.
20. McElligott S, *et al.* Angioedema after substituting lisinopril for captopril. *Ann Intern Med* 1992; **116:** 426–7.
21. Chin HL, Buchan DA. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. *Ann Intern Med* 1990; **112:** 312–13.
22. Edwards TB. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
23. Chu TJ, Chow N. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
24. Adverse Drug Reactions Advisory Committee (ADRAC). Angioedema – still a problem with ACE inhibitors. *Aust Adverse Drug React Bull* 2005; **24:** 7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.htm (accessed 06/11/06)
25. Mullins RJ, *et al.* Visceral angioedema related to treatment with an ACE inhibitor. *Med J Aust* 1996; **165:** 319–21.
26. Byrne TJ, *et al.* Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? *Mayo Clin Proc* 2000; **75:** 1201–4.
27. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J* 2007; **97:** 244–5.

Overdosage. There have been reports of overdosage with captopril,[1,2] enalapril,[3-6] and lisinopril.[7,8] The main adverse effect is hypotension which usually responds to supportive treatment and volume expansion. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. If hypotension persists, sympathomimetics may be given, although they are not usually required. Specific therapy with angiotensinamide (p.1216) may be considered if conventional therapy is ineffective,[5,6,8] but it is not widely available. There has also been a report[9] of the successful use of naloxone after captopril overdosage.

1. Augenstein WL, *et al.* Captopril overdose resulting in hypotension. *JAMA* 1988; **259:** 3302–5.
2. Graham SR, *et al.* Captopril overdose. *Med J Aust* 1989; **151:** 111.
3. Waeber B, *et al.* Self poisoning with enalapril. *BMJ* 1984; **288:** 287–8.
4. Lau CP. Attempted suicide with enalapril. *N Engl J Med* 1986; **315:** 197.
5. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
6. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
7. Dawson AH, *et al.* Lisinopril overdose. *Lancet* 1990; **335:** 487–8.
8. Trilli LE, Johnson KA. Lisinopril overdose and management with intravenous angiotensin II. *Ann Pharmacother* 1994; **28:** 1165–8.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.

Precautions

ACE inhibitors are usually contra-indicated in patients with aortic stenosis or outflow tract obstruction (but see below). They should not generally be used in patients with renovascular disease or suspected renovascular disease, but are occasionally necessary for severe resistant hypertension in such patients, when they should only be given with great caution and under close specialist supervision. The elderly, or patients with peripheral vascular diseases or generalised atherosclerosis, may be at high risk because they may have clinically silent renovascular disease. Renal function should be assessed in all patients before use of ACE inhibitors and should be monitored during therapy. Patients with existing renal disease or taking high doses should be monitored regularly for proteinuria. Regular white blood cell counts may be necessary in patients with collagen vascular disorders, such as systemic lupus erythematosus and scleroderma, or in patients receiving immunosuppressive therapy, especially when they also have impaired renal function. ACE inhibitors should be used with caution in patients with a history of idiopathic or hereditary angioedema.

Patients with heart failure and patients who are likely to be sodium or water depleted (for example, those receiving treatment with diuretics or dialysis) may experience symptomatic hypotension during the initial stages of ACE inhibitor therapy. Treatment should therefore be started under close medical supervision, using a low dose and with the patient in a recumbent position to minimise this effect.

Anaphylactoid reactions have occurred in patients taking ACE inhibitors during haemodialysis using high-flux polyacrylonitrile membranes, during LDL-apheresis with dextran sulfate columns, and during desensitisation with wasp or bee venom (see Hypersensitivity under Adverse Effects, above).

ACE inhibitors have been associated with fetal toxicity and should not be used during pregnancy (see below).

Aortic stenosis. Vasodilators, including ACE inhibitors, are usually contra-indicated in obstructive cardiac disorders such as aortic stenosis since cardiac output cannot increase to compensate for systemic vasodilatation and there is a risk of severe hypotension. However, a study[1] in patients with symptomatic aortic stenosis found that enalapril was well-tolerated and improved symptoms, and a drug withdrawal study[2] in hypertensive patients with asymptomatic aortic stenosis suggested that ACE inhibitors had beneficial haemodynamic effects. Another study[3] in patients with heart failure and perceived contra-indications to ACE inhibitors (including 17.3% with aortic stenosis) found that survival was improved in those given ACE inhibitors. There is also some evidence that ACE inhibitors may slow the progression of calcific aortic stenosis, but this remains to be confirmed.[4]

1. Chockalingam A, *et al.* Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J* 2004; **147:** E19.

2. Jiménez-Candil J, *et al.* Effects of angiotensin converting enzyme inhibitors in hypertensive patients with aortic valve stenosis: a drug withdrawal study. *Heart* 2005; **91:** 1311–18.
3. Ahmed A, *et al.* A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. *Am Heart J* 2005; **149:** 737–43.
4. Newby DE, *et al.* Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both? *Heart* 2006; **92:** 729–34.

Diarrhoea. Several reports have indicated that life-threatening hypotension and signs of renal failure may develop in patients receiving captopril[1-3] or enalapril[3] after volume depletion due to diarrhoea.

1. McMurray J, Matthews DM. Effect of diarrhoea on a patient taking captopril. *Lancet* 1985; **i:** 581.
2. Benett PR, Cairns SA. Captopril, diarrhoea, and hypotension. *Lancet* 1985; **i:** 1105.
3. McMurray J, Matthews DM. Consequences of fluid loss in patients treated with ACE inhibitors. *Postgrad Med J* 1987; **63:** 385–7.

Ethnicity. ACE inhibitors are less effective as antihypertensives in Afro-Caribbean black patients than in white patients. A similar difference has been reported in heart failure; in a pooled analysis[1] of the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials, treatment with enalapril significantly reduced the risk of hospitalisation for heart failure in white patients with left ventricular dysfunction, but not in similar black patients. However, analysis[2] of the prevention arm alone showed that enalapril reduced the relative risk of disease progression to a similar extent in black and white patients.

1. Exner DV, *et al.* Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001; **344:** 1351–7.
2. Dries DL, *et al.* Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am Coll Cardiol* 2002; **40:** 311–17. Correction. *ibid.*; 1019.

Hepatic cirrhosis. It has been suggested that in patients with cirrhosis, captopril could cause a marked reduction in arterial pressure and severely compromise renal function, since maintenance of glomerular filtration rate might be mediated by angiotensin II in these patients.[1] This theory was supported by a report of a reduction in glomerular filtration rate in response to a fall in mean arterial pressure in 4 patients with resistant ascites secondary to hepatic cirrhosis.[2] The fall in mean arterial pressure was associated with orthostatic hypotension and increasing encephalopathy. Severe confusion has also been reported in 2 patients with cirrhosis during treatment with captopril 6.25 to 12.5 mg three times daily.[3]

1. Ring T. Captopril and resistant ascites: a word of caution. *Lancet* 1983; **ii:** 165.
2. Wood LJ, *et al.* Adverse effects of captopril in treatment of resistant ascites, a state of functional bilateral renal artery stenosis. *Lancet* 1985; **ii:** 1008–9.
3. Jørgensen F, *et al.* Captopril and resistant ascites. *Lancet* 1983; **ii:** 405.

Huntington's disease. The condition of a woman with Huntington's disease deteriorated dramatically during treatment with captopril and improved on withdrawal of the drug.[1]

1. Goldblatt J, Bryer A. Huntington's disease: deterioration in clinical state during treatment with angiotensin converting enzyme inhibitor. *BMJ* 1987; **294:** 1659–60.

Peripheral vascular disease. Patients with peripheral vascular disease may have a high incidence of renal artery stenosis and are therefore at high risk of renal failure with ACE inhibitor therapy (see Effects on the Kidneys, above). Mild renal artery stenosis was found in 64 of 374 patients (17%) with peripheral vascular disease, and severe renal artery stenosis in 52 (14%); the stenosis was bilateral in 43 (12%).[1] Renal function should be carefully monitored in any patient with peripheral vascular disease who receives ACE inhibitors.

1. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. *Lancet* 1990; **336:** 321.

Pregnancy. There is evidence from *animal* studies that use of ACE inhibitors during pregnancy is associated with fetal toxicity and an increase in still-births.[1] In humans, the main effect of ACE inhibitors is on the kidneys. Several case reports have described the development of fetal renal failure, with oligohydramnios or neonatal anuria, in the offspring of mothers receiving captopril[2-4] or enalapril;[5] there have been fetal[4] and neonatal[3] deaths. A literature search up to the end of 1989 indicated that the use of ACE inhibitors during pregnancy can cause severe disturbances of fetal and neonatal renal function, long-lasting neonatal anuria, and pulmonary hypoplasia.[6] There are also 2 case reports in which maternal captopril[7] or enalapril[8] therapy, in association with other drugs, was associated with birth defects including defective ossification of the skull. A registry study[9] found that 2 of 19 infants exposed to ACE inhibitors during pregnancy had serious life-threatening conditions: one had prolonged anuria requiring dialysis; the other had microcephaly and a large occipital encephalocele.

The FDA has re-emphasised that ACE inhibitors can cause injury and even death to the developing fetus in the second and third trimester.[10] Although use of ACE inhibitors in the first trimester had been thought to carry a lesser risk,[11-13] a review of the available experimental and clinical data concluded that the use of ACE inhibitors should be avoided throughout pregnancy.[14] Also, a later cohort study[15] of 29 507 infants found a significantly increased risk of major congenital malformations in 209 who had been exposed to ACE inhibitors alone in the first trimester and concluded that such use should be avoided.

1. Broughton Pipkin F, *et al.* Possible risk with captopril in pregnancy: some animal data. *Lancet* 1980; **i:** 1256.
2. Boutroy M-J, *et al.* Captopril administration in pregnancy impairs fetal angiotensin converting enzyme activity and neonatal adaptation. *Lancet* 1984; **ii:** 935–6.
3. Guignard JP, *et al.* Persistent anuria in a neonate: a side effect of captopril? *Int J Pediatr Nephrol* 1981; **2:** 133.
4. Knott PD, *et al.* Congenital renal dysgenesis possibly due to captopril. *Lancet* 1989; **i:** 451.
5. Schubiger G, *et al.* Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. *Ann Intern Med* 1988; **108:** 215–16. Correction. *ibid.*: 777.
6. Hanssens M, *et al.* Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991; **78:** 128–35.
7. Duminy PC, Burger P du T. Fetal abnormality associated with use of captopril during pregnancy. *S Afr Med J* 1981; **60:** 805.
8. Mehta N, Modi N. ACE inhibitors in pregnancy. *Lancet* 1989; **ii:** 96.
9. Piper JM, *et al.* Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992; **80:** 429–32.
10. Nightingale SL. Warnings on use of ACE inhibitors in second and third trimester of pregnancy. *JAMA* 1992; **267:** 2445.
11. CDC. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987-1995. *JAMA* 1997; **277:** 1193–4.
12. Lip GYH, *et al.* Angiotensin-converting-enzyme inhibitors in early pregnancy. *Lancet* 1997; **350:** 1446–7.
13. Steffensen FH, *et al.* Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet* 1998; **351:** 596.
14. Shotan A, *et al.* Risk of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med* 1994; **96:** 451–6.
15. Cooper WO, *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; **354:** 2443–51.

Interactions

Excessive hypotension may occur when ACE inhibitors are used with diuretics, other antihypertensives, or other agents, including alcohol, that lower blood pressure. An additive hyperkalaemic effect is possible in patients receiving ACE inhibitors with potassium-sparing diuretics, potassium supplements (including potassium-containing salt substitutes), or other drugs that can cause hyperkalaemia (such as ciclosporin or indometacin), and serum-potassium concentrations should be monitored. Potassium-sparing diuretics and potassium supplements should generally be stopped before starting ACE inhibitors in patients with heart failure. However, ACE inhibitor therapy does not obviate the possible need for potassium supplementation in patients given potassium-wasting diuretics and potassium concentrations should also be monitored in these patients. The adverse effects of ACE inhibitors on the kidneys may be potentiated by other drugs, such as NSAIDs, that can affect renal function.

◊ General references.

1. Shionoiri H. Pharmacokinetic drug interactions with ACE inhibitors. *Clin Pharmacokinet* 1993; **25:** 20–58.
2. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–7.

Allopurinol. For reports of reactions in patients taking captopril and allopurinol, see p.553.

Antacids. Use of captopril with antacids reduced the bioavailability of captopril although this did not significantly alter the effects on blood pressure and heart rate.[1] The bioavailability of fosinopril, and possibly other ACE inhibitors, may also be reduced by use with antacids.

1. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 626–9.

Antidiabetics. Hypoglycaemia was noted in 3 type 1 diabetics when captopril was added to their therapeutic regimen; it was also seen in a type 2 diabetic, in whom withdrawal of hypoglycaemic drugs became necessary.[1] Subsequent study suggested that the effect was due to enhanced insulin sensitivity.[1] Similar instances of a reduction in blood sugar in both non-diabetic[2] and diabetic[3] patients given enalapril have occurred. Two case-control studies in diabetic patients receiving insulin or oral hypoglycaemics suggested that patients treated with ACE inhibitors were at increased risk of developing severe hypoglycaemia.[4,5] However, other studies in diabetic patients given captopril or enalapril have failed to find any significant alterations in blood-glucose control,[6,7] and ACE inhibitors are widely used in the treatment of hypertension in diabetic patients (see p.1171) and also have a role in the management of diabetic complications such as nephropathy (see Kidney Disorders under Uses, below).

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. Helgeland A, *et al.* Enalapril, atenolol, and hydrochlorothiazide in mild to moderate hypertension: a comparative multicentre study in general practice in Norway. *Lancet* 1986; **i:** 872–5.
3. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
7. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; **ii:** 461.

Azathioprine. Leucopenia has been reported in a patient given captopril with azathioprine; the effect did not occur when either drug was given alone.[1] In a similar report, neutropenia in a patient taking a regimen including azathioprine and captopril did not recur when captopril was reintroduced after stopping azathioprine.[2]

1. Kirchertz EJ, *et al.* Successful low dose captopril rechallenge following drug-induced leucopenia. *Lancet* 1981; **i:** 1363.
2. Edwards CRW, *et al.* Successful reintroduction of captopril following neutropenia. *Lancet* 1981; **i:** 723.

Ciclosporin. An additive hyperkalaemic effect with ACE inhibitors and ciclosporin is possible. Also, acute renal failure has been reported in 2 patients on ciclosporin after renal transplantation who were given enalapril.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

Digoxin. For reports of an increase in serum-digoxin concentrations during therapy with ACE inhibitors, see p.1261.

Diuretics. Excessive hypotension may occur when ACE inhibitors are used with diuretics. Deterioration in renal function has also been reported with *metolazone* (see p.1337). Severe hyperkalaemia may occur if ACE inhibitors are used with *spironolactone* (see p.1401).

Epoetins. An additive hyperkalaemic effect may occur when ACE inhibitors are given with epoetins. ACE inhibitors have also been reported to antagonise the haematopoietic effects of epoetins.

General anaesthetics. Marked hypotension may occur during general anaesthesia in patients taking ACE inhibitors. In addition corrected cerebral blood flow was significantly lower in 11 patients who took captopril before general anaesthesia induced with thiopental and maintained with nitrous oxide and enflurane, than in 9 patients pretreated with metoprolol and 9 untreated controls.[1] Although there were no complications of anaesthesia associated with captopril pretreatment, stopping ACE inhibitor therapy before anaesthesia should be considered. However, others have suggested[2] that since there is no clear evidence for stopping them, ACE inhibitors may be continued with care.

1. Jensen K, *et al.* Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril. *Br J Anaesth* 1989; **62:** 321–3.
2. Anonymous. Drugs in the peri-operative period: 4 – cardiovascular drugs. *Drug Ther Bull* 1999; **37:** 89–92.

Gold salts. The nitritoid reaction (flushing, nausea, dizziness, and hypotension associated with the first weeks of gold treatment) occurred soon after commencing treatment with an ACE inhibitor (captopril, lisinopril, or enalapril) in 4 patients who had been receiving sodium aurothiomalate for at least 2 years.[1]

1. Healey LA, Backes MB. Nitritoid reactions and angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1989; **321:** 763.

Interferons. Severe granulocytopenia has been reported[1] in 3 patients with mixed cryoglobulinaemia treated with interferon alfa-2a who also received ACE inhibitors. The effect was considered to be due to synergistic haematological toxicity. However, in a further report,[2] 2 patients developed only mild granulocytopenia that was reversible despite continued therapy, while a third patient retained a normal granulocyte count.

1. Casato M, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1995; **99:** 386–91.
2. Jacquot C, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1996; **101:** 235–6.

Interleukin-3. Marked hypotension occurred in 3 patients[1] receiving ACE inhibitors who were given interleukin-3 following chemotherapy; blood pressure returned to normal when the ACE inhibitors were stopped.

1. Dercksen MW, *et al.* Hypotension induced by interleukin-3 in patients on angiotensin-converting enzyme inhibitors. *Lancet* 1995; **345:** 448.

Lithium. For reports of lithium toxicity in patients taking ACE inhibitors, see p.404.

Muscle relaxants. For a report of severe hypotension in a patient taking lisinopril and tizanidine, see p.1898.

NSAIDs. *Indometacin* and possibly other NSAIDs, including aspirin, have been reported to reduce or abolish the hypotensive action of ACE inhibitors. A similar effect has been reported[1] with *rofecoxib*. NSAIDs cause sodium and water retention and thus may attenuate the effects of various antihypertensives. It has also been suggested that part of the hypotensive effect of ACE inhibitors is prostaglandin-dependent, which might explain this interaction with drugs such as NSAIDs that block prostaglandin synthesis. However, in a double-blind study designed to assess the role of prostaglandins,[2] indometacin did not influence the hypotensive effect of captopril or enalapril, suggesting that the effects on prostaglandins are not significant.

The possibility of an interaction between low-dose *aspirin* and ACE inhibitors has caused concern.[3-5] Retrospective analysis of some studies of ACE inhibitors in patients with heart failure after myocardial infarction suggested that outcome was poorer in those who were also receiving aspirin. A number of small studies have investigated the effects of aspirin plus ACE inhibitors on haemodynamic parameters, but results have been conflicting and the clinical relevance of these findings is not clear. Given the well-established benefits of both ACE inhibitors and aspirin in patients with heart failure associated with ischaemic heart disease, it is generally recommended that patients should continue to receive treatment with both.[4,5] A systematic review[6] of long-term studies using ACE inhibitors came to a similar conclusion, and an observational study[7] in patients with both ischaemic and non-ischaemic heart failure found that ACE inhibitors improved outcomes, irrespective of whether or not patients were taking aspirin.

The combination of NSAIDs and ACE inhibitors may also have variable effects on renal function since they act at different parts of the glomerulus.[8] When given to patients whose kidneys are underperfused, for example because of heart failure, liver cirrhosis, or haemorrhage, renal function may deteriorate. Use of NSAIDs in patients taking ACE inhibitors with diuretics may be particularly hazardous.[9] However, specific patient groups without reduced renal perfusion may benefit from combining an NSAID with an ACE inhibitor.

Indometacin, and possibly other NSAIDs, may have an additive hyperkalaemic effect.

1. Brown CH. Effect of rofecoxib on the antihypertensive activity of lisinopril. *Ann Pharmacother* 2000; **34:** 1486.
2. Gerber JG, *et al.* The hypotensive action of captopril and enalapril is not prostacyclin dependent. *Clin Pharmacol Ther* 1993; **54:** 523–32.
3. Stys T, *et al.* Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med* 2000; **160:** 1409–13.
4. Mahé I, *et al.* Interaction between aspirin and ACE inhibitors in patients with heart failure. *Drug Safety* 2001; **24:** 167–82.
5. Olson KL. Combined aspirin/ACE inhibitor treatment for CHF. *Ann Pharmacother* 2001; **35:** 1653–8.
6. Teo KK, *et al.* Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; **360:** 1037–43. Correction. *ibid.* 2003; **361:** 90.
7. McAlister FA, *et al.* Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation* 2006; **113:** 2572–8.
8. Sturrock NDC, Struthers AD. Non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. *Br J Clin Pharmacol* 1993; **35:** 343–8.
9. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Beware the triple whammy! *Aust Adverse Drug React Bull* 2006; **25:** 18. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 04/04/08)

Probenecid. Giving probenecid to 4 healthy subjects during intravenous infusion of captopril caused increases in the steady-state plasma-captopril concentration. The interaction was considered to be due to a reduction of tubular secretion of captopril by probenecid.[1]

1. Singhvi SM, *et al.* Renal handling of captopril: effect of probenecid. *Clin Pharmacol Ther* 1982; **32:** 182–9.

Pharmacokinetics

Most ACE inhibitors are given orally. Apart from captopril and lisinopril, they are generally prodrugs and after absorption undergo rapid metabolism by ester hydrolysis to the active diacid form; for example, enalapril is converted to enalaprilat. Metabolism occurs mainly in the liver. Excretion as active drug or active metabolite is principally in the urine; some, such as benazeprilat and fosinoprilat, are also excreted via the biliary tract. Elimination of the diacid is polyphasic and there is a prolonged terminal elimination phase, which is considered to represent binding to the angiotensin-converting enzyme at a saturable binding site. This bound fraction does not contribute to accumulation of drug following multiple doses. The terminal elimination half-life does not therefore predict the kinetics observed with multiple dosing and the effective half-life for accumulation is the value usually quoted.

◊ Reviews.

1. Burnier M, Biollaz J. Pharmacokinetic optimisation of angiotensin converting enzyme (ACE) inhibitor therapy. *Clin Pharmacokinet* 1992; **22:** 375–84.
2. Hoyer J, *et al.* Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. *Clin Pharmacokinet* 1993; **24:** 230–54.
3. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.

Uses and Administration

ACE inhibitors are antihypertensive drugs that act as vasodilators and reduce peripheral resistance. They inhibit angiotensin-converting enzyme (ACE), which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect. ACE is identical to bradykininase (kininase II) and ACE inhibitors also reduce the degradation of bradykinin, which is a direct vasodilator and is also involved in the generation of prostaglandins. The pharmacological actions of ACE inhibitors are thought to be primarily due to the inhibition of the renin-angiotensin-aldosterone system, but since they also effectively reduce blood pressure in patients with low renin concentrations other mechanisms are probably also involved. ACE inhibitors produce a reduction in both preload and afterload in patients with heart failure. They also reduce left ventricular remodelling, a process that sometimes follows myocardial infarction. Normally, renal blood flow is increased without a change in glomerular filtration rate. ACE inhibitors also reduce proteinuria associated with glomerular kidney disease.

ACE inhibitors are used in the treatment of hypertension and heart failure and are given to improve survival after myocardial infarction and for the prophylaxis of cardiovascular events in patients with certain risk factors. They are also used in the treatment of diabetic nephropathy. They are generally given orally.

In some hypertensive patients there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor and the first dose should preferably be given at bedtime; if possible, any diuretic therapy should be stopped a few days beforehand and resumed later if necessary.

In patients with heart failure taking loop diuretics, severe first-dose hypotension is common on introduction of an ACE inhibitor, but temporary withdrawal of the diuretic may cause rebound pulmonary oedema. Thus treatment should start with a low dose under close medical supervision.

◊ Reviews.

1. Lopéz-Sendón J, *et al.* The Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. *Eur Heart J* 2004; **25:** 1454–70. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-ACEI-FT.pdf (accessed 25/07/08)

Action. The renin-angiotensin system plays a major role in regulation of cardiovascular and renal function and blockade of this system has complex physiological effects.[1] Although the main target for ACE inhibitors was initially thought to be the endocrine renin-angiotensin system in the circulation this mechanism alone cannot readily explain all the actions of ACE inhibitors.[2] Endogenous renin-angiotensin systems exist in many tissues and ACE inhibitors also have localised effects.[3] This may underlie some of the long-term effects of ACE inhibition, including improved endothelial function, increased arterial wall compliance, improved left ventricular function in heart failure, regression of vascular and left ventricular hypertrophy, and delayed progression of diabetic nephropathy. ACE inhibitors differ in their degree of binding to tissue ACE and in their tissue distribution, but the clinical significance of this is not clear. In one study[4] endothelial function improved with quinapril, which has high tissue specificity, but a similar effect was not seen with the less-specific enalapril, despite an earlier study[5] showing it to be effective.

ACE inhibitors also have effects on the kinin system and there is some evidence that the cardiovascular actions of ACE inhibitors also involve localised accumulation of kinins.[6-8] It has been suggested[9] that the free radical scavenging property of captopril may contribute to some of its actions, although not all studies have confirmed this effect.[10]

1. Schmieder RE, *et al.* Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; **369:** 1208–19.
2. Tabibiazar R, *et al.* Formulating clinical strategies for angiotensin antagonism: a review of preclinical and clinical studies. *Am J Med* 2001; **110:** 471–80.
3. Zarnke KB, Feldman RD. Direct angiotensin converting enzyme inhibitor-mediated venodilation. *Clin Pharmacol Ther* 1996; **59:** 559–68.
4. Anderson TJ, *et al.* Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). *J Am Coll Cardiol* 2000; **35:** 60–6.
5. O'Driscoll G, *et al.* Improvement in endothelial function by angiotensin converting enzyme inhibition in insulin-dependent diabetes mellitus. *J Clin Invest* 1997; **100:** 678–84.
6. Linz W, *et al.* Contribution of kinins to the cardiovascular actions of angiotensin-converting enzyme inhibitors. *Pharmacol Rev* 1995; **47:** 25–49.
7. Bönner G. The role of kinins in the antihypertensive and cardioprotective effects of ACE inhibitors. *Drugs* 1997; **54** (suppl 5): 23–30.
8. Gainer JV, *et al.* Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. *N Engl J Med* 1998; **339:** 1285–92.
9. Chopra M, *et al.* Captopril: a free radical scavenger. *Br J Clin Pharmacol* 1989; **27:** 396–9.
10. Lapenna D, *et al.* Captopril has no significant scavenging antioxidant activity in human plasma in vitro or in vivo. *Br J Clin Pharmacol* 1996; **42:** 451–6.

Bartter's syndrome. Captopril has been reported to produce beneficial responses in patients with Bartter's syndrome[1-5] (p.1670), which is characterised by hyperaldosteronism, hypokalaemia, and hyperreninaemia, but with normal or reduced blood pressure. Captopril may also be used diagnostically with scintigraphy.[6]

1. Aurell M, Rudin A. Effects of captopril in Bartter's syndrome. *N Engl J Med* 1981; **304:** 1609.
2. Hené RJ, *et al.* Long-term treatment of Bartter's syndrome with captopril. *BMJ* 1982; **285:** 695.
3. James JM, Davies D. The use of captopril in Bartter's syndrome. *BMJ* 1984; **289:** 162.
4. Savastano A, *et al.* Treatment of Bartter's disease with captopril: a case report. *Curr Ther Res* 1986; **39:** 408–13.
5. Jest P, *et al.* Angiotensin-converting enzyme inhibition as a therapeutic principle in Bartter's syndrome. *Eur J Clin Pharmacol* 1991; **41:** 303–5.
6. Dondi M, *et al.* Bartter's syndrome: renal scintigraphic appearance after captopril administration. *J Nucl Med* 1996; **37:** 1688–90.

Diabetic complications. Control of blood pressure plays a major role in the prevention of the sequelae of diabetes mellitus (p.433). ACE inhibitors have been reported[1] to reduce the risk of major cardiovascular events in patients, including a broad range of diabetics, with either a history of cardiovascular disease or at least one additional cardiovascular risk factor. A study[2] of diabetics with no cardiovascular disease (but unknown risk factors) also found a reduction in mortality with use of ACE inhibitors. Some of the studies of ACE inhibitors for cardiovascular risk reduction have also suggested that ACE inhibitors may prevent the development of diabetes in non-diabetic patients,[3-7] but a randomised study[8] in subjects with moderately impaired glucose metabolism but low cardiovascular risk was unable to confirm this effect.

ACE inhibitors may also have benefits in other diabetic complications. They have an established role in the management of nephropathy in patients with type 1 and type 2 diabetes (see Kidney Disorders, below).

It has been reported[9] that ACE inhibitors may reduce the progression of retinopathy in normotensive patients with type 1 diabetes mellitus. However, progression of retinopathy was a secondary end-point of the study and it was suggested that further studies were needed to confirm the beneficial results.

A preliminary report[10] has suggested that ACE inhibitors may improve peripheral neuropathy in diabetic patients, but again further studies are needed.

1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355:** 253–9. Correction. *ibid.*; **356:** 860.
2. Eurich DT, *et al.* Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 1330–4.
3. Yusuf S, *et al.* Ramipril and the development of diabetes. *JAMA* 2001; **286:** 1882–5.
4. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
5. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
6. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.
8. Bosch J, *et al.* DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; **355:** 1551–62.

9. Chaturvedi N, *et al.* Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998; **351:** 28–31.
10. Malik RA, *et al.* Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; **352:** 1978–81.

Erythrocytosis. Secondary erythrocytosis (secondary polycythaemia) is an absolute increase in red cell mass that may occur as a result of tissue hypoxia (as in chronic obstructive airways disease), or excessive erythropoietin production (as in some renal tumours or after renal transplantation). Treatment may be necessary for hyperviscosity symptoms and to reduce the risk of thromboembolic complications, and mainly involves removal of red blood cells by venesection and the use of drugs such as ACE inhibitors that inhibit erythropoiesis.

Post-transplantation erythrocytosis may resolve spontaneously in some patients but for the remainder the aim of therapy is to minimise the risk of thromboembolic and other complications by reducing the haematocrit to less than 45%. Originally treatment was by venesection but this led to severe iron deficiency. There is now evidence of beneficial effects using ACE inhibitors[1-4] or angiotensin II receptor antagonists such as losartan[5-9] and current guidelines recommend these drugs for first-line therapy.[10,11] Theophylline may also be used but appears to be less effective than ACE inhibitors[1] and is usually reserved for patients who do not respond to first-line therapy; it may also be used with an ACE inhibitor but venesection may need to be used until the haematocrit falls to 45%.

Guidelines[11] recommend that patients who develop **erythrocytosis secondary to hypoxic pulmonary disease** should first be considered for methods to improve oxygenation, including long-term oxygen therapy. Those who have hyperviscosity or a haematocrit greater than 56% should undergo venesection. ACE inhibitors or angiotensin II receptor antagonists might be of use for patients who do not tolerate venesection;[11] beneficial responses have been reported with enalapril in altitude polycythaemia,[12] and with losartan in erythrocytosis secondary to chronic obstructive pulmonary disease.[13] Theophylline has also been reported to be of benefit.

1. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
2. Beckingham IJ, *et al.* A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant* 1995; **10:** 2316–20.
3. Hernández E, *et al.* Usefulness and safety of treatment with captopril in posttransplant erythrocytosis. *Transplant Proc* 1995; **27:** 2239–41.
4. MacGregor MS, *et al.* Treatment of postrenal transplant erythrocytosis. *Nephron* 1996; **74:** 517–21.
5. Klaassen RJL, *et al.* Losartan, an angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttransplant erythrocytosis. *Transplantation* 1997; **64:** 780–2.
6. Navarro JF, *et al.* Effects of losartan on the treatment of posttransplant erythrocytosis. *Clin Nephrol* 1998; **49:** 370–2.
7. Julian BA, *et al.* Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. *J Am Soc Nephrol* 1998; **9:** 1104–8.
8. Iñigo P, *et al.* Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. *Transplant Proc* 1999; **31:** 2321.
9. Yildiz A, *et al.* Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. *Transplantation* 2001; **72:** 542–5.
10. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.3. Haematological complications: erythrocytosis. *Nephrol Dial Transplant* 2002; **17** (suppl 4): 49–50. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/17/suppl_4/49-a.pdf (accessed 20/11/06)
11. McMullin MF, *et al.* British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 20/11/06)
12. Plata R, *et al.* Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: a prospective randomised trial. *Lancet* 2002; **359:** 663–6.
13. Vlahakos DV, *et al.* Losartan reduces hematocrit in patients with chronic obstructive pulmonary disease and secondary erythrocytosis. *Ann Intern Med* 2001; **134:** 426–7.

Genetic disorders. Small studies have suggested that ACE inhibitors may be of benefit in patients with cardiac disorders associated with Marfan syndrome,[1,2] as well as in Duchenne muscular dystrophy.[3,4]

1. Yetman AT, *et al.* Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005; **95:** 1125–7.
2. Ahimastos AA, *et al.* Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA* 2007; **298:** 1539–47.
3. Duboc D, *et al.* Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; **45:** 855–7.
4. Duboc D, *et al.* Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007; **154:** 596–602.

Heart failure. ACE inhibitors given orally produce clinical benefit in all stages of chronic heart failure (p.1165) additional to that seen with diuretics. They relieve symptoms and improve survival and reduce the progression of mild or moderate heart failure to more severe stages. Thus, it is now recommended that all patients with heart failure due to left ventricular systolic dysfunction should receive ACE inhibitors, even if they are asymptomatic with diuretics alone. The studies that have shown a benefit with ACE inhibitors have tended to use higher doses than those used in practice. A study[1] with lisinopril found that higher doses reduced the combined end-point of death or hospitalisation more than low doses and were equally well tolerated, suggesting that higher doses should be used. Studies with enalapril have failed to show a benefit of standard doses over lower doses,[2] or high doses over standard doses.[3] It is now recommended[4,5] that doses should be titrated to those found to be effective in randomised trials, rather than according to symptomatic response, although lower doses may still be of benefit if higher doses are not tolerated.[4] Combination of ACE inhibitors with angiotensin II receptor antagonists to produce a more complete blockade of the renin-angiotensin system may also be of benefit,[6-8] and may therefore be considered[4,5] in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers. ACE inhibitors may also have a role in patients with asymptomatic left ventricular dysfunction, although this is less well established; no effect on short-term mortality was found in asymptomatic patients in the SOLVD trial, but a significant survival benefit was found on long-term follow-up.[9] In patients with heart failure and preserved left ventricular function (diastolic dysfunction) the role of ACE inhibitors is unclear, although they may provide symptomatic benefit.[10] ACE inhibitors may be beneficial in patients with heart failure associated with valve disorders (but see under Precautions, above for discussion of their use in aortic stenosis). There is also some evidence that ACE inhibitors may prevent the development of antineoplastic-induced cardiotoxicity,[11] although this remains to be confirmed.

The mechanism of action in heart failure is not established. ACE inhibitors have beneficial haemodynamic effects; they produce arterial and venous dilatation,[12] reducing both preload and afterload and thus improving cardiac output without increasing heart rate. Their neurohormonal effects also play a part,[13] as do their effects on cytokines. Further actions that may contribute include reduction of left ventricular hypertrophy, and an indirect action to prevent cardiac arrhythmias.[14-16]

Captopril and enalapril have both been used in infants with severe heart failure (see Administration in Children, p.1240, and p.1277, respectively).

1. Packer M, *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; **100:** 2312–18.
2. The NETWORK investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998; **19:** 481–9.
3. Nanas JN, *et al.* Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol* 2000; **36:** 2090–5.
4. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 25/07/08)
5. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CHF-FT.pdf (accessed 25/07/08)
6. Struckman DR, Rivey MP. Combined therapy with an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure. *Ann Pharmacother* 2001; **35:** 242–8.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. Jong P, *et al.* Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003; **361:** 1843–8.
10. Cleland JGF, *et al.* PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27:** 2338–45.
11. Cardinale D, *et al.* Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; **114:** 2474–81.
12. Capewell S, *et al.* Acute and chronic arterial and venous effects of captopril in congestive cardiac failure. *BMJ* 1989; **299:** 942–5.
13. Deedwania PC. Angiotensin-converting enzyme inhibitors in congestive heart failure. *Arch Intern Med* 1990; **150:** 1798–1805.
14. Wesseling H, *et al.* Cardiac arrhythmias—a new indication for angiotensin-converting enzyme inhibitors? *J Hum Hypertens* 1989; **3** (suppl 1): 89–95.
15. Campbell RWF. ACE inhibitors and arrhythmias. *Heart* 1996; **76** (suppl 3): 79–82.
16. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.

Hypertension. ACE inhibitors have an established role in the management of hypertension (p.1171) and appear to have comparable effects to the other main groups of antihypertensives.[1] The Captopril Prevention Project (CAPPP) trial,[2] which compared captopril-based therapy with beta blocker- or diuretic-based therapy, suggested that cardiovascular mortality was lower with captopril, although the risk of stroke was increased in those receiving captopril and overall mortality did not differ between the groups. In the large ALLHAT study,[3] which compared an ACE inhibitor with a calcium-channel blocker or a diuretic, overall mortality did not differ significantly between any of the groups, although there were slightly higher rates of stroke and heart failure in those given the ACE inhibitor compared with the diuretic group. ACE inhibitors are particularly recommended in diabetic patients with nephropathy as they may have beneficial effects on the kidney, and also in patients with heart failure. Other advantages that have been suggested include their lack of adverse effects on serum lipids, a reduction in left ventricular hypertrophy,[4] and a reduction in plasma fibrinogen levels,[5] but the clinical significance of these effects is not established.

The antihypertensive actions of ACE inhibitors may be potentiated by drugs that activate the renin-angiotensin system. Hence, combination therapy with diuretics or with calcium-channel blockers may be particularly useful.

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362:** 1527–35.
2. Hansson L, *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; **353:** 611–16.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.
4. Schmieder RE, *et al.* Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA* 1996; **275:** 1507–13.
5. Fogari R, *et al.* Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 471–6.

DIAGNOSIS OF RENOVASCULAR HYPERTENSION. Captopril has been used to diagnose renovascular hypertension, since the increase in plasma renin activity after blockade of the conversion of angiotensin I to angiotensin II is greater in renovascular hypertension than in primary hypertension.[1] However, a meta-analysis[2] of various tests used for the diagnosis of renovascular hypertension found that the accuracy of the captopril test is low when compared with imaging methods such as computed tomography or magnetic resonance angiography. Captopril is also used to enhance the sensitivity and specificity of renal scintigraphy.[3] For reference to the use of captopril scintigraphy to diagnose Bartter's syndrome see above.

1. Muller FB, *et al.* The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986; **80:** 633–44.
2. Vasbinder GBC, *et al.* Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med* 2001; **135:** 401–411.
3. Dowling RJ, *et al.* Imaging and stenting for renal artery stenosis. *Hosp Med* 1999; **60:** 329–34.

Ischaemic heart disease. ACE inhibitors have clinical benefits in patients with ischaemic heart disease and other atherosclerotic conditions. They have an established role in the treatment of patients after acute myocardial infarction (see below) and may also have a preventative effect; in the SAVE[1] and SOLVD[2] studies, use of ACE inhibitors in patients with heart failure was noted to lead to a reduction in the incidence of myocardial infarction. In the HOPE study,[3] treatment with ramipril significantly reduced the rate of death, myocardial infarction, and stroke in patients at high risk for cardiovascular disease, while in the EUROPA study[4] perindopril was found to reduce cardiovascular events in patients with stable ischaemic heart disease. In the QUO VADIS study,[5] giving quinapril for 1 year after coronary artery bypass grafting reduced the incidence of clinical ischaemic events although there was no effect on ischaemia during exercise testing or Holter monitoring.

The mechanisms by which ACE inhibitors produce benefit in these patients is less clear. Although a direct action to reduce atherosclerosis (p.1159) has been suggested, studies have failed to confirm this effect. In the TREND study,[6] giving quinapril for 6 months was reported to improve endothelial dysfunction in patients with ischaemic heart disease, but apparently no effects on the progression of atherosclerosis or the incidence of cardiac events were found in the QUIET study[7] which used a lower dose of quinapril given for 3 years. In the PART-2 study,[8] ramipril had no effect on the progression of carotid atherosclerosis, while the PARIS study[9] found an increase in angiographic restenosis after use of quinapril.

A lack of acute anti-ischaemic effect has been found with short-term use of captopril and enalapril in patients with stable angina,[10] and with enalapril in Prinzmetal's angina;[11] however, a further study[12] in patients with stable angina reported an improvement in the results of maximal exercise testing after sublingual captopril dosage. Symptomatic benefit has also been reported[13] in patients with atherosclerotic peripheral arterial disease, and a case-control study[14] has suggested that patients with aortic disease may have a lower risk of ruptured aortic aneurysm if they are taking ACE inhibitors.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; **327:** 669–77.
2. Yusuf S, *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992; **340:** 1173–8.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.
4. EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362:** 782–8.
5. Oosterga M, *et al.* Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study): QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol* 2001; **87:** 542–6.
6. Mancini GBJ, *et al.* Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing Endothelial Dysfunction) study. *Circulation* 1996; **94:** 258–65.
7. Cashin-Hemphill L, *et al.* Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. *Am J Cardiol* 1999; **83:** 43–7.
8. MacMahon S, *et al.* Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol* 2000; **36:** 438–43.
9. Meurice T, *et al.* Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2001; **357:** 1321–4.
10. Longobardi G, *et al.* Failure of protective effect of captopril and enalapril on exercise and dipyridamole-induced myocardial ischemia. *Am J Cardiol* 1995; **76:** 255–8.
11. Guazzi M, *et al.* Ineffectiveness of angiotensin converting enzyme inhibition (enalapril) on overt and silent myocardial ischemia in vasospastic angina and comparison with verapamil. *Clin Pharmacol Ther* 1996; **59:** 476–81.
12. Gemici K, *et al.* The effects of sublingual administration of captopril on parameters of exercise test and neurohormonal activation in patients with stable angina pectoris. *Int J Angiol* 1998; **7:** 238–43.
13. Ahimastos AA, *et al.* Ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med* 2006; **144:** 660–4.
14. Hackam DG, *et al.* Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006; **368:** 659–65.

Kidney disorders. The effects of ACE inhibitors on the kidney are complex. Although they may reduce renal function and should be used with caution in patients with renal impairment (see Adverse Effects and Treatment, above), ACE inhibitors may also have beneficial effects in diabetic and nondiabetic renal disease. Reducing blood pressure protects renal function regardless of the class of antihypertensive used,[1] since hypertension and the resultant proteinuria both cause kidney damage. A number of studies have shown that ACE inhibitors and other drugs that block the renin-angiotensin-aldosterone system (RAS), such as angiotensin II receptor antagonists, are particularly effective[1] and they may therefore be preferred for blood pressure control in kidney disorders. However, whether they have a specific renoprotective effect beyond their antihypertensive effect is unclear.[2]

Most experience has been gained in patients with diabetic nephropathy (see Diabetic Complications, p.433), which is often associated with hypertension and may progress from microalbuminuria to the nephrotic syndrome and end-stage renal failure. In patients with proteinuria, the use of ACE inhibitors now appears to be of established benefit, whether they are hypertensive or normotensive or whether they have type 1 or type 2 diabetes mellitus. Angiotensin II receptor antagonists are also effective[3,4] and may be used as an alternative, although only ACE inhibitors have been shown to have a mortality benefit;[5] dual therapy with an ACE inhibitor and an angiotensin II receptor antagonist has also been tried and may be more effective than either alone.[6,7] In patients with early diabetic nephropathy, ACE inhibitors also slow progression of microalbuminuria,[4,8] and they have been recommended, in conjunction with tight glycaemic control, in all diabetic patients with microalbuminuria.[9] They may also have benefits in patients with normal renal albumin excretion and have been reported to reduce the incidence of microalbuminuria in both hypertensive and normotensive type 2 diabetics,[10] although the clinical significance remains to be established.

ACE inhibitors may also be of benefit in renal disease unrelated to diabetes, although their role is less established. Proteinuria is an important indicator of glomerular kidney disease (p.1504) of various causes and may range from asymptomatic to severe. A number of studies[11-18] have reported that ACE inhibitors reduce both proteinuria and the rate of decline of renal function in patients with various non-diabetic renal disorders. Meta-analyses[19,20] have concluded that ACE inhibitors are more effective than other antihypertensives, although others suggest this is uncertain.[2] As in diabetic nephropathy, dual therapy with an ACE inhibitor and an angiotensin II receptor antagonist may provide additional benefit,[6] although there is less evidence for angiotensin II receptor antagonists alone in non-diabetic renal disease.[3]

Patients with systemic sclerosis (see Scleroderma, p.1817) are considered to be at high risk of adverse effects from ACE inhibitors; however there is evidence that these drugs are of benefit in the management of scleroderma-associated hypertension and renal crisis.[21]

1. Ravera M, *et al.* Importance of blood pressure control in chronic kidney disease. *J Am Soc Nephrol* 2006; **17** (4 suppl 2): S98–S103.
2. Casas JP, *et al.* Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; **366:** 2026–33.
3. Thurman JM, Schrier RW. Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure and the kidney. *Am J Med* 2003; **114:** 588–98.
4. Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs* 2006; **66:** 2213–34.
5. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 25/04/08).
6. MacKinnon M, *et al.* Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; **48:** 8–20.
7. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
8. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001; **134:** 370–9.
9. Mogensen CE, *et al.* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; **346:** 1080–4.
10. Strippoli GFM, *et al.* Antihypertensive agents for preventing diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 04/04/08).
11. Gansevoort RT, *et al.* Long-term benefits of the antiproteinuric effect of angiotensin-converting enzyme inhibition in nondiabetic renal disease. *Am J Kidney Dis* 1993; **22:** 202–6.
12. Hannedouche T, *et al.* Randomised controlled trial of enalapril and β blockers in non-diabetic chronic renal failure. *BMJ* 1994; **309:** 833–7.
13. Maschio G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; **334:** 939–45.
14. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349:** 1857–63.
15. Ruggenenti P, *et al.* Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998; **352:** 1252–6.
16. Ruggenenti P, *et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; **354:** 359–64.
17. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; **285:** 2719–28.
18. Hou FF, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; **354:** 131–40.
19. Giatras I, *et al.* Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med* 1997; **127:** 337–45.
20. Jafar TH, *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data. *Ann Intern Med* 2001; **135:** 73–87.
21. Steen VD, *et al.* Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; **113:** 352–7.

Malignant neoplasms. *Animal* and *in vitro* studies have suggested that ACE inhibitors may protect against the development of cancer, and there has been a case report[1] of regression of Kaposi's sarcoma in a patient treated with captopril (but see Effects on the Skin, above). A retrospective cohort study[2] suggested that the incidence of cancer in hypertensive patients receiving ACE inhibitors was lower than expected. However, a subsequent case control study[3] in postmenopausal women found no evidence of a reduced risk of breast cancer associated with ACE inhibitor therapy.

See under Heart Failure, above for a suggestion that ACE inhibitors may protect against antineoplastic-induced cardiotoxicity.

1. Vogt B, Frey FJ. Inhibition of angiogenesis in Kaposi's sarcoma by captopril. *Lancet* 1997; **349:** 1148.
2. Lever AF, *et al.* Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; **352:** 179–84.
3. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.

Marfan syndrome. For mention of the use of ACE inhibitors in patients with Marfan syndrome see Genetic Disorders, above.

Migraine. Observations that attacks of migraine occurred less frequently in hypertensive patients treated with lisinopril, were confirmed by a small placebo-controlled study[1] in 47 non-hypertensive patients with migraine (p.616).

1. Schrader H, *et al.* Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001; **322:** 19–22.

Muscular dystrophy. For reference to the use of ACE inhibitors in patients with Duchenne muscular dystrophy see Genetic Disorders, above.

Myocardial infarction. ACE inhibitors may be of benefit in both the prevention and treatment of myocardial infarction (p.1175). They reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Studies in patients with evidence of left ventricular dysfunction have shown benefit from long-term oral use of ACE inhibitors such as captopril (the SAVE study),[1] ramipril (the AIRE and AIRE extension (AIREX) studies),[2-4] or trandolapril (the TRACE study)[5,6] started about 3 days, or more, after infarction, and long-term ACE inhibitors are now established therapy in such patients.[7,8]

Early treatment with ACE inhibitors as an adjunct to standard thrombolytic therapy is less well established. Favourable results have been reported in the GISSI-3[9] and the ISIS-4[10] studies where lisinopril and captopril, respectively, were given orally starting within 24 hours of the onset of chest pain and in the Chinese Cardiac Study[11] (CCS-1) where captopril was given orally within 36 hours of the onset of symptoms. In the GISSI-3 study the beneficial effects were maintained at 6 months.[12] However, the CONSENSUS II study was stopped early when it was found that enalapril, given intravenously as enalaprilat and begun within 24 hours of the onset of chest pain, did not improve survival during the 180 days after infarction.[13] A substudy on some of the patients did however suggest that they may have benefited from early treatment since left ventricular dilatation was attenuated.[14] An interaction between aspirin and enalapril was postulated as one of the reasons for the overall lack of benefit seen, and further analysis of the CONSENSUS II results found that the beneficial effect of enalapril was reduced in those patients already taking aspirin,[15] although a systematic overview[16] failed to support this finding. A systematic review of the CONSENSUS II, GISSI-3, ISIS-4, and CCS-1 studies found lower 30-day cumulative mortality and incidence of non-fatal heart failure among ACE inhibitor recipients.[17] However, the size of benefit in these studies of largely unselected patients is much smaller than in the studies of patients with left ventricular dysfunction, and there remains no clear consensus as to whether all patients should be given ACE inhibitors or only those who develop evidence of left ventricular dysfunction.

1. Pfeffer MA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; **327:** 669–77.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342:** 821–8.
3. Hall AS, *et al.* Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE extension (AIREX) study. *Lancet* 1997; **349:** 1493–7.
4. Cleland JGF, *et al.* Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE study investigators. *Eur Heart J* 1997; **18:** 41–51.
5. Køber L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; **333:** 1670–6.
6. Torp-Pedersen C, Køber L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet* 1999; **354:** 9–12.
7. Borghi C, Ambrosioni E. A risk-benefit assessment of ACE inhibitor therapy post-myocardial infarction. *Drug Safety* 1996; **14:** 277–87.
8. Murdoch DR, McMurray JJV. ACE inhibitors in acute myocardial infarction. *Hosp Med* 1998; **59:** 111–15.
9. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
10. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
11. Chinese Cardiac Study collaborative group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; **345:** 686–7.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
13. Swedberg K, *et al.* Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; **327:** 678–84.
14. Bonarjee VVS, *et al.* Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol* 1993; **72:** 1004–9.
15. Nguyen KN, *et al.* Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997; **79:** 115–19.
16. Latini R, *et al.* Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. *J Am Coll Cardiol* 2000; **35:** 1801–7.
17. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998; **97:** 2202–12.

Raynaud's syndrome. ACE inhibitors are among many drugs that have been tried in Raynaud's syndrome, a vasospastic peripheral vascular disease (p.1178). Variable effects have been reported. In a patient with Raynaud's syndrome captopril improved blood circulation in the fingers both acutely and during long-term therapy with a dose of 37.5 mg daily; the effect was apparently related to its effects on kinins rather than inhibition of angiotensin II formation.[1] However, a double-blind crossover study in 15 patients with Raynaud's phenomenon given captopril 25 mg or placebo three times daily for 6 weeks found that the drug improved blood flow but not the frequency or severity of attacks,[2] and a similar study in patients given enalapril failed to find any subjective or objective benefits.[3]

There has also been a report[4] of a patient in whom peripheral ischaemia induced by ergotamine was rapidly reversed by captopril.

1. Miyazaki S, *et al.* Relief from digital vasospasm by treatment with captopril and its complete inhibition by serine proteinase inhibitors in Raynaud's phenomenon. *BMJ* 1982; **284:** 310–11.
2. Rustin MHA, *et al.* The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. *Br J Dermatol* 1987; **117:** 751–8.
3. Challenor VF, *et al.* Subjective and objective assessment of enalapril in primary Raynaud's phenomenon. *Br J Clin Pharmacol* 1991; **31:** 477–80.
4. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.

Stroke. Antihypertensive therapy reduces the risk of stroke (p.1185) in patients with hypertension. However, in patients who have had a stroke, antihypertensive therapy has often been avoided due to the perceived risk of reducing cerebral perfusion. A study[1] of blood-pressure lowering with the ACE inhibitor perindopril, alone or with a diuretic, found that the risk of recurrent stroke was reduced in patients with a history of stroke or transient ischaemic attack, irrespective of whether they had a normal or raised blood pressure at study entry. Retrospective studies[2,3] have also suggested that stroke severity may be reduced in patients who are already taking ACE inhibitors. The beneficial effects of ACE inhibitors in stroke may not be entirely due to their antihypertensive effects; in the HOPE study,[4] ramipril reduced the incidence of stroke in patients with high cardiovascular risk despite only a small reduction in blood pressure.

There have also been reports[5,6] that ACE inhibitors may reduce the risk of pneumonia in patients with a history of stroke, possibly by an effect on symptomless dysphagia.[7]

1. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358:** 1033–41. Corrections. *ibid.*; 1556 and 2002; **359:** 2120.
2. Kumar S, *et al.* Antiplatelets, ACE inhibitors, and statins combination reduces stroke severity and tissue at risk. *Neurology* 2006; **66:** 1153–8.
3. Chitravas N, *et al.* Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? *Neurology* 2007; **68:** 1687–93.
4. Bosch J, *et al.* Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; **324:** 699–702.
5. Sekizawa K, *et al.* ACE inhibitors and pneumonia. *Lancet* 1998; **352:** 1069.
6. Arai T, *et al.* ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; **352:** 1937–8.
7. Arai T, *et al.* ACE inhibitors and symptomless dysphagia. *Lancet* 1998; **352:** 115–6.

Acebutolol *(BAN, USAN, rINN)* ⊗

Acébutolol; Acebutololum; Asebutolol; Asebutololi. (±)-3′-Acetyl-4′-(2-hydroxy-3-isopropylaminopropoxy)butyranilide.

Ацебутолол

$C_{18}H_{28}N_2O_4$ = 336.4.

CAS — 37517-30-9.

ATC — C07AB04.

ATC Vet — QC07AB04.

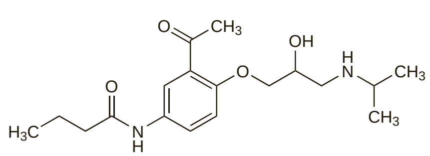

Acebutolol Hydrochloride *(BANM, rINNM)* ⊗

Acébutolol, chlorhydrate d'; Acebutolol-hidroklorid; Acebutolol-hydrochlorid; Acebutololhydroklorid; Acebutololi hydrochloridum; Acebutololio hidrochloridas; Acebutololu chlorowodorek; Asebutololihydrokloridi; Hidrocloruro de acebutolol; IL-17803A; M&B-17803A.

Ацебутолола Гидрохлорид

$C_{18}H_{28}N_2O_4$,HCl = 372.9.

CAS — 34381-68-5.

ATC — C07AB04.

ATC Vet — QC07AB04.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Acebutolol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 31 (Acebutolol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane; practically insoluble in ether. pH of a 1% solution in water is between 4.5 and 7.0. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Concentrations of acebutolol and its active metabolite diacetolol in breast milk are higher than those in maternal plasma.[1] Pharmacological effects in the neonate, including hypotension, bradycardia, and tachypnoea, have been reported,[1] and the American Academy of Pediatrics therefore considers[2] that acebutolol should be given with caution to breast-feeding mothers.

1. Boutroy MJ, *et al.* To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur J Clin Pharmacol* 1986; **30:** 737–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the liver. Six cases of hepatotoxicity associated with acebutolol were reported[1] in the USA to the FDA between 1985 and 1989. The syndrome consisted of markedly elevated transaminase concentrations, moderately elevated alkaline phosphatase concentrations, and other constitutional symptoms such as fever, nausea, abdominal pain, and headache. The duration of therapy before onset of symptoms ranged from 10 to 31 days; 5 patients received a daily dose of 400 mg; the dose was unspecified in the sixth patient. The syndrome resolved when acebutolol was stopped but reappeared in 2 patients who were rechallenged.

1. Tanner LA, *et al.* Hepatic toxicity after acebutolol therapy. *Ann Intern Med* 1989; **111:** 533–4.

Effects on respiratory function. Bronchospasm is a recognised adverse effect of beta blockers, but other respiratory disorders have also been reported. Pleurisy and pulmonary granulomas developed in a patient given acebutolol and a diuretic; acebutolol was considered to be responsible.[1] Hypersensitivity pneumonitis has also been reported in a patient taking acebutolol.[2]

1. Wood GM, *et al.* Pleurisy and pulmonary granulomas after treatment with acebutolol. *BMJ* 1982; **285:** 936.
2. Akoun GM, *et al.* Acebutolol-induced hypersensitivity pneumonitis. *BMJ* 1983; **286:** 266–7.

Hypersensitivity. See Effects on Respiratory Function, above and Lupus, below.

Lupus. An increase in antinuclear antibodies has been seen with acebutolol.[1] A report of a lupus syndrome in an elderly patient given acebutolol and clonidine described remission of symptoms when acebutolol was withdrawn, but the high antinuclear antibody titre persisted for more than 9 months.[2] Acebutolol was also reported to have caused subacute cutaneous lupus erythematosus in a 57-year-old woman. The condition had resolved completely 4 months after acebutolol was stopped.[3] The authors noted that there had been 9 previous reports of lupus in patients taking acebutolol, but only one had skin manifestations.

1. Wilson JD. Antinuclear antibodies and cardiovascular drugs. *Drugs* 1980; **19:** 292–305.
2. Hourdebaigt-Larrusse P, *et al.* Une nouvelle observation de lupus induit par acébutolol. *Ann Cardiol Angeiol (Paris)* 1985; **34:** 421–3.
3. Fenniche S,*et al.* Acebutolol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005; **18:** 230–3.

Pregnancy. Both acebutolol and its active metabolite diacetolol cross the placenta. In a study[1] in 29 pregnant women who had received acebutolol for at least one month before delivery, there was evidence of bradycardia in 12 of the 31 offspring and tachypnoea in 6.

1. Boutroy MJ, *et al.* Infants born to hypertensive mothers treated by acebutolol. *Dev Pharmacol Ther* 1982; **4** (suppl 1): 109–15.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Acebutolol is well absorbed from the gastrointestinal tract, but undergoes extensive first-pass metabolism in the liver. Although the bioavailability of acebutolol is reported to be only about 40%, the major metabolite diacetolol is active. After oral doses, peak plasma concentrations of acebutolol and diacetolol are reached in about 2 and 4 hours, respectively.

Acebutolol and diacetolol are widely distributed in the body, but they have low to moderate lipid solubility and penetration into the CSF is poor. They cross the placenta and higher concentrations are achieved in breast milk than in maternal plasma. Acebutolol is only about 26% bound to plasma proteins, but is about 50% bound to erythrocytes. The plasma elimination half-lives for acebutolol and diacetolol are 3 to 4 hours and 8 to 13 hours respectively. Half-life values for acebutolol and diacetolol may be increased in the elderly and the half-life for diacetolol may be prolonged up to 32 hours in patients with severe renal impairment. Acebutolol and diacetolol are excreted in the urine and in the bile and may undergo enterohepatic recycling; acebutolol is also reported to be excreted directly from the intestinal wall, and more than 50% of an oral dose can be recovered from the faeces. Acebutolol and diacetolol are removed by dialysis.

Uses and Administration

Acebutolol is a cardioselective beta blocker (p.1225). It is reported to have some intrinsic sympathomimetic activity and membrane stabilising properties.

Acebutolol is used in the management of hypertension (p.1171), angina pectoris (p.1157), and cardiac arrhythmias (p.1160).

Acebutolol is used as the hydrochloride, but doses are usually expressed in terms of the base; 110.8 mg of acebutolol hydrochloride is equivalent to 100 mg of base. It is generally given orally although slow intravenous injection has been used for the emergency treatment of arrhythmias.

In **hypertension** the usual initial oral dose is 400 mg once daily or 200 mg twice daily, increased if necessary after 2 weeks to 400 mg twice daily. Doses up to 1.2 g daily in divided doses may be given.

The usual oral dose for **angina pectoris** is 400 mg once daily or 200 mg twice daily, but up to 300 mg three times daily may be required for severe cases and total daily doses of 1.2 g have been given.

The usual initial oral dose for **cardiac arrhythmias** is 200 mg twice daily, increased according to response; up to 1.2 g daily in divided doses has been required.

Reduced doses may be required in patients with impaired renal function (see below). Elderly patients may also require lower maintenance doses; doses greater than 800 mg daily should be avoided.

Action. Acebutolol is generally considered to be a cardioselective beta blocker but there has been considerable controversy as to the degree of its selectivity and the selectivity of its primary metabolite, diacetolol.[1-3] In a review of beta blockers,[4] acebutolol was stated to be less cardioselective than other drugs such as atenolol or metoprolol. It was proposed[5] that this may be because the metabolite accumulates during chronic dosage to reach concentrations that affect both $beta_1$ and $beta_2$ receptors since cardioselectivity is only a relative and dose-related phenomenon. This remains uncertain and there is some evidence[6] that at least after single doses, diacetolol is actually more cardioselective than acebutolol itself.

1. Whitsett TL, *et al.* Comparison of the beta and beta adrenoceptor blocking properties of acebutolol and propranolol. *Chest* 1982; **82:** 668–73.
2. Nair S, *et al.* The effect of acebutolol, a beta adrenergic blocking agent, and placebo on pulmonary functions in asthmatics. *Int J Clin Pharmacol Ther Toxicol* 1981; **19:** 519–26.
3. Leary WP, *et al.* Respiratory effects of acebutolol hydrochloride: a new selective beta-adrenergic blocking agent. *S Afr Med J* 1973; **47:** 1245–8.
4. Feely J, *et al.* Beta-blockers and sympathomimetics. *BMJ* 1983; **286:** 1043–7.
5. Feely J, Maclean D. New drugs: beta blockers and sympathomimetics. *BMJ* 1983; **286:** 1972.
6. Thomas MS, Tattersfield AE. Comparison of beta-adrenoceptor selectivity of acebutolol and its metabolite diacetolol with metoprolol and propranolol in normal man. *Eur J Clin Pharmacol* 1986; **29:** 679–83.

Administration in renal impairment. The dose of acebutolol should be reduced in patients with renal impairment. It is recommended that the dose should be reduced by 50% in patients with a creatinine clearance between 25 and 50 mL/minute and by 75% in those with a creatinine clearance of less than 25 mL/minute. The dose frequency should not exceed once daily.

Preparations

BP 2008: Acebutolol Capsules; Acebutolol Tablets;
USP 31: Acebutolol Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Belg.: Sectral; ***Canad.:*** Monitan; Rhotral; Sectral; ***Chile:*** Beloc; Grifobutol; ***Cz.:*** Acecor; Apo-Acebutol; Sectral; ***Denm.:*** Diasectral; ***Fin.:*** Diasectral; Espesil; ***Fr.:*** Sectral; ***Ger.:*** Prent; ***Hong Kong:*** Sectral; ***Irl.:*** Sectral†; ***Israel:*** Sectral; ***Ital.:*** Prent; Sectral; ***Malaysia:*** Sectral†; ***Neth.:*** Sectral; ***NZ:*** ACB; ***Pol.:*** Abutol; Sectral; ***Port.:*** Prent; ***S.Afr.:*** Butobloc; Sectral; ***Singapore:*** ACB†; Sectral; ***Spain:*** Sectral†; ***Switz.:*** Sectral†; ***Turk.:*** Prent; ***UK:*** Sectral; ***USA:*** Sectral; ***Venez.:*** Flebutol†.

Multi-ingredient: ***Belg.:*** Sectrazide; ***Ger.:*** Sali-Prent; Tredalat; ***Indon.:*** Sectrazide; ***Neth.:*** Secadrex†; ***Spain:*** Secadrex†; ***UK:*** Secadrex†.

Acenocoumarol *(BAN, rINN)*

Acénocoumarol; Acenocoumarolum; Acenocumarin; Acenocumarol; Acenokumarol; Asenokumarol; G-23350; Nicoumalone; Nikumalon. (*RS*)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-coumarin.

Аценокумарол

$C_{19}H_{15}NO_6$ = 353.3.

CAS — 152-72-7.

ATC — B01AA07.

ATC Vet — QB01AA07.

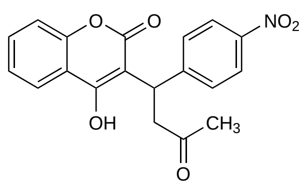

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Acenocoumarol). An almost white to buff-coloured odourless or almost odourless powder. It exhibits polymorphism. Practically insoluble in water and in ether; slightly soluble in alcohol and in chloroform; dissolves in aqueous solutions of alkali hydroxides.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425.

Effects on the fetus. In a group of women who received acenocoumarol for anticoagulant prophylaxis of mechanical heart valves during pregnancy,[1] fetal loss occurred in 13 of 61 pregnancies where oral anticoagulation was continued during the first trimester. Apart from 1 case of hydrocephalus no malformations were reported in the remaining neonates.

1. Meschengieser SS, *et al.* Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart* 1999; **82:** 23–6.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving acenocoumarol can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antifungals; antigout drugs; antihistamines; antineoplastics; antiplatelets; antivirals; diuretics; gastrointestinal drugs; immunosuppressants; lipid regulating drugs; sex hormones; and vaccines.

Pharmacokinetics

Acenocoumarol is readily absorbed from the gastrointestinal tract and is excreted chiefly in the urine mainly as metabolites. It is extensively bound to plasma proteins. Figures reported for elimination half-life vary; UK licensed product information gives a range of 8 to 11 hours. Acenocoumarol crosses the placenta; only small quantities have been detected in breast milk. It is given as a racemic mixture; the *R*-isomer is more potent. The stereo-isomers have different pharmacokinetics. Metabolism of the *S*-isomer is mediated mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes as well are involved in the metabolism of the *R*-isomer.

◊ References.

1. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.

Uses and Administration

Acenocoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187). The usual dose is 4 to 12 mg on the first day and 4 to 8 mg on the second day; subsequent maintenance doses range from 1 to 8 mg depending on the response. Acenocoumarol is given in a single dose at the same time every day.

Preparations

BP 2008: Acenocoumarol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acenotromb; Antitrom; Azecar; Cumarol; Fortonol; Saxion; Sintrom; ***Austria:*** Sintrom; ***Belg.:*** Sintrom; ***Canad.:*** Sintrom; ***Chile:*** Acenox; Coarol; Isquelium; Neo-Sintrom; ***Fr.:*** Mini-sintrom; Sintrom; ***Gr.:*** Sintrom; ***Hung.:*** Syncumar; ***India:*** Acitrom; ***Israel:*** Sintrom; ***Ital.:*** Sintrom; ***Mex.:*** Sintrom; ***Neth.:*** Sintrom Mitis; ***Pol.:*** Sintrom; Syncumar; ***Port.:*** Sintrom; ***Spain:*** Sintrom; ***Switz.:*** Sintrom; ***UK:*** Sinthrome.

Acetyldigoxin

Acetildigoxina; Acetyldigoxin-beta; Acetyldigoxinum; β-Acetyldigoxinum; Acetyldigoxinum Beta; β-Acetylodigoksyna; Asetyylidigoksiini; Desglucolanatoside C. 3β-[(*O*-3-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,-14-dihydroxy-5β,14β-card-20(22)-enolide (α-acetyldigoxin); 3β-[(*O*-4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (β-acetyldigoxin).

$C_{43}H_{66}O_{15}$ = 823.0.

CAS — 5511-98-8 (α-acetyldigoxin); 5355-48-6 (β-acetyldigoxin).

ATC — C01AA02.

ATC Vet — QC01AA02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (β-Acetyldigoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Acetyldigoxin is a cardiac glycoside with positive inotropic activity. It has the general properties of digoxin (p.1259) and has been used similarly in the management of some cardiac arrhythmias (p.1160) and in heart failure (p.1165). Usual oral maintenance doses for the β-isomer are 200 to 400 micrograms daily; the α-isomer has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Corotal; Lanatilin; Novodigal; ***Ger.:*** Digostada; Digotab; Digox; Digoxin "Didier"†; Novodigal; Stillacor; ***Ital.:*** Cardioreg†.

Multi-ingredient: ***Austria:*** Digi-Aldopur; Gladixol.

Acipimox *(BAN, rINN)*

Acipimoxum; Asipimoks; Asipimoksi; K-9321. 5-Methylpyrazine-2-carboxylic acid 4-oxide.

Аципимокс

$C_6H_6N_2O_3$ = 154.1.

CAS — 51037-30-0.

ATC — C10AD06.

ATC Vet — QC10AD06.

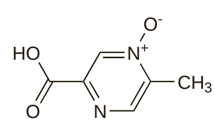

Adverse Effects and Precautions

Acipimox may cause peripheral vasodilatation resulting in flushing, itching, and a sensation of heat. Rash and erythema may occur. Gastrointestinal disturbances including heartburn, epigastric pain, nausea, and diarrhoea have been reported, as well as headache, malaise, myalgia, myositis, arthralgia, and dry eye. Urticaria, angioedema, and bronchospasm may occur rarely.

Acipimox is contra-indicated in patients with peptic ulcer disease. It should be used with caution in renal impairment.

Incidence of adverse effects. In a study involving 3009 hyperlipidaemic patients with type 2 diabetes,[1] adverse effects associated with acipimox occurred in 8.8%, resulting in withdrawal in 5.5% of patients. The most frequent adverse effects involved the skin (57.6%), gastrointestinal tract (25.8%), and CNS (9.7%). Labial oedema occurred in 3 cases and an urticarial eruption, collapse, and dyspnoea in another. The incidence of adverse effects was almost twice as high in females as in males, the difference being mainly due to a greater incidence of flushing, pruritus, and skin rashes. The incidence was not affected by age. There was a mean 15.3% reduction in fasting blood-glucose concentrations and an 8.5% reduction in glycosylated haemoglobin during treatment with acipimox.

1. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.

Pharmacokinetics

Acipimox is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 hours. It does not bind to plasma proteins and the plasma half-life is about 2 hours. It is not significantly metabolised and is excreted in the urine, largely unchanged.

Uses and Administration

Acipimox is a lipid regulating drug related to nicotinic acid (p.1957). It is used to reduce cholesterol and triglycerides in the management of hyperlipidaemias (see Action, below), including type IIa, IIb, or IV hyperlipoproteinaemias.

Acipimox is given orally in a usual dose of 250 mg two or three times daily, taken with meals. Doses of up to 1200 mg daily have been used. The dose should be adjusted in renal impairment (see below).

Action. Acipimox is used in the management of hyperlipidaemias (p.1169); it is a derivative of nicotinic acid and has similar effects on plasma lipoproteins but is better tolerated.[1] Its primary action is inhibition of lipolysis, leading to a reduction in circulating free fatty acids and consequently a reduction in very-low-density lipoprotein (VLDL) production in the liver. This results in a reduction of triglycerides, particularly in patients with hypertriglyceridaemia;[2] there may also be a decrease in low-density lipoprotein (LDL)-cholesterol and total cholesterol, and an increase in high-density lipoprotein (HDL)-cholesterol. Similar effects have been reported in patients with mixed hyperlipoproteinaemias, although the reduction of triglycerides and LDL-cholesterol was not significant.[3]

Reduction of free fatty acids by acipimox has a number of other physiological effects that have been utilised. Insulin secretion and sensitivity may be modified, and acipimox has been tried in type 2 diabetes mellitus; it improves plasma lipids and may also reduce blood-glucose concentrations,[4] and has been of benefit in patients with type A insulin resistance.[5] Beneficial effects have also been reported[6] in patients with HIV-associated lipodystrophy and insulin resistance. Growth hormone secretion is stimulated in obese subjects, and acipimox has been used in the investigation of growth hormone disorders.[7] There is also an increase in glucose uptake by the heart, and acipimox has been used to enhance myocardial imaging in ^{18}F-fluorodeoxyglucose positron-emission tomography.[8]

1. Tornvall P, Walldius G. A comparison between nicotinic acid and acipimox in hypertriglyceridaemia—effects on serum lipids, lipoproteins, glucose tolerance and tolerability. *J Intern Med* 1991; **230:** 415–21.
2. Ball MJ, *et al.* Acipimox in the treatment of patients with hyperlipidaemia: a double blind trial. *Eur J Clin Pharmacol* 1986; **31:** 201–4.
3. Otto C, *et al.* Effects of acipimox on haemorheology and plasma lipoproteins in patients with mixed hyperlipoproteinaemia. *Br J Clin Pharmacol* 1998; **46:** 473–8.
4. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.
5. Kumar S, *et al.* Suppression of non-esterified fatty acids to treat type A insulin resistance syndrome. *Lancet* 1994; **343:** 1073–4.
6. Hadigan C, *et al.* Inhibition of lipolysis improves insulin sensitivity in protease inhibitor-treated HIV-infected men with fat redistribution. *Am J Clin Nutr* 2003; **77:** 490–4.
7. Cordido F, *et al.* Effect of acute pharmacological reduction of plasma free fatty acids on growth hormone (GH) releasing hormone-induced GH secretion in obese adults with and without hypopituitarism. *J Clin Endocrinol Metab* 1998; **83:** 4350–4.
8. Knuuti MJ, *et al.* Enhancement of myocardial [fluorine-18]fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 1994; **35:** 989–98.

Administration in renal impairment. Acipimox is contra-indicated in patients with a creatinine clearance below 30 mL/minute. In patients with creatinine clearance between 30 and 60 mL/minute, the interval between doses should be increased.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Olbetam; ***Belg.:*** Olbetam; ***Braz.:*** Olbetam†; ***Chile:*** Olbetam; ***Denm.:*** Olbetam; ***Ger.:*** Olbemox†; ***Gr.:*** Olbetam; ***Hong Kong:*** Olbetam; ***Hung.:*** Olbetam; ***Irl.:*** Olbetam†; ***Israel:*** Olbetam; ***Ital.:*** Olbetam; ***Mex.:*** Olbetam†; ***Neth.:*** Nedios; Olbetam; ***NZ:*** Olbetam; ***S.Afr.:*** Olbetam; ***Singapore:*** Olbetam; ***Switz.:*** Olbetam; ***Thai.:*** Olbetam; ***UK:*** Olbetam.

Adenosine *(BAN, USAN)*

Adenocin; Adenosiini; Adenosin; Adenosina; Adénosine; Adenosinum; Adenozin; Adenozinas; Adenozyna; SR-96225; SUNY-4001. 6-Amino-9-β-D-ribofuranosyl-9*H*-purine.

Аденозин

$C_{10}H_{13}N_5O_4$ = 267.2.

CAS — 58-61-7.

ATC — C01EB10.

ATC Vet — QC01EB10.

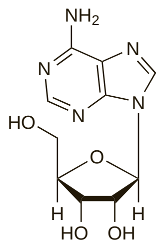

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Adenosine). A white, or almost white, crystalline powder. Slightly soluble in water; soluble in hot water; practically insoluble in alcohol and in dichloromethane; dissolves in dilute mineral acids.

USP 31 (Adenosine). A white, odourless crystalline powder. Slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

Stability. Adenosine was found to be stable[1] when it was mixed with glucose 5%, lactated Ringer's, sodium chloride 0.9%, or a mixture of glucose 5% and lactated Ringer's and stored in polypropylene syringes or PVC bags.

1. Ketkar VA, *et al.* Stability of undiluted and diluted adenosine at three temperatures in syringes and bags. *Am J Health-Syst Pharm* 1998; **55:** 466–70.

Adverse Effects, Treatment, and Precautions

Adverse effects of adenosine are usually transient, lasting less than a minute, due to its very short plasma half-life. They include nausea, lightheadedness, flushing, headache, angina-like chest pain, apprehension, and dyspnoea. Bronchospasm has been reported. Like other antiarrhythmics, adenosine may worsen arrhythmias. Bradycardia and heart block have been reported. Adenosine is a vasodilator and reduces blood pressure; the larger doses given by intravenous infusion may rarely produce significant hypotension and reflex tachycardia. Infusion may also be associated with abdominal, throat, neck, and jaw discomfort. Treatment is rarely needed for adverse effects but in persistent cases aminophylline or theophylline may be given.

Adenosine is contra-indicated in patients with second- or third-degree AV block or in those with sick sinus syndrome (unless they have a pacemaker) and should be avoided or used with caution in patients with QT prolongation since torsade de pointes has occurred very rarely. It is also contra-indicated in asthmatic subjects and should be used with caution in patients with obstructive pulmonary disease. Intravenous infusion of adenosine should be used with caution in patients who may develop hypotensive complications such as those with autonomic dysfunction, pericarditis, or stenotic valvular heart disease. Patients with recent heart transplantation may have increased sensitivity to the cardiac effects of adenosine.

◊ Use of the *University of Wisconsin solution* [UW Solution; Belzer UW Solution (commercially available as *Viaspan*)] for the hypothermic storage of kidneys before transplantation has been associated with bradycardia, prolonged PR intervals, and heart block.[1,2] The solution contains hetastarch, allopurinol, glutathione, and adenosine. The adenosine was considered to be the arrhythmogenic factor. Some centres had used the solution to flush kidneys before implantation,[2] a use for which it was never intended.[3] When used properly the adenosine in solution is catabolised to hypoxanthine and inosine, which do not cause cardiac problems, but this takes some time in hypothermic conditions.[3]

1. Prien T, *et al.* Bradyarrhythmia with University of Wisconsin preservation solution. *Lancet* 1989; **i:** 1319–20.
2. Vanrenterghem Y, *et al.* University of Wisconsin preservation solute and bradyarrhythmia. *Lancet* 1989; **ii:** 745.
3. Belzer FO. Correct use of University of Wisconsin preservation solution. *Lancet* 1990; **335:** 362.

Effects on the heart. Like most antiarrhythmics, adenosine can worsen arrhythmias, and both bradyarrhythmias and tachyarrhythmias have been reported.[1] Atrial fibrillation may develop in patients given adenosine for paroxysmal supraventricular tachycardia, and in a prospective study[2] occurred in 12% of 200 patients. Although most arrhythmias are of minor importance, ventricular arrhythmias and haemodynamic compromise have been reported[3,4] in patients given adenosine for presumed supraventricular tachycardia who were later discovered to have Wolff-Parkinson-White syndrome. Fatal cardiac arrest has also occurred[5] after the use of adenosine for arrhythmias in 2 patients with underlying cardiopulmonary disorders.

There have also been reports[6,7] of myocardial infarction in patients with ischaemic heart disease given adenosine during stress imaging.

For arrhythmias associated with the use of adenosine in organ preservation solutions see above.

1. Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. *Emerg Med J* 2004; **21:** 408–10.
2. Strickberger SA, *et al.* Adenosine-induced atrial arrhythmia: a prospective analysis. *Ann Intern Med* 1997; **127:** 417–22.
3. Exner DV, *et al.* Proarrhythmia in patients with the Wolff-Parkinson-White syndrome after standard doses of intravenous adenosine. *Ann Intern Med* 1995; **122:** 351–2.
4. Nagappan R, *et al.* Potential dangers of the Valsalva maneuver and adenosine in paroxysmal supraventricular tachycardia—beware preexcitation. *Crit Care Resusc* 2002; **4:** 107–11.
5. Haynes BE. Two deaths after prehospital use of adenosine. *J Emerg Med* 2001; **21:** 151–4.
6. Polad JE, Wilson LM. Myocardial infarction during adenosine stress test. Abstract: *Heart* 2002; **87:** 106. Full version: http://heart.bmj.com/cgi/reprint/87/2/e2.pdf (accessed 10/07/07)
7. Reyes E, *et al.* Acute myocardial infarction during adenosine myocardial perfusion imaging. *J Nucl Cardiol* 2004; **11:** 97–9.

Effects on the respiratory system. Acute exacerbation of asthma can be provoked by inhalation of adenosine. Bronchospasm has also been reported in patients with asthma[1,2] or a history of asthma[3] given adenosine intravenously and bronchospasm followed by respiratory failure in a patient with obstructive pulmonary disease.[4] Respiratory arrest has also been reported in an asthmatic patient.[5]

1. DeGroff CG, Silka MJ. Bronchospasm after intravenous administration of adenosine in a patient with asthma. *J Pediatr* 1994; **125:** 822–3.
2. Drake I, *et al.* Bronchospasm induced by intravenous adenosine. *Hum Exp Toxicol* 1994; **13:** 263–5.
3. Hintringer F, *et al.* Supraventricular tachycardia. *N Engl J Med* 1995; **333:** 323.
4. Burkhart KK. Respiratory failure following adenosine administration. *Am J Emerg Med* 1993; **11:** 249–50.
5. Patton JW, Sharma GK. Adenosine-induced respiratory arrest in an asthmatic patient. *South Med J* 2008; **101:** 328–9.

Migraine. A 35-year-old man with a history of migraine developed symptoms identical to those of his usual episodes of migraine immediately after 2 intravenous bolus doses of adenosine.[1]

1. Brown SGA, Waterer GW. Migraine precipitated by adenosine. *Med J Aust* 1995; **162:** 389–91.

Interactions

Dipyridamole inhibits adenosine uptake and therefore may potentiate the action of adenosine; if use of the two drugs is essential the dosage of adenosine should be reduced. Theophylline and other xanthines are competitive antagonists of adenosine. The risk of AV block may be increased if adenosine is used with other drugs that slow AV conduction.

Pharmacokinetics

Intravenous adenosine is rapidly taken up by an active transport system into erythrocytes and vascular endothelial cells where it is metabolised to inosine and adenosine monophosphate. The plasma half-life is less than 10 seconds.

Uses and Administration

Adenosine is an endogenous adenine nucleoside that is one of the components of nucleic acids (p.2355) and many coenzymes; as such, it is involved in many biological processes. It acts as an antiarrhythmic by stimulating adenosine A_1-receptors and slowing conduction through the AV node. It does not fit into the usual classification of antiarrhythmics (p.1153). It also produces peripheral and coronary vasodilatation by stimulating adenosine A_2-receptors.

Adenosine is used to restore sinus rhythm in the treatment of paroxysmal supraventricular tachycardia, including that associated with the Wolff-Parkinson-White syndrome (but see Effects on the Heart, above). It is also used for the differential diagnosis of broad or narrow complex supraventricular tachycardias and in myocardial imaging.

In the treatment of **paroxysmal supraventricular tachycardia**, adenosine may be given in an initial dose of 3 mg by rapid intravenous injection. If this dose is not effective within 1 to 2 minutes, 6 mg may be given and if necessary, 12 mg after a further 1 to 2 minutes. Alternatively, an initial dose of 6 mg followed if necessary by two further doses of 12 mg at 1 to 2 minute intervals may be used, but this higher initial dose should not be given to heart transplant patients as they have an increased sensitivity to adenosine. For differential **diagnosis of supraventricular tachycardias** a similar dosage regimen is used, beginning with a dose of 3 mg followed by 6 mg and then 12 mg at 1 to 2 minute intervals if required. Doses for children with paroxysmal supraventricular tachycardia are discussed below.

In **myocardial imaging** adenosine is given by intravenous infusion in a dose of 140 micrograms/kg per minute for 6 minutes. The radionuclide is injected after 3 minutes of the infusion.

Adenosine and its derivatives, such as adenosine phosphate (p.2247) and adenosine triphosphate (p.2247), have been used in various metabolic disorders because of their role in biological processes. Adenosine triphosphate, as the disodium salt, has been used as an antiarrhythmic.

Administration in children. Adenosine may be used for the management of paroxysmal supraventricular tachycardia in children. Dosage recommendations vary. Licensed product information in the USA states that children weighing less than 50 kg, including neonates and infants, may be given an initial dose of 50 to 100 micrograms/kg; if this is not effective the dose may be increased by 50 to 100 micrograms/kg increments at 1 to 2 minute intervals until the arrhythmia is controlled or a single dose of 300 micrograms/kg is reached. Paediatric advanced cardiac life support guidelines[1] in the USA recommend an initial dose of 100 micrograms/kg (maximum 6 mg) followed by a second dose of 200 micrograms/kg (maximum 12 mg) if required, and are applicable to infants and children. In the UK, the BNFC recommends an initial dose of 100 micrograms/kg for children aged 1 to 12 years, or 150 micrograms/kg for neonates and infants up to 1 year; the dose may be increased by increments of 50 to 100 micrograms/kg at 2 minute intervals, to a maximum single dose of 300 micrograms/kg for neonates and 500 micrograms/kg for infants and children.

1. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: pediatric advanced life support. *Circulation* 2005; **112:** (suppl 1): IV167–IV187. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-167 (accessed 10/07/07)

Cardiac arrhythmias. Adenosine is used for the termination of paroxysmal supraventricular tachycardia[1-4] (p.1160) and may often be the drug of choice. Bolus intravenous injection of adenosine produces a rapid response and the extremely short plasma half-life (less than 10 seconds) allows dosage titration every 1 to 2 minutes so that most episodes can be controlled within 5 minutes without the danger of drug accumulation.

Adenosine has been used successfully in pregnant women with paroxysmal supraventricular tachycardia[5-8] and cardioversion of fetal supraventricular tachycardia by direct fetal therapy with adenosine has been reported.[9,10]

Adenosine can be used for the differential **diagnosis** of broad complex tachycardia where the mechanism is not known.[1] If the cause is supraventricular, adenosine will terminate the arrhythmia or produce AV block to reveal the underlying atrial rhythm. If the cause is ventricular, adenosine will have no effect on the tachycardia, whereas if an alternative treatment such as verapamil is given to these patients severe hypotension and cardiac arrest can occur.

1. Faulds D, *et al.* Adenosine: an evaluation of its use in cardiac diagnostic procedures, and in the treatment of paroxysmal supraventricular tachycardia. *Drugs* 1991; **41:** 596–624.
2. Garratt CJ, *et al.* Adenosine and cardiac arrhythmias. *BMJ* 1992; **305:** 3–4.
3. Rankin AC, *et al.* Adenosine and the treatment of supraventricular tachycardia. *Am J Med* 1992; **92:** 655–64.

4. Anonymous. Adenosine for acute cardiac arrhythmias. *Drug Ther Bull* 1993; **31:** 49–50.
5. Mason BA, *et al.* Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* 1992; **80:** 478–80.
6. Afridi I, *et al.* Termination of supraventricular tachycardia with intravenous adenosine in a pregnant woman with Wolff-Parkinson-White syndrome. *Obstet Gynecol* 1992; **80:** 481–3.
7. Hagley MT, Cole PL. Adenosine use in pregnant women with supraventricular tachycardia. *Ann Pharmacother* 1994; **28:** 1241–2.
8. Hagley MT, *et al.* Adenosine use in a pregnant patient with supraventricular tachycardia. *Ann Pharmacother* 1995; **29:** 938.
9. Blanch G, *et al.* Cardioversion of fetal tachyarrhythmia with adenosine. *Lancet* 1994; **344:** 1646.
10. Kohl T, *et al.* Direct fetal administration of adenosine for the termination of incessant supraventricular tachycardia. *Obstet Gynecol* 1995; **85:** 873–4.

Ischaemic heart disease. Adenosine produces coronary vasodilatation and may be used to provide a pharmacological stress in patients undergoing assessment of their ischaemic heart disease when exercise stress is inappropriate.[1] It has been used with radionuclide imaging, echocardiography, and magnetic resonance imaging.

Adenosine has also been tried as an adjunct to prevent reperfusion injury in the management of acute myocardial infarction. Improved coronary blood flow has been reported[2] with intracoronary adenosine, and both intracoronary[3] and intravenous[4] adenosine have reduced infarct size, but no improvement in clinical outcomes has been shown.[5-7] A reduction in myonecrosis has also been reported[8] with intracoronary adenosine given at the start of non-urgent percutaneous coronary interventions.

1. Ali Raza J, *et al.* Pharmacological stress agents for evaluation of ischemic heart disease. *Int J Cardiol* 2001; **81:** 157–67.
2. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
3. Claeys MJ, *et al.* Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 9–13.
4. Mahaffey KW, *et al.* Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999; **34:** 1711–20.
5. Ross AM, *et al.* A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005; **45:** 1775–80.
6. Quintana M, *et al.* Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis: results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003; **59:** 1–9.
7. Petronio AS, *et al.* Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005; **150:** 1015. Full version: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870305007313.pdf (accessed 26/06/07)
8. Lee C-H, *et al.* Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after non-urgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J* 2007; **28:** 19–25.

Pain. Adenosine receptors are present in the CNS and there is some evidence[1,2] that adenosine, given intravenously or intrathecally, may have an analgesic effect.

1. Hayashida M, *et al.* Clinical application of adenosine and ATP for pain control. *J Anesth* 2005; **19:** 225–35.
2. Gan TJ, Habib AS. Adenosine as a non-opioid analgesic in the perioperative setting. *Anesth Analg* 2007; **105:** 487–94.

Pulmonary hypertension. Vasodilators have been tried in persistent pulmonary hypertension of the newborn (p.1179), but their use is generally restricted by lack of selectivity for the pulmonary circulation. A randomised placebo-controlled study[1] in 18 term infants with persistent pulmonary hypertension indicated that intravenous infusion of adenosine improved oxygenation without causing hypotension or tachycardia; however, the study was too small to assess any effect on mortality and/or the need for extracorporeal membrane oxygenation. Another observational study[2] in neonates with an inadequate response to inhaled nitric oxide suggested that addition of adenosine infusion also improved oxygenation.

1. Konduri GG, *et al.* Adenosine infusion improves oxygenation in term infants with respiratory failure. *Pediatrics* 1996; **97:** 295–300.
2. Ng C, *et al.* Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. *Pediatr Crit Care Med* 2004; **5:** 10–13.

Preparations

USP 31: Adenosine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Euritsin†; ***Austral.:*** Adenocor; Adenoscan; ***Austria:*** Adenoscan; Adrekar; ***Belg.:*** Adenocor; ***Braz.:*** Adenocard; ***Canad.:*** Adenocard; ***Chile:*** Tricor; ***Cz.:*** Adenocor; Adenoscan†; ***Denm.:*** Adenocor; ***Fin.:*** Adenocor; Adenoscan†; ***Fr.:*** Adenoscan; Krenosin; ***Ger.:*** Adenoscan; Adrekar; ***Gr.:*** Adenocor; ***Hong Kong:*** Adenoscan; ***Hung.:*** Adenocor; ***India:*** Adenoject; ***Irl.:*** Adenocor; ***Israel:*** Adenocor; ***Ital.:*** Adenoscan; Krenosin; ***Jpn:*** Adenoscan; ***Malaysia:*** Adenocor; ***Mex.:*** Krenosin; ***Neth.:*** Adenocor; Adenoscan; ***Norw.:*** Adenocor; ***NZ:*** Adenocor; ***Philipp.:*** Cardiovert; ***Pol.:*** Adenocor; ***Rus.:*** Vita-Iodurol (Вита-иодурол); ***S.Afr.:*** Adenocor; ***Singapore:*** Adenocor; ***Spain:*** Adenocor; Adenoscan; ***Switz.:*** Krenosine; ***Thai.:*** Adenocor; ***UK:*** Adenocor; Adenoscan; ***USA:*** Adenocard; Adenoscan; ***Venez.:*** Adenocor†.

Multi-ingredient: *Belg.:* Vitacic; ***Braz.:*** Aminotox†; Anekron; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Hepacitron†; Hepatobe†; Hepatox; Hormo Hepatico†; Necro B-6; ***Cz.:*** Laevadosin†; ***Hung.:*** Vitacic†; ***Mon.:*** Vitacic; ***Philipp.:*** Godex; ***Rus.:*** Oftan Catachrom (Офтан Катахром); Vitacic (Витасик)†; ***Spain:*** Vitaphakol.

Adrenaline *(BAN)* ⊗

Epinephrine *(BAN, rINN)*; Adrenaliini; Adrenalin; Adrenalina; Adrénaline; Adrenalinum; Epinefriini; Epinefrin; Epinefrina; Epinefryna; Épinéphrine; Epinephrinum; Epirenamine; Levorenin; Suprarenin. (*R*)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol.

Эпинефрин

$C_9H_{13}NO_3$ = 183.2.

CAS — 51-43-4.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

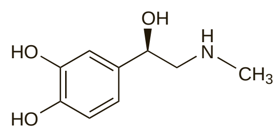

NOTE. Endogenous adrenaline and the monograph substance are the laevo-isomer.

ADN and EPN are codes approved by the BP 2008 for use on single unit doses of eye drops containing adrenaline where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

US also includes the racemic substances Racepinephrine (Racepinefrine (*rINN*)) and Racepinephrine Hydrochloride (Racepinefrine Hydrochloride (*rINNM*)).

Ph. Eur. 6.2 (Adrenaline). A white or almost white crystalline powder, becoming coloured on exposure to air and light. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in hydrochloric acid. Store under nitrogen. Protect from light.

USP 31 (Epinephrine). A white to practically white, odourless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Very slightly soluble in water and in alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Adrenaline Acid Tartrate *(BANM)* ⊗

Epinephrine Bitartrate *(rINNM)*; Adrenaliinitartraatti; Adrenaline Bitartrate; Adrenaline Tartrate; Adrénaline, Tartrate d'; Adrenalini Bitartras; Adrenalini tartras; Adrenalinii Tartras; Adrenalinium Hydrogentartaricum; Adrenalino tartratas; Adrenalin-tartarát; Adrenalintartrat; Bitartrato de epinefrina; Epinefrin-tartarát; Epinefryny wodorowinian; Epinephrine Acid Tartrate *(BANM)*; Épinéphrine, Bitartrate d'; Epinephrine Hydrogen Tartrate; Epinephrini Bitartras; Epinephrini Tartras; Epirenamine Bitartrate.

Эпинефрина Битартрат

$C_9H_{13}NO_3,C_4H_6O_6$ = 333.3.

CAS — 51-42-3.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Adrenaline Tartrate; Adrenaline Acid Tartrate BP 2008; Epinephrine Acid Tartrate BP 2008). A white to greyish-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably in a sealed tube under vacuum or under an inert gas. Protect from light.

USP 31 (Epinephrine Bitartrate). A white, or greyish-white or light brownish-grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 3 of water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its solutions in water are acid to litmus, having a pH of about 3.5. Store in airtight containers. Protect from light.

Stability. Studies on the stability of adrenaline injections.

1. Taylor JB, *et al.* Effect of sodium metabisulphite and anaerobic processing conditions on the oxidative degradation of adrenaline injection BP [1980]. *Pharm J* 1984; **232:** 646–8.
2. Stepensky D *et al.* Long-term stability study of -adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation. *J Pharm Sci* 2004; **93:** 969–80.

Adrenaline Hydrochloride *(BANM)* ⊗

Epinephrine Hydrochloride *(BANM, rINNM)*; Adrenalin Hidroklorür; Épinéphrine, Chlorhydrate d'; Epinephrini Hydrochloridum; Hidrocloruro de epinefrina.

Эпинефрина Гидрохлорид

$C_9H_{13}NO_3$,HCl = 219.7.

CAS — 55-31-2.

ATC — A01AD01; B02BC09; C01CA24; R01AA14; R03AA01; S01EA01.

ATC Vet — QA01AD01; QB02BC09; QC01CA24; QR01AA14; QR03AA01; QS01EA01.

Adverse Effects

Adrenaline is a potent sympathomimetic and may exhibit the adverse effects typical of both alpha- and beta-adrenoceptor stimulation (see p.1407). Adverse effects such as anxiety, dyspnoea, hyperglycaemia, restlessness, palpitations, tachycardia (sometimes with anginal pain), tremors, sweating, hypersalivation, weakness, dizziness, headache, and coldness of extremities may occur even with low doses. Since adrenaline does not readily cross the blood-brain barrier, its central effects may be largely a somatic response to its peripheral effects. Overdosage may cause cardiac arrhythmias and a sharp rise in blood pressure (sometimes leading to cerebral haemorrhage and pulmonary oedema); these effects may occur at normal dosage in susceptible subjects.

Adrenaline is a potent vasoconstrictor and gangrene may occur if adrenaline-containing local anaesthetic solutions are infiltrated into digits. Extravasation of parenteral adrenaline also results in intense vasoconstriction, leading to tissue necrosis and sloughing. Topical application of adrenaline to mucosal surfaces similarly causes vasoconstriction, which may induce hypoxia leading to compensatory rebound congestion of the mucosa. Inhalation of adrenaline has been associated with epigastric pain, which has been attributed to ingestion of some of the inhalation; it can be minimised by rinsing the mouth and throat with water after inhaling.

Adrenaline eye drops may produce severe smarting, blurred vision, and photophobia on instillation; they may also leave melanin-like deposits in the cornea and conjunctiva, and this has led to obstruction of the nasolachrymal ducts. Repeated use may cause oedema, hyperaemia, and inflammation of the eyes.

Effects on the eyes. In addition to the possibility of pigment deposition and local pain (see above) adrenaline eye drops have been associated with maculopathy, particularly in aphakic eyes (those devoid of a lens).[1] In one report,[2] maculopathy was noted in 15 patients over a period of 4 years; the patients were using adrenaline eye drops containing the hydrochloride, acid tartrate, or adrenaline borate complex (epinephryl borate). Blurring and distortion of vision were followed by decreased visual acuity, and by the appearance of oedema and sometimes haemorrhage in the macular region. A few patients developed cysts near the fovea. These effects appeared within a few weeks of, or several months after, starting therapy and were usually reversible. All except 1 of the patients were aphakic, and retrospective studies have suggested that the incidence of this complication may be up to 30% in aphakic patients.[1,2]

1. Classé JG. Epinephrine maculopathy. *J Am Optom Assoc* 1980; **51:** 1091–3.
2. Kolker AE, Becker B. Epinephrine maculopathy. *Arch Ophthalmol* 1968; **79:** 552–62.

Overdosage. Solutions of racepinefrine for nebulisation have inadvertently been given intravenously, resulting in severe overdosage of adrenaline. A 13-month-old infant[1] was given the equivalent of about 327 micrograms/kg of laevo-adrenaline. Marked pallor, pulselessness, and profound bradycardia developed, but the child responded to cardiopulmonary resuscitation and was subsequently discharged with no evidence of long-term sequelae. However, a 2-year-old child[2] given the equivalent of about 1800 micrograms/kg developed hypertension, tachycardia, and pulmonary oedema, followed by hypotension and subsequent renal failure, requiring transplantation. Subcutaneous overdosage with laevo-adrenaline in another child[3] led to arrhythmias and myocardial ischaemia, and there has also been a report[4] of myocardial infarction and acute renal failure in an adult after injection of the solution from an adrenaline inhaler.

1. Kurachek SC, Rockoff MA. Inadvertent intravenous administration of racemic epinephrine. *JAMA* 1985; **253:** 1441–2.

2. Dybvik T, *et al.* Accidental intravenous administration of 50 mg of racemic adrenaline in a 2-year-old boy. *Eur J Anaesthesiol* 1995; **12:** 181–3.
3. Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care* 1999; **15:** 116–18.
4. Woodard ML, Brent LD. Acute renal failure, anterior myocardial infarction, and atrial fibrillation complicating epinephrine abuse. *Pharmacotherapy* 1998; **18:** 656–8.

Treatment of Adverse Effects

As for Sympathomimetics, p.1407. Adrenaline has a short duration of activity due to inactivation in the body and treatment of severe toxic reactions in hypersensitive patients or after overdose is primarily supportive.

Digital injection. Inadvertent digital injection of adrenaline from autoinjector devices may cause acute ischaemia. Phentolamine injection has been successfully used to reverse the vasoconstriction,[1] and there has also been a report[2] of the use of iloprost infusion followed by a stellate ganglion block.

1. Velissariou I, *et al.* Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. *Emerg Med J* 2004; **21:** 387–8.
2. Barkhordarian AR, *et al.* Accidental digital injection of adrenaline from an autoinjector device. *Br J Dermatol* 2000; **143:** 1359.

Precautions

As for Sympathomimetics, p.1407. Adrenaline is frequently used in emergency situations and any contra-indications are therefore relative.

Adrenaline may delay the second stage of labour and some licensed product information recommends that it should not be used during this time.

Adrenaline eye drops are contra-indicated in angle-closure glaucoma unless an iridectomy has been carried out.

Contact lenses. Adrenochrome staining of soft-contact lenses of patients using adrenaline eye drops has been reported.[1] Melanin deposits may also become locked into the lens; such deposits may be broken down by hydrogen peroxide. The prodrug, dipivefrine hydrochloride (p.2295) has been used without staining soft lenses.

1. Ingram DV. Spoiled soft contact lenses. *BMJ* 1986; **292:** 1619.

Infection. An open study[1] comparing adrenaline with dopamine for cardiovascular support in 23 patients critically ill with severe sepsis or malaria suggested that use of adrenaline was limited by the development of lactic acidosis. However, it has been pointed out[2] that 20 of the patients had responded to fluids, a situation in which the use of inotropic or vasopressor support was considered questionable, and that adrenaline has been widely used in the treatment of septic shock. A further controlled study[3] found that although adrenaline led to higher lactate concentrations than noradrenaline with dobutamine, the effect was transient. Nevertheless, it has been recommended[4] that adrenaline should only be used in septic shock if other treatments are ineffective.

1. Day NPJ, *et al.* The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; **348:** 219–23. Correction. *ibid.*; 902.
2. Barry B, Bodenham A. Effects of dopamine and adrenaline infusions in severe infection. *Lancet* 1996; **348:** 1099–1100.
3. Levy B, *et al.* Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997; **23:** 282–7.
4. Hollenberg SM, *et al.* American College of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; **32:** 1928–48.

Interactions

As for Sympathomimetics, p.1407; adrenaline has direct alpha- and beta-agonist actions and its interactions are complex and may be hazardous. Particular caution is needed if adrenaline is given to patients taking beta blockers since severe hypertension may result; patients taking beta blockers may also have an impaired response to adrenaline if it is needed for anaphylaxis.

Local anaesthetics. It is common practice to give adrenaline with a local anaesthetic to produce vasoconstriction; the lowest effective concentration of adrenaline should be used. However, use with *cocaine* may increase the risk of cardiac arrhythmias and particular caution is required. See p.1860 for a report of severe complications with use of such a combination in otolaryngology.

Pharmacokinetics

As a result of enzymatic degradation in the gut and first-pass metabolism in the liver, adrenaline is almost totally inactive when given orally. Systemic absorption can occur after topical application for example of eye drops. Adrenaline acts rapidly after intramuscular and subcutaneous injection; the latter route is, however, sometimes considered to be slower and therefore less reliable for emergency use. Although absorption is slowed by local vasoconstriction it can be hastened by massaging the injection site.

Most adrenaline that is either injected into the body or released into the circulation from the adrenal medulla, is very rapidly inactivated by processes that include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues. The half-life of circulating adrenaline is only about 1 minute. One of the enzymes responsible for the chemical inactivation of adrenaline is catechol-*O*-methyltransferase (COMT), the other is monoamine oxidase (MAO). In general, adrenaline is methylated to metanephrine by COMT followed by oxidative deamination by MAO and eventual conversion to 4-hydroxy-3-methoxymandelic acid (formerly termed vanillylmandelic acid; VMA), or oxidatively deaminated by MAO and converted to 3,4-dihydroxymandelic acid which, in turn, is methylated by COMT, once again to 4-hydroxy-3-methoxymandelic acid; the metabolites are excreted in the urine mainly as their glucuronide and ethereal sulfate conjugates.

The ability of COMT to effect introduction of a methyl group is an important step in the chemical inactivation of adrenaline and similar catecholamines (in particular, noradrenaline). It means that the termination of the pharmacological response of catecholamines is not simply dependent upon MAO. In its role of neurotransmitter intraneuronal catecholamine (mainly noradrenaline) is, however, enzymatically regulated by MAO.

Adrenaline crosses the placenta to enter fetal circulation.

Uses and Administration

Adrenaline is an endogenous substance that is produced in the adrenal medulla and has important physiological effects. It is also used pharmacologically as a direct-acting sympathomimetic (see p.1408). It is a potent agonist at both alpha and beta adrenoceptors, although the effect on beta adrenoceptors is more marked, particularly at lower doses. These properties explain many aspects of its pharmacology, although the reflex compensating responses of the body also modulate its effects.

The major effects of adrenaline are dose-related and include:

- increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha receptors increases peripheral resistance)
- increased blood flow to skeletal muscle (reduced with higher doses); reduced blood flow in the kidneys, mucosa, and skin; little direct effect on cerebral blood flow
- relaxation of bronchial smooth muscle
- hyperglycaemia and markedly increased oxygen consumption due to metabolic effects

Adrenaline has an important role in the management of acute allergic reactions and can be life-saving in patients with anaphylaxis and anaphylactic shock (below). It is also used in advanced cardiac life support (below). Adrenaline has been used in the treatment of acute asthma but more selective drugs are available, and it has no role in the chronic management of asthma (p.1108). It has been given by nebulisation in severe croup (p.1502). Other uses include the control of minor bleeding from the skin and mucous membranes, the management of open-angle (simple) glaucoma (p.1873), and use as an adjunct to local anaesthesia (p.1852). Adrenaline was formerly incorporated into creams used in the treatment of rheumatic and muscular disorders, and in rectal preparations used in the treatment of haemorrhoids. Racepinefrine (racemic adrenaline) and racepinefrine hydrochloride have been used for bronchodilatation.

Adrenaline is usually given by intramuscular injection, although it may also be given subcutaneously. In extreme emergencies, where a more rapid effect is required, adrenaline may be given as a dilute solution (1 in 10 000 or 1 in 100 000) by very slow intravenous injection or by slow intravenous infusion. Alternatively, if intravenous access cannot be obtained, it may also be given by the intraosseous (usually into the marrow of the tibia) or endotracheal routes. Adrenaline has sometimes been injected directly in the heart but current guidelines for the management of cardiac emergencies recommend intravenous injection; this may be into a central vein or peripherally, but in the latter case should be followed by 20 mL of intravenous fluid. Adrenaline may also be applied topically or given by inhalation. Aqueous solutions of adrenaline are usually prepared using the acid tartrate or the hydrochloride but the dosage is generally stated in terms of the equivalent content of adrenaline. Adrenaline acid tartrate 1.8 mg or adrenaline hydrochloride 1.2 mg is equivalent to about 1 mg of adrenaline.

The usual dose of adrenaline in **anaphylactic shock** is 500 micrograms (0.5 mL of a 1 in 1000 solution) by intramuscular injection repeated as necessary every 5 minutes. A dose of 300 micrograms (0.3 mL of a 1 in 1000 solution) may be appropriate for emergency self-administration, for example by autoinjector. The dose for children depends on age and weight, but is usually about 10 micrograms/kg by intramuscular injection. For further details on doses for children and for intravenous doses, see Anaphylaxis and Anaphylactic Shock, below.

In **advanced cardiac life support** the initial dose of adrenaline for adults is 1 mg intravenously (10 mL of a 1 in 10 000 solution) and this may be repeated as often as every 2 to 3 minutes throughout the resuscitation procedure. The dose for children is 10 micrograms/kg intravenously. Higher intravenous doses have been used in both adults and children for the second and subsequent doses but are no longer generally recommended. Intraosseous doses for adults and children are the same as those used intravenously. Endotracheal doses for adults are 2 to 3 times the intravenous dose; children may be given 100 micrograms/kg.

Adrenaline relaxes the bronchial musculature and has sometimes been injected subcutaneously or intramuscularly in the management of **acute asthmatic attacks**. However, in general, the use of adrenaline in asthma has been superseded by beta$_2$ agonists, such as salbutamol, which can alleviate bronchospasm with fewer effects on the heart. If adrenaline is to be used, the adult dose is 0.3 to 0.5 mL of a 1 in 1000 aqueous solution (300 to 500 micrograms); children have received 0.01 mL/kg (10 micrograms/kg) to a maximum of 0.5 mL (500 micrograms). Aqueous solutions with an adrenaline content equivalent to 1 in 100 have occasionally been used by inhalation as a spray to alleviate asthmatic attacks; these solutions must never be confused with the weaker strength used for injection. Pressurised aerosols delivering metered doses equivalent to about 160 micrograms to 275 micrograms of adrenaline have also been used; adults have been given 1 or 2 metered inhalations, repeated, if necessary, after 3 hours.

Adrenaline is often added to **local anaesthetics** to retard diffusion and limit absorption, to prolong the duration of effect, and to lessen the danger of toxicity. A concentration of 1 in 200 000 (5 micrograms/mL) is usually used; adrenaline should not be added when procedures involve digits, ears, nose, penis, or scrotum because of the risk of ischaemic tissue necrosis. A concentration of up to 1 in 80 000 (12.5 micrograms/mL) may be used in dental preparations where the total dose given is small.

Adrenaline constricts arterioles and capillaries and causes blanching when applied locally to mucous membranes and exposed tissues. It is used as an aqueous solution in strengths up to a 1 in 1000 dilution to check capillary **bleeding**, epistaxis, and bleeding from superficial wounds and abrasions, but it does not stop internal haemorrhage. It is usually applied as a spray or on pledgets of cotton wool or gauze.

In ophthalmology, adrenaline solutions of 0.5%, 1%, or 2% are used as eye drops instilled once or twice daily to reduce intra-ocular pressure in open-angle **glaucoma** and ocular hypertension. An adrenaline borate complex (epinephryl borate) is also used.

Advanced cardiac life support. Adrenaline has an important role in advanced cardiac life support (p.1156) since, through its alpha agonist effects, it causes peripheral vasoconstriction, thus increasing myocardial and cerebral blood flow. This should improve the efficacy of cardiopulmonary resuscitation or basic life support procedures, although there is no clinical study evidence for benefit.[1] Depending on the arrhythmia that has led to cardiac arrest, treatment starts with cardiopulmonary resuscitation and defibrillation. If these measures fail to restore a conventional rhythm, the next step involves the use of adrenaline.

For **adults**, adrenaline is given in a dose of 1 mg, ideally intravenously into a central vein. If such venous access is not practicable adrenaline may be given through a peripheral vein followed by a flush of 20 mL or more of sodium chloride injection; however, the response is slower than with central venous injection. This intravenous dose of 1 mg may be given about every 3 to 5 minutes[2-5] in further cycles of cardiopulmonary resuscitation and, if necessary, shocks. A higher dose of 5 mg or 100 micrograms/kg has been given but there is insufficient evidence of benefit and this is not recommended.[2-5] In ventricular fibrillation or pulseless ventricular tachycardia, a resuscitation attempt may reasonably last for anything from 10 minutes to 1 hour with adrenaline being given every 3 to 5 minutes during this period. Where the arrest is associated with asystole it is unlikely that a response will be achieved after 15 to 20 minutes.

The initial dose of 1 mg is reported to be based on the dose that was given by intracardiac injection, so it would be expected that a higher dose would be required for intravenous use. Although myocardial and cerebral perfusion are increased more with higher doses, a meta-analysis[6] of studies in adults found no evidence that this gave any survival benefit.

The intravenous dose for **children** is 10 micrograms/kg. Higher doses of 100 or 200 micrograms/kg have been used for the second and subsequent doses; however, as with adults, the use of the higher dose is not routinely recommended and both retrospective[7] and prospective[8] studies have found no improvement in outcome.

The intraosseous route is a practicable alternative to intravenous injection for adults as well as for children; doses are identical to those given intravenously. Alternatively, adrenaline can be given through the endotracheal tube that will have been inserted, but only if the intravenous or intraosseous route is unavailable. Endotracheal doses for adults should be 2 to 3 times those used intravenously; for children doses of 100 micrograms/kg have been suggested. The adrenaline solution should be diluted and administered deeply using a catheter; several rapid ventilations or inflations should follow. It is recognised that the endotracheal route is imperfect[2-4] and some workers consider it to be ineffective.[9]

Although covering a somewhat different clinical situation some guidelines also include resuscitation of newborn infants (during the first few hours after birth).[2-5] Adrenaline may be used when the heart rate remains below 60 beats/minute despite adequate ventilation and chest compression. The dose of adrenaline is 10 to 30 micrograms/kg given intravenously (generally into the umbilical vein) or by intraosseous injection. If neither of these routes are available, it may be given via the endotracheal tube; standard doses are probably ineffective[10] and doses of up to 100 micrograms/kg may be required, although there is little evidence to support this.[2,4,5]

1. Morley P. Vasopressin or epinephrine: which initial vasopressor for cardiac arrests? *Lancet* 2001; **358:** 85–6.
2. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. *Resuscitation* 2005; **67** (suppl 1): S1–S190. Also available at: http://www.erc.edu/index.php/guidelines_download_2005/en/? (accessed 09/02/06)
3. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 09/02/06)
4. The International Liaison Committee on Resuscitation (ILCOR). 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2005; **112** (suppl I): III1–III136. Also available at: http://intl-circ.ahajournals.org/content/vol112/22_suppl/ (accessed 09/02/06) Also published in *Resuscitation* 2005; **67:** 157–341.
5. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112** (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 09/02/06)
6. Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis. *Resuscitation* 2000; **45:** 161–6.
7. Carpenter TC, Stenmark KR. High-dose epinephrine is not superior to standard-dose epinephrine in pediatric in-hospital cardiopulmonary arrest. *Pediatrics* 1997; **99:** 403–8.
8. Perondi MBM, *et al.* A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; **350:** 1722–30.
9. McCrirrick A, Monk CR. Comparison of i.v. and intra-tracheal administration of adrenaline. *Br J Anaesth* 1994; **72:** 529–32.
10. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* 2006; **118:** 1028–34.

Anaphylaxis and anaphylactic shock. Anaphylaxis is usually a type 1 hypersensitivity reaction (p.561) in which there is IgE-mediated activation of mast cells and basophils, usually as a result of exposure to allergens such as drugs, foods, latex, and insect venoms. A clinically identical reaction can, however, be provoked by a type II mechanism, as in blood transfusion reactions, or a type III mechanism, as in drug-induced serum sickness reactions; anaphylactoid reactions are similar, but are caused by direct histamine release rather than hypersensitivity. Symptoms of anaphylaxis and anaphylactoid reactions include erythema, pruritus, urticaria, and angioedema; respiratory obstruction may result from oedema of the larynx or epiglottis. Gastrointestinal disturbances, bronchospasm, hypotension, and coma can occur in severe reactions.

Anaphylaxis is a medical emergency and prompt treatment of laryngeal oedema, bronchospasm, and hypotension is necessary. Adrenaline causes bronchodilatation and peripheral vasoconstriction, reducing oedema and increasing blood pressure, and is the cornerstone of management.[1-11] However, it may not always be effective,[5] and its use is not without hazard.[12] Antihistamines and corticosteroids may also have a role.

In early anaphylaxis, adrenaline is given by intramuscular injection. At this stage, vasodilatation is the main pathological change and cardiac output and blood flow to skin and muscle may be increased enabling intramuscular absorption of adrenaline to be sufficiently rapid and effective. The subcutaneous route has been used, especially by patients treating themselves, but intramuscular absorption is more rapid and is generally preferred.[3,5,6] Prefilled syringes for intramuscular or subcutaneous use may be given to those known to be at high risk of developing anaphylactic shock, allowing patients to self-administer their initial emergency treatment; however, they should still seek medical assistance as additional treatment may be required. Adrenaline has been given by inhalation in milder reactions, often with an antihistamine.[13] However, this should not be a substitute for adrenaline injection in patients with severe symptoms or a history of acute attacks, and the number of inhalations required may limit the use of this route in children.[14] As anaphylaxis progresses the intravascular volume becomes depleted, leading to the development of shock. At this stage it is probably necessary to give adrenaline intravenously, since absorption from other routes will be compromised; however, this route is hazardous and should only be used in life-threatening situations,[3,5,12] and by those experienced in its use.[5] The general principles used in the management of hypovolaemia and hypotension in shock are outlined on p.1183.

The dose of adrenaline for intramuscular injection is usually 500 micrograms (0.5 mL of a 1 in 1000 solution); this may be repeated at 5-minute intervals, according to blood pressure and pulse, until improvement occurs. A lower dose of 300 micrograms may be used,[3] and may be the highest dose available as an auto-injector.[5] Similar doses have been given subcutaneously. A more dilute solution of 1 in 10 000 is used intravenously; the dose is 500 micrograms (5 mL) given slowly at a rate of 100 micrograms/minute (1 mL/minute), stopping when a response has been obtained.[3] Alternatively, the UK Resuscitation Council recommends[5] that an intravenous bolus dose of 50 micrograms should be given, titrated according to response.

Various adrenaline dosage regimens have been suggested for children,[2,5,6] although there is little evidence to guide choice.[15] Most regimens are based on a dose of 10 micrograms/kg, and the following age-specific intramuscular doses, given as a 1 in 1000 solution, have been widely used:

- under 6 months: 50 micrograms (0.05 mL)
- 6 months to 6 years: 120 micrograms (0.12 mL)
- 6 to 12 years: 250 micrograms (0.25 mL)

However, to simplify dosing, particularly where auto-injectors are used, the UK Resuscitation Council now recommends[5] an intramuscular dose of 150 micrograms (0.15 mL) for children aged 6 years and younger (including those under 6 months) and 300 micrograms (0.3 mL) for those aged over 6 years; children aged over 12 years may be given 300 or 500 micrograms depending on body size and pubertal status. This may represent a relative overdose in children aged under 6 months but this may be considered acceptable if it allows an auto-injector to be used.[15] Intravenous therapy should only be used in specialist paediatric settings.[5] The *BNFC* recommends use of the 1 in 10 000 solution in a dose of 1 microgram/kg, given by slow intravenous injection over several minutes, repeated as required; a maximum single dose of 50 micrograms should not be exceeded.

A slow intravenous injection of an antihistamine, such as chlorphenamine, may be given immediately after the adrenaline and repeated over the next 24 to 48 hours to prevent relapse. Although antihistamines are particularly effective in the management of angioedema, pruritus, and urticaria, they remain second-line treatment. Intravenous corticosteroids have little place in the immediate management of anaphylaxis, since their beneficial effects are delayed for several hours, but in severely ill patients early use of hydrocortisone may help prevent deterioration after the primary treatment has been given. Patients should also be given oxygen as required.

Continuing deterioration with circulatory collapse, bronchospasm, or laryngeal oedema requires further treatment including intravenous fluids, a nebulised beta$_2$ agonist (such as salbutamol or terbutaline), intravenous aminophylline, assisted respiration (if necessary), and possibly, emergency tracheostomy.[3,4]

Patients taking non-cardioselective beta blockers may be relatively refractory to the effects of adrenaline used for anaphylactic shock (see Interactions for Sympathomimetics, p.1407); in such cases the use of a more selective beta$_2$ agonist such as salbutamol by intravenous injection should be considered. Glucagon is another alternative to adrenaline in such patients.[3,16] Vasopressin has also been used successfully,[17] including in a patient who failed to respond to adrenaline.

Prevention of anaphylaxis is important[7,8] and primarily involves avoidance of known allergens; other measures include desensitisation, particularly in patients who have reacted to bee or wasp venom.

1. Ewan PW. Treatment of anaphylactic reactions. *Prescribers' J* 1997; **37:** 125–32.
2. Ewan PW. Anaphylaxis. *BMJ* 1998; **316:** 1442–5. Correction. *ibid.*; 1587.
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4. Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Safety* 2001; **24:** 843–53.
5. Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions: guidelines for healthcare providers (revised January 2008). Available at: http://www.resus.org.uk/pages/reaction.pdf (accessed 05/06/08)
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9. McLean-Tooke APC, *et al.* Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003; **327:** 1332–5.
10. Brown SGA, *et al.* Anaphylaxis: diagnosis and management. *Med J Aust* 2006; **185:** 283–9. Correction. *ibid.*; 400. [dose]
11. Kemp SF. Office approach to anaphylaxis: sooner better than later. *Am J Med* 2007; **120:** 664–8.
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13. Hourihane JO'B, Warner JO. Management of anaphylactic reactions to food. *Arch Dis Child* 1995; **72:** 274.
14. Simons FER, *et al.* Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? *Pediatrics* 2000; **106:** 1040–4.
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16. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; **12:** 299–304.
17. Kill C, *et al.* Successful treatment of severe anaphylactic shock with vasopressin: two case reports. *Int Arch Allergy Immunol* 2004; **134:** 260–1.

Haemorrhage. Adrenaline has a long history of topical use to check minor bleeding. It constricts arterioles and capillaries and causes blanching. Local injection of adrenaline under endoscopic control is highly effective in controlling bleeding peptic ulcers (p.1702), and has also been combined with other therapies such as a contact thermal probe.[1] Nebulised adrenaline has been reported[2] to successfully control oropharyngeal haemorrhage.

1. Chung SSC, *et al.* Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ* 1997; **314:** 1307–11.
2. Rowlands RG, *et al.* Novel use of nebulised adrenaline in the treatment of secondary oropharyngeal haemorrhage. *J Laryngol Otol* 2002; **116:** 123–4.

Priapism. Alpha agonists such as adrenaline may be effective in the treatment of priapism (see under Metaraminol, p.1333). Low doses of dilute adrenaline solution have been given by intracavernosal injection in priapism caused by alprostadil (see p.2184). Aspiration of blood followed by intracavernosal irrigation with a dilute adrenaline solution was also reported to be effective treatment for priapism in a group of young patients (age range, 3.9 to 18.3 years) with sickle-cell disease.[1]

1. Mantadakis E, *et al.* Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood* 2000; **95:** 78–82.

Respiratory-tract disorders. Nebulised adrenaline may be used to reverse airway obstruction in inflammatory disorders such as croup since it relieves inflammation and also causes bronchodilatation. Although some studies in acute viral bronchiolitis (see Respiratory Syncytial Virus Infection, p.860) have shown improvement in clinical scores,[1,2] randomised studies have failed to find any difference in outcome between infants treated with adrenaline and either salbutamol[3] or placebo.[4] A systematic review[5] found insufficient evidence to support the use of adrenaline in inpatients, although there was a suggestion that it might be of short-term benefit in outpatients.

However, the *BNF* states that for severe croup not effectively controlled with corticosteroids, nebulised adrenaline solution 1 in 1000 may be given with close clinical monitoring in a dose of 400 micrograms/kg (up to a maximum of 5 mg) repeated after 30 minutes if necessary. The effects of nebulised adrenaline are expected to last 2 to 3 hours.

There has also been a report[6] of the successful use of nebulised adrenaline in a 15-month-old child with airway inflammation secondary to the ingestion of sodium hypochlorite.

1. Reijonen T, *et al.* The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–92.
2. Menon K, *et al.* A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–7.
3. Patel H, *et al.* A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002; **141:** 818–24.
4. Wainwright C, *et al.* A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003; **349:** 27–35.
5. Hartling L, *et al.* Epinephrine for bronchiolitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 07/10/05).
6. Ziegler D, Bent G. Caustic-induced upper airway obstruction responsiveness to nebulized adrenaline. *Pediatrics* 2001; **107:** 807–8.

Preparations

BP 2008: Adrenaline Eye Drops; Adrenaline Injection; Adrenaline Solution; Bupivacaine and Adrenaline Injection; Dilute Adrenaline Injection 1 in 10,000; Lidocaine and Adrenaline Injection;
USP 31: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Epinephrine Bitartrate for Ophthalmic Solution; Epinephrine Bitartrate Inhalation Aerosol; Epinephrine Bitartrate Ophthalmic Solution; Epinephrine Inhalation Aerosol; Epinephrine Inhalation Solution; Epinephrine Injection; Epinephrine Nasal Solution; Epinephrine Ophthalmic Solution; Epinephryl Borate Ophthalmic Solution; Lidocaine Hydrochloride and Epinephrine Injection; Prilocaine and Epinephrine Injection; Procaine Hydrochloride and Epinephrine Injection; Racepinephrine Inhalation Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: EpiPen; ***Austral.:*** EpiPen; ***Austria:*** EpiPen; Suprarenin; ***Belg.:*** EpiPen; ***Braz.:*** Drenalin; Nefrin†; ***Canad.:*** EpiPen; Twinject; Vaponefrin; ***Cz.:*** Anapen; EpiPen; Glaucon†; ***Denm.:*** EpiPen; ***Fin.:*** EpiPen; ***Fr.:*** Anahelp; Anapen; ***Ger.:*** Anapen; Fastjekt; InfectoKrupp; Suprarenin; ***Gr.:*** Anapen; EpiPen; ***Hung.:*** Anapen; EpiPen; Tonogen; ***Irl.:*** Anapen; Eppy†; ***Israel:*** EpiPen; ***Ital.:*** Fastjekt; ***Malaysia:*** EpiPen; ***Mex.:*** Pinadrina; ***Neth.:*** EpiPen; ***Norw.:*** EpiPen; ***NZ:*** EpiPen; ***Philipp.:*** Adrenin; ***Pol.:*** Anapen; EpiPen; Fastjekt; ***Port.:*** Anapen; EpiPen; ***S.Afr.:*** Adrenotone; Ana-Guard; EpiPen; Eppy; Simplene; ***Spain:*** Adreject; ***Swed.:*** Anapen; EpiPen; Eppy†; ***Switz.:*** EpiPen; ***UK:*** Anapen; EpiPen; ***USA:*** AsthmaHaler Mist; AsthmaNefrin; Epifrin†; Epinal; EpiPen; Glaucon†; microNefrin; Nephron; Primatene Mist; Primatene Mist Suspension; S-2.

Multi-ingredient: ***Arg.:*** Asmopul†; Yanal; ***Austral.:*** Rectinol; ***Ger.:*** Links-Glaukosan†; Mydrial-Atropin†; ***Hung.:*** Hemorid; Noditran†; ***India:*** Brovon; ***Irl.:*** Ganda; ***Ital.:*** Pilodren†; Rinantipiol†; ***Port.:*** Adrinex†; ***Spain:*** Coliriocilina Adren Astr; Epistaxol; ***Switz.:*** Haemocortin; ***UK:*** Brovon; ***USA:*** Ana-Kit; E-Pilo†; Emergent-Ez; PE†.

Used as an adjunct in: ***Arg.:*** Caina G; Duracaine; Gobbicaina; Larjancaina; Xylocaina; ***Austral.:*** Citanest Dental; Lignospan†; Marcain; Nurocain; Scandonest†; Xylocaine; ***Austria:*** Neo-Xylestesin; Neo-Xylestesin forte; Scandonest; Septanest; Ubistesin; Ultracain Dental; Xylanaest; Xylocain; ***Belg.:*** Citanest; Marcaine; Ubistesin†; Xylocaine; ***Braz.:*** Bupiabbott Plus; Lidocabbott; Lidogeyer†; Marcaina; Neocaina; Novabupi; Xylestesin; Xylocaina; ***Canad.:*** Astracaine†; Citanest†; Marcaine; Sensorcaine; Xylocaine; ***Cz.:*** Marcaine; Scandonest; Septanest S; Supracain; Ubistesin; Ultracain D-S†; Xylestesin-A†; ***Denm.:*** Carbocain; Marcain; Scandonest; Septanest; Septocaine; Ubistesin; Xylocain; Xyloplyin; ***Fin.:*** Marcain; Septocaine; Ubistesin; Ultracain D-Suprarenin; Xylocain; ***Fr.:*** Alphacaine; Marcaine†; Predesic†; Ubistesin Adrenalinee; Xylocaine; ***Ger.:*** Ubistesin; Ultracain D-S; Ultracain Suprarenin; Xylestesin-A, Xylestesin centro†; Xylestesin-S†; Xylocain; Xylocitin; Xylonest; ***Gr.:*** Marcaine; Xylocaine; ***Hong Kong:*** Marcain; Ubistesin; Xylestesin-A; Xylocaine; ***Hung.:*** Ubistesin; Ultracain D-S; ***India:*** Gesicain; Xylocaine; ***Indon.:*** Extracaine; Pehacain; ***Irl.:*** Marcain; Xylocaine; ***Israel:*** Kamacaine; Lidocadren†; Marcaine; ***Ital.:*** Alfacaina; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Carbocaina; Carbosen; Cartidont; Citocartin; Ecocain; Lident Adrenalina†; Lident Andrenor†; Marcaina; Mepi-Mynol; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Molcain†; Optocain; Primacaine†; Sarticain; Scandonest; Septanest; Ubistesin; Xilo-Mynol; Xylonor; Xyloplyina; ***Malaysia:*** Denkan; Marcain; ***Mex.:*** Buvacaina; Pisacaina; Unicaine; Xylocaina; ***Neth.:*** Bupiforan; Citanest; Lignospan; Marcaine; Scandicaine; Septanest; Ubistesin; Ultracain D-S; Xylocaine; ***Norw.:*** Marcain; Septocaine; Xylocain; ***NZ:*** Marcain; Septanest; Topicaine; Xylestesin-A; Xylocaine; ***Philipp.:*** Dentocaine; ***Pol.:*** Marcaine; ***Port.:*** Alphacaine; Artinibsa; Artinostrum; Bupinostrum; Lidonostrum; Lincaina; Meganest; Octocaine; Scandinibsa; Septanest; Ubistesin; Xilonibsa; ***Rus.:*** Ultracain (Ультракаин); ***S.Afr.:*** Lignospan Special†; Macaine; Scandonest†; Xylotox; ***Singapore:*** Xylocaine; ***Spain:*** Anestesia Topi Braun C/A; Articaina C/E; Meganest; Octocaine; Scandinibsa; Ultracain; Xilonibsa; Xylonor Especial; ***Swed.:*** Carbocain; Marcain; Xylocain; ***Switz.:*** Alphacaine; Carbostesin; Lignospan†; Rapidocaine; Rudocaine; Scandonest; Septanest; Ubistesin; Ultracaine D-S; Xylestesin-S "special"†; Xylocain; Xylonest; Xyloplyin†; ***Thai.:*** Lidocation; Lidocaton†; Xylocaine; ***Turk.:*** Jetokain; Jetosel; Ultracain; ***UAE:*** Ecocain; ***UK:*** Lignostab-A†; Septanest; Xylocaine; Xylotox†; ***USA:*** Citanest; Duranest†; Marcaine; Octocaine; Sensorcaine; Septocaine; Xylocaine.

Ajmaline

Aimaliini; Ajmalin; Ajmalina; Ajmalinum; Rauwolfine. (17*R*,21*R*)-Ajmalan-17,21-diol.

Аймалин

$C_{20}H_{26}N_2O_2$ = 326.4.
CAS — 4360-12-7.
ATC — C01BA05.
ATC Vet — QC01BA05.

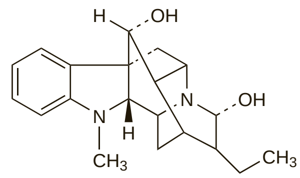

Pharmacopoeias. In *Jpn.*

Adverse Effects

Ajmaline depresses the conductivity of the heart, and at high doses can cause heart block. At very high doses it may produce a negative inotropic effect. High doses may cause cardiac arrhythmias, coma, and death. Arrhythmias have also been reported after usual intravenous doses (see below). Adverse neurological effects have been reported including eye twitching, convulsions, and respiratory depression. Hepatotoxicity and agranulocytosis may occasionally occur.

Effects on the heart. Electrophysiologic study[1] in 1955 patients revealed that ajmaline 1 mg/kg given intravenously could induce arrhythmias; 63 developed a supraventricular arrhythmia and 7 an atrioventricular re-entrant tachycardia. Ventricular tachycardia[2,3] and torsade de pointes[4] have been reported during diagnostic use.

1. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. *Int J Cardiol* 1992; **34:** 189–98.
2. Rolf S, *et al.* The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.
3. Pinar Bermúdez E, *et al.* Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000; **23:** 407–9.
4. Haverkamp W, *et al.* Torsade de pointes induced by ajmaline. *Z Kardiol* 2001; **90:** 586–90.

Precautions

As for Quinidine, p.1384.

Interactions

Antiarrhythmics. Oral use of *quinidine* with ajmaline increased plasma concentrations of ajmaline considerably in 4 healthy subjects; the elimination half-life of ajmaline was increased about twofold.[1] The pharmacokinetics of quinidine did not seem to be affected by ajmaline.

1. Hori R, *et al.* Quinidine-induced rise in ajmaline plasma concentration. *J Pharm Pharmacol* 1984; **36:** 202–4.

Uses and Administration

Ajmaline is an alkaloid obtained from the root of *Rauwolfia serpentina* (Apocynaceae). It is a class Ia antiarrhythmic (p.1153) used in the treatment of supraventricular and ventricular arrhythmias (p.1160) and for differential diagnosis of Wolff-Parkinson-White syndrome. Ajmaline is given by intravenous injection in a usual dose of 50 mg over at least 5 minutes. It may also be given by intravenous infusion, and has been given orally and by intramuscular injection.

Ajmaline has also been used as the hydrochloride, monoethanolate, and phenobarbital salts.

Brugada syndrome. Brugada syndrome is a congenital disorder affecting myocardial sodium channels and may be associated with sudden cardiac death. Class 1a antiarrhythmics such as ajmaline block the sodium channel and may have a role in the diagnosis of Brugada syndrome, although they are not suitable for treatment.

References.

1. Rolf S, *et al.*The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003; **24:** 1104–12.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gilurytmal; ***Cz.:*** Gilurytmal†; ***Ger.:*** Gilurytmal.

Alacepril *(rINN)*

Alacépril; Alaceprilum; DU-1219. *N*-{1-[(*S*)-3-Mercapto-2-methylpropionyl]-L-prolyl}-3-phenyl-L-alanine acetate.

Алацеприл

$C_{20}H_{26}N_2O_5S$ = 406.5.
CAS — 74258-86-9.

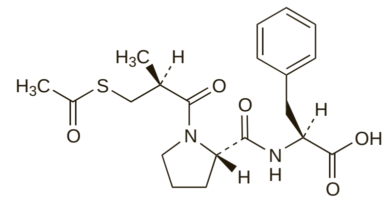

Pharmacopoeias. In *Jpn.*

Profile

Alacepril is an ACE inhibitor (p.1193) used in the treatment of hypertension (p.1171). It is converted to captopril and desacetylalacepril (DU-1227) in the body after oral doses. It is given orally in a usual dose of 25 to 75 mg daily, as a single dose or in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cetapril.

Aliskiren Fumarate *(USAN, rINNM)*

Aliskiren Hemifumarate; Aliskirène, Fumarate de; Aliskireni Fumaras; CGP-60536B; Fumarato de aliskireno; SPP-100 (aliskiren or aliskiren fumarate). Bis(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide fumarate (2:1).

Алискирена Фумарат

$(C_{30}H_{53}N_3O_6)_2,C_4H_4O_4$ = 1219.6.
CAS — 173334-57-1 (aliskiren); 173334-58-2 (aliskiren fumarate).
ATC — C09XA02.
ATC Vet — QC09XA02.

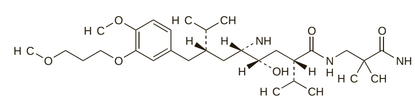

(aliskiren)

Adverse Effects and Precautions

Aliskiren is generally well-tolerated but may produce dose-related gastrointestinal adverse effects including diarrhoea, abdominal pain, dyspepsia, and gastro-oesophageal reflux. Other adverse effects include hypotension, headache, dizziness, fatigue, back pain, and cough; rashes, hyperuricaemia, gout, and renal calculi may also occur. Angioedema has been reported rarely, and there have also been reports of seizures. As with other inhibitors of the renin-angiotensin system, dose-related decreases in haemoglobin have been reported.

Aliskiren should be avoided in pregnancy since drugs acting on the renin-angiotensin system have been associated with fetal and neonatal morbidity and mortality. It should be used with caution in patients with renal impairment or renovascular hypertension. Patients with sodium or volume depletion (for example those receiving high-dose diuretics) may experience symptomatic hypotension on starting aliskiren and treatment should begin under close medical supervision.

Interactions

Use of aliskiren with other antihypertensives or drugs that cause hypotension may have an additive effect. Renal function and electrolytes should be monitored in diabetic patients taking aliskiren and ACE inhibitors since there is an increased risk of hyperkalaemia and renal impairment.

Aliskiren is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4 but few significant interactions have been reported. Plasma-aliskiren concentrations may be reduced by irbesartan and increased by atorvastatin and ketoconazole but the clinical relevance is not clear. Aliskiren has caused significant decreases in furosemide concentrations.

Pharmacokinetics

Aliskiren is poorly absorbed from the gastrointestinal tract with a bioavailability of about 2.5%. Peak plasma concentrations are reached about 1 to 3 hours after an oral dose. Absorption is reduced when aliskiren is taken with a high-fat meal. Aliskiren is about 50% bound to plasma proteins. It is excreted mainly in the faeces, possibly via the bile; about 25% of the absorbed dose is excreted in the urine as unchanged drug. Aliskiren is a substrate for the cytochrome P450 isoenzyme CYP3A4 but metabolism appears to be minimal. The elimination half-life is about 24 to 40 hours, and steady-state concentrations are reached in about 7 to 8 days.

Uses and Administration

Aliskiren is an orally active renin inhibitor used in the management of hypertension; it prevents the conversion of angiotensinogen into angiotensin I and therefore inhibits the production of angiotensin II and aldosterone. It is given as the fumarate, although licensed product information in some countries specifies the base. Doses are expressed in terms of the base; 165.8 mg of aliskiren fumarate is equivalent to about 150 mg of aliskiren. The usual initial oral dose of aliskiren is 150 mg once daily, increased to 300 mg once daily if necessary. Doses may be taken before or after food, but patients should establish a routine pattern with regard to meals.

Aliskiren is also under investigation in heart failure and diabetic nephropathy.

◊ Reviews.

1. Van Tassell BW, Munger MA. Aliskiren for renin inhibition: a new class of antihypertensives. *Ann Pharmacother* 2007; **41:** 456–64.
2. Frampton JE, Curran MP. Aliskiren: a review of its use in the management of hypertension. *Drugs* 2007; **67:** 1767–92.
3. Chrysant SG. Aliskiren-hydrochlorothiazide combination for the treatment of hypertension. *Expert Rev Cardiovasc Ther* 2008; **6:** 305–14.
4. Jensen C, *et al.* Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov* 2008; **7:** 399–410.
5. Sureshkumar KK, *et al.* Aliskiren: clinical experience and future perspectives of renin inhibition. *Expert Opin Pharmacother* 2008; **9:** 825–37.
6. Kappert K, *et al.* Aliskiren. *Dtsch Med Wochenschr* 2008; **133:** 1308–12.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Enviage; Rasilez; Riprazo; Sprimeo; Tekturna; ***Fr.:*** Rasilez; ***Port.:*** Enviage; Rasilez; Riprazo; Tekturna; ***UK:*** Rasilez; ***USA:*** Tekturna.

Alprenolol *(BAN, rINN)* ⊗

Alprénolol; Alprenololi; Alprenololum. 1-(2-Allylphenoxy)-3-isopropylaminopropan-2-ol.

Альпренолол

$C_{15}H_{23}NO_2$ = 249.3.
CAS — 13655-52-2.
ATC — C07AA01.
ATC Vet — QC07AA01.

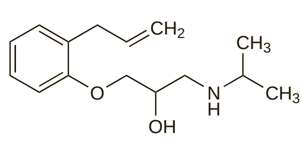

Alprenolol Benzoate *(BANM, rINNM)* ⊗

Alprénolol, benzoate d'; Alprenololi benzoas; Benzoato de alprenolol.

Альпренолола Бензоат

$C_{22}H_{29}NO_4$ = 371.5.
ATC — C07AA01.
ATC Vet — QC07AA01.

Alprenolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Alprénolol, chlorhydrate d'; Alprenolol-hidroklorid; Alprenolol-hydrochlorid; Alprenololhydroklorid; Alprenololi hydrochloridum; Alprenololihydrokloridi; Alprenololio hidrochloridas; H56/28; Hidrocloruro de alprenolol.

Альпренолола Гидрохлорид

$C_{15}H_{23}NO_2$,HCl = 285.8.
CAS — 13707-88-5.
ATC — C07AA01.
ATC Vet — QC07AA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Alprenolol Hydrochloride). A white, or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Alprenolol is a non-cardioselective beta blocker (p.1225). It is reported to have intrinsic sympathomimetic activity and some membrane-stabilising properties.

Alprenolol has been given orally, as the benzoate or hydrochloride, in the management of hypertension, angina pectoris, and cardiac arrhythmias.

Alteplase *(BAN, USAN, rINN)*

Alteplaasi; Alteplas; Alteplasa; Altéplase; Alteplasum; Alteplaz; G-11035; G-11044; G-11021 (2-chain form); Recombinant Tissue-type Plasminogen Activator; rt-PA.

Альтеплаза

CAS — 105857-23-6.
ATC — B01AD02; S01XA13.
ATC Vet — QB01AD02; QS01XA13.

Description. Alteplase is a glycosylated protein of 527 residues having the amino acid sequence of human tissue plasminogen activator (t-PA) and produced by recombinant DNA technology.

Pharmacopoeias. In *US. Eur.* (see p.vii) includes Alteplase for Injection.
Ph. Eur. 6.2 (Alteplase for Injection; Alteplasum ad Iniectabile). A sterile, freeze-dried preparation of alteplase, a tissue plasminogen activator produced by recombinant DNA technology. It has a potency of not less than 500 000 units/mg of protein. It is a white or slightly yellow powder or friable mass. The reconstituted preparation has a pH of 7.1 to 7.5. Store in colourless glass containers, under vacuum or an inert gas, at a temperature between 2° and 30°. Protect from light. Alteplase consists of 527 amino acids with carbohydrate moieties attached.
USP 31 (Alteplase). A highly purified glycosylated serine protease with fibrin-binding properties and plasminogen-specific proteolytic activities. It is produced by recombinant DNA synthesis in mammalian cell culture. It has a potency of 522 000 to 667 000 USP units/mg of protein. Store in airtight containers in the frozen state at a temperature of –20° or below.

Incompatibility and stability. Alteplase has been reported[1] to be incompatible with dobutamine, dopamine, glyceryl trinitrate, and heparin, although a subsequent study found no incompatibility between alteplase and glyceryl trinitrate.[2] Another study[3] found that dilution of a proprietary preparation of alteplase (Activase) to 0.09 and 0.16 mg/mL with glucose 5% resulted in precipitation of the drug. Alteplase is formulated with arginine as a solubilising agent, and dilution with glucose 5% to concentrations below 0.5 mg/mL of alteplase makes precipitation possible. Dilution with sodium chloride 0.9% is possible to concentrations down to 0.2 mg/mL before precipitation becomes a risk.

Studies[4,5] have suggested that a 1 mg/mL solution of alteplase retains its activity when frozen at –20° or below for up to 6 months.

1. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
2. Lam XM, *et al.* Stability and activity of alteplase with injectable drugs commonly used in cardiac therapy. *Am J Health-Syst Pharm* 1995; **52:** 1904–9.
3. Frazin BS. Maximal dilution of Activase. *Am J Hosp Pharm* 1990; **47:** 1016.
4. Calis KA, *et al.* Bioactivity of cryopreserved alteplase solutions. *Am J Health-Syst Pharm* 1999; **56:** 2056–7.
5. Wiernikowski JT, *et al.* Stability and sterility of recombinant tissue plasminogen activator at –30°C. *Lancet* 2000; **355:** 2221–2.

Units

The activity of alteplase can be measured in terms of international units using the third International Standard for tissue plasminogen activator recombinant, human, established in 1999, although doses are generally expressed by weight.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Allergic reactions are less likely with alteplase than with streptokinase and repeated use may be possible.

Hypersensitivity. An anaphylactoid reaction to alteplase occurred in a patient with a history of atopy.[1] For comment on this unexpected reaction, see Hypersensitivity under Adverse Effects of Streptokinase, p.1404. (See also ACE Inhibitors under Interactions, below).

1. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; **341:** 966–7.

Thrombin generation. Alteplase produces considerable thrombin generation which may result from direct activation of the coagulation system by plasmin or by positive feedback of the coagulation system by clot-bound thrombin. This excessive thrombin generation was considered a possible cause of myocardial infarction in a patient undergoing thrombolytic therapy with alteplase for venous thrombosis.[1] Streptokinase produced no evidence of excessive thrombin generation.

1. Baglin TP, *et al.* Thrombin generation and myocardial infarction during infusion of tissue-plasminogen activator. *Lancet* 1993; **341:** 504–5.

Interactions

As for Streptokinase, p.1404.

ACE inhibitors. Angioedema has been reported rarely in patients treated with alteplase, but the risk may be increased in those taking ACE inhibitors. A prospective study[1] found that out of 176 patients treated with alteplase for acute stroke, 9 developed angioedema; the risk was strongly associated with use of an ACE inhibitor (7 of the 9).

1. Hill MD, *et al.* Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology* 2003; **60:** 1525–7.

Glyceryl trinitrate. Although thrombolytics and nitrates are both frequently used in acute myocardial infarction a report suggested that this combination may result in impaired thrombolysis. Giving alteplase and glyceryl trinitrate intravenously to 36 patients with acute myocardial infarction produced lower plasma-antigen concentrations of tissue-plasminogen activator than alteplase given alone to 11 patients.[1] Reperfusion was sustained in only 44% of patients receiving both drugs compared with 91% of patients given alteplase alone. The authors of a subsequent study[2] suggested that these lower plasma concentrations may be due to increased hepatic metabolism of alteplase as a result of glyceryl trinitrate's effect of increasing hepatic blood flow.

1. Nicolini FA, *et al.* Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 1994; **74:** 662–6.
2. Romeo F, *et al.* Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* 1995; **130:** 692–7.

Pharmacokinetics

Alteplase is cleared rapidly from the plasma, mainly by metabolism in the liver. It has an initial half-life of 4 to 5 minutes and a terminal half-life of about 40 minutes.

◊ References.

1. Krause J. Catabolism of tissue-type plasminogen activator (t-PA), its variants, mutants and hybrids. *Fibrinolysis* 1988; **2:** 133–42.

Uses and Administration

Alteplase is a thrombolytic drug. It is a mainly single-chain form of the endogenous enzyme tissue plasminogen activator and is produced by recombinant DNA technology. Like endogenous tissue plasminogen activator, alteplase converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Alteplase has relatively little effect on circulating, unbound plasminogen and thus may be termed a fibrin-specific thrombolytic (see p.1156).

Alteplase is used similarly to streptokinase (p.1404) in the treatment of thromboembolic disorders, particularly myocardial infarction (p.1175) and venous thromboembolism (p.1189), and to clear occluded catheters (see below). Alteplase may also be used in patients with acute ischaemic stroke (p.1185).

In the treatment of acute **myocardial infarction**, alteplase is given intravenously as soon as possible after the onset of symptoms in a total dose of 100 mg; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The total dose may be given either over 1½ hours (accelerated or 'front-loaded' alteplase) or over 3 hours. The accelerated schedule has been recommended if given within 6 hours of myocardial infarction, while the 3-hour schedule has been recommended when used more than 6 hours after myocardial infarction. The schedule over $1\frac{1}{2}$ hours is as follows: 15 mg as an intravenous bolus, then 0.75 mg/kg, up to a maximum of 50 mg, by intravenous infusion over 30 minutes, followed by the remainder infused over the subsequent 60 minutes. The schedule over 3 hours is as follows: 10 mg as an intravenous bolus, then 50 mg by intravenous infusion over 1 hour, followed by the remainder infused over the subsequent 2 hours.

In the treatment of acute, massive **pulmonary embolism** a total dose of 100 mg is given; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The first 10 mg is given as an intravenous bolus and the remainder by intravenous infusion over 2 hours.

In acute **ischaemic stroke**, alteplase is given within 3 hours of the onset of symptoms in a dose of 0.9 mg/kg up to a maximum total dose of 90 mg. The dose is given intravenously over 60 minutes with 10% of it as a bolus during the first minute.

To **restore function in central venous lines,** alteplase is instilled into the catheter at a concentration of 1 mg/mL. The usual dose is 2 mg, repeated after 2 hours if necessary. A total dose of 4 mg should not be exceeded. For patients weighing less than 30 kg, the dose is 110% of the internal lumen volume of the catheter, but should not exceed 2 mg, and may be repeated after 2 hours if necessary.

◊ General references.

1. Gillis JC, *et al.* Alteplase: a reappraisal of its pharmacological properties and therapeutic use in acute myocardial infarction. *Drugs* 1995; **50:** 102–36.
2. Wagstaff AJ, *et al.* Alteplase: a reappraisal of its pharmacology and therapeutic use in vascular disorders other than acute myocardial infarction. *Drugs* 1995; **50:** 289–316.
3. Semba CP, *et al.* Society of Cardiovascular and Interventional Radiology (SCVIR). Alteplase and tenecteplase: applications in the peripheral circulation. *Tech Vasc Interv Radiol* 2001; **4:** 99–106.
4. Lindley RI, *et al.* Alteplase and ischaemic stroke: have new reviews of old data helped? *Lancet Neurol* 2005; **4:** 249–53.
5. De Keyser J, *et al.* Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke* 2007; **38:** 2612–8.
6. Quinn TJ, *et al.* Past, present and future of alteplase for acute ischemic stroke. *Expert Rev Neurother* 2008; **8:** 181–92.

Arterial and venous thromboembolism. For the use of alteplase for arterial or venous thromboembolism in children, see Administration in Children under Streptokinase, p.1405.

Catheters and cannulas. Alteplase has been used successfully to clear thrombi in central venous catheters.[1,2] Typical doses have been 2 mg injected as a bolus into the blocked catheter. Children have been treated similarly; in one study[3] where patients' weight started from 3 kg, doses ranged from 0.1 to 2.0 mg (as a 1 mg/mL solution), depending on the size of the catheter. Similarly, a later study using a 1 mg/mL solution gave doses of 2 mg to children weighing 30 kg or more, and a volume equal to 110% of the calculated internal volume of the catheter (rounded to the nearest 0.1 mL and not to exceed 2 mL in total) in children weighing less than 30 kg.[4] The dwell time was up to 2 hours, and doses were repeated once in patients in whom catheter function was not restored after this period. A cohort study[5] used doses of 0.5 mg for children weighing 10 kg or under, and 1 to 2 mg above this weight, with a dwell time of 2 to 4 hours. In another report, 2 children[6] were successfully treated with intravenous alteplase in doses of 0.01 to 0.05 mg/kg per hour for venous thrombosis associated with indwelling intravascular catheters.

Alteplase has also been instilled into central haemodialysis lines to preserve patency between dialysis sessions.[7] Urokinase has been used similarly in children with long-term venous access devices for antineoplastic therapy.[8]

For reports covering the use of alteplase to treat intracardiac thrombosis resulting from the placement of central venous lines, see Intracardiac Thrombosis, below.

1. Paulsen D, *et al.* Use of tissue plasminogen activator for reopening of clotted dialysis catheters. *Nephron* 1993; **64:** 468–9.
2. Haire WD, *et al.* Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. *Thromb Haemost* 1994; **72:** 543–7.
3. Jacobs BR, *et al.* Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001; **139:** 593–6.
4. Blaney M, *et al.* CAPS Investigators. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). *J Vasc Interv Radiol* 2006; **17:** 1745–51.
5. Choi M, *et al.* The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. *J Pediatr* 2001; **139:** 152–6.
6. Doyle E, *et al.* Thrombolysis with low dose tissue plasminogen activator. *Arch Dis Child* 1992; **67:** 1483–4.
7. Gittins NS, *et al.* Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Arch Dis Child* 2007; **92:** 499–501.
8. Dillon PW, *et al.* Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. *J Clin Oncol* 2004; **22:** 2718–23.

Intracardiac thrombosis. Alteplase has been used, in a dose of 100 mg given intravenously over 2 hours, for thrombosis of prosthetic heart valves.[1]

Alteplase has been used successfully in a neonate to treat intracardiac thrombosis associated with the use of a central venous line.[2] A dose of 500 micrograms/kg given over 10 minutes was followed by infusion of 200 micrograms/kg per hour for 3 days. In another report,[3] 4 preterm infants were treated successfully. All received 400 to 500 micrograms/kg of alteplase in a 20 to 30 minute bolus. This was followed in one case by a 3-hour infusion at 100 micrograms/kg per hour.

Although thrombolytics are usually contra-indicated in patients with infective endocarditis (see Precautions for Streptokinase, p.1404), alteplase has been used successfully in children with indwelling catheters who developed infective endocarditis; coagulation was monitored and fresh frozen plasma was given to maintain fibrinogen concentrations.[4]

1. Astengo D, *et al.* Recombinant tissue plasminogen activator for prosthetic mitral-valve thrombosis. *N Engl J Med* 1995; **333:** 259.
2. Van Overmeire B, *et al.* Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992; **67:** 443–5.
3. Ferrari F, *et al.* Early intracardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator. *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F66–F69.
4. Levitas A, *et al.* Successful treatment of infective endocarditis with recombinant tissue plasminogen activator. *J Pediatr* 2003; **143:** 649–52.

Microvessel thrombosis. Alteplase has been used in conditions where the underlying pathology is occlusion of small blood vessels by microthrombi.

Purpura and loss of circulation in the hands of a patient recovering from **fulminant meningococcaemia**[1] responded to intra-arterial infusion of alteplase 20 to 40 micrograms/kg per hour for 22 hours in the right hand, and 20 micrograms/kg per hour for 11 hours in the left. Perfusion was successfully restored to both hands, and full function subsequently attained in them. Improvement was also achieved when alteplase was given to 2 infants with septic shock and purpura fulminans caused by meningococcal infection.[2]

Six patients[3] with ulcers caused by **livedoid vasculitis** and refractory to conventional treatment were treated with alteplase 10 mg infused intravenously over 4 hours daily for 14 days. Most ulcers healed rapidly; one patient required re-treatment with concomitant anticoagulation. Healing of ulcers associated with **calciphylaxis** has also been reported[4] with a similar alteplase regimen.

A 4-year-old girl[5] with **haemolytic-uraemic syndrome** (see under Thrombotic Microangiopathies, p.1076) responded to treatment with an intravenous infusion of alteplase 200 micrograms/kg per hour for 5 hours, subsequently reduced to 50 micrograms/kg per hour for 14 days.

Alteplase use has been reviewed[6] and mixed results found, in patients with **veno-occlusive disease of the liver**, a serious complication of bone marrow transplantation that may be caused by diffuse thrombi in the hepatic venules. Although results in patients with established veno-occlusive disease have been disappointing,[7] one study[8] suggested that alteplase given early in the course of the disease improves response rate.

1. Keeley SR, *et al.* Tissue plasminogen activator for gangrene in fulminant meningococcaemia. *Lancet* 1991; **337:** 1359.
2. Zenz W, *et al.* Recombinant tissue plasminogen activator treatment in two infants with fulminant meningococcemia. *Pediatrics* 1995; **96:** 44–8.
3. Klein KL, Pittelkow MR. Tissue plasminogen activator for treatment of livedoid vasculitis. *Mayo Clin Proc* 1992; **67:** 923–33.
4. Sewell LD, *et al.* Low-dose tissue plasminogen activator for calciphylaxis. *Arch Dermatol* 2004; **140:** 1045–8.
5. Kruez W, *et al.* Successful treatment of haemolytic uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.
6. Terra SG, *et al.* A review of tissue plasminogen activator in the treatment of veno-occlusive liver disease after bone marrow transplantation. *Pharmacotherapy* 1997; **17:** 929–37.
7. Bearman SI, *et al.* Treatment of hepatic venocclusive disease with recombinant human tissue plasminogen activator and heparin in 42 marrow transplant patients. *Blood* 1997; **89:** 1501–6.
8. Schriber J, *et al.* Tissue plasminogen activator (tPA) as therapy for hepatotoxicity following bone marrow transplantation. *Bone Marrow Transplant* 1999; **24:** 1311–14.

Ocular disorders. Intra-ocular alteplase has been used to treat postoperative fibrinous deposits that can form after procedures such as surgery for cataracts[1] or glaucoma,[2] including cataracts in children.[3] Doses ranging from 6 to 25 micrograms have been used. Intra-ocular bleeding has occurred as a complication of such use.[2,4] Alteplase has also been used prophylactically in children undergoing surgery for congenital cataracts.[5]

Intra-ocular alteplase has also been used for treatment of subhyaloid haemorrhage,[6,7] including that seen in shaken baby syndrome.[8] Successful treatment of subretinal macular haemorrhage with alteplase injected directly into the subretinal area around the clot has also been reported.[9]

1. Heiligenhaus A, *et al.* Recombinant tissue plasminogen activator in cases with fibrin formation after cataract surgery: a prospective randomised multicentre study. *Br J Ophthalmol* 1998; **82:** 810–15.
2. Lundy DC, *et al.* Intracameral tissue plasminogen activator after glaucoma surgery: indications, effectiveness, and complications. *Ophthalmology* 1996; **103:** 274–82.
3. Mehta JS, Adams GGW. Recombinant tissue plasminogen activator following paediatric cataract surgery. *Br J Ophthalmol* 2000; **84:** 983–6.
4. Azuara-Blanco A, Wilson RP. Intraocular and extraocular bleeding after intracameral injection of tissue plasminogen activator. *Br J Ophthalmol* 1998; **82:** 1345–6.
5. Siatiri H, *et al.* Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery. *Br J Ophthalmol* 2005; **89:** 1458–61.
6. Schmitz K, *et al.* Therapy of subhyaloidal haemorrhage by intravitreal application of rtPA and SF gas. *Br J Ophthalmol* 2000; **84:** 1324–5.
7. Koh HJ, *et al.* Treatment of subhyaloid haemorrhage with intravitreal tissue plasminogen activator and C F gas injection. *Br J Ophthalmol* 2000; **84:** 1329–30.
8. Conway MD, *et al.* Intravitreal tPA and SF promote clearing of premacular subhyaloid hemorrhages in shaken and battered baby syndrome. *Ophthalmic Surg Lasers* 1999; **30:** 435–41.
9. Singh RP, *et al.* Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. *Br J Ophthalmol* 2006; **90:** 429–31.

Peripheral arterial thromboembolism. Thrombolytics, including alteplase, may be used in the management of peripheral arterial thromboembolism (p.1178). Alteplase has been injected intravenously or intra-arterially directly into the clot as an alternative to surgical treatment of the occlusion. It has also been infused intra-arterially to remove distal clots during a surgical procedure. Alteplase is claimed to produce more rapid thrombolysis than streptokinase although studies have been too small to provide evidence of reduced limb loss or mortality.[1] The most common dose range is 0.5 to 1 mg/hour given *intra-arterially.*[1-3]

An *intravenous* dose of 500 micrograms/kg per hour for the first hour followed by 250 micrograms/kg per hour until clot lysis occurred has been used in infants.[4] Treatment of arterial thrombosis in neonates has been reported, using doses of alteplase ranging from 100 to 500 micrograms/kg per hour *intravenously.*[5,6] The *BNFC* recommends a dose for any intravascular thrombosis in neonates and children of 100 to 500 micrograms/kg per hour by intravenous infusion over 3 to 6 hours; a second dose may be given if needed. The maximum daily dose should not exceed 100 mg. However, a retrospective study[7] of 80 infants and children with arterial or venous thrombi found that although treatment with alteplase may be effective, it is associated with a low safety margin and an unknown risk-benefit ratio.

Where a thrombolytic is used to remove distal clots during a surgical procedure alteplase has been given *intra-arterially* as three doses of 5 mg at 10-minute intervals.[8]

1. Wolfe JH. Critical limb ischaemia. *Prescribers' J* 1994; **34:** 50–8.
2. Anonymous. Non-coronary thrombolysis. *Lancet* 1990; **335:** 691–3.
3. Ward AS, *et al.* Peripheral thrombolysis with tissue plasminogen activator: results of two treatment regimens. *Arch Surg* 1994; **129:** 861–5.
4. Zenz W, *et al.* Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. *Br Heart J* 1993; **70:** 382–5.
5. Weiner GM, *et al.* Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998; **133:** 133–6.
6. Farnoux C, *et al.* Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. *J Pediatr* 1998; **133:** 137–40.
7. Gupta AA, *et al.* Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001; **139:** 682–8.
8. Chester JF, *et al.* Peroperative t-PA thrombolysis. *Lancet* 1991; **337:** 861–2.

Preparations

USP 31: Alteplase for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Actilyse; ***Austral.:*** Actilyse; ***Austria:*** Actilyse; ***Belg.:*** Actilyse; ***Braz.:*** Actilyse; ***Canad.:*** Activase; Cathflo; ***Chile:*** Actilyse; ***Cz.:*** Actilyse; ***Denm.:*** Actilyse; ***Fin.:*** Actilyse; ***Fr.:*** Actilyse; ***Ger.:*** Actilyse; ***Gr.:*** Actilyse; ***Hong Kong:*** Actilyse; ***Hung.:*** Actilyse; ***India:*** Actilyse; ***Indon.:*** Actilyse; ***Irl.:*** Actilyse; ***Israel:*** Actilyse; ***Ital.:*** Actilyse; ***Jpn:*** Activacin; ***Malaysia:*** Actilyse; ***Mex.:*** Actilyse; ***Neth.:*** Actilyse; ***Norw.:*** Actilyse; ***NZ:*** Actilyse; ***Philipp.:*** Actilyse; ***Pol.:*** Actilyse; ***Port.:*** Actilyse; ***Rus.:*** Actilyse (Актилизе); ***S.Afr.:*** Actilyse; ***Singapore:*** Actilyse; ***Spain:*** Actilyse; ***Swed.:*** Actilyse; ***Switz.:*** Actilyse; ***Thai.:*** Actilyse; ***Turk.:*** Actilyse; ***UK:*** Actilyse; ***USA:*** Activase; ***Venez.:*** Actilyse.

Altizide (rINN) ⊗

Althiazide (USAN); Altizida; Altizidum; P-1779. 3-Allylthiomethyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Альтизид

$C_{11}H_{14}ClN_3O_4S_3$ = 383.9.

CAS — 5588-16-9.

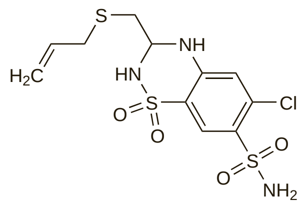

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Altizide). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane. It exhibits polymorphism.

Profile

Altizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that is used in the treatment of oedema and hypertension. It is frequently used with spironolactone.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Aldactazine; ***Fr.:*** Aldactazine; Practazin; Spiroctazine; ***Port.:*** Aldactazine; ***Spain:*** Aldactacine.

Ambrisentan (BAN, rINN)

Ambrisentán; Ambrisentanum; BSF-208075; LU-208075. (+)-(2*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

Амбризентан

$C_{22}H_{22}N_2O_4$ = 378.4.

CAS — 177036-94-1.

ATC — C02KX02.

ATC Vet — QC02KX02.

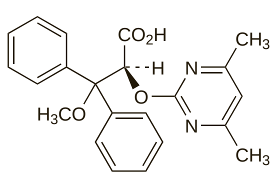

Adverse Effects and Precautions

As for Bosentan, p.1235.

Interactions

Ambrisentan is a substrate for a number of enzymes and transporters and interactions could potentially occur with inducers or inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19, P-glycoprotein, uridine diphosphate glucuronosyltransferases, and organic anion transporting polypeptide (OATP).

Pharmacokinetics

Ambrisentan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It is about 99% bound to plasma proteins. Ambrisentan is excreted mainly by the liver, although the relative contribution of hepatic metabolism and biliary excretion is not known. The terminal elimination half-life is about 15 hours.

Uses and Administration

Ambrisentan is an endothelin receptor antagonist (p.1155) with similar actions to bosentan (p.1235), although it has a higher selectivity for the endothelin ET_A-receptor. It is used in the management of pulmonary hypertension functional class II or III (p.1179). It is given orally in an initial dose of 5 mg once daily; the dose may be increased to 10 mg once daily if tolerated.

◊ References.

1. Galié N, *et al.* Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 529–35.
2. Vatter H, Seifert V. Ambrisentan, a non-peptide endothelin receptor antagonist. *Cardiovasc Drug Rev* 2006; **24:** 63–76.
3. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. *Vasc Health Risk Manag* 2007; **3:** 11–22.
4. Anonymous. Ambrisentan (Letairis) for pulmonary arterial hypertension. *Med Lett Drugs Ther* 2007; **49:** 87–8.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Volibris; ***USA:*** Letairis.

Amezinium Metilsulfate (rINN) ⊗

Ametsiniummetilsulfaatti; Amezinii Metilsulfas; Amezinium Methylsulphate; Amézinium, Métilsulfate d'; Ameziniummetilsulfat; Metilsulfato de amezinio. 4-Amino-6-methoxy-1-phenylpyridazinium methylsulfate.

Амезиния Метилсульфат

$C_{12}H_{15}N_3O_5S$ = 313.3.

CAS — 30578-37-1.

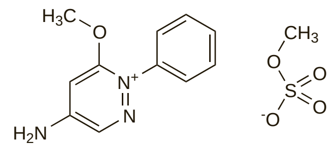

Profile

Amezinium metilsulfate is a sympathomimetic (p.1407) used for its vasopressor effects in the treatment of hypotensive states (p.1174). It is given orally in a usual dose of 10 mg up to three times daily. It has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Regulton; ***Ger.:*** Regulton; Supratonin.

Amiloride Hydrochloride

(BANM, USAN, rINNM) ⊗

Amilorid Hidroklorür; Amilorid hydrochlorid dihydrát; Amiloride, chlorhydrate d'; Amilorid-hidroklorid; Amiloridhydroklorid; Amiloridi hydrochloridum; Amiloridi Hydrochloridum Dihydricum; Amiloridihydrokloridi; Amilorido hidrochloridas; Amilorydu chlorowodorek; Amipramizide; Cloridrato de Amilorida; Hidrocloruro de amilorida; MK-870. *N*-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate.

Амилорида Гидрохлорид

$C_6H_8ClN_7O,HCl,2H_2O$ = 302.1.

CAS — 2609-46-3 (amiloride); 2016-88-8 (anhydrous amiloride hydrochloride); 17440-83-4 (amiloride hydrochloride dihydrate).

ATC — C03DB01.

ATC Vet — QC03DB01.

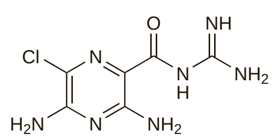

(amiloride)

NOTE. Compounded preparations of amiloride hydrochloride may be represented by the following names:

- Co-amilofruse (*BAN*)—amiloride hydrochloride 1 part and furosemide 8 parts (w/w)
- Co-amilozide (*BAN*)—amiloride hydrochloride 1 part and hydrochlorothiazide 10 parts (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Amiloride Hydrochloride). A pale yellow to greenish-yellow powder. Slightly soluble in water and in dehydrated alcohol. Protect from light.

USP 31 (Amiloride Hydrochloride). A yellow to greenish-yellow, odourless or practically odourless, powder. Slightly soluble in water; insoluble in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethyl sulfoxide; sparingly soluble in methyl alcohol.

Adverse Effects

Amiloride can cause hyperkalaemia, particularly in elderly patients, diabetics, and patients with renal impairment. Hyponatraemia has been reported in patients taking amiloride with other diuretics. Amiloride may cause nausea, vomiting, abdominal pain, diarrhoea or constipation, paraesthesia, thirst, dizziness, skin rash, pruritus, weakness, muscle cramps, headache, and minor psychiatric or visual changes. Orthostatic hypotension and rises in blood-urea-nitrogen concentrations have been reported. Other adverse effects of amiloride may include alopecia, cough, dyspnoea, jaundice, encephalopathy, impotence, angina pectoris, arrhythmias, and palpitations.

Effects on electrolyte balance. There have been reports of metabolic acidosis associated with amiloride or triamterene[1] and with co-amilozide.[2]

1. Kushner RF, Sitrin MD. Metabolic acidosis: development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. *Arch Intern Med* 1986; **146:** 343–5.
2. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

POTASSIUM. Hyperkalaemia is the main adverse effect when amiloride is given alone but may also occur when amiloride is given with a potassium-wasting diuretic. Severe hyperkalaemia has been reported during co-amilozide therapy, particularly in patients with renal impairment[1,2] and has been accompanied by metabolic acidosis in one such patient.[3]

1. Whiting GFM, *et al.* Severe hyperkalaemia with Moduretic. *Med J Aust* 1979; **1:** 409.
2. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet* 1981; **i:** 1272.
3. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

SODIUM. For reports of severe hyponatraemia in patients taking diuretics such as amiloride with potassium-wasting diuretics, see Hydrochlorothiazide, p.1308.

Effects on the skin. For a report of photosensitivity reactions in patients taking co-amilozide, see Hydrochlorothiazide, p.1309.

Precautions

Amiloride has the same precautions as spironolactone with regard to hyperkalaemia (see p.1400). It should be stopped at least 3 days before glucose-tolerance tests are performed in patients who may have diabetes mellitus because of the risks of provoking severe hyperkalaemia.

Interactions

There is an increased risk of hyperkalaemia if amiloride is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may also occur in patients given amiloride with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients taking amiloride with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity, but this does not appear to occur with amiloride. Severe hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients taking chlorpropamide. Amiloride may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, amiloride may enhance the effects of other antihypertensive drugs.

Digoxin. For the effects of amiloride on digoxin clearance, see p.1262.

Quinidine. For a report of amiloride producing arrhythmias in patients receiving quinidine, see p.1384.

Pharmacokinetics

Amiloride is incompletely absorbed from the gastrointestinal tract; bioavailability is about 50% and is reduced by food. It is not significantly bound to plasma proteins and has a plasma half-life of 6 to 9 hours; the terminal half-life may be 20 hours or more. It is excreted unchanged by the kidneys.

◊ General references.

1. Weiss P, *et al.* The metabolism of amiloride hydrochloride in man. *Clin Pharmacol Ther* 1969; **10:** 401–6.

Hepatic impairment. In patients with acute hepatitis the terminal half-life of amiloride was 33 hours compared with 21 hours in healthy subjects.[1] The proportion of the dose excreted in the urine was increased from 49 to 80%.

1. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.

Renal impairment. Studies of the pharmacokinetics of amiloride[1,2] have reported an increase in terminal elimination half-life from 20 hours in healthy subjects to 100 hours in patients with end-stage renal disease. The natriuretic effect of amiloride was reduced[1] in patients with creatinine clearance below 50 mL/minute. In patients with renal impairment amiloride could aggravate potassium retention due to renal disease. Studies in elderly patients have found increased half-life[3] and steady-state concentrations[4] associated with reduced renal function.

1. Knauf H, *et al.* Limitation on the use of amiloride in early renal failure. *Eur J Clin Pharmacol* 1985; **28:** 61–6.

2. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.
3. Sabanathan K, *et al.* A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. *Eur J Clin Pharmacol* 1987; **32:** 53–60.
4. Ismail Z, *et al.* The pharmacokinetics of amiloride-hydrochlorothiazide combination in the young and elderly. *Eur J Clin Pharmacol* 1989; **37:** 167–71.

Uses and Administration

Amiloride is a weak diuretic that appears to act mainly on the distal renal tubules. It is described as potassium-sparing since, like spironolactone, it increases the excretion of sodium and reduces the excretion of potassium. Unlike spironolactone, however, it does not act by specifically antagonising aldosterone. Amiloride does not inhibit carbonic anhydrase. It takes effect about 2 hours after oral dosage and its diuretic action reaches a peak in 6 to 10 hours and has been reported to persist for about 24 hours.

Amiloride diminishes the kaliuretic effects of other diuretics, and may produce an additional natriuretic effect. It is mainly used as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the long-term treatment of oedema associated with hepatic cirrhosis (including ascites, p.1159) and heart failure (p.1165). It is also used with other diuretics in the treatment of hypertension (p.1171). Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics such as amiloride, is discussed under Effects on Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p.1308. Amiloride is sometimes used to manage hypokalaemia in primary hyperaldosteronism (p.1402).

Amiloride by inhalation has also been investigated in the management of cystic fibrosis patients with lung disease (see below).

In the treatment of **oedema** amiloride is given orally as the hydrochloride and doses are expressed in terms of the anhydrous substance. 1 mg of anhydrous hydrochloride is equivalent to about 1.14 mg of the hydrated substance. Treatment may be started with a dose of 5 to 10 mg daily, increased, if necessary, to a maximum of 20 mg daily. An initial dose of 2.5 mg once daily may be used in patients already taking other diuretics or antihypertensives. Similar doses to those given for oedema are used to reduce potassium loss in patients receiving thiazide or loop diuretics.

Potassium supplements should not be given.

Cystic fibrosis. Pulmonary disease is the major cause of mortality in cystic fibrosis (p.166). Experimental treatment aimed at modifying the pulmonary disease process has included giving amiloride by inhalation.[1,2] No evidence of pulmonary or systemic toxicity was seen in 14 patients treated for 25 weeks.[1] The mechanism of action is unclear but could be the sodium-channel blocking effect[1] or anti-inflammatory effects[3] of amiloride. Concern has been expressed[4] over possible consequences of the inhibition of endogenous urokinase by amiloride although others[5] considered this to be unlikely at the concentrations studied. However, a systematic review[6] found no evidence that amiloride was of clinical benefit.

1. Knowles MR, *et al.* A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **322:** 1189–94.
2. App EM, *et al.* Acute and long-term amiloride inhalation in cystic fibrosis lung disease: a rational approach to cystic fibrosis therapy. *Am Rev Respir Dis* 1990; **141:** 605–12.
3. Gallo RL. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 996–7.
4. Henkin J. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997.
5. Knowles MR, *et al.* Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997–8.
6. Burrows E, *et al.* Sodium channel blockers for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/04/08).

Diabetes insipidus. Thiazide diuretics are commonly used in nephrogenic diabetes insipidus (p.2179) and NSAIDs may also be employed; both result in an overall decrease in urine production. Hydrochlorothiazide with amiloride has been reported to be at least as effective as hydrochlorothiazide plus indometacin in 5 patients.[1] In addition, amiloride obviated the need for potassium supplements. Hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Renal calculi. Patients with idiopathic hypercalciuria and a history of renal calculi (p.2181) are usually given a thiazide diuretic such as hydrochlorothiazide to reduce calcium excretion. In patients with calcium oxalate calculi an inherited cellular defect in oxalate transport may also be involved and this might be corrected by amiloride.[1]

1. Baggio B, *et al.* An inheritable anomaly of red-cell oxalate transport in "primary" calcium nephrolithiasis correctable with diuretics. *N Engl J Med* 1986; **314:** 599–604.

Preparations

BP 2008: Amiloride Tablets; Co-amilofruse Tablets; Co-amilozide Oral Solution; Co-amilozide Tablets;
USP 31: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Amiloride Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Kaluril; Midamor; ***Austria:*** Midamor; ***Canad.:*** Midamor; ***Cz.:*** Amiclaran; ***Denm.:*** Amikal†; Nirulid; ***Fin.:*** Medamor†; ***Fr.:*** Modamide; ***NZ:*** Midamor; ***Swed.:*** Midamor†; ***Switz.:*** Midamor†; ***UK:*** Amilamont; ***USA:*** Midamor.

Multi-ingredient: ***Arg.:*** Amiloclor†; Diflux; Diur Pot; Diurex A; Errolon A; Furdiuren†; Hidrenox A; Lasiride; Moducren†; Moduretic; Nuriban A; Plenacor D; Prenomod†; Ren-Ur; Vericordin Compuesto; ***Austral.:*** Amizide; Moduretic; ***Austria:*** Aldoretic; Amiloral/HCT; Amiloretik; Amilorid comp; Amilostad HCT; Lanuretic; Loradur; Moducrin; Moduretic; ***Belg.:*** Belidral†; Co-Amiloride; Frusamil; Kalten†; Moduretic; ***Braz.:*** Amiretic; Diupress; Diurezin-A; Diurisa; Moduretic; ***Canad.:*** Apo-Amilzide; Gen-Amilazide; Moduret; Novamilor; Nu-Amilzide; ***Chile:*** Furdiuren; Hidrium; Hidropid; ***Cz.:*** Amicloton; Amilorid/HCT; Apo-Amilzide; Limorid†; Loradur; Moduretic; Rhefluin; ***Denm.:*** Amilco; Buram; Frusamil; Moduretic†; Sparkal; ***Fin.:*** Amitrid; Diuramin; Diurex; Miloride; Moduretic; Sparkal; ***Fr.:*** Logirene; Moducren; Moduretic; ***Ger.:*** Amilocomp beta; Amiloretik; Amilorid comp; Amilorid/HCT; Amilozid†; Aquaretic†; Diaphal; Diursan; durarese†; Esmalorid†; Moducrin; Moduretik; Tensoflux; ***Gr.:*** Frumil; Ividol; Moduretic; Tiaden; ***Hong Kong:*** Amilco†; Amithiazide; Apo-Amilzide; Moducren; Moduretic; Navispare; Sefaretic; ***Hung.:*** Amilorid Comp; Amilozid-B; ***India:*** Biduret; Frumil; Hipres-D; ***Indon.:*** Lorinid; ***Irl.:*** Amilco†; Buram; Fru-Co; Frumil; Lasoride†; Moducren; Moduret; ***Israel:*** Kaluril; ***Ital.:*** Moduretic; ***Malaysia:*** Ami-Hydrotride; Amizide; Apo-Amilzide; Moduretic; ***Mex.:*** Moduretic; ***Neth.:*** Moduretic; ***Norw.:*** Moduretic; Normorix; ***NZ:*** Amizide; Frumil; ***Pol.:*** Tialorid; ***Port.:*** Aldoretic†; Amiloride Composto†; Chibretico†; Diurene; Moducren†; Moduretic; ***S.Afr.:*** Adco-Retic; Amiloretic; Betaretic; Hexaretic; Moducren; Moduretic; Servatrin; ***Singapore:*** Apo-Amilzide; ***Spain:*** Ameride; Diuzine; Kalten; ***Swed.:*** Amiloferm; Moduretic; Normorix; Sparkal; ***Switz.:*** Agorex†; Amilo-basan†; Amiloride/HCTZ; Betadiur†; Co-Amilorid†; Comilorid; Ecodurex; Escoretic; Frumil†; Grodurex; Kalten; Moducren; Moduretic; Rhefluin; ***Thai.:*** Bilduretic; Hydrozide Plus; Hyperretic; Miduret†; Milorex†; Miretic; Modulan†; Moduretic; Moure-M; Poli-Uretic; Renase; Sefaretic; ***Turk.:*** Moduretic; ***UK:*** Amil-Co; Aridil; Burinex A; Froop Co†; Fru-Co; Frumil; Kalten; Komil; Lasoride†; Moducren†; Moduret; Moduretic; Navispare; ***USA:*** Moduretic; ***Venez.:*** Furdiuren; Moduretic.

Amiodarone *(BAN, USAN, rINN)*

Amiodaron; Amiodarona; Amiodaroni; Amiodaronum; L-3428; 51087-N; SKF-33134-A. 2-Butylbenzofuran-3-yl 4-(2-diethylaminoethoxy)-3,5-di-iodophenyl ketone.

Амиодарон

$C_{25}H_{29}I_2NO_3$ = 645.3.

CAS — 1951-25-3.

ATC — C01BD01.

ATC Vet — QC01BD01.

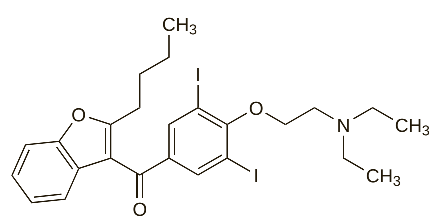

Amiodarone Hydrochloride *(BANM, rINNM)*

Amiodaron Hidroklorür; Amiodarone, chlorhydrate d'; Amiodaron-hidroklorid; Amiodaron-hydrochlorid; Amiodaronhydroklorid; Amiodaroni hydrochloridum; Amiodaronihydrokloridi; Amjodarono hidrochloridas; Hidrocloruro de amiodarona.

Амиодарона Гидрохлорид

$C_{25}H_{29}I_2NO_3$,HCl = 681.8.

CAS — 19774-82-4.

ATC — C01BD01.

ATC Vet — QC01BD01.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Amiodarone Hydrochloride). A white or almost white, fine crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Store at a temperature not exceeding 30°. Protect from light.

Adsorption. Amiodarone is known to be adsorbed by PVC, although the amount of adsorption has varied in different studies. A study[1] using amiodarone hydrochloride 600 micrograms/mL in glucose 5% found that the concentration fell by 10% in 3 hours followed by a steady decrease to 60% of the initial concentration after 5 days when stored in flexible PVC bags at ambient temperature.[1] However, another study[2] using amiodarone hydrochloride 1.8 to 2 mg/mL in glucose 5% found only that the concentration remained 97.3% of the initial value after 24 hours in PVC infusion bags. In the first study, perfusion of the solution through PVC giving sets resulted in the concentration falling to 82% after 15 minutes, whereas the second study found the concentration fell to 95.1% after 1 hour but then returned to the initial value. No loss was noted in either study when glass or rigid PVC containers were used, suggesting that the losses were caused by the plasticiser, di-2-ethylhexylphthalate (DEHP). Amiodarone may also leach out DEHP and other plasticisers, and it has been suggested that bags and tubing containing DEHP should not be used for giving amiodarone in order to minimise patient exposure.

1. Weir SJ, *et al.* Sorption of amiodarone to polyvinyl chloride infusion bags and administration sets. *Am J Hosp Pharm* 1985; **42:** 2679–83.
2. Peters PG, Hayball PJ. A comparative analysis of the loss of amiodarone from small and large volume PVC and non-PVC infusion systems. *Anaesth Intensive Care* 1990; **18:** 241–5.

Incompatibility. Amiodarone injection has been reported to be incompatible with aminophylline,[1] flucloxacillin,[2] heparin,[3] and sodium bicarbonate.[4] A further study[5] reported incompatibility with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin sodium, piperacillin/tazobactam sodium, potassium phosphate, and sodium phosphate. UK licensed product information states that it is incompatible with sodium chloride solutions.

1. Hasegawa GR, Eder JF. Visual compatibility of amiodarone hydrochloride injection with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 1379–80.
2. Taylor A, Lewis R. Amiodarone and injectable drug incompatibility. *Pharm J* 1992; **248:** 533.
3. Cairns CJ. Incompatibility of amiodarone. *Pharm J* 1986; **236:** 68.
4. Korth-Bradley JM. Incompatibility of amiodarone hydrochloride and sodium bicarbonate injections. *Am J Health-Syst Pharm* 1995; **52:** 2340.
5. Chalmers JR, *et al.* Visual compatibility of amiodarone hydrochloride injection with various intravenous drugs. *Am J Health-Syst Pharm* 2001; **58:** 504–6.

Stability. An oral suspension prepared from tablets[1] and containing amiodarone hydrochloride 5 mg/mL was stable for 3 months at 4° and 6 weeks at 25°.

1. Nahata MC. Stability of amiodarone in an oral suspension stored under refrigeration and at room temperature. *Ann Pharmacother* 1997; **31:** 851–2.

Adverse Effects and Treatment

Adverse effects are common with amiodarone. Many are dose-related and reversible with reduction in dose; however, because of its long half-life this can take some time and adverse effects may develop after treatment is stopped.

Adverse cardiovascular effects associated with amiodarone include severe bradycardia, sinus arrest, and conduction disturbances. Severe hypotension may follow intravenous use, particularly (though not exclusively) at rapid infusion rates. Amiodarone may also produce ventricular tachyarrhythmias; torsade de pointes has been reported but appears to be less of a problem with amiodarone than other antiarrhythmics. Rarely, heart failure may be precipitated or aggravated.

Amiodarone reduces the peripheral transformation of thyroxine (T_4) to tri-iodothyronine (T_3) and increases the formation of reverse-T_3. It can affect thyroid function and may induce hypo- or hyperthyroidism.

There have been reports of severe pulmonary toxicity including pulmonary fibrosis and interstitial pneumonitis. These effects are usually reversible on withdrawal of amiodarone but are potentially fatal.

Amiodarone can adversely affect the liver. There may be abnormal liver function tests and cirrhosis or hepatitis; fatalities have been reported.

Prolonged use of amiodarone causes the development of benign yellowish-brown corneal microdeposits in the majority of patients, sometimes associated with coloured haloes of light; these are reversible on stopping therapy. Photosensitivity reactions are also common and more rarely blue-grey discoloration of the skin may occur.

Other adverse effects reported include benign intracranial hypertension, haemolytic or aplastic anaemia, peripheral neuropathy, paraesthesias, myopathy, ataxia, tremor, nausea, vomiting, a metallic taste, nightmares, headaches, sleeplessness, fatigue, and epididymitis.

Thrombophlebitis can occur if amiodarone is injected regularly or infused for prolonged periods into a peripheral vein. Rapid intravenous injection has been associated with anaphylactic shock, hot flushes, sweating, and nausea.

It has been suggested that amiodarone-induced phospholipidosis may explain some of its adverse effects. Amiodarone's iodine content contributes to its thyrotoxicity.

◊ Reviews of the adverse effects of amiodarone.

1. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.
2. Kerin NZ, *et al.* Long-term efficacy and toxicity of high- and low-dose amiodarone regimens. *J Clin Pharmacol* 1989; **29:** 418–23.
3. Perkins MW, *et al.* Intraoperative complications in patients receiving amiodarone: characteristics and risk factors. *DICP Ann Pharmacother* 1989; **23:** 757–63.
4. Vrobel TR, *et al.* A general overview of amiodarone toxicity: its prevention, detection, and management. *Prog Cardiovasc Dis* 1989; **31:** 393–426.
5. Morgan DJR. Adverse reactions profile: amiodarone. *Prescribers' J* 1991; **31:** 104–11.
6. Committee on Safety of Medicines/Medicines Control Agency. Amiodarone (Cordarone X). *Current Problems* 1996; **22:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 21/06/07)
7. Vorperian VR, *et al.* Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997; **30:** 791–8.
8. Bongard V, *et al.* Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. *Am J Ther* 2006; **13:** 315–19.

Effects on electrolyte balance. Hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone has been reported[1-4] in patients taking amiodarone. In each case, the hyponatraemia improved when the dose was reduced or amiodarone was stopped.

1. Odeh M, *et al.* Hyponatremia during therapy with amiodarone. *Arch Intern Med* 1999; **159:** 2599–2600.
2. Ikegami H, *et al.* Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by amiodarone: a report on two cases. *J Cardiovasc Pharmacol Ther* 2002; **7:** 25–8.
3. Patel GP, Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002; **22:** 649–51.
4. Aslam MK, *et al.* Syndrome of inappropriate antidiuretic hormone secretion induced by amiodarone therapy. *Pacing Clin Electrophysiol* 2004; **27:** 831–2.

Effects on the eyes. Slit-lamp examination showed corneal abnormalities in 103 of 105 patients treated with amiodarone for 3 months to 7 years.[1] The most advanced abnormality comprised whorled patterns with uniform granular opacities. The corneal deposits became denser if amiodarone dosage was increased and regressed if dosage was reduced. Ocular symptoms were reported in only 12 patients. Photophobia was reported in 3 patients, while 2 had visual haloes, 1 had blurring of vision, and a further 6 had lid irritation. However, lid irritation was considered a photosensitive skin reaction and blurred vision was probably not due to amiodarone. No patient had any deterioration in visual acuity attributable to amiodarone. In 16 patients amiodarone was withdrawn with complete clearing of corneal abnormalities within 7 months and routine ophthalmological monitoring was considered unnecessary in patients without ocular symptoms. However, optic neuropathy[2-4] and neuritis with visual impairment have been reported with amiodarone and UK licensed product information recommends that annual ophthalmological examinations should be performed.

A sicca syndrome with diminished tear and saliva production has been reported[5] during amiodarone treatment.

1. Ingram DV, *et al.* Ocular changes resulting from therapy with amiodarone. *Br J Ophthalmol* 1982; **66:** 676–9.
2. Feiner LA, *et al.* Optic neuropathy and amiodarone therapy. *Mayo Clin Proc* 1987; **62:** 702–17.
3. Macaluso DC, *et al.* Features of amiodarone-induced optic neuropathy. *Am J Ophthalmol* 1999; **127:** 610–12.
4. Johnson LN, *et al.* The clinical spectrum of amiodarone-associated optic neuropathy. *J Natl Med Assoc* 2004; **96:** 1477–91.
5. Dickinson EJ, Wolman RL. Sicca syndrome associated with amiodarone therapy. *BMJ* 1986; **293:** 510.

Effects on the genitalia. Epididymal swelling and scrotal pain have been reported with amiodarone.[1-3] Time to onset varied from 7 to 71 months after starting treatment, and resolution occurred within 10 weeks despite continuation of amiodarone in some patients. The mechanism of the reaction is unknown, but in 1 patient[2] the concentration of desethylamiodarone in semen was fivefold that in serum.

Brown discoloration of semen and sweat has also been associated with amiodarone therapy.[4]

1. Gasparich JP, *et al.* Non-infectious epididymitis associated with amiodarone therapy. *Lancet* 1984; **ii:** 1211–12.
2. Ward MJ, *et al.* Association of seminal desethylamiodarone concentration and epididymitis with amiodarone treatment. *BMJ* 1988; **296:** 19–20.
3. Sadek I, *et al.* Amiodarone-induced epididymitis: report of a new case and literature review of 12 cases. *Can J Cardiol* 1993; **9:** 833–6.
4. Adams PC, *et al.* Amiodarone in testis and semen. *Lancet* 1985; **i:** 341.

Effects on the heart. Amiodarone has the potential to provoke arrhythmias; it prolongs the QT interval and there have been reports of torsade de pointes. However, a review of the literature[1] indicated that the frequency of proarrhythmic events was low. The risk of torsade de pointes also appears to be lower with amiodarone than with other class III antiarrhythmics, possibly due to additional actions of amiodarone such as blockade of calcium channels.[2]

1. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
2. Brendorp B, *et al.* A benefit-risk assessment of class III antiarrhythmic agents. *Drug Safety* 2002; **25:** 847–65.

Effects on lipid metabolism. Amiodarone increases phospholipid concentrations in tissues and this may be responsible for some of its adverse effects.[1] Although hyperlipidaemia may result from hypothyroidism, amiodarone can also increase serum-cholesterol concentrations independently of any effect on the thyroid.[2,3] The effect on triglyceride concentrations is not clear.[3]

1. Kodavanti UP, Mehendale HM. Cationic amphiphilic drugs and phospholipid storage disorder. *Pharmacol Rev* 1990; **42:** 327–54.
2. Wiersinga WM, *et al.* An increase in plasma cholesterol independent of thyroid function during long-term amiodarone therapy: a dose-dependent relationship. *Ann Intern Med* 1991; **114:** 128–32.
3. Lakhdar AA, *et al.* Long-term amiodarone therapy raises serum cholesterol. *Eur J Clin Pharmacol* 1991; **40:** 477–80.

Effects on the liver. Plasma concentrations of liver enzymes are often increased in patients taking amiodarone but this is usually asymptomatic. However, there have been reports of hepatic injury,[1,2] including hepatitis and cirrhosis, with histological changes resembling alcoholic liver disease.[1] Fatal cirrhosis has been reported, usually in patients receiving high doses or long-term therapy,[3-8] and may develop after stopping amiodarone. However, rapidly progressive fatal hepatic failure has occurred[9] only one month after starting treatment. There have also been reports of severe cholestasis, including a case that was reversible,[10] and another that was fatal, despite amiodarone being stopped.[11] Acute hepatitis occurring within 24 hours of intravenous amiodarone has been reported,[12-14] but in 1 case[13] did not recur with subsequent oral therapy, suggesting that the reaction may have been related to the vehicle used in the intravenous formulation.

1. Simon JB, *et al.* Amiodarone hepatotoxicity simulating alcoholic liver disease. *N Engl J Med* 1984; **311:** 167–72.
2. Babatin M, *et al.* Amiodarone hepatotoxicity. *Curr Vasc Pharmacol* 2008; **6:** 228–36.
3. Lim PK, *et al.* Neuropathy and fatal hepatitis in a patient receiving amiodarone. *BMJ* 1984; **288:** 1638–9.
4. Tordjman K, *et al.* Amiodarone and the liver. *Ann Intern Med* 1985; **102:** 411–12.
5. Rinder HM, *et al.* Amiodarone hepatotoxicity. *N Engl J Med* 1986; **314:** 318–19.
6. Richer M, Robert S. Fatal hepatotoxicity following oral administration of amiodarone. *Ann Pharmacother* 1995; **29:** 582–6.
7. Singhal A, *et al.* Low dose amiodarone causing pseudo-alcoholic cirrhosis. *Age Ageing* 2003; **32:** 224–5.
8. Oikawa H, *et al.* Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. *World J Gastroenterol* 2005; **11:** 5394–7.
9. Lwakatare JM, *et al.* Fatal fulminating liver failure possibly related to amiodarone treatment. *Br J Hosp Med* 1990; **44:** 60–1.
10. Morse RM, *et al.* Amiodarone-induced liver toxicity. *Ann Intern Med* 1988; **109:** 838–40.
11. Chang C-C, *et al.* Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Arch Pathol Lab Med* 1999; **123:** 251–6.
12. Pye M, *et al.* Acute hepatitis after parenteral amiodarone administration. *Br Heart J* 1988; **59:** 690–1.
13. James PR, Hardman SMC. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. *Heart* 1997; **77:** 583–4.
14. Chan AL, *et al.* Fatal amiodarone-induced hepatotoxicity: a case report and literature review. *Int J Clin Pharmacol Ther* 2008; **46:** 96–101.

Effects on the lungs. Pulmonary toxicity is one of the most severe adverse effects associated with amiodarone therapy. Reviews[1] have suggested that it may occur in up to 10% of patients (although the incidence in controlled studies appears to be lower[2]) and fatalities have been reported.[3,4] The onset is usually chronic, and patients often present several months after starting amiodarone with increasing dyspnoea, cough, and pleuritic chest pain; however, the onset may also be more acute, and in one patient[5] occurred within days of starting amiodarone. Acute reactions have also developed in patients undergoing surgery or other procedures;[2,6] two patients with amiodarone pulmonary toxicity died less than 1 hour and 24 hours, respectively after pulmonary angiography.[7] Different forms of toxicity have been reported, including interstitial and alveolar infiltration,[8] fibrosis,[3] and pneumonitis;[9] amiodarone-induced asthma has also been reported.[10] Although there is some evidence that toxicity is dose-related,[8] it has also occurred at low doses,[11] and different mechanisms may be involved;[1,6] some patients have evidence of direct toxicity, while in others[9] an immunological reaction appears to be involved. Most patients recover gradually if amiodarone is stopped, but treatment with corticosteroids may be given if necessary,[1,8] and has been particularly recommended[6] in acute lung injury.

1. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: recognition and pathogenesis. *Chest* 1988; **93:** 1067–75 (part 1) and 1242–8 (part 2).
2. Sunderji R, *et al.* Pulmonary effects of low dose amiodarone: a review of the risks and recommendations for surveillance. *Can J Cardiol* 2000; **16:** 1435–40.
3. Morera J, *et al.* Amiodarone and pulmonary fibrosis. *Eur J Clin Pharmacol* 1983; **24:** 591–3.
4. Committee on Safety of Medicines. Recurrent ventricular tachycardia: adverse drug reactions. *BMJ* 1986; **292:** 50.
5. Goldstein I, *et al.* Very early onset of acute amiodarone pulmonary toxicity presenting with hemoptysis. *Chest* 1997; **111:** 1446–7.
6. Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? *Chest* 2001; **120:** 275–82.
7. Wood DL, *et al.* Amiodarone pulmonary toxicity: report of two cases associated with rapidly progressive fatal adult respiratory distress syndrome after pulmonary angiography. *Mayo Clin Proc* 1985; **60:** 601–3.
8. Marchlinski FE, *et al.* Amiodarone pulmonary toxicity. *Ann Intern Med* 1982; **97:** 839–45.
9. Venet A, *et al.* Five cases of immune-mediated amiodarone pneumonitis. *Lancet* 1984; **i:** 962–3.
10. Yavuzgil O, *et al.* New-onset bronchial asthma induced by low-dose amiodarone. *Ann Pharmacother* 2005; **39:** 385–6.
11. Ott MC, *et al.* Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest* 2003; **123:** 646–51.

Effects on mental state. There have been isolated reports of patients (age range 54 to 80 years) developing delirium within about 4 to 17 days of starting amiodarone therapy.[1-3] Mental status improved on withdrawal of amiodarone.

1. Trohman RG, *et al.* Amiodarone-induced delirium. *Ann Intern Med* 1988; **108:** 68–9.
2. Barry JJ, Franklin K. Amiodarone-induced delirium. *Am J Psychiatry* 1999; **156:** 1119.
3. Athwal H, *et al.* Amiodarone-induced delirium. *Am J Geriatr Psychiatry* 2003; **11:** 696–7.

Effects on the nervous system. Neurological toxicity is a recognised adverse effect of amiodarone. A study[1] in 10 patients treated with amiodarone for more than 2 years found that 3 had evidence of peripheral neuropathy, possibly correlated with high doses and high serum concentrations of amiodarone.

1. Fraser AG, McQueen INF. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 612.

Effects on the pancreas. Pancreatitis has been reported[1] in a patient 4 days after starting amiodarone. Symptoms resolved after withdrawal of the drug but returned on re-exposure.

1. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone. *Lancet* 1997; **350:** 1300.

Effects on the skin and hair. The most common adverse skin reaction associated with amiodarone is photosensitivity. This is a phototoxic rather than a photoallergic reaction[1-3] and the wavelengths responsible extend from the long-wave ultraviolet (UVA) into the visible light range.[1] Affected patients should be advised to wear protective clothing and avoid exposure to sunlight. Topical sunblock preparations, such as those containing zinc or titanium oxides, may reduce the risk of reaction and a reduction in amiodarone dosage may also be useful.[1] Although pyridoxine has been reported[4] to protect against amiodarone-induced photosensitivity, results from a double-blind placebo-controlled study[5] indicated that it may enhance the photosensitivity. Photosensitivity may continue for several weeks after withdrawal of amiodarone due to its extensive distribution, and persistence for longer periods has been reported.[6] There have also been reports[7] of basal cell carcinoma, possibly related to amiodarone-induced photosensitivity.

Blue-grey[2,3,8] and golden-brown[3] pigmentation of light-exposed skin have been reported during long-term amiodarone use. The pigmentation is usually slowly reversible on withdrawing amiodarone but may not completely disappear. The mean concentrations of amiodarone and its desethyl metabolite in light-exposed pigmented skin have been found to be 10 times the concentrations in non-exposed skin.[2] Discoloration of semen and sweat has also been noted (see Effects on the Genitalia, above).

Cutaneous vasculitis,[9,10] exfoliative dermatitis,[11] and fatal toxic epidermal necrolysis[12,13] have been reported. Alopecia[14,15] has been associated with amiodarone but increased hair growth,[3] possibly due to the vasodilator activity of amiodarone, has also been reported. Extravasation of amiodarone injection has caused severe skin necrosis.[16]

1. Ferguson J, *et al.* Prevention of amiodarone-induced photosensitivity. *Lancet* 1984; **ii:** 414.
2. Zachary CB, *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110:** 451–6.
3. Ferguson J, *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113:** 537–49.
4. Kaufmann G. Pyridoxine against amiodarone-induced photosensitivity. *Lancet* 1984; **i:** 51–2.
5. Mulrow JP, *et al.* Pyridoxine and amiodarone-induced photosensitivity. *Ann Intern Med* 1985; **103:** 68–9.
6. Yones SS, *et al.* Persistent severe amiodarone-induced photosensitivity. *Clin Exp Dermatol* 2005; **30:** 500–502.

7. Hall MA, *et al.* Basalioma after amiodarone therapy—not only in Britain. *Br J Dermatol* 2004; **151:** 932–3.
8. Ammoury A, *et al.* Photodistribution of blue-gray hyperpigmentation after amiodarone treatment: molecular characterization of amiodarone in the skin. *Arch Dermatol* 2008; **144:** 92–6.
9. Starke ID, Barbatis C. Cutaneous vasculitis associated with amiodarone therapy. *BMJ* 1985; **291:** 940.
10. Gutierrez R, *et al.* Vasculitis associated with amiodarone treatment. *Ann Pharmacother* 1994; **28:** 537.
11. Moots RJ, Banerjee A. Exfoliative dermatitis after amiodarone treatment. *BMJ* 1988; **296:** 1332–3.
12. Bencini PL, *et al.* Toxic epidermal necrolysis and amiodarone treatment. *Arch Dermatol* 1985; **121:** 838.
13. Yung A, *et al.* Two unusual cases of toxic epidermal necrolysis. *Australas J Dermatol* 2002; **43:** 35–8.
14. Samanta A, *et al.* Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 503.
15. Samuel LM, *et al.* Amiodarone and hair loss. *Postgrad Med J* 1992; **68:** 771.
16. Russell SJ, Saltissi S. Amiodarone induced skin necrosis. *Heart* 2006; **92:** 1395.

Effects on thyroid function. Amiodarone has complex effects on thyroid function[1-3] and, while the majority of euthyroid patients receiving amiodarone remain clinically euthyroid, both hypo- and hyperthyroidism may occur. Amiodarone has direct effects on the thyroid gland, but also alters serum concentrations of thyroid hormones, complicating the interpretation of thyroid function tests. Use of amiodarone results in a reduction of the peripheral conversion of thyroxine (T_4) to tri-iodothyronine (T_3) with a resulting increase in T_4, a modest fall in T_3, and an increase in reverse-T_3 concentrations; the basal serum-TSH (thyroid-stimulating hormone; thyrotrophin) concentration rises initially but tends to return to normal after about 3 months of treatment.

The prevalence of clinical hypo- and hyperthyroidism appears to correlate with dietary iodine intake, with hypothyroidism being more common in areas of adequate iodine intake and hyperthyroidism in areas of lower intake; the overall incidence of thyroid disorders has been suggested[2] to be anywhere between 1 to 32%. Although the exact mechanism for the toxicity is not known, amiodarone has a high iodine content (about 75 mg of iodine in each 200-mg tablet) and the large iodine load may affect the thyroid, particularly in patients with an underlying subclinical thyroid defect. Auto-immune mechanisms may also contribute and antithyroid antibodies have been detected during amiodarone therapy. The high iodine load appears to be the main mechanism for hypothyroidism, but for hyperthyroidism two mechanisms may be involved. Type I amiodarone-induced thyrotoxicosis appears to be precipitated by the iodine load, whereas type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that is probably caused by a direct toxic effect on the thyroid gland.

Assessment of thyroid function is recommended in patients before starting amiodarone treatment and periodically during treatment; TSH concentrations should be measured, along with free T_3 and T_4.

Amiodarone-induced hypothyroidism usually presents similarly to other forms of hypothyroidism[1-3] and treatment is with levothyroxine, starting with a low dose and gradually increasing until control is achieved; amiodarone may be continued.

Amiodarone-induced hyperthyroidism is a more complex problem and may be difficult to diagnose and manage.[1-4] Patients may present with classical symptoms such as tachycardia, tremor, weight loss, nervousness, and irritability, but in other cases reappearance of angina, or a worsening of arrhythmia may be the only indication. Amiodarone is usually stopped if clinical hyperthyroidism develops, but may be continued if necessary while the hyperthyroidism is treated.[1-5] Management depends on whether the patient has type I or type II hyperthyroidism. Treatment of type I is usually with the thiourea drugs carbimazole, thiamazole, or propylthiouracil; in resistant cases potassium perchlorate may be used with a thiourea to reduce the thyroid iodine load. Lithium carbonate has been used as an alternative, but its role is not yet established.[1,2] In type II thyrotoxicosis, treatment is usually with corticosteroids, and they may also be used with thioureas where the type is mixed or unclear. Oral cholecystographic contrast media such as iopanoic acid have also been used, but appear to be less effective.[6] Radio-iodine can be used but may not be effective if the uptake of radio-iodine by the thyroid is low due to the iodine load from amiodarone; radio-iodine has also been used[7] to allow amiodarone to be restarted in patients with a history of amiodarone-induced hyperthyroidism. Thyroidectomy may have a role[1-4,8] in the treatment of resistant amiodarone-induced hyperthyroidism.

1. Loh K-C. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000; **76:** 133–40.
2. Martino E, *et al.* The effects of amiodarone on the thyroid. *Endocr Rev* 2001; **22:** 240–54.
3. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med* 2005; **118:** 706–14.
4. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.
5. Uzan L, *et al.* Continuation of amiodarone therapy despite type II amiodarone-induced thyrotoxicosis. *Drug Safety* 2006; **29:** 231–6.
6. Bogazzi F, *et al.* Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab* 2003; **88:** 1999–2002.
7. Hermida J-S, *et al.* Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis. *Am J Med* 2004; **116:** 345–8.
8. Gough IR, Gough J. Surgical management of amiodarone-associated thyrotoxicosis. *Med J Aust* 2002; **176:** 128–9.

Lupus. There have been reports[1-3] of lupus developing in patients treated with amiodarone; the condition improved when amiodarone was stopped.

1. Susano R, *et al.* Amiodarone induced lupus. *Ann Rheum Dis* 1999; **58:** 655–6.
2. Sheikhzadeh A, *et al.* Drug-induced lupus erythematosus by amiodarone. *Arch Intern Med* 2002; **162:** 834–6.
3. Kundu AK. Amiodarone-induced systemic lupus erythematosus. *J Assoc Physicians India* 2003; **51:** 216–17.

Precautions

Amiodarone should not be given to patients with bradycardia, sino-atrial block, AV block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure. It may be used, but with caution, in patients with heart failure. Electrolyte disorders should be corrected before starting treatment. The use of amiodarone should be avoided in patients with iodine sensitivity, or evidence or history of thyroid disorders. Patients taking amiodarone should avoid exposure to sunlight.

Thyroid function should be monitored regularly in order to detect amiodarone-induced hyper- or hypothyroidism. Thyroxine, tri-iodothyronine, and thyrotrophin (thyroid-stimulating hormone; TSH) concentrations should be measured; clinical assessment is important but is unreliable alone. See also Effects on Thyroid Function under Adverse Effects and Treatment, above.

Tests of liver and pulmonary function should also be carried out regularly in patients on long-term therapy. Ophthalmological examinations should be performed annually. Although urinary excretion is not a major route for the elimination of amiodarone or its metabolites, there is a possibility of iodine accumulation in renal impairment.

Intravenous injections of amiodarone should be given slowly: if prolonged or repeated infusions are envisaged, the use of a central venous catheter should be considered.

Some of the contra-indications for amiodarone may not apply when it is given intravenously in emergency situations.

Administration. For the problems of controlling the delivery rate of amiodarone by intravenous infusion, see under Uses and Administration, below.

Breast feeding. Amiodarone is distributed into breast milk[1,2] and significant amounts may be ingested if infants are breast fed. Licensed product information therefore contra-indicates the use of amiodarone during breast feeding, and the American Academy of Pediatrics considers[3] that the use of amiodarone may be of concern due to the risk of hypothyroidism in the infant. In one study,[2] amiodarone was still detectable in breast milk several weeks after amiodarone was stopped, suggesting that caution is still required. However, there has been a report[4] of an infant who was successfully breast fed with close monitoring of thyroid function; the mother stopped amiodarone at delivery.

1. Pitcher D, *et al.* Amiodarone in pregnancy. *Lancet* 1983; **i:** 597–8.
2. Plomp TA, *et al.* Use of amiodarone during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; **43:** 201–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)
4. Hall CM, McCormick KPB. Amiodarone and breast feeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F255–F258.

Porphyria. Amiodarone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy. Each 200-mg tablet of amiodarone contains about 75 mg of iodine. The potential effect of this iodine load on the fetus has limited the use of amiodarone in pregnancy since iodine freely crosses the placenta and may cause thyroid disorders in the fetus. In addition, amiodarone and desethylamiodarone both cross the placenta, with respective concentrations in cord blood at delivery of about 10% and 25% of the maternal plasma concentrations, and direct effects on the fetus are therefore possible. However, a review[1] of 64 reported cases of amiodarone use during pregnancy found no evidence of an increased incidence of fetal malformations; hypothyroidism occurred in 14 neonates (22%), but only 2 had detectable goitre, and 2 neonates had transient hyperthyroidism. Neurodevelopmental follow-up was limited, but mild abnormalities were reported in some cases; this appeared to be independent of thyroid status, suggesting it may have been due to a direct effect of amiodarone.

1. Bartalena L, *et al.* Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001; **24:** 116–30.

Interactions

Amiodarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly drugs that prolong the QT interval such as phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with amiodarone. Amiodarone is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8 and interactions may occur with inhibitors of these enzymes, particularly with inhibitors of CYP3A4 such as HIV-protease inhibitors, cimetidine, and grapefruit juice. Enzyme inducers such as rifampicin and phenytoin may reduce amiodarone concentrations. In addition, amiodarone is an inhibitor of some cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6, resulting in higher plasma concentrations of other drugs metabolised by these enzymes. Examples of these include ciclosporin, clonazepam, digoxin, flecainide, phenytoin, procainamide, quinidine, simvastatin, and warfarin. Amiodarone also inhibits P-glycoprotein and could affect drugs that are P-glycoprotein substrates.

◊ Reviews.

1. Marcus FI. Drug interactions with amiodarone. *Am Heart J* 1983; **106:** 924–30.
2. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.

Agalsidase. For the effect of the use of amiodarone with *agalsidase alfa* or *beta*, see p.2252.

Antibacterials. Palpitations and activation of an implantable cardioverter defibrillator occurred[1] in a woman receiving amiodarone when *rifampicin* was added. Serum concentrations of amiodarone were reduced, probably due to induction of metabolising enzymes by rifampicin.

1. Zarembski DG, *et al.* Impact of rifampin on serum amiodarone concentrations in a patient with congenital heart disease. *Pharmacotherapy* 1999; **19:** 249–51.

Antiepileptics. The interaction between *phenytoin* and amiodarone resulting in increased plasma-phenytoin concentrations is widely recognised (see p.498). However, phenytoin is a hepatic enzyme inducer and has been reported[1] to decrease serum-amiodarone concentrations by 32 and 49% after 1 and 2 weeks of use respectively.

1. Nolan PE, *et al.* Effect of phenytoin on the clinical pharmacokinetics of amiodarone. *J Clin Pharmacol* 1990; **30:** 1112–19.

Antivirals. A potential interaction has been suggested between amiodarone and HIV-protease inhibitors due to inhibition of amiodarone metabolism. Raised serum concentrations of amiodarone have been reported[1] in a patient who received *indinavir* for postexposure prophylaxis; no clinical signs of toxicity occurred.

1. Lohman JJHM, *et al.* Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* 1999; **33:** 645–6.

Grapefruit juice. A study[1] in healthy subjects reported that grapefruit juice decreased the metabolism of amiodarone; the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration of amiodarone were both increased.

1. Libersa CC, *et al.* Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* 2000; **49:** 373–8.

Histamine H_2-antagonists. *Cimetidine* inhibits hepatic metabolism and an increase in the serum-amiodarone concentration has been reported[1] in 8 out of 12 patients given amiodarone and cimetidine.

1. Hogan C, *et al.* Cimetidine-amiodarone interaction. *J Clin Pharmacol* 1988; **28:** 909.

Theophylline. For a report of increased serum-theophylline concentrations and resultant adverse effects in a patient when amiodarone was added to therapy, see Antiarrhythmics, p.1142.

Pharmacokinetics

Amiodarone is absorbed variably and erratically from the gastrointestinal tract; the average bioavailability is about 50%, but varies widely, and both the rate and extent of absorption are increased by food. It is extensively distributed to body tissues and accumulates notably in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen; it has been reported to be about 96% bound to plasma proteins. The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for a month or more. A major metabolite, desethylamiodarone, has antiarrhythmic properties. There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur. Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

After intravenous injection the maximum effect is achieved within 1 to 30 minutes and persists for 1 to 3 hours.

◊ Reviews.

1. Latini R, *et al.* Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet* 1984; **9:** 136–56.
2. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; **72:** 45F–50F.

Uses and Administration

Amiodarone is an antiarrhythmic with mainly class III properties (see p.1153). It is used in the control of ventricular and supraventricular arrhythmias, including arrhythmias associated with Wolff-Parkinson-White syndrome. It has been tried for the prevention of arrhythmias in patients with myocardial infarction or heart failure.

Amiodarone hydrochloride is given orally in initial doses of 200 mg three times daily for a week, then 200 mg twice daily for a week, and then a usual maintenance dosage of 200 mg or less daily, according to response. In the USA, amiodarone is only licensed for ventricular arrhythmias and higher doses are used: loading doses of amiodarone hydrochloride are up to 1.6 g daily for 1 to 3 weeks, followed by 600 to 800 mg daily for a month, then a usual maintenance dose of 400 mg daily. Consideration should be given to potential adverse effects, and patients should be given the minimum effective dose.

Amiodarone hydrochloride may be given intravenously where facilities for close monitoring of cardiac function and resuscitation are available. It is usually given as a dilute solution in glucose 5%. Solutions containing less than 600 micrograms/mL are unstable but high concentrations are irritating to the veins, and solutions containing more than 2 mg/mL should be given via a central catheter; a central catheter is also preferred if repeated or continuous infusion is required. The usual dose is 1 to 1.2 g over 24 hours, given by intermittent or continuous infusion as follows:

- in the UK, an initial infusion of 5 mg/kg in 250 mL of glucose 5% is given over 20 to 120 minutes; the infusion may be repeated if required, up to a total dose of 1.2 g in 24 hours, diluted in up to 500 mL of glucose 5%
- in the USA, an initial dose of 150 mg in 100 mL of glucose 5% is given over 10 minutes, followed by 900 mg in 500 mL of glucose 5% over 24 hours, given at a rate of 1 mg/minute for 6 hours and then 500 micrograms/minute for 18 hours; if necessary the maintenance infusion may be continued at a rate of 500 micrograms/minute using a 1 to 6 mg/mL solution
- In emergencies, amiodarone hydrochloride may be given in doses of 150 to 300 mg in 10 to 20 mL of glucose 5% by slow intravenous injection over a period of not less than 3 minutes; a second injection should not be given until at least 15 minutes after the first

For the use of amiodarone in children, see below.

◊ General references.

1. Goldschlager N, *et al.* Practical guidelines for clinicians who treat patients with amiodarone. *Arch Intern Med* 2000; **160:** 1741–8.
2. Anonymous. Using oral amiodarone safely. *Drug Ther Bull* 2003; **41:** 9–12. Correction. *ibid.*; 40.
3. Siddoway LA. Amiodarone: guidelines for use and monitoring. *Am Fam Physician* 2003; **68:** 2189–96.
4. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007; **298:** 1312–22.

Administration. Addition of amiodarone hydrochloride to an intravenous infusion solution reduces the drop size delivered[1,2] and the reduction in size is greater as the concentration of amiodarone is increased. This resulted[1] in a reduction of about 30% in the expected delivery rate when amiodarone hydrochloride 1.2 g was given in 500 mL of glucose 5%. The reduction in drop size has been attributed to a reduction in surface tension caused by inclusion of Tween 80 (polysorbate 80) in the commercial injection.[1] Allowances should be made for the changes in drop size causing a reduction of the delivery rate of infusions of amiodarone hydrochloride. US licensed product information contra-indicates the use of drop-counter infusion sets and requires the use of a volumetric infusion pump when intravenous amiodarone is given.

1. Capps PA, Robertson AL. Influence of amiodarone injection on the delivery rate of intravenous fluids. *Pharm J* 1985; **234:** 14–15.
2. Chouhan UM, Lynch E. Amiodarone intravenous infusion. *Pharm J* 1985; **235:** 466.

Administration in children. Amiodarone has been used orally and intravenously in infants and children[1-3] although use of the injection is generally contra-indicated in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see Neonates, under Benzyl Alcohol, p.1632) and may cause adverse effects in children up to 3 years old. In the management of cardiac arrhythmias, amiodarone hydrochloride may be given orally in a loading dose of 10 to 20 mg/kg daily (or 500 mg/m^2 daily) for 7 to 10 days, followed by the lowest possible maintenance dose, ranging from 5 to 10 mg/kg daily (or 250 mg/m^2 daily) according to response. It has also been given intravenously in a loading dose of 5 mg/kg given over 20 minutes to 2 hours, followed by a maintenance dose of 10 to 15 mg/kg daily. The *BNFC* suggests intravenous doses of 5 mg/kg given over 30 minutes and repeated every 12 to 24 hours for neonates, and 5 to 10 mg/kg given over 20 minutes to 2 hours and followed by continuous infusion of 300 micrograms/kg per hour (maximum 1.5 mg/kg per hour) for infants and children.

1. Shuler CO, *et al.* Efficacy and safety of amiodarone in infants. *Am Heart J* 1993; **125:** 1430–2.
2. Figa FH, *et al.* Clinical efficacy and safety of intravenous amiodarone in infants and children. *Am J Cardiol* 1994; **74:** 573–7.
3. Saul JP, *et al.* Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation* 2005; **112:** 3470–7.

Advanced cardiac life support. Cardiac arrest should be treated by starting full life support measures (see Advanced Cardiac Life Support, p.1156). Amiodarone may be considered in cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia that is refractory to rapid defibrillation. Although higher doses have been used, guidelines[1-3] now recommend an intravenous dose of 300 mg, with a further dose of 150 mg if necessary; it may be given by intraosseous injection if the intravenous route is not available.[2] In the UK[1] and European guidelines,[3] this may be followed by an infusion of 900 mg over 24 hours. A study[4] in patients with cardiac arrest outside hospital found that amiodarone improved survival to admission, while another study[5] found that it was more effective than lidocaine in this setting. Retrospective studies[6,7] of its use in cardiac arrest occurring in hospital, however, have not found it to be of benefit.

1. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 10/07/07)
2. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112:** (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 10/07/07)
3. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. *Resuscitation* 2005; **67** (suppl 1): S1–S190. Also available at: http://www.erc.edu/index.php/guidelines_download_2005/en/? (accessed 10/07/07)
4. Kudenchuk PJ, *et al.* Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; **341:** 871–8.
5. Dorian P, *et al.* Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; **346:** 884–90. Correction. *ibid.*; **347:** 955.
6. Pollak PT, *et al.* The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. *Can J Cardiol* 2006; **22:** 199–202.
7. Rea RS, *et al.* Comparing intravenous amiodarone or lidocaine, or both, outcomes for inpatients with pulseless ventricular arrhythmias. *Crit Care Med* 2006; **34:** 1617–23.

Cardiac arrhythmias. Amiodarone is an effective drug for the treatment of symptomatic supraventricular and ventricular arrhythmias[1,2] (p.1160); it has a relatively low risk of cardiovascular adverse effects and may be particularly useful in patients with structural heart disease. It is also used to prevent recurrence of both supraventricular and ventricular arrhythmias, although non-cardiac toxicity may limit its long-term use;[2] a small study[3] suggested that short-term use (4 weeks) delayed the recurrence of atrial fibrillation after electrical cardioversion, but the benefits of this approach require confirmation in larger studies. Amiodarone has been used in children (see above), and has been given by various routes to terminate fetal arrhythmias.[4,5]

Perioperative use[6-8] reduces the incidence of atrial fibrillation and other arrhythmias after cardiac surgery. Amiodarone may also have a role in the management of **cardiac arrest** (see Advanced Cardiac Life Support, above); it has been tried for its antiarrhythmic effect in the management of **heart failure** (see below).

Amiodarone has been used for the prevention of sudden cardiac death in patients with asymptomatic ventricular arrhythmias following myocardial infarction, in patients with a history of aborted sudden cardiac death, and in patients with hypertrophic cardiomyopathy or other cardiac disorders that place them at high risk. Although amiodarone may reduce mortality the effect appears to be small,[2,9,10] and early use of high doses after myocardial infarction may be detrimental.[11] For long-term prophylaxis, implantable cardioverter defibrillators are more effective than antiarrhythmic drugs and are usually preferred; amiodarone may have a role as an adjunct to implantable cardioverter defibrillators to prevent frequent shocks,[12] and may also be used in patients who cannot be given an implantable cardioverter defibrillator.

While amiodarone can cause torsade de pointes it appears to do so rarely[13] and patients who have had this form of ventricular tachycardia as a result of other antiarrhythmic therapy have been given amiodarone subsequently without a recurrence.[14]

1. Desai AD, *et al.* The role of intravenous amiodarone in the management of cardiac arrhythmias. *Ann Intern Med* 1997; **127:** 294–303. Correction. *ibid.* 1998; **128:** 505.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; **100:** 2025–34.
3. Boos C, *et al.* A short course of oral amiodarone improves sinus rhythm maintenance post-cardioversion for atrial fibrillation. *Heart* 2004; **90:** 1063–4.
4. Flack NJ, *et al.* Amiodarone given by three routes to terminate fetal atrial flutter associated with severe hydrops. *Obstet Gynecol* 1993; **82:** 714–16.
5. Strasburger JF, *et al.* Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; **109:** 375–9.
6. Aasbo JD, *et al.* Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. *Ann Intern Med* 2005; **143:** 327–36.
7. Mitchell LB, *et al.* Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. *JAMA* 2005; **294:** 3093–3100.
8. Khanderia U, *et al.* Amiodarone for atrial fibrillation following cardiac surgery: development of clinical practice guidelines at a university hospital. *Clin Cardiol* 2008; **31:** 6–10.
9. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
10. Hilleman DE, Bauman JL. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: an evidence-based review. *Pharmacotherapy* 2001; **21:** 556–75.
11. Elizari MV, *et al.* Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. *Eur Heart J* 2000; **21:** 198–205.
12. Connolly SJ, *et al.* Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006; **295:** 165–71.
13. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
14. Mattioni TA, *et al.* Amiodarone in patients with previous drug-mediated torsade de pointes: long-term safety and efficacy. *Ann Intern Med* 1989; **111:** 574–80.

Heart failure. Sudden deaths in patients with severe heart failure (p.1165) have been attributed to ventricular arrhythmias but routine use of antiarrhythmics is not recommended since many have a negative inotropic effect. Amiodarone, which is not a negative inotrope, is usually the drug of choice in patients with heart failure and symptomatic arrhythmias, but its role for prophylaxis is less clear. In the GESICA study (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina)[1] amiodarone appeared to reduce mortality in patients with severe chronic heart failure who were without symptomatic ventricular arrhythmias. The decrease in mortality appeared to be greater than could be expected from antiarrhythmic activity alone. However, in the CHF-STAT study (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure)[2] involving patients with heart failure and premature ventricular contractions, overall survival did not appear to be improved by amiodarone. A meta-analysis[3] including these and 3 further studies concluded that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality. However a further study[4] found that amiodarone had no effect on long-term survival, whereas implantable cardioverter defibrillators reduced mortality by 23%, and a retrospective analysis[5] of a study in patients with heart failure after acute myocardial infarction found that mortality was higher in those taking amiodarone. Although some studies[1,6,7] have suggested that amiodarone may also improve cardiac function, adverse effects limit its use, and it is not currently recommended in heart failure except in patients with symptomatic ventricular arrhythmias.

1. Doval HC, *et al.* Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344:** 493–8.

2. Singh SN, *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; **333:** 77–82.
3. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
4. Bardy GH, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–37.
5. Thomas KL, *et al.* Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J* 2008; **155:** 87–93.
6. Takemura K, *et al.* Low-dose amiodarone for patients with advanced heart failure who are intolerant of beta-blockers. *Circ J* 2002; **66:** 441–4.
7. Choo DC, *et al.* Amiodarone rescue therapy for severe decompensated heart failure initially unsuitable for beta-blockers. *J Cardiovasc Pharmacol Ther* 2003; **8:** 187–92.

Preparations

BP 2008: Amiodarone Intravenous Infusion; Amiodarone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Amiocar; Angoten; Asulblan; Atlansil; Coronax; Coronovo; Miodarona; Miotenk; Ritmocardyl; ***Austral.:*** Aratac; Cardinorm; Cordarone X; Rithmik; ***Austria:*** Sedacoron; ***Belg.:*** Cordarone; ***Braz.:*** Amiobal; Amioron†; Ancoron; Angiodarona; Angyton†; Atlansil; Cardicoron; Cor Mio†; Diodarone; Miocoron; Miodarid; Miodaron; ***Canad.:*** Cordarone; ***Chile:*** Atlansil; Cordarone; Ritmocardyl; ***Cz.:*** Amiohexal; Amiokordin; Cordarone; Ritmopuls; Rivodaron; Sedacoron; ***Denm.:*** Cordan; Cordarone; ***Fin.:*** Cordarone; ***Fr.:*** Corbionax; Cordarone; ***Ger.:*** Amiobeta†; Amiod†; Amiodarex; Amiodura; Amiogamma; Amiohexal; Cordarex; Cornaron; Tachydaron†; ***Gr.:*** Angoron; ***Hong Kong:*** Cordarone; Sedacoron; ***Hung.:*** Amiokordin†; Cordarone; Sedacoron; ***India:*** Aldarone†; Cordarone; Eurythmic; ***Indon.:*** Cordarone; Kendaron; Tiaryt; ***Irl.:*** Cordarone X; ***Israel:*** Amiodacore; Procor; ***Ital.:*** Amiodar; Cordarone; ***Jpn:*** Ancaron; ***Malaysia:*** Aratac; Cordarone; ***Mex.:*** Braxan; Cardiorona†; Cordarone; Forken; Keritmon; Sinarona; ***Neth.:*** Cordarone; ***Norw.:*** Cordarone; ***NZ:*** Aratac; Cordarone X; ***Philipp.:*** Cordarone; ***Pol.:*** Amiokordin; Cordarone; Opacorden; ***Port.:*** Corbionax; Cordarone; Miodrone; ***Rus.:*** Amiokordin (Амиокордин); Cardiodarone (Кардиодарон); Cordarone (Кордарон); Rhythmiodarone (Ритмиодарон); Sedacoron (Седакорон); ***S.Afr.:*** Arycor; Cordarone X; Hexarone; ***Singapore:*** Aratac; Cordarone; ***Spain:*** Trangorex; ***Swed.:*** Cordarone; ***Switz.:*** Amiodar; Cordarone; Escodarone; Rivodarone†; ***Thai.:*** Amdarone; Amidarone 200; Aratac; Cordarone; ***Turk.:*** Cordarone; ***UAE:*** Amirone; ***UK:*** Amyben; Cordarone X; ***USA:*** Cordarone; Pacerone; ***Venez.:*** Arycor†; Coradona; Diarona; Eudarona; Novarona; Trangorex.

Amlodipine Besilate *(BANM, rINNM)*

Amlodipiinibesilaatti; Amlodipin Besilat; Amlodipinbesilat; Amlodipin-besylát; Amlodipin-bezilát; Amlodipine, bésilate d'; Amlodipine Besylate *(USAN)*; Amlodipini besilas; Amlodipino besilatas; Besilato de amlodipino; UK-48340-26; UK-48340-11 (amlodipine maleate). 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate monobenzenesulphonate.

Амлодипина Безилат

$C_{20}H_{25}ClN_2O_5,C_6H_6O_3S = 567.1.$

CAS — 88150-42-9 (amlodipine); 111470-99-6 (amlodipine besilate); 88150-47-4 (amlodipine maleate).

ATC — C08CA01.

ATC Vet — QC08CA01.

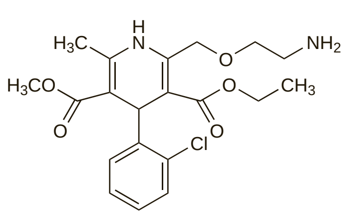

(amlodipine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Amlodipine Besilate). A white or almost white powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in dehydrated alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Amlodipine Besylate). A white or almost white powder. Slightly soluble in water and isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Incidence of adverse effects. Of 1091 patients prescribed amlodipine for hypertension, 128 (11.7%) stopped the drug because of adverse effects.[1] The commonest adverse effects were ankle oedema, flushing, headache, skin rash, and fatigue.

1. Benson E, Webster J. The tolerability of amlodipine in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 578P–579P.

Heart failure. Calcium-channel blockers are normally avoided in patients with heart failure but amlodipine has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure receiving the drug.[1] Therefore, it may be a suitable treatment for angina pectoris or hypertension in such patients. However, a study[2] in hypertensive patients (ALLHAT) found that amlodipine was less effective than the diuretic chlortalidone in preventing the development of heart failure.

1. Packer M, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996; **335:** 1107–14.
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.

Porphyria. Although there have been reports[1,2] of the successful use of amlodipine in patients with porphyria, acute exacerbation has also occurred.[3]

1. Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. *Br J Clin Pharmacol* 1997; **43:** 339–40.
2. Cinemre H, *et al.* Safety of amlodipine use in patients with acute intermittent porphyria. *Br J Clin Pharmacol* 2007; **64:** 246–7.
3. Kepple A, Cernek PK. Amlodipine-induced acute intermittent porphyria exacerbation. *Ann Pharmacother* 1997; **31:** 253.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Amlodipine is well absorbed after oral doses with peak blood concentrations occurring after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 97.5% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolised in the liver; metabolites are mostly excreted in urine together with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

◊ General reviews.

1. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992; **22:** 22–31.
2. Kang D, *et al.* Population analyses of amlodipine in patients living in the community and patients living in nursing homes. *Clin Pharmacol Ther* 2006; **79:** 114–24.

Absorption. Results of studies involving 24 healthy subjects indicated that absorption of amlodipine from a capsule was equivalent to that from a solution, suggesting that the slow transfer of amlodipine into the blood is a property of the drug not of the dosage form; it was also shown that absorption was not affected by food.[1]

1. Faulkner JK, *et al.* Absorption of amlodipine unaffected by food: solid dose equivalent to solution dose. *Arzneimittelforschung* 1989; **39:** 799–801.

Metabolism. The metabolites of amlodipine have been characterised in *animals* and in human subjects.[1] Metabolism of amlodipine is complex and extensive, and in common with other dihydropyridines oxidation to the pyridine analogue represents a major step. About 5% of a dose was recovered from urine as unchanged amlodipine.

1. Beresford AP, *et al.* Biotransformation of amlodipine. *Arzneimittelforschung* 1989; **39:** 201–9.

Uses and Administration

Amlodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Amlodipine is given orally as the besilate, but doses are usually expressed in terms of the base; amlodipine besilate 6.9 mg is equivalent to about 5 mg of amlodipine. The camsilate, maleate, and mesilate are also used.

In hypertension the usual initial dose is 5 mg once daily, increased, if necessary, to 10 mg once daily. Similar doses are given in the treatment of stable angina and Prinzmetal's angina. Lower initial doses may be used in elderly patients and those with hepatic impairment (see below).

The (*S*)-isomer of amlodipine besilate has also been used.

◊ Reviews.

1. Murdoch D, Heel RC. Amlodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1991; **41:** 478–505.
2. Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs* 1995; **50:** 560–86.

Administration in children. Amlodipine has been used to reduce blood pressure in children and adolescents with hypertension. In a study[1] in 28 children aged 3 to 19 years, amlodipine 5 to 10 mg (about 200 to 300 micrograms/kg) once daily significantly reduced blood pressure; therapy was withdrawn in 5 patients due to oedema and flushing. Another study[2] in 268 children aged 6 to 16 years found that amlodipine in a dose of 2.5 or 5 mg (ranging from about 20 to 340 micrograms/kg) once daily was well tolerated; doses above 60 micrograms/kg daily significantly reduced blood pressure. Younger children may need higher doses than older children. In a study[3] in 21 patients aged 6 to 17 years, the mean dose required in children under 13 years was 290 micrograms/kg daily compared with 160 micrograms/kg daily for children 13 years and over. Another study[4] in 55 children aged 13 months to 20 years reported similar mean doses, but also found that many of the younger children needed twice daily dosing. Amlodipine was well tolerated in both studies. The need for a higher dose was supported by a pharmacokinetic study,[5] which found that amlodipine clearance was increased in younger children.

1. Pfammatter JP, *et al.* Amlodipine once-daily in systemic hypertension. *Eur J Pediatr* 1998; **157:** 618–21.
2. Flynn JT, *et al.* A randomized, placebo-controlled trial of amlodipine in children with hypertension. *J Pediatr* 2004; **145:** 353–9.
3. Tallian KB, *et al.* Efficacy of amlodipine in pediatric patients with hypertension. *Pediatr Nephrol* 1999; **13:** 304–10.
4. Flynn JT, *et al.* Treatment of hypertensive children with amlodipine. *Am J Hypertens* 2000; **13:** 1061–6.
5. Flynn JT, *et al.* Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; **46:** 905–16.

Administration in hepatic impairment. The clearance of amlodipine is reduced in patients with hepatic impairment and lower doses should be considered; an initial dose of 2.5 mg once daily has been recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Abloom; Amloc; Amlodine; Amlotens; Amze; Anexa; Angiofilina; Angipec; Arteriosan; Calpres; Carboplex; Cardiorex; Cardivas; Coroval; Dronalden; Hipertensal; Ilduc; Mitokor; Nexotensil; Nikor; Pelmec; Sinop†; Terloc; Tervalon; Zundic; ***Austral.:*** Norvasc; Perivasc; ***Austria:*** Amlodanorm; Amloreg; Norvasc; ***Belg.:*** Amlogal; Amlor; ***Braz.:*** Amilopil; Amlocor; Amloprax†; Amlovasc†; Anlo; Anlodibal; Cordarex; Cordipina; Lodipen†; Lodipil; Nemodine†; Nicord; Norvasc; Pressat; Roxflan; Tensaliv; Tensodin; ***Canad.:*** Norvasc; ***Chile:*** Amdipin; Amloc; Avirin†; Norvasc; Presilam; Presovasc; Terloc; ***Cz.:*** Afiten; Agen; Alozur; Amilostad; Amlodigamma; Amlopp; Amlotenz; Amlozek; Apo-Amlo; Cardilopin; Genam; Hipres; Normodipine; Norvasc; Orcal; Recotens; Tensigal; Torella; Zeppeliton; Zorem; Zufalm; ***Denm.:*** Norvasc; ***Fin.:*** Norvasc; ***Fr.:*** Amlor; ***Ger.:*** Amlo Tad; Amlo Wolff; Amlo-corax; Amlo-Isis; Amlo-Q; Amlobeta; Amlocard; Amloclair; Amlodigamma; Amlodoc; AmloLich; Amparo; Norvasc; ***Gr.:*** Aggovask; Amlibon; Amlodil; Amlopen; Amlopress; Amloretin; Amlosilat; Amlotens; Amodipan; Baruden; Dafor; Evangio; Flodil; Hypertel; Kaprin; Lodipin; Naxuril; Nolvac; Nordex; Norfan; Normodin; Norvasc; Precardin; Ramlet; Rovoxid; Vascodin; ***Hong Kong:*** Norvasc; ***Hung.:*** Agen; Amlodep; Amlodigamma; Amlodowin; Amlozek; Cardilopin; Normodipine; Norvasc; Tenox; ***India:*** Amdepin; Amlodac; Amlogard; Amlopres; Amlosafe†; Amlostat; Amlotrust; Calchek; Lama; Myodura; S-Amlip; ***Indon.:*** Amdixal; Norvask; Tensivask; ***Irl.:*** Amlid; Amlist; Amlode; Istin; Myostin; ***Israel:*** Amlow; Norvasc; ***Ital.:*** Antacal; Monopina; Norvasc; ***Jpn:*** Amlodin; Norvasc; ***Malaysia:*** Nordipine; Norvasc; Sunvasc; Vamlo; ***Mex.:*** Amlibon; Nexus; Norvas; Oralcam; ***Neth.:*** Amlo; Amlonor; Amlostad; Amlosyl; Norvasc; ***Norw.:*** Norvasc; ***NZ:*** Calvasc; Norvasc; ***Philipp.:*** Norvasc; ***Pol.:*** Aldan; Amlopin; Amloratio; Amlozek; Apo-Amlo; Cardilopin; Normodipine; Norvasc; Suplar; Tenox; Vilpin; ***Port.:*** Cardionox; Corpress†; Famonor; Ibotec; Mibral; Monodin; Nivelcor†; Norvasc; Tiflodipine; ***Rus.:*** Akridipin (Акридипин); Amlodil (Амлодил); Amlotop (Амлотоп); Amlovas (Амловас); Calchek (Калчек); Cardilopin (Кардилопин); Corvadil (Корвадил); Normodipine (Нормодипин); Norvasc (Норваск); Omelar Cardio (Омелар Кардио); ***S.Afr.:*** Amlate; Amloc; Amlosyn; Norvasc; ***Singapore:*** Norvasc; ***Spain:*** Amlodeq†; Amlor; Amlotabs†; Astudal; Kerniox; Norvas; Presdeten; ***Swed.:*** Norvasc; ***Switz.:*** Alzar; Amlo eco; Amlopin; Amlovasc; Norvasc; ***Thai.:*** Amlopine; Deten; Lovas; Norvasc; ***Turk.:*** Amlodis; Amlokard; Amlovas; Biocard; Dilopin; Monovas; Nipidol; Norlopin; Normopres; Norvadin; Norvasc; Vasocard; Vazkor; ***UK:*** Amlostin; Istin; ***USA:*** Amvaz†; Norvasc; ***Venez.:*** Amlibon; Amlip; Amloc†; Amlopin; Amlovas; Angiovan; Dilotex; Lodipin; Nilan†; Norvasc; Pinam; Stamlo†; Unidoscor†.

Multi-ingredient: ***Arg.:*** Adrebloc†; Amlopril; Amzepril†; Arteriosan Plus; Coroval B; Diovan A; Diovan Triple; Hipertensal Combi; Ilduc Duo; Lipoarteriosan; Pelmec Duo; Terloc Duo; ***Austral.:*** Caduet; ***Braz.:*** Atmos; Betalor; Caduet; Diovan Amlo; Naprix A; Sinergen; ***Chile:*** Caduet; ***Cz.:*** Caduet; Copalia; Dafiro; Exforge; Imprida; ***Fr.:*** Caduet; ***Gr.:*** Copalia; Dafiro; Exforge; ***Hung.:*** Caduet; Lisonorm; ***India:*** Alsartan-AM; Amace-BP; Amdepin-AT; Amlopres AT; Amlopres L; Amlopres Z; Amlosafe-AT†; Amlosafe-LS†; Amlostat-AT; Biopril-AM†; Calchek L; Dilvas AM; Tenochek; Tenolol-AM; ***Malaysia:*** Caduet; ***Mex.:*** Amlidual; Caduet; ***Philipp.:*** Envacar; ***Port.:*** Caduet; Copalia; Dafiro; Imprida; ***Rus.:*** Ampliton (Амплитон); Tenochek (Теночек); ***S.Afr.:*** Caduet; ***Singapore:*** Caduet; ***UK:*** Exforge; ***USA:*** Azor; Caduet; Exforge; Lotrel; ***Venez.:*** Amlibon B; Caduet; Diovan/Amlibon; Duopres.

Amosulalol Hydrochloride *(rINNM)* ⊗

Amosulalol, Chlorhydrate d'; Amosulaloli Hydrochloridum; Hidrocloruro de amosulalol; YM-09538. (±)-5-(1-Hydroxy-2-{[2-(*o*-methoxyphenoxy)ethyl]amino}ethyl)-*o*-toluenesulphonamide hydrochloride.

Амосулалола Гидрохлорид

$C_{18}H_{24}N_2O_5S,HCl = 416.9.$

CAS — 85320-68-9 (amosulalol); 70958-86-0 (amosulalol hydrochloride); 93633-92-2 (amosulalol hydrochloride).

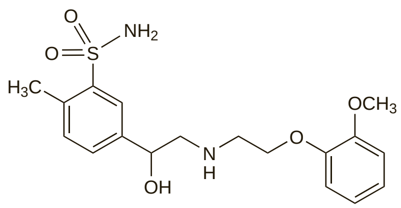

(amosulalol)

Profile

Amosulalol is a beta blocker (p.1225); it also has alpha-blocking activity. It has been given orally as the hydrochloride in the management of hypertension.

Amrinone *(BAN, rINN)*

Amrinon; Amrinona; Amrinoni; Amrinonum; Inamrinone *(USAN)*; Win-40680. 5-Amino-3,4′-bipyridyl-6(1*H*)-one.

Амринон

$C_{10}H_9N_3O = 187.2.$

CAS — 60719-84-8.

ATC — C01CE01.

ATC Vet — QC01CE01.

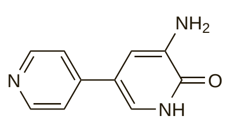

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Inamrinone). A pale yellow to tan powder; odourless or with a faint odour. Practically insoluble in water and in chloroform; slightly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Amrinone Lactate *(BANM, rINNM)*

Amrinone, Lactate d'; Amrinoni Lactas; Lactato de amrinona.

Амринона Лактат

$C_{10}H_9N_3O,C_3H_6O_3 = 277.3.$

CAS — 75898-90-7.

ATC — C01CE01.

ATC Vet — QC01CE01.

Incompatibility. The manufacturer has reported that amrinone lactate injection is physically incompatible with glucose-containing solutions and with furosemide.

Precipitation occurred[1] when amrinone was mixed with sodium bicarbonate injection, probably because of the reduced solubility of amrinone in alkaline solutions.

1. Riley CM, Junkin P. Stability of amrinone and digoxin, procainamide hydrochloride, propranolol hydrochloride, sodium bicarbonate, potassium chloride, or verapamil hydrochloride in intravenous admixtures. *Am J Hosp Pharm* 1991; **48:** 1245–52.

Adverse Effects

Amrinone produces gastrointestinal disturbances that may necessitate withdrawal of treatment. It produces dose-dependent thrombocytopenia. Hepatotoxicity may occur, particularly during long-term oral treatment. Hypotension and cardiac arrhythmias have been reported. Other adverse effects include headache, fever, chest pain, nail discoloration, and decreased tear production. Hypersensitivity reactions including myositis and vasculitis have been reported. Local pain and burning may occur at the site of intravenous injection.

The adverse effects associated with oral use have made this route unacceptable and amrinone is now only given intravenously for short-term use. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can increase the mortality rate.

◊ References.

1. Wynne J, *et al*. Oral amrinone in refractory congestive heart failure. *Am J Cardiol* 1980; **45:** 1245–9.
2. Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; **49:** 447–51.
3. Wilmshurst PT, *et al.* The effects of amrinone on platelet count, survival and function in patients with congestive cardiac failure. *Br J Clin Pharmacol* 1984; **17:** 317–24.
4. Silverman BD, *et al.* Clinical effects and side effects of amrinone: a study of 24 patients with chronic congestive heart failure. *Arch Intern Med* 1985; **145:** 825–9.
5. Webster MWI, Sharpe DN. Adverse effects associated with the newer inotropic agents. *Med Toxicol* 1986; **1:** 335–42.
6. Mattingly PM, *et al.* Pancytopenia secondary to short-term, high-dose intravenous infusion of amrinone. *DICP Ann Pharmacother* 1990; **24:** 1172–4.
7. Ross MP, *et al.* Amrinone-associated thrombocytopenia: pharmacokinetic analysis. *Clin Pharmacol Ther* 1993; **53:** 661–7.

Precautions

Amrinone should be used with caution in severe obstructive aortic or pulmonary valvular disease or in hypertrophic cardiomyopathy. Blood pressure and heart rate should be monitored during parenteral use. The fluid and electrolyte balance should be maintained. Platelet counts and liver function should also be monitored.

Pharmacokinetics

Although amrinone is rapidly absorbed from the gastrointestinal tract it is no longer given orally. The half-life is variable and after intravenous injection has been reported to be about 4 hours in healthy subjects and about 6 hours in patients with heart failure. Binding to plasma proteins is generally low. Amrinone is partially metabolised in the liver and excreted in the urine as unchanged drug and metabolites; up to about 40% is excreted as unchanged drug after intravenous use. About 18% of an oral dose has been detected in the faeces over 72 hours.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).

Infants. For reference to the pharmacokinetics of amrinone in neonates and infants, see under Uses and Administration, below.

Renal impairment. Studies in a child with multi-organ failure and anuria[1] and in 3 adults with anuria after cardiac surgery[2] have shown that amrinone is effectively removed by haemofiltration but clearance varies widely between patients. Non-renal clearance may also be altered in critically ill patients and monitoring of plasma-amrinone concentrations has been suggested.[2]

1. Lawless S, *et al.* Effect of continuous arteriovenous haemofiltration on pharmacokinetics of amrinone. *Clin Pharmacokinet* 1993; **25:** 80–2.
2. Hellinger A, *et al.* Elimination of amrinone during continuous veno-venous haemofiltration after cardiac surgery. *Eur J Clin Pharmacol* 1995; **48:** 57–9.

Uses and Administration

Amrinone is a phosphodiesterase inhibitor that has vasodilator and positive inotropic properties. It is used in the management of heart failure (p.1165). Although amrinone is effective when given orally this route has been associated with an unacceptable level of adverse effects, and the drug is now only given intravenously for the short-term management of heart failure unresponsive to other forms of therapy.

The mode of action is not fully known, but appears to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increased contractile force in cardiac muscle.

Amrinone is given intravenously as the lactate and doses are expressed in terms of the base. Amrinone lactate 1.48 mg is equivalent to about 1 mg of amrinone. The initial loading dose is 750 micrograms/kg by slow intravenous injection over 2 to 3 minutes. This is followed by a maintenance infusion, although the loading dose may be repeated after 30 minutes if necessary. Maintenance doses are 5 to 10 micrograms/kg per minute by infusion to a usual maximum total dose (including loading doses) of 10 mg/kg in 24 hours. Doses of up to 18 mg/kg daily have been used for short periods in a limited number of patients.

Administration in infants. Pharmacokinetic and pharmacodynamic studies[1,2] in infants undergoing cardiac surgery indicated that the dose needed for infants to achieve a plasma-amrinone concentration of 2 to 7 micrograms/mL was an initial intravenous bolus of 3 to 4.5 mg/kg in divided doses followed by a continuous infusion of 10 micrograms/kg per minute. Neonates appear to eliminate amrinone more slowly than infants, possibly due to their immature renal function;[1,3] it was therefore suggested[1] that neonates should receive a similar bolus dose to infants, followed by a continuous infusion of 3 to 5 micrograms/kg per minute. In a further study[4] that included mainly infants and older children, amrinone clearance and volume of distribution varied widely between patients but did not appear to be related to age.

1. Lawless S, *et al.* Amrinone in neonates and infants after cardiac surgery. *Crit Care Med* 1989; **17:** 751–4.
2. Lawless ST, *et al.* The acute pharmacokinetics and pharmacodynamics of amrinone in pediatric patients. *J Clin Pharmacol* 1991; **31:** 800–3.
3. Laitinen P, *et al.* Pharmacokinetics of amrinone in neonates and infants. *J Cardiothorac Vasc Anesth* 2000; **14:** 378–82.
4. Allen-Webb EM, *et al.* Age-related amrinone pharmacokinetics in a pediatric population. *Crit Care Med* 1994; **22:** 1016–24.

Preparations

USP 31: Inamrinone Injection.

Proprietary Preparations (details are given in Part 3)

Cz.: Wincoram†; ***Ger.:*** Wincoram†; ***India:*** Amicor; Cardiotone†; ***Israel:*** Inocor; ***Ital.:*** Inocor†; ***Jpn:*** Amcoral†; Cartonic†; ***Malaysia:*** Inocor†; ***Mex.:*** Inocor; ***Port.:*** Inocor†; ***Spain:*** Wincoram†; ***USA:*** Inocor.

Ancrod *(BAN, USAN, rINN)*

Ancrodum.

Анкрод

CAS — 9046-56-4.

ATC — B01AD09.

ATC Vet — QB01AD09.

Description. Ancrod is an enzyme obtained from the venom of the Malayan pit-viper (*Calloselasma rhodostoma = Agkistrodon rhodostoma*).

Adverse Effects and Treatment

Haemorrhage may occur during treatment with ancrod and usually responds to its withdrawal. If haemorrhage is severe, cryoprecipitate can be used to raise plasma fibrinogen concentrations; plasma may be used if cryoprecipitate is not available. An antivenom has been used to neutralise ancrod.

Skin rash, transient chills, and fever have been reported with the use of ancrod.

Precautions

As for Heparin, p.1303.

Ancrod should not be given to patients with severe infections or disseminated intravascular coagulation. It should be used cautiously in patients with cardiovascular disorders that may be complicated by defibrination. It is very important that when ancrod is given by intravenous infusion it should be given slowly to prevent the formation of large amounts of unstable fibrin.

Ancrod is not recommended during pregnancy; high doses in *animals* have caused placental haemorrhage and fetal death.

Interactions

Ancrod should not be used with antifibrinolytics such as aminocaproic acid or with plasma volume expanders such as dextrans.

Uses and Administration

Ancrod is an anticoagulant. It reduces the blood concentration of fibrinogen by the cleavage of microparticles of fibrin which are rapidly removed from the circulation by fibrinolysis or phagocytosis. It reduces blood viscosity but has no effect on established thrombi. Haemostatic concentrations of fibrinogen are normally restored in about 12 hours and normal concentrations in 10 to 20 days.

Ancrod has been used in the treatment of thromboembolic disorders, particularly in deep-vein thrombosis and to prevent thrombosis after surgery in patients requiring anticoagulation but who have developed heparin-induced thrombocytopenia or thrombosis (see Venous Thromboembolism, p.1189). It is under investigation in the treatment of ischaemic stroke and has also been given for priapism.

◊ References.

1. Sherman DG, *et al.* Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *JAMA* 2000; **283:** 2395–2403.
2. Hennerici MG, *et al.* ESTAT investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet* 2006; **368:** 1871–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Arwin.

Angiotensinamide *(BAN, rINN)*

Angiotensiiniamidi; Angiotensin Amide *(USAN)*; Angiotensinamid; Angiotensinamida; Angiotensinamidum; NSC-107678. Asn-Arg-Val-Tyr-Val-His-Pro-Phe; [1-Asparagine,5-valine]angiotensin II.

Ангиотенсинамид

$C_{49}H_{70}N_{14}O_{11}$ = 1031.2.
CAS — 11128-99-7 (angiotensin II); 53-73-6 (angiotensinamide).
ATC — C01CX06.
ATC Vet — QC01CX06.

Profile

Angiotensinamide is a vasopressor related to the naturally occurring peptide angiotensin II. It increases the peripheral resistance mainly in cutaneous, splanchnic, and renal blood vessels. The increased blood pressure is accompanied by a reflex reduction in heart rate, and cardiac output may also be reduced.

Angiotensinamide has been used in the treatment of hypotension associated with shock. It has also been given in the management of overdosage of ACE inhibitors, when conventional therapy has been ineffective.

Angiotensinamide should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment as a hypertensive crisis may be precipitated.

◊ References.

1. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
2. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
3. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; **82:** 388–9.

Anisindione *(BAN, rINN)*

Anisindiona; Anisindionum. 2-(4-Methoxyphenyl)indan-1,3-dione.

Анизиндион

$C_{16}H_{12}O_3$ = 252.3.
CAS — 117-37-3.

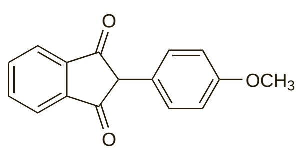

Profile

Anisindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1425). It has been used in the management of thromboembolic disorders (p.1187) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p.1369), its use is limited.

Use of anisindione may colour the urine pink or orange.

Anistreplase *(BAN, USAN, rINN)*

Anisoylated Plasminogen Streptokinase Activator Complex; Anistreplaasi; Anistreplas; Anistreplasa; Anistreplasum; APSAC; BRL-26921. *p*-Anisoylated (human) lys-plasminogen streptokinase activator complex (1:1).

Анистреплаза

CAS — 81669-57-0.
ATC — B01AD03.
ATC Vet — QB01AD03.

Storage. The manufacturer recommends that anistreplase should be stored at 2° to 8°.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Like streptokinase, anistreplase appears to be antigenic and may be neutralised by streptokinase antibodies.

Back pain. For references to back pain associated with anistreplase infusion, see under Streptokinase, p.1402.

Interactions

As for Streptokinase, p.1404.

Pharmacokinetics

Anistreplase is reported to be cleared from plasma at about half the rate of streptokinase and has a fibrinolytic half-life of about 90 minutes. It is metabolised to the plasminogen-streptokinase complex at a steady rate.

◊ References.

1. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Uses and Administration

Anistreplase is a thrombolytic drug. It consists of a complex of the lys-form of plasminogen and streptokinase with the addition of a *p*-anisoyl group. After intravenous injection the anisoyl group undergoes deacylation at a steady rate to release the active complex which converts plasminogen to plasmin, a proteolytic enzyme that has fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045.

Anistreplase is used similarly to streptokinase (p.1404) in the treatment of acute myocardial infarction (p.1175). It is given as a single intravenous injection in a dose of 30 units over 5 minutes, as soon as possible after the onset of symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Eminase; ***Belg.:*** Eminase†; ***Ger.:*** Eminase; ***Neth.:*** Eminase†.

Multi-ingredient: ***Israel:*** Eminase†.

Aprindine Hydrochloride *(BANM, USAN, rINNM)*

AC-1802; Aprindine, Chlorhydrate d'; Aprindini Hydrochloridum; Compound 83846; Compound 99170 (aprindine); Hidrocloruro de aprindina. *N*-(3-Diethylaminopropyl)-*N*-indan-2-ylaniline hydrochloride; *NN*-Diethyl-*N′*-indan-2-yl-*N′*-phenyltrimethylenediamine hydrochloride.

Априндина Гидрохлорид

$C_{22}H_{30}N_2$,HCl = 358.9.
CAS — 37640-71-4 (aprindine); 33237-74-0 (aprindine hydrochloride).
ATC — C01BB04.
ATC Vet — QC01BB04.

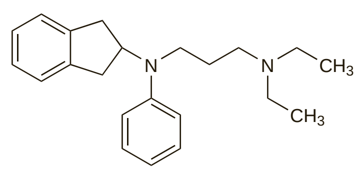

(aprindine)

Adverse Effects and Precautions

Adverse effects of aprindine are usually dose-related and most commonly affect the CNS. They include tremor, vertigo, ataxia, diplopia, memory impairment, hallucinations, and convulsions. Gastrointestinal effects include nausea, vomiting, and bloating. There have been reports of agranulocytosis, including fatalities. Hepatitis and cholestatic jaundice have occasionally been reported; blood and liver function tests should be performed during treatment.

Aprindine is contra-indicated in patients with advanced heart failure or severe conduction disturbances. Some licensed product information has recommended that aprindine should not be used in patients with parkinsonism or convulsive disorders. It should be used with caution in patients with bradycardia, hypotension, and hepatic or renal impairment.

Interactions

Antiarrhythmics. Steady-state plasma-aprindine concentrations increased in 2 patients after starting *amiodarone* and this coincided with the appearance of adverse effects.[1]

1. Southworth W, *et al*. Possible amiodarone-aprindine interaction. *Am Heart J* 1982; **104:** 323.

Pharmacokinetics

Aprindine is readily absorbed from the gastrointestinal tract. It has a long plasma half-life, usually between 20 and 27 hours, and is about 85 to 95% bound to plasma proteins. It is excreted in the urine and the bile.

Uses and Administration

Aprindine is a class Ib antiarrhythmic (p.1153) used in the management of ventricular and supraventricular arrhythmias (p.1160).

Aprindine is given as the hydrochloride in usual oral maintenance doses of 50 to 100 mg daily. Initial doses of 150 to 200 mg daily, in divided doses, may be given under strict surveillance for the first 2 to 3 days; up to 300 mg may be given on the first day if necessary. Therapy should be monitored by ECG during initial stabilisation of the dose and intermittently thereafter. Aprindine has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Fiboran†; ***Fr.:*** Fiboran†; ***Neth.:*** Fiboran.

Aranidipine *(rINN)*

Aranidipino; Aranidipinum; MPC-1304. (±)-Acetonyl methyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.

Аранидипин

$C_{19}H_{20}N_2O_7$ = 388.4.
CAS — 86780-90-7.

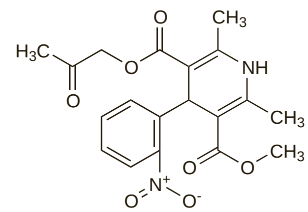

Profile

Aranidipine is a dihydropyridine calcium-channel blocker used in the management of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Bec; Flaspas†; Sapresta.

Arbutamine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Arbutamine, Chlorhydrate d'; Arbutamini Hydrochloridum; GP-2-121-3 (arbutamine or arbutamine hydrochloride); Hidrocloruro de arbutamina. (*R*)-4-(1-Hydroxy-2-[4-(4-hydroxyphenyl)-butylamino]ethyl)pyrocatechol hydrochloride.

Арбутамина Гидрохлорид

$C_{18}H_{23}NO_4$,HCl = 353.8.
CAS — 128470-16-6 (arbutamine); 125251-66-3 (arbutamine hydrochloride).
ATC — C01CA22.
ATC Vet — QC01CA22.

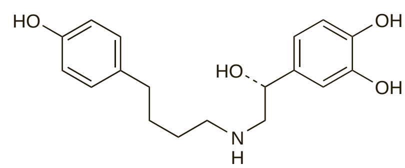

(arbutamine)

Profile

Arbutamine hydrochloride is a sympathomimetic (p.1407) with beta-agonist properties and like dobutamine (p.1272) has been used for cardiac stress testing in patients unable to exercise.

◊ References.

1. Anonymous. Arbutamine for stress testing. *Med Lett Drugs Ther* 1998; **40:** 19–20.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Genesa†.

Ardeparin Sodium *(USAN, rINN)*

Ardeparina sódica; Ardéparine Sodique; Ardeparinum Natricum; Wy-90493-RD.

Ардепарин Натрий

CAS — 9041-08-1.

Description. Ardeparin sodium is prepared by peroxide degradation of heparin obtained from the intestinal mucosa of pigs. The end chain structure appears to be the same as the starting material with no unusual sugar residues present. The molecular weight of 98% of the components is between 2000 and 15 000 and the average molecular weight is about 5500 to 6500. The degree of sulfation is about 2.7 per disaccharide unit.

Profile

Ardeparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity that has been used for the prevention of postoperative venous thromboembolism.

Argatroban *(BAN, USAN, rINN)*

Argatrobanum; Argipidine; DK-7419; GN-1600; MCI-9038; MD-805. (2*R*,4*R*)-4-Methyl-1-[(*S*)-N^2-{[(*RS*)-1,2,3,4-tetrahydro-3-methyl-8-quinolyl]sulfonyl}arginyl]pipecolic acid.

Аргатробан

$C_{23}H_{36}N_6O_5S$ = 508.6.

CAS — 74863-84-6 (anhydrous argatroban); 141396-28-3 (argatroban monohydrate).

ATC — B01AE03.

ATC Vet — QB01AE03.

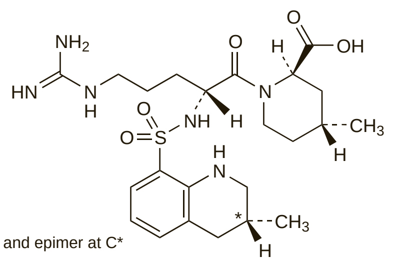

and epimer at C*

Incompatibility. Trace evidence of precipitation was seen immediately after mixing solutions of argatroban and amiodarone.[1] No visual incompatibility was noted for solutions of argatroban with furosemide, nesiritide, sodium nitroprusside, or a total parenteral nutrition solution, but changes in pH occurred over 24 hours, suggesting such mixtures should be used with caution.[1]

1. Honisko ME, *et al.* Compatibility of argatroban with selected cardiovascular agents. *Am J Health-Syst Pharm* 2004; **61:** 2415–18.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

If argatroban and warfarin are given together there is an effect on the measurement of the INR values. The manufacturer provides guidelines for interpreting the INR during the change from combined therapy to warfarin alone.

Administration in the critically ill. Four critically ill patients became excessively anticoagulated[1] when treatment with argatroban was started after cardiac surgery, despite use of only the recommended doses or lower. All four had relatively normal hepatic function. Clearance of the drug appeared to be prolonged after it was stopped. In a patient[2] who had no significant direct hepatic dysfunction but severe hepatic congestion secondary to acute renal failure, the effect of argatroban was prolonged and reduction in dose was necessary. Haemodialysis had little or no effect on clearance. Further cases of excessive anticoagulation have been reported in patients with multiple organ failure,[3] and in an elderly patient with multiple comorbidities.[4] Patients developing heparin-induced thrombocytopenia after cardiac surgery may also be more sensitive to argatroban, and an initial dose of 500 nanograms/kg per minute has been suggested.[5]

1. Reichert MG, *et al.* Excessive argatroban anticoagulation for heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 652–4.
2. de Denus S, Spinler SA. Decreased argatroban clearance unaffected by hemodialysis in anasarca. *Ann Pharmacother* 2003; **37:** 1237–40.
3. Beiderlinden M, *et al.* Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; **41:** 749–54.
4. Kubiak DW, *et al.* Extensive prolongation of aPTT with argatroban in an elderly patient with improving renal function, normal hepatic enzymes, and metastatic lung cancer. *Ann Pharmacother* 2005; **39:** 1119–23.
5. Hoffman WD, *et al.* Reduced argatroban doses after coronary artery bypass graft surgery. *Ann Pharmacother* 2008; **42:** 309–16.

Overdosage. A critically ill patient receiving low-dose continuous intravenous argatroban for thromboembolism prophylaxis was mistakenly given an additional infusion of 125 mg of argatroban over 1 hour (26.1 micrograms/kg per minute).[1] He was given repeated doses of fresh frozen plasma and no bleeding complications occurred, but the prothrombin time remained prolonged for over 48 hours. Although the total dose given was comparable to doses used in other indications, critically ill patients may be particularly sensitive to the effects of argatroban (see above).

1. Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. *Ann Pharmacother* 2006; **40:** 336–9.

Interactions

As for Lepirudin, p.1323.

Warfarin. Although caution is necessary in interpreting the INR when argatroban and warfarin are given together (see Adverse Effects and Precautions, above), a study in healthy subjects[1] showed no pharmacokinetic interaction.

1. Brown PM, Hursting MJ. Lack of pharmacokinetic interactions between argatroban and warfarin. *Am J Health-Syst Pharm* 2002; **59:** 2078–83.

Pharmacokinetics

Argatroban is about 54% bound to plasma proteins. Metabolism, mainly hydroxylation and aromatisation, takes place in the liver, with the main metabolite having weak anticoagulant activity. Anticoagulant effects are seen immediately upon starting infusion; steady-state concentrations occur within 1 to 3 hours and are maintained until the infusion is stopped or the dose adjusted. The terminal elimination half-life of argatroban is between 39 and 51 minutes. It is excreted primarily in the faeces, via the bile as metabolites and as unchanged drug. About 16% of a dose is excreted unchanged in the urine, and at least 14% unchanged in faeces.

Uses and Administration

Argatroban is a synthetic direct thrombin inhibitor (see Lepirudin, p.1323) with anticoagulant and antiplatelet activity. It is used for the treatment and prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Heparin, p.1302), and as an adjunct in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p.1181) who have or are at risk of heparin-induced thrombocytopenia. It has also been used in other thromboembolic disorders.

In the management of heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 2 micrograms/kg per minute, adjusted according to the activated partial thromboplastin time (APTT), to a maximum dose of 10 micrograms/kg per minute.

In percutaneous coronary interventions in patients at risk of or with heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 25 micrograms/kg per minute, and an intravenous injection of 350 micrograms/kg is given simultaneously over 3 to 5 minutes. Close monitoring of the activated clotting time (ACT) is required. If necessary, additional intravenous bolus doses of 150 micrograms/kg may be given, and the infusion rate adjusted to between 15 and 40 micrograms/kg per minute.

Doses should be reduced in patients with hepatic impairment (see below).

◊ References.

1. Kondo LM, *et al.* Argatroban for prevention and treatment of thromboembolism in heparin-induced thrombocytopenia. *Ann Pharmacother* 2001; **35:** 440–51.
2. McKeage K, Plosker GL. Argatroban. *Drugs* 2001; **61:** 515–22.
3. Verme-Gibboney CN, Hursting MJ. Argatroban dosing in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 970–5.
4. Lewis BE, *et al.* Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 2006; **129:** 1407–16.
5. Martin ME, *et al.* Argatroban for anticoagulation during cardiac surgery. *Eur J Haematol* 2007; **78:** 161–6.
6. Bartholomew JR, *et al.* Argatroban anticoagulation for heparin-induced thrombocytopenia in elderly patients. *Drugs Aging* 2007; **24:** 489–99.
7. Beiderlinden M, *et al.* Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; **31:** 461–5.
8. Boggio LN, Oza VM. Argatroban use in heparin-induced thrombocytopenia. *Expert Opin Pharmacother* 2008; **9:** 1963–7.

Administration in hepatic impairment. In patients with heparin-induced thrombocytopenia with hepatic impairment the initial dose of argatroban should be reduced.[1] US licensed product information recommends an initial dose of 500 nanograms/kg per minute in moderate hepatic impairment. Reversal of anticoagulant effects after stopping argatroban may take more than 4 hours, due to decreased clearance and increased elimination half-life. High doses of argatroban should not be used in patients with significant hepatic impairment undergoing percutaneous coronary interventions.

1. Levine RL, *et al.* Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; **129:** 1167–75.

Administration in renal impairment. Argatroban is not significantly excreted by the kidneys and dosage adjustment is not usually required in renal impairment, although excessive anticoagulation has been reported in critically ill patients, including some with compromised renal function (see Administration in the Critically Ill under Adverse Effects, above). Argatroban has been successfully used for anticoagulation in patients undergoing chronic haemodialysis who developed thrombocytopenia with heparin.[1] Argatroban was not significantly removed by dialysis and no dosage adjustment was required. The use of argatroban in patients with renal impairment has been reviewed.[2]

1. Tang IY, *et al.* Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2005; **39:** 231–6.
2. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract* 2008; **109:** c80–c94.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Novastan; ***Neth.:*** Arganova; ***Swed.:*** Novastan; ***USA:*** Argatroban.

Arotinolol Hydrochloride *(rINNM)* ⊗

Arotinolol, Chlorhydrate d'; Arotinololi Hydrochloridum; Hidrocloruro de arotinolol; S-596. (±)-5-[2-{[3-(*tert*-Butylamino)-2-hydroxypropyl]thio}-4-thiazolyl]-2-thiophenecarboxamide hydrochloride.

Аротинолола Гидрохлорид

$C_{15}H_{21}N_3O_2S_3$,HCl = 408.0.

CAS — 68377-92-4 (arotinolol); 68377-91-3 (arotinolol hydrochloride).

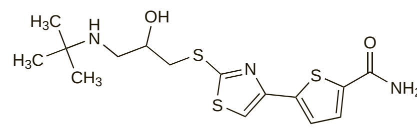

(arotinolol)

Pharmacopoeias. In *Jpn.*

Profile

Arotinolol is a non-cardioselective beta blocker (p.1225); it also has alpha$_1$-blocking activity. It is used as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and essential tremor (p.1231). The usual oral dose is 20 mg daily in 2 divided doses although up to 30 mg daily may be given. The initial dose for essential tremor is 10 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Almarl.

Atenolol *(BAN, USAN, rINN)* ⊗

Aténolol; Atenololi; Atenololis; Atenololum; ICI-66082. 2-{*p*-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide.

Атенолол

$C_{14}H_{22}N_2O_3$ = 266.3.

CAS — 29122-68-7; 60966-51-0.

ATC — C07AB03.

ATC Vet — QC07AB03.

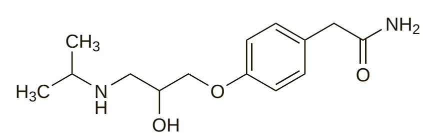

NOTE. Compounded preparations of atenolol may be represented by the following names:

- Co-tenidone (*BAN*)—atenolol 4 parts and chlortalidone 1 part (w/w)
- Co-tenidone (*PEN*)—atenolol and chlortalidone.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Atenolol). A white or almost white powder. Sparingly soluble in water; soluble in dehydrated alcohol; slightly soluble in dichloromethane.

USP 31 (Atenolol). White or practically white, odourless powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Atenolol is distributed into breast milk and there has been a report of cyanosis and bradycardia in a breast-fed neonate whose mother had been taking atenolol (see under Pharmacokinetics, below). The American Academy of Pediatrics therefore considers[1] that it should be given with caution to breast-feeding mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the eyes. Visual symptoms without headache were associated with atenolol for migraine prophylaxis in a patient who had experienced a similar reaction with nadolol.[1]

1. Kumar KL, Cooney TG. Visual symptoms after atenolol therapy for migraine. *Ann Intern Med* 1990; **112:** 712–13. Correction. *ibid.*; **113:** 257.

Effects on the heart. Beta blockers are used in the management of cardiac arrhythmias. However, atenolol 2.5 mg by intravenous injection induced atrial fibrillation in 6 of 12 predisposed patients.[1]

1. Rassmussen K, *et al*. Atrial fibrillation induced by atenolol. *Eur Heart J* 1982; **3:** 276–81.

Effects on lipid metabolism. For a report of acute pancreatitis due to hypertriglyceridaemia in a patient taking atenolol and metoprolol, see p.1227.

Effects on the liver. Adverse hepatic reactions in patients receiving atenolol have included reversible cholestatic hepatitis in one[1] and hepatic dysfunction in another.[2]

1. Schwartz MS, *et al.* Atenolol-associated cholestasis. *Am J Gastroenterol* 1989; **84:** 1084–6.
2. Yusuf SW, Mishra RM. Hepatic dysfunction associated with atenolol. *Lancet* 1995; **346:** 192.

Overdosage. Atenolol appears to lack membrane-stabilising activity and may have fewer adverse cardiac effects than some other beta blockers. However, cardiovascular toxicity has been noted after massive overdosage: ventricular asystole[1] and hypotension with ECG abnormalities[2] have been reported. Severe cardiovascular effects also occurred[3] in a patient with mixed overdosage including atenolol and diltiazem, and were attributed to additive toxicity.

1. Stinson J, *et al*. Ventricular asystole and overdose with atenolol. *BMJ* 1992; **305:** 693.
2. Love JN, Elshami J. Cardiovascular depression resulting from atenolol intoxication. *Eur J Emerg Med* 2002; **9:** 111–14.
3. Snook CP, *et al.* Severe atenolol and diltiazem overdose. *J Toxicol Clin Toxicol* 2000; **38:** 661–5.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

About 50% of an oral dose of atenolol is absorbed. Peak plasma concentrations are reached in 2 to 4 hours. Atenolol has low lipid solubility. It crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved. Only small amounts are reported to cross the blood-brain barrier, and plasma-protein binding is minimal. The plasma half-life is about 6 to 7 hours. Atenolol undergoes little or no hepatic metabolism and is excreted mainly in the urine. It is removed by haemodialysis.

Breast feeding. Atenolol diffuses into breast milk in concentrations similar[1] to or higher[2] than those in maternal blood. Cyanosis and bradycardia associated with ingestion of atenolol in breast milk has been reported in a 5-day-old term infant. The baby improved when breast feeding was stopped.[3]

1. Thorley KJ, McAinsh J. Levels of the beta-blockers atenolol and propranolol in the breast milk of women treated for hypertension in pregnancy. *Biopharm Drug Dispos* 1983; **4:** 299–301.
2. White WB, *et al.* Atenolol in human plasma and breast milk. *Obstet Gynecol* 1984; **63:** 42S–44S.
3. Schimmel MS, *et al.* Toxic effects of atenolol consumed during breast feeding. *J Pediatr* 1989; **114:** 476–8.

Pregnancy. Creatinine clearance increases during pregnancy, and a study in 17 pregnant patients found that the elimination half-life was shorter and renal clearance of atenolol faster during the second and third trimesters compared with three months post partum.[1] In another study,[2] postpartum samples were taken from the maternal and umbilical serum of 6 women who had been taking atenolol for at least 6 days before delivery; atenolol was detected in both maternal and cord blood in about equal concentrations. Atenolol was not detected in the maternal or cord blood of another patient who had stopped taking atenolol one day before delivery; the authors concluded that atenolol levels in the mother and fetus are equal at steady state, and that fetal accumulation does not occur. Atenolol concentrations in 35 term neonates whose mothers had received atenolol were examined.[3] It was found that the elimination rate for the neonates was 4 times slower than in adults, possibly because of immaturity of renal function. Transient bradycardia developed in 14 neonates.

1. Hebert MF, *et al.* Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. *J Clin Pharmacol* 2005; **45:** 25–33.
2. Melander A, *et al.* Transplacental passage of atenolol in man. *Eur J Clin Pharmacol* 1978; **14:** 93–4.
3. Rubin PC, *et al.* Atenolol elimination in the neonate. *Br J Clin Pharmacol* 1983; **16:** 659–62.

Uses and Administration

Atenolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Atenolol is used in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and myocardial infarction (p.1175). It may also be used for the prophylaxis of migraine (p.616).

In **hypertension** atenolol is given orally in a dose of 50 to 100 mg daily, as a single dose, although 50 mg daily is generally adequate. The full effect is usually evident within 1 to 2 weeks.

The usual dose for **angina pectoris** is 50 to 100 mg daily orally, given as a single dose or in divided doses. Additional benefit is not usually obtained from higher doses of atenolol although up to 200 mg daily has been given.

For the emergency treatment of **cardiac arrhythmias** atenolol may be given by intravenous injection in a dose of 2.5 mg injected at a rate of 1 mg/minute, repeated if necessary every 5 minutes to a maximum total dosage of 10 mg. Alternatively atenolol may be given by intravenous infusion over 20 minutes in a dose of 150 micrograms/kg. The injection or infusion procedure may be repeated every 12 hours if necessary. When control is achieved maintenance oral doses of 50 to 100 mg daily may be given.

Atenolol is also used in the early management of acute **myocardial infarction**. Treatment should be given within 12 hours of the onset of chest pain; atenolol 5 to 10 mg should be given by slow intravenous injection at a rate of 1 mg/minute, followed after 15 minutes with 50 mg orally, provided no adverse effects result from the injection; alternatively an intravenous dose of 5 mg may be repeated after 10 minutes followed by an oral dose of 50 mg after a further 10 minutes. A further 50 mg may be given orally after 12 hours, and subsequent dosage maintained, after a further 12 hours, with 100 mg daily.

In the prophylaxis of **migraine** an oral dose of 50 to 100 mg daily has been used.

Reduced doses may be required in patients with impaired renal function (see below).

Administration in renal impairment. The dose of atenolol should be reduced in patients with renal impairment, depending on the creatinine clearance (CC) as follows:

- CC 15 to 35 mL/minute per 1.73 m^2: 50 mg daily orally or 10 mg once every two days intravenously
- CC less than 15 mL/minute per 1.73 m^2: 25 mg daily or 50 mg on alternate days orally or 10 mg once every four days intravenously
- dialysis patients: 25 to 50 mg orally after each dialysis.

Preparations

BP 2008: Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets; Co-tenidone Tablets;
USP 31: Atenolol and Chlorthalidone Tablets; Atenolol Injection; Atenolol Oral Solution; Atenolol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Atel; Atenoblock; Atenovit; Cardioblock; Corpaz; Fabotenol; Felobits; Ilaten; Myocord; Plenacor; Prenormine; Telvodin; Tensilol; Tozolden; Vericordin; ***Austral.:*** Anselol; Atehexal; Noten; Tenormin; Tensig; ***Austria:*** Arcablock; Atehexal; Atenolan; Atenotyrol†; Betasyn; Tenormin; ***Belg.:*** Atenotop; Athenol†; Docateno; Tenormin; ***Braz.:*** Ablok; Angipress; Atecard; Atenegran; Ateneo; Atenobal; Atenokin; Atenol; Atenolab; Atenopress†; Atenorm; Atenuol; Atepress; Biotenor†; Ditenol†; Neotenol†; Plenacor; Sifnolol†; ***Canad.:*** Apo-Atenol; Novo-Atenol; Nu-Atenol; Tenolin†; Tenormin; ***Chile:*** Betacar; Grifotenol; Labotensil; Tenormin†; ***Cz.:*** Apo-Atenol; Ateblocor†; Atehexal; Atenobene; Catenol†; Corotenol†; Tenormin; ***Denm.:*** Atenet; Atenodan; Atenor; Tenormin; Uniloc; ***Fin.:*** Atenblock; Atenol; Tenoblock; Tenoprin; ***Fr.:*** Betatop; Tenormine; ***Ger.:*** Ate Lich; Ate†; Atebeta; Atehexal; Atendol†; Ateno; Atenogamma; Blocotenol†; Cuxanorm; duratenol†; Evitocor†; Falitonsin†; Jenatenol; Juvental; Tenormin; ***Gr.:*** Adenamin; Azectol; Blocotenol; Estanolin†; Fealin; Galol†; Hemon†; Mesonex; Mezarid†; Neocardon; Silder†; Synarome; Tenormin; Tradiver†; Umoder; ***Hong Kong:*** Adoll; Antipressan; Apo-Atenol; Ateno†; CP-Atenol; Hypernol; Lo-Ten; Martenol; Normaten; Nortelol; Oraday; Tenormin; Ternolol; Tredol; Vascoten; Velorin; ***Hung.:*** Atenobene; Atenomel; Blokium; Huma-Atenol†; Prinorm; ***India:*** Atecard†; Aten; Beta; Beten; Cadpres; Hipres; Lonol; Teno; Tenolol; Tenormin; Tensimin†; ***Indon.:*** Betablok; Farnormin; Hiblok; Internolol; Tenblok; Tenormin; Tensinorm; Zumablok; ***Irl.:*** Amolin; Atecor; Ateni; Atenogen; Atenomel; Tenormin; Trantalol; ***Israel:*** Normalol; Normiten; ***Ital.:*** Atenol; Atermin; Seles Beta; Tenomax; Tenormin; ***Malaysia:*** Apo-Atenol; Beten; Corotenol†; Loten; Normaten†; Noten; Oraday†; Ranlol; Renotol†; Tenormin; Ternolol†; Uphanormin†; Urosin; Vascoten; ***Mex.:*** Atenol; Atoken; Biofilen; Blotex; Min-T; Nosbal; Tenormin; Trebanol; ***Neth.:*** Tenormin; ***Norw.:*** Alinor†; Tenormin; Uniloc; ***NZ:*** Anselol†; Lo-Ten; ***Philipp.:*** Atestad; Cardioten; Durabeta; Tenor-Bloc; Tenormin; Tenostat; Tensimin; Therabloc; Velorin; ***Pol.:*** Normocard; ***Port.:*** Ancoren†; Atenolac†; Blokium†; Tenormin; Tessifol; ***Rus.:*** Atenolan (Атенолан); Betacard (Бетакард); Catenol (Катенол); Hypoten (Хайпотен); Tenolol (Тенолол); ***S.Afr.:*** Atenoblok; B-Vasc†; Hexa-Blok; Ten-Bloka; Tenormin; Venapulse; ***Singapore:*** Alonet†; Apo-Atenol; Hypernol; Normaten; Noten; Prenolol; Tenolol; Tenormin; Ternolol†; Vascoten; Velorin†; ***Spain:*** Blokium; Neatenol; Tanser; Tenormin; ***Swed.:*** Selinol†; Tenormin; Uniloc†; ***Switz.:*** Atenil; ateno-basan†; Atesifar†; Cardaxen; Primatenol†; Selobloc; Tenormin; ***Thai.:*** Atcard; Atenol; Coratol; Nolol; Nortelol; Oraday; Preloc; Prenolol; Tenocor; Tenol; Tenolol; Tenormin; Tetalin; Vascoten; Velorin; ***Turk.:*** Nortan; Tensidif; Tensinor; ***UAE:*** Tensotin; ***UK:*** Antipressan; Atenix; Tenormin; ***USA:*** Tenormin; ***Venez.:*** Artenolol†; Atenoval†; Beloc; Blokium; Ritmilan; Tenormin.

Multi-ingredient: ***Arg.:*** Atel C†; Atel N†; Plenacor D; Prenomod†; Prenoretic; Vericordin Compuesto; ***Austria:*** Arcablock comp; Atenolan comp; Atenolol comp; Atenotyrol comp†; Beta-Adalat; Nif-Ten; Polinorm; Tenoretic; ***Belg.:*** Beta-Adalat†; Kalten†; Tenif; Tenoretic; ***Braz.:*** Ablok Plus; Angipress CD; Atenoclor†; Atenoric; Atenuol CRT; Betalor; Nifelat; Tenoretic; ***Canad.:*** Apo-Atenidone; Tenoretic; ***Chile:*** Tenoretic†; ***Cz.:*** Atedon†; Atenolol Compositum†; Tenoretic; ***Denm.:*** Tenidon; Tenoretic; ***Fin.:*** Nif-Ten; ***Fr.:*** Beta-Adalate; Tenordate; Tenoretic; ***Ger.:*** Ate Lich comp; Atehexal comp; Atel; AteNif beta; Ateno comp; Atenogamma comp; Atenolol AL comp; Atenolol comp; Blocotenol comp†; Bresben; Diu-Atenolol; duratenol comp†; Nif-Ten; Nifatenol; Sigabloc†; Teneretic; TRI-Normin; ***Gr.:*** Apress†; Chlotenor; Obosan; Tenoretic; Typofen; ***Hong Kong:*** Nif-Ten; Target; Tenoret; Tenoretic; ***Hung.:*** Atenolol Comp†; Blokium Diu; ***India:*** Amdepin-AT; Amlopres AT; Amlosafe-AT†; Amlostat-AT; Atecard-D†; Beta Nicardia†; Cardif Beta; Cardules Plus; Depten; Hipres-D; Lerez-AT†; Nifetolol; Presolar; Tenochek; Tenoclor; Tenofed; Tenolol-AM; Tenolol-D†; Tenoric; ***Indon.:*** Nif-Ten; Tenoret; Tenoretic; ***Irl.:*** Atecor CT; Atenetic; Beta-Adalat; Nif-Ten; Tenoret; Tenoretic; ***Ital.:*** Atenigron; Atinorm; Carmian; Clortanol; Diube; Eupres; Igroseles; Mixer; Nif-Ten; Nor-Pa; Normopress; Target; Tenolone†; Tenoretic; ***Malaysia:*** Apo-Atenidone; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.:*** Plenacor; Tenoretic; ***Neth.:*** Nif-Ten†; Tenoretic; ***Philipp.:*** Nif-Ten; Tenoretic; ***Port.:*** Blokium Diu†; Tenoretic; ***Rus.:*** Atehexal Compositum (Атегексал Композитум); Tenochek (Теночек); Tenoric (Тенорик); Tenorox (Тенорокс); ***S.Afr.:*** Adco-Loten; Atenoblok Co†; Tenchlor; Tenoretic; ***Singapore:*** Beta Nicardia; Nif-Ten; Nifetex; Tenoret; Tenoretic; ***Spain:*** Blokium Diu; Kalten; Neatenol Diu; Neatenol Diuvas; Normopresil; Tenoretic; ***Switz.:*** Atedurex; ateno-basan comp†; Beta-Adalat; Cardaxen plus; Co-Atenolol†; Cotenolol-Neo; Cotesifar†; Kalten; Nif-Atenil; Nif-Ten; Primatenol Plus†; Tenoretic; ***Thai.:*** Tenoret†; Tenoretic†; ***Turk.:*** Tenoretic; ***UK:*** AtenixCo; Beta-Adalat; Kalten; Tenchlor; Tenif; Tenoret; Tenoretic; Totaretic; ***USA:*** Tenoretic; ***Venez.:*** Blokiuret; Tenoretic.

Atorvastatin Calcium *(BANM, USAN, rINNM)*

Atorvastatina cálcica; Atorvastatine calcique; Atorvastatinum calcicum; Calcii Atorvastatinum; CI-981. Calcium (βR,δR)-2-(p-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate.

Кальций Аторвастатин

$C_{66}H_{68}CaF_2N_4O_{10}$,$3H_2O$ = 1209.4.

CAS — 134523-00-5 (atorvastatin); 134523-03-8 (atorvastatin calcium).

ATC — C10AA05.

ATC Vet — QC10AA05.

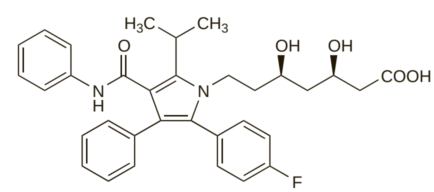

(atorvastatin)

Adverse Effects and Precautions

As for Simvastatin, p.1390.

◊ General references.

1. Black DM, *et al.* An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med* 1998; **158:** 577–84.
2. Bernini F, *et al.* Safety of HMG-CoA reductase inhibitors: focus on atorvastatin. *Cardiovasc Drugs Ther* 2001; **15:** 211–18.
3. Waters DD. Safety of high-dose atorvastatin therapy. *Am J Cardiol* 2005; **96** (suppl 5A): 69F–75F.
4. Arca M. Atorvastatin: a safety and tolerability profile. *Drugs* 2007; **67** (suppl 1): 63–9.

Effects on the skin. Toxic epidermal necrolysis apparently caused by atorvastatin has been reported.[1] The authors were not aware of this adverse effect previously having been associated with any of the statin lipid regulating drugs.

1. Pfeiffer CM, *et al.* Toxic epidermal necrolysis from atorvastatin. *JAMA* 1998; **279:** 1613–14.

Interactions

As for Simvastatin, p.1392.

Pharmacokinetics

Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability of about 12% due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to a number of active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile.

◊ Reviews.

1. Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; **42:** 1141–60.

Uses and Administration

Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III). Atorvastatin can be effective as adjunctive therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. It is also used for primary and secondary prophylaxis of cardiovascular events (see Cardiovascular Risk Reduction, p.1164) in patients with multiple risk factors, including diabetes mellitus.

Atorvastatin is given orally as the calcium salt although doses are expressed in terms of the base; 10.82 mg of atorvastatin calcium trihydrate is equivalent to 10 mg of base. The usual initial dose is 10 to 20 mg of atorvastatin once daily; an initial dose of 40 mg daily may be used in patients who require a large reduction in LDL-cholesterol. The dose may be adjusted at intervals of 4 weeks up to a maximum of 80 mg daily.

For patients taking drugs that interact with atorvastatin, dose reduction is advised as follows:

- patients taking *ciclosporin*, maximum dose 10 mg once daily
- patients taking *clarithromycin*, initial dose 10 mg once daily and maximum dose 20 mg once daily
- patients taking *itraconazole*, initial dose 10 mg once daily and maximum dose 40 mg once daily
- patients taking *ritonavir-boosted lopinavir* or *ritonavir-boosted saquinavir*, doses above 20 mg once daily should be used with caution

For the use of atorvastatin in children and adolescents, see below.

◊ General reviews.

1. Lea AP, McTavish D. Atorvastatin: a review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. *Drugs* 1997; **53:** 828–47.
2. Malinowski JM. Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. *Am J Health-Syst Pharm* 1998; **55:** 2253–67.
3. Malhotra HS, Goa KL. Atorvastatin: an updated review of its pharmacological properties and use in dyslipidaemia. *Drugs* 2001; **61:** 1835–81.
4. Croom KF, Plosker GL. Atorvastatin: a review of its use in the primary prevention of cardiovascular events in patients with type 2 diabetes mellitus. *Drugs* 2005; **65:** 137–52.
5. Poli A. Atorvastatin: pharmacological characteristics and lipid-lowering effects. *Drugs* 2007; **67** (suppl 1): 3–15.
6. Bybee KA, *et al.* Cumulative clinical trial data on atorvastatin for reducing cardiovascular events: the clinical impact of atorvastatin. *Curr Med Res Opin* 2008; **24:** 1217–29.

Administration in children. In children and adolescents aged 10 to 17 years with hypercholesterolaemia or combined (mixed) hyperlipidaemia, atorvastatin is licensed for use orally in an initial dose of 10 mg once daily, adjusted if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg once daily. A 6-month study[1] with this dose regimen in children with familial or severe hypercholesterolaemia found that atorvastatin was both safe and effective. Atorvastatin has also been used in children with hyperlipidaemia associated with renal[2] or heart[3] transplantation.

1. McCrindle BW, *et al.* Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003; **143:** 74–80.
2. Argent E, *et al.* Atorvastatin treatment for hyperlipidemia in pediatric renal transplant recipients. *Pediatr Transplant* 2003; **7:** 38–42.
3. Chin C, *et al.* Efficacy and safety of atorvastatin after pediatric heart transplantation. *J Heart Lung Transplant* 2002; **21:** 1213–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ampliar; Atarva; Ateroclar; Atorvastan; Finlipol; Liparex; Lipibec; Lipifen; Lipitor; Lipocambi; Lipofin; Liponorm; Lipostop; Lipovastinklonal; Normalip; Plan; Tialipol; Torivas; Vastina; Zarator; ***Austral.:*** Lipitor; ***Austria:*** Sortis; ***Belg.:*** Lipitor; ***Braz.:*** Citalor; Lipitor; ***Canad.:*** Lipitor; ***Chile:*** Atenfar; Atorlip; Dislipor; Hipolixan; Lipitor; Lipotropic; Lipox; Lowden; Zarator; Zurinel; ***Cz.:*** Atogal; Atoris; Atorpharm; Bisatum; Sortis; Torvacard; Triglyx; Tulip; Vaston; ***Denm.:*** Zarator; ***Fin.:*** Lipitor; ***Fr.:*** Tahor; ***Ger.:*** Sortis; ***Gr.:*** Altoram; Antorcin; Arvastatil; Ator-Chol; Atorgon; Atorolnga; Atorstat; Atorval; Atorvanox; Atorvin; Atrost; Atrosterol; Atrovita; Biger; Delipost; Holisten; Lipigan; Lipitor; Lipizem; Lipodial; Lipostatin; Lipovast; Lorvaten; Rotova; Torvastin; Vastazor; Xanator; Zarator; ***Hong Kong:*** Lipitor; ***Hung.:*** Atoris; Atorva; Atorvox; Hypolip; Liprimar; Sortis; Torvacard; ***India:*** Atorlip; Atorva; Attor; Liporest; X'tor; ***Indon.:*** Atorsan; Lipitor; ***Irl.:*** Lipitor; ***Israel:*** Lipitor; Torid; ***Ital.:*** Lipitor†; Torvast; Totalip; Xarator†; ***Jpn:*** Lipitor; ***Malaysia:*** Lipitor; Storvas; ***Mex.:*** Lipitor; ***Neth.:*** Cardyl; Lipitor; Prevencor; Zarator; ***Norw.:*** Lipitor; ***NZ:*** Lipitor; ***Philipp.:*** Lipitor; ***Pol.:*** Atoris; Atrox; Sortis; Torvacard; Tulip; ***Port.:*** Sortis; Zarator; ***Rus.:*** Atomax (Атомакс); Atoris (Аторис); Liprimar (Липримар); Liptonorm (Липтонорм); Torvacard (Торвакард); Tulip (Тулип); ***S.Afr.:*** Lipitor; ***Singapore:*** Lipitor; ***Spain:*** Cardyl; Prevencor; Zarator; ***Swed.:*** Lipitor; ***Switz.:*** Sortis; ***Thai.:*** Lipitor; ***Turk.:*** Ator; Kolestor; Lipitaksin; Lipitor; Saphire; Tarden; ***UK:*** Lipitor; ***USA:*** CTR; Lipitor; ***Venez.:*** Atovarol; Glustar; Lipitor; Tarimyl.

Multi-ingredient: ***Arg.:*** Ampliar Duo; Ateroclar Duo; Hipertensal Combi; Liparex Duo; Lipibec Duo; Lipoarteriosan; Liponorm Duo; Torimibe; ***Austral.:*** Caduet; ***Braz.:*** Caduet; ***Chile:*** Caduet; ***Cz.:*** Caduet; ***Fr.:*** Caduet; ***Hung.:*** Caduet; ***India:*** Zetitor†; ***Malaysia:*** Caduet; ***Mex.:*** Caduet; ***Philipp.:*** Envacar; ***Port.:*** Caduet; ***S.Afr.:*** Caduet; ***Singapore:*** Caduet; ***USA:*** Caduet; ***Venez.:*** Caduet.

Atropine *(BAN)*

Atropiini; Atropin; Atropina; Atropinas; Atropinum; (±)-Hyoscyamine. (1*R*,3*r*,5*S*,8*r*)-Tropan-3-yl (*RS*)-tropate.

$C_{17}H_{23}NO_3 = 289.4.$
CAS — 51-55-8.
ATC — A03BA01; S01FA01.
ATC Vet — QA03BA01; QS01FA01.

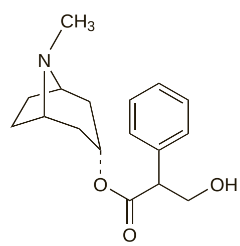

Description. Atropine is an alkaloid that may be obtained from solanaceous plants, or prepared by synthesis.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Atropine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Atropine). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 460 of water, 1 in 90 of water at 80°, 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 25 of ether; soluble in glycerol. Its saturated solution in water is alkaline to phenolphthalein. Store in airtight containers. Protect from light.

Atropine Methobromide *(BANM)*

Atropina, metilbromuro de; Atropine Methylbromide; Methylatropine Bromide; Méthylatropine, bromure de; Methylatropini bromidum; Methylatropinii Bromidum; Methylatropinium Bromatum; Methylatropinium-bromid; Metilatropin-bromid; Metilatropino bromidas; Metylatropinbromid; Metyyliatropiinibromidi; Mydriasine. (1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium bromide.

$C_{18}H_{26}BrNO_3 = 384.3.$
CAS — 2870-71-5.
ATC — A03BA01.
ATC Vet — QA03BA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Methylatropine Bromide; Atropine Methobromide BP 2008). Colourless crystals or a white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

Atropine Methonitrate *(BANM, rINN)*

Atrop. Methonit.; Atropiinimetonitraatti; Atropine, Méthonitrate d'; Atropini Methonitras; Atropinmetonitrat; Methylatropine Nitrate *(USAN)*; Méthylatropine, nitrate de; Methylatropini nitras; Methylatropinii Nitras; Methylatropinium nitrát; Metilatropin-nitrát; Metilatropino nitratas; Metilnitrato de atropina; Metonitrato de atropina; Metylatropinnitrat; Metyyliatropiininitraatti. (1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium nitrate.

Атропина Метонитрат

$C_{18}H_{26}N_2O_6 = 366.4.$
CAS — 52-88-0.
ATC — A03BB02.
ATC Vet — QA03BB02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Methylatropine Nitrate; Atropine Methonitrate BP 2008). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. Protect from light.

Stability. Aqueous solutions of atropine methonitrate are unstable; stability is enhanced in acid solutions of pH below 6.

Atropine Sulfate

Atrop. Sulph.; Atropiinisulfaatti; Atropin Sülfat; Atropina, sulfato de; Atropine, sulfate d'; Atropine Sulphate *(BANM)*; Atropini sulfas; Atropini Sulfas Monohydricus; Atropino sulfatas; Atropinsulfat; Atropin-sulfát monohydrát; Atropin-szulfát; Atropiny siarczan.

$(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O = 694.8.$
CAS — 55-48-1 (anhydrous atropine sulfate); 5908-99-6 (atropine sulfate monohydrate).
ATC — A03BA01; S01FA01.
ATC Vet — QA03BA01; QS01FA01.

NOTE. Compounded preparations of atropine sulfate may be represented by the following names:

- Co-phenotrope (*BAN*)—atropine sulfate 1 part and diphenoxylate hydrochloride 100 parts (w/w).

ATR is a code approved by the BP 2008 for use on single unit dose eye drops containing atropine sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Atropine Sulphate). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Protect from light.

USP 31 (Atropine Sulfate). Odourless, colourless crystals or white crystalline powder. It effloresces in dry air. Soluble 1 in 0.5 of water, 1 in 2.5 of boiling water, 1 in 5 of alcohol, and 1 in 2.5 of glycerol. Store in airtight containers.

Incompatibility. Incompatibility between atropine sulfate and hydroxybenzoate preservatives has been seen,[1] resulting in a total loss of the atropine in 2 to 3 weeks.

1. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230:** 481.

Adverse Effects

The pattern of adverse effects seen with atropine and other antimuscarinics can mostly be related to their pharmacological actions at muscarinic and, at high doses, nicotinic receptors (see Actions of Antimuscarinics, below). These effects are dose-related and are usually reversible when therapy is stopped. The **peripheral** effects of atropine and other antimuscarinics are a consequence of their inhibitory effect on muscarinic receptors within the autonomic nervous system. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the gastrointestinal tract leading to constipation. Some of the **central** effects of atropine and other tertiary antimuscarinics seen at toxic doses (see below) may also occur at therapeutic doses.

In **overdosage**, the peripheral effects become more pronounced and other symptoms such as hyperthermia, hypertension, increased respiratory rate, and nausea and vomiting may occur. A rash may appear on the face or upper trunk. Toxic doses also cause CNS stimulation marked by restlessness, confusion, excitement, ataxia, incoordination, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures. However, in severe intoxication, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure, and death.

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg for children.

Quaternary ammonium antimuscarinics, such as atropine methobromide or methonitrate and propantheline bromide, have some ganglion-blocking activity and high doses may cause orthostatic hypotension and impotence; in toxic doses non-depolarising neuromuscular block may be produced.

Systemic toxicity may be produced by the **local** instillation of antimuscarinic eye drops, particularly in children and in the elderly. Prolonged application of atropine to the eye may lead to local irritation, hyperaemia, oedema, and conjunctivitis. An increase in intra-ocular pressure may occur, especially in patients with angle-closure glaucoma.

Hypersensitivity to atropine is not uncommon and may occur as conjunctivitis or a skin rash.

Effects on body temperature. Atropine can cause hyperthermia as a result of inhibition of sweating. This may be attenuated by atropine's ability to dilate cutaneous blood vessels. However, there has been a report of hypothermia in a 14-year-old feverish patient after intravenous use of atropine.[1]

For reports of fatal heat stroke in patients taking an antimuscarinic with an antipsychotic see under Interactions in Benzatropine, p.797.

1. Lacouture PG, *et al.* Acute hypothermia associated with atropine. *Am J Dis Child* 1983; **137:** 291–2.

Effects on the eyes. In addition to the expected ocular effects of atropine (see above) there have been instances of acute angle-closure glaucoma in patients receiving nebulised atropine.[1]

1. Berdy GJ, *et al.* Angle closure glaucoma precipitated by aerosolized atropine. *Arch Intern Med* 1991; **151:** 1658–60.

Effects on the gastrointestinal tract. Antimuscarinics reduce gastrointestinal tone and paralytic ileus has been reported[1] in a 77-year-old man with Parkinson's disease who had been receiving atropine sulfate orally to control excess salivation. An increased risk of oesophageal cancer has also been reported[2] with antimuscarinics, possibly due to reductions in lower oesophageal sphincter tone increasing the risk of gastro-oesophageal reflux.

1. Beatson N. Atropine and paralytic ileus. *Postgrad Med J* 1982; **58:** 451–3.
2. Lagergren J, *et al.* Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000; **133:** 165–75.

Effects on the heart. Atropine sulfate, to a total of 1 mg per 70 kg body-weight, given intravenously to 79 patients before surgery produced arrhythmias in over 20% of patients, especially in the young.[1] Atrioventricular dissociation was the most common disturbance in adults and in children atrial rhythm disturbances were common. In another study[2] premedication including atropine or glycopyrronium given intramuscularly resulted in a significantly greater incidence of tachycardia during anaesthetic induction and intubation compared with controls who received no antimuscarinic drug. Patients who received glycopyrronium also had a higher incidence of tachycardia during surgery than the controls. No significant difference in bradycardia or extrasystoles was found in the atropine- or the glycopyrronium-treated patients. Atrial fibrillation has been reported in 2 elderly glaucoma patients after post-surgical application of atropine ointment or eye drops to the eye.[3]

1. Dauchot P, Gravenstein JS. Effects of atropine on the electrocardiogram in different age groups. *Clin Pharmacol Ther* 1971; **12:** 274–80.
2. Shipton EA, Roelofse JA. Effects on cardiac rhythm of premedication with atropine or glycopyrrolate. *S Afr Med J* 1984; **66:** 287–8.
3. Merli GJ, *et al.* Cardiac dysrhythmias associated with ophthalmic atropine. *Arch Intern Med* 1986; **146:** 45–7.

Effects on mental function. A study[1] in patients with Parkinson's disease and healthy control subjects suggested that although short-term memory was impaired in patients receiving long-term antimuscarinic therapy the effect was reversible on stopping. An epidemiological study[2] similarly reported lower cognitive performance in elderly patients receiving antimuscarinics.

See also under Trihexyphenidyl (p.820) and under Oxybutynin (p.2191).

1. Van Herwaarden G, *et al.* Short-term memory in Parkinson's disease after withdrawal of long-term anticholinergic therapy. *Clin Neuropharmacol* 1993; **16:** 438–43.
2. Lechevallier-Michel N, *et al.* Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol* 2005; **59:** 143–51.

Hypersensitivity. A report[1] of anaphylactic shock developing in a 38-year-old woman after an intravenous injection of atropine.

1. Aguilera L, *et al.* Anaphylactic reaction after atropine. *Anaesthesia* 1988; **43:** 955–7.

Overdosage. Reports of atropine poisoning or overdosage have included a respiratory therapist[1] who had given 10 atropine sulfate aerosol treatments in the preceding 24 hours and children who had taken overdoses of a preparation containing diphenoxylate and atropine.[2]

1. Larkin GL. Occupational atropine poisoning via aerosol. *Lancet* 1991; **337:** 917.
2. McCarron MM, *et al.* Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics* 1991; **87:** 694–700.

Treatment of Adverse Effects

If a patient presents within an hour of an overdose of atropine by mouth the stomach may be emptied or activated charcoal given to reduce absorption. Supportive therapy should be given as required.

Physostigmine has been tried for antimuscarinic poisoning (see p.1884) but such use can be hazardous and is not generally recommended. Diazepam may be given to control marked excitement and convulsions; phenothiazines should not be given as they may exacerbate antimuscarinic effects. Antiarrhythmics are not recommended if arrhythmias develop; hypoxia and acidosis should be corrected and sodium bicarbonate may be given even if acidosis is not present.

Precautions

Atropine should be used with caution in children and the elderly, who may be more susceptible to its adverse effects. It is contra-indicated in patients with prostatic enlargement, in whom it may lead to urinary retention, and in those with paralytic ileus or pyloric stenosis. In patients with ulcerative colitis its use may lead to ileus or megacolon, and its effects on the lower oesophageal sphincter may exacerbate reflux. Caution is generally advisable in any patient with diarrhoea. It should not be given to patients with myasthenia gravis except to reduce adverse muscarinic effects of an anticholinesterase.

Atropine should not be given to patients with angle-closure glaucoma or with a narrow angle between the iris and the cornea, since it may raise intra-ocular pressure and precipitate an acute attack. Acute angle-closure glaucoma has been reported in patients receiving nebulised atropine. Some licensed product information recommends that atropine eye drops should not be used in infants aged less than 3 months due to the possible association between the induced cycloplegia and the development of amblyopia. Systemic reactions have followed the absorption of atropine from eye drops; overdosage is less likely if the eye ointment is used. In the event of blurred vision after topical application of atropine to the eye patients should not drive or operate machinery. Systemic use of antimuscarinics may also cause blurred vision, dizziness, and other effects that may impair a patient's ability to perform skilled tasks such as driving.

Because of the risk of provoking hyperthermia, atropine should not be given to patients, especially children, when the ambient temperature is high. It should also be used cautiously in patients with fever.

Atropine and other antimuscarinics need to be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, heart failure, and in cardiac surgery, where they may further accelerate the heart rate. Care is required in patients with acute myocardial infarction, as ischaemia and infarction may be made worse, and in patients with hypertension.

Atropine may cause confusion, especially in the elderly. Reduced bronchial secretion caused by systemic atropine may be associated with the formation of mucous plugs.

In the treatment of parkinsonism, increases in dosage and transfer to other forms of treatment should be gradual and the antimuscarinic should not be withdrawn abruptly. Minor reactions may be controlled by reducing the dose until tolerance has developed.

Persons with Down's syndrome appear to have an increased susceptibility to some of the actions of atropine, whereas those with albinism may have a reduced susceptibility.

Breast feeding. No adverse effects have been observed in breast-feeding infants whose mothers were receiving atropine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)

Interactions

The effects of atropine and other antimuscarinics may be enhanced by use with other drugs having antimuscarinic properties, such as amantadine, some antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Inhibition of drug-metabolising enzymes by MAOIs may possibly enhance the effects of antimuscarinics. The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs. Antimuscarinics may also antagonise the gastrointestinal effects of cisapride, domperidone, and metoclopramide. Antimuscarinics and parasympathomimetics may counteract each others effects.

Pharmacokinetics

Atropine is readily absorbed from the gastrointestinal tract; it is also absorbed from mucous membranes, the eye, and to some extent through intact skin. It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier. It is incompletely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites. A half-life of about 4 hours has been reported. Atropine crosses the placenta and traces appear in breast milk.

Quaternary ammonium salts of atropine, such as the methonitrate, are less readily absorbed after oral doses. They are highly ionised in body fluids and being poorly soluble in lipids they do not readily cross the blood-brain barrier.

Pregnancy. Studies of the pharmacokinetics of atropine in mother and fetus in late pregnancy[1-3] indicated that atropine rapidly crosses the placenta. However, whereas peak concentrations of atropine in fetal cord blood were reached about 5 minutes after intravenous doses, the maximum effect on fetal heart rate occurred after about 25 minutes.

1. Barrier G, *et al.* La pharmacocinétique de l'atropine chez la femme enceinte et le foetus en fin de grossesse. *Anesth Analg Reanim* 1976; **33:** 795–800.
2. Onnen I, *et al.* Placental transfer of atropine at the end of pregnancy. *Eur J Clin Pharmacol* 1979; **15:** 443–6.
3. Kanto J, *et al.* Placental transfer and pharmacokinetics of atropine after a single maternal intravenous and intramuscular administration. *Acta Anaesthesiol Scand* 1981; **25:** 85–8.

Uses and Administration

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions (see below). It is usually given as the sulfate. It first stimulates and then depresses the CNS and has antispasmodic actions on smooth muscle and reduces secretions, especially salivary and bronchial secretions; it also reduces perspiration, but has little effect on biliary or pancreatic secretion. Atropine depresses the vagus and thereby increases the heart rate. When given orally atropine reduces smooth-muscle tone and diminishes gastric and intestinal motility but has little effect on gastric secretion in usual therapeutic doses. Quaternary ammonium derivatives, such as the methonitrate, have less effect on the CNS but strong ganglion-blocking activity.

Because of its effects on heart rate, atropine is used in the treatment of bradycardia and asystole of various causes, including in acute cardiopulmonary resuscitation procedures. It has also had many other uses, including: in anaesthetic practice as a premedicant and to counteract the muscarinic effects of anticholinesterases such as neostigmine and other parasympathomimetics; as an antispasmodic in gastrointestinal disorders; as an adjunct to opioid analgesics for the symptomatic relief of biliary or renal colic; to treat or prevent bronchospasm; and in the treatment of poisoning with mushrooms that contain muscarine and in organophosphorus pesticide poisoning. Atropine is used topically as a mydriatic and cycloplegic in ophthalmology.

See under headings below for details of dosage and administration of atropine and its derivatives in specific indications.

Actions of antimuscarinics. Antimuscarinic drugs such as atropine are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves; they are also inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation. They have been described as parasympatholytic, atropinic, atropine-like, and as anticholinergic, although the latter term should encompass compounds that also have antinicotinic actions.

At least 5 different pharmacologically identifiable types of **muscarinic receptor** (M_1, M_2, M_3, M_4, and M_5) have been described as have 5 different molecular forms (m_1, m_2, m_3, m_4, and m_5) of these receptors. While the traditional antimuscarinics appear to be relatively non-specific, newer compounds like pirenzepine and telenzepine have a selective action on the M_1 receptors within ganglia supplying cholinergic postganglionic nerves to the gastrointestinal tract.

Antimuscarinics can be classified as **tertiary amine** or **quaternary ammonium** compounds. Atropine and other naturally occurring alkaloids such as hyoscine and hyoscyamine are tertiary amines, that is they have a tertiary nitrogen atom; semisynthetic derivatives or synthetic antimuscarinics may be either tertiary (e.g. homatropine or trihexyphenidyl) or quaternary ammonium (e.g. homatropine methylbromide or ipratropium) compounds.

At therapeutic doses tertiary amine antimuscarinics have little effect on the actions of acetylcholine at nicotinic receptors. However, the quaternary ammonium antimuscarinics exhibit a greater degree of antinicotinic potency, and some of their effects at high doses are due to ganglionic blockade; excessively high doses may even produce neuromuscular block. There are also pharmacokinetic differences between tertiary amine and quaternary ammonium antimuscarinics. Quaternary ammonium compounds are less lipid soluble than tertiary amines; their gastrointestinal absorption is poor and they do not readily pass the blood-brain barrier or conjunctiva.

Antimuscarinics can produce a wide range of effects at therapeutic doses. The **peripheral** antimuscarinic effects that are produced as the dose increases are:

- decreased production of secretions from the salivary, bronchial, and sweat glands
- dilatation of the pupils (mydriasis) and paralysis of accommodation (cycloplegia)
- increased heart rate
- inhibition of micturition and reduction in gastrointestinal tone
- inhibition of gastric acid secretion

As for **central** effects, with the exception of hyoscine, which causes CNS depression at therapeutic doses, tertiary amines stimulate the medulla and higher cerebral centres producing mild central vagal excitation and respiratory stimulation. At toxic doses all tertiary amines, including hyoscine, cause stimulation of the CNS with restlessness, disorientation, hallucinations, and delirium. As the dose increases stimulation is followed by central depression and death from respiratory paralysis. Synthetic tertiary amines are less potent in their central effects than natural tertiary amines; quaternary ammonium compounds have negligible central effects.

Anaesthesia. Antimuscarinics, including *atropine, hyoscine,* and *glycopyrronium*, have been used pre-operatively to inhibit salivation and excessive secretions of the respiratory tract during anaesthesia (p.1780), although this use is less important now that less irritating anaesthetics are used. Atropine and glycopyrronium are also given to reduce intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol, or following vagal stimulation. Glycopyrronium causes less tachycardia than atropine when given intravenously. When hyoscine is used as a premedicant it also provides some amnesia, sedation, and antiemesis but, unlike atropine, may cause bradycardia rather than tachycardia. Atropine or, preferably, glycopyrronium is also used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects (see Uses and Administration of Neostigmine, p.632).

For **premedication** 300 to 600 micrograms of atropine sulfate may be given by subcutaneous or intramuscular injection, usually 30 to 60 minutes before anaesthesia. Alternatively 300 to 600 micrograms of atropine sulfate may be given intravenously immediately before induction of anaesthesia. Suitable paediatric subcutaneous or intramuscular premedication doses of atropine sulfate are:

- children up to 3 kg in weight: 100 micrograms
- children 7 to 9 kg in weight: 200 micrograms
- children 12 to 16 kg in weight: 300 micrograms
- children over 20 kg in weight: the adult dose.

For intra-operative **bradycardia** the *BNF* states that 300 to 600 micrograms may be given intravenously; larger doses may be used in emergencies. Children may be given 10 to 20 micrograms/kg.

To counteract the muscarinic effects of **anticholinesterases** when they are used to reverse the effects of competitive muscle relaxants adults are given atropine sulfate 0.6 to 1.2 mg by intravenous injection before or with the anticholinesterase. Neonates, infants, and children may be given a dose of 20 micrograms/kg (maximum dose 600 micrograms).

Anoxic seizures. A reflex anoxic seizure is a paroxysmal event triggered by a noxious stimulus which, by vagal stimulation, causes pronounced bradycardia or cardiac arrest and consequent relative cerebral ischaemia.[1] Certain features of the attack may lead to a misdiagnosis of epilepsy. To avoid confusion with epileptic seizures (p.465), reflex anoxic seizures have also been called white or type 2 breath holding attacks. Depending on the degree of vagal hypersensitivity or noxious stimulus, attacks may occur infrequently or several times a day.

Infants and young children are mainly affected, however, the condition usually resolves by early childhood. It is generally benign and children do not suffer cardiac or cerebral damage. Treatment is seldom necessary, but atropine has been advocated to prevent vagal hypersensitivity in those children with frequent, persistent attacks. As atropine may require frequent doses with an attendant risk of overdosage, transdermal hyoscine has been tried as an alternative.[2]

1. Appleton RE. Reflex anoxic seizures. *BMJ* 1993; **307:** 214–5.
2. Palm L, Blennow G. Transdermal anticholinergic treatment of reflex anoxic seizures. *Acta Paediatr Scand* 1985; **74:** 803–4.

Biliary and renal colic. Atropine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p.5).

Cardiac disorders. Atropine depresses the vagus and thereby increases the heart rate. It is therefore used in a variety of disorders or circumstances in which bradyarrhythmias occur. It is frequently used in sudden onset bradyarrhythmias and although it may also be given for the initial treatment of chronic arrhythmias (p.1160), cardiac pacing is generally preferred for long-term control. Examples of acute use include the prevention and treatment of arrhythmias associated with anaesthesia (see above), the treatment of other drug-induced arrhythmias, and in cardiac arrest due to asystole or electromechanical dissociation (pulseless electrical activity—p.1156). Atropine sulfate has been used in the management of bradycardia of acute myocardial infarction; however, caution is required, as atropine may exacerbate ischaemia or infarction in these patients.

For **advanced life support** in adults with asystole or electromechanical dissociation, European[1] and UK guidelines[2] recommend atropine in a single dose of 3 mg intravenously; US guidelines[3] recommend repeated doses of 1 mg to a total maximum dose of 3 mg.

In **bradycardia**, atropine is given[1-3] in doses of 500 micrograms intravenously repeated every 3 to 5 minutes to a total dose of 3 mg.

If an intravenous line cannot be established, atropine can be given via an endotracheal tube; 2 to 3 times the intravenous dose should be given, diluted in 10 mL of sterile water or sodium chloride 0.9%.

1. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. *Resuscitation* 2005; **67** (suppl 1): S1–S190. Also available at: http://www.erc.edu/index.php/guidelines_download_2005/en/? (accessed 07/03/06)
2. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 07/03/06)
3. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112** (suppl 1): IV1–IV203. Also available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 09/02/06)

Eye disorders. Atropine is used to produce mydriasis and cycloplegia (p.1874) for ophthalmic examination. One local application can take up to 40 minutes or more to produce mydriasis, which lasts for a week or more; marked paralysis of accommodation is obtained in 1 to 3 hours with recovery in 6 to 12 days. However, other antimuscarinics such as cyclopentolate, homatropine, or tropicamide may be preferred because they have a more rapid onset and shorter duration of action than atropine. Atropine is also used in the management of uveitis and iritis, and in strabismus. It is used in the treatment of iritis and uveitis to immobilise the ciliary muscle and iris and to prevent or break down adhesions. Because of its powerful cycloplegic action atropine is also used in the determination of refraction in children below the age of 6 and in children with convergent strabismus (p.1874).

In the treatment of **inflammatory eye disorders** such as uveitis or iritis (p.1515), the dose of atropine sulfate for adults is 1 or 2 drops of a 0.5 or 1% solution instilled into the eye(s) up to four times daily. The dose in children is 1 or 2 drops of a 0.5% solution (or one drop of a 1% solution) instilled up to three times daily. For **refraction** in adults the dose is one drop of a 1% solution of atropine sulfate; this may be instilled either twice daily for 1 or 2 days before the procedure or on a single occasion one hour before the procedure. In children the dose for refraction is 1 or 2 drops of a 0.5% solution (or one drop of a 1% solution) instilled twice daily for 1 to 3 days before the procedure, with a further dose given one hour before the procedure. An ophthalmic ointment of atropine sulfate 1% may be preferred for children under 5 years and particularly in infants under 3 months who are at increased risk of systemic effects with eye drops. Some manufacturers recommend that atropine sulfate should not be used in the eyes of children younger than 3 months due to a possible association between the cycloplegia produced and the development of amblyopia.

Atropine borate has also been used in ophthalmic preparations.

References.

1. Stolovitch C, *et al.* Atropine cycloplegia: how many instillations does one need? *J Pediatr Ophthalmol Strabismus* 1992; **29:** 175–6.
2. Foley-Nolan A, *et al.* Atropine penalisation versus occlusion as the primary treatment for amblyopia. *Br J Ophthalmol* 1997; **81:** 54–7.
3. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002; **120:** 268–78.

Gastrointestinal disorders. Antimuscarinics may be used in gastrointestinal disorders as antispasmodics (see p.1692), because of their marked inhibitory effect on gastrointestinal motility, and for their antisecretory effects. Atropine (as the sulfate or quaternary derivatives such as the methobromide or methonitrate) has been used to reduce smooth-muscle tone and diminish motility, but has little effect on gastric secretion at usual therapeutic doses (about 200 micrograms of atropine sulfate). It has been tried as an adjunct to the treatment of benign gastric and duodenal ulcers and the antispasmodic action of atropine has been used to facilitate radiological examination of the gut. Atropine sulfate has also been used in the treatment of irritable bowel syndrome. Atropine oxide hydrochloride is also used for gastrointestinal disorders.

Poisoning. Atropine is used in the management of overdosage or poisoning due to anticholinesterase compounds including organophosphorus pesticides,[1,2] chemical warfare nerve gases,[3] and parasympathomimetics such as neostigmine. It is also used to antagonise the effects of cholinomimetic substances in the treatment of overdosage with parasympathomimetics such as bethanechol, and in the treatment of poisoning with mushrooms that contain muscarine. Atropine blocks the action of these compounds at muscarinic receptors, reversing bradycardia and decreasing tracheobronchial secretions, bronchoconstriction, intestinal secretions, and intestinal motility.

- In the treatment of poisoning with organophosphorus **pesticides** or chemical warfare **nerve gases** atropine sulfate may be given to adults in an initial dose of 2 mg intramuscularly or intravenously every 10 to 30 minutes until muscarinic effects disappear or signs of atropine toxicity are seen. In severe cases injections have been given as often as every 5 minutes in some centres. Continuous infusion has also been used.[4,5] A dose of at least 50 micrograms/kg has been suggested for children by some;[6] the *BNF* includes a dose of 20 micrograms/kg given every 5 to 10 minutes.
- In moderate to severe poisoning a state of atropinisation is usually maintained for at least 2 days and continued for as long as symptoms are evident. In severely poisoned patients this may entail prolonged treatment.[7,8] As large amounts of atropine may be required it is important to use a preservative-free preparation to avoid the potential toxicity associated with use of excess quantities of preservatives such as benzyl alcohol or chlorobutanol.
- Since atropine is ineffective against any nicotinic effects of these compounds a cholinesterase reactivator such as pralidoxime (p.1460) may be used as an adjunct.

The use of atropine in poisoning or overdosage with **other compounds** having muscarinic actions is similar to that for organophosphorus pesticides but the duration of treatment necessary is usually shorter. An initial dose of 0.6 to 1 mg given subcutaneously, intramuscularly, or intravenously and repeated every 2 hours may be adequate for overdosage with cholinomimetics such as bethanechol.

1. Singh S, *et al.* Is atropine alone sufficient in acute severe organophosphorus poisoning: experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995; **33:** 628–30.
2. Eddleston M, *et al.* Management of severe organophosphorus pesticide poisoning. *Crit Care* 2002; **6:** 259.
3. Anonymous. Treatment of nerve gas poisoning. *Med Lett Drugs Ther* 1995; **37:** 43–4.
4. Ram JS, *et al.* Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India* 1991; **39:** 190–3.
5. Sungur M, Güven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001; **5:** 211–15.
6. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
7. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; **4:** 339–40.
8. Afzaal S, *et al.* High dose atropine in organophosphorus poisoning. *Postgrad Med J* 1990; **66:** 70–1.

Respiratory-tract disorders. Although atropine is a potent bronchodilator its use in the management of reversible airways obstruction has largely been replaced by other antimuscarinics such as ipratropium (p.1124). Atropine is sometimes used in combination preparations with antihistamines and decongestants for the symptomatic relief of symptoms of the common cold.

References.

1. Sur S, *et al.* A random double-blind trial of the combination of nebulized atropine methylnitrate and albuterol in nocturnal asthma. *Ann Allergy* 1990; **65:** 384–8.
2. Vichyanond P, *et al.* Efficacy of atropine methylnitrate alone and in combination with albuterol in children with asthma. *Chest* 1990; **98:** 637–42.

Preparations

BP 2008: Atropine Eye Drops; Atropine Eye Ointment; Atropine Injection; Atropine Tablets; Morphine and Atropine Injection;
USP 31: Atropine Sulfate Injection; Atropine Sulfate Ophthalmic Ointment; Atropine Sulfate Ophthalmic Solution; Atropine Sulfate Tablets; Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Endotropina; Klonatropina; ***Austral.:*** Atropt; ***Belg.:*** Stellatropine; ***Braz.:*** Atropion; Sulfatina†; ***Canad.:*** Atropisol†; ***Fin.:*** Oftan Atropin†; ***Ger.:*** Atropinol†; Dysurgal; ***India:*** Bell Pino-Atrin; ***Indon.:*** Isotic Cycloma; ***Israel:*** Atrospan; ***Malaysia:*** Atropt†; ***Mex.:*** Atro Grin†; Atro Ofteno; Atropisa; Tropyn; ***NZ:*** Atropt; ***Port.:*** Atropocil; ***Switz.:*** Bellafit N; Skiatropine†; ***Turk.:*** Atrosol; ***USA:*** AtroPen; Ocu-Tropine; Sal-Tropine; ***Venez.:*** Atropicel†.

Multi-ingredient: ***Arg.:*** Asmopul†; Otorinazol†; Saldeva†; Trixol†; Yanal; ***Austral.:*** Donnagel; Donnalix; Donnatab; Neo-Diophen†; ***Austria:*** Causat; Ichtho-Bellol; Lactolavol; Myocardon; ***Braz.:*** Espasmocron; Neogrein; Ormigrein; Sedabel†; Tonaton; Vagostesyl; ***Chile:*** Buton; Dipatropin; Dispasmol†; Dolospam; Papatropin†; ***Cz.:*** Spasmoveralgin Neo†; ***Ger.:*** Ichtho-Bellol compositum S†; Ichtho-Bellol†; Mydrial-Atropin†; ***Hong Kong:*** Virulex Forte; ***Hung.:*** Meristin†; ***India:*** Atrisolon; Brovon; Pino-Cort; ***Indon.:*** Aludonna; ***Israel:*** Patropin; Spasmalgin; ***Ital.:*** Cardiostenol; Deltamidrina; Genatrop; ***Mex.:*** Paliatil; Redotex; Redotex NF; ***Pol.:*** Tolargin; ***Port.:*** Cosmaxil†; ***S.Afr.:*** Colstat; Donnatal; Famucaps; Millerspas; Virobis†; ***Spain:*** Abdominol; Midriati; Sulmetin Papaver; Sulmetin Papaverina†; Tabletas Quimpe; ***Swed.:*** Dilaudid-Atropin; ***Switz.:*** Dilaudid-Atropin†; Dolopyrine†; Nardyl; Spasmosol; ***Thai.:*** Alkamine; Alumag; Alupep; Donnatal†; Droximag†; Stomac; ***UK:*** Actonorm; Brovon; Nerve Agent Antidote L4A1; Valonorm; ***USA:*** Accuhist LA†; Alkabel; Antispasmodic Elixir; Atrosept; Barbidonna†; Bellahist-D; Bellatal; Dolsed†; Donnatal; DuoDote; Emergent-Ez; Hyosophen; MHP-A; Prosed/DS; Stahist; Susano; Trac Tabs 2X†; UAA; Uridon Modified†; Urised; Uriseptic; Uritact; ***Venez.:*** Butropina; Carbargal con Atropina; Eumidral; Fenopol†.

Used as an adjunct in: ***Austral.:*** Lofenoxal; Lomotil; ***Braz.:*** Colestase; Lomotil; ***Canad.:*** Lomotil; ***Cz.:*** Reasec; ***Fr.:*** Diarsed; ***Hong Kong:*** Dhamotil; Dimotil; Lomotil; ***Hung.:*** Reasec; ***India:*** Lomofen; Lomotil; ***Irl.:*** Lomotil; ***Malaysia:*** Atrotil†; Beamotil; Dhamotil; Lomotil†; Setmotil†; ***NZ:*** Diastop; Lomotil†; ***Pol.:*** Reasec; ***Port.:*** Lomotil†; ***S.Afr.:*** Lomotil; ***Singapore:*** Beamotil; Dhamotil; Lomotil; Remodil†; ***Thai.:*** Dilomil†; Lomotil; ***Turk.:*** Lomotil; ***UAE:*** Intard; ***UK:*** Dymotil; Lomotil; ***USA:*** Enlon-Plus†; Logen; Lomotil; Lonox; Motofen; Neostigmine Min-I-Mix; ***Venez.:*** Lomotil†.

Azamethonium Bromide *(BAN, rINN)*

Azamethonii Bromidum; Azaméthonium, Bromure d'; Bromuro de azametonio; Pentamethazene Bromide; Pentaminum. 2,2′-Methyliminobis(diethyldimethylammonium) dibromide.

Азаметония Бромид

$C_{13}H_{33}Br_2N_3$ = 391.2.
CAS — 60-30-0 (azamethonium); 306-53-6 (azamethonium bromide).

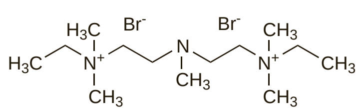

Profile

Azamethonium bromide is a ganglion blocker used in the treatment of hypertension.

Azapetine Phosphate *(BANM)*

Atsapetiinifosfaatti; Azapethine Phosphate; Azapetinfosfat; Azepine Phosphate; Ro-2-3248. 6-Allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine dihydrogen phosphate.

$C_{17}H_{17}N,H_3PO_4$ = 333.3.
CAS — 146-36-1 (azapetine); 130-83-6 (azapetine phosphate).
ATC — C04AX30.
ATC Vet — QC04AX30.

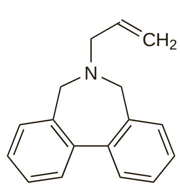

(azapetine)

Profile

Azapetine is a vasodilator that has been used, as the phosphate, in peripheral vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Peridil.

Azelnidipine *(rINN)*

Azelnidipino; Azelnidipinum; CS-905. 3-[1-(Diphenylmethyl)-3-azetidinyl] 5-isopropyl (±)-2-amino-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

Азелнидипин

$C_{33}H_{34}N_4O_6$ = 582.6.
CAS — 123524-52-7.

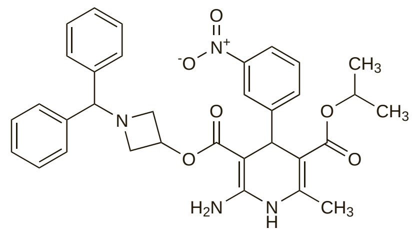

Profile

Azelnidipine is a long-acting dihydropyridine calcium-channel blocker used in the management of hypertension.

◊ Reviews.

1. Wellington K, Scott LJ. Azelnidipine. *Drugs* 2003; **63:** 2613–21.

Azimilide Hydrochloride *(BANM, rINNM)*

Azimilide, Chlorhydrate d'; Azimilide Dihydrochloride *(USAN)*; Azimilidi Hydrochloridum; Hidrocloruro de azimilida; NE-10064. 1-{[5-(*p*-Chlorophenyl)furfurylidene]amino}-3-[4-(4-methyl-1-piperazinyl)butyl]hydantoin dihydrochloride.

Азимилида Гидрохлорид

$C_{23}H_{28}ClN_5O_3,2HCl$ = 530.9.
CAS — 149908-53-2 (azimilide); 149888-94-8 (azimilide hydrochloride).

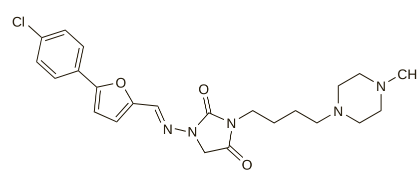

(azimilide)

Profile

Azimilide hydrochloride is a class III antiarrhythmic (p.1153) being studied in the management of supraventricular arrhythmias. It has also been tried in ventricular arrhythmias.

◊ References.

1. Clemett D, Markham A. Azimilide. *Drugs* 2000; **59:** 271–7.
2. Pritchett ELC, *et al.* Effects of azimilide on heart rate and ECG conduction intervals during sinus rhythm in patients with a history of atrial fibrillation. *J Clin Pharmacol* 2002; **42:** 388–94.
3. Connolly SJ, *et al.* Symptoms at the time of arrhythmia recurrence in patients receiving azimilide for control of atrial fibrillation or flutter: results from randomized trials. *Am Heart J* 2003; **146:** 489–93.
4. Singer I, *et al.* Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004; **43:** 39–43.
5. Camm AJ, *et al.* Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; **109:** 990–6.
6. Dorian P, *et al.* Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004; **110:** 3646–54.
7. Pritchett ELC, *et al.* Antiarrhythmic efficacy of azimilide in patients with atrial fibrillation: maintenance of sinus rhythm after conversion to sinus rhythm. *Am Heart J* 2006; **151:** 1043–9.
8. Kerr CR, *et al.* Efficacy of azimilide for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation in the presence and absence of structural heart disease. *Am J Cardiol* 2006; **98:** 215–18.
9. Pratt CM, *et al.* Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. *J Am Coll Cardiol* 2006; **48:** 471–7.
10. Lombardi F, *et al.* Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial. *Eur Heart J* 2006; **27:** 2224–31.

Azosemide *(USAN, rINN)* ⊗

Azosemida; Azosémide; Azosemidum; BM-02001; Ple-1053. 2-Chloro-5-(1*H*-tetrazol-5-yl)-4-(2-thenylamino)benzenesulphonamide.

Азосемид

$C_{12}H_{11}ClN_6O_2S_2$ = 370.8.
CAS — 27589-33-9.

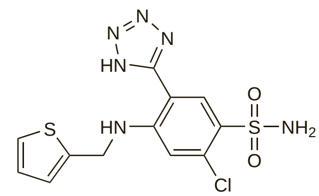

Profile

Azosemide is a diuretic with actions similar to those of furosemide (p.1292) that has been used in the management of oedema.

Bamethan Sulfate *(USAN, rINNM)*

Bametanu siarczan; Baméthan, Sulfate de; Bamethan Sulphate *(BANM)*; Bamethani Sulfas; Sulfato de bametán. 2-Butylamino-1-(4-hydroxyphenyl)ethanol sulfate.

Баметана Сульфат

$(C_{12}H_{19}NO_2)_2,H_2SO_4$ = 516.6.
CAS — 3703-79-5 (bamethan); 5716-20-1 (bamethan sulfate).
ATC — C04AA31.
ATC Vet — QC04AA31.

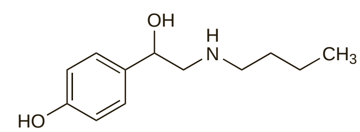

(bamethan)

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Bamethan sulfate is a vasodilator used in the management of peripheral vascular disorders.

Bamethan nicotinate and bamethan succinate have been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dilartan; ***Braz.:*** Vasculat; ***Ger.:*** Emasex A†.

Multi-ingredient: ***Arg.:*** Flaval; Grafic Forte; Vefluxan†; ***Fr.:*** Escinogel†; ***Ger.:*** Emasex-N†; Medigel†.

Barnidipine Hydrochloride *(rINNM)*

Barnidipine, Chlorhydrate de; Barnidipini Hydrochloridum; Hidrocloruro de barnidipino; LY-198561; Mepirodipine Hydrochloride; YM-730; YM-09730-5. (+)-(3′*S*,4*S*)-1-Benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

Барнидипина Гидрохлорид

$C_{27}H_{29}N_3O_6,HCl$ = 528.0.
CAS — 104713-75-9 (barnidipine); 104757-53-1 (barnidipine hydrochloride).
ATC — C08CA12.
ATC Vet — QC08CA12.

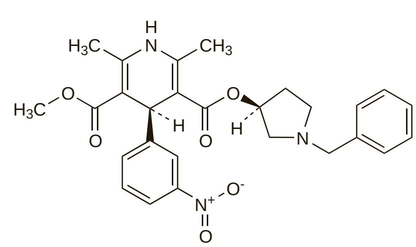

(barnidipine)

Profile

Barnidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is given orally as the hydrochloride in the management of hypertension (p.1171). The initial dose is 5 to 10 mg once daily, increased, according to response, to a usual maintenance dose of 10 to 20 mg once daily.

◊ Reviews.

1. Malhotra HS, Plosker GL. Barnidipine. *Drugs* 2001; **61:** 989–96.
2. Liau CS. Barnidipine: a new calcium channel blocker for hypertension treatment. *Expert Rev Cardiovasc Ther* 2005; **3:** 207–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dilacor†; ***Belg.:*** Vasexten; ***Cz.:*** Vasexten; ***Gr.:*** Vasexten; ***Ital.:*** Libradin; Osipine; Vasexten; ***Jpn:*** Hypoca; ***Neth.:*** Cyress; Libradin; Vasexten; ***Philipp.:*** Hypoca; ***Port.:*** Cyress; Libradin; Vasexten; ***Spain:*** Libradin; ***Thai.:*** Hypoca.

Bemetizide *(BAN, rINN)* ⊗

Bemetizida; Bémétizide; Bemetizidum; Diu-60. 6-Chloro-3,4-dihydro-3-(α-methylbenzyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Беметизид

$C_{15}H_{16}ClN_3O_4S_2$ = 401.9.

CAS — 1824-52-8.

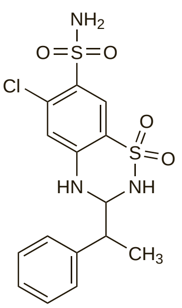

Profile

Bemetizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that is used, often with triamterene, in the treatment of oedema and hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Diucomb†; ***Ger.:*** dehydro sanol tri; Diucomb.

Bemiparin Sodium *(BAN, rINN)*

Bemiparina sódica; Bémiparine Sodique; Bemiparinum Natricum.

Бемипарин Натрий

CAS — 9041-08-1.

ATC — B01AB12.

ATC Vet — QB01AB12.

Description. Bemiparin sodium is prepared by alkaline degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The average relative molecular mass is about 3600 (3000 to 4200). The degree of sulfation is about 2 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with bemiparin sodium may be reduced by intravenous protamine sulfate; 1.4 mg of protamine sulfate is stated to inhibit the effects of 100 units of bemiparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Bemiparin sodium is rapidly absorbed after subcutaneous injection with a bioavailability of about 96%. Peak plasma activity is reached in about 2 to 4 hours, depending on the dose. The elimination half-life is about 5 to 6 hours.

Uses and Administration

Bemiparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity. It is used for the prevention and treatment of venous thromboembolism (p.1189), and to prevent clotting during extracorporeal circulation.

In the prophylaxis of **venous thromboembolism** during general surgery with moderate risk, bemiparin sodium is given subcutaneously in a dose of 2500 units once daily, with the first dose given 2 hours before or 6 hours after surgery; in patients undergoing orthopaedic surgery with high risk of thromboembolism the dose should be 3500 units initially and then once daily. Treatment should be continued for at least 7 to 10 days and until the patient is fully ambulant. For treatment of thromboembolism, a dose of 115 units/kg is given subcutaneously once daily.

In some countries bemiparin sodium is used for prophylaxis in non-surgical patients at moderate or high risk of venous thromboembolism, a dose of 2500 or 3500 units being given daily according to risk. Bemiparin sodium is also used in some countries for secondary prevention of venous thromboembolism in patients with transitory risk factors, a dose of 3500 units being given daily for up to 3 months as an alternative to oral anticoagulant therapy.

For the prevention of clotting in the extracorporeal circulation during **haemodialysis**, bemiparin sodium is given into the arterial side of the dialyser in a single dose of 2500 units for patients weighing less than 60 kg and 3500 units for patients weighing more than 60 kg.

◊ References.

1. Kakkar VV, *et al*. A comparative double-blind, randomised trial of a new second generation LMWH (bemiparin) and UFH in the prevention of post-operative venous thromboembolism. *Thromb Haemost* 2000; **83:** 523–9.
2. Chapman TM, Goa KL. Bemiparin: a review of its use in the prevention of venous thromboembolism and treatment of deep vein thrombosis. *Drugs* 2003; **63:** 2357–77.
3. Martínez-González J, *et al*. Bemiparin: second-generation, low-molecular-weight heparin for treatment and prophylaxis of venous thromboembolism. *Expert Rev Cardiovasc Ther* 2008; **6:** 793–802.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Badyket; ***Cz.:*** Zibor; ***Gr.:*** Ivor; Ivormax; ***Hung.:*** Zibor; ***Ital.:*** Ivor; ***Port.:*** Ivor; ***Spain:*** Hibor; ***UK:*** Zibor.

Benazepril Hydrochloride

(BANM, USAN, rINNM)

Benatsepriilihydrokloridi; Bénazépril, chlorhydrate de; Benazepril Hidroklorür; Benazeprilhydroklorid; Benazeprili hydrochloridum; Benazeprili Hydrochloridum; CGS-14824A (benazepril or benazepril hydrochloride); Hidrocloruro de benazepril. {(3*S*)-3-[(1*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-1-yl}acetic acid hydrochloride; 1-Carboxymethyl-3-[1-ethoxycarbonyl-3-phenyl-(1*S*)-propylamino]-2,3,4,5-tetrahydro-1*H*-1(3*S*)-benzazepin-2-one hydrochloride.

Беназеприла Гидрохлорид

$C_{24}H_{28}N_2O_5$,HCl = 461.0.

CAS — 86541-75-5 (benazepril); 86541-74-4 (benazepril hydrochloride).

ATC — C09AA07.

ATC Vet — QC09AA07.

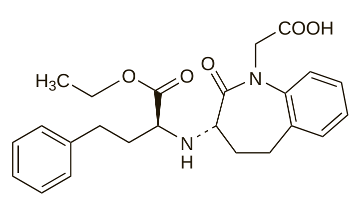

(benazepril)

Pharmacopoeias. In *US.*

USP 31 (Benazepril Hydrochloride). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol. Store at a temperature below 30°, preferably between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Benazepril acts as a prodrug of the diacid benazeprilat, its active metabolite. At least 37% of an oral dose of benazepril is absorbed. Benazepril is almost completely metabolised in the liver to benazeprilat. Peak plasma concentrations of benazeprilat after an oral dose of benazepril have been achieved in 1 to 2 hours in the fasting state or 2 to 4 hours in the nonfasting state. Both benazepril and benazeprilat are about 95% bound to plasma proteins. Benazeprilat is excreted mainly in the urine; about 11 to 12% is excreted in the bile. The effective half-life for accumulation of benazeprilat is 10 to 11 hours after multiple doses of benazepril. The elimination of benazeprilat is slowed in renal impairment, although biliary excretion may compensate to some extent. Small amounts of benazepril and benazeprilat are distributed into breast milk.

◊ References.

1. Kaiser G, *et al.* Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril HCl (CGS 14 824A) in healthy volunteers after single and repeated administration. *Biopharm Drug Dispos* 1989; **10:** 365–76.
2. Kaiser G, *et al.* Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations. *Am Heart J* 1989; **117:** 746–51.
3. Kaiser G, *et al.* Pharmacokinetics and pharmacodynamics of the ace inhibitor benazepril hydrochloride in the elderly. *Eur J Clin Pharmacol* 1990; **38:** 379–85.
4. Macdonald N-J, *et al.* A comparison in young and elderly subjects of the pharmacokinetics and pharmacodynamics of single and multiple doses of benazepril. *Br J Clin Pharmacol* 1993; **36:** 201–4.

Uses and Administration

Benazepril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Benazepril owes its activity to benazeprilat to which it is converted after oral dosage. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Benazepril is given orally as the hydrochloride.

In the treatment of **hypertension**, the usual initial dose of benazepril hydrochloride is 10 mg once daily. An initial dose of 5 mg once daily is suggested for patients with renal impairment (see below) or who are receiving a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before benazepril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose; doses of up to 80 mg daily have been used.

In the treatment of **heart failure** the usual initial dose of benazepril hydrochloride is 2.5 mg once daily, adjusted according to response to a maximum dose of 20 mg daily.

Administration in children. Experience with benazepril in children is limited. US licensed product information recommends an initial oral dose of 200 micrograms/kg once daily for hypertension in children 6 years of age and over. Maintenance doses up to 600 micrograms/kg daily (maximum 40 mg daily) have been studied. Insufficient evidence is available to recommend doses for younger children or for any children with creatinine clearance below 30 mL/minute.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, the initial dose of benazepril hydrochloride for hypertension is 5 mg once daily and the maintenance dose should not exceed 40 mg daily.

Preparations

USP 31: Benazepril Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Boncordin†; ***Belg.:*** Cibacen; ***Braz.:*** Lotensin; ***Canad.:*** Lotensin; ***Denm.:*** Cibacen; ***Fr.:*** Briem; Cibacene; ***Ger.:*** Cibacen; ***Gr.:*** Cibacen; ***Hung.:*** Lotensin; ***India:*** Benace; ***Indon.:*** Cibacen; ***Irl.:*** Cibacen; ***Israel:*** Cibacen; ***Ital.:*** Cibacen; Tensanil; Zinadril; ***Mex.:*** Lotensin; ***Neth.:*** Cibacen; ***Philipp.:*** Cibacen; ***Pol.:*** Lisonid; Lotensin; ***Rus.:*** Lotensin (Лотензин); ***S.Afr.:*** Cibace; ***Spain:*** Cibacen; Labopal; ***Switz.:*** Cibacen; ***Turk.:*** Cibacen; ***USA:*** Lotensin; ***Venez.:*** Lotensin†.

Multi-ingredient: ***Arg.:*** Adrebloc†; Amlopril; Amzepril†; Arteriosan Plus; Coroval B; Ilduc Duo; Pelmec Duo; Terloc Duo; ***Braz.:*** Lotensin H; ***Fr.:*** Briazide; Cibadrex; ***Ger.:*** Benazeplus; Benazepril comp; Benazepril HCT; Cibadrex; ***Gr.:*** Cibadrex; ***Hung.:*** Lotensin HCT; ***India:*** Amace-BP; ***Ital.:*** Cibadrex; Tensadiur; Zinadiur; ***Neth.:*** Cibadrex; ***Pol.:*** Lotensin HCT; ***S.Afr.:*** Cibadrex; ***Spain:*** Cibadrex; Labodrex; ***Switz.:*** Cibadrex; ***Turk.:*** Cibadrex; ***USA:*** Lotensin HCT; Lotrel; ***Venez.:*** Amlibon B.

Bencyclane Fumarate *(rINNM)*

Bencyclane, Fumarate de; Bencyclane Hydrogen Fumarate; Bencyclani Fumaras; Bensiklan Hidrojen Fumarat; Fumarato de benciclano. 3-(1-Benzylcycloheptyloxy)-*NN*-dimethylpropylamine hydrogen fumarate.

Бенциклана Фумарат

$C_{19}H_{31}NO,C_4H_4O_4$ = 405.5.

CAS — 2179-37-5 (bencyclane); 14286-84-1 (bencyclane fumarate).

ATC — C04AX11.

ATC Vet — QC04AX11.

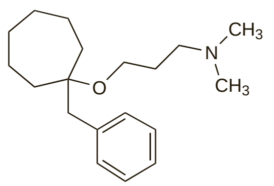

(bencyclane)

Profile

Bencyclane fumarate is a vasodilator used in the management of peripheral (p.1178) and cerebral vascular disorders (p.1165) in usual oral doses of 100 to 200 mg three times daily. It has also been given intravenously.

Bencyclane acefyllinate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Ludilat; ***Braz.:*** Fludilat; ***Ger.:*** Fludilat; ***Hung.:*** Halidor; ***Indon.:*** Fludilat; ***Pol.:*** Halidor; ***Port.:*** Fludilat†; Fluxema†; ***Rus.:*** Halidor (Галидор); ***Thai.:*** Fludilat; ***Turk.:*** Angiodel; ***Venez.:*** Dantifar†; Fludilat.

Bendroflumethiazide *(BAN, rINN)* ⊗

Bendrofluaz.; Bendrofluazide; Bendroflumethiazid; Bendrofluméthiazide; Bendroflumethiazidum; Bendroflumetiatsidi; Bendroflumetiazid; Bendroflumetiazida; Bendroflumetiazidas; Benzydroflumethiazide; FT-81. 3-Benzyl-3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Бендрофлуметиазид

$C_{15}H_{14}F_3N_3O_4S_2$ = 421.4.

CAS — 73-48-3.

ATC — C03AA01.

ATC Vet — QC03AA01.

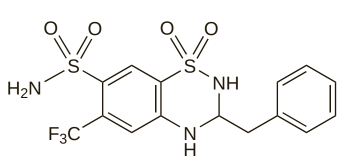

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Bendroflumethiazide). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone.

USP 31 (Bendroflumethiazide). A white to cream-coloured, finely divided, crystalline powder. Is odourless or has a slight odour. Practically insoluble in water; soluble 1 in 23 of alcohol and 1 in 200 of ether; freely soluble in acetone. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Breast feeding. Bendroflumethiazide is used to suppress lactation (see Uses below). However, the American Academy of Pediatrics considers[1] that it is usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. Bendroflumethiazide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Overdosage. Tonic-clonic convulsions occurred in a previously healthy 14-year-old girl after ingestion of bendroflumethiazide 150 to 200 mg.[1] The convulsions were not associated with any measurable disturbance of serum electrolytes.

1. Hine KR, *et al.* Bendrofluazide convulsions. *Lancet* 1982; **i:** 564.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and to have a plasma half-life of about 3 or 4 hours. It is highly bound to plasma proteins. There are indications that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine.

◊ References.

1. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide. *Clin Pharmacol Ther* 1977; **22:** 385–8.
2. Beermann B, *et al.* Pharmacokinetics of bendroflumethiazide in hypertensive patients. *Eur J Clin Pharmacol* 1978; **13:** 119–24.

Uses and Administration

Bendroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is used for hypertension (p.1171), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. It is also used for oedema, including that associated with heart failure (p.1165), and with renal or hepatic disorders. Other indications have included the suppression of lactation.

Bendroflumethiazide is given orally; diuresis starts in about 2 hours after a dose, peaks after about 3 to 6 hours, and lasts for 12 to 18 hours or longer.

In the treatment of **hypertension** bendroflumethiazide 2.5 mg daily, either alone or with other antihypertensives, is usually adequate although doses of up to 20 mg daily have sometimes been suggested.

In the treatment of **oedema** the usual initial dose is 5 to 10 mg daily or on alternate days; in some cases initial doses of up to 20 mg may be necessary. Maintenance dosage schedules have varied from 2.5 to 10 mg once to three times weekly in the UK to 2.5 to 5 mg daily or intermittently in the USA.

An initial dose for children is up to 400 micrograms/kg daily, reduced to 50 to 100 micrograms/kg for maintenance.

Doses of 5 mg twice daily for about 5 days have been used to **suppress lactation**.

In the management of **idiopathic hypercalciuria** (see Renal Calculi, p.2181) the *BNF* considers that, with increased fluid intake, a sufficient dose is 2.5 mg daily.

Preparations

BP 2008: Bendroflumethiazide Tablets;
USP 31: Bendroflumethiazide Tablets; Nadolol and Bendroflumethiazide Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Aprinox; ***Denm.:*** Centyl; ***Irl.:*** Centyl; ***Norw.:*** Centyl; ***NZ:*** Neo-NaClex; ***Swed.:*** Salures; ***UK:*** Aprinox; Neo-NaClex; ***USA:*** Naturetin†.

Multi-ingredient: ***Arg.:*** Hidromens†; Pertenso; Sumal; ***Austria:*** Inderetic†; Sali-Aldopur; ***Belg.:*** Inderetic†; ***Braz.:*** Diserim; ***Denm.:*** Centyl med Kaliumklorid; ***Fr.:*** Precyclan; Tensionorme; ***Ger.:*** Docidrazin†; Dociretic; Pertenso N; Sali-Aldopur†; Sotaziden N; Spirostada comp†; Tensoflux; ***Irl.:*** Centyl K; Low Centyl K; ***Mex.:*** Corgaretic; ***Neth.:*** Inderetic; ***Norw.:*** Centyl med Kaliumklorid; ***S.Afr.:*** Corgaretic; Inderetic†; ***Spain:*** Betadipresan Diu†; Neatenol Diu; Neatenol Diuvas; Spirometon; ***Swed.:*** Centyl K; Salures-K; ***Switz.:*** Inderetic†; ***UK:*** Centyl K; Corgaretic†; Inderetic†; Inderex†; Neo-NaClex-K; Prestim; ***USA:*** Corzide; Rauzide†.

Benfluorex Hydrochloride *(BANM, pINNM)*

Benfluoreksihydrokloridi; Benfluorekso hidrochloridas; Benfluorex, chlorhydrate de; Benfluorex-hidroklorid; Benfluorex-hydrochlorid; Benfluorexhydroklorid; Benfluorexi hydrochloridum; Hidrocloruro de benfluorex; JP-992; SE-780. 2-[α-Methyl-3-(trifluoromethyl)phenethylamino]ethyl benzoate hydrochloride.

Бенфлуорекса Гидрохлорид

$C_{19}H_{20}F_3NO_2,HCl$ = 387.8.

CAS — 23602-78-0 (benfluorex); 35976-51-3 (± benfluorex); 23642-66-2 (benfluorex hydrochloride).

ATC — C10AX04.

ATC Vet — QC10AX04.

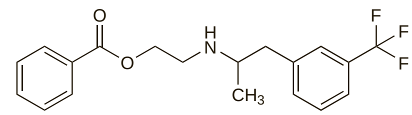

(benfluorex)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Benfluorex Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble or soluble in alcohol; soluble in dichloromethane; freely soluble in methyl alcohol.

Profile

Benfluorex hydrochloride is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). It has also been used as an adjunct in the management of type 2 diabetes mellitus (p.431).

Benfluorex hydrochloride is given orally in usual doses of 150 mg three times daily with meals.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Mediator; ***Gr.:*** Lipophoral; ***Hong Kong:*** Mediaxal; ***Ital.:*** Mediaxal†; ***Malaysia:*** Axal; Mediaxal; ***Port.:*** Mediator; ***Singapore:*** Mediaxal; ***Spain:*** Modulator†; ***Venez.:*** Lipascor.

Benidipine Hydrochloride *(rINNM)*

Bénidipine, Chlorhydrate de; Benidipini Hydrochloridum; Hidrocloruro de benidipino; KW-3049; Nakadipine Hydrochloride. (±)-(R^*)-3-[(R^*)-1-Benzyl-3-piperidyl]methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

Бенидипина Гидрохлорид

$C_{28}H_{31}N_3O_6,HCl$ = 542.0.

CAS — 105979-17-7 (benidipine); 91599-74-5 (benidipine hydrochloride).

ATC — C08CA15.

ATC Vet — QC08CA15.

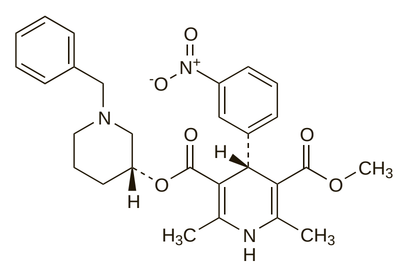

(benidipine)

Pharmacopoeias. In *Jpn.*

Profile

Benidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is given orally as the hydrochloride in the management of hypertension (p.1171) and angina pectoris (p.1157). In hypertension, the usual dose is 2 to 4 mg once daily, increased to 8 mg once daily if necessary. In angina pectoris, the usual dose is 4 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Caritec; ***Jpn:*** Coniel; ***Philipp.:*** Coniel.

Benzthiazide *(BAN, rINN)* ⊗

Benzthiazidum; Benztiazida; P-1393. 3-Benzylthiomethyl-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Бензтиазид

$C_{15}H_{14}ClN_3O_4S_3$ = 431.9.
CAS — 91-33-8.

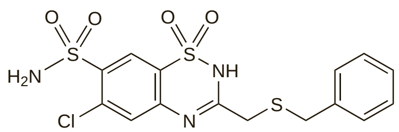

Profile

Benzthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is used for oedema, including that associated with heart failure (p.1165), and has also been used for hypertension (p.1171). It has been given alone but is often given with triamterene. The usual initial oral dose for oedema is 75 mg daily, although higher doses have been given. The dose is reduced for maintenance; intermittent dosing may be adequate.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Exna†.

Multi-ingredient: ***India:*** Ditide; ***Switz.:*** Dyrenium compositum; ***UK:*** Dytide.

Bepridil Hydrochloride *(BANM, USAN, rINNM)*

Bepridiilihydrokloridi; Bépridil, Chlorhydrate de; Bepridilhydroklorid; Bepridili Hydrochloridum; CERM-1978; Hidrocloruro de bepridil; Org-5730. *N*-Benzyl-*N*-(3-isobutoxy-2-pyrrolidin-1-ylpropyl)aniline hydrochloride monohydrate.

Бепридила Гидрохлорид

$C_{24}H_{34}N_2O,HCl,H_2O$ = 421.0.
CAS — 64706-54-3 (bepridil); 49571-04-2 (bepridil); 64616-81-5 (anhydrous bepridil hydrochloride); 74764-40-2 (bepridil hydrochloride monohydrate).
ATC — C08EA02.
ATC Vet — QC08EA02.

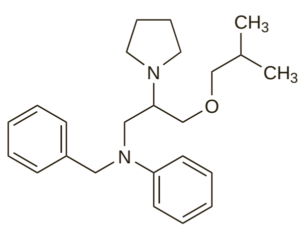

(bepridil)

Profile

Bepridil is a calcium-channel blocker (p.1154). It has similar properties to nifedipine (p.1350) but reduces the heart rate and does not usually cause reflex tachycardia. It also has antiarrhythmic activity. It is not related chemically to other calcium-channel blockers such as diltiazem, nifedipine, or verapamil.

Bepridil is used as the hydrochloride in the management of angina pectoris (p.1157). Ventricular arrhythmias, including torsade de pointes, and agranulocytosis have been associated with bepridil and, as a result, it is usually reserved for patients who have not responded adequately to other anti-anginal drugs. The usual initial dose is 200 mg of bepridil hydrochloride orally once daily. Provided that prolongation of the QT interval has not occurred after 2 to 4 weeks, the dose may be increased, if necessary, to a maximum of 300 mg once daily. Elderly patients and those with hepatic or renal impairment may be given an initial dose of 100 mg once daily; in exceptional circumstances this may be increased to a maximum of 200 mg once daily.

◊ References.

1. Hollingshead LM, *et al.* Bepridil: a review of its pharmacological properties and therapeutic use in stable angina pectoris. *Drugs* 1992; **44:** 835–57.
2. Awni WM, *et al.* Pharmacokinetics of bepridil and two of its metabolites in patients with end-stage renal disease. *J Clin Pharmacol* 1995; **35:** 379–83.

Porphyria. Bepridil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Unicordium; ***USA:*** Vascor†.

Beraprost Sodium *(USAN, rINNM)*

Beraprost sódico; Béraprost Sodique; ML-1129; ML-1229 (beraprost); Natrii Beraprostum; TRK-100. Sodium (±)-(1*R*,2*R*,3a*S*,8b*S*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1*H*-cyclopenta[*b*]benzofuran-5-butyrate.

Натрий Берапрост

$C_{24}H_{29}NaO_5$ = 420.5.
CAS — 88430-50-6 (beraprost); 88475-69-8 (beraprost sodium).
ATC — B01AC19.
ATC Vet — QB01AC19.

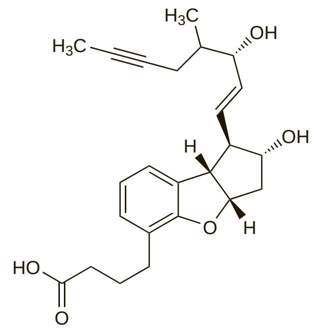

(beraprost)

Profile

Beraprost is a synthetic analogue of epoprostenol (prostacyclin) that causes vasodilatation and prevents platelet aggregation. It is given orally as the sodium salt in the management of pulmonary hypertension (p.1179) and peripheral vascular disease (p.1178).

In primary pulmonary hypertension, beraprost sodium is given in an initial dose of 60 micrograms daily in three divided doses; this may be increased gradually if necessary to 180 micrograms daily in three or four divided doses. For peripheral vascular disease a dose of 120 micrograms daily in three divided doses is used.

Adverse effects of beraprost include headache, flushing, nausea, diarrhoea, and increased liver enzyme, bilirubin, and triglyceride concentrations.

Cardiovascular disorders. References to the use of beraprost for pulmonary hypertension or intermittent claudication;[1-7] results of studies for the latter indication have been conflicting. It has been tried with sildenafil in patients with pulmonary hypertension.[8]

1. Nagaya N, *et al.* Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999; **34:** 1188–92.
2. Lievre M, *et al.* Oral beraprost sodium, a prostaglandin I analogue, for intermittent claudication: a double-blind, randomized, multicenter controlled trial. *Circulation* 2000; **102:** 426–31.
3. Melian EB, Goa KL. Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 2002; **62:** 107–33.
4. Galiè N, *et al.* Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; **39:** 1496–1502.
5. Mohler ER, *et al.* Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I analogue: a double-blinded, randomized, controlled trial. *J Am Coll Cardiol* 2003; **41:** 1679–86.
6. Barst RJ, *et al.* Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; **41:** 2119–25.
7. Hashiguchi M, *et al.* Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication. *Yakugaku Zasshi* 2004; **124:** 321–32.
8. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Dorner; ***Jpn:*** Dorner; ***Philipp.:*** Dorner; ***Thai.:*** Dorner.

Beta Blockers ⊗

β-Bloqueantes.

Бета-блокаторы

Beta blockers (beta-adrenoceptor blocking drugs or antagonists) are competitive antagonists of catecholamines at beta-adrenergic receptors in a wide range of tissues. Although they have broadly similar properties they differ in their affinity for $beta_1$ or $beta_2$ receptor subtypes, intrinsic sympathomimetic activity, membrane-stabilising activity, blockade of alpha-adrenergic receptors, and pharmacokinetic properties including differences in lipid solubility (see Table 4, below, for some of these characteristics). These differences may affect the choice of drug in specific situations.

Table 4. Characteristics of beta blockers.

Beta blocker	$Beta_1$ selectivity	ISA*	MSA**	Vasodilator activity
Acebutolol	+	+	+	0
Alprenolol	0	+	0	0
Atenolol	+	0	0	0
Betaxolol	+	0	0	0
Bisoprolol	+	0	0	0
Carteolol	0	+	0	0
Carvedilol	0	0	0	+
Celiprolol	+	+	–	+
Esmolol	+	0	0	0
Labetalol	0	0	0	+
Levobunolol	0	0	0	0
Metipranolol	0	0	0	0
Metoprolol	+	0	0	0
Nadolol	0	0	0	0
Nebivolol	+	0	0	+
Oxprenolol	0	+	+	0
Penbutolol	0	0	0	0
Pindolol	0	++	0	0
Propranolol	0	0	++	0
Sotalol	0	0	0	0
Timolol	0	0	0	0

0 = absent or low; + = moderate; ++ = high; – = no information
* ISA = Intrinsic sympathomimetic activity
** MSA = Membrane-stabilising activity

Adverse Effects

Beta blockers are generally well tolerated and most adverse effects are mild and transient. Reactions may be more severe after intravenous than oral doses; ocular use has also been associated with systemic adverse effects. The most frequent and serious adverse effects are related to their beta-adrenergic blocking activity. Among the most serious adverse effects are heart failure, heart block, and bronchospasm. Troublesome subjective effects include fatigue and coldness of the extremities; when beta blockers are used for long-term treatment of asymptomatic diseases such as hypertension, such effects may be an important determinant of patient compliance.

Cardiovascular effects include bradycardia and hypotension; heart failure or heart block may be precipitated or worsened in patients with underlying cardiac disorders. Abrupt withdrawal of beta blockers may exacerbate angina and may lead to sudden death. (For further details on withdrawal of beta blockers, see Precautions, below.)

Bronchospasm, shortness of breath, and dyspnoea may be precipitated, particularly in patients with a history of obstructive airways disease, due to blockade of $beta_2$ receptors in bronchial smooth muscle. Drugs with selectivity for $beta_1$ receptors or with intrinsic sympathomimetic activity at $beta_2$ receptors may be less likely to induce bronchospasm (but see Precautions, below). Pneumonitis, pulmonary fibrosis, and pleurisy have also been reported.

CNS effects include headache, depression, dizziness, hallucinations, confusion, amnesia, and sleep disturbances including nightmares. Coma and convulsions have been reported after beta-blocker overdosage. Beta blockers that are lipid soluble are more likely to enter the brain and would be expected to be associated with a higher incidence of CNS adverse effects, although this is not proven.

Fatigue is a common adverse-effect of beta blockers. Paraesthesia, arthralgia, and myopathies, including muscle cramps, have been reported. Reduced peripheral circulation can produce coldness of the extremities and may exacerbate peripheral vascular disease such as Raynaud's syndrome.

Adverse gastrointestinal effects include nausea and vomiting, diarrhoea, constipation, and abdominal cramping.

Beta blockers interfere with carbohydrate and lipid metabolism and can produce hypoglycaemia, hyperglycaemia, and changes in blood concentrations of triglycerides and cholesterol (see below for further details).

Skin rash, pruritus, exacerbation of psoriasis, excess sweating, and reversible alopecia have occurred with use of beta blockers.

Decreased tear production, blurred vision, conjunctivitis, and soreness are among the ocular symptoms that have been reported. Adverse effects specific to ocular use are also discussed below.

Haematological reactions include nonthrombocytopenic purpura, thrombocytopenia, and rarely agranulocytosis. Transient eosinophilia can occur.

An asymptomatic increase in antinuclear antibodies has occurred with many beta blockers; SLE has also been reported. Other adverse effects reported with some beta blockers include dry mouth, raised liver enzymes, male impotence, sclerosing peritonitis, and retroperitoneal fibrosis.

Carcinogenicity. An apparent excess of deaths from cancer was noted in elderly men, but not women, given atenolol during a study of antihypertensive therapy.[1] However, 2 subsequent studies found no evidence of a link between atenolol and cancer.[2,3]

1. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304:** 405–12.
2. Fletcher AE, *et al.* Cancer mortality and atenolol treatment. *BMJ* 1993; **306:** 622–3.
3. Hole DJ, *et al.* Incidence of and mortality from cancer in hypertensive patients. *BMJ* 1993; **306:** 609–11.

Effects on bones and joints. Adverse effects on the bones and joints have occurred in patients receiving beta blockers. Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA;[1] there had also been 6 reports of similar symptoms with propranolol, and 1 with atenolol. A case of polymyalgia rheumatica-like syndrome has also been reported.[2]

However, epidemiological studies have also suggested that beta blockers may increase bone mineral density[3] and reduce the risk of fractures,[3,4] although another study[5] could not confirm this effect.

1. Sills JM, Bosco L. Arthralgia associated with β-adrenergic blockade. *JAMA* 1986; **255:** 198–9.
2. Snyder S. Metoprolol-induced polymyalgia-like syndrome. *Ann Intern Med* 1991; **114:** 96–7.
3. Pasco JA, *et al.* β-Adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004; **19:** 19–24.
4. Schlienger RG, *et al.* Use of β-blockers and risk of fractures. *JAMA* 2004; **292:** 1326–32.
5. Reid IR, *et al.* β-Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res* 2005; **20:** 613–18.

Effects on the breast. A 54-year-old woman developed breast pain and swelling a few weeks after starting atenolol for hypertension;[1] it resolved when the atenolol was stopped.

1. Kelleher JA. Atenolol-induced breast pain in a woman with hypertension. *Ann Pharmacother* 2006; **40:** 990–2.

Effects on carbohydrate metabolism. The sympathetic nervous system is involved in the control of carbohydrate metabolism and beta blockers can interfere with carbohydrate and insulin regulation; both hypoglycaemia and hyperglycaemia have been reported in patients with no history of diabetes, as well as in patients with types 1 or 2 diabetes mellitus.

Beta blockers cause hypoglycaemia in non-diabetics, possibly by increasing peripheral glucose uptake through increased insulin sensitivity.[1] Those most at risk include fasting or nutritionally-compromised patients, haemodialysis patients, neonates after maternal treatment with beta blockers, and patients with liver disease;[1] those undertaking vigorous exercise[2] and children may also be at risk. Glucose metabolism is controlled by the action of catecholamines at the $beta_2$ receptor, and therefore cardioselective beta blockers are less likely to cause hypoglycaemia than their non-cardioselective counterparts;[1] however, hypoglycaemia was reported[3] in a non-diabetic patient given the cardioselective beta blocker metoprolol pre-operatively for cardiovascular protection.

Traditionally beta blockers have been considered unsafe in diabetics because of reports that they may precipitate and prolong hypoglycaemia, an effect that was first seen in the 1960s in adult type 1 diabetics taking propranolol; however, in a long-term study[4] in type 2 diabetics, there was no difference in the incidence of hypoglycaemia in patients receiving captopril or the cardioselective beta blocker atenolol, and both significantly improved outcome. A case-control study[5] and a review[6] of the use of beta blockers in diabetic patients both concluded that the incidence of hypoglycaemia was not increased and that beta blockers were appropriate therapy for diabetics. Nonetheless, beta blockers may mask the adrenaline-mediated symptoms of hypoglycaemia such as tachycardia and tremor, and non-cardioselective beta blockers may delay recovery in patients given glucose for hypoglycaemia;[6] cardioselective beta blockers are less likely to mask the signs of hypoglycaemia and are therefore preferred in diabetics.[7]

Both cardioselective and non-cardioselective beta blockers may increase fasting blood glucose concentrations in non-diabetic hypertensive patients,[8,9] and epidemiological studies have shown that the risk of developing diabetes mellitus is increased by beta blockers.[10-12] The mechanism is possibly through inhibition of pancreatic insulin release,[1,13] although it has been suggested that hypertensive patients are predisposed to diabetes mellitus and beta blockers act as a precipitating factor;[10,14] changes in bodyweight in some of the studies may also have confounded the results.[6] Hyperglycaemia can also occur in diabetic patients treated with beta blockers;[14] however, the established benefits generally outweigh the risk.

Although the adverse effects of beta blockers on carbohydrate metabolism are well-established, there is some evidence that the newer, vasodilating beta blockers, such as carvedilol[15,16] and nebivolol,[17,18] may have beneficial effects on insulin resistance or glucose control, and weight gain may be less with carvedilol.[19] New onset diabetes was also more likely to occur with metoprolol than carvedilol in a study on patients with heart failure.[20]

1. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
2. Holm G, *et al.* Severe hypoglycaemia during physical exercise and treatment with beta-blockers. *BMJ* 1981; **282:** 1360.
3. Brown DR, Brown MJ. Hypoglycemia associated with preoperative metoprolol administration. *Anesth Analg* 2004; **99:** 1427–8.
4. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; **317:** 713–20.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.
6. Sawicki PT, Siebenhofer A. Betablocker treatment in diabetes mellitus. *J Intern Med* 2001; **250:** 11–17.
7. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
8. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol or hydrochlorothiazide alone for the initial treatment of hypertension IV: effect on plasma glucose and glucose tolerance. *Hypertension* 1985; **7:** 1008–16.
9. Pollare T, *et al.* Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 1989; **298:** 1152–7.
10. Samuelsson O, *et al.* Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial in Göteborg, Sweden. *J Hum Hypertens* 1994; **8:** 257–63.
11. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
12. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
13. Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA* 2001; **286:** 1945–8.
14. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part 1). *Drugs* 1990; **40:** 6–18.
15. Bakris GL, *et al.* Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; **292:** 2227–36. Correction. *ibid.*; 2583.
16. Giugliano D, *et al.* Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension: a randomized, controlled trial. *Ann Intern Med* 1997; **126:** 955–9.
17. Celik T, *et al.* Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens* 2006; **24:** 591–6.
18. Poirier L, *et al.* Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. *J Hypertens* 2001; **19:** 1429–35.
19. Messerli FH, *et al.* Body weight changes with beta-blocker use: results from GEMINI. *Am J Med* 2007; **120:** 610–15.
20. Torp-Pedersen C, *et al.* Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93:** 968–73.

Effects on the circulation. Hypotension is a recognised adverse effect of beta blockers, and severe reactions have been reported. Near-fatal shock occurred[1] in an elderly patient with chronic bronchitis and angina pectoris within 40 minutes of taking acebutolol 400 mg. Hypotension, leading to a rise in serum creatinine indicative of kidney ischaemia, occurred[2] in 2 women after a single oral dose of atenolol 100 mg or 2 oral doses of atenolol 50 mg; both had presented with severe hypertension, hyponatraemia, hypokalaemia, and high renin activity. Renal artery thrombosis believed to be due to the hypotensive effect of atenolol was reported[3] in a 70-year-old man with a history of circulatory and cardiac disorders. He had received atenolol 100 mg for treatment of moderate hypertension.

Beta blockers have been tried in neurally mediated hypotension (see Hypotension under Uses, below), but this may be hazardous: a 27-year-old man had[4] ten episodes of syncope with severe bradycardia after taking atenolol for recurrent vasovagal syncope; episodes ceased on stopping the atenolol. The authors suggested that the atenolol aggravated the vasovagal syncope, and recommended careful monitoring of patients given beta blockers for this condition.

1. Tirlapur VG, *et al.* Shock syndrome after acebutolol. *Br J Clin Pract* 1986; **40:** 33–4.
2. Kholeif M, Isles C. Profound hypotension after atenolol in severe hypertension. *BMJ* 1989; **298:** 161–2.
3. Shaw AB, Gopalka SK. Renal artery thrombosis caused by antihypertensive treatment. *BMJ* 1982; **285:** 1617.
4. Wang C-C, *et al.* Worsening of vasovagal syncope after betablocker therapy. *Chest* 1994; **106:** 963–5.

Effects on the gastrointestinal tract. Sclerosing peritonitis was noted as part of the 'oculomucocutaneous syndrome' that occurred with practolol. However, while both sclerosing peritonitis and retroperitoneal fibrosis have also been reported with a number of other beta blockers, including atenolol,[1,2] metoprolol,[3,4] oxprenolol,[5] propranolol,[6] sotalol,[7] and timolol,[8,9] a review[10] of 100 cases of retroperitoneal fibrosis concluded that beta blockers could not be considered as the cause.

Abdominal pain and bloody diarrhoea were reported[11] in a patient the day after treatment was started with propranolol; symptoms were attributed to splanchnic vasoconstriction caused by the drug, which may have exacerbated pre-existing mesenteric ischaemia.

1. Nielsen BV, Pedersen KG. Sclerosing peritonitis associated with atenolol. *BMJ* 1985; **290:** 518.
2. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol. *BMJ* 1980; **280:** 864.
3. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. *BMJ* 1982; **284:** 83–4.
4. Clark CV, Terris R. Sclerosing peritonitis associated with metoprolol. *Lancet* 1983; **i:** 937.
5. McCluskey DR, *et al.* Oxprenolol and retroperitoneal fibrosis. *BMJ* 1980; **281:** 1459–60.
6. Pierce JR, *et al.* Propranolol and retroperitoneal fibrosis. *Ann Intern Med* 1981; **95:** 244.
7. Laakso M, *et al.* Retroperitoneal fibrosis associated with sotalol. *BMJ* 1982; **285:** 1085–6.
8. Baxter-Smith DC, *et al.* Sclerosing peritonitis in patient on timolol. *Lancet* 1978; **ii:** 149.
9. Rimmer E, *et al.* Retroperitoneal fibrosis associated with timolol. *Lancet* 1983; **i:** 300.

10. Pryor JP, *et al.* Do beta-adrenoceptor blocking drugs cause retroperitoneal fibrosis? *BMJ* 1983; **287:** 639–41.
11. Köksal AŞ, *et al.* Propranolol-exacerbated mesenteric ischemia in a patient with hyperthyroidism. *Ann Pharmacother* 2005; **39:** 559–62.

Effects on lipid metabolism. The adrenergic system is involved in the control of lipid metabolism and beta blockers may therefore have effects on plasma-lipid concentrations. In general, beta blocker therapy results in increased concentrations of very-low-density lipoprotein and triglycerides, a reduction in high-density lipoprotein, and no change in low-density lipoprotein.[1] These effects may be less pronounced with $beta_1$ cardioselective drugs, beta blockers with intrinsic sympathomimetic activity, and beta blockers that also block alpha-adrenergic receptors. For example, pindolol,[2,3] a beta blocker with intrinsic sympathomimetic activity, and arotinolol[4] and carvedilol,[5] which possess alpha-adrenergic blocking properties, are reported to have no adverse effects on plasma-lipid concentrations, although acute pancreatitis due to severe hypertriglyceridaemia has been reported[6] in a patient treated with metoprolol followed by atenolol. However, the effects on lipid concentrations are generally fairly small, and a review of the subject[7] concluded that there was little or no evidence that such effects negated the beneficial effects of beta blockers on cardiovascular outcomes.

1. Krone W, Nägele H. Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* 1988; **116:** 1729–34.
2. Hunter Hypertension Research Group. Effects of pindolol, or a pindolol/clopamide combination preparation, on plasma lipid levels in essential hypertension. *Med J Aust* 1989; **150:** 646–52.
3. Terént A, *et al.* Long-term effect of pindolol on lipids and lipoproteins in men with newly diagnosed hypertension. *Eur J Clin Pharmacol* 1989; **36:** 347–50.
4. Sasaki J, *et al.* Effects of arotinolol on serum lipid and apolipoprotein levels in patients with mild essential hypertension. *Clin Ther* 1989; **11:** 580–3.
5. Sharp RP, *et al.* Impact of carvedilol on the serum lipid profile. *Ann Pharmacother* 2008; **42:** 564–71.
6. Durrington PN, Cairns SA. Acute pancreatitis: a complication of beta-blockade. *BMJ* 1982; **284:** 1016.
7. Weir MR, Moser M. Diuretics and β-blockers: is there a risk for dyslipidemia? *Am Heart J* 2000; **139:** 174–84.

Effects on mental state. Beta blockers can cross the blood-brain barrier and there are numerous reports of adverse psychiatric effects. Theoretically this is more likely with lipophilic drugs (such as propranolol, timolol, and metoprolol) but there have also been reports of psychosis[1] and delirium[2] with atenolol.

Although beta blockers have been associated with depression,[3] the risk may not be as high as has sometimes been suggested; a review[4] of randomised studies in myocardial infarction, heart failure, or hypertension, which included over 35 000 patients, found no significant increase in the risk of depression in those taking beta blockers.

1. Viadero JJ, *et al.* Acute psychotic behavior associated with atenolol. *Am J Psychiatry* 1983; **140:** 1382.
2. Arber N, *et al.* Delirium induced by atenolol. *BMJ* 1988; **297:** 1048.
3. Parker WA. Propranolol-induced depression and psychosis. *Clin Pharm* 1985; **4:** 214–18.
4. Ko DT, *et al.* β-Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; **288:** 351–7.

Effects after ophthalmic use. Ophthalmic use of beta blockers may produce ocular irritation (including hypersensitivity), blepharitis, keratitis, decreased corneal sensitivity, visual disturbances, diplopia, photophobia, and ptosis. Uveitis has been reported with metipranolol eye drops.[1] Iris depigmentation has occurred[2] after the use of topical levobunolol. Older patients using topical beta blockers may be at greater risk of decreased corneal sensitivity or corneal anaesthesia with the consequent risk of keratitis.[3]

Systemic absorption may occur after the use of beta blockers in eye drops. Excess drug can drain into the lachrymal ducts to be absorbed through the nasal mucosa. Absorption also occurs via the ophthalmic and facial veins. After such absorption the beta blocker reaches the systemic circulation without undergoing first-pass hepatic metabolism.

The main systemic effects associated with topical ocular use of beta blockers are on the pulmonary, cardiovascular, and central nervous systems.[4,5]

Both cardioselective and non-cardioselective topical beta blockers have been shown to cause pulmonary effects, and these can occur in patients without a history of obstructive airways disease.[6] Reported events include acute pulmonary oedema associated with use of metipranolol eye drops,[7] and wheezing after a single dose of topical levobunolol, which developed into severe respiratory distress requiring hospitalisation after a second dose.[8] Myocardial infarction has been reported[9] shortly after a single dose of betaxolol eye drops; the patient was also taking atenolol and indapamide for hypertension. Systemic effects have also been reported in patients using timolol eye drops, including depression and bradycardia, with a rise in blood pressure and neurological signs of stroke after rapid withdrawal of the drops,[10] syncope and falls,[11] and severe nausea and vomiting, which resolved within a few days of withdrawal but recurred on rechallenge.[12] A number of cases of alopecia associated with ocular use of beta blockers have also been reported.[13]

1. Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol* 1991; **75:** 519–23.
2. Doyle E, Liu C. A case of acquired iris depigmentation as a possible complication of levobunolol eye drops. *Br J Ophthalmol* 1999; **83:** 1405–6.
3. Weissman SS, Asbell PA. Effects of topical timolol (0.5%) and betaxolol (0.5%) on corneal sensitivity. *Br J Ophthalmol* 1990; **74:** 409–12.
4. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
5. Vander Zanden JA, *et al.* Systemic adverse effects of ophthalmic β-blockers. *Ann Pharmacother* 2001; **35:** 1633–7.
6. Kirwan JF, *et al.* Do selective topical β antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004; **88:** 196–8.
7. Johns MD, Ponte CD. Acute pulmonary edema associated with ocular metipranolol use. *Ann Pharmacother* 1995; **29:** 370–3.
8. Stubbs GM. Betagan drops. *Med J Aust* 1994; **161:** 576.
9. Chamberlain TJ. Myocardial infarction after ophthalmic betaxolol. *N Engl J Med* 1989; **321:** 1342.
10. Rao MR, *et al.* Systemic hazards of ocular timolol. *Br J Hosp Med* 1993; **50:** 553.
11. Müller ME, *et al.* Syncope and falls due to timolol eye drops. *BMJ* 2006; **332:** 960–1.
12. Wolfhagen FHJ, *et al.* Severe nausea and vomiting with timolol eye drops. *Lancet* 1998; **352:** 373.
13. Fraunfelder FT, *et al.* Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; **263:** 1493–4.

Hypersensitivity. For the suggestion that beta blockers may exacerbate anaphylactic reactions, see under Precautions, below.

Overdosage. Many cases of beta-blocker overdosage[1] are uneventful, but some patients develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, cardiac conduction block, hypotension, heart failure, and cardiogenic shock. Convulsions, coma, respiratory depression, and bronchoconstriction can also occur, although infrequently. Most reports of serious toxic reactions after overdosage concern beta blockers with significant membrane-stabilising activity, such as propranolol or oxprenolol, which may have quinidine-like effects (see p.1383). Overdosage of beta blockers with intrinsic sympathomimetic activity may present with tachycardia and hypertension. Overdosage of sotalol, a beta blocker with class II and III antiarrhythmic properties, usually presents as ventricular tachyarrhythmia.

1. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and β-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.

Treatment of Adverse Effects

Beta blockers are generally well tolerated and adverse effects usually respond to a reduction in dose. In overdosage, use of activated charcoal or gastric lavage should be considered if the patient presents within 1 hour of ingestion. Mild hypotension may respond to intravenous fluids. If hypotension continues, intravenous glucagon should be given; sympathomimetics may be used as an alternative or given with glucagon. Isoprenaline has been the sympathomimetic of choice since it acts mainly at beta receptors, but other sympathomimetics are often used; very high doses may be required (see below). Atropine may be given intravenously for bradycardia; sympathomimetics or a cardiac pacemaker may also be required. $Beta_2$ agonists or xanthines may be given for bronchospasm; hypoglycaemia may respond to glucose or glucagon. Haemodialysis may be of benefit for severe overdosage with renally excreted beta blockers, but is usually unnecessary.

Overdosage. Atropine, glucagon, and sympathomimetics are the mainstay of treatment for severe beta blocker overdosage (see above). Very high doses of sympathomimetics have been used in some patients; a woman[1] who had taken acebutolol, labetalol, and trimipramine required isoprenaline at a rate of 1660 micrograms/minute and dopamine at a rate of 200 micrograms/kg per minute to maintain her blood pressure. However, standard therapy is not effective in all patients and alternatives have been tried.

The phosphodiesterase inhibitor enoximone has been used successfully in patients resistant to standard treatment,[2,3] and a dramatic response to calcium chloride has been reported in a patient with electromechanical dissociation after propranolol overdosage.[4] It has been suggested[5,6] that high doses of insulin given with glucose (hyperinsulinaemia/euglycaemia therapy) may be of benefit, although there is no clinical evidence to support this. There has also been a report[7] of the successful use of sodium bicarbonate in a patient with cardiac arrest after overdosage with multiple drugs, including propranolol; it was suggested that the increased sodium load counteracted the sodium-channel blocking effect of propranolol.

1. Lewis M, *et al.* Survival following massive overdose of adrenergic blocking agents (acebutolol and labetalol). *Eur Heart J* 1983; **4:** 328–32.
2. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
3. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.
4. Brimacombe JR, *et al.* Propranolol overdose—a dramatic response to calcium chloride. *Med J Aust* 1991; **155:** 267–8.
5. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
6. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and β-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
7. Shanker UR, *et al.* Sodium bicarbonate to treat massive β blocker overdose. *Emerg Med J* 2003; **20:** 393.

Precautions

Beta blockers should not be given to patients with bronchospasm or asthma or to those with a history of obstructive airways disease. This contra-indication generally applies even to those beta blockers considered to be cardioselective. However, cardioselective beta blockers may be used with extreme caution when there is no alternative treatment (see Obstructive Airways Disease, below). Other contra-indications include metabolic acidosis, cardiogenic shock, hypotension, severe peripheral arterial disease, sinus bradycardia, and second- or third-degree AV block; caution should be observed in first-degree block. Although beta blockers are used in the management of heart failure, they should not be given to patients with uncontrolled heart failure and treatment should be begun with great care, starting with a low dose and cautiously titrating upwards. Patients with phaeochromocytoma should not be given beta blockers without alpha-adrenoceptor blocking therapy as well.

Beta blockers may mask the symptoms of hyperthyroidism and of hypoglycaemia. They may unmask myasthenia gravis. Psoriasis may be aggravated. Beta blockers may increase the number of attacks of chest pain in patients with Prinzmetal's angina; this occurs especially with non-cardioselective beta blockers, which should be avoided. Beta blockers increase sensitivity to allergens and also the severity of anaphylactoid reactions; patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking beta blockers (see Hypersensitivity, below).

Abrupt withdrawal of beta blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. Patients on long-term treatment with a beta blocker should have their medication stopped gradually over a period of 1 to 2 weeks. In patients undergoing surgery, beta blockers may reduce the risk of arrhythmias but increase the risk of hypotension; the decision to withdraw or continue therapy depends on individual patient risk—see Cardiovascular Risk Reduction, below. If beta blockers are withdrawn, this should take place at least 24 to 48 hours before surgery; if they are continued, atropine may be given to counter increases in vagal tone and anaesthetics causing myocardial depression, such as ether, cyclopropane, and trichloroethylene, are best avoided. It is of the greatest importance that the anaesthetist is aware that beta blockers are being taken.

Use of beta blockers in pregnancy shortly before delivery has occasionally resulted in bradycardia and other adverse effects such as hypoglycaemia and hypotension in the neonate. Many beta blockers are distributed into breast milk.

Similar precautions apply when beta blockers are used as eye drops since systemic absorption can occur.

Contact lenses. Beta blockers may reduce tear flow, leading to irritation of the eye in wearers of contact lenses and potentially to the dehydration of soft lenses.[1]

1. McGuire T. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Hypersensitivity. Anaphylactic reactions to stings and other antigens may be potentiated by beta blockers[1-3] and the risk of serious reactions may be increased. In addition, beta blockers may antagonise the effects of adrenaline in the management of anaphylaxis (see Interactions under Sympathomimetics, p.1408). Particular caution is necessary when beta blockers are used in patients with a history of anaphylaxis.[3]

1. Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983; **308:** 1536.
2. Pedersen DL. Hymenoptera stings and beta-blockers. *Lancet* 1989; **ii:** 619.
3. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of β-blockers. *Drug Safety* 1995; **12:** 299–304.

Obstructive airways disease. Beta blockers may precipitate bronchospasm and are generally contra-indicated in patients with obstructive airways disease.[1,2] However, systematic reviews have suggested that short-term use of cardioselective beta blockers does not produce adverse respiratory effects in patients with mild to moderate asthma[3] or chronic obstructive pulmonary disease.[4] The reviewers concluded that, given the established benefits of beta blockers in cardiovascular disorders, they should not be withheld in such patients, although patients should be carefully monitored since long-term effects were less clear. A retrospective study[5] found that use of beta blockers increased the rate of hospitalisations and emergency department visits in patients with asthma, but not in those with non-asthmatic chronic obstructive pulmonary disease, suggesting that the benefits and risks need to be assessed for each patient individually. Another study[6] found that patients with acute exacerbations of chronic obstructive pulmonary disease who were given beta blockers had lower mortality than those who were not.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: beta-blockers contraindicated in asthma. *Current Problems* 1996; **22:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 10/01/08)
2. The Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
3. Salpeter S, *et al.* Cardioselective beta-blockers for reversible airway disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 10/01/08).
4. Salpeter S, *et al.* Cardioselective beta-blockers for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 10/01/08).
5. Brooks TWA, *et al.* Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking β-blockers. *Pharmacotherapy* 2007; **27:** 684–90.
6. Dransfield MT, *et al.* Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63:** 301–5.

Pregnancy. Many beta blockers cross the placenta, and giving them to pregnant women shortly before delivery may result in neonatal adrenergic blockade, with symptoms of bradycardia, hypoglycaemia or hypotension. Furthermore, the treatment of maternal hypertension with beta blockers, particularly atenolol, in early pregnancy or for a long duration has been associated with growth retardation of the fetus.[1-3] However, beta blockers are recommended therapy for maternal conditions such as hypertension, pre-eclampsia, cardiac arrhythmias, and ischaemic heart disease;[4,5] cardioselective agents with no effect on uterine contraction are preferred.[5]

1. Butters L, *et al.* Atenolol in essential hypertension during pregnancy. *BMJ* 1990; **301:** 587–9.
2. Lydakis C, *et al.* Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; **12:** 541–7.
3. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 10/01/08).
4. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24:** 761–81.
5. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.

Withdrawal. The abrupt withdrawal of beta blockers may lead to rebound hypertension or overshoot hypertension where the patient's blood pressure is higher than before treatment. Angina can be exacerbated, myocardial infarction induced, and fatalities have occurred.[1,2]

1. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. *Am Heart J* 1988; **116:** 515–23.
2. Psaty BM, *et al.* The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. *JAMA* 1990; **263:** 1653–7.

Interactions

Both pharmacodynamic and pharmacokinetic interactions have been reported with beta blockers. **Pharmacodynamic** interactions may occur with drugs whose actions enhance or antagonise the various effects of beta blockers at $beta_1$ and $beta_2$ receptors, including their antihypertensive effect, cardiodepressant effect, effect on carbohydrate metabolism, or effect on bronchial $beta_2$ receptors. The characteristics of the individual beta blocker must therefore be borne in mind when considering likely interactions; for more details on the characteristics of different beta blockers, see Uses and Administration, below.

Drugs that enhance the antihypertensive effects of beta blockers, such as ACE inhibitors, calcium-channel blockers, and clonidine may be useful in controlling hypertension (but see Antihypertensives, below). Drugs that cause hypotension such as aldesleukin and general anaesthetics also enhance the antihypertensive effects of beta blockers while other drugs, for example NSAIDs, antagonise the antihypertensive effects.

Use of beta blockers with other cardiac depressants such as antiarrhythmics and rate-limiting calcium-channel blockers can precipitate bradycardia and heart block; the combination of intravenous verapamil and beta blockers should especially be avoided. Sotalol is particularly prone to interactions with other drugs affecting cardiac conduction (see p.1398). Beta blockers may potentiate bradycardia due to digoxin.

The interaction between beta blockers and sympathomimetics is complex and depends on the selectivity of both drugs (see under Sympathomimetics, p.1408). Patients taking beta blockers may have an exaggerated hypertensive response to adrenaline, caused by unopposed alpha-mediated vasoconstriction, while the bronchodilator effects are inhibited; the response to adrenaline given for anaphylaxis may also be reduced in patients on long-term treatment with beta blockers.

In diabetic patients beta blockers can reduce the response to insulin and oral hypoglycaemics through their effects on pancreatic beta receptors (see Effects on Carbohydrate Metabolism, above).

Pharmacokinetic interactions occur with drugs that alter the absorption or metabolism of beta blockers. Although these interactions may alter the beta blocker plasma concentration, they are not usually clinically significant since there is little association between plasma concentrations and therapeutic effect or toxicity and there are wide interindividual differences in steady-state plasma concentrations of beta blockers.

Drugs that reduce absorption include aluminium salts (but see also Antacids, below) and bile-acid binding resins such as colestyramine.

Metabolism of some beta blockers can be increased by drugs such as barbiturates and rifampicin and decreased with drugs such as cimetidine, erythromycin, fluvoxamine, and hydralazine. Drugs that alter hepatic blood flow also affect metabolism of some beta blockers. For example, cimetidine and hydralazine decrease hepatic blood flow and this contributes to the decreased hepatic clearance seen with these drugs. Drugs that influence hepatic metabolism affect beta blockers that are extensively metabolised, such as labetalol, propranolol, and timolol, while beta blockers that are excreted largely unchanged, for example atenolol and nadolol, are unaffected.

Since systemic absorption can occur after ocular use of beta blockers the possibility of similar interactions should be considered.

◊ General references.

1. McDevitt DG. Interactions that matter: 12. β-adrenoceptor antagonists. *Prescribers' J* 1988; **28:** 25–30.
2. Blaufarb I, *et al.* β-Blockers: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 359–70.
3. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung* 2003; **53:** 814–22.

Antacids. Bioavailability of metoprolol was increased when given with an antacid containing aluminium and magnesium salts, but the bioavailability of atenolol was reduced. Variable results on bioavailability of propranolol have been reported when aluminium hydroxide was given with propranolol.[1]

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.

Antiarrhythmics. Use of beta blockers with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block.

Bradycardia, cardiac arrest, and ventricular fibrillation have been reported shortly after starting beta-blocker therapy in patients receiving *amiodarone*.[1] Amiodarone was found to increase plasma-metoprolol concentrations in patients with cardiac arrhythmias, probably through inhibition of the cytochrome P450 isoenzyme CYP2D6 by the metabolite desethylamiodarone.[2] However, an analysis[3] of the CAMIAT and EMIAT studies in patients after myocardial infarction found that patients taking amiodarone and beta blockers had better outcomes than patients on one, or neither, drug, suggesting that any interaction may not always be detrimental. Use of *flecainide* with propranolol produced additive negative inotropic effects on the heart and increased serum concentrations of both drugs.[4] In a pharmacokinetic study in 12 healthy males, giving *propafenone* with propranolol resulted in increases in serum-propranolol concentrations but only modest enhancement of beta-blocking activity.[5] An increase in serum-metoprolol concentration has been reported after use of propafenone with metoprolol.[6] The metabolism of metoprolol may be decreased by *quinidine*.[7] Both quinidine and beta blockers have a negative inotropic action on the heart; bradycardia[8] and hypotension[9] have occurred in patients given quinidine with beta blockers.

For a report of reduced clearance of *disopyramide* by atenolol, see p.1270.

The interactions of sotalol are discussed on p.1398.

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Fukumoto K, *et al.* Effect of amiodarone on the serum concentration/dose ratio of metoprolol in patients with cardiac arrhythmia. *Drug Metab Pharmacokinet* 2006; **21:** 501–5.
3. Boutitie F, *et al.* Amiodarone interaction with β-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 1999; **99:** 2268–75.
4. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
5. Kowey PR, *et al.* Interaction between propranolol and propafenone in healthy volunteers. *J Clin Pharmacol* 1989; **29:** 512–17.
6. Wagner F, *et al.* Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987; **24:** 213–20.
7. Leemann T, *et al.* Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. *Eur J Clin Pharmacol* 1986; **29:** 739–41.
8. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
9. Loon NR, *et al.* Orthostatic hypotension due to quinidine and propranolol. *Am J Med* 1986; **81:** 1101–4.

Antibacterials. Serum-atenolol concentrations in 6 healthy subjects were reduced by a 1-g oral dose of *ampicillin*.[1] Plasma concentrations of propranolol,[2] metoprolol,[3] celiprolol,[4] and bisoprolol[5] may be reduced by *rifampicin*. Licensed product information for *telithromycin* states that it causes increased plasma concentrations of metoprolol.

1. Schäfer-Korting M, *et al.* Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* 1983; **33:** 283–8.
2. Shaheen O, *et al.* Influence of debrisoquin phenotype on the inducibility of propranolol metabolism. *Clin Pharmacol Ther* 1989; **45:** 439–43.
3. Bennett PN, *et al.* Effect of rifampicin on metoprolol and antipyrine kinetics. *Br J Clin Pharmacol* 1982; **13:** 387–91.
4. Lilja JJ, *et al.* Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol* 2004; **59:** 819–24.
5. Kirch W, *et al.* Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol* 1986; **31:** 59–62.

Anticoagulants. For the effect of beta blockers on the pharmacokinetics of some oral anticoagulants, see p.1430.

Antidepressants. Bradycardia and heart block, occurring shortly after starting *fluoxetine* therapy, have been reported in patients receiving metoprolol[1] and propranolol.[2] Possible mechanisms include impaired conduction through the AV node and inhibition by fluoxetine of the oxidative metabolism of beta blockers. Use of fluoxetine also increased the plasma concentration of carvedilol in patients with heart failure but no clinical effects were noted.[3]

Fluvoxamine inhibits oxidative metabolism, and increased plasma concentrations of propranolol have been noted in patients receiving fluvoxamine.

1. Walley T, *et al.* Interaction of metoprolol and fluoxetine. *Lancet* 1993; **341:** 967–8.
2. Drake WM, Gordon GD. Heart block in a patient on propranolol and fluoxetine. *Lancet* 1994; **343:** 425–6.
3. Graff DW, *et al.* Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* 2001; **41:** 97–106.

Antihypertensives. An enhanced antihypertensive effect is seen when other antihypertensives are given with beta blockers. However, some combinations should be avoided (see Calcium-channel Blockers, below). Beta blockers can potentiate the severe orthostatic hypotension that may follow the initial dose of alpha blockers such as prazosin and can exacerbate rebound hypertension after withdrawal of clonidine treatment (see Precautions, p.1247).

Antimalarials. Antimalarials such as *halofantrine*, *mefloquine*, and *quinine* can cause cardiac conduction defects and caution is necessary if they are used with beta blockers. Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient taking propranolol.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32:** 13–14.

Antimigraine drugs. For the effect of propranolol on *rizatriptan*, see p.625.

See also under Ergotamine Tartrate, p.621, for further interactions with drugs used in the treatment of migraine.

Anxiolytics and antipsychotics. Plasma concentrations of some beta blockers may be reduced by *barbiturates*.[1-3] Increased plasma-propranolol concentrations and bioavailability, and reduced metabolism, have been reported in healthy subjects also given *chlorpromazine*.[4]

See p.990 for the effect of beta blockers on the pharmacokinetics of some *benzodiazepines*.

1. Sotaniemi EA, *et al.* Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin Pharmacol Ther* 1979; **26:** 153–61.
2. Haglund K, *et al.* Influence of pentobarbital on metoprolol plasma levels. *Clin Pharmacol Ther* 1979; **26:** 326–9.
3. Seideman P, *et al.* Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension. *Br J Clin Pharmacol* 1987; **23:** 267–71.
4. Vestal RE, *et al.* Inhibition of propranolol metabolism by chlorpromazine. *Clin Pharmacol Ther* 1979; **25:** 19–24.

Calcium-channel blockers. Use of calcium-channel blockers with beta blockers has resulted in hypotension, bradycardia, conduction defects, and heart failure.[1]

Beta blockers should be avoided if possible with rate-limiting calcium-channel blockers such as *verapamil* (see p.1422) and *diltiazem*. Although they are reportedly safe with dihydropyridines such as *nifedipine*,[2] heart failure and severe hypotension have been reported (see under Nifedipine, p.1353). Reported pharmacokinetic interactions include increased plasma concentrations of propranolol and of metoprolol with concurrent use of diltiazem[3] or verapamil,[1] and increased plasma concentrations of propranolol with *nicardipine*.[4]

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Reid JL. First-line and combination treatment for hypertension. *Am J Med* 1989; **86** (suppl 4A): 2–5.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.
4. Schoors DF, *et al.* Influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers. *Br J Clin Pharmacol* 1990; **29:** 497–501.

Cardiac glycosides. For reference to an interaction between beta blockers and *digoxin*, see p.1262.

Ciclosporin. For the effect of carvedilol on plasma-ciclosporin concentrations, see p.1827.

Ergot derivatives. *Nicergoline* enhanced the cardiac depressant action of propranolol in healthy subjects.[1]

For reports of enhanced vasoconstrictor action in patients taking *ergot alkaloids* and beta blockers, see p.621.

1. Boismare F, *et al.* Potentiation by an alpha-adrenolytic agent, nicergoline, of the cardiac effects of propranolol. *Methods Find Exp Clin Pharmacol* 1983; **5:** 83–8.

Food. Studies in healthy subjects found that *grapefruit juice* greatly reduced the plasma concentration of celiprolol[1] and talinolol,[2] but had much less effect on acebutolol.[3] An effect on gastrointestinal absorption was suggested as the mechanism.[1,2] Studies with *orange juice* have found a similar effect on celiprolol[4] and, to a lesser extent, atenolol.[5]

1. Lilja JJ, *et al.* Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther* 2003; **73:** 192–8.
2. Schwarz UI, *et al.* Grapefruit juice ingestion significantly reduces talinolol bioavailability. *Clin Pharmacol Ther* 2005; **77:** 291–301.
3. Lilja JJ, *et al.* Effects of grapefruit juice on the pharmacokinetics of acebutolol. *Br J Clin Pharmacol* 2005; **60:** 659–63.
4. Lilja JJ, *et al.* Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther* 2004; **75:** 184–90.
5. Lilja JJ, *et al.* Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol* 2005; **61** 337–40.

General anaesthetics. Beta blockers are usually continued perioperatively although the anaesthetist must be informed of their use (see Precautions, above). However, the hypotensive effects of beta blockers may be potentiated by general anaesthetics, and anaesthetics that cause myocardial depression, such as *ether, cyclopropane*, and *trichloroethylene* should preferably be avoided.

Histamine H_2-antagonists. Plasma concentrations of propranolol and metoprolol may be increased by *cimetidine*;[1] pharmacokinetic studies indicate that cimetidine exerts its effect by reducing hepatic blood flow and impairing beta blocker metabolism. Cimetidine has been reported to increase the bioavailability of labetalol,[1] and to increase the systemic effects of timolol eye drops.[2]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
2. Ishii Y, *et al.* Drug interaction between cimetidine and timolol ophthalmic solution: effect on heart rate and intraocular pressure in healthy Japanese volunteers. *J Clin Pharmacol* 2000; **40:** 193–9.

Local anaesthetics. For details of the effect of beta blockers in reducing the clearance of *bupivacaine*, see p.1855, and of *lidocaine*, see p.1863. For the effects of propranolol with *cocaine*, see p.1860.

Neuromuscular blockers. For the effects of beta blockers on neuromuscular blockers, see under Atracurium, p.1904.

NSAIDs. The antihypertensive effect of beta blockers may be impaired by some NSAIDs, possibly due to their inhibition of renal synthesis of vasodilating prostaglandins. This interaction probably occurs with all beta blockers but may not occur with all NSAIDs. For example, *sulindac* appears to affect blood pressure control less than *indometacin*.[1]

A randomised study[2] in 12 healthy subjects found that *celecoxib* significantly inhibited the metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6.

1. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic and genetic considerations. *Clin Pharmacokinet* 1990; **18:** 295–317.
2. Werner U, *et al.* Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin Pharmacol Ther* 2003; **74:** 130–7.

Opioid analgesics. Bioavailability of propranolol and metoprolol was increased in subjects given *dextropropoxyphene*;[1] dextropropoxyphene is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and was reported[2] to increase serum concentrations of metoprolol, a CYP2D6 substrate, in a patient given both drugs, resulting in bradycardia. Intravenous *morphine* may increase serum concentrations of esmolol.[3]

1. Lundborg P, *et al.* The effect of propoxyphene pretreatment on the disposition of metoprolol and propranolol. *Clin Pharmacol Ther* 1981; **29:** 263–4.
2. Marraffa JM, *et al.* Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther* 2006; **79:** 282–6.
3. Lowenthal DT, *et al.* Clinical pharmacology, pharmacodynamics and interactions with esmolol. *Am J Cardiol* 1985; **56:** 14F–17F.

Oral contraceptives. Plasma-metoprolol concentrations were increased in some women taking oral contraceptives.[1]

1. Kendall MJ, *et al.* Metoprolol pharmacokinetics and the oral contraceptive pill. *Br J Clin Pharmacol* 1982; **14:** 120–2.

Parasympathomimetics. For the effect of beta blockers on the response to *anticholinesterases*, see p.632.

Thyroid drugs. For a discussion of thyroid status and its effect on plasma-propranolol concentrations and the effects of propranolol on *thyroid hormone* metabolism, see p.2172.

Xanthines. For details of reduced *theophylline* clearance in patients receiving some beta blockers, see p.1144.

Pharmacokinetics

Beta blockers differ widely in their pharmacokinetic properties. Differences in lipid solubility contribute to these varying pharmacokinetic properties.

Beta blockers with high lipid solubility (lipophilic beta blockers) include alprenolol and propranolol.

Hydrophilic beta blockers, such as atenolol and nadolol, have low lipid solubility and when compared with lipophilic beta blockers generally:

- tend to be less readily absorbed from the gastrointestinal tract
- are less extensively metabolised
- have low plasma-protein binding
- have relatively long plasma half-lives
- cross the blood-brain barrier less readily

Beta blockers cross the placenta and most are known to distribute into breast milk.

There is no clear correlation between plasma concentrations of beta blockers and therapeutic activity, especially when the beta blocker undergoes metabolism to active metabolites.

Uses and Administration

Beta blockers are competitive antagonists of the effects of catecholamines at beta-adrenergic receptor sites. The different types of adrenergic receptor are described under the Actions and Uses of Sympathomimetics (see p.1408). Blockade of beta receptors has the following effects:

- $beta_1$ blockade mainly affects the heart, reducing heart rate, myocardial contractility, and rate of conduction of impulses through the conducting system (class II antiarrhythmic effect, see p.1153). It also leads to suppression of adrenergic-induced renin release and lipolysis
- $beta_2$ blockade leads to increased bronchial resistance and inhibition of catecholamine-induced glucose metabolism; there may also be an effect on heart rate. $Beta_2$ blockade also appears to be the main mechanism for the reduction in intra-ocular pressure associated with beta blockers
- the role of $beta_3$ blockade is not clear

Beta blockers differ in their affinity for the subtypes of beta receptor, as well as in their actions at other receptors and ancillary properties (see Table 4, p.1225). The cardiovascular effects of beta blockers relate to their action at $beta_1$ receptors, and all clinically used beta blockers are $beta_1$ antagonists. Propranolol and other nonselective beta blockers also have antagonist effects at $beta_2$ receptors, and this may be responsible for many of their adverse effects. Beta blockers with a higher affinity for $beta_1$ than $beta_2$ receptors, such as atenolol and metoprolol, cause fewer noncardiovascular effects and are described as cardioselective or second generation. However, selectivity is relative and, as doses are increased, activity at $beta_2$ receptors becomes clinically important. Beta blockers with additional properties such as vasodilatation have been described as third generation, and include carvedilol, celiprolol, and nebivolol.

Beta blockers such as acebutolol, celiprolol, oxprenolol, and pindolol also possess intrinsic (partial) sympathomimetic activity in that they activate beta receptors in the absence of catecholamines and are therefore partial agonists. Beta blockers with intrinsic sympathomimetic activity produce less resting bradycardia than beta blockers without.

At high blood concentrations, propranolol and some other beta blockers also possess a membrane-stabilising effect. This effect may not be evident at therapeutic doses but may be important in overdose. The non-cardioselective beta blocker sotalol also has class III antiarrhythmic activity.

Beta blockers that cause vasodilatation may do so by a number of mechanisms: carvedilol and labetalol block $alpha_1$ receptors; celiprolol has $beta_2$ agonist effects; and nebivolol has a direct action on the endothelium, possibly involving nitric oxide release.

Beta blockers are used in the treatment of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and myocardial infarction (p.1175) and also have a role in heart failure (below). They are also used to control symptoms of sympathetic overactivity in the management of alcohol withdrawal (p.1626), in anxiety disorders (below), in hyperthyroidism (p.2165), and in tremor (below). Beta blockers are used in the prophylaxis of migraine (below) and of variceal bleeding associated with portal hypertension (p.2346). They are also used, with an alpha blocker, in the initial management of phaeochromocytoma (below). Some beta blockers are used as eye drops in the management of glaucoma and ocular hypertension (below).

Choice of beta blocker. The selection of a specific beta blocker for an individual patient depends on the condition being treated and patient characteristics such as liver and kidney function or existing disease such as diabetes. Patient tolerance also varies for different beta blockers. The characteristics of the beta blocker, for example, $beta_1$ selectivity and intrinsic sympathomimetic activity may also influence selection, as may additional pharmacological properties such as vasodilator activity. Although the clinical significance of these differences has been debated, only certain beta blockers have a proven benefit in some conditions (for example, heart failure) and this will also influence choice.

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1. Anonymous. Which beta-blocker? *Med Lett Drugs Ther* 2001; **43:** 9–11.
2. Brown MJ. A rational basis for selection among drugs of the same class. *Heart* 2003; **89:** 687–94.

Anxiety disorders. Beta blockers have been used in patients with various anxiety disorders,[1] including generalised anxiety disorder (p.952), panic disorder (p.952), and performance anxiety[1] (see under Phobic Disorders, p.953). However, their benefits do not appear to be particularly great and they are probably most useful in reducing symptoms such as tremor or palpitations that are mediated through beta stimulation. Improvement usually occurs within 1 to 2 hours with relatively low doses of beta blockers (propranolol 40 mg, oxprenolol 40 to 80 mg, nadolol 40 mg). Some patients require higher doses and longer periods of treatment for a beneficial effect.

1. Tyrer P. Current status of β-blocking drugs in the treatment of anxiety disorders. *Drugs* 1988; **36:** 773–83.

Burns. Beta blockers have been tried in major burn injury (p.1578) to attenuate the hypermetabolism and marked catabolism that may result. A study[1] in children with severe burns found that oral propranolol reduced energy expenditure and muscle-protein catabolism, suggesting beta blockers could have an anabolic effect.

1. Herndon DN, *et al.* Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001; **345:** 1223–9.

Cardiomyopathy. See Heart Failure, below.

Cardiovascular risk reduction. Beta blockers have established benefits in patients with *ischaemic heart disease*,[1] and long-term therapy with beta blockers has an important role in reducing cardiovascular risk in patients with angina pectoris (p.1157), and particularly in patients who have had a myocardial infarction (p.1175). They have also been used to reduce ischaemia and cardiac events in patients undergoing surgery, but their benefits in this situation are less clear.

Perioperative use of beta blockers is controversial (see Precautions, above); they reduce the risk of ischaemia and arrhythmias, but increase the risk of hypotension, and they have often been stopped pre-operatively to enable better control of blood pressure during surgery. However, there is some evidence that continuing or starting beta blockers perioperatively may be of benefit in patients at risk of cardiovascular events, although not all studies have come to the same conclusions. A systematic review[2] of studies with beta blockers suggested a reduction in myocardial ischaemia, non-fatal myocardial infarction, and mortality from cardiovascular causes in patients at high cardiovascular risk undergoing major noncardiac surgery, and a retrospective study[3] also suggested that perioperative beta blockers reduced in-hospital mortality in high-risk patients, although there was no benefit (and possible harm) in low-risk patients. However, another systematic review and meta-analysis[4] concluded that, while the evidence for the use of beta blockers was encouraging, it was too unreliable for definitive conclusions to be drawn. More recent studies[5,6] using perioperative metoprolol have found no benefit, and a further large study[7] found fewer cardiac events but a higher risk of stroke and death in patients given metoprolol. The conflicting conclusions may relate to the wide range of protocols used in the beta blocker studies, whether patients were already taking beta blockers, and the different selection criteria used for the reviews and analyses. Recognising these limitations, consensus guidelines for non-cardiac surgery in the USA recommend[8] that beta blockers should be continued perioperatively in patients receiving them for accepted indications, and that patients undergoing vascular surgery who are at high risk of cardiovascular events (confirmed by pre-operative testing) should have beta blockers started; in patients at lower risk, use of beta blockers may be considered, but there is less evidence of benefit. It is not clear which beta blockers should be preferred, but a retrospective study[9] found that patients who took atenolol pre- and postoperatively had a lower risk of events than patients who took metoprolol.

Beta blockers may also have benefits in patients undergoing cardiac surgery. Observational studies have found that prior[10] or pre-operative[11] use of beta blockers reduces ischaemic complications, while perioperative[12] and postoperative[13] beta blockers have been shown to reduce the risk of atrial fibrillation, although one study found[14] that the effects on atrial fibrillation only applied to patients already taking beta blockers pre-operatively.

Although beta blockers effectively lower blood pressure, they do not reduce cardiovascular events to the same extent as some other antihypertensives and may not be first choice for *hypertension* (p.1171).[15,16]

1. Ellison KE, Gandhi G. Optimising the use of β-adrenoceptor antagonists in coronary artery disease. *Drugs* 2005; **65:** 787–97.
2. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002; **287:** 1435–44.
3. Lindenauer PK, *et al.* Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005; **353:** 349–61.
4. Devereaux PJ, *et al.* How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; **331:** 313–16.
5. The DIPOM Trial Group. Effect of perioperative β blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. Abridged version: *BMJ* 2006; **332:** 1482–5. Full version: http://www.bmj.com/cgi/reprint/332/7556/1482 (accessed 10/01/08)
6. Yang H, *et al.* The effects of perioperative β-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006; **152:** 983–90.
7. Devereaux PJ, *et al.* Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371:** 1839–47.
8. Fleisher LA, *et al.* ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. *Circulation* 2006; **113:** 2662–74. Also available at: http://circ.ahajournals.org/cgi/reprint/113/22/2662 (accessed 10/01/08)
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10. Sharma SK, *et al.* Cardioprotective effect of prior β-blocker therapy in reducing creatine kinase-MB elevation after coronary intervention: benefit is extended to improvement in intermediate-term survival. *Circulation* 2000; **102:** 166–72.
11. Ferguson TB, *et al.* Preoperative β-blocker use and mortality and morbidity following CABG surgery in North America. *JAMA* 2002; **287:** 2221–7. Correction. *ibid.*; 3212.
12. Crystal E, *et al.* Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 10/01/08).
13. Coleman CI, *et al.* Impact of prophylactic postoperative β-blockade on post-cardiothoracic surgery length of stay and atrial fibrillation. *Ann Pharmacother* 2004; **38:** 2012–16.
14. Crystal E, *et al.* Metoprolol prophylaxis against postoperative atrial fibrillation increases length of hospital stay in patients not on pre-operative beta blockers: the beta blocker length of stay (BLOS) trial. *Heart* 2004; **90:** 941–2.
15. Lindholm LH, *et al.* Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; **366:** 1545–53.
16. Wiysonge CS, *et al.* Beta-blockers for hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 12/06/08).

Extrapyramidal disorders. Beta blockers (in low doses) have been suggested for the management of antipsychotic-induced akathisia although evidence of benefit is limited (see under Chlorpromazine, p.971).

Glaucoma and ocular hypertension. Topical beta blockers are often the drugs of first choice for the initial treatment and maintenance of open-angle glaucoma and other chronic glaucomas (p.1873). They are believed to inhibit beta receptors in the ciliary epithelium and reduce the secretion of aqueous humour. Clinical studies have established that betaxolol, carteolol, levobunolol, metipranolol, and timolol are effective, generally reducing intra-ocular pressure to a similar extent,[1-5] although a meta-analysis suggested that timolol might be slightly more effective than betaxolol in lowering intra-ocular pressure.[6] The possibility of systemic effects after topical use needs to be borne in mind (see Effects after Ophthalmic Use, above), especially in the elderly.[7]

Beta blockers have also been used for prophylaxis of postoperative ocular hypertension.[8,9]

1. LeBlanc RP, *et al.* Timolol: long-term Canadian Multicentre Study. *Can J Ophthalmol* 1985; **20:** 128–30.
2. Stewart RH, *et al.* Betaxolol vs timolol: a six-month double-blind comparison. *Arch Ophthalmol* 1986; **104:** 46–8.
3. Geyer O, *et al.* Levobunolol compared with timolol: a four-year study. *Br J Ophthalmol* 1988; **72:** 892–6.
4. Krieglstein GK, *et al.* Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol* 1987; **71:** 250–3.
5. Scoville B, *et al.* A double-masked comparison of carteolol and timolol in ocular hypertension. *Am J Ophthalmol* 1988; **105:** 150–4.
6. van der Valk R, *et al.* Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; **112:** 1177–85.
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8. West DR, *et al.* Comparative efficacy of the β-blockers for the prevention of increased intraocular pressure after cataract extraction. *Am J Ophthalmol* 1988; **106:** 168–73.
9. Odberg T. Primary argon laser trabeculoplasty after pretreatment with timolol. *Acta Ophthalmol (Copenh)* 1990; **68:** 317–19.

Heart failure. Beta blockers have negative inotropic properties and have in the past been contra-indicated in patients with heart failure (p.1165). However, there is increasing evidence that they are in fact of benefit since persistent activation of the sympathetic nervous system appears to be associated with disease progression. Reviews,[1-3] meta-analyses,[4,5] and long-term studies[6,7] have confirmed that the beta blockers bisoprolol, carvedilol, and metoprolol all improve mortality in patients with chronic heart failure, and another study[8] has shown benefit with nebivolol in elderly patients. A further meta-analysis[9] found that fewer patients were withdrawn from treatment with beta blockers than placebo, suggesting that the benefits outweigh their adverse effects. Subgroup analysis[10] of one of the large studies also confirmed that metoprolol was well tolerated and of benefit in diabetics, despite potential effects on diabetic control (see Effects on Carbohydrate Metabolism under Adverse Effects, above). Beta blockers have also improved functional status in patients with chronic heart failure.[11] Beta blockers are therefore now recommended, as part of standard therapy, given with ACE inhibitors and diuretics, in all patients with clinically stable heart failure due to left ventricular systolic dysfunction where there are no contra-indications; the benefit in patients with preserved left ventricular function is less clear, although the empirical use of beta blockers to reduce heart rate and improve myocardial ischaemia has been suggested.[12]

The benefit of beta blockers in heart failure may not be a class effect, and in general only those with an established benefit should be used. Not all beta blockers have been studied in heart failure, but there is also evidence that some are ineffective; a study[13] with bucindolol was stopped early because no mortality benefit was found. For those that have been shown to improve mortality, it is not clear if they are all equally effective.[14] A meta-analysis[15] has suggested that vasodilating beta blockers such as carvedilol have a greater effect on overall mortality than those that do not produce vasodilatation, and a large study[16] comparing carvedilol with metoprolol also found a greater mortality reduction with carvedilol, although the equivalence of the doses used in the study has been questioned.[17] The optimum dose is also unclear; many patients are unable to tolerate the target doses used in clinical studies, but an analysis[18] of a study with metoprolol suggested that the mortality benefit was equal in those receiving low or high doses.

Beta blockers may also be of value in some patients with heart failure due to cardiomyopathy (p.1163). A number of beta blockers have provided symptomatic benefit in idiopathic dilated cardiomyopathy, and the heart failure studies that showed a mortality benefit included patients with dilated cardiomyopathy. In hypertrophic cardiomyopathy, beta blockers may be of value for symptomatic management to curtail tachycardia, reduce anginal pain, and prevent syncope.

1. Foody JM, *et al.* β-Blocker therapy in heart failure: scientific review. *JAMA* 2002; **287:** 883–9.
2. Pritchett AM, Redfield MM. β-Blockers: new standard therapy for heart failure. *Mayo Clin Proc* 2002; **77:** 839–46.
3. Goldstein S. Benefits of β-blocker therapy for heart failure: weighing the evidence. *Arch Intern Med* 2002; **162:** 641–8.
4. Lechat P, *et al.* Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998; **98:** 1184–91.
5. Brophy JM, *et al.* β-Blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med* 2001; **134:** 550–60.
6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.
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8. Flather MD, *et al.* Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26:** 215–25.
9. Ko DT, *et al.* Adverse effects of β-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. *Arch Intern Med* 2004; **164:** 1389–94.
10. Deedwania PC, *et al.* Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005; **149:** 159–67.
11. Abdulla J, *et al.* Effect of beta-blocker therapy on functional status in patients with heart failure: a meta-analysis. *Eur J Heart Fail* 2006; **8:** 522–31.
12. Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. *Eur Heart J* 2004; **25:** 1341–62.
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14. McBride BF, White CM. Critical differences among beta-adrenoreceptor antagonists in myocardial failure: debating the MERIT of COMET. *J Clin Pharmacol* 2005; **45:** 6–24.
15. Bonet S, *et al.* β-Adrenergic blocking agents in heart failure: benefits of vasodilating and nonvasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Arch Intern Med* 2000; **160:** 621–7.
16. Poole-Wilson PA, *et al.* Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; **362:** 7–13.
17. Dargie HJ. β-Blockers in heart failure. *Lancet* 2003; **362:** 2–3.
18. Wikstrand J, *et al.* Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002; **40:** 491–8.

Hypotension. Beta blockers have a hypotensive effect and are usually used to reduce blood pressure in patients with hypertension, or occasionally to produce controlled hypotension during surgery. Paradoxically, however, they may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p.1174), although there is limited evidence to support their use, and adverse effects may be a concern. Beta blockers with partial agonist activity have been used in orthostatic hypotension due to autonomic failure (p.1530) but are potentially dangerous.

Migraine and tension type headache. Beta blockers (usually propranolol or metoprolol) are considered[1] by many to be the drugs of choice in patients requiring prophylactic treatment for migraine (p.616). Their mechanism of action in this disorder is not fully understood. Other beta blockers reported to be effective include atenolol, nadolol, and timolol; those with intrinsic sympathomimetic activity may not be effective.

Beta blockers may sometimes also be of benefit in patients with chronic tension-type headache (p.617).

Propranolol has been tried in the treatment of children with abdominal migraine (see under Pizotifen, p.624).

1. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on β-adrenoceptor blockers. *Br J Clin Pharmacol* 2001; **52:** 237–43.

Peripheral vascular disease. Beta blockers may cause coldness of the extremities and have been reported to induce secondary Raynaud's syndrome. However, they may be of some help in the management of erythromelalgia (see under Vasospastic Arterial Disorders on p.1188).

Phaeochromocytoma. Beta blockers are used, with an alpha blocker, in the initial management of phaeochromocytoma (p.1179). Beta blockers reduce the responses to the beta-adrenoceptor stimulating effects of adrenaline. Treatment must be started with the alpha blocker and only when alpha blockade is successfully established can tachycardia be controlled by the cautious use of a beta blocker. A beta$_1$-selective blocker is preferred so that peripheral beta$_2$-mediated vasodilatation is unaffected. In most cases modest doses are sufficient although higher doses may be required for a tumour that is mainly adrenaline-secreting.

Tetanus. Autonomic overactivity, usually due to excessive catecholamine release, may occur as a complication of tetanus and is usually controlled with sedation (see p.1901). Beta blockers have also been used but may produce severe hypertension and are therefore not usually recommended. Labetalol has both alpha- and beta-blocking properties and intravenous labetalol has been used successfully to control the cardiovascular effects of tetanus,[1] although it has not been shown to offer any advantage over propranolol in this situation. Esmolol, a short-acting beta blocker, has also been used.[2]

1. Domenighetti GM, *et al.* Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. *BMJ* 1984; **288:** 1483–4.
2. King WW, Cave DR. Use of esmolol to control autonomic instability of tetanus. *Am J Med* 1991; **91:** 425–8.

Tetralogy of Fallot. For the use of beta blockers in the management of tetralogy of Fallot, see under Uses of Propranolol, p.1381.

Tremor. Tremor is a rhythmical oscillation of part of the body caused by involuntary contraction of opposing muscles. It may occur during action, maintenance of posture, or at rest, and varies in frequency and amplitude. Resting tremor is associated mainly with parkinsonism (p.791), whereas action tremor, which includes postural tremor and kinetic tremor, occurs in a wide variety of disorders. Treatment of the underlying disorder may remove the tremor. Drugs such as bronchodilators, tricyclic antidepressants, lithium, and caffeine may induce tremor; withdrawal of the causative drug usually alleviates the tremor. However, tremor often has no known underlying cause. Such tremor is referred to as **essential tremor** or benign essential tremor; it is usually postural and tends to affect the hands, head, voice, and sometimes the legs and trunk. It is exacerbated by emotional stress and anxiety. Essential tremor may appear at any age and is a lifelong condition that may progress with increasing age. In many cases there is a family history of the disorder (familial essential tremor).

Mild cases of essential tremor may not require regular drug treatment. Single doses of a beta blocker or a benzodiazepine may be useful in acute circumstances to control exacerbations provoked by stress. A single dose of propranolol usually produces a maximum effect after 1 to 2 hours and the effect may persist for several hours. Small amounts of alcohol may also provide effective temporary relief of essential tremor, although its regular use is obviously discouraged.

For more severe cases of essential tremor long-term drug treatment may be required (and may also be tried in other forms of tremor).[1-5] A beta blocker (usually a non-cardioselective beta blocker such as propranolol) is often the first drug used. Up to 70% of people have been reported to respond, although the average tremor reduction is only about 50 to 60%. The beneficial effect appears to be mainly due to blockade of peripheral beta$_2$ receptors on extrafusal muscle fibres and muscle spindles, although there may also be a CNS effect. Adverse effects may be troublesome on long-term use. Primidone may also be tried[6] although there may be a high incidence of acute adverse reactions after initial doses. Concern has been expressed that patients may become tolerant to these drugs given long-term. However, 3 small studies found a reduced response on long-term therapy in only a few patients.[7-9] Local injection of botulinum A toxin has been tried in refractory essential tremor. Benzodiazepines, and antimuscarinic or dopaminergic antiparkinsonian drugs may be effective in some forms of tremor.[1] Other drugs that have shown some benefit include gabapentin and topiramate.[1-4,10] Many other drugs have been tried, but there is little evidence to support their use.[10] In very severe disabling cases, surgery (thalamotomy or deep brain stimulation) may have to be considered.

1. Habib-ur-Rehman. Diagnosis and management of tremor. *Arch Intern Med* 2000; **160:** 2438–44.
2. Louis ED. Essential tremor. *N Engl J Med* 2001; **345:** 887–91.
3. Lyons K, *et al.* Benefits and risks of pharmacological treatments for essential tremor. *Drug Safety* 2003; **26:** 461–81.
4. Pahwa R, Lyons KE. Essential tremor: differential diagnosis and current therapy. *Am J Med* 2003; **115:** 134–42.
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6. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
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10. Zesiewicz TA, *et al.* Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005; **64:** 2008–20. Also available at: http://www.neurology.org/cgi/reprint/64/12/2008.pdf (accessed 10/01/08)

Betaxolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ALO-1401-02; Betaksolol Hidroklorür; Betaksololihydrokloridi; Betaksololio hidrochloridas; Bétaxolol, chlorhydrate de; Betaxolol-hidroklorid; Betaxolol-hydrochlorid; Betaxololhydroklorid; Betaxololi hydrochloridum; Hidrocloruro de betaxolol; SL-75212-10. 1-{4-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylaminopropan-2-ol hydrochloride.

Бетаксолола Гидрохлорид

$C_{18}H_{29}NO_3$,HCl = 343.9.

CAS — 63659-18-7 (betaxolol); 63659-19-8 (betaxolol hydrochloride).

ATC — C07AB05; S01ED02.

ATC Vet — QC07AB05; QS01ED02.

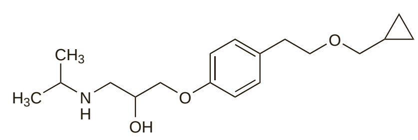

(betaxolol)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Betaxolol Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in dichloromethane. Protect from light.

USP 31 (Betaxolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. pH of a 2% solution in water is between 4.5 and 6.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Betaxolol is completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism, resulting in a high oral bioavailability of about 90%. It has high lipid solubility. Betaxolol is about 50% bound to plasma proteins. It crosses the placenta and is distributed into breast milk where higher concentrations have been achieved than in maternal blood. The plasma elimination half-life of betaxolol ranges from 14 to 22 hours. The primary route of elimination is via hepatic metabolism and urinary excretion; only about 15% is excreted in the urine as unchanged drug.

Pregnancy and breast feeding. The pharmacokinetics of betaxolol were investigated in the perinatal period in 28 pregnant hypertensive patients receiving doses of 10 to 40 mg daily.[1] Pharmacokinetic values were similar to those seen in non-pregnant patients. Umbilical-cord concentrations were similar to maternal blood concentrations and showed a negative correlation between concentration in cord blood and timing of the last dose of betaxolol. Thus the betaxolol concentration in neonates can be considerably reduced by stopping maternal drug use 16 to 18 hours before birth. The blood-betaxolol half-life in the neonates ranged from 14.8 to 38.5 hours. The mean apparent half-life in infants with gestational age less than 36 weeks was about 32% higher than in full-term neonates. Betaxolol concentrations in milk and/or colostrum were determined in 3 mothers. In all samples the milk-to-blood ratio was greater than 2.

1. Morselli PL, *et al.* Placental transfer and perinatal pharmacokinetics of betaxolol. *Eur J Clin Pharmacol* 1990; **38:** 477–83.

Uses and Administration

Betaxolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), and glaucoma (p.1873).

In **hypertension** betaxolol hydrochloride is given in an initial oral dose of 10 mg once daily, which may be doubled if necessary after 1 to 2 weeks. Doses above 20 mg daily do not usually give additional benefit, but up to 40 mg daily has been tolerated. Similar doses are used in **angina pectoris**.

An initial dose of 5 mg daily is suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment (see below).

Eye drops containing the equivalent of 0.25 or 0.5% betaxolol as the hydrochloride are instilled twice daily to reduce raised intra-ocular pressure in ocular hypertension and open-angle **glaucoma**.

◊ General references.

1. Buckley MM-T, *et al.* Ocular betaxolol: a review of its pharmacological properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs* 1990; **40:** 75–90.

Administration in renal impairment. The clearance of betaxolol is reduced in patients with renal impairment and the dose may therefore need to be reduced. Licensed US product information recommends an initial dose of betaxolol hydrochloride 5 mg daily in patients with severe renal impairment or on dialysis; the dose may be increased by 5 mg every 2 weeks, to a maximum of 20 mg daily.

Speech disorders. A 50-year-old man who had stuttered since childhood obtained striking improvement in his stuttering when he was given betaxolol 20 mg daily for essential hypertension.[1]

1. Burris JF, *et al.* Betaxolol and stuttering. *Lancet* 1990; **335:** 223.

Preparations

BP 2008: Betaxolol Eye Drops, Solution; Betaxolol Eye Drops, Suspension; ***USP 31:*** Betaxolol Ophthalmic Solution; Betaxolol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Betasel; Tonobexol; ***Austral.:*** Betoptic; Betoquin; ***Austria:*** Betoptic; Kerlone; ***Belg.:*** Betoptic; Kerlone; ***Braz.:*** Betoptic; Presmin; ***Canad.:*** Betoptic; ***Chile:*** Bemaz; Beof; Betoptic; ***Cz.:*** Betalmic; Betaxa; Betoptic; Lokren; ***Denm.:*** Betoptic; Kerlon†; ***Fin.:*** Betoptic; Kerlon; ***Fr.:*** Betoptic; Kerlone; ***Ger.:*** Betoptima; Kerlone; ***Gr.:*** Armament; Betoptic; Eifel; Kerlone; Pertaxol†; ***Hong Kong:*** Betoptic; ***Hung.:*** Betoptic; Lokren; ***India:*** Optipres; ***Indon.:*** Betoptima; Optibet; ***Irl.:*** Betoptic; ***Israel:*** Betoptic; Kerlone; ***Ital.:*** Betoptic; Kerlon; ***Jpn:*** Kerlong; ***Malaysia:*** Betac; Betoptic; Kerlone; ***Mex.:*** Beofta†; Betoptic; BTX-HA Ofteno; ***Neth.:*** Betoptic; Kerlon; ***Norw.:*** Betoptic; ***NZ:*** Betoptic; ***Philipp.:*** Betoptic; Kerlone; ***Pol.:*** Betabion; Betoptic; Lokren; Optibetol; ***Port.:*** Bertocil; Betaglau; Betoptic; Davixolol; ***Rus.:*** Betac (Бетак); Betoptic (Бетоптик); Lokren (Локрен); ***S.Afr.:*** Betoptic; ***Singapore:*** Betac; Betoptic; Kerlone; ***Spain:*** Betoptic; ***Swed.:*** Betoptic; Kerlon†; ***Switz.:*** Betoptic; Kerlon†; ***Thai.:*** Betoptic; ***Turk.:*** Betoptic; ***UK:*** Betoptic; ***USA:*** Betoptic; Kerlone; ***Venez.:*** Betaxol; Betoptic.

Bevantolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Bévantolol, Chlorhydrate de; Bevantololhydroklorid; Bevantololi Hydrochloridum; Bevantololihydrokloridi; CI-775; Hidrocloruro de bevantolol; NC-1400. 1-(3,4-Dimethoxyphenethylamino)-3-*m*-tolyloxypropan-2-ol hydrochloride.

Бевантолола Гидрохлорид

$C_{20}H_{27}NO_4$,HCl = 381.9.

CAS — 59170-23-9 (bevantolol); 42864-78-8 (bevantolol hydrochloride).

ATC — C07AB06.

ATC Vet — QC07AB06.

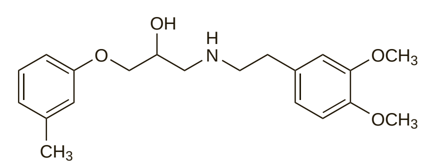

(bevantolol)

Profile

Bevantolol is a cardioselective beta blocker (p.1225). It is reported to lack significant intrinsic sympathomimetic activity but has weak membrane-stabilising properties and also has vasodilator activity. It has been given orally as the hydrochloride in the management of hypertension and angina pectoris.

◊ References.

1. Frishman WH, *et al.* Bevantolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1988; **35:** 1–21.

Bezafibrate *(BAN, USAN, rINN)*

Betsafibraatti; Bezafibrát; Bezafibrat; Bezafibratas; Bézafibrate; Bezafibrato; Bezafibratum; BM-15075; LO-44. 2-[4-(2-*p*-Chlorobenzamidoethyl)phenoxy]-2-methylpropionic acid.

Безафибрат

$C_{19}H_{20}ClNO_4$ = 361.8.

CAS — 41859-67-0.

ATC — C10AB02.

ATC Vet — QC10AB02.

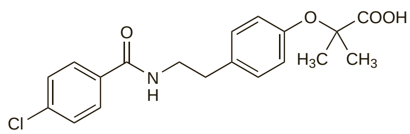

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Bezafibrate). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dimethylformamide; it dissolves in dilute solutions of alkali hydroxides.

Adverse Effects and Precautions

The commonest adverse effects of bezafibrate therapy are gastrointestinal disturbances including anorexia, nausea, and gastric discomfort. Other adverse effects reported to occur less frequently include headache, dizziness, vertigo, fatigue, skin rashes, pruritus, photosensitivity, alopecia, impotence, anaemia, leucopenia, and thrombocytopenia. Raised serum-aminotransferase concentrations have occasionally been reported. Elevated creatine phosphokinase concentrations during bezafibrate therapy may be associated with a syndrome of myositis, myopathy, and rarely rhabdomyolysis; patients with hypoalbuminaemia resulting from nephrotic syndrome or with renal impairment may be at increased risk. Bezafibrate should not be given with statins in patients with risk factors for myopathy. Bezafibrate may increase the lithogenic index, and there have been isolated reports of gallstones, although the risk from fibrates as a class is unclear (see Gallstones, below).

Bezafibrate should not be given to patients with severe hepatic impairment or significant liver disease, gallstones or gallbladder disorders, or hypoalbuminaemic states such as nephrotic syndrome. It should be used with caution in renal impairment and is contra-indicated if creatinine clearance is below 15 mL/minute unless the patient is on dialysis (see under Uses and Administration, below).

◊ Reviews.

1. Davidson MH, *et al.* Safety considerations with fibrate therapy. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 3C–18C.

Effects on glucose metabolism. Use of fibrates in diabetic patients has generally been reported to either improve[1-3] or have no effect[4-6] on insulin sensitivity and glucose metabolism, and they are considered a suitable treatment for type 2 diabetics with hypertriglyceridaemia.[7] There is also some evidence that fibrates may reduce the incidence or delay the onset of diabetes in patients with obesity[8] or impaired glucose tolerance.[9] However, there has been a report[10] of recurrent hypoglycaemia in a type 2 diabetic when gemfibrozil was added to high-dose insulin therapy although eventually a reduced insulin dosage, with fibrate therapy, produced good glucose control. Gemfibrozil is contra-indicated in patients receiving repaglinide due to the risk of severe hypoglycaemia (see p.458). Conversely, a study in 20 diabetic patients[11] given gemfibrozil reported a slight increase in requirements for antidiabetic therapy (oral hypoglycaemics or insulin) in 9 and a decrease in 1.

1. Ogawa S, *et al.* Bezafibrate reduces blood glucose in type 2 diabetes mellitus. *Metabolism* 2000; **49:** 331–4.
2. Jones IR, *et al.* Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. *Diabetes Care* 1990; **13:** 855–63.
3. Notarbartolo A, *et al.* Effects of gemfibrozil in hyperlipidemic patients with or without diabetes. *Curr Ther Res* 1993; **53:** 381–93.
4. Leaf DA, *et al.* The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. *JAMA* 1989; **262:** 3154–60.
5. Pagani A, *et al.* Effect of short-term gemfibrozil administration on glucose metabolism and insulin secretion in non-insulin-dependent diabetics. *Curr Ther Res* 1989; **45:** 14–20.
6. Hernández-Mijares A, *et al.* Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. *Nutr Metab Cardiovasc Dis* 2000; **10:** 1–6.
7. Buse JB, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; **115:** 114–26. Also published in *Diabetes Care* 2007; **30:** 162–72.
8. Tenenbaum A, *et al.* Effect of bezafibrate on incidence of type 2 diabetes mellitus in obese patients. *Eur Heart J* 2005; **26:** 2032–8.
9. Tenenbaum A, *et al.* Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 2004; **109:** 2197–2202.
10. Klein J, *et al.* Recurrent hypoglycaemic episodes in a patient with type 2 diabetes under fibrate therapy. *J Diabetes Complications* 2002; **16:** 246–8.
11. Konttinen A, *et al.* The effect of gemfibrozil on serum lipids in diabetic patients. *Ann Clin Res* 1979; **11:** 240–5.

Effects on the kidneys. Small increases in creatinine concentration are common during treatment with bezafibrate and have also been reported with other fibrates,[1] although possibly not with gemfibrozil. There have also been reports of acute renal failure associated with treatment with bezafibrate,[2] and with clofibrate,[3,4] and an accelerated decline in renal function has been reported with bezafibrate in patients with chronic renal failure.[5] Renal failure may also occur due to rhabdomyolysis in patients receiving fibrates, including gemfibrozil (see Effects on Skeletal Muscle, below).

1. Broeders N, *et al.* Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant* 2000; **15:** 1993–9.
2. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
3. Dosa S, *et al.* Acute-on-chronic renal failure precipitated by clofibrate. *Lancet* 1976; **i:** 250.
4. Cumming A. Acute renal failure and interstitial nephritis after clofibrate treatment. *BMJ* 1980; **281:** 1529–30.
5. Williams AJ, *et al.* The short term effects of bezafibrate on the hypertriglyceridaemia of moderate to severe uraemia. *Br J Clin Pharmacol* 1984; **18:** 361–7.

Effects on the nervous system. Adverse effects on the peripheral nervous system have been reported with fibrates. Peripheral neuropathy has been reported[1] with bezafibrate, and was substantiated by nerve conduction studies. There have also been reports of peripheral neuropathy with clofibrate,[2] and with fenofibrate,[3] which resolved when therapy was withdrawn. In addition, by 1993, the Adverse Drug Reactions Advisory Committee in Australia had received reports of paraesthesia occurring in 6 patients in association with gemfibrozil treatment.[4]

1. Ellis CJ, *et al.* Peripheral neuropathy with bezafibrate. *BMJ* 1994; **309:** 929.
2. Gabriel R, Pearce JMS. Clofibrate-induced myopathy and neuropathy. *Lancet* 1976; **ii:** 906.
3. Corcia P, *et al.* Severe toxic neuropathy due to fibrates. *J Neurol Neurosurg Psychiatry* 1999; **66:** 410.
4. Anonymous. Paraesthesia and neuropathy with hypolipidaemic agents. *Aust Adverse Drug React Bull* 1993; **12:** 6.

Effects on the pancreas. Acute pancreatitis has been reported[1] in a patient receiving bezafibrate, and recurred on 2 occasions when bezafibrate was restarted. There has also been a report[2] of acute pancreatitis in a patient receiving both fenofibrate and simvastatin, although simvastatin was considered more likely to be responsible. An increased incidence of pancreatitis was also reported with fenofibrate in the FIELD study,[3] although the number of cases was small.

1. Gang N, *et al.* Relapsing acute pancreatitis induced by re-exposure to the cholesterol lowering agent bezafibrate. *Am J Gastroenterol* 1999; **94:** 3626–8.
2. McDonald KB, *et al.* Pancreatitis associated with simvastatin plus fenofibrate. *Ann Pharmacother* 2002; **36:** 275–9.
3. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.

Effects on sexual function. Sexual dysfunction has occurred with some fibrates. *Erectile dysfunction* and *loss of libido* has been reported in 3 patients[1-3] during gemfibrozil treatment. In 2 of the men[1,2] bezafibrate did not produce this adverse effect. The UK CSM was reported to be aware of a further 6 cases.[2] Of a further 3 cases of erectile dysfunction associated with gemfibrozil reported from Spain, 1 patient had previously reacted similarly to clofibrate.[4] A systematic review,[5] including these and other reports, supported the conclusion that fibrates could cause erectile dysfunction.

Gynaecomastia was reported[6] in a 56-year-old man receiving fenofibrate and recurred on rechallenge; there were no other effects on sexual function.

1. Pizarro S, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; **336:** 1135.
2. Bain SC, *et al.* Gemfibrozil-induced impotence. *Lancet* 1990; **336:** 1389.
3. Bharani A. Sexual dysfunction after gemfibrozil *BMJ* 1992; **305:** 693.
4. Figueras A, *et al.* Gemfibrozil-induced impotence. *Ann Pharmacother* 1993; **27:** 982.
5. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
6. Gardette V, *et al.* Gynecomastia associated with fenofibrate. *Ann Pharmacother* 2007; **41:** 508–11.

Effects on skeletal muscle. Muscle disorders including myositis and myopathy are well known to occur with lipid regulating drugs such as fibrates.[1] Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, has also been reported but appears to be rare. Patients with renal impairment, and possibly with hypothyroidism, may be at increased risk of muscle toxicity. The UK CSM has advised[1] that patients treated with fibrates should consult their doctor if they develop muscle pain, tenderness, or weakness, and treatment should be stopped if muscle toxicity is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising.

Other lipid regulating drugs, particularly the statins, have also been associated with myopathy and the risk of muscle toxicity is increased if fibrates and statins are taken together (see Lipid Regulating Drugs under Interactions of Simvastatin, p.1393); combination therapy may be appropriate in some patients but careful monitoring is required.[2]

1. Committee on Safety of Medicines/Medicines Control Agency. Rhabdomyolysis associated with lipid-lowering drugs. *Current Problems* 1995; **21:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.

Gallstones. Fibrates, including fenofibrate[1-3] and gemfibrozil[4] have been reported to increase indices of bile lithogenicity, and some studies[5,6] have suggested an increased risk of gallstones in patients receiving fibrates. However, in the Helsinki Heart Study[7] no significant increase in gallstone operations was reported among 2051 patients taking gemfibrozil compared with 2030 taking placebo, although a follow-up study[8] reported that cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period.

1. Brown WV. Treatment of hypercholesterolaemia with fenofibrate: a review. *Curr Med Res Opin* 1989; **11:** 321–30.
2. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med* 1987; **83** (suppl 5B): 26–36.
3. Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *Am J Med* 1987; **83** (suppl 5B): 37–43.
4. Leiss O, *et al.* Effect of gemfibrozil on biliary lipid metabolism in normolipemic subjects. *Metabolism* 1985; **34:** 74–82.
5. Mamdani MM, *et al.* Is there an association between lipid-lowering drugs and cholecystectomy? *Am J Med* 2000; **108:** 418–21.
6. Caroli-Bosc F-X, *et al.* Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation: epidemiological study in an unselected population. *Dig Dis Sci* 2001; **46:** 540–4.
7. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
8. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.

Headache. Severe recurrent headaches have been reported[1] in a patient receiving bezafibrate. The headaches started about 24 hours after therapy with bezafibrate began, and recurred about 1 hour after each dose. Headaches occurred 30 to 90 minutes after each dose of gemfibrozil in 2 patients.[2,3] In both patients, the headaches were accompanied by dry mouth, and in 1 also by blurred vision. The headaches stopped when gemfibrozil was withdrawn and recurred one week after re-exposure.

1. Hodgetts TJ, Tunnicliffe C. Bezafibrate-induced headache. *Lancet* 1989; **i:** 163.
2. Arellano F, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **i:** 705.
3. Alvarez-Sabin J, *et al.* Gemfibrozil-induced headache. *Lancet* 1988; **ii:** 1246.

Hyperhomocysteinaemia. Hyperhomocysteinaemia has been associated with an increased risk for cardiovascular disease. Small studies have found that both bezafibrate[1,2] and fenofibrate[1,3] increase plasma-homocysteine concentrations, although the clinical significance of this is not clear.[4] Folic acid and vitamin B_{12} have been given[4,5] with fenofibrate to reduce homocysteine concentrations, but the role of such treatment is not established.

1. Dierkes J, *et al.* Serum homocysteine increases after therapy with fenofibrate or bezafibrate. *Lancet* 1999; **354:** 219–20.
2. Jonkers IJAM, *et al.* Implication of fibrate therapy for homocysteine. *Lancet* 1999; **354:** 1208.
3. de Lorgeril M, *et al.* Lipid-lowering drugs and homocysteine. *Lancet* 1999; **353:** 209–10.
4. Dierkes J, *et al.* Fenofibrate-induced hyperhomocysteinaemia: clinical implications and management. *Drug Safety* 2003; **26:** 81–91.
5. Melenovsky V, *et al.* Effect of folic acid on fenofibrate-induced elevation of homocysteine and cysteine. *Am Heart J* 2003; **146:** 110. Full version available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870303001224.pdf (accessed 30/05/08)

Photosensitivity. Fibrates have been associated with photosensitivity reactions[1] and there may be cross-sensitivity with ketoprofen (see under Adverse Effects of Ketoprofen, p.73).

1. Serrano G, *et al.* Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen *J Am Acad Dermatol* 1992; **27:** 204–8.

Interactions

Bezafibrate and other fibrates are highly protein-bound and may displace other drugs from protein binding sites. Interactions may also occur through changes in the activity of cytochrome P450 isoenzymes, particularly CYP3A4.

Fibrates may enhance the effects of oral anticoagulants; the dose of anticoagulant should be reduced when treatment with a fibrate is started, and then adjusted gradually if necessary. Recommendations vary; licensed product information for bezafibrate suggests a reduction of up to 50% in the dosage of anticoagulant. The mechanism of the interaction is unclear; fibrates have been reported to displace warfarin from protein binding sites but other mechanisms are probably also involved.

Other drugs that may be displaced from plasma proteins by fibrates include tolbutamide and other sulfonylurea antidiabetics, phenytoin, and, in patients with hypoalbuminaemia, furosemide. The interaction with antidiabetics is complex since fibrates may alter glucose tolerance in diabetic patients (see Effects on Glucose Metabolism, above). The dosage of antidiabetics may need adjusting during bezafibrate therapy.

There is an increased risk of myopathy if fibrates are used with statins (see Lipid Regulating Drugs under Interactions of Simvastatin, p.1393).

Fibrates may interact with ciclosporin, although reports have been conflicting (see p.1827). However, nephrotoxicity associated with increased ciclosporin concentrations has been reported with bezafibrate and renal function should be monitored.

Cholestasis has been reported in a patient given fenofibrate with raloxifene (see p.2128).

◊ Reviews.

1. Lozada A, Dujovne CA. Drug interactions with fibric acids. *Pharmacol Ther* 1994; **63:** 163–76.

Lipid regulating drugs. The bioavailability of gemfibrozil was reduced by *colestipol*, but was unaffected when gemfibrozil was taken either 2 hours before or 2 hours after colestipol.[1]

For discussion of the interaction between fibrates and *statins*, see p.1393.

1. Forland SC, *et al.* Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* 1990; **30:** 29–32.

NSAIDs. Acute renal failure due to rhabdomyolysis in a patient has been attributed to an interaction between ciprofibrate and *ibuprofen*.[1] Ibuprofen was believed to have displaced ciprofibrate from protein binding sites. The use of radiological contrast media may also have been a contributory factor.

1. Ramachandran S, *et al.* Acute renal failure due to rhabdomyolysis in presence of concurrent ciprofibrate and ibuprofen treatment. *BMJ* 1997; **314:** 1593.

Pharmacokinetics

Bezafibrate is readily absorbed from the gastrointestinal tract. Plasma protein binding is about 95%. The plasma elimination half-life is about 1 to 2 hours. Most of a dose is excreted in the urine, about half as unchanged drug, the remainder as metabolites including 20% as glucuronides. A small proportion (about 3%) of the dose appears in the faeces. Elimination may be increased by forced diuresis. The drug is not dialysable.

◊ References.

1. Abshagen U, *et al.* Disposition pharmacokinetics of bezafibrate in man. *Eur J Clin Pharmacol* 1979; **16:** 31–8.
2. Abshagen U, *et al.* Steady-state kinetics of bezafibrate and clofibrate in healthy female volunteers. *Eur J Clin Pharmacol* 1980; **17:** 305–8.

The elderly. In a study comparing the pharmacokinetics of bezafibrate in 19 elderly patients with younger healthy subjects,[1] maximum plasma concentrations were 1.6 times higher in the elderly group (median 12.1 mg/litre against 7.7 mg/litre) and half-life was increased by 3.8 times (median 6.6 hours against 1.7 hours). The differences could not be attributed solely to diminished renal function in elderly patients. Dosage adjustments in elderly patients should not therefore be based on renal function alone.

1. Neugebauer G, *et al.* Steady-state kinetics of bezafibrate retard in hyperlipidemic geriatric patients. *Klin Wochenschr* 1988; **66:** 250–6.

Renal impairment. The half-life of bezafibrate may be prolonged in patients with renal impairment (see under Uses and Administration, below).

Uses and Administration

Bezafibrate, a fibric acid derivative, is a lipid regulating drug. It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. Bezafibrate and other fibrates reduce triglycerides by reducing the concentration of very-low-density lipoprotein (VLDL). They reduce low-density lipoprotein (LDL)-cholesterol to a lesser extent, although the effect is variable, and may also increase high-density lipoprotein (HDL)-cholesterol. Although evidence that this leads to a reduction in cardiovascular events is less good than for statins, some fibrates may have a role in cardiovascular risk reduction (see below).

Bezafibrate is given in a usual oral dose of 200 mg three times daily taken with or after food; gastrointestinal disturbances may be reduced in susceptible patients by increasing the dose gradually over 5 to 7 days; 200 mg twice daily may occasionally be adequate for maintenance particularly in the treatment of hypertriglyceridaemia. A modified-release tablet is also available and is given as a single daily dose of 400 mg.

The dose of bezafibrate should be reduced in patients with renal impairment (see below).

◊ General reviews.

1. Goa KL, *et al.* Bezafibrate: an update of its pharmacology and use in the management of dyslipidaemia. *Drugs* 1996; **52:** 725–53.
2. Goldenberg I, *et al.* Update on the use of fibrates: focus on bezafibrate. *Vasc Health Risk Manag* 2008; **4:** 131–41.

Action. Bezafibrate is a typical member of the fibric acid derivative group of drugs (the fibrates) used in the treatment of hyperlipidaemias (p.1169). One of the primary actions of the fibrates is to promote the catabolism of triglyceride-rich lipoproteins, in particular very-low-density lipoproteins (VLDL), apparently mediated by an enhanced activity of lipoprotein lipase.[1] They may also interfere with the synthesis of VLDL, possibly by inhibiting hepatic acetyl coenzyme A carboxylase. The effect of fibrates on low-density lipoprotein (LDL)-cholesterol depends on the overall lipoprotein status of the patient but concentrations tend to decrease if high at baseline and increase if low at baseline. High-density lipoprotein (HDL)-cholesterol concentrations are increased, although there have been a few reports of unexpected falls in HDL-cholesterol with bezafibrate[2,3] and ciprofibrate.[4,5]

Fibrates have three actions on sterol metabolism:[1] they inhibit the synthesis of cholesterol, they inhibit the synthesis of bile acids, and they enhance the secretion of cholesterol in bile. It is these latter two effects which are responsible for the raised cholesterol saturation of bile, which may lead to the formation of gallstones in some patients (see Gallstones, under Adverse Effects, above).

The effects of fibrates are mediated by their agonist action at peroxisome proliferator-activated receptors (PPARs).[6,7] Fibrates are agonists of PPAR-α, which plays an important role in fatty acid metabolism; some, such as bezafibrate, may also activate other receptors including PPAR-γ (which plays a role in glucose homoeostasis).[7]

1. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. *Am J Med* 1987; **83** (suppl 5B): 9–20.
2. Capps NE. Lipid profiles on fibric-acid derivatives. *Lancet* 1994; **344:** 684–5.
3. McLeod AJ, *et al.* Abnormal lipid profiles on fibrate derivatives. *Lancet* 1996; **347:** 261.
4. Chandler HA, Batchelor AJ. Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 128–9.
5. McLeod AJ, *et al.* Ciprofibrate and lipid profile. *Lancet* 1994; **344:** 955.
6. Fruchart J-C, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today* 2006; **42:** 39–64.
7. Robinson JG. Should we use PPAR agonists to reduce cardiovascular risk? *PPAR Res* 2008; **2008:** 891425.

Administration in renal impairment. Bezafibrate is mainly excreted in the urine and dosage alterations may be necessary in patients with renal impairment; fibrates may also impair renal function (see Effects on the Kidneys under Adverse Effects, above). Modified-release preparations are contra-indicated in patients with creatinine clearance (CC) below 60 mL/minute and the dosage of conventional-release formulations should be reduced depending on CC, as follows:

- CC 40 to 60 mL/minute: 400 mg daily
- CC 15 to 40 mL/minute: 200 mg daily or on alternate days
- CC less than 15 mL/minute unless on dialysis: contra-indicated
- dialysis patients: 200 mg every 3 days, with careful monitoring

In a study in patients with renal impairment[1] the half-life of bezafibrate was reported to be prolonged to 4.6 hours in 3 patients with CC greater than 40 mL/minute, 7.8 hours in 8 patients with CC of 20 to 40 mL/minute, and 20.1 hours in a patient with CC of 13 mL/minute.

1. Anderson P, Norbeck H-E. Clinical pharmacokinetics of bezafibrate in patients with impaired renal function. *Eur J Clin Pharmacol* 1981; **21:** 209–14.

Cardiovascular risk reduction. Lipid lowering therapy has an important role in patients at risk of cardiovascular disease (p.1164). Although the evidence is less good than for statins, several studies have shown that fibrates may reduce both the progression of atherosclerosis and the incidence of cardiovascular events.[1]

In the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)[2,3] treatment with bezafibrate for 5 years in young men (less than 45 years of age) after myocardial infarction resulted in fewer coronary events and slowed the progression of focal coronary atherosclerosis when compared with placebo. However, in older men with peripheral vascular disease,[4] bezafibrate had no effect on the incidence of coronary events and stroke together, although the severity of intermittent claudication was reduced and, in men under 65 years, there were fewer non-fatal coronary events. In the Diabetes Atherosclerosis Intervention Study (DAIS),[5] fenofibrate reduced the angiographic progression of coronary atherosclerosis in type 2 diabetics, and there were also fewer clinical events in those receiving fenofibrate; further analysis showed[6] reduced progression to microalbuminuria in the fenofibrate group. However, another study in type 2 diabetics, the FIELD study,[7] found no reduction in the risk of major coronary events with fenofibrate, although there were fewer non-fatal myocardial infarctions and revascularisations. A meta-analysis[8] of studies including type 2 diabetics concluded that fibrates reduce the incidence of cardiovascular events, but the effect on mortality was not significant.

The best evidence for a reduction in cardiovascular events is for gemfibrozil. The Helsinki Heart Study[9] assessed gemfibrozil for the primary prevention of ischaemic heart disease in 4081 middle-aged men with hyperlipidaemia. There was an overall reduction of 34% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the greatest reduction seen during years 3 to 5. Follow-up for a further 3.5 years[10] suggested that long-term treatment with gemfibrozil seemed to postpone coronary events for about 5 years. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[11] assessed gemfibrozil for the secondary prevention of ischaemic heart disease in 2531 older men (mean age 64 years) whose primary lipid abnormality was a low HDL-cholesterol level. There was an overall reduction of 22% in the incidence of fatal and non-fatal myocardial infarctions and cardiac deaths in the gemfibrozil group compared with the placebo group, with the beneficial effects of gemfibrozil becoming apparent about 2 years after randomisation. There was also a reduction in the incidence of stroke.[12]

1. Després J-P, *et al.* Role of fibric acid derivatives in the management of risk factors for coronary heart disease. *Drugs* 2004; **64:** 2177–98.
2. Ericsson C-G, *et al.* Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 1996; **347:** 849–53.
3. Ericsson C-G, *et al.* Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)). *Am J Cardiol* 1997; **80:** 1125–9.
4. Meade T, *et al.* Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002; **325:** 1139–43.
5. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; **357:** 905–910. Correction. *ibid.*; 1890.
6. Ansquer J-C, *et al.* Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005; **45:** 485–93.
7. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366:** 1849–61. Corrections. *ibid.* 2006; **368:** 1415 and 1420.
8. Allemann S, *et al.* Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2006; **22:** 617–23.
9. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
10. Heinonen OP, *et al.* The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med* 1994; **235:** 41–9.
11. Bloomfield Rubins H, *et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; **341:** 410–18.
12. Bloomfield Rubins H, *et al.* Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 2001; **103:** 2828–33.

Dementia. For reference to a possible reduction in the incidence of dementia associated with lipid regulating drugs, including fibrates, see under Uses of Simvastatin, p.1395.

Preparations

BP 2008: Bezafibrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bezacur; Bezalip; Elpi Lip; Nebufur; ***Austria:*** Bezacur; Bezalip; Bezaretard; Bezastad; ***Belg.:*** Cedur; Eulitop; ***Braz.:*** Cedur; ***Canad.:*** Bezalip; ***Chile:*** Nimus; Oralipin; ***Cz.:*** Regadrin B; ***Fin.:*** Bezalip; ***Fr.:*** Befizal; ***Ger.:*** Azufibrat†; Befibrat; Beza; Beza-Puren†; Bezabeta; Bezacur†; Bezadoc; Bezagamma; Bezamerck†; Bezapham†; Cedur; Lipox; Regadrin B†; Sklerofibrat†; ***Gr.:*** Bezalip; Getup†; Verbital; ***Hong Kong:*** Bezalip; Zafibral†; ***Hung.:*** Bezalip; ***India:*** Beza†; Bezalip; ***Israel:*** Bezalip; Norlip; ***Ital.:*** Bezalip; Hadiel; ***Jpn:*** Bezalip; ***Malaysia:*** Bezalip; ***Mex.:*** Befitec; Bexalcor; Bezafisal;

Bezalex; Bezalip; Bifaren; Bionolip; Colser; Fazebit; Klestran†; Lesbest; Lipocin; Neptalip; Nivetril; Redalip; Solibay†; Zaf; ***Neth.:*** Bezalip; ***NZ:*** Bezalip; Fibalip; ***Philipp.:*** Bezastad; ***Pol.:*** Bezamidin; ***Port.:*** Bezalip; ***S.Afr.:*** Bezalip; ***Singapore:*** Bezalip; Zafibral; ***Spain:*** Difaterol; Eulitop; Reducterol†; ***Swed.:*** Bezalip; ***Switz.:*** Cedur; ***Thai.:*** Bezalip; Bezamil; Polyzalip; Raset†; ***UAE:*** Lipitrol; ***UK:*** Bezagen; Bezalip; Bezalip Mono; Fibrazate; Zimbacol; ***Venez.:*** Bezalip; Detrex†.

Binifibrate *(rINN)*

Binifibrato; Binifibratum. 2-(4-Chlorophenoxy)-2-methylpropionic acid ester with 1,3-dinicotinoyloxypropan-2-ol.

Бинифибрат

$C_{25}H_{23}ClN_2O_7$ = 498.9.

CAS — 69047-39-8.

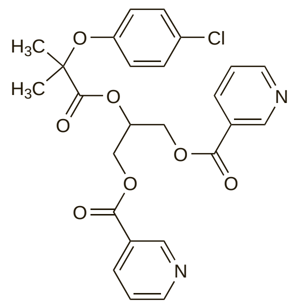

Profile

Binifibrate, a derivative of clofibrate (p.1246) and nicotinic acid (p.1957), is a lipid regulating drug that has been used in the treatment of hyperlipidaemias.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Antopal†; Biniwas†.

Bisoprolol Fumarate

(BANM, USAN, rINNM) ⊗

Bisoprolol Fumarat; Bisoprolol, Fumarate de; Bisoprolol Hemifumarate; Bisoprolol, hémifumarate de; Bisoprololfumarat; Bisoprololi Fumaras; Bisoprololi hemifumaras; Bisoprololifumaraatti; CL-297939; EMD-33512 (bisoprolol or bisoprolol fumarate); Fumarato de bisoprolol. 1-[4-(2-Isopropoxyethoxymethyl)phenoxy]-3-isopropylaminopropan-2-ol fumarate.

Бизопролола Фумарат

$(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ = 767.0.

CAS — 66722-44-9 (bisoprolol); 66722-45-0 (bisoprolol fumarate); 104344-23-2 (bisoprolol fumarate).

ATC — C07AB07.

ATC Vet — QC07AB07.

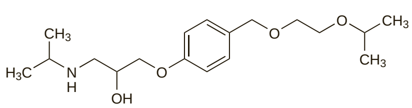

(bisoprolol)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Bisoprolol Fumarate). A white or almost white, slightly hygroscopic powder. It exhibits polymorphism. Very soluble in water; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Bisoprolol Fumarate). A white crystalline powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol, in chloroform, and in glacial acetic acid; slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Bisoprolol is almost completely absorbed from the gastrointestinal tract and undergoes only minimal first-pass metabolism resulting in an oral bioavailability of about 90%. Peak plasma concentrations are reached 2 to 4 hours after oral doses. Bisoprolol is about 30% bound to plasma proteins. It has a plasma elimination half-life of 10 to 12 hours. Bisoprolol is moderately lipid-soluble. It is metabolised in the liver and excreted in urine, about 50% as unchanged drug and 50% as metabolites.

Uses and Administration

Bisoprolol is a cardioselective beta blocker (p.1225). It is reported to be devoid of intrinsic sympathomimetic and membrane-stabilising properties.

Bisoprolol is given as the fumarate in the management of hypertension (p.1171) and angina pectoris (p.1157). It is also used as an adjunct to standard therapy in patients with stable chronic heart failure (p.1165).

In **hypertension** or **angina pectoris** the usual dose of bisoprolol fumarate is 5 to 10 mg orally as a single daily dose; the maximum recommended dose is 20 mg daily. A reduction in dose may be necessary in patients with hepatic or renal impairment (see below).

In **heart failure** the initial oral dose of bisoprolol fumarate is 1.25 mg once daily. If tolerated, the dose should be doubled after 1 week, and then increased gradually at 1 to 4 week intervals to the maximum dose tolerated; this should not exceed 10 mg once daily.

◊ References.

1. Johns TE, Lopez LM. Bisoprolol: is this just another beta-blocker for hypertension or angina? *Ann Pharmacother* 1995; **29:** 403–14.
2. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.
3. McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs* 2002; **62:** 2677–96.

Administration in hepatic or renal impairment. US licensed product information recommends that the initial dose of bisoprolol fumarate for hypertension should be 2.5 mg daily and that the dose should be increased cautiously in patients with severe hepatic impairment or renal impairment (creatinine clearance less than 40 mL/minute). UK licensed product information recommends a maximum dose of 10 mg daily for both angina pectoris and hypertension in patients with severe hepatic impairment or with a creatinine clearance of less than 20 mL/minute. Bisoprolol is not dialysable.

Preparations

USP 31: Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Bisoprolol Fumarate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Concor; Corbis; Lostaprolol; ***Austral.:*** Bicor; ***Austria:*** Bisocor; Bisostad; Bisotyrol†; Cardiocor; Concor; Darbalan; Nanalan; Rivacor; ***Belg.:*** Bisoprotop; Docbisopro; Emconcor; Isoten; ***Braz.:*** Concor; ***Canad.:*** Monocor; ***Chile:*** Concor; ***Cz.:*** Bisoblock; Bisocard; Bisogamma; Bivaxol; Concor; Concor Cor; Kordobis; Rivocor; ***Denm.:*** Biscor; Cardicor; Emconcor; ***Fin.:*** Bisomerck; Bisopral; Emconcor; Orloc; ***Fr.:*** Cardensiel; Cardiocor; Detensiel; Soprol†; ***Ger.:*** Biso; Biso Lich; Biso-Puren; BisoAPS; Bisobeta; Bisobloc†; Bisogamma; Bisohexal; Bisomerck; Concor; Cordalin†; Fondril; Jutabis; ***Gr.:*** Abitrol; Blocatens; Pactens; Speridol; ***Hong Kong:*** Concor; ***Hung.:*** Bisoblock; Bisocard; Bisogamma; Bisogen; Concor; Concor Cor; Coviogal; ***India:*** Concor; ***Indon.:*** B-Beta; Concor; Hapsen; Lodoz; Maintate; ***Irl.:*** Bisocor; Bispine; Cardicor; Emcolol; Emcor; Soprol; ***Israel:*** Bisolol; Cardiloc; Concor; ***Ital.:*** Cardicor; Concor; Congescor; Pluscor; Sequacor; ***Jpn:*** Maintate; ***Malaysia:*** Concor; ***Mex.:*** Concor; ***Neth.:*** Bisobloc†; Bisoblock; Cardicor†; Emcor; ***Norw.:*** Emconcor; ***Philipp.:*** Concore; ***Pol.:*** Biscard; Bisohexal; Bisopromerck; Bisoratio; Concor; Corectin; ***Port.:*** Concor; Libracor; ***Rus.:*** Biprol (Бипрол); Bisocard (Бисокард); Bisogamma (Бисогамма); Concor (Конкор); Corbis (Корбис); ***S.Afr.:*** Adcobisocor; Bilocor; Bisohexal; Cardicor; Concor; ***Singapore:*** Concor; ***Spain:*** Emconcor; Euradal; Godal; ***Swed.:*** Bisomerck; Emconcor; ***Switz.:*** Bilol; Concor; ***Thai.:*** Concor; Novacor; ***Turk.:*** Concor; ***UK:*** Bipranix†; Cardicor; Emcor; Monocor†; Soloc†; Vivacor; ***USA:*** Zebeta; ***Venez.:*** Concor.

Multi-ingredient: ***Arg.:*** Corbis D; Ziac; ***Austria:*** Bisocombin; Bisoprolol comp; Bisoprolol-HCT; Bisostad plus; Concor Plus; Darbalan Plus; Nanalan Plus; Rivacor Plus; ***Belg.:*** Co-Bisoprolol; Emcoretic; Lodoz; Maxsoten; Merck-Co-Bisoprolol; ***Braz.:*** Biconcor; ***Chile:*** Ziac; ***Cz.:*** Concor Plus†; Lodoz; Tebis Plus H; ***Fin.:*** Bisoprolol Comp; Emconcor Comp; Orloc Comp; ***Fr.:*** Lodoz; Wytens; ***Ger.:*** Biso comp; Biso-Puren comp; Bisobeta comp; Bisohexal plus; BisoLich comp; Bisomerck Plus; Bisoplus; Bisoprolol Comp; Bisoprolol HCT; Bisoprolol Plus; Concor Plus; Fondril HCT; ***Hong Kong:*** Lodoz; ***Hung.:*** Concor Plus; Lodoz; ***India:*** Lodoz; ***Ital.:*** Lodoz; ***Mex.:*** Biconcor; ***Neth.:*** Emcoretic; ***Norw.:*** Lodoz; ***Philipp.:*** Ziac; ***Port.:*** Concor Plus; ***S.Afr.:*** Ziak; ***Singapore:*** Lodoz; ***Spain:*** Emcoretic; ***Switz.:*** Concor Plus; Lodoz; ***Thai.:*** Lodoz; ***USA:*** Ziac; ***Venez.:*** Biconcor; Ziac.

Bivalirudin *(BAN, USAN, rINN)*

BG-8967; Bivalirudina; Bivalirudine; Bivalirudinum; Hirulog.

Бивалирудин

$C_{98}H_{138}N_{24}O_{33}$ = 2180.3.

CAS — 128270-60-0.

ATC — B01AE06.

ATC Vet — QB01AE06.

Incompatibility. The manufacturer of bivalirudin states that it is incompatible with: alteplase, amiodarone hydrochloride, amphotericin B, chlorpromazine hydrochloride, diazepam, prochlorperazine edisilate, reteplase, streptokinase, and vancomycin hydrochloride.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

Interactions

As for Lepirudin, p.1323.

Pharmacokinetics

Bivalirudin is partly metabolised and partly excreted by the kidney. When given intravenously the plasma half-life is about 25 minutes in patients with normal renal function but is prolonged in renal impairment. Bivalirudin does not bind to plasma proteins and is removed by haemodialysis.

◊ References.

1. Robson R, *et al.* Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002; **71:** 433–9.

Uses and Administration

Bivalirudin, an analogue of the peptide hirudin (p.1305), is a direct thrombin inhibitor with actions similar to Lepirudin, p.1323. It is used as an anticoagulant in patients undergoing percutaneous coronary interventions, including those with, or at risk of, heparin-induced thrombocytopenia. It is also used in patients with acute coronary syndromes in whom early intervention is planned, and has been investigated in patients with acute coronary syndromes treated medically (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p.1323).

Some preparations state that bivalirudin is present as the hydrate of the trifluoroacetate salt but doses are given in terms of bivalirudin.

In the management of patients undergoing **planned percutaneous coronary intervention** (PCI), the initial dose of bivalirudin is 750 micrograms/kg by intravenous injection followed immediately by an intravenous infusion of 1.75 mg/kg per hour; the activated clotting time should be measured 5 minutes after the initial injection and a second injection of 300 micrograms/kg should be given if anticoagulation is inadequate. The infusion should be given for the duration of the procedure and may be continued for up to 4 hours afterwards; licensed prescribing information in the USA allows the infusion to then be continued at a lower dose of 200 micrograms/kg per hour for up to 20 hours if required.

As part of the management of patients with **acute coronary syndromes**, the initial dose of bivalirudin is 100 micrograms/kg by intravenous injection, followed by an intravenous infusion of 250 micrograms/kg per hour. In patients managed *medically*, the infusion may be continued for up to 72 hours. For those who proceed to *PCI or coronary artery bypass surgery without cardiopulmonary bypass*, a further intravenous injection of 500 micrograms/kg should be given, and the infusion should be increased to 1.75 mg/kg per hour for the duration of the procedure; after PCI, the infusion may be continued at a dose of 250 micrograms/kg per hour for a further 4 to 12 hours if required. For those who proceed to *coronary artery bypass surgery with cardiopulmonary bypass*, the infusion should be stopped 1 hour before the procedure and the patient should be treated with unfractionated heparin.

The dose of bivalirudin should be reduced in patients with renal impairment (see below).

◊ References.

1. Carswell CI, Plosker GL. Bivalirudin: a review of its potential place in the management of acute coronary syndromes. *Drugs* 2002; **62:** 841–70.
2. Sciulli TM, Mauro VF. Pharmacology and clinical use of bivalirudin. *Ann Pharmacother* 2002; **36:** 1028–41.
3. Moen MD, *et al.* Bivalirudin: a review of its use in patients undergoing percutaneous coronary intervention. *Drugs* 2005; **65:** 1869–91.

4. Stone GW, *et al.* ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.
5. Ahrens I, *et al.* Direct thrombin inhibition with bivalirudin as an antithrombotic strategy in general and interventional cardiology. *Expert Opin Drug Metab Toxicol* 2007; **3:** 609–20.
6. Hartmann F. Safety and efficacy of bivalirudin in acute coronary syndromes. *Curr Pharm Des* 2008; **14:** 1191–6.

Administration in renal impairment. The dose of bivalirudin may need to be adjusted in patients with renal impairment and the activated clotting time should be monitored. UK licensed product information recommends the following doses, depending on the glomerular filtration rate (GFR):

- GFR 30 to 59 mL/minute, usual bolus doses (see Uses and Administration, above) but in those undergoing percutaneous coronary intervention (PCI) for any indication the infusion rate should be reduced to 1.4 mg/kg per hour during the procedure
- GFR below 30 mL/minute or dialysis-dependent, contra-indicated

US licensed product information recommends the following doses for those undergoing PCI, based on creatinine clearance (CC):

- CC 30 to 59 mL/minute, usual bolus and infusion doses
- CC below 30 mL/minute, usual bolus doses but infusion rate reduced to 1 mg/kg per hour
- Haemodialysis patients, usual bolus doses but infusion rate reduced to 250 micrograms/kg per hour

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Angiomax; ***Austral.:*** Angiomax; ***Canad.:*** Angiomax; ***Cz.:*** Angiox; ***Denm.:*** Angiox; ***Fin.:*** Angiox; ***Fr.:*** Angiox; ***Ger.:*** Angiox; ***Gr.:*** Angiox; ***Hung.:*** Angiox; ***Israel:*** Angiomax; ***Ital.:*** Angiox; ***Neth.:*** Angiox; ***Norw.:*** Angiox; ***NZ:*** Angiomax; ***Port.:*** Angiox; ***Spain:*** Angiox; ***Swed.:*** Angiox; ***UK:*** Angiox; ***USA:*** Angiomax.

Bopindolol Malonate *(rINNM)* ⊗

Bopindolol Hydrogen Malonate; Bopindolol, Malonate de; Bopindololi Malonas; LT-31-200; Malonato de bopindolol. (±)-1-(*tert*-Butylamino)-3-[(2-methylindol-4-yl)oxy]propan-2-ol benzoate malonate.

Бопиндолола Малонат

$C_{23}H_{28}N_2O_3,C_3H_4O_4$ = 484.5.

CAS — 62658-63-3 (bopindolol); 82857-38-3 (bopindolol malonate).

ATC — C07AA17.

ATC Vet — QC07AA17.

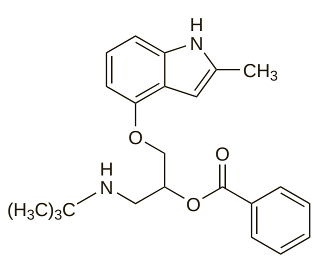

(bopindolol)

Profile

Bopindolol is a non-cardioselective beta blocker (p.1225). It is reported to possess some intrinsic sympathomimetic activity.

Bopindolol is given orally as the malonate but doses are expressed in terms of the base; 1.27 mg of bopindolol malonate is equivalent to about 1 mg of base. It is used in the management of hypertension (p.1171) and angina pectoris (p.1157) in daily doses equivalent to 0.5 to 2 mg of bopindolol.

◊ References.

1. Harron DWG, *et al.* Bopindolol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1991; **41:** 130–49.
2. Nagatomo T, *et al.* Bopindolol: pharmacological basis and clinical implications. *Cardiovasc Drug Rev* 2001; **19:** 9–24.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Sandonorm; ***Ger.:*** Wandonorm†; ***Gr.:*** Sandonorm†; ***Hung.:*** Sandonorm; ***Switz.:*** Sandonorm.

Multi-ingredient: *Switz.:* Sandoretic.

Bosentan *(BAN, USAN, rINN)*

Bosentaani; Bosentán; Bosentano; Bosentanum; Ro-47-0203/029. *p-tert*-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide.

Бозентан

$C_{27}H_{29}N_5O_6S$ = 551.6.

CAS — 147536-97-8 (anhydrous bosentan); 157212-55-0 (bosentan monohydrate).

ATC — C02KX01.

ATC Vet — QC02KX01.

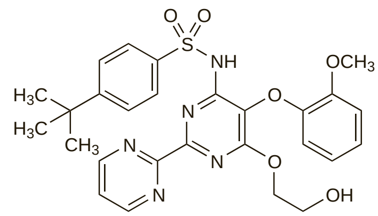

Adverse Effects

Adverse effects reported with bosentan include headache, nasopharyngitis, flushing, oedema, hypotension, dizziness, palpitations, gastrointestinal disturbances, pruritus, skin rashes, fatigue, muscle cramps, and anaemia. Anaphylaxis and angioedema have been reported rarely. Dose-related increases in liver aminotransferases may also occur, and hepatic cirrhosis and liver failure have been reported.

Bosentan is teratogenic in *animals*.

Effects on the liver. In a postmarketing study,[1] increases in liver aminotransferases to more than 3 times the upper limit of normal occurred in 352 (7.6%) of 4623 patients started on bosentan for pulmonary hypertension; treatment was continued or successfully reintroduced after temporary withdrawal in 165 (47%) of these patients.

1. Humbert M, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; **30:** 338–44.

Effects on the skin. Vasculitis was reported[1] in a patient receiving bosentan shortly after the dose was increased to 125 mg twice daily. She was also taking metolazone and acenocoumarol long term, and spironolactone had recently been added. The skin lesions improved slowly over a period of weeks after bosentan was stopped. All other treatment was continued and it was concluded that the lesions were attributable to bosentan alone or to a previously unknown interaction.

1. Gasser S, *et al.* Severe necrotising leucocytoclastic vasculitis in a patient taking bosentan. *BMJ* 2004; **329:** 430.

Precautions

Bosentan is contra-indicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C). Liver-aminotransferase concentrations should be measured before starting therapy, at monthly intervals during therapy, and 2 weeks after any increase in dose:

- bosentan therapy should not be *started* in patients with concentrations more than 3 times the upper limit of normal
- if concentrations increase to between 3 and 5 times the upper limit of normal *during* treatment, bosentan should be stopped or the dose reduced and concentrations should be monitored every 2 weeks until they are below the pretreatment value; therapy may then be continued or reintroduced, but aminotransferase concentrations should be checked after 3 days, after a further 2 weeks, and then monthly
- if concentrations increase to more than 5 times the upper limit of normal bosentan should be stopped; reintroduction may be considered when concentrations return to below the pretreatment value
- if concentrations increase above 8 times the upper limit of normal or there are symptoms of hepatotoxicity or increases in total bilirubin levels greater than twice the upper limit of normal, treatment should be stopped and not reintroduced

Haemoglobin concentrations should be monitored every 3 months during therapy, more frequently at the start.

Bosentan should not be given to patients with hypotension. Although there is no evidence of rebound effects after stopping bosentan, it is recommended that therapy should be withdrawn gradually.

Bosentan and related endothelin receptor antagonists are teratogenic in *rats* and should not be used in pregnancy or in women of child-bearing potential who are not using a reliable method of contraception; hormonal contraceptives alone may not be adequate and additional measures may be required (see Interactions, below).

Interactions

Bosentan is metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is also an inducer of the same isoenzymes. It may also possibly induce CYP2C19. Interactions may therefore occur with other drugs that are either metabolised by, or inhibit, these isoenzymes. Use with ciclosporin is contra-indicated since plasma concentrations of bosentan are significantly increased (see below). There is an increased risk of hepatotoxicity if bosentan is given with glibenclamide and such use should be avoided; the hypoglycaemic effect of glibenclamide may also be reduced. Bosentan has reduced the plasma concentrations of some hormonal contraceptives and additional contraceptive measures are advised (see Endothelin Receptor Antagonists, p.2068).

Anticoagulants. For reports of bosentan decreasing the anticoagulant effect of *warfarin*, see Endothelin Receptor Antagonists, p.1430.

Ciclosporin. There appears to be a complex interaction between bosentan and ciclosporin. In a pharmacokinetic study[1] in healthy subjects given both drugs, doses of ciclosporin needed increasing to achieve target trough ciclosporin concentrations; it was calculated that plasma concentrations of ciclosporin would otherwise have been reduced by about half in the presence of bosentan. In addition, plasma concentrations of bosentan were almost doubled by ciclosporin. Licensed product information for bosentan states that plasma concentrations at steady state are 3 to 4 times higher in the presence of ciclosporin and contra-indicates the combination.

1. Binet I, *et al.* Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporine A. *Kidney Int* 2000; **57:** 224–31.

Pharmacokinetics

Bosentan is absorbed from the gastrointestinal tract with an absolute bioavailability of about 50%. Peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is more than 98% bound to plasma proteins, mainly to albumin. Bosentan is metabolised in the liver by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and is an inducer of these enzymes and possibly also of CYP2C19; after multiple dosing, plasma concentrations of bosentan decrease gradually to 50 to 65% of those seen after a single dose. Bosentan has three metabolites, one of which is active. Bosentan is excreted almost entirely as metabolites in the bile; less than 3% of an oral dose is excreted in the urine. The terminal elimination half-life is about 5 hours.

◊ References.

1. Weber C, *et al.* Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 703–14.
2. van Giersbergen PLM, *et al.* Influence of mild liver impairment on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol* 2003; **43:** 15–22.

Uses and Administration

Bosentan is an endothelin receptor antagonist (p.1155) used in the management of pulmonary hypertension (below) and systemic sclerosis (see Scleroderma, below). It has also been investigated in heart failure and in hypertension.

In **pulmonary hypertension**, patients over 12 years of age may be given bosentan orally in an initial dose of 62.5 mg twice daily, increased after 4 weeks to a maintenance dose of 125 mg twice daily. In those with low body weight (below 40 kg) both the initial and maintenance doses are 62.5 mg twice daily. For the use of bosentan in children, see below.

In **systemic sclerosis** with ongoing digital ulcer disease, bosentan is given in the same doses as for pulmonary hypertension; there are no data on safety or efficacy in patients under 18 years of age.

◊ References.

1. Krum H, *et al.* The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Engl J Med* 1998; **338:** 784–90.
2. Sutsch G, *et al.* Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation* 1998; **98:** 2262–8.
3. Kenyon KW, Nappi JM. Bosentan for the treatment of pulmonary arterial hypertension. *Ann Pharmacother* 2003; **37:** 1055–62.
4. Cohen H, *et al.* Bosentan therapy for pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2004; **61:** 1107–19.
5. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* 2004; **43:** 1089–1115.

Administration in children. A short-term study[1] in 19 children with pulmonary hypertension aged 3 to 15 years found that treatment with bosentan resulted in haemodynamic improvement and was well tolerated, and another small study[2] suggested that addition of bosentan allowed epoprostenol dosage to be reduced or stopped. Longer-term studies[3,4] have reported that benefit is maintained and that bosentan may have a role in children with both idiopathic pulmonary hypertension and pulmonary hypertension secondary to heart or lung disease.

Licensed product information in the UK states that the safety and efficacy of bosentan has not been substantially documented in children under the age of 12 years (some postmarketing data has subsequently been published[5]) but notes that the studies cited above used the following doses; these doses are also recommended in the *BNFC*, but for children aged 3 to 18 years:

- body-weight 10 to 20 kg: initial dose 31.25 mg once daily, increased to 31.25 mg twice daily after 4 weeks
- body-weight 20 to 40 kg: initial dose 31.25 mg twice daily, increased to 62.5 mg twice daily after 4 weeks
- body-weight over 40 kg and age 12 to 18 years: as for adults (see above)

1. Barst RJ, *et al.* Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther* 2003; **73:** 372–82.
2. Ivy DD, *et al.* Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol* 2004; **93:** 943–6.
3. Maiya S, *et al.* Response to bosentan in children with pulmonary hypertension. *Heart* 2006; **92:** 664–70.
4. Rosenzweig EB, *et al.* Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 697–704.
5. Beghetti M, *et al.* Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. *Pediatr Res* 2008; **64:** 200–4.

Pulmonary hypertension. Pulmonary hypertension (p.1179) is a progressive and incurable disease associated with an increase in pulmonary arterial pressure. Treatment usually involves the use of vasodilators such as calcium-channel blockers or intravenous epoprostenol, but systemic effects limit their use. Patients with pulmonary hypertension have raised plasma concentrations of the potent vasoconstrictor endothelin I, and endothelin antagonists such as bosentan have therefore been tried. Studies[1,2] with oral bosentan have shown improvement in exercise tolerance and in time to clinical progression; an open study[3] showed sustained benefit with treatment for 1 year or more. However, no effect on mortality has yet been found in randomised studies, although there is some evidence[4,5] that survival may be improved. Bosentan has also been tried with epoprostenol.[6] There was a non-significant trend towards greater improvement in the group receiving both drugs compared with epoprostenol alone.

There is some evidence that bosentan may be of benefit in pulmonary hypertension associated with congenital heart disease,[7,8] including Eisenmenger syndrome,[8-10] and in pulmonary hypertension associated with HIV infection.[11] Positive results have also been reported[12-14] in chronic thromboembolic pulmonary hypertension.

1. Channick RN, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; **358:** 1119–23.
2. Rubin LJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346:** 896–903. Correction. *ibid.*; 1258.
3. Sitbon O, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003; **124:** 247–54.
4. McLaughlin VV, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; **25:** 244–9.
5. Sitbon O, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005; **60:** 1025–30.
6. Humbert M, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; **24:** 353–9.
7. Apostolopoulou SC, *et al.* Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. *Heart* 2007; **93:** 350–4.
8. Diller G-P, *et al.* Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. *Heart* 2007; **93:** 974–6.
9. Galiè N, *et al.* for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; **114:** 48–54.
10. D'Alto M, *et al.* Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. *Heart* 2007; **93:** 621–5.
11. Barbaro G, *et al.* Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006; **92:** 1164–6.
12. Hughes R, *et al.* Bosentan in inoperable chronic thromboembolic pulmonary hypertension. *Thorax* 2005; **60:** 707.
13. Hoeper MM, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2363–7.
14. Bonderman D, *et al.* Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; **128:** 2599–2603.

Scleroderma. Bosentan has an established role in pulmonary hypertension secondary to scleroderma (p.1817) or other connective tissue disorders, but may also have additional benefits. Several case reports[1-3] have suggested that treatment with bosentan may be associated with healing of refractory digital ulcers in patients with scleroderma, and a controlled study[4] found that bosentan reduced the incidence of new digital ulcers, although there was no improvement in the healing of existing ulcers. Relatively long-term treatment may need to be given.[5]

1. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2003; **42:** 191–3.
2. Snyder MJ, *et al.* Resolution of severe digital ulceration during a course of bosentan therapy. *Ann Intern Med* 2005; **142:** 802–3.
3. Tillon J, *et al.* Successful treatment of systemic sclerosis-related digital ulcers and sarcoidosis with endothelin receptor antagonist (bosentan) therapy. *Br J Dermatol* 2006; **154:** 1000–1002.
4. Korn JH, *et al.* Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; **50:** 3985–93.
5. García de la Peña-Lefebvre P, *et al.* Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. *Rheumatology (Oxford)* 2008; **47:** 464–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Tracleer; ***Belg.:*** Tracleer; ***Canad.:*** Tracleer; ***Cz.:*** Tracleer; ***Denm.:*** Tracleer; ***Fin.:*** Tracleer; ***Fr.:*** Tracleer; ***Ger.:*** Tracleer; ***Gr.:*** Tracleer; ***Hung.:*** Tracleer; ***Irl.:*** Tracleer; ***Israel:*** Tracleer; ***Ital.:*** Tracleer; ***Malaysia:*** Tracleer; ***Neth.:*** Tracleer; ***Norw.:*** Tracleer; ***NZ:*** Tracleer; ***Port.:*** Tracleer; ***Singapore:*** Tracleer; ***Spain:*** Tracleer; ***Swed.:*** Tracleer; ***Switz.:*** Tracleer; ***Thai.:*** Tracleer; ***UK:*** Tracleer; ***USA:*** Tracleer.

Bretylium Tosilate *(BAN, rINN)*

ASL-603; Bretyli Tosilas; Bretylii Tosilas; Brétylium, Tosilate de; Bretylium Tosylate *(USAN)*; Bretyltosilat; Bretyylitosilaatti; Tosilato de bretilio. (2-Bromobenzyl)ethyldimethylammonium toluene-4-sulphonate.

Бретилия Тозилат

$C_{11}H_{17}BrN,C_7H_7O_3S$ = 414.4.

CAS — 59-41-6 (bretylium); 61-75-6 (bretylium tosilate).

ATC — C01BD02.

ATC Vet — QC01BD02.

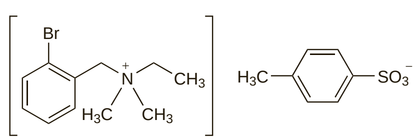

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Bretylium Tosilate). A white crystalline powder. M.p. about 98°. It exhibits polymorphism. Freely soluble in water, in alcohol, and in methyl alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

USP 31 (Bretylium Tosylate). A white, hygroscopic, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ether, in ethyl acetate, and in hexane. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

The most common adverse effect of bretylium is hypotension, which may be severe. Bretylium may also cause a transient initial increase in blood pressure and heart rate, and a worsening of cardiac arrhythmias due to a release of noradrenaline. Nausea and vomiting may occur particularly during rapid intravenous infusion. Intramuscular injection of bretylium can lead to local tissue necrosis and muscle atrophy. Caution is required in patients with renal impairment, and in patients with severe aortic stenosis or pulmonary hypertension in whom cardiac output may not increase in response to the fall in peripheral resistance produced by bretylium.

Interactions

Bretylium may exacerbate arrhythmias caused by digitalis toxicity and may enhance the effects of sympathomimetics.

Pharmacokinetics

Bretylium is incompletely absorbed from the gastrointestinal tract. It is well absorbed after intramuscular injection. It is not metabolised and is largely excreted unchanged in the urine. The half-life is reported to be between 4 and 17 hours in patients with normal renal function and is prolonged in patients with renal impairment. Bretylium is dialysable.

Uses and Administration

Bretylium is a quaternary ammonium compound with class II and class III antiarrhythmic activity (p.1153); it causes an initial release of noradrenaline and then blocks adrenergic transmission by preventing noradrenaline release from adrenergic nerve endings. It suppresses ventricular fibrillation and other ventricular arrhythmias, but its exact mode of action is unknown. It has been given parenterally as the tosilate in the management of ventricular arrhythmias.

Bretylium has also been investigated in complex regional pain syndrome.

Preparations

BP 2008: Bretylium Injection;
USP 31: Bretylium Tosylate in Dextrose Injection; Bretylium Tosylate Injection.

Proprietary Preparations (details are given in Part 3)
Israel: Bretylate†; ***S.Afr.:*** Bretylol†.

Bucindolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Bucindolol, Chlorhydrate de; Bucindololi Hydrochloridum; Hidrocloruro de bucindolol; MJ-13105-1. 2-[2-Hydroxy-3-(2-indol-3-yl-1,1-dimethylethylamino)propoxy]benzonitrile hydrochloride.

Буциндолола Гидрохлорид

$C_{22}H_{25}N_3O_2,HCl$ = 399.9.

CAS — 71119-11-4 (bucindolol); 70369-47-0 (bucindolol hydrochloride).

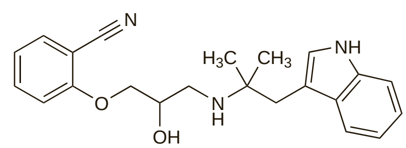

(bucindolol)

Profile

Bucindolol is a non-cardioselective beta blocker (p.1225). It is reported to possess weak alpha$_1$-blocking activity and direct vasodilating activity; the degree of intrinsic sympathomimetic activity is unclear. Bucindolol hydrochloride has been investigated in the management of hypertension, heart failure, and other cardiac disorders, but development was halted. However, it has been suggested that it may be of benefit in a genetically identifiable subgroup of patients.

◊ References.

1. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; **344:** 1659–67.

Buflomedil Hydrochloride *(BANM, rINNM)*

Buflomediilihydrokloridi; Buflomédil, chlorhydrate de; Buflomedil-hidroklorid; Buflomedil-hydrochlorid; Buflomedilhydroklorid; Buflomedili hydrochloridum; Buflomedilio hidrochloridas; Hidrocloruro de buflomedil; LL-1656. 2′,4′,6′-Trimethoxy-4-(pyrrolidin-1-yl)butyrophenone hydrochloride.

Буфломедила Гидрохлорид

$C_{17}H_{25}NO_4,HCl$ = 343.8.

CAS — 55837-25-7 (buflomedil); 35543-24-9 (buflomedil hydrochloride).

ATC — C04AX20.

ATC Vet — QC04AX20.

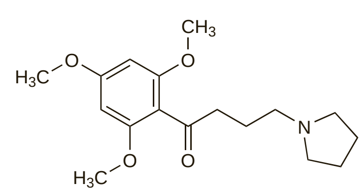

(buflomedil)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Buflomedil Hydrochloride). A white or almost white microcrystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 6.5.

Adverse Effects

Buflomedil has been reported to cause gastrointestinal disturbances, headache, vertigo, syncope, rash, pruritus, and paraesthesia. Overdosage may produce severe hypotension, tachycardia, and convulsions.

◊ References.

1. Bachand RT, Dubourg AY. A review of long-term safety data with buflomedil. *J Int Med Res* 1990; **18:** 245–52.

Pharmacokinetics

Buflomedil hydrochloride is absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1.5 to 4 hours after oral doses. Buflomedil is subject to first-pass metabolism; bioavailability is reported to be between 50 and 80%.

Buflomedil is widely distributed. Binding to plasma proteins is dose-dependent and varies between 60 and 80% at therapeutic concentrations. Buflomedil is metabolised in the liver and is mainly excreted in the urine both as unchanged drug and metabolites. The elimination half-life is about 2 to 3 hours. Elimination may be impaired in patients with renal or hepatic impairment.

Uses and Administration

Buflomedil hydrochloride is a vasodilator used in the treatment of cerebrovascular (p.1165) and peripheral vascular disease (p.1178). Usual oral doses are 300 to 600 mg daily, doses by intramuscular injection are up to 100 mg daily, by slow intravenous injection up to 200 mg daily, and by intravenous infusion up to 400 mg daily. In patients with hepatic or renal impairment, doses may need to be reduced (see below).

◊ References.

1. Clissold SP, *et al.* Buflomedil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in peripheral and cerebral vascular diseases. *Drugs* 1987; **33:** 430–60.
2. de Backer TLM, *et al.* Buflomedil for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 08/05/08).

Administration in hepatic or renal impairment. The dose of buflomedil should be reduced in patients with hepatic or renal impairment. It should not be used in patients with creatinine clearance (CC) below 30 mL/minute and the maximum oral dose in those with CC between 30 and 80 mL/minute is 150 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Arteriol; Buflomed; Lofton; ***Austria:*** Buflohexal; Buflomed; Buftyl; Loftyl; ***Belg.:*** Buflomemed; Buflotop; Docbuflome; Kelomedil; Loftyl; ***Braz.:*** Bufedil; ***Chile:*** Loftyl†; Vaselastic†; ***Fr.:*** Fonzylane; Loftyl†; ***Ger.:*** Bufedil; Buflo; Buflo-POS; Buflo-Puren; Buflohexal; Complamin; Defluina; ***Gr.:*** Bladiron; Botamiral; Buflodil; Chlorofarm-S; Cordimedil; Dialon-T; Dicasin; Farmidil†; Flubir; Gaveril; Gondofil†; Irrodan†; Loftyl; Meligran†; Ostramont; Penpurin; Spediol†; Sulodil; Thiocodin; Vanogel; Vardolin; Zelian; ***Hong Kong:*** Fonzylane; Irrodan; ***Indon.:*** Loftyl; ***Ital.:*** Buflan; Buflocit; Buflofar†; Flomed; Irrodan; Loftyl; Perfudan†; Pirxane†; ***Mex.:*** Loftyl†; ***Neth.:*** Loftyl; ***Pol.:*** Buflox; Buvasodil; ***Port.:*** Loftyl; ***S.Afr.:*** Loftyl; ***Spain:*** Lofton; Sinoxis†; ***Switz.:*** Loftyl; ***Thai.:*** Irrodan; ***Venez.:*** Loftyl.

Multi-ingredient: ***Arg.:*** Mimixin.

Bumetanide *(BAN, USAN, rINN)* ⊗

Bumetanid; Bumetanida; Bumetanidas; Bumétanide; Bumetanidi; Bumetanidum; Ro-10-6338. 3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid.

Буметанид

$C_{17}H_{20}N_2O_5S$ = 364.4.

CAS — 28395-03-1.

ATC — C03CA02.

ATC Vet — QC03CA02.

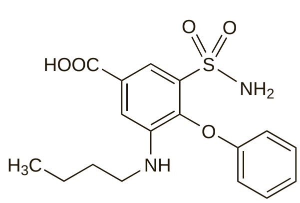

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Bumetanide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol and in acetone; slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Bumetanide). A practically white powder. Slightly soluble in water; soluble in alkaline solutions. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

As for Furosemide, p.1292. Bumetanide may cause muscle pain, particularly at high doses.

Effects on the ears. Early reports suggested that bumetanide might be less ototoxic than furosemide.[1] However, both drugs can cause deafness, especially when given in large doses to patients with renal impairment.

1. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.

Effects on the lungs. Alveolitis, presenting as haemoptysis and steadily increasing dyspnoea in a 79-year-old man, was found to coincide with the use of bumetanide for congestive heart failure.[1] When the diuretic was replaced with furosemide the condition gradually resolved.

1. van Tellingen C. Suspension of disbelief - or the bumetanide paradox. *Neth Heart J* 2007; **15:** 31–2.

Effects on the muscles. Bumetanide, particularly in high doses in patients with chronic renal impairment, may cause severe musculoskeletal pain. A curious muscle stiffness distinct from cramp, with tenderness to compression and pain on movement, was noted in 4 patients with end-stage renal failure.[1] The calf muscles were the first to be affected; shoulder girdle and thigh muscle tenderness also occurred in 2 patients, and 1 patient also had neck stiffness. The adverse effect appeared to be dose-related for the individual patients.

1. Barclay JE, Lee HA. Clinical and pharmacokinetic studies on bumetanide in chronic renal failure. *Postgrad Med J* 1975; **51** (suppl 6): 43–6.

Effects on the skin. Bullous pemphigoid developed in a patient about 6 weeks after starting bumetanide.[1] Healing occurred after withdrawal without the need for corticosteroids.

1. Boulinguez S, *et al.* Bullous pemphigoid induced by bumetanide. *Br J Dermatol* 1998; **138:** 548–9.

Precautions

Bumetanide's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309).

Interactions

As for Furosemide, p.1293.

Pharmacokinetics

Bumetanide is almost completely and fairly rapidly absorbed from the gastrointestinal tract; the bioavailability is reported to be about 80 to 95%. It has a plasma elimination half-life of about 1 to 2 hours. It is about 95% bound to plasma proteins. About 80% of the dose is excreted in the urine, about 50% as unchanged drug, and 10 to 20% in the faeces.

◊ References to the pharmacokinetics of bumetanide in healthy subjects.

1. Halladay SC, *et al.* Diuretic effect and metabolism of bumetanide in man. *Clin Pharmacol Ther* 1977; **22:** 179–87.
2. Pentikäinen PJ, *et al.* Fate of [C]-bumetanide in man. *Br J Clin Pharmacol* 1977; **4:** 39–44.
3. Holazo AA, *et al.* Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administrations to normal subjects. *J Pharm Sci* 1984; **73:** 1108–13.
4. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.
5. McCrindle JL, *et al.* Effect of food on the absorption of frusemide and bumetanide in man. *Br J Clin Pharmacol* 1996; **42:** 743–6.

Hepatic impairment. In a study of 8 patients with chronic hepatic disease,[1] the diuretic response to bumetanide 1 mg was impaired but bumetanide excretion rates were normal.

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.

Renal impairment. Renal excretion of bumetanide has been shown to be reduced in patients with chronic renal impairment with a subsequent attenuation of diuretic effect.[1-3] The cumulative pharmacodynamic effects of oral and intravenous doses were essentially similar in patients with renal impairment and transition from intravenous to oral maintenance regimens should pose no special problems.[2]

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.
2. Lau HSH, *et al.* Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure. *Clin Pharmacol Ther* 1986; **39:** 635–45.
3. Howlett MR, *et al.* Metabolism of the diuretic bumetanide in healthy subjects and patients with renal impairment. *Eur J Clin Pharmacol* 1990; **38:** 583–6.

Uses and Administration

Although chemically unrelated, bumetanide is a loop diuretic with actions and uses similar to those of furosemide (p.1294). Bumetanide is used in the treatment of oedema associated with heart failure (p.1165) and with renal and hepatic disorders. It is given in high doses in the management of oliguria due to renal failure or insufficiency. Bumetanide has also been used in hypertension (p.1171).

Diuresis starts within about 30 minutes to an hour after an oral dose, reaches a maximum at 1 to 2 hours, and lasts for about 4 hours but may be prolonged to 6 hours after high doses; after intravenous injection its effects are evident within a few minutes and last for about 2 hours. As a general guide bumetanide 1 mg produces a diuretic effect similar to furosemide 40 mg although this should not be used for direct substitution at higher doses.

In the treatment of **oedema** the usual oral dose is 1 mg in the morning or early evening; a second dose may be given 6 to 8 hours later if necessary. A dose of 500 micrograms daily may be adequate in some elderly patients.

In refractory oedema higher doses may be necessary. An initial dose of 5 mg daily has been advocated, increased by 5 mg every 12 to 24 hours as required; however other sources have suggested a maximum total dose of 10 mg daily. Twice daily dosing may be preferred at higher doses. For maintenance therapy doses may be given daily or intermittently. In an emergency or when oral therapy cannot be given 0.5 to 1 mg may be given by intramuscular or slow intravenous injection, subsequently adjusted according to response. A dose for pulmonary oedema is 1 to 2 mg by intravenous injection, repeated 20 minutes later if necessary. Alternatively, 2 to 5 mg may be given over 30 to 60 minutes in 500 mL of a suitable infusion fluid.

In the treatment of **hypertension** bumetanide has been given in oral doses of 0.5 to 1 mg daily, although higher doses have been used.

When very high doses of bumetanide are used careful laboratory control is essential as described under the uses for furosemide (see, p.1294; high-dose therapy).

Preparations

BP 2008: Bumetanide and Prolonged-release Potassium Tablets; Bumetanide Injection; Bumetanide Oral Solution; Bumetanide Tablets;
USP 31: Bumetanide Injection; Bumetanide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Butinat†; ***Austral.:*** Burinex; ***Austria:*** Burinex; ***Belg.:*** Burinex; ***Braz.:*** Burinax; ***Canad.:*** Burinex; ***Denm.:*** Burinex; ***Fr.:*** Burinex; ***Ger.:*** Burinex; ***Gr.:*** Burinex; ***Hong Kong:*** Burinex; ***Irl.:*** Burinex; ***Malaysia:*** Burinex; ***Mex.:*** Bumedyl†; Drenural; Miccil; ***Neth.:*** Burinex; ***Norw.:*** Burinex; ***NZ:*** Burinex; ***Philipp.:*** Burinex; ***S.Afr.:*** Burinex; ***Singapore:*** Burinex; ***Spain:*** Fordiuran; ***Swed.:*** Burinex; ***Switz.:*** Burinex; ***Thai.:*** Burinex†; ***UK:*** Burinex; ***USA:*** Bumex; ***Venez.:*** Biulan†; Bumelex; Takomen†.

Multi-ingredient: ***Denm.:*** Buram; Burinex med kaliumklorid; ***Irl.:*** Buram; Burinex K†; ***Malaysia:*** Burinex K†; ***Norw.:*** Burinex K; ***S.Afr.:*** Burinex K; ***Singapore:*** Burinex K; ***UK:*** Burinex A; Burinex K†.

Bunazosin Hydrochloride *(rINNM)*

Bunazosine, Chlorhydrate de; Bunazosini Hydrochloridum; E-643; Hidrocloruro de bunazosina. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-butyrylhexahydro-1*H*-1,4-diazepine monohydrochloride.

Буназозина Гидрохлорид

$C_{19}H_{27}N_5O_3$,HCl = 409.9.

CAS — 80755-51-7 (bunazosin); 52712-76-2 (bunazosin hydrochloride).

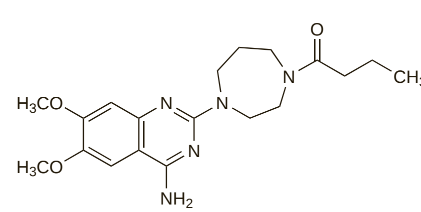

(bunazosin)

Pharmacopoeias. In *Jpn.*

Profile

Bunazosin is an alpha$_1$-adrenoceptor blocker (p.1153) with general properties similar to those of prazosin (p.1375). It is given orally as the hydrochloride in the management of hypertension; the usual maintenance dose of bunazosin hydrochloride is 3 to 6 mg daily but up to 12 mg daily has been given.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Andante; ***Indon.:*** Detantol; ***Jpn:*** Detantol; ***Thai.:*** Detantol.

Bupranolol Hydrochloride *(rINNM)* ⊗

B-1312; Bupranolol, Chlorhydrate de; Bupranololi Hydrochloridum; Hidrocloruro de bupranolol; KL-255. 1-*tert*-Butylamino-3-(6-chloro-*m*-tolyloxy)propan-2-ol hydrochloride.

Бупранолола Гидрохлорид

$C_{14}H_{22}ClNO_2,HCl$ = 308.2.

CAS — 14556-46-8 (bupranolol); 15148-80-8 (bupranolol hydrochloride).

ATC — C07AA19.

ATC Vet — QC07AA19.

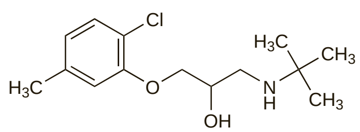

(bupranolol)

Pharmacopoeias. In *Jpn.*

Profile

Bupranolol is a beta blocker (p.1225). It is given as the hydrochloride in usual oral doses of 100 to 400 mg daily in the management of cardiovascular disorders.

Bupranolol eye drops have been used in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Betadrenol.
Multi-ingredient: *Austria:* Betamed.

Butalamine Hydrochloride *(BANM, rINNM)*

Butalamine, Chlorhydrate de; Butalamini Hydrochloridum; Hidrocloruro de butalamina; LA-1221. *NN*-Dibutyl-*N′*-(3-phenyl-1,2,4-oxadiazol-5-yl)ethylenediamine hydrochloride.

Буталамина Гидрохлорид

$C_{18}H_{28}N_4O,HCl$ = 352.9.

CAS — 22131-35-7 (butalamine); 56974-46-0 (butalamine hydrochloride).

ATC — C04AX23.

ATC Vet — QC04AX23.

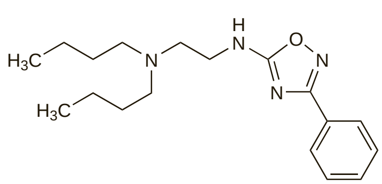

(butalamine)

Profile

Butalamine hydrochloride is a vasodilator that has been used in the management of peripheral and cerebral vascular disorders.

Butizide *(rINN)* ⊗

Buthiazide *(USAN)*; Butitsidi; Butizid; Butizida; Butizidum; Isobutylhydrochlorothiazide; Thiabutazide. 6-Chloro-3,4-dihydro-3-isobutyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Бутизид

$C_{11}H_{16}ClN_3O_4S_2$ = 353.8.

CAS — 2043-38-1.

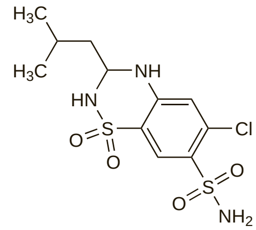

Profile

Butizide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Butizide is given orally, usually with spironolactone; the usual maintenance dose for oedema or hypertension is 5 to 10 mg daily. It has also been given with other antihypertensive drugs.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Austria:* Aldactone Saltucin; Buti-Spirobene; ***Ger.:*** Aldactone Saltucin†; Modenol†; Torrat†; Tri-Torrat†; ***Hong Kong:*** Torrat†; ***Indon.:*** Aldazide; ***Ital.:*** Kadiur; Saludopin; ***Mex.:*** Aldazida; ***Philipp.:*** Aldazide; ***S.Afr.:*** Aldazide; ***Switz.:*** Aldozone; ***Thai.:*** Iso-Triraupin†.

Cadralazine *(BAN, rINN)*

Cadralazina; Cadralazinum; CGP-18684/E; ISF-2469; Kadralatsiini; Kadralazin. Ethyl 3-{6-[ethyl(2-hydroxypropyl)amino]pyridazin-3-yl}carbazate.

Кадралазин

$C_{12}H_{21}N_5O_3$ = 283.3.

CAS — 64241-34-5.

ATC — C02DB04.

ATC Vet — QC02DB04.

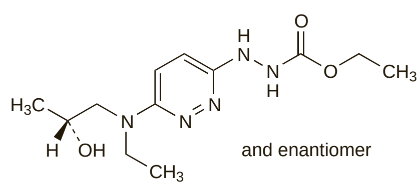

Profile

Cadralazine is a vasodilator with actions and uses similar to those of hydralazine (p.1305). It has been given in oral doses of 10 mg once daily in the management of hypertension (p.1171).

◊ Reviews.

1. McTavish D, *et al.* Cadralazine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990; **40:** 543–60.

ADVERSE EFFECTS. Unlike hydralazine, cadralazine is reported not to produce a lupus-like syndrome.[1,2]

1. Andersson OK. Cadralazine did not produce the SLE-syndrome when hydralazine did. *Eur J Clin Pharmacol* 1987; **31:** 741.
2. Mulder H. Conversion of drug-induced SLE-syndrome by the vasodilating agent cadralazine. *Eur J Clin Pharmacol* 1990; **38:** 303.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Cadraten.

Cafedrine Hydrochloride *(BANM, pINNM)*

Cafédrine, Chlorhydrate de; Cafedrini Hydrochloridum; H-8351; Hidrocloruro de cafedrina; Kafedrin Hydrochloride. 7-[2-(β-Hydroxy-α-methylphenethylamino)ethyl]theophylline hydrochloride.

Кафедрина Гидрохлорид

$C_{18}H_{23}N_5O_3,HCl$ = 393.9.

CAS — 58166-83-9 (cafedrine); 3039-97-2 (cafedrine hydrochloride).

ATC — C01CA21.

ATC Vet — QC01CA21.

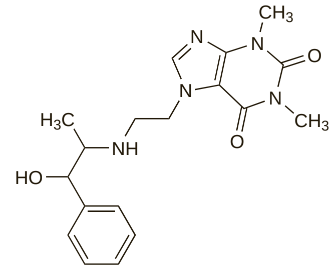

(cafedrine)

Profile

Cafedrine hydrochloride is a derivative of theophylline (p.1140), used mainly in preparations with theodrenaline hydrochloride in the treatment of hypotensive states.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Austria:* Akrinor; ***Fr.:*** Praxinor; ***Ger.:*** Akrinor†; ***S.Afr.:*** Akrinor; ***Spain:*** Bifort†.

Calcitonin Gene-related Peptide

CGRP; Péptido relacionado con el gen de la calcitonina.

Profile

Calcitonin gene-related peptide is an endogenous peptide derived from the calcitonin gene. It has vasodilating activity and has been investigated in the management of peripheral vascular disease (Raynaud's syndrome), heart failure, and for ischaemia following neurosurgery for subarachnoid haemorrhage.

◊ References.

1. Johnston FG, *et al.* Effect of calcitonin-gene-related peptide on postoperative neurological deficits after subarachnoid haemorrhage. *Lancet* 1990; **335:** 869–72.
2. Shawkett S, *et al.* Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. *Br J Clin Pharmacol* 1991; **32:** 209–13.
3. Shekhar YC, *et al.* Effects of prolonged infusion of human alpha calcitonin gene-related peptide on haemodynamics, renal blood flow and hormone levels in congestive heart failure. *Am J Cardiol* 1991; **67:** 732–6.
4. European CGRP in Subarachnoid Haemorrhage Study Group. Effect of calcitonin-gene-related peptide in patients with delayed postoperative cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *Lancet* 1992; **339:** 831–4.
5. Bunker CB, *et al.* Calcitonin gene-related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. *Lancet* 1993; **342:** 80–2.
6. Feuerstein G, *et al.* Clinical perspectives of calcitonin gene related peptide pharmacology. *Can J Physiol Pharmacol* 1995; **73:** 1070–4.
7. Gherardini G, *et al.* Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal peptide. *Plast Reconstr Surg* 1998; **101:** 90–3.

Candesartan Cilexetil *(BANM, USAN, rINNM)*

Candésartan, Cilexétil de; Candesartán cilexetilo; Candesartani Cilexetilum; CV-11974 (candesartan); H-212/91; Kandesartan Sileksetil; TCV-116. Cyclohexyl carbonate ester of (±)-1-hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate.

Кандесартана Силексетил

$C_{33}H_{34}N_6O_6$ = 610.7.

CAS — 139481-59-7 (candesartan); 145040-37-5 (candesartan cilexetil).

ATC — C09CA06.

ATC Vet — QC09CA06.

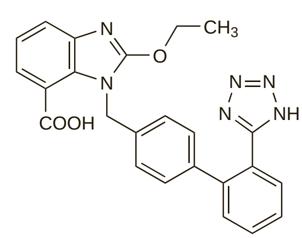

(candesartan)

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Candesartan cilexetil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form candesartan. The absolute bioavailability for candesartan is about 40% when candesartan cilexetil is given as a solution and about 14% when given as tablets. Peak plasma concentrations of candesartan occur about 3 to 4 hours after oral doses as tablets. Candesartan is more than 99% bound to plasma proteins. It is excreted in urine and bile mainly as unchanged drug and a small amount of inactive metabolites. The terminal elimination half-life is about 9 hours. Candesartan is not removed by haemodialysis.

◊ Reviews.

1. Gleiter CH, Mörike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; **41:** 7–17.

Uses and Administration

Candesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171) and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors, (see under Losartan Potassium, p.1327).

Candesartan is given orally as the ester prodrug candesartan cilexetil. Onset of antihypertensive action occurs about 2 hours after a dose and the maximum effect is achieved within about 4 weeks of starting therapy.

In the management of **hypertension** the usual initial dose of candesartan cilexetil is 8 mg once daily in the UK, or 16 mg once daily in the USA. The dose should be adjusted according to response; the usual maintenance dose is 8 mg once daily, but doses up to 32 mg daily, as a single dose or in 2 divided doses, may be used. Lower initial doses should be considered in patients with intravascular volume depletion; in the UK an initial dose of 4 mg once daily is suggested. Patients with renal or hepatic impairment may also require lower initial doses (see below).

In **heart failure,** candesartan cilexetil is given in an initial dose of 4 mg once daily; the dose should be doubled at intervals of not less than two weeks up to 32 mg once daily if tolerated.

◊ Reviews.

1. Sever P, Ménard J, eds. Angiotensin II antagonism refined: candesartan cilexetil. *J Hum Hypertens* 1997; **11** (suppl 2): S1–S95.
2. McClellan KJ, Goa KL. Candesartan cilexetil: a review of its use in essential hypertension. *Drugs* 1998; **56:** 847–69.
3. Stoukides CA, *et al.* Candesartan cilexetil: an angiotensin II receptor blocker. *Ann Pharmacother* 1999; **33:** 1287–98.
4. See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. *Am J Health-Syst Pharm* 2000; **57:** 739–46.
5. Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; **62:** 1253–87.
6. Fenton C, Scott LJ. Candesartan cilexetil: a review of its use in the management of chronic heart failure. *Drugs* 2005; **65:** 537–58.
7. McKelvie RS. Candesartan for the management of heart failure: more than an alternative. *Expert Opin Pharmacother* 2006; **7:** 1945–56.
8. Meredith PA. Candesartan cilexetil—a review of effects on cardiovascular complications in hypertension and chronic heart failure. *Curr Med Res Opin* 2007; **23:** 1693–1705.

Administration in hepatic or renal impairment. The elimination of candesartan may be reduced in patients with hepatic or renal impairment and lower doses may therefore be required. Candesartan may also have adverse effects on renal function and regular monitoring is advised in patients with heart failure.

In the UK, candesartan is contra-indicated in severe hepatic impairment and an initial dose of 2 mg once daily is recommended for hypertension in patients with mild to moderate impairment. In the USA, consideration of a lower dose is recommended for moderate hepatic impairment.

For patients with renal impairment, an initial dose of 4 mg once daily is recommended in the UK for hypertension, including for patients on haemodialysis. In the USA, no initial dose adjustment is recommended for mild renal impairment, although dose reduction may be considered if patients are volume depleted. For patients with heart failure, dose reduction or discontinuation of candesartan may be necessary if renal function deteriorates.

Migraine. For reference to the use of angiotensin II receptor antagonists, including candesartan, in the prophylaxis of migraine, see under Losartan, p.1328.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Atacand; Dacten; Tiadyl; ***Austral.:*** Atacand; ***Austria:*** Atacand; Blopress; ***Belg.:*** Atacand; ***Braz.:*** Atacand; Blopress; ***Canad.:*** Atacand; ***Chile:*** Atacand; Bilaten; Blopress; Blox; ***Cz.:*** Atacand; Blopress†; ***Denm.:*** Atacand; ***Fin.:*** Atacand; ***Fr.:*** Atacand; Kenzen; ***Ger.:*** Atacand; Blopress; ***Gr.:*** Atacand; ***Hong Kong:*** Blopress; ***Hung.:*** Atacand; ***India:*** Candesar; ***Indon.:*** Blopress; ***Irl.:*** Atacand; ***Israel:*** Atacand; ***Ital.:*** Blopress; Ratacand; ***Jpn:*** Blopress; ***Malaysia:*** Atacand; Blopress; ***Mex.:*** Atacand; Blopress; ***Neth.:*** Amias; Atacand; Blopress; Ratacand; ***Norw.:*** Atacand; ***NZ:*** Atacand; ***Philipp.:*** Blopress; ***Pol.:*** Atacand; ***Port.:*** Atacand; Blopress; ***Rus.:*** Atacand (Атаканд); ***S.Afr.:*** Atacand; ***Singapore:*** Atacand; ***Spain:*** Atacand; Blopress; Parapres; ***Swed.:*** Atacand; ***Switz.:*** Atacand; Blopress; ***Thai.:*** Blopress; ***Turk.:*** Atacand; Ayra; ***UK:*** Amias; ***USA:*** Atacand; Candepressin; ***Venez.:*** Atacand; Blopress.

Multi-ingredient: ***Arg.:*** Atacand-D; Dacten D; Tiadyl Plus; ***Austral.:*** Atacand Plus; ***Austria:*** Atacand Plus; Blopress Plus; ***Belg.:*** Atacand Plus; ***Braz.:*** Atacand HCT; ***Canad.:*** Atacand Plus; ***Chile:*** Bilaten-D; Blopress D; Blox-D; ***Cz.:*** Atacand Plus; ***Denm.:*** AtacandZid; Atazid; ***Fin.:*** Atacand Plus; ***Fr.:*** Cokenzen; Hytacand; ***Ger.:*** Atacand Plus; Blopress Plus; ***Gr.:*** Atacand Plus; ***Hong Kong:*** Blopress Plus; ***Hung.:*** Atacand Plus; ***Indon.:*** Blopress Plus; ***Irl.:*** Atacand Plus; ***Israel:*** Atacand Plus; ***Ital.:*** Blopresid; Ratacand Plus; ***Malaysia:*** Atacand Plus; ***Mex.:*** Atacand Plus; Blopress Plus; ***Neth.:*** Atacand Plus; Blopresid; ***Norw.:*** Atacand Plus; ***Philipp.:*** Blopress Plus; ***Port.:*** Blopress 16 mg + 12,5 mg; Blopress Comp; Hytacand; ***S.Afr.:*** Atacand Plus; ***Singapore:*** Atacand Plus; ***Spain:*** Atacand Plus; Parapres Plus; ***Swed.:*** Atacand Plus; ***Switz.:*** Atacand Plus; Blopress Plus; ***Thai.:*** Blopress Plus; ***Turk.:*** Atacand Plus; ***USA:*** Atacand HCT; Candepressin Plus; ***Venez.:*** Atacand Plus; Blopress Plus.

Canrenone *(USAN, pINN)* ⊗

Canrenona; Canrénone; Canrenonum; SC-9376. 17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylic acid γ-lactone.

Канренон

$C_{22}H_{28}O_3$ = 340.5.

CAS — 976-71-6.

ATC — C03DA03.

ATC Vet — QC03DA03.

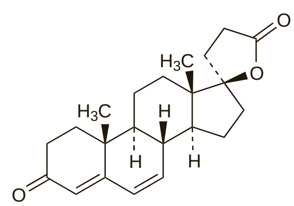

Profile

Canrenone is a potassium-sparing diuretic with properties similar to those of spironolactone (p.1400) and is given orally in the treatment of refractory oedema associated with heart failure (p.1165), renal, or hepatic disease, and in hypertension (p.1171). It is a metabolite of both spironolactone and potassium canrenoate (p.1374). It is given in usual doses of 50 to 200 mg daily. Doses of up to 300 mg daily may be required in some patients.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Contaren†; ***Ital.:*** Luvion.

Captopril *(BAN, USAN, rINN)*

Captoprilum; Kaptopriili; Kaptopril; Kaptoprilis; SQ-14225. 1-[(2*S*)-3-Mercapto-2-methylpropionyl]-L-proline.

Каптоприл

$C_9H_{15}NO_3S$ = 217.3.

CAS — 62571-86-2.

ATC — C09AA01.

ATC Vet — QC09AA01.

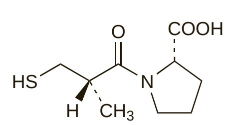

NOTE. Compounded preparations of captopril may be represented by the following names:

- Co-zidocapt (*BAN*)—captopril 2 parts and hydrochlorothiazide 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Captopril). A white or almost white crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 2.0 to 2.6. Store in airtight containers.

USP 31 (Captopril). A white or off-white crystalline powder which may have a characteristic sulfide-like odour. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers.

Stability. Although captopril itself is relatively stable[1] at temperatures up to 50°, and extemporaneously prepared powders (made by triturating the tablets with lactose) have been reported to be stable for at least 12 weeks at room temperature,[2] aqueous solutions are subject to oxidative degradation, mainly to captopril disulfide,[1] which increases[3] with increase in pH above 4. The manufacturers report that a liquid form of captopril prepared from pulverised tablets in distilled water containing 1 mg/mL retained 96.6% of the original concentration of drug after storage at room temperature for 5 days, but they advise that since it contains no preservative it should be used within 2 days of preparation.[4] Others have reported wide variations in stability depending upon the formulation. In one study[5] the shelf-life of a solution of captopril 1 mg/mL prepared from crushed tablets and tap water was estimated to be 27 days when stored at 5°. However, in another study[6] captopril was much less stable; in sterile water for irrigation captopril was stable for at least 3 days when stored at 5°, but in tap water it disappeared at a much faster rate. Increased stability has been reported after the addition of sodium ascorbate to the solution,[7] and with captopril powder rather than crushed tablets.[8] A 1 mg/mL preparation made with crushed tablets and undiluted syrup has also been reported to be stable for 30 days at 5° and may be more palatable than aqueous formulations.[9]

1. Lund W, Cowe HJ. Stability of dry powder formulations. *Pharm J* 1986; **237:** 179–80.
2. Taketomo CK, *et al.* Stability of captopril in powder papers under three storage conditions. *Am J Hosp Pharm* 1990; **47:** 1799–1801.
3. Timmins P, *et al.* Factors affecting captopril stability in aqueous solution. *Int J Pharmaceutics* 1982; **11:** 329–36.
4. Andrews CD, Essex A. Captopril suspension. *Pharm J* 1986; **237:** 734–5.
5. Pereira CM, Tam YK. Stability of captopril in tap water. *Am J Hosp Pharm* 1992; **49:** 612–15.
6. Anaizi NH, Swenson C. Instability of aqueous captopril solutions. *Am J Hosp Pharm* 1993; **50:** 486–8.
7. Nahata MC, *et al.* Stability of captopril in three liquid dosage forms. *Am J Hosp Pharm* 1994; **51:** 95–6.
8. Chan DS, *et al.* Degradation of captopril in solutions compounded from tablets and standard powder. *Am J Hosp Pharm* 1994; **51:** 1205–7.
9. Lye MYF, *et al.* Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 2483–7.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Captopril has been reported to cause false positive results in tests for acetone in urine.

Incidence of adverse effects. Results of postmarketing surveillance[1] in 30 515 hypertensive patients taking captopril showed that 4.9% had their therapy stopped because of adverse effects thought to be due to the drug. The mean initial daily dose was 46 mg; at final evaluation the mean daily dose was 58 mg. The adverse effect most commonly reported was headache (in 1.8%); others included dizziness (1.6%), rashes (1.1%), nausea (1.0%), taste disturbances (0.9%), and cough (0.8%). This study excluded patients with renal impairment but an earlier survey[2] in 6737 patients taking captopril alone or in combination found that rash and dysgeusia were more frequent in patients with renal impairment (occurring in 6.2% and 3.2% respectively of those receiving 150 mg daily or less of captopril) than in those with normal serum creatinine (4.3% and 2.2%). The frequency of both symptoms was somewhat higher in those given higher doses. Symptoms of hypotension occurred in about 5% of patients and were not influenced by dose or renal function. The cumulative frequency of withdrawal due to adverse effects was estimated at 5.8% in this study, which is similar to that in the larger survey. In another postmarketing surveillance study[3] involving more than 60 000 patients, captopril was withdrawn in 8.9% because of adverse effects.

For further reference to some of these adverse effects, see under ACE Inhibitors, p.1193.

1. Schoenberger JA, *et al.* Efficacy, safety, and quality-of-life assessment of captopril antihypertensive therapy in clinical practice. *Arch Intern Med* 1990; **150:** 301–6.
2. Jenkins AC, *et al.* Captopril in hypertension: seven years later. *J Cardiovasc Pharmacol* 1985; **7** (suppl 1): S96–S101.
3. Chalmers D, *et al.* Postmarketing surveillance of captopril for hypertension. *Br J Clin Pharmacol* 1992; **34:** 215–23.

Breast feeding. Captopril is distributed into breast milk and licensed product information advises that breast feeding should be avoided. However, a study[1] in 12 women found that the concentration of captopril in breast milk was about 1% of maternal blood concentrations, suggesting that the amount ingested by the infant would be very low. No adverse effects were noted in the infants in this study, and the American Academy of Pediatrics considers[2] that captopril is therefore usually compatible with breast feeding.

1. Devlin RG, Fleiss PM. Captopril in human blood and breast milk. *J Clin Pharmacol* 1981; **21:** 110–113.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. Captopril is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

About 60 to 75% of a dose of captopril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about an hour. Absorption has been reported to be reduced in the presence of food, but this may not be clinically relevant (see below). Captopril is about 30% bound to plasma proteins. It crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations. It is largely excreted in the urine, 40 to 50% as unchanged drug, the rest as disulfide and other metabolites. The elimination half-life has been reported to be 2 to 3 hours but this is increased in renal impairment. Captopril is removed by haemodialysis.

◊ Reviews.

1. Duchin KL, *et al.* Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. *Clin Pharmacokinet* 1988; **14:** 241–59.

Absorption. The bioavailability and peak plasma concentrations of captopril have been shown to be reduced by 25 to 55% when given with food in single dose studies[1-4] and with chronic dosing.[5] However, this may not be clinically significant since several studies[3,4,6] indicated that food intake had no effect on the antihypertensive activity of captopril.

1. Williams GM, Sugerman AA. The effect of a meal, at various times relative to drug administration, on the bioavailability of captopril. *J Clin Pharmacol* 1982; **22:** 18A.
2. Singhvi SM, *et al.* Effect of food on the bioavailability of captopril in healthy subjects. *J Clin Pharmacol* 1982; **22:** 135–40.
3. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 626–9.
4. Müller HM, *et al.* The influence of food intake on pharmacodynamics and plasma concentration of captopril. *J Hypertens* 1985; **3** (suppl 2): S135–S136.
5. Öhman KP, *et al.* Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake. *J Cardiovasc Pharmacol* 1985; **7** (suppl 1): S20–S24.
6. Izumi Y, *et al.* Influence of food on the clinical effect of angiotensin I converting enzyme inhibitor (SQ 14225). *Tohoku J Exp Med* 1983; **139:** 279–86.

Renal impairment. A study of 9 patients with chronic renal failure undergoing dialysis found that peak plasma concentrations of captopril were 2.5 times higher and peak concentrations of the disulfide metabolites were 4 times higher than in patients with normal renal function following a single dose of captopril.[1] Peak concentrations occurred later in uraemic patients and the apparent half-life of total captopril was 46 hours in uraemic patients compared with 2.95 hours in patients with normal renal function.

1. Drummer OH, *et al.* The pharmacokinetics of captopril and captopril disulfide conjugates in uraemic patients on maintenance dialysis: comparison with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **32:** 267–71.

Uses and Administration

Captopril is a sulfhydryl-containing ACE inhibitor (p.1193). It is used in the management of hypertension (p.1171), in heart failure (p.1165), after myocardial infarction (p.1175), and in diabetic nephropathy (see Kidney Disorders, p.1199).

After oral doses captopril produces a maximum effect within 1 to 2 hours, although the full effect may not develop for several weeks during chronic dosing. The duration of action is dose-dependent and may persist for 6 to 12 hours.

In the treatment of **hypertension** the initial oral dose is 12.5 mg twice daily, increased gradually at intervals of 2 to 4 weeks according to the response. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 6.25 mg twice daily is recommended if captopril is given in addition to a *diuretic* or to elderly patients; if possible the diuretic should be stopped 2 or 3 days before introducing captopril. The usual maintenance dose is 25 to 50 mg twice daily and should not normally exceed 50 mg three times daily. If hypertension is not satisfactorily controlled at this dosage, addition of a second drug or substitution of an alternative drug should be considered. In the USA higher doses of up to 150 mg three times daily have been suggested for patients with hypertension uncontrolled by lower doses of captopril in conjunction with diuretic therapy.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus an initial oral dose of 6.25 to 12.5 mg of captopril is given under close medical supervision; the usual maintenance dose is 25 mg two or three times daily, and doses should not normally exceed 50 mg three times daily. Again, in the USA higher doses of up to 150 mg three times daily have been suggested.

After **myocardial infarction**, captopril is used prophylactically in clinically stable patients with symptomatic or asymptomatic left ventricular dysfunction to improve survival, delay the onset of symptomatic heart failure, and reduce recurrent infarction. It may be started 3 days after myocardial infarction in an initial oral dose of 6.25 mg, increased over several weeks to 150 mg daily in divided doses if tolerated.

In **diabetic nephropathy** (microalbuminuria greater than 30 mg/day) in type 1 diabetics, 75 to 100 mg of captopril may be given daily, in divided oral doses. Other antihypertensives may be used with captopril if a further reduction in blood pressure is required.

Doses may need to be reduced in patients with renal impairment (see below).

Administration. Captopril is generally given orally. Sublingual[1] and intravenous[2,3] dosage has also been tried, but these routes are not established.

1. Angeli P, *et al.* Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies: a randomized, single-blind clinical trial. *Arch Intern Med* 1991; **151:** 678–82.
2. Savi L, *et al.* A new therapy for hypertensive emergencies: intravenous captopril. *Curr Ther Res* 1990; **47:** 1073–81.
3. Langes K, *et al.* Efficacy and safety of intravenous captopril in congestive heart failure. *Curr Ther Res* 1993; **53:** 167–76.

Administration in children. Experience with captopril in children is limited. UK licensed product information suggests an initial dose of 300 micrograms/kg in children and adolescents; half this dose should be given initially to neonates and infants (including premature infants), and children with renal impairment. The dose is adjusted according to response and is usually given three times daily.

Captopril, given in an initial dose of 250 micrograms/kg daily, increased to up to 2.5 or 3.5 mg/kg daily in 3 divided doses has also been reported to produce benefit in infants with severe heart failure secondary to congenital defects (mainly manifesting as left-to-right shunt).[1,2]

The following doses of captopril are suggested by the *BNFC* for hypertension, heart failure, proteinuria in nephritis, or diabetic nephropathy:

- neonate: test dose, 10 to 50 micrograms/kg (10 micrograms/kg if the neonate is less than 37 weeks postmenstrual age); if tolerated, give 10 to 50 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 2 mg/kg daily in divided doses (maximum of 300 micrograms/kg daily in divided doses if the neonate is less than 37 weeks postmenstrual age)
- child 1 month to 12 years: test dose, 100 micrograms/kg (maximum 6.25 mg); if tolerated, give 100 to 300 micrograms/kg 2 or 3 times daily, increased as necessary to a maximum of 6 mg/kg daily in divided doses (maximum of 4 mg/kg daily in divided doses in child 1 month to 1 year)
- child 12 years to 18 years: test dose, 100 micrograms/kg or 6.25 mg; if tolerated, give 12.5 to 25 mg 2 or 3 times daily, increased as necessary to a maximum of 150 mg daily in divided doses

1. Scammell AM, *et al.* Captopril in treatment of infant heart failure: a preliminary report. *Int J Cardiol* 1987; **16:** 295–301.
2. Shaw NJ, *et al.* Captopril in heart failure secondary to a left to right shunt. *Arch Dis Child* 1988; **63:** 360–3.

Administration in renal impairment. The dose of captopril should be reduced or the dosage interval increased in adults with renal impairment, depending on their creatinine clearance (CC). The following doses have been suggested:

- CC 21 to 40 mL/minute per 1.73 m^2: initial daily dose 25 mg and maximum daily dose 100 mg
- CC 10 to 20 mL/minute per 1.73 m^2: initial daily dose 12.5 mg and maximum daily dose 75 mg
- CC below 10 mL/minute per 1.73 m^2: initial daily dose 6.25 mg and maximum daily dose 37.5 mg

If a diuretic also needs to be given, a loop diuretic should be chosen rather than a thiazide.

Nitrate tolerance. For reference to the use of captopril as a sulfhydryl donor in the management of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p.1297.

Preparations

BP 2008: Captopril Tablets;
USP 31: Captopril and Hydrochlorothiazide Tablets; Captopril Oral Solution; Captopril Oral Suspension; Captopril Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Antasten; ***Austral.:*** Acenorm; Capoten; Captohexal; Enzace†; Topace; ***Austria:*** Capace; Capostad; Captomed; Captor; Captotyrol†; Debax; Lopirin; ***Belg.:*** Capoten; Capriltop; Captoprimed; Doccaptopri; ***Braz.:*** Cabioten†; Capobal; Capoten; Capotrat; Capotril†; Capox; Capril; Captil†; Captobel†; Captocord†; Captolab; Captolin†; Captomed; Capton†; Captopiril; Captopron; Captosen†; Captosif†; Captotec†; Captozen†; Captrizin; Cardilom†; Carditril†; Catoprol; Ductopril; Hipoten; Normapril; Pressomax; Prilpressin; Tompril†; Venopril†; ***Canad.:*** Apo-Capto; Capoten; Novo-Captoril; Nu-Capto; ***Chile:*** Capoten; Properil; ***Cz.:*** Alkadil†; Apo-Capto†; Capoten; Katopil†; Tensiomin; ***Denm.:*** Capoten; Captodan; Captol; Catonet†; ***Fin.:*** Capoten; Captomin; Captostad†; Lopril; ***Fr.:*** Captolane; Lopril; ***Ger.:*** ACE-Hemmer; Acenorm†; Adocor; Capto; Capto-dura M†; Captobeta; Captodoc; Captoflux; Captogamma; Captohexal; Captomerck†; Captopress; Cardiagen; cor tensobon; Coronorm; Epicordin†; Jucapt; Lopirin; Mundil†; Phamopril†; Sigacap Cor†; Tensiomin; Tensiomin-Cor; Tensobon; Tensostad; ***Gr.:*** Capoten; Ftonavil†; Hypotensor; Neo-Ipertas; Normolose; Odupril†; Pertacilon; Sancap†; ***Hong Kong:*** Apo-Capto; Capocard†; Capoten; Capril; Dexacap†; Epsitron†; Kimafan; Novo-Captoril; Rilcapton†; Ropril; Tensiomin; ***Hung.:*** Aceomel; Capin†; Captogamma; Huma-Captoril†; Tensiomin; ***India:*** Aceten; Capace; ***Indon.:*** Acepress; Capoten; Captensin; Casipril; Dexacap; Farmoten; Forten; Locap; Lotensin; Metopril; Otoryl; Praten; Scantensin; Tenofax; Tensicap; Tensobon; ***Irl.:*** Aceomel; Actopril†; Capoten; Caprill; Captor; Geroten; Tensopril†; ***Israel:*** Aceril; Capti†; Inhibace†; ***Ital.:*** Acepress; Aceprilex; Capoten; Maxipril; Merapril†; Tenpril; ***Malaysia:*** Apo-Capto†; Apuzin; Capoten†; ***Mex.:*** Altiver; Atrisol; Biodezil; Bioxil; Brucap; Bugazon; Capotena; Captoser; Captral; Cardipril; Catona; Cryopril; Eca Presan; Ecapril; Ecaten; Enlace; Hipertex; Kenapril†; Kenolan; Keyerpril†; Lenpryl; Midrat; Miocap; Novapres; Precaptil; Prinarten; Proldin; Reductel; Reduprec; Romir; Tensil; Toprilem; Tropisol†; Tropix-HC; Varaxil; ***Neth.:*** Capoten; ***Norw.:*** Capoten; ***NZ:*** Capoten; Captohexal; ***Philipp.:*** Capomed; Capoten; Hartylox; Normil; Prelat; Primace; Retensin; Tensoril; Unihype; Vasostad; ***Port.:*** Calpix†; Capoten; Capritin; Carencil†; Convertal†; Hipertil; Hipotensil; Mereprine†; Pressil; Prilovase; Tensopril†; Vidapril; Xenam; ***Rus.:*** Aceten (Ацетен); Angiopril (Ангиоприл); Apo-Capto (Апо-капто); Capoten (Капотен); Rilcapton (Рилкаптон); ***S.Afr.:*** Aceten; Capace; Capoten; Captohexal; Captomax; Cardiace; Zapto; ***Singapore:*** Apo-Capto; Capoten†; Catoplin; Ketanine†; Pertacilon†; Rilcapton; Tensoprel†; ***Spain:*** Alopresin†; Capoten; Captosina; Cesplon; Dardex†; Dilabar; Garanil; Tensoprel; ***Swed.:*** Capoten; ***Switz.:*** capto-basan†; Captosol; Lopirin; ***Thai.:*** Capoten; Epsitron; Gemzil; Tensiomin†; ***Turk.:*** Kapril; Kaptoril; ***UAE:*** Captophar; ***UK:*** Acepril; Capoten; Ecopace; Kaplon; Tensopril; ***USA:*** Capoten; ***Venez.:*** Capoten; Ceplon†; Tabulan.

Multi-ingredient: ***Austria:*** Capozide; Captocomp; Captohexal Comp; Captopril Compositum; Captopril-HCT; Co-Captopril; Co-Captotyrol†; Veracapt; ***Braz.:*** Capox H; Captotec + HCT†; Hidropril; Lopril; ***Cz.:*** Captohexal Comp†; ***Denm.:*** Capozid; ***Fr.:*** Captea; Ecazide; ***Ger.:*** ACE-Hemmer comp; Acenorm HCT†; Adocomp; Capozide; Capto Comp; Capto Plus; Captobeta Comp; Captodoc Comp; Captogamma HCT; Captohexal Comp; Captopril Comp; Captopril HCT; Captopril Plus; Cardiagen HCT; Jutacor comp; Tensobon comp; ***Gr.:*** Anastol; Captopress; Captospes+H; Dosturel; Ekzevit†; Empirol; Fetylan; Kifarol; Normolose-H; Pentatec; Piesital; Return; Sancazid; Sedapressin; Superace; Uresan; Zidepril; ***Indon.:*** Capozide; ***Irl.:*** Capozide; Captor-HCT; Half Capozide; ***Ital.:*** Acediur; Aceplus; ***Mex.:*** Capozide; Captral ASA; Co-Captral; ***Neth.:*** Capozide†; ***NZ:*** Capozide; ***Port.:*** Lopiretic; Normotil†; ***Rus.:*** Capozide (Капозид); ***S.Afr.:*** Capozide; Captoretic; Zapto Co; ***Spain:*** Alopresin Diu†; Cesplon Plus; Decresco†; Dilabar Diu; Ecadiu; Ecazide; ***Switz.:*** Capozide; Captosol comp; Tensobon comp; ***UK:*** Acezide; Capozide; Capto-Co; ***USA:*** Capozide; ***Venez.:*** Capozide; Cartazid†.

Carazolol *(BAN, rINN)* ⊗

BM-51052; Carazololum. 1-(Carbazol-4-yloxy)-3-isopropylaminopropan-2-ol.

Каразолол

$C_{18}H_{22}N_2O_2$ = 298.4.
CAS — 57775-29-8.
ATC Vet — QC07AA90.

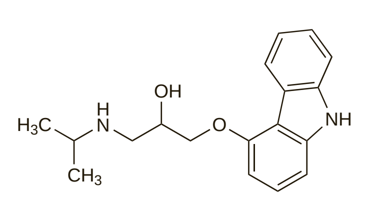

Profile

Carazolol is a beta blocker (p.1225) that has been given orally in the management of various cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Conducton†; ***Ger.:*** Conducton†.

Carbocromen Hydrochloride *(rINNM)*

A-27053; AG-3; Carbocromène, Chlorhydrate de; Carbocromeni Hydrochloridum; Cassella-4489; Chromonar Hydrochloride *(USAN)*; Hidrocloruro de carbocromeno; NSC-110430. Ethyl 3-(2-diethylaminoethyl)-4-methylcoumarin-7-yloxyacetate hydrochloride.

Карбокромена Гидрохлорид

$C_{20}H_{27}NO_5,HCl = 397.9.$

CAS — 804-10-4 (carbocromen); 655-35-6 (carbocromen hydrochloride).

ATC — C01DX05.

ATC Vet — QC01DX05.

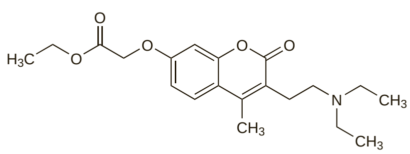

(carbocromen)

Profile

Carbocromen hydrochloride is a vasodilator that has been used in ischaemic heart disease.

Carperitide *(USAN, rINN)* ⊗

Carperitida; Carpéritide; Carperitidum; SUN-4936.

Карперитид

CAS — 89213-87-6.

Profile

Carperitide is a recombinant atrial natriuretic peptide (see p.1347) used in the management of acute heart failure.

◊ References.

1. Suwa M, *et al.* Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the 'real world' of therapy. *Circ J* 2005; **69:** 283–90.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Hanp.

Carteolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Abbott-43326; Cartéolol, chlorhydrate de; Carteololi hydrochloridum; Hidrocloruro de carteolol; Karteolol Hidroklorür; Karteolol-hidroklorid; Karteolol-hydrochlorid; Karteololhydroklorid; Karteololihydrokloridi; Karteololio hidrochloridas; OPC-1085. 5-(3-*tert*-Butylamino-2-hydroxypropoxy)-3,4-dihydroquinolin-2(1*H*)-one hydrochloride.

Картеолола Гидрохлорид

$C_{16}H_{24}N_2O_3,HCl = 328.8.$

CAS — 51781-06-7 (carteolol); 51781-21-6 (carteolol hydrochloride).

ATC — C07AA15; S01ED05.

ATC Vet — QC07AA15; QS01ED05.

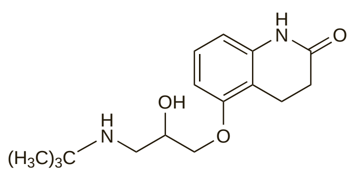

(carteolol)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Carteolol Hydrochloride). White or almost white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A 1% solution in water has a pH of 5.0 to 6.0. Store in airtight containers.

USP 31 (Carteolol Hydrochloride). pH of a 1% solution in water is between 5.0 and 6.0.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Carteolol is well absorbed from the gastrointestinal tract with a peak plasma concentration being reached within 1 to 4 hours of oral doses. The bioavailability is about 84%. It has low lipid solubility. About 20 to 30% is protein bound. The plasma half-life is reported to be 3 to 6 hours. The major route of elimination is renal with 50 to 70% of a dose being excreted unchanged in the urine; carteolol therefore accumulates in patients with renal disease. Major metabolites are 8-hydroxycarteolol and glucuronic acid conjugates of carteolol and 8-hydroxycarteolol. The 8-hydroxycarteolol metabolite is active; its half-life is reported to be 8 to 12 hours.

Uses and Administration

Carteolol is a non-cardioselective beta blocker (see p.1225). It is reported to possess intrinsic sympathomimetic activity but lacks significant membrane-stabilising activity.

Carteolol is used as the hydrochloride in the management of glaucoma (p.1873), hypertension (p.1171), and some cardiac disorders such as angina pectoris (p.1157) and cardiac arrhythmias (p.1160).

Eye drops containing carteolol hydrochloride 1% or 2% are instilled twice daily to reduce raised intra-ocular pressure in open-angle **glaucoma** and ocular hypertension.

In **hypertension** carteolol hydrochloride is given orally in a usual dose range of 2.5 to 20 mg daily, adjusted according to response, although up to 40 mg daily has been given. In cardiac disorders such as **angina pectoris** and **arrhythmias** carteolol hydrochloride has been used in doses of up to 30 mg daily.

The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Chrisp P, Sorkin EM. Ocular carteolol: a review of its pharmacological properties, and therapeutic use in glaucoma and ocular hypertension. *Drugs Aging* 1992; **2:** 58–77. Correction. *ibid.* 1994; **4:** 62.

Administration in renal impairment. The oral dose of carteolol hydrochloride should be reduced in patients with renal impairment. A suggested regimen based on creatine clearance (CC) for patients with hypertension is as follows:

- CC 30 to 80 mL/minute: 10 mg daily
- CC less than 30 mL/minute: use not recommended

Preparations

BP 2008: Carteolol Eye Drops;
USP 31: Carteolol Hydrochloride Ophthalmic Solution; Carteolol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Elebloc; Glacout; Glauteolol; Poenglaucol; Singlauc; Tenoftal†; ***Austria:*** Arteoptic; Endak; ***Belg.:*** Arteoptic; Carteol; ***Cz.:*** Arteoptic; Carteol; ***Denm.:*** Arteoptic†; ***Fin.:*** Arteoptic†; ***Fr.:*** Carteabak; Carteol; Mikelan; ***Ger.:*** Arteoptic; Endak; ***Gr.:*** Carteodose†; Fortinol; Napolit†; Vinitus; Zymoptic†; ***Hong Kong:*** Arteoptic; ***Hung.:*** Arteoptic†; ***Irl.:*** Teoptic; ***Ital.:*** Carteol; ***Jpn:*** Mikelan; ***Neth.:*** Arteoptic; Carteabak; Teoptic; ***Philipp.:*** Mikelan; ***Pol.:*** Arteoptic; ***Port.:*** Arteoptic; Carteabak; Physioglau; ***S.Afr.:*** Mikelan†; Teoptic; ***Spain:*** Arteolol; Elebloc; Mikelan; ***Swed.:*** Arteoptic†; ***Switz.:*** Arteoptic; ***Thai.:*** Arteoptic; ***Turk.:*** Carteol; ***UK:*** Teoptic; ***USA:*** Cartrol; Ocupress†.

Multi-ingredient: ***Belg.:*** Carteopil; ***Fr.:*** Carpilo; ***Switz.:*** Arteopilo.

Carvedilol *(BAN, USAN, rINN)* ⊗

BM-14190; Carvédilol; Carvedilolum; Karvedilol; Karvediloli; Karvedilolis. 1-Carbazol-4-yloxy-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol.

Карведилол

$C_{24}H_{26}N_2O_4 = 406.5.$

CAS — 72956-09-3.

ATC — C07AG02.

ATC Vet — QC07AG02.

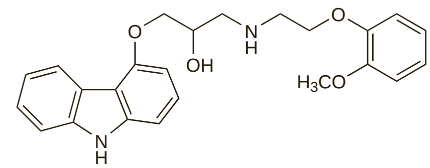

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Carvedilol). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dilute acids.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Liver function abnormalities, reversible on stopping treatment with carvedilol, have been reported rarely. Carvedilol is extensively metabolised in the liver and is not recommended in patients with hepatic impairment. Acute renal failure and renal abnormalities have been reported in patients with heart failure who also suffered from diffuse vascular disease and/or renal impairment.

The risk of hypotension may be reduced by taking carvedilol with food to decrease the rate of absorption.

Effects on the liver. Pruritus and elevated serum transaminase concentrations occurred[1] in a man who had been taking carvedilol for 6 months. Liver function tests returned to normal within 3 weeks of stopping carvedilol. However, pruritus recurred when the patient was started on metoprolol about 1 year later.

1. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. *Ann Pharmacother* 2001; **35:** 1364–6.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; the absolute bioavailability is about 25%. Peak plasma concentrations occur 1 to 2 hours after an oral dose. It has high lipid solubility. Carvedilol is more than 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP2C9, and the metabolites are excreted mainly in the bile. The elimination half-life is about 6 to 10 hours. Carvedilol has been shown to accumulate in breast milk in *animals*.

◊ References.

1. McTavish D, *et al.* Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993; **45:** 232–58.
2. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; **26:** 335–46.
3. Tenero D, *et al.* Steady-state pharmacokinetics of carvedilol and its enantiomers in patients with congestive heart failure. *J Clin Pharmacol* 2000; **40:** 844–53.

Uses and Administration

Carvedilol is a non-cardioselective beta blocker (p.1225). It has vasodilating properties, which are attributed mainly to its blocking activity at $alpha_1$ receptors; at higher doses calcium-channel blocking activity may contribute. It also has antoxidant properties. Carvedilol is reported to have no intrinsic sympathomimetic activity and only weak membrane-stabilising activity.

Carvedilol is used in the management of hypertension (p.1171) and angina pectoris (p.1157), and as an adjunct to standard therapy in symptomatic heart failure (p.1165). It is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction.

In **hypertension** carvedilol is given in an initial oral dose of 12.5 mg once daily, increased after two days to 25 mg once daily. Alternatively, an initial dose of 6.25 mg is given twice daily, increased after one to two weeks to 12.5 mg twice daily. The dose may be increased further, if necessary, at intervals of at least two weeks, to 50 mg once daily or in divided doses. A dose of 12.5 mg once daily may be adequate for elderly patients.

In **angina pectoris** an initial oral dose of 12.5 mg is given twice daily, increased after two days to 25 mg twice daily.

In **heart failure**, the initial oral dose is 3.125 mg twice daily. It should be taken with food to reduce the risk of hypotension. If tolerated, the dose should be doubled after two weeks to 6.25 mg twice daily and then increased gradually, at intervals of not less than two weeks, to the maximum dose tolerated; this should not exceed 25 mg twice daily in patients with severe heart failure or in those weighing less than 85 kg, or 50 mg twice daily in patients with mild to moderate heart failure weighing more than 85 kg. For doses in children, see below.

In patients with **left ventricular dysfunction after myocardial infarction**, the initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients.

A controlled-release preparation containing carvedilol phosphate hemihydrate is available in some countries.

◊ References.

1. Ruffolo RR, *et al.* The pharmacology of carvedilol. *Eur J Clin Pharmacol* 1990; **38:** S82–S88.
2. McTavish D, *et al.* Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993: **45:** 232–58.
3. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; **26:** 335–46.
4. Louis WJ, *et al.* A risk-benefit assessment of carvedilol in the treatment of cardiovascular disorders. *Drug Safety* 1994; **11:** 86–93.
5. Dunn CJ, *et al.* Carvedilol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1997; **54:** 161–85.
6. Frishman WH. Carvedilol. *N Engl J Med* 1998; **339:** 1759–65.
7. Keating GM, Jarvis B. Carvedilol: a review of its use in chronic heart failure. *Drugs* 2003; **63:** 1697–1741.
8. Naccarelli GV, Lukas MA. Carvedilol's antiarrhythmic properties: therapeutic implications in patients with left ventricular dysfunction. *Clin Cardiol* 2005; **28:** 165–73.

Administration in children. Carvedilol has been used in children with heart failure, although experience is limited.[1] Beneficial effects have been reported, including improvement in symptoms and ejection fraction, and delaying the need for heart transplantation, and carvedilol appears to be well tolerated. Doses used have varied, with initial oral doses ranging from 10 to 180 micrograms/kg daily and average oral maintenance doses ranging from 200 to 700 micrograms/kg (maximum 50 mg) daily, usually given in two divided doses. However, a randomised study[2] in 161 children and adolescents with heart failure found that carvedilol was not significantly better than placebo: clinical improvement occurred in 56% of those taking carvedilol and 56% of those taking placebo.

In the UK, the *BNFC* recommends that children aged 2 to 18 years with heart failure may be given an initial oral dose of 50 micrograms/kg (maximum 3.125 mg) twice daily, increased as tolerated, by doubling the dose at intervals of at least 2 weeks, to a maintenance dose of 350 micrograms/kg (maximum 25 mg) twice daily.

1. Greenway SC, Benson LN. The use of carvedilol in pediatric heart failure. *Cardiovasc Hematol Disord Drug Targets* 2006; **6:** 35–42.
2. Shaddy RE, *et al.* Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007; **298:** 1171–9.

Administration in the elderly. Licensed product information for carvedilol recommends an initial dose of 12.5 mg daily for all adults with hypertension. A study in 16 elderly hypertensive patients (mean age 70 years) given single doses of 12.5 mg and 25 mg found a high incidence of orthostatic hypotension[1] and the authors suggested that a starting dose lower than 12.5 mg may be necessary in elderly patients.

A retrospective study[2] found that standard initial doses for heart failure (see Uses and Administration, above) were well tolerated in elderly patients and that the mean achieved dose was similar in those aged under 70 years and those aged 70 years and older, after adjustment for weight. Adverse effects were more common in the older group, but could generally be managed without stopping carvedilol.

1. Krum H, *et al.* Postural hypotension in elderly patients given carvedilol. *BMJ* 1994; **309:** 775–6.
2. Lawless CE, *et al.* Titration of carvedilol in elderly heart failure patients. *Am J Geriatr Cardiol* 2005; **14:** 230–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Antibloc; Bidecar; Carvedil; Carvel†; Corafen; Coritensil; Corubin; Dilatrend; Duobloc; Filten; Hipoten; Isobloc; Kollosteril; Rodipal; Rudoxil; Veraten; Vicardol; ***Austral.:*** Dilatrend; Kredex; ***Austria:*** Dilatrend; Hybridil; ***Belg.:*** Dimitone; Kredex; ***Braz.:*** Cardiol; Carvedilat; Coreg; Dilatrend†; Divelol; Ictus; Karvil; ***Canad.:*** Coreg; ***Chile:*** Betaplex; Blocar; Dilatrend; Dualten; Lodipres; Novocar†; Off-Ten; ***Cz.:*** Apo-Carve; Atram; Carvedigamma; Carvesan; Carvetrend; Coryol; Dilatrend; Talliton; ***Denm.:*** Carvetone; Dimitone; ***Fin.:*** Cardiol; ***Fr.:*** Kredex; ***Ger.:*** CarLich; Carve; Carve-Q; Carvecard; Carvedigamma; Dilatrend; Dimetil; Querto; ***Gr.:*** Carvedilen; Carvepen; Dilatrend; ***Hong Kong:*** Dilatrend; ***Hung.:*** Carvedigamma; Carvol; Coryol; Dilatrend; Talliton; ***India:*** Carloc; Carvil; Cevas; ***Indon.:*** Carbloxal; Dilbloc; V-Bloc; ***Irl.:*** Biocard; Eucardic; ***Israel:*** Carvedexxon; Dimitone; ***Ital.:*** Carvipress; Colver; Dilatrend; Dilocar; ***Malaysia:*** Caslot; Cavel; Dilatrend; ***Mex.:*** Dilatrend; ***Neth.:*** Eucardic; ***Norw.:*** Kredex; ***NZ:*** Dilatrend; ***Philipp.:*** Dilatrend; ***Pol.:*** Atram; Carvedigamma; Carvetrend; Coryol; Dilatrend; Vivacor; ***Port.:*** Dilbloc; ***Rus.:*** Acridilole (Акридилол); Cardivas (Кардивас); Carvetrend (Карветренд); Carvidil (Карвидил); Coryol (Кориол); Talliton (Таллитон); ***S.Afr.:*** Carloc; Carvetrend; Dilatrend; ***Singapore:*** Dilatrend; ***Spain:*** Coropres; ***Swed.:*** Kredex; ***Switz.:*** Dilatrend; ***Thai.:*** Dilatrend; ***Turk.:*** Dilatrend; ***UK:*** Eucardic; ***USA:*** Coreg; ***Venez.:*** Carbatil; Carvedil; Coventrol; Dilatrend.

Multi-ingredient: ***Arg.:*** Carvedil D; ***Austria:*** Co-Dilatrend; Dilaplus.

Celiprolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Céliprolol, chlorhydrate de; Celiprolol-hydrochlorid; Celiprololhydroklorid; Celiprololi hydrochloridum; Celiprololio hidrochloridas; Celiprololu chlorowodorek; Hidrocloruro de celiprolol; Seliprololihydrokloridi. 3-{3-Acetyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl}-1,1-diethylurea hydrochloride.

Целипролола Гидрохлорид

$C_{20}H_{33}N_3O_4,HCl = 416.0.$

CAS — 56980-93-9 (celiprolol); 57470-78-7 (celiprolol hydrochloride).

ATC — C07AB08.

ATC Vet — QC07AB08.

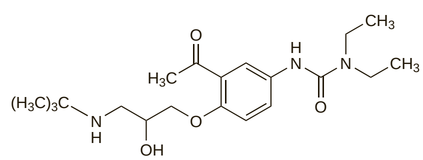

(celiprolol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Celiprolol Hydrochloride). A white or very slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Tremor and palpitations associated with intrinsic sympathomimetic activity at $beta_2$ receptors have been reported.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Celiprolol is absorbed from the gastrointestinal tract in a non-linear fashion; the percentage of the dose absorbed increases with increasing dose. The plasma elimination half-life is about 5 to 6 hours. Celiprolol crosses the placenta. It has low lipid solubility and is about 25% bound to plasma proteins. Metabolism is minimal and celiprolol is mainly excreted unchanged in the urine and faeces.

Uses and Administration

Celiprolol is a cardioselective beta blocker (p.1225). It is reported to possess intrinsic sympathomimetic activity and direct vasodilator activity. Celiprolol is used as the hydrochloride in the management of hypertension (p.1171) and angina pectoris (p.1157). The usual oral dose of celiprolol hydrochloride is 200 to 400 mg once daily before food. Reduced doses may be required in patients with renal impairment (see below).

◊ References.

1. Milne RJ, Buckley MM-T. Celiprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. *Drugs* 1991; **41:** 941–69.
2. Anonymous. Celiprolol: theory and practice. *Lancet* 1991; **338:** 1426–7.
3. Anonymous. Celiprolol—a better beta blocker? *Drug Ther Bull* 1992; **30:** 35–6.
4. Kendall MJ, Rajman I. A risk-benefit assessment of celiprolol in the treatment of cardiovascular disease. *Drug Safety* 1994; **10:** 220–32.
5. Riddell J. Drugs in focus 18: celiprolol. *Prescribers' J* 1996; **36:** 165–8.

Administration in renal impairment. Celiprolol should not be given to patients with a creatinine clearance (CC) of less than 15 mL/minute. Patients with a CC between 15 and 40 mL/minute may be given 100 to 200 mg daily.

Preparations

BP 2008: Celiprolol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Selectol; ***Belg.:*** Selectol; ***Chile:*** Selectol; ***Cz.:*** Celectol†; Tenoloc; ***Fin.:*** Selectol; ***Fr.:*** Celectol; ***Ger.:*** Celip; Celipro; Celiprogamma; Selectol; ***Gr.:*** Aplonit; Selectol; Versatil; ***Hong Kong:*** Selectol; ***Irl.:*** Selectol; ***Ital.:*** Cordiax; ***Jpn:*** Selectol; ***Neth.:*** Dilanorm; ***NZ:*** Celol; ***Pol.:*** Celipres; ***Spain:*** Cardem; ***Switz.:*** Selectol; ***UK:*** Celectol.

Multi-ingredient: ***Austria:*** Selecturon.

Certoparin Sodium *(BAN, rINN)*

Certoparin; Certoparina sódica; Certoparine Sodique; Certoparinum Natricum.

Цертопарин Натрий

Description. Certoparin sodium is prepared by amyl nitrite degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannose structure at the reducing end of their chain. The molecular weight of 70% of the components is less than 10 000 and the average molecular weight is about 6000. The degree of sulfation is about 2 to 2.5 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with certoparin may be reduced by the slow intravenous injection of protamine salts; 1 mg of protamine hydrochloride is stated to inhibit the effects of 80 to 120 units of certoparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Certoparin sodium is rapidly and completely absorbed after subcutaneous injection. Peak plasma activity is reached within 2 to 4 hours. The half-life of anti-factor Xa activity is about 4 hours.

Uses and Administration

Certoparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity used for the prevention of postoperative venous thromboembolism (p.1189). It is given by subcutaneous injection in a dose of 3000 units 1 to 2 hours before the procedure, followed by 3000 units daily for 7 to 10 days or until the patient is fully ambulant.

◊ References.

1. Kolb G, *et al.* Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thromb Haemost* 2003; **90:** 1100–5.
2. Riess H, *et al.* Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003; **90:** 252–9.
3. Diener HC, *et al.* Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke* 2006; **37:** 139–44.
4. Tebbe U, *et al.* AFFECT: a prospective, open-label, multicenter trial to evaluate the feasibility and safety of a short-term treatment with subcutaneous certoparin in patients with persistent non-valvular atrial fibrillation. *Clin Res Cardiol* 2008; **97:** 389–96.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sandoparin; Troparin; ***Cz.:*** Troparin†; ***Ger.:*** Mono-Embolex; ***Hung.:*** Sandoparin†; ***Switz.:*** Sandoparine; ***UK:*** Alphaparin†.

Multi-ingredient: ***Austria:*** Troparin compositum; ***Ger.:*** Embolex NM†.

Cetiedil Citrate (USAN, rINNM)

Cétiédil, Citrate de; Cetiedili Citras; Citrato de cetiedil. 2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl)acetate dihydrogen citrate monohydrate.

Цетиедила Цитрат

$C_{20}H_{31}NO_2S,C_6H_8O_7,H_2O$ = 559.7.

CAS — 14176-10-4 (cetiedil); 16286-69-4 (anhydrous cetiedil citrate).

ATC — C04AX26.

ATC Vet — QC04AX26.

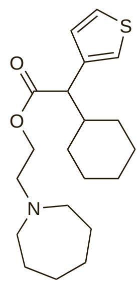

(cetiedil)

Profile

Cetiedil citrate is a vasodilator with antimuscarinic activity that has been used in the management of peripheral vascular disease.

Chlorothiazide (BAN, rINN) ⊗

Chlorothiazid; Chlorothiazidum; Chlorotiazidas; Chlorotiazyd; Clorotiazida; Klooritiatsidi; Klorotiazid; Klortiazid. 6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Хлоротиазид

$C_7H_6ClN_3O_4S_2$ = 295.7.

CAS — 58-94-6.

ATC — C03AA04.

ATC Vet — QC03AA04.

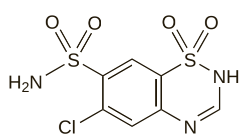

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Chlorothiazide). A white or almost white crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Chlorothiazide). A white or practically white, odourless, crystalline powder. Very slightly soluble in water; practically insoluble in chloroform, in ether, and in benzene; freely soluble in dimethylformamide and dimethyl sulfoxide; slightly soluble in methyl alcohol and in pyridine. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Alkaline solutions undergo decomposition due to hydrolysis upon standing or heating.

Chlorothiazide Sodium (BANM, USAN, rINNM) ⊗

Chlorothiazide Sodique; Clorotiazida sódica; Natrii Chlorothiazidum; Sodium Chlorothiazide.

Натрий Хлоротиазид

$C_7H_5ClN_3NaO_4S_2$ = 317.7.

CAS — 7085-44-1.

ATC — C03AA04.

ATC Vet — QC03AA04.

Pharmacopoeias. *US* includes Chlorothiazide Sodium for Injection.

Incompatibility. The alkaline nature of chlorothiazide in injectable form suggests that incompatibilities with acidic drugs could be expected; US licensed product information states that the injection may be diluted with glucose or sodium chloride solutions.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307. Chlorothiazide sodium injection is alkaline: when giving chlorothiazide by intravenous infusion, care should be taken to ensure that extravasation does not occur.

Breast feeding. Chlorothiazide is distributed into breast milk in small amounts. A single 500-mg oral dose of chlorothiazide was given[1] to 11 lactating women and blood and milk samples taken after 1, 2, and 3 hours; all the samples had concentrations below 1 microgram/mL and it was calculated that an infant would receive no more than 1 mg of drug each day. The American Academy of Pediatrics states that no adverse effects have been seen in infants and therefore considers[2] that chlorothiazide is usually compatible with breast feeding.

1. Werthmann MW, Krees SV. Excretion of chlorothiazide in human breast milk. *J Pediatr* 1972; **81:** 781–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Chlorothiazide is incompletely and variably absorbed from the gastrointestinal tract. It has been estimated to have a plasma half-life of 45 to 120 minutes although the clinical effects may last for up to about 12 hours. It is excreted unchanged in the urine. Chlorothiazide crosses the placental barrier and small amounts are reported to be distributed into breast milk.

Uses and Administration

Chlorothiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

After oral doses of chlorothiazide diuresis usually occurs in about 2 hours, reaches a maximum at about 4 hours, and is maintained for 6 to 12 hours.

In the treatment of **oedema** the usual dose of chlorothiazide is 0.25 to 1 g orally once or twice daily; therapy on alternate days or on 3 to 5 days weekly may be adequate. The dose should not normally exceed 2 g daily.

In the treatment of **hypertension** the usual initial dose is 250 to 500 mg daily orally, given as a single or divided dose. A dose of 125 mg may be adequate in some patients. Patients may rarely require up to 1 g daily.

For the use of chlorothiazide in children, see below.

Chlorothiazide has also been given intravenously as the sodium salt, in doses similar to those given orally. Chlorothiazide sodium 537 mg is equivalent to about 500 mg of chlorothiazide. It is not suitable for subcutaneous or intramuscular injection and extravasation should be avoided. The diuretic effect lasts for up to 2 hours after intravenous injection.

Administration in children. Chlorothiazide may be used in children for the management of *heart failure* or *hypertension*. Usual oral doses are as follows:

- neonates and infants aged 1 to 6 months: 10 to 20 mg/kg twice daily
- age 6 months to 12 years: 10 mg/kg twice daily, to a maximum of 1 g daily
- age 12 to 18 years: 0.25 to 1 g once daily or 125 to 500 mg twice daily

For *diabetes insipidus* in children, the *BNFC* suggests an oral dose of 10 to 20 mg/kg twice daily, to a maximum of 1 g daily.

Chlorothiazide also has a hyperglycaemic effect and has been used in children with *chronic hypoglycaemia* (see under Uses of Glucagon, p.1447). It is usually given with diazoxide and has the added benefit of reducing diazoxide-associated sodium and water retention. The *BNFC* suggests an oral dose of 3 to 5 mg/kg twice daily.

Preparations

USP 31: Chlorothiazide Oral Suspension; Chlorothiazide Sodium for Injection; Chlorothiazide Tablets; Methyldopa and Chlorothiazide Tablets; Reserpine and Chlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Singapore: Chlorzide†; ***USA:*** Diurigen; Diuril.

Multi-ingredient: ***Canad.:*** Supres†; ***Gr.:*** Neourizine; ***USA:*** Aldoclor; Diupres.

Chlortalidone (BAN, rINN) ⊗

Chlorotalidon; Chlortalidon; Chlortalidonas; Chlortalidonum; Chlorthalidone (USAN); Clorotalidona; Clortalidona; G-33182; Klooritalidoni; Klórtalidon; Klortalidon; NSC-69200. 2-Chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide.

Хлорталидон

$C_{14}H_{11}ClN_2O_4S$ = 338.8.

CAS — 77-36-1.

ATC — C03BA04.

ATC Vet — QC03BA04.

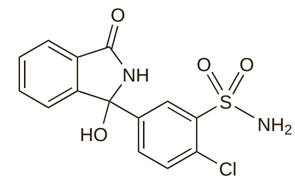

NOTE. Compounded preparations of chlortalidone may be represented by the following names:

- Co-tenidone (*BAN*)—chlortalidone 1 part and atenolol 4 parts (w/w).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Chlortalidone). A white or yellowish-white powder. Very slightly soluble in water; soluble in acetone and in methyl alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism.

USP 31 (Chlorthalidone). A white or yellowish-white crystalline powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol; soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Breast feeding. Chlortalidone is distributed into breast milk, but a study[1] in 9 women given a dose of 50 mg daily found that the concentration in milk was only about 5% of that in the blood. However, caution was advised since chlortalidone elimination may be slower in neonates. The American Academy of Pediatrics considers[2] that chlortalidone is usually compatible with breast feeding.

1. Mulley BA, *et al.* Placental transfer of chlorthalidone and its elimination in maternal milk. *Eur J Clin Pharmacol* 1978; **13:** 129–31.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p.1309.

Anticoagulants. For references to the interaction between *warfarin* and chlortalidone, see p.1430.

Pharmacokinetics

Chlortalidone is erratically absorbed from the gastrointestinal tract and bioavailability varies according to the preparation used. It has a prolonged elimination half-life from plasma and blood of 40 to 60 hours and is highly bound to red blood cells; the receptor to which it is bound has been identified as carbonic anhydrase. Chlortalidone is much less strongly bound to plasma proteins. Chlortalidone is mainly excreted unchanged in the urine. It crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Riess W, *et al*. Pharmacokinetic studies with chlorthalidone (Hygroton) in man. *Eur J Clin Pharmacol* 1977; **12:** 375–82.
2. Fleuren HLJ, *et al.* Absolute bioavailability of chlorthalidone in man: a cross-over study after intravenous and oral administration. *Eur J Clin Pharmacol* 1979; **15:** 35–50.
3. Fleuren HLJ, *et al.* Dose-dependent urinary excretion of chlorthalidone. *Clin Pharmacol Ther* 1979; **25:** 806–12.
4. Mulley BA, *et al.* Pharmacokinetics of chlorthalidone: dependence of biological half life on blood carbonic anhydrase levels. *Eur J Clin Pharmacol* 1980; **17:** 203–7.

Uses and Administration

Chlortalidone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165). Other indications include diabetes insipidus (p.2179).

Diuresis begins about 2 hours after an oral dose and lasts for 48 to 72 hours.

The usual dose in the treatment of **hypertension** is 25 mg daily, given either alone or with other antihypertensives, increasing to 50 mg daily if necessary.

In the treatment of **oedema** the usual initial dose is 25 to 50 mg daily. In severe cases a daily dose of 100 to 200 mg may be given. If possible lower doses should be used for maintenance; 25 to 50 mg daily or on alternate days may be adequate.

A dose for children is up to 2 mg/kg on alternate days.

In **diabetes insipidus** an initial dose of 100 mg twice daily has been used, reduced to a maintenance dose of 50 mg daily.

In the US, a preparation is available with improved bioavailability; suggested doses range from 15 to 50 mg daily for hypertension and 30 to 120 mg daily for oedema.

Preparations

BP 2008: Chlortalidone Tablets; Co-tenidone Tablets;
USP 31: Atenolol and Chlorthalidone Tablets; Chlorthalidone Tablets; Clonidine Hydrochloride and Chlorthalidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Euretico; Hygroton; ***Austral.:*** Hygroton; ***Austria:*** Hydrosan; Hygroton; ***Belg.:*** Hygroton; ***Braz.:*** Clordilon†; Clortalil; Clortil; Clorton†; Drenidra; Higroton; Neolidona; Taluron†; ***Cz.:*** Urandil†; ***Ger.:*** Hydrolong†; Hygroton; ***Gr.:*** Hygroton; ***Hong Kong:*** Hygroton†; ***Hung.:*** Hygroton; ***India:*** Hythalton†; Thalizide; ***Indon.:*** Hygroton; ***Israel:*** Aquadon; ***Ital.:*** Igroton; ***Malaysia:*** Hygroton†; ***Mex.:*** Anilid; Bioralin; Diuprol†; Hidrona; Hidropharm; Higroton; Sinhidron; ***Neth.:*** Hygroton; ***NZ:*** Hygroton; ***Pol.:*** Hygroton; Urandil; ***Port.:*** Hygroton; ***S.Afr.:*** Hygroton; ***Spain:*** Higrotona; ***Switz.:*** Hygroton; ***Turk.:*** Hygroton; ***UK:*** Hygroton; ***USA:*** Hygroton; Thalitone; ***Venez.:*** Higroton†.

Multi-ingredient: ***Arg.:*** Atel C†; Bemplas; Hygroton-Reserpina†; Prenoretic; ***Austria:*** Arcablock comp; Atenolan comp; Atenolol comp; Atenotyrol comp†; Darebon; Polinorm; Selecturon; Tenoretic; Trasitensin; Trepress; ***Belg.:*** Logroton; Tenoretic; ***Braz.:*** Ablok Plus; Angipress CD; Atenoclor†; Atenoric; Atenuol CRT; Diupress; Higroton Reserpina; Tenoretic; ***Canad.:*** Apo-Atenidone; Tenoretic; ***Chile:*** Tenoretic†; ***Cz.:*** Amicloton; Atedon†; Atenolol Compositum†; Neocrystepin; Tenoretic; Trimecryton†; ***Denm.:*** Tenidon; Tenoretic; ***Fr.:*** Logroton; Tenoretic; Trasitensine; ***Ger.:*** Ate Lich comp; Atehexal comp; Atel; Ateno comp; Atenogamma comp; Atenolol AL comp; Atenolol comp; Blocotenol comp†; Combipresan†; Darebon†; Diu-Atenolol; duratenol comp†; Impresso†; Prelis comp; Sigabloc†; Teneretic; Trasitensin†; Trepress; TRI-Normin; ***Gr.:*** Apress†; Chlotenor; Hygroton-Reserpine; Obosan; Tenoretic; Trasitensin; Typofen; ***Hong Kong:*** Target; Tenoret; Tenoretic; ***Hung.:*** Atenolol Comp†; Blokium Diu; ***India:*** Atecard-D†; Catapres Diu; Tenoclor; Tenoric; ***Indon.:*** Tenoret; Tenoretic; ***Irl.:*** Atecor CT; Atenetic; Tenoret; Tenoretic; ***Ital.:*** Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Igroton-Lopresor; Igroton-Reserpina; Target; Tenolone†; Tenoretic; Trandiur; Trasitensin; ***Malaysia:*** Apo-Atenidone; Logroton; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.:*** Higroton-Res; Tenoretic; ***Neth.:*** Tenoretic; ***Philipp.:*** Tenoretic; ***Port.:*** Blokium Diu†; Tenoretic; ***Rus.:*** Atehexal Compositum (Атегексал Композитум); Tenoric (Тенорик); Tenorox (Тенорокс); ***S.Afr.:*** Adco-Loten; Atenoblok Co†; Hygroton-Reserpine†; Tenchlor; Tenoretic; ***Singapore:*** Tenoret; Tenoretic; ***Spain:*** Aldoleo; Blokium Diu; Higrotensin; Higrotona Reserpina†; Normopresil; Tenoretic; Trasitensin; ***Switz.:*** Atedurex; ateno-basan comp†; Cardaxen plus; Co-Atenolol†; Cotenolol-Neo; Cotesifar†; Hygroton-Reserpine; Logroton; Primatenol Plus†; Sandoretic; Slow-Trasitensine; Tenoretic; ***Thai.:*** Tenoret†; Tenoretic†; ***Turk.:*** Regroton; Tenoretic; ***UK:*** Atenix-Co; Kalspare; Tenchlor; Tenoret; Tenoretic; Totaretic; ***USA:*** Clorpres; Combipres†; Demi-Regroton; Regroton; Tenoretic; ***Venez.:*** Blokiuret; Tenoretic.

Cibenzoline *(BAN, rINN)*

Cibenzolina; Cibenzolinum; Cifenline *(USAN)*; Ro-22-7796; Ro-22-7796/001 (cibenzoline succinate); UP-339-01. (±)-2-(2,2-Diphenylcyclopropyl)-2-imidazoline.

Цибензолин

$C_{18}H_{18}N_2$ = 262.3.
CAS — 53267-01-9 (cibenzoline); 100678-32-8 (cibenzoline succinate).
ATC — C01BG07.
ATC Vet — QC01BG07.

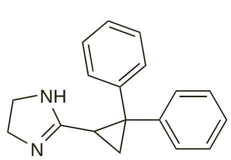

Adverse Effects and Precautions

Cibenzoline may cause neurological and gastrointestinal adverse effects including vertigo, tremor, nausea, vomiting, and diarrhoea. Other adverse effects include fatigue, visual disturbances, and hypoglycaemia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias. It also has a negative inotropic effect and may reduce blood pressure.

Cibenzoline is contra-indicated in patients with heart block and severe heart failure. It should be used with caution in the elderly and in renal impairment, and doses should be reduced.

Effects on the neuromuscular system. Myasthenia-like symptoms have been reported[1-3] in patients with renal impairment taking cibenzoline, including severe respiratory depression in some cases.[2,3]

1. Kasuga A, *et al.* Myasthenia-like syndrome induced by overdosage of cibenzoline. *Intern Med* 1996; **35:** 512–14.
2. Similowski T, *et al.* Neuromuscular blockade with acute respiratory failure in a patient receiving cibenzoline. *Thorax* 1997; **52:** 582–4.
3. Inada K, *et al.* A case of severe respiratory depression due to cibenzoline overdosage induced by a transient renal dysfunction. *Int J Cardiol* 2002; **82:** 177–8.

Hypoglycaemia. Cibenzoline therapy was associated with severe hypoglycaemia in a 67-year-old patient.[1] The plasma-cibenzoline concentration was 1800 nanograms/mL which would probably be considered toxic since the accepted therapeutic trough range is 200 to 600 nanograms/mL. A case-control study[2] also suggested that the risk of hypoglycaemia is increased by cibenzoline.

1. Hilleman DE, *et al.* Cibenzoline-induced hypoglycemia. *Drug Intell Clin Pharm* 1987; **21:** 38–40.
2. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Interactions

Cibenzoline should not be used with other drugs that prolong the QT interval since the risk of arrhythmias may be increased.

Histamine H_2-antagonists. Increased blood concentrations and prolonged half-lives of cibenzoline occurred in healthy subjects given *cimetidine* but the clinical importance of this was unknown.[1] The interaction did not occur with *ranitidine*.

1. Massarella JW. The effects of cimetidine and ranitidine on the pharmacokinetics of cifenline. *Br J Clin Pharmacol* 1991; **31:** 481–3.

Pharmacokinetics

Cibenzoline is well absorbed from the gastrointestinal tract after oral use, with a bioavailability of about 90%. It is about 50 to 60% bound to plasma proteins. About 60% of a dose is excreted unchanged in the urine and the elimination half-life is reported to be about 7 hours.

Uses and Administration

Cibenzoline is a class I antiarrhythmic (p.1153) that has been classified as either Ia or Ic; it also has some class III and class IV properties. It is used in the management of ventricular and supraventricular arrhythmias (p.1160). Cibenzoline is given by mouth as the succinate or intravenously as a mixture of the base and succinate, but doses for both routes are expressed in terms of the base; 145 mg of cibenzoline succinate is equivalent to about 100 mg of base. The usual oral dose of cibenzoline succinate is the equivalent of 260 to 390 mg cibenzoline daily. The usual intravenous dose is the equivalent of 1 mg/kg cibenzoline base given over 2 to 5 minutes. Dosage should be reduced in the elderly (below), and in renal impairment (below).

◊ Reviews.

1. Harron DW, *et al.* Cibenzoline: a review of its pharmacological properties and therapeutic potential in arrhythmias. *Drugs* 1992; **43:** 734–59.

Administration in the elderly. The renal and non-renal clearance of cibenzoline was found to decrease with increasing age in healthy subjects.[1] The mean elimination half-life was 7 hours in the 20- to 30-year age group and 10.5 hours in the 70- to 80-year age group. The reduction in renal clearance was considered to be related to the decrease in creatinine clearance with increasing age. The results suggested that older patients may need lower doses than younger patients to maintain therapeutic plasma-cibenzoline concentrations. Licensed product information recommends a dosage of 130 mg daily in two divided doses in elderly patients.

1. Brazzell RK, *et al.* Age and cibenzoline disposition. *Clin Pharmacol Ther* 1984; **36:** 613–19.

Administration in renal impairment. A study[1] in patients with normal or impaired renal function has suggested that in renal impairment initial loading doses of cibenzoline may be equivalent to those used in normal renal function although maintenance doses should be reduced to about two-thirds of normal. Oral doses recommended in licensed product information, based on creatinine clearance (CC), are as follows:

- CC 20 to 40 mL/min: the equivalent of 3 mg/kg daily
- CC 10 to 20 mL/min: the equivalent of 2.5 mg/kg daily

1. Aronoff G, *et al.* Bioavailability and kinetics of cibenzoline in patients with normal and impaired renal function. *J Clin Pharmacol* 1991; **31:** 38–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cipralan; ***Fr.:*** Cipralan; Exacor; ***Jpn:*** Cibenol.

Cicletanine *(BAN, USAN, rINN)* ⊗

(±)-BN-1270; Cicletanina; Ciclétanine; Cicletaninum; (±)-Cycletanide; Win-90000. (±)-3-(*p*-Chlorophenyl)-1,3-dihydro-6-methylfuro[3,4-*c*]pyridin-7-ol.

Циклетанин

$C_{14}H_{12}ClNO_2$ = 261.7.
CAS — 89943-82-8;.
ATC — C03BX03.
ATC Vet — QC03BX03.

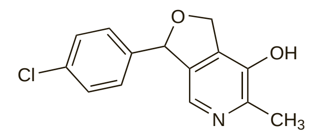

Cicletanine Hydrochloride *(BANM, rINNM)* ⊗

Ciclétanine, Chlorhydrate de; Cicletanini Hydrochloridum; Hidrocloruro de cicletanina.

Циклетанина Гидрохлорид

$C_{14}H_{12}ClNO_2,HCl$ = 298.2.
CAS — 89943-82-8;.
ATC — C03BX03.
ATC Vet — QC03BX03.

Profile

Cicletanine hydrochloride is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307). It is used in the treatment of hypertension (p.1171) in a usual oral dose of 50 to 100 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Tenstaten†; ***Fr.:*** Tenstaten; ***Ger.:*** Justar.

Cilazapril *(BAN, USAN, rINN)*

Cilazapril monohydrát; Cilazaprilis; Cilazaprilum; Cilazaprilum Monohydricum; Ro-31-2848 (anhydrous cilazapril); Ro-31-2848/006 (cilazapril monohydrate); Silatsapriili; Silazapril. (1*S*,9*S*)-9-[(*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-10-oxoperhydropyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid monohydrate.

Цилазаприл

$C_{22}H_{31}N_3O_5,H_2O$ = 435.5.
CAS — 88768-40-5 (anhydrous cilazapril); 92077-78-6 (cilazapril monohydrate).
ATC — C09AA08.
ATC Vet — QC09AA08.

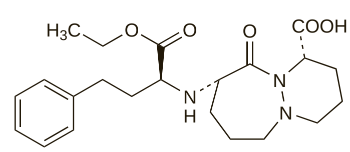

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cilazapril). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Cilazapril acts as a prodrug of the diacid cilazaprilat, its active metabolite. After oral dosage and absorption of cilazapril it is rapidly metabolised in the liver to cilazaprilat, the bioavailability of which is about 60%. Peak plasma concentrations of cilazaprilat occur within 2 hours of an oral dose of cilazapril. Cilazaprilat is eliminated unchanged in the urine. The effective half-life of cilazaprilat is reported to be 9 hours after once-daily dosing. The elimination of cilazaprilat is reduced in renal impairment. Both cilazapril and cilazaprilat are removed to a limited extent by haemodialysis.

◊ Reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors: a review. *Clin Pharmacokinet* 1990; **19:** 177–96.
2. Kloke HJ, *et al.* Pharmacokinetics and haemodynamic effects of the angiotensin converting enzyme inhibitor cilazapril in hypertensive patients with normal and impaired renal function. *Br J Clin Pharmacol* 1996; **42:** 615–20.

Uses and Administration

Cilazapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Cilazapril owes its activity to cilazaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 3 to 7 hours. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Cilazapril is given orally as the monohydrate, but doses are expressed in terms of the anhydrous substance. Cilazapril 1.04 mg as the monohydrate is equivalent to about 1 mg of anhydrous cilazapril.

In the treatment of **hypertension** the initial dose is 1 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 2.5 to 5 mg daily. In the elderly, in patients with mild to moderate renal impairment, or those taking *diuretics*, a usual initial dose is 500 micrograms daily. If possible the diuretic should be withdrawn 2 to 3 days before cilazapril is started and resumed later if necessary.

In the treatment of **heart failure** severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus therapy should be initiated with a low dose under close medical supervision. Cilazapril is given in an initial dose of 500 micrograms once daily, increased if tolerated to a usual maintenance dose of 1 to 2.5 mg once daily. The usual maximum dose is 5 mg daily.

Reduced doses may be necessary in patients with renal impairment (see below).

◊ References.

1. Deget F, Brogden RN. Cilazapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cardiovascular disease. *Drugs* 1991; **41:** 799–820.

Administration in renal impairment. In patients with a creatinine clearance of 10 to 40 mL/minute, the initial dose of cilazapril is 500 micrograms once daily and the maintenance dose should not exceed 2.5 mg once daily. Cilazapril should be avoided in patients with a creatinine clearance below 10 mL/minute. In patients receiving haemodialysis, cilazapril should be given on the non-dialysis days and the dose should be adjusted according to response.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Inhibace; ***Belg.:*** Inhibace; ***Braz.:*** Vascase; ***Canad.:*** Inhibace; ***Chile:*** Inhibace; ***Cz.:*** Cazaprol; Inhibace; ***Fr.:*** Justor; ***Ger.:*** Dynorm; ***Gr.:*** Vascase; ***Hong Kong:*** Inhibace; ***Hung.:*** Inhibace; ***Irl.:*** Vascace; ***Israel:*** Vascase; ***Ital.:*** Inibace; Initiss; ***Jpn:*** Inhibace; ***Mex.:*** Inhibace†; ***Neth.:*** Vascase; ***NZ:*** Inhibace; ***Philipp.:*** Vascace; ***Pol.:*** Inhibace; ***Port.:*** Inibace; Vascase; ***S.Afr.:*** Inhibace; ***Singapore:*** Inhibace†; ***Spain:*** Inhibace; Inocar; ***Swed.:*** Inhibace; ***Switz.:*** Inhibace; ***Thai.:*** Inhibace; ***Turk.:*** Inhibace; ***UK:*** Vascace; ***Venez.:*** Inhibace.

Multi-ingredient: ***Austria:*** Inhibace Plus; ***Belg.:*** Co-Inhibace; ***Braz.:*** Vascase Plus; ***Canad.:*** Inhibace Plus; ***Chile:*** Inhibace Plus; ***Cz.:*** Inhibace Plus; ***Ger.:*** Dynorm Plus; ***Gr.:*** Vascase Plus; ***Hung.:*** Inhibace Plus; ***Israel:*** Vascace Plus; ***Ital.:*** Inibace Plus; Initiss Plus; ***NZ:*** Inhibace Plus; ***Philipp.:*** Vascace Plus; ***Pol.:*** Inhibace Plus; ***Port.:*** Inibace Plus; Vascase Plus; ***Rus.:*** Ampliton (Амплитон); Sonoprel (Сонопрел); ***S.Afr.:*** Inhibace Plus; ***Spain:*** Inhibace Plus; Inocar Plus; ***Swed.:*** Inhibace comp; ***Switz.:*** Inhibace Plus; ***Turk.:*** Inhibace Plus.

Cilnidipine *(rINN)*

Cilnidipino; Cilnidipinum; FRC-8653. (±)-(*E*)-Cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

Цилнидипин

$C_{27}H_{28}N_2O_7$ = 492.5.

CAS — 132203-70-4.

ATC — C08CA14.

ATC Vet — QC08CA14.

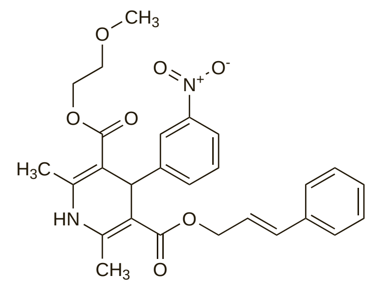

Profile

Cilnidipine is a dihydropyridine calcium-channel blocker (p.1154) given orally in the management of hypertension (p.1171). The usual dose is 5 to 10 mg once daily, increased to 20 mg once daily if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Atelec; Cinalong; ***Port.:*** Tenvasc.

Cilostazol *(BAN, USAN, pINN)*

Cilostazolum; OPC-21; OPC-13013. 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril.

Цилостазол

$C_{20}H_{27}N_5O_2$ = 369.5.

CAS — 73963-72-1.

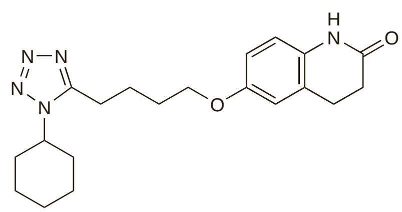

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Cilostazol). White to off-white crystals. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in chloroform. Store in airtight containers.

Adverse Effects and Precautions

Adverse effects of cilostazol include headache, dizziness, palpitations, and diarrhoea; oedema, nausea and vomiting, other cardiac arrhythmias, chest pain, rhinitis, ecchymosis, and skin rashes have also been reported. Cardiovascular toxicity has been reported in *animal* studies of cilostazol, and prolonged oral use of other phosphodiesterase inhibitors (such as amrinone, p.1215) for the treatment of heart failure has been associated with increased mortality. The use of cilostazol in patients with any degree of heart failure is therefore contra-indicated. It is also contra-indicated in patients with a known predisposition to bleeding, a history of ventricular arrhythmias, QT interval prolongation, severe renal impairment, or moderate to severe hepatic impairment. Cilostazol should be avoided or used in reduced doses in patients taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19 (see Interactions, below).

Interactions

Cilostazol is extensively metabolised to active and inactive metabolites by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Cilostazol should therefore be used with caution in patients taking drugs metabolised by these enzymes; in patients taking enzyme inhibitors it should be avoided or a reduced dose of 50 mg twice daily should be considered.

Pharmacokinetics

Cilostazol is absorbed after oral doses and absorption is increased if taken with a high fat meal. Cilostazol is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19, to both active and inactive metabolites; these are mainly excreted in the urine (74%) with the remainder in the faeces (20%). The active metabolites have apparent elimination half-lives of 11 to 13 hours. Cilostazol is 95 to 98% protein bound.

◊ References.

1. Woo SK, *et al.* Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; **71:** 246–52.

Uses and Administration

Cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilating activity. It is used in the management of peripheral vascular disease (p.1178).

The usual dose of cilostazol for the reduction of symptoms of intermittent claudication is 100 mg orally twice daily, at least 30 minutes before or 2 hours after food; doses should be reduced in patients taking enzyme inhibitors (see Interactions, above). Response to treatment may occur in 2 to 4 weeks, but up to 12 weeks may be required.

Cilostazol is under investigation for its antiplatelet effect after coronary stent implantation.

◊ Reviews.

1. El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. *Ann Pharmacother* 2001; **35:** 1108–13.
2. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005; **6:** 3–11.
3. Matsumoto M. Cilostazol in secondary prevention of stroke: impact of the Cilostazol Stroke Prevention Study. *Atheroscler Suppl* 2005; **6:** 33–40.
4. Weintraub WS. The vascular effects of cilostazol. *Can J Cardiol* 2006; **22** (suppl B): 56B–60B.
5. Dalainas I. Cilostazol in the management of vascular disease. *Int Angiol* 2007; **26:** 1–7.

Peripheral vascular disease. Intermittent claudication is a major feature of occlusive arterial disease of the lower limbs (a form of peripheral vascular disease, p.1178) and is characterised by pain in the legs, which develops during exercise but usually disappears at rest. Many drugs have been used for symptom control, but none is of established benefit.

Several randomised, double-blind studies[1-4] have shown that cilostazol improves walking distances in patients with intermittent claudication, and one study[5] suggested that it was more effective than pentoxifylline. Cilostazol may therefore have a role for symptom control in patients with intermittent claudication.[6] However, long-term benefit has not been assessed[4] and, since patients with intermittent claudication are at high risk of other cardiovascular events, appropriate therapy to reduce cardiovascular risk (p.1164) is still required.

1. Money SR, *et al.* Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg* 1998; **27:** 267–75.
2. Beebe HG, *et al.* A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med* 1999; **159:** 2041–50.
3. Strandness DE, *et al.* Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind, placebo-controlled study. *Vasc Endovascular Surg* 2002; **36:** 83–91.
4. Robless P, *et al.* Cilostazol for peripheral arterial disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).
5. Dawson DL, *et al.* A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000; **109:** 523–30.
6. Crouse JR, *et al.* Clinical manifestation of atherosclerotic peripheral arterial disease and the role of cilostazol in treatment of intermittent claudication. *J Clin Pharmacol* 2002; **42:** 1291–8.

Preparations

USP 31: Cilostazol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cibrogan; Cilostal; Cilovas; Licuagen; Pletaal; Policor; Trastocir; Trombonot; ***Braz.:*** Cebralat; Vasogard; ***Chile:*** Artesol; Ilostal; Kostal; ***Hong Kong:*** Pletaal; ***India:*** Cilodac; Pletoz; Stiloz†; Zilast; ***Indon.:*** Aggravan; Agrezol; Alista; Citaz; Naletal; Pletaal; Qital; Stazol; ***Jpn:*** Pletaal; ***Malaysia:*** Pletaal; ***Philipp.:*** Ciletin; Pletaal; ***Thai.:*** Pletaal; ***UK:*** Pletal; ***USA:*** Pletal.

Cinepazet Maleate *(BANM, USAN, pINNM)*

Cinépazet, Maléate de; Cinepazeti Maleas; Cinepazic Acid Ethyl Ester Maleate; Maleato de cinepazet. Ethyl 4-(3,4,5-trimethoxycinnamoyl)piperazin-1-ylacetate hydrogen maleate.

Цинепазета Малеат

$C_{20}H_{28}N_2O_6,C_4H_4O_4$ = 508.5.
CAS — 23887-41-4 (cinepazet); 50679-07-7 (cinepazet maleate).
ATC — C01DX14.
ATC Vet — QC01DX14.

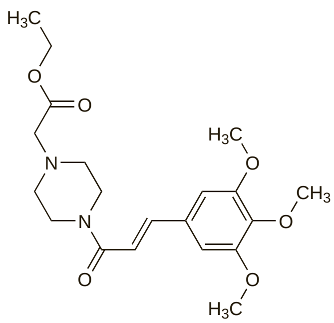

(cinepazet)

Profile

Cinepazet maleate is a vasodilator that has been used in angina pectoris.

Cinepazide Maleate *(BANM, rINNM)*

Cinépazide, Maléate de; Cinepazidi Maleas; Maleato de cinepazida; MD-67350. 1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

Цинепазида Малеат

$C_{22}H_{31}N_3O_5,C_4H_4O_4$ = 533.6.
CAS — 23887-46-9 (cinepazide); 26328-04-1 (cinepazide maleate).
ATC — C04AX27.
ATC Vet — QC04AX27.

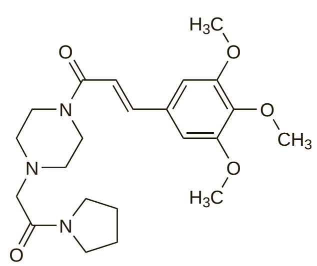

(cinepazide)

Profile

Cinepazide maleate is a vasodilator that has been used in peripheral vascular disorders, but has been withdrawn from the market in some countries after reports of agranulocytosis.

Ciprofibrate *(BAN, USAN, rINN)*

Ciprofibrát; Ciprofibrat; Ciprofibratas; Ciprofibrato; Ciprofibratum; Siprofibraatti; Win-35833. 2-[4-(2,2-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid.

Ципрофибрат

$C_{13}H_{14}Cl_2O_3$ = 289.2.
CAS — 52214-84-3.
ATC — C10AB08.
ATC Vet — QC10AB08.

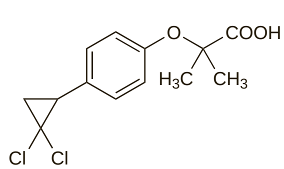

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ciprofibrate). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in toluene. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Interactions

As for Bezafibrate, p.1232.

Pharmacokinetics

Ciprofibrate is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours. Ciprofibrate is highly protein bound. It is excreted in the urine as unchanged drug and as glucuronide conjugates. The elimination half-life varies from about 38 to 86 hours in patients on long-term therapy.

Uses and Administration

Ciprofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, and type IV hyperlipoproteinaemias. The usual oral dose is 100 mg daily. The dose should be reduced in renal impairment (see below).

Administration in renal impairment. Ciprofibrate is contra-indicated in patients with severe renal impairment. Licensed product information suggests reducing the dose to 100 mg every other day for patients with moderate renal impairment.

Renal clearance of ciprofibrate was reduced and elimination half-life about doubled in patients with severe renal impairment.[1] Mild renal impairment slowed the urinary excretion of ciprofibrate but not its extent. The clearance of ciprofibrate was unaffected by haemodialysis.

1. Ferry N, *et al.* The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate. *Br J Clin Pharmacol* 1989; **28:** 675–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Estaprol; ***Belg.:*** Hyperlipen; ***Braz.:*** Lipless; Oroxadin; ***Chile:*** Estaprol; ***Cz.:*** Lipanor; ***Fr.:*** Lipanor; ***Gr.:*** Savilen; ***Hung.:*** Lipanor; ***Indon.:*** Modalim; ***Israel:*** Lipanor; ***Malaysia:*** Modalim; ***Mex.:*** Oroxadin; ***Neth.:*** Hyperlipen; Modalim; ***Philipp.:*** Modalim; ***Pol.:*** Lipanor; ***Port.:*** Fibranin; Lipanor; ***Singapore:*** Modalim; ***Switz.:*** Hyperlipen; ***UK:*** Modalim; ***Venez.:*** Hiperlipen.

Clinofibrate *(rINN)*

Clinofibrato; Clinofibratum; S-8527. 2,2′-[Cyclohexylidenebis(4-phenyleneoxy)]bis[2-methylbutyric acid].

Клинофибрат

$C_{28}H_{36}O_6$ = 468.6.
CAS — 30299-08-2.

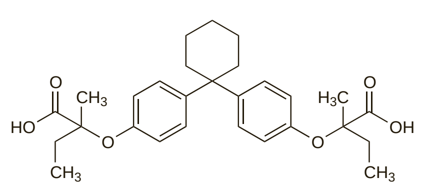

Pharmacopoeias. In *Jpn.*

Profile

Clinofibrate, a fibric acid derivative (see Bezafibrate, p.1232), is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lipoclin.

Clofibrate *(BAN, USAN, rINN)*

AY-61123; Clofibrato; Clofibratum; Ethyl *p*-Chlorophenoxyisobutyrate; Ethyl Clofibrate; ICI-28257; Klofibraatti; Klofibrát; Klofibrat; Klofibratas; NSC-79389. Ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

Клофибрат

$C_{12}H_{15}ClO_3$ = 242.7.
CAS — 637-07-0 (clofibrate); 882-09-7 (clofibric acid).
ATC — C10AB01.
ATC Vet — QC10AB01.

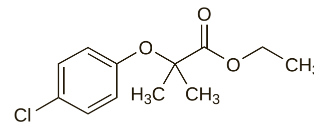

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Clofibrate). A clear, almost colourless liquid. Very slightly soluble in water; miscible with alcohol.
USP 31 (Clofibrate). A colourless to pale yellow liquid with a characteristic odour. Insoluble in water; soluble in alcohol, in acetone, in chloroform, and in benzene. Store in airtight containers. Protect from light.

Aluminium Clofibrate *(BAN, rINN)*

Alufibrate; Aluminii Clofibras; Aluminium, Clofibrate d'; Aluminiumklofibraatti; Aluminiumklofibrat; Aluminum Clofibrate; Clofibrato de aluminio. Bis[2-(4-chlorophenoxy)-2-methylpropionato]hydroxyaluminium.

Алюминия Клофибрат

$C_{20}H_{21}AlCl_2O_7$ = 471.3.
CAS — 24818-79-9; 14613-01-5.
ATC — C10AB03.
ATC Vet — QC10AB03.

Calcium Clofibrate *(rINN)*

Calcii Clofibras; Clofibrate de Calcium; Clofibrato de calcio.

Кальция Клофибрат

$C_{20}H_{20}CaCl_2O_6$ = 467.4.
CAS — 39087-48-4.

Magnesium Clofibrate *(rINN)*

Clofibrato de magnesio; Clomag; Magnesii Clofibras; Magnésium, Clofibrate de; UR-112.

Магния Клофибрат

$C_{20}H_{20}Cl_2MgO_6$ = 451.6.
CAS — 14613-30-0.

Profile

Clofibrate, a fibric acid derivative, is a lipid regulating drug with similar properties to bezafibrate (p.1233). It is used to reduce triglycerides and possibly total cholesterol in the management of hyperlipidaemias (p.1169), particularly in patients with hypertriglyceridaemia. Because of the incidence of adverse effects during long-term treatment it should not be used for the prophylaxis of ischaemic heart disease (see Adverse Effects, below).

The usual oral dose is 2 g daily in divided doses.

The aluminium, calcium, and magnesium salts of clofibrate have also been used.

Adverse effects. Large-scale, long-term studies[1,2] with clofibrate indicated that it was generally well-tolerated but that there was an increased incidence of serious effects, including cholelithiasis, cholecystitis, thromboembolic disorders, and certain cardiac arrhythmias. In one of the studies,[2] an increased mortality rate was unexpectedly found in patients taking clofibrate, producing serious concern over its long-term safety and its use is now generally restricted; the causes of death were spread over a range of malignant and non-malignant disorders.

1. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; **231:** 360–80.
2. Oliver MF, *et al.* A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978; **40:** 1069–1118.

Neonatal jaundice. Clofibrate has been used in the treatment of jaundice in term infants[1,2] and for prophylaxis in premature infants.[1] In a study[1] involving 93 term infants with jaundice, clofibrate 50 mg/kg as a single oral dose reduced the intensity and duration of jaundice compared with placebo. As a prophylactic measure, clofibrate was shown[1] to reduce the degree of jaundice in premature infants when the plasma concentration of clofibric acid reached 140 micrograms/mL within 24 hours of an oral dose. The dose required to achieve this was estimated to be 100 to 150 mg/kg.

1. Gabilan JC, *et al.* Clofibrate treatment of neonatal jaundice. *Pediatrics* 1990; **86:** 647–8.
2. Mohammadzadeh A, *et al.* Effect of clofibrate in jaundiced term newborns. *Indian J Pediatr* 2005; **72:** 123–6.

Preparations

BP 2008: Clofibrate Capsules;
USP 31: Clofibrate Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Elpi; ***Austria:*** Arterioflexin; ***Hong Kong:*** Lipilim; ***Port.:*** Atromid-S†.

Multi-ingredient: ***Braz.:*** Lipofacton.

Clonidine *(BAN, USAN, rINN)*

Clonidina; Clonidinum; Klonidiini; Klonidin; ST-155-BS. 2-(2,6-Dichloroanilino)-2-imidazoline; 2,6-Dichloro-*N*-(imidazolidin-2-ylidene)aniline.

Клонидин

$C_9H_9Cl_2N_3$ = 230.1.

CAS — 4205-90-7.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

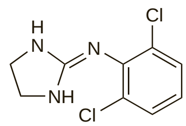

Pharmacopoeias. In *US.*

USP 31 (Clonidine). A white to almost white, crystalline powder. Freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Clonidine Hydrochloride *(BANM, USAN, rINNM)*

Clonidine, chlorhydrate de; Clonidini hydrochloridum; Hidrocloruro de clonidina; Klonidiinihydrokloridi; Klonidin-hidroklorid; Klonidin-hydrochlorid; Klonidinhydroklorid; Klonidino hidrochloridas; Klonidyny chlorowodorek; ST-155.

Клонидина Гидрохлорид

$C_9H_9Cl_2N_3$,HCl = 266.6.

CAS — 4205-91-8.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Clonidine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 4.0 to 5.0.

USP 31 (Clonidine Hydrochloride). pH of a 5% solution in water is between 3.5 and 5.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Treatment

Drowsiness, dry mouth, dizziness, and headache are common when starting therapy with clonidine. Constipation is also common, and other adverse effects reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, orthostatic hypotension, and dry, itching, or burning sensations in the eye. Fluid retention may occur and is usually transient, but may be responsible for a reduction in the hypotensive effect during continued treatment. Clonidine can cause rashes and pruritus, and these are more common with transdermal delivery systems. Bradycardia, including sinus bradycardia with AV block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynaecomastia, and transient abnormalities in liver function tests have been reported less often. Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

Symptoms of overdosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma. Treatment consists of general supportive measures. An alpha blocker may be given if necessary for hypertension, and atropine may be required for bradycardia and associated hypotension. Cardiac pacing may be needed rarely.

Sudden withdrawal of clonidine may produce rebound hypertension—see Precautions, below.

Effects on the gastrointestinal tract. Constipation is a relatively common adverse effect of clonidine, US licensed product information reporting an incidence of about 10%. Ileus or pseudo-obstruction of the bowel have been reported;[1-3] withdrawal of clonidine was associated with a return of bowel function to normal. Abdominal pain mimicking acute appendicitis occurred in another patient; symptoms recurred on restarting the drug and subsided on withdrawal.[4]

1. Davidov M, *et al.* The antihypertensive effects of an imidazoline compound. *Clin Pharmacol Ther* 1967; **8:** 810–16.
2. Bear R, Steer K. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 197.
3. Bauer GE, Hellestrand KJ. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1:** 769.
4. Mjörndal T, Mellbring G. Abdominal pain associated with clonidine. *BMJ* 1986; **292:** 174.

Effects on the heart. Clonidine has been associated with impaired atrioventricular conduction in a few patients,[1,2] although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition. Other ECG abnormalities may also occur. Sudden death has been reported in 3 children receiving clonidine and methylphenidate,[3,4] although the significance of these reports has been questioned.[5]

1. Kibler LE, Gazes PC. Effect of clonidine on atrioventricular conduction. *JAMA* 1977; **238:** 1930–2.
2. Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 1978; **240:** 108–9.
3. Maloney MJ, Schwam, JS. Clonidine and sudden death. *Pediatrics* 1995; **96:** 1176–7.
4. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
5. Blackman JA, *et al.* Clonidine and electrocardiograms. *Pediatrics* 1996; **98:** 1223–4.

Effects on mental function. There have been occasional reports of disturbed mental state in patients given clonidine.[1-4]

1. Lavin P, Alexander CP. Dementia associated with clonidine therapy. *BMJ* 1975; **1:** 628.
2. Enoch MD, Hammad GEM. Acute hallucinosis due to clonidine. *Curr Med Res Opin* 1977; **4:** 670–1.
3. Brown MJ, *et al.* Clonidine hallucinations. *Ann Intern Med* 1980; **93:** 456–7.
4. Delaney J, *et al.* Clonidine-induced delirium. *Int J Cardiol* 2006; **113:** 276–8.

Effects on the skin. Skin reactions have been reported in up to 50% of patients using clonidine transdermal patches.[1] Localised erythema and irritation during early treatment are usually mild, but allergic contact dermatitis may develop.[2-4] Skin reactions may become commoner during prolonged treatment; although only mild skin reactions were seen in a study of transdermal clonidine during 8 to 14 weeks of treatment in 15 patients, severe skin reactions occurred after an average of 20 weeks in 4 of 5 patients who continued treatment.[5] Despite a claim that skin reactions were due to a component in the patch and not to clonidine itself,[6] positive patch tests to clonidine have been obtained.[2,4] Subsequent reaction to oral clonidine in patients who develop skin reactions to the transdermal patch is reported to be rare.[7,8]

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.
2. Groth H, *et al.* Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 850–1.
3. McMahon FG, Weber MA. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii:** 851.
4. Boekhorst JC. Allergic contact dermatitis with transdermal clonidine. *Lancet* 1983; **ii:** 1031–2.
5. Dick JBC, *et al.* Skin reactions to long-term transdermal clonidine. *Lancet* 1987; **i:** 516.
6. Anonymous. Transdermal clonidine sensitiser identified? *Pharm J* 1984; **233:** 16.
7. Bigby M. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819.
8. Burris JF. Transdermal clonidine dermatitis. *JAMA* 1987; **258:** 1819–20.

PEMPHIGOID. Anogenital cicatricial pemphigoid has been reported[1] in a patient receiving long-term clonidine therapy.

1. van Joost T, *et al.* Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102:** 715–18.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Analysis by the UK National Poisons Information Service[1] of poisoning by clonidine in 133 children and 37 adults between 1976 and 1977 revealed that there were no deaths but clinical features were often severe. Supportive measures were usually adequate but atropine was often needed for severe and persistent bradycardia. Forced diuresis was not advised because hypotension could be enhanced and there was no evidence that excretion of clonidine was increased. More recently, death has been reported[2] in a 23-month old child.

Direct medical evaluation has been recommended[3] for children who have ingested the following amounts: 100 micrograms or more in those aged 4 years and under; more than 200 micrograms in those aged 5 to 8 years; and 400 micrograms or more in older children; 4 hours may be long enough to detect full onset of symptoms. However, others[4] believe that medical evaluation is indicated in any child who has unintentionally ingested more than a weight-appropriate therapeutic dose.

Although naloxone has been suggested as an antidote for clonidine overdose, no reversal of the hypotensive effects of clonidine 300 micrograms was noted in 6 hypertensive subjects given naloxone by intravenous infusion.[5] In a retrospective analysis of 47 children with clonidine poisoning, only 3 of 19 given naloxone showed definite improvement;[6] it was concluded that naloxone is at best an inconsistent antidote for clonidine poisoning.

Severe symptoms of overdosage have also been reported after the ingestion of clonidine transdermal patches,[7] and following probable subcutaneous injection during filling of an epidural pump reservoir.[8]

1. Stein B, Volans GN. Dixarit overdose: the problem of attractive tablets. *BMJ* 1978; **2:** 667–8.
2. Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med* 2002; **156:** 392–6.
3. Spiller HA, *et al.* Toxic clonidine ingestion in children. *J Pediatr* 2005; **146:** 263–6.
4. Langhan M, Chan GM. Clonidine exposures, not toxicity. *J Pediatr* 2006; **148:** 565.
5. Rogers JF, Cubeddu LX. Naloxone does not antagonise the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* 1983; **34:** 68–73.
6. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
7. Raber JH, *et al.* Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993; **27:** 719–22. Correction. *ibid.*; 1143.
8. Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 2000; **34:** 611–15.

Precautions

Clonidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Clonidine causes drowsiness and patients should not drive or operate machinery where loss of attention could be dangerous.

Systemic effects also occur after epidural use and patients should be closely monitored, particularly during the first few days of therapy.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already taking other antihypertensives such as guanethidine or reserpine.

Withdrawal of clonidine therapy should be gradual as stopping suddenly may cause rebound hypertension, sometimes severe. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta blockers can exacerbate the rebound hypertension and if both are being used, clonidine should not be stopped until several days after the withdrawal of the beta blocker. Patients should be warned of the risk of missing a dose or stopping the drug without consulting their doctor and should carry a reserve supply.

Although hypotension may occur during anaesthesia in clonidine-treated patients clonidine should not be withdrawn; indeed, if necessary it should be given intravenously during the operation to avoid the risk of rebound hypertension.

Abuse. Despite its central effects and ability to cause a form of physical dependence, WHO rated the likelihood of abuse as very low.[1] However, clonidine may potentiate the psychoactive effects of morphine and abuse has been reported.[2]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 19/08/08)
2. Sullivan JT, *et al.* Does clonidine alter the abuse potential of morphine? *Clin Pharmacol Ther* 1995; **57:** 163.

Diabetes mellitus. The effects of clonidine on carbohydrate metabolism appear to be variable. Some studies suggest that it does not affect carbohydrate metabolism in diabetic[1] or non-diabetic hypertensive patients,[2] although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values,[3] and increased insulin requirements were noted in a diabetic child treated with clonidine for tics.[4] Conversely, clonidine was associated with severe hypoglycaemia in children when used as a provocative test for growth hormone deficiency (see Growth Retardation, below). However, a study in 10 diabetic hypertensive patients found that although clonidine impaired response to an acute glucose load, it did not significantly affect diabetic control over a 10-week period.[5] Problems may arise when clonidine is given to diabetics with autonomic neuropathy: both severe orthostatic hypotension[6] and paradoxical hypertension[7] have been reported.

For discussion of the use of clonidine in diabetic diarrhoea see below.

1. Nilsson-Ehle P, *et al.* Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. *Acta Med Scand* 1988; **224:** 131–4.
2. Molitch ME, *et al.* Effects of antihypertensive medications on carbohydrate metabolism. *Curr Ther Res* 1986; **39:** 398–407.
3. Okada S, *et al.* Effect of clonidine on insulin secretion: a case report. *J Int Med Res* 1986; **14:** 299–302.
4. Mimouni-Bloch A, Mimouni M. Clonidine-induced hyperglycemia in a young diabetic girl. *Ann Pharmacother* 1993; **27:** 980.
5. Guthrie GP, *et al.* Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 1983; **34:** 713–17.
6. Moffat B. Postural hypotension induced by clonidine in insulin dependent diabetes. *BMJ* 1985; **290:** 822.
7. Young E, *et al.* Paradoxical hypertension from clonidine. *Ann Intern Med* 1984; **101:** 282–3.

ECT. Maximal ECT stimuli were unsuccessful in producing seizures in 4 of 7 treatment attempts in a 66-year-old patient receiving clonidine.[1] It was suggested that clonidine may elevate the seizure threshold.

1. Elliott RL. Case report of a potential interaction between clonidine and electroconvulsive therapy. *Am J Psychiatry* 1983; **140:** 1237–8.

Porphyria. Clonidine hydrochloride has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The hypotensive effect of clonidine may be enhanced by diuretics, other antihypertensives, and drugs that cause hypotension. However, beta blockers may exacerbate rebound hypertension following clonidine withdrawal (see Precautions, above), and tricyclic antidepressants may antagonise the hypotensive effect. The sedative effect of clonidine may be enhanced by CNS depressants.

Antidepressants. Although tricyclic antidepressants commonly cause orthostatic hypotension, they may antagonise the hypotensive effects of clonidine. Blood pressure control was lost in 4 of 5 hypertensive patients taking clonidine and a diuretic when they were given *desipramine* 75 mg daily.[1] Increase in blood pressure generally occurred in the second week of treatment, but 1 patient had a dramatic rise in blood pressure within 24 hours of starting treatment. The mechanism is thought to be due to a central interaction between clonidine and the tricyclic antidepressant, although a peripheral effect cannot be completely excluded.[2] Loss of blood pressure control also occurred in a patient receiving guanfacine, another $alpha_2$-adrenoceptor agonist, when *amitriptyline* was given.[3] The reaction recurred with *imipramine*. However, in another study clonidine was given to 11 patients taking amitriptyline or imipramine, and 10 achieved good blood pressure control, although 4 developed an acute rise in blood pressure when methyldopa or guanethidine was added.[4] *Maprotiline*[5] or *mianserin*[6] do not appear to interact with clonidine.

1. Briant RH, *et al*. Interaction between clonidine and desipramine in man. *BMJ* 1973; **1:** 522–3.
2. van Spanning HW, van Zwieten PA. The interference of tricyclic antidepressants with the central hypotensive effect of clonidine. *Eur J Pharmacol* 1973; **24:** 402–4.
3. Buckley M, Feely J. Antagonism of antihypertensive effect of guanfacine by tricyclic antidepressants. *Lancet* 1991; **337:** 1173–4.
4. Raftos J, *et al*. Clonidine in the treatment of severe hypertension. *Med J Aust* 1973; **1:** 786–93.
5. Gundert-Remy U, *et al*. Lack of interaction between the tetracyclic antidepressant maprotiline and the centrally acting antihypertensive drug clonidine. *Eur J Clin Pharmacol* 1983; **25:** 595–9.
6. Elliott HL, *et al*. Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients. *Eur J Clin Pharmacol* 1983; **24:** 15–19.

Antipsychotics. Acute, severe hypotension occurred in 2 agitated hypertensive patients after use of clonidine with either *chlorpromazine* or *haloperidol*. Both patients had mitral insufficiency.[1]

1. Fruncillo RJ, *et al*. Severe hypotension associated with concurrent clonidine and antipsychotic medication. *Am J Psychiatry* 1985; **142:** 274.

Dopaminergic antiparkinsonian drugs. For a report of the inhibition of the therapeutic effect of *levodopa* by clonidine, see Antihypertensives, p.807.

Immunosuppressants. For a report of clonidine increasing whole blood-*ciclosporin* concentrations, see p.1827.

Pharmacokinetics

Clonidine is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 3 to 5 hours after an oral dose. It is about 20 to 40% protein bound. About 50% of a dose is metabolised in the liver. It is excreted in the urine as unchanged drug and metabolites, 40 to 60% of an oral dose being excreted in 24 hours as unchanged drug; about 20% of a dose is excreted in the faeces, probably via enterohepatic circulation. The elimination half-life has been variously reported to range between 6 and 24 hours, extended to up to 41 hours in patients with renal impairment. Clonidine crosses the placenta and is distributed into breast milk.

It is absorbed through the skin; absorption is reported to be better from the chest or arm than from the thigh. Therapeutic plasma concentrations are achieved 2 or 3 days after application of a transdermal patch and are roughly equivalent to trough concentrations achieved after oral dosage. Therapeutic plasma concentrations are maintained for about 8 hours after removal of the delivery system and then decline slowly over several days.

◊ Reviews.

1. Lowenthal DT, *et al*. Clinical pharmacokinetics of clonidine. *Clin Pharmacokinet* 1988; **14:** 287–310.

Pregnancy. A study in 5 pregnant women treated with clonidine for pre-eclampsia[1] reported an average ratio of cord- to plasma-concentrations of 0.87, indicating placental transfer of clonidine.

1. Boutroy MJ, *et al*. Clonidine placental transfer and neonatal adaptation. *Early Hum Dev* 1988; **17:** 275–86.

Uses and Administration

Clonidine is an imidazoline antihypertensive that appears to act centrally to reduce sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate. The exact mechanism is unclear; clonidine stimulates $alpha_2$ adrenoceptors and central imidazoline receptors, but it is not known which receptors mediate which effects. It also acts peripherally, and this peripheral activity may be responsible for the transient increase in blood pressure seen during rapid intravenous injection as well as contributing to the hypotensive effect during chronic use. Peripheral resistance is reduced during continuous treatment. Cardiovascular reflexes remain intact so orthostatic hypotension is uncommon.

Clonidine is used in the management of hypertension (p.1171), including hypertensive crises, although other drugs with fewer adverse effects are now generally preferred. It may be given with a thiazide diuretic, but use with a beta blocker should be avoided where possible. Clonidine has also been used in the prophylactic treatment of migraine or recurrent vascular headaches (but see below) and in the treatment of menopausal flushing. It is used with opioids in the management of cancer pain and has been tried for various other forms of pain (below). Other uses of clonidine have included the symptomatic treatment of opioid withdrawal (see under Substance Dependence, below), the diagnosis of phaeochromocytoma (below), and as eye drops in the management of glaucoma (p.1873). It has also been tried in Tourette's syndrome (below) and numerous other disorders.

Clonidine is used as the hydrochloride. When given orally, its haemodynamic effects appear in about 30 to 60 minutes, reaching a maximum after 2 to 4 hours and lasting up to 8 hours. Tolerance to clonidine has been reported. Withdrawal of clonidine should be gradual because of the risk of rebound hypertension.

In **hypertension**, the usual initial oral dose of clonidine hydrochloride is 50 to 100 micrograms three times daily (or in the USA, 100 micrograms twice daily), increased every second or third day according to response; the usual maintenance dose is 300 to 1200 micrograms daily but doses of 1800 micrograms or more daily may sometimes be required. Modified-release preparations have been used. Clonidine may also be given by transdermal delivery systems that are applied once a week and deliver 100 to 300 micrograms of clonidine base daily at a constant rate.

Clonidine hydrochloride may be given by slow intravenous injection over 10 to 15 minutes in hypertensive crises, usually in doses of 150 to 300 micrograms. The effect usually appears within 10 minutes, but transient hypertension may precede hypotension if the injection is given too rapidly. The hypotensive effect reaches a maximum about 30 to 60 minutes after injection and the duration is about 3 to 7 hours; up to 750 micrograms may be given intravenously over 24 hours. Although oral dosage does not produce a sufficiently rapid hypotensive effect for use in an emergency situation, a dose of 100 to 200 micrograms initially followed by 50 to 100 micrograms every hour until control of blood pressure is achieved or a maximum of 500 to 800 micrograms is reached, has been recommended for the control of severe hypertension.

In the prophylaxis of **migraine** or recurrent vascular headaches and in the treatment of **menopausal flushing**, an oral dose of 50 micrograms twice daily has been used, increased, if there is no remission after 2 weeks, to 75 micrograms twice daily.

In the management of severe **cancer pain**, clonidine hydrochloride may be given by continuous epidural infusion with an opioid, in an initial dose of 30 micrograms/hour, adjusted according to response.

Anxiety disorders. Clonidine has been tried in various anxiety disorders but evidence of efficacy is limited. A review[1] of its use in panic disorder (p.952) considered that it might be useful as a last-line anxiolytic in patients unresponsive to standard treatment as occasional success had been obtained in a few patients. There have also been isolated reports of small numbers of patients with post-traumatic stress disorder (p.953) who have benefited from clonidine.[2]

For mention of clonidine as an adjuvant to sedative drugs in the intensive care unit see p.957.

1. Puzantian T, Hart LL. Clonidine in panic disorder. *Ann Pharmacother* 1993; **27:** 1351–3.
2. Harmon RJ, Riggs PD. Clonidine for posttraumatic stress disorder in preschool children. *J Am Acad Child Adolesc Psychiatry* 1996; **35:** 1247–9.

Cardiac arrhythmias. Atrial fibrillation (p.1160) is managed by treatment to slow the increased ventricular responses or by cardioversion. Control of ventricular rate is usually achieved with digoxin, beta blockers, or calcium-channel blockers but clonidine, which reduces sympathetic tone and thus reduces heart rate, has also been tried.[1-3]

1. Roth A, *et al*. Clonidine for patients with rapid atrial fibrillation. *Ann Intern Med* 1992; **116:** 388–90.
2. Scardi S, *et al*. Oral clonidine for heart rate control in chronic atrial fibrillation. *Lancet* 1993; **341:** 1211–12.
3. Simpson CS, *et al*. Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation; a prospective, randomized clinical trial. *Am Heart J* 2001; **142:** e3.

Diarrhoea. Some studies have shown that clonidine possesses antidiarrhoeal properties. Clonidine may stimulate $alpha_2$ adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility or rectal sphincter tone.

Most experience with clonidine is in diabetic diarrhoea (see Diabetic Complications, p.433). Clonidine 100 to 600 micrograms by mouth every 12 hours reduced diabetic diarrhoea in 3 patients with type 1 diabetes[1] and good results have also been reported in such patients when transdermal clonidine was used.[2,3] Benefit has also been reported in patients with symptoms of diabetic gastroparesis in addition to diarrhoea.[3,4] However, oral (but perhaps not transdermal) clonidine may worsen orthostatic hypotension in patients with diabetic diarrhoea and this may limit its usefulness.[5] Clonidine has also been tried in patients with high intestinal output after small bowel transplantation[6] or jejunostomy,[7] and in diarrhoea-predominant irritable bowel syndrome[8] or for the gastrointestinal effects of opioid withdrawal.[9]

1. Fedorak RN, *et al*. Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985; **102:** 197–9.
2. Sacerdote A. Topical clonidine for diabetic diarrhea. *Ann Intern Med* 1986; **105:** 139.
3. Sacerdote AS. Topical clonidine and diabetic gastroparesis. *Ann Intern Med* 1990; **112:** 796.
4. Migliore A, *et al*. Diabetic diarrhea and clonidine. *Ann Intern Med* 1988; **109:** 170–1.
5. Ogbonnaya KI, Arem R. Diabetic diarrhea: pathophysiology, diagnosis, and management. *Arch Intern Med* 1990; **150:** 262–7.
6. Rovera G, *et al*. The use of clonidine for the treatment of high intestinal output following small bowel transplantation. *Transplant Proc* 1997; **29:** 1853–4.
7. Buchman AL, *et al*. Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study. *J Parenter Enteral Nutr* 2006; **30:** 487–91.
8. Camilleri M, *et al*. A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003; **1:** 111–21.
9. Ma H, *et al*. The effect of clonidine on gastrointestinal side effects associated with ultra-rapid opioid detoxification. *Anesth Analg* 2003; **96:** 1409–12.

Extrapyramidal disorders. There is limited evidence[1] from small studies that clonidine might reduce symptoms of antipsychotic-induced akathisia and tardive dyskinesia (p.971). However, adverse effects such as sedation and hypotension may limit use.

1. Ahmed I, Takeshita J. Clonidine: a critical review of its role in the treatment of psychiatric disorders. *CNS Drugs* 1996; **6:** 53–70.

Growth retardation. Clonidine has been reported to be a stimulant of growth hormone release, presumably as a result of central alpha-adrenergic stimulation, and has been tried in the diagnosis and management of growth retardation (p.1798). It may be given orally as a provocative test for growth hormone deficiency,[1,2] particularly in children,[3] although some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) to be more useful than provocative tests. A combination of both may be required to confirm diagnosis;[4] guidelines have been suggested.[5] Caution is required when performing the test in children since severe hypoglycaemia has been reported.[6] Clonidine has also been tried in the treatment of growth retardation, both in children with growth hormone deficiency and in short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[7-9]

1. Gil-Ad I, *et al.* Oral clonidine as a growth hormone stimulation test. *Lancet* 1979; **ii:** 278–80.
2. Hoffman WH, *et al.* Relationship of plasma clonidine to growth hormone concentrations in children and adolescents. *J Clin Pharmacol* 1989; **29:** 538–42.
3. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
4. Cianfarani S, *et al.* Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)* 2002; **57:** 161–7.
5. Evans C, Gregory JW. The investigation of short stature: a survey of practice in Wales and suggested practical guidelines. *J Clin Pathol* 2004; **57:** 126–30.
6. Huang C, *et al.* Hypoglycemia associated with clonidine testing for growth hormone deficiency. *J Pediatr* 2001; **139:** 323–4.
7. Pintor C, *et al.* Clonidine treatment for short stature. *Lancet*; 1987; **i:** 1226–30.
8. Pescovitz OH, Tan E. Lack of benefit of clonidine treatment for short stature in a double-blind, placebo-controlled trial. *Lancet* 1988; **ii:** 874–7.
9. Allen DB. Effects of nightly clonidine administration on growth velocity in short children without growth hormone deficiency: a double-blind, placebo-controlled study. *J Pediatr* 1993; **122:** 32–6.

Hyperactivity. Drug treatment of attention deficit hyperactivity disorder (ADHD, p.2148) is usually begun with a central stimulant; clonidine has been tried mainly as an adjunct to stimulant therapy. A meta-analysis[1] of clonidine used to treat this disorder occurring alone or with other conditions, including tic disorders (see Tourette's Syndrome, below), concluded that clonidine may be a useful second-line treatment but is less effective than stimulants and is associated with many adverse effects. There have been reports[2] of sudden death when clonidine has been used with stimulants, but the role of the drugs in these events is unclear. A study[3] in children with both ADHD and Tourette's syndrome found that clonidine used with methylphenidate was more effective than either drug alone, and only 1 child had evidence of adverse cardiac effects. Others have since reported on the efficacy[4] and safety[5] of clonidine in ADHD, alone or with methylphenidate.

Clonidine has also been tried in the management of children with disturbed behaviour (p.954).

1. Connor DF, *et al.* A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 1551–9.
2. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5:** 155–6.
3. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* 2002; **58:** 527–36.
4. Palumbo DR, *et al.* Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 180–8.
5. Daviss WB, *et al.* Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 189–98.

Menopausal disorders. Although HRT is the mainstay of treatment for menopausal disorders (p.2077) clonidine has been of some use in countering vasomotor symptoms in patients who cannot use HRT;[1,2] however, some studies have failed to show a reduction in hot flushes. The adverse effects reported in normotensive women, including orthostatic hypotension, may mean that it is best reserved for women who are also hypertensive.

Clonidine has also been tried[3] for hot flushes in women receiving tamoxifen.

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40:** 220–30.
2. Lucero MA, McCloskey WW. Alternatives to estrogen for the treatment of hot flashes. *Ann Pharmacother* 1997; **31:** 915–17.
3. Pandya KJ, *et al.* Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000; **132:** 788–93.

Migraine. Propranolol is probably the most well established drug for prophylaxis of migraine (p.616). Many other drugs have been used, including clonidine, but a review of clinical studies[1] indicated that it was a poor first choice and seemed unlikely to work even as a last resort. It has been used in patients whose attacks may be precipitated by tyramine-containing foods.

1. Anonymous. Clonidine in migraine prophylaxis—now obsolete. *Drug Ther Bull* 1990; **28:** 79–80.

Orthostatic hypotension. Paradoxically, clonidine has produced beneficial effects in a few patients with orthostatic hypotension (p.1530), including that due to autonomic neuropathy[1] and that possibly due to brimonidine and betaxolol eye drops in a hypertensive woman with glaucoma;[2] clonidine improved both the orthostatic hypotension and the supine hypertension.

1. Acott PD, *et al.* Effectiveness of clonidine in congenital orthostatic hypotension. *J Pediatr* 1990; **116:** 666–7.
2. Brahmbhatt R, *et al.* Normalization of blood pressure in a patient with severe orthostatic hypotension and supine hypertension using clonidine. *Hypertension* 2001; **37:** e24.

Pain. Giving opioids and local anaesthetics by the epidural or intrathecal routes can produce effective analgesia but adverse effects are common. Many other drugs, including clonidine, have been tried by these routes, alone or as adjuncts. Clonidine is thought to produce analgesia by a direct action on alpha$_2$ adrenoceptors in the spinal cord. It has been used in various types of pain, such as postoperative pain (p.4), labour pain (p.7), and the pain associated with cancer (p.5), particularly neuropathic pain (p.8). It has been used alone but is more usually given with local anaesthetics and/or opioids; it has been given by various routes including epidural, intrathecal, intravenous, intramuscular, oral, and transdermal use. An early meta-analysis[1] of postoperative epidural use of clonidine was unable to reach a conclusion owing to the large number of variables. Two subsequent systematic reviews considered that addition of clonidine to intermediate-acting local anaesthetics improved their activity in certain peripheral nerve blocks,[2] and that adding clonidine to intrathecal local anaesthetics reduced intra-operative pain, although it increased the risk of hypotension.[3] However, the role and appropriate dosage of clonidine in local anaesthesia remained unclear.[2,3] For further discussion of pain and its management, see p.2. See also Premedication, below.

1. Armand S, *et al.* Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task. *Br J Anaesth* 1998; **81:** 126–34.
2. McCartney CJL, *et al.* Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* 2007; **32:** 330–8.
3. Elia N, *et al.* Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* 2008; **33:** 159–67.

Phaeochromocytoma. Clonidine acts centrally to suppress catecholamine release and may be used[1] in the diagnosis of phaeochromocytoma (p.1179). Experience gained with the clonidine suppression test and a review of published studies indicated that it is of value in selected patients with moderately elevated plasma and/or urinary catecholamine concentrations.[2]

1. Bravo EL, *et al.* Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981; **305:** 623–6.
2. Lenz T, *et al.* Clonidine suppression test revisited. *Blood Pressure* 1998; **7:** 153–9.

Premedication. Clonidine has been given pre-operatively for its sedative, anxiolytic, and analgesic effects (see also Pain, above), and to provide haemodynamic stability and reduce anaesthetic requirements; it is often given orally, although other routes such as intranasal and intravenous have also been tried. It has often been tried in children,[1] in whom pre-operative use has also been reported to reduce postoperative vomiting[2] (similar results have been reported in adult women[3]). Clonidine may attenuate the perioperative stress response and has been shown to reduce perioperative oxygen consumption, which is a marker of sympathetic activation.[4] It may also reduce the risk of perioperative myocardial ischaemia.[5]

1. Bergendahl H, *et al.* Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. *Acta Anaesthesiol Scand* 2006; **50:** 135–43.
2. Mikawa K, *et al.* Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42:** 977–81.
3. Oddby-Muhrbeck E, *et al.* Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. *Anesthesiology* 2002; **96:** 1109–14.
4. Taittonen MT, *et al.* Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; **78:** 400–406.
5. Nishina K, *et al.* Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology* 2002; **96:** 323–9.

Restless legs syndrome. Numerous drugs have been tried for the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p.958). Symptomatic improvement has been reported with clonidine in a number of case studies[1,2] and small controlled trials,[3] but adverse effects may limit its use.

1. Handwerker JV, Palmer RF. Clonidine in the treatment of "restless leg" syndrome. *N Engl J Med* 1985; **313:** 1228–9.
2. Zoe A, *et al.* High-dose clonidine in a case of restless legs syndrome. *Ann Pharmacother* 1994; **28:** 878–81.
3. Wagner ML, *et al.* Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996; **19:** 52–8.

Shivering. Numerous drugs, including clonidine, have been tried for the treatment of postoperative shivering (p.1779). Clonidine's central and peripheral effects could both account for its antishivering activity, but some have suggested that it acts by resetting the central threshold temperature for shivering. Several studies[1-3] have suggested that clonidine is effective for the treatment of postoperative shivering. Typical doses of 75 to 150 micrograms intravenously have been used. Clonidine given intra-operatively,[4-7] including to neurosurgical patients after mild hypothermia,[8] has also been reported to reduce the incidence of postoperative shivering. However, one study[9] has found nefopam to be superior to clonidine for prevention of postoperative shivering.

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Capogna G, Celleno D. IV clonidine for post-extradural shivering in parturients: a preliminary study. *Br J Anaesth* 1993; **71:** 294–5.
3. Schwarzkopf KRG, *et al.* A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. *Anesth Analg* 2001; **92:** 257–60.
4. Steinfath M, *et al.* Clonidine administered intraoperatively prevents postoperative shivering. *Br J Clin Pharmacol* 1995; **39:** 580P–581P.
5. Vanderstappen I, *et al.* The effect of prophylactic clonidine on postoperative shivering: a large prospective double-blind study. *Anaesthesia* 1996; **51:** 351–5.
6. Sia S. I.v. clonidine prevents post-extradural shivering. *Br J Anaesth* 1998; **81:** 145–6.
7. Piper SN, *et al.* A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. *Anesth Analg* 2000; **90:** 954–7.
8. Stapelfeldt C, *et al.* Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* 2005; **100:** 226–32.
9. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.

Spasticity. Clonidine, given alone or as an adjunct to baclofen, has been tried in patients with various forms of spasticity (p.1887) including those refractory to baclofen.[1-5]

1. Nance PW, *et al.* Clonidine in spinal cord injury. *Can Med Assoc J* 1985; **133:** 41–2.
2. Donovan WH, *et al.* Clonidine effect on spasticity: a clinical trial. *Arch Phys Med Rehabil* 1988; **69:** 193–4.
3. Sandford PR, *et al.* Clonidine in the treatment of brainstem spasticity: case report. *Am J Phys Med Rehabil* 1992; **71:** 301–3.
4. Middleton JW, *et al.* Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. *Arch Phys Med Rehabil* 1996; **77:** 824–6.
5. Lubsch L, *et al.* Oral baclofen and clonidine for treatment of spasticity in children. *J Child Neurol* 2006; **21:** 1090–2.

Substance dependence. *ALCOHOL.* Although drug treatment of alcohol withdrawal (p.1626) is usually with a benzodiazepine, clonidine has shown benefit[1] in mild to moderate withdrawal, although it has no effect on convulsions or delirium tremens and should not be used as sole therapy. It may be considered with a benzodiazepine when opioid withdrawal is also taking place.

1. Mayo-Smith MF, *et al.* Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278:** 144–51.

OPIOID ANALGESICS. Clonidine has been reported to be useful in controlling withdrawal symptoms after abrupt withdrawal of opioids (p.101). However, a systematic review[1] of the use of alpha$_2$-adrenoceptor agonists, including clonidine, concluded that, for gradual withdrawal, they were no more effective than reducing doses of methadone over a period of around 10 days, and patients experienced more adverse effects and stopped treatment sooner with clonidine. Clonidine is usually given orally in three or four divided doses to a maximum of 1 mg daily.

Clonidine has also been used with naltrexone to shorten the withdrawal syndrome, allowing withdrawal to be achieved within 6 days.[2] Subsequent modification to the regimen allowed 38 of 40 patients addicted to methadone to withdraw completely in 4 to 5 days.[3] Patients required a mean of 2.3 mg of clonidine on the first day which reduced, but did not abolish, symptoms. A further modification was reported allowing opioid withdrawal with minimal drop-out over 2 to 3 days.[4]

Clonidine has also been used in the management of neonatal abstinence syndrome (p.102) in infants born to opioid-addicted mothers maintained on methadone.[5,6] Benefit occurred in 6 of 7 such infants given an initial clonidine dose of 0.5 to 1 microgram/kg orally, increased over 1 to 2 days to 3 to 5 micrograms/kg daily in divided doses. Total length of treatment ranged from 6 to 17 days. The infant who failed to respond was born to a mother also given haloperidol, desipramine, and theophylline.[6] However, a systematic review[7] found insufficient evidence to support the use of clonidine in the management of neonatal abstinence syndrome.

1. Gowing L, *et al.* Alpha2 adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 26/09/05).
2. Charney DS, *et al.* Clonidine and naltrexone: a safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. *Arch Gen Psychiatry* 1982; **39:** 1327–32.
3. Charney DS, *et al.* The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986; **143:** 831–7.
4. Brewer C, *et al.* Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. *Br J Psychiatry* 1988; **153:** 340–3.
5. Hoder EL, *et al.* Clonidine in neonatal narcotic-abstinence syndrome. *N Engl J Med* 1981; **305:** 1284.
6. Hoder EL, *et al.* Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res* 1984; **13:** 243–51.
7. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 03/03/06).

SMOKING. Nicotine dependence may be managed using behavioural or psychological counselling. In addition, nicotine replacement therapy (see Smoking Cessation, p.2354) can help alleviate withdrawal symptoms. A number of other drugs, including clonidine, have also been tried. A systematic review[1] found clonidine given in doses of 200 to 400 micrograms daily orally or the equivalent transdermally to be effective; however adverse effects limit its usefulness and clonidine should be reserved for second-line treatment under close medical supervision in those who experience severe agitation and anxiety when stopping smoking.

Some individual studies have found clonidine to be more effective in women although the authors of the systematic review[1] recommended that these results be interpreted cautiously since some studies also found that women were less successful in giving up smoking unaided than men; treatment with clonidine, however, resulted in similar success rates in both men and women.

1. Gourlay SG, *et al.* Clonidine for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 26/09/05).

Tourette's syndrome. Clonidine is one of many drugs that have been tried in the management of Tourette's syndrome (see Tics, p.954).

Disturbance of monoamine metabolism (including dopamine, noradrenaline, and serotonin) has been implicated in Tourette's syndrome. Clonidine is thought to reduce central noradrenergic activity and may also affect other neurochemical systems, and these properties may account for its beneficial effects in this disorder. Studies of clonidine in Tourette's syndrome have produced mixed results,[1-5] although this may reflect the difficulty in study design for a disease that can vary considerably in severity and presence of comorbid conditions and whose symptoms wax and wane. A retrospective study[6] in juvenile patients given clonidine suggested that those showing improvement in the attention deficit hyperactivity disorder associated with Tourette's syndrome had previously had a longer duration of vocal tics; older children had a better overall response than younger children, who tended to suffer more from clonidine-induced drowsiness. However, no predictors of response could be identified. Nevertheless, clonidine is increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects when compared to the commonly used antipsychotics pimozide and haloperidol, although exacerbation of tics and a marked sensation of heat have been reported[7] in one patient. Clonidine has also been reported to successfully control symptoms in some children with Tourette's syndrome unresponsive to haloperidol.[1]

Clonidine has also been used with stimulants in children with Tourette's syndrome and attention deficit hyperactivity disorder, although there have been concerns about the toxicity of such combinations (see Hyperactivity, above).

1. Cohen DJ, *et al.* Clonidine in Tourette's syndrome. *Lancet* 1979; **ii:** 551–3.
2. Shapiro AK, *et al.* Treatment of Gilles de la Tourette's syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983; **40:** 1235–40.
3. Leckman JF, *et al.* Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. *Neurology* 1985; **35:** 343–51.
4. Goetz CG, *et al.* Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. *Ann Neurol* 1987; **21:** 307–10.
5. Leckman JF, *et al.* Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991; **48:** 324–8.
6. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. *J Child Neurol* 1996; **11:** 93–7.
7. Kessler AR. Clonidine treatment increases tics in patients with Tourette syndrome: case report. *J Child Neurol* 2001; **16:** 380–1.

Preparations

BP 2008: Clonidine Injection; Clonidine Tablets;
USP 31: Clonidine Hydrochloride and Chlorthalidone Tablets; Clonidine Hydrochloride Tablets; Clonidine Transdermal System.

Proprietary Preparations (details are given in Part 3)
Arg.: Clonidural; ***Austral.:*** Catapres; ***Austria:*** Catapresan; Isoglaucon; ***Belg.:*** Catapressan; Dixarit; ***Braz.:*** Atensina; Clonesina†; Neo Clodil†; ***Canad.:*** Catapres; Dixarit; ***Chile:*** Catapresan; ***Cz.:*** Aruclonin; Catapresan; ***Denm.:*** Catapresan; ***Fin.:*** Catapresan; ***Fr.:*** Catapressan; ***Ger.:*** Aruclonin†; Catapresan; Clonid-Ophtal; Clonistada; Dispaclonidin; Dixarit†; Haemiton†; Isoglaucon; Mirfat†; Paracefan; ***Gr.:*** Catapresan; ***Hong Kong:*** Catapres†; Dixarit; ***Hung.:*** Aruclonin; ***India:*** Arkamin; Catapres; ***Indon.:*** Catapres; ***Irl.:*** Catapres; Dixarit; ***Israel:*** Clonnirit; Normopresan; ***Ital.:*** Adesipress-TTS†; Catapresan; Isoglaucon; ***Jpn:*** Catapres; ***Malaysia:*** Dixarit†; ***Mex.:*** Catapresan; Epiclodina; ***Neth.:*** Catapresan; Dixarit; ***Norw.:*** Catapresan; ***NZ:*** Catapres; Dixarit; ***Philipp.:*** Catapres; ***Pol.:*** Iporel; ***Port.:*** Catapresan; Edolglau; ***Rus.:*** Haemiton (Гемитон); ***S.Afr.:*** Dixarit; Menograine; ***Singapore:*** Dixarit†; ***Spain:*** Catapresan; Isoglaucon; ***Swed.:*** Catapresan; ***Switz.:*** Catapresan; ***Thai.:*** Catapres; Hypodine; ***UK:*** Catapres; Dixarit; ***USA:*** Catapres; Duraclon; ***Venez.:*** Catapresan; Clonipres†; Lowpres; Naclodin; Velaril.

Multi-ingredient: ***Arg.:*** Bemplas; Pertenso; ***Ger.:*** Combipresan†; Haemiton compositum†; ***India:*** Arkamin-H; Catapres Diu; ***USA:*** Clorpres; Combipres†.

Clopamide *(BAN, USAN, rINN)* ⊗

Clopamida; Clopamidum; DT-327; Klopamid; Klopamidi. 4-Chloro-*N*-(2,6-dimethylpiperidino)-3-sulphamoylbenzamide; *cis*-3-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethyl-1-piperidinyl)benzamide.

Клопамид

$C_{14}H_{20}ClN_3O_3S = 345.8$.

CAS — 636-54-4.

ATC — C03BA03.

ATC Vet — QC03BA03.

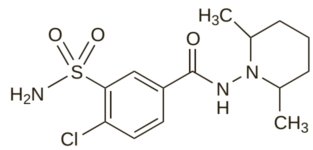

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clopamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in anhydrous alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Clopamide is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307) even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis starts in 1 to 2 hours after an oral dose, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours.

In the treatment of oedema the usual oral dose is 10 to 20 mg daily or on alternate days. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Adurix; ***Ger.:*** Brinaldix†; ***Hung.:*** Brinaldix; ***India:*** Brinaldix.

Multi-ingredient: ***Austria:*** Brinerdin; ***Belg.:*** Viskaldix; ***Braz.:*** Viskaldix; ***Chile:*** Viskaldix; ***Cz.:*** Crystepin; ***Fr.:*** Viskaldix; ***Ger.:*** Briserin N; Viskaldix; ***Gr.:*** Viskaldix; ***Hung.:*** Viskaldix; ***Irl.:*** Viskaldix; ***Ital.:*** Brinerdina; ***Malaysia:*** Viskaldix; ***Neth.:*** Viskaldix; ***Philipp.:*** Viskaldix; ***Pol.:*** Normatens; ***Port.:*** Brinerdine†; ***Rus.:*** Crystepin (Кристепин); Viskaldix (Вискалдикс); ***S.Afr.:*** Brinerdin; ***Spain:*** Brinerdina†; ***Switz.:*** Brinerdine; Viskaldix; ***Thai.:*** Bedin; Brinerdin; Hyperdine†; Viskaldix†; ***UK:*** Viskaldix; ***Venez.:*** Viskaldix†.

Clopidogrel Bisulfate *(USAN, rINNM)*

Bisulfato de clopidogrel; Clopidogrel, Bisulfate de; Clopidogrel Bisulphate *(BANM)*; Clopidogrel Hydrogen Sulphate; Clopidogreli Bisulfas; PCR-4099 (clopidogrel); SR-25990C. Methyl (*S*)-2-chlorophenyl(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)acetate bisulphate; Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno-[3,2-*c*]pyridine-5(4*H*)-acetate sulphate.

Клопидогрела Бисульфат

$C_{16}H_{16}ClNO_2S,H_2SO_4 = 419.9$.

CAS — 113665-84-2 (clopidogrel); 94188-84-8 (clopidogrel); 120202-66-6 (clopidogrel bisulfate).

ATC — B01AC04.

ATC Vet — QB01AC04.

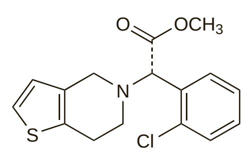

(clopidogrel)

Pharmacopoeias. In *US.*

USP 31 (Clopidogrel Bisulfate). A white to off-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in ether.

Adverse Effects and Precautions

As for Ticlopidine, p.1411.

The incidence of adverse effects, particularly blood dyscrasias, is lower with clopidogrel, although fatalities have been reported (see Effects on the Blood, p.1411). Routine blood counts are not necessary, although they should be performed promptly when clinical signs suggest blood dyscrasias. Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, erythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia.

Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery.

Effects on the blood. For reports of blood dyscrasias associated with clopidogrel therapy see under Adverse Effects of Ticlopidine, p.1411.

Effects on taste. Loss of taste occurred in 2 patients 6 to 8 weeks after starting treatment with clopidogrel, but recovered fully when clopidogrel was withdrawn.[1] Rechallenge in 1 of the patients led to recurrence of the taste loss, which persisted when treatment was stopped.

1. Golka K, *et al.* Reversible ageusia as an effect of clopidogrel treatment. *Lancet* 2000; **355:** 465–6.

Hypersensitivity. Clopidogrel has been associated with hypersensitivity reactions including angioedema.[1] There have also been reports[2-5] of a hypersensitivity syndrome comprising fever, rash, and varying additional symptoms.

1. Fischer TC, *et al.* Clopidogrel-associated angioedema. *Am J Med* 2003; **114:** 77–8.
2. Sarrot-Reynauld F, *et al.* Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001; **135:** 305–6.
3. Phillips EJ, *et al.* Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003; **56:** 583.
4. Wolf I, *et al.* Clopidogrel-induced systemic inflammatory response syndrome. *Mayo Clin Proc* 2003; **78:** 618–20.
5. Doogue MP, *et al.* Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; **80:** 1368–70.

Resistance. Results from platelet aggregation studies suggest that there is considerable variation in response to clopidogrel, although the clinical relevance of a low response (clopidogrel resistance) is unclear.[1,2] There is some evidence that the risk of cardiovascular events is higher in patients with clopidogrel resistance,[3] but this is not established. Factors that may contribute to clopidogrel resistance include drug interactions and genetic variation in platelet sensitivity or clopidogrel metabolism.[1,2] Patients with diabetes mellitus also appear to have a lower response.[4]

1. Nguyen TA, *et al.* Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005; **45:** 1157–64.
2. Angiolillo DJ, *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; **49:** 1505–16.
3. Geisler T, *et al.* Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27:** 2420–5.
4. Geisler T, *et al.* Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007; **30:** 372–4.

Interactions

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Clopidogrel may inhibit the cytochrome P450 isoenzyme CYP2C9 and interactions with drugs metabolised by this isoenzyme are theoretically possible; it may also inhibit CYP2B6 (see Bupropion, below).

Antifungals. A study[1] in healthy subjects found that *ketoconazole* decreased the plasma concentration of the active metabolite of clopidogrel; platelet inhibitory action was also reduced.

1. Farid NA, *et al.* Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; **81:** 735–41.

Bupropion. A study[1] in healthy subjects found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

1. Turpeinen M, *et al.* Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; **77:** 553–9.

Ciclosporin. For reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin, see Statins, below.

Statins. There have been reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin (atorvastatin[1,2], lovastatin[3], or simvastatin[3]). Rhabdomyolysis is a recognised adverse effect when ciclosporin and statins are used together (see Immunosuppressants under Interactions of Simvastatin, p.1393), but the patients in these reports had previously received the combination without incident and developed rhabdomyolysis 1 to 3 weeks after clopidogrel was started. It has been suggested[2] that the mechanism is a three way interaction involving competition for binding sites on the cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Although it has been suggested that statins may decrease the antiplatelet effect of clopidogrel, evidence for such an interaction is conflicting and the clinical relevance has not been established.[4]

1. Anon. Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis. *Can Adverse React News* 2005; **15** (Apr): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2_e.pdf (accessed 01/09/05)
2. Burton JR, *et al.* Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. *Ann Pharmacother* 2007; **41:** 133–7.
3. Uber PA, *et al.* Clopidogrel and rhabdomyolysis after heart transplantation. *J Heart Lung Transplant* 2003; **22:** 107–8.
4. Tafreshi MJ, *et al.* Combination of clopidogrel and statins: a hypothetical interaction or therapeutic dilemma? *Pharmacotherapy* 2006; **26:** 388–94.

Pharmacokinetics

Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolised in the liver, mainly to the inactive carboxylic acid derivative; metabolism is mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, and to a lesser extent by CYP1A2, CYP1A1, and CYP2C19. The active metabolite appears to be a thiol derivative; it has been identified *in vitro* but appears to be too unstable to be isolated from plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

Uses and Administration

Clopidogrel is a thienopyridine antiplatelet drug used in thromboembolic disorders. It is an analogue of ticlopidine (p.1411) and acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It is given prophylactically as an alternative to aspirin in patients with atherosclerosis who are at risk of thromboembolic disorders such as myocardial infarction (p.1175), peripheral arterial disease (p.1178), and stroke (p.1185). Clopidogrel is also used with aspirin in acute coronary syndromes, including acute myocardial infarction and unstable angina (p.1157), and in coronary stenting (see Reperfusion and Revascularisation Procedures, below).

Clopidogrel is given orally as the bisulfate, but doses are expressed in terms of the base; 97.86 mg of clopidogrel bisulfate is equivalent to 75 mg of base.

For the **prophylaxis of thromboembolic events**, the usual dose of clopidogrel is 75 mg once daily.

In the management of **acute ST-elevation myocardial infarction**, clopidogrel is used with aspirin as an adjunct in medically-treated patients. It is given in a dose of 75 mg once daily; patients under 75 years of age may be given a loading dose of 300 mg. Treatment should be continued for at least 4 weeks.

In the management of **unstable angina** and **non-Q-wave myocardial infarction**, clopidogrel is used with aspirin as an adjunct to either medical or interventional treatment, including coronary stenting. A single loading dose of 300 mg is given, followed by 75 mg once daily.

◊ Reviews.

1. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.
2. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* 2000; **60:** 347–77.
3. Solet DJ, *et al.* The role of adenosine 5′-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001; **111:** 45–53.
4. Zambahari R, *et al.* Clinical use of clopidogrel in acute coronary syndrome. *Int J Clin Pract* 2007; **61:** 473–81.
5. Eshaghian S, *et al.* Role of clopidogrel in managing atherothrombotic cardiovascular disease. *Ann Intern Med* 2007; **146:** 434–41.
6. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007; **67:** 613–46.

Administration in children. Clopidogrel is not licensed for paediatric use in either the UK or the USA, although it has been given to small numbers of patients.

A retrospective study[1] of the use of clopidogrel in 15 children aged from 6 weeks to 16 years, 14 of whom had congenital heart disease, found that it was safe and effective; nearly all of the children were also taking aspirin and/or anticoagulants, and severe bleeding was reported in only 1 of them. The usual dose ranged from 1 to 3 mg/kg once daily, although a dose of 6 mg/kg daily was tolerated when given in error to 1 patient. A cohort study[2] of the use of clopidogrel alone or with aspirin in 17 children aged 1.5 to 17 years with arterial ischaemic stroke found that a daily dose of 0.5 to 2.4 mg/kg (target dose 1 mg/kg) was well tolerated, although subdural haematomas developed in 2 patients who were also taking aspirin.

1. Finkelstein Y, *et al.* Clopidogrel use in children. *J Pediatr* 2005; **147:** 657–61.
2. Soman T, *et al.* The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke* 2006; **37:** 1120–2.

Atherosclerotic disorders. The use of aspirin to reduce the risk of cardiovascular events in patients with atherosclerotic vascular disorders is well established. Clopidogrel may have a role as an alternative. The CAPRIE trial[1] compared clopidogrel with aspirin in 19 185 patients at risk of ischaemic events, and found that clopidogrel reduced the risk of ischaemic stroke, myocardial infarction, or death from vascular causes to a greater extent than aspirin, although the absolute difference was small.

In acute coronary syndromes, clopidogrel may provide benefit when used in addition to aspirin. In patients with *unstable angina or non-ST elevation myocardial infarction*, the CURE trial[2] found that the risk of cardiovascular death, myocardial infarction, or stroke was lower in patients treated with clopidogrel and aspirin, compared with those receiving aspirin alone. Clopidogrel was given in a loading dose of 300 mg, started within 24 hours of the onset of symptoms, followed by 75 mg daily for 3 to 12 months.

Similar results have been reported in patients with acute *ST-elevation myocardial infarction*. Clopidogrel given with aspirin and thrombolytic therapy improved the patency of the affected artery and reduced the incidence of ischaemic complications at 30 days,[3] while a further study[4] found that addition of clopidogrel to aspirin and standard therapy (including thrombolytics in over half of the patients) also reduced early mortality.

Use of clopidogrel with aspirin has also been studied in *ischaemic stroke* but any benefit appears to be outweighed by an increased risk of bleeding. In the MATCH study,[5] adding aspirin to clopidogrel did not reduce the incidence of vascular events compared with clopidogrel alone, but the risk of major or life-threatening bleeding was increased. Similarly, in the CHARISMA study in patients with *stable atherosclerotic disease or multiple risk factors*, addition of clopidogrel to aspirin had no significant effect on the incidence of cardiovascular events, but the risk of moderate to severe bleeding was increased.[6]

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348:** 1329–39.
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502. Correction. *ibid.*; 1716.
3. Sabatine MS, *et al.* for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.
4. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1607–21.
5. Diener H-C, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364:** 331–7.
6. Bhatt DL, *et al.* CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354:** 1706–17.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention (PCI) has an established role in the management of both acute and stable coronary disease (see p.1181). Adjunctive antiplatelet therapy is given to reduce the risk of thrombosis, both during and after the procedure; a regimen of clopidogrel with aspirin improves outcomes[1] and is now generally recommended,[2,3] particularly if coronary stents are used. Although ticlopidine with aspirin was used initially in patients receiving stents, clopidogrel appears to be as effective as ticlopidine[4,5] but has a lower risk of haematological toxicity and is now generally preferred. A randomised study (CLASSICS)[6] found that, in patients given long-term aspirin, clopidogrel in a dose of 75 mg daily for 28 days, with or without a 300-mg loading dose, was as effective as ticlopidine; it was also better tolerated.

Pretreatment with clopidogrel appears to be most effective, but the increased bleeding risk may be of concern if emergency surgery is required. Use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention, and there is some evidence that it needs to be given at least 15 hours before.[7] A higher dose of 600 mg may be effective if given at least 2 hours before PCI,[8,9] and has been recommended in patients undergoing PCI for non-ST elevation acute coronary syndromes.[2]

The duration of combination therapy depends on the clinical situation. For patients given bare-metal stents, clopidogrel in a dose of 75 mg daily is usually given with aspirin for 2 to 4 weeks, and aspirin is then continued indefinitely. In patients with drug-eluting stents, the risk of occlusion persists for longer and combination therapy is usually recommended for at least 3 to 6 months; there is some evidence[10-12] that extending the duration further may provide additional benefit, and treatment for 12 months or longer has been suggested.[3] Prolonged combination therapy may also be of benefit in patients undergoing PCI for unstable angina, whether or not they receive stents.[1]

1. Mehta SR, *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358:** 527–33.
2. Harrington RA, *et al.* Antithrombotic therapy for non-ST-elevation acute coronary syndromes: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 670S–707S.
3. Becker RC, *et al.* The primary and secondary prevention of coronary artery disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 776S–814S.
4. Mishkel GJ, *et al.*. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999; **34:** 1884–90.
5. Berger PB. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999; **34:** 1891–4.
6. Bertrand ME, *et al.* Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; **102:** 624–9.
7. Steinhubl SR, *et al.* The CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *J Am Coll Cardiol* 2006; **47:** 939–43.
8. Longstreth KL, Wertz JR. High-dose clopidogrel loading in percutaneous coronary intervention. *Ann Pharmacother* 2005; **39:** 918–22.
9. Hochholzer W, *et al.* Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005; **111:** 2560–4.
10. Zimarino M, *et al.* Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* 2005; **65:** 725–32.
11. Steinhubl SR, *et al.* Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288:** 2411–20. Correction. *ibid.* 2003; **289:** 987.
12. Eisenstein EL, *et al.* Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007; **297:** 159–68.

Preparations

USP 31: Clopidogrel Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiplaq; Clodian; Clodrel†; Iscover; Nabratin; Nefazan; Plavix; Pleyar; Troken; ***Austral.:*** Iscover; Plavix; ***Austria:*** Plavix; ***Belg.:*** Plavix; ***Braz.:*** Iscover; Plavix; ***Canad.:*** Plavix; ***Chile:*** Artevil; Iskimil; Plavix; ***Cz.:*** Iscover; Plavix; ***Denm.:*** Plavix; ***Fin.:*** Plavix; ***Fr.:*** Plavix; ***Ger.:*** Iscover; Plavix; ***Gr.:*** Iscover; Plavix; ***Hong Kong:*** Plavix; ***Hung.:*** Plavix; ***India:*** Cloflow; Clopact; Clopivas; Clopod; Noklot; Plavix; ***Indon.:*** Plavix; ***Irl.:*** Plavix; ***Israel:*** Plavix; ***Ital.:*** Iscover†; Plavix; ***Malaysia:*** Plavix; ***Mex.:*** Iscover; Plavix; ***Neth.:*** Iscover; Plavix; ***Norw.:*** Plavix; ***NZ:*** Plavix; ***Philipp.:*** Plavix; ***Pol.:*** Areplex; Plavix; Zyllt; ***Port.:*** Iscover†; Plavix; ***Rus.:*** Plavix (Плавикс); Zillt (Зилт); ***S.Afr.:*** Plavix; ***Singapore:*** Plavix; ***Spain:*** Iscover; Plavix; ***Swed.:*** Plavix; ***Switz.:*** Plavix; ***Thai.:*** Plavix; ***Turk.:*** Plavix; ***UK:*** Plavix; ***USA:*** Plavix; ***Venez.:*** Plavix.

Multi-ingredient: ***Arg.:*** Nefazan Compuesto; ***India:*** Cloflow Plus†; Clopact A; Clopivas AP; Clopod-A.

Cloricromen *(rINN)*

Cloricromène; Cloricromeno; Cloricromenum. Ethyl ({8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl}oxy)acetate.

Клорикромен

$C_{20}H_{26}ClNO_5$ = 395.9.
CAS — 68206-94-0.
ATC — B01AC02.
ATC Vet — QB01AC02.

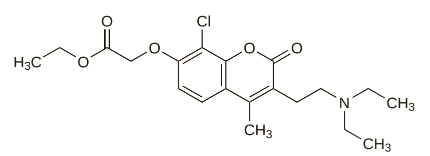

Profile

Cloricromen is an antiplatelet drug with vasodilating activity and is used in thromboembolic disorders (p.1187). It is given as the hydrochloride in arterial vascular disorders where there is a risk of thrombosis. It may be given orally in a dose of 100 mg two or three times daily or intravenously in a dose of 30 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Proendotel.

Cloridarol *(rINN)*

Clobenfurol; Cloridarolum. α-(Benzofuran-2-yl)-α-(4-chlorophenyl)methanol.

Клоридарол

$C_{15}H_{11}ClO_2$ = 258.7.
CAS — 3611-72-1.
ATC — C01DX15.
ATC Vet — QC01DX15.

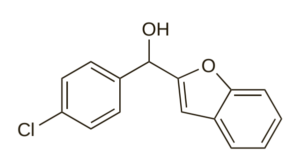

Profile

Cloridarol is a vasodilator that has been used in ischaemic heart disease.

Colesevelam Hydrochloride

(USAN, rINNM)

Colésévélam, Chlorhydrate de; Colesevelami Hydrochloridum; GT31-104HB; Hidrocloruro de colesevelam. Allylamine polymer with epichlorohydrin (1-chloro-2,3-epoxypropane), [6-(allylamino)hexyl]trimethylammonium chloride and *N*-allyldecylamine, hydrochloride.

Колесевелама Гидрохлорид

$(C_3H_7N)_m(C_3H_5ClO)_n(C_{12}H_{27}ClN_2)_o(C_{13}H_{27}N)_p$,xHCl.

CAS — 182815-44-7.

ATC — C10AC04.

ATC Vet — QC10AC04.

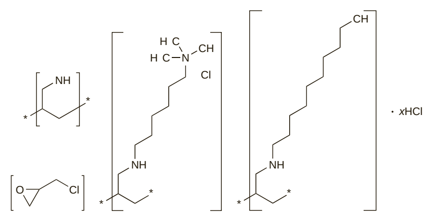

Adverse Effects and Precautions

As for Colestyramine, p.1252.

Interactions

Colesevelam, like colestyramine (see p.1253), has the potential to interfere with the absorption of other drugs; those with a narrow therapeutic range should be given at least 1 hour before or 4 hours after colesevelam unless there is known to be no interaction.

◊ References.

1. Donovan JM, *et al.* Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 2000; **14:** 681–90.

Uses and Administration

Colesevelam hydrochloride is a nonabsorbable hydrogel. It binds bile acids in the intestine and has actions similar to those of colestyramine (p.1253). It is used for the treatment of hypercholesterolaemia (p.1169), particularly type IIa hyperlipoproteinaemia, either alone or with a statin. It may also be used as an adjunct to improve glycaemic control in type 2 diabetes mellitus (p.431). The usual oral dose is 3.75 g daily, as a single dose or in two divided doses, with meals. When used as monotherapy for hypercholesterolaemia, the dose may be increased to 4.375 g daily if required. When used with a statin, the dose is 2.5 to 3.75 g daily.

◊ References.

1. Davidson MH, *et al.* Colesevelam hydrochloride (Cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999; **159:** 1893–1900.
2. Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother* 2001; **35:** 898–907.
3. Steinmetz KL. Colesevelam hydrochloride. *Am J Health-Syst Pharm* 2002; **59:** 932–9.
4. Zieve FJ, *et al.* Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *Clin Ther* 2007; **29:** 74–83.
5. Bays H, Jones PH. Colesevelam hydrochloride: reducing atherosclerotic coronary heart disease risk factors. *Vasc Health Risk Manag* 2007; **3:** 733–42.
6. Florentin M, *et al.* Colesevelam hydrochloride in clinical practice: a new approach in the treatment of hypercholesterolaemia. *Curr Med Res Opin* 2008; **24:** 995–1009.
7. Goldberg RB, *et al.* Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med* 2008; **168:** 1531–40.
8. Fonseca VA, *et al.* Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 2008; **31:** 1479–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Cholestagel; ***Neth.:*** Cholestagel; ***Port.:*** Cholestagel; ***UK:*** Cholestagel; ***USA:*** Welchol.

Colestilan *(rINN)*

Colestilan Chloride *(USAN)*; Colestilanum; Colestimide; MCI-196. 2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane.

Колестилан

$(C_4H_6N_2.C_3H_5ClO)_n$.

CAS — 95522-45-5.

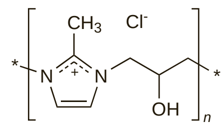

Profile

Colestilan, a bile-acid binding resin, is a lipid regulating drug with similar properties to colestyramine (p.1252). It is used to reduce cholesterol in the management of hyperlipidaemias (p.1169) and is given orally in a usual dose of 1.5 g twice daily. It is also under investigation in diabetes mellitus and as a phosphate binder in haemodialysis patients.

◊ References.

1. Kurihara S, *et al.* Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. *Nephrol Dial Transplant* 2005; **20:** 424–30.
2. Yamakawa T, *et al.* Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. *Endocr J* 2007; **54:** 53–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Cholebine.

Colestipol Hydrochloride

(BANM, USAN, rINNM)

Colestipol, chlorhydrate de; Colestipoli hydrochloridum; Hidrocloruro de colestipol; Kolestipol Hidroklorür; U-26597A.

Колестипола Гидрохлорид

CAS — 26658-42-4 (colestipol); 50925-79-6 (colestipol); 37296-80-3 (colestipol hydrochloride).

ATC — C10AC02.

ATC Vet — QC10AC02.

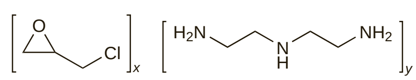

(colestipol)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Colestipol Hydrochloride). A copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.7 mEq of sodium cholate, calculated as the cholate binding capacity and with reference to the dried substance. Yellow to orange hygroscopic beads. Swells but does not dissolve in water and in dilute solutions of acids or alkalis. Practically insoluble in alcohol and in dichloromethane. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

USP 31 (Colestipol Hydrochloride). A basic anion-exchange resin. It is the hydrochloride of a copolymer of diethylenetriamine and epichlorohydrin (1-chloro-2,3-epoxypropane). Each g binds not less than 1.1 mEq and not more than 1.6 mEq of sodium cholate, calculated as cholate binding capacity. Yellow to orange beads. Swells but does not dissolve in water or dilute aqueous solutions of acids or alkalis. Insoluble in common organic solvents. The supernatant of a 10% w/w suspension in water has a pH of 6.0 to 7.5. Store in airtight containers.

Adverse Effects and Precautions

As for Colestyramine, p.1252.

Effects on thyroid function. Reductions in total serum-thyroxine and thyroxine-binding globulin concentrations were found during routine monitoring of thyroid function in patients receiving colestipol and nicotinic acid, but were considered to be benign.[1] This effect has been used therapeutically in patients with hyperthyroidism (see under Uses of Colestyramine, p.1253).

1. Cashin-Hemphill L, *et al.* Alterations in serum thyroid hormonal indices with colestipol-niacin therapy. *Ann Intern Med* 1987; **107:** 324–9.

Interactions

As for Colestyramine, p.1253.

Uses and Administration

Colestipol hydrochloride is a bile-acid binding resin and lipid regulating drug with actions similar to those of colestyramine (p.1253). It is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly type IIa hyperlipoproteinaemia.

Colestipol hydrochloride is available as granules and is given orally as a suspension in water or a flavoured vehicle. The initial dose is 5 g daily or twice daily, increasing gradually at intervals of 1 to 2 months to up to 30 g daily in a single dose or two divided doses as necessary.

Colestipol hydrochloride is also available as tablets; doses range from 2 to 16 g daily.

Preparations

BP 2008: Colestipol Granules;
USP 31: Colestipol Hydrochloride for Oral Suspension; Colestipol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Colestid; ***Belg.:*** Colestid; ***Canad.:*** Colestid; ***Cz.:*** Colestid†; ***Denm.:*** Lestid; ***Fin.:*** Lestid; ***Ger.:*** Cholestabyl; Colestid; ***Gr.:*** Lestid†; ***Irl.:*** Colestid†; ***Israel:*** Colestid; ***Mex.:*** Colestid†; ***Neth.:*** Colestid†; ***Norw.:*** Lestid; ***NZ:*** Colestid; ***Port.:*** Colestid; ***Spain:*** Colestid; ***Swed.:*** Lestid; ***Switz.:*** Colestid; ***UK:*** Colestid; ***USA:*** Colestid.

Colestyramine *(BAN, rINN)*

Cholestyramine; Cholestyramine Resin; Colestiramina; Colestyraminum; Divistyramine; Kolestiramin; Kolestiraminas; Kolestyramiini; Kolestyramin; Kolestyramina; MK-135.

Колестирамин

CAS — 11041-12-6.

ATC — C10AC01.

ATC Vet — QC10AC01.

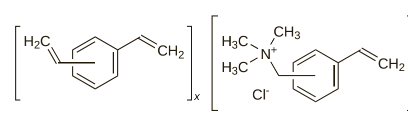

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Colestyramine). A strongly basic anion-exchange resin in the chloride form, consisting of styrene-divinylbenzene copolymer with quaternary ammonium groups. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated with reference to the dried material. A white or almost white, fine, hygroscopic powder. Insoluble in water, in alcohol, and in dichloromethane. A 1% suspension in water has a pH of 4.0 to 6.0 after standing for 10 minutes. Store in airtight containers.

USP 31 (Cholestyramine Resin). A strongly basic anion-exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer. Each g exchanges not less than 1.8 g and not more than 2.2 g of sodium glycocholate, calculated on the dried basis. It is used in the chloride form. A white to buff-coloured, hygroscopic, fine powder, odourless or has not more than a slight amine-like odour. It loses not more than 12% of its weight on drying. Insoluble in water, in alcohol, in chloroform, and in ether. A 1% slurry in water has a pH of 4.0 to 6.0. Store in airtight containers.

Adverse Effects

The most common adverse effect of colestyramine is constipation; faecal impaction may develop and haemorrhoids may be aggravated. Other gastrointestinal adverse effects include abdominal discomfort or pain, heartburn, flatulence, nausea, vomiting, and diarrhoea.

Colestyramine in high doses may cause steatorrhoea by interfering with the absorption of fats from the gastrointestinal tract and therefore decreased absorption of fat-soluble vitamins, such as vitamins A, D, E, and K, may occur. Chronic use of colestyramine may thus result in an increased bleeding tendency due to hypoprothrombinaemia associated with vitamin K deficiency; it also has a potential to cause osteoporosis due to impaired calcium and vitamin D absorption.

Colestyramine is the chloride form of an anion-exchange resin and prolonged use may produce hyperchloraemic acidosis, particularly in children.

Skin rashes and pruritus of the tongue, skin, and perianal region have occasionally occurred.

◊ Reviews.

1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 47C–55C.

Incidence of adverse effects. Results of the Lipid Research Clinics Coronary Primary Prevention Trial[1] involving 3806 men given colestyramine or placebo for an average of 7.4 years showed that gastrointestinal adverse effects occurred frequently in both groups but especially in the colestyramine group. In the first year 68% of the colestyramine group had at least 1 gastrointestinal adverse effect compared with 43% of the placebo group; by the seventh year the incidence had fallen to 29% and 26% respectively. Constipation and heartburn, especially, were more frequent in the colestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. These adverse effects were usually not severe and could be dealt with by standard clinical means.

The incidence of malignant neoplasms was similar in the 2 groups although there were differences in incidence at some sites. In particular, there were 21 cases of malignancy in the gastrointestinal tract (8 fatal) in the colestyramine group compared with 11 cases (1 fatal) in the placebo group. Rare cancers of the buccal cavity or pharynx were more common with colestyramine; during the study[1] there were 6 cases in the colestyramine group and none in the placebo group, and after follow-up[2] for a further 6 years and reassessment of the original diagnoses the incidences were 8 and 2, respectively. However, there was no clear dose relationship, and cigarette smoking may have been a confounder.[2] Colorectal malignancies were similar in the 2 groups, although at follow-up more non-malignant colorectal neoplasms had occurred in the colestyramine group.[2]

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA* 1984; **251:** 351–64.
2. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: results of 6 years of post-trial follow-up. *Arch Intern Med* 1992; **152:** 1399–1410.

Precautions

Colestyramine powder should be given as a suspension in water or a flavoured vehicle to minimise the risk of oesophageal obstruction.

Colestyramine should not be used in patients with complete biliary obstruction as it is unlikely to be effective.

Because of the risk of vitamin deficiencies, supplements of vitamins A, D, E, and K should be considered during prolonged therapy with colestyramine; if given orally they need to be in a water-miscible form. Parenteral supplementation, particularly of vitamin K for hypoprothrombinaemia, may be necessary if a deficiency becomes established. Reduced serum-folate concentrations have also been reported in children with familial hypercholesterolaemia and supplementation with folic acid should be considered in such circumstances.

Interactions

Colestyramine may delay or reduce the absorption of other drugs, particularly acidic drugs. Enterohepatic circulation may be reduced. Delayed or reduced absorption of thiazide diuretics, propranolol, digoxin and related glycosides, loperamide, phenylbutazone, barbiturates, oestrogens, progestogens, thyroid hormones, warfarin, and some antibacterials, has either been reported or may be expected. It is therefore recommended that other drugs should be taken at least 1 hour before, or 4 to 6 hours after, the use of colestyramine.

Uses and Administration

Colestyramine is a bile-acid binding resin and lipid regulating drug. It is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly type IIa hyperlipoproteinaemia, and for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164) in middle-aged men with primary hypercholesterolaemia. Colestyramine is also used for the relief of diarrhoea associated with ileal resection, Crohn's disease, vagotomy, diabetic vagal neuropathy, and radiation, and to relieve the pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction or primary biliary cirrhosis.

Colestyramine is not absorbed from the gastrointestinal tract and binds with bile acids in the intestine to form an insoluble complex that is excreted in the faeces. The normal reabsorption of bile acids is thus prevented and this leads to an increased oxidation of cholesterol to bile acids to replace those partially removed from the enterohepatic circulation, and an increased synthesis of low-density lipoprotein (LDL)-cholesterol receptors on hepatocytes. The overall effect is a reduction of total plasma-cholesterol concentration, mainly by lowering LDL-cholesterol; this may be accompanied by moderate increases in plasma triglyceride and high-density lipoprotein (HDL)-cholesterol concentrations. Since the uses of colestyramine are based upon the removal of intestinal bile acids it is unlikely that a response will be achieved in patients with complete biliary obstruction.

Colestyramine may be introduced gradually over 3 to 4 weeks to minimise gastrointestinal effects.

In hyperlipidaemias and diarrhoea the usual oral dose is 12 to 24 g daily, given either as a single dose or in up to 4 divided doses. Dosage should be adjusted according to the patient's response and may be increased to 36 g daily if necessary. Lower doses may be adequate in some forms of hyperlipidaemia.

In pruritus doses of 4 to 8 g daily are usually sufficient.

For the use of colestyramine in children, see below.

Colestyramine should be given as a suspension in water or a flavoured vehicle.

◊ General references.

1. Insull W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J* 2006; **99:** 257–73.

Administration in children. Colestyramine has been used in children and small studies[1,2] have found that it is effective in familial hypercholesterolaemia with no adverse effects on physical growth when taken long-term;[2] however, compliance may be a problem.[1]

For *hypercholesterolaemia*, the *BNFC* gives the usual oral dose for children aged 6 to 12 years as 4 g once daily, increased to 4 g up to 3 times daily according to response. Children aged 12 to 18 years may be given an initial dose of 4 g once daily, increased to 4 to 8 g up to 4 times daily, with a maximum daily dose of 36 g. Alternatively, licensed doses are calculated from body weight, either as a percentage of the adult (70 kg) dose, or as a dose of 240 mg/kg daily in divided doses.

For *pruritus* or *diarrhoea*, the *BNFC* recommends the following oral doses based on age:

- 1 month to 1 year: initially 1 g once daily, adjusted according to response to a maximum dose of 9 g daily in 2 to 4 divided doses
- 1 to 6 years: initially 2 g once daily, adjusted according to response to a maximum dose of 18 g daily in 2 to 4 divided doses
- 6 to 12 years: initially 4 g once daily, adjusted according to response to a maximum dose of 24 g daily in 2 to 4 divided doses
- 12 to 18 years: initially 4 to 8 g once daily, adjusted according to response to a maximum dose of 36 g daily in 2 to 4 divided doses

1. West RJ, Lloyd JK. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet* 1980; **ii:** 873–5.
2. Tonstad S, *et al.* Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996; **129:** 42–9.

Antibiotic-associated colitis. Colestyramine binds *Clostridium difficile* toxins and there are a few reports of use as an alternative, or as an adjunct, to vancomycin or metronidazole in patients with diarrhoea associated with *C. difficile* toxins after antibiotic therapy (p.171). However, evidence of benefit is limited and in general its use is not recommended.

Biliary disorders. Colestyramine is used to relieve diarrhoea (p.1694) associated with bile acid malabsorption and to manage pruritus and hypercholesterolaemia in patients with primary biliary cirrhosis (p.2408). It has been used for pruritus in cholestasis of pregnancy,[1] although such use has been associated with severe fetal intracranial haemorrhage.[2] Beneficial responses have been reported with colestyramine in the management of congenital nonobstructive nonhaemolytic hyperbilirubinaemia (Crigler-Najjar disease)[3,4] and in sclerosing cholangitis.[5]

1. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002; **36:** 1462–5.
2. Sadler LC, *et al.* Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol* 1995; **102:** 169–70.
3. Arrowsmith WA, *et al.* Comparison of treatments for congenital nonobstructive nonhaemolytic hyperbilirubinaemia. *Arch Dis Child* 1975; **50:** 197–201.
4. Odièvre M, *et al.* Case of congenital nonobstructive, nonhaemolytic jaundice: successful long-term phototherapy at home. *Arch Dis Child* 1978; **53:** 81–2.
5. Polter DE, *et al.* Beneficial effect of cholestyramine in sclerosing cholangitis. *Gastroenterology* 1980; **79:** 326–33.

Diabetes mellitus. Bile acids may have a role in modulating carbohydrate metabolism and small studies have shown that bile-acid binding resins such as colestyramine reduce blood glucose.[1] Their role in type 2 diabetes mellitus (p.431) is under investigation; colesevelam (p.1252) may be used as an adjunct to standard therapy to improve glycaemic control.

1. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; **67:** 1383–92.

Diarrhoea. In addition to its use in diarrhoea (p.1694) associated with biliary disorders (above), colestyramine has been investigated in the management of diarrhoea and faecal incontinence from other causes.[1-4] See also Antibiotic-associated Colitis, above.

1. Baert D, *et al.* Chronic diarrhoea in non collagenous microscopic colitis: therapeutic effect of cholestyramine. *Acta Clin Belg* 2004; **59:** 258–62.
2. Balagani R, *et al.* Cholestyramine improves tropical-related diarrhea. *Am J Ther* 2006; **13:** 281–2.
3. Flieger D, *et al.* Phase II clinical trial for prevention of delayed diarrhea with cholestyramine/levofloxacin in the second-line treatment with irinotecan biweekly in patients with metastatic colorectal carcinoma. *Oncology* 2007; **72:** 10–16.
4. Remes-Troche JM, *et al.* Cholestyramine—a useful adjunct for the treatment of patients with fecal incontinence. *Int J Colorectal Dis* 2008; **23:** 189–94.

Hyperthyroidism. Bile-acid binding resins also bind thyroid hormones and may interfere with their enterohepatic circulation. Reduced serum-thyroxine concentrations have occurred in patients given bile-acid binding resins for hyperlipidaemias (see Effects on Thyroid Function under Colestipol, p.1252) and both colestyramine[1,2] and colestipol[3] have been tried as adjunctive treatment for hyperthyroidism (p.2165). Colestyramine has also been used in thyroxine overdose.[4,5]

1. Mercado M, *et al.* Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. *J Clin Endocrinol Metab* 1996; **81:** 3191–3.
2. Tsai W-C, *et al.* The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol (Oxf)* 2005; **62:** 521–4.
3. Hagag P, *et al.* Role of colestipol in the treatment of hyperthyroidism. *J Endocrinol Invest* 1998; **21:** 725–31.
4. Shakir KMM, *et al.* The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med* 1993; **118:** 112–13.
5. de Luis DA, *et al.* Light symptoms following a high-dose intentional L-thyroxine ingestion treated with cholestyramine. *Horm Res* 2002; **57:** 61–3.

Preparations

BP 2008: Colestyramine Oral Powder;
USP 31: Cholestyramine for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Questran; ***Austral.:*** Questran; ***Austria:*** Quantalan; ***Belg.:*** Questran; ***Braz.:*** Questran; ***Canad.:*** Novo-Cholamine; Questran†; ***Cz.:*** Questran; Vasosan†; ***Denm.:*** Questran; ***Fin.:*** Questran; ***Fr.:*** Questran; ***Ger.:*** Colesthexal†; Colestyr; Lipocol; Quantalan; Vasosan; ***Gr.:*** Questran; ***Hong Kong:*** Questran; ***Indon.:*** Questran; ***Irl.:*** Questran; ***Israel:*** Chol-Less†; ***Ital.:*** Questran; ***Malaysia:*** Questran†; ***Mex.:*** Questran; ***Neth.:*** Questran; ***Norw.:*** Questran; ***NZ:*** Questran; ***Pol.:*** Vasosan; ***Port.:*** Quantalan; ***S.Afr.:*** Questran; ***Singapore:*** Questran; Resincolestiramina†; ***Spain:*** Efensol; Lismol†; Questran†; Resincolestiramina; ***Swed.:*** Questran; ***Switz.:*** Ipocol; Quantalan; ***Thai.:*** Questran; Resincolestiramina; ***Turk.:*** Kolestran; ***UK:*** Questran; ***USA:*** Locholest; Prevalite; Questran.

Colextran Hydrochloride *(rINNM)*

Colextran, Chlorhydrate de; Colextrani Hydrochloridum; DEAE-dextran Hydrochloride; Detaxtran Hydrochloride; Diethylaminoethyl-dextran Hydrochloride; Hidrocloruro de colextrán. Dextran 2-(diethylamino)ethyl ether hydrochloride.

Колекстрана Гидрохлорид

CAS — 9015-73-0 (colextran); 9064-91-9 (colextran hydrochloride).
ATC — C10AC03.
ATC Vet — QC10AC03.

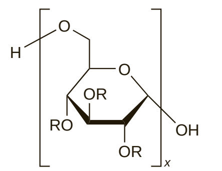

Profile

Colextran hydrochloride, an anion-exchange resin that binds bile acids in the intestine, is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). It is given in a usual dose of 2 to 3 g daily orally in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Pulsar; Rationale; ***Spain:*** Dexide.

Cyclandelate *(BAN, rINN)*

BS-572; Ciclandelato; Cyclandélate; Cyclandelatum; Cyklandelat; Syklandelaatti. 3,3,5-Trimethylcyclohexyl mandelate.

Цикланделат

$C_{17}H_{24}O_3$ = 276.4.
CAS — 456-59-7.
ATC — C04AX01.
ATC Vet — QC04AX01.

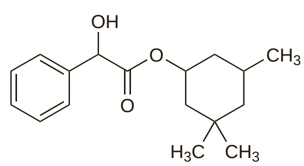

Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Cyclandelate). A white crystalline powder. M.p. about 58°. Practically insoluble in water; very soluble in alcohol, in acetonitrile, and in ether. Store in airtight containers below 40°, preferably between 15° and 30°. Protect from light.

Profile

Cyclandelate is a vasodilator used in the management of cerebrovascular (p.1165) and peripheral vascular disorders (p.1178). It is given orally in an initial dosage of up to 2 g daily in divided doses; a usual maintenance dose is 0.8 to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cyclospasmol†; ***Fin.:*** Cyclospasmol†; ***Fr.:*** Cyclergine†; Vasculnormyl†; ***Ger.:*** Natil; Spasmocyclon†; ***India:*** Martispasmol†; ***Ital.:*** Ciclospasmol†; ***Neth.:*** Cyclospasmol; ***Port.:*** Cyclospasmol†; ***Swed.:*** Cyclomandol†.

Cyclopenthiazide *(BAN, USAN, rINN)* ⊗

Ciclopentiazida; Cyclopenthiaz.; Cyclopenthiazidum; Cyklopentiazid; NSC-107679; Su-8341; Syklopentiatsidi. 6-Chloro-3-cyclopentylmethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Циклопентиазид

$C_{13}H_{18}ClN_3O_4S_2$ = 379.9.
CAS — 742-20-1.
ATC — C03AA07.
ATC Vet — QC03AA07.

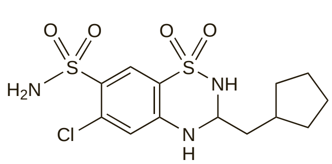

NOTE. Compounded preparations of cyclopenthiazide may be represented by the following names:

- Co-prenozide (*BAN*)—cyclopenthiazide 1 part and oxprenolol hydrochloride 640 parts (w/w).

Pharmacopoeias. In *Br.*
BP 2008 (Cyclopenthiazide). A white, odourless or almost odourless powder. Practically insoluble in water; soluble in alcohol and in acetone; practically insoluble in chloroform; very slightly soluble in ether.

Profile

Cyclopenthiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis is induced in 1 to 3 hours after an oral dose, reaches a maximum in 4 to 8 hours, and lasts up to about 12 hours.

In the treatment of hypertension the usual dose is 250 to 500 micrograms daily either alone, or with other antihypertensives. In the treatment of oedema the usual initial dose is 250 to 500 micrograms daily; up to 1 mg daily may be given in heart failure but higher doses rarely achieve any further benefit. The dose should be reduced to the lowest effective dose for maintenance.

Porphyria. Cyclopenthiazide is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

BP 2008: Cyclopenthiazide Tablets.

Proprietary Preparations (details are given in Part 3)
NZ: Navidrex†; ***UK:*** Navidrex.

Multi-ingredient: ***Hong Kong:*** Navispare; ***S.Afr.:*** Lenurex-K; ***UK:*** Navispare; Trasidrex.

Cyclothiazide *(BAN, USAN, rINN)* ⊗

Ciclotiazida; Compound 35483; Cyclothiazidum; Cyklotiazid; MDi-193; Syklotiatsidi. 6-Chloro-3,4-dihydro-3-(norborn-5-en-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Циклотиазид

$C_{14}H_{16}ClN_3O_4S_2$ = 389.9.
CAS — 2259-96-3.
ATC — C03AA09.
ATC Vet — QC03AA09.

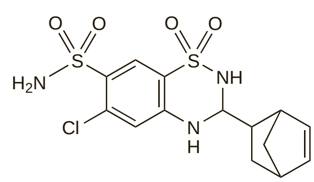

Profile

Cyclothiazide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used, usually in combination preparations, in the management of hypertension and oedema.

Dabigatran Etexilate *(rINN)*

BIBR-1048; BIBR-953 (dabigatran); Dabigatran Étexilate; Dabigatrán etexilato; Dabigatranum Etexilatum. Ethyl 3-({[2-({[4-({[(hexyloxy)carbonyl]amino}iminomethyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate.

Дабигатран Этексилат

$C_{34}H_{41}N_7O_5$ = 627.7.
CAS — 211914-51-1 (dabigatran); 211915-06-9 (dabigatran etexilate).
ATC — B01AE07.
ATC Vet — QB01AE07.

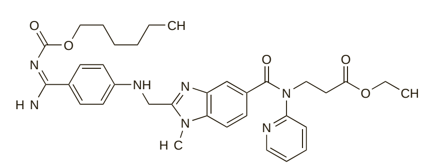

Adverse Effects and Treatment

The most common adverse effect with dabigatran is bleeding. Raised liver enzyme values have been reported but are uncommon. There is no antidote to dabigatran. If haemorrhagic complications occur treatment should be stopped; surgical haemostasis or transfusion of fresh frozen plasma may be considered.

Precautions

Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding. It should be used with caution in patients with hepatic or renal impairment and is contra-indicated if creatinine clearance is less than 30 mL/minute.

Interactions

Dabigatran should not be given with other drugs that affect coagulation, such as anticoagulants, thrombolytics, or antiplatelet drugs. It should be used with caution with NSAIDs since the risk of bleeding may be increased. Dabigatran is a substrate for the efflux transporter P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function; use of dabigatran with quinidine is contra-indicated, and the dose of dabigatran should be reduced in patients receiving amiodarone (see Uses and Administration, below).

Pharmacokinetics

When given orally, dabigatran etexilate is rapidly and completely hydrolysed to its active metabolite, dabigatran, by an esterase-catalysed reaction. The absolute oral bioavailability of dabigatran when given as dabigatran etexilate is about 6.5%. Peak plasma concentrations of dabigatran occur within 0.5 to 2 hours after an oral dose. Food delays the time to peak concentrations but the bioavailability is not affected. Dabigatran has low plasma-protein binding. It is metabolised to a limited extent to active acylglucuronide conjugates; about 85% of a dose is excreted in the urine, mainly as unchanged dabigatran. The terminal plasma half-life is about 12 to 17 hours. Dabigatran is removed by dialysis.

◊ Reviews.

1. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008; **47:** 285–95.

Uses and Administration

Dabigatran is a direct thrombin inhibitor that is used for the prophylaxis of venous thromboembolism (p.1189) in patients undergoing elective orthopaedic surgery; it has also been investigated in other thromboembolic disorders.

Dabigatran is given orally as the mesilate of the prodrug dabigatran etexilate. The usual initial dose is the equivalent of 110 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 220 mg once daily; the dose should be reduced in the elderly and in patients with renal impairment (see below). Treatment should be continued for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

◊ References.

1. Stangier J, *et al.* The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007; **64:** 292–303.
2. Eriksson BI, *et al.* Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5:** 2178–85.
3. Eriksson BI, *et al.* RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007; **370:** 949–56.
4. Ezekowitz MD, *et al.* Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007; **100:** 1419–26.
5. Sanford M, Plosker GL. Dabigatran etexilate. *Drugs* 2008; **68:** 1699–1709.

Administration in the elderly. There is limited clinical experience with dabigatran in patients over the age of 75 years but plasma concentrations appear to be higher in older subjects[1] and dose reduction is recommended. UK licensed product information recommends an initial dose of 75 mg of dabigatran etexilate (as the mesilate) given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

1. Stangier J, *et al.* Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008; **47:** 47–59.

Administration in renal impairment. Dabigatran is excreted mainly by the kidneys but there is limited clinical experience with its use in renal impairment. It is contra-indicated in patients with creatinine clearance (CC) below 30 mL/minute. In patients with CC between 30 and 50 mL/minute the initial dose should be the equivalent of 75 mg of dabigatran etexilate given within 1 to 4 hours of the completion of surgery, followed by 150 mg once daily for a total of 10 days after knee replacement and 28 to 35 days after hip replacement.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Pradaxa; ***UK:*** Pradaxa.

Dalteparin Sodium *(BAN, USAN, rINN)*

Daltepariininatrium; Dalteparin sodná sůl; Dalteparin Sodyum; Dalteparina sódica; Daltéparine sodique; Dalteparinnatrium; Dalteparin-nátrium; Dalteparino natrio druska; Dalteparinum natricum; Dalteparyna sodowa; Kabi-2165; Tedelparin Sodium.

Дальтепарин Натрий

CAS — 9041-08-1.

ATC — B01AB04.

ATC Vet — QB01AB04.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dalteparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000. The mass percentage of chains lower than 3000 is not more than 13.0% and the mass percentage of chains higher than 8000 ranges between 15.0% and 25.0%. The degree of sulfation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 units and not more than 210 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with dalteparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of 100 units of dalteparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Dalteparin is almost completely absorbed after subcutaneous doses, with a bioavailability of about 87%. Peak plasma activity is reached in about 4 hours. The terminal half-life is about 2 hours after intravenous injection and 3 to 5 hours after subcutaneous injection. Dalteparin is excreted via the kidneys and the half-life is prolonged in patients with renal impairment.

Uses and Administration

Dalteparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p.1157).

Dalteparin is given by subcutaneous or intravenous injection. Doses are expressed in terms of units of anti-factor Xa activity.

For *prophylaxis* of **venous thromboembolism** during surgical procedures, dalteparin is usually started preoperatively.

- For patients at moderate risk of thrombosis 2500 units of dalteparin sodium are given by subcutaneous injection 1 to 2 hours before the procedure, followed by 2500 units once daily for 5 to 7 days or until the patient is fully ambulant.
- For patients at high risk, such as those undergoing orthopaedic surgery, 2500 units are given 1 to 2 hours before and 8 to 12 hours after the procedure followed by 5000 units daily. Alternatively, 5000 units may be given the evening before surgery followed by 5000 units each subsequent evening. This dosage may be continued for up to 5 weeks after hip replacement surgery.
- A further option in patients undergoing hip replacement surgery is to omit the pre-operative dose; treatment is begun with a dose of 2500 units given 4 to 8 hours postoperatively followed by 5000 units daily.
- For prophylaxis in medical patients, a dose of 5000 units once daily may be given for 14 days or longer.

In the *treatment* of established deep-vein thrombosis, pulmonary embolism, or both, dalteparin sodium is given subcutaneously in a dose of 200 units/kg daily. This may be given as a single dose or, in patients at higher risk of bleeding complications, in two divided doses. The maximum recommended dose is 18 000 units daily. Patients with symptomatic venous thromboembolism and cancer may be given 200 units/kg subcutaneously once daily for 30 days, followed by 150 units/kg once daily for up to 5 months.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** or **haemofiltration** in adults with chronic renal impairment an intravenous injection of dalteparin sodium 30 to 40 units/kg is followed by an intravenous infusion of 10 to 15 units/kg per hour. A single injection of 5000 units may be given for a haemodialysis or haemofiltration session lasting less than 4 hours. The dose of dalteparin sodium should be reduced in patients at high risk of bleeding complications or who are in acute renal failure; in such patients an intravenous injection of 5 to 10 units/kg is followed by an infusion of 4 to 5 units/kg per hour.

In the management of **unstable angina**, dalteparin sodium is given subcutaneously in a dose of 120 units/kg every 12 hours; the maximum dose is 10 000 units every 12 hours. Treatment is continued for 5 to 8 days and low-dose aspirin should also be given. For patients who require treatment for longer than 8 days while awaiting a revascularisation procedure, a dose of 5000 units (7500 units in men weighing 70 kg or over and women weighing 80 kg or over) may be given every 12 hours for up to 45 days until the procedure is performed.

◊ References.

1. Dunn CJ, Sorkin EM. Dalteparin sodium: a review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs* 1996; **52:** 276–305.
2. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother* 1997; **31:** 192–203.
3. Dunn CJ, Jarvis B. Dalteparin: an update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2000; **60:** 203–37.
4. Pineo GF, Hull RD. Dalteparin: pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic diseases. *Eur J Med Res* 2004; **9:** 215–24.
5. Bick RL. Cancer-associated thrombosis: focus on extended therapy with dalteparin. *J Support Oncol* 2006; **4:** 115–20.
6. Linkins LA. Management of venous thromboembolism in patients with cancer: role of dalteparin. *Vasc Health Risk Manag* 2008; **4:** 279–87.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Ligofragmin; ***Austral.:*** Fragmin; ***Austria:*** Fragmin; ***Belg.:*** Fragmin; ***Braz.:*** Fragmin; ***Canad.:*** Fragmin; ***Chile:*** Fragmin; ***Cz.:*** Fragmin; ***Denm.:*** Fragmin; ***Fin.:*** Fragmin; ***Fr.:*** Fragmine; ***Ger.:*** Fragmin; ***Gr.:*** Fragmin; ***Hong Kong:*** Fragmin; ***Hung.:*** Fragmin; ***Israel:*** Fragmin; ***Ital.:*** Fragmin; ***Mex.:*** Fragmin†; ***Neth.:*** Fragmin; ***Norw.:*** Fragmin; ***NZ:*** Fragmin; ***Philipp.:*** Fragmin; ***Pol.:*** Fragmin; ***Port.:*** Fragmin; ***Rus.:*** Fragmin (Фрагмин); ***S.Afr.:*** Fragmin; ***Singapore:*** Fragmin; ***Spain:*** Boxol†; Fragmin; ***Swed.:*** Fragmin; ***Switz.:*** Fragmin; ***Turk.:*** Fragmin; ***UK:*** Fragmin; ***USA:*** Fragmin; ***Venez.:*** Fragmin.

Danaparoid Sodium *(BAN, USAN, rINN)*

Danaparoid sodná sůl; Danaparoid sodowy; Danaparoide sódico; Danaparoïde sodique; Danaparoidum natricum; Lomoparan; Org-10172.

Данапароид Натрий

CAS — 83513-48-8.

ATC — B01AB09.

ATC Vet — QB01AB09.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Danaparoid Sodium). A preparation containing the sodium salts of a mixture of sulfated glycosaminoglycans present in porcine tissues. It is prepared from the intestinal mucosa of pigs and the major constituents are suleparoid (heparan sulfate) (p.1406) and dermatan sulfate (p.1256). It has a potency of 11.0 to 17.0 anti-factor Xa units per milligram, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Adverse Effects and Treatment

Haemorrhage may occur after use of danaparoid sodium, although there is a possible decreased risk of bleeding complications compared with heparin. Liver enzymes may be transiently elevated. Other adverse effects include hypersensitivity reactions, thrombocytopenia, and pain at the site of injection.

Protamine sulfate only partially neutralises the anticoagulant effect of danaparoid sodium and cannot be relied on to reverse bleeding associated with overdosage.

Precautions

As for Heparin, p.1303.

Danaparoid sodium should not be given to patients who have developed thrombocytopenia with heparin if they show cross-reactivity in an *in-vitro* test.

Pharmacokinetics

After subcutaneous dosage danaparoid sodium is well absorbed and peak anti-factor Xa activity is reached in about 4 to 5 hours. The elimination half-lives of anti-factor Xa and anti-factor IIa (antithrombin) activities are about 25 and 7 hours, respectively. Danaparoid sodium is excreted in the urine.

Uses and Administration

Danaparoid sodium is a low-molecular-weight heparinoid. It is an anticoagulant and, like heparin (p.1303), enhances the action of antithrombin III. Like low-molecular-weight heparins (p.1329) it has a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin, but is reported to be a much more selective inhibitor of factor Xa than the low-molecular-weight heparins. It was therefore hoped that danaparoid might be associated with a low incidence of bleeding complications, although this has not been established.

Danaparoid sodium is used in the prophylaxis of venous thromboembolism (p.1189) in patients undergoing surgery. It may be used as an anticoagulant for prophylaxis or treatment in patients with heparin-induced thrombocytopenia providing there is no cross-reactivity. Danaparoid has been investigated in acute ischaemic stroke.

Doses of danaparoid sodium are expressed in terms of units of anti-factor Xa activity. In the prophylaxis of venous thromboembolism it is given by subcutaneous injection in a dose of 750 units twice daily for 7 to 10 days. The first dose should be given 1 to 4 hours before surgery.

For patients with heparin-induced thrombocytopenia requiring anticoagulation, danaparoid sodium is given intravenously. The initial bolus dose is 2500 units (or 1250 units for patients weighing less than 55 kg, or 3750 units for patients weighing more than 90 kg) followed by an infusion of 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days. Monitoring of plasma anti-factor Xa activity is recommended for patients with renal impairment, or those weighing more than 90 kg.

◊ References.

1. Skoutakis VA. Danaparoid in the prevention of thromboembolic complications. *Ann Pharmacother* 1997; **31:** 876–87.
2. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; **54:** 903–24.
3. Ibbotson T, Perry CM. Danaparoid: a review of its use in thromboembolic and coagulation disorders. *Drugs* 2002; **62:** 2283–2314.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Orgaran; ***Austria:*** Orgaran; ***Belg.:*** Orgaran; ***Canad.:*** Orgaran; ***Fr.:*** Orgaran; ***Ger.:*** Orgaran; ***Gr.:*** Orgaran; ***Neth.:*** Orgaran; ***NZ:*** Orgaran; ***Port.:*** Orgaran; ***Swed.:*** Orgaran; ***Switz.:*** Orgaran; ***UK:*** Orgaran; ***USA:*** Orgaran†.

Debrisoquine Sulfate *(rINNM)*

Debrisoquin Sulfate *(USAN)*; Débrisoquine, Sulfate de; Debrisoquine Sulphate *(BANM)*; Debrisoquini Sulfas; Isocaramidine Sulfate; Ro-5-3307/1; Sulfato de debrisoquina. 1,2,3,4-Tetrahydroisoquinoline-2-carboxamidine sulfate.

Дебризохина Сульфат

$(C_{10}H_{13}N_3)_2,H_2SO_4 = 448.5.$

CAS — 1131-64-2 (debrisoquine); 581-88-4 (debrisoquine sulfate).

ATC — C02CC04.

ATC Vet — QC02CC04.

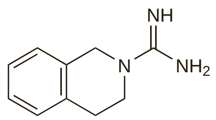

(debrisoquine)

Pharmacopoeias. In *Br.*

BP 2008 (Debrisoquine Sulphate). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 3% solution in water has a pH of 5.3 to 6.8. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Guanethidine Monosulfate, p.1300.

Diarrhoea is rare with debrisoquine sulfate. Treatment should not be stopped abruptly as this may lead to rebound hypertension.

The metabolism of debrisoquine is subject to genetic polymorphism and non-metabolisers may show a marked response to doses that have little or no effect in metabolisers.

Interactions

As for Guanethidine Monosulfate, p.1300.

Pharmacokinetics

Debrisoquine is rapidly absorbed from the gastrointestinal tract. The major metabolite is 4-hydroxydebrisoquine; metabolism is subject to genetic polymorphism.

◊ A study[1] in 15 hypertensive patients and 4 healthy subjects indicated that debrisoquine undergoes pre-systemic metabolism to 4-hydroxydebrisoquine, but the mechanism appears to be saturable and increases in the dose of debrisoquine could therefore produce disproportionate decreases in blood pressure. The estimated half-life of elimination for debrisoquine and 4-hydroxydebrisoquine ranged from 11.5 to 26 hours and from 5.8 to 14.5 hours respectively.

1. Silas JH, *et al*. The disposition of debrisoquine in hypertensive patients. *Br J Clin Pharmacol* 1978; **5:** 27–34.

Genetic polymorphism. Debrisoquine, along with sparteine and a number of other drugs, is a substrate for the cytochrome P450 isoenzyme CYP2D6, a polymorphic enzyme coded by a gene mapped to chromosome 22. Patients homozygous for the mutant allele are termed *poor metabolisers* and express little or no active enzyme. The prevalence of the poor-metaboliser phenotype is about 5% in most Caucasian populations, while studies in other genetic groups have indicated a range of about 2 to 10% although in some groups, such as the Japanese, poor metabolisers have yet to be identified. Poor metabolisers of debrisoquine are unable to 4-hydroxylate the drug adequately to its inactive metabolite and are thus prone to excessive hypotension. Many other drugs are metabolised by the same enzyme, but the clinical consequences of polymorphism in patients taking them depends on the relative activity and toxicity of parent drug and metabolite, and the availability and relative importance of other routes of metabolism. Phenotype has been determined by giving a drug that is metabolised by this enzyme and assaying parent drug and metabolite in urine collected over a defined period of time, but DNA-based tests may represent a more convenient and safer alternative.

References.

1. Relling MV. Polymorphic drug metabolism. *Clin Pharm* 1989; **8:** 852–63.
2. Zanger UM, *et al*. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004; **369:** 23–37.

Uses and Administration

Debrisoquine is an antihypertensive with actions and uses similar to those of guanethidine (p.1300), but it causes less depletion of noradrenaline stores. When given orally, debrisoquine acts within about 4 to 10 hours and has effects lasting for 9 to 24 hours. It has been used in the management of hypertension (p.1171), but has largely been superseded by other drugs.

For reference to the use of debrisoquine in identifying metabolic phenotypes, see Genetic Polymorphism, above.

Defibrotide *(BAN, rINN)*

Defibrotida; Défibrotide; Defibrotidum.

Дефибротид

CAS — 83712-60-1.

ATC — B01AX01.

ATC Vet — QB01AX01.

Profile

Defibrotide consists of polydeoxyribonucleotides from bovine lung; the molecular weights range between 45 000 and 55 000. Preparations derived from porcine tissues and with a lower molecular weight range are also used. Defibrotide has antithrombotic and fibrinolytic properties, although its mechanism of action is uncertain; it appears to increase levels of prostaglandin E_2 and prostacyclin, to alter platelet activity, and to increase tissue plasminogen activator function at the same time as decreasing activity of tissue plasminogen activator inhibitor. It is used in the management of thromboembolic disorders. Oral and parenteral formulations have been used in doses of up to 800 mg daily.

Defibrotide is being investigated for use in the treatment of hepatic veno-occlusive disease and thrombotic thrombocytopenic purpura.

◊ References.

1. Palmer KJ, Goa KL. Defibrotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. *Drugs* 1993; **45:** 259–94.
2. Richardson PG, *et al*. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* 1998; **92:** 737–44.
3. Pogliani EM, *et al*. Defibrotide in recurrent thrombotic thrombocytopenic purpura. *Clin Appl Thromb Hemost* 2000; **6:** 69–70.
4. Chopra R, *et al*. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol* 2000; **111:** 1122–9.
5. Corti P, *et al*. Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. *Bone Marrow Transplant* 2002; **29:** 542–3.
6. Richardson PG, *et al*. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood* 2002; **100:** 4337–43.
7. Kornblum N, *et al*. Defibrotide, a polydisperse mixture of single-stranded phosphodiester oligonucleotides with lifesaving activity in severe hepatic veno-occlusive disease: clinical outcomes and potential mechanisms of action. *Oligonucleotides* 2006; **16:** 105–14.
8. Ho VT, *et al*. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* 2008; **41:** 229–37.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Noravid; Prociclide.

Delapril Hydrochloride *(USAN, rINNM)*

Alindapril Hydrochloride; CV-3317; Délapril, Chlorhydrate de; Delaprili Hydrochloridum; Hidrocloruro de delapril; Indalapril Hydrochloride; REV-6000A. Ethyl (*S*)-2-{[(*S*)-1-(carboxymethyl-2-indanylcarbamoyl)ethyl]amino}-4-phenylbutyrate hydrochloride.

Делаприла Гидрохлорид

$C_{26}H_{32}N_2O_5,HCl = 489.0.$

CAS — 83435-66-9 (delapril); 83435-67-0 (delapril hydrochloride).

ATC — C09AA12.

ATC Vet — QC09AA12.

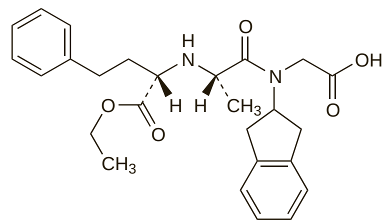

(delapril)

Profile

Delapril is an ACE inhibitor (p.1193). It is converted in the body to two metabolites to which it owes its activity. It is given orally as the hydrochloride in the treatment of hypertension (p.1171), in usual maintenance doses of 30 to 60 mg daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Delacard; ***Braz.:*** Delakete†; ***Gr.:*** Delacard; ***Ital.:*** Delaket; ***Jpn:*** Adecut; ***Malaysia:*** Cupressin†; ***Philipp.:*** Cupressin; ***Singapore:*** Cupressin; ***Spain:*** Beniod; Trinordiol; ***Thai.:*** Cupressin†.

Multi-ingredient: ***Austria:*** Delapride; ***Braz.:*** Hipertil; ***Gr.:*** Dinapres; Vivace; ***Ital.:*** Delapride; Dinapres.

Denopamine *(rINN)*

Denopamina; Dénopamine; Denopaminum; TA-064. (−)-(*R*)-α-{[(3,4-Dimethoxyphenethyl)amino]methyl}-*p*-hydroxybenzyl alcohol.

Денопамин

$C_{18}H_{23}NO_4 = 317.4.$

CAS — 71771-90-9.

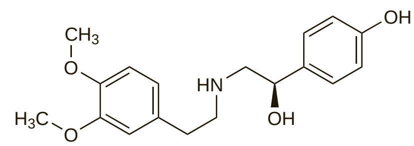

Profile

Denopamine is a sympathomimetic (p.1407) with predominantly beta-adrenergic activity selective to $beta_1$ receptors. It acts as a partial agonist (see Xamoterol, p.1433) and has been used for the treatment of heart failure.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Kalgut.

Dermatan Sulfate

Chondroitin Sulfate B; Dermatán, sulfato de; Dermatan Sulphate; LMW-DS (depolymerised dermatan sulfate); MF-701; OP-370 (depolymerised dermatan sulfate).

CAS — 24967-94-0 (dermatan sulfate).

ATC — B01AX04.

ATC Vet — QB01AX04.

Dermatan Sulfate Sodium

Chondroitin Sulfate B Sodium; Dermatan Sulphate Sodium.

CAS — 54328-33-5.

ATC — B01AX04.

ATC Vet — QB01AX04.

Profile

Dermatan sulfate is a naturally occurring glycosaminoglycan used as an anticoagulant for prophylaxis of venous thromboembolism (p.1189). It is given as the sodium salt in a dose of 100 to 300 mg daily by intramuscular injection. The dose may be increased to 300 mg twice daily in patients at high risk of thromboembolism, such as those undergoing major orthopaedic surgery.

Dermatan sulfate is a component of sulodexide (p.1406) and its sodium salt is a component of danaparoid sodium (p.1255).

Dermatan sulfate has been investigated for the treatment of venous thromboembolism, heparin-induced thrombocytopenia, and to prevent clotting during haemodialysis. Low-molecular-weight (depolymerised) dermatan sulfate has also been studied.

◊ References.

1. Dawes J, *et al*. The pharmacokinetics of dermatan sulphate MF701 in healthy human volunteers. *Br J Clin Pharmacol* 1991; **32:** 361–6.
2. Agnelli G, *et al*. Randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. *Thromb Haemost* 1992; **67:** 203–8.
3. Gianese F, *et al*. The pharmacokinetics and pharmacodynamics of dermatan sulphate MF701 during haemodialysis for chronic renal failure. *Br J Clin Pharmacol* 1993; **35:** 335–9.
4. Legnani C, *et al*. Acute and chronic effects of a new low molecular weight dermatan sulphate (Desmin 370) on blood coagulation and fibrinolysis in healthy subjects. *Eur J Clin Pharmacol* 1994; **47:** 247–52.
5. Miglioli M, *et al*. Bioavailability of Desmin, a low molecular weight dermatan sulfate, after subcutaneous administration to healthy volunteers. *Int J Clin Lab Res* 1997; **27:** 195–8.
6. Taliani MR *et al*. Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; **104:** 87–9.
7. Di Carlo V, *et al*. Dermatan sulphate for the prevention of post-operative venous thromboembolism in patients with cancer. *Thromb Haemost* 1999; **82:** 30–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Aclotan†; Mistral; ***Port.:*** Venorix.

Deserpidine (BAN, rINN)

Canescine; Deserpidiini; Deserpidin; Deserpidina; Déserpidine; Deserpidinum; 11-Desmethoxyreserpine; Raunormine; Recanescine. Methyl 11-demethoxy-*O*-(3,4,5-trimethoxybenzoyl)reserpate.

Дезерпидин

$C_{32}H_{38}N_2O_8$ = 578.7.

CAS — 131-01-1.

ATC — C02AA05.

ATC Vet — QC02AA05.

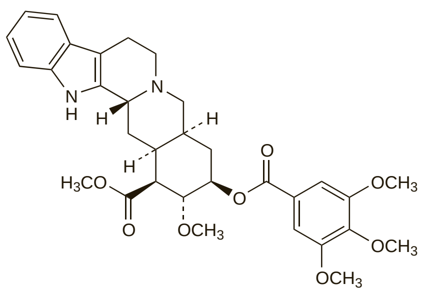

Profile

Deserpidine is an ester alkaloid isolated from the root of *Rauwolfia canescens*. It has properties similar to those described under reserpine (p.1387) and has been used in the treatment of hypertension and psychoses.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Enduronyl†.

Desirudin (BAN, USAN, rINN)

CGP-39393; Desirudiini; Desirudina; Désirudine; Desirudinum; Desulphatohirudin. 63-Desulfohirudin (*Hirudo medicinalis* isoform HV1).

Дезирудин

$C_{287}H_{440}N_{80}O_{110}S_6$ = 6963.4.

CAS — 120993-53-5.

ATC — B01AE01.

ATC Vet — QB01AE01.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

Teratogenicity has been observed in *animals*.

Interactions

As for Lepirudin, p.1323.

Pharmacokinetics

Maximum plasma concentrations of desirudin are reached 1 to 3 hours after subcutaneous injection. Desirudin is metabolised and excreted by the kidney, and 40 to 50% of a dose is excreted unchanged in the urine. After subcutaneous or intravenous injection the terminal elimination half-life of desirudin is 2 to 3 hours.

◊ References.

1. Lefèvre G, *et al.* Effect of renal impairment on the pharmacokinetics and pharmacodynamics of desirudin. *Clin Pharmacol Ther* 1997; **62:** 50–9.

Uses and Administration

Desirudin is a recombinant hirudin (p.1305) that is a direct inhibitor of thrombin with actions similar to Lepirudin, p.1323. It is used as an anticoagulant for the prevention of postoperative venous thromboembolism (p.1189) in patients undergoing orthopaedic surgery. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina, and as an adjunct in angioplasty procedures (see Ischaemic Heart Disease, under Uses and Administration of Lepirudin, p.1323).

In the prevention of venous thromboembolism, desirudin is given subcutaneously in a dose of 15 mg twice daily, the first dose 5 to 15 minutes before surgery, but after induction of regional block anaesthesia, if used. Treatment is continued until the patient is fully ambulant, usually for 9 to a maximum of 12 days.

Response to desirudin should be monitored using activated partial thromboplastin time (APTT) in patients with hepatic or renal impairment, or increased risk of bleeding. Doses may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Matheson AJ, Goa KL. Desirudin: a review of its use in the management of thrombotic disorders. *Drugs* 2000; **60:** 679–700.

Administration in renal impairment. The dose of desirudin should be reduced in patients with renal impairment, depending on creatinine clearance (CC) and activated partial thromboplastin time (APPT), which should be measured daily. US licensed product information recommends the following doses:

- CC 31 to 60 mL/minute per 1.73 m^2, initial dose 5 mg every 12 hours, subsequently adjusted according to APPT
- CC below 31 mL/minute per 1.73 m^2, initial dose 1.7 mg every 12 hours, subsequently adjusted according to APPT

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Revasc; ***Cz.:*** Revasc; ***Fr.:*** Revasc†; ***Ger.:*** Revasc; ***Gr.:*** Revasc†; ***Hung.:*** Revasc†; ***Neth.:*** Revasc; ***Norw.:*** Revasc†; ***NZ:*** Revasc; ***Port.:*** Revasc; ***Spain:*** Revasc; ***Switz.:*** Revasc†; ***USA:*** Iprivask.

Deslanoside (BAN, rINN)

Deacetyl-lanatoside C; Desacetyl-lanatoside C; Deslanosid; Deslanosídeo; Deslanosidi; Deslanósido; Deslanosidum; Deslanozidas; Dezlanozid. 3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)-oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

Дезланозид

$C_{47}H_{74}O_{19}$ = 943.1.

CAS — 17598-65-1.

ATC — C01AA07.

ATC Vet — QC01AA07.

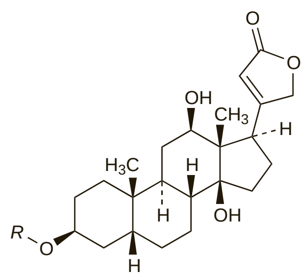

R = β-D-glucose–(β-D-digitoxose)$_3$

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Deslanoside). A white or almost white, crystalline or finely crystalline hygroscopic powder. Practically insoluble in water; very slightly soluble in alcohol. In an atmosphere of low relative humidity, it loses water. Store in airtight, glass containers at a temperature below 10°. Protect from light.

USP 31 (Deslanoside). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Deslanoside, a cardiac glycoside with positive inotropic activity, is a derivative of lanatoside C. It has the general properties of digoxin (p.1259) and has been used similarly in the management of some cardiac arrhythmias and in heart failure.

Preparations

USP 31: Deslanoside Injection.

Proprietary Preparations (details are given in Part 3)

Braz.: Cedilanide.

Detajmium Bitartrate (rINN)

Bitartrato de detajmio; Detajmii Bitartras; Détajmium, Bitartrate de. 4-[3-(Diethylamino)-2-hydroxypropyl]ajmalinium hydrogen tartrate monohydrate.

Детаймия Битартрат

$C_{31}H_{47}N_3O_9,H_2O$ = 623.7.

CAS — 53862-81-0.

Profile

Detajmium is a class I antiarrhythmic (p.1153). It is given orally as the bitartrate, in the treatment of supraventricular and ventricular arrhythmias (p.1160). The dose range is from 75 to 300 mg daily depending upon the arrhythmia.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Tachmalcor; ***Ger.:*** Tachmalcor.

Diazoxide (BAN, USAN, rINN)

Diatsoksidi; Diazoksidas; Diazoksit; Diazoxid; Diazóxido; Diazoxidum; NSC-64198; Sch-6783; SRG-95213. 7-Chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide.

Диазоксид

$C_8H_7ClN_2O_2S$ = 230.7.

CAS — 364-98-7.

ATC — C02DA01; V03AH01.

ATC Vet — QC02DA01; QV03AH01.

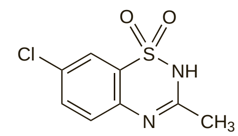

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Diazoxide). A white or almost white, fine or crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide; very soluble in dilute solutions of alkali hydroxides.

USP 31 (Diazoxide). White or cream-white crystals or crystalline powder. Practically insoluble to sparingly soluble in water and in most organic solvents; freely soluble in dimethylformamide; very soluble in strong alkaline solutions. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

In addition to inappropriate hypotension and hyperglycaemia (which includes ketoacidosis and hyperosmolar nonketotic coma), adverse effects often include oedema due to salt and water retention, which may precipitate heart failure. Other adverse effects include: dysgeusia, nausea, anorexia, and other gastrointestinal disturbances; mild hyperuricaemia; extrapyramidal symptoms; eosinophilia and thrombocytopenia; dyspnoea; hypertrichosis; and headache, dizziness, tinnitus, and blurred vision. Hypersensitivity has occurred, manifesting as rashes, leucopenia, and fever.

During intravenous therapy, particularly after large bolus injections, adverse effects may be associated with too rapid a reduction in blood pressure and include: coronary ischaemia leading to angina, cardiac arrhythmias, marked ECG changes, tachycardia, palpitations, and bradycardia; cerebral ischaemia leading to confusion, convulsions, loss of consciousness, and neurological deficit; renal impairment; and symptoms of vasodilatation.

Diazoxide may cause a burning sensation in the injected vein; extravasation of the alkaline solution is painful.

Effects on the blood. A 26-year-old man with hypertension developed reversible haemolytic anaemia when treated with diazoxide orally on 3 separate occasions.[1]

1. Best RA, Clink HM. Haemolysis associated with diazoxide, used for the control of hypertension. *Postgrad Med J* 1975; **51:** 402–4.

Effects on the hair. *Hirsutism* and *hypertrichosis* are different types of excessive hair growth, but the terms have often been used interchangeably. Hirsutism is androgen-related whereas hypertrichosis is thought to be independent of hormone stimulation. Hypertrichosis is acknowledged to be a frequent adverse effect of diazoxide in children receiving long-term treatment for idiopathic hypoglycaemia.[1] Two such children had unusually deep (low-pitched) voices as well as marked hypertrichosis.[2] A woman on continuous diazoxide therapy who developed so-called hirsutism without signs of virilisation had raised serum concentrations of androgens.[3]

Alopecia has been reported[4] in 4 infants born to mothers who had been on long-term treatment with diazoxide during pregnancy; the condition was still present to some extent when the infants were last observed at the ages of 5 months to 1 year.

1. Burton JL, *et al.* Hypertrichosis due to diazoxide. *Br J Dermatol* 1975; **93:** 707–11.
2. West RJ. Side effects of diazoxide. *BMJ* 1978; **2:** 506.
3. Hallengren B, Hökfelt B. Increase of serum androgens during diazoxide treatment. *Lancet* 1984; **ii:** 1044–5.
4. Milner RDG, Chouksey SK. Effects of fetal exposure to diazoxide in man. *Arch Dis Child* 1972; **47:** 537–43.

Extrapyramidal effects. In a study[1] of 100 hypertensive patients receiving diazoxide, the incidence of extrapyramidal symptoms was 15%.

1. Pohl JEF. Development and management of extrapyramidal symptoms in hypertensive patients treated with diazoxide. *Am Heart J* 1975; **89:** 401–2.

Pancreatitis. Ten patients with severe hypertension and renal failure were treated with diazoxide in a last attempt to avert nephrectomy; 1 patient developed acute pancreatitis and another diabetic ketoacidosis.[1] Both patients recovered from these effects when diazoxide was withdrawn.

1. De Broe M, *et al*. Oral diazoxide for malignant hypertension. *Lancet* 1972; **i:** 1397.

Voice changes. See Effects on the Hair, above.

Treatment of Adverse Effects

Treatment is largely symptomatic. Severe hyperglycaemia may be corrected by giving insulin: less severe hyperglycaemia may respond to oral hypoglycaemics. Hypotension may be managed with intravenous fluids. Severe hypotension may require sympathomimetics. Antiparkinsonian drugs, such as procyclidine, have been given to control extrapyramidal effects while a diuretic may be required for salt and water retention. Diazoxide can be removed from the body by dialysis but recovery is relatively low owing to extensive protein binding.

Precautions

Diazoxide should be used with care in patients with impaired cardiac or cerebral circulation and in patients with aortic coarctation, arteriovenous shunt, heart failure, or other cardiac disorders in which an increase in cardiac output could be detrimental. During prolonged therapy blood-glucose concentrations and blood pressure should be monitored and the blood should be examined regularly for signs of leucopenia and thrombocytopenia; in children, bone and psychological maturation, and growth, should be regularly assessed. Caution is necessary in patients with renal impairment.

If given during labour, diazoxide may cause cessation of uterine contractions and delay delivery unless oxytocin is also given.

Pregnancy. Transplacental transfer of diazoxide was considered[1] to be responsible for an inappropriately low plasma-insulin concentration in an infant whose mother had received a dose of 150 mg daily for 47 days prior to delivery. For reference to alopecia in neonates whose mothers had received diazoxide during pregnancy, see Effects on the Hair under Adverse Effects, above.

For reports of sedation, hypotonia, or apnoea among infants born to mothers given both diazoxide and clomethiazole for the treatment of toxaemia of pregnancy, see Precautions, Pregnancy, in Clomethiazole Edisilate, p.978. Diazoxide is nonetheless one of the drugs that has been used for hypertensive emergencies in pregnancy (see Hypertension, p.1171) and a study found that mini-boluses of diazoxide 15 mg intravenously successfully reduced blood pressure and were well tolerated.[2]

1. Smith MJ, *et al*. Neonatal hyperglycaemia after prolonged maternal treatment with diazoxide. *BMJ* 1982; **284:** 1234.
2. Hennessy A, *et al*. A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007; **47:** 279–85.

Interactions

The hyperglycaemic, hyperuricaemic, and hypotensive actions of diazoxide may be enhanced by diuretics. Use of diazoxide with other antihypertensives or vasodilators may lead to increased risk of hypotension.

Chlorpromazine. Chlorpromazine was reported[1] to enhance the hyperglycaemic effect of diazoxide in a 2-year-old child.

1. Aynsley-Green A, Illig R. Enhancement by chlorpromazine of hyperglycaemic action of diazoxide. *Lancet* 1975; **ii:** 658–9.

Phenytoin. For the effect of diazoxide on serum-phenytoin concentrations, see Antihypertensives, p.499.

Pharmacokinetics

Diazoxide is readily absorbed from the gastrointestinal tract and more than 90% bound to plasma proteins, although protein binding is decreased in uraemic patients. Its plasma half-life has been estimated to range from about 20 to 45 hours but values of up to 60 hours have been reported. The half-life is reported to be prolonged in renal impairment and shorter for children. The plasma half-life greatly exceeds the duration of vascular activity. Diazoxide is partly metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites; only small amounts are recovered from the faeces. It crosses the placenta and the blood-brain barrier.

Children. In 4 children with hypoglycaemia the plasma half-life of diazoxide was 9.5 to 24 hours, which is considerably shorter than that in adults.[1]

1. Pruitt AW, *et al*. Disposition of diazoxide in children. *Clin Pharmacol Ther* 1973; **14:** 73–82.

Uses and Administration

Diazoxide increases the concentration of glucose in the plasma; it inhibits the secretion of insulin by the beta cells of the pancreas, and may increase the hepatic output of glucose. When given intravenously, it produces a fall in blood pressure by a vasodilator effect on the arterioles and a reduction in peripheral resistance. Diazoxide is closely related structurally to the thiazide diuretics, but has an antidiuretic action and thus produces fluid and electrolyte retention; it may be given with a diuretic to reduce fluid retention.

Diazoxide is used orally in the management of intractable hypoglycaemia (p.1447) and intravenously in the management of hypertensive crises (p.1171), particularly when first-line drugs such as sodium nitroprusside are ineffective or unsuitable. Diazoxide is not suitable for the chronic treatment of hypertension because of its severe adverse effects.

In **hypoglycaemia**, the initial dose is 3 to 5 mg/kg daily in 2 or 3 divided oral doses, then adjusted according to response. Usual maintenance doses are from 3 to 8 mg/kg daily but total doses of up to 1 g daily have been given to adults with insulinomas (see Carcinoid Tumours and other Secretory Neoplasms, p.643). In neonates the initial dose is 5 mg/kg twice daily; usual maintenance doses range from 3 to 9 mg/kg daily, although up to 21 mg/kg daily may be required. In children from 1 month of age, the initial dose is 1.7 mg/kg three times daily, and the usual maintenance doses are as for neonates; up to 15 mg/kg daily may be required. The hyperglycaemic effect normally begins within 1 hour of a dose and lasts for up to 8 hours. The doses for neonates and children may be given intravenously if necessary.

In **hypertensive crises**, a bolus intravenous injection of 1 to 3 mg/kg is given within 30 seconds, up to a maximum dose of 150 mg, and repeated after 5 to 15 minutes if required.

Reduced doses may be necessary in patients with renal impairment.

Preparations

BP 2008: Diazoxide Injection; Diazoxide Tablets;
USP 31: Diazoxide Capsules; Diazoxide Injection; Diazoxide Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Proglicem; ***Braz.:*** Tensuril; ***Canad.:*** Hyperstat†; Proglycem; ***Fr.:*** Proglicem; ***Ger.:*** Hypertonalum†; Proglicem; ***Gr.:*** Eudemine; Hyperstat†; Proglycem; ***Ital.:*** Hyperstat†; Proglicem; ***Mex.:*** Hyperstat†; Sefulken; ***Neth.:*** Proglicem; ***Swed.:*** Hyperstat†; ***Switz.:*** Proglicem; ***UK:*** Eudemine; ***USA:*** Hyperstat; Proglycem.

Dicoumarol *(rINN)*

Bishydroxycoumarin; Dicoumarin; Dicoumarolum; Dicumarol *(USAN)*; Dikumarol; Dikumaroli; Melitoxin. 3,3′-Methylenebis(4-hydroxycoumarin).

Дикумарол

$C_{19}H_{12}O_6$ = 336.3.
CAS — 66-76-2.
ATC — B01AA01.
ATC Vet — QB01AA01.

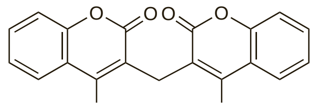

Pharmacopoeias. In *Int.*

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425, although gastrointestinal adverse effects are reported to occur more frequently. The absorption of dicoumarol is affected by food.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving dicoumarol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving dicoumarol can be found under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antidiabetics; antiepileptics; antigout drugs; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; sex hormones; and vitamins.

Pharmacokinetics

Dicoumarol is slowly and erratically absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites.

Uses and Administration

Dicoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It has been used in the management of thromboembolic disorders (p.1187). The usual daily maintenance dose, adjusted according to coagulation tests, is 25 to 200 mg.

Because of its unpredictability of response and high incidence of gastrointestinal effects, dicoumarol has been largely replaced by warfarin.

Digitalis Leaf

Digit. Fol.; Digit. Leaf; Digital, hoja de; Digitale Pourprée; Digitale Pourprée, Feuille de; Digitaliksenlehti; Digitalis; Digitalis Folium; Digitalis purpureae folium; Digitalisblad; Feuille de Digitale; Fingerhutblatt; Folha de Dedaleira; Foxglove Leaf; Hoja de Digital; List náprstníku červeného; Piros gyűszűviráglevél; Rusmenių lapai.

ATC — C01AA03.
ATC Vet — QC01AA03.

NOTE. The term 'digitalis' is often used to describe the entire class of cardiac glycosides.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Digitalis Leaf). The dried leaf of *Digitalis purpurea*. It contains not less than 0.3% of cardenolic glycosides, expressed as digitoxin, and calculated with reference to the drug dried at 100° to 105°. Protect from light and moisture.

USP 31 (Digitalis). The dried leaf of *Digitalis purpurea* (Scrophulariaceae). The potency is such that, when assayed as directed, 100 mg is equivalent to not less than 1 USP unit. Store in containers that protect it from absorbing moisture.

Profile

Digitalis leaf contains a number of cardiac glycosides with positive inotropic activity, including digitoxin, gitoxin, and gitaloxin. It has the general properties described under digoxin (p.1259) and has been used similarly in the management of heart failure. However, when treatment with a cardiac glycoside is required a single glycoside is preferred to digitalis, and digoxin or digitoxin are most commonly used.

Digitalis is used in herbal medicine.

Homoeopathy. Digitalis leaf has been used in homoeopathic medicines under the following names: Digitalis; Digitalis purpurea; Dig. pur.

Preparations

USP 31: Digitalis Capsules; Digitalis Tablets.

Proprietary Preparations (details are given in Part 3)
Ger.: Digophton†.

Multi-ingredient: ***Austria:*** Augentropfen Stulln; ***Ger.:*** Augentropfen Stulln Mono; Unguentum lymphaticum; ***Switz.:*** Augentonicum; Collypan; ***Venez.:*** Linfoderm.

Digitalis Lanata Leaf

Austrian Digitalis; Austrian Foxglove; Digitalis lanata, hoja de; Digitalis Lanatae Folium; Woolly Foxglove Leaf.

CAS — 17575-20-1 (lanatoside A).

Profile

Digitalis lanata leaf consists of the dried leaves of the woolly foxglove, *Digitalis lanata* (Scrophulariaceae), containing about 1 to 1.4% of a mixture of cardioactive glycosides, including digoxin, digitoxin, acetyldigoxin, acetyldigitoxin, lanatoside A, and deslanoside.

Digitalis lanata leaf is used as a source for the manufacture of digoxin and other glycosides.

◊ There have been reports[1] of toxicity after ingestion of dietary supplements contaminated with digitalis lanata.

1. Slifman NR, *et al.* Contamination of botanical dietary supplements by digitalis lanata. *N Engl J Med* 1998; **339:** 806–11.

Digitoxin *(BAN, rINN)*

Digitaline Cristallisée; Digitoksiini; Digitoksinas; Digitoksyna; Digitoxina; Digitoxine; Digitoxinum; Digitoxoside; Dijitoksin. 3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14β-hydroxy-5β-card-20(22)-enolide.

Дигитоксин

$C_{41}H_{64}O_{13}$ = 764.9.

CAS — 71-63-6.

ATC — C01AA04.

ATC Vet — QC01AA04.

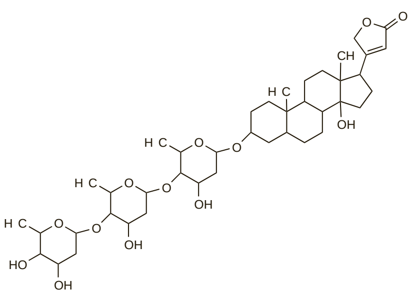

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Digitoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in a mixture of equal volumes of chloroform and methyl alcohol. Protect from light.

USP 31 (Digitoxin). A cardiotonic glycoside obtained from *Digitalis purpurea*, *Digitalis lanata* (Scrophulariaceae), or other suitable species of *Digitalis.* A white or pale buff-coloured, odourless, microcrystalline powder. Practically insoluble in water; soluble 1 in 150 of alcohol and 1 in 40 of chloroform; very slightly soluble in ether. Store in airtight containers.

Adsorption. Binding to an in-line intravenous filter containing a cellulose ester membrane accounted for a reduction[1] in digitoxin concentration of up to 25% from solutions of digitoxin 200 micrograms in 50 mL of glucose 5% or sodium chloride 0.9%. Pretreatment of the filter with a polymer coating reduced adsorption by about half.[2]

Digitoxin was found to be adsorbed onto glass and plastic in substantial amounts from simple aqueous solutions but not from solutions in 30% alcohol, or in plasma, or urine.[3]

1. Butler LD, *et al.* Effect of inline filtration on the potency of low-dose drugs. *Am J Hosp Pharm* 1980; **37:** 935–41.
2. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
3. Molin L, *et al.* Solubility, partition, and adsorption of digitalis glycosides. *Acta Pharm Suec* 1983; **20:** 129–44.

Adverse Effects, Treatment, and Precautions

As for Digoxin, below. Toxicity may be more prolonged after withdrawal of digitoxin because of the longer half-life.

◊ References.

1. Lely AH, van Enter CHJ. Large-scale digitoxin intoxication. *BMJ* 1970; **3:** 737–40.
2. Gilfrich H-J, *et al.* Treatment of massive digitoxin overdose by charcoal haemoperfusion and cholestyramine. *Lancet* 1978; **i:** 505.
3. Pond S, *et al.* Treatment of digitoxin overdose with oral activated charcoal. *Lancet* 1981; **ii:** 1177–8.
4. Kurowski V, *et al.* Treatment of a patient with severe digitoxin intoxication by Fab fragments of anti-digitalis antibodies. *Intensive Care Med* 1992; **18:** 439–42.
5. Schmitt K, *et al.* Massive digitoxin intoxication treated with digoxin-specific antibodies in a child. *Pediatr Cardiol* 1994; **15:** 48–9.
6. Lehmann G, *et al.* Digitoxin intoxication in a 79-year-old patient: a description of a case and review of the literature. *Int J Cardiol* 2000; **75:** 109–13.
7. Hippius M, *et al.* Adverse drug reaction monitoring—digitoxin overdosage in the elderly. *Int J Clin Pharmacol Ther* 2001; **39:** 336–43.

Interactions

As for Digoxin, below. Since digitoxin is significantly metabolised in the liver it may be affected by drugs that induce microsomal enzymes, including rifampicin (see below) and antiepileptics such as phenobarbital.

Antibacterials. Acute heart failure has been reported in a patient taking digitoxin when treatment with *rifampicin* and isoniazid was started; plasma-digitoxin concentrations fell from a pretreatment steady-state value of 27 nanograms/mL to 10 nanograms/mL. The reduction in the digitoxin concentration was attributed to induction of digitoxin metabolism by rifampicin.[1]

Digitoxin toxicity has been described in 2 patients after addition of *azithromycin* to their therapy.[2]

1. Boman G, *et al.* Acute cardiac failure during treatment with digitoxin—an interaction with rifampicin. *Br J Clin Pharmacol* 1980; **10:** 89–90.
2. Thalhammer F, *et al.* Azithromycin-related toxic effects of digitoxin. *Br J Clin Pharmacol* 1998; **45:** 91–2.

Antineoplastics. A mean overall increase of 109% was seen in digitoxin clearance in 5 patients also given *aminoglutethimide*. The interaction was attributed to the induction of hepatic enzymes by aminoglutethimide.[1]

1. Lønning PE, *et al.* Effect of aminoglutethimide on antipyrine, theophylline, and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* 1984; **36:** 796–802.

Calcium-channel blockers. Steady-state plasma concentrations of digitoxin increased by an average of 35% over 2 to 3 weeks in 8 of 10 patients when *verapamil* 240 mg daily was added to their therapy. Total body clearance and extra-renal clearance of digitoxin were reduced by 27% and 29% respectively although renal excretion was unchanged. Plasma-digitoxin concentrations increased by a mean of 21% in 5 of 10 patients treated with *diltiazem* but were not increased by *nifedipine*.[1]

1. Kuhlman J. Effects of verapamil, diltiazem, and nifedipine on plasma levels and renal excretion of digitoxin. *Clin Pharmacol Ther* 1985; **38:** 667–73.

Diuretics. *Spironolactone* has been reported to decrease the half-life and the urinary elimination of unchanged digitoxin when given for at least 10 days to 8 patients on oral maintenance digitoxin therapy.[1] However, increased digitoxin half-life has been reported[2] in 3 healthy subjects when spironolactone was added to digitoxin therapy. The interaction was judged to be of minor clinical importance.

1. Wirth KE, *et al.* Metabolism of digitoxin in man and its modification by spironolactone. *Eur J Clin Pharmacol* 1976; **9:** 345–54.
2. Carruthers SG, Dujovne CA. Cholestyramine and spironolactone and their combination in digitoxin elimination. *Clin Pharmacol Ther* 1980; **27:** 184–7.

Pharmacokinetics

Digitoxin is readily and completely absorbed from the gastrointestinal tract. Therapeutic plasma concentrations may range from 10 to 35 nanograms/mL but there is considerable interindividual variation. Digitoxin is more than 90% bound to plasma proteins. It is very slowly eliminated from the body and is metabolised in the liver. Most metabolites are inactive; the major active metabolite is digoxin. Enterohepatic recycling occurs and digitoxin is excreted in the urine, mainly as metabolites. It is also excreted in the faeces and this route becomes significant in renal impairment. Digitoxin has an elimination half-life of up to 7 days or more. The half-life is generally unchanged in renal impairment.

The pharmacokinetics of digitoxin may be affected by age and by concurrent diseases (see under Uses and Administration, below).

Uses and Administration

Digitoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (below) and is used in the management of some cardiac arrhythmias (p.1160) and in heart failure (p.1165).

Digitoxin is the most potent of the digitalis glycosides and is the most cumulative in action. The onset of its action is slower than that of the other cardiac glycosides and it may therefore be less suitable than digoxin for rapid digitalisation; after oral doses its effects may be evident in about 2 hours and its full effects in about 12 hours. Its effects persist for about 3 weeks.

As described under digoxin, dosage should be carefully adjusted to the needs of the individual patient. Steady-state therapeutic plasma concentrations of digitoxin may range from 10 to 35 nanograms/mL; higher values may be associated with toxicity. In adults 1 to 1.5 mg has been given orally in divided doses over 24 hours for rapid digitalisation, while for slow digitalisation an oral dose of 200 micrograms twice daily for 4 days has been given. The usual maintenance dose is 100 to 200 micrograms daily, but 100 micrograms on alternate days may be adequate. Digitoxin may also be given by slow intravenous injection when vomiting or other conditions prevent oral use; maintenance doses of 70 to 100 micrograms daily have been used. It has also been given intramuscularly but injections may be irritant.

Administration in children. Children were found to have a greater volume of distribution of digitoxin than adults and a shorter mean half-life, although individual variation was considerable. The increase in total clearance in children compared with adults was attributed to greater metabolic clearance. Digitalisation doses of 20 micrograms/kg were well tolerated.[1]

1. Larsen A, Storstein L. Digitoxin kinetics and renal excretion in children. *Clin Pharmacol Ther* 1983; **33:** 717–26.

Administration in the elderly. Digitoxin half-life, apparent volume of distribution, and clearance were not found to differ in elderly subjects compared with young adults after intravenous injection in a single-dose study. The long half-life may make once weekly dosing possible in poorly compliant patients.[1]

1. Donovan MA, *et al.* The effect of age on digitoxin pharmacokinetics. *Br J Clin Pharmacol* 1981; **11:** 401–2.

Administration in renal disease. The pharmacokinetics of digitoxin were changed significantly in 5 patients with nephrotic syndrome. The apparent volume of distribution of digitoxin was increased and protein binding decreased. Such patients should be maintained at lower serum-digitoxin concentrations than other patients but will need larger doses because of the shortened serum half-life and the increased renal excretion of digitoxin and its cardioactive metabolites.[1]

1. Storstein L. Studies on digitalis VII: influence of nephrotic syndrome on protein binding, pharmacokinetics, and renal excretion of digitoxin and cardioactive metabolites. *Clin Pharmacol Ther* 1976; **20:** 158–66.

Malignant neoplasms. There has been some interest in the potential anticancer activity of digitoxin and related compounds.

References.

1. Haux J. Digitoxin is a potential anticancer agent for several types of cancer. *Med Hypotheses* 1999; **53:** 543–8.
2. Haux J, *et al.* Digitoxin medication and cancer: case control and internal dose-response studies. *BMC Cancer* 2001; **1:** 11.
3. Johansson S, *et al.* Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. *Anticancer Drugs* 2001; **12:** 475–83.
4. López-Lázaro M, *et al.* Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. *J Nat Prod* 2005; **68:** 1642–5.
5. López-Lázaro M. Digitoxin as an anticancer agent with selectivity for cancer cells: possible mechanisms involved. *Expert Opin Ther Targets* 2007; **11:** 1043–53.

Preparations

BP 2008: Digitoxin Tablets;
USP 31: Digitoxin Injection; Digitoxin Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Digimerck; Ditaven†; ***Belg.:*** Digitaline†; ***Braz.:*** Digitaline; ***Ger.:*** Coramedan†; Digimed; Digimerck; Tardigal†; ***Hung.:*** Digimerck; ***Swed.:*** Digitrin†; ***USA:*** Crystodigin.

Digoxin *(BAN, rINN)*

Digoksiini; Digoksin; Digoksinas; Digoksyna; Digoxina; Digoxine; Digoxinum; Digoxosidum. 3β-[(*O*-2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14β-dihydroxy-5β-card-20(22)-enolide.

Дигоксин

$C_{41}H_{64}O_{14}$ = 780.9.

CAS — 20830-75-5.

ATC — C01AA05.

ATC Vet — QC01AA05.

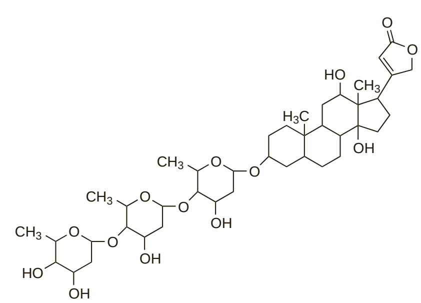

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Digoxin). A white or almost white powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol; freely soluble in a mixture of equal volumes of dichloromethane and methyl alcohol. Protect from light.

USP 31 (Digoxin). A cardiotonic glycoside obtained from the leaves of *Digitalis lanata* (Scrophulariaceae). Clear to white, odourless, crystals, or a white, odourless, crystalline powder. Practically insoluble in water and in ether; slightly soluble in diluted alcohol and in chloroform; freely soluble in pyridine. Store in airtight containers.

Adverse Effects

Digoxin and the other cardiac glycosides commonly produce adverse effects because the margin between the therapeutic and toxic doses is small; plasma concentrations of digoxin in excess of 2 nanograms/mL are considered to be an indication that the patient is at special risk although there is considerable interindividual variation. There have been many fatalities, particularly due to cardiac toxicity.

Nausea, vomiting, and anorexia may be among the earliest symptoms of digoxin toxicity or overdosage; diarrhoea and abdominal pain may occur. Certain neurological effects are also common symptoms of digoxin overdosage and include headache, facial pain, fatigue, weakness, dizziness, drowsiness, disorientation, mental confusion, bad dreams and more rarely delirium, acute psychoses, and hallucinations. Convulsions have been reported. Visual disturbances including blurred vision may occur; colour vision may be affected with objects appearing yellow or, less frequently, green, red, brown, blue, or white. Hypersensitivity reactions are rare; thrombocytopenia has been reported. The cardiac glycosides may have some oestrogenic activity and occasionally cause gynaecomastia at therapeutic doses.

Rapid intravenous injection of digoxin may cause vasoconstriction and transient hypertension. Intramuscular or subcutaneous injection can cause local irritation.

The most serious adverse effects are those on the heart. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage, particularly in children. In general the incidence and severity of arrhythmias is related to the severity of the underlying heart disease. Almost any arrhythmia may ensue, but particular note should be made of supraventricular tachycardia, especially AV junctional tachycardia and atrial tachycardia with block. Ventricular arrhythmias including extrasystoles, sinoatrial block, sinus bradycardia, and AV block may also occur.

Hypokalaemia predisposes to digoxin toxicity; adverse reactions to digoxin may be precipitated if hypokalaemia occurs, for example after prolonged use of diuretics. Hyperkalaemia occurs in acute digoxin overdosage.

As digoxin has a shorter half-life than digitalis or digitoxin any toxic effects will tend to resolve more rapidly.

◊ General references to digitalis toxicity.

1. Pentel PR, Salerno DM. Cardiac drug toxicity: digitalis glycosides and calcium-channel and β-blocking agents. *Med J Aust* 1990; **152:** 88–94.
2. Wells TG, *et al.* Age-related differences in digoxin toxicity and its treatment. *Drug Safety* 1992; **7:** 135–51.
3. Johnston GD. Adverse reaction profile: digoxin. *Prescribers' J* 1993; **33:** 29–35.
4. Kernan WN, *et al.* Incidence of hospitalization for digitalis toxicity among elderly Americans. *Am J Med* 1994; **96:** 426–31.
5. Li-Saw-Hee FL, Lip GYH. How safe is digoxin? *Adverse Drug React Bull* 1998; (Feb): 715–18.
6. Gittelman MA, *et al.* Acute pediatric digoxin ingestion. *Pediatr Emerg Care* 1999; **15:** 359–62.
7. López-Gómez D, *et al.* Intoxicación grave por digoxina: utilización exitosa del tratamiento clásico. *Rev Esp Cardiol* 2000; **53:** 471–2.
8. Ma G, *et al.* Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; **20:** 145–52.
9. Demiryürek AT, Demiryürek S. Cardiotoxicity of digitalis glycosides: roles of autonomic pathways, autacoids and ion channels. *Auton Autacoid Pharmacol* 2005; **25:** 35–52.
10. Bauman JL, *et al.* Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs* 2006; **6:** 77–86.

Effects on the blood. Thrombocytopenia has been reported[1] in a small number of patients taking digoxin. An association between several cardiovascular drugs, including digitalis glycosides (digoxin and acetyldigoxin), and agranulocytosis was also found in an international study[2] although again the incidence was low.

1. George JN, *et al.* Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; **129:** 886–90.
2. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: the international agranulocytosis and aplastic anemia study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects in the elderly. Elderly patients may be particularly susceptible to digoxin toxicity, even at therapeutic plasma concentrations.[1] Adverse effects reported in elderly patients with toxic plasma-digoxin concentrations have included chorea,[2] profuse watery diarrhoea,[3] and dysphagia with dysphonia.[4]

1. Miura T, *et al.* Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000; **34:** 427–32.
2. Mulder LJMM, *et al.* Generalised chorea due to digoxin toxicity. *BMJ* 1988; **296:** 1262.
3. Andrews PA, Wilkinson PR. Diarrhoea as a side effect of digoxin. *BMJ* 1990; **301:** 1398.
4. Cordeiro MF, Arnold KG. Digoxin toxicity presenting as dysphagia and dysphonia. *BMJ* 1991; **302:** 1025.

Hypersensitivity. Hypersensitivity reactions to cardiac glycosides are rare but skin reactions have been reported. An 86-year-old man developed a generalised, pruritic, erythematous rash after digoxin was given intravenously.[1] The rash recurred on rechallenge with digoxin tablets.

1. Martin SJ, Shah D. Cutaneous hypersensitivity reaction to digoxin. *JAMA* 1994; **271:** 1905.

Treatment of Adverse Effects

In *acute poisoning*, gastric lavage may be considered if the patient presents within one hour of ingestion. Repeated doses of activated charcoal may be given to reduce the absorption and enterohepatic recycling of cardiac glycosides; colestyramine and colestipol have also been tried. Attempts to remove cardiac glycosides by haemodialysis or peritoneal dialysis have generally been ineffective and the value of haemoperfusion is controversial. Forced diuresis with furosemide is generally ineffective and may be dangerous; serious electrolyte imbalance may result from the use of such potent diuretics.

Cardiac toxicity in acute or chronic poisoning should be treated under ECG control and serum electrolytes should be monitored. Antiarrhythmic treatment may be necessary and should be determined by the specific arrhythmia present (see p.1160). Atropine is given intravenously to correct bradycardia and in patients with heart block. Pacing may be necessary if atropine is not effective. Potassium chloride may be given in hypokalaemic patients provided that renal function is normal and heart block is not present. Potassium has also been given to normokalaemic patients but caution is needed since hyperkalaemia can occur rapidly. Other electrolyte imbalances should be corrected.

In *massive overdosage* progressive hyperkalaemia occurs and is fatal unless reversed. Soluble insulin with glucose has been given and, if the hyperkalaemia is refractory, dialysis may be tried. Massive life-threatening overdosage has been treated successfully with digoxin-specific antibody fragments (p.1443).

For the treatment of *chronic poisoning* temporary withdrawal of digoxin or other cardiac glycosides may be all that is necessary, with subsequent doses adjusted according to the needs of the patient. Serum electrolytes should be measured and the ECG monitored. Potassium supplements should be given to correct hypokalaemia.

◊ References.

1. Allen NM, Dunham GD. Treatment of digitalis intoxication with emphasis on the clinical use of digoxin immune Fab. *DICP Ann Pharmacother* 1990; **24:** 991–8.
2. Dick M, *et al.* Digitalis intoxication recognition and management. *J Clin Pharmacol* 1991; **31:** 444–7.
3. Critchley JAJH, Critchley LAH. Digoxin toxicity in chronic renal failure: treatment by multiple dose activated charcoal intestinal dialysis. *Hum Exp Toxicol* 1997; **16:** 733–5.

Precautions

Digoxin is generally contra-indicated in patients with hypertrophic obstructive cardiomyopathy unless there is severe cardiac failure, since the outflow obstruction may be worsened. It is also contra-indicated in patients with the Wolff-Parkinson-White syndrome or other evidence of an accessory pathway, especially if it is accompanied by atrial fibrillation, since ventricular tachycardia or fibrillation may be precipitated. Digoxin is not an appropriate form of therapy for any ventricular arrhythmia.

Digoxin toxicity is common and may result from raised plasma concentrations or an increase in sensitivity to digoxin. Almost any deterioration in the condition of the heart or circulation may increase the sensitivity to digoxin and it should be used with caution in all patients with cardiovascular disease. Early signs of digoxin toxicity should be watched for and the heart rate should generally be maintained above 60 beats per minute. Toxicity may result from giving loading doses too rapidly and from accumulation of maintenance doses as well as from acute poisoning. Even with intravenous doses a response may take a number of hours, and persistence of tachycardia is therefore not a reason to exceed the recommended intravenous dose.

Digoxin should be used with caution in partial heart block since complete heart block may be induced; it should also be used with care in sinus node disorders. Caution is also required in acute myocarditis (such as rheumatic carditis), in acute myocardial infarction, in advanced heart failure, and in severe pulmonary disease, due to the increased myocardial sensitivity. Digoxin may also enhance the occurrence of arrhythmias in patients undergoing cardioversion and should be withdrawn 1 to 2 days before such procedures if possible. If cardioversion is essential and digoxin has already been given, low energy shocks must be used.

Electrolyte imbalances may affect the sensitivity to digoxin, as may thyroid dysfunction. The effects of digoxin are enhanced by hypokalaemia, hypomagnesaemia, hypercalcaemia, hypoxia, and hypothyroidism and doses may need to be reduced until these conditions are corrected. Resistance to the effects of digoxin may occur in hyperthyroidism. Digoxin should be given with care, and possibly in reduced dosage, to patients who have received it or other cardiac glycosides within the previous 2 to 3 weeks.

Digoxin doses should generally be reduced and plasma-digoxin concentrations monitored in patients with renal impairment, in the elderly, and in premature infants (see Uses and Administration, below).

Breast feeding. Studies[1,2] have shown that digoxin is distributed into breast milk, although the amount was considered too small to have an effect on the child. No adverse effects have been seen in breast-feeding infants whose mothers were receiving digoxin, and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Levy M, *et al.* Excretion of drugs in human milk. *N Engl J Med* 1997; **297:** 789.
2. Chan V, *et al.* Transfer of digoxin across the placenta and into breast milk. *Br J Obstet Gynaecol* 1978; **85:** 605–9.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Gastrointestinal disorders. Absorption from tablets of digoxin may be decreased due to inadequate dissolution in patients with malabsorption syndromes or small bowel resections and it has been recommended that liquid dosage forms of digoxin should be used in the latter case.[1] However, only 40 to 60% of a digoxin dose given as elixir was absorbed in a patient with a small bowel resection[2] compared with about 80% in patients with normal gastrointestinal function, suggesting a need for slightly increased oral maintenance doses of digoxin in patients with resections. In a further patient with a similar resection[3] a therapeutic plasma-digoxin concentration was not achieved with any oral formulation.

1. Kumer KP, *et al.* Perspectives on digoxin absorption from small bowel resections. *Drug Intell Clin Pharm* 1983; **17:** 121–3.
2. Vetticaden SJ, *et al.* Digoxin absorption in a patient with short-bowel syndrome. *Clin Pharm* 1986; **5:** 62–4.
3. Ehrenpreis ED, *et al.* Malabsorption of digoxin tablets, gel caps, and elixir in a patient with an end jejunostomy. *Ann Pharmacother* 1994; **28:** 1239–40.

Heart surgery. Patients undergoing cardiac surgery appear to have increased sensitivity to digoxin toxicity and thus an increased risk of arrhythmias.[1] Digoxin has been found[2] to be no better than placebo in preventing postoperative arrhythmias after coronary artery bypass surgery, and actually induced supraventricular arrhythmias in 2 patients. Arrhythmias compatible with digoxin intoxication have occurred postoperatively[1] although serum-digoxin concentrations ranged from 0 to 2.8 nanograms/mL; therefore, the arrhythmias may have been due to either the surgical procedures or to increased sensitivity to digoxin.

1. Rose MR, *et al.* Arrhythmias following cardiac surgery: relation to serum digoxin levels. *Am Heart J* 1975; **89:** 288–94.
2. Weiner B, *et al.* Digoxin prophylaxis following coronary artery bypass surgery. *Clin Pharm* 1986; **5:** 55–8.

Interference with digoxin assays. The presence of endogenous digoxin-like substances in neonates, and in patients with liver or kidney dysfunction, may be responsible for elevated values or false-positive results in some plasma-digoxin assays.[1] Some patients may have antibodies that react with the assay system and produce falsely elevated values.[2]

Some drugs may also interfere with plasma-digoxin assays; these include prednisolone[1] and ginseng.[3] Raised serum-digoxin concentrations (but without signs of digoxin toxicity) were noted in an elderly man after the use of Siberian ginseng (*Eleutherococcus senticosus*). However, concentrations remained high even when digoxin was discontinued and returned to the therapeutic range only after the ginseng was stopped. Siberian ginseng contains eleutherosides, which are chemically related to cardiac glycosides such as digoxin, and the assay may have measured these compounds, or their derivatives, as well as digoxin. Although it has been suggested that this reaction may have been due to the substitution of the unrelated cardiotoxic herb *Periploca sepium*,[4] both ginseng and Siberian ginseng have been shown to interfere with some digoxin assays *in vitro* and *in vivo*.[5] Spironolactone may interfere with digoxin assays but may also produce changes in digoxin concentrations (see Diuretics under Interactions, below).

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–89.
2. Liendo C, *et al.* A new interference in some digoxin assays: anti-murine heterophilic antibodies. *Clin Pharmacol Ther* 1996; **60:** 593–8.
3. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can Med Assoc J* 1996; **155:** 293–5.
4. Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. *Can Med Assoc J* 1996; **155:** 1237.
5. Dasgupta A, *et al.* Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays: significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* 2003; **119:** 298–303.

Pregnancy. There is considerable evidence that digoxin crosses the placenta freely with serum-digoxin concentrations at term similar in the newborn and mother. No significant adverse effects attributed to digoxin have been noted in the fetus or neonate although adverse fetal effects, including fetal death, have been reported in mothers with digitalis toxicity. Some concern has been expressed that maternal digitalis therapy may occasionally cause low birth-weights in infants of mothers with heart disease, but the underlying disease might also be important.[1] The presence of endogenous digoxin-like immunoreactive substances in the serum of pregnant women and neonates could make the interpretation of digoxin assays difficult. In one study,[2] high concentrations of endogenous digoxin-like immunoreactivity in cord blood suggested that it might be synthesised during delivery, in which case the placental transfer of digoxin might be overestimated.

1. Rotmensch HH, *et al.* Management of cardiac arrhythmias during pregnancy: current concepts. *Drugs* 1987; **33:** 623–33.
2. Lupoglazoff JM, *et al.* Endogenous digoxin-like immunoreactivity during pregnancy and at birth. *Br J Clin Pharmacol* 1993; **35:** 251–4.

Interactions

There may be interactions between digoxin and drugs that alter its absorption, interfere with its excretion, or have additive effects on the myocardium. Drugs that cause electrolyte disturbances increase the risk of toxicity from cardiac glycosides. Thiazides and loop *diuretics* cause hypokalaemia and also hypomagnesaemia which may lead to cardiac arrhythmias. Other causes of hypokalaemia include treatment with *corticosteroids, beta$_2$ agonists* (such as salbutamol), *amphotericin B, sodium polystyrene sulfonate, carbenoxolone,* and dialysis. Hypercalcaemia may also increase toxicity and intravenous use of *calcium salts* is best avoided in patients taking cardiac glycosides. Serum-digoxin concentrations may be significantly increased by *quinidine, amiodarone,* and *propafenone* and reduction of digoxin dosage may be required. Other antiarrhythmics may have additive effects on the myocardium increasing the likelihood of adverse effects; *beta blockers* may potentiate bradycardia due to digoxin. *Calcium-channel blockers* may increase digoxin concentrations.

Digoxin is a substrate for P-glycoprotein and interactions may occur with drugs that affect P-glycoprotein function (see Metabolism and Excretion under Pharmacokinetics, below).

◊ Reviews of drug interactions occurring with digoxin.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Magnani B, Malini PL. Cardiac glycosides: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 97–109.

ACE inhibitors. Although increased serum-digoxin concentrations have been reported in patients with severe chronic heart failure given *captopril*,[1] other studies have failed to confirm this effect.[2,3] Studies with various other ACE inhibitors have also failed to show any significant effect on serum-digoxin concentrations. However, ACE inhibitors may cause a deterioration in renal function and this could lead to an increase in serum-digoxin concentration due to impaired digoxin excretion.[4]

1. Cleland JGF, *et al.* Interaction of digoxin and captopril. *Br J Clin Pharmacol* 1984; **17:** 214P.
2. Magelli C, *et al.* Lack of effect of captopril on serum digoxin in congestive heart failure. *Eur J Clin Pharmacol* 1989; **36:** 99–100.
3. Rossi GP, *et al.* Effect of acute captopril administration on digoxin pharmacokinetics in normal subjects. *Curr Ther Res* 1989; **46:** 439–44.
4. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Alpha blockers. *Prazosin*[1] has been reported to increase the mean plasma-digoxin concentration in patients receiving a maintenance dose of digoxin.

1. Çopur S, *et al.* Effects of oral prazosin on total plasma digoxin levels. *Fundam Clin Pharmacol* 1988; **2:** 13–17.

Angiotensin II receptor antagonists. In a study[1] in healthy subjects, *telmisartan* increased peak serum-digoxin concentrations but trough concentrations were unaffected and it was suggested that the effect was unlikely to be clinically significant. No interaction was found when digoxin was given with *losartan*[2] or with *eprosartan*[3] in healthy subjects.

1. Stangier J, *et al.* The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol* 2000; **40:** 1373–9.
2. de Smet M, *et al.* Effect of multiple doses of losartan on the pharmacokinetics of single doses of digoxin in healthy volunteers. *Br J Clin Pharmacol* 1995; **40:** 571–5.
3. Martin DE, *et al.* Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 661–4.

Antiarrhythmics. *AMIODARONE.* An interaction between digoxin and amiodarone resulting in increased plasma-digoxin concentrations has been reported[1-5] on several occasions; the concentration may be doubled.[5] An increase in serum-digoxin concentrations of 68 to 800% has been reported[2] during amiodarone therapy in children. The interaction does not appear to be due to a reduction in urinary excretion alone[3,4] and seems to be dose-related. It has been recommended[1,6] that the initial dose of digoxin should be halved when amiodarone is given.

1. Moysey JO, *et al.* Amiodarone increases plasma digoxin concentrations. *BMJ* 1981; **282:** 272.
2. Koren G, *et al.* Digoxin toxicity associated with amiodarone therapy in children. *J Pediatr* 1984; **104:** 467–70.
3. Douste-Blazy P, *et al.* Influence of amiodarone on plasma and urine digoxin concentrations. *Lancet* 1984; **i:** 905.
4. Mingardi G. Amiodarone and plasma digoxin levels. *Lancet* 1984; **i:** 1238.
5. Johnston A, *et al.* The digoxin-amiodarone interaction. *Br J Clin Pharmacol* 1987; **24:** 253P.
6. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.

DISOPYRAMIDE. Disopyramide appears to have no clinically significant effect on the pharmacokinetics of digoxin in healthy subjects[1,2] but has been reported to modify the cardiovascular effects of digoxin.[1]

1. Elliott HL, *et al.* Pharmacodynamic and pharmacokinetic evaluation of the interaction between digoxin and disopyramide. *Br J Clin Pharmacol* 1982; **14:** 141P.
2. Risler T, *et al.* On the interaction between digoxin and disopyramide. *Clin Pharmacol Ther* 1983; **34:** 176–80.

FLECAINIDE. Giving flecainide 200 mg twice daily to 15 healthy subjects taking digoxin caused a mean increase of 24% in predose digoxin concentrations and of 13% in digoxin concentrations 6 hours after the digoxin dose.[1] It was considered that in most cases these increases in plasma-digoxin concentrations would not present a clinical problem, but that patients with higher plasma-digoxin concentrations or atrioventricular nodal dysfunction should be monitored.

1. Weeks CE, *et al.* The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol* 1986; **26:** 27–31.

PROPAFENONE. Increased serum-digoxin concentrations have been reported when propafenone is also given.[1-4] There is considerable interindividual variation in the extent of the interaction; increases in serum-digoxin concentrations of up to 254% have been reported. If digoxin and propafenone are given together, the dose of digoxin should be reduced and serum-digoxin concentration should be monitored.

1. Nolan PE, *et al.* Effects of coadministration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. *J Clin Pharmacol* 1989; **29:** 46–52.
2. Calvo MV, *et al.* Interaction between digoxin and propafenone. *Ther Drug Monit* 1989; **11:** 10–15.
3. Zalzstein E, *et al.* Interaction between digoxin and propafenone in children. *J Pediatr* 1990; **116:** 310–12.
4. Bigot M-C, *et al.* Serum digoxin levels related to plasma propafenone levels during concomitant treatment. *J Clin Pharmacol* 1991; **31:** 521–6.

QUINIDINE. Quinidine causes an increase in serum-digoxin concentration in almost all patients given the two drugs together.[1-3] The serum-digoxin concentration may be increased by up to 500% but is usually approximately doubled.[1] Signs and symptoms of digoxin toxicity may occur although some workers[4] have suggested that these may be accounted for by an additive effect of the 2 drugs rather than by the effect on serum-digoxin concentration. The exact mechanism of interaction is not clear but a substantial decrease in the renal and nonrenal clearance of digoxin has been found.[5] The distribution volume of digoxin may also be reduced[2] reflecting impaired tissue binding, and there is increased systemic availability.[1] It is generally recommended that the dose of digoxin is halved in digitalised patients who are to be given quinidine.[2] Subsequently, serum-digoxin concentrations should be monitored, especially during the first 1 to 2 weeks after which the new steady-state digoxin concentration should be achieved.[2]

1. Bigger JT, Leahey EB. Quinidine and digoxin: an important interaction. *Drugs* 1982; **24:** 229–39.
2. Pedersen KE. Digoxin interactions: the influence of quinidine and verapamil on the pharmacokinetics and receptor binding of digitalis glycosides. *Acta Med Scand* 1985; **697** (suppl): 1–40.
3. Mordel A, *et al.* Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther* 1993; **53:** 457–62.
4. Walker AM, *et al.* Drug toxicity in patients receiving digoxin and quinidine. *Am Heart J* 1983; **105:** 1025–8.
5. Hedman A, *et al.* Interactions in the renal and biliary elimination of digoxin: stereoselective difference between quinine and quinidine. *Clin Pharmacol Ther* 1990; **47:** 20–6.

VERAPAMIL. For a discussion on the interaction between digoxin and verapamil, see under Calcium-channel Blockers, below.

Antibacterials. About 10% of patients receiving digoxin may metabolise 40% or more of the drug to cardio-inactive metabolites.[1] Gut flora contribute greatly to this process, and the use of antibacterials such as *erythromycin* or *tetracycline* in these patients appears to reduce this metabolic process resulting in higher serum concentrations.[2] Digoxin toxicity has been reported in digitalised patients given erythromycin,[3,4] *azithromycin*,[5] *clarithromycin*,[6-8] and *roxithromycin*.[9] It has been postulated[5,10] that the macrolide antibacterials may also inhibit P-glycoprotein-mediated renal tubular secretion of digoxin. Oral *neomycin* may reduce serum-digoxin concentrations by reducing digoxin absorption.

Rifampicin may reduce serum-digitoxin concentrations by inducing its metabolism (see p.1259) although a study[11] in healthy subjects suggested that this reduction might rather be due to induction of intestinal P-glycoprotein. Digoxin is mainly excreted unchanged in the urine but rifampicin increased digoxin dose requirements substantially in 2 patients dependent on dialysis.[12] When rifampicin was stopped digoxin requirements fell by about 50%.

1. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
2. Lindenbaum J, *et al.* Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med* 1981; **305:** 789–94.
3. Maxwell DL, *et al.* Digoxin toxicity due to interaction of digoxin with erythromycin. *BMJ* 1989; **298:** 572.
4. Morton MR, Cooper JW. Erythromycin-induced digoxin toxicity. *DICP Ann Pharmacother* 1989; **23:** 668–70.
5. Ten Eick AP, *et al.* Possible drug interaction between digoxin and azithromycin in a young child. *Clin Drug Invest* 2000; **20:** 61–64.
6. Midoneck SR, Etingin OR. Clarithromycin-related toxic effects of digoxin. *N Engl J Med* 1995; **333:** 1505.
7. Nawarskas JJ, *et al.* Digoxin toxicity secondary to clarithromycin therapy. *Ann Pharmacother* 1997; **31:** 864–6.
8. Laberge P, Martineau P. Clarithromycin-induced digoxin intoxication. *Ann Pharmacother* 1997; **31:** 999–1002.
9. Corallo CE, Rogers IR. Roxithromycin-induced digoxin toxicity. *Med J Aust* 1996; **165:** 433–4.
10. Wakasugi H, *et al.* Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther* 1998; **64:** 123–8.
11. Greiner B, *et al.* The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest* 1999; **104:** 147–53.
12. Gault H, *et al.* Digoxin-rifampin interaction. *Clin Pharmacol Ther* 1984; **35:** 750–4.

Antidepressants. In a study[1] in healthy subjects, use of digoxin together with an extract of *St John's wort* for 10 days resulted in a significant decrease in the plasma-digoxin concentration. It was suggested that the interaction might be due to induction of the P-glycoprotein transporter. In a study[2] in healthy male subjects, *nefazodone* increased steady-state plasma-digoxin concentrations by about 30% but no adverse or clinical effects were associated with the increase. However, due to the narrow therapeutic range of digoxin, it was suggested that plasma-digoxin concentrations should be monitored in patients also given nefazodone. Similar recommendations have been made for *trazodone*.

Digoxin toxicity developed in a patient shortly after starting *paroxetine* and was associated with increased serum-digoxin concentrations.[3] However, the role of paroxetine in the reaction has been queried.[4,5]

1. Johne A, *et al.* Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). *Clin Pharmacol Ther* 1999; **66:** 338–45.
2. Dockens RC, *et al.* Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol* 1996; **36:** 160–7.
3. Yasui-Furukori N, Kaneko S. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **367:** 788.
4. Bateman DN, *et al.* Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1962–3.
5. Hallberg P, Melhus H. Digitalis intoxication induced by paroxetine co-administration. *Lancet* 2006; **368:** 1963.

Antidiabetics. Subtherapeutic plasma-digoxin concentrations were noted in a diabetic woman receiving *acarbose* and digoxin.[1] The plasma concentration of digoxin increased to a therapeutic level when acarbose was stopped. A study[2] in healthy subjects suggested that the interaction was due to inhibition of the absorption of digoxin by acarbose.

1. Serrano JS, *et al.* A possible interaction of potential clinical interest between digoxin and acarbose. *Clin Pharmacol Ther* 1996; **60:** 589–92.
2. Miura T, *et al.* Impairment of absorption of digoxin by acarbose. *J Clin Pharmacol* 1998; **38:** 654–7.

Antiepileptics. *Phenytoin* caused a marked decrease in steady-state serum-digoxin concentrations when given with digoxin and acetyldigoxin to 6 healthy subjects for 7 days.[1] Total digoxin clearance was increased by an average of 27% and elimination half-life was reduced by an average of 30%. This interaction may be more likely with digitoxin, since digitoxin is more dependent on the liver for elimination.

A brief report of an open study[2] in 12 subjects indicated a slight but significant decrease in digoxin bioavailability when *topiramate* was also given, although half-life and renal clearance of digoxin did not appear to be affected.

1. Rameis H. On the interaction between phenytoin and digoxin. *Eur J Clin Pharmacol* 1985; **29:** 49–53.
2. Liao S, Palmer M. Digoxin and topiramate drug interaction study in male volunteers. *Pharm Res* 1993; **10** (suppl): S405.

Antifungals. Two men given *itraconazole* while receiving digoxin developed signs and symptoms of digoxin toxicity and elevated serum-digoxin concentrations.[1,2] A further case report[3] suggested that the interaction was due to a reduction in the renal clearance of digoxin when itraconazole was given.

Additive adverse effects due to hypokalaemia may occur when digoxin is given with *amphotericin B*.

1. Rex J. Itraconazole–digoxin interaction. *Ann Intern Med* 1992; **116:** 525.
2. Alderman CP, Jersmann HPA. Digoxin–itraconazole interaction. *Med J Aust* 1993; **159:** 838–9.
3. Alderman CP, Allcroft PD. Digoxin-itraconazole interaction: possible mechanisms. *Ann Pharmacother* 1997; **31:** 438–40.

Antimalarials. In 6 subjects given *quinine sulfate*, total body clearance of digoxin after an intravenous dose was decreased by 26%, primarily through a reduction in nonrenal clearance.[1] Increased urinary excretion of digoxin was consistent with alterations in the nonrenal clearance of digoxin and might be due to changes in the metabolism or biliary secretion of digoxin. Quinine increased the mean elimination half-life of digoxin from 34.2 to 51.8 hours but did not consistently change the volume of distribution.

An increase in the plasma-digoxin concentration, but without symptoms of toxicity, was noted in 2 women given *hydroxychloroquine* (for rheumatoid arthritis) in addition to long-term digoxin therapy.[2]

1. Wandell M, *et al.* Effect of quinine on digoxin kinetics. *Clin Pharmacol Ther* 1980; **28:** 425–30.
2. Leden I. Digoxin–hydroxychloroquine interaction? *Acta Med Scand* 1982; **211:** 411–12.

Antineoplastics. A study[1] in patients undergoing antineoplastic therapy found that the absorption of digoxin from tablets was reduced by an average of 46.5%, whereas that of digoxin from liquid-filled capsules was not significantly changed. Another study[2] in similar patients found that the steady-state concentration of digoxin after giving acetyldigoxin was reduced, but that digitoxin concentrations were maintained. It was suggested that the interaction was due to reduced absorption of digitalis glycosides through the damaged gastrointestinal mucosa and that liquid-filled capsules or digitoxin might be preferred in these patients.

Licensed product information for *lenalidomide* states that it may increase plasma exposure of digoxin and recommends that digoxin concentrations should be monitored.

1. Bjornsson TD, *et al.* Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. *Clin Pharmacol Ther* 1986; **39:** 25–8.
2. Kuhlmann J. Inhibition of digoxin absorption but not of digitoxin during cytostatic drug therapy. *Arzneimittelforschung* 1982; **32:** 698–704.

Antithyroid drugs. Reduced peak serum-digoxin concentrations were noted in 9 of 10 healthy subjects after a single oral dose of *carbimazole* although conversely in the tenth subject digoxin concentrations rose.[1] Caution is also needed since changes in thyroid function may independently affect sensitivity to digoxin (see Precautions, above).

1. Rao BR, *et al.* Influence of carbimazole on serum levels and haemodynamic effects of digoxin. *Clin Drug Invest* 1997; **13:** 350–4.

Antivirals. A woman stabilised on digoxin and tolerating lamivudine, indinavir and stavudine for HIV infection, developed symptoms of digoxin toxicity 3 days after *ritonavir* was added to her treatment.[1] It was suggested that the interaction might be due to inhibition of the P-glycoprotein transporter system by ritonavir. A pharmacokinetic study[2] showing significant inhibition of renal digoxin clearance by ritonavir seemed to support this hypothesis.

1. Phillips EJ, *et al.* Digoxin toxicity and ritonavir: a drug interaction mediated through p-glycoprotein? *AIDS* 2003; **17:** 1577–8.
2. Ding R, *et al.* Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers. *Clin Pharmacol Ther* 2004; **76:** 73–84.

Benzodiazepines. Raised serum-digoxin concentrations have been reported in patients also taking *diazepam*[1] or *alprazolam*.[2,3] The clearance of digoxin was reduced by these benzodiazepines.

1. Castillo-Ferrando JR, *et al.* Digoxin levels and diazepam. *Lancet* 1980; **ii:** 368.
2. Tollefson G, *et al.* Alprazolam-related digoxin toxicity. *Am J Psychiatry* 1984; **141:** 1612–14.
3. Guven H, *et al.* Age-related digoxin-alprazolam interaction. *Clin Pharmacol Ther* 1993; **54:** 42–4.

Beta$_2$ agonists. A single intravenous[1,2] or oral[3] dose of *salbutamol* has been reported to decrease steady-state serum-digoxin concentrations by up to 16% and 22% respectively in healthy subjects. Although salbutamol had no significant effect on the concentration of digoxin in skeletal muscle, it was considered that increased binding to skeletal muscle could explain the interaction. Beta$_2$ agonists such as salbutamol can also cause hypokalaemia which may increase susceptibility to digoxin-induced arrhythmias.

1. Edner M, Jogestrand T. Effect of salbutamol on digoxin concentration in serum and skeletal muscle. *Eur J Clin Pharmacol* 1989; **36:** 235–8.
2. Edner M, *et al.* Effect of salbutamol on digoxin pharmacokinetics. *Eur J Clin Pharmacol* 1992; **42:** 197–201.
3. Edner M, Jogestrand T. Oral salbutamol decreases serum digoxin concentration. *Eur J Clin Pharmacol* 1990; **38:** 195–7.

Beta blockers. Beta blockers may increase the risk of heart block and bradycardia with digoxin. In addition, *carvedilol* has been reported[1-3] to increase plasma concentrations of digoxin, although the effect is generally small and probably not clinically significant. However, a study[4] in 8 children (aged 2 weeks to 7.8 years) found that the clearance of digoxin was about halved by carvedilol and 2 of the children developed digoxin toxicity. An increase in digoxin bioavailability has also been reported with *talinolol*.[5]

1. Grunden JW, *et al.* Augmented digoxin concentrations with carvedilol dosing in mild-moderate heart failure. *Am J Ther* 1994; **1:** 157–161.
2. Wermeling DP, *et al.* Effects of long-term oral carvedilol on the steady-state pharmacokinetics of oral digoxin in patients with mild to moderate hypertension. *Pharmacotherapy* 1994; **14:** 600–6.
3. De Mey C, *et al.* Carvedilol increases the systemic bioavailability of oral digoxin. *Br J Clin Pharmacol* 1990; **29:** 486–90.
4. Ratnapalan S, *et al.* Digoxin-carvedilol interactions in children. *J Pediatr* 2003; **142:** 572–4.
5. Westphal K, *et al.* Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. *Clin Pharmacol Ther* 2000; **68:** 6–12.

Calcium-channel blockers. Studies on interactions between digoxin and calcium-channel blockers appear to show that *verapamil* increases plasma-digoxin concentrations[1-3] by up to 70%. The effect of *nifedipine* is not as clear. Although it has been reported[1] to produce a 45% increase in plasma-digoxin concentrations, other studies[4,5] have reported little or no increase and the interaction is unlikely to be of clinical significance for most patients. Studies on the interaction between digoxin and *diltiazem* have also produced conflicting results. Increases in plasma-digoxin concentrations of 20% and up to 59% have been reported[6,7] and an increase in metildigoxin concentrations[7] of up to 51%. However, other studies[8,9] have shown no diltiazem-induced change in digoxin pharmacokinetics or plasma concentration. *Bepridil*,[10] *gallopamil*,[1] *mibefradil*,[11] *nisoldipine*,[12] and *nitrendipine*[13] have all been reported to increase plasma-digoxin concentrations. Bepridil increased the concentration by 34% and it was recommended that patients given this combination be monitored carefully. *Felodipine*[14,15] and *isradipine*[3] have both been reported to increase peak serum-digoxin concentrations, but steady-state digoxin concentrations were not affected and the interactions were unlikely to be of clinical relevance.

The mechanism of interaction between calcium-channel blockers and digoxin is not completely understood but appears to be related to decreased renal and nonrenal clearance of digoxin. The pharmacodynamic effects of digoxin and calcium-channel blockers may also be additive.

1. Belz GG, *et al.* Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. *Clin Pharmacol Ther* 1983; **33:** 410–17.
2. Pedersen KE, *et al.* Influence of verapamil on the inotropism and pharmacokinetics of digoxin. *Eur J Clin Pharmacol* 1983; **25:** 199–206.
3. Rodin SM, *et al.* Comparative effects of verapamil and isradipine on steady-state digoxin kinetics. *Clin Pharmacol Ther* 1988; **43:** 668–72.
4. Schwartz JB, Migliore PJ. Effect of nifedipine on serum digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1984; **36:** 19–24.
5. Kleinbloesem CH, *et al.* Interactions between digoxin and nifedipine at steady state in patients with atrial fibrillation. *Ther Drug Monit* 1985; **7:** 372–6.
6. Rameis H, *et al.* The diltiazem-digoxin interaction. *Clin Pharmacol Ther* 1984; **36:** 183–9.
7. Oyama Y, *et al.* Digoxin-diltiazem interaction. *Am J Cardiol* 1984; **53:** 1480–1.
8. Beltrami TR, *et al.* Lack of effects of diltiazem on digoxin pharmacokinetics. *J Clin Pharmacol* 1985; **25:** 390–2.
9. Elkayam U, *et al.* Effect of diltiazem on renal clearance and serum concentration of digoxin in patients with cardiac disease. *Am J Cardiol* 1985; **55:** 1393–5.
10. Belz GG, *et al.* Digoxin and bepridil: pharmacokinetic and pharmacodynamic interactions. *Clin Pharmacol Ther* 1986; **39:** 65–71.
11. Siepmann M, *et al.* The interaction of the calcium antagonist RO 40-5967 with digoxin. *Br J Clin Pharmacol* 1995; **39:** 491–6.
12. Kirch W, *et al.* Influence of nisoldipine on haemodynamic effects and plasma levels of digoxin. *Br J Clin Pharmacol* 1986; **22:** 155–9.
13. Kirch W, *et al.* Nitrendipine increases digoxin plasma levels dose dependently. *J Clin Pharmacol* 1986; **26:** 553.
14. Rehnqvist N, *et al.* Pharmacokinetics of felodipine and effect on digoxin plasma levels in patients with heart failure. *Drugs* 1987; **34** (suppl 3): 33–42.
15. Dunselman PHJM, *et al.* Digoxin-felodipine interaction in patients with congestive heart failure. *Eur J Clin Pharmacol* 1988; **35:** 461–5.

Diuretics. *Amiloride* increased renal clearance of digoxin and reduced the extrarenal digoxin clearance in 6 healthy subjects after a single intravenous dose of digoxin.[1] Amiloride also inhibited the digoxin-induced positive inotropic effect, but the clinical implications in cardiac patients are unknown. A further study[2] failed to confirm this effect.

Spironolactone and its metabolites have been reported to interfere with serum-digoxin determinations by radio-immunoassay or fluorescence-polarisation immunoassay resulting in falsely elevated measurements.[3,4] The interference with digoxin assays is neither consistent nor predictable and falsely low readings have also been reported.[5] Serum-digoxin concentrations should be interpreted with caution when digoxin is given together with spironolactone or *canrenoate*, especially since spironolactone has also been reported to decrease digoxin clearance by a median of 26% resulting in a true increase in the serum-digoxin concentration.[6]

Diuretic therapy with *triamterene* in association with a thiazide or loop diuretic increased the mean serum-digoxin concentration; this interaction was considered unlikely to be of clinical importance, except perhaps in patients with renal impairment.[7]

1. Waldorff S, *et al.* Amiloride-induced changes in digoxin dynamics and kinetics: abolition of digoxin-induced inotropism with amiloride. *Clin Pharmacol Ther* 1981; **30:** 172–6.
2. Richter JP, *et al.* The acute effects of amiloride and potassium canrenoate on digoxin-induced positive inotropism in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 195–6.
3. Paladino JA, *et al.* Influence of spironolactone on serum digoxin concentration. *JAMA* 1984; **251:** 470–1.
4. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
5. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.
6. Waldorff S, *et al.* Spironolactone-induced changes in digoxin kinetics. *Clin Pharmacol Ther* 1978; **24:** 162–7.
7. Impivaara O, Iisalo E. Serum digoxin concentrations in a representative digoxin-consuming adult population. *Eur J Clin Pharmacol* 1985; **27:** 627–32.

Gastrointestinal drugs. Some gastrointestinal drugs can affect the absorption of digoxin by binding to it or by changing gastrointestinal motility. The problem has often been related to the bioavailability of the digoxin formulation and appears to be less important with currently used preparations. Some *antacids*,[1,2] particularly liquid formulations, and *adsorbents*[1] such as kaolin-pectin, can reduce the absorption of digoxin from the gastrointestinal tract and doses should probably be separated by at least 2 hours. *Activated charcoal*, and *ion-exchange resins* such as colestyramine and colestipol, also reduce digoxin absorption. *Sucralfate*[3] may also reduce the absorption of digoxin.

Omeprazole and possibly other gastric acid inhibitors may reduce the gastrointestinal metabolism and enhance the absorption of unchanged digoxin,[4] although the clinical relevance of this is uncertain.[5]

Drugs that increase gastrointestinal motility can reduce the absorption of digoxin, especially if digoxin is given as a slowly dissolving formulation. Reduced absorption of digoxin has occurred when digoxin and *metoclopramide* have been given together,[6] and a similar effect has been reported with *cisapride*[7] and *tegaserod*.[8] Conversely, *anticholinergics* reduce motility, and propantheline has increased digoxin absorption.

Sulfasalazine has been found to impair the absorption of digoxin and to reduce the serum-digoxin concentration,[9] but the mechanism is unclear.

1. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; **15:** 227–44.
2. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.
3. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
4. Cohen AF, *et al.* Influence of gastric acidity on the bioavailability of digoxin. *Ann Intern Med* 1991; **115:** 540–5.
5. Oosterhuis B, *et al.* Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991; **32:** 569–72.
6. Johnson BF, *et al.* Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; **36:** 724–30.
7. Kubler PA, *et al.* Possible interaction between cisapride and digoxin. *Ann Pharmacother* 2001; **35:** 127–8.
8. Zhou H, *et al.* The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. *J Clin Pharmacol* 2001; **41:** 1131–9.
9. Juhl RP, *et al.* Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* 1976; **20:** 387–94.

Ginseng. Varieties of ginseng may interfere with plasma-digoxin assays (see under Precautions, above).

Immunosuppressants. Increased serum-digoxin concentrations with symptoms of toxicity have been reported in patients when *ciclosporin* was added to their digoxin therapy.[1,2]

1. Dorian P, *et al.* Digoxin-cyclosporine interaction: severe digitalis toxicity after cyclosporine treatment. *Clin Invest Med* 1988; **ii:** 108–12.
2. Robieux I, *et al.* The effects of cardiac transplantation and cyclosporine therapy on digoxin pharmacokinetics. *J Clin Pharmacol* 1992; **32:** 338–43.

Lipid regulating drugs. Small increases in plasma-digoxin concentrations have been reported with some *statins*, although the clinical significance is not clear. *Atorvastatin* at doses of 80 mg, but not of 10 mg, has been shown[1] to increase plasma-digoxin concentrations by about 20%. This may be due to the inhibition of P-glycoprotein-mediated secretion of digoxin in the intestine by atorvastatin.

1. Boyd RA, *et al.* Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol* 2000; **40:** 91–98.

Neuromuscular blockers. *Pancuronium* or *suxamethonium* may interact with digitalis glycosides resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.[1]

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

NSAIDs. An increase in serum-digoxin concentration has been reported with *aspirin*, *ibuprofen*, *indometacin*, *fenbufen*, and *diclofenac*.[1] Potentially toxic serum-digoxin concentrations occurred in preterm infants[2] with patent ductus arteriosus receiving digoxin when given indometacin orally in a mean total dose of 320 micrograms/kg; it was recommended that the dose of digoxin should be halved initially if indometacin is also given. (For the possible effect of digoxin on indometacin see Half-life, under Pharmacokinetics of Indometacin, p.68.) Lack of increase in serum-digoxin concentrations has also been reported with aspirin or indometacin, as well as with *ketoprofen*, and *tiaprofenic acid*,[1] and also with *rofecoxib*,[3] but some of these studies were in healthy subjects and it is advised that digoxin therapy be monitored carefully whenever any NSAID is started or stopped in digitalised patients.

1. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1990; **19:** 44–66.
2. Koren G, *et al.* Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr Pharmacol* 1984; **4:** 25–30.
3. Schwartz JI, *et al.* Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; **41:** 107–112.

Pharmacokinetics

The absorption of digoxin from the gastrointestinal tract is variable depending upon the formulation used. About 70% of a dose is absorbed from tablets which comply with BP or USP specifications, 80% is absorbed from an elixir, and over 90% is absorbed from liquid-filled soft gelatin capsules. The generally accepted therapeutic plasma concentration range is 0.5 to 2.0 nanograms/mL but there is considerable interindividual variation. Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes, and skeletal muscle. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% is bound to plasma proteins. Digoxin has been detected in CSF and breast milk; it also crosses the placenta. It has an elimination half-life of 1.5 to 2 days.

Digoxin is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion; reabsorption also occurs. Extensive metabolism has been reported in a minority of patients (see under Metabolism and Excretion, below). Excretion of digoxin is proportional to the glomerular filtration rate. After intravenous injection 50 to 70% of the dose is excreted unchanged. Digoxin is not removed from the body by dialysis, and only small amounts are removed by exchange transfusion and during cardiopulmonary bypass.

◊ Reviews of the clinical pharmacokinetics of digoxin.

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Aronson JK. Clinical pharmacokinetics of digoxin 1980. *Clin Pharmacokinet* 1980; **5:** 137–49.
3. Mooradian AD. Digitalis: an update of clinical pharmacokinetics, therapeutic monitoring techniques and treatment recommendations. *Clin Pharmacokinet* 1988; **15:** 165–79.

Absorption. Studies in 6 healthy subjects found that food decreased the rate but not the extent of absorption of digoxin.[1]

1. Johnson BF, *et al.* Effect of a standard breakfast on digoxin absorption in normal subjects. *Clin Pharmacol Ther* 1978; **23:** 315–19.

Bioavailability. Large variations in the content, disintegration, and dissolution of solid dosage forms of digoxin preparations have led to large variations in plasma concentrations from different proprietary preparations. Other factors involved in varying bioavailability include the pharmaceutical formulation and presentation (capsules, solution, or tablets), particle size, and biological factors. Serious problems occurred in the UK[1] in 1972 and in Israel[2] in 1975 after changes in the manufacturing procedure for *Lanoxin* led to a twofold increase in bioavailability.

1. Anonymous. Therapeutic non-equivalence. *BMJ* 1972; **3:** 599–600.
2. Danon A, *et al.* An outbreak of digoxin intoxication. *Clin Pharmacol Ther* 1977; **21:** 643–6.

Distribution and protein binding. Digoxin has been reported to be 5 to 60% bound to plasma proteins,[1] depending partly on the method of measurement, but the figure is usually around 20%. Protein binding is reduced in patients undergoing haemodialysis; mean reductions of about 8 and 10% have been reported.[1,2] Injection of heparin has produced a similar reduction.[2]

Digoxin is widely distributed to tissues and serum-digoxin concentrations have been reported to be increased during immobilisation[3] and decreased during exercise[4,5] due to changes in binding to tissues such as skeletal muscle.

1. Storstein L. Studies on digitalis V: the influence of impaired renal function, hemodialysis, and drug interaction on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 6–14.
2. Storstein L, Janssen H. Studies on digitalis VI: the effect of heparin on serum protein binding of digitoxin and digoxin. *Clin Pharmacol Ther* 1976; **20:** 15–23.
3. Pedersen KE, *et al.* Effects of physical activity and immobilization on plasma digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1983; **34:** 303–8.
4. Joreteg T, Jogestrand T. Physical exercise and digoxin binding to skeletal muscle: relation to exercise intensity. *Eur J Clin Pharmacol* 1983; **25:** 585–8.
5. Joreteg T, Jogestrand T. Physical exercise and binding of digoxin to skeletal muscle—effect of muscle activation frequency. *Eur J Clin Pharmacol* 1984; **27:** 567–70.

The elderly. For references to alterations in the pharmacokinetics of digoxin in the elderly, see under Uses and Administration, below.

Infants and neonates. Digoxin has been widely used in the treatment of cardiac disorders in neonates and infants and its pharmacokinetics in this age group have been reviewed.[1,2] In full-term neonates or infants, 80 to 90% of a dose of digoxin given orally in liquid form is absorbed, with peak plasma concentrations occurring within 30 to 120 minutes. The rate of absorption may be slower in preterm and low birth-weight infants, with peak concentrations achieved at 90 to 180 minutes, and may be significantly reduced in severe heart failure and in malabsorption syndromes. After digoxin is given intravenously there is a rapid distribution phase with an apparent half-life of 20 to 40 minutes followed by a slower exponential decay of plasma concentrations. In full-term neonates, digoxin has an apparent volume of distribution of 6 to 10 litres/kg. Low birth-weight infants have a volume of distribution of 4.3 to 5.7 litres/kg while in older infants the volume may range from 10 to 22 litres/kg which is 1.5 to 2 times reported adult values. This large volume of distribution in full-term neonates and infants is thought to be due to increased tissue binding, a larger extracellular fluid volume, and slightly lower plasma protein binding.

The apparent plasma half-life in healthy and sick neonates is generally very long and may range from 20 to 70 hours in full-term neonates or from 40 to 180 hours in preterm neonates. Digoxin is eliminated at a considerably faster rate in infants than in neonates and, in parallel with maturation of kidney function, a marked increase in clearance rate is usually observed between the second and third month of life. The large apparent volume of distribution, higher clearance values, and greater concentrations of digoxin in the myocardial tissue and red cells of infants might justify the traditional assumption that infants tolerate digoxin better than adults and that higher doses are consequently needed in infants. However, studies have shown that in infants, as in adults, toxic signs become evident at plasma-digoxin concentrations above 3 nanograms/mL and that the therapeutic range may be 1.5 to 2 nanograms/mL.

1. Morselli PL, *et al.* Clinical pharmacokinetics in newborns and infants: age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980; **5:** 485–527.
2. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface. *Clin Pharmacokinet* 1988; **14:** 189–216 (part I) and 261–86 (part II).

Metabolism and excretion. Although digoxin is reported to be excreted mainly unchanged in the urine there is evidence to suggest that metabolism may sometimes be extensive. Metabolites that have been detected in the urine include digoxigenin, dihydrodigoxigenin, the mono- and bisdigitoxosides of digoxigenin, and dihydrodigoxin. Digoxigenin mono- and bisdigitoxosides are known to be cardioactive whereas dihydrodigoxin is probably much less active than digoxin.[1]

In about 10% of patients there is considerable reduction to cardio-inactive metabolites, chiefly dihydrodigoxin, and 40% or more of a dose may be excreted in the urine as dihydrodigoxin.[2-4] Bacterial flora in the gastrointestinal tract appear to be responsible for this metabolism and antibacterials can reduce the process. Oral digoxin formulations with a high bioavailability are mostly absorbed in the stomach and upper small intestine and little digoxin is available in the lower intestine for bacterial degradation to dihydrodigoxin.[4]

The excretion of digoxin is thought to be mediated by the efflux pump, P-glycoprotein,[5] which transports its substrates out of the cell. This may be the basis for some interactions hitherto poorly understood,[6] although the hypothesis has been questioned.[7]

1. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; **2:** 1–16.
2. Doherty JE. A digoxin-antibiotic drug interaction. *N Engl J Med* 1981; **305:** 827–8.
3. Rund DG, *et al.* Decreased digoxin cardioinactive-reduced metabolites after administration of an encapsulated liquid concentrate. *Clin Pharmacol Ther* 1983; **34:** 738–43.
4. Lofts F, *et al.* Digoxin metabolism to reduced products: clinical significance. *Br J Clin Pharmacol* 1986; **21:** 600P.
5. Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit* 2000; **22:** 137–40.
6. Fromm MF. P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. *Int J Clin Pharmacol Ther* 2000; **38:** 69–74.
7. Chiou WL, *et al.* A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. *Int J Clin Pharmacol Ther* 2001; **39:** 93–101.

Renal impairment. For references to alterations in the pharmacokinetics of digoxin in patients with renal impairment, see under Uses and Administration, below.

Uses and Administration

Digoxin is a cardiac glycoside used in the management of supraventricular arrhythmias, particularly atrial fibrillation (p.1160), and in heart failure (p.1165).

The principal actions of digoxin are an increase in the force of myocardial contraction (positive inotropic activity) and a reduction in the conductivity of the heart, particularly in conduction through the atrioventricular (AV) node. Digoxin also has a direct action on vascular smooth muscle and indirect effects mediated primarily by the autonomic nervous system, and particularly by an increase in vagal activity. There are also reflex alterations in autonomic activity due to the effects on the circulation. Overall, these actions result in positive inotropic effects, negative chronotropic effects, and decreased AV nodal activity.

Cardiac arrhythmias. In atrial arrhythmias digoxin's actions cause a decrease in the conduction velocity through the AV node and an increase in the effective refractory period, thus reducing ventricular rate. In addition there is a decrease in the refractory period of the cardiac muscle and depression of the sinus node partly in response to the increase in vagal activity.

Digoxin is thus given to slow the increased ventricular rate that occurs in response to *atrial fibrillation*, although other drugs may be preferred; treatment is usually long term. In patients with the Wolff-Parkinson-White syndrome and atrial fibrillation, digoxin can cause rapid ventricular rates, and possibly ventricular fibrillation, and should be avoided. In *atrial flutter*, the ventricular rate is normally more difficult to control with digoxin. Drug therapy is not the preferred method of treatment, but treatment with digoxin may restore sinus rhythm, or it may convert the flutter to fibrillation and sinus rhythm may then be induced by subsequent withdrawal of digoxin. Digoxin may be given to relieve an attack of *paroxysmal supraventricular tachycardia* and has also been given to prevent further attacks.

Heart failure. Digoxin and other cardiac glycosides directly inhibit the activity of the enzyme sodium-potassium adenosine triphosphatase (Na/K-ATPase), which is required for the active transport of sodium from myocardial cells. The result is a gradual increase in the intracellular sodium concentration and a decrease in the intracellular potassium concentration. The increased concentration of sodium inside the cells leads, by stimulation of sodium-calcium exchange, to an increase in the intracellular calcium concentration with enhancement of mechanical contractile activity and an increased inotropic effect.

When used in heart failure the increased force of myocardial contraction results in increased cardiac output, decreased end-systolic volume, decreased heart size, and decreased end-diastolic pressure and volume. Increased blood flow through the kidneys results in diuresis with a reduction in oedema and blood volume. The decrease in pulmonary venous pressure relieves dyspnoea and orthopnoea. Digoxin may thus provide symptomatic improvement in patients with heart failure and is mainly used for adjunctive therapy.

Dosage. When given orally, digoxin may take effect within about 2 hours and the maximum effect may be reached in about 6 hours. Initially a loading dose may be given to digitalise the patient, although this may not be necessary in, for example, mild heart failure.

Dosage should be carefully adjusted to the needs of the individual patient. Factors which may be considered include the patient's age, lean body-mass, renal status, thyroid status, electrolyte balance, degree of tissue oxygenation, and the nature of the underlying cardiac or pulmonary disease. Bearing in mind the above factors, steady-state plasma-digoxin concentrations (in a sample taken at least 6 hours after a dose) of 0.5 to 2 nanograms/mL are generally considered acceptable, although in patients with heart failure concentrations at the lower end of the range may be more appropriate. For reference to therapeutic drug monitoring, see below.

If rapid digitalisation is required then a loading dose is given to allow for the large volume of distribution. A total loading dose of 750 to 1500 micrograms of digoxin may be given by mouth during the initial 24-hour period, either as a single dose, or where there is less urgency or greater risk of toxicity, in divided doses at 6-hourly intervals. In some patients, for example those with mild heart failure, a loading dose may not be necessary, and digitalisation may be achieved more slowly with doses of 250 micrograms once or twice daily; steady-state plasma concentrations are achieved in about 7 days in patients with normal renal function. The usual maintenance dose of digoxin is 125 to 250 micrograms by mouth daily, but may range from 62.5 to 500 micrograms daily. In elderly patients therapy should generally start gradually and with smaller doses (but see under Administration in the Elderly, below).

In urgent cases, provided that the patient has not received cardiac glycosides during the previous 2 weeks, digoxin may be given intravenously initially. The intravenous dose ranges from 500 to 1000 micrograms and generally produces a definite effect on the heart rate in about 10 minutes, reaching a maximum within about 2 hours. It is given by intravenous infusion, either as a single dose given over 2 or more hours, or in divided doses each over 10 to 20 minutes. Maintenance treatment is then usually given by mouth. Digoxin has also been given intramuscularly but this route is not generally recommended since such injections may be painful and tissue damage has been reported. Digoxin should not be given subcutaneously as intense local irritation may occur.

Children's doses are complex. They are based on body-weight and the developmental stage of the child as well as on response. Premature infants are especially sensitive to digoxin but, along with all other neonates, infants, and children up to about 10 years of age, still require doses that are higher per kg body-weight than those used for adults. Preterm infants receive lower doses than full-term infants, while children aged 2 to 10 years require lower doses than children up to 2 years of age. As an indication of the doses used, oral loading doses recommended by licensed product information in the UK range from 25 to 45 micrograms/kg over 24 hours and in the USA the range is 20 to 60 micrograms/kg; the range for intravenous loading doses given over 24 hours is 20 to 35 micrograms/kg in the UK and 15 to 50 micrograms/kg in the USA.

Doses should be reduced in patients with renal impairment (see below).

◊ General reviews on the actions and uses of digoxin and the other cardiac glycosides.

1. Opie LH. Digitalis and sympathomimetic stimulants. *Lancet* 1980; **i:** 912–18.
2. Taggart AJ, McDevitt DG. Digitalis: its place in modern therapy. *Drugs* 1980; **20:** 398–404.
3. Chamberlain DA. Digitalis: where are we now? *Br Heart J* 1985; **54:** 227–33.
4. Doherty JE. Clinical use of digitalis glycosides: an update. *Cardiology* 1985; **72:** 225–54.
5. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988; **318:** 358–65.
6. Hampton JR. Digoxin. *Br J Hosp Med* 1997; **58:** 321–3.
7. Riaz K, Forker AD. Digoxin use in congestive heart failure: current status. *Drugs* 1998; **55:** 747–58.
8. Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. *Med J Aust* 2003; **179:** 98–102.

Administration in the elderly. The volume of distribution of digoxin and the elimination half-life increase with age.[1] Therefore there are problems in giving digoxin to elderly patients since steady-state plasma concentrations may not be reached for up to 2 weeks. Fears of toxicity have led some practitioners to use a fixed 'geriatric' dose of 62.5 micrograms daily. However, such a dose can produce subtherapeutic concentrations.[2] The routine use of very low doses of digoxin in the elderly is inappropriate and dosage should be individualised.

1. McMurray J, McDevitt DG. Treatment of heart failure in the elderly. *Br Med Bull* 1990; **46:** 202–29.
2. Nolan L, *et al.* The need for reassessment of digoxin prescribing for the elderly. *Br J Clin Pharmacol* 1989; **27:** 367–70.

Administration in renal impairment. The pharmacokinetics of cardiac glycosides in patients with renal impairment have been reviewed.[1] The rate but not the extent of digoxin absorption is reduced in renal impairment but this is unlikely to be clinically important. Plasma-protein binding may also be reduced but since digoxin is poorly bound to these proteins and has a large apparent volume of distribution this also is unlikely to be important. The apparent volume of distribution is reduced by one-third to one-half and the loading dose of digoxin should therefore be reduced; an oral loading dose of 10 micrograms/kg is suggested (but see also under Therapeutic Drug Monitoring, below). Non-renal clearance of digoxin is unaffected or only slightly reduced but renal clearance is reduced, the extent being closely related to creatinine clearance. The elimination half-life of digoxin is prolonged and it therefore takes longer to reach steady state and longer for toxicity to resolve. Because of the reduction in renal clearance of digoxin, maintenance doses must be reduced in line with renal function. Serum-digoxin concentration should be monitored although the presence of digoxin-like immunoreactive substances may make interpretation difficult. In addition, the presence of hyperkalaemia in patients with renal impairment may reduce sensitivity to the effects of digoxin.[2]

Since digoxin has such a large distribution volume, procedures such as peritoneal dialysis and haemodialysis remove only very small amounts of drug from the body and no dosage supplement is needed.

1. Aronson JK. Clinical pharmacokinetics of cardiac glycosides in patients with renal dysfunction. *Clin Pharmacokinet* 1983; **8:** 155–78.
2. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Safety* 1997; **16:** 205–31.

Therapeutic drug monitoring. Digoxin has a narrow therapeutic index. It is generally considered that plasma-digoxin concentrations required for a therapeutic effect are usually between 0.5 and 2.0 nanograms/mL,[1-3] although some studies[4-6] have suggested that concentrations of 0.5 to 0.9 nanograms/mL are adequate for heart failure; concentrations at the upper end of the range may be associated with worse outcomes.[5,6] The factor for converting nanograms/mL to nanomoles/litre is 1.28.

Digoxin dosage can be calculated in uncomplicated cases by considering the patient's weight, renal function, and clinical status. Therapeutic drug monitoring is *not* considered to be necessary in patients with a satisfactory clinical response to conventional doses in the absence of signs or symptoms of toxicity.[1,2] Measurement of plasma-digoxin concentrations is useful if poor compliance is suspected, if response is poor or there is a deterioration in response without apparent reason, if renal function is fluctuating, when it is unknown if a cardiac glycoside has been previously taken, during drug interactions, and to confirm clinical toxicity.[1,3,7] A plasma concentration should never be considered in isolation and should be used with other patient data as an important component in clinical decision making. This is particularly important in the diagnosis of digoxin toxicity since signs and symptoms of toxicity may be difficult to distinguish from the underlying disease and can occur within the usual therapeutic range.

A number of factors may influence the response to digoxin and thus the interpretation of digoxin assays. These include renal impairment, extremes of age, thyroid disease, patient compliance, drug interactions, and electrolyte disturbances.[1-3,7] Variations in the bioavailability of different digoxin preparations have also caused problems. Renal impairment and hypokalaemia are two of the most important factors affecting dosage of digoxin and whenever plasma-digoxin concentrations are assayed renal function and plasma potassium should also be measured. A dosing nomogram has been proposed[8] relating dose in patients with heart failure to renal function and either height or ideal body weight: for most patients with moderate or severe renal impairment (creatinine clearance below 60 mL/minute) an oral dose of 125 micrograms every other day was considered sufficient. The interpretation of digoxin assays is further confounded by the presence of digoxin-like immunoreactive substances in patients with renal or hepatic impairment, in pregnant women, and in neonates. Blood samples for digoxin assay should be taken at least 6 hours after a dose to allow for distribution.[1,3,7]

The usefulness of plasma-digoxin concentrations in the diagnosis of toxicity in children is unclear. For children older than 12 months the adult guidelines can probably be followed, and for younger children the trend for increased risk of toxicity at increased plasma-digoxin concentrations appears to hold but the threshold for toxicity may be higher, especially in children less than 3 months old.[1]

1. Aronson JK. Indications for the measurement of plasma digoxin concentrations. *Drugs* 1983; **26:** 230–42.
2. Lee TH, Smith TW. Serum digoxin concentration and diagnosis of digitalis toxicity: current concepts. *Clin Pharmacokinet* 1983; **8:** 279–85.
3. Aronson JK, Hardman M. Digoxin. *BMJ* 1992; **305:** 1149–52.
4. Adams KF, *et al.* Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; **39:** 946–53.
5. Rathore SS, *et al.* Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; **289:** 871–8.
6. Adams KF, *et al.* Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005; **46:** 497–504.
7. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ* 1988; **296:** 1110–14.
8. Bauman JL, *et al.* A method of determining the dose of digoxin for heart failure in the modern era. *Arch Intern Med* 2006; **166:** 2539–45.

Preparations

BP 2008: Digoxin Injection; Digoxin Tablets; Paediatric Digoxin Injection; Paediatric Digoxin Oral Solution;
USP 31: Digoxin Elixir; Digoxin Injection; Digoxin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cardiogoxin; Digocard-G; Lanicor; Lanoxin; ***Austral.:*** Lanoxin; Sigmaxin; ***Austria:*** Lanicor; ***Belg.:*** Lanoxin; ***Braz.:*** Cardcor; Cardionil; Cimecard; Digitax; Digixina†; Digobal; Digox†; Digoxan†; Digoxen; Digoxil; Lanoxin†; Valoxin; ***Canad.:*** Lanoxin; ***Fr.:*** Hemigoxine Nativelle; ***Ger.:*** Digacin; Digoregen†; Dilanacin†; Lanicor; Lenoxin; ***Hong Kong:*** Lanoxin; ***India:*** Cardioxin†; Lanoxin; ***Indon.:*** Fargoxin; Lanoxin; ***Irl.:*** Lanoxin; ***Israel:*** Lanoxin; ***Ital.:*** Eudigox; Lanoxin; ***Jpn:*** Digosin; ***Malaysia:*** Lanoxin; ***Mex.:*** Lanoxin; Mapluxin; ***Neth.:*** Lanoxin; ***Norw.:*** Lanoxin; ***NZ:*** Lanoxin; ***Philipp.:*** Lanoxin; ***Port.:*** Lanoxin; ***S.Afr.:*** Lanoxin; Purgoxin; ***Singapore:*** Lanoxin; ***Spain:*** Lanacordin; ***Swed.:*** Lanacrist; Lanoxin; ***Thai.:*** Grexin; Lanoxin; Toloxin; ***UK:*** Lanoxin; ***USA:*** Digitek; Lanoxicaps†; Lanoxin; ***Venez.:*** Lanicor.

Dihydralazine Sulfate *(rINNM)*

Dihidralazino sulfatas, hidratuotas; Dihidralazin-szulfát-hidrát; Dihydralatsiinisulfaatti, hydratoitu; Dihydralazine, Sulfate de; Dihydralazine (sulfate de) hydraté; Dihydralazine Sulphate *(BANM)*; Dihydralazini Sulfas; Dihydralazini sulfas hydricus; Dihydralazinsulfát; Dihydralazinsulfat, hydratiserat; Dihydralazinum Sulfuricum; Dihydralazyny siarczan; Dihydrallazine Sulphate; Sulfato de dihidralazina. Phthalazine-1,4-diyldihydrazine sulfate hemipentahydrate.

Дигидралазина Сульфат

$C_8H_{10}N_6,H_2SO_4,2\frac{1}{2}H_2O = 333.3.$

CAS — 484-23-1 (dihydralazine); 7327-87-9 (dihydralazine sulfate).

ATC — C02DB01.

ATC Vet — QC02DB01.

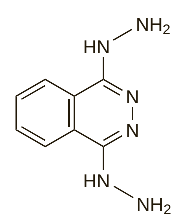

(dihydralazine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dihydralazine Sulphate, Hydrated). A white or slightly yellow crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol. It dissolves in dilute mineral acids.

Profile

Dihydralazine is a vasodilator with actions and uses similar to those of hydralazine (p.1305). It is given orally as the sulfate. Dihydralazine sulfate hemipentahydrate 14.45 mg is equivalent to about 12.5 mg of anhydrous dihydralazine sulfate. In hypertension (p.1171) the usual initial dose is the equivalent of 12.5 mg of anhydrous dihydralazine sulfate twice daily and the maximum recommended dose is 50 mg twice daily. Higher doses have been used in the management of heart failure.

Other salts of dihydralazine that have been used in oral preparations include the hydrochloride and the tartrate. The mesilate is given by injection.

Porphyria. Dihydralazine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nepresol; ***Belg.:*** Nepresol; ***Cz.:*** Nepresol†; ***Fr.:*** Nepressol; ***Ger.:*** Depressan; Nepresol; ***Gr.:*** Nepresol; ***Hong Kong:*** Nepresol†; ***Hung.:*** De-

pressan; ***India:*** Nepresol; ***Malaysia:*** Nepresol†; ***S.Afr.:*** Nepresol†; ***Swed.:*** Nepresol†; ***Switz.:*** Nepresol†; ***Thai.:*** Nepresol.

Multi-ingredient: ***Braz.:*** Adelfan-Esidrex†; ***Ger.:*** Adelphan-Esidrix†; Obsilazin N†; Tri-Torrat†; Triniton; ***Hong Kong:*** Adelphane-Esidrex; ***India:*** Adelphane; Adelphane-Esidrex; Beptazine; Beptazine-H; ***Indon.:*** Dellasidrex; ***Rus.:*** Adelphane-Esidrex (Адельфан-эзидрекс); Triresid K (Трирезид К); ***Spain:*** Adelfan-Esidrex†; ***Switz.:*** Adelphan-Esidrex; ***Turk.:*** Adelphan; Adelphan-Esidrex.

Di-isopropylammonium Dichloroacetate

Diisopropilamina, dicloroacetato de; Di-isopropylamine Dichloroacetate; Di-isopropylamine Dichloroethanoate; DIPA-DCA.

$C_8H_{17}Cl_2NO_2$ = 230.1.

CAS — 660-27-5.

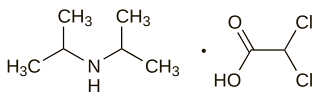

Profile

Di-isopropylammonium dichloroacetate is a vasodilator that has been given in peripheral and cerebral vascular disorders. Preparations containing it have sometimes been described as 'pangamic acid' (p.2362).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Disotat†; Oxypangam†; ***Mex.:*** Ditrei.

Multi-ingredient: ***Hong Kong:*** Liverall†; ***Spain:*** Vitaber A E.

Dilazep Hydrochloride *(rINNM)*

Asta C-4898; Dilazep, Chlorhydrate de; Dilazepi Hydrochloridum; Hidrocloruro de dilazep. Perhydro-1,4-diazepin-1,4-diylbis(trimethylene 3,4,5-trimethoxybenzoate) dihydrochloride.

Дилазепа Гидрохлорид

$C_{31}H_{44}N_2O_{10}$,2HCl = 677.6.

CAS — 35898-87-4 (dilazep); 20153-98-4 (dilazep hydrochloride).

ATC — C01DX10.

ATC Vet — QC01DX10.

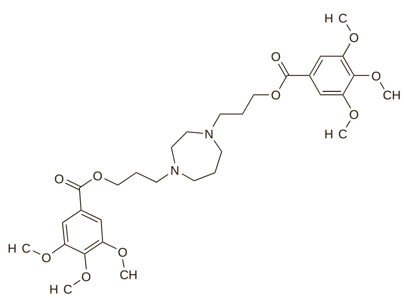

(dilazep)

Pharmacopoeias. *Jpn* includes the monohydrate.

Profile

Dilazep hydrochloride is a vasodilator that is used in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Cormelian; ***Jpn:*** Comelian.

Diltiazem Hydrochloride

(BANM, USAN, rINNM)

CRD-401; Diltiatseemihydrokloridi; Diltiazem, chlorhydrate de; Diltiazem Hidroklorür; Diltiazem hydrochlorid; Diltiazem-hidroklorid; Diltiazemhydroklorid; Diltiazemi hydrochloridum; Diltiazemo hidrochloridas; Diltiazemu chlorowodorek; Hidrocloruro de diltiazem; Latiazem Hydrochloride; MK-793 (diltiazem malate). (+)-*cis*-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride; (2*S*,3*S*)-5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate hydrochloride.

Дилтиазема Гидрохлорид

$C_{22}H_{26}N_2O_4S$,HCl = 451.0.

CAS — 42399-41-7 (diltiazem); 33286-22-5 (diltiazem hydrochloride); 144604-00-2 (diltiazem malate).

ATC — C08DB01.

ATC Vet — QC08DB01.

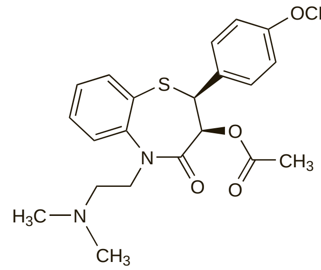

(diltiazem)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Diltiazem Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol; slightly soluble in dehydrated alcohol. The pH of a 1% solution in water is 4.3 to 5.3. Store in airtight containers. Protect from light.

USP 31 (Diltiazem Hydrochloride). A white, odourless, crystalline powder, or small crystals. Freely soluble in water, in chloroform, in formic acid, and in methyl alcohol; sparingly soluble in dehydrated alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Adverse Effects

Treatment with diltiazem is generally well tolerated. Headache, ankle oedema, hypotension, dizziness, flushing, fatigue, and nausea and other gastrointestinal disturbances (including anorexia, vomiting, constipation or diarrhoea, taste disturbances, and weight gain) may occur. Gingival hyperplasia has been reported. Rashes, possibly due to hypersensitivity, are normally mild and transient, but in a few cases erythema multiforme or exfoliative dermatitis has developed; photosensitivity reactions may also occur. Transient elevations in liver enzyme values, and occasionally hepatitis, have been reported.

Diltiazem may depress cardiac conduction and has occasionally led to AV block, bradycardia, and rarely asystole or sinus arrest.

Overdosage with diltiazem may be associated with bradycardia, with or without AV conduction defects, and hypotension.

Diltiazem has been shown to cause teratogenicity in *animal* studies.

Effects on mortality. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see under Adverse Effects of Nifedipine, p.1350.

Angioedema. Periorbital angioedema, accompanied by pruritus or burning and erythema developed in 2 patients given diltiazem.[1]

1. Sadick NS, *et al.* Angioedema from calcium channel blockers. *J Am Acad Dermatol* 1989; **21:** 132–3.

Effects on the blood. Thrombocytopenia has been reported in association with diltiazem.[1,2]

1. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
2. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on carbohydrate metabolism. Although raised blood-glucose concentrations and insulin requirements have been reported[1] in a patient with type 1 diabetes mellitus during diltiazem therapy, particularly at high doses, a study[2] in 11 obese black women, who were nondiabetic but had a family history of type 2 diabetes, failed to find any effect of diltiazem 240 mg daily on plasma-glucose and C-peptide concentrations, nor any clinical signs of glucose intolerance.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Jones BJ, *et al.* Effects of diltiazem hydrochloride on glucose tolerance in persons at risk for diabetes mellitus. *Clin Pharm* 1988; **7:** 235–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the gastrointestinal tract. Gastrointestinal disturbances including nausea, vomiting, and constipation, may occur with calcium-channel blockers. A case[1] of intestinal pseudo-obstruction was reported in a 74-year-old neutropenic man receiving chemotherapy for leukaemia after diltiazem was added to treat new-onset atrial fibrillation. A diagnosis of neutropenic enterocolitis was ruled out and symptoms resolved when diltiazem was stopped; it was concluded that diltiazem was the probable cause.

A similar case attributed to verapamil[2] has been reported.

1. Young RP, Wu H. Intestinal pseudo-obstruction caused by diltiazem in a neutropenic patient. *Ann Pharmacother* 2005; **39:** 1749–51.
2. Schultz HS, Vernon B. Intestinal pseudo-obstruction related to using verapamil. *West J Med* 1989; **151:** 556–8.

Effects on the heart. *AV BLOCK.* AV block appears to be uncommon in patients receiving diltiazem, but is potentially serious when it occurs. Prescription-event monitoring[1] of a cohort of 10 119 patients for 1 year revealed 22 reports of AV block during diltiazem treatment. At least 8 patients had third-degree heart block, and 12 required a pacemaker; 3 died within 72 hours of the onset of heart block. A high proportion of these patients were also receiving beta blockers, which is in line with other reports.[2,3] (See also Beta Blockers under Interactions, below.) There is some evidence that the incidence of this effect may depend on the serum concentration of diltiazem. In a study[4] in patients receiving diltiazem after myocardial infarction, patients with serum-diltiazem concentrations greater than 150 nanograms/mL were more likely to experience AV block than patients with concentrations of diltiazem below this value.

1. Waller PC, Inman WHW. Diltiazem and heart block. *Lancet* 1989; **i:** 617.
2. Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982; **307:** 953–4.
3. Ishikawa T, *et al.* Atrioventricular dissociation and sinus arrest induced by oral diltiazem. *N Engl J Med* 1983; **309:** 1124–5.
4. Nattel S, *et al.* Determinants and significance of diltiazem plasma concentrations after acute myocardial infarction. *Am J Cardiol* 1990; **66:** 1422–8.

MYOCARDIAL INFARCTION. Results from at least one large multicentre study (the Multicenter Diltiazem Postinfarction Trial) suggest that diltiazem, although apparently of benefit after myocardial infarction in patients with normal left ventricular function (as indicated by absence of pulmonary congestion), was associated with an increased risk of cardiac death or nonfatal re-infarction in patients with impaired left ventricular function.[1] Long-term follow-up[2] indicated that diltiazem also increased the risk of late-onset heart failure in postinfarction patients with left ventricular dysfunction.

1. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
2. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.

WITHDRAWAL. Life-threatening coronary vasospasm, which was fatal in one patient, occurred in 4 patients after coronary revascularisation for unstable angina.[1] Treatment with a calcium-channel blocker (diltiazem or nifedipine) had been discontinued between 8 and 18 hours before the procedure and this abrupt withdrawal was thought to be responsible for the rebound vasospasm. The coronary vasospasm was managed with glyceryl trinitrate and nifedipine.

Withdrawal of diltiazem over a 4-day period from a patient with stable angina pectoris was followed by recurrence of anginal attacks.[2] Ambulatory ECG monitoring confirmed worsening myocardial ischaemia that responded to re-introduction of diltiazem. Two further patients had a similar withdrawal effect.

1. Engelman RM, *et al.* Rebound vasospasm after coronary revascularization in association with calcium antagonist withdrawal. *Ann Thorac Surg* 1984; **37:** 469–72.
2. Subramanian VB, *et al.* Calcium antagonist withdrawal syndrome: objective demonstration with frequency-modulated ambulatory ST-segment monitoring. *BMJ* 1983; **286:** 520–1.

Effects on the kidneys. Diltiazem may be of benefit in various kidney disorders (see under Uses, below). However, there are a few reports of acute renal failure associated with diltiazem use.[1,2] Acute interstitial nephritis has been proposed as a mechanism.[2,3]

1. ter Wee PM, *et al.* Acute renal failure due to diltiazem. *Lancet* 1984; **ii:** 1337–8.
2. Abadín JA, *et al.* Probable diltiazem-induced acute interstitial nephritis. *Ann Pharmacother* 1998; **32:** 656–8.
3. Achenbach V, *et al.* Acute renal failure due to diltiazem. *Lancet* 1985; **i:** 176.

Effects on mental function. By September 1989, the WHO collaborative programme for international drug monitoring had gathered 8 cases of mental depression (severe in 2) associated with diltiazem therapy.[1] Time of onset of symptoms varied from a few hours to a few months after starting treatment with diltiazem. There was some evidence that the problem might be dose-related as 5 of the 8 cases were receiving doses of 180 mg daily or more.

Psychoses have been reported rarely in association with diltiazem. A patient[2] who developed hallucinations (both auditory and visual) and paranoid delusions after 2 days of diltiazem therapy was subsequently treated with nifedipine without abnormal effects. Another patient[3] with bipolar affective disorder that had been well-controlled by lithium carbonate for some years developed acute psychosis with extrapyramidal symptoms of cogwheel rigidity and ataxia, which was thought to represent an interaction between diltiazem and lithium.

1. Biriell C, *et al.* Depression associated with diltiazem. *BMJ* 1989; **299:** 796.
2. Bushe CJ. Organic psychosis caused by diltiazem. *J R Soc Med* 1988; **81:** 296–7.
3. Binder EF. Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.

Effects on the mouth. A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important side-effect that may occur with calcium-channel blockers.[1]

1. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the nervous system. Akathisia has been reported in a patient the day after starting treatment with diltiazem. Symptoms disappeared when diltiazem was withdrawn and recurred on rechallenge after the third dose.[1] Similar symptoms in association with mania have also been reported in another patient given diltiazem.[2]

1. Jacobs MB. Diltiazem and akathisia. *Ann Intern Med* 1983; **99:** 794–5.
2. Brink DD. Diltiazem and hyperactivity. *Ann Intern Med* 1984; **100:** 459–60.

PARKINSONISM. Parkinsonism developed in an elderly patient with heart disease and hypertension when diltiazem was added to existing drug therapy.[1] Symptoms worsened over 3 months but improved significantly when diltiazem was slowly withdrawn. On rechallenge severe tremor, impaired gait, and cogwheel rigidity recurred, but resolved when the drug was stopped again except for slight residual cogwheel rigidity.

An acute parkinsonian syndrome also developed[2] in a patient taking lithium and tiotixene when diltiazem was added, and was thought to represent an interaction between lithium and diltiazem. See also Effects on Mental Function, above.

1. Dick RS, Barold SS. Diltiazem-induced parkinsonism. *Am J Med* 1989; **87:** 95–6.
2. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.

Effects on the skin. A variety of skin disorders have been associated with diltiazem therapy, including acute pustular dermatitis,[1-3] cutaneous vasculitis,[4,5] erythema multiforme,[6,7] pruritic macular rashes,[3,8] severe toxic erythema,[9] subacute lupus erythematosus-like eruptions,[10] and photosensitivity reactions.[11] Analysis of cutaneous adverse reactions to diltiazem indicated that acne, rash, and urticaria were among the commonest.[12] There have also been a few reports of exfoliative dermatitis, erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis.[3,12]

For a report of periorbital skin rash associated with diltiazem, see Angioedema, above.

Cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between diltiazem and amlodipine.[13]

1. Lambert DG, *et al.* Acute generalized exanthematous pustular dermatitis induced by diltiazem. *Br J Dermatol* 1988; **118:** 308–9.
2. Vicente-Calleja JM, *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; **137:** 837–9.
3. Knowles S, *et al.* The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38:** 201–6.
4. Carmichael AJ, Paul CJ. Vasculitic leg ulcers associated with diltiazem. *BMJ* 1988; **297:** 562.
5. Sheehan-Dare RA, Goodfield MJ. Severe cutaneous vasculitis induced by diltiazem. *Br J Dermatol* 1988; **119:** 134.
6. Berbis P, *et al.* Diltiazem associated erythema multiforme. *Dermatologica* 1989; **179:** 90.
7. Sanders CJG, Neumann HAM. Erythema multiforme, Stevens-Johnson syndrome, and diltiazem. *Lancet* 1993; **341:** 967.
8. Wirebaugh SR, Geraets DR. Reports of erythematous macular skin eruptions associated with diltiazem therapy. *DICP Ann Pharmacother* 1990; **24:** 1046–9.
9. Wakeel RA, *et al.* Severe toxic erythema caused by diltiazem. *BMJ* 1988; **296:** 1071.
10. Crowson AN, Magro CM. Diltiazem and subacute cutaneous lupus erythematosus-like lesions. *N Engl J Med* 1995; **333:** 1429.
11. Saladi RN, *et al.* Diltiazem induces severe photodistributed hyperpigmentation: case series, histoimmunopathology, management, and review of the literature. *Arch Dermatol* 2006; **142:** 206–10.
12. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
13. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p.1352, but see also below.

Diltiazem and its metabolites are poorly dialysable.

Overdosage. The consequences and treatment of diltiazem overdosage are similar to nifedipine (p.1352), although death and life-threatening complications might be more common with diltiazem.[1] Up to 1994, 6 cases of fatal overdose with diltiazem had been reported in the literature.[2] Measurement of diltiazem concentrations to assist in diagnosis and management of overdosage has been suggested,[2] but others[3] have disputed its value.

The following are individual reports of overdosage with diltiazem:

- A patient who took about 10.8 g of diltiazem developed hypotension and complete heart block. Dopamine, isoprenaline, and calcium chloride were required to maintain the blood pressure. The ECG reverted to sinus rhythm after 31 hours. The plasma-diltiazem concentration was 1670 nanograms/mL 43 hours after ingestion and fell to 12.1 nanograms/mL over a further 55.5 hours with an elimination half-life of 7.9 hours.[4]
- In a further case a patient took 5.88 g of diltiazem with alcohol, and developed severe junctional bradycardia, hypotension, and reduced cardiac function that did not respond to intravenous calcium gluconate. The maximum plasma-diltiazem concentration of 6090 nanograms/mL occurred 7 hours after presentation. About half of the dose was vomited after treatment with activated charcoal. The patient was treated with cardiac pacing and a dopamine infusion; he reverted to sinus rhythm within 24 hours, and a subsequent episode of atrial fibrillation was treated successfully with digoxin.[5]
- Charcoal haemoperfusion had a limited effect in improving the clearance of diltiazem in a patient who had taken 14.94 g of diltiazem.[6] The patient developed severe hypotension, complete heart block, and acute renal failure. Supportive care included cardiac pacing and numerous vasopressors including intravenous glucagon and infusions of dopamine, adrenaline, and noradrenaline.

1. Buckley NA, *et al.* Overdose with calcium channel blockers. *BMJ* 1994; **308:** 1639.
2. Roper TA. Overdose of diltiazem. *BMJ* 1994; **308:** 1571.
3. Lip GYH, Ferner RE. Overdose of diltiazem. *BMJ* 1994; **309:** 193.
4. Malcolm N, *et al.* Massive diltiazem overdosage: clinical and pharmacokinetic observations. *Drug Intell Clin Pharm* 1986; **20:** 888.
5. Ferner RE, *et al.* Pharmacokinetics and toxic effects of diltiazem in massive overdose. *Hum Toxicol* 1989; **8:** 497–9.
6. Williamson KM, Dunham GD. Plasma concentrations of diltiazem and desacetyldiltiazem in an overdose situation. *Ann Pharmacother* 1996; **30:** 608–11.

Precautions

Diltiazem is contra-indicated in patients with the sick sinus syndrome, pre-existing second- or third-degree AV block, or marked bradycardia, and should be used with care in patients with lesser degrees of AV block or bradycardia. Diltiazem has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. Sudden withdrawal of diltiazem might be associated with an exacerbation of angina.

Treatment with diltiazem should begin with reduced doses in elderly patients and in patients with hepatic or renal impairment.

Abuse. Abuse of diltiazem by body builders and rugby players has been alleged. Such abuse is possibly because of evidence that diltiazem increases maximum oxygen consumption after training. A body builder who admitted to taking diltiazem in high doses suffered severe abdominal cramps.[1]

1. Richards H, *et al.* Use of diltiazem in sport. *BMJ* 1993; **307:** 940.

Breast feeding. Diltiazem is distributed into breast milk; in a woman receiving oral diltiazem 60 mg four times daily, concentrations in breast milk were similar to those in serum.[1] The manufacturers therefore recommend that diltiazem should generally be avoided during breast feeding. However, in another report,[2] a mother breast fed twins for at least 6 months while receiving diltiazem and no adverse effects were reported in the infants. Since there have been no reports of adverse effects, the American Academy of Pediatrics considers[3] that diltiazem is usually compatible with breast feeding.

1. Okada M, *et al.* Excretion of diltiazem in human milk. *N Engl J Med* 1985; **312:** 992–3.
2. Lubbe WF. Use of diltiazem during pregnancy. *N Z Med J* 1987; **100:** 121.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Porphyria. Diltiazem is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Renal impairment. A patient with end-stage renal failure requiring haemodialysis developed hypotension, bradycardia, metabolic acidosis, hyperkalaemia, and acute congestive heart failure about 60 hours after his last haemodialysis.[1] The patient had been taking diltiazem 60 mg three times daily. The symptoms were attributed to diltiazem toxicity due to accumulation of diltiazem and its metabolites which are poorly dialysed and normally excreted partially in the urine.

1. Patel R, *et al.* Toxic effects of diltiazem in a patient with chronic renal failure. *J Clin Pharmacol* 1994; **34:** 273–4.

Interactions

Increased depression of cardiac conduction with risk of bradycardia and AV block may occur when diltiazem is given with drugs such as amiodarone, beta blockers, digoxin, and mefloquine. Enhanced antihypertensive effect may occur if used with other antihypertensive drugs or drugs that cause hypotension such as aldesleukin and antipsychotics. Diltiazem is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 and may also inhibit the metabolism of drugs sharing the same pathway. Interactions may also be expected with enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and rifampicin, and with enzyme inhibitors, such as cimetidine and HIV-protease inhibitors.

Antidepressants. For a report of diltiazem increasing the bioavailability of *imipramine* and *nortriptyline*, see Calcium-channel Blockers under the Interactions of Amitriptyline, p.380.

Antiepileptics. For reports of diltiazem use precipitating *carbamazepine* and *phenytoin* toxicity, see p.475 and p.499, respectively.

Anxiolytics. For the effect of diltiazem on plasma-*buspirone* concentrations, see p.966.

Benzodiazepines. For the effects of diltiazem on plasma concentrations of *midazolam* or *triazolam*, see Calcium-channel Blockers under Interactions of Diazepam, p.990.

Beta blockers. Profound bradycardia has been reported in a number of patients when diltiazem was used with a beta blocker.[1,2] Diltiazem decreases the clearance of a single dose of *propranolol* or *metoprolol*, though not *atenolol*, and elevated concentrations of beta blocker may be responsible for the bradycardic effects.[3] This is unlikely to be the full story, however, since atenolol, which was unaffected in this study, has been implicated in producing bradycardia when diltiazem was added in a patient with myocardial ischaemia.[2]

1. Hassell AB, Creamer JE. Profound bradycardia after the addition of diltiazem to a β blocker. *BMJ* 1989; **298:** 675.
2. Nagle RE, *et al.* Diltiazem and heart block. *Lancet* 1989; **i:** 907.
3. Tateishi T, *et al.* Effect of diltiazem on the pharmacokinetics of propranolol, metoprolol and atenolol. *Eur J Clin Pharmacol* 1989; **36:** 67–70.

Calcium-channel blockers. For the effect of diltiazem and *nifedipine* on each other's plasma concentrations, see p.1353.

Ciclosporin. For reports of a potentially beneficial interaction between diltiazem and ciclosporin, see Transplantation under Uses and Administration, below.

Corticosteroids. Diltiazem has been reported to reduce the clearance of *methylprednisolone* (see Calcium-channel Blockers, p.1495).

Digoxin. For a discussion of interactions between digoxin and calcium-channel blockers including diltiazem, see p.1262.

General anaesthetics. Two patients on diltiazem therapy developed impaired myocardial conduction during anaesthesia with *enflurane*;[1] one of the patients had severe sinus bradycardia that progressed to asystole. Additive cardiodepressant effects of diltiazem and enflurane were considered responsible.

1. Hantler CB, *et al.* Impaired myocardial conduction in patients receiving diltiazem therapy during enflurane anesthesia. *Anesthesiology* 1987; **67:** 94–6.

Histamine H_2-antagonists. *Cimetidine* caused increases in plasma-diltiazem concentrations and in plasma-deacetyldiltiazem concentrations in 6 subjects given a single oral dose of diltiazem 60 mg. *Ranitidine* produced a similar, though less marked effect.[1]

1. Winship LC, *et al.* The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. *Pharmacotherapy* 1985; **5:** 16–19.

Lithium. Neurotoxicity has been reported in patients receiving lithium and diltiazem, see Effects on Mental Function and Parkinsonism under Effects on the Nervous System, above.

Theophylline. For the effect of diltiazem on plasma-theophylline concentrations, see p.1144.

Pharmacokinetics

Diltiazem is almost completely absorbed from the gastrointestinal tract after oral doses, but undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations occur about 3 to 4 hours after an oral dose. The bioavailability has been reported to be about 40%, although there is considerable interindividual variation in plasma concentrations. Diltiazem is about 80% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4; one of the metabolites, desacetyldiltiazem, has been reported to have 25 to 50% of the activity of the parent compound. The half-life of diltiazem is reported to be about 3 to 5 hours. About 2 to 4% of a dose is excreted in urine as unchanged diltiazem with the remainder excreted as metabolites in bile and urine. Diltiazem and its metabolites are poorly dialysable.

◊ General reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

Bioavailability. Studies of the pharmacokinetics of diltiazem in healthy subjects after single and multiple doses,[1-3] indicated that bioavailability was increased after multiple doses, probably because of decreased presystemic elimination.[3]

1. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated multiple-dose treatments in healthy volunteers. *Ther Drug Monit* 1989; **11:** 543–50.
2. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after repeated single dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 551–7.
3. Höglund P, Nilsson L-G. Pharmacokinetics of diltiazem and its metabolites after single and multiple dosing in healthy volunteers. *Ther Drug Monit* 1989; **11:** 558–66.

Renal impairment. The pharmacokinetics of diltiazem and its major metabolite desacetyldiltiazem in patients with severe renal impairment were similar to those in patients with normal renal function.[1] Nevertheless, reduced doses may be necessary in patients with renal impairment (see under Uses and Administration below). See also under Precautions, above.

1. Pozet N, *et al*. Pharmacokinetics of diltiazem in severe renal failure. *Eur J Clin Pharmacol* 1983; **24:** 635–8.

Uses and Administration

Diltiazem is a benzothiazepine calcium-channel blocker (p.1154) and class IV antiarrhythmic (p.1153). It is a peripheral and coronary vasodilator with limited negative inotropic activity but its vasodilator properties are less marked than those of the dihydropyridine calcium-channel blocker nifedipine (p.1350). Unlike nifedipine, diltiazem inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes.

Diltiazem hydrochloride is given orally in the management of angina pectoris (p.1157) and hypertension (p.1171) and is available in a number of formulations for dosage once, twice, or three times daily. In some countries it is available for intravenous use in the treatment of various cardiac arrhythmias (atrial fibrillation or flutter and paroxysmal supraventricular tachycardia) (p.1160). It has also been used topically in the management of anal fissure (see below).

The variety of formulations means that dosage is dependent on the preparation used. Reduced doses may be required in the elderly or those with renal or hepatic impairment (see below).

In **angina pectoris** an initial dose is 60 mg orally three times daily (or 30 mg four times daily in the USA), increased if necessary to 360 mg daily; up to 480 mg daily has sometimes been given. Formulations suitable for once- or twice-daily use may be given in doses of 120 to 480 mg daily; up to 540 mg daily has been given.

In **hypertension** diltiazem hydrochloride may be given as modified-release capsules or tablets. Depending on the formulation, an initial dose is 60 to 120 mg twice daily, increased as required to a maximum of 360 mg daily. Formulations suitable for once-daily dosage may be given in similar daily doses, although up to 540 mg daily has been given.

In **cardiac arrhythmias** an initial dose of 250 micrograms/kg by bolus intravenous injection over 2 minutes has been suggested; a further dose of 350 micrograms/kg may be given after 15 minutes if the response is inadequate. Subsequent doses should be individualised for each patient. For those with atrial fibrillation or flutter, a continued reduction in heart rate may be achieved with an intravenous infusion of diltiazem hydrochloride after the bolus injection. An initial infusion rate of 5 to 10 mg/hour, may be increased as necessary in increments of 5 mg/hour up to a rate of 15 mg/hour. The infusion may be continued for up to 24 hours.

◊ General reviews.

1. Buckley MM-T, *et al*. Diltiazem: a reappraisal of its pharmacological properties and therapeutic use. *Drugs* 1990; **39:** 757–806.
2. Fisher M, Grotta J. New uses for calcium channel blockers: therapeutic implications. *Drugs* 1993; **46:** 961–75.
3. Weir MR. Diltiazem: ten years of clinical experience in the treatment of hypertension. *J Clin Pharmacol* 1995; **35:** 220–32.

Action. The haemodynamic and electrophysiological effects of diltiazem appear to resemble those of verapamil more than those of nifedipine.[1] It inhibits sino-atrial and atrioventricular nodal function in doses used clinically. The effects on sino-atrial function are more pronounced than those observed after verapamil. Diltiazem causes a decrease in the rate-pressure product indicating that decreased oxygen demand is a likely mechanism of action in relieving angina pectoris. Like verapamil, but unlike nifedipine, diltiazem does not appear to cause significant increases in coronary blood flow. The negative inotropic effect of diltiazem is presumably counteracted by afterload reduction.

1. Soward AL, *et al*. The haemodynamic effects of nifedipine, verapamil and diltiazem in patients with coronary artery disease: a review. *Drugs* 1986; **32:** 66–101.

Administration in hepatic or renal impairment. The dose of diltiazem hydrochloride may need to be reduced in patients with hepatic or renal impairment, and in the elderly. In the UK an initial dose of 120 mg daily is usually suggested, as a single dose or in 2 divided doses by mouth depending on the formulation. The dose may be increased cautiously, but only if the heart rate remains above 50 beats/minute.

Anorectal disorders. Beneficial responses to diltiazem reported[1,2] in 2 patients with *proctalgia fugax* may have been due to smooth muscle relaxation. The resting pressure of the internal anal sphincter was decreased by a mean of 20.6% in all but 1 of 13 subjects given a single 60-mg oral dose of diltiazem.[2] A small study[3] has compared oral with topical diltiazem in the management of *anal fissure* (p.1891). Despite a higher response rate with the topical drug, no significant difference in benefit was seen between the 2 routes. A subsequent study[4] suggested topical diltiazem (2%) might be of benefit in patients with anal fissure unresponsive to topical nitrates. Sustained benefit after a 6-week treatment course has also been reported in some patients.[5]

1. Boquet J, *et al*. Diltiazem for proctalgia fugax. *Lancet* 1986; **i:** 1493.
2. Jonard P, Essamri B. Diltiazem and internal anal sphincter. *Lancet* 1987; **i:** 754.
3. Jonas M, *et al*. A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
4. Jonas M, *et al*. Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
5. Nash GF, *et al*. The long-term results of diltiazem treatment for anal fissure. *Int J Clin Pract* 2006; **60:** 1411–13.

Cardiomyopathies. Although calcium-channel blockers should be used with caution in patients with heart failure, symptomatic improvement has been reported in patients with dilated cardiomyopathy (p.1163) given diltiazem.[1]

1. Figulla HR, *et al*. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; **94:** 346–52.

Connective tissue and muscular disorders. Subcutaneous deposition of calcium (calcinosis) can occur in a number of inflammatory conditions, particularly in juvenile dermatomyositis (see Polymyositis and Dermatomyositis, p.1510). Treatment of calcinosis is difficult, but there have been a number of reports of the successful use of diltiazem in children[1,2] and adults[3] with dermatomyositis, as well as in adults with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome,[4] scleroderma,[5] and lupus panniculitis.[6] Another study,[7] however, found only a limited response in patients with systemic sclerosis.

1. Oliveri MB, *et al*. Regression of calcinosis during diltiazem treatment in juvenile dermatomyositis. *J Rheumatol* 1996; **23:** 2152–5.
2. Ichiki Y, *et al*. An extremely severe case of cutaneous calcinosis with juvenile dermatomyositis, and successful treatment with diltiazem. *Br J Dermatol* 2001; **144:** 894–7.
3. Vinen CS, *et al*. Regression of calcinosis associated with adult dermatomyositis following diltiazem therapy. *Rheumatology (Oxford)* 2000; **39:** 333–4.
4. Palmieri GMA, *et al*. Treatment of calcinosis with diltiazem. *Arthritis Rheum* 1995; **38:** 1646–54.
5. Dolan AL, *et al*. Diltiazem induces remission of calcinosis in scleroderma. *Br J Rheumatol* 1995; **34:** 576–8.
6. Morgan KW, *et al*. Calcifying lupus panniculitis in a patient with subacute cutaneous lupus erythematosus: response to diltiazem and chloroquine. *J Rheumatol* 2001; **28:** 2129–32.
7. Vayssairat M, *et al*. Clinical significance of subcutaneous calcinosis in patients with systemic sclerosis: does diltiazem induce its regression? *Ann Rheum Dis* 1998; **57:** 252–4.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p.1355). Diltiazem has been reported to reduce urinary protein excretion without exacerbating pre-existing renal dysfunction in diabetic patients.[1,2] A small study[3] in 15 hypertensive patients with type 2 diabetes mellitus, albuminuria, and renal impairment found that diltiazem only reduced urinary albumin excretion when patients received a restricted dietary sodium intake of 50 mmol daily.

Diltiazem may also reduce the nephrotoxicity associated with certain drugs. Reduced nephrotoxicity has been reported when diltiazem is given to healthy subjects receiving netilmicin,[4] but diltiazem does not appear to modify the acute renal failure associated with tubular damage which may be caused by methotrexate.[5] Diltiazem may reduce ciclosporin-induced nephrotoxicity (see Transplantation, below).

1. Bakris GL. Effects of diltiazem or lisinopril on massive proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **112:** 707–8.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996; **125:** 201–4.
4. Lortholary O, *et al*. Calcium antagonists and aminoglycoside nephrotoxicity. *Am J Med* 1990; **88:** 445.
5. Deray G, *et al*. The effects of diltiazem on methotrexate-induced nephrotoxicity. *Eur J Clin Pharmacol* 1989; **37:** 337–40.

Migraine. For reference to the use of calcium-channel blockers, including diltiazem, in the management of migraine, see under Nifedipine, p.1355.

Myocardial infarction. For reference to the use of diltiazem in the acute and long-term management of myocardial infarction, see under Uses of Verapamil, p.1424.

Transplantation. Diltiazem increases blood-ciclosporin concentrations when given by mouth in doses of 60 to 180 mg daily to transplant patients receiving ciclosporin therapy.[1-3] In consequence, ciclosporin doses can be reduced by about one-third, at a considerable saving in cost.[2,3] However, the effect may not occur in all patients,[4] and may vary with differing formulations,[5] and it has been suggested that blood-ciclosporin concentrations should be closely monitored if diltiazem is used for this purpose. In addition to this effect, which is apparently due to non-competitive inhibition of ciclosporin metabolism by diltiazem,[6] there is evidence of improved renal graft-function in patients given the combined therapy, suggesting that diltiazem may reduce ciclosporin-induced nephrotoxicity.[1,2] However, a 4-year follow-up study in patients treated with ciclosporin and diltiazem found that diltiazem had no effect on the progression to chronic allograft nephropathy.[7] Improved survival has been reported[8] in a retrospective study of patients given diltiazem for its ciclosporin-sparing effect, but it was unclear if this was a direct effect of diltiazem or was related to other factors associated with its use.

1. Wagner K, Neumayer H-H. Prevention of delayed graft function in cadaver kidney transplants by diltiazem. *Lancet* 1985; **ii:** 1355–6.
2. Neumayer H-H, Wagner K. Diltiazem and economic use of cyclosporin. *Lancet* 1986; **ii:** 523.
3. Bourge RC, *et al*. Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.
4. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
5. Jones TE, *et al*. Formulation of diltiazem affects cyclosporin-sparing activity. *Eur J Clin Pharmacol* 1997; **52:** 55–8.
6. Brockmöller J, *et al*. Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
7. Ingsathit A, *et al*. Co-administration of diltiazem and cyclosporine for kidney transplant recipients: a four year follow-up study. *J Med Assoc Thai* 2006; **89** (suppl 2): S235–S241.
8. McDonald SP, Russ GR. Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients. *Kidney Int* 2002; **61:** 2259–65.

Preparations

USP 31: Diltiazem Hydrochloride Extended-release Capsules; Diltiazem Hydrochloride Oral Solution; Diltiazem Hydrochloride Oral Suspension; Diltiazem Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acalix; Corodrox; Dilahim; Diltenk; Diltiacor†; Dilzen-G; Hart; Incoril; Kaltiazem; Ritmocit†; Tilazem; ***Austral.:*** Auscard†; Cardizem; Coras; Diltahexal; Dilzem; Vasocardol; ***Austria:*** Corazem†; Diltahexal; Diltiastad; Dilzem; ***Belg.:*** Progor; Tildiem; ***Braz.:*** Angiolong; Balcor; Calzem; Cardizem; Cordil; Diltiacor; Diltipress; Diltizem; Diltor; Incoril; ***Canad.:*** Apo-Diltiaz; Cardizem; Novo-Diltazem; Nu-Diltiaz; Tiazac; ***Chile:*** Acasmul; Grifodilzem; Incoril; Tilazem; Tildiem; ***Cz.:*** Aldizem†; Altiazem†; Blocalcin; Diacordin; Dilzem†; Etizem†; Tiakem†; ***Denm.:*** Cardil; Cardizem; Dilcor; Myonil; Tilker; Viazem†; ***Fin.:*** Cardizem; Dilmin; Dilpral; Dilzem; ***Fr.:*** Bi-Tildiem; Deltazen; Diacor; Dilrene; Mono-Tildiem; Tildiem; ***Ger.:*** Corazet†; Dil-Sanorania; Dilsal; Dilta; Diltabeta; Diltahexal; Diltapham†; Diltaretard; Dilti; Diltiagamma; Diltiuc†; Dilzanton; Dilzem; Dilzicardin†; ***Gr.:*** Alfener; Cardil; Diltelan; Diltem†; Dilzanol†; Dipen; Elvesil; Ergoclavin; Mavitalon; Mycarzem†; Rubiten; Saubasin; Ternel; Tildiem; Zem†; Zilden; ***Hong Kong:*** Altiazem; Apo-Diltiaz; Cardium; Diltan†; Herbesser; Retalzem†; Wontizem; ***Hung.:*** Blocalcin; Dilrene; Diltan†; Dilzem; ***India:*** Dilcardia†; Dilcontin; Dilgard; Dilzem; DTM; Iski; Kaizem; ***Indon.:*** Cordizem; Dilmen; Dilso; Farmabes; Herbesser; Lanodil; ***Irl.:*** Adizem; Diltam; Dilzem; Entrydil; Tildiem; ***Israel:*** Adizem; Dilatam; Levodex; ***Ital.:*** Altiazem; Angidil†; Angipress†; Angizem; Citizem†; Diacardin; Diladel; Dilem; Diliter; Dilzene; Etyzem; Longazem; Tildiem; ***Jpn:*** Herbesser; ***Malaysia:*** Cardil; Cascor; Dilcard†; Dilem†; Herbesser; Mono-Tildiem; ***Mex.:*** Angiotrofin; Anremed; Presoken†; Presoquim†; Sertidel; Tilazem; ***Neth.:*** Diloc; Surazem; Tiadil; Tildiem; ***Norw.:*** Cardizem; Tilker†; ***NZ:*** Cardizem; Dilcard†; Diltahexal; Dilzem; ***Philipp.:*** Angiozem; Cordazem; Dilatam; Dilcardia; Diltelan; Diltime; Dilzem; Dyalac; Filazem; Mono-Tildiem; Tildiem; Vasmulax; Zandil; Zemtrial; ***Pol.:*** Blocalcin; Diacordin; Dilocard; Dilzem; Oxycardil; ***Port.:*** Alandiem; Balcor†; Cal-Antagon; Carzem†; Diacardyne†; Dilfar; Dilongo†; Diltiangina; Diltiem; Duplide†; Etizem; Herbesser; Lacerol†; Tiadil†; Tilker; ***Rus.:*** Altiazem (Алтиазем); Blocalcin (Блокальцин); Cardil (Кардил); Diazem (Диазем); Dilcardia (Дилкардия); ***S.Afr.:*** Dilatam; Tilazem; Zildem; ***Singapore:*** Beatizem; Cardil; Cardium; Dilatam†; Herbesser; Mono-Tildiem; ***Spain:*** Angiodrox; Cardiser; Carreldon; Clobendian; Corolater; Cronodine; Dilaclan; Diltiwas; Dinisor; Doclis; Lacerol; Masdil; Tilker; Trumsal; Uni Masdil; ***Swed.:*** Cardizem; Coramil; Viazem†; ***Switz.:*** Coridil; Dilzem; Escozem†; Tildiem; ***Thai.:*** Altiazem†; Angizem†; Cardil; Carzem; Cascor; Denazox; Dilem; Dilizem; Diltec; Dilzem†; Ditizem; Herbesser; Medozem†; Progor; ***Turk.:*** Altizem; Dilticard; Diltizem; Kardil; Tildiem; ***UK:*** Adizem; Angiozem†; Angitil; Calcicard; Dilcardia; Dilzem; Disogram; Optil; Slozem; Tildiem; Viazem; Zemtard; ***USA:*** Cardizem; Cartia; Dilacor; Dilt-CD; Dilt-XR; Diltia; Taztia; Tiazac; ***Venez.:*** Acalix; Corazem; Cordisil; Daltazen; Presoquin; Tilazem.

Multi-ingredient: *Arg.:* Lotrix†; ***USA:*** Teczem.

Dimetofrine Hydrochloride *(rINNM)* ⊗

Dimétofrine, Chlorhydrate de; Dimetofrini Hydrochloridum; Dimetophrine Hydrochloride; Hidrocloruro de dimetofrina. 4-Hydroxy-3,5-dimethoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

Диметофрина Гидрохлорид

$C_{11}H_{17}NO_4,HCl = 263.7.$

CAS — 22950-29-4 (dimetofrine); 22775-12-8 (dimetofrine hydrochloride).

ATC — C01CA12.

ATC Vet — QC01CA12.

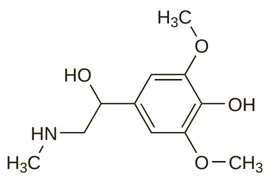

(dimetofrine)

Profile

Dimetofrine hydrochloride is a sympathomimetic (p.1407) that has been used for its vasopressor effects in the treatment of hypotensive states. It has also been used in preparations for cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Pressamina†.

Multi-ingredient: *Ital.:* Raffreddoremed.

Dipyridamole *(BAN, USAN, rINN)*

Dipiridamol; Dipiridamolis; Dipirydamol; Dipyridamol; Dipyridamoli; Dipyridamolum; NSC-515776; RA-8. 2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.

Дипиридамол

$C_{24}H_{40}N_8O_4 = 504.6.$

CAS — 58-32-2.

ATC — B01AC07.

ATC Vet — QB01AC07.

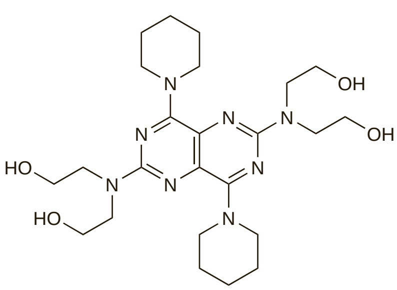

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Dipyridamole). A bright yellow crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. It dissolves in dilute solutions of mineral acids. Protect from light.

USP 31 (Dipyridamole). An intensely yellow, crystalline powder or needles. Slightly soluble in water; very soluble in chloroform, in alcohol, and in methyl alcohol; very slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Gastrointestinal disturbances, including nausea, vomiting, and diarrhoea, headache, dizziness, faintness, hypotension, facial flushing, and skin rash and other hypersensitivity reactions may occur after use of dipyridamole. Dipyridamole can also induce chest pain or lead to a worsening of the symptoms of angina. Cardiac arrhythmias have been reported in patients given dipyridamole during thallium-201 imaging. Aminophylline may reverse some of the adverse effects.

Dipyridamole should be used with caution in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, or coagulation disorders. Intravenous dipyridamole should not be given to patients with these conditions or to those with arrhythmias, conduction disorders, asthma, or a history of bronchospasm (but see Myocardial Imaging, below). Oral dipyridamole should be stopped 24 hours before intravenous use for stress testing.

Effects on the biliary tract. Gallstones containing unconjugated dipyridamole were removed from 2 patients who had been taking dipyridamole for 15 and 10 years, respectively.[1] A gallstone containing unconjugated dipyridamole recurred in a patient who continued to take the drug after endoscopic removal of a similar stone 18 months earlier.[2]

1. Moesch C, *et al.* Biliary drug lithiasis: dipyridamole gallstones. *Lancet* 1992; **340:** 1352–3.
2. Sautereau D, *et al.* Recurrence of biliary drug lithiasis due to dipyridamole. *Endoscopy* 1997; **29:** 421–3.

Effects on the heart. Transient myocardial ischaemia occurred in 4 patients with unstable angina and multivessel coronary artery disease during oral treatment with dipyridamole.[1] See Myocardial Imaging, below, for additional reports.

1. Keltz TN, *et al.* Dipyridamole-induced myocardial ischemia. *JAMA* 1987; **257:** 1515–16.

Effects on the muscles. Symptoms resembling acute pseudopolymyalgia rheumatica developed in a patient taking dipyridamole.[1]

1. Chassagne P, *et al.* Pseudopolymyalgia rheumatica with dipyridamole. *BMJ* 1990; **301:** 875.

Effects on taste. A disagreeable taste associated with other gastrointestinal symptoms occurred in a patient taking dipyridamole.[1] Two similar cases had been reported to the UK CSM.

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983; **100:** 368–71.

Myocardial imaging. Dipyridamole may be used in association with thallium-201 in myocardial stress imaging. Safety data from over 3900 patients has been summarised.[1] Adverse effects which occurred within 24 hours of dipyridamole intravenously (mean dose 560 micrograms/kg) were recorded. Ten patients had major adverse effects and 1820 patients experienced minor adverse effects. Myocardial infarction occurred in 4 patients, 3 of whom had unstable angina before scanning. Six patients developed acute bronchospasm, 4 of whom had a history of asthma or had wheezing before using dipyridamole. Adverse effects considered to be minor included chest pain in 19.7% of patients, ST-T-segment depression in 7.5%, ventricular extrasystoles in 5.2%, headache in 12.2%, dizziness in 11.8%, nausea in 4.6%, and hypotension in 4.6%. Aminophylline was effective in relieving symptoms of adverse effects in 97% of 454 patients.

Hypersensitivity reactions including anaphylaxis and angioedema have been reported.[2,3]

UK licensed product information contra-indicates intravenous dipyridamole in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, coagulation disorders, arrhythmias, conduction disorders, asthma, or a history of bronchospasm. However, a review[4] of pharmacological stress testing suggested that with appropriate patient selection and adequate monitoring, the incidence of life-threatening adverse reactions is negligible. It was also considered that dipyridamole-thallium-201 imaging could be safely performed in the early post-myocardial infarction period.

1. Ranhosky A, *et al.* The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990; **81:** 1205–9.
2. Weinmann P, *et al.* Anaphylaxis-like reaction induced by dipyridamole during myocardial scintigraphy. *Am J Med* 1994; **97:** 488.
3. Angelides S, *et al.* Acute reaction to dipyridamole during myocardial scintigraphy. *N Engl J Med* 1999; **340:** 394.
4. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.

Interactions

Dipyridamole may enhance the actions of oral anticoagulants due to its antiplatelet effect. It inhibits the reuptake of adenosine and may enhance its effects; the dose of adenosine must be reduced if both drugs are given. Dipyridamole may also inhibit the uptake of fludarabine and may reduce its efficacy.

The absorption of dipyridamole may be reduced by drugs such as antacids that increase gastric pH.

Anticoagulants. Dipyridamole may induce bleeding in patients receiving oral anticoagulants without altering prothrombin times (see Antiplatelets, under Warfarin, Interactions, p.1429).

Xanthines. Xanthines may antagonise some of the effects of dipyridamole due to their action as adenosine antagonists. *Aminophylline* may be used to reverse some of the adverse effects of dipyridamole. Intravenous *caffeine* has been reported[1] to attenuate the haemodynamic response to dipyridamole and it has been suggested that caffeine should be avoided for at least 24 hours before the test in patients receiving dipyridamole for myocardial imaging.

1. Smits P, *et al.* Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; **50:** 529–37.

Pharmacokinetics

Dipyridamole is incompletely absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 75 minutes after an oral dose. Dipyridamole is more than 90% bound to plasma proteins. A terminal half-life of 10 to 12 hours has been reported. Dipyridamole is metabolised in the liver and is mainly excreted as glucuronides in the bile. Excretion may be delayed by enterohepatic recirculation. A small amount is excreted in the urine. Dipyridamole is distributed into breast milk.

◊ References.

1. Mahony C, *et al.* Dipyridamole kinetics. *Clin Pharmacol Ther* 1982; **31:** 330–8.
2. Mahony C, *et al.* Plasma dipyridamole concentrations after two different dosage regimens in patients. *J Clin Pharmacol* 1983; **23:** 123–6.

Uses and Administration

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with antiplatelet and vasodilating activity and is used in thromboembolic disorders (p.1187). Oral dipyridamole is used for the prophylaxis of thromboembolism after cardiac valve replacement (p.1187) and in the management of stroke (below); it has also been used in the management of myocardial infarction (p.1175). Dipyridamole given intravenously results in marked coronary vasodilatation and is used in stress testing in patients with ischaemic heart disease (see Myocardial Imaging, below).

For the prophylaxis of **thromboembolism** after cardiac valve replacement, dipyridamole is given with an oral anticoagulant. The usual adult dose is 300 to 600 mg daily by mouth in divided doses before meals. Children have been given 5 mg/kg by mouth daily in divided doses.

For the secondary prevention of **stroke** or transient ischaemic attack dipyridamole is given as a modified-release preparation, alone or with aspirin, in a dose of 200 mg twice daily.

◊ General references.

1. FitzGerald GA. Dipyridamole. *N Engl J Med* 1987; **316:** 1247–57.
2. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998; **45:** 323–8.

Myocardial imaging. Perfusion abnormalities due to coronary artery disease are usually absent at rest but are present during stress, and stress imaging may therefore be used in the assessment of myocardial function. The stress is usually supplied by exercise, but when exercise is inappropriate pharmacological methods such as dipyridamole may be used.

Dipyridamole has been used with thallium-201 scintigraphy in adults and children and is usually given intravenously in a dose of 567 micrograms/kg over 4 minutes. Thallium-201 is given within 3 to 5 minutes after completion of the infusion of dipyridamole. Initial images are obtained after 5 minutes and delayed images are obtained 2.5 to 4 hours later. Dipyridamole (300 to 400 mg) has also been given as an oral suspension; thallium-201 is given about 45 minutes later to coincide with peak dipyridamole-serum concentrations.

Dipyridamole has also been used in echocardiography.[1,2] The intravenous dipyridamole dose used to obtain maximum sensitivity is often higher (750 to 840 micrograms/kg) than the dose used in scintigraphy.[1]

1. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.
2. Buchalter MB, *et al.* Dipyridamole echocardiography: the bedside stress test for coronary artery disease. *Postgrad Med J* 1990; **66:** 531–5.

Stroke. The value of long-term antiplatelet therapy with aspirin in patients who have suffered an ischaemic stroke (p.1185) or transient ischaemic attack is well-established, with a reduction in the risk of both stroke and other vascular events.[1] The use of dipyridamole has been more controversial. Early studies with dipyridamole, used alone or with aspirin, failed to show any benefit over aspirin alone. The European Stroke Prevention Study-2 (ESPS-2),[2] which compared aspirin and dipyridamole, alone or together, with placebo, found that both drugs reduced the risk of stroke and that the effects appeared to be additive. The study used a low dose of aspirin and a modified-release formulation of dipyridamole, which may explain the discrepancy with earlier studies.[3] Subsequent meta-analyses[3-6] have confirmed that dipyridamole, alone or with aspirin, reduces the risk of recurrent stroke, but have been based mainly on the ESPS-2, which may be a limitation.[3] However, a further large study[7] comparing aspirin alone with aspirin and dipyridamole also found that the incidence of vascular events (including stroke) was lower in those receiving both drugs. Most guidelines[8,9] therefore now recommend aspirin with dipyridamole as one of the preferred options for long-term management of ischaemic stroke.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106. Correction. *ibid.*; 1540.
2. Diener HC, *et al.* European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143:** 1–13.
3. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999; **56:** 1087–92.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86. Correction. *ibid.*; 141.
5. Leonardi-Bee J, *et al.* Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005; **36:** 162–8.
6. De Schryver ELLM, *et al.* Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
7. Halkes PH, *et al.* ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367:** 1665–73. Correction. *ibid.* 2007; **369:** 274.
8. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25:** 457–507. Also available at: http://www.eso-stroke.org/pdf/ESO08_Guidelines_English.pdf (accessed 11/07/08)
9. Albers GW, *et al.* Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 630S–669S.

Preparations

BP 2008: Dipyridamole Tablets;
USP 31: Dipyridamole Injection; Dipyridamole Oral Suspension; Dipyridamole Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Maxicardil; Persantin; Sedangor; ***Austral.:*** Persantin; ***Austria:*** Persantin; ***Belg.:*** Coronair; Dipyridan†; Docdipyri; Persantine; ***Braz.:*** Persantin; ***Canad.:*** Novo-Dipiradol†; Persantine; ***Chile:*** Persantin; ***Cz.:*** Curantyl N†; Persantin†; ***Denm.:*** Persantin; ***Fin.:*** Atrombin; Dipyrin; Persantin; ***Fr.:*** Cleridium†; Persantine; ***Ger.:*** Curantyl N†; ***Gr.:*** Adezan; Persantin; ***Hong Kong:*** Persantin; Procardin; ***India:*** Persantin; ***Indon.:*** Cardial; Persantin; Vasokor; Vasotin; ***Irl.:*** Persantin; ***Israel:*** Cardoxin; ***Ital.:*** Corosan; Novodil; Persantin; ***Jpn:*** Persantin; ***Malaysia:*** Persantin†; ***Mex.:*** Digal; Dipres; Dirinol; Lodimol; Persantin; Pracem; Trepol; Trompersantin†; Vadinar; ***Neth.:*** Persantin; ***Norw.:*** Persantin; ***NZ:*** Persantin; Pytazen; ***Philipp.:*** Persantin; ***Port.:*** Persantin; ***Rus.:*** Curantyl (Курантил); Persantin (Персантин); ***S.Afr.:*** Persantin; Plato; ***Singapore:*** Persantin; Procardin; ***Spain:*** Persantin; ***Swed.:*** Persantin; ***Thai.:*** Agremol; Persantin; Posanin; ***Turk.:*** Drisentin; Kardisentin; Tromboliz; ***UK:*** Persantin; ***USA:*** Persantine; ***Venez.:*** Megalis†; Meranol†; Persantin; Precar†.

Multi-ingredient: ***Arg.:*** Agrenox; Licuamon; ***Austral.:*** Asasantin; ***Austria:*** Asasantin; Thrombohexal; ***Belg.:*** Aggrenox; ***Canad.:*** Aggrenox; ***Cz.:*** Aggrenox; ***Denm.:*** Asasantin; ***Fin.:*** Asasantin; ***Fr.:*** Asasantine; ***Ger.:*** Aggrenox; Asasantin†; ***Gr.:*** Aggrenox; ***Hong Kong:*** Aggrenox; ***Hung.:*** Asasantin; ***India:*** Dynasprin; ***Indon.:*** Aggrenox; ***Irl.:*** Asasantin; ***Mex.:*** Asasantin†; ***Neth.:*** Asasantin; ***Norw.:*** Asasantin; ***Philipp.:*** Aggrenox; ***Port.:*** Aggrenox; ***S.Afr.:*** Asasantin; ***Swed.:*** Asasantin; ***Switz.:*** Asasantine; ***Thai.:*** Aggrenox; ***UK:*** Asasantin; ***USA:*** Aggrenox.

Disopyramide *(BAN, USAN, rINN)*

Disopiramida; Disopyramid; Disopyramidi; Disopyramidum; Dizopiramid; Dizopiramidas; SC-7031. 4-Di-isopropylamino-2-phenyl-2-(2-pyridyl)butyramide.

Дизопирамид

$C_{21}H_{29}N_3O$ = 339.5.
CAS — 3737-09-5.
ATC — C01BA03.
ATC Vet — QC01BA03.

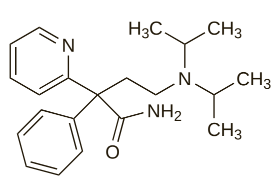

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Disopyramide). A white or almost white powder. Slightly soluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

Disopyramide Phosphate *(BANM, USAN, rINNM)*

Disopyramide, phosphate de; Disopyramidfosfat; Disopyramidfosfát; Disopyramidi phosphas; Disopyramidifosfaatti; Dizopiramid Fosfata; Dizopiramid-foszfát; Dizopiramido fosfatas; Dyzopiramidu fosforan; Fosfato de disopiramida; SC-13957.

Дизопирамида Фосфат

$C_{21}H_{29}N_3O,H_3PO_4$ = 437.5.
CAS — 22059-60-5.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Disopyramide Phosphate). A white or almost white powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Disopyramide Phosphate). A white or practically white, odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

The adverse effects most commonly associated with disopyramide relate to its antimuscarinic properties and are dose-related. They include dry mouth, blurred vision, urinary hesitancy, impotence, and constipation; the most serious effect is urinary retention. Gastrointestinal effects, which are less common, include nausea, bloating, and abdominal pain. Other adverse effects reported include skin rashes, hypoglycaemia, dizziness, fatigue, muscle weakness, headache, and urinary frequency. Insomnia and depression have also been associated with disopyramide. There have been rare reports of psychosis, cholestatic jaundice, elevated liver enzymes, thrombocytopenia, and agranulocytosis. Disopyramide prolongs the QT interval and may induce or worsen arrhythmias, particularly ventricular tachycardia and fibrillation; heart block and conduction disturbances may occur. It is also a negative inotrope and may cause heart failure, and hypotension.

Over-rapid intravenous injection of disopyramide may cause profuse sweating and severe cardiovascular depression.

In overdose cardiovascular and antimuscarinic effects are pronounced, and there may be apnoea, loss of consciousness, loss of spontaneous respiration, and asystole. Treatment of overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

◊ A review of the adverse effects associated with the class Ia antiarrhythmic drugs disopyramide, procainamide, and quinidine, and their clinical management.[1]

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Incidence of adverse effects. During long-term therapy with disopyramide 400 to 1600 mg daily in 40 patients, 28 (70%) had one or more adverse effects.[1] Dry mouth occurred in 15 (38%), constipation in 12 (30%), blurred vision in 11 (28%), urinary hesitancy in 9 (23%), nausea in 9 (23%), impotence in 2 (5%), and dyspareunia in one patient (3%). In addition 3 of the 9 patients with pre-existing heart failure had worsening of their condition due to disopyramide. Adverse effects were sufficiently severe for disopyramide to be stopped in 7 patients, and for dosage reductions in another 7.

1. Bauman JL, *et al.* Long-term therapy with disopyramide phosphate: side effects and effectiveness. *Am Heart J* 1986; **111:** 654–60.

Effects on the blood. Granulocytopenia was associated on 2 occasions with the use of disopyramide phosphate in a 61-year-old man.[1]

1. Conrad ME, *et al.* Agranulocytosis associated with disopyramide therapy. *JAMA* 1978; **240:** 1857–8.

Effects on the eyes. The antimuscarinic activity of disopyramide may cause adverse effects such as dilated pupils,[1] severe blurring of vision,[1] and acute glaucoma.[2,3] Disopyramide should be avoided in patients with glaucoma and used with caution if there is a family history of glaucoma.

1. Frucht J, *et al.* Ocular side effects of disopyramide. *Br J Ophthalmol* 1984; **68:** 890–1.
2. Trope GE, Hind VMD. Closed-angle glaucoma in patient on disopyramide. *Lancet* 1978, **i:** 329.
3. Ahmad S. Disopyramide: pulmonary complications and glaucoma. *Mayo Clin Proc* 1990; **65:** 1030–1.

Effects on the heart. Disopyramide has a strong negative inotropic effect and reversible heart failure has been reported[1] after its use. As many as 50% of patients with a history of heart failure may have a recurrence of the disease with an incidence of less than 5% in other patients.

As disopyramide can prolong the QT interval it can induce ventricular tachyarrhythmias. A case of fatal torsade de pointes has been reported.[2]

1. Podrid PJ, *et al.* Congestive heart failure caused by oral disopyramide. *N Engl J Med* 1980; **302:** 614–17.
2. Schattner A, *et al.* Fatal torsade de pointes following jaundice in a patient treated with disopyramide. *Postgrad Med J* 1989; **65:** 333–4.

Effects on the liver. Cholestatic jaundice with raised liver enzyme values has been associated with disopyramide.[1-3] Laboratory and clinical abnormalities disappear on withdrawal although liver enzyme values may remain elevated for several months.

Severe hepatocellular damage with disseminated intravascular coagulation[4] has also been reported.

1. Craxi A, *et al.* Disopyramide and cholestasis. *Ann Intern Med* 1980; **93:** 150–1.
2. Edmonds ME, Hayler AM. *Eur J Clin Pharmacol* 1980; **18:** 285–6.
3. Bakris GL, *et al.* Disopyramide-associated liver dysfunction. *Mayo Clin Proc* 1983; **58:** 265–7.
4. Doody PT. Disopyramide hepatotoxicity and disseminated intravascular coagulation. *South Med J* 1982; **75:** 496–8.

Effects on mental state. Agitation and distress leading to paranoia and auditory and visual hallucinations have been reported[1,2] in patients shortly after starting disopyramide therapy. Complete recovery occurred on withdrawal.

1. Falk RH, *et al.* Mental distress in patient on disopyramide. *Lancet* 1977; **i:** 858–9.
2. Padfield PL, *et al.* Disopyramide and acute psychosis. *Lancet* 1977; **i:** 1152.

Effects on the nervous system. Peripheral neuropathy affecting the feet and severe enough to prevent walking was associated with disopyramide in a 72-year-old patient.[1] There was gradual improvement on withdrawal of disopyramide with the patient being symptom-free after 4 months. Another patient[2] developed a peripheral polyneuropathy 4 years after starting disopyramide; symptoms improved over a number of months after disopyramide was stopped.

A 75-year-old woman with atrial fibrillation suffered a tonic-clonic seizure followed by respiratory arrest after receiving disopyramide 150 mg intravenously over a period of 10 minutes.[3] On recovery she complained of a dry mouth and blurred vision and it was considered that the seizure was caused by the antimuscarinic action of disopyramide, although it may have been due to a direct stimulant action.

1. Dawkins KD, Gibson J. Peripheral neuropathy with disopyramide. *Lancet* 1978; **i:** 329.
2. Briani C, *et al.* Disopyramide-induced neuropathy. *Neurology* 2002; **58:** 663.
3. Johnson NM, *et al.* Epileptiform convulsion with intravenous disopyramide. *Lancet* 1978; **ii:** 848.

Effects on sexual function. Impotence has been reported[1-3] in patients receiving disopyramide, and is usually attributed to its antimuscarinic effects, although other antimuscarinic symptoms may not be apparent. In one patient[1] full recovery of sexual function occurred when the dose was reduced (plasma concentration reduced from 14 to 3 micrograms/mL); another patient[3] developed impotence shortly after starting disopyramide, despite a low plasma concentration (1.5 micrograms/mL), but the condition resolved without changing therapy.

1. McHaffie DJ, *et al.* Impotence in patient on disopyramide. *Lancet* 1977; **i:** 859.
2. Ahmad S. Disopyramide and impotence. *South Med J* 1980; **73:** 958.
3. Hasegawa J, Mashiba H. Transient sexual dysfunction observed during antiarrhythmic therapy by long-acting disopyramide in a male Wolff-Parkinson-White patient. *Cardiovasc Drugs Ther* 1994; **8:** 277.

Effects on the urinary tract. In a report of 9 cases of urinary retention associated with disopyramide and a review of the literature,[1] it was noted that urinary retention secondary to disopyramide use was most likely to develop in male patients over the age of 65 in whom there was some pre-existing renal dysfunction; there was an increased risk in patients with evidence of prostatic hyperplasia.

1. Danziger LH, Horn JR. Disopyramide-induced urinary retention. *Arch Intern Med* 1983; **143:** 1683–6.

Hypersensitivity. Worsening of ventricular arrhythmia and an anaphylactoid reaction occurred in a 58-year-old man after a single oral dose of disopyramide 300 mg.[1] Two hours later he complained of a swollen tongue and difficulty in breathing. He became cyanotic but his respiratory status improved when given diphenhydramine 25 mg intravenously.

1. Porterfield JG, *et al.* Respiratory difficulty after use of disopyramide. *N Engl J Med* 1980; **303:** 584.

Hypoglycaemia. After the manufacturer received reports of hypoglycaemia associated with disopyramide, 2 controlled studies were conducted in healthy subjects.[1] Disopyramide produced a small decrease in blood-glucose concentration but there were no symptoms of hypoglycaemia, although it was considered that the glucose-lowering effect might be clinically significant in patients with hepatic or renal impairment. A review[2] found that renal impairment, advanced age, and malnutrition were the main risk factors for hypoglycaemia, and hypoglycaemia with reduced insulin requirements has also been reported[3] in a patient with type 2 diabetes mellitus. An interaction with clarithromycin has also been reported as a possible cause (see Antibacterials under

Interactions, below). However, the overall incidence appears to be low[2] and a case-control study[4] in 91 patients with hypoglycaemia failed to confirm an association with disopyramide.

1. Strathman I, *et al*. Hypoglycemia in patients receiving disopyramide phosphate. *Drug Intell Clin Pharm* 1983; **17:** 635–8.
2. Cacoub P, *et al*. Disopyramide-induced hypoglycemia: case report and review of the literature. *Fundam Clin Pharmacol* 1989; **3:** 527–35.
3. Reynolds RM, Walker JD. Hypoglycaemia induced by disopyramide in a patient with type 2 diabetes mellitus. *Diabet Med* 2001; **18:** 1009–10.
4. Takada M, *et al*. The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Overdosage. A 2-year-old boy suffered hypotension, cardiac arrhythmias, and convulsions and died 28 hours after ingestion of 600 mg of disopyramide.[1] In a report[2] of 5 cases of fatal overdosage with disopyramide the most common clinical finding appeared to be an early loss of consciousness after an episode of respiratory arrest. Four of the patients responded to resuscitation at first but then deteriorated rapidly, with cardiac arrhythmias and loss of spontaneous respiration; in 4 of the cases post-mortem examination found pulmonary congestion secondary to left ventricular failure.

1. Hutchison A, Kilham H. Fatal overdosage of disopyramide in a child. *Med J Aust* 1978; **2:** 335–6.
2. Hayler AM, *et al*. Fatal overdosage with disopyramide. *Lancet* 1978; **i:** 968–9.

Precautions

Disopyramide is contra-indicated in complete heart block (unless the patient has a pacemaker) and in cardiogenic shock. It should be used with extreme caution in patients with other conduction disorders or uncompensated heart failure. As for quinidine (see Precautions for Quinidine, p.1384), if disopyramide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Hypokalaemia should be corrected before disopyramide is started. Care should be taken in patients susceptible to hypoglycaemia, including those with heart failure, hepatic or renal impairment, and patients taking drugs that affect glucose metabolism.

Intravenous injections of disopyramide should be given slowly to avoid hypotension and it is recommended that facilities for cardiac monitoring and defibrillation should be available when the injection is used.

Dosage reduction may be necessary in patients with hepatic or renal impairment and in patients with heart failure.

Owing to its antimuscarinic properties, disopyramide should be avoided in patients with glaucoma or a tendency to urinary retention, as in benign prostatic hyperplasia, and also in patients with myasthenia gravis because of the risk of precipitating a myasthenic crisis. It should be used with caution in patients with a family history of glaucoma.

◊ For dosage adjustments in the elderly and in patients with hepatic or renal impairment, see under Uses and Administration, below.

Breast feeding. Disopyramide is distributed into breast milk and milk to plasma ratios of 0.4, about 0.5, and 0.9 have been reported.[1-3] Disopyramide has been detected in the plasma of breast-fed infants, but was not associated with adverse effects. The American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, the infant should be monitored for adverse effects, especially antimuscarinic effects.

1. MacKintosh D, Buchanan N. Excretion of disopyramide in human breast milk. *Br J Clin Pharmacol* 1985; **19:** 856–7.
2. Hoppu K, *et al*. Disopyramide and breast feeding. *Br J Clin Pharmacol* 1986; **21:** 553.
3. Barnett DB, *et al*. Disopyramide and its N-monodesalkyl metabolite in breast milk. *Br J Clin Pharmacol* 1982; **14:** 310–12.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. Disopyramide is not usually recommended in pregnancy since it may induce uterine contractions. Although no adverse effects were noted in a patient given disopyramide 200 mg every 8 hours from 26 weeks of gestation until delivery,[1] another patient who was given 4 oral doses of disopyramide 100 to 300 mg at six-hourly intervals in week 32 of pregnancy had uterine contractions 1 to 2 hours after each dose.[2] A further patient[3] given disopyramide at 36 weeks of gestation developed painful uterine contractions 40 minutes after a single 150-mg dose orally; active labour and haemorrhage developed after a second dose was given, and an emergency caesarean section was required. A double-blind, placebo-controlled study[4] involving 20 women hospitalised for induction of labour confirmed that disopyramide induces uterine contractions. All 10 women given disopyramide 150 mg every 6 hours for 48 hours began contractions and in 8 delivery was induced.

1. Shaxted EJ, Milton PJ. Disopyramide in pregnancy: a case report. *Curr Med Res Opin* 1979; **6:** 70–2.
2. Leonard RF, *et al*. Initiation of uterine contractions by disopyramide during pregnancy. *N Engl J Med* 1978; **299:** 84–5.
3. Abbi M, *et al*. Preterm labor and accidental hemorrhage after disopyramide therapy in pregnancy: a case report. *J Reprod Med* 1999; **44:** 653–5.
4. Tadmor OP, *et al*. The effect of disopyramide on uterine contractions during pregnancy. *Am J Obstet Gynecol* 1990; **162:** 482–6.

Interactions

Disopyramide should be used cautiously with drugs that have negative inotropic effects or that affect conduction, including beta blockers and other class I antiarrhythmics; it prolongs the QT interval and should not be given with other arrhythmogenic drugs. Disopyramide is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with inhibitors or inducers of this enzyme and with other drugs metabolised by CYP3A4. Use of disopyramide with other antimuscarinic drugs produces enhanced antimuscarinic effects.

Anti-anginals. For reference to disopyramide reducing the effectiveness of sublingual *isosorbide dinitrate*, see p.1318.

Antiarrhythmics. The effects of disopyramide on cardiac conduction are additive to those of other class I antiarrhythmic drugs.[1] Disopyramide may prolong the QT interval, a factor associated with torsade de pointes, particularly when given with drugs that have a similar effect; this effect was noted in a few patients given *amiodarone* with disopyramide.[2] Also the serum concentration of disopyramide has been increased by *quinidine*;[3] there was a reciprocal decrease in the serum-quinidine concentration but this was less important clinically.

1. Ellrodt G, Singh BN. Adverse effects of disopyramide (Norpace): toxic interactions with other antiarrhythmic agents. *Heart Lung* 1980; **9:** 469–74.
2. Tartini R, *et al*. Dangerous interaction between amiodarone and quinidine. *Lancet* 1982; **i:** 1327–9.
3. Baker BJ, *et al*. Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J* 1983; **105:** 12–15.

Antibacterials. The metabolism of disopyramide may be increased by enzyme inducers such as *rifampicin*;[1,2] the increased clearance of disopyramide may lead to subtherapeutic plasma concentrations.

Conversely, enzyme inhibitors may increase serum-disopyramide concentrations[3] and ventricular arrhythmias have been noted in patients given azithromycin,[4] clarithromycin,[5-7] and erythromycin.[3] Hypoglycaemia attributed to increased disopyramide concentrations has also been reported[8,9] with clarithromycin.

1. Aitio M-L, *et al*. The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.
2. Staum JM. Enzyme induction: rifampin-disopyramide interaction. *DICP Ann Pharmacother* 1990; **24:** 701–3.
3. Ragosta M, *et al*. Potentially fatal interaction between erythromycin and disopyramide. *Am J Med* 1989; **86:** 465–6.
4. Granowitz EV, *et al*. Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* 2000; **23:** 1433–5.
5. Paar D, *et al*. Life-threatening interaction between clarithromycin and disopyramide. *Lancet* 1997; **349:** 326–7.
6. Hayashi Y, *et al*. Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. *Pacing Clin Electrophysiol* 1999; **22:** 672–4.
7. Choudhury L, *et al*. Torsades de pointes due to drug interaction between disopyramide and clarithromycin. *Heart Dis* 1999; **1:** 206–7.
8. Iida H, *et al*. Hypoglycemia induced by interaction between clarithromycin and disopyramide. *Jpn Heart J* 1999; **40:** 91–96.
9. Morlet-Barla N, *et al*. Hypoglycémie grave et récidivante secondaire à l'interaction disopyramide-clarithromicine. *Presse Med* 2000; **29:** 1351.

Antiepileptics. The clearance of disopyramide may be increased by enzyme inducers such as *phenytoin* and *phenobarbital*, and a small study[1] found that phenytoin reduced serum-disopyramide concentrations.

1. Aitio M-L, *et al*. The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.

Beta blockers. Beta blockers have negative inotropic effects that may be potentiated if they are given with disopyramide. A pharmacokinetic interaction may also occur with beta blockers since the clearance of disopyramide has been reported[1] to be reduced by about 16% during *atenolol* therapy.

1. Bonde J, *et al*. Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol* 1985; **28:** 41–3.

Pharmacokinetics

Disopyramide is readily and almost completely absorbed from the gastrointestinal tract, peak plasma concentrations being attained about 0.5 to 3 hours after oral doses.

Disopyramide is partially metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4. The major metabolite is mono-*N*-dealkylated disopyramide which retains some antiarrhythmic and antimuscarinic activity. The major route of excretion is through the kidney, about 50% as the unchanged drug, 20% as the *N*-dealkylated metabolite, and 10% as other metabolites. About 10% is excreted in the faeces. The clearance of disopyramide does not appear to be influenced by urinary pH.

Disopyramide protein binding varies with the plasma concentration, limiting the usefulness of plasma concentration monitoring as a guide to therapy; protein binding is reported to be 50 to 65% at therapeutic plasma concentrations (about 2 to 4 micrograms/mL). Estimations of the plasma half-life of disopyramide range from about 4 to 10 hours. The half-life is increased in hepatic and renal impairment, and in heart failure.

Disopyramide crosses the placental barrier and is distributed into breast milk.

◊ Reviews.

1. Siddoway LA, Woosley RL. Clinical pharmacokinetics of disopyramide. *Clin Pharmacokinet* 1986; **11:** 214–22.

Uses and Administration

Disopyramide is a class Ia antiarrhythmic (p.1153) with an action on the heart similar to that of quinidine (p.1385). It also has antimuscarinic and negative inotropic properties.

Disopyramide is used in the management of supraventricular and ventricular arrhythmias (p.1160).

It may be given orally as either the base or the phosphate or intravenously as the phosphate; doses are expressed in terms of the base. Disopyramide phosphate 1.3 g is equivalent to about 1 g of disopyramide. The usual oral dose is 300 to 800 mg daily in divided doses adjusted according to response. A modified-release preparation can be used, enabling 12-hourly dosage intervals.

Disopyramide may be given by slow intravenous injection in a dose of 2 mg/kg to a maximum of 150 mg, at a rate not exceeding 30 mg/minute; this is followed by 200 mg orally immediately on completion of the injection and every 8 hours for 24 hours. If the arrhythmia recurs the intravenous injection may be repeated, but a total intravenous dose of 4 mg/kg (maximum 300 mg) should not be exceeded in the first hour, nor should the total by both intravenous and oral routes exceed 800 mg in 24 hours. Alternatively, the initial intravenous injection may be followed by intravenous infusion of 400 micrograms/kg per hour (or 20 to 30 mg/hour) to a maximum of 800 mg daily. Patients receiving disopyramide intravenously or in high oral doses should be monitored by ECG.

Dosage reduction and/or increased dosage interval may be necessary in patients with hepatic or renal impairment (see below) and in some elderly patients (see, below). Doses should also be adjusted in patients with heart failure to compensate for the prolonged half-life.

For the dosage of disopyramide in children, see below.

Action. A study in 6 patients with atrial flutter suggested that the antiarrhythmic activity of racemic disopyramide resides in the S(+)-enantiomer.[1]

1. Lima JJ, *et al*. Antiarrhythmic activity and unbound concentrations of disopyramide enantiomers in patients. *Ther Drug Monit* 1990; **12:** 23–8.

Administration in children. An optimum dosage regimen for children has not been fully established, but US product information suggests the following oral doses:

- under 1 year: 10 to 30 mg/kg daily
- age 1 to 4 years: 10 to 20 mg/kg daily
- age 4 to 12 years: 10 to 15 mg/kg daily
- age 12 to 18 years: 6 to 15 mg/kg daily

Administration in the elderly. The clearance of disopyramide was reduced in elderly non-smoking patients compared with young subjects, but the reduction was less marked in elderly patients who smoked more than 20 cigarettes daily.[1] It was recommended that the dose of disopyramide should be reduced by about 30% in elderly non-smokers.

1. Bonde J, *et al*. The influence of age and smoking on the elimination of disopyramide. *Br J Clin Pharmacol* 1985; **20:** 453–8.

Administration in hepatic impairment. The plasma half-life of disopyramide may be increased in hepatic impairment and dosage reduction should be considered; US licensed product information recommends an oral dose of 400 mg daily in divided doses. In patients with liver cirrhosis there is also a significant reduction in the plasma concentration of α_1-acid glycoprotein;[1,2] in addition, its binding capacity for disopyramide is reduced.[1] This is associated with an increase in the free fraction of disopyramide such that measurement of total disopyramide in plasma may not be a safe indicator for dosing, and a therapeutic range 50% lower than in patients with normal hepatic function should be considered.[2]

1. Bonde J, *et al.* Kinetics of disopyramide in decreased hepatic function. *Eur J Clin Pharmacol* 1986; **31:** 73–7.
2. Echizen H, *et al.* Protein binding of disopyramide in liver cirrhosis and in nephrotic syndrome. *Clin Pharmacol Ther* 1986; **40:** 274–80.

Administration in renal impairment. Disopyramide is excreted mainly in the urine and a reduction in clearance with an increase in elimination half-life has been reported[1] in patients with renal impairment. Dosage reduction should therefore be considered. US licensed product information recommends the following oral doses based on creatinine clearance (CC):

- CC greater than 40 mL/minute: 400 mg daily in divided doses
- CC 30 to 40 mL/minute: 100 mg every 8 hours
- CC 15 to 30 mL/minute: 100 mg every 12 hours
- CC less than 15 mL/minute: 100 mg every 24 hours

Modified-release preparations should be avoided in patients with CC less than 40 mL/minute.

At therapeutic concentrations disopyramide is not significantly removed by haemodialysis;[2] the half-life is similar both on and off dialysis (16.8 versus 16.1 hours). An increased free fraction of disopyramide has been seen[3] during haemodialysis associated with an elevation in free fatty acids in plasma and in such cases free plasma-disopyramide concentrations should be monitored.

1. Francois B, *et al.* Pharmacokinetics of disopyramide in patients with chronic renal failure. *Eur J Drug Metab Pharmacokinet* 1983; **8:** 85–92.
2. Sevka MJ, *et al.* Disopyramide hemodialysis and kinetics in patients requiring long-term hemodialysis. *Clin Pharmacol Ther* 1981; **29:** 322–6.
3. Horiuchi T, *et al.* Inhibitory effect of free fatty acids on plasma protein binding of disopyramide in haemodialysis patients. *Eur J Clin Pharmacol* 1989; **36:** 175–80.

Hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy (p.1163) may have exercise intolerance due to left ventricular outflow obstruction. Beta blockers are usually used when symptoms are associated with exercise or emotional factors, but may not be effective in patients with symptoms at rest. Disopyramide has been used for its negative inotropic effect in such patients and a retrospective study[1] found that it improved symptoms without having a proarrhythmic effect.

1. Sherrid MV, *et al.* Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; **45:** 1251–8.

Hypotension. Disopyramide has been widely used in the management of neurally mediated hypotension (p.1174) but there is limited evidence to support its use. Although some reports[1,2] have suggested benefit, a controlled study[3] found that it was no more effective than placebo in preventing tilt-induced syncope. Adverse effects also limit the use of disopyramide, and it is generally no longer considered first line.

1. Milstein S, *et al.* Usefulness of disopyramide for prevention of upright tilt-induced hypotension-bradycardia. *Am J Cardiol* 1990; **65:** 1339–44.
2. Bhaumick SK, *et al.* Oral disopyramide in the treatment of recurrent neurocardiogenic syncope. *Int J Clin Pract* 1997; **51:** 342.
3. Morillo CA, *et al.* A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993; **22:** 1843–8.

Preparations

BP 2008: Disopyramide Capsules; Disopyramide Phosphate Capsules;
USP 31: Disopyramide Phosphate Capsules; Disopyramide Phosphate Extended-release Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Rythmodan; ***Austria:*** Rythmodan; ***Belg.:*** Rythmodan; ***Braz.:*** Dicorantil; ***Canad.:*** Rythmodan; ***Cz.:*** Rythmodan†; ***Denm.:*** Durbis†; ***Fin.:*** Disomet; ***Fr.:*** Isorythm; Rythmodan; ***Ger.:*** Diso-Duriles†; Norpace†; Rythmodul†; ***Gr.:*** Dicorynan; Ritmodan†; Rythmodan; Rythmodul†; ***Hung.:*** Palpitin-PP; ***India:*** Norpace; ***Irl.:*** Rythmodan; ***Israel:*** Rythmical; ***Ital.:*** Ritmodan; ***Jpn:*** Rythmodan; ***Mex.:*** Dimodan; ***Neth.:*** Ritmoforine; Rythmodan†; ***Norw.:*** Durbis; ***NZ:*** Rythmodan; ***Port.:*** Ritmodan†; ***S.Afr.:*** Norpace; Rythmodan; ***Spain:*** Dicorynan; ***Swed.:*** Dirytmin†; Durbis; ***Switz.:*** Norpace†; ***Turk.:*** Norpace; ***UK:*** Rythmodan; ***USA:*** Norpace.

Disufenton Sodium *(USAN, rINN)*

ARL-16556; CPI-22; CXY-059; Disufentón de sodio; Disufenton Sodique; Disufentonum Natricum; NXY-059. Disodium 4-(*tert*-butyliminomethyl)benzene-1,3-disulfonate *N*-oxide.

Дисуфентон Натрия

$C_{11}H_{13}NNa_2O_7S_2$ = 381.3.

CAS — 168021-79-2.

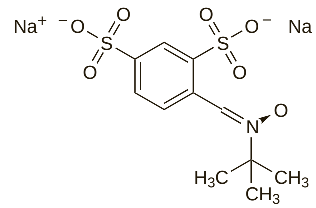

Profile

Disufenton sodium traps free radicals. It has been investigated as a neuroprotectant for acute ischaemic and haemorrhagic stroke but results have been disappointing.

◊ References.

1. Lees KR, *et al.* The Stroke-Acute Ischemic NXY Treatment (Saint I) Trial Investigators. NXY-059 for acute ischemic stroke. *N Engl J Med* 2006; **354:** 588–600.
2. Shuaib A, *et al.* SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med* 2007; **357:** 562–71.
3. Lyden PD, *et al.* Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT trial. *Stroke* 2007; **38:** 2262–9.

Ditazole *(rINN)*

Diethamphenazole; Ditazol; Ditazolum; S-222. 2,2′-[(4,5-Diphenyloxazol-2-yl)imino]diethanol.

Дитазол

$C_{19}H_{20}N_2O_3$ = 324.4.

CAS — 18471-20-0.
ATC — B01AC01.
ATC Vet — QB01AC01.

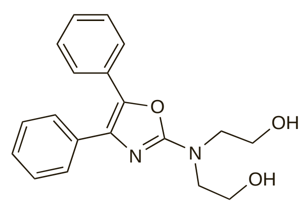

Profile

Ditazole is an inhibitor of platelet aggregation used in the management of thromboembolic disorders (p.1187) in doses of 400 mg two or three times daily by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Fendazol†; ***Spain:*** Ageroplas.

Dobutamine Hydrochloride

(BANM, USAN, rINNM)

46236; Compound 81929 (dobutamine); Dobutamiinihydrokloridi; Dobutamine, chlorhydrate de; Dobutamin-hidroklorid; Dobutamin-hydrochlorid; Dobutaminhydroklorid; Dobutamini hydrochloridum; Dobutamino hidrochloridas; Hidrocloruro de dobutamina; LY-174008 (dobutamine tartrate). (±)-4-(2-{[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino}ethyl)pyrocatechol hydrochloride.

Добутамина Гидрохлорид

$C_{18}H_{23}NO_3$,HCl = 337.8.

CAS — 34368-04-2 (dobutamine); 49745-95-1 (dobutamine hydrochloride); 101626-66-8 (dobutamine tartrate).
ATC — C01CA07.
ATC Vet — QC01CA07.

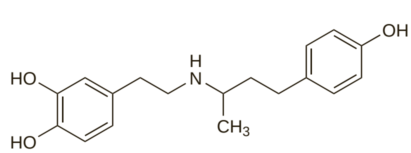

(dobutamine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Dobutamine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; soluble in methyl alcohol. Protect from light.

USP 31 (Dobutamine Hydrochloride). A white to practically white crystalline powder. Sparingly soluble in water and in methyl alcohol; soluble in alcohol and in pyridine. Store in airtight containers at a temperature of 15° to 30°.

Incompatibility. Dobutamine is incompatible with alkaline solutions such as sodium bicarbonate 5% and alkaline drugs such as aminophylline, furosemide,[1] and thiopental sodium;[1] physical incompatibility with bumetanide, calcium gluconate, insulin, diazepam, and phenytoin has also been suggested. There have also been reports of incompatibility with alteplase,[2] heparin,[3] and warfarin sodium.[4]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
4. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Adverse Effects and Treatment

As for Sympathomimetics, p.1407. Dobutamine has mainly beta$_1$-agonist properties and its principal adverse effects include dose-related increases in heart rate and blood pressure, ectopic beats, angina or chest pain, and palpitations; dosage should be reduced or temporarily stopped if they occur. Ventricular tachycardia may occur rarely; cardiac rupture has been reported rarely during dobutamine stress testing.

Effects on body temperature. A 71-year-old woman with heart failure developed a fever on 2 separate occasions 8 to 12 hours after starting an infusion of dobutamine.[1]

1. Robison-Strane SR, Bubik JS. Dobutamine-induced fever. *Ann Pharmacother* 1992; **26:** 1523–4.

Effects on the cardiovascular system. For reference to severe cardiovascular complications of dobutamine stress echocardiography, see Diagnosis and Testing under Uses and Administration, below.

For reference to fatalities occurring in patients given dobutamine, see Heart Failure under Uses and Administration, below.

Effects on the neuromuscular system. Myoclonus has been reported[1,2] in patients with renal impairment given dobutamine infusion for heart failure.

1. Wierre L, *et al.* Dobutamine-induced myoclonia in severe renal failure. *Nephrol Dial Transplant* 2004; **19:** 1336–7.
2. Boord A, Benson B. Myoclonus associated with continuous dobutamine infusion in a patient with end-stage renal disease. *Am J Health-Syst Pharm* 2007; **64:** 2241–3.

Effects on the skin. Troublesome pruritus of the scalp has been reported[1] in a patient receiving dobutamine infusions. It was suggested that this might be a direct effect of dobutamine since the reaction was so localised.

1. McCauley CS, Blumenthal MS. Dobutamine and pruritus of the scalp. *Ann Intern Med* 1986; **105:** 966.

Hypersensitivity. Hypersensitivity reactions have been reported in patients receiving dobutamine infusions, possibly due to sodium sulfite in the formulation. Redness, swelling, itching, and a sensation of warmth developed[1] around the infusion site in a patient receiving dobutamine; the reaction recurred when the infusion was repeated a week later. Eosinophilic reactions have also been reported, including hypersensitivity myocarditis[2-4] and asthma.[5]

1. Cernek PK. Dermal cellulitis—a hypersensitivity reaction from dobutamine hydrochloride. *Ann Pharmacother* 1994; **28:** 964.
2. Spear GS. Eosinophilic explant carditis with eosinophilia: ?hypersensitivity to dobutamine infusion. *J Heart Lung Transplant* 1995; **14:** 755–60.
3. Takkenberg JJM, *et al.* Eosinophilic myocarditis in patients awaiting heart transplantation. *Crit Care Med* 2004; **32:** 714–21.
4. Butany J, *et al.* Hypersensitivity myocarditis complicating hypertrophic cardiomyopathy heart. *Can J Cardiol* 2004; **20:** 911–14.
5. Aranda JM, *et al.* Dobutamine-related asthma in a patient awaiting cardiac transplantation: the eosinophilic dilemma. *J Heart Lung Transplant* 2004; **23:** 260–1.

Overdosage. A patient received an accidental overdose[1] of dobutamine when given an intravenous infusion at a rate of more than 130 micrograms/kg per minute for 30 minutes, this being three times the recommended maximum. Characteristic adverse effects such as emesis, palpitations, chest pain, dyspnoea, and paraesthesia developed, together with urinary incontinence, an effect not previously associated with dobutamine.

1. Paulman PM, *et al.* Dobutamine overdose. *JAMA* 1990; **264:** 2386–7.

Precautions

As for Sympathomimetics, p.1407. Dobutamine has primarily inotropic effects and should be avoided or used only with great caution in patients with marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis. It should also be used with caution in patients with acute myocardial infarction, and in cardiogenic shock complicated by severe hypotension. Hypovolaemia should be corrected before treatment.

Interference with diagnostic tests. Contamination of blood samples with dobutamine has been reported to produce falsely decreased creatinine values in an enzymatic test.[1] Colorimetric measurements of creatinine were not affected.

1. Daly TM, *et al.* "Bouncing" creatinine levels. *N Engl J Med* 1996; **334:** 1749–50.

Interactions

As for Sympathomimetics, p.1407. Most interactions with dobutamine are due to its direct $beta_1$ agonist effects on the heart, but use with beta blockers may allow its alpha- and $beta_2$-agonist effects to become apparent.

Pharmacokinetics

Like adrenaline (p.1204), dobutamine is inactive when given orally, and it is rapidly inactivated in the body by similar processes. It has a half-life of about 2 minutes. Conjugates of dobutamine and its major metabolite 3-*O*-methyldobutamine are excreted primarily in urine, with small amounts eliminated in the faeces.

◊ The primary mechanism of clearance of dobutamine appears to be distribution to other tissues, and not metabolism or elimination. It has a half-life of about 2 minutes and plasma concentrations of dobutamine reach steady state about 10 to 12 minutes after the start of an infusion. Dobutamine is used mainly for the short-term treatment of heart failure and any pharmacokinetic changes in this condition have no clinical implications in dosage titration.[1]

The pharmacokinetics of dobutamine and other cardiovascular drugs in children have been reviewed.[2]

1. Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure: an updated review. *Clin Pharmacokinet* 1988; **15:** 94–113.
2. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; **27:** 345–67.

Uses and Administration

Dobutamine is a sympathomimetic (p.1408) with direct effects on $beta_1$-adrenergic receptors, giving it a prominent inotropic action on the heart. It also has some alpha- and $beta_2$-agonist properties. Although it is structurally related to dopamine (p.1273), it has no specific dopaminergic properties; however, like dopamine, the inotropic action of dobutamine on the heart is associated with less cardiac-accelerating effect than that of isoprenaline.

Dobutamine is used to increase the contractility of the heart in acute heart failure, as occurs in cardiogenic shock (p.1183) and myocardial infarction (p.1175); it is also used in septic shock. Other circumstances in which its inotropic activity may be useful are during cardiac surgery and positive end-expiratory pressure ventilation.

Dobutamine is used as the hydrochloride but doses are expressed in terms of the base; 1.12 micrograms of the hydrochloride is equivalent to about 1 microgram of base. It is given by intravenous infusion as a dilute solution (0.25 to 5 mg/mL), in glucose 5% or sodium chloride 0.9%; other fluids may also be suitable and the manufacturers' guidelines should be consulted.

In the management of **acute heart failure**, dobutamine is given at a usual rate of 2.5 to 10 micrograms/kg per minute, according to the patient's heart rate, blood pressure, cardiac output, and urine output. A range of 0.5 up to 40 micrograms/kg per minute has occasionally been required. It has been recommended that treatment with dobutamine should be discontinued gradually.

Dobutamine is also used as an alternative to exercise in **cardiac stress testing**. A solution containing 1 mg/mL is given via an infusion pump in a dose of 5 micrograms/kg per minute for 8 minutes. The dose is then increased by increments of 5 micrograms/kg per minute up to a usual maximum of 20 micrograms/kg per minute, with each dose being infused for 8 minutes before the next increase; doses of up to 40 micrograms/kg per minute have sometimes been used. The ECG should be monitored continuously and the infusion stopped if arrhythmias, marked ST segment depression, or other adverse effects occur.

Action. Although dobutamine is usually considered to be a $beta_1$ agonist, *animal* studies suggest that its ability to stimulate $alpha_1$- and $beta_2$-adrenergic receptors may be as great as its $beta_1$-stimulant properties. It has been proposed that the inotropic action results from a combination of alpha-stimulant activity on myocardial $alpha_1$ receptors, a property residing mainly in the (−)-enantiomer, with $beta_1$ stimulation by the (+)-enantiomer; peripherally, alpha-mediated vasoconstriction would be opposed by the $beta_2$-agonist properties of the (+)-enantiomer, resulting in the net inotropic action with relatively little effect on blood pressure seen with the racemic mixture used clinically.[1]

Dobutamine has a thermogenic effect,[2] increasing oxygen delivery and utilisation in healthy volunteers. However, using it for this purpose in critically ill patients did not improve patient outcome and in some cases might have been harmful.[3]

1. Ruffolo RR. The mechanism of action of dobutamine. *Ann Intern Med* 1984; **100:** 313–14.
2. Bhatt SB, *et al.* Effect of dobutamine on oxygen supply and uptake in healthy volunteers. *Br J Anaesth* 1992; **69:** 298–303.
3. Hayes MA, *et al.* Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330:** 1717–22.

Administration in children. Dobutamine and dopamine are both used for inotropic support in children. A study[1] in children undergoing cardiac surgery suggested that dobutamine may be preferred to dopamine since the latter could cause pulmonary vasoconstriction (see under Precautions for Dopamine, p.1273). In preterm infants, one study[2] reported that dobutamine may have a greater effect on systemic blood flow than dopamine, but a systematic review[3] found that dopamine was more effective than dobutamine in the short-term treatment of hypotension although there was insufficient evidence of long-term benefit or safety with either drug for firm recommendations to be made.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; **74:** 419–23.
2. Osborn D, *et al.* Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002; **140:** 183–91.
3. Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 07/10/05).

Diagnosis and testing. Dynamic exercise is the established mode of stress for the assessment of cardiac function. In patients who are unable to exercise, a dobutamine infusion is one of the best alternative ways of producing a pharmacological stress.[1,2] It is widely used as an adjunct in echocardiography, often combined with atropine, and may give better sensitivity than adenosine or dipyridamole;[1,3] it may also have a role with other imaging techniques such as magnetic resonance imaging.[4] However there have been instances of severe cardiovascular complications attributable to dobutamine.[5]

1. Cheitlin MD, *et al.* ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Summary article: *Circulation* 2003; **108:** 1146–62. Full text: http://www.americanheart.org/downloadable/heart/1060182581039Echocleanfulltext.pdf (accessed 07/10/05)
2. Marwick TH. Stress echocardiography. *Heart* 2003; **89:** 113–18.
3. Martin TW, *et al.* Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. *Ann Intern Med* 1992; **116:** 190–6.
4. Paetsch I, *et al.* Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation* 2004; **110:** 835–42.
5. Lattanzi F, *et al.* Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. *Drug Safety* 2000; **22:** 251–62.

Heart failure. Dobutamine may be used in the management of acute heart failure, including decompensated chronic heart failure (see Cardiogenic Shock, under Shock, p.1183). It may also have a role in patients with severe chronic heart failure (p.1165), either as a bridge to transplantation or for palliative therapy. In less severe cases, intermittent infusions of dobutamine have been tried. A study[1] using pulsed therapy with dobutamine (30 minutes daily for 4 days each week for 3 weeks) reported symptomatic improvements similar to those achieved with exercise, but another study[2] using intermittent therapy (24 hours every 2 to 3 weeks for 6 months) failed to show any benefit. There have also been reports of sudden death in patients receiving dobutamine as infusions for 48 hours per week, and another study[3] was halted for this reason. Long-term use of intermittent dobutamine is therefore not generally recommended.[4]

1. Adamopoulos S, *et al.* Effects of pulsed β-stimulant therapy on β-adrenoceptors and chronotropic responsiveness in chronic heart failure. *Lancet* 1995; **345:** 344–9.
2. Elis A, *et al.* Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther* 1998; **63:** 682–5.
3. Dies F, *et al.* Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986; **74:** (suppl II): 38.
4. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 19/08/08)

Preparations

BP 2008: Dobutamine Intravenous Infusion;
USP 31: Dobutamine for Injection; Dobutamine in Dextrose Injection; Dobutamine Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Dobucard; Dobuject†; Dobutrex†; Duvig; ***Austral.:*** Dobutrex; ***Austria:*** Inotop; ***Belg.:*** Dobutrex†; Dobutrexmerck; ***Braz.:*** Biodobutin†; Dobtan; Dobutabbott; Dobutal†; Dobutil†; Dobuton; Dobutrex†; Neobutamina; ***Canad.:*** Dobutrex†; ***Chile:*** Bagobutam†; Dobutrex†; ***Cz.:*** Dobuject; Dobutrex; ***Denm.:*** Dobutrex†; ***Fin.:*** Dobuject; Dobutrex†; ***Fr.:*** Dobutrex†; ***Gr.:*** Dobutan; Inotrex; ***Hong Kong:*** Dobutrex†; ***Hung.:*** Dobutrex†; ***India:*** Dobutrex; ***Indon.:*** Cardiject; Dobuject; Dobutel; Inotrop; ***Irl.:*** Dobutrex†; Posiject†; ***Israel:*** Butamine; Dobuject; Dobutam†; ***Ital.:*** Dobutrex†; Miozac; ***Jpn:*** Dobupum; ***Malaysia:*** Dobucard†; Dobutrex†; ***Mex.:*** Cryobutol; Dobuject; Dobutrex; Kardion†; Oxiken; ***Norw.:*** Dobutrex†; ***NZ:*** Dobutrex†; ***Philipp.:*** Dobuject; Dobutrex; ***Pol.:*** Dobuject; ***Port.:*** Dobucor; Dobutina; Inotrex; ***S.Afr.:*** Cardiject; Dobutrex; Posiject†; ***Singapore:*** Dobuject†; ***Spain:*** Dobucor; Dobutrex†; ***Swed.:*** Dobutrex; ***Switz.:*** Dobutrex; ***Thai.:*** Cardiject; Dobuject; Dobutrex†; ***UK:*** Dobutrex†; Posiject†; ***USA:*** Dobutrex†; ***Venez.:*** Doburan; Dobutrex†; Dobuxin.

Docarpamine *(rINN)*

Docarpamina; Docarpaminum; TA-870; TA-8704. (−)-(*S*)-2-Acetamido-*N*-(3,4-dihydroxyphenethyl)-4-(methylthio)butyramide bis(ethyl carbonate) ester.

Докарпамин

$C_{21}H_{30}N_2O_8S$ = 470.5.
CAS — 74639-40-0.

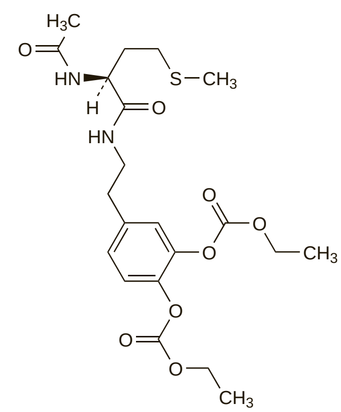

Profile

Docarpamine is an orally active prodrug of dopamine (p.1273) that has been used in the treatment of acute heart failure.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Tanadopa†.

Dofetilide *(BAN, USAN, rINN)*

Dofetilid; Dofetilida; Dofétilide; Dofetilidi; Dofetilidum; UK-68798. β-[(*p*-Methanesulfonamidophenethyl)methylamino]methanesulfono-*p*-phenetidide.

Дофетилид

$C_{19}H_{27}N_3O_5S_2$ = 441.6.
CAS — 115256-11-6.
ATC — C01BD04.
ATC Vet — QC01BD04.

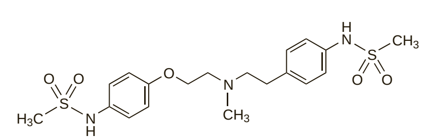

Adverse Effects and Precautions

The most frequent adverse effects with dofetilide are headache, chest pain, and dizziness. Dofetilide prolongs the QT interval and may cause severe ventricular arrhythmias, including torsade de pointes; it should not be given to patients with congenital or acquired long QT syndromes. Hypokalaemia increases the risk of arrhythmias and potassium concentrations should be corrected before starting dofetilide. The dosage of dofetilide must be individualised according to QT interval and creatinine clearance, which must be measured before starting therapy; dofetilide is contra-indicated if the corrected QT interval is above 440 milliseconds (or above 500 milliseconds in patients with ventricular conduction abnormalities) or if the creatinine clearance is less than 20 mL/minute. Treatment should begin under ECG monitoring, which must be continued for at least 3 days, and both ECG and renal function should be monitored at least every 3 months during treatment.

Interactions

Dofetilide should not be given with other drugs that prolong the QT interval. Class I or class III antiarrhythmics should be stopped at least 3 half-lives before dofetilide is given. Potassium-depleting diuretics may cause hypokalaemia or hypomagnesaemia, increasing the potential for torsade de pointes; US licensed product information for dofetilide states that hydrochlorothiazide is contra-indicated since it also causes significant increases in plasma-dofetilide concentrations. Dofetilide is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4, and drugs or foods that inhibit this isoenzyme, such as macrolide antibacterials, HIV-protease inhibitors, diltiazem, and grapefruit juice, should be used with caution. Cimetidine, trimethoprim, ketoconazole, prochlorperazine, and megestrol, should not be given as they inhibit the renal excretion of dofetilide; verapamil is also contra-indicated as it too may substantially increase dofetilide concentrations.

◊ References.

1. Yamreudeewong W, *et al.* Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Safety* 2003; **26:** 421–38.

Pharmacokinetics

The oral bioavailability of dofetilide is more than 90%. Peak plasma concentrations occur after 2 to 3 hours and steady state concentrations after 2 to 3 days. The terminal half-life is about 10 hours. Protein binding is 60 to 70%. Dofetilide undergoes limited metabolism. About 80% of a dose is excreted in the urine, with about 80% of this as unchanged drug and 20% as 5 minimally active or inactive metabolites; metabolism may be mediated to some extent by the cytochrome P450 isoenzyme CYP3A4. Renal elimination involves both glomerular filtration and active tubular secretion via the cation transport system. The clearance of dofetilide decreases with decreasing creatinine clearance.

◊ References.

1. Allen MJ, *et al.* The pharmacokinetics and pharmacodynamics of oral dofetilide after twice daily and three times daily dosing. *Br J Clin Pharmacol* 2000; **50:** 247–53.

Uses and Administration

Dofetilide is a class III antiarrhythmic (p.1153); it selectively blocks one of the potassium channels involved in repolarisation and therefore prolongs the action potential. It is used in the treatment of atrial fibrillation and flutter (p.1160) in patients who are highly symptomatic. The initial oral dose in patients with a corrected QT interval of 440 milliseconds or less is 500 micrograms twice daily; the maintenance dose must be reduced if the QT interval becomes prolonged after the first dose, and treatment should be stopped if the QT interval exceeds 500 milliseconds. Doses should be reduced in renal impairment (see below).

◊ References.

1. McClellan KJ, Markham A. Dofetilide: a review of its use in atrial fibrillation and atrial flutter. *Drugs* 1999; **58:** 1043–59.
2. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. *Ann Pharmacother* 2000; **34:** 44–56.
3. Mounsey JP, DiMarco JP. Dofetilide. *Circulation* 2000; **102:** 2665–70.
4. Roukoz H, Saliba W. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev Cardiovasc Ther* 2007; **5:** 9–19.

Administration in renal impairment. Doses of dofetilide should be reduced in patients with renal impairment based on creatinine clearance (CC). Initial doses are:

- CC 40 to 60 mL/minute: 250 micrograms twice daily
- CC 20 to 39 mL/minute: 125 micrograms twice daily
- CC below 20 mL/minute: contra-indicated

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Tikosyn.

Dopamine Hydrochloride

(BANM, USAN, pINNM)

ASL-279; Dopamiinihydrokloridi; Dopamin Hidroklorür; Dopamine, chlorhydrate de; Dopamin-hidroklorid; Dopamin-hydrochlorid; Dopaminhydroklorid; Dopamini hydrochloridum; Dopamino hidrochloridas; Dopaminy chlorowodorek; Hidrocloruro de dopamina; 3-Hydroxytyramine Hydrochloride. 4-(2-Aminoethyl)pyrocatechol hydrochloride.

Допамина Гидрохлорид

$C_8H_{11}NO_2,HCl = 189.6.$

CAS — 51-61-6 (dopamine); 62-31-7 (dopamine hydrochloride).

ATC — C01CA04.

ATC Vet — QC01CA04.

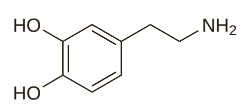

(dopamine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Dopamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; sparingly soluble in acetone and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Dopamine Hydrochloride). A white to off-white crystalline powder that may have a slight odour of hydrochloric acid. Freely soluble in water and in aqueous solutions of alkali hydroxides; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 4% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Dopamine is inactivated in alkaline solutions such as sodium bicarbonate 5% and is incompatible with alkaline drugs such as furosemide[1] and thiopental sodium;[1] incompatibility with insulin[2] and with alteplase[3] has also been reported, and licensed product information states that it is incompatible with ampicillin and with amphotericin B, and that mixtures with gentamicin sulfate, cefalotin sodium, or oxacillin sodium should be avoided.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.

Adverse Effects and Treatment

As for Sympathomimetics, p.1407; dopamine may have adverse effects relating to both its alpha- and beta-agonist properties.

Dopamine has a short duration of action and most adverse effects respond to stopping the infusion or reducing its rate; infiltration with phentolamine may relieve pain and prevent necrosis following extravasation.

Effects on the CNS. Movement disorders are well known adverse effects of the dopamine precursor, levodopa (p.804) but do not usually occur with dopamine since it does not enter the CNS. However, there has been a report[1] of choreoathetosis in a patient receiving dopamine infusion; it was suggested that there must have been disruption to her blood-brain barrier to allow this to occur.

1. Walker VA, Massoumi M. Choreoathetosis with dopamine. *Ann Intern Med* 2005; **142:** 478–9.

Effects on the endocrine system. Dopamine has complex actions on the anterior pituitary[1] and dopamine infusion is associated with a number of endocrine effects, including suppression of prolactin, growth hormone, and thyroid hormone release. In postoperative or critically ill patients, dopamine infusion may affect the endocrine response to stress, even when given in low doses. Depression of serum-prolactin concentrations has been reported[2] in critically ill patients given dopamine in a dose of 2.5 micrograms/kg per minute to maintain renal blood flow, while a study[3] in postoperative patients given dopamine 5 micrograms/kg per minute to maintain splanchnic blood flow found that serum concentrations of both prolactin and thyroid stimulating hormone were decreased. It was suggested that these changes could adversely affect immunological function and add to morbidity in such patients.

1. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996; **24:** 1580–90.
2. Bailey AR, Burchett KR. Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. *Br J Anaesth* 1997; **78:** 97–9.
3. Schilling T, *et al.* Endocrine effects of dopexamine vs. dopamine in high-risk surgical patients. *Intensive Care Med* 2001; **27:** 1908–15.

Effects on the heart. For mention of the arrhythmogenic effects of dopamine on the heart, see p.1407.

Ischaemia and gangrene. Dopamine is converted to noradrenaline, a powerful vasoconstrictor, and there have been reports[1-3] of ischaemia and gangrene of the extremities in patients receiving dopamine infusion, as well as local necrosis after extravasation.[4] Extravasation of catecholamines is usually treated with an alpha blocker such as phentolamine, but there have also been reports of the use of topical glyceryl trinitrate ointment to improve capillary blood flow in patients with dopamine-induced ischaemia of the digits. The ointment was applied either to the affected area,[5] or to the warmest area of skin,[6] such as the chest or abdominal wall.

1. Alexander CS, *et al.* Pedal gangrene associated with the use of dopamine. *N Engl J Med* 1975; **293:** 591.
2. Julka NK, Nora JR. Gangrene aggravation after use of dopamine. *JAMA* 1976; **235:** 2812–13.
3. Maggi JC, *et al.* Gangrene in a neonate following dopamine therapy. *J Pediatr* 1982; **100:** 323–5.
4. Boltax RS, *et al.* Gangrene resulting from infiltrated dopamine solution. *N Engl J Med* 1977; **296:** 823.
5. Gibbs NM, Oh TE. Nitroglycerine ointment for dopamine induced peripheral digital ischaemia. *Lancet* 1983; **ii:** 290.
6. Coakley J. Nitroglycerin ointment for dopamine-induced peripheral ischaemia. *Lancet* 1983; **ii:** 633.

Precautions

As for Sympathomimetics, p.1407.

Children. There have been reports of increased pulmonary artery pressure with the use of dopamine in children after cardiac surgery,[1] and in premature infants with hypotension.[2] It has therefore been suggested that dopamine should be used with caution in children at risk of developing pulmonary hypertension.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; **74:** 419–23.
2. Liet J-M, *et al.* Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. *J Pediatr* 2002; **140:** 373–5.

Interactions

As for Sympathomimetics, p.1407. Dopamine has both direct and indirect actions and may therefore interact with MAOIs; the dose of dopamine should be substantially reduced in patients taking MAOIs, and an initial dose of one-tenth the usual dose has been suggested.

Antiepileptics. Following a report in 1976 to the FDA of hypotension in patients given *phenytoin* in addition to dopamine infusion, a study[1] of this potential interaction found that dopamine given by intravenous infusion with phenytoin infusion to *dogs,* did not alter the CNS effects of phenytoin nor result in hypotension and cardiovascular collapse. Large doses of phenytoin alone had a reproducible hypotensive effect that was reduced by dopamine, suggesting a possible supportive role in phenytoin-induced hypotension.

1. Smith RD, Lomas TE. Modification of cardiovascular responses to intravenous phenytoin by dopamine in dogs: evidence against an adverse interaction. *Toxicol Appl Pharmacol* 1978; **45:** 665–73.

Dopaminergics. Severe hypertension occurred[1] in a patient who had been receiving *selegiline* for Parkinson's disease when a dopamine infusion was started. Although selegiline is considered to be a selective monoamine oxidase type B inhibitor, at higher doses it also affects monoamine oxidase type A and could have reduced the metabolism of dopamine in this patient. Caution may be necessary if dopamine is given to patients who have been receiving selegiline within the previous 2 weeks.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Pharmacokinetics

The vasoconstrictor properties of dopamine preclude its use by the subcutaneous or intramuscular route. Like adrenaline (p.1204) it is inactive when given orally, and it is rapidly inactivated in the body by similar processes, with a half-life of about 2 minutes. Dopamine is a metabolic precursor of noradrenaline and a proportion is excreted as the metabolites of noradrenaline. Nevertheless, the majority appears to be directly metabolised into dopamine-related metabolites.

◊ References.

1. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; **27:** 345–67.
2. Juste RN, *et al.* Dopamine clearance in critically ill patients. *Intensive Care Med* 1998; **24:** 1217–20.
3. MacGregor DA, *et al.* Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; **92:** 338–46.
4. Johnston AJ, *et al.* Pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients. *Intensive Care Med* 2004; **30:** 45–50.

Uses and Administration

Dopamine is a catecholamine sympathomimetic (p.1408) with both direct and indirect effects. It is formed in the body by the decarboxylation of levodopa, and is both a neurotransmitter in its own right (notably in the brain) and a precursor of noradrenaline. Dopamine differs from adrenaline and noradrenaline in dilating renal and mesenteric blood vessels and increasing urine output, apparently by a specific dopaminergic mechanism. This effect is predominant at low infusion rates (about 2 micrograms/kg per minute); at slightly higher infusion rates (around 2 to 10 micrograms/kg per minute) it also stimulates $beta_1$-adrenergic receptors in the myocardium, and at 10 to 20 micrograms/kg per minute the effects of alpha-adrenergic stimulation, such as vasoconstriction, predominate. The inotropic action of dopamine on the heart is associated with less cardiac-accelerating effect, and a lower incidence of arrhythmias, than that of isoprenaline.

Dopamine also inhibits release of prolactin from the anterior pituitary.

Dopamine is used in acute heart failure, as occurs in cardiogenic shock (p.1183) and myocardial infarction (p.1175); it is also used in renal failure (but see below, under Surgery and Intensive Care), in cardiac surgery, and in septic shock.

Dopamine is given as the hydrochloride by intravenous infusion as a dilute solution (usually 1.6 or 3.2 mg/mL, although more dilute solutions may be used where fluid expansion is not a problem), in glucose 5%, sodium chloride 0.9%, or other suitable diluents; many fluids are suitable and licensed product information should be consulted. The initial rate is 1 to 5 micrograms/kg per minute, gradually increased by up to 5 to 10 micrograms/kg per minute according to the patient's blood pressure, cardiac output, and urine output. Up to 20 to 50 micrograms/kg per minute may be required in seriously ill patients; higher doses have been given. A reduction in urine flow, without hypotension, may indicate a need to reduce the dose. To avoid tissue necrosis dopamine is best given via a large vein high up in a limb, preferably the arm. When gradually stopping dopamine it is advised that care be taken to avoid undue hypotension associated with very low dosage levels, where vasodilatation could predominate.

Surgery and intensive care. Dopamine has an established role as an inotrope in cardiogenic shock and in cardiac surgery; it has also been used as a **renal protectant,** due to the apparently beneficial effects of lower doses on renal function. Studies in healthy *animals* and human subjects have shown that low-dose dopamine increases renal blood flow, natriuresis, diuresis, and possibly glomerular filtration rate. Low doses of dopamine (sometimes termed 'renal-dose' dopamine) have therefore been widely used in patients at risk of renal failure, such as those undergoing major surgery or in intensive care, as well as for the treatment of acute renal failure. However, clinical studies have failed to convincingly demonstrate that low-dose dopamine is effective in either preventing acute renal failure in patients at high risk, or in improving renal function or outcome in patients with established acute renal failure. A placebo-controlled, randomised study[1] in critically-ill patients with early renal dysfunction and meta-analyses[2,3] including studies of varying design, failed to show any clinical benefit in those receiving dopamine. It is now generally considered[2,4,5] that low-dose dopamine has no place as a renal protectant in the routine management of critically ill patients.

Dopexamine, which like dopamine acts as a peripheral dopamine agonist, has been used similarly but evidence of benefit is limited and it is generally not recommended (see Critical Care under Dopexamine, p.1274).

1. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; **356:** 2139–43.
2. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; **29:** 1526–31.
3. Friedrich JO, *et al.* Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; **142:** 510–24.
4. Galley HF. Renal-dose dopamine: will the message now get through? *Lancet* 2000; **356:** 2112–13. Correction. *ibid.* 2001; **357:** 890.
5. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003; **123:** 1266–75.

Preparations

BP 2008: Dopamine Intravenous Infusion;
USP 31: Dopamine Hydrochloride and Dextrose Injection; Dopamine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Dopatropin; Hettytropin†; Inotropin; Megadose; ***Belg.:*** Dynatra; ***Braz.:*** Constriction; Dopabane; Dopacris; Revimine; Revivan; Vasomine†; ***Canad.:*** Intropin†; ***Cz.:*** Tensamin; ***Denm.:*** Abbodop; Dopmin; Giludop; ***Fin.:*** Abbodop; Dopmin; ***Gr.:*** Giludop; ***Hong Kong:*** Intropin†; ***India:*** Dopinga; ***Indon.:*** Cetadop; Dopac; Indop; ***Israel:*** Docard; ***Ital.:*** Revivan; ***Jpn:*** Inovan; Pre Dopa; ***Malaysia:*** Dopmin; ***Mex.:*** Clorpamina†; Drynalken; Flemina†; Inotropisa; Miocina; Zetarina; ***Neth.:*** Dynatra; ***Norw.:*** Abbodop; ***Philipp.:*** Docard; Myocard; ***Port.:*** Cordodopa; Medopa; ***S.Afr.:*** Dynos; Intropin; ***Singapore:*** Dopmin†; ***Swed.:*** Abbodop; Giludop; Intropin†; ***Thai.:*** Dopamex; Dopaminex; Dopmin; Inopin; ***Turk.:*** Dopmin; ***USA:*** Intropin†; ***Venez.:*** Dopina; Rascordin†.

Dopexamine Hydrochloride

(BANM, USAN, rINNM) ⊗

Dopeksamiinihydrokloridi; Dopeksamin Hidroklorür; Dopéxamine, Chlorhydrate de; Dopexamine, dichlorhydrate de; Dopexamine dihydrochloride; Dopexaminhydroklorid; Dopexamini dihydrochloridum; Dopexamini Hydrochloridum; FPL-60278 (dopexamine); FPL-60278AR; Hidrocloruro de dopexamina. 4-{2-[6-(Phenethylamino)hexylamino]ethyl}pyrocatechol dihydrochloride.

Допексамина Гидрохлорид

$C_{22}H_{32}N_2O_2,2HCl = 429.4.$

CAS — 86197-47-9 (dopexamine); 86484-91-5 (dopexamine dihydrochloride).

ATC — C01CA14.

ATC Vet — QC01CA14.

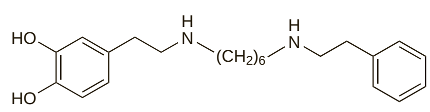

(dopexamine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dopexamine Dihydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 3.7 to 5.7. Protect from light.

Incompatibility. Dopexamine is inactivated in alkaline solutions such as sodium bicarbonate 5%.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Dopexamine has mainly beta-agonist and dopaminergic actions; its most common adverse effect is tachycardia, and transient hypotension may also occur. Dopexamine may cause a small reduction in platelet counts and should not be given to thrombocytopenic patients.

Interactions

As for Sympathomimetics, p.1407. The interactions of dopexamine are mainly due to its beta-agonist and dopaminergic actions; it may also potentiate the effects of noradrenaline and some other sympathomimetics by inhibiting neuronal uptake of noradrenaline.

Pharmacokinetics

Dopexamine has a short half-life in blood of about 6 to 7 minutes. It is excreted as metabolites in bile and in urine.

Uses and Administration

Dopexamine is a sympathomimetic (p.1408) with direct and indirect effects. It stimulates $beta_2$ adrenoceptors and peripheral dopamine receptors and also inhibits the neuronal reuptake of noradrenaline. These actions result in an increased cardiac output, peripheral vasodilatation, and an increase in renal and mesenteric blood flow.

Dopexamine hydrochloride is used to provide short-term haemodynamic support, for example after cardiac surgery or in exacerbations of chronic heart failure. It is given as an intravenous infusion of either 400 or 800 micrograms/mL in glucose 5%, sodium chloride 0.9%, or other suitable diluents, through a central or large peripheral vein; more concentrated solutions may be given via a central vein but concentrations should not exceed 4 mg/mL. The initial dose is generally 0.5 micrograms/kg per minute and is then increased to 1 microgram/kg per minute; further increases, in increments of 0.5 to 1 microgram/kg per minute at intervals of not less than 15 minutes, may be made up to a total of 6 micrograms/kg per minute if necessary. Heart rate, blood pressure, urine output, and cardiac output should be monitored. On withdrawal, the dose should be reduced gradually.

◊ References.

1. Fitton A, Benfield P. Dopexamine hydrochloride. *Drugs* 1990; **39:** 308–30.
2. Anonymous. Dopexamine after cardiac surgery. *Drug Ther Bull* 1995; **33:** 30–2.

Critical care. Dopexamine has been reported to increase splanchnic blood flow and it has been used with the aim of preventing renal and gastrointestinal dysfunction in critically-ill patients.[1] Although there may be a reduction in ischaemic damage to the gut,[2] a study[3] in critically-ill patients failed to show any improvement in outcome with the use of dopexamine. Studies[4,5] using dopexamine to increase oxygen delivery in high-risk surgical patients have also failed to show any benefit in terms of postoperative mortality or organ function, and a systematic review[6] found insufficient evidence to recommend the use of dopexamine in either patient group. A later meta-analysis[7] found that overall, perioperative dopexamine infusion reduced the length of hospital stay in patients having major surgery, but showed no survival benefit; however, at low doses (up to 1 microgram/kg per minute) dopexamine infusion seemed also to be associated with improved survival.

Use of low-dose dopamine for renal protection is not recommended (see Surgery and Intensive Care, p.1274).

1. Lisbon A. Dopexamine, dobutamine, and dopamine increase splanchnic blood flow: what is the evidence? *Chest* 2003; **123** (suppl): 460S–463S.
2. Baguneid MS, *et al.* A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery. *J Vasc Surg* 2001; **33:** 758–63.
3. Ralph CJ, *et al.* A randomised controlled trial investigating the effects of dopexamine on gastrointestinal function and organ dysfunction in the critically ill. *Intensive Care Med* 2002; **28:** 884–90. Correction. *ibid*; 1001. [dose]
4. Takala J, *et al.* Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. *Crit Care Med* 2000; **28:** 3417–23.
5. Stone MD, *et al.* Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; **91:** 619–24.
6. Renton MC, Snowden CP. Dopexamine and its role in the protection of hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients. *Br J Anaesth* 2005; **94:** 459–67.
7. Pearse RM, *et al.* Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med* 2008; **36:** 1323–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Dopacard†; ***Denm.:*** Dopacard; ***Fin.:*** Dopacard; ***Fr.:*** Dopacard; ***Ger.:*** Dopacard; ***Irl.:*** Dopacard; ***NZ:*** Dopacard†; ***Swed.:*** Dopacard†; ***Switz.:*** Dopacard†; ***UK:*** Dopacard.

Doxazosin Mesilate *(BANM, rINNM)*

Doksazosyny mezylan; Doxazosin Mesylate *(USAN)*; Doxazosin Methanesulphonate; Doxazosine, mésilate de; Doxazosini mesilas; Doxazosin-mesylát; Mesilato de doxazosina; UK-33274-27. 1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulphonate.

Доксазозина Мезилат

$C_{23}H_{25}N_5O_5,CH_3SO_3H$ = 547.6.

CAS — 74191-85-8 (doxazosin); 77883-43-3 (doxazosin mesilate).

ATC — C02CA04.

ATC Vet — QC02CA04.

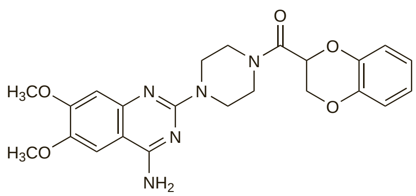

(doxazosin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*.

Ph. Eur. 6.2 (Doxazosin Mesilate). A white or almost white crystalline powder. It exhibits polymorphism and some forms may be hygroscopic. Slightly soluble in water and in methyl alcohol; soluble in a mixture of 15 volumes of water and 35 volumes of tetrahydrofuran; practically insoluble in acetone. Store in airtight containers.

USP 31 (Doxazosin Mesylate). A white to tan-coloured powder. Very slightly soluble in water and in methyl alcohol; freely soluble in formic acid. Store at a temperature below 30°.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375.

Effects on mental function. For a report of acute psychosis associated with doxazosin use, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Hypotension. Six of 18 hypertensive patients had first-dose orthostatic hypotension after receiving doxazosin 1 mg; three others had substantial but asymptomatic reductions in supine systolic blood pressure after the first dose.[1] The effect might have been exacerbated since all these patients were also receiving beta blockers or diuretics, or both. A further patient, who was also taking methyldopa, withdrew from the study with persistent orthostatic hypotension.

1. Oliver RM, *et al.* The pharmacokinetics of doxazosin in patients with hypertension and renal impairment. *Br J Clin Pharmacol* 1990; **29:** 417–22.

Urinary incontinence. For reference to urinary incontinence associated with doxazosin, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Pharmacokinetics

Doxazosin is well absorbed after oral doses, peak plasma concentrations occurring 2 to 3 hours after a dose. Oral bioavailability is about 65%. It is extensively metabolised in the liver, and excreted in faeces as metabolites and a small amount of unchanged drug. Elimination from plasma is biphasic, with a mean terminal half-life of about 22 hours. The pharmacokinetics are not altered in patients with renal impairment. Doxazosin is about 98% bound to plasma proteins and is not removed by dialysis.

◊ Reviews.

1. Elliott HL, *et al.* Pharmacokinetic overview of doxazosin. *Am J Cardiol* 1987; **59:** 78G–81G.

Uses and Administration

Doxazosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions and uses similar to those of prazosin (p.1376), but a longer duration of action. It is used in the management of hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction (below).

Doxazosin is given orally as the mesilate, but doses are usually expressed in terms of the base. Doxazosin mesilate 1.2 mg is equivalent to about 1 mg of doxazosin. After an oral dose maximum reduction in blood pressure is reported to occur in 2 to 6 hours and the effects are maintained for 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose, the initial dose is 1 mg, preferably at bedtime. Dosage may be increased after 1 or 2 weeks according to response. Usual maintenance doses for **hypertension** are up to 4 mg once daily; doses of 16 mg daily should not be exceeded. For **benign prostatic hyperplasia** the usual maintenance dose is 2 to 4 mg daily; doses of 8 mg daily should not be exceeded.

Doxazosin may also be given as a modified-release preparation.

◊ Reviews.

1. Fulton B, *et al.* Doxazosin: an update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. *Drugs* 1995; **49:** 295–320.

Benign prostatic hyperplasia. References to the use of doxazosin in patients with benign prostatic hyperplasia (p.2178).

1. Doggrell SA. After ALLHAT: doxazosin for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2004; **5:** 1957–64.
2. MacDonald R, *et al.* Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. *BJU Int* 2004; **94:** 1263–70.
3. Goldsmith DR, Plosker GL. Doxazosin gastrointestinal therapeutic system: a review of its use in benign prostatic hyperplasia. *Drugs* 2005; **65:** 2037–47.
4. Wilt TJ, MacDonald R. Doxazosin in the treatment of benign prostatic hypertrophy: an update. *Clin Interv Aging* 2006; **1:** 389–401.
5. Bhardwa J, *et al.* Finasteride and doxazosin alone or in combination for the treatment of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2007; **8:** 1337–44.

Hypertension. Alpha blockers are among the drug groups that have been used as first-line therapy for hypertension (p.1171). However, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] the doxazosin arm of the study was terminated early due to an increased incidence of heart failure in patients receiving doxazosin compared with those receiving chlortalidone and alpha blockers are now only recommended for third-line therapy unless indicated for another reason.

1. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; **283:** 1967–75. Correction. *ibid.* 2002; **288:** 2976.

Pain. For reference to the use of doxazosin in pain, see under Uses of Phentolamine Mesilate, p.1371.

Preparations

USP 31: Doxazosin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cardura; Doxasin; Doxolbran; Lafedoxin; Prostazosina; Vazosin; ***Austria:*** Adoxa; Ascalan; Doxano†; Doxapress; Hibadren; Prostadilat; Supressin; ***Braz.:*** Carduran; Doxsol; Euprostatin; Prodil†; Unoprost; Zoflux; ***Canad.:*** Cardura; ***Chile:*** Alfadoxin; Angicon; Cardura; Dorbantil; ***Cz.:*** Cardura; Dosano; Dozone; Kamiren; Windoxa; Zoxon; ***Denm.:*** Biozosin; Cardosin; Carduran; Doxacar†; ***Fr.:*** Zoxan; ***Ger.:*** Alfamedin; Cardular; Diblocin; Doxa-Puren; Doxacor; Doxagamma; Doxamax†; DoxaUro†; Doxazoflo; Doxazomerck†; Jutalar; Uriduct; ***Gr.:*** Cardura; Maguran; Protectura; ***Hong Kong:*** Cardura; Doxasyn; ***Hung.:*** Cardura; Doxagal; Doxicard; ***India:*** Doxacard; ***Indon.:*** Cardura; ***Irl.:*** Cardura; Doxatan; ***Israel:*** Cadex; Cardoral; Doxaloc; ***Ital.:*** Benur; Cardura; Dedralen; Normothen; ***Jpn:*** Cardenalin†; ***Malaysia:*** Cardura; Magurol; Pencor; ***Mex.:*** Cardura; ***Neth.:*** Cardura; Progandol; Zoxan; ***Norw.:*** Carduran; ***NZ:*** Cardoxan; Dosan; ***Pol.:*** Apo-Doxan; Cardura; Doxanorm; Doxar; Doxaratio; Doxonex; Kamiren; Prostatic; Vaxosin; Zoxon; ***Port.:*** Cardura; ***Rus.:*** Artezine (Артезин); Cardura (Кардура); Kamiren (Камирен); Magurol (Магурол); Tonocardin (Тонокардин); Zoxon (Зоксон); ***S.Afr.:*** Cardugen; Cardura; ***Singapore:*** Cardura; Pencor; ***Spain:*** Carduran; Doxatensa; Doximax Neo; Progandol; ***Swed.:*** Alfadil; ***Switz.:*** Cardura; ***Thai.:*** Cardura; Carxasin; Cazosin; Dezcard; Dozozin; Duracard; Genzosin; Pencor; ***Turk.:*** Cardura; Doksura; Doxacor; ***UK:*** Cardura; Doxadura; ***USA:*** Cardura; ***Venez.:*** Cardura.

Dronedarone *(rINN)*

Dronedarona; Dronédarone; Dronedaronum; SR-33589. *N*-(2-Butyl-3-{*p*-[3-(dibutylamino)propoxy]benzoyl}-5-benzofuranyl)methanesulfonamide.

Дронедарон

$C_{31}H_{44}N_2O_5S$ = 556.8.

CAS — 141626-36-0.

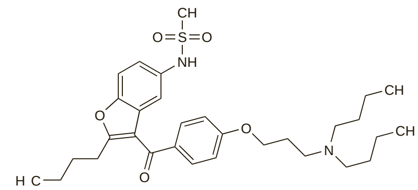

Profile

Dronedarone is structurally related to amiodarone and is under investigation as an antiarrhythmic.

◊ References.

1. Touboul P, *et al.* Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003; **24:** 1481–7.
2. Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007; **41:** 599–605.
3. Singh BN, *et al.* EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; **357:** 987–99.

Duteplase *(rINN)*

Duteplasa; Dutéplase; Duteplasum; 245-L-Methionine Plasminogen Activator; SM-9527.

Дутеплаза

$C_{2736}H_{4174}N_{914}O_{824}S_{46}$ = 64529.0.

CAS — 120608-46-0.

Profile

Duteplase is a thrombolytic drug. It is a biosynthetic derivative of endogenous tissue plasminogen activator and has been used similarly to alteplase (p.1207) in the treatment of thromboembolic disorders, particularly acute myocardial infarction.

◊ References.

1. Hayashi H, *et al.* Effects of intravenous SM-9527 (double-chain tissue plasminogen activator) on left ventricular function in the chronic stage of acute myocardial infarction. *Clin Cardiol* 1993; **16:** 409–14.
2. Malcolm AD, *et al.* ESPRIT: a European study of the prevention of reocclusion after initial thrombolysis with duteplase in acute myocardial infarction. *Eur Heart J* 1996; **17:** 1522–31.

Edaravone *(rINN)*

Edaravona; Édaravone; Edaravonum; MCI-186; Norphenazone. 3-Methyl-1-phenyl-2-pyrazolin-5-one.

Эдаравон

$C_{10}H_{10}N_2O$ = 174.2.

CAS — 89-25-8.

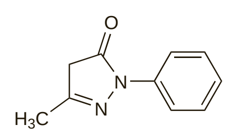

Profile

Edaravone is a free-radical scavenger used in the management of acute ischaemic stroke (p.1185). It is given by intravenous infusion in a dose of 30 mg twice daily, infused over 30 minutes, beginning within 24 hours of stroke onset and continued for up to 14 days.

◊ References.

1. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003; **15:** 222–9.
2. Tsujita K, *et al.* Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94:** 481–4.
3. Tsujita K, *et al.* Long-term efficacy of edaravone in patients with acute myocardial infarction. *Circ J* 2006; **70:** 832–7.
4. Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; **11:** 292–6.
5. Watanabe T, *et al.* The novel antioxidant edaravone: from bench to bedside. *Cardiovasc Ther* 2008; **26:** 101–14.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Radicut.

Efonidipine Hydrochloride *(rINNM)*

Éfonidipine, Chlorhydrate d'; Efonidipini Hydrochloridum; Hidrocloruro de efonidipino; NZ-105; Serefodipine Hydrochloride. Cyclic 2,2-dimethyltrimethylene ester of 2-(*N*-benzylanilino)ethyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-5-phosphononicontinate hydrochloride .

Эфонидипина Гидрохлорид

$C_{34}H_{38}N_3O_7P,HCl = 668.1.$

CAS — 111011-63-3 (efonidipine); 111011-53-1 (efonidipine hydrochloride).

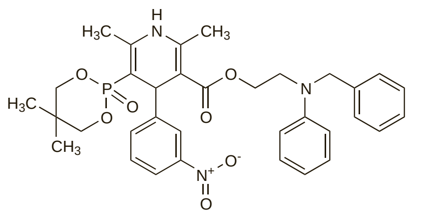

(efonidipine)

Profile

Efonidipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is used as the hydrochloride in the treatment of hypertension.

◊ References.

1. Tanaka H, Shigenobu K. Efonidipine hydrochloride: a dual blocker of L- and T-type Ca channels. *Cardiovasc Drug Rev* 2002; **20:** 81–92.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Landel.

Enalapril *(BAN, rINN)*

Enalapriili; Énalapril; Enalaprilum. *N*-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-L-proline.

Эналаприл

$C_{20}H_{28}N_2O_5 = 376.4.$

CAS — 75847-73-3.

ATC — C09AA02.

ATC Vet — QC09AA02.

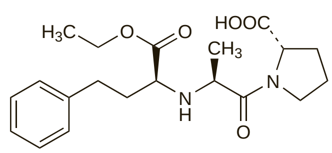

Enalapril Maleate *(BANM, USAN, rINNM)*

Enalapriilimaleaatti; Enalapril Maleat; Énalapril, maléate d'; Enalapril maleinát; Enalaprili maleas; Enalaprilio maleatas; Enalaprilmaleat; Enalapril-maleát; Maleato de enalapril; MK-421. *N*-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-L-proline hydrogen maleate.

Эналаприла Малеат

$C_{20}H_{28}N_2O_5,C_4H_4O_4 = 492.5.$

CAS — 76095-16-4.

ATC — C09AA02.

ATC Vet — QC09AA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Enalapril Maleate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 1% solution in water has a pH of 2.4 to 2.9. Protect from light.

USP 31 (Enalapril Maleate). An off-white crystalline powder. Sparingly soluble in water; soluble in alcohol; freely soluble in dimethylformamide and in methyl alcohol; slightly soluble in semipolar organic solvents; practically insoluble in nonpolar organic solvents.

Stability. Enalapril has been reported[1,2] to be stable for at least 56 days in extemporaneously compounded oral liquids containing enalapril maleate 1 mg/mL in a number of vehicles.

1. Nahata MC, *et al.* Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1155–7.
2. Allen LV, Erickson MA. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1915–20.

Enalaprilat *(BAN, USAN, rINN)*

Énalaprilate; Énalaprilate dihydraté; Enalaprilatum; Enalaprilatum dihydricum; Enalaprilic acid; MK-422. *N*-{*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl}-L-proline dihydrate.

Эналаприлат

$C_{18}H_{24}N_2O_5,2H_2O = 384.4.$

CAS — 76420-72-9 (anhydrous enalaprilat); 84680-54-6 (enalaprilat dihydrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Enalaprilat Dihydrate). A white or almost white, hygroscopic, crystalline powder. It exhibits pseudopolymorphism. Very slightly soluble or slightly soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetonitrile. Store in airtight containers.

USP 31 (Enalaprilat). A white to nearly white, hygroscopic, crystalline powder. Soluble 1 in 200 of water, 1 in 40 of dimethylformamide, and 1 in 68 of methyl alcohol; very slightly soluble in alcohol, in acetone, and in hexane; practically insoluble in acetonitrile and in chloroform; slightly soluble in isopropyl alcohol.

Incompatibility. Enalaprilat was visually incompatible[1] with phenytoin sodium in sodium chloride 0.9%, producing a crystalline precipitate; there was also some visual evidence of incompatibility when mixed with amphotericin B in glucose 5%.

1. Thompson DF, *et al.* Visual compatibility of enalaprilat with selected intravenous medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 2530–1.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Incidence of adverse effects. Postmarketing surveillance for enalapril was carried out by prescription-event monitoring of 12 543 patients.[1] There were 374 skin events including facial oedema or angioedema in 29 (leading to withdrawal of treatment in 10), 15 cases of photosensitivity, and urticaria in 32 (leading to withdrawal in 5). Syncope and dizziness occurred in 155 and 483 patients respectively, sometimes in association with hypotension. Hypotension occurred in 218 patients, 71 in the first month. Treatment was stopped in 121 patients with hypotension, and dosage reduced in 36. Other adverse effects reported included headache in 310 patients, paraesthesias in 126, taste disturbances in 25, conjunctivitis in 67, tachycardia in 194, cough in 360, renal failure in 82, muscle cramp in 96, diarrhoea in 236, and nausea and vomiting in 326. Of 1098 deaths only 10, due to renal failure, were thought possibly related to enalapril therapy. Dysgeusia and skin reactions appeared to be less common than has been reported for captopril, but precise comparisons were difficult; the range of adverse effects was similar.[2]

Deafness was a possible side-effect of enalapril noted earlier;[2] it was reported in 19 of the 12 543 patients monitored, but only while they were taking enalapril, there being no record of deafness after treatment stopped.

For further reference to some of these adverse effects, see under ACE Inhibitors, p.1193.

1. Inman WHW, *et al.* Postmarketing surveillance of enalapril I: results of prescription-event monitoring. *BMJ* 1988; **297:** 826–9.
2. Inman WHW, Rawson NSB. Deafness with enalapril and prescription event monitoring. *Lancet* 1987; **i:** 872.

Breast feeding. After a single dose of enalapril 20 mg in 5 women enalaprilat was detected[1] in breast milk in concentrations of 1 to 2.3 nanograms/mL (mean peak 1.72 nanograms/mL); enalapril was also present (mean peak 1.74 nanograms/mL). This compared with peak serum values of 39 to 112 nanograms/mL for enalaprilat and 92 to 151 nanograms/mL for enalapril. Another study[2] found no detectable enalaprilat in the milk of 3 women, while in a further woman[3] both enalapril and enalaprilat were detected, but the concentrations were low. Although enalapril and its metabolite are thus present in small amounts in breast milk it was calculated that the average total daily dose to the neonate would only be about 2 micrograms of enalaprilat.[1] The American Academy of Pediatrics[4] lists no reports of any clinical effect on the infant associated with the use of enalapril by breast-feeding mothers, and states that therefore it may be considered to be usually compatible with breast feeding.

1. Redman CWG, *et al.* The excretion of enalapril and enalaprilat in human breast milk. *Eur J Clin Pharmacol* 1990; **38:** 99.
2. Huttunen K, *et al.* Enalapril treatment of a nursing mother with slightly impaired renal function. *Clin Nephrol* 1989; **31:** 278.
3. Rush JE, *et al.* Comment. *Clin Nephrol* 1991; **35:** 234.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/07/04)

Porphyria. Enalapril has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Enalapril acts as a prodrug of the diacid enalaprilat, its active form, which is poorly absorbed orally. About 60% of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about 1 hour. Enalapril is extensively hydrolysed in the liver to enalaprilat; peak plasma concentrations of enalaprilat are achieved 3 to 4 hours after an oral dose of enalapril. Enalaprilat is 50 to 60% bound to plasma proteins. After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged drug, with the urinary route predominating; more than 90% of an intravenous dose of enalaprilat is excreted in the urine. The elimination of enalaprilat is multiphasic but the effective half-life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function. Enalaprilat is removed by haemodialysis and by peritoneal dialysis.

◊ References.

1. MacFadyen RJ, *et al.* Enalapril clinical pharmacokinetics and pharmacokinetic-pharmacodynamic relationships: an overview. *Clin Pharmacokinet* 1993; **25:** 274–82.
2. Wells T, *et al.* The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; **41:** 1064–74.

Renal impairment. Comparison of the pharmacokinetics of enalapril in 6 diabetics with persistent proteinuria and glomerular filtration rates (GFR) of 44.1 to 58.4 mL/minute with those in 8 age-matched controls showed that in the diabetic group the peak serum concentration of enalaprilat was higher, the time to peak concentration longer, renal clearance lower, and the areas under the concentration/time curve greater than in controls.[1] Renal clearance of enalaprilat in the diabetics ranged from 56 to 66 mL/minute compared with 105 to 133 mL/minute in controls; clearance correlated with GFR.

1. Baba T, *et al.* Enalapril pharmacokinetics in diabetic patients. *Lancet* 1989; **i:** 226–7.

Uses and Administration

Enalapril is an ACE inhibitor (p.1193) used in the treatment of hypertension (p.1171) and heart failure (p.1165). It may also be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in patients with left ventricular dysfunction to reduce the incidence of coronary ischaemic events, including myocardial infarction (p.1175).

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6 hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the treatment of **hypertension**, an initial oral dose of 5 mg of enalapril maleate daily may be given. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be given to patients with renal impairment or to those who are receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before enalapril is started and resumed later if necessary. The usual maintenance dose is 10 to 20 mg given once daily, although doses of up to 40 mg daily may be required in severe hypertension. It may be given in 2 divided doses if control is inadequate with a single dose.

When oral therapy of hypertension is impractical enalaprilat may be given in a dose of 1.25 mg by slow intravenous injection or infusion over at least 5 minutes, repeated every 6 hours if necessary; the initial dose should be halved in patients with renal impairment (creatinine clearance less than 30 mL/minute) or those who are receiving a diuretic.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. In patients with heart failure or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

Administration in children. Enalapril may be used in the management of hypertension in children.[1] The initial dose is 80 micrograms/kg once daily, with a maximum of 5 mg, adjusted according to response. Alternatively, children weighing 20 to below 50 kg may be given an initial dose of 2.5 mg once daily, increased to a maximum of 20 mg daily, while children weighing 50 kg or over may be given an initial dose of 5 mg once daily, increased to a maximum of 40 mg daily. Doses above 580 micrograms/kg or 40 mg daily have not been studied.

Enalapril has also been given to infants with severe heart failure in doses of 100 to 500 micrograms/kg daily as an oral suspension produced by suspending a crushed tablet in water.[2] In this study one infant, with severe myocarditis, developed hypotension and the drug had to be withdrawn; the remaining 7 showed clinical improvement on a mean enalapril dose of 260 micrograms/kg daily and were able markedly to reduce the dose of concomitant diuretic required. Another study in 10 infants found that enalapril was less bioavailable and probably had a shorter duration of action in infants than in adults, and that doses of 80 micrograms/kg daily were inadequate in the treatment of infant heart failure.[3] A larger study in 63 infants and children (median age 5.4 months) with heart failure found enalapril 360 micrograms/kg daily to be of benefit, whereas there was no improvement with a lower dose of 240 micrograms/kg daily.[4]

1. Wells T, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol* 2002; **42:** 870–80.
2. Frenneaux M, *et al.* Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989; **64:** 219–23.
3. Lloyd TR, *et al.* Orally administered enalapril for infants with congestive heart failure: a dose-finding study. *J Pediatr* 1989; **114:** 650–4.
4. Leversha AM, *et al.* Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994; **70:** 35–9.

Preparations

BP 2008: Enalapril Tablets;
USP 31: Enalapril Maleate and Hydrochlorothiazide Tablets; Enalapril Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baypril; Defluin; Dentromin; Ecaprilat; Enalafel; Enalapoten; Enaldun; Enatral; Enatrial; Eritril; Fabotensil; Gadopril; Glioten; Hipertan; Kinfil; Lotrial; Maxen; Nalapril; Presi Regul; Priltenk; Renitec; Sulocten; Tencas; Vapresan; Vasopril; ***Austral.:*** Alphapril; Amprace; Auspril; Enahexal; Enalabell; Renitec; ***Austria:*** Alapril; Enac; Enalanorm; Enapril; Enaran; Enatyrol†; Mepril; Renistad; Renitec; ***Belg.:*** Renitec; ***Braz.:*** Angiopril†; Atens; Blootec†; Enalabal; Enalamed; Enalaplex†; Enalatec; Enalil; Enalprin†; Enaprotec†; Enatec†; Enaton†; Eupressin; Glioten; Hipertin†; Lowpress†; Maleapril†; Multipressim; Nalaprix†; Neolapril†; Pressel; Pressotec; Prodopressin; Pryltec; Renalapril; Renipress; Renitec; Renopress†; Sanvapress; Sifpryl†; Vasopril; ***Canad.:*** Vasotec; ***Chile:*** Bajaten; Enalten; Esalfon; Glioten; Grifopril; Hiperson; Hipoartel†; Lotrial; Vasolat†; ***Cz.:*** Acetensil†; Berlipril; E-Cor†; Ednyt; Enap; Enapirex†; Enapril; Invoril; Renitec; ***Denm.:*** Aceren†; Alacor†; Corodil; Enacodan; Enadil†; Renitec; ***Fin.:*** Enaloc†; Enapress†; Linatil; Renitec; ***Fr.:*** Renitec; ***Ger.:*** Benalapril; Corvo; Ena; Ena-Puren; Enabeta; enadura; Enahexal; Enal†; Enalagamma; EnaLich; Enalind†; Jutaxan; Pres; Xanef; ***Gr.:*** Agioten; Analept; Antiprex; Erxetilan; Gnostocardin; Kaparlon-S; Kontic†; Leovinezal; Megapress; Octorax; Ofnifenil; Protal†; Rablas; Renitec; Stadelant; Supotron; Ulticadex; Virfen; Vitobel†; ***Hong Kong:*** Anapril; Danssan; Enaldun; Lapril; Renitec; ***Hung.:*** Acepril; Berlipril; Ednyt; Enap; Enapril; Invoril; Renapril; Renitec; ***India:*** BQL; Dilvas; Ena; EnAce; Envas; Nuril; ***Indon.:*** Meipril; Renacardon; Tenace; ***Irl.:*** Ednyt†; Enap; Innomel†; Innovace; ***Israel:*** Convertin; Enaladex; ***Ital.:*** Converten; Enapren; Naprilene; Silverit; ***Malaysia:*** Acetec; Enapril; Invoril; Renitec; Zynace†; ***Mex.:*** Adytenn; Albec; Apo-Pyl; Bimetdad; Bionafil; Blocatril; EK-3; Enaladil; Enoval; Euronal; Feliberal; Glioten; Imotoran; Kenopril†; Lipraken; Nalabest; Norpril; Palane; Pulsol; Quimalan†; Ralser; Renitec; Vexotil; ***Neth.:*** Renitec; ***Norw.:*** Linatil†; Renitec; ***NZ:*** Enahexal; Renitec; ***Philipp.:*** Acebitor; Hipertal; Hypace; Naprilate; Renitec; Stadenace; Vasopress; ***Pol.:*** Benalapril; Ednyt; Enap; Enarenal; Enazil; Epril; Mapryl; ***Port.:*** Balpril; Cetampril; Chipil; Denapril; Diasistol; Enapress; Hipobar; Hipten†; Malen†; Prilan; Renipril†; Renitec; Tensazol; ***Rus.:*** Bagopril (Багоприл); Berlipril (Берлиприл); Ednyt (Эднит); Enafarm (Энафарм); Enam (Энам); Enap (Энап); Enarenal (Энаренал); Enazil (Эназил)†; Envas (Энвас); Invoril (Инворил); Kalpiren (Кальпирен); Myopril (Миоприл); Renipril (Рениприл); Renitec (Ренитек); Vasopren (Вазопрен)†; ***S.Afr.:*** Alapren; Ciplatec; Enap; Hypace†; Pharmapress; Renitec; ***Singapore:*** Anapril; Corprilor; Daren†; Enap; Enaril; Invoril; Korandil; Renaton†; Renitec; ***Spain:*** Acetensil; Baripril; Bitensil; Clipto; Controlvas; Corprilor; Crinoren; Dabonal; Ditensor; Herten; Hipoartel; Iecatec; Insup; Nacor†; Naprilene; Neotensin; Pressitan; Reca; Renitec; ***Swed.:*** Linatil; Renitec; ***Switz.:*** Acepril; Elpradil; ena-basan†; Enasifar†; Enatec; Epril; Reniten; Vasocor; ***Thai.:*** Anapril; Enam; Enapril; Enaril; Envas; Iecatec†; Invoril; Istopril; Korandil; Lapril; Nalopril; Naritec; Renitec; Unaril; ***Turk.:*** Enalap; Enapril; Konveril; Renitec; Vasolapril; ***UAE:*** Narapril; ***UK:*** Enacard†; Innovace; Pralenal†; ***USA:*** Vasotec; ***Venez.:*** Cosil; Dinid; Enalaprin†; Enam†; Enaprival†; Enecal; Fibrosan; Hiperpril; Lapril†; Prilace; Redopril; Reminal; Renitec; Tesoren†.

Multi-ingredient: ***Arg.:*** Co-Renitec; Defluin Plus; Fabotensil D; Gadopril D; Gliotenzide; Kinfil D; Lotrial D; Lotrix†; Maxen D; Nikion†; Presi Regul D; Tencas D; Vapresan Diur; ***Austral.:*** Renitec Plus; ***Austria:*** Co-Enac; Co-Enalapril; Co-Enaran; Co-Enatyrol†; Co-Mepril; Co-Renitec; Corenistad; Enacostad†; Enalapril Comp; Enalapril/HCT; Renitec Plus; Synerpril; ***Belg.:*** Co-Enalapril; Co-Renitec; ***Braz.:*** Atens H; Atmos; Co-Enalil; Co-Enaprotec†; Co-Pressoless; Co-Pressotec; Co-Renitec; Duopril; Enatec F†; Eupressin H; Gliotenzide; Malena HCT; Pryltec-H; Sinergen; Vasopril Plus; ***Canad.:*** Vaseretic; ***Chile:*** Bajaten D; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hiperson-D; Hipoartel H†; Lotrial D; Normaten; Normaten Plus; ***Cz.:*** Enap-H; Enap-HL; ***Denm.:*** Co-Renitec†; Corodil Comp; Enacozid; Synerpril; ***Fin.:*** Enalapril Comp; Enaloc Comp†; Linatil Comp; Renitec Comp; Renitec Plus; ***Fr.:*** Co-Renitec; ***Ger.:*** Benalapril Plus; Corvo HCT; Enabeta comp; Enadura Plus; Enahexal comp; Enala-Q comp; Enalagamma HCT; Enalapril Comp; Enalapril HCT; Enalapril plus; Enalapril-saar Plus; EnaLich comp; Enaplus; Eneas; Pres plus; Renacor; ***Gr.:*** Bumeftyl; Co-Renitec; Coredopril; Eneas; Enit; Iperton; Modinexil†; Nolarmin; Penopril; Protal complex; Savosan; Siberian; ***Hong Kong:*** Co-Renitec; ***Hung.:*** Acepril PlusZ; Co-Enalapril; Co-Renitec; Ednyt HCT; Ednyt Plus; Enalapril Hexal Plus; Enalapril-HCT; Enap-HL; Renapril Plus; Renitec Plus; ***India:*** Dilvas AM; EnAce-D; Invozide; ***Indon.:*** Tenazide; ***Irl.:*** Innozide; ***Israel:*** Naprizide; ***Ital.:*** Acesistem; Condiuren; Gentipress; Neoprex; Sinertec; Vasoretic; ***Mex.:*** Co-Renitec; Gliotenzide; ***Neth.:*** Co-Renitec; Enacostad†; Renitec Plus; ***Norw.:*** Enalapril Comp; Renitec Comp; ***NZ:*** Co-Renitec; ***Philipp.:*** Co-Renitec; ***Pol.:*** Enap H; Enap HL; ***Port.:*** Enatia; Eneas; Enit; Laprilen; Neodur; Norpramin; Renidur; Renipril Plus; ***Rus.:*** Co-Renitec (Ко-Ренитек); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Enzix (Энзикс); Renipril HT (Рениприл ГТ); ***S.Afr.:*** Co-Renitec; Enap-Co; Pharmapress Co; ***Singapore:*** Co-Renitec; Enap-HL; Gliotenzide; ***Spain:*** Acediur; Acetensil Plus; Baripril Diu; Bitensil Diu; Co-Renitec; Crinoretic; Dabonal Plus; Ditenside; Eneas; Enit; Hipoartel Plus; Neotensin Diu; Pressitan Plus; Renitecmax; Vipres; Zorail; ***Swed.:*** Enalapril Comp; Linatil Comp; Renitec Comp; Synerpril; ***Switz.:*** Co-Acepril; Co-Enalapril; Co-Enatec; Co-Epril; Co-Reniten; Co-Vasocor; Elpradil HCT; Epril Plus; Reniten Plus; ***Turk.:*** Konveril Plus; ***UK:*** Innozide; ***USA:*** Lexxel; Teczem; Vaseretic; ***Venez.:*** Co-Renitec; Duopres; Prirretic†; Reminalet.

Endralazine Mesilate *(BANM, rINNM)*

BQ-22-708; Compound 22-708; Endralazine, Mésilate d'; Endralazine Mesylate *(USAN)*; Endralazini Mesilas; Mesilato de endralazina. 6-Benzoyl-5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazin-3-ylhydrazone monomethanesulfonate.

Эндралазина Мезилат

$C_{14}H_{15}N_5O,CH_4O_3S = 365.4.$
CAS — 39715-02-1 (endralazine); 65322-72-7 (endralazine mesilate).
ATC — C02DB03.
ATC Vet — QC02DB03.

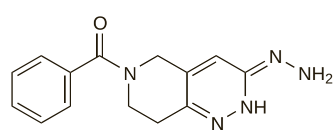

(endralazine)

Profile

Endralazine is a vasodilator with properties similar to those of hydralazine (p.1305). It has been used as the mesilate in the management of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Miretilan†.

Enoxaparin Sodium *(BAN, USAN, rINN)*

Enoksapariininatrium; Enoksaparin Sodyum; Enoksaparino natrio druska; Enoksaparyna sodowa; Enoxaparin sodná sůl; Enoxaparina sódica; Énoxaparine sodique; Enoxaparinnatrium; Enoxaparin-nátrium; Enoxaparinum natricum; PK-10169; RP-54563.

Эноксапарин Натрий

CAS — 9041-08-1; 679809-58-6.
ATC — B01AB05.
ATC Vet — QB01AB05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Enoxaparin Sodium). The sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain; 15 to 25% of the components have a 1,6-anhydro structure at the reducing end of their chain. The mass-average molecular mass ranges between 3800 and 5000 with a characteristic value of about 4500. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 90 units and not more than 125 units of anti-factor Xa activity per mg, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20 units and not more than 35 units per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7.

USP 31 (Enoxaparin Sodium). The sodium salt of a depolymerised heparin obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised. The majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. About 20% of the components contain a 1,6-anhydro derivative on the reducing end of the chain. The mass-average molecular weight of enoxaparin sodium is 4,500, the range being between 3,800 and 5,000.

It has a potency of not less than 90 units and not more than 125 units of anti-factor Xa per mg, and not less than 20 units and not more than 35 units of anti-factor IIa per mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

A 10% solution in water has a pH of 6.2 to 7.7. Store in airtight containers at a temperature below 40°.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329. Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring.

Severe bleeding with enoxaparin may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of 1 mg (100 units) of enoxaparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Enoxaparin is rapidly and almost completely absorbed after subcutaneous injection with a bioavailability of about 100%. Peak plasma activity is reached within 1 to 5 hours. The elimination half-life is about 4 to 5 hours but anti-factor Xa activity persists for up to 24 hours after a 40-mg dose. Elimination is prolonged in patients with renal impairment. Enoxaparin is metabolised in the liver and excreted in the urine, as unchanged drug and metabolites.

◊ References.

1. Hulot JS, *et al.* Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit* 2004; **26:** 305–10.
2. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J* 2004; **148:** 582–9.

Uses and Administration

Enoxaparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p.1157) and in ST-elevation myocardial infarction (p.1175).

In the *prophylaxis* of **venous thromboembolism** during surgical procedures, enoxaparin sodium is given by subcutaneous injection; treatment is continued for 7 to 10 days or until the patient is ambulant.

- Patients at low to moderate risk are given 20 mg (2000 units) once daily with the first dose about 2 hours pre-operatively.
- In patients at high risk, such as those undergoing orthopaedic surgery, the dose should be increased to 40 mg (4000 units) once daily with the initial dose given about 12 hours before the procedure. Alternatively, a dose of 30 mg (3000 units) may be given subcutaneously twice daily, starting within 12 to 24

hours after operation. After hip replacement surgery, enoxaparin sodium may be continued in a dose of 40 mg (4000 units) once daily for a further 3 weeks.

- For the prophylaxis of thromboembolism in immobilised medical patients, the dose is 40 mg (4000 units) once daily for at least 6 days; treatment should be continued until the patient is fully ambulant, up to a maximum of 14 days.

For the *treatment* of deep-vein thrombosis enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours, or 1.5 mg/kg (150 units/kg) once daily, for at least 5 days and until oral anticoagulation is established.

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, enoxaparin sodium 1 mg/kg (100 units/kg) is introduced into the arterial line of the circuit at the beginning of the dialysis session. A further dose of 0.5 to 1 mg/kg (50 to 100 units/kg) may be given if required. The dose should be reduced in patients at high risk of haemorrhage.

In the management of **unstable angina**, enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours. Treatment is usually continued for 2 to 8 days.

In acute ST-elevation **myocardial infarction** the initial dose of enoxaparin is 30 mg (3000 units) intravenously, with a subcutaneous dose of 1 mg/kg (100 units/kg) given at the same time. Further doses of 1 mg/kg (100 units/kg) should be given subcutaneously every 12 hours for 8 days or until hospital discharge. The first 2 subcutaneous doses should not exceed 100 mg (10 000 units) each. For patients who undergo a percutaneous coronary intervention, an additional intravenous dose of 300 micrograms/kg (30 units/kg) should be given at the time of the procedure if the last subcutaneous dose was given more than 8 hours previously. Patients aged 75 years and older with acute myocardial infarction should be given subcutaneous doses only; the recommended dose is 750 micrograms/kg (75 units/kg) every 12 hours, with a maximum of 75 mg (7500 units) for each of the first 2 doses.

The dose of enoxaparin sodium should be reduced in patients with severe renal impairment (see below).

◊ References.

1. Noble S, *et al.* Enoxaparin: a reappraisal of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disease. *Drugs* 1995; **49:** 388–410.
2. Noble S, Spencer CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. *Drugs* 1998; **56:** 259–72.
3. Harvey DM, Offord RH. Management of venous and cardiovascular thrombosis: enoxaparin. *Hosp Med* 2000; **61:** 628–36.
4. Ibbotson T, Goa KL. Enoxaparin: an update of its clinical use in the management of acute coronary syndromes. *Drugs* 2002; **62:** 1407–31.
5. Fareed J, *et al.* Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. *Clin Pharmacokinet* 2003; **42:** 1043–57.
6. Siddiqui MAA, Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; **65:** 1025–36.
7. Carter NJ, *et al.* Enoxaparin: a review of its use in ST-segment elevation myocardial infarction. *Drugs* 2008; **68:** 691–710.

Administration in infants and children. Increasing numbers of infants and children are given anticoagulants for the management of thromboembolism. Few controlled studies have been carried out in this age group and recommendations for therapy have generally been adapted from adult guidelines. Low-molecular-weight heparins may have a number of advantages in children. Enoxaparin has been used for the prophylaxis[1] of thromboembolism in children including neonates, and for treatment in children including neonates[1-3] and preterm infants.[1,3-5] Younger children may require a higher dose than older children. US guidelines recommend the following doses for *treatment*[6] of thromboembolism:

- under 2 months of age: 1.5 mg/kg (150 units/kg) every 12 hours
- over 2 months of age: 1 mg/kg (100 units/kg) every 12 hours

Doses for *prophylaxis*[6] are:

- under 2 months of age: 750 micrograms/kg (75 units/kg) every 12 hours
- over 2 months of age: 500 micrograms/kg (50 units/kg) every 12 hours

Similar doses are recommended in the UK by the *BNFC*, although it specifies slightly modified doses in neonates, in whom it recommends 1.5 to 2 mg/kg twice daily for *treatment* and 750 micrograms/kg twice daily for *prophylaxis*.

1. Dix D, *et al.* The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000; **136:** 439–45.
2. Massicotte P, *et al.* Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996; **128:** 313–18.
3. Streif W, *et al.* Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F365–F370.
4. Dunaway KK, *et al.* Use of enoxaparin in a preterm infant. *Ann Pharmacother* 2000; **34:** 1410–13.
5. Michaels LA, *et al.* Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics* 2004; **114:** 703–7.
6. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Administration in renal impairment. Careful monitoring is required when enoxaparin sodium is given to patients with mild to moderate renal impairment.[1] In severe renal impairment (creatinine clearance less than 30 mL/minute) the dose should be reduced. For prophylaxis of venous thromboembolism, UK licensed product information recommends a dose of 20 mg (2000 units) subcutaneously once daily whereas US licensed product information recommends a subcutaneous dose of 30 mg (3000 units) once daily. For treatment of venous thromboembolism, unstable angina, or acute myocardial infarction in patients aged 75 years or older, a dose of 1 mg/kg (100 units/kg) subcutaneously once daily is advised; patients under 75 years with myocardial infarction should additionally be given a single intravenous dose of 30 mg (3000 units) with the first subcutaneous dose. However, the adequacy of a once-daily dose in patients with acute coronary syndromes has been questioned and alternative dosage regimens have been suggested.2,3

1. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. *Drug Safety* 2007; **30:** 991–4.
2. Hulot J-S, *et al.* Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther* 2005; **77:** 542–52.
3. Green B, *et al.* Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; **59:** 281–90.

Preparations

USP 31: Enoxaparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Clexane; Dilutol; ***Austral.:*** Clexane; ***Austria:*** Lovenox; ***Belg.:*** Clexane; ***Braz.:*** Clexane; Cutenox†; Dripanina; ***Canad.:*** Lovenox; ***Chile:*** Clexane; Nu-Rox; ***Cz.:*** Clexane; ***Denm.:*** Klexane; ***Fin.:*** Klexane; ***Fr.:*** Lovenox; ***Ger.:*** Clexane; ***Gr.:*** Clexane; ***Hong Kong:*** Clexane; ***Hung.:*** Clexane; ***India:*** Clexane; ***Indon.:*** Lovenox; ***Irl.:*** Clexane; ***Israel:*** Clexane; ***Ital.:*** Clexane; ***Malaysia:*** Clexane; ***Mex.:*** Clexane; ***Neth.:*** Clexane; ***Norw.:*** Klexane; ***NZ:*** Clexane; ***Philipp.:*** Clexane; ***Pol.:*** Clexane; ***Port.:*** Klexane; Lovenox; ***Rus.:*** Clexane (Клексан); ***S.Afr.:*** Clexane; ***Singapore:*** Clexane; ***Spain:*** Clexane; Decipar; ***Swed.:*** Klexane; ***Switz.:*** Clexane; ***Thai.:*** Clexane; ***Turk.:*** Clexane; ***UK:*** Clexane; ***USA:*** Lovenox; ***Venez.:*** Clexane; Enoparin.

Multi-ingredient: ***Cz.:*** Clexane anti Xa-IU.

Enoximone *(BAN, USAN, rINN)*

Enoksimoni; Enoximon; Enoximona; Énoximone; Enoximonum; Fenoximone; MDL-17043; MDL-19438; RMI-17043; YMDL-17043. 4-Methyl-5-[4-(methylthio)benzoyl]-4-imidazolin-2-one.

Эноксимон

$C_{12}H_{12}N_2O_2S$ = 248.3.

CAS — 77671-31-9.

ATC — C01CE03.

ATC Vet — QC01CE03.

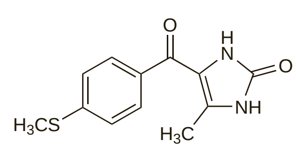

Incompatibility. Crystal formation has occurred when enoximone injection was mixed in glass containers or syringes; the manufacturer recommends that only plastic containers or syringes are used for dilutions. The manufacturer also recommends that only sodium chloride 0.9% or water be used as diluents. Glucose solutions should not be used for dilution as crystal formation may occur.

Adverse Effects

Long-term oral treatment with enoximone has been reported to increase the mortality rate and enoximone is now only given intravenously for short-term use.

Enoximone may cause ventricular and supraventricular tachyarrhythmias, ectopic beats, and hypotension. Adverse effects of enoximone affecting the gastrointestinal tract include diarrhoea, nausea, and vomiting. Other adverse effects include headache, insomnia, chills, oliguria, fever, urinary retention, and limb pain. There have been reports of thrombocytopenia and abnormal liver enzyme values.

Effects on the nervous system. Tonic-clonic convulsions have been reported[1] in a patient given enoximone 6 micrograms/kg per minute by intravenous infusion. The convulsions subsided when enoximone was stopped.

1. Appadurai I, *et al.* Convulsions induced by enoximone administered as a continuous intravenous infusion. *BMJ* 1990; **300:** 613–14.

Hyperosmolality. Hyperosmolality occurred in an infant during intravenous infusion of enoximone 20 micrograms/kg per minute. The probable cause was propylene glycol in the enoximone injection providing a dose of 2.4 mg/kg per minute.[1]

1. Huggon I, *et al.* Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990; **301:** 19–20.

Precautions

Enoximone should be used with caution in patients with hypertrophic cardiomyopathy or severe obstructive aortic or pulmonary valvular disease.

Blood pressure, heart rate, ECG, fluid and electrolyte status, and renal function should be monitored during therapy. Platelet count and liver enzyme values should also be monitored.

The injection has a high pH (about 12) and must be diluted before use (but see Incompatibility, above). Extravasation should be avoided.

Doses may need to be reduced in hepatic or renal impairment (see under Uses and Administration, below).

Pharmacokinetics

Although enoximone is absorbed from the gastrointestinal tract it is no longer given orally. The plasma elimination half-life varies widely; it may be about 1 to 4 hours in healthy subjects and about 3 to 8 hours in patients with heart failure, but longer times have been reported. Enoximone is about 85% bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites. After intravenous doses about 70% of a dose is excreted in the urine as metabolites and less than 1% as unchanged drug.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Uses and Administration

Enoximone is a phosphodiesterase inhibitor similar to amrinone (p.1215) with positive inotropic and vasodilator activity. It is given intravenously in the short-term management of heart failure. In some long-term studies it was given orally, but an increased mortality rate was reported.

The usual initial dose of enoximone by intravenous injection is 0.5 to 1.0 mg/kg given at a rate not greater than 12.5 mg/minute. This may be followed by doses of 500 micrograms/kg every 30 minutes until a satisfactory response is obtained or a total dose of 3 mg/kg has been given. Alternatively, the initial dose may be given as a continuous intravenous infusion in a dose of 90 micrograms/kg per minute over 10 to 30 minutes until the desired response is achieved.

For maintenance therapy the initial dose (up to a total of 3 mg/kg) may be repeated as required every 3 to 6 hours or a continuous or intermittent infusion may be given in a dose of 5 to 20 micrograms/kg per minute. The total dose over 24 hours should not exceed 24 mg/kg.

Dosage may need to be reduced in patients with hepatic or renal impairment (see below).

◊ General references.

1. Vernon MW, *et al.* Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; **42:** 997–1017.

Administration in hepatic and renal impairment. The elimination half-life of enoximone after intravenous administration was 2.16 hours in a patient with hepatic impairment and 1.33 hours in a patient with renal impairment. The mean elimination half-life in patients with normal hepatic and renal function was 1.26 hours. It was suggested that patients with renal impairment should be monitored and have plasma concentrations measured during continuous infusions and that in hepatic disease the dosage may need to be modified.[1] Similarly, in a study[2] in paediatric patients receiving intravenous enoximone clearance was reduced in those with renal or hepatic impairment and it was suggested that the infusion rate should be decreased in such patients.

1. Desager JP, *et al.* Plasma enoximone concentrations in cardiac patients. *Curr Ther Res* 1990; **47:** 743–52.
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Beta blocker overdosage. Enoximone, given intravenously as a bolus dose of 0.5 mg/kg followed by an infusion of 15 micrograms/kg per minute, successfully increased the cardiac output and stroke volume in a woman who had ingested 10 g of metoprolol.[1] It was suggested that enoximone may be useful in such patients since its action does not involve the beta-adrenergic system. Use to treat propranolol overdose has also been described.[2]

1. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
2. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.

Heart failure. Enoximone is one of several drugs that may be used in heart failure (p.1165), but because of an increased mortality rate reported following long-term oral use it is only given intravenously for short-term management of heart failure unresponsive to other treatments. In a comparison of oral enoximone and placebo in patients with moderate to moderately severe heart failure,[1] enoximone was no better than placebo in improving exercise duration over the 16-week study period. Although the overall incidence of adverse effects was similar in the two groups, 5 patients receiving enoximone died compared with none in the placebo group. Low doses of oral enoximone (generally 25 or 50 mg three times daily) have been tried in an attempt to wean patients with severe (NYHA class IV) heart failure from intravenous inotropic support, but with little or only limited success.[2]

1. Uretsky BF, *et al.* Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. *Circulation* 1990; **82:** 774–80.
2. Feldman AM, *et al.* EMOTE Study Group. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; **154:** 861–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Perfan; ***Fr.:*** Perfane†; ***Ger.:*** Perfan; ***Irl.:*** Perfan; ***Ital.:*** Perfan; ***Neth.:*** Perfan; ***UK:*** Perfan.

Epitizide *(BAN, rINN)* ⊗

Epithiazide *(USAN)*; Epitizida; Épitizide; Epitizidum; Epitizida; NSC-108164; P-2105. 6-Chloro-3,4-dihydro-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Эпитизид

$C_{10}H_{11}ClF_3N_3O_4S_3$ = 425.9.
CAS — 1764-85-8.

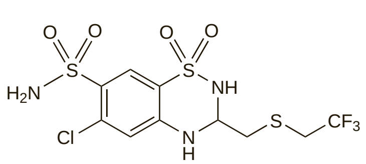

Profile

Epitizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) used in the treatment of hypertension and oedema, often with triamterene.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Dyta-Urese; ***Neth.:*** Dyta-Urese.

Eplerenone *(USAN, rINN)* ⊗

Eplerenona; Éplérénone; Eplerenonum; SC-66110. 9,11α-Epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone methyl ester.

Эплеренон

$C_{24}H_{30}O_6$ = 414.5.
CAS — 107724-20-9.
ATC — C03DA04.
ATC Vet — QC03DA04.

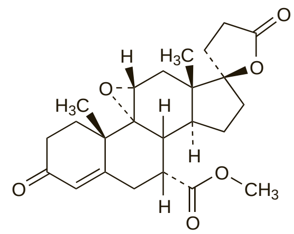

Adverse Effects

As for Spironolactone, p.1400. Hypercholesterolaemia, hypertriglyceridaemia, and increases in liver enzymes have also occurred.

Precautions

As for Spironolactone, p.1400.

Interactions

As for Spironolactone, p.1401.

Eplerenone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and significantly increased plasma concentrations of eplerenone have occurred when potent inhibitors of this enzyme have been given. These include clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, and ritonavir, and use with eplerenone is contra-indicated. Mild to moderate inhibitors of this enzyme, such as erythromycin, fluconazole, saquinavir, and verapamil, have a less marked effect, although a reduced dose of eplerenone may be necessary (see under Uses, below). Grapefruit juice causes only a small increase in exposure to eplerenone. Conversely, inducers of this enzyme system, such as carbamazepine, St John's wort, phenobarbital, phenytoin, and rifampicin, may reduce plasma concentrations of eplerenone.

Pharmacokinetics

Peak plasma concentrations of eplerenone are reached about 1.5 hours after an oral dose; they are dose proportional for doses of 25 to 100 mg, and less than proportional above 100 mg. Protein binding, primarily to α_1-acid glycoprotein, is about 50%. Eplerenone metabolism is mainly mediated by the cytochrome P450 isoenzyme CYP3A4; less than 5% of a dose is excreted unchanged. About 32% of a dose is excreted in the faeces, and the remainder in the urine. The elimination half-life is about 4 to 6 hours. Eplerenone is not removed by dialysis.

◊ References.

1. Ravis WR, *et al.* Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *J Clin Pharmacol* 2005; **45:** 810–21.

Uses and Administration

Eplerenone is an aldosterone antagonist with properties similar to those of spironolactone (p.1401) but with a higher selectivity for the aldosterone receptor. It is given orally in the management of hypertension (p.1171) and heart failure (p.1165).

In the management of **hypertension**, eplerenone may be given alone or with other antihypertensives. It is given in an initial dose of 50 mg daily, increasing if necessary to a maximum of 50 mg twice daily. While eplerenone should not be given with potent CYP3A4 inhibitors (see Interactions, above), patients taking mild to moderate inhibitors may be given eplerenone; the initial dose should be reduced to 25 mg daily.

For the management of **heart failure** after myocardial infarction, eplerenone is given in an initial dose of 25 mg daily, increasing to 50 mg daily within 4 weeks if tolerated. Eplerenone should be withdrawn or the dose should be reduced to 25 mg daily, or on alternate days, if hyperkalaemia develops. Eplerenone may be used in patients given mild to moderate CYP3A4 inhibitors, at a dose not exceeding 25 mg daily.

◊ References and reviews.

1. Zillich AJ, Carter BL. Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother* 2002; **36:** 1567–76.
2. Pitt B, *et al*, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309–21. Correction. *ibid.*; 2271.
3. Keating GM, Plosker GL. Eplerenone: a review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004; **64:** 2689–707.
4. Pitt B, *et al.* Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; **46:** 425–31.
5. Anonymous. Eplerenone after myocardial infarction? *Drug Ther Bull* 2008; **46:** 1–3.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Inspra; ***Austria:*** Inspra; ***Chile:*** Inspra; ***Cz.:*** Inspra; ***Denm.:*** Inspra; ***Fin.:*** Inspra; ***Fr.:*** Inspra; ***Gr.:*** Inspra; ***Hong Kong:*** Inspra; ***Hung.:*** Inspra; ***Irl.:*** Inspra; ***Mex.:*** Inspra; ***Neth.:*** Inspra; ***Norw.:*** Inspra; ***Port.:*** Inovic; Inspra; ***Spain:*** Elecor; Inspra; ***Swed.:*** Inspra; ***UK:*** Inspra; ***USA:*** Inspra.

Epoprostenol *(USAN, rINN)*

Époprosténol; Epoprostenoli; Epoprostenolum; PGI_2; PGX; Prostacyclin; Prostacyclinum; Prostacyklin; Prostaglandin I_2; Prostaglandin X; Prostasykliini; U-53217. (5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-5,13-dienoic acid; (*Z*)-5-{(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]perhydrocyclopenta[*b*]furan-2-ylidene}valeric acid.

Эпопростенол

$C_{20}H_{32}O_5$ = 352.5.
CAS — 35121-78-9.
ATC — B01AC09.
ATC Vet — QB01AC09.

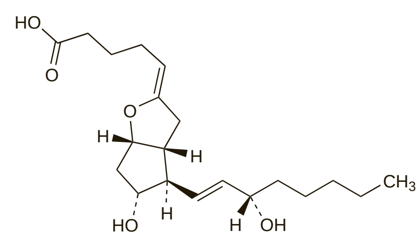

NOTE. In *Martindale* the term epoprostenol is used for the exogenous substance and prostacyclin for the endogenous substance.

Epoprostenol Sodium *(BAN, USAN, rINNM)*

Epoprostenol sódico; Époprosténol Sodique; Natrii Epoprostenolum; U-53217A.

Натрий Эпопростенол

$C_{20}H_{31}NaO_5$ = 374.4.
CAS — 61849-14-7.
ATC — B01AC09.
ATC Vet — QB01AC09.

Stability in solution. Epoprostenol is unstable at physiological pH and solutions for infusion are prepared in an alkaline glycine buffer at pH 10.5. The half-life in aqueous solution of pH 7.4 has been reported[1] to be less than 3 minutes at 37°, but increased stability has been reported in plasma, albumin, or whole blood.[1,2]

1. El Tahir KEH, *et al.* Stability of prostacyclin in human plasma. *Clin Sci* 1980; **59:** 28P–29P.
2. Mikhailidis DP, *et al.* Infusion of prostacyclin (epoprostenol). *Lancet* 1982; **ii:** 767.

Adverse Effects and Precautions

The incidence of adverse reactions to epoprostenol is dose-related. Adverse effects during intravenous infusion commonly include hypotension, increased heart rate, flushing, and headache. Dosage should be reduced or the epoprostenol infusion stopped if excessive hypotension occurs. Bradycardia with pallor, sweating, nausea, and abdominal discomfort may occur. Erythema over the intravenous infusion site has been noted. Other adverse effects reported have included nausea and vomiting, diarrhoea, jaw pain or nonspecific musculoskeletal pain, anxiety, nervousness, tremor, flu-like symptoms, hyperglycaemia, drowsiness, and chest pain.

Coagulation of blood in the dialysis circuit has been reported rarely in patients given epoprostenol but no conventional anticoagulant. The use of epoprostenol for pulmonary hypertension is contra-indicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction, and in patients who develop pulmonary oedema during dose-ranging. Sudden withdrawal of epoprostenol should be avoided because of the risk of rebound pulmonary hypertension. Haematological and cardiovascular monitoring is required in patients receiving epoprostenol infusions. Care should be taken to avoid extravasation.

Incidence of adverse effects. A study in 24 healthy subjects investigated the incidence of adverse effects with intravenous infusions of epoprostenol of up to 10 nanograms/kg per minute for up to 100 minutes.[1] Subjects varied in their susceptibility to epoprostenol but the same sequence of events was usually present. A change in pre-ejection period and facial flushing was often apparent at an infusion rate of 2 to 2.5 nanograms/kg per minute. A rise in heart rate and change in other cardiovascular variables was present when the infusion rate had increased to 4 to 5 nanograms/kg per minute; headache, generally the dose-limiting factor, was usually present at this dose and increased as the dose was raised, as did the other effects. Erythema over the vein and 'vagal reflex' only appeared after at least 1 hour of infusion; 'vagal reflex' took only a few seconds to develop.

Early studies showing that high doses were well tolerated had been conducted using a form of epoprostenol probably only half as potent as the commercially available product. It was proposed that 4 nanograms/kg per minute should in general be the maximum infusion rate for prolonged infusions, although higher rates could be tolerated in anaesthetised patients. Careful attention to infusion technique is necessary and monitoring of the heart rate is advisable in view of the suddenness with which the 'vagal reflex' can occur. Most of the adverse effects reported here have responded to a reduction in dosage.

1. Pickles H, O'Grady J. Side effects occurring during administration of epoprostenol (prostacyclin, PGI), in man. *Br J Clin Pharmacol* 1982; **14:** 177–85.

Effects on the blood. Reports of rebound platelet activation during continuous epoprostenol infusion.[1,2]

1. Yardumian DA, Machin SJ. Altered platelet function in patients on continuous infusion of epoprostenol. *Lancet* 1984; **i:** 1357.
2. Sinzinger H, *et al.* Rebound platelet activation during continuous epoprostenol infusion. *Lancet* 1984; **ii:** 759.

Effects on the cardiovascular system. Evidence that epoprostenol and its analogue iloprost can induce myocardial ischaemia in patients with coronary artery disease.[1]

1. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.

Effects on mental state. Symptoms of depression were associated with intravenous epoprostenol therapy in 4 patients.[1]

1. Ansell D, *et al.* Depression and prostacyclin infusion. *Lancet* 1986; **ii:** 509.

Hypersensitivity. Severe erythroderma occurred in a woman with undifferentiated connective tissue disease who was treated with epoprostenol for pulmonary hypertension.[1] Diffuse erythema, pruritus, and scaling, with chills, nausea, vomiting, and diarrhoea, developed about 2 months after starting therapy, and resolved with epoprostenol withdrawal and corticosteroid treatment.

1. Ahearn GS, *et al.* Severe erythroderma as a complication of continuous epoprostenol therapy. *Chest* 2002; **122:** 378–80.

Interactions

Since epoprostenol is a potent vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants. Epoprostenol may slightly increase serum concentrations of digoxin, and may reduce the thrombolytic effect of alteplase by increasing its hepatic clearance. The hypotensive effects of epoprostenol may be exacerbated by using acetate in dialysis fluids.

Anticoagulants. The incidence of bleeding complications was examined in a retrospective review[1] of 31 patients with primary pulmonary hypertension who had been treated with continuous intravenous epoprostenol and oral *warfarin*. Nine patients developed 11 bleeding episodes, including 9 episodes of alveolar haemorrhage. The international normalised ratio (INR) was maintained in the therapeutic range for 8 of these patients, suggesting that the effect was not caused by overdose of warfarin. The risk of bleeding appeared to be increased in patients who received high-dose epoprostenol (mean dose 89 nanograms/kg per minute).

1. Ogawa A, *et al.* Risk of alveolar hemorrhage in patients with primary pulmonary hypertension—anticoagulation and epoprostenol therapy. *Circ J* 2005; **69:** 216–20.

Pharmacokinetics

Endogenous prostacyclin is a product of arachidonic acid metabolism with a very short half-life. On intravenous infusion epoprostenol is hydrolysed rapidly to the more stable but much less active 6-keto-prostaglandin $F_{1\alpha}$ (6-oxo-prostaglandin $F_{1\alpha}$). A second metabolite, 6,15-diketo-13,14-dihydro-prostaglandin $F_{1\alpha}$, is formed by enzymatic degradation. Unlike many other prostaglandins, epoprostenol is not inactivated in the pulmonary circulation.

Uses and Administration

Epoprostenol is a prostaglandin (p.2374) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostacyclin. Epoprostenol is used mainly in extracorporeal procedures and in pulmonary hypertension.

Epoprostenol is given as the sodium salt and doses are expressed in terms of the base; 1.06 nanograms of epoprostenol sodium is equivalent to about 1 nanogram of epoprostenol. The drug is unstable in solution at physiological pH and also has a very short duration of action because of its rapid hydrolysis *in vivo*. It must therefore be given by continuous infusion. Great care must be taken in preparing a suitably diluted solution for infusion and only diluent as supplied by the manufacturer should be used to reconstitute epoprostenol.

Epoprostenol is used to **prevent platelet aggregation** when blood is brought into contact with nonbiological surfaces in procedures such as extracorporeal circulation, especially in renal dialysis patients. It is indicated for use when heparin carries a high risk of causing or exacerbating bleeding, or is otherwise contra-indicated. Epoprostenol is given by continuous intravenous infusion or into the blood supplying the extracorporeal circulation. The usual dose for renal dialysis is 4 nanograms/kg per minute intravenously before dialysis, then 4 nanograms/kg per minute into the arterial inlet of the dialyser during dialysis.

In the long-term treatment of primary **pulmonary hypertension** or pulmonary hypertension associated with scleroderma a dose-ranging procedure is performed first. Epoprostenol infusion is started at a rate of 2 nanograms/kg per minute, then increased by increments of 2 nanograms/kg per minute at intervals of at least 15 minutes until the maximum haemodynamic benefit or dose-limiting effects occur. Epoprostenol is then given by continuous infusion through a central venous catheter, the initial rate being 4 nanograms/kg per minute *less than* the maximum-tolerated infusion rate; if the maximum-tolerated infusion rate is less than 5 nanograms/kg per minute, then the initial rate should be one-half of this maximum rate. The maintenance dose is subsequently adjusted according to the patient's response. If symptoms recur or if adverse effects occur the dosage may be increased or decreased by steps of 1 to 2 nanograms/kg per minute at intervals of at least 15 minutes until a new maintenance dose is established.

For the use of epoprostenol in neonates and children, see below.

Action. The discovery, properties, and clinical applications of prostacyclin have been reviewed.[1] Prostacyclin is the main product of arachidonic acid in vascular tissues, endothelial cells from vessel walls being the most active producers. It is a strong hypotensive agent through vasodilatation of vascular beds, including the pulmonary and cerebral circulations, and is also a potent endogenous inhibitor of platelet aggregation. Inhibition of aggregation is achieved by stimulation of adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) levels in the platelets. By inhibiting several steps in the activation of the arachidonic acid metabolic cascade, prostacyclin exerts an overall control of platelet aggregability.

Endogenous prostacyclin and thromboxane A_2 may be of more physiological and pathological importance[2] than the more classical prostanoids prostaglandin E_2 and prostaglandin F_2 . They have directly opposing pharmacological actions in many systems, such as on platelet function, vascular smooth muscle, bronchopulmonary function, and gastrointestinal integrity. Thus prostanoid-mediated control of cellular and tissue function may reflect an interactive modulation between prostacyclin and thromboxane A_2 with imbalance resulting in dysfunction, for example in platelet and vascular disorders. Thromboxane A_2 has both bronchoconstrictor and pulmonary irritant actions and has brought about marked changes in respiratory function in experimental models; prostacyclin may oppose these effects on both the pulmonary vasculature and bronchial smooth muscle. Thromboxane A_2 has induced marked renal vasoconstriction *in vitro* whereas renal vasodilatation and stimulation of the release of renin has followed the administration of epoprostenol [exogenous prostacyclin] in *animals*. In contrast to the pro-ulcerogenic actions of thromboxane A_2, epoprostenol and its analogues, like other prostaglandins, have potent gastrointestinal anti-ulcer properties which can be disassociated from their gastric antisecretory properties. The term 'cytoprotection' has been used to describe this ability of exogenous prostaglandins to prevent gastrointestinal damage; endogenous prostaglandins might have a similar protective role. Epoprostenol also has a cytoprotective effect against experimental damage in the gastric mucosa, myocardium, and liver whereas thromboxane A_2 has a cytolytic effect.

1. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995; **75:** 3A–10A.
2. Whittle BJR, Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull* 1983; **39:** 232–8.

Acute respiratory distress syndrome. Encouraging results[1-3] have been seen with inhaled epoprostenol in the treatment of acute respiratory distress syndrome (p.1498).

1. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342:** 961–2.
2. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153:** 991–6.
3. van Heerden PV, *et al.* Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000; **117:** 819–27.

Administration in children. Although epoprostenol is not licensed for the treatment of children, it has been used successfully in children with primary pulmonary hypertension[1,2] and in neonates with persistent pulmonary hypertension of the newborn.[3] It is usually given by continuous intravenous infusion, but in neonates the inhaled[4] and endotracheal[5] routes have also been used.

For children aged 1 month to 18 years with *primary pulmonary hypertension*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, increasing as necessary to 40 nanograms/kg per minute. Children on prolonged treatment can become tolerant to epoprostenol and higher doses have been used.[1,2]

For neonates with *persistent pulmonary hypertension of the newborn*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, adjusted according to response up to a usual maximum of 20 nanograms/kg per minute (rarely up to 40 nanograms/kg per minute).

1. Barst RJ, *et al.* Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999; **99:** 1197–1208.
2. Lammers AE, *et al.* Epoprostenol treatment in children with severe pulmonary hypertension. *Heart* 2007; **93:** 739–43.
3. Eronen M, *et al.* Prostacyclin treatment for persistent pulmonary hypertension of the newborn. *Pediatr Cardiol* 1997; **18:** 3–7.
4. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.
5. De Jaegere APMC, van den Anker JN. Endotracheal instillation of prostacyclin in preterm infants with persistent pulmonary hypertension. *Eur Respir J* 1998; **12:** 932–4.

Heart failure. Epoprostenol has been investigated for the treatment of heart failure but development was abandoned due to an increase in mortality associated with long-term use.[1,2]

1. Phillips BB, Gandhi AJ. Epoprostenol in the treatment of congestive heart failure. *Am J Health-Syst Pharm* 1997; **54:** 2613–15.
2. Califf RM, *et al.* A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; **134:** 44–54.

Peripheral vascular disease. Various prostaglandins including epoprostenol have been used for their vasodilating effect in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy.

References.

1. Szczeklik A, *et al.* Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. *Lancet* 1979; **i:** 1111–14.
2. Belch JJF, *et al.* Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome: a double-blind controlled trial. *Lancet* 1983; **i:** 313–15.
3. Belch JJF, *et al.* Epoprostenol (prostacyclin) and severe arterial disease: a double-blind trial. *Lancet* 1983; **i:** 315–17.
4. De San Lazaro C, *et al.* Prostacyclin in severe peripheral vascular disease. *Arch Dis Child* 1985; **60:** 370–84.
5. Leaker B, *et al.* Treatment of acute renal failure, symmetrical peripheral gangrene, and septicaemia with plasma exchange and epoprostenol. *Lancet* 1987; **i:** 156.
6. Negus D, *et al.* Intra-arterial prostacyclin compared to Praxilene in the management of severe lower limb ischaemia: a double-blind trial. *J Cardiovasc Surg* 1987; **28:** 196–9.

7. Kingma K, *et al.* Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. *J Cardiovasc Pharmacol* 1995; **26:** 388–93.
8. Denton CP, Black CM. Raynaud's phenomenon and scleroderma. In: Snaith ML, ed. *ABC of rheumatology.* 3rd ed. London: BMJ Publishing Group, 2004: 87–91.

Pulmonary hypertension. Epoprostenol was originally introduced into the management of end-stage pulmonary hypertension (p.1179) to sustain patients long enough for them to have heart-lung transplantation. However, long-term therapy may also have a role as an alternative to transplantation; sustained clinical improvement and improved survival have been reported[1-4] in some patients with idiopathic pulmonary arterial hypertension given long-term intravenous therapy using portable infusion pumps, as well as in patients with pulmonary arterial hypertension associated with other diseases.[4-7]

Inhaled epoprostenol, a route that may overcome some of the adverse effects associated with parenteral use, has had some success in adults[8,9] with pulmonary hypertension and in neonates[10,11] with persistent pulmonary hypertension.

1. Higenbottam T, *et al.* Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80:** 151–5.
2. Herner SJ, Mauro LS. Epoprostenol in primary pulmonary hypertension. *Ann Pharmacother* 1999; **33:** 340–7.
3. McLaughlin VV, *et al.* Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106:** 1477–82.
4. Kuhn KP, *et al.* Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; **167:** 580–6.
5. McLaughlin VV, *et al.* Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999; **130:** 740–3.
6. Badesch DB, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 425–34.
7. Fisher KA, *et al.* Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest* 2006; **130:** 1481–8.
8. Olschewski H, *et al.* Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; **124:** 820–4.
9. Mikhail G, *et al.* An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J* 1997; **18:** 1499–1504.
10. Bindl L, *et al.* Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994; **71:** F214–F216.
11. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.

Stroke. Results with epoprostenol in patients with acute stroke have been inconclusive and a systematic review of randomised studies concluded that too few patients had been studied for the effect of epoprostenol on survival to be determined.[1]

1. Bath PMW. Prostacyclin and analogues for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 04/07/05).

Thrombotic microangiopathies. Platelet aggregation has a major role in the pathogenesis of thrombotic thrombocytopenic purpura and the related disorder, haemolytic-uraemic syndrome (p.1076). Prostacyclin deficiency has been demonstrated in both conditions, but case reports of epoprostenol[1,2] or iloprost[3,4] treatment have indicated variable results.

1. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
2. Series C, *et al.* Interet de la prostacycline dans le traitement du syndrome hémolytique et urémique: à propos d'un cas. *Rev Med Interne* 1996; **17:** 76–8.
3. Sagripanti A, *et al.* Iloprost in the treatment of thrombotic microangiopathy: report of thirteen cases. *Biomed Pharmacother* 1996; **50:** 350–6.
4. Salvi F, *et al.* Unsuccessful treatment of resistant thrombotic thrombocytopenic purpura with prostacyclin. *Haematologica* 2000; **85:** 1329–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Flolan; ***Austria:*** Epoallen; Flolan; Glaxoprost; ***Belg.:*** Flolan; ***Canad.:*** Flolan; ***Cz.:*** Flolan; ***Denm.:*** Flolan; ***Fr.:*** Flolan; ***Gr.:*** Flolan; ***Irl.:*** Flolan; ***Israel:*** Flolan; ***Ital.:*** Flolan; ***Neth.:*** Flolan; ***Norw.:*** Flolan; ***Singapore:*** Flolan; ***Spain:*** Flolan; ***Switz.:*** Flolan; ***UK:*** Flolan; ***USA:*** Flolan.

Eprosartan Mesilate *(BANM, rINNM)*

Éprosartan, Mésilate d'; Eprosartan Mesylate *(USAN)*; Eprosartani Mesilas; Mesilato de eprosartán; SKF-108566-J. (*E*)-2-Butyl-1-(*p*-carboxybenzyl)-α-2-thenylimidazole-5-acrylic acid methanesulfonate.

Эпрозартана Мезилат

$C_{23}H_{24}N_2O_4S,CH_4O_3S$ = 520.6.

CAS — 133040-01-4 (eprosartan); 144143-96-4 (eprosartan mesilate).

ATC — C09CA02.

ATC Vet — QC09CA02.

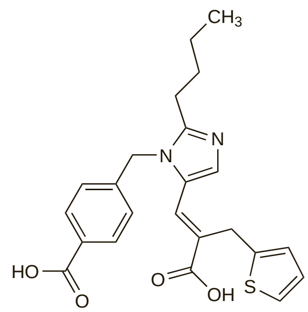

(eprosartan)

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Eprosartan is absorbed from the gastrointestinal tract with an absolute oral bioavailability of about 13%. Peak plasma concentrations occur about 1 to 2 hours after an oral dose in the fasted state; giving doses with food delays absorption but this is not clinically significant. Eprosartan is about 98% bound to plasma proteins. It is excreted in the bile and in the urine, primarily as the unchanged drug; after oral doses approximately 7% of the drug is excreted in the urine, with about 2% as the acyl glucuronide. The terminal elimination half-life is about 5 to 9 hours.

◊ References.

1. Martin DE, *et al.* Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 1998; **38:** 129–37.
2. Tenero DM, *et al.* Effect of age and gender on the pharmacokinetics of eprosartan. *Br J Clin Pharmacol* 1998; **46:** 267–70.

Uses and Administration

Eprosartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171).

Eprosartan is given orally as the mesilate but doses are expressed in terms of the base; eprosartan mesilate 1.2 mg is equivalent to about 1 mg of eprosartan. The onset of antihypertensive effect occurs about 1 to 2 hours after administration and the maximum effect is achieved within 2 to 3 weeks after initiating therapy.

In the management of hypertension, eprosartan is given in an initial dose of 600 mg once daily. A lower initial dose of 300 mg once daily may be used in elderly patients over 75 years and has been recommended in renal or hepatic impairment (but see below). The dose should be adjusted according to response; the usual maintenance dose is 400 to 800 mg daily in a single dose or in two divided doses.

◊ Reviews.

1. McClellan KJ, Balfour JA. Eprosartan. *Drugs* 1998; **55:** 713–18.
2. Plosker GL, Foster RH. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2000; **60:** 177–201.
3. Robins GW, Scott LJ. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2005; **65:** 2355–77.
4. Ram CV, Rudmann MA. Unique dual mechanism of action of eprosartan: effects on systolic blood pressure, pulse pressure, risk of stroke and cognitive decline. *Expert Rev Cardiovasc Ther* 2007; **5:** 1003–11.

Administration in hepatic or renal impairment. In the UK a lower initial dose of 300 mg daily of eprosartan is recommended in patients with renal impairment (creatinine clearance less than 60 mL/minute) or mild to moderate hepatic impairment; this seems to be due to lack of clinical experience in such patients. In the USA, however, no reduction in the initial dose is considered necessary in hepatic or renal impairment, but a maximum dose of 600 mg daily is recommended for patients with moderate or severe renal impairment.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Teveten; ***Austria:*** Teveten; ***Belg.:*** Teveten; ***Canad.:*** Teveten; ***Cz.:*** Teveten; ***Denm.:*** Teveten; ***Fin.:*** Teveten; ***Fr.:*** Teveten; ***Ger.:*** Emestar Mono; Teveten; ***Gr.:*** Epratenz†; Teveten; ***Hong Kong:*** Teveten; ***Hung.:*** Teveten; ***Irl.:*** Teveten; ***Ital.:*** Tevetenz; ***Neth.:*** Teveten; ***Norw.:*** Teveten; ***Philipp.:*** Teveten; ***Pol.:*** Teveten; ***Port.:*** Teveten; ***Rus.:*** Teveten (Теветен); ***S.Afr.:*** Teveten; ***Spain:*** Futuran; Navixen; Regulaten; Tevetens; ***Swed.:*** Teveten; ***Switz.:*** Teveten; ***Thai.:*** Teveten; ***UK:*** Teveten; ***USA:*** Teveten.

Multi-ingredient: ***Austral.:*** Teveten Plus; ***Austria:*** Teveten Plus; ***Belg.:*** Teveten Plus; ***Canad.:*** Teveten Plus; ***Cz.:*** Teveten Plus H; ***Denm.:*** Teveten Comp; ***Fin.:*** Teveten Comp; ***Fr.:*** Coteveten; ***Ger.:*** Emestar plus; Teveten Plus; ***Gr.:*** Teveten Plus; ***Hong Kong:*** Teveten Plus; ***Irl.:*** Teveten Plus; ***Neth.:*** Teveten Plus; ***Norw.:*** Teveten Comp; ***Philipp.:*** Teveten Plus; ***Port.:*** Medinor; Tensival; Teveten Plus; ***Rus.:*** Teveten Plus (Теветен Плюс); ***Spain:*** Futuran Plus; Navixen Plus; Regulaten Plus; Tevetens Plus; ***Swed.:*** Teveten Comp; ***Switz.:*** Teveten Plus; ***USA:*** Teveten HCT.

Eptifibatide *(BAN, rINN)*

C68-22; Eptifibatid; Eptifibatida; Eptifibatidi; Eptifibatidum; Integrelin; SB-1; Sch-60936. N^6-Amidino-N^2-(3-mercaptopropionyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide; S^1,S^6-Cyclo[N^6-carbamimidoyl-N^2-(3-sulfanylpropanoyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide].

Эптифибатид

$C_{35}H_{49}N_{11}O_9S_2$ = 832.0.

CAS — 148031-34-9; 157630-07-4.

ATC — B01AC16.

ATC Vet — QB01AC16.

Adverse Effects

Bleeding is the most common adverse effect of eptifibatide. Hypotension has been reported. Antibodies to eptifibatide have not been detected.

Effects on the blood. Thrombocytopenia is an established adverse effect of the glycoprotein IIb/IIIa-receptor antagonist abciximab (see p.1192) but appears to be less common with eptifibatide. However, there have been several reports[1-5] of severe thrombocytopenia associated with eptifibatide.

1. Paradiso-Hardy FL, *et al.* Severe thrombocytopenia possibly related to readministration of eptifibatide. *Catheter Cardiovasc Interv* 2001; **54:** 63–7.
2. Hongo RH, Brent BN. Association of eptifibatide and acute profound thrombocytopenia. *Am J Cardiol* 2001; **88:** 428–31.
3. Yoder M, Edwards RF. Reversible thrombocytopenia associated with eptifibatide. *Ann Pharmacother* 2002; **36:** 628–30.
4. Coons JC, *et al.* Eptifibatide-associated acute, profound thrombocytopenia. *Ann Pharmacother* 2005; **39:** 368–72.
5. Refaat M, *et al.* Eptifibatide-induced thrombocytopenia. *J Thromb Thrombolysis* 2008; **25:** 204–6.

Precautions

As for Abciximab, p.1192.

Pharmacokinetics

Antiplatelet effects of eptifibatide persist for about 4 hours after stopping a continuous infusion. Plasma elimination half-life is about 2.5 hours. Eptifibatide is about 25% bound to plasma proteins. Renal clearance, as eptifibatide and metabolites excreted in the urine, accounts for about 50% of total body clearance.

Uses and Administration

Eptifibatide is an antiplatelet drug that reversibly inhibits binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the glycoprotein IIb/IIIa receptor of platelets. It is used, usually in combination with aspirin and heparin, in the management of unstable angina and in patients undergoing coronary angioplasty and stenting procedures.

In the management of **unstable angina**, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection, followed by 2 micrograms/kg per minute by intravenous infusion, for up to 72 hours. If percutaneous coronary intervention is performed during eptifibatide therapy, the infusion should be continued for 18 to 24 hours after the procedure, to a maximum total duration of 96 hours of therapy.

In patients undergoing **angioplasty**, though not presenting with unstable angina, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection immediately before the procedure, followed by 2 micrograms/kg per minute by intravenous infusion, with a second 180 micrograms/kg intravenous injection given 10 minutes after the first. The infusion should be continued until hospital discharge or for up to 18 to 24 hours; a minimum of 12 hours is recommended.

The dose of eptifibatide may need to be reduced in patients with renal impairment (see below).

◊ General references.

1. Gilchrist IC. Platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention: focus on the pharmacokinetic-pharmacodynamic relationships of eptifibatide. *Clin Pharmacokinet* 2003; **42:** 703–20.
2. Curran MP, Keating GM. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 2005; **65:** 2009–35.
3. Tricoci P, *et al.* Present and evolving role of eptifibatide in the treatment of acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2007; **5:** 401–12.
4. Zeymer U. The role of eptifibatide in patients undergoing percutaneous coronary intervention. *Expert Opin Pharmacother* 2007; **8:** 1147–54.
5. Zeymer U, Wienbergen H. A review of clinical trials with eptifibatide in cardiology. *Cardiovasc Drug Rev* 2007; **25:** 301–15.

Administration in renal impairment. The clearance of eptifibatide is reduced in renal impairment and plasma-eptifibatide concentrations are about doubled in patients with a creatinine clearance (CC) below 50 mL/minute.[1] Eptifibatide should not be used in severe renal impairment; it is contra-indicated in patients with CC below 30 mL/minute in the UK, and in dialysis-dependent patients in the USA. In patients with moderate renal impairment (CC below 50 mL/minute), the same bolus doses may be given as in those with normal renal function but the infusion dose should be reduced to 1 microgram/kg per minute.

1. Gretler DD, *et al.* Pharmacokinetic and pharmacodynamic properties of eptifibatide in subjects with normal or impaired renal function. *Clin Ther* 2004; **26:** 390–398.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. In patients with *unstable angina* (p.1157), eptifibatide has been used as an adjunct to both medical and interventional therapy. In the PURSUIT study,[1] which compared eptifibatide with placebo in over 10 000 patients with ischaemic chest pain, the incidence of death and non-fatal myocardial infarction up to 30 days after treatment was reduced in those receiving eptifibatide; most patients also received aspirin and heparin and the number of percutaneous interventions was similar in each group.

Eptifibatide has also been of benefit as an adjunct to standard therapy in patients undergoing *elective percutaneous interventions* (see Reperfusion and Revascularisation Procedures, p.1181). In the IMPACT-II study[2] of over 4000 patients undergoing elective or emergency percutaneous coronary revascularisation, the incidence of death, myocardial infarction, and further unplanned coronary intervention was reduced in those receiving eptifibatide compared with placebo. Similar results were also obtained in a further study (ESPRIT)[3] in patients who were undergoing percutaneous coronary revascularisation with stent implantation, and benefit was maintained at 6-month follow-up.[4] Although most studies have given eptifibatide with unfractionated heparin, use with low-molecular-weight heparin also appears to be safe.[5]

In patients with *acute myocardial infarction* (p.1175), eptifibatide has been tried as an adjunct to thrombolysis or percutaneous intervention. In a study (INTRO AMI)[6] comparing eptifibatide and thrombolysis with thrombolysis alone, early patency rates were improved in those receiving eptifibatide but there was no significant difference in outcomes at 30 days. In patients undergoing interventional therapy, an observational study[7] found that eptifibatide was less effective than abciximab, but other studies[8,9] have reported similar outcomes in patients treated with abciximab or eptifibatide. Positive results have also been seen[10] with eptifibatide given in addition to thrombolytics before percutaneous intervention.

There have been reports of successful intracoronary use[11] of eptifibatide, and also prolonged intravenous use[12] in a patient unable to take oral antiplatelet drugs.

1. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339:** 436–43.
2. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; **349:** 1422–8.
3. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000; **356:** 2037–44. Correction. *ibid.* 2001; **357:** 1370.
4. O'Shea JC, *et al.* Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT Trial: a randomized controlled trial. *JAMA* 2001; **285:** 2468–73.
5. Bhatt DL, *et al.* Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol* 2003; **41:** 20–5.
6. Brener SJ, *et al.* Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol* 2002; **39:** 377–86.
7. Deliargyris EN, *et al.* Superior in-hospital and 30-day outcomes with abciximab versus eptifibatide: a contemporary analysis of 495 consecutive percutaneous coronary interventions. *J Invasive Cardiol* 2004; **16:** 611–16.
8. Suleiman M, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, eptifibatide and abciximab: outcomes, complications and thrombocytopenia during percutaneous coronary intervention. *J Invasive Cardiol* 2003; **15:** 319–23.
9. Raveendran G, *et al.* Eptifibatide vs abciximab as adjunctive therapy during primary percutaneous coronary intervention for acute myocardial infarction. *Mayo Clin Proc* 2007; **82:** 196–202.
10. ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. *Am Heart J* 2005; **150:** 116–22. Correction. *ibid.*; 391.
11. Deibele AJ, *et al.* Intracoronary bolus administration of eptifibatide during percutaneous coronary stenting for non ST elevation myocardial infarction and unstable angina. *J Thromb Thrombolysis* 2006; **22:** 47–50.
12. Jaffe R, *et al.* Prolonged intravenous eptifibatide infusion for prevention of coronary stent thrombosis. *Int J Cardiol* 2007; **114:** 409–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Integrilin; ***Belg.:*** Integrilin; ***Canad.:*** Integrilin; ***Chile:*** Integrilin†; ***Cz.:*** Integrilin; ***Denm.:*** Integrilin; ***Fin.:*** Integrilin; ***Fr.:*** Integrilin; ***Ger.:*** Integrilin; ***Gr.:*** Integrilin; ***Hong Kong:*** Integrilin; ***Hung.:*** Integrilin; ***Irl.:*** Integrilin; ***Israel:*** Integrilin; ***Ital.:*** Integrilin; ***Malaysia:*** Integrilin; ***Neth.:*** Integrilin; ***Norw.:*** Integrilin; ***NZ:*** Integrilin; ***Philipp.:*** Integrilin; ***Pol.:*** Integrilin; ***Port.:*** Integrilin; ***Rus.:*** Integrilin (Интегрилин); ***S.Afr.:*** Integrilin; ***Singapore:*** Integrilin; ***Spain:*** Integrilin; ***Swed.:*** Integrilin; ***Switz.:*** Integrilin; ***Thai.:*** Integrilin; ***UK:*** Integrilin; ***USA:*** Integrilin.

Eritrityl Tetranitrate *(rINN)*

Érititryle, Tétranitrate d'; Eritrityli Tetranitras; Eritrityltetranitrat; Eritrityylitetranitraatti; Erythritol Tetranitrate; Erythrityl Tetranitrate *(USAN)*; Erythrol Nitrate; Erythrol Tetranitrate; Nitroerythrite; Nitroerythrol; NSC-106566; Tetranitrato de eritritilo; Tetranitrol. Butane-1,2,3,4-tetrol tetranitrate.

Эритритила Тетранитрат

$C_4H_6(NO_3)_4 = 302.1.$

CAS — 7297-25-8.

ATC — C01DA13.

ATC Vet — QC01DA13.

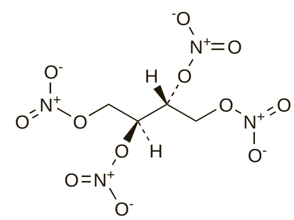

Profile

Eritrityl tetranitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296). It has been used in angina pectoris.

Diluted eritrityl tetranitrate is a mixture of eritrityl tetranitrate and lactose or other suitable inert excipients, the excipients being added to minimise the risk of explosion.

Handling. Undiluted eritrityl tetranitrate can be exploded by percussion or excessive heat.

Esatenolol *(rINN)* ⊗

(−)-Atenolol; *S*-Atenolol; Ésaténolol; Esatenololum. 2-{*p*-[(2*S*)-2-Hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide.

Эзатенолол

$C_{14}H_{22}N_2O_3 = 266.3.$

CAS — 93379-54-5.

ATC — C07AB11.

ATC Vet — QC07AB11.

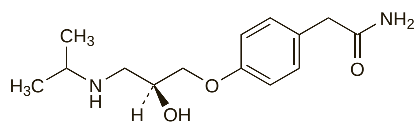

Profile

Esatenolol, the *S*(−)-isomer of atenolol, has been used similarly to atenolol (p.1217) in the treatment of cardiovascular disorders in usual oral doses of 25 to 100 mg daily.

◊ References.

1. McCoy RA, *et al.* Pharmacodynamics of racemic and S(-)-atenolol in humans. *J Clin Pharmacol* 1994; **34:** 816–22.
2. Clementi WA, *et al.* Single dose pharmacokinetics of (S)-atenolol administered orally as a single enantiomer formulation and as a racemic mixture (Tenormin). *Chirality* 1994; **6:** 169–74.

Esmolol Hydrochloride

(BANM, USAN, rINNM) ⊗

ASL-8052; Esmolol, Chlorhydrate d'; Esmolol Hidroklorür; Esmololi Hydrochloridum; Hidrocloruro de esmolol. Methyl 3-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]propionate hydrochloride.

Эсмолола Гидрохлорид

$C_{16}H_{25}NO_4,HCl = 331.8.$

CAS — 81147-92-4 (esmolol); 84057-94-3 (esmolol); 103598-03-4 (esmolol); 81161-17-3 (esmolol hydrochloride).

ATC — C07AB09.

ATC Vet — QC07AB09.

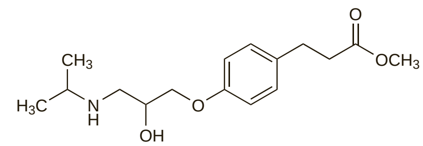

(esmolol)

Incompatibility. Licensed product information advises against admixture of esmolol hydrochloride with sodium bicarbonate because of incompatibility. There has also been a report[1] of immediate haze formation after admixture of esmolol hydrochloride with warfarin sodium.

1. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Hypotension is the most frequently reported adverse effect associated with the infusion of esmolol hydrochloride; it generally resolves within 30 minutes once the dosage is reduced or the infusion is stopped. Local irritation at the site of infusion, inflammation, induration, and thrombophlebitis have occurred and necrosis is a hazard of extravasation. These local effects have occurred with concentrations of 20 mg/mL and it is recommended that concentrations of standard formulations should not normally exceed 10 mg/mL, particularly if given peripherally, and that the infusion should not be made into a small vein.

Effects on the CNS. Generalised tonic-clonic seizures occurred in an elderly patient given esmolol hydrochloride.[1]

1. Das G, Ferris JC. Generalized convulsions in a patient receiving ultra short-acting beta-blocker infusion. *Drug Intell Clin Pharm* 1988; **22:** 484–5.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

After intravenous doses esmolol is rapidly hydrolysed by esterases in the red blood cells. Steady-state blood concentrations are reached within 30 minutes with doses of 50 to 300 micrograms/kg per minute. The time to steady state may be reduced to 5 minutes by giving an appropriate loading dose. Blood concentrations decline in a biphasic manner with a distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Esmolol has low lipid solubility and is about 55% bound to plasma proteins. It is excreted in urine, primarily as the de-esterified metabolite.

Uses and Administration

Esmolol is a cardioselective short-acting beta blocker (p.1225). It is reported to be lacking in intrinsic sympathomimetic and membrane-stabilising properties.

Esmolol is used as the hydrochloride in the management of supraventricular arrhythmias (p.1160). It is also used for the control of hypertension (p.1171) and tachycardia during the perioperative period.

Esmolol hydrochloride is given intravenously at a concentration usually not exceeding 10 mg/mL.

For the rapid temporary control of ventricular rate in patients with **supraventricular arrhythmias**, a loading dose of 500 micrograms/kg given over 1 minute is followed by an initial maintenance infusion of 50 micrograms/kg per minute for 4 minutes. If the response is satisfactory this maintenance infusion should be continued at 50 micrograms/kg per minute. If a suitable response is not obtained within the first 5 minutes a further loading dose of 500 micrograms/kg over 1 minute may be given and the maintenance infusion may be increased to 100 micrograms/kg per minute for 4 minutes. If necessary, this procedure may be repeated once or twice more, until a satisfactory response is obtained, increasing the maintenance infusion each time by 50 micrograms/kg per minute to a maximum of 200 micrograms/kg per minute. Little additional benefit is obtained from further increases in maintenance dosage. Once a satisfactory response is obtained infusion may be continued, if necessary, for up to 48 hours.

When transferring a patient to another antiarrhythmic drug, the infusion rate of esmolol hydrochloride is reduced by 50% thirty minutes after starting the alternative drug, and may be stopped one hour after the second dose of that drug.

In the control of perioperative **hypertension** and/or **tachycardia**, esmolol hydrochloride may be given intravenously as follows:

- *during* anaesthesia, a loading dose of 80 mg over 15 to 30 seconds followed by an infusion of 150 micrograms/kg per minute, increased as necessary up to 300 micrograms/kg per minute
- on *waking* from anaesthesia, an infusion of 500 micrograms/kg per minute for 4 minutes, followed by an infusion of 300 micrograms/kg per minute as required
- *postoperatively*, a stepped dosage schedule, as described under control of supraventricular arrhythmias above, although maintenance infusions may be increased up to 300 micrograms/kg per minute as necessary.

◊ References.

1. Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet* 1995; **28:** 190–202.

Tetralogy of Fallot. Beta blockers have been used in the management of tetralogy of Fallot (see under Uses of Propranolol, p.1381). The *BNFC* recommends that neonates may be given esmolol hydrochloride in an initial dose of 600 micrograms/kg by intravenous injection over 1 to 2 minutes; if necessary, this may be followed by an intravenous infusion at a dose of 300 to 900 micrograms/kg per minute.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Brevibloc†; Dublon; ***Austral.:*** Brevibloc; ***Austria:*** Brevibloc; ***Belg.:*** Brevibloc; ***Braz.:*** Brevibloc; ***Canad.:*** Brevibloc; ***Cz.:*** Brevibloc; ***Denm.:*** Brevibloc; ***Fin.:*** Brevibloc; ***Fr.:*** Brevibloc†; ***Ger.:*** Brevibloc; ***Gr.:*** Brevibloc; ***Hong Kong:*** Brevibloc†; ***Hung.:*** Brevibloc; ***India:*** Miniblock; ***Irl.:*** Brevibloc; ***Israel:*** Brevibloc†; ***Ital.:*** Brevibloc; ***Malaysia:*** Brevibloc†; ***Mex.:*** Brevibloc†; ***Neth.:*** Brevibloc; ***NZ:*** Brevibloc; ***Port.:*** Brevibloc; ***S.Afr.:*** Brevibloc; ***Singapore:*** Brevibloc†; ***Spain:*** Brevibloc; ***Swed.:*** Brevibloc; ***Switz.:*** Brevibloc; ***Turk.:*** Brevibloc; ***UK:*** Brevibloc; ***USA:*** Brevibloc.

Etacrynic Acid *(BAN, rINN)* ⊗

Acide étacrynique; Ácido etacrínico; Acidum etacrynicum; Etacrynsäure; Etakrino rūgštis; Etakrinsav; Etakrynsyra; Etakryynihappo; Ethacrynic Acid *(USAN)*; Kwas etakrynowy; Kyselina etakrynová; MK-595; NSC-85791. [2,3-Dichloro-4-(2-ethylacryloyl)phenoxy]acetic acid; [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid.

Этакриновая Кислота

$C_{13}H_{12}Cl_2O_4$ = 303.1.
CAS — 58-54-8.
ATC — C03CC01.
ATC Vet — QC03CC01.

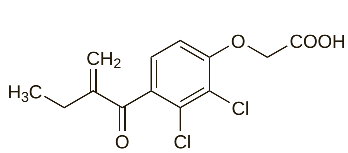

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Etacrynic Acid). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol. It dissolves in ammonia and in dilute solutions of alkali hydroxides and carbonates.

USP 31 (Ethacrynic Acid). A white or practically white, odourless or practically odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 1.6 of alcohol, 1 in 6 of chloroform, and 1 in 3.5 of ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Sodium Etacrynate *(BANM, rINNM)* ⊗

Etacrinato sódico; Étacrynate de Sodium; Etacrynate Sodium; Ethacrynate Sodium *(USAN)*; Natrii Etacrynas; Sodium Ethacrynate.

Натрий Этакринат

$C_{13}H_{11}Cl_2NaO_4$ = 325.1.
CAS — 6500-81-8.
ATC — C03CC01.
ATC Vet — QC03CC01.

Pharmacopoeias. In *Chin.*
Pol. and *US* include sodium etacrynate for injection.

Stability. Solutions in water of sodium etacrynate containing the equivalent of etacrynic acid 0.1% have a pH of 6.3 to 7.7. Solutions are relatively stable at about pH 7 at room temperatures for short periods and less stable at higher pH values and temperatures. They are incompatible with solutions with a pH below 5. The injection should be protected from light.

Adverse Effects

As for Furosemide, p.1292. Gastrointestinal disturbances may be more common and severe with etacrynic acid; profuse watery diarrhoea is an indication for stopping therapy. Gastrointestinal bleeding has been associated with etacrynic acid. Tinnitus and deafness, particularly after high parenteral doses, may also be more common. Other adverse effects include confusion, fatigue, nervousness, and apprehension. Haematuria has been reported rarely.

Local irritation and pain may follow intravenous injection.

Effects on carbohydrate metabolism. Although etacrynic acid is generally considered to have less pronounced effects on carbohydrate metabolism than furosemide or the thiazide diuretics, adverse effects have been reported. Reductions in glucose tolerance[1] after etacrynic acid 200 mg daily for 6 weeks were similar to those produced by hydrochlorothiazide 200 mg daily. The effect was most pronounced in diabetic patients. Hyperosmolar hyperglycaemic coma[2] and symptomatic hypoglycaemia with convulsions[3] have been reported in patients receiving high doses of etacrynic acid.

1. Russell RP, *et al.* Metabolic and hypotensive effects of ethacrynic acid: comparative study with hydrochlorothiazide. *JAMA* 1968; **205:** 11–16.
2. Cowley AJ, Elkeles RS. Diabetes and therapy with potent diuretics. *Lancet* 1978; **i:** 154.
3. Maher JF, Schreiner GE. Studies on ethacrynic acid in patients with refractory edema. *Ann Intern Med* 1965; **62:** 15–29.

Effects on the ears. Drug-induced deafness occurred in 2 of 184 patients given etacrynic acid intravenously.[1,2] Deafness accompanied by nystagmus was reported in a patient[3] after an intravenous infusion of etacrynic acid. Symptoms resolved within 1 hour. He had previously been taking furosemide and etacrynic acid orally.

1. Boston Collaborative Drug Surveillance Program. Drug-induced deafness: a cooperative study. *JAMA* 1973; **224:** 515–16.
2. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; **i:** 587–8.
3. Gomolin IH, Garshick E. Ethacrynic acid-induced deafness accompanied by nystagmus. *N Engl J Med* 1980; **303:** 702.

Precautions

Etacrynic acid's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Etacrynic acid, especially in the form of dust, is irritating to the skin, eyes, and mucous membranes.

Interactions

As for Furosemide, p.1293. The risks of gastrointestinal bleeding may be enhanced by use of etacrynic acid with other gastric irritants or with anticoagulants.

Anticoagulants. For reference to the interaction between *warfarin* and etacrynic acid, see p.1430.

Pharmacokinetics

Etacrynic acid is fairly rapidly absorbed from the gastrointestinal tract. The plasma half-life is 30 to 60 minutes. It is excreted both in the bile and the urine, partly unchanged and partly in the form of metabolites. It is extensively bound to plasma proteins.

Uses and Administration

Although chemically unrelated, etacrynic acid is a loop diuretic with actions and uses similar to those of furosemide (p.1294). Etacrynic acid is used in the treatment of oedema associated with heart failure (p.1165) and with renal and hepatic disorders.

Diuresis begins within about 30 minutes after an oral dose, and lasts for about 6 to 8 hours; after intravenous injection of its sodium salt, the effects are evident within a few minutes and last for about 2 hours.

In the treatment of **oedema**, the usual initial oral dose is 50 mg in the morning. The dose may be increased, if necessary, by 25- to 50-mg increments daily to the minimum effective dose. Severe cases have required gradual titration of the dose up to a maximum of 400 mg daily, but the effective range is usually between 50 and 150 mg daily. Dosage of more than 50 mg daily should be given in divided doses. All doses should be taken with food. Maintenance doses may be taken daily or intermittently.

In emergencies, such as acute pulmonary oedema, or when oral therapy cannot be given, etacrynic acid may be given intravenously. It is given as its salt, sodium etacrynate, but doses are expressed in terms of the acid. 10.7 mg of sodium etacrynate is equivalent to about 10 mg of etacrynic acid. The usual dose is 50 mg, or 0.5 to 1 mg/kg, as a 1 mg/mL solution in glucose 5% (provided the pH is above 5) or sodium chloride 0.9%, given by slow intravenous injection either directly or into the tubing of a running infusion. Should a subsequent injection be required the site should be changed to avoid thrombophlebitis. Single doses of 100 mg have been given intravenously in critical situations. It is not suitable for subcutaneous or intramuscular injection.

For children over 2 years of age an initial dose of etacrynic acid is 25 mg daily by mouth, cautiously increased as necessary by 25 mg daily.

If very high doses of etacrynic acid are used careful laboratory control is essential as described for furosemide (p.1294; high-dose therapy).

Preparations

BP 2008: Sodium Etacrynate Injection;
USP 31: Ethacrynate Sodium for Injection; Ethacrynic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Edecrin; ***Austria:*** Edecrin; ***Canad.:*** Edecrin; ***Cz.:*** Uregyt†; ***Ger.:*** Hydromedin†; ***Hung.:*** Uregyt; ***Ital.:*** Reomax; ***Rus.:*** Uregyt (Урегит); ***Swed.:*** Edecrina†; ***USA:*** Edecrin.

Etafenone Hydrochloride *(rINNM)*

Étafénone, Chlorhydrate d'; Etafenoni Hydrochloridum; Hidrocloruro de etafenona; LG-11457. 2′-(2-Diethylaminoethoxy)-3-phenylpropiophenone hydrochloride.

Этафенона Гидрохлорид

$C_{21}H_{27}NO_2$,HCl = 361.9.
CAS — 90-54-0 (etafenone); 2192-21-4 (etafenone hydrochloride).
ATC — C01DX07.
ATC Vet — QC01DX07.

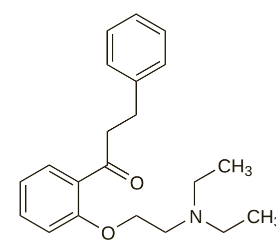

(etafenone)

Profile

Etafenone hydrochloride is a vasodilator that has been used in ischaemic heart disease.

Ethacizine

Aethacizin; Etacizin; Ethacizin; Ethacyzin; EZ-55; NIK-244. Ethyl 10-[3-(diethylamino)propionyl]phenothiazine-2-carbamate.

Этацизин

$C_{22}H_{27}N_3O_3S$ = 413.5.
CAS — 33414-33-4 (ethacizine); 57530-40-2 (ethacizine hydrochloride).

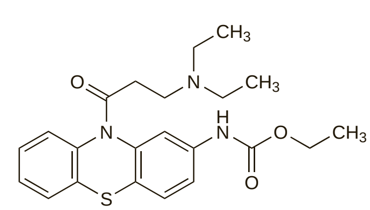

Profile

Ethacizine, an analogue of moracizine (p.1344), is reported to be a class Ic antiarrhythmic. It is used in the treatment of ventricular and supraventricular arrhythmias and has been given orally in doses starting at 50 mg three times daily, increased if necessary to a maximum of 100 mg three times daily. It has also been given intravenously.

Ethyl Biscoumacetate *(BAN, rINN)*

Aethylis Biscoumacetas; Biscumacetato de etilo; Ethyldicoumarol; Éthyle, Biscoumacétate d'; Ethylis Biscoumacetas; Neodicumarinum. Ethyl bis(4-hydroxycoumarin-3-yl)acetate.

Этил Бискумацетат

$C_{22}H_{16}O_8$ = 408.4.
CAS — 548-00-5.
ATC — B01AA08.
ATC Vet — QB01AA08.

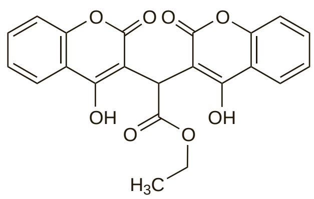

Profile

Ethyl biscoumacetate is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It has been used in the management of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Pelentan†; Pelentanettae†.

Etilefrine Hydrochloride *(BANM, rINNM)* ⊗

Ethyladrianol Hydrochloride; Ethylnorphenylephrine Hydrochloride; Etilefriinihydrokloridi; Étiléfrine, chlorhydrate d'; Etilefrin-hidroklorid; Etilefrin-hydrochlorid; Etilefrinhydroklorid; Etilefrini hydrochloridum; Etilefrino hidrochloridas; Hidrocloruro de etilefrina; M-I-36. 2-Ethylamino-1-(3-hydroxyphenyl)ethanol hydrochloride.

Этилэфрина Гидрохлорид

$C_{10}H_{15}NO_2,HCl$ = 217.7.
CAS — 709-55-7 (etilefrine); 943-17-9 (etilefrine hydrochloride).
ATC — C01CA01.
ATC Vet — QC01CA01.

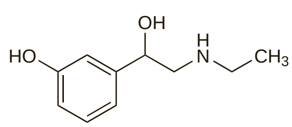

(etilefrine)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Etilefrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Etilefrine is a direct-acting sympathomimetic (p.1407) with $beta_1$-agonist properties, and some alpha- and $beta_2$-agonist actions. It is used for the treatment of hypotensive states (p.1174). It is given orally as the hydrochloride in usual doses of 5 or 10 mg three times daily; modified-release dosage forms may be given in doses of 25 mg once or twice daily. Etilefrine hydrochloride can also be given parenterally.

Etilefrine polistirex has been used in the management of rhinitis.

Priapism. Priapism is a common complication of sickle-cell disease (p.1044) and is often treated with intracavernosal alpha agonists (see under Uses of Metaraminol, p.1333). There have also been reports of the successful use of etilefrine, both by intracavernosal injection for acute treatment,[1,2] and orally for prophylaxis.[1-3]

1. Virag R, *et al.* Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine. *Urology* 1996; **47:** 777–81.
2. Gbadoé AD, *et al.* Management of sickle cell priapism with etilefrine. *Arch Dis Child* 2001; **85:** 52–3.
3. Okpala I, *et al.* Etilefrine for the prevention of priapism in adult sickle cell disease. *Br J Haematol* 2002; **118:** 918–21.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Corcanfol†; Effortil; Etil Adrianol†; Menegradil†; ***Austria:*** Agilo†; Circupon; Effortil; ***Belg.:*** Effortil; ***Braz.:*** Efortil; Etilefril; ***Chile:*** Effortil; ***Fin.:*** Effortil; ***Fr.:*** Effortil; ***Ger.:*** Adrenam†; Bioflutin; Cardanat; Cardialgine†; Circuvit E†; Effortil†; Eti-Puren†; Etil; Pholdyston; Thomasin; ***Gr.:*** Effortil; ***Ital.:*** Effortil; ***Jpn:*** Effortil; ***Mex.:*** Effortil; ***Norw.:*** Effortil†; ***Pol.:*** Effortil; ***Port.:*** Effortil; ***S.Afr.:*** Effortil; ***Spain:*** Efortil; ***Swed.:*** Effortil; ***Switz.:*** Effortil; ***Thai.:*** Effortil; Efxine†; Hyprosia; ***Venez.:*** Effontil.

Multi-ingredient: ***Austria:*** Agilan; Amphodyn; Effortil comp; Hypodyn; Influbene; ***Ger.:*** Agit plus†; Amphodyn†; Dihydergot plus; Effortil plus; Ergolefrin; Ergomimet plus†; ***Switz.:*** Dihydergot plus; Effortil plus.

Etofibrate *(rINN)*

Étofibrate; Etofibrato; Etofibratum. 2-Nicotinoyloxyethyl 2-(4-chlorophenoxy)-2-methylpropionate.

Этофибрат

$C_{18}H_{18}ClNO_5$ = 363.8.
CAS — 31637-97-5.
ATC — C10AB09.
ATC Vet — QC10AB09.

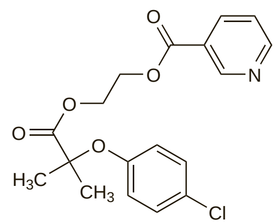

Profile

Etofibrate, a derivative of clofibrate (p.1246) and nicotinic acid (p.1957), is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 500 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Lipo-Merz; ***Braz.:*** Tricerol; ***Chile:*** Lipo-Merz†; ***Ger.:*** Lipo-Merz; ***Hong Kong:*** Lipo-Merz; ***Malaysia:*** Lipo-Merz†; ***Mex.:*** Tricerol†; ***Port.:*** Lipo-Merz; ***Singapore:*** Lipo-Merz†; ***Switz.:*** Lipo-Merz.

Etofylline Clofibrate *(rINN)*

Clofibrato de etofilina; Étofylline, Clofibrate d'; Etofyllini Clofibras; ML-1024; Theofibrate *(USAN)*. 2-(Theophyllin-7-yl)ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

Этофиллина Клофибрат

$C_{19}H_{21}ClN_4O_5$ = 420.8.
CAS — 54504-70-0.

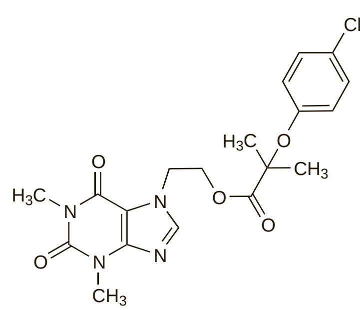

Profile

Etofylline clofibrate, a fibric acid derivative (see Bezafibrate, p.1232), is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 250 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Duolip; ***Cz.:*** Duolip; ***Ger.:*** Duolip; ***Hong Kong:*** Duolip; ***Malaysia:*** Duolip†; ***Switz.:*** Duolip†.

Etozolin *(USAN, rINN)* ⊗

Etozolina; Étozoline; Etozolinum; Gö-687; W-2900A. Ethyl (3-methyl-4-oxo-5-piperidinothiazolidin-2-ylidene)acetate.

Этозолин

$C_{13}H_{20}N_2O_3S$ = 284.4.
CAS — 73-09-6.
ATC — C03CX01.
ATC Vet — QC03CX01.

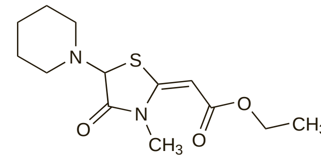

Profile

Etozolin is a loop diuretic with properties similar to those of furosemide (p.1292), but with a longer duration of action. It has been used in the treatment of oedema and hypertension (p.1171). Etozolin is reported to be rapidly metabolised to ozolinone which also has diuretic activity.

◊ References.

1. Knauf H, *et al.* Pharmacodynamics and kinetics of etozolin/ozolinone in hypertensive patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; **26:** 687–93.
2. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Elkapin†.

Ezetimibe *(BAN, USAN, rINN)*

Ezetimiba; Ézétimibe; Ezetimibum; Sch-58235. (3*R*,4*S*)-1-(*p*-Fluorophenyl)-3-[(3*S*)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone.

Эзетимиб

$C_{24}H_{21}F_2NO_3$ = 409.4.
CAS — 163222-33-1.
ATC — C10AX09.
ATC Vet — QC10AX09.

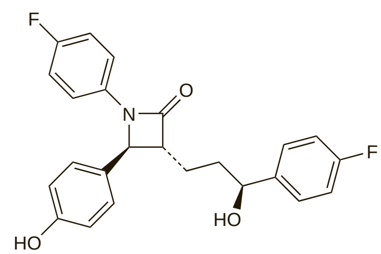

Adverse Effects and Precautions

Ezetimibe is generally well tolerated. The most common adverse effects include headache, abdominal pain, and diarrhoea; other gastrointestinal disorders, hypersensitivity reactions including rash and angioedema, fatigue, chest pain, and arthralgia have also been reported. Rare adverse effects include raised liver enzymes or hepatitis, pancreatitis, thrombocytopenia, cholelithiasis, and cholecystitis. Myalgia has occurred in patients taking ezetimibe either alone or when added to a statin (see below). Ezetimibe should be stopped if myopathy is suspected or creatine phosphokinase increases significantly.

Ezetimibe should be avoided in patients with moderate or severe hepatic impairment.

◊ Reviews.

1. Jacobson TA, *et al.* Safety considerations with gastrointestinally active lipid-lowering drugs. *Am J Cardiol* 2007; **99** (Issue 6 suppl 1): 47C–55C.
2. Kashani A, *et al.* Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. *Am J Cardiol* 2008; **101:** 1606–13.

Effects on the liver. Ezetimibe may cause an increase in liver enzymes and there have also been reports of acute hepatitis,[1] sometimes developing after addition of ezetimibe to long-term statin therapy.[2,3] Both auto-immune[2,3] and cholestatic hepatitis[3] have been described. In some patients,[1,2] symptoms resolved and liver enzymes normalised when ezetimibe was stopped, and in 1 patient a statin was successfully restarted.[2] However, of 2 patients who had been receiving ezetimibe and atorvastatin, 1 required treatment with corticosteroids,[3] while the other[3] had persistent liver changes 4 months later, despite both drugs being stopped in each case.

1. Liu Q, *et al.* Drug-induced liver injury associated with ezetimibe therapy. *Dig Dis Sci* 2007; **52:** 602–5.

2. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. *Ann Clin Biochem* 2005; **42:** 402–4.
3. Stolk MF, *et al.* Severe hepatic side effects of ezetimibe. *Clin Gastroenterol Hepatol* 2006; **4:** 908–11.

Effects on the pancreas. Pancreatitis has been reported[1] in patients taking ezetimibe. In one case,[2] acute pancreatitis developed 2 weeks after starting ezetimibe and resolved when the drug was stopped, suggesting an immunological cause.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 30/05/08)
2. Ahmad I, *et al.* Ezetimibe-induced acute pancreatitis. *South Med J* 2007; **100:** 409–10.

Effects on skeletal muscle. Muscle disorders such as myalgia and myopathy are well known to occur with lipid regulating drugs such as statins and fibrates and have also been reported with ezetimibe, both alone,[1,2] and when added to treatment with statins;[1,3] rhabdomyolysis has also occurred, but is rare in patients taking ezetimibe alone. Up to August 2005, the Australian Adverse Drug Reactions Advisory Committee[4] had received 44 reports of muscle disorders with ezetimibe, including myalgia, muscle cramp, weakness and pain; in 5 of these cases a statin was also being taken.

1. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006; **22:** 141–4.
2. Havranek JM, *et al.* Monotherapy with ezetimibe causing myopathy. *Am J Med* 2006; **119:** 285–6.
3. Fux R, *et al.* Ezetimibe and statin-associated myopathy. *Ann Intern Med* 2004; **140:** 671–2.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Ezetimibe and muscle disorders. *Aust Adverse Drug React Bull* 2005; **24:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 30/05/08)

Interactions

Colestyramine reduces the absorption of ezetimibe and should not be given at the same time of day. Ciclosporin has been reported to increase the plasma concentration of ezetimibe (see below) and patients receiving both drugs should be carefully monitored; the effect may be greater in patients with severe renal impairment. An increased INR has been reported in patients given ezetimibe and oral anticoagulants.

Ciclosporin. Pharmacokinetic studies[1] have shown that plasma-ezetimibe concentrations are higher in renal transplant patients taking ciclosporin than in historical controls, and there has been a report[2] of a supratherapeutic response to ezetimibe in a heart transplant patient taking ciclosporin. Ezetimibe causes a small increase in plasma-ciclosporin concentrations,[3] but the clinical relevance of this is not clear.

1. Bergman AJ, *et al.* Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. *J Clin Pharmacol* 2006; **46:** 328–36.
2. Koshman SL, *et al.* Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005; **39:** 1561–5.
3. Bergman AJ, *et al.* Effects of ezetimibe on cyclosporine pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2006; **46:** 321–7.

Pharmacokinetics

Ezetimibe is rapidly absorbed when given orally and undergoes extensive conjugation in the small intestine and liver to an active glucuronide metabolite, which is the main circulating form. Both ezetimibe and the glucuronide are more than 90% bound to plasma proteins. Ezetimibe is excreted primarily in the faeces via bile and undergoes enterohepatic recycling; after an oral dose, about 78% is excreted in the faeces, mainly as ezetimibe, and about 11% is excreted in the urine, mainly as the glucuronide. The elimination half-life for both ezetimibe and the glucuronide is about 22 hours. Ezetimibe is distributed into breast milk in *rats*.

◊ Reviews

1. Kosoglou T, *et al.* Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; **44:** 467–94.

Uses and Administration

Ezetimibe is an inhibitor of intestinal sterol absorption and inhibits the absorption of cholesterol and plant sterols. It is used to reduce total cholesterol, low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B in the management of hyperlipidaemias (below), and to reduce sitosterol and campesterol in patients with homozygous familial sitosterolaemia. It is given orally in a usual dose of 10 mg once daily.

◊ Reviews.

1. Sudhop T, von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; **62:** 2333–47.
2. Mauro VF, Tuckerman CE. Ezetimibe for management of hypercholesterolemia. *Ann Pharmacother* 2003; **37:** 839–48.

Hyperlipidaemias. Ezetimibe inhibits the absorption of dietary cholesterol[1] and, although there is a compensatory increase in cholesterol synthesis in the liver,[1] overall plasma LDL-cholesterol concentrations are reduced.[2] Ezetimibe may be used alone in the management of hyperlipidaemias (p.1169) but use with lipid regulating drugs that act by reducing cholesterol synthesis may produce additive effects. In patients already taking statins, addition of ezetimibe results in a further reduction in LDL-cholesterol,[3] which may increase the number of patients achieving lipid targets, or allow lower doses of statins to be used. However, the clinical relevance of this is unclear; a study[4] in patients with familial hypercholesterolaemia found no difference in the progression of carotid atherosclerosis (measured by intima-media thickness) in those given ezetimibe with simvastatin compared with those given simvastatin alone, despite a larger reduction in LDL-cholesterol. Similar effects on LDL-cholesterol have been reported[5] for ezetimibe with fibrates.

As well as inhibiting cholesterol absorption, ezetimibe also blocks the absorption of plant sterols such as campesterol and sitosterol, and may be effective in patients with sitosterolaemia,[6] an inherited disorder in which increased absorption of plant sterols leads to premature atherosclerosis.

1. Sudhop T, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002; **106:** 1943–8.
2. Knopp RH, *et al.* Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003; **24:** 729–41.
3. Pearson TA, *et al.* A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005; **80:** 587–95.
4. Kastelein JJP, *et al.* The ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; **358:** 1431–43.
5. McKenney JM, *et al.* Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* 2006; **47:** 1584–7.
6. Salen G, *et al.* Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004; **109:** 966–71.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acotral; Alin; Alipas; Cerclerol; Cetrakam; Coracil; Ezetrol; Ixacor; Lipimibe; Nalecol; Sinterol; Trilip; Vadel; Zetia; ***Austral.:*** Ezetrol; ***Austria:*** Ezetrol; ***Belg.:*** Ezetrol; ***Braz.:*** Ezetrol; Zetia; ***Canad.:*** Ezetrol; ***Chile:*** Ezetrol; Zient; ***Cz.:*** Ezetrol; Zient; ***Denm.:*** Ezetrol; ***Fin.:*** Ezetrol; ***Fr.:*** Ezetrol; ***Ger.:*** Ezetrol; ***Gr.:*** Ezetrol; ***Hong Kong:*** Ezetrol; ***Hung.:*** Ezetrol; ***India:*** Ezetib; Ezzicad†; Imbibe; ***Indon.:*** Ezetrol; ***Irl.:*** Ezetrol; ***Israel:*** Ezetrol; ***Malaysia:*** Ezetrol; ***Mex.:*** Ezetrol; Zient; ***Neth.:*** Ezetrol; ***Norw.:*** Ezetrol; ***NZ:*** Ezetrol; ***Philipp.:*** Ezetrol; ***Port.:*** Ezetrol; ***Rus.:*** Ezetrol (Эзетрол); ***S.Afr.:*** Ezetrol; ***Singapore:*** Ezetrol; ***Spain:*** Ezetrol; ***Swed.:*** Ezetrol; ***Switz.:*** Ezetrol; ***Thai.:*** Ezetrol; ***UK:*** Ezetrol; ***USA:*** Zetia; ***Venez.:*** Ezetrol; Zetia; Zient.

Multi-ingredient: ***Arg.:*** Alipas Duo; Ampliar Duo; Ateroclar Duo; Labistatin Duo; Liparex Duo; Lipibec Duo; Liponorm Duo; Redusterol Duo; Torimibe; Vasotenal EZ; Vytorin; ***Austral.:*** Vytorin; ***Austria:*** Inegy; Vytorin; ***Braz.:*** Vytorin; Zetsim; ***Chile:*** Adacai; Vytorin; Zintrepid; ***Cz.:*** Inegy; ***Fr.:*** Inegy; ***Ger.:*** Inegy; ***Gr.:*** Inegy; Vytorin; ***Hong Kong:*** Vytorin; ***Hung.:*** Inegy; ***India:*** Zetitor†; ***Indon.:*** Vytorin; ***Irl.:*** Inegy; ***Ital.:*** Inegy; Vytorin; ***Malaysia:*** Vytorin; ***Mex.:*** Vytorin; Zintrepid; ***Neth.:*** Inegy; Vytorin; ***Norw.:*** Inegy; ***NZ:*** Vytorin; ***Philipp.:*** Vytorin; ***Port.:*** Inegy; ***Singapore:*** Vytorin; ***UK:*** Inegy; ***USA:*** Vytorin; ***Venez.:*** Adacai; Vytorin; Zintrepid.

Fasudil Hydrochloride *(rINNM)*

AT-877; Fasudil, Chlorhydrate de; Fasudili Hydrochloridum; HA-1077; Hidrocloruro de fasudil. Hexahydro-1-(5-isoquinolylsulfonyl)-1*H*-1,4-diazepine hydrochloride.

Фазудила Гидрохлорид

$C_{14}H_{17}N_3O_2S,HCl$ = 327.8.

CAS — 103745-39-7 (fasudil); 105628-07-7 (fasudil hydrochloride).

ATC — C04AX32.

ATC Vet — QC04AX32.

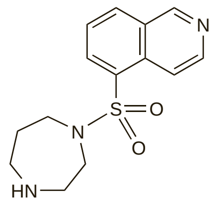

(fasudil)

Profile

Fasudil is a selective inhibitor of Rho-kinase, a protein kinase involved in contraction of vascular smooth muscle. Fasudil is used as the hydrochloride for its vasodilating properties in the management of cerebrovascular disorders including vasospasm after surgery for subarachnoid haemorrhage. It is under investigation for the treatment of angina pectoris, acute cerebral thrombosis, and pulmonary hypertension.

◊ References.

1. Shibuya M, *et al.* Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial. *J Neurosurg* 1992; **76:** 571–7.
2. Masumoto A, *et al.* Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation* 2002; **105:** 1545–7.
3. Shimokawa H, *et al.* Anti-anginal effect of fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol* 2002; **40:** 751–61.
4. Vicari RM, *et al.* Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol* 2005; **46:** 1803–11.
5. Suzuki Y, *et al.* A postmarketing surveillance study of fasudil treatment after aneurysmal subarachnoid hemorrhage. *Surg Neurol* 2007; **68:** 126–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Eril†.

Felodipine *(BAN, USAN, rINN)*

Felodipiini; Felodipin; Felodipinas; Félodipine; Felodipino; Felodipinum; H-154/82. Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

Фелодипин

$C_{18}H_{19}Cl_2NO_4$ = 384.3.

CAS — 72509-76-3; 86189-69-7.

ATC — C08CA02.

ATC Vet — QC08CA02.

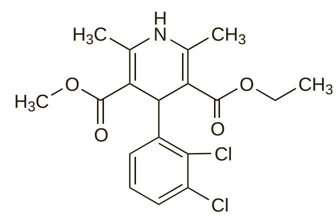

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Felodipine). A white or light yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Protect from light.

USP 31 (Felodipine). A light yellow to yellow, crystalline powder. Insoluble in water; freely soluble in acetone and in methyl alcohol; very slightly soluble in heptane. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism, with a bioavailability of about 15% (range 10 to 25%). It is extensively metabolised in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and the remainder in faeces. The terminal elimination half-life is reported to be about 11 to 16 hours after oral dosage with an immediate-release preparation, but longer with a modified-release formulation. Felodipine is about 99% bound to plasma proteins (mainly albumin).

◊ General reviews.

1. Dunselman PHJM, Edgar B. Felodipine clinical pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 418–30.

Uses and Administration

Felodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Felodipine is given orally, generally in a modified-release formulation for use once daily in the morning. In **hypertension** the usual initial dose is 5 mg daily, adjusted as required; the usual maintenance dose is 2.5 to 10 mg daily and doses above 20 mg daily are not usually needed. In **angina** the usual initial dose is 5 mg daily increased if necessary to 10 mg daily.

Lower doses may be required in patients with hepatic impairment (see below) and in the elderly.

◊ Reviews.

1. Todd PA, Faulds D. Felodipine: a review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. *Drugs* 1992; **44:** 251–77.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel-blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.

Administration in hepatic impairment. In 9 patients with liver cirrhosis given felodipine 750 micrograms by intravenous infusion over 20 minutes and 10 mg orally as single doses on separate occasions the mean oral bioavailability was 17.1% which was not significantly different from published values in healthy subjects, but the maximum plasma concentrations were almost twice as high as normal, apparently due to reduced systemic clearance and volume of distribution.[1] The fact that bioavailability was not increased suggests that much pre-systemic metabolism takes place in the gut rather than the liver. Although increased adverse effects were not associated with the raised felodipine concentrations in this study it is recommended that therapy in cirrhotic patients begin at lower doses than in patients with normal liver function. US licensed product information recommends that an initial dose of 2.5 mg once daily should be used in patients with hepatic impairment.

1. Regårdh CG, *et al.* Pharmacokinetics of felodipine in patients with liver disease. *Eur J Clin Pharmacol* 1989; **36:** 473–9.

Preparations

USP 31: Felodipine Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Munobal; Plendil; ***Austral.:*** Agon†; Felodur; Plendil; ***Austria:*** Felodistad; Munobal; Plendil; ***Belg.:*** Plendil; Renedil; ***Braz.:*** Splendil; ***Canad.:*** Plendil; Renedil; ***Chile:*** Splendil; ***Cz.:*** Auronal; Felocor; Plendil; Presid; ***Denm.:*** Felodin; Hydac†; Plendil; Plendur; ***Fin.:*** Hydac; Plendil; ***Fr.:*** Flodil; ***Ger.:*** Felo-Puren; Felobeta; Felocor; Felogamma; Modip; Munobal; ***Gr.:*** Plendil; ***Hong Kong:*** Plendil; ***Hung.:*** Plendil; Presid; ***India:*** Felogard; ***Indon.:*** Nirmadil; Plendil; ***Irl.:*** Plendil; ***Israel:*** Penedil; ***Ital.:*** Feloday; Plendil; Prevex; ***Jpn:*** Splendil†; ***Malaysia:*** Plendil; ***Mex.:*** Fedin; Munobal; Plendil; ***Neth.:*** Plendil; Renedil; ***Norw.:*** Plendil; ***NZ:*** Felo; Plendil; ***Philipp.:*** Dilahex; Felim; Felop; Lodistad; Plendil; Versant; ***Pol.:*** Felohexal; Plendil; ***Port.:*** Mencor; Preslow; ***Rus.:*** Felodip (Фелодип); Plendil (Плендил); ***S.Afr.:*** Plendil; ***Singapore:*** Plendil; ***Spain:*** Fensel; Perfudal; Plendil; ***Swed.:*** Plendil; ***Switz.:*** Felodil; Munobal†; Plendil; ***Thai.:*** Felim; Felohexal; Feloten; Plendil; ***Turk.:*** Plendil; ***UK:*** Cardioplen; Felotens; Keloc; Neofel; Plendil; Vascalpha; ***USA:*** Plendil; ***Venez.:*** Munobal†; Plendil.

Multi-ingredient: ***Arg.:*** Nikion†; Triacor; ***Austral.:*** Triasyn; ***Austria:*** Triapin; Unimax; ***Belg.:*** Logimat; ***Cz.:*** Logimax†; Triasyn; Unimax†; ***Denm.:*** Logimax; ***Fin.:*** Logimax; Unimax; ***Fr.:*** Logimax; ***Ger.:*** Delmuno; Mobloc; Unimax; ***Gr.:*** Logimax; Triacor; Unitens; ***Hong Kong:*** Logimax; ***Hung.:*** Logimax; Triasyn; ***Irl.:*** Triapin; ***Israel:*** Logimax; ***Mex.:*** Logimax; Triacor; ***Neth.:*** Logimax; Triapin; Unimax; ***Philipp.:*** Logimax; Triapin; ***Port.:*** Unimax; ***Rus.:*** Logimax (Логимакс); ***S.Afr.:*** Tri-Plen; ***Spain:*** Logimax; ***Swed.:*** Logimax; ***Switz.:*** Logimax; Unimax; ***UK:*** Triapin; ***USA:*** Lexxel.

Fendiline Hydrochloride *(pINNM)*

Fendiline, Chlorhydrate de; Fendilini Hydrochloridum; Hidrocloruro de fendilina. *N*-(2-Benzhydrylethyl)-α-methylbenzylamine hydrochloride.

Фендилина Гидрохлорид

$C_{23}H_{25}N,HCl = 351.9.$

CAS — 13042-18-7 (fendiline); 13636-18-5 (fendiline hydrochloride).

ATC — C08EA01.

ATC Vet — QC08EA01.

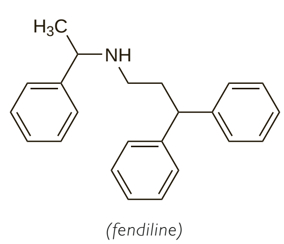

(fendiline)

Profile

Fendiline hydrochloride is a calcium-channel blocker used as a vasodilator in ischaemic heart disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sensit†; ***Ger.:*** Sensit; ***Gr.:*** Sensit.

Fenofibrate *(BAN, rINN)*

Fenofibraatti; Fenofibrát; Fenofibrat; Fenofibratas; Fénofibrate; Fenofibrato; Fenofibratum; LF-178; Procetofen; Procetofene. Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate.

Фенофибрат

$C_{20}H_{21}ClO_4 = 360.8.$

CAS — 49562-28-9.

ATC — C10AB05.

ATC Vet — QC10AB05.

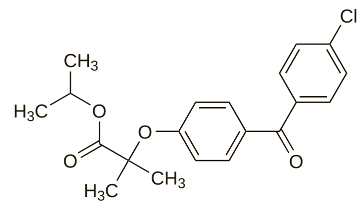

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Fenofibrate). A white or almost white, crystalline powder. M.p. 79° to 82°. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Fenofibrate). A white or almost white, crystalline powder. M.p. 79° to 82°. Practically insoluble in water; slightly soluble in alcohol; very soluble in dichloromethane. Protect from light.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Interactions

As for Bezafibrate, p.1232.

UK licensed product information for fenofibrate suggests that in patients taking oral anticoagulants, the dose of anticoagulant should be reduced by about one-third when treatment with fenofibrate is started, and then adjusted gradually if necessary.

Pharmacokinetics

Fenofibrate is readily absorbed from the gastrointestinal tract when taken with food; absorption may be reduced if fenofibrate is given on an empty stomach, although this depends on the formulation (see Bioavailability, below). It is rapidly hydrolysed to its active metabolite fenofibric acid which is about 99% bound to plasma albumin. The plasma elimination half-life is about 20 hours. Fenofibric acid is excreted mainly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronide. It is not removed by haemodialysis.

◊ References.

1. Chapman MJ. Pharmacology of fenofibrate. *Am J Med* 1987; **83** (suppl 5B): 21–5.

Bioavailability. Fenofibrate is poorly soluble in water and has a low bioavailability when given orally.[1] Bioavailability is increased by food, particularly if there is a high fat content, and fenofibrate is therefore usually given with meals. Changes to the formulation, particularly with regard to the particle size, have been made to improve solubility,[1] with the aim of increasing bioavailability and reducing the influence of food. Micronisation improves bioavailability to a certain extent, and allows a lower dose to be given; 300 mg of non-micronised fenofibrate is usually considered equivalent to about 200 mg of the standard micronised form. Microcoating may further improve bioavailability,[2] but absorption is still affected by the presence of food.[3] Nanoparticle,[4] stabilised microparticle,[3] or semi-solid formulations,[5] however, appear to have a more consistent bioavailability and may be given with or without food.

1. Vogt M, *et al.* Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. *Eur J Pharm Biopharm* 2008; **68:** 283–8.
2. Guichard JP, *et al.* A new formulation of fenofibrate: suprabioavailable tablets. *Curr Med Res Opin* 2000; **16:** 134–8.
3. Guivarc'h PH, *et al.* A new fenofibrate formulation: results of six single-dose, clinical studies of bioavailability under fed and fasting conditions. *Clin Ther* 2004; **26:** 1456–69.
4. Sauron R, *et al.* Absence of a food effect with a 145 mg nanoparticle fenofibrate tablet formulation. *Int J Clin Pharmacol Ther* 2006; **44:** 64–70.
5. Sonet B, *et al.* Randomised crossover studies of the bioequivalence of two fenofibrate formulations after administration of a single oral dose in healthy volunteers. *Arzneimittelforschung* 2002; **52:** 200–4.

Uses and Administration

Fenofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

It is used to reduce low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and apolipoprotein B, and to increase high-density lipoprotein (HDL)-cholesterol, in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias.

Fenofibrate is given orally. It is usually given with food to improve bioavailability although this may not be necessary with all preparations (see Bioavailability, above). It is available in a range of formulations with differing bioavailabilities and the dose is therefore specific to the preparation.

Standard micronised formulations of fenofibrate are available as 67-mg capsules to be taken several times daily, or as 200- or 267-mg capsules for once daily dosage. The usual initial dose is 67 mg three times daily or 200 mg once daily; the dose may be reduced to 67 mg twice daily or increased to 67 mg four times daily or 267 mg once daily according to response.

Preparations with improved bioavailability may be given in doses of around 40 to 160 mg once daily.

Non-micronised formulations may also be available and are given in an initial dose of 200 to 300 mg daily in divided doses, adjusted according to response to between 200 and 400 mg daily; 100 mg of non-micronised fenofibrate is therapeutically equivalent to 67 mg of the standard micronised form.

The dose of fenofibrate should be reduced in renal impairment (see below). For the dose of fenofibrate in children, see also below.

◊ Reviews.

1. Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* 2007; **67:** 121–53.

Administration in children. Experience with fenofibrate in children is limited and it should only be given under specialist advice. The dose depends on the formulation:

- For *standard micronised* fenofibrate the *BNFC* recommends that children are given the 67-mg capsule formulation. The oral dose is one 67-mg capsule per 20 kg body-weight daily for children aged 4 to 15 years; those aged 15 to 18 years may be given the adult dose (see above).
- *Non-micronised* fenofibrate is licensed for use in some countries in children from the age of 10 years, in an oral dose of 5 mg/kg daily.

Administration in renal impairment. A single-dose study[1] in patients with mild (creatinine clearance (CC) 30 to 50 mL/minute) or severe renal impairment (CC below 10 mL/minute or undergoing haemodialysis) found that the plasma elimination half-life of fenofibric acid was prolonged, with a range of 54 to 362 hours; no correlation was found between half-life and serum creatinine or CC. Fenofibrate metabolites were not removed by haemodialysis, and repeated dosing in patients undergoing regular haemodialysis led to significant accumulation of fenofibric acid.[1]

Fenofibrate is therefore not generally recommended in patients with severe renal impairment although UK licensed product information allows a dose of 134 mg of standard micronised fenofibrate daily for patients with CC between 20 and 60 mL/minute and 67 mg daily for patients with CC below 20 mL/minute. US licensed product information for improved bioavailability formulations suggests initial daily doses of about 40 to 50 mg (equivalent to about 67 mg of standard micronised fenofibrate) in patients with renal impairment, but contra-indicates use in those with severe impairment.

1. Desager JP, *et al.* Effect of hemodialysis on plasma kinetics of fenofibrate in chronic renal failure. *Nephron* 1982; **31:** 51–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Craveril; Fenobrate; Fenolip†; Lipidil†; Lipoplasmin†; Minuslip; Procetoken; Qualecon†; Sclerofin; ***Austral.:*** Lipidil; ***Austria:*** Fenolip; Lipcor; Lipsin; ***Belg.:*** Docfenofi; Fenofitop; Fenogal; Lipanthyl; ***Braz.:*** Lipanon; Lipidil; ***Canad.:*** Apo-Feno; Lipidil; ***Chile:*** Lipidil; ***Cz.:*** Apo-Feno; Febira; Fenofix; Grofibrat†; Hypolip†; Lipanthyl; Lipirex; Lipohexal; Suprelip; ***Fin.:*** Lipanthyl; ***Fr.:*** Fegenor; Lipanthyl; Lipirex; Secalip; ***Ger.:*** CIL; durafenat; Fenobeta; Fenofanton; Lipanthyl; Lipidil; Normalip pro; ***Gr.:*** Lipanthyl; Lipidil; Neo-Disterin; Planitrix†; Zerlubron†; ***Hong Kong:*** Apo-Feno-Micro; Fegenor; Lexemin; Lipanthyl; Qualipantyl; Trolip†; ***Hung.:*** Feno-Micro; Fenobrat; Lipanthyl†; Lipidil; ***India:*** Fenolip; Lipicard; ***Indon.:*** Evothyl; Felosma; Hyperchol; Lipanthyl; Trichol; Trolip; Yosenob; Zumafib; ***Irl.:*** Lipantil; ***Ital.:*** Fulcro; Lipanthyl†; Lipofene; Lipsin; Nolipax; Scleril; Tilene; Volutine†; ***Jpn:*** Tricor; ***Malaysia:*** Apo-Feno-Micro; Lexemin; Lipanthyl; ***Mex.:*** Controlip;

Lipidil†; **Philipp.:** Fibrafen; Lipanthyl; Lipway; Nubrex; Trolip; **Pol.:** Apo-Feno; Fenardin; Fenoratio; Grofibrat; Lipanthyl; **Port.:** Apteor; Catalip; Lipanthyl; Lipofen; Supralip; **Rus.:** Lipanthyl (Липантил); **S.Afr.:** Lipsin†; **Singapore:** Fenogal Lidose; Lexemin; Lipanthyl; **Spain:** Liparison; Secalip; **Swed.:** Lipanthyl; **Switz.:** Lipanthyl; **Thai.:** Fenox; Fibrolan; Lexemin; Lipanthyl; Supralip; **Turk.:** Lipanthyl; Lipofen; **UK:** Fenogal; Lipantil; Supralip; **USA:** Antara; Lipofen; Lofibra; Tricor; Triglide.

Fenoldopam Mesilate *(BANM, rINNM)*

Fénoldopam, Mésilate de; Fenoldopam Mesylate *(USAN)*; Fenoldopami Mesilas; Mesilato de fenoldopam; SKF-82526-j. 6-Chloro-2,3,4,5-tetrahydro-1-(*p*-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol methanesulfonate.

Фенолдопама Мезилат

$C_{16}H_{16}ClNO_3,CH_4O_3S$ = 401.9.

CAS — 67227-56-9 (fenoldopam); 67227-57-0 (fenoldopam mesilate).

ATC — C01CA19.

ATC Vet — QC01CA19.

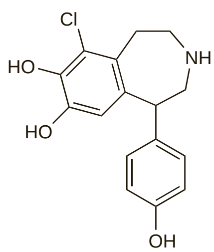

(fenoldopam)

Pharmacopoeias. In *US*.

USP 31 (Fenoldopam Mesylate). A white to off-white powder. Soluble in water. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from moisture.

Incompatibility. Physical incompatibility has been reported[1] with fenoldopam 80 micrograms/mL (as the mesilate) in 0.9% sodium chloride injection and the following drugs during simulated Y-site administration: aminophylline; ampicillin sodium; amphotericin B; bumetanide; cefoxitin sodium; dexamethasone sodium phosphate; diazepam; fosphenytoin sodium; furosemide; ketorolac tromethamine; methohexital sodium; methylprednisolone sodium succinate; pentobarbital sodium; phenytoin sodium; prochlorperazine edisilate; sodium bicarbonate; and thiopental sodium.

1. Trissel LA, *et al.* Compatibility of fenoldopam mesylate with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2003; **60:** 80–5.

Stability. Fenoldopam mesilate, at concentrations ranging from 4 to 300 micrograms/mL in glucose 5% or sodium chloride 0.9%, has been reported[1] to be stable for 72 hours when stored at temperatures of 4° or 23°.

1. Trissel LA, *et al.* Stability of fenoldopam mesylate in two infusion solutions. *Am J Health-Syst Pharm* 2002; **59:** 846–8.

Adverse Effects and Precautions

The adverse effects of fenoldopam are mainly due to vasodilatation and include hypotension, flushing, dizziness, headache, and reflex tachycardia. Nausea and vomiting, and ECG abnormalities have also been reported. Hypokalaemia has occurred and serum-electrolyte concentrations should be monitored during therapy; blood pressure and heart rate should also be monitored. Fenoldopam may increase intra-ocular pressure and it should be used with caution in patients with glaucoma. Caution is also required in patients in whom hypotension could be deleterious, such as those with acute cerebral infarction or haemorrhage.

Effects on the heart. Although fenoldopam is usually associated with reflex tachycardia, precipitous bradycardia in 2 patients given fenoldopam infusion in a clinical study[1] forced the drug to be stopped.

1. Taylor AA, *et al.* Sustained hemodynamic effects of the selective dopamine-1 agonist, fenoldopam, during 48-hour infusions in hypertensive patients: a dose-tolerability study. *J Clin Pharmacol* 1999; **39:** 471–9.

Interactions

The hypotensive effects of fenoldopam may be enhanced by other drugs with hypotensive actions. Beta blockers may block fenoldopam-induced reflex tachycardia and use of the drugs together is not recommended.

Pharmacokinetics

Steady-state plasma concentrations of fenoldopam are reached about 20 minutes after starting continuous intravenous infusion. Fenoldopam is extensively metabolised with only about 4% of a dose being excreted unchanged. It is metabolised by conjugation (mainly glucuronidation, methylation, and sulfation). Fenoldopam and its metabolites are excreted mainly in the urine, and the remainder in the faeces. The elimination half-life of fenoldopam is about 5 minutes.

Uses and Administration

Fenoldopam is a dopamine agonist that is reported to have a selective action at dopamine D_1-receptors, leading to vasodilatation. It is used in the short-term management of severe hypertension (below) and has also been tried in heart failure.

Fenoldopam is given intravenously as the mesilate, although doses are expressed in terms of the base; 1.31 micrograms of fenoldopam mesilate is equivalent to about 1 microgram of fenoldopam.

In the management of hypertensive crises, fenoldopam mesilate is given by continuous intravenous infusion for up to 48 hours, as a solution containing 40 micrograms/mL of fenoldopam. The dose should be adjusted according to response, in usual increments of 50 to 100 nanograms/kg per minute at not less than 15-minute intervals. The usual dose range is from 100 to 1600 nanograms/kg per minute.

In the management of hypertensive crises in children, fenoldopam mesilate is given by continuous intravenous infusion for up to 4 hours, as a solution containing 60 micrograms/mL of fenoldopam. US licensed product information states that the initial dose used in clinical studies was 200 nanograms/kg per minute; adjustments according to response every 20 to 30 minutes up to 500 nanograms/kg per minute were usually well-tolerated. No benefit was seen from doses above 800 nanograms/kg per minute.

Hypertension. Fenoldopam has a rapid onset of action and short elimination half-life and may be used as an alternative to sodium nitroprusside in the management of hypertensive crises (see under Hypertension, p.1171). Its use has been reviewed.[1-3] Comparative studies with sodium nitroprusside in patients with acute severe hypertension have shown fenoldopam to be equally effective in rapidly lowering blood pressure. Additionally, in contrast to nitroprusside, urine output, creatinine clearance, and sodium excretion may be increased by fenoldopam. Fenoldopam may therefore be particularly useful in patients with renal impairment, although this remains to be established.

1. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. *Drugs* 1997; **54:** 634–50.
2. Post JB, Frishman WH. Fenoldopam: a new dopamine agonist for the treatment of hypertensive urgencies and emergencies. *J Clin Pharmacol* 1998; **38:** 2–13.
3. Murphy MB, *et al.* Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med* 2001; **345:** 1548–57.

Nephrotoxicity. Fenoldopam increases renal blood flow and has been tried to reduce the renal toxicity that may be associated with use of contrast media (see Effects on the Kidneys under Adverse Effects of Amidotrizoic Acid, p.1476). Small studies in patients at risk of renal toxicity have shown benefit with fenoldopam,[1,2] but larger randomised trials[3,4] have found no advantage with fenoldopam plus hydration compared with hydration using sodium chloride 0.45% alone. However, a later meta-analysis[5] in patients undergoing cardiovascular surgery, who are at risk of acute renal failure, found that fenoldopam consistently reduced the need for renal replacement therapy, and reduced mortality.

A study[6] in patients undergoing liver transplantation (p.1815) suggested that fenoldopam may have a role in preserving renal function, possibly by counteracting the renal toxicity associated with ciclosporin.

1. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; **35:** 1278–82. Correction. *ibid.*; 1677.
2. Lepor NE. A review of contemporary prevention strategies for radiocontrast nephropathy: a focus on fenoldopam and N-acetylcysteine. *Rev Cardiovasc Med* 2003; **4** (suppl 1): S15–S20.
3. Allaqaband S, *et al.* Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv* 2002; **57:** 279–83.
4. Stone GW, *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; **290:** 2284–91.
5. Landoni G, *et al.* Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2008; **22:** 27–33.
6. Biancofiore G, *et al.* Use of fenoldopam to control renal dysfunction early after liver transplantation. *Liver Transpl* 2004; **10:** 986–92.

Preparations

USP 31: Fenoldopam Mesylate Injection.

Proprietary Preparations (details are given in Part 3)
Irl.: Corlopam†; **Ital.:** Corlopam; **Neth.:** Corlopam; **USA:** Corlopam.

Fenquizone *(USAN, rINN)* ⊗

Fenquizona; Fenquizonum; MG-13054. 7-Chloro-1,2,3,4-tetrahydro-4-oxo-2-phenylquinazoline-6-sulphonamide.

Фенхизон

$C_{14}H_{12}ClN_3O_3S$ = 337.8.

CAS — 20287-37-0.

ATC — C03BA13.

ATC Vet — QC03BA13.

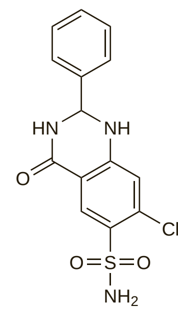

Fenquizone Potassium *(rINNM)* ⊗

Fenquizona potásica; Fenquizone Potassique; Kalii Fenquizonum.

Калия Фенхизон

$C_{14}H_{12}ClN_3O_3S,K$ = 376.9.

CAS — 52246-40-9.

ATC — C03BA13.

ATC Vet — QC03BA13.

Profile

Fenquizone potassium is a diuretic that is given orally in the treatment of oedema and hypertension (p.1171) in doses equivalent to 10 to 20 mg of fenquizone daily. 11.2 mg of the potassium salt is equivalent to about 10 mg of the base.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.
2. Costa FV, *et al.* Hemodynamic and humoral effects of chronic antihypertensive treatment with fenquizone: importance of aldosterone response. *J Clin Pharmacol* 1990; **30:** 254–61.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Idrolone.

Fibrinolysin

Fibrinolysin (Human) *(BAN, rINN)*; Fibrinase; Fibrinolisina (humana); Fibrinolysine (humaine); Fibrinolysinum (humanum); Plasmiini; Plasmin; Plasminum.

Фибринолизин (Человека)

CAS — 9001-90-5 (fibrinolysin); 9004-09-5 (human fibrinolysin).

ATC — B01AD05.

ATC Vet — QB01AD05.

NOTE. In *Martindale* the term fibrinolysin is used for the exogenous substance and plasmin for the endogenous substance.

Profile

Fibrinolysin is a proteolytic enzyme derived from the activation of human plasminogen. Fibrinolysin derived from cattle (bovine fibrinolysin) and other animals is also available. Fibrinolysin converts fibrin into soluble products and also hydrolyses some other proteins. The role of plasmin (endogenous fibrinolysin) in the control of haemostasis is described further on p.1045.

Fibrinolysin is used (generally as bovine fibrinolysin) with deoxyribonuclease for the debridement of wounds. It was formerly given parenterally for the treatment of thrombotic disorders. A modified form of fibrinolysin, microplasmin, is under investigation for use in ophthalmic surgery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Clorfibrase; ***Austria:*** Fibrolan; ***Braz.:*** Cauterex; Dermofibrin C†; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino-Cauterex; Gino-Fibrase; Procutan†; ***Chile:*** Elase; ***Cz.:*** Fibrolan; ***Fr.:*** Elase; ***Ger.:*** Fibrolan†; ***Hung.:*** Fibrolan; ***Ital.:*** Elase†; ***Malaysia:*** Elase; ***Mex.:*** Fibrase; Fibrase SA; ***Pol.:*** Fibrolan; ***Switz.:*** Fibrolan.

Flecainide Acetate *(BANM, USAN, rINNM)*

Acetato de flecainida; Flécaïnide, acétate de; Flecainidi acetas; Flekainidacetat; Flekainid-acetát; Flekainidiasetaatti; Flekainido acetatas; R-818. *N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate.

Флекаинида Ацетат

$C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ = 474.4.

CAS — 54143-55-4 (flecainide); 54143-56-5 (flecainide acetate).

ATC — C01BC04.

ATC Vet — QC01BC04.

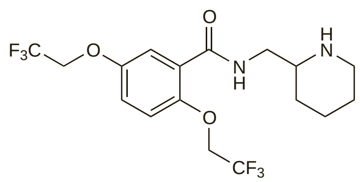

(flecainide)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Flecainide Acetate). A white or almost white, very hygroscopic crystalline powder. Soluble in water and in dehydrated alcohol; freely soluble in dilute acetic acid; practically insoluble in dilute hydrochloric acid. A 2.5% solution in water has a pH of 6.7 to 7.1. Protect from light.

USP 31 (Flecainide Acetate). A white to slightly off-white crystalline powder; pK_a is 9.3. Soluble in water; freely soluble in alcohol.

Stability. Storage of an extemporaneously prepared flecainide syrup in a refrigerator led to crystallisation of the drug and a toxic dose being given.[1] It was suggested that oral liquid formulations of flecainide should be freshly reconstituted from a powder before each dose. However, other extemporaneous formulations have been reported[2,3] to be stable at room temperature and under refrigeration.

1. Stuart AG, *et al.* Is there a genetic factor in flecainide toxicity? *BMJ* 1989; **298:** 117–18.
2. Wiest DB, *et al.* Stability of flecainide acetate in an extemporaneously compounded oral suspension. *Am J Hosp Pharm* 1992; **49:** 1467–70.
3. Allen LV, Erickson MA. Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996; **53:** 2179–84.

Adverse Effects

The most common adverse effects caused by flecainide affect the CNS and include dizziness, visual disturbances, and lightheadedness. Nausea, vomiting, headache, tremor, peripheral neuropathy, ataxia, and paraesthesia may also occur. These effects are generally transient and respond to dosage reduction. Other adverse CNS effects that have been reported rarely include hallucinations, amnesia, confusion, depression, dyskinesias, and convulsions. Skin reactions, including rare cases of urticaria, have also occurred and there have been isolated cases of photosensitivity. Disturbances of liver function have been reported rarely. Corneal deposits, pulmonary fibrosis, and pneumonitis have occurred during long-term therapy. Cardiovascular effects are less common than those on the CNS, but can be serious and sometimes fatal. Ventricular tachyarrhythmias have been reported, particularly in patients with a history of ventricular tachyarrhythmias and taking high doses of flecainide. Chest pain and myocardial infarction have also occurred. Flecainide produced an increased mortality rate when it was assessed for the control of asymptomatic ventricular arrhythmias in patients who had previously suffered a myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, below).

Incidence of adverse effects. In a report of the non-cardiac adverse effects of flecainide from 1 short-term and 3 longer-term studies,[1] the most common adverse effects during both short- and long-term studies were dizziness and visual disturbances, which occurred in about 30% of patients. Headache and nausea both occurred in about 10% of patients. Other adverse effects reported include dyspnoea, chest pain, asthenia, fatigue, and tremor. Therapy was stopped because of non-cardiac adverse effects in 10% of patients in the short-term trial, and in 6% of those in the chronic studies. A review of 60 studies using flecainide[2] reported that non-cardiac adverse effects (mainly gastrointestinal and CNS adverse effects) occurred in 12% of patients. The UK CSM stated in June 1991 that it had received reports of neurological (4 patients with sensory neuropathy, 2 with ataxia), corneal (2 with corneal deposits), and pulmonary (3 with pulmonary fibrosis and pneumonitis) reactions associated with the long-term use of flecainide.[3]

1. Gentzkow GD, Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984; **53:** 101B–105B.
2. Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. *Am J Cardiol* 1992; **70:** 3A–10A.
3. Committee on Safety of Medicines. Multi-system adverse reactions following long-term flecainide therapy. *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 08/05/07)

Effects on the blood. Severe granulocytopenia believed to be related to flecainide occurred in a 66-year-old man 3 months after starting therapy.[1] Haematological findings suggested an immune-mediated reaction in which flecainide binds to normal neutrophils with subsequent recognition by specific antibodies resulting in enhanced destruction of mature granulocytes in peripheral blood and bone marrow.

1. Samlowski WE, *et al.* Flecainide-induced immune neutropenia: documentation of a hapten-mediated mechanism of cell destruction. *Arch Intern Med* 1987; **147:** 383–4.

Effects on the eyes. In addition to visual disturbance, symptomatic corneal deposits have been reported[1] in patients taking flecainide. A study[2] in 38 patients found small corneal deposits in 14.5%, but visual function tests were normal.

1. Ulrik H, *et al.* Corneal deposits associated with flecainide. *BMJ* 1991; **302:** 506–7.
2. Ikäheimo K, *et al.* Adverse ocular effects of flecainide. *Acta Ophthalmol Scand* 2001; **79:** 175–6.

Effects on the heart. Like most antiarrhythmics, flecainide can have proarrhythmic effects,[1] and severe ventricular arrhythmias have been reported,[2] including fatal ventricular fibrillation[3] in a neonate given flecainide for supraventricular tachycardia. There has also been a report[4] of torsade de pointes, although this is generally less common with class Ic than with class Ia antiarrhythmics. For reports of increased cardiac mortality in patients given flecainide for asymptomatic arrhythmias, see Cardiac Arrhythmias under Uses and Administration, below.

1. Herre JM, *et al.* Inefficacy and proarrhythmic effects of flecainide and encainide for sustained ventricular tachycardia and ventricular fibrillation. *Ann Intern Med* 1990; **113:** 671–6.
2. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med* 1989; **111:** 107–11.
3. Ackland F, *et al.* Flecainide induced ventricular fibrillation in a neonate. *Heart* 2003; **89:** 1261.
4. Nogales Asensio JM, *et al.* Torsade-de-pointes in a patient under flecainide treatment: an unusual case of proarrhythmicity. *Int J Cardiol* 2007; **114:** e65–e67.

Effects on the liver. Elevated liver enzymes and jaundice, reversible on stopping treatment, have been reported rarely with flecainide.

Conjugated hyperbilirubinaemia with jaundice developed in a newborn infant after maternal treatment with flecainide for fetal supraventricular tachycardia.[1]

1. Vanderhal AL, *et al.* Conjugated hyperbilirubinemia in a newborn infant after maternal (transplacental) treatment with flecainide acetate for fetal tachycardia and fetal hydrops. *J Pediatr* 1995; **126:** 988–90.

Effects on the lungs. There have been reports[1-4] of interstitial pneumonitis associated with flecainide. See also under Incidence of Adverse Effects, above.

1. Akoun GM, *et al.* Flecainide-associated pneumonitis. *Lancet* 1991; **337:** 49.
2. Hanston P, *et al.* Flecainide-associated interstitial pneumonitis. *Lancet* 1991; **337:** 371–2.
3. Robain A, *et al.* Flecainide-associated pneumonitis with acute respiratory failure in a patient with the LEOPARD syndrome. *Acta Cardiol* 2000; **55:** 45–7.
4. Pesenti S, *et al.* Diffuse infiltrative lung disease associated with flecainide: report of two cases. *Respiration* 2002; **69:** 182–5.

Effects on mental state. Dysarthria and visual hallucinations were associated with elevated plasma concentration of flecainide (2500 nanograms/mL) in a patient.[1] A serial rise and fall in plasma-bilirubin concentration during flecainide therapy also suggested possible direct hepatotoxicity. There has also been a report[2] of paranoid psychosis in a patient receiving flecainide for neuropathic pain.

1. Ramhamadany E, *et al.* Dysarthria and visual hallucinations due to flecainide toxicity. *Postgrad Med J* 1986; **62:** 61–2.
2. Bennett MI. Paranoid psychosis due to flecainide toxicity in malignant neuropathic pain. *Pain* 1997; **70:** 93–4.

Effects on the nervous system. Peripheral neuropathy, reversible on stopping treatment, has been reported[1,2] in patients receiving flecainide long-term. The authors of one report[1] stated that, at the time (1992), the UK CSM had received 4 other reports possibly associated with flecainide and 3 reports of aggravation of pre-existing neuropathy;[1] not all cases were reversible.

1. Palace J, *et al.* Flecainide induced peripheral neuropathy. *BMJ* 1992; **305:** 810.
2. Malesker MA, *et al.* Flecainide-induced neuropathy. *Ann Pharmacother* 2005; **39:** 1580.

Lupus erythematosus. There has been a report[1] of a patient who developed painful eye movement during flecainide therapy. The pain resolved on withdrawal but recurred when flecainide was restarted, and was accompanied by lateral rectus spasm, a facial rash, and positive antinuclear factor, suggestive of lupus erythematosus.

1. Skander M, Isaacs PET. Flecainide, ocular myopathy, and antinuclear factor. *BMJ* 1985; **291:** 450.

Treatment of Adverse Effects

In oral overdosage with flecainide activated charcoal may be considered if the patient presents within 1 hour of ingestion. Treatment is largely symptomatic and supportive and may need to be continued for extended periods of time because of the long half-life and the possibility of non-linear elimination at very high doses. Haemodialysis or haemoperfusion are unlikely to enhance elimination.

Overdosage. Severe cardiovascular toxicity in flecainide overdosage may be resistant to pacing and inotropes, and hypoperfusion of the kidneys and liver may reduce the elimination of flecainide, prolonging the toxic effects. Gastric decontamination is of uncertain benefit; forced diuresis has been used,[1] but probably had a negligible effect, and haemodialysis and haemoperfusion are not effective.[2] Patients may therefore require intensive and prolonged supportive treatment,[1,3] and there have been reports of the use of extracorporeal membrane oxygenation,[4] cardiopulmonary bypass,[5,6] or intra-aortic balloon pumping,[7] to maintain organ perfusion and allow flecainide elimination to occur, with complete recovery in some cases.[3,4,6,7] There have been reports[8,9] of the successful use of intravenous hypertonic sodium bicarbonate, and it has been suggested that it may antagonise the sodium channel blockade produced by flecainide, as well as reversing the metabolic acidosis that commonly occurs.

1. Winkelmann BR, Leinberger H. Life-threatening flecainide toxicity: a pharmacodynamic approach. *Ann Intern Med* 1987; **106:** 807–14.
2. Braun J, *et al.* Failure of haemoperfusion to reduce flecainide intoxication: a case study. *Med Toxicol* 1987; **2:** 463–7.
3. Hanley NA, *et al.* Survival in a case of life-threatening flecainide overdose. *Intensive Care Med* 1998; **24:** 740–2.
4. Auzinger GM, Scheinkestel CD. Successful extracorporeal life support in a case of severe flecainide intoxication. *Crit Care Med* 2001; **29:** 887–90.
5. Yasui RK, *et al.* Flecainide overdose: is cardiopulmonary support the treatment? *Ann Emerg Med* 1997; **29:** 680–2.
6. Corkeron MA, *et al.* Extracorporeal circulatory support in near-fatal flecainide overdose. *Anaesth Intensive Care* 1999; **27:** 405–8.
7. Timperley J, *et al.* Flecainide overdose—support using an intra-aortic balloon pump. *BMC Emerg Med* 2005; **5:** 10.
8. Goldman MJ, *et al.* Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. *J Emerg Med* 1997; **15:** 183–6.
9. Lovecchio F, *et al.* Hypertonic sodium bicarbonate in an acute flecainide overdose. *Am J Emerg Med* 1998; **16:** 534–7.

Precautions

Flecainide treatment should be started in hospital or under specialist supervision and pacing rescue should be available when it is used in patients with conduction defects. Its use is limited to serious or life-threatening arrhythmias and it should not be given to control asymptomatic arrhythmias especially in patients with a history of myocardial infarction (see Cardiac Arrhythmias under Uses and Administration, below). Flecainide has some negative inotropic activity and may precipitate or aggravate heart failure in patients with compromised left ventricular function; it should therefore be used with extreme caution, if at all, in patients with heart failure. Flecainide has been shown to increase the endocardial pacing threshold and should be used with caution in patients with pacemakers. Electrolyte imbalances should be corrected before starting flecainide therapy. Reduction of dosage may be necessary in patients with renal impairment; extreme caution is needed in patients with pronounced hepatic impairment.

Breast feeding. Flecainide is distributed into breast milk but there have been no reports of infant exposure. Flecainide 100 mg was given orally every 12 hours to 11 healthy women, beginning 1 day after delivery and continuing for 5 ⁄ days.[1] The mean elimination half-life of flecainide from milk was 14.7 hours, very similar to the plasma elimination half-life. The mean milk to plasma ratios on study days 2 to 5 were 3.7, 3.2, 3.5, and 2.6 respectively but it was considered that the risk to breast-fed infants of ingesting toxic amounts of flecainide in breast milk would be very low. In another woman[2] who had been taking flecainide 100 mg twice daily since before pregnancy for ventricular arrhythmias, the ratio was 1.57 on day 5 postpartum and 2.18 on day 7. The American Academy of Pediatrics considers[3] flecainide to be usually compatible with breast feeding.

1. McQuinn RL, *et al.* Flecainide excretion in human breast milk. *Clin Pharmacol Ther* 1990; **48:** 262–7.
2. Wagner X, *et al.* Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. Flecainide crosses the placenta (see under Pharmacokinetics, below) and has been used for transplacental therapy of fetal cardiac arrhythmias (see under Uses and Administration, below). However, hyperbilirubinaemia was reported in an infant after maternal treatment with flecainide (see Effects on the Liver, above).

Interactions

Use of flecainide with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Use with a beta blocker produces additive negative inotropic effects. Flecainide undergoes hepatic metabolism and its activity may be influenced by drugs that affect the enzymes responsible for its metabolism, including the cytochrome P450 isoenzyme CYP2D6.

Antiarrhythmics. *Amiodarone* increases the plasma-flecainide concentration when the two drugs are given together.[1] It has been recommended that the dose of flecainide should be reduced by about one-half, but because the effect of amiodarone differs widely between patients, plasma-flecainide concentrations should be monitored. The clearance of flecainide may be decreased by *quinidine* in patients who are extensive metabolisers, since quinidine inhibits the enzyme responsible for the metabolism of flecainide.[2] Cardiogenic shock and asystole occurred in 2 patients receiving flecainide when *verapamil* was added to their therapy.[3]

1. Shea P, *et al.* Flecainide and amiodarone interaction. *J Am Coll Cardiol* 1986; **7:** 1127–30.
2. Birgersdotter UM, *et al.* Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br J Clin Pharmacol* 1992; **33:** 275–80.
3. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.

Antimalarials. *Quinine* has been reported[1] to inhibit metabolism of flecainide in healthy subjects without altering its renal elimination, resulting in a reduction of total clearance and prolongation of the elimination half-life.

1. Munafo A, *et al.* Altered flecainide disposition in healthy volunteers taking quinine. *Eur J Clin Pharmacol* 1990; **38:** 269–73.

Beta blockers. Use of flecainide and *propranolol* in healthy subjects increases the plasma concentration of both drugs. The negative inotropic effects of the two drugs on cardiac function are at most only additive, but combined treatment should be started with caution in patients with impaired left ventricular function.[1] Addition of *sotalol* to flecainide has produced profound bradycardia and AV block followed by cardiac arrest and death in a man with ventricular tachycardia.[2]

1. Holtzman JL, *et al.* The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: effects on cardiac function and drug clearance. *Eur J Clin Pharmacol* 1987; **33:** 97–9.
2. Warren R, *et al.* Serious interactions of sotalol with amiodarone and flecainide. *Med J Aust* 1990; **152:** 277.

Digoxin. For reference to an interaction between flecainide and digoxin leading to increased concentrations of digoxin, see Antiarrhythmics, under Interactions of Digoxin, p.1261.

Food. *Milk* feeds reduced the absorption of flecainide in an infant who required a dose of 40 mg/kg daily to control supraventricular tachycardias. When milk feeds were replaced by glucose, the serum-flecainide concentration increased from 990 to 1824 nanograms/mL. Milk-fed infants on high doses of flecainide should have the dose reduced if milk is stopped or reduced.[1]

1. Russell GAB, Martin RP. Flecainide toxicity. *Arch Dis Child* 1989; **64:** 860–2.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase the bioavailability of flecainide in healthy subjects, probably due to a decrease in the metabolism of flecainide. Elimination half-life and renal clearance were unchanged.[1]

1. Tjandra-Maga TB, *et al.* Altered pharmacokinetics of oral flecainide by cimetidine. *Br J Clin Pharmacol* 1986; **22:** 108–10.

Pharmacokinetics

Flecainide is almost completely absorbed after oral doses and does not undergo extensive first-pass hepatic metabolism. Although absorption is not affected by food or antacids, milk may inhibit absorption in infants (see above). Flecainide is metabolised to 2 major metabolites, *m-O*-dealkylated flecainide and *m-O*-dealkylated lactam of flecainide; both may have some activity, but this is unlikely to be clinically significant. Metabolism of flecainide appears to involve the cytochrome P450 isoenzyme CYP2D6 and is subject to genetic polymorphism (see Metabolism, below). It is excreted mainly in the urine, about 30% as unchanged drug and the remainder as metabolites. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal impairment, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of an oral dose as unchanged flecainide.

The therapeutic plasma concentration range is generally accepted as 200 to 1000 nanograms/mL. The elimination half-life of flecainide is about 20 hours and it is about 40% bound to plasma proteins.

Flecainide crosses the placenta and is distributed into breast milk.

Metabolism. Oxidative metabolism is an important route of flecainide elimination.[1] It is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. The mean elimination half-life of flecainide in poor metabolisers (5 to 10% of the population) was found to be 11.8 hours compared with 6.8 hours in extensive metabolisers and the amounts of a dose excreted as unchanged drug in the urine were 51% and 31% respectively. These differences in pharmacokinetics will not usually be of clinical importance. However, in patients with renal impairment who are poor metabolisers, special care should be taken with dosage adjustments.

1. Mikus G, *et al.* The influence of the sparteine-debrisoquin phenotype on the disposition of flecainide. *Clin Pharmacol Ther* 1989; **45:** 562–7.

Pregnancy. A study of the pharmacokinetics of flecainide, given to a mother during the third trimester of pregnancy for the treatment of fetal supraventricular tachycardia,[1] indicated that close to term flecainide crosses the placenta easily without accumulating in fetal blood, but with a high concentration in the amniotic fluid.

See also Effects on the Liver, above.

1. Bourget P, *et al.* Flecainide distribution, transplacental passage and accumulation in the amniotic fluid during the third trimester of pregnancy. *Ann Pharmacother* 1994; **28:** 1031–4.

Uses and Administration

Flecainide is a class Ic antiarrhythmic (p.1153) used for the treatment of severe symptomatic ventricular arrhythmias such as sustained ventricular tachycardia; for premature ventricular contractions or non-sustained ventricular tachycardia resistant to other therapy; and for severe symptomatic supraventricular arrhythmias (AV nodal reciprocating tachycardia, arrhythmias associated with the Wolff-Parkinson-White syndrome, and paroxysmal atrial fibrillation in the absence of left ventricular dysfunction).

Flecainide is given orally or intravenously as the acetate. Treatment should be started in hospital. Doses should be adjusted after 3 to 5 days and reduced once control has been achieved. A suggested therapeutic plasma concentration range is 200 to 1000 nanograms/mL.

In ventricular arrhythmias the usual initial oral dose of flecainide acetate is 100 mg twice daily; the maximum total dose is 400 mg daily although most patients will not need more than 300 mg daily. In supraventricular arrhythmias the usual initial oral dose is 50 mg twice daily and the maximum total dose is 300 mg daily.

For rapid control of arrhythmias flecainide acetate 2 mg/kg may be given intravenously over 10 to 30 minutes, to a maximum dose of 150 mg; the ECG should be monitored. If longer term parenteral therapy is necessary it is started with intravenous injection of 2 mg/kg over 30 minutes, as above, then continued by intravenous infusion of 1.5 mg/kg over the first hour, and 100 to 250 micrograms/kg per hour thereafter. The maximum cumulative dose in the first 24 hours should not exceed 600 mg. Infusion should not generally continue for more than 24 hours and oral therapy should be substituted as soon as possible.

The dose of flecainide should be reduced in renal impairment (see below).

For the use of flecainide in children, see below.

Flecainide has also been tried in the treatment of refractory neuropathic pain.

Administration. Flecainide is usually given orally or intravenously, but rapid and reliable absorption has been reported from a rectal solution in healthy subjects.[1] The mean time to achieve peak serum concentration was 0.67 hours and the mean bioavailability was 98%, compared with 1 hour and 78% for an oral solution and 4 hours and 81% for a tablet. The absorption of flecainide given rectally to 2 critically ill patients was good in one but poor in the other[2] and it was recommended that rectal dosage be reserved for patients unresponsive to maximal parenteral therapy and in whom the oral or nasogastric routes cannot be used.

1. Lie-A-Huen L, *et al.* Absorption kinetics of oral and rectal flecainide in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 595–8.
2. Quattrocchi FP, Karim A. Flecainide acetate administration by enema. *DICP Ann Pharmacother* 1990; **24:** 1233–4.

Administration in children. Flecainide has been used successfully to treat arrhythmias in children,[1,2] and beneficial results have also been reported[3] with flecainide and sotalol together. US licensed product information recommends an initial oral dose of flecainide acetate 50 mg/m^2 daily in divided doses for those aged under 6 months and 100 mg/m^2 daily for those aged over 6 months; a dose of 200 mg/m^2 daily should not be exceeded.

The *BNFC* recommends the following doses of flecainide acetate:

- neonates: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response, or 1 to 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled
- children aged 1 month to 12 years: an **oral** dose of 2 mg/kg 2 or 3 times daily, adjusted according to response to a maximum of 8 mg/kg or 300 mg daily, or 2 mg/kg **intravenously** over 10 to 30 minutes, followed if necessary by continuous infusion at a rate of 100 to 250 micrograms/kg per hour until arrhythmia is controlled (maximum cumulative dose 600 mg in 24 hours)
- children aged 12 to 18 years: as for adults (see Uses and Administration, above); the maximum oral dose should not exceed 300 mg daily

1. Perry JC, Garson A. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature on efficacy, safety, and dosing. *Am Heart J* 1992; **124:** 1614–21.
2. O'Sullivan JJ, *et al.* Digoxin or flecainide for prophylaxis of supraventricular tachycardia in infants? *J Am Coll Cardiol* 1995; **26:** 991–4.
3. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.

Administration in renal impairment. The plasma elimination half-life for flecainide may be prolonged in patients with renal impairment[1-3] and doses should be reduced. For patients with a creatinine clearance equal to or less than 35 mL/minute per 1.73 m^2 licensed product information states that the initial oral dose of flecainide acetate should not exceed 100 mg daily and plasma concentrations should be monitored; intravenous doses should be halved.

Special care with dosage adjustments should be taken in patients with renal impairment who are also poor metabolisers (see under Metabolism, above).

1. Braun J, *et al.* Pharmacokinetics of flecainide in patients with mild and moderate renal failure compared with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **31:** 711–14.
2. Forland SC, *et al.* Oral flecainide pharmacokinetics in patients with impaired renal function. *J Clin Pharmacol* 1988; **28:** 259–67.
3. Williams AJ, *et al.* Pharmacokinetics of flecainide acetate in patients with severe renal impairment. *Clin Pharmacol Ther* 1988; **43:** 449–55.

Cardiac arrhythmias. Flecainide has an established role in the management of ventricular and supraventricular arrhythmias (p.1160). It has been used in children (see above) and has also been successfully given to pregnant women (transplacental therapy) to treat fetal arrhythmias,[1,2] although there have been reports[3,4] of neonatal toxicity.

Use in patients with asymptomatic arrhythmias after myocardial infarction is not recommended since an increase in mortality was found in the Cardiac Arrhythmia Suppression Trial (CAST), in which flecainide[5-7] and the related class Ic antiarrhythmics encainide[5-7] and moracizine[8] were used in an attempt to reduce the risk of sudden death in post-infarction patients with premature ventricular contractions.

Flecainide has also been used in the diagnosis of Brugada syndrome.[9] This syndrome is characterised by syncope or aborted cardiac arrest due to ventricular tachycardia in the absence of organic heart disease, and is thought to be due to a deficiency in the inward sodium current in cardiac cells. Flecainide, because of its sodium-channel blocking action, exaggerates this deficiency and the resulting ST-segment elevation, and aids in diagnosis; however, it may precipitate serious ventricular arrhythmias[10] and must not be used for treatment.

1. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.
2. Krapp M, *et al.* Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002; **19:** 158–64.
3. Rasheed A, *et al.* Neonatal ECG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart* 2003; **89:** 470.
4. Hall CM, Ward Platt MP. Neonatal flecainide toxicity following supraventricular tachycardia treatment. *Ann Pharmacother* 2003; **37:** 1343–4.
5. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. CAST and beyond: implications of the cardiac arrhythmias suppression trial. *Circulation* 1990; **81:** 1123–7. [Simultaneous publication occurred in *Eur Heart J* 1990; **11:** 194–9].
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; **321:** 406–12.
7. Echt DS, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; **324:** 781–8.
8. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
9. Singleton CB, McGuire MA. The Brugada syndrome: a recently recognised genetic disease causing sudden cardiac death. *Med J Aust* 2000; **173:** 415–8.
10. Gasparini M, *et al.* Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003; **26:** 338–41.

Pain. Class Ic antiarrhythmics such as flecainide are among the drugs that have been used as analgesic adjuvants in neuropathic pain (p.8), although the evidence for benefit with flecainide is limited. A positive response has been reported[1,2] in patients with severe pain due to nerve infiltration, but a controlled trial had to be stopped[3] when supplies of the drug were withdrawn after the finding of increased mortality in a study in post-infarction patients (CAST; see Cardiac Arrhythmias, above), and a later study[4] found that flecainide was effective in only a minority of patients with cancer pain. A small study[5] has suggested that flecainide may be effective in postherpetic neuralgia.

1. Dunlop R, *et al.* Analgesic effects of oral flecainide. *Lancet* 1988; **i:** 420–1.
2. Sinnott C, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
3. Dunlop RJ, *et al.* Flecainide in cancer nerve pain. *Lancet* 1991; **337:** 1347.
4. Chong SF, *et al.* Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997; **13:** 112–17.
5. Ichimata M, *et al.* Analgesic effects of flecainide on postherpetic neuralgia. *Int J Clin Pharmacol Res* 2001; **21:** 15–19.

Preparations

BP 2008: Flecainide Injection; Flecainide Tablets;
USP 31: Flecainide Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diondel; Tambocor†; ***Austral.:*** Flecatab; Tambocor; ***Austria:*** Aristocor; ***Belg.:*** Apocard; Tambocor; ***Canad.:*** Tambocor; ***Chile:*** Tambocor; ***Cz.:*** Tambocor; ***Denm.:*** Tambocor; ***Fin.:*** Tambocor; ***Fr.:*** Flecaine; ***Ger.:*** flecadura; Tambocor; ***Gr.:*** Tambocor; ***Hong Kong:*** Tambocor; ***Irl.:*** Tambocor; ***Israel:*** Tambocor; ***Ital.:*** Almarytm; ***Malaysia:*** Tambocor; ***Mex.:*** Tambocor; ***Neth.:*** Tambocor; ***Norw.:*** Tambocor; ***NZ:*** Tambocor; ***Philipp.:*** Tambocor; ***Port.:*** Apocard; ***S.Afr.:*** Tambocor; ***Singapore:*** Tambocor; ***Spain:*** Apocard; ***Swed.:*** Tambocor; ***Switz.:*** Tambocor; ***Thai.:*** Tambocor; ***UK:*** Tambocor; ***USA:*** Tambocor.

Flosequinan *(BAN, USAN, rINN)*

BTS-49465; Flosequinan; Flosequinán; Flosequinanum. 7-Fluoro-1-methyl-3-methylsulphinyl-4-quinolone.

Флосехинан

$C_{11}H_{10}FNO_2S = 239.3.$

CAS — 76568-02-0.

ATC — C01DB01.

ATC Vet — QC01DB01.

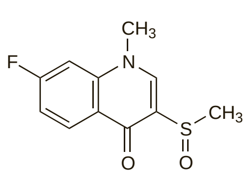

Profile

Flosequinan is a direct-acting arteriovenous vasodilator that was used as an adjunct to the conventional treatment of heart failure, but was withdrawn from the market after findings of excess mortality.

◊ References.

1. Kamali F, Edwards C. Possible role of metabolite in flosequinan-related mortality. *Clin Pharmacokinet* 1995; **29:** 396–403.

Fluindione *(rINN)*

Fluindiona; Fluindionum; Fluorindione; LM-123. 2-(4-Fluorophenyl)indan-1,3-dione.

Флуиндион

$C_{15}H_9FO_2 = 240.2.$

CAS — 957-56-2.

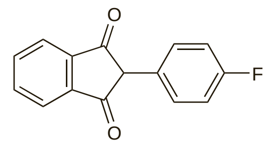

Profile

Fluindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1425). It is used in the management of thromboembolic disorders (p.1187) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p.1369), its use is limited.

The usual initial dose is 20 mg daily; the dose is then adjusted according to coagulation tests.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Previscan.

Fluvastatin Sodium *(BANM, USAN, rINNM)*

Fluvastatina sódica; Fluvastatine sodique; Fluvastatinum natricum; Natrii Fluvastatinum; XU-62-320. Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate.

Натрий Флувастатин

$C_{24}H_{25}FNNaO_4 = 433.4.$

CAS — 93957-54-1 (fluvastatin); 93957-55-2 (fluvastatin sodium).

ATC — C10AA04.

ATC Vet — QC10AA04.

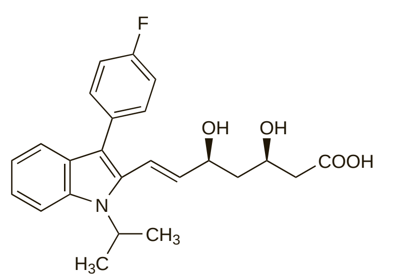

(fluvastatin)

Pharmacopoeias. In *US.*

USP 31 (Fluvastatin Sodium). A white to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in water, in alcohol, and in methyl alcohol. A 1% solution in water has a pH of 8.0 to 10.0. Store in airtight containers at a temperature not exceeding 40°. Protect from light and moisture.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Interactions

The interactions of statins with other drugs are described under simvastatin (p.1392). Fluvastatin is metabolised mainly by the cytochrome P450 isoenzyme CYP2C9 and does not have the same interactions with CYP3A4 inhibitors as simvastatin, although caution has been advised when such combinations are used. However, interactions may occur with inhibitors of CYP2C9, such as fluconazole; use with rifampicin, a CYP2C9 inducer, may reduce the bioavailability of fluvastatin by about 50%.

Pharmacokinetics

Fluvastatin is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. Metabolism is mainly by the cytochrome P450 isoenzyme CYP2C9, with only a small amount metabolised by CYP3A4. An absolute bioavailability of about 24% has been reported. It is more than 98% bound to plasma proteins. About 90% is excreted in the faeces, mainly as metabolites, with only about 6% being excreted in the urine.

◊ General reviews.

1. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet* 2001; **40:** 263–81.

Uses and Administration

Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol, in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias). It is also given as secondary prophylaxis for cardiovascular risk reduction (p.1164) in patients with ischaemic heart disease, including patients who have had a percutaneous coronary intervention.

Fluvastatin is given orally as the sodium salt, but doses are expressed in terms of the base; 21.06 mg of fluvastatin sodium is equivalent to about 20 mg of base. The usual initial dose is 20 to 40 mg of fluvastatin once daily in the evening. This may be increased, if necessary, at intervals of 4 weeks or more, up to 80 mg daily, in two divided doses or as a once-daily modified-release preparation; patients requiring a large reduction in LDL-cholesterol may be started on the 80 mg daily dose. A dose of 80 mg daily may also be used in patients who have had a percutaneous coronary intervention.

For the use of fluvastatin in children, see below.

◊ References.

1. Langtry HD, Markham A. Fluvastatin: a review of its use in lipid disorders. *Drugs* 1999; **57:** 583–606.
2. Corsini A, *et al.* Fluvastatin: clinical and safety profile. *Drugs* 2004; **64:** 1305–23.
3. Winkler K, *et al.* Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007; **29:** 1987–2000.
4. McDonald KJ, Jardine AG. The use of fluvastatin in cardiovascular risk management. *Expert Opin Pharmacother* 2008; **9:** 1407–14.

Administration in children. Fluvastatin may be used in the management of children aged 10 to 16 years with heterozygous familial hypercholesterolaemia.[1] US licensed product information recommends an initial oral dose of 20 mg once daily, increased as required, at intervals of 6 weeks, to a maximum dose of 80 mg daily in 2 divided doses or as a once-daily modified-release preparation.

1. van der Graaf A, *et al.* Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. *Acta Paediatr* 2006; **95:** 1461–6.

Preparations

USP 31: Fluvastatin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Lescol; ***Austral.:*** Lescol; Vastin; ***Austria:*** Lescol; ***Belg.:*** Lescol; ***Braz.:*** Lescol; ***Canad.:*** Lescol; ***Cz.:*** Lescol; ***Denm.:*** Canef; Lescol; ***Fin.:*** Canef; Lescol; ***Fr.:*** Fractal; Lescol; ***Ger.:*** Cranoc; LOCOL; ***Gr.:*** Hovalin; Lescol; ***Hong Kong:*** Lescol; ***Hung.:*** Lescol; Lochol; ***Indon.:*** Lescol; ***Irl.:*** Lescol; ***Israel:*** Lescol; ***Ital.:*** Lescol; Lipaxan; Primesin; ***Jpn:*** Lochol; ***Malaysia:*** Lescol; ***Mex.:*** Canef†; Lescol; ***Neth.:*** Canef; Lescol; Vaditon; ***Norw.:*** Lescol; ***NZ:*** Lescol†; ***Philipp.:*** Lescol; ***Pol.:*** Lescol; ***Port.:*** Canef; Cardiol; Lescol; ***Rus.:*** Lescol (Лескол); ***S.Afr.:*** Lescol; ***Singapore:*** Lescol; ***Spain:*** Digaril; Lescol; Liposit; Lymetel; Princess Prolib†; Vaditon; ***Swed.:*** Canef; Lescol; ***Switz.:*** Lescol; Primesin; ***Thai.:*** Lescol; ***Turk.:*** Lescol; ***UK:*** Lescol; ***USA:*** Lescol; ***Venez.:*** Lescol†.

Fondaparinux Sodium *(BAN, USAN, rINN)*

Fondaparin Sodium; Fondaparinuks Sodyum; Fondaparinuuksinatrium; Fondaparinux sódico; Fondaparinux Sodique; Fondaparinuxnatrium; Fondaparinuxum Natricum; Fondaparinuxum Natrium; Org-31540; SR-90107A.

Фондапаринукс Натрия

CAS — 114870-03-0.

ATC — B01AX05.

ATC Vet — QB01AX05.

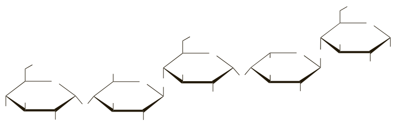

(fondaparinux)

Adverse Effects

As for Heparin, p.1301.

Treatment of Adverse Effects

If bleeding occurs fondaparinux should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for fondaparinux (but see below).

Overdosage. Activated eptacog alfa (recombinant factor VIIa) given 2 hours after an injection of fondaparinux was found[1] in healthy subjects to normalise coagulation times and thrombin generation for up to 6 hours, suggesting that it may be useful to treat bleeding complications, or if acute surgery is needed.

1. Bijsterveld NR, *et al.* Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; **106:** 2550–54.

Precautions

As for Heparin, p.1303.

Fondaparinux should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) in the presence of fondaparinux itself.

Fondaparinux is contra-indicated in severe renal impairment, and special care is required in patients with body-weight below 50 kg.

Interactions

As for Heparin, p.1303.

Pharmacokinetics

After subcutaneous injection fondaparinux sodium is rapidly and completely absorbed, with bioavailability of 100%. It is extensively bound in plasma, predominantly to antithrombin III. It is excreted in the urine, with 64 to 77% of a dose excreted unchanged. The elimination half-life is between 17 and 21 hours, but is prolonged in patients with renal impairment, in the elderly, and in those weighing less than 50 kg.

◊ References.

1. Donat F, *et al.* The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; **41** (suppl 2): 1–9.
2. Paolucci F, *et al.* Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin Pharmacokinet* 2002; **41** (suppl 2): 11–18.

Pregnancy. Although an *in vitro* study[1] reported that fondaparinux does not cross the placenta, a small study[2] in pregnant women who had received fondaparinux found that anti-factor Xa activity was elevated in umbilical cord blood, suggesting that a small amount of placental transfer had taken place.

1. Lagrange F, *et al.* Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet* 2002; **41** (suppl 2): 47–9.
2. Dempfle C-EH. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; **350:** 1914–15.

Uses and Administration

Fondaparinux is a synthetic pentasaccharide that acts as a selective inhibitor of activated factor X. It is used as the sodium salt as an anticoagulant in the management of venous thromboembolism (p.1189), unstable angina (p.1157), and acute myocardial infarction (p.1175). It has also been used in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Adverse Effects of Heparin, p.1302).

For *prophylaxis* of **venous thromboembolism** in abdominal and orthopaedic surgery, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily, starting 6 to 8 hours after surgery and continued for at least 5 to 9 days, or up to 32 days in hip fracture. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6 to 14 days.

In the initial *treatment* of venous thromboembolism, fondaparinux sodium is given by subcutaneous injection once daily at a dose of 5 mg for patients weighing less than 50 kg, 7.5 mg for weight 50 to 100 kg, and 10 mg for weight over 100 kg. Treatment is usually continued for 5 to 9 days, and at least until oral anticoagulation is established.

Fondaparinux is also used in **unstable angina** and acute ST-elevation **myocardial infarction**, but is only indicated in patients for whom urgent percutaneous coronary intervention is not planned. It is given in a dose of 2.5 mg subcutaneously once daily for up to 8 days, with the first dose given intravenously in acute ST-elevation myocardial infarction. Heparin should be given at the time of the procedure if percutaneous coronary intervention is performed and fondaparinux should be restarted when clinically appropriate.

Doses of fondaparinux may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Keam SJ, Goa KL. Fondaparinux sodium. *Drugs* 2002; **62:** 1673–85.
2. Tran AH, Lee G. Fondaparinux for prevention of venous thromboembolism in major orthopedic surgery. *Ann Pharmacother* 2003; **37:** 1632–43.
3. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; **349:** 1695–1702.
4. Reynolds NA, *et al.* Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. *Drugs* 2004; **64:** 1575–96.
5. Büller HR, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; **140:** 867–73.
6. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295:** 1519–30.
7. Cohen AT, *et al.* ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Abridged version: *BMJ* 2006; **332:** 325–9. Full version: http://www.bmj.com/cgi/reprint/332/7537/325 (accessed 14/05/08)
8. Yusuf S, *et al.* Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.
9. Efird LE, Kockler DR. Fondaparinux for thromboembolic treatment and prophylaxis of heparin-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 1383–7.

Administration in renal impairment. Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. US licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 30 mL/minute, and advises caution in those with CC between 30 and 50 mL/minute. UK licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 20 mL/minute; for patients with CC between 20 and 50 mL/minute a subcutaneous dose of 1.5 mg once daily is recommended for prophylaxis of venous thromboembolism, but no dosage alteration is required for unstable angina or myocardial infarction.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Arixtra; ***Belg.:*** Arixtra; ***Braz.:*** Arixtra; ***Canad.:*** Arixtra; ***Cz.:*** Arixtra; ***Denm.:*** Arixtra; ***Fin.:*** Arixtra; ***Fr.:*** Arixtra; ***Ger.:*** Arixtra; ***Gr.:*** Arixtra; ***Hong Kong:*** Arixtra†; ***Indon.:*** Arixtra; ***Ital.:*** Arixtra; ***Malaysia:*** Arixtra; ***Mex.:*** Arixtra; ***Neth.:*** Arixtra; Quixidar; ***Norw.:*** Arixtra; ***NZ:*** Arixtra†; ***Pol.:*** Arixtra; ***Port.:*** Arixtra; Quixidar†; ***Rus.:*** Arixtra (Арикстра); ***Singapore:*** Arixtra; ***Spain:*** Arixtra; ***Swed.:*** Arixtra; ***Switz.:*** Arixtra; ***Thai.:*** Arixtra; ***UK:*** Arixtra; ***USA:*** Arixtra.

Fosinopril Sodium *(BANM, USAN, rINNM)*

Fosinopriilinatrium; Fosinopril sódico; Fosinopril sodique; Fosinopril Sodyum; Fosinoprilnatrium; Fosinoprilum natricum; Natrii Fosinoprilum; SQ-28555. (4*S*)-4-Cyclohexyl-1-{[(*RS*)-2-methyl-1-(propionyloxy)propoxy]-(4-phenylbutyl)phosphinylacetyl}-L-proline sodium.

Натрий Фозиноприл

$C_{30}H_{45}NNaO_7P = 585.6.$

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.

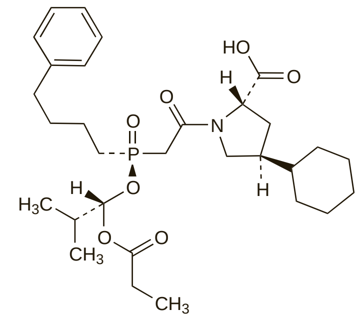

(fosinopril)

Pharmacopoeias. In *US.*

USP 31 (Fosinopril Sodium). Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat are achieved about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

◊ References.

1. Singhvi SM, *et al.* Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; **25:** 9–15.
2. Kostis JB, *et al.* Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; **58:** 660–5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with varying degrees of impairment,[1-5] including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al.* Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; **49:** 457–67.
2. Gehr TWB, *et al.* Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; **41:** 165–9.
3. Sica DA, *et al.* Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; **20:** 420–7.
4. Gehr TWB, *et al.* The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; **45:** 431–6.
5. Greenbaum R, *et al.* Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; **49:** 23–31.

Uses and Administration

Fosinopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Fosinopril owes its activity to fosinoprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 2 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Fosinopril is given orally as the sodium salt.

In the treatment of **hypertension**, the initial dose of fosinopril sodium is 10 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 10 to 40 mg once daily. In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Fosinopril sodium is given in an initial dose of 10 mg once daily and, if well tolerated, increased to a maximum of 40 mg once daily. An initial dose of 5 mg may be given in patients at high risk of hypotension.

◊ Reviews.

1. Murdoch D, McTavish D. Fosinopril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in essential hypertension. *Drugs* 1992; **43:** 123–40.
2. Wagstaff AJ, *et al.* Fosinopril: a reappraisal of its pharmacology and therapeutic efficacy in essential hypertension. *Drugs* 1996; **51:** 777–91.
3. Davis R, *et al.* Fosinopril: a review of its pharmacology and clinical efficacy in the management of heart failure. *Drugs* 1997; **54:** 103–16.

Preparations

USP 31: Fosinopril Sodium and Hydrochlorothiazide Tablets; Fosinopril Sodium Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Fosipril; Monace; Monopril; ***Austria:*** Fositens; ***Belg.:*** Fosinil; ***Braz.:*** Monopril; ***Canad.:*** Monopril; ***Chile:*** Monopril; ***Cz.:*** Apo-Fosinop; Fosinogen; Monopril; ***Denm.:*** Monopril; ***Fr.:*** Fozitec; ***Ger.:*** Dynacil; Fosinorm; ***Gr.:*** Monopril; Sinopril†; ***Hong Kong:*** Monopril; ***Hung.:*** Monopril; Noviform; ***India:*** Fovas; ***Indon.:*** Acenor-M; ***Israel:*** Vasopril†; ***Ital.:*** Eliten; Fosipres; Tensogard; ***Malaysia:*** Monopril†; ***Mex.:*** Monopril; ***Neth.:*** NewAce; ***Philipp.:*** BPNorm; ***Pol.:*** Monopril; ***Port.:*** Fositen; ***Rus.:*** Fosicard (Фозикард); Monopril (Моноприл); ***S.Afr.:*** Monopril; ***Singapore:*** Monopril; ***Spain:*** Fosinil†; Fositens; Hiperlex; Tenso Stop; Tensocardil; ***Swed.:*** Monopril; ***Switz.:*** Fositen; ***Thai.:*** Monopril; ***Turk.:*** Monopril; ***UAE:*** Fosipril; ***UK:*** Staril; ***USA:*** Monopril; ***Venez.:*** Monopril.

Multi-ingredient: ***Austral.:*** Monoplus; ***Austria:*** Aceplus; Fosicomb; ***Belg.:*** Foside†; ***Braz.:*** Monoplus; ***Chile:*** Monopril Plus; ***Cz.:*** Foprin Plus H; ***Fr.:*** Foziretic; ***Ger.:*** Dynacil comp; Fosinorm comp; ***Gr.:*** Fozide; Monoplus†; ***Hung.:*** Duopril; ***Israel:*** Vasopril Plus†; ***Ital.:*** Elidiur; Fosicombi; Tensozide; ***Neth.:*** Diurace; ***Port.:*** Fositen Plus; ***Rus.:*** Fosicard H (Фозикард Н); Fozide (Фозид); ***S.Afr.:*** Monozide; ***Spain:*** Fositens Plus; Hiperlex Plus; Tenso Stop Plus; ***Swed.:*** Monopril comp†; ***Switz.:*** Fosicomp; ***Thai.:*** Monoplus; ***Turk.:*** Monopril Plus; ***USA:*** Monopril-HCT; ***Venez.:*** Monopril Plus.

Furosemide *(BAN, USAN, rINN)* ⊗

Frusemide; Furosemid; Furosemida; Furosémide; Furosemidi; Furosemidum; Furoszemid; Furozemidas; LB-502. 4-Chloro-*N*-furfuryl-5-sulphamoylanthranilic acid.

Фуросемид

$C_{12}H_{11}ClN_2O_5S$ = 330.7.

CAS — 54-31-9.

ATC — C03CA01.

ATC Vet — QC03CA01.

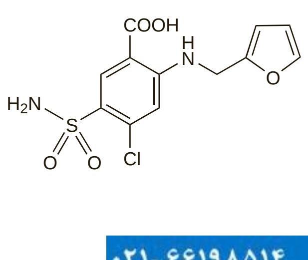

NOTE. Compounded preparations of furosemide may be represented by the following names:

- Co-amilofruse (*BAN*)—furosemide 8 parts and amiloride hydrochloride 1 part (w/w).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Furosemide). A white or almost white, crystalline powder. Practically insoluble in water and in dichloromethane; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Furosemide). A white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; very slightly soluble in chloroform; slightly soluble in ether; soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Solutions for injection are prepared with the aid of sodium hydroxide, giving solutions with a pH of 8.0 to 9.3.

Incompatibility. Solutions of furosemide for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

Furosemide injection has been reported[1] to be visually incompatible with injections of diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, labetalol hydrochloride, midazolam hydrochloride, milrinone lactate, nicardipine hydrochloride, and vecuronium bromide. Incompatibility has also been noted with parenteral nutrient solutions,[2] with cisatracurium besilate,[3] with levofloxacin,[4] with phenylephrine,[5] and with vasopressin.[5]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–1300.
3. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
4. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
5. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; **63:** 906–8.

Stability. A study[1] showed that furosemide injection (10 mg/mL) in 25% human albumin solution was stable for 48 hours at room temperature when protected from light, and for 14 days under refrigeration. No bacterial or fungal growth was found.

1. Elwell RJ, *et al.* Stability of furosemide in human albumin solution. *Ann Pharmacother* 2002; **36:** 423–6.

Adverse Effects

Most adverse effects of furosemide occur with high doses, and serious effects are uncommon. The most common adverse effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, and hypochloraemic alkalosis, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, oliguria, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolaemia and dehydration may occur, especially in the elderly. Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics such as furosemide than with thiazide diuretics. Unlike the thiazides, furosemide increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants.

Furosemide may cause hyperuricaemia and precipitate gout in some patients. It may provoke hyperglycaemia and glycosuria, but probably to a lesser extent than the thiazide diuretics.

Pancreatitis and cholestatic jaundice seem to occur more often than with the thiazides. Other adverse effects include blurred vision, yellow vision, dizziness, headache, and orthostatic hypotension. Other adverse effects occur rarely. Skin rashes and photosensitivity reactions may be severe; hypersensitivity reactions include interstitial nephritis and vasculitis; fever has also been reported. Bone marrow depression may occur: there have been reports of agranulocytosis, thrombocytopenia, and leucopenia. Tinnitus and deafness may occur, in particular during rapid high-dose parenteral furosemide. Deafness may be permanent, especially in patients taking other ototoxic drugs.

Incidence of adverse effects. In a survey of 553 hospital inpatients[1] receiving furosemide 220 patients (40%) had 480 adverse reactions. Electrolyte disturbances occurred in 130 (23.5%) patients and extracellular volume depletion in 50 (9%). Adverse reactions were more common in those with liver disease, and hepatic coma occurred in 20 patients with hepatic cirrhosis. A similar survey in 585 hospital inpatients[2] revealed 177 adverse effects in 123 (21%). These included volume depletion in 85 patients (14.5%), hypokalaemia in 21 (3.6%), and hyponatraemia in 6 (1%). Hypokalaemia was considered to be life-threatening in 2 patients. Hyperuricaemia occurred in 54 patients (9.2%), of whom 40 also had volume depletion, and clinical gout developed in 2.

1. Naranjo CA, *et al.* Frusemide-induced adverse reactions during hospitalization. *Am J Hosp Pharm* 1978; **35:** 794–8.
2. Lowe J, *et al.* Adverse reactions to frusemide in hospital inpatients. *BMJ* 1979; **2:** 360–2.

Carcinogenicity. See under Hydrochlorothiazide, p.1308.

Effects on the ears. Ototoxicity and deafness during furosemide therapy is most frequently associated with elevated blood concentrations resulting from rapid intravenous infusion[1] or delayed excretion in patients with renal impairment.[2] Of 29 cases of furosemide-induced deafness reported to the FDA[3] in the USA, most patients had renal disease or had received the drug intravenously. Eight patients had also received another ototoxic drug. However, deafness occurred in 11 patients after oral use, and in 4 of these hearing loss occurred in the absence of renal disease or other ototoxic drugs. Hearing loss was generally transient, lasting from one-half to 24 hours, but permanent hearing loss occurred in 3 patients, one of whom had taken furosemide orally. Deafness was not always associated with high doses; six patients had received a total of 200 mg or less of furosemide.

See also Precautions, below.

1. Heidland A, Wigand ME. Einfluss hoher Furosemiddosen auf die Gehörfunktion bei Urämie. *Klin Wochenschr* 1970; **48:** 1052–6.
2. Schwartz GH, *et al.* Ototoxicity induced by furosemide. *N Engl J Med* 1970; **282:** 1413–14.
3. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med* 1979; **91:** 744–5.

Effects on electrolyte balance. *CALCIUM.* Furosemide increases renal calcium excretion. There is a danger of hypocalcaemic tetany during furosemide use in hypoparathyroid patients[1] and it has also been reported[2] in a patient with latent hypoparathyroidism following thyroidectomy.

The decrease in serum-calcium concentrations could also induce hyperparathyroidism. In a study involving 36 patients with heart failure, furosemide was associated with elevations in both parathyroid hormone and alkaline phosphatase concentrations, possibly indicating accelerated bone remodelling such as that found in primary hyperparathyroidism.[3]

For reports of hypercalciuria, rickets, renal calculi, and hyperparathyroidism in neonates given furosemide, see Effects in Infants and Neonates, below.

1. Gabow PA, *et al.* Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. *Ann Intern Med* 1977; **86:** 579–81.
2. Bashey A, MacNee W. Tetany induced by frusemide in latent hypoparathyroidism. *BMJ* 1987; **295:** 960–1.
3. Elmgreen J, *et al.* Elevated serum parathyroid hormone concentration during treatment with high ceiling diuretics. *Eur J Clin Pharmacol* 1980; **18:** 363–4.

MAGNESIUM, POTASSIUM, AND SODIUM. For discussions of the effects of diuretics on these electrolytes see under the Adverse Effects of Hydrochlorothiazide, p.1308.

Effects in infants and neonates. Furosemide is commonly used in the treatment of cardiac and pulmonary disorders in premature infants and neonates. This age group appears to be particularly susceptible to adverse effects arising from the increase in urinary calcium excretion which occurs during long-term use. Increases in parathyroid hormone concentration[1,2] and evidence of bone resorption[1,3] support the suggestion that the increased calcium loss causes secondary hyperparathyroidism. There have been reports of decreased mineral content of bone,[1,3] rickets,[4] fractures,[3] and renal calcification.[1,5-7] An observation[5] that renal calcification could be reversed by the addition of a thiazide diuretic was supported by other workers.[6] There is evidence[8] that furosemide-related renal calcifications in very low birth-weight infants might be associated with long-term renal impairment. Renal calcification has also been reported after furosemide use in older infants.[9]

It has been suggested[10] that a sodium deficit in infants given furosemide for heart failure may contribute to a failure to thrive.

Concern has been expressed over the finding[11] that furosemide use in premature infants with respiratory distress syndrome increases the incidence of patent ductus arteriosus. The mechanism is thought to be connected with stimulation of renal prostaglandin E_2. However, the increased incidence of patent ductus arteriosus did not adversely affect the mortality in infants given furosemide, and a subsequent study[12] failed to find any increase in the incidence of patent ductus arteriosus in infants treated with furosemide compared with a control group. Paradoxically, furosemide has been used in the management of delayed closure of ductus (see Patent Ductus Arteriosus under Uses and Administration, below). There is a possibility that furosemide may not be effective in infants given indometacin[13] but it can prevent the decline in urine output which occurs during indometacin use.[14,15]

1. Venkataraman PS, *et al.* Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child* 1983; **187:** 1157–61.
2. Vileisis RA. Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease. *Pediatrics* 1990; **85:** 316–22.
3. Morgan MEI, Evans SE. Osteopenia in very low birthweight infants. *Lancet* 1986; **ii:** 1399–1400.
4. Chudley AE, *et al.* Nutritional rickets in 2 very low birthweight infants with chronic lung disease. *Arch Dis Child* 1980; **55:** 687–90.
5. Hufnagle KG, *et al.* Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982; **70:** 360–3.
6. Noe HN, *et al.* Urolithiasis in pre-term neonates associated with furosemide therapy. *J Urol (Baltimore)* 1984; **132:** 93–4.
7. Pearse DM, *et al.* Sonographic diagnosis of furosemide-induced nephrocalcinosis in newborn infants. *J Ultrasound Med* 1984; **3:** 553–6.
8. Downing GJ, *et al.* Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years. *J Pediatr* 1992; **120:** 599–604.
9. Alon US, *et al.* Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. *J Pediatr* 1994; **125:** 149–51.
10. Salmon AP, *et al.* Sodium balance in infants with severe congestive heart failure. *Lancet* 1989; **ii:** 875.
11. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
12. Yeh TF, *et al.* Early furosemide therapy in premature infants (≤ 2000 gm) with respiratory distress syndrome: a randomized controlled trial. *J Pediatr* 1984; **105:** 603–9.
13. Friedman Z, *et al.* Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low-birth-weight infants. *J Pediatr* 1978; **93:** 512–15.
14. Yeh TF, *et al.* Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. *J Pediatr* 1982; **101:** 433–7.
15. Nahata MC, *et al.* Furosemide can prevent decline in urine output in infants receiving indomethacin for patent ductus closure: a multidose study. *Infusion* 1988; **12:** 11–12 and 15.

Effects on lipid metabolism. Most studies into the effects of diuretics on blood-lipid concentrations have used thiazides (see Hydrochlorothiazide, p.1308). The few studies into the effects of furosemide suggest that, like thiazides, it may adversely influence blood-lipid concentrations during short-term use.[1]

1. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins I: diuretics. *Drugs* 1986; **32:** 260–78.

Precautions

Precautions and contra-indications for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. Furosemide should not be given in pre-comatose states associated with hepatic cirrhosis. It should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

To reduce the risk of ototoxicity, licensed product information recommends that furosemide should not be injected intravenously at a rate exceeding 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Furosemide should be used with caution during pregnancy and breast feeding since it crosses the placenta and also appears in breast milk. Furosemide may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

Hepatic impairment. In patients with chronic heart failure and moderate liver congestion, high-dose furosemide therapy could produce increases in liver enzymes suggestive of hepatitis.[1] Special care should be taken with the dosage and mode of administration of furosemide in such patients to avoid severe ischaemic liver damage caused by a drop in systemic blood pressure.

As with the thiazides, furosemide should be avoided in patients with severe hepatic impairment.

1. Lang I, *et al.* Furosemide and increases in liver enzymes. *Ann Intern Med* 1988; **109:** 845.

Hypersensitivity. Furosemide is a sulfur-containing diuretic and hypersensitivity reactions may occur, although they are rare; cross-reactivity with other sulfur-containing drugs is also possible. However, 2 patients who had in the distant past shown serious adverse reactions to sulfur-containing diuretics were successfully treated[1] with furosemide using a rechallenge protocol. They were given an initial dose of 50 micrograms which was increased gradually each day to 20 mg by day 10, and were discharged from hospital on a maintenance dose of 40 mg twice daily. Another patient[2] with a history of sulfonamide-induced pancreatitis developed pancreatitis with furosemide, which recurred with bumetanide and torasemide and on rechallenge with furosemide. She underwent a rapid desensitisation regimen and was subsequently successfully stabilised on oral furosemide.

1. Earl G, *et al.* Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; **138:** 358–9.
2. Juang P, *et al.* Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. *Ann Pharmacother* 2006; **40:** 128–34.

Hypoparathyroidism. For comments on the possibility of hypocalcaemic tetany in hypoparathyroid patients taking furosemide, see Effects on Electrolyte Balance, above.

Infants and neonates. Caution must be exercised in using furosemide in infants, particularly for long periods. The immaturity of the renal system can result in unexpectedly high blood concentrations and extended half-lives. Fluid and electrolyte balances should therefore be monitored carefully. Neonates appear to be particularly susceptible to increases in urinary calcium concentrations after long-term use. There have also been reports[1] of an increased incidence of patent ductus arteriosus in infants given furosemide, although this did not adversely affect mortality.

Secondly, several studies[2-4] have shown furosemide to be a potent displacer of bilirubin from albumin binding sites and it should be used with caution in jaundiced infants. On a molar basis chlorothiazide, furosemide, and etacrynic acid were at least as potent as sulfafurazole in displacing bilirubin from albumin.[3] Doses of furosemide 1 mg/kg probably do not produce a significant increase in free bilirubin in most jaundiced infants,[3,4] although doses greater than 1.5 mg/kg or repeated dosing could potentially do so.[4] Chlorothiazide 15 to 20 mg/kg would not be an appropriate alternative to furosemide[3] since it could produce higher plasma bilirubin concentrations in jaundiced infants.

In addition, there is some evidence from an *in vitro* study[5] that bilirubin may displace furosemide from binding sites to a greater extent in neonates than in adults. The clearance of furosemide is much slower in neonates than in adults, with an eightfold prolongation in plasma half-life, and this should be taken into account during repeat dosing.[4]

1. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
2. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1977; **90:** 642–6.
3. Wennberg RP, *et al.* Displacement of bilirubin from human albumin by three diuretics. *J Pediatr* 1977; **90:** 647–50.
4. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.
5. Viani A, Pacifici GM. Bilirubin displaces furosemide from serum protein: the effect is greater in newborn infants than adult subjects. *Dev Pharmacol Ther* 1990; **14:** 90–5.

Porphyria. Furosemide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The interactions of furosemide that are due to its effects on fluid and electrolyte balance are similar to those of hydrochlorothiazide (see p.1309).

Furosemide may enhance the nephrotoxicity of cephalosporin antibacterials such as cefalotin and can enhance the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs.

Aliskiren. Licensed product information for aliskiren states that it may significantly decrease furosemide concentrations.

Antiepileptics. The diuretic effect of furosemide has been shown to be substantially reduced by mixed antiepileptic therapy that included *phenytoin*.[1,2] The mean diuretic effect of furosemide 20 mg or 40 mg by mouth in patients on such therapy was 68% and 51% that of healthy controls respectively.[1]

For the effect of furosemide on *phenobarbital*, see p.493.

Symptomatic hyponatraemia has been associated with the use of furosemide or hydrochlorothiazide with *carbamazepine*.[3]

1. Ahmad S. Renal insensitivity to frusemide caused by chronic anticonvulsant therapy. *BMJ* 1974; **3:** 657–9.
2. Fine A, *et al.* Malabsorption of frusemide caused by phenytoin. *BMJ* 1977; **2:** 1061–2.
3. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Diuretics. Severe electrolyte disturbances may occur in patients given *metolazone* with furosemide.

Hypnotics. A syndrome of flushing, tachycardia, elevated blood pressure, and severe diaphoresis was reported after intravenous dosage of furosemide in 6 patients who had taken *cloral hydrate* orally during the preceding 24 hours.[1] The reaction recurred in 1 patient on a subsequent occasion when given both drugs but not when furosemide was used without cloral hydrate. A subsequent retrospective study[2] among 43 patients who had received both cloral hydrate and furosemide showed that 1 patient had suffered a similar reaction; of 2 further patients who had possibly been affected, 1 had subsequently taken both drugs without adverse effects. A similar interaction has been reported in an 8-year-old child.[3]

1. Malach M, Berman N. Furosemide and chloral hydrate: adverse drug interaction. *JAMA* 1975; **232:** 638–9.
2. Pevonka MP, *et al.* Interaction of chloral hydrate and furosemide: a controlled retrospective study. *Drug Intell Clin Pharm* 1977; **11:** 332–5.
3. Dean RP, *et al.* Interaction of chloral hydrate and intravenous furosemide in a child. *Clin Pharm* 1991; **10:** 385–7.

Lithium. For reports of a possible increase in plasma-lithium concentrations in patients receiving loop diuretics, see p.405.

NSAIDs. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics.[1] Use of NSAIDs with diuretics may increase the risk of nephrotoxicity, although it has also been suggested that furosemide may protect against the renal effects of *indometacin* in infants (see Effects in Infants and Neonates, above).

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Probenecid. Probenecid has been shown[1-4] to reduce the renal clearance of furosemide, and to reduce the diuretic effect.[2,3]

1. Honari J, *et al.* Effects of probenecid on furosemide kinetics and natriuresis in man. *Clin Pharmacol Ther* 1977; **22:** 395–401.
2. Odlind B, Beermann B. Renal tubular secretion and effects of furosemide. *Clin Pharmacol Ther* 1980; **27:** 784–90.
3. Smith DE, *et al.* Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* 1980; **69:** 571–5.
4. Vree TB, *et al.* Probenecid inhibits the renal clearance of frusemide and its acyl glucuronide. *Br J Clin Pharmacol* 1995; **39:** 692–5.

Tobacco. The effects of tobacco smoking on the pharmacokinetics of furosemide have been reviewed.[1,2] Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide. However, this effect is attenuated in habitual smokers.

1. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; **17:** 90–108.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.

Xanthines. For the effect of furosemide on *theophylline*, see p.1144.

Pharmacokinetics

Furosemide is fairly rapidly absorbed from the gastrointestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to 99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk. The clearance of furosemide is not increased by haemodialysis.

◊ The pharmacokinetics of furosemide have been extensively reviewed.[1-6] The development of an analytical method using HPLC with fluorescence has produced greater sensitivity and more consistent results. Absorption after oral use is erratic and is subject to large inter- and intra-individual variation. It is influenced by the dosage form, underlying disease processes, and by the presence of food. Furosemide absorption in patients with heart failure has been reported to be even more erratic than in healthy subjects. The bioavailability of furosemide from oral dosage forms is also highly variable with reported values ranging from 20 to 100%. It is influenced by factors affecting absorption but the poor solubility of furosemide does not appear to have a major influence on bioavailability and *in vitro* dissolution data may not reflect *in vivo* bioavailability. Bioavailability tends to be decreased by about 10% in patients with renal disease, and slightly increased in liver disease. Values are erratic in patients with heart disease.

Furosemide is highly bound to plasma proteins, almost exclusively to albumin. The proportion of free (unbound) furosemide is higher in patients with heart disease, renal impairment, and cirrhosis of the liver. Patients with liver disease also have an increased apparent volume of distribution which is proportionally greater than the observed decrease in protein binding. Patients with nephrotic syndrome have significant proteinuria and secondary hypoalbuminaemia. This results in reduced protein binding in the blood, particularly at higher blood concentrations, and binding to proteins present in the urine, which may account for the resistance to furosemide therapy reported in these patients.

A glucuronide metabolite of furosemide is produced in varying amounts. The site of metabolism is unknown at present. There is debate over another potential metabolite, 4-chloro-5-sulfamoyl anthranilic acid (CSA). It has been argued[3] that it is an artefact produced during the extraction procedures although there is some evidence to refute this.[4]

A half-life for furosemide in healthy subjects has generally been reported in the range of 30 to 120 minutes. In patients with end-stage renal disease the average half-life is 9.7 hours. The half-life may be slightly longer in patients with hepatic dysfunction and a range of 50 to 327 minutes has been reported in patients with heart failure. In severe multi-organ failure the half-life may range from 20 to 24 hours.

Furosemide clearance is influenced by age, underlying disease state, and drug interactions. Clearance reduces with increasing age, probably due to declining renal function. Renal impairment in renal or cardiac disease reduces renal clearance, although this may be compensated for by increases in non-renal clearance. Hepatic impairment has little impact on clearance. Renal and non-renal clearance may be reduced by probenecid and indometacin.

The effectiveness of furosemide as a diuretic depends upon it reaching its site of action, the renal tubules, unchanged. About one-half to two-thirds of an intravenous dose or one-quarter to one-third of an oral dose are excreted unchanged, the difference being largely due to the poor bioavailability from the oral route. The effect of furosemide is more closely related to its urinary excretion than to the plasma concentration. Urinary excretion may be reduced in renal impairment due to reduced renal blood flow and reduced tubular secretion.

1. Cutler RE, Blair AD. Clinical pharmacokinetics of frusemide. *Clin Pharmacokinet* 1979; **4:** 279–96.
2. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979; **7:** 1–27.
3. Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; **17:** 1–46.
4. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
5. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part II). *Clin Pharmacokinet* 1990; **18:** 460–71.
6. Vrhovac B, *et al.* Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet* 1995; **28:** 405–18.

Infants and neonates. The half-life of furosemide in term and preterm neonates is markedly prolonged compared with that in adults.[1,2] Half-lives of 4.5 to 46 hours have been reported and it has been suggested that the prolongation may be greater in preterm than in term neonates. This effect is due primarily to immature renal function and if repeated doses are necessary over a short period accumulation may occur.[1]

1. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988; **14:** 261–86.
2. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.

Uses and Administration

Furosemide is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure (below), including pulmonary oedema, and with renal and hepatic disorders (but see Precautions, above) and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension (p.1171), either alone or with other antihypertensives.

Furosemide inhibits the reabsorption of electrolytes primarily in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. See Action, below, for further reference to its mechanism of action.

Administration and dosage. Furosemide's effects are evident within 30 minutes to 1 hour after an oral dose, peak at 1 to 2 hours, and last for about 4 to 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours. It is given orally, usually in the morning. Alternatively it may be given intramuscularly or intravenously as the sodium salt; doses are expressed in terms of furosemide base. 10.7 mg of furosemide sodium is equivalent to about 10 mg of furosemide base. Licensed product information recommends that whether by direct intravenous injection or by infusion the rate of intravenous dosage should not exceed 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Unlike the thiazide diuretics where, owing to their flat dose-response curve, very little is gained by increasing the dose, furosemide has a steep dose-response curve, which gives it a wide therapeutic range.

In the treatment of **oedema**, the usual initial oral dose is 40 mg once daily, adjusted as necessary according to response. Mild cases may respond to 20 mg daily or 40 mg on alternate days. Some patients may need doses of 80 mg or more daily given as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. In an emergency or when oral therapy cannot be given, 20 to 50 mg of furosemide may be given by slow intravenous injection; intramuscular injection may be given in exceptional cases but is not suitable for acute conditions. If necessary further doses may be given, increasing by 20-mg increments and not given more often than every 2 hours. If doses above 50 mg are required they should be given by slow intravenous infusion. For pulmonary oedema, if an initial slow intravenous injection of 40 mg does not produce a satisfactory response within one hour, a further 80 mg may be given slowly intravenously.

For children, the usual oral dose is 1 to 3 mg/kg daily up to a maximum of 40 mg daily; doses by injection are 0.5 to 1.5 mg/kg daily up to a maximum of 20 mg daily.

In the treatment of **hypertension**, furosemide is given in oral doses of 40 to 80 mg daily, either alone, or with other antihypertensives.

High-dose therapy. In the management of **oliguria** in acute or chronic renal failure where the glomerular filtration rate is less than 20 mL/minute but greater than 5 mL/minute, furosemide 250 mg diluted to 250 mL in a suitable diluent is infused over one hour. If urine output is insufficient within the next hour, this dose may be followed by 500 mg added to an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, and infused over about 2 hours. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion then a third dose of 1 g may be infused over about 4 hours. The rate of infusion should never exceed 4 mg/minute. In oliguric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant rate infusion pump with a micrometer screw-gauge adjustment; the rate should still never exceed 4 mg/minute. Patients who do not respond to a dose of 1 g probably require dialysis. If the response to either dosage method is satisfactory, the effective dose (of up to 1 g) may then be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, oral treatment may be maintained; 500 mg should be given orally for each 250 mg required by injection.

When used in chronic renal impairment, an initial oral dose of 250 mg may be given, increased, if necessary in steps of 250 mg every 4 to 6 hours to a maximum of 1.5 g in 24 hours; in exceptional cases up to 2 g in 24 hours may be given. Dosage adjustments should subsequently be made according to the patient's response.

During treatment with these high-dose forms of furosemide therapy, careful laboratory control is essential. Fluid balance and electrolytes should be carefully controlled and, in particular, in patients with shock, measures should be taken to correct the blood pressure and circulating blood volume, before commencing this type of treatment. High-dose furosemide therapy is contra-indicated in renal failure caused by nephrotoxic or hepatotoxic drugs, and in renal failure associated with hepatic coma.

Action. The mechanism of action of furosemide is not fully understood.[1] It appears to act primarily by inhibiting active reabsorption of chloride ions in the ascending limb of the loop of Henle. Urinary excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is increased; the chloride excretion exceeds that of sodium and there is an enhanced exchange of sodium for potassium leading to greater excretion of potassium. The resulting low osmolality of the medulla inhibits the reabsorption of water by the kidney. There is a possibility that furosemide may also act at a more proximal site.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance.

Furosemide has been shown to increase plasma-renin activity, plasma-noradrenaline concentrations, and plasma-arginine-vasopressin concentrations. Alterations in the renin-angiotensin-aldosterone system may play a part in the development of acute tolerance. Furosemide increases renal-prostaglandin concentrations but it is not known whether this is due to increased synthesis or inhibition of degradation or both. Prostaglandins appear to mediate the diuretic/natriuretic action. The primary effects appear to be alterations in renal haemodynamics with subsequent increases in electrolyte and fluid excretion.

The diuretic response to furosemide is related to the concentration in the urine, not to that in the plasma. Furosemide is delivered to the renal tubules by a non-specific organic acid pump in the proximal tubules.[1]

In some cases sodium intake may be sufficient to overcome the diuretic effect, and limiting sodium intake could restore responsiveness.[2]

1. Ponto LLB, Schaenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
2. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. *Drugs* 1985; **30:** 427–43.

Administration. Continuous intravenous infusion of loop diuretics may be more effective than intermittent intravenous bolus injection and may provide a more consistent urine flow with fewer alterations in urine balance.[1,2] Bumetanide was more effective by continuous infusion than as bolus doses in 8 patients with severe chronic renal impairment.[3] In 20 patients with chronic heart failure requiring high-dose furosemide therapy, furosemide given by continuous infusion was more effective than the same dose by bolus injection.[4] The lower plasma concentrations associated with continuous infusion may also reduce the risk of toxicity.

1. Yelton SL, *et al.* The role of continuous infusion loop diuretics. *Ann Pharmacother* 1995; **29:** 1010–14.
2. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; **40:** 1797–1803.
3. Rudy DW, *et al.* Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; **115:** 360–6.
4. Dormans TPJ, *et al.* Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; **28:** 376–82.

Ascites. Dietary sodium restriction and diuretics are mainstays of the management of cirrhotic ascites (p.1159). Spironolactone is usually the diuretic of first choice, but furosemide may be added to therapy as necessary.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids (see p.1500). Additional supportive therapy may include the use of diuretics such as furosemide.

Alternate-day therapy with oral furosemide 4 mg/kg has produced modest benefits in pulmonary status in the absence of a diuretic effect, and few adverse effects.[1] Improved pulmonary function has occurred in infants given furosemide 1 mg/kg parenterally after packed red blood cell transfusions, given to improve oxygen-carrying capacity.[2] The successful use of nebulised furosemide in a dose of 1 mg/kg has been reported;[3,4] again pulmonary status was improved without production of diuresis or renal side-effects. However, a single inhaled dose of 1 mg/kg failed to improve pulmonary mechanics in another study involving older infants with more severe disease.[5] Systematic reviews of the use of intravenous or oral,[6] or nebulised[7] diuretics in preterm infants with chronic lung disease concluded that, although there were improvements in pulmonary function, there was insufficient evidence to recommend routine use.

1. Rush MG, *et al.* Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 112–18.
2. Stefano JL, Bhutani VK. Role of furosemide therapy after booster-packed erythrocyte transfusions in infants with bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 965–8.
3. Rastogi A, *et al.* Nebulized furosemide in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; **125:** 976–9.
4. Prabhu VG, *et al.* Pulmonary function changes after nebulised and intravenous frusemide in ventilated premature infants. *Arch Dis Child* 1997; **77:** F32–F35.
5. Kugelman A, *et al.* Pulmonary effect of inhaled furosemide in ventilated infants with severe bronchopulmonary dysplasia. *Pediatrics* 1997; **99:** 71–5.
6. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 24/06/05).
7. Brion LP, *et al.* Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/05/08).

Haemolytic-uraemic syndrome. Renal failure is a possible consequence of the haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p.1076). Correction of any hypovolaemic state with adequate fluids and of oliguria by inducing diuresis with furosemide may be used to prevent this.

Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.[1] In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urate clearance.

1. Rousseau E, *et al.* Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; **34:** 22–5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p.1165) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions[1] or high doses (up to 8 g daily) of furosemide given by intravenous infusion[2,3] or orally.[3] A patient who was successfully maintained on intravenous furosemide at home has been described.[4] Combination of furosemide with thiazide diuretics[5] or metolazone[6,7] has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.[8] Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine[9] or captopril.[10] The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.[11] In elderly patients not responding adequately to low-dose furosemide together with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported[12] to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study[13] in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported[14] to augment the effect of furosemide.

1. Lawson DH, *et al.* Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; **2:** 476.
2. O'Rourke MF, *et al.* High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; **144:** 2429.
3. Gerlag PGG, van Meijel JJM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; **148:** 286–91.
4. Hattersley AT, *et al.* Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; **i:** 446.
5. Channer KS, *et al.* Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; **335:** 922–3.
6. Aravot DJ, *et al.* Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727.
7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727–8.
8. Oster JR, *et al.* Combined therapy with thiazide-type and loop diuretic agents for resistant-sodium retention. *Ann Intern Med* 1983; **99:** 405–6.
9. Nomura A, *et al.* Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; **30:** 177–82.
10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100:** 777–82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; **100:** 902–4.
12. Waterer G, Donaldson M. High-dose frusemide for cardiac failure. *Lancet* 1995; **346:** 254.
13. Cotter G, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62:** 187–93.
14. Paterna S, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2:** 305–13.

Hypercalcaemia. Hypercalcaemia (p.1668) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This primarily involves rehydration, but loop diuretics such as furosemide have been used after rehydration, to promote urinary calcium excretion. Doses used have ranged from 20 to 240 mg of furosemide daily, given intravenously.

Obstructive airways disease. In patients with *asthma*, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise[1] and external stimuli,[2,3] although it did not improve bronchial hyperresponsiveness in a 4-week study[4] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[5] A number of mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.[6] The potential for clinical applications remains unclear[6] and furosemide is not a part of the accepted schedules for the treatment of asthma (p.1108).

A small study[7] in patients with *chronic obstructive pulmonary disease* found that inhalation of furosemide relieved bronchoconstriction and dyspnoea induced by exercise.

Inhaled furosemide has also been used to relieve *dyspnoea in patients with terminal cancer*.[8]

1. Munyard P, *et al.* Inhaled frusemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; **50:** 677–9.
2. Bianco S, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; **321:** 1069–73.
3. Seidenberg J, *et al.* Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; **67:** 214–17.
4. Yates DH, *et al.* Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; **152:** 2173–5.
5. González-Sánchez R, *et al.* Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; **23:** 181–4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; **3:** 30–41.
7. Ong K-C, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169:** 1028–33.
8. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indometacin is generally given to promote closure of the ductus (see p.68).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome — see Effects in Infants and Neonates under Adverse Effects, above). A systematic review[1] of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised intracranial pressure (p.1181) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p.1866), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Preparations

BP 2008: Co-amilofruse Tablets; Furosemide Injection; Furosemide Tablets;
USP 31: Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Eliur†; Errolon; Fabofurox; Frecuental†; Furagrand; Furital; Furix; Fursemida; Furtenk; Kolkin; Lasix; Nuriban; Retep; Viafurox†; ***Austral.:*** Frusehexal; Frusid; Lasix; Uremide; Urex; ***Austria:*** Fural; Furohexal; Furon; Furostad; Lasix; ***Belg.:*** Docfurose; Furotop; Lasix; ***Braz.:*** Diuremida; Diuret†; Diurit†; Diurix; Fluxil; Furesin; Furosan; Furosecord†; Furosem; Furosen†; Furosetron; Furosix; Furozix; Fursemida; Lasix; Neosemid; Normotensor†; Rovelan; Urasix; ***Canad.:*** Lasix; Novo-Semide; ***Chile:*** Asax; Lasix†; ***Cz.:*** Dryptal†; Furanthril†; Furon; Furorese; Lasix†; ***Denm.:*** Diural; Furese; Furix; Lasix; ***Fin.:*** Furesis; Furomin; Lasix; Vesix; ***Fr.:*** Lasilix; ***Ger.:*** Diurapid; durafurid†; Furanthril; Furo; Furo-Puren; Furobeta; Furogamma; Furomed; Furorese; Furosal; Fusid; Jufurix; Lasix; Odemase†; ***Gr.:*** Hydroflux; Lasix; Semid; ***Hong Kong:*** CP-Furo; Lasix; Naqua; Urex; ***Hung.:*** Furon; Huma-Semide†; ***India:*** Diucontin-K; Frusemix; Frusenex; Frusix; Lasix; Petsix†; ***Indon.:*** Cetasix; Classic; Diurefo; Edemin; Farsix; Furosix; Impugan; Lasix; Uresix; ***Irl.:*** Fruside; Lasix; ***Israel:*** Fusid; Lasix†; Miphar; ***Ital.:*** Lasix; ***Malaysia:*** Dirine; Furmide†; Lasix; Rasitol; Suopinchon; Usix†; ***Mex.:*** Biomisen†; Butosali; Diurmessel; Edenol; Furomil†; Furosan; Furoter†; Henexal; Lasix; Osemin; Selectofur; Zafimida; ***Neth.:*** Lasiletten; Lasix; ***Norw.:*** Diural; Furix; Lasix; ***NZ:*** Diurin; Frusid; Lasix; ***Philipp.:*** Diuril; Diuspec; Edemann; Fremid; Fretic; Frusema; Furoscan; Fusimex; Lasix; Pharmix; Rofunil; ***Port.:*** Aquedux†; Lasix; Naqua; ***Rus.:*** Lasix (Лазикс); ***S.Afr.:*** Aquarid; Beurises; Lasix; Puresis; Uretic; ***Singapore:*** Dirine; Furmide; Lasix; ***Spain:*** Seguril; ***Swed.:*** Furix; Impugan; Lasix; ***Switz.:*** furo-basan†; Furodrix; Furosifar†; Fursol; Impugan†; Lasix; Oedemex; ***Thai.:*** Aldic†; Dirine; Frusid†; Fudirine†; Furetic; Furide; Furine; Fuseride; H-Mide; Hawkmide†; Impugan†; Lasiven; Lasix; Mediuresix†; Urasin†; ***Turk.:*** Desal; Furomid; Lasix; Lizik; Urex; ***UAE:*** Salurin; ***UK:*** Froop; Frusid; Frusol; Lasix; Rusyde; ***USA:*** Lasix; ***Venez.:*** Biosemida; Edemid; Fromil†; Inclens; Lasix; Lifurox; Nacua†; Resimida†; Salca; Terysol.

Multi-ingredient: *Arg.:* Aldactone-D; Diflux; Errolon A; Furdiuren†; Lasilacton; Lasiride; Nuriban A; ***Austria:*** Furo-Aldopur; Furo-Spirobene; Furolacton; Hydrotrix; Lasilacton; Lasitace; Spirono comp; ***Belg.:*** Frusamil; ***Braz.:*** Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; ***Chile:*** Furdiuren; Hidrium; Hidropid; ***Cz.:*** Spiro Compositum†; ***Denm.:*** Frusamil; ***Fin.:*** Furesis comp; ***Fr.:*** Aldalix; Logirene; ***Ger.:*** Betasemid; Diaphal; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Hydrotrix; Osyrol Lasix; Spiro comp; Spiro-D; Spironolacton Plus†; ***Gr.:*** Frumil; ***India:*** Frumil; Lasilactone; Spiromide; ***Irl.:*** Diumide-K Continus; Fru-Co; Frumil; Lasoride†; ***Ital.:*** Fluss 40; Lasitone; Spirofur; ***Mex.:*** Lasilacton; ***NZ:*** Frumil; ***Philipp.:*** Diumide-K; ***Spain:*** Salidur; ***Switz.:*** Frumil†; Furocombin; Furospir; Lasilactone; ***UK:*** Aridil; Froop Co†; Fru-Co; Frumil; Frusene; Komil; Lasikal; Lasilactone; Lasoride†; ***Venez.:*** Furdiuren.

Gallopamil Hydrochloride *(BANM, rINNM)*

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydroklorid; Gallopamilli Hydrochloridum; Gallopamillihydrokloridi; Hidrocloruro de galopamilo; Methoxyverapamil Hydrochloride. 5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

Галлопамила Гидрохлорид

$C_{28}H_{40}N_2O_5,HCl = 521.1.$

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.

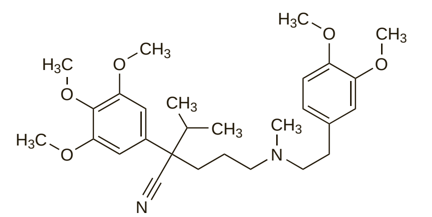

(gallopamil)

Profile

Gallopamil is a calcium-channel blocker (see p.1154) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p.1157), cardiac arrhythmias (p.1160), and hypertension (p.1171). Gallopamil hydrochloride is given by mouth in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

◊ General references.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; **47:** 93–115.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Procorum; ***Ger.:*** Gallobeta; Procorum; ***Hung.:*** Procorum; ***Ital.:*** Algocor; Procorum; ***Mex.:*** Procorum; ***Philipp.:*** Procorum; ***Thai.:*** Procorum.

Gemfibrozil *(BAN, USAN, rINN)*

CI-719; Gemfibrotsiili; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl. 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

Гемфиброзил

$C_{15}H_{22}O_3 = 250.3.$

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.

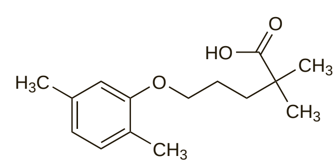

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58° to 61°. Practically insoluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Gemfibrozil). A white waxy crystalline solid. M.p. 58° to 61°. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Incidence of adverse effects. In the Helsinki Heart Study,[1] 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.

There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study[2] reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.[3]

1. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
2. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.
3. Tenkanen L, *et al.* Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; **166:** 743–8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.[1]

1. Fisher DA, *et al.* Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124:** 854–5.

Interactions

As for Bezafibrate, p.1232.

Gemfibrozil is an inhibitor of a number of cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p.686), pioglitazone (see p.456), and rosiglitazone (see p.459) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contra-indicated due to the risk of serious hypoglycaemia (see p.458).

Pharmacokinetics

Gemfibrozil is readily absorbed from the gastrointestinal tract; bioavailability is close to 100% and is highest when gemfibrozil is taken 30 minutes before food. Peak concentrations in plasma occur within 1 to 2 hours; the half-life is about 1.5 hours. Plasma protein binding of gemfibrozil is about 98%. About 70% of a dose is excreted in the urine mainly as glucuronide conjugates of gemfibrozil and its metabolites; little is excreted in the faeces.

Uses and Administration

Gemfibrozil, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

Gemfibrozil is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. It is also indicated for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164) in hyperlipidaemic men: in the USA this use is restricted to type IIb patients who also have low HDL-cholesterol concentrations and who have not responded to dietary and other measures. The usual oral dose is 1.2 g daily in 2 divided doses given 30 minutes before the morning and evening meals. Alternatively, a single daily dose of 900 mg has been given 30 minutes before the evening meal.

◊ Reviews.

1. Spencer CM, Barradell LB. Gemfibrozil: a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. *Drugs* 1996; **51:** 982–1018.

Administration in renal impairment. Gemfibrozil is contra-indicated in patients with severe renal impairment. However, UK licensed prescribing information allows its use in patients with mild to moderate impairment (glomerular filtration rate 30 to 80 mL/minute per 1.73 m^2); the initial dose should be reduced to 900 mg daily and renal function should be assessed before increasing the dose.

In a study[1] of the pharmacokinetics of gemfibrozil in 17 patients with stable chronic renal failure the mean plasma half-life was 1.8 and 1.9 hours after multiple and single doses respectively, which was comparable with that reported in patients with normal renal function. Gemfibrozil clearance was independent of renal function, but the kinetics of gemfibrozil metabolites were not evaluated.

Beneficial responses[2] were seen in lipid and lipoprotein concentrations in 5 of 6 uraemic patients treated with gemfibrozil 1.2 g daily for six months and in 6 nephrotic patients given gemfibrozil 800 mg daily for 4 months. No significant adverse effects or signs of organ toxicity were seen. Results of a secondary prevention study[3] also suggested that gemfibrozil at a dose of 1.2 g daily was safe and effective in patients with mild to moderate renal impairment.

1. Evans JR, *et al.* The effect of renal function on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* 1987; **27:** 994–1000.
2. Manninen V, *et al.* Gemfibrozil treatment of dyslipidaemias in renal failure with uraemia or in the nephrotic syndrome. *Res Clin Forums* 1982; **4:** 113–18.
3. Tonelli M, *et al.* for the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66:** 1123–30.

Preparations

BP 2008: Gemfibrozil Capsules; Gemfibrozil Tablets;
USP 31: Gemfibrozil Capsules; Gemfibrozil Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Gedun; Hipolixan; Lopid; ***Austral.:*** Ausgem; Gemhexal; Jezil; Lipazil; Lopid; ***Austria:*** Gevilon; ***Braz.:*** Lopid; Lozil; ***Canad.:*** Lopid; ***Chile:*** Grifogemzilo; Lipotril; Lopid; ***Cz.:*** Gevilon†; Innogem†; Ipolipid†; ***Denm.:*** Lopid; ***Fin.:*** Gevilon; Lopid; ***Fr.:*** Lipur; ***Ger.:*** Gemfi; Gevilon; Lipox Gemfi†; ***Gr.:*** Adratan†; Amedran; Antilipid; Cholhepan; Clipostat; Dosamont; Drisofal†; Eklipid; Entianthe†; Fibrolip; Fibrospes; Gebrozil†; Gedizil; Gemfolid; Gemlipid; Gineton; Hobatolex; Lisolip; Lopid; Noxobran†; Parnoxil; Prelisin; Renolip; Solulip; Terostrant; Tiazam; ***Hong Kong:*** Gemzil; Ipolipid; Lipison; Lipistorol; Lipofor; Lopid; Lowin; Marbrozil; Qualipid; Saffid; Synbrozil; ***Hung.:*** Innogem; Minilip; ***India:*** Lopid; Normolip; ***Indon.:*** Detrichol; Fetinor; Fibralip; Hypofil; Inobes; Lapibroz; Lifibron; Lipira; Lipitrop; Lokoles; Lopid; Lowlip; Mersikol; Nufalemzil; Progemzal; Renabrazin; Scantipid; Zilop; ***Irl.:*** Lopid; ***Ital.:*** Fibrocit; Gemlipid; Genlip; Genozil; Lipogen; Lipozid; Lopid; ***Malaysia:*** Brozil; Fibrol†; Ipolipid; Lipistorol†; Lipofor; Lopid†; Mariston†; ***Mex.:*** Apo-Fide; Lopid; Raypid; ***Neth.:*** Lopid; ***NZ:*** Gemizol†; ***Philipp.:*** Lipigem; Lipison; Lipizile; Lipozid; Lopid; Reducel; ***Port.:*** Lipoite; Lopid; ***Rus.:*** Ipolipid (Иполипид); ***S.Afr.:*** Lopid; ***Singapore:*** Brozil; Gemd†; Hidil; Ipolipid; Lipison†; Lipofor; Lopid†; Recozil; ***Spain:*** Bolutol†; Decrelip†; Lopid; Pilder; Trialmin; ***Swed.:*** Lopid; ***Switz.:*** Gevilon; ***Thai.:*** Bisil; Chlorestrol†; Deopid†; Dropid; Gemfibril; GFB; Gozid; Hidil; Lipidys; Lipison; Lipolo; Lipozil; Locholes; Lopid; Manobrozil; Mariston; Norpid; Pharzil; Polifibrozil; Polyxit; Tiba; ***Turk.:*** Lopid; ***UK:*** Lopid; ***USA:*** Lopid; ***Venez.:*** Lipontal; Lopid.

Glyceryl Trinitrate

Glicerin-trinitrát; Glicerolio trinitratas; Gliseril Trinitrat; Glonoin; Glyceroli Trinitras; Glyceroli trinitratis; Glycerol-trinitrát; Glycéryle, trinitrate de; Glyceryltrinitrat; Glyseryylitrinitraatti; GTN; Nitroglicerina; Nitrogliserin; Nitroglycerin; Nitroglycerol; NTG; Trinitrin; Trinitroglycerin. Propane-1,2,3-triol trinitrate.

$C_3H_5(NO_3)_3$ = 227.1.

CAS — 55-63-0.

ATC — C01DA02; C05AE01.

ATC Vet — QC01DA02; QC05AE01.

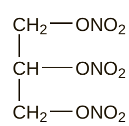

Pharmacopoeias. *Chin., Eur.* (see p.vii), *US,* and *Viet.* include glyceryl trinitrate as diluted solutions.

Ph. Eur. 6.2 (Glyceryl Trinitrate Solution). An ethanolic solution containing 1 to 10% w/w of glyceryl trinitrate. It is a clear, colourless or slightly yellow solution. Miscible with dehydrated alcohol and with acetone.

Pure glyceryl trinitrate is practically insoluble in water; freely soluble in dehydrated alcohol; miscible with acetone.

Protect from light. Diluted solutions (1%) should be stored at 2° to 15°; more concentrated solutions may be stored at 15° to 20°.

USP 31 (Diluted Nitroglycerin). A mixture of glyceryl trinitrate with lactose, glucose, alcohol, propylene glycol, or other suitable inert excipient, usually containing not more than 10% glyceryl trinitrate. When diluted in either alcohol or propylene glycol it is a clear, colourless, or pale yellow liquid. When diluted with lactose, it is a white odourless powder. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Prevent exposure to temperatures above 40°. Protect from light.

Undiluted glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. Slightly soluble in water; soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in dichloromethane, in ether, in ethyl acetate, in glacial acetic acid, in methyl alcohol, in benzene, in toluene, in nitrobenzene, and in phenol.

Handling. Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat and only exceedingly small amounts should be isolated.

Incompatibility. Studies have found glyceryl trinitrate to be incompatible with phenytoin,[1] alteplase,[2] and levofloxacin.[3]

1. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability. *INTRAVENOUS SOLUTIONS.* The loss of glyceryl trinitrate from solution by adsorption or absorption into some plastics of intravenous giving sets has been recognised for some years,[1,2] although adsorption does not appear to occur to any great extent with polyolefin[3,4] or polyethylene.[5-7] It is not only infusion containers and plastic tubing that may be involved; some in-line filters can adsorb glyceryl trinitrate.[8,9]

1. Grouthamel WG, *et al.* Loss of nitroglycerin from plastic intravenous bags. *N Engl J Med* 1978; **299:** 262.
2. Roberts MS, *et al.* The availability of nitroglycerin from parenteral solutions. *J Pharm Pharmacol* 1980; **32:** 237–44.
3. Wagenknecht DM, *et al.* Stability of nitroglycerin solutions in polyolefin and glass containers. *Am J Hosp Pharm* 1984; **41:** 1807–11.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
5. Schaber DE, *et al.* Nitroglycerin adsorption to a combination polyvinyl chloride, polyethylene intravenous administration set. *Drug Intell Clin Pharm* 1985; **19:** 572–5.
6. Tracy TS, *et al.* Nitroglycerin delivery through a polyethylene-lined intravenous administration set. *Am J Hosp Pharm* 1989; **46:** 2031–5.
7. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
8. Baaske DM, *et al.* Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. *Am J Hosp Pharm* 1980; **37:** 201–5.
9. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.

TABLETS. Many studies have shown that glyceryl trinitrate tablets are unstable and subject to considerable loss of potency in contact with packaging components such as adhesive labels, cotton and rayon fillers, and plastic bottles and caps. Both the Council of the Royal Pharmaceutical Society of Great Britain and the FDA in the USA have issued packaging and dispensing guidelines. Glyceryl trinitrate tablets should be dispensed only in glass containers sealed with a foil lined cap and containing no cotton wool wadding. In addition, the Council of the Royal Pharmaceutical Society of Great Britain recommends that no more than 100 tablets should be supplied and that the container should be labelled with an indication that any tablets should be discarded after 8 weeks in use.

Adverse Effects

Glyceryl trinitrate may cause flushing of the face, dizziness, tachycardia, and throbbing headache. Large doses cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methaemoglobinaemia; impairment of respiration and bradycardia may ensue. Contact dermatitis has been reported in patients using topical glyceryl trinitrate preparations; local irritation and erythema may also occur. Preparations applied to the oral mucosa frequently produce a localised burning sensation.

Chronic poisoning may occur in industry but tolerance develops when glyceryl trinitrate is regularly handled and nitrate dependence can lead to severe withdrawal symptoms in subjects abruptly removed from chronic exposure. Loss of such tolerance is rapid and may cause poisoning on re-exposure. Tolerance may occur during clinical use and is usually associated with preparations that produce sustained plasma concentrations.

Effects on the heart. Tachycardia, hypotension, and bradycardia are recognised adverse cardiac effects of glyceryl trinitrate. Rarely reported adverse effects include asystole[1] and complete heart block.[2]

1. Ong EA, *et al.* Nitroglycerin-induced asystole. *Arch Intern Med* 1985; **145:** 954.
2. Lancaster L, Fenster PE. Complete heart block after sublingual nitroglycerin. *Chest* 1983; **84:** 111–12.

Effects on taste. A 61-year-old man experienced loss of bitter and salty taste sensations 2 weeks after addition of glyceryl trinitrate patches to his post-myocardial infarction drug regimen.[1] The patient had complete loss of taste after 6 weeks; his taste sensation returned to normal within 1 week of stopping glyceryl trinitrate patches. Taste sensation was again altered on rechallenge.

1. Ewing RC, *et al.* Ageusia associated with transdermal nitroglycerin. *Clin Pharm* 1989; **8:** 146–7.

Hypersensitivity. Contact dermatitis has been reported in patients using glyceryl trinitrate ointment and patches.[1] Both glyceryl trinitrate and formulation components may be involved in these reactions.

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.

Intravenous administration. Some formulations of glyceryl trinitrate for intravenous use may contain substantial quantities of alcohol in the solvent. There have been several reports of alcohol intoxication occurring in patients during high-dose intravenous glyceryl trinitrate infusion.[1-3] In a patient[3] who required glyceryl trinitrate 2 mg/minute, a blood-alcohol concentration of 2.67 mg/mL was reported. PVC tubing had been used for the infusion and it was suggested that adsorption of glyceryl trinitrate onto the tubing may have increased the dose requirement and thus the amount of alcohol given.

Propylene glycol is also used as a solvent in some formulations of glyceryl trinitrate. Infusion of solutions with propylene glycol can lead to hyperosmolarity: see under Propylene Glycol, p.2374, for details.

1. Shook TL, *et al.* Ethanol intoxication complicating intravenous nitroglycerin therapy. *Ann Intern Med* 1984; **101:** 498–9.
2. Daly TJ, *et al.* "Cocktail"-coronary care. *N Engl J Med* 1984; **310:** 1123.
3. Korn SH, Comer JB. Intravenous nitroglycerin and ethanol intoxication. *Ann Intern Med* 1985; **102:** 274.

Treatment of Adverse Effects

Syncope and hypotension should be treated by keeping the patient in a recumbent position with the head lowered; pressor agents may be necessary in extreme hypotension. Oxygen, with assisted respiration, may be needed in severe poisoning and infusion of plasma expanders or suitable electrolyte solutions may be required to maintain the circulation. If methaemoglobinaemia occurs methylthioninium chloride may be given intravenously. In the case of severe poisoning with tablets the stomach may be emptied by lavage. If large amounts have been ingested within 1 hour, activated charcoal may be considered.

Precautions

Glyceryl trinitrate should not be used in patients with severe hypotension, hypovolaemia, marked anaemia, heart failure due to obstruction (including constrictive pericarditis), or raised intracranial pressure due to head trauma or cerebral haemorrhage. Although it has been suggested that glyceryl trinitrate may increase intra-ocular pressure in patients with angle-closure glaucoma and should be avoided in such patients there appears to be no evidence for such a contra-indication.

Glyceryl trinitrate should be used with caution in patients with severe renal or severe hepatic impairment, hypothyroidism, malnutrition, or hypothermia. Metal-containing transdermal patches should be removed before cardioversion or diathermy.

Nitrate tolerance. Although organic nitrates are effective anti-anginal drugs, their use is limited by the development of tolerance and the loss or attenuation of their anti-anginal and anti-ischaemic effects.[1,2] This can occur with all of the organic nitrates, particularly if frequent or continuous dosing is used.[1-3]

The mechanisms of nitrate tolerance are incompletely understood. The vasodilator effect of organic nitrates may depend on their conversion to nitric oxide, a process which requires the presence of a sulfhydryl donor such as cysteine or another thiol. Repeated doses of a nitrate exhaust tissue stores of sulfhydryl groups and this is one mechanism that may account for the development of tolerance.[1,2] The activation of neurohormonal systems, which releases vasoconstrictor hormones that counteract the effects of organic nitrates, has also been proposed as a mechanism.[1,2] An increase in free-radical production during nitrate therapy has also been suggested,[1] and may inhibit bioactivation of the nitrate.[3] Nitrate-induced expansion of plasma volume may also contribute, leading to reversal of the effects of nitrates on ventricular preload.[1,2]

The method most commonly used to avoid the development of tolerance is to provide a nitrate-free interval.[1,2] The optimum duration is not clear, but a nitrate-free period of 10 to 12 hours has been suggested.[1,2] With transdermal glyceryl trinitrate systems, the patch can be removed at night. For oral, buccal, and ointment preparations, the dose given at the end of the day can be omitted. However, rebound myocardial ischaemia may occur during this time,[1] and may require the use of short-acting nitrate preparations.[2] Whether a nitrate-free interval is necessary for all patients is unknown as many patients using continuous nitrates do not experience clinical tolerance. A transdermal patch with a higher release rate during the first part of a 24-hour period has been found not to prevent the development of tolerance.[4]

Various drugs have been reported to reduce the development of nitrate tolerance, including sulfhydryl donors and drugs with antoxidant properties, but none has an established role.[1,3]

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med* 1998; **338:** 520–31.
2. Rutherford JD. Nitrate tolerance in angina therapy: how to avoid it. *Drugs* 1995; **49:** 196–9.
3. Münzel T, *et al.* Explaining the phenomenon of nitrate tolerance. *Circ Res* 2005; **97:** 618–28.
4. Wiegand A, *et al.* Pharmacodynamic and pharmacokinetic evaluation of a new transdermal delivery system with a time-dependent release of glyceryl trinitrate. *J Clin Pharmacol* 1992; **32:** 77–84.

Transdermal patches. An explosion occurred during defibrillation in a patient with a glyceryl trinitrate transdermal patch on the left side of the chest.[1] There was no visible injury to the patient. Subsequent studies suggested that this was caused by an electrical arc between the defibrillator paddle and the aluminium backing of the patch rather than explosion of the glyceryl trinitrate.

Although removal of transdermal patches before diathermy is usually recommended, a maximum rise in patch temperature of only 2.2° was reported when patches were exposed to power densities up to 800 watts/m^2. It was considered that exposure of transdermal patches to microwave diathermy, for example as part of physiotherapy treatment, was unlikely to cause direct thermal injury to the wearer.[2]

1. Babka JC. Does nitroglycerin explode? *N Engl J Med* 1983; **309:** 379.
2. Moseley H, *et al.* The influence of microwave radiation on transdermal delivery systems. *Br J Dermatol* 1990; **122:** 361–3.

Interactions

The hypotensive effects of glyceryl trinitrate may be enhanced by alcohol, and by vasodilators and other drugs with hypotensive actions. The effectiveness of sublingual and buccal tablet preparations may be reduced by drugs that cause dry mouth since dissolution may be delayed.

Anticoagulants. For the effects of glyceryl trinitrate on *heparin*, see p.1303.

Antimuscarinics. Delayed dissolution of glyceryl trinitrate tablets due to dry mouth has been reported in a patient taking *imipramine*[1] and in a patient treated with *atropine*;[2] this effect should be considered whenever glyceryl trinitrate sublingual tablets are given to patients taking other drugs that can cause dry mouth. Use of the lingual spray[2] rather than a sublingual tablet or addition of 1 mL of saline under the tongue[3] may be used to overcome the problem.

1. Robbins LJ. Dry mouth and delayed dissolution of sublingual nitro-glycerin. *N Engl J Med* 1983; **309:** 985.
2. Kimchi A. Dry mouth and delayed dissolution of nitroglycerin. *N Engl J Med* 1984; **310:** 1122.
3. Rasler FE. Ineffectiveness of sublingual nitroglycerin in patients with dry mucous membranes. *N Engl J Med* 1986; **314:** 181.

Ergot alkaloids. For the effects of glyceryl trinitrate on *dihydroergotamine*, see under Interactions of Ergotamine, p.621.

Phosphodiesterase type-5 inhibitors. The concurrent use of nitrates and phosphodiesterase type-5 inhibitors such as sildenafil is contra-indicated. Significant hypotension may occur due to potentiation of the vasodilator actions of nitrates.[1] Deaths due to a possible interaction have been reported.[2]

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.
2. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850.

Thrombolytics. For the effects of glyceryl trinitrate on *alteplase*, see p.1207.

Pharmacokinetics

Glyceryl trinitrate is rapidly absorbed from the oral mucosa. It is also well absorbed from the gastrointestinal tract and through the skin. Bioavailability is less than 100% when given by any of these routes due to pre-systemic clearance; bioavailability is further reduced after oral use owing to extensive first-pass metabolism in the liver.

Therapeutic effect is apparent within 1 to 3 minutes of use of sublingual tablets, sublingual spray, or buccal tablets; within 30 to 60 minutes of applying an ointment or transdermal patch; and within 1 to 2 minutes after intravenous doses.

Duration of action is about 30 to 60 minutes with sublingual tablets or spray and 3 to 5 hours with modified-release buccal tablets. Transdermal patches are designed to release a stated amount of drug over 24 hours, while therapeutic effects after application of glyceryl trinitrate ointment 2% persist for up to 8 hours. Duration of action after intravenous dosage is about 3 to 5 minutes.

Glyceryl trinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. This reaction requires the presence of cysteine or another thiol. Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly metabolised in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. The dinitrates are less potent vasodilators than glyceryl trinitrate; the mononitrates may have some vasodilator activity.

◊ References.

1. Bogaert MG. Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. *Clin Pharmacokinet* 1987; **12:** 1–11.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. Ridout G, *et al.* Pharmacokinetic considerations in the use of newer transdermal formulations. *Clin Pharmacokinet* 1988; **15:** 114–31.
4. Hashimoto S, Kobayashi A. Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. *Clin Pharmacokinet* 2003; **42:** 205–21.

Uses and Administration

Glyceryl trinitrate is a nitrovasodilator used in the management of angina pectoris (p.1157), heart failure (p.1165), and myocardial infarction (below). Other indications include inducing hypotension and controlling hypertension during surgery.

Glyceryl trinitrate is believed to exert its vasodilator effect through release of nitric oxide, which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. In its action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Glyceryl trinitrate also has a coronary vasodilator effect, which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Glyceryl trinitrate may be given by the sublingual, buccal, oral, transdermal, or intravenous route. The dose and choice of formulation depend upon the clinical situation.

In the management of **acute angina** glyceryl trinitrate is given as sublingual tablets, a sublingual aerosol spray, or buccal tablets, which all produce a rapid onset of therapeutic effect and provide rapid relief of anginal pain. These dosage forms may also be used before an activity or stress which might provoke an attack. One sublingual tablet (usual strength 300 to 600 micrograms) is placed under the tongue. The dose may be repeated as required but patients should be advised to seek medical care if pain persists after a total of 3 doses within 15 minutes. If an aerosol spray is used one or two sprays of 400 micrograms each are directed onto or under the tongue, then the mouth is closed; three sprays may be used if necessary. Buccal tablets of glyceryl trinitrate are placed between the upper lip and gum (see below for precautions to be observed during use). The usual dose is 2 mg when required, increased to 3 mg if necessary; a dose of 5 mg may be given in severe angina.

In the long-term management of **stable angina** glyceryl trinitrate is given as modified-release tablets or capsules, transdermal formulations, or buccal tablets, which all provide a long duration of action. Dosage varies according to the specific formulation. In the UK, for example, modified-release oral tablets are available that allow doses of up to 12.8 mg to be given up to three times daily. The transdermal formulations available are ointments and patches. With the ointment a measured amount (½ to 2 inches of glyceryl trinitrate ointment 2%) is applied 3 or 4 times daily, or every 3 to 4 hours if necessary, to the chest, arm, thigh, or back. Transdermal patches applied to the chest, upper arm, or shoulder are more convenient. Patches are generally designed to release glyceryl trinitrate at a constant rate; they are available in a range of sizes, releasing about 0.1 to 0.8 mg/hr (equivalent to about 2.5 to 20 mg in 24 hours, although the patches are generally removed for part of this period to prevent tolerance developing). A maximum daily dose of 20 mg has been suggested. Glyceryl trinitrate ointment and patches should be applied to a fresh area of skin and several days should elapse before re-application to formerly used sites. Buccal tablets are used in doses of 2 to 5 mg three times daily. The tablets are retained in the buccal cavity; the rate of dissolution of the tablet can be increased by touching the tablet with the tongue or drinking hot liquids. It is common practice to remove the tablets at bedtime because of the risk of aspiration. Also patients using buccal tablets should be advised to alternate placement sites and pay close attention to oral hygiene to reduce the risk of dental caries. The tablets are not intended to be chewed; if the buccal tablet is inadvertently swallowed, another may be placed in the buccal cavity.

Tolerance tends to develop in the majority of patients on continuous nitrate therapy and nitrate-free intervals are often employed to avoid this problem (see above under Precautions, Nitrate Tolerance for further details).

In the management of **unstable angina** glyceryl trinitrate may be given by intravenous infusion. Manufacturers' guidelines for dilution of glyceryl trinitrate injection specify glucose 5% or sodium chloride 0.9% as the diluent. During intravenous use of glyceryl trinitrate there should be haemodynamic monitoring of the patient with the dose being adjusted gradually to produce the desired response. The plastic used in the infusion equipment may adsorb glyceryl trinitrate (see Stability, above) and allowance may have to be made for this. The usual initial dose for unstable angina is 5 to 10 micrograms/minute. Most patients respond to doses between 10 and 200 micrograms/minute. The sublingual and buccal routes may also be used; doses of up to 5 mg as buccal tablets may be required to relieve pain in patients with unstable angina.

In the management of acute **heart failure** glyceryl trinitrate is given intravenously in an initial dose of 5 to 25 micrograms/minute. Buccal tablets have been used in doses of 5 mg repeated as needed until symptoms are controlled. In chronic heart failure buccal tablets may be given in doses of 5 to 10 mg three times daily.

Glyceryl trinitrate is also used intravenously in acute **myocardial infarction**, and to induce hypotension or control hypertension during **surgery**. The initial dose is 5 to 25 micrograms/minute, adjusted according to response. The usual range is 10 to 200 micrograms/minute but some surgical patients may require up to 400 micrograms/minute.

Glyceryl trinitrate has also been used as transdermal patches in the prophylactic treatment of **phlebitis and extravasation** secondary to venous cannulation. One 5-mg patch is applied distal to the intravenous site; the patch should be replaced at a different skin site either daily or after 3 to 4 days, depending on the patch. This treatment should continue only as long as the intravenous infusion is maintained.

Glyceryl trinitrate may also be used as a 0.4% ointment for the relief of pain due to chronic **anal fissure** (below). A measured amount equivalent to about 1.5 mg is applied intra-anally every 12 hours for up to 8 weeks.

Anal fissure. Nitrates such as glyceryl trinitrate are used for the treatment of chronic anal fissure (p.1891) because of their ability to relax the anal sphincter. Topical application of glyceryl trinitrate ointment in concentrations of 0.2 to 0.8% has relieved pain and aided healing of anal fissures both in uncontrolled[1-3] and controlled studies,[4,5] although only the effect on pain appears to be significant.[6] One study[5] found that a concentration of 0.6% had no additional benefit over 0.2%. Follow-up[5,7] of some of the patients indicated that after 6 to 38 months most had not had further problems or had had occasional recurrences (relapses of about one-quarter to one-third) which in the majority of cases had responded to further topical treatment. A small placebo-controlled study specifically in children, however, did not find topical glyceryl trinitrate to be of benefit in this patient population.[8]

There is evidence that application of a glyceryl trinitrate patch may be as effective as topical application of a 0.2% ointment.[9]

Encouraging results have also been obtained in an uncontrolled study using a 1% ointment of isosorbide dinitrate.[10]

1. Gorfine SR. Topical nitroglycerin therapy for anal fissures and ulcers. *N Engl J Med* 1995; **333:** 1156–7.
2. Lund JN *et al.* Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br J Surg* 1996; **83:** 776–7.
3. Watson SJ, *et al.* Topical glyceryl trinitrate in the treatment of chronic anal fissure. *Br J Surg* 1996; **83:** 771–5.
4. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*; 656.
5. Carapeti EA, *et al.* Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut* 1999; **44:** 727–30.
6. Fenton C, *et al.* 0.4% Nitroglycerin ointment: in the treatment of chronic anal fissure pain. *Drugs* 2006; **66:** 343–9.
7. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
8. Kenny SE, *et al.* Double blind randomised controlled trial of topical glyceryl trinitrate in anal fissure. *Arch Dis Child* 2001; **85:** 404–7.
9. Zuberi BF, *et al.* A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. *Int J Colorectal Dis* 2000; **15:** 243–5.
10. Schouten WR, *et al.* Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut* 1996; **39:** 465–9.

Erectile dysfunction. Erectile dysfunction (p.2179) has been managed by the penile injection of drugs such as papaverine or alprostadil although oral treatment with drugs such as sildenafil is now available. Penile injections are not always acceptable to the patient and a number of studies have investigated topical therapies, mostly glyceryl trinitrate applied either as ointment or as a transdermal patch to the penis.[1-4] Such treatment can produce erections in some subjects, although response rates vary. However, patients must wear a condom to protect their partner against potential adverse effects resulting from the transfer of glyceryl trinitrate. The action of glyceryl trinitrate is believed to be due to smooth muscle relaxation and vasodilatation which are necessary prerequisites for penile erection.

Topical application of a cream containing isosorbide dinitrate, codergocrine mesilate, and aminophylline produced satisfactory erections in 21 of 36 men with erectile dysfunction due to various causes.[5] Eight out of 9 men with erectile dysfunction of psychogenic origin reported a satisfactory response. However, another study[6] was abandoned after the cream produced no effect in 10 consecutive patients. A further study in 14 patients who received a total of 77 applications of the cream reported no benefit over placebo.[7] Topical treatment with a cream containing isosorbide dinitrate, codergocrine mesilate, and testosterone has also been tried for erectile dysfunction; in a study in 42 men with low sexual interest and low or slightly depressed testosterone levels, 28 reported beneficial results.[8]

It should be noted that topical nitrates must not be employed in patients already using sildenafil (see Phosphodiesterase Type-5 Inhibitors, under Interactions, above).

1. Heaton JPW, *et al.* Topical glyceryl trinitrate causes measurable penile arterial dilation in impotent men. *J Urol (Baltimore)* 1990; **143:** 729–31.
2. Meyhoff HH, *et al.* Non-invasive management of impotence with transcutaneous nitroglycerin. *Br J Urol* 1992; **69:** 88–90.
3. Nunez BD, Anderson DC. Nitroglycerin ointment in the treatment of impotence. *J Urol (Baltimore)* 1993; **150:** 1241–3.
4. Anderson DC, Seifert CF. Topical nitrate treatment of impotence. *Ann Pharmacother* 1993; **27:** 1203–5.
5. Gomaa A, *et al.* Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate. *BMJ* 1996; **312:** 1512–15.
6. Naude JH, Le Roux PJ. Topical treatment of erectile dysfunction did not show results. *BMJ* 1998; **316:** 1318.
7. Le Roux PJ, Naude JH. Topical vasoactive cream in the treatment of erectile failure: a prospective, randomized placebo-controlled trial. *BJU Int* 1999; **83:** 810–11.
8. Gomaa A, *et al.* The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *Int J Impot Res* 2001; **13:** 93–9.

Gallstones. Endoscopic removal of gallstones (p.2409) in a small series of 15 patients was facilitated by glyceryl trinitrate 1.2 to 3.6 mg applied as a spray to the tongue. Glyceryl trinitrate 1.2 mg was shown to relax the sphincter of Oddi to about 30% of its normal pressure.[1] The ability of glyceryl trinitrate to relax smooth muscle has also been used to relieve biliary colic (p.5) in 3 patients with gallstones;[2] in one of these patients standard managements for the pain such as oral opioids had been only moderately effective.

1. Staritz M, *et al.* Nitroglycerine dilatation of sphincter of Oddi for endoscopic removal of bileduct stones. *Lancet* 1984; **i:** 956.
2. Hassel B. Treatment of biliary colic with nitroglycerin. *Lancet* 1993; **342:** 1305.

Migraine. Although use of glyceryl trinitrate may precipitate or exacerbate migraine (p.616) inhalation of glyceryl trinitrate at the onset of a migraine aura aborted attacks in a patient at risk of permanent neurological damage from migraine. Standard prophylactic therapy had previously been unsuccessful.[1]

1. Mitchell GK. Nitroglycerine by inhaler as treatment for migraine causing cerebral ischaemia. *Med J Aust* 1999; **171:** 336.

Myocardial infarction. Intravenous nitrates are widely used in acute myocardial infarction (p.1175), although evidence to support their use in patients undergoing reperfusion is limited. An overview of studies carried out before reperfusion (thrombolysis or percutaneous coronary intervention) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality,[1] but whether they are of benefit in addition to reperfusion is less clear. However, empirical use of intravenous glyceryl trinitrate appears to be safe, and it should therefore be given where clinically indicated for ongoing ischaemic pain. In the GISSI-3 study,[2] glyceryl trinitrate was given by intravenous infusion during the first 24 hours, starting at 5 micrograms/minute and increasing by 5 to 20 micrograms/minute every 5 minutes for the first half hour until systolic blood pressure fell by at least 10% provided it remained above 90 mmHg; after 24 hours it was replaced by a transdermal patch providing 10 mg daily.

Long-term use of nitrates after myocardial infarction may be indicated in patients with myocardial ischaemia or poor left ventricular function, but there is no evidence to support their routine use. In the GISSI-3 study there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks[2] and 6 months[3] post-infarction and in the ISIS-4 study[4] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Yusuf S, *et al.* Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; **i:** 1088–92.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
4. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Obstetrics and gynaecology. The smooth muscle relaxant properties of glyceryl trinitrate have been used in various obstetric or gynaecological situations although most reports are anecdotal or include small numbers of patients. The intravenous injection of glyceryl trinitrate 50 to 100 micrograms repeated to a total dose of 200 micrograms if necessary has produced sufficient uterine relaxation in postpartum women for the manual extraction of retained placentas.[1,2] Use as a sublingual spray has also successfully aided breech extraction in a set of twins.[3]

Glyceryl trinitrate has been given as a sublingual spray to relax the cervix before IUD insertion. In a series of over 100 patients one or two doses of 400 micrograms sublingually were usually adequate.[4]

Beneficial results have been reported in women with possible premature labour (p.2003) after application of glyceryl trinitrate patches to the abdomen.[5,6] In one study[7] this was as effective as ritodrine infusion, but another[8] found transdermal glyceryl trinitrate to be less effective than beta agonists. A study[9] comparing glyceryl trinitrate and magnesium sulfate, both given intravenously, found that glyceryl trinitrate was associated with a higher failure rate and a greater reduction in maternal blood pressure. A systematic review[10] concluded that there was insufficient evidence to support the routine use of glyceryl trinitrate.

Transdermal glyceryl trinitrate has been tried for controlling pain in severe and moderate-to-severe dysmenorrhoea[11,12] (p.6).

Glyceryl trinitrate has been given intravenously in the management of pre-eclampsia (see under Hypertension, p.1171) and is reported to reduce blood pressure without compromising uterine blood flow.[13]

Isosorbide mononitrate given vaginally has been found to produce cervical ripening[14] and although there is some evidence[15] that it is less effective, it may be an alternative to standard treatments such as prostaglandins (see Termination of Pregnancy p.2004). Isosorbide dinitrate has been used similarly after missed abortion.[16]

1. DeSimone CA, *et al*. Intravenous nitro-glycerin aids manual extraction of a retained placenta. *Anesthesiology* 1990; **73:** 787.
2. Lowenwirt IP, *et al*. Safety of intravenous glyceryl trinitrate in management of retained placenta. *Aust N Z J Obstet Gynaecol* 1997; **37:** 20–4.
3. Greenspoon JS, Kovacic A. Breech extraction facilitated by glyceryl trinitrate sublingual spray. *Lancet* 1991; **338:** 124–5.
4. Yadava RP. Sublingual glyceryl trinitrate spray facilitates IUD insertion. *Br J Sex Med* 1990; **17:** 217.
5. Lees C, *et al*. Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994; **343:** 1325–6.
6. Smith GN, *et al*. Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999; **106:** 736–9.
7. Lees CC, *et al*. Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; **94:** 403–8.
8. Bisits A, *et al*. The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; **191:** 683–90.
9. El-Sayed YY, *et al*. Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. *Obstet Gynecol* 1999; **93:** 79–83.
10. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 28/11/07).
11. Pittrof R, *et al*. Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea. *BMJ* 1996; **312:** 884.
12. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. *J Int Med Res* 1997; **25:** 41–4.
13. Grunewald C, *et al*. Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. *Obstet Gynecol* 1995; **86:** 600–4.
14. Thomson AJ, *et al*. Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. *Lancet* 1998; **352:** 1093–6.
15. Chen FC-K, *et al*. Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *Eur J Obstet Gynecol Reprod Biol* 2008; **138:** 176–9.
16. Arteaga-Troncoso G, *et al*. Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG* 2005; **112:** 1615–19.

Oesophageal motility disorders. Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. Nitrates such as isosorbide dinitrate have been reported to produce effective relaxation and to reduce symptoms when given sublingually. They have a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p.1702).

Nitrates may also be employed in oesophageal disorders such as variceal haemorrhage (see below).

Pain. Nitrates have been tried topically in the management of pain. Beneficial results have been reported with glyceryl trinitrate, applied as patches[1] or as a spray,[2] and isosorbide dinitrate spray,[3] in patients with painful diabetic neuropathy. Glyceryl trinitrate has also been used topically in musculoskeletal disorders[4] (see also Soft-tissue Rheumatism, below), and in surgical pain,[5] and intravenously as an adjunct to regional anaesthesia.[6]

Glyceryl trinitrate is also used topically to relieve pain in patients with anal fissure (above). For reference to its use in biliary colic, see Gallstones, above.

1. Rayman G, *et al*. Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; **26:** 2697–8.
2. Agrawal RP, *et al*. Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract* 2007; **77:** 161–7.
3. Yuen KCJ, *et al*. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care* 2002; **25:** 1699–1703.
4. Paoloni JA, *et al*. Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. *Am J Sports Med* 2003; **31:** 915–20.
5. McCabe JE, *et al*. A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. *BJU Int* 2007; **100:** 536–8.
6. Sen S, *et al*. The analgesic effect of nitroglycerin added to lidocaine on intravenous regional anesthesia. *Anesth Analg* 2006; **102:** 916–20.

Peripheral vascular disease. In peripheral vascular disease (p.1178) nitrates have been tried as vasodilators and smooth muscle relaxants in order to improve resting blood flow. Glyceryl trinitrate has been applied topically in patients with Raynaud's syndrome[1-3] and in distal limb ischaemia[4] resulting in some benefit but this form of therapy is not widely used in these disorders.

1. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet* 1982; **i:** 76–7.
2. Coppock JS, *et al*. Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; **62:** 15–18.
3. Teh LS, *et al*. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; **34:** 636–41.
4. Fletcher S, *et al*. Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997; **51:** 324–5.

Pulmonary hypertension. Glyceryl trinitrate reduces total pulmonary resistance in most patients with pulmonary arterial hypertension (p.1179),[1,2] including when given by inhalation.[3] However, other vasodilators such as calcium-channel blockers, epoprostenol, or bosentan are generally preferred for long-term treatment.

1. Pearl RG, *et al*. Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. *Ann Intern Med* 1983; **99:** 9–13.
2. Weir EK, *et al*. The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; **140:** 1623–30.
3. Goyal P, *et al*. Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. *Br J Anaesth* 2006; **97:** 208–14.

Quinine oculotoxicity. Intravenous nitrate has been suggested for the management of quinine oculotoxicity (p.613) and its benefit may be due to an increase in retinal vascular bed flow.[1]

1. Moore D, *et al*. Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Soft-tissue rheumatism. There is evidence from animal studies that nitric oxide plays an important role in tendon healing, and randomised studies in patients with tennis elbow (epicondylitis), Achilles tendinosis (tendinitis), and supraspinatus tendinosis showed enhanced subjective and objective recovery when a glyceryl trinitrate patch (releasing 1.25 mg over 24 hours) was applied over the area of tenderness once daily.[1] Glyceryl trinitrate has also been tried in musculoskeletal pain (see Pain, above). For the general management of soft-tissue rheumatism see p.13.

1. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; **41:** 227–31.

Variceal haemorrhage. The usual treatment in variceal haemorrhage (p.2346) is injection sclerotherapy or banding ligation which may be performed during the emergency endoscopy procedure. Where endoscopy is unavailable drug therapy may be used; it may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy. Vasoconstrictors that are used include vasopressin and its analogue terlipressin, given with glyceryl trinitrate which counteracts the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure; somatostatin is also used.

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed. It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought and isosorbide mononitrate (as adjunctive therapy with a beta blocker) is under investigation, both for prophylaxis of a first bleed[1,2] and in the prevention of rebleeding.[3] Early emergency treatment (before endoscopy) with terlipressin given intravenously and glyceryl trinitrate transdermally controlled bleeding and lowered mortality rates in patients with gastrointestinal bleeding and a history or clinical signs of cirrhosis.[4] However, use of oral isosorbide mononitrate with somatostatin infusion for acute variceal bleeding was less effective than somatostatin alone and induced more adverse effects.[5]

1. Angelico M, *et al*. Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; **104:** 1460–5.
2. Merkel C, *et al*. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; **348:** 1677–81.
3. Villanueva C, *et al*. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; **334:** 1624–9.
4. Levacher S, *et al*. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; **346:** 865–8.
5. Junquera F, *et al*. Somatostatin plus isosorbide 5-mononitrate versus somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double blind, randomised, placebo controlled clinical trial. *Gut* 2000; **46:** 127–32.

Venepuncture. Glyceryl trinitrate patches applied to skin adjacent to intravenous infusion sites are used in the prophylactic treatment of phlebitis and extravasation.[1]

Local application of glyceryl trinitrate 1 to 2 mg as ointment was found to be a useful aid to venepuncture in a study of 50 patients undergoing surgery,[2] but conflicting results have been reported in children and neonates.[3,4]

1. Tjon JA, Ansani NT. Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; **34:** 1189–92.
2. Hecker JF, *et al*. Nitroglycerine ointment as an aid to venepuncture. *Lancet* 1983; **i:** 332–3.
3. Vaksmann G, *et al*. Nitroglycerine ointment as aid to venous cannulation in children. *J Pediatr* 1987; **111:** 89–91.
4. Maynard EC, Oh W. Topical nitroglycerin ointment as an aid to insertion of peripheral venous catheters in neonates. *J Pediatr* 1989; **114:** 474–6.

Preparations

BP 2008: Glyceryl Trinitrate Sublingual Spray; Glyceryl Trinitrate Tablets; Glyceryl Trinitrate Transdermal Patches;

USP 31: Nitroglycerin Injection; Nitroglycerin Ointment; Nitroglycerin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dauxona; Enetege; Minitran†; Niglinar; Nitradisc†; Nitro-Dur; Nitroderm TTS; Nitrodom; Nitrogray; ***Austral.:*** Anginine; Lycinate; Minitran; Nitro-Dur; Nitrolingual; Rectogesic; Transiderm-Nitro; ***Austria:*** Cordiplast; Deponit; Minitran; Nitro; Nitro Mack; Nitro Pohl; Nitro-Dur; Nitroderm; Nitrolingual; Perlinganit; ***Belg.:*** Deponit; Diafusor; Minitran; Nitro-Dyl†; Nitroderm; Nitrolingual; Nysconitrine; Trinipatch; Willlong; ***Braz.:*** Nitradisc; Nitroderm TTS; Nitronal†; Tridil; ***Canad.:*** Gen-Nitro; Minitran; Nitro-Dur; Nitroject; Nitrol; Nitrolingual; Nitrong†; Nitrostat; Rho-Nitro; Transderm-Nitro; ***Chile:*** Angiolingual; Nitrocor; Nitroderm; Nitronal†; ***Cz.:*** Deponit†; Maycor Nitrospray†; Minitran†; Nit-Ret; Nitrangin†; Nitrilex†; Nitro Mack†; Nitro Pohl; Nitrolingual†; Nitromint; Perlinganit; Rectogesic; ***Denm.:*** Buccard; Discotrine; Glytrin; Nitrolingual; Nitromex; ***Fin.:*** Deponit; Minitran; Nitro; Nitromex; Perlinganit; Transiderm-Nitro; ***Fr.:*** Cordipatch; Diafusor; Discotrine; Epinitril; Lenitral†; Natispray; Nitriderm TTS; Rectogesic; Trinipatch; ***Ger.:*** Aquo-Trinitrosan; Corangin Nitrospray; Coro-Nitro†; Deponit; Gepan†; MinitranS; neos nitro OPT†; Nitrangin; Nitro Mack†; Nitro Solvay; Nitro-Pflaster-ratiopharm TL†; Nitroderm TTS; Nitrokor†; Nitrolingual; Perlinganit; Trinitrosan; ***Gr.:*** Cardiplast; Epinitril; Nitro Mack†; Nitrodyl; Nitrolingual; Nitrong; Nitroretard; Nitrosylon; Pancoran; Rectogesic; Sodemethin†; Supranitrin; Trinipatch; Trinitrine Simple Laleuf†; ***Hong Kong:*** Angised; Deponit; Lenitral†; Nitro Mack; Nitro Pohl†; Nitro-Dur; Nitrocine; Nitroderm TTS; Nitrolingual; Tridil†; ***Hung.:*** Nitro Pohl; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitromint; Perlinganit†; Sustac; ***India:*** Angised; Millisrol; Myonit; Myovin; Nitrocontin; Nitroderm TTS; Nitrogesic; Nitrolingual; ***Indon.:*** Nitrocine; Nitrokaf; ***Irl.:*** Deponit; Epinitril†; Glytrin; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Suscard; Sustac; Transiderm-Nitro; ***Israel:*** Angised†; Deponit; Nitrocine; Nitroderm TTS; Nitrolingual; Nitronal; Trinipatch†; ***Ital.:*** Adesitrin; Deponit; Dermatrans; Epinitril; Keritrina; Minitran; Natispray; Nitraket; Nitro-Dur; Nitrocor; Nitroderm TTS; Nitrosylon; Perganit; Top-Nitro; Triniplas; Trinitrina; Venitrin; ***Jpn:*** Millisrol; ***Malaysia:*** Deponit; Glytrin†; Nitrocine; Nitroderm; ***Mex.:*** Anglix; Cardinit; Minitran; Nitradisc; Nitro-Dur; Nitroder; Nitroderm TTS; ***Neth.:*** Deponit; Glytrin; Lenitral; Minitran; Nitro Pohl; Nitro-Dur; Nitrolingual; Transiderm-Nitro; Trinipatch; ***Norw.:*** Minitran; Nitro-Dur; Nitrolingual; Nitromex; Nitroven; Transiderm-Nitro; ***NZ:*** Anginine†; Glytrin; Lycinate; Minitran; Nitroderm; Nitrolingual; Nitronal; ***Philipp.:*** Deponit; Minitran; Nitrolingual; Nitronal; Nitrostat; Perlinganit; Transderm-Nitro; ***Pol.:*** Nitracor; Nitrocard; Nitroderm; Nitromint; Perlinganit; Sustonit; Trimonit; ***Port.:*** Dermatrans; Diafusor; Discotrine; Epinitril; Glytrin; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitromint; Plastranit; Rectogesic; Trinipatch†; ***Rus.:*** Deponit (Депонит); Nirmin (Нирмин); Nitro (Нитро); Nitrocor (Нитрокор); Nitroject (Нитроджект); Nitromint (Нитроминт); Nitrong (Нитронг); Nitrospray (Нитроспрей); Perlinganit (Перлинганит); Sustac (Сустак); Sustonit (Сустонит); ***S.Afr.:*** Angised; Nitrocine; Nitrolingual; Tridil; ***Singapore:*** Angised; Deponit; Glytrin†; Nitro Mack†; Nitrocine; Rectogesic; ***Spain:*** Cordiplast; Dermatrans; Diafusor; Epinitril; Minitran; Nitradisc; Nitro-Dur; Nitroderm; Nitroplast; Solinitrina; Trinipatch; Trinispray; Vernies; ***Swed.:*** Glytrin; Minitran; Nitrolingual; Nitromex; Perlinganit†; Suscard; Transiderm-Nitro; ***Switz.:*** Deponit; Minitran; Nitro Mack; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitronal; Perlinganit; Trinitrine; ***Thai.:*** Amitacon†; Angised†; Glytrin; Nitro Mack†; Nitrocine; Nitroderm; Nitroject; ***Turk.:*** Deponit; Nitroderm TTS; Nitrolingual; Perlinganit; ***UAE:*** Cardispray†; ***UK:*** Coro-Nitro; Deponit; Glytrin; Minitran; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Percutol; Rectogesic; Suscard; Sustac†; Transiderm-Nitro; Trintek; ***USA:*** Minitran; Nitrek; Nitro-Bid; Nitro-Derm; Nitro-Dur; Nitro-Time; Nitrodisc; Nitrogard; Nitroglyn†; Nitrolingual; NitroMist; Nitrong†; NitroQuick; Nitrostat; NitroTab†; Transderm-Nitro; Transdermal-NTG; Tridil†; ***Venez.:*** Minitran†; Nitro Mack; Nitrocor; Nitroderm; Tridil†.

Multi-ingredient: ***Arg.:*** Trinitron; ***Austria:*** Myocardon; Percucor†; Spasmocor; ***Ger.:*** Nitrangin compositum†; ***Pol.:*** Pentaerythritol Compositum; ***Spain:*** Cafinitrina; ***USA:*** Emergent-Ez.

Guabenxan *(rINN)*

Guabenxán; Guabenxane; Guabenxanum. (1,4-Benzodioxan-6-ylmethyl)guanidine.

Гуабенксан

$C_{10}H_{13}N_3O_2$ = 207.2.

CAS — 19889-45-3.

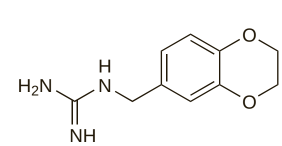

Profile

Guabenxan is an antihypertensive with properties similar to guanethidine (below). It has been given orally as the sulfate.

Guanabenz Acetate *(USAN, rINNM)*

Acetato de guanabenzo; Guanabenz, Acétate de; Guanabenzi Acetas; NSC-68982 (guanabenz); Wy-8678 (guanabenz). (2,6-Dichlorobenzylideneamino)guanidine acetate.

Гуанабенза Ацетат

$C_8H_8Cl_2N_4,C_2H_4O_2$ = 291.1.

CAS — 5051-62-7 (guanabenz); 23256-50-0 (guanabenz acetate).

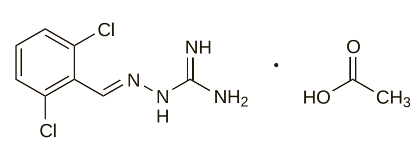

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Guanabenz Acetate). A white or almost white powder with not more than a slight odour. Sparingly soluble in water and in 0.1N hydrochloric acid; soluble in alcohol and in propylene glycol. A 0.7% solution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p.1247.

Overdosage. Overdosage with guanabenz has been reported.[1] The main symptoms were lethargy, drowsiness, bradycardia, and hypotension. A 45-year-old woman who had taken 200 to 240 mg of guanabenz with alcohol recovered after gastric lavage and intravenous fluids; a 3-year-old child who had taken 12 mg of guanabenz responded to atropine and dopamine. Naloxone had little effect in either patient.

1. Hall AH, *et al*. Guanabenz overdose. *Ann Intern Med* 1985; **102:** 787–8.

Interactions

As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics

About 75% of an oral dose of guanabenz is absorbed and undergoes extensive first-pass metabolism. Peak plasma concentrations occur about 2 to 5 hours after a dose. It is about 90% bound to plasma proteins. Guanabenz is mainly excreted in urine, almost entirely as metabolites, with less than 1% as unchanged drug; about 10 to 30% is excreted in faeces. The average elimination half-life is reported to range from 4 to 14 hours.

Uses and Administration

Guanabenz is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p.1248). It is used in the management of hypertension (p.1171), either alone or with other antihypertensives, particularly thiazide diuretics.

Guanabenz is given orally as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz.

In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4 to 8 mg every 1 to 2 weeks according to response. Doses of up to 32 mg twice daily have been used.

Preparations

USP 31: Guanabenz Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Lisapres; ***USA:*** Wytensin.

Guanadrel Sulfate *(USAN, rINNM)*

CL-1388R; Guanadrel, Sulfate de; Guanadrel Sulphate; Guanadreli Sulfas; Sulfato de guanadrel; U-28288D. 1-(Cyclohexanespiro-2′-[1′,3′]dioxolan-4′-ylmethyl)guanidine sulfate; 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine sulfate.

Гуанадрела Сульфат

$(C_{10}H_{19}N_3O_2)_2,H_2SO_4 = 524.6.$
CAS — 40580-59-4 (guanadrel); 22195-34-2 (guanadrel sulfate).

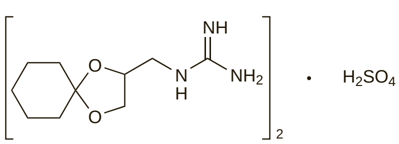

Pharmacopoeias. In *US.*

USP 31 (Guanadrel Sulfate). A white to off-white crystalline powder. Soluble in water; slightly soluble in alcohol and in acetone; sparingly soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Guanethidine Monosulfate, below. Guanadrel has been reported to cause less diarrhoea, and less orthostatic hypotension on rising in the morning, than guanethidine, but orthostatic symptoms seem to occur with a similar frequency to guanethidine during the day.

Interactions

As for Guanethidine Monosulfate, below.

Pharmacokinetics

Guanadrel is rapidly and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 85%. It is widely distributed throughout the body and about 20% is bound to plasma proteins. It is reported not to cross the blood-brain barrier. Plasma concentrations decline in a biphasic manner: the half-life varies widely between individuals, in the initial phase from 1 to 4 hours, and in the terminal phase from 5 to 45 hours, with a mean of about 10 hours. Guanadrel is metabolised in the liver and about 85% is excreted in the urine over 24 hours as the unchanged drug and its metabolites. About 40 to 50% of the drug is excreted unchanged.

Uses and Administration

Guanadrel is an antihypertensive with actions and uses similar to those of guanethidine (below). After oral administration, guanadrel acts within 2 hours with the maximum effect after 4 to 6 hours. The hypotensive effect is reported to last for 4 to 14 hours following a single dose. It has been given orally as the sulfate in the management of hypertension, although it has largely been superseded by other drugs less likely to cause orthostatic hypotension.

Preparations

USP 31: Guanadrel Sulfate Tablets.

Guanethidine Monosulfate *(USAN, rINNM)*

Guanéthidine, monosulfate de; Guanethidine Monosulphate *(BANM)*; Guanethidini Monosufas; Guanethidini monosulfas; Guanethidini Sulfas; Guanethidin-monosulfát; Guanetidiinimonosulfaatti; Guanetidinmonosulfat; Guanetidin-monoszulfát; Guanetidino monosulfatas; Monosulfato de guanetidina; NSC-29863 (guanethidine hemisulfate); Su-5864 (guanethidine hemisulfate). 1-[2-(Perhydroazocin-1-yl)ethyl]guanidine monosulfate.

Гуанетидина Моносульфат

$C_{10}H_{22}N_4,H_2SO_4 = 296.4.$
CAS — 55-65-2 (guanethidine); 60-02-6 (guanethidine hemisulfate); 645-43-2 (guanethidine monosulfate).
ATC — C02CC02; S01EX01.
ATC Vet — QC02CC02; QS01EX01.

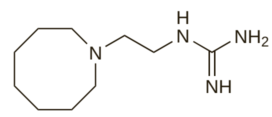

(guanethidine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*
Chin. includes the hemisulfate.

Ph. Eur. 6.2 (Guanethidine Monosulphate). A colourless crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 4.7 to 5.5. Protect from light.

USP 31 (Guanethidine Monosulfate). A white to off-white crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform. A 2% solution in water has a pH of 4.7 to 5.7.

Adverse Effects

The commonest adverse effects of guanethidine are severe postural and exertional hypotension and diarrhoea which may be particularly troublesome during the initial stages of therapy and during dose adjustment. Dizziness, syncope, muscle weakness, and lassitude are liable to occur, especially on rising from sitting or lying. Orthostatic hypotension may be severe enough to provoke angina, renal impairment, and transient cerebral ischaemia. Other frequent adverse effects are bradycardia, failure of ejaculation, fatigue, headache, and salt and water retention and oedema, which may be accompanied by breathlessness and may occasionally precipitate overt heart failure.

Nausea, vomiting, dry mouth, nasal congestion, parotid tenderness, blurring of vision, depression, myalgia, muscle tremor, paraesthesias, hair loss, dermatitis, disturbed micturition, priapism, aggravation or precipitation of asthma, and exacerbation of peptic ulcer disease have also been reported. Guanethidine may possibly cause anaemia, leucopenia, and thrombocytopenia.

When guanethidine is used as eye drops, common adverse effects are conjunctival hyperaemia and miosis. Burning sensations and ptosis have also occurred. Superficial punctate keratitis has been reported particularly after prolonged use of high doses.

Treatment of Adverse Effects

Withdrawal of guanethidine or dose reduction reverses many adverse effects. Diarrhoea may also be controlled by giving codeine phosphate or antimuscarinics. If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour. Hypotension may respond to placing the patient in the supine position with the feet raised. If hypotension is severe it may be necessary to give intravenous fluid replacement and small doses of vasopressors may be given cautiously. The patient must be monitored for several days.

Precautions

Guanethidine should not be given to patients with phaeochromocytoma, as it may cause a hypertensive crisis, or to patients with heart failure not caused by hypertension.

It should be used with caution in patients with renal impairment, cerebrovascular disorders, or ischaemic heart disease, or with a history of peptic ulcer disease or asthma. Exercise and heat may increase the hypotensive effect of guanethidine, and dosage requirements may be reduced in patients who develop fever.

There may be an increased risk of cardiovascular collapse or cardiac arrest in patients undergoing surgery while taking guanethidine, but authorities have differed as to whether the drug should be stopped before elective surgery. Former US licensed product information recommended stopping up to 2 or 3 weeks beforehand. In patients undergoing emergency procedures or where treatment has not been interrupted large doses of atropine should be given before induction of anaesthesia.

Patients undergoing treatment with eye drops containing guanethidine should be examined regularly for signs of conjunctival damage.

Interactions

Patients taking guanethidine may show increased sensitivity to the action of adrenaline, amfetamine, and other sympathomimetics, resulting in exaggerated pressor effects. The hypotensive effects may also be antagonised by tricyclic antidepressants, MAOIs, and phenothiazine derivatives and related antipsychotics (although phenothiazines may also exacerbate orthostatic hypotension, which may be more relevant clinically). In the UK licensed product information suggests that MAOIs should be stopped at least 14 days before beginning guanethidine, although in the USA a minimum of a week has been recommended as adequate. It has been reported that oral contraceptives may reduce the hypotensive action of guanethidine. Use of digoxin or other digitalis derivatives with guanethidine may cause excessive bradycardia.

The hypotensive effects of guanethidine may be enhanced by thiazide diuretics, other antihypertensives, and levodopa. Alcohol may cause orthostatic hypotension in patients taking guanethidine.

Pharmacokinetics

Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is actively taken up into adrenergic neurones by the mechanism responsible for noradrenaline reuptake. A plasma concentration of 8 nanograms/mL is reported to be necessary for adrenergic blockade, but the dose required to achieve this varies between individuals due to differences in absorption and metabolism. Guanethidine is partially metabolised in the liver, and is excreted in the urine as metabolites and unchanged guanethidine. It has a terminal half-life of about 5 days. Guanethidine does not penetrate the blood-brain barrier significantly.

Uses and Administration

Guanethidine is an antihypertensive that acts by selectively inhibiting transmission in postganglionic adrenergic nerves. It is believed to act mainly by preventing the release of noradrenaline at nerve endings. Guanethidine causes the depletion of noradrenaline stores in peripheral sympathetic nerve terminals but does not prevent the secretion of catecholamines by the adrenal medulla.

When given orally its maximal effects may take 1 to 3 weeks to appear on continued dosing and persist for 1 to 3 weeks after treatment has been stopped. It causes an initial reduction in cardiac output but its main hypotensive effect is to cause peripheral vasodilatation; it reduces the vasoconstriction which normally results from standing up and which is the result of reflex sympathetic nervous activity. In the majority of patients it reduces standing blood pressure but has a lesser effect on supine blood pressure. When applied topically to the eye guanethidine reduces the production of aqueous humour.

Guanethidine is used in the management of hypertension (p.1171). Eye drops of guanethidine have been used for open-angle glaucoma (p.1873) and for lid retraction associated with hyperthyroidism. Guanethidine has also been used in the management of neuropathic pain syndromes (see below).

Guanethidine is used in the treatment of hypertension when other drugs have proved inadequate, but it has largely been superseded by other drugs less likely to cause orthostatic hypotension. Tolerance to guanethidine has occurred in some patients; this may be countered by concomitant diuretic therapy.

In **hypertension**, the usual initial oral dose of guanethidine monosulfate has been 10 mg daily. This is increased by increments of 10 to 12.5 mg, not more often than every 5 to 7 days, according to response. The usual maintenance dose has been 25 to 50 mg once daily.

Children have been given 200 micrograms/kg daily with increments of 200 micrograms/kg every 7 to 10 days until a satisfactory response is achieved.

Guanethidine monosulfate has been given intramuscularly in the treatment of hypertensive crises, including severe pre-eclampsia, but more suitable drugs are available. An intramuscular dose of 10 to 20 mg is reported to produce a fall in blood pressure within 30 minutes.

Eye drops containing guanethidine monosulfate have been used in the treatment of open-angle **glaucoma** (usually combined with adrenaline), and for the lid retraction that may accompany hyperthyroidism.

Pain syndromes. Sympathetic nerve blocks may be used in the management of acute or chronic pain associated with a well-defined anatomical site. Guanethidine is one of a number of drugs that have been used for intravenous regional sympathetic block in the management of neuropathic pain (see Complex Regional Pain Syndrome, p.6), to reduce pain and to maintain blood flow.

However, reviews and studies[1,2] in patients with reflex sympathetic dystrophy failed to find any benefit from guanethidine.

1. Jadad AR, *et al.* Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; **10:** 13–20.
2. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br* 2002; **84:** 380–6.

Preparations

BP 2008: Guanethidine Tablets;
USP 31: Guanethidine Monosulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Ismelin; ***Gr.:*** Ismelin; ***UK:*** Ismelin; ***USA:*** Ismelin†.

Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Thilodigon†; ***Ger.:*** Esimil†; Thilodigon; ***Irl.:*** Ganda; ***USA:*** Esimil.

Guanfacine Hydrochloride *(BANM, USAN, rINNM)*

BS-100-141; Guanfacine, Chlorhydrate de; Guanfacini Hydrochloridum; Hidrocloruro de guanfacina; LON-798. *N*-Amidino-2-(2,6-dichlorophenyl)acetamide hydrochloride.

Гуанфацина Гидрохлорид

$C_9H_9Cl_2N_3O,HCl = 282.6.$

CAS — 29110-47-2 (guanfacine); 29110-48-3 (guanfacine hydrochloride).

ATC — C02AC02.

ATC Vet — QC02AC02.

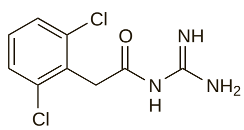

(guanfacine)

Pharmacopoeias. In *US.*

USP 31 (Guanfacine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Clonidine Hydrochloride, p.1247. Rebound hypertension may occur but is delayed due to the longer half-life.

◊ Reviews.

1. Jerie P. Clinical experience with guanfacine in long-term treatment of hypertension, part II: adverse reactions to guanfacine. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 157S–164S.
2. Board AW, *et al.* A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. *Clin Ther* 1988; **10:** 761–75.

Withdrawal. Rapid reduction of the guanfacine dosage resulted in rebound hypertension leading to generalised seizures and coma in a 47-year-old patient with renal failure who was receiving haemodialysis.[1] Use with phenobarbital may have enhanced the metabolism of guanfacine and contributed to the development of the withdrawal effect.

1. Kiechel JR, *et al.* Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* 1983; **25:** 463–6.

Interactions

As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics

Guanfacine is rapidly absorbed after oral doses and peak plasma concentrations occur 1 to 4 hours after ingestion. The oral bioavailability is reported to be about 80%. It is about 70% bound to plasma proteins. It is excreted in urine as unchanged drug and metabolites; about 50% of a dose is reported to be eliminated unchanged. The normal elimination half-life ranges from 10 to 30 hours, tending towards the upper range in older patients.

Renal impairment. A study[1] in patients with normal or impaired renal function found that guanfacine clearance and serum concentrations were not significantly different in the 2 groups, suggesting that non-renal elimination plays an important role in patients with renal impairment.

1. Kirch W, *et al.* Elimination of guanfacine in patients with normal and impaired renal function. *Br J Clin Pharmacol* 1980; **10** (suppl 1): 33S–35S.

Uses and Administration

Guanfacine is a centrally acting alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p.1248). It is used in the management of hypertension (p.1171), although other drugs are usually preferred. It may be used alone or with other antihypertensives, particularly thiazide diuretics. It has also been tried in the management of opioid withdrawal and in hyperactivity disorders.

Guanfacine is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Guanfacine hydrochloride 1.15 mg is equivalent to about 1 mg of guanfacine. In hypertension the usual initial dose is 1 mg daily increasing after 3 to 4 weeks to 2 mg daily if necessary.

◊ Reviews.

1. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. *Clin Pharm* 1988; **7:** 187–97.

Tourette's syndrome. Guanfacine may be used as an alternative to clonidine in the management of patients with mild to moderate symptoms of Tourette's syndrome (see Tics, p.954). First-line use of these drugs is increasingly favoured in such patients because of a relative lack of serious adverse effects when compared with the commonly used antipsychotics.

Preparations

USP 31: Guanfacine Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Estulic; ***Cz.:*** Estulic†; ***Fr.:*** Estulic; ***Hung.:*** Estulic; ***Jpn:*** Estulic†; ***Neth.:*** Estulic†; ***Rus.:*** Estulic (Эстулик); ***USA:*** Tenex.

Heparin *(BAN)*

Hepariini; Heparina; Heparinum; Heparyna.

CAS — 9005-49-6.

ATC — B01AB01; C05BA03; S01XA14.

ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Description. Heparin is an anionic polysaccharide of mammalian origin with irregular sequence. It consists principally of alternating iduronate and glucosamine residues, most of which are sulfated. It may be described as a sulfated glucosaminoglycan. Heparin has the characteristic property of delaying the clotting of freshly shed blood. It may be prepared from the lungs of oxen or the intestinal mucosa of oxen, pigs, or sheep.
Heparin is often described in the literature as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins.

Heparin Calcium *(BANM)*

Calcium Heparin; Hepariinikalsium; Heparin Kalsiyum; Heparin Sodyum; Heparin vápenatá sůl; Heparina cálcica; Héparine calcique; Heparinkalcium; Heparino kalcio druska; Heparinum calcicum; Heparyna wapniowa.

CAS — 37270-89-6.

ATC — B01AB01; C05BA03; S01XA14.

ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Heparin Calcium). The potency of heparin calcium intended for parenteral use is not less than 150 international units per mg and the potency of heparin calcium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

USP 31 (Heparin Calcium). The calcium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. See Heparin Sodium, below.

Heparin Sodium *(BANM, rINN)*

Hepariininatrium; Heparin sodná sůl; Heparina sódica; Héparine sodique; Heparinnatrium; Heparino natrio druska; Heparinum natricum; Heparyna sodowa; Sodium Heparin; Soluble Heparin.

Гепарин Натрий

CAS — 9041-08-1.

ATC — B01AB01; C05BA03; S01XA14.

ATC Vet — QB01AB01; QC05BA03; QS01XA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Heparin Sodium). The potency of heparin sodium intended for parenteral use is not less than 150 international units per mg and the potency of heparin sodium not intended for parenteral use is not less than 120 international units per mg, both calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

USP 31 (Heparin Sodium). The sodium salt of heparin with a potency, calculated on the dried basis, of not less than 140 USP units in each mg. USP heparin units are not equivalent to international units. The source of the material is usually the intestinal mucosa or other suitable tissues of domestic mammals used for food by man and should be stated on the label. A white or pale-coloured amorphous, odourless or almost odourless, hygroscopic powder. Soluble 1 in 20 of water. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at temperatures below 40°, preferably between 15 and 30°.

Incompatibility. Incompatibility has been reported between heparin calcium or sodium and alteplase, amikacin sulfate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin potassium or sodium, cefalotin sodium, ciprofloxacin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulfate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, meticillin sodium, netilmicin sulfate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulfate, streptomycin sulfate, tetracycline hydrochloride, tobramycin sulfate, vancomycin hydrochloride, and vinblastine sulfate. Heparin sodium has also been reported to be incompatible with cisatracurium besilate,[1] labetalol hydrochloride,[2] levofloxacin,[3] nicardipine hydrochloride,[4] reteplase,[5] and vinorelbine tartrate.[6] Although visually compatible,[7] cefmetazole sodium is reported to inactivate heparin sodium.

Glucose can have variable effects,[8,9] but glucose-containing solutions are generally considered suitable diluents for heparin. Incompatibility has also been reported between heparin and fat emulsion.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Committee on Safety of Medicines/Medicines Control Agency. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; **26:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
6. Balthasar JP. Concentration-dependent incompatibility of vinorelbine tartrate and heparin sodium. *Am J Health-Syst Pharm* 1999; **56:** 1891.
7. Hutching SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
8. Anderson W, Harthill JE. The anticoagulant activity of heparins in dextrose solutions. *J Pharm Pharmacol* 1982; **34:** 90–6.
9. Wright A, Hecker J. Long term stability of heparin in dextrose-saline intravenous fluids. *Int J Pharm Pract* 1995; **3:** 253–5.

Units

The fifth International Standard for unfractionated heparin was established in 1998. The USP 31 states that USP and international units are not equivalent, although doses expressed in either appear to be essentially the same.

Adverse Effects

Heparin can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated. The incidence of thrombocytopenia is reported to be greater with bovine than porcine heparin.

Hypersensitivity reactions may occur, as may local irritant effects, and skin necrosis. Alopecia and osteoporosis resulting in spontaneous fractures have occurred after prolonged use of heparin.

Effects on the adrenal glands. Heparin inhibits the secretion of aldosterone and so may cause hyperkalaemia.[1] Although all patients treated with heparin may develop reduced aldosterone concentrations, most are able to compensate through the renin-angiotensin system. Patients on prolonged heparin therapy or those unable to compensate, such as patients with diabetes mellitus or renal impairment or those also receiving potassium-sparing drugs such as ACE inhibitors, may present with symptoms of hyperkalaemia. The UK CSM suggests[2] that plasma-potassium concentration should be monitored in all patients with risk factors, particularly those receiving heparin for more than 7 days. The hyperkalaemia is usually transient or resolves when heparin is stopped and treatment is not generally required; fludrocortisone was successfully used to treat resistant hyperkalaemia in a patient in whom continued heparin therapy was necessary.[3]

Adrenal insufficiency secondary to adrenal haemorrhage has also been associated with heparin; heparin-induced thrombocytopenia may be implicated.[4]

1. Oster JR, *et al.* Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; **98:** 575–86.
2. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

3. Sherman DS, *et al.* Fludrocortisone for the treatment of heparin-induced hyperkalemia. *Ann Pharmacother* 2000; **34:** 606–10.
4. Dahlberg PJ, *et al.* Adrenal insufficiency secondary to adrenal hemorrhage: two case reports and a review of cases confirmed by computed tomography. *Arch Intern Med* 1990; **150:** 905–9.

Effects on the blood. *Haemorrhage* is a recognised risk with heparin.[1] The risk of major bleeding may be lower with continuous intravenous infusion than with intermittent intravenous injection; risk may increase with heparin dose and patient age.[2]

Heparin has been associated with the development of *thrombocytopenia*. The reported incidence has varied greatly; up to 6% appears to be a reasonable estimate[3,4] although up to 10% has also been quoted.[5] Thrombocytopenia induced by heparin may be of two types. The first is an acute, but usually mild, fall in platelet count occurring within 1 to 4 days of starting therapy and which often resolves without stopping treatment. A direct effect of heparin on platelet aggregation appears to be responsible. The second type of thrombocytopenia, which has an immunological basis, is more serious. It usually occurs after 5 to 11 days although its onset may be more rapid in patients previously exposed to heparin;[6] delayed presentation up to 40 days after stopping heparin has also been reported.[7-9] It is often associated with thromboembolic complications due to platelet-rich thrombi (the 'white clot syndrome') or, more rarely, bleeding. Of 34 cases of heparin-associated thrombocytopenia reported to the UK CSM from 1964 to 1989, bleeding or thromboembolic complications occurred in 11 patients, 7 of whom died.[3] This type of thrombocytopenia appears to occur more often with bovine heparin than with heparin from other species,[10] and least frequently with low-molecular-weight-heparins;[11] the mechanism appears to be development of antibodies to a complex formed between heparin and platelet factor-4 (found on platelets and endothelial cells), which then cause platelet activation and thrombin generation.[12] Patients with lupus anticoagulant may also be more susceptible.[13] The reaction is independent of dose or route of administration; there have been reports of thrombocytopenia after use of heparin flushes[14] or heparin-coated catheters.[15]

Monitoring of platelet counts is therefore advised in patients given heparin. A baseline platelet count should be obtained in all patients. This should be repeated at least every 2 to 3 days in those given therapeutic doses of unfractionated heparin;[11] monitoring on alternate days from days 4 to 14 is recommended when unfractionated heparin is used for prophylaxis.[11,16] For low-molecular-weight heparins the risk may be lower but monitoring is recommended in most patients; platelet counts should be checked every 2 to 4 days from days 4 to 14.[16] Patients exposed to heparin within the previous 100 days may be sensitised to it and after re-exposure should have a platelet count within 24 hours.[11,16]

The **management** of heparin-induced thrombocytopenia has been reviewed.[11,12,16-19] Heparin should be stopped immediately in those who develop thrombocytopenia. It should be noted, however, that thrombosis has occurred in patients whose reduction in platelet count was relatively mild and who may not be considered to be thrombocytopenic.[20-23] On withdrawal of heparin, a heparinoid such as danaparoid[16,24,25] may be tried, provided that an *in-vitro* platelet aggregation test shows that there is no cross-reactivity with heparin. Alternatively, the direct thrombin inhibitors lepirudin[16,25,26] or argatroban[25,27] may be used; bivalirudin[11,12,19] or fondaparinux[11,28] are further options. Similar recommendations have been made for children.[29] Low-molecular-weight heparins have been used; they are associated with a lower incidence of induced thrombocytopenia than unfractionated heparin[30] but the rate of cross-reactivity is high and they are not generally recommended.[16,25,27] Oral anticoagulants have also been used, but an increased risk of venous limb gangrene has been reported[31] with warfarin and it should not be given until the platelet count has recovered.[11,16] Dermatan sulfate[32] has also been used. Thrombocytopenia has been managed with aspirin and dipyridamole or with normal immunoglobulin.[33] A fibrinolytic such as urokinase has been used in a few cases of occlusive thrombosis.[34,35]

There may be a relationship between heparin-induced thrombocytopenia and skin necrosis (see below).

There have been reports[36] of spinal haematomas developing spontaneously after the use of low-molecular-weight heparins.

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; **244:** 1209–12.
2. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
3. CSM. Heparin-induced thrombocytopenia. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 22/05/08)
4. Derlon A, *et al.* Thrombopénies induites par l'héparine: symptomatologie, détection, fréquence. *Therapie* 1988; **43:** 199–203.
5. Aster RH. Heparin-induced thrombocytopenia and thrombosis. *N Engl J Med* 1995; **332:** 1374–6.
6. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; **344:** 1286–92.
7. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med* 2001; **135:** 502–6.
8. Rice L, *et al.* Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; **136:** 210–15.
9. Warkentin TE, Bernstein RA. Delayed-onset heparin-induced thrombocytopenia and cerebral thrombosis after a single administration of unfractionated heparin. *N Engl J Med* 2003; **348:** 1067–9.
10. Bell WR, Royall RM. Heparin-associated thrombocytopenia: a comparison of three heparin preparations. *N Engl J Med* 1980; **303:** 902–7.
11. Warkentin T, *et al.* Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 340S–380S.
12. Menajovsky LB. Heparin-induced thrombocytopenia: clinical manifestations and management strategies. *Am J Med* 2005; **118** (suppl 8A): 21S–30S.
13. Auger WR, *et al.* Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. *Am J Med* 1995; **99:** 392–6.
14. Heeger PS, Backstrom JT. Heparin flushes and thrombocytopenia. *Ann Intern Med* 1986; **105:** 143.
15. Laster JL, *et al.* Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern Med* 1989; **149:** 2285–7.
16. Keeling D, *et al.* on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin induced thrombocytopenia. *Br J Haematol* 2006; **133:** 259–69. Also available at: http://www.bcshguidelines.com/pdf/bjh_020606.pdf (accessed 07/06/06)
17. Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 489–503.
18. Messmore HL, *et al.* Benefit-risk assessment of treatments for heparin-induced thrombocytopenia. *Drug Safety* 2003; **26:** 625–41.
19. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355:** 809–17.
20. Phelan BK. Heparin-associated thrombosis without thrombocytopenia. *Ann Intern Med* 1983; **99:** 637–8.
21. Trono DP, *et al.* Thrombocytopenia and heparin-associated thrombosis. *Ann Intern Med* 1984; **100:** 464–5.
22. Ramirez-Lassepas M, Cipolle RJ. Heparin and thrombocytopenia. *Ann Intern Med* 1984; **100:** 613.
23. Hach-Wunderle V, *et al.* Heparin-associated thrombosis despite normal platelet counts. *Lancet* 1994; **344:** 469–70.
24. Wilde MI, Markham A. Danaparoid: a review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. *Drugs* 1997; **54:** 903–24.
25. Januzzi JL, Jang I-K. Heparin induced thrombocytopenia: diagnosis and contemporary antithrombin management. *J Thromb Thrombolysis* 1999; **7:** 259–64.
26. Greinacher A, *et al.* Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation* 1999; **99:** 73–80.
27. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis, frequency, avoidance and management. *Drug Safety* 1997; **17:** 325–41.
28. Parody R, *et al.* Fondaparinux (ARIXTRA) as an alternative anti-thrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins. *Haematologica* 2003; **88:** ECR32. Also available at: http://www.haematologica.org/cgi/reprint/88/11/ECR32.pdf (accessed 19/08/08)
29. Risch L, *et al.* Heparin-induced thrombocytopenia in paediatrics: clinical characteristics, therapy and outcomes. *Intensive Care Med* 2004; **30:** 1615–24.
30. Warkentin TE, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332:** 1330–5.
31. Warkentin TE, *et al.* The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997; **127:** 804–12.
32. Taliani MR, *et al.* Dermatan sulphate in patients with heparin-induced thrombocytopenia. *Br J Haematol* 1999; **104:** 87–9.
33. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
34. Krueger SK, *et al.* Thrombolysis in heparin-induced thrombocytopenia with thrombosis. *Ann Intern Med* 1985; **103:** 159.
35. Clifton GD, Smith MD. Thrombolytic therapy in heparin-associated thrombocytopenia with thrombosis. *Clin Pharm* 1986; **5:** 597–601.
36. Heppner PA, *et al.* Spontaneous spinal hematomas and low-molecular-weight heparin: report of four cases and review of the literature. *J Neurosurg Spine* 2004; **1:** 232–6.

Effects on the bones. Osteoporosis is a rare complication of long-term heparin therapy. Treatment and prophylaxis of thromboembolism in pregnancy is one of the few indications for long term use of heparin, so most reports and studies of heparin-induced osteoporosis have been in pregnant women.[1] The incidence of symptomatic osteoporosis in patients given heparin long term has been estimated to be about 2%.[1,2] Subclinical reduction in bone density occurs in up to one-third of patients,[2] but it is not possible to predict which of these patients will develop osteoporotic fractures. Pregnancy normally causes reversible bone demineralisation, so the combination of pregnancy and heparin therapy may therefore result in symptomatic osteoporosis in susceptible individuals.[1,3] Bone changes may be reversible.[1] Although some evidence suggests that bone demineralisation is dose- and duration-dependent, this has not been conclusively established.[1,3] Use of low-molecular-weight heparins is associated with a lower risk of heparin-induced osteoporosis.[2]

1. Nelson-Piercy C. Heparin-induced osteoporosis. *Scand J Rheumatol* 1998; **27** (suppl 107): 68–71.
2. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.
3. Farquharson RG. Heparin, osteoporosis and pregnancy. *Br J Hosp Med* 1997; **58:** 205–7.

Effects on electrolyte balance. See Effects on the Adrenal Glands, above.

Effects on lipid metabolism. Use of heparin leads to the release of lipoprotein lipase into the plasma. Postprandial lipidaemia is reduced due to increased hydrolysis of triglycerides into free fatty acids and glycerol. Raised concentrations of free fatty acids have been reported after heparin use but the magnitude of this effect may have been overestimated.[1] Rebound hyperlipidaemia may occur when heparin is withdrawn. With long-term use reserves of lipoprotein lipase may be depleted; severe hypertriglyceridaemia reported in a pregnant woman was attributed to long-term heparin prophylaxis that was thought to have resulted in lipoprotein lipase deficiency.[2]

1. Riemersma RA, *et al.* Heparin-induced lipolysis, an exaggerated risk. *Lancet* 1981; **ii:** 471.
2. Watts GF, *et al.* Lipoprotein lipase deficiency due to long-term heparinization presenting as severe hypertriglyceridaemia in pregnancy. *Postgrad Med J* 1991; **67:** 1062–4.

Effects on the liver. Increases in transaminase values, usually reversible on discontinuing therapy, have been reported in patients given therapeutic[1-3] or prophylactic[3] doses of heparin. A prospective study[4] found increased transaminases that were assessed as probably due to heparin in 8 of 54 patients; the reaction seemed to occur more frequently with therapeutic doses. Increased transaminases have also been reported[5] in 2 patients receiving low-molecular-weight-heparins.

1. Sonnenblick M, *et al.* Hyper-transaminasemia with heparin therapy. *BMJ* 1975; **3:** 77.
2. Dukes GE, *et al.* Transaminase elevations in patients receiving bovine or porcine heparin. *Ann Intern Med* 1984; **100:** 646–50.
3. Monreal M, *et al.* Adverse effects of three different forms of heparin therapy: thrombocytopenia, increased transaminases, and hyperkalaemia. *Eur J Clin Pharmacol* 1989; **37:** 415–18.
4. Guevara A, *et al.* Heparin-induced transaminase elevations: a prospective study. *Int J Clin Pharmacol Ther Toxicol* 1993; **31:** 137–41.
5. Hui C-K, *et al.* Low molecular weight heparin-induced liver toxicity. *J Clin Pharmacol* 2001; **41:** 691–4.

Effects on sexual function. There have been several reports of priapism associated with the use of heparin. The prognosis is poor, impotence following more often than in priapism of other aetiologies. The mechanism of heparin-induced priapism is unclear.[1]

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.

Effects on the skin. Skin necrosis is a rare complication of heparin use.[1,2] It may be a localised reaction at the site of subcutaneous injection or possibly be related to heparin-induced thrombocytopenia (see Effects on the Blood, above). An immune mechanism may be responsible.

Eczematous plaque reactions have developed several days after starting subcutaneous heparin. A type IV hypersensitivity reaction has been implicated.[3] Low-molecular-weight heparins may be an alternative but cross-reactivity can occur.[4]

Recurrent fixed eczematous lesions have been attributed to heparin used intravenously during haemodialysis.[5]

1. Ulrick PJ, Manoharan A. Heparin-induced skin reaction. *Med J Aust* 1984; **140:** 287–9.
2. Fowlie J, *et al.* Heparin-associated skin necrosis. *Postgrad Med J* 1990; **66:** 573–5.
3. Bircher AJ, *et al.* Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; **123:** 507–14.
4. O'Donnell BF, Tan CY. Delayed hypersensitivity reactions to heparin. *Br J Dermatol* 1993; **129:** 634–6.
5. Mohammed KN. Symmetric fixed eruption to heparin. *Dermatology* 1995; **190:** 91.

Hypersensitivity. An increased incidence of severe hypersensitivity reactions, including fatalities, was reported with some heparin preparations in early 2008;[1] it was suggested that the presence of an over-sulfated chondroitin sulfate contaminant may have been responsible.[1,2]

See Effects on the Blood and Effects on the Skin, above, for further hypersensitivity reactions associated with heparin.

1. FDA. Update to healthcare facilities and healthcare professionals about heparin and heparin-containing medical products. Available at: http://www.fda.gov/cdrh/safety/heparin-healthcare-update.pdf (accessed 22/05/08)
2. Kishimoto TK, *et al.* Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008; **358:** 2457–67.

Treatment of Adverse Effects

Slight haemorrhage due to overdosage can usually be treated by stopping heparin. Severe bleeding may be reduced by the slow intravenous injection of protamine sulfate (p.1461). The dose is dependent on the amount of heparin to be neutralised and ideally should be titrated against assessments of the coagulability of the patient's blood. As heparin is being continuously excreted, the dose of protamine should be reduced if it is more than 15 minutes since the last dose of heparin; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required. The Ph. Eur. 6.2 specifies that 1 mg of protamine sulfate precipitates not less than 100 international units of heparin, but adds that this potency is based on a specific reference batch of heparin sodium. UK licensed product information has stated that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous), and US information that each mg of protamine sulfate neutralises approximately 90 USP units of heparin (lung) or about 115 USP units of heparin (mucous).

Thrombocytopenia. For reference to the treatment of heparin-induced thrombocytopenia and associated thromboembolic complications, see Effects on the Blood under Adverse Effects, above.

Precautions

Heparin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, thrombocytopenia, peptic ulcer disease, cerebrovascular disorders, bacterial endocarditis, severe hypertension, oesophageal varices, or patients who have recently undergone surgery at sites where haemorrhage would be an especial risk. Caution is required in hepatic and renal impairment; severe hepatic or renal impairment may be a contra-indication. Heparin should not be given by intramuscular injection. Since heparin has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in all patients (see Effects on the Blood, under Adverse Effects, above). Heparin should be stopped if thrombocytopenia develops. A test dose has been recommended for patients with a history of allergy.

Dosage of heparin may need to be reduced in the elderly; elderly women appear to be especially susceptible to haemorrhage after use of heparin.

Catheters and cannulas. Serum concentrations of sodium and potassium could be falsely elevated in samples obtained through heparin-bonded umbilical catheters due to release of benzalkonium chloride used in the manufacturing process of some catheters.[1] It was unknown if the amount released would be toxic to small premature neonates.

1. Gaylord MS, *et al.* Release of benzalkonium chloride from a heparin-bonded umbilical catheter with resultant factitious hypernatremia and hyperkalemia. *Pediatrics* 1991; **87:** 631–5.

Hyperkalaemia. For recommendations concerning the monitoring of patients susceptible to developing hyperkalaemia, such as those with diabetes mellitus or renal impairment, see Effects on the Adrenal Glands under Adverse Effects, above.

Pregnancy. Heparin does not cross the placenta, and therefore adverse effects on the fetus would not be expected.[1,2] A review[1] of the literature, however, indicated 2 spontaneous abortions and 17 still-births in 135 pregnancies exposed to heparin; 29 infants were premature, 10 of whom died. Another literature review[2] found adverse outcomes in 21.7% of heparin-treated patients, but this dropped to 10.4% when pregnancies with co-morbid conditions were excluded. A further drop to 3.6% was observed when cases of prematurity with normal outcome were also excluded. The death rate of 2.5% and prematurity rate of 6.8% in heparin-treated patients was similar to that found in the normal population. It was concluded that heparin appears safer for the fetus than warfarin when used during pregnancy. Similar results have also been reported with low-molecular-weight heparins; a systematic review[3] found an adverse outcome in 9.3% of 486 pregnancies in which low-molecular-weight heparin was used, but this dropped to 3.1% in women without comorbid conditions.

For further details on the use of heparin and low-molecular-weight heparins in pregnancy, see under Uses and Administration, below.

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Ginsberg JS, Hirsh J. Optimum use of anticoagulants in pregnancy. *Drugs* 1988; **36:** 505–12.
3. Sanson B-J, *et al.* Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; **81:** 668–72.

Preservative. The preservatives used in heparin preparations have been implicated in unwanted effects. Benzyl alcohol in heparinised flushing solutions has been suspected of causing toxicity in neonates (see p.1631). Chlorobutanol present in another heparin preparation caused a sharp fall in blood pressure (see Effects on the Cardiovascular System under Chlorobutanol, p.1639).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred after spinal or epidural anaesthesia or analgesia in patients given heparin or low-molecular-weight heparins. The risk of haematoma appears to be higher in patients with indwelling epidural catheters or in those also given other drugs that affect haemostasis.[1] It is generally recommended that central nerve block should be avoided in patients on full-dose anticoagulation.[2] However, the use of prophylactic doses of anticoagulants with central nervous blockade is less clear.[2,3] The reported risk of haematoma with low-molecular-weight heparins has been higher in the USA where higher doses have been used for prophylaxis.[3] Recommendations to reduce the risk of spinal haematoma include waiting until after blockade has been completed to give prophylactic heparin or low-molecular-weight heparin. Where anticoagulant prophylaxis has already been given, blockade should be delayed if possible until 4 to 6 hours after heparin, and the catheter should not be removed until 4 hours after heparin.[2] It is recommended that low-molecular-weight heparin should not be given within 8 to 10 hours before or after central nerve block or catheter removal.[2,3]

There have also been cases of spontaneous spinal haematomas (unrelated to trauma, surgery, or lumbar puncture) occurring after use of low-molecular-weight heparins (see Effects on the Blood, above).

1. Wysowski DK, *et al.* Spinal and epidural hematoma and low-molecular-weight heparin. *N Engl J Med* 1998; **338:** 1774.
2. Armstrong RF, *et al.* Epidural and spinal anaesthesia and the use of anticoagulants. *Hosp Med* 1999; **60:** 491–6.
3. Dolenska S. Neuroaxial blocks and LMWH thromboprophylaxis. *Hosp Med* 1998; **59:** 940–3.

Interactions

Heparin should be used with care with oral anticoagulants or drugs, such as aspirin and dipyridamole, that affect platelet function. NSAIDs may also increase the risk of haemorrhage. Other drugs that affect the coagulation process and which may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins and some cephalosporins, some contrast media, asparaginase, and epoprostenol; for use of heparin with drotrecogin alfa (activated) see p.1078. Estimations of oral anticoagulant control may be modified by heparin's action on prothrombin.

ACE inhibitors. For reference to hyperkalaemia in patients on heparin and ACE inhibitors, see Effects on the Adrenal Glands under Adverse Effects, above.

Alcohol. Heavy drinkers were found to be at greater risk of major heparin-associated bleeding than moderate drinkers or non-drinkers.[1]

1. Walker AM, Jick H. Predictors of bleeding during heparin therapy. *JAMA* 1980; **244:** 1209–12.

Aprotinin. For comment on the use of heparin with aprotinin, see Effects on Coagulation Tests under Aprotinin, p.1055.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are given simultaneously by the intravenous route.[1] This effect has been seen even with low doses of glyceryl trinitrate.[2] Propylene glycol present in the glyceryl trinitrate formulation may[3] or may not[1] contribute to the effect. No interaction was reported when glyceryl trinitrate was given immediately after heparin.[4]

1. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. *Arch Intern Med* 1987; **147:** 857–60.
2. Brack MJ, *et al.* The effect of low dose nitroglycerine on plasma heparin concentrations and activated partial thromboplastin times. *Blood Coag Fibrinol* 1993; **4:** 183–6.
3. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.
4. Bode V, *et al.* Absence of drug interaction between heparin and nitroglycerin. *Arch Intern Med* 1990; **150:** 2117–19.

Tobacco. Reduced half-life and increased elimination of heparin have been reported in smokers compared with non-smokers.[1]

1. Cipolle RJ, *et al.* Heparin kinetics: variables related to disposition and dosage. *Clin Pharmacol Ther* 1981; **29:** 387–93.

Pharmacokinetics

Heparin is not absorbed from the gastrointestinal tract. After intravenous or subcutaneous injection heparin is extensively bound to plasma proteins. It does not cross the placenta and it is not distributed into breast milk. The half-life of heparin depends on its dose and route as well as the method of calculation and is subject to wide inter- and intra-individual variation; a range of 1 to 6 hours with an average of 1.5 hours has been cited. It may be slightly prolonged in renal impairment, decreased in patients with pulmonary embolism, and either increased or decreased in patients with liver disorders. Heparin is taken up by the reticuloendothelial system. It is excreted in the urine, mainly as metabolites, although after large doses up to 50% may be excreted unchanged.

◊ References.

1. Estes JW. Clinical pharmacokinetics of heparin. *Clin Pharmacokinet* 1980; **5:** 204–20.
2. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.

Uses and Administration

Heparin is an anticoagulant used principally in the treatment and prophylaxis of thromboembolic disorders (p.1187). It is often described as standard heparin or unfractionated heparin to distinguish it from low-molecular-weight heparins (p.1329).

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). Heparin increases the rate of this inhibition, but in a manner that is dependent on its dose. With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The inhibition of thrombin blocks the conversion of fibrinogen to fibrin, and the inhibition of factor Xa blocks the conversion of prothrombin to thrombin. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p.1045.

Heparin is used in the treatment and prophylaxis of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189), especially prophylaxis in surgical patients and in those pregnant women at particular risk. It is also used in the management of arterial thromboembolism including that associated with unstable angina pectoris (p.1157), myocardial infarction (p.1175), acute peripheral arterial occlusion (p.1178), and stroke (p.1185). It is often used as a precursor to oral anticoagulation and is withdrawn once the oral anticoagulant is exerting its full effect.

Heparin has been tried in the treatment of disseminated intravascular coagulation. It is also used to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures such as cardiopulmonary bypass. Other uses include the anticoagulation of blood for transfusion or blood samples and the flushing of catheters and cannulas to maintain patency.

Heparin and its salts are constituents of many topical preparations for the treatment of various inflammatory disorders.

Administration and dosage. Heparin is given intravenously, preferably by continuous infusion, or by subcutaneous injection. It may be given as the calcium or sodium salt and it is generally accepted that there is little difference in their effects. Oral formulations of heparin are under investigation.

Doses of heparin for treatment (sometimes termed 'full-dose' heparin), and in some cases prophylaxis, of thromboembolism should be monitored and determined as discussed below under Control of Heparin Therapy. The subcutaneous doses of heparin commonly used for prophylaxis (often termed 'low-dose') do not require routine monitoring. A test dose has been recommended for patients with a history of allergy. Although international and USP units are not strictly equivalent, doses expressed in either appear to be essentially the same.

For **treatment of venous thromboembolism**, an intravenous loading dose of 5000 units (10 000 units may be required in severe pulmonary embolism) is followed by continuous intravenous infusion of 1000 to 2000 units/hour or subcutaneous injection of

15 000 units every 12 hours. Alternatively, intermittent intravenous injection of 5000 to 10 000 units every 4 to 6 hours is suggested in some product literature. Children and small adults are given a lower intravenous loading dose followed by maintenance with continuous intravenous infusion of 15 to 25 units/kg per hour or subcutaneous injection of 250 units/kg every 12 hours.

For **prophylaxis** of **postoperative venous thromboembolism**, subcutaneous doses used are 5000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with a history of deep-vein thrombosis or pulmonary embolism; the dosage may need to be increased to 10 000 units every 12 hours during the third trimester.

In the management of **unstable angina** or acute **peripheral arterial embolism,** heparin may be given by continuous intravenous infusion in the same doses as those recommended for the treatment of venous thromboembolism. Doses that have been recommended for the prevention of re-occlusion of the coronary arteries following thrombolytic therapy in **myocardial infarction** include 5000 units intravenously followed by 1000 units/hour intravenously with alteplase; a dose of 12 500 units subcutaneously every 12 hours for at least 10 days may be used to prevent mural thrombosis.

Control of heparin therapy. Treatment with full-dose heparin must be monitored to ensure that the dose is providing the required effect on antithrombin III. The most commonly used test to monitor the action of heparin is the activated partial thromboplastin time (APTT). The APTT of patients on full-dose heparin should generally be maintained at 1.5 to 2.5 times the control value although the optimum therapeutic range varies between individual laboratories depending on the APTT reagent in use. Regular monitoring is essential, preferably on a daily basis. Prophylaxis with low-dose subcutaneous heparin is not routinely monitored; the APTT is not significantly prolonged in these patients. A dose-adjusted regimen to maintain minimal prolongation of the APTT may be required in patients with malignancy or undergoing orthopaedic surgery to ensure adequate protection against thromboembolism. Other tests used include the activated clotting time (ACT). The value of measurements of heparin concentration in the blood remains to be established.

◊ General references to anticoagulation with heparin.

1. Hirsh J. Heparin. *N Engl J Med* 1991; **324:** 1565–74.
2. Freedman MD. Pharmacodynamics, clinical indications, and adverse effects of heparin. *J Clin Pharmacol* 1992; **32:** 584–96.
3. Hyers TM. Heparin therapy: regimens and treatment considerations. *Drugs* 1992; **44:** 738–49.
4. Hirsh J, Fuster V. Guide to anticoagulant therapy part 1: heparin. *Circulation* 1994; **89:** 1449–68.
5. Baglin T, *et al.* for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133:** 19–34. Also available at: http://www.bcshguidelines.com/pdf/heparin_220506.pdf (accessed 01/06/06)
6. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.

Action. Heparin is well established as an anticoagulant and antithrombotic and acts primarily by binding to, and enhancing the activity of, antithrombin III. However, the physiological role of endogenous heparin has not been clearly defined, despite its presence in mast cells, its ability to interact with numerous proteins, and its close structural similarity to heparan sulfate (suleparoid), the ubiquitous cell-surface glycosaminoglycan.[1,2] Endogenous heparin activity may have a role in protecting against atherosclerosis.[3] Non-anticoagulant properties of heparin or low-molecular-weight heparins have been reported to include anti-inflammatory activity, with a possible application in, for example, asthma[4-6] or inflammatory bowel disease; however, studies in patients with active ulcerative colitis have not found any benefit.[7] For mention of the use of aerosolised heparin with acetylcysteine to treat inhalation injury, see Burns, under Acetylcysteine, p.1549. The risk of bleeding is a major obstacle to the use of heparin for non-anticoagulant purposes.

1. Lane DA, Adams L. Non-anticoagulant uses of heparin. *N Engl J Med* 1993; **329:** 129–30.
2. Page CP. Proteoglycans: the "Teflon" of the airways? *Thorax* 1997; **52:** 924–5.
3. Engelberg H. Actions of heparin in the atherosclerotic process. *Pharmacol Rev* 1996; **48:** 327–52.
4. Martineau P, Vaughan LM. Heparin inhalation for asthma. *Ann Pharmacother* 1995; **29:** 71–2.
5. Ahmed T, *et al.* Prevention of exercise-induced bronchoconstriction by inhaled low-molecular-weight heparin. *Am J Respir Crit Care Med* 1999; **160:** 576–81.
6. Stelmach I, *et al.* The effect of inhaled heparin on airway responsiveness to histamine and leukotriene D4. *Allergy Asthma Proc* 2003; **24:** 59–65.
7. Chande N, *et al.* Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).

Administration. The activated partial thromboplastin time (APTT) is the test most commonly used to monitor intravenous full-dose heparin therapy. Heparin dosing algorithms have been developed[1,2] so that the time taken to achieve a therapeutic APTT and maintain it in the therapeutic range (usually 1.5 to 2.5 times the control value) is shortened and thus the risk of recurrent thrombosis and major bleeding complications is reduced. An automated method of monitoring and regulation has been tried.[3] Although use of ideal body-weight for dosage calculation in obese patients has been suggested, actual body-weight may be more appropriate,[4,5] but maximum bolus doses and infusion rates should be set, to avoid overdosage in morbidly obese patients.

However, the therapeutic ranges used in such algorithms are not applicable to all APTT reagents because the latter vary in their sensitivity to heparin.[6] The optimum therapeutic range therefore varies between individual laboratories depending on the APTT reagent used. Dosing algorithms may be adapted by calibrating the therapeutic APTT with plasma-heparin concentrations.[6,7]

A weight-based algorithm for treatment doses of subcutaneous heparin in deep-vein thrombosis has also been proposed.[8]

1. Cruickshank MK, *et al.* A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991; **151:** 333–7.
2. Raschke RA, *et al.* The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. *Ann Intern Med* 1993; **119:** 874–81.
3. Newby LK, *et al.* An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from PARAGON A. *J Thromb Thrombolysis* 2002; **14:** 33–42.
4. Yee WP, Norton LL. Optimal weight base for a weight-based heparin dosing protocol. *Am J Health-Syst Pharm* 1998; **55:** 159–62.
5. Yee WP, Norton LL. Clarification of weight-based heparin protocol. *Am J Health-Syst Pharm* 2002; **59:** 1788.
6. Brill-Edwards P, *et al.* Establishing a therapeutic range for heparin therapy. *Ann Intern Med* 1993; **119:** 104–9.
7. Volles DF, *et al.* Establishing an institution-specific therapeutic range for heparin. *Am J Health-Syst Pharm* 1998; **55:** 2002–6.
8. Prandoni P, *et al.* Use of an algorithm for administering subcutaneous heparin in the treatment of deep venous thrombosis. *Ann Intern Med* 1998; **129:** 299–302.

Catheters and cannulas. Solutions of heparin sodium 10 or 100 units/mL in sodium chloride 0.9% are used for the flushing of intravenous catheters, cannulas, and other indwelling intravenous infusion devices used for intermittent dosing (heparin locks). A meta-analysis[1] of controlled studies was, however, unable to show any major advantage of either strength of heparin sodium solution over sodium chloride 0.9% alone in maintaining peripheral cannula patency or reducing the incidence of thrombophlebitis, and sodium chloride 0.9% is therefore recommended for cannulas intended to be in place for 48 hours or less. Less use of heparin flush solutions could minimise the risk of adverse effects such as thrombocytopenia and reduce the risk of incompatibilities with intravenous drugs.

Use of heparin-bonded catheters or the addition of heparin to intravenous fluids such as total parenteral nutrition solutions has also been tried in an attempt to maintain indwelling intravenous infusion devices (but see Catheters and Cannulas under Precautions, above). Continuous infusion of heparin-containing fluids may prolong the patency of peripheral arterial catheters.[1] To maintain the patency of umbilical artery catheters in neonates, US guidelines[2] suggest continuous infusion of heparin at a concentration of 0.25 to 1 unit/mL.

Central venous catheters are also subject to thrombus formation and their use may be complicated by vascular thrombosis and systemic infection. A meta-analysis[3] of prophylactic heparin used with central venous and pulmonary artery catheters suggested that heparin reduces catheter-related vascular thrombosis and may reduce catheter-related infection. This analysis included a range of heparin doses and methods of administration, as well as heparin-bonded catheters, and the authors suggested that further study was needed. More specific systematic reviews have found that continuous infusion of heparin reduces the incidence of catheter occlusion in neonates with peripherally-placed central venous catheters,[4] and that heparin-bonded catheters may reduce the risk of catheter occlusion in children with central venous catheters.[5] Further evidence that heparin infusion reduces the risk of catheter-related infection has also been reported.[6] Very low doses of warfarin (1 mg daily) may protect against thrombosis in patients with central venous catheters.[7]

1. Randolph AG, *et al.* Benefit of heparin in meta-analysis of randomised controlled trials. *BMJ* 1998; **316:** 969–75.
2. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.
3. Randolph AG, *et al.* Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998; **113:** 165–71.
4. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/05/08).
5. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 15/05/08).
6. Abdelkefi A, *et al.* Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *J Clin Oncol* 2005; **23:** 7864–70.
7. Bern MM, *et al.* Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 1990; **112:** 423–8.

Disseminated intravascular coagulation. Heparin has been used with some success in disseminated intravascular coagulation (p.1048) associated with a variety of conditions. However, this use is considered by some to be controversial and should be reserved for specific situations where the risk of bleeding is relatively minor in comparison with the possible beneficial effect on formation of microthromboses. A suggested intravenous dose is 500 units/hour, adjusted if necessary according to clinical response.[1] The maximum dose given intravenously is usually 1000 units/hour because of the risk of bleeding.

1. Baglin T, *et al.* for the British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. *Br J Haematol* 2006; **133:** 19–34. Also available at: http://www.bcshguidelines.com/pdf/heparin_220506.pdf (accessed 01/06/06)

Extracorporeal circulation. Anticoagulation with heparin is necessary during procedures such as cardiopulmonary bypass and haemodialysis and haemofiltration. In the case of bypass, heparin is added to the crystalloid solution and any stored blood used for priming the bypass machine and is given intravenously before cannulation of the heart and major blood vessels. Activated clotting time (ACT) is monitored throughout. After bypass is stopped, anticoagulation can be reversed with protamine but caution is advised because of potential toxicity on the cardiopulmonary circulation.

At the start of haemodialysis sessions patients generally get a loading dose of heparin followed by continuous infusion into the exit line of the extracorporeal circuit until about one hour before the end of dialysis. The dose of heparin varies widely depending on body-weight, volume of the extracorporeal circulation, dialysis membrane biocompatibility, and pump speed.

Idiopathic thrombocytopenic purpura. Subcutaneous injection of a low dose of heparin improved platelet counts in a small number of patients with idiopathic thrombocytopenic purpura (p.1505) that was resistant to standard corticosteroid therapy.[1] However, heparin may itself cause thrombocytopenia, even at very low doses (see Effects on the Blood under Adverse Effects, above).

1. Shen ZX, *et al.* Thrombocytopoietic effect of heparin given in chronic immune thrombocytopenic purpura. *Lancet* 1995; **346:** 220–1.

Malignant neoplasms. Cancer is a risk factor for thromboembolism and anticoagulants are often used in patients with malignant neoplasms. There is some evidence that outcomes are improved in patients treated with heparin, and both unfractionated and low-molecular-weight heparins have therefore been studied in patients with malignant neoplasms but no other indication for anticoagulation. Systematic reviews[1,2] have found that there is a clinically significant improvement in survival, although the risk of bleeding is also increased.

1. Akl EA, *et al.* Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/05/08).
2. Lazo-Langner A, *et al.* The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. *J Thromb Haemost* 2007; **5:** 729–37.

Pregnancy. Heparin or low-molecular-weight heparins are the anticoagulants of choice for use in pregnancy although they are not without risk for the fetus (see Pregnancy, under Precautions, above), and for the mother.

Guidelines on thrombosis associated with pregnancy have been published.[1-3] Pregnant women may require anticoagulation for the treatment or prophylaxis of venous thromboembolism (p.1189), or for the prevention of systemic thromboembolism associated with prosthetic heart valves (p.1187). Patients with a history of thromboembolism or a thrombophilic abnormality such as inherited deficiencies of antithrombin III, protein C, or protein S or acquired antiphospholipid antibodies may be at particular risk. Women with antiphospholipid antibodies may also be at increased risk of fetal loss (see Systemic Lupus Erythematosus, p.1513) and treatment with low-dose aspirin is usually recommended.[2] Addition of heparin has been reported to further reduce the risk,[4,5] and treatment with heparin or low-molecular-weight heparin, in addition to aspirin, has therefore also been recommended.[3]

1. Royal College of Obstetricians and Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (February 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top_28_thromboembolic_minorrevision.pdf (accessed 05/02/08)
2. Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis during pregnancy, labour and after vaginal delivery (January 2004). Available at: http://www.rcog.org.uk/index.asp?PageID=535 (accessed 23/05/05)
3. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.
4. Rai R, *et al.* Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; **314:** 253–7.
5. Empson M, *et al.* Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials. *Obstet Gynecol* 2002; **99:** 135–44.

Reperfusion and revascularisation procedures. Heparin has an established role as an adjunct to percutaneous vascular interventions and bypass surgery, to prevent perioperative thrombosis of the target artery, and is usually given with aspirin or other antiplatelet drugs (see Reperfusion and Revascularisation Procedures, p.1181). High doses are used, particularly in patients undergoing bypass surgery with extracorporeal circulation, and bleeding is a common problem. Although heparin may have an antiproliferative effect, treatment with systemic heparin (unfractionated or low-molecular-weight) appears to have no effect on restenosis;[1] however, a study using local application of enoxaparin suggested that restenosis was reduced.[2] Heparin-coated intracoronary stents have also been used; they improve outcomes compared with balloon angioplasty,[3] but have not been shown to be superior to bare-metal stents[4] or to have any additional effect on restenosis.[5,6] Heparin-coated stents have also been used successfully in cerebrovascular interventions.[7]

1. Grassman ED, *et al.* A randomized trial of the low-molecular-weight heparin certoparin to prevent restenosis following coronary angioplasty. *J Invasive Cardiol* 2001; **13:** 723–8.
2. Kiesz RS, *et al.* Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 2001; **103:** 26–31.
3. Serruys PW, *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352:** 673–81. Correction. *ibid.*; 1478.
4. Mehran R, *et al.* An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J* 2005; **150:** 1171–6.
5. Wöhrle J, *et al.*Comparison of the heparin coated vs the uncoated Jostent —no influence on restenosis or clinical outcome. *Eur Heart J* 2001; **22:** 1808–16.
6. Semiz E, *et al.* Comparison of initial efficacy and long-term follow-up of heparin-coated Jostent with conventional NIR stent. *Jpn Heart J* 2003; **44:** 889–98.
7. Parkinson RJ, *et al.* Use of heparin-coated stents in neurovascular interventional procedures: preliminary experience with 10 patients. *Neurosurgery* 2006; **59:** 812–21.

Preparations

BP 2008: Heparin Injection;
USP 31: Anticoagulant Heparin Solution; Heparin Calcium Injection; Heparin Lock Flush Solution; Heparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Calciparine; Cervep; Croneparina; Parinix†; Riveparin; Serianon; Sobrius; Sodiparin; ***Austral.:*** Calcihep†; Calciparine†; Uniparin†; ***Austria:*** Lipohep; Liquemin; Thrombophob; Thrombophob-S; Venoruton Heparin; Viatromb; ***Belg.:*** Calparine; Liquemine†; ***Braz.:*** Actparin; Alimax; Disotron; Heptar; Liquemine; Parinorth†; Trombofob; ***Canad.:*** Hepalean; Hepalean-Lok; ***Cz.:*** Hepa-Gel†; Hepa-Salbe†; Lioton; Lipohep†; Trombex†; Viatromb; ***Fin.:*** Hepaflex; ***Fr.:*** Calciparine; ***Ger.:*** Calciparin; Essaven 60 000; Exhirud Heparin; Hepa-Gel; Hepa-Salbe; Hepaplus†; Hepathromb; Hepathrombin; Liquemin N; Perivar Venensalbe†; Sportino; Thrombareduct; Thrombophob; Traumalitan†; Venalitan; Venoruton Emulgel; Vetren; ***Gr.:*** Calciparine; Croneparina†; Hep Lok†; Hepsal; Monoparin; Multiparin; Pump-Hep†; ***Hong Kong:*** Lioton; ***Hung.:*** Heparibene; Lioton; ***India:*** Beparine; Thrombophob; ***Indon.:*** Inviclot; Thrombophob; ***Irl.:*** Calciparine†; Hep-Rinse†; Heplok†; Hepsal; Minihep†; Monoparin; Multiparin; Unihep†; ***Israel:*** Calciparin; ***Ital.:*** Ateroclar; Bioclaril†; Calciparina; Clarisco; Croneparina; Disebrin; Ecabil; Ecafast; Ecasolv; Emoklar; Epacalcica; Eparical†; Eparinlider; Eparinovis; Eparven; Epsoclar; Epsodil†; Epsodilave; Eudipar†; Flusolv; Hemofluss†; Isoclar; Lioton; Liquemin†; Mica; Normoparin; Pharepa; Reoflus; Sosefluss; Trombolisin; Zepac; ***Mex.:*** Hep-Tec; Inhepar†; Proparin; ***NZ:*** Monoparin†; Multiparin; ***Pol.:*** Coaparin; Heparizen; Lioton; Lipohep; ***Port.:*** Calciparina†; ***Rus.:*** Lioton (Лиотон); Trombless (Тромблесс); ***S.Afr.:*** Calciparine; Thrombophob; ***Spain:*** Calciparina†; Menaven; ***Switz.:*** Calciparine; Demovarin; Gelparine; HepaGel; Hepasol Lipogel; HepaSpray†; Lioton; Liquemine; ***Turk.:*** Calciparine; Liquemine; Nevparin; ***UK:*** Calciparine†; Canusal; Hepsal; Monoparin; Multiparin; ***USA:*** Hep-Lock; Hepflush; ***Venez.:*** Hirox; Liquemine†; Riveparin.

Multi-ingredient: ***Arg.:*** Contractubex; Venostasin; ***Austria:*** Ambenat; Contractubex; Derivon; Dolo-Menthoneurin; Dolobene; Etrat; Heparin Comp; Ichthalgan forte; Lipactin; Pasta Cool; Pertrombon; Sensicutan; Thrombophob; Venobene; Venostasin compositum; Vetren; ***Belg.:*** Lipactin; ***Braz.:*** Contractubex; Dolobene; Trombofob; Venalot H; Venostasin†; ***Canad.:*** Lipactin; ***Cz.:*** Contractubex; Dolo-Rubriment†; Dolobene; Heparin-Gel†; Sensicutan; ***Fin.:*** Lipactin; Trombosol; ***Fr.:*** Cirkan a la Prednacinolone; Esberiven; ***Ger.:*** Contractubex; Dolo-Menthoneurin†; Dolobene; Enelbin-Salbe N†; Essaven Tri-Complex†; Essaven†; Etrat Sportgel†; Heparin Comp†; Heparin Kombi-Gel†; Heparin Plus†; Ichthalgan†; Kelofibrase†; Lipactin; Ostochont†; Sensicutan; Trauma-Puren†; Venengel†; Venoplant AHS†; ***Hong Kong:*** Contractubex; Dolobene; ***Hung.:*** Contractubex; Dolobene; ***India:*** Beparine; Contractubex; Proctosedyl; Thrombophob; ***Indon.:*** Thrombophob; ***Ital.:*** Edeven; Essaven; Flebs; Idracemi Eparina; Luxazone Eparina; Proctosoll; Reparil; Venotrauma†; Via Mal Traumagel; Vit Eparin; Xantervit Eparina; ***Philipp.:*** Contractubex; ***Pol.:*** Alcepalan; Biherpan; Cepan; Contractubex; Dolobene; Savarix; Tointex; ***Port.:*** DM Gel; ***Rus.:*** Contractubex (Контрактубекс); Dolobene (Долобене); Heparin Ointment (Гепариновая Мазь); Hepatrombin (Гепатромбин); Hepatrombin H (Гепатромбин Г); Nigepan (Нигепан); Venolife (Венолайф); ***S.Afr.:*** Essaven†; ***Spain:*** Essavenon; Venacol; ***Switz.:*** Assan; Assan thermo; Butaparin; Contractubex; Dolo-Arthrosenex; Dolobene; Gorgonium; Hepabuzone; Heparinol; Hepathrombine†; Keli-med; Keppur; Lipactin; Lyman; Phlebostasin compositum†; Ralur†; Sportium; Sportusal; Venoplant comp; Venoplant-N†; Venucreme; Venugel.

Heparinoids

Heparinoides.

Profile

The term heparinoid includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly-sulfated polysaccharides of similar structure. Such compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans; glycosaminoglycan polysulfate compounds; or sulfated mucopolysaccharides.

The following anticoagulants may be described as heparinoids:

- Danaparoid Sodium, p.1255
- Dermatan Sulfate, p.1256
- Pentosan Polysulfate Sodium, p.1367
- Sodium Apolate, p.1397
- Suleparoid, p.1406
- Sulodexide, p.1406

Heparinoid preparations are available with uses ranging from anticoagulation to the alleviation of inflammation (applied topically); some are claimed to have hypolipidaemic properties.

The proprietary names listed in this monograph refer to preparations containing undefined or less readily defined heparinoids that are used in a range of conditions including musculoskeletal and joint disorders, haemorrhoids, lipid disorders, and thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fleboderma; Hemeran†; Hirudoid; ***Austral.:*** Hirudoid; Lasonil; ***Austria:*** Hemeran; Hirudoid; Lasonil; ***Belg.:*** Hemeran; Hirudoid; Lasonil; ***Braz.:*** Hirudoid; Topcoid; ***Chile:*** Hirudoid; ***Cz.:*** Heparoid; Hirudoid; ***Denm.:*** Hirudoid; ***Fin.:*** Hirudoid; ***Ger.:*** Etrat Sportsalbe MPS†; Hirudoid; Lasonil N†; Sanaven MPS; ***Gr.:*** Hemeran; Lasonil N; ***Hong Kong:*** Bruise Cream†; Hepacare; Hirudoid; ***Hung.:*** Hirudoid; ***India:*** Hirudoid; ***Indon.:*** Hirudoid; ***Ital.:*** Angioflux; Ateran†; Ateroid; Ateroxide; Condral; Erevan†; Glicamin†; Hirudoid; Lasonil†; Lasoven†; Matrix; ***Neth.:*** Hirudoid; Lasonil; ***Norw.:*** Hirudoid; ***NZ:*** Hirudoid; Lasonil; ***Philipp.:*** Hirudoid; ***Pol.:*** Hirudoid; ***Port.:*** Hemeran; Hirudoid; Lasonil; ***Rus.:*** Heparoid (Гепароид); ***Singapore:*** Hirudoid; ***Spain:*** Dinoven; Hirudoid; ***Swed.:*** Hirudoid; ***Switz.:*** Hemeran; Hirudoid; ***Thai.:*** Hirudoid; Varidoid; ***Turk.:*** Hirudoid; Lasonil; ***UK:*** Bruiseze; Hirudoid; Lasonil†; ***Venez.:*** Hirudoid.

Multi-ingredient: ***Arg.:*** Mantus; ***Austral.:*** Movelat†; ***Austria:*** Lemuval; Mobilat; Mobilisin; Mobilisin plus; Moviflex; ***Belg.:*** Mobilat; Mobilisin; ***Braz.:*** Etrat†; Mobilat; Mobilisin Composto; ***Chile:*** Mobilat; Repariven; ***Cz.:*** Ibu-Hepa; Ketazon Compositum†; Mobilat; ***Fin.:*** Mobilat; Moviflex†; ***Ger.:*** Dolo Mobilat†; Mobilat Aktiv; Mobilat†; Sanaven†; ***Gr.:*** Bayolin; ***Hong Kong:*** Mobilat†; Prelloran†; ***Hung.:*** Bayolin†; Mobilat N; Mobilisin†; ***Ital.:*** Flebs; Mobilat; Mobilisin; Momendol; Traumal†; ***Mex.:*** Mobilat; ***Neth.:*** Mobilat; ***NZ:*** Movelat†; ***Philipp.:*** Mobilat; ***Pol.:*** Helason; Ibalgin Sport; Lumbolin; Mobilat; ***Port.:*** Anacal; Mobilat; Mobilisin; Rimanal; ***Singapore:*** Mobilat†; ***Spain:*** Lasonil†; Movilat; Movilisin; ***Switz.:*** Dolo-Veniten†; Mobilat N; Mobilisin; Prelloran†; ***Thai.:*** Mobilat; Movelat†; ***UK:*** Anacal; Movelat; ***Venez.:*** Bargonil; Permucal.

Hexobendine *(BAN, USAN, rINN)*

Hexobendina; Hexobendinum.

Гексобендин

$C_{30}H_{44}N_2O_{10}$ = 592.7.

CAS — 54-03-5.

ATC — C01DX06.

ATC Vet — QC01DX06.

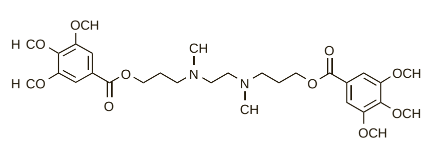

Hexobendine Hydrochloride *(BANM, rINNM)*

Hexobendine, Chlorhydrate d'; Hexobendini Hydrochloridum; Hidrocloruro de hexobendina; ST-7090. *NN'*-Ethylenebis(3-methylaminopropyl 3,4,5-trimethoxybenzoate) dihydrochloride.

Гексобендина Гидрохлорид

$C_{30}H_{44}N_2O_{10}$,2HCl = 665.6.

CAS — 50-62-4.

ATC — C01DX06.

ATC Vet — QC01DX06.

Profile

Hexobendine hydrochloride is a vasodilator that has been used in ischaemic heart disease. It is also included in multi-ingredient preparations used in cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ustimon.

Multi-ingredient: ***Austria:*** Instenon; ***Hong Kong:*** Instenon; ***Rus.:*** Instenon (Инстенон); ***Thai.:*** Instenon†.

Hirudin

Hirudina; Hirudine.

Profile

Hirudin is a 65-amino-acid protein that is a direct inhibitor of thrombin (see Lepirudin, p.1323). It has been extracted from leeches (p.1323) and this form is used in various topical preparations for peripheral vascular disorders. Recombinant hirudins, such as desirudin (p.1257) and lepirudin (p.1323) and analogues of hirudin, such as bivalirudin (p.1234), are used as anticoagulants.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exhirud; ***Fr.:*** Hirucreme; ***Ger.:*** Exhirud†.

Multi-ingredient: ***Ger.:*** Haemo-Exhirud†; ***Ital.:*** Hirudex†.

Hydralazine Hydrochloride

(BANM, rINNM)

Apressinum; Hidralazin-hidroklorid; Hidralazino hidrochloridas; Hidrocloruro de hidralazina; Hydralatsiinihydrokloridi; Hydralazin hydrochlorid; Hydralazin Hydrochloridum; Hydralazine, chlorhydrate d'; Hydralazinhydroklorid; Hydralazini hydrochloridum; Hydrallazine Hydrochloride; Idralazina. 1-Hydrazinophthalazine hydrochloride.

Гидралазина Гидрохлорид

$C_8H_8N_4$,HCl = 196.6.

CAS — 86-54-4 (hydralazine); 304-20-1 (hydralazine hydrochloride).

ATC — C02DB02.

ATC Vet — QC02DB02.

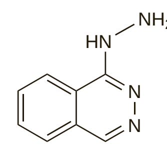

(hydralazine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Hydralazine Hydrochloride). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 3.5 to 4.2. Protect from light.

USP 31 (Hydralazine Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 25 of water and 1 in 500 of alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 3.5 to 4.2. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Discoloration of hydralazine injection was observed on several occasions after storage in a syringe for up to 12 hours.[1] Hydralazine reacts with metals and therefore the injection should be prepared using a nonmetallic filter and should be used as quickly as possible after being drawn through a needle into a syringe.

A study of the rate of degradation of hydralazine hydrochloride, 1 mg/mL in sweetened, aqueous oral liquids showed that glucose, fructose, lactose, and maltose reduced the stability of the drug.[2] In solutions containing mannitol or sorbitol, there was less than 10% degradation of hydralazine after 3 weeks. UK licensed product information states that contact with glucose causes hydralazine to be rapidly broken down and that hydralazine injection is therefore not compatible with glucose solutions.

1. Enderlin G. Discoloration of hydralazine injection. *Am J Hosp Pharm* 1984; **41:** 634.
2. Das Gupta V, *et al.* Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986; **11:** 215–23.

Adverse Effects

Adverse effects are common with hydralazine, particularly tachycardia, palpitations, angina pectoris, severe headache, and gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhoea. These adverse effects, and flushing, dizziness, and nasal congestion, which occur less often, may be seen at the start of treatment, especially if the dose is increased quickly. They generally subside with continued treatment. Other less common adverse effects include orthostatic hypotension, fluid retention with oedema and weight gain, conjunctivitis, lachrymation, tremor, and muscle cramps.

Hydralazine may deplete pyridoxine in the body, and can produce peripheral neuropathy with numbness and tingling of the extremities. Occasionally, hepatotoxicity, blood dyscrasias, haemolytic anaemia, difficulty in urinating, glomerulonephritis, constipation, paralytic ileus, depression, and anxiety occur.

Hypersensitivity reactions including fever, chills, pruritus, and rashes have been reported, and eosinophilia may occur.

Antinuclear antibodies may develop after prolonged use of large doses, and a condition resembling SLE may occur. The incidence is greater in slow acetylators, patients with renal impairment, women, and patients taking more than 100 mg of hydralazine daily. The symptoms usually disappear when the drug is withdrawn; some patients may require treatment with corticosteroids.

Acute overdosage may produce hypotension, tachycardia, myocardial ischaemia, arrhythmias, shock, and coma.

Carcinogenicity. Although earlier reports suggested that hydralazine might be carcinogenic, there was no evidence from a survey of 1978 patients with lung or colorectal cancer and 6807 controls that there was an increased risk of these neoplasms.[1]

1. Kaufman DW, *et al.* Hydralazine use in relation to cancers of the lung, colon, and rectum. *Eur J Clin Pharmacol* 1989; **36:** 259–64.

Effects on the blood. Three cases of thrombocytopenia were reported[1] in neonates whose mothers had been treated with hydralazine for some months before delivery. The thrombocytopenia and bleeding was transient with full recovery occurring within a few weeks. No adverse effects were noticed in the mothers.

1. Widerlöv E, *et al.* Hydralazine-induced neonatal thrombocytopenia. *N Engl J Med* 1980; **303:** 1235.

Effects on the cardiovascular system. Paradoxical severe hypertension developed after oral or intramuscular hydralazine on 3 occasions in a patient with renal artery stenosis.[1]

1. Webb DB, White JP. Hypertension after taking hydrallazine. *BMJ* 1980; **280:** 1582.

Effects on the kidneys. Rapidly progressive glomerulonephritis with focal and segmental lesions, usually accompanied by necrosis and crescent formation, has been reported in patients given hydralazine.[1-3] The condition is reported to be associated with the presence of antinuclear antibodies[3] and slow acetylator status,[2] factors associated with the development of hydralazine-induced lupus erythematosus.[4] However, renal involvement is much less common in drug-induced lupus,[4] and in a report of 15 such cases men and women and fast and slow acetylators were equally affected;[3] in addition the criteria for SLE were not usually fulfilled in these patients and it was suggested that the condition should be distinguished from lupus nephritis. Immediate withdrawal of hydralazine generally results in some improvement in renal function but complete recovery is uncommon; severe cases may require immunosuppressive therapy.[3]

1. Björck S, *et al.* Rapidly progressive glomerulonephritis after hydralazine. *Lancet* 1983; **ii:** 42.
2. Kincaid-Smith P, Whitworth JA. Hydralazine-associated glomerulonephritis. *Lancet* 1983; **ii:** 348.
3. Björck S, *et al.* Hydralazine-induced glomerulonephritis. *Lancet* 1985; **i:** 392.
4. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.

Effects on the skin. Pruritus and skin rashes have been reported with hydralazine use.

A 59-year-old woman who had been taking hydralazine 25 mg three times daily for 6 months developed symptoms of Sweet's syndrome (erythematous plaques and nodules and haemorrhagic blisters).[1] Symptoms began to subside on withdrawal of the drug but recurred on rechallenge. The condition resolved on discontinuation of hydralazine and treatment with prednisolone.

1. Gilmour E, *et al.* Drug-induced Sweet's syndrome (acute febrile neutrophilic dermatosis) associated with hydralazine. *Br J Dermatol* 1995; **133:** 490–1.

Lupus erythematosus. Lupus erythematosus is a well-documented adverse effect of hydralazine. Onset is typically delayed from 1 month to 5 years from the start of treatment, and the most common symptoms are arthralgia or arthritis, usually non-deforming, in up to 95% of patients, fever and myalgia in about 50%, and pleuropulmonary involvement, manifesting as pleurisy, pleural effusions, or pulmonary infiltrates in up to 30%.[1-3] Renal involvement is reported to be less common than in idiopathic SLE and there is some uncertainty as to whether the glomerulonephritis sometimes seen in patients receiving hydralazine should be considered lupus nephritis (see Effects on the Kidneys, above). Nonetheless, a 20% incidence of renal involvement has been reported.[1] Other complications and symptoms associated with lupus erythematosus in patients taking hydralazine include cutaneous vasculitis,[4-6] orogenital and cutaneous ulceration,[7] bilateral retinal vasculitis,[8] reactive hypoglycaemia (although the attribution is uncertain),[9] life-threatening cardiac tamponade,[10] and hoarseness and stridor secondary to vocal cord palsy, which progressed to respiratory arrest.[11] Skin rashes are reported to be less prominent than with the idiopathic form of the disease.[1] Fatalities have occurred,[12] but appear to be rare.

Estimates of the overall incidence of hydralazine-associated lupus erythematosus vary from about 1.2 to 5% or more.[13-16] The syndrome appears to occur only in patients who develop antinuclear antibodies while receiving hydralazine, but the incidence of positive antinuclear antibody tests is much higher than that of lupus, at up to 60%, so the presence of antinuclear antibodies alone is not diagnostic.[15] There is a strong relationship with drug dose,[14,16] acetylator status,[13,15,16] and patient gender,[16] the syndrome being more common in slow acetylators and women, and in patients receiving 100 mg daily or more.

Although it has been reported that hydralazine-associated lupus was more frequent in patients with the HLA-DR4 antigen[17] this was not confirmed by others[18] and subsequent work has suggested that the association is rather with the non-expressing or null forms of the adjacent complement C4 gene.[19] Hydralazine can inactivate complement C4 *in vitro*[20] and might exacerbate complement deficiency (which is known to be associated with idiopathic SLE) in patients with an already low level of C4 due to a null allele.[19]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; (Apr.): 460–3.
2. Cohen MG, Prowse MV. Drug-induced rheumatic syndromes: diagnosis, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 199–218.
3. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
4. Bernstein RM, *et al.* Hydrallazine-induced cutaneous vasculitis. *BMJ* 1980; **280:** 156–7.
5. Peacock A, Weatherall D. Hydralazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1121–2.
6. Finlay AY, *et al.* Hydrallazine-induced necrotising vasculitis. *BMJ* 1981; **282:** 1703–4.
7. Neville E, *et al.* Orogenital ulcers, SLE and hydrallazine. *Postgrad Med J* 1981; **57:** 378–9.
8. Doherty M, *et al.* Hydralazine induced lupus syndrome with eye disease. *BMJ* 1985; **290:** 675.
9. Blackshear PJ, *et al.* Reactive hypoglycaemia and insulin autoantibodies in drug-induced lupus erythematosus. *Ann Intern Med* 1983; **99:** 182–4.
10. Anandadas JA, Simpson P. Cardiac tamponade, associated with hydralazine therapy, in a patient with rapid acetylator status. *Br J Clin Pract* 1986; **40:** 305–6.
11. Chong WK, *et al.* Acute laryngeal stridor with respiratory arrest in drug induced systemic lupus erythematosus. *BMJ* 1988; **297:** 660–1.
12. Sturman SG, *et al.* Fatal hydralazine-induced systemic lupus erythematosus. *Lancet* 1988; **ii:** 1304.
13. Bing RF, *et al.* Hydralazine in hypertension: is there a safe dose? *BMJ* 1980; **281:** 353–4.
14. Freestone S, *et al.* Incidence of hydrallazine-associated autoimmune disease. *Br J Clin Pharmacol* 1982; **13:** 291P–292P.
15. Mansilla-Tinoco R, *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; **284:** 936–9.
16. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *BMJ* 1984; **289:** 410–12.
17. Batchelor JR, *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i:** 1107–9.
18. Brand C, *et al.* Hydralazine-induced lupus: no association with HLA-DR4. *Lancet* 1984; **i:** 462.
19. Speirs C, *et al.* Complement system protein C4 and susceptibility to hydralazine-induced systemic lupus erythematosus. *Lancet* 1989; **i:** 922–4.
20. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Withdrawal of hydralazine or dosage reduction reverses many of the adverse effects. Peripheral neuropathy has been reported to be alleviated by pyridoxine.

If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour of ingestion. Symptomatic and supportive treatment, including plasma expanders for shock and a beta blocker for tachycardia, should be given as necessary. Hypotension may respond to placing the patient in the supine position with the feet raised. If possible, pressor drugs should be avoided. If a pressor is necessary, one should be chosen that will not cause tachycardia or exacerbate arrhythmias; adrenaline should not be used.

Precautions

Hydralazine is contra-indicated in patients with severe tachycardia, dissecting aortic aneurysm, heart failure with high cardiac output, cor pulmonale, or myocardial insufficiency due to mechanical obstruction, for example aortic or mitral stenosis or constrictive pericarditis. Hydralazine is also contra-indicated in patients with idiopathic SLE and related disorders.

Hydralazine-induced vasodilatation produces myocardial stimulation. It should therefore be used with caution in patients with ischaemic heart disease since it can increase angina and it should not be given after myocardial infarction until the patient's condition has stabilised. Patients with suspected or confirmed ischaemic heart disease should be given hydralazine under cover of a beta blocker, which should be started a few days before hydralazine, in order to prevent myocardial stimulation. If given to patients with heart failure they should be monitored for orthostatic hypotension and tachycardia during the initial stages of therapy, preferably in hospital. If treatment with hydralazine is to be stopped in patients with heart failure it should generally be withdrawn gradually. Hydralazine should be used with caution in patients with cerebrovascular disorders.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment. Complete blood counts and antinuclear antibody determinations should be carried out about every 6 months during long-term therapy. Urine analysis (for microhaematuria and proteinuria) is also recommended.

Hydralazine is teratogenic in some species of *animals* and should therefore be avoided during the first two trimesters of pregnancy.

Patients may experience impaired reactions, especially at the start of therapy, and should not drive or operate machinery if affected.

Breast feeding. Hydralazine is distributed into breast milk in small amounts (see Pregnancy, below) but no adverse effects have been seen in infants and the American Academy of Pediatrics therefore considers[1] hydralazine to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. Hydralazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Hydralazine should be avoided during the first two trimesters of pregnancy.

Hydralazine concentrations were found to be similar in maternal and umbilical-cord blood in a study of 6 women being treated with hydralazine for pronounced hypertension during pregnancy.[1] Hydralazine was determined in the breast milk of 1 mother, but amounts detected were unlikely to produce clinically relevant concentrations in the infant.

For a report of thrombocytopenia occurring in neonates following maternal treatment with hydralazine during pregnancy, see Effects on the Blood under Adverse Effects, above.

1. Liedholm H, *et al.* Transplacental passage and breast milk concentrations of hydralazine. *Eur J Clin Pharmacol* 1982; **21:** 417–19.

Interactions

The hypotensive effect of hydralazine may be enhanced by other drugs with a hypotensive action. Severe hypotension may occur if hydralazine and diazoxide are given together. However, some interactions with antihypertensives may be beneficial: thiazide diuretics also counteract the fluid retention caused by hydralazine, and beta blockers diminish the cardiac-accelerating effects.

Indometacin. A study[1] in 9 healthy subjects found that indometacin 100 mg daily did not lessen the hypotensive effect of hydralazine. However, another study[2] showed that indometacin 200 mg daily, while having no effect on heart rate, renal or limb blood flow, or plasma-catecholamine concentration, did reduce the hypotensive effect of hydralazine.

1. Jackson SHD, Pickles H. Indomethacin does not attenuate the effects of hydralazine in normal subjects. *Eur J Clin Pharmacol* 1983; **25:** 303–5.
2. Cinquegrani MP, Liang C. Indomethacin attenuates the hypotensive action of hydralazine. *Clin Pharmacol Ther* 1986; **39:** 564–70.

Pharmacokinetics

Hydralazine given orally is rapidly absorbed from the gastrointestinal tract but undergoes considerable first-pass metabolism by acetylation in the gastrointestinal mucosa and liver. The rate of metabolism is genetically determined and depends upon the acetylator status of the individual. The bioavailability of hydralazine has been reported to be about 35% in slow acetylators and less in fast acetylators; thus plasma concentrations after a given dose are higher in slow acetylators.

Peak plasma concentrations have been reported to occur after about one hour. Hydralazine is chiefly present in plasma as a hydrazone conjugate with pyruvic acid. Plasma protein binding is about 90%. The drug is widely distributed, notably into arterial walls.

Systemic metabolism in the liver is by hydroxylation of the ring system and conjugation with glucuronic acid; most sources suggest that *N*-acetylation is not of major importance in systemic clearance and that therefore acetylator status does not affect elimination. Hydralazine is excreted mainly in urine as metabolites.

The apparent average half-life for hydralazine has been reported to vary from about 45 minutes to about 8 hours, with a number of sources giving the average as about 2 to 4 hours. Some of the variation may be due to problems with the analytical procedures—see below. The half-life is prolonged in renal impairment and may be up to 16 hours in patients with a creatinine clearance of less than 20 mL/minute.

Hydralazine crosses the placenta and is distributed into breast milk.

◊ Attempts to describe the pharmacokinetics of hydralazine have been complicated by the instability of the drug itself in plasma and in alkaline solutions, and the instability of its circulating metabolites during analysis. This has meant that many techniques for the measurement of hydralazine have proved non-selective and yield overestimates of unchanged drug.[1] Studies using less selective methods have yielded an apparent bioavailability for oral hydralazine of 38 to 69% in slow acetylators and 22 to 32% in fast acetylators; in contrast, more selective assays have yielded values of 31 to 35% and 10 to 16% for slow and rapid acetylators respectively. Similarly, hydralazine plasma clearance is lower and the half-life longer when based upon the results of non-selective assay procedures; mean elimination half-life has ranged from 2.2 to 3.6 hours based upon these methods compared with 0.67 to 0.96 hours using a more selective assay. Improved pharmacokinetic data has indicated that while the first-pass effect is dependent upon acetylator phenotype, systemic clearance is only minimally dependent upon acetylation. The formation of the pyruvic acid hydrazone, which is without significant vasodilator activity, contributes to extrahepatic phenotype-independent clearance.

Although some workers have correlated the hypotensive effect of hydralazine with concentrations,[2] others have been unable to do so.[3] Moreover, the duration of hypotensive effect has been shown to exceed considerably that predicted from the rate of elimination.[4,5] Possible explanations are the accumulation of hydralazine at its sites of action in the arterial walls[6] or the existence of active metabolites.[7-9]

Concurrent intake of food has been found to enhance considerably the bioavailability of hydralazine[10] but food-related reductions in plasma-hydralazine concentrations with reduced vasodilator effect have also been reported.[11] The discrepancy was thought to be due to the greater specificity of the assay used in the latter study and to differences in the timing of food and hydralazine administration in the two studies.[12,13]

1. Ludden TM, *et al.* Clinical pharmacokinetics of hydralazine. *Clin Pharmacokinet* 1982; **7:** 185–205.
2. Zacest R, Koch-Weser J. Relation of hydralazine plasma concentration to dosage and hypotensive action. *Clin Pharmacol Ther* 1972; **13:** 420–5.
3. Talseth T, *et al.* Hydralazine slow-release: observations on serum profile and clinical efficacy in man. *Curr Ther Res* 1977; **21:** 157–68.
4. O'Malley K, *et al.* Duration of hydralazine action in hypertension. *Clin Pharmacol Ther* 1975; **18:** 581–6.
5. Shepherd AMM, *et al.* Hydralazine kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1980; **28:** 804–11.
6. Moore-Jones D, Perry HM. Radioautographic localization of hydralazine-1-C in arterial walls. *Proc Soc Exp Biol Med* 1966; **122:** 576–9.
7. Barron K, *et al.* Comparative evaluation of the in vitro effects of hydralazine and hydralazine acetonide on arterial smooth muscle. *Br J Pharmacol* 1977; **61:** 345–9.
8. Haegele KD, *et al.* Identification of hydrallazine and hydrallazine hydrazone metabolites in human body fluids and quantitative in vitro comparisons of their smooth muscle relaxant activity. *Br J Clin Pharmacol* 1978; **5:** 489–94.
9. Reece PA, *et al.* Interference in assays for hydralazine in humans by a major plasma metabolite, hydralazine pyruvic acid hydrazone. *J Pharm Sci* 1978; **67:** 1150–3.
10. Melander A, *et al.* Enhancement of hydralazine bioavailability by food. *Clin Pharmacol Ther* 1977; **22:** 104–7.
11. Shepherd AMM, *et al.* Effect of food on blood hydralazine levels and response in hypertension. *Clin Pharmacol Ther* 1984; **36:** 14–18.
12. Melander A, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475.
13. Shepherd AMM, *et al.* Concomitant food intake does enhance the bioavailability and effect of hydralazine. *Clin Pharmacol Ther* 1985; **38:** 475–6.

Uses and Administration

Hydralazine is a direct-acting vasodilator that acts mainly on the arterioles. It reduces blood pressure and peripheral resistance but produces fluid retention. Tachycardia and an increase in cardiac output occur mainly as a reflex response to the reduction in peripheral resistance. Hydralazine tends to improve renal and cerebral blood flow and its effect on diastolic pressure is more marked than on systolic pressure.

Hydralazine hydrochloride is given orally for the treatment of hypertension (p.1171), usually with a beta blocker and a thiazide diuretic. In addition to an additive antihypertensive effect, this combination reduces the reflex tachycardia and fluid retention caused by hydralazine. Hydralazine may be given intravenously in hypertensive crises. It is also used with isosorbide dinitrate in the management of heart failure (but see Precautions, above). For further discussion of this use of hydralazine, see below.

The dose of hydralazine should be reduced or the dosage interval prolonged in patients with hepatic or renal impairment.

In **hypertension**, the usual initial oral dose of hydralazine hydrochloride is 40 to 50 mg daily in divided doses, increased according to response. In the UK it is recommended that the dose should not be increased above 100 mg daily without checking acetylator status, although the recommended maximum dose for hypertension is 200 mg daily; doses above 100 mg daily are associated with an increased incidence of lupus erythematosus, particularly in women and in slow acetylators.

In hypertensive crises, hydralazine hydrochloride is given in doses of 5 to 10 mg by slow intravenous injection, repeated if necessary after 20 to 30 minutes. Alternatively, it may be given by continuous intravenous infusion in an initial dose of 200 to 300 micrograms/minute; the usual maintenance dose range is 50 to 150 micrograms/minute. Hydralazine hydrochloride has also been given by intramuscular injection.

For **heart failure** in self-identified black patients, hydralazine may be given as an oral combination preparation with isosorbide dinitrate; the dose is 37.5 mg of hydralazine with 20 mg of isosorbide dinitrate three times daily, and may be doubled if necessary.

Heart failure. Hydralazine with isosorbide dinitrate may have a role in the management of patients with heart failure (p.1165) who remain symptomatic despite standard therapy or in whom standard therapy is contra-indicated or not tolerated. Although a meta-analysis of a number of studies[1] of vasodilator therapy for heart failure failed to show a benefit in terms of improved functional status or reduced mortality in patients given hydralazine alone, there is evidence from the Veterans Administration Cooperative Study[2] of reduced mortality from the use of hydralazine with nitrates. This has been confirmed in a second study (V-HeFTII),[3] although hydralazine with isosorbide dinitrate was less effective than enalapril. Subgroup analysis suggested that the effect might be greater in black patients, and a later study[4] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

Hydralazine has also been tried in children with heart failure,[5,6] but experience is limited.

1. Mulrow CD, *et al.* Relative efficacy of vasodilator therapy in chronic congestive heart failure: implications of randomized trials. *JAMA* 1988; **259:** 3422–6.
2. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1986; **314:** 1547–52.
3. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
4. Taylor AL, *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.
5. Artman M, *et al.* Hemodynamic effects of hydralazine in infants with idiopathic dilated cardiomyopathy and congestive heart failure. *Am Heart J* 1987; **113:** 144–50.
6. Rao PS, Andaya WG. Chronic afterload reduction in infants and children with primary myocardial disease. *J Pediatr* 1986; **108:** 530–4.

Preparations

BP 2008: Hydralazine Injection; Hydralazine Tablets;
USP 31: Hydralazine Hydrochloride Injection; Hydralazine Hydrochloride Oral Solution; Hydralazine Hydrochloride Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hidral; Hydrapres; ***Austral.:*** Alphapress; Apresoline; ***Braz.:*** Apresolina; Nepresol; ***Canad.:*** Apresoline; Novo-Hylazin; Nu-Hydral; ***Hong Kong:*** Apresoline†; ***Irl.:*** Apresoline; ***Mex.:*** Apresolina; Bionobal; ***Norw.:*** Apresolin; ***NZ:*** Apresoline; ***Philipp.:*** Apresoline; ***S.Afr.:*** Apresoline; Hyperphen; ***Spain:*** Hydrapres; ***Swed.:*** Apresolin; ***Thai.:*** Apresoline; Cesoline; ***UK:*** Apresoline; ***USA:*** Apresoline; ***Venez.:*** Apresolina†.

Multi-ingredient: *Austria:* Polinorm; Trepress; Triloc; ***Ger.:*** Docidrazin†; Impresso†; Pertenso N; Treloc; Trepress; TRI-Normin; ***India:*** Corbetazine; ***Indon.:*** Ser-Ap-Es; ***Spain:*** Betadipresan Diu†; Betadipresan†; Neatenol Diuvas; Tensiocomplet; ***Thai.:*** Hydrares; Hypery†; Mano-Ap-Es; Reser; Ser-Ap-Es; ***USA:*** Apresazide†; BiDil; Hydra-zide; Hydrap-ES†; Marpres; Ser-Ap-Es†; Tri-Hydroserpine†.

Hydrochlorothiazide *(BAN, rINN)* ⊗

Hidrochlorotiazidas; Hidroclorotiazida; Hidroklorotiazid; Hydrochlorothiazid; Hydrochlorothiazidum; Hydrochlorotiazyd; Hydroklooritiatsidi; Hydroklortiazid. 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Гидрохлоротиазид

$C_7H_8ClN_3O_4S_2$ = 297.7.

CAS — 58-93-5.

ATC — C03AA03.

ATC Vet — QC03AA03.

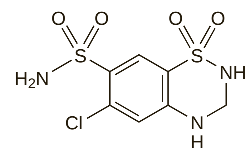

NOTE. Compounded preparations of hydrochlorothiazide may be represented by the following names:

- Co-amilozide (*BAN*)—hydrochlorothiazide 10 parts and amiloride hydrochloride 1 part (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide
- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide
- Co-zidocapt (*BAN*)—hydrochlorothiazide 1 part and captopril 2 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Hydrochlorothiazide). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Hydrochlorothiazide). A white or practically white, practically odourless crystalline powder. Slightly soluble in water; insoluble in chloroform, in ether, and in dilute mineral acids; freely soluble in dimethylformamide, in *n*-butylamine, and in sodium hydroxide solution; sparingly soluble in methyl alcohol.

Adverse Effects

Hydrochlorothiazide and other thiazide diuretics may cause a number of metabolic disturbances especially at high doses. They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may cause hyperuricaemia and precipitate attacks of gout in some patients. Thiazide diuretics may be associated with electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia, and hypokalaemia. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and treatment with digitalis or its glycosides may have to be temporarily suspended. Patients with cirrhosis of the liver are particularly at risk from hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet. The urinary excretion of calcium is reduced. Hypomagnesaemia has also occurred. Adverse changes in plasma lipids have also been noted but their clinical significance is unclear.

Signs of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain and cramps, seizures, oliguria, hypotension, and gastrointestinal disturbances.

Other adverse effects include anorexia, gastric irritation, nausea, vomiting, constipation, diarrhoea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paraesthesia, impotence, and yellow vision. Hypersensitivity reactions include skin rashes, fever, pulmonary oedema, pneumonitis, anaphylaxis, and toxic epidermal necrolysis. Cholestatic jaundice, pancreatitis, and blood dyscrasias including thrombocytopenia and, more rarely, granulocytopenia, leucopenia, and aplastic and haemolytic anaemia have been reported.

Intestinal ulceration has occurred after the use of tablets containing thiazides with an enteric-coated core of potassium chloride (see also under Potassium, p.1684).

Carcinogenicity. Several studies have suggested that long-term diuretic therapy may be associated with the development of cancer. A meta-analysis[1] of 9 case control studies and 3 cohort studies found an increased risk of renal cell carcinoma in patients receiving diuretics, and a further retrospective study[2] found that the risk of colon cancer was also increased. While the risk is probably not significant in most patients, it was suggested[1,2] that it should be taken into consideration when choosing long-term therapy for younger patients.

1. Grossman E, *et al.* Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol* 1999; **83:** 1090–3.
2. Tenenbaum A, *et al.* Is diuretic therapy associated with an increased risk of colon cancer? *Am J Med* 2001; **110:** 143–5.

Effects on the blood. There have been case reports of intravascular immune haemolysis in patients taking hydrochlorothiazide and methyldopa.[1-3] In each of these 3 cases the hydrochlorothiazide was identified as the probable cause of haemolysis on serological data, although methyldopa could have been a contributory factor. One of these patients died[3] during the haemolytic episode although post-mortem examination failed to reveal a cause of death.

1. Vila JM, *et al.* Thiazide-induced immune hemolytic anemia. *JAMA* 1976; **236:** 1723–4.
2. Garratty G, *et al.* Acute immune intravascular hemolysis due to hydrochlorothiazide. *Am J Clin Pathol* 1981; **76:** 73–8.
3. Beck ML, *et al.* Fatal intravascular immune hemolysis induced by hydrochlorothiazide. *Am J Clin Pathol* 1984; **81:** 791–4.

Effects on electrolyte balance. *MAGNESIUM AND POTASSIUM.* The clinical consequences of diuretic-induced hypokalaemia have been controversial.[1-3] Of major concern has been the possibility that diuretic-induced hypokalaemia could predispose to cardiac arrhythmias and sudden cardiac death in some patients, and it has been suggested that this could explain the lower than expected reduction in deaths due to ischaemic heart disease found in some hypertension trials. Indeed, some case-control studies[4,5] have suggested an association between an increased risk of sudden cardiac death and the use of thiazides or other non-potassium-sparing diuretics; the addition of a potassium supplement had little effect on this risk, whereas addition of a potassium-sparing diuretic to the thiazide lowered the risk.[4] However, no reduction in cardiac arrhythmias after the correction of hypokalaemia has been seen[6] nor any evidence of increased arrhythmias associated with diuretic-induced hypokalaemia.[7] Several reviews[8,9] have argued that there is no proof of a causal relationship between hypokalaemia and serious dysrhythmias and this was endorsed by a randomised study.[10]

It is generally agreed that routine potassium supplementation in patients taking diuretics is unnecessary; however, supplementation will be required if the serum-potassium concentration falls below 3.0 mmol/litre. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia[11] such as those with severe heart disease, those taking digitalis preparations or high doses of diuretics, and in patients with severe liver disease.

The amount of potassium in fixed combination diuretic and potassium preparations has long been considered insufficient to correct hypokalaemia and the effectiveness of oral potassium supplements in increasing body stores of potassium has been questioned.[12-14] Hypokalaemia may be overcome by adding a potassium-sparing diuretic such as amiloride or triamterene[15] to the regimen, but there is a danger of hyperkalaemia if they are used indiscriminately. The *routine* use of fixed-dose combination preparations of a thiazide or loop diuretic with a potassium-sparing diuretic is considered unnecessary.[16] Potassium-sparing diuretics will not correct the potassium deficit unrelated to diuretic therapy in patients with severe heart failure.[17] When thiazides are given with drugs that may induce hyperkalaemia, such as beta blockers, ACE inhibitors, or angiotensin II receptor antagonists, the diuretic-induced hypokalaemia may be ameliorated, but not necessarily corrected completely. Hypokalaemia has been reported[18-20] in patients taking fixed-dose combinations of thiazides and beta blockers.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium,[21] although it is unlikely to be of clinical significance.[22] Magnesium depletion has also been implicated as a risk factor for arrhythmias.[9,23]

1. Materson BJ. Diuretic-associated hypokalemia. *Arch Intern Med* 1985; **145:** 1966–7.
2. Kaplan NM, *et al.* Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985; **312:** 746–9.
3. Kassirer JP, Harrington JT. Fending off the potassium pushers. *N Engl J Med* 1985; **312:** 785–7.
4. Siscovick DS, *et al.* Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; **330:** 1852–7.
5. Hoes AW, *et al.* Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; **123:** 481–7.
6. Papademetriou V, *et al.* Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction on cardiac arrhythmias. *Am J Cardiol* 1983; **52:** 1017–22.
7. Papademetriou V, *et al.* Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med* 1988; **148:** 1272–6.
8. Harrington JT, *et al.* Our national obsession with potassium. *Am J Med* 1982; **73:** 155–9.
9. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149**: 2640–8.
10. Siegel D, *et al.* Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992; **267:** 1083–9.
11. Anonymous. Potassium-sparing diuretics—when are they really needed? *Drug Ther Bull* 1985; **23:** 17–20.
12. Jackson PR, *et al.* Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced hypokalaemia. *Br J Clin Pharmacol* 1982; **14:** 257–63.
13. Shenfield GM. Fixed combination drug therapy. *Drugs* 1982; **23:** 462–80.
14. Papademetriou V, *et al.* Effectiveness of potassium chloride or triamterene in thiazide hypokalemia. *Arch Intern Med* 1985; **145:** 1986–90.
15. Kohvakka A. Maintenance of potassium balance during long-term diuretic therapy in chronic heart failure patients with thiazide-induced hypokalemia: comparison of potassium supplementation with potassium chloride and potassium-sparing agents, amiloride and triamterene. *Int J Clin Pharmacol Ther Toxicol* 1988; **26:** 273–7.
16. Anonymous. Routine use of potassium-sparing diuretics. *Drug Ther Bull* 1991; **29:** 85–7.
17. Davidson C, *et al.* The effects of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. *Postgrad Med J* 1978; **54:** 405–9.
18. Skehan JD, *et al.* Hypokalaemia induced by a combination of a beta-blocker and a thiazide. *BMJ* 1982; **284:** 83.
19. Odugbesan O, *et al.* Hazards of combined beta-blocker/diuretic tablets. *Lancet* 1985; **i:** 1221–2.
20. Jacobs L. Hypokalaemia with beta-blocker/thiazide combinations. *J R Coll Gen Pract* 1986; **36:** 39.
21. Dyckner T. Relation of cardiovascular disease to potassium and magnesium deficiencies. *Am J Cardiol* 1990; **65:** 44–6.
22. Papademetriou V. Magnesium depletion and thiazide hypokalemia. *Arch Intern Med* 1986; **146:** 1026.
23. Ryan MP. Diuretics and potassium/magnesium depletion: directions for treatment. *Am J Med* 1987; **82** (suppl 3A): 38–47.

SODIUM. Diuretics are a common cause of hyponatraemia.[1-5] Dilutional hyponatraemia may occur in patients with heart failure, but hyponatraemia may also result from sodium depletion[1] or inappropriate antidiuretic hormone secretion.[6] Other suggested mechanisms include decreased renal clearance of free water, hypomagnesaemia, and intracellular potassium depletion.[3,7] There have been a number of reports suggesting that hyponatraemia may be a particular problem with combinations of hydrochlorothiazide and potassium-sparing diuretics,[8-10] especially in elderly patients. The effect may be exacerbated by the relatively high doses of thiazide present in some fixed-dose preparations.[11] The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, mental confusion, and anorexia,[1,2] but it may be an important cause of morbidity.[2,7] Severe sequelae of hyponatraemia include tonic-clonic seizures[12] and clinical features resembling subarachnoid haemorrhage.[13,14] Some patients, especially the elderly, may be particularly susceptible to the hyponatraemic effects of thiazides, possibly as a result of inappropriate secretion of antidiuretic hormone.[6] Plasma electrolyte concentrations should be monitored in patients taking long-term diuretic therapy.[3,12] Measurement of serum-sodium concentration and body-weight after a single dose of thiazide could be useful in identifying patients at increased risk of developing hyponatraemia.[7]

1. Roberts CJC, *et al.* Hyponatraemia: adverse effect of diuretic treatment. *BMJ* 1977; **1:** 210.
2. Kennedy PGE, *et al.* Severe hyponatraemia in hospital inpatients. *BMJ* 1978; **2:** 1251–3.
3. Walters EG, *et al.* Hyponatraemia associated with diuretics. *Br J Clin Pract* 1987; **41:** 841–4.
4. Spital A. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; **19:** 447–52.
5. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)* 2008; **10:** 477–84.
6. Sonnenblick M, *et al.* Thiazide-induced hyponatremia and vasopressin release. *Ann Intern Med* 1989; **110:** 751.
7. Friedman E, *et al.* Thiazide-induced hyponatremia: reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med* 1989; **110:** 24–30.
8. Strykers PH, *et al.* Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984; **252:** 389.
9. Roberts CJC, *et al.* Hyponatraemia induced by a combination of hydrochlorothiazide and triamterene. *BMJ* 1984; **288:** 1962.
10. Millson D, *et al.* Hyponatraemia and Moduretic (amiloride plus hydrochlorothiazide). *BMJ* 1984; **289:** 1308–9.
11. Bayer AJ, *et al.* Plasma electrolytes in elderly patients taking fixed combination diuretics. *Postgrad Med J* 1986; **62:** 159–62.
12. Johnston C, *et al.* Hyponatraemia and Moduretic-grand mal seizures: a review. *J R Soc Med* 1989; **82:** 479–83.
13. Benfield GFA, *et al.* Dilutional hyponatraemia masquerading as subarachnoid haemorrhage in patient on hydrochlorothiazide/amiloride/timolol combined drug. *Lancet* 1986; **ii:** 341.
14. Bain PG, *et al.* Thiazide-induced dilutional hyponatraemia masquerading as subarachnoid haemorrhage. *Lancet* 1986; **ii:** 634.

Effects on the gallbladder. There is an increased risk of cholecystitis in patients taking thiazides, with some indication that risk increases with the duration of use;[1,2] some workers concluded that this increased risk was confined to patients with pre-existing gallstones.[2] In a study in 10 healthy subjects,[3] hydrochlorothiazide was found to induce modest changes in biliary lipid concentrations although it was not associated with supersaturation of the bile. These changes could not wholly explain any increase in gallbladder disease in patients taking thiazides. However, evidence is conflicting; other studies[4,5] have found no association between thiazides and cholecystitis, except possibly in women who are not overweight.[5]

1. Rosenberg L, *et al.* Thiazides and acute cholecystitis. *N Engl J Med* 1980; **303:** 546–8.
2. van der Linden W, *et al.* Acute cholecystitis and thiazides. *BMJ* 1984; **289:** 654–5.
3. Angelin B. Effect of thiazide treatment on biliary lipid composition in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 95–6.
4. Porter JB, *et al.* Acute cholecystitis and thiazides. *N Engl J Med* 1981; **304:** 954–5.
5. Kakar F, *et al.* Thiazide use and the risk of cholecystectomy in women. *Am J Epidemiol* 1986; **124:** 428–33.

Effects on glucose metabolism. The adverse effects of thiazides on glucose metabolism, such as insulin resistance, impaired glucose tolerance, precipitation of overt diabetes, and worsening of diabetic control, are well established but appear to be dose-related and may not be significant at lower doses (for example, hydrochlorothiazide 6.25 or 12.5 mg).[1] A study[2] in 16 non-diabetic hypertensive patients found that bendroflumethiazide, in a dose of 1.25 mg daily, had no effect on insulin sensitivity whereas a daily dose of 5 mg produced hepatic insulin resistance. Similarly, the high doses, for example bendroflumethiazide 5 mg twice daily, used in the Medical Research Council Study on Mild to Moderate Hypertension[3] resulted in an incidence of glucose intolerance that led to withdrawal from the study of 9.38 per 1000 patient-years in men and 6.01 per 1000 patient-years in women compared with 2.51 and 0.82 per 1000 patient-years respectively in patients taking placebo. A later prospective study[4] in non-diabetic hypertensive patients found that those taking thiazides [doses not specified] were at no greater risk for developing diabetes than those not receiving antihypertensive therapy. However, a prospective cohort study[5] in men aged between 50 and 60 found that those taking antihypertensive treatment (mainly thiazides, beta blockers, or both) showed an increase in blood-glucose concentrations which was an independent risk factor for myocardial infarction, even when baseline insulin resistance was accounted for. Another prospective study[6] of 3 cohorts of men or women also found that use of thiazides was independently associated with a higher risk of diabetes.

It has been suggested[7] that the effect of thiazides on glucose metabolism is related to their effect on potassium and that control of hypokalaemia may prevent the development of diabetes, but this remains to be confirmed.

1. Neutel JM. Metabolic manifestations of low-dose diuretics. *Am J Med* 1996; **101** (suppl 3A): 71S–82S.
2. Harper R, *et al.* Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 1994; **309:** 226–30.
3. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
4. Gress TW, *et al.* Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 905–12.
5. Dunder K, *et al.* Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study. *BMJ* 2003; **326:** 681–4.
6. Taylor EN, *et al.* Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29:** 1065–70.
7. Zillich AJ, *et al.* Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006; **48:** 219–24.

Effects on the kidneys. Thiazides can produce acute renal failure either from over-enthusiastic use producing sodium depletion and hypovolaemia or, occasionally, as a result of a hypersensitivity reaction.[1] Acute interstitial nephritis has been reported.[2,3] They can occasionally cause the formation of non-opaque urate calculi.[4]

1. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: I. *BMJ* 1977; **2:** 242–4.
2. Linton AL, *et al.* Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med* 1980; **93:** 735–41.
3. Anonymous. Case records of the Massachusetts General Hospital: case 42-1983. *N Engl J Med* 1983; **309:** 970–8.
4. Curtis JR. Diseases of the urinary system: drug-induced renal disorders: II. *BMJ* 1977; **2:** 375–7.

Effects on lipid metabolism. Thiazides have been reported to adversely affect the plasma-lipid profile in the short term by increasing concentrations of low-density and very-low-density lipoprotein cholesterol, as well as of triglycerides, but not of high-density lipoprotein cholesterol.[1] These effects are probably dose-related[2] and it has been argued that changes in plasma lipids are likely to be slight at the relatively low doses now used in hypertension. There is some evidence to suggest that these lipid changes may not persist long-term.[3] In the Treatment of Mild Hypertension Study (TOMHS),[4] plasma total cholesterol concentrations were increased after 12 months in patients receiving chlortalidone but this effect was no longer present after 24 months. Although there has been concern that any hyperlipidaemic effect might offset the benefits of treating hypertension in patients at risk of ischaemic heart disease, studies such as ALLHAT[5] have shown that thiazide-like diuretics (in this case chlortalidone) are as effective as other antihypertensives in reducing the incidence of cardiovascular events in patients with hypertension and at least one other risk factor for ischaemic heart disease.

1. Ames R. Effects of diuretic drugs on the lipid profile. *Drugs* 1988; **36** (suppl 2): 33–40.
2. Carlsen JE, *et al.* Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990; **300:** 975–8.
3. Freis ED. Critique of the clinical importance of diuretic-induced hypokalemia and elevated cholesterol level. *Arch Intern Med* 1989; **149:** 2640–8.
4. Grimm RH, *et al.* Long-term effects on plasma lipids of diet and drugs to treat hypertension. *JAMA* 1996; **275:** 1549–56.
5. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.

Effects on the nervous system. A 40-year old woman appeared sleepy and confused 1 week after starting hydrochlorothiazide.[1] Although her plasma-potassium concentrations had fallen they were still in the normal range, and it was concluded that her symptoms were due to an adverse reaction to the drug itself.

1. Daugherty KK, Subramanian J. Cognitive and neurologic impairment with hydrochlorothiazide. *Am J Health-Syst Pharm* 2005; **62:** 2630–3.

Effects on respiratory function. Acute interstitial pneumonitis and acute pulmonary oedema are rare but potentially dangerous complications of thiazides and may be due to a hypersensitivity reaction. Several cases have been reported,[1-7] frequently after a single dose of hydrochlorothiazide or chlorothiazide. The presenting symptoms could be mistakenly attributed to myocardial infarction.

1. Steinberg AD. Pulmonary edema following ingestion of hydrochlorothiazide. *JAMA* 1968; **204:** 167–9.
2. Beaudry C, Laplante L. Severe allergic pneumonitis from hydrochlorothiazide. *Ann Intern Med* 1973; **78:** 251–3.
3. Parfrey NA, Herlong HF. Pulmonary oedema after hydrochlorothiazide. *BMJ* 1984; **288:** 1880.
4. Watrigant Y, *et al.* Pneumopathie à l'hydrochlorothiazide d'évolution subaiguë: etude cytologique du lavage broncho-alvéolaire. *Rev Mal Respir* 1986; **4:** 227–9.
5. Klein MD. Noncardiogenic pulmonary edema following hydrochlorothiazide ingestion. *Ann Emerg Med* 1987; **16:** 901–3.
6. Bowden FJ. Non-cardiogenic pulmonary oedema after ingestion of chlorothiazide. *BMJ* 1989; **298:** 605.
7. Bernal C, Patarca R. Hydrochlorothiazide-induced pulmonary edema and associated immunologic changes. *Ann Pharmacother* 1999; **33:** 172–4.

Effects on sexual function. Adverse effects on sexual function have been reported in hypertensive patients given thiazides and other antihypertensives but it is not clear how much this is due to the underlying disease and how much is due to the drugs. In the Treatment of Mild Hypertension Study (TOMHS),[1] a double-blind randomised controlled trial that allocated patients to treatment with one of five groups of antihypertensives, the incidence of erectile dysfunction in men was relatively low but was highest in the diuretic group (chlortalidone treatment). The incidence was significantly higher in chlortalidone recipients than in placebo recipients at 24 months (17.1 and 8.1% respectively), but the difference was no longer significant at 48 months (18.3 and 16.7% respectively).

1. Grimm RH, *et al.* Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 1997; **29:** 8–14.

Effects on the skin. Rashes and skin reactions have been reported in patients taking thiazides. *Photosensitivity* reactions are among the most frequently reported skin reactions. In Australia[1] co-amilozide was the preparation most commonly implicated in photosensitivity reactions in reports to the Australian Drug Reactions Advisory Committee, although this may reflect the high usage of this preparation. The most likely mechanism is thought to be phototoxicity[1,2] involving mainly UVA radiation although UVB may be involved in some cases.[2] Chronic photosensitivity does not usually occur after stopping the drug[2] although photosensitivity may persist for longer in some patients than in others.[2,3] Eruptions resembling *lichen planus*[4] and *subacute cutaneous lupus erythematosus*[5-7] may be due to photosensitivity reactions.

Other reported skin reactions include *vasculitis*,[8,9] *erythema multiforme*,[9] and *pseudoporphyria*.[10]

1. Stone K. Photosensitivity reactions to drugs. *Aust J Pharm* 1985; **66:** 415–18.
2. Addo HA, *et al.* Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; **116:** 749–60.
3. Robinson HN, *et al.* Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121:** 522–4.
4. Graham-Brown R. Lichen planus and lichen-planus-like reactions. *Br J Hosp Med* 1986; **36:** 281–4.
5. Jones SK, *et al.* Thiazide diuretic-induced subacute cutaneous lupus-like syndrome. *Br J Dermatol* 1985; **113** (suppl 29): 25.
6. Reed BR, *et al.* Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; **103:** 49–51.
7. Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; **18:** 38–42.
8. Björnberg A, Gisslén H. Thiazides: a cause of necrotising vasculitis? *Lancet* 1965; **ii:** 982–3.
9. Hardwick N, Saxe N. Patterns of dermatology referrals in a general hospital. *Br J Dermatol* 1986; **115:** 167–76.
10. Motley RS. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; **300:** 1468.

Gout. Thiazides have been associated with hyperuricaemia and gout in some patients. In the Medical Research Council Study on Mild to Moderate Hypertension,[1] a single-blinded trial, men taking bendroflumethiazide had higher incidences of gout than those receiving placebo (12.23 and 1.03 per 1000 patient-years, respectively). The risk appears to be dose-related; in a retrospective study[2] in patients aged 65 or older receiving antihypertensive therapy, there was a significantly increased risk of starting anti-gout therapy in patients taking the equivalent of 25 mg hydrochlorothiazide or more daily, but not in those on lower doses.

1. Greenburg G. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension: report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981; **ii:** 539–43.
2. Gurwitz JH, *et al.* Thiazide diuretics and the initiation of anti-gout therapy. *J Clin Epidemiol* 1997; **50:** 953–9.

Withdrawal. For a report of oedema after abrupt withdrawal of thiazides, see under Precautions, below.

Treatment of Adverse Effects

Hypokalaemia in patients treated with thiazides may be avoided or treated by use with potassium or a potassium-sparing diuretic (but see the discussion on potassium supplements, under Effects on Electrolyte Balance in Adverse Effects, above). Hypokalaemia can also be reduced by moderate sodium restriction. With the exception of patients with conditions such as hepatic failure or renal disease, chloride deficiency is usually mild and does not require specific treatment. Apart from the rare occasions when it is life-threatening, dilutional hyponatraemia is best treated with water restriction rather than salt therapy; in true hyponatraemia, appropriate replacement is the treatment of choice (see p.1670).

In massive overdosage, treatment should be symptomatic and directed at fluid and electrolyte replacement. Use of activated charcoal should be considered if the patient presents within 1 hour of ingestion.

Precautions

All diuretics produce changes in fluid and electrolyte balance (see Adverse Effects, above). They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly. They should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also more likely to develop hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses of thiazides and restricted salt intake. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Thiazides should not be given to patients with Addison's disease.

Diuretics should also be given with caution in renal impairment since they can further reduce renal function. Most thiazides are not effective in patients with a creatinine clearance of less than 30 mL/minute. They should not be used in patients with severe renal impairment or anuria.

Thiazides may precipitate attacks of gout in susceptible patients. They may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. Thiazides can reduce urinary excretion of calcium, sometimes resulting in mild hypercalcaemia; they should not be given to patients with pre-existing hypercalcaemia. There is a possibility that thiazides may exacerbate or activate systemic lupus erythematosus in susceptible patients. For a suggestion that thiazides may increase the risk of developing gallstones, see Effects on the Gallbladder, above.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion. Treatment with large doses can inhibit lactation.

Breast feeding. Hydrochlorothiazide has been shown to pass into breast milk. In a woman taking 50 mg hydrochlorothiazide daily, peak milk concentrations were found[1] 5 to 10 hours after a dose and were about 25% of peak blood concentrations. No drug could be detected in the infant's blood, and his serum electrolytes, blood glucose, and blood urea nitrogen were normal. The American Academy of Pediatrics considers[2] that hydrochlorothiazide is usually compatible with breast feeding.

1. Miller ME, *et al.* Hydrochlorothiazide disposition in a mother and her breast-fed infant. *J Pediatr* 1982; **101:** 789–91.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Hyperparathyroidism. Hypertension is a complication of primary hyperparathyroidism but thiazides have often been withheld for fear of exacerbating hypercalcaemia. However, no differences in plasma-calcium concentrations were found in 13 patients given thiazides intermittently for up to 18 months. It was therefore concluded that thiazides are not contra-indicated in such patients.[1] They should, however, be stopped before parathyroid function is tested.

1. Farquhar CW, *et al.* Failure of thiazide diuretics to increase plasma calcium in mild primary hyperparathyroidism. *Postgrad Med J* 1990; **66:** 714–16.

Porphyria. Hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Withdrawal. In patients with mild hypertension whose blood pressure is consistently controlled, reduction in dosage or withdrawal of antihypertensive drugs may be possible. Serious oedema occurred in 8 patients with controlled hypertension within 2 weeks of abrupt withdrawal of thiazide diuretics.[1] Thiazides were resumed and gradually tapered without recurrence of oedema.

1. Brandspigel K. Diuretic-withdrawal edema. *N Engl J Med* 1986; **314:** 515.

Interactions

Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance. Diuretic-induced hypokalaemia may enhance the toxicity of digitalis glycosides and may also increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozide, and sotalol. Thiazides may enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect. The potassium-depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, $beta_2$ agonists such as salbutamol, carbenoxolone, amphotericin B, or reboxetine.

Diuretics may enhance the effect of other antihypertensives, particularly the first-dose hypotension that occurs with alpha blockers or ACE inhibitors. Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates, or opioids. The antihypertensive effects of diuretics may be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone; diuretics may enhance the nephrotoxicity of NSAIDs. Thiazides have been reported to diminish the response to pressor amines, such as noradrenaline, but the clinical significance of this effect is uncertain.

Thiazides should not usually be used with lithium since the association may lead to toxic blood concentrations of lithium. Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracyclines. Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

Antibacterials. Severe hyponatraemia has been reported in patients taking *trimethoprim* with co-amilozide[1] and hydrochlorothiazide.[2]

1. Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. *BMJ* 1984; **289:** 1658–9.
2. Hart TL, *et al.* Hyponatremia secondary to thiazide-trimethoprim interaction. *Can J Hosp Pharm* 1989; **42:** 243–6.

Antiepileptics. There has been a report of symptomatic hyponatraemia associated with the use of hydrochlorothiazide or furosemide and *carbamazepine*.[1]

1. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Bile-acid binding resins. Gastrointestinal absorption of both chlorothiazide and hydrochlorothiazide has been reported to be reduced by *colestipol* and *colestyramine*.[1-3] In a study in healthy subjects[2] colestyramine had the greatest effect on hydrochlorothiazide, decreasing absorption by 85% compared with a decrease of 43% with colestipol. Even when colestyramine was given 4 hours after hydrochlorothiazide[3] reductions of absorption of at least 30 to 35% could be expected.

1. Kauffman RE, Azarnoff DL. Effect of colestipol on gastrointestinal absorption of chlorothiazide in man. *Clin Pharmacol Ther* 1973; **14:** 886–90.
2. Hunninghake DB, *et al.* The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. *Int J Clin Pharmacol Ther Toxicol* 1982; **20:** 151–4.
3. Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. *Clin Pharmacol Ther* 1986; **39:** 329–34.

Calcium salts. The milk-alkali syndrome, characterised by hypercalcaemia, metabolic alkalosis, and renal failure, developed in a patient taking chlorothiazide and moderately large doses of calcium carbonate.[1] Patients taking thiazides may be at increased risk of developing the syndrome because of their reduced ability to excrete excess calcium. Hypercalcaemia may also occur in patients taking thiazides with drugs that increase calcium levels, such as vitamin D.

1. Gora ML, *et al.* Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharm* 1989; **8:** 227–9.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p.793.

NSAIDs. NSAIDs cause fluid retention and may antagonise the diuretic actions of thiazides.[1]

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Pharmacokinetics

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Beermann B, *et al.* Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther* 1976: **19:** 531–7.
2. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. *Eur J Clin Pharmacol* 1977; **12:** 297–303.
3. Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in patients with congestive heart failure. *Br J Clin Pharmacol* 1979: **7:** 579–83.

Uses and Administration

Hydrochlorothiazide and the other thiazide diuretics are used in the treatment of hypertension (p.1171), either alone or with other antihypertensives such as ACE inhibitors and beta blockers. They are also used to treat oedema associated with heart failure (p.1165) and with renal and hepatic disorders. Other indications have included the treatment of oedema accompanying the premenstrual syndrome (p.2099), the prevention of water retention associated with corticosteroids and oestrogens, the treatment of diabetes insipidus (below), and the prevention of renal calculus formation in patients with hypercalciuria (below).

Thiazides are moderately potent diuretics and exert their diuretic effect by reducing the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. They act mainly at the beginning of the distal tubules. The excretion of other electrolytes, notably potassium and magnesium, is also increased. The excretion of calcium is reduced. They also reduce carbonic-anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. They may also reduce the glomerular filtration rate.

Their hypotensive effect is probably partly due to a reduction in peripheral resistance; they also enhance the effects of other antihypertensives. Paradoxically, thiazides have an antidiuretic effect in patients with diabetes insipidus.

Administration and dosage. Thiazides are usually given in the morning so that sleep is not interrupted by diuresis. Diuresis starts in about 2 hours after oral doses of hydrochlorothiazide, reaches a maximum in about 4 hours, and lasts for 6 to 12 hours.

The dosage of thiazides should be adjusted to the minimum effective dose. In general lower doses are required for the treatment of hypertension than for oedema, although the maximum therapeutic effect may not be seen for several weeks.

They may be given to patients with mild renal impairment, but thiazides are generally not effective at a creatinine clearance of less than 30 mL/minute.

Hydrochlorothiazide is given orally.

In the treatment of **hypertension** an initial dose of 12.5 mg may be sufficient, increasing to 25 to 50 mg daily if necessary, either alone or with other antihypertensives. Doses of up to 100 mg have been suggested but are rarely necessary.

In the treatment of **oedema** the usual dose is 25 to 100 mg daily, reduced to a dose of 25 to 50 mg daily or intermittently; in severe cases initial doses of up to 200 mg daily have been suggested, but the more powerful loop diuretics (see Furosemide, p.1292) are preferred in such patients.

In the treatment of nephrogenic **diabetes insipidus** an initial dose of up to 100 mg daily may be used.

An initial dose for children has been 1 to 2 mg/kg daily in single or 2 divided doses. Infants under 6 months may need doses of up to 3 mg/kg daily.

For discussion of potassium supplementation in patients taking thiazide diuretics see Effects on Electrolyte Balance, under Adverse Effects, above.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p.1500) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p.1294); results with hydrochlorothiazide or spironolactone have been more ambiguous. No beneficial effects on lung function or oxygenation were found in a study of 12 infants after 1 week of treatment with hydrochlorothiazide and spironolactone.[1] However, hydrochlorothiazide and spironolactone therapy was found to improve total respiratory system compliance with decreased lung damage and increased survival rate in 34 premature infants with bronchopulmonary dysplasia after 8 weeks of therapy.[2] In the latter study furosemide was also given if clinically indicated.

1. Engelhardt B, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989; **114:** 619–24.
2. Albersheim SG, *et al.* Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; **115:** 615–20.

Diabetes insipidus. Thiazide diuretics are used in nephrogenic diabetes insipidus (p.2179), sometimes with potassium-sparing diuretics. For instance, hydrochlorothiazide with amiloride was effective in controlling nephrogenic diabetes insipidus in 5 boys and compared favourably with treatment with hydrochlorothiazide and indometacin.[1] Treatment was well tolerated in 4 patients. Abdominal pain and anorexia necessitated withdrawal of amiloride in the fifth patient after 6 months. The use of hydrochlorothiazide with amiloride avoided the need for potassium supplements, which were required with hydrochlorothiazide and indometacin. The use of hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Hypoparathyroidism. In hypoparathyroidism (p.1087), treatment is usually with oral vitamin D compounds to correct the hypocalcaemia. Thiazides may be useful in some patients. Beneficial effects on serum-calcium concentrations in patients with hypoparathyroidism have been reported after chlortalidone plus dietary salt restriction,[1] and with bendroflumethiazide.[2] However, chlortalidone has not been found to be effective in all patients,[3] and the reduction in urinary calcium excretion by thiazides has been shown to be diminished in patients with hypoparathyroidism,[4] suggesting that this effect may be dependent on the presence of active parathyroid hormone. Care should be taken when giving diuretics to hypoparathyroid patients with co-existing adrenal insufficiency[3] or metabolic alkalosis.[5]

1. Porter RH, *et al.* Treatment of hypoparathyroid patients with chlorthalidone. *N Engl J Med* 1978; **298:** 577–81.
2. Newman GH, *et al.* Effect of bendrofluazide on calcium reabsorption in hypoparathyroidism. *Eur J Clin Pharmacol* 1984; **27:** 41–6.
3. Gertner JM, Genel M. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **298:** 1478.
4. Middler S, *et al.* Thiazide diuretics and calcium metabolism. *Metabolism* 1973; **22:** 139–45.
5. Barzel US. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **289:** 1478.

Ménière's disease. In Ménière's disease (p.564) there is an excess of endolymph fluid in the ear and diuretics such as hydrochlorothiazide have been used in attempts to relieve symptoms by reducing the amount of fluid.

Osteoporosis. Although some epidemiological studies have indicated beneficial effects of thiazides on bone (reduced rates of bone loss[1] and a reduced risk of hip fracture[2-5]) a comprehensive analysis involving 9704 women over the age of 65 years[6] showed only a small effect on bone mass, no effect on the risk for falls, and no overall protective effect against fractures. A further prospective study[7] reported a reduction in forearm fracture, but hip fracture was only reduced in postmenopausal women. Randomised, controlled studies[8,9] have confirmed that hydrochlorothiazide reduces bone loss, but again the effects were small. Thus, thiazides have no established role in the prevention or treatment of osteoporosis (p.1084). They might, however, be useful to reduce hypercalciuria in patients taking glucocorticoids[10] but serum-potassium concentrations should be monitored closely.

1. Wasnich R, *et al.* Effect of thiazide on rates of bone mineral loss: a longitudinal study. *BMJ* 1990; **301:** 1303–5. Correction. *ibid.* 1991; **302:** 218.
2. Ray WA, *et al.* Long-term use of thiazide diuretics and risk of hip fracture. *Lancet* 1989; **i:** 687–90.
3. LaCroix AZ, *et al.* Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med* 1990; **322:** 286–90.
4. Felson DT, *et al.* Thiazide diuretics and the risk of hip fracture: results from the Framingham Study. *JAMA* 1991; **265:** 370–3.
5. Schoofs MWCJ, *et al.* Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003; **139:** 476–82.
6. Cauley JA, *et al.* Effects of thiazide diuretic therapy on bone mass, fractures, and falls. *Ann Intern Med* 1993; **118:** 666–73.
7. Feskanich D, *et al.* A prospective study of thiazide use and fractures in women. *Osteoporosis Int* 1997; **7:** 79–84.
8. Reid IR, *et al.* Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. *Am J Med* 2000; **109:** 362–70.
9. LaCroix AZ, *et al.* Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 516–26.
10. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112:** 352–64.

Renal calculi. A thiazide diuretic may be given to prevent the recurrence of calcium-containing renal calculi (p.2181) in patients with hypercalciuria.[1,2]

1. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13:** 679–85.
2. Tiselius H-G, *et al.* European Association of Urology. Guidelines on urolithiasis (issued March 2008). Available at: http://www.uroweb.org/count.php?f=fileadmin%2Ftx_eauguidelines%2FUrolithiasis.pdf (accessed 24/07/08)

Preparations

BP 2008: Co-amilozide Oral Solution; Co-amilozide Tablets; Co-triamterzide Tablets; Hydrochlorothiazide Tablets;

USP 31: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Bisoprolol Fumarate and Hydrochlorothiazide Tablets; Captopril and Hydrochlorothiazide Tablets; Enalapril Maleate and Hydrochlorothiazide Tablets; Fosinopril Sodium and Hydrochlorothiazide Tablets; Hydrochlorothiazide Tablets; Irbesartan and Hydrochlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Propranolol Hydrochloride and Hydrochlorothiazide Extended-release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets; Spironolactone and Hydrochlorothiazide Tablets; Timolol Maleate and Hydrochlorothiazide Tablets; Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Valsartan and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Diural; Diurex; Tandiur; ***Austral.:*** Dichlotride†; Dithiazide; ***Austria:*** Esidrex; ***Braz.:*** Clorana; Clorizin; Diurepina; Diuretic†; Diuretil; Diurezin; Drenol; Hidroclorana†; Hidroclorozil; Hidrofall†; Hidrolan; Hidromed; Mictrin†; Neo Hidroclor; ***Canad.:*** Apo-Hydro; HydroDiuril†; Novo-Hydrazide; ***Chile:*** Hidroronol; ***Denm.:*** Dichlotride†; ***Fin.:*** Hydrex; ***Fr.:*** Esidrex; ***Ger.:*** Disalunil; diu-melusin; Esidrix; HCT; HCT-Beta; HCT-gamma; HCT-ISIS; HCTad; ***Hong Kong:*** Hydrozide; ***Hung.:*** Hypothiazid; ***India:*** Aquazide; BPzide; Esidrex†; Hydrazide; Selopres; ***Indon.:*** HCT; Lodoz; ***Israel:*** Disothiazide; ***Ital.:*** Esidrex; ***Malaysia:*** Apo-Hydro; Dichlotride†; Hydrozide; ***Mex.:*** Rofucal; ***Norw.:*** Esidrex; ***Pol.:*** Disalunil†; ***Port.:*** Dichlotride†; ***Rus.:*** Hypothiazid (Гипотиазид); ***S.Afr.:*** Hexazide; Ridaq; ***Singapore:*** Apo-Hydro; Di-Ertride†; Hydrozide; ***Spain:*** Acuretic; Esidrex;

Hidrosaluretil; ***Swed.:*** Esidrex; ***Switz.:*** Esidrex; ***Thai.:*** Dichlotride; Diuret-P†; Hychlozide; Hydrozide; ***USA:*** Esidrix†; HydroDiuril; Microzide; Mictrin; Oretic†; ***Venez.:*** Di-Eudrin.

Multi-ingredient: ***Arg.:*** Accuretic; Adana Plus; Aldazida; Amiloclor†; Atacand-D; Avapro HCT; Carvedil D; Co-Renitec; CoAprovel; Corbis D; Cozaarex D; Dacten D; Defluin Plus; Diovan D; Diovan Triple; Diubeloc†; Diur Pot; Diurex A; Fabotensil D; Fensartan D; Gadopril D; Gliosartan Plus; Gliotenzide; Hidrenox A; Kinfil D; Klosartan D; Loctenk D; Loplac-D; Losacor D; Lotrial D; Maxen D; Micardis Plus; Moducren†; Moduretic; Niten D; Normatensil†; Paxon-D; Plenacor D; Prenomod†; Presi Regul D; Presinor D; Propayerst Plus†; Ren-Ur; Simultan D; Tacardia D; Tencas D; Tenopres D†; Tensopril D; Tiadyl Plus; Tritace-HCT; Vapresan Diur; Vericordin Compuesto; Zestoretic; Ziac; ***Austral.:*** Accuretic; Amizide; Atacand Plus; Avapro HCT; Hydrene; Karvezide; Micardis Plus; Moduretic; Monoplus; Olmetec Plus; Renitec Plus; Teveten Plus; ***Austria:*** Accuzide; Acecomb; Acelisino comp; Aceplus; Aldoretic; Amiloral/HCT; Amiloretik; Amilorid comp; Amilostad HCT; Atacand Plus; Beloc comp; Bisocombin; Bisoprolol comp; Bisoprolol-HCT; Bisostad plus; Blopress Plus; Capozide; Captohexal Comp; Captopril Compositum; Captopril-HCT; Co-Acetan; Co-Angiosan; Co-Captopril; Co-Captyrol†; Co-Dilatrend; Co-Diovan; Co-Enac; Co-Enalapril; Co-Enaran; Co-Enatyrol†; Co-Hypomed; Co-Lisinostad; Co-Mepril; Co-Renitec; Concor Plus; Confit; Corenistad; Cosaar Plus; Darbalan Plus; Deverol mit Thiazid; Dilaplus; Dytide H; Enacostad†; Enalapril Comp; Enalapril/HCT; Fempress Plus; Fosicomb; Hypren plus; Inhibace Plus; Lannapril plus; Lanuretic; Lisihexal comb; Lisinocomp; Lisinopril comp; Loradur; Metoprolol compositum; MicardisPlus; Moducrin; Moduretic; Nanalan Plus; Ramicomp; Ramipharm comb; Renitec Plus; Rivacor Plus; Salodiur; Seloken retard Plus; Supracid; Synerpril; Teveten Plus; Triamteren comp; Triastad HCT; Triloc; Trioral/HCT; Tritazide; Valsartan/HCTZ†; Zestoretic; ***Belg.:*** Accuretic; Atacand Plus; Belidral†; Co-Amiloride; Co-Bisoprolol; Co-Diovane; Co-Enalapril; Co-Inhibace; Co-Lisinopril; Co-Quinapril; Co-Renitec; CoAprovel; Cozaar Plus; Docspirochlor; Dytenzide; Emcoretic; Foside†; Kalten†; Kinzalkomb; Lodoz; Loortan Plus; Maxsoten; Merck-Co-Bisoprolol; Merck-Co-Lisinopril; Micardis Plus; Moduretic; Novazyd†; Olmetec Plus; Sectrazide; Selozide; Teveten Plus; Tritazide; Zestoretic; Zok-Zid; ***Braz.:*** Adelfan-Esidrex†; Aldazida; Amiretic; Aprozide; Aradois H; Atacand HCT; Atens H; Benicar HCT; Biconcor; Capox H; Captotec + HCT†; Co-Enalil; Co-Enaprotec†; Co-Pressoless; Co-Pressotec; Co-Renitec; Corus H; Cotareg†; Diovan HCT; Diurezin-A; Duopril; Ecator H; Enatec F†; Eupressin H; Gliotenzide; Hidropril; Hydromet; Hyzaar; Iguassina; Lisinoretic†; Lisoclor; Lisonotec†; Lonipril-H; Lopril; Lorsar + HCT†; Lotensin H; Malena HCT; Micardis HCT; Moduretic; Monoplus; Naprix D; Neopress; Olmetec HCT; Polol-H; Prinzide; Pritor HCT; Pryltec-H; Selopress; Tenadren; Torlos H; Triatec D; Vascase Plus; Vasopril Plus; Zestoretic; ***Canad.:*** Accuretic; Aldactazide; Apo-Amilzide; Apo-Methazide; Apo-Triazide; Atacand Plus; Avalide; Diovan HCT; Gen-Amilazide; Hyzaar; Inhibace Plus; Micardis Plus; Moduret; Novamilor; Novo-Spirozine; Novo-Triamzide; Nu-Amilzide; Nu-Triazide; PMS-Dopazide; Prinzide; Teveten Plus; Timolide†; Vaseretic; Viskazide; Zestoretic; ***Chile:*** Accuretic; Acerdil-D; Aratan D; Bajaten D; Bilaten-D; Blopress D; Blox-D; CoAprovel; Corodin D; Drinamil; Enalten D; Enalten DN; Esalfon-D; Grifopril-D; Hidroronol T; Hiperson-D; Hipoartel H†; Hyzaar; Inhibace Plus; Losapres-D; Lotrial D; Micardis Plus; Monopril Plus; Normaten; Normaten Plus; Sanipresin-D; Simperten-D; Tareg-D; Tonotensil D; Uren; Valaplex-D; Vartalan D; Zestoretic†; Ziac; ***Cz.:*** Accuzide; Amilorid/HCT; Amprilan H; Apo-Amilzide; Atacand Plus; Captohexal Comp†; Co-Diovan; CoAprovel; Concor Plus†; Enap-H; Enap-HL; Foprin Plus H; Giovax plus H; Hartil-H; Hyzaar†; Inhibace Plus; Karvezide; Kinzalkomb; Limorid†; Lipribela plus H; Lodoz; Loradur; Lorista H; Losaratio Plus H; Lozap H; Medoram plus H; MicardisPlus; Miril plus H; Moduretic; Nopretens Plus H; Olmetec Plus H; PritorPlus; Ramil H; Ramixa Plus H; Rhefluin; Sarten Plus H; Stadapress; Tebis Plus H; Teveten Plus H; Tritazide; ***Denm.:*** Amilco; AtacandZid; Atazid; Capozid; Co-Renitec†; CoAprovel; Corodil Comp; Cozaar Comp; Diovan Comp; Enacozid; Fortzaar; Kinzalkomb†; Lisinoplus; MicardisPlus; Moduretic†; Sparkal; Synerpril; Teveten Comp; Triatec Comp; Vivazid†; Zestoretic; Zok-Zid; ***Fin.:*** Accupro Comp; Acercomp†; Amitrid; Atacand Plus; Bisoprolol Comp; Cardace Comp; Cozaar Comp; Diovan Comp; Diuramin; Diurex; Emconcor Comp; Enalapril Comp; Enaloc Comp†; Kinzalkomb; Linatil Comp; Lisipril Comp; MicardisPlus; Miloride; Moduretic; Orloc Comp; Renitec Comp; Renitec Plus; Selocomp ZOC; Sparkal; Teveten Comp; Vivatec Comp; ***Fr.:*** Acuilix; Alteisduo; Briazide; Captea; Cibadrex; Co-Renitec; CoAprovel; Cokenzen; Coolmetec; Cotareg; Coteveten; Cotriatec; Ecazide; Fortzaar; Foziretic; Hytacand; Hyzaar; Koretic; Lodoz; MicardisPlus; Moducren; Moduretic; Nisisco; Prestole; Prinzide; PritorPlus; Wytens; Zestoretic; Zofenilduo; ***Ger.:*** Accuzide; ACE-Hemmer comp; Acenorm HCT†; Acercomp; Adelphan-Esidrix†; Adocomp; Amilocomp beta; Amiloretik; Amilorid comp; Amilorid/HCT; Amilozid†; Aquaretic†; Atacand Plus; Azumetop HCT†; Barotonal†; Beloc-Zok comp; Benalapril Plus; Benazeplus; Benazepril comp; Benazepril HCT; Beta-Turfa; Biso comp; Biso-Puren comp; Bisobeta comp; Bisohexal plus; BisoLich comp; Bisomerck Plus; Bisoplus; Bisoprolol Comp; Bisoprolol HCT; Bisoprolol Plus; Blopress Plus; Capozide; Capto Comp; Capto Plus; Captobeta Comp; Captodoc Comp; Captogamma HCT; Captohexal Comp; Captopril Comp; Captopril HCT; Captopril Plus; Cardiagen HCT; Cibadrex; Co-Diovan; CoAprovel; Concor Plus; Cordinate plus; Coric Plus; Corindocomb†; Corvo HCT; Delix Plus; Disalpin†; Diu Venostasin; Diuretikum Verla; Diursan; Diutensat comp†; Diutensat†; Dociteren; duradiuret†; durarese†; Dynacil comp; Dynorm Plus; Dytide H; Emestar plus; Enabeta comp; Enadura Plus; Enahexal comp; Enala-Q comp; Enalagamma HCT; Enalapril Comp; Enalapril HCT; Enalapril plus; Enalapril-saar Plus; EnaLich comp; Enaplus; Esimil†; Fempress Plus; Fondril HCT; Fortzaar; Fosinorm comp; Haemiton compositum†; Isoptin plus; Jenateren comp†; Jutacor comp; Karvezide; Kinzalkomb; Lisi-Puren comp; Lisibeta comp; Lisigamma HCT; LisiLich comp; Lisinopril comp; Lisinopril HCT; Lisiplus; Lisodura plus; Lorzaar plus; Meprolol Comp; Meto comp†; Meto-Isis comp†; meto-thiazid†; Metobeta comp; Metodura comp; Metohexal comp; Metoprolol comp; Metostad Comp; MicardisPlus; Moducrin; Moduretik; Nephral; Olmetec Plus; Pres plus; Propra comp; Provas comp; QuinaLich comp; Quinaplus; Quinapril comp; Rami-Q comp; Ramicard Plus; Ramigamma HCT; RamiLich comp; Ramiplus; Ramipril comp; Ramipril HCT; Ramipril HCTad; Ramipril Plus; Renacor; Risicordin†; Sali-Puren†; Spironothiazid; Tensobon comp; Teveten Plus; Thiazid-comp; Treloc; Tri-Thiazid; Tri-Thiazid Reserpin†; Triampur Compositum; Triamteren comp; Triamteren HCT; Triamteren tri-comp; Triamteren-H†; Triarese; triazid†; Triniton; Turfa; Veratide; Vesdil plus; Votum Plus; ***Gr.:*** Accuretic; Anastol; Atacand Plus; Bumeftyl; Captopress; Captospes+H; Cibadrex; Co-Dalzad; Co-Diovan; Co-Renitec; CoAprovel; Coredopril; Dosturel; Ekzevit†; Empirol; Fetylan; Fozide; Hydromet†; Hyzaar; Iperton; Ividol; Karvezide; Kifarol; Micardis Plus; Modinexil†; Moduretic; Monoplus†; Nolarmin; Normolose-H; Olartan Plus; Olmetec Plus; Penopril; Pentatec; Piesital; Prinzide; Pritor Plus; Protal complex; Quimea; Return; Sancazid; Savosan; Sedapressin; Siberian; Stibenyl HCT; Superace; Teveten Plus; Tiaden; Triatec Plus; Uresan; Vascase Plus; Z-Bec Plus; Zestoretic; Zidepril; Zofepril Plus; Zopranol Plus; ***Hong Kong:*** Adelphane-Esidrex; Amilco†; Amithiazide; Apo-Amilzide; Apo-Triazide; Aprovel HCT†; Betaloc Comp; Blopress Plus; Co-Diovan; Co-Renitec; CoAprovel; CP-Metolol Co; Dyazide; Hyzaar; Lodoz; Micardis Plus; Moducren; Moduretic; Sefaretic; Teveten Plus; Triam-Co†; Zestoretic; ***Hung.:*** Accuzide; Acepril PlusZ; Amilorid Comp; Amilozid-B; Amprilan HD; Amprilan HL; Atacand Plus; Co-Enalapril; Co-Renitec; CoAprovel; Concor Plus; Diovan HCT; Duopril; Ednyt HCT; Ednyt Plus; Enalapril Hexal Plus; Enalapril-HCT; Enap-HL; Hartil HCT; Hyzaar; Inhibace Plus; Lodoz; Lotensin HCT; Meramyl HCT; MicardisPlus; PritorPlus; Ramace Plusz; Ramiwin HCT; Renapril Plus; Renitec Plus; Tritace-HCT; Varexan HCT; ***India:*** Adelphane-Esidrex; Alsartan-H; Arkamin-H; Beptazine-H; Biduret; Ciplar-H; Cipril-H; Covance-D; EnAce-D; Hipres-D; Invozide; Lisoril-5HT; Lodoz; Losacar-H; Metolar-H; Ramcor H; Ramipres H; Telma-H†; Telpres-H; Xarb-H; Zaart-H; ***Indon.:*** Blopress Plus; Capozide; Co-Diovan; CoAprovel; Dellasidrex; Irtan Plus; Lorinid; Micardis Plus; Sectrazide; Ser-Ap-Es; Tenazide; Zestoretic; ***Irl.:*** Accuretic; Amilco†; Atacand Plus; Capozide; Captor-HCT; Carace Plus; Co-Betaloc; Co-Diovan; CoAprovel; Cozaar Comp; Dyazide; Half Capozide; Innozide; Lispril-hydrochlorothiazide; MicardisPlus; Moducren; Moduret; Teveten Plus; Zesger Plus; Zestoretic; ***Israel:*** Atacand Plus; Co-Diovan; Irban Plus†; Kaluril; Naprizide; Ocsaar Plus; Tritace Comp; Vascace Plus; Vasopril Plus†; ***Ital.:*** Accuretic; Acediur; Aceplus; Acequide; Acesistem; Aldactazide; Bifrizide; Blopresid; Cibadrex; CoAprovel; Combisartan; Condiuren; Corixil; Cotareg; Elidiur; Enulid; Femipres Plus; Forzaar; Fosicombi; Gentipress; Hizaar; Idroquark; Inibace Plus; Initiss Plus; Karvezide; Lodoz; Losazid; Medozide; Micardis Plus; Moduretic; Nalapres; Neo-Lotan Plus; Neoprex; Prinzide; PritorPlus; Quinazide; Ratacand Plus; Selozide†; Sinertec; Spiridazide; Tensadiur; Tensozide; Triatec HCT; Uniprildiur; Vasoretic; Zantipride; Zestoretic; Zinadiur; Zoprazide; ***Malaysia:*** Ami-Hydrotride; Amizide; Apo-Amilzide; Apo-Triazide†; Atacand Plus; Co-Diovan; CoAprovel; Fortzaar; Hyzaar; Micardis Plus; Moduretic; Olmetec Plus; ***Mex.:*** Atacand Plus; Avalide; Biconcor; Blopress Plus; Capozide; Co-Captral; Co-Diovan; Co-Renitec; CoAprovel; Dyazide; Gliotenzide; Hyzaar; Micardis Plus; Moduretic; Predxal Plus; Prinzide; Selopres; Tritazide; Zestoretic; ***Neth.:*** Acuzide; Atacand Plus; Blopresid; Capozide†; Cibadrex; Co-Diovan; Co-Renitec; CoAprovel; Cotareg; Cozaar Plus; Delitab-HCT; Diurace; Dytenzide; Emcoretic; Enacostad†; Fortzaar; Hyzaar; Karvezide; Kinzalkomb; Lisidigal HCT; Losazid; Micardis Plus; Moduretic; Novazyd; Prilitab-HCT; Prilitaril-HCT; PritorPlus; Ramitab-HCT; Rataril-HCT; Renitec Plus; Secadrex†; Selokomb; Teveten Plus; Tritazide; Zestoretic; ***Norw.:*** Atacand Plus; CoAprovel; Cozaar Comp; Diovan Comp; Enalapril Comp; Lodoz; MicardisPlus; Moduretic; Normorix; Renitec Comp; Teveten Comp; Vivatec Comp; Zestoretic; ***NZ:*** Accuretic; Amizide; Capozide; Co-Renitec; Hyzaar; Inhibace Plus; Karvezide; Triamizide; ***Philipp.:*** Accuzide; Betazide; Blopress Plus; Co-Diovan; Co-Renitec; CoAprovel; Combizar; Hyzaar; Micardis Plus; Norplus; PritorPlus; Teveten Plus; Uniretic; Vascace Plus; Vascoride; Zestoretic; Ziac; ***Pol.:*** Accuzide; Co-Diovan; Enap H; Enap HL; Hyzaar; Inhibace Plus; Lorista H; Lotensin HCT; Micardis Plus; Pritor Plus; Ramicor Comb; Tialorid; ***Port.:*** Acuretic; Aldoretic†; Amiloride Composto†; Blopress 16 mg + 12,5 mg; Blopress Comp; Chibretico†; Co-Diovan; Co-Tareg; CoAprovel; Concor Plus; Cozaar Plus; Diurene; Dyazide; Ecamais; Enatia; Fortzaar; Fositen Plus; Hytacand; Inibace Plus; Karvezide; Kinzalkomb; Laprilen; Lisoplus; Lopiretic; Lortaan Plus; Medinor; Micardis Plus; Moducren†; Moduretic; Neodur; Normotil†; Norpramin; Olsar Plus; Ondolen; Prinzide; PritorPlus; Ramicor D; Renidur; Renipril Plus; Siaara; Tensival; Teveten Plus; Tiazinol; Triam Tiazida R; Triatec Composto; Vascase Plus; Zestoretic; Zofenil Plus; ***Rus.:*** Adelphane-Esidrex (Адельфан-эзидрекс); Apo-Triazide (Апо-триазид); Capozide (Капозид); Co-Diovan (Ко-Диован); Co-Renitec (Ко-Ренитек); Enap-H (Энап Н); Enap-HL (Энап-НЛ); Fosicard H (Фозикард Н); Fozide (Фозид); Hyzaar (Гизаар); Iruzid (Ирузид); Lisoretic (Лизоретик); Lozap Plus (Лозап Плюс); MicardisPlus (МикардисПлюс); Moex Plus (Моэкс Плюс); Renipril HT (Рениприл ГТ); Sinorezid (Синорезид); Teveten Plus (Теветен Плюс); Triam-Co (Триам-ко); Triampur Compositum (Триампур Композитум); Triresid K (Трирезид К); ***S.Afr.:*** Accuretic; Adco-Retic; Amiloretic; Atacand Plus; Betaretic; Capozide; Captoretic; Cibadrex; Co-Diovan; Co-Micardis; Co-Renitec; CoAprovel; Cozaar Comp; Dyazide; Enap-Co; Fortzaar; Hexaretic; Inhibace Plus; Lisoretic; Moducren; Moduretic; Monozide; Pharmapress Co; Renezide; Servatrin; Sotazide; Urirex-K; Zapto Co; Zestoretic; Zetomax Co; Ziak; ***Singapore:*** Apo-Amilzide; Apo-Triazide; Atacand Plus; Co-Diovan; Co-Renitec; CoAprovel; Enap-HL; Gliotenzide; Hyzaar; Lodoz; Micardis Plus; Olmetec Plus; ***Spain:*** Acediur; Acetensil Plus; Adelfan-Esidrex†; Alopresin Diu†; Ameride; Atacand Plus; Baripril Diu; Bicetil; Bitensil Diu; Cesplon Plus; Cibadrex; Co-Diovan; Co-Renitec; Co-Vals; CoAprovel; Cozaar Plus; Crinoretic; Dabonal Plus; Decresco†; Dilabar Diu; Ditenside; Diuzine; Doneka Plus; Ecadiu; Ecazide; Emcoretic; Fortzaar; Fositens Plus; Futuran Plus; Hiperlex Plus; Hipoartel Plus; Inhibace Plus; Inocar Plus; Iricil Plus; Kalpress Plus; Kalten; Karvezide; Labodrex; Lidaltrin Diu; Micardis Plus; Miscidon†; Miten Plus; Navixen Plus; Neotensin Diu; Parapres Plus; Pressitan Plus; Prinivil Plus; Pritor Plus; Regulaten Plus; Renitecmax; Rulun; Secadrex†; Secubar Diu; Selopresin†; Tensikey Complex; Tensiocomplet; Tenso Stop Plus; Tevetens Plus; Zestoretic; ***Swed.:*** Accupro Comp; Amiloferm; Atacand Plus; CoAprovel; Cozaar Comp; Diovan Comp; Enalapril Comp; Inhibace comp; Kinzalkomb†; Linatil Comp; Micardis Plus; Moduretic; Monopril comp†; Normorix; Renitec Comp; Sparkal; Synerpril; Teveten Comp; Triatec Comp; Zestoretic; ***Switz.:*** Accuretic; Adelphan-Esidrex; Agorex†; Amilo-basan†; Amiloride/HCTZ; Atacand Plus; Betadiur†; Blopress Plus; Capozide; Captosol comp; Cibadrex; Co-Acepril; Co-Amilorid†; Co-Diovan; Co-Enalapril; Co-Enatec; Co-Epril; Co-Lisinopril; Co-Reniten; Co-Vasocor; CoAprovel; Comilorid; Concor Plus; Corpriretic; Cosaar Plus; Dyazide; Ecodurex; Elpradil HCT; Epril Plus; Escoretic; Fosicomp; Grodurex; Inhibace Plus; Kalten; Kinzalplus; Lisitril comp; Lisopril plus; Lodoz; MicardisPlus; Moducren; Moduretic; Olmetec Plus; Prinzide; Provas comp; Provas maxx; Reniten Plus; Rhefluin; t/h-basan; Tensobon comp; Teveten Plus; Tobicor Plus; Triatec Comp; Votum Plus; Zestoretic; ***Thai.:*** Aprovel HCT†; Bilduretic; Blopress Plus; Co-Diovan; CoAprovel; Dazid†; Dinazide; Dyazide; Dyterene†; Fortzaar; Hydrares; Hydrozide Plus; Hyperretic; Hypery†; Hyzaar; Lodoz; Mano-Ap-Es; Medeserpine Co†; Micardis Plus; Miduret†; Milorex†; Miretic; Modulan†; Moduretic; Monoplus; Moure-M; Poli-Uretic; Renase; Reser; Sefaretic; Ser-Ap-Es; ***Turk.:*** Accuzide; Adelphan-Esidrex; Aldactazide; Atacand Plus; Cibadrex; Co-Diovan; Delix Plus; Eklips Plus; Hyzaar; Inhibace Plus; Karvezide; Konveril Plus; Micardis Plus; Moduretic; Monopril Plus; Pritor Plus; Rilace Plus; Sinoretik; Triamteril; Zestoretic; ***UK:*** Accuretic; Acezide; Amil-Co; Capozide; Capto-Co; Carace Plus; Caralpha; Co-Betaloc†; Co-Diovan; CoAprovel; Cozaar Comp; Dyazide; Innozide; Kalten; Lisicostad; MicardisPlus; Moducren†; Moduret; Moduretic; Olmetec Plus; Secadrex†; Triamaxco†; Triamco; Zestoretic; ***USA:*** Accuretic; Aldactazide; Aldoril†; Apresazide†; Atacand HCT; Avalide; Benicar HCT; Candepressin Plus; Capozide; Diovan HCT; Dyazide; Esimil; Hydra-zide; Hydrap-ES†; Hydro-Serp†; Hydropres; Hydroserpine†; Hyzaar; Inderide†; Lopressor HCT; Lotensin HCT; Marpres; Maxzide; Micardis HCT; Moduretic; Monopril-HCT; Prinzide; Quinaretic; Ser-Ap-Es†; Teveten HCT; Timolide; Tri-Hydroserpine†; Uniretic; Vaseretic; Zestoretic; Ziac; ***Venez.:*** Accuretic; Aldactazida; Altace Plus; Atacand Plus; Biconcor; Blopress Plus; Capozide; Cartazid†; Co-Renitec; CoAprovel; Cormatic; Diovan HCT; Hyzaar Plus; Lisiletic; Micardis Plus; Moduretic; Monopril Plus; Nefrotal H; Priretic†; Pritor Plus; Quinaretic; Reminalet; Vasaten HCT; Ziac.

Hydroflumethiazide *(BAN, rINN)* ⊗

Hidroflumetiazida; Hydrofluméthiazide; Hydroflumethiazidum; Hydroflumetiatsidi; Hydroflumetiazid; Trifluoromethylhydrothiazide. 3,4-Dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Гидрофлуметиазид

$C_8H_8F_3N_3O_4S_2$ = 331.3.

CAS — 135-09-1.

ATC — C03AA02.

ATC Vet — QC03AA02.

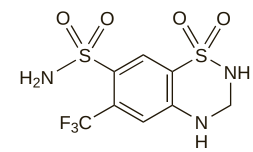

NOTE. Compounded preparations of hydroflumethiazide may be represented by the following names:

- Co-flumactone (*BAN*)—hydroflumethiazide and spironolactone in equal parts (w/w).

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Hydroflumethiazide). White or almost white, odourless or almost odourless, glistening crystals or crystalline powder. Practically insoluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

USP 31 (Hydroflumethiazide). A white to cream-coloured, odourless, finely divided crystalline powder. Very slightly soluble in water and in chloroform; soluble 1 in 39 of alcohol and 1 in 2500 of ether; freely soluble in acetone. A 1% dispersion in water has a pH of 4.5 to 7.5. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Hydroflumethiazide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a beta-phase biological half-life of about 17 hours and a metabolite with a longer half-life that is extensively bound to red blood cells. Hydroflumethiazide is excreted in the urine; its metabolite has also been detected in the urine.

◊ References.

1. Brørs O, *et al.* Pharmacokinetics of a single dose of hydroflumethiazide in health and in cardiac failure. *Eur J Clin Pharmacol* 1978; **14:** 29–37.

Uses and Administration

Hydroflumethiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis begins about 2 hours after an oral dose and has been reported to last for up to 24 hours.

In the treatment of **oedema** the usual initial dose is 50 to 100 mg daily, in one or two divided doses, reduced to a dose of 25 to 50 mg on alternate days or intermittently. Doses of up to 200 mg daily may be required by some patients. In the treatment of **hypertension** the usual dose is 25 to 50 mg daily either alone, or with other antihypertensives. An initial dose of 12.5 mg has been used.

An initial dose for children is 1 mg/kg daily, reduced for maintenance.

Preparations

BP 2008: Hydroflumethiazide Tablets;
USP 31: Hydroflumethiazide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Diucardin†; Saluron.

Multi-ingredient: ***Irl.:*** Aldactide; ***S.Afr.:*** Protensin-M; ***UK:*** Aldactide; ***USA:*** Salutensin†.

Hydroquinidine Hydrochloride

Dihydrochinidin Hydrochloride; Dihydroquinidine Hydrochloride; Hidrocloruro de dihidroquinidina; Hidroquinidina, hidrocloruro de; Hydroconchinine Hydrochloride. (8*R*,9*S*)-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrochloride.

Гидрохинидина Гидрохлорид

$C_{20}H_{26}N_2O_2,HCl = 362.9.$

CAS — 1435-55-8 (hydroquinidine); 1476-98-8 (hydroquinidine hydrochloride).

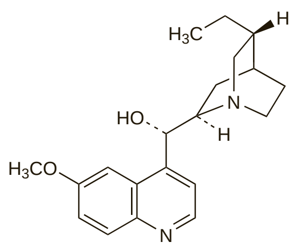

(hydroquinidine)

Pharmacopoeias. In *Fr.*

Profile

Hydroquinidine is a class Ia antiarrhythmic with actions and uses similar to those of quinidine (p.1383). It is given orally as the hydrochloride in a usual maintenance dose of 600 mg daily in divided doses.

Hydroquinidine alginate and quinalbital (the hydroquinidine salt of amobarbital) have also been used in the treatment of cardiac arrhythmias.

◊ References.

1. Hermida J-S, *et al.* Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004; **43:** 1853–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Serecor; ***Spain:*** Lentoquine.

Ibopamine *(BAN, USAN, rINN)* ⊗

Ibopamina; Ibopaminum; SB-7505; SKF-100168. 4-(2-Methylaminoethyl)-*o*-phenylene di-isobutyrate.

Ибопамин

$C_{17}H_{25}NO_4 = 307.4.$

CAS — 66195-31-1.

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

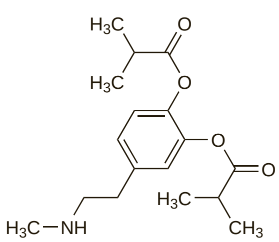

Ibopamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de ibopamina; Ibopamiinihydrokloridi; Ibopamine, Chlorhydrate d'; Ibopaminhydroklorid; Ibopamini Hydrochloridum.

Ибопамина Гидрохлорид

$C_{17}H_{25}NO_4,HCl = 343.8.$

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Ibopamine should not be used in patients with severe heart failure in whom, similarly to xamoterol (p.1433), it has been reported to increase the risk of death.

Effects on the cardiovascular system. A multicentre study (PRIME II) of the use of ibopamine in patients with severe (NYHA class III or IV) heart failure was stopped early when it was found that the drug was associated with an increased risk of death.[1] Subgroup analysis found that use of an antiarrhythmic drug was independently predictive of an adverse effect in ibopamine-treated patients. Excess mortality in heart failure has also been reported with dobutamine and xamoterol, and with flosequinan and the phosphodiesterase inhibitors amrinone, enoximone, milrinone, and vesnarinone, all of which produce positive inotropic effects through catecholamine-receptor stimulation or post-receptor pathway stimulation.[2] The association with antiarrhythmic therapy in the ibopamine study might reflect an interaction with amiodarone, the most commonly used antiarrhythmic in this study, or might simply be a marker for patients at risk of ibopamine-induced tachyarrhythmias.

1. Hampton JR, *et al.* Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997; **349:** 971–7.
2. Niebauer J, Coats AJS. Treating chronic heart failure: time to take stock. *Lancet* 1997; **349:** 966–7.

Interactions

As for Sympathomimetics, p.1407. It has been recommended that ibopamine should not be given to patients taking amiodarone in the light of the increased mortality seen in the PRIME II study in patients given both drugs (see above), although it is not clear that this represents a genuine interaction.

Uses and Administration

Ibopamine is a prodrug and is rapidly converted to its active metabolite, epinine, which is a peripheral dopamine agonist and sympathomimetic (p.1408). At low doses its dopaminergic effects predominate, leading to vasodilatation and a weak positive inotropic effect; at high concentrations it has a stimulant action on alpha and beta adrenoceptors.

Ibopamine is used in the management of mild heart failure (p.1165). It is given as the hydrochloride but doses are often expressed in terms of the base; 111.9 mg of hydrochloride is equivalent to about 100 mg of base. Doses of 100 to 200 mg orally two or three times daily have been used.

Ibopamine is also used topically as a mydriatic (p.1874) in the form of eye drops containing ibopamine hydrochloride 2%.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Scandine; ***Braz.:*** Escandine†; ***Ital.:*** Scandine; Trazyl; ***Neth.:*** Inopamil; ***Spain:*** Escandine†.

Ibutilide Fumarate *(BANM, USAN, rINNM)*

Fumarato de ibutilida; Ibutilide, Fumarate d'; Ibutilidi Fumaras; U-70226E. (±)-4′-[4-(Ethylheptylamino)-1-hydroxybutyl]methanesulfonanilide fumarate (2:1).

Ибутилида Фумарат

$(C_{20}H_{36}N_2O_3S)_2,C_4H_4O_4 = 885.2.$

CAS — 122647-31-8 (ibutilide); 122647-32-9 (ibutilide fumarate).

ATC — C01BD05.

ATC Vet — QC01BD05.

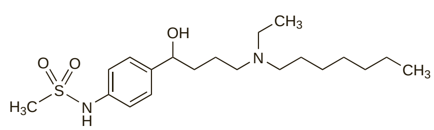

(ibutilide)

Adverse Effects

Adverse cardiovascular effects associated with ibutilide include heart block, hypotension, hypertension, and bradycardia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias, including torsade de pointes. Other adverse effects include nausea and vomiting.

Effects on the heart. Ibutilide prolongs the QT interval and has been associated with torsade de pointes, particularly in women.[1] A small study[2] suggested that this effect could be prevented by magnesium sulfate (p.1679), which might therefore be suitable for use as prophylaxis. Although magnesium could theoretically reduce the antiarrhythmic effect of ibutilide as well as the proarrhythmic effect, a retrospective study[3] found that the rate of cardioversion was higher in patients given both ibutilide and magnesium than in those given ibutilide alone, an effect confirmed in a later study.[4]

1. Gowda RM, *et al.* Female preponderance in ibutilide-induced torsade de pointes. *Int J Cardiol* 2004; **95:** 219–22.
2. Caron MF, *et al.* Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. *Pharmacotherapy* 2003; **23:** 296–300.
3. Kalus JS, *et al.* Impact of prophylactic i.v. magnesium on the efficacy of ibutilide for conversion of atrial fibrillation or flutter. *Am J Health-Syst Pharm* 2003; **60:** 2308–12.
4. Tercius AJ, *et al.* Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. *Pacing Clin Electrophysiol* 2007; **30:** 1331–5.

Effects on the kidneys. Acute renal failure with biopsy evidence of acute tubular necrosis developed in a 52-year-old man shortly after he received 2 doses of ibutilide for an episode of atrial flutter.[1] Renal function returned to normal after 4 sessions of haemodialysis.

1. Franz M, *et al.* Acute renal failure after ibutilide. *Lancet* 1999; **353:** 467.

Precautions

ECG monitoring should be carried out during, and for at least 4 hours after, ibutilide infusion, and the infusion should be stopped if the QT interval becomes markedly prolonged. Electrolyte abnormalities should be corrected before treatment is started.

Interactions

Use of ibutilide with other antiarrhythmics or drugs that prolong the QT interval should be avoided.

Magnesium. For the synergistic effect of magnesium and ibutilide in producing cardioversion, see Effects on the Heart, above.

Pharmacokinetics

Ibutilide is widely distributed in the body after intravenous infusion. It has low plasma protein binding (about 40%) and undergoes extensive metabolism in the liver to form several metabolites. Ibutilide is excreted mainly in the urine, as metabolites and a small amount of unchanged drug (about 7%), with about 19% being excreted in the faeces. The elimination half-life is reported to range from 2 to 12 hours.

Uses and Administration

Ibutilide is a class III antiarrhythmic (p.1153) used for the acute treatment of atrial fibrillation or flutter (p.1160).

Ibutilide is given intravenously as the fumarate. For the termination of atrial fibrillation or flutter, ibutilide fumarate is given as a single dose of 1 mg in patients weighing 60 kg and over, or 10 micrograms/kg in patients weighing less than 60 kg, infused over 10 minutes; the infusion should be stopped as soon as the arrhythmia is terminated. If the arrhythmia persists 10 minutes after completion of the infusion, a second infusion of the same dose may be given.

◊ References.

1. Foster RH, *et al.* Ibutilide: a review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. *Drugs* 1997; **54:** 312–30.
2. Granberry MC. Ibutilide: a new class III antiarrhythmic agent. *Am J Health-Syst Pharm* 1998; **55:** 255–60.
3. Howard PA. Ibutilide: an antiarrhythmic agent for the treatment of atrial fibrillation or flutter. *Ann Pharmacother* 1999; **33:** 38–47.
4. Doggrell SA, Hancox JC. Ibutilide—recent molecular insights and accumulating evidence for use in atrial flutter and fibrillation. *Expert Opin Invest Drugs* 2005; **14:** 655–69.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Corvert; ***Cz.:*** Corvert†; ***Fin.:*** Corvert; ***Fr.:*** Corvert†; ***Gr.:*** Corvert; ***Ital.:*** Corvert; ***Neth.:*** Corvert; ***Norw.:*** Corvert; ***Swed.:*** Corvert; ***Switz.:*** Corvert; ***USA:*** Corvert.

Idraparinux Sodium *(USAN, rINN)*

Idraparinux sódico; Idraparinux Sodique; Idraparinuxum Natricum; Org-34006; SANORG-34006; SR-34006. Methyl *O*-2,3,4-tri-*O*-methyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside nonasodium.

Идрапаринукс Натрия

$C_{38}H_{55}Na_9O_{49}S_7 = 1727.2.$

CAS — 162610-17-5 (idraparinux); 149920-56-9 (idraparinux sodium).

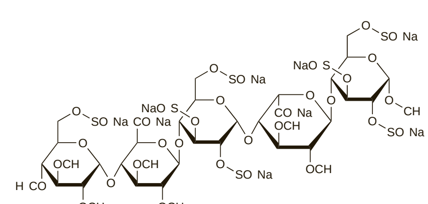

Profile

Idraparinux is a factor Xa inhibitor under investigation in the management of thromboembolism.

◊ References.

1. Buller HR, *et al.* van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007; **357:** 1094–1104.
2. Buller HR, *et al.* van Gogh Investigators. Extended prophylaxis of venous thromboembolism with idraparinux. *N Engl J Med* 2007; **357:** 1105–12.
3. Bousser MG, *et al.* Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008; **371:** 315–21.
4. Prandoni P, *et al.* Idraparinux: review of its clinical efficacy and safety for prevention and treatment of thromboembolic disorders. *Expert Opin Invest Drugs* 2008; **17:** 773–7.

Ifenprodil Tartrate *(rINNM)*

Ifenprodil, Tartrate d'; Ifenprodili Tartras; RC-61-91; Tartrato de ifenprodil. (±)-2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)propan-1-ol tartrate.

Ифенпродила Тартрат

$(C_{21}H_{27}NO_2)_2,C_4H_6O_6$ = 801.0.

CAS — 23210-56-2 (ifenprodil); 23210-58-4 (ifenprodil tartrate).

ATC — C04AX28.

ATC Vet — QC04AX28.

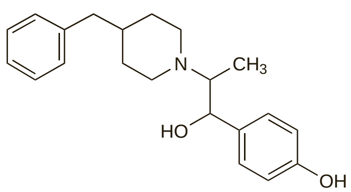

(ifenprodil)

Pharmacopoeias. In *Jpn.*

Profile

Ifenprodil tartrate is a vasodilator, with alpha-adrenoceptor blocking properties, used in peripheral vascular disease (p.1178). It is given in usual oral doses of 40 to 60 mg daily, and has also been given by deep intramuscular injection, slow intravenous injection, or intravenous infusion.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Vadilex.

Iloprost *(BAN, USAN, rINN)*

Ciloprost; Iloprosti; Iloprostum; ZK-36374; ZK-00036374. (*E*)-(3a*S*,4*R*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),}$ -pentalenevaleric acid.

Илопрост

$C_{22}H_{32}O_4$ = 360.5.

CAS — 73873-87-7; 78919-13-8.

ATC — B01AC11.

ATC Vet — QB01AC11.

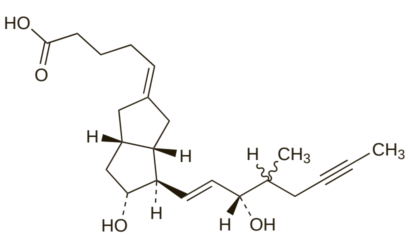

Iloprost Trometamol *(BANM, rINNM)*

Ciloprost Tromethamine; Iloprost Trométamol; Iloprost Tromethamine; Iloprostum Trometamolum.

Илопрост Трометамол

$C_{22}H_{32}O_4,C_4H_{11}NO_3$ = 481.6.

ATC — B01AC11.

ATC Vet — QB01AC11.

Adverse Effects and Precautions

As for Epoprostenol, p.1279. Inhaled iloprost may cause cough.

Effects on the cardiovascular system. Hypotension was observed[1] in 2 of 6 patients given iloprost. Both patients recovered rapidly when iloprost was stopped, although one required intravenous atropine to correct sinus bradycardia.

Evidence of myocardial ischaemia was reported in 4 of 33 patients with coronary artery disease during iloprost infusion.[2] The same authors[3] noted a similar effect in 4 of 28 patients with stable angina in a subsequent study. According to one study,[4] there might be an increased risk of thromboembolism in some patients given iloprost, due to platelet activation and enhanced coagulation.

1. Upward JW, *et al.* Hypotension in response to iloprost, a prostacyclin analogue. *Br J Clin Pharmacol* 1986; **21:** 241–3.
2. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.
3. Bugiardini R, *et al.* Effects of iloprost, a stable prostacyclin analog, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol* 1986; **58:** 453–9.
4. Kovacs IB, *et al.* Infusion of a stable prostacyclin analogue, iloprost, to patients with peripheral vascular disease: lack of antiplatelet effect but risk of thromboembolism. *Am J Med* 1991; **90:** 41–6.

Pregnancy. For reference to the successful use of iloprost in pregnancy see Pulmonary Hypertension, under Uses and Administration, below.

Interactions

Iloprost may increase the effect of other vasodilators and antihypertensives. The use of iloprost with other inhibitors of platelet aggregation may increase the risk of bleeding.

Pharmacokinetics

On intravenous infusion iloprost is rapidly cleared from the plasma by oxidation. About 80% of the metabolites are excreted in urine and 20% in the bile.

Uses and Administration

Iloprost, a vasodilator and platelet aggregation inhibitor, is a stable analogue of the prostaglandin epoprostenol (prostacyclin). It is given as the trometamol salt in the treatment of peripheral vascular disease and pulmonary hypertension but doses are described in terms of iloprost; 1.3 nanograms of iloprost trometamol is equivalent to about 1 nanogram of iloprost.

The usual dose for peripheral vascular disease is the equivalent of iloprost 0.5 to 2 nanograms/kg per minute for 6 hours daily by intravenous infusion. The course of treatment may be up to 4 weeks. For pulmonary hypertension, the dose is 1 to 8 nanograms/kg per minute for 6 hours daily; alternatively, iloprost may be given by nebulised solution at a dose of 2.5 or 5 micrograms inhaled 6 to 9 times daily. Doses should be reduced in patients with hepatic or renal impairment (see below).

Oral iloprost is under investigation.

◊ Reviews.

1. Grant SM, Goa KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. *Drugs* 1992; **43:** 889–924.

Administration in hepatic or renal impairment. The dose of intravenous iloprost should be reduced, and may need to be halved, in patients with liver cirrhosis or renal impairment requiring dialysis. In hepatic impairment, the initial dose of inhaled iloprost should be 2.5 micrograms given at intervals of at least 3 hours to a maximum of 6 times daily; the dose may be cautiously increased or given more frequently according to patient response.

Peripheral vascular disease. Prostaglandins, including iloprost,[1-10] have been used in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy. Systematic review[10] suggests that intravenous iloprost produces prolonged benefit in Raynaud's phenomenon secondary to scleroderma. The benefits of oral iloprost are less clear. It is also unclear whether iloprost infusion is of benefit in occlusive peripheral arterial disease due to atherosclerosis: although a meta-analysis of (conflicting) controlled trials did suggest an effect,[6] firm conclusions are difficult.

1. Waller PC, *et al.* Placebo controlled trial of iloprost in patients with stable intermittent claudication. *Br J Clin Pharmacol* 1986; **21:** 562P–563P.
2. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
3. Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. *Lancet* 1990; **335:** 555–7.
4. Zahavi J, *et al.* Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost. *Lancet* 1993; **342:** 862.
5. Tait IS, *et al.* Management of intra-arterial injection injury with iloprost. *Lancet* 1994; **343:** 419.
6. Loosemore TM, *et al.* A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994; **13:** 133–42.
7. Wigley FM, *et al.* Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum* 1998; **41:** 670–7.
8. Black CM, *et al.* Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998; **37:** 952–60.
9. Scorza R, *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001; **19:** 503–8.
10. Pope J, *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 16/06/05).

Pulmonary hypertension. Epoprostenol is an accepted part of the management of pulmonary hypertension (p.1179) and the use of iloprost, a stable analogue, has been studied. Inhaled iloprost may have a role;[1] it was found[2] to improve walking-test distances, reduce severity of heart failure, and stabilise haemodynamic measures in a 12-week study of patients with severe pulmonary hypertension, while long-term treatment of at least 1 year has been reported to have sustained beneficial effects.[3] Iloprost has also been used successfully in a few cases to manage pulmonary hypertension in pregnant women.[4] There are also reports of effective combination therapy using inhaled iloprost with intravenous epoprostenol,[5] oral sildenafil,[6] or oral bosentan.[7] Continuous intravenous infusion[8] has also been tried with beneficial results over several weeks, and short-term intravenous infusion for 7 days[9] has been successfully used for pulmonary hypertension after pulmonary thromboendarterectomy.

1. Baker SE, Hockman RH. Inhaled iloprost in pulmonary arterial hypertension. *Ann Pharmacother* 2005; **39:** 1265–73.
2. Olschewski H, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; **347:** 322–9.
3. Hoeper MM, *et al.* Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; **342:** 1866–70.
4. Elliot CA, *et al.* The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. *Eur Respir J* 2005; **26:** 168–73.
5. Petkov V, *et al.* Aerosolised iloprost improves pulmonary haemodynamics in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment. *Thorax* 2001; **56:** 734–6.
6. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
7. McLaughlin VV, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; **174:** 1257–63.
8. Higenbottam TW, *et al.* Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998; **79:** 175–9.
9. Hsu H-H, *et al.* Short-term intravenous iloprost for treatment of reperfusion lung oedema after pulmonary thromboendarterectomy. *Thorax* 2007; **62:** 459–61.

Thrombotic microangiopathies. For reports of the use of iloprost in patients with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, see under Epoprostenol, p.1281.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Ilomedine†; Ventavis†; ***Austria:*** Ilomedin; ***Chile:*** Ventavis; ***Cz.:*** Ilomedin; Ventavis; ***Denm.:*** Ilomedin; Ventavis; ***Fin.:*** Ilomedin; Ventavis; ***Fr.:*** Ilomedine; Ventavis; ***Ger.:*** Ilomedin; Ventavis; ***Gr.:*** Ilomedin; Ventavis; ***Hong Kong:*** Ilomedin; Ventavis; ***Hung.:*** Ilomedin; Ventavis; ***Indon.:*** Ventavis; ***Irl.:*** Ventavis; ***Israel:*** Ilomedin; ***Ital.:*** Endoprost; Ventavis; ***Malaysia:*** Ilomedin†; ***Neth.:*** Ilomedine; Ventavis; ***Norw.:*** Ilomedin; Ventavis; ***NZ:*** Ilomedin; ***Pol.:*** Ilomedin; Ventavis; ***Port.:*** Ilomedin; Ventavis; ***Singapore:*** Ventavis; ***Spain:*** Ilocit; Ilomedin; Ventavis; ***Swed.:*** Ilomedin; Ventavis; ***Switz.:*** Ilomedin; ***Thai.:*** Ilomedin; ***Turk.:*** Ilomedin; ***UK:*** Ventavis; ***USA:*** Ventavis.

Imidapril Hydrochloride *(BANM, rINNM)*

Hidrocloruro de imidapril; Imidapriilihydrokloridi; Imidapril, Chlorhydrate d'; Imidaprilhydroklorid; Imidaprili Hydrochloridum; TA-6366. (*S*)-3-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1-methyl-2-oxoimidazoline-4-carboxylic acid hydrochloride.

Имидаприла Гидрохлорид

$C_{20}H_{27}N_3O_6,HCl$ = 441.9.

CAS — 89371-37-9 (imidapril); 89396-94-1 (imidapril hydrochloride).

ATC — C09AA16.

ATC Vet — QC09AA16.

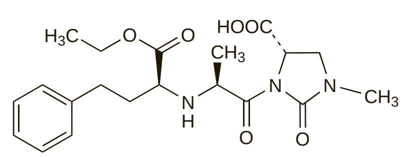

(imidapril)

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Imidapril acts as a prodrug of the diacid imidaprilat, its active metabolite. After oral doses, imidapril is rapidly but incompletely absorbed; absorption is about 70% and is reduced in the presence of food. Imidapril is metabolised in the liver to imidaprilat. The bioavailability of imidaprilat is about 42% after oral doses of imidapril, and peak plasma concentrations of imidaprilat are reached in about 7 hours. Both imidapril and imidaprilat are moderately bound to plasma proteins. About 40% of an oral dose is excreted in the urine, the rest in the faeces. The terminal half-life of imidaprilat is more than 24 hours. Imidapril and imidaprilat are removed by haemodialysis.

◊ References.

1. Hoogkamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with impaired liver function. *Eur J Clin Pharmacol* 1997; **51:** 489–91.
2. Hoogkamer JFW, *et al.* Pharmacokinetics of imidapril and its active metabolite imidaprilat following single dose and during steady state in patients with chronic renal failure. *Eur J Clin Pharmacol* 1998; **54:** 59–61.
3. Harder S, *et al.* Single dose and steady state pharmacokinetics and pharmacodynamics of the ACE-inhibitor imidapril in hypertensive patients. *Br J Clin Pharmacol* 1998; **45:** 377–80.
4. Tsuruoka S, *et al.* Clearance of imidapril, an angiotensin-converting enzyme inhibitor, during hemodialysis in hypertensive renal failure patients: comparison with quinapril and enalapril. *J Clin Pharmacol* 2007; **47:** 259–63.

Uses and Administration

Imidapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171). Imidapril owes its activity to imidaprilat, to which it is converted after oral doses. The maximum haemodynamic effect occurs 6 to 8 hours after a dose, although the full effect may not develop for several weeks during chronic dosing. Imidapril is given orally as the hydrochloride.

In the treatment of hypertension, the usual initial dose of imidapril hydrochloride is 5 mg once daily, before food. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily should be used in the elderly, in patients with renal or hepatic impairment, or in those receiving a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before imidapril is started and resumed later if necessary. The usual maintenance dose is 10 mg daily, although up to 20 mg daily may be given if required. The maximum dose for elderly patients is 10 mg daily.

◊ Reviews.

1. Robinson DM, *et al.* Imidapril: a review of its use in essential hypertension, type 1 diabetic nephropathy and chronic heart failure. *Drugs* 2007; **67:** 1359–78.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Tanatril; ***Austria:*** Tanatril; ***Cz.:*** Tanatril; ***Fin.:*** Tanatril; ***Fr.:*** Tanatril; ***Ger.:*** Tanatril; ***Gr.:*** Tanatril; ***Hong Kong:*** Tanatril; ***India:*** Tanatril; ***Indon.:*** Tanapress; ***Jpn:*** Novarok†; Tanatril; ***Malaysia:*** Tanatril; ***Philipp.:*** Norten; Vascor; ***Pol.:*** Tanatril; ***Port.:*** Cardipril; Tanatril†; ***Singapore:*** Tanatril; ***Spain:*** Hipertene; ***Thai.:*** Tanatril; ***UK:*** Tanatril.

Multi-ingredient: ***Philipp.:*** Norplus; Vascoride.

Indapamide *(BAN, USAN, rINN)* ⊗

Indapamid; Indapamida; Indapamidi; Indapamidum; SE-1520. 4-Chloro-*N*-(2-methylindolin-1-yl)-3-sulphamoylbenzamide.

Индапамид

$C_{16}H_{16}ClN_3O_3S$ = 365.8.

CAS — 26807-65-8 (anhydrous indapamide).

ATC — C03BA11.

ATC Vet — QC03BA11.

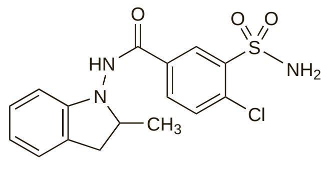

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Indapamide). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 31 (Indapamide). A white to off-white crystalline powder. Practically insoluble in water; soluble in alcohol, in glacial acetic acid, in acetonitrile, in ethyl acetate, and in methyl alcohol; very slightly soluble in chloroform and in ether.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Effects on the blood. A 58-year-old woman[1] had bleeding from the mucous membrane of the tongue 18 months after starting treatment with a modified-release form of indapamide; she was found to have mild thrombocytopenia, and petechiae were observed. After withdrawal of the drug, bleeding stopped immediately; the platelet count returned to normal within 10 days and the skin lesions faded quickly.

1. Hasanova EA, Agasiyeva NE. Bleeding associated with indapamide SR therapy. *Ann Pharmacother* 2005; **39:** 199–200.

Effects on carbohydrate and lipid metabolism. Several studies have reported no changes in blood-glucose concentrations during indapamide treatment,[1-3] although elevated concentrations have been reported in individual patients.[4,5] There have been reports of increases in total cholesterol[2] and of no change.[3] No adverse biochemical changes were found in studies[6] of a modified-release preparation.

1. Velussi M, *et al.* Treatment of mild-to-moderate hypertension with indapamide in type II diabetics: midterm (six months) evaluation. *Curr Ther Res* 1988; **44:** 1076–86.
2. Prisant LM, *et al.* Biochemical, endocrine, and mineral effects of indapamide in black women. *J Clin Pharmacol* 1990; **30:** 121–6.
3. Leonetti G, *et al.* Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension. *Am J Cardiol* 1990; **65:** 674–714.
4. Slotkoff L. Clinical efficacy and safety of indapamide in the treatment of edema. *Am Heart J* 1983; **106:** 233–7.
5. Beling S, *et al.* Long term experience with indapamide. *Am Heart J* 1983; **106:** 258–62.
6. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Safety* 2001; **24:** 1155–65.

Effects on electrolyte balance. It has been claimed that indapamide produces few adverse biochemical effects at the usual dose of 2.5 mg daily. However, by 2002, 164 cases of hyponatraemia had been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1], of which 68 also described hypokalaemia. Most patients were elderly women. A review[2] of some of these cases suggested that hyponatraemia was more commonly reported with indapamide than with chlorothiazide, although it was pointed out[3] that the true incidence cannot be determined from spontaneous reports. ADRAC recommends that indapamide should be used cautiously. It may be that indapamide has no clinical advantage over low-dose thiazide diuretics.

1. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Indapamide and hyponatraemia. *Aust Adverse Drug React Bull* 2002; **21:** 11. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.htm (accessed 06/07/04)
2. Chapman MD, *et al.* Hyponatraemia and hypokalaemia due to indapamide. *Med J Aust* 2002; **176:** 219–21.
3. Howes LG. Hyponatraemia and hypokalaemia caused by indapamide. *Med J Aust* 2002; **177:** 53–4.

Effects on the kidneys. Acute interstitial nephritis was associated with indapamide treatment in a 74-year-old patient.[1]

1. Newstead CG, *et al.* Interstitial nephritis associated with indapamide. *BMJ* 1990; **300:** 1344.

Effects on the skin. Sixteen cases of skin rash attributed to indapamide had been reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs.[1] All patients had taken indapamide 2.5 mg daily for hypertension. The skin rash was accompanied by fever in 5 cases. In all cases the rash subsided within 14 days of withdrawal, and 11 patients subsequently took thiazides, furosemide, or clopamide without recurrence. Among 188 cases of skin rash attributed to indapamide reported to the WHO Collaborating Centre for International Drug Monitoring were 4 cases of erythema multiforme and 2 of epidermal necrolysis. A further case of toxic epidermal necrolysis was reported by independent authors.[2]

1. Stricker BHC, Biriell C. Skin reactions and fever with indapamide. *BMJ* 1987; **295:** 1313–14.
2. Black RJ, *et al.* Toxic epidermal necrolysis associated with indapamide. *BMJ* 1990; **301:** 1280–1.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Elimination is biphasic with a half-life in whole blood of about 14 hours. Indapamide is strongly bound to red blood cells. It is extensively metabolised. About 60 to 70% of the dose has been reported to be excreted in the urine; only about 5 to 7% is excreted unchanged. About 16 to 23% of dose is excreted in the faeces. Indapamide is not removed by haemodialysis but does not accumulate in patients with renal impairment.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Uses and Administration

Indapamide is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is used for hypertension (p.1171), and also for oedema, including that associated with heart failure (p.1165).

In some countries indapamide is described as the hemihydrate. In the treatment of **hypertension** the usual oral dose is 1.25 to 2.5 mg once daily, either alone, or with other antihypertensives; a modified-release preparation may be given in a dose of 1.5 mg daily. At higher doses the diuretic effect may become apparent without appreciable additional antihypertensive effect although US licensed product information suggests that the dose may be increased to 5 mg after 4 weeks. In the treatment of **oedema** the usual dose is 2.5 mg once daily increasing to 5 mg daily after 1 week if necessary.

◊ Reviews.

1. Chaffman M, *et al.* Indapamide: a review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs* 1984; **28:** 189–235.
2. Robinson DM, Wellington K. Indapamide sustained release: a review of its use in the treatment of hypertension. *Drugs* 2006; **66:** 257–71.

Preparations

BP 2008: Indapamide Tablets;
USP 31: Indapamide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bajaten; Duremid; Natrilix; Noranat; ***Austral.:*** Dapa-Tabs; Indahexal; Insig; Napamide; Natrilix; ***Austria:*** Fludex; ***Belg.:*** Docindapa; Fludex; ***Braz.:*** Indapen; Natrilix; ***Canad.:*** Lozide; ***Chile:*** Indapress; Natrilix; ***Cz.:*** Indap; Rawel; Tertensif; ***Denm.:*** Fludex†; Indacar; Natrilix; ***Fin.:*** Natrilix; ***Fr.:*** Fludex; ***Ger.:*** Inda-Puren; Natrilix; Sicco†; ***Gr.:*** Dixamid†; Fludex; Magniton-R; Transipen; ***Hong Kong:*** Agelan†; Dapa-Tabs; Diflerix; Frumeron; Indalix; Millibar; Natrilix; ***Hung.:*** Apadex; Pretanix; Rawel; ***India:*** Indicontin; Inditor; Lorvas; Natrilix; ***Indon.:*** Natrilix; ***Irl.:*** Agelan†; Inamide†; Natrilix; ***Israel:*** Pamid; ***Ital.:*** Damide; Indaflex; Indamol; Indolin†; Ipamix; Millibar; Natrilix; Pressural; Veroxil; ***Malaysia:*** Dapa; Diflerix; Napamide; Natrilix; Rinalix†; ***Mex.:*** Natrilix; ***Neth.:*** Fludex; ***NZ:*** Napamide; Naplin†; Natrilix; ***Philipp.:*** Natrilix; ***Pol.:*** Apo-Indap; Diuresin; Indapen; Indapres; Indapsan; Indix; Ipres; Rawel; Tertensif; ***Port.:*** Arifon; Fludex; Fluidema; Tandix; Vasodipin; ***Rus.:*** Akripamide (Акрипамид); Arifon (Арифон); Arindap (Ариндап); Indap (Индап); Indiur (Индиур); Ionik (Ионик); Rawel (Равел); Retapres (Ретапрес); ***S.Afr.:*** Catexan; Dapamax; Daptril; Hydro-Less; Indalix; Lixamide; Natrilix; ***Singapore:*** Dapa-Tabs; Millibar†; Napamide; Natrilix; Rinalix; ***Spain:*** Extur; Tertensif; ***Switz.:*** Fludapamide; Fludex; ***Thai.:*** Frumeron; Inpamide; Napamide; Natrilix; ***Turk.:*** Flubest; Fludex; Fludin; Flupamid; Flutans; Indamid; Indapen; Indurin; ***UAE:*** Indanorm; ***UK:*** Natrilix; Nindaxa†; ***USA:*** Lozol; ***Venez.:*** Natrilix.

Multi-ingredient: ***Arg.:*** Bipreterax; Preterax; ***Austral.:*** Coversyl Plus; ***Austria:*** Delapride; Predonium; Preterax; ***Belg.:*** Bi Preterax; Coversyl Plus; Preterax; ***Braz.:*** Coversyl Plus; ***Canad.:*** Coversyl Plus; Preterax; ***Cz.:*** Noliprel; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.:*** Coversyl Comp; ***Fin.:*** Coversyl Comp; ***Fr.:*** Bipreterax; Preterax; ***Ger.:*** Coversum Combi; Preterax; ***Gr.:*** Dinapres; Preterax; ***Hong Kong:*** Predonium; ***Hung.:*** Armix Komb; Armix Prekomb; Co-Prenessa; Coverex Komb; Coverex Prekomb; Noliprel†; Noriplex†; ***India:*** Coversyl Plus; Perigard D; Perigard DF; Tenolol-D†; ***Irl.:*** Bipreterax; Coversyl Plus; Preterax; ***Ital.:*** Atinorm; Delapride; Dinapres; Nor-Pa; Normopress; Prelectal; Preterax; ***Malaysia:*** Coversyl Plus; ***Mex.:*** Preterax; ***Neth.:*** Coversyl Plus; Predonium; Preterax; ***NZ:*** Coversyl Plus; Predonium; ***Philipp.:*** Bi-Preterax; Preterax; ***Pol.:*** Noliprel; Prestarium Plus; ***Port.:*** Bi Predonium; Bi Preterax; Predonium; Preterax; ***Rus.:*** Enzix (Энзикс); Noliprel (Нолипрел); Sonoprel (Сонопрел); ***S.Afr.:*** Bipreterax; Coversyl Plus; Preterax; Prexum Plus; ***Singapore:*** Coversyl Plus; Preterax; ***Spain:*** Bipredonium†; Bipreterax; Preterax; ***Switz.:*** Coversum Combi; Preterax; ***Turk.:*** Coversyl Plus; Preterax; ***UK:*** Coversyl Plus; ***Venez.:*** Bipreterax; Preterax.

Indenolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de indenolol; Indénolol, Chlorhydrate d'; Indenololi Hydrochloridum; Sch-28316Z (indenolol); YB-2.

Инденолола Гидрохлорид

$C_{15}H_{21}NO_2$,HCl = 283.8.

CAS — 60607-68-3 (indenolol); 68906-88-7 (indenolol hydrochloride).

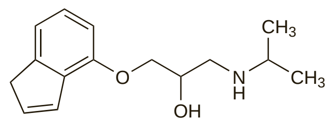

(indenolol)

Description. Indenolol hydrochloride is a 2:1 tautomeric mixture of 1-(inden-7-yloxy)-3-isopropylaminopropan-2-ol hydrochloride and 1-(inden-4-yloxy)-3-isopropylaminopropan-2-ol hydrochloride.

Pharmacopoeias. In *Jpn.*

Profile

Indenolol is a non-cardioselective beta blocker (p.1225). It is reported to possess potent membrane-stabilising properties and intrinsic sympathomimetic activity.

Indenolol has been used orally as the hydrochloride in the management of various cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Securpres†.

Indobufen *(rINN)*

Indobufén; Indobufène; Indobufenum; K-3920. (±)-2-[4-(1-Oxoisoindolin-2-yl)phenyl]butyric acid.

Индобуфен

$C_{18}H_{17}NO_3$ = 295.3.

CAS — 63610-08-2.
ATC — B01AC10.
ATC Vet — QB01AC10.

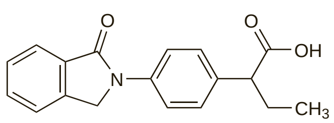

Profile

Indobufen is an inhibitor of platelet aggregation used in various thromboembolic disorders (p.1187) in oral doses of 200 to 400 mg daily given in 2 divided doses. For patients over the age of 65, the dose should be reduced to 100 to 200 mg daily. Doses should also be reduced in renal impairment (see below). Indobufen has also been given parenterally as the sodium salt.

◊ References.

1. Wiseman LR, *et al.* Indobufen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. *Drugs* 1992; **44:** 445–64.
2. Bhana N, McClellan KJ. Indobufen: an updated review of its use in the management of atherothrombosis. *Drugs Aging* 2001; **18:** 369–88.

Administration in renal impairment. In patients with renal impairment the dose of indobufen should be reduced to 100 mg twice daily; it should not be used if the creatinine clearance is under 30 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ibustrin; ***Cz.:*** Ibustrin; ***Ital.:*** Ibustrin; ***Mex.:*** Ibustrin; ***Pol.:*** Ibustrin; ***Port.:*** Ibustrin; ***Venez.:*** Ibustrin.

Indoramin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de indoramina; Indoramine, Chlorhydrate d'; Indoramini Hydrochloridum; Wy-21901 (indoramin). *N*-[1-(2-Indol-3-ylethyl)-4-piperidyl]benzamide hydrochloride.

Индорамина Гидрохлорид

$C_{22}H_{25}N_3O$,HCl = 383.9.

CAS — 26844-12-2 (indoramin); 33124-53-7 (indoramin hydrochloride); 38821-52-2 (indoramin hydrochloride).
ATC — C02CA02.
ATC Vet — QC02CA02.

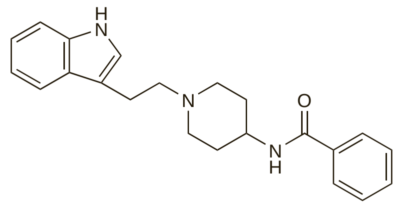

(indoramin)

Pharmacopoeias. In *Br.*
BP 2008 (Indoramin Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; sparingly soluble in alcohol; very slightly soluble in ether; soluble in methyl alcohol. A 2% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects, Treatment, and Precautions

The most common adverse effects in patients receiving indoramin are sedation and dizziness; dry mouth, nasal congestion, headache, fatigue, depression, weight gain (almost certainly due to fluid retention), and failure of ejaculation may also occur. Tachycardia does not seem to be a problem with therapeutic doses but orthostatic hypotension may occur and may produce syncope. Extrapyramidal disturbances have been reported.

After overdosage, coma, convulsions, and hypotension may occur; hypothermia has been reported in *animals.* In acute poisoning appropriate symptomatic and supportive care should be given; if the patient presents within 1 hour, activated charcoal may be considered.

Indoramin should be avoided in patients with heart failure; it has been recommended that incipient heart failure should be controlled before giving indoramin. Caution should be observed in patients with hepatic or renal impairment, a history of depression, epilepsy, or Parkinson's disease. Elderly patients may respond to lower doses.

Because indoramin can cause drowsiness care should be taken in patients who drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Surgical Procedures, under Precautions for Tamsulosin Hydrochloride, p.2197.

Effects on mental function. Sleep disturbances and vivid dreams were reported during a study in hypertensive patients when indoramin was added to therapy with a thiazide diuretic and a beta blocker.[1]

1. Marshall AJ, *et al.* Evaluation of indoramin added to oxprenolol and bendrofluazide as a third agent in severe hypertension. *Br J Clin Pharmacol* 1980; **10:** 217–21.

Overdosage. A 43-year-old woman with a long history of heavy alcohol intake died after taking 100 tablets of indoramin 25 mg.[1] The main clinical features were deep sedation, respiratory depression, hypotension, and convulsions. Although the hypotension was satisfactorily controlled the CNS effects were resistant to treatment and proved fatal. Other clinical features included areflexia, metabolic acidosis, tachycardia, and later bradyarrhythmias.

1. Hunter R. Death due to overdose of indoramin. *BMJ* 1982; **285:** 1011.

Interactions

The hypotensive effects of indoramin may be enhanced by diuretics and other antihypertensives. It has been reported that the ingestion of alcohol can increase the rate and extent of absorption and the sedative effects of indoramin (see below) and that indoramin should not be given to patients already receiving MAOIs.

Alcohol. In a study[1] in 9 healthy subjects alcohol 500 mg/kg significantly enhanced plasma-indoramin concentrations after an oral dose of 50 mg. The effect was most marked in the early period, corresponding to the absorptive phase. The mean maximum plasma-indoramin concentration was increased from 15.0 to 23.7 nanograms/mL by alcohol; the area under the concentration/time curve was increased by 25%. Alcohol did not affect the pharmacokinetics of intravenous indoramin. The results suggest that alcohol increases indoramin bioavailability either by enhancing absorption or reducing first-pass metabolism. The combination was more sedative than either drug alone.

1. Abrams SML, *et al.* Pharmacokinetic interaction between indoramin and ethanol. *Hum Toxicol* 1989; **8:** 237–41.

Pharmacokinetics

Indoramin is readily absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism. It is reported to be about 90% bound to plasma proteins. It has a half-life of about 5 hours which is reported to be prolonged in elderly patients. It is extensively metabolised and is excreted mainly as metabolites in the urine and faeces. There is evidence to suggest that some metabolites may have some alpha-adrenoceptor blocking activity.

The elderly. The plasma half-life of indoramin in 5 healthy elderly subjects following a single oral dose ranged from 6.6 to 32.8 hours with a mean of 14.7 hours.[1] The increased half-life may have been caused by reduced clearance in elderly patients.

1. Norbury HM, *et al.* Pharmacokinetics of oral indoramin in elderly and middle-aged female volunteers. *Eur J Clin Pharmacol* 1984; **27:** 247–9.

Uses and Administration

Indoramin is a selective and competitive $alpha_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376); it is also reported to have membrane-stabilising properties and to be a competitive antagonist at histamine H_1 and 5-hydroxytryptamine receptors. Indoramin is used in the management of hypertension (p.1171), and in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction. It has also been used in the prophylactic treatment of migraine.

Indoramin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Indoramin hydrochloride 11.0 mg is equivalent to about 10 mg of indoramin.

In **hypertension**, the initial dose is 25 mg twice daily, increased in steps of 25 or 50 mg at intervals of 2 weeks to a maximum of 200 mg daily in 2 or 3 divided doses.

In **benign prostatic hyperplasia**, the initial dose is 20 mg twice daily, increased if necessary by 20 mg at 2-week intervals, to a maximum of 100 mg daily in divided doses.

Lower doses may be required in the elderly.

◊ Reviews.

1. Holmes B, Sorkin EM. Indoramin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and related vascular, cardiovascular and airway diseases. *Drugs* 1986; **31:** 467–99.

Migraine. Propranolol is probably the most well-established drug for prophylaxis of migraine (p.616). Many other drugs have been used including indoramin. In a double-blind study,[1] indoramin in a dose of 25 mg twice daily was reported to be as effective as dihydroergotamine mesilate in reducing the frequency of migraine attacks.

1. Pradalier A, *et al.* Etude comparative indoramine versus dihydroergotamine dans le traitement préventif de la migraine. *Therapie* 1988; **43:** 293–7.

Preparations

BP 2008: Indoramin Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Wypresin†; ***Fr.:*** Vidora; ***Ger.:*** Wydora; ***Irl.:*** Baratol†; Doralese; ***S.Afr.:*** Baratol; ***UK:*** Baratol; Doralese.

Inositol Nicotinate *(BAN, rINN)*

Inositol Niacinate *(USAN)*; Inositol, Nicotinate d'; Inositoli Nicotinas; Inositolinikotinaatti; Inositolnikotinat; Nicotinato de inositol; NSC-49506; Win-9154. *meso*-Inositol hexanicotinate; *myo*-Inositol hexanicotinate.

Инозитола Никотинат

$C_{42}H_{30}N_6O_{12}$ = 810.7.

CAS — 6556-11-2.

ATC — C04AC03.

ATC Vet — QC04AC03.

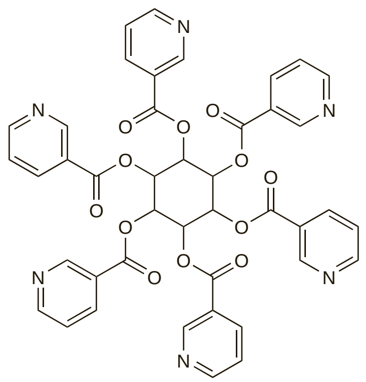

Pharmacopoeias. In *Br.*

BP 2008 (Inositol Nicotinate). A white or almost white, odourless or almost odourless powder. Practically insoluble in water, in alcohol, in acetone, and in ether; sparingly soluble in chloroform. It dissolves in dilute mineral acids.

Profile

Inositol nicotinate is a vasodilator and is believed to be slowly hydrolysed to nicotinic acid (p.1957). It is given orally in the management of peripheral vascular disease (p.1178). The usual dose is 3 g daily given in divided doses. The dose may be increased to 4 g daily if necessary.

Inositol nicotinate has been used in hyperlipidaemias.

Preparations

BP 2008: Inositol Nicotinate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Evicyl†; ***Ger.:*** Hamovannad†; Nicolip; ***Irl.:*** Hexogen†; Hexopal; ***Neth.:*** Palohex; ***UK:*** Hexopal.

Multi-ingredient: ***Ger.:*** Zellaforte N Plus†; ***S.Afr.:*** Geratar.

Irbesartan *(BAN, USAN, rINN)*

BMS-186295; Irbesartaani; Irbésartan; Irbesartán; Irbesartanum; SR-47436. 2-Butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Ирбесартан

$C_{25}H_{28}N_6O$ = 428.5.

CAS — 138402-11-6.

ATC — C09CA04.

ATC Vet — QC09CA04.

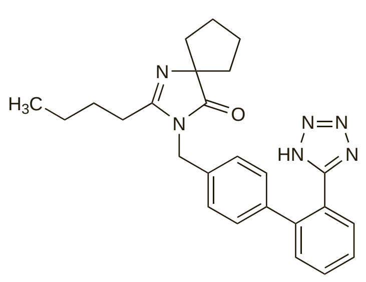

Pharmacopoeias. In *US.*

USP 31 (Irbesartan). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Store in airtight containers at a temperature below 30°.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Irbesartan is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of 60 to 80%. Peak plasma concentrations of irbesartan occur 1.5 to 2 hours after an oral dose. Irbesartan is about 96% bound to plasma proteins. It undergoes some metabolism in the liver, primarily by the cytochrome P450 isoenzyme CYP2C9, to inactive metabolites. It is excreted as unchanged drug and metabolites in the bile and in urine; about 20% of an oral or intravenous dose is excreted in the urine, with less than 2% as unchanged drug. The terminal elimination half-life is about 11 to 15 hours.

◊ References.

1. Sica DA, *et al.* The pharmacokinetics of irbesartan in renal failure and maintenance hemodialysis. *Clin Pharmacol Ther* 1997; **62:** 610–18.
2. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects. *J Clin Pharmacol* 1998; **38:** 246–55.
3. Marino MR, *et al.* Pharmacokinetics and pharmacodynamics of irbesartan in patients with hepatic cirrhosis. *J Clin Pharmacol* 1998; **38:** 347–56.
4. Vachharajani NN, *et al.* Oral bioavailability and disposition characteristics of irbesartan, an angiotensin antagonist, in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 702–7.
5. Vachharajani NN, *et al.* The effects of age and gender on the pharmacokinetics of irbesartan. *Br J Clin Pharmacol* 1998; **46:** 611–13.
6. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; **41:** 742–9.

Uses and Administration

Irbesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171) including the treatment of renal disease in hypertensive diabetic patients (see Kidney Disorders, under Uses of Losartan, p.1328). Irbesartan is also under investigation in heart failure.

Irbesartan is given orally. After a dose the hypotensive effect peaks within 3 to 6 hours and persists for at least 24 hours. The maximum hypotensive effect is achieved within 4 to 6 weeks after starting therapy.

In **hypertension**, irbesartan is given in a dose of 150 mg once daily increased, if necessary, to 300 mg once daily. A lower initial dose of 75 mg once daily may be considered in elderly patients over 75 years, for patients with intravascular volume depletion, and for those receiving haemodialysis.

For the treatment of **renal disease** in hypertensive type 2 diabetics, irbesartan should be given in an initial dose of 150 mg once daily, increased to 300 mg once daily for maintenance.

◊ Reviews.

1. Gillis JC, Markham A. Irbesartan: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the management of hypertension. *Drugs* 1997; **54:** 885–902.
2. Brown MJ. Irbesartan treatment in hypertension. *Hosp Med* 1998; **59:** 808–11.
3. Markham A, *et al.* Irbesartan: an updated review of its use in cardiovascular disorders. *Drugs* 2000; **59:** 1187–1206.
4. Croom KF, *et al.* Irbesartan: a review of its use in hypertension and in the management of diabetic nephropathy. *Drugs* 2004; **64:** 999–1028.
5. Ravera M, *et al.* Prevention and treatment of diabetic nephropathy: the program for irbesartan mortality and morbidity evaluation. *J Am Soc Nephrol* 2005; **16** (suppl 1): S48–S52.
6. Palmer AJ, *et al.* Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis. *Int J Clin Pract* 2007; **61:** 1626–33.
7. Flack JM. Maximising antihypertensive effects of angiotensin II receptor blockers with thiazide diuretic combination therapy: focus on irbesartan/hydrochlorothiazide. *Int J Clin Pract* 2007; **61:** 2093–1102.

Administration in children. Although irbesartan appears to be well-tolerated in children with hypertension and has been shown to reduce blood pressure in small studies,[1] US licensed product information notes that doses of up to 4.5 mg/kg once daily were ineffective in children aged 6 to 16 years and no longer recommends use in such patients.

In children with chronic kidney diseases, irbesartan has been reported to reduce blood pressure and proteinuria.[2,3] The initial dose was 37.5 mg once daily for children weighing 10 to 20 kg, 75 mg once daily for those weighing 21 to 40 kg, and 150 mg once daily for those weighing more than 40 kg; doses could be doubled if the blood pressure response was inadequate.

1. Sakarcan A, *et al.* The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J Clin Pharmacol* 2001; **41:** 742–9.
2. Franscini LMD, *et al.* Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. *Am J Hypertens* 2002; **15:** 1057–63.
3. Gartenmann AC, *et al.* Better renoprotective effect of angiotensin II antagonist compared to dihydropyridine calcium channel blocker in childhood. *Kidney Int* 2003; **64:** 1450–4.

Preparations

USP 31: Irbesartan and Hydrochlorothiazide Tablets; Irbesartan Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Adana; Aprovel; Avapro; ***Austral.:*** Avapro; Karvea; ***Belg.:*** Aprovel; ***Braz.:*** Aprovel; Avapro; ***Canad.:*** Avapro; ***Chile:*** Aprovel; ***Cz.:*** Aprovel; Karvea; ***Denm.:*** Aprovel; ***Fin.:*** Aprovel; ***Fr.:*** Aprovel; ***Ger.:*** Aprovel; Karvea; ***Gr.:*** Aprovel; Karvea; ***Hong Kong:*** Aprovel; ***Hung.:*** Aprovel; ***India:*** Irovel; Xarb; ***Indon.:*** Aprovel; Fristens; Iretensa; Irvell; ***Irl.:*** Aprovel; ***Israel:*** Irban†; ***Ital.:*** Aprovel; Karvea; ***Malaysia:*** Aprovel; ***Mex.:*** Aprovel; Avapro; ***Neth.:*** Aprovel; Karvea; ***Norw.:*** Aprovel; ***NZ:*** Karvea; ***Philipp.:*** Aprovel; ***Pol.:*** Aprovel; ***Port.:*** Aprovel; Karvea; ***Rus.:*** Aprovel (Апровель); ***S.Afr.:*** Aprovel; ***Singapore:*** Aprovel; ***Spain:*** Aprovel; Karvea; ***Swed.:*** Aprovel; ***Switz.:*** Aprovel; ***Thai.:*** Aprovel; ***Turk.:*** Karvea; ***UK:*** Aprovel; ***USA:*** Avapro; ***Venez.:*** Aprovel.

Multi-ingredient: ***Arg.:*** Adana Plus; Avapro HCT; CoAprovel; ***Austral.:*** Avapro HCT; Karvezide; ***Belg.:*** CoAprovel; ***Braz.:*** Aprozide; ***Canad.:*** Avalide; ***Chile:*** CoAprovel; ***Cz.:*** CoAprovel; Karvezide; ***Denm.:*** CoAprovel; ***Fr.:*** CoAprovel; ***Ger.:*** CoAprovel; Karvezide; ***Gr.:*** CoAprovel; Karvezide; ***Hong Kong:*** Aprovel HCT†; CoAprovel; ***Hung.:*** CoAprovel; ***India:*** Xarb-H; ***Indon.:*** CoAprovel; Irtan Plus; ***Irl.:*** CoAprovel; ***Israel:*** Irban Plus†; ***Ital.:*** CoAprovel; Karvezide; ***Malaysia:*** CoAprovel; ***Mex.:*** Avalide; CoAprovel; ***Neth.:*** CoAprovel; Karvezide; ***Norw.:*** CoAprovel; ***NZ:*** Karvezide; ***Philipp.:*** CoAprovel; ***Port.:*** CoAprovel; Karvezide; ***S.Afr.:*** CoAprovel; ***Singapore:*** CoAprovel; ***Spain:*** CoAprovel; Karvezide; ***Swed.:*** CoAprovel; ***Switz.:*** CoAprovel; ***Thai.:*** Aprovel HCT†; CoAprovel; ***Turk.:*** Karvezide; ***UK:*** CoAprovel; ***USA:*** Avalide; ***Venez.:*** CoAprovel.

Isoprenaline *(BAN, rINN)* ⊗

Isoprenaliini; Isoprenalin; Isoprenalina; Isoprénaline; Isoprenalinum; Isopropylarterenol; Isopropylnoradrenaline; Isoproterenol. 1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol.

Изопреналин

$C_{11}H_{17}NO_3$ = 211.3.

CAS — 7683-59-2.

ATC — C01CA02; R03AB02; R03CB01.

ATC Vet — QC01CA02; QR03AB02; QR03CB01.

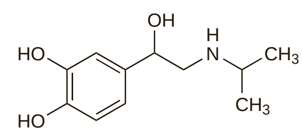

Isoprenaline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isoprenalina; Isoprenaliinihydrokloridi; Isoprénaline, chlorhydrate d'; Isoprenalin-hydrochlorid; Isoprenalinhydroklorid; Isoprenalini hydrochloridum; Isopropylarterenol Hydrochloride; Isopropylnoradrenaline Hydrochloride; Isoproterenol Hydrochloride; Izoprenalin Hidroklorür; Izoprenalin-hidroklorid; Izoprenalino hidrochloridas.

Изопреналина Гидрохлорид

$C_{11}H_{17}NO_3,HCl$ = 247.7.

CAS — 51-30-9.

ATC — C01CA02; R03AB02; R03CB01.

ATC Vet — QC01CA02; QR03AB02; QR03CB01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Isoprenaline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Isoproterenol Hydrochloride). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to air and light. Soluble 1 in 3 of water and 1 in 50 of alcohol; less soluble in dehydrated alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Isoprenaline Sulfate *(rINNM)* ⊗

Isoprenaliinisulfaatti; Isoprenalin sulfát dihydrát; Isoprénaline, sulfate d'; Isoprenaline Sulphate *(BANM)*; Isoprenalini sulfas; Isoprenalini Sulfas Dihydricus; Isoprenalinsulfat; Isopropylarterenol Sulphate; Isopropylnoradrenaline Sulphate; Isoproterenol Sulfate; Izoprenalino sulfatas; Izoprenalin-szulfát; Izoprenaliny siarczan; Sulfato de isoprenalina.

Изопреналина Сульфат

$(C_{11}H_{17}NO_3)_2,H_2SO_4,2H_2O$ = 556.6.

CAS — 299-95-6 (anhydrous isoprenaline sulfate); 6700-39-6 (isoprenaline sulfate dihydrate).

ATC — C01CA02; R03AB02; R03CB01.

ATC Vet — QC01CA02; QR03AB02; QR03CB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Isoprenaline Sulphate). A white or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Isoproterenol Sulfate). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to light and air. Soluble 1 in 4 of water; very slightly soluble in alcohol, in chloroform, in ether, and in benzene. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air, and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Isoprenaline has almost exclusively beta-agonist properties but also stimulates the CNS; its main adverse effects include tachycardia and cardiac arrhythmias, palpitations, hypotension, tremor, headache, sweating, and facial flushing. Prolonged use of isoprenaline has been associated with swelling of the parotid glands.

Prolonged use of sublingual tablets may also cause severe damage to the teeth due to the acidic nature of the drug. Sublingual use or inhalation may colour the saliva or sputum red.

Increased mortality. For a discussion of the increased mortality and morbidity that has sometimes been observed in asthmatic patients using beta agonists and reference to an early epidemic associated with isoprenaline inhalers, see Fenoterol, p.1121.

Interactions

As for Sympathomimetics, p.1407. Due to the risk of arrhythmias, isoprenaline should not be used with other potent $beta_1$ agonists such as adrenaline.

Theophylline. For reports of increased theophylline clearance following use of isoprenaline, see p.1145.

Pharmacokinetics

As a result of sulfate conjugation in the gut, isoprenaline is considerably less active orally than after parenteral doses. It is absorbed through the oral mucosa and has accordingly been given sublingually, but absorption by this route remains very erratic. Isoprenaline in the body is resistant to metabolism by monoamine oxidase, but is metabolised by catechol-*O*-methyltransferase in the liver, lungs, and other tissues, the metabolite then being conjugated before excretion in the urine. Whereas the sulfate conjugate of isoprenaline is inactive the methylated metabolite exhibits weak activity.

After intravenous injection isoprenaline has a plasma half-life of about one to several minutes according to whether the rate of injection is rapid or slow; it is almost entirely excreted in the urine as unchanged drug and metabolites within 24 hours. A much slower onset of action and a more extended initial half-life has been found after oral dosage. Isoprenaline is reported to have a duration of action of up to about 2 hours after inhalation; it has been shown that a large proportion of an inhaled dose is swallowed.

◊ References.

1. Blackwell EW, *et al.* The fate of isoprenaline administered by pressurized aerosols. *Br J Pharmacol* 1970; **39:** 194P–195P.
2. Conolly ME, *et al.* Metabolism of isoprenaline in dog and man. *Br J Pharmacol* 1972; **46:** 458–72.
3. Blackwell EW, *et al.* Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br J Pharmacol* 1974; **50:** 587–91.
4. Reyes G, *et al.* The pharmacokinetics of isoproterenol in critically ill pediatric patients. *J Clin Pharmacol* 1993; **33:** 29–34.

Uses and Administration

Isoprenaline is a sympathomimetic (p.1408) that acts almost exclusively on beta-adrenergic receptors. It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate; it also causes peripheral vasodilatation and produces a fall in diastolic blood pressure and usually maintains or slightly increases systolic blood pressure. In addition, isoprenaline has bronchodilating properties. It also stimulates the CNS.

Isoprenaline has been used in a variety of cardiac disorders. It may be used for the temporary prevention or control of Stokes-Adams attacks and in severe bradycardia unresponsive to atropine, but use of a pacemaker is preferred. It has also been advocated as an adjunct for other cardiac disorders including shock (p.1183) and torsade de pointes (see Cardiac Arrhythmias, p.1160). It has been used in the diagnosis of congenital heart defects.

In the management of **cardiac disorders**, isoprenaline is usually given as the hydrochloride by slow intravenous infusion under ECG control. Infusion rates may range from 0.5 to 10 micrograms/minute depending on the clinical condition of the patient; 1 to 4 micrograms/minute may be adequate to correct bradycardia but rates of 4 to 8 micrograms/minute may be required for acute Stokes-Adams attacks. Isoprenaline hydrochloride can be given by intracardiac injection in extreme cases. It has also been given subcutaneously or intramuscularly in initial doses of 200 micrograms (as 1 mL of a 0.02% solution) and by slow intravenous injection in initial doses of 20 to 60 micrograms (as 1 to 3 mL of a 0.002% solution); doses are subsequently adjusted according to ventricular rate. Tablets of isoprenaline hydrochloride have been given orally or sublingually.

Isoprenaline has been used as a bronchodilator in the management of **reversible airways obstruction** but sympathomimetics with a selective action on $beta_2$ receptors, such as salbutamol, are now preferred (see Asthma, p.1108). It has been given as the sulfate or hydrochloride, usually by inhalation; sublingual tablets and intravenous injections have also been used.

Preparations

BP 2008: Isoprenaline Injection;
USP 31: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Isoproterenol Hydrochloride Inhalation Aerosol; Isoproterenol Hydrochloride Injection; Isoproterenol Hydrochloride Tablets; Isoproterenol Inhalation Solution; Isoproterenol Sulfate Inhalation Aerosol; Isoproterenol Sulfate Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciapar†; Proternal†; ***Austral.:*** Isuprel; ***Austria:*** Ingelan; ***Belg.:*** Isuprel; ***Cz.:*** Isuprel; ***Fr.:*** Isuprel; ***Ger.:*** Ingelan†; ***Gr.:*** Isuprel†; Saventrine†; ***Hung.:*** Isuprel†; ***India:*** Autohaler†; Isolin; ***Indon.:*** Isuprel; ***Irl.:*** Saventrine†; ***Israel:*** Isuprel; ***NZ:*** Isuprel; ***S.Afr.:*** Imuprel; Lenoprel†; ***Singapore:*** Isuprel†; Saventrine†; ***Spain:*** Aleudrina; ***Thai.:*** Isuprel; ***USA:*** Isuprel; Medihaler-Iso.

Multi-ingredient: ***Arg.:*** Zantril†; ***Austria:*** Ingelan; ***Ger.:*** Ingelan†; ***Mex.:*** Isobutil†; ***Port.:*** Prelus†; ***Spain:*** Aldo Asma; Frenal Compositum; ***USA:*** Norisodrine with Calcium Iodide.

Isosorbide *(BAN, USAN, rINN)* ⊗

AT-101; Isosorbida; Isosorbidum; NSC-40725. 1,4:3,6-Dianhydro-D-glucitol.

Изосорбид

$C_6H_{10}O_4$ = 146.1.

CAS — 652-67-5.

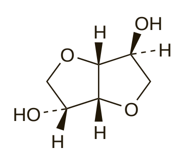

Pharmacopoeias. In *Jpn.*

US includes Isosorbide Concentrate.

USP 31 (Isosorbide Concentrate). An aqueous solution containing 70.0 to 80.0% w/w of isosorbide. A colourless to slightly yellow liquid. Soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Isosorbide is an osmotic diuretic with properties similar to those of mannitol (p.1330). It is reported to cause less nausea and vomiting than other oral osmotic diuretics.

Isosorbide is used for short-term reduction of intra-ocular pressure in acute glaucoma or prior to surgery (p.1873). The usual oral dose is 1 to 3 g/kg 2 to 4 times daily. The onset of action is usually within 30 minutes and lasts for up to 5 or 6 hours.

Preparations

USP 31: Isosorbide Concentrate; Isosorbide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Mex.: Biordyn; ***USA:*** Ismotic.

Isosorbide Dinitrate *(BAN, USAN, rINN)*

Dinitrato de isosorbida; ISDN; Isosorbid dinitrát; Isosorbiddinitrat; Isosorbide, dinitrate d'; Isosorbidi dinitras; Isosorbididinitraatti; Izosorbid Dinitrat; Izosorbido dinitratas; Izosorbidu diazotan; Izoszorbid-dinitrát; Sorbide Nitrate. 1,4:3,6-Dianhydro-D-glucitol 2,5-dinitrate.

Изосорбида Динитрат

$C_6H_8N_2O_8$ = 236.1.

CAS — 87-33-2.

ATC — C01DA08; C05AE02.

ATC Vet — QC01DA08; QC05AE02.

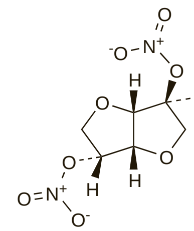

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p.vii), *Int.*, and *US* include diluted isosorbide dinitrate.

Ph. Eur. 6.2 (Isosorbide Dinitrate, Diluted). A dry mixture of isosorbide dinitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone.

USP 31 (Diluted Isosorbide Dinitrate). A dry mixture of isosorbide dinitrate (usually about 25%) with lactose, mannitol, or other suitable inert excipients, the latter being added to minimise the risk of explosion. It may contain up to 1% of a suitable stabiliser such as ammonium phosphate. It is an ivory-white, odourless powder. Store in airtight containers.

Undiluted isosorbide dinitrate occurs as white crystalline rosettes. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone; freely soluble in chloroform.

Handling. Undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat.

Stability. The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC plastic intravenous infusion sets but negligible when polyolefin or glass delivery systems were used.[1] Another study reported a 23% decrease in isosorbide dinitrate concentration after 24 hours of storage at 21° in PVC containers; most of the loss occurred in the first 6 hours. Loss of potency was not noted when isosorbide dinitrate was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags.[2]

1. Kowaluk EA, *et al.* Drug loss in polyolefin infusion systems. *Am J Hosp Pharm* 1983; **40:** 118–19.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p.1296.

Effects on the blood. Haemolysis occurred in 2 patients with G6PD deficiency during treatment with isosorbide dinitrate.[1]

1. Aderka D, *et al.* Isosorbide dinitrate-induced hemolysis in G6PD-deficient subjects. *Acta Haematol (Basel)* 1983; **69:** 63–4.

Headache. The most common adverse effect of nitrate therapy is headache which usually decreases after a few days. There has been a report[1] of a severe continuous unilateral headache with an oculosympathetic paresis on the same side associated with isosorbide dinitrate therapy.

1. Mueller RA, Meienberg O. Hemicrania with oculosympathetic paresis from isosorbide dinitrate. *N Engl J Med* 1983; **308:** 458–9.

Hypersensitivity. Laryngeal oedema developed on two occasions in a woman after the use of isosorbide dinitrate spray;[1] nifedipine was also given sublingually which on the second occasion caused a noticeable increase in the laryngeal swelling induced by the nitrate.

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Nitrate tolerance. Continuous use of organic nitrates is associated with tolerance to their haemodynamic effects; for an overview of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p.1297.

A study in 12 patients with chronic stable angina[1] showed that after treatment for one week with isosorbide dinitrate 30 mg two or three times daily, treadmill-walking time was longer throughout a 5-hour testing period compared with placebo. In contrast, after treatment for one week with isosorbide dinitrate 30 mg four times daily, treadmill-walking time was prolonged at 1 hour but not at 3 or 5 hours. These results support the concept that clinical efficacy of isosorbide dinitrate is maintained if given in a dose schedule which provides a nitrate-free or a low-nitrate period.

The effect of sublingual isosorbide dinitrate in patients receiving chronic therapy with isosorbide dinitrate was evaluated in 24 patients with angina.[2] Sublingual use produced less reduction of aortic systolic pressure and left ventricular end-diastolic pressure and less dilatation of coronary artery diameter in patients who received chronic isosorbide dinitrate therapy compared with patients not receiving chronic therapy.

1. Parker JO, *et al.* Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med* 1987; **316:** 1440–4.
2. Naito H, *et al.* Effects of sublingual nitrate in patients receiving sustained therapy of isosorbide dinitrate for coronary artery disease. *Am J Cardiol* 1989; **64:** 565–68.

Oedema. Reports of ankle oedema associated with isosorbide dinitrate therapy in 3 patients with heart failure.[1]

1. Rodger JC. Peripheral oedema in patients treated with isosorbide dinitrate. *BMJ* 1981; **283:** 1365–6.

Interactions

As for Glyceryl Trinitrate, p.1297.

Disopyramide. The effectiveness of sublingual isosorbide dinitrate was reduced in a patient taking disopyramide.[1] The interaction was considered to be due to diminished salivary secretions caused by the antimuscarinic action of disopyramide which inhibited the dissolution of the sublingual isosorbide dinitrate tablet.

1. Barletta MA, Eisen H. Isosorbide dinitrate-disopyramide phosphate interaction. *Drug Intell Clin Pharm* 1985; **19:** 764.

Pharmacokinetics

Like glyceryl trinitrate, isosorbide dinitrate is readily absorbed from the oral mucosa. Isosorbide dinitrate is also readily absorbed when given orally but owing to extensive first-pass metabolism in the liver and presystemic clearance its bioavailability is reduced. Isosorbide dinitrate is also absorbed through the skin from an ointment basis.

After sublingual doses, anti-anginal effect is apparent within 2 to 5 minutes and persists for about 1 to 2 hours. After oral dosage with conventional tablets, anti-anginal activity is present in less than 1 hour and lasts for 4 to 6 hours.

Isosorbide dinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. It is also rapidly metabolised in the liver to the major active metabolites isosorbide 2-mononitrate and isosorbide 5-mononitrate (see Isosorbide Mononitrate, below).

After sublingual doses, isosorbide dinitrate has a plasma half-life of 45 to 60 minutes. Plasma half-lives of 20 minutes and 4 hours have been reported after intravenous and oral dosage, respectively. During prolonged use, the half-life is increased due to accumulation of the isosorbide 5-mononitrate metabolite which reduces hepatic isosorbide dinitrate extraction. Both primary metabolites have longer half-lives than the parent compound.

◊ References.

1. Abshagen U, *et al.* Pharmacokinetics and metabolism of isosorbide-dinitrate after intravenous and oral administration. *Eur J Clin Pharmacol* 1985; **27:** 637–44.
2. Straehl P, Galeazzi RL. Isosorbide dinitrate bioavailability, kinetics, and metabolism. *Clin Pharmacol Ther* 1985; **38:** 140–9.
3. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
4. Schneider W, *et al.* Concentrations of isosorbide dinitrate, isosorbide-2-mononitrate and isosorbide-5-mononitrate in human vascular and muscle tissue under steady-state conditions. *Eur J Clin Pharmacol* 1990; **38:** 145–7.
5. Vogt D, *et al.* Pharmacokinetics and haemodynamic effects of ISDN following different dosage forms and routes of administration. *Eur J Clin Pharmacol* 1994; **46:** 319–24.
6. Bergami A, *et al.* Pharmacokinetics of isosorbide dinitrate in healthy volunteers after 24-hour intravenous infusion. *J Clin Pharmacol* 1997; **37:** 828–33.

Uses and Administration

Isosorbide dinitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1297). It is used in the management of angina pectoris (p.1157) and of heart failure (below). It has also been investigated in myocardial infarction (p.1175).

Isosorbide dinitrate may be given by the sublingual, oral, transdermal, or intravenous route.

In **angina** isosorbide dinitrate may be given as sublingual tablets or spray for the relief of an acute attack, although glyceryl trinitrate may be preferred because it has a faster onset of action. Isosorbide dinitrate may also be used before an activity or stress which might provoke an attack. The usual dose in acute angina is 2.5 to 10 mg sublingually. As an alternative, one to three sprays (1.25 mg/spray) may be directed under the tongue.

Isosorbide dinitrate is also used in the long-term management of angina in oral doses of 20 to 120 mg daily in divided doses according to the patient's needs. Increases in dosage should be gradual to avoid adverse effects. Up to 240 mg daily in divided doses may be necessary. Modified-release formulations may be used in equivalent doses. Transdermal preparations such as topical sprays or ointments may also be used.

Isosorbide dinitrate is given by intravenous infusion for unstable angina. The dose is titrated according to patient response; doses in the range of 2 to 12 mg/hour are usually suitable but up to 20 mg/hour may be necessary in some patients. The plastic used in the infusion equipment may adsorb isosorbide dinitrate (see Stability, above) and allowance may have to be made for this.

During percutaneous transluminal coronary angioplasty isosorbide dinitrate may be given by the intracoronary route to allow prolonged balloon inflation and to prevent or relieve coronary spasm. Only injections of isosorbide dinitrate which are approved for intracoronary use should be given by this route as preparations intended for normal intravenous use may contain additives that are harmful if injected into diseased coronary vessels. The usual dose is 1 mg as a bolus before balloon inflation. The maximum recommended dose is 5 mg within a 30-minute time period.

Isosorbide dinitrate is also used in the management of **heart failure**. It is given in doses of 5 to 10 mg sublingually every 2 to 3 hours, or in oral doses of 30 to 160 mg daily in divided doses. Oral doses of up to 240 mg daily may be required. It may also be given intravenously using the intravenous doses given above for angina. An oral combination preparation with hydralazine is also available for use in self-identified black patients. It is given in a dose of 20 mg of isosorbide dinitrate with 37.5 mg of hydralazine three times daily; the dose may be doubled if necessary.

Heart failure. Although direct-acting vasodilators do not have a major role in the management of chronic heart failure (p.1165) there is some evidence that use of hydralazine with isosorbide dinitrate may be of benefit,[1] although the effect on mortality is less than that seen with ACE inhibitors.[2] Subgroup analysis suggested that the effect might be greater in black patients, and a later study[3] in black patients found that addition of isosorbide dinitrate and hydralazine to standard therapy improved both morbidity and mortality.

1. Cohn JN, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314:** 1547–52.
2. Cohn JN, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; **325:** 303–10.
3. Taylor AL, *et al.* African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049–57. Correction. *ibid.* 2005; **352:** 1276.

Non-cardiovascular disorders. Nitrates such as isosorbide dinitrate have been tried in conditions including anal fissure, erectile dysfunction, obstetric and gynaecological disorders, oesophageal motility disorders such as achalasia and spasm, and pain. Further details of these uses are given under Glyceryl Trinitrate (p.1298).

Preparations

BP 2008: Isosorbide Dinitrate Injection; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets;

USP 31: Isosorbide Dinitrate Chewable Tablets; Isosorbide Dinitrate Extended-release Capsules; Isosorbide Dinitrate Extended-release Tablets; Isosorbide Dinitrate Sublingual Tablets; Isosorbide Dinitrate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cortespasmo; Isoket; Isordil; ***Austral.:*** Isordil; Sorbidin; ***Austria:*** Cedocard; Hexanitrat; Iso Mack; Isoket; Vasorbate; ***Belg.:*** Cedocard; Isordil†; ***Braz.:*** Angil; Dilatrat†; Isocord†; Isorbid†; Isordil; ***Canad.:*** Apo-ISDN; Cedocard†; Novo-Sorbide; ***Cz.:*** Apo-ISDN†; Cardiket; Dinisan; Iso Mack; Isoket; Isopelet; Maycor†; ***Denm.:*** Cardopax; Iso Mack†; ***Fin.:*** Dinit; Nitrosid; ***Fr.:*** Isocard; Langoran; Risordan; ***Ger.:*** Diconpin; duranitrat†; Iso Mack†; Iso-Puren; Isoket; Isostenase†; Jenacard; Maycor†; Nitrosorbon; TD Spray Iso Mack; ***Gr.:*** Orbipront†; Pensordil; ***Hong Kong:*** Apo-ISDN; Iso Mack†; Isoket; Isordil†; Isorem; ***Hung.:*** Iso Mack†; Isoket†; ***India:*** Anzidin; Isordil; Sorbitrate; ***Indon.:*** Cedocard; Farsorbid; Hapisor; Isoket; Isordil; Sorbidin; Vascardin; ***Irl.:*** Isoket; Isordil†; ***Israel:*** Cordil; Isocardide; Isoket; Isolong; Isotard†; ***Ital.:*** Carvasin; Diniket; Nitrosorbide; ***Jpn:*** Antup R; Nitorol; ***Malaysia:*** Apo-ISDN†; Isoket; Isordil†; Nitorol†; Sorbidin†; ***Mex.:*** Biderit; Debisor; Insucar; Isoket; Isorbid; ***Neth.:*** Cedocard; Isordil; ***Norw.:*** Sorbangil; ***NZ:*** Coronex†; ***Philipp.:*** Bideren; Isobar; Isoket; Isordil; Nitrosorbon; ***Pol.:*** Aerosonit; Cardonit; Isoket; Sorbonit; ***Port.:*** Flindix; Isoket; Isopront†; ***Rus.:*** Isoket (Изокет); Isolong (Изолонг)†; Kardiket (Кардикет); ***S.Afr.:*** Angi-Spray; Dinospray; Isoket; Isordil; ***Singapore:*** Apo-ISDN; Iso Mack†; Isobin†; Isoket; Isordil†; ***Spain:*** Iso; Isordil†; ***Swed.:*** Sorbangil; ***Switz.:*** Acordin; Esconitro†; Iso Mack; Isoket; Isosifar†; Sorbidilat; ***Thai.:*** Angitrit; Hartsorb; Iso Mack†; Isobinate; Isoket; Isordil; Isorem; Isotrate; Izo†; Sorbidin; Sornil; ***Turk.:*** Cardioket; Isordil; Nitrofix; ***UK:*** Angitak; Cedocard; Isoket; ***USA:*** Dilatrate; Isochron; Isordil; Sorbitrate†; ***Venez.:*** Isoket; Isomack; Isordil†.

Multi-ingredient: ***Austria:*** Viskenit; ***Ger.:*** Stenoptin†; ***USA:*** BiDil.

Isosorbide Mononitrate *(BAN, USAN, rINN)*

AHR-4698; BM-22145; IS-5-MN; Isosorbid mononitrát; Isosorbide, mononitrate d'; Isosorbide-5-mononitrate; Isosorbidi mononitras; Izosorbid Mononitrat; Izosorbido mononitratas; Izoszorbid-mononitrát; Mononitrato de isosorbida. 1,4:3,6-Dianhydro-D-glucitol 5-nitrate.

Изозорбида Мононитрат

$C_6H_9NO_6$ = 191.1.

CAS — 16051-77-7.

ATC — C01DA14.

ATC Vet — QC01DA14.

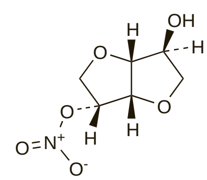

Pharmacopoeias. *Eur.* (see p.vii) and *US* include diluted isosorbide mononitrate.

Ph. Eur. 6.2 (Isosorbide Mononitrate, Diluted). A dry mixture of isosorbide mononitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.

Undiluted isosorbide mononitrate is a white or almost white, crystalline powder. Freely soluble in water, in alcohol, in acetone, and in dichloromethane.

USP 31 (Diluted Isosorbide Mononitrate). A dry mixture of isosorbide mononitrate with lactose or other suitable excipients to permit safe handling. Store in airtight containers between 20° and 30°.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p.1296.

Myalgia has been reported very rarely.

Interactions

As for Glyceryl Trinitrate, p.1297.

Pharmacokinetics

Isosorbide mononitrate is readily absorbed from the gastrointestinal tract. After oral doses of conventional tablets, peak plasma levels are reached in 30 minutes to 1 hour; onset of action occurs within 20 minutes and lasts for about 8 to 10 hours. Unlike isosorbide dinitrate, isosorbide mononitrate does not undergo first-pass hepatic metabolism and bioavailability is nearly 100%. Isosorbide mononitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. Isosorbide mononitrate is metabolised to inactive metabolites, including isosorbide and isosorbide glucuronide. Only about 2% of isosorbide mononitrate is excreted unchanged in the urine. An elimination half-life of about 4 to 5 hours has been reported.

◊ References.

1. Taylor T, *et al.* Isosorbide 5-mononitrate pharmacokinetics in humans. *Biopharm Drug Dispos* 1981; **2:** 255–63.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. McClennen W, *et al.* The plasma concentrations of isosorbide 5-mononitrate (5-ISMN) administered in an extended-release form to patients with acute myocardial infarction. *Br J Clin Pharmacol* 1995; **39:** 704–8.
4. Hutt V, *et al.* Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide-5-mononitrate preparations in healthy volunteers. *Arzneimittelforschung* 1995; **45:** 142–5.
5. Baxter T, Eadie CJ. Twenty-four hour plasma profile of sustained-release isosorbide mononitrate in healthy volunteers and in patients with chronic stable angina: two open label trials. *Br J Clin Pharmacol* 1997; **43:** 333–5.

Uses and Administration

Isosorbide mononitrate is an active metabolite of the vasodilator isosorbide dinitrate and is used in the long-term management of angina pectoris (p.1157) and heart failure (p.1165). It has also been investigated in myocardial infarction (below).

The usual oral dose is 20 mg two or three times daily, although doses ranging from 20 to 120 mg daily have been given. Modified-release oral preparations have been developed for use in angina.

Myocardial infarction. Long-term management of myocardial infarction (p.1175) can involve numerous drug therapies and some patients, for example those with myocardial ischaemia or poor left ventricular function, may require the long-term use of nitrates, although recent studies have thrown doubt on their routine use. In the GISSI-3 study[1] there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks post-infarction and in the ISIS-4 study[2] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
2. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Termination of pregnancy. For mention of the use of isosorbide mononitrate to ripen the cervix before termination of pregnancy, see Obstetrics and Gynaecology, under Glyceryl Trinitrate, p.1298.

Variceal haemorrhage. For reference to the use of isosorbide mononitrate in the management of variceal haemorrhage, see under Glyceryl Trinitrate, p.1299.

Preparations

BP 2008: Isosorbide Mononitrate Tablets; Prolonged-release Isosorbide Mononitrate Tablets;
USP 31: Isosorbide Mononitrate Extended-Release Tablets; Isosorbide Mononitrate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cilatron; Isolan†; Medocor; Misordil†; Monoket; Monotrin; ***Austral.:*** Arsorb; Duride; Imdur; Imtrate; Isomonit; Monodur; ***Austria:*** Elantan; Epicordin; Isomonat; Mono Mack; Monoket; Myocardon mono; Olicardin; ***Belg.:*** Promocard†; ***Braz.:*** Cincordil; Coronar; Monocordil; Revange†; ***Canad.:*** Imdur; ***Chile:*** Ismo; Mono Mack†; Monopack; ***Cz.:*** Conpin; Effox†; Imdur†; Ismin; Mono Mack; Monosan; Monosor; Monotab; Olicard; Sorbimon; ***Denm.:*** Fem-Mono; Imdur; Isodur; ***Fin.:*** Imdur; Isangina; Ismexin; Ismox; Isosor; Ormox; ***Fr.:*** Monicor; ***Ger.:*** Coleb; Conpin; Corangin; duramonitat†; Elantan; IS 5 Mono; Ismanton; Ismo; Isomonit; Moni-Sanorania; Monit-Puren; Mono Acis†; mono corax; Mono Mack; Mono Wolff; Monobeta; Monoclair; Monolong; Mononitrat; Monopur; Monostenase†; Olicard; Orasorbil†; Sigacora†; Turimonit; ***Gr.:*** Angioval†; Dilavenil; G-Dil; Imdur; Isomon; Monoginal; Monoket; Monorythm; Monosordil; Nitramin; Nitrilan†; Procardol; ***Hong Kong:*** Corangin†; Elantan; Imdex; Imdur; Ismo†; Mono Mack†; Monocinque; ***Hung.:*** Cardisorb; Isospan; Mono Mack; Olicard; Rangin; Sorbimon†; ***India:*** 5-Mono; IHD; Ismo; Isomin; Monicor; Monocontin; Monosorbitrate; Monotrate; ***Indon.:*** Imdur; Isomonit; Monecto; Pentacard; ***Irl.:*** Elantan; Imdur; Isomel; Isomonit; Sormon; ***Israel:*** Monocord; Monolong; Mononit; ***Ital.:*** Duronitrin; Elan; Ismo; Kiton†; Leicester; Monocinque; Monoket; Nitrex†; Vasdilat; ***Malaysia:*** Duride; Elantan; Imdex; Imdur; Ismo; ***Mex.:*** Elantan; Imdur; Kenbrid; Mono Mack†; Monocorat; ***Neth.:*** Mono-Cedocard; Promocard; ***Norw.:*** Imdur; Ismo; Monoket; ***NZ:*** Corangin; Duride; Imtrate; Ismo; ***Philipp.:*** Angistad; Elantan; Imdur; Isomonit; Monosorb; ***Pol.:*** Effox; Isomonit; Izonit; Mono Mack; Monocard; Mononit; ***Port.:*** Amplexol†; Imdur; Ismo; Monoket; Mononitril; Monopront; Orasorbil; ***Rus.:*** Effox (Эфокс); Monisol (Монизол); Monocinque (Моночинкве); Monolong (Монолонг)†; Monosan (Моносан); Olicard Retard (Оликард Ретард); Pektrol (Пектрол); ***S.Afr.:*** Angitrate; Elantan; Imdur; Ismo; ***Singapore:*** Elantan; Imdex; Imdur; Ismo†; Vasotrate; ***Spain:*** Cardionil; Cardiovas; Coronur; Dolak; Isonitril; Pertil; Uniket; ***Swed.:*** Fem-Mono†; Imdur; Ismo; Isodur; Monoket; ***Switz.:*** Corangine; Ismo†; ***Thai.:*** Elantan; Imdex; Imdur; Ismo; Isopen; Mono Mack†; Monolin; Monotrate; Solotrate; ***Turk.:*** Isorat; Monodur; Monoket; Monolong; ***UK:*** Angeze; Chemydur; Cibral; Dynamin; Elantan; Imdur; Isib; Ismo; Isodur; Isotard; Isotrate†; MCR-50†; Modisal; Monigen; Monit†; Monomax; Monomil; Monosorb; Trangina; Xismox; Zemon; ***USA:*** Imdur; Ismo; Monoket; ***Venez.:*** Elantan; Ismo; Mono Mack.

Multi-ingredient: ***Braz.:*** Vasclin; ***India:*** Aspitrate†; Mono-A; Solosprin; ***UK:*** Imazin†.

Isradipine *(BAN, USAN, rINN)*

Isradipiini; Isradipin; Isradipinas; Isradipino; Isradipinum; Izradypina; PN-200-110. Isopropyl methyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

Исрадипин

$C_{19}H_{21}N_3O_5$ = 371.4.

CAS — 75695-93-1.

ATC — C08CA03.

ATC Vet — QC08CA03.

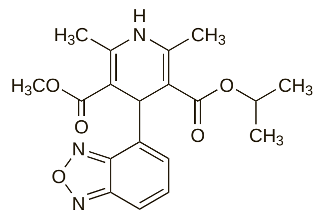

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Isradipine). A yellow crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol. Protect from light.

USP 31 (Isradipine). A yellow fine crystalline powder. Protect from light.

Stability. An oral preparation of isradipine 1 mg/mL, prepared using the powder from capsules of isradipine suspended in syrup,[1] was stable when stored at 4° for up to 35 days after preparation.

1. MacDonald JL, *et al.* Stability of isradipine in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1994; **51:** 2409–11.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

◊ In a multicentre study[1] involving 74 patients allocated to antihypertensive therapy with isradipine 2.5 to 10 mg twice daily, and 72 allocated to treatment with hydrochlorothiazide, adverse effects were reported in 44 of the isradipine group but only 29 of the thiazide group. Flushing, palpitation, and oedema were more common in patients receiving isradipine, while headache, dizziness, and dyspnoea were reported in both groups with similar frequency. In another study,[2] spontaneously reported adverse effects occurred less frequently in patients taking isradipine (18.4% of 103 patients) than in those taking amlodipine (33.3% of 102 patients). In particular, ankle oedema was less frequent, severe, and prolonged with isradipine than with amlodipine. A multicentre study[3] comparing isradipine and enalapril antihypertensive therapy reported adverse effects in 51% of 71 patients taking isradipine and 45% of 64 patients taking enalapril. The commonest side-effects with isradipine were dizziness (14%), oedema (10%), fatigue (9%), headache (9%), and pruritus (7%).

1. Carlsen JE, Køber L. Blood pressure lowering effect and adverse events during treatment of arterial hypertension with isradipine and hydrochlorothiazide. *Drug Invest* 1990; **2:** 10–16.
2. Hermans L, *et al.* At equipotent doses, isradipine is better tolerated than amlodipine in patients with mild-to-moderate hypertension: a double-blind, randomized, parallel-group study. *Br J Clin Pharmacol* 1994; **38:** 335–40.
3. Johnson BF, *et al.* A multicenter comparison of adverse reaction profiles of isradipine and enalapril at equipotent doses in patients with essential hypertension. *J Clin Pharmacol* 1995; **35:** 484–92.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Cimetidine increases the bioavailability of isradipine and the dose of isradipine should be reduced by 50% in patients receiving both drugs.

Pharmacokinetics

Isradipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism; the bioavailability is reported to be 15 to 24%. Peak plasma concentrations occur about 2 hours after oral dosage. It is about 95% bound to plasma proteins. Isradipine is extensively metabolised in the liver, at least partly by the cytochrome P450 isoenzyme CYP3A4. About 70% of an oral dose is reported to be excreted as metabolites in urine, the remainder in faeces. The terminal elimination half-life is often stated to be about 8 hours although a value of less than 4 hours has also been reported.

◊ In single-dose and steady-state studies of the pharmacokinetics of isradipine in 9 hypertensive subjects using a specific high performance liquid chromatographic assay, isradipine was found to be rapidly absorbed with peak concentrations occurring 1.2 (steady state) to 1.5 (single dose) hours after dosing.[1] The mean terminal elimination half-life at steady state was 3.8 hours, suggesting that duration of action is likely to be short and that isradipine would need to be given at least twice daily. There was considerable interindividual variation in the pharmacokinetics. In an earlier study[2] in healthy subjects the effective half-life of isradipine was calculated to be 8.8 hours, but radiolabelled isradipine was used and the assay method might have been less specific for unchanged drug.

1. Shenfield GM, *et al.* The pharmacokinetics of isradipine in hypertensive subjects. *Eur J Clin Pharmacol* 1990; **38:** 209–11.
2. Tse FLS, Jaffe JM. Pharmacokinetics of PN 200-110 (isradipine), a new calcium antagonist, after oral administration in man. *Eur J Clin Pharmacol* 1987; **32:** 361–5.

Hepatic impairment. Systemic availability after a radiolabelled oral dose of isradipine 5 mg was no different at 15.6% in 7 patients with non-cirrhotic chronic liver disease from the value of 16.5% in 8 healthy subjects.[1] However, in 8 patients with cirrhosis of the liver availability was markedly increased to a mean of 36.9%; this was associated with decreased clearance (1.6 litres/minute, compared with 9.9 in controls). Terminal half-life, as measured after intravenous dosage, was greater at 11.9 hours in cirrhotic patients than the 5.1 hours seen in controls.

1. Cotting J, *et al.* Pharmacokinetics of isradipine in patients with chronic liver disease. *Eur J Clin Pharmacol* 1990; **38:** 599–603.

Uses and Administration

Isradipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual initial dose of isradipine is 2.5 mg by mouth twice daily increased if necessary after 3 to 4 weeks to 5 mg twice daily. Some patients may require 10 mg twice daily. In elderly patients an initial dose of 1.25 mg twice daily may be preferable; a maintenance dose of 2.5 or 5 mg once daily may sometimes be sufficient. A reduced dose should also be considered in patients with hepatic or renal impairment (see below).

The dose of isradipine should be reduced in patients who are also taking cimetidine (see Interactions, above).

A modified-release preparation allowing once-daily dosing is available in some countries.

◊ Reviews.

1. Fitton A, Benfield P. Isradipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1990; **40:** 31–74.
2. Walton T, Symes LR. Felodipine and isradipine: new calcium-channel blocking agents for the treatment of hypertension. *Clin Pharm* 1993; **12:** 261–75.
3. Brogden RN, Sorkin EM. Isradipine: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of mild to moderate hypertension. *Drugs* 1995; **49:** 618–49.

Administration in hepatic or renal impairment. In patients with hepatic or renal impairment UK licensed product information recommends an initial dose of isradipine of 1.25 mg twice daily. The dose may be increased as required, but a maintenance dose of 2.5 or 5 mg once daily may be sufficient in some patients.

Preparations

BP 2008: Isradipine Tablets;
USP 31: Isradipine Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Dynacirc†; ***Austria:*** Lomir; ***Belg.:*** Lomir; ***Braz.:*** Lomir; ***Chile:*** Dynacirc†; ***Cz.:*** Lomir; ***Denm.:*** Lomir; ***Fin.:*** Lomir; ***Fr.:*** Icaz; ***Ger.:*** Lomir; Vascal; ***Gr.:*** Lomir; ***Hong Kong:*** Dynacirc; ***Hung.:*** Lomir; ***Ital.:*** Clivoten; Esradin; Lomir; ***Malaysia:*** Dynacirc; ***Mex.:*** Dynacirc; ***Neth.:*** Lomir; ***Norw.:*** Lomir; ***NZ:*** Dynacirc; ***Philipp.:*** Icaz; ***Pol.:*** Lomir; ***Port.:*** Dilatol; Lomir; ***Rus.:*** Lomir (Ломир); ***S.Afr.:*** Dynacirc; ***Singapore:*** Dynacirc; ***Spain:*** Lomir; ***Swed.:*** Lomir; ***Switz.:*** Lomir; ***Thai.:*** Dynacirc; ***Turk.:*** Dynacirc; ***UK:*** Prescal; ***USA:*** Dynacirc; ***Venez.:*** Dynacirc†.

Ivabradine *(rINN)*

Ivabradina; Ivabradinum; S-16257; S-16257-2 (ivabradine hydrochloride). 3-[3-({[(7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}methylamino)propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one.

Ивабрадин

$C_{27}H_{36}N_2O_5$ = 468.6.

CAS — 155974-00-8 (ivabradine); 148849-67-6 (ivabradine hydrochloride).

ATC — C01EB17.

ATC Vet — QC01EB17.

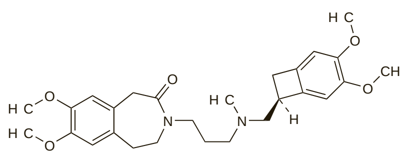

Adverse Effects

The most common adverse effects seen with ivabradine are luminous phenomena in the visual field (phosphenes). Other adverse effects include blurred vision, bradycardia, which may be severe, and other cardiac arrhythmias, nausea, constipation, diarrhoea, headache, dizziness, dyspnoea, and muscle cramps. Hyperuricaemia, eosinophilia, and elevated blood-creatinine concentrations have been reported.

◊ Reviews.

1. Savelieva I, Camm AJ. I inhibition with ivabradine: electrophysiological effects and safety. *Drug Safety* 2008; **31:** 95–107.

Precautions

Ivabradine should not be given to patients with resting heart rate below 60 beats/minute, or to patients with cardiogenic shock, severe conduction defects, acute myocardial infarction, or unstable angina. Heart failure should be controlled before ivabradine is started; it has not been studied in severe heart failure. Ivabradine should not be used in patients with congenital QT prolongation. Ivabradine is not recommended in atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function, and regular monitoring for such arrhythmias should be performed. If resting heart rate falls below 50 beats/minute the dose should be reduced; treatment should be stopped if this rate persists.

Ivabradine is contra-indicated in severe hypotension and severe hepatic impairment, and should be used with caution in severe renal impairment.

If unexpected deterioration in visual function occurs, stopping treatment may be considered. Caution should be observed in patients with retinitis pigmentosa.

Studies in *animals* have shown that ivabradine is embryotoxic and teratogenic, and is distributed into breast milk.

Interactions

Ivabradine should not generally be used with drugs that prolong the QT interval.

Ivabradine is metabolised by the cytochrome P450 isoenzyme CYP3A4, and should not be used with potent inhibitors of this enzyme, including azole antifungals such as ketoconazole and itraconazole, macrolide antibacterials such as clarithromycin, HIV-protease inhibitors such as nelfinavir and ritonavir, and nefazodone. Use with the moderate CYP3A4 inhibitors diltiazem and verapamil is also not recommended as the increase in exposure to ivabradine may cause an additional reduction in heart rate. Ivabradine may be used cautiously with other moderate inhibitors, such as fluconazole, at a lower starting dose of 2.5 mg twice daily, with monitoring of the heart rate. Consumption of grapefruit juice should be restricted.

Use with CYP3A4 inducers, such as rifampicin and phenytoin, may require an increase in the dose of ivabradine. St John's wort reduces the exposure to ivabradine by half and its use should be restricted.

Pharmacokinetics

Ivabradine is almost completely absorbed after oral doses but bioavailability is about 40% because of first-pass metabolism. Peak plasma concentrations are achieved after about 1 hour in the fasting state but this is delayed by 1 hour by food and the extent of absorption increased by 20 to 30%. Ivabradine is about 70% bound to plasma proteins.

Ivabradine undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite *N*-desmethylivabradine (S-18982). This is further metabolised to some degree by CYP3A4. Ivabradine has an elimination half-life of 2 hours. Its metabolites are excreted to a similar extent in the urine and faeces. About 4% of a dose appears in the urine as the parent drug. *Animal* studies indicate that ivabradine is distributed into breast milk.

Uses and Administration

Ivabradine is a selective sinus node I_f inhibitor used in the treatment of angina pectoris in patients unable to take beta blockers. It is given as the hydrochloride, but doses are described in terms of the base; 5.4 mg of ivabradine hydrochloride is equivalent to about 5 mg of ivabradine. It is given orally with food in a usual initial dose of 5 mg twice daily, increased after 3 or 4 weeks if necessary to 7.5 mg twice daily. If the heart rate falls persistently below 50 beats/minute or there are symptoms of bradycardia the dose should be titrated downwards, to as low as 2.5 mg twice daily if necessary. Treatment should be stopped if this low rate or symptoms of bradycardia persist.

In the elderly (75 years or above), a lower initial dose of 2.5 mg twice daily should be considered, before increasing if necessary.

◊ Reviews.

1. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; **64:** 1757–65.
2. Sulfi S, Timmis AD. Ivabradine—the first selective sinus node I channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006; **60:** 222–8.
3. Menown IBA. Ivabradine: a new strategy for management of stable angina. *Br J Hosp Med* 2007; **68:** 321–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Coralan; ***Cz.:*** Corlentor; Procoralan; ***Fr.:*** Corlentor; Procoralan; ***Ger.:*** Procoralan; ***Gr.:*** Procoralan; ***Irl.:*** Procoralan; ***Neth.:*** Corlentor; Procoralan; ***Pol.:*** Procoralan; ***Port.:*** Corlentor; Procoralan; ***Rus.:*** Coraxan (Кораксан); ***UK:*** Procoralan.

Ketanserin *(BAN, USAN, rINN)*

Ketanseriini; Ketanserina; Kétansérine; Ketanserinum; R-41468. 3-{2-[4-(4-Fluorobenzoyl)piperidino]ethyl}quinazoline-2,4(1*H*,3*H*)-dione.

Кетансерин

$C_{22}H_{22}FN_3O_3$ = 395.4.

CAS — 74050-98-9.

ATC — C02KD01.

ATC Vet — QC02KD01; QD03AX90.

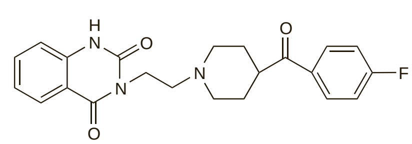

Ketanserin Tartrate *(BANM, rINNM)*

Kétansérine, Tartrate de; Ketanserini Tartras; R-49945; Tartrato de ketanserina.

Кетансерина Тартрат

$C_{22}H_{22}FN_3O_3,C_4H_6O_6$ = 545.5.

CAS — 83846-83-7.

ATC — C02KD01.

ATC Vet — QC02KD01.

Adverse Effects and Precautions

Ketanserin has been reported to cause sedation, fatigue, light-headedness, dizziness, headache, dry mouth, and gastrointestinal disturbances. Oedema has been reported rarely. In patients with predisposing factors such as QT prolongation, chronic use of ketanserin has been associated with ventricular arrhythmias including torsade de pointes; ketanserin should be used with caution in patients taking antiarrhythmics and should not be used in second- or third-degree AV block. Care should be taken to avoid the development of hypokalaemia in patients taking ketanserin, for example if diuretics are also given.

Because ketanserin may cause drowsiness care should be taken in patients who drive or operate machinery.

Ketanserin is reported to be better tolerated in elderly than in younger patients.

Interactions

The hypotensive effects of ketanserin may be enhanced by diuretics and other antihypertensives. Ketanserin should be used with caution in patients taking antiarrhythmics or drugs that cause hypokalaemia since the risk of arrhythmias is increased.

Beta blockers. Profound hypotension occurred in 2 patients one hour after taking ketanserin 40 mg orally.[1] Both patients were also taking a beta blocker which may have exacerbated the reaction.

1. Waller PC, *et al.* Profound hypotension after the first dose of ketanserin. *Postgrad Med J* 1987; **63:** 305–7.

Pharmacokinetics

Ketanserin is rapidly absorbed from the gastrointestinal tract but has a bioavailability of about 50% due to first-pass hepatic metabolism. Peak plasma concentrations occur between 30 and 120 minutes after an oral dose. Ketanserin is about 95% bound to plasma proteins. The terminal half-life is stated to be between 13 and 18 hours but some studies report that following multiple doses the half-life is 19 to 29 hours. The metabolite ketanserinol has a terminal half-life of 31 to 35 hours after multiple doses, and it has been suggested that reconversion of ketanserinol to ketanserin may be responsible for the prolonged half-life of the parent compound during chronic use.

About 68% of an oral dose is excreted in urine, and 24% in faeces, mainly as metabolites. Studies in *animals* suggest that ketanserin may cross the placenta and that some is present, with metabolites, in breast milk.

◊ References.

1. Persson B, *et al.* Clinical pharmacokinetics of ketanserin. *Clin Pharmacokinet* 1991; **20:** 263–79.

Uses and Administration

Ketanserin is a serotonin antagonist with a high affinity for peripheral serotonin-2 ($5\text{-}HT_2$) receptors and thus inhibits serotonin-induced vasoconstriction, bronchoconstriction, and platelet aggregation. It also has some $alpha_1$-antagonist and histamine H_1-antagonist properties, but the clinical significance of these is controversial.

Ketanserin is used in the management of hypertension (p.1171) and has also been tried in other conditions (see below).

Ketanserin is given as the tartrate, but doses are usually expressed in terms of the base. Ketanserin tartrate 27.6 mg is equivalent to about 20 mg of ketanserin.

Ketanserin produces a gradual hypotensive effect when given orally, and 2 or 3 months of therapy may be required to produce the maximum reduction in blood pressure. After intravenous injection a fall in blood pressure is generally produced in 1 or 2 minutes and lasts for 30 to 60 minutes.

In **hypertension** the usual initial oral dose is 20 mg twice daily, increasing, if necessary, after 2 to 4 weeks, to 40 mg twice daily. It has also been given by intravenous or intramuscular injection. The dose of ketanserin may need to be reduced, or the dosage intervals increased, in patients with hepatic impairment (see below).

◊ Reviews.

1. Brogden RN, Sorkin EM. Ketanserin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. *Drugs* 1990; **40:** 903–49.

Administration in hepatic impairment. A study[1] in patients with cirrhosis found that the half-life and volume of distribution of ketanserin were decreased but the area under the concentration-time curve was markedly increased; the rate of metabolism was reduced. The results suggested that the dosage should be reduced or the dosage interval increased when ketanserin is given to patients with cirrhosis.

Licensed product information recommends a maximum oral dose of 20 mg twice daily for patients with severe hepatic impairment.

1. Lebrec D, *et al.* Pharmacokinetics of ketanserin in patients with cirrhosis. *Clin Pharmacokinet* 1990; **19:** 160–6.

Administration in renal impairment. Results from a study in 12 patients with chronic renal impairment, of whom 6 required haemodialysis, suggested that no adjustment of a dose of ketanserin 20 mg twice daily was required in patients with renal impairment.[1]

1. Barendregt JNM, *et al.* Ketanserin pharmacokinetics in patients with renal failure. *Br J Clin Pharmacol* 1990; **29:** 715–23.

Peripheral vascular disease. Ketanserin is one of many drugs that have been tried in the management of peripheral vascular disease (p.1178) but results have been contradictory. Subgroup analysis of the multicentre Prevention of Atherosclerotic Complications with Ketanserin Trial (PACK),[1] involving 3899 patients with intermittent claudication, suggested that ketanserin might be of benefit in preventing limb amputation in some patients. Conflicting results have also been reported in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188). A systematic review[2] found that ketanserin led to a small improvement in Raynaud's syndrome in patients with systemic sclerosis but that adverse effects increased; the authors concluded that ketanserin was not clinically beneficial in such patients.

Ketanserin has also been tried in other conditions associated with impaired peripheral blood flow: see Wounds and Ulcers, below.

1. Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* 1989; **298:** 424–30. Correction. *ibid.*: 644.
2. Pope JE, *et al.* Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 26/09/05).

Shivering. Numerous drugs, including ketanserin, have been tried for the treatment of postoperative shivering (p.1779). Ketanserin 10 mg given intravenously has stopped shivering after general anaesthesia.[1,2]

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Crisinel D, *et al.* Efficacité de la kétansérine sur le frisson postanesthésique. *Ann Fr Anesth Reanim* 1997; **16:** 120–5.

Wounds and ulcers. Several controlled studies[1-5] have noted improved healing of decubitus, venous, and ischaemic ulcers (see Wounds and Ulcers, p.1585) after topical use of ketanserin 2%. However, when applied topically to surgical wounds no improvement was found and it was suggested that ketanserin is only of benefit where blood supply is compromised.[6]

1. Tytgat H, van Asch H. Topical ketanserin in the treatment of decubitus ulcers: a double-blind study with 2% ketanserin ointment against placebo. *Adv Therapy* 1988; **5:** 143–52.
2. Roelens P. Double-blind placebo-controlled study with topical 2% ketanserin ointment in the treatment of venous ulcers. *Dermatologica* 1989; **178:** 98–102.
3. Janssen PAJ, *et al.* Use of topical ketanserin in the treatment of skin ulcers: a double-blind study. *J Am Acad Dermatol* 1989; **21:** 85–90.
4. Martinez-de Jesus FR, *et al.* Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Arch Med Res* 1997; **28:** 95–9.
5. Salazar JJ, *et al.* Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian J Lepr* 2001; **73:** 103–10.
6. Lawrence CM, *et al.* The effect of ketanserin on healing of fresh surgical wounds. *Br J Dermatol* 1995; **132:** 580–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Serefrex†; ***Belg.:*** Sufrexal; ***Ital.:*** Serepress; ***Mex.:*** Sufrexal; ***Neth.:*** Ketensin; ***Port.:*** Sufrexal†; ***Thai.:*** Sufrexal†.

Multi-ingredient: ***Mex.:*** Sufrexal P.

Labetalol Hydrochloride

(BANM, USAN, rINNM) ⊗

AH-5158A; Hidrocloruro de labetalol; Ibidomide Hydrochloride; Labétalol, chlorhydrate de; Labetalol hydrochlorid; Labetalol-hidroklorid; Labetalolhydroklorid; Labetaloli hydrochloridum; Labetalolihydrokloridi; Labetalolio hidrochloridas; Sch-15719W. 5-[1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylamide hydrochloride.

Лабеталола Гидрохлорид

$C_{19}H_{24}N_2O_3,HCl = 364.9.$

CAS — 36894-69-6 (labetalol); 32780-64-6 (labetalol hydrochloride).

ATC — C07AG01.

ATC Vet — QC07AG01.

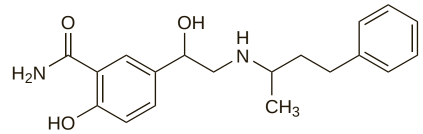

(labetalol)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Labetalol Hydrochloride). A white or almost white powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.0.

USP 31 (Labetalol Hydrochloride). A white to off-white powder. Soluble in water and in alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Labetalol hydrochloride is compatible with standard intravenous solutions such as glucose 5% and sodium chloride 0.9%. However, precipitation has been reported when labetalol hydrochloride is added to sodium bicarbonate injection 5%.[1] The precipitate is probably labetalol base.[2]

Immediate formation of a precipitate has also been reported when labetalol (generally 5 mg/mL in glucose 5%) was mixed with other drugs including ceftriaxone,[3] furosemide,[4] heparin,[5] insulin,[5] proton pump inhibitors such as pantoprazole,[6] and thiopental.[4] There has also been a report of immediate haze after admixture of labetalol hydrochloride (800 micrograms/mL) with warfarin sodium.[7]

1. Yuen P-HC, *et al.* Compatibility and stability of labetalol hydrochloride in commonly used intravenous solutions. *Am J Hosp Pharm* 1983; **40:** 1007–9.
2. Alam AS. Identification of labetalol precipitate. *Am J Hosp Pharm* 1984; **41:** 74.
3. Leader WG, Jones JM. Incompatibility between ceftriaxone sodium and labetalol hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 2639.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
6. Péré H, *et al.* Compatibilité du pantoprazole injectable lors d'administration en Y. *Pharmactuel* 2004; **37:** 193–6.
7. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Adverse Effects

The adverse effects associated with beta blockers are described on p.1226. Labetalol also has alpha-blocking activity, which contributes to its adverse effects and these effects may predominate. Orthostatic hypotension may be a problem with high doses or at the start of treatment. Other effects associated with alpha blockade include dizziness, scalp tingling, and nasal congestion. Male sexual function may be impaired to a greater extent than with beta blockade alone. Muscle weakness, tremor, urinary retention, hepatitis, and jaundice have also been reported.

Effects on the liver. By 1990, the FDA had received 11 reports of hepatocellular damage associated with labetalol therapy.[1] Three patients died. Liver function should be monitored and labetalol stopped in patients who develop liver function abnormalities. The *R,R*-isomer of labetalol, dilevalol, was withdrawn from the market because of hepatotoxicity.[2]

1. Clark JA, *et al.* Labetalol hepatotoxicity. *Ann Intern Med* 1990; **113:** 210–13.
2. Harvengt C. Labetalol hepatotoxicity. *Ann Intern Med* 1991; **114:** 341.

Hypersensitivity. Hypersensitivity reactions associated with labetalol may manifest as fever.[1,2] Anaphylactoid reaction to labetalol has also been reported.[3]

1. D'Arcy PF. Drug reactions and interactions: drug fever with labetalol. *Int Pharm J* 1987; **1:** 43–4.
2. Stricker BH, *et al.* Fever induced by labetalol. *JAMA* 1986; **256:** 619–20.
3. Ferree CE. Apparent anaphylaxis from labetalol. *Ann Intern Med* 1986; **104:** 729–30.

Overdosage. Acute oliguric renal failure developed after a short period of moderate hypotension in a patient who ingested labetalol 16 g. Renal function subsequently recovered.[1] Renal failure has also been reported[2] after ingestion of labetalol 6 g. The patient recovered after treatment with glucagon, isoprenaline, and dialysis. Another patient[3] developed circulatory collapse and impaired consciousness after being given labetalol 800 mg orally for hypertensive crisis; glucagon and sympathomimetics were given to restore blood pressure, but amrinone infusion was also needed to improve cardiac output and mental state.

1. Smit AJ, *et al.* Acute renal failure after overdose of labetalol. *BMJ* 1986; **293:** 1142–3.
2. Korzets A, *et al.* Acute renal failure associated with a labetalol overdose. *Postgrad Med J* 1990; **66:** 66–7.
3. Kollef MH. Labetalol overdose successfully treated with amrinone and alpha-adrenergic receptor agonists. *Chest* 1994; **105:** 626–7.

Precautions

As for Beta Blockers, p.1227.

Because labetalol causes orthostatic hypotension it is recommended that injections are given to patients when they are lying down and that patients should remain lying down for the next 3 hours.

Labetalol should be withdrawn from patients who develop signs of hepatic impairment.

Breast feeding. Labetalol is distributed into breast milk, although it has been suggested[1] that the proportion of a maternal dose likely to be ingested by the infant is very low. In a study[2] in 25 patients, the mean concentration of labetalol in breast milk was less than in maternal plasma in patients given doses between 330 and 800 mg daily, although in 1 patient given 1200 mg daily a higher concentration was found in breast milk. In another study,[3] the concentration of drug in milk exceeded maternal plasma concentration in 2 of 3 mothers, and in 1 infant the plasma-labetalol concentration was similar to that of the mother. However, no adverse effects have been seen in breast-feeding infants whose mothers were given labetalol, and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. *J Pediatr* 1990; **116:** 156.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Labetalol is readily absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism. Bioavailability varies widely between patients and may be increased in the presence of food. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Labetalol has low lipid solubility and only very small amounts appear to cross the blood-brain barrier in *animals*. It is about 50% protein bound. Labetalol crosses the placenta and is distributed into breast milk (see above). Labetalol is metabolised mainly in the liver, the metabolites being excreted in the urine with only small amounts of unchanged labetalol; its major metabolite has not been found to have significant alpha- or beta-blocking effects. Excretion also occurs in the faeces via the bile. The elimination half-life at steady state is reported to be about 6 to 8 hours. On intravenous infusion, the elimination half-life is about 5.5 hours. Labetalol is not removed by dialysis.

The elderly. Analysis[1] of data from 4 single-dose studies and 3 multidose studies indicated that age did not appear to be a significant factor in oral clearance in elderly patients receiving labetalol for long-term management of hypertension.

1. Rocci ML, *et al.* Effects of age on the elimination of labetalol. *Clin Pharmacokinet* 1989; **17:** 452–7.

Pregnancy. The concentration of labetalol has been found to be lower in amniotic fluid[1] and fetal plasma[2] than in maternal plasma. A ratio of infant to maternal drug concentration of 0.2 to 0.8 has been reported[2] based on concentration in infant cord blood at delivery [time since last maternal dose not stated]. In another study,[3] however, higher concentrations were found in cord plasma than in maternal plasma at delivery when infants were delivered 12 to 24 hours after the last maternal dose.

The half-life of labetalol was reported as 24 hours in a neonate of 37 weeks' gestation whose mother had received labetalol 600 mg daily for 11 weeks prior to delivery.[4]

1. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Boulton DW, *et al.* Transplacental distribution of labetalol stereoisomers at delivery. *Br J Clin Pharmacol* 1999; **47:** 573–4.
4. Haraldsson A, Geven W. Half-life of maternal labetalol in a premature infant. *Pharm Weekbl (Sci)* 1989; **11:** 229–31.

Uses and Administration

Labetalol is a non-cardioselective beta blocker (p.1225). It is reported to possess some intrinsic sympathomimetic and membrane-stabilising activity. In addition, it has selective $alpha_1$-blocking properties which decrease peripheral vascular resistance. The ratio of alpha- to beta-blocking activity has been estimated to be about 1:3 after oral doses and 1:7 after intravenous doses.

Labetalol is used as the hydrochloride in the management of hypertension (p.1171). It is also used to induce hypotension during surgery. Labetalol decreases blood pressure more rapidly than other beta blockers; the full antihypertensive effect may be seen within 1 to 3 hours of an oral dose.

In **hypertension** labetalol hydrochloride is usually given in an initial oral dose of 100 mg twice daily with food, gradually increased if necessary according to response and standing blood pressure, to 200 to 400 mg twice daily; total daily doses of 2.4 g, in two to four divided doses, have occasionally been required. Lower doses may be adequate in elderly patients; an initial dose of 50 to 100 mg twice daily has been recommended, and the usual maintenance dose is 100 to 200 mg twice daily.

For the emergency treatment of hypertension labetalol hydrochloride may be given by slow intravenous injection. In the UK a dose of 50 mg is recommended, given over a period of at least 1 minute; if necessary this dose may be repeated at intervals of 5 minutes until a total of 200 mg has been given. In the USA an initial dose of 20 mg is recommended, given over 2 minutes; subsequent doses of 40 to 80 mg may be given every 10 minutes, if necessary, up to a maximum of 300 mg. Blood pressure should be monitored, and the patient should remain supine during the injection and for 3 hours afterwards, to avoid excessive orthostatic hypotension. After bolus intravenous injection a maximum effect is usually obtained within 5 minutes and usually lasts up to 6 hours, although it may extend as long as 18 hours.

Labetalol hydrochloride has also been given by intravenous infusion in usual doses of 2 mg/minute. Suggested concentrations for intravenous infusions are 1 mg/mL or 2 mg/3 mL of suitable diluent. In hypertension in pregnancy, labetalol infusion may be started at the rate of 20 mg/hour, then doubled every 30 minutes until a satisfactory response is obtained or a dose of 160 mg/hour is reached. In hypertension after myocardial infarction, labetalol infusion may be started at the rate of 15 mg/hour and gradually increased until a satisfactory response is obtained or a dose of 120 mg/hour is reached.

The initial dose in **hypotensive anaesthesia** is 10 to 20 mg intravenously, with increments of 5 to 10 mg if satisfactory hypotension is not achieved after 5 minutes. A higher initial dose may be required in patients who do not receive halothane anaesthesia.

For the use of labetalol in children, see below.

Action. Labetalol has 2 optical centres; it is used as the racemic mixture of the 4 stereoisomers. The *R,R*- isomer is responsible for the beta-blocking activity and has limited alpha-blocking activity; it also has beta-adrenergic mediated peripheral vasodilating activity. The *S,R*-isomer has the most potent alpha-blocking activity. The *S,S*-isomer has some alpha-blocking activity and the *R,S*-isomer does not appear to have either alpha- or beta-adrenergic blocking effect.[1] The pure *R,R*-isomer, dilevalol, was withdrawn from the market because of hepatotoxicity.

1. Gold EH, *et al.* Synthesis and comparison of some cardiovascular properties of the stereoisomers of labetalol. *J Med Chem* 1982; **25:** 1363–70.

Administration in children. Labetalol has been used in the management of hypertension in children,[1] although experience is limited. The *BNFC* suggests the following doses:

for **hypertensive emergencies**, labetalol hydrochloride may be given by intravenous infusion as follows:

- neonates: 500 micrograms/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 4 mg/kg per hour
- 1 month to 12 years: 0.5 to 1 mg/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 3 mg/kg per hour
- 12 to 18 years: 30 to 120 mg/hour adjusted at intervals of at least 15 minutes according to response

for **hypertension**, labetalol hydrochloride may be given as follows:

- 1 month to 12 years: 1 to 2 mg/kg three or four times daily by mouth or a single intravenous injection in a dose of 250 to 500 micrograms/kg to a maximum of 20 mg
- 12 to 18 years: similar doses to adults (see above) although a lower initial oral dose of 50 to 100 mg twice daily is recommended

1. Bunchman TE, *et al.* Intravenously administered labetalol for treatment of hypertension in children. *J Pediatr* 1992; **120:** 140–4.

Preparations

BP 2008: Labetalol Injection; Labetalol Tablets;
USP 31: Labetalol Hydrochloride Injection; Labetalol Hydrochloride Oral Suspension; Labetalol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Biascor; ***Austral.:*** Presolol; Trandate; ***Austria:*** Trandate; ***Belg.:*** Trandate; ***Canad.:*** Trandate; ***Chile:*** Trandate; ***Cz.:*** Coreton†; Trandate; ***Denm.:*** Trandate; ***Fin.:*** Albetol; ***Fr.:*** Trandate; ***Gr.:*** Trandate; ***Hong Kong:*** Trandate; ***Irl.:*** Trandate; ***Israel:*** Trandate; ***Ital.:*** Ipolab; Trandate; ***Malaysia:*** Tolbetol†; Trandate; ***Neth.:*** Trandate; ***Norw.:*** Trandate; ***NZ:*** Hybloc; Trandate; ***Port.:*** Trandate†; ***S.Afr.:*** Trandate; ***Singapore:*** Trandate; ***Spain:*** Trandate; ***Swed.:*** Trandate; ***Switz.:*** Trandate; ***UK:*** Trandate; ***USA:*** Normodyne†; Trandate; ***Venez.:*** Trandate†.

Multi-ingredient: ***Ital.:*** Trandiur.

Lacidipine *(BAN, USAN, rINN)*

GR-43659X; GX-1048; Lacidipin; Lacidipino; Lacidipinum; Lasidipiini; Lasidipin. Diethyl 4-{2-[(*tert*-butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

Лацидипин

$C_{26}H_{33}NO_6$ = 455.5.
CAS — 103890-78-4.
ATC — C08CA09.
ATC Vet — QC08CA09.

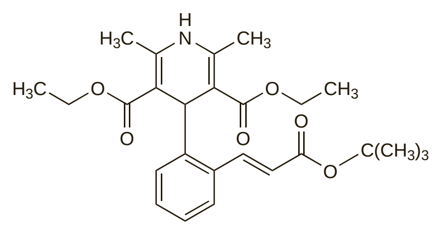

Pharmacopoeias. In *Br.*
BP 2008 (Lacidipine). A white to pale yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Lacidipine is rapidly but poorly absorbed from the gastrointestinal tract after oral doses and undergoes extensive first-pass metabolism; the bioavailability has been reported to be 2 to 9%, or 18.5% (range 4 to 52%) using a more sensitive assay method. It is more than 95% bound to plasma proteins. Lacidipine is eliminated by metabolism in the liver and metabolites are excreted mainly by the biliary route. About 70% of an oral dose is eliminated in the faeces, the remainder in the urine. The average steady-state terminal elimination half-life of lacidipine is 13 to 19 hours.

Uses and Administration

Lacidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual initial dose of lacidipine is 2 mg once daily by mouth increased if necessary after 3 to 4 weeks or more to 4 mg daily; a further increase in dose to 6 mg daily may be necessary in some patients.

◊ Reviews.

1. Lee CR, Bryson HM. Lacidipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of hypertension. *Drugs* 1994; **48:** 274–96.
2. Zanchetti A, ed. Cardiovascular advantages of a third generation calcium antagonist: symposium on lacidipine. *Drugs* 1999; **57** (suppl 1): 1–29.
3. McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. *Drugs* 2003; **63:** 2327–56.

Preparations

BP 2008: Lacidipine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lacipil†; Midotens†; ***Belg.:*** Motens; ***Braz.:*** Lacipil; Midotens; ***Cz.:*** Lacipil; ***Denm.:*** Midotens; ***Fr.:*** Caldine; ***Ger.:*** Motens; ***Gr.:*** Balnox; Lacipil; Lacitens; Motens; ***Hong Kong:*** Lacipil; ***Hung.:*** Lacipil; ***India:*** Sinopil; ***Indon.:*** Lacipil; ***Ital.:*** Aponil; Lacipil; Lacirex; Ladip; Viapres; ***Malaysia:*** Lacipil; ***Mex.:*** Lacipil; Midotens; ***Neth.:*** Motens; ***Philipp.:*** Lacipil; ***Pol.:*** Lacipil; ***Port.:*** Lacipil; Tens; ***Rus.:*** Lacipil (Лаципил); ***Singapore:*** Lacipil; ***Spain:*** Lacimen; Lacipil; Motens; ***Switz.:*** Motens; ***Thai.:*** Motens; ***Turk.:*** Lacipil; ***UK:*** Motens; ***Venez.:*** Lacipil; Tens†.

Lamifiban *(USAN, rINN)*

Lamifibán; Lamifibanum; Ro-44-9883; Ro-44-9883/000. ({1-[*N*-(*p*-Amidinobenzoyl)-L-tyrosyl]-4-piperidyl}oxy)acetic acid.

Ламифибан

$C_{24}H_{28}N_4O_6$ = 468.5.
CAS — 144412-49-7 (lamifiban); 243835-65-6 (lamifiban hydrochloride).

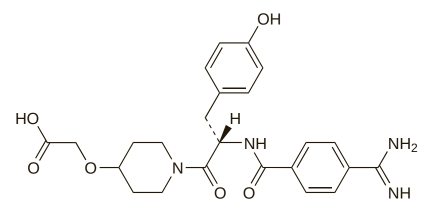

Profile

Lamifiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an antiplatelet drug given intravenously for the management of thromboembolic disorders, such as unstable angina and myocardial infarction.

◊ References.

1. Théroux P, *et al.* Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina: the Canadian Lamifiban Study. *Circulation* 1996; **94:** 899–905.
2. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. *Circulation* 1998; **97:** 2386–95.
3. The PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial. *J Am Coll Cardiol* 1998; **32:** 2003–10.
4. Global Organization Network (PARAGON)-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation* 2002; **105:** 316–21.

Lanatoside C *(BAN, rINN)*

Celanide; Celanidum; Lanatosid C; Lanatosidi C; Lanatósido C; Lanatosidum C; Lanatozyd c. 3-[(*O*-β-D-Glucopyranosyl-(1→4)-*O*-3-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

Ланатозид C

$C_{49}H_{76}O_{20}$ = 985.1.
CAS — 17575-22-3.
ATC — C01AA06.
ATC Vet — QC01AA06.

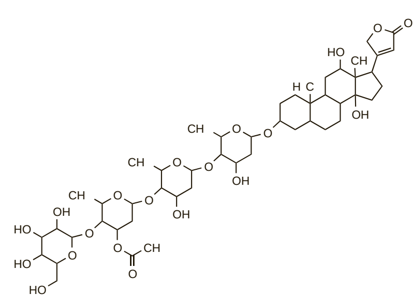

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Lanatoside C is a cardiac glycoside with positive inotropic activity. It is obtained from digitalis lanata leaf (p.1258). It has general properties similar to those of digoxin (p.1259) and has been used in the treatment of some cardiac arrhythmias and in heart failure.

Mixtures of lanatosides A, B, and C have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Develanid†; ***Mex.:*** Cedilanid.

Landiolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de landiolol; Landiolol, Chlorhydrate de; Landiololi Hydrochloridum; ONO-1101. (−)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl *p*-((*S*)-2-hydroxy-3-{[2-(4-morpholinecarboxamido)ethyl]amino}propoxy)hydrocinnamate hydrochloride.

Ландиолола Гидрохлорид

$C_{25}H_{39}N_3O_8$,HCl = 546.1.

CAS — 133242-30-5 (landiolol); 144481-98-1 (landiolol hydrochloride).

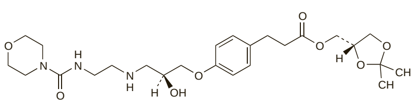

(landiolol)

Profile

Landiolol is a short-acting, cardioselective beta blocker given intravenously as the hydrochloride in the management of intra- and postoperative cardiac arrhythmias.

◊ References.

1. Kitamura A, *et al.* Efficacy of an ultrashort-acting beta-adrenoceptor blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. *Eur J Clin Pharmacol* 1997; **51:** 467–71.
2. Atarashi H, *et al.* Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000; **68:** 143–50.
3. Mizuno J, *et al.* Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. *Eur J Clin Pharmacol* 2007; **63:** 243–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Onoact.

Lanoteplase *(USAN, rINN)*

BMS-200980; Lanoteplasa; Lanotéplase; Lanoteplasum; Sun-9216. *N*-[N^2-(*N*-Glycyl-L-alanyl)-L-arginyl]-117-L-glutamine-245-L-methionine-(1-5)-(87-527)-plasminogen activator (human tissue-type protein moiety).

Ланотеплаза

$C_{2184}H_{3323}N_{633}O_{666}S_{29}$ = 50032.5.

CAS — 171870-23-8.

Profile

Lanoteplase is a thrombolytic that has been investigated in acute myocardial infarction; development was stopped after an unacceptable rate of intracranial haemorrhage was found.

◊ References.

1. The InTIME-II Investigators. Intravenous NPA for the treatment of infarcting myocardium early: InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000; **21:** 2005–13.

Lappaconitine Hydrobromide

(1α,14α,16β)-20-Ethyl-1,14,16-trimethoxyaconitane-4,8,9-triol 4-[2-(acetylamino)benzoate] hydrobromide.

Лаппаконитина Гидробромид

$C_{32}H_{44}N_2O_8$,HBr = 665.6.

CAS — 32854-75-4 (lappaconitine); 97792-45-5 (lappaconitine hydrobromide).

Profile

Lappaconitine hydrobromide is an antiarrhythmic drug given orally in a usual dose of 25 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Allapinin (Аллапинин).

Leech

Blutegel; Hirudo; Sangsue; Sanguessugas; Sanguijuela; Sanguisuga.

Description. *Hirudo medicinalis* is the leech commonly used in medicine and is a fresh-water annelid.

NOTE. The substance described in the *Chin. P.* as Hirudo (Leech) is the dried body of *Whitmania pigra, Hirudo nipponica*, or *Whitmania acranulata.*

Profile

Leeches are used for withdrawing blood from congested areas and have been found to be of value in plastic surgery. The buccal secretion of the leech contains the anticoagulant hirudin (p.1305). Once used a leech should not be applied to another patient.

There have been reports of wound infection from *Aeromonas hydrophila* transmitted by leeches. Prolonged bleeding for up to 10 hours may occur from the site of attachment after removal of the leech.

◊ Leeches are commonly used in plastic surgery and this has been reviewed.[1]

Wound infection by *Aeromonas hydrophila*, an organism normally found in the gut of the leech, is a recognised complication of the use of leeches for decongestion after plastic surgery. Other infecting organisms include *Aeromonas sobria* and *Serratia marcescens.* Infections have caused minor wound drainage, cellulitis, abscess, tissue loss, and sepsis, and a case of meningitis secondary to *Aeromonas* infection has been reported.[2] The following protocol has been suggested:[1] the site of application should first be cleaned with heparinised saline, and antibacterial prophylaxis with a quinolone and an aminoglycoside given for the duration of application. Patients discharged with open wounds should continue with oral antibacterials until wound closure.

In addition to its anticoagulant properties the buccal secretion of the leech contains anti-inflammatory substances, and leeches have been reported to provide subjective relief of symptoms[3,4] in osteoarthritis.

1. Whitaker IS, *et al.* Hirudo medicinalis and the plastic surgeon. *Br J Plast Surg* 2004; **57:** 348–53.
2. Ouderkirk JP, *et al.* Aeromonas meningitis complicating medicinal leech therapy. Abstract: *Clin Infect Dis* 2004; **38:** 603. Full version: http://www.journals.uchicago.edu/doi/full/10.1086/381438 (accessed 19/08/08)
3. Michalsen A, *et al.* Effect of leeches therapy (Hirudo medicinalis) in painful osteoarthritis of the knee: a pilot study. *Ann Rheum Dis* 2001; **60:** 986.
4. Michalsen A, *et al.* Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003; **139:** 724–30.

Lepirudin *(BAN, rINN)*

HBW-023; Lepirudiini; Lepirudina; Lépirudine; Lepirudinum. 1-L-Leucine-2-L-threonine-63-desulfohirudin (*Hirudo medicinalis* isoform HV1).

Лепирудин

$C_{287}H_{440}N_{80}O_{111}S_6$ = 6979.4.

CAS — 138068-37-8.

ATC — B01AE02.

ATC Vet — QB01AE02.

Adverse Effects and Precautions

The most frequent adverse effect of the direct thrombin inhibitors is bleeding. Hypersensitivity reactions have been reported. There have been reports of severe anaphylactic reactions, including death, with many occurring on re-exposure. There may be cross-reactivity with other hirudins or hirudin analogues.

Intramuscular injection should be avoided as it may cause local haematoma.

Direct thrombin inhibitors should be used with caution or avoided in patients with hepatic or renal impairment, and in those who are bleeding or at serious risk of bleeding, including those with haemorrhagic blood disorders, recent major bleeding, cerebrovascular disorders, bacterial endocarditis, severe hypertension, or patients who have recently undergone major surgery or puncture of large vessels or organ biopsy.

Hypersensitivity. The EMEA reported[1] in October 2002 that they were aware of 7 cases of severe anaphylactic reactions in patients given lepirudin; in 6 cases this followed re-exposure to the drug, and in 5 cases the patient died. A review[2] of the manufacturer's safety database identified 9 patients with severe anaphylactic reactions associated with lepirudin; 4 patients died, all of whom had received lepirudin within the previous 1 to 12 weeks. Although the risk of severe anaphylaxis was estimated to be low (0.015% on first exposure and 0.16% on re-exposure),[2] alternative treatment should be considered before re-exposure to lepirudin and it should only be used where treatment for an anaphylactic reaction is available.[1,2]

1. EMEA. EMEA public statement on Refludan (lepirudin)—fatal anaphylactic reactions (issued October 2002). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/2771702en.pdf (accessed 16/05/08)
2. Greinacher A, *et al.* Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; **108:** 2062–5.

Interactions

Use of direct thrombin inhibitors with thrombolytics, oral anticoagulants, or drugs that affect platelet function may increase the risk of bleeding.

Pharmacokinetics

Lepirudin is metabolised and excreted by the kidney. About 45% of an intravenous dose is detected in the urine and about 35% is excreted unchanged. The terminal elimination half-life of lepirudin is about 1.3 hours. In patients with severe renal impairment the half-life may be prolonged to about 2 days.

Breast feeding. Three hours after injection, plasma concentrations of hirudin in a woman receiving lepirudin 50 mg subcutaneously twice daily were 0.5 to 1 microgram/mL, but no hirudin was detected in the breast milk.

1. Lindhoff-Last E, *et al.* Hirudin treatment in a breastfeeding woman. *Lancet* 2000; **355:** 467–8.

Uses and Administration

Lepirudin is a recombinant hirudin (p.1305) that is a direct inhibitor of thrombin. It is used as an anticoagulant in the management of thromboembolic disorders (p.1187) in patients with heparin-induced thrombocytopenia. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina.

In the management of thromboembolism in patients with heparin-induced thrombocytopenia lepirudin is given in an initial dose of 400 micrograms/kg by slow intravenous injection. This is followed by a maintenance dose of 150 micrograms/kg per hour by continuous intravenous infusion, adjusted according to response, usually for 2 to 10 days. Response should be monitored according to the activated partial thromboplastin time (APTT) ratio to achieve a target of 1.5 to 2.5. Doses must not exceed those based on a patient weight of 110 kg and in general an infusion rate of 210 micrograms/kg per hour should not be exceeded.

Doses of lepirudin should be reduced in patients with renal impairment, and infusions should be avoided in those on haemodialysis (see below).

Administration in renal impairment. Doses of lepirudin should be reduced in patients with renal impairment. The initial dose is reduced to 200 micrograms/kg, and the maintenance infusion rate is reduced according to creatinine clearance (CC):

- CC 45 to 60 mL/minute: infusion rate 50% of normal rate
- CC 30 to 44 mL/minute: 30% of normal rate
- CC 15 to 29 mL/minute: 15% of normal rate
- CC below 15 mL/minute: infusion of lepirudin should be avoided, although in haemodialysis patients or cases of acute renal failure further intravenous bolus doses of 100 micrograms/kg may be used on alternate days, according to response

Heparin-induced thrombocytopenia. Lepirudin is effective for the management of thromboembolism in patients with heparin-induced thrombocytopenia[1] (see Effects on the Blood under Adverse Effects of Heparin p.1302). Bleeding is the main complication during treatment, particularly with usual doses (see Uses and Administration, above) and in patients with renal impairment,[2] and use of lower doses has been suggested.[1,2]

1. Lubenow N, *et al.* HIT Investigators Group. Lepirudin in patients with heparin-induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005; **3:** 2428–36.
2. Tardy B, *et al.* GEHT-HIT Study Group. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood* 2006; **108:** 1492–6.

Ischaemic heart disease. Recombinant hirudins have been investigated as alternatives to heparin in the management of acute ST-elevation myocardial infarction (p.1175) and in non-ST elevation myocardial infarction and unstable angina (see Angina Pectoris, p.1157), and have been used as adjuncts to medical or interventional treatment. Overall they appear to have some benefit over heparin,[1] but their precise role in each situation remains to be confirmed.

Initial studies comparing heparin with the recombinant hirudins desirudin[2,3] (p.1257) or lepirudin[4] in patients with acute ST-elevation **myocardial infarction** treated with thrombolytics had to be stopped because of higher than expected haemorrhagic stroke rates,[5,6] and subsequent studies using lower doses of desirudin[7,8] or lepirudin[9] failed to show a clear benefit over heparin. A study[10] with bivalirudin, a synthetic analogue of hirudin, in similar patients also found no mortality benefit; there were fewer reinfarctions in the bivalirudin group, but the risk of bleeding was increased. The role of hirudins is therefore not established, although they may be useful in patients with heparin-induced thrombocytopenia.

Studies in patients with **acute coronary syndromes** (non-ST elevation myocardial infarction and unstable angina) suggest that lepirudin is superior to heparin in preventing cardiovascular death, myocardial infarction, and refractory angina.[11,12] A study[13] comparing desirudin with heparin in unstable angina found that angiographic outcomes were better with desirudin, but another study[7] found little benefit in terms of mortality or recurrent ischaemia. Bivalirudin appears to be as effective as heparin in patients with acute coronary syndromes, but unlike the other hirudins the risk of major bleeding may be reduced.[14,15]

Hirudins have also been studied in patients undergoing **percutaneous coronary interventions** (see Reperfusion and Revascularisation Procedures, p.1181). Desirudin has been used in patients undergoing angioplasty[16,17] and appears to be safe, although no benefit has been shown over heparin. Lepirudin has been used as an alternative to heparin in patients with heparin-induced thrombocytopenia.[18-20] Bivalirudin is effective in patients with stable coronary artery disease[21,22] or acute coronary syndromes[21-23] undergoing percutaneous coronary interventions, and may reduce the need for adjunctive glycoprotein IIb/IIIa inhibitors.[21-23]

In patients undergoing **coronary artery bypass grafting**, hirudins may be an alternative to unfractionated heparin, and positive results have been reported with bivalirudin[24] and with lepirudin;[25] however, postoperative bleeding is increased and it was suggested[25] that hirudins should be reserved for patients with contra-indications to heparin, such as those with heparin-induced thrombocytopenia.

1. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 2002; **359:** 294–302.
2. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994; **90:** 1631–7.
3. Antman EM, *et al.* Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation* 1994; **90:** 1624–30.
4. Neuhaus K-L, *et al.* Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study: a study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALKK). *Circulation* 1994; **90:** 1638–42.
5. Zeymer U, Neuhaus K-L. Hirudin and excess bleeding: implications for future use. *Drug Safety* 1995; **12:** 234–9.
6. Conrad KA. Clinical pharmacology and drug safety: lessons from hirudin. *Clin Pharmacol Ther* 1995; **58:** 123–6.
7. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; **335:** 775–82.
8. Antman EM. Hirudin in acute myocardial infarction: thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation* 1996; **94:** 911–21.
9. Neuhaus K-L, *et al.* Recombinant hirudin (lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. *J Am Coll Cardiol* 1999; **34:** 966–73.
10. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; **358:** 1855–63.
11. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. *Circulation* 1997; **96:** 769–77.
12. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999; **353:** 429–38.
13. Topol EJ, *et al.* Recombinant hirudin for unstable angina pectoris: a multicenter, randomized angiographic trial. *Circulation* 1994; **89:** 1557–66.
14. Kong DF, *et al.* Clinical outcomes of bivalirudin for ischemic heart disease. *Circulation* 1999; **100:** 2049–53.
15. Stone GW, *et al.* The ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355:** 2203–16.
16. van den Bos AA, *et al.* Safety and efficacy of recombinant hirudin (CGP 39 393) versus heparin in patients with stable angina undergoing coronary angioplasty. *Circulation* 1993; **88:** 2058–66.
17. Serruys PW, *et al.* A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995; **333:** 757–63.
18. Manfredi JA, *et al.* Lepirudin as a safe alternative for effective anticoagulation in patients with known heparin-induced thrombocytopenia undergoing percutaneous coronary intervention: case reports. *Catheter Cardiovasc Interv* 2001; **52:** 468–72.
19. Pinto DS, *et al.* Combination platelet glycoprotein IIb/IIIa receptor and lepirudin administration during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. *Catheter Cardiovasc Interv* 2003; **58:** 65–8.
20. Cochran K, *et al.* Use of lepirudin during percutaneous vascular interventions in patients with heparin-induced thrombocytopenia. *J Invasive Cardiol* 2003; **15:** 617–21.
21. Lincoff AM, *et al.* Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003; **289:** 853–63. Correction. *ibid.*; 1638.
22. Lincoff AM, *et al.* Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004; **292:** 696–703. Correction. *ibid.* 2006; **296:** 46.
23. Stone GW, *et al.* Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007; **369:** 907–19.
24. Dyke CM, *et al.* A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. *J Thorac Cardiovasc Surg* 2006; **131:** 533 –9.
25. Riess F-C, *et al.* Recombinant hirudin for cardiopulmonary bypass anticoagulation: a randomized, prospective, and heparin-controlled pilot study. *Thorac Cardiovasc Surg* 2007; **55:** 233–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Refludan; ***Austria:*** Refludan; ***Belg.:*** Refludan; ***Canad.:*** Refludan; ***Cz.:*** Refludan; ***Denm.:*** Refludan†; ***Fin.:*** Refludan†; ***Fr.:*** Refludan; ***Ger.:*** Refludan; ***Gr.:*** Refludan†; ***Hung.:*** Refludan; ***Irl.:*** Refludan; ***Ital.:*** Refludan; ***Neth.:*** Refludan; ***Norw.:*** Refludan; ***NZ:*** Refludan; ***Port.:*** Refludan; ***S.Afr.:*** Refludin; ***Spain:*** Refludin; ***Swed.:*** Refludan†; ***Switz.:*** Refludan; ***UK:*** Refludan; ***USA:*** Refludan.

Lercanidipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lercanidipino; Lercanidipine, Chlorhydrate de; Lercanidipini Hydrochloridum; Lerkanidipin Hidroklorür; Masnidipine Hydrochloride; R-75; Rec-15-2375. (±)-2-[(3,3-Diphenylpropyl)methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

Лерканидипина Гидрохлорид

$C_{36}H_{41}N_3O_6,HCl = 648.2.$

CAS — 100427-26-7 (lercanidipine); 132866-11-6 (lercanidipine hydrochloride).

ATC — C08CA13.

ATC Vet — QC08CA13.

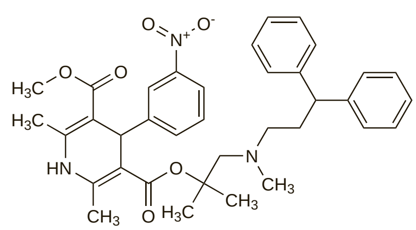

(lercanidipine)

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Lercanidipine is completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive saturable first-pass metabolism. Bioavailability is low but is increased in the presence of food. Peak plasma concentrations occur about 1.5 to 3 hours after oral dosage. Lercanidipine is rapidly and widely distributed. It is more than 98% bound to plasma proteins. Lercanidipine is extensively metabolised, primarily by the cytochrome P450 isoenzyme CYP3A4, mainly to inactive metabolites; about 50% of an oral dose is excreted in the urine. A terminal elimination half-life of about 2 to 5 hours has been reported, but studies using a more sensitive assay have suggested a value of 8 to 10 hours.

Uses and Administration

Lercanidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

Lercanidipine is given by mouth as the hydrochloride in a usual initial dose of 10 mg once daily before food, increased if necessary, after at least 2 weeks, to 20 mg daily.

◊ Reviews.

1. McClellan KJ, Jarvis B. Lercanidipine: a review of its use in hypertension. *Drugs* 2000; **60:** 1123–40.
2. Bang LM, *et al.* Lercanidipine : a review of its efficacy in the management of hypertension. *Drugs* 2003; **63:** 2449–72.
3. Beckey C, *et al.* Lercanidipine in the treatment of hypertension. *Ann Pharmacother* 2007; **41:** 465–74.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lercadip; ***Austral.:*** Zanidip; ***Austria:*** Zanidip; ***Belg.:*** Zanidip; ***Braz.:*** Zanidip; ***Chile:*** Zanidip; ***Cz.:*** Lerpin; ***Denm.:*** Zanidip; ***Fin.:*** Zanidip; ***Fr.:*** Lercan; Zanidip; ***Ger.:*** Carmen; Corifeo; ***Gr.:*** Lercadip; Zanidip; ***Hong Kong:*** Zanidip; ***Hung.:*** Lercaton; Zanidip; ***India:*** Lerez; ***Indon.:*** Zanidip; ***Irl.:*** Zanidip; ***Israel:*** Vasodip; ***Ital.:*** Cardiovasc; Lercadip; Zanedip; ***Malaysia:*** Zanidip; ***Mex.:*** Evipress; Zanidip; ***Neth.:*** Lerdip; ***Norw.:*** Zanidip; ***NZ:*** Zanidip; ***Philipp.:*** Zanidip; ***Port.:*** Zanicor; Zanidip; ***S.Afr.:*** Zanidip; ***Singapore:*** Zanidip†; ***Spain:*** Lercadip; Lerzam; Zanidip; ***Swed.:*** Zanidip; ***Switz.:*** Zanidip; ***Thai.:*** Zanidip; ***Turk.:*** Lercadip; ***UK:*** Zanidip; ***Venez.:*** Lercadip; Zanidip.

Multi-ingredient: ***India:*** Lerez-AT†.

Levosimendan *(USAN, rINN)*

Lévosimendan; Levosimendán; Levosimendanum; (−)-OR-1259. Mesoxalonitrile (−)-{*p*-[(*R*)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl}hydrazone.

Левосимендан

$C_{14}H_{12}N_6O = 280.3.$

CAS — 141505-33-1.

ATC — C01CX08.

ATC Vet — QC01CX08.

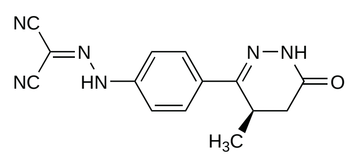

Profile

Levosimendan is a cardiac inotrope and vasodilator with calcium-sensitising properties, used in the management of acute heart failure (p.1165). It is given intravenously in a loading dose of 6 to 24 micrograms/kg over 10 minutes followed by a continuous infusion of 50 to 200 nanograms/kg per minute, adjusted according to response.

◊ References.

1. Figgitt DP, *et al.* Levosimendan. *Drugs* 2001; **61:** 613–27.
2. Follath F, *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; **360:** 196–202.
3. McBride BF, White CM. Levosimendan: implications for clinicians. *J Clin Pharmacol* 2003; **43:** 1071–81.
4. Innes CA, Wagstaff AJ. Levosimendan: a review of its use in the management of acute decompensated heart failure. *Drugs* 2003; **63:** 2651–71.
5. Earl GL, Fitzpatrick JT. Levosimendan: a novel inotropic agent for treatment of acute, decompensated heart failure. *Ann Pharmacother* 2005; **39:** 1888–96.
6. De Luca L, *et al.* Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; **27:** 1908–20.
7. Antila S, *et al.* Clinical pharmacology of levosimendan. *Clin Pharmacokinet* 2007; **46:** 535–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Simdax; ***Austria:*** Simdax; ***Chile:*** Daxim; ***Cz.:*** Simdax; ***Fin.:*** Simdax; ***Gr.:*** Simdax; ***Hong Kong:*** Simdax; ***Hung.:*** Simdax; ***Israel:*** Simdax; ***Ital.:*** Simdax; ***Mex.:*** Simdax; ***Norw.:*** Simdax; ***NZ:*** Simdax; ***Port.:*** Simdax; ***Rus.:*** Simdax (Симдакс); ***Spain:*** Simdax; ***Swed.:*** Simdax; ***Turk.:*** Simdax; ***Venez.:*** Daxim.

Lidoflazine (BAN, USAN, rINN)

Lidoflazina; Lidoflazinum; McN-JR-7904; Ordiflazine; R-7904. 4-[3-(4,4′-Difluorobenzhydryl)propyl]piperazin-1-ylaceto-2′,6′-xylidide.

Лидофлазин

$C_{30}H_{35}F_2N_3O$ = 491.6.
CAS — 3416-26-0.
ATC — C08EX01.
ATC Vet — QC08EX01.

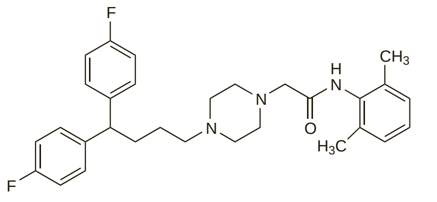

Profile

Lidoflazine is a calcium-channel blocker (p.1154) that reduces AV conduction. It has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Clinium; ***S.Afr.:*** Clinium.

Limaprost (rINN)

Limaprostum; ONO-1206; OP-1206. (*E*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl}-2-heptenoic acid.

Лимапрост

$C_{22}H_{36}O_5$ = 380.5.
CAS — 74397-12-9 (limaprost); 88852-12-4 (limaprost alfadex).

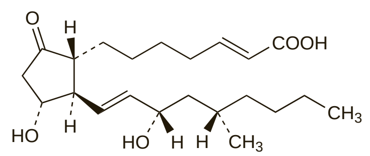

Pharmacopoeias. *Jpn* includes limaprost alfadex.

Profile

Limaprost is a synthetic analogue of alprostadil (prostaglandin E_1) used in the management of peripheral vascular disease (p.1178). It is given orally as limaprost alfadex, in a dose equivalent to limaprost 15 to 30 micrograms daily in three divided doses.

◊ References.

1. Shono T, Ikeda K. Rapid effect of oral limaprost in Raynaud's disease in childhood. *Lancet* 1989; **i:** 908.
2. Murai C, *et al.* Oral limaprost for Raynaud's phenomenon. *Lancet* 1989; **ii:** 1218.
3. Aoki Y, *et al.* Possible participation of a prostaglandin E1 analogue in the aggravation of diabetic nephropathy. *Diabetes Res Clin Pract* 1992; **16:** 233–8.
4. Sato Y, *et al.* Effect of oral administration of prostaglandin E1 on erectile dysfunction. *Br J Urol* 1997; **80:** 772–5.
5. Swainston Harrison T, Plosker GL. Limaprost. *Drugs* 2007; **67:** 109–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Opalmon.

Linsidomine Hydrochloride (rINNM)

Hidrocloruro de linsidomina; Linsidomine, Chlorhydrate de; Linsidomini Hydrochloridum. 3-Morpholinosydnonimine hydrochloride.

Линсидомина Гидрохлорид

$C_6H_{10}N_4O_2,HCl$ = 206.6.
CAS — 33876-97-0 (linsidomine); 16142-27-1 (linsidomine hydrochloride).
ATC — C01DX18.
ATC Vet — QC01DX18.

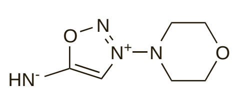

(linsidomine)

Profile

Linsidomine is a nitrovasodilator and a metabolite of molsidomine (p.1343) and has been given intravenously or via the intracoronary route for coronary vasodilatation.

◊ References.

1. Delonca J, *et al.* Comparative efficacy of the intravenous administration of linsidomine, a direct nitric oxide donor, and isosorbide dinitrate in severe unstable angina: a French multicentre study. *Eur Heart J* 1997; **18:** 1300–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Corvasal†.

Lisinopril (BAN, USAN, rINN)

L-154826; Lisinopriili; Lisinoprilum; Lizinopril; Lizinoprilis; MK-521. *N*-{*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl}-L-proline dihydrate.

Лизиноприл

$C_{21}H_{31}N_3O_5,2H_2O$ = 441.5.
CAS — 76547-98-3 (anhydrous lisinopril); 83915-83-7 (lisinopril dihydrate).
ATC — C09AA03.
ATC Vet — QC09AA03.

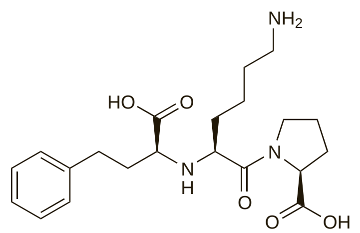

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Lisinopril Dihydrate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dehydrated alcohol and in acetone; sparingly soluble in methyl alcohol.

USP 31 (Lisinopril). A white crystalline powder. Soluble 1 in 10 of water and 1 in 70 of methyl alcohol; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in ether.

Suspension. The US licensed prescribing information provides the following method for making 200 mL of a suspension containing lisinopril 1 mg/mL. Add 10 mL of purified water to a polyethylene terephthalate bottle containing ten 20-mg tablets (*Prinivil, Merck* or *Zestril, AstraZeneca*) and shake for at least 1 minute. Add 30 mL of *Bicitra* (*Alza, USA*) and 160 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and gently shake for several seconds. The suspension should be stored at or below 25° and can be stored for up to 4 weeks. Studies of the characteristics of this and other liquid dosage forms of lisinopril have been published.[1,2]

1. Thompson KC, *et al.* Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health-Syst Pharm* 2003; **60:** 69–74.
2. Nahata MC, Morosco RS. Stability of lisinopril in two liquid dosage forms. *Ann Pharmacother* 2004; **38:** 396–9.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Porphyria. Lisinopril has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Lisinopril is slowly and incompletely absorbed after oral doses. About 25% of a dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 to 60%. It is already an active diacid and does not need to be metabolised *in vivo*. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation after multiple doses is 12 hours in patients with normal renal function. Lisinopril is removed by haemodialysis.

◊ References.

1. Till AE, *et al.* The pharmacokinetics of lisinopril in hospitalized patients with congestive heart failure. *Br J Clin Pharmacol* 1989; **27:** 199–204.
2. Neubeck M, *et al.* Pharmacokinetics and pharmacodynamics of lisinopril in advanced renal failure: consequence of dose adjustment. *Eur J Clin Pharmacol* 1994; **46:** 537–43.

Uses and Administration

Lisinopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165), prophylactically after myocardial infarction (p.1175), and in diabetic nephropathy (see Kidney Disorders, p.1199).

The haemodynamic effects of lisinopril are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours after once-daily dosing. Lisinopril is given orally as the dihydrate, but doses are expressed in terms of the anhydrous substance. Lisinopril 2.72 mg as the dihydrate is equivalent to about 2.5 mg of anhydrous lisinopril. The dose of lisinopril should be reduced in patients with renal impairment (see below).

In the treatment of **hypertension**, the usual initial dose is 10 mg daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and such patients should be given a lower initial dose of 2.5 to 5 mg once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before lisinopril is started and resumed later if required; if this is not possible, an initial dose of 5 mg once daily should be given. The usual maintenance dose is 20 mg given once daily, though up to 80 mg daily may be given if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be started with a low dose under close medical supervision. Lisinopril is given in an initial dose of 2.5 mg daily. In the USA an initial dose of 5 mg daily is suggested. Usual maintenance doses range from 5 to 40 mg daily.

After **myocardial infarction**, treatment with lisinopril may be started within 24 hours of the onset of symptoms in an initial dose of 5 mg once daily for two days, then increased to 10 mg once daily. An initial dose of 2.5 mg once daily is recommended for patients with a low systolic blood pressure.

In the management of **diabetic nephropathy**, hypertensive type 2 diabetics with microalbuminuria may be given a dose of 10 mg once daily, increased if necessary to 20 mg once daily to achieve a sitting diastolic blood pressure below 90 mmHg.

◊ Reviews.

1. Lancaster SG, Todd PA. Lisinopril: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1988; **35:** 646–69.
2. Goa KL, *et al.* Lisinopril: a review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. *Drugs* 1996; **52:** 564–88.
3. Goa KL, *et al.* Lisinopril: a review of its pharmacology and use in the management of the complications of diabetes mellitus. *Drugs* 1997; **53:** 1081–1105.
4. Simpson K, Jarvis B. Lisinopril: a review of its use in congestive heart failure. *Drugs* 2000; **59:** 1149–67.

Administration in children. Lisinopril has been reported to be an effective and well-tolerated antihypertensive in children 6 years of age and older,[1] although it has been used successfully in younger children.[2] US licensed product information recommends an oral starting dose for lisinopril of 70 micrograms/kg (up to 5 mg) once daily for children 6 years of age and older (but see also Administration in Renal Impairment, below). The *BNFC* recommends similar doses for children aged 6 to 12 years and states that this dose may be increased at intervals of 1 to 2 weeks to a maximum of 600 micrograms/kg or 40 mg once daily. For children between 12 and 18 years of age the *BNFC* recommends an initial dose of 2.5 mg daily increased as necessary to a maximum of 40 mg daily.

In the treatment of heart failure in children between 12 and 18 years of age the *BNFC* recommends an initial dose of 2.5 mg daily increased as necessary to a usual maintenance dose of 5 to 20 mg daily.

1. Soffer B, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens* 2003; **16:** 795–800.
2. Raes A, *et al.* Lisinopril in paediatric medicine: a retrospective chart review of long-term treatment in children. *J Renin Angiotensin Aldosterone Syst* 2007; **8:** 3–12.

Administration in renal impairment. In *adult* patients with renal impairment, the initial dose of lisinopril should be reduced depending on the creatinine clearance (CC) as follows:

- CC 31 to 80 mL/minute: 5 to 10 mg once daily
- CC 10 to 30 mL/minute: 2.5 to 5 mg once daily
- CC less than 10 mL/minute or on dialysis: 2.5 mg once daily

The dose should be adjusted according to response, to a maximum of 40 mg once daily.

US licensed prescribing information states that lisinopril should not be given to *children* with a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2 but gives no guidance on dosage in other children with renal impairment.

Preparations

BP 2008: Lisinopril Tablets;
USP 31: Lisinopril Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Doxapril; Lisinal; Sedotensil; Tensopril; Tersif; Zestril; ***Austral.:*** Fibsol; Liprace; Lisinobell; Lisodur; Prinivil; Zestril; ***Austria:*** Acemin; Acetan; Lisihexal; Lisinostad; Lisinotyrol†; Prinivil; ***Belg.:*** Novatec; Zestril; ***Braz.:*** Lisopril; Listril; Lonipril; Prilcor; Prinivil; Prinopril; Vasojet; Zestril; Zinopril; ***Canad.:*** Prinivil; Zestril; ***Chile:*** Acerdil; Lipreren; Presokin; Tonotensil; Zestril†; ***Cz.:*** Dapril; Diroton; Irumed†; Lipribela; Lisigamma; Lisipril; Listril†; Prinivil; ***Denm.:*** Acepril†; Lanatin†; Lisinogen; Vivatec†; Zestril; ***Fin.:*** Lisipril; Vivatec; Zestril†; ***Fr.:*** Prinivil; Zestril; ***Ger.:*** Acerbon; Coric; Lisi; Lisi Lich; Lisi-Puren; Lisibeta; Lisidoc; Lisigamma; Lisihexal; Lisodura; ***Gr.:*** Adicanil; Axelvin; Gnostoval; Hyperliz; Icoran; Landolaxin†; Leruze; Lisinospes; Lisodinol; Mealis; Nafordyl; Perenal; Press-12; Pressuril; Prinivil; Terolinal; Thriusedon; Tivirlon; Vercol; Veroxil; Z-Bec; Zestril; ***Hong Kong:*** Acepril; Cipril; Prinivil; Zestril; ***Hung.:*** Conpres; Lisdene; Lisopress; Press-12; ***India:*** Biopril; Cipril; Linoril; Linvas; Lipril; Lisoril; Normopril; ***Indon.:*** Interpril; Linoxal; Noperten; Nopril; Odace; Zestril; ***Irl.:*** ByZestra; Carace; Lisopress; Lispril; Zesger; Zestan; Zestril; ***Israel:*** Tensopril; ***Ital.:*** Alapril; Prinivil; Zestril; ***Jpn:*** Longes; ***Malaysia:*** Acepril; Dapril; Prinivil†; Ranopril; Zestril; ***Mex.:*** Alfaken; Dosteril; Linospril; Priniser; Prinivil; Zestril; ***Neth.:*** Novatec; Zestril; ***Norw.:*** Vivatec; Zestril; ***NZ:*** Prinivil; Zestril†; ***Philipp.:*** Sinolip; Zestril; ***Pol.:*** Diroton; Lisdene; Lisihexal; Lisinoratio; Lisiprol; Prinivil; ***Port.:*** Benzin; Ecapril; Farpresse; Lipril; Lisinol; Lisopress; Prinivil; Zestril; ***Rus.:*** Dapril (Даприл); Diroton (Диротон); Irumed (Ирумед); Lisinoton (Лизинотон); Lisoril (Лизорил); Listril (Листрил); Liten (Литэн); Sinopril (Синоприл); ***S.Afr.:*** Prilosin†; Prinivil; Renotens†; Sinopren; Zemax; Zeprosil; Zestril; Zetomax; ***Singapore:*** Dapril; Lisdene; Lisoril; Prinivil; Zestril; ***Spain:*** Doneka; Iricil; Likenil; Prinivil; Secubar†; Tensikey; Zestril; ***Swed.:*** Vivatec†; Zestril; ***Switz.:*** Corprilin; Lisitril; Lisopril; Prinil; Tobicor; Zestril; ***Thai.:*** Lisdene; Lispril; Zestril; ***Turk.:*** Acerilin; Rilace; Sinopryl; Zestril; ***UAE:*** Lisotec; ***UK:*** Carace; Zestril; ***USA:*** Prinivil; Zestril; ***Venez.:*** Cotensil; Lisilet; Prinivil; Rantex; Tonoten.

Multi-ingredient: ***Arg.:*** Tensopril D; Zestoretic; ***Austria:*** Acecomb; Acelisino comp; Co-Acetan; Co-Hypomed; Co-Lisinostad; Lisihexal comb; Lisinocomp; Lisinopril comp; Zestoretic; ***Belg.:*** Co-Lisinopril; Merck-Co-Lisinopril; Novazyd†; Zestoretic; ***Braz.:*** Lisinoretic†; Lisoclor; Lisonotec†; Lonipril-H; Prinzide; Zestoretic; ***Canad.:*** Prinzide; Zestoretic; ***Chile:*** Acerdil-D; Tonotensil D; Zestoretic†; ***Cz.:*** Lipribela plus H; ***Denm.:*** Lisinoplus; Vivazid†; Zestoretic; ***Fin.:*** Acercomp†; Lisipril Comp; Vivatec Comp; ***Fr.:*** Prinzide; Zestoretic; ***Ger.:*** Acercomp; Coric Plus; Lisi-Puren comp; Lisibeta comp; Lisigamma HCT; LisiLich comp; Lisinopril comp; Lisinopril HCT; Lisiplus; Lisodura plus; ***Gr.:*** Prinzide; Z-Bec Plus; Zestoretic; ***Hong Kong:*** Zestoretic; ***Hung.:*** Lisonorm; ***India:*** Amlopres L; Amlosafe-LS†; Biopril-AM†; Calchek L; Cipril-H; Lisoril-5HT; ***Indon.:*** Zestoretic; ***Irl.:*** Carace Plus; Lispril-hydrochlorothiazide; Zesger Plus; Zestoretic; ***Ital.:*** Nalapres; Prinzide; Zestoretic; ***Mex.:*** Prinzide; Zestoretic; ***Neth.:*** Lisidigal HCT; Novazyd; Zestoretic; ***Norw.:*** Vivatec Comp; Zestoretic; ***Philipp.:*** Zestoretic; ***Port.:*** Ecamais; Lisoplus; Prinzide; Tiazinol; Zestoretic; ***Rus.:*** Iruzid (Ирузид); Lisoretic (Лизоретик); Sinorezid (Синорезид); ***S.Afr.:*** Lisoretic; Zestoretic; Zetomax Co; ***Spain:*** Doneka Plus; Iricil Plus; Prinivil Plus; Secubar Diu; Tensikey Complex; Zestoretic; ***Swed.:*** Zestoretic; ***Switz.:*** Co-Lisinopril; Corpriretic; Lisitril comp; Lisopril plus; Prinzide; Tobicor Plus; Zestoretic; ***Turk.:*** Rilace Plus; Sinoretik; Zestoretic; ***UK:*** Carace Plus; Caralpha; Lisicostad; Zestoretic; ***USA:*** Prinzide; Zestoretic; ***Venez.:*** Lisiletic.

Losartan Potassium *(BANM, USAN, rINNM)*

DuP-753; E-3340; Kalii Losartanum; Losartaanikalium; Losartán potásico; Losartan potassique; Losartan Potasyum; Losartankalium; Losartanum kalicum; MK-0954. 2-Butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol potassium.

Калия Лозартан

$C_{22}H_{22}ClKN_6O$ = 461.0.

CAS — 114798-26-4 (losartan); 124750-99-8 (losartan potassium).

ATC — C09CA01.

ATC Vet — QC09CA01.

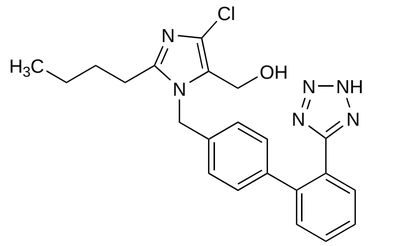

(losartan)

Pharmacopoeias. In *US.*

USP 31 (Losartan Potassium). A white to off-white powder. Freely soluble in water; slightly soluble in acetonitrile; soluble in isopropyl alcohol.

Adverse Effects

Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. Losartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia. Rhabdomyolysis has been reported rarely.

◊ Reviews.

1. Mazzolai L, Burnier M. Comparative safety and tolerability of angiotensin II receptor antagonists. *Drug Safety* 1999; **21:** 23–33.

Angioedema. Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. Although angiotensin II receptor antagonists were thought to lack effects on bradykinin, several have been associated with reports[1-6] of angioedema, and increased levels of bradykinin have been shown[7] with losartan. In some cases patients had previously experienced angioedema with ACE inhibitors and caution is advised when using angiotensin II receptor antagonists in such patients.[4,8]

1. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995; **333:** 1572.
2. van Rijnsoever EW, *et al.* Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998; **158:** 2063–5.
3. Adverse Drug Reactions Advisory Committee. Angiotensin II receptor antagonists. *Aust Adverse Drug React Bull* 1999; **18:** 2. Available at: http://www.tga.gov.au/adr/aadrb/aadr9902.pdf (accessed 13/03/08)
4. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? *Drug Safety* 2002; **25:** 73–6.
5. Irons BK, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 2003; **37:** 1024–7.
6. Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. *Ann Pharmacother* 2007; **41:** 518–20.
7. Campbell DJ, *et al.* Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005; **111:** 315–20.
8. Warner KK, *et al.* Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000; **34:** 526–8.

Effects on the blood. Symptomatic anaemia occurred[1] in a patient with a renal transplant 6 weeks after starting therapy with losartan. Decreased haemoglobin concentrations have also been reported[2] in patients with severe renal impairment undergoing haemodialysis.

Immune thrombocytopenia has been reported[3] in a patient shortly after starting losartan.

1. Horn S, *et al.* Losartan and renal transplantation. *Lancet* 1998; **351:** 111.
2. Schwarzbeck A, *et al.* Anaemia in dialysis patients as a side-effect of sartanes. *Lancet* 1998; **352:** 286.
3. Ada S, *et al.* Immune thrombocytopenia after losartan therapy. *Ann Intern Med* 2002; **137:** 704.

Effects on the liver. Raised liver enzyme values have occurred rarely in patients receiving losartan. Severe, acute hepatotoxicity developed in a patient 1 month after losartan was substituted for enalapril because of ACE inhibitor-induced cough.[1] The patient recovered when losartan was withdrawn but symptoms and raised liver enzyme concentrations recurred following rechallenge. Acute, reversible hepatotoxicity also occurred in a patient who had been taking losartan 150 mg daily for 6 weeks.[2] A case of cholestatic jaundice associated with irbesartan therapy has also been reported;[3] the jaundice resolved slowly once irbesartan was withdrawn.

1. Bosch X. Losartan-induced hepatotoxicity. *JAMA* 1997; **278:** 1572.
2. Andrade RJ, *et al.* Hepatic injury associated with losartan. *Ann Pharmacother* 1998; **32:** 1371.
3. Hariraj R, *et al.* Prolonged cholestasis associated with irbesartan. *BMJ* 2000; **321:** 547.

Effects on the skin. Atypical cutaneous lymphoid infiltrates developed in 2 patients receiving losartan for hypertension.[1] In both cases the lesions disappeared within a few weeks of stopping the drug.

Henoch-Schönlein purpura has been reported[2,3] in patients taking losartan; in 1 case[2] the reaction recurred on rechallenge. A purpuric rash with evidence of vasculitis has been reported with candesartan;[4] the patient also developed acute nephritis.

A polycyclic rash associated with systemic illness developed in a patient who had been taking irbesartan for 2 years;[5] improvement occurred within 2 days of stopping the drug.

There has also been a report[6] of a number of patients in whom psoriasis either developed or was exacerbated following treatment with an angiotensin II receptor antagonist; the drugs involved included candesartan, irbesartan, losartan, and valsartan. In most cases the lesions regressed after the drug was withdrawn.

1. Viraben R, *et al.* Losartan-associated atypical cutaneous lymphoid hyperplasia. *Lancet* 1997; **350:** 1366.
2. Bosch X. Henoch-Schönlein purpura induced by losartan therapy. *Arch Intern Med* 1998; **158:** 191–2.
3. Brouard M, *et al.* Schönlein-Henoch purpura associated with losartan treatment and presence of antineutrophil cytoplasmic antibodies of x specificity. *Br J Dermatol* 2001; **145:** 362–3.
4. Morton A, *et al.* Rash and acute nephritic syndrome due to candesartan. *BMJ* 2004; **328:** 25.
5. Constable S, *et al.* Systemic illness with skin eruption, fever and positive lymphocyte transformation test in a patient on irbesartan. *Br J Dermatol* 2006; **155:** 491–3.
6. Marquart-Elbaz C, *et al.* Sartans, angiotensin II receptor antagonists, can induce psoriasis. *Br J Dermatol* 2002; **147:** 617–8.

Effects on taste. Taste disturbances, in some cases progressing to complete taste loss, have occurred[1,2] in patients receiving losartan for hypertension. In each case taste returned to normal after stopping losartan therapy. Taste impairment has also been reported with both candesartan[3,4] and valsartan[4] in healthy subjects.

1. Schlienger RG, *et al.* Reversible ageusia associated with losartan. *Lancet* 1996; **347:** 471–2.
2. Heeringa M, van Puijenbroek EP. Reversible dysgeusia attributed to losartan. *Ann Intern Med* 1998; **129:** 72.
3. Tsuruoka S, *et al.* Subclinical alteration of taste sensitivity induced by candesartan in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 807–12.
4. Tsuruoka S, *et al.* Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan. *Br J Clin Pharmacol* 2005; **60:** 204–7.

Hypersensitivity. See Angioedema,and Effects on the Skin, above.

Migraine. Severe migraine has been reported[1] in a patient after use of losartan. The patient had no history of migraine and symptoms recurred on rechallenge. However, angiotensin II receptor antagonists have also been reported to reduce the incidence of migraine (see under Uses and Administration, below).

1. Ahmad S. Losartan and severe migraine. *JAMA* 1995; **274:** 1266–7.

Pancreatitis. Acute pancreatitis has been reported[1,2] in 2 patients receiving losartan. However, 1 of the patients subsequently developed pancreatitis unrelated to losartan.[3] The other patient[2] had also developed acute pancreatitis during enalapril therapy. Acute pancreatitis has also been reported[4] with irbesartan; the patient was also taking hydrochlorothiazide but in a dose lower than that usually associated with thiazide-induced pancreatitis. Biochemical alterations suggestive of acute pancreatitis have been reported after telmisartan overdosage.[5]

1. Bosch X. Losartan-induced acute pancreatitis. *Ann Intern Med* 1997; **127:** 1043–4.
2. Birck R, *et al.* Pancreatitis after losartan. *Lancet* 1998; **351:** 1178.
3. Bosch X. Correction: losartan, pancreatitis, and microlithiasis. *Ann Intern Med* 1998; **129:** 755.
4. Fisher AA, Bassett ML. Acute pancreatitis associated with angiotensin II receptor antagonists. *Ann Pharmacother* 2002; **36:** 1883–6.
5. Baffoni L, *et al.* Acute pancreatitis induced by telmisartan overdose. *Ann Pharmacother* 2004; **38:** 1088.

Vasculitis. For mention of the development of Henoch-Schönlein purpura and other vasculitic disorders in patients receiving angiotensin II receptor antagonists see Effects on the Skin, above.

Precautions

Losartan is contra-indicated in pregnancy (see below). It should be used with caution in patients with renal artery stenosis. Losartan is excreted in urine and in bile and reduced doses may therefore be required in patients with renal impairment and should be considered in patients with hepatic impairment. Patients with volume depletion (for example those who have received high-dose diuretic therapy) may experience hypotension; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided.

Diabetes mellitus. After reports of reduced awareness of hypoglycaemia in type 1 diabetic patients receiving losartan, a study[1] in healthy subjects found that losartan slightly attenuated the symptomatic and hormonal responses to hypoglycaemia. Although the clinical significance was not established, the authors recommended that losartan should be used with caution in diabetics with reduced awareness of hypoglycaemia. However, losartan and other angiotensin II receptor antagonists may have a role in type 2 diabetics with nephropathy (see Kidney Disorders under Uses, below). There is also some evidence[2-6] that angiotensin II receptor antagonists may prevent the development of diabetes in non-diabetic patients.

1. Deininger E, *et al.* Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin Pharmacol Ther* 2001; **70:** 362–9.
2. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
3. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
4. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
5. Yusuf S, *et al.* Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112:** 48–53. Correction. *ibid.*; e292.
6. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.

Pregnancy. Losartan is contra-indicated in pregnancy since it has been associated with fetal toxicity in *animal* studies and other drugs that act on the renin-angiotensin system, such as ACE inhibitors, have been associated with fetal toxicity in humans (see p.1196). Oligohydramnios with subsequent fetal death occurred in a patient who received losartan during weeks 20 to 31 of pregnancy;[1] the effects on the fetus were similar to those reported with ACE inhibitors. A number of similar cases have subsequently been reported with losartan,[2,3] candesartan,[4] and valsartan.[3,5,6]

1. Saji H, *et al.* Losartan and fetal toxic effects. *Lancet* 2001; **357:** 363.
2. Lambot M-A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1619–20.
3. Martinovic J, *et al.* Fetal toxic effects and angiotensin-II-receptor antagonists. *Lancet* 2001; **358:** 241–2.
4. Hinsberger A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1620.
5. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 2001; **35:** 859–61.
6. Bos-Thompson M-A, *et al.* Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up after birth. *Ann Pharmacother* 2005; **39:** 157–61. Correction. *ibid.*; 389.

Interactions

The antihypertensive effects of losartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking losartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of losartan. Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Lithium. For reference to a possible interaction between lithium and angiotensin II receptor antagonists, see p.404.

Pharmacokinetics

Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial first-pass metabolism resulting in a systemic bioavailability of about 33%. It is metabolised to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

◊ References.

1. Sica DA, *et al.* Clinical pharmacokinetics of losartan. *Clin Pharmacokinet* 2005; **44:** 797–814.

Uses and Administration

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. It is used in the management of hypertension (p.1171), particularly in patients who develop cough with ACE inhibitors and to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy (see Kidney Disorders, below). It has also been tried in heart failure (below) and in myocardial infarction (p.1175).

Losartan is given orally as the potassium salt. The maximum hypotensive effect is achieved in about 3 to 6 weeks after starting treatment.

In **hypertension** the usual dose of losartan potassium is 50 mg once daily. The dose may be increased, if necessary, to 100 mg daily as a single dose or in two divided doses. An initial dose of 25 mg once daily should be given to patients with intravascular fluid depletion, and is recommended in the UK in patients over 75 years of age. Similar reductions may be appropriate in patients with hepatic or renal impairment (but see below).

There are limited data on the use of losartan in children with hypertension. In the UK, the recommended initial dose of losartan potassium for children weighing between 20 and 50 kg is 25 mg once daily; this may be increased to a maximum of 50 mg once daily. In the USA, children aged 6 years or over may be given an initial dose of 700 micrograms/kg once daily, with a maximum of 50 mg, adjusted according to response. There are no data to recommend doses for children with glomerular filtration rate below 30 mL/min per 1.73 m^2, and in the UK losartan should not be given to children with hepatic impairment.

In **diabetic nephropathy** losartan potassium is given in an initial dose of 50 mg once daily, increased to 100 mg once daily depending on the blood pressure.

◊ Reviews.

1. Carr AA, Prisant LM. Losartan: first of a new class of angiotensin antagonists for the management of hypertension. *J Clin Pharmacol* 1996; **36:** 3–12.
2. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs* 1996; **51:** 820–45.
3. Schaefer KL, Porter JA. Angiotensin II receptor antagonists: the prototype losartan. *Ann Pharmacother* 1996; **30:** 625–36.
4. Burrell LM. A risk-benefit assessment of losartan potassium in the treatment of hypertension. *Drug Safety* 1997; **16:** 56–65.
5. McConnaughey MM, *et al.* Practical considerations of the pharmacology of angiotensin receptor blockers. *J Clin Pharmacol* 1999; **39:** 547–59.
6. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; **355:** 637–45.
7. Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health-Syst Pharm* 2000; **57:** 1231–41.
8. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. *Am J Health-Syst Pharm* 2001; **58:** 671–81. Correction. *ibid.*; 1658.
9. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; **65:** 2657–74.

Administration in children. References.

1. Ellis D, *et al.* Long-term antiproteinuric and renoprotective efficacy and safety of losartan in children with proteinuria. *J Pediatr* 2003; **143:** 89–97.
2. Ellis D, *et al.* Antihypertensive and renoprotective efficacy and safety of losartan: a long-term study in children with renal disorders. *Am J Hypertens* 2004; **17:** 928–35.
3. Shahinfar S, *et al.* A double-blind, dose-response study of losartan in hypertensive children. *Am J Hypertens* 2005; **18:** 183–90.
4. Lubrano R, *et al.* Renal and cardiovascular effects of angiotensin-converting enzyme inhibitor plus angiotensin II receptor antagonist therapy in children with proteinuria. Abstract: *Pediatrics* 2006; **118:** e833. Full text: http://pediatrics.aappublications.org/cgi/reprint/118/3/e833 (accessed 13/03/08)

Administration in hepatic or renal impairment. Licensed product information in both the UK and the USA recommend a reduced dose of losartan in patients with hepatic impairment; the suggested initial dose in the USA is 25 mg daily. In the UK an initial dose of 25 mg daily is also recommended in those with moderate to severe renal impairment (creatinine clearance less than 20 mL/minute), but in the USA dosage reduction is considered unnecessary.

Cardiac arrhythmias. See under Heart Failure, below.

Cardiovascular risk reduction. The benefits of ACE inhibitors in patients with high cardiovascular risk are well-established (see Cardiovascular Risk Reduction, p.1164) but whether angiotensin II receptor antagonists have comparable effects is less clear. In the LIFE study,[1] losartan reduced cardiovascular events more than a beta blocker (atenolol), despite a similar effect on blood pressure. In VALUE,[2] there was no difference in the incidence of cardiovascular events between valsartan and a calcium-channel blocker (amlodipine), although the calcium-channel blocker reduced blood pressure to a greater extent. However, in hypertensive stroke patients,[3] eprosartan reduced the risk of cardiovascular and cerebrovascular events more than another calcium-channel blocker (nitrendipine); blood pressure reduction was similar with both drugs. A study[4] comparing telmisartan with the ACE inhibitor ramipril, found that both reduced cardiovascular events to a similar extent; there was no additional benefit in patients given both drugs.

Based on the results of VALUE, there has been concern that angiotensin II receptor antagonists may increase the risk of myocardial infarction, but a systematic review[5] was unable to confirm a significant effect.

1. Dahlöf B, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.
2. Julius S, *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363:** 2022–31.
3. Schrader J, *et al.* Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; **36:** 1218–24.
4. Yusuf S, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358:** 1547–59.
5. McDonald MA, *et al.* Angiotensin receptor blockers and risk of myocardial infarction: systematic review. *BMJ* 2005; **331:** 873–6.

Erythrocytosis. For reference to the use of losartan in the management of secondary erythrocytosis, see under ACE inhibitors, p.1198

Heart failure. Diuretics, ACE inhibitors, and beta blockers are the standard drugs used in the management of heart failure (p.1165). Angiotensin II receptor antagonists have been studied as an alternative to ACE inhibitors since they may be better tolerated. In the ELITE study,[1] which compared losartan with captopril, both drugs had similar effects on renal function but other adverse effects were fewer with losartan and there was also a reduction in mortality in patients receiving losartan. However, the larger ELITE II study[2] failed to confirm any survival benefit with losartan, and studies with losartan[3] and valsartan[4] in patients with heart failure following myocardial infarction have also failed to show superiority over ACE inhibitors. ACE inhibitors therefore remain first-line therapy, although angiotensin II receptor antagonists may be used as an alternative, particularly in patients unable to tolerate ACE inhibitors.[5,6] The combination of angiotensin II receptor antagonists with ACE inhibitors has also shown some benefit.[6] In the ValHeFT study,[7] valsartan was added to standard therapy (including ACE inhibitors in most patients) and reduced the combined end-point of death or hospitalisation for heart failure, although the effect on mortality alone was not significant. In the CHARM-Added trial,[8] addition of candesartan to therapy including an ACE inhibitor also led to a reduction in cardiovascular events. However, in the VALIANT study,[4] no additional benefit was found from using valsartan with captopril. There has been some concern that use of triple therapy with angiotensin II receptor antagonists, ACE inhibitors, and beta blockers, might be detrimental, but this has not been confirmed. In ValHeFT,[7] mortality appeared to be increased in patients receiving all three drug classes, but in both CHARM-Added[8] and VALIANT[4] use of beta blockers had no effect on the results. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.[9,10]

There is some evidence[11] that angiotensin II receptor antagonists may reduce the incidence of arrhythmias in patients with heart failure.

1. Pitt B, *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349:** 747–52.
2. Pitt B, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355:** 1582–7.

3. Dickstein K, *et al.* Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360:** 752–60.
4. Pfeffer MA, *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349:** 1893–1906. Correction. *ibid.* 2004; **350:** 203.
5. Granger CB, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362:** 772–6.
6. Jong P, *et al.* Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; **39:** 463–70.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 24/07/08)
10. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CHF-FT.pdf (accessed 24/07/08)
11. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.

Kidney disorders. ACE inhibitors have an established role in the management of type 1 and type 2 diabetics with nephropathy, whether or not they are hypertensive, and may also slow the progression of nephropathy in diabetics with microalbuminuria (see p.1199). A number of studies have investigated the effects of angiotensin II receptor antagonists in type 2 diabetics with varying degrees of nephropathy (see Diabetic Complications, p.433). Irbesartan,[1,2] losartan,[3,4] and valsartan[5] have all been reported to reduce the progression of nephropathy independently of their effect on blood pressure. The magnitude of the benefit in retarding progression of nephropathy seems to be similar with angiotensin II receptor antagonists and ACE inhibitors,[6-8] and the American Diabetes Association considers them equal first choices in the management of the condition.[9]

Angiotensin II receptor antagonists have also reduced urinary albumin excretion in non-diabetic patients, including those with hypertension,[10] and those with IgA nephropathy.[11]

A study[12] in diabetics using a combination of candesartan with lisinopril found that blood pressure and microalbuminuria were reduced more with combination therapy than with either drug alone. Benefit has also been reported[13] with a combination of losartan and trandolapril in patients with non-diabetic renal disease.

1. Lewis EJ, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345:** 851–60.
2. Parving H-H, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345:** 870–8.
3. Brenner BM, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345:** 861–9.
4. Zandbergen AAM, *et al.* Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med* 2003; **139:** 90–6.
5. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002; **106:** 672–8.
6. Strippoli GFM, *et al.* Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; **329:** 828–31.
7. Barnett AH, *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351:** 1952–61. Correction. *ibid.* 2005; **352:** 1731.
8. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
9. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S79–S83. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s79.pdf (accessed 01/08/05)
10. Vogt L, *et al.* Angiotensin II Receptor Antagonist Telmisartan Micardis in Isolated Systolic Hypertension (ARAMIS) Study Group. The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2005; **23:** 2055–61.
11. Li PK-T, *et al.* Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006; **47:** 751–60.
12. Mogensen CE, *et al.* Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; **321:** 1440–4.
13. Nakao N, *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; **361:** 117–24. Correction. *ibid.*; 1230.

Migraine. Angiotensin II receptor antagonists may reduce the incidence of headache. A randomised trial[1] in 60 patients with migraine suggested that candesartan might be effective for prophylaxis, and beneficial results have also been reported[2] with olmesartan. However, there has been a report of migraine caused by an angiotensin II receptor antagonist (see under Adverse Effects, above).

1. Tronvik E, *et al.* Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; **289:** 65–9.
2. Charles JA, *et al.* Prevention of migraine with olmesartan in patients with hypertension/prehypertension. *Headache* 2006; **46:** 503–7.

Uricosuric action. Losartan has been found to increase urinary uric acid excretion and reduce serum uric acid concentrations in healthy subjects[1] and in hypertensive patients.[2,3] However, the effect is generally small and the clinical significance is not clear. Other angiotensin II receptor antagonists do not appear to have such an effect.[2,3]

1. Nakashima M, *et al.* Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* 1992; **42:** 333–5.
2. Puig JG, *et al.* Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens* 1999; **17:** 1033–9.
3. Würzner G, *et al.* Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001; **19:** 1855–60.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cartan; Cliarvas†; Corticosan; Cozaarex; Enromic; Fensartan; Klosartan; Loctenk; Loplac; Losacor; Losargal; Losarlan; Niten; Paxon; Prelertan†; Presinor; Tacardia; Tacicul; Temisartan; Tenopres†; ***Austral.:*** Cozaar; ***Austria:*** Cosaar; ***Belg.:*** Cozaar; Loortan; ***Braz.:*** Aradois; Corus; Cozaar; Lanzacor; Lorsacor†; Losartec; Losatal†; Redupress†; Torlos; Valtrian; Zaarpress; ***Canad.:*** Cozaar; ***Chile:*** Aratan; Corodin; Cozaar; Losapres; Sanipresin; Simperten; ***Cz.:*** Arionecs; Cozaar†; Giovax; Lakea; Lorista; Losartic; Lozap; Nopretens; ***Denm.:*** Cozaar; ***Fin.:*** Cozaar; ***Fr.:*** Cozaar; ***Ger.:*** Lorzaar; ***Gr.:*** Cozaar; Hypozar; Lorfast; Mozartan; Rabolan; Rapifast; ***Hong Kong:*** Cozaar; ***Hung.:*** Cozaar; Lavestra; Portiron; Tervalon; ***India:*** Alsartan; Covance; Lara; Losacar; Losanorm†; Losium; Lozitan; Zaart; ***Indon.:*** Acetensa; Angioten; Cozaar; Insaar; Sartaxal; Tensaar; ***Irl.:*** Cozaar; ***Israel:*** Ocsaar; ***Ital.:*** Lortaan; Losaprex; Neo-Lotan; ***Jpn:*** Nu-Lotan; ***Malaysia:*** Cozaar; ***Mex.:*** Bimidal; Cozaar; ***Neth.:*** Cozaar; Jalvase; ***Norw.:*** Cozaar; ***NZ:*** Cozaar; ***Philipp.:*** Bepsar; Cozaar; Lifezar; Normoten; ***Pol.:*** Cozaar; Lakea; Lorista; Losacor; Lozap; Xartan; ***Port.:*** Cozaar; Lortaan; Tarnasol; Tiasar; ***Rus.:*** Cozaar (Козаар); Lozap (Лозап); Presartan (Презартан); ***S.Afr.:*** Cozaar; ***Singapore:*** Cozaar; ***Spain:*** Cozaar; ***Swed.:*** Cozaar; ***Switz.:*** Cosaar; ***Thai.:*** Cozaar; ***Turk.:*** Cozaar; Eklips; ***UK:*** Cozaar; ***USA:*** Cozaar; ***Venez.:*** Biortan; Cormac; Cozaar; Hyzaar; Nefrotal; Presartan; Sortal; Tenserpil†.

Multi-ingredient: ***Arg.:*** Cozaarex D; Fensartan D; Klosartan D; Loctenk D; Loplac-D; Losacor D; Niten D; Paxon-D; Presinor D; Tacardia D; Tenopres D†; ***Austria:*** Cosaar Plus; ***Belg.:*** Cozaar Plus; Loortan Plus; ***Braz.:*** Aradois H; Corus H; Hyzaar; Lorsar + HCT†; Neopress; Torlos H; ***Canad.:*** Hyzaar; ***Chile:*** Aratan D; Corodin D; Hyzaar; Losapres-D; Sanipresin-D; Simperten-D; ***Cz.:*** Giovax plus H; Hyzaar†; Lorista H; Losaratio Plus H; Lozap H; Nopretens Plus H; ***Denm.:*** Cozaar Comp; Fortzaar; ***Fin.:*** Cozaar Comp; ***Fr.:*** Fortzaar; Hyzaar; ***Ger.:*** Fortzaar; Lorzaar plus; ***Gr.:*** Hyzaar; ***Hong Kong:*** Hyzaar; ***Hung.:*** Hyzaar; ***India:*** Alsartan-AM; Alsartan-H; Amlopres Z; Covance-D; Losacar-H; Zaart-H; ***Irl.:*** Cozaar Comp; ***Israel:*** Ocsaar Plus; ***Ital.:*** Forzaar; Hizaar; Losazid; Neo-Lotan Plus; ***Malaysia:*** Fortzaar; Hyzaar; ***Mex.:*** Hyzaar; ***Neth.:*** Cozaar Plus; Fortzaar; Hyzaar; Losazid; ***Norw.:*** Cozaar Comp; ***NZ:*** Hyzaar; ***Philipp.:*** Combizar; Hyzaar; ***Pol.:*** Hyzaar; Lorista H; ***Port.:*** Cozaar Plus; Fortzaar; Lortaan Plus; Siaara; ***Rus.:*** Hyzaar (Гизаар); Lozap Plus (Лозап Плюс); ***S.Afr.:*** Cozaar Comp; Fortzaar; ***Singapore:*** Hyzaar; ***Spain:*** Cozaar Plus; Fortzaar; ***Swed.:*** Cozaar Comp; ***Switz.:*** Cosaar Plus; ***Thai.:*** Fortzaar; Hyzaar; ***Turk.:*** Eklips Plus; Hyzaar; ***UK:*** Cozaar Comp; ***USA:*** Hyzaar; ***Venez.:*** Cormatic; Hyzaar Plus; Nefrotal H.

Lovastatin *(BAN, USAN, rINN)*

L-154803; Lovastatiini; Lovastatina; Lovastatinas; Lovastatine; Lovastatinum; Lovasztatin; MB-530B; 6α-Methylcompactin; Mevinolin; MK-803; Monacolin K; MSD-803. (3*R*,5*R*)-7-{(1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl}-3-hydroxyheptan-5-olide.

Ловастатин

$C_{24}H_{36}O_5$ = 404.5.

CAS — 75330-75-5.

ATC — C10AA02.

ATC Vet — QC10AA02.

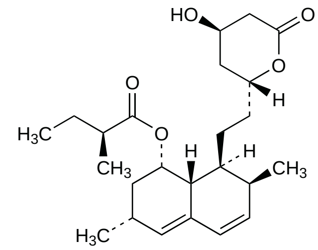

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Lovastatin). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone. Store under nitrogen at a temperature of 2° to 8°.

USP 31 (Lovastatin). A white to off-white crystalline powder. Insoluble in water; sparingly soluble in alcohol; practically insoluble in petroleum spirit; freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methyl alcohol. Store under nitrogen in airtight containers at a temperature not exceeding 8°.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Incidence of adverse effects. Adverse effects led to withdrawal of lovastatin in 21 of 745 patients receiving the drug for about 5 years.[1] They included asymptomatic elevation of hepatic aminotransferases in 10 patients, gastrointestinal symptoms in 3, rash in 2, myopathy in 2, myalgia in 1, arthralgia in 1, insomnia in 1, and weight gain in 1.

1. Lovastatin Study Groups. Lovastatin 5-year safety and efficacy study: Lovastatin Study Groups I through IV. *Arch Intern Med* 1993; **153:** 1079–87.

Interactions

As for Simvastatin, p.1392.

For specific dosage reductions in patients taking lovastatin with interacting drugs, see Uses and Administration, below.

Pharmacokinetics

Lovastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Three other metabolites have also been isolated. Lovastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action; less than 5% of an oral dose has been reported to reach the circulation. Peak plasma concentrations occur within 2 to 4 hours, and steady-state concentrations are achieved after 2 to 3 days with daily dosage. Both lovastatin and its β-hydroxyacid metabolite are more than 95% bound to plasma proteins. Lovastatin is mainly excreted in the bile as metabolites; about 85% of a dose has been recovered from the faeces and about 10% from the urine. The half-life of the active metabolite is 1 to 2 hours.

◊ General reviews.

1. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
2. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.

Uses and Administration

Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394).

Lovastatin is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly in type IIa and IIb hyperlipoproteinaemias. It is also given for cardiovascular risk reduction (p.1164) in both primary and secondary prevention of ischaemic heart disease.

Lovastatin is given in an initial oral dose of 10 to 20 mg daily in the evening with food, increased, if necessary, at intervals of 4 weeks or more to 80 mg daily as a single dose or in 2 divided doses. Lower doses of lovastatin should be used in patients at risk of myopathy, including patients with severe renal impairment (see below) and those taking drugs that interact with lovastatin; an initial dose of 10 mg daily is recommended in patients taking *ciclosporin* or *danazol*, and the daily dose should not exceed 20 mg in patients taking *ciclosporin, danazol, fibric acid derivatives*, or *nicotinic acid*, or 40 mg in those taking *amiodarone* or *verapamil*.

For the use of lovastatin in children, see below.

◊ General reviews.

1. Curran MP, Goa KL. Lovastatin extended release: a review of its use in the management of hypercholesterolaemia. *Drugs* 2003; **63:** 685–99.

Administration in children. Lovastatin reduces plasma-cholesterol concentrations in children and adolescents with heterozygous familial hypercholesterolaemia[1-3] and has been given safely for up to 48 weeks in boys,[2] and up to 24 weeks in girls.[3] In the USA it is licensed in children aged 10 to 17 years and is given orally in an initial dose of 10 to 20 mg once daily, increased at intervals of 4 weeks or more, if necessary, to a maximum dose of 40 mg once daily.

1. Lambert M, *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996; **97:** 619–28.
2. Stein EA, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; **281:** 137–44.
3. Clauss SB, *et al.* Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics* 2005; **116:** 682–8.

Administration in renal impairment. Patients with renal impairment may be at increased risk of myopathy and US licensed product information states that doses of lovastatin above 20 mg daily should be used cautiously in patients with a creatinine clearance below 30 mL/minute.

Adrenoleucodystrophy. A preliminary study[1] has shown that lovastatin may be useful in the treatment of adrenoleucodystrophy (see under Lorenzo's Oil, p.2334). Lovastatin reduced the plasma levels of very-long-chain fatty acids which are known to be elevated in patients with this rare metabolic disorder.

1. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Preparations

USP 31: Lovastatin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hipovastin; Loriter†; Mevlor; Sivlor†; ***Austria:*** Mevacor; ***Braz.:*** Lipoclin; Lovast†; Lovaton†; Lovax†; Mevacor; Mevalip; Minor†; Neolipid†; Reducol; ***Canad.:*** Mevacor; ***Chile:*** Colevix†; Hiposterol; Lispor; Lovacol; Mevacor†; Nij-Terol†; Sanelor; ***Cz.:*** Holetar; Lovacard†; Medostatin; Mevacor; Rancor; ***Denm.:*** Lovacodan; Mevacor; ***Fin.:*** Lovacol; Mevacor; ***Ger.:*** Lova†; Lovabeta; Lovadura; Lovagamma; Lovahexal; Mevinacor; ***Gr.:*** Aurostatin; B-Lovatin†; Cecural; Ilopar; Liferzit; Lipidless; Lostin; Lovadrug; Lovapen; Lovasten; Lovatex; Lovatop; Lowlipid; Medovascin; Mevacor; Mevastin; Mevinol†; Misodomin; Nabicortin; Terveson; Velkalov; Viking; ***Hong Kong:*** Ellanco; Lofacol†; Lomar; Medostatin; Mevacor; ***Hung.:*** Mevacor; Stoplip; ***India:*** Lovacard; Pro-HDL; Rovacor; ***Indon.:*** Cholvastin; Lipovas; Lofacol; Lotyn; Lovatrol; ***Israel:*** Lovalip†; ***Ital.:*** Lovinacor; Rextat; Tavacor; ***Malaysia:*** Lestric; Lostatin; Lovarem; Lovastin; Medostatin; Mevacor†; ***Mex.:*** Casbame; Dilucid; Liperol; Mevacor; ***Norw.:*** Mevacor; ***Pol.:*** Anlostin; Apo-Lova; Liprox; Lovasterol; Lovastin; ***Port.:*** Flozul; Lipdaune; Lipus; Mevinacor; Mevlor; Tecnolip; ***Rus.:*** Cardiostatin (Кардиостатин); Holetar (Холетар); Lovasterol (Ловастерол); Medostatin (Медостатин); Rovacor (Ровакор); ***S.Afr.:*** Lovachol; ***Singapore:*** Elstatin; Lostatin; Lovastin; Medostatin; Rovacor; ***Spain:*** Aterkey; Colesvir; Lipofren†; Liposcler; Mevacor; Mevasterol; Nergadan; Taucor; ***USA:*** Altoprev; Mevacor; ***Venez.:*** Dislipin†; Levistan; Lostatin†; Lovanil; Lovas†; Mevacor.

Multi-ingredient: *USA:* Advicor.

Low-molecular-weight Heparins

Depolymerised Heparins; Heparina massae molecularis minoris; Heparinas de bajo peso molecular; Hepariner, lågmolekylära; Héparines de basse masse moléculaire; Hepariny nízkomolekulární; LMW Heparins; Low-molecular-mass Heparins; Mažos molekulinės masės heparinai; Pienimolekyyliset hepariinit.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Heparins, Low-molecular Mass; Low-molecular-weight Heparins BP 2008). Salts of sulfated glucosaminoglycans having a mass-average molecular mass less than 8000. They are obtained by fractionation or depolymerisation of heparin of natural origin and display different chemical structures at the reducing or the non-reducing end of the polysaccharide chains.

The potency is not less than 70 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is not less than 1.5.

A white or almost white hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Units

The second International Standard for low-molecular-weight heparin was agreed in 2003 and is used to calibrate products for both anti-factor Xa and anti-factor IIa activities. Potency is expressed in terms of units of anti-factor Xa activity per mg and the ratio of anti-factor Xa to anti-factor IIa activity. This ratio differs for individual low-molecular-weight heparins and neither they nor unfractionated heparin can be used interchangeably unit for unit.

Adverse Effects

As for Heparin, p.1301.

◊ Reviews.

1. Gouin-Thibault I, *et al.* Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Safety* 2005; **28:** 333–49.

Effects on the adrenal glands. Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.[1-3] The UK CSM suggests[4] that plasma-potassium concentrations should be monitored in all patients with risk factors for hyperkalaemia, particularly those receiving low-molecular-weight heparins for more than 7 days (see Heparin, p.1301).

1. Levesque H, *et al.* Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; **300:** 1437–8.
2. Canova CR, *et al.* Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; **349:** 1447–8.
3. Wiggam MI, Beringer TRO. Effect of low-molecular-weight heparin on serum concentrations of potassium. *Lancet* 1997; **350:** 292–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

Effects on the blood. It was hoped that, because of their higher ratio of anti-factor Xa to anti-thrombin activity compared with heparin, low-molecular-weight heparins might cause less bleeding while maintaining their antithrombotic activity. Some large studies[1,2] have suggested less bleeding with low-molecular-weight heparins than with unfractionated heparin. However, meta-analyses and reviews[3,4] have been unable to confirm a significant reduction in major haemorrhage in patients treated with low-molecular-weight heparins, compared with heparin, for venous thromboembolism, although they confirmed that low-molecular-weight heparins are not associated with an increase in risk. There may be an increased risk of bleeding in patients with renal impairment,[5,6] (see Precautions, below) although the criterion of creatinine clearance 30 mL/minute or less as a guide to selecting patients at increased risk has been questioned;[7] pharmacokinetic response may vary according to the low-molecular-weight heparin used.

Thrombocytopenia has also been reported with low-molecular-weight heparins[8-10] although in one study the incidence was less than with unfractionated heparin.[11]

Thrombocytosis has also been reported.[12,13]

1. Levine MN, *et al.* Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; **114:** 545–51.
2. Hull RD, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; **326:** 975–82. Correction. *ibid.* **327:** 140.
3. Gould MK, *et al.* Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; **130:** 800–809.
4. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
5. Cestac P, *et al.* Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Safety* 2003; **26:** 197–207.
6. Lim W, *et al.* Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; **144:** 673–84.
7. Nagge J, *et al.* Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; **162:** 2605–9.
8. Eichinger S, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **337:** 1425–6.
9. Lecompte T, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
10. Tardy B, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
11. Warkentin TE, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332:** 1330–5.
12. Rizzieri DA, *et al.* Thrombocytosis associated with low-molecular-weight heparin. *Ann Intern Med* 1996; **125:** 157.
13. Liautard C, *et al.* Low-molecular-weight heparins and thrombocytosis. *Ann Pharmacother* 2002; **36:** 1351–4.

Effects on the skin. Adverse effects of low-molecular-weight heparins on the skin have been reviewed[1] and are estimated to be rare. Most low-molecular-weight heparins have been implicated. Urticarial rash or immediate hypersensitivity has been reported (see below). Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the postpartum period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.

Skin necrosis reactions are usually localised to the subcutaneous injection site, although distant lesions have also been reported. There has been a report[2] of diffuse skin necrosis leading to fatality in a patient given enoxaparin.

1. Wütschert R, *et al.* Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Safety* 1999; **20:** 515–25.
2. Nadir Y, *et al.* A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; **77:** 166–8.

Hypersensitivity. Reports of hypersensitivity reactions associated with low-molecular-weight heparins are rare. However, a patient being treated with enoxaparin 20 mg subcutaneously daily developed a widespread pruritic urticaria and swelling of lips and tongue after 3 days of treatment.[1] Antihistamines and prednisone given with enoxaparin failed to control the reaction and enoxaparin was stopped after a further 3 days. Urticaria and angioedema rapidly resolved on withdrawal.

Delayed hypersensitivity skin reactions have also been reported (see above).

1. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992; **340:** 972–3.

Treatment of Adverse Effects

Severe bleeding with low-molecular-weight heparins, usually caused by accidental overdosage, may be reduced by the slow intravenous injection of protamine sulfate (p.1461). The recommended doses of protamine sulfate are given in the individual monographs and should completely neutralise the anti-thrombin effect of the low-molecular-weight heparin but will only partially neutralise the anti-factor-Xa effect. Not more than 50 mg of protamine sulfate should be injected for any one dose.

Precautions

As for Heparin, p.1303.

Low-molecular-weight heparins should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) with the particular low-molecular-weight heparin to be used.

Monitoring of plasma-anti-factor-Xa activity may be considered in patients with an increased risk of bleeding, for example the elderly or those with renal impairment or extremes of body-weight, and in patients with active bleeding.

Licensed product information for some low-molecular-weight heparins contra-indicates their use in patients with prosthetic heart valves as they may not provide adequate prophylaxis against thromboembolism even at high doses (but see under Valvular Heart Disease, p.1187, for references to their use).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred in patients receiving low-molecular-weight heparins with spinal or epidural anaesthesia or analgesia (see p.1303).

Interactions

As for Heparin, p.1303.

Pharmacokinetics

Although the precise pharmacokinetic parameters of different low-molecular-weight heparins vary (see individual monographs), they generally have a greater bioavailability after subcutaneous injection and a longer half-life than heparin.

◊ References.

1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.
2. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; **26** (suppl 1): 31–8.

Uses and Administration

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Those included in *Martindale* are:

- Ardeparin, p.1216
- Bemiparin, p.1223
- Certoparin, p.1242

- Dalteparin, p.1255
- Enoxaparin, p.1277
- Nadroparin, p.1346
- Parnaparin, p.1366
- Reviparin, p.1388
- Tinzaparin, p.1413

Like heparin (p.1303), these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin. Low-molecular-weight heparins have less effect on platelet aggregation than heparin. They have no significant effect on blood coagulation tests such as activated partial thromboplastin time (APTT). Therapy may be monitored by measurement of plasma-anti-factor-Xa activity but monitoring is less frequently required than with heparin since low-molecular-weight heparins have a more predictable effect.

Low-molecular-weight heparins are used in the management of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189). They are used for prophylaxis, particularly during surgery, and for treatment of established thromboembolism. They are given by subcutaneous injection once or twice daily. They are also used intravenously to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures. They may be given subcutaneously in the management of unstable angina (p.1157) and both intravenously and subcutaneously in acute myocardial infarction (p.1175).

Doses are expressed either in terms of the weight of low-molecular-weight heparin or in terms of units of anti-factor Xa activity. Since low-molecular-weight heparins differ in their relative inhibition of factor Xa and thrombin, doses, even when expressed in terms of anti-factor-Xa activity, cannot be equated. Different preparations of the same low-molecular-weight heparin may appear to have different doses depending on the reference preparation used.

◊ References.

1. Green D, *et al.* Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994; **46:** 89–109.
2. Nurmohamed MT, *et al.* Low molecular weight heparin(oid)s: clinical investigations and practical recommendations. *Drugs* 1997; **53:** 736–51.
3. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; **337:** 688–98. Correction. *ibid.*: 1567.
4. Deitelzweig SB, *et al.* Venous thromboembolism prevention with LMWHs in medical and orthopedic surgery patients. *Ann Pharmacother* 2003; **37:** 402–11.
5. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.

Lubeluzole *(BAN, USAN, rINN)*

Lubeluzol; Lubéluzole; Lubeluzolum; R-87926. (*S*)-1-{4-[1,3-Benzothiazol-2-yl(methyl)amino]piperidino}-3-(3,4-difluorophenoxy)propan-2-ol.

Любелузол

$C_{22}H_{25}F_2N_3O_2S$ = 433.5.
CAS — 144665-07-6.

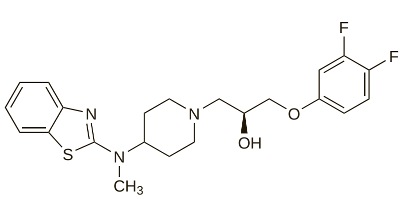

Profile

Lubeluzole is a neuroprotectant that has been investigated for ischaemic stroke, but results have been disappointing.

◊ References.

1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

Manidipine Hydrochloride *(rINNM)*

CV-4093; Franidipine Hydrochloride; Hidrocloruro de manidipino; Manidipine, Chlorhydrate de; Manidipini Hydrochloridum. 2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride.

Манидипина Гидрохлорид

$C_{35}H_{38}N_4O_6,2HCl$ = 683.6.
CAS — 120092-68-4 (manidipine); 89226-75-5 (manidipine hydrochloride); 126229-12-7 (manidipine hydrochloride).
ATC — C08CA11.
ATC Vet — QC08CA11.

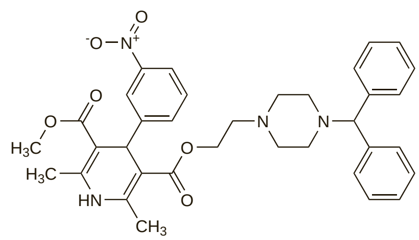

(manidipine)

Profile

Manidipine is a dihydropyridine calcium-channel blocker (see Nifedipine, p.1350). It is given by mouth as the hydrochloride in the management of hypertension (p.1171) in a usual dose of 10 to 20 mg once daily.

◊ Reviews.

1. McKeage K, Scott LJ. Manidipine: a review of its use in the management of hypertension. *Drugs* 2004; **64:** 1923–40.
2. Roca-Cusachs A, Triposkiadis F. Antihypertensive effect of manidipine. *Drugs* 2005; **65** (suppl 2): 11–19.
3. Otero ML. Manidipine-delapril combination in the management of hypertension. *Vasc Health Risk Manag* 2007; **3:** 255–63.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Iperten; ***Braz.:*** Manivasc; ***Fr.:*** Iperten; ***Ger.:*** Manyper; ***Gr.:*** Manyper; ***Ital.:*** Iperten; Vascoman; ***Jpn:*** Calslot; ***Philipp.:*** Caldine; ***Spain:*** Artedil; ***Thai.:*** Madiplot.

Multi-ingredient: ***Braz.:*** Hipertil; ***Gr.:*** Vivace.

Mannitol ⊗

Cordycepic Acid; E421; Manita; Manitol; Manitolis; Manna Sugar; Mannit; Mannite; Mannitoli; Mannitolum. D-Mannitol.

Маннит; Маннитол

$C_6H_{14}O_6$ = 182.2.
CAS — 69-65-8.
ATC — A06AD16; B05BC01; B05CX04.
ATC Vet — QA06AD16; QB05BC01; QB05CX04.

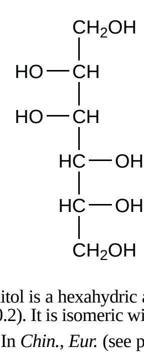

Description. Mannitol is a hexahydric alcohol related to mannose ($C_6H_{12}O_6$ = 180.2). It is isomeric with sorbitol (p.1965).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Mannitol). A white or almost white crystalline powder or free-flowing granules. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol.

USP 31 (Mannitol). A white odourless crystalline powder or free-flowing granules with a sweet taste. Soluble 1 in 5.5 of water; very slightly soluble in alcohol; practically insoluble in ether; slightly soluble in pyridine; soluble in alkaline solutions.

Incompatibility. Mannitol should never be added to whole blood for transfusion or given through the same set by which blood is being infused. For details of the adverse effects of mannitol on red blood cells, see Effects on the Blood under Adverse Effects, below.

Supersaturated solutions. Supersaturated aqueous solutions are prepared with the aid of heat. Any crystals that form during storage of the injection should be dissolved by warming before use; this may be a particular problem with the 20 and 25% injections which are supersaturated. A 5.07% solution in water is iso-osmotic with serum.

Adverse Effects

The most common adverse effect associated with mannitol therapy is fluid and electrolyte imbalance including circulatory overload and acidosis at high doses. The expansion of extracellular volume can precipitate pulmonary oedema and patients with diminished cardiac reserve are at special risk. The shift of fluid from the intracellular to extracellular compartment can cause tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms.

When given orally, mannitol causes diarrhoea. Intravenous infusion of mannitol has been associated with nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension. Large doses have been associated rarely with acute renal failure. Hypersensitivity reactions have occurred.

Extravasation of the solution may cause oedema and skin necrosis; thrombophlebitis may occur.

Effects on the blood. Agglutination and irreversible crenation of erythrocytes occurred when blood was mixed with varying proportions of a 10% mannitol solution.[1] It was suggested that intravenous infusions should be carefully controlled and given at a slow rate. This observation could have particular relevance to patients with sickle-cell disease.[2,3] Although agglutination and crenation had been observed *in vitro*, dilutional effects would make *in-vivo* interaction with blood cells less likely.[4]

1. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 421–2.
2. Konotey-Ahulu FID. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
3. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
4. Samson JH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 1191.

Effects on the gastrointestinal tract. Potentially explosive intracolonic concentrations of hydrogen gas have been measured in patients given mannitol before colonoscopy,[1,2] and cases of colonic explosion, including fatalities, have been reported in patients undergoing colonoscopic electrocautery, who had received mannitol bowel preparation. However, the risk of explosion was considered to be small when air or carbon dioxide insufflation and suction were used during the colonoscopy procedure.[2,3]

Colonic perforation and subsequent death has been attributed to the use of mannitol for the treatment of constipation.[4]

1. La Brooy SJ, *et al.* Potentially explosive colonic concentrations of hydrogen after bowel preparation with mannitol. *Lancet* 1981; **i:** 634–6.
2. Avgerinos A, *et al.* Bowel preparation and the risk of explosion during colonoscopic polypectomy. *Gut* 1984; **25:** 361–4.
3. Trotman I, Walt R. Mannitol and explosions. *Lancet* 1981; **i:** 848.
4. Moses FM. Colonic perforation due to oral mannitol. *JAMA* 1988; **260:** 640.

Effects on the kidneys. Focal osmotic nephrosis occurred in a patient given mannitol 20% intravenously.[1]

Acute oliguric renal failure has been associated with the use of large doses of mannitol in patients with previously normal renal function,[2-4] and acute renal failure developed[5] in a patient with diabetes mellitus complicated by nephropathy after he was given 420 g of mannitol intravenously over 4 days.

1. Goodwin WE, Latta H. Focal osmotic nephrosis due to the therapeutic use of mannitol: a case of perirenal hematoma after renal biopsy. *J Urol (Baltimore)* 1970; **103:** 11–14.
2. Whelan TV, *et al.* Acute renal failure associated with mannitol intoxication. *Arch Intern Med* 1984; **144:** 2053–5.
3. Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion: appropriate response of tubuloglomerular feedback? *Arch Intern Med* 1984; **144:** 2214–16.
4. Rabetoy GM, *et al.* Where the kidney is concerned, how much mannitol is too much? *Ann Pharmacother* 1993; **27:** 25–8.
5. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* 2001; **110:** 331.

Overdosage. Severe mannitol intoxication was reported in 8 patients with renal failure given large, and sometimes enormous, amounts of mannitol intravenously over 1 to 3 days.[1] These patients had CNS involvement out of proportion to uraemia, severe hyponatraemia, a large osmolality gap, and fluid overload. Six patients were treated with haemodialysis and this was considered to be more effective than peritoneal dialysis, which was used in 1 patient.

1. Borges HF, *et al.* Mannitol intoxication in patients with renal failure. *Arch Intern Med* 1982; **142:** 63–6.

Precautions

Mannitol is contra-indicated in patients with pulmonary congestion or pulmonary oedema, intracranial bleeding (except during craniotomy), heart failure (in patients with diminished cardiac reserve, expansion of the extracellular fluid may lead to fulminating heart failure), and in patients with renal failure unless a test dose has produced a diuretic response (if urine flow is inadequate, expansion of the extracellular fluid may lead to acute water intoxication).

Mannitol should not be given with whole blood.

All patients given mannitol should be carefully observed for signs of fluid and electrolyte imbalance and renal function should be monitored.

Pharmacokinetics

Only small amounts of mannitol are absorbed from the gastrointestinal tract. After intravenous injection mannitol is excreted rapidly by the kidneys before any very significant metabolism can take place in the liver. Mannitol does not cross the blood-brain barrier or penetrate the eye. An elimination half-life of about 100 minutes has been reported.

Uses and Administration

Mannitol is an osmotic agent. Although an isomer of sorbitol, it has little energy value, since it is largely eliminated from the body before any metabolism can take place.

Mannitol is mainly used, with adequate rehydration, to increase urine flow in patients with acute renal failure and to reduce raised intracranial pressure (p.1181) and treat cerebral oedema. It is also used in the short-term management of glaucoma (p.1873), especially to reduce intra-ocular pressure prior to ophthalmic surgery, and to promote the excretion of toxic substances by forced diuresis.

Other indications include bladder irrigation during transurethral resection of the prostate in order to reduce haemolysis and as an oral osmotic laxative for bowel preparation. Mannitol is used as a diluent and excipient in pharmaceutical preparations and as a bulk sweetener. It is under investigation for use in bronchiectasis and cystic fibrosis.

When given parenterally, mannitol raises the osmotic pressure of the plasma thus drawing water out of body tissues and producing an osmotic diuresis. Reduction of CSF and intra-ocular fluid pressure occurs within 15 minutes of the start of a mannitol infusion and lasts for 3 to 8 hours after the infusion is stopped; diuresis occurs after 1 to 3 hours.

When used as an osmotic diuretic, mannitol is given by intravenous infusion. Careful monitoring of fluid balance, electrolytes, renal function, and vital signs is necessary during infusion to prevent fluid and electrolyte imbalance, including circulatory overload and tissue dehydration. Solutions containing more than 15% of mannitol may crystallise during storage, particularly at low temperatures; crystals may be redissolved by warming before use; the giving set should include a filter.

Mannitol may be used to treat patients in the oliguric phase of **renal failure** or those suspected of inadequate renal function after correction of plasma volume, provided a test dose of about 200 mg/kg given by rapid intravenous infusion of a 15 to 25% solution over 3 to 5 minutes produces a diuresis of at least 30 to 50 mL/hour during the next 2 to 3 hours; a second test dose is permitted if the response to the first is inadequate. The usual adult dose of mannitol ranges from 50 to 100 g in a 24 hour period, given by intravenous infusion of a 5 to 25% solution. The rate of infusion is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour.

For children, a dose of 0.25 to 2 g/kg has been used.

The total dosage, the concentration, and the rate of infusion depend on the fluid requirement, the urinary output, and the nature and severity of the condition being treated. Mannitol infusion has also been used to prevent acute renal failure during cardiovascular and other types of surgery, or after trauma.

To reduce **raised intracranial** or **intra-ocular pressure** mannitol may be given by intravenous infusion as a 15 to 25% solution in a dose of 0.25 to 2 g/kg over 30 to 60 minutes. Rebound increases in intracranial or intra-ocular pressure may occur but are less frequent than with urea.

During **transurethral prostatic resection** a 2.5 to 5% solution of mannitol has been used for irrigating the bladder.

Ciguatera poisoning. Ciguatera poisoning occurs throughout the Caribbean and Indopacific as a result of the consumption of certain fish contaminated with ciguatoxin; it is increasingly seen in Europe, in travellers returning from these areas, or as a result of eating imported fish. Symptoms can be severe, including a bizarre reversal of hot and cold sensation. Some neurological symptoms, pruritus, arthralgia, and fatigue, may persist for years.[1] Treatment is usually symptomatic since there is no specific antidote. Dramatic reversal of neuromuscular symptoms with slower resolution of gastrointestinal upset has been reported after giving mannitol 1 g/kg by intravenous infusion over 30 to 45 minutes in the acute phase of the illness.[2-4] Mannitol may also be beneficial up to a week after poisoning.[5] However, a double-blind study[6] found mannitol to be no better than normal saline at relieving symptoms at 24 hours. Amitriptyline has been found on several occasions[7-9] to relieve neurological symptoms (dysaesthesias and paraesthesias) and pruritus. Gabapentin has also been reported to be of benefit.[10]

1. Lehane L. Ciguatera update. *Med J Aust* 2000; **172:** 176–9.
2. Palafox NA, *et al.* Successful treatment of ciguatera fish poisoning with intravenous mannitol. *JAMA* 1988; **259:** 2740–2.
3. Pearn JH, *et al.* Ciguatera and mannitol: experience with a new treatment regimen. *Med J Aust* 1989; **151:** 77–80.
4. Williamson J. Ciguatera and mannitol: a successful treatment. *Med J Aust* 1990; **153:** 306–7.
5. Fenner PJ, *et al.* A Queensland family with ciguatera after eating coral trout. *Med J Aust* 1997; **166:** 473–5.
6. Schnorf H, *et al.* Ciguatera fish poisoning: a double-blind randomized trial of mannitol therapy. *Neurology* 2002; **58:** 873–80.
7. Bowman PB. Amitriptyline and ciguatera. *Med J Aust* 1984; **140:** 802.
8. Davis RT, Villar LA. Symptomatic improvement with amitriptyline in ciguatera fish poisoning. *N Engl J Med* 1986; **315:** 65.
9. Calvert GM, *et al.* Treatment of ciguatera fish poisoning with amitriptyline and nifedipine. *J Toxicol Clin Toxicol* 1987; **25:** 423–8.
10. Perez CM, *et al.* Treatment of ciguatera poisoning with gabapentin. *N Engl J Med* 2001; **344:** 692–3.

Gastrointestinal disorders. BOWEL PREPARATION. Mannitol, 1000 mL of a 10% solution or 500 mL of 10 or 20% solution, given orally, has been used to prepare the bowel for surgical and diagnostic procedures.[1,2] The potential for formation of explosive gas in the bowel should be borne in mind (see Effects on the Gastrointestinal Tract, above).

1. Palmer KR, Khan AN. Oral mannitol: a simple and effective bowel preparation for barium enema. *BMJ* 1979; **2:** 1038.
2. Newstead GL, Morgan BP. Bowel preparation with mannitol. *Med J Aust* 1979; **2:** 582–3.

DIAGNOSIS AND TESTING. Mannitol has been used with lactulose[1,2] and with cellobiose[3,4] in the detection of abnormal small bowel permeability, particularly that occurring in coeliac disease. For further information on the use of differential sugar absorption tests, see Lactulose, p.1739.

1. Pearson ADJ, *et al.* The gluten challenge—biopsy v permeability. *Arch Dis Child* 1983; **58:** 653.
2. Cooper BT. Intestinal permeability in coeliac disease. *Lancet* 1983; **i:** 658–9.
3. Juby LD, *et al.* Cellobiose/mannitol sugar test—a sensitive tubeless test for coeliac disease: results on 1010 unselected patients. *Gut* 1989; **30:** 476–80.
4. Hodges S, *et al.* Cellobiose: mannitol differential permeability in small bowel disease. *Arch Dis Child* 1989; **64:** 853–5.

Respiratory disorders. Inhalation of dry powder mannitol improves mucus clearance and small studies have suggested it may be of benefit in bronchiectasis,[1] although further studies are needed to confirm this.

1. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 07/05/08).

Preparations

BP 2008: Mannitol Intravenous Infusion;
USP 31: Mannitol in Sodium Chloride Injection; Mannitol Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Mede-Prep; Osmitrol; ***Canad.:*** Osmitrol; ***Cz.:*** Ardeaosmosol MA; Mannisol; Osmofundin 15% N†; ***Ger.:*** Deltamannit; Mannit-Losung; Osmofundin 15% N; Osmosteril 20%; Thomaemannit†; ***Hung.:*** Mannisol; ***Ital.:*** Isotol; Mannistol†; ***Mex.:*** Osmorol; ***Neth.:*** Osmosteril; ***NZ:*** Mede-Prep†; ***Port.:*** Osmofundina; ***Spain:*** Osmofundina Concentrada; ***Switz.:*** Mannite; ***Thai.:*** Maniton†; ***Turk.:*** Resectisol; Rezosel; ***USA:*** Osmitrol; Resectisol†.

Multi-ingredient: Austria: Osmofundin 10%; Resectal; ***Chile:*** Gelsolets; ***Denm.:*** Pharmalgen Albumin; ***Fin.:*** Somanol + Ethanol; ***Ger.:*** Flacar; Freka-Drainjet Purisole; Osmosteril 10%; ***Ital.:*** Levoplus; Naturalass; ***Mex.:*** Jarabe de Manzanas; ***Pol.:*** Purisole SM; ***Port.:*** Purisole; Xarope de Macas Reinetas; ***Rus.:*** Rheogluman (Реоглюман); ***Spain:*** Salcemetic†; Salmagne; ***Switz.:*** Cital†.

Mebutamate *(BAN, USAN, rINN)*

Mébutamate; Mebutamato; Mebutamatum; W-583. 2-sec-Butyl-2-methyltrimethylene dicarbamate.

Мебутамат

$C_{10}H_{20}N_2O_4$ = 232.3.
CAS — 64-55-1.
ATC — N05BC04.
ATC Vet — QN05BC04.

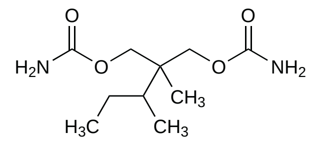

Profile

Mebutamate is a carbamate with general properties similar to those of meprobamate (p.1006). It has been given by mouth as an adjunct in the treatment of hypertension.

Mebutizide *(rINN)* ⊗

Mebutizida; Mébutizide; Mebutizidum. 6-Chloro-3-(1,2-dimethylbutyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Мебутизид

$C_{13}H_{20}ClN_3O_4S_2$ = 381.9.
CAS — 3568-00-1.
ATC — C03AA13.
ATC Vet — QC03AA13.

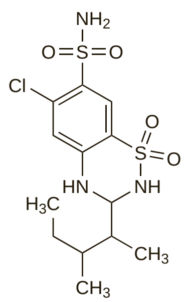

Profile

Mebutizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of oedema and hypertension.

Mecamylamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecamilamina; Mecamine Hydrochloride; Mécamylamine, Chlorhydrate de; Mecamylamini Hydrochloridum. *N*-Methyl-2,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

Мекамиламина Гидрохлорид

$C_{11}H_{21}N,HCl$ = 203.8.
CAS — 60-40-2 (mecamylamine); 826-39-1 (mecamylamine hydrochloride).
ATC — C02BB01.
ATC Vet — QC02BB01.

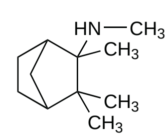

(mecamylamine)

Pharmacopoeias. In *US.*

USP 31 (Mecamylamine Hydrochloride). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Trimetaphan Camsilate, p.1419. Mecamylamine may also cause tremor, convulsions, choreiform movements, insomnia, sedation, dysarthria, and mental aberrations.

Pharmacokinetics
Mecamylamine hydrochloride is almost completely absorbed from the gastrointestinal tract. It crosses the placenta and the blood-brain barrier. About 50% of the dose is excreted unchanged in the urine over 24 hours, but the rate is diminished in alkaline urine.

Uses and Administration
Mecamylamine hydrochloride is a ganglion blocker with actions similar to those of trimetaphan (p.1419). It is given orally in the management of hypertension (p.1171), although other antihypertensives with fewer adverse effects are preferred.

The usual initial dosage is 2.5 mg twice daily, gradually increased or decreased, usually in steps of 2.5 mg at intervals of not less than 2 days, until a satisfactory response is obtained. The average maintenance dose is 25 mg daily in three divided doses. Tolerance may develop.

◊ Reviews.

1. Young JM, *et al.* Mecamylamine: new therapeutic uses and toxicity/risk profile. *Clin Ther* 2001; **23:** 532–65.

Smoking cessation. Mecamylamine acts centrally as a nicotinic antagonist and might be of some benefit in assisting withdrawal from smoking. Two studies[1,2] have shown that addition of low-dose oral mecamylamine (2.5 to 5 mg twice daily) appeared to enhance the effectiveness of nicotine skin patches. However, a later controlled study[3] found that a patch containing both mecamylamine and nicotine was not significantly better than transdermal nicotine alone. Smoking cessation is discussed under Nicotine, p.2354.

1. Rose JE, *et al.* Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994; **56:** 86–99.
2. Rose JE, *et al.* Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998; **6:** 331–43.
3. Glover ED, *et al.* A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* 2007; **102:** 795–802.

Tourette's syndrome. Mecamylamine has been tried[1-3] in the management of Tourette's syndrome (see under Tics, p.954) although results have been mixed.

1. Sanberg PR, *et al.* Treatment of Tourette's syndrome with mecamylamine. *Lancet* 1998; **352:** 705–6.
2. Silver AA, *et al.* Mecamylamine in Tourette's syndrome: a two-year retrospective case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 59–68.
3. Silver AA, *et al.* Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 1103–10.

Preparations
USP 31: Mecamylamine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Inversine.

Mefruside *(BAN, USAN, rINN)* ⊗

Bay-1500; FBA-1500; Mefrusid; Mefrusida; Méfruside; Mefrusidi; Mefrusidum. 4-Chloro-*N*[1]-methyl-*N*[1]-(tetrahydro-2-methylfurfuryl)benzene-1,3-disulphonamide.

Мефрузид

$C_{13}H_{19}ClN_2O_5S_2$ = 382.9.
CAS — 7195-27-9.
ATC — C03BA05.
ATC Vet — QC03BA05.

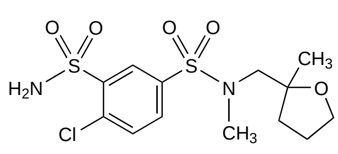

Pharmacopoeias. In *Jpn.*

Profile
Mefruside is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis begins about 2 to 4 hours after an oral dose and reaches a maximum between 6 and 12 hours.

In the treatment of oedema the usual dose is 25 to 50 mg daily, increasing if necessary to 75 to 100 mg. For long-term therapy a dose of 25 to 50 mg every second or third day is preferable.

In the treatment of hypertension the usual dose is 25 mg daily, either alone, or with other antihypertensives; initial doses of 25 to 50 mg daily have been recommended; alternate-day maintenance dosage may be used.

Preparations
Proprietary Preparations (details are given in Part 3)
Neth.: Baycaron†.

Multi-ingredient: ***Ger.:*** Bendigon N†; duranifin Sali†; Sali-Adalat; Sali-Prent.

Meglutol *(USAN, rINN)*

CB-337; Méglutol; Meglutolum. 3-Hydroxy-3-methylglutaric acid.

Меглутол

$C_6H_{10}O_5$ = 162.1.
CAS — 503-49-1.
ATC — C10AX05.
ATC Vet — QC10AX05.

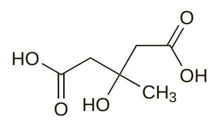

Profile
Meglutol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Mevalon†.

Melagatran *(rINN)*

H-319/68; Mélagatran; Melagatrán; Melagatranum. *N*-[(*R*)-({(2*S*)-2-[(*p*-Amidinobenzyl)carbamoyl]-1-azetidinyl}carbonyl)cyclohexylmethyl]glycine.

Мелагатран

$C_{22}H_{31}N_5O_4$ = 429.5.
CAS — 159776-70-2.
ATC — B01AE04.
ATC Vet — QB01AE04.

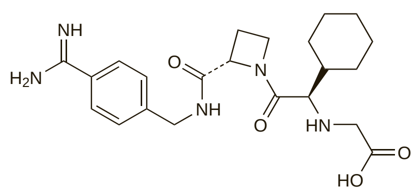

Ximelagatran *(USAN, rINN)*

H-376/95; Ximélagatran; Ximelagatrán; Ximelagatranum. Ethyl *N*-{(*R*)-cyclohexyl[((2*S*)-2-{[4-(hydroxycarbamimidoyl)benzyl]carbamoyl}-1-azetidinyl)carbonyl]methyl}glycinate.

Ксимелагатран

$C_{24}H_{35}N_5O_5$ = 473.6.
CAS — 192939-46-1.
ATC — B01AE05.
ATC Vet — QB01AE05.

Profile
Melagatran is a direct thrombin inhibitor with actions similar to lepirudin, p.1323, that was used as an anticoagulant in the prevention of postoperative venous thromboembolism in patients undergoing hip or knee replacement surgery. It is the active metabolite of ximelagatran and was given subcutaneously; ximelagatran was given orally. It was withdrawn worldwide because of reported liver toxicity.

◊ References.

1. Wallentin L, *et al.* Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet* 2003; **362:** 789–97.
2. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; **362:** 1691–8.
3. Evans HC, *et al.* Ximelagatran/Melagatran: a review of its use in the prevention of venous thromboembolism in orthopaedic surgery. *Drugs* 2004; **64:** 649–78.
4. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005; **293:** 690–8.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Exanta†; ***Austria:*** Exanta†; ***Denm.:*** Exanta†; ***Fin.:*** Exanta†; ***Fr.:*** Exanta†; ***Ger.:*** Exanta†; ***Neth.:*** Exanta†; ***Norw.:*** Exanta†; ***Swed.:*** Exarta†.

Meldonium *(rINN)*

Meldonio; MET-88; 3-(2,2,2-Trimethylhydrazinium)propionate. 3-(2,2,2-Trimethyldiazaniumyl)propanoate.

Мельдоний

$C_6H_{14}N_2O_2$ = 146.2.
CAS — 76144-81-5 (meldonium); 86426-17-7 (meldonium dihydrate).

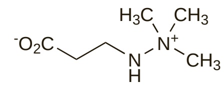

Profile
Meldonium is an inhibitor of carnitine synthesis and is reported to have cardioprotective and anti-ischaemic effects. It has been used in a variety of disorders. In the management of ischaemic heart disease and ischaemic cerebrovascular disturbances oral doses have ranged from 500 mg to 1 g daily. A course of 500 mg given four times daily for 7 to 10 days has been used in alcohol abstinence syndrome. Meldonium has also been given intravenously in doses similar to those used orally.

◊ References.

1. Dambrova M, *et al.* Mildronate: cardioprotective action through carnitine-lowering effect. *Trends Cardiovasc Med* 2002; **12:** 275–9.
2. Sjakste N, *et al.* Mildronate: an antiischemic drug for neurological indications. *CNS Drug Rev* 2005; **11:** 151–68.

Preparations
Proprietary Preparations (details are given in Part 3)
Rus.: Mildronate (Милдронат); Mildroxyn (Милдроксин).

Mephentermine Sulfate *(rINNM)* ⊗

Méphentermine, Sulfate de; Mephentermine Sulphate *(BANM)*; Mephentermini Sulfas; Mephetedrine Sulphate; Sulfato de mefentermina. *N*,α,α-Trimethylphenethylamine sulphate dihydrate.

Мефентермина Сульфат

$(C_{11}H_{17}N)_2,H_2SO_4,2H_2O$ = 460.6.
CAS — 100-92-5 (mephentermine); 1212-72-2 (anhydrous mephentermine sulfate); 6190-60-9 (mephentermine sulfate dihydrate).
ATC — C01CA11.
ATC Vet — QC01CA11.

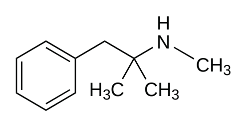

(mephentermine)

Adverse Effects, Treatment, and Precautions
As for Sympathomimetics, p.1407; adverse effects may be related to alpha- or beta-adrenergic stimulation. Mephentermine may produce CNS stimulation, especially in overdosage; anxiety, drowsiness, incoherence, hallucinations, and convulsions have been reported.

Interactions
As for Sympathomimetics, p.1407.

Pharmacokinetics
Mephentermine acts in about 5 to 15 minutes after intramuscular injection and has a duration of action of up to about 4 hours; it acts almost immediately after intravenous injection with a duration of action of up to about 30 minutes. It is rapidly metabolised in the body by demethylation; hydroxylation may follow. It is excreted as unchanged drug and metabolites in the urine; excretion is more rapid in acidic urine.

Uses and Administration
Mephentermine is a sympathomimetic (p.1408) with mainly indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, and a slight stimulating effect on the CNS. It has an inotropic effect on the heart.

Mephentermine has been used to maintain blood pressure in hypotensive states, for example after spinal anaesthesia. It is given as the sulfate but doses are expressed in terms of the base; 21 mg of sulfate is equivalent to about 15 mg of base. Typical doses are up to 45 mg by slow intravenous injection, or 15 to 30 mg intramuscularly.

Preparations
Proprietary Preparations (details are given in Part 3)
India: Mephentine; ***USA:*** Wyamine†.

Multi-ingredient: ***USA:*** Emergent-Ez.

Mepindolol Sulfate *(rINNM)* ⊗

LF-17895 (mepindolol); Mépindolol, Sulfate de; Mepindolol Sulphate *(BANM)*; Mepindololi Sulfas; SHE-222; Sulfato de mepindolol. 1-Isopropylamino-3-(2-methylindol-4-yloxy)propan-2-ol sulfate.

Мепиндолола Сульфат

$(C_{15}H_{22}N_2O_2)_2,H_2SO_4$ = 622.8.

CAS — 23694-81-7 (mepindolol); 56396-94-2 (mepindolol sulfate).

ATC — C07AA14.

ATC Vet — QC07AA14.

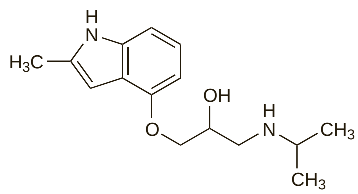

(mepindolol)

Profile

Mepindolol, the methyl analogue of pindolol, is a non-cardioselective beta blocker (p.1225). It is reported to possess intrinsic sympathomimetic activity. It has been given orally as the sulfate in the management of various cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Corindolan.

Multi-ingredient: *Ger.:* Corindocomb†.

Mersalyl Acid ⊗

Acidum Mersalylicum; Mersal. Acid; Mersálico, ácido; Mersalylum Acidum. A mixture of {3-[2-(carboxymethoxy)benzamido]-2-methoxypropyl}hydroxymercury and its anhydrides.

$C_{13}H_{17}HgNO_6$ = 483.9.

CAS — 486-67-9.

ATC — C03BC01.

ATC Vet — QC03BC01.

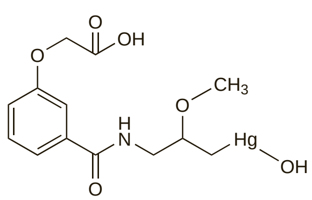

Mersalyl Sodium ⊗

Mersalyl *(pINN)*; Mersalilo; Mersalylum; Mersalyyli. The sodium salt of mersalyl acid.

Мерсалил

$C_{13}H_{16}HgNNaO_6$ = 505.8.

CAS — 492-18-2.

ATC — C03BC01.

ATC Vet — QC03BC01.

Profile

Mersalyl acid, in the form of its salts, is a powerful diuretic that acts on the renal tubules, increasing the excretion of sodium and chloride, in about equal amounts, and of water. Organic mercurial diuretics were widely used before the introduction of thiazide and other diuretics but have now been almost completely superseded by these orally active drugs, which are both potent and less toxic. The most frequent adverse effects of mersalyl are stomatitis, gastric disturbance, vertigo, febrile reactions, and skin eruptions and irritation. Thrombocytopenia, neutropenia, and agranulocytosis have followed the use of mercurial diuretics. Intravenous injection may cause severe hypotension and cardiac arrhythmias and has been followed by sudden death.

Mersalyl acid was usually given by injection as the sodium salt with theophylline as this lessened the local irritant reaction and increased absorption. It was given by deep intramuscular injection after a test dose for hypersensitivity. Other organic mercurial diuretics include chlormerodrin, meralluride, mercaptomerin sodium, mercurophylline sodium, and merethoxylline procaine. They were mainly given by intramuscular injection or, for those which were less irritant, subcutaneous injection.

Metaraminol Tartrate *(BANM, rINNM)* ⊗

Hydroxynorephedrine Bitartrate; Metaradrine Bitartrate; Metaraminol Acid Tartrate; Metaraminol Bitartrate; Métaraminol, Tartrate de; Metaraminoli Tartras; Tartrato de metaraminol. (−)-2-Amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen tartrate.

Метараминола Тартрат

$C_9H_{13}NO_2,C_4H_6O_6$ = 317.3.

CAS — 54-49-9 (metaraminol); 33402-03-8 (metaraminol tartrate).

ATC — C01CA09.

ATC Vet — QC01CA09.

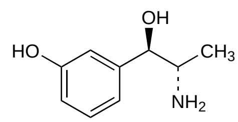

(metaraminol)

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2008 (Metaraminol Tartrate). An odourless or almost odourless, white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 3.2 to 3.5.

USP 31 (Metaraminol Bitartrate). A 5% solution in water has a pH of between 3.2 and 3.5. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p.1407. The adverse effects of metaraminol primarily relate to its alpha-agonist action. Metaraminol has a longer duration of action than adrenaline or noradrenaline and therefore an excessive vasopressor response may cause a prolonged rise in blood pressure. Tissue necrosis can occur as a result of accidental extravasation during intravenous injection.

Interactions

As for Sympathomimetics, p.1407. The interactions of metaraminol relate to both its direct and indirect actions.

Pharmacokinetics

Metaraminol acts about 10 minutes after intramuscular injection with a duration of action of up to about 1 hour. Effects are seen 1 to 2 minutes after intravenous injection with a duration of action of about 20 minutes.

Uses and Administration

Metaraminol is a sympathomimetic (p.1408) with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, the former being predominant. Metaraminol has an inotropic effect and acts as a peripheral vasoconstrictor, thus increasing cardiac output, peripheral resistance, and blood pressure. Coronary blood flow is increased and the heart rate slowed.

Metaraminol tartrate is used for its pressor action in **hypotensive states** such as those that may occur after spinal anaesthesia. Doses are expressed in terms of the base; metaraminol tartrate 9.5 mg is equivalent to about 5 mg of metaraminol. An intravenous infusion of 15 to 100 mg of metaraminol in 500 mL of glucose 5% or sodium chloride 0.9% may be used for maintaining the blood pressure, the rate of infusion being adjusted according to blood pressure response. Higher concentrations have been given. As the maximum effects are not immediately apparent, at least 10 minutes should elapse before increasing the dose and the possibility of a cumulative effect should be borne in mind. In an emergency an initial dose of 0.5 to 5 mg may be given by direct intravenous injection followed by an intravenous infusion as above.

Metaraminol tartrate has also been given by intramuscular or subcutaneous injection for the prevention of hypotension in doses equivalent to 2 to 10 mg of metaraminol. Subcutaneous injection increases the risk of local tissue necrosis and sloughing.

Priapism. Priapism[1,2] or prolonged penile erection may occur due to either decreased venous outflow (low-flow priapism) or increased arterial inflow (high-flow priapism). Low-flow priapism is a medical emergency since inflow is also impaired, leading to the development of ischaemia. It may be related to the use of drugs that cause smooth muscle relaxation, such as alpha blockers; intraluminal obstruction, such as in sickle-cell disease, may also be a cause. It is usually treated with corporal aspiration, followed if necessary by irrigation with a low dosage of a dilute solution of an alpha agonist such as metaraminol.

Intracavernosal metaraminol has been used successfully to treat drug-induced priapism,[3] as well as priapism associated with chronic myeloid leukaemia,[4] haemodialysis,[5] spinal block,[6] or fentanyl-induced general anaesthesia.[6] It may also be used to reverse the effects of alprostadil or papaverine given intracavernosally for the management of some types of erectile dysfunction, although this has been associated with fatal hypertensive crisis (see also Alprostadil, p.2184).

Alternative alpha agonists that have been used include intracavernosal phenylephrine,[7] and intracavernosal adrenaline, again in a low dosage and dilute solution. Phenylpropanolamine,[7] or pseudoephedrine,[8] given orally, have also been used. In patients with priapism due to sickle-cell disease, intracavernosal irrigation with a dilute adrenaline solution or intracavernosal injection of etilefrine have been used (see p.1205); oral etilefrine has been given for prophylaxis. Many other drugs have been tried or suggested, including baclofen, gabapentin, terbutaline, and, paradoxically, low doses of phosphodiesterase type-5 inhibitors such as sildenafil or tadalafil.[2] Surgery is usually favoured in low-flow priapism unresponsive to drug therapy.

In high-flow priapism, which is less of an emergency, embolisation of the source of abnormal inflow is the usual treatment.

1. Maan Z, *et al.* Priapism—a review of the medical management. *Expert Opin Pharmacother* 2003; **4:** 2271–7.
2. Yuan J, *et al.* Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl* 2008; **10:** 88–101.
3. Brindley GS. New treatment for priapism. *Lancet* 1984; **ii:** 220–1.
4. Stanners A, Colin-Jones D. Metaraminol for priapism. *Lancet* 1984; **ii:** 978.
5. Branger B, *et al.* Metaraminol for haemodialysis-associated priapism. *Lancet* 1985; **i:** 641.
6. Tsai SK, Hong CY. Intracavernosal metaraminol for treatment of intraoperative penile erection. *Postgrad Med J* 1990; **66:** 831–3.
7. Harmon WJ, Nehra A. Priapism: diagnosis and management. *Mayo Clin Proc* 1997; **72:** 350–5.
8. Millard RJ, *et al.* Risks of self-injection therapy for impotence. *Med J Aust* 1996; **165:** 117–18.

Preparations

BP 2008: Metaraminol Injection;
USP 31: Metaraminol Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fadamine; ***Austral.:*** Aramine; ***Braz.:*** Aramin; ***Gr.:*** Aramine†; Levicor†; ***Norw.:*** Aramine†; ***NZ:*** Aramine; ***Thai.:*** Aramine†; ***USA:*** Aramine.

Methoxamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metoxamina; Methoxamedrine Hydrochloride; Méthoxamine, Chlorhydrate de; Methoxamini Hydrochloridum. 2-Amino-1-(2,5-dimethoxyphenyl)propan-1-ol hydrochloride.

Метоксамина Гидрохлорид

$C_{11}H_{17}NO_3,HCl$ = 247.7.

CAS — 390-28-3 (methoxamine); 61-16-5 (methoxamine hydrochloride).

ATC — C01CA10.

ATC Vet — QC01CA10.

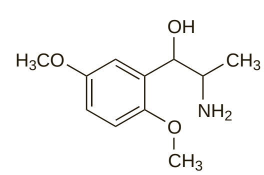

(methoxamine)

Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Methoxamine Hydrochloride). Colourless crystals or white plate-like crystals or white crystalline powder; odourless or almost odourless. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. A 2% solution in water has a pH of 4.0 to 6.0.

Profile

Methoxamine is a sympathomimetic (p.1407) with mainly direct effects on adrenergic receptors. It has alpha-adrenergic activity entirely; beta-adrenergic activity is not demonstrable and beta-adrenoceptor blockade may occur at high doses. Methoxamine hydrochloride has been used parenterally for its pressor action in the management of hypotensive states, particularly in anaesthesia, and also in the management of paroxysmal supraventricular tachycardia. It has also been used topically as a vasoconstrictor in the management of nasal congestion.

Preparations

BP 2008: Methoxamine Injection.

Proprietary Preparations (details are given in Part 3)
Irl.: Vasoxine†.

Methyclothiazide *(BAN, USAN, rINN)* ⊗

Méthyclothiazide; Methyclothiazidum; Meticlotiazida; Metyklotiatsidi; Metyklotiazid; NSC-110431. 6-Chloro-3-chloromethyl-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Метиклотиазид

$C_9H_{11}Cl_2N_3O_4S_2$ = 360.2.
CAS — 135-07-9.
ATC — C03AA08.
ATC Vet — QC03AA08.

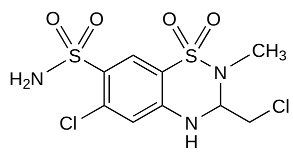

Pharmacopoeias. In *US.*

USP 31 (Methyclothiazide). A white or practically white crystalline powder, odourless or with a slight odour. Very slightly soluble to practically insoluble in water and in chloroform; soluble 1 in 92.5 of alcohol and 1 in 2700 of ether; freely soluble in acetone and in pyridine; sparingly soluble in methyl alcohol; very slightly soluble in benzene.

Profile

Methyclothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (see p.1307). It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis starts in about 2 hours, reaches a peak at about 6 hours, and lasts for 24 hours or more.

In the treatment of oedema the usual initial dose is 2.5 to 5 mg daily, increasing to a maximum dose of 10 mg daily if necessary. In the treatment of hypertension the usual dose is 2.5 to 5 mg daily, either alone, or with other antihypertensives. Doses of up to 10 mg daily have been suggested, but this may not result in an increased hypotensive effect.

Children have been given a dose of 50 to 200 micrograms/kg daily.

Preparations

USP 31: Methyclothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Hong Kong: Enduron†; ***USA:*** Aquatensen†; Enduron.

Multi-ingredient: ***Fr.:*** Isobar; ***Hong Kong:*** Enduronyl†; ***USA:*** Diutensen-R†.

Methyldopa *(BAN, USAN, rINN)*

Alpha-methyldopa; Méthyldopa; Methyldopum; Methyldopum Hydratum; Metildopa; Metyldopa; Metyylidopa; MK-351. (−)-3-(3,4-Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate; (−)-2-Amino-2-(3,4-dihydroxybenzyl)propionic acid sesquihydrate.

Метилдопа

$C_{10}H_{13}NO_4,1\frac{1}{2}H_2O$ = 238.2.
CAS — 555-30-6 (anhydrous methyldopa); 41372-08-1 (methyldopa sesquihydrate).
ATC — C02AB01; C02AB02.
ATC Vet — QC02AB01; QC02AB01 (laevorotary); QC02AB02; QC02AB02 (racemic).

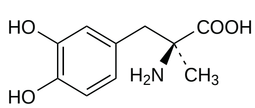

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Methyldopa). Colourless or almost colourless crystals or a white to yellowish-white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dilute mineral acids. Protect from light.

USP 31 (Methyldopa). A white to yellowish-white odourless fine powder which may contain friable lumps. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in ether; very soluble in 3N hydrochloric acid. Protect from light.

Methyldopate Hydrochloride *(BANM, USAN)*

Cloridrato de Metildopato; Metildopato, hidrocloruro de. The hydrochloride of the ethyl ester of anhydrous methyldopa; Ethyl (−)-2-amino-2-(3,4-dihydroxybenzyl)propionate hydrochloride.

$C_{12}H_{17}NO_4,HCl$ = 275.7.
CAS — 2544-09-4 (methyldopate); 2508-79-4 (methyldopate hydrochloride).

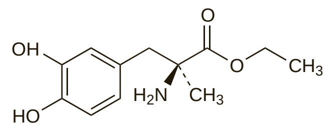

(methyldopate)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 31 (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of between 3.0 and 5.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. A haze developed over 3 hours when methyldopate hydrochloride 1 mg/mL was mixed with amphotericin B 200 micrograms/mL in glucose; crystals were produced with methohexital sodium 200 micrograms/mL in sodium chloride, and a haze developed when they were mixed in glucose. A crystalline precipitate occurred with tetracycline hydrochloride 1 mg/mL in glucose, and with sulfadiazine sodium 4 mg/mL in glucose or sodium chloride.[1]

1. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.

Adverse Effects

The adverse effects of methyldopa are mostly consequences of its pharmacological action. The incidence of adverse effects overall may be as high as 60% but most are transient or reversible. Drowsiness is common, especially initially and after an increase in dosage. Dizziness and lightheadedness may be associated with orthostatic hypotension; nausea, headache, weakness and fatigue, and decreased libido and impotence have also been reported quite often.

The mental and neurological effects of methyldopa have included impaired concentration and memory, mild psychoses, depression, disturbed sleep and nightmares, paraesthesias, Bell's palsy, involuntary choreoathetotic movements, and parkinsonism.

As well as orthostatic hypotension, methyldopa is often associated with fluid retention and oedema, which responds to diuretics but may rarely progress to heart failure. Angina pectoris may be aggravated. Bradycardia, syncope, and prolonged carotid sinus hypersensitivity have been reported. Intravenous methyldopate has been associated with a paradoxical rise in blood pressure.

Methyldopa may produce gastrointestinal disturbances including nausea and vomiting, diarrhoea, constipation, and rarely pancreatitis and colitis. A black or sore tongue, and inflammation of the salivary glands, have occurred, and dry mouth is quite common.

A positive Coombs' test may occur in 10 to 20% of all patients on prolonged therapy but only a small proportion develop haemolytic anaemia. Thrombocytopenia and leucopenia, notably granulocytopenia, have occurred and warrant prompt withdrawal. Other hypersensitivity effects have included myocarditis, fever, eosinophilia, and disturbances of liver function. Hepatitis may develop, particularly in the first 2 or 3 months of therapy, and is generally reversible on stopping, but fatal hepatic necrosis has occurred. Antinuclear antibodies may develop and cases of a lupus-like syndrome have been reported.

Other adverse effects that have been reported in patients taking methyldopa include rashes, lichenoid and granulomatous eruptions, toxic epidermal necrolysis, a flu-like syndrome (of fever, myalgia, and mild arthralgia), nocturia, uraemia, nasal congestion, and retroperitoneal fibrosis. Hyperprolactinaemia may occur, with breast enlargement or gynaecomastia, galactorrhoea, and amenorrhoea.

Methyldopa may occasionally cause urine to darken on exposure to the air because of the breakdown of the drug or its metabolites.

◊ Reviews.

1. Furhoff A-K. Adverse reactions with methyldopa—a decade's reports. *Acta Med Scand* 1978; **203:** 425–8.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.

Effects on the blood. An analysis of drug-induced blood dyscrasias reported to the Swedish Adverse Drug Reaction Committee for the 10-year period 1966 to 1975 showed that haemolytic anaemia attributable to methyldopa had been reported on 69 occasions and had caused 3 deaths. This represented the vast majority of all the reports of drug-induced haemolytic anaemia.[1] However, the actual incidence of haemolytic anaemia in patients receiving methyldopa is quite low; data from the Boston Collaborative Drug Surveillance Program indicated that only 2 of 1067 patients receiving methyldopa developed haemolytic anaemia,[2] an incidence of about 0.2%. The proportion of patients with a positive Coombs' test is much higher, being variously reported[3-5] at 10 to 20%. It has been suggested that the high incidence of autoantibody formation may be due to inhibition of suppressor T-cells by methyldopa[4] while the relatively low incidence of resultant haemolysis may be due to drug-associated impairment of the reticuloendothelial system which would normally clear the antibody-sensitised cells from the circulation.[5]

1. Böttiger LE, *et al.* Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Lawson DH, *et al.* Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.
3. Carstairs K, *et al.* Methyldopa and haemolytic anaemia. *Lancet* 1966; **i:** 201.
4. Kirtland HH, *et al.* Methyldopa inhibition of suppressor-lymphocyte function: a proposed cause of autoimmune hemolytic anemia. *N Engl J Med* 1980; **302:** 825–32.
5. Kelton JG. Impaired reticuloendothelial function in patients treated with methyldopa. *N Engl J Med* 1985; **313:** 596–600.

Effects on the gastrointestinal tract. *COLITIS.* There has been a report of 6 cases of colitis associated with methyldopa.[1] An auto-immune mechanism was proposed.

1. Graham CF, *et al.* Acute colitis with methyldopa. *N Engl J Med* 1981; **304:** 1044–5.

DIARRHOEA. Severe chronic diarrhoea was associated with methyldopa over periods of 2 and 7 years;[1,2] it stopped in both cases on withdrawal of the drug.

1. Quart BD, Guglielmo BJ. Prolonged diarrhea secondary to methyldopa therapy. *Drug Intell Clin Pharm* 1983; **17:** 462.
2. Gloth FM, Busby MJ. Methyldopa-induced diarrhea: a case of iatrogenic diarrhea leading to request for nursing home placement. *Am J Med* 1989; **87:** 480–1.

PANCREATITIS. Increases in serum- and urinary-amylase activity accompanied by fever and suggestive of pancreatitis were associated with methyldopa in 2 patients,[1] one of whom had symptoms of severe pancreatitis. Symptoms reappeared on rechallenge in both patients. A further report of acute pancreatitis in a patient who had recently begun methyldopa therapy (with a diuretic) also confirmed a recurrence of symptoms on rechallenge.[2] In contrast to the acute form, chronic pancreatitis is not generally attributable to drug use.[3] However, a case of florid chronic pancreatitis, with exocrine and endocrine insufficiency and heavy calcification over 30 months, associated with 2 periods of methyldopa treatment, has been reported.[4] Symptoms in this patient, who was also receiving a thiazide, included severe diabetic ketoacidosis.

1. van der Heide H, *et al.* Pancreatitis caused by methyldopa. *BMJ* 1981; **282:** 1930–1.
2. Anderson JR, *et al.* Drug-associated recurrent pancreatitis. *Dig Surg* 1985; **2:** 24–6.
3. Banergee AK, *et al.* Drug-induced acute pancreatitis. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
4. Ramsay LE, *et al.* Methyldopa-induced chronic pancreatitis. *Practitioner* 1982; **226:** 1166–9.

Effects on the heart. Sudden death in a number of patients receiving methyldopa has been associated with myocarditis (often with hepatitis and pneumonitis).[1,2] The effect is thought to be due to hypersensitivity. Hypersensitivity myocarditis is generally marked by ECG changes, a slight rise in cardiac enzymes, cardiomegaly, and persistent sinus tachycardia, along with peripheral blood eosinophilia, and most patients will recover within days if the drug is withdrawn in time.[3]

1. Mullick FG, McAllister HA. Myocarditis associated with methyldopa therapy. *JAMA* 1977; **237:** 1699–1701. Correction. *ibid.*; **238:** 399.
2. Seeverens H, *et al.* Myocarditis and methyldopa. *Acta Med Scand* 1982; **211:** 233–5.
3. Anonymous. Myocarditis related to drug hypersensitivity. *Lancet* 1985; **ii:** 1165–6.

Effects on the liver. In a report of 6 cases of hepatitis in patients taking methyldopa, including a review of 77 cases from the literature,[1] most patients presented with symptoms including malaise, fatigue, anorexia, weight loss, nausea, and vomiting, and histopathological changes resembling those of viral hepatitis. Fever occurred in 28 of the 83 patients; rashes and eosinophilia occurred rarely. Symptoms usually began 1 to 4 weeks after the first dose of methyldopa. Clinically apparent jaundice occurred as early as 1 week and as late as 3 years after the start of therapy, although only 6 or 7 patients presented with jaundice later than 3 months. Liver damage was not dose-related and had features suggestive of an immunologically-mediated hypersensitivity reaction. The histological changes included chronic active hepatitis, massive fatal necrosis, and cirrhosis.

In a further analysis of 36 patients with liver damage due to methyldopa, hepatic injury tended to occur in 2 phases—acute and chronic.[2] Acute damage developed within a few months of starting treatment, and was considered to be an allergic reaction to methyldopa metabolites. The chronic form usually occurred at least a year after starting methyldopa, and was characterised by an accumulation of fat in the liver. Recovery after withdrawal of methyldopa was directly related to duration of exposure and degree of liver damage. There was also a suggestion of genetic predisposition, as acute methyldopa-induced liver damage occurred in 4 members of a family. Idiosyncratic metabolism of methyldopa in susceptible patients may be responsible for expression of an antigen on the surface of liver cells with which circulating antibodies react.[3]

See also Fever, below.

1. Rodman JS, *et al*. Methyldopa hepatitis: a report of six cases and review of the literature. *Am J Med* 1976; **60:** 941–8.
2. Sotaniemi EA, *et al*. Hepatic injury and drug metabolism in patients with alpha-methyldopa-induced liver damage. *Eur J Clin Pharmacol* 1977; **12:** 429–35.
3. Neuberger J, *et al*. Antibody mediated hepatocyte injury in methyldopa induced hepatotoxicity. *Gut* 1985; **26:** 1233–9.

Effects on mental function. Anecdotal reports have implicated methyldopa in disturbances of mental acuity including inability to concentrate, impaired calculating ability, and forgetfulness.[1-3] These have been confirmed to some extent by psychometric studies. Impaired verbal but not visual memory has been reported in 10 patients receiving methyldopa with a diuretic.[4] A crossover study in 16 patients also indicated impairment of cognitive function by methyldopa.[5]

1. Adler S. Methyldopa-induced decrease in mental activity. *JAMA* 1974; **230:** 1428–9.
2. Ghosh SK. Methyldopa and forgetfulness. *Lancet* 1976; **i:** 202–3.
3. Fernandez PG. Alpha methyldopa and forgetfulness. *Ann Intern Med* 1976; **85:** 128.
4. Solomon S, *et al*. Impairment of memory function by antihypertensive medication. *Arch Gen Psychiatry* 1983; **40:** 1109–12.
5. Johnson B, *et al*. Effects of methyldopa on psychometric performance. *J Clin Pharmacol* 1990; **30:** 1102–5.

DEPRESSION. Depression has been associated with methyldopa therapy, although the exact relationship is unclear.[1] One review[2] reported the incidence to be 3.6% and suggested that depression was more common in patients with a previous history.

1. Patten SB, Love EJ. Drug-induced depression. *Drug Safety* 1994; **10:** 203–19.
2. Paykel ES, *et al*. Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol* 1982; **2:** 14–39.

Effects on the nervous system. Involuntary choreoathetotic movements resembling those of Huntington's chorea began in a 59-year-old man with cerebrovascular disease after an increase of his methyldopa dose from 1 to 1.5 g daily. He recovered when the drug was withdrawn.[1] In another report methyldopa was associated with the development of bilateral choreiform movements in a patient without cerebrovascular disease but with chronic renal failure.[2]

1. Yamadori A, Albert ML. Involuntary movement disorder caused by methyldopa. *N Engl J Med* 1972; **286:** 610.
2. Neil EM, Waters AK. Generalized choreiform movements as a complication of methyldopa therapy in chronic renal failure. *Postgrad Med J* 1981; **57:** 732–3.

Effects on sexual function. Methyldopa has been associated with numerous cases of sexual dysfunction. In males failure to maintain erection, decreased libido, impaired ejaculation, and gynaecomastia have occurred, while in females decreased libido, painful breast enlargement, and delayed or absent orgasm have been reported.[1] The reported incidence varies and there is some evidence[2] that sexual dysfunction may be underreported: while only 2 of 30 men receiving methyldopa spontaneously reported erection failure the actual incidence on questioning was 16 of 30.

1. Stevenson JG, Umstead GS. Sexual dysfunction due to antihypertensive agents. *Drug Intell Clin Pharm* 1984; **18:** 113–21.
2. Alexander WD, Evans JI. Side effects of methyldopa. *BMJ* 1975; **2:** 501.

Fever. In a report of 78 cases of methyldopa-induced fever,[1] fever occurred 5 to 35 days after the first exposure to methyldopa in 77 patients and one day after recommencing methyldopa in the remaining patient. Rigors, headache, and myalgia were common accompanying symptoms, but eosinophilia and skin rashes were not seen. The majority of patients did not appear seriously ill, but 4 patients presented with symptoms of septic shock. Biochemical evidence of liver damage was found in 61% of patients but jaundice was uncommon. In the majority of patients, symptoms were relieved within 48 hours of stopping the drug.

1. Stanley P, Mijch A. Methyldopa: an often overlooked cause of fever and transient hepatocellular dysfunction. *Med J Aust* 1986; **144:** 603–5.

Lupus erythematosus. The incidence of antinuclear antibodies was 13% in 269 hypertensive patients taking methyldopa (irrespective of other medication), compared with 3.8% in 448 hypertensive patients not taking methyldopa.[1] However, methyldopa-induced lupus has been reported[2] only rarely.

1. Wilson JD, *et al*. Antinuclear antibodies in patients receiving non-practolol beta-blockers. *BMJ* 1978; **1:** 14–16.
2. Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; **285:** 693–4.

Overdosage. Ingestion of methyldopa 2.5 g produced coma, hypothermia, hypotension, bradycardia, and dry mouth in a 19-year-old man.[1] His serum-methyldopa concentration 10 hours after ingestion was 19.2 micrograms/mL compared with serum concentrations of about 2 micrograms/mL in patients receiving therapeutic doses of methyldopa. He recovered after treatment with intravenous fluids.

1. Shnaps Y, *et al*. Methyldopa poisoning. *J Toxicol Clin Toxicol* 1982; **19:** 501–3.

Retroperitoneal fibrosis. A 60-year-old patient developed retroperitoneal fibrosis and a positive direct Coombs' test associated with methyldopa given in a daily dose of 750 mg with bendroflumethiazide 2.5 mg for about 5 years.[1]

1. Iversen BM, *et al*. Retroperitoneal fibrosis during treatment with methyldopa. *Lancet* 1975; **ii:** 302–4.

Treatment of Adverse Effects

Withdrawal of methyldopa or reduction in dosage causes the reversal of many adverse effects. If overdosage occurs, the benefit of gastric decontamination is uncertain, but patients who present within 1 hour may be given activated charcoal. Treatment is largely symptomatic, but if necessary, intravenous fluid infusions may be given to promote urinary excretion, and vasopressors given cautiously. Atropine may be given for bradycardia. Severe hypotension may respond to placing the patient in the supine position with the feet raised.

Methyldopa is dialysable.

Precautions

Methyldopa should be used with caution in the elderly, and in patients with hepatic or renal impairment or with a history of haemolytic anaemia, liver disease, or depression. Care is also advisable in patients with parkinsonism. It should not be given to patients with active liver disease or depression and it is not recommended for phaeochromocytoma.

It is advisable to make periodic blood counts and to perform liver function tests at intervals during the first 6 to 12 weeks of treatment or if the patient develops an unexplained fever. Patients taking methyldopa may produce a positive response to a direct Coombs' test; if blood transfusion is required, prior knowledge of a positive direct Coombs' test reaction will aid cross-matching.

Methyldopa may cause sedation; if affected, patients should not drive or operate machinery.

Breast feeding. Methyldopa is distributed into breast milk in small amounts.[1] In a study[2] of 3 breast-feeding women, concentrations of free methyldopa in the breast milk were found to be between 19 and 30% of those in the plasma after a 500-mg dose. Detectable levels were found in the plasma of only 1 infant and adverse effects were seen in none. It was estimated that the amount of methyldopa a breast-fed infant would receive would be about 0.02% of the maternal dose. In another study[3] over a 3-month period no adverse effects were found in a breast-feeding infant whose mother was taking methyldopa, although the drug was detectable in the infant's urine. The American Academy of Pediatrics considers[4] that methyldopa is therefore usually compatible with breast feeding.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. White WB, *et al*. Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants. *Clin Pharmacol Ther* 1985; **37:** 387–90.
3. Hauser GJ, *et al*. Effect of α-methyldopa excreted in human milk on the breast-fed infant. *Helv Paediatr Acta* 1985; **40:** 83–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. Methyldopa has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Methyldopa is commonly used in the management of hypertension during pregnancy (p.1171). There is little evidence of adverse effects on fetal development. However, it crosses the placenta[1] and reduced blood pressure has been reported in infants born to mothers receiving the drug.[2] There has also been a report of tremor in 7 infants associated with maternal methyldopa use in pregnancy.[3] Depressed noradrenaline concentrations in the CSF were noted in the 3 infants examined leading to successful treatment of the other 4 infants with atropine: tremor was abolished in 2 and substantially reduced in the other 2.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. Whitelaw A. Maternal methyldopa treatment and neonatal blood pressure. *BMJ* 1981; **283:** 471.
3. Bódis J, *et al*. Methyldopa in pregnancy hypertension and the newborn. *Lancet* 1982; **ii:** 498–9.

Interactions

The hypotensive effects of methyldopa are potentiated by diuretics, other antihypertensives, and drugs with hypotensive effects. However, there have been reports of paradoxical antagonism of the hypotensive effects by tricyclic antidepressants, antipsychotics, and beta blockers. Sympathomimetics may also antagonise the hypotensive effects.

There may be an interaction between methyldopa and MAOIs and care is required if they are given together. Caution is also needed with catechol-*O*-methyltransferase inhibitors, such as entacapone, since they might reduce the metabolism of methyldopa.

Patients receiving methyldopa may require lower doses of general anaesthetics.

Alpha blockers. Urinary incontinence occurred when methyldopa was given with *phenoxybenzamine* in a patient who had undergone bilateral lumbar sympathectomy.[1]

1. Fernandez PG, *et al*. Urinary incontinence due to interaction of phenoxybenzamine and α-methyldopa. *Can Med Assoc J* 1981; **124:** 174–5.

Antipsychotics. Antipsychotics may enhance the hypotensive effects of methyldopa but a paradoxical increase in blood pressure has also been reported. A woman with SLE taking *trifluoperazine* up to 15 mg daily and prednisone up to 120 mg daily was given methyldopa up to 2 g and triamterene for high blood pressure.[1] Her blood pressure rose further to 200/140 mmHg. After stopping trifluoperazine blood pressure returned to 160/100 mmHg.

In another report, 2 patients with essential hypertension who had been taking methyldopa for 3 years and 18 months respectively developed symptoms of dementia within days of taking *haloperidol* for anxiety.[2] In both patients the symptoms resolved rapidly on stopping haloperidol.

1. Westervelt FB, Atuk NO. Methyldopa-induced hypertension. *JAMA* 1974; **227:** 557.
2. Thornton WE. Dementia induced by methyldopa with haloperidol. *N Engl J Med* 1976; **294:** 1222.

Cephalosporins. A pustular pruritic eruption occurred after use of *cefazolin* by a patient taking methyldopa.[1] A previous similar case involved use of *cefradine* with methyldopa.

1. Stough D, *et al*. Pustular eruptions following administration of cefazolin: a possible interaction with methyldopa. *J Am Acad Dermatol* 1987; **16:** 1051–2.

Digoxin. Syncope associated with carotid sinus hypersensitivity has been reported to be possibly enhanced by methyldopa in a patient taking digoxin and chlortalidone.[1] In another report,[2] sinus bradycardia developed in 2 patients taking methyldopa and digoxin.

1. Bauernfeind R, *et al*. Carotid sinus hypersensitivity with alpha methyldopa. *Ann Intern Med* 1978; **88:** 214–15.
2. Davis JC, *et al*. Sinus node dysfunction caused by methyldopa and digoxin. *JAMA* 1981; **245:** 1241–3.

Iron. After results in healthy subjects indicated that the absorption of methyldopa was reduced by 73% and 61% respectively when taken with a dose of *ferrous sulfate* or *ferrous gluconate*, 5 hypertensive patients taking methyldopa were also given ferrous sulfate 325 mg three times daily for 2 weeks.[1] All patients experienced a rise in systolic pressure, and 4 had a rise in diastolic pressure, amounting to more than 15/10 mmHg in some patients after 2 weeks. Blood pressure fell again when the ferrous sulfate was stopped.

1. Campbell N, *et al*. Alteration of methyldopa absorption, metabolism, and blood pressure control caused by ferrous sulfate and ferrous gluconate. *Clin Pharmacol Ther* 1988; **43:** 381–6.

Levodopa. For reference to a mutual interaction between methyldopa and levodopa, see Antihypertensives, under Levodopa, Interactions, p.807.

Lithium. For reference to the development of lithium toxicity when given with methyldopa, see p.405.

Sympathomimetics. A 31-year-old man whose hypertension was well controlled with methyldopa and oxprenolol suffered a severe hypertensive episode when he took a preparation containing *phenylpropanolamine* for a cold.[1]

1. McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. *BMJ* 1976; **2:** 283–4.

Pharmacokinetics

After oral use methyldopa is variably and incompletely absorbed, apparently by an amino-acid active transport system. The mean bioavailability has been reported to be about 50%. It is extensively metabolised and is excreted in urine mainly as unchanged drug and the *O*-sulfate conjugate. It crosses the blood-brain barrier and is decarboxylated in the CNS to active alpha-methylnoradrenaline.

The elimination is biphasic with a half-life of about 1.7 hours in the initial phase; the second phase is more prolonged. Clearance is decreased and half-life prolonged in renal impairment. Plasma protein binding is reported to be minimal. Methyldopa crosses the placenta; small amounts are distributed into breast milk.

Uses and Administration

Methyldopa is an antihypertensive that is thought to have a mainly central action. It is decarboxylated in the CNS to alpha-methylnoradrenaline, which is thought to stimulate $alpha_2$ adrenoceptors resulting in a reduction in sympathetic tone and a fall in blood pressure. It may also act as a false neurotransmitter, and have some inhibitory actions on plasma renin activity. Methyldopa reduces the tissue concentrations of dopamine, noradrenaline, adrenaline, and serotonin.

Methyldopa is used in the management of hypertension (p.1171), although other drugs with fewer adverse effects are generally preferred. Methyldopa may, however, be the treatment of choice for hypertension in pregnancy. Oedema and tolerance sometimes associated with methyldopa therapy may be reduced when it is given with a thiazide diuretic.

Methyldopa is given orally as the sesquihydrate, but doses are usually expressed in terms of anhydrous methyldopa. Methyldopa sesquihydrate 1.13 g is equivalent to about 1 g of anhydrous methyldopa. For hypertensive crises, methyldopa has been given intravenously as methyldopate hydrochloride.

When methyldopa is given orally its effects reach a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment; some effect is usually apparent for 48 hours after withdrawal of methyldopa. When given intravenously the hypotensive effect may be obtained within 4 to 6 hours and last for 10 to 16 hours. It lowers the standing, and to a lesser extent the supine, blood pressure.

In hypertension, the usual initial adult oral dose is 250 mg of methyldopa two or three times daily for 2 days; this is then adjusted, not more frequently than every 2 days according to response, up to a usual maximum dose of 3 g daily. The usual maintenance dosage is 0.5 to 2 g of methyldopa daily. In the elderly an initial dose of 125 mg twice daily has been used; this dose may be increased gradually if necessary, but should not exceed 2 g daily.

An initial dose for children is 10 mg/kg daily in 2 to 4 divided doses, increased as necessary to a maximum of 65 mg/kg or 3 g daily, whichever is less.

Preparations

BP 2008: Methyldopa Tablets; Methyldopate Injection;
USP 31: Methyldopa and Chlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Methyldopa Oral Suspension; Methyldopa Tablets; Methyldopate Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Aldomet; Dopagrand; Dopatral; ***Austral.:*** Aldomet; Hydopa; ***Austria:*** Aldometil; ***Belg.:*** Aldomet; ***Braz.:*** Aldomet; Aldotensin; Alfuzina; Angimet; Cardiodopa†; Dimipress; Dopametil; Ductomet; Etildopanan; Kindomet; Metil-DT; Metilbio†; Metilcord†; Metilpress; Metilprod; Pressodopa†; Tensioval; Tildomet; ***Canad.:*** Aldomet†; Nu-Medopa; ***Chile:*** Aloset†; ***Cz.:*** Dopegyt; ***Denm.:*** Aldomet; ***Fr.:*** Aldomet; ***Ger.:*** Dopegyt; Presinol; ***Gr.:*** Aldomet; ***Hong Kong:*** Aldomet; Dopamet; Dopegyt; ***Hung.:*** Dopegyt; ***India:*** Alphadopa; Dopagyt; ***Indon.:*** Dopamet; Medopa; ***Irl.:*** Aldomet; Meldopa†; ***Israel:*** Aldomin; ***Ital.:*** Aldomet; Medopren†; ***Malaysia:*** Aldomet†; Dopamet†; Dopegyt; ***Mex.:*** Aldomet; Amender; Biotenzol†; Hipermessel; Prodop†; Selm; Toparal; ***Neth.:*** Aldomet; ***Norw.:*** Aldomet; ***NZ:*** Prodopa; ***Philipp.:*** Aldomet; ***Pol.:*** Dopegyt; ***Port.:*** Aldomet; ***Rus.:*** Dopegyt (Допегит); ***S.Afr.:*** Aldomet; Hy-Po-Tone; Normopress; ***Singapore:*** Dopegyt; ***Spain:*** Aldomet; ***Swed.:*** Aldomet; ***Switz.:*** Aldomet; ***Thai.:*** Aldomet; Dopamed; Dopasian; Dopegyt; Isomet; Medopa; Mefpa; Metpata; Servidopa†; Siamdopa; ***Turk.:*** Alfamet; ***UK:*** Aldomet; ***Venez.:*** Aldomet; Alfadopan†; Almepan†.

Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Aldoretic; ***Braz.:*** Hydromet; ***Canad.:*** Apo-Methazide; PMS-Dopazide; Supres†; ***Gr.:*** Hydromet†; ***Ital.:*** Medozide; Saludopin; ***Port.:*** Aldoretic†; ***USA:*** Aldoclor; Aldoril†.

Meticrane *(rINN)* ⊗

Méticrane; Meticrano; Meticranum; SD-17102. 6-Methylthiochroman-7-sulphonamide 1,1-dioxide.

Метикран

$C_{10}H_{13}NO_4S_2$ = 275.3.
CAS — 1084-65-7.
ATC — C03BA09.
ATC Vet — QC03BA09.

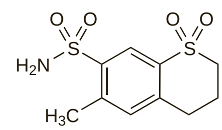

Pharmacopoeias. In *Jpn.*

Profile

Meticrane is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of hypertension.

Metildigoxin *(BAN, rINN)*

Medigoxin; β-Methyl Digoxin; β-Methyldigoxin; Metildigoksiini; Metildigoxina; Météldigoxine; Metildigoxinum; Metyylidigoksiini. 3β-[(*O*-2,6-Dideoxy-4-*O*-methyl-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide.

Метилдигоксин

$C_{42}H_{66}O_{14}$ = 795.0.
CAS — 30685-43-9.
ATC — C01AA08.
ATC Vet — QC01AA08.

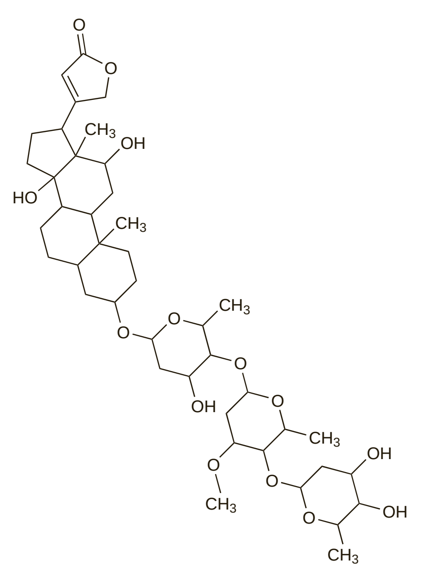

Pharmacopoeias. In *Chin.* In *Jpn.* as $C_{42}H_{66}O_{14}, \frac{1}{3}C_3H_6O$.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p.1259.

Interactions

As for Digoxin, p.1261.

Calcium-channel blockers. For a report of an interaction between metildigoxin and *diltiazem*, see Calcium-channel Blockers, under Interactions of Digoxin, p.1262.

Pharmacokinetics

Metildigoxin is rapidly and almost completely absorbed from the gastrointestinal tract and at steady state has a half-life of 36 to 47.5 hours. Demethylation to digoxin occurs. About 60% of an oral or intravenous dose is excreted in the urine as unchanged drug and metabolites over 7 days.

Hepatic impairment. Hepatic demethylation of metildigoxin was reduced in 12 patients with cirrhosis of the liver compared with 12 healthy subjects. This resulted in a reduction in metildigoxin clearance, a smaller volume of distribution, and a significantly higher serum concentration.[1]

1. Rameis H, *et al.* Changes in metildigoxin pharmacokinetics in cirrhosis of the liver: a comparison with β-acetyldigoxin. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 145–51.

Renal impairment. For reference to the pharmacokinetics of metildigoxin in patients with renal impairment, see under Uses and Administration, below.

Uses and Administration

Metildigoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (p.1263) and may be used in the treatment of some cardiac arrhythmias (p.1160) and in heart failure (p.1165).

The onset of action of metildigoxin is more rapid than that of digoxin. When metildigoxin is given orally an effect may appear within 5 to 20 minutes and a maximum effect on the myocardium may be seen in 15 to 30 minutes. The duration of action is similar to or a little longer than that of digoxin; therapeutic plasma concentrations are also similar. In stabilised patients on oral therapy a dose of 300 micrograms of metildigoxin is as effective as 500 micrograms of digoxin.

Metildigoxin may be given orally or intravenously. Initial oral doses of 100 to 600 micrograms daily may be given depending upon whether rapid or slow digitalisation is desired; digitalisation is usually performed over about 2 to 4 days and the larger doses are given in divided daily doses. Similar doses may also be given intravenously. Oral maintenance therapy is continued with 50 to 300 micrograms daily in divided doses.

Dosage should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Fairly good non-linear correlation was found between creatinine clearance and metildigoxin half-life in a study of 15 patients with chronic renal impairment, including 8 undergoing haemodialysis, and 4 patients with heart failure and unimpaired renal function. The mean elimination half-life was 5.62 days in patients undergoing dialysis (clearance essentially 0 mL/minute) and 3.41 days in the other patients with chronic renal impairment (clearance 15 to 50 mL/minute) compared with 1.49 days in patients with normal renal function (clearance 62 to 96 mL/minute). It was recommended that patients undergoing dialysis should be given 30 to 50% of the usual dose initially.[1] Other studies have suggested[2] that dose reduction may be necessary in renal impairment when creatinine clearance is below 50 mL/minute per 1.48 m^2.

1. Trovato GM, *et al.* Relationship between β-methyl-digoxin pharmacokinetic and degree of renal impairment. *Curr Ther Res* 1983; **33:** 158–64.
2. Tsutsumi K, *et al.* Pharmacokinetics of beta-methyldigoxin in subjects with normal and impaired renal function. *J Clin Pharmacol* 1993; **33:** 154–60.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Lanitop; ***Belg.:*** Lanitop; ***Braz.:*** Lanitop†; ***Ger.:*** Lanitop; ***Gr.:*** Lanitop; ***Hong Kong:*** Lanitop; ***Ital.:*** Lanitop; ***Jpn:*** Lanirapid; ***Pol.:*** Bemecor; Medigox; ***Port.:*** Lanitop; ***Spain:*** Lanirapid; ***Switz.:*** Lanitop†; ***Venez.:*** Lanitop.

Metipamide ⊗

Metipamid; Metipamidum; VÚFB-14429. 3-(Aminosulfonyl)-4-chlorobenzoic acid 2-methyl-2-phenylhydrazide.

$C_{14}H_{14}ClN_3O_3S$ = 339.8.
CAS — 85683-41-6.

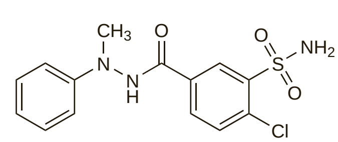

Profile

Metipamide is a diuretic structurally related to indapamide (p.1314); it is used as an antihypertensive.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Hypotylin.

Metirosine *(BAN, rINN)*

L-588357-0; Metirosiini; Metirosin; Metirosina; Métirosine; Metirosinum; Metyrosine *(USAN)*; MK-781. (–)-α-Methyl-L-tyrosine; 4-Hydroxy-α-methylphenylalanine.

Метирозин

$C_{10}H_{13}NO_3$ = 195.2.

CAS — 672-87-7 (metirosine); 620-30-4 (racemetirosine).

ATC — C02KB01.

ATC Vet — QC02KB01.

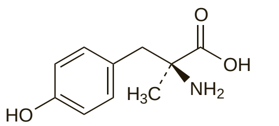

NOTE. The term α-methyltyrosine (α-MPT; α-MT; α-methyl-*p*-tyrosine) is used below since although metirosine, the (–)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; (±)-α-methyl-DL-tyrosine) is produced during synthesis but that the material supplied contains mainly (–)-isomer with a small amount of (+)-isomer.
The code name MK-781, applied to earlier investigational material, may have described a racemate or a preparation containing a smaller proportion of (–)-isomer than the product now available commercially.
Potency of the proprietary preparation (*Demser*) is expressed in terms of metirosine.

Pharmacopoeias. In *US.*

Adverse Effects

Sedation occurs in almost all patients receiving α-methyltyrosine. Other adverse effects include extrapyramidal symptoms, such as trismus and frank parkinsonism; anxiety, depression, and psychic disturbances including hallucinations, disorientation, and confusion; and diarrhoea, which may be severe. Crystalluria, transient dysuria, and haematuria have been seen in a few patients. There have also been occasional reports of slight swelling of the breast, galactorrhoea, nasal congestion, decreased salivation, gastrointestinal disturbances, headache, impotence or failure of ejaculation, and hypersensitivity reactions. Eosinophilia, raised serum aspartate aminotransferase, and peripheral oedema have been reported rarely.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome occurred after the use of the dopamine-depleting drugs tetrabenazine and α-methyltyrosine in a patient with Huntington's chorea.[1]

1. Burke RE, *et al.* Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. *Neurology* 1981; **31:** 1022–6.

Precautions

To minimise the risk of crystalluria, patients receiving α-methyltyrosine should have a fluid intake sufficient to maintain a urine volume of at least 2 litres daily and their urine should be examined regularly for the presence of crystals.

α-Methyltyrosine has sedative effects and patients should be warned of the hazards of driving a motor vehicle or operating machinery while receiving the drug. Symptoms of psychic stimulation and insomnia may occur when α-methyltyrosine is withdrawn.

When α-methyltyrosine is used pre-operatively in patients with phaeochromocytoma, blood pressure and the ECG should be monitored continuously during surgery as the danger of hypertensive crises and arrhythmias is not eliminated. Concomitant alpha blockade (e.g. with phentolamine) may be required; a beta blocker or lidocaine may be needed for the management of arrhythmias. Blood volume must be maintained during and after surgery, particularly if an alpha blocker is used, to avoid hypotension.

Interactions

The sedative effects of α-methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

Pharmacokinetics

α-Methyltyrosine is well absorbed from the gastrointestinal tract and is excreted mainly unchanged by the kidneys. A plasma half-life of 3.4 to 7.2 hours has been reported. Less than 1% of a dose may be excreted as the metabolites α-methyldopa, α-methyldopamine, α-methylnoradrenaline, and α-methyltyramine.

Uses and Administration

α-Methyltyrosine is an inhibitor of the enzyme tyrosine hydroxylase, and consequently of the synthesis of catecholamines. It is used to control the symptoms of excessive sympathetic stimulation in patients with phaeochromocytoma (p.1179) and decreases the frequency and severity of hypertensive attacks and related symptoms in most patients. It may be given for pre-operative preparation, or for long-term management in those for whom surgery is contra-indicated or who have malignant phaeochromocytoma.

In the management of phaeochromocytoma, α-methyltyrosine is given orally in a dose of 250 mg four times daily, increased daily by 250 mg or 500 mg to a maximum of 4 g daily in divided doses. The optimum dose, achieved by monitoring clinical symptoms and catecholamine excretion, is usually in the range of 2 to 3 g daily and when used pre-operatively it should be given for at least 5 to 7 days before surgery. The use of alpha blockers may also be necessary.

α-Methyltyrosine is not effective in controlling essential hypertension.

α-Methyltyrosine has also been tried in patients with schizophrenia.

Preparations

USP 31: Metyrosine Capsules.

Proprietary Preparations (details are given in Part 3)
USA: Demser.

Metolazone *(BAN, USAN, rINN)* ⊗

Metolatsoni; Metolazon; Metolazona; Métolazone; Metolazonum; SR-720-22. 7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolylquinazoline-6-sulphonamide.

Метолазон

$C_{16}H_{16}ClN_3O_3S$ = 365.8.

CAS — 17560-51-9.

ATC — C03BA08.

ATC Vet — QC03BA08.

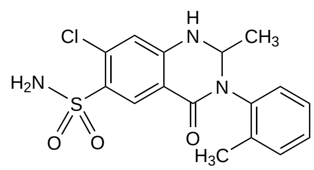

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Metolazone). A white or slightly yellowish, crystalline powder. It exhibits polymorphism. Very slightly soluble in water and dichloromethane; sparingly soluble in methyl alcohol; slightly soluble in ethyl acetate. Protect from light.

USP 31 (Metolazone). Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Hydrochlorothiazide, p.1307. Metolazone has also been reported to cause palpitations, chest pain, and chills.

Effects on the blood. Profound neutropenia was seen in a 58-year-old woman within 10 days of starting treatment with metolazone.[1] Neutropenia persisted for a further 10 days after metolazone was withdrawn. No other haematological abnormalities were seen.

1. Donovan KL. Neutropenia and metolazone. *BMJ* 1989; **299:** 981.

Effects on the nervous system. Two patients had acute muscle cramps with impairment of consciousness and epileptiform movements after taking metolazone 5 mg (single dose) or 2.5 mg daily for 3 days.[1]

1. Fitzgerald MX, Brennan NJ. Muscle cramps, collapse, and seizures in two patients taking metolazone. *BMJ* 1976; **1:** 1381–2.

Precautions

As for Hydrochlorothiazide, p.1309.

Interactions

As for Hydrochlorothiazide, p.1309. Severe electrolyte disturbances may occur when metolazone and furosemide are used together.

ACE inhibitors. Deterioration in renal function occurred in a 65-year-old woman when metolazone 5 mg [daily] was added to *captopril*, furosemide, spironolactone, and digoxin for heart failure.[1] An interaction between captopril and metolazone was suspected and both drugs were stopped with a subsequent return to normal renal function. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic may have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril.

1. Hogg KJ, Hillis WS. Captopril/metolazone induced renal failure. *Lancet* 1986; **i:** 501–2.

Antidiabetics. Hypoglycaemia occurred in a patient with type 2 diabetes mellitus controlled with *glibenclamide* 40 hours after starting therapy with metolazone 5 mg daily.[1] Studies of protein binding *in vitro* did not reveal any evidence of displacement of glibenclamide from binding sites.

1. George S, *et al.* Possible protein binding displacement interaction between glibenclamide and metolazone. *Eur J Clin Pharmacol* 1990; **38:** 93–5.

Ciclosporin. An increase in serum-creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and ciclosporin.[1] Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.

Pharmacokinetics

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

◊ References.

1. Tilstone WJ, *et al.* Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther* 1974; **16:** 322–9.

Uses and Administration

Metolazone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Unlike thiazides in general, metolazone is reported to be effective in patients with a glomerular filtration rate of less than 20 mL/minute. Diuresis starts in about 1 hour, reaches a peak in about 2 hours, and lasts for 12 to 24 hours depending on the dose.

A preparation with enhanced bioavailability, which is effective in lower doses than conventional formulations, is available in some countries. Doses given in *Martindale* refer to the conventional tablet formulation unless otherwise stated.

In the treatment of **oedema** the usual dose is 5 to 10 mg daily; in some cases doses of 20 mg or more may be required. No more than 80 mg should be given in any 24-hour period. In refractory cases, metolazone has been used with furosemide or other loop diuretics, but the electrolyte balance should be monitored closely.

In the treatment of **hypertension** the usual dose is 2.5 to 5 mg daily either alone, or with other antihypertensives. An initial dose of 1.25 mg has also been used. The dosage may be adjusted after 3 to 4 weeks according to response. A maintenance dose of 5 mg on alternate days may be used.

Formulations with enhanced bioavailability are given in doses of 0.5 to 1 mg daily in the treatment of hypertension. They are not bioequivalent to the conventional tablet formulation and should not be used interchangeably.

Preparations

USP 31: Metolazone Oral Suspension; Metolazone Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Zaroxolyn; ***Chile:*** Pavedal; ***Ger.:*** Zaroxolyn†; ***Gr.:*** Metenix; Zaroxolyn†; ***Hong Kong:*** Zaroxolyn; ***India:*** Metoz; ***Israel:*** Zaroxolyn; ***Ital.:*** Zaroxolyn; ***Port.:*** Diulo; ***S.Afr.:*** Zaroxolyn†; ***Switz.:*** Zaroxolyne†; ***UK:*** Metenix; ***USA:*** Mykrox; Zaroxolyn.

Metoprolol (BAN, USAN, rINN) ⊗

Métoprolol; Metoprololi; Metoprololum. (±)-1-Isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

Метопролол

$C_{15}H_{25}NO_3$ = 267.4.

CAS — 54163-88-1; 37350-58-6.

ATC — C07AB02.

ATC Vet — QC07AB02.

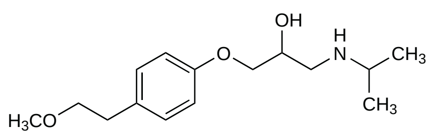

Metoprolol Fumarate (BANM, USAN, rINNM) ⊗

CGP-2175C; Fumarato de metoprolol; Métoprolol, Fumarate de; Metoprololi Fumaras.

Метопролола Фумарат

$(C_{15}H_{25}NO_3)_2,C_4H_4O_4$ = 650.8.

CAS — 119637-66-0.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *US.*

USP 31 (Metoprolol Fumarate). A 10% solution in water has a pH of between 5.5 and 6.5. Store in airtight containers. Protect from light.

Metoprolol Succinate (BANM, USAN, rINNM) ⊗

Métoprolol, succinate de; Metoprolol Süksinat; Metoprololi succinas; Metoprololio sukcinatas; Metoprololisuksinaatti; Metoprololsuccinat; Metoprolol-sukcinát; Metoprolol-szukcinát; Succinato de metoprolol.

Метопролола Суксинат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_4$ = 652.8.

CAS — 98418-47-4.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Metoprolol Succinate). A white or almost white crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; very slightly soluble in ethyl acetate. A 2% solution in water has a pH of between 7.0 and 7.6. Protect from light.

USP 31 (Metoprolol Succinate). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol. A 6.5% solution in water has a pH of between 7.0 and 7.6. Store in airtight containers at controlled room temperature.

Metoprolol Tartrate (BANM, USAN, rINNM) ⊗

CGP-2175E; H-93/26; Metoprolol tartarát; Metoprolol Tartarat; Métoprolol, tartrate de; Metoprololi tartras; Metoprololio tartratas; Metoprololitartraatti; Metoprolol-tartarát; Metoprololtartrat; Tartrato de metoprolol.

Метопролола Тартрат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ = 684.8.

CAS — 56392-17-7.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Metoprolol Tartrate). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of between 6.0 and 7.0. Protect from light.

USP 31 (Metoprolol Tartrate). A white crystalline powder. Very soluble in water; freely soluble in alcohol, in chloroform, and in dichloromethane; slightly soluble in acetone; insoluble in ether. A 10% solution in water has a pH of between 6.0 and 7.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. Metoprolol tartrate 400 micrograms/mL in glucose 5% or sodium chloride 0.9% was stable for 36 hours when stored at 24° in PVC bags.[1]

1. Belliveau PP, *et al.* Stability of metoprolol tartrate in 5% dextrose injection or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1993; **50:** 950–2.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Metoprolol is distributed into breast milk and studies[1-3] have shown that the concentration in milk is higher than that in plasma. However, the amount ingested by an infant is likely to be small, and the concentration of metoprolol in infant plasma has been found[3] to be undetectable or very low. No adverse effects have been seen in breast-fed infants whose mothers were given metoprolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Sandström B, Regårdh C-G. Metoprolol excretion into breast milk. *Br J Clin Pharmacol* 1980; **9:** 518–19.
2. Liedholm H, *et al.* Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 229–31.
3. Kulas J, *et al.* Atenolol and metoprolol: a comparison of their excretion into human breast milk. *Acta Obstet Gynecol Scand Suppl* 1984; **118:** 65–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on hearing. Loss of hearing in a patient receiving metoprolol appeared to be dose-related;[1] hearing gradually improved over several months once the drug was withdrawn.

1. Fäldt R, *et al.* β Blockers and loss of hearing. *BMJ* 1984; **289:** 1490–2.

Effects on lipid metabolism. Beta blockers may increase serum-triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in a patient taking atenolol and metoprolol, see p.1227.

Effects on the liver. Acute hepatitis associated with metoprolol has been reported in a 56-year-old woman.[1] The hepatotoxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

For a discussion of the relationship between polymorphic oxidation of metoprolol and the incidence of adverse effects, see Metabolism, under Pharmacokinetics, below.

1. Larrey D, *et al.* Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. *Ann Intern Med* 1988; **108:** 67–8.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of metoprolol and that the dose of metoprolol may need to be reduced if used together.

Pharmacokinetics

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble.

Metoprolol is widely distributed; it crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

The elderly. Several studies[1-3] indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

1. Quarterman CP, *et al.* The effect of age on the pharmacokinetics of metoprolol and its metabolites. *Br J Clin Pharmacol* 1981; **11:** 287–94.
2. Regårdh CG, *et al.* Pharmacokinetics of metoprolol and its metabolite α-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol* 1983; **24:** 221–6.
3. Larsson M, *et al.* Pharmacokinetics of metoprolol in healthy, elderly, non-smoking individuals after a single dose and two weeks of treatment. *Eur J Clin Pharmacol* 1984; **27:** 217–22.

Metabolism. Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6 and therefore exhibits a debrisoquine-type genetic polymorphism.[1-3] Poor, intermediate, extensive, and ultrarapid metabolisers of metoprolol have been identified, and studies[4-6] have confirmed that plasma-metoprolol concentrations correlate with metaboliser status. However, the clinical relevance of these differences is less clear. A retrospective study[7] found that the proportion of poor metabolisers among patients who had severe adverse effects was higher than expected, but other studies[8,9] have found no correlation between the incidence of adverse effects and metaboliser status. Controlled studies in patients with hypertension[5] and in healthy subjects[4] have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy.

The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians[10] failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

1. Lennard MS, *et al.* Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1982; **14:** 301–3.
2. Lennard MS, *et al.* Oxidation phenotype—a major determinant of metoprolol metabolism and response. *N Engl J Med* 1982; **307:** 1558–60.
3. McGourty JC, *et al.* Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985; **20:** 555–66.
4. Kirchheiner J, *et al.* Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2004; **76:** 302–12.
5. Zineh I, *et al.* Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* 2004; **76:** 536–44.
6. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther* 2006; **31:** 99–109.
7. Wuttke H, *et al.* Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; **72:** 429–37.
8. Clark DWJ, *et al.* Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol* 1984; **18:** 965–6.
9. Fux R, *et al.* Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther* 2005; **78:** 378–87.
10. Iyun AO, *et al.* Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin Pharmacol Ther* 1986; **40:** 387–94.

Pregnancy. The clearance of metoprolol was increased fourfold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant state.[1]

The disposition of metoprolol was investigated in neonates of mothers treated with metoprolol 50 to 100 mg twice daily.[2] In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the postnatal period, then declined over the next 15 hours; 5 of these infants had no detectable metoprolol concentrations in the umbilical plasma. No infant showed signs of beta blockade.

1. Högstedt S, *et al.* Increased oral clearance of metoprolol in pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 217–20.
2. Lundborg P, *et al.* Disposition of metoprolol in the newborn. *Br J Clin Pharmacol* 1981; **12:** 598–600.

Renal impairment. A single dose of a modified-release tablet of metoprolol produced similar plasma-metoprolol concentrations and values for the area under the concentration/time curve in both normal subjects and those with renal impairment.[1] Mean plasma concentrations of the metabolite α-hydroxymetoprolol were increased two to threefold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

1. Lloyd P, *et al.* The effect of impaired renal function on the pharmacokinetics of metoprolol after single administration of a 14/190 metoprolol OROS system. *Am Heart J* 1990; **120:** 478–82.

Uses and Administration

Metoprolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilising activity.

It is used in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), myocardial infarction (p.1175), and heart failure (p.1165). It is also used in the management of hyperthyroidism (p.2165) and in the prophylactic treatment of migraine (p.616).

Metoprolol is given orally and intravenously as the tartrate. Modified-release tablets usually contain the tartrate or the succinate, but the fumarate has also been used. Doses are usually expressed in terms of the tartrate; 95 mg of metoprolol fumarate or metoprolol succinate is equivalent to about 100 mg of metoprolol tartrate.

The bioavailability of metoprolol is increased if taken with food and it has been recommended that some preparations are taken with or immediately after a meal.

Reduced doses should be given to patients with hepatic impairment.

In **hypertension** metoprolol tartrate is usually given in an initial oral dose of 100 mg daily, as a single dose or in two divided doses. The dose may be increased weekly, according to response; the usual maintenance dose is 100 to 200 mg daily, but up to 400 mg daily may be given.

The usual oral dose for **angina pectoris** is 50 to 100 mg two or three times daily.

In the treatment of **cardiac arrhythmias** the usual oral dose is 50 mg two or three times daily, increased if necessary up to 300 mg daily in divided doses.

For the emergency treatment of cardiac arrhythmias metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg, at a rate of 1 to 2 mg/minute; this may be repeated, if necessary, at intervals of 5 minutes to a total dose of 10 to 15 mg. When acute arrhythmias have been controlled, maintenance therapy may be started 4 to 6 hours after intravenous therapy, at oral doses not exceeding 50 mg three times daily.

Arrhythmias may be prevented on induction of anaesthesia, or controlled during anaesthesia, by the slow intravenous injection of 2 to 4 mg; further injections of 2 mg may be repeated as necessary to a maximum total dose of 10 mg.

Metoprolol is also used as an adjunct in the early management of acute **myocardial infarction.** Treatment should be given within 12 hours of the onset of chest pain; metoprolol tartrate 5 mg should be given intravenously at 2-minute intervals to a total of 15 mg, where tolerated. After 15 minutes, in patients who have received the full intravenous dose, oral treatment should be started; 50 mg is given every 6 hours for 2 days. In patients who have failed to tolerate the full intravenous dose a reduced oral dose should be given as, and when, their condition permits. Subsequent maintenance dosage is 100 mg given twice daily by mouth. In patients who did not receive metoprolol by intravenous injection as part of the early management of myocardial infarction, metoprolol may be started once the clinical condition of the patient stabilises, in a dose of 200 mg daily in 2 or 4 divided doses.

In the management of stable, symptomatic **heart failure** metoprolol succinate may be given as an oral modified-release preparation. The initial dose is the equivalent of metoprolol tartrate 12.5 to 25 mg once daily, increased as tolerated, at intervals of 2 weeks, with a target dose of 200 mg once daily.

As an adjunct in the treatment of **hyperthyroidism** metoprolol tartrate may be given in oral doses of 50 mg four times daily. Doses of 100 to 200 mg are given daily in divided doses for **migraine** prophylaxis.

◊ General references.

1. Plosker GL, Clissold SP. Controlled release metoprolol formulations: a review of their pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. *Drugs* 1992; **43:** 382–414.
2. Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. *Drugs* 2000; **60:** 647–78.
3. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother* 2003; **37:** 701–10.

Administration in children. Metoprolol has been used in children, although experience is limited. A study[1] in children aged 6 to 16 years with hypertension found that modified-release metoprolol succinate was well tolerated in doses of up to the equivalent of metoprolol tartrate 2 mg/kg daily, although efficacy was not established. US licensed product information nevertheless allows the use of oral doses of metoprolol succinate once daily in children aged 6 to 16 years; the initial dose is the equivalent of metoprolol tartrate 1 mg/kg daily (maximum 50 mg), adjusted according to response to a maximum of 2 mg/kg (not more than 200 mg) daily.

The *BNFC* recommends that for hypertension children aged 1 month to 12 years may be given standard formulations of metoprolol tartrate in an initial dose of 1 mg/kg twice daily orally, increased if necessary to a maximum dose of 8 mg/kg daily in 2 to 4 divided doses. Children over 12 years may be given the adult dose (see above).

1. Batisky DL, *et al.* Efficacy and safety of extended release metoprolol succinate in hypertensive children 6 to 16 years of age: a clinical trial experience. *J Pediatr* 2007; **150:** 134–9.

Preparations

BP 2008: Metoprolol Injection; Metoprolol Tartrate Tablets;
USP 31: Metoprolol Succinate Extended-Release Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Metoprolol Tartrate Injection; Metoprolol Tartrate Oral Solution; Metoprolol Tartrate Oral Suspension; Metoprolol Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Beloc†; Belozok; Lopresor; ***Austral.:*** Betaloc; Lopresor; Metohexal; Metolol†; Metrol; Minax; Toprol; ***Austria:*** Beloc; Lanoc; Metohexal; MetoMed; Metopal†; Metostadol; Metotyrol†; Seloken; ***Belg.:*** Lopresor; Selo-Zok; Seloken; Slow-Lopresor; ***Braz.:*** Lopressor; Selo-Zok; Seloken; ***Canad.:*** Betaloc; Lopresor; Novo-Metoprol; Nu-Metop; ***Cz.:*** Betaloc; Corvitol†; Egilok; Emzok; Metohexal†; Vasocardin; ***Denm.:*** Dura-Zok†; Mepronet; Metocar; Metozoc†; Selo-Zok; Seloken; ***Fin.:*** Metblock†; Metoprolin; Metozoc†; Seloken; Seloken ZOC; Selopral; Spesicor; ***Fr.:*** Lopressor; Seloken; Selozok; ***Ger.:*** Azumetop†; Beloc; Beloc-Zok; Jeprolol; Jutabloc; Lopresor; Meprolol; Meto; Meto-Succinat; Meto-Tablinen; Metobeta; Metodoc; Metodura; Metohexal; Metok†; Metomerck†; Metoprogamma; Prelis; Sigaprolol†; ***Gr.:*** Lopresor; ***Hong Kong:*** Betaloc; CP-Metolol; Denex†; Minax; Novo-Metoprol; Sefloc; ***Hung.:*** Betaloc; Egilok; Huma-Metoprol†; Ritmetol†; ***India:*** Betaloc; Metolar; Revelol; Selopres; ***Indon.:*** Cardiosel; Lopresor; Loprolol; Seloken; ***Irl.:*** Betaloc; Lopresor; Metocor; Metop; ***Israel:*** Lopresor; Metopress†; Neobloc; ***Ital.:*** Lopresor; Seloken; ***Jpn:*** Seloken; ***Malaysia:*** Beatrolol†; Betaloc; Betatab†; Denex; ***Mex.:*** Bioprol; Eurolol; Futaline; Kenaprol; Lopresor; Metopresol; Proken M†; Prolaken; Promiced; Prontol; Ritmolol; Selectadril†; Seloken; Sermetrol; Synadrenol†; ***Neth.:*** Lopresor; Selokeen; ***Norw.:*** Metozoc†; Selo-Zok; Seloken; ***NZ:*** Betaloc; Lopresor; Slow-Lopresor; ***Philipp.:*** Betaloc; Betaryx; Betazok; Cardiosel; Cardiostat; Cardiotab; Metocare; Metoprim; Metospec; Metostad; Montebloc; Neobloc; Prolohex; Valvexin; ***Pol.:*** Betaloc; Beto; Metocard; Metohexal; ***Port.:*** Lopresor; ***Rus.:*** Betaloc ZOK (Беталок ЗОК); Corvitol (Корвадил); Egilok (Эгилок); Emzok (Эмзок); Metocard (Метокард); Serdol (Сердол); Vasocardin (Вазокардин); ***S.Afr.:*** Lopresor; ***Singapore:*** Betaloc; Denex; ***Spain:*** Beloken; Lopresor; ***Swed.:*** Seloken; Seloken ZOC; ***Switz.:*** Beloc; Beloc COR†; Beloc-Zok; Lopresor; Metopress; ***Thai.:*** Betaloc; Cardeloc; Cardoxone; Denex†; Melol; Metoblock; Metolol; Minax; Sefloc; ***Turk.:*** Beloc; Lopresor; Problok; ***UK:*** Betaloc; Lopresor; ***USA:*** Lopressor; Toprol; ***Venez.:*** Lopresor.

Multi-ingredient: ***Arg.:*** Diubeloc†; ***Austria:*** Beloc comp; Metoprolol compositum; Seloken retard Plus; Triloc; ***Belg.:*** Logimat; Logroton; Selozide; Zok-Zid; ***Braz.:*** Selopress; ***Cz.:*** Logimax†; ***Denm.:*** Logimax; Zok-Zid; ***Fin.:*** Logimax; Selocomp ZOC; Seloken ZOC/ASA†; ***Fr.:*** Logimax; Logroton; ***Ger.:*** Azumetop HCT†; Belnif; Beloc-Zok comp; Meprolol Comp; Meto comp†; Meto-Isis comp†; meto-thiazid†; Metobeta comp; Metodura comp; Metohexal comp; Metoprolol comp; Metostad Comp; Mobloc; Prelis comp; Treloc; ***Gr.:*** Logimax; ***Hong Kong:*** Betaloc Comp; CP-Metolol Co; Logimax; ***Hung.:*** Logimax; ***India:*** Metolar-H; ***Irl.:*** Co-Betaloc; ***Israel:*** Logimax; ***Ital.:*** Igroton-Lopresor; Selozide†; ***Malaysia:*** Logroton; ***Mex.:*** Logimax; Selopres; ***Neth.:*** Logimax; Selokomb; ***Philipp.:*** Betazide; Logimax; ***Rus.:*** Logimax (Логимакс); ***Spain:*** Higrotensin; Logimax; Selopresin†; ***Swed.:*** Logimax; Seloken ZOC/ASA†; ***Switz.:*** Logimax; Logroton; ***UK:*** Co-Betaloc†; ***USA:*** Lopressor HCT.

Mevastatin *(rINN)*

Compactin; CS-500; Mevastatina; Mévastatine; Mevastatinum; ML-236B. (1*S*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl (*S*)-2-methylbutyrate.

Мевастатин

$C_{23}H_{34}O_5$ = 390.5.

CAS — 73573-88-3.

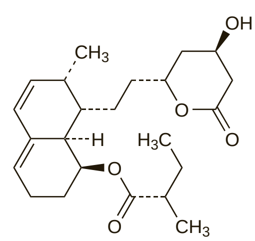

Profile

Mevastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin) (see Simvastatin, p.1390) that has been isolated from *Penicillium citrinum.* It is a lipid regulating drug but is no longer used in clinical practice because of reports of toxicity in *animals.*

Mexiletine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mexiletina; Kö-1173; Meksiletiinihydrokloridi; Meksiletin Hidroklorür; Meksiletino hidrochloridas; Mexilétine, chlorhydrate de; Mexiletin-hidroklorid; Mexiletin-hydrochlorid; Mexiletinhydroklorid; Mexiletini hydrochloridum. 1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.

Мексилетина Гидрохлорид

$C_{11}H_{17}NO,HCl$ = 215.7.

CAS — 31828-71-4 (mexiletine); 5370-01-4 (mexiletine hydrochloride).

ATC — C01BB02.

ATC Vet — QC01BB02.

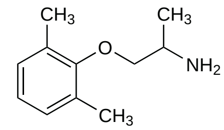

(mexiletine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Mexiletine Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5.

USP 31 (Mexiletine Hydrochloride). A white powder. Freely soluble in water and in dehydrated alcohol; practically insoluble in ether; slightly soluble in acetonitrile. A 10% solution in water has a pH of between 3.5 and 5.5. Store in airtight containers.

Adverse Effects and Treatment

Mexiletine has a narrow therapeutic ratio; many adverse effects of mexiletine are dose-related and will respond to dosage reduction but may be severe enough to force mexiletine to be stopped and symptomatic and supportive therapy to be given. Toxicity is common with oral or parenteral loading doses when plasma concentrations are high.

The most common adverse effects involve the gastrointestinal tract and CNS. Effects on the gastrointestinal tract include nausea, vomiting, constipation, and diarrhoea; oesophageal ulceration has also been reported. Effects on the nervous system include tremor, confusion, lightheadedness, dizziness, blurred vision and other visual disturbances, sleep disturbances, and speech difficulties. The most frequent cardiovascular effects are hypotension, sinus bradycardia, heart block and AV dissociation, and atrial fibrillation. As with other antiarrhythmics mexiletine may exacerbate arrhythmias. Other adverse effects that have been reported include skin rashes, abnormal liver function tests, thrombocytopenia, positive antinuclear factor titres, and convulsions. The Stevens-Johnson syndrome has been reported rarely.

Incidence of adverse effects. In a study involving 100 patients with ventricular arrhythmias, mexiletine had to be stopped in 49 patients because of intolerable adverse effects.[1] The most common of these affected the gastrointestinal system (27%) and included nausea (10%), vomiting (6%), heartburn (6%), and oesophageal spasm (3%). Intolerable effects on the CNS occurred in 10% of patients and these were most commonly tremor (4%), ataxia (2%), dyskinesia (1%), and tinnitus (1%). When mexiletine was used with another antiarrhythmic, the incidence of intolerable effects was 56%.

Tolerable adverse effects with mexiletine alone were transient and dose-dependent and occurred in 18% of patients. They most often affected the gastrointestinal tract. No irreversible adverse effects were reported and no proarrhythmic effects were seen.

1. Kerin NZ, *et al.* Mexiletine: long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990; **150:** 381–4.

Effects on the lungs. Pulmonary fibrosis has been reported in an elderly patient receiving mexiletine; the manufacturer was aware of 3 other cases.[1]

1. Bero CJ, Rihn TL. Possible association of pulmonary fibrosis with mexiletine. *DICP Ann Pharmacother* 1991; **25:** 1329–31.

Precautions

Mexiletine is contra-indicated in cardiogenic shock and in second- or third-degree AV block (unless the patient has a pacemaker). It should be used with caution in patients with sinus node dysfunction, other conduction disorders, bradycardia, hypotension, heart failure, or hepatic impairment. ECG and blood pressure monitoring should be carried out during treatment.

Absorption of oral mexiletine may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Breast feeding. Mexiletine is distributed into human breast milk in higher concentrations than in maternal serum. A woman[1] given 200 mg of mexiletine three times daily during the last trimester of pregnancy (see below), went on to breast feed the infant. Concentrations of mexiletine in the maternal milk and serum were found to be 0.6 and 0.3 micrograms/mL respectively on the second day postpartum, and 0.8 and 0.7 micrograms/mL respectively after 6 weeks. This represented a milk to serum ratio of 2.0 and 1.1 respectively. However, mexiletine was undetectable in the infant's serum on both occasions and no adverse effects were seen. In another report[2] a woman taking a similar dose of mexiletine for the last 5 months of her pregnancy also breast fed her infant. In samples of maternal milk and blood collected between the second and fifth day postpartum the milk to plasma ratio varied between 0.78 and 1.89 with a mean of 1.45. It was considered unlikely that the infant would ingest more than 1.25 mg of mexiletine in any 24-hour period, and this amount was not thought to be enough to cause adverse effects. Failure to feed was noted[3] in the first 17 days in an infant whose mother was taking 750 mg daily of mexiletine and 50 mg daily of atenolol. After maternal education and formula supplementation an acceptable growth curve was established. Breast feeding continued until the infant was 3 months old, and no adverse effects were seen at 10 months. The American Academy of Pediatrics[4] therefore considers that mexiletine is usually compatible with breast feeding.

1. Timmis AD, *et al*. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lewis AM, *et al*. Mexiletine in human blood and breast milk. *Postgrad Med J* 1981; **57:** 546–7.
3. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. Mexiletine crosses the placenta but there have been several reports of its use in pregnant women with no apparent long-term effects on the infants. A normal infant was born to a woman given mexiletine with propranolol for the control of ventricular tachycardia during the third trimester of pregnancy.[1] During the first 6 hours after delivery the infant had a heart rate of only 90 beats/minute, probably due to the propranolol; it was normal thereafter. At delivery the serum concentration of mexiletine in mother and infant was the same. A woman[2] who received mexiletine and atenolol throughout pregnancy also delivered a normal infant; failure to feed was noted at 17 days but at 10 months no adverse effects were seen. In another case[3] where the mother took mexiletine throughout pregnancy, the infant had a low Apgar score at 1 minute and hypoglycaemia was also noted, but the relationship to mexiletine was unclear; cord and maternal blood concentrations at the time of delivery were 400 nanograms/mL and 600 nanograms/mL, respectively.

1. Timmis AD, *et al*. Mexiletine for control of ventricular dysrhythmias in pregnancy. *Lancet* 1980; **ii:** 647–8.
2. Lownes HE, Ives TJ. Mexiletine use in pregnancy and lactation. *Am J Obstet Gynecol* 1987; **157:** 446–7.
3. Gregg AR, Tomich PG. Mexilitene [sic] use in pregnancy. *J Perinatol* 1988; **8:** 33–5.

Interactions

Mexiletine undergoes extensive metabolism in the liver particularly by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6, and possibly CYP3A4, and interactions may occur with other drugs metabolised by the same enzymes. Plasma concentrations of mexiletine may be reduced by hepatic enzyme inducers such as phenytoin and rifampicin; increased plasma concentrations may occur with enzyme inhibitors.

Absorption of mexiletine may be delayed by drugs that slow gastric emptying such as opioid analgesics and atropine. The rate of absorption may be increased by metoclopramide; the extent of absorption is unaffected.

Drugs that acidify or alkalinise the urine enhance or reduce the rate of elimination of mexiletine, respectively.

There may be an increased risk of arrhythmias if mexiletine is used with other antiarrhythmics or with arrhythmogenic drugs.

Mexiletine has been reported to increase theophylline concentrations (p.1142) and to precipitate lidocaine toxicity (p.1863).

Pharmacokinetics

Mexiletine is readily and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 90%, although absorption may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Mexiletine is metabolised in the liver to a number of metabolites; metabolism may involve cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4, and genetic polymorphism in relation to CYP2D6 has been identified. Mexiletine is excreted in the urine, mainly in the form of its metabolites with about 10% excreted unchanged; clearance is increased in acid urine.

Mexiletine is widely distributed throughout the body and is about 50 to 70% bound to plasma proteins. Mexiletine crosses the placenta and is distributed into breast milk. It has an elimination half-life of about 10 hours in healthy subjects but this may be prolonged in patients with heart disease, hepatic impairment, or severe renal impairment. Its therapeutic effect has been correlated with plasma concentrations of 0.5 to 2 micrograms/mL, but the margin between therapeutic and toxic concentrations is narrow, and severe toxicity may occur within this range.

◊ References.

1. Labbé L, Turgeon J. Clinical pharmacokinetics of mexiletine. *Clin Pharmacokinet* 1999; **37:** 361–84.

Uses and Administration

Mexiletine is a class Ib antiarrhythmic (p.1153) with actions similar to those of lidocaine (p.1864), to which it is structurally related. Unlike lidocaine it undergoes little hepatic first-pass metabolism and can be given orally.

Mexiletine is used for the treatment of ventricular **arrhythmias** (p.1160). It is given orally or intravenously as the hydrochloride.

Mexiletine hydrochloride is given orally in a usual loading dose of 400 mg followed by 200 to 250 mg three or four times daily, starting 2 hours after the loading dose. The usual maintenance dosage is 600 to 900 mg daily in divided doses; doses up to 1.2 g daily may be given. Oral doses should be taken with food and swallowed with plenty of liquid to avoid oesophageal ulceration. Modified-release preparations have been used. Higher loading doses (for example, of 600 mg) may be necessary in patients after myocardial infarction to overcome delayed absorption, especially if they have received an opioid analgesic.

Mexiletine hydrochloride may be given by slow intravenous injection in doses of 100 to 250 mg at a rate of 25 mg/minute, followed by an infusion at a rate of 250 mg over 1 hour, 250 mg over the next 2 hours, and then at about 500 micrograms/minute for maintenance, according to response; when appropriate the patient may be transferred to oral therapy with doses of 200 to 250 mg three or four times daily. Alternatively, an initial intravenous dose of 200 mg at a rate of 25 mg/minute, may be followed by an oral dose of 400 mg on completion of the injection, with subsequent oral therapy as above.

Mexiletine has also been tried in the treatment of refractory neuropathic **pain** (see below).

Administration in children. Mexiletine may be effective for ventricular arrhythmias in children; a study[1] of 42 children and young adults (age range 5 months to 34 years) found that mexiletine, given orally in a dose of 1.4 to 5 mg/kg every 8 hours, was effective in 30 patients (71%), with long-term control reported in 18. Treatment was more effective in children with congenital heart disease than in those with cardiomyopathy or no heart disease. Another report[2] found that young children required higher mg/kg doses than adults; a 2-week-old girl and a 20-month-old boy required oral doses of 25 and 15 mg/kg daily, respectively, to produce therapeutic plasma concentrations and control of tachycardia.

1. Moak JP, *et al*. Mexiletine: an effective antiarrhythmic drug for treatment of ventricular arrhythmias in congenital heart disease. *J Am Coll Cardiol* 1987; **10:** 824–9.
2. Holt DW, *et al*. Paediatric use of mexiletine and disopyramide. *BMJ* 1979; **2:** 1476–7.

Administration in the elderly. The rate of absorption of mexiletine was slower in a group of 7 elderly subjects compared with 8 young subjects given mexiletine 100 mg by mouth, but the extent of absorption was probably not affected.[1] Elimination of mexiletine was not significantly different between the 2 groups and there was no pharmacokinetic basis for dosage modification of mexiletine in the elderly. An observational study[2] in patients receiving mexiletine found a small decrease in clearance with age, but again this was not considered to warrant dosage adjustment.

1. Grech-Bélanger O, *et al*. Pharmacokinetics of mexiletine in the elderly. *J Clin Pharmacol* 1989; **29:** 311–15.
2. Ueno K, *et al*. Pharmacokinetics of mexiletine in middle-aged and elderly patients. *Clin Pharm* 1993; **12:** 768–70.

Administration in renal impairment. The pharmacokinetics of mexiletine do not appear to be affected by renal impairment,[1] although one study[2] found that in patients with creatinine clearance below 10 mL/minute the steady-state plasma concentration and half-life were increased, suggesting that dosage should be adjusted according to plasma concentrations in such patients. Haemodialysis[1] and continuous ambulatory peritoneal dialysis[3] do not appear to affect mexiletine clearance.

1. Wang T, *et al*. Pharmacokinetics and nondialyzability of mexiletine in renal failure. *Clin Pharmacol Ther* 1985; **37:** 649–53.
2. El Allaf D, *et al*. Pharmacokinetics of mexiletine in renal insufficiency. *Br J Clin Pharmacol* 1982; **14:** 431–5.
3. Guay DRP, *et al*. Mexiletine clearance during peritoneal dialysis. *Br J Clin Pharmacol* 1985; **19:** 857–8.

Pain. Neuropathic pain (p.8) is often insensitive to opioid analgesics and various drugs, including mexiletine, have been tried. Mexiletine may be of benefit in diabetic neuropathy,[1] although studies have given conflicting results; two of the studies that reported no difference between treatment and placebo found that a subset of patients (those with stabbing or burning pain, heat sensations, and formication) appeared to benefit.[2,3] There have also been reports of improvement in patients with central post-stroke pain (thalamic pain syndrome),[4] and in neuropathic pain associated with cancer,[5-7] and a systematic review[8] concluded that mexiletine was safe and effective in various types of neuropathic pain.

Other painful states in which mexiletine has been reported to be of benefit include: Dercum's disease (a condition involving painful fatty deposits),[9] and erythromelalgia.[10,11]

1. Jarvis B, Coukell AJ. Mexiletine: a review of its therapeutic use in painful diabetic neuropathy. *Drugs* 1998; **56:** 691–707.
2. Stracke H, *et al*. Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992; **15:** 1550–5.
3. Wright JM, *et al*. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997; **31:** 29–34.
4. Awerbuch GI, Sandyk R. Mexiletine for thalamic pain syndrome. *Int J Neurosci* 1990; **55:** 129–33.
5. Colclough G, *et al*. Mexiletine for chronic pain. *Lancet* 1993; **342:** 1484–5.
6. Sloan P, *et al*. Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. *Anesth Analg* 1999; **89:** 760–1.
7. Fassoulaki A, *et al*. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* 2002; **95:** 985–91.
8. Challapalli V, *et al*. Systemic administration of local anesthetic agents to relieve neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/07).
9. Petersen P, *et al*. Treating the pain of Dercum's disease. *BMJ* 1984; **288:** 1880.
10. Nathan A, *et al*. Primary erythromelalgia in a child responding to intravenous lidocaine and oral mexiletine treatment. Abstract: *Pediatrics* 2005; **115:** 1066. Full version: http://pediatrics.aappublications.org/cgi/content/full/115/4/e504 (accessed 10/07/07)
11. Kuhnert SM, *et al*. Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999; **135:** 1447–9.

Preparations

BP 2008: Mexiletine Capsules; Mexiletine Injection;
USP 31: Mexiletine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Mexitilen; ***Austral.:*** Mexitil; ***Austria:*** Mexitil; ***Belg.:*** Mexitil; ***Braz.:*** Mexitil; ***Canad.:*** Mexitil†; ***Cz.:*** Katen; ***Fin.:*** Mexitil; ***Fr.:*** Mexitil†; ***Ger.:*** Mexitil; ***Gr.:*** Mexitil; Myovek†; ***Hong Kong:*** Mexitil†; ***Hung.:*** Ritalmex; ***India:*** Mexitil; ***Irl.:*** Mexitil; ***Israel:*** Mexilen; ***Ital.:*** Mexitil; ***Jpn:*** Mexitil; ***Mex.:*** Mexitil†; ***Neth.:*** Mexitil†; ***NZ:*** Mexitil; ***Pol.:*** Mexicord; ***S.Afr.:*** Mexitil†; ***Spain:*** Mexitil; ***Swed.:*** Mexitil†; ***Thai.:*** Mexitil†; ***Turk.:*** Mexitil; ***UK:*** Mexitil†; ***USA:*** Mexitil; ***Venez.:*** Tumetil.

Mibefradil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mibefradil; Mibéfradil, Chlorhydrate de; Mibefradil Dihydrochloride *(USAN)*; Mibefradili Hydrochloridum; Ro-40-5967 (mibefradil); Ro-40-5967/001 (mibefradil hydrochloride). (1*S*,2*S*)-(2-{[3-(2-Benzimidazolyl)propyl]methylamino}-ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride.

Мибефрадила Гидрохлорид

$C_{29}H_{38}FN_3O_3,2HCl = 568.6.$

CAS — 116644-53-2 (mibefradil); 116666-63-8 (mibefradil hydrochloride).

ATC — C08CX01.

ATC Vet — QC08CX01.

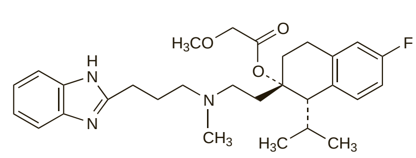

(mibefradil)

Profile

Mibefradil is a calcium-channel blocker that acts principally on fast T-type calcium channels, unlike conventional calcium-channel blockers that act on slow L-type channels (see p.1154). Mibefradil was introduced for the management of hypertension and angina pectoris but was withdrawn worldwide several months later due to increasing reports of serious interactions with a wide range of drugs.

Midodrine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de midodrina; Midodrine, Chlorhydrate de; Midodrini Hydrochloridum; ST-1085 (midodrine or midodrine hydrochloride). 2-Amino-*N*-(β-hydroxy-2,5-dimethoxyphenethyl)-acetamide hydrochloride; (*RS*)-N^1-(β-Hydroxy-2,5-dimethoxyphenethyl)glycinamide hydrochloride.

Мидодрина Гидрохлорид

$C_{12}H_{18}N_2O_4$,HCl = 290.7.

CAS — 42794-76-3 (midodrine); 3092-17-9 (midodrine hydrochloride).

ATC — C01CA17.

ATC Vet — QC01CA17.

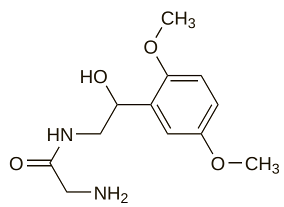

(midodrine)

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p.1407. Midodrine has mainly alpha-agonist properties and the most serious adverse effect of midodrine is supine hypertension. Paraesthesias, dysuria, pilomotor reaction (goose flesh), pruritus and rashes have been reported.

Interactions

As for Sympathomimetics, p.1407.

Pharmacokinetics

Midodrine is well absorbed from the gastrointestinal tract and undergoes enzymatic hydrolysis in the systemic circulation to its active metabolite, deglymidodrine (desglymidodrine; ST-1059). Midodrine itself reaches its peak plasma concentrations about half an hour after an oral dose, and has a plasma half-life of about 25 minutes. The active metabolite reaches its peak plasma concentration about an hour after oral dosage and has a terminal elimination half-life of about 3 hours. Deglymidodrine undergoes some further metabolism in the liver. Midodrine is primarily excreted in the urine as metabolites and a small amount of unchanged drug.

Uses and Administration

Midodrine is a direct-acting sympathomimetic (p.1408) with selective alpha-agonist activity; the main active moiety has been stated to be its major metabolite, deglymidodrine. It acts as a peripheral vasoconstrictor but has no direct cardiac stimulatory effects.

Midodrine hydrochloride is used in the treatment of hypotensive states (p.1174) and in particular of orthostatic hypotension (p.1530). Alpha-agonist drugs such as midodrine have also been used as an adjunct in the management of urinary incontinence (p.2180).

In **hypotensive states**, the usual initial oral dose of midodrine hydrochloride is 2.5 mg two or three times daily, adjusted gradually according to response; up to 10 mg three times daily may be required. The potential for supine hypertension is reduced by taking the last dose of the day at least 4 hours before bedtime.

An oral dose for **urinary incontinence** is 2.5 to 5 mg two or three times daily.

Midodrine hydrochloride can also be given in similar doses by slow intravenous injection. It has also been used orally or by injection in the treatment of **retrograde ejaculation**.

◊ References.

1. McClellan KJ, *et al.* Midodrine: a review of its therapeutic use in the management of orthostatic hypotension. *Drugs Aging* 1998; **12:** 76–86.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; **19:** 2553–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Gutron; ***Canad.:*** Amatine; ***Chile:*** Gutron; ***Cz.:*** Gutron; ***Fr.:*** Gutron; ***Ger.:*** Gutron; ***Hong Kong:*** Gutron; ***Hung.:*** Gutron; ***Irl.:*** Midon; ***Israel:*** Gutron; ***Ital.:*** Gutron; Xerotil; ***Jpn:*** Metligine; ***Neth.:*** Gutron; ***NZ:*** Gutron; ***Pol.:*** Gutron; ***Port.:*** Gutron; ***Rus.:*** Gutron (Гутрон); ***Singapore:*** Gutron; ***Switz.:*** Gutron; ***Thai.:*** Gutron†; ***USA:*** ProAmatine.

Milrinone *(BAN, USAN, rINN)*

Milrinona; Milrinonum; Win-47203-2. 1,6-Dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile.

Мильринон

$C_{12}H_9N_3O$ = 211.2.

CAS — 78415-72-2.

ATC — C01CE02.

ATC Vet — QC01CE02.

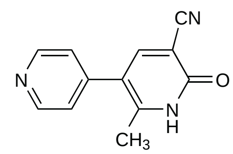

Pharmacopoeias. In *US.*

USP 31 (Milrinone). A white to tan, hygroscopic, crystalline solid. Practically insoluble in water and in chloroform; very slightly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers.

Milrinone Lactate *(BANM, rINNM)*

Lactato de milrinona; Milrinone, Lactate de; Milrinoni Lactas.

Мильринона Лактат

$C_{12}H_9N_3O,C_3H_6O_3$ = 301.3.

ATC — C01CE02.

ATC Vet — QC01CE02.

Incompatibility. UK licensed product information states that milrinone lactate injection is incompatible with furosemide and bumetanide, and it should not be diluted with sodium bicarbonate injection. Physical incompatibility with imipenem-cilastatin sodium has also been reported.[1]

1. Veltri MA, Conner KG. Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health-Syst Pharm* 2002; **59:** 452–4.

Adverse Effects and Precautions

Prolonged oral use of milrinone has increased the mortality rate and milrinone is now only used intravenously for short-term use.

Supraventricular and ventricular arrhythmias, hypotension, angina-like chest pain, and headache have been reported. Hypokalaemia, tremor, and thrombocytopenia may occur. The incidence of arrhythmias may be lower in *children* whereas the risk of thrombocytopenia may be higher (see Administration in Children, below).

Milrinone should be used with caution in patients with severe obstructive aortic or pulmonary valvular disease or with hypertrophic cardiomyopathy. Since milrinone may facilitate conduction through the atrioventricular node it can increase the ventricular response rate in patients with atrial flutter or fibrillation. Digitalisation should be considered in these patients before milrinone therapy is started.

Blood pressure, heart rate, ECG, fluid and electrolyte balance, and renal function should be monitored during milrinone therapy.

Milrinone should be given in reduced doses to patients with renal impairment.

Pharmacokinetics

Although milrinone is rapidly and almost completely absorbed from the gastrointestinal tract, it is only given intravenously. It is about 70% bound to plasma proteins. Elimination occurs mainly via the urine; about 83% of a dose is excreted as unchanged drug. The elimination half-life is about 2.3 hours.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).

Uses and Administration

Milrinone is a phosphodiesterase inhibitor similar to amrinone (p.1215) with positive inotropic and vasodilator activity. It is, however, reported to have greater positive inotropic activity than amrinone. It is given intravenously, as the lactate, in the short-term management of severe heart failure unresponsive to other forms of therapy and in acute heart failure after cardiac surgery. In some longer-term studies milrinone was given by mouth, but an increased mortality rate was reported.

Doses of milrinone lactate are expressed in terms of the base; milrinone lactate 1.43 mg is equivalent to about 1 mg of milrinone. The initial loading dose is the equivalent of milrinone 50 micrograms/kg given over 10 minutes followed by a continuous maintenance infusion. The maintenance infusion may be titrated between 375 and 750 nanograms/kg per minute but a total daily dose of 1.13 mg/kg should not be exceeded.

Dosage should be reduced in patients with renal impairment (see below).

Administration in children. Milrinone has been used in children with septic shock or heart failure after cardiac surgery. Pharmacokinetic studies[1,2] have suggested that steady-state plasma concentrations of milrinone are lower in children than in adults given similar doses, and that milrinone clearance is faster in children. Higher doses in proportion to body-weight may therefore be necessary in children than in adults. For neonates and children aged 1 month to 18 years with heart failure, low cardiac output after cardiac surgery, or shock, the *BNFC* recommends an initial dose of 50 to 75 micrograms/kg by intravenous infusion over 30 to 60 minutes, followed by continuous intravenous infusion at a dose of 30 to 45 micrograms/kg per hour (500 to 750 nanograms/kg per minute). The infusion may be continued for 2 to 3 days, but is usually given for 12 hours after cardiac surgery.

Milrinone also appears to be effective for the prevention of low cardiac output in children undergoing cardiac surgery.[3] It has been tried for the prevention of low systemic blood flow in premature infants, but further studies are needed to confirm its role.[4]

A study[5] of adverse effects in children given milrinone has suggested that arrhythmias are less common than in adults whereas thrombocytopenia is more common.

1. Lindsay CA, *et al.* Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; **132:** 329–34.
2. Ramamoorthy C, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998; **86:** 283–9.
3. Hoffman TM, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; **107:** 996–1002.
4. Paradisis M, *et al.* Pilot study of milrinone for low systemic blood flow in very preterm infants. *J Pediatr* 2006; **148:** 306–13.
5. Watson S, *et al.* Use of milrinone in the pediatric critical care unit. *Pediatrics* 1999; **104** (suppl): 681–2.

Administration in renal impairment. Doses of milrinone should be reduced in patients with renal impairment. The following doses for maintenance infusion are recommended based on creatinine clearance (CC):

- CC 50 mL/minute: 430 nanograms/kg per minute
- CC 40 mL/minute: 380 nanograms/kg per minute
- CC 30 mL/minute: 330 nanograms/kg per minute
- CC 20 mL/minute: 280 nanograms/kg per minute
- CC 10 mL/minute: 230 nanograms/kg per minute
- CC 5 mL/minute: 200 nanograms/kg per minute

Heart failure. Milrinone is one of several drugs that may be used in heart failure (p.1165), but because of an increased mortality rate reported following long-term oral use it is usually only given intravenously for short-term management of heart failure unresponsive to other treatments. The PROMISE (Prospective Randomized Milrinone Survival Evaluation) study[1] showed that oral milrinone increased morbidity and mortality in patients with severe chronic heart failure. However, more recently, longer-term continuous intravenous use for up to 8 weeks has been studied in patients awaiting heart transplantation and appeared to be well tolerated.[2] Intermittent use on several days a week has also been tried.[3]

In patients with acute exacerbation of heart failure, a prospective study[4] found no benefit from the routine use of short-term intravenous milrinone.

1. Packer M, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; **325:** 1468–75.
2. Mehra MR, *et al.* Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; **80:** 61–4.
3. Cesario D, *et al.* Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. *Am Heart J* 1998; **135:** 121–9.
4. Cuffe MS, *et al.* Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287:** 1541–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Corotrope; ***Austral.:*** Primacor; ***Austria:*** Corotrop; ***Belg.:*** Corotrope; ***Braz.:*** Primacor; ***Canad.:*** Primacor†; ***Chile:*** Corotrope; ***Cz.:*** Corotrop; ***Fr.:*** Corotrope; ***Ger.:*** Corotrop; ***Gr.:*** Corotrope; ***Hong Kong:*** Primacor; ***Hung.:*** Corotrope; ***India:*** Milicor; ***Israel:*** Primacor; ***Jpn:*** Milrila;

Malaysia: Primacor; ***Mex.:*** Primacor; ***Neth.:*** Corotrope; ***NZ:*** Primacor; ***Pol.:*** Corotrope; ***Port.:*** Corotrope; ***Singapore:*** Primacor; ***Spain:*** Corotrope; ***Swed.:*** Corotrop; ***Switz.:*** Corotrop; ***Thai.:*** Primacor; ***UK:*** Primacor; ***USA:*** Primacor; ***Venez.:*** Corotrope.

Minoxidil *(BAN, USAN, rINN)*

Minoksidiili; Minoksidilis; Minoxidilum; U-10858. 2,6-Diamino-4-piperidinopyrimidine 1-oxide.

Миноксидил

$C_9H_{15}N_5O$ = 209.2.

CAS — 38304-91-5.

ATC — C02DC01; D11AX01.

ATC Vet — QC02DC01.

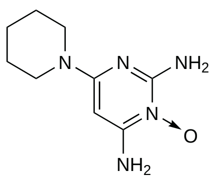

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Minoxidil). A white or almost white crystalline powder. Slightly soluble in water; soluble in methyl alcohol and in propylene glycol. Protect from light.

USP 31 (Minoxidil). A white or off-white crystalline powder. Slightly soluble in water; soluble in alcohol and in propylene glycol; practically insoluble in acetone, in chloroform, in ethyl acetate, and in petroleum spirit; sparingly soluble in methyl alcohol.

Adverse Effects and Treatment

Adverse effects commonly caused by minoxidil include reflex tachycardia, fluid retention accompanied by weight gain, oedema, and sometimes deterioration of existing heart failure and changes in the ECG. Hypertrichosis develops in up to 80% of patients within 3 to 6 weeks of the start of minoxidil therapy but is slowly reversible on discontinuation. Pericardial effusion, sometimes with associated tamponade, has been reported in about 3% of patients. Pericarditis may also occur. Minoxidil may aggravate or uncover angina pectoris. Other less frequent adverse effects include headache, nausea, gynaecomastia and breast tenderness, polymenorrhoea, allergic skin rashes, Stevens-Johnson syndrome, and thrombocytopenia.

Reflex tachycardia can be overcome by the use of a beta blocker, or alternatively methyldopa, and a diuretic (usually a loop diuretic) is used to reduce fluid retention. If excessive hypotension occurs, an intravenous infusion of sodium chloride 0.9% can be given to maintain the blood pressure. If a pressor agent is necessary, drugs such as adrenaline, which can aggravate tachycardia, should be avoided; phenylephrine, angiotensinamide, vasopressin, or dopamine may be given if there is evidence of inadequate perfusion of a vital organ.

Topical application of minoxidil may be associated with contact dermatitis, pruritus, local burning, and flushing; sufficient may be absorbed to produce systemic adverse effects. Changes in hair colour or texture may occur.

Effects on the eyes. Bilateral optic neuritis and retinitis occurred in a patient during treatment with minoxidil for hypertension after a renal transplant.[1] The patient was also taking prednisolone and azathioprine.

1. Gombos GM. Bilateral optic neuritis following minoxidil administration. *Ann Ophthalmol* 1983; **15:** 259–61.

Effects on the hair. The hypertrichosis frequently associated with oral minoxidil makes it generally unsuitable for women. There have also been reports of changes in hair colour.[1] In addition a case has been reported of increased hair loss, followed by subsequent regrowth of differently-coloured hair.[2] Substantial hair loss occurred in a woman after withdrawal of minoxidil and she had to wear a wig.[3]

Severe hypertrichosis has also been reported in 5 of 56 women applying minoxidil 5% solution topically for androgenetic alopecia.[4] Facial, arm, and leg hypertrichosis were reported 2 to 3 months after starting treatment. Hypertrichosis had disappeared 5 months after discontinuation of minoxidil.

1. Traub YM, *et al.* Treatment of severe hypertension with minoxidil. *Isr J Med Sci* 1975; **11:** 991–8.
2. Ingles RM, Kahn T. Unusual hair changes with minoxidil therapy. *Int J Dermatol* 1983; **22:** 120–2.
3. Kidwai BJ, George M. Hair loss with minoxidil withdrawal. *Lancet* 1992; **340:** 609–10.
4. Peluso AM, *et al.* Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; **136:** 118–20.

Effects on skeletal muscle. A polymyalgia syndrome, manifesting as fatigue, anorexia, weight loss, and severe pain in the shoulders and pelvic girdle, was seen in 4 men using topical minoxidil.[1] All symptoms improved within 2 to 4 weeks of stopping the drug. In 2 of the patients rechallenge produced a recurrence of symptoms.

1. Colamarino R, *et al.* Polymyalgia and minoxidil. *Ann Intern Med* 1990; **113:** 256–7.

Effects on the skin. Although skin reactions to systemic minoxidil do not appear to be common, cases of classic Stevens-Johnson syndrome have been reported.[1,2] The syndrome generally responds to withdrawal and corticosteroid therapy; in one case[1] subsequent rechallenge provoked a recurrence. In another patient an extensive erythematous weeping rash with lesions consistent with actinic keratosis also appeared to be due to minoxidil; bullous lesions recurred on re-exposure.[3] After topical application itching, scaling, flushing, and dermatitis have been the most common adverse effects; allergic contact dermatitis has been reported in rare instances.[4]

For other lesions associated with Kaposi's sarcoma and angioma, see Neoplasms, below, and for effects on the hair, see above.

1. DiSantis DJ, Flanagan J. Minoxidil-induced Stevens-Johnson syndrome. *Arch Intern Med* 1981; **141:** 1515.
2. Callen EC, *et al.* Stevens-Johnson syndrome associated with oral minoxidil: a case report. *J Nephrol* 2007; **20:** 91–3.
3. Ackerman BH, *et al.* Pruritic rash with actinic keratosis and impending exfoliation in a patient with hypertension managed with minoxidil. *Drug Intell Clin Pharm* 1988; **22:** 702–3.
4. Clissold SP, Heel RC. Topical minoxidil: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in alopecia areata and alopecia androgenetica. *Drugs* 1987; **33:** 107–22.

Neoplasms. Two haemorrhagic lesions with Kaposi's features appeared on the forehead, an unusual location for HIV-associated Kaposi's sarcoma, in an HIV-positive patient who had applied topical minoxidil there for 3 months.[1] In a healthy patient an angioma of the scalp developed after 2 months of topical minoxidil therapy. The patient had had a similar lesion as a baby. Minoxidil may induce angiogenesis or may stimulate endothelial cells, fibroblasts, and muscle cells to proliferate. Care should be taken when minoxidil is applied to the skin of people who are predisposed to neo-angiogenesis, or who are HIV-positive.

For other effects of minoxidil on the skin following topical application, see above.

1. Pavlovitch JH, *et al.* Angiogenesis and minoxidil. *Lancet* 1990; **336:** 889.

Precautions

Minoxidil is contra-indicated in phaeochromocytoma. It should be used with caution after a recent myocardial infarction, and in patients with pulmonary hypertension, angina pectoris, chronic heart failure, and significant renal impairment.

Topical application of minoxidil should be restricted to the scalp; it should not be applied to inflamed scalp skin or areas affected by psoriasis, severe sunburn, or severe excoriations, because of the risk of increased absorption. Patients being treated for hypertension should be monitored if topical minoxidil is used concurrently.

AIDS. For recommendations that topical minoxidil should be used with caution in HIV-positive patients, see Neoplasms under Adverse Effects, above.

Breast feeding. Study[1] of a breast-feeding mother showed that minoxidil was rapidly distributed into breast milk, achieving similar concentrations to those in the maternal plasma. No adverse effects were seen in the infant after 2 months and the American Academy of Pediatrics considers[2] that minoxidil is therefore usually compatible with breast feeding.

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. Minoxidil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Pregnancy. A patient who took minoxidil, propranolol, and furosemide throughout pregnancy delivered a normal infant at 37 weeks. Pregnancy was uneventful.[1]

1. Valdivieso A, *et al.* Minoxidil in breast milk. *Ann Intern Med* 1985; **102:** 135.

Interactions

The antihypertensive effect of minoxidil may be enhanced by use of other hypotensive drugs. Severe orthostatic hypotension may occur if minoxidil and sympathetic blocking drugs such as guanethidine are given concurrently.

Topical minoxidil should not be used with other topical agents known to enhance absorption, such as corticosteroids, retinoids, or occlusive ointment bases.

Tretinoin. Percutaneous absorption of minoxidil is enhanced by tretinoin as a result of increased stratum corneum permeability.[1]

1. Ferry JJ, *et al.* Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther* 1990; **47:** 439–46.

Pharmacokinetics

About 90% of an oral dose of minoxidil is absorbed from the gastrointestinal tract. The plasma half-life is about 4.2 hours although the haemodynamic effect may persist for up to 75 hours, presumably due to accumulation at its site of action. Minoxidil is not bound to plasma proteins. It is distributed into breast milk. Minoxidil is extensively metabolised by the liver. It requires sulfation to become active, but the major metabolite is a glucuronide conjugate. Minoxidil is excreted predominantly in the urine mainly in the form of metabolites. Minoxidil and its metabolites are dialysable, although the pharmacological effect is not reversed.

About 0.3 to 4.5% of a topical dose of minoxidil is absorbed from intact scalp.

◊ References.

1. Pacifici GM, *et al.* Minoxidil sulphation in human liver and platelets: a study of interindividual variability. *Eur J Clin Pharmacol* 1993; **45:** 337–41.

Uses and Administration

Minoxidil is an antihypertensive that acts mainly by causing direct peripheral vasodilatation of the arterioles. It produces effects on the cardiovascular system similar to those of hydralazine (p.1307). Minoxidil is given orally for the treatment of severe hypertension unresponsive to standard therapy (p.1171). When applied topically to the scalp minoxidil may stimulate hair growth to a limited extent and is used in the treatment of alopecia.

In the treatment of **hypertension** minoxidil is given with a beta blocker, or with methyldopa, to diminish the cardiac-accelerating effects, and with a diuretic, usually a loop diuretic, to control oedema. After a single oral dose, the maximum hypotensive effect usually occurs after 2 to 3 hours, although the full effects may not occur until after 3 to 7 days of continuous treatment. An initial dose of 5 mg of minoxidil daily (or 2.5 mg daily in the elderly) is gradually increased at intervals of not less than 3 days to 40 or 50 mg daily according to response; in exceptional circumstances up to 100 mg daily has been given. If more rapid control of blood pressure is required, dosage changes may be made every 6 hours with careful monitoring. The daily dose may be given as a single dose or in 2 divided doses. For children, the initial dose is 200 micrograms/kg daily, increased in steps of 100 to 200 micrograms/kg at intervals of not less than 3 days, until control of blood pressure has been achieved or a maximum of 1 mg/kg or 50 mg daily has been reached.

Reduced doses may be required in patients with renal impairment (see below).

In the treatment of **alopecia androgenetica** (male-pattern baldness) 1 mL of a 2% or 5% solution of minoxidil is applied twice daily to the scalp. The 5% solution is not recommended for women.

Administration in renal impairment. A study of the pharmacokinetics of minoxidil in patients with varying degrees of renal impairment found that the non-renal clearance was also impaired as renal function worsened.[1] Substantial accumulation of minoxidil might occur in these patients during multiple-dose therapy. It was advised that minoxidil be started with smaller doses or at longer dosage intervals in patients with renal impairment.

1. Halstenson CE, *et al.* Disposition of minoxidil in patients with various degrees of renal function. *J Clin Pharmacol* 1989; **29:** 798–802.

Alopecia. Minoxidil is used topically to stimulate hair growth in alopecia (p.1577), although its mechanism of action is poorly understood.[1] Increases in pigmented non-vellus hair may be due to thickening and pigmentation of existing vellus rather than new growth.[2] Measurement over 96 weeks showed[3] that minoxidil in solutions of 2 or 5% had a greater effect on hair weight than number of hairs in men with androgenetic alopecia (male-pattern baldness) with the 5% solution being more effective; 24 weeks after treatment was stopped both values had returned to baseline. Another study[4] also showed that 5% minoxidil had a greater effect than 2%, and produced an earlier response. However, 5% minoxidil has been found[5] less effective than oral finasteride. Even with continued use there is a waning of effect with minoxidil.[6,7] It may be more effective in retarding the progression of male-pattern baldness than in reversing it,[2] and users are advised to abandon treatment if there is insufficient benefit after a year.[8]

Minoxidil has also been used in women with female pattern hair loss, and as with men the 5% solution has been found[9] more effective than the 2%. In women with no evidence of biochemical hyperandrogenism minoxidil 2% was more effective[10] than oral cyproterone; where there was such evidence, cyproterone was superior.

Topical minoxidil has been shown to be safe in a large prospective study[11] of men and women with androgenetic alopecia.

Minoxidil appeared to have no beneficial effect on alopecia areata,[12] although one study indicated that topical minoxidil with 0.5% dithranol cream was more effective than either treatment alone.[13]

1. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol* 2004; **150:** 186–94.
2. Katz HI. Topical minoxidil: review of efficacy and safety. *Cutis* 1989; **43:** 94–8.
3. Price VH, *et al.* Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. *J Am Acad Dermatol* 1999; **41:** 717–21.
4. Olsen EA, *et al.* A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2002; **47:** 377–85.
5. Arca E, *et al.* An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia. *Dermatology* 2004; **209:** 117–25.
6. de Groot AC, *et al.* Minoxidil: hope for the bald? *Lancet* 1987; **i:** 1019–22.
7. Anonymous. Topical minoxidil does little for baldness. *Drug Ther Bull* 1989; **27:** 74–5.
8. Shrank AB. Treating young men with hair loss. *BMJ* 1989; **298:** 847–8.
9. Lucky AW, *et al.* A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol* 2004; **50:** 541–53.
10. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146:** 992–9.
11. Shapiro J. Safety of topical minoxidil solution: a one-year, prospective, observational study. *J Cutan Med Surg* 2003; **7:** 322–9.
12. Anonymous. Topical minoxidil for baldness: a reappraisal. *Med Lett Drugs Ther* 1994; **36:** 9–10.
13. Fiedler VC, *et al.* Treatment-resistant alopecia areata. *Arch Dermatol* 1990; **126:** 756–9.

CHEMOTHERAPY-INDUCED ALOPECIA. Minoxidil 2% solution was applied daily to the scalp of a boy with acute lymphoblastic leukaemia whose hair had failed to regrow satisfactorily after intensive chemotherapy.[1] Almost normal hair growth, achieved over a 9-month period, was attributed to the use of minoxidil.

A small study[2] in women undergoing combination chemotherapy including doxorubicin found that topical minoxidil applied throughout therapy and for up to 4 months afterwards reduced the duration of alopecia by an average of 50 days.

Other methods for reducing chemotherapy-induced alopecia are described under the Treatment of Adverse Effects of Antineoplastics, p.639.

1. Vickers MA, Barton CJ. Minoxidil induced hair growth after leukaemia treatment? *Arch Dis Child* 1995; **73:** 184.
2. Duvic M, *et al.* A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol* 1996; **35:** 74–8.

Preparations

BP 2008: Minoxidil Scalp Application;
USP 31: Minoxidil Tablets; Minoxidil Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Anagen; Ivix; Locemix; Macbirs Minoxidil; Minoxile; Toneon†; Tricolocion; Tricoplus; Tricoxane†; Ylox; ***Austral.:*** Loniten; Regaine; ***Austria:*** Loniten; Regaine; Rogaine; ***Belg.:*** Neoxidil; Regaine; ***Braz.:*** Loniten; Neoxidil†; Regaine; ***Canad.:*** Apo-Gain; Loniten; Minox†; Rogaine; ***Chile:*** Alopek; Regaine; Tricoxane; ***Cz.:*** Minoxitrim†; Neocapil; Regaine; ***Denm.:*** Regaine; ***Fin.:*** Recrea; Regaine†; Rogaine; ***Fr.:*** Alopexy; Alostil; Lonoten; Regaine; ***Ger.:*** Lonolox; Regaine; ***Gr.:*** Axelan; Botafex; Dermolantyl; Ebersedin; Hairway; Loniten; Lotorin; Minodril; Monoxidil†; Neo-Pruristam; Nherea; Oxofenil; Regaine; Stemeral; ***Hong Kong:*** Apo-Gain†; Hairgrow; Headway; Loniten; Minoxi; Neoxidil†; Regaine; Regro; ***Hung.:*** Neocapil; Regaine; ***India:*** Mintop; ***Indon.:*** Aloxid; Eminox; Regaine; Regrou; ***Irl.:*** Loniten; Rogaine; ***Israel:*** Alopexy; Hair-Treat; Hairgaine; Minoxi; Neoxidil; Regaine; ***Ital.:*** Aloxidil; Loniten; Minovital; Minoximen; Normoxidil†; Regaine; Tricoxidil; ***Malaysia:*** Apo-Gain; Epokelan†; Headway; Regaine; Regro; ***Mex.:*** Folcres†; Regaine; ***Neth.:*** Alopexy; Lonnoten; Regaine; ***Norw.:*** Regaine†; Rogaine; ***NZ:*** Headway; Rogaine; ***Philipp.:*** Regroe; ***Pol.:*** Loxon; Piloxidil; Regaine; ***Port.:*** Biocrinal; Crinalsofex; Hairtene; Loniten†; Mantai; Minocalve; Minox; Neoxidil; Regaine; Tricovivax; Zeldilon; ***Rus.:*** Regaine (Регейн); ***S.Afr.:*** Loniten; Regaine; ***Singapore:*** Growell; Minoxitrim; Neoxidil†; Regaine; Regro; ***Spain:*** Alopexy; Carexidil; Dinaxil Capilar; Lacovin; Loniten; Regaine; Regaxidil; Riteban†; ***Swed.:*** Recrea; Regaine†; Revexan; Rogaine; ***Switz.:*** Alopexy; Loniten; Neocapil; Piloxil†; Regaine; ***Thai.:*** Loniten; Manoxidil; Minoxitrim†; Modil; Noxidil; Nuhair; Regaine; Regrowth; Reten; ***UK:*** Loniten; Regaine; ***USA:*** Loniten†; Rogaine; ***Venez.:*** Guayaten; Regaine†; Topixidil; Zitoxil.

Multi-ingredient: ***Arg.:*** Tricoplus Conef†.

Mivazerol *(rINN)*

Mivazérol; Mivazerolum; UCB-22073. α-Imidazol-4-yl-2,3-cresotamide.

Мивазерол

$C_{11}H_{11}N_3O_2$ = 217.2.
CAS — 125472-02-8.

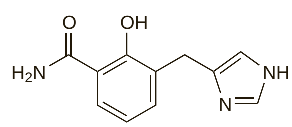

Profile

Mivazerol is an alpha$_2$-adrenoceptor agonist that has been investigated for the prevention of perioperative complications resulting from myocardial ischaemia in patients with ischaemic heart disease undergoing non-cardiac surgery.

◊ References.

1. Oliver MF, *et al.* Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: the European Mivazerol Trial (EMIT). *Anesthesiology* 1999; **91:** 951–61.

Moexipril Hydrochloride

(BANM, USAN, rINNM)

CI-925; Hidrocloruro de moexipril; Moeksipril Hidroklorür; Moexipril, Chlorhydrate de; Moexiprili Hydrochloridum; RS-10085-197; SPM-925. (3S-{2[R*(R*)],3R*})-2-(2-{[1-(Ethoxycarbonyl)-3-phenylpropyl]amino}-1-oxopropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline-carboxylic acid hydrochloride.

Моэксиприла Гидрохлорид

$C_{27}H_{34}N_2O_7,HCl$ = 535.0.
CAS — 103775-10-6 (moexipril); 82586-52-5 (moexipril hydrochloride).
ATC — C09AA13.
ATC Vet — QC09AA13.

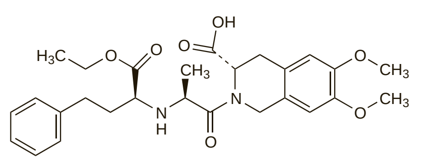

(moexipril)

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Moexipril acts as a prodrug of the diacid moexiprilat, its active metabolite. After oral doses moexipril is rapidly but incompletely absorbed and is metabolised to moexiprilat in the gastrointestinal mucosa and liver. Absorption is reduced in the presence of food. The bioavailability of moexiprilat is about 13% after oral doses of moexipril, and peak plasma concentrations of moexiprilat are reached in about 1.5 hours. Both moexipril and moexiprilat are moderately bound to plasma proteins. Moexipril is excreted mainly in the urine as moexiprilat, unchanged drug, and other metabolites; some moexiprilat may also be excreted in the faeces. The functional elimination half-life of moexiprilat is about 12 hours.

Uses and Administration

Moexipril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171).

Moexipril owes its activity to moexiprilat, to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for 2 to 4 weeks during chronic dosing. Moexipril is given orally as the hydrochloride.

In the treatment of hypertension, the usual initial dose of moexipril hydrochloride is 7.5 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 3.75 mg once daily, given under close medical supervision, is suggested for patients who are taking a *diuretic*; if possible the diuretic should be withdrawn 2 or 3 days before moexipril is started and resumed later if necessary. An initial dose of 3.75 mg once daily is also recommended for patients with renal or hepatic impairment and for the elderly.

The usual maintenance dose is 7.5 to 30 mg daily, which may be given in 2 divided doses if control is inadequate with a single dose.

◊ Reviews.

1. Brogden RN, Wiseman LR. Moexipril: a review of its use in the management of essential hypertension. *Drugs* 1998; **55:** 845–60.
2. Chrysant SG, Chrysant GS. Pharmacological and clinical profile of moexipril: a concise review. *J Clin Pharmacol* 2004; **44:** 827–36.

Administration in renal impairment. In patients with renal impairment (creatinine clearance 40 mL/minute or less) an initial dose of moexipril hydrochloride 3.75 mg is given; in the USA it is required that the maximum dose in such patients should not exceed 15 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Fempress; ***Cz.:*** Moex; ***Fr.:*** Moex; ***Ger.:*** Fempress; ***Gr.:*** Tensotec†; ***Hong Kong:*** Moex; ***Irl.:*** Perdix†; ***Israel:*** Perdix; ***Ital.:*** Femipres; ***Malaysia:*** Tensotec†; ***Philipp.:*** Univasc; ***Pol.:*** Cardiotensin; ***Port.:*** Tensotec; ***Rus.:*** Moex (Моэкс); ***S.Afr.:*** Perdix; ***Turk.:*** Univasc; ***UK:*** Perdix; ***USA:*** Univasc.

Multi-ingredient: ***Austria:*** Fempress Plus; ***Ger.:*** Fempress Plus; ***Ital.:*** Enulid; Femipres Plus; ***Philipp.:*** Uniretic; ***Rus.:*** Moex Plus (Моэкс Плюс); ***USA:*** Uniretic.

Molsidomine *(BAN, USAN, rINN)*

CAS-276; Molsidomiini; Molsidomin; Molsidomina; Molsidominum; Morsydomine; SIN-10. *N*-Ethoxycarbonyl-3-morpholinosydnonimine.

Молсидомин

$C_9H_{14}N_4O_4$ = 242.2.
CAS — 25717-80-0.
ATC — C01DX12.
ATC Vet — QC01DX12.

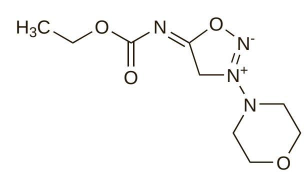

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Molsidomine). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in anhydrous alcohol and in dichloromethane. A 1% solution in water has a pH of 5.5 to 7.5. Protect from light.

Profile

Molsidomine is a nitrovasodilator used in angina pectoris (p.1157). It may also be used in heart failure (p.1165) and after myocardial infarction (below).

Molsidomine is given in usual oral doses of 1 to 4 mg two to four times daily. Modified-release preparations are also available. It is also given intravenously in single doses of 2 to 4 mg and doses of 2 mg may be repeated at intervals of at least 2 hours if necessary; total doses of up to 40 mg daily have been given. Infusions may be given at a rate of up to 3 mg/hour.

Molsidomine is metabolised to linsidomine (p.1325), an active metabolite.

Carcinogenicity. Molsidomine tends to degrade into morpholine (even when protected from the light), a compound considered potentially carcinogenic. This finding led to the suspension of marketing of one molsidomine formulation;[1] an earlier temporary suspension was related to evidence of carcinogenicity in some *animals*, although this has not been confirmed in humans.

1. Anonymous. Corvaton Tropfen. *Dtsch Apotheker Ztg* 1989; **129** (49): VI.

Myocardial infarction. Although intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) may be used in the management of acute myocardial infarction (p.1175), molsidomine and its active metabolite linsidomine (a nitric oxide donor) had no effect on mortality.[1]

1. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. *Lancet* 1994; **344:** 91–7.

Pharmacokinetics. The pharmacokinetics of molsidomine have been reviewed.[1] Molsidomine is metabolised in the liver to linsidomine and other morpholine derivatives. Prolonged elimination half-lives of molsidomine and linsidomine due to reduced plasma clearance have been reported in patients with liver cirrhosis.[2]

1. Rosenkranz B, *et al.* Clinical pharmacokinetics of molsidomine. *Clin Pharmacokinet* 1996; **30:** 372–84.
2. Spreux-Varoquaux O, *et al.* Pharmacokinetics of molsidomine and its active metabolite, linsidomine, in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; **32:** 399–401.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Molsicor; Molsidaine; ***Austria:*** Molsidolat; Molsihexal; ***Belg.:*** Coruno; Corvatard†; Corvaton; ***Cz.:*** Corvaton; Molsihexal; Molsiket; ***Fr.:*** Corvasal; ***Ger.:*** Corvaton; duracoron†; Molsi-Azu†; Molsi-Puren; Molsi†; Molsibeta; Molsihexal; molsiket; ***Hung.:*** Corvaton; ***Port.:*** Corvaton†; ***Rus.:*** Dilasidom (Диласидом); Sydnopharm (Сиднофарм); ***Spain:*** Corpea; Molsidain; ***Switz.:*** Corsifar†; Corvaton.

Monteplase *(rINN)*

E-6010; Monteplasa; Montéplase; Monteplasum.

Монтеплаза

$C_{2569}H_{3896}N_{746}O_{783}S_{39}$ = 59009.5.
CAS — 156616-23-8.

Profile

Monteplase is a thrombolytic related to alteplase (p.1207) that is used in acute myocardial infarction (p.1175) and venous thromboembolism (p.1189). For acute myocardial infarction, the usual dose is 27 500 units/kg given by intravenous injection as soon as possible after the onset of symptoms. For pulmonary embolism, the usual dose is 13 750 units/kg to 27 500 units/kg.

◊ References.

1. Kawai C, *et al.* A prospective, randomized, double-blind multicenter trial of a single bolus injection of the novel modified t-PA E6010 in the treatment of acute myocardial infarction: comparison with native t-PA. *J Am Coll Cardiol* 1997; **29:** 1447–53.
2. Inoue T, *et al.* A new thrombolytic agent, monteplase, is independent of the plasminogen activator inhibitor in patients with acute myocardial infarction: initial results of the COmbining Monteplase with Angioplasty (COMA) trial. *Am Heart J* 2002; **144:** E5.
3. Inoue T, *et al.* Long-term benefits of monteplase before coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 2005; **95:** 506–8.
4. Inoue T, *et al.* Therapeutic potential of monteplase in acute myocardial infarction. *Am J Cardiovasc Drugs* 2005; **5:** 225–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cleactor.

Moracizine *(BAN, rINN)*

EN-313; Moracizina; Moracizinum; Moricizine *(USAN)*. Ethyl [10-(3-morpholinopropionyl)phenothiazin-2-yl]carbamate.

Морацизин

$C_{22}H_{25}N_3O_4S$ = 427.5.
CAS — 31883-05-3.
ATC — C01BG01.
ATC Vet — QC01BG01.

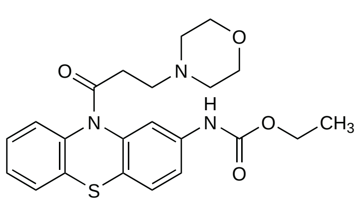

Moracizine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moracizina; Moracizine, Chlorhydrate de; Moracizinhydroklorid; Moracizini Hydrochloridum; Morasitsiinihydrokloridi.

Морацизина Гидрохлорид

$C_{22}H_{25}N_3O_4S,HCl$ = 464.0.
CAS — 29560-58-5.
ATC — C01BG01.
ATC Vet — QC01BG01.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Moricizine Hydrochloride). A white to off-white crystalline powder. Soluble in water and in alcohol. Store in airtight containers.

Adverse Effects

The most common adverse effects associated with moracizine affect the CNS and the gastrointestinal tract and include dizziness, headache, fatigue, nausea, and abdominal pain. Other adverse effects include dyspnoea, dry mouth, blurred vision, impotence, and urinary-tract disorders. There have been occasional reports of fever, thrombocytopenia, hepatic dysfunction, hypothermia, and skin rash.

Like other antiarrhythmics moracizine can provoke or worsen arrhythmias. This may range from an increase in the frequency of premature ventricular contractions to induction or worsening of ventricular tachycardia.

An increased mortality rate occurred when moracizine was tested in the control of asymptomatic ventricular arrhythmias in post-infarction patients (see Cardiac Arrhythmias under Uses and Administration, below).

Effects on body temperature. Fever with elevated creatine phosphokinase and hepatic transaminase concentrations was associated with moracizine in 2 patients.[1] The fever abated within 48 hours of stopping moracizine and recurred within 24 hours of rechallenge in both patients. Results suggested a similarity to the neuroleptic malignant syndrome that is associated with other phenothiazine derivatives.

1. Miura DS, *et al.* Ethmozine toxicity: fever of unknown origin. *J Clin Pharmacol* 1986; **26:** 153–5.

Precautions

As for Flecainide Acetate, p.1288.

Interactions

Use of moracizine with other antiarrhythmics or arrhythmogenic drugs may increase the incidence of cardiac arrhythmias. Moracizine undergoes metabolism in the liver and its activity may be influenced by other drugs affecting the enzymes responsible for its metabolism; it is an enzyme inducer and may also affect the activity of other hepatically-metabolised drugs.

Pharmacokinetics

Moracizine is readily and almost completely absorbed from the gastrointestinal tract. It undergoes significant first-pass hepatic metabolism so that the oral bioavailability is about 38%. Moracizine is extensively metabolised and some of the numerous metabolites may be active. It induces its own metabolism; the plasma elimination half-life is about 2 hours after multiple doses. Although plasma concentrations are reduced with multiple dosing, clinical response is not affected. It is about 95% bound to plasma proteins. Moracizine is distributed into breast milk. About 56% of a dose is excreted in the faeces and about 39% in the urine.

◊ References.

1. Benedek IH, *et al.* Enzyme induction by moricizine: time course and extent in healthy subjects. *J Clin Pharmacol* 1994; **34:** 167–75.

Uses and Administration

Moracizine is a phenothiazine compound that has class I antiarrhythmic activity (p.1153) but does not readily fall into the subclasses a, b, or c. It is used as the hydrochloride in the treatment of serious symptomatic ventricular arrhythmias. Moracizine hydrochloride is given orally in a usual dose of 600 to 900 mg daily in 2 or 3 divided doses. Treatment should be started in hospital, and doses should be adjusted at intervals of not less than 3 days. Doses should be reduced in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. Clyne CA, *et al.* Moricizine. *N Engl J Med* 1992; **327:** 255–60.

Administration in hepatic or renal impairment. The initial dose of moracizine hydrochloride in hepatic or renal impairment should be 600 mg or less daily and patients should be monitored closely (including ECG) before any adjustment of dose is made.

Cardiac arrhythmias. Moracizine is effective in various arrhythmias but is usually reserved for life-threatening ventricular arrhythmias; like other class I antiarrhythmics (see Cardiac Arrhythmias under Flecainide, p.1289), it has been associated with increased mortality when used prophylactically after myocardial infarction,[1] and is not recommended in such patients. However, there is limited evidence that it may be useful in some patients with supraventricular arrhythmias.[2,3]

1. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; **327:** 227–33.
2. Mehta AV, *et al.* Experience with moricizine HCl in children with supraventricular tachycardia. *Int J Cardiol* 1996; **57:** 31–5.
3. Geller JC, *et al.* Efficacy and safety of moricizine in the maintenance of sinus rhythm in patients with recurrent atrial fibrillation. *Am J Cardiol* 2001; **87:** 172–7.

Preparations

USP 31: Moricizine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Ethmozine†.

Moxisylyte Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxisilita; Moksisylyyttihydrokloridi; Moxisilita Clorhidrato; Moxisylyte, Chlorhydrate de; Moxisylythydroklorid; Moxisylyti Hydrochloridum; Moxisylytum Hydrochloridum; Thymoxamine Hydrochloride. 4-(2-Dimethylaminoethoxy)-5-isopropyl-2-methylphenyl acetate hydrochloride.

Моксизилита Гидрохлорид

$C_{16}H_{25}NO_3,HCl$ = 315.8.
CAS — 54-32-0 (moxisylyte); 964-52-3 (moxisylyte hydrochloride).
ATC — C04AX10; G04BE06.
ATC Vet — QC04AX10; QG04BE06.

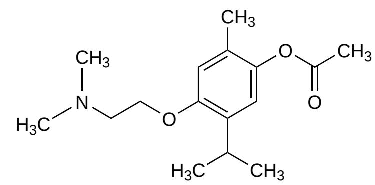

(moxisylyte)

NOTE. MOX, formerly THY, is a code approved by the BP 2008 for use on single unit doses of eye drops containing moxisylyte hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*

BP 2008 (Moxisylyte Hydrochloride). A white, odourless or almost odourless, crystalline powder. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether and in petroleum spirit. A 5% solution in water has a pH of 4.5 to 5.5. Protect from light.

Adverse Effects

Moxisylyte hydrochloride may cause nausea, diarrhoea, headache, vertigo, flushing of the skin, dry mouth, and nasal congestion. Hepatotoxicity has been reported. Overdosage may cause hypotension.

Transient ptosis has occurred occasionally after ophthalmic application. Prolonged erections or priapism have occurred rarely after intracavernosal injection and systemic effects may also occur.

Effects on the liver. Hepatic adverse reactions with moxisylyte first appeared in France after its use in benign prostatic hyperplasia, a condition in which relatively high doses were used (up to 480 mg daily compared with up to 320 mg daily for peripheral vascular disease). Since then the UK CSM has received reports associated with lower doses.[1] Thirteen hepatic reactions, accounting for 17% of all reports of suspected adverse reactions to moxisylyte, had been received. These comprised 3 cases of hepatic function abnormalities, 3 of jaundice, 4 of cholestatic jaundice, 2 of hepatitis, and 1 of hepatitis with jaundice. In most cases the reaction occurred within 5 weeks of the start of treatment and resolved on drug withdrawal. In 9 cases the dosage of moxisylyte was known and varied from 80 to 320 mg daily with 7 patients receiving 160 mg or less daily.

1. Committee on Safety of Medicines/Medicines Control Agency. Hepatic reactions with thymoxamine (Opilon). *Current Problems* 1993; **19:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 10/04/08)

Precautions

Moxisylyte hydrochloride should not be given to patients with active liver disease and should be given with care to patients with diabetes mellitus as it may theoretically decrease insulin requirements. Monitoring of liver function is recommended, especially if therapy is prolonged or if high doses are being used. Intracavernosal injection of moxisylyte is contra-indicated in patients with conditions that predispose to priapism.

Interactions

Moxisylyte may enhance the effects of antihypertensives and the hypotensive effect of moxisylyte may be enhanced by tricyclic antidepressants.

Uses and Administration

Moxisylyte is an alpha-adrenoceptor blocker with vasodilating activity. It is used by mouth in the treatment of peripheral vascular disease (p.1178) and has been self-administered by intracavernosal injection in erectile dysfunction (p.2179).

Moxisylyte is given as the hydrochloride but the dose may be expressed in terms of the base. Moxisylyte hydrochloride 45.2 mg is equivalent to about 40 mg of moxisylyte.

In the management of **peripheral vascular disease**, the usual oral dose is the equivalent of 40 mg of moxisylyte four times daily increased if necessary to 80 mg four times daily. It should be withdrawn if there is no response in 2 weeks.

Moxisylyte has been used locally in the eye to reverse the mydriasis caused by phenylephrine and other sympathomimetics. It has also been used orally in benign prostatic hyperplasia, although such use has been associated with hepatotoxicity; the doses used in prostatic hyperplasia were generally higher than those in peripheral vascular disease.

◊ Reviews.

1. Marquer C, Bressolle F. Moxisylyte: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in impotence. *Fundam Clin Pharmacol* 1998; **12:** 377–87.

Preparations

BP 2008: Moxisylyte Tablets.

Proprietary Preparations (details are given in Part 3)
Fr.: Carlytene; Icavex†; ***Irl.:*** Opilon; ***Port.:*** Arlitene†; ***UK:*** Opilon.

Moxonidine *(BAN, USAN, rINN)*

BDF-5895; BDF-5896; BE-5895; LY-326869; Moksonidi; Moksonidiini; Moksonidin; Moksonidinas; Moxonid; Moxonidin; Moxonidina; Moxonidinum; Moxonidum. 4-Chloro-5-(2-imidazolin-2-ylamino)-6-methoxy-2-methylpyrimidine.

Моксонидин

$C_9H_{12}ClN_5O$ = 241.7.

CAS — 75438-57-2.

ATC — C02AC05.

ATC Vet — QC02AC05.

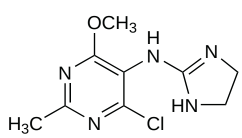

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Moxonidine). A white or almost white powder. Very slightly soluble in water and in acetonitrile; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol.

Adverse Effects and Treatment

Moxonidine has similar adverse effects to clonidine (p.1247) but causes less sedation. The incidence of dry mouth may also be lower.

Precautions

Moxonidine should not be used in patients with conduction disorders, bradycardia, severe arrhythmias, severe heart failure, severe ischaemic heart disease, severe hepatic or renal impairment, or a history of angioedema. Licensed product information suggests that it should also be avoided in patients with intermittent claudication or Raynaud's disease, Parkinson's disease, epilepsy, glaucoma, and depression. Moxonidine is distributed into breast milk and should not be used during breast feeding.

Although rebound hypertension has not been reported after moxonidine withdrawal it should not be stopped abruptly but should be withdrawn gradually over 2 weeks. As for clonidine (p.1247), if patients are also receiving a beta blocker, this should be stopped several days before moxonidine is withdrawn.

Interactions

The hypotensive effect of moxonidine may be enhanced by other antihypertensives and drugs that cause hypotension. The effect of sedatives and hypnotics, including benzodiazepines, may be enhanced by moxonidine.

Pharmacokinetics

Moxonidine is well absorbed when given orally and has a bioavailability of about 88%. Peak plasma concentrations occur 0.5 to 3 hours after an oral dose. It is excreted almost entirely in the urine as unchanged drug and metabolites; about 50 to 75% of an oral dose is excreted as unchanged drug. The mean plasma elimination half-life is 2 to 3 hours and is prolonged in renal impairment. Moxonidine is about 7% bound to plasma proteins. It is distributed into breast milk.

Uses and Administration

Moxonidine is a centrally acting antihypertensive structurally related to clonidine (p.1247). It appears to act through stimulation of central imidazoline receptors to reduce sympathetic tone, and also has alpha$_2$-adrenoceptor agonist activity. It is used in the treatment of hypertension (p.1171) and has also been investigated for heart failure (but see below).

In the treatment of hypertension, moxonidine is given orally in a usual initial dose of 200 micrograms once daily. The dose may be increased if necessary, after 3 weeks, to 400 micrograms daily as a single dose or in 2 divided doses, and after a further 3 weeks, to a maximum dose of 600 micrograms daily in 2 divided doses. The dose should be reduced in patients with renal impairment (see below).

◊ References.

1. Chrisp P, Faulds D. Moxonidine: a review of its pharmacology, and therapeutic use in essential hypertension. *Drugs* 1992; **44:** 993–1012.
2. Schachter M, *et al.* Safety and tolerability of moxonidine in the treatment of hypertension. *Drug Safety* 1998; **19:** 191–203.
3. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; **58:** 799–812.
4. Schachter M. Moxonidine. *Prescribers' J* 1999; **39:** 113–17.
5. Fenton C, *et al.* Moxonidine: a review of its use in essential hypertension. *Drugs* 2006; **66:** 477–96.

Administration in renal impairment. UK licensed product information states that in patients with moderate renal impairment (GFR 30 to 60 mL/minute) single doses of moxonidine should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms; moxonidine should not be given in severe impairment (GFR less than 30 mL/minute).

Heart failure. Heart failure is usually treated with diuretics, ACE inhibitors, and beta blockers (see p.1165). Beta blockers are thought to act by suppressing the sympathetic nervous system, which is activated in heart failure. Centrally-acting antihypertensives such as moxonidine also suppress sympathetic activation and might therefore have a role in heart failure. A study[1] in patients with heart failure found that moxonidine reduced plasma-noradrenaline concentrations and increased left ventricular ejection fraction, but also led to an increase in adverse effects. A further study[2] was stopped early due to increased mortality in the group receiving moxonidine.

1. Swedberg K, *et al.* Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002; **105:** 1797–1803.
2. Cohn JN, *et al.* Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003; **5:** 659–67.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Physiotens; ***Austria:*** Monox; Moxin; Normoxin; ***Belg.:*** Gilutens†; Moxon; ***Braz.:*** Cynt; ***Cz.:*** Cynt; Moxogamma; Moxostad; Physiotens; ***Denm.:*** Moxonat; Physiotens; ***Fin.:*** Physiotens; ***Fr.:*** Physiotens; ***Ger.:*** Cynt; Moxobeta; Moxocard; moxodura; Moxogamma; Physiotens; ***Gr.:*** Cynt; Fisiotens; ***Hong Kong:*** Physiotens; ***Hung.:*** Cynt; Moxogamma; Moxostad; Physiotens; ***Indon.:*** Physiotens; ***Ital.:*** Fisiotens; ***Malaysia:*** Physiotens; ***Neth.:*** Moxamar; Moxaviv; Moxoham; Moxonur; Moxotel; Moxovasc; Normatens; Ratiomox; ***Norw.:*** Physiotens; ***Philipp.:*** Physiotens; ***Pol.:*** Moxogamma; Physiotens; ***Port.:*** Moxon; ***Rus.:*** Cynt (Цинт)†; Physiotens (Физиотенз); ***S.Afr.:*** Physiotens; ***Singapore:*** Physiotens†; ***Spain:*** Moxon; ***Swed.:*** Physiotens; ***Switz.:*** Physiotens; ***Turk.:*** Cynt; ***UK:*** Physiotens.

Nadolol *(BAN, USAN, rINN)* ⊗

Nadololi; Nadololis; Nadololum; SQ-11725. (2*R*,3*S*)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.

Надолол

$C_{17}H_{27}NO_4$ = 309.4.

CAS — 42200-33-9.

ATC — C07AA12.

ATC Vet — QC07AA12.

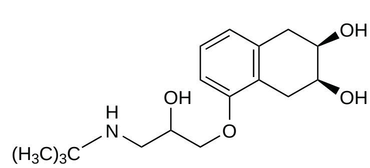

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Nadolol). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in alcohol; practically insoluble in acetone.

USP 31 (Nadolol). A white or off-white, practically odourless, crystalline powder. Soluble in water at pH 2; slightly soluble in water at pH 7 to 10; freely soluble in alcohol and in methyl alcohol; insoluble in acetone, in ether, in petroleum spirit, in trichloroethane, and in benzene; slightly soluble in chloroform, in dichloromethane, and in isopropyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Nadolol is distributed into breast milk and concentrations in milk are higher than those in maternal plasma. In a study[1] in 12 normotensive women given nadolol 80 mg daily by mouth for 5 days, the mean nadolol concentration in milk for the 24 hours after the last dose was 357 nanograms/mL; the equivalent mean serum-nadolol concentration was only 77 nanograms/mL. It was calculated that a 5-kg infant would therefore ingest about 2 to 7% of an equivalent adult dose. No adverse effects have been seen in breast-fed infants whose mothers were given nadolol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Devlin RG, *et al.* Nadolol in human serum and breast milk. *Br J Clin Pharmacol* 1981; **12:** 393–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Hypersensitivity pneumonitis was associated with nadolol in a patient given the drug for migraine.[1] Symptoms improved when nadolol was withdrawn.

1. Levy MB, *et al.* Nadolol and hypersensitivity pneumonitis. *Ann Intern Med* 1986; **105:** 806–7.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Nadolol is incompletely absorbed from the gastrointestinal tract to give peak plasma concentrations about 3 or 4 hours after a dose. It has low lipid solubility. Nadolol is widely distributed and concentrations found in breast milk have been higher than those in serum. It is only about 30% bound to plasma proteins. It does not appear to be metabolised and is excreted mainly in the urine. The plasma half-life has been reported as ranging from about 12 to 24 hours. Nadolol is reported to be dialysable.

◊ In 4 patients with mild hypertension given nadolol 2 mg orally or intravenously, the elimination half-life from plasma was an average of 10 to 12 hours (a range of 5.9 to 12.2 hours after intravenous doses, and a range of 9.6 to 14.2 hours after oral doses). Calculations based on urinary excretion and plasma concentration data suggested that about 33% was absorbed after oral dosage. There was evidence of biliary as well as urinary excretion since after intravenous dosage about 73% was excreted in urine and 23% in faeces. Nadolol did not appear to be metabolised.[1] In a similar study of therapeutic oral doses, terminal half-lives ranging from 14 to 17 hours were reported for nadolol 80 mg given as a single dose and the same dose daily in a multiple dosage regimen.[2]

1. Dreyfuss J, *et al*. Metabolic studies in patients with nadolol: oral and intravenous administration. *J Clin Pharmacol* 1977; **17:** 300–7.
2. Dreyfuss J, *et al.* Pharmacokinetics of nadolol, a beta-receptor antagonist: administration of therapeutic single- and multiple-dosage regimens to hypertensive patients. *J Clin Pharmacol* 1979; **19:** 712–20.

Children. The pharmacokinetics of nadolol given intravenously and orally were studied in six children aged 3 months to 14 years.[1] The elimination half-lives for the two oldest children aged 10 and 14 years were 7.3 and 15.7 hours, respectively. These values are similar to those reported for adults whereas in the children 22 months of age or younger, shorter half-lives of 3.2 to 4.3 hours were found. The shorter half-lives were probably a result of a reduction in the total apparent volume of distribution of nadolol in the youngest children. Elimination rates were similar after either intravenous or oral dosage.

1. Mehta AV, *et al.* Pharmacokinetics of nadolol in children with supraventricular tachycardia. *J Clin Pharmacol* 1992; **32:** 1023–7.

Uses and Administration

Nadolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity. Nadolol is given orally in the management of hypertension (p.1171), angina pectoris (p.1157), and cardiac arrhythmias (p.1160). It is also used in the management of hyperthyroidism (p.2165) and in the prophylactic treatment of migraine (p.616).

In the treatment of **hypertension**, nadolol is usually given in an initial dose of 40 to 80 mg once daily, increased weekly according to response to 240 mg or more daily.

In **angina pectoris**, the usual initial dose is 40 mg once daily, increased weekly according to response to usual doses of up to 160 mg daily; some patients may require up to 240 mg daily. Doses of 40 to 160 mg once daily have also been given for **cardiac arrhythmias**.

Doses of 40 to 160 mg once daily are used in **migraine** prophylaxis.

As an adjunct in the treatment of **hyperthyroidism**, doses of 80 to 160 mg once daily have been given; most patients are reported to require the higher dose.

Patients with renal impairment may require a reduction in dose (see below).

Administration in renal impairment. Nadolol is excreted mainly in the urine and doses should be reduced in patients with renal impairment, usually by increasing the dosage interval. For patients with hypertension or angina pectoris, US licensed product information recommends the following dosage intervals, based on creatinine clearance (CC):

- CC between 31 and 50 mL/minute per 1.73 m^2: give every 24 to 36 hours
- CC between 10 and 30 mL/minute per 1.73 m^2: give every 24 to 48 hours
- CC less than 10 mL/minute per 1.73 m^2: give every 40 to 60 hours.

Preparations

USP 31: Nadolol and Bendroflumethiazide Tablets; Nadolol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Corgard; ***Belg.:*** Corgard; ***Braz.:*** Corgard; ***Canad.:*** Apo-Nadol; Corgard; ***Chile:*** Corgard; ***Fr.:*** Corgard; ***Ger.:*** Solgol; ***Hong Kong:*** Apo-Nadol; Corgard†; ***Ital.:*** Corgard; ***Malaysia:*** Corgard†; ***Mex.:*** Corgard; ***NZ:*** Corgard; ***Port.:*** Anabet; ***S.Afr.:*** Corgard; ***Spain:*** Corgard; Solgol; ***Switz.:*** Corgard; ***UK:*** Corgard; ***USA:*** Corgard; ***Venez.:*** Corgard.

Multi-ingredient: ***Ger.:*** Sotaziden N; ***Mex.:*** Corgaretic; ***S.Afr.:*** Corgaretic; ***UK:*** Corgaretic†; ***USA:*** Corzide.

Nadroparin Calcium *(BAN, rINN)*

CY-216; Nadropariinikalsium; Nadroparin Kalsiyum; Nadroparin vápenatá sůl; Nadroparina cálcica; Nadroparine calcique; Nadroparinkalcium; Nadroparin-kalcium; Nadroparino kalcio druska; Nadroparinum calcicum.

Надропарин Кальций

ATC — B01AB06.
ATC Vet — QB01AB06.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nadroparin Calcium). It is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3600 and 5000, with a characteristic value of 4300. The mass percentage of chains lower than 2000 is not more than 15%. The degree of sulfation is about 2 per disaccharide unit.

The potency is not less than 95 units and not more than 130 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 2.5 and 4.0.

Profile

Nadroparin calcium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p.1157).

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used. For *prophylaxis* of **venous thromboembolism** during surgery, patients at moderate risk of thrombosis are given 2850 units of nadroparin calcium by subcutaneous injection daily for at least 7 days or until the patient is ambulant; the first dose is given 2 to 4 hours before the procedure. For patients at high risk of thrombosis the dose is adjusted according to body-weight. Usual doses are 38 units/kg 12 hours before surgery, 12 hours postoperatively and then daily until 3 days after the procedure; the dose is then increased by 50% to 57 units/kg daily. The total duration of treatment should be at least 10 days.

For the *treatment* of thromboembolism, nadroparin calcium is given in a dose of 85 units/kg by subcutaneous injection every 12 hours for up to 10 days. Alternatively, a dose of 171 units/kg is given once daily.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** sessions lasting less than 4 hours, nadroparin calcium is given into the arterial line of the circuit at the beginning of the dialysis session. The usual dose is 2850 units for patients weighing less than 50 kg, 3800 units for patients weighing 50 to 69 kg, and 5700 units for patients weighing 70 kg or more. Doses should be reduced in patients at high risk of haemorrhage.

In the management of unstable **angina**, nadroparin calcium is given subcutaneously in a dose of 86 units/kg every 12 hours, for about 6 days. An initial dose of 86 units/kg may be given intravenously. Low-dose aspirin should also be given.

Elimination of nadroparin is prolonged in renal impairment, and doses may need to be reduced in moderate or severe impairment.

◊ References.

1. Barradell LB, Buckley MM. Nadroparin calcium: a review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs* 1992; **44:** 858–88.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fraxiparine; ***Austria:*** Fraxiparin; ***Belg.:*** Fraxiparine; Fraxodi; ***Braz.:*** Fraxiparina; ***Canad.:*** Fraxiparine; ***Chile:*** Fraxiparine; ***Cz.:*** Fraxiparine; ***Fr.:*** Fraxiparine; Fraxodi; ***Ger.:*** Fraxiparin; Fraxodi; ***Gr.:*** Fraxiparine; ***Hong Kong:*** Fraxiparine; ***Hung.:*** Fraxiparine; Fraxodi; ***Indon.:*** Fraxiparine; ***Israel:*** Fraxiparine; ***Ital.:*** Fraxiparina; Fraxodi; Seledie; Seleparina; ***Malaysia:*** Fraxiparine; ***Mex.:*** Fraxiparine; Fraxodi; ***Neth.:*** Fraxiparine; Fraxodi; ***Norw.:*** Fraxiparine†; ***NZ:*** Fraxiparine†; ***Philipp.:*** Fraxiparine; ***Pol.:*** Fraxiparine; Fraxodi; ***Port.:*** Fraxiparina; Fraxodi; ***Rus.:*** Fraxiparine (Фраксипарин); ***S.Afr.:*** Fraxiparine; ***Singapore:*** Fraxiparine; ***Spain:*** Fraxiparina; ***Swed.:*** Fraxiparine†; ***Switz.:*** Fraxiforte; Fraxiparine; ***Thai.:*** Fraxiparine; ***Turk.:*** Fraxiparine; Fraxodi; ***Venez.:*** Fraxiparina.

Naftidrofuryl Oxalate *(BANM, rINNM)*

EU-1806; LS-121; Nafronyl Oxalate *(USAN)*; Naftidrofuril-hidrogén-oxalát; Naftidrofurilio-vandenilio oksalatas; Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl, hydrogénooxalate de; Naftidrofuryl, Oxalate de; Naftidrofuryli hydrogenooxalas; Naftidrofuryli Oxalas; Naftidrofuryl-oxalát; Naftidrofurylväteoxalat; Naftidrofuryylivetyoksalaatti; Oxalato de naftidrofurilo. 2-Diethylaminoethyl 3-(1-naphthyl)-2-tetrahydrofurfurylpropionate hydrogen oxalate.

Нафтидрофурила Оксалат

$C_{24}H_{33}NO_3,C_2H_2O_4$ = 473.6.
CAS — 31329-57-4 (naftidrofuryl); 3200-06-4 (naftidrofuryl oxalate).
ATC — C04AX21.
ATC Vet — QC04AX21.

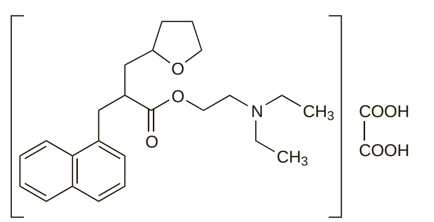

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl Oxalate BP 2008). A white or almost white powder. Freely soluble in water; freely soluble or soluble in alcohol; slightly or sparingly soluble in acetone.

Adverse Effects

Naftidrofuryl oxalate given orally may cause nausea and epigastric pain. Rash has been reported occasionally. Hepatitis or hepatic failure has occurred rarely. Convulsions and depression of cardiac conduction may occur after overdosage. After intravenous use cardiac arrhythmias, hypotension, and convulsions have been reported and intravenous preparations have been withdrawn from the market (see below).

◊ In early 1995 the UK CSM published details of adverse reactions to naftidrofuryl.[1] After parenteral doses of naftidrofuryl 47 reports of 79 reactions had been received, the most serious consequences being 9 cases of cardiac arrhythmias, 3 of convulsions, and 2 of hypotension. It was also noted that 2 fatal cases of cardiac arrest had occurred in Germany after bolus intravenous doses and it was stressed that the drug must not be given as a bolus but as a slow intravenous infusion. Additionally, 16 reports, including one fatality, of hepatitis or hepatic failure associated with oral naftidrofuryl had been received although this appeared to be a rare reaction.

Later in 1995, after a review conducted in the UK and Europe, it was announced by the CSM that intravenous naftidrofuryl was to be withdrawn.[2] It was considered that the risks of cardiac and neurological toxicity outweighed the benefits of intravenous dosage in peripheral vascular disease. The oral form of naftidrofuryl would remain available.

1. Committee on Safety of Medicines/Medicines Control Agency. Adverse reactions with naftidrofuryl (Praxilene). *Current Problems* 1995; **21:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Withdrawal of naftidrofuryl infusion (Praxilene Forte). *Current Problems* 1995; **21:** 7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)

Effects on the kidneys. Calcium oxalate crystals in the renal tubules of 2 patients with acute renal failure[1] were associated with the high amounts of oxalate they had received when naftidrofuryl oxalate was given intravenously.

1. Moesch C, *et al.* Renal intratubular crystallisation of calcium oxalate and naftidrofuryl oxalate. *Lancet* 1991; **338:** 1219–20.

Uses and Administration

Naftidrofuryl oxalate is used as a vasodilator in the treatment of peripheral (p.1178) and cerebral vascular disorders (p.1165). It is also claimed to enhance cellular oxidative capacity thereby protecting cells against the results of ischaemia.

Naftidrofuryl oxalate is given orally in usual doses of 100 to 200 mg three times daily for peripheral vascular disorders and 100 mg three times daily for cerebrovascular disorders.

Naftidrofuryl oxalate has also been given parenterally. However, intravenous use has been associated with serious adverse effects (see above) and intravenous preparations have been withdrawn.

◊ References.

1. De Backer TLM, *et al.* Naftidrofuryl for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

Preparations

BP 2008: Naftidrofuryl Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Iridus†; ***Austria:*** Dusodril; Naftodril; ***Belg.:*** Praxilene; ***Braz.:*** Iridux; ***Cz.:*** Enelbin; ***Fr.:*** Di-Actane; Gevatran; Naftilux; Praxilene; ***Ger.:*** Artocoron†; Azunaftil†; Dusodril; Nafti; Naftilong; ***Gr.:*** Praxilene; ***Hong Kong:*** Praxilene; ***Hung.:*** Naftilong; ***Indon.:*** Frilix; Nafoxal; Praxilene; Vascuprax; ***Irl.:*** Praxilene; ***Ital.:*** Praxilene; ***Mex.:*** Iridus; ***Philipp.:*** Praxilene; ***Port.:*** Praxilene; ***Singapore:*** Praxilene; ***Spain:*** Praxilene; ***Switz.:*** Praxilene; Sodipryl retard; ***Thai.:*** Praxilene; ***UK:*** Praxilene; ***Venez.:*** Fuxaten†; Iridus.

Nasaruplase *(rINN)*

Nasaruplasa; Nasaruplasum; Prourokinase, Glycosylated. Prourokinase (enzyme-activating) (human clone pA3/pD2/pF1 protein moiety), glycosylated.

Назаруплаза

CAS — 99821-44-0.

NOTE. The term prourokinase has been used for both nasaruplase and saruplase (p.1390).

Nasaruplase Beta *(USAN, rINN)*

Abbott-74187; ABT-187; Nasaruplasa beta; Nasaruplase Bêta; Nasaruplasum Beta. Prourokinase (enzyme-activating) human (clone pUK4/pUK18 protein moiety), glycosylated (murine cell line SP2/0).

Назаруплаза Бета

CAS — 136653-69-5.

Profile

Nasaruplase is a thrombolytic under investigation in acute ischaemic stroke.

◊ References.

1. Furlan A, *et al.* Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA* 1999; **282:** 2003–11.

Nateplase *(rINN)*

Nateplasa; Natéplase; Nateplasum. A mixture of *N*-[N^2-(*N*-glycyl-L-alanyl)-L-arginyl]plasminogen activator (human tissue-type 1-chain form, protein moiety), glycoform β (major component) and plasminogen activator (human tissue-type 1-chain form, protein moiety), glycoform β.

Натеплаза

CAS — 159445-63-3.

Profile

Nateplase is a thrombolytic related to alteplase (p.1207) that has been used in acute myocardial infarction (p.1175).

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Milyzer†.

Natriuretic Peptides ⊗

Péptidos natriuréticos.

Profile

Natriuretic peptides are endogenous substances that possess diuretic, natriuretic, and vasodilator properties. Three types are known. *Atrial natriuretic peptide* (ANP), also known as atrial natriuretic factor (ANF), atriopeptin, auriculin, or cardionatrin, is produced mainly in the cardiac atria, although another form, ularitide (urodilatin), is produced in the kidney. *Brain natriuretic peptide* (BNP, B-type natriuretic peptide) was originally isolated from brain tissue but is now known to be mainly produced by the cardiac ventricles. *C-type natriuretic peptide* (CNP) is produced by the endothelium and appears to act locally as a vasodilator but has little natriuretic effect.

Natriuretic peptides have an important physiological role in fluid and electrolyte homoeostasis and in the regulation of blood pressure, and they interact closely with other complex systems such as the renin-angiotensin-aldosterone cascade. Plasma concentrations of atrial natriuretic peptide and brain natriuretic peptide are altered in some pathological states and have been used as indicators of cardiac function. Natriuretic peptides that have been investigated for therapeutic use include anaritide, a synthetic form of atrial natriuretic peptide, and ularitide; both have been studied in acute renal failure, and ularitide has also been studied in heart failure. Recombinant forms of atrial natriuretic peptide (carperitide, p.1241) and brain natriuretic peptide (nesiritide, p.1347) are used in the management of acute heart failure.

The currently available natriuretic peptides have short half-lives and have to be given parenterally. Other approaches to manipulating their effects have been investigated, including the use of atriopeptidase inhibitors (neutral endopeptidase inhibitors; neutral metalloendopeptidase inhibitors), such as candoxatrilat and ecadotril (sinorphan) to prolong the half-life of endogenous atrial natriuretic peptide. Compounds such as omapatrilat (p.1361) that inhibit both neutral endopeptidase and angiotensin-converting enzyme are also being studied.

◊ References.

1. Tan ACITL, *et al.* Atrial natriuretic peptide: an overview of clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 1993; **24:** 28–45.
2. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart* 1996; **76** (suppl 3): 36–44.
3. Wilkins MR, *et al.* The natriuretic-peptide family. *Lancet* 1997; **349:** 1307–10.
4. Levin ER, *et al.* Natriuretic peptides. *N Engl J Med* 1998; **339:** 321–8.
5. Lewis J, *et al.* Atrial natriuretic factor in oliguric acute renal failure: Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis* 2000; **36:** 767–74.
6. Forssmann W, *et al.* The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001; **51:** 450–62.
7. de Lemos JA, *et al.* B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003; **362:** 316–22.
8. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; **92:** 843–9.
9. Mitrovic V, *et al.* Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006; **27:** 2823–32.
10. Lüss H, *et al.* Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008; **155:** 1012.e1–8.

Nebivolol *(BAN, USAN, rINN)* ⊗

Narbivolol; Nébivolol; Nebivololi; Nebivololum; R-65824.
(1*RS*,1′*RS*)-1,1′-[(2*RS*,2′*SR*)-Bis(6-fluorochroman-2-yl)]-2,2′-iminodiethanol.

Небиволол

$C_{22}H_{25}F_2NO_4$ = 405.4.

CAS — 99200-09-6; 118457-14-0.

ATC — C07AB12.

ATC Vet — QC07AB12.

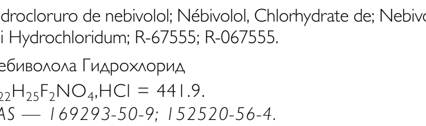

Nebivolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de nebivolol; Nébivolol, Chlorhydrate de; Nebivololi Hydrochloridum; R-67555; R-067555.

Небиволола Гидрохлорид

$C_{22}H_{25}F_2NO_4$,HCl = 441.9.

CAS — 169293-50-9; 152520-56-4.

ATC — C07AB12.

ATC Vet — QC07AB12.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Nebivolol is rapidly absorbed after oral doses. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, *N*-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolisers the elimination half-life of nebivolol is about 10 hours and that of the hydroxy metabolites is about 24 hours. Peak plasma concentrations of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.

Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and faeces, almost entirely as metabolites. Nebivolol is distributed into breast milk in *animals*.

Uses and Administration

Nebivolol is a cardioselective beta blocker (p.1225). It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Nebivolol is used in the management of hypertension (p.1171), and as an adjunct to standard therapy in patients aged 70 years and older with stable chronic heart failure (p.1165). It is given orally as the hydrochloride although doses are expressed in terms of the base; 5.45 mg of nebivolol hydrochloride is equivalent to about 5 mg of base.

In **hypertension** the usual initial dose of nebivolol is 5 mg once daily. US licensed product information allows the dose to be increased, if necessary, at intervals of 2 weeks, to a maximum dose of 40 mg once daily. Dosage reduction may be necessary in the elderly and in patients with hepatic or renal impairment (see below).

In **heart failure** the initial dose of nebivolol is 1.25 mg once daily. If tolerated, the dose should be doubled every 1 to 2 weeks up to a maximum of 10 mg once daily.

◊ Reviews.

1. Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006; **66:** 1389–1409.
2. Veverka A, *et al.* Nebivolol: a third-generation β-adrenergic blocker. *Ann Pharmacother* 2006; **40:** 1353–60.
3. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. *Drugs* 2007; **67:** 1097–1107.
4. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory β -blocker. *J Clin Pharmacol* 2008; **48:** 225–39.

Administration in the elderly. UK licensed product information states that, for hypertension, patients over 65 years of age should be given an initial dose of 2.5 mg of nebivolol once daily, increased to 5 mg once daily if required.

Administration in hepatic impairment. UK licensed product information contra-indicates the use of nebivolol in patients with hepatic impairment. In the USA, licensed product information also contra-indicates nebivolol in severe hepatic impairment (Child-Pugh higher than class B) but patients with moderate hepatic impairment may be given nebivolol for hypertension in an initial oral dose of 2.5 mg once daily, increased with caution if required.

Administration in renal impairment. UK licensed product information states that in hypertension the initial dose of nebivolol should be reduced to 2.5 mg once daily in patients with renal impairment, increased to 5 mg once daily for maintenance if required. US licensed product information similarly recommends an initial dose of 2.5 mg once daily in patients with severe renal impairment (creatinine clearance below 30 mL/minute); the dose may be increased cautiously if required.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nebilet; ***Austria:*** Nomexor; ***Belg.:*** Nobiten; ***Chile:*** Nebilet; ***Cz.:*** Nebilet; Nebispes; ***Fr.:*** Nebilox; Temerit; ***Ger.:*** Nebilet; ***Gr.:*** Lobivon; ***Hung.:*** Nebilet; ***India:*** Nodon; ***Irl.:*** Nebilet; ***Ital.:*** Lobivon; Nebilox; ***Neth.:*** Hypoloc; Lobivon; Nebilet; Nebiloc; ***Pol.:*** Nebilet; ***Port.:*** Hypoloc; Nebilet; ***Rus.:*** Nebilet (Небилет); ***S.Afr.:*** Nebilet; ***Singapore:*** Nebilet; ***Spain:*** Lobivon; Nebilet; Nebilox; Silostar; ***Switz.:*** Nebilet; ***Thai.:*** Nebilet; ***Turk.:*** Vasoxen; ***UK:*** Nebilet; ***USA:*** Bystolic; ***Venez.:*** Nebilet.

Nesiritide Citrate *(USAN, rINNM)* ⊗

Citrato de nesiritida; Nésiritide, Citrate de; Nesiritidi Citras.

Незиритида Цитрат

$C_{143}H_{244}N_{50}O_{42}S_4,xC_6H_8O_7$.

CAS — 124584-08-3 (nesiritide); 189032-40-4 (nesiritide citrate).

ATC — C01DX19.

ATC Vet — QC01DX19.

Incompatibility. The manufacturer states that nesiritide injection is physically and/or chemically incompatible with heparin, insulin, sodium etacrynate, bumetanide, enalaprilat, hydralazine, furosemide, and the preservative sodium metabisulfite. Nesiritide binds to heparin and should not be given through heparin-coated central catheters.

Adverse Effects and Precautions

The most common adverse effects of nesiritide relate to vasodilatation and include hypotension, headache, and dizziness. Nausea and vomiting, abdominal pain, back pain, angina pectoris, insomnia, and anxiety, have also been reported. Cardiac arrhythmias have occurred but may be associated with the underlying condition. Adverse effects on renal function have been reported. If hypotension occurs the infusion of nesiritide should be stopped or the dose reduced and general supportive measures should be used; the hypotension may persist for several hours.

Nesiritide should not be used as primary therapy in patients with cardiogenic shock or with hypotension. It is not recommended in patients with low cardiac filling pressures or in those for whom vasodilators are inappropriate, such as those with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade.

Effects on the kidneys. Nesiritide has both haemodynamic and neurohormonal effects on the kidneys and has been reported to worsen renal function. A meta-analysis[1] found that nesiritide significantly increased the risk of worsening renal function in patients with acute heart failure, and there is some evidence[2] that this may be related to the duration of treatment. However, a randomised trial[3] in patients with acute heart failure and pre-existing renal impairment found that the effect of nesiritide on renal function was neutral.

1. Sackner-Bernstein JD, *et al.* Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; **111:** 1487–91. Correction. *ibid.*; 2274.
2. Chow SL, *et al.* Effect of nesiritide infusion duration on renal function in acutely decompensated heart failure patients. *Ann Pharmacother* 2007; **41:** 556–61.
3. Witteles RM, *et al.* Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; **50:** 1835–40.

Effects on mortality. Although nesiritide improves haemodynamics in patients with acute decompensated heart failure, its effects on mortality are controversial.[1] A retrospective study[2] comparing nesiritide with inotrope therapy or glyceryl trinitrate in patients with acute decompensated heart failure found a similar risk of in-hospital mortality with nesiritide and glyceryl trinitrate, which was significantly lower than the risk with inotrope therapy. However, a meta-analysis[3] of controlled studies comparing nesiritide with non-inotrope control therapy found that there was a trend to higher mortality at 30 days in patients given nesiritide; the results were not statistically significant, but became so after correction of the number of deaths in one of the studies.[4] A later meta-analysis[5] also found a trend towards increased mortality with nesiritide at 30 days, but the results again were not statistically significant, and there was no difference in mortality between nesiritide and control patients at 180 days.

1. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; **30:** 765–81.
2. Abraham WT, *et al.* In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46:** 57–64.
3. Sackner-Bernstein JD, *et al.* Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293:** 1900–5.
4. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006; **296:** 1465–6.
5. Arora RR, *et al.* Short and long-term mortality with nesiritide. *Am Heart J* 2006; **152:** 1084–90.

Interactions

The risk of hypotension may be increased in patients receiving nesiritide with other drugs that lower blood pressure.

Pharmacokinetics

Nesiritide is cleared from the circulation by 3 mechanisms: uptake into cells; proteolytic cleavage by endopeptidases; and excretion by the kidneys. It has a biphasic elimination, with a terminal elimination half-life of 18 minutes.

Uses and Administration

Nesiritide is a recombinant brain natriuretic peptide (see p.1347) used in the management of acutely decompensated heart failure (p.1165). It is given intravenously as the citrate, but dosage is expressed in terms of the base. The initial dose of nesiritide is 2 micrograms/kg by intravenous injection over 1 minute, followed by a maintenance infusion of 10 nanograms/kg per minute.

Heart failure. The use of nesiritide in acute decompensated heart failure (p.1165) has been reviewed.[1,2] It may be used for short-term treatment as an alternative to standard intravenous therapy with vasodilators, inotropes, or diuretics, and appears to have no proarrhythmic effects; however, its effects on mortality are controversial (see under Adverse Effects and Precautions, above) and its role in therapy remains unclear. There is some evidence from retrospective studies that it may be safely used in addition to standard therapy[3,4] and may have a role as a more prolonged treatment in patients awaiting cardiac transplantation.[5] Although nesiritide has also been given intermittently for outpatient management of chronic heart failure, this use is not currently recommended.[6]

1. Vichiendilokkul A, *et al.* Nesiritide: a novel approach for acute heart failure. *Ann Pharmacother* 2003; **37:** 247–58.
2. Keating GM, Goa KL. Nesiritide: a review of its use in acute decompensated heart failure. *Drugs* 2003; **63:** 47–70.
3. O'Dell KM, *et al.* Nesiritide for secondary pulmonary hypertension in patients with end-stage heart failure. *Am J Health-Syst Pharm* 2005; **62:** 606–9.
4. Smull DL, Jorde UP. Concomitant use of nesiritide and milrinone in decompensated congestive heart failure. *Am J Health-Syst Pharm* 2005; **62:** 291–5.
5. Witteles R, *et al.* B-type natriuretic peptide is effective therapy before care. *Ann Intern Med* 2004; **141:** 895.
6. Bauer JB, Randazzo MA. Nesiritide for outpatient treatment of heart failure. *Am J Health-Syst Pharm* 2005; **62:** 2639–42.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Natrecor; ***Indon.:*** Natrecor; ***Israel:*** Noratak; ***Switz.:*** Noratak; ***USA:*** Natrecor; ***Venez.:*** Natrecor.

Nicardipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de nicardipino; Nicardipine, Chlorhydrate de; Nicardipini Hydrochloridum; Nikardipiinihydrokloridi; Nikardipin Hidroklorür; Nikardipinhydroklorid; RS-69216; RS-69216-XX-07-0; YC-93. 2-[Benzyl(methyl)amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate hydrochloride.

Никардипина Гидрохлорид

$C_{26}H_{29}N_3O_6,HCl = 516.0.$

CAS — 55985-32-5 (nicardipine); 54527-84-3 (nicardipine hydrochloride).

ATC — C08CA04.

ATC Vet — QC08CA04.

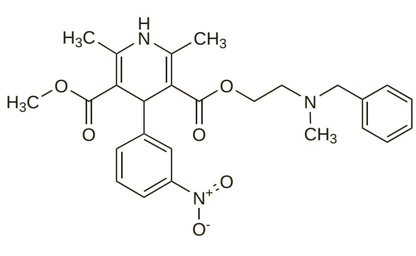

(nicardipine)

Pharmacopoeias. In *Chin.* and *Jpn.*

Incompatibility. The manufacturers recommend that a solution containing nicardipine hydrochloride 100 micrograms/mL is used for intravenous infusion. Suitable diluents are solutions of glucose or sodium chloride. Sodium bicarbonate and lactated Ringer's are incompatible with nicardipine infusion. Nicardipine hydrochloride (1 mg/mL in glucose 5%) has also been reported[1] to be visually incompatible with furosemide, heparin, and thiopental.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nicardipine is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first-pass hepatic metabolism. Bioavailability of about 35% has been reported after a 30-mg dose at steady state. The pharmacokinetics of nicardipine are non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. There is also considerable interindividual variation in plasma-nicardipine concentrations. Nicardipine is more than 95% bound to plasma proteins. Nicardipine is extensively metabolised in the liver and is excreted in the urine and faeces, mainly as inactive metabolites. The terminal plasma half-life is about 8.6 hours, thus steady-state plasma concentrations are achieved after 2 to 3 days of dosing three times daily.

◊ References.

1. Graham DJM, *et al.* Pharmacokinetics of nicardipine following oral and intravenous administration in man. *Postgrad Med J* 1984; **60** (suppl 4): 7–10.
2. Graham DJM, *et al.* The metabolism and pharmacokinetics of nicardipine hydrochloride in man. *Br J Clin Pharmacol* 1985; **20:** 23S–28S.
3. Razak TA, *et al.* The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. *Clin Pharmacol Ther* 1990; **47:** 463–9.
4. Porchet HC, Dayer P. Serum concentrations and effects of (±)-nicardipine compared with nifedipine in a population of healthy subjects. *Clin Pharmacol Ther* 1990; **48:** 155–60.

Uses and Administration

Nicardipine is a dihydropyridine calcium-channel blocker with actions and uses similar to nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Nicardipine hydrochloride is generally given orally although the intravenous route has been used for the short-term treatment of hypertension.

Oral doses of nicardipine hydrochloride are similar for both **hypertension** and **angina**. The initial dose is 20 mg three times daily and may be increased at intervals of at least 3 days until the required effect is achieved. The usual maintenance dose is 30 mg three times daily, but daily doses of between 60 and 120 mg in divided doses may be given. Modified-release preparations of nicardipine hydrochloride for dosage twice daily are also available.

Nicardipine hydrochloride may be given by slow intravenous infusion as a 100 micrograms/mL solution in the short-term treatment of hypertension. An initial infusion rate of 5 mg/hour is recommended, increased, as necessary, up to a maximum of 15 mg/hour and subsequently reduced to 3 mg/hour. For use in children, see below.

Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. Curran MP, *et al.* Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs* 2006; **66:** 1755–82.

Administration in children. Intravenous infusion of nicardipine has been used in both infants and children for the management of hypertension. In studies[1-4] in children aged between 2 days and 17 years, initial doses ranged from 0.2 to 5 micrograms/kg per minute, with maintenance infusions of 0.15 to 6 micrograms/kg per minute. Adverse effects were rare; one study[4] reported adverse effects in 5 of 31 treatment courses, including tachycardia, flushing, palpitations, and hypotension. There has also been a report[5] of the successful use of intravenous infusion of nicardipine in 8 preterm infants (gestational age 28 to 36 weeks). Infusions were given at a dose of 0.5 to 2 micrograms/kg per minute and continued for periods of 3 to 36 days. No hypotension, oedema, or tachycardia were observed.

The *BNFC* suggests that neonates and children up to age 18 years may be given nicardipine hydrochloride by continuous intravenous infusion for the management of hypertensive crises. The initial dose is 500 nanograms/kg per minute, adjusted according to response; the usual maintenance dose is 1 to 4 micrograms/kg per minute, with a maximum dose of 250 micrograms/minute.

1. Treluyer JM, *et al.* Intravenous nicardipine in hypertensive children. *Eur J Pediatr* 1993; **152:** 712–4.
2. Sartori SC, *et al.* Intravenous nicardipine for treatment of systemic hypertension in children. *Pediatrics* 1999; **104** (suppl): 676–7.
3. Tobias JD. Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001; **8:** 3–6.
4. Flynn JT, *et al.* Intravenous nicardipine for treatment of severe hypertension in children. *J Pediatr* 2001; **139:** 38–43.
5. Gouyon JB, *et al.* Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child* 1997; **76:** F126–F127.

Administration in hepatic or renal impairment. Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment. The US manufacturers recommend an initial dose of 20 mg twice daily by mouth in patients with hepatic impairment.

Cerebrovascular disorders. Nicardipine has been reported to increase cerebral blood flow[1] and use by various routes has been investigated for possible benefit in haemorrhagic[2-5] and ischaemic stroke[6,7] (p.1185), although nimodipine (p.1357) is the dihydropyridine calcium-channel blocker usually used. Nicardipine has also been tried[8] in patients with cerebrovascular insufficiency. However, studies have produced inconclusive results.

1. Savage I, James I. The effect of nicardipine hydrochloride on cerebral blood flow in normotensive volunteers. *Br J Clin Pharmacol* 1986; **21:** 591P–592P.
2. Suzuki M, *et al.* Intrathecal administration of nicardipine hydrochloride to prevent vasospasm in patients with subarachnoid hemorrhage. *Neurosurg Rev* 2001; **24:** 180–4.
3. Kasuya H, *et al.* Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans. *Stroke* 2002; **33:** 1011–15.
4. Dorhout Mees SM, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/07/08).
5. Barth M, *et al.* Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study. *Stroke* 2007; **38:** 330–6.
6. Yao L, Ding D. Effect of nicardipine on somatosensory evoked potentials in patients with acute cerebral infarction. *J Neurol Neurosurg Psychiatry* 1990; **53:** 844–6.
7. Rosenbaum D, *et al.* Early treatment of ischemic stroke with a calcium antagonist. *Stroke* 1991; **22:** 437–41.
8. Silva APE, Diament CK. Nicardipine versus cinnarizine in cerebrovascular insufficiency. *Curr Ther Res* 1988; **43:** 888–99.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Karden; ***Belg.:*** Rydene; ***Fr.:*** Loxen; ***Ger.:*** Antagonil; ***Indon.:*** Perdipine; ***Irl.:*** Cardene†; ***Ital.:*** Bionicard; Cardioten; Cardip; Cordisol†; Lisanirc; Neucor; Nicant†; Nicapress; Nicardal; Nicarpin; Nicaven; Nimicor; Niven†; Perdipina; Ranvil†; Vasodin; ***Jpn:*** Perdipine; ***Malaysia:*** Cardepine; ***Neth.:*** Cardene; ***Philipp.:*** Cardepine; ***Port.:*** Nerdipina; ***Singapore:*** Cardibloc; ***Spain:*** Dagan; Flusemide; Lecibral; Lincil; Lucenfal; Nerdipina; Vasonase; ***Thai.:*** Cardepine; Nerdipine†; ***Turk.:*** Loxen; ***UK:*** Cardene; ***USA:*** Cardene.

Niceritrol *(BAN, rINN)*

Nicéritrol; Niceritrolum; Nikeritroli; PETN. Pentaerythritol tetranicotinate; 2,2-Bis(hydroxymethyl)propane-1,3-diol tetranicotinate.

Ницеритрол

$C_{29}H_{24}N_4O_8 = 556.5.$

CAS — 5868-05-3.

ATC — C10AD01.

ATC Vet — QC10AD01.

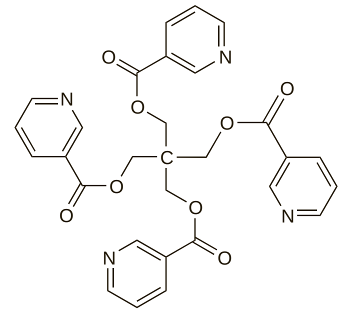

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. In *Jpn.*

Profile

Niceritrol, an ester of pentaerythritol and nicotinic acid, has general properties similar to those of nicotinic acid (p.1957), to which it is slowly hydrolysed. Niceritrol has been used as a lipid regulating drug in hyperlipidaemias and as a vasodilator in the treatment of peripheral vascular disease.

◊ References.

1. Owada A, *et al.* Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med* 2003; **114:** 347–53.

Nicorandil *(BAN, USAN, rINN)*

Nicorandilum; SG-75. *N*-[2-(Nitroxy)ethyl]-3-pyridinecarboxamide.

Никорандил

$C_8H_9N_3O_4$ = 211.2.

CAS — 65141-46-0.

ATC — C01DX16.

ATC Vet — QC01DX16.

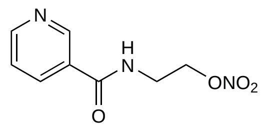

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Adverse effects reported with nicorandil are headache (which is usually transitory and seen at the start of therapy), cutaneous vasodilatation and flushing, nausea, vomiting, dizziness, and weakness. Rarely reported effects include myalgia, skin rashes, and oral ulceration, and there have been very rare reports of angioedema and hepatic function abnormalities. A reduction in blood pressure and/or an increase in heart rate may occur with high doses.

Nicorandil is contra-indicated in patients with cardiogenic shock, left ventricular failure with low filling pressures, and hypotension. In patients with hypovolaemia, low systolic blood pressure, acute pulmonary oedema, or acute myocardial infarction with acute left ventricular failure and low filling pressures, nicorandil should preferably be avoided but may be used with caution.

Incidence of adverse effects. Postmarketing surveillance for nicorandil was carried out by prescription-event monitoring[1] of 13 620 patients, and showed that adverse reactions occurred in 175. The most frequent was headache, occurring in 58 patients, mainly in the first month of treatment. Unspecified adverse effects occurred in 36 patients. Other effects included dizziness (19), nausea (17), malaise (13), palpitations (8), flushing and vomiting (6 each), and lassitude (4). Rare adverse effects included 3 cases each of angioedema and photosensitivity.

1. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.

Ulceration. Nicorandil has been associated with ulceration of mucosal surfaces. Painful, large aphthous ulcers on the *tongue* and *oral mucosa* have been reported[1-3] in patients receiving nicorandil for angina. The ulcers were usually resistant to treatment but all healed when nicorandil was withdrawn. Colchicine or thalidomide treatment has improved ulcers associated with nicorandil in a few patients, but relapse occurred when the colchicine or thalidomide was stopped.[3] However, a large study[4] casts some doubt on the evidence for a causal link between nicorandil and oral ulceration, although it was suggested that this could be further investigated.

Anal ulceration has been reported[5-7] in patients taking nicorandil. Healing of the ulcers occurred in those patients in whom nicorandil was withdrawn.

Multiple ulcers of the upper and lower *gastrointestinal tract*, in addition to oral and anal ulceration, have been reported[8] in a patient taking nicorandil; all of the ulcers healed when nicorandil was stopped. There have also been several cases of *peristomal* ulceration, which resolved after stopping nicorandil.[9]

Perivulval ulceration has also been reported, and in 1 case was associated with a *cutaneous* ulcer.[10] Another patient[11] developed both perianal and leg ulcers, both of which improved rapidly when nicorandil was stopped.

1. Cribier B, *et al.* Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998; **138:** 372–3.
2. Desruelles F, *et al.* Giant oral aphthous ulcers induced by nicorandil. *Br J Dermatol* 1998; **138:** 712–13.
3. Agbo-Godeau S, *et al.* Association of major aphthous ulcers and nicorandil. *Lancet* 1998; **352:** 1598–9.
4. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.
5. Watson A, *et al.* Nicorandil associated anal ulceration. *Lancet* 2002; **360:** 546–7.
6. Vella M, Molloy RG. Nicorandil-associated anal ulceration. *Lancet* 2002; **360:** 1979.
7. Passeron T, *et al.* Chronic anal ulceration due to nicorandil. *Br J Dermatol* 2004; **150:** 394–6.
8. Egred M, *et al.* Nicorandil may be associated with gastrointestinal ulceration. *BMJ* 2006; **332:** 889.
9. Ogden S, *et al.* Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; **156:** 608–9.
10. Claeys A, *et al.* Cutaneous, perivulvar and perianal ulcerations induced by nicorandil. *Br J Dermatol* 2006; **155:** 494–6.
11. McKenna DJ, *et al.* Nicorandil-induced leg ulceration. *Br J Dermatol* 2007; **156:** 394–6.

Interactions

Nicorandil should not be used with phosphodiesterase type-5 inhibitors such as sildenafil as the hypotensive effect of nicorandil may be significantly enhanced.

Pharmacokinetics

Nicorandil is well absorbed from the gastrointestinal tract and maximum plasma concentrations are achieved 30 to 60 minutes after oral doses. Metabolism is mainly by denitration and about 20% of a dose is excreted in the urine mainly as metabolites. The elimination half-life is about 1 hour. Nicorandil is only slightly bound to plasma proteins.

Uses and Administration

Nicorandil is a nitrate derivative of nicotinamide (p.1957) and acts as a vasodilator. It is a potassium-channel opener (p.1155) providing vasodilatation of arterioles and large coronary arteries and its nitrate component produces venous vasodilatation through stimulation of guanylate cyclase. It thus reduces both preload and afterload, and improves coronary blood flow.

Nicorandil is given orally for prevention and long-term treatment of **angina pectoris**, including reduction of the risk of acute coronary events in high-risk patients (p.1157). The usual initial oral dose is 10 mg twice daily (or 5 mg twice daily in patients susceptible to headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10 to 20 mg twice daily.

Nicorandil is also given intravenously in the management of **unstable angina** and **acute heart failure** (p.1165). For unstable angina, a solution containing 100 to 300 micrograms/mL is given by intravenous infusion in a dose of 2 mg/hour, adjusted according to response, to a maximum dose of 6 mg/hour. For acute heart failure, a solution containing 400 to 2500 micrograms/mL is used; the usual dose is 200 micrograms/kg given by intravenous injection over 5 minutes, followed by continuous intravenous infusion at a dose of 200 micrograms/kg per hour. The dosage should be adjusted according to response, within the range of 50 to 200 micrograms/kg per hour.

◊ General references.

1. Markham A, *et al.* Nicorandil: an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000; **60:** 955–74.
2. Gomma AH, *et al.* Potassium channel openers in myocardial ischaemia: therapeutic potential of nicorandil. *Drugs* 2001; **12:** 1705–10.
3. Anonymous. Nicorandil for angina – an update. *Drug Ther Bull* 2003; **41:** 86–8.
4. Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs* 2004; **64:** 1941–55.

Ischaemic heart disease. A large multicentre double-blind randomised placebo-controlled study[1] suggested that nicorandil, in addition to its anti-anginal effects, may have cardioprotective properties. The incidence of major coronary events, particularly unplanned admission for chest pain, was significantly reduced in patients with stable angina at high risk of future adverse events. Nicorandil may mimic the mechanism of ischaemic pre-conditioning, whereby a brief period of ischaemia makes the myocardium resistant to damage from a further episode,[2] but it is not clear how much this mechanism contributes to its effects. There is some evidence[3-7] that nicorandil improves outcomes when given at the time of percutaneous coronary intervention, although a large study[8] in patients with myocardial infarction failed to confirm a benefit. It has been suggested[5] that an antioxidant effect may be part of the mechanism involved.

1. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002; **359:** 1269–75. Correction. *ibid.*; **360:** 806.
2. Lesnefsky EJ. The IONA study: preparing the myocardium for ischaemia? *Lancet* 2002; **359:** 1262–3.
3. Matsuo H, *et al.* Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K+ channel opener nicorandil. *Eur Heart J* 2003; **24:** 1296–1303.
4. Ikeda N, *et al.* Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. *Heart* 2004; **90:** 181–5.
5. Ono H, *et al.* Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. *Am Heart J* 2004; **148:** E15.
6. Ishii H, *et al.* Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; **112:** 1284–8.
7. Ishii H, *et al.* Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. *Diabetes Care* 2006; **29:** 202–6.
8. Kitakaze M, *et al.* J-WIND investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet* 2007; **370:** 1483–93.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Ikorel; ***Austria:*** Dancor; ***Denm.:*** Angicor; ***Fr.:*** Adancor; Ikorel; ***India:*** Corflo; Zynicor; ***Irl.:*** Ikorel; ***Ital.:*** Andilex†; ***Jpn:*** Sigmart; ***Neth.:*** Dancor; Ikorel; ***NZ:*** Ikorel; ***Port.:*** Dancor; Nikoril; ***Spain:*** Dancor; ***Switz.:*** Dancor; ***UK:*** Ikorel.

Nicotinyl Alcohol *(BAN, USAN)*

3-Hydroxymethylpyridine; Nicotinic Alcohol; Nicotinílico, alcohol; NSC-526046; NU-2121; 3-Pyridinemethanol; β-Pyridylcarbinol; Ro-1-5155. 3-Pyridylmethanol.

C_6H_7NO = 109.1.

CAS — 100-55-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

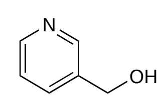

Nicotinyl Alcohol Tartrate *(BANM)*

Alcohol nicotinílico, tartrato de; Nicotinyl Tartrate. 3-Pyridylmethanol hydrogen (2*R*,3*R*)-tartrate.

$C_6H_7NO,C_4H_6O_6$ = 259.2.

CAS — 6164-87-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

Pharmacopoeias. In *Br.*

BP 2008 (Nicotinyl Alcohol Tartrate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.8 to 3.7.

Profile

Nicotinyl alcohol is a vasodilator and lipid regulating drug with general properties similar to those of nicotinic acid (p.1957), to which it is partly hydrolysed.

Nicotinyl alcohol has been given orally, as the tartrate, in the management of peripheral vascular disease, and has also been used in Ménière's disease and in hyperlipidaemias.

Preparations

BP 2008: Nicotinyl Alcohol Tablets.

Proprietary Preparations (details are given in Part 3)
Indon.: Cetacol; ***Pol.:*** Nicotol†.

Multi-ingredient: ***Braz.:*** Lipofacton.

Nifedipine *(BAN, USAN, rINN)*

Bay-a-1040; Nifedipiini; Nifedipin; Nifedipina; Nifedipinas; Nifédipine; Nifedipino; Nifedipinum. Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

Нифедипин

$C_{17}H_{18}N_2O_6$ = 346.3.

CAS — 21829-25-4.

ATC — C08CA05.

ATC Vet — QC08CA05.

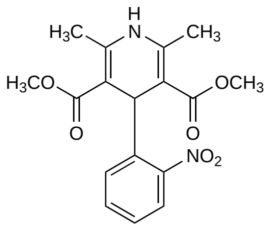

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 31 (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.

Stability. Yellow food colourings such as curcumin have been used[1] to slow photodegradation of nifedipine solutions. An extemporaneously prepared solution of nifedipine in a peppermint-flavoured vehicle was reported[2] to be stable for at least 35 days when stored in amber glass bottles.

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.
2. Dentinger PJ, *et al.* Stability of nifedipine in an extemporaneously compounded oral solution. *Am J Health-Syst Pharm* 2003; **60:** 1019–22.

Adverse Effects

The most common adverse effects of nifedipine are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, and palpitations. Nausea and other gastrointestinal disturbances, increased micturition frequency, lethargy, eye pain, visual disturbances, and mental depression have also occurred. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

There have been reports of rashes (including erythema multiforme), fever, and abnormalities in liver function, including cholestasis, due to hypersensitivity reactions. Gingival hyperplasia, myalgia, tremor, and impotence have been reported.

Some tablets formulated for once-daily use are covered in a membrane which is not digested and may cause gastrointestinal obstruction; bezoars may rarely occur.

Overdosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur.

Nifedipine has been reported to be teratogenic in *animals*.

Effects on mortality. Since 1995 there have been reports and reviews that have implicated calcium-channel blockers (particularly short-acting nifedipine and high doses) in increasing cardiovascular[1] and overall mortality.[2] Possible links with cancer, haemorrhage, and depression and suicide are discussed separately (see Cancer Occurrence, Effects on the Blood, and Effects on Mental Function, below, respectively).

In response, the US National Heart, Lung, and Blood Institute issued a statement warning that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and myocardial infarction,[3] and in some countries short-acting nifedipine preparations have been withdrawn. However, there has been much debate and controversy over the reports that questioned the safety of calcium-channel blockers.[4-6]

A review by the WHO/ISH pointed out that much of the evidence for adverse effects comes from observational studies or small randomised studies and concluded that, as there was insufficient evidence to confirm either benefit or harm, recommendations on the management of angina, hypertension, and myocardial infarction should remain unchanged.[7] In addition, many of the studies that led to the negative reports used the older short-acting calcium-channel blockers. The calcium-channel blockers used now are largely modified-release formulations of short half-life blockers or are calcium-channel blockers with long half-lives.

Studies completed after the WHO/ISH review have generally failed to show any increase in mortality with calcium-channel blockers, although their effects on cardiovascular outcomes remain less clear. A placebo-controlled study (SYST-EUR) reported[8] a reduction in incidence of stroke and cardiovascular events in 4695 elderly patients treated with nitrendipine (and enalapril and hydrochlorothiazide in addition if necessary) for isolated systolic hypertension, while a retrospective cohort study[9] in post-myocardial infarction patients failed to show any increase in mortality after one year in those receiving calcium-channel blockers. Another cohort study[10] in patients with hypertension also found no overall increase in mortality with calcium-channel blockers, although there was a trend towards a higher rate with short-acting formulations. A meta-analysis[11] of randomised studies comparing calcium-channel blockers with other antihypertensives in patients with hypertension suggested that calcium-channel blockers were associated with an increased risk of major cardiovascular events (except stroke) although all-cause mortality was not increased. However, large, long-term studies have found no difference in cardiovascular outcomes or overall mortality in patients randomised to amlodipine or chlortalidone,[12] while a lower incidence of cardiovascular events was reported for amlodipine compared with atenolol.[13] A long-term study[14] of nifedipine added to standard therapy in patients with stable angina also found no increased mortality, and there was a reduced need for coronary interventions.

1. Psaty BM, *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274:** 620–5.
2. Furberg CD, *et al.* Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92:** 1326–31.
3. McCarthy M. US NIH issues warning on nifedipine. *Lancet* 1995; **346:** 689–90.
4. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation* 1995; **92:** 1068–72.
5. Grossman E, Messerli FH. Calcium antagonists in cardiovascular disease: a necessary controversy but an unnecessary panic. *Am J Med* 1997; **102:** 147–9.
6. Stanton AV. Calcium channel blockers. *BMJ* 1998; **316:** 1471–3.
7. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
8. Staessen JA, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350:** 757–64. Correction. *ibid.*; 1636.
9. Jollis JG, *et al.* Calcium channel blockers and mortality in elderly patients with myocardial infarction. *Arch Intern Med* 1999; **159:** 2341–8.
10. Abascal VM, *et al.* Calcium antagonists and mortality risk in men and women with hypertension in the Framingham Heart Study. *Arch Intern Med* 1998; **158:** 1882–6.
11. Pahor M, *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356:** 1949–54.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.
13. Dahlöf B, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.
14. Poole-Wilson PA, *et al* on behalf of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004; **364:** 849–57.

Carcinogenicity. An observational study carried out between 1988 and 1992 suggested that calcium-channel blockers were associated with an increased risk of cancer.[1] Subsequent studies have failed to support this finding.[2-7] A review by the WHO/ISH concluded that there is no good evidence that calcium-channel blockers increase cancer risk,[8] and the biological basis for an effect of calcium-channel blockers on cancer risk has also been questioned.[9] The large, long-term, randomised Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[10] found no increase in the incidence of cancer in patients receiving a calcium-channel blocker (amlodipine) compared with those receiving a diuretic (chlortalidone).

1. Pahor M, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348:** 493–7.
2. Jick H, *et al.* Calcium-channel blockers and risk of cancer. *Lancet* 1997; **349:** 525–8.
3. Rosenberg L, *et al.* Calcium channel blockers and the risk of cancer. *JAMA* 1998; **279:** 1000–4.
4. Braun S, *et al.* Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol* 1998; **31:** 804–8.
5. Sajadieh A, *et al.* Verapamil and risk of cancer in patients with coronary artery disease. *Am J Cardiol* 1999; **83:** 1419–22.
6. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.
7. Cohen HJ, *et al.* Calcium channel blockers and cancer. *Am J Med* 2000; **108:** 210–15.
8. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
9. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999; **34:** 1857–66.
10. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.

Effects on the blood. Treatment with nifedipine significantly reduces platelet aggregation *in vitro*[1] and results indicating inhibition of platelet function in healthy subjects receiving oral (but not intravenous) nifedipine have been reported.[2,3] Thus, concern has been expressed[4] that calcium-channel blockers may have the potential to produce haemorrhagic complications in surgical patients (specifically, those undergoing coronary bypass surgery). Major surgical bleeding was associated with nimodipine in patients undergoing cardiac valve replacement,[5] although it has been used in other situations apparently without an increased risk of bleeding.[6]

Conflicting results have been reported with regard to the risk of gastrointestinal bleeding. A prospective cohort study in 1636 elderly hypertensive patients,[7] and a subsequent case-control study,[8] reported that calcium-channel blockers were associated with an increased risk of gastrointestinal haemorrhage compared with beta blockers. However, it was suggested[9] that this may have been due to a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers, and another study[10] also suggested that the risk of gastrointestinal bleeding was not materially increased by calcium-channel blockers.

Calcium-channel blockers have also been associated with a number of blood dyscrasias; there have been case reports of aplastic anaemia with nifedipine,[11] and of thrombocytopenia with amlodipine[12] and with diltiazem.[13,14]

1. Ośmiałwska Z, *et al.* Effect of nifedipine monotherapy on platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1990; **39:** 403–4.
2. Winther K, *et al.* Dose-dependent effects of verapamil and nifedipine on in vivo platelet function in normal volunteers. *Eur J Clin Pharmacol* 1990; **39:** 291–3.
3. Walley TJ, *et al.* The effects of intravenous and oral nifedipine on ex vivo platelet function. *Eur J Clin Pharmacol* 1989; **37:** 449–52.
4. Becker RC, Alpert JS. The impact of medical therapy on hemorrhagic complications following coronary artery bypass grafting. *Arch Intern Med* 1990; **150:** 2016–21.
5. Wagenknecht LE, *et al.* Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995; **310:** 776–7.
6. Öhman J and others. Surgical bleeding and calcium antagonists. *BMJ* 1995; **311:** 388–9. [Several letters.]
7. Pahor M, *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347:** 1061–5.
8. Kaplan RC, *et al.* Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; **160:** 1849–55.
9. Suissa S, *et al.* Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; **105:** 230–5.
10. Kelly JP, *et al.* Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; **353:** 559.
11. Laporte J-R, *et al.* Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; **352:** 619–20.
12. Usalan C, *et al.* Severe thrombocytopenia associated with amlodipine treatment. *Ann Pharmacother* 1999; **33:** 1126–7.
13. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
14. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on the brain. Cerebral ischaemia[1,2] has been reported in small numbers of patients given nifedipine.

1. Nobile-Orazio E, Sterzi R. Cerebral ischaemia after nifedipine treatment. *BMJ* 1981; **283:** 948.
2. Schwartz M, *et al.* Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med* 1990; **150:** 686–7.

Effects on carbohydrate metabolism. There are reports of deterioration of diabetes,[1] reduction in glucose tolerance,[2] and development of diabetes[1,3] in patients given nifedipine. Nifedipine has also been reported to increase plasma-glucose concentrations.[3,4] However, other reports and studies have found no change in glucose tolerance in either diabetic or non-diabetic patients taking nifedipine.[5-10]

See also Diabetes Mellitus under Precautions, below.

1. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
2. Giugliano D, *et al.* Impairment of insulin secretion in man by nifedipine. *Eur J Clin Pharmacol* 1980; **18:** 395–8.
3. Zezulka AV, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 437–8.
4. Charles S, *et al.* Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 19–20.
5. Harrower ADB, Donnelly T. Hyperglycaemic effect of nifedipine. *BMJ* 1981; **283:** 796.
6. Greenwood RH. Hyperglycaemic effect of nifedipine. *BMJ* 1982; **284:** 50.
7. Abadie E, Passa P. Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 438.
8. Dante A. Nifedipine and fasting glycemia. *Ann Intern Med* 1986; **104:** 125–6.
9. Whitcroft I, *et al.* Calcium antagonists do not impair long-term glucose control in hypertensive non-insulin dependent diabetics (NIDDS). *Br J Clin Pharmacol* 1986; **22:** 208P.
10. Tentorio A, *et al.* Insulin secretion and glucose tolerance in non-insulin dependent diabetic patients after chronic nifedipine treatment. *Eur J Clin Pharmacol* 1989; **36:** 311–13.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the eyes. Individual reports have implicated nifedipine in the development of transient retinal ischaemia and blindness,[1] and of periorbital oedema.[2] In a postmarketing survey painful or stinging eyes were more common in patients receiving nifedipine (178 of 757 evaluable) than in those given captopril (45 of 289), although the cause was uncertain.[3] Nifedipine has also been suggested as a risk factor in the development of cataract,[4,5] but the numbers involved in this analysis are small[6] and it is possible that the risk, if it exists,[7] relates to hypertension rather than nifedipine treatment.[6]

1. Pitlik S, *et al.* Transient retinal ischaemia induced by nifedipine. *BMJ* 1983; **287:** 1845–6.
2. Silverstone PH. Periorbital oedema caused by nifedipine. *BMJ* 1984; **288:** 1654.
3. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
4. van Heyningen R, Harding JJ. Do aspirin-like analgesics protect against cataract? *Lancet* 1986; **i:** 1111–13.
5. Harding JJ, van Heyningen R. Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide. *Br J Ophthalmol* 1988; **72:** 809–14.
6. van Heyningen R, Harding JJ. Aspirin-like analgesics and cataract. *Lancet* 1986; **ii:** 283.
7. Kewitz H, *et al.* Aspirin and cataract. *Lancet* 1986; **ii:** 689.

Effects on the heart. The use of nifedipine has been associated with the development of various heart disorders in some patients. Complete heart block has been reported in an elderly patient who had previously developed heart block with verapamil,[1] and sudden circulatory collapse has been reported in 4 patients receiving nifedipine who underwent routine coronary bypass surgery.[2] One patient died despite all attempts at resuscitation.[2] However, probably the majority of reports have concerned the development or aggravation of cardiac ischaemia, up to and including frank myocardial infarction after use of short-acting nifedipine.[3-6] Such cases appear to be chiefly associated with a too-rapid fall in blood pressure after the use of sublingual nifedipine for hypertensive urgencies or emergencies,[5,6] or occur in patients with a history of ischaemic heart disease.[3,4]

For discussion of the effects of calcium-channel blockers on cardiovascular mortality, see above.

1. Chopra DA, Maxwell RT. Complete heart block with low dose nifedipine. *BMJ* 1984; **288:** 760.
2. Goiti JJ. Calcium channel blocking agents and the heart. *BMJ* 1985; **291:** 1505.
3. Sia STB, *et al.* Aggravation of myocardial ischaemia by nifedipine. *Med J Aust* 1985; **142:** 48–50.
4. Boden WE, *et al.* Nifedipine-induced hypotension and myocardial ischemia in refractory angina pectoris. *JAMA* 1985; **253:** 1131–5.
5. O'Mailia JJ, *et al.* Nifedipine-associated myocardial ischemia or infarction in the treatment of hypertensive urgencies. *Ann Intern Med* 1987; **107:** 185–6.
6. Leavitt AD, Zweifler AJ. Nifedipine, hypotension, and myocardial injury. *Ann Intern Med* 1988; **108:** 305–6.

WITHDRAWAL. Exacerbation of coronary ischaemia and thrombosis of arteriovenous graft could have resulted from withdrawal of nifedipine in a patient.[1] Abrupt withdrawal of nisoldipine from 15 patients with stable angina pectoris after 6 weeks of therapy resulted in severe unstable angina in 2 patients and acute myocardial infarction in another.[2] It was postulated that the withdrawal effect could be due to an increase in sensitivity of vascular α_2 adrenoceptors to circulating adrenaline.

1. Mysliwiec M, *et al.* Calcium antagonist withdrawal syndrome. *BMJ* 1983; **286:** 1898.
2. Mehta J, Lopez LM. Calcium-blocker withdrawal phenomenon: increase in affinity of alpha adrenoceptors for agonist as a potential mechanism. *Am J Cardiol* 1986; **58:** 242–6.

Effects on the kidneys. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see under Uses and Administration, below). However, reversible deterioration in renal function without any appreciable accompanying decline in systemic arterial blood pressure has been reported[1] in 4 patients with underlying renal insufficiency receiving nifedipine,[1] and in another report[2] nifedipine increased urinary protein excretion and exacerbated renal impairment in 14 type 2 diabetic patients.

Excessive diuresis occurred in a patient given nifedipine for angina pectoris,[3] and nocturia in 9 patients referred for prostatic surgery was also attributed to nifedipine.[4]

1. Diamond JR, *et al.* Nifedipine-induced renal dysfunction: alterations in renal hemodynamics. *Am J Med* 1984; **77:** 905–9.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Antonelli D, *et al.* Excessive nifedipine diuretic effect. *BMJ* 1984; **288:** 760.
4. Williams G, Donaldson RM. Nifedipine and nocturia. *Lancet* 1986; **i:** 738.

Effects on the liver. A number of cases of hepatitis, apparently due to a hypersensitivity reaction, and frequently accompanied by fever, sweating, chills, rigor, and arthritic symptoms, have been reported in patients receiving nifedipine.[1-4]

1. Rotmensch HH, *et al.* Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 976–7.
2. Davidson AR. Lymphocyte sensitisation in nifedipine-induced hepatitis. *BMJ* 1980; **281:** 1354.
3. Abramson M, Littlejohn GO. Hepatic reactions to nifedipine. *Med J Aust* 1985; **142:** 47–8.
4. Shaw DR, *et al.* Nifedipine hepatitis. *Aust N Z J Med* 1987; **17:** 447–8.

Effects on the menstrual cycle. Menorrhagia in 2 women[1] and menstrual irregularity with heavy bleeding in another[2] have been reported in association with nifedipine treatment.

1. Rodger JC, Torrance TC. Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 460.
2. Singh G, *et al.* Can nifedipine provoke menorrhagia? *Lancet* 1983; **ii:** 1022.

Effects on mental function. Insomnia, hyperexcitability, pacing, agitation, and depression were reported[1] in a patient in association with nifedipine therapy. The symptoms disappeared within 2 days of withdrawal of nifedipine. Four further cases of major depression, which developed within a week of starting nifedipine and resolved within a week of stopping the drug, have been reported.[2]

Although 2 epidemiological studies suggested that calcium-channel blockers may promote suicide,[3] a subsequent study[4] found no evidence of an association between depression and the use of calcium-channel blockers, and the number of suicides was low. Further studies[5,6] have also failed to find an increased risk of suicide with calcium-channel blockers compared with other antihypertensive drugs.

1. Ahmad S. Nifedipine-induced acute psychosis. *J Am Geriatr Soc* 1984; **32:** 408.
2. Hullett FJ, *et al.* Depression associated with nifedipine-induced calcium channel blockade. *Am J Psychiatry* 1988; **145:** 1277–9.
3. Lindberg G, *et al.* Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998; **316:** 741–5.
4. Dunn NR, *et al.* Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression. *Br J Clin Pharmacol* 1999; **48:** 230–3.
5. Gasse C, *et al.* Risk of suicide among users of calcium channel blockers: population based, nested case-control study. *BMJ* 2000; **320:** 1251.
6. Sørensen HT, *et al.* Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001; **52:** 313–8.

Effects on the mouth. *GINGIVAL HYPERPLASIA.* A number of reports have implicated nifedipine in the development of gingival hyperplasia.[1-4] In most cases it has occurred about 1 to 6 months after starting therapy and has resolved after stopping nifedipine. A patient who had taken nifedipine for 12 years developed gingival hyperplasia shortly after the dosage of nifedipine was increased.[5] Amlodipine has also induced gingival overgrowth.[6] A study involving 115 patients given nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[7] Dihydropyridine calcium-channel blockers were among the most common drugs associated with reports of gingival hyperplasia in the Australian Adverse Drug Reactions Advisory Committee database.[8]

1. Ramon Y, *et al.* Gingival hyperplasia caused by nifedipine—a preliminary report. *Int J Cardiol* 1984; **5:** 195–204.
2. van der Wall EE, *et al.* Gingival hyperplasia induced by nifedipine, an arterial vasodilating drug. *Oral Surg* 1985; **60:** 38–40.
3. Shaftic AA, *et al.* Nifedipine-induced gingival hyperplasia. *Drug Intell Clin Pharm* 1986; **20:** 602–5.
4. Jones CM. Gingival hyperplasia associated with nifedipine. *Br Dent J* 1986; **160:** 416–17.
5. Johnson RB. Nifedipine-induced gingival overgrowth. *Ann Pharmacother* 1997; **31:** 935.
6. Ellis JS, *et al.* Gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth. *Lancet* 1993; **341:** 1102–3.
7. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced gingival overgrowth. *Aust Adverse Drug React Bull* 1999; **18:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9906.pdf (accessed 25/07/08)

PAROTITIS. Acute swelling of the parotid glands occurred in a patient after sublingual administration of nifedipine.[1]

1. Bosch X, *et al.* Nifedipine-induced parotitis. *Lancet* 1986; **ii:** 467.

Effects on the neuromuscular system. Severe muscle cramps have been reported in a few patients taking nifedipine;[1,2] in one patient[2] the cramps were associated with widespread paraesthesia. Reversible myoclonic dystonia associated with nifedipine has been reported in a patient.[3] Severe rhabdomyolysis developed in a patient with a transplanted kidney who was receiving an intravenous infusion of nifedipine.[4] The patient recovered rapidly once the infusion was stopped. There has also been a report[5] of myopathy, myalgia, and arthralgia associated with amlodipine, and of arthralgia in a patient[6] receiving diltiazem.

Parkinsonism is a recognised adverse effect of flunarizine and cinnarizine, which have calcium-channel blocking properties (see Extrapyramidal Disorders under Flunarizine, p.580). It has also been reported with diltiazem (see p.1266) and with amlodipine.[7,8]

1. Keidar S, *et al.* Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1241–2.
2. Macdonald JB. Muscle cramps during treatment with nifedipine. *BMJ* 1982; **285:** 1744.
3. de Medina A, *et al.* Nifedipine and myoclonic dystonia. *Ann Intern Med* 1985; **104:** 125.
4. Horn S, *et al.* Severe rhabdomyolysis in a kidney-transplant recipient receiving intravenous nifedipine. *Lancet* 1995; **346:** 848–9.
5. Phillips BB, Muller BA. Severe neuromuscular complications possibly associated with amlodipine. *Ann Pharmacother* 1998; **32:** 1165–7.
6. Smith KM. Arthralgia associated with calcium-channel blockers. *Am J Health-Syst Pharm* 2000; **57:** 55–7.
7. Sempere AP, *et al.* Parkinsonism induced by amlodipine. *Mov Disord* 1995; **10:** 115–6.
8. Teive HA, *et al.* Parkinsonian syndrome induced by amlodipine: case report. *Mov Disord* 2002; **17:** 833–5.

Effects on the oesophagus. Calcium-channel blockers decrease lower oesophageal sphincter pressure and have been used in oesophageal motility disorders (see below), but a retrospective cohort study[1] found that calcium-channel blockers may also precipitate or exacerbate gastro-oesophageal reflux disease.

1. Hughes J, *et al.* Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? *Br J Clin Pharmacol* 2007; **64:** 83–9.

Effects on the peripheral circulation. An erythromelalgia-like eruption occurred in a patient 8 weeks after starting therapy with nifedipine. Symptoms included severe burning pain and swelling in the feet and lower legs, which were fiery red, tender, and warm to the touch. Symptoms resolved in 2 days when nifedipine was stopped.[1] Similar effects have been reported in other patients on nifedipine.[2-4] Erythromelalgia has also been reported with nicardipine.[5] This type of erythromelalgia may be termed secondary erythermalgia.[6]

1. Fisher JR, *et al.* Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **98:** 671–2.
2. Grunwald Z. Painful edema, erythematous rash, and burning sensation due to nifedipine. *Drug Intell Clin Pharm* 1982; **16:** 492.
3. Brodmerkel GJ. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **99:** 415.
4. Sunahara JF, *et al.* Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. *Ann Pharmacother* 1996; **30:** 484–6.
5. Levesque H, *et al.* Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?) *BMJ* 1989; **298:** 1252–3.
6. Drenth JPH, Michiels JJ. Three types of erythromelalgia. *BMJ* 1990; **301:** 454–5.

Effects on the respiratory system. There have been some reports of pulmonary oedema being precipitated by nifedipine therapy in patients with aortic stenosis.[1,2] Nifedipine has also been reported to exacerbate impaired tissue oxygenation in patients with cor pulmonale secondary to obstructive airways disease.[3]

For a report of exacerbation of laryngeal oedema, see under Hypersensitivity, below.

1. Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. *BMJ* 1980; **280:** 1420–1.
2. Aderka D, Pinkhas J. Pulmonary oedema precipitated by nifedipine. *BMJ* 1984; **289:** 1272.
3. Kalra L, Bone MF. Nifedipine and impaired oxygenation in patients with chronic bronchitis and cor pulmonale. *Lancet* 1989; **i:** 1135–6.

Effects on the skin and nails. The commonest skin reactions to nifedipine have been rash, pruritus, urticaria, alopecia, and exfoliative dermatitis;[1] there have been a few reports of erythema multiforme and the Stevens-Johnson syndrome.[1] Erythema multiforme occurred in a patient after substitution of amlodipine for nifedipine[2] and cross-sensitivity, manifest as a pruritic maculopapular rash, has been reported between amlodipine and diltiazem.[3] Generalised pruritus has been reported with amlodipine.[4] Other skin reactions that have been reported with nifedipine include severe photosensitivity reactions,[5] nonthrombocytopenic purpuric rashes,[6] and telangiectasias,[7] including photodistributed telangiectasias,[8] and pemphigoid nodularis.[9] Photodistributed telangiectasias have also been reported with amlodipine,[10,11] and in one case[10] recurred 3 years later. Amlodipine has also been associated[12] with a case of lichen planus.

For reference to erythromelalgia, see under Effects on the Peripheral Circulation, above.

Nail and periungual pigmentation developed[13] in a 75-year-old man 18 months after starting amlodipine; it was much improved 2 years after the drug was stopped.

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Bewley AP, *et al.* Erythema multiforme following substitution of amlodipine for nifedipine. *BMJ* 1993; **307:** 241.
3. Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28:** 118–19.
4. Orme S, *et al.* Generalised pruritus associated with amlodipine. *BMJ* 1997; **315:** 463.
5. Thomas SE, Wood ML. Photosensitivity reactions associated with nifedipine. *BMJ* 1986; **292:** 992.
6. Oren R, *et al.* Nifedipine-induced nonthrombocytopenic purpura. *DICP Ann Pharmacother* 1989; **23:** 88.
7. Tsele E, Chu AC. Nifedipine and telangiectasias. *Lancet* 1992; **339:** 365–6.
8. Collins P, Ferguson J. Photodistributed nifedipine-induced facial telangiectasia. *Br J Dermatol* 1993; **129:** 630–3.
9. Ameen M, *et al.* Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 2000; **142:** 575–7.
10. Basarab T, *et al.* Calcium antagonist-induced photo-exposed telangiectasia. *Br J Dermatol* 1997; **136:** 974–5.
11. Grabczynska SA, Cowley N. Amlodipine induced-photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; **142:** 1255–6.
12. Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; **144:** 920–1.
13. Sladden MJ, *et al.* Longitudinal melanonychia and pseudo-Hutchinson sign associated with amlodipine. *Br J Dermatol* 2005; **153:** 219–20.

Effects on taste. Distortion of taste and smell has been reported in 2 patients taking nifedipine,[1] but a large survey involving 922 patients receiving nifedipine and 343 taking captopril did not show any association of taste disturbances with nifedipine.[2] Sudden loss of taste has also been reported[3] in a patient who had been taking amlodipine for several years; the sense of taste returned when amlodipine was stopped, but taste loss recurred on rechallenge.

1. Levenson JL, Kennedy K. Dysomia, dysgeusia, and nifedipine. *Ann Intern Med* 1985; **102:** 135–6.
2. Coulter DM. Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance. *BMJ* 1988; **296:** 1086–8.
3. Sadasivam B, Jhaj R. Dysgeusia with amlodipine—a case report. *Br J Clin Pharmacol* 2007; **63:** 253.

Gynaecomastia. Unilateral gynaecomastia developed in 3 men 4, 6, and 26 weeks after starting nifedipine therapy.[1]

1. Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; **292:** 380.

Haemorrhage. See Effects on the Blood, above.

Hypersensitivity. Nifedipine is associated with various hypersensitivity reactions including skin rashes and effects on the liver(see above).

Nifedipine, given sublingually, exacerbated laryngeal swelling that developed in a woman after the use of isosorbide dinitrate spray.[1]

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Oedema. Oedema of the feet and ankles is a common adverse effect of nifedipine and other dihydropyridine calcium-channel blockers. It occurs typically 2 or more weeks after starting treatment and is caused by pre-capillary arteriolar dilatation rather than fluid retention.[1] Evidence from a study in 10 diabetic subjects beginning nifedipine therapy, 5 of whom developed ankle oedema, suggested that nifedipine abolished the reflex vasoconstriction produced when the feet are below the level of the heart which is believed to prevent excessive fluid filtration into the tissues.[2]

The oedema may respond to simple measures such as elevation of the feet or to a reduction in dosage but if it persists the calcium-channel blocker should be withdrawn.[1]

Generalised oedema[3] and facial and upper extremity oedema[4] have been reported in patients taking amlodipine, but in both cases symptoms resolved on withdrawal of the drug.

1. Maclean D, MacConnachie AM. Selective side-effects: peripheral oedema with dihydropyridine calcium antagonists. *Prescribers' J* 1991; **31:** 4–6.
2. Williams SA, *et al.* Dependent oedema and attenuation of postural vasoconstriction associated with nifedipine therapy for hypertension in diabetic patients. *Eur J Clin Pharmacol* 1989; **37:** 333–5.
3. Şener D, *et al.* Anasarca edema with amlodipine treatment. *Ann Pharmacother* 2005; **39:** 761–3.
4. Ganeshalingham A, Wong W. Amlodipine-induced bilateral upper extremity edema. *Ann Pharmacother* 2007; **41:** 1536–8.

Treatment of Adverse Effects

Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting a potentially toxic overdose of nifedipine. Alternatively, gastric lavage may be considered in adults. Supportive and symptomatic care should be given. Hypotension may respond to placing the patient in the supine position with the feet raised; plasma expanders may be given, although cardiac overload should be avoided. If hypotension is not corrected, calcium should be given intravenously. The usual initial dose is 10 to 20 mL of 10% calcium gluconate given by slow intravenous injection or infusion; alternatively, up to 10 mL of 10% calcium chloride may be given. Glucagon may also be used. If hypotension persists, an intravenous sympathomimetic such as isoprenaline, dopamine, or noradrenaline may also be necessary. Bradycardia may be treated with atropine, isoprenaline, or cardiac pacing.

Dialysis is not useful as nifedipine is highly protein bound. Plasmapheresis may be beneficial.

Overdosage. The management of calcium-channel blocker overdosage is mainly supportive (see Treatment of Adverse Effects, above). Cardiovascular effects usually predominate and, although severe toxicity is more likely in overdosage with non-dihydropyridines such as verapamil or diltiazem, treatment of overdosage is similar for all calcium-channel blockers.[1-4] Prompt gastrointestinal decontamination, atropine to reverse bradycardia, and cardiovascular support with intravenous fluids, sympathomimetics, and possibly inotropes, are the mainstays of treatment. Intravenous calcium is also widely used, and high doses may be required; intravenous glucagon may also be given. Fampridine has been suggested[5] as a specific antagonist, and successful use of vasopressin[6] or terlipressin[7] has been reported in patients with resistant hypotension. There is also some evidence that high-dose insulin, with glucose if required to maintain normal blood-glucose concentrations, may be of benefit.[8-11]

Most reports of overdosage have been with verapamil (see p.1421). The following are some individual reports with nifedipine:

- Hypotension, tachycardia, and flushing, followed by hypokalaemia, were seen in a patient who took nifedipine 600 mg as modified-release tablets together with an overdose of paracetamol, but there was no evidence of heart block.[12] The patient was given calcium gluconate intravenously and subsequently activated charcoal and lactulose. Absorption of nifedipine was essentially complete 10 hours after ingestion. Potassium chloride was given orally to treat hypokalaemia and acetylcysteine was used to manage the paracetamol poisoning.
- Third-degree AV block, progressing to asystole, developed in a 14-month-old child who ingested about 800 mg of nifedipine.[13] During cardiopulmonary resuscitation a total of 700 mg of calcium chloride was given, together with atropine, adrenaline, and sodium bicarbonate. The stomach was subsequently emptied by gastric lavage and activated charcoal given. The patient remained tachycardic and hypotensive, with evidence of pulmonary oedema and hyperglycaemia, and was given intravenous electrolytes and dopamine infusions and assisted ventilation, together with treatment to control subsequent tonic-clonic seizures. She eventually made an apparently complete recovery apart from a moderate speech delay.

1. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003; **26:** 65–79.
2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. *Toxicol Rev* 2004; **23:** 223–38.
3. Olson KR, *et al.* Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2005; **43:** 797–822.
4. Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health-Syst Pharm* 2006; **63:** 1828–35.
5. Stevens JJWM, Ghosh S. Overdose of calcium channel blockers. *BMJ* 1994; **309:** 193.
6. Kanagarajan K, *et al.* The use of vasopressin in the setting of recalcitrant hypotension due to calcium channel blocker overdose. *Clin Toxicol* 2007; **45:** 56–9.
7. Leone M, *et al.* Terlipressin: a new therapeutic for calcium-channel blockers overdose. *J Crit Care* 2005; **20:** 114–15.
8. Yuan TH, *et al.* Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *J Toxicol Clin Toxicol* 1999; **37:** 463–74.
9. Boyer EW, Shannon M. Treatment of calcium-channel-blocker intoxication with insulin infusion. *N Engl J Med* 2001; **344:** 1721–2.
10. Mégarbane B, *et al.* The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev* 2004; **23:** 215–22.
11. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
12. Ferner RE, *et al.* Pharmacokinetics and toxic effects of nifedipine in massive overdose. *Hum Exp Toxicol* 1990; **9:** 309–11.
13. Wells TG, *et al.* Nifedipine poisoning in a child. *Pediatrics* 1990; **86:** 91–4.

Precautions

Nifedipine should be used with caution in patients with hypotension, in patients whose cardiac reserve is poor, and in those with heart failure since deterioration of heart failure has been noted. Nifedipine should not be used in cardiogenic shock, in patients who have suffered a myocardial infarction in the previous 2 to 4 weeks, or in acute unstable angina. Nifedipine should not be used to treat an anginal attack in chronic stable angina. In patients with severe aortic stenosis nifedipine may increase the risk of developing heart failure. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina. The dose may need to be reduced in patients with hepatic impairment.

Nifedipine should be stopped in patients who experience ischaemic pain after use.

Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been used in hypertension in pregnancy (see Hypertension, under Uses and Administration, below).

Breast feeding. Nifedipine is distributed into breast milk[1,2] but the amount present is probably too small to be harmful. There have been no reports of any clinical effects in breast-fed infants whose mothers were receiving nifedipine and the American Academy of Pediatrics therefore considers[3] that it is usually compatible with breast feeding.

1. Ehrenkranz RA, *et al.* Nifedipine transfer into human milk. *J Pediatr* 1989; **114:** 478–80.
2. Penny WJ, Lewis MJ. Nifedipine is excreted in human milk. *Eur J Clin Pharmacol* 1989; **36:** 427–8.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Diabetes mellitus. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism under Adverse Effects, above) calling for adjustments in antidiabetic therapy. Also some studies have suggested that nifedipine may worsen proteinuria and renal dysfunction in diabetic patients with some degree of renal insufficiency,[1,2] but other studies, (see Kidney Disorders under Uses and Administration, below), have suggested that nifedipine may have a beneficial effect on proteinuria.

Some studies have suggested that patients with diabetes mellitus[3,4] or impaired glucose metabolism[5] may be more susceptible to adverse cardiovascular effects of calcium-channel blockers. The calcium-channel blockers used in these studies were nisoldipine, amlodipine, and isradipine (long-acting or intermediate-acting calcium-channel blockers). However, two of the studies[3,4] compared the calcium-channel blocker with an ACE inhibitor and it has been suggested that ACE inhibitors may have a protective effect in patients with diabetes that is additional to their antihypertensive action. Thus, ACE inhibitors may be particularly beneficial in these patients rather than calcium-channel blockers being particularly harmful.[6]

1. Mimran A, *et al.* Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens* 1988; **6:** 919–23.
2. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
3. Estacio RO, *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; **338:** 645–52. Correction. *ibid.*; **339:** 1339.
4. Tatti P, *et al.* Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21:** 597–603.
5. Byington RP, *et al.* Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1997; **350:** 1075–6.
6. Poulter NR. Calcium channel blockers and cardiovascular risk in diabetes. *Lancet* 1998; **351:** 1809–10.

Interference with laboratory estimations. Nifedipine may give falsely elevated spectrophotometric values of urinary vanillylmandelic acid; HPLC estimations are unaffected.

Porphyria. Nifedipine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Withdrawal. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina.

For a report of life-threatening coronary vasospasm occurring after withdrawal of nifedipine before a revascularisation procedure, see under Effects on the Heart, in Diltiazem, p.1265.

Interactions

Nifedipine may enhance the antihypertensive effects of other antihypertensive drugs such as beta blockers although the combination is generally well tolerated. Enhanced antihypertensive effects may also be seen if used with drugs such as aldesleukin and antipsychotics that cause hypotension. Nifedipine may modify insulin and glucose responses (see Effects on Carbohydrate Metabolism, above) and therefore diabetic patients may need to adjust their antidiabetic treatment when receiving nifedipine. Nifedipine is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4, and interactions may occur with other drugs, such as quinidine, sharing the same metabolic pathway, and with enzyme inducers, such as carbamazepine, phenytoin, and rifampicin, and enzyme inhibitors, such as cimetidine, erythromycin, and HIV-protease inhibitors.

Alcohol. A study involving 10 healthy subjects showed that the area under the concentration-time profile for nifedipine 20 mg was increased by 54% when taken orally with alcohol, and maximum pulse rate was achieved more rapidly, which was in line with *animal* and *in-vitro* studies suggesting that the metabolism of nifedipine is inhibited by alcohol.[1]

1. Qureshi S, *et al.* Nifedipine-alcohol interaction. *JAMA* 1990; **264:** 1660–1.

Antiarrhythmics. Nifedipine and *quinidine* probably have a common metabolic pathway in the liver and might be expected to interact if given concurrently. In one study,[1] quinidine appeared to inhibit nifedipine metabolism resulting in increased serum concentrations of nifedipine; quinidine concentrations were unchanged. However, conflicting effects on serum-quinidine concentrations have been reported, see p.1384.

1. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.

Antibacterials. The macrolide antibacterials are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may inhibit the metabolism of calcium-channel blockers. Two days after *clarithromycin* was started,[1] vasodilatory shock and heart block occurred in a 77-year-old man whose antihypertensive medication included nifedipine. Clarithromycin was continued and when his condition improved nifedipine was reintroduced at half the previous dose; his blood pressure was stable on discharge.

1. Gerónimo-Pardo M, *et al.* Clarithromycin–nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* 2005; **39:** 538–42.

Antidiabetics. See Diabetes Mellitus under Precautions and Effects on Carbohydrate Metabolism under Adverse Effects, above.

Antiepileptics. The effects of dihydropyridine calcium-channel blockers may be reduced by enzyme-inducing antiepileptics such as *carbamazepine*, *phenobarbital*, and *phenytoin*.[1-4] In contrast, *sodium valproate* has been reported to increase plasma-nimodipine concentrations.[3]

For reports of an interaction between dihydropyridines and *phenytoin* resulting in raised serum-phenytoin concentration, see p.499.

1. Capewell S, *et al.* Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* 1988; **ii:** 480–2.
2. Schellens JHM, *et al.* Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. *J Pharmacol Exp Ther* 1989; **249:** 638–45.
3. Tartara A, *et al.* Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* 1991; **32:** 335–40.
4. Yasui-Furukori N, Tateishi T. Carbamazepine decreases antihypertensive effect of nilvadipine. *J Clin Pharmacol* 2002; **42:** 100–103.

Antifungals. Azole antifungals inhibit the cytochrome P450 enzyme system and may therefore interfere with metabolism of calcium-channel blockers. Two women who had been taking felodipine for about a year developed peripheral oedema a few days after starting treatment with *itraconazole*.[1] Plasma-felodipine concentrations were measured in one of the women before and during a subsequent course of itraconazole and increased considerably when the two drugs were used together. A similar interaction occurred when itraconazole therapy was started in a patient already taking nifedipine.[2] Potentiation of the effects of nifedipine by *fluconazole* has also been reported.[3]

1. Neuvonen PJ, Suhonen R. Itraconazole interacts with felodipine. *J Am Acad Dermatol* 1995; **33:** 134–5.
2. Tailor SAN, *et al.* Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; **132:** 350–2.
3. Kremens B, *et al.* Loss of blood pressure control on withdrawal of fluconazole during nifedipine therapy. *Br J Clin Pharmacol* 1999; **47:** 707–8.

Antihistamines. Severe angina developed in a patient stabilised on nifedipine who took *terfenadine* 60 mg for seasonal allergy. The pain resolved within an hour or two.[1]

1. Falkenberg HM. Possible interaction report. *Can Pharm J* 1988; **121:** 294.

Antineoplastics. For reports of increased *vincristine* toxicity in children also receiving itraconazole and nifedipine concomitantly, see Antifungals under Interactions of Vincristine, p.787.

Antivirals. The HIV-protease inhibitors are known to inhibit the cytochrome P450 isoenzyme CYP3A4 and may therefore interfere with the metabolism of calcium-channel blockers. A woman stable on felodipine developed oedema[1] in both legs when she was given *nelfinavir* after a needle-stick injury. The oedema resolved on withdrawal of felodipine, and was attributed to inhibition of felodipine metabolism. A study[2] in healthy subjects found that *indinavir plus ritonavir* increased exposure to both amlodipine and diltiazem.

1. Izzedine H, *et al.* Nelfinavir and felodipine: a cytochrome P450 3A4-mediated drug interaction. *Clin Pharmacol Ther* 2004; **75:** 362–3.
2. Glesby MJ, *et al.* Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. *Clin Pharmacol Ther* 2005; **78:** 143–53.

Beta blockers. Although nifedipine is often used with beta blockers without untoward effects, heart failure has been reported in a few patients with angina who were given nifedipine and a beta blocker.[1,2] Severe hypotension has been reported in 1 of 15 angina patients given nifedipine and *atenolol*;[3] withdrawal of the beta blocker precipitated severe unstable angina in this patient. Severe hypotension in a patient was attributed to the use of nifedipine with *propranolol*, and was thought to have contributed to fatal myocardial infarction.[4]

1. Anastassiades CJ. Nifedipine and beta-blocker drugs. *BMJ* 1980; **281:** 1251–2.
2. Robson RH, Vishwanath MC. Nifedipine and beta-blockade as a cause of cardiac failure. *BMJ* 1982; **284:** 104.
3. Opie LH, White DA. Adverse interaction between nifedipine and β-blockade. *BMJ* 1980; **281:** 1462.
4. Staffurth JS, Emery P. Adverse interaction between nifedipine and beta-blockade. *BMJ* 1981; **282:** 225.

Calcium-channel blockers. Plasma concentrations of nifedipine were increased in a study in 6 healthy subjects when pretreated with *diltiazem*; the elimination half-life of nifedipine was prolonged from 2.54 hours to 3.40 hours after pretreatment with diltiazem 30 mg daily and to 3.47 hours after 90 mg daily. The effect was probably due to reduced hepatic metabolism of nifedipine.[1] Nifedipine and diltiazem are reported to be metabolised by the same hepatic enzyme and, conversely, pretreatment with nifedipine has resulted in increased concentrations of diltiazem.[2]

1. Tateishi T, *et al.* Dose dependent effect of diltiazem on the pharmacokinetics of nifedipine. *J Clin Pharmacol* 1989; **29:** 994–7.
2. Tateishi T, *et al.* The effect of nifedipine on the pharmacokinetics and dynamics of diltiazem: the preliminary study in normal volunteers. *J Clin Pharmacol* 1993; **33:** 738–40.

Digoxin. For the effect of nifedipine and other dihydropyridine calcium-channel blockers on digoxin, see p.1262.

Grapefruit juice. Grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4, particularly in the intestinal wall, and has been shown to increase markedly the bioavailability of oral calcium-channel blockers;[1-3] calcium-channel blockers given intravenously appear to be unaffected.[4] The interaction may be less significant with calcium-channel blockers such as amlodipine that have a higher bioavailability,[5] but most calcium-channel blockers should not be taken orally at the same time as grapefruit juice.[6] A stereoselective effect has also been reported.[7]

1. Bailey DG, *et al.* Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991; **337:** 268–9.
2. Bailey DG, *et al.* Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993; **54:** 589–94.
3. Lundahl J, *et al.* Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* 1995; **49:** 61–7.
4. Rashid TJ, *et al.* Factors affecting the absolute bioavailability of nifedipine. *Br J Clin Pharmacol* 1995; **40:** 51–8.
5. Vincent J, *et al.* Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000; **50:** 455–63.
6. Committee on Safety of Medicines/Medicines Control Agency. Drug interactions with grapefruit juice. *Current Problems* 1997; **23:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
7. Uno T, *et al.* Effect of grapefruit juice on the disposition of manidipine enantiomers in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 533–7.

Histamine H_2-antagonists. Pharmacokinetic studies have indicated that use of nifedipine with *cimetidine* can increase the bioavailability of nifedipine.[1-4] An increase in the area under the plasma concentration-time curve of between 77 and 92% has been reported.[2,3] Potentiation of the hypotensive effect of nifedipine by cimetidine was also shown in 7 hypertensive patients.[1] The mechanism of the interaction was thought to be due to inhibition of the cytochrome P450 system by cimetidine and thus inhibition of the metabolism of nifedipine.

Ranitidine was found to have little effect on the pharmacokinetics of nifedipine, although there was an increase in the bioavailability of nifedipine during use of ranitidine.[5] *Famotidine* has been reported not to interact with nifedipine.[6]

1. Kirch W, *et al.* Einfluß von cimetidin und ranitidin auf pharmakokinetik und antihypertensiven effekt von nifedipin. *Dtsch Med Wochenschr* 1983; **108:** 1757–61.
2. Renwick AG, *et al.* Factors affecting the pharmacokinetics of nifedipine. *Eur J Clin Pharmacol* 1987; **32:** 351–5.
3. Smith SR, *et al.* Ranitidine and cimetidine: drug interactions with single dose and steady-state nifedipine administration. *Br J Clin Pharmacol* 1987; **23:** 311–15.
4. Schwartz JB, *et al.* Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1988; **43:** 673–80.
5. Kirch W, *et al.* Ranitidine increases bioavailability of nifedipine. *Clin Pharmacol Ther* 1985; **37:** 204.
6. Kirch W, *et al.* Negative effects of famotidine on cardiac performance assessed by noninvasive hemodynamic measurements. *Gastroenterology* 1989; **96:** 1388–92.

Immunosuppressants. Flushing, paraesthesias, and rashes were reported in 2 patients given nifedipine 40 mg daily while taking *ciclosporin* for psoriasis.[1] A study in 8 psoriatic patients indicated that giving nifedipine with ciclosporin resulted in reduced recovery of the principal metabolite of nifedipine, presumably because ciclosporin reduced nifedipine metabolism through competition for the cytochrome P450 metabolising enzymes.

For reference to the effects of calcium-channel blockers on ciclosporin concentrations in blood, see p.1827. For the possible protective effect of nifedipine against ciclosporin-induced nephrotoxicity, see Transplantation under Uses and Administration, below.

For the effect of nifedipine on *tacrolimus*, see p.1845.

1. McFadden JP, *et al.* Cyclosporin decreases nifedipine metabolism. *BMJ* 1989; **299:** 1224.

Magnesium salts. Profound hypotension has been reported in 2 women in whom a single oral dose of nifedipine 10 mg was added to treatment with magnesium sulfate infusion for pre-eclampsia; both women were also receiving methyldopa.[1] Neuromuscular blockade has been reported in 2 women after use of nifedipine with intravenous magnesium sulfate. In one woman receiving nifedipine as a tocolytic, symptoms of neuromuscular blockade occurred immediately on injection of magnesium sulfate and resolved within 25 minutes of stopping the injection.[2] In another woman who was receiving a magnesium sulfate infusion for pre-eclampsia, symptoms developed 30 minutes after the second of 2 doses of nifedipine had been given and improved after receiving calcium gluconate injection.[3]

1. Waisman GD, *et al.* Magnesium plus nifedipine: potentiation of hypotensive effect in pre-eclampsia? *Am J Obstet Gynecol* 1988; **159:** 308–9.
2. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* 1989; **161:** 35–6.
3. Ben-Ami M, *et al.* The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; **101:** 262–3.

Melatonin. Melatonin may cause a reduction in blood pressure and might be expected to have additive effects if given with antihypertensives. However, in a study[1] in hypertensive patients taking nifedipine, giving melatonin led to an increase in both blood pressure and heart rate.

1. Lusardi P, *et al.* Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol* 2000; **49:** 423–7.

Tobacco. In a study of the effects of cigarette smoking and the treatment of angina with nifedipine, propranolol, or atenolol, smoking was shown to have direct and adverse effects on the heart and to interfere with the efficacy of all 3 anti-anginal drugs, with nifedipine being the most affected.[1]

1. Deanfield J, *et al.* Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med* 1984; **310:** 951–4.

Xanthines. For the effect of nifedipine on *theophylline*, see p.1144.

Pharmacokinetics

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but undergoes extensive hepatic first-pass metabolism. Bioavailability of oral liquid-filled capsules is between 45 and 75%, but is lower for longer-acting formulations. Peak blood concentrations are reported to occur 30 minutes after oral doses of liquid-filled capsules.

Nifedipine is about 92 to 98% bound to plasma proteins. It is distributed into breast milk. It is extensively metabolised in the liver and 70 to 80% of a dose is excreted in the urine almost entirely as inactive metabolites. The half-life is about 2 hours after intravenous doses or oral liquid-filled capsules.

◊ General reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.

◊ The pharmacokinetics of nifedipine have been reviewed.[1] Studies have been complicated by the difficulty in preparing a stable intravenous formulation and the problems in developing a sufficiently sensitive and specific method of analysis. Nearly 100% of an oral dose of nifedipine is absorbed in the small intestine although the bioavailability from capsules is 45 to 68%. The rate of absorption from both oral and sublingual capsules varies widely among individuals: there has been a report that high plasma-nifedipine concentrations are achieved more rapidly if the capsule is bitten and swallowed than from standard oral and sublingual administration (but this is no longer recommended—see Hypertension, below). The absorption of nifedipine from tablets is slower than from capsules, with maximum plasma concentrations occurring at 1.6 to 4.2 hours compared with 0.5 to 2.17 hours, and absorption may still be occurring at 24 to 32 hours after a dose.

Nifedipine undergoes almost complete hepatic oxidation to 3 pharmacologically inactive metabolites which are excreted in the urine. It has been reported that after oral doses 30 to 40% of the amount absorbed is metabolised during the first pass through the liver. The elimination half-life of nifedipine is apparently dependent upon the dosage form in which it is given, with half-lives of 6 to 11 hours, 2 to 3.4 hours, and 1.3 to 1.8 hours measured after oral tablet, oral capsule, and intravenous doses respectively. The total systemic clearance of nifedipine from plasma ranges from 27 to about 66 litres/hour. Renal impairment does not substantially alter nifedipine pharmacokinetics.

1. Sorkin EM, *et al.* Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. *Drugs* 1985; **30:** 182–274.

Absorption. Although studies have indicated that the absorption of nifedipine may be affected by food the results appear to vary depending upon the preparation used. A reduction in peak plasma-nifedipine concentrations, and a delay in achieving them, was reported[1] when nifedipine *capsules* were given after a meal compared with 30 minutes before. In contrast, the bioavailability and maximum serum concentrations of nifedipine were markedly increased when a *modified-release tablet* (*Adalat L*) was given after a meal rather than fasting,[2] although another modified-release tablet (*Slofedipine*) showed delayed absorption when given after food.[3] A further tablet formulation (*Adalat OROS*) was unaffected by food,[3] while a *modified-release capsule* containing uncoated and enteric-coated granules (*Sepamit R*) was reported to have essentially the same bioavailability when taken before or after a meal.[4]

1. Hirasawa K, *et al.* Effect of food ingestion on nifedipine absorption and haemodynamic response. *Eur J Clin Pharmacol* 1985; **28:** 105–7.
2. Ueno K, *et al.* Effect of food on nifedipine sustained-release preparation. *DICP Ann Pharmacother* 1989; **23:** 662–5.
3. Schug BS, *et al.* The effect of food on the pharmacokinetics of nifedipine in two slow release formulations: pronounced lag-time after a high fat breakfast. *Br J Clin Pharmacol* 2002; **53:** 582–8.
4. Ueno K, *et al.* Effect of a light breakfast on the bioavailability of sustained-release nifedipine. *DICP Ann Pharmacother* 1991; **25:** 317–19.

Hepatic impairment. The pharmacokinetics of nifedipine were found to be considerably altered in 7 patients with liver cirrhosis.[1] Systemic plasma clearance was substantially reduced and the elimination half-life was considerably longer than in healthy subjects. In addition, systemic availability of oral nifedipine was much higher in patients with cirrhosis and was complete in 3 patients with surgical portacaval shunt. Patients with liver cirrhosis seemed to be more sensitive to the effects of nifedipine on diastolic blood pressure and heart rate, and this could be explained by the higher free drug concentrations observed. It was concluded that lower doses of nifedipine may be required in patients with liver cirrhosis, and the patient's response should be closely monitored.

1. Kleinbloesem CH, *et al.* Nifedipine: kinetics and hemodynamic effects in patients with liver cirrhosis after intravenous and oral administration. *Clin Pharmacol Ther* 1986; **40:** 21–8.

Interindividual variation. A study in 53 Dutch subjects found a bimodal distribution of plasma concentrations of nifedipine after a single oral dose; it was proposed that the higher plasma concentrations in 17% of subjects represented a slow metaboliser phenotype, with the majority of the population being fast metabolisers.[1] Although further studies[2,3] in European populations have not confirmed these results, a study in 12 Mexican subjects supported the concept of polymorphic metabolism, with 5 fast and 7 slow metabolisers, a much higher proportion of slow metabolisers than in the European studies.[4] Studies have also reported a markedly increased area under the concentration-time curve in South Asian,[5,6] Mexican,[7] and Nigerian[8] subjects compared with Caucasians. The difference did not appear to be due to diet.[5,6] The initial dose of nifedipine might need to be lower in these ethnic groups. Another population study[9] found that clearance was slower in blacks compared with whites, and in men compared with women; alcohol ingestion and smoking both also reduced nifedipine clearance.

1. Kleinbloesem CH, *et al.* Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem Pharmacol* 1984; **33:** 3721–4.
2. Renwick AG, *et al.* The pharmacokinetics of oral nifedipine—a population study. *Br J Clin Pharmacol* 1988; **25:** 701–8.
3. Lobo J, *et al.* The intra- and inter-subject variability of nifedipine pharmacokinetics in young volunteers. *Eur J Clin Pharmacol* 1986; **30:** 57–60.
4. Hoyo-Vadillo C, *et al.* Pharmacokinetics of nifedipine slow release tablet in Mexican subjects: further evidence for an oxidation polymorphism. *J Clin Pharmacol* 1989; **29:** 816–20.
5. Ahsan CH, *et al.* Ethnic differences in the pharmacokinetics of oral nifedipine. *Br J Clin Pharmacol* 1991; **31:** 399–403.
6. Ahsan CH, *et al.* The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. *Clin Pharmacol Ther* 1993; **54:** 329–38.
7. Castañeda-Hernández G, *et al.* Interethnic variability in nifedipine disposition: reduced systemic plasma clearance in Mexican subjects. *Br J Clin Pharmacol* 1996; **41:** 433–4.
8. Sowunmi A, *et al.* Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians. *Br J Clin Pharmacol* 1995; **40:** 489–93.
9. Krecic-Shepard ME, *et al.* Race and sex influence clearance of nifedipine: results of a population study. *Clin Pharmacol Ther* 2000; **68:** 130–42.

Uses and Administration

Nifedipine is a dihydropyridine calcium-channel blocker (p.1154). It is a peripheral and coronary vasodilator, but, unlike the rate-limiting calcium-channel blockers verapamil or diltiazem, has little or no effect on cardiac conduction and negative inotropic activity is rarely seen at therapeutic doses. Use of nifedipine results primarily in vasodilatation, with reduced peripheral resistance, blood pressure, and afterload, increased coronary blood flow, and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output. Nifedipine has no antiarrhythmic activity. Nicardipine and newer dihydropyridines such as amlodipine, felodipine, isradipine, and lacidipine may be even more selective than nifedipine for vascular smooth muscle. Nimodipine acts particularly on cerebral blood vessels. Most of the dihydropyridine calcium-channel blockers (nifedipine and lacidipine are exceptions) are chiral compounds used as racemic mixtures.

Nifedipine is used in the management of hypertension; in the management of angina pectoris (p.1157), particularly when a vasospastic element is present, as in Prinzmetal's angina, but is not suitable for relief of an acute attack; and in the treatment of Raynaud's syndrome. Nifedipine has also been tried in numerous non-vascular disorders.

Nifedipine is usually given orally. It is available in several formulations. Liquid-filled capsules with a relatively rapid onset but short duration of action are given three times daily. This short-acting preparation is not recommended for the management of hypertension (see below). There are also tablets and capsules with a slower onset and longer duration of action, enabling twice-daily dosage; although these are often referred to by nomenclature implying extended or sustained release they should be distinguished from the true extended-release preparations available in some countries that allow dosage once daily.

Doses of nifedipine are dependent upon the formulation used; they may need to be reduced in the elderly or those with impaired liver function.

For **hypertension** a long-acting preparation of nifedipine may be given in doses of 10 to 40 mg twice daily, or 20 to 90 mg once daily, depending on the preparation used.

For **angina pectoris**, nifedipine may be given as a long-acting preparation in a dose of 10 to 40 mg twice daily or 30 to 90 mg once daily, depending on the preparation. Alternatively, the liquid-filled capsules have been given in a dose of 5 to 20 mg three times daily, but longer-acting preparations are preferred.

Nifedipine has been given by injection via a coronary catheter for the treatment of coronary spasm during coronary angiography and balloon angioplasty. Blood pressure and heart rate should be monitored carefully.

In the management of **Raynaud's syndrome**, nifedipine may be given as liquid-filled capsules in a dose of 5 to 20 mg three times daily.

For the use of nifedipine in children, see below.

◊ General reviews.

1. Fisher M, Grotta J. New uses for calcium channel blockers: therapeutic implications. *Drugs* 1993; **46:** 961–75.
2. Croom KF, Wellington K. Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 2006; **66:** 497–528.

Administration in children. Nifedipine has been used in the management of various disorders in children. The *BNFC* recommends the following oral doses:

Hypertension; angina in Kawasaki disease or progeria:
- age 1 month to 12 years: 200 to 300 micrograms/kg 3 times daily, increased to a maximum daily dose of 3 mg/kg or 100 mg
- age 12 to 18 years: 5 to 20 mg 3 times daily, increased to a maximum daily dose of 100 mg

Hypertensive crises:
- age 1 month to 18 years: 250 to 500 micrograms/kg as a single dose

Raynaud's syndrome:
- age 2 to 18 years: 2.5 to 10 mg 2 to 4 times daily; treatment should start with low doses at night, increased gradually to avoid postural hypotension

Neonatal hyperinsulinaemic hypoglycaemia:
- see below.

Use of nifedipine capsules for acute hypertension is no longer recommended in adults because of the risk of severe adverse effects related to precipitous reductions in blood pressure (see Effects on Mortality under Adverse Effects, above). Although there have been reports of adverse effects in children,[1-3] they may be less susceptible than adults, and the use of nifedipine capsules may still be appropriate. A study[4] in 12 children aged 6 to 15 years with acute severe hypertension reported that sublingual nifedipine in a mean dose of 240 micrograms/kg (range 180 to 320 micrograms/kg) was safe and effective. A retrospective study[1] in 117 children found that nifedipine safely reduced blood pressure, and that precipitous declines only occurred with doses higher than 250 micrograms/kg, while another retrospective study[2] in 166 children found that nifedipine in a mean dose of 300 micrograms/kg (range 40 to 1300 micrograms/kg) was generally safe, although children with acute CNS injury were at higher risk of neurological adverse effects.

Other routes that have been used include rectal[5] and intranasal,[6] but these are less established.

1. Blaszak RT, *et al.* The use of short-acting nifedipine in pediatric patients with hypertension. *J Pediatr* 2001; **139:** 34–7.
2. Egger DW, *et al.* Evaluation of the safety of short-acting nifedipine in children with hypertension. *Pediatr Nephrol* 2002; **17:** 35–40.
3. Flynn JT. Nifedipine in the treatment of hypertension in children. *J Pediatr* 2002; **140:** 787–8.
4. Evans JHC, *et al.* Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988; **63:** 975–7.
5. Uchiyama M, Ogawa I. Rectal nifedipine in acute severe hypertension in young children. *Arch Dis Child* 1989; **64:** 632–3.
6. Lopez-Herce J, *et al.* Treatment of hypertensive crisis with intranasal nifedipine. *Crit Care Med* 1988; **9:** 914.

Amaurosis fugax. Amaurosis fugax is a form of monocular visual loss that is usually attributed to a transient ischaemic attack and is treated with antiplatelet drugs or anticoagulants (see Stroke, p.1185). Vasospasm may be an alternative cause and might explain the efficacy of the calcium-channel blockers nifedipine and verapamil reported[1] in a few patients unresponsive to standard therapy.

1. Winterkorn JMS, *et al.* Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 1993; **329:** 396–8.

Anal fissure. Calcium antagonists, including oral and topical nifedipine, have been tried[1-9] in the treatment of chronic anal fissure (p.1891).

1. Antropoli C, *et al.* Nifedipine for local use in conservative treatment of anal fissures: preliminary results of a multicenter study. *Dis Colon Rectum* 1999; **42:** 1011–5.
2. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.
3. Perrotti P, *et al.* Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. *Dis Colon Rectum* 2002; **45:** 1468–75.
4. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
5. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. *Br J Surg* 2005; **92:** 403–8.
6. Katsinelos P, *et al.* Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. *Int J Colorectal Dis* 2006; **21:** 179–83.
7. Tranqui P, *et al.* Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; **49:** 41–5.
8. Lysy J, *et al.* Long-term results of "chemical sphincterotomy" for chronic anal fissure: a prospective study. *Dis Colon Rectum* 2006; **49:** 858–64.
9. Katsinelos P, *et al.* Aggressive treatment of acute anal fissure with 0.5% nifedipine ointment prevents its evolution to chronicity. *World J Gastroenterol* 2006; **12:** 6203–6.

Atherosclerosis. The use of drugs that interfere with atherogenesis (the development of atheromas) has been suggested as a means of reducing diseases associated with atherosclerosis (p.1159). Calcium is thought to be necessary for several steps in atherogenesis and studies in *animals* have shown that calcium-channel blockers slow the development and progression of atherosclerotic lesions. However, studies in humans have been less convincing.[1] In a placebo-controlled study,[2] amlodipine had no demonstrable effect on angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events although it was associated with fewer admissions to hospital for unstable angina and revascularisation. Similar results have been reported with nisoldipine.[3] In another study,[4] comparing lacidipine with a beta blocker, there was less progression of atherosclerosis in those receiving lacidipine and also a trend towards fewer cardiovascular events.

Calcium-channel blockers have also been tried in the prevention of restenosis after percutaneous coronary interventions. A meta-analysis[5] found that addition of calcium-channel blockers to standard therapy reduced the risk of restenosis and the occurrence of clinical events.

1. Borcherding SM, *et al.* Calcium-channel antagonists for prevention of atherosclerosis. *Ann Pharmacother* 1993; **27:** 61–7.
2. Pitt B, *et al.* Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000; **102:** 1503–10.
3. Dens JA, *et al.* Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. *Heart* 2003; **89:** 887–92.
4. Zanchetti A, *et al.* Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; **106:** 2422–7.
5. Dens J, *et al.* An updated meta-analysis of calcium-channel blockers in the prevention of restenosis after coronary angioplasty. *Am Heart J* 2003; **145:** 404–8.

Cardiomyopathies. Calcium-channel blockers may have a role in some forms of cardiomyopathy (p.1163). In *hypertrophic cardiomyopathy* verapamil is probably the calcium-channel blocker of choice (see p.1424). Nifedipine does not appear to reduce left ventricular outflow tract obstruction, and conflicting results have been found with respect to improvement in the diastolic function abnormality with this drug.[1] The use of calcium-channel blockers is not standard therapy in *dilated cardiomyopathy* although symptomatic improvement has been reported[2] with diltiazem.

1. Richardson PJ. Calcium antagonists in cardiomyopathy. *Br J Clin Pract* 1988; **42** (suppl 60): 33–7.
2. Figulla HR, *et al.* Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy: results of the Diltiazem in Dilated Cardiomyopathy Trial. *Circulation* 1996; **94:** 346–52.

Cough. Nifedipine has been reported to reduce the severity of cough induced by captopril,[1] possibly by inhibiting prostaglandin synthesis. For further details on cough associated with ACE inhibitors, see p.1194.

1. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; **19:** 670–3.

Hiccup. Hiccups (p.976) result from involuntary spasmodic contraction of the diaphragm. Intractable hiccups resolved completely with nifedipine 20 mg every 8 hours in a patient.[1] In a further 7 such patients,[2] nifedipine in doses of 20 to 80 mg daily stopped hiccups in 4 and improved them in another. Resolution of intractable hiccups has also been reported[3] in 2 patients given nimodipine; the drug was given orally in one patient and intravenously in the other.

For the treatment of hiccups in palliative care the *BNF* recommends nifedipine at a dose of 10 mg three times daily.

1. Mukhopadhyay P, *et al.* Nifedipine for intractable hiccups. *N Engl J Med* 1986; **314:** 1256.
2. Lipps DC, *et al.* Nifedipine for intractable hiccups. *Neurology* 1990; **40:** 531–2.
3. Hernández JL, *et al.* Nimodipine treatment for intractable hiccups. *Am J Med* 1999; **106:** 600.

High-altitude disorders. Nifedipine lowers pulmonary artery pressure and is one of several drugs that are used in high-altitude disorders (p.1168), success being reported for both the treatment[1,2] and prevention[2,3] of symptoms of pulmonary oedema. In a study conducted at 4559 m above sea-level[1] nifedipine 10 mg sublingually and 20 mg as a modified-release dosage form was given to 6 subjects with symptoms of high-altitude pulmonary oedema. The sublingual dose was repeated if tolerated after 15 minutes and the subjects subsequently received modified-release nifedipine 20 mg every 6 hours while they remained at high altitude. Symptoms of high-altitude pulmonary oedema were relieved within 1 hour of beginning nifedipine and radiographic signs of oedema regressed during treatment despite remaining at high altitude for 36 hours and participating in mountaineering activities. Raised pulmonary arterial pressure was also reduced to control values by nifedipine. Successful treatment of pulmonary oedema in a climber at 6550 m has been described with doses of 20 mg every 8 hours for 36 hours and such doses also prevented the development of symptoms in 2 climbers who had taken nifedipine from the start of the climb.[2] Doses of 20 mg every 8 hours have been reported to allow rapid ascent to 4559 m without development of pulmonary oedema in 9 of 10 subjects who received nifedipine compared with 4 of 11 who received only placebo.[3] However, the point has been made that although it is reasonable that many climbers carry nifedipine in case of an attack, prophylactic nifedipine should not be considered an alternative to slow ascent and acclimatisation.[4]

1. Oelz O, *et al.* Nifedipine for high altitude pulmonary oedema. *Lancet* 1989; **ii:** 1241–4. Correction. *ibid.* 1991; **337:** 556.
2. Jamieson A, Kerr GW. Treatment of high-altitude pulmonary oedema. *Lancet* 1992; **340:** 1468.
3. Bärtsch P, *et al.* Prevention of high-altitude pulmonary oedema by nifedipine. *N Engl J Med* 1991; **325:** 1284–9.
4. A'Court CHD, *et al.* Doctor on a mountaineering expedition. *BMJ* 1995; **310:** 1248–52.

Hyperinsulinaemic hypoglycaemia. Nifedipine may have effects on blood-glucose levels due to inhibition of insulin release[1] (see Effects on Carbohydrate Metabolism, under Adverse Effects, above). There have been reports[1-4] of the successful use of nifedipine to increase blood-glucose levels in infants with hyperinsulinaemic hypoglycaemia (see under Uses of Glucagon, p.1447), and it may have a role[5] as adjunctive therapy in such patients. The *BNFC* suggests that neonates with persistent hyperinsulinaemic hypoglycaemia may be given oral nifedipine in a dose of 100 to 200 micrograms/kg 4 times daily, increased to a maximum of 600 micrograms/kg 4 times daily if required.

1. Lindley KJ, *et al.* Ionic control of beta cell function in nesidioblastosis: a possible therapeutic role for calcium channel blockade. *Arch Dis Child* 1996; **74:** 373–8.
2. Eichmann D, *et al.* Treatment of hyperinsulinaemic hypoglycaemia with nifedipine. *Eur J Pediatr* 1999; **158:** 204–6.
3. Bas F, *et al.* Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 1999; **12:** 873–8.
4. Shanbag P, *et al.* Persistent hyperinsulinemic hypoglycemia of infancy—successful therapy with nifedipine. *Indian J Pediatr* 2002; **69:** 271–2.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.

Hypertension. Long-acting calcium-channel blockers are among the drug groups that may be used as first-line therapy in uncomplicated hypertension (p.1171); meta-analyses[1] and large studies[2] have shown them to be as safe and effective as other first-line antihypertensives and they are particularly recommended in older patients. Dihydropyridine calcium-channel blockers are also useful in patients who require combination therapy[3] and are particularly effective when given with a beta blocker or an ACE inhibitor. The use of short-acting calcium-channel blockers is not recommended since they may increase mortality (see under Adverse Effects, above).

Calcium-channel blockers may also be used in **hypertensive crises**, particularly in hypertensive urgencies where oral therapy is suitable. Nifedipine has been given sublingually, or by biting the capsule and swallowing the contents, but such use may cause dangerous hypotension and is no longer recommended. In hypertensive emergencies, where parenteral antihypertensives are required, intravenous nicardipine may be used. One study concluded that intravenous nicardipine was as effective as sodium nitroprusside in the treatment of postoperative hypertension.[4]

For **hypertension in pregnancy**, first-line treatment is usually methyldopa or a beta blocker but calcium-channel blockers may also be used. Nifedipine is reported to be teratogenic in *animals* and may inhibit labour, but it has been tried in a limited number of patients with pre-eclampsia. Although a high rate of caesarean deliveries, premature births, and small-for-date infants was reported[5] in patients given nifedipine as a second-line drug, assessment of the role of nifedipine is difficult because outcome is often poor in such severely compromised pregnancies.[6] Fetal nifedipine concentrations have been reported to be 75% of maternal values 2 to 3 hours after sublingual administration.[7] However, nifedipine in a single 20-mg oral dose lowered blood pressure without compromising blood flow in the fetus in 9 women in the third trimester with normal haemodynamics.[6] This is in line with other reports,[8] although there has also been a report[9] of severe hypotension and fetal distress after sublingual nifedipine administration. In a randomised controlled study,[10] nifedipine 10 to 30 mg sublingually followed by 10 mg as capsules by mouth every 6 hours increasing to 20 mg every 4 hours if necessary, was compared with hydralazine 12.5 mg intravenously as required followed by 20 to 30 mg orally every 6 hours, with added methyldopa if necessary. Both groups also received intravenous magnesium sulfate. Effective control of blood pressure was achieved in 23 of 24 patients given nifedipine compared with only 17 of 25 given hydralazine and 9 nifedipine patients achieved term delivery compared with only 2 of those receiving hydralazine. The average gestational age was greater in infants in the nifedipine group; hence these neonates weighed more and had fewer neonatal complications when compared with neonates from the hydralazine treated group.

1. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; **39:** 315–22. Correction. *ibid.*; 1409–10.
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.
3. Epstein BJ, *et al.* Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007; **67:** 1309–27.
4. Halpern NA, *et al.* Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992; **20:** 1637–43.
5. Constantine G, *et al.* Nifedipine as a second line antihypertensive drug in pregnancy. *Br J Obstet Gynaecol* 1987; **94:** 1136–42.
6. Hanretty KP, *et al.* Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. *BMJ* 1989; **299:** 1205–6.
7. Pirhonen JP, *et al.* Single dose of nifedipine in normotensive pregnancy: nifedipine concentrations, hemodynamic responses, and uterine and fetal flow velocity waveforms. *Obstet Gynecol* 1990; **76:** 807–11.
8. Pirhonen JP, *et al.* Uterine and fetal flow velocity wave forms in hypertensive pregnancy: the effect of a single dose of nifedipine. *Obstet Gynecol* 1990; **76:** 37–41.
9. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. *Br J Obstet Gynaecol* 1993; **100:** 959–61.
10. Fenakel K, *et al.* Nifedipine in the treatment of severe preeclampsia. *Obstet Gynecol* 1991; **77:** 331–7.

Kidney disorders. Although nifedipine may adversely affect renal function (see under Adverse Effects, above) there is evidence that calcium-channel blockers may be of benefit in various forms of kidney disorder. Proteinuria is an important indicator of glomerular kidney disease (p.1504) of various causes and the effects of calcium-channel blockers on proteinuria and renal dysfunction have been studied in a variety of patients. Results have been mixed,[1-5] and it is not clear whether any protective effect of calcium-channel blockers on renal function is only due to their antihypertensive action or whether they also have additional effects. The benefits of ACE inhibitors in kidney disorders are much better established (see p.1199) and a study[6] in African American hypertensives was stopped early when treatment with ramipril was found to be superior to treatment with amlodipine. A further study[7] in patients with non-diabetic proteinuria found that addition of felodipine to ACE inhibitor therapy provided no additional benefit in terms of renal outcomes.

Nifedipine has also been used in the management of renal calculi (see below), and has been reported to protect against ciclosporin-induced nephrotoxicity in renal transplant patients (see Transplantation, below).

1. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990; **113:** 987–8.
2. Melbourne Diabetic Nephropathy Study Group. Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. *BMJ* 1991; **302:** 210–16.
3. Reams G, *et al.* The effect of nifedipine GITS on renal function in hypertensive patients with renal insufficiency. *J Clin Pharmacol* 1991; **31:** 468–72.
4. Abbott K, *et al.* Effects of dihydropyridine calcium antagonists on albuminuria in patients with diabetes. *J Clin Pharmacol* 1996; **36:** 274–9.
5. Bouhanick B, *et al.* Equivalent effects of nicardipine and captopril on urinary albumin excretion of type 2, non-insulin-dependent diabetic subjects with mild to moderate hypertension. *Therapie* 1996; **51:** 41–7.
6. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; **285:** 2719–28.
7. Ruggenenti P, *et al.* Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365:** 939–46.

Migraine and cluster headache. Drugs with calcium-channel blocking activity have been given in the management of headaches considered to have a vascular component such as migraine (p.616) and cluster headache (p.616).

In migraine prophylaxis, of those drugs with calcium-channel blocking activity studied, flunarizine (p.580) has the best documented efficacy, and verapamil may be useful. Other calcium-channel blockers such as diltiazem, nifedipine, and nimodipine have been tried, but results have been conflicting. Verapamil has also been used successfully in patients with hemiplegic migraine, both intravenously to abort attacks,[1,2] and orally for prophylaxis.[2]

Beneficial effects have been reported[3-6] with calcium-channel blockers in the prevention of cluster headache during cluster periods. Verapamil appears to have been the most widely used. In one double-blind study it was found to be of similar efficacy to lithium[7] and appeared to produce fewer adverse effects. There have also been reports[8] of the successful use of nimodipine in patients with thunderclap headache.

1. Ng TMH, *et al.* The effect of intravenous verapamil on cerebral hemodynamics in a migraine patient with hemiplegia. *Ann Pharmacother* 2000; **34:** 39–43.
2. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology* 2003; **60:** 120–1.
3. Jónsdóttir M, *et al.* Efficacy, side effects and tolerance compared during headache treatment with three different calcium blockers. *Headache* 1987; **27:** 364–9.
4. Gabai IJ, Spierings ELH. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; **29:** 167–8.
5. Leone M, *et al.*. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; **54:** 1382–5.
6. Matharu MS, *et al.* Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; **63:** 1637–77.
7. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
8. Lu S-R, *et al.* Nimodipine for treatment of primary thunderclap headache. *Neurology* 2004; **62:** 1414–16.

Oesophageal motility disorders. Results from a number of studies have indicated that nifedipine, usually in doses of 10 to 20 mg sublingually, may be of benefit in patients with achalasia, reducing lower oesophageal sphincter pressure and producing some symptomatic improvement.[1-5] Nifedipine has a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p.1702).

See also Effects on the Oesophagus under Adverse Effects, above.

1. Bortolotti M, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981; **80:** 39–44.

2. Gelfond M, *et al.* Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. *Gastroenterology* 1982; **83:** 963–9.
3. Traube M, *et al.* Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1984; **252:** 1733–6.
4. Román FJ, *et al.* Effects of nifedipine in achalasia and patients with high-amplitude peristaltic esophageal contractions. *JAMA* 1985; **253:** 2046.
5. Coccia G, *et al.* Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut* 1991; **32:** 604–6.

Peripheral vascular disease. Vasospastic arterial disease (p.1178) is due to an inappropriate response to temperature, usually cold, when vasoconstriction and/or vasospasm occurs. The most important of these disorders is Raynaud's syndrome. Calcium-channel blockers have been of benefit in Raynaud's syndrome,[1] but it is not entirely clear which of their pharmacological actions is responsible. The most widely used and studied is nifedipine. Evidence of subjective benefit has been seen both in primary idiopathic disease[2-5] and in Raynaud's phenomenon secondary to systemic sclerosis,[3,4,6,7] systemic lupus erythematosus,[3,4] rheumatoid arthritis,[4] and cancer chemotherapy,[8] or associated with breastfeeding.[9-11] Objective improvement as demonstrated by evidence of improved digital blood flow has been demonstrated in some[5,6,12,13] but not all[7] studies. Doses have varied; 10 mg of nifedipine twice daily initially, increased after a week to a maximum of 20 mg twice daily has been suggested,[14] but in many studies doses of up to 60 mg daily have been used, although side-effects have proved intolerable in some patients given such doses.[7] A modified-release preparation has also been used[15] and may reduce the incidence of adverse effects.

Nifedipine in doses of 20 to 60 mg daily has also been reported to be of benefit in the treatment of another vasospastic condition, chilblains, both for established chilblains and in the prevention of relapse.[16]

1. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005; **44:** 145–50.
2. Roath S. Management of Raynaud's phenomenon: focus on newer treatments. *Drugs* 1989; **37:** 700–12.
3. Smith CD, McKendry RJR. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; **ii:** 1299–1301.
4. Kahan A, *et al.* Nifedipine for Raynaud's phenomenon. *Lancet* 1983; **i:** 131.
5. Gasser P. Reaction of capillary blood cell velocity in nailfold capillaries to nifedipine and ketanserin in patients with vasospastic disease. *J Int Med Res* 1991; **19:** 24–31.
6. Thomas RHM, *et al.* Nifedipine in the treatment of Raynaud's phenomenon in patients with systemic sclerosis. *Br J Dermatol* 1987; **117:** 237–41.
7. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
8. Hantel A, *et al.* Nifedipine and oncologic Raynaud phenomenon. *Ann Intern Med* 1988; **108:** 767.
9. Garrison CP. Nipple vasospasms, Raynaud's syndrome, and nifedipine. *J Hum Lact* 2002; **18:** 382–5.
10. Anderson JE, *et al.* Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding. *Pediatrics* 2004; **113:** e360–4.
11. Page SM, McKenna DS. Vasospasm of the nipple presenting as painful lactation. *Obstet Gynecol* 2006; **108:** 806–8.
12. Nilsson H, *et al.* Treatment of digital vasospastic disease with the calcium-entry blocker nifedipine. *Acta Med Scand* 1984; **215:** 135–9.
13. Finch MB, *et al.* The peripheral vascular effects of nifedipine in Raynaud's disease. *Br J Clin Pharmacol* 1986; **21:** 100P–101P.
14. Grigg MH, Wolfe JHN. Raynaud's syndrome and similar conditions. *BMJ* 1991; **303:** 913–16.
15. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000; **160:** 1101–8.
16. Rustin MHA, *et al.* The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. *Br J Dermatol* 1989; **120:** 267–75.

Phaeochromocytoma. Pharmacological management of phaeochromocytoma (p.1179) is principally achieved by alpha-adrenergic blockade and tachycardia may subsequently be controlled by cautious addition of a beta blocker. There have also been some reports[1-4] of the use of nifedipine to treat cardiovascular symptoms in adults and children with phaeochromocytoma.

1. Serfas D, *et al.* Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. *Lancet* 1983; **ii:** 711–13.
2. Lenders JWM, *et al.* Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. *BMJ* 1985; **290:** 1624–5.
3. Favre L, Vallotton MB. Nifedipine in pheochromocytoma. *Ann Intern Med* 1986; **104:** 125.
4. Deal JE, *et al.* Phaeochromocytoma—investigation and management of 10 cases. *Arch Dis Child* 1990; **65:** 269–74.

Premature labour. Although $beta_2$ agonists or magnesium are the drugs that have been most commonly used as tocolytics to postpone premature labour (p.2003), there is increasing interest in calcium-channel blockers such as nifedipine, either given alone or added to other tocolytics, as first-line drugs. Labour was successfully postponed in a patient given nifedipine 20 mg three times daily and oral terbutaline.[1] Terbutaline by subcutaneous injection was also occasionally necessary. Nifedipine was given from the twenty-sixth week of pregnancy for 55 days. A normal, healthy infant was delivered in the thirty-sixth week of pregnancy. In a study[2] in 20 patients, oral nifedipine 30 mg initially, then 20 mg every 8 hours, was more effective in suppressing premature labour than ritodrine given intravenously or no treatment. However, a similar study[3] in 33 patients found nifedipine to be no more effective than ritodrine infusion, although associated with a lower incidence of adverse effects. Similar results have been reported with nicardipine.[4] Meta-analyses[5,6] have concluded that nifedipine is at least as effective as $beta_2$ agonists and is associated with fewer maternal adverse effects, and this was supported by the results of further studies.[7,8] The larger[7] of these involved 185 women using oral nifedipine in an initial dose of up to 40 mg followed by 60 to 160 mg daily, reduced after 3 days to a maintenance dose of at least 20 mg 3 times daily. However, a systematic review[9] which examined 31 studies of the effectiveness of nifedipine in premature labour concluded that their overall quality was poor. Others[10] have expressed concern about the safety of calcium-channel blockers, reviewing cases of dyspnoea and pulmonary oedema in particular. They suggest that these drugs should not be used with intravenous beta agonists, that high doses should be avoided in women with cardiovascular compromise or multiple gestations, and that blood pressure and fetal heart rate should be monitored during use of short-acting preparations, which should not be chewed.

1. Kaul AF, *et al.* The management of preterm labor with the calcium channel-blocking agent nifedipine combined with the β-mimetic terbutaline. *Drug Intell Clin Pharm* 1985; **19:** 369–71.
2. Read MD, Wellby DE. The use of a calcium antagonist (nifedipine) to suppress preterm labour. *Br J Obstet Gynaecol* 1986; **93:** 933–7.
3. Ferguson JE, *et al.* A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome. *Am J Obstet Gynecol* 1990; **163:** 105–11.
4. Jannet D, *et al.* Nicardipine versus salbutamol in the treatment of premature labor: a prospective randomized study. *Eur J Obstet Gynecol Reprod Biol* 1997; **73:** 11–16.
5. Ray JG. Meta-analysis of nifedipine versus beta-sympathomimetic agents for tocolysis during preterm labour. *J Soc Obstet Gynaecol Can* 1998; **20:** 259–69.
6. Tsatsaris V, *et al.* Tocolysis with nifedipine or beta-adrenergic agonists: a meta-analysis. *Obstet Gynecol* 2001; **97:** 840–7.
7. Papatsonis DNM, *et al.* Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol* 1997; **90:** 230–4.
8. Van De Water M, *et al.* Tocolytic effectiveness of nifedipine versus ritodrine and follow-up of newborns: a randomised controlled trial. *Acta Obstet Gynecol Scand* 2008; **87:** 340–5.
9. Lamont RF, *et al.* Steering Group of the International Preterm Labour Council. The quality of nifedipine studies used to assess tocolytic efficacy: a systematic review. *J Perinat Med* 2005; **33:** 287–95.
10. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006; **126:** 137–45.

Pulmonary hypertension. Vasodilators have been tried in primary pulmonary hypertension (p.1179) on the premise that pulmonary vasoconstriction is an important component of the condition. Calcium-channel blockers are the most widely-used. Improved survival over a 5-year period has been noted in a study in patients treated with high doses of calcium-channel blockers (nifedipine or diltiazem).[1] However, treatment failures have occurred with nifedipine, and at least one death has been reported shortly after starting therapy.[2] Other reports have also stressed the potentially deleterious effects of nifedipine (or other vasodilator) therapy in pulmonary hypertension. Increased dyspnoea and a fall in arterial PO_2 have been reported in a patient with primary pulmonary hypertension given nifedipine, probably due to preferential vasodilatation of underventilated hypoxic tissues resulting in an increased physiological shunt.[3] Invasive investigations, notably blood-gas monitoring, are therefore recommended when giving nifedipine to these patients[2,3] and it has been advised that an acute response test should be performed before embarking on long-term treatment.[1]

1. Rich S, *et al.* The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327:** 76–81.
2. McLeod AA, Jewitt DE. Drug treatment of primary pulmonary hypertension. *Drugs* 1986; **31:** 177–84.
3. Krol RC, *et al.* Primary pulmonary hypotension, nifedipine, and hypoxemia. *Ann Intern Med* 1984; **100:** 163.

Renal calculi. There is some interest in the possible use of drug treatment to ease the spontaneous passage of renal calculi (p.2181) in patients with uncomplicated lower ureteral stones. It has been suggested that the combination of a calcium-channel blocker (to reduce ureteral spasm) with a corticosteroid (to reduce oedema) may be useful. Small studies[1-3] have used modified-release preparations of nifedipine, given in oral doses of 30 mg daily for up to 28 days, with oral deflazacort 30 mg daily for up to 10 days. If the stone had not been expelled within 28 days, the patient was treated with extracorporeal shock wave lithotripsy or ureteroscopy. Treatment with nifedipine and deflazacort was found to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements.

The use of a 10-day course of nifedipine and deflazacort has also been studied[4] as adjunctive therapy after lithotripsy. It was found to ease the passage of stone fragments, reduce analgesic requirements, and increase the number of patients who were stone-free after 45 days.

1. Porpiglia F, *et al.* Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology* 2000; **56:** 579–83.
2. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; **172:** 568–71.
3. Dellabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; **174:** 167–72.
4. Porpiglia F, *et al.* Role of adjunctive medical therapy with nifedipine and deflazacort after extracorporeal shock wave lithotripsy of ureteral stones. *Urology* 2002; **59:** 835–8.

Tardive dyskinesia. Calcium-channel blockers have been tried in the treatment of tardive dyskinesia (see under Extrapyramidal Disorders, p.971). However, a systematic review[1] concluded that their effects are unclear and they should not be used.

1. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 28/03/06).

Transplantation. The main adverse effect of ciclosporin is reversible, dose-related nephrotoxicity. There is some evidence that nifedipine may be of value in protecting against this effect. Retrospective analysis[1] of 106 ciclosporin-treated renal transplant patients found that patients receiving nifedipine for hypertension had better graft function, despite having shorter graft duration and therefore requiring higher dosage of ciclosporin, than hypertensive patients receiving other drug treatment. Subsequent studies have similarly reported improved graft function[2] in patients receiving nifedipine and suggest that graft survival is also improved.[3,4] A nephroprotective effect has also been reported with nitrendipine,[5] felodipine,[6] isradipine,[7] and with the non-dihydropyridine diltiazem (see p.1267), although a study[8] with nicardipine failed to demonstrate any improvement in graft function.

For a report of adverse effects attributed to reduced metabolism of nifedipine in patients taking ciclosporin, see Immunosuppressants, under Interactions, above.

1. Feehally J, *et al.* Does nifedipine ameliorate cyclosporin A nephrotoxicity? *BMJ* 1987; **295:** 310.
2. Shin GT, *et al.* Effect of nifedipine on renal allograft function and survival beyond one year. *Clin Nephrol* 1997; **47:** 33–6.
3. Weinrauch LA, *et al.* Role of calcium channel blockers in diabetic renal transplant patients: preliminary observations on protection from sepsis. *Clin Nephrol* 1995; **44:** 185–92.
4. Mehrens T, *et al.* The beneficial effects of calcium channel blockers on long-term kidney transplant survival are independent of blood-pressure reduction. *Clin Transplant* 2000; **14:** 257–61.
5. Rahn K-H, *et al.* Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. *Lancet* 1999; **354:** 1415–20.
6. Madsen JK, *et al.* The effect of felodipine on renal function and blood pressure in cyclosporin-treated renal transplant recipients during the first three months after transplantation. *Nephrol Dial Transplant* 1998; **13:** 2327–34.
7. van Riemsdijk IC, *et al.* Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transplantation* 2000; **70:** 122–6.
8. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.

Urticaria. Oral antihistamines are the main drugs used in the management of urticaria (p.1584). Addition of a calcium-channel blocker, such as nifedipine, has been suggested for patients unresponsive to treatment with oral antihistamines alone, but results have been mixed.[1,2]

1. Lawlor F, *et al.* Calcium antagonist in the treatment of symptomatic dermographism: low-dose and high-dose studies with nifedipine. *Dermatologica* 1988; **177:** 287–91.
2. Bressler RB, *et al.* Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 1989; **83:** 756–63.

Preparations

BP 2008: Nifedipine Capsules;
USP 31: Nifedipine Capsules; Nifedipine Extended-release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Adalat; Nifecor†; Nifed Sol; Nifedel; Nifelat†; Prudencial†; ***Austral.:*** Adalat; Addos; Adefin; Nifecard; Nifehexal; Nyefax; Nypine; ***Austria:*** Adalat; Buconif; Fedip; Majolat; Nifal; Nifebene; Nifehexal; Nifestad; Ospocard; ***Belg.:*** Adalat; Hypan; ***Braz.:*** Adalat; Adalex†; Cardalin; Dilaflux; Dipinal; Loncord†; Neo Fedipina; Nifadil; Nifedax†; Nifedicard; Nifedin†; Nifehexal†; Nioxil; Normopres; Oxcord; Prodopina; ***Canad.:*** Adalat; Apo-Nifed; Novo-Nifedin†; Nu-Nifed; ***Chile:*** Adalat; Carbloc†; Cardicon; Coronovo; Nipress; Pabalat†; Sulotil; ***Cz.:*** Adalat; Aprical†; Cordafen†; Cordipin; Corinfar; Nifecard; Nifehexal†; Sponif†; Supracordin†; ***Denm.:*** Adalat; Hexadilat; Nifecodan; ***Fin.:*** Adalat; Nifangin; Nifdemin†; Nifecor†; ***Fr.:*** Adalate; Chronadalate; ***Ger.:*** Adalat; Aprical; Cordicant†; Corinfar; Dignokonstant†; duranifin†; Jedipin; Jutadilat; Nife; nife uno†; Nifeclair; Nifecor; Nifedipat†; Nifehexal; Nifelat; Nifical; Pidilat; ***Gr.:*** Adalat; Antiblut; Coracten; Flecor-N; Glopir; Macorel; Nefelid; Nifedicor; Nifedipat†; Viscard†; ***Hong Kong:*** Adalat; Cardilate MR†; Coracten†; Fenamon†; Nadipinia; Nifecard; Nifelat; Vidalat; Waridipin†; ***Hung.:*** Adalat; Cordaflex; Cordipin†; Corinfar; Nifecard; ***India:*** Calcigard; Calnif; Cardules; Depicor; Depin; Edip†; Myogard; Nicardia†; Nifedine; Nifelat; ***Indon.:*** Adalat; Calcianta; Carvas; Cordalat; Coronipin; Farmalat; Fedipin; Ficor; Nifedin; Vasdalat; Xepalat; ***Irl.:*** Adalat; Nifed; Nifelease†; Pinifed†; Systepin†; Vasofed†; ***Israel:*** Megalat†; Osmo-Adalat; Pressolat; ***Ital.:*** Adalat; Bionif†; Citilat; Coral; Euxat; Fenidina; Nifedicor; Nifedicron†; Nifedin†; Nifesal; Nipin; ***Jpn:*** Adalat; ***Malaysia:*** Adalat; Adifen†; Fenamon; Nifecip; ***Mex.:*** Adalat; Apo-

Fedipisal†; Atenses; Cordilat; Corogal; Corotrend; Fusepina; Gelprim; Nifedigel; Nifedipres; Nifezzard; Nifser; Noviken; ***Neth.:*** Adalat; ***Norw.:*** Adalat; ***NZ:*** Adalat; Adefin; Nyefax; ***Philipp.:*** Adalat; Calcheck; Calcibloc; Calcigard; Cardicap; Darat; Heblopin; Nelapine; Nifestad; Normadil; Odipin; Tensibloc; ***Pol.:*** Adalat; Cordafen; Cordipin; ***Port.:*** Adalat; Angipina; Meborilan; Medipina†; Nifedate†; Zenusin; ***Rus.:*** Adalat (Адалат); Calcigard (Кальцигард); Cordafen (Кордафен); Cordaflex (Кордафлекс); Cordipin (Кордипин); Corinfar (Коринфар); Depin-E (Депин-Е); Fenamon (Фенамон); Nicardia (Никардия); Nifecard (Нифекард); Osmo-Adalat (Осмо-Адалат); ***S.Afr.:*** Adalat; Cardifen; Cardilat†; Cipalat; Nifedalat; Vascard; ***Singapore:*** Adalat; Apo-Nifed; Calcigard; Cordipin; Fenamon; Nifecard†; Nifedi-Denk†; Nifelat†; Nipin; Stada Uno; Vasdalat†; ***Spain:*** Adalat; Dilcor; Pertensal; ***Swed.:*** Adalat; ***Switz.:*** Adalat; Aldipin†; Cardipin; Corotrend; Ecodipine; nife-basan†; Nifedicor; ***Thai.:*** Adalat; Calcigard; Coracten; Fenamon; Nelapine; Nifecard; Nifelat; Nifiran†; Nyefax; Stada Uno; ***Turk.:*** Adalat; Kardilat; Nidicard; Nidilat; ***UAE:*** Cardiopine; ***UK:*** Adalat; Adipine; Angiopine†; Calchan; Cardilate MR; Coracten; Coroday†; Fortipine; Hypolar Retard; Nifedipress; Nifopress; Slofedipine; Tensipine; ***USA:*** Adalat; Afeditab; Nifediac; Nifedical; Procardia; ***Venez.:*** Adalat; Conducil; Fedilex†; Nifal; Tensomax; Tensopin.

Multi-ingredient: ***Arg.:*** Atel N†; ***Austria:*** Beta-Adalat; Nif-Ten; Pontuc; ***Belg.:*** Beta-Adalat†; Tenif; ***Braz.:*** Nifelat; ***Fin.:*** Nif-Ten; ***Fr.:*** Beta-Adalate; Tenordate; ***Ger.:*** AteNif beta; Belnif; Bresben; duranifin Sali†; Nif-Ten; Nifatenol; Sali-Adalat; Tredalat; ***Hong Kong:*** Nif-Ten; ***India:*** Beta Nicardia†; Cardules Plus; Depten; Nifetolol; Presolar; Tenofed; ***Indon.:*** Nif-Ten; ***Irl.:*** Beta-Adalat; Nif-Ten; ***Ital.:*** Antrolin; Mixer; Nif-Ten; ***Mex.:*** Plenacor; ***Neth.:*** Nif-Ten†; ***Philipp.:*** Nif-Ten; ***Singapore:*** Beta Nicardia; Nif-Ten; Nifetex; ***Switz.:*** Beta-Adalat; Nif-Atenil; Nif-Ten; ***UK:*** Beta-Adalat; Tenif.

Nifekalant Hydrochloride *(rINNM)*

Hidrocloruro de nifekalant; MS-551; Nifékalant, Chlorhydrate de; Nifekalanti Hydrochloridum. 6-[(2-{(2-Hydroxyethyl)[3-(*p*-nitrophenyl)propyl]amino}ethyl)amino]-1,3-dimethyluracil hydrochloride.

Нифекаланта Гидрохлорид

$C_{19}H_{27}N_5O_5,HCl = 441.9.$

CAS — 130636-43-0 (nifekalant); 130656-51-8 (nifekalant hydrochloride).

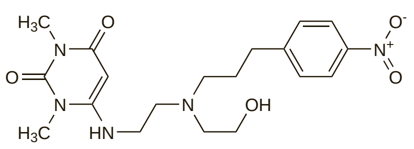

(nifekalant)

Profile

Nifekalant is a class III antiarrhythmic (p.1153) used intravenously as the hydrochloride in the management of life-threatening ventricular arrhythmias (p.1160).

◊ References.

1. Katoh T, *et al.* Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. *Circ J* 2005; **69:** 1237–43.

Effects on the heart. A woman who had been receiving intravenous nifekalant continuously for 10 months was found[1] to have a round mass in the right atrium. This was resected and shown to be a fibrin thrombus containing a large amount of nifekalant in the form of needle crystals.

1. Okamura H, *et al.* Crystals in the heart. *Heart* 2004; **90:** 1106.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Shinbit.

Nilvadipine *(USAN, rINN)*

CL-287389; FK-235; Nilvadipidiini; Nilvadipidin; Nilvadipidinum; Nilvadipin; Nilvadipino; Nilvadipinum; Nivadipine; SKF-102362. 5-Isopropyl 3-methyl 2-cyano-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

Нильвадипин

$C_{19}H_{19}N_3O_6 = 385.4.$

CAS — 75530-68-6.

ATC — C08CA10.

ATC Vet — QC08CA10.

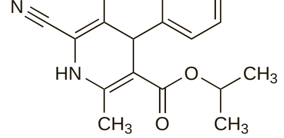

Pharmacopoeias. In *Jpn.*

Profile

Nilvadipine is a dihydropyridine calcium-channel blocker with general properties similar to those of nifedipine (p.1350). It is used in the management of hypertension (p.1171). Nilvadipine is given orally, usually as a modified-release preparation, in a dose of up to 16 mg daily.

◊ Reviews.

1. Brogden RN, McTavish D. Nilvadipine: a review of its pharmacodynamic and pharmacokinetic properties, therapeutic use in hypertension and potential in cerebrovascular disease and angina. *Drugs Aging* 1995; **6:** 150–71. Correction. *ibid.*; **7:** 116.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Tensan; ***Cz.:*** Escor; ***Fin.:*** Escor; ***Ger.:*** Escor; Nivadil; ***Gr.:*** Peroma; ***Irl.:*** Nivadil; ***Jpn:*** Nivadil; ***Port.:*** Nivadil; ***Switz.:*** Nivadil†; ***Turk.:*** Nilvadis.

Nimodipine *(BAN, USAN, rINN)*

Bay-e-9736; Nimodipiini; Nimodipin; Nimodipinas; Nimodipino; Nimodipinum; Nimodypina. Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

Нимодипин

$C_{21}H_{26}N_2O_7 = 418.4.$

CAS — 66085-59-4.

ATC — C08CA06.

ATC Vet — QC08CA06.

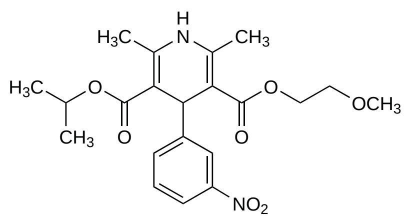

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Nimodipine). A light yellow or yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 31 (Nimodipine). A light yellow or yellow crystalline powder, affected by light. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in ethyl acetate. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Licensed product information states that solutions of nimodipine are incompatible with some plastics, including PVC, and that the only plastics suitable for use are polyethylene and polypropylene.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Nimodipine should be used with caution in patients with cerebral oedema or severely raised intracranial pressure.

Effects on the heart. Marked bradycardia developed in a patient with acute ischaemic stroke during treatment with nimodipine and was suspected to be related to the drug therapy.[1]

1. Fagan SC, Nacci N. Nimodipine and bradycardia in acute stroke—drug or disease? *DICP Ann Pharmacother* 1991; **25:** 247–9.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nimodipine is rapidly absorbed from the gastrointestinal tract after oral doses but undergoes extensive first-pass metabolism in the liver. The oral bioavailability is reported to be about 13%. Nimodipine is more than 95% bound to plasma proteins. It crosses the blood-brain barrier, but concentrations in CSF are lower than those in plasma. Nimodipine is extensively metabolised in the liver. It is excreted in faeces via the bile, and in urine, almost entirely as metabolites. The terminal elimination half-life is reported to be about 9 hours but the initial decline in plasma concentration is much more rapid, equivalent to a half-life of 1 to 2 hours.

Uses and Administration

Nimodipine is a dihydropyridine calcium-channel blocker that has the general properties of nifedipine (p.1354), but acts particularly on cerebral blood vessels. It is used in cerebrovascular disorders (see below), particularly in the prevention and treatment of ischaemic neurological deficits after aneurysmal subarachnoid haemorrhage.

To reduce the incidence and severity of neurological deficit after aneurysmal haemorrhage nimodipine is given orally in a dose of 60 mg every 4 hours. Treatment should begin within 4 days of onset of haemorrhage and should continue for 21 days. In patients with hepatic impairment the dose may be reduced (see below) and blood pressure should be closely monitored.

If cerebral ischaemia occurs or has already occurred, neurological deficit may be treated by intravenous infusion of nimodipine. It should be given via a bypass into a running intravenous infusion into a central vein. The initial dose should be nimodipine 1 mg/hour for 2 hours, increased (provided that no severe decrease in blood pressure occurs) to 2 mg/hour. The starting dose should be reduced to 500 micrograms/hour, or even lower if necessary, in patients weighing less than 70 kg and in those with unstable blood pressure; a similar reduction in dosage has been suggested in hepatic impairment, and blood pressure should be closely monitored. Treatment should be started as soon as possible and continued for at least 5 and no more than 14 days; if the patient has already received oral nimodipine, the total duration of nimodipine use should not exceed 21 days.

Administration in hepatic impairment. The clearance of nimodipine is reduced in patients with cirrhosis, and blood pressure should be closely monitored in such patients. US licensed product information recommends that the oral dose of nimodipine should be halved to 30 mg every 4 hours in patients with hepatic cirrhosis. Some manufacturers have also suggested a reduction in the initial intravenous dose to 500 micrograms or less per hour.

Cerebrovascular disorders. Nimodipine is used orally and intravenously in the prevention and treatment of ischaemic neurological deficits caused by arterial vasospasm after aneurysmal subarachnoid haemorrhage (see Stroke, p.1185), although the evidence for benefit after intravenous use is limited.[1] Nimodipine has also been used for traumatic subarachnoid haemorrhage,[2] but results have been mixed.[3,4] In addition to dilating cerebral blood vessels and improving cerebral blood flow, nimodipine may also prevent or reverse ischaemic damage to the brain by limiting transcellular calcium influx.

These effects have led to the investigation of nimodipine in other conditions associated with cerebral ischaemia. Studies[5,6] of nimodipine given orally after ischaemic stroke have produced conflicting results. A meta-analysis[7] of controlled studies suggested that nimodipine is beneficial if given within 12 hours of stroke onset but a further study[8] failed to confirm these findings. In a controlled study[9] of 155 patients suffering a cardiac arrest, nimodipine was given by intravenous infusion for 24 hours. Nimodipine had no effect on overall survival, although it did improve survival of patients in whom advanced life support was delayed for more than 10 minutes after arrest. Nimodipine has also been tried in dementia (p.362). Two multicentre studies[10] involving a total of 755 patients with dementia of vascular or degenerative origin given nimodipine for up to 6 months reported improvements in cognitive function and disability, and a systematic review[11] concluded that nimodipine could be of some benefit in patients with various forms of dementia.

1. Dorhout Mees SM, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 12/03/08).
2. Harders A, *et al.* Traumatic subarachnoid hemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; **85:** 82–9.
3. Langham J, *et al.* Calcium channel blockers for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/03/08).
4. Vergouwen MDI, *et al.* Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. *Lancet Neurol* 2006; **5:** 1029–32.
5. Gelmers HJ, *et al.* A controlled trial of nimodipine in acute ischemic stroke. *N Engl J Med* 1988; **318:** 203–7.
6. Trust Study Group. Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet* 1990; **336:** 1205–9.

7. Mohr JP, *et al.* Meta-analysis of oral nimodipine trials in acute ischemic stroke. *Cerebrovasc Dis* 1994; **4:** 197–203.
8. Horn J, *et al.* Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke* 2001; **32:** 461–5.
9. Roine RO, *et al.* Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. *JAMA* 1990; **264:** 3171–7.
10. Parnetti L, *et al.* Nimodipine Study Group. Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. *Clin Ther* 1993; **15:** 394–406.
11. López-Arrieta J, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/07/05).

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including nimodipine, in the management of migraine and cluster headache, see under Nifedipine, p.1355.

Preparations

BP 2008: Nimodipine Intravenous Infusion; Nimodipine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: AC Vascular; Acival; Ampina; Aniduv; Cebrofort; Cletonol†; Eugerial; Explaner; Finacilen; Macobal; Nimo-Somazina; Nimodilat; Nimotop; Nivas; Tenocard; ***Austral.:*** Nimotop; ***Austria:*** Nimotop; ***Belg.:*** Nimotop; ***Braz.:*** Eugerial; Neuron; Nimobal; Nimopax; Nimotop; Nimovas†; Noodipina; Norton†; Oxigen; Vasodipina; ***Canad.:*** Nimotop; ***Chile:*** Brainal†; Grifonimod; Neurogeron†; Nimotop; Regental; Vasoflex†; ***Cz.:*** Brainal†; Dilceren; Nimotop; ***Denm.:*** Nimotop; ***Fin.:*** Nimotop; ***Fr.:*** Nimotop; ***Ger.:*** Nim†; Nimotop; ***Gr.:*** Aurodipine; Befimat; Curban; Figozant; Genovox; Myodipine; Naborel; Nelbinex†; Nimodil; Nimotop; Nimovac-V; Nortolan; Rosital; Stigmicarpin; Thrionipen; Vastripine; Ziremex; ***Hong Kong:*** Nimotop; ***Hung.:*** Nimotop; ***India:*** Vasotop; ***Indon.:*** Nimotop; ***Irl.:*** Nimotop; ***Israel:*** Nimotop; ***Ital.:*** Nimotop; Periplum; ***Malaysia:*** Nimotop†; ***Mex.:*** Kenzolol; Nimotop; Vacer; ***Neth.:*** Nimotop; ***Norw.:*** Nimotop; ***NZ:*** Nimotop; ***Philipp.:*** Nimotop; ***Pol.:*** Nimotop; ***Port.:*** Brainox; Genogris; Modibloq; Modina; Nimotop; Sobrepina; Trinalion; ***Rus.:*** Brainal (Бреинал)†; Nemotan (Немотан); Nimotop (Нимотоп); ***S.Afr.:*** Nimotop; ***Singapore:*** Nimotop; ***Spain:*** Admon; Brainal; Calnit; Kenesil; Modus; Nimotop; Remontal; ***Swed.:*** Nimotop; ***Switz.:*** Nimotop; ***Thai.:*** Nimotop; ***Turk.:*** Nimotop; ***UK:*** Nimotop; ***USA:*** Nimotop; ***Venez.:*** Kleren†; Nemodine; Nimotop; Tropocer.

Multi-ingredient: ***Arg.:*** Idesole Plus; Nemocebral Plus; Nimodilat Plus; Nimoreagin; Nivas Plus.

Nisoldipine *(BAN, USAN, rINN)*

Bay-k-5552; Nisoldipiini; Nisoldipin; Nisoldipino; Nisoldipinum. Isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

Низольдипин

$C_{20}H_{24}N_2O_6$ = 388.4.
CAS — 63675-72-9.
ATC — C08CA07.
ATC Vet — QC08CA07.

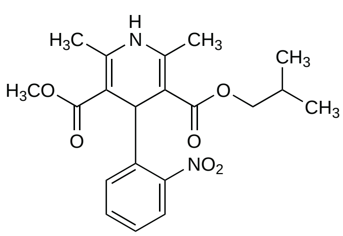

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nisoldipine is well absorbed from the gastrointestinal tract after oral doses but undergoes rapid and extensive first-pass metabolism in the gut wall and liver and bioavailability has been reported to be only about 4 to 8%. About 60 to 80% of an oral dose is excreted in the urine and the remainder in the faeces, mainly as metabolites. The terminal elimination half-life is about 7 to 12 hours. Nisoldipine is more than 99% bound to plasma proteins.

◊ A study[1] in 11 patients given oral nisoldipine 10 mg once or twice daily indicated that the pharmacokinetics of nisoldipine could best be described by an open 2-compartment model. Peak plasma concentrations occurred 1 hour after a single oral dose, and varied greatly between the patients. The mean plasma elimination half-life was 11.4 hours after a single dose and 14.0 hours after repeated dosing, which was longer than had been previously reported, perhaps reflecting the greater sensitivity of the assay.

In another study oral, but not intravenous, nisoldipine increased liver blood flow in 10 healthy subjects and thus affected its own systemic availability.[2] Variations in liver blood flow may account for the interindividual variation in the pharmacokinetics of nisoldipine.

1. Ottosson A-M, *et al.* Analysis and pharmacokinetics of nisoldipine in hypertensive patients. *Curr Ther Res* 1989; **45:** 347–58.
2. van Harten J, *et al.* Variability in the pharmacokinetics of nisoldipine as caused by differences in liver blood flow response. *J Clin Pharmacol* 1989; **29:** 714–21.

Uses and Administration

Nisoldipine is a dihydropyridine calcium-channel blocker with actions and uses similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Nisoldipine is given orally usually as a modified-release preparation. Absorption is affected by food and the modified-release preparation should be taken on an empty stomach; it should not be taken with high fat meals. Doses are similar for both hypertension and angina. The initial dose is 10 mg once daily and the usual maintenance dose is 20 to 40 mg once daily.

◊ Reviews.

1. Mitchell J, *et al.* Nisoldipine: a new dihydropyridine calcium-channel blocker. *J Clin Pharmacol* 1993; **33:** 46–52.
2. Plosker GL, Faulds D. Nisoldipine coat-core: a review of its pharmacology and therapeutic efficacy in hypertension. *Drugs* 1996; **52:** 232–53.
3. Langtry HD, Spencer CM. Nisoldipine coat-core; a review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of ischaemic heart disease. *Drugs* 1997; **53:** 867–84.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nisodipen†; ***Austria:*** Syscor; ***Belg.:*** Sular; Syscor; ***Braz.:*** Syscor; ***Chile:*** Nivas; ***Cz.:*** Syscor†; ***Fin.:*** Syscor; ***Ger.:*** Baymycard; ***Gr.:*** Syscor; ***Hung.:*** Baymycard; ***Ital.:*** Syscor; ***NZ:*** Syscor; ***S.Afr.:*** Syscor†; ***Spain:*** Cornel†; Sular; Syscor; ***Switz.:*** Syscor†; ***UK:*** Syscor; ***USA:*** Sular.

Nitrendipine *(BAN, USAN, rINN)*

Bay-e-5009; Nitrendipiini; Nitrendipin; Nitrendipinas; Nitrendipino; Nitrendipinum. Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

Нитрендипин

$C_{18}H_{20}N_2O_6$ = 360.4.
CAS — 39562-70-4.
ATC — C08CA08.
ATC Vet — QC08CA08.

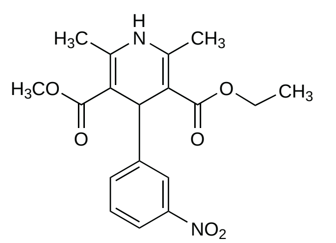

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Nitrendipine). A yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nitrendipine is reported to be well absorbed after oral doses but undergoes extensive first-pass metabolism; the absolute oral bioavailability is reported to range from about 10 to 20%, depending in part on the dosage form. Nitrendipine is about 98% bound to plasma proteins. It is extensively metabolised in the liver and is excreted as metabolites, mainly in urine, with small amounts in the faeces. Although early studies reported a terminal elimination half-life of about 2 to 4 hours, later studies, using more sensitive assay procedures, have recorded values between about 10 and 22 hours.

◊ References.

1. Soons PA, Breimer DD. Stereoselective pharmacokinetics of oral and intravenous nitrendipine in healthy male subjects. *Br J Clin Pharmacol* 1991; **32:** 11–16.

Uses and Administration

Nitrendipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual dose is 20 mg daily as a single oral dose or as 2 divided doses. The dose may be increased to 20 mg twice daily if necessary for the control of resistant hypertension. In the elderly, an initial dose of 10 mg daily should be used. The dose should also be reduced in hepatic impairment (see below).

◊ Reviews.

1. Santiago TM, Lopez LM. Nitrendipine: a new dihydropyridine calcium-channel antagonist for the treatment of hypertension. *DICP Ann Pharmacother* 1990; **24:** 167–75.

Administration in hepatic impairment. The initial dose of nitrendipine should be reduced to 5 to 10 mg once daily in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nirapel; Nitrendil; Tocrat†; ***Austria:*** Baypress; ***Belg.:*** Baypress; ***Braz.:*** Caltren; Nitrencord; ***Chile:*** Cardiazem; Grifonitren; Nitrendicor†; Presabet†; Tensofar; ***Cz.:*** Baypress; Lusopress; Nitrepress; Nitresan; Unipres; ***Denm.:*** Baypress; ***Fr.:*** Baypress; Nidrel; ***Ger.:*** Bayotensin; Jutapress; Nitre-Puren; Nitregamma; Nitren Lich; Nitren†; Nitrendepat†; Nitrendidoc; Nitrendimerck†; Nitrensal; Nitrepress; ***Gr.:*** Aroselin; Baypress; Crivion; G-Press; Lanocardique†; Leonitren; Lisba; Lostradyl; Midonat†; Nelconil; Nifecard; Nivitron; Pallohyman†; Potional; Pressodipin; Spidox; Tepanil†; Ufocard; ***Hong Kong:*** Baypress; ***Hung.:*** Baypress; Unipres; ***Ital.:*** Baypress; Deiten; ***Jpn:*** Baylotensin; ***Mex.:*** Baypress†; ***Neth.:*** Baypress; ***Port.:*** Baypress; Farnitran; Hiperdipina; Hipertenol†; ***Spain:*** Balminil†; Baypresol; Gericin; Niprina; Sub Tensin; Tensogradal; Trendinol†; Vastensium; ***Switz.:*** Baypress; ***Thai.:*** Baypress; Ditrenil; Miniten; ***Turk.:*** Baypress; ***Venez.:*** Baypress; Nitrendil; Retencal†.

Multi-ingredient: ***Ger.:*** Eneas; ***Gr.:*** Eneas; Enit; ***India:*** Cardif Beta; ***Port.:*** Eneas; Enit; ***Spain:*** Eneas; Enit; Vipres; Zorail.

Nitric Oxide *(USAN)*

Azote, monoxyde d'; Azoto oksidas; Azotu(II) tlenek; Kväveoxid; Mononitrogen Monoxide; Nitrogen Monoxide; Nitrogenii oxidum; Nitrogén-monoxid; OHM-11771; Oxid dusnatý; Óxido nítrico; Typpioksidi.

NO = 30.01.
CAS — 10102-43-9.
ATC — R07AX01.
ATC Vet — QR07AX01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nitric Oxide). A colourless gas that turns brown when exposed to air. At 20° and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water. Store compressed at a pressure not exceeding 2.5 MPa measured at 15° in suitable containers.

Adverse Effects

Inhaled nitric oxide may lead to the development of methaemoglobinaemia, particularly at higher doses. Although it is a selective pulmonary vasodilator, systemic hypotension may occur. Abrupt withdrawal of therapy may lead to a deterioration in oxygenation and the development of rebound pulmonary hypertension.

Nitrogen dioxide produced when nitric oxide combines with oxygen can cause acute lung injury; high concentrations of inhaled nitric oxide are directly irritant to the lungs.

◊ A potential complication of inhaled nitric oxide is methaemoglobinaemia but this is probably related to the dose; the risk does not appear to be increased during low-dose (20 ppm) therapy.[1] Another possible adverse event is an increased risk of bleeding due to inhibition of platelet aggregation.[2-5] Rebound pulmonary hypertension[6] and deterioration in oxygenation[7,8] have been reported in some children after stopping nitric oxide therapy. Severe systemic hypotension has also been reported[9] after starting therapy in a neonate with severe left ventricular dysfunction. Pulmonary oedema has been associated with the use of nitric oxide in 2 patients with CREST syndrome, a form of systemic sclerosis.[10] Motor neurone disease in a patient with alcoholism has been partly attributed[11] to the use of nitric oxide for pulmonary hypertension.

1. Kinsella JP, Abman SH. Methaemoglobin during nitric oxide therapy with high-frequency ventilation. *Lancet* 1993; **342:** 615.

2. Högman M, *et al.* Bleeding time prolongation and NO inhalation. *Lancet* 1993; **341:** 1664–5.
3. Joannidis M, *et al.* Inhaled nitric oxide. *Lancet* 1996; **348:** 1448–9.
4. Cheung P-Y, *et al.* Inhaled nitric oxide and inhibition of platelet aggregation in critically ill neonates. *Lancet* 1998; **351:** 1181–2.
5. George TN, *et al.* The effect of inhaled nitric oxide therapy on bleeding time and platelet aggregation in neonates. *J Pediatr* 1998; **132:** 731–4.
6. Miller OI, *et al.* Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. *Lancet* 1995; **346:** 51–2.
7. Aly H, *et al.* Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. *Arch Dis Child Fetal Neonatal Ed* 1997; **76:** F118–F122.
8. Davidson D, *et al.* Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. *Pediatrics* 1999; **104:** 231–6.
9. Henrichsen T, *et al.* Inhaled nitric oxide can cause severe systemic hypotension. *J Pediatr* 1996; **129:** 183.
10. Preston IR, *et al.* Pulmonary edema caused by inhaled nitric oxide therapy in two patients with pulmonary hypertension associated with the CREST syndrome. *Chest* 2002; **121:** 656–9.
11. Tsai GE, Gastfriend DR. Nitric oxide-induced motor neuron disease in a patient with alcoholism. *N Engl J Med* 1995; **332:** 1036.

Precautions

Patients given inhaled nitric oxide should be monitored for methaemoglobinaemia and oxygenation. Inhaled nitric oxide and nitrogen dioxide levels should also be monitored. Treatment should not be stopped abruptly since rebound pulmonary hypertension and deterioration in oxygenation may occur.

The exposure of workers to nitric oxide and nitrogen dioxide should be limited.

◊ References.

1. CSM/MCA. Inhaled nitric oxide. *Current Problems* 1996; **22:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 02/06/08)
2. Cuthbertson BH, *et al.* Use of inhaled nitric oxide in British intensive therapy units. *Br J Anaesth* 1997; **78:** 696–700.
3. Phillips ML, *et al.* Assessment of medical personnel exposure to nitrogen oxides during inhaled nitric oxide treatment of neonatal and pediatric patients. *Pediatrics* 1999; **104:** 1095–1100.

Pharmacokinetics

Nitric oxide is absorbed systemically after inhalation but is rapidly inactivated by reaction with haemoglobin to form methaemoglobin and nitrate; it has a half-life of only a few seconds. It is excreted mainly in the urine as nitrate.

Uses and Administration

Nitric oxide is an endogenous chemical messenger that acts mainly by stimulating guanylate cyclase in smooth muscle to cause vasodilatation. It is also involved in platelet aggregation, neurotransmission, and the immune system, and possesses antimicrobial, antitumour, and antiviral activity.

Endogenous nitric oxide is now recognised to be the same substance as endothelium-derived relaxing factor (EDRF). It is synthesised from L-arginine by the enzyme, nitric oxide synthase, of which three isoforms have been identified. Constitutive isoforms occur in endothelial cells (such as in vascular endothelium, platelets, and the heart) and neuronal cells (in some central and peripheral neurones). Small amounts of nitric oxide are regularly produced by these systems. In contrast, an inducible isoform producing larger amounts of nitric oxide is expressed only after activation by external stimuli such as infection or inflammation. This inducible nitric oxide synthase may be expressed in many cells, including macrophages and cells in vascular smooth muscle, the heart, gastrointestinal tract, and liver.

Inhaled nitric oxide is a highly selective pulmonary vasodilator. It is used in the management of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. It is also used as a diagnostic tool to test acute vasoreactivity in patients with pulmonary hypertension of various aetiologies, and is being studied in other bronchopulmonary disorders and in different age groups.

In the management of hypoxic respiratory failure in neonates, nitric oxide is given by inhalation in a usual concentration of 20 ppm. Doses have been titrated above and below this concentration but due to the risk of methaemoglobinaemia, doses above 20 ppm are not generally recommended. The concentration should be reduced gradually before stopping treatment.

◊ General reviews.

1. Hart CM. Nitric oxide in adult lung disease. *Chest* 1999; **115:** 1407–17.
2. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. *Heart* 2001; **85:** 342–50.
3. Ichinose F, *et al.* Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation* 2004; **109:** 3106–11.
4. Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; **353:** 2683–95.

Respiratory disorders. Inhaled nitric oxide is a potent and highly selective pulmonary vasodilator used in the management of persistent pulmonary hypertension of the newborn (below) and other conditions leading to hypoxic respiratory failure in neonates.

Nitric oxide has also been tried in acute respiratory distress syndrome (below), severe acute respiratory syndrome,[1] respiratory failure,[2] acute severe asthma,[3] primary pulmonary hypertension[4,5] including that in pregnancy,[6,7] and in pulmonary hypertension associated with a wide range of conditions including chronic obstructive pulmonary disease,[8] heart failure,[9] post-cardiac surgery,[10-12] heart or lung transplantation,[13] and high-altitude disorders.[14]

1. Chen L, *et al.* Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004; **39:** 1531–5.
2. Dobyns EL, *et al.* Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; **134:** 406–12.
3. Nakagawa TA, *et al.* Life-threatening status asthmaticus treated with inhaled nitric oxide. *J Pediatr* 2000; **137:** 119–22.
4. Kinsella JP, *et al.* Selective and sustained pulmonary vasodilation with inhalational nitric oxide therapy in a child with idiopathic pulmonary hypertension. *J Pediatr* 1993; **122:** 803–6.
5. Goldman AP, *et al.* Is it time to consider domiciliary nitric oxide? *Lancet* 1995; **345:** 199–200.
6. Lam GK, *et al.* Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. *Obstet Gynecol* 2001; **98:** 895–8.
7. Decoene C, *et al.* Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. *Can J Anaesth* 2001; **48:** 584–7.
8. Vonbank K, *et al.* Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; **58:** 289–93.
9. Matsumoto A, *et al.* Inhaled nitric oxide and exercise capacity in congestive heart failure. *Lancet* 1997; **349:** 999–1000. Correction. *ibid.*; **350:** 818.
10. Haydar A, *et al.* Inhaled nitric oxide for postoperative pulmonary hypertension in patients with congenital heart defects. *Lancet* 1992; **340:** 1545.
11. Miller OI, *et al.* Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000; **356:** 1464–9.
12. Journois D, *et al.* Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. *Chest* 2005; **128:** 3537–44.
13. Rea RS, *et al.* Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother* 2005; **39:** 913–17.
14. Scherrer U, *et al.* Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; **334:** 624–9.

ACUTE RESPIRATORY DISTRESS SYNDROME. Although inhalation of nitric oxide has been reported to improve oxygenation in patients with acute respiratory distress syndrome (p.1498), meta-analyses[1,2] have failed to confirm any significant mortality benefit, and there is some evidence[2] that nitric oxide increases the risk of renal dysfunction.

1. Sokol J, *et al.* Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 26/09/05).
2. Adhikari NKJ, *et al.* Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Abridged version: *BMJ* 2007; **334:** 779–82. Full version: http://www.bmj.com/cgi/reprint/334/7597/779 (accessed 31/07/08)

RESPIRATORY DISORDERS IN NEONATES. Inhaled nitric oxide is used in the management of hypoxic respiratory failure in term and near-term neonates.[1-3] It has also been studied in premature neonates.

Most studies have been in neonates with persistent pulmonary hypertension of the newborn (p.1179), although varying definitions have been used. A systematic review[4] of controlled studies in term and near-term neonates with hypoxic respiratory failure found that oxygenation was improved with inhaled nitric oxide, with a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been shown. A randomised trial[5] also found no mortality benefit when nitric oxide was started early in the disease process, although progression was slowed. Neonates with congenital diaphragmatic hernia (CDH), however, have not been shown to benefit,[6,7] and nitric oxide is not recommended in such patients,[4] although the optimal treatment of this condition is controversial; one study[8] suggested that inhaled nitric oxide may have a role in patients with CDH who develop late pulmonary hypertension. Another study[9] suggested that the improvement in oxygenation may not be sustained, and that neonates with pulmonary hypoplasia and dysplasia are less sensitive to nitric oxide.

The dose of nitric oxide found to be effective in most studies has been from 20 to 80 ppm. However, since nitric oxide is associated with dose-related toxicity, lower doses (1 to 2 ppm) have also been studied. One study[10] found no significant difference between high and low doses, but another study[11] found that low doses did not improve oxygenation and diminished the response to subsequent higher doses.

Inhaled nitric oxide has also been reported to improve oxygenation in premature neonates with hypoxic respiratory failure, but its use is not yet established.[12,13] A study[14] in premature infants with respiratory distress syndrome suggested that the incidence of chronic lung disease and death was reduced by nitric oxide, and an open study[15] in very premature infants who had already developed chronic lung disease also found an improvement in oxygenation with nitric oxide therapy. However, a systematic review[16] found that use of rescue nitric oxide therapy in severely ill infants was ineffective, and that late use to prevent chronic lung disease also had no effect. There was some evidence that early routine use in mildly sick infants might improve outcomes, but further studies were needed to identify those infants who were most likely to benefit.

There have been concerns that use of inhaled nitric oxide might adversely affect neurodevelopmental outcome more than conventional therapy particularly in premature infants, but follow-up studies have reported mixed results. Studies in term and near-term infants,[17-19] and in premature infants,[20] have found that use of nitric oxide has no effect on neurodevelopment, but there have also been reports of poor neurodevelopmental outcome[21] and of improved outcome.[22,23] Differences in study design make comparisons between studies difficult, and the effect on neurodevelopment remains to be confirmed.

1. American Academy of Pediatrics Committee on Fetus and Newborn. Use of inhaled nitric oxide. *Pediatrics* 2000; **106:** 344–5.
2. Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. *J Pediatr* 2000; **136:** 717–26.
3. Hoehn T, Krause MF. Response to inhaled nitric oxide in premature and term neonates. *Drugs* 2001; **61:** 27–39.
4. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 04/06/08).
5. Konduri GG, *et al.* A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. *Pediatrics* 2004; **113:** 559–64.
6. Clark RH, *et al.* Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med* 2000; **342:** 469–74.
7. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics* 1997; **99:** 838–45.
8. Kinsella JP, *et al.* Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. *J Pediatr* 2003; **142:** 397–401.
9. Goldman AP, *et al.* Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics* 1996; **98:** 706–13.
10. Finer NN, *et al.* Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. *Pediatrics* 2001; **108:** 949–55.
11. Cornfield DN, *et al.* Randomized, controlled trial of low-dose inhaled nitric oxide in the treatment of term and near-term infants with respiratory failure and pulmonary hypertension. *Pediatrics* 1999; **104:** 1089–94.
12. Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F337–F341.
13. Kinsella JP, Abman SH. Inhaled nitric oxide in the premature newborn. *J Pediatr* 2007; **151:** 10–15.
14. Schreiber MD, *et al.* Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med* 2003; **349:** 2099–2107.
15. Clark PL, *et al.* Safety and efficacy of nitric oxide in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002; **86:** F41–F45.
16. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 04/06/08).
17. Rosenberg AA, *et al.* Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension. *J Pediatr* 1997; **131:** 70–5.
18. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the Neonatal Inhaled Nitric Oxide Study Group (NINOS). *J Pediatr* 2000; **136:** 611–17.
19. Konduri GG, *et al.* Neonatal Inhaled Nitric Oxide Study Group. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr* 2007; **150:** 235–40.
20. Hintz SR, *et al.* NICHD Neonatal Research Network. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr* 2007; **151:** 16–22.

21. Cheung P-Y, *et al.* The outcome of very low birth weight neonates (≤1500g) rescued by inhaled nitric oxide: neurodevelopment in early childhood. *J Pediatr* 1998; **133:** 735–9.
22. Mestan KKL, *et al.* Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005; **353:** 23–32.
23. Tanaka Y, *et al.* Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **119:** 1159–64.

Sickle-cell disease. Sickle-cell crisis due to vaso-occlusion is an acute complication of sickle-cell disease (p.1044), requiring hospitalisation, with the use of large volumes of intravenous fluids for dehydration, and analgesia including opioids for pain. Concentrations of nitric oxide metabolites and L-arginine have been found to be low in vaso-occlusive crisis and a study[1] in paediatric patients showed that inhaled nitric oxide may be of benefit.

1. Weiner DL, *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003; **289:** 1136–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: INOmax; ***Denm.:*** INOmax; ***Gr.:*** INOmax; ***Neth.:*** INOmax; ***Pol.:*** INOmax; ***Port.:*** INOmax; ***Spain:*** INOmax; ***Switz.:*** INOmax; ***USA:*** INOmax.

Noradrenaline *(BAN)* ⊗

Norepinephrine *(BAN, rINN)*; Levarterenol; Noradrenaliini; Noradrenalin; Noradrenalinum; Norepinefriini; Norepinefrin; Norepinefrina; Norépinéphrine; Norepinephrinum; Norepirenamine. (*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol.

Норэпинефрин

$C_8H_{11}NO_3$ = 169.2.

CAS — 51-41-2.

ATC — C01CA03.

ATC Vet — QC01CA03.

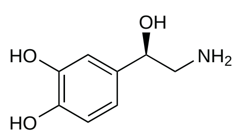

Pharmacopoeias. *Jpn* includes the racemic form.

Noradrenaline Acid Tartrate *(BANM)* ⊗

Norepinephrine Bitartrate *(USAN, rINNM)*; Arterenol Acid Tartrate; *l*-Arterenol Bitartrate; Bitartrato de norepinefrina; Levarterenol Acid Tartrate; Levarterenol Bitartrate; Levarterenoli Bitartras; Noradrenaliinitartraatti; Noradrenaline Bitartrate; Noradrenaline Tartrate; Noradrénaline, tartrate de; Noradrenalini tartras; Noradrenalino tartratas; Noradrenalin-tartarát; Noradrenalintartrat; Norepinefrin tartarát monohydrát; Norepinefryny wodorowinian; Norepinephrine Acid Tartrate *(BANM)*; *l*-Norepinephrine Bitartrate; Norépinéphrine, Bitartrate de; Norepinephrini Bitartras; Norepinephrini Tartras Monohydricus.

Норэпинефрина Битартрат

$C_8H_{11}NO_3,C_4H_6O_6,H_2O$ = 337.3.

CAS — 51-40-1 (anhydrous noradrenaline acid tartrate); 69815-49-2 (noradrenaline acid tartrate monohydrate).

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Noradrenaline Tartrate; Noradrenaline Acid Tartrate BP 2008; Norepinephrine Acid Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

USP 31 (Norepinephrine Bitartrate). A white or faintly grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 2.5 of water and 1 in 300 of alcohol; practically insoluble in chloroform and in ether. Its solutions in water have a pH of about 3.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Noradrenaline acid tartrate is strongly acidic in solution, and would be expected to be incompatible with drugs having an alkaline pH. Licensed product information in the UK states that solutions are reportedly incompatible with alkalis and oxidising agents, barbiturates, chlorphenamine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, and streptomycin. Incompatibility with insulin has also been reported.[1]

1. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.

Noradrenaline Hydrochloride *(BANM)* ⊗

Norepinephrine Hydrochloride *(BANM, rINNM)*; Hidrocloruro de norepinefrina; Noradrenaliinihydrokloridi; Noradrénaline, chlorhydrate de; Noradrenalin-hidroklorid; Noradrenalinhydroklorid; Noradrenalini hydrochloridum; Noradrenalino hidrochloridas; Norepinefrin hydrochlorid; Norépinéphrine, Chlorhydrate de; Norepinephrini Hydrochloridum.

Норэпинефрина Гидрохлорид

$C_8H_{11}NO_3,HCl$ = 205.6.

CAS — 329-56-6.

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Noradrenaline Hydrochloride; Norepinephrine Hydrochloride BP 2008). A white or brownish-white, crystalline powder. It becomes coloured on exposure to air and light. Very soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.5 to 4.5. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

Adverse Effects

As for Sympathomimetics, p.1407. Noradrenaline is an extremely potent peripheral vasoconstrictor and its adverse effects include hypertension (possibly associated with reflex bradycardia), headache, and peripheral ischaemia, which may be severe enough to result in gangrene of the extremities. Extravasation may lead to severe phlebitis and sloughing.

Dental use. Severe headache,[1,2] including fatal cerebral haemorrhage,[1,3] has been reported after the use of lidocaine with noradrenaline 1 in 25 000 for dental anaesthesia. It was suggested[1-3] that preparations containing noradrenaline 1 in 25 000 should not be used, and that a concentration of 1 in 80 000 was to be preferred. However, in the UK the *Dental Practitioners' Formulary*[4] had stated that noradrenaline should not be used as a vasoconstrictor in local anaesthetic solutions since it presented no advantage over adrenaline and carried additional hazard.

1. Boakes AJ, *et al.* Adverse reactions to local anaesthetic/vasoconstrictor preparations: a study of the cardiovascular responses to Xylestesin and Hostacain-with-Noradrenaline. *Br Dent J* 1972; **133:** 137–40.
2. van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog* 1992; **39:** 87–9.
3. Okada Y, *et al.* Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J* 1989; **34:** 323–5.
4. *Dental Practitioners' Formulary.* 2002–2004. London: British Dental Association, British Medical Association, and the Royal Pharmaceutical Society of Great Britain; 2002. D6.

Treatment of Adverse Effects

As for Sympathomimetics, p.1407. If extravasation occurs, infiltration with phentolamine (see p.1370) as soon as possible, and certainly within 12 hours, may relieve pain and prevent tissue necrosis.

Precautions

As for Sympathomimetics, p.1407. Noradrenaline has mainly alpha-agonist properties and must be avoided in the presence of hypertension; blood pressure and infusion rate must be monitored frequently. Noradrenaline-induced cardiac arrhythmias are more likely in patients with hypoxia or hypercapnia.

Noradrenaline is a severe tissue irritant and only very dilute solutions should be used. It should be infused centrally or into a large vein if possible, and care should be taken to avoid extravasation.

Noradrenaline may reduce placental perfusion throughout pregnancy and some consider that it and similar vasoconstrictor sympathomimetics are best avoided; also in late pregnancy noradrenaline provokes uterine contractions which can result in fetal asphyxia.

Interactions

As for Sympathomimetics, p.1407. Severe hypertension may occur if noradrenaline is given to patients taking tricyclic antidepressants since tricyclics block the uptake of noradrenaline into nerve endings.

Pharmacokinetics

Like adrenaline (p.1204), noradrenaline is inactive when given orally, and it is rapidly inactivated in the body by similar processes. When given intravenously it is extensively metabolised and only small amounts are excreted unchanged in the urine.

Uses and Administration

Noradrenaline is a direct-acting catecholamine sympathomimetic (p.1408) with pronounced effects on alpha-adrenergic receptors; it also stimulates $beta_1$ receptors but has little effect on $beta_2$ receptors. It is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Some is also present in the adrenal medulla and is released with adrenaline.

The major effects of noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

Noradrenaline is used for the emergency restoration of blood pressure in acute hypotensive states such as shock (p.1183). It has also been used in the management of cardiac arrest. Noradrenaline has been used in local anaesthesia to diminish the absorption and localise the effect of the local anaesthetic (p.1852) but adrenaline is now preferred (see also Dental use under Adverse Effects, above). Locally applied solutions have been used to control bleeding in upper gastrointestinal haemorrhage and similar disorders.

In **acute hypotensive states**, noradrenaline is used as the acid tartrate, or occasionally as the hydrochloride, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms or noradrenaline hydrochloride 1.2 micrograms are equivalent to about 1 microgram of noradrenaline. It is given by intravenous infusion of a solution containing the equivalent of 4 micrograms of the base per mL in glucose 5%, or sodium chloride 0.9% and glucose 5%. To avoid tissue necrosis the infusion should be given through a central venous catheter or into a large vein high up in a limb, preferably the arm. Some sources have suggested that addition of phentolamine 5 to 10 mg/litre to the infusion may prevent sloughing, should extravasation occur, without affecting the vasopressor action. The infusion is usually given initially at a rate of 2 to 3 mL/minute (8 to 12 micrograms/minute) and adjusted according to the blood pressure response. Blood pressure is initially recorded every 2 minutes and the rate of infusion continuously monitored. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure. The average maintenance dose is 0.5 to 1 mL/minute (2 to 4 micrograms/minute), but there is a wide variation and higher doses may be required. The concentration of the infusion may be altered according to clinical needs. Alternatively a solution containing the equivalent of 40 micrograms of the base per mL may be given at an initial rate of 0.16 to 0.33 mL/minute via a central venous catheter, using a syringe pump or drip counter.

Preparations

BP 2008: Noradrenaline Injection;
USP 31: Norepinephrine Bitartrate Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fioritina; ***Austral.:*** Levophed; ***Belg.:*** Levophed; Norepine†; ***Braz.:*** Levophed; Norephed†; ***Canad.:*** Levophed; ***Chile:*** Adine; ***Ger.:*** Arterenol; ***Gr.:*** Levophed; Noradren; ***Hong Kong:*** Levophed†; ***India:*** Adrenor; ***Indon.:*** Levophed; N-Epi; Raivas; Vascon; ***Irl.:*** Levophed; ***Israel:*** Levophed; ***Malaysia:*** Levophed; ***Mex.:*** Pridam; ***NZ:*** Levophed; ***Philipp.:*** Inotrop; Levophed; ***Pol.:*** Levonor; ***Singapore:*** Levophed†; ***Spain:*** Norages; ***Thai.:*** Levophed; ***USA:*** Levophed.

Used as an adjunct in: ***Austria:*** Neo-Xylestesin forte; Scandonest; ***Braz.:*** Xylestesin; Xylocaina; ***Ger.:*** Xylestesin-S†; Xylestesin, Xylestesin-F†; ***Ital.:*** Lident Andrenor†; Xylonor; ***Port.:*** Scandonest; Xilonibsa; ***S.Afr.:*** Xylotox; ***Spain:*** Xylonor Especial; ***Switz.:*** Scandonest; Xylestesin-F†; Xylestesin-S "special"†; ***Thai.:*** Neo-Lidocaton†.

Norfenefrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de norfenefrina; Norfenefrin Hidroklorür; Norfénéfrine, Chlorhydrate de; Norfenefrini Hydrochloridum; Norphenylephrine Hydrochloride; *m*-Norsynephrine Hydrochloride; WV-569. 2-Amino-1-(3-hydroxyphenyl)ethanol hydrochloride.

Норфенефрина Гидрохлорид

$C_8H_{11}NO_2,HCl = 189.6.$

CAS — 536-21-0 (norfenefrine); 15308-34-6 (norfenefrine hydrochloride).

ATC — C01CA05.

ATC Vet — QC01CA05.

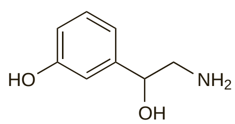

(norfenefrine)

NOTE. *m*-Octopamine has been used as a synonym for norfenefrine. Care should be taken to avoid confusion with octopamine, which is the *p*-isomer.

Profile

Norfenefrine is a sympathomimetic (p.1407) with predominantly alpha-adrenergic activity. It is used as the hydrochloride for its vasopressor effect in the treatment of hypotensive states (p.1174). The usual oral dose is 15 mg three times daily of norfenefrine hydrochloride, as a modified-release preparation. Norfenefrine hydrochloride has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Novadral; ***Ger.:*** Novadral†; ***Mex.:*** AS Cor; ***Switz.:*** Novadral; ***Turk.:*** Novadral.

Multi-ingredient: ***Ger.:*** Adyston†; Normotin-R†; Ordinal Forte†; ***Switz.:*** Ortho-Maren retard.

Octodrine *(USAN, rINN)* ⊗

Octodrina; Octodrinum; SKF-51. 1,5-Dimethylhexylamine.

Октодрин

$C_8H_{19}N = 129.2.$

CAS — 543-82-8.

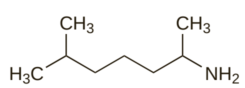

Profile

Octodrine is a sympathomimetic (p.1407) with mainly alpha-adrenergic activity. It has been given orally as the camsilate, in combination with norfenefrine (p.1361), in the treatment of hypotensive states. Octodrine phosphate has been used as an ingredient of preparations for obstructive airways disease.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Ambredin; ***Ger.:*** Ordinal Forte†.

Olmesartan Medoxomil *(BAN, USAN, rINN)*

CS-866; Olmésartan Médoxomil; Olmesartán medoxomilo; Olmesartanum Medoxomilum; RNH-6270 (olmesartan). (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid.

Ольмезартан Медоксомил

$C_{29}H_{30}N_6O_6 = 558.6.$

CAS — 144689-24-7 (olmesartan); 144689-63-4 (olmesartan medoxomil).

ATC — C09CA08.

ATC Vet — QC09CA08.

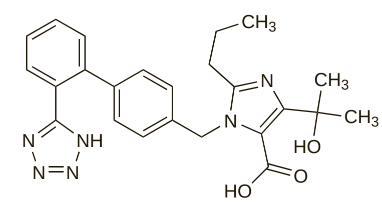

(olmesartan)

NOTE. The name olmesartan has been applied to both the base and to the medoxomil ester.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. The absolute bioavailability is about 26%. Peak plasma concentrations of olmesartan occur about 1 to 2 hours after oral doses. Olmesartan is at least 99% bound to plasma proteins. It is excreted in the urine and the bile as olmesartan; about 35 to 50% of the absorbed dose is excreted in the urine and the remainder in the bile. The terminal elimination half-life is between 10 and 15 hours.

◊ References.

1. Yoshihara K, *et al.* Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. *Clin Pharmacokinet* 2005; **44:** 1329–42.

Uses and Administration

Olmesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171).

Olmesartan is given orally as the ester prodrug olmesartan medoxomil. After a dose the hypotensive effect lasts for 24 hours. Most of the hypotensive effect is apparent within 2 weeks after starting therapy and is maximal within about 8 weeks.

In hypertension, olmesartan medoxomil is given in a usual dose of 20 mg once daily, although in the UK an initial dose of 10 mg once daily is recommended. The dose may be increased to 40 mg once daily if required.

For doses in hepatic or renal impairment, see below.

◊ References.

1. Brunner HR. The new oral angiotensin II antagonist olmesartan medoxomil: a concise overview. *J Hum Hypertens* 2002; **16** (suppl 2): S13–S16.
2. Warner GT, Jarvis B. Olmesartan medoxomil. *Drugs* 2002; **62:** 1345–53. Correction. *ibid.*; 1852.
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10. Barrios V, Escobar C. Olmesartan medoxomil plus hydrochlorothiazide for treating hypertension. *Expert Opin Pharmacother* 2008; **9:** 129–36.

Administration in hepatic or renal impairment. Olmesartan is excreted in both urine and bile and raised plasma concentrations have been noted in patients with renal or hepatic impairment. In patients with *renal impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment (creatinine clearance (CC) below 20 mL/minute) since experience is limited, and the maximum dose in mild to moderate impairment (CC 20 to 60 mL/minute) is 20 mg once daily. Similarly, in patients with *hepatic impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment since there is no experience. Those with moderate hepatic impairment should be given an initial dose of 10 mg once daily and the maximum dose is 20 mg once daily.

Migraine. For reference to the use of angiotensin II receptor antagonists, including olmesartan, in the prophylaxis of migraine, see under Losartan, p.1328.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Olmec; Tensonit; Vasexten; ***Austral.:*** Olmetec; ***Austria:*** Olmetec; ***Belg.:*** Belsar; Olmetec; ***Braz.:*** Benicar; Olmetec; ***Cz.:*** Olmetec; Sarten; ***Denm.:*** Olmetec; ***Fin.:*** Benetor; Olmetec; ***Fr.:*** Alteis; Olmetec; ***Ger.:*** Olmetec; Votum; ***Gr.:*** Olartan; Olmetec; ***Hong Kong:*** Olmetec; ***Indon.:*** Olmetec; ***Irl.:*** Benetor; Omesar; ***Israel:*** Olmetec; ***Ital.:*** Olmetec; Olpress; Plaunac; ***Jpn:*** Olmetec; ***Malaysia:*** Olmetec; ***Neth.:*** Olmes; Olmetec; ***Norw.:*** Olmetec; ***Philipp.:*** Olmetec; ***Port.:*** Olmetec; Olsar; ***Singapore:*** Olmetec; ***Spain:*** Ixia; Olmetec; Openvas; ***Switz.:*** Olmetec; Votum; ***Thai.:*** Olmetec; ***UK:*** Olmetec; ***USA:*** Benicar; ***Venez.:*** Benicar; Olmetec.

Multi-ingredient: ***Austral.:*** Olmetec Plus; ***Belg.:*** Olmetec Plus; ***Braz.:*** Benicar HCT; Olmetec HCT; ***Cz.:*** Olmetec Plus H; Sarten Plus H; ***Fr.:*** Alteisduo; Coolmetec; ***Ger.:*** Olmetec Plus; Votum Plus; ***Gr.:*** Olartan Plus; Olmetec Plus; ***Malaysia:*** Olmetec Plus; ***Port.:*** Olsar Plus; ***Singapore:*** Olmetec Plus; ***Switz.:*** Olmetec Plus; Votum Plus; ***UK:*** Olmetec Plus; ***USA:*** Azor; Benicar HCT.

Olprinone Hydrochloride *(rINNM)*

Hidrocloruro de olprinona; Olprinone, Chlorhydrate d'; Olprinoni Hydrochloridum. 1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxonicotinonitrile hydrochloride.

Ольпринона Гидрохлорид

$C_{14}H_{10}N_4O,HCl = 286.7.$

CAS — 106730-54-5 (olprinone); 119615-63-3 (olprinone hydrochloride).

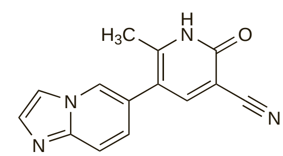

(olprinone)

Profile

Olprinone is a phosphodiesterase inhibitor with positive inotropic and vasodilator activity, used in acute heart failure (p.1165). It is given intravenously as the hydrochloride in an initial dose of 10 micrograms/kg given over 5 minutes, followed by a continuous infusion at a rate of 100 to 400 nanograms/kg per minute, according to response.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Coretec.

Omapatrilat *(BAN, USAN, rINN)*

BMS-186716; BMS-186716-01; Omapatrilate; Omapatrilato; Omapatrilatum. (4*S*,7*S*,10a*S*)-Octahydro-4-[(*S*)-α-mercaptohydrocinnamamido]-5-oxo-7*H*-pyrido[2,1-*b*][1,3]thiazepine-7-carboxylic acid.

Омапатрилат

$C_{19}H_{24}N_2O_4S_2 = 408.5.$

CAS — 167305-00-2.

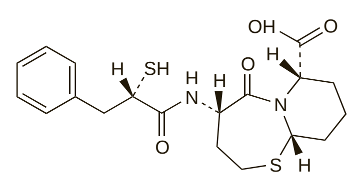

Profile

Omapatrilat is a vasopeptidase inhibitor. It inhibits both angiotensin-converting enzyme and neutral endopeptidase and is under investigation in the management of hypertension and heart failure. However, its use may be limited by severe angioedema.

◊ References.

1. Tabrizchi R. Dual ACE and neutral endopeptidase inhibitors: novel therapy for patients with cardiovascular disorders. *Drugs* 2003; **63:** 2185–2202.
2. Kostis JB, *et al.* Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17:** 103–11.

Omega-3 Fatty Acids

Ácidos grasos omega 3.

Омега-3 Жирные Кислоты

ATC — C10AX06.

ATC Vet — QC10AX06.

Docosahexaenoic Acid

Doconexent (*rINN*); Cervonic Acid; DHA; Doconexento; Doconexentum. (*all-Z*)-Docosahexa-4,7,10,13,16,19-enoic acid.

Доконексент

$C_{22}H_{32}O_2$ = 328.5.

CAS — 6217-54-5; 25167-62-8.

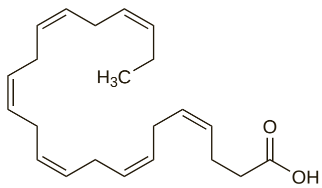

NOTE. DHA is also used as a synonym for dihydroxyacetone (p.1594).

Docosahexaenoic Acid Ethyl Ester

Doconexent Ethyl (*rINNM*); Cervonic Acid Ethyl Ester; Doconexent d'Éthyle; Doconexento de etilo; Ethyl Docosahexaenoate; Ethylum Doconexentum.

Этил Доконексент

$C_{24}H_{36}O_2$ = 356.5.

CAS — 81926-94-5 (all-Z); 84494-72-4.

Eicosapentaenoic Acid

Icosapent (*rINN*); Acidum Eicosapentaenoicum; Eikosapentaeenihappo; Eikosapentaensyra; EPA; Icosapento; Icosapentum; Timnodonic Acid. (*all-Z*)-Eicosapenta-5,8,11,14,17-enoic acid.

Икозапент

$C_{20}H_{30}O_2$ = 302.5.

CAS — 10417-94-4 (all-z); 1553-41-9.

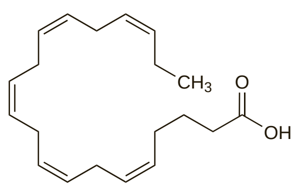

NOTE. EPA is also used as a synonym for pheneturide.

Eicosapentaenoic Acid Ethyl Ester

Icosapent Ethyl (*rINNM*); Ethyl Eicosapentaenoate; Ethyl Icosapentate; Ethylum Icosapentum; Icosapent d'Ethyle; Icosapento de etilo; Timnodonic Acid Ethyl Ester.

Этил Икозапент

$C_{22}H_{34}O_2$ = 330.5.

CAS — 73310-10-8 (all-Z); 86227-47-6 (all-Z); 84494-70-2.

Pharmacopoeias. In *Jpn.*

Linolenic Acid

ALA; Alpha-linolenic Acid; Kwas linolenowy; α-Linolenic Acid. (*all-Z*)-9,12,15-Octadecatrienoic acid.

Линоленовая Кислота

$C_{18}H_{30}O_2$ = 278.4.

CAS — 463-40-1.

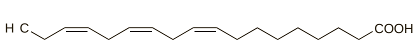

NOTE. Do not confuse with γ-linolenic acid (Gamolenic Acid, p.2308)

Omega-3-acid Ethyl Esters (*USAN*)

Ethylestery omega-3-kyselin; K-85; Omega-3 Acidorum Esteri Ethylici; Omega-3 Acidorum Esteri Ettylici; Omega-3 rūgščių etilo esteriai; Omega-3-sav-etilészterek.

Омега-3-кислоты Этиловых Эфиров

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Omega-3-Acid Ethyl Esters 60). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fat fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters, eicosapentaenoic acid ethyl esters, and docosahexaenoic acid ethyl esters should be stated on the label. For a total omega-3 acid ethyl ester content of 55%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of eicosapentaenoic acid ethyl esters is not less than 40%; for a total omega-3 acid ethyl ester content of 60%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50% and the content of docosahexaenoic acid ethyl esters is not less than 40%; and for a total omega-3 acid ethyl ester content of 65%, the amount of eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is not less than 50%, the content of eicosapentaenoic acid ethyl esters is not less than 25%, and the content of docosahexaenoic acid ethyl esters is not less than 20%. Tocopherol may be added as an antioxidant.

A light yellow liquid with a slight fish-like odour. Practically insoluble in water; very soluble in acetone, in dehydrated alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

Ph. Eur. 6.2 (Omega-3-Acid Ethyl Esters 90). A mixture of ethyl esters of omega-3 acids. They are obtained by transesterification of the body oil of fat fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acid ethyl esters is not less than 90%, and that of both eicosapentaenoic acid ethyl esters and docosahexaenoic acid ethyl esters together is 80%; the content of eicosapentaenoic acid ethyl esters is not less than 40% and of docosahexaenoic acid ethyl esters is not less than 34%. Tocopherol may be added as an antioxidant.

A light yellow liquid with a slight fish-like odour. Practically insoluble in water; very soluble in acetone, in dehydrated alcohol, in heptane, and in methyl alcohol. Store in airtight containers under inert gas. Protect from light.

Omega-3 Marine Triglycerides

Deniz Kaynaklı Omega-3 Trigliseridler; Poisson (huile de) riche en acides oméga-3 (fish oil, rich in omega-3-acids); Saumon d'élevage, huile de (salmon oil, farmed); Triglicéridos marinos omega 3.

Омега-3 Триглицериды Морского Происхождения

NOTE. Omega-3 Marine Triglycerides (BAN) is a mixture of triglycerides of fatty acids from marine fish containing the equivalent of about 18% of eicosapentaenoic acid and 12% of docosahexaenoic acid. The content of triglycerides is not the same as that in Omega-3-Marine Triglycerides BP.

Pharmacopoeias. *Eur.* (see p.vii) includes Omega-3-Acid Triglycerides, Fish Oil, Rich in Omega-3-Acids, and Salmon Oil, Farmed. *US* includes Fish Oil containing Omega-3 Acids.

Ph. Eur. 6.2 (Omega-3-Acid Triglycerides; Omega-3 Acidorum Triglycerida; Omega-3-Marine Triglycerides). A mixture of mono-, di-, and triesters of omega-3 acids with glycerol, containing mainly triesters. They are obtained by esterification of concentrated and purified omega-3 acids with glycerol or by transesterification of the omega-3 acid ethyl esters with glycerol. The omega-3 acids are from the body oil of fatty fish species coming from families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae, and Scombridae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The total amount of omega-3 acids expressed as triglycerides is not less than 60% and that of both eicosapentaenoic acid and docosahexaenoic acid together, expressed as triglycerides, is not less than 45%. Tocopherol may be added as an antioxidant.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 6.2 (Fish Oil, Rich in Omega-3-Acids; Piscis Oleum Omega-3 Acidis Abundans). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Scombridae, and Ammodytidae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (timnodonic acid), heneicosapentaenoic acid, clupanodonic acid, and docosahexaenoic acid (cervonic acid). The minimum content, expressed as triglycerides, is eicosapentaenoic acid 13%, docosahexaenoic acid 9%, and total omega-3 acids 28%. Antoxidants may be added.

A pale yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled, airtight containers under inert gas. Protect from light.

Ph. Eur. 6.2 (Salmon Oil, Farmed; Salmonis Domestici Oleum). The purified fatty oil obtained from fresh farmed *Salmo salar.* The positional distribution (β(2)-acyl) is 60 to 70% for docosahexaenoic acid (cervonic acid), 25 to 35% for eicosapentaenoic acid (timnodonic acid), and 40 to 55% for moroctic acid. The sum of the contents of eicosapentaenoic acid and docosahexaenoic acid, expressed as triglycerides, is 10.0 to 28.0%. Authorised antoxidants may be added. A pale pink liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; very soluble in acetone and in heptane. Store in well-filled airtight containers under an inert gas. Protect from light.

USP 31 (Fish Oil containing Omega-3 Acids). The purified, winterised, and deodorised fatty oil obtained from fish of the families Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombroidae, and Ammodytidae. The acids consist of alpha-linolenic acid, moroctic acid, eicosatetraenoic acid, eicosapentaenoic acid (EPA), heneicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid (DHA). It contains not less than 28% (w/w) of total omega-3 acids (expressed as free acids) consisting of not less than 13% of EPA and not less than 9% of DHA. Antoxidants may be added. A pale yellow liquid. Practically insoluble in water; slightly soluble in anhydrous alcohol; very soluble in acetone and in heptane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. It may be stored under vacuum or under an inert gas. Protect from light.

Adverse Effects and Precautions

The most common adverse effects of omega-3 fatty acid preparations are gastrointestinal disturbances, particularly at high doses, including nausea, eructation, vomiting, abdominal distension, diarrhoea, and constipation. There have been rare reports of acne and eczema. Moderate increases in hepatic transaminases have been reported in patients with hypertriglyceridaemia.

Preparations vary widely in concentration and purity. Some preparations contain significant amounts of vitamins A and D and long-term use could cause toxicity. There is a theoretical possibility of vitamin E deficiency with long-term use, although many preparations contain vitamin E as an antoxidant. Concern has been expressed over the high calorific value and cholesterol content of some preparations.

Omega-3 fatty acids have antithrombotic activity and should be given with caution to patients with haemorrhagic disorders or to those receiving anticoagulants or other drugs affecting coagulation. Hepatic function should be monitored in patients with hepatic impairment, particularly if receiving high doses. Caution may also be required in asthmatic patients sensitive to aspirin since omega-3 fatty acids may affect prostaglandin synthesis (but see Inflammatory and Auto-immune Disorders, below, for studies of fish oils in the management of asthma).

◊ Reviews.

1. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007; **99** (suppl): 35C–43C.

Effects on the blood. Omega-3 fatty acids have antithrombotic effects and may increase bleeding. In a study[1] in adolescents with familial hypercholesterolaemia, epistaxis occurred in 8 of 11 patients treated with a fish oil supplement; prolonged bleeding time was noted in 3 patients. There have also been case reports of INR elevation and haematoma in patients taking fish oil preparations with antithrombotics (see Lipid Regulating Drugs under Interactions of Warfarin, p.1431), although controlled studies have failed to show an effect.

1. Clarke JTR, *et al.* Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr* 1990; **116:** 139–41.

Effects on glucose metabolism. Although a deterioration in glycaemic control has been reported in diabetic patients taking omega-3 fatty acids and fish oil preparations, a meta-analysis[1] of studies in type 1 and type 2 diabetics, and a systematic review[2] of controlled studies in type 2 diabetics, both concluded that fish oils effectively lowered triglycerides without a deleterious effect on glycaemic control.

1. Friedberg CE, *et al.* Fish oil and glycemic control in diabetes: a meta-analysis. *Diabetes Care* 1998; **21:** 494–500.
2. Hartweg J, *et al.* Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 30/05/08).

Uses and Administration

Omega-3 fatty acids are long-chain polyunsaturated fatty acids containing 18 to 22 carbon atoms and a varying number of double bonds, the first of which is in the n-3 position. They are essential fatty acids and must be obtained from the diet. They have an important role as eicosanoid precursors and as components of cell membranes; in humans, they compete with arachidonic acid, an omega-6 fatty acid precursor. Their actions in humans include a hypolipidaemic action (especially a reduction in plasma triglycerides), an anti-inflammatory action, and an antiplatelet effect. The main dietary omega-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid and are derived from marine fish; other omega-3 fatty acids found in fish oils (defined in terms of number of carbon atoms and number of double bonds) include alpha-linolenic acid, moroctic acid (C18:4), eicosatetraenoic acid (C20:4), heneicosapentaenoic acid (C21:5), and clupanodonic acid (C22:5). Alpha-linolenic acid is also found in some plant sources and is converted to a limited extent in the body to eicosapentaenoic acid and docosahexaenoic acid.

Fish oils and purified omega-3 fatty acid preparations are used in patients with severe hypertriglyceridaemia (see Hyperlipidaemias, p.1169) and for secondary prevention after myocardial infarction (see Cardiovascular Disorders below). They are also marketed as dietary supplements, and are used in preparations for parenteral nutrition.

The preparations available vary widely in purity and omega-3 fatty acid content, usually expressed in terms of eicosapentaenoic acid and docosahexaenoic acid; the fatty acids may be present as triglycerides or as ethyl esters. Typical oral doses of fish oil for the treatment of hypertriglyceridaemia are 5 g twice daily of a preparation containing 17% eicosapentaenoic acid and 11.5% docosahexaenoic acid, or 2 to 4 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid. For the secondary prevention of myocardial infarction, 1 g daily of a preparation containing 46% eicosapentaenoic acid and 38% docosahexaenoic acid may be given. Eicosapentaenoic acid ethyl ester may also be used alone in the treatment of hyperlipidaemia, and to improve the symptoms associated with arteriosclerosis obliterans.

Action. Interest in omega-3 fatty acids arose from observations that populations with a diet rich in marine fish oils generally have a low incidence of cardiovascular disease, while the incidence of asthma, psoriasis, and auto-immune diseases appears to be lower among Eskimos (Inuit) than in populations consuming a typical western diet (although the incidence of haemorrhagic stroke and epilepsy may be higher). Increased omega-3 fatty acid intake has been suggested to underlie these differences, and fish oil and other omega-3 preparations have therefore been promoted as dietary supplements, with benefit suggested for many conditions.

The beneficial health effects of omega-3 fatty acids have been attributed to their effects on eicosanoid balance, lipid metabolism, and cell membranes. Essential fatty acids of both the omega-3 and omega-6 series have an important role as components of cell membranes and as precursors of eicosanoids (prostaglandins, leukotrienes, and thromboxanes). Eicosanoids derived from omega-3 fatty acids generally have anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilator effects, while those derived from omega-6 fatty acids tend to be pro-inflammatory and prothrombotic. Since omega-3 and omega-6 fatty acids compete for the same enzymatic pathways, increasing the intake of omega-3 fatty acids promotes the formation of anti-inflammatory and antithrombotic eicosanoids, and may have beneficial effects. Production of inflammatory cytokines such as interleukins and tumour necrosis factor alpha may also be affected.

For further information on the actions of omega-3 fatty acids in cardiovascular disorders, inflammatory and auto-immune disorders, malignant neoplasms, and neurological and psychiatric disorders, see below.

References.

1. Connor WE. Importance of n-3 fatty acids in health and disease. *Am J Clin Nutr* 2000; **71** (suppl): 171S–175S.
2. Covington MB. Omega-3 fatty acids. *Am Fam Physician* 2004; **70:** 133–40.

Cardiovascular disorders. Omega-3 fatty acids have a number of actions that are potentially beneficial for patients at risk of cardiovascular disease.[1-6] They have a hypolipidaemic effect due to inhibition of very-low-density lipoprotein (VLDL) synthesis in the liver, and this particularly reduces triglyceride concentrations.[7] Heart rate may be reduced,[8] and they also have an antiarrhythmic effect,[5] possibly due to a direct action on myocardial cells. Omega-3 fatty acids may also reduce blood pressure in hypertensive patients,[9] as well as increasing erythrocyte deformability and decreasing blood viscosity. They appear to stabilise atherosclerotic plaques,[10] and may reduce progression of atherosclerosis[11] and of restenosis after percutaneous coronary intervention.[12]

Despite these benefits, the role of dietary or supplementary omega-3 fatty acids for cardiovascular risk reduction (p.1164) remains controversial. Epidemiological studies have suggested that increased dietary fish intake is associated with a reduced risk of fatal coronary events,[13] and possibly also ischaemic stroke,[14,15] and there is also evidence for benefit with omega-3 fatty acid supplements, particularly for secondary prevention.[1-4,16] In the GISSI-Prevenzione study,[17] long-term use of omega-3 fatty acid supplements reduced the risk of fatal cardiovascular events in a large group of Italian post-infarction patients studied for 3.5 years,[17] while the JELIS investigators[18] reported a reduction in primary and secondary cardiovascular events in Japanese patients with hypercholesterolaemia. However, a systematic review[19] found no clear benefit from omega-3 fatty acids, whether dietary or supplemental, in people with or without cardiac risk factors.

1. Carroll DN, Roth MT. Evidence for the cardioprotective effects of omega-3 fatty acids. *Ann Pharmacother* 2002; **36:** 1950–6.
2. Kris-Etherton PM, *et al.* Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002; **106:** 2747–57. Correction. *ibid.* 2003; **107:** 512.
3. Din JN, *et al.* Omega 3 fatty acids and cardiovascular disease—fishing for a natural treatment. *BMJ* 2004; **328:** 30–5.
4. Holub BJ. Clinical nutrition 4: omega-3 fatty acids in cardiovascular care. *CMAJ* 2002; **166:** 608–15.
5. Breslow JL. n-3 Fatty acids and cardiovascular disease. *Am J Clin Nutr* 2006; **83** (suppl 6): 1477S–1482S.
6. Lee JH, *et al.* Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc* 2008; **83:** 324–32.
7. McKenney JM, Sica D. Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia. *Am J Health-Syst Pharm* 2007; **64:** 595–605.
8. Mozaffarian D, *et al.* Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* 2005; **112:** 1945–52.
9. Geleijnse JM, *et al.* Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens* 2002; **20:** 1493–9.
10. Thies F, *et al.* Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003; **361:** 477–85.
11. von Schacky C, *et al.* The effect of dietary ω-3 fatty acids on coronary atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **130:** 554–62.
12. Balk EM, *et al.* Effects of omega-3 fatty acids on coronary restenosis, intima-media thickness, and exercise tolerance: a systematic review. *Atherosclerosis* 2006; **184:** 237–46.
13. He K, *et al.* Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* 2004; **109:** 2705–11.
14. He K, *et al.* Fish consumption and risk of stroke in men. *JAMA* 2002; **288:** 3130–6.
15. Iso H, *et al.* Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001; **285:** 304–12.
16. Wang C, *et al.* n-3 Fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006; **84:** 5–17.
17. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999; **354:** 447–55. Correction. *ibid.* 2001; **357:** 642.
18. Yokoyama M, *et al.* The Japan EPA Lipid Intervention Study (JELIS) investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007; **369:** 1090–8. Correction. *ibid.*; **370:** 220.
19. Hooper L, *et al.* Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 30/05/08).

Inflammatory and auto-immune disorders. Omega-3 fatty acids have effects on several immunological and inflammatory mediators[1,2] and have been tried in a number of inflammatory and auto-immune disorders. Beneficial effects have been reported in rheumatoid arthritis[3] (p.11) and in glomerular kidney disease[4-6] (p.1504), but results in kidney transplantation (p.1813) have been mixed, and systematic reviews[7,8] suggest no significant effect on rejection episodes or graft survival. Some studies have shown benefit in psoriasis (p.1583), both with oral[9,10] and with intravenous dosage,[11,12] but other studies found neither the oral[13] nor the topical[14] route to be effective. Variable benefit has been seen in inflammatory bowel disease[15] (p.1697) although this may relate to the different formulations used. In Crohn's disease, a systematic review found that enteric-coated formulations helped to maintain remission,[16] but a subsequent randomised study using a gelatin capsule formulation found no benefit.[17] Similarly, a systematic review found that conventional formulations were not of benefit in patients with ulcerative colitis.[18] Fish oils have also been tried in lung disorders, although systematic reviews have found little evidence of benefit in asthma;[19,20] in cystic fibrosis, limited benefit has been reported,[21] with one study[22] reporting that fish oil supplementation reduced the need for antibacterial treatment. Preliminary evidence[23] also suggests that omega-3 supplementation may reduce inflammatory markers and improve dyspnoea in chronic obstructive pulmonary disease.

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12. Mayser P, *et al.* n-3 Fatty acids in psoriasis. *Br J Nutr* 2002; **87** (suppl 1): S77–S82.
13. Søyland E, *et al.* Effect of dietary supplementation with very-long-chain n-3 fatty acids in patients with psoriasis. *N Engl J Med* 1993; **328:** 1812–16.
14. Henneicke-von Zepelin H-H, *et al.* Highly purified omega-3-polyunsaturated fatty acids for topical treatment of psoriasis: results of a double-blind, placebo-controlled multicentre study. *Br J Dermatol* 1993; **129:** 713–17.
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17. Feagan BG, *et al.* Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA* 2008; **299:** 1690–7.
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19. Thien FCK, *et al.* Dietary marine fatty acids (fish oil) for asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 30/05/08).
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23. Matsuyama W, *et al.* Effects of omega-3 polyunsaturated fatty acids on inflammatory markers in COPD. *Chest* 2005; **128:** 3817–27.

Malignant neoplasms. There is some evidence that the incidence of cancer may be lower in populations with a high fish intake, and *animal* studies have suggested that omega-3 fatty acids may slow the progression of some cancers.[1] However, studies of omega-3 fatty acid intake and cancer incidence in humans have given conflicting results, and systematic reviews[2,3] have found no evidence of a beneficial effect. It has also been suggested that omega-3 fatty acids might be beneficial in patients with cancer cachexia, but a randomised study[4] found that eicosapentaenoic acid supplementation was less effective than megestrol acetate, and a systematic review[5] found insufficient evidence to establish whether eicosapentaenoic acid was more effective than placebo.

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Neurological and psychiatric disorders. Omega-3 fatty acids concentrate in neuronal membranes and appear to have an important role in brain development and function. Supplementation during pregnancy and in infants has been investigated, but there is little evidence that maternal supplements improve neonatal outcomes,[1] and only limited evidence of a benefit on growth and neurodevelopment in preterm infants given milk formulas supplemented with both omega-3 and omega-6 fatty acids.[2,3] However, in older children with phenylketonuria treated with dietary restriction, omega-3 fatty acid supplements may improve motor skills.[4]

Omega-3 fatty acids have also been tried in the treatment of neurological and psychiatric disorders.[5,6] There appears to be a link between deficient fatty acid intake and mood disorders,[7] and there is reasonable evidence to support the use of omega-3 fatty acids as adjuncts in the treatment of depression, including possible benefit in the depressive symptoms of bipolar disorder, but further studies are needed to confirm this.[8-10] Benefit has been shown in schizophrenia, but results have been mixed and the role of omega-3 fatty acids is not established.[11] Some positive results have been reported in hyperactivity and in autism, but further studies are needed.[12] Omega-3 fatty acids have also been tried in dementia, but there is not yet sufficient evidence[13] to recommend them for prevention.

Eicosapentaenoic acid ethyl ester has been tried in Huntington's disease, and may improve motor function,[14] but this remains to be confirmed.

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2. Fewtrell MS, *et al.* Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. *J Pediatr* 2004; **144:** 471–9.
3. Clandinin MT, *et al.* Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. *J Pediatr* 2005; **146:** 461–8.
4. Beblo S, *et al.* Effect of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria. *J Pediatr* 2007; **150:** 479–84.
5. Freeman MP, *et al.* Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* 2006; **67:** 1954–67.
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10. Montgomery P, Richardson AJ. Omega-3 fatty acids for bipolar disorder. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 13/08/08).
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12. Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *Int Rev Psychiatry* 2006; **18:** 155–72.
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Preparations

USP 31: Fish Oil containing Omega-3 Acids Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Regulip; ***Austral.:*** Bioglan Maxepa; Fishaphos; Maxepa†; ***Austria:*** Eicosapen; Omacor; Omegaven; ***Belg.:*** Omacor; ***Braz.:*** Votag; ***Canad.:*** Focus 425; ***Chile:*** Epasan Omega 3; Eykosacol; Neuromins†; Omegaven; Sanepa Forte†; ***Cz.:*** Omacor; Omegaven; ***Denm.:*** Omegaven; ***Fr.:*** Epabiol; Maxepa; OM3; Omacor; Omega 3; Omega 3+; Omegaven; Psoriacalm; Triglistab; ***Ger.:*** Ameu; Eicosan; Eicosapen; Lipiscor; Omacor; Omegaven; Zodin; ***Gr.:*** Farlipid; Maxepa; Omacor; Zodin; ***Hong Kong:*** Lipomega; Smartfish; ***Hung.:*** Omacor; Omegaven; ***India:*** Maxepa; ***Indon.:*** Champs DHA; Prolacta with DHA; Prolacta with DHA for Mother; ***Irl.:*** Maxepa; Omacor; ***Israel:*** Omegaven; ***Ital.:*** Almic; Esapent; Eskim; Fish Factor; Maxepa; Omegaven; Seacor; Triolip; Triomar; ***Jpn:*** Epadel; ***Malaysia:*** Champs DHA; Hovid Omega-3†; Mepa; Quest Gamma EPA Plus; VitaEPA†; ***Mex.:*** Colega-3; Fresomega; ***Neth.:*** Omacor; Omegaven; Zodin; ***Norw.:*** Omacor; ***Philipp.:*** Fisol; Omacor; Zymechol; ***Pol.:*** BioCardine; Galomega†; Omega-3; Omegaven; Trienyl; ***Port.:*** Omacor; Omegaven; Zodin; ***Rus.:*** Omacor (Омакор); ***Singapore:*** Champs DHA; ***Spain:*** Omacor; ***Swed.:*** Omegaven; ***Switz.:*** Ameu†; Eicosapen; Epacaps; Omega-3; Omegaven; ***Thai.:*** Omacor; ***Turk.:*** Marincap; Omega III; Omegaven; ***UK:*** Maxepa; Omacor; Pure Omega; ***USA:*** Cardi-Omega 3; Cholestin; Lovasa; Lovaza; Maxepa; Promega; SuperEPA; ***Venez.:*** Epax; Fizoil; Marina; Maxepa; Ometrix.

Multi-ingredient: ***Arg.:*** Cholesterol Reducing Plan†; ***Austral.:*** APR Cream†; Arthriforte; Bioglan Arthri Plus; Bioglan Zellulean with Escin; Curaderm†; Efalex†; Efamarine†; ER Cream†; Himega†; Lifechange Circulation Aid†; Macro Maxepa†; Maxepa & EPO†; Naudicelle Marine†; Pre Natal†; Vita-Preg†; ***Austria:*** SMOFlipid; ***Braz.:*** Borag; Glavit; Lipcor†; Lisacol†; ***Canad.:*** Bionagre plus E; Efalex†; ***Chile:*** Acnoxyl Jabon†; Celltech Gold; ***Cz.:*** Lipoplus; SMOFlipid; ***Denm.:*** SMOFlipid; ***Fin.:*** Lipoplus; ***Fr.:*** A-Flam; Arthrolib; Bio-Marine Plus†; Bionagrol Plus; Cardiom3; Dioptec; Effadiane relipidantes; Elteans; Molval; OM3junior; Omegacoeur; Phytophanere; Reti-Nat; Synerbiol; ***Ger.:*** SMOFlipid; ***Gr.:*** Atroil; Dynapen-3; Emfrastop; Epadoc; Lipemia; Pazeril; Prolipid; Salmon Oil; SMOFlipid; ***Hong Kong:*** Biomega-3†; Doctor's Choice Omega 3; Eye Q; Himega†; Mumomega; ***Hung.:*** SMOFlipid; ***India:*** Cadvion; Dicloran MS; Megasoft-E; ***Indon.:*** Co-Q-10; Flexasur; Maxitrin; Nulacta Li; Obipluz; Prenatin-DF; Vitazym; ***Irl.:*** MorDHA; MorEPA; ***Israel:*** Triomar; ***Ital.:*** Agedin Plus; Derman-Oil; Dermana Crema; Dermana Pasta; DHA; Ditrevit; Fitogenase; Fotrec DHA; Gammaplus; Ictom 3†; Memoactive†; Secril; Trofinerv; Trofinerv Antiox; Venactive†; Venoton; ***Malaysia:*** Adult Citrex Multivitamin + Ginseng + Omega 3; VitaEPA Plus†; ***Neth.:*** Lipoplus; SMOFlipid; ***Norw.:*** SMOFlipid; ***NZ:*** Efacal†; Efalex; Efamarine; Efamax; ***Philipp.:*** Memori Plus; OB Smart SG; ***Pol.:*** SMOFlipid; ***Port.:*** Lipoplus; ***Singapore:*** CardioCare; Celatrac; Gissicor; Seven Seas JointCare; Seven Seas JointCare High Strength; Seven Seas JointCare Max; VitaEPA; VitaEPA Plus; ***Swed.:*** Lipoplus; SMOFlipid; ***Switz.:*** Vitafissan N; ***UK:*** Chol-Aid; Efalex; Efamarine; GlucOsamax; Lipidem; Omegaven; Pregnacare Plus; ProBrain; SMOFlipid; ***USA:*** Animi-3; Citracal Prenatal + DHA; Duet DHA; Marine Lipid Concentrate; Optinate Omega-3; Sea-Omega; ***Venez.:*** Eidoca; Piscis 3.

Orbofiban Acetate *(USAN, rINNM)*

Acetato de orbofibrán; CS-511; Orbofiban, Acétate d'; Orbofibani Acetas; SC-57099-B. *N*-{[(3*S*)-1-(*p*-Amidinophenyl)-2-oxo-3-pyrrolidinyl]carbamoyl}-β-alanine ethyl ester monoacetate quadrantihydrate.

Орбофибана Ацетат

$C_{17}H_{23}N_5O_4,C_2H_4O_2,¼H_2O$ = 426.0.
CAS — 163250-90-6 (orbofiban); 165800-05-5 (orbofiban acetate).

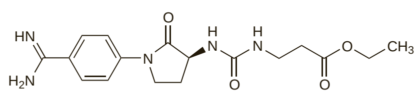

(orbofiban)

Profile

Orbofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but has been associated with an increase in mortality.

◊ References.

1. Cannon CP, *et al.* Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000; **102:** 149–56.

Ouabain

Acocantherin; G-Strophanthin; Ouabaiini; Ouabain oktahydrát; Ouabaína; Ouabainas; Ouabaïne; Ouabainum; Ouabainum Octahydricum; Strophanthin-G; Strophanthinum; Strophanthoside-G; Uabaina; Ubaína. 3β-(α-L-Rhamnopyranosyloxy)-1β,5,11α,-14,19-pentahydroxy-5β,14β-card-20(22)-enolide octahydrate.

$C_{29}H_{44}O_{12},8H_2O$ = 728.8.
CAS — 630-60-4 (anhydrous ouabain); 11018-89-6 (ouabain octahydrate).
ATC — C01AC01.
ATC Vet — QC01AC01.

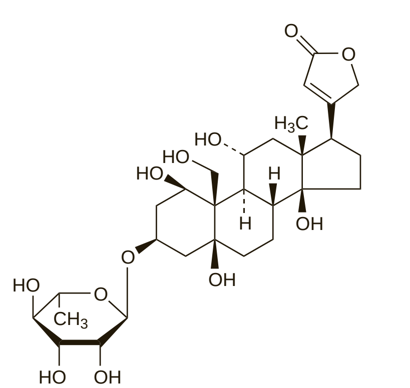

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.*

Ph. Eur. 6.2 (Ouabain). Colourless crystals or white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; practically insoluble in ethyl acetate. Protect from light.

Profile

Ouabain is a cardiac glycoside with positive inotropic activity that is obtained from the seeds of *Strophanthus gratus* or from the wood of *Acokanthera schimperi* or *A. ouabaio* (Apocynaceae). It has general properties similar to those of digoxin (p.1259) and may be used in the treatment of heart failure (p.1165). Ouabain is given orally in a dose of up to 24 mg daily; it has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Strodival.

Oxedrine *(BAN)* ⊗

Oksedriini; Oxedrin; Oxedrinum; Sinefrina; Sympaethaminum; Synephrine; *p*-Synephrine. (*RS*)-1-(4-Hydroxyphenyl)-2-(methylamino)ethanol.

$C_9H_{13}NO_2$ = 167.2.
CAS — 94-07-5.
ATC — C01CA08; S01GA06.
ATC Vet — QC01CA08; QS01FB90; QS01GA06.

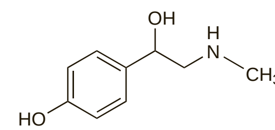

NOTE. Synephrine and *p*-synephrine have been used as synonyms for oxedrine. Care should be taken to avoid confusion with *m*-synephrine, which is phenylephrine (p.1568).

Oxedrine Hydrochloride *(BANM)* ⊗

Sinefrina, hidrocloruro de.

$C_9H_{13}NO_2,HCl$ = 203.7.
ATC — C01CA08; S01GA06.
ATC Vet — QC01CA08; QS01GA06.

Oxedrine Tartrate *(BANM)* ⊗

Aetaphen. Tartrat.; Aethaphenum Tartaricum; Oksedriinitartraatti; Oxedrini Tartras; Oxedrintartrat; Oxyphenylmethylaminoethanol Tartrate; Sinefrina Tartrato; Sinefrina, tartrato de; Synephrine Tartrate.

$(C_9H_{13}NO_2)_2,C_4H_6O_6$ = 484.5.
CAS — 16589-24-5 (oxedrine tartrate); 67-04-9 (±oxedrine tartrate).
ATC — C01CA08; S01GA06.
ATC Vet — QC01CA08; QS01GA06.

Profile

Oxedrine is a sympathomimetic (p.1407) given as the tartrate in the treatment of hypotensive states in oral doses of about 100 to 150 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection.

Oxedrine is also used in eye drops as an ocular decongestant, usually as the tartrate in a concentration of 0.5% in combination preparations. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sympatol; ***Hong Kong:*** Ocuton; ***Hung.:*** Sympathomim; ***Ital.:*** Sympatol; ***Switz.:*** Sympalept.

Multi-ingredient: ***Austria:*** Dacrin; Pasuma-Dragees; ***Fr.:*** Dacryne; Dacryoboraline; Polyfra; Posine†; Sedacollyre; Uvicol.

Oxilofrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de oxilofrina; *p*-Hydroxyephedrine Hydrochloride; Methylsynephrine Hydrochloride; Oxilofrine, Chlorhydrate d'; Oxilofrini Hydrochloridum; Oxyephedrine Hydrochloride. *erythro*-*p*-Hydroxy-α-[1-(methylamino)ethyl]benzyl alcohol hydrochloride.

Оксилофрина Гидрохлорид

$C_{10}H_{15}NO_2,HCl$ = 217.7.
CAS — 942-51-8.

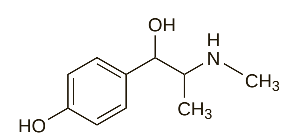

(oxilofrine)

Profile
Oxilofrine is a sympathomimetic (p.1407) related to ephedrine (p.1558). It is given orally as the hydrochloride in the treatment of hypotensive states in usual doses of 16 mg three times daily, although higher doses have been given. It has also been used in antitussive preparations.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Carnigen; ***Ger.:*** Carnigen.

Multi-ingredient: ***Canad.:*** Cophylac.

Oxprenolol Hydrochloride
(BANM, USAN, rINNM) ⊗

Ba-39089; Hidrocloruro de oxiprenolol; Hidrocloruro de oxprenolol; Okspreonolol Hidroklorür; Oksprenololihydrokloridi; Oksprenololio hidrochloridas; Oksprenololu chlorowodorek; Oxprénolol, chlorhydrate d'; Oxprenolol hydrochlorid; Oxprenolol-hidroklorid; Oxprenololhydroklorid; Oxprenololi hydrochloridum; Oxyprenolol Hydrochloride. 1-(o-Allyloxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

Окспренолола Гидрохлорид

$C_{15}H_{23}NO_3,HCl = 301.8.$

CAS — 6452-71-7 (oxprenolol); 6452-73-9 (oxprenolol hydrochloride).

ATC — C07AA02.

ATC Vet — QC07AA02.

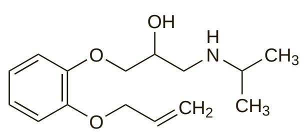

(oxprenolol)

NOTE. Compounded preparations of oxprenolol hydrochloride may be represented by the following names:

- Co-prenozide (*BAN*)—oxprenolol hydrochloride 640 parts and cyclopenthiazide 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*. *Chin.* includes the base.

Ph. Eur. 6.2 (Oxprenolol Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Oxprenolol Hydrochloride). A white crystalline powder. Freely soluble in water, in alcohol, and in chloroform; sparingly soluble in acetone; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 6.0.

Adverse Effects, Treatment, and Precautions
As for Beta Blockers, p.1226.

Breast feeding. Oxprenolol is distributed into breast milk but the amount likely to be ingested by an infant is small (see under Pharmacokinetics, below). No adverse effects have been seen in breast-fed infants whose mothers were given oxprenolol and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Oxprenolol-induced drug fever has been reported[1] in a patient and was confirmed by a challenge test.

1. Hasegawa K, *et al*. Drug fever due to oxprenolol. *BMJ* 1980; **281:** 27–8.

Overdosage. Rhabdomyolysis with myoglobinuria has been reported[1] as a complication of severe overdosage with oxprenolol.

1. Schofield PM, *et al*. Recovery after severe oxprenolol overdose complicated by rhabdomyolysis. *Hum Toxicol* 1985; **4:** 57–60.

Interactions
The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics
Oxprenolol is well absorbed from the gastrointestinal tract, but is subject to first-pass metabolism resulting in variable bioavailability (20 to 70%). Peak plasma concentrations occur about 1 or 2 hours after a dose. Oxprenolol is about 80% bound to plasma proteins. It crosses the placenta and is distributed into breast milk. It is moderately lipid-soluble and crosses the blood-brain barrier. Oxprenolol is metabolised in the liver and almost entirely excreted in the urine. An elimination half-life of 1 to 2 hours has been reported.

Pregnancy and breast feeding. The placental transfer of oxprenolol and its passage into breast milk was studied[1] in 32 pregnant women given a preparation containing oxprenolol and dihydralazine (*Trasipressol*). At delivery the mean maternal plasma concentration was 0.386 nanomoles/mL compared with 0.071 and 0.081 nanomoles/mL in plasma from the umbilical artery and vein respectively. Oxprenolol plasma concentrations in the newborn ranged from 0 to 0.186 nanomoles/mL during the first 24 hours of life. The concentrations of oxprenolol in breast milk 3 to 6 days after delivery ranged from 0 to 1.342 nanomoles/mL, and the milk to plasma concentration ratio was 0.45:1. Based on the highest milk concentration seen it was calculated that a breast-fed infant could receive, at a maximum, a daily dose at least 60 times less than an average adult daily dose (240 mg daily) for hypertension. In another study[2] in 12 women given oxprenolol, mean milk to plasma concentration ratios were 0.21:1 to 0.43:1, depending on dose.

1. Sioufi A, *et al*. Oxprenolol placental transfer, plasma concentrations in newborns and passage into breast milk. *Br J Clin Pharmacol* 1984; **18:** 453–6.
2. Fidler J, *et al*. Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90:** 961–5.

Uses and Administration
Oxprenolol is a non-cardioselective beta blocker (p.1225). It is reported to possess intrinsic sympathomimetic and membrane-stabilising activity.

Oxprenolol is given orally as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), and cardiac arrhythmias (p.1160). It is also used in anxiety disorders (p.952).

In **hypertension** oxprenolol hydrochloride is given in a usual dose of 80 to 160 mg daily in two or three divided doses. The dose may be increased at weekly or fortnightly intervals until a satisfactory response is achieved. The usual maximum dose is 320 mg daily although up to 480 mg daily has been given.

The usual dose for **angina pectoris** is 80 to 160 mg daily in two or three divided doses with a usual maximum of 320 mg daily.

For **cardiac arrhythmias** a dose of 40 mg daily to not more than 240 mg daily in two or three divided doses may be used.

To relieve **anxiety** in stressful situations oxprenolol hydrochloride is given in usual doses of 40 to 80 mg daily, either as a single dose or in two divided doses.

Modified-release preparations allowing once daily dosing are also available.

Preparations
BP 2008: Oxprenolol Tablets;
USP 31: Oxprenolol Hydrochloride Extended-release Tablets; Oxprenolol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Corbeton; ***Austria:*** Trasicor; ***Canad.:*** Slow-Trasicor†; Trasicor; ***Denm.:*** Trasicor†; ***Fr.:*** Trasicor; ***Ger.:*** Trasicor; ***Gr.:*** Trasicor; ***Hung.:*** Trasicor†; ***Neth.:*** Trasicor; ***NZ:*** Captol†; Slow-Trasicor†; ***Spain:*** Trasicor; ***Switz.:*** Slow-Trasicor; Trasicor; ***Turk.:*** Trasicor; ***UK:*** Slow-Trasicor; Trasicor.

Multi-ingredient: ***Austria:*** Trasitensin; Trepress; ***Fr.:*** Trasitensine; ***Ger.:*** Impresso†; Trasitensin†; Trepress; ***Gr.:*** Trasitensin; ***Ital.:*** Trasitensin; ***Spain:*** Trasitensin; ***Switz.:*** Slow-Trasitensine; ***UK:*** Trasidrex.

Oxyfedrine Hydrochloride *(BANM, rINNM)*

D-563; Hidrocloruro de oxifedrina; Oxifedrini Chloridum; Oxyfédrine, Chlorhydrate d'; Oxyfedrini Hydrochloridum. L-3-(β-Hydroxy-α-methylphenethylamino)-3′-methoxypropiophenone hydrochloride.

Оксифедрина Гидрохлорид

$C_{19}H_{23}NO_3,HCl = 349.9.$

CAS — 15687-41-9 (oxyfedrine); 16777-42-7 (oxyfedrine hydrochloride).

ATC — C01DX03.

ATC Vet — QC01DX03.

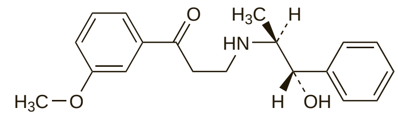

(oxyfedrine)

Profile
Oxyfedrine hydrochloride has vasodilator properties and has been used in angina pectoris, and myocardial infarction. It is metabolised to phenylpropanolamine (p.1569).

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Ildamen; ***Cz.:*** Myofedrin†; ***Ger.:*** Ildamen†; Myofedrin†; ***India:*** Ildamen; ***Philipp.:*** Ildamen; ***Port.:*** Ildamen.

Pamabrom *(USAN)* ⊗

Pamabromo. 2-Amino-2-methylpropan-1-ol 8-bromotheophyllinate.

$C_4H_{11}NO,C_7H_7BrN_4O_2 = 348.2.$

CAS — 606-04-2.

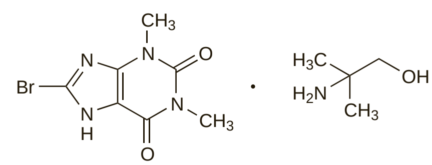

Pharmacopoeias. In *US*.

Profile
Pamabrom is a weak diuretic that has been used, with analgesics and antihistamines, for symptomatic relief of the premenstrual syndrome.

Preparations
Proprietary Preparations (details are given in Part 3)
USA: Maximum Strength Aqua-Ban.

Multi-ingredient: ***Arg.:*** Everfem; ***Canad.:*** Extra Strength Multi-Symptom PMS Relief†; Midol PMS Extra Strength; Painaid PMF; Pamprin; Relievol PMS; Trendar PMS†; Tylenol Menstrual; ***Chile:*** Kitadol Periodo Menstrual; Minfaden; Predual; Tapsin Periodo Menstrual; ***Malaysia:*** Panadol Menstrual; ***Mex.:*** Femsedin Kutz; ***Singapore:*** Panadol Menstrual; ***USA:*** Fem-1†; Lurline PMS; Midol Pre-Menstrual Syndrome; Midol Teen Formula; Painaid PMF Premenstrual Formula; Pamprin; Premsyn PMS; Womens Tylenol Multi-Symptom Menstrual Relief.

Pamiteplase *(rINN)*

Pamiteplasa; Pamitéplase; Pamiteplasum; YM-866. 275-L-Glutamic acid-(1–91)-(174–527)-plasminogen activator (human tissue-type protein moiety).

Памитеплаза

CAS — 151912-42-4.

Profile
Pamiteplase is a thrombolytic related to alteplase (p.1207) used in acute myocardial infarction. It has been investigated in ischaemic stroke.

Preparations
Proprietary Preparations (details are given in Part 3)
Jpn: Solinase†.

Pantethine

Pantetina. (*R*)-*NN*′-[Dithiobis(ethyleneiminocarbonylethylene)]-bis(2,4-dihydroxy-3,3-dimethylbutyramide).

Пантетин

$C_{22}H_{42}N_4O_8S_2 = 554.7.$

CAS — 16816-67-4.

ATC — A11HA32.

ATC Vet — QA11HA32.

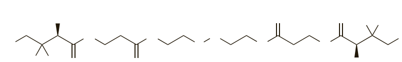

Pharmacopoeias. In *Jpn*.

Profile
Pantethine, a derivative of pantothenic acid (p.1959), is a component of coenzyme A. It is used as a lipid regulating drug in the

treatment of hyperlipidaemias (p.1169). The usual oral dose is 600 to 1200 mg daily in divided doses.

Pantethine is also used as a nutritional supplement.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Pantomin†; ***Ital.:*** Pantetina; ***Jpn:*** Pantosin; ***Spain:*** Liponet†; Obliterol†.

Multi-ingredient: ***Ital.:*** Carpantin†.

Pargyline Hydrochloride *(BANM, USAN, rINNM)*

A-19120; Hidrocloruro de pargilina; MO-911; NSC-43798; Pargyline, Chlorhydrate de; Pargylini Hydrochloridum. *N*-Methyl-*N*-2-propynylbenzylamine hydrochloride; Benzylmethylprop-2-ynylamine hydrochloride.

Паргилина Гидрохлорид

$C_{11}H_{13}N,HCl = 195.7.$

CAS — 555-57-7 (pargyline); 306-07-0 (pargyline hydrochloride).

ATC — C02KC01.

ATC Vet — QC02KC01.

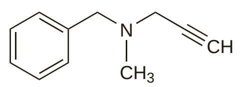

(pargyline)

Profile

Pargyline hydrochloride is an MAOI (see Phenelzine Sulfate, p.415) that was formerly used in the treatment of moderate to severe hypertension.

Parnaparin Sodium *(BAN, rINN)*

OP-21-23; Parnapariininatrium; Parnaparin sodná sůl; Parnaparin Sodyum; Parnaparina sódica; Parnaparine sodique; Parnaparinnatrium; Parnaparin-nátrium; Parnaparino natrio druska; Parnaparinum natricum.

Парнапарин Натрий

CAS — 9041-08-1.

ATC — B01AB07.

ATC Vet — QB01AB07.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Parnaparin Sodium). It is prepared by hydrogen peroxide and cupric salt depolymerisation of heparin obtained from the intestinal mucosa of pigs and cattle. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average molecular mass ranges between 4000 and 6000, with a characteristic value of about 5000. The mass percentage of chains lower than 3000 is not more than 30%. The degree of sulfation is 2.0 to 2.6 per disaccharide unit. Potency is not less than 75 units and not more than 110 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 3.0.

Profile

Parnaparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity used in the prevention of postoperative venous thromboembolism (p.1189); it has also been used in other thromboembolic disorders. For general surgical procedures it is given by subcutaneous injection in a dose of 3200 units 2 hours before the procedure, followed by 3200 units once daily for 7 days or until the patient is fully ambulant. For higher risk or orthopaedic patients a dose of 4250 units is given 12 hours before the procedure, followed by 4250 units 12 hours postoperatively and then once daily for 10 days.

For treatment of thromboembolism a dose of 6400 units may be given by subcutaneous injection for 7 to 10 days.

◊ References.

1. Frampton JE, Faulds D. Parnaparin: a review of its pharmacology, and clinical application in the prevention and treatment of thromboembolic and other vascular disorders. *Drugs* 1994; **47:** 652–76.
2. McKeage K, Keating GM. Parnaparin: a review of its use in the management of venous thromboembolism, chronic venous disease and other vascular disorders. *Drugs* 2008; **68:** 105–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tromboparin†; ***Cz.:*** Fluxum; ***Gr.:*** Thromboparin; Tromboparin†; ***Hung.:*** Fluxum; ***Ital.:*** Fluxum; ***Mex.:*** Fluxum; ***Pol.:*** Fluxum; ***Port.:*** Fluxum; Tromboparin; ***Turk.:*** Fluxum; ***Venez.:*** Tromboparin.

Penbutolol Sulfate *(USAN, rINNM)* ⊗

Hoe-39-893d; Hoe-893d; Levopenbutolol Sulfate; Penbutolol Hemisulfate; Penbutolol sulfát; Penbutolol, sulfate de; Penbutolol Sulphate *(BANM)*; Penbutololi sulfas; Penbutololio sulfatas; Penbutololisulfaatti; Penbutololsulfat; Penbutolol-szulfát; Sulfato de penbutolol. (*S*)-1-*tert*-Butylamino-3-(2-cyclopentylphenoxy)propan-2-ol hemisulfate.

Пенбутолола Сульфат

$(C_{18}H_{29}NO_2)_2,H_2SO_4 = 680.9.$

CAS — 38363-40-5 (penbutolol); 38363-32-5 (penbutolol sulfate).

ATC — C07AA23.

ATC Vet — QC07AA23.

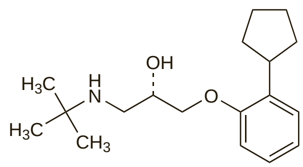

(penbutolol)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Penbutolol Sulphate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in cyclohexane; soluble in methyl alcohol. Protect from light.

USP 31 (Penbutolol Sulfate). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Penbutolol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 3 hours after a dose. Penbutolol is 80 to 98% bound to plasma proteins. It has a high lipid solubility. It is extensively metabolised in the liver by hydroxylation and glucuronidation, the metabolites being excreted in the urine with only small amounts of unchanged penbutolol. A plasma elimination half-life of about 20 hours has been reported.

Renal impairment. Glucuronidation was considered more prominent than hydroxylation in the metabolism of penbutolol and its activity was not altered in patients with renal impairment.[1]

1. Bernard N, *et al.* Pharmacokinetics of penbutolol and its metabolites in renal insufficiency. *Eur J Clin Pharmacol* 1985; **29:** 215–19.

Uses and Administration

Penbutolol is a non-cardioselective beta blocker (p.1225). It is reported to possess some intrinsic sympathomimetic activity but lacks membrane-stabilising properties.

Penbutolol is used as the sulfate in the management of hypertension (p.1171). It may also be used in cardiac disorders such as angina pectoris (p.1157).

In **hypertension** penbutolol sulfate is given in an initial oral dose of 20 mg daily; the dose may be increased if necessary to 40 to 80 mg daily. Maximum antihypertensive efficacy is reported to occur within 2 weeks in patients given a dose of 20 mg daily but about 4 weeks may be required for maximum effect in patients given 10 mg daily.

Penbutolol sulfate has also been used in similar doses in cardiac disorders such as **angina**.

Preparations

USP 31: Penbutolol Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Ger.: Betapressin; ***USA:*** Levatol.

Multi-ingredient: ***Ger.:*** Betarelix; Betasemid.

Pentaerithrityl Tetranitrate *(BAN, rINN)*

Erynite; Nitropentaerythrol; Nitropenthrite; Pentaérithrityle, Tétranitrate de; Pentaerithrityli Tetranitras; Pentaeritritilio tetranitratas; Pentaeritritol Tetranitrat; Pentaeritrit-tetranitrát; Pentaerityltetranitrat; Pentaeritrityylitetranitraatti; Pentaerythritol Tetranitrate; Pentaerythritolum Tetranitricum; Pentaerythrityl Tetranitrate; Pentaérythrityle, tétranitrate de; Pentaerythrityli tetranitras; Pentaerythrityl-tetranitrát; Pentaerytrityltetranitrat; Pentaerytrityylitetranitraatti; Pentaerytrytylu tetraazotan; Pentanitrol; PETN; Tetranitrato de pentaeritritilo. 2,2-Bis(hydroxymethyl)propane-1,3-diol tetranitrate.

Пентаэритритила Тетранитрат

$C_5H_8N_4O_{12} = 316.1.$

CAS — 78-11-5.

ATC — C01DA05.

ATC Vet — QC01DA05.

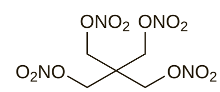

NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.

Pharmacopoeias. *Chin.* and *Eur.* (see p.vii) include as diluted pentaerithrityl tetranitrate.

Ph. Eur. 6.2 (Pentaerithrityl Tetranitrate, Diluted). A mixture of pentaerithrityl tetranitrate with lactose monohydrate or mannitol. Its solubility depends on the diluent and its concentration. Protect from light and heat.

Undiluted pentaerithrityl tetranitrate is a white or slightly yellowish powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone.

Handling. Undiluted pentaerithrityl tetranitrate can be exploded by percussion or excessive heat.

Profile

Pentaerithrityl tetranitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) but its duration of action is more prolonged.

It is used in angina pectoris (p.1157) in usual oral doses of up to 240 mg daily, in divided doses, before a meal. It is also given as modified-release preparations.

Pentaerithrityl trinitrate, an active metabolite of pentaerithrityl tetranitrate, has also been used clinically under the name pentrinitrol.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardiosedantol; ***Cz.:*** Pentalong; ***Fr.:*** Nitrodex†; ***Ger.:*** Dilcoran; Nirason N; Pentalong; ***Hung.:*** Nitropenton; ***India:*** Peritrate; ***Ital.:*** Peritrate; ***Switz.:*** Nitrodex†; ***Thai.:*** Peritrate; ***Turk.:*** Danitrin.

Multi-ingredient: ***Austria:*** Spasmocor; ***Ger.:*** Nitro-Crataegutt†; Nitro-Obsidan†; VisanoCor N†; ***Pol.:*** Pentaerythritol Compositum.

Pentifylline *(BAN, rINN)*

1-Hexyltheobromine; Pentifilina; Pentifylliini; Pentifyllin; Pentifyllinum; SK-7. 1-Hexyl-3,7-dimethylxanthine.

Пентифиллин

$C_{13}H_{20}N_4O_2 = 264.3.$

CAS — 1028-33-7.

ATC — C04AD01.

ATC Vet — QC04AD01.

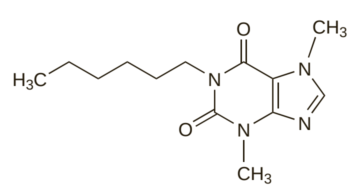

Profile

Pentifylline is a xanthine derivative that has been used as a vasodilator in the management of peripheral or cerebral vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Cosaldon†.
Multi-ingredient: *S.Afr.:* Cosaldon†.

Pentosan Polysulfate Sodium *(BAN, USAN, rINN)*

Natrii pentosani polusulfas; Natrii Pentosani Polysulfas; Natriumpentosaanipolys Ulfaatti; Natriumpentosanpolysulfat; Pentosan Polysulphate Sodium; Pentosane polysulfate sodique; Pentosano polisulfato de sodio; PZ-68; Sodium Pentosan Polysulphate; Sodium Xylanpolysulphate; SP-54.

Натрия Пентозана Полисульфат

CAS — 37319-17-8; 116001-96-8.
ATC — C05BA04.
ATC Vet — QC05BA04.

Description. Pentosan polysulfate sodium is a mixture of linear polymers of β-1→4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally (approximately 1 in every 4 residues) substituted at the 2-position with 4-*O*-methyl-α-D-glucuronic acid 2,3-*O*-sulfate. The average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40 000.

Adverse Effects and Precautions

As for Heparin, p.1301. Gastrointestinal disturbances may also occur.

Uses and Administration

Pentosan polysulfate sodium is a heparinoid with anticoagulant and fibrinolytic properties; it may also have hypolipidaemic and anti-inflammatory effects. It is used in thromboembolic disorders, although its anticoagulant effect is less than that of heparin. It is also used in the management of interstitial cystitis (see below) and has been tried in a number of other conditions, including variant Creutzfeldt-Jakob disease (see below). Pentosan polysulfate sodium has been used orally, parenterally, and topically.

In the management of interstitial cystitis, pentosan polysulfate sodium is given orally in a dose of 100 mg three times daily.

Cystitis. Pentosan polysulfate sodium has been used in inflammatory conditions of the bladder, including interstitial cystitis (p.2179) and is thought to act by enhancing the protective effect of mucins at the bladder surface.[1] Studies have differed concerning its efficacy in the treatment of interstitial cystitis and an analysis[2] of placebo-controlled trials concluded that pentosan polysulfate sodium was more effective in treating pain, urgency, and frequency, but that the difference was small. Any benefit is usually apparent within 3 to 6 months and only occurs in a minority of patients.[3] Pentosan polysulfate sodium was reported[4] to have minimal long-term efficacy in a group of patients with severe or refractory interstitial cystitis.

Pentosan polysulfate sodium has also been reported[5-7] to be useful in the control of radiation-induced haemorrhagic cystitis (p.2178).

1. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; **66:** 821–35.
2. Hwang P, *et al.* Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology* 1997; **50:** 39–43.
3. Anonymous. Pentosan for interstitial cystitis. *Med Lett Drugs Ther* 1997; **39:** 56.
4. Jepsen JV, *et al.* Long-term experience with pentosanpolysulfate in interstitial cystitis. *Urology* 1998; **51:** 381–7.
5. Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. *J Urol (Baltimore)* 1986; **136:** 813–14.
6. Hampson SJ, Woodhouse CRJ. Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; **25:** 40–2.
7. Sandhu SS, *et al.* The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int* 2004; **94:** 845–7.

Prostatitis. Pentosan polysulfate sodium is one of a number of drugs that have been tried in the management of prostatitis (p.2181). An improvement in symptoms was reported[1] in an uncontrolled study of oral pentosan polysulfate sodium in men with chronic prostatitis/chronic pelvic pain syndrome. A randomised study[2] using pentosan polysulfate sodium 300 mg three times daily found that symptoms were moderately or markedly improved at the end of the 16-week treatment period in more members of the active treatment group than in the group given placebo.

1. Nickel JC, *et al.* Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category IIIA): a prospective multicenter clinical trial. *Urology* 2000; **56:** 413–17.
2. Nickel JC, *et al.* Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol (Baltimore)* 2005; **173:** 1252–5.

Variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease (vCJD) is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. Pentosan polysulfate sodium has been tried in small numbers of patients with vCJD, although there is little published research data. In 2003 the UK Department of Health[1] took advice from the CJD Therapy Advisory Group and the CSM; both groups considered that there was insufficient information on which to base prescribing regimens, and further work was needed.

1. UK Department of Health. Use of pentosan polysulphate in the treatment of, or prevention of, vCJD. Available at: http://www.dh.gov.uk/en/Publichealth/Communicablediseases/CJD/CJDgeneralinformation/DH_4031039 (accessed 19/08/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Elmiron; ***Austral.:*** Elmiron†; ***Austria:*** Polyanion; ***Canad.:*** Elmiron; ***Fr.:*** Hemoclar; ***Ger.:*** Fibrezym; ***Hong Kong:*** Elmiron; SP 54†; ***Hung.:*** SP 54; ***Ital.:*** Fibrase; ***Malaysia:*** SP 54; ***Port.:*** Fibrocide; ***S.Afr.:*** Tavan-SP 54; ***Spain:*** Thrombocid; ***USA:*** Elmiron.

Multi-ingredient: *Austria:* Thrombocid; ***Cz.:*** Thrombocid; ***Ger.:*** Thrombocid; ***Hong Kong:*** Anso; Thrombocid; ***Port.:*** Thrombocid; ***Spain:*** Anso; ***Switz.:*** Thrombocid.

Pentoxifylline *(BAN, USAN, rINN)*

BL-191; Okspentifilin; Oxpentifylline; Pentoksifilin; Pentoksifilinas; Pentoksifylliini; Pentoxifilina; Pentoxifillin; Pentoxifylin; Pentoxifyllin; Pentoxifyllinum. 3,7-Dimethyl-1-(5-oxohexyl)xanthine.

Пентоксифиллин

$C_{13}H_{18}N_4O_3$ = 278.3.
CAS — 6493-05-6.
ATC — C04AD03.
ATC Vet — QC04AD03.

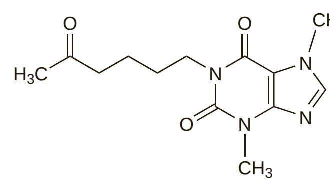

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Pentoxifylline). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Pentoxifylline). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform and in methyl alcohol; slightly soluble in ether.

Adverse Effects

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing, angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions may also occur. Bleeding events have been reported rarely, usually in association with bleeding risk factors.

Overdosage with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.

Haemorrhage. Three major bleeding episodes including 2 fatal cerebral haemorrhages were reported in a group of patients receiving pentoxifylline 400 mg three times daily together with acenocoumarol for intermittent claudication.[1] Gastrointestinal bleeding occurred in a 67-year-old patient with a history of duodenal ulcer after a single dose of pentoxifylline for optic neuropathy.[2]

1. APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication: a controlled clinical study. *Angiology* 1989; **40:** 237–48.
2. Oren R, *et al.* Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* 1991; **25:** 315–16.

Overdosage. A 22-year-old woman who took pentoxifylline 4 to 6 g with suicidal intent experienced severe bradycardia and first- and second-degree AV block; other effects included nausea, vomiting, abdominal cramps, hypokalaemia, excitation, and insomnia.[1] She recovered after intensive supportive and symptomatic treatment.

1. Sznajder IJ, *et al*. First and second degree atrioventricular block in oxpentifylline overdose. *BMJ* 1984; **288:** 26.

Precautions

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, severe cardiac arrhythmias, and acute myocardial infarction. It should be used with caution in patients with ischaemic heart disease or hypotension. The dose of pentoxifylline may need to be reduced in patients with hepatic or renal impairment (see under Uses and Administration, below).

Porphyria. Pentoxifylline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Pentoxifylline may potentiate the effect of antihypertensives. High parenteral doses of pentoxifylline may enhance the action of insulin and oral hypoglycaemics in diabetic patients. Pentoxifylline should not be given with ketorolac as there is reported to be an increased risk of bleeding and/or prolongation of the prothrombin time. There may also be an increased risk of bleeding during use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.

Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half-life of pentoxifylline is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine, mainly as metabolites, and less than 4% is recovered in the faeces. Elimination of pentoxifylline is decreased in elderly patients and patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.

◊ References.

1. Beermann B, *et al.* Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; **37:** 25–8.
2. Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *Am J Obstet Gynecol* 1985; **151:** 1094–7.
3. Smith RV, *et al.* Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986; **75:** 47–52.
4. Rames A, *et al.* Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
5. Paap CM, *et al.* Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Uses and Administration

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease (p.1178). Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine, tumour necrosis factor alpha (TNFα), and this property is under investigation in a number of diseases (see below).

In the treatment of peripheral vascular disease the usual oral dose is 400 mg three times daily in a modified-release formulation; this may be reduced to 400 mg twice daily for maintenance or if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. In severe hepatic or renal impairment, doses may need to be reduced (see below). Beneficial effects may not be evident until after 2 to 8 weeks of treatment. Pentoxifylline may also be given parenterally.

◊ General references.

1. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987; **34:** 50–97.
2. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; **30:** 603–21.

Administration in hepatic and renal impairment. The elimination half-life of pentoxifylline and its metabolites is significantly prolonged in patients with hepatic cirrhosis,[1] and some metabolites have a prolonged half-life in renal impairment.[2] The UK manufacturers state that in patients with severely impaired hepatic function the dose of pentoxifylline may need to be reduced, while accumulation may occur in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) who receive more than 400 mg once or twice daily.

References.

1. Rames A, *et al.* Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
2. Paap CM, *et al.* Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Inhibition of tumour necrosis factor alpha. Pentoxifylline inhibits production of tumour necrosis factor alpha (TNFα), a cytokine that is implicated in the pathogenesis of many diseases, and investigative work with pentoxifylline is being, or has been, carried out in many such disorders. Studies have been performed in patients with alcoholic hepatitis,[1] cardiomyopathy,[2] cerebral malaria,[3,4] diabetic nephropathy,[5] leishmaniasis,[6,7] leprosy,[8,9] membranous nephropathy,[10] radiation-induced damage,[11-13] severe sepsis or septic shock,[14] recurrent aphthous stomatitis,[15-17] and various vasculitic syndromes, including Behçet's syndrome.[18] Pentoxifylline has also been tried for improving graft survival in kidney transplantation.[19,20] For mention of a possible benefit in sarcoidosis, see p.1512. Although promising results have been reported in some of these studies, the place of pentoxifylline in the overall management of these disorders remains to be established.

1. Akriviadis E, *et al.* Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119:** 1637–48.
2. Skudicky D, *et al.* Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. *Circulation* 2001; **103:** 1083–8.
3. Di Perri, *et al.* Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995; **171:** 1317–22.
4. Looareesuwan S, *et al.* Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. *Am J Trop Med Hyg* 1998; **58:** 348–53.
5. Navarro JF, *et al.* Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. *Am J Kidney Dis* 1999; **33:** 458–63.
6. Lessa HA, *et al.* Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *Am J Trop Med Hyg* 2001; **65:** 87–9.
7. Machado PRL, *et al.* Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis* 2007; **44:** 788–93.
8. Nery JAC, *et al.* The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. *Indian J Lepr* 2000; **72:** 457–67.
9. Dawlah ZM, *et al.* A phase 2 open trial of pentoxifylline for the treatment of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2002; **70:** 38–43.
10. Ducloux D, *et al.* Use of pentoxifylline in membranous nephropathy. *Lancet* 2001; **357:** 1672–3.
11. Okunieff P, *et al.* Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004; **22:** 2207–13.
12. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother* 2005; **39:** 516–22.
13. Delanian S, *et al.* Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; **23:** 8570–9.
14. Staubach K-H, *et al.* Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg* 1998; **133:** 94–100.
15. Pizarro A, *et al.* Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; **133:** 659–60.
16. Chandrasekhar J, *et al.* Oxypentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87:** 564–7.
17. Thornhill MH, *et al.* A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; **143:** 463–70.
18. Hisamatsu T, *et al.* Combination therapy including pentoxifylline for entero-Behçet's disease. *Bull Tokyo Dent Coll* 2001; **42:** 169–76.
19. Noel C, *et al.* Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor α and adhesion molecules. *Transplantation* 2000; **69:** 1102–7.
20. Shu K-H, *et al.* Effect of pentoxifylline on graft function of renal transplant recipients complicated with chronic allograft nephropathy. *Clin Nephrol* 2007; **67:** 157–63.

Venous leg ulcers. A systematic review[1] of pentoxifylline used in the treatment of venous leg ulcers (p.1585) concluded that it was an effective adjunct to compression bandaging, and may be effective alone.

1. Jull A, *et al.* Pentoxifylline for treating venous leg ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 08/05/08).

Preparations

USP 31: Pentoxifylline Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dospan Pento; Pentolab; Previscan; Tamixol; Trental; ***Austral.:*** Trental; ***Austria:*** Haemodyn; Pentohexal; Pentomer; Pentoxi; Pentoximed; Trental; Vasonit; ***Belg.:*** Torental; ***Braz.:*** Arteron; Chemopent†; Pentox; Pentral; Perental†; Peripan; Prodoxifilina; Trental; Vascer; ***Canad.:*** Trental; ***Chile:*** Trental; ***Cz.:*** Agapurin; Pentilin; Pentohexal†; Pentomer; Rentylin†; Trental; Vasonit; ***Denm.:*** Trental; ***Fin.:*** Artal; Pentoxin; Trental; ***Fr.:*** Hatial†; Pentoflux; Torental; ***Ger.:*** Agapurin; Azupentat†; Claudicat; durapental†; Pento; Pento-Puren; Pentohexal; Pentox; Pentoxy†; Ralofekt; Rentylin; Trental; ***Gr.:*** Tarontal; ***Hong Kong:*** Pentong; Trenlin; Trental; ***Hung.:*** Angiopurin†; Chinotal; Pentoxyl-EP; Trental; ***India:*** Kinetal; Trental; ***Indon.:*** Erytral; Lentrin; Pentoxifillene; Platof; Reotal; Tarontal; Tioxad; Trenat; Trenfyl; Trental; Trentox; Trenxy; ***Irl.:*** Trental; ***Israel:*** Oxopurin; Trental; ***Ital.:*** Trental; ***Malaysia:*** Trenlin; Trental; ***Mex.:*** Artelife; Eurotofi; Fixoten; Kentadin; Pensiral; Peridane; Profiben; Sufisal; Trental; Vantoxyl; Vasofyl; Vaxolem; Xipen; ***Neth.:*** Trental; ***Norw.:*** Trental; ***NZ:*** Trental; ***Philipp.:*** C-Vex; Pentox; Trental; ***Pol.:*** Agapurin; Apo-Pentox; Dartelin; Pentilin; Pentohexal; Polfilin; Trental; ***Port.:*** Claudicat; Trental; ***Rus.:*** Flexital (Флекситал); Mellinorm (Меллинорм); Pentilin (Пентилин); Trental (Трентал 400); Vasonit (Вазонит); ***S.Afr.:*** Trental; ***Singapore:*** Agapurin†; Trenlin; Trental; ***Spain:*** Elorgan; Hemovas; Nelorpin; Retimax; ***Switz.:*** Dinostral†; Pentoxi; Trental; ***Thai.:*** Agapurin; Elastab; Flexital; Herden†; Penlol; Sipental; Trental; Trepal; ***Turk.:*** Pentox; Trental; Trentilin; Vasoplan; ***UK:*** Neotren; Trental; ***USA:*** Trental; ***Venez.:*** Agapurin; Trental.

Multi-ingredient: ***Arg.:*** Ikatral Periferico.

Perhexiline Maleate *(BANM, USAN, rINNM)*

Maleato de perhexilina; Perhexiline, Maléate de; Perhexilini Maleas; WSM-3978G. 2-(2,2-Dicyclohexylethyl)piperidine hydrogen maleate.

Пергексиллина Малеат

$C_{19}H_{35}N,C_4H_4O_4$ = 393.6.

CAS — 6621-47-2 (perhexiline); 6724-53-4 (perhexiline maleate).

ATC — C08EX02.

ATC Vet — QC08EX02.

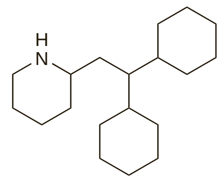

(perhexiline)

Profile

Perhexiline maleate may be used in the long-term management of severe angina pectoris (p.1157) in patients who have not responded to other anti-anginal drugs. Its mode of action is complex.

The usual initial oral dose is 100 mg daily, subsequently either increased or decreased, as necessary, at intervals of 2 to 4 weeks; it is generally recommended not to give more than 300 mg daily although doses of 400 mg daily have been necessary in some patients. The maintenance of plasma-perhexiline concentrations between 0.15 and 0.60 micrograms/mL has been recommended.

Perhexiline occasionally produces severe adverse effects including peripheral neuropathy affecting all four limbs with associated papilloedema, severe and occasionally fatal hepatic toxicity, and metabolic abnormalities with marked weight loss, hypertriglyceridaemia, and profound hypoglycaemia. It is contra-indicated in patients with hepatic or renal impairment. Perhexiline should be used with caution in diabetic patients. Hepatic metabolism of perhexiline is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore caution is advised if perhexiline is used with other drugs that inhibit or are metabolised by this enzyme, and perhexiline toxicity has been reported with SSRIs such as fluoxetine or paroxetine.

Porphyria. Perhexiline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Pexsig; ***NZ:*** Pexsig.

Perindopril *(BAN, USAN, rINN)*

McN-A-2833; Perindopriili; Périndopril; Perindoprilum; S-9490. (2S,3aS,7aS)-1-{N-[(S)-1-Ethoxycarbonylbutyl]-L-alanyl}perhydroindole-2-carboxylic acid.

Периндоприл

$C_{19}H_{32}N_2O_5$ = 368.5.

CAS — 82834-16-0.

ATC — C09AA04.

ATC Vet — QC09AA04.

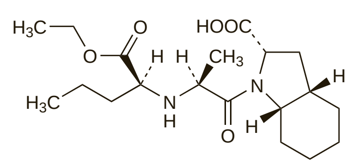

Perindopril Arginine *(BANM, rINNM)*

Perindopril arginina; Périndopril Arginine; Perindoprilum Argininum.

Периндоприл Аргинин

CAS — 612548-45-5.

ATC — C09AA04.

ATC Vet — QC09AA04.

Perindopril Erbumine *(BANM, USAN, rINNM)*

tert-Butilamino perindoprilis; Butylamini Perindoprilum; *Tert*-Butylamini Perindoprilum; Butylamin-perindopril; Erbumina de perindopril; McN-A-2833-109; Perindopriili-*tert*-butyyliamiini; Perindopril *tert*-Butylamine; Périndopril, Erbumine de; Perindopril Terbutalamin; Périndopril tert-butylamine; Perindopril-*tert*-butylamin; Perindopril-erbumin; Perindoprili Erbuminum; Perindoprilum Erbuminum; Peryndopryl z tert-butyloaminą; S-9490-3; tert-Butylamini perindoprilum.

Периндоприла Эрбумин

$C_{19}H_{32}N_2O_5,C_4H_{11}N$ = 441.6.

CAS — 107133-36-8.

ATC — C09AA04.

ATC Vet — QC09AA04.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Perindopril *tert*-Butylamine; Perindopril Erbumine BP 2008). A white or almost white, slightly hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water and in alcohol; soluble or sparingly soluble in dichloromethane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

◊ In a postmarketing surveillance study[1] of 47 351 patients receiving perindopril for hypertension, no unexpected adverse effects were reported and serious reactions were rare; 1587 (6.3%) women and 782 (3.5%) men withdrew from therapy due to adverse effects.

Although a study[2] of perindopril use in patients with stable chronic heart failure reported no significant first-dose hypotension, there has been a case report[3] of ischaemic stroke, possibly associated with hypotension, after a single dose of perindopril in a patient with post-infarction heart failure. Standard precautions as for other ACE inhibitors (p.1195) should be followed when starting perindopril therapy.

1. Speirs C, *et al.* Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. *Br J Clin Pharmacol* 1998; **46:** 63–70.
2. MacFadyen RJ, *et al.* Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991; **66:** 206–11.
3. Bagger JP. Adverse event with first-dose perindopril in congestive heart failure. *Lancet* 1997; **349:** 1671–2.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Perindopril acts as a prodrug of the diacid perindoprilat, its active form. After oral doses perindopril is rapidly absorbed with a bioavailability of about 65 to 75%. It is extensively metabolised, mainly in the liver, to perindoprilat and inactive metabolites including glucuronides. The presence of food is reported to reduce the conversion of perindopril to perindoprilat. Peak plasma concentrations of perindoprilat are achieved 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10 to 20% bound to plasma proteins. Perindopril is excreted predominantly in the urine, as unchanged drug, as perindoprilat, and as other metabolites. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer, the latter half-life probably representing strong binding to angiotensin-converting enzyme. The excretion of perindoprilat is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

◊ References.

1. Lecocq B, *et al.* Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. *Clin Pharmacol Ther* 1990; **47:** 397–402.
2. Verpooten GA, *et al.* Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. *Br J Clin Pharmacol* 1991; **32:** 187–92.
3. Sennesael J, *et al.* The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol* 1992; **33:** 93–9.
4. Thiollet M, *et al.* The pharmacokinetics of perindopril in patients with liver cirrhosis. *Br J Clin Pharmacol* 1992; **33:** 326–8.
5. Guérin A, *et al.* The effect of haemodialysis on the pharmacokinetics of perindoprilat after long-term perindopril. *Eur J Clin Pharmacol* 1993; **44:** 183–7.

Uses and Administration

Perindopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165). It is also used to reduce the risk of cardiovascular events in patients with stable ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164).

Perindopril is converted in the body into its active metabolite perindoprilat. ACE inhibition is reported to occur within 1 hour of a dose, to be at a maximum at about 4 to 8 hours, and to be maintained for 24 hours. Perindopril is given orally as the erbumine salt and should be taken before food. In some countries perindopril is also available as the arginine salt; 5 mg of perindopril arginine is equivalent to about 4 mg of perindopril erbumine.

In the treatment of **hypertension** perindopril is given in an initial dose of 4 mg of the erbumine or 5 mg of the arginine salt once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and in such patients the initial dose may be halved to 2 or 2.5 mg respectively once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly. The same lower initial dose may also be used in the elderly. The dose of perindopril may be increased according to response to a maximum of 8 mg of the erbumine or 10 mg of the arginine salt daily. In the USA a maximum dose of 16 mg of perindopril erbumine daily is allowed in uncomplicated hypertension.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be initiated with a low dose under close medical supervision. Perindopril is given in an initial dose of 2 mg of the erbumine or 2.5 mg of the arginine salt in the morning. The usual maintenance dose is 4 mg or 5 mg respectively daily.

In the management of patients with **ischaemic heart disease** perindopril is given in an initial dose of 4 mg (erbumine) or 5 mg (arginine) once daily for 2 weeks, then titrated up to a maintenance dose of 8 or 10 mg respectively once daily if tolerated. Elderly patients should be started on 2 or 2.5 mg once daily for the first week.

Dosage should be reduced in patients with impaired renal function (see below).

◊ References.

1. Todd PA, Fitton A. Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991; **42:** 90–114.
2. Doyle AE, ed. Angiotensin-converting enzyme (ACE) inhibition: benefits beyond blood pressure control. *Am J Med* 1992; **92** (suppl 4B): 1S–107S.
3. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. *Drugs* 2001; **61** 867–96.
4. Simpson D, *et al.* Perindopril: in congestive heart failure. *Drugs* 2002; **62:** 1367–77.
5. Curran MP, *et al.* Perindopril: a review of its use in patients with or at risk of developing coronary artery disease. *Drugs* 2006; **66:** 235–55.
6. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Curr Med Res Opin* 2007; **23:** 953–60.

Administration in renal impairment. The dose of perindopril should be reduced in patients with renal impairment. UK licensed product information recommends the following doses:

- creatinine clearance (CC) between 30 and 60 mL/minute: 2 mg of the erbumine or 2.5 mg of the arginine salt daily
- CC between 15 and 30 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on alternate days
- CC less than 15 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on dialysis days.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Coverene; ***Austral.:*** Coversyl; Perindo; ***Austria:*** Coversum; ***Belg.:*** Coversyl; ***Braz.:*** Coversyl; ***Canad.:*** Coversyl; ***Chile:*** Coversyl; ***Cz.:*** Apo-Perindo; Cordesyl; Covedaspen; Covemarin; Covemedal; Covepet; Coverdosyn; Coverdyne; Coverex; Coversidin; Coversyspes; Covethanar; Prenessa; Prestarium; Prestarium Neo; Prexanil; Pricoron; ***Denm.:*** Coversyl; ***Fin.:*** Coversyl; ***Fr.:*** Coversyl; ***Ger.:*** Coversum; ***Gr.:*** Coversyl; ***Hong Kong:*** Acertil; ***Hung.:*** Armix; Coverex; Perindan; Prenessa; ***India:*** Coversyl; Perigard; ***Indon.:*** Prexum; ***Irl.:*** Coversyl; ***Ital.:*** Coversyl; Procaptan; ***Jpn:*** Coversyl; ***Malaysia:*** Covapril; Coversyl; Perinace; ***Mex.:*** Coversyl; ***Neth.:*** Coverex; Coversyl; ***NZ:*** Coversyl; ***Philipp.:*** Coversyl; ***Pol.:*** Coverex; Irpax; Prenessa; Prestarium; ***Port.:*** Coversyl; Ostion; Prexum; ***Rus.:*** Prestarium (Престариум); ***S.Afr.:*** Coversyl; Prexum; ***Singapore:*** Coversyl; ***Spain:*** Coversyl; ***Switz.:*** Coversum; ***Thai.:*** Coversyl; ***Turk.:*** Coversyl; ***UK:*** Coversyl; ***USA:*** Aceon; ***Venez.:*** Coversyl.

Multi-ingredient: ***Arg.:*** Bipreterax; Preterax; ***Austral.:*** Coversyl Plus; ***Austria:*** Predonium; Preterax; ***Belg.:*** Bi Preterax; Coversyl Plus; Preterax; ***Braz.:*** Coversyl Plus; ***Canad.:*** Coversyl Plus; Preterax; ***Cz.:*** Noliprel; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.:*** Coversyl Comp; ***Fin.:*** Coversyl Comp; ***Fr.:*** Bipreterax; Preterax; ***Ger.:*** Coversum Combi; Preterax; ***Gr.:*** Preterax; ***Hong Kong:*** Predonium; ***Hung.:*** Armix Komb; Armix Prekomb; Co-Prenessa; Coverex Komb; Coverex Prekomb; Noliprel†; Noriplex†; ***India:*** Coversyl Plus; Perigard D; Perigard DF; ***Irl.:*** Bipreterax; Coversyl Plus; Preterax; ***Ital.:*** Prelectal; Preterax; ***Malaysia:*** Coversyl Plus; ***Mex.:*** Preterax; ***Neth.:*** Coversyl Plus; Predonium; Preterax; ***NZ:*** Coversyl Plus; Predonium; ***Philipp.:*** Bi-Preterax; Preterax; ***Pol.:*** Noliprel; Prestarium Plus; ***Port.:*** Bi Predonium; Bi Preterax; Predonium; Preterax; ***Rus.:*** Noliprel (Нолипрел); ***S.Afr.:*** Bipreterax; Coversyl Plus; Preterax; Prexum Plus; ***Singapore:*** Coversyl Plus; Preterax; ***Spain:*** Bipredonium†; Bipreterax; Preterax; ***Switz.:*** Coversum Combi; Preterax; ***Turk.:*** Coversyl Plus; Preterax; ***UK:*** Coversyl Plus; ***Venez.:*** Bipreterax; Preterax.

Phenindione *(BAN, rINN)*

Fenindion; Fenindiona; Fenindione; Fenindioni; Phénindione; Phenindionum; Phenylindanedione; Phenylinium. 2-Phenylindan-1,3-dione.

Фениндион

$C_{15}H_{10}O_2$ = 222.2.
CAS — 83-12-5.
ATC — B01AA02.
ATC Vet — QB01AA02.

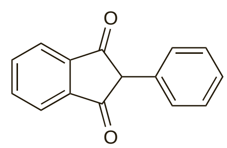

Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Phenindione). Soft, odourless or almost odourless, white or creamy-white crystals. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Solutions are yellow to red.

Adverse Effects and Treatment

As for Warfarin Sodium, p.1425. However, phenindione and the other indanediones are generally more toxic than warfarin with hypersensitivity reactions involving many organs and sometimes resulting in death. Some of the reactions include skin rashes and exfoliative dermatitis, pyrexia, diarrhoea, vomiting, sore throat, liver and kidney damage, myocarditis, agranulocytosis, leucopenia, eosinophilia, and a leukaemoid syndrome.

Phenindione may discolour the urine pink or orange and this is independent of any haematuria. Taste disturbances have been reported.

Effects on the gastrointestinal tract. There have been cases of paralytic ileus, one fatal, associated with phenindione.[1,2]

1. Menon IS. Phenindione and paralytic ileus. *Lancet* 1966; **i:** 1421–2.
2. Nash AG. Phenindione and paralytic ileus. *Lancet* 1966; **ii:** 51–2.

Precautions

As for Warfarin Sodium, p.1426.

Phenindione is not recommended in pregnancy.

Breast feeding. Phenindione is distributed into breast milk, with reported concentrations[1] of 1 to 5 micrograms/mL after a single dose of 50 or 75 mg. A woman receiving phenindione 50 mg each morning and 50 and 25 mg on alternate nights breast-fed her infant son,[2] who required a herniotomy at 5 weeks. After surgery he had an enormous scrotal haematoma and oozing from the wound, and was found to have extended prothrombin and partial thromboplastin times. The American Academy of Pediatrics therefore considers[3] that phenindione should be given with caution to breast-feeding mothers.

1. Goguel M, *et al.* Thérapeutique anticoagulante et allaitement: etude du passage de la phényl-2-dioxo, 1,3 indane dans le lait maternel. *Rev Fr Gynecol Obstet* 1970; **65:** 409–12.
2. Eckstein HB, Jack B. Breast-feeding and anticoagulant therapy. *Lancet* 1970; **i:** 672–3.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

The interactions associated with oral anticoagulants are described in detail under warfarin (p.1427). Specific references to interactions involving phenindione can be found there under the headings for the following drug groups: analgesics; antibacterials; antifungals; antiplatelets; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenindione is absorbed from the gastrointestinal tract. It crosses the placenta and is distributed into breast milk. Metabolites of phenindione excreted in the urine are responsible for any discoloration that may occur.

Uses and Administration

Phenindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187), but because of its higher incidence of severe adverse effects it is now rarely employed.

The usual initial dose of phenindione is 200 mg on the first day, 100 mg on the second day, and then maintenance doses of 50 to 150 mg daily according to coagulation tests.

Preparations

BP 2008: Phenindione Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dindevan; ***Fr.:*** Pindione†; ***India:*** Dindevan.

Phenoxybenzamine Hydrochloride

(BANM, rINNM)

Fenoksybenzaminy chlorowodorek; Hidrocloruro de fenoxibenzamina; Phénoxybenzamine, Chlorhydrate de; Phenoxybenzamini Hydrochloridum; SKF-688A. Benzyl(2-chloroethyl)(1-methyl-2-phenoxyethyl)amine hydrochloride.

Феноксибензамина Гидрохлорид

$C_{18}H_{22}ClNO,HCl$ = 340.3.
CAS — 59-96-1 (phenoxybenzamine); 63-92-3 (phenoxybenzamine hydrochloride).
ATC — C04AX02.
ATC Vet — QC04AX02.

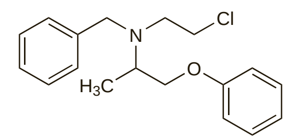

(phenoxybenzamine)

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2008 (Phenoxybenzamine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform.

Adverse Effects and Treatment

The adverse effects of phenoxybenzamine are mainly due to its alpha-adrenoceptor blocking activity. They include orthostatic hypotension and dizziness, reflex tachycardia, nasal congestion, and miosis. Inhibition of ejaculation may occur. These effects may be minimised by using a low initial dose, and may diminish with continued use, but the hypotensive effect can be exaggerated by exercise, heat, a large meal, or alcohol ingestion. Other side-effects include dry mouth, decreased sweating, drowsiness, fatigue, and confusion. Gastrointestinal effects are usually slight. When phenoxybenzamine is given intravenously, idiosyncratic profound hypotension can occur within a few minutes of starting the infusion. Convulsions have been reported after rapid intravenous infusion of phenoxybenzamine.

Severe hypotension may occur in overdose and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement. Sympathomimetics are considered to be of little value, and adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia. Sources differ as to the value of noradrenaline in overcoming alpha-receptor blockade.

Phenoxybenzamine has been shown to be mutagenic in *in vitro* tests and carcinogenic in *rodents.*

Precautions

Phenoxybenzamine should be given with care to patients with heart failure, ischaemic heart disease, cerebrovascular disease, or renal impairment, and should be avoided if a fall in blood pressure would be dangerous. Phenoxybenzamine may aggravate the symptoms of respiratory infections.

The symbol † denotes a preparation no longer actively marketed

When given intravenously, phenoxybenzamine hydrochloride should always be diluted and given by infusion. Intravenous fluids must always be given beforehand to ensure an adequate circulating blood volume and to prevent a precipitous fall in blood pressure. Care should be taken to avoid extravasation. Contamination of the skin should also be avoided since contact sensitisation may occur.

Porphyria. Phenoxybenzamine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Since phenoxybenzamine only blocks alpha receptors, leaving the beta receptors unopposed, use with drugs such as adrenaline that also stimulate beta receptors may enhance the cardiac-accelerating and hypotensive action of phenoxybenzamine.

Pharmacokinetics

Phenoxybenzamine is incompletely and variably absorbed from the gastrointestinal tract. After oral dosage the onset of action is gradual over several hours and persists for 3 or 4 days following a single dose. The maximum effect is attained in about 1 hour after an intravenous dose. The plasma half-life after intravenous dosage is about 24 hours. Phenoxybenzamine is metabolised in the liver and excreted in the urine and bile, but small amounts remain in the body for several days. The duration of action is thought to depend on the rate of synthesis of new alpha receptors following irreversible covalent bonding to existing alpha receptors by a reactive intermediate of phenoxybenzamine.

Uses and Administration

Phenoxybenzamine is a powerful alpha-adrenoceptor blocker (p.1153) with a prolonged duration of action; it binds covalently to alpha receptors in smooth muscle to produce an irreversible ('non-competitive') blockade. A single large dose of phenoxybenzamine can cause alpha-adrenoceptor blockade for 3 days or longer.

Phenoxybenzamine is used in the management of phaeochromocytoma (p.1179). It has also been employed in severe shock (p.1183) and in the treatment of urinary retention (p.2180).

Phenoxybenzamine is used as the hydrochloride. It is given orally or by intravenous infusion as a dilute solution.

In **phaeochromocytoma** it is used to control the hypertension associated with excessive catecholamine release during the pre-operative period and in patients whose tumours are inoperable. A beta blocker may also be given to control tachycardia, but not before alpha blockade has completely suppressed the pressor effects of the phaeochromocytoma. The usual initial oral dose of phenoxybenzamine hydrochloride is 10 mg once or twice daily, increased gradually, according to the patient's response, to a usual dose of 1 to 2 mg/kg daily in 2 divided doses. It may be given intravenously for operative cover in patients with phaeochromocytoma in a daily dose of 1 mg/kg in 200 mL of sodium chloride 0.9% infused over at least 2 hours. A similar intravenous dose in 200 to 500 mL of sodium chloride 0.9% has been given in the management of severe **shock**.

For **urinary retention** due to neurogenic bladder an oral dose of 10 mg twice daily has been given.

Preparations

BP 2008: Phenoxybenzamine Capsules;
USP 31: Phenoxybenzamine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Dibenyline; ***Austria:*** Dibenzyran; ***Ger.:*** Dibenzyran; ***Gr.:*** Dibenyline; ***Hong Kong:*** Dibenyline; ***India:*** Fenoxene; ***Israel:*** Dibenyline; ***Neth.:*** Dibenyline; ***NZ:*** Dibenyline; ***S.Afr.:*** Dibenyline; ***UK:*** Dibenyline; ***USA:*** Dibenzyline.

Phenprocoumon *(BAN, USAN, rINN)*

Fenprocomón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumone; Phenprocoumonum; Phenylpropylhydroxycoumarin. 4-Hydroxy-3-(1-phenylpropyl)coumarin.

Фенпрокумон

$C_{18}H_{16}O_3$ = 280.3.
CAS — 435-97-2.
ATC — B01AA04.
ATC Vet — QB01AA04.

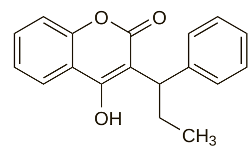

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425.

Effects on the liver. A woman who had twice previously developed jaundice while taking phenprocoumon developed jaundice and parenchymal liver damage when, after some years, phenprocoumon was again given.[1] Other cases of phenprocoumon-associated liver damage have been reported.[2-4]

1. den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. *Lancet* 1976; **i:** 912.
2. Slagboom G, Loeliger EA. Coumarin-associated hepatitis: report of two cases. *Arch Intern Med* 1980; **140:** 1028–9.
3. Cordes A, *et al.* Phenprocoumon-induziertes Leberversagen. *Dtsch Med Wochenschr* 2003; **128:** 1884–6.
4. Bulang T, *et al.* Akutes Leberversagen durch Phenprocoumon–drei Fallberichte. *Z Gastroenterol* 2004; **42:** 1055–8.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving phenprocoumon can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antidepressants; antidiabetics; antigout drugs; antineoplastics; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenprocoumon is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Metabolism is mediated partly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. The half-life is 5 to 6 days. It is excreted in the urine and faeces as conjugated hydroxy metabolites and parent compound. Phenprocoumon is given as a racemic mixture; the *S*-isomer is more potent. The stereoisomers have different pharmacokinetics.

◊ References.

1. Husted S, Andreasen F. Individual variation in the response to phenprocoumon. *Eur J Clin Pharmacol* 1977; **11:** 351–8.
2. Toon S, *et al.* Metabolic fate of phenprocoumon in humans. *J Pharm Sci* 1985; **74:** 1037–40.
3. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.

Uses and Administration

Phenprocoumon is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187). Initial doses are up to 9 mg on the first day followed by 6 mg on the second day. Maintenance doses are usually from 1.5 to 6 mg daily, depending on the response.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Marcoumar; ***Belg.:*** Marcoumar; ***Braz.:*** Marcoumar; ***Denm.:*** Marcoumar; ***Ger.:*** Falithrom; Marcumar; marcuphen; Phenpro; Phenprogamma; ***Neth.:*** Marcoumar; ***Switz.:*** Marcoumar.

Phentolamine Mesilate *(BANM, rINNM)*

Fentolamiinimesilaatti; Fentolamin mesylát; Fentolaminmesilat; Fentolamin-mezilát; Fentolamino mesilatas; Mesilato de fentolamina; Phentolamine, mésilate de; Phentolamine Mesylate; Phentolamine Methanesulphonate; Phentolamini mesilas. 3-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol methanesulphonate.

Фентоламина Мезилат

$C_{17}H_{19}N_3O,CH_4SO_3$ = 377.5.
CAS — 50-60-2 (phentolamine); 73-05-2 (phentolamine hydrochloride); 65-28-1 (phentolamine mesilate).
ATC — C04AB01; G04BE05.
ATC Vet — QC04AB01; QG04BE05.

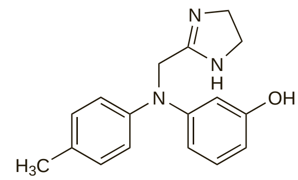

(phentolamine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Phentolamine Mesilate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Phentolamine Mesylate). A white or off-white, odourless crystalline powder. Soluble 1 in 1 of water, 1 in 4 of alcohol, and 1 in 700 of chloroform. Its solutions in water have a pH of about 5 and slowly deteriorate. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Treatment

The adverse effects of phentolamine are primarily due to its alpha-adrenoceptor blocking activity and include orthostatic hypotension and tachycardia. Myocardial infarction and cerebrovascular spasm or occlusion have been reported occasionally, usually in association with marked hypotension; flushing, sweating, and feelings of apprehension may accompany hypotensive episodes. Anginal pain and arrhythmias have been reported rarely. Nausea, vomiting, and diarrhoea may also occur. Other side-effects include weakness, dizziness, flushing, and nasal congestion. Hypoglycaemia has been reported following overdosage.

Severe hypotension may occur in overdosage although phentolamine has a short duration of action. Treatment may include support of the circulation by postural measures and parenteral fluid volume replacement. Noradrenaline may be given cautiously to overcome alpha-adrenoceptor blockade. Adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia.

When injected into the corpus cavernosum of the penis phentolamine has been associated with local pain; induration and fibrosis may occur with repeated use. Priapism has occurred.

Precautions

Phentolamine should not generally be given to patients with angina pectoris or other evidence of ischaemic heart disease. Care should be taken in patients with peptic ulcer disease, which may be exacerbated.

Interactions

Since phentolamine only blocks alpha receptors, use with drugs such as adrenaline may lead to severe hypotension and tachycardia due to unopposed beta-adrenoceptor stimulation.

Pharmacokinetics

After intravenous dosage, the half-life of phentolamine has been reported to be 19 minutes. It is extensively metabolised and about 13% of an intravenous dose is excreted unchanged in the urine.

Uses and Administration

Phentolamine is an alpha-adrenoceptor blocker (p.1153) which also has a direct action on vascular smooth muscle. It produces vasodilatation, an increase in cardiac output, and has a positive inotropic effect, but is reported to have little effect on the blood pressure of patients with essential hypertension. The alpha-receptor blocking action is reversible ('competitive') and non-selective, and the duration of effect is relatively short.

Phentolamine is given in the management of hypertensive crises, particularly those due to excessive catecholamine release associated with surgery for phaeochromocytoma (p.1179). It has been used for the differential diagnosis of phaeochromocytoma, but has largely been superseded by estimations of catecholamines in blood and urine.

Phentolamine is also used to prevent or treat dermal necrosis and sloughing associated with the intravenous infusion or extravasation of noradrenaline. It has been used in the treatment of erectile dysfunction (p.2179).

Phentolamine is given by injection as the mesilate.

In patients with hypertensive crises during surgery for **phaeochromocytoma**, a dose of 2 to 5 mg of phentolamine mesilate is given intravenously and repeated if necessary; blood pressure should be monitored. A dose of 1 mg intravenously is used for children. The intramuscular route may be used pre-operatively and for diagnostic procedures.

For prevention of **dermal necrosis** during intravenous infusion of noradrenaline, 10 mg of phentolamine mesilate is added to each litre of solution containing noradrenaline. For treatment of extravasation of noradrenaline, 5 to 10 mg of phentolamine mesilate in 10 mL of sodium chloride 0.9% is injected into the affected area.

For **erectile dysfunction**, phentolamine mesilate is given by injection into the corpora cavernosa of the penis. It is usually given with papaverine, but a preparation containing phentolamine with aviptadil (vasoactive intestinal peptide) may also be used. Phentolamine has also been tried orally.

Hyperhidrosis. Hyperhidrosis (p.1580) is usually treated with topical aluminium salts or topical antimuscarinics, but intradermal botulinum A toxin or procedures such as endoscopic transthoracic sympathectomy may be needed in severe cases. Phentolamine has been tried as an alternative. Improvement in symptoms has been reported[1] in 2 patients with generalised hyperhidrosis given 100 mg of phentolamine mesilate by intravenous infusion over 6 hours. Improvement lasted for 2 to 3 months and the infusion was repeated, in 1 patient several times.

1. McCleane G. The use of intravenous phentolamine mesilate in the treatment of hyperhidrosis. *Br J Dermatol* 2002; **146:** 533–4.

Pain. Sympathetic nerve block (p.1853) is used in a number of pain syndromes and usually involves injection of local anaesthetics. Phentolamine has been used as an alternative and beneficial results have been reported in pain associated with chronic pancreatitis,[1] pancreatic and other visceral cancers,[2,3] and chronic gastroparesis.[4]

Complete resolution of pain has also been reported in 2 patients with cutaneous leiomyomata given oral doxazosin.[5]

1. McCleane GJ. Phentolamine abolishes the pain of chronic pancreatitis. *Br J Hosp Med* 1996; **55:** 521.
2. McCleane GJ. Intravenous phentolamine mesylate alleviates the pain of pancreatic carcinoma. *Pain* 1997; **73:** 263–4.
3. Yasukawa M, *et al.* Intravenous phentolamine infusion alleviates the pain of abdominal visceral cancer, including pancreatic carcinoma. *J Anesth* 2007; **21:** 420–3.
4. Phillips WJ, *et al.* Relief of acute pain in chronic idiopathic gastroparesis with intravenous phentolamine. *Ann Pharmacother* 2006; **40:** 2032–6.
5. Batchelor RJ, *et al.* Successful treatment of pain in two patients with cutaneous leiomyomata with the oral alpha-1 adrenoceptor antagonist, doxazosin. *Br J Dermatol* 2004; **150:** 775–6.

Preparations

BP 2008: Phentolamine Injection;
USP 31: Phentolamine Mesylate for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Regitina; ***Austral.:*** Regitine; ***Belg.:*** Regitine; ***Braz.:*** Herivyl; Regitina†; Vigamed; ***Canad.:*** Rogitine; ***Denm.:*** Regitin; ***Gr.:*** Regitine; Rogitine†; ***Hung.:*** Regitine; ***Israel:*** Regitine; ***Mex.:*** Z-Max†; ***Neth.:*** Regitine; ***NZ:*** Invicorp; Regitine; ***S.Afr.:*** Regitine†; ***Switz.:*** Regitine; ***UK:*** Rogitine; ***USA:*** Regitine†; ***Venez.:*** Regitina†.

Multi-ingredient: ***Austria:*** Androskat; ***Neth.:*** Androskat; ***USA:*** Tri-Mix.

Pholedrine Sulfate *(rINNM)* ⊗

Isodrine Sulphate; Pholédrine, Sulfate de; Pholedrine Sulphate *(BANM)*; Pholedrini Sulfas; Sulfato de foledrina; Sympropaminum (pholedrine). 4-(2-Methylaminopropyl)phenol sulfate.

Фоледрина Сульфат

$(C_{10}H_{15}NO)_2,H_2SO_4$ = 428.5.
CAS — 370-14-9 (pholedrine); 6114-26-7 (pholedrine sulfate).

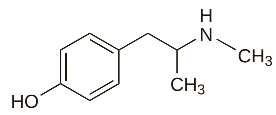

(pholedrine)

Profile

Pholedrine is a sympathomimetic (p.1407) used in the treatment of hypotensive states. It is usually given orally as the sulfate, often in combination with other drugs, and has also been included in preparations promoted for vascular disorders. Pholedrine eye drops have been used as an alternative to hydroxyamfetamine (p.2322) in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Adyston†; Zellaforte N Plus†; ***Switz.:*** Ortho-Maren retard.

Picotamide *(BAN)*

G-137; Picotamida; Picotamide, monohydrate de; Picotamid-monohidrát; Picotamidum monohydricum; Pikotamid monohydrát; Pikotamidimonohydraatti; Pikotamidmonohydrat; Pikotamido monohidratas. 4-Methoxy-*N*,*N*′-bis(3-pyridinylmethyl)-1,3-benzenedicarboxamide monohydrate.

$C_{21}H_{20}N_4O_3,H_2O$ = 394.4.
CAS — 32828-81-2 (anhydrous picotamide); 80530-63-8 (picotamide monohydrate).
ATC — B01AC03.
ATC Vet — QB01AC03.

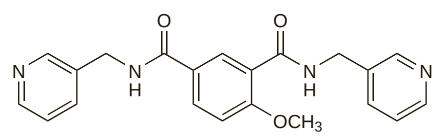

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Picotamide Monohydrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water; soluble in dehydrated alcohol and in dichloromethane; dissolves in dilute mineral acids.

Profile

Picotamide is a thromboxane synthase inhibitor and thromboxane receptor antagonist with antiplatelet activity. It is given by mouth in thromboembolic disorders (p.1187) in initial doses of 900 to 1200 mg daily in divided doses, reducing to a maintenance dose of 300 to 600 mg daily.

ACE inhibitor-induced cough. Cough is a recognised adverse effect of ACE inhibitors and has been treated with a number of drugs (see p.1194). Picotamide led to the disappearance of cough in 8 of 9 patients receiving enalapril for hypertension,[1] suggesting that thromboxanes may be involved in the aetiology of ACE inhibitor-induced cough.

1. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; **350:** 15–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Plactidil.

Pilsicainide Hydrochloride *(rINNM)*

Hidrocloruro de pilsicainida; Pilsicaïnide, Chlorhydrate de; Pilsicainidi Hydrochloridum; SUN-1165. Tetrahydro-1*H*-pyrrolizine-7a(5*H*)-aceto-2′,6′-xylidide hydrochloride.

Пильсикаинида Гидрохлорид

$C_{17}H_{24}N_2O,HCl$ = 308.8.
CAS — 88069-67-4 (pilsicainide); 88069-49-2 (pilsicainide hydrochloride).

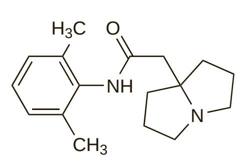

(pilsicainide)

Profile

Pilsicainide hydrochloride is an antiarrhythmic with class Ic activity (p.1153).

◊ References.

1. Takabatake T, *et al.* Pharmacokinetics of SUN 1165, a new antiarrhythmic agent, in renal dysfunction. *Eur J Clin Pharmacol* 1991; **40:** 411–14.
2. Okishige K, *et al.* Pilsicainide for conversion and maintenance of sinus rhythm in chronic atrial fibrillation: a placebo-controlled, multicenter study. *Am Heart J* 2000; **140:** 437–44.
3. Kumagai K, *et al.* Single oral administration of pilsicainide versus infusion of disopyramide for termination of paroxysmal atrial fibrillation: a multicenter trial. *Pacing Clin Electrophysiol* 2000; **23:** 1880–2.
4. Ogawa R, *et al.* Population pharmacokinetic and pharmacodynamic analysis of a class IC antiarrhythmic, pilsicainide, in patients with cardiac arrhythmias. *J Clin Pharmacol* 2006; **46:** 59–68.
5. Kumagai K, *et al.* Pilsicainide for atrial fibrillation. *Drugs* 2006; **66:** 2067–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Sunrythm.

Pimobendan *(BAN, USAN, rINN)*

Pimobendaani; Pimobendán; Pimobendanas; Pimobendane; Pimobendanum; UDCG-115. 4,5-Dihydro-6-[2-(*p*-methoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2*H*)-pyridazinone.

Пимобендан

$C_{19}H_{18}N_4O_2$ = 334.4.
CAS — 74150-27-9; 118428-36-7.
ATC Vet — QC01CE90.

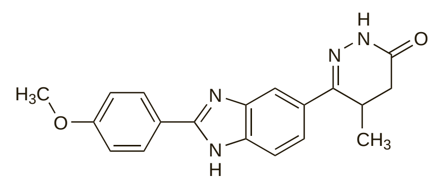

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Pimobendan). A white or slightly yellowish, hygroscopic powder. Practically insoluble in water; slightly soluble in acetone and in methyl alcohol; freely soluble in dimethylformamide. Store in airtight containers.

Profile

Pimobendan is a phosphodiesterase inhibitor with calcium-sensitising properties. It has positive inotropic and vasodilator activity and is used as an adjunct to standard therapy in the management of heart failure (p.1165). It is given orally in a dose of 1.25 to 2.5 mg twice daily.

Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate.

◊ References.

1. Przechera M, *et al.* Pharmacokinetic profile and tolerability of pimobendan in patients with terminal renal insufficiency. *Eur J Clin Pharmacol* 1991; **40:** 107–11.
2. The Pimobendan in Congestive Heart Failure (PICO) Investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996; **76:** 223–31.
3. Yoshikawa T, *et al.* Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000; **85:** 1495–7.
4. The EPOCH Study Group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure: the effects of pimobendan on chronic heart failure study (EPOCH study). *Circ J* 2002; **66:** 149–57.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Acardi.

Pinacidil *(USAN, rINN)*

P-1134; Pinacidilum; Pinasidiili. (±)-2-Cyano-1-(4-pyridyl)-3-(1,2,2-trimethylpropyl)guanidine.

Пинацидил

$C_{13}H_{19}N_5$ = 245.3.
CAS — 60560-33-0 (anhydrous pinacidil); 85371-64-8 (pinacidil monohydrate).
ATC — C02DG01.
ATC Vet — QC02DG01.

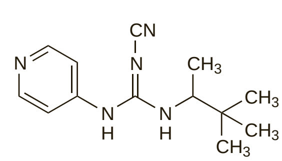

Profile
Pinacidil is a potassium-channel opener (p.1155) that produces direct peripheral vasodilatation of the arterioles. It has been used in the management of hypertension. It reduces blood pressure and peripheral resistance and produces fluid retention. Tachycardia and an increase in cardiac output occur mainly as a reflex response to the reduction in peripheral resistance.

◊ Reviews.

1. Friedel HA, Brogden RN. Pinacidil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990; **39:** 929–67.

Pindolol *(BAN, USAN, rINN)* ⊗

LB-46; Pindololi; Pindololis; Pindololum; Prindolol; Prinodolol. 1-(Indol-4-yloxy)-3-isopropylaminopropan-2-ol.

Пиндолол

$C_{14}H_{20}N_2O_2$ = 248.3.

CAS — 13523-86-9.

ATC — C07AA03.

ATC Vet — QC07AA03.

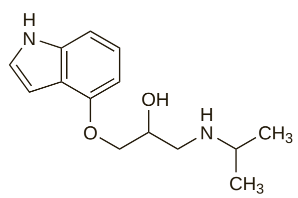

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Pindolol). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Protect from light.

USP 31 (Pindolol). A white to off-white, crystalline powder with a faint odour. Practically insoluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions
As for Beta Blockers, p.1226.

Effects on lipid metabolism. Beta blockers can affect plasma-lipid concentrations, although this may be less of a problem with those that have intrinsic sympathomimetic activity. For reference to the lack of effect of pindolol, see p.1227.

Tremor. Fine tremor in the extremities of 5 patients during pindolol therapy was considered to have been due to its partial agonist activity.[1]

1. Hod H, *et al*. Pindolol-induced tremor. *Postgrad Med J* 1980; **56:** 346–7.

Interactions
The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics
Pindolol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are obtained about 1 to 2 hours after an oral dose. It has a bioavailability of about 87%. About 40 to 60% is reported to be bound to plasma proteins. It is moderately lipid-soluble. Pindolol crosses the placenta and is distributed into breast milk. It is only partially metabolised in the liver and is excreted in the urine both unchanged and in the form of metabolites. A plasma elimination half-life of 3 to 4 hours has been reported in healthy adults. The half-life may be prolonged in elderly hypertensive patients and in patients with renal or hepatic impairment.

Uses and Administration
Pindolol is a non-cardioselective beta blocker (p.1225). It is reported to have intrinsic sympathomimetic activity but little membrane-stabilising activity.

Pindolol is used in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and other cardiovascular disorders. It is also used in glaucoma (p.1873).

In **hypertension** pindolol is usually given initially in an oral dosage of 5 mg two or three times daily, or 15 mg once daily, subsequently increased according to response. The usual maintenance dose is 15 to 30 mg once daily, but up to 45 mg daily, as a single dose or in divided doses, may be required. Additional benefit is rarely obtained from doses higher than 45 mg daily, although doses up to 60 mg daily have been given.

The usual oral dose for **angina pectoris** is 2.5 to 5 mg up to three times daily; however, doses of up to 40 mg daily have been used.

Eye drops containing pindolol 1% are used in the management of **glaucoma**.

Pindolol has also been given intravenously in the management of cardiac arrhythmias.

Psychiatric disorders. In addition to its beta-blocking properties, pindolol is also a partial agonist at serotonin 5-HT_1-receptors and has been used to augment the effects of SSRIs in patients with depression (p.373). Results have been conflicting,[1] but a meta-analysis[2] found that the time to response was shorter in patients given pindolol with an SSRI, although there was no effect on long-term outcomes. Small studies have also reported positive effects with pindolol augmentation of SSRIs in obsessive-compulsive disorder[3] (p.952) and in panic disorder[4] (p.952), although no effect was seen in social phobia.[5] Another study[6] found that pindolol augmentation of antipsychotic therapy reduced aggression in patients with schizophrenia (p.955).

1. Segrave R, Nathan PJ. Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. *Hum Psychopharmacol* 2005; **20:** 163–74.
2. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J Affect Disord* 2004; **79:** 137–47.
3. Dannon PN, *et al.* Pindolol augmentation in treatment-resistant obsessive compulsive disorder: a double-blind placebo controlled trial. *Eur Neuropsychopharmacol* 2000; **10:** 165–9.
4. Hirschmann S, *et al.* Pindolol augmentation in patients with treatment-resistant panic disorder: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2000; **20:** 556–9.
5. Stein MB, *et al.* Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry* 2001; **158:** 1725–7.
6. Caspi N, *et al.* Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study. *Int Clin Psychopharmacol* 2001; **16:** 111–5.

Preparations
BP 2008: Pindolol Tablets;
USP 31: Pindolol Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Barbloc; Visken; ***Austria:*** Visken; ***Belg.:*** Visken; ***Braz.:*** Visken; ***Canad.:*** Apo-Pindol; Novo-Pindol; Nu-Pindol; Visken; ***Cz.:*** Apo-Pindol†; Visken†; ***Denm.:*** Hexapindol; Visken; ***Fin.:*** Pindocor; Pinloc; Visken; ***Fr.:*** Visken; ***Ger.:*** durapindol†; Glauco-Stulln; Visken; ***Gr.:*** Visken; ***Hong Kong:*** Visken; ***Hung.:*** Visken; ***India:*** Visken; ***Irl.:*** Visken; ***Israel:*** Pinden; ***Ital.:*** Visken; ***Mex.:*** Visken; ***Neth.:*** Visken; ***NZ:*** Pindol; ***Philipp.:*** Pyndale; Visken; ***Pol.:*** Visken; ***Rus.:*** Visken (Вискен); ***Swed.:*** Visken; ***Switz.:*** Viskene; ***Turk.:*** Visken; ***UK:*** Visken; ***USA:*** Visken; ***Venez.:*** Visken†.

Multi-ingredient: ***Austria:*** Viskenit; ***Belg.:*** Viskaldix; ***Braz.:*** Viskaldix; ***Canad.:*** Viskazide; ***Chile:*** Viskaldix; ***Fr.:*** Viskaldix; ***Ger.:*** Viskaldix; ***Gr.:*** Viskaldix; ***Hung.:*** Viskaldix; ***Irl.:*** Viskaldix; ***Malaysia:*** Viskaldix; ***Neth.:*** Viskaldix; ***Philipp.:*** Viskaldix; ***Rus.:*** Viskaldix (Вискалдикс); ***Switz.:*** Viskaldix; ***Thai.:*** Viskaldix†; ***UK:*** Viskaldix; ***Venez.:*** Viskaldix†.

Pipratecol *(rINN)*

Pipratécol; Pipratecolum; 711-SE. 1-(3,4-Dihydroxyphenyl)-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethanol.

Пипратекол

$C_{19}H_{24}N_2O_4$ = 344.4.

CAS — 15534-05-1.

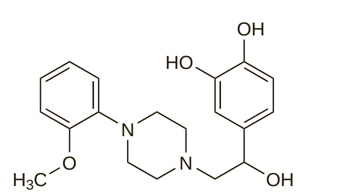

Profile
Pipratecol is a vasodilator that has been given with raubasine (p.1386) in the treatment of cerebrovascular disorders.

Piretanide *(BAN, USAN, rINN)* ⊗

Hoe-118; Piretanid; Piretanida; Piretanidas; Pirétanide; Piretanidi; Piretanidum; S73-4118. 4-Phenoxy-3-(pyrrolidin-1-yl)-5-sulphamoylbenzoic acid.

Пиретанид

$C_{17}H_{18}N_2O_5S$ = 362.4.

CAS — 55837-27-9.

ATC — C03CA03.

ATC Vet — QC03CA03.

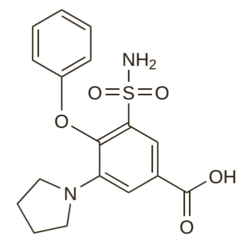

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Piretanide). A yellowish-white to yellowish powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in dehydrated alcohol. Protect from light.

Adverse Effects
As for Furosemide, p.1292. Muscle cramps have been reported after high doses of piretanide.

Precautions
Piretanide's precautions and contra-indications, which are dependent on its effects on fluid and electrolyte balance, are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Patients with impaired micturition or prostatic hyperplasia may develop retention of urine with piretanide.

Interactions
As for Furosemide, p.1293.

Pharmacokinetics
Piretanide has been reported to be almost completely absorbed after oral doses. It is extensively bound to plasma proteins, and is reported to have a half-life of about 1 hour after an oral dose.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Uses and Administration
Piretanide is a loop diuretic with actions and uses similar to those of furosemide (p.1294). It is used for oedema, including that associated with heart failure (p.1165), in oral doses of 3 to 6 mg daily. In the treatment of hypertension (p.1171) it is given in a usual oral dose of 6 to 12 mg daily. The sodium salt is given by injection.

◊ References.

1. Clissold SP, Brogden RN. Piretanide: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1985; **29:** 489–530.

Preparations
Proprietary Preparations (details are given in Part 3)

Austria: Arelix; ***Braz.:*** Arelix; ***Fr.:*** Eurelix; ***Ger.:*** Arelix; ***Irl.:*** Arelix; ***Ital.:*** Tauliz; ***Mex.:*** Diural; ***S.Afr.:*** Arelix; ***Spain:*** Perbilen; ***Switz.:*** Arelix.

Multi-ingredient: ***Austria:*** Trialix; ***Ger.:*** Arelix ACE; Aretensin; Betarelix; ***Irl.:*** Trialix; ***Ital.:*** Prilace; ***Switz.:*** Trialix.

Pirifibrate *(rINN)*

EL-466; Pirifibrato; Pirifibratum. 6-Hydroxymethyl-2-pyridylmethyl 2-(4-chlorophenoxy)-2-methylpropionate.

Пирифибрат

$C_{17}H_{18}ClNO_4$ = 335.8.

CAS — 55285-45-5.

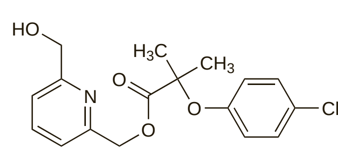

Profile
Pirifibrate, a fibric acid derivative (see Bezafibrate, p.1232), is a lipid regulating drug that has been used in the treatment of hyperlipidaemias.

Pirmenol Hydrochloride *(USAN, rINNM)*

CI-845; CL-845; Hidrocloruro de pirmenol; Pirménol, Chlorhydrate de; Pirmenoli Hydrochloridum. (±)-*cis*-2,6-Dimethyl-α-phenyl-α-2-pyridyl-1-piperidinebutanol hydrochloride.

Пирменола Гидрохлорид

$C_{22}H_{30}N_2O,HCl = 374.9.$

CAS — 68252-19-7 (pirmenol); 61477-94-9 (pirmenol hydrochloride).

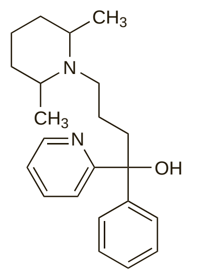

(pirmenol)

Profile

Pirmenol hydrochloride is an antiarrhythmic with class Ia activity (p.1153).

◊ References.

1. Hampton EM, *et al.* Initial and long-term outpatient experience with pirmenol for control of ventricular arrhythmias. *Eur J Clin Pharmacol* 1986; **31:** 15–22.
2. Stringer KA, *et al.* Enhanced pirmenol elimination by rifampin. *J Clin Pharmacol* 1988; **28:** 1094–7.
3. Janiczek N, *et al.* Pharmacokinetics of pirmenol enantiomers and pharmacodynamics of pirmenol racemate in patients with premature ventricular contractions. *J Clin Pharmacol* 1997; **37:** 502–13.

Pitavastatin *(rINN)*

Itavastatin; Nisvastatin; NK-104; Pitavastatina; Pitavastatine; Pitavastatinum. (3*R*,5*S*,6*E*)-7-[2-Cyclopropyl-4-(*p*-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoic acid.

Питавастатин

$C_{25}H_{24}FNO_4 = 421.5.$

CAS — 147511-69-1 (pitavastatin); 147526-32-7 (pitavastatin calcium).

ATC — C10AA08.

ATC Vet — QC10AA08.

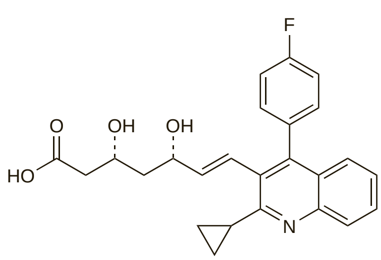

Profile

Pitavastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with similar properties to simvastatin (p.1390). It is used as the calcium salt in the treatment of hyperlipidaemias.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Livalo.

Plant Stanols and Sterols

Phytosterols.

Станолы и Стерины из Растений

Phytosterol

Fitosterolis; Fitoszterin; Fytosterol; Fytosteroli; Phytosterin; Phytostérol; Phytosterolum.

Фитостерин; Фитостерол

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Phytosterol). A natural mixture of sterols obtained from plants of the genera *Hypoxis*, *Pinus*, and *Picea*. It contains not less than 70% β-sitosterol, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in tetrahydrofuran; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Sitostanol

Dihydro-β-sitosterol; Fucostanol; β-Sitostanol; Stigmastanol. (3β,5α)-Stigmastan-3-ol.

Ситостанол

$C_{29}H_{52}O = 416.7.$

CAS — 83-45-4.

Sitosterol

β-Sitosterin; β-Sitosterol. (3β)-Stigmast-5-en-3-ol.

Ситостерин; Ситостерол

$C_{29}H_{50}O = 414.7.$

CAS — 83-46-5.

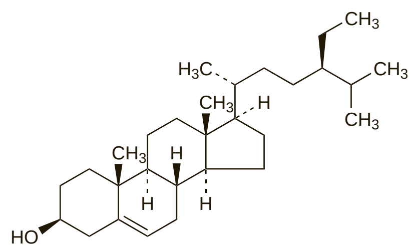

Profile

Stanols and sterols occur naturally in plants and are chemically related to cholesterol. The term phytosterol is used to describe both unsaturated plant sterols and their saturated (hydrogenated) counterparts, plant stanols (phytostanols). Sitosterol, campesterol, and stigmasterol are the commonest phytosterols; their respective stanols are found in lower amounts naturally, but can be produced by hydrogenation of sterols.

Dietary phytosterols have a cholesterol-lowering action; they reduce cholesterol absorption from the intestine and may also have other mechanisms. Sitosterol has been used as a lipid regulating drug, and both sterol and stanol esters (formed by esterification with unsaturated fatty acids) have been incorporated into margarines and other food products for use in the dietary management of hypercholesterolaemia. Sitosterol, sitostanol, and other phytosterols, are also used in nutritional supplements.

Sitosterol is also used in benign prostatic hyperplasia (p.2178), although its mechanism of action is not clear. It is given orally in usual initial doses of 20 mg three times daily.

There have been reports of bleeding complications associated with supplements containing phytosterols.

◊ References.

1. Wilt T, *et al.* Beta-sitosterols for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 24/06/05).
2. Law M. Plant sterol and stanol margarines and health. *BMJ* 2000; **320:** 861–4.
3. Lichtenstein AH, Deckelbaum RJ. Stanol/sterol ester-containing foods and blood cholesterol levels: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2001; **103:** 1177–9. Also available at: http://circ.ahajournals.org/cgi/reprint/103/8/1177.pdf (accessed 01/06/08)
4. Katan MB, *et al.* Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* 2003; **78:** 965–78.
5. Health Canada. Sterol and sterolin-containing products: hematologic adverse reactions. *Can Adverse React News* 2004; **14** (2): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n2-eng.pdf (accessed 19/08/08)
6. Miettinen TA, Gylling H. Plant stanol and sterol esters in prevention of cardiovascular diseases: a review. *Int J Clin Pharmacol Ther* 2006; **44:** 247–50.
7. Devaraj S, Jialal I. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutr Rev* 2006; **64:** 348–54.
8. Moruisi KG, *et al.* Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. *J Am Coll Nutr* 2006; **25:** 41–8.
9. Naruszewicz M, Kozlowska-Wojciechowska M. Plant sterols beyond low-density lipoprotein-cholesterol. *Br J Nutr* 2007; **98:** 454–5.
10. Weingärtner O, *et al.* Pflanzliche Sterole als Nahrungsmittelad-ditiva zur Prävention kardiovaskulärer Erkrankungen. *Dtsch Med Wochenschr* 2008; **133:** 1201–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Prostacur; ***Austria:*** Harzol; ***Ger.:*** Azuprostat; Flemun†; Harzol; Prostasal†; Sito-Lande†; Sitosterin; Triastonal; ***Indon.:*** Cholbalance; ***Pol.:*** Prostalizyna; Prosterol; ***Thai.:*** Mebo; ***UAE:*** Mebo.

Multi-ingredient: ***Arg.:*** Cholesterol Reducing Plan†; Sojasterol†; SX-22; ***Fr.:*** Bakol; ***Hong Kong:*** Basikol; Physiogel; ***Rus.:*** Herbion Urtica (Гербион Уртика); ***UK:*** Kolestop; Lestrin; ***USA:*** Better Cholesterol; Better Prostate†; Cholesterol Support; Prostate Support; Super Beta Prostate.

Plasminogen *(BAN)*

Plasminógeno.

CAS — 9001-91-6.

Profile

Plasminogen is the specific substance derived from plasma which, when activated to plasmin, has the property of lysing fibrinogen, fibrin, and some other proteins. Its role in the control of haemostasis is described further on p.1045. Plasminogen has been investigated as a thrombolytic and has been used with other blood products in wound-sealant preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Tissucol Duo Quick†; ***Austria:*** Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Canad.:*** Tisseel; ***Cz.:*** Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Tissucol; ***Ger.:*** Tissucol Duo S; Tissucol-Kit; ***Hong Kong:*** Tisseel; ***Hung.:*** Tissucol-Kit; ***Israel:*** Tisseel; ***Mex.:*** Tissucol†; ***Spain:*** Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Tissucol; Tissucol Duo S; ***UK:*** Tisseel.

Policosanol

Поликосанол

CAS — 142583-61-7.

ATC — C10AX08.

ATC Vet — QC10AX08.

Octacosanol

Cluytyl Alcohol; Montanyl Alcohol; Octacosyl Alcohol. 1-Octacosanol.

Октакосанол

$C_{28}H_{58}O = 410.8.$

CAS — 557-61-9.

Profile

Policosanol is a mixture of higher primary aliphatic alcohols (fatty alcohols) derived from plant waxes such as sugar cane wax; it is also found in beeswax and in wheat-germ oil (p.2415). The main component is octacosanol. Policosanol appears to have cholesterol-lowering properties and has been used in the treatment of hypercholesterolaemias, although its benefit has been disputed. Both policosanol and octacosanol are used in nutritional supplements.

◊ References.

1. Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* 2002; **143:** 356–65.
2. Pepping J. Policosanol. *Am J Health-Syst Pharm* 2003; **60:** 1112–5.
3. Berthold HK, *et al.* Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. *JAMA* 2006; **295:** 2262–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lipex; ***Austral.:*** Policor; ***Chile:*** PPG; ***Indon.:*** Polikos; ***Mex.:*** Mercol; ***S.Afr.:*** Phytocor; ***Venez.:*** Dupla†.

Multi-ingredient: ***Ital.:*** Colesterase; Novostatin; ***UK:*** Chol-Aid; Octacosanol.

Polythiazide *(BAN, USAN, rINN)* ⊗

NSC-108161; P-2525; Politiazida; Polythiazidum; Polytiatsidi; Polytiazid. 6-Chloro-3,4-dihydro-2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Политиазид

$C_{11}H_{13}ClF_3N_3O_4S_3 = 439.9.$

CAS — 346-18-9.

ATC — C03AA05.

ATC Vet — QC03AA05.

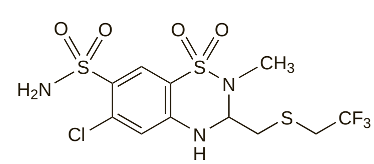

Pharmacopoeias. In *Br.*

BP 2008 (Polythiazide). A white or almost white, crystalline powder with an alliaceous odour. Practically insoluble in water and in chloroform; sparingly soluble in alcohol.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Polythiazide is fairly readily absorbed from the gastrointestinal tract. The estimated plasma elimination half-life is about 26 hours. More than 80% may be bound to plasma proteins. It is excreted mainly in the urine as unchanged polythiazide and metabolites.

◊ References.

1. Hobbs DC, Twomey TM. Kinetics of polythiazide. *Clin Pharmacol Ther* 1978; **23:** 241–6.

Uses and Administration

Polythiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis begins within about 2 hours of an oral dose, and lasts for 24 to 48 hours.

In the treatment of **hypertension** the usual dose is stated to be 2 to 4 mg daily, either alone or with other antihypertensives although doses of only 0.5 to 1 mg may be adequate. In the treatment of **oedema** the usual dose is 1 to 4 mg daily.

Preparations

BP 2008: Polythiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Renese†; ***USA:*** Renese†.

Multi-ingredient: ***Ger.:*** Polypress†; ***USA:*** Minizide†; Renese R†.

Potassium Canrenoate *(BANM, rINN)* ⊗

Aldadiene Potassium; Canrénoate de Potassium; Canrenoate Potassium *(USAN)*; Canrenoato de potasio; Kalii Canrenoas; Kaliumkanrenoaatti; Kaliumkanrenoat; MF-465a; SC-14266. Potassium 17-hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylate.

Калия Канреноат

$C_{22}H_{29}KO_4$ = 396.6.

CAS — 4138-96-9 (canrenoic acid); 2181-04-6 (potassium canrenoate).

ATC — C03DA02.

ATC Vet — QC03DA02.

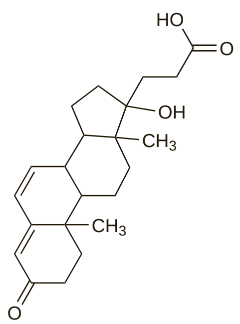

(canrenoic acid)

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

As for Spironolactone, p.1400. Irritation or pain may occur at the site of injection.

Effects on endocrine function. A lower incidence of gynaecomastia has been reported in patients with hepatic cirrhosis and ascites during use of potassium canrenoate than with equivalent doses of spironolactone,[1] and spironolactone-induced gynaecomastia disappeared when spironolactone was replaced by potassium canrenoate in a patient with hyperaldosteronism.[2] This suggests that metabolites other than canrenone (a common metabolite of both canrenoate and spironolactone thought to be responsible for their activity) or possibly spironolactone itself may be responsible for the anti-androgenic effects of spironolactone.[3,4]

1. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
2. Dupont A. Disappearance of spironolactone-induced gynaecomastia during treatment with potassium canrenoate. *Lancet* 1985; **ii:** 731.
3. Gardiner P. Spironolactone and potassium canrenoate metabolism. *Lancet* 1985; **ii:** 1432.
4. Overdiek JWPM, Merkus FWHM. Spironolactone metabolism and gynaecomastia. *Lancet* 1986; **i:** 1103.

Interactions

As for Spironolactone, p.1401.

Uses and Administration

Potassium canrenoate is a potassium-sparing diuretic with actions and uses similar to those of spironolactone (p.1401). Canrenone (p.1239) is a metabolite common to both drugs, but its contribution to the pharmacological action is unclear. Potassium canrenoate is used in the treatment of refractory oedema associated with heart failure (p.1165) or hepatic disease when an injectable aldosterone antagonist is required. It may be given in doses of 200 to 400 mg daily, increasing to 800 mg daily in exceptional cases; it is given by slow intravenous injection over a period of 2 to 3 minutes for each 200 mg or by intravenous infusion in glucose 5% or sodium chloride 0.9%.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Aldactone; ***Belg.:*** Canrenol; Soldactone; ***Cz.:*** Aldactone; Canrenol†; ***Fr.:*** Soludactone; ***Ger.:*** Aldactone; Kalium-Can; ***Hung.:*** Aldactone†; ***Ital.:*** Dikantal; Diurek; Kanrenol; Luvion; Venactone†; ***Neth.:*** Soldactone; ***Norw.:*** Soldactone†; ***Pol.:*** Aldactone; ***Switz.:*** Soldactone.

Multi-ingredient: ***Ital.:*** Kadiur.

Prajmalium Bitartrate *(BAN, rINN)*

Bitartrato de prajmalio; GT-1012; NPAB; Prajmalii Bitartras; Prajmaline Bitartrate; Prajmalium, Bitartrate de. *N*-Propylajmalinium hydrogen tartrate.

Праймалия Битартрат

$C_{23}H_{33}N_2O_2,C_4H_5O_6$ = 518.6.

CAS — 35080-11-6 (prajmalium); 2589-47-1 (prajmalium bitartrate).

ATC — C01BA08.

ATC Vet — QC01BA08.

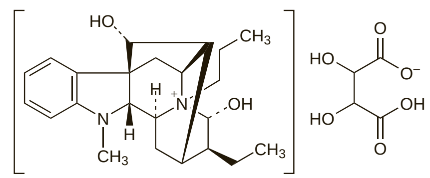

Adverse Effects and Precautions

As for Ajmaline, p.1206.

Effects on the liver. Cholestatic jaundice associated with pruritus, chills, and eosinophilia[1] was attributed to an allergic reaction to prajmalium bitartrate in a patient 20 days after the start of treatment.

1. Rotmensch HH, *et al.* Cholestatic jaundice: an immune response to prajmalium bitartrate. *Postgrad Med J* 1980; **56:** 738–41.

Effects on mental state. Confusion and disorientation in time and place[1] occurred on 2 occasions in a 67-year-old man given prajmalium bitartrate 100 mg daily for the control of tachycardia; the confusion rapidly disappeared when prajmalium was withdrawn.

1. Lessing JB, Copperman IJ. Severe cerebral confusion produced by prajmalium bitartrate. *BMJ* 1977; **2:** 675.

Uses and Administration

Prajmalium is a class I antiarrhythmic (p.1153) and is the *N*-propyl derivative of ajmaline (p.1206). It is given orally as the bitartrate in the management of supraventricular and ventricular arrhythmias (p.1160) in initial doses of 60 to 80 mg daily. Maintenance doses of 20 to 40 mg daily in divided doses are used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Neo-Gilurytmal; ***Cz.:*** Neo-Gilurytmal; ***Ger.:*** Neo-Gilurytmal; ***Hung.:*** Neo-Gilurytmal; ***Indon.:*** Neo-Gilurytmal; ***Israel:*** Neo-Gilurythmal†.

Multi-ingredient: ***Spain:*** Cresophene.

Prasugrel Hydrochloride *(USAN, rINNM)*

LY-640315; Prasugrel, Chlorhydrate de; Prasugrel, hidrocloruro de; Prasugreli Hydrochloridum. 5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride.

Празугрела Гидрохлорид

$C_{20}H_{20}FNO_3S,HCl$ = 409.9.

CAS — 389574-19-0.

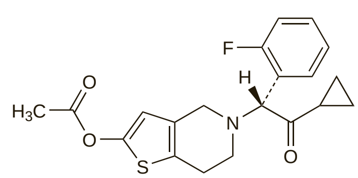

(prasugrel)

Profile

Prasugrel hydrochloride is a thienopyridine antiplatelet drug with similar properties to clopidogrel (p.1250). It is under development for cardiovascular disorders.

◊ References.

1. Wiviott SD, *et al.* Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005; **111:** 3366–73.
2. Jakubowski JA, *et al.* A multiple dose study of prasugrel (CS-747), a novel thienopyridine P2Y inhibitor, compared with clopidogrel in healthy humans. *Br J Clin Pharmacol* 2006; **63:** 421–30.
3. Brandt JT, *et al.* A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007; **153:** 66.
4. Wiviott SD, *et al.* TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.
5. Wiviott SD, *et al.* PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007; **116:** 2923–32.
6. Antman EM, *et al.* Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008; **51:** 2028–33.

Pravastatin Sodium *(BANM, USAN, rINNM)*

CS-514; Eptastatin Sodium; 3β-Hydroxycompactin Sodium; Natrii Pravastatinum; Pravastatiininatrium; Pravastatin sodná sůl; Pravastatina sódica; Pravastatine sodique; Pravastatinnatrium; Pravastatino natrio druska; Pravastatinum natricum; Pravasztatinnátrium; SQ-31000. Sodium (3*R*,5*R*)-7-{(1*S*,2*S*,6*S*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-6-hydroxy-2-methyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl}-3,5-dihydroxyheptanoate.

Натрий Правастатин

$C_{23}H_{35}O_7Na$ = 446.5.

CAS — 81093-37-0 (pravastatin); 81131-70-6 (pravastatin sodium).

ATC — C10AA03.

ATC Vet — QC10AA03.

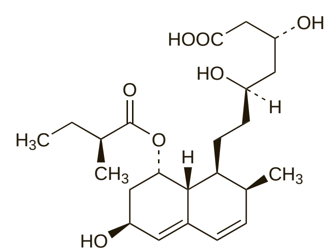

(pravastatin)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Pravastatin Sodium). A white to yellowish-white, hygroscopic, powder or crystalline powder. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol. A 5% solution in water has a pH of 7.2 to 9.0. Store in airtight containers.

USP 31 (Pravastatin Sodium). A white to yellowish white hygroscopic powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; practically insoluble in chloroform, in ether, and in ethyl acetate; very slightly soluble in acetonitrile. Store in airtight containers.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Interactions

The interactions of statins with other drugs are described under simvastatin (p.1392). Pravastatin is not significantly metabolised by the cytochrome P450 enzyme system and does not have the same interactions with enzyme inhibitors as simvastatin, although caution has been advised when such combinations are used. Increased plasma-pravastatin concentrations have been reported in some patients receiving ciclosporin and low doses should be used (see Uses and Administration, below).

Pharmacokinetics

Pravastatin is rapidly but incompletely absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver, its primary site of action. The absolute bioavailability of pravastatin is 17%. About 50% of the circulating drug is bound to plasma proteins. The plasma elimination half-life of pravastatin is 1.5 to 2 hours. About 70% of an oral dose of pravastatin is excreted in the faeces, as unabsorbed drug and via the bile, and about 20% is excreted in the urine.

◊ General reviews.

1. Quion JAV, Jones PH. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet* 1994; **27:** 94–103.
2. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet* 2000; **39:** 397–412.

Uses and Administration

Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394).

Pravastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), dysbetalipoproteinaemia (type III), and post-transplantation hyperlipidaemia. It is also used for cardiovascular risk reduction (p.1164), including primary prophylaxis in hypercholesterolaemic patients, and secondary prophylaxis, including prevention of stroke, in patients with clinically-evident ischaemic heart disease.

Pravastatin is given orally as the sodium salt; the usual dose is 10 to 40 mg of pravastatin sodium once daily at bedtime. The dose may be adjusted, according to response, at intervals of not less than 4 weeks. UK licensed product information states that the maximum dose is 40 mg once daily, but US licensed product information allows a maximum of 80 mg once daily in patients with hypercholesterolaemia. Low initial doses are recommended in patients with hepatic or renal impairment (see below).

In patients also taking *ciclosporin*, UK licensed product information recommends an initial dose of 20 mg once daily, but US licensed product information states an initial dose of 10 mg; dose increases should be made with caution.

For the use of pravastatin in children and adolescents, see below.

◊ General reviews.

1. McTavish D, Sorkin EM. Pravastatin: a review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1991; **42:** 65–89.
2. Haria M, McTavish D. Pravastatin: a reappraisal of its pharmacological properties and clinical effectiveness in the management of coronary heart disease. *Drugs* 1997; **53:** 299–336.

Administration in children. In children with heterozygous familial hypercholesterolaemia, pravastatin sodium is licensed in doses of 10 to 20 mg once daily in those aged 8 to 13 years and 10 to 40 mg once daily in those aged 14 to 18 years. Short-term studies have suggested that pravastatin effectively reduces cholesterol and is safe in children with familial hypercholesterolaemia[1] and in children taking immunosuppressants after heart transplant,[2] although plasma concentrations may be higher in the latter group. A randomised controlled study[3] and a prospective study[4] have also found that pravastatin is effective and well tolerated in familial hypercholesterolaemia, and there is some evidence[3] that carotid intima media thickness (a marker of atherosclerosis) may be reduced.

1. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther* 2003; **74:** 178–85.
2. Hedman M, *et al.* Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. *Clin Pharmacol Ther* 2004; **75:** 101–109.
3. Wiegman A, *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; **292:** 331–7.
4. Hedman M, *et al.* Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab* 2005; **90:** 1942–52.

Administration in hepatic or renal impairment. Patients with moderate or severe renal or significant hepatic impairment should be given pravastatin sodium in an initial dose of 10 mg daily, and the dose should be increased with caution.

Preparations

BP 2008: Pravastatin Tablets;
USP 31: Pravastatin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Pravacol; ***Austral.:*** Cholstat; Lipostat; Pravachol; ***Austria:*** Panchol; Pravachol; Sanaprav†; Selipran; ***Belg.:*** Merckprareduct; Prareduct†; Pravasine; ***Braz.:*** Mevalotin; Pravacol; ***Canad.:*** Pravachol; ***Chile:*** Pravacol; ***Cz.:*** Lipostat†; ***Denm.:*** Pravachol; ***Fin.:*** Pravachol; ***Fr.:*** Elisor; Vasten; ***Ger.:*** Mevalotin; Prava Basics; Pravabeta; Pravagamma; PravaLich; Pravalip; Pravasin; ***Gr.:*** Antisterin; Asto-Chol; Cholipravin; Cosivatin; Lipoprav; Maxudin; Ositron; Panlipol; Pravachol; Pravafact; Pravahelp; Pravalip; Pravalong; Pravanox; Pravedol; Pravin; Pravostin; Privast; Sosmin; Vastil; Zoter; Zyon; ***Hong Kong:*** Pravachol; ***Hung.:*** Nikron; Prastin; Pravastar; ***India:*** Pravator; ***Indon.:*** Cholespar; Koleskol; Mevachol; Novales; Pravachol; ***Irl.:*** ByStat; Cholstat; Lipostat; Pravamel; Pravat; Pravitin; ***Israel:*** Lipidal†; Pravalip; ***Ital.:*** Aplactin; Prasterol; Pravaselect; Sanaprav; Selectin; ***Jpn:*** Mevalotin; ***Malaysia:*** Pravachol; ***Mex.:*** Astin; Brakhor; Colpradin; Kenstatin; Kenvastin; Lexet; Loretsin; Mavitina; Novina; Paver; Prascolend; Prasiver; Pravacol; Striacol; Tissulest; Tratinal; Tridanil-H; Vaprasil; Varlex; Xipral; ***Neth.:*** Lipitifi; Lipratif; Pratiflip†; Pravandrea; Selektine; Statifil; Tifistat†; Vastatifix; ***Norw.:*** Pravachol; ***NZ:*** Lipostat; Pravachol; ***Philipp.:*** Lipostat; Stanidine; ***Pol.:*** Apo-Prava; ***Port.:*** Pravacol; Pritanol; Sanaprav; ***S.Afr.:*** Pranalip; Prava; ***Singapore:*** Pravachol; ***Spain:*** Bristacol; Lipemol; Liplat; Prareduct; Pravalipem†; Pritadol; ***Swed.:*** Pravachol; ***Switz.:*** Mevalotin; Pravalotin; Pravasta eco; Pravatine; Selipran; ***Thai.:*** Mevalotin; ***Turk.:*** Pravachol; ***UK:*** Lipostat; ***USA:*** Pravachol; ***Venez.:*** Mevalotin; Pravacol.

Multi-ingredient: ***Fr.:*** Pravadual; ***Neth.:*** Selektine Plus; ***USA:*** Pravigard PAC†.

Prazosin Hydrochloride

(BANM, USAN, rINNM)

CP-12299-1; Furazosin Hydrochloride; Hidrocloruro de prazosina; Pratsosiinihydrokloridi; Prazosin Hidroklorür; Prazosine, chlorhydrate de; Prazosin-hydrochlorid; Prazosinhydroklorid; Prazosini hydrochloridum; Prazozin-hidroklorid; Prazozino hidrochloridas. 2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine hydrochloride.

Празозина Гидрохлорид

$C_{19}H_{21}N_5O_4,HCl = 419.9.$

CAS — 19216-56-9 (prazosin); 19237-84-4 (prazosin hydrochloride).

ATC — C02CA01.

ATC Vet — QC02CA01.

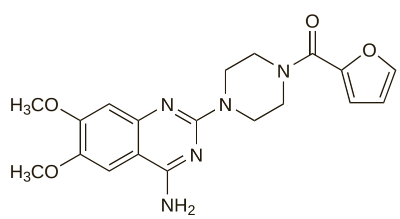

(prazosin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Prazosin Hydrochloride). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. Protect from light.

USP 31 (Prazosin Hydrochloride). A white to tan powder. Slightly soluble in water, in dimethylacetamide, in dimethylformamide, and in methyl alcohol; very slightly soluble in alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers. Protect from light.

Adverse Effects

Prazosin hydrochloride can cause orthostatic hypotension which may be severe and produce syncope after the initial dose; it may be preceded by tachycardia. This reaction can be avoided by starting treatment with a low dose, preferably at night (see Uses and Administration, below). The hypotensive effects may be exaggerated by exercise, heat, or alcohol ingestion.

The more common adverse effects include dizziness, drowsiness, headache, lack of energy, nausea, and palpitations, and may diminish with continued prazosin therapy or with a reduction in dosage. Other adverse effects include oedema, chest pain, dyspnoea, constipation, diarrhoea, vomiting, depression and nervousness, sleep disturbances, vertigo, hallucinations, paraesthesia, nasal congestion, epistaxis, dry mouth, urinary frequency and incontinence, reddened sclera, blurred vision, tinnitus, abnormal liver enzyme values, pancreatitis, arthralgia, alopecia, lichen planus, skin rashes, pruritus, and diaphoresis. Impotence and priapism have also been reported.

◊ General reviews.

1. Carruthers SG. Adverse effects of α -adrenergic blocking drugs. *Drug Safety* 1994; **11:** 12–20.

Effects on the cardiovascular system. Orthostatic hypotension, preceded by tachycardia and sometimes producing syncope, is an established adverse effect of the initial dose of prazosin. Sinus bradycardia was associated with prazosin in a patient who had light headedness after each daily dose.[1]

1. Ball J. Symptomatic sinus bradycardia due to prazosin. *Lancet* 1994; **343:** 121.

Effects on the gastrointestinal tract. Faecal incontinence in a 52-year-old man receiving prazosin was exacerbated by haemorrhoidectomy and appeared to be due to diminished resting anal tone, presumably because of smooth muscle relaxation secondary to alpha-adrenoceptor blockade.[1] Symptoms ceased almost immediately on stopping the drug.

1. Holmes SAV, *et al.* Faecal incontinence resulting from α -adrenoceptor blockade. *Lancet* 1990; **336:** 685–6.

Effects on mental function. Psychiatric symptoms including confusion, paranoia, and hallucinations developed in 3 patients associated with prazosin treatment.[1] Two of the patients had chronic renal failure and the other had mild renal impairment. Acute psychosis has also been reported with doxazosin.[2]

1. Chin DKF, *et al.* Neuropsychiatric complications related to use of prazosin in patients with renal failure. *BMJ* 1986; **293:** 1347.
2. Evans M, *et al.* Drug induced psychosis with doxazosin. *BMJ* 1997; **314:** 1869.

Hypersensitivity. Urticaria and angioedema were attributed to prazosin in a 70-year-old woman.[1]

1. Ruzicka T, Ring J. Hypersensitivity to prazosin. *Lancet* 1983; **i:** 473–4.

Lupus erythematosus. One study has reported the formation of antinuclear antibodies in patients receiving prazosin,[1] but this is not in agreement with other reports,[2,3] and commentators consider the association unproven.[4] There is no evidence of the development of lupus erythematosus.[1]

1. Marshall AJ, *et al.* Positive antinuclear factor tests with prazosin. *BMJ* 1979; **1:** 165–6.
2. Wilson JD, *et al.* Antinuclear factor in patients on prazosin. *BMJ* 1979; **1:** 553–4.
3. Melkild A, Gaarder PI. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 620–1.
4. Kristensen BØ. Does prazosin induce formation of antinuclear factor? *BMJ* 1979; **1:** 621.

Urinary incontinence. There have been reports of urinary incontinence developing in patients receiving prazosin. Analysis[1] of 56 cases reported to the Australian Adverse Drug Reactions Advisory Committee indicated that typically symptoms appeared within 1 or 2 days of the start of therapy and persisted until the drug was withdrawn or the dose reduced. Both stress and urge incontinence occurred, sometimes in the same patient. Of the 56 patients, 51 were women and most were elderly. In a study[2] in women attending a hypertension clinic urinary incontinence was reported in 40.8% of 49 women receiving alpha blockers (prazosin, terazosin, or doxazosin) and in 16.3% of controls. Incontinence might be due to a reduction in urethral pressure induced by alpha-adrenoceptor blockade.

Interestingly, faecal incontinence has also been reported with prazosin—see Effects on the Gastrointestinal Tract, above.

1. Mathew TH, *et al.* Urinary incontinence secondary to prazosin. *Med J Aust* 1988; **148:** 305–6.
2. Marshall HJ, Beevers DG. α-Adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. *Br J Clin Pharmacol* 1996; **42:** 507–9.

Treatment of Adverse Effects

If overdosage with prazosin occurs activated charcoal should be given if the patient presents within 1 hour of ingestion. Severe hypotension may occur and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement, and if necessary cautious intravenous infusion of a vasopressor. Prazosin is not removed by dialysis.

Precautions

Treatment with prazosin should be introduced cautiously because of the risk of sudden collapse following the initial dose. Extra caution is necessary in patients with hepatic or renal impairment and in the elderly.

Prazosin is not recommended for the treatment of heart failure caused by mechanical obstruction, for example aortic or mitral valve stenosis, pulmonary embolism, and restrictive pericardial disease. It should be used with caution in patients with angina pectoris. Prazosin may cause drowsiness or dizziness; patients so affected should not drive or operate machinery.

Cataract surgery. For a warning about intraoperative floppy iris syndrome during cataract surgery in patients taking alpha blockers, see Surgical Procedures under Precautions for Tamsulosin Hydrochloride, p.2197.

Cerebral haemorrhage. Hypotension with disturbance of consciousness[1] occurred in 3 patients with recent cerebral haemorrhage after an initial dose of prazosin 500 micrograms.

1. Lin M-S, Hsieh W-J. Prazosin-induced first-dose phenomenon possibly associated with hemorrhagic stroke: a report of three cases. *Drug Intell Clin Pharm* 1987; **21:** 723–6.

Tolerance. Although prazosin may be of initial benefit in patients with chronic heart failure, some studies[1,2] have reported the development of tolerance to its haemodynamic effects on prolonged therapy. This may be partly due to upregulation of $alpha_1$ adrenoceptors.[3]

1. Packer M, *et al*. Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. *J Am Coll Cardiol* 1986; **7:** 671–80.
2. Bayliss J, *et al*. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. *BMJ* 1985; **290:** 1861–5.
3. Kersting F, *et al*. Preliminary evidence for the mechanism underlying the development of tolerance to prazosin in congestive heart failure: the α-agonistic properties of dobutamine unmasked by prazosin treatment. *J Cardiovasc Pharmacol* 1993; **21:** 537–43.

Interactions

The hypotensive effects of prazosin may be enhanced by use with diuretics and other antihypertensives, and by alcohol and other drugs that cause hypotension. The risk of first-dose hypotension may be particularly increased in patients receiving beta blockers or calcium-channel blockers.

Analgesics. *Indometacin* reduced prazosin-induced hypotension in 4 of 9 subjects.[1]

1. Rubin P, *et al*. Studies on the clinical pharmacology of prazosin II: the influence of indomethacin and of propranolol on the action and disposition of prazosin. *Br J Clin Pharmacol* 1980; **10:** 33–9.

Antidepressants and antipsychotics. A patient who was taking *amitriptyline* and *chlorpromazine* developed acute agitation on receiving prazosin.[1] The symptoms settled rapidly when prazosin was discontinued. Antidepressants and antipsychotics may enhance the hypotensive effect of prazosin and other alpha blockers.

1. Bolli P, Simpson FO. New vasodilator drugs for hypertension. *BMJ* 1974; **1:** 637.

Calcium-channel blockers. An enhanced hypotensive effect has been reported in normotensive subjects given prazosin and *verapamil* concurrently; the effect may be due in part to enhanced bioavailability of prazosin.[1] Markedly increased hypotensive responses have also been reported with combined use of prazosin and *nifedipine*,[2,3] although the validity of such reports has been questioned.[4]

1. Pasanisi F, *et al*. Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. *Clin Pharmacol Ther* 1984; **36:** 716–23.
2. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. *BMJ* 1983; **287:** 1514.
3. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238–9.
4. Elliott HL, *et al*. Acute hypotensive response to nifedipine added to prazosin. *BMJ* 1984; **288:** 238.

Digoxin. For reference to the effect of prazosin on serum-digoxin concentrations, see under Digoxin, p.1261.

Pharmacokinetics

Prazosin is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 to 3 hours after an oral dose. The bioavailability is variable and a range of 43 to 85% has been reported. Prazosin is highly bound to plasma proteins. It is extensively metabolised in the liver and some of the metabolites are reported to have hypotensive activity. It is excreted as the metabolites and 5 to 11% as unchanged prazosin mainly in the faeces via the bile. Less than 10% is excreted in the urine. Small amounts are distributed into breast milk. Its duration of action is longer than would be predicted from its relatively short plasma half-life of about 2 to 4 hours. Half-life is reported to be increased to about 7 hours in patients with heart failure.

The elderly. The bioavailability of prazosin was significantly reduced in the elderly, about 40% less unchanged drug reaching the systemic circulation compared with the young.[1] This was attributed to a reduction in the absorption from the gastrointestinal tract. The half-life was also prolonged in the elderly and this was associated with an increase in the volume of distribution at steady state. However, it was considered unlikely that these effects would have major clinical significance.

1. Rubin PC, *et al*. Prazosin disposition in young and elderly subjects. *Br J Clin Pharmacol* 1981; **12:** 401–4.

Protein binding. Although a study[1] found that prazosin was about 80 to 85% bound to serum albumin and only about 10 to 30% bound to α_1-acid glycoprotein *in vitro*, potential interactions between the binding proteins *in vivo* were not taken into account; binding to α_1-acid glycoprotein might be more significant in clinical practice. A subsequent study[2] indicated that variations in prazosin protein binding pre- and post-operatively were related to variations in concentration of the glycoprotein.

1. Brunner F, Müller WE. Prazosin binding to human α -acid glycoprotein (orosomucoid), human serum albumin, and human serum: further characterisation of the 'single drug binding site' of orosomucoid. *J Pharm Pharmacol* 1985; **37:** 305–9.
2. Sager G, *et al*. Binding of prazosin and propranolol at variable α -acid glycoprotein and albumin concentrations. *Br J Clin Pharmacol* 1989; **27:** 229–34.

Uses and Administration

Prazosin is an alpha blocker (p.1153) that acts by selective blockade of $alpha_1$-adrenoceptors. It is used in the management of hypertension (p.1171), in Raynaud's syndrome (see Peripheral Vascular Disease, below), and to relieve symptoms of urinary obstruction in benign prostatic hyperplasia (p.2178). It has also been used in heart failure (p.1165).

Prazosin produces peripheral dilatation of both arterioles and veins and reduction of peripheral resistance, usually without reflex tachycardia. It reduces both standing and supine blood pressure with a greater effect on the diastolic pressure. It is reported to have no effect on renal blood flow or glomerular filtration rate, and has little effect on cardiac output in hypertensive patients. In patients with heart failure, prazosin reduces both preload and afterload and produces an improvement in cardiac output, although tolerance may develop. In benign prostatic hyperplasia, prazosin may relieve the symptoms of urinary obstruction by reducing smooth muscle tone in the prostate and bladder neck.

Prazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Prazosin hydrochloride 1.1 mg is equivalent to about 1 mg of prazosin. After oral dosage the hypotensive effect is seen within 2 to 4 hours and persists for several hours. Full effects are seen after 4 to 6 weeks.

A low starting dose is given in the evening to lessen the risk of collapse which may occur in some patients after the first dose (see Adverse Effects, above). Doses may need to be reduced in the elderly and in patients with hepatic or renal impairment.

In **hypertension**, the usual initial dose in the UK is 500 micrograms two or three times daily for 3 to 7 days; if tolerated the dose may then be increased to 1 mg two or three times daily for a further 3 to 7 days, and thereafter gradually increased, according to the patient's response, to a usual maximum of 20 mg daily in divided doses. In the US the recommended starting dose is 1 mg two or three times daily and up to 40 mg daily in divided doses has been given; however, the usual maintenance dose is between 6 and 15 mg daily. Smaller doses may be required in patients also taking other antihypertensives. Modified-release preparations may allow once daily dosing.

In **Raynaud's syndrome** and in **benign prostatic hyperplasia** an initial dose of 500 micrograms twice daily may be given, increasing to a maintenance dose not exceeding 2 mg twice daily.

In **heart failure**, treatment has been started with 500 micrograms two to four times daily and increased gradually according to response; the usual maintenance dose has been 4 to 20 mg daily.

Erectile dysfunction. Prazosin has been given transurethrally with alprostadil[1] in the management of erectile dysfunction (p.2179).

1. Peterson CA, *et al*. Erectile response to transurethral alprostadil, prazosin and alprostadil-prazosin combinations. *J Urol (Baltimore)* 1998; **159:** 1523–8.

Familial Mediterranean fever. Familial Mediterranean fever (p.557) is usually treated with prophylactic colchicine, but its use may be limited by adverse effects. A Japanese man who had suffered from attacks for 16 years was treated[1] with prazosin 3 mg daily. There were no further attacks for more than a year after starting treatment, but stopping prazosin resulted in a recurrence.

1. Kataoka H, *et al*. Treating familial Mediterranean fever with prazosin hydrochloride. *Ann Intern Med* 1998; **129:** 424–5.

Muscle cramp. Skeletal muscle cramp may occur during haemodialysis, possibly due to activation of the sympathetic nervous system. Prazosin was reported[1] to reduce the incidence of cramp in 4 of 5 patients with frequent haemodialysis-associated muscle cramp. However, the increased incidence of hypotension reported might limit its use for this indication.

1. Sidhom OA, *et al*. Low-dose prazosin in patients with muscle cramps during hemodialysis. *Clin Pharmacol Ther* 1994; **56:** 445–51.

Peripheral vascular disease. Alpha blockers, including prazosin, may be used in the management of Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188). Studies of the benefits of prazosin have produced varying results. A short-term reduction in number and duration of attacks was reported in 5 of 7 patients given prazosin 2 mg daily but only 1 patient had complete relief from attacks and few could tolerate doses higher than 6 mg daily.[1] Improvements were not maintained during continued treatment for 2 months. Others[2,3] have reported benefit from prazosin 1 mg two or three times daily in the majority of patients, with one study suggesting greater benefit in Raynaud's disease (the primary, idiopathic form) than in secondary Raynaud's syndrome.[2] In a subsequent study, higher doses of prazosin (2 or 4 mg three times daily) were no more effective than 1 mg three times daily, and were associated with a significantly greater incidence of adverse effects.[4] A systematic review[5] concluded that prazosin was modestly effective in the treatment of Raynaud's syndrome secondary to scleroderma.

1. Nielsen SL, *et al*. Prazosin treatment of primary Raynaud's phenomenon. *Eur J Clin Pharmacol* 1983; **24:** 421–3.
2. Allegra C, *et al*. Pharmacological treatment of Raynaud's phenomenon: a new therapeutic approach. *Curr Ther Res* 1986; **40:** 303–11.
3. Wollersheim H, *et al*. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986, **40:** 219–25.
4. Wollersheim H, Thien T. Dose-response study of prazosin in Raynaud's phenomenon: clinical effectiveness versus side effects. *J Clin Pharmacol* 1988; **28:** 1089–93.
5. Pope J, *et al*. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 24/06/05).

Post-traumatic stress disorder. Post-traumatic stress disorder (p.953) is usually treated with psychotherapy or drugs such as SSRIs. Increased $alpha_1$-adrenergic receptor activity may be a contributory factor, and several small studies have reported that treatment with prazosin improves nightmares and sleep disturbances in patients with this condition.[1,2] A reduction in nightmares occurred in 5 patients taking part in a small 6-week open-label study;[3] doses ranged from 1 mg at night to 2 mg night and morning. A similar improvement was found in a retrospective study[4] of combat veterans with chronic treatment-resistant symptoms, where doses of prazosin were increased gradually from 1 mg at night up to a maximum daily dose of 20 mg if required, and in a placebo-controlled study[5] in similar patients given doses of up to 15 mg at night. Another small study[6] and a case report[7] have also reported benefit; doses varied from 1 mg at night to 10 mg daily in 2 divided doses.

1. Dierks MR, *et al*. Prazosin treatment of nightmares related to posttraumatic stress disorder. *Ann Pharmacother* 2007; **41:** 1013–17.
2. Taylor HR, *et al*. Prazosin for treatment of nightmares related to posttraumatic stress disorder. *Am J Health-Syst Pharm* 2008; **65:** 716–22.
3. Taylor F, Raskind MA. The α -adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol* 2002; **22:** 82–5.
4. Raskind MA, *et al*. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2002; **63:** 565–8.
5. Raskind MA, *et al*. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 2007; **61:** 928–34.
6. Raskind MA, *et al*. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003; **160:** 371–3.
7. Griffith LJ. Case report: use of prazosin for treatment of posttraumatic stress disorder. *Am Fam Physician* 2005; **72:** 758, 761.

Renal calculi. For the potential use of alpha blockers to aid the passage of renal calculi, see under Uses of Tamsulosin Hydrochloride, p.2197.

Scorpion stings. Stings from the Indian red scorpion (*Mesobuthus tamulus*) are potentially fatal. The scorpion venom is a potent sympathetic stimulator resulting in high circulating catecholamines, hypertension, arrhythmias, pulmonary oedema, and circulatory failure. The efficacy of antivenom is questionable and treatment for cardiotoxicity is supportive (see p.2237). Prazosin, given orally, appears to be beneficial and has been suggested[1,2] as first-line treatment, except in cases of severe pulmonary oedema. Prazosin has also been used in other countries to treat stings by dangerous scorpion species.[3,4]

1. Bawaskar HS, Bawaskar PH. Scorpion envenoming and the cardiovascular system. *Trop Doct* 1997; **27:** 6–9.
2. Bawaskar HS, Bawaskar PH. Utility of scorpion antivenin vs prazosin in the management of severe Mesobuthus tamulus (Indian red scorpion) envenoming at rural setting. *J Assoc Physicians India* 2007; **55:** 14–21.
3. Koseoglu Z, Koseoglu A. Use of prazosin in the treatment of scorpion envenomation. *Am J Ther* 2006; **13:** 285–7.
4. Al-Asmari AK, *et al*. Role of prazosin on cardiovascular manifestations and pulmonary edema following severe scorpion stings in Saudi Arabia. *Saudi Med J* 2008; **29:** 299–302.

Preparations

BP 2008: Prazosin Tablets;
USP 31: Prazosin Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Decliten; Minipres†; ***Austral.:*** Minipress; Prasig†; Pratsiol; Prazohexal†; Pressin; ***Austria:*** Minipress; ***Belg.:*** Minipress; ***Braz.:*** Minipress; ***Canad.:*** Apo-Prazo; Minipress; Novo-Prazin; Nu-Prazo; ***Cz.:*** Deprazolin; ***Denm.:*** Hexapress; Peripress†; Prazac; ***Fin.:*** Peripress†; Pratsiol; ***Fr.:*** Alpress; Minipress; ***Ger.:*** Adversuten†; duramipress†; Minipress; ***Hong Kong:*** Apo-Prazo; CP-Prazo; Minipress; Mizosin; ***Hung.:*** Huma-Prazin†; Minipress; ***India:*** Minipress; Prazocip; ***Irl.:*** Hypovase; ***Israel:*** Hypotens; ***Jpn:*** Minipress†; ***Malaysia:*** Atodel; Minipress; Minison; ***Mex.:*** Anapres; Ensibest; Minipres; Sinozzard; ***NZ:*** Apo-Prazo; Hyprosin; Pratsiol; ***Pol.:*** Polpressin†; ***S.Afr.:*** Minipress†; Pratsiol; ***Singapore:*** Apo-Prazo; Minipress; ***Spain:*** Minipres; ***Switz.:*** Minipress†; ***Thai.:*** Atodel; Lopress; Minipress; Parabowl†; Polypress; Pratsiol†; Pressin; ***Turk.:*** Minipress; ***UK:*** Hypovase; Kentovase†; ***USA:*** Minipress; ***Venez.:*** Minpres.

Multi-ingredient: ***Ger.:*** Polypress†; ***USA:*** Minizide†.

Prenalterol Hydrochloride *(BANM, USAN, rINNM)*

C-50005/A-Ba (racemate); CGP-7760B; H133/22; H-80/62 (racemate); Hidrocloruro de prenalterol; Prénaltérol, Chlorhydrate de; Prenalteroli Hydrochloridum. (*S*)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

Преналътерола Гидрохлорид

$C_{12}H_{19}NO_3,HCl = 261.7.$
CAS — 57526-81-5 (prenalterol); 61260-05-7 (prenalterol hydrochloride).
ATC — C01CA13.
ATC Vet — QC01CA13.

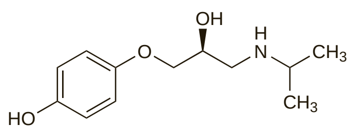

(prenalterol)

Profile

Prenalterol is a sympathomimetic (p.1407) with stimulant effects on $beta_1$ adrenoceptors. It has an inotropic action on the heart with relatively little chronotropic effect. Prenalterol hydrochloride has been given parenterally in the treatment of heart failure and shock. It has also been promoted for the reversal of beta blockade.

Probucol *(BAN, USAN, rINN)*

DH-581; Probucolum. 4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol).

Пробукол

$C_{31}H_{48}O_2S_2 = 516.8.$
CAS — 23288-49-5.
ATC — C10AX02.
ATC Vet — QC10AX02.

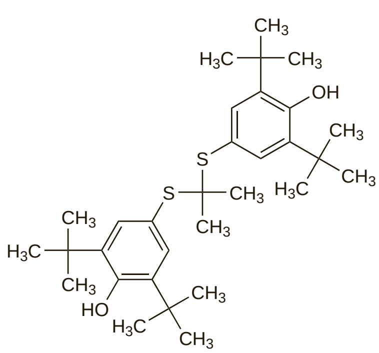

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Probucol). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in petroleum spirit; freely soluble in chloroform and in propyl alcohol. Protect from light.

Profile

Probucol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p.1169). It lowers total plasma-cholesterol concentrations, mainly by reducing low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol concentrations but has little effect on triglyceride or very-low-density lipoprotein (VLDL)-cholesterol concentrations. It has also been used to prevent restenosis after reperfusion and revascularisation procedures (below), and in scleroderma.

Probucol prolongs the QT interval and has been associated with cardiac arrhythmias.

Reperfusion and revascularisation procedures. Restenosis is common after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Probucol, started a few weeks before the procedure, has been reported to reduce the rate of restenosis after coronary angioplasty,[1] and to reduce the need for repeat interventions,[1,2] although another study[3] found no effect.

1. Tardif J-C, *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997; **337:** 365–72.
2. Daida H, *et al.* Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). *Am J Cardiol* 2000; **86:** 550–2.
3. Nunes GL, *et al.* Role of probucol in inhibiting intimal hyperplasia after coronary stent implantation: a randomized study. Abstract: *Am Heart J* 2006; **152:** 914. Full version: http://www.ahjonline.com/article/S0002-8703(06)00463-7/pdf (accessed 07/08/07)

Preparations

USP 31: Probucol Tablets.

Proprietary Preparations (details are given in Part 3)
Mex.: Serterol†; ***Port.:*** Lisosterol; ***S.Afr.:*** Lurselle†; ***Spain:*** Superlipid†; ***Thai.:*** Lurselle†.

Procainamide Hydrochloride

(BANM, rINNM)

Hidrocloruro de procainimida; Novocainamidum; Procaïnamide, chlorhydrate de; Procainamidi Chloridum; Procainamidi hydrochloridum; Prokaiiniamidihydrokloridi; Prokainamid-hidroklorid; Prokainamid-hydrochlorid; Prokainamidhydroklorid; Prokainamido hidrochloridas; Prokainamidu chlorowodorek. 4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride.

Прокаинамида Гидрохлорид

$C_{13}H_{21}N_3O,HCl = 271.8.$
CAS — 51-06-9 (procainamide); 614-39-1 (procainamide hydrochloride).
ATC — C01BA02.
ATC Vet — QC01BA02.

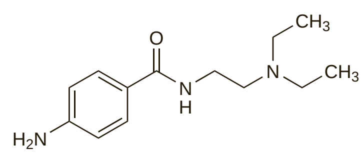

(procainamide)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Procainamide Hydrochloride). A white or very slightly yellow, hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 5.6 to 6.3. Store in airtight containers. Protect from light.

USP 31 (Procainamide Hydrochloride). A white to tan, odourless, crystalline powder. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether and in benzene. A 10% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Procainamide is more stable in neutral solutions such as sodium chloride, than in acidic solutions such as glucose, but patients requiring intravenous procainamide often have heart failure and cannot tolerate the sodium load associated with sodium chloride injections. The stability of procainamide in glucose 5% is improved by neutralising the glucose using sodium bicarbonate, or storing the admixture at 5°. The concentration of procainamide remained above 90% of the initial concentration for 24 hours if the glucose was first neutralised and this was considered more practical than refrigeration if extended stability was required.[1]

The compound formed by mixing procainamide hydrochloride with glucose 5% was shown to be a mixture of α- and β-glucosylamines[2] and about 10 to 15% of the procainamide was lost in this way after 10 hours at room temperature.

An oral liquid,[3] prepared from procainamide capsules, containing 5, 50, or 100 mg/mL of the hydrochloride was stable for at least 6 months when stored at 4° to 6°.

1. Raymond GG, *et al.* Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988; **45:** 2513–17.
2. Sianipar A, *et al.* Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994; **46:** 951–5.
3. Metras JI, *et al.* Stability of procainamide hydrochloride in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1992; **49:** 1720–4.

Adverse Effects

Cardiac effects occur particularly during intravenous use of procainamide and in overdose. Rapid intravenous dosage may result in severe hypotension, ventricular fibrillation, and asystole. High plasma concentrations are also associated with impaired cardiac conduction.

Hypersensitivity reactions to procainamide are common. Procainamide is a frequent cause of drug-induced SLE and the incidence has been reported to be as high as 30% during long-term use. Antinuclear antibodies may be detected in a high proportion of patients, but they do not necessarily develop the symptoms of SLE, which include arthralgia, arthritis, myalgia, pleural effusion, pericarditis, and fever. Agranulocytosis, eosinophilia, neutropenia, thrombocytopenia, and haemolytic anaemia have been reported. Other symptoms of hypersensitivity not necessarily related to SLE may also occur including hepatomegaly, angioedema, skin rashes, pruritus, urticaria, flushing, and hypergammaglobulinaemia.

Anorexia, nausea, vomiting, a bitter taste, and diarrhoea are more common with higher oral doses. Effects on the CNS such as mental depression, dizziness, and psychosis with hallucinations, have been reported.

Incidence of adverse effects. Out of 488 hospitalised patients in the Boston Collaborative Drug Surveillance Program who had received procainamide, 45 had acute adverse effects attributed to the drug.[1] Life-threatening reactions included heart block (3), tachyarrhythmias (2), and bradycardia and/or hypotension (2). Other reactions included gastrointestinal upsets (19), pyrexia (8), bradycardia and hypotension (5), tachyarrhythmias (3), heart block (1), eosinophilia (1), and urticaria (1).

1. Lawson DH, Jick H. Adverse reactions to procainamide. *Br J Clin Pharmacol* 1977; **4:** 507–11.

Effects on the blood. Adverse haematological effects reported during procainamide therapy include neutropenia,[1-3] agranulocytosis,[2-6] thrombocytopenia,[5] haemolytic anaemia,[7] and pancytopenia.[8] These disorders are usually reversible on withdrawing procainamide although some fatalities have been reported.[3,4] It has been suggested[2,6] that agranulocytosis or severe neutropenia is more likely in patients taking modified-release preparations, but others have found no difference in the incidence between modified-release and conventional-release preparations.[3] An increased risk of agranulocytosis with procainamide has been documented in one large study.[9] Although the precise estimate of excess risk could not be calculated, the order of magnitude was about 3 per million exposed for up to one week. This excess risk was low and of little relevance in the initial choice of therapy.

1. Riker J, *et al.* Bone marrow granulomas and neutropenia associated with procainamide. *Arch Intern Med* 1978; **138:** 1731–2.
2. Ellrodt AG, *et al.* Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 1984; **100:** 197–201.
3. Meyers DG, *et al.* Severe neutropenia associated with procainamide: comparison of sustained release and conventional preparations. *Am Heart J* 1985; **109:** 1393–5.
4. Fleet S. Agranulocytosis, procainamide, and phenytoin. *Ann Intern Med* 1984; **100:** 616–17.
5. Christensen DJ, *et al.* Agranulocytosis, thrombocytopenia, and procainamide. *Ann Intern Med* 1984; **100:** 918.
6. Thompson JF, *et al.* Procainamide agranulocytosis: a case report and review of the literature. *Curr Ther Res* 1988; **44:** 872–81.
7. Kleinman S, *et al.* Positive direct antiglobulin tests and immune hemolytic anemia in patients receiving procainamide. *N Engl J Med* 1984; **311:** 809–12.
8. Bluming AZ, *et al.* Severe transient pancytopenia associated with procainamide ingestion. *JAMA* 1976; **236:** 2520–1.
9. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects on the gastrointestinal tract. Pseudo-obstruction of the bowel occurred in a diabetic patient when given procainamide both orally and intravenously. It was believed that the anticholinergic properties of procainamide, together with the diabetic state, contributed to the severe hypomotility of the gastrointestinal tract.[1]

1. Peterson AM, *et al.* Procainamide-induced pseudo-obstruction in a diabetic patient. *DICP Ann Pharmacother* 1991; **25:** 1334–5.

Effects on the heart. Procainamide prolongs the QT interval and has been associated with the development of torsade de pointes,[1,2] and fatal cardiovascular toxicity has been reported[3] in patients with renal impairment. Toxicity appears to be related to accumulation of the major metabolite, *N*-acetylprocainamide, and haemodialysis has been used to reduce plasma concentrations and control symptoms,[1,4] although its benefits have been disputed (see Dialysis, under Treatment of Adverse Effects,

The symbol † denotes a preparation no longer actively marketed

below). However, symptoms developed in 1 patient[2] despite plasma concentrations of both procainamide and *N*-acetylprocainamide being within the therapeutic range.

1. Nguyen KPV, *et al*. N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
2. Habbab MA, El-Sherif N. Drug-induced torsades de pointes: role of early afterdepolarizations and dispersion of repolarization. *Am J Med* 1990; **89:** 241–6.
3. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.
4. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.

Effects on the liver. There have been reports of granulomatous hepatitis[1] and intrahepatic cholestasis[2,3] due to hypersensitivity reactions in patients taking procainamide. Fever and elevation of liver enzyme values also occurred. The reactions were reversible on withdrawing procainamide.

1. Rotmensch HH, *et al*. Granulomatous hepatitis: a hypersensitivity response to procainamide. *Ann Intern Med* 1978; **89:** 646–7.
2. Ahn C-S, Tow DE. Intrahepatic cholestasis due to hypersensitivity reaction to procainamide. *Arch Intern Med* 1990; **150:** 2589–90.
3. Chuang LC, *et al.* Possible case of procainamide-induced intrahepatic cholestatic jaundice. *Ann Pharmacother* 1993; **27:** 434–7.

Effects on mental function. Acute psychosis has been reported[1] in patients receiving therapy with procainamide.

1. Bizjak ED, *et al.* Procainamide-induced psychosis: a case report and review of the literature. *Ann Pharmacother* 1999; **33:** 948–51.

Effects on the muscles. Procainamide may affect neuromuscular transmission and there have been reports of severe generalised skeletal muscle weakness[1-3] in patients receiving procainamide. In 2 patients this was associated with respiratory failure[1,2] and developed shortly after starting therapy. Concentrations of procainamide and its *N*-acetyl metabolite exceeded the normal therapeutic ranges and rapid cycling peritoneal dialysis was used to remove the drug in 1 patient.[2] Adverse muscle symptoms are a feature of procainamide-induced lupus erythematosus (see below), but in such instances symptoms usually develop on long-term treatment.

1. Lewis CA, *et al.* Myopathy after short term administration of procainamide. *BMJ* 1986; **292:** 593–4.
2. Javaheri S, *et al.* Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.
3. Sayler DJ, DeJong DJ. Possible procainamide-induced myopathy. *DICP Ann Pharmacother* 1991; **25:** 436.

Lupus erythematosus. Procainamide is a well-known cause of drug-induced lupus erythematosus.[1,2] It occurs in about 20% of patients on long-term therapy,[2] although the majority of patients taking procainamide for more than 1 year have detectable antinuclear antibodies. There is some evidence[3] that slow acetylators are more likely to develop antibodies than rapid acetylators, and that the antibodies appear more rapidly in slow acetylators, but this may not correlate with the development of clinical symptoms.[4] The clinical syndrome may include fever, polyarthritis, arthralgia, myalgia, and pleuropulmonary and pericardial features, and is usually spontaneously reversible on withdrawal of procainamide.

1. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
2. Rubin RL. Drug-induced lupus. *Toxicology* 2005; **209:** 135–47.
3. Woosley RL, *et al.* Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 1978; **298:** 1157–9.
4. Mongey A-B, *et al.* Acetylation status is associated with serological changes but not clinically significant disease in patients receiving procainamide. *J Rheumatol* 1999; **26:** 1721–6.

Treatment of Adverse Effects

In overdosage with procainamide treatment is largely symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion. The ECG, blood pressure, and renal function should be monitored. Supportive measures include correction of hypotension, assisted ventilation, and electrical pacing. Haemodialysis or haemoperfusion increase the elimination of procainamide and *N*-acetylprocainamide, see below.

SLE will normally respond to withdrawal of procainamide but corticosteroids may be required.

Dialysis. In the UK, the National Poisons Information Service does not recommend the use of haemodialysis or haemofiltration in the treatment of poisoning with class Ia antiarrhythmics. Nonetheless, both procainamide and *N*-acetylprocainamide are removed by haemodialysis, and there are reports[1-4] of the successful use of haemodialysis in patients with procainamide toxicity. However, toxicity has occurred in patients undergoing regular haemodialysis,[2,5,6] suggesting that some accumulation still takes place, and rebound increases in plasma concentrations have also been reported[4,7] after dialysis. Haemoperfusion[5,7] and haemofiltration[6] have also been used, and may be more effective. Peritoneal dialysis may also remove a small amount of procainamide and *N*-acetylprocainamide,[7] and there has been a report[8] of the successful use of rapid cycling peritoneal dialysis in a patient on maintenance peritoneal dialysis who developed procainamide-induced diaphragmatic paralysis.

1. Atkinson AJ, *et al*. Hemodialysis for severe procainamide toxicity: clinical and pharmacokinetic observations. *Clin Pharmacol Ther* 1976; **20:** 585–92.
2. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.
3. Nguyen KPV, *et al*. N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
4. Rosansky SJ, Brady ME. Procainamide toxicity in a patient with acute renal failure. *Am J Kidney Dis* 1986; **7:** 502–6.
5. Braden GL, *et al.* Hemoperfusion for treatment of N-acetylprocainamide intoxication. *Ann Intern Med* 1986; **105:** 64–5.
6. Domoto DT, *et al.* Removal of toxic levels of N-acetylprocainamide with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration. *Ann Intern Med* 1987; **106:** 550–2.
7. Low CL, *et al.* Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. *Nephrol Dial Transplant* 1996; **11:** 881–4.
8. Javaheri S, *et al.* Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.

Precautions

Procainamide is contra-indicated in heart block (unless the patient has a pacemaker) and in SLE, and should be used with caution in patients with myocardial damage or severe organic heart disease. The *BNF* considers that it should not be used in heart failure or hypotension. Patients with torsade de pointes may deteriorate if given procainamide. If procainamide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Procainamide should preferably not be used in patients with myasthenia gravis or digoxin toxicity. There may be cross-sensitivity between procaine and procainamide.

Accumulation of procainamide may occur in patients with heart failure or hepatic or renal impairment and dosage reduction may be necessary.

Blood counts and screening for lupus erythematosus and serum antinuclear factor should be carried out regularly during therapy.

Intravenous use of procainamide may lead to severe hypotension; it should be injected slowly and blood pressure and ECG should be monitored.

Breast feeding. There was evidence of accumulation of procainamide and *N*-acetylprocainamide in the breast milk of a woman taking procainamide 500 mg four times daily.[1] Milk and serum samples were obtained at three-hourly intervals for 15 hours. Mean serum concentrations of the drug and metabolite were found to be 1.1 and 1.6 micrograms/mL respectively; those in the milk were 5.4 and 3.5 micrograms/mL respectively. The mean milk:serum ratios were 4.3 (range 1.0 to 7.3) and 3.8 (range 1.0 to 6.2) respectively. However, it was considered that the amount ingested by the infant would not yield clinically significant serum concentrations. Although licensed product information states that procainamide should be avoided in breast-feeding women, there have been no reports of adverse effects in infants, and the American Academy of Pediatrics considers[2] that its use is therefore usually compatible with breast feeding.

1. Pittard WB, Glazier H. Procainamide excretion in human milk. *J Pediatr* 1983; **102:** 631–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Interactions

Procainamide may enhance the effects of antihypertensives, other antiarrhythmics and arrhythmogenic drugs, antimuscarinics, and neuromuscular blockers, and diminish those of parasympathomimetics, such as neostigmine. Procainamide is actively secreted by kidney tubules and interactions may occur with drugs secreted by the same pathway, such as cimetidine and trimethoprim.

Alcohol. The total body clearance of procainamide is increased by alcohol[1] and the elimination half-life reduced. The acetylation rate of procainamide is also increased resulting in a greater proportion of drug present as the active metabolite *N*-acetylprocainamide.

1. Olsen H, Mørland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* 1982; **13:** 203–8.

Antacids. Procainamide is adsorbed by some antacids and reduced bioavailability has been reported[1] in healthy subjects given procainamide with *kaolin-pectin*; the authors recommended that procainamide and adsorbents should not be used together.

1. Al-Shora HI, *et al.* Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* 1988; **47:** 209–13.

Antiarrhythmics. *Amiodarone* given orally alters the pharmacokinetic properties of an intravenous dose of procainamide,[1] decreasing clearance and prolonging the plasma elimination half-life. The dosage of intravenous procainamide should be reduced by 20 to 30% during concurrent use. Increased serum-procainamide concentrations have also been reported[2] in patients stabilised on oral procainamide who had amiodarone added to their therapy; the dosage of procainamide had to be reduced in some patients due to signs of toxicity. *Quinidine* has also been reported[3] to increase plasma-procainamide concentrations.

1. Windle J, *et al.* Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther* 1987; **41:** 603–10.
2. Saal AK, *et al.* Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol* 1984; **53:** 1264–7.
3. Hughes B, *et al.* Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J* 1987; **114:** 908–9.

Antibacterials. The renal clearance of procainamide and *N*-acetylprocainamide is reduced by *trimethoprim*[1,2] through competition for renal tubular secretion. Serum concentrations may be increased with a resulting increase in pharmacodynamic response. The fluoroquinolones *ciprofloxacin*,[3] *levofloxacin*,[3] and *ofloxacin*[4] have also been reported to reduce the renal clearance of procainamide.

1. Kosoglou T, *et al.* Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; **44:** 467–77.
2. Vlasses PH, *et al.* Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; **149:** 1350–3.
3. Bauer LA, *et al.* Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; **49:** 1649–51.
4. Martin DE, *et al.* Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; **36:** 85–91.

Histamine H_2-antagonists. Histamine H_2-antagonists compete with other basic drugs for renal tubular secretion. *Cimetidine* reduces the renal clearance of procainamide and *N*-acetylprocainamide[1,2] and a dosage reduction may be necessary. Increases[3,4] and decreases[4] in renal and metabolic clearances of procainamide have occurred with *ranitidine*.

1. Christian CD, *et al.* Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* 1984; **36:** 221–7.
2. Somogyi A, *et al.* Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 339–45.
3. Somogyi A, Bochner F. Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man. *Br J Clin Pharmacol* 1984; **18:** 175–81.
4. Rocci ML, *et al.* Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther* 1989; **248:** 923–8.

Pharmacokinetics

Procainamide is readily and almost completely absorbed from the gastrointestinal tract. It is widely distributed throughout the body and is only about 15 to 20% bound to plasma proteins. The therapeutic effect of procainamide has been correlated with plasma concentrations of about 3 to 10 micrograms/mL in most patients; progressively severe toxicity is noted at concentrations above 12 micrograms/mL.

Some procainamide undergoes acetylation in the liver to *N*-acetylprocainamide, which also has antiarrhythmic properties. The rate of acetylation of procainamide is genetically determined, there being slow and fast acetylators. Procainamide also undergoes hydrolysis in plasma to para-aminobenzoic acid.

Procainamide is excreted in the urine by active renal secretion, 30 to 70% as unchanged procainamide, with the remainder as *N*-acetylprocainamide and other metabolites. The elimination half-life of procainamide is 2.5 to 5 hours and that of its acetyl metabolite 6 to 7 hours. *N*-Acetylprocainamide may represent a significant fraction of the total drug in the circulation.

Procainamide crosses the placenta and is distributed into breast milk.

◊ References.

1. Grasela TH, Sheiner LB. Population pharmacokinetics of procainamide from routine clinical data. *Clin Pharmacokinet* 1984; **9:** 545–54.

Bioavailability. Modified-release procainamide preparations have been shown[1] to produce similar steady-state serum concentrations of procainamide and *N*-acetylprocainamide when compared with equivalent total doses of immediate-release capsules. However, tablet matrices of a modified-release preparation have been recovered from the stools of a patient with diarrhoea[2] and 3.5 g of procainamide was recovered in these matrices over an 18-hour collection period; the patient had correspondingly low plasma-procainamide concentrations.

1. Vlasses PH, *et al.* Immediate-release and sustained-release procainamide: bioavailability at steady state in cardiac patients. *Ann Intern Med* 1983; **98:** 613–14.
2. Woosley RL, *et al.* Antiarrhythmic therapy: clinical pharmacology update. *J Clin Pharmacol* 1984; **24:** 295–305.

The elderly. Reduced renal clearance of procainamide has been reported in the elderly.[1,2]

1. Reidenberg MM, *et al.* Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharmacol Ther* 1980; **28:** 732–5.
2. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.

Hepatic impairment. In 20 healthy subjects and 20 patients with chronic liver disease given a single 500-mg oral dose of procainamide hydrochloride about 64 and 33% respectively of the dose was excreted in the urine within 6 hours.[1] Decreased procainamide acetylation in the patients compared with the control group was not correlated with the severity of liver disease, whereas decreased procainamide hydrolysis and increased procainamide-derived aminobenzoic acid acetylation appeared to be related to the degree of hepatic impairment. It was suggested that the decrease in excretion of procainamide and its metabolites in the urine of the patients with liver disease could be due to an impairment in oral absorption since renal function was within the normal range but the variations in acetylation and hydrolysis were related to hepatic function.

1. du Souich P, Erill S. Metabolism of procainamide and p-aminobenzoic acid in patients with chronic liver disease. *Clin Pharmacol Ther* 1977; **22:** 588–95.

Renal impairment. Procainamide and its active *N*-acetyl metabolite are mainly excreted in the urine and accumulation, particularly of the metabolite, may occur in renal impairment. A study[1] in 20 patients found that procainamide clearance correlated with renal function, and that the ratio of *N*-acetylprocainamide to procainamide in the serum increased as renal function declined. Fatal toxicity in patients with renal impairment and plasma-procainamide concentrations within the therapeutic range has been attributed[2] to accumulation of *N*-acetylprocainamide. Both procainamide and *N*-acetylprocainamide are removed by dialysis, although the benefit of these procedures has been disputed (see Dialysis under Treatment of Adverse Effects, above).

1. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.
2. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.

Uses and Administration

Procainamide is a class Ia antiarrhythmic (p.1153); it has properties similar to those of quinidine (p.1385).

Procainamide is usually reserved for the short-term management of severe or symptomatic ventricular arrhythmias (p.1160) such as those following myocardial infarction. It may also be used for cardioversion and management of atrial fibrillation.

Therapeutic effect is generally associated with plasma concentrations of 3 to 10 micrograms/mL. The dose of procainamide hydrochloride required will depend on the age, renal and hepatic function, and underlying cardiac condition of the patient: an adult with normal renal function generally requires up to 50 mg/kg daily in divided oral doses every 3 to 6 hours. Higher doses may be necessary for atrial arrhythmias. Modified-release preparations are available.

In an emergency and under continuous ECG and blood pressure monitoring, procainamide hydrochloride may be given intravenously. The injection should be diluted in glucose 5% to permit better control of the speed of injection, and should be given in doses of 100 mg every 5 minutes at a rate not exceeding 50 mg/minute until the arrhythmia has been suppressed or a maximum dose of 1 g has been reached. A response may be obtained after 100 to 200 mg has been given and more than 500 or 600 mg is not generally required. Alternatively, procainamide hydrochloride may be given by continuous infusion of 500 to 600 mg over 25 to 30 minutes. Therapeutic plasma concentrations may then be maintained by infusion at a rate of 2 to 6 mg/minute. When transferring to oral therapy, a period of about 3 to 4 hours should elapse between the last intravenous dose and the first oral dose.

Procainamide hydrochloride has also been given intramuscularly.

Procainamide hydrochloride may need to be given in reduced doses or at longer dosing intervals in the elderly and in patients with hepatic or renal impairment. For use in children, see below.

Acecainide (*N*-acetylprocainamide), the active metabolite of procainamide, has class III antiarrhythmic activity and has been used in ventricular arrhythmias.

Administration in children. In a study in 5 children treated with procainamide for various cardiac arrhythmias the mean elimination half-life was found to be 1.7 hours, and the plasma clearance was higher than that reported in adults.[1] In contrast the total serum clearance of procainamide in 3 neonates with supraventricular tachycardia was found to be similar to that in adults and the mean elimination half-life was 5.3 hours.[2] A loading dose of 10 to 12 mg/kg intravenously was given followed by a continuous infusion of 20 to 75 micrograms/kg per minute.

An oral dose of 15 to 50 mg/kg daily in 4 divided doses has been used in children.

1. Singh S, *et al.* Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 1982; **32:** 607–11.
2. Bryson SM, *et al.* Therapeutic monitoring and pharmacokinetic evaluation of procainamide in neonates. *DICP Ann Pharmacother* 1991; **25:** 68–71.

Preparations

BP 2008: Procainamide Injection; Procainamide Tablets;
USP 31: Procainamide Hydrochloride Capsules; Procainamide Hydrochloride Extended-release Tablets; Procainamide Hydrochloride Injection; Procainamide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pronestyl; ***Braz.:*** Procamide; ***Canad.:*** Procan; Pronestyl†; ***Gr.:*** Pronestyl; ***Hong Kong:*** Pronestyl†; ***India:*** Pronestyl; ***Irl.:*** Pronestyl; ***Israel:*** Pronestyl†; ***Neth.:*** Pronestyl; ***NZ:*** Pronestyl; ***S.Afr.:*** Pronestyl; ***Spain:*** Biocoryl; ***UK:*** Pronestyl†; ***USA:*** Procanbid.

Propafenone Hydrochloride

(BANM, USAN, rINNM)

Fenopraine Hydrochloride; Hidrocloruro de propafenona; Propafenon Hidroklorür; Propafénone, chlorhydrate de; Propafenon-hydrochlorid; Propafenonhydroklorid; Propafenoni hydrochloridum; Propafenonihydrokloridi; Propafenono hidrochloridas; SA-79; WZ-884642; WZ-884643. 2′-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride.

Пропафенона Гидрохлорид

$C_{21}H_{27}NO_3,HCl = 377.9.$

CAS — 54063-53-5 (propafenone); 34183-22-7 (propafenone hydrochloride).

ATC — C01BC03.

ATC Vet — QC01BC03.

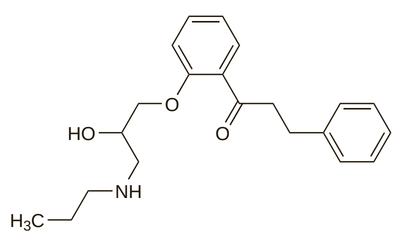

(propafenone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Propafenone Hydrochloride). Colourless crystals or a white or almost white powder. Slightly soluble in cold water; soluble in hot water and in methyl alcohol; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.0 to 6.2.

USP 31 (Propafenone Hydrochloride). A white powder. Soluble in hot water and in methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in ether and in toluene. A 0.5% solution in water has a pH of 5.0 to 6.2. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Adverse Effects

Propafenone can cause disturbances in cardiac conduction which can result in bradycardia, heart block, and sinus arrest. It may aggravate heart failure and may cause hypotension. In common with other antiarrhythmics, propafenone may induce or worsen arrhythmias in some patients.

Among the most common adverse effects are gastrointestinal intolerance, dry mouth, a bitter or metallic taste, dizziness, blurred vision, headache, and fatigue. Convulsions, blood dyscrasias, liver disorders, lupus erythematosus, skin rashes, impotence, and increased breathlessness and worsening of asthma have also been reported.

Effects on the heart. Propafenone may worsen ventricular arrhythmias and there have been reports[1,2] of fatal exacerbations occurring hours to days after starting treatment. Cardiovascular toxicity may also occur in overdosage.[3] Torsade de pointes has been reported[2,4,5] but appears to be less frequent than with class Ia antiarrhythmics.

1. Nathan AW, *et al.* Fatal ventricular tachycardia in association with propafenone, a new class IC antiarrhythmic agent. *Postgrad Med J* 1984; **60:** 155–6.
2. Buss J, *et al.* Malignant ventricular tachyarrhythmias in association with propafenone treatment. *Eur Heart J* 1985; **6:** 424–8.
3. Clarot F, *et al.* Fatal propafenone overdoses: case reports and a review of the literature. *J Anal Toxicol* 2003; **27:** 595–9.
4. Rosengarten M, Brooks R. Torsade de pointes ventricular tachycardia in a hypothyroid patient treated with propafenone. *Can J Cardiol* 1987; **3:** 234–9.
5. Hii JT, *et al.* Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol* 1991; **14:** 1568–70.

Effects on the liver. A review of liver injury secondary to propafenone therapy concluded that it is a rare occurrence and appears to be due to hepatocellular injury, cholestasis, or a combination.[1]

1. Spinler SA, *et al.* Propafenone-induced liver injury. *Ann Pharmacother* 1992; **26:** 926–8.

Effects on mental function. Delusions, hallucinations, and paranoia have been reported in an elderly patient after 2 doses of propafenone. The manufacturer had received reports of mania and psychosis.[1] Amnesia developed in a 61-year-old man 6 days after starting treatment with propafenone.[2] Symptoms resolved 6 to 7 hours after stopping the drug.

1. Robinson AJ. Paranoia after propafenone. *Pharm J* 1991; **247:** 556.
2. Jones RJ, *et al.* Probable propafenone-induced transient global amnesia. *Ann Pharmacother* 1995; **29:** 586–90.

Effects on the nervous system. Myoclonus has been reported in a patient receiving propafenone.[1] In another patient peripheral neuropathy developed 10 months after starting treatment but symptoms had resolved 6 months after stopping the drug.[2] There have also been reports of ataxia.[3]

1. Chua TP, *et al.* Myoclonus associated with propafenone. *BMJ* 1994; **308:** 113.
2. Galasso PJ, *et al.* Propafenone-induced peripheral neuropathy. *Mayo Clin Proc* 1995; **70:** 469–72.
3. Odeh M, *et al.* Propafenone-induced ataxia: report of three cases. *Am J Med Sci* 2000; **320:** 151–3.

Lupus erythematosus. Symptoms of lupus erythematosus and raised antinuclear antibody titres were associated with propafenone therapy on 2 occasions in a 63-year-old woman.[1]

1. Guindo J, *et al.* Propafenone and a syndrome of the lupus erythematosus type. *Ann Intern Med* 1986; **104:** 589.

Precautions

Propafenone is contra-indicated in patients with uncontrolled heart failure, conduction disturbances including heart block unless controlled by artificial pacing, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, or pronounced hypotension. It may alter the endocardial pacing threshold and adjustment may be necessary in patients with pacemakers.

Propafenone has beta-blocking activity and may exacerbate obstructive airways disease; it should be used with great caution in such disorders and is contra-indicated in severe disease. Propafenone may aggravate myasthenia gravis and should be avoided in patients with this condition. Electrolyte disturbances should be corrected before beginning treatment. Propafenone should be used with caution in patients with hepatic or renal impairment.

Pregnancy and breast feeding. Experience in a patient given propafenone throughout the last trimester of pregnancy indicated that despite transplacental diffusion propafenone could safely be used at this time without harm to the fetus. Propafenone and its metabolite were detected in breast milk at concentrations considered to represent a markedly subtherapeutic dose to an infant.[1]

1. Libardoni M, *et al.* Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol* 1991; **32:** 527–8.

Interactions

Propafenone is extensively metabolised by the cytochrome P450 enzyme system, mainly by the isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Interactions may therefore occur with other drugs that are metabolised by these enzymes. Plasma-propafenone concentrations may be reduced by enzyme inducers such as rifampicin; enzyme inhibitors, such as cimetidine, fluoxetine, quinidine, and HIV-protease inhibitors, may increase plasma-propafenone concentrations. Propafenone itself may alter the plasma concentrations of other drugs, including beta blockers, ciclosporin, desipramine, digoxin, theophylline, venlafaxine, and warfarin. The absorption of propafenone may be reduced by orlistat. There may be an increased risk of arrhythmias if propafenone is given with other antiarrhythmics or arrhythmogenic drugs.

Antiarrhythmics. *Quinidine* inhibits the hepatic metabolism of propafenone and has been reported[1] to increase plasma-propafenone concentrations in extensive metabolisers;[1] the plasma concentration of the active 5-hydroxy metabolite was reduced and that of the *N*-depropyl metabolite increased but there was no change in the clinical response. Another study,[2] however, found that quinidine increased the beta-blocking effect of propafenone in extensive metabolisers, and a study[3] in patients with refractory atrial fibrillation found that addition of quinidine to propafenone was as effective and possibly better tolerated than increasing the propafenone dose.

1. Funck-Brentano C, *et al.* Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 1989; **27:** 435–44.
2. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* 1994; **55:** 28–34.
3. Lau C-P, *et al.* Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 2000; **86:** 1327–32.

Antibacterials. *Rifampicin* has lowered steady-state plasma concentrations of propafenone with the reappearance of arrhythmia.[1]

1. Castel JM, *et al.* Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* 1990; **30:** 155–6.

Histamine H_2-antagonists. *Cimetidine* has been reported[1] to raise plasma-propafenone concentrations. The mean steady-state concentration increased by 22% but the wide interindividual variability meant this change was not significant.

1. Pritchett ELC, *et al.* Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* 1988; **28:** 619–24.

Pharmacokinetics

Propafenone is readily and almost completely absorbed from the gastrointestinal tract. It is metabolised in the liver, largely by the cytochrome P450 isoenzyme CYP2D6, but also to a small extent by CYP1A2 and CYP3A4; the extent of metabolism is genetically determined. In subjects with the extensive metaboliser phenotype there is extensive first-pass metabolism to two active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone, and to other minor inactive metabolites. In the small proportion of subjects with the slow metaboliser phenotype (lacking CYP2D6) little or no 5-hydroxypropafenone is formed. The bioavailability of propafenone is dependent upon metaboliser phenotype but more importantly on dosage as the first-pass metabolism is saturable. In practice doses are high enough to compensate for differences in phenotype. Propafenone and its metabolites also undergo glucuronidation.

Propafenone is more than 95% protein bound.

Propafenone is excreted in the urine and faeces mainly in the form of conjugated metabolites. The elimination half-life is reported to be 2 to 10 hours in extensive metabolisers and 10 to 32 hours in slow metabolisers.

Propafenone crosses the placenta and is distributed into breast milk.

◊ General references.

1. Hii JTY, *et al.* Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; **21:** 1–10.

Uses and Administration

Propafenone is a class Ic antiarrhythmic (p.1153) with some negative inotropic and beta-adrenoceptor blocking activity. It is used in the management of supraventricular and ventricular arrhythmias.

Treatment should be started under close monitoring of the ECG and blood pressure. The usual initial oral dose of propafenone hydrochloride is 150 mg three times daily and this may be increased, if necessary, at intervals of 3 to 4 days up to a maximum of 300 mg three times daily. Reduced doses may be appropriate in patients weighing less than 70 kg and in the elderly; dose reduction may also be necessary in hepatic impairment (see below).

Propafenone hydrochloride is available in some countries as a modified-release preparation. It has also been given by slow intravenous injection or by infusion.

Administration in hepatic impairment. The clearance of propafenone may be reduced in hepatic impairment; careful monitoring is required and lower doses should be considered. US licensed product information states that the dose should be only 20 to 30% of that given in normal hepatic function.

Administration in renal impairment. A study[1] of the disposition of propafenone found that renal function did not affect the pharmacokinetics of propafenone or 5-hydroxypropafenone, and another study[2] suggested that propafenone could be used safely for atrial fibrillation in patients with chronic renal failure. Nevertheless, UK and US licensed product information states that caution is necessary if propafenone is given to patients with renal impairment.

Propafenone does not appear to be removed by haemofiltration.[3]

1. Fromm MF, *et al.* Influence of renal function on the steady-state pharmacokinetics of the antiarrhythmic propafenone and its phase I and phase II metabolites. *Eur J Clin Pharmacol* 1995; **48:** 279–83.
2. Napoli C, *et al.* Propafenone in the conversion of atrial fibrillation in patients suffering from chronic renal failure. *Am J Ther* 1997; **4:** 130–3.
3. Seto W, *et al.* Propafenone disposition during continuous venovenous hemofiltration. *Ann Pharmacother* 1999; **33:** 957–9.

Cardiac arrhythmias. Propafenone is effective in many cardiac arrhythmias.[1,2] It may have a role in the management of supraventricular arrhythmias (see p.1160), including as a single oral loading dose for recent-onset atrial fibrillation.[3,4] It may also be used in ventricular arrhythmias, although in many cases non-pharmacological therapy is preferred. Successful use in children with various arrhythmias has also been reported.[5,6]

1. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias: a risk-benefit appraisal. *Drug Safety* 1995; **12:** 55–72.
2. Reimold SC, *et al.* Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. *Am J Cardiol* 1998; **82:** 66N–71N.
3. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001; **37:** 542–7.
4. Boriani G, *et al.* Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. *Drugs* 2002; **62:** 415–23.
5. Heusch A, *et al.* Clinical experience with propafenone for cardiac arrhythmias in the young. *Eur Heart J* 1994; **15:** 1050–6.
6. Janoušek J, Paul T. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European Retrospective Multicenter Study). *Am J Cardiol* 1998; **81:** 1121–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Normorytmin; ***Austria:*** Asonacor†; Rhythmocor; Rytmonorma; ***Belg.:*** Rytmonorm; ***Braz.:*** Ritmonorm; ***Canad.:*** Rythmol; ***Chile:*** Ritmocor; Rytmonorm†; ***Cz.:*** Prolekofen; Propa-Tabletten†; Propanorm; Rytmonorm; ***Denm.:*** Rytmonorm; ***Fin.:*** Rytmonorm; ***Fr.:*** Rythmol; ***Ger.:*** Cuxafenon; Jutanorm†; Propamerck†; Rytmo-Puren; Rytmogenat†; Rytmonorm; ***Gr.:*** Rythmonorm; ***Hong Kong:*** Rytmonorm; ***Hung.:*** Rytmonorm; ***Indon.:*** Rytmonorm; ***Irl.:*** Arythmol; ***Israel:*** Profex; Rythmex; ***Ital.:*** Cardiofenone; Fenorit; Rytmonorm; ***Malaysia:*** Rytmonorm†; ***Mex.:*** Biopafen; Homopafen†; Nistaken; Norfenon; ***Neth.:*** Rytmonorm; ***NZ:*** Rytmonorm; ***Philipp.:*** Rytmocard; ***Pol.:*** Polfenon; Rytmonorm; ***Port.:*** Arythmol; Rytmonorm; ***Rus.:*** Propanorm (Пропанорм); Rytmonorm (Ритмонорм); ***S.Afr.:*** Rythmol; ***Singapore:*** Rytmonorm; ***Spain:*** Rytmonorm; ***Swed.:*** Rytmonorm; ***Switz.:*** Rytmonorm; ***Thai.:*** Rytmonorm; ***Turk.:*** Rytmonorm; ***UK:*** Arythmol; ***USA:*** Rythmol; ***Venez.:*** Rytmonorm.

Propatylnitrate *(BAN, rINN)*

ETTN; Ettriol Trinitrate; Propatilnitrato; Propatyl Nitrate *(USAN)*; Propatylnitrat; Propatylnitratum; Propatyylinitraatti; Trinettriol; Win-9317. 2-Ethyl-2-hydroxymethylpropane-1,3-diol trinitrate.

Пропатилнитрат

$C_6H_{11}N_3O_9$ = 269.2.
CAS — 2921-92-8.
ATC — C01DA07.
ATC Vet — QC01DA07.

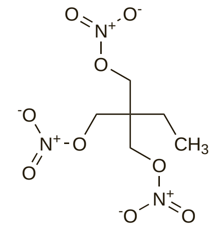

Profile

Propatylnitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) that has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Sustrate.

Propentofylline *(BAN, rINN)*

HWA-285; Propentofilina; Propentofylliini; Propentofyllin; Propentofyllinum. 3-Methyl-1-(5-oxohexyl)-7-propylxanthine.

Пропентофиллин

$C_{15}H_{22}N_4O_3$ = 306.4.
CAS — 55242-55-2.
ATC — N06BC02.
ATC Vet — QC04AD90; QN06BC02; QR03DA90.

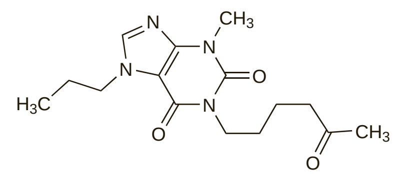

Profile

Propentofylline is a xanthine derivative that has been investigated in cerebrovascular disorders including dementia. It is also used in veterinary medicine.

Propranolol Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-64043; Hidrocloruro de propranolol; ICI-45520; NSC-91523; Propanolol-hidroklorid; Propanololi Hydrochloridum; Propranolol, chlorhydrate de; Propranolol Hidroklorür; Propranolol-hydrochlorid; Propranololhydroklorid; Propranololi hydrochloridum; Propranololihydrokloridi; Propranololio hidrochloridas; Propranololu chlorowodorek. (±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride.

Пропранолола Гидрохлорид

$C_{16}H_{21}NO_2,HCl$ = 295.8.
CAS — 525-66-6 (propranolol); 13013-17-7 (propranolol); 318-98-9 (propranolol hydrochloride); 3506-09-0 (propranolol hydrochloride).
ATC — C07AA05.
ATC Vet — QC07AA05.

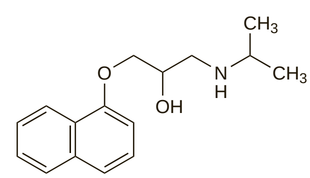

(propranolol)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Propranolol Hydrochloride). A white or almost white powder. Soluble in water and in alcohol.

USP 31 (Propranolol Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. In aqueous solutions propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a reduction in pH and discoloration of the solution. Solutions are most stable at pH 3 and decompose rapidly when alkaline.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Propranolol is distributed into breast milk. A milk/plasma ratio range of 0.33 to 1.65 was reported in a study of 3 women.[1] It was calculated that the maximum dose likely to be ingested by a breast-fed infant would be less than 0.1% of the maternal dose. Other small studies[2,3] have reported similar results. No adverse effects have been seen in breast-fed infants whose mothers were given propranolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Smith MT, *et al.* Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Ther Drug Monit* 1983; **5:** 87–93.
2. Karlberg B, *et al.* Excretion of propranolol in human breast milk. *Acta Pharmacol Toxicol (Copenh)* 1974; **34:** 222–4.
3. Bauer JH, *et al.* Propranolol in human plasma and breast milk. *Am J Cardiol* 1979; **43:** 860–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic-tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma concentrations vary greatly between individuals. Propranolol has high lipid solubility. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins. It is metabolised in the liver and at least one of its metabolites (4-hydroxypropranolol) is considered to be active, but the contribution of metabolites to its overall activity is uncertain. The metabolites and small amounts of unchanged drug are excreted in the urine. The plasma half-life of propranolol is about 3 to 6 hours. Propranolol is reported not to be significantly dialysable.

Pregnancy. A study in 6 pregnant patients (32 to 36 weeks' gestation) showed that the disposition of propranolol 120 mg orally and 10 mg intravenously was not altered in pregnancy compared with the postnatal period.[1] Another study[2] in 13 pregnant patients given propranolol to control hypertension showed that the pharmacokinetics of propranolol and most of its major metabolites were not altered during pregnancy. Samples at term[3] in 10 of the women showed that propranolol and all of its known metabolites were present in maternal plasma, cord plasma, and neonatal plasma. At delivery plasma protein binding of propranolol was reported as 87.5% in maternal plasma and 67.2% in cord plasma. Similar results for maternal and cord plasma protein binding have been reported by others.[4]

1. O'Hare MFO, *et al.* Pharmacokinetics of propranolol during pregnancy. *Eur J Clin Pharmacol* 1984; **27:** 583–7.
2. Smith MT, *et al.* Chronic propranolol administration during pregnancy: maternal pharmacokinetics. *Eur J Clin Pharmacol* 1983; **25:** 481–90.
3. Smith MT, *et al.* Metabolism of propranolol in the human maternal-placental-foetal unit. *Eur J Clin Pharmacol* 1983; **24:** 727–32.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29:** 522–6.

Uses and Administration

Propranolol is a non-cardioselective beta blocker (p.1225). It is reported to have membrane-stabilising properties, but does not possess intrinsic sympathomimetic activity.

Propranolol is used as the hydrochloride in the management of hypertension (p.1171), phaeochromocytoma (p.1179), angina pectoris (p.1157), myocardial infarction (p.1175), and cardiac arrhythmias (p.1160). It is also used in hypertrophic cardiomyopathy (p.1163). It is used to control symptoms of sympathetic overactivity in the management of hyperthyroidism (p.2165), anxiety disorders (p.952), and tremor (p.1231). Other indications include the prophylaxis of migraine (p.616) and of upper gastrointestinal bleeding in patients with portal hypertension (see Variceal Haemorrhage under Monoethanolamine Oleate, p.2346).

Propranolol hydrochloride is usually given orally. In **hypertension** it is given in initial doses of 40 to 80 mg twice daily increased as required to a usual range of 160 to 320 mg daily; some patients may require up to 640 mg daily. Propranolol is *not* suitable for the emergency treatment of hypertension; it should not be given intravenously in hypertension.

In **phaeochromocytoma**, patients treated surgically may be given 60 mg daily on the 3 days before the operation, always with alpha blockade. If the tumour is inoperable prolonged treatment may be given with a daily dose of 30 mg.

In **angina,** initial doses of propranolol hydrochloride 40 mg given 2 or 3 times daily are increased as required to a usual range of 120 to 240 mg daily. Some patients may require up to 320 mg daily.

Propranolol hydrochloride is given within 5 to 21 days of **myocardial infarction** in doses of 40 mg given four times daily for 2 or 3 days followed by 80 mg twice daily. Another regimen is to give 180 to 240 mg daily in divided doses.

Propranolol may be given in doses of 30 to 160 mg daily in divided doses in the long-term management of **cardiac arrhythmias**. For the emergency treatment of cardiac arrhythmias, propranolol hydrochloride may be given by slow intravenous injection over a period of 1 minute, in a dose of 1 mg, repeated if necessary every 2 minutes until a maximum total of 10 mg has been given in conscious patients and 5 mg in patients under anaesthesia. Patients receiving propranolol intravenously should be carefully monitored.

In **hypertrophic cardiomyopathy** the usual dose of propranolol hydrochloride is 10 to 40 mg given three or four times daily.

In **hyperthyroidism** propranolol hydrochloride is given in doses of 10 to 40 mg three or four times daily. If intravenous administration is necessary 1 mg is given over 1 minute, repeated at 2-minute intervals until a response is seen or to a maximum dose of 10 mg in conscious patients or 5 mg in patients under anaesthesia.

The dose for **anxiety** is 40 mg daily; this may be increased to 40 mg two or three times daily.

Essential tremor may be treated with 40 mg given two or three times daily; the dose can be increased at weekly intervals to 160 mg daily although doses up to 320 mg daily may be necessary.

An initial dose of 40 mg two or three times daily is used in **migraine** prophylaxis; the dose can be increased at weekly intervals up to 160 mg daily. Some patients have been given 240 mg daily.

In **portal hypertension,** propranolol hydrochloride should be given in initial doses of 40 mg twice daily; the dose may be increased as required up to 160 mg twice daily.

For the use of propranolol in children, see below.

Administration in children. Propranolol hydrochloride has been used both orally and intravenously in children, although it is not licensed for all indications. Suggested doses are:

for **hypertension**:
- neonates: 250 micrograms/kg orally three times daily, increased as required to a maximum of 2 mg/kg three times daily
- 1 month to 12 years: 0.25 to 1 mg/kg orally three times daily, increased as required to a maximum of 5 mg/kg daily in divided doses
- over 12 years: an adult dose (see above)

for **arrhythmias, phaeochromocytoma, and hyperthyroidism**:
- neonates: 250 to 500 micrograms/kg orally three times daily. *Alternatively* 20 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring
- 1 month to 18 years: 250 to 500 micrograms/kg orally three or four times daily, adjusted according to response, to a maximum of 1 mg/kg four times daily or a total daily dose of 160 mg. *Alternatively* 25 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring

for **prophylaxis of migraine**:
- children up to 12 years: 10 to 20 mg orally two or three times daily
- over 12 years: an adult dose (see above)

for **tetralogy of Fallot**, see below

Administration in hepatic impairment. A study of the disposition of oral propranolol at steady state in 9 normal subjects and 7 with cirrhosis found a mean threefold increase in unbound blood-propranolol concentrations in patients with cirrhosis when compared with the controls. Mean half-lives for the 2 groups were 11.2 and 4 hours respectively.[1] Another study of propranolol given as a single dose of a 20-mg tablet and as a 160-mg modified-release preparation daily for 7 days in 10 patients with cirrhosis and portal hypertension found higher plasma concentrations in patients with severe liver disease compared with those reported in normal controls.[2] Others have reported similar findings.[3]

In patients with severe liver disease, it has been suggested that propranolol therapy be started at a low dose such as 20 mg three times daily,[2] 80 mg of a modified-release preparation given once daily,[2] or 160 mg of a modified-release preparation given every other day.[3] Monitoring of beta blockade is essential; checking the heart rate[2] or exercise testing[3] have been suggested as suitable methods to assess the extent of beta blockade in patients with cirrhosis.

1. Wood AJJ, *et al.* The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin Pharmacokinet* 1978; **3:** 478–87.
2. Arthur MJP, *et al.* Pharmacology of propranolol in patients with cirrhosis and portal hypertension. *Gut* 1985; **26:** 14–19.
3. Calès P, *et al.* Pharmacodynamic and pharmacokinetic study of propranolol in patients with cirrhosis and portal hypertension. *Br J Clin Pharmacol* 1989; **27:** 763–70.

Administration in renal impairment. A study of the pharmacokinetics of propranolol in 11 patients with chronic renal insufficiency showed no impairment in the elimination kinetics of propranolol compared with 8 subjects with normal renal function.[1] Peak concentrations of propranolol reported in patients with chronic renal failure have been 2 to 3 times higher than those in patients receiving dialysis or in normal subjects.[1,2] Additional studies indicate that there is no pharmacokinetic reason to amend the dosage of propranolol in patients with renal impairment.[3]

Findings from a study in 8 patients on haemodialysis include a slight elevation of plasma-propranolol concentrations, no elevation of plasma concentration of 4-hydroxypropranolol, but extremely high plasma concentrations of other propranolol metabolites.[4]

1. Lowenthal DT, *et al.* Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther* 1974; **16:** 761–9.
2. Bianchetti G, *et al.* Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet* 1976; **1:** 373–84.
3. Wood AJJ, *et al.* Propranolol disposition in renal failure. *Br J Clin Pharmacol* 1980; **10:** 561–6.
4. Stone WJ, Walle T. Massive propranolol metabolite retention during maintenance hemodialysis. *Clin Pharmacol Ther* 1980; **28:** 449–55.

Tetralogy of Fallot. Beta blockers, particularly propranolol, have been used for the treatment[1] and prophylaxis[1-3] of cyanotic attacks in infants and children with tetralogy of Fallot and reversible right-ventricular outflow tract obstruction, although caution is required since bradycardia may develop.[4] Esmolol may be preferred during surgery.[5-7]

In the UK, licensed prescribing information allows an oral dose of propranolol hydrochloride of up to 1 mg/kg given 3 or 4 times daily. It may also be given intravenously in a dose of up to 100 micrograms/kg 3 or 4 times daily, injected slowly under ECG control.

The *BNFC* recommends the following doses:
- Neonates: 0.25 to 1 mg/kg orally 2 or 3 times daily, to a maximum of 2 mg/kg 3 times daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 12 hours if necessary
- Children aged 1 month to 12 years: 0.25 to 1 mg/kg orally 3 or 4 times daily, to a maximum of 5 mg/kg daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 6 to 8 hours if necessary.

1. Cumming GR. Propranolol in tetralogy of Fallot. *Circulation* 1970; **41:** 13–15.
2. Eriksson BO, *et al.* Long-term treatment with propranolol in selected cases of Fallot's tetralogy. *Br Heart J* 1969; **31:** 37–44.
3. Ponce FE, *et al.* Propranolol palliation of tetralogy of Fallot: experience with long-term drug treatment in pediatric patients. *Pediatrics* 1973; **52:** 100–108.
4. Clark DJ, *et al.* Propranolol induced bradycardia in tetralogy of Fallot. *Br Heart J* 1989; **61:** 378–9.
5. Nussbaum J, *et al.* Esmolol for the treatment of hypercyanotic spells in infants with tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 200–2.
6. Geary V, *et al.* Esmolol in tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 524–6.
7. Dhir AK, Dhir S. Esmolol in infundibular spasm. *Anaesthesia* 1991; **46:** 998.

Preparations

BP 2008: Prolonged-release Propranolol Capsules; Propranolol Injection; Propranolol Tablets;
USP 31: Propranolol Hydrochloride and Hydrochlorothiazide Extended-

release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Propranolol Hydrochloride Extended-release Capsules; Propranolol Hydrochloride Injection; Propranolol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Inderal; Pirimetan; Propalong†; Propaneitor; Propayerst†; ***Austral.:*** Deralin; Inderal; ***Austria:*** Inderal; Proprahexal; ***Belg.:*** Inderal; ***Braz.:*** Antitensin; Cardiopranol†; Cardix; Hipernolol; Inderal; Neo Propranol†; Polol; Pradinolol; Pranolal; Propacor; Propalol†; Propanox†; Proparil†; Propramed; Propranol†; Propranolil†; Propranolum†; Rebaten; Sanpronol; Uni Propralol; ***Canad.:*** Inderal; Novo-Pranol; ***Chile:*** Coriodal; ***Denm.:*** Inderal†; Propal; ***Fin.:*** Inderal†; Propral; Ranoprin; ***Fr.:*** Adrexan†; Avlocardyl; Hemipralon†; ***Ger.:*** Beta-Tablinen; Dociton; Efektolol†; Elbrol; Obsidan; Propabloc†; Prophylux; propra; Propra-ratiopharm; Propranur; ***Gr.:*** Inderal; ***Hong Kong:*** Becardin†; Hopranolol†; Inderal; Inpanol; Palon†; Prolol†; Propa†; ***Hung.:*** Huma-Pronol; ***India:*** Betabloc; Betaspan; Ciplar; Corbeta; Inderal; Propal; ***Indon.:*** Farmadral; Inderal; ***Irl.:*** Half Inderal; Inderal; Tiperal†; ***Israel:*** Deralin; Inderal; Prolol; Slow Deralin; ***Ital.:*** Inderal; ***Malaysia:*** Inderal; Indon†; Propanol†; ***Mex.:*** Acifol†; Inderalici; Pranoral†; Prochor†; Propalem; Propalgin†; Sintaser; ***Norw.:*** Inderal; Pranolol; ***NZ:*** Angilol; Cardinol; Inderal; ***Philipp.:*** Duranol; Inderal; Phanerol; ***Port.:*** Corpendol†; Inderal; ***Rus.:*** Anaprilin (Анаприлин); Obsidan (Обзидан); ***S.Afr.:*** Cardiblok; Inderal; Prodorol; Pur-Bloka; ***Singapore:*** Inderal; Inpanol; ***Spain:*** Sumial; ***Swed.:*** Inderal; ***Switz.:*** Inderal; ***Thai.:*** Alperol; Atensin†; Betalol; Betapress; Cardenol; Emforal; Inderal; Normpress; Palon; Perlol; Pralol; Prolol; Syntonol; ***Turk.:*** Dideral; ***UAE:*** Cardilol; ***UK:*** Angilol; Bedranol; Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; Slo-Pro; Syprol; ***USA:*** Inderal; InnoPran; ***Venez.:*** Algoren; Docitral; Galenol†; Indal†; Inderal; Parinex†.

Multi-ingredient: ***Arg.:*** Propayerst Plus†; ***Austria:*** Inderetic†; ***Belg.:*** Inderetic†; ***Braz.:*** Polol-H; Tenadren; ***Ger.:*** Beta-Turfa; Diutensat comp†; Docidrazin†; Docitetic; Dociteren; Nitro-Obsidan†; Obsilazin N†; Pertenso N; Propra comp; Triamteren tri-comp; ***India:*** Beptazine; Beptazine-H; Ciplar-H; Corbetazine; Zopax Plus; ***Neth.:*** Inderetic; ***S.Afr.:*** Inderetic†; ***Spain:*** Betadipresan Diu†; Betadipresan†; ***Switz.:*** Inderetic†; ***UK:*** Inderetic†; Inderex†; ***USA:*** Inderide†.

Proroxan *(pINN)*

Proroxano; Proroxanum. 1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-(3-phenyl-1-pyrrolidinyl)-1-propanone.

Пророксан

$C_{21}H_{23}NO_3$ = 337.4.

CAS — 33743-96-3 (proroxan).

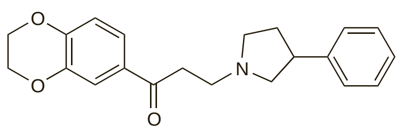

Proroxan Hydrochloride *(USAN, pINNM)*

AY-24269; Hidrocloruro de proroxano; Proroxan, Chlorhydrate de; Proroxani Hydrochloridum.

Пророксана Гидрохлорид

$C_{21}H_{23}NO_3HCl$ = 373.9.

CAS — 33025-33-1.

Profile

Proroxan has been used as an antihypertensive and in the treatment of Ménière's disease, motion sickness, and allergic dermatitis.

Proscillaridin *(BAN, USAN, rINN)*

2936; A-32686; Proscilaridina; Proscillaridiini; Proscillaridin A; Proscillaridine; Proscillaridinum; PSC-801. 14-Hydroxy-3β-(α-L-rhamnopyranosyloxy)-14β-bufa-4,20,22-trienolide.

Просцилларидин

$C_{30}H_{42}O_8$ = 530.6.

CAS — 466-06-8.

ATC — C01AB01.

ATC Vet — QC01AB01.

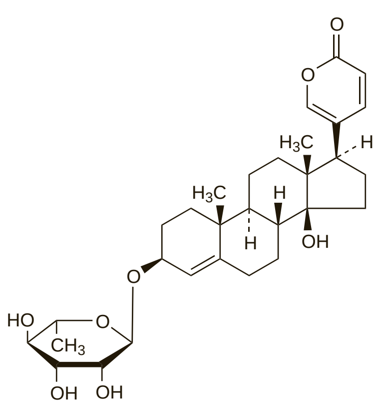

Profile

Proscillaridin is a cardiac glycoside obtained from *Drimia maritima* (Liliaceae). It is a positive inotrope with general properties similar to those of digoxin (p.1259). It is reported to have a rapid onset and a short duration of action.

Proscillaridin is used in the treatment of heart failure (p.1165). It is given orally in usual initial and maintenance doses of 1 to 1.5 mg daily; maintenance doses may range from 0.75 to 2 mg daily as required.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Talusin; ***Pol.:*** Talusin.

Quinapril Hydrochloride

(BANM, USAN, rINNM)

CI-906 (quinapril); Hidrocloruro de quinapril; Kinapril Hidroklorür; Quinapril, chlorhydrate de; Quinaprili hydrochloridum. (3*S*)-2-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid hydrochloride.

Хинаприла Гидрохлорид

$C_{25}H_{30}N_2O_5,HCl$ = 475.0.

CAS — 85441-61-8 (quinapril); 82586-55-8 (quinapril hydrochloride).

ATC — C09AA06.

ATC Vet — QC09AA06.

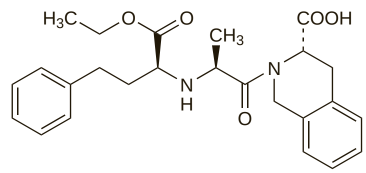

(quinapril)

Pharmacopoeias. In *US.*

USP 31 (Quinapril Hydrochloride). A white to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.

Suspension. Extemporaneous formulations of quinapril 1 mg/mL made by adding crushed Accupril tablets (*Pfizer, US*) to the following vehicles were found to be stable for 6 weeks when stored at 5°:

- *Kphos* 15% (*Beach, US*), *Bicitra* 15% (*Draxis Pharma, US*), *OraSweet* 70% (*Paddock, US*)
- *Kphos* 15%, *Bicitra* 15%, *OraSweet SF* 70%
- *Kphos* 15%, *Bicitra* 15%, simple syrup 70%

The suspension containing *OraSweet SF* was considered to be the formulation of choice.[1]

1. Freed AL, *et al.* The development and stability assessment of extemporaneous pediatric formulations of Accupril. *Int J Pharm* 2005;**304:** 135–44.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Breast feeding. After of a single dose of quinapril 20 mg in 6 women, quinapril was detected in the breast milk in a milk to plasma ratio of 0.12; no quinaprilat was detected.[1] It was estimated that the dose received by the infant would only be about 1.6% of the maternal dose.

1. Begg EJ, *et al.* Quinapril and its metabolite quinaprilat in human milk. *Br J Clin Pharmacol* 2001; **51:** 478–81.

Interactions

As for ACE inhibitors, p.1196.

Antibacterials. Quinapril has been reported to reduce the absorption of *tetracyclines* due to the presence of magnesium carbonate in the tablet formulation.

Pharmacokinetics

Quinapril acts as a prodrug of the diacid quinaprilat, its active metabolite. About 60% of an oral dose of quinapril is absorbed. Quinapril is metabolised mainly in the liver to quinaprilat and inactive metabolites. Peak plasma concentrations of quinaprilat are achieved within 2 hours of an oral dose of quinapril. Quinaprilat is about 97% bound to plasma proteins. After an oral dose, quinapril is excreted in the urine and faeces, as quinaprilat, other metabolites, and unchanged drug, with the urinary route predominating; up to 96% of an intravenous dose of quinaprilat is excreted in the urine. The effective half-life for accumulation of quinaprilat is about 3 hours after multiple doses of quinapril; a long terminal phase half-life of 25 hours may represent strong binding of quinaprilat to angiotensin-converting enzyme.

The pharmacokinetics of both quinapril and quinaprilat are affected by renal and hepatic impairment. Dialysis has little effect on the excretion of quinapril or quinaprilat.

Small amounts of quinapril are distributed into breast milk.

◊ References.

1. Begg EJ, *et al.* The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment. *Br J Clin Pharmacol* 1990; **30:** 213–20.
2. Halstenson CE, *et al.* The pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with various degrees of renal function. *J Clin Pharmacol* 1992; **32:** 344–50.
3. Wolter K, Fritschka E. Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S53–6.
4. Begg EJ, *et al.* The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **37:** 302–4.
5. Squire IB, *et al.* Haemodynamic response and pharmacokinetics after the first dose of quinapril in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **38:** 117–23.
6. Breslin E, *et al.* A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. *J Clin Pharmacol* 1996; **36:** 414–21.

Uses and Administration

Quinapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Quinapril is converted in the body to its active metabolite quinaprilat. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic use. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Quinapril is given orally as the hydrochloride, but doses are expressed in terms of the base. Quinapril hydrochloride 10.8 mg is equivalent to about 10.0 mg of quinapril.

In the treatment of **hypertension** the initial dose is 10 mg of quinapril once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily is recommended in the elderly, in patients with renal impairment, or in those taking a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before quinapril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, as a single dose or divided into 2 doses, although up to 80 mg daily has been given.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Quinapril is given in an initial dose of 2.5 mg daily. Usual maintenance doses range from 10 to 20 mg daily, as a single dose or divided into 2 doses; up to 40 mg daily has been given.

Quinaprilat may be given intravenously in patients unable to take quinapril orally; doses range from 1.25 to 10 mg twice daily.

◊ Reviews.

1. Wadworth AN, Brogden RN. Quinapril: a review of its pharmacological properties, and therapeutic efficacy in cardiovascular disorders. *Drugs* 1991; **41:** 378–99.
2. Plosker GL, Sorkin EM. Quinapril: a reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders. *Drugs* 1994; **48:** 227–52.
3. Culy CR, Jarvis B. Quinapril: a further update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 2002; **62:** 339–85.

Preparations

USP 31: Quinapril Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Accupril; ***Austral.:*** Accupril; Acquin; Asig; Filpril; ***Austria:*** Accupro; ***Belg.:*** Accupril; ***Braz.:*** Accupril; ***Canad.:*** Accupril; ***Chile:*** Accupril; ***Cz.:***

Accupro; **Denm.:** Accupro; **Fin.:** Accupro; **Fr.:** Acuitel; Korec; **Ger.:** Accupro; QuinaLich; **Gr.:** Accupron; **Hong Kong:** Accupril; **Hung.:** Accupro; Acumerck; **Indon.:** Accupril; **Irl.:** Accupro; Quinapro; **Ital.:** Accuprin; Acequin; Quinazil; **Jpn:** Conan; **Malaysia:** Accupril†; **Mex.:** Acupril; **Neth.:** Acupril; **NZ:** Accupril; **Philipp.:** Accupril; **Pol.:** Accupro; Acurenal; AprilGen; **Port.:** Acupril; Vasocor†; **Rus.:** Accupro (Аккупро); **S.Afr.:** Accupril; Quinaspen; **Singapore:** Accupril†; **Spain:** Acuprel; Acuretic; Ectren; Lidaltrin; **Swed.:** Accupro; **Switz.:** Accupro; **Thai.:** Accupril; **Turk.:** Acuitel; **UK:** Accupro; Quinil; **USA:** Accupril; **Venez.:** Accupril; Quinalar; Solpres.

Multi-ingredient: **Arg.:** Accuretic; **Austral.:** Accuretic; **Austria:** Accuzide; **Belg.:** Accuretic; Co-Quinapril; **Canad.:** Accuretic; **Chile:** Accuretic; **Cz.:** Accuzide; Stadapress; **Fin.:** Accupro Comp; **Fr.:** Acuilix; Koretic; **Ger.:** Accuzide; QuinaLich comp; Quinaplus; Quinapril comp; **Gr.:** Accuretic; Quimea; **Hung.:** Accuzide; **Irl.:** Accuretic; **Ital.:** Accuretic; Acequide; Quinazide; **Neth.:** Acuzide; **NZ:** Accuretic; **Philipp.:** Accuzide; **Pol.:** Accuzide; **Port.:** Acuretic; **S.Afr.:** Accuretic; **Spain:** Bicetil; Lidaltrin Diu; **Swed.:** Accupro Comp; **Switz.:** Accuretic; **Turk.:** Accuzide; **UK:** Accuretic; **USA:** Accuretic; Quinaretic; **Venez.:** Accuretic; Quinaretic.

Quinethazone *(BAN, rINN)* ⊗

Chinethazonum; Kinetatsoni; Kinetazon; Quinetazona; Quinéthazone; Quinethazonum. 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxoquinazoline-6-sulphonamide.

Хинетазон

$C_{10}H_{12}ClN_3O_3S$ = 289.7.

CAS — 73-49-4.

ATC — C03BA02.

ATC Vet — QC03BA02.

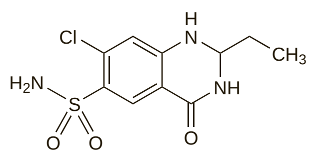

Profile

Quinethazone is a diuretic that is related chemically to metolazone and has properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307). It has been used for oedema, including that associated with heart failure, and for hypertension.

Quinidine *(BAN)*

Chinidinum; Chinidyna; Kinidiini; Kinidin; Kinin; Quinidina. (8*R*,9*S*)-6′-Methoxycinchonan-9-ol; (+)-(α*S*)-α-(6-Methoxy-4-quinolyl)-α-[(2*R*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

Хинидин

$C_{20}H_{24}N_2O_2$ = 324.4.

CAS — 56-54-2 (anhydrous quinidine); 63717-04-4 (quinidine dihydrate); 72402-50-7 (± quinidine).

ATC — C01BA01.

ATC Vet — QC01BA01.

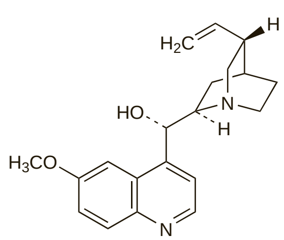

Description. Quinidine is an isomer of quinine, obtained from the bark of species of *Cinchona* and their hybrids; it may also be obtained from *Remijia pedunculata*, or prepared from quinine.

Quinidine Bisulfate

Quinidina, bisulfato de; Quinidine Bisulphate *(BANM)*.

Хинидина Бисульфат

$C_{20}H_{24}N_2O_2,H_2SO_4$ = 422.5.

CAS — 747-45-5 (anhydrous quinidine bisulfate); 6151-39-9 (quinidine bisulfate tetrahydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *Br.*

BP 2008 (Quinidine Bisulphate). Colourless, odourless or almost odourless, crystals. It contains not more than 15% of hydroquinidine bisulfate. Freely soluble in water and in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 2.6 to 3.6. Protect from light.

Quinidine Gluconate *(BANM)*

Quinidina, gluconato de; Quinidinium Gluconate.

Хинидина Глюконат

$C_{20}H_{24}N_2O_2,C_6H_{12}O_7$ = 520.6.

CAS — 7054-25-3.

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *US.*

USP 31 (Quinidine Gluconate). A white, odourless powder. It contains not more than 20% of hydroquinidine gluconate. Freely soluble in water; slightly soluble in alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adsorption. More than 40% of a dose of quinidine gluconate was lost when the drug was given by intravenous infusion using a PVC infusion bag and tubing.[1]

1. Darbar D, *et al.* Loss of quinidine gluconate injection in a polyvinyl chloride infusion system. *Am J Health-Syst Pharm* 1996; **53:** 655–8.

Quinidine Polygalacturonate

Quinidina, poligalacturonato de. Quinidine poly(D-galacturonate) hydrate.

Хинидина Полигалактуронат

$C_{20}H_{24}N_2O_2,(C_6H_{10}O_7)_x,xH_2O$.

CAS — 27555-34-6 (anhydrous quinidine polygalacturonate); 65484-56-2 (quinidine polygalacturonate hydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Quinidine Sulfate

Chinidin sulfát dihydrát; Chinidini sulfas; Chinidino sulfatas; Chinidinsulfate; Chinidinum Sulfuricum; Chinidyny siarczan; Kinidiinisulfaatti; Kinidin Sülfat; Kinidinsulfat; Kinidin-szulfát; Quinidina, sulfato de; Quinidine, sulfate de; Quinidine Sulphate *(BANM)*; Quinidini Sulfas; Quinidini Sulfas Dihydricus.

Хинидина Сульфат

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$ = 782.9.

CAS — 50-54-4 (anhydrous quinidine sulfate); 6591-63-5 (quinidine sulfate dihydrate).

ATC — C01BA01.

ATC Vet — QC01BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Quinidine Sulphate). White or almost white, crystalline powder, or silky, colourless needles. It contains not more than 15% of hydroquinidine sulfate. Slightly soluble in water; soluble in boiling water and in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

USP 31 (Quinidine Sulfate). Fine, needle-like, white crystals, frequently cohering in masses, or a fine, white powder. It is odourless and darkens on exposure to light. It contains not more than 20% of hydroquinidine sulfate. Its solutions are neutral or alkaline to litmus. Soluble 1 in 100 of water, 1 in 10 of alcohol, and 1 in 15 of chloroform; insoluble in ether. Protect from light.

Stability. Quinidine sulfate was reported[1] to be stable for up to 60 days in several extemporaneously prepared oral liquid formulations.

1. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1804–9.

Adverse Effects and Treatment

Quinidine and its salts have both cardiac and non-cardiac adverse effects. Gastrointestinal irritation is common, with nausea, vomiting, and diarrhoea.

Hypersensitivity similar to that occurring with quinine may also occur and a test dose has been recommended (see Uses and Administration, below). Reactions include respiratory difficulties, urticaria, pruritus, skin rashes, purpura, thrombocytopenia and other blood dyscrasias, and, rarely, fever and anaphylaxis. Granulomatous hepatitis and a lupus-like syndrome have been reported.

Quinidine may give rise to cinchonism (see Quinine, p.612) with tinnitus, impaired hearing, visual disturbances, headache, confusion, vertigo, vomiting, and abdominal pain; it is usually associated with large doses, but may occur in idiosyncratic subjects given small doses.

Quinidine may induce hypotension, particularly in overdosage or if intravenous infusions are given too rapidly. It prolongs the QT interval and may precipitate ventricular arrhythmias, including torsade de pointes.

In quinidine overdosage, the cardiac symptoms of intoxication predominate. Quinidine is cumulative in action and inappropriately high plasma concentrations may induce ECG changes, heart block, asystole, ventricular tachycardia, ventricular fibrillation, syncope, seizures, coma, and sometimes death. Treatment of adverse effects and overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

◊ Reviews.

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Effects on the blood. Quinidine-induced thrombocytopenia is not uncommon and it is one of the best documented cases of drug-dependent thrombocytopenia.[1] It appears to be a hypersensitivity reaction, with quinidine inducing the production of autoantibodies that cause platelet destruction. Highly specific quinidine-dependent antibodies have been detected in patients with thrombocytopenia, and may have a role in diagnosis.[2] The exact mechanism of the reaction is unclear but it is generally thought that binding of quinidine to the platelet surface induces antibody production;[1] alternatively, an antibody-quinidine complex may be formed, which is then deposited on the platelets.[1,3] The antigenic constituent of the platelet membrane may be glycoprotein Ib although other surface glycoproteins have also been implicated.[3,4]

1. van den Bemt PMLA, *et al.* Drug-induced immune thrombocytopenia. *Drug Safety* 2004; **27:** 1243–52.
2. Reid DM, Shulman NR. Drug purpura due to surreptitious quinidine intake. *Ann Intern Med* 1988; **108:** 206–8.
3. Stricker RB, Shuman MA. Quinidine purpura: evidence that glycoprotein V is a target platelet antigen. *Blood* 1986; **67:** 1377–81.
4. Visentin GP, *et al.* Characteristics of quinine- and quinidine-induced antibodies specific for platelet glycoproteins IIb and IIIa. *Blood* 1991; **77:** 2668–76.

Effects on the eyes. Corneal deposits resembling those found in keratopathy developed in a patient who had been taking quinidine for 2 years.[1] Symptoms had improved and both corneas had cleared completely within 2 months of stopping the drug.

A small number of patients have also been identified[2] who developed uveitis during quinidine treatment.

1. Zaidman GW. Quinidine keratopathy. *Am J Ophthalmol* 1984; **97:** 247–9.
2. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis: incidence, prevention and treatment. *Drug Safety* 1997; **17:** 197–207.

Effects on the joints. Quinidine has been associated with a number of rheumatic disorders.[1] It is a recognised, though uncommon, cause of drug-induced lupus (see below), but there have also been reports[2-4] of reversible, symmetrical polyarthritis developing in patients with no evidence of antinuclear antibodies. Symptoms were generally milder than in drug-induced lupus, and onset was more rapid; recovery occurred within a week of stopping quinidine and in some patients symptoms recurred on rechallenge. Polymyalgia rheumatica-like symptoms have also been reported.[1]

1. Alloway JA, Salata MP. Quinidine-induced rheumatic syndromes. *Semin Arthritis Rheum* 1995; **24:** 315–22.
2. Kertes P, Hunt D. Polyarthritis complicating quinidine treatment. *BMJ* 1982; **284:** 1373–4.
3. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.
4. Naschitz JE, Yeshurun D. Quinidine and rheumatic syndromes. *Ann Intern Med* 1988; **109:** 248–9.

Effects on the liver. Hypersensitivity reactions involving the liver have been reported in about 2% of patients receiving quinidine.[1,2] The main clinical symptom is fever[1-3] but skin rash,[1-3] purpura,[2] and hepatomegaly[1] may also occur. Liver enzyme values are raised[1-4] and the platelet count may be reduced.[3] The reaction is reversible on withdrawing quinidine with fever resolving in about 48 hours and liver enzymes values returning to normal within about 2 weeks. Liver biopsy often shows granulomatous hepatitis,[1-3] but other inflammatory changes[2] and cholestatic jaundice[4] have been found.

1. Geltner D, *et al.* Quinidine hypersensitivity and liver involvement: a survey of 32 patients. *Gastroenterology* 1976; **70:** 650–2.
2. Knobler H, *et al.* Quinidine-induced hepatitis. *Arch Intern Med* 1986; **146:** 526–8.
3. Bramlet DA, *et al.* Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. *Arch Intern Med* 1980; **140:** 395–7.
4. Hogan DB, *et al.* Unusual hepatotoxic reaction to quinidine. *Can Med Assoc J* 1984; **130:** 973.

Effects on mental state. Gradually progressive cerebral dysfunction characterised by intermittent confusion, agitation, restlessness, personality change, and paranoid features occurred in a 62-year-old man who had taken quinidine for about 15 years.[1] Within 24 hours of stopping quinidine there was a marked improvement and after 5 days he had returned to normal with no cognitive deficits. It was considered that quinidine had precipitated or exacerbated the functional psychosis.

1. Johnson AG, *et al.* A functional psychosis precipitated by quinidine. *Med J Aust* 1990; **153:** 47–9.

Effects on the skin. Skin reactions reported with quinidine include exacerbation of psoriasis,[1] blue-grey pigmentation,[2] photosensitivity,[3] and fatal toxic epidermal necrolysis.[4] Purpuric bruising, attributed to inhalation of quinidine dust in the workplace, has also been reported.[5]

1. Harwell WB. Quinidine-induced psoriasis. *J Am Acad Dermatol* 1983; **9:** 278.
2. Mahler R, *et al.* Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; **122:** 1062–4.
3. Marx JL, *et al.* Quinidine photosensitivity. *Arch Dermatol* 1983; **119:** 39–43.
4. Adornato MC. Toxic epidermal necrolysis associated with quinidine administration. *N Y State Dent J* 2000; **66:** 38–40.
5. Salom IL. Purpura due to inhaled quinidine. *JAMA* 1991; **266:** 1220.

Hypoglycaemia. Mean plasma-insulin concentrations increased and mean plasma-glucose concentrations decreased in 8 healthy subjects and 10 patients with malaria given quinidine intravenously.[1] Profound hypoglycaemia occurred in 1 patient with cerebral malaria and acute renal failure. These effects were considered to be associated with stimulation of β-cell secretion of insulin by quinidine and it was concluded that hypoglycaemia may occur in any severely ill fasting patient given parenteral quinidine.

1. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.

Lupus erythematosus. There are several well-documented reports of quinidine-induced lupus erythematosus.[1-4] The syndrome involves polyarthritis with a positive antinuclear antibody test. Symptoms do not usually occur until several months after starting quinidine and resolve slowly on stopping the drug. A recurrence of lupus-like symptoms has occurred in patients with a previous reaction to procainamide.[2]

1. West SG, *et al.* Quinidine-induced lupus erythematosus. *Ann Intern Med* 1984; **100:** 840–2.
2. Amadio P, *et al.* Procainamide, quinidine, and lupus erythematosus. *Ann Intern Med* 1985; **102:** 419.
3. Lavie CJ, *et al.* Systemic lupus erythematosus (SLE) induced by quinidine. *Arch Intern Med* 1985; **145:** 446–8.
4. Cohen MG, *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108:** 369–71.

Oesophageal stricture. Oral quinidine is a recognised cause of oesophageal injury[1,2] and has been associated with ulceration and stricture formation.

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.
2. Jaspersen D. Drug-induced oesophageal disorders: pathogenesis, incidence, prevention and management. *Drug Safety* 2000; **22:** 237–49.

Precautions

Quinidine is contra-indicated in complete heart block (unless the patient has a pacemaker). It should be used with extreme caution in patients with a prolonged QT interval or a history of torsade de pointes, incomplete heart block, uncompensated heart failure, myocarditis, or severe myocardial damage. Patients should be monitored closely for hypersensitivity reactions after the first dose and quinidine should not be given to those who develop a reaction or those with a history of hypersensitivity to quinidine, including patients who have previously developed thrombocytopenia with quinidine or quinine. Antiarrhythmic therapy with quinidine should be begun with extreme caution, if at all, during acute infections or fever as hypersensitivity reactions may be masked. Care is also required in patients with myasthenia gravis as quinidine can exacerbate the symptoms and may reduce the effectiveness of parasympathomimetic drugs.

When quinidine is used to treat atrial flutter or fibrillation, the reduction in AV block may result in a very rapid ventricular rate. This can be avoided by prior digitalisation or by use of a rate-limiting calcium-channel blocker or beta blocker. However, quinidine should be avoided in digitalis overdosage as markedly increased plasma concentrations of digoxin may occur.

Reduced dosage should be considered for the elderly, for patients with hepatic or renal impairment, and on the occasions when it is used in heart failure.

Breast feeding. A woman[1] receiving 2.1 g quinidine daily throughout pregnancy had milk and serum concentrations 5 days after delivery of 6.4 and 9.0 micrograms/mL respectively, giving a milk to serum ratio of 0.71. It was estimated that the amount of quinidine that would be ingested by an infant would be far below the therapeutic range for its weight. No adverse effects have been reported in infants and the American Academy of Pediatrics considers[2] that quinidine is therefore usually compatible with breast feeding.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. In a report[1] on the use of quinidine sulfate by a woman throughout pregnancy, concentrations in the infant's serum at delivery were similar to the mother's although amniotic fluid concentrations were raised. The infant's weight, ECG, haemoglobin concentration, and platelet count were all found to be within normal limits.

1. Hill LM, Malkasian GD. The use of quinidine sulfate throughout pregnancy. *Obstet Gynecol* 1979; **54:** 366–8.

Interactions

Quinidine has the potential for both pharmacodynamic and pharmacokinetic interactions with many other drugs.

Use of quinidine with drugs that increase the QT interval or have arrhythmogenic effects should generally be avoided, since there is an increased risk of toxicity. Although quinidine is sometimes given with other antiarrhythmics, caution is required since there may be both pharmacodynamic and pharmacokinetic interactions (see below). Interactions may also occur with other drugs because of the antimuscarinic and alpha-adrenoceptor blocking properties of quinidine; potentiation of the effects of neuromuscular blockers has also been reported.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and may interact with inhibitors or inducers of this isoenzyme. Rifampicin, phenobarbital, and phenytoin increase the metabolism of quinidine and increased doses may be required; HIV-protease inhibitors, which inhibit CYP3A4, may produce toxic concentrations of quinidine.

Urinary excretion of quinidine is dependent on urinary pH; drugs that increase urinary pH such as sodium bicarbonate, some antacids, and carbonic anhydrase inhibitors tend to increase the plasma concentration of quinidine since the proportion of nonionised drug in the urine is increased allowing greater renal tubular reabsorption.

Quinidine itself may also have effects on other drugs; it inhibits cytochrome P450 isoenzyme CYP2D6 and may affect drugs metabolised by this route. Examples of further drugs that may be affected by quinidine include oral anticoagulants, beta blockers, and digoxin; more details are given under the monographs for these drugs.

Antiarrhythmics. *Amiodarone* may increase the plasma concentration of quinidine, increasing the risk of toxicity; prolongation of the QT interval with torsade de pointes has been reported.[1] This is probably because amiodarone inhibits hepatic or renal clearance of quinidine or displaces quinidine from binding sites. If the two drugs are used together the dose of quinidine may need to be reduced and the patient should be closely monitored. *Verapamil* given intravenously has been reported[2] to cause severe hypotension in patients also taking quinidine by mouth. Studies *in vitro* suggest this is due to the additive blockade of α-adrenergic receptors by both drugs and the simultaneous blockade of calcium channels by verapamil; verapamil may also increase the plasma concentration of quinidine. Quinidine itself may increase the plasma concentration of some other antiarrhythmics (see Ajmaline, p.1206, Digoxin, p.1261, Disopyramide, p.1270, Flecainide Acetate, p.1289, Procainamide, p.1378, and Propafenone Hydrochloride, p.1380).

1. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Torsade de pointes has been reported[1] in a patient taking *erythromycin* with quinidine. Like quinidine, erythromycin prolongs the QT interval, and the effect may be greater if the drugs are given together;[2] there is also some evidence[3-5] that erythromycin reduces quinidine clearance.

1. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy* 1997; **17:** 626–30.
2. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacodynamics in healthy volunteers. *Pharmacotherapy* 1997; **17:** 1111.
3. Spinler SA, *et al.* Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther* 1995; **57:** 89–94.
4. Stanford RH, *et al.* Effect of oral erythromycin on quinidine pharmacokinetics in healthy volunteers. *Pharmacotherapy* 1998; **18:** 426–7.
5. Damkier P, *et al.* Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999; **48:** 829–38.

Antifungals. *Ketoconazole* temporarily increased the plasma-quinidine concentration in a patient through reduced hepatic elimination.[1] Another antifungal that inhibits hepatic metabolism, *itraconazole*, has also been reported[2] to increase plasma-quinidine concentrations.

1. McNulty RM, *et al.* Transient increase in plasma quinidine concentrations during ketoconazole-quinidine therapy. *Clin Pharm* 1989; **8:** 222–5.
2. Kaukonen K-M, *et al.* Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 1997; **62:** 510–17.

Beta blockers. Quinidine and beta blockers may have additive adverse effects, and pharmacokinetic interactions may also occur. Sinus bradycardia has been reported in a patient prescribed oral quinidine and *timolol* eye drops,[1] and orthostatic hypotension has occurred when quinidine was used with *atenolol*.[2] Use of quinidine or the beta blocker alone was well tolerated in each case with no adverse effects.

1. Dinai Y, *et al.* Bradycardia induced by interaction between quinidine and ophthalmic timolol. *Ann Intern Med* 1985; **103:** 890–1.
2. Manolis AS, Estes NAM. Orthostatic hypotension due to quinidine and atenolol. *Am J Med* 1987; **82:** 1083–4.

Calcium-channel blockers. *Nifedipine* has been reported[1] to reduce plasma-quinidine concentrations and increasing the dose of quinidine to up to 20 mg/kg failed to increase the plasma concentration. Withdrawal of nifedipine resulted in a doubling of the quinidine concentration. A pharmacokinetic and pharmacodynamic study in healthy subjects, however, failed to show that modified-release *felodipine* or nifedipine had any effect on quinidine disposition.[2] Another study in healthy subjects suggested that quinidine may inhibit nifedipine metabolism.[3] *Diltiazem* has also been reported[4] to decrease the clearance and increase the half-life of quinidine in healthy subjects, although it was noted that another study had failed to show any interaction.

For the effects of *verapamil* used with quinidine, see Antiarrhythmics, above.

1. Green JA, *et al.* Nifedipine-quinidine interaction. *Clin Pharm* 1983; **2:** 461–5.
2. Bailey DG, *et al.* Quinidine interaction with nifedipine and felodipine: pharmacokinetic and pharmacodynamic evaluation. *Clin Pharmacol Ther* 1993; **53:** 354–9.
3. Bowles SK, *et al.* Evaluation of the pharmacokinetic and pharmacodynamic interaction between quinidine and nifedipine. *J Clin Pharmacol* 1993; **33:** 727–31.
4. Laganière S, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin Pharmacol Ther* 1996; **60:** 255–64.

Diuretics. *Carbonic anhydrase inhibitors* increase urinary pH and may increase plasma-quinidine concentrations by increasing renal tubular reabsorption. *Thiazides* and *loop diuretics* may increase the risk of arrhythmias by causing hypokalaemia. Arrhythmias occurred in 4 of 10 patients receiving *amiloride* when given quinidine,[1] possibly due to additive sodium-channel blockade.

1. Wang L, *et al.* Amiloride-quinidine interaction: adverse outcomes. *Clin Pharmacol Ther* 1994; **56:** 659–67.

Histamine H_2-antagonists. *Cimetidine* inhibits the hepatic metabolism of quinidine and increases in plasma concentration and half-life with a reduction in clearance have been reported.[1-3]

1. Hardy BG, *et al.* Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. *Am J Cardiol* 1983; **52:** 172–5.
2. Kolb KW, *et al.* Effect of cimetidine on quinidine clearance. *Ther Drug Monit* 1984; **6:** 306–12.
3. MacKichan JJ, *et al.* Effect of cimetidine on quinidine bioavailability. *Biopharm Drug Dispos* 1989; **10:** 121–5.

Pharmacokinetics

Quinidine is rapidly absorbed from the gastrointestinal tract; the time to peak plasma concentration depends on the salt and formulation but is about 2 hours for quinidine sulfate immediate-release tablets. Bioavailability is variable, owing to first-pass metabolism in the liver.

Quinidine is metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to a number of metabolites, at least some of which are pharmacologically active. It is excreted in the urine, mainly in the form of its metabolites. The proportion excreted unchanged is dependent on urinary pH; in acidic urine about 20% is excreted as unchanged quinidine but in alkaline urine this is reduced to about 5% due to increased renal tubular reabsorption.

Quinidine is widely distributed throughout the body and is 80 to 90% bound to plasma proteins including α_1-acid glycoprotein. It has a plasma half-life of about 6 to 8 hours but this may show wide variation. Its therapeutic effect has been correlated with plasma concentrations of about 1 to 6 micrograms/mL, depending on the assay method used; older methods that do not differentiate quinidine from its metabolites may give misleading results.

Quinidine crosses the placenta and is distributed into breast milk. Only small amounts are removed by haemodialysis.

◊ Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has been noted;[1] in one study the half-life ranged from about 1 to 16 hours regardless of whether the drug was given as a tablet, capsule, oral solution, or intramuscular injection. There may also be considerable variations in absorption depending upon the formulation and the salt used.[2,3] The effect of food on absorption is not clear.[4,5] The heart condition being treated or associated with the arrhythmia may alter quinidine's pharmacokinetics[6,7] as may the age of the patient.[8-10] Hepatic impairment may affect protein binding and prolong quinidine's half-life.[11] Protein binding increases in patients with renal impairment, although it returns to normal during dialysis procedures.[12] Accumulation of quinidine metabolites may occur in patients with renal dysfunction.[13-15]

1. Mason WD, *et al*. Comparative plasma concentrations of quinidine following administration of one intramuscular and three oral formulations to 13 human subjects. *J Pharm Sci* 1976; **65:** 1325–9.
2. Frigo GM, *et al*. Comparison of quinidine plasma concentration curves following oral administration of some short- and long-acting formulations. *Br J Clin Pharmacol* 1977; **4:** 449–54.
3. Mahon WA, *et al*. Comparative bioavailability study of three sustained release quinidine formulations. *Clin Pharmacokinet* 1987; **13:** 118–24.
4. Woo E, Greenblatt DJ. Effect of food on enteral absorption of quinidine. *Clin Pharmacol Ther* 1980; **27:** 188–93.
5. Martinez MN, *et al.* Effect of dietary fat content on the bioavailability of a sustained release quinidine gluconate tablet. *Biopharm Drug Dispos* 1990; **11:** 17–29.
6. Ueda CT, Dzindzio BS. Quinidine kinetics in congestive heart failure. *Clin Pharmacol Ther* 1978; **23:** 158–64.
7. Ueda CT, Dzindzio BS. Bioavailability of quinidine in congestive heart failure. *Br J Clin Pharmacol* 1981; **11:** 571–7.
8. Drayer DE, *et al.* Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 1980; **27:** 72–5.
9. Szefler SJ, *et al.* Rapid elimination of quinidine in pediatric patients. *Pediatrics* 1982; **70:** 370–5.
10. Pickoff AS, *et al.* Age-related differences in the protein binding of quinidine. *Dev Pharmacol Ther* 1981; **3:** 108–15.
11. Kessler KM, *et al.* Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. *Am Heart J* 1978; **96:** 627–35.
12. Kessler KM, Perez GO. Decreased quinidine plasma protein binding during haemodialysis. *Clin Pharmacol Ther* 1981; **30:** 121–6.
13. Kessler KM, *et al.* Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 1974; **290:** 706–9.
14. Drayer DE, *et al.* Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin Pharmacol Ther* 1978; **24:** 31–9.
15. Hall K, *et al.* Clearance of quinidine during peritoneal dialysis. *Am Heart J* 1982; **104:** 646–7.

Uses and Administration

Quinidine is a class Ia antiarrhythmic (p.1153). It also has antimuscarinic and alpha-adrenoceptor blocking properties. Quinidine is used in the management of supraventricular and ventricular arrhythmias, including cardioversion and maintenance of sinus rhythm in atrial fibrillation, but other drugs or methods are usually preferred.

Quinidine is an isomer of quinine and may be used as an alternative to quinine in the treatment of malaria when quinine is not immediately available.

Quinidine is usually given orally and various salts have been used, including the bisulfate, the gluconate, the polygalacturonate, and the sulfate. Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine bisulfate (anhydrous) 260 mg, quinidine gluconate (anhydrous) 321 mg, quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).

For the management of **cardiac arrhythmias**, a typical dose of *quinidine sulfate dihydrate* is 200 to 400 mg three or four times daily, adjusted according to response; an initial test dose of 200 mg has been recommended for detecting hypersensitivity. Modified-release preparations may be preferred for maintenance.

Quinidine has also been given parenterally but absorption after intramuscular injection is erratic and incomplete, and intravenous use is associated with a risk of severe hypotension. If parenteral use is necessary for acute conversion of supraventricular or ventricular arrhythmias, *quinidine gluconate* may be given by intravenous infusion at a rate no faster than 250 micrograms/kg per minute; most patients respond to a total dose of less than 5 mg/kg, but up to 10 mg/kg may be given if required. ECG and blood pressure should be monitored throughout the infusion.

For the use of quinidine in the management of **malaria**, see below.

◊ General references.

1. Grace AA, Camm AJ. Quinidine. *N Engl J Med* 1998; **338:** 35–45.

Cardiac arrhythmias. Quinidine is a class Ia antiarrhythmic and has been used in the management of supraventricular and ventricular arrhythmias, but other drugs or non-pharmacological therapies are usually preferred (see Cardiac Arrhythmias, p.1160). Although use of quinidine may have increased after the CAST studies, which found an increased mortality with the use of encainide, flecainide, and moracizine in asymptomatic ventricular arrhythmias, a meta-analysis[1] of studies using quinidine for benign or potentially lethal ventricular arrhythmias found that it was associated with at least as high an incidence of adverse events, including death and early proarrhythmia, as the class Ic drugs flecainide and propafenone. Another meta-analysis[2] found that quinidine was more effective than placebo in maintaining sinus rhythm after cardioversion of atrial fibrillation, but again total mortality was increased.

Quinidine has been used[3] in patients with Brugada syndrome, a congenital channelopathy that predisposes to ventricular arrhythmias, and may have a role as an alternative to an implantable cardioverter defibrillator.

1. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation* 1991; **84:** 1977–83.
2. Coplen SE, *et al.* Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; **82:** 1106–16. Correction. *ibid.* 1991; **83:** 714.
3. Belhassen B, *et al.* Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; **110:** 1731–7.

Congenital myasthenia. Although quinidine may exacerbate the symptoms of myasthenia gravis and should be used with great caution in such patients, beneficial responses have been reported in patients with the slow-channel congenital myasthenic syndrome (see p.630).

Hiccup. Quinidine is one of several drugs that have been tried in intractable hiccups. For details of a protocol for the control of hiccups see Chlorpromazine, p.976.

Malaria. Quinidine may be more potent than quinine as an antimalarial but it is more likely to cause cardiac toxicity and hypersensitivity and WHO[1,2] has recommended that parenteral formulations of quinidine should only be used when parenteral quinine or artemisinin derivatives are not immediately available. In these situations intravenous infusions of quinidine could be used to begin treatment for severe chloroquine-resistant malaria. Patients should be transferred to oral therapy with quinine as soon as possible to complete a 7-day course; alternatively a single oral treatment of pyrimethamine-sulfadoxine may be given.

In the USA, the CDC[3,4] have recommended parenteral quinidine gluconate as the drug of choice for the treatment of complicated falciparum malaria, but only because of the lack of availability of parenteral quinine.

Quinidine is given intravenously as the gluconate and doses have been expressed in terms of the base or salt; it should be given under close control, preferably with continuous ECG monitoring and frequent measurements of blood pressure. Regimens used include one[1,5] where the equivalent of 15 mg of the base per kg is infused over 4 hours as a loading dose followed by the equivalent of 7.5 mg of the base per kg every 8 hours as infusions over 4 hours; the patient should be transferred to an oral form of antimalarial as soon as possible. An alternative regimen[6] consists of a loading dose of 10 mg of quinidine gluconate per kg given by intravenous infusion over a period of 1 to 2 hours followed by a constant intravenous infusion of 20 micrograms/kg per minute for a maximum of 72 hours or until oral therapy with quinine can be instituted to complete a total 3-day course of treatment. It is generally recommended that loading doses should not be used if the patient has received quinine or quinidine within the previous 24 hours or mefloquine within the preceding 7 days.

The overall management of malaria is discussed in the chapter on Antimalarials, p.594.

1. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO, 2000. Available at: http://www.who.int/malaria/docs/hbsm_toc.htm (accessed 16/07/07)
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 10/07/07)
3. CDC. Treatment with quinidine gluconate of persons with severe Plasmodium falciparum infection: discontinuation of parenteral quinine from CDC drug service. *MMWR* 1991; **40** (RR-4): 21–3. Also available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00043932.htm (accessed 10/07/07)
4. CDC. Availability and use of parenteral quinidine gluconate for severe or complicated malaria. *MMWR* 2000; **49:** 1138–40.
5. Phillips RE, *et al.* Intravenous quinidine for the treatment of severe falciparum malaria: clinical pharmacokinetic studies. *N Engl J Med* 1985; **312:** 1273–8.
6. Miller KD, *et al.* Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989; **321:** 65–70.

Neurological disorders. For reference to the use of quinidine with dextromethorphan for the management of amyotrophic lateral sclerosis, see p.1556.

Preparations

BP 2008: Quinidine Sulphate Tablets;
USP 31: Quinidine Gluconate Extended-release Tablets; Quinidine Gluconate Injection; Quinidine Sulfate Capsules; Quinidine Sulfate Extended-release Tablets; Quinidine Sulfate Oral Suspension; Quinidine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Kinidin; ***Belg.:*** Kinidine†; ***Braz.:*** Quinicardine; ***Canad.:*** Biquin; ***Cz.:*** Kinidin†; ***Denm.:*** Kinidin; ***Fin.:*** Kiniduron; ***Gr.:*** Kinidine; Ydroquinidine; ***Hong Kong:*** Kinidin†; ***Irl.:*** Kinidin; ***Israel:*** Quiniduran; ***Ital.:*** Chinteina; Longachin; Naticardina†; Natisedina; Ritmocor; ***Mex.:*** Quini†; ***Neth.:*** Kinidine†; ***Philipp.:*** Kinidin; ***S.Afr.:*** Quinaglute; ***Spain:*** Longacor†; ***Swed.:*** Kinidin; ***Switz.:*** Kinidin; Longacor†; ***Turk.:*** Longacor; Natisedine; Quinicardine; ***UK:*** Kinidin†; ***USA:*** Quinidex†.

Multi-ingredient: ***Fr.:*** Quinimax; ***Ger.:*** Cordichin.

Ramipril *(BAN, USAN, rINN)*

Hoe-498; Ramipriili; Ramiprilis; Ramiprilum. (2*S*,3a*S*,6a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]L-alanyl}perhydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

Рамиприл

$C_{23}H_{32}N_2O_5$ = 416.5.

CAS — 87333-19-5.

ATC — C09AA05.

ATC Vet — QC09AA05.

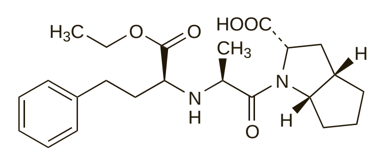

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ramipril). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Protect from light.

USP 31 (Ramipril). A white to almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Ramipril acts as a prodrug of the diacid ramiprilat, its active metabolite. After oral doses at least 50 to 60% is absorbed. Ramipril is metabolised in the liver to ramiprilat; other metabolites are inactive. Peak plasma concentrations of ramiprilat are achieved 2 to 4 hours after an oral dose of ramipril. Ramiprilat is about 56% bound to plasma proteins. After oral doses ramipril is excreted primarily in the urine, as ramiprilat, other metabolites, and some unchanged drug. About 40% of an oral dose appears in the faeces; this may represent both biliary excretion and unabsorbed drug. The effective half-life for accumulation of ramiprilat is 13 to 17 hours after multiple doses of ramipril 5 to 10 mg, but is much longer for doses of 1.25 to 2.5 mg daily; the difference relates to the long terminal half-life associated with saturable binding to the angiotensin-converting enzyme. The clearance of ramiprilat is reduced in renal impairment.

◊ Reviews.

1. Meisel S, *et al.* Clinical pharmacokinetics of ramipril. *Clin Pharmacokinet* 1994; **26:** 7–15.
2. van Griensven JMT, *et al.* Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril. *Eur J Clin Pharmacol* 1995; **47:** 513–8.
3. Fillastre JP, *et al.* Kinetics, safety, and efficacy of ramipril after long-term administration in hemodialyzed patients. *J Cardiovasc Pharmacol* 1996; **27:** 269–74.

Uses and Administration

Ramipril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171), heart failure (p.1165), and after myocardial infarction (p.1175) to improve survival in patients with clinical evidence of heart failure. It is also used to reduce the risk of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p.1164).

Ramipril owes its activity to ramiprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic effect is maintained for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** an initial oral dose of 1.25 mg once daily is given. Since there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Patients taking diuretics should, if possible, have the diuretic stopped 2 to 3 days before starting ramipril, and resumed later if necessary. The usual maintenance dose is 2.5 to 5 mg daily as a single dose, although up to 10 mg daily may be required. In the USA an initial dose of 2.5 mg once daily in hypertensive patients not taking a diuretic and a maintenance dose of 2.5 to 20 mg daily, as a single dose or in two divided doses, have been suggested.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision; high doses of diuretics should be reduced before starting ramipril. Ramipril is given in an initial dose of 1.25 mg once daily. The usual maximum dose is 10 mg daily; doses of 2.5 mg or more daily may be taken in 1 or 2 divided doses.

After **myocardial infarction**, treatment with ramipril may be started in hospital 3 to 10 days after the infarction at a usual initial dose of 2.5 mg twice daily, increased after two days to 5 mg twice daily. The usual maintenance dose is 2.5 to 5 mg twice daily.

For the **prophylaxis of cardiovascular events** in patients considered to be at high risk, ramipril is given in an initial dose of 2.5 mg once daily. The dose should be increased, if tolerated, to 5 mg once daily after 1 week, then to the usual maintenance dose of 10 mg once daily after a further 3 weeks. In patients with hypertension or recent myocardial infarction it may also be given in divided doses.

A reduction in dosage of ramipril may be necessary in patients with impaired hepatic or renal function (see below).

◊ References.

1. Todd PA, Benfield P. Ramipril: a review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. *Drugs* 1990; **39:** 110–35.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342:** 821–8.
3. Frampton JE, Peters DH. Ramipril: an updated review of its therapeutic use in essential hypertension and heart failure. *Drugs* 1995; **49:** 440–66.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.
5. Warner GT, Perry CM. Ramipril: a review of its use in the prevention of cardiovascular outcomes. *Drugs* 2002; **62:** 1381–1405.
6. Vuong AD, Annis LG. Ramipril for the prevention and treatment of cardiovascular disease. *Ann Pharmacother* 2003; **37:** 412–19.
7. Rokoss MJ, Teo KK. Ramipril in the treatment of vascular diseases. *Expert Opin Pharmacother* 2005; **6:** 1911–19.
8. Anderson VR, *et al.* Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. *Am J Cardiovasc Drugs* 2006; **6:** 417–32.
9. Lüders S, *et al.*. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure - a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* 2008; **26:** 1487–1496.

Administration in hepatic or renal impairment. The UK licensed product information states that in patients with hepatic impairment, or renal impairment with a creatinine clearance of less than 30 mL/minute, the initial dose of ramipril should not exceed 1.25 mg daily. In hepatic impairment higher doses should be used with caution. In renal impairment the maintenance dose should not exceed 5 mg daily; for those with a creatinine clearance of less than 10 mL/minute, the maintenance dose should not exceed 2.5 mg daily.

Preparations

BP 2008: Ramipril Capsules; Ramipril Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lostapres; Tritace; ***Austral.:*** Prilace; Ramace; Tritace; ***Austria:*** Hypren; Lannapril; Ramipharm; Tritace; ***Belg.:*** Ramace; Tritace; ***Braz.:*** Atensec; Ecator; Naprix; Triatec; ***Canad.:*** Altace; ***Chile:*** Ramipres; Triatec; ***Cz.:*** Acesial; Amprilan; Hartil; Miril; Piramil; Ramicard; Ramil; Ramistada; Ramitren; Tritace; ***Denm.:*** Ramace; Triatec; ***Fin.:*** Cardace; Ramace†; ***Fr.:*** Triatec; ***Ger.:*** Delix; Ramicard; Ramigamma; RamiLich; Vesdil; ***Gr.:*** Stibenyl; Triatec; ***Hong Kong:*** Tritace; ***Hung.:*** Amprilan; Corpril; Emren; Hartil; Meramyl; Piramil; Ramace; Ramicard; Ramiwin; Tritace; ***India:*** Cardace; Hopecard; Preface; R-Pril; Ramcor; Ramipres; Sclerace; ***Indon.:*** Cardace; Hyperil; Ramixal; Tenapril; Triatec; ***Irl.:*** ByTrite; Ramic; Ramilo; Tritace; ***Israel:*** Ramitens; Tritace; ***Ital.:*** Quark; Triatec; Unipril; ***Malaysia:*** Tritace; ***Mex.:*** Intemipril; Ramace†; Tritace; ***Neth.:*** Remik†; Tritace; ***Norw.:*** Triatec; ***NZ:*** Tritace; ***Philipp.:*** Tritace; ***Pol.:*** Axtil; Mitrip; Piramil; Ramicor; Tritace; Vivace; ***Port.:*** Ramik; Triatec; Verzatec; ***Rus.:*** Hartil (Хартил); ***S.Afr.:*** Ramace; Ramiwin; Rampil; Tritace; ***Singapore:*** Tritace; ***Spain:*** Acovil; Carasel; ***Swed.:*** Pramace; Triatec; ***Switz.:*** Triatec; Vesdil; ***Thai.:*** Corpril; Piramil; Ramiril; Ramtace; Tritace; ***Turk.:*** Delix; ***UK:*** Tritace; ***USA:*** Altace; ***Venez.:*** Altace; Piramil.

Multi-ingredient: ***Arg.:*** Triacor; Tritace-HCT; ***Austral.:*** Triasyn; ***Austria:*** Hypren plus; Lannapril plus; Lasitace; Ramicomp; Ramipharm comb; Trialix; Triapin; Tritazide; Unimax; ***Belg.:*** Tritazide; ***Braz.:*** Ecator H; Naprix A; Naprix D; Triatec D; ***Cz.:*** Amprilan H; Hartil-H; Medoram plus H; Miril plus H; Ramil H; Ramixa Plus H; Triasyn; Tritazide; Unimax†; ***Denm.:*** Triatec Comp; ***Fin.:*** Cardace Comp; Unimax; ***Fr.:*** Cotriatec; ***Ger.:*** Arelix ACE; Aretensin; Delix Plus; Delmuno; Rami-Q comp; Ramicard Plus; Ramigamma HCT; RamiLich comp; Ramiplus; Ramipril comp; Ramipril HCT; Ramipril HCTad; Ramipril Plus; Unimax; Vesdil plus; ***Gr.:*** Stibenyl HCT; Triacor; Triatec Plus; Unitens; ***Hung.:*** Amprilan HD; Amprilan HL; Hartil HCT; Meramyl HCT; Ramace Plusz; Ramiwin HCT; Triasyn; Tritace-HCT; ***India:*** Ramcor H; Ramipres H; ***Irl.:*** Trialix; Triapin; ***Israel:*** Tritace Comp; ***Ital.:*** Idroquark; Prilace; Triatec HCT; Unipridiur; ***Mex.:*** Triacor; Tritazide; ***Neth.:*** Delitab-HCT; Prilitab-HCT; Prilitaril-HCT; Ramitab-HCT; Rataril-HCT; Triapin; Tritazide; Unimax; ***Philipp.:*** Triapin; ***Pol.:*** Ramicor Comb; ***Port.:*** Ramicor D; Triatec Composto; Unimax; ***S.Afr.:*** Tri-Plen; ***Swed.:*** Triatec Comp; ***Switz.:*** Trialix; Triatec Comp; Unimax; ***Turk.:*** Delix Plus; ***UK:*** Triapin; ***Venez.:*** Altace Plus.

Ranolazine *(USAN, rINN)*

CVT-303; Ranolazina; Ranolazinum; RS-43285-003. (±)-*N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide.

Ранолазин

$C_{24}H_{33}N_3O_4$ = 427.5.

CAS — 95635-55-5.

ATC — C01EB18.

ATC Vet — QC01EB18.

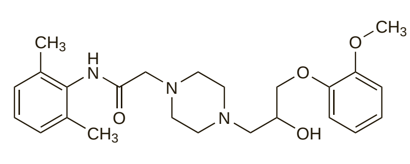

Ranolazine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ranolazina; Ranolazine, Chlorhydrate de; Ranolazini Hydrochloridum; RS-43285.

Ранолазина Гидрохлорид

$C_{24}H_{33}N_3O_4$,2HCl = 500.5.

CAS — 95635-56-6.

ATC — C01EB18.

ATC Vet — QC01EB18.

Adverse Effects and Precautions

Adverse effects most commonly seen with ranolazine are nausea, constipation, dizziness, and headache. Palpitations, tinnitus, vertigo, dry mouth, abdominal pain, vomiting, peripheral oedema, and dyspnoea have also been reported. Rarely reported effects include bradycardia, haematuria, paraesthesia, hypotension, and blurred vision.

Dose-related prolongation of the QT interval may occur; ranolazine is therefore contra-indicated in patients with pre-existing QT prolongation, and in those at increased risk of QT prolongation, including patients with hepatic impairment (Child-Pugh classes A to C) and those taking interacting drugs (see Interactions, below). Blood pressure may be increased in patients with severe renal impairment and should be monitored regularly.

Interactions

Ranolazine is primarily metabolised by the P450 isoenzyme CYP3A and should not be given with other drugs that are potent or moderately potent inhibitors of this enzyme, such as ketoconazole, diltiazem, macrolide antibacterials, HIV protease inhibitors, and grapefruit juice or grapefruit products. Simvastatin is also metabolised by this enzyme and plasma concentrations are reported to be doubled when given with ranolazine. Ranolazine is an inhibitor of CYP2D6 and drugs metabolised by this enzyme, such as tricyclic antidepressants or some antipsychotics, may need dose reductions. Ranolazine is both a substrate for, and inhibitor of, P-glycoprotein, and the dose of other substrates, such as digoxin, may need reducing.

Pharmacokinetics

Absorption of ranolazine is highly variable with peak plasma concentrations occurring about 2 to 5 hours after an oral dose of the modified-release preparation. Ranolazine is extensively metabolised in the gastrointestinal tract and liver. Four main metabolites have been identified. Protein binding of ranolazine is about 62%. About 75% of a dose is excreted in the urine with the remainder in the faeces, with less than 5% as unchanged drug. The apparent terminal half-life for the modified-release preparation of ranolazine is 7 hours, and steady state occurs within 3 days.

◊ Reviews.

1. Jerling M. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet* 2006; **45:** 469–91.

Uses and Administration

Ranolazine is an antianginal drug. Its mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; it also inhibits fatty acid oxidation, but this does not appear to occur at therapeutic plasma concentrations. It is used for the treatment of angina pectoris (p.1157) in patients who have not responded satisfactorily to other antianginals and should be given as an adjunct to standard therapy. It is given in a modified-release form in an initial oral dose of 500 mg twice daily, increasing to a maximum of 1 g twice daily if necessary.

◊ Reviews.

1. Siddiqui MAA, Keam SJ. Ranolazine: a review of its use in chronic stable angina pectoris. *Drugs* 2006; **66:** 693–710.
2. Tafreshi MJ, Fisher E. Ranolazine: a new approach to management of patients with angina. *Ann Pharmacother* 2006; **40:** 689–93.
3. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006; **113:** 2462–72.
4. Zerumsky K, McBride BF. Ranolazine in the management of chronic stable angina. *Am J Health-Syst Pharm* 2006; **63:** 2331–8.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ranexa.

Raubasine

Ajmalicine; Alkaloid F; Raubasiini; Raubasin; Raubasina; Raubasinum; δ-Yohimbine. Methyl 16,17-didehydro-19α-methyl-18-oxayohimban-16-carboxylate.

$C_{21}H_{24}N_2O_3$ = 352.4.

CAS — 483-04-5.

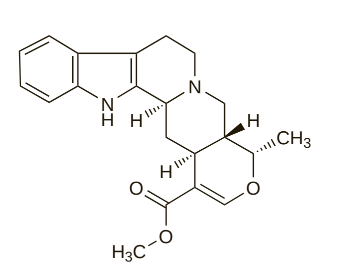

Pharmacopoeias. In *Chin.*

Profile

Raubasine is an alkaloid obtained from *Rauwolfia serpentina* (Apocynaceae). It is a vasodilator related chemically to reserpine (p.1387) and has been given orally and by injection in peripheral and cerebral vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Lamuran.

Multi-ingredient: ***Austria:*** Defluina; ***Fr.:*** Duxil†; Iskedyl; ***Hong Kong:*** Duxaril; ***Philipp.:*** Duxaril; ***Port.:*** Duxil; Transoxyl†; ***Singapore:*** Duxaril; ***Spain:*** Duxor†; ***Thai.:*** Duxaril; Iso-Triraupin†.

Rauwolfia Serpentina

Chotachand; Rauwolfia; Rauwolfia; Rauwolfiae Radix; Rauwolfiawurzel.

CAS — 8063-17-0 (rauwolfia).
ATC — C02AA04.

Pharmacopoeias. In *Ger.* and *US.*

USP 31 (Rauwolfia Serpentina). The dried roots of *Rauwolfia serpentina* (Apocynaceae). It contains not less than 0.15% of reserpine-rescinnamine group alkaloids calculated as reserpine. Store at 15° to 30° in a dry place.

Profile

Rauwolfia serpentina contains numerous alkaloids, the most active as hypotensive agents being the ester alkaloids, reserpine and rescinnamine. Other alkaloids present have structures related to reserpic acid, but are not esterified, and include ajmaline (rauwolfine), ajmalinine, ajmalicine, isoajmaline (isorauwolfine), serpentine, rauwolfinine, and sarpagine. The actions of rauwolfia serpentina are those of its alkaloids and it has been used for the same purposes as reserpine, p.1387. It has been given orally as the powdered whole root.

Rauwolfia vomitoria has also been used.

A crude form of rauwolfia serpentina has been used in India for centuries as preparations such as Sarpagandha, in the treatment of insomnia and certain forms of mental illness.

Preparations

USP 31: Rauwolfia Serpentina Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Hyperforat-forte†; ***Rus.:*** Speman Forte (Спеман Форте); ***Spain:*** Rulun; ***USA:*** Rauzide†.

Regadenoson *(BAN, USAN, rINN)*

CVT-3146; Régadénoson; Regadenosón; Regadenosonum. 1-(6-Amino-9-β-D-ribofuranosyl-9*H*-purin-2-yl)-*N*-methyl-1*H*-pyrazole-4-carboxamide monohydrate.

Регаденозон

$C_{15}H_{18}N_8O_5,H_2O = 408.4.$
CAS — 313348-27-5 (regadenoson); 875148-45-1 (regadenoson monohydrate).

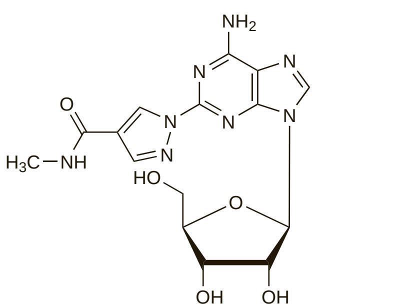

Adverse Effects, Treatment, and Precautions

As for Adenosine, p.1202. Regadenoson may be used with caution in patients with asthma or chronic obstructive pulmonary disease.

Interactions

As for Adenosine, p.1202.

Pharmacokinetics

After intravenous injection of regadenoson, peak plasma concentrations are reached within 1 to 4 minutes and decline in a multi-exponential fashion. The initial half-life is about 2 to 4 minutes, followed by an intermediate stage with a half-life of about 30 minutes, during which the pharmacodynamic effect is lost; the half-life during the terminal phase is about 2 hours. Regadenoson does not appear to be metabolised; about 57% of a dose is excreted unchanged in the urine.

◊ References.

1. Gordi T, *et al.* A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A -receptor agonist, in healthy male volunteers. *Clin Pharmacokinet* 2006; **45:** 1201–12.
2. Gordi T, *et al.* Regadenoson pharmacokinetics and tolerability in subjects with impaired renal function. *J Clin Pharmacol* 2007; **47:** 825–33.

Uses and Administration

Regadenoson has similar properties to adenosine (p.1202) but has a greater selectivity for the adenosine A_{2A}-receptor. It is a coronary vasodilator and increases coronary blood flow and is used to provide a pharmacological stress as an adjunct to radionuclide myocardial perfusion imaging. It is given intravenously in a single dose of 400 micrograms by rapid injection over about 10 seconds, followed by 5 mL of sodium chloride 0.9%; the radionuclide should be given 10 to 20 seconds after the sodium chloride.

◊ References.

1. Hendel RC, *et al.* Initial clinical experience with regadenoson, a novel selective A agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 2005; **46:** 2069–75.
2. Iskandrian AE, *et al.* Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007; **14:** 645–58.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Lexiscan.

Remikiren *(rINN)*

Rémikirène; Remikireno; Remikirenum; Ro-42-5892. (α*S*)-α-[(α*S*)-α-[(*tert*-Butylsulfonyl)methyl]hydrocinnamamido]-*N*-[(1*S*,2*R*,3*S*)-1-(cyclohexylmethyl)-3-cyclopropyl-2,3-dihydroxypropyl]imidazole-4-propionamide.

Ремикирен

$C_{33}H_{50}N_4O_6S = 630.8.$
CAS — 126222-34-2.
ATC — C09XA01.
ATC Vet — QC09XA01.

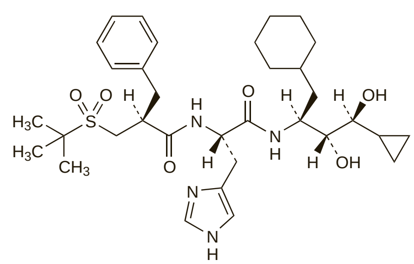

Profile

Remikiren inhibits the actions of renin and thus prevents the conversion of angiotensinogen into angiotensin I. It is orally active and has been investigated in the management of hypertension and heart failure.

◊ A number of renin antagonists have been investigated as specific inhibitors of the renin-angiotensin system.[1,2] Remikiren is a nonpeptide that is active intravenously and orally, but it is reported to have a very low oral bioavailability.

1. Frishman WH, *et al.* Renin inhibition: a new approach to cardiovascular therapy. *J Clin Pharmacol* 1994; **34:** 873–80.
2. Rongen GA, *et al.* Clinical pharmacokinetics and efficacy of renin inhibitors. *Clin Pharmacokinet* 1995; **29:** 6–14.

Rescinnamine *(BAN, rINN)*

Rescinamina; Rescinnamin; Rescinnaminum; Resinnamiini. Methyl-*O*-(3,4,5-trimethoxycinnamoyl)reserpate.

Ресциннамин

$C_{35}H_{42}N_2O_9 = 634.7.$
CAS — 24815-24-5.
ATC — C02AA01.
ATC Vet — QC02AA01.

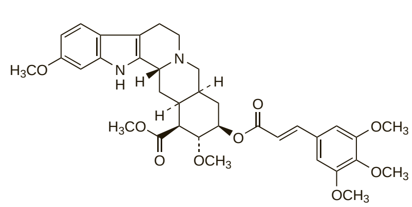

Profile

Rescinnamine is an ester alkaloid isolated from the root of *Rauwolfia serpentina* or *R. vomitoria*. It has properties similar to those described under reserpine (below) and has been used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Thai.:*** Iso-Triraupin†.

Reserpine *(BAN, rINN)*

Reserpiini; Reserpin; Reserpina; Réserpine; Reserpinum; Reszerpin; Rezerpin; Rezerpina; Rezerpinas. Methyl 11,17α-dimethoxy-18β-(3,4,5-trimethoxybenzoyloxy)-3β,20α-yohimbane-16β-carboxylate; Methyl *O*-(3,4,5-trimethoxybenzoyl)reserpate.

Резерпин

$C_{33}H_{40}N_2O_9 = 608.7.$
CAS — 50-55-5.
ATC — C02AA02.
ATC Vet — QC02AA02.

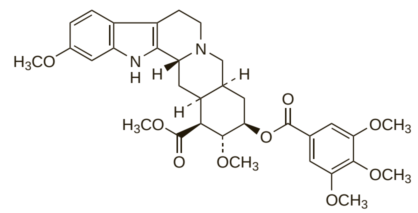

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Reserpine). It occurs as small, white to slightly yellow crystals or a crystalline powder. It darkens slowly on exposure to light. Practically insoluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Reserpine). A white or pale buff to slightly yellowish, odourless, crystalline powder. It darkens slowly on exposure to light, but more rapidly when in solution. Insoluble in water; soluble 1 in 1800 of alcohol and 1 in 6 of chloroform; freely soluble in acetic acid; very slightly soluble in ether; slightly soluble in benzene. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. Reserpine is unstable in the presence of alkalis, particularly when the drug is in solution.

Adverse Effects

Adverse effects commonly include nasal congestion, headache and CNS symptoms including depression, drowsiness, dizziness, lethargy, nightmares, and symptoms of increased gastrointestinal tract motility including diarrhoea, abdominal cramps, and, at higher doses, increased gastric acid secretion. Respiratory distress, cyanosis, anorexia, and lethargy may occur in infants whose mothers have taken reserpine before delivery.

Higher doses may cause flushing, bradycardia, severe depression which may lead to suicide, and extrapyramidal effects. Hypotension, coma, convulsions, respiratory depression, and hypothermia also occur in overdosage. Hypotension is also more common in patients after a cerebrovascular accident.

Breast engorgement and galactorrhoea, gynaecomastia, increased prolactin concentrations, decreased libido, impotence, sodium retention, oedema, decreased or increased appetite, weight gain, miosis, dry mouth, sialorrhoea, dysuria, rashes, pruritus, and thrombocytopenic purpura have also been reported.

Large doses of reserpine have been shown to be tumorigenic in *rodents*. Several reports have suggested an association between reserpine and the development of neoplasms of the breast (see below) but other surveys have failed to confirm this.

Neoplasms of the breast. Although early studies suggested that the incidence of breast cancer was up to 3 to 4 times greater in hypertensive women treated with rauwolfia preparations than in control groups, analysis[1] of both prospective trials and case-control studies found only a low-grade association between use of rauwolfia preparations and risk of malignancy.

1. Grossman E, *et al.* Antihypertensive therapy and the risk of malignancies. *Eur Heart J* 2001; **22:** 1343–52.

Treatment of Adverse Effects

Withdrawal of reserpine or reduction of the dosage causes the reversal of many adverse effects although mental disorders may persist for months and hypotensive effects may persist for weeks after the cessation of treatment. If overdosage occurs activated charcoal may be considered within 1 hour of ingestion. Treatment is generally supportive and symptomatic. Severe hypotension may respond to placing the patient in the supine position with the feet raised. Direct-acting sympathomimetics may be effective for treatment of severe hypotension, but should be given with caution. The patient must be observed for at least 72 hours.

Precautions

Reserpine should not be used in patients with depression or a history of depression, with active peptic ulcer disease or ulcerative colitis, or in patients with Parkinson's disease. It should also be avoided in phaeochromocytoma.

It should be used with caution in debilitated or elderly patients, and in the presence of cardiac arrhythmias, myocardial infarction, renal insufficiency, gallstones, epilepsy, or allergic conditions such as bronchial asthma.

Reserpine is contra-indicated in patients having ECT and an interval of at least 7 to 14 days should be allowed between the last dose of reserpine and the start of any ECT.

It is probably not necessary to stop reserpine during anaesthesia, although the effects of CNS depressants may be enhanced by reserpine.

Interactions

Patients taking reserpine may be hypersensitive to adrenaline and other direct-acting sympathomimetics, which should not be given except to antagonise reserpine. The effects of indirect-acting sympathomimetics such as ephedrine may be decreased by reserpine. The hypotensive effects of reserpine are enhanced by thiazide diuretics and other antihypertensives. Reserpine may cause excitation and hypertension in patients receiving MAOIs. Use of digitalis or quinidine with reserpine may cause cardiac arrhythmias. Reserpine may enhance the effects of CNS depressants.

Antiparkinsonian drugs. For the inhibitory effect of reserpine on the antiparkinsonian actions of *levodopa,* see Antihypertensives, p.807.

Pharmacokinetics

Reserpine is absorbed from the gastrointestinal tract with a bioavailability of 50%. It is extensively metabolised and is excreted slowly in the urine and faeces. In the first 4 days, about 8% is excreted in the urine, mainly as metabolites, and about 60% in the faeces, mainly unchanged. Reserpine crosses the placenta and the blood-brain barrier and also appears in breast milk.

Uses and Administration

Reserpine is an alkaloid obtained from the roots of certain species of *Rauwolfia* (Apocynaceae), mainly *Rauwolfia serpentina* and *R. vomitoria,* or by synthesis. The material obtained from natural sources may contain closely related alkaloids.

Reserpine is an antihypertensive drug that causes depletion of noradrenaline stores in peripheral sympathetic nerve terminals and depletion of catecholamine and serotonin stores in the brain, heart, and many other organs resulting in a reduction in blood pressure, bradycardia, and CNS depression. The hypotensive effect is mainly due to a reduction in cardiac output and a reduction in peripheral resistance. Cardiovascular reflexes are partially inhibited, but orthostatic hypotension is rarely a problem at the doses used in hypertension. When given orally the full effect is only reached after several weeks of treatment and persists for up to 6 weeks after treatment is stopped.

Reserpine has been used in the management of hypertension (p.1171) and in chronic psychoses (p.954) such as schizophrenia. It has also been used in the treatment of Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188).

In **hypertension**, reserpine may be given orally in an initial dose of up to 500 micrograms daily for about 2 weeks, subsequently reduced to the lowest dose necessary to maintain the response; some sources recommend an initial dose of 50 to 100 micrograms. A maintenance dose of about 100 to 250 micrograms daily may be adequate and 500 micrograms should not normally be exceeded. To reduce adverse effects and tolerance smaller doses of reserpine may be used with a thiazide diuretic.

Reserpine has been used in chronic **psychoses** in daily doses of up to 1 mg.

Preparations

USP 31: Reserpine and Chlorothiazide Tablets; Reserpine and Hydrochlorothiazide Tablets; Reserpine Elixir; Reserpine Injection; Reserpine Tablets; Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)

Braz.: Ortoserpina†; ***Indon.:*** Resapin; Serpasil; ***Port.:*** Serfinato†.

Multi-ingredient: ***Arg.:*** Hygroton-Reserpina†; Normatensil†; ***Austria:*** Brinerdin; Darebon; ***Braz.:*** Adelfan-Esidrex†; Higroton Reserpina; Id Sedin†; Vagoplex†; ***Cz.:*** Crystepin; Neocrystepin; ***Fr.:*** Tensionorme; ***Ger.:*** Adelphan-Esidrix†; Barotonal†; Bendigon N†; Briserin N; Darebon†; Disalpin†; Durotan†; Modenol†; Tri-Thiazid Reserpin†; Triniton; ***Gr.:*** Hygroton-Reserpine; Neourizine; ***Hong Kong:*** Adelphane-Esidrex; ***India:*** Adelphane; Adelphane-Esidrex; ***Indon.:*** Dellasidrex; Ser-Ap-Es; ***Ital.:*** Brinerdina; Igroton-Reserpina; ***Mex.:*** Higroton-Res; ***Pol.:*** Normatens; ***Port.:*** Brinerdine†; ***Rus.:*** Adelphane-Esidrex (Адельфан-эзидрекс); Crystepin (Кристепин); Triresid K (Трирезид К); ***S.Afr.:*** Brinerdin; Hygroton-Reserpine†; Protensin-M; ***Spain:*** Adelfan-Esidrex†; Brinerdina†; Higrotona Reserpina†; Tensiocomplet; ***Switz.:*** Adelphan-Esidrex; Brinerdine; Hygroton-Reserpine; ***Thai.:*** Bedin; Brinerdin; Hydrares; Hyperdine†; Hypery†; Iso-Triraupin†; Mano-Ap-Es; Medeserpine Co†; Reser; Ser-Ap-Es; ***Turk.:*** Adelphan; Adelphan-Esidrex; Regroton; ***USA:*** Demi-Regroton; Diupres; Diutensen-R†; Hydrap-ES†; Hydro-Serp†; Hydropres; Hydroserpine†; Marpres; Metatensin†; Regroton; Renese R†; Salutensin†; Ser-Ap-Es†; Tri-Hydroserpine†.

Reteplase *(BAN, USAN, rINN)*

BM-06.022; Reteplaasi; Reteplas; Reteplasa; Rétéplase; Reteplasum; rPA. 173-L-Serine-174-L-tyrosine-175-L-glutamine-173–527-plasminogen activator (human tissue-type).

Ретеплаза

$C_{1736}H_{2653}N_{499}O_{522}S_{22}$ = 39571.1.

CAS — 133652-38-7.

ATC — B01AD07.

ATC Vet — QB01AD07.

Description. Reteplase is a nonglycosylated protein produced by recombinant DNA technology. It consists of selected domains of human tissue plasminogen activator.

Incompatibility. Reteplase may precipitate out of solution if it is given with heparin in the same intravenous line.[1] Reteplase and heparin must therefore be given separately; if a single intravenous line is used it must be flushed thoroughly with sodium chloride 0.9% or with glucose 5% before, and after, reteplase injection.

1. Committee on Safety of Medicines/Medicines Control Agency. Reteplase (Rapilysin): incompatibility with heparin. *Current Problems* 2000; **26:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Allergic reactions may be less likely to occur with reteplase than with streptokinase.

Interactions

As for Streptokinase, p.1404.

Pharmacokinetics

Based on fibrinolytic activity, reteplase is reported to have an initial half-life of about 14 minutes and a terminal half-life of 1.6 hours in patients with myocardial infarction.

Uses and Administration

Reteplase is a thrombolytic drug. It converts plasminogen to plasmin, a proteolytic enzyme which has fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Reteplase has some fibrin specificity (see Thrombolytics, p.1156).

Reteplase is used similarly to streptokinase (p.1404) in acute myocardial infarction (p.1175). It is given intravenously as soon as possible after the onset of symptoms. The dose is 10 units given by slow intravenous injection (but over not more than 2 minutes), and this dose of 10 units is repeated once, 30 minutes after the start of the first injection.

◊ General references.

1. Noble S, McTavish D. Reteplase: a review of its pharmacological properties and clinical efficacy in the management of acute myocardial infarction. *Drugs* 1996; **52:** 589–605.
2. Wooster MB, Luzier AB. Reteplase: a new thrombolytic for the treatment of acute myocardial infarction. *Ann Pharmacother* 1999; **33:** 318–24.
3. Llevadot J, *et al.* Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; **286:** 442–9.
4. Simpson D, *et al.* Reteplase: a review of its use in the management of thrombotic occlusive disorders. *Am J Cardiovasc Drugs* 2006; **6:** 265–85.

Catheters and cannulas. Reteplase has been used[1] successfully to clear thrombi in central venous catheters. A single dose of 0.4 units of reteplase was given as a 1 unit/mL solution, further diluted to the volume required to fill the catheter. The minimum dwell time was 30 minutes and the solution was aspirated after treatment. A second dose of 0.4 units was given if necessary.

1. Owens L. Reteplase for clearance of occluded venous catheters. *Am J Health-Syst Pharm* 2002; **59:** 1638–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Rapilysin; ***Austria:*** Rapilysin; ***Belg.:*** Rapilysin; ***Canad.:*** Retavase; ***Cz.:*** Rapilysin; ***Denm.:*** Rapilysin; ***Fin.:*** Rapilysin; ***Fr.:*** Rapilysin; ***Ger.:*** Rapilysin; ***Gr.:*** Rapilysin; Repilysin†; ***Irl.:*** Rapilysin; ***Ital.:*** Rapilysin; ***Neth.:*** Rapilysin; ***Norw.:*** Rapilysin; ***NZ:*** Rapilysin; ***Port.:*** Rapilysin; ***Spain:*** Rapilysin; ***Swed.:*** Rapilysin; ***Switz.:*** Rapilysin; ***UK:*** Rapilysin; ***USA:*** Retavase.

Reviparin Sodium *(BAN, rINN)*

Repariininatrium; Reviparina sódica; Réviparine Sodique; Reviparinnatrium; Reviparinum Natricum.

Ревипарин Натрий

CAS — 9041-08-1.

ATC — B01AB08.

ATC Vet — QB01AB08.

Description. Reviparin sodium is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3150 and 5150 with a characteristic value of about 4150. The degree of sulfation is about 2.1 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with reviparin sodium may be reduced by the slow intravenous injection of protamine sulfate; about 1.2 mg of protamine sulfate is stated to inhibit the effect of 100 units of reviparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Reviparin sodium is absorbed after subcutaneous administration with a bioavailability of about 95%. Peak plasma concentrations are reached after about 3 hours. Reviparin sodium is excreted mainly in the urine; the elimination half-life is about 3 hours.

Uses and Administration

Reviparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity. It is used in the prevention and treatment of venous thromboembolism (p.1189) and has been used to prevent coagulation during haemodialysis.

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used.

In the prophylaxis of venous thromboembolism during surgery, reviparin sodium is given subcutaneously in a dose of 1432 units once daily, with the first dose given 2 hours before surgery.

◊ References.

1. Wellington K, *et al.* Reviparin: a review of its efficacy in the prevention and treatment of venous thromboembolism. *Drugs* 2001; **61:** 1185–209.
2. Yusuf S, *et al.* CREATE Trial Group Investigators. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA* 2005; **293:** 427–35.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Clivarin; ***Cz.:*** Clivarin; ***Denm.:*** Clivarin†; ***Fr.:*** Clivarine†; ***Ger.:*** Clivarin; ***Gr.:*** Clivarin; ***Hong Kong:*** Clivarine; ***Hung.:*** Clivarin; ***India:*** Clivarine; ***Ital.:*** Clivarina; ***Pol.:*** Clivarin; ***Port.:*** Clivarin; ***UK:*** Clivarine†.

Rilmenidine Phosphate *(rINNM)*

Fosfato de rilmenidina; Oxaminozoline Phosphate; Rilmenidiinidivetyfosfaatti; Rilmenidin Dihdrojen Fosfat; Rilmenidin fosfát; Rilmenidin-dihidrogén-foszfát; Rilmenidindivätefosfat; Rilmenidine Acid Phosphate; Rilmenidine Dihydrogen Phosphate; Rilménidine, dihydrogénophosphate de; Rilmenidine Hydrogen Phosphate; Rilménidine, Phosphate de; Rilmenidini dihydrogenophosphas; Rilmenidini Phosphas; Rilmenidino divandenilio fosfatas; S-3341-3. 2-[(Dicyclopropylmethyl)amino]-2-oxazoline phosphate.

Рильменидина Фосфат

$C_{10}H_{16}N_2O,H_3PO_4$ = 278.2.

CAS — 54187-04-1 (rilmenidine); 85409-38-7 (rilmenidine phosphate).

ATC — C02AC06.

ATC Vet — QC02AC06.

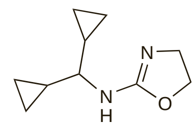

(rilmenidine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Rilmenidine Dihydrogen Phosphate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

Profile

Rilmenidine is a centrally acting antihypertensive that appears to act through stimulation of central imidazoline receptors and also has alpha$_2$-adrenoceptor agonist activity. It has general properties similar to those of clonidine (p.1247), but is reported to cause less sedation and central adverse effects. In the management of hypertension (p.1171) it has been given as the phosphate, but doses are expressed in terms of the base. Rilmenidine phosphate 1.5 mg is equivalent to about 1 mg of rilmenidine. The dose is 1 mg daily, as a single oral dose; this may be increased if necessary, after 1 month, to 2 mg daily in divided doses.

◊ References.

1. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; **58:** 799–812.

2. Reid JL. Rilmenidine: a clinical overview. *Am J Hypertens* 2000; **13:** 106S–111S.
3. Reid JL. Update on rilmenidine: clinical benefits. *Am J Hypertens* 2001; **14:** 322S–324S.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Hyperium; ***Austria:*** Iterium; ***Braz.:*** Hyperium; ***Cz.:*** Albarel; Tenaxum; ***Fr.:*** Hyperium; ***Hong Kong:*** Iperdix; ***Hung.:*** Hyperlex; Tenaxum; ***Philipp.:*** Hyperdix; ***Pol.:*** Tenaxum; ***Port.:*** Hyperium; ***Rus.:*** Albarel (Альбарел); ***Thai.:*** Hyperdix; ***Turk.:*** Hyperium; ***Venez.:*** Hyperium.

Rivaroxaban *(USAN, rINN)*

Bay-59-7939; Rivaroxabán; Rivaroxabanum. 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide.

Ривароксабан

$C_{19}H_{18}ClN_3O_5S = 435.9.$

CAS — 366789-02-8.

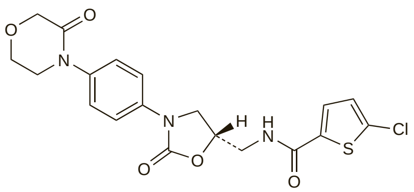

Profile

Rivaroxaban is an oral direct inhibitor of activated factor X that is under investigation in thromboembolic disorders.

◊ References.

1. Fisher WD, *et al.* Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. *Thromb Haemost* 2007; **97:** 931–7.
2. Agnelli G, *et al.* Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007; **116:** 180–7.
3. Eriksson BI, *et al.* RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358:** 2765–75.
4. Lassen MR, *et al.* RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358:** 2776–86.
5. Kakkar AK, *et al.* RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; **372:** 31–9.
6. Piccini JP, *et al.* Rivaroxaban, an oral direct factor Xa inhibitor. *Expert Opin Invest Drugs* 2008; **17:** 925–37.

Rosuvastatin Calcium *(BANM, USAN, rINNM)*

Calcii Rosuvastatinum; Rosuvastatina calcica; Rosuvastatine Calcique; S-4522; ZD-4522 (rosuvastatin). (*E*)-(3*R*,5*S*)-7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium (2:1).

Кальций Розувастатин

$(C_{22}H_{27}FN_3O_6S)_2Ca = 1001.1.$

CAS — 287714-41-4 (rosuvastatin); 147098-20-2 (rosuvastatin calcium).

ATC — C10AA07.

ATC Vet — QC10AA07.

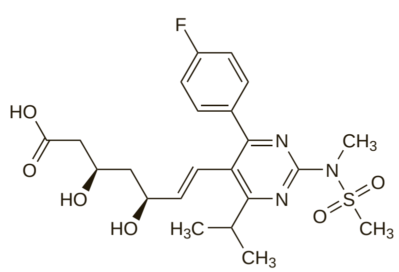

(rosuvastatin)

Adverse Effects and Precautions

As for Simvastatin, p.1390. Systemic exposure to rosuvastatin may be higher in Asian patients (see Ethnicity under Pharmacokinetics, below) and lower doses are advised in Asians and in other patients at high risk of myopathy (see Uses and Administration, below).

Incidence of adverse effects. An analysis[1] of adverse effects reported to the FDA in the first year of marketing found that rosuvastatin was significantly more likely to be associated with severe adverse effects than some other statins. However, further analyses of data from clinical studies[2] and post-marketing studies[3,4] suggest that the risk of adverse effects is similar for all the statins. Another observational study[5] with a median treatment period of 9.8 months found that rosuvastatin was generally well tolerated, although 17.5% of patients stopped taking the drug, with myalgia being the most common reason. Abnormal liver function tests were more common in patients taking higher doses.

1. Alsheikh-Ali AA, *et al.* The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005; **111:** 3051–7.
2. Shepherd J, *et al.* Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; **107:** 433–43.
3. Goettsch WG, *et al.* Results from a rosuvastatin historical cohort study in more than 45 000 Dutch statin users, a PHARMO study. *Pharmacoepidemiol Drug Saf* 2006; **15:** 435–43.
4. McAfee AT, *et al.* The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48 000 initiators of statin therapy. *Pharmacoepidemiol Drug Saf* 2006; **15:** 444–53.
5. Kasliwal R, *et al.* Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11 680 patients. *Drug Safety* 2007; **30:** 157–70.

Interactions

The interactions of statins with other drugs are described under simvastatin, p.1392. Rosuvastatin undergoes limited metabolism, principally by the cytochrome P450 isoenzyme CYP2C9, and may not have the same interactions with enzyme inhibitors as simvastatin. However, increased plasma-rosuvastatin concentrations have been reported with ciclosporin, HIV-protease inhibitors, and, to a lesser extent, with gemfibrozil, and such combinations should be avoided. If they must be given together, lower doses of rosuvastatin should be used (see Uses and Administration, below); in UK licensed product information, rosuvastatin is contra-indicated with ciclosporin.

Pharmacokinetics

Rosuvastatin is incompletely absorbed from the gastrointestinal tract, with an absolute bioavailability of about 20%. Peak plasma concentrations are achieved about 5 hours after an oral dose. It is taken up extensively by the liver, its primary site of action, and undergoes limited metabolism, mainly by the cytochrome P450 isoenzyme CYP2C9. It is about 90% bound to plasma proteins. The plasma elimination half-life of rosuvastatin is about 19 hours. About 90% of an oral dose of rosuvastatin appears in the faeces, including absorbed and non-absorbed drug, and the remainder is excreted in the urine; about 5% of a dose is excreted unchanged in urine.

Ethnicity. A pharmacokinetic study[1] found that plasma exposure to rosuvastatin and its metabolites was significantly higher in Asian (Chinese, Malay, or Indian) than in Caucasian subjects and lower doses should be used (see Uses and Administration, below).

1. Lee E, *et al.* Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005; **78:** 330–41.

Uses and Administration

Rosuvastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the management of hyperlipidaemias (p.1169), including primary hypercholesterolaemia (type IIa), mixed dyslipidaemia (type IIb), and hypertriglyceridaemia (type IV), as well as in patients with homozygous familial hypercholesterolaemia. It is also used to reduce the progression of atherosclerosis.

Rosuvastatin is given orally as the calcium salt, although doses are expressed in terms of the base; 10.4 mg of rosuvastatin calcium is equivalent to about 10 mg of base.

The usual initial dose of rosuvastatin is 5 or 10 mg once daily, depending on plasma-cholesterol concentrations, cardiovascular risk factors, and risk factors for adverse effects. The maintenance dose ranges from 5 to 40 mg once daily, although the 40-mg dose is reserved for patients with high cardiovascular risk who do not achieve their target cholesterol concentration at lower doses and who do not have risk factors for adverse effects. Specific dosage recommendations vary; for dosage in renal impairment, see below.

UK licensed product information recommends an initial dose of 5 or 10 mg once daily; elderly patients, Asians, and those at risk of myopathy should be given the 5-mg dose. The dose may be increased at intervals of 4 weeks, if necessary, to a usual maximum of 20 mg once daily. A higher dose of 40 mg once daily may be given under specialist supervision in severe hypercholesterolaemia, but should not be given to patients at high risk of myopathy, including those receiving fibrates, and Asian patients; use with *ciclosporin* is contra-indicated.

US licensed product information recommends a usual initial dose of 10 mg once daily. However, a lower initial dose of 5 mg once daily may be adequate and is recommended for patients at risk of myopathy, including Asian patients; patients with marked hypercholesterolaemia, such as those with homozygous familial hypercholesterolaemia, may be started on 20 mg once daily. The dose should be adjusted after 2 to 4 weeks, to a usual maximum of 20 mg once daily; a dose of 40 mg once daily may be necessary in some patients. Patients receiving *ciclosporin* may be given a maximum of 5 mg once daily, and in those receiving *gemfibrozil* or *ritonavir-boosted lopinavir* the maximum dose is 10 mg once daily; dosage increases should be made with caution in Asian patients.

◊ General reviews.

1. Chong PH, Yim BT. Rosuvastatin for the treatment of patients with hypercholesterolemia. *Ann Pharmacother* 2002; **36:** 93–101.
2. Carswell CI, *et al.* Rosuvastatin. *Drugs* 2002; **62:** 2075–85.
3. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002; **42:** 963–70.
4. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health-Syst Pharm* 2005; **62:**1033–47.
5. Olsson AG. Expanding options with a wider range of rosuvastatin doses. *Clin Ther* 2006; **28:** 1747–63.
6. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; **5:** 161–75.
7. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. *Expert Rev Cardiovasc Ther* 2007; **5:** 177–93.
8. Crouse JR. An evaluation of rosuvastatin: pharmacokinetics, clinical efficacy and tolerability. *Expert Opin Drug Metab Toxicol* 2008; **4:** 287–304.

Administration in renal impairment. Patients with renal impairment have an increased risk of developing myopathy and statins should be used with caution, particularly in higher doses. In severe renal impairment plasma-rosuvastatin concentrations may be increased and dosage reduction may be necessary.

UK licensed product information recommends the following oral doses according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: initial oral dose of 5 mg once daily and a maximum dose of 20 mg once daily
- CC below 30 mL/minute: contra-indicated

In the USA usual doses (see above) are allowed in moderate impairment but an initial dose of 5 mg once daily and a maximum dose of 10 mg once daily is recommended in those with CC below 30 mL/minute per 1.73 m^2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Crestor; Rosuvast; Rovartal; Sinlip; ***Austral.:*** Crestor; ***Austria:*** Crestor; ***Belg.:*** Crestor; ***Braz.:*** Vivacor; ***Canad.:*** Crestor; ***Chile:*** Cresadex; Crestor; Rosumed; ***Cz.:*** Crestor; ***Denm.:*** Crestor; ***Fin.:*** Crestor; ***Fr.:*** Crestor; ***Gr.:*** Crestor; ***Hong Kong:*** Crestor; ***Hung.:*** Crestor; ***India:*** Razel†; Rosuvas; ***Indon.:*** Crestor; ***Irl.:*** Crestor; ***Israel:*** Crestor; ***Ital.:*** Crestor; Provisacor; Simestat; ***Jpn:*** Crestor; ***Malaysia:*** Crestor; ***Mex.:*** Crestor; ***Neth.:*** Cirantan; Crestor; Provisacor; ***Philipp.:*** Crestor; ***Port.:*** Crestor; Visacor; ***Rus.:*** Crestor (Крестор); ***S.Afr.:*** Crestor; ***Singapore:*** Crestor; ***Swed.:*** Crestor; ***Thai.:*** Crestor; ***UK:*** Crestor; ***USA:*** Crestor; ***Venez.:*** Crestor.

Saralasin Acetate *(BANM, USAN, rINNM)*

Acetato de sarasalina; P-113; Saralasine, Acétate de; Saralasini Acetas; The acetate of 1-Sar-8-Ala-angiotensin II. The hydrated acetate of Sar-Arg-Val-Tyr-Val-His-Pro-Ala; [1-(*N*-Methylglycine)-5-L-valine-8-L-alanine]-angiotensin II acetate hydrate.

Саралазина Ацетат

$C_{42}H_{65}N_{13}O_{10},xCH_3COOH,xH_2O$ = 912.0 (saralasin).
CAS — 34273-10-4 (saralasin); 54194-01-3 (anhydrous saralasin); 39698-78-7 (saralasin acetate hydrate).

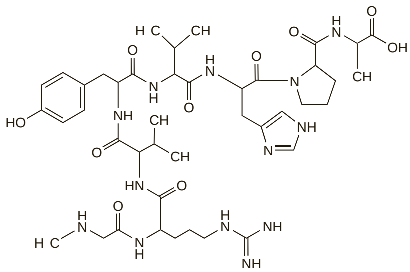

(saralasin)

Profile

Saralasin acetate is a competitive antagonist of angiotensin II and thus blocks its pressor action. It is also a partial agonist and causes a transient initial rise in blood pressure. Saralasin has a short half-life and has been used in the differential diagnosis of renovascular hypertension but its use has largely been superseded.

Sarpogrelate Hydrochloride *(rINNM)*

Hidrocloruro de sarpogrelato; MCI-9042; Sarpogrélate, Chlorhydrate de; Sarpogrelati Hydrochloridum. (±)-2-(Dimethylamino)-1-{[o-(*m*-methoxyphenethyl)phenoxy]methyl}ethyl hydrogen succinate hydrochloride.

Сарпогрелата Гидрохлорид

$C_{24}H_{31}NO_6,HCl$ = 466.0.
CAS — 125926-17-2 (sarpogrelate); 135159-51-2 (sarpogrelate hydrochloride).

Profile

Sarpogrelate is a serotonin 5-HT_2-receptor antagonist used as an inhibitor of platelet aggregation in thromboembolic disorders. It is given for occlusive arterial disease (see Peripheral Vascular Disease, p.1178) in oral doses of 100 mg of the hydrochloride three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Anplag.

Saruplase *(BAN, rINN)*

Prourokinase, Non-glycosylated; Recombinant Human Single-Chain Urokinase-type Plasminogen Activator; Saruplasa; Saruplasum; scuPA. Prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated.

Саруплаза

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$ = 46343.1.
CAS — 99149-95-8.
ATC — B01AD08.
ATC Vet — QB01AD08.

NOTE. The term prourokinase has been used for both saruplase and nasaruplase (p.1346).

Profile

Saruplase is a thrombolytic drug. It is a urokinase-type plasminogen activator with a single chain structure prepared via recombinant DNA technology and is converted to urokinase (p.1420) in the body by plasmin. It also has some intrinsic plasminogen-activating properties. Saruplase has been investigated in acute myocardial infarction.

◊ References.

1. Tebbe U, *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. *J Am Coll Cardiol* 1998; **31:** 487–93.

Sibrafiban *(BAN, USAN, rINN)*

G-7333; Ro-48-3657/001; Sibrafibán; Sibrafibanum. Ethyl (*Z*)-[(1-{*N*-[(*p*-hydroxyamidino)benzoyl]-L-alanyl}-4-piperidyl)oxy]acetate.

Сибрафибан

$C_{20}H_{28}N_4O_6$ = 420.5.
CAS — 172927-65-0.

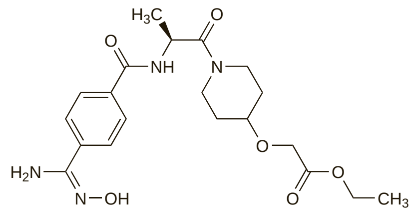

Profile

Sibrafiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but results have been disappointing.

◊ References.

1. Cannon CP, *et al.* Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. *Circulation* 1998; **97:** 340–9.
2. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. *Lancet* 2000; **355:** 337–45.
3. Second SYMPHONY Investigators. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. *Circulation* 2001; **103:** 1727–33.

Simvastatin *(BAN, USAN, rINN)*

L-644128-000U; MK-733; Simvastatiini; Simvastatina; Simvastatinas; Simvastatine; Simvastatinum; Sinvinolina; Synvinolin; Szimvasztatin; Velastatin; Velastatina. (1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl 2,2-dimethylbutyrate.

Симвастатин

$C_{25}H_{38}O_5$ = 418.6.
CAS — 79902-63-9.
ATC — C10AA01.
ATC Vet — QC10AA01.

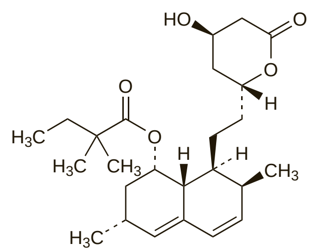

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Simvastatin). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store under nitrogen in airtight containers. Protect from light.

USP 31 (Simvastatin). A white to off-white powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store at a temperature between 15° and 30°, or at 2° to 8°.

Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, insomnia, and dysgeusia. Reversible increases in serum-aminotransferase concentrations may occur and liver function should be monitored (see Precautions, below). Hepatitis and pancreatitis have been reported. Hypersensitivity reactions including anaphylaxis and angioedema have also occurred. Myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported, especially in patients also taking ciclosporin, fibric acid derivatives, or nicotinic acid. Rarely, rhabdomyolysis with acute renal failure may develop.

◊ General references.

1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Safety* 2000; **23:** 197–213.
2. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs* 2001; **61:** 197–206.
3. Pasternak RC, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 29/05/08)
4. Karthikeyan VJ. Adverse effects of statins: an update. *Adverse Drug React Bull* 2005; (Aug): 895–8.
5. McKenney JM, *et al.* Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; **97** (Issue 8 suppl 1): 89C–94C.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; **370:** 1781–90.

Incidence of adverse effects. By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]

1. Committee on Safety of Medicines. Simvastatin. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Kashani A, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114:** 2788–97.
3. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007; **49:** 1753–62.
4. Silva M, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; **29:** 253–60.

Carcinogenicity. For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, below.

Effects on the blood. *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, below); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.

1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; **352:** 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; **80:** 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; **77:** 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; **67:** 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; **352:** 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; **99:** 328–9.
7. Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; **20:** 179–82.

Effects on the eyes. Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see above.

1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; **259:** 354–5.

2. Laties AM, *et al.* The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med* 1990; **323:** 683–4.
3. Schlienger RG, *et al.* Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; **161:** 2021–6.
4. Klein BEK, *et al.* Statin use and incident nuclear cataract. *JAMA* 2006; **295:** 2752–8.
5. Tan JSL, *et al.* Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; **143:** 687–9.

Effects on the hair. Between its introduction in Australia and 1993, 16 cases of alopecia associated with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee.[1] Most cases involved either excessive hair loss or hair thinning, although 2 cases of hair loss in patches and 1 resembling alopecia areata were reported. Onset occurred between 3 days and 15 months after starting therapy. Progressive hair loss has also been reported[2] in a woman within 6 weeks of commencing atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

1. Anonymous. Simvastatin and alopecia. *Aust Adverse Drug React Bull* 1993; **12:** 7.
2. Segal AS. Alopecia associated with atorvastatin. *Am J Med* 2002; **113:** 171.

Effects on the kidneys. *Proteinuria* was reported in 10 patients taking simvastatin 40 mg daily.[1] The protein loss was of a pattern typical for increased glomerular permeability. In 2 patients proteinuria disappeared when simvastatin was withdrawn and recurred on its subsequent reintroduction. However, there is also some evidence that statins may improve proteinuria (see Kidney Disorders under Uses, below).

Acute tubulointerstitial *nephritis* developed[2] in a patient receiving high-dose therapy with rosuvastatin. It resolved over 3 weeks when rosuvastatin was stopped, but recurred 2 weeks after rechallenge. A similar reaction was noted with atorvastatin, but improved with dose reduction, and the patient was finally stabilised on simvastatin without a further recurrence.

Renal failure due to rhabdomyolysis has been reported rarely (see under Effects on Skeletal Muscle, below).

1. Deslypere JP, *et al.* Proteinuria as complication of simvastatin treatment. *Lancet* 1990; **336:** 1453.
2. van Zyl-Smit R, *et al.* Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol Dial Transplant* 2004; **19:** 3176–9.

Effects on the liver. Statins cause dose-related increases in liver enzymes but the incidence appears to be low with low to moderate doses[1] and serious hepatic effects appear to be rare.[2] Although monitoring of liver function tests is advised, the value of routine assessment has been questioned.[3] There is some evidence[4] that the incidence of hepatic reactions may be higher with fluvastatin than with other statins, but this is not yet established.

There have also been case reports[5-7] of cholestasis in patients receiving statins.

1. de Denus S, *et al.* Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; **24:** 584–91.
2. Charles EC, *et al.* Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; **118:** 618–24.
3. Kostner K, Howes LG. Statins and monitoring of liver function tests. *Drug Safety* 2007; **30:** 1–4.
4. Conforti A, *et al.* Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. *Drug Safety* 2006; **29:** 1163–72.
5. Jiménez-Alonso J, *et al.* Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. *Arch Intern Med* 1999; **159:** 1811–12.
6. Wierzbicki AS, Crook MA. Cholestatic liver dysfunction. *Lancet* 1999; **354:** 954.
7. Batey RG, Harvey M. Cholestasis associated with the use of pravastatin sodium. *Med J Aust* 2002; **176:** 561.

Effects on the lungs. Interstitial lung disorders, including hypersensitivity pneumonitis, have been reported with a number of statins.[1-4] In some cases the condition improved when the statin was stopped[2] but treatment with corticosteroids and immunosuppressants was required in some patients[1-4] and progressive disease and fatalities have occurred.[4]

1. de Groot REB, *et al.* Interstitial lung disease with pleural effusion caused by simvastin [sic]. *J Intern Med* 1996; **239:** 361–3.
2. Liebhaber MI, *et al.* Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors: a report of ten cases. *Chest* 1999; **115:** 886–9.
3. Lantuejoul S, *et al.* Statin-induced fibrotic nonspecific interstitial pneumonia. *Eur Respir J* 2002; **19:** 577–80.
4. Walker T, *et al.* Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. *Med J Aust* 2007; **186:** 91–4.

Effects on mental function. There have been conflicting reports of the effects of statins on mental function, and a number of adverse psychiatric reactions have been reported with statins and with other lipid regulating drugs, although the exact association is unclear.

There have been a few case reports of *depressive symptoms* developing in patients treated with pravastatin[1] or simvastatin.[2] The symptoms appeared during the first few weeks or months of treatment. However, randomised studies investigating the effects of lowering cholesterol on mental function have found no effect on mood disorders (with simvastatin[3]) or psychological well-being (with lovastatin[4] or pravastatin[5]), and epidemiological studies have suggested that use of statins may be associated with improved psychological status[6] and a reduction in the risk of depression and suicide.[7]

Impairment of cognitive function has been reported with statins. In the study using lovastatin,[4] reductions in some measures of cognitive function were noted, and similar results were found in a study using simvastatin.[8] New onset cognitive impairment in a patient a week after starting simvastatin resolved when the drug was stopped but recurred on rechallenge with a lower dose,[9] while analyses of reports to adverse drug reaction reporting databases[10,11] have found a number of cases of memory loss in patients receiving statins, some of which were confirmed by rechallenge. However, clinical studies have not found statins to have an adverse effect on cognition, and there is epidemiological evidence that use of statins may reduce the incidence of dementia (see under Uses, below). A study with atorvastatin[12] also found beneficial effects on cognitive function.

Other psychiatric effects that have been noted in reports to another adverse drug reaction reporting database[13] include 5 cases of aggressive reactions, all of which resolved when the statin was stopped.

See also Effects on Sleep Patterns, below.

1. Lechleitner M, *et al.* Depressive symptoms in hypercholesterolaemic patients treated with pravastatin. *Lancet* 1992; **340:** 910.
2. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. *Lancet* 1993; **341:** 114.
3. Wardle J, *et al.* Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996; **313:** 75–8.
4. Muldoon MF, *et al.* Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; **108:** 538–47.
5. Stewart RA, *et al.* Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. *Arch Intern Med* 2000; **160:** 3144–52.
6. Young-Xu Y, *et al.* Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003; **42:** 690–7.
7. Yang C-C, *et al.* Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003; **163:** 1926–32.
8. Muldoon MF, *et al.* Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004; **117:** 823–9.
9. Padala KP, *et al.* Simvastatin-induced decline in cognition. *Ann Pharmacother* 2006; **40:** 1880–3.
10. Wagstaff LR, *et al.* Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003; **23:** 871–80.
11. Health Canada. Statins and memory loss. *Can Adverse React News* 2005; **15** (4): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n4-eng.pdf (accessed 19/08/08)
12. Parale GP, *et al.* Effects of atorvastatin on higher functions. *Eur J Clin Pharmacol* 2006; **62:** 259–65.
13. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Safety* 2007; **30:** 195–201.

Effects on the nervous system. Treatment with statins may be associated with the development of peripheral neuropathy,[1] although the reaction appears to be rare. Up to 2005, the Australian Adverse Drug Reactions Advisory Committee had received 281 reports[2] of both sensory and sensorimotor peripheral neuropathies associated with statins. Time to onset of symptoms ranged from after the first dose to 4.5 years. Recovery was seen on withdrawal in about half of the cases, including in some diabetics, and there were some reports of positive rechallenge. In 21 cases symptoms persisted at the time of reporting, up to 8 months after the statin was stopped, and in a further 2 reports the symptoms were unresolved after 3 and 5 years respectively. Similar patterns have been noted elsewhere.[3] A case-control study[4] found that the risk of neuropathy was substantially increased in users of statins although the number of cases was small, and the authors concluded that the benefits of therapy generally outweighed the risks.

Upper motor neurone lesions similar to amyotrophic lateral sclerosis have also been reported in patients taking statins,[5] although the association is not yet confirmed.

1. Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother* 2003; **37:** 274–8.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Statins and peripheral neuropathy. *Aust Adverse Drug React Bull* 2005; **24:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.pdf (accessed 30/05/08)
3. de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre. *Neth J Med* 2006; **64:** 334–8.
4. Gaist D, *et al.* Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002; **58:** 1333–7.
5. Edwards IR, *et al.* Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from Vigibase. *Drug Safety* 2007; **30:** 515–25.

Effects on the pancreas. Statins may cause pancreatitis but the incidence appears to be low,[1,2] and a case-control study[3] failed to support a strong association.

1. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. *Drug Safety* 2006; **29:** 1123–32.
2. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. *Pharmacotherapy* 2006; **26:** 414–22.
3. Thisted H, *et al.* Statins and the risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2006; **23:** 185–90.

Effects on sexual function. There have been reports of *erectile dysfunction* in some men receiving statins. Five men receiving simvastatin developed impotence,[1] which resolved when fluvastatin was substituted in 4 of them. In another case,[2] impotence occurred in a patient receiving lovastatin, and recurred when therapy was changed to pravastatin. Up to 1995, the Australian Adverse Drug Reactions Advisory Committee[3] had received 28 reports of impotence associated with simvastatin, which had recurred on rechallenge in 4 cases. A report[4] from the French and Spanish drug monitoring systems, and an observational study[5] in high-risk cardiovascular patients, supported the association between statins and erectile dysfunction, and a systematic review[6] came to similar conclusions. However, it has been pointed out[7] that the increased risk of sexual dysfunction with statins in the Scandinavian Simvastatin Survival Study was not statistically significant, and there has also been a small study[8] suggesting that atorvastatin may improve erectile function in men with hyperlipidaemia as the only risk factor.

Decreased libido has also been reported with statins. Serum-testosterone concentrations were measured in 2 of 8 patients reported to the Netherlands Pharmacovigilance Centre and were found to be low;[9] they rose after the statin was stopped.

Testicular pain has been reported[10] in a 54-year-old patient 7 months after starting lovastatin. The pain resolved when lovastatin was stopped, but recurred with both simvastatin and atorvastatin. The mechanism for the reaction was unclear.

There has also been a report[11] of a *low sperm count* in a patient receiving lovastatin.

Gynaecomastia occurred in a patient 6 months after changing from simvastatin to atorvastatin.[12] Symptoms improved when atorvastatin was stopped and did not recur when treatment with simvastatin was restarted.

1. Jackson G. Simvastatin and impotence. *BMJ* 1997; **315:** 31.
2. Halkin A, *et al.* HMG-CoA reductase inhibitor-induced impotence. *Ann Pharmacother* 1996; **30:** 192.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Simvastatin and adverse endocrine effects in men. *Aust Adverse Drug React Bull* 1995; **14:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/05/08)
4. Carvajal A, *et al.* HMG CoA reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. *Drug Safety* 2006; **29:** 143–9.
5. Solomon H, *et al.* Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006; **60:** 141–5.
6. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
7. Pedersen TR, Færgeman O. Simvastatin seems unlikely to cause impotence. *BMJ* 1999; **318:** 192.
8. Saltzman EA, *et al.* Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol (Baltimore)* 2004; **172:** 255–8.
9. de Graaf L, *et al.* Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? *Br J Clin Pharmacol* 2004; **58:** 326–8.
10. Linnebur AS, Hiatt WH. Probable statin-induced testicular pain. *Ann Pharmacother* 2007; **41:** 138–42.
11. Hildebrand RD, Hepperlen TW. Lovastatin and hypospermia. *Ann Intern Med* 1990; **112:** 549–50.
12. Hammons KB, *et al.* Golf-inhibiting gynecomastia associated with atorvastatin therapy. *Pharmacotherapy* 2006; **26:** 1165–8.

Effects on skeletal muscle. The association between muscle disorders and statins is well known.[1-8] Mild *myalgia* is relatively common, but *myositis* and *myopathy,* with elevation of creatine kinase, may also occur. *Rhabdomyolysis,*[9,10] which involves severe muscle damage, substantial elevation of creatine kinase and myoglobulinuria leading to renal impairment, occurs more rarely, but has resulted in fatalities. Muscle toxicity is dose-related and the risk appears to be broadly similar with all of the currently-marketed statins;[5,6,11] the incidence with cerivastatin was found to be considerably higher and this led to its withdrawal worldwide in 2001. Patients with complex medical problems, including renal impairment and possibly endocrine disorders such as hypothyroidism, may be at increased risk of muscle toxicity; drug interactions may also contribute (see below). Myopathy has been reported with other lipid regulating drugs, particularly fibrates, and the risk may be increased in patients with severe hyperlipidaemia who require combination therapy; careful monitoring is required if statins and fibrates are used together.[6,12] The UK CSM[1] and a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute,[6] have both advised that patients treated with statins should consult their doctor if they develop muscle pain, tenderness, or weakness and that treatment should be stopped if muscle toxicity occurs or is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising. If continued therapy is required, the dose may be reduced or another statin or alternative lipid regulating drug may be tried, although the risk of recurrent muscle problems appears quite high.[10] An algorithm for diagnosis and management of statin-associated myalgia has been suggested.[13]

The mechanism by which statins cause muscle toxicity is not clear, but it has been suggested that depletion of ubidecarenone concentrations may be involved.[14] Although positive results have been reported with ubidecarenone supplementation[15] evidence of benefit is limited and it is not generally recommended.[16]

Other muscular disorders that have been reported in patients receiving statins include *dermatomyositis* and *polymyositis,*[17] and *myasthenia gravis.*[18-20]

1. Committee on Safety of Medicines/Medicines Control Agency. HMG CoA reductase inhibitors (statins) and myopathy. *Current Problems* 2002; **28:** 8–9. Also available at:

http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Fluvastatin and muscle disorders—a class effect. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 30/05/08)
3. Ucar M, *et al.* HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* 2000; **22:** 441–57.
4. Omar MA, *et al.* Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001; **35:** 1096–1107.
5. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002; **36:** 288–95.
6. Pasternak RC, *et al.* ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 30/05/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Risk factors for myopathy and rhabdomyolysis with the statins. *Aust Adverse Drug React Bull* 2004; **23:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0402.pdf (accessed 30/05/08)
8. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004; **116:** 408–16.
9. Graham DJ, *et al.* Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; **292:** 2585–90.
10. Antons KA, *et al.* Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006; **119:** 400–9.
11. Staffa JA, *et al.* Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; **346:** 539–540.
12. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.
13. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc* 2008; **83:** 687–700.
14. Hargreaves IP, *et al.* The effect of HMG-CoA reductase inhibitors on coenzyme Q : possible biochemical/clinical implications. *Drug Safety* 2005; **28:** 659–76.
15. Walravens PA, *et al.* Lovastatin, isoprenes, and myopathy. *Lancet* 1989; **ii:** 1097–8.
16. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q during statin therapy. *Ann Pharmacother* 2006; **40:** 290–4.
17. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; **21:** 17–24.
18. Parmar B, *et al.* Statins, fibrates, and ocular myasthenia. *Lancet* 2002; **360:** 717.
19. Cartwright MS, *et al.* Statin-associated exacerbation of myasthenia gravis. *Neurology* 2004; **63:** 2188.
20. Purvin V, *et al.* Statin-associated myasthenia gravis: report of 4 cases and review of the literature *Medicine (Baltimore)* 2006; **85:** 82–5.

Effects on sleep patterns. Changes to sleep patterns have been reported with lipophilic statins such as lovastatin[1-3] and simvastatin,[4] but appear to be less common with pravastatin,[1] possibly because it is hydrophilic and less likely to penetrate the brain. However, a large placebo-controlled study[5] found that simvastatin had no effect on sleep patterns, and smaller studies assessing sleep using questionnaires[6] or polysomnography,[7-9] have found no significant effects with any of the statins, although some patients appeared to have underlying sleep disorders.

Nightmares and sleep disturbances in a patient taking simvastatin and metoprolol resolved when treatment was changed to pravastatin and atenolol.[10] There has been a report of nightmares with atorvastatin, which resolved when the drug was stopped but recurred on rechallenge.[11]

1. Schaefer EJ. HMG-CoA reductase inhibitors for hypercholesterolemia. *N Engl J Med* 1988; **319:** 1222.
2. Rosenson RS, Goranson NL. Lovastatin-associated sleep and mood disturbances. *Am J Med* 1993; **95:** 548–9.
3. Sinzinger H, *et al.* Sleep disturbance and appetite loss after lovastatin. *Lancet* 1994; **343:** 973.
4. Barth JD, *et al.* Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. *BMJ* 1990; **301:** 669.
5. Keech AC, *et al.* Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. *Br J Clin Pharmacol* 1996; **42:** 483–90.
6. Black DM, *et al.* Sleep disturbances and HMG CoA reductase inhibitors. *JAMA* 1990; **264:** 1105.
7. Eckernäs S-Å, *et al.* The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. *Br J Clin Pharmacol* 1993; **35:** 284–9.
8. Kostis JB, *et al.* Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol* 1994; **34:** 989–96.
9. Ehrenberg BL, *et al.* Comparison of the effects of pravastatin and lovastatin on sleep disturbance in hypercholesterolemic subjects. *Sleep* 1999; **22:** 117–21.
10. Boriani G, *et al.* Nightmares and sleep disturbances with simvastatin and metoprolol. *Ann Pharmacother* 2001; **35:** 1292.
11. Gregoor PJHS. Atorvastatin may cause nightmares. *BMJ* 2006; **332:** 950.

Precautions

Statins should not be given to patients with active liver disease. Liver function should be assessed before starting treatment and subsequently when clinically indicated; additional assessment after 3 months and before and after dosage increases has been advised for some statins, particularly when high doses are given. Statins should not be used in patients who already have unexplained persistently raised serum-aminotransferase concentrations and should be stopped if marked or persistent increases in serum-aminotransferase concentrations occur. They should be avoided during pregnancy since there is a possibility that they could interfere with fetal sterol synthesis; there have been a number of reports of congenital abnormalities associated with statins (see Pregnancy, below). Statins may cause myopathy and rhabdomyolysis, especially at higher doses, and they should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin (see Interactions, below); the statin should be stopped if creatine phosphokinase increases significantly or if myopathy is diagnosed.

Statins should be used with caution in patients with renal impairment as the risk of myopathy is increased. Dose reduction may be required for statins that are excreted by the kidney and for those with a particularly high risk of myopathy (see Administration in Renal Impairment under Uses of the individual drugs for further details).

Children. For discussion of concerns relating to the use of statins in children, see Administration in Children under Uses, below.

Porphyria. Simvastatin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. Statins are generally contra-indicated in pregnancy since there is a possibility that they might affect fetal sterol synthesis whereas the risk to the mother from stopping treatment temporarily is usually very low. Evidence that statins have adverse effects on the fetus, however, is limited. Studies based on postmarketing surveillance[1,2] or pregnancy registry data[3] have generally found that the frequency and range of congenital anomalies reported was similar to that expected in the general population. However, reviews of case reports[4,5] found that the incidence of CNS defects and limb anomalies was higher than expected, suggesting a possible adverse effect of statin exposure; 1 of the 5 cases reported as a CNS defect was later found to have cardiac anomalies only.[6]

1. Manson JM, *et al.* Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol* 1996; **10:** 439–46.
2. Pollack PS, *et al.* Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 888–96.
3. Ofori B, *et al.* Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007; **64:** 496–509.
4. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med* 2004; **350:** 1579–82.
5. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet* 2004; **131A:** 287–98.
6. Edison RJ, Muenke M. Gestational exposure to lovastatin followed by cardiac malformation misclassified as holoprosencephaly. *N Engl J Med* 2005; **352:** 2759.

Interactions

The most serious consequence of drug interactions with simvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by drugs that increase the plasma concentrations of statins, by inhibiting their metabolism or by inhibiting their uptake into the liver. Since the statins have different metabolic pathways, these interactions depend on the individual drug concerned. Simvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4, as are atorvastatin and lovastatin, and interactions may occur with drugs that inhibit this enzyme, including ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, and verapamil; there may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be advised (see Uses and Administration, below); UK licensed product information contra-indicates the use of simvastatin in patients receiving potent CYP3A4 inhibitors. Fluvastatin is metabolised mainly by CYP2C9, while pravastatin and rosuvastatin are not significantly metabolised; interactions specific to these statins are discussed on p.1290, p.1374, and p.1389, respectively.

Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking simvastatin or other statins with coumarin anticoagulants.

◊ General reviews.

1. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; **41:** 343–70.
2. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? *Drug Safety* 2003; **26:** 13–21.
3. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Statins and cytochrome P450 interactions. *Current Problems* 2004; **30:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
4. Rätz Bravo AE, *et al.* Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Safety* 2005; **28:** 263–75.
5. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006; **97** (suppl 8A): 27C–31C.
6. Neuvonen PJ, *et al.* Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; **80:** 565–81.

Antiarrhythmics. *Amiodarone* is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations of statins metabolised by this enzyme, increasing the risk of toxicity. There have been reports[1-3] of myopathy and rhabdomyolysis in patients taking amiodarone and simvastatin (in some cases with other CYP3A4 inhibitors), and a pharmacokinetic study[4] found that amiodarone increased plasma-simvastatin concentrations in healthy subjects. High doses of simvastatin are not recommended in patients taking amiodarone (see Uses and Administration, below).

An asymptomatic increase in serum aminotransferases in a patient receiving rosuvastatin and amiodarone may have been the result of an interaction between the drugs.[5]

1. Roten L, *et al.* Rhabdomyolysis in association with simvastatin and amiodarone. *Ann Pharmacother* 2004; **38:** 978–81.
2. Chouhan UM, *et al.* Simvastatin interaction with clarithromycin and amiodarone causing myositis. *Ann Pharmacother* 2005; **39:** 1760–1.
3. Ricaurte B, *et al.* Simvastatin–amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity. *Ann Pharmacother* 2006; **40:** 753–7.
4. Becquemont L, *et al.* Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. *Clin Pharmacol Ther* 2007; **81:** 679–84.
5. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health-Syst Pharm* 2007; **64:** 1818–21.

Antibacterials. *Erythromycin* and other *macrolides* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Increased plasma concentrations of simvastatin have been reported with erythromycin,[1] and increased plasma concentrations of atorvastatin have been found with erythromycin[2] and *clarithromycin*,[3] but not with *azithromycin*.[3] There have been reports of myopathy or rhabdomyolysis in patients receiving simvastatin with clarithromycin,[4] and in patients receiving lovastatin with azithromycin,[5] clarithromycin,[5] or erythromycin.[6]

Rifampicin, an inducer of CYP2C9 and CYP3A4, may reduce the bioavailability of fluvastatin, and has also been reported to reduce the plasma concentration of simvastatin[7] and atorvastatin.[8]

There have been reports of rhabdomyolysis in patients receiving atorvastatin[9] or simvastatin[10] with *fusidic acid*.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Siedlik PH, *et al.* Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; **39:** 501–4.
3. Amsden GW, *et al.* A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; **42:** 444–9.
4. Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001; **35:** 26–31.
5. Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997; **31:** 859–63.
6. Ayanian JZ, *et al.* Lovastatin and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 682–3.
7. Kyrklund C, *et al.* Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 2000; **68:** 592–7.
8. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
9. Wenisch C, *et al.* Acute rhabdomyolysis after atorvastatin and fusidic acid therapy. *Am J Med* 2000; **109:** 78.
10. Yuen SLS, McGarity B. Rhabdomyolysis secondary to interaction of fusidic acid and simvastatin. *Med J Aust* 2003; **179:** 172.

Anticoagulants. For reports of bleeding and increased prothrombin time in patients receiving oral anticoagulants with statins, see Lipid Regulating Drugs, p.1431.

Antidepressants. Myositis and rhabdomyolysis, with raised liver enzyme values, have been reported[1-4] in patients given simvastatin with *nefazodone*; in one case[3] the reaction appeared to be precipitated by the addition of azithromycin. Increased creatine kinase concentrations also occurred in a patient given pravastatin with nefazodone.[5]

A study[6] in healthy subjects found that *St John's wort* reduced the plasma concentration of simvastatin but had no effect on pravastatin.

1. Jacobson RH, *et al.* Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA* 1997; **277:** 296.
2. Thompson M, Samuels S. Rhabdomyolysis with simvastatin and nefazodone. *Am J Psychiatry* 2002; **159:** 1607.
3. Skrabal MZ, *et al.* Two cases of rhabdomyolysis associated with high-dose simvastatin. *Am J Health-Syst Pharm* 2003; **60:** 578–81.
4. Karnik NS, Maldonado JR. Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. *Psychosomatics* 2005; **46:** 565–8.
5. Alderman CP. Possible interaction between nefazodone and pravastatin. *Ann Pharmacother* 1999; **33:** 871.
6. Sugimoto K-i, *et al.* Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001; **70:** 518–24.

Antifungals. *Itraconazole* and *ketoconazole* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Raised plasma concentrations of simvastatin,[1,2] lovastatin,[3,4] and atorvastatin[5] have been reported with itraconazole, whereas the effect on pravastatin,[1] rosuvastatin,[6] or fluvastatin[4] appears to be minimal. Myopathy and rhabdomyolysis have been reported with simvastatin and itraconazole[2,7] or ketoconazole,[8] and with lovastatin and itraconazole.[9] *Fluconazole* inhibits CYP2C9 and has been reported[10] to increase the plasma concentration of fluvastatin. There has also been a report[11] of rhabdomyolysis in a patient taking fluconazole and simvastatin.

1. Neuvonen PJ, *et al.* Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998; **63:** 332–41.
2. Segaert MF, *et al.* Drug-interaction-induced rhabdomyolysis. *Nephrol Dial Transplant* 1996; **11:** 1846–7.
3. Neuvonen PJ, Jalava K-M. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996; **60:** 54–61.
4. Kivistö KT, *et al.* Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998; **46:** 49–53.
5. Kantola T, *et al.* Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998; **64:** 58–65.
6. Cooper KJ, *et al.* Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2003; **73:** 322–9.
7. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996; **132:** 1254.
8. Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. *Clin Neuropharmacol* 1999; **22:** 295–7.
9. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med* 1995; **333:** 664–5.
10. Kantola T, *et al.* Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000; **56:** 225–9.
11. Shaukat A, *et al.* Simvastatin–fluconazole causing rhabdomyolysis. *Ann Pharmacother* 2003; **37:** 1032–5.

Antiplatelet drugs. For discussion of a possible interaction between statins and clopidogrel, see p.1250

Antivirals. *HIV-protease inhibitors* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of simvastatin and other statins. Studies have shown increased plasma concentrations of both simvastatin and atorvastatin with *nelfinavir*,[1] and with *ritonavir-boosted saquinavir*,[2] whereas the plasma concentration of pravastatin was reduced with ritonavir-boosted saquinavir.[2] Rhabdomyolysis has been reported[3] in a patient taking simvastatin when ritonavir was added to her therapy. Although rosuvastatin is not significantly metabolised, increased plasma concentrations have been reported with *ritonavir-boosted lopinavir*.[4,5]

There has also been a report[6] of rhabdomyolysis in a patient receiving atorvastatin with the non-nucleoside reverse transcriptase inhibitor *delavirdine*.

Efavirenz is an inducer of CYP3A4 and a study in healthy subjects[7] found that it could reduce plasma concentrations of atorvastatin and simvastatin; plasma concentrations of pravastatin were also reduced, although it is not metabolised by CYP3A4.

1. Hsyu P-H, *et al.* Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; **45:** 3445–50.
2. Fichtenbaum CJ, *et al.* Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; **16:** 569–77.
3. Cheng CH, *et al.* Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health-Syst Pharm* 2002; **59:** 728–30.
4. van der Lee M, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. *Antivir Ther* 2007; **12:** 1127–32.
5. Kiser JJ, *et al.* Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; **47:** 570–8.
6. Castro JG, Gutierrez L. Rhabdomyolysis with acute renal failure probably related to the interaction of atorvastatin and delavirdine. *Am J Med* 2002; **112:** 505.
7. Gerber JG, *et al.* Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; **39:** 307–12.

Calcium-channel blockers. Calcium-channel blockers may increase plasma concentrations of some statins, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4. Pharmacokinetic studies have reported increased plasma concentrations of simvastatin with *verapamil*,[1] and with *diltiazem*,[2] and of lovastatin with diltiazem;[3] the small increase with simvastatin and *lacidipine* was not considered clinically relevant.[4]

The interaction between statins and diltiazem has also been reported in patients. A retrospective study[5] found that the cholesterol-lowering effect of simvastatin was greater in patients who were also receiving diltiazem, and there have also been reports[6-8] of rhabdomyolysis, associated with hepatitis in 1 case,[6] in patients receiving simvastatin and diltiazem together. Rhabdomyolysis[8,9] and hepatitis[9] have also been reported in patients receiving atorvastatin with diltiazem.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Mousa O, *et al.* The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000; **67:** 267–74.
3. Azie NE, *et al.* The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998; **64:** 369–77.
4. Ziviani L, *et al.* The effects of lacidipine on the steady/state plasma concentrations of simvastatin in healthy subjects. *Br J Clin Pharmacol* 2001; **51:** 147–52.
5. Yeo KR, *et al.* Enhanced cholesterol reduction by simvastatin in diltiazem-treated patients. *Br J Clin Pharmacol* 1999; **48:** 610–615.
6. Kanathur N, *et al.* Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. *Tenn Med* 2001; **94:** 339–41.
7. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001; **89:** 117–118.
8. Gladding P, *et al.* Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004; **140:** W31. Available at: http://www.annals.org/cgi/reprint/140/8/W-31.pdf (accessed 14/11/07)
9. Lewin JJ, *et al.* Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002; **36:** 1546–9.

Colchicine. For reports of additive muscle toxicity with statins and colchicine, see Cardiovascular Drugs under Interactions of Colchicine, p.556.

Danazol. Rhabdomyolysis has been reported[1] in a patient receiving lovastatin with a number of other drugs; it was considered that an interaction with danazol was the most likely cause. A similar reaction has been reported[2] with simvastatin.

1. Dallaire M, Chamberland M. Rhabdomyolyse sévère chez un patient recevant lovastatine, danazol et doxycycline. *Can Med Assoc J* 1994; **150:** 1991–4.
2. Andreou ER, Ledger S. Potential drug interaction between simvastatin and danazol causing rhabdomyolysis. *Can J Clin Pharmacol* 2003; **10:** 172–4.

Endothelin receptor antagonists. *Bosentan* is an inducer of the cytochrome P450 isoenzyme CYP3A4 and has been reported[1] to reduce plasma-simvastatin concentrations in healthy subjects.

1. Dingemanse J, *et al.* Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Clin Pharmacokinet* 2003; **42:** 293–301.

Fruit juices. *Grapefruit juice* inhibits the cytochrome P450 isoenzyme CYP3A4 and studies using concentrated grapefruit juice have reported increased plasma concentrations of simvastatin,[1] lovastatin,[2] and atorvastatin.[3] A study[4] using less concentrated grapefruit juice found only minimal effect on the activity of lovastatin, but the conclusions of this study have been criticised;[5] studies using normal strength grapefruit juice have found considerable increases in plasma concentrations of atorvastatin[6] and simvastatin.[7] There is also a case report[8] of a woman receiving simvastatin who developed symptoms of rhabdomyolysis 4 days after she started eating one grapefruit each day. Statins that are not significantly metabolised by CYP3A4, such as pitavastatin[6] and pravastatin,[3,9] do not appear to be affected.

Rhabdomyolysis has also been reported[10] in a patient taking rosuvastatin and ezetimibe when he started drinking *pomegranate juice* regularly.

1. Lilja JJ, *et al.* Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998; **64:** 477–83.
2. Kantola T, *et al.* Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998; **63:** 397–402.
3. Lilja JJ, *et al.* Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999; **66:** 118–27.
4. Rogers JD, *et al.* Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Clin Pharmacol Ther* 1999; **66:** 358–66.
5. Bailey DG, Dresser GK. Grapefruit juice–lovastatin interaction. *Clin Pharmacol Ther* 2000; **67:** 690.
6. Ando H, *et al.* Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br J Clin Pharmacol* 2005; **60:** 494–7.
7. Lilja JJ, *et al.* Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol* 2004; **58:** 56–60.
8. Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology* 2004; **62:** 670.
9. Fukazawa I, *et al.* Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol* 2004; **57:** 448–55.
10. Sorokin AV, *et al.* Rhabdomyolysis associated with pomegranate juice consumption. *Am J Cardiol* 2006; **98:** 705–6.

Immunosuppressants. Myopathy and rhabdomyolysis have been reported in patients receiving atorvastatin,[1] lovastatin,[2-4] or simvastatin[5-7] with immunosuppressant regimens including *ciclosporin*. The mechanism of the interaction may be additive toxicity, since both statins and ciclosporin are known to cause myopathy, but effects on plasma concentrations may also be involved. Pharmacokinetic studies have shown that ciclosporin increases the plasma concentrations of atorvastatin,[8,9] fluvastatin,[10,11] lovastatin,[12] pravastatin,[12,13] rosuvastatin,[14] and simvastatin.[15] For the effects of statins on plasma-ciclosporin concentrations, see p.1827.

1. Maltz HC, *et al.* Rhabdomyolysis associated with concomitant use of atorvastatin and cyclosporine. *Ann Pharmacother* 1999; **33:** 1176–9.
2. Norman DJ, *et al.* Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med* 1988; **318:** 46–7.
3. East C, *et al.* Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med* 1988; **318:** 47–8.
4. Corpier CL, *et al.* Rhabdomyolysis and renal injury with lovastatin use: report of two cases in cardiac transplant recipients. *JAMA* 1988; **260:** 239–41.
5. Blaison G, *et al.* Rhabdomyolyse causée par la simvastatine chez un transplanté cardiaque sous ciclosporine. *Rev Med Interne* 1992; **13:** 61–3.
6. Meier C, *et al.* Rhabdomyolyse bei mit Simvastatin und Ciclosporin behandelten Patienten: Rolle der aktivität des Cytochrom-P450-Enzymsystems der Leber. *Schweiz Med Wochenschr* 1995; **125:** 1342–6.
7. Gumprecht J, *et al.* Simvastatin-induced rhabdomyolysis in a CsA-treated renal transplant recipient. *Med Sci Monit* 2003; **9:** CS89–CS91.
8. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
9. Hermann M, *et al.* Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. *Clin Pharmacol Ther* 2004; **76:** 388–91.
10. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; **62:** 1559–64.
11. Park J-W, *et al.* Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. *J Cardiovasc Pharmacol Ther* 2001; **6:** 351–61.
12. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; **62:** 311–21.
13. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; **25:** 2732–4.
14. Simonson SG, *et al.* Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; **76:** 167–77.
15. Arnadottir M, *et al.* Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* 1993; **65:** 410–13.

Levothyroxine. For reference to the effect of lovastatin and simvastatin in patients receiving levothyroxine, see Lipid Regulating Drugs, p.2173.

Lipid regulating drugs. Myopathy and myositis are recognised adverse effects of both statins and fibric acid derivatives, including *fibrates* and *gemfibrozil*, and the risk is increased if they are given together. There has also been a report[1] of both hepatotoxicity and rhabdomyolysis in a patient given a statin and gemfibrozil together. The interaction between gemfibrozil and statins may also have a pharmacokinetic basis; studies have shown increased plasma concentrations of atorvastatin,[2] lovastatin,[3] pravastatin,[4] rosuvastatin,[5] and simvastatin[6] when given with gemfibrozil.

Myopathy has also been reported[7,8] in patients given statins with *nicotinic acid*, although a study[9] of adverse effects reported to the FDA found no increase in reports for lovastatin given with nicotinic acid compared with either drug alone.

For reports of increased hepatotoxicity when statins were given with *ezetimibe* see Effects on the Liver, p.1284.

1. Akoglu H, *et al.* Combined organ failure with combination antihyperlipidemic treatment: a case of hepatic injury and acute renal failure. *Ann Pharmacother* 2007; **41:** 143–7.
2. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
3. Kyrklund C, *et al.* Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001; **69:** 340–5.
4. Kyrklund C, *et al.* Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003; **73:** 538–44.
5. Schneck DW, *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004; **75:** 455–63.
6. Backman JT, *et al.* Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000; **68:** 122–9.
7. Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 597–8.

8. Hill MD, Bilbao JM. Case of the month: February 1999—54 year old man with severe muscle weakness. *Brain Pathol* 1999; **9:** 607–8.
9. Alsheikh-Ali AA, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration adverse event reporting system). *Am J Cardiol* 2007; **99:** 379–81.

Proton pump inhibitors. There is a report[1] of rhabdomyolysis causing AV block in a patient receiving atorvastatin when *esomeprazole* and clarithromycin were added to her treatment. As symptoms started before the introduction of clarithromycin, it was thought that a possible contributory mechanism for the interaction was a reduction in the first-pass metabolism of atorvastatin due to the inhibition of p-glycoprotein by esomeprazole.

1. Sipe BE, *et al.* Rhabdomyolysis causing AV blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. *Ann Pharmacother* 2003; **37:** 808–11.

Ranolazine. A study[1] in healthy subjects showed that ranolazine moderately increased plasma concentrations of simvastatin but it was not thought that the interaction would be clinically significant.

1. Jerling M, *et al.* Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol* 2005; **45:** 422–33.

Pharmacokinetics

Simvastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Other active metabolites have been detected and a number of inactive metabolites are also formed. Simvastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action. Less than 5% of the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β-hydroxyacid metabolite are about 95% bound to plasma proteins. Simvastatin is mainly excreted in the faeces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. The half-life of the active β-hydroxyacid metabolite is 1.9 hours.

◊ General reviews.

1. Mauro VF. Clinical pharmacokinetics and practical applications of simvastatin. *Clin Pharmacokinet* 1993; **24:** 195–202.
2. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
3. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.

Genetic variation. The pharmacokinetics of statins are influenced not only by metabolising enzymes but also by their affinity for organ-specific transporter proteins responsible for their uptake and efflux from cells, in particular in the intestine and liver.[1,2] Statins differ not only in their affinity for cytochrome P450 isoenzymes, but also in their affinity for transporter proteins such as organic anion transporting polypeptides (OATPs) and P-glycoprotein (multi-drug resistance 1; MDR1). Both metabolising enzymes and transporter proteins may be subject to ethnic and genetic variation, and it has been suggested that this may explain some of the variability in the efficacy and the risk of adverse effects in different populations.

1. Kim RB. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and genetic variability (single nucleotide polymorphisms) in a hepatic drug uptake transporter: what's it all about? *Clin Pharmacol Ther* 2004; **75:** 381–5.
2. Tirona RG. Ethnic differences in statin disposition. *Clin Pharmacol Ther* 2005; **78:** 311–16.

Uses and Administration

Simvastatin is a lipid regulating drug; it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme for cholesterol synthesis. Inhibition of HMG-CoA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations; this stimulates an increase in low-density-lipoprotein (LDL)-cholesterol receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. HMG-CoA reductase inhibitors (also called statins) reduce total cholesterol, LDL-cholesterol, and very-low-density lipoprotein (VLDL)-cholesterol concentrations in plasma. They also tend to reduce triglycerides and to increase high-density lipoprotein (HDL)-cholesterol concentrations.

Simvastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169). It is used in hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and primary dysbetalipoproteinaemia (type III), and may also be used as adjunct therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. Simvastatin is also used for cardiovascular risk reduction (p.1164).

Simvastatin is given orally and doses range from 5 to 80 mg daily. For the treatment of **hyperlipidaemias**, the usual initial dose is 10 to 20 mg in the evening; an initial dose of 40 mg may be used in patients who require a large reduction in cholesterol or who are at high cardiovascular risk. The dose may be adjusted at intervals of not less than 4 weeks up to a maximum of 80 mg once daily in the evening. Patients with homozygous familial hypercholesterolaemia may be treated with 40 mg once daily in the evening, or 80 mg daily in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg.

For **cardiovascular risk reduction** in high-risk patients, such as those with atherosclerotic cardiovascular disease or diabetes mellitus, the usual dose is 20 to 40 mg once daily. Patients who are at moderate risk may be given a dose of 10 mg once daily.

The dose of simvastatin should be reduced in patients at risk of myopathy, including patients with severe renal impairment (see below). For patients taking drugs that interact with simvastatin, dose reduction is also advised, as follows:

- patients taking *ciclosporin* or *danazol*, initial dose 5 mg once daily and maximum dose 10 mg once daily
- patients taking *gemfibrozil* or other *fibrates*, or *nicotinic acid*, maximum dose 10 mg once daily
- patients taking *amiodarone* or *verapamil*, maximum dose 20 mg once daily
- patients taking *diltiazem*, maximum dose 40 mg once daily

For the use of simvastatin in children, see below.

◊ General reviews.

1. Mauro VF, MacDonald JL. Simvastatin: a review of its pharmacology and clinical use. *DICP Ann Pharmacother* 1991; **25:** 257–64.
2. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. *Drugs* 1995; **50:** 334–63.
3. Schectman G, Hiatt J. Dose–response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996; **125:** 990–1000.
4. White CM. Pharmacological effects of HMG CoA reductase inhibitors other than lipoprotein modulation. *J Clin Pharmacol* 1999; **39:** 111–18.
5. Mata P, *et al.* Benefits and risks of simvastatin in patients with familial hypercholesterolaemia. *Drug Safety* 2003; **26:** 769–86.

Action. The effects of statins on *plasma lipids* are well established.[1-4] Their primary action is to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol is an important precursor for synthesis of a number of substances by the liver, and reduced intracellular concentrations stimulate an increase in the expression of low-density lipoprotein (LDL) receptors in the liver. This leads to increased uptake of LDL-cholesterol from the plasma into liver cells, with a subsequent reduction in both LDL and total cholesterol. Triglycerides are also decreased, due to decreased synthesis of very-low-density lipoprotein (VLDL), while high-density lipoprotein (HDL)-cholesterol is either modestly increased or unchanged, leading to an improvement in the LDL:HDL ratio. An effect on LDL-cholesterol may also occur independent of the effect on receptors; some statins have been shown to lower LDL-cholesterol in patients with homozygous familial hypercholesterolaemia, despite their lack of functional LDL receptors. Statins generally provide a greater reduction in LDL-cholesterol than other classes of lipid regulating drugs, but where large reductions are required combination therapy may be necessary. Statins have been used with bile-acid binding resins and with ezetimibe; they have also been given with fibrates or nicotinic acid, although the increased risk of adverse effects needs to be considered. Cholesterol synthesis in the liver peaks during the early morning (midnight to 3 a.m.) and there is some evidence that statins with short half-lives, such as simvastatin, should be taken in the evening.[5]

Statins have a number of additional (pleiotropic) actions,[1-4,6,7] although whether these contribute to their cardiovascular effects is controversial.[8] In *atherosclerosis* they have beneficial effects on endothelial function, which may be partly independent of their effect on lipids, and also appear to stabilise atherosclerotic plaques. A number of studies[9,10] have also shown that statins reduce concentrations of C-reactive protein (CRP), a marker of inflammation that is raised in atherosclerosis, and there is some evidence that the reduction in CRP is independently associated with a reduction in cardiovascular events[11] and regression of atherosclerotic lesions,[12] although results have been mixed in a related condition, calcific aortic stenosis.[13] Statins have a number of actions that may be beneficial in *heart failure*,[14] but detrimental effects are also possible and their role specifically for heart failure is unclear.[15] Evidence from cohort studies[16-18] suggests statins may improve mortality in heart failure, and analyses of cardiovascular risk reduction studies[19,20] also suggest benefit. However, a randomised study[21] of rosuvastatin in patients with heart failure of ischaemic origin failed to show an effect on mortality, although there were fewer hospitalisations in patients given the active drug. Statins may also have *antihypertensive*[22] and *antiarrhythmic* effects; they reduce the incidence of atrial fibrillation,[23] and have also been associated with a reduced risk of ventricular arrhythmias,[24,25] although this requires confirmation. Beneficial effects have also been reported on some measures of *haemostasis*,[26] and a reduced incidence of venous thromboembolism has been noted in some studies.[27]

Statins also appear to have anti-inflammatory and immunomodulatory actions and these may contribute to their beneficial effects. There is evidence from epidemiological studies that they reduce the risk of bacterial infections, although this has been attributed to a 'healthy-user' effect,[28,29] and they may also reduce mortality in patients with sepsis.[29] Benefit has also been reported in *rheumatoid arthritis* and other inflammatory arthropathies.[30-33] In patients with *organ transplantation*, both cardiovascular and immunomodulatory actions may be of benefit (see below). However, the use of statins in these diseases remains to be confirmed.

For discussion of the use of statins in other non-cardiovascular disorders, including dementia, kidney disorders, malignant neoplasms, and osteoporosis, see below.

1. Maron DJ, *et al.* Current perspectives on statins. *Circulation* 2000; **101:** 207–13.
2. Shepherd J. The statin era: in search of the ideal lipid regulating agent. *Heart* 2001; **85:** 259–64.
3. Chong PH, *et al.* Clinically relevant differences between the statins: implications for therapeutic selection. *Am J Med* 2001; **111:** 390–400.
4. Igel M, *et al.* Pharmacology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), including rosuvastatin and pitavastatin. *J Clin Pharmacol* 2002; **42:** 835–45.
5. Plakogiannis R, Cohen H. Optimal low-density lipoprotein cholesterol lowering—morning versus evening statin administration. *Ann Pharmacother* 2007; **41:** 106–10.
6. Sotiriou CG, Cheng JWM. Beneficial effects of statins in coronary artery disease—beyond lowering cholesterol. *Ann Pharmacother* 2000; **34:** 1432–9.
7. Balk EM, *et al.* Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann Intern Med* 2003; **139:** 670–82.
8. Robinson JG, *et al.* Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005; **46:** 1855–62.
9. Ridker PM, *et al.* Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; **344:** 1959–65.
10. Albert MA, *et al.* Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286:** 64–70.
11. Ridker PM, *et al.* Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; **352:** 20–8.
12. Nissen SE, *et al.* Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005; **352:** 29–38.
13. Chua D, Kalb K. Statins and progression of calcified aortic stenosis. *Ann Pharmacother* 2006; **40:** 2195–9.
14. Laufs U, *et al.* HMG-CoA reductase inhibitors in chronic heart failure: potential mechanisms of benefit and risk. *Drugs* 2006; **66:** 145–54.
15. van der Harst P, *et al.* Statins in the treatment of chronic heart failure: a systematic review. *PLoS Med* 2006; **3:** e333.
16. Horwich TB, *et al.* Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol* 2004; **43:** 642–8.
17. Foody JM, *et al.* Statins and mortality among elderly patients hospitalized with heart failure. *Circulation* 2006; **113:** 1086–92.
18. Go AS, *et al.* Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006; **296:** 2105–11.
19. Scirica BM, *et al.* PROVE IT-TIMI 22 Investigators. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 2006; **47:** 2326–31.
20. Khush KK, *et al.* Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. *Circulation* 2007; **115:** 576–83.
21. Kjekshus J, *et al.* CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357:** 2248–61.
22. Strazzullo P, *et al.* Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hypertension* 2007; **49:** 792–8.
23. Patel AA, *et al.* The relationship between statin use and atrial fibrillation. *Curr Med Res Opin* 2007; **23:** 1177–85.

24. Mitchell LB, *et al.* Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Am Coll Cardiol* 2003; **42:** 81–7.
25. Vyas AK, *et al.* Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006; **47:** 769–73.
26. Krysiak R, *et al.* Effects of HMG-CoA reductase inhibitors on coagulation and fibrinolysis processes. *Drugs* 2003; **63:** 1821–54.
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Administration in children. The management of hyperlipidaemias in children and adolescents is controversial and is usually reserved for those with familial hyperlipidaemias who have a high risk of premature cardiovascular disease. Dietary measures and bile-acid binding resins have traditionally been first-line therapy in children, but may be poorly tolerated or inadequate. Studies with statins in children aged 8 to 18 years with familial hypercholesterolaemia have shown[1,2] that they effectively lower total cholesterol and low-density lipoprotein (LDL)-cholesterol and they are now increasingly preferred where drug therapy is indicated.[3,4] However, there have been concerns about the potential adverse effects of statins on growth and sexual development, since these patients require life-long treatment. Although this does not appear to be a problem, most studies have been relatively short-term, and longer follow-up is needed to confirm statin safety.[3,4] Preliminary evidence suggests that statins may also be effective in children with hyperlipidaemia related to nephrotic syndrome[5] or organ transplantation.[3,4]

US licensed product information for simvastatin allows its use in children aged 10 to 17 years with familial heterozygous hypercholesterolaemia in an initial oral dose of 10 mg at night, increased at intervals of 4 weeks as required to a maximum dose of 40 mg daily. A placebo-controlled study[6] in 173 such children found that simvastatin given orally in a dose of up to 40 mg daily for 48 weeks effectively reduced LDL-cholesterol and was well tolerated, with no effect on growth or sexual development.

The *BNFC* recommends the following doses for children with hyperlipidaemia:

- age 5 to 10 years: initial dose 5 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg at night
- age 10 to 18 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 40 mg at night

Doses should be reduced in children who are taking drugs that may interact with simvastatin (see Interactions, above).

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4. Belay B, *et al.* The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics* 2007; **119:** 370–80.
5. Prescott WA, *et al.* The potential role of HMG-CoA reductase inhibitors in pediatric nephrotic syndrome. *Ann Pharmacother* 2004; **38:** 2105–14.
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Administration in renal impairment. Statins appear to be safe and effective in patients with dyslipidaemia and renal impairment, and there is some evidence that they may have beneficial effects on renal function (see Kidney Disorders, below). However, patients with severe renal impairment may be at increased risk of developing myopathy or rhabdomyolysis and lower doses may be appropriate in such patients. Dose reduction may also be needed for statins that are excreted by the kidneys.

Simvastatin does not undergo significant renal excretion and no dose modification is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment the recommended initial dose is 5 mg once daily and doses above 10 mg once daily should be used with caution.

Cardiovascular risk reduction. Lipid regulating drugs have an important role in cardiovascular risk reduction (p.1164), and statins are widely used for both primary and secondary prevention. The rationale for their use has been the established link between hypercholesterolaemia and atherosclerosis, but they may have additional actions that contribute to their effect (see Action, above). The efficacy of statins in reducing cardiovascular events has been established in a wide range of patient groups and is generally believed to be a class effect, although outcome studies have not been performed for all the statins in every case.

In patients with established ischaemic heart disease, statins reduce the risk of further cardiovascular events, and also reduce both cardiovascular and overall mortality.[1] Statins shown to be effective for secondary prevention in large, randomised studies include simvastatin,[2] pravastatin,[3,4] and fluvastatin.[5,6] For primary prevention in patients at high risk but without prior cardiovascular events, statins similarly reduce the risk of cardiovascular events, although an effect on mortality has not been shown.[7] Benefit has been established in studies using pravastatin,[8,9] lovastatin,[10] simvastatin,[11] and atorvastatin;[12] the negative results of the ALLHAT-LLT study[13] with pravastatin were attributed to the substantial use of statins in the control group.

Although the main benefit of statins is to reduce mortality and major coronary events, there may also be a reduction in the incidence[14-17] and severity[18] of stroke (although there may be an increase in haemorrhagic stroke[16]), and the incidence of peripheral vascular disease;[19] some studies have also shown a reduction in coronary[19,20] and peripheral[19,21] ischaemic symptoms. Observational studies have suggested that statins may also reduce postoperative mortality in patients with high cardiovascular risk undergoing surgery, although this remains to be confirmed,[22] and there is some evidence that statins may reduce the risk of myocardial damage in patients undergoing percutaneous interventions,[23] although they have not been shown to affect restenosis.[24,25] Early use of statins may also have a role in patients with acute coronary syndromes; one meta-analysis[26] found no evidence of benefit at 1 or 4 months after the initial event, but another[27] reported a reduction in cardiovascular events with statin therapy for 6 months or longer, and some studies[28] have suggested earlier benefit with high-dose regimens.

The main effect of statins appears to relate to their action on lipid concentrations, and increased benefit has been reported[29] with the use of intensive lipid lowering regimens, including a reduction in mortality in patients with acute coronary syndromes.[30] However, studies have shown that statins improve outcomes in patients with both raised[8,26] and average[3,4,10,12] cholesterol concentrations, and meta-analyses[31,32] have concluded that the absolute benefit of statin treatment depends on both the initial cardiovascular risk and the degree of cholesterol reduction achieved. Most benefit has been reported in patients at the highest risk; subgroups in whom particular benefit has been reported include patients with metabolic syndrome compared with those without,[33] and diabetics compared with non-diabetics,[34] although a study[35] with atorvastatin in diabetics undergoing haemodialysis found no benefit. Early studies included mainly middle-aged men, but later studies[11] and meta-analyses[9,31] have confirmed that statins also improve outcomes in women and in the elderly. Observational studies[36,37] have confirmed that these benefits extend to the clinical situation.

Statins differ in potency,[38-40] but evidence that they differ in efficacy for cardiovascular risk reduction when given at comparable lipid-lowering doses is limited.[41] Patients who do not achieve target lipid concentrations or who experience adverse effects with one statin may find an alternative statin effective and tolerable, although recurrence of myalgia is not uncommon.[42]

1. Wilt TJ, *et al.* Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med* 2004; **164:** 1427–36.
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Dementia. There is conflicting evidence on the link between statin use and dementia. Epidemiological studies have reported[1,2] that the prevalence of dementia (p.362) is lower in patients taking statins, although it has been suggested that this may be due to bias in prescribing.[3] (Prevalence may also be reduced in patients taking fibrates.[2]) Some longitudinal studies have reported[4,5] that statins also reduce the incidence of dementia, but others have found no evidence of a reduction in risk,[6-8] and it has been suggested[6] that inappropriate analysis may explain the positive results. Prospective, randomised trials are therefore needed to determine their role, if any, in the prevention of dementia.[3]

There is also some evidence that statins[9-11] and other lipid regulating drugs[11] may reduce the progression of cognitive decline in patients with dementia, although the effect has generally been small. However, negative effects on mental function have been reported with some statins (see under Adverse Effects, above) and their use in the management of dementia is not established.

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7. Zandi PP, *et al.* Cache County Study investigators. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* 2005; **62:** 217–24.
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Kidney disorders. Although proteinuria has been reported with statins (see Effects on the Kidney under Adverse Effects, above) there is also some evidence that statins modestly reduce the progression of proteinuria and loss of renal function.[1-4] However, further studies are required to confirm these effects.

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3. Agarwal R. Effects of statins on renal function. *Mayo Clin Proc* 2007; **82:** 1381–90.
4. Strippoli GFM, *et al.* Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ* 2008; **336:** 645–51.

Malignant neoplasms. Although studies in *animals* suggest[1] that statins could be carcinogenic, evidence for a detrimental effect in humans is limited, and some studies have suggested that statins may be protective. Low plasma-cholesterol concentrations have been associated with cancer, and an increased incidence of cancer was reported in a randomised study of pravastatin for cardiovascular risk reduction in elderly patients,[2] although this was attributed to chance. Conversely, several observational studies have reported[3-7] that statins reduce the incidence of cancer, although the effect has generally been small. A number of meta-analyses have been performed and have generally found no association between the use of statins and the incidence of cancer. Analyses including only randomised studies[8,9] have found no significant effect on overall risk, although follow-up may not have been long enough in most studies to be conclusive; there is also little evidence of a protective effect for specific cancers.[10-12] However, another large cohort study[13] in elderly patients found no evidence that statins either increased or reduced the risk, and longer follow-up in a randomised study[14] using simvastatin also found no significant effect.

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8. Dale KM, *et al.* Statins and cancer risk: a meta-analysis. *JAMA* 2006; **295:** 74–80.
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10. Bonovas S, *et al.* Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005; **23:** 8606–12.
11. Bonovas S, *et al.* Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007; **25:** 3462–8.
12. Bonovas S, *et al.* Use of statins and risk of haematological malignancies: a meta-analysis of six randomized clinical trials and eight observational studies. *Br J Clin Pharmacol* 2007; **64:** 255–62.
13. Setoguchi S, *et al.* Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007; **115:** 27–33.
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Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] A meta-analysis of patients who had undergone heart transplantation (p.1812) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[2] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p.1815),[3] although prospective controlled studies are lacking.

1. Paraskevas KI. Applications of statins in cardiothoracic surgery: more than just lipid-lowering. *Eur J Cardiothorac Surg* 2008; **33:** 377–90.
2. Mehra MR, Raval NY. Metaanalysis of statins and survival in de novo cardiac transplantation. *Transplant Proc* 2004; **36:** 1539–41.
3. Johnson BA, *et al.* Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003; **167:** 1271–8.

Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4-6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p.1084).

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9. Bauer DC, *et al.* Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 2004; **164:** 146–52.
10. Reid IR, *et al.* Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. *Lancet* 2001; **357:** 509–12.
11. Pedersen TR, Kjekshus J. 4S Study Group. Statin drugs and the risk of fracture. *JAMA* 2000; **284:** 1921–2.
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Preparations

BP 2008: Simvastatin Tablets;
USP 31: Simvastatin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Coledis†; Colesterminol; Dosavastatin; Gemistatin; Klonastin; Labistatin; Lipimibe; Lisac; Nivelipol; Nosterol; Redusterol; Sevacol; Several; Tanavat; Vasotenal; Zocor; ***Austral.:*** Lipex; Ransim†; Simvabell; Simvahexal; Simvar; Zimstat; Zocor; ***Austria:*** Gerosim; Nyzoc; SimcorHexal†; Simstin†; Simvarcana; Simvastad; Simvatin; Zocord; ***Belg.:*** Cholemed; Docsimvasta; Simvafour; Simvastamed; Zocor; ***Braz.:*** Androlip†; Clinfar; Cordiron†; Lipotex; Liptrat; Lovacor†; Menocol; Mivalen; Revastin; Sinvalip; Sinvascor; Sinvastacor†; Sinvastamed; Sinvastin†; Sinvatrox; Sinvax; Sinvaz†; Sivastin†; Vaslip; Vastatil; Zocor; ***Canad.:*** Zocor; ***Chile:*** Arterosan†; Nimicor; Simvass; Vasomed; Vasotenal; Zocor; ***Cz.:*** Apo-Simva; Corsim; Egilipid; Sim; Simbela; Simgal; Simirex; Simva; Simvacard; Simvax; Simvor; Vasilip; Zocor; ***Denm.:*** Perichol; Zocolip; Zocor; ***Fin.:*** Corolin†; Lipcut; Zocor; ***Fr.:*** Lodales; Zocor; ***Ger.:*** BeL; Denan†; Simva; SimvaAPS; Simvabeta; Simvacard; Simvacor; Simvadoc; Simvadura; Simvagamma; Simvalip; Zemox†; Zocor; ***Gr.:*** Antichol; Arstatin; Avatratin; Bevostatin; Christatin; Doctiverine; Extrastatin; Glipal; Goldastatin; Iamastatin; Ipramid; Kymazol; Lepur; Lip-Down; Lipomin; Lipopress; Liporex; Lipozid; Lowcholid; Lusimva; Medistatin; Nitastin; Normotherin; Placol; Prelon; Priacin; Prizelip; Raptor; Ravostan; Redusterol; Simplaqor; Simvachol†; Simvacor; Simvalark; Simvalid; Simvaprol; Simvatin; Sivinar; Sotovastin; Starezin; Stasiva; Statinal; Statinum; Stativer; Statosan; Stazor; Sterylip; Vassor; Vastatin; Velkastatin; Zocor; Zurocid; ***Hong Kong:*** Avastinee; Corstat; Covastin; Qualicor; Simcard; Simtin; Vasilip; Vidastat; Zocor; ***Hung.:*** Awestatin; Sicor; Simvacol; Simvagamma; Simvep; Simvor; Vasilip; Zocor; ***India:*** Biosim†; Simcard; Simchol; Simlo; Simvotin; ***Indon.:*** Cholestat; Detrovel; Esvat; Ethicol; Lipinorm; Mersivas; Normofat; Pontizoc; Rechol; Rendapid; Simbado; Simchol; Simcor; Sinova; Valemia; Vazim; Vidastat; Zocor; Zovast; ***Irl.:*** Ritechol; Simator; Simtan; Simzor; Sivatin; Zocor; ***Israel:*** Simovil; Simvacor; Simvaxon; ***Ital.:*** Liponorm; Medipo; Sinvacor; Sivastin; Zocor; ***Malaysia:*** Covastin; Simcard; Simtin; Simvacor; Simvor; Stavid; Vascor; Zocor; ***Mex.:*** Apomastina; Colesken; Fansia; Imbistad; Josken†; Pulsar-AT Dual; Simplaqor; Tulip; Zeid; Zocor; Zorced; ***Neth.:*** Altercor†; Simva†; Zocor; ***Norw.:*** Zocor; ***NZ:*** Lipex; Sim-Statin; ***Philipp.:*** Cholestad; Eurocor; Euvasten; Forcad; Ivast; Lipivas; Normastin; Orovas; Simtin; Simvahex; Uni-Per; Vastilan; Vidastat; Wilsim; Zivas; Zocor; Zolvastin; Zovast; ***Pol.:*** Cardin; Simgal; Simratio; Simredin; Simvacard; Simvachol; Simvacor; Simvahexal; Simvasterol; Vasilip; Vastan; Ximve; Zocor; ***Port.:*** Colvastina; Dislipina; Jabastatina; Lipaz; Simvacol; Simvasim; Sinpor; Sintar; Sinvastil; Sumaclina†; Tavitan; Vascorim; Zera; Zocor; ***Rus.:*** Actalipid (Акталипид); Aterostat (Атеростат); Simgal (Симгал); Simlo (Симло); Simvacard (Симвакард); Simvahexal (Симвагексал); Simvalimit (Симвалимит); Simvastol (Симвастол); Simvor (Симвор); Vasilip (Вазилип); Zocor (Зокор); Zorstat (Зорстат); Zovatin (Зоватин); ***S.Afr.:*** Lipidex; Simaspen; Simcard; Simvacor; Simvotin; Zocor; ***Singapore:*** Covastin; Ifistatin; Simtin; Simvacor; Simvor; Vascor†; Zocor; ***Spain:*** Arudel; Belmalip; Colemin; Glutasey; Histop; Lipociden; Pantok; Simvasten†; Simvastur†; Teylor; Zocor; ***Swed.:*** Zocord; ***Switz.:*** Adipur; Simcora; Simvasine; Simvast; Simvastin; Zocor; ***Thai.:*** Bestatin; Eucor; Lochol; Simvor; Torio; Vascor; Zimmex; Zocor; ***Turk.:*** Lipovas; Simvakol; Zocor; Zovatin; ***UAE:*** Simvast; ***UK:*** Simvador; Zocor; ***USA:*** Zocor; ***Venez.:*** Cynt; Hisplenil†; Kavelor; Rowestin†; Simplaqor; Sinvaz; Tavor; Tinasin; Vasotenal; Vastan; Zocor.

Multi-ingredient: ***Arg.:*** Alipas Duo; Labistatin Duo; Redusterol Duo; Vasotenal EZ; Vytorin; ***Austral.:*** Vytorin; ***Austria:*** Inegy; Vytorin; ***Braz.:*** Diocomb SI; Prevencor; Vytorin; Zetsim; ***Chile:*** Adacai; Vytorin; Zintrepid; ***Cz.:*** Inegy; ***Fr.:*** Inegy; ***Ger.:*** Inegy; ***Gr.:*** Inegy; Vytorin; ***Hong Kong:*** Vytorin; ***Hung.:*** Inegy; ***Indon.:*** Vytorin; ***Irl.:*** Inegy; ***Ital.:*** Inegy; Vytorin; ***Malaysia:*** Vytorin; ***Mex.:*** Amlidual; Vytorin; Zintrepid; ***Neth.:*** Inegy; Vytorin; ***Norw.:*** Inegy; ***NZ:*** Vytorin; ***Philipp.:*** Vytorin; ***Port.:*** Inegy; ***Singapore:*** Vytorin; ***Swed.:*** Zocord/ASA†; ***UK:*** Inegy; ***USA:*** Simcor; Vytorin; ***Venez.:*** Adacai; Vytorin; Zintrepid.

Sitaxentan Sodium *(rINNM)*

Natrii Sitaxentanum; Sitaxentán sódico; Sitaxentan Sodique; Sitaxsentan Sodium; TBC-11251 (sitaxentan or sitaxentan sodium). *N*-(4-Chloro-3-methyl-5-isoxazolyl)-2-{[4,5-(methylenedioxy)-*o*-tolyl]acetyl}-3-thiophenesulfonamide sodium.

Натрий Ситаксентан

$C_{18}H_{14}ClN_2NaO_6S_2 = 476.9.$

CAS — 184036-34-8 (sitaxentan); 210421-74-2 (sitaxentan sodium).

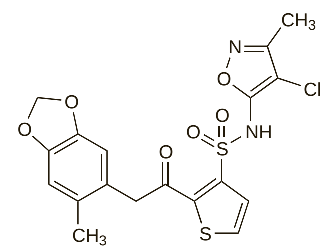

(sitaxentan)

Adverse Effects

As for Bosentan, p.1235. Increases in INR and prolongation of the prothrombin time have also been reported.

Sitaxentan is teratogenic in *rats.*

Precautions

As for Bosentan, p.1235. Sitaxentan is contra-indicated in patients with mild to severe hepatic impairment (Child-Pugh Class A to C).

Although, like bosentan, sitaxentan is teratogenic in *rats* and similar precautions apply, its effects on combined oral contraceptives may differ (see Interactions below).

Interactions

Sitaxentan is both an inhibitor of and a substrate for the cytochrome P450 isoenzyme CYP2C9 and interactions may therefore occur with other drugs that are either metabolised by, or inhibit, this isoenzyme. Plasma concentrations of oral anticoagulants such as warfarin may be increased.

Use with ciclosporin is contra-indicated as plasma concentrations of sitaxentan are greatly increased (see below).

Sitaxentan has increased exposure to ethinylestradiol and norethisterone in those taking oral contraceptives and may possibly increase the associated risk of thromboembolism.

Ciclosporin. Licensed product information for sitaxentan states that its concentration was increased sixfold when given with ciclosporin 3.5 mg/kg twice daily. Although the mechanism of action is unknown it has been postulated that sitaxentan sodium is a substrate for the organic anion transporting polypeptide (OATP) transporter protein and should therefore be used with caution with other, more potent, OATP inhibitors.

Pharmacokinetics

Sitaxentan sodium is absorbed after oral doses with peak plasma concentrations being achieved within 1 to 4 hours. Its absolute bioavailability is 70 to 100%. A high-fat meal delays the rate of absorption but does not affect the extent. Sitaxentan is more than 99% bound to plasma proteins, mainly albumin.

Sitaxentan is highly metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 to weakly active metabolites. About 50 to 60% of a dose is excreted in the urine with the remainder appearing in the faeces; less than 1% is excreted unchanged. Sitaxentan has a terminal elimination half-life of 10 hours and steady state is achieved within about 6 days.

Uses and Administration

Sitaxentan is an endothelin receptor antagonist (p.1155) with similar actions to bosentan (p.1235), although it has a higher selectivity for the endothelin ET_A-receptor. It is used in the management of pulmonary hypertension functional class III (p.1179). It is also being investigated in the management of heart failure.

In the treatment of pulmonary hypertension sitaxentan sodium is given orally in a dose of 100 mg once daily. Alternate therapy should be considered if there is no response after 12 weeks but a further 12 weeks of treatment may be tried.

◊ Reviews.

1. Wittbrodt ET, Abubakar A. Sitaxsentan for treatment of pulmonary hypertension. *Ann Pharmacother* 2007; **41:** 100–105.
2. Benedict NJ. Sitaxsentan in the management of pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2007; **64:** 363–8.
3. Scott LJ. Sitaxentan: in pulmonary arterial hypertension. *Drugs* 2007; **67:** 761–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Thelin; ***Cz.:*** Thelin; ***Fr.:*** Thelin; ***Port.:*** Thelin; ***UK:*** Thelin.

Sodium Apolate *(BAN, rINN)*

Apolate de Sodium; Apolato de sodio; Lyapolate Sodium *(USAN)*; Natrii Apolas; Natriumapolaatti; Natriumapolat; Sodium Lyapolate. Poly(sodium ethylenesulphonate).

Натрия Аполат

$(C_2H_3NaO_3S)_n$.

CAS — 25053-27-4.
ATC — C05BA02.
ATC Vet — QC05BA02.

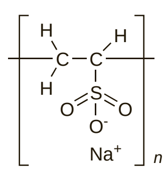

Profile

Sodium apolate is a synthetic heparinoid anticoagulant. It has been used in the topical treatment of haematomas and superficial thromboses and for the relief of sprains and contusions.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Arg.:* Pergalen.

Sodium Nitroprusside

Disodium (*OC*-6-22)-Pentakis(cyano-*C*)nitrosylferrate Dihydrate; Natrii nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprusszid-nátrium; Sodium Nitroferricyanide Dihydrate; Sodium Nitroprussiate; Sodium, nitroprussiate de; Sodu nitroprusydek; Sodyum Nitroprusid. Sodium nitrosylpentacyanoferrate(III) dihydrate.

$Na_2Fe(CN)_5NO,2H_2O = 297.9$.

CAS — 14402-89-2 (anhydrous sodium nitroprusside); 13755-38-9 (sodium nitroprusside dihydrate).
ATC — C02DD01.
ATC Vet — QC02DD01.

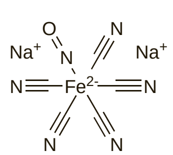

(anhydrous sodium nitroprusside)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Sodium Nitroprusside). Reddish-brown crystals or powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Sodium Nitroprusside). Reddish-brown, practically odourless crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Sodium nitroprusside has been reported to be visually incompatible with cisatracurium besilate[1] and with levofloxacin[2] during simulated Y-site administration.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability in solution. Solutions of sodium nitroprusside decompose when exposed to light and must be protected during infusion by wrapping the container with aluminium foil or some other light-proof material. Nitroprusside will react with minute quantities of organic and inorganic substances forming highly coloured products. If this occurs the solution should be discarded. Solutions should not be used more than 24 hours after preparation.

The instability of sodium nitroprusside solutions has been the subject of considerable investigation. Although stated to be more stable in acid than in alkaline solution,[1] a later study[2] found that whereas the initial light-induced darkening of a 1% solution was independent of pH, further degradation leading to the development of a blue precipitate required an acid pH. If protected from light by wrapping in aluminium foil, sodium nitroprusside 50 or 100 micrograms/mL was found to be stable in 5% glucose, lactated Ringer's, and normal saline solutions for 48 hours.[3] In clinical practice the infusion container should be opaque or protected with foil, but an amber giving set may be used, to allow visual monitoring.[4,5]

Various substances have been reported to increase the stability of nitroprusside solutions, including dimethyl sulfoxide,[6] glycerol,[1] sodium citrate,[1] and other salts with anionic chelating potential such as sodium acetate or phosphate.[1] In contrast sodium bisulfite and the hydroxybenzoates are reported to reduce stability.[1]

1. Schumacher GE. Sodium nitroprusside injection. *Am J Hosp Pharm* 1966; **23:** 532.
2. Hargrave RE. Degradation of solutions of sodium nitroprusside. *J Hosp Pharm* 1974; **32:** 188–91.
3. Mahony C, *et al.* In vitro stability of sodium nitroprusside solutions for intravenous administration. *J Pharm Sci* 1984; **73:** 838–9.
4. Davidson SW, Lyall D. Sodium nitroprusside stability in light-protective administration sets. *Pharm J* 1987; **239:** 599–601.
5. Lyall D. Sodium nitroprusside stability. *Pharm J* 1988; **240:** 5.
6. Asker AF, Gragg R. Dimethyl sulfoxide as a photoprotective agent for sodium nitroprusside solutions. *Drug Dev Ind Pharm* 1983; **9:** 837–48.

Adverse Effects

Sodium nitroprusside rapidly reduces blood pressure and is converted in the body to cyanide and then thiocyanate. Its adverse effects can be attributed mainly to excessive hypotension and excessive cyanide accumulation; thiocyanate toxicity may also occur, especially in patients with renal impairment. Intravenous infusion of sodium nitroprusside may produce nausea and vomiting, apprehension, headache, dizziness, restlessness, perspiration, palpitations, retrosternal discomfort, abdominal pain, and muscle twitching, but these effects may be reduced by slowing the infusion rate.

An excessive amount of cyanide in plasma (more than 80 nanograms/mL), because of overdosage or depletion of endogenous thiosulfate (which converts cyanide to thiocyanate *in vivo*), may result in tachycardia, sweating, hyperventilation, arrhythmias, and profound metabolic acidosis. Metabolic acidosis may be the first sign of cyanide toxicity. Methaemoglobinaemia may also occur.

Adverse effects attributed to thiocyanate include tinnitus, miosis, and hyperreflexia; confusion, hallucinations, and convulsions have also been reported.

Other adverse effects include thrombocytopenia and phlebitis.

Effects on the blood. *THROMBOCYTOPENIA.* Platelet counts decreased in 7 of 8 patients with heart failure 1 to 6 hours after intravenous infusion of nitroprusside was started.[1] The counts began to return to normal 24 hours after the infusion was stopped.

1. Mehta P, *et al.* Nitroprusside lowers platelet count. *N Engl J Med* 1978; **299:** 1134.

Effects on the gastrointestinal tract. Five out of 38 patients who were given sodium nitroprusside intravenously for controlled hypotension during surgery developed symptoms of adynamic ileus postoperatively.[1] The symptoms could have been secondary to intestinal ischaemia due to diminished mesenteric arterial blood flow. However, other explanations have been proposed including sympathetic stimulation[2,3] or the concomitant use of opioid analgesics.[4]

1. Chen JW, *et al.* Adynamic ileus following induced hypotension. *JAMA* 1985; **253:** 633.
2. Gelman S. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
3. Lampert BA. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
4. Lemmo J, Karnes J. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.

Effects on intracranial pressure. A significant increase in intracranial pressure while the mean blood pressure was 80 or 90% of initial values was reported[1] in 14 normocapnic patients given an infusion of sodium nitroprusside to produce controlled hypotension prior to neurosurgery; values reverted towards normal at mean blood pressures of 70% of controls. A similar but insignificant trend occurred in 5 hypocapnic patients. In another report[2] a rise in intracranial pressure was noted after the use of nitroprusside in a patient with Reye's syndrome.

1. Turner JM, *et al.* Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 1977; **49:** 419–24.
2. Griswold WR, *et al.* Nitroprusside-induced intracranial hypertension. *JAMA* 1981; **246:** 2679–80.

Phlebitis. Acute transient phlebitis has occurred after infusion of sodium nitroprusside.[1]

1. Miller R, Stark DCC. Acute phlebitis from nitroprusside. *Anesthesiology* 1978; **49:** 372.

Treatment of Adverse Effects

Adverse effects due to excessive hypotension may be treated by slowing or stopping the infusion.

For details of the treatment of cyanide poisoning see Hydrocyanic Acid, p.2045. Thiocyanate can be removed by dialysis.

Precautions

Sodium nitroprusside should not be used in the presence of compensatory hypertension (for example, in arteriovenous shunts or coarctation of the aorta). It should be used with caution, if at all, in patients with hepatic impairment, and in patients with low plasma-cobalamin concentrations or Leber's optic atrophy. It should also be used with caution in patients with impaired renal or pulmonary function and with particular caution in patients with impaired cerebrovascular circulation. Thiocyanate, a metabolite of sodium nitroprusside, inhibits iodine binding and uptake and sodium nitroprusside should be used with caution in patients with hypothyroidism. The blood-thiocyanate concentration should be monitored if treatment continues for more than 3 days and should not exceed 100 micrograms/mL although toxicity may be apparent at lower thiocyanate concentrations. Thiocyanate concentrations do not reflect cyanide toxicity and cyanide concentrations should also be monitored; the blood concentration of cyanide should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. The acid–base balance should also be monitored. Care should be taken to ensure that extravasation does not occur. Sodium nitroprusside should not be withdrawn abruptly due to the risk of rebound effects.

Aortic stenosis. Vasodilators such as sodium nitroprusside are usually contra-indicated in conditions where cardiac outflow is obstructed since cardiac output cannot increase to compensate for the fall in blood pressure. However, a study[1] in patients with aortic stenosis and severe left ventricular dysfunction found that sodium nitroprusside was well tolerated and that it rapidly and markedly improved cardiac function.

1. Khot UN, *et al.* Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003; **348:** 1756–63.

Pregnancy. Although there are concerns that nitroprusside given to the mother might produce cyanide toxicity in the fetus, a systematic review[1] was unable to find sufficient evidence to determine the risk.

1. Sass N, *et al.* Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007; **125:** 108–11.

Tachyphylaxis. Tachyphylaxis to sodium nitroprusside was associated with high plasma concentrations of cyanide without metabolic acidosis in 3 patients undergoing hypotensive anaesthesia.[1]

1. Cottrell JE, *et al.* Nitroprusside tachyphylaxis without acidosis. *Anesthesiology* 1978; **49:** 141–2.

Withdrawal. Rebound haemodynamic changes, including hypertension and increased heart rate, occurred 10 to 30 minutes after stopping intravenous sodium nitroprusside infusion in 20 patients with heart failure.[1] The changes generally resolved spontaneously within 1 to 3 hours and produced only minimal exacerbation of symptoms in most patients, although 3 developed pulmonary oedema 20 to 30 minutes after stopping the infusion, needing restarting of nitroprusside in 2 cases. A study[2] investigating a possible mechanism for this effect found that plasma-renin concentrations were increased during infusion of nitroprusside and remained elevated for 30 minutes after the infusion was stopped. It was suggested that this persistence of elevated plasma-renin concentrations after clearance of short-lived nitroprusside may be responsible for the rebound effects.

1. Packer M, *et al.* Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. *N Engl J Med* 1979; **301:** 1193–7.
2. Cottrell JE, *et al.* Rebound hypertension after sodium nitroprusside-induced hypotension. *Clin Pharmacol Ther* 1980; **27:** 32–6.

Interactions

Enhanced hypotension should be expected if sodium nitroprusside is used with other antihypertensives or drugs that produce hypotension.

Alteplase. Sodium nitroprusside infusion prolonged the fibrinolytic activity of alteplase when given to *animals*; use of nitrovasodilators with alteplase may be responsible for the enhanced bleeding tendency seen in some patients on thrombolytic therapy.[1]

1. Korbut R, *et al.* Prolongation of fibrinolytic activity of tissue plasminogen activator by nitrovasodilators. *Lancet* 1990; **335:** 669.

Pharmacokinetics

Sodium nitroprusside is rapidly metabolised to cyanide in erythrocytes and smooth muscle and, *in vivo*, this is followed by the release of nitric oxide, the active metabolite. Cyanide is further metabolised in the liver to thiocyanate, which is slowly excreted in the urine; this metabolism is mediated by the enzyme rhodanase and requires the presence of thiosulfate. The plasma half-life of thiocyanate is reported to be about 3 days, but may be much longer in patients with renal impairment.

◊ Reviews.

1. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* 1984; **9:** 239–51.

Uses and Administration

Sodium nitroprusside is a short-acting hypotensive drug with a duration of action of 1 to 10 minutes. It produces peripheral vasodilatation and reduces peripheral resistance by a direct action on both veins and arterioles. It has been termed a nitrovasodilator because it releases nitric oxide *in vivo*. Its effects appear within a few seconds of intravenous infusion. Sodium nitroprusside is used in the treatment of hypertensive crises (p.1171) and to produce controlled hypotension during general anaesthesia. It has also been used to reduce preload and afterload in severe heart failure (p.1165) including that associated with myocardial infarction (p.1175).

It is given by continuous intravenous infusion of a solution containing 50 to 200 micrograms/mL. A controlled infusion device must be used. The solution should be prepared immediately before use by dissolving sodium nitroprusside in glucose 5% and then diluting with glucose 5%; the solution must be protected from light during infusion. Blood pressure should be monitored closely and care should be taken to prevent extravasation. In general, treatment should not continue for more than 72 hours. If required for several days concentrations of cyanide should be monitored; the blood concentration should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. Thiocyanate concentrations in blood should also be measured if infusion continues for more than 72 hours and should not exceed 100 micrograms/mL. Since rebound hypertension has been reported when sodium nitroprusside is withdrawn, the infusion should be tailed off gradually over 10 to 30 minutes.

For **hypertensive crises** in patients not receiving antihypertensive drugs, an initial dose of 0.3 to 1.5 micrograms/kg per minute may be given, increasing gradually under close supervision until the desired reduction in blood pressure is achieved. The average dose required to maintain the blood pressure 30 to 40% below the pretreatment diastolic blood pressure is 3 micrograms/kg per minute and the usual dose range is 0.5 to 6 micrograms/kg per minute. Lower doses should be used in patients already receiving other antihypertensives. The maximum recommended rate is about 8 micrograms/kg per minute in the UK, and 10 micrograms/kg per minute in the USA; infusions at these rates should be used for no longer than 10 minutes and should be stopped after 10 minutes if there is no response. If there is a response, sodium nitroprusside should ideally be given for only a few hours to avoid the risk of cyanide toxicity. Treatment with an oral antihypertensive should be introduced as soon as possible.

For the **induction of hypotension** during anaesthesia a maximum dose of 1.5 micrograms/kg per minute is recommended.

In **heart failure** an initial dose of 10 to 15 micrograms/minute has been used, increasing by 10 to 15 micrograms/minute every 5 to 10 minutes according to response. The usual dosage range is 10 to 200 micrograms/minute and the dose should not exceed 280 micrograms/minute (or 4 micrograms/kg per minute).

Sodium nitroprusside has also been used as a reagent for detecting ketones in urine.

Administration in children. Although experience is more limited than with adults, sodium nitroprusside has been successfully used in infants and children. Continuous infusion of nitroprusside at a rate of 2 to 4 micrograms/kg per minute for 28 days was reported[1] in an 11-year-old child with refractory hypertension, without any signs of thiocyanate toxicity. In a series of 58 neonates with cardiovascular disorders or respiratory distress syndrome,[2] sodium nitroprusside was given in a usual initial dose of 250 to 500 nanograms/kg per minute, and the rate was then repeatedly doubled at intervals of 15 to 20 minutes until the desired effect was achieved, adverse effects supervened, or it was judged ineffective. The maximum rate did not exceed 6 micrograms/kg per minute. Infusion of sodium nitroprusside in doses of 0.5 to 8 micrograms/kg per minute to produce controlled reduction of blood pressure has also been reported[3] in 28 children with hypertensive crises; 16 had also received labetalol.[3]

1. Luderer JR, *et al.* Long-term administration of sodium nitroprusside in childhood. *J Pediatr* 1977; **91:** 490–1.
2. Benitz WE, *et al.* Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr* 1985; **106:** 102–10.
3. Deal JE, *et al.* Management of hypertensive emergencies. *Arch Dis Child* 1992; **67:** 1089–92.

Ergotamine poisoning. For the use of sodium nitroprusside in the treatment of cyanosis of the extremities due to ergotamine overdosage, see Cardiovascular Effects, p.620.

Preparations

BP 2008: Sodium Nitroprusside Intravenous Infusion;
USP 31: Sodium Nitroprusside for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Doketrol; Niprusodio; Nitroprus; ***Braz.:*** Nipride; Nitropresabbott; Nitroprus; ***Canad.:*** Nipride; ***Cz.:*** Nipruss; ***Fr.:*** Nitriate; ***Ger.:*** Nipruss; ***Gr.:*** Nitriate; ***India:*** Sonide; ***Irl.:*** Nipride†; ***Israel:*** Nipruss; ***Jpn:*** Nitopro; ***Mex.:*** Nitan†; ***Rus.:*** Naniprus (Нанипрус); ***S.Afr.:*** Hypoten; SNP; ***Spain:*** Nitroprussiat; ***Turk.:*** Nipruss; ***USA:*** Nitropress.

Sotalol Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de sotalol; MJ-1999; Sotalol, chlorhydrate de; Sotalol Hidroklorür; *d,l*-Sotalol Hydrochloride; Sotalol-hydrochlorid; Sotalolhydroklorid; Sotaloli hydrochloridum; Sotalolihydrokloridi; Sotalolio hidrochloridas; Szotalol-hidroklorid. 4′-(1-Hydroxy-2-isopropylaminoethyl)methanesulphonanilide hydrochloride.

Соталола Гидрохлорид

$C_{12}H_{20}N_2O_3S,HCl$ = 308.8.

CAS — 3930-20-9 (sotalol); 959-24-0 (sotalol hydrochloride).

ATC — C07AA07.

ATC Vet — QC07AA07.

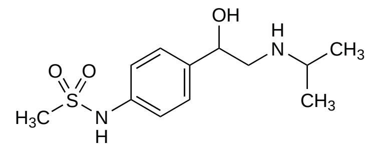

(sotalol)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Sotalol Hydrochloride). A white or almost white powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Sotalol Hydrochloride). A white to off-white powder. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform.

Stability. Suspensions of sotalol hydrochloride 5 mg/mL made using either commercially available or extemporaneously prepared vehicles were found[1] to be stable for up to 3 months when stored at 4° or 25°. Prolonged storage at 25° was not recommended, however, because of the risk of microbial growth.

1. Nahata MC, Morosco RS. Stability of sotalol in two liquid formulations at two temperatures. *Ann Pharmacother* 2003; **37:** 506–9.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Torsade de pointes has been reported in patients given sotalol, usually due to prolongation of the QT interval. The QT interval should be monitored: extreme caution is required if the QT interval exceeds 500 milliseconds and sotalol should be stopped or the dose reduced if the QT interval exceeds 550 milliseconds. As hypokalaemia or hypomagnesaemia may predispose patients to arrhythmias, serum-electrolyte concentrations should be monitored before and during treatment with sotalol.

Sotalol should be used with caution in renal impairment (see under Uses and Administration, below) and is contra-indicated in patients whose creatinine clearance is less than 10 mL/minute.

Breast feeding. Sotalol is distributed into breast milk and milk to serum ratios have been reported[1-3] to range from 2.2 to 8.8. In one report[2] it was calculated that a breast-fed infant might ingest 20 to 23% of a maternal dose; however, no bradycardia was noted in the infant in this study. The American Academy of Pediatrics states[4] that there have been no reports of clinical effects in breast-fed infants whose mothers were receiving sotalol and that therefore it may be considered to be usually compatible with breast feeding.

1. O'Hare MF, *et al.* Sotalol as a hypotensive agent in pregnancy. *Br J Obstet Gynaecol* 1980; **87:** 814–20.
2. Hackett LP, *et al.* Excretion of sotalol in breast milk. *Br J Clin Pharmacol* 1990; **29:** 277–8.
3. Wagner X, *et al.* Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Interactions

There is an increased risk of precipitating ventricular arrhythmias if sotalol is given with other drugs that prolong the QT interval, and use with the following drugs is therefore not recommended: class Ia antiarrhythmics (including disopyramide, procainamide, and quinidine), amiodarone, phenothiazine antipsychotics, tricyclic antidepressants, certain antihistamines (astemizole or terfenadine), cisapride, erythromycin, halofantrine, pentamidine, quinolones, sultopride, and vincamine. Caution is required if sotalol is given with drugs that cause electrolyte disturbances, such as diuretics, since this also increases the risk of arrhythmias.

Other interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Sotalol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are obtained about 2 to 4 hours after a dose. The plasma elimination half-life is about 10 to 20 hours. Sotalol has low lipid solubility. Very little is metabolised and it is excreted unchanged in the urine. Binding to plasma proteins is reported to be low. It crosses the placenta and is distributed into breast milk; concentrations in milk may be higher than those in maternal serum (see Breast Feeding, above). Only small amounts are reported to cross the blood-brain barrier and enter the CSF. Sotalol is removed by dialysis.

◊ General references.

1. Singh BN, *et al*. Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs* 1987; **34:** 311–49.
2. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; **46:** 678–719.

Pregnancy. The systemic clearance of sotalol in 6 healthy women after an intravenous dose was significantly higher during pregnancy than in the postnatal period, and the mean elimination half-life was shorter (6.6 versus 9.3 hours), although the latter difference was not significant.[1] Clearance after an oral dose was also higher during pregnancy than afterwards, but half-lives (10.9 versus 10.3 hours) and mean bioavailability were similar. The changes were probably due to alterations in renal function in the antenatal period.

In a study[2] of transplacental therapy, sotalol was found to cross the placenta easily and completely, with steady-state plasma concentrations similar in mother and fetus. Sotalol accumulated in the amniotic fluid but not in the fetus; it was not associated with fetal growth restriction.

1. O'Hare MF, *et al*. Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 521–4.
2. Oudijk MA, *et al*. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; **42:** 765–70.

Uses and Administration

Sotalol is a non-cardioselective beta blocker (p.1225). It is reported to lack both intrinsic sympathomimetic and membrane-stabilising properties. In addition to the class II antiarrhythmic activity of beta blockers, sotalol lengthens the duration of the action potential resulting in class III antiarrhythmic activity. For a classification and explanation of antiarrhythmic activity, see p.1153.

Sotalol is used in the management of ventricular and supraventricular arrhythmias (p.1160). Because of its proarrhythmic effects, it is usually reserved for severe or life-threatening arrhythmias, and it should not be used in patients with asymptomatic ventricular arrhythmias. Although it was formerly used for its beta-blocking effects in the management of angina pectoris, hypertension, and myocardial infarction, it is no longer recommended for these indications because of the risk of precipitating arrhythmias.

Sotalol is given as the hydrochloride. Treatment should be started in hospital with suitable monitoring facilities. The QT interval should be assessed before the start of treatment and whenever the dosage is adjusted (see Precautions above); plasma-electrolyte concentrations and renal function should also be monitored. The dose should be reduced in patients with renal impairment (see below).

The usual initial oral dose of sotalol hydrochloride is 80 mg daily, as a single dose or in two divided doses. The dosage is then individualised according to response, and doses are increased gradually allowing 2 or 3 days between increments. US licensed product information recommends a higher initial dose of 80 mg twice daily and this should not be increased for at least 3 days. Most patients respond to doses of 160 to 320 mg daily (usually given in two divided doses). Some patients with ventricular arrhythmias may require doses as high as 640 mg daily.

Sotalol may be given intravenously to control acute arrhythmias, to substitute for oral therapy, and for programmed electrical stimulation. To control acute arrhythmias, sotalol hydrochloride is given in a dose of 20 to 120 mg (500 to 1500 micrograms/kg) intravenously over 10 minutes. This dose may be repeated every 6 hours if necessary. To substitute for oral therapy an intravenous infusion of 200 to 500 micrograms/kg per hour may be used. The total daily dose should not exceed 640 mg. For programmed electrical stimulation (to test antiarrhythmic efficacy) an initial dose of 1.5 mg/kg is given over 10 to 20 minutes, followed by an intravenous infusion of 200 to 500 micrograms/kg per hour.

Sotalol is used as a racemic mixture; *d*-sotalol (dexsotalol; (+)-sotalol) has also been investigated as an antiarrhythmic but development was stopped when it was found to increase mortality (see Action, below).

◊ General references.

1. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; **46:** 678–719.
2. Nappi JM, McCollam PL. Sotalol: a breakthrough antiarrhythmic? *Ann Pharmacother* 1993; **27:** 1359–68.
3. Zanetti LAF. Sotalol: a new class III antiarrhythmic agent. *Clin Pharm* 1993; **12:** 883–91.
4. Hohnloser SH, Woosley RL. Sotalol. *N Engl J Med* 1994; **331:** 31–8.
5. Anderson JL, Prystowsky EN. Sotalol: an important new antiarrhythmic. *Am Heart J* 1999; **137:** 388–409.

Action. Sotalol is used as the racemic mixture of the two stereoisomers, *d*-sotalol (dexsotalol; (+)-sotalol) and *l*-sotalol ((–)-sotalol). A comparison of the effects of *d*-sotalol and racemic sotalol in 6 healthy subjects[1] showed that the beta-blocking activity resided almost entirely in the *l*-isomer, while the effects on the QT interval, which are consistent with type III antiarrhythmic activity, appear to be due to both isomers. A study in 8 healthy subjects also showed a lack of beta blockade by *d*-sotalol.[2] This would suggest that the electrophysiological effects of sotalol are unrelated to its beta-blocking properties. *d*-Sotalol has been investigated as an antiarrhythmic.[3] However, a preliminary placebo-controlled study in patients with myocardial infarction at high risk of arrhythmia due to impaired left ventricular function was terminated early when increased mortality was seen in the treatment group.[4,5]

1. Johnston GD, *et al*. A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol* 1985; **20:** 507–10.
2. Yasuda SU, *et al*. d-Sotalol reduces heart rate in vivo through a β-adrenergic receptor-independent mechanism. *Clin Pharmacol Ther* 1993; **53:** 436–42.
3. Advani SV, Singh BN. Pharmacodynamic, pharmacokinetic and antiarrhythmic properties of d-sotalol, the dextro-isomer of sotalol. *Drugs* 1995; **49:** 664–79.
4. Choo V. SWORD slashed. *Lancet* 1994; **344:** 1358.
5. Waldo AL, *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; **348:** 7–12. Correction. *ibid.*; 416.

Administration in children. Sotalol has been used to treat both ventricular and supraventricular arrhythmias in children aged from newborn to adolescent;[1-3] it appears to be effective and well-tolerated, although proarrhythmic effects may occur. Neonates may be more sensitive to the QT-prolonging effects of sotalol[3] and lower doses may be appropriate. In the UK, the *BNFC* recommends the following oral doses of sotalol hydrochloride:

- Neonates: initial dose 1 mg/kg twice daily, increased as necessary every 3 to 4 days to a maximum of 4 mg/kg twice daily
- Children aged 1 month to 12 years: initial dose 1 mg/kg twice daily, increased as necessary every 2 to 3 days to a maximum of 4 mg/kg twice daily (maximum total dose 80 mg twice daily)

Licensed product information in the USA recommends doses of sotalol hydrochloride based on body surface area. Children aged 2 years and over may be given an initial dose of 30 mg/m^2 three times daily, increased as necessary at intervals of at least 36 hours to a maximum of 60 mg/m^2 three times daily. For children under 2 years of age the dose should be further reduced, and nomograms are available providing age-specific recommendations.

In children with refractory supraventricular tachycardia, sotalol has been given with flecainide; in a study[4] in children aged under 1 year, doses used ranged from 100 to 250 mg/m^2 daily of sotalol and from 40 to 150 mg/m^2 daily of flecainide.

Sotalol has also been used transplacentally to treat fetal tachycardias, including atrial flutter and supraventricular tachycardia. It may be effective as second-line therapy in addition to digoxin,[5] and has also been used first-line.[6,7] However, one retrospective study[6] of 21 fetuses given sotalol transplacentally found that it was more effective in atrial flutter than in supraventricular tachycardia; mortality was also higher in fetuses with supraventricular tachycardia, and the authors therefore suggested that sotalol should only be used in resistant cases.

1. Çeliker A, *et al*. Sotalol in treatment of pediatric cardiac arrhythmias. *Pediatr Int* 2001; **43:** 624–30.
2. Beaufort-Krol GCM, Bink-Boelkens MTE. Effectiveness of sotalol for atrial flutter in children after surgery for congenital heart disease. *Am J Cardiol* 1997; **79:** 92–4.
3. Läer S, *et al.* Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol* 2005; **46:** 1322–30.
4. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39:** 517–20.
5. Sonesson S-E, *et al.* Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatr* 1998; **87:** 584–7.
6. Oudijk MA, *et al.* Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000; **101:** 2721–6.
7. Rebelo M, *et al.* Sotalol in the treatment of fetal tachyarrhythmia. *Rev Port Cardiol* 2006; **25:** 477–81.

Administration in renal impairment. Sotalol is excreted mainly unchanged by the kidneys and may accumulate in renal impairment. The usual daily dosage (see above) should therefore be reduced, either by decreasing the size of each dose, or by increasing the interval between doses. UK licensed product information for oral or intravenous sotalol recommends the following doses based on creatinine clearance (CC):

- CC 30 to 60 mL/minute: half usual dose
- CC 10 to 30 mL/minute: quarter usual dose
- CC less than 10 mL/minute: not recommended

Dosage recommendations in the USA depend on both the indication and CC, and incremental increases should not be made until 5 or 6 doses have been given. In the treatment of ventricular arrhythmias, licensed product information for oral sotalol recommends that in renal impairment doses should be given at the following intervals:

- CC 30 to 59 mL/minute: every 24 hours
- CC 10 to 29 mL/minute: every 36 to 48 hours
- CC less than 10 mL/minute: dosage should be individualised

For the treatment of atrial fibrillation, the same dosage intervals are recommended but sotalol is contra-indicated if CC is less than 40 mL/minute.

In a study of 10 hypertensive patients with varying degrees of renal impairment,[1] the apparent first-order elimination rate constant and plasma clearance of sotalol correlated with glomerular filtration rate. Another study[2] compared kinetics in patients with normal renal function, renal impairment, and renal failure. Elimination half-lives of 8.1 and 24.2 hours were reported in patients with CC above 39 mL/minute and between 8 and 38 mL/minute, respectively. It was suggested that an increase in the dosage interval to 48 or 72 hours may be necessary to compensate for longer half-lives. Caution is required when sotalol is used in patients on dialysis; a half-life of 33.9 hours was reported in patients with renal failure but this fell to 5.8 hours during dialysis which removed about 43% of sotalol.

1. Berglund G, *et al.* Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur J Clin Pharmacol* 1980; **18:** 321–6.
2. Blair AD, *et al.* Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther* 1981; **29:** 457–63.

Preparations

BP 2008: Sotalol Injection; Sotalol Tablets;
USP 31: Sotalol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Darob†; Sotacor; ***Austral.:*** Cardol; Solavert; Sotab†; Sotacor; Sotahexal; ***Austria:*** Darob; Sotacor; Sotahexal; Sotamed; Sotanorm; Sotastad; Ventricor†; ***Belg.:*** Sotalex; ***Braz.:*** Sotacor; ***Canad.:*** Sotacor†; ***Chile:*** Hipecor; ***Cz.:*** Darob†; Rentibloc†; Sotahexal; Sotalex; ***Denm.:*** Dutacor; Sotabet†; Sotacor; ***Fin.:*** Sotacor; Sotalin; ***Fr.:*** Sotalex; ***Ger.:*** CorSotalol†; Darob; Favorex; Gilucor; Jutalex; Rentibloc; Sota; Sota Lich; Sota-Puren; Sota-saar; Sotabeta; Sotagamma; Sotahexal; Sotalex; Sotalodoc; Sotaryt†; Sotastad; ***Hong Kong:*** Sotacor; ***Hung.:*** Sotahexal; Sotalex; ***Irl.:*** Sotacor; Sotoger; ***Israel:*** Sotacor†; ***Ital.:*** Rytmobeta; Sotalex; ***Jpn:*** Sotacor†; ***Malaysia:*** Sotacor; ***Mex.:*** Sotaper; ***Neth.:*** Sotacor; ***Norw.:*** Sotacor; ***NZ:*** Sotacor; Sotahexal; ***Philipp.:*** Sotalex; ***Pol.:*** Biosotal; Darob; Sotahexal; ***Port.:*** Darob; ***Rus.:*** Sotahexal (Сотагексал); Sotalex (Соталекс); ***S.Afr.:*** Sotacor; Sotahexal; ***Singapore:*** Sotacor; ***Spain:*** Sotapor; ***Swed.:*** Sotabet†; Sotacor; ***Switz.:*** Sotalex; ***Turk.:*** Darob; Sotarit; Talozin; ***UK:*** Beta-Cardone; Sotacor; ***USA:*** Betapace.

Multi-ingredient: *S.Afr.:* Sotazide.

Spirapril Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de espirapril; Sch-33844; Spiraprilihydrokloridi; Spirapril, chlorhydrate de; Spirapril-hydrochlorid; Spiraprilhydroklorid; Spiraprili hydrochloridum; Spiraprilio hidrochloridas; TI-211-950. (*S*)-7-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride.

Спираприла Гидрохлорид

$C_{22}H_{30}N_2O_5S_2$,HCl = 503.1.

CAS — 83647-97-6 (spirapril); 94841-17-5 (spirapril hydrochloride).

ATC — C09AA11.

ATC Vet — QC09AA11.

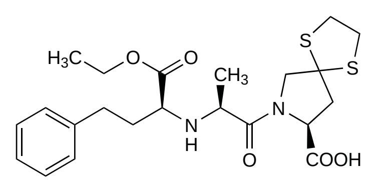

(spirapril)

Pharmacopoeias. *Eur.* includes the monohydrate.
Ph. Eur. 6.2 (Spirapril Hydrochloride Monohydrate). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in acetonitrile; practically insoluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Spirapril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171). It owes its activity to the diacid spiraprilat, to which it is converted after oral doses. It is given orally as the hydrochloride in a usual maintenance dose of 6 mg once daily.

◊ References.

1. Noble S, Sorkin EM. Spirapril: a preliminary review of its pharmacology and therapeutic efficacy in the treatment of hypertension. *Drugs* 1995; **49:** 750–66.
2. Widimský J, *et al.* Czech and Slovak spirapril intervention study (CASSIS): a randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur J Clin Pharmacol* 1995; **49:** 95–102.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Quadropril; ***Cz.:*** Renpress; ***Ger.:*** Quadropril; ***Hung.:*** Quadropril; ***Ital.:*** Renormax; Setrilan; ***Neth.:*** Quadropril; ***Rus.:*** Quadropril (Квадроприл); ***Spain:*** Renormax; Renpress; ***Switz.:*** Cardiopril†.

Spironolactone *(BAN, rINN)* ⊗

Espironolactona; SC-9420; Spirolactone; Spironolactonum; Spironolakton; Spironolaktonas; Spironolaktoni. 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone; (7α,17α)-7-(Acetylthio)-17-hydroxy-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone.

Спиронолактон

$C_{24}H_{32}O_4S$ = 416.6.
CAS — 52-01-7.
ATC — C03DA01.
ATC Vet — QC03DA01.

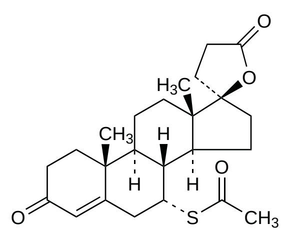

NOTE. Compounded preparations of spironolactone may be represented by the following names:

- Co-flumactone (*BAN*)—spironolactone and hydroflumethiazide in equal parts (w/w)
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Spironolactone). A white or yellowish-white powder. Practically insoluble in water; soluble in alcohol. It exhibits polymorphism. Protect from light.
USP 31 (Spironolactone). A light cream-coloured to light tan, crystalline powder with a faint to mild mercaptan-like odour. Practically insoluble in water; soluble in alcohol and in ethyl acetate; freely soluble in chloroform and in benzene; slightly soluble in methyl alcohol and in fixed oils.

Stability. There was no appreciable loss of spironolactone from extemporaneously prepared suspensions of spironolactone, 2.5, 5 and 10 mg/mL, in a cherry syrup after storage for 2 weeks at 5° or 30° or at ambient room temperature under intense fluorescent light.[1] Degradation was less than 5% for samples stored for 4 weeks, but was more noticeable in suspensions with a higher initial concentration. There were no changes in colour or odour. Bacterial and fungal counts were well within acceptable limits after 4 weeks at 30°.

1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989; **46:** 2040–2.

Adverse Effects

Spironolactone may give rise to headache and drowsiness, and gastrointestinal disturbances, including cramp and diarrhoea. Ataxia, mental confusion, and skin rashes have been reported as adverse effects. Gynaecomastia is not uncommon and in rare cases breast enlargement may persist. Other endocrine disorders include hirsutism, deepening of the voice, menstrual irregularities, and impotence. Transient increases in blood-urea-nitrogen concentrations may occur and mild acidosis has been reported. Spironolactone has been shown to cause tumours in *rats*.

Spironolactone may cause hyponatraemia and hyperkalaemia.

Incidence of adverse effects. A survey found that of 788 patients given spironolactone 164 developed adverse effects.[1] These included hyperkalaemia in 8.6%, dehydration in 3.4%, hyponatraemia in 2.4%, gastrointestinal disorders in 2.3%, neurological disorders in 2%, rash, and gynaecomastia. Hyperkalaemia was associated with renal impairment and the use of potassium supplements: only 2.8% of nonuraemic patients not receiving potassium chloride developed hyperkalaemia, while 42.1% of those with marked uraemia and treated with potassium chloride became hyperkalaemic.

In a study[2] of 54 patients (53 female, 1 male) taking spironolactone 200 mg daily for hirsutism or acne adverse effects were reported in 91%.[2] Menstrual disturbances occurred in 72% of patients, breast tenderness in 39%, dry skin in 39%, and breast enlargement in 24%. Other adverse effects included nausea and vomiting, dizziness, headache, drowsiness, and skin rashes. Two patients developed a chloasma-like pigmentation of the face. The gynaecological effects were reduced in patients taking oral contraceptives.

1. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.
2. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Carcinogenicity. Breast cancer was reported in 5 patients taking spironolactone and hydrochlorothiazide for prolonged periods[1] although it was suggested[2] that the association with spironolactone therapy was unlikely to be causal.

Although the *rat* may not be an appropriate model for determining long-term safety in man,[3,4] evidence of carcinogenicity in this species prompted the UK CSM to limit the product licences of spironolactone-containing products to exclude use in essential hypertension or idiopathic oedema.[5]

1. Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; **i:** 1428–9.
2. Jick H, Armstrong B. Breast cancer and spironolactone. *Lancet* 1975; **ii:** 368–9.
3. Lumb G, *et al.* Effects in animals of chronic administration of spironolactone—a review. *J Environ Pathol Toxicol* 1978; **i:** 641–60.
4. Wagner BM. Long-term toxicology studies of spironolactone in animals and comparison with potassium canrenoate. *J Drug Dev* 1987; **1** (suppl 2): 7–11.
5. Committee on Safety of Medicines. Spironolactone. *Current Problems* 1988; 21. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)

Effects on the blood. Agranulocytosis has been reported[1,2] in association with the use of spironolactone.

1. Stricker BHC, Oei TT. Agranulocytosis caused by spironolactone. *BMJ* 1984; **289:** 731.
2. Whitling AM, *et al.* Spironolactone-induced agranulocytosis. *Ann Pharmacother* 1997; **31:** 582–5.

Effects on electrolyte balance. *CALCIUM.* A report[1] suggested that spironolactone may have a calcium-sparing effect, in addition to its well known potassium-sparing properties.

1. Puig JG, *et al.* Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J Clin Pharmacol* 1991; **31:** 455–61.

POTASSIUM. There have been reports[1-3] of severe hyperkalaemia in patients taking spironolactone, including patients with renal impairment and those with a high potassium intake from either dietary sources or potassium supplements. In the Boston Collaborative Drug Surveillance Program[4] hyperkalaemia was reported in 42.1% of patients with uraemia taking spironolactone and receiving potassium supplements compared with 2.8% of those without uraemia and not receiving potassium supplements. Two deaths were attributed to hyperkalaemia in patients taking spironolactone and potassium chloride. Potassium supplements should be avoided in patients receiving spironolactone, and plasma-potassium concentrations should be carefully monitored in those with renal impairment.

1. Pongpaew C, *et al.* Hyperkalemic cardiac arrhythmia secondary to spironolactone. *Chest* 1973; **63:** 1023–5.
2. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgrad Med J* 1980; **56:** 254–5.
3. O'Reilly PH, *et al.* Life-threatening hyperkalaemia after bladder decompression for high pressure chronic retention. *Lancet* 1987; **ii:** 859.
4. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.

Effects on endocrine function. Spironolactone has been associated with disturbances of endocrine function. The most prominent in men is gynaecomastia which appears to be related to both dose and duration of treatment. Incidences of 62%[1] and 100%[2] have been reported. Gynaecomastia has also been accompanied by impotence.[3,4] The effects are generally reversible on stopping treatment. Reversal of male-pattern baldness has also been reported.[5]

In women symptoms include breast enlargement and tenderness.[6] The incidence of menstrual abnormalities may be high: unspecified disturbances have been reported in 33 of 53 women,[6] secondary amenorrhoea in 6 of 9,[7] and secondary and primary amenorrhoea in 1 and 2 patients, respectively.[8] The incidence of gynaecological disturbances has been found to be lower in women taking oral contraceptives.[6]

The mechanism of the effects of spironolactone on the endocrine system is unclear. Some workers[9] suggested that although spironolactone affects testosterone synthesis, the more likely explanation was its anti-androgenic action, and reduction in 17-hydroxylase activity. Others[10] found an alteration in the testosterone/oestrogen ratio due to an increase in testosterone clearance and increased peripheral conversion to estradiol. In addition, spironolactone is reported to inhibit binding of dihydrotestosterone to receptors.

1. Huffman DH, *et al.* Gynecomastia induced in normal males by spironolactone. *Clin Pharmacol Ther* 1978; **24:** 465–73.
2. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
3. Greenblatt DJ, Koch-Weser J. Gynecomastia and impotence complications of spironolactone therapy. *JAMA* 1973; **223:** 82.
4. Greenlaw C. Spironolactone induced gynecomastia: a case report. *Drug Intell Clin Pharm* 1977; **11:** 70–3.
5. Thomas PS. Hair: wanted and unwanted. *BMJ* 1986; **293:** 698.
6. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.
7. Levitt JI. Spironolactone therapy and amenorrhea. *JAMA* 1970; **211:** 2014–15.
8. Potter C, *et al.* Primary and secondary amenorrhea associated with spironolactone therapy in chronic liver disease. *J Pediatr* 1992; **121:** 141–3.
9. Loriaux DL, *et al.* Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85:** 630–6.
10. Rose LI, *et al.* Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87:** 398–403.

Effects on lipid metabolism. Unlike thiazide diuretics, spironolactone appeared not to increase serum-cholesterol concentrations in a study of 23 patients.[1]

1. Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. *Arch Intern Med* 1984; **144:** 710–14.

Effects on the liver. Hepatotoxicity characterised by cholestatic lesions has been reported in a patient receiving spironolactone.[1] Only one other published case of spironolactone-associated hepatotoxicity was known to the authors.

1. Renkes P, *et al.* Spironolactone and hepatic toxicity. *JAMA* 1995; **273:** 376–7.

Effects on the skin. Lichen-planus-like skin eruptions developed in a 62-year-old woman who was taking digoxin, propranolol, diazepam, spironolactone, and iron tablets.[1] Flares of the lichen-planus-like eruption seemed to be associated with use of spironolactone and there was evidence of resolution when spironolactone was withdrawn. Cutaneous vasculitis was associated with spironolactone on 3 occasions in an 80-year-old man.[2] A chloasma-like pigmentation of the face was reported in 2 patients receiving spironolactone for hirsutism or acne.[3]

1. Downham TF. Spironolactone-induced lichen planus. *JAMA* 1978; **240:** 1138.
2. Phillips GWL, Williams AJ. Spironolactone induced vasculitis. *BMJ* 1984; **288:** 368.
3. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Hypersensitivity. Eosinophilia and a rash developed in 2 patients with alcoholic cirrhosis while taking spironolactone.[1]

1. Wathen CG, *et al.* Eosinophilia associated with spironolactone. *Lancet* 1986; **i:** 919–20.

Precautions

Spironolactone should not be used in patients with hyperkalaemia or severe renal impairment. It should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include the elderly, those with diabetes mellitus, and those with some degree of renal or hepatic impairment. It should also be given with care to patients likely to develop acidosis. Serum electrolytes and blood-urea-nitrogen should be measured periodically.

Breast feeding. The concentration of canrenone was measured[1] in the serum and milk of a breast-feeding woman taking 25 mg of spironolactone four times daily. The milk to serum concentration ratios of canrenone at 2 and 14.5 hours after a dose of spironolactone were 0.72 and 0.51 respectively, and it was estimated that the amount of canrenone ingested by the infant would be 0.2% of the mother's daily dose of spironolactone. The serum potassium and sodium levels of the infant were in the normal range. The American Academy of Pediatrics[2] considers that spironolactone is therefore usually compatible with breast feeding.

1. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977; **66:** 1203.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Diabetes mellitus. Severe hyperkalaemia was reported in a type 1 diabetic woman with hyporeninaemic hypoaldosteronism given spironolactone.[1]

1. Large DM, *et al.* Hyperkalaemia in diabetes mellitus—potential hazards of coexisting hyporeninaemic hypoaldosteronism. *Postgrad Med J* 1984; **60:** 370–3.

Interference with laboratory estimations. Spironolactone and canrenoate can interfere with some assays for plasma-digoxin concentrations.[1-3] However, spironolactone may also produce actual changes in digoxin concentrations (see p.1262) and results of assays should be interpreted with caution.

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
2. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
3. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.

Porphyria. Spironolactone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

There is an increased risk of hyperkalaemia if spironolactone is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may occur as well in patients also given ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients given spironolactone with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity. Hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients given chlorpropamide. Spironolactone may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, spironolactone may enhance the effects of other antihypertensive drugs and may reduce vascular responses to noradrenaline.

ACE inhibitors and angiotensin II receptor antagonists. Severe hyperkalaemia has been reported in patients given spironolactone with ACE inhibitors or angiotensin II receptor antagonists and fatalities have occurred. In a study[1] of 44 patients taking such combinations for heart failure who were admitted to hospital with life-threatening hyperkalaemia, 37 required haemodialysis and 2 developed fatal complications. In another group[2] of 25 patients given spironolactone with ACE inhibitors who were admitted with severe hyperkalaemia, 2 died and 4 others developed severe cardiac arrhythmias. Advanced age, renal impairment or diabetes mellitus were risk factors for hyperkalaemia in both studies. It was suggested that combinations of spironolactone with ACE inhibitors or angiotensin II receptor antagonists should be used with caution in such patients and that they should not be given doses of spironolactone above 25 mg daily.

1. Wrenger E, *et al.* Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ* 2003; **327:** 147–9.
2. Schepkens H, *et al.* Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110:** 438–41.

Aspirin. Aspirin has been shown to produce substantial reductions in sodium excretion[1] in healthy subjects taking spironolactone and to reduce the excretion of spironolactone's active metabolite, canrenone.[2] However, use of aspirin in hypertensive patients[3] did not alter the effect of spironolactone on blood pressure, serum electrolytes, blood urea nitrogen, or plasma-renin activity.

1. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* 1973; **289:** 198–200.
2. Ramsay LE, *et al.* Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects. *Eur J Clin Pharmacol* 1976; **10:** 43–8.
3. Hollifield JW. Failure of aspirin to antagonize the antihypertensive effect of spironolactone in low-renin hypertension. *South Med J* 1976; **69:** 1034–6.

Cardiac glycosides. For discussions of the effects of spironolactone on *digoxin* and *digitoxin*, see p.1262 and p.1259, respectively. See also Interference with Laboratory Estimations, under Precautions, above.

Mitotane. For a report of the inhibition of the action of mitotane by spironolactone, see p.753.

Warfarin. For reference to the interaction between warfarin and spironolactone, see p.1430.

Pharmacokinetics

Spironolactone is well absorbed from the gastrointestinal tract, with a bioavailability of about 90%. It is about 90% bound to plasma proteins.

Spironolactone is metabolised extensively to a number of metabolites including canrenone and 7α-thiomethylspirolactone, both of which are pharmacologically active. The major metabolite may be 7α-thiomethylspirolactone, although it is uncertain to what extent the actions of spironolactone are dependent on the parent compound or its metabolites.

Spironolactone is excreted mainly in the urine and also in the faeces, in the form of metabolites. Spironolactone or its metabolites may cross the placental barrier, and canrenone is distributed into breast milk.

◊ References.

1. Overdiek HWPM, Merkus FWHM. The metabolism and biopharmaceutics of spironolactone in man. *Rev Drug Metab Drug Interact* 1987; **5:** 273–302.
2. Gardiner P, *et al.* Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol* 1989; **29:** 342–7.
3. Sungaila I, *et al.* Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. *Gastroenterology* 1992; **102:** 1680–5.

Uses and Administration

Spironolactone, a steroid with a structure resembling that of the natural adrenocortical hormone aldosterone, acts on the distal portion of the renal tubule as a competitive antagonist of aldosterone. It acts as a potassium-sparing diuretic, increasing sodium and water excretion and reducing potassium excretion.

Spironolactone is reported to have a relatively slow onset of action, requiring 2 or 3 days for maximum effect, and a similarly slow diminishment of action over 2 or 3 days on stopping.

Spironolactone is used in the management of heart failure, both to treat refractory oedema and in lower doses as an adjunct to standard therapy (see below). It is also used for refractory oedema associated with cirrhosis of the liver (with or without ascites, p.1159), or the nephrotic syndrome, and in ascites associated with malignancy. It is frequently given with the thiazides, furosemide, or similar diuretics, where it adds to their natriuretic but diminishes their kaliuretic effects, hence conserving potassium in those at risk from hypokalaemia. Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics, is discussed under Effects on the Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p.1308. It has been used in the treatment of essential hypertension (in lower doses than for oedema), but in the UK is no longer recommended for use in either essential hypertension or idiopathic oedema; doubts have been expressed over its safety during long-term administration.

Spironolactone is also used in the diagnosis and treatment of primary hyperaldosteronism (below).

Other conditions in which spironolactone has been tried on the basis of its anti-androgenic properties include hirsutism, particularly in the polycystic ovary syndrome.

In the treatment of **oedema**, spironolactone is usually given in an initial oral dose of 100 mg daily, subsequently adjusted as necessary; some patients may require doses of up to 400 mg daily. In hepatic cirrhosis with ascites and oedema, patients with a urinary sodium/potassium ratio greater than 1 may be given an initial dose of spironolactone 100 mg daily while patients with a ratio of less than 1 may be given initial doses of 200 to 400 mg daily.

Spironolactone is given in doses of 400 mg daily in the presumptive diagnosis of primary **hyperaldosteronism**; in doses of 100 to 400 mg daily for the preoperative management of hyperaldosteronism; and in the lowest effective dosage for long-term maintenance therapy in the absence of surgery.

Suggested doses of spironolactone for children range from 1 to 3 mg/kg daily, in divided doses.

Potassium supplements should not be given with spironolactone.

◊ References and reviews.

1. Skluth HA, Gums JG. Spironolactone: a re-examination. *DICP Ann Pharmacother* 1990; **24:** 52–9.
2. Doggrell SA, Brown L. The spironolactone renaissance. *Expert Opin Invest Drugs* 2001; **10:** 943–54.
3. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother* 2005; **39:** 823–8.

Acne. Spironolactone has been used for its anti-androgenic properties in some cases of acne (p.1577) where standard therapy is unsuccessful. Beneficial responses to oral therapy have been reported in patients with acne from both open[1] and placebo-controlled[2,3] studies. Topical application has been tried[4,5] but response has been variable. It is possible that the vehicle may affect the response. In women, spironolactone may be useful when treatment with an oestrogen is contra-indicated.

1. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
2. Goodfellow A, *et al.* Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol* 1984; **111:** 209–14.
3. Muhlemann MF, *et al.* Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986; **115:** 227–32.
4. Messina M, *et al.* A new therapeutic approach to acne: an antiandrogen percutaneous treatment with spironolactone. *Curr Ther Res* 1983; **34:** 319–24.
5. Walton S, *et al.* Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol* 1986; **114:** 261–4.

Alopecia. Anti-androgens have a role in the treatment of hirsutism (see below) but have also been used in patients with androgenetic alopecia (p.1577), and there is some evidence that spironolactone may be effective.[1]

1. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.

Bartter's syndrome. Spironolactone may be used to reduce potassium wasting in patients with Bartter's syndrome (p.1670).

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p.1500) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p.1294); results with hydrochlorothiazide or spironolactone have been more ambiguous (p.1310).

Heart failure. Drug therapy of heart failure (p.1165) is based on the use of diuretics, ACE inhibitors, cardiac glycosides, beta blockers, and vasodilators. Spironolactone has been used as a diuretic for refractory oedema, but it also has an additional role as an aldosterone antagonist.[1,2] Although the precise neurohormonal mechanisms leading to the development of heart failure are still not clear, there is evidence that raised levels of aldosterone may contribute to the pathophysiology.[3,4] ACE inhibitor therapy suppresses aldosterone production but this effect is not complete and the use of spironolactone with ACE inhibitors has therefore been studied. In the Randomized Aldactone Evaluation Study (RALES)[5] in patients with severe heart failure, addition of spironolactone in a dose of 25 to 50 mg daily to therapy with ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation,[5] and the use of spironolactone should therefore be considered in such patients.[6-8] A small study[9] has also shown benefit in patients with less severe heart failure. However, use of spironolactone with ACE inhibitors may lead to hyperkalaemia and careful monitoring of potassium concentrations is required[10,11] (see Interactions, above). A retrospective analysis[12] of heart failure patients found that over 10% had to stop spironolactone because of hyperkalaemia, and a further 10% stopped because of worsening renal function. Risk factors were advanced age and higher baseline plasma-potassium concentrations.

1. Tang WHW, *et al.* Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc* 2005; **80:** 1623–30.
2. Marcy TR, Ripley TL. Aldosterone antagonists in the treatment of heart failure. *Am J Health-Syst Pharm* 2006; **63:** 49–58.
3. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999; **47:** 479–82.
4. Rocha R, Williams GH. Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 2002; **62:** 723–31.
5. Pitt B, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341:** 709–17.
6. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Also available at: http://circ.ahajournals.org/cgi/reprint/112/12/e154 (accessed 07/05/08)
7. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/NR/rdonlyres/8A2848B4-5DEB-41B9-9A0A-5B5A90494B64/0/CHFFullTextehi205FVFW170505.pdf (accessed 07/05/08)
8. Scottish Intercollegiate Guidelines Network. Management of chronic heart failure (February 2007). Available at: http://www.sign.ac.uk/pdf/sign95.pdf (accessed 07/05/08)

9. Macdonald JE, *et al.* Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 2004; **90:** 765–70.
10. Georges B, *et al.* Spironolactone and congestive heart-failure. *Lancet* 2000; **355:** 1369–70.
11. Juurlink DN, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351:** 543–51.
12. Witham MD, *et al.* Tolerability of spironolactone in patients with chronic heart failure—a cautionary message. *Br J Clin Pharmacol* 2004; **58:** 554–7.

High-altitude disorders. Acetazolamide is generally the drug of choice for prophylaxis of high-altitude disorders (p.1168). Anecdotal reports[1-4] and a small-scale double-blind study[5] suggested that spironolactone could be useful in preventing acute mountain sickness, although a deterioration in pulmonary function despite spironolactone prophylaxis has been noted in a patient.[6]

1. Currie TT, *et al.* Spironolactone and acute mountain sickness. *Med J Aust* 1976; **2:** 168–70.
2. Snell JA, Cordner EP. Spironolactone and acute mountain sickness. *Med J Aust* 1977; **1:** 828.
3. Turnbull G. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **280:** 1453.
4. Rutter LD. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **281:** 618.
5. Brown GV, *et al.* Spironolactone in acute mountain sickness. *Lancet* 1977; **i:** 855.
6. Meyers DH. Spironolactone prophylaxis of mountain sickness. *BMJ* 1980; **281:** 1569.

Hirsutism. Hirsutism (p.2089) is frequently treated with anti-androgens, usually cyproterone or spironolactone. Spironolactone in doses of 50 to 200 mg daily has produced both subjective and objective improvement in hirsutism in patients with idiopathic hirsutism or polycystic ovary syndrome,[1-4] and its use has been reviewed.[5] It is preferably used with oral contraceptives,[6,7] to improve efficacy and avoid the menstrual irregularity and to avoid the risk of feminisation to a male fetus. Most studies have involved premenopausal women and it has been suggested[4,8] that spironolactone would be useful in women in whom cyproterone is contra-indicated or not tolerated. A randomised study (not placebo-controlled) found spironolactone 100 mg daily and cyproterone 100 mg daily to be equally effective,[9] while a systematic review[10] of the use of spironolactone in hirsutism concluded that it was significantly more effective than both cyproterone and finasteride for up to 12 months after treatment.

For reference to the use of spironolactone in alopecia, see above.

1. Cumming DC, *et al.* Treatment of hirsutism with spironolactone. *JAMA* 1982; **247:** 1295–8.
2. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
3. Evans DJ, Burke CW. Spironolactone in the treatment of idiopathic hirsutism and the polycystic ovary syndrome. *J R Soc Med* 1986; **79:** 451–3.
4. Barth JH, *et al.* Spironolactone therapy for hirsute women. *Br J Dermatol* 1988; **119** (suppl 33): 17.
5. Christy NA, *et al.* Spironolactone for hirsutism in polycystic ovary syndrome. *Ann Pharmacother* 2005; **39:** 1517–21. Correction. *ibid.*; 1765.
6. Chapman MG, *et al.* Spironolactone in combination with an oral contraceptive: an alternative treatment for hirsutism. *Br J Obstet Gynaecol* 1985; **92:** 983–5.
7. Rittmaster RS. Hirsutism. *Lancet* 1997; **349:** 191–5.
8. West TET. Does spironolactone have a place in treating facial hirsutism in women? *BMJ* 1988; **296:** 1456.
9. O'Brien RC, *et al.* Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J Clin Endocrinol Metab* 1991; **72:** 1008–13.
10. Farquhar C, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/06/05).

Hyperaldosteronism. Hyperaldosteronism (aldosteronism) is a disorder characterised by mineralocorticoid excess due to high circulating levels of aldosterone.[1-4] Mineralocorticoid excess due to other mineralocorticoids is rare. Primary hyperaldosteronism is usually caused by an aldosterone-producing adenoma (Conn's syndrome) or primary adrenal hyperplasia. Other causes include aldosterone-producing adrenal carcinoma, and glucocorticoid-suppressible hyperaldosteronism.

Secondary hyperaldosteronism is more common and results from conditions in which there is activation of the renin-angiotensin-aldosterone system, including diuretic therapy, and oedematous conditions such as heart failure, hepatic cirrhosis, and nephrotic syndrome. Bartter's syndrome (p.1670) also results in hyperaldosteronism.

Most patients with primary hyperaldosteronism are asymptomatic, although they may present with signs or symptoms of mineralocorticoid excess (p.1490). Diagnosis often follows the incidental discovery of hypokalaemia. Symptomatic hypokalaemia (p.1669) may develop in some patients, particularly those taking diuretics.

Diagnosis is confirmed by the presence of raised plasma and urinary aldosterone concentrations. However, the concentrations may be affected by serum-potassium concentration, posture, and time of day, and interpretation may be difficult. The plasma aldosterone:renin ratio may also be measured. In primary hyperaldosteronism the aldosterone concentration is raised but renin is suppressed, although this does not necessarily prove the diagnosis; in secondary hyperaldosteronism both are raised. Radiological and nuclear imaging are useful for further differentiating between adenoma and hyperplasia.

Hyperaldosteronism due to an aldosterone-producing adenoma is usually treated surgically. The aldosterone antagonist spironolactone may be given pre-operatively to lower the blood pressure and normalise the serum potassium. In patients who are not suitable for surgery, long-term medical management involves spironolactone, initially in high doses but reduced to the lowest dose for maintenance. If spironolactone is not tolerated, amiloride may be used as an alternative, but high doses are required. There has also been a report[5] of the successful use of eplerenone, another aldosterone antagonist; gynaecomastia had developed with spironolactone but resolved when treatment was changed to eplerenone. Trilostane, an adrenal suppressant, has been used to inhibit aldosterone synthesis.

In primary adrenal hyperplasia surgery is not usually effective and medical management with spironolactone or amiloride is required. Additional antihypertensive therapy may also be needed. Glucocorticoid-suppressible hyperaldosteronism, also known as familial hyperaldosteronism type I (FH-I), is a rare autosomal dominant form and may be treated with dexamethasone. However, this may not control the blood pressure and spironolactone or amiloride may be required in addition.

In secondary hyperaldosteronism the underlying condition should be treated, but spironolactone may be of benefit as part of the therapy.

1. Ganguly A. Primary aldosteronism. *N Engl J Med* 1998; **339:** 1828–34.
2. Stewart PM. Mineralocorticoid hypertension. *Lancet* 1999; **353:** 1341–7.
3. Kaplan NM. Cautions over the current epidemic of primary aldosteronism. *Lancet* 2001; **357:** 953–4.
4. Fraser R, *et al.* Cautions over idiopathic aldosteronism. *Lancet* 2001; **358:** 332.
5. Karagiannis A, *et al.* Eplerenone relieves spironolactone-induced painful gynaecomastia in a patient with primary aldosteronism. *Nephrol Dial Transplant* 2007; **22:** 293.

Precocious puberty. Spironolactone (as an anti-androgen) and testolactone were given to boys with familial precocious puberty (p.2081) for periods of up to 18 months. Rates of growth and bone maturation were restored to normal during combination therapy but not with either drug given alone.[1] However, after further treatment for 2 to 4.2 years there was a diminishing response manifested by the recurrence of clinical features of puberty and an increase in the bone maturation rate.[2] Addition of deslorelin appeared to restore the control of puberty,[2] and in a long-term study[3] growth rate remained normal for 6 years.

1. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
2. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
3. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Premenstrual syndrome. Spironolactone has been used for its diuretic and anti-androgenic properties in premenstrual syndrome (p.2099).

Preparations

BP 2008: Spironolactone Tablets;
USP 31: Spironolactone and Hydrochlorothiazide Tablets; Spironolactone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aldactone; Drimux A; Espimax; Expal; Lanx; Modulactone; Normital; Osiren†; Rediun-E; ***Austral.:*** Aldactone; Spiractin; ***Austria:*** Aldactone; Spirobene; Spirohexal; Spirono; ***Belg.:*** Aldactone; Docspirono; Spirotop; ***Braz.:*** Aldactone; Aldosterin†; Espirolona; Spiroctan; ***Canad.:*** Aldactone; Novo-Spiroton; ***Chile:*** Alizar; Cardactona; ***Cz.:*** Spirolone†; Uractone†; Verospiron; Xenalon†; ***Denm.:*** Hexalacton; Spirix; Spiron; ***Fin.:*** Aldactone; Spiresis; Spirix; ***Fr.:*** Aldactone; Flumach; Practon; Spiroctan; Spironone; ***Ger.:*** Aldactone; Aquareduct†; duraspiron†; Jenaspiron; Osyrol; Spiro; Spirobeta; Spirogamma; Spirono; Verospiron; ***Gr.:*** Aldactone; Uridactone†; ***Hong Kong:*** Aldactone; ***Hung.:*** Huma-Spiroton; Spirolone†; Spiron; Verospiron; ***India:*** Aldactone; ***Indon.:*** Aldactone; Carpiaton; Letonal; Spirola; ***Irl.:*** Aldactone; ***Israel:*** Aldactone; Aldospirone; Spironol; ***Ital.:*** Aldactone; Spiroderm†; Spirolang; Uractone; ***Mex.:*** Aldactone; Biolactona; Quimolactona†; Vivitar; ***Neth.:*** Aldactone; ***Norw.:*** Aldactone; Spirix; ***NZ:*** Aldactone†; Spirotone; ***Philipp.:*** Aldactone; ***Pol.:*** Spironol; Verospiron; ***Port.:*** Aldactone; Aldonar; Nefrolactona†; ***Rus.:*** Aldactone (Альдактон)†; Verospiron (Верошпирон); ***S.Afr.:*** Aldactone; Spiractin; ***Singapore:*** Aldactone; Uractonum; ***Spain:*** Aldactone; ***Swed.:*** Aldactone; Spirix; Spiroscand†; ***Switz.:*** Aldactone; Primacton; Xenalon; ***Thai.:*** Aldactone; Altone; Berlactone†; Hyles; Pondactone; Spironex†; ***Turk.:*** Aldacton; ***UK:*** Aldactone; Spirospare†; ***USA:*** Aldactone; ***Venez.:*** Aldactone; Spiroctan†.

Multi-ingredient: ***Arg.:*** Aldactone-D; Aldazida; Lasilacton; ***Austria:*** Aldactone Saltucin; Buti-Spirobene; Deverol mit Thiazid; Digi-Aldopur; Furo-Aldopur; Furo-Spirobene; Furolacton; Lasilacton; Sali-Aldopur; Spirono comp; Supracid; ***Belg.:*** Aldactazine; Docspirochlor; ***Braz.:*** Aldazida; Lasilactona; ***Canad.:*** Aldactazide; Novo-Spirozine; ***Cz.:*** Spiro Compositum†; ***Fr.:*** Aldactazine; Aldalix; Practazin; Spiroctazine; ***Ger.:*** Aldactone Saltucin†; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Osyrol Lasix; Risicordin†; Sali-Aldopur†; Spiro comp; Spiro-D; Spironolacton Plus†; Spironothiazid; Spirostada comp†; ***India:*** Lasilactone; Spiromide; ***Indon.:*** Aldazide; ***Irl.:*** Aldactide; ***Ital.:*** Aldactazide; Lasitone; Spiridazide; Spirofur; ***Mex.:*** Aldazida; Lasilacton; ***Philipp.:*** Aldazide; ***Port.:*** Aldactazine; Ondolen; ***S.Afr.:*** Aldazide; ***Spain:*** Aldactacine; Aldoleo; Miscidon†; Spirometon; ***Switz.:*** Aldozone; Furocombin; Furospir; Lasilactone; ***Turk.:*** Aldactazide; ***UK:*** Aldactide; Lasilactone; ***USA:*** Aldactazide; ***Venez.:*** Aldactazida; Teradal†.

Staphylokinase

Estafiloquinasa.

Profile

Staphylokinase is a thrombolytic derived from *Staphylococcus aureus*. Recombinant and modified forms are under investigation for the treatment of thromboembolic disorders, including acute myocardial infarction.

◊ References.

1. Vanderschueren S, *et al.* Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; **92:** 2050–57.
2. Vanderschueren S, *et al.* Randomized coronary patency trial of double-bolus recombinant staphylokinase versus front-loaded alteplase in acute myocardial infarction. *Am Heart J* 1997; **134:** 213–19.
3. Armstrong PW, *et al.* Collaborative angiographic patency trial of recombinant staphylokinase (CAPTORS II). *Am Heart J* 2003; **146:** 484–8.

Streptokinase *(BAN, rINN)*

Estreptoquinasa; Plasminokinase; Sterptokinasum; Streptokinaasi; Streptokinas; Streptokinasum; Sztreptokináz.

Стрептокиназа

CAS — 9002-01-1.
ATC — B01AD01.
ATC Vet — QB01AD01.

Pharmacopoeias. *Eur.* (see p.vii) includes a concentrated solution.

Ph. Eur. 6.2 (Streptokinase Concentrated Solution; Streptokinasi Solutio Concentrata). A preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C. It has the property of combining with human plasminogen to form plasminogen activator. The potency is not less than 510 international units per microgram of nitrogen. A clear, colourless liquid. pH 6.8 to 7.5. Store in airtight containers at a temperature of –20°. Protect from light.

Stability. The incorporation of albumin in commercial preparations of streptokinase has reduced the incidence of flocculation with streptokinase solutions. However, flocculation has occurred with small volumes prepared with sodium chloride 0.9% in sterilised glass containers apparently because of residual acid buffers that remain in empty evacuated containers after sterilisation.[1]

1. Thibault L. Streptokinase flocculation in evacuated glass bottles. *Am J Hosp Pharm* 1985; **42:** 278.

Units

The potency of streptokinase is expressed in international units and preparations are assayed using the second International Standard (1989).

The Christensen unit is the quantity of streptokinase that will lyse a standard blood clot completely in 10 minutes and is equivalent to the international unit.

Adverse Effects

In common with other thrombolytics streptokinase may cause haemorrhage, particularly from puncture sites; severe internal bleeding has occurred and may be difficult to control. Streptokinase is antigenic, and allergic reactions ranging from rashes to rarer anaphylactoid and serum-sickness-like symptoms have occurred. Fever, sometimes high, and associated symptoms such as chills and back or abdominal pain are quite frequent. Nausea and vomiting may occur. There have been a few reports of Guillain-Barré syndrome.

Streptokinase infusion may be associated with hypotension, both direct or as a result of reperfusion; bradycardia and arrhythmias may also occur due to reperfusion. The break-up of existing clots may occasionally produce emboli elsewhere; pulmonary embolism and acute renal failure due to cholesterol embolisation have been reported.

Back pain. Streptokinase infusion has been associated with the development of very severe low back pain, which resolves within a few minutes of stopping the infusion, and may be severe enough to warrant opioid analgesia.[1-4] The back pain may represent a hypersensitivity reaction. Providing that the pain is controlled and that dissecting aortic aneurysm is not suspected, it may still be possible to complete the streptokinase infusion.[4,5] Alternatively, immediate substitution with a different thrombolytic has been suggested.[6]

There have also been a few reports of low back pain associated with anistreplase infusion.[7,8]

1. Shah M, Taylor RT. Low back pain associated with streptokinase. *BMJ* 1990; **301:** 1219.
2. Dickinson RJ, Rosser A. Low back pain associated with streptokinase. *BMJ* 1991; **302:** 111–12.

3. Porter NJ, Nikoletatos K. Low back pain associated with streptokinase. *BMJ* 1991; **302:** 112.
4. Pinheiro RF, *et al.* Low back pain during streptokinase infusion. *Arq Bras Cardiol* 2002; **78:** 233–5.
5. Lear J, *et al.* Low back pain associated with streptokinase. *Lancet* 1992; **340:** 851.
6. Fishwick D, *et al.* Thrombolysis and low back pain. *BMJ* 1995; **310:** 504.
7. Hannaford P, Kay CR. Back pain and thrombolysis. *BMJ* 1992; **304:** 915.
8. Lear J, Rajapakse R. Low back pain associated with anistreplase. *BMJ* 1993; **306:** 896.

Effects on the blood. Although falls in the haemoglobin value of patients receiving thrombolytics are most likely to be due to blood loss from haemorrhage, there has been a report of a patient who had signs of haemolytic anaemia after intravenous infusion of streptokinase.[1] In a subsequent test *in vitro* the patient's serum caused strong agglutination of streptokinase-treated red blood cells, supporting the view that streptokinase was responsible for the haemolysis.

1. Mathiesen O, Grunnet N. Haemolysis after intravenous streptokinase. *Lancet* 1989; **i:** 1016–17.

Effects on the eyes. Acute uveitis[1,2] and iritis,[3,4] associated with transient renal impairment in one patient,[3] have followed treatment of myocardial infarction with intravenous streptokinase. In one case uveitis was associated with serum sickness[2] and in all of them hypersensitivity to streptokinase was suspected.

1. Kinshuck D. Bilateral hypopyon and streptokinase. *BMJ* 1992; **305:** 1332.
2. Proctor BD, Joondeph BC. Bilateral anterior uveitis: a feature of streptokinase-induced serum sickness. *N Engl J Med* 1994; **330:** 576–7.
3. Birnbaum Y, *et al.* Acute iritis and transient renal impairment following thrombolytic therapy for acute myocardial infarction. *Ann Pharmacother* 1993; **27:** 1539–40.
4. Gray MY, Lazarus JH. Iritis after treatment with streptokinase. *BMJ* 1994; **309:** 97.

Effects on the kidneys. Transient proteinuria has been reported after use of streptokinase. In some patients proteinuria and renal impairment have developed about 7 days after thrombolytic therapy and have been associated with a syndrome resembling serum sickness,[1,2] suggesting a delayed hypersensitivity reaction; a similar case in a patient receiving anistreplase was associated with Henoch-Schönlein-like vasculitis.[3] These delayed reactions should be distinguished from the transient and apparently self-limiting proteinuria that has been reported in some patients in the first 24 to 72 hours after beginning streptokinase.[4,5] Proteinuria within the first 24 hours has been attributed to deposition of an immune complex in the glomeruli,[6] although haemodynamic and neurohormonal changes associated with acute myocardial infarction may be responsible since proteinuria has occurred in patients not receiving thrombolytic therapy.[7,8]

Streptokinase infusion has also been associated with acute oliguric acute renal failure due to acute tubular necrosis, apparently as a result of hypotension during the infusion, in a patient with existing renovascular narrowing.[9] Interestingly, it has been pointed out that a variant streptokinase may be the pathogenic agent in glomerulonephritis occurring after *Streptococcus pyogenes* infection.[10]

Renal failure has developed as a consequence of streptokinase-induced cholesterol embolism, see under Embolism, below.

1. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; **ii:** 1398.
2. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
3. Ali A, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106–7.
4. Argent N, Adams PC. Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
5. More RS, Peacock F. Haematuria and proteinuria after thrombolytic therapy. *Lancet* 1990; **336:** 1454.
6. Lynch M, *et al.* Proteinuria with streptokinase. *Lancet* 1993; **341:** 1024.
7. Pickett TM, Hilton PJ. Proteinuria and streptokinase. *Lancet* 1993; **341:** 1538.
8. von Eyben FE, *et al.* Albuminuria with or without streptokinase. *Lancet* 1993; **342:** 365–6.
9. Kalra PA, *et al.* Acute tubular necrosis induced by coronary thrombolytic therapy. *Postgrad Med J* 1991; **67:** 212.
10. Barnham M. Hypersensitivity and streptokinase. *Lancet* 1990; **335:** 535.

Effects on the liver. Raised serum-alanine aminotransferase values, and in some cases raised aspartate aminotransferase activity, were seen more frequently in 95 patients who received streptokinase than in 94 given placebo as part of a study in patients with myocardial infarction.[1] The mechanism for the raised aminotransferase activity was not clear; a concomitant rise in γ-glutamyltransferase activity and bilirubin concentration suggested an hepatic source.

For references to rupture of the liver occurring during treatment with streptokinase, see Haemorrhage, below.

1. Maclennan AC, *et al.* Activities of aminotransferases after treatment with streptokinase for acute myocardial infarction. *BMJ* 1990; **301:** 321–2.

Effects on the nervous system. There have been a few reports of Guillain-Barré syndrome after treatment with streptokinase.[1-4] Whether streptokinase was the cause is not certain although its antigenic properties do suggest that induction of an immunological reaction might be responsible.[3]

For discussion of cerebrovascular effects of streptokinase, see Haemorrhage, below.

1. Eden KV. Possible association of Guillain-Barré syndrome with thrombolytic therapy. *JAMA* 1983; **249:** 2020–1.
2. Leaf DA, *et al.* Streptokinase and the Guillain-Barré syndrome. *Ann Intern Med* 1984; **100:** 617.
3. Barnes D, Hughes RAC. Guillain-Barré syndrome after treatment with streptokinase. *BMJ* 1992; **304:** 1225.
4. Taylor BV, *et al.* Guillain-Barré syndrome complicating treatment with streptokinase. *Med J Aust* 1995; **162:** 214–15.

Effects on the respiratory system. Fatal acute respiratory distress syndrome occurred in a patient given streptokinase for pulmonary embolism.[1] It was suggested that streptokinase may have caused the pulmonary injury by altering vascular permeability due to generation of fibrinolytic products or via reperfusion oedema.

1. Martin TR, *et al.* Adult respiratory distress syndrome following thrombolytic therapy for pulmonary embolism. *Chest* 1983; **83:** 151–3.

Effects on the skin. Rashes may occur as an allergic reaction to streptokinase. For a report of skin necrosis possibly associated with cholesterol embolisation, see Embolism, below.

Embolism. Thrombolytic therapy has occasionally and paradoxically been associated with further embolism. This may be due to clots that break away from the treated thrombus, or to cholesterol crystals released after removal of fibrin from atheromatous plaques by thrombolysis.

Fatal pulmonary embolism has been reported,[1] apparently due to breakaway from a deep-vein thrombus under treatment. However, comparative studies have suggested that there is no evidence of a higher rate of such complications with streptokinase than with heparin.[2] When they do occur a good clinical response is usually seen to continued streptokinase.[2] Complications due to multiple microemboli were reported[3] in 7 of 475 consecutive patients treated with streptokinase or anistreplase for acute myocardial infarction. The sites of embolism were the legs (in 4) and brain (in 3); one patient apparently had systemic effects with skin infarction and renal impairment. Five of the 7 patients died. There has also been a report[4] of acute peripheral arterial thromboembolism in a patient given alteplase for ischaemic stroke.

Cholesterol embolisation can have many clinical manifestations depending on the location of the emboli. A classic presentation is livedo reticularis, gangrenous lower extremities, and acute renal failure.[5,6] Symptoms may appear within a few hours of starting thrombolytic treatment,[7] although in some cases they may not become evident for several days.[8-11]

1. Hill LN. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 411–12.
2. Rogers LQ, Lutcher CL. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; **90:** 412–13.
3. Stafford PJ, *et al.* Multiple microemboli after disintegration of clot during thrombolysis for acute myocardial infarction. *BMJ* 1989; **299:** 1310–12.
4. Gomez-Beldarrain M, *et al.* Peripheral arterial embolism during thrombolysis for stroke. *Neurology* 2006; **67:** 1096–7.
5. Blankenship JC. Cholesterol embolisation after thrombolytic therapy. *Drug Safety* 1996; **14:** 78–84.
6. Wong FKM, *et al.* Acute renal failure after streptokinase therapy in a patient with acute myocardial infarction. *Am J Kidney Dis* 1995; **26:** 508–10.
7. Pochmalicki G, *et al.* Cholesterol embolisation syndrome after thrombolytic therapy for myocardial infarction. *Lancet* 1992; **339:** 58–9.
8. Ridker PM, Michel T. Streptokinase therapy and cholesterol embolization. *Am J Med* 1989; **87:** 357–8.
9. Pirson Y, *et al.* Cholesterol embolism in a renal graft after treatment with streptokinase. *BMJ* 1988; **296:** 394–5.
10. Dass H, Fescharek R. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 1513–14.
11. Penswick J, Wright AL. Skin necrosis induced by streptokinase. *BMJ* 1994; **309:** 378.

Haemorrhage. Haemorrhage is a common adverse effect of thrombolytic therapy, and the problem and its management have been reviewed.[1] Thrombolytics are used to lyse pathological thrombi, but can also produce a 'lytic state' due to depletion of the natural plasmin inhibitor α_2-antiplasmin by excess plasmin production; they may also cause lysis of thrombi required for haemostasis.

Haemorrhage is a particular risk where there is existing or concomitant trauma. More than 70% of bleeding episodes occur at vascular puncture sites,[1] so invasive procedures should be avoided if possible; if catheterisation is considered essential meticulous care of the vascular puncture site is necessary. Bleeding or severe bruising in patients receiving thrombolytic therapy have also been associated with intramuscular injection of analgesics,[2] the use of an automatic blood-pressure measuring machine,[3] a pre-existing prosthetic abdominal aortic graft,[4] and recent dental extraction.[5] Other disease states may also contribute: haemospermia has been reported after thrombolysis in a patient with mild prostatic symptoms,[6] haemorrhagic bullae have been reported in a patient with lichen sclerosus et atrophicus,[7] and diabetic patients are at risk of retinal haemorrhage if they have diabetic retinopathy,[8] although any increase in risk seems to be small.[9] A review of the GUSTO-I Study[10] (40 903 patients) identified older age, low body-weight, female sex, and African ancestry as other factors that increased the risk of haemorrhage.

Intracranial haemorrhage leading to stroke is the most serious bleeding complication with thrombolytics, and has a high mortality. Assessment of data from national registries and large-scale trials has identified a number of risk factors for intracranial haemorrhage, including those mentioned above for overall haemorrhage, hypertension on admission, a history of stroke, and thrombolysis with current alteplase regimens.[11-14] The benefits and risks must be assessed for each patient and thrombolytic therapy should still be given to the elderly and to those with hypertension if the expected benefits are great. Intracranial haemorrhage is a particular concern with the use of thrombolytics for the treatment of ischaemic stroke. In the NINDS study, using alteplase, clinical outcome appeared to be improved despite an increased incidence of symptomatic intracerebral haemorrhage. Subgroup analysis[15] suggested that severe neurological deficit, brain oedema, and mass effect, before treatment, were risks associated with the increased incidence of haemorrhage.

Fibrin-specific thrombolytics such as alteplase were developed in the hope that they would have less systemic effect than fibrin-nonspecific thrombolytics such as streptokinase and therefore cause less bleeding. However, studies that have assessed comparative bleeding rates have failed to confirm this, although the use of adjunctive antithrombotics and different dose regimens makes comparison difficult. In GUSTO-I,[10] the bleeding rate with alteplase plus intravenous heparin was lower than with streptokinase plus intravenous heparin, but was similar to that with streptokinase plus subcutaneous heparin. However, the rate of intracranial haemorrhage was higher with alteplase.[16] In ASSENT-2,[17] which compared bolus doses of the highly fibrin-specific thrombolytic tenecteplase with front-loaded alteplase, tenecteplase produced fewer major non-cerebral bleeds than alteplase but the rates of intracranial haemorrhage were nearly identical. Although a meta-analysis[18] suggested that rates of intracranial haemorrhage may be higher with bolus thrombolytics, others have suggested that this may not be a problem with newer bolus regimens.[19]

Other bleeding complications reported with thrombolytics include rupture of the spleen[20,21] and liver,[22] and rupture of a follicle has been reported in a menstruating woman.[23] Rupture of the heart with fatal consequences has been reported, although thrombolytics do not appear to increase the overall risk of cardiac rupture following myocardial infarction,[24] except possibly for early rupture in women.[25]

Diffuse alveolar haemorrhage has been reported[26] in a patient treated with streptokinase after myocardial infarction. Intrapleural use was associated with life-threatening haemorrhage in empyema following cardiac surgery,[27] and with fatal haemorrhage in a case of aortic dissection misdiagnosed as empyema.[28]

1. Sane DC, *et al.* Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989; **111:** 1010–22.
2. Morris GC, Sterry MJG. [case report]. *BMJ* 1991; **302:** 246.
3. Gibson P. [case report]. *BMJ* 1991; **302:** 1412.
4. London NJM, *et al.* Systemic thrombolysis causing haemorrhage around a prosthetic abdominal aortic graft. *BMJ* 1993; **306:** 1530–1.
5. Lustig JP, *et al.* Thrombolytic therapy for acute myocardial infarction after oral surgery. *Oral Surg Oral Med Oral Pathol* 1993; **75:** 547–8.
6. Keeling PJ, Lawson CS. Haemospermia: a complication of thrombolytic therapy. *Br J Hosp Med* 1990; **44:** 244.
7. Dunn HM, Fulton RA. Haemorrhagic bullae in a patient with lichen sclerosus et atrophicus treated with streptokinase. *Heart* 1996; **76:** 448.
8. Caramelli B, *et al.* Retinal haemorrhage after thrombolytic therapy. *Lancet* 1991; **337:** 1356–7.
9. Ward H, Yudkin JS. Thrombolysis in patients with diabetes. *BMJ* 1995; **310:** 3–4.
10. Berkowitz SD, *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997; **95:** 2508–16.
11. Simoons ML, *et al.* Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; **342:** 1523–8.
12. Aylward PE, *et al.* Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction: a randomized trial. *Ann Intern Med* 1996; **125:** 891–900.
13. Bovill EG, *et al.* Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, Phase IIIB trial). *Am J Cardiol* 1997; **79:** 391–6.
14. Gurwitz JH, *et al.* Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998; **129:** 597–604.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997; **28:** 2109–18.
16. Gore JM, *et al.* Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation* 1995; **92:** 2811–18.
17. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
18. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; **356:** 449–54.
19. Armstrong PW, *et al.* Bolus fibrinolysis: risk, benefit, and opportunities. *Circulation* 2001; **103:** 1171–3.
20. Wiener RS, Ong LS. Streptokinase and splenic rupture. *Am J Med* 1989; **86:** 249.
21. Blankenship JC, Indeck M. Spontaneous splenic rupture complicating anticoagulant or thrombolytic therapy. *Am J Med* 1993; **94:** 433–7.
22. Eklöf B, *et al.* Spontaneous rupture of liver and spleen with severe intra-abdominal bleeding during streptokinase treatment of deep venous thrombosis. *Vasa* 1977; **6:** 369–71.

23. Müller C-H, *et al.* Near-fatal intra-abdominal bleeding from a ruptured follicle during thrombolytic therapy. *Lancet* 1996; **347:** 1697.
24. Massel DR. How sound is the evidence that thrombolysis increases the risk of cardiac rupture? *Br Heart J* 1993; **69:** 284–7.
25. Becker RC, *et al.* Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. *J Am Coll Cardiol* 1999; **33:** 479–87.
26. Yigla M, *et al.* Diffuse alveolar hemorrhage following thrombolytic therapy for acute myocardial infarction. *Respiration* 2000; **67:** 445–8.
27. Porter J, Banning AP. Intrapleural streptokinase. *Thorax* 1998; **53:** 720.
28. Srivastava P, *et al.* Fatal haemorrhage from aortic dissection following instillation of intrapleural streptokinase. *Scott Med J* 2000; **45:** 86–7.

Hypersensitivity. Streptokinase is a bacterial protein and has antigenic activity. The formation of streptokinase-neutralising antibodies may reduce the efficacy of subsequent doses and increase the risk of hypersensitivity reactions.

In a series of 25 patients given intravenous streptokinase for myocardial infarction, titres of streptokinase-neutralising antibodies rose from a mean neutralisation capacity of 0.16 million units before treatment to a mean of 25.54 million units 2 weeks after treatment, the highest individual titre being 93 million units. After 12 weeks the neutralisation capacity was still sufficient in 24 patients to have neutralised a standard 1.5-million unit dose of streptokinase. After 17 to 34 weeks titres were still high enough in 18 of 20 patients examined to neutralise at least half a standard dose.[1] As these results indicate, giving standard doses of streptokinase within up to a year of a previous course may lead to reduced effect. Thus, the period in which it should not be repeated is usually between 5 days and 12 months post infarction (see Precautions, below). However, high titres of neutralising antibodies persisting for up to 7.5 years after use of streptokinase have been reported.[2-4] Since readministration also increases the risk of hypersensitivity reactions, it has been suggested[2,5] that repeat courses should not be given within 4 or more years, and that if a repeat course is needed a non-antigenic thrombolytic such as alteplase or urokinase should be used until it is known whether or not high *in-vitro* titres affect efficacy. Increased titres of streptokinase-neutralising antibodies have also been measured in patients given topical streptokinase for wounds.[6]

Anistreplase also appears susceptible to neutralisation by streptokinase antibodies.[7]

Plasmacytosis,[8,9] serum-sickness,[8,10,11] rhabdomyolysis,[12] renal impairment (see Effects on the Kidneys, above), uveitis and iritis (see Effects on the Eyes, above), arthritis,[13] and anaphylaxis[14-17] have been reported in patients receiving streptokinase and are thought to represent hypersensitivity reactions, in some cases perhaps due to previous exposure to streptococcal antigens during infection. Back pain (see above) may also represent a hypersensitivity reaction. In some patients there may be a delay of between 1 and 10 days before appearance of the reaction.[18] The incidence of severe hypersensitivity reactions is probably fairly low, however; in the GISSI study anaphylaxis was reported in only 7 of 5860 patients although other hypersensitivity reactions leading to withdrawal of streptokinase were reported in 99 patients, with a further 42 such reactions after completion of the infusion.[15] Some episodes of apparent anaphylaxis seen with streptokinase may be fibrinolysin-mediated rather than antibody-antigen reactions. Alteplase, which is considered non-antigenic, produced an anaphylactoid reaction in a patient who had a history of atopy.[19] Fibrinolysin, which activates complement cascade and the kinin system, is formed in quantity after the use of a thrombolytic. In most patients these effects are clinically insignificant, but in those who are strongly atopic there is the possibility of precipitating an anaphylactoid reaction.

1. Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; **335:** 184–5.
2. Elliott JM, *et al.* Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. *Am J Cardiol* 1993; **71:** 640–5.
3. Lee HS, *et al.* Raised levels of antistreptokinase antibody and neutralization titres from 4 days to 54 months after administration of streptokinase or anistreplase. *Eur Heart J* 1993; **14:** 84–9.
4. Squire IB, *et al.* Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; **20:** 1245–52.
5. Jennings K. Antibodies to streptokinase. *BMJ* 1996; **312:** 393–4.
6. Green C. Antistreptokinase titres after topical streptokinase. *Lancet* 1993; **341:** 1602–3.
7. Binette MJ, Agnone FA. Failure of APSAC thrombolysis. *Ann Intern Med* 1993; **119:** 637.
8. Straub PW, *et al.* Plasmozytose nach thrombolytischer Therapie mit Streptokinase. *Schweiz Med Wochenschr* 1974; **104:** 1891–2.
9. Chan NS, *et al.* Plasmacytosis and renal failure after readministration of streptokinase for threatened myocardial reinfarction. *BMJ* 1988; **297:** 717–18.
10. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; **ii:** 1398.
11. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; **335:** 106.
12. Montgomery HE, *et al.* Rhabdomyolysis and multiple system organ failure with streptokinase. *BMJ* 1995; **311:** 1472.
13. Kelly MP, Bielawska C. Recurrence of a reactive arthritis following streptokinase therapy. *Postgrad Med J* 1991; **67:** 402.
14. McGrath KG, Patterson R. Anaphylactic reactivity to streptokinase. *JAMA* 1984; **252:** 1314–17.
15. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **i:** 397–401.
16. Bednarczyk EM, *et al.* Anaphylactic reaction to streptokinase with first exposure: case report and review of the literature. *DICP Ann Pharmacother* 1989; **23:** 869–72.
17. Tisdale JE, *et al.* Streptokinase-induced anaphylaxis. *DICP Ann Pharmacother* 1989; **23:** 984–7.
18. Seibert WJ, *et al.* Streptokinase morbidity—more common than previously recognised. *Aust N Z J Med* 1992; **22:** 129–33.
19. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; **341:** 966–7.

Treatment of Adverse Effects

Allergic reactions may require treatment with antihistamines and corticosteroids, which have sometimes been given prophylactically. Anaphylaxis requires the use of adrenaline (for further details, see p.1205).

Severe haemorrhage not controlled by local pressure requires the streptokinase infusion to be stopped. Tranexamic acid, aminocaproic acid, or aprotinin may be of benefit. Packed red blood cells may be preferable to whole blood for replacement therapy; factor VIII preparations may also be given. Volume expansion may be necessary, but the use of dextrans should be avoided because of their platelet-inhibiting properties.

Precautions

Streptokinase should be used with great care, if at all, in patients at increased risk of bleeding, or those in whom haemorrhage is likely to prove particularly dangerous. It should thus be avoided in patients with active internal bleeding or a recent history of peptic ulcer disease, oesophageal varices, ulcerative colitis or other bleeding gastrointestinal lesions, in patients with pancreatitis, in patients with subacute bacterial endocarditis, in patients with coagulation defects including those due to liver or kidney disease, or after recent surgery, childbirth, or trauma. It should not be given to patients at increased risk of cerebral bleeding including those with severe hypertension, haemorrhage or recent stroke, or to patients with cerebral neoplasm. It should not be given in pregnancy, particularly in the first 18 weeks because of the risk of placental separation and it has been suggested that it should not be used during heavy vaginal bleeding.

Invasive procedures, including intramuscular injections, should be avoided during, and immediately before and after, streptokinase therapy as they may increase the risk of bleeding; care should be taken when physically handling patients. Streptokinase should also be used with care in elderly patients. Patients with mitral stenosis associated with atrial fibrillation are more likely to have left heart thrombus which may lead to cerebral embolism after thrombolytic therapy. Although there is a theoretical risk of retinal bleeding in patients with diabetic retinopathy the benefits of treatment generally outweigh the risk.

Anti-streptokinase antibodies are formed after streptokinase use, with antibody titres rising abruptly after about 5 days. These antibodies may cause resistance or hypersensitivity to subsequent doses of streptokinase. Therefore, further doses of streptokinase should not be given in the period between 5 days and 12 months after the initial dose (even longer periods have been suggested, see Hypersensitivity, under Adverse Effects, above); if thrombolytic therapy is required in this period an alternative non-antigenic drug should be used. High titres of anti-streptokinase antibodies may also occur in patients after some streptococcal infections such as streptococcal pharyngitis or acute rheumatic fever or in those with acute glomerulonephritis secondary to streptococcal infections; in such patients there may be resistance to streptokinase or a reduced effect.

Administration. Overinfusion of streptokinase may occur if a drop-counting infusion pump is employed.[1] This arises as a result of flocculation of the streptokinase solution producing translucent fibres that affect the drop-forming mechanism so increasing the drop size.

For a comment on the incidence of flocculation in streptokinase solutions, see Stability, above.

1. Schad RF, Jennings RH. Overinfusions of streptokinase. *Am J Hosp Pharm* 1982; **39:** 1850.

Aortic dissection. A report of 4 cases of the inappropriate use of streptokinase in patients with aortic dissection misdiagnosed as myocardial infarction.[1] Thrombolytics are likely to extend aortic dissection and adversely affect the outcome. Of the 2 patients who died, one, who would have been suitable for early operation, died through the delay caused by impaired clotting. Although early intervention with thrombolytics may be of major benefit in acute myocardial infarction it is important that accurate differential diagnosis takes place to exclude conditions such as aortic dissection and prevent avoidable deaths.

For a report of fatal haemorrhage with streptokinase used in aortic dissection misdiagnosed as empyema, see Haemorrhage under Adverse Effects, above.

1. Butler J, *et al.* Streptokinase in acute aortic dissection. *BMJ* 1990; **300:** 517–19.

Cardiopulmonary resuscitation. Thrombolytics are not recommended after prolonged or traumatic cardiopulmonary resuscitation because of the risk of haemorrhage. However, studies[1,2] in patients given cardiopulmonary resuscitation for cardiac arrest associated with acute myocardial infarction have suggested that thrombolytics are generally safe and that any increase in bleeding complications is outweighed by the benefits of thrombolysis.

1. Cross SJ, *et al.* Safety of thrombolysis in association with cardiopulmonary resuscitation. *BMJ* 1991; **303:** 1242.
2. Kurkciyan I, *et al.* Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. *J Intern Med* 2003; **253:** 128–35.

Pregnancy. Thrombolytics are generally contra-indicated in pregnancy. However there are a few reports of their use and these have been briefly reviewed.[1] In most cases, thrombolytics were given at 28 weeks of pregnancy or later to patients with deep-vein thrombosis, pulmonary embolism, or prosthetic valve thrombosis. There were some reports of favourable maternal and fetal outcomes although therapy was associated with maternal haemorrhage, including spontaneous abortion and minor vaginal bleeding, especially when given near the time of delivery. There was one report of placental abruption with fetal death.

1. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996; **125:** 751–62.

Interactions

Oral anticoagulants, heparin, and antiplatelet drugs such as aspirin are often used with streptokinase, but may increase the risk of haemorrhage. The risk may also be increased with dextrans, and with other drugs that affect coagulation or platelet function.

◊ References.

1. Harder S, Klinkhardt U. Thrombolytics: drug interactions of clinical significance. *Drug Safety* 2000; **23:** 391–9.

Pharmacokinetics

Streptokinase is rapidly cleared from the circulation after intravenous use. Clearance is biphasic with the initial and more rapid phase being due to specific antibodies. A half-life of 23 minutes has been reported for the streptokinase-activator complex.

◊ References.

1. Grierson DS, Bjornsson TD. Pharmacokinetics of streptokinase in patients based on amidolytic activator complex activity. *Clin Pharmacol Ther* 1987; **41:** 304–13.
2. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Uses and Administration

Streptokinase is a thrombolytic drug derived from various streptococci. It rapidly activates endogenous plasminogen, indirectly by means of a streptokinase-plasminogen complex, to plasmin (see Fibrinolysin, p.1287), which has fibrinolytic effects and can dissolve intravascular blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Streptokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p.1156).

Streptokinase is given by intravenous or sometimes intra-arterial infusion in the treatment of thromboembolic disorders such as myocardial infarction (p.1175), peripheral arterial thromboembolism (below), and venous thromboembolism (deep-vein thrombosis and pulmonary embolism) (p.1189). It has also been tried in ischaemic stroke (below), although alteplase is generally preferred. Streptokinase may be used to clear cannulas and shunts and is used topically with streptodornase to clear clots and purulent matter.

In acute **myocardial infarction** streptokinase is usually given intravenously as a single dose of 1.5 million units infused over 1 hour as soon as possible after the onset of symptoms. Streptokinase has also been given in a suitable dose by intracoronary infusion but coronary catheterisation with the aid of angiography is required, thus restricting use to suitably equipped centres.

In the treatment of **pulmonary embolism** and other **arteriovenous occlusions** an initial loading dose of streptokinase, normally 250 000 units infused intravenously over 30 minutes, is given to overcome any resistance due to circulating antibodies. This is followed by infusion of a maintenance dose of 100 000 units/hour for 24 to 72 hours, depending on the condition to be treated; for central retinal thrombosis, 12 hours may be adequate. Treatment should be controlled by monitoring the thrombin clotting time, which should be maintained at 2 to 4 times normal values. Since thrombolytic activity rapidly fades when the infusion stops, streptokinase treatment is generally followed after 3 to 4 hours by intravenous heparin infusion, and then oral anticoagulation, to prevent re-occlusion.

Streptokinase, as a solution containing 250 000 units in 2 mL is used to clear occluded cannulas; 1000 units/mL has been used to clear shunts of occluding thrombi.

◊ General references.

1. Fears R. Biochemical pharmacology and therapeutic aspects of thrombolytic agents. *Pharmacol Rev* 1990; **42:** 201–21.
2. Stringer KA. Beyond thrombolysis: other effects of thrombolytic drugs. *Ann Pharmacother* 1994; **28:** 752–6.
3. Ludlam CA, *et al.* Guidelines for the use of thrombolytic therapy. *Blood Coag Fibrinol* 1995; **6:** 273–85.

Administration in children. There are limited data on the use of systemic thrombolytic therapy for arterial or venous thromboembolism in children and various dosage regimens have been used, based on case studies. The most widely used drugs are streptokinase and alteplase. For streptokinase, the Eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy[1] suggests a loading dose of 2000 units/kg to be given intravenously, followed by continuous infusion of 2000 units/kg per hour for 6 to 12 hours. In the UK, the *BNFC* suggests a loading dose of 2500 to 4000 units/kg over 30 minutes, followed by infusion of 500 to 1000 units/kg per hour, continued until reperfusion occurs, up to a maximum of 3 days.

Alteplase may be preferred because of its fibrin specificity and low immunogenicity. The dose of alteplase suggested by the ACCP is 100 to 600 micrograms/kg per hour by continuous intravenous infusion over 6 hours, while the dose recommended by the *BNFC* is 100 to 500 micrograms/kg per hour for 3 to 6 hours. The use of alteplase to clear occluded catheters in children is discussed on p.1208.

1. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 454S–545S.

Empyema and pleural effusion. Thoracic empyema is treated with antibacterials and pleural drainage. Efficient removal of fluid may be impaired by fibrinous clots within the pleural cavity. Intrapleural instillation of streptokinase (100 000 to 750 000 units in up to 100 mL of sodium chloride 0.9%) has been reported to be effective in small series of patients[1-4] and there have been reports of the successful use of alteplase[5-7] and urokinase.[4,8] However, a double-blind trial[9] involving 454 patients found no benefit with streptokinase, and the role of thrombolytics remains unclear. A meta-analysis[10] found no evidence of benefit, although a systematic review[11] suggested that thrombolytics may reduce the need for surgical intervention. Intrapleural streptokinase has also been used successfully in a few patients with malignant multiloculated pleural effusion resistant to standard pleural drainage.[12]

Intrapericardial instillation of thrombolytics has been tried in a few patients with pericardial empyema to prevent the development of constrictive pericarditis.[13,14]

For reports of haemorrhage associated with intrapleural use of streptokinase, see Haemorrhage, under Adverse Effects, above.

1. Temes RT, *et al.* Intrapleural fibrinolytics in management of empyema thoracis. *Chest* 1996; **110:** 102–6.
2. Bouros D, *et al.* Role of streptokinase in the treatment of acute loculated parapneumonic pleural effusions and empyema. *Thorax* 1994; **49:** 852–5.
3. Davies RJO, *et al.* Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; **52:** 416–21.
4. Bouros D, *et al.* Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. *Am J Respir Crit Care Med* 1997; **155:** 291–5.
5. Bishop NB, *et al.* Alteplase in the treatment of complicated parapneumonic effusion: a case report. Abstract: *Pediatrics* 2003; **111:** 423. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/2/e188 (accessed 16/06/04)
6. Walker CA, *et al.* Intrapleural alteplase in a patient with complicated pleural effusion. *Ann Pharmacother* 2003; **37:** 376–9.
7. Weinstein M, *et al.* Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. Abstract: *Pediatrics* 2004; **113:** 610. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e182 (accessed 30/04/08)
8. Thomson AH, *et al.* Randomised trial of intrapleural urokinase in the treatment of childhood empyema. *Thorax* 2002; **57:** 343–7.
9. Maskell NA, *et al.* U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; **352:** 865–74. Correction. *ibid.*; 2146.
10. Tokuda Y, *et al.* Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. *Chest* 2006; **129:** 783–90.
11. Cameron R, Davies HR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 30/04/08).
12. Davies CWH, *et al.* Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. *Chest* 1999; **115:** 729–33.
13. Winkler W-B, *et al.* Treatment of exudative fibrinous pericarditis with intrapericardial urokinase. *Lancet* 1994; **344:** 1541–2.
14. Juneja R, *et al.* Intrapericardial streptokinase in purulent pericarditis. *Arch Dis Child* 1999; **80:** 275–7.

Intracardiac thrombosis. Thrombosis of prosthetic heart valves (see p.1187) is usually treated surgically, but thrombolytics have also been used. In a study[1] of patients with left-sided prosthetic valve thrombosis, thrombolytic therapy was found to be more successful than surgery, especially in those who were critically ill; most patients were given streptokinase. Another retrospective study[2] in which patients were given streptokinase, urokinase, or alteplase, concluded that thrombolytics were effective but embolic and haemorrhagic complications might limit their use.

1. Lengyel M, Vándor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis* 2001; **10:** 636–49.
2. Roudaut R, *et al.* Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003; **41:** 653–8.

Ischaemic heart disease. Thrombolytics such as alteplase, streptokinase, and urokinase have an established role in the early management of acute myocardial infarction (p.1175). Myocardial infarction is caused by coronary artery occlusion, usually due to thrombosis, and thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium. Reduction of ECG abnormalities and modification of ventricular remodelling may also contribute to their effect. Other antithrombotics, in particular aspirin and heparin, are given as adjunctive therapy.

Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and 1-year mortality figures;[1,2] benefit has been maintained in 5-year[3] and 10-year[4,5] follow-up studies. Benefit is greatest with early treatment. Trials such as the GISSI-1 study[6] and the ISIS-2 study[7] helped to establish that mortality is reduced if thrombolytics are given within 6 hours of the onset of symptoms[8] and further studies provided evidence[9,10] that patients presenting within 12 hours should receive a thrombolytic. Use after 12 hours has been associated with an increase in adverse effects,[8] and is usually reserved for patients with evidence of ongoing ischaemia. Prehospital thrombolysis is feasible and reduces the time to thrombolysis and short-term mortality.[11] Five-year follow-up of one study[12] has suggested that there is also a beneficial effect on long-term mortality.

Choice of thrombolytic depends on factors such as cost, method of administration, and contra-indications. Although streptokinase has been the most widely used, several large studies have compared clinical benefit in terms of improved left ventricular function and mortality and have shown no difference between streptokinase and other thrombolytics, including saruplase,[13] the tissue plasminogen activator alteplase,[14] anistreplase,[15] and reteplase[16] in overall efficacy. In the GUSTO-I study,[17] accelerated or 'front loaded' alteplase (that is, rapid intravenous dosage over 1⁄ hours rather than the conventional 3 hours) was more effective than streptokinase, although the study was criticised for not comparing like with like. On the other hand, alteplase might be associated with a greater risk of stroke than streptokinase.[18] Studies comparing bolus injections of reteplase with accelerated alteplase (GUSTO-III)[19] and tenecteplase with alteplase (ASSENT-2)[20] have also found no difference in mortality rate.

The overall effectiveness of thrombolytics is limited by persistent coronary occlusion, re-occlusion, and bleeding complications. Different thrombolytic regimens, such as bolus injections of reteplase, and combinations of thrombolytics, for example alteplase with streptokinase and alteplase with saruplase, have been investigated in attempts to improve patency rates. However, there has been concern that adverse effects may be higher with bolus injection. A study[21] comparing double-bolus alteplase with accelerated alteplase was terminated early when excess deaths were found in the group receiving bolus injections, and a subsequent meta-analysis[22] found a higher incidence of intracranial haemorrhage associated with bolus doses of various thrombolytics. Although use of thrombolytics before percutaneous coronary intervention (PCI) does not appear to be beneficial, a small study[23] has suggested that intracoronary streptokinase given immediately after PCI may improve microvascular reperfusion; however, there was no effect on clinical outcomes.

Thrombolytics have also been tried in other acute coronary syndromes, including unstable angina and non-ST elevation myocardial infarction (p.1157). Although small-scale studies reported some benefit the results were variable, and an overview[8] of trials in patients with suspected myocardial infarction, which included some patients with unstable angina, found that there was no mortality benefit in patients without ST elevation. In 2 studies that investigated alteplase (the TIMI-IIIB study[24] with 1473 patients) and anistreplase (the UNASEM study[25] involving 159 patients), thrombolysis failed to improve outcome and was associated with an excess of bleeding complications. Thrombolytic therapy is therefore not recommended for patients with unstable angina or non-ST elevation myocardial infarction.

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987; **ii:** 871–4.
2. Wilcox RG, *et al.* Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. *Lancet* 1990; **335:** 1175–8.
3. Simoons ML, *et al.* Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989; **14:** 1609–15.
4. Baigent C, *et al.* ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 1998; **316:** 1337–43.
5. Franzosi MG, *et al.* Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 Study. *Circulation* 1998; **98:** 2659–65.
6. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **i:** 397–402.
7. Second International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **ii:** 349–60.
8. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; **343:** 311–22.
9. LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993; **342:** 759–66.
10. EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 1993; **342:** 767–72.
11. Morrison LJ, *et al.* Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000; **283:** 2686–92.
12. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1997; **30:** 1181–6.
13. PRIMI Trial Study Group. Randomised double-blind trial of recombinant pro-urokinase against streptokinase in acute myocardial infarction. *Lancet* 1989; **i:** 863–8.
14. GISSI-2 and International Study Group. Six-month survival in 20 891 patients with acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *Eur Heart J* 1992; **13:** 1692–7.
15. Third International Study of Infarct Survival Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1992; **339:** 753–70.
16. International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995; **346:** 329–36.
17. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329:** 673–82.
18. Vaitkus PT, *et al.* Stroke complicating acute myocardial infarction: a meta-analysis of risk modification by anticoagulation and thrombolytic therapy. *Arch Intern Med* 1992; **152:** 2020–4.
19. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997; **337:** 1118–23.
20. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
21. The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators. A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction. *N Engl J Med* 1997; **337:** 1124–30.
22. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; **356:** 449–54.
23. Sezer M, *et al.* Intracoronary streptokinase after primary percutaneous coronary intervention. *N Engl J Med* 2007; **356:** 1823–34.

24. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. *Circulation* 1994; **89:** 1545–56.
25. Bär FW, *et al.* Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome: results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. *Circulation* 1992; **86:** 131–7.

Peripheral arterial thromboembolism. Thrombolytics including streptokinase may be used in the management of peripheral arterial thromboembolism (p.1178). Streptokinase has been injected intravenously or intra-arterially directly into the clot as an alternative to surgical treatment of the occlusion. It has also been infused intra-arterially to remove distal clots during surgery. The *intravenous* dose generally used is 250 000 units over 30 minutes followed by 100 000 units/hour. A lower dose of 5000 units/hour has been used *intra-arterially* directly into the clot[1] and for removal of distal clots during surgery streptokinase has been given intra-arterially in a dose of 100 000 units over 30 minutes or as five bolus doses of 20 000 units at 5-minute intervals.[2]

1. Anonymous. Non-coronary thrombolysis. *Lancet* 1990; **335:** 691–3.
2. Earnshaw JJ, Beard JD. Intraoperative use of thrombolytic agents. *BMJ* 1993; **307:** 638–9.

Stroke. Stroke (p.1185) is normally considered a contra-indication to the use of thrombolytics, and clearly they would be inappropriate in acute haemorrhagic stroke. However, when stroke is associated with thrombotic occlusion there is evidence, as with myocardial infarction, that a degree of neuronal recovery is possible if the occlusion is reversed sufficiently quickly, and thrombolytics may therefore have a role in some patients with acute ischaemic stroke.

Early studies with intravenous thrombolytics in acute *ischaemic stroke* suggested a reduction in early death, although subsequent randomised trials produced disappointing results, with the exception of one with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial).[1] The studies using streptokinase—MAST-E (Multicentre Acute Stroke Trial-Europe),[2] ASK (Australian Streptokinase Trial),[3] and MAST-I (Multicentre Acute Stroke Trial-Italy)[4,5]—were terminated before completion because of adverse outcomes (intracranial bleeding and increased mortality) in the treatment groups, particularly in those receiving therapy more than 3 hours after stroke onset.[3] The study investigating alteplase given within 6 hours of the onset of symptoms (ECASS I—European Cooperative Acute Stroke Study)[6] reported that, although some patients might benefit, overall alteplase was associated with higher mortality rates and an increase in some intracranial bleeding (parenchymal haemorrhage). In the NINDS randomised study,[1] alteplase given within 3 hours of the onset of ischaemic stroke appeared to improve clinical outcome despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[1] and this benefit was maintained at 12 months.[7] However, there was no difference in mortality or rate of recurrence of stroke. A second ECASS study (ECASS II)[8] that hoped to confirm the early findings of the NINDS study failed to confirm a statistical benefit for alteplase over placebo and found no significant differences between patients who received alteplase within 3 hours or between 3 and 6 hours. A review[9] of several studies confirmed that alteplase needed to be given early, and preferably within 90 minutes, if it was to be effective.

On the basis of the NINDS study, alteplase given within 3 hours of the onset of ischaemic stroke is now recommended for selected patients in most guidelines on stroke management.[10-14] Despite their own disappointing results, the ECASS II investigators reached a similar conclusion. However, these recommendations have been criticised.[15,16] It has been pointed out[17,18] that very few patients will be eligible for treatment with alteplase, since the time of onset of symptoms is often uncertain and in many patients more than 3 hours elapses before a definite diagnosis of ischaemic stroke is made. In addition, the NINDS study[1] excluded patients with severe stroke and those taking anticoagulants. The rationale for exclusion of patients with severe stroke is that haemorrhagic transformation is more likely to occur with large areas of infarction.[17] However, size of infarct is difficult to identify by CT scanning.[17] Anticoagulants or antiplatelets are also contra-indicated in the first 24 hours after use of alteplase. The poor results obtained in studies using streptokinase have led to recommendations that streptokinase should be avoided in ischaemic stroke,[13] although an overview of thrombolytic studies[18] suggested that it may not be worse than alteplase and that the apparent hazards of streptokinase may be accounted for by differences in trial design (for example use with anticoagulants) and in patient population. Thus, while alteplase can be considered for those few patients meeting the entry criteria for the NINDS study, a systematic review[19] concluded that further large studies are required to establish more clearly the overall role of thrombolytics in acute ischaemic stroke. Studies of the use of alteplase outside the setting of a clinical trial have had mixed results.[20-22] However, an observational study[23] found that alteplase was safe and effective when used in accordance with guidelines, while another study[24] found that it could be used in elderly patients (80 years-of-age and older), a group normally excluded from clinical trials.

Intra-arterial thrombolytics may have advantages over intravenous use and may be used in selected patients.[12-14] Studies with nasaruplase[25] and urokinase[26] have suggested benefit up to 6 hours after stroke due to middle cerebral artery occlusion, and use of intra-arterial thrombolytics may therefore be considered in such patients.[12-14] Intra-arterial thrombolytics are also used in basilar artery occlusion, although evidence to support this is limited;[12,13,27] intravenous alteplase may be an alternative.[28] Combined use of intravenous and intra-arterial alteplase,[29] as well as use of adjunctive therapies such as therapeutic ultrasound[30] or antithrombotics, are under investigation but do not yet have an established role.[13]

Intravenous thrombolytics have no role in the management of acute *haemorrhagic stroke*, but they have been given locally to facilitate the aspiration of haematomas in both intracerebral[31] and subarachnoid haemorrhage. Small studies with urokinase have shown benefit in patients with intraventricular haemorrhage.

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333:** 1581–7.
2. The Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 1996; **335:** 145–50.
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4. Multicentre Acute Stroke Trial - Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995; **346:** 1509–14.
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23. Wahlgren N, *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; **369:** 275–82.
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30. Alexandrov AV, *et al.* Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med* 2004; **351:** 2170–8.
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Preparations

BP 2008: Streptokinase Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Streptase; ***Austral.:*** Streptase; ***Austria:*** Streptase; ***Belg.:*** Streptase; ***Braz.:*** Kabikinase†; Solustrep; Streptase; Streptokin; Streptonase; Unitinase†; ***Canad.:*** Streptase; ***Chile:*** Streptase†; ***Cz.:*** Kabikinase†; Streptase; ***Denm.:*** Streptase; ***Fin.:*** Streptase; ***Fr.:*** Streptase; ***Ger.:*** Streptase; ***Gr.:*** Streptase; ***Hong Kong:*** Streptase; ***Hung.:*** Streptase; ***India:*** Fibrokinase; STpase; Streptase; Zykinase; ***Indon.:*** Streptase; ***Irl.:*** Streptase†; ***Israel:*** Kabikinase; Streptase; ***Ital.:*** Streptase†; ***Malaysia:*** Streptase†; ***Mex.:*** Streptase; ***Neth.:*** Streptase; ***Norw.:*** Kabikinase†; Streptase; ***NZ:*** Streptase; ***Pol.:*** Streptase; ***Port.:*** Streptase; ***S.Afr.:*** Streptase; ***Spain:*** Kabikinase†; Streptase; ***Swed.:*** Streptase; ***Switz.:*** Streptase; ***Thai.:*** Streptase; ***UK:*** Streptase; ***USA:*** Streptase; ***Venez.:*** Streptase.

Multi-ingredient: ***Arg.:*** Varidasa†; ***Austral.:*** Varidase†; ***Austria:*** Varidase; ***Denm.:*** Varidase; ***Fin.:*** Varidase; ***Ger.:*** Varidase; ***Irl.:*** Varidase†; ***Ital.:*** Varidase†; ***Mex.:*** Varidasa; ***Norw.:*** Varidase; ***Pol.:*** Distreptaza; ***Port.:*** Varidasa†; ***Spain:*** Ernodasa; Varidasa; ***Swed.:*** Varidase; ***UK:*** Varidase†.

Strophanthin-K

Estrofantina; Kombé Strophanthin; Strophanthin; Strophanthoside-K.

CAS — 11005-63-3.

NOTE. Do not confuse with K-strophanthin-α which is Cymarin.

Pharmacopoeias. In *Chin.*

Profile

Strophanthin-K is a cardiac glycoside or a mixture of cardiac glycosides from strophanthus, the seeds of *Strophanthus kombe* (Apocynaceae) or other spp., adjusted by admixture with a suitable diluent such as lactose so as generally to possess 40% of the activity of anhydrous ouabain.

Strophanthin-K is a positive inotrope with general properties similar to those of digoxin (p.1259). It is poorly absorbed from the gastrointestinal tract but may be given intravenously in maintenance doses of 125 to 250 micrograms daily in the management of heart failure (p.1165).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Kombetin.

Suleparoid *(rINNM)*

Heparan Sulfate; Heparan Sulphate; Heparitin Sulfate; Suléparoïde; Suleparoide; Suleparoidum.

Сулепароид

CAS — 9050-30-0.

Suleparoid Sodium *(rINN)*

Heparan Sulfate Sodium; Sodium Heparitin Sulphate; Suleparoide sódico; Suléparoïde Sodique; Suleparoidum Natricum.

Сулепароид Натрий

CAS — 57459-72-0.

Profile

Suleparoid is a naturally occurring glycosaminoglycan given orally in the management of thromboembolic disorders; it is also used topically. Suleparoid sodium is a component of danaparoid sodium (p.1255).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Aremin; Arteven; Clarema; Hemovasal; Leparan†; Spatix†; Tavidan; Vas; Vasorema†.

Multi-ingredient: ***Ital.:*** Osmogel.

Sulodexide *(rINN)*

KRX-101; Sulodexida; Sulodexidum. Glucurono-2-amino-2-deoxyglucoglucan sulfate.

Сулодексид

CAS — 57821-29-1.
ATC — B01AB11.
ATC Vet — QB01AB11.

Profile

Sulodexide is a heparinoid consisting of a mixture of low-molecular-weight heparin and dermatan sulfate. It is used as a hypolipidaemic and antithrombotic and has been given orally and parenterally for peripheral vascular disease and cerebrovascular disease. It is also included in preparations used topically for local vascular inflammation and soft-tissue disorders. Sulodexide has also been investigated for the treatment of diabetic nephropathy.

◊ References.

1. Ofosu FA. Pharmacological actions of sulodexide. *Semin Thromb Hemost* 1998; **24:** 127–38.
2. Weiss R, *et al.* The role of sulodexide in the treatment of diabetic nephropathy. *Drugs* 2007; **67:** 2681–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Vessel Due F; ***Hung.:*** Vessel Due F; ***Ital.:*** Clarens; Provenal; Ravenol; Treparin; Vessel; ***Malaysia:*** Vessel Due F; ***Philipp.:*** Vessel Due F; ***Pol.:*** Vessel Due F; ***Port.:*** Vessel; ***Rus.:*** Vessel Due F (Вессел Дуэ Ф); ***Spain:*** Aterina; Luzone; ***Venez.:*** Vessel Due.

Multi-ingredient: ***Ital.:*** Dermoangiopan†; Vessiflex†.

Sympathomimetics ⊗

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, generally resembling the effect of excessive stimulation of the sympathetic nervous system. These effects are mediated by the different types of adrenergic receptor, and the effects of individual drugs depend to a large extent on their relative activity at the different receptors, as well as the body's homoeostatic response. While many sympathomimetics are relatively selective for specific receptors, this depends on the dose, and at higher doses most have effects on all receptors.

Central effects may occur with all sympathomimetics and include anxiety, fear, restlessness, insomnia, confusion, irritability, headache, and psychotic states; dyspnoea, weakness, anorexia, nausea, and vomiting are also common. Although some sympathomimetics have direct effects, others do not cross the blood-brain barrier and their central effects appear to be a somatic response.

The most important adverse effects of the sympathomimetics are those that affect the cardiovascular system. Palpitations, tachycardia, and arrhythmias mainly result from stimulation of cardiac beta receptors, and there is also an increase in cardiac contractility; this may result in angina or cardiac arrest.

The effects on blood vessels depend on the relative effects at alpha and beta receptors, since most blood vessels have both. Stimulation of alpha receptors produces vasoconstriction, with resultant hypertension, and this may be severe enough to lead to cerebral haemorrhage or pulmonary oedema, particularly in overdosage. There may also be reflex bradycardia. Conversely, hypotension, with dizziness and fainting, and flushing, may occur due to beta$_2$-induced vasodilatation, and may contribute to tachycardia.

Alpha-mediated vasoconstriction causes cold extremities, since blood vessels supplying the skin and mucosa have only alpha receptors; this may lead to gangrene, particularly when sympathomimetics are infiltrated into digits. Extravasation similarly may cause tissue necrosis and sloughing. Topical application to mucosal surfaces also causes vasoconstriction, pain, and irritation; hypoxia may lead to rebound mucosal congestion.

Other effects include mydriasis, difficulty in micturition and urinary retention, piloerection, sweating, and increased salivation, all of which result from alpha$_1$ stimulation. Hypokalaemia and muscle tremor may occur as a result of beta$_2$ stimulation, although tremor may also occur as a somatic response. Effects on the uterus are complex and depend on the stage of the menstrual cycle; labour may be inhibited by beta$_2$ stimulation. Hyperglycaemia may occur due to complex metabolic effects, and lactic acidosis has also been reported.

Effects on the heart. The heart has mainly beta$_1$ adrenoceptors and cardiac arrhythmias are most likely with beta$_1$ agonists; increased mortality has been reported with the use of beta agonists in heart failure (see Ibopamine, p.1312). A review[1] of vasopressor sympathomimetics, which are mainly used for their alpha-agonist properties, concluded that dopamine and adrenaline were associated with the highest risk, mainly of dose-related sinus tachycardia and ventricular arrhythmias. However, the clinical significance of most arrhythmias occurring with dopamine was considered questionable; supraventricular or ventricular arrhythmias with adrenaline were most likely in patients receiving general anaesthesia or with underlying disorders of cardiac conduction. The risk with noradrenaline was uncertain, though there are few clinical reports, while phenylephrine and methoxamine were thought unlikely to cause problems. Overall the frequency of serious problems with this class of drugs did not seem to be high, and benefits outweighed the risks in most patients.

Sympathomimetics may cause myocardial ischaemia, particularly in patients with ischaemic heart disease, and severe cardiovascular effects have occurred with the use of dobutamine for cardiac stress testing (see Diagnosis and Testing, p.1272). In addition, myocardial infarction has been reported in an 11-year-old boy treated with nebulised racepinefrine for symptoms of croup,[2] and there have also been reports of myocardial ischaemia associated with adrenaline overdosage (see p.1203).

1. Tisdale JE, *et al.* Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995; **29:** 269–81.
2. Butte MJ, *et al.* Pediatric myocardial infarction after racemic epinephrine administration. Abstract: *Pediatrics* 1999; **104:** 103–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e9 (accessed 07/10/05)

Topical use. Systemic effects may occasionally follow the local or topical use of sympathomimetics, for example as eye drops for the treatment of glaucoma.[1] Psychiatric effects including hallucinations and paranoia have also occurred after both proper and improper use of sympathomimetics in decongestant preparations.[2]

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Anonymous. Drugs that cause psychiatric symptoms. *Med Lett Drugs Ther* 1993; **35:** 65–70.

Treatment of Adverse Effects

Most sympathomimetics have a short duration of action and treatment of adverse effects is mainly supportive; if given by infusion, stopping it or reducing the rate will be sufficient in many cases. A rapidly-acting alpha blocker, such as phentolamine, may be given to reverse alpha$_1$-mediated effects such as hypertension, while a beta blocker may be given for beta$_1$-mediated effects such as cardiac arrhythmias. In severe hypertension, rapidly-acting vasodilators such as glyceryl trinitrate have also been used.

In the case of extravasation of an alpha agonist, or injection into a digit, an alpha blocker such as phentolamine should be given as soon as possible to prevent tissue necrosis and ischaemic damage.

Non-catecholamine sympathomimetics may have a longer duration of action and adverse effects, particularly hypertension, may be prolonged.

Precautions

Sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia. Beta$_1$ agonists are a particular hazard in tachycardia. Sympathomimetics with beta$_2$ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful.

Sympathomimetics should be avoided in phaeochromocytoma. Caution is also needed in patients with hyperthyroidism, who may be at increased risk of effects on the heart; elevated thyroid hormone concentrations may also enhance adrenoceptor sensitivity. Diabetics and elderly patients have a high incidence of atherosclerotic disease and may also be at higher risk; the effects of sympathomimetics on blood glucose should also be considered.

Alpha agonists in particular should be used with caution in angle-closure glaucoma, as well as in patients with prostate disorders, who may be at increased risk of urinary retention. Sympathomimetics with vasoconstrictor effects may reduce placental perfusion and should possibly be avoided in pregnancy; adrenaline and others with beta$_2$-mediated effects may also inhibit labour.

If sympathomimetics are used for circulatory support, hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be corrected either before starting the sympathomimetic or while it is being given. Blood pressure should be monitored regularly during treatment.

Interactions

Interactions with sympathomimetics are complex and may be hazardous; they result mainly from their pharmacological actions at alpha and beta receptors.

Increased cardiac effects may occur with drugs that increase the sensitivity of the myocardium to beta$_1$ agonists; hazardous arrhythmias may occur with volatile anaesthetics, particularly cyclopropane or halothane. Caution is also required with thyroid hormones, and with drugs that affect cardiac conduction, such as cardiac glycosides and antiarrhythmics.

All sympathomimetics affect blood pressure and should be used with caution with antihypertensive drugs or drugs that cause hypotension, particularly those whose action involves the sympathetic nervous system. Direct-acting sympathomimetics with alpha-agonist actions specifically reverse the hypotensive effect of adrenergic neurone blockers such as guanethidine, and severe hypertension may result. There are also complex interactions between both alpha and beta blockers and sympathomimetics, particularly those that have actions at both types of receptor. Alpha blockers antagonise the effects at alpha receptors but leave the beta-mediated effects unopposed, leading to an increased risk of hypotension and tachycardia. Beta blockers, especially those that are non-selective, antagonise the effects at beta receptors but leave the alpha-mediated effects unopposed, increasing the risk of hypertension and reflex bradycardia. They also antagonise the bronchodilating effects of beta$_2$ agonists. Severe anaphylaxis in patients taking non-cardioselective beta blockers may not respond to adrenaline (see below).

Hazardous interactions resulting in severe hypertension may occur with MAOIs (including RIMAs) and sympathomimetics, especially those that have indirect actions, since MAOIs increase the amount of noradrenaline stored in adrenergic nerve endings. Sympathomimetics for which the risk is particularly high include dexamfetamine, dopamine, dopexamine, ephedrine, isometheptene, mephentermine, metaraminol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine. The effects of direct-acting sympathomimetics such as adrenaline and noradrenaline may also be slightly enhanced. For additional warnings see under Phenelzine (p.418) and Moclobemide (p.411).

Tricyclic antidepressants block the inactivation of adrenaline and noradrenaline by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur. Conversely, the effect of indirectly-acting sympathomimetics could theoretically be reduced by tricyclics, although there is little clinical evidence that this occurs. There is also no evidence that an interaction occurs when local anaesthetic solutions containing adrenaline or noradrenaline are used in patients taking MAOIs or tricyclics, although great care needs to be taken to avoid inadvertent intravenous injection of these local anaesthetic preparations.

Interactions may also occur between sympathomimetics and drugs that have similar or opposing effects through non-adrenergic mechanisms. Sympathomimetics with central actions may potentiate the effects of CNS stimulants, while the vasoconstrictor and pressor effects of alpha agonists may be enhanced by drugs with similar effects, such as ergot alkaloids or oxytocin. Beta$_2$-mediated hypokalaemia may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, and aminophylline or theophylline; patients given high doses of beta$_2$ agonists with such drugs should have their plasma-potassium concentration monitored (see Interactions of Salbutamol, p.1132). Hypokalaemia may also contribute to the increased susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides.

Antiparkinsonian drugs. Additive cardiovascular toxicity may occur when some sympathomimetics are given with antiparkinsonian drugs such as *levodopa* (see p.808) and *bromocriptine* (see p.800). Severe hypertension may also occur with some sympathomimetics and *selegiline* (see p.818), possibly due to inhibition of peripheral monoamine oxidase.

Beta blockers. The interactions between beta blockers and sympathomimetics are complex and depend on the selectivity of both drugs. Patients given adrenaline (including the low doses used with local anaesthetics) while taking non-selective beta blockers such as *propranolol* can develop raised blood pressure due to alpha-mediated vasoconstriction, followed by reflex bradycardia, and occasionally cardiac arrest;[1] the bronchodilator effects of adrenaline and other beta$_2$ agonists are also inhibited. In contrast, cardioselective beta blockers such as *metoprolol*, have minimal effects on blood pressure and heart rate since they only inhibit the beta$_1$- mediated effects, leaving the beta$_2$-mediated vasodilatation to balance the vasoconstrictor effect. However, beta blockers that also have alpha-blocking effects, such as *carvedilol*, may cause hypotension since only the beta$_2$-induced vasodilatation remains; such an interaction has been reported with dobutamine.[2] Low doses of cardioselective beta blockers do not appear to interfere with sympathomimetic (isoprenaline)-induced bronchodilatation,[3] although the effect of larger doses is uncertain.

Propranolol has also been shown to inhibit the favourable pressor and bronchodilator responses to adrenaline when given for anaphylaxis.[4] Thus, patients on long-term treatment with some non-cardioselective beta blockers who develop anaphylaxis may be relatively refractory to adrenaline.

1. Jay GT, Chow MSS. Interaction of epinephrine and β-blockers. *JAMA* 1995; **274:** 1830–2.
2. Lindenfeld J, *et al.* Hypotension with dobutamine: β-adrenergic antagonist selectivity at low doses of carvedilol. *Ann Pharmacother* 1999; **33:** 1266–9.
3. Decalmer PBS, *et al.* Beta blockers and asthma. *Br Heart J* 1978; **40:** 184–9.
4. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; **47:** 35–7.

General anaesthetics. Anaesthesia may sensitise the myocardium to the effects of sympathomimetics, increasing the risk of arrhythmias, and fatalities have been attributed to the use of adrenaline with *halothane* anaesthesia.[1] It has been suggested[2] that the use of adrenaline for haemostasis during surgery is a particular risk, although use of a low dose may be safe in patients anaesthetised with *cyclopropane*, *halothane*, or similar volatile anaesthetics; other factors likely to increase the irritability of the myocardium, such as carbon-dioxide retention, hypoxia, or the use of cocaine, should be avoided.[2,3] For *halothane* or *trichloroethylene* anaesthesia a maximum strength for the adrenaline solution of 1 in 100 000, given at a rate not exceeding 10 mL in any 10-minute period or 30 mL in 1 hour, has been recommended;[3] this may also apply for cyclopropane, although the risk of arrhythmias is higher.[3] Other volatile anaesthetics generally appear to carry less risk.

1. Buzik SC. Fatal interaction? Halothane, epinephrine and tooth implant surgery. *Can Pharm J* 1990; **123:** 68–9 and 81.
2. Anonymous. Anaesthetics and the heart. *Lancet* 1967; **i:** 484–5.
3. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. *Anesthesiology* 1968; **29:** 763.

Theophylline. For discussion of possible interactions between sympathomimetics with beta-agonist actions and theophylline, see p.1145.

Vasodilators. Paradoxical hypotension may occur when sympathomimetics with both alpha- and beta-agonist properties are given with *tolazoline*, and there has been a report[1] of fatal hypotension in a patient given tolazoline and dopamine together. The mechanism of the interaction appears to be antagonism of the alpha-mediated vasoconstrictor effect of the sympathomimetic by the alpha-blocking effects of tolazoline, leaving the vasodilator effects unopposed.

1. Carlon GC. Fatal association of tolazoline and dopamine. *Chest* 1979; **76:** 336.

Actions and Uses

Sympathomimetics have actions that mimic the effects of stimulation of postganglionic (adrenergic) nerves. They include the endogenous catecholamines adrenaline, noradrenaline, and dopamine, and other drugs that directly stimulate adrenergic receptors, as well as drugs that have an indirect action by stimulating the release of noradrenaline from storage vesicles in adrenergic nerve endings. Phenylephrine is an example of a direct-acting sympathomimetic, whereas ephedrine and many other sympathomimetics have both direct and indirect effects.

The endogenous sympathomimetics are catecholamines, consisting of a catechol portion (characterised by hydroxy groups at adjacent positions on a benzene ring) and an aliphatic amine portion. Adrenaline and noradrenaline both have direct actions on adrenergic receptors, whereas dopamine has direct and indirect actions, as well as stimulating specific dopamine receptors. Although sympathetic nerves are generally termed adrenergic, the principal neurotransmitter is actually noradrenaline; it also acts as a neurotransmitter in the CNS. The major physiological role of adrenaline is metabolic. Dopamine is an important neurotransmitter within the CNS, but also has a role peripherally within the renal, mesenteric, and coronary vasculature.

Adrenergic receptors are classified as either alpha or beta receptors, and these are subdivided into a number of types. Dopamine receptors are a distinct group of receptors that are mainly found in the CNS, and at least 5 subtypes are known (see p.791); D$_1$ receptors also occur in some vascular beds. The effects of adrenergic stimulation depend on the location and activity of the receptors:

- alpha$_1$ receptors are found primarily in blood vessels, as well as in the skin, eye, bladder, uterus, and liver. Stimulation leads to vasoconstriction, particularly in the vessels of the skin and mucosa, abdominal viscera, and kidney; this results in an increase in blood pressure, sometimes with compensatory reflex bradycardia. Alpha$_1$ stimulation also results in contraction of other smooth muscle, including the urinary sphincter and the uterus, and induces mydriasis in the eye
- alpha$_2$ receptors are mainly found presynaptically. Stimulation appears to play a role in feedback inhibition of neurotransmitter release and may be involved in the inhibition of intestinal activity; it also plays a role in the inhibition of insulin secretion
- beta$_1$ receptors are found predominantly in the heart. Stimulation produces an increase in the rate and force of contraction, increased conduction velocity, and greater automaticity
- beta$_2$ receptors are mainly found in blood vessels and the lung, as well as in the uterus, the gastrointestinal tract, the liver, and the ciliary body of the eye. Stimulation leads to vasodilatation, bronchodilatation, uterine relaxation, and a decrease in gastrointestinal motility; it also results in release of insulin and enhances gluconeogenesis and glycogenolysis
- beta$_3$ receptors are found in fat cells and are thought to have a role in lipolysis and thermogenesis; they have also been found in the heart, uterus, and bladder but their role is not clear
- D$_1$ receptors are found in the renal, mesenteric, and coronary vascular beds. Stimulation leads to vasodilatation

Sympathomimetics differ in their relative affinity for each type of receptor, and also in whether they have direct or indirect actions (see Table 5, below). Their effects generally reflect these characteristics, although both may depend on the dose. Feedback mechanisms and the homoeostatic response of the body are also important. The specific effects of the different sympathomimetics are described in more detail in the individual monographs.

The endogenous catecholamines all have a very short action and are inactive by mouth; they are also highly polar and do not cross the blood-brain barrier. Other sympathomimetics are analogues of catecholamines but generally have a longer duration of action and are orally active; many also cross the blood-brain barrier and have central effects. For example, dexamfetamine has marked central stimulant effects, while the seemingly paradoxical antihypertensive action of alpha$_2$ agonists such as clonidine may be due to central effects that outweigh their effects in vascular smooth muscle.

The differing characteristics of the sympathomimetics mean that they are used in a wide range of disorders. Those with alpha$_1$-agonist effects are mainly used to increase the blood pressure in hypotensive disorders and in shock (p.1183). Some alpha agonists, such as phenylephrine (p.1568), are also applied topically to produce vasoconstriction of mucosal surfaces and are used for the symptomatic relief of nasal congestion and in eye disorders; they may also be used as mydriatics. Alpha$_2$ agonists are used as central antihypertensives (see Clonidine, p.1247), or in the treatment of glauco-

Table 5. Actions of sympathomimetics.

	Action		Receptor specificity			
	Direct	Indirect	α	β_1	β_2	DA*
Adrenaline	+		+	+	+	
Dobutamine	+		+	+	+	
Dopamine	+	+	+	+		+
Dopexamine	+	+			+	+
Ephedrine	+	+	+	+	+	
Etilefrine	+		+	+	+	
Ibopamine		+	+	+	+	+
Isoprenaline	+			+	+	
Mephentermine	+	+	+	+		
Metaraminol	+	+	+	+		
Methoxamine	+		+			
Midodrine	+		+			
Noradrenaline	+		+	+		
Phenylephrine	+		+			

* = Dopaminergic

ma (see Apraclonidine, p.1877). Beta$_1$ agonists are mainly used for their inotropic actions in acute heart failure and shock, while beta$_2$ agonists such as salbutamol (p.1131) are used for their bronchodilator effects and as uterine relaxants in premature labour. Sympathomimetics with mainly CNS effects may be used as central stimulants (see Dexamfetamine, p.2153).

Talinolol *(rINN)* ⊗

Talinololum. (±)-1-{*p*-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-phenyl}-3-cyclohexylurea.

Талинолол

$C_{20}H_{33}N_3O_3$ = 363.5.
CAS — 57460-41-0.
ATC — C07AB13.
ATC Vet — QC07AB13.

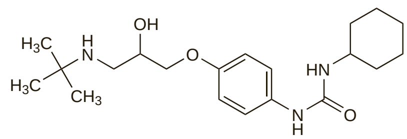

Profile

Talinolol is a cardioselective beta blocker (p.1225). It is given orally in the management of hypertension (p.1171) and other cardiovascular disorders, in doses of up to 300 mg daily. It has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Cordanum†; ***Ger.:*** Cordanum; ***Rus.:*** Cordanum (Корданум).

Teclothiazide Potassium *(BANM, rINNM)* ⊗

Kalii Teclothiazidum; Téclothiazide Potassique; Teclotiazida potásica; Tetrachlormethiazide Potassium. 6-Chloro-3,4-dihydro-3-trichloromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide potassium.

Калия Теклотиазид

$C_8H_7Cl_4N_3O_4S_2$,K = 454.2.
CAS — 4267-05-4 (teclothiazide); 5306-80-9 (teclothiazide potassium).

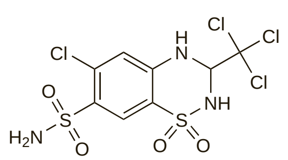

(teclothiazide)

Profile

Teclothiazide potassium is a thiazide diuretic (see Hydrochlorothiazide, p.1307) used in the treatment of oedema.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Quimodril.

Tedisamil *(USAN, rINN)*

KC-8857; Tédisamil; Tedisamilum. 3′,7′-Bis(cyclopropylmethyl)-spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane].

Тедизамил

$C_{19}H_{32}N_2$ = 288.5.
CAS — 90961-53-8.
ATC — C01EB12.
ATC Vet — QC01EB12.

Profile

Tedisamil is an antiarrhythmic under investigation for the treatment of atrial arrhythmias.

◊ References.

1. Hohnloser SH, *et al.* Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol* 2004; **44:** 99–104.

Telmisartan *(BAN, USAN, rINN)*

BIBR-277; BIBR-277-SE; Telmisartaani; Telmisartán; Telmisartanum. 4′-{[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl}-2-biphenylcarboxylic acid.

Тельмизартан

$C_{33}H_{30}N_4O_2$ = 514.6.
CAS — 144701-48-4.
ATC — C09CA07.
ATC Vet — QC09CA07.

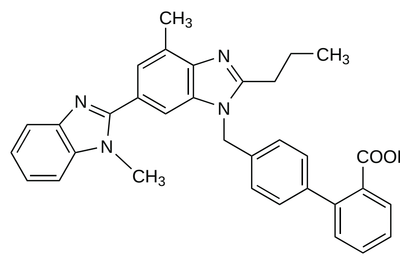

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. it dissolves in 1M sodium hydroxide. It exhibits polymorphism.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326. Telmisartan should be used with caution in patients with hepatic impairment or biliary obstruction.

◊ References.

1. Michel MC, *et al.* Safety of telmisartan in patients with arterial hypertension : an open-label observational study. *Drug Safety* 2004; **27:** 335–44.

Interactions

As for Losartan Potassium, p.1327.

Digoxin. Telmisartan may increase serum concentrations of digoxin (see Angiotensin II Receptor Antagonists under Interactions of Digoxin, p.1261) but the interaction is probably not clinically significant.

Pharmacokinetics

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% after a 40-mg dose and 58% after a 160-mg dose. Peak plasma concentrations of telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours.

◊ References.

1. Stangier J, *et al.* Absorption, metabolism, and excretion of intravenously and orally administered [C]telmisartan in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1312–22.

Uses and Administration

Telmisartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171).

Telmisartan is given orally. After a dose the hypotensive effect peaks within 3 hours and persists for at least 24 hours. The maximum hypotensive effect occurs within about 4 to 8 weeks after starting therapy.

In hypertension, telmisartan is given in an initial dose of 40 mg once daily. This may be increased, if necessary, to a maximum dose of 80 mg once daily. Lower doses should be considered in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. McClellan KJ, Markham A. Telmisartan. *Drugs* 1998; **56:** 1039–44.
2. Sharpe M, *et al.* Telmisartan: a review of its use in hypertension. *Drugs* 2001; **61:** 1501–29.
3. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs* 2006; **66:** 51–83.
4. Gosse P. A review of telmisartan in the treatment of hypertension: blood pressure control in the early morning hours. *Vasc Health Risk Manag* 2006; **2:** 195–201.
5. Yamagishi S, *et al.* Potential utility of telmisartan, an angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor-γ (PPAR-γ)-modulating activity for the treatment of cardiometabolic disorders. *Curr Mol Med* 2007; **7:** 463–9.
6. Francischetti EA, *et al.* Treatment of hypertension in individuals with the cardiometabolic syndrome: role of an angiotensin II receptor blocker, telmisartan. *Expert Rev Cardiovasc Ther* 2008; **6:** 289–303.

Administration in hepatic or renal impairment. Giving telmisartan to patients with hepatic impairment resulted in an increase in bioavailability and a reduction in clearance compared with healthy subjects.[1] Although telmisartan was well tolerated, it was suggested that lower doses should be considered in patients with hepatic impairment. In the UK telmisartan is contra-indicated in severe hepatic impairment and a maximum dose of 40 mg once daily is recommended for patients with mild to moderate impairment

Telmisartan appears to be well tolerated in patients with renal impairment, including those on dialysis.[2] However, in the UK, an initial dose of 20 mg once daily is recommended for patients with severe renal impairment or on haemodialysis.

1. Stangier J, *et al.* Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1355–64.
2. Sharma AM, *et al.* Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol* 2005; **63:** 250–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gliosartan; Micardis; Pritor†; ***Austral.:*** Micardis; Pritor†; ***Austria:*** Micardis; ***Belg.:*** Kinzalmono; Micardis; ***Braz.:*** Micardis; Pritor; ***Canad.:*** Micardis; ***Chile:*** Micardis; Pritoral†; Samertan; ***Cz.:*** Kinzalmono; Micardis; Pritor; ***Denm.:*** Kinzalmono†; Micardis; ***Fin.:*** Kinzalmono; Micardis; ***Fr.:*** Micardis; Pritor; ***Ger.:*** Kinzalmono; Micardis; ***Gr.:*** Micardis; Pritor; ***Hong Kong:*** Micardis; ***Hung.:*** Micardis; Pritor; ***India:*** Telma; Telpres; ***Indon.:*** Micardis; ***Irl.:*** Micardis; ***Ital.:*** Micardis; Pritor; ***Jpn:*** Micardis; ***Malaysia:*** Micardis; ***Mex.:*** Micardis; Predxal; ***Neth.:*** Kinzalmono; Micardis; Pritor; ***Norw.:*** Micardis; ***NZ:*** Micardis; ***Philipp.:*** Micardis; Pritor; ***Pol.:*** Micardis; Pritor; ***Port.:*** Kinzalmono; Micardis; Pritor; ***Rus.:*** Micardis (Микардис); Pritor (Прайтор); ***S.Afr.:*** Micardis; ***Singapore:*** Micardis; ***Spain:*** Micardis; Pritor; ***Swed.:*** Kinzalmono†; Micardis; ***Switz.:*** Kinzal; Micardis; ***Thai.:*** Micardis; ***Turk.:*** Micardis; Pritor; ***UK:*** Micardis; ***USA:*** Micardis; ***Venez.:*** Micardis; Pritor.

Multi-ingredient: ***Arg.:*** Gliosartan Plus; Micardis Plus; ***Austral.:*** Micardis Plus; ***Austria:*** MicardisPlus; ***Belg.:*** Kinzalkomb; Micardis Plus; ***Braz.:*** Micardis HCT; Pritor HCT; ***Canad.:*** Micardis Plus; ***Chile:*** Micardis Plus; ***Cz.:*** Kinzalkomb; MicardisPlus; PritorPlus; ***Denm.:*** Kinzalkomb†; MicardisPlus; ***Fin.:*** Kinzalkomb; MicardisPlus; ***Fr.:*** MicardisPlus; PritorPlus; ***Ger.:*** Kinzalkomb; MicardisPlus; ***Gr.:*** Micardis Plus; Pritor Plus; ***Hong Kong:*** Micardis Plus; ***Hung.:*** MicardisPlus; PritorPlus; ***India:*** Telma-H†; Telpres-H; ***Indon.:*** Micardis Plus; ***Irl.:*** MicardisPlus; ***Ital.:*** Micardis Plus; PritorPlus; ***Malaysia:*** Micardis Plus; ***Mex.:*** Micardis Plus; Predxal Plus; ***Neth.:*** Kinzalkomb; Micardis Plus; PritorPlus; ***Norw.:*** MicardisPlus; ***Philipp.:*** Micardis Plus; Pritor-Plus; ***Pol.:*** Micardis Plus; Pritor Plus; ***Port.:*** Kinzalkomb; Micardis Plus; PritorPlus; ***Rus.:*** MicardisPlus (МикардисПлюс); ***S.Afr.:*** Co-Micardis; ***Singapore:*** Micardis Plus; ***Spain:*** Micardis Plus; Pritor Plus; ***Swed.:*** Kinzalkomb†; Micardis Plus; ***Switz.:*** Kinzalplus; MicardisPlus; ***Thai.:*** Micardis Plus; ***Turk.:*** Micardis Plus; Pritor Plus; ***UK:*** MicardisPlus; ***USA:*** Micardis HCT; ***Venez.:*** Micardis Plus; Pritor Plus.

Temocapril Hydrochloride *(BANM, USAN, rINNM)*

CS-622; Hidrocloruro de temocapril; Témocapril, Chlorhydrate de; Temocaprili Hydrochloridum. (+)-(2*S*,6*R*)-6-{[(1*S*)-1-Ethoxycarbonyl-3-phenylpropyl]amino}tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid hydrochloride.

Темокаприла Гидрохлорид

$C_{23}H_{28}N_2O_5S_2$,HCl = 513.1.
CAS — 111902-57-9 (temocapril); 110221-44-8 (temocapril hydrochloride).
ATC — C09AA14.
ATC Vet — QC09AA14.

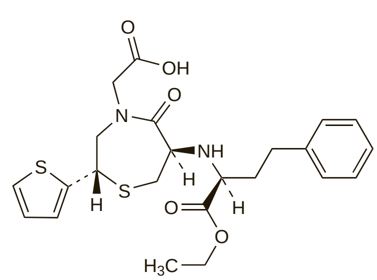

(temocapril)

Profile

Temocapril is an ACE inhibitor (p.1193) that has been used in the treatment of hypertension (p.1171). It owes its activity to the diacid temocaprilat to which it is converted after oral doses.

◊ References.

1. Nakashima M, *et al.* Pharmacokinetics of temocapril hydrochloride, a novel angiotensin converting enzyme inhibitor, in renal insufficiency. *Eur J Clin Pharmacol* 1992; **43:** 657–9.

2. Oguchi H, *et al.* Pharmacokinetics of temocapril and enalapril in patients with various degrees of renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 421–7.
3. Furuta S, *et al.* Pharmacokinetics of temocapril, an ACE inhibitor with preferential biliary excretion, in patients with impaired liver function. *Eur J Clin Pharmacol* 1993; **44:** 383–5.
4. Arakawa M, *et al.* Pharmacokinetics and pharmacodynamics of temocapril during repeated dosing in elderly hypertensive patients. *Eur J Clin Pharmacol* 2001; **56:** 775–9.
5. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.
6. Yasunari K, *et al.* Pharmacological and clinical studies with temocapril, an angiotensin converting enzyme inhibitor that is excreted in the bile. *Cardiovasc Drug Rev* 2004; **22:** 189–98.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Acecol.

Tenecteplase *(BAN, USAN, rINN)*

Tenecteplasa; Ténectéplase; Tenecteplasum; TNK-tPA. [103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]plasminogen activator (human tissue-type).

Тенектеплас

CAS — 191588-94-0.
ATC — B01AD11.
ATC Vet — QB01AD11.

Description. Tenecteplase is a 527 amino acid glycoprotein produced by recombinant DNA technology. It is a modified form of human tissue plasminogen activator.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402

Interactions

As for Streptokinase, p.1404

Pharmacokinetics

After intravenous injection in patients with acute myocardial infarction, tenecteplase has a biphasic clearance from plasma with an initial half-life of 20 to 24 minutes and a terminal phase half-life of 90 to 130 minutes. It is cleared mainly by hepatic metabolism.

◊ Reviews.

1. Tanswell P, *et al.* Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet* 2002; **41:** 1229–45.

Uses and Administration

Tenecteplase is a thrombolytic drug. It converts plasminogen to plasmin, a proteolytic enzyme that has fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Tenecteplase is a fibrin-specific thrombolytic (see p.1156).

Tenecteplase is used similarly to streptokinase (p.1404) in acute myocardial infarction (p.1175). It is given intravenously as a single bolus dose over 5 to 10 seconds as soon as possible after the onset of symptoms. The dose is based on body-weight and ranges from 30 mg in patients less than 60 kg to a maximum of 50 mg in those 90 kg or above.

◊ References.

1. Cannon CP, *et al.* TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998; **98:** 2805–14.
2. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
3. Llevadot J, *et al.* Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; **286:** 442–9.
4. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358:** 605–13.
5. Turcasso NM, Nappi JM. Tenecteplase for treatment of acute myocardial infarction. *Ann Pharmacother* 2001; **35:** 1233–40.
6. Dunn CJ, Goa KL. Tenecteplase: a review of its pharmacology and therapeutic efficacy in patients with acute myocardial infarction. *Am J Cardiovasc Drugs* 2001; **1:** 51–66.
7. Melzer C, *et al.* Fibrinolysis of acute peripheral arterial occlusion with tenecteplase—a new weight-optimized treatment regimen. *J Thromb Thrombolysis* 2004; **18:** 43–6.
8. Spöhr F, *et al.* International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. *Eur J Clin Invest* 2005; **35:** 315–23.
9. Kelly RV, *et al.* Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. *Catheter Cardiovasc Interv* 2005; **66:** 327–32.
10. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; **367:** 569–78.
11. Kline JA, *et al.* Tenecteplase to treat pulmonary embolism in the emergency department. *J Thromb Thrombolysis* 2007; **23:** 101–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Metalyse; ***Austria:*** Metalyse; ***Belg.:*** Metalyse; ***Braz.:*** Metalyse; ***Canad.:*** TNKase; ***Chile:*** Metalyse; ***Cz.:*** Metalyse; ***Denm.:*** Metalyse; ***Fin.:*** Metalyse; ***Fr.:*** Metalyse; ***Ger.:*** Metalyse; ***Gr.:*** Metalyse; ***Hong Kong:*** Metalyse; ***Hung.:*** Metalyse; ***Irl.:*** Metalyse; ***Ital.:*** Metalyse; ***Malaysia:*** Metalyse; ***Mex.:*** Metalyse; ***Neth.:*** Metalyse; ***Norw.:*** Metalyse; ***NZ:*** Metalyse; ***Pol.:*** Metalyse; ***Port.:*** Metalyse; ***Rus.:*** Metalyse (Метализе); ***S.Afr.:*** Metalyse; ***Spain:*** Metalyse; ***Swed.:*** Metalyse; ***Switz.:*** Metalyse; ***Thai.:*** Metalyse; ***UK:*** Metalyse; ***USA:*** TNKase.

Tenitramine

Tenitramina. *NNN′N′*-Tetrakis(2-hydroxyethyl)ethylenediamine tetranitrate.

$C_{10}H_{20}N_6O_{12}$ = 416.3.
CAS — 21946-79-2.
ATC — C01DA38.
ATC Vet — QC01DA38.

Profile

Tenitramine is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) that has been used in angina pectoris (p.1157).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tenitran†.

Teprotide *(BAN, USAN, rINN)*

BPF_{9a}; L-Pyroglutamyl-L-tryptophyl-L-prolyl-L-arginyl-L-prolyl-L-glutaminyl-L-isoleucyl-L-prolyl-L-proline; SQ-20881; Teprotida; Téprotide; Teprotidum; 2-L-Tryptophan-3-de-L-leucine-4-de-L-proline-8-L-glutaminebradykinin potentiator B. 5-oxo-Pro-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro.

Тепротид

$C_{53}H_{76}N_{14}O_{12}$ = 1101.3.
CAS — 35115-60-7.

Profile

Teprotide is a nonapeptide originally found in the venom of *Bothrops jararaca*, a South American pit-viper. It is an ACE inhibitor with a short duration of action and has been given parenterally as an investigational tool.

Terazosin Hydrochloride

(BANM, USAN, rINNM)

Abbott-45975; Hidrocloruro de terazosina; Teratsosiinihydrokloridi; Terazosin Hidroklorür; Térazosine, chlorhydrate de; Terazosinhydroklorid; Terazosini hydrochloridum. 1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(tetrahydro-2-furoyl)piperazine hydrochloride dihydrate; 6,7-Dimethoxy-2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]quinazolin-4-ylamine hydrochloride dihydrate.

Теразозина Гидрохлорид

$C_{19}H_{25}N_5O_4,HCl,2H_2O$ = 459.9.
CAS — 63590-64-7 (terazosin); 63074-08-8 (anhydrous terazosin hydrochloride); 70024-40-7 (terazosin hydrochloride dihydrate).
ATC — G04CA03.
ATC Vet — QG04CA03.

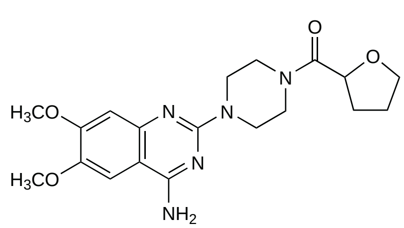

(terazosin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Terazosin Hydrochloride Dihydrate). White or slightly yellow, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol; practically insoluble in acetone. A 2% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 31 (Terazosin Hydrochloride). A white to pale yellow, crystalline powder. soluble in water and in methyl alcohol; freely soluble in isotonic saline solution; slightly soluble in alcohol and in 0.1N hydrochloric acid; practically insoluble in acetone and in hexanes; very slightly soluble in chloroform. Store in airtight containers at a temperature between 20° and 25°.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375.

Urinary incontinence. For reference to urinary incontinence associated with terazosin, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Interactions

As for Prazosin Hydrochloride, p.1376.

Pharmacokinetics

Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses; the bioavailability is reported to be about 90%. Peak plasma concentrations are achieved in about 1 hour. Terazosin is 90 to 94% protein bound. It is metabolised in the liver; one of the metabolites is reported to possess antihypertensive activity. The half-life in plasma is about 12 hours. Terazosin is excreted in faeces via the bile, and in the urine, as unchanged drug and metabolites.

Uses and Administration

Terazosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376), but a longer duration of action.

It is used in the management of hypertension (p.1171) and in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction.

Terazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Terazosin hydrochloride 1.2 mg is equivalent to about 1 mg of terazosin. After oral doses its hypotensive effects are seen within 15 minutes and may last for up to 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose the initial dose for both hypertension and benign prostatic hyperplasia is 1 mg of terazosin at bedtime, increasing gradually at intervals of 7 days according to the patient's response. For **hypertension** the usual maintenance dose is 2 to 10 mg once daily and the usual maximum dose is 20 mg daily in a single dose or two divided doses. For **benign prostatic hyperplasia** the usual maintenance dose is 5 to 10 mg once daily.

◊ Reviews.

1. Titmarsh S, Monk JP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987; **33:** 461–77.
2. Achari R, Laddu A. Terazosin: a new alpha adrenoceptor blocking drug. *J Clin Pharmacol* 1992; **32:** 520–3.
3. Wilt TJ, *et al.* Terazosin for benign prostatic hyperplasia. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 01/02/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Andrin; Benaprost; Blavin; Eglidon; Flumarc; Fosfomik; Geriprost; Isontyn; Panaprost; Proxatan; Rotiaz; ***Austral.:*** Hytrin; ***Austria:*** Urocard; Uroflo; Vicard; ***Belg.:*** Hytrin; Terazosabb; Uro-Hytrin; ***Braz.:*** Hytrin; ***Canad.:*** Hytrin; ***Chile:*** Adecur; Hytrin; ***Cz.:*** Hytrin; Kornam; ***Denm.:*** Sinalfa; ***Fr.:*** Dysalfa; Hytrine; ***Ger.:*** Flotrin; Heitrin; Tera; Terablock; Teranar; Terazid; Terazoflo; ***Gr.:*** Hytrin; Vlanodrin; ***Hong Kong:*** Hytrin; ***Hung.:*** Hyron†; Hytrin; Kornam†; Setegis; ***India:*** Hytrin; Olyster; Zytrin; ***Indon.:*** Hytrin; ***Irl.:*** Benph; Hytrin; ***Israel:*** Hytrin; ***Ital.:*** Ezosina; Ibiprovir†; Itrin; Prostatil; Terafluss; Teraprost; Unoprost; Urodie; ***Malaysia:*** Hytrin; Terasin; ***Mex.:*** Adecur; Hytrin; Romaken; ***Neth.:*** Hytrin; ***Norw.:*** Sinalfa; ***NZ:*** Hytrin; ***Philipp.:*** Conmy; Hytrin; Lotencin; ***Pol.:*** Hytrin; Kornam; Setegis; Tesin; ***Port.:*** Hytrin; ***Rus.:*** Hytrin (Хитрин)†; Kornam (Корнам); Setegis (Сетегис); ***S.Afr.:*** Hytrin; ***Singapore:*** Hytrin; ***Spain:*** Alfaprost; Deflox; Magnurol; Mayul; Sutif; Tazusin†; Teraumon; Zayasel; ***Swed.:*** Hytrinex; Sinalfa; ***Switz.:*** Hytrin BPH; ***Thai.:*** Hytrin; ***Turk.:*** Hytrin; ***UK:*** Hytrin; ***USA:*** Hytrin; ***Venez.:*** Adecur; Hytrin.

Tertatolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tertatolol; S-2395 (tertatolol or tertatolol hydrochloride); SE-2395 (tertatolol or tertatolol hydrochloride); Tertatolol, Chlorhydrate de; Tertatololi Hydrochloridum. (±)-1-(*tert*-Butylamino)-3-(thiochroman-8-yloxy)propan-2-ol hydrochloride.

Тертатолола Гидрохлорид

$C_{16}H_{25}NO_2S,HCl = 331.9.$

CAS — 34784-64-0 (tertatolol); 33580-30-2 (tertatolol hydrochloride).

ATC — C07AA16.

ATC Vet — QC07AA16.

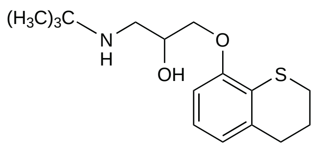

(tertatolol)

Profile

Tertatolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity.

Tertatolol is given orally as the hydrochloride in the management of hypertension (p.1171) in a dose of 5 mg tertatolol hydrochloride once daily, increased to 10 mg once daily if required.

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Artexal; ***Fr.:*** Artex; ***Irl.:*** Artexal; ***Neth.:*** Artex; ***Port.:*** Artex.

Tezosentan *(BAN, rINN)*

Tézosentan; Tezosentán; Tezosentanum. *N*-{6-(2-Hydroxyethoxy)-5-(o-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)-4-pyridyl]-4-pyrimidinyl}-5-isopropyl-2-pyridinesulfonamide.

Тезозентан

$C_{27}H_{27}N_9O_6S = 605.6.$

CAS — 180384-57-0.

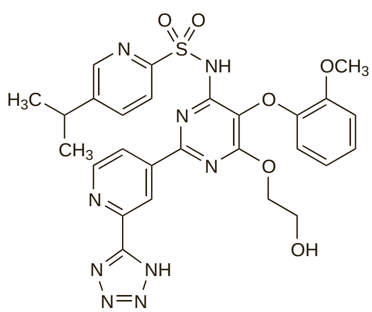

Profile

Tezosentan is an endothelin receptor antagonist that has been studied in acute heart failure.

◊ References.

1. Torre-Amione G, *et al.* Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure. *Circulation* 2001; **103:** 973–80.
2. Tovar JM, Gums JG. Tezosentan in the treatment of acute heart failure. *Ann Pharmacother* 2003; **37:** 1877–83.
3. Cotter G, *et al.* The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. *Eur J Heart Fail* 2004; **6:** 601–9.
4. McMurray JJV, *et al.* Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007; **298:** 2009–19.

Tiadenol *(rINN)*

LL-1558; Tiadénol; Tiadenolum. 2,2′-(Decamethylenedithio)diethanol.

Тиаденол

$C_{14}H_{30}O_2S_2 = 294.5.$

CAS — 6964-20-1.

ATC — C10AX03.

ATC Vet — QC10AX03.

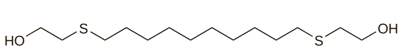

Profile

Tiadenol is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 1.2 to 2.4 g daily in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Fonlipol.

Ticlopidine Hydrochloride

(BANM, USAN, rINNM)

4-C-32; 53-32C; Hidrocloruro de ticlopidina; Ticlopidine, chlorhydrate de; Ticlopidini hydrochloridum; Tiklopidiinihydrokloridi; Tiklopidin Hidroklorür; Tiklopidinhidroklorid; Tiklopidin-hydrochlorid; Tiklopidinhydroklorid; Tiklopidino hidrochloridas. 5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride.

Тиклопидина Гидрохлорид

$C_{14}H_{14}ClNS,HCl = 300.2.$

CAS — 55142-85-3 (ticlopidine); 53885-35-1 (ticlopidine hydrochloride).

ATC — B01AC05.

ATC Vet — QB01AC05.

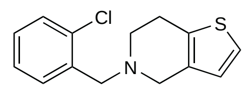

(ticlopidine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; very slightly soluble in ethyl acetate. A 2.5% solution in water has a pH of 3.5 to 4.0.

Adverse Effects and Precautions

Gastrointestinal disturbances, skin rashes, and bleeding are the most commonly reported adverse effects associated with ticlopidine therapy. Blood dyscrasias, including neutropenia, thrombotic thrombocytopenic purpura, and aplastic anaemia, have also occurred. There have been reports of hepatitis and cholestatic jaundice. Blood-lipid concentrations may increase during long-term therapy.

Ticlopidine should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or conditions with an increased risk of bleeding such as peptic ulcer disease, acute cerebral haemorrhage, or severe liver dysfunction. Full blood counts should be performed before starting treatment and every 2 weeks during the first 3 months of therapy. If ticlopidine is stopped during this period, a full blood count should be performed within 2 weeks of stopping treatment. Consideration should be given to stopping ticlopidine therapy 10 to 14 days before elective surgery.

Effects on the blood. Severe *neutropenia* or *agranulocytosis* may occur in about 1% of patients given ticlopidine[1] and fatal infection has been reported.[2] Neutropenia usually develops within the first 3 months of therapy and is reversible on stopping ticlopidine, but there has been a report[3] of a delayed reaction that occurred 18 days after ticlopidine was stopped. Isolated *thrombocytopenia* occurs in about 0.4% of patients and *thrombotic thrombocytopenic purpura*, sometimes fatal, has occurred.[1,4-7] Conversely, good results have been achieved with ticlopidine as a treatment for thrombotic thrombocytopenic purpura,[8,9] but it should only be used with extreme caution.[10] Aplastic anaemia has also occurred rarely with ticlopidine.[1,11]

Clopidogrel has also been associated with blood dyscrasias. Up to August 2004, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[12] had received 80 reports of blood dyscrasias associated with clopidogrel, although ticlopidine was associated with a much higher rate of reports. Individual cases of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome,[13-16] aplastic anaemia,[17] leucopenia,[18] and acquired haemophilia A,[19] have also been reported. However the most frequently reported adverse effect of clopidogrel, as with other antithrombotics, is bleeding, particularly when given with other drugs affecting coagulation; ADRAC had received 130 reports of haemorrhagic events, leading to fatalities in 18 cases.[12]

1. Love BB, *et al.* Adverse haematological effects of ticlopidine: prevention, recognition and management. *Drug Safety* 1998; **19:** 89–98.
2. Carlson JA, Maesner JE. Fatal neutropenia and thrombocytopenia associated with ticlopidine. *Ann Pharmacother* 1994; **28:** 1236–8.
3. Farver DK, Hansen LA. Delayed neutropenia with ticlopidine. *Ann Pharmacother* 1994; **28:** 1344–6.
4. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; **128:** 541–4.
5. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura after stenting and ticlopidine. *Lancet* 1998; **352:** 1036–7.
6. Steinhubl SR, *et al.* Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. *JAMA* 1999; **281:** 806–10.
7. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med* 1999; **159:** 2524–8.
8. Vianelli N, *et al.* Thrombotic thrombocytopenic purpura and ticlopidine. *Lancet* 1991; **337:** 1219.
9. Bobbio-Pallavicini E, *et al.* Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP): results of a randomized multicenter trial by the Italian Cooperative Group for TTP. *Haematologica* 1997; **82:** 429–35.
10. Rock G, *et al.* Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000; **85:** 410–19.
11. Symeonidis A, *et al.* Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 55 additional cases. *Am J Hematol* 2002; **71:** 24–32.
12. Adverse Drug Reactions Advisory Committee (ADRAC). Clopidogrel—haemorrhage and haematological disorders. *Aust Adverse Drug React Bull* 2004; **23:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0408.htm (accessed 17/08/05)
13. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; **342:** 1773–7.
14. Oomen PHN, *et al.* Hemolytic uremic syndrome in a patient treated with clopidogrel. *Ann Intern Med* 2000; **132:** 1006.
15. Andersohn F, *et al.* Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome associated with clopidogrel: report of two new cases. Abstract: *Heart* 2004; **90:** e57. Full version: http://heart.bmjjournals.com/cgi/content/full/90/9/e57 (accessed 17/08/05)
16. von Mach M-A, *et al.* Subacute coronary stent thrombosis in a patient developing clopidogrel associated thrombotic thrombocytopenic purpura. Abstract: *Heart* 2005; **91:** e14. Full version: http://heart.bmjjournals.com/cgi/content/full/91/2/e14 (accessed 17/08/05)
17. Trivier J-M, *et al.* Fatal aplastic anaemia associated with clopidogrel. *Lancet* 2001; **357:** 446.
18. McCarthy MW, Kockler DR. Clopidogrel-associated leukopenia. *Ann Pharmacother* 2003; **37:** 216–19.
19. Haj M, *et al.* Acquired haemophilia A may be associated with clopidogrel. *BMJ* 2004; **329:** 323.

Effects on the gastrointestinal tract. Diarrhoea is a common adverse effect of ticlopidine therapy; it usually occurs during the first few months of therapy and resolves within 1 to 2 weeks without stopping therapy. However, there has been a report[1] of diarrhoea and weight loss of 2 months duration that first presented 2 years after ticlopidine was started; diarrhoea resolved when ticlopidine was withdrawn.

1. Mansoor GA, Aziz K. Delayed chronic diarrhea and weight loss possibly due to ticlopidine therapy. *Ann Pharmacother* 1997; **31:** 870–2.

Effects on the joints. Acute arthritis associated with a diffuse rash developed in a patient shortly after starting treatment with ticlopidine.[1] Both the rash and the arthritis resolved on withdrawal, and it was suggested that a hypersensitivity reaction might be involved. One case of polyarthritis and 3 cases of arthralgia associated with ticlopidine had been reported to the UK CSM up to March 2001. Two cases of acute arthritis have also been reported[2] with clopidogrel; symptoms developed 2 to 3 weeks after starting treatment and resolved after stopping.

1. Dakik HA, *et al.* Ticlopidine associated with acute arthritis. *BMJ* 2002; **324:** 27.
2. Garg A, *et al.* Clopidogrel associated with acute arthritis. *BMJ* 2000; **320:** 483.

Effects on the kidneys. A reversible deterioration in renal function has been reported in patients given ticlopidine after coronary stent implantation.[1,2] There has also been a report[3] of membranous nephropathy with nephrotic syndrome in a patient receiving clopidogrel.

1. Elsman P, Zijlstra F. Ticlopidine and renal function. *Lancet* 1996; **348:** 273–4.
2. Virdee M, *et al.* Ticlopidine and renal function. *Lancet* 1996; **348:** 1031–2.
3. Tholl U, *et al.* Clopidogrel and membranous nephropathy. *Lancet* 1999; **354:** 1443–4.

Effects on the liver. Cholestatic hepatitis has been reported in patients receiving ticlopidine and is usually reversible when ticlopidine is stopped.[1-3] However, there have been reports of persistent cholestasis after ticlopidine withdrawal.[4,5] A case of granulomatous hepatitis has also been reported.[6] Clopidogrel was substituted for ticlopidine in a patient who had developed raised liver enzymes during ticlopidine treatment;[7] liver enzyme values returned to normal during continued clopidogrel therapy. However, there has been a report[8] of hepatotoxicity with clopidogrel.

1. Cassidy LJ, *et al.* Probable ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 1995; **29:** 30–2.
2. Pérez-Balsa AM, *et al.* Hepatotoxicity due to ticlopidine. *Ann Pharmacother* 1998; **32:** 1250–1.
3. Skurnik YD, *et al.* Ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 2003; **37:** 371–5.

4. Colivicchi F, *et al.* Ticlopidine-induced chronic cholestatic hepatitis: a case report. *Curr Ther Res* 1994; **55:** 929–31.
5. Mambelli E, *et al.* Severe ticlopidine-induced cholestatic syndrome. *Blood Purif* 2007; **25:** 441–5.
6. Ruiz-Valverde P, *et al.* Ticlopidine-induced granulomatous hepatitis. *Ann Pharmacother* 1995; **29:** 633–4.
7. Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 939–41.
8. Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000; **7:** 317–18.

Effects on the lungs. Bronchiolitis obliterans-organising pneumonia developed in a 76-year-old woman receiving ticlopidine and prednisone for temporal arteritis.[1] The condition resolved over several months when ticlopidine was withdrawn.

1. Alonso-Martinez JL, *et al.* Bronchiolitis obliterans-organizing pneumonia caused by ticlopidine. *Ann Intern Med* 1998; **129:** 71–2.

Interactions

Ticlopidine should be used with caution in patients receiving other drugs, such as anticoagulants and antiplatelets, that increase the risk of bleeding. Ticlopidine is an inhibitor of cytochrome P450, including the isoenzymes CYP2C19, CYP2D6, and CYP2B6, and may inhibit the metabolism of other drugs that are metabolised by this route. The clearance of ticlopidine may be reduced by cimetidine. Corticosteroids may antagonise the effect of ticlopidine on bleeding time.

Anticoagulants. Use of ticlopidine with anticoagulants may increase the risk of bleeding. However, ticlopidine has been reported to antagonise the effect of *acenocoumarol* (see Antiplatelets under Interactions of Warfarin, p.1429).

Antiepileptics. For a report of acute *phenytoin* toxicity in a well-stabilised patient following addition of ticlopidine, see p.500.

Xanthines. For reference to the effect of ticlopidine on *theophylline* half-life, see p.1145.

Pharmacokinetics

Ticlopidine is rapidly and almost completely absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins. The terminal half-life during chronic dosing is reported to be about 30 to 50 hours. Ticlopidine is extensively metabolised in the liver. About 60% of a dose is excreted in the urine as metabolites and 25% in the faeces.

◊ References.

1. Desager J-P. Clinical pharmacokinetics of ticlopidine. *Clin Pharmacokinet* 1994; **26:** 347–55.
2. Buur T, *et al.* Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; **37:** 108–15.

Uses and Administration

Ticlopidine hydrochloride is a thienopyridine antiplatelet drug used in thromboembolic disorders (p.1187). It appears to act by inhibiting adenosine diphosphate-mediated platelet aggregation. It may be given prophylactically as an alternative to aspirin in patients at risk of thrombotic stroke (p.1185) and in the management of intermittent claudication (see Peripheral Vascular Disease, p.1178) and ischaemic heart disease. It is also licensed as an adjunct to aspirin for the prevention of subacute stent occlusion after intracoronary stenting (but see Reperfusion and Revascularisation Procedures, below). Ticlopidine may also be used to prevent occlusion and platelet loss during extracorporeal circulatory procedures.

In the prevention of thrombotic **stroke**, and in **intermittent claudication**, ticlopidine hydrochloride is given orally in a dose of 250 mg twice daily, with meals. For the prevention of subacute stent occlusion after **intracoronary stenting** ticlopidine hydrochloride is given in a dose of 250 mg twice daily for 4 weeks, starting at the time of stent placement.

Regular haematological monitoring is required during ticlopidine therapy (see Adverse Effects and Precautions, above).

◊ References.

1. McTavish D, *et al.* Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; **40:** 238–59.
2. Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. *Ann Pharmacother* 1993; **27:** 1090–8.
3. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.

Reperfusion and revascularisation procedures. Coronary stents are widely used as an adjunct to angioplasty to prevent acute vessel closure and to reduce restenosis (see Reperfusion and Revascularisation Procedures, p.1181). Subacute thrombosis is a major complication of their use and patients were initially treated with an aggressive combination of anticoagulants and antiplatelets. However, it is now generally recognised that antiplatelet drugs alone are adequate in most patients.

Early studies[1-4] found that ticlopidine for 4 to 6 weeks after stenting, given with long-term aspirin, was at least as effective as an oral anticoagulant with aspirin, with some studies showing benefit in terms of thrombosis[1,4] or bleeding complications.[1] However, the risk of neutropenia limits the use of ticlopidine, and clopidogrel is now generally preferred, although there is some evidence[5] that shorter courses of ticlopidine (2 weeks) may be acceptable.

Ticlopidine has also been reported[6] to improve the long-term patency of saphenous vein bypass grafts used to treat peripheral vascular disease in the legs.

1. Schömig A, *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334:** 1084–9.
2. Kastrati A, *et al.* Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation* 1997; **96:** 462–7.
3. Bertrand ME, *et al.* Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998; **98:** 1597–1603.
4. Leon MB, *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998; **339:** 1665–71.
5. Berger PB, *et al.* Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999; **99:** 248–53.
6. Becquemin J-P. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. *N Engl J Med* 1997; **337:** 1726–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dosier; Ticlid; Trombenal; ***Austral.:*** Ticlid; Tilodene; ***Austria:*** Thrombodine; Ticlodone; Tiklid; ***Belg.:*** Ticlid; ***Braz.:*** Plaketar; Ticlid; Ticlobal; ***Canad.:*** Ticlid; ***Chile:*** Ateroclar; Plaquetil; Ticlid; ***Cz.:*** Aplaket†; Apo-Tic; Ipaton; Platigren†; Tagren; Ticlid; ***Fr.:*** Ticlid; Ticlomed†; ***Ger.:*** Desiticlopidin; Tiklyd; ***Gr.:*** Anchostam-100†; Anghostam-100; Etfariol; Neo Fulvigal; Neoomnipen; Ruxicolan; Ticlid; Ticlodone; ***Hong Kong:*** Aplaket; Ticlid; Tipidin; ***Hung.:*** Aclotin; Aplatic; Ipaton; Placor; Ticlid; ***India:*** Ticlobest; Ticlop; Ticlopid; Tikleen†; Tyklid; ***Indon.:*** Agulan; Cartrilet; Goclid; Nufaclapide; Piclodin; Ticard; Ticlid; Ticlon; Ticuring; ***Israel:*** Ticlidil; ***Ital.:*** Anagregal†; Antigreg; Aplaket; Clox; Fluilast; Flupid; Fluxidin; Klodin; Opteron; Parsilid†; Ticlodone; Ticlogi†; Ticloproge†; Tiklid; ***Jpn:*** Panaldine; ***Malaysia:*** Antigreg; Aplaket; Ticlid; Ticlopine; Tipidin; ***Mex.:*** Ticlid; ***Norw.:*** Ticlid; ***Philipp.:*** Clotidone; Ticlid; ***Pol.:*** Aclotin; Apo-Clodin; Iclopid; Ifapidin; Ticlid; Ticlo; ***Port.:*** Agregamina†; Aplaket; Betlife; Isaxion†; Klodipin; Movin; Opidina†; Plaquetal; Previta; Ticlodix; Ticlopat; Tiklyd; Tiropa; Trombopat; ***Rus.:*** Ticlo (Тикло); Tikleen (Тиклин); ***S.Afr.:*** Ticlid†; ***Singapore:*** Antigreg; Aplaket; Tacron†; Ticlid; Tipidin; ***Spain:*** Ticlodone; Tiklid; ***Swed.:*** Ticlid; ***Thai.:*** Aplaket; Cenpidine; Siclot; Ticdine†; Ticlid; Ticlo; Ticlopine; Tikol†; Tilopin; Tipidine; Viladil; ***Turk.:*** Agretik; Ticlid; Ticlocard; ***UAE:*** Ticopar; ***USA:*** Ticlid; ***Venez.:*** Ticlid; Ticlopin†.

Tilisolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de tilisolol; N-696; Tilisolol, Chlorhydrate de; Tilisololi Hydrochloridum. (±)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-methylisocarbostyril hydrochloride.

Тилизолола Гидрохлорид

$C_{17}H_{24}N_2O_3,HCl = 340.8.$

CAS — 85136-71-6 (tilisolol); 62774-96-3 (tilisolol hydrochloride).

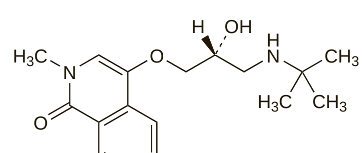

Profile

Tilisolol hydrochloride is a non-cardioselective beta blocker (p.1225) with direct vasodilator activity. It is used in the management of angina pectoris (p.1157) and hypertension (p.1171) in oral doses of 10 to 20 mg once daily; up to a maximum of 30 mg once daily may be used if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Selecal.

Timolol Maleate *(BANM, USAN, rINNM)* ⊗

Maleato de timolol; MK-950; Timolol Maleat; Timolol, maléate de; Timolol maleinát; Timololi maleas; Timololimaleaatti; Timololio maleatas; Timololmaleat; Timolol-maleát. (*S*)-1-*tert*-Butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

Тимолола Малеат

$C_{13}H_{24}N_4O_3S,C_4H_4O_4 = 432.5.$

CAS — 26839-75-8 (timolol); 91524-16-2 (timolol hemihydrate); 26921-17-5 (timolol maleate).

ATC — C07AA06; S01ED01.

ATC Vet — QC07AA06; QS01ED01.

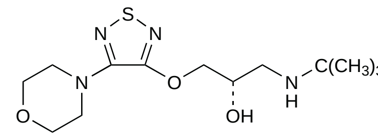

(timolol)

NOTE. TIM is a code approved by the BP 2008 for use on single unit doses of eye drops containing timolol maleate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Timolol Maleate). A white or almost white, crystalline powder or colourless crystals. Soluble in water and in alcohol. A 2% solution in water has a pH of 3.8 to 4.3. Protect from light.

USP 31 (Timolol Maleate). A white to practically white, odourless or practically odourless powder. Soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform and in propylene glycol; insoluble in cyclohexane and in ether. A 2% solution in water has a pH of 3.8 to 4.3.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Timolol is distributed into breast milk. After instillation of timolol 0.5% eye drops twice daily, concentrations of timolol in breast milk of a woman were about 6 times greater than those in serum, the values being 5.6 and 0.93 nanograms/mL respectively.[1] In a study[2] in patients given oral timolol 5 mg three times daily, the mean concentration in breast milk was 15.9 nanograms/mL, and the ratio of milk to plasma concentrations was 0.8; a similar ratio was found at higher doses, and the authors considered that the amount ingested by an infant would not be important. No adverse effects were seen in these studies and the American Academy of Pediatrics considers[3] that timolol is therefore usually compatible with breast feeding.

1. Lustgarten JS, Podos SM. Topical timolol and the nursing mother. *Arch Ophthalmol* 1983; **101:** 1381–2.
2. Fidler J, *et al.* Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90:** 961–5.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of timolol and that the dose of timolol may need to be reduced if used together.

Pharmacokinetics

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged timolol. Timolol is not removed by haemodialysis.

Metabolism. Timolol appears to be metabolised[1] by the cytochrome P450 isoenzyme CYP2D6 and studies[2-4] have shown that it is influenced by genetic polymorphism.

1. Volotinen M, *et al*. Timolol metabolism in human liver microsomes is mediated principally by CYP2D6. *Drug Metab Dispos* 2007; **35:** 1135–41.
2. McGourty JC, *et al*. Pharmacokinetics and beta-blocking effects of timolol in poor and extensive metabolizers of debrisoquin. *Clin Pharmacol Ther* 1985; **38:** 409–13.
3. Lewis RV, *et al*. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1985; **19:** 329–33.
4. Lennard MS, *et al*. Timolol metabolism and debrisoquine oxidation polymorphism: a population study. *Br J Clin Pharmacol* 1989; **27:** 429–34.

Uses and Administration

Timolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Timolol is used as the maleate in the management of glaucoma (p.1873), hypertension (p.1171), angina pectoris (p.1157), and myocardial infarction (p.1175). It is also used in the prophylactic treatment of migraine (p.616). The hemihydrate is also used.

Eye drops containing timolol maleate or hemihydrate equivalent to 0.25 and 0.5% of timolol are instilled twice daily to reduce **raised intra-ocular pressure** in open-angle **glaucoma** and ocular hypertension. Once-daily use may suffice when the intra-ocular pressure has been controlled. Gel-forming eye drops are also available that are instilled once daily.

For other indications timolol is given orally. In **hypertension** timolol maleate is usually given in initial doses of 10 mg daily, increased according to response at intervals of 7 or more days. Usual maintenance doses are 10 to 40 mg daily, but doses up to 60 mg daily may be required in some patients; doses above 30 mg daily should be given in 2 equally divided doses.

In **angina pectoris** the initial dose is 5 mg twice daily, increased at intervals of 3 or more days by 10 mg daily. Most patients respond to 35 to 45 mg daily in divided doses, but some patients may require up to 60 mg daily.

In patients who have had a **myocardial infarction** timolol maleate is given in initial doses of 5 mg twice daily for 2 days, starting 7 to 28 days after infarction, and increased subsequently in the absence of any contra-indicating adverse effects, to 10 mg twice daily.

Doses of 10 to 20 mg daily of timolol maleate are used in the prophylaxis of **migraine**.

Reduced doses may be required in renal or hepatic impairment.

Preparations

BP 2008: Timolol Eye Drops; Timolol Tablets;
USP 31: Timolol Maleate and Hydrochlorothiazide Tablets; Timolol Maleate Ophthalmic Solution; Timolol Maleate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Glatim; Ingetim; Klonalol; Ofal; Plostim; Poentimol; Proflax; Protevis; Timed; Timoler; Timolpres; Timoptic; Zopirol; ***Austral.:*** Nyogel; Optimol†; Tenopt; Timoptol; Timoptol-XE; ***Austria:*** Blocadren; Dispatim; Ophtilan†; Tim-Ophtal; Timabak; Timax; Timo-COMOD; Timoftal; Timohexal; Timoptic; ***Belg.:*** Blocadren; Nyogel; Nyolol; Timabak; Timo-POS; Timoptol; Timoptolgel; ***Braz.:*** Glaucotrat; Glautimol; Nyolol; Tenoftal; Timabak; Timoptol; ***Canad.:*** Apo-Timol; Apo-Timop; Novo-Timol; Tim-Ak†; Timoptic; ***Chile:*** Glausolets; Nyolol; Timabak; Timop; Timoptol-XE; Tiof; ***Cz.:*** Arutimol; Oftan; Oftensin†; Ophthalmo-Timogal; Timo-COMOD; Timogal†; Timohexal; Timoptol; Uni Timolol; ***Denm.:*** Aquanil; Oftamolol; Optimol; Timacar; Timosan; ***Fin.:*** Aquanil†; Blocanol; Timosan; ***Fr.:*** Digaol; Nyogel; Ophtim; Timabak; Timacor; Timo-COMOD; Timoptol; ***Ger.:*** Arutimol; Chibro-Timoptol; Dispatim; Nyogel; Tim-Ophtal; Timo-COMOD; Timo-Stulln; TimoEDO; Timohexal; Timomann; Timosine†; ***Gr.:*** Flumetol†; Glafemak; Lithimole; Noval; Nyogel; Nyolol; Temserin; Thilotim; Timabak; Timodose†; Waucosin†; Yesan; ***Hong Kong:*** Apo-Timop; Glauco-Oph†; Nyolol; Oftan; Optimol; Timabak; Timoptol; ***Hung.:*** Arutimol; Cusimolol; Nyolol; Oftan Timolol; ***India:*** Glucomol; Glucotim; Ocupres; Ocutim; Timolo; ***Indon.:*** Isotic Adretor; Kentimol; Nyolol; Tim-Ophtal; Ximex Opticom; ***Irl.:*** Nyogel; Timoptol; ***Israel:*** Nyolol; Octil†; Tiloptic; V-Optic; ***Ital.:*** Blocadren; Cusimolol; Droptimol; Ialutim; Nyogel; Oftimolo; Timolabak; Timolux; Timoptol; Timosoft; ***Jpn:*** Timoptol; ***Malaysia:*** Cusimolol; Nyolol†; Timo-COMOD†; Timolast; Timoptol; ***Mex.:*** Blocadren; Horex; Imot; Jertz; Nyolol; Shemol; Timoptol; Timozzard; Tiof†; ***Mon.:*** Nyolol; ***Neth.:*** Loptomit†; Nyogel; Timo-COMOD; Timoptol; ***Norw.:*** Aquanil; Blocadren; Oftamolol; Oftan; Timosan; ***NZ:*** Apo-Timol; Apo-Timop; Gen-Timolol†; Hypermol; Nyogel†; Tilmat; Timolux; Timoptol; ***Philipp.:*** Elevex; Glocure-Opta; Nyolol; Oftan; Timabak; Timoptol; ***Pol.:*** Cusimolol; Nyolol; Oftan; Oftensin; Timo-COMOD; Timohexal; Timoptic; ***Port.:*** Blocadren†; Cusimolol†; Nyogel; Nyolol; Timabak; Timogel; Timoglau; Timolen; Timoptol; ***Rus.:*** Arutimol (Арутимол); Glymol (Глимол); Nyolol (Ниолол); Ocumed (Окумед); Ocupres-E (Окупрес-Е); Oftan Timolol (Офтан Тимолол); Optimol (Оптимол); Timohexal (Тимогексал); ***S.Afr.:*** Glaucosan; Nyogel; Timoptol; ***Singapore:*** Nyolol; Timabak; Timoptol; ***Spain:*** Cusimolol; Nyolol; Timabak; Timoftol; Timogel; ***Swed.:*** Aquanil†; Blocadren; Optimol; Timosan; ***Switz.:*** Nyolol; Oftan†; Timisol; Timo-COMOD; Timoptic; ***Thai.:*** Glauco-Oph; Nyolol; Oftan†; Timo-Optal; Timodrop; Timoptol; Timosil; ***Turk.:*** Cusimolol; Nyolol; Timo-COMOD; Timoftal; Timoptic; Timosol; ***UK:*** Betim; Glau-opt†; Nyogel; Timoptol; ***USA:*** Betimol; Blocadren; Isatol; Istalol; Timoptic; ***Venez.:*** Globitan; Imot†; Matigel; Matilol; Nyolol; Timoptol.

Multi-ingredient: ***Arg.:*** Combigan; Cosopt; Dorlamida T; Dorzoflax†; Glaucocin†; Glaucotensil; Glaucotensil TD; Louten T; Moducren†; Ocuprostim; Ofal P†; Pilotim; Timed 0.5; Timed D; Timpilo†; Xalacom; ***Austral.:*** Combigan; Cosopt; Timpilo; Xalacom; ***Austria:*** Cosopt; Fotil; Moducrin; Timpilo; Timsopt; Xalacom; ***Belg.:*** Cosopt; Xalacom; ***Braz.:*** Combigan; Cosopt; Xalacom; ***Canad.:*** Combigan; Cosopt; Timolide†; Timpilo†; Xalacom; ***Chile:*** Combigan; Cosopt; Dorsof T; Gaax T; Glaucotensil T; Glausolets Plus; Latof-T; Tiof Plus; Xalacom; ***Cz.:*** Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Timpilo†; Xalacom; ***Denm.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Fin.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Fr.:*** Cosopt; Moducren; Pilobloq; Timpilo†; Xalacom; ***Ger.:*** Cosopt; Fotil; Moducrin; Timpilo†; TP-Ophtal; Xalacom; ***Gr.:*** Combigan; Cosopt; Dropiltim; DuoTrav; Fotil†; Ganfort; T+P; Tesol†; Timpilo; Xalacom; Yvano; ***Hong Kong:*** Cosopt; Moducren; Timpilo; Xalacom; ***Hung.:*** Combigan; Cosopt; DuoTrav; Fotil; Xalacom; ***Indon.:*** Xalacom; ***Irl.:*** Combigan; Cosopt; Moducren; Xalacom; ***Israel:*** Cosopt; Timpilo; Xalacom; ***Ital.:*** Cosopt; Equiton; Glautimol; Pilobloc; Timicon; Xalacom; ***Malaysia:*** Cosopt; Timpilo†; Xalacom; ***Mex.:*** Combigan-D; Cosopt; Xalacom; ***Neth.:*** Cosopt; Fotil; Xalacom; ***Norw.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***NZ:*** Combigan; Cosopt; DuoTrav; Timpilo; Xalacom; ***Philipp.:*** Cosopt; Fotil; Xalacom; ***Pol.:*** Cosopt; DuoTrav; Fotil; Xalacom; ***Port.:*** Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Moducren†; Tavu; Timoglau Plus; Timosopt; Xalacom; ***Rus.:*** Fotil (Фотил); Xalacom (Ксалаком); ***S.Afr.:*** Cosopt; Moducren; Servatrin; Xalacom; ***Singapore:*** Cosopt; Timpilo†; Xalacom; ***Spain:*** Xalacom; ***Swed.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Switz.:*** Combigan; Cosopt; Fotil†; Moducren; Timpilo†; Xalacom; ***Thai.:*** Cosopt; Fotil†; Xalacom; ***Turk.:*** Cosopt; ***UK:*** Combigan; Cosopt; DuoTrav; Ganfort; Moducren†; Prestim; Xalacom; ***USA:*** Combigan; Cosopt; Timolide; ***Venez.:*** Cosopt; Dobet; Glaucotensil T; Xalacom.

Tinzaparin Sodium *(BAN, USAN, rINN)*

Tintsapariininatrium; Tinzaparin sodná sůl; Tinzaparin Sodyum; Tinzaparina sódica; Tinzaparine sodique; Tinzaparinnatrium; Tinzaparin-nátrium; Tinzaparino natrio druska; Tinzaparinum natricum.

Тинзапарин Натрий

CAS — 9041-08-1.

ATC — B01AB10.

ATC Vet — QB01AB10.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tinzaparin Sodium). It is prepared by enzymatic depolymerisation, using heparinase from *Flavobacterium heparinum*, of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5500 and 7500, with a characteristic value of about 6500. The mass percentage of chains lower than 2000 is not more than 10%. The degree of sulfation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 units and not more than 120 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 2.5.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with tinzaparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of 100 units of tinzaparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Tinzaparin sodium is absorbed after subcutaneous injection with a bioavailability of about 90%. Peak plasma activity is reached within 4 to 6 hours. The elimination half-life is about 90 minutes but detectable anti-factor Xa activity persists for up to 24 hours.

Uses and Administration

Tinzaparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the prevention and treatment of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation.

For *prophylaxis* of **venous thromboembolism** tinzaparin sodium is given by subcutaneous injection in a variety of dosage regimens.

- For patients undergoing general surgical procedures 3500 units of tinzaparin sodium are given 2 hours before the procedure, followed by 3500 units once daily for 7 to 10 days.
- In patients at high risk, such as those undergoing orthopaedic surgery, a dose of 50 units/kg has been recommended; alternatively, a dose of 4500 units may be given 12 hours before surgery, followed by 4500 units once daily.

For the *treatment* of venous thromboembolism tinzaparin sodium is given in a dose of 175 units/kg by subcutaneous injection once daily for at least 6 days and until adequate oral anticoagulation is established.

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, tinzaparin sodium may be given into the arterial side of the dialyser or intravenously. The dialyser may be primed with 500 to 1000 mL sodium chloride 0.9% containing 5000 units tinzaparin sodium/litre. For dialysis sessions lasting less than 4 hours a single dose of 2000 to 2500 units tinzaparin sodium is given; for longer sessions an initial dose of 2500 units is followed by an infusion of 750 units/hour.

◊ References.

1. Friedel HA, Balfour JA. Tinzaparin: a review of its pharmacology and clinical potential in the prevention and treatment of thrombo-embolic disorders. *Drugs* 1994; **48:** 638–60.
2. Neely JL, *et al*. Tinzaparin sodium: a low-molecular-weight heparin. *Am J Health-Syst Pharm* 2002; **59:** 1426–36.
3. Nutescu EA, *et al*. Tinzaparin: considerations for use in clinical practice. *Ann Pharmacother* 2003; **37:** 1831–40.
4. Cheer SM, *et al*. Tinzaparin sodium: a review of its pharmacology and clinical use in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2004; **64:** 1479–502.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Innohep†; ***Belg.:*** Innohep; ***Canad.:*** Innohep; ***Denm.:*** Innohep; ***Fin.:*** Innohep†; ***Fr.:*** Innohep; ***Ger.:*** Innohep; ***Gr.:*** Innohep; ***Hong Kong:*** Innohep; ***Irl.:*** Innohep; ***Israel:*** Innohep†; ***Malaysia:*** Innohep; ***Neth.:*** Innohep; ***Norw.:*** Innohep; ***NZ:*** Innohep; ***Philipp.:*** Innohep; ***Port.:*** Innohep; ***Singapore:*** Innohep; ***Spain:*** Innohep; ***Swed.:*** Innohep; ***Thai.:*** Innohep; ***Turk.:*** Innohep; ***UK:*** Innohep; ***USA:*** Innohep.

Tioclomarol *(rINN)*

LM-550; Tioclomarolum. 3-[5-Chloro-α-(4-chloro-β-hydroxyphenethyl)-2-thenyl]-4-hydroxycoumarin.

Тиокломарол

$C_{22}H_{16}Cl_2O_4S$ = 447.3.

CAS — 22619-35-8.

ATC — B01AA11.

ATC Vet — QB01AA11.

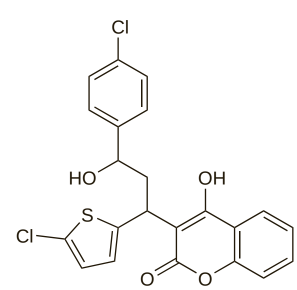

Profile

Tioclomarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1425) that has been used in the management of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Apegmone†.

Tirilazad Mesilate *(BANM, rINNM)*

Mesilato de tirilazad; Tirilatsadiinimesilaatti; Tirilazad, Mésilate de; Tirilazad Mesylate *(USAN)*; Tirilazadi Mesilas; Tirilazadini Mesilas; Tirilazadinmesilat; U-74006F (tirilazad or tirilazad mesilate). 21-[4-(2,6-Di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate hydrate.

Тирилазада Мезилат

$C_{38}H_{52}N_6O_2,CH_4O_3S,xH_2O$ = 721.0 (anhydrous).

CAS — 110101-66-1 (tirilazad); 111793-42-1 (tirilazad mesilate); 149042-61-5 (tirilazad mesilate).

ATC — N07XX01.

ATC Vet — QN07XX01.

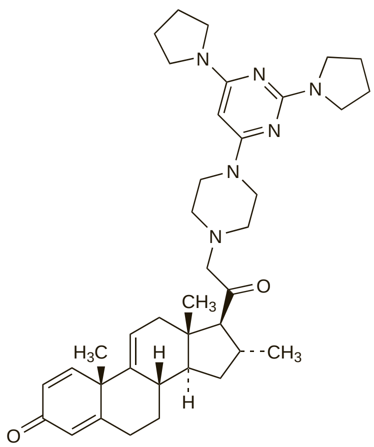

(tirilazad)

Profile

Tirilazad, a lazaroid, is an inhibitor of lipid peroxidation thought to have a cytoprotective effect against radicals produced in response to tissue trauma. It has been used in the prevention of secondary tissue damage in subarachnoid haemorrhage. It has also been investigated in spinal cord injuries, head injuries, and ischaemic stroke.

◊ References.

1. Fleishaker JC, *et al.* Evaluation of the pharmacokinetics and tolerability of tirilazad mesylate, a 21-aminosteroid free radical scavenger: multiple-dose administration. *J Clin Pharmacol* 1993; **33:** 182–90.
2. Hulst LK, *et al.* Effect of age and gender on tirilazad pharmacokinetics in humans. *Clin Pharmacol Ther* 1994; **55:** 378–84.
3. Haley EC, *et al.* Phase II trial of tirilazad in aneurysmal subarachnoid haemorrhage: a report of the Cooperative Aneurysm Study. *J Neurosurg* 1995; **82:** 786–90.
4. Clark WM, *et al.* Lazaroids: CNS pharmacology and current research. *Drugs* 1995; **50:** 971–83.
5. Marshall LF, *et al.* A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg* 1998; **89:** 519–25.
6. Fleishaker JC, *et al.* Hormonal effects on tirilazad clearance in women: assessment of the role of CYP3A. *J Clin Pharmacol* 1999; **39:** 260–7.
7. The Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/06/05).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Freedox†; ***Belg.:*** Freedox†; ***S.Afr.:*** Freedox†; ***Switz.:*** Freedox†.

Tirofiban Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tirofibán; L-700462; MK-383; MK-0383; Tirofiban, Chlorhydrate de; Tirofiban Hidroklorür; Tirofibani Hydrochloridum. *N*-(Butylsulfonyl)-4-[4-(4-piperidyl)butoxy]-L-phenylalanine hydrochloride monohydrate.

Тирофибана Гидрохлорид

$C_{22}H_{36}N_2O_5S,HCl,H_2O$ = 495.1.

CAS — 144494-65-5 (tirofiban); 142373-60-2 (anhydrous tirofiban hydrochloride); 150915-40-5 (tirofiban hydrochloride monohydrate);.

ATC — B01AC17.

ATC Vet — QB01AC17.

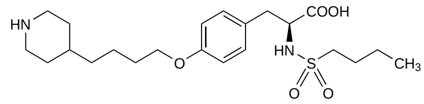

(tirofiban)

Adverse Effects

Bleeding is the most common adverse effect of tirofiban. Other side-effects include nausea, headache, fever, rashes and other hypersensitivity reactions, and thrombocytopenia.

Effects on the blood. References[1,2] to tirofiban-associated thrombocytopenia.

1. Mulot A, *et al.* Practical approach to the diagnosis and management of thrombocytopenia associated with tirofiban treatment. *Am J Hematol* 2004; **77:** 67–71.
2. Patel S, *et al.* Profound thrombocytopenia associated with tirofiban: case report and review of literature. *Angiology* 2005; **56:** 351–5.

Precautions

As for Abciximab, p.1192.

Pharmacokinetics

After stopping an infusion of tirofiban, the antiplatelet effect persists for about 4 to 8 hours. The plasma half-life is about 2 hours. Tirofiban is not highly bound to plasma proteins; the unbound fraction in plasma is about 35%. Tirofiban is eliminated largely unchanged in the urine, with some biliary excretion in the faeces. Tirofiban is removed by haemodialysis.

◊ Reviews.

1. Kondo K, Umemura K. Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody abciximab. *Clin Pharmacokinet* 2002; **41:** 187–95.

Uses and Administration

Tirofiban hydrochloride is an antiplatelet drug that reversibly inhibits binding of fibrinogen to the glycoprotein IIb/IIIa receptors of platelets. It is given with heparin and aspirin for the management of unstable angina, both in patients managed medically and in those undergoing percutaneous coronary procedures. Tirofiban is used as the hydrochloride, but the dose is expressed in terms of the base; 110 nanograms of tirofiban hydrochloride monohydrate is equivalent to 100 nanograms of tirofiban base.

Tirofiban is given intravenously, at an initial rate of 400 nanograms/kg per minute for 30 minutes, and then continued at 100 nanograms/kg per minute. The recommended duration of treatment is at least 48 hours. Tirofiban infusion may be continued during coronary angiography, and should be maintained for 12 to 24 hours after angioplasty or atherectomy. The entire duration of treatment should not exceed 108 hours.

The dose of tirofiban should be reduced in patients with renal impairment (see below).

◊ General references.

1. McClellan KJ, Goa KL. Tirofiban: a review of its use in acute coronary syndromes. *Drugs* 1998; **56:** 1067–80.
2. Menozzi A, *et al.* Tirofiban in acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2005; **3:** 193–206.
3. Shanmugam G. Tirofiban and emergency coronary surgery. *Eur J Cardiothorac Surg* 2005; **28:** 546–50.
4. Bukow SC, *et al.* Tirofiban for the treatment of ischaemic stroke. *Expert Opin Pharmacother* 2006; **7:** 73–9.
5. Mukherjee D, Roffi M. Current strategies with high-dose tirofiban. *Expert Opin Drug Metab Toxicol* 2007; **3:** 275–80.
6. Winter JP, Juergens CP. The role of tirofiban in the management of coronary artery disease. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 138–46.

Administration in renal impairment. Patients with renal impairment (creatinine clearance less than 30 mL/minute) should receive half the usual infusion dose of tirofiban.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. Tirofiban, given with heparin and aspirin, has been tried as adjunctive therapy. A study[1] comparing tirofiban with heparin in the **medical management** of unstable angina (p.1157) or non-Q-wave myocardial infarction reported an initial benefit, at 2 days, of reduced risk of refractory ischaemia, myocardial infarction, or death with tirofiban. This benefit was not maintained at 7 or 30 days after treatment, although a further analysis[2] found that the risk of death or myocardial infarction at 30 days was reduced in patients with raised troponin I concentrations who received tirofiban. In another study,[3] the combination of heparin and tirofiban also reduced the risk of refractory ischaemia, myocardial infarction, or death, compared with heparin alone, and benefit was maintained at 6 months. About half of these patients also underwent revascularisation procedures or surgery if required.

Tirofiban has also been studied in patients undergoing **interventional therapy** (see Reperfusion and Revascularisation Procedures, p.1181), but results have been mixed. The RESTORE trial[4] found short-term benefit with tirofiban as an adjunct to heparin in patients undergoing angioplasty or atherectomy for acute coronary syndromes (unstable angina or myocardial infarction), but this was not maintained at 30 days and there was no effect on restenosis after 6 months. However, another study using a higher loading dose found a reduced rate of clinical events in patients given tirofiban, both early after the procedure and on longer-term follow-up,[5] and an observational study[6] in patients with acute myocardial infarction also found improved outcomes. Pretreatment with tirofiban for 24 to 48 hours before intervention was found to improve angiographic outcomes compared with periprocedural treatment,[7] but there was no difference in clinical events at 30 days. In patients undergoing planned interventions, tirofiban was found to improve outcomes compared with placebo;[8] another study found that it was less effective than abciximab at 30 days,[9] although this difference was no longer apparent after 6 months.[10]

1. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338:** 1498–1505.
2. Heeschen C, *et al.* Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; **354:** 1757–62.
3. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338:** 1488–97.
4. Gibson CM, *et al.* Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. *J Am Coll Cardiol* 1998; **32:** 28–34.
5. Valgimigli M, *et al.* The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004; **44:** 14–19.
6. De Luca G, *et al.* Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *Thromb Haemost* 2005; **93:** 820–3.
7. van 't Hof AWJ, *et al.* A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. *Eur Heart J* 2003; **24:** 1401–5.
8. Bonz AW, *et al.* Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol* 2002; **40:** 662–8.
9. Topol EJ, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; **344:** 1888–94.
10. Moliterno DJ, *et al.* Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002; **360:** 355–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Agrastat; ***Austral.:*** Aggrastat; ***Austria:*** Aggrastat; ***Belg.:*** Aggrastat; ***Braz.:*** Agrastat; ***Canad.:*** Aggrastat; ***Chile:*** Agrastat; ***Cz.:*** Aggrastat; ***Denm.:*** Aggrastat; ***Fin.:*** Aggrastat; ***Fr.:*** Agrastat; ***Ger.:*** Aggrastat; ***Gr.:*** Aggrastat; Avastar†; ***Hong Kong:*** Aggrastat; ***Hung.:*** Aggrastat; ***India:*** Aggribloc; ***Irl.:*** Aggrastat; ***Israel:*** Aggrastat; ***Ital.:*** Aggrastat; ***Malaysia:*** Aggrastat; ***Mex.:*** Agrastat; ***Neth.:*** Aggrastat; ***Norw.:*** Aggrastat; ***NZ:*** Aggrastat; ***Philipp.:*** Aggrastat; ***Pol.:*** Aggrastat; ***S.Afr.:*** Aggrastet; ***Singapore:*** Aggrastat; ***Spain:*** Agrastat; ***Swed.:*** Aggrastat; ***Switz.:*** Aggrastat; ***Thai.:*** Aggrastat; ***Turk.:*** Aggrastat; ***UK:*** Aggrastat; ***USA:*** Aggrastat; ***Venez.:*** Agrastat.

Tocainide *(BAN, USAN, rINN)*

Tocainida; Tocaïnide; Tocainidum; Tokainid; Tokainidi; W-36095. 2-Aminopropiono-2′,6′-xylidide.

Токаинид

$C_{11}H_{16}N_2O$ = 192.3.

CAS — 41708-72-9.

ATC — C01BB03.

ATC Vet — QC01BB03.

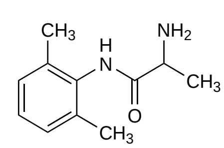

Tocainide Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tocainida; Tocaïnide, Chlorhydrate de; Tocainidi Hydrochloridum.

Токаинида Гидрохлорид

$C_{11}H_{16}N_2O,HCl = 228.7.$

CAS — 35891-93-1.

ATC — C01BB03.

ATC Vet — QC01BB03.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Tocainide Hydrochloride). A fine, white, odourless powder. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Profile

Tocainide is a class Ib antiarrhythmic (p.1153) with similar properties to mexiletine (p.1339); like mexiletine it is structurally related to lidocaine (p.1862). Tocainide hydrochloride has been given orally and intravenously in the management of ventricular arrhythmias but severe haematological and pulmonary toxicity limit its use.

◊ General references.

1. Holmes B, *et al.* Tocainide: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1983; **26:** 93–123.

Preparations

USP 31: Tocainide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Ger.: Xylotocan†; ***USA:*** Tonocard†.

Tocoferil Nicotinate

Tocoferilo, nicotinato de; Tocopheryl Nicotinate; Vitamin E Nicotinate. (±)-α-Tocopherol nicotinate.

Токоферола Никотинат

$C_{35}H_{53}NO_3 = 535.8.$

CAS — 51898-34-1; 16676-75-8.

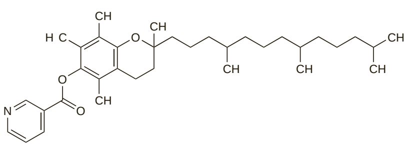

Pharmacopoeias. In *Jpn.*

Profile

Tocoferil nicotinate is a lipid regulating drug and a vasodilator. It is used in the treatment of hyperlipidaemias (p.1169), and in peripheral (p.1178) and cerebral vascular disorders (p.1165). The usual oral dose is 100 to 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Hijuven; ***Indon.:*** Enico; ***Jpn:*** Juvela; ***Malaysia:*** Hijuven; ***Philipp.:*** Hijuven; ***Port.:*** Nicojuvel†; Reoferol.

Multi-ingredient: ***Arg.:*** Anaphase; ***Fr.:*** Anaphase; ***Ital.:*** Evitex; ***Spain:*** Evitex A E Fuerte.

Todralazine Hydrochloride *(BANM, pINNM)*

BT-621; CEPH; Ecarazine Hydrochloride; Hidrocloruro de todralazina; Todralazine, Chlorhydrate de; Todralazini Hydrochloridum; Todralazyny chlorowodorek. Ethyl 3-(phthalazin-1-yl)carbazate hydrochloride monohydrate.

Тодралазина Гидрохлорид

$C_{11}H_{12}N_4O_2,HCl,H_2O = 286.7.$

CAS — 14679-73-3 (todralazine); 3778-76-5 (anhydrous todralazine hydrochloride).

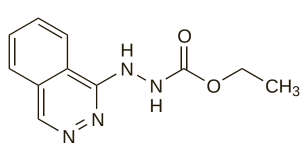

(todralazine)

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Todralazine hydrochloride is an antihypertensive structurally related to hydralazine (p.1305) and with similar properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Binazin.

Tolazoline Hydrochloride *(BANM, rINNM)*

Benzazoline Hydrochloride; Hidrocloruro de tolazolina; Tolazol. Hydrochlor.; Tolazoline, Chlorhydrate de; Tolazolini Hydrochloridum; Tolazolinium Chloratum. 2-Benzyl-2-imidazoline hydrochloride.

Толазолина Гидрохлорид

$C_{10}H_{12}N_2,HCl = 196.7.$

CAS — 59-98-3 (tolazoline); 59-97-2 (tolazoline hydrochloride).

ATC — C04AB02; M02AX02.

ATC Vet — QC04AB02; QM02AX02.

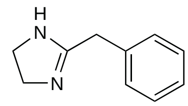

(tolazoline)

NOTE. Do not confuse with benazoline (see Metizoline, p.1565), which is a sympathomimetic vasoconstrictor, or with benazolin, which is a herbicide.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Tolazoline Hydrochloride). A white to off-white, crystalline powder. Its solutions are slightly acid to litmus. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 3 of chloroform, and 1 in 10 000 of ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

Adverse effects of tolazoline include piloerection, headache, flushing, tachycardia, cardiac arrhythmias, tingling, chilliness, shivering, sweating, nausea, vomiting, diarrhoea, and epigastric pain. Orthostatic hypotension or marked hypertension may occur, especially with large doses. Tolazoline stimulates gastric acid and may exacerbate peptic ulcer disease. Oliguria, haematuria, myocardial infarction, gastrointestinal haemorrhage, thrombocytopenia and other blood dyscrasias have been reported.

Intra-arterial injection has been followed by a burning sensation in the limb.

Effects in the neonate. Hypochloraemic metabolic alkalosis,[1] acute renal failure,[2] and duodenal perforation[3] have been reported in neonates given tolazoline.

1. Adams JM, *et al.* Hypochloremic metabolic alkalosis following tolazoline-induced gastric hypersecretion. *Pediatrics* 1980; **65:** 298–300.
2. Trompeter RS, *et al.* Tolazoline and acute renal failure in the newborn. *Lancet* 1981; **i:** 1219.
3. Wilson RG, *et al.* Duodenal perforation associated with tolazoline. *Arch Dis Child* 1985; **60:** 878–9.

Treatment of Adverse Effects

In the event of overdosage hypotension is best treated by keeping the patient recumbent with the head lowered. If necessary the circulation may be maintained by infusion of suitable electrolyte solutions. Hypotension may be treated with ephedrine. Adrenaline is not suitable for the reversal of hypotension induced by alpha blockers since it may activate the hypotension by stimulating beta receptors.

Precautions

Tolazoline should not be given to patients with hypotension and when used for peripheral vascular disease should be avoided in ischaemic heart disease or after a cerebrovascular accident. Since tolazoline stimulates gastric secretion of hydrochloric acid it may activate stress ulcers and may cause significant hypochloraemic alkalosis. Pretreatment of infants with antacids may prevent gastrointestinal bleeding, although use of intravenous ranitidine is not recommended (see below under Interactions). Tolazoline should not be used in the presence of peptic ulcer disease and should be used with caution in patients with mitral stenosis.

Interactions

Tolazoline should not be used with sympathomimetics such as adrenaline since the hypotensive effect may be potentiated due to unopposed beta-adrenoceptor stimulation. Tolazoline may cause a disulfiram-like reaction if given with alcohol.

Ranitidine. Intravenous ranitidine reversed the falls in pulmonary and systemic vascular resistances in 12 children who had been given tolazoline as a pulmonary vasodilator.[1]

1. Bush A, *et al.* Cardiovascular effects of tolazoline and ranitidine. *Arch Dis Child* 1987; **62:** 241–6.

Sympathomimetics. For a report of fatal hypotension associated with the use of tolazoline with *dopamine*, see Vasodilators under the Interactions of Sympathomimetics, p.1408.

Pharmacokinetics

Tolazoline is absorbed from the gastrointestinal tract. It is more rapidly absorbed after intramuscular injection. An elimination half-life in neonates of 3 to 13 hours has been reported after intravenous use, although it may be as high as about 40 hours and is inversely related to urine output. Tolazoline is rapidly excreted in the urine, largely unchanged.

Uses and Administration

Tolazoline hydrochloride is a vasodilator that has a direct dilator action on the peripheral blood vessels. It has some alpha-adrenoceptor blocking activity and also stimulates smooth muscle in the gastrointestinal tract, increases gastrointestinal secretion, can cause mydriasis, and has a stimulant effect on the heart.

Tolazoline hydrochloride is used intravenously to reduce pulmonary artery pressure in persistent pulmonary hypertension in neonates with persistent fetal circulation (see below). It has been used orally and by subcutaneous, intramuscular, intravenous, or slow intra-arterial injection in the treatment of peripheral vascular disease. It has also been given in some ophthalmic conditions.

Pulmonary hypertension. Tolazoline and other vasodilators have been tried in persistent pulmonary hypertension in the newborn (p.1179) in an attempt to induce selective pulmonary vasodilatation and improve gas exchange. The response is variable and often unsuccessful due to concomitant systemic hypotension, a failure to achieve or sustain pulmonary vasodilatation, and adverse effects, and other therapies such as high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, and inhaled nitric oxide are now more widely used.

The loading dose for pulmonary hypertension in neonates that has been recommended by licensed product information is 1 to 2 mg/kg over 5 to 10 minutes by intravenous infusion; this is then followed by doses of up to 1 to 2 mg/kg per hour. Infants with reduced urine output may require lower maintenance doses. The high incidence of adverse effects has, however, led to several studies investigating the use of lower doses. One group suggested that a loading dose of 500 micrograms/kg given intravenously followed by a continuous infusion of 500 micrograms/kg per hour was more appropriate and safer than standard doses.[1] In a retrospective study[2] of extremely preterm infants (mean gestational age 24 weeks) with severe hypoxaemia (possibly attributable to persistent pulmonary hypertension), tolazoline was given as a slow bolus infusion, with most patients receiving a dose of 0.5 to 1 mg/kg; some required further doses.

Tolazoline has also been given via the endotracheal route,[3,4] although as it is acid in solution it may contribute to alveolar injury. In a study[4] of 12 neonates with gestational age ranging from 25 to 42 weeks, endotracheal tolazoline at doses from 1 to 2.5 mg/kg was found to cause no adverse systemic effects.

The *BNFC* gives a dose of 1 mg/kg by slow intravenous injection, followed by 200 micrograms/kg per hour by infusion if necessary. It warns that doses in excess of 300 micrograms/kg per hour are associated with cardiotoxicity and renal failure. A suggested dose for endotracheal use is 200 micrograms/kg diluted in 0.5 to 1 mL of sodium chloride 0.9%.

1. Monin P, *et al.* Treatment of persistent fetal circulation syndrome of the newborn: comparison of different doses of tolazoline. *Eur J Clin Pharmacol* 1987; **31:** 569–73.
2. Nuntnarumit P, *et al.* Efficacy and safety of tolazoline for treatment of severe hypoxemia in extremely preterm infants. *Pediatrics* 2002; **109:** 852–6.
3. Welch JC, *et al.* Endotracheal tolazoline for severe persistent pulmonary hypertension of the newborn. *Br Heart J* 1995; **73:** 99–100.
4. Parida SK, *et al.* Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997; **17:** 461–4.

Preparations

USP 31: Tolazoline Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Divascol; ***Gr.:*** Priscol†; Priscoline†.

Multi-ingredient: ***Switz.:*** Lunadon.

Torasemide *(BAN, rINN)* ⊗

AC-4464; BM-02015; Torasemid; Torasemid bezvodý; Torasemid, vattenfri; Torasemida; Torasémide; Torasémide anhydre; Torasemidi; Torasemidi, vedetön; Torasemidum; Torasemidum anhydricum; Torazemidas, bevandenis; Torsemide *(USAN)*. 1-Isopropyl-3-(4-*m*-toluidinopyridine-3-sulphonyl)urea.

Торасемид

$C_{16}H_{20}N_4O_3S = 348.4.$

CAS — 56211-40-6 (torasemide); 72810-59-4 (torasemide sodium).

ATC — C03CA04.

ATC Vet — QC03CA04.

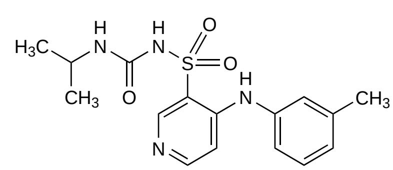

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Torasemide, Anhydrous). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol. It is sparingly soluble in dilute solu-

tions of alkali hydroxides and slightly soluble in dilute acids. Protect from light.
USP 31 (Torsemide). A white to off-white, crystalline powder. Practically insoluble in water and in ether; slightly soluble in alcohol, in methyl alcohol, in 0.1N sodium hydroxide, and in 0.1N hydrochloric acid; very slightly soluble in acetone and in chloroform.

Adverse Effects and Precautions

As for Furosemide, p.1292.

Interactions

As for Furosemide, p.1293.

Pharmacokinetics

Torasemide is well absorbed from the gastrointestinal tract. Peak serum concentrations are achieved within 1 hour of oral doses. Torasemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. Metabolism takes place in the liver and inactive metabolites are excreted in the urine. The elimination half-life of torasemide is about 3.5 hours. Torasemide is extensively bound to plasma proteins. In patients with heart failure both hepatic and renal clearance are reduced. In patients with renal impairment, the renal clearance is reduced but total plasma clearance is not significantly altered.

◊ References.

1. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clin Pharmacokinet* 1998; **34:** 1–24.
2. Vormfelde SV, *et al.* CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther* 2004; **76:** 557–66.

Uses and Administration

Torasemide is a loop diuretic with actions similar to those of furosemide (p.1294).

Torasemide is used for oedema associated with heart failure (p.1165), including pulmonary oedema, and with renal and hepatic disorders. It is also used in the treatment of hypertension (p.1171), either alone or with other antihypertensives.

Diuresis after oral use starts within 1 hour, reaches a maximum in about 1 to 2 hours, and lasts for up to 8 hours; after intravenous injection its effects are evident within 10 minutes but like oral use can last up to 8 hours.

In the treatment of **oedema** the usual oral dose is 5 mg once daily increased according to response to 20 mg once daily; doses of up to 40 mg daily have been required in some patients. Torasemide may also be given intravenously in usual initial doses of 10 to 20 mg daily. Higher doses may sometimes be necessary, especially in oedema of renal origin; the dose should be increased stepwise as necessary to a maximum of 200 mg daily, although doses should not exceed 40 mg daily in patients with hepatic cirrhosis.

In the treatment of **hypertension** torasemide is given in initial oral doses of 2.5 to 5 mg daily; US licensed product information allows the dose to be increased to 10 mg daily if required, although UK licensed product information suggests that doses above 5 mg are unlikely to produce additional benefit.

◊ Reviews.

1. Blose JS, *et al.* Torsemide: a pyridine-sulfonylurea loop diuretic. *Ann Pharmacother* 1995; **29:** 396–402.
2. Dunn CJ, *et al.* Torasemide: an update of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; **49:** 121–42.
3. Brater DC. Benefits and risks of torasemide in congestive heart failure and essential hypertension. *Drug Safety* 1996; **14:** 104–120.
4. Ishido H, Senzaki H. Torasemide for the treatment of heart failure. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 127–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Torem; ***Austria:*** Unat; ***Belg.:*** Torrem; ***Chile:*** Unat†; ***Cz.:*** Diuver; Trifas†; ***Ger.:*** Toracard; Toragamma; Torasid; Torem; Unat; ***Hong Kong:*** Unat; ***India:*** Dytor; ***Ital.:*** Diuremid; Diuresix; Toradiur; ***Jpn:*** Luprac; ***Pol.:*** Diuver; Trifas; ***Rus.:*** Diuver (Диувер); ***S.Afr.:*** Unat; ***Spain:*** Dilutol; Isodiur; Sutril; Tadegan; ***Swed.:*** Torem; ***Switz.:*** Toramide; Torasem; Torasis; Torem; ***Thai.:*** Unat; ***UK:*** Torem; ***USA:*** Demadex.

Torcetrapib *(USAN, rINN)*

CP-529414; Torcétrapib; Torcetrapibum. Ethyl (2*R*,4*S*)-4-{[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl)amino}-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate.
Торцетрапиб
$C_{26}H_{25}F_9N_2O_4$ = 600.5.
CAS — 262352-17-0.

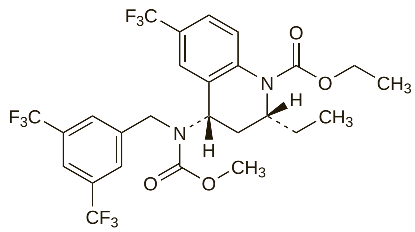

Profile

Torcetrapib is a cholesteryl ester transfer protein inhibitor. It increases plasma concentrations of high-density lipoprotein (HDL)-cholesterol and has been investigated in the management of lipid disorders. Development was stopped after the finding of increased mortality associated with torcetrapib in randomised, controlled studies.

Trandolapril *(BAN, rINN)*

RU-44570; Trandolapriili; Trandolaprilum; Trandolapryl. Ethyl (2*S*,3a*R*,7a*S*)-1-{(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl}hexahydro-2-indolinecarboxylate; (2*S*,3a*R*,7a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}perhydroindole-2-carboxylic acid.
Трандолаприл
$C_{24}H_{34}N_2O_5$ = 430.5.
CAS — 87679-37-6.
ATC — C09AA10.
ATC Vet — QC09AA10.

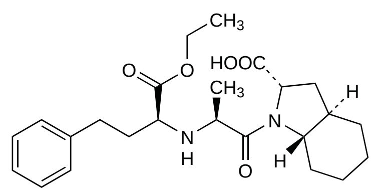

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Trandolapril acts as a prodrug of the diacid trandolaprilat, its active metabolite. After oral doses of trandolapril the bioavailability of trandolaprilat is 40 to 60%. Trandolapril is metabolised in the liver to trandolaprilat and to some inactive metabolites. Peak plasma concentrations of trandolaprilat are achieved 4 to 6 hours after an oral dose of trandolapril. Trandolaprilat is more than 80% bound to plasma proteins. About 33% of an oral dose of trandolapril is excreted in the urine, mainly as trandolaprilat; the rest is excreted in the faeces. The effective half-life for accumulation of trandolaprilat is 16 to 24 hours after multiple doses of trandolapril.

Impaired renal function decreases the excretion of trandolaprilat. Trandolaprilat is removed by haemodialysis.

◊ References.

1. Bevan EG, *et al.* Effect of renal function on the pharmacokinetics and pharmacodynamics of trandolapril. *Br J Clin Pharmacol* 1993; **35:** 128–35.

Uses and Administration

Trandolapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and in left ventricular dysfunction following myocardial infarction (p.1175).

Trandolapril owes its activity to trandolaprilat to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after 8 to 12 hours. The haemodynamic action lasts for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** the initial oral dose is 500 micrograms once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. In patients already taking a diuretic, the diuretic should be stopped, if possible, 2 to 3 days before starting trandolapril and resumed later if necessary. In patients with co-existing heart failure treatment with trandolapril should begin under close medical supervision. The usual maintenance dose for hypertension is 1 to 2 mg once daily, although up to 4 mg daily may be given, as a single dose or in 2 divided doses.

In **myocardial infarction**, treatment with trandolapril may be started 3 days after the infarction in an initial dose of 500 micrograms once daily, gradually increased to a maximum of 4 mg once daily.

A reduction in dosage may be necessary in patients with renal impairment (see below).

◊ References.

1. Zannad F. Trandolapril: How does it differ from other angiotensin converting enzyme inhibitors? *Drugs* 1993; **46** (suppl 2): 172–82.
2. Wiseman LR, McTavish D. Trandolapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. *Drugs* 1994; **48:** 71–90.
3. Køber L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; **333:** 1670–6.
4. Peters DC, *et al.* Trandolapril: an update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 1998; **56:** 871–93.

Administration in renal impairment. The initial dose of trandolapril in patients with renal impairment should not exceed 500 micrograms daily. UK licensed product information states that the maximum maintenance dose should be 2 mg daily in patients with a creatinine clearance of less than 10 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nortensin†; ***Austral.:*** Gopten; Odrik; Tranalpha; ***Austria:*** Gopten; ***Braz.:*** Gopten; Odrik†; ***Canad.:*** Mavik; ***Cz.:*** Gopten; Tanap; ***Denm.:*** Gopten; Odrik; ***Fin.:*** Gopten†; ***Fr.:*** Gopten†; Odrik; ***Ger.:*** Gopten†; Udrik; ***Gr.:*** Afenil; Odrik; ***Hung.:*** Gopten; ***Indon.:*** Gopten; ***Irl.:*** Gopten; Odrik; ***Ital.:*** Gopten; ***Jpn:*** Odric; Preran; ***Mex.:*** Gopten†; ***Neth.:*** Gopten; Odrik; ***Norw.:*** Gopten; ***NZ:*** Gopten; Odrik; ***Pol.:*** Gopten; ***Port.:*** Gopten; Odrik; ***Rus.:*** Gopten (Гоптен); ***S.Afr.:*** Gopten†; Mavik; ***Spain:*** Gopten; Odrik; ***Swed.:*** Gopten; ***Switz.:*** Gopten; ***Turk.:*** Gopten; ***UK:*** Gopten; Odrik†; ***USA:*** Mavik.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Tarka; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Tarka; Udramil†; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

Trapidil *(BAN, rINN)*

AR-12008; Tarpidil; Trapidiili; Trapidilis; Trapidilum. 7-Diethylamino-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine.
Трапидил
$C_{10}H_{15}N_5$ = 205.3.
CAS — 15421-84-8.
ATC — C01DX11.
ATC Vet — QC01DX11.

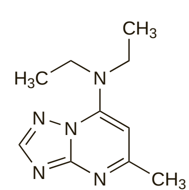

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Trapidil). A white or almost white crystalline powder. Freely soluble in water; soluble in dehydrated alcohol and in dichloromethane. Protect from light.

Profile

Trapidil is a vasodilator and an inhibitor of platelet aggregation. It is also an antagonist of platelet-derived growth factor. It is used orally in the management of ischaemic heart disease in doses of 400 to 600 mg daily, in divided doses; doses of up to 600 mg daily may be used to prevent restenosis after angioplasty (but see below). Ischaemic heart disease is discussed under Atherosclerosis (p.1159) and the treatment of its clinical manifestations is described under Angina Pectoris (p.1157) and Myocardial Infarction (p.1175).

◊ References to anti-platelet activity.

1. Yasue H, *et al.* Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction: Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. *Am J Cardiol* 1999; **83:** 1308–13.

◊ References to pharmacokinetics.

1. Harder S, *et al.* Pharmacokinetics of trapidil, an antagonist of platelet derived growth factor, in healthy subjects and in patients with liver cirrhosis. *Br J Clin Pharmacol* 1996; **42:** 443–9.

Angioplasty and stenting. Although angiographic studies[1-3] have found that trapidil reduces the rate of restenosis after balloon angioplasty (see Reperfusion and Revascularisation Procedures, p.1181), no effect on clinical outcomes[3] has been shown. Studies investigating the use of trapidil after coronary stenting[3,4] have shown no benefit in terms of restenosis or clinical events, and it was concluded that trapidil is not indicated for this purpose.

1. Okamoto S, *et al.* Effects of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, in preventing restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1992; **123:** 1439–44.
2. Maresta A, *et al.* Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty: results of the randomized, double-blind STARC study. *Circulation* 1994; **90:** 2710–15.
3. Maresta A, *et al.* Starc II, a multicenter randomized placebo-controlled double-blind clinical trial of trapidil for 1-year clinical events and angiographic restenosis reduction after coronary angioplasty and stenting. *Catheter Cardiovasc Interv* 2005; **64:** 375–82.
4. Serruys PW, *et al.* The TRAPIST study: a multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound. *Eur Heart J* 2001; **22:** 1938–47.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Rocornal†; ***Braz.:*** Travisco; ***Cz.:*** Rocornal†; ***Ger.:*** Rocornal; ***Ital.:*** Avantrin†; Travisco; ***Jpn:*** Rocornal.

Treprostinil *(USAN, rINN)*

LRX-15; Tréprostinil; Treprostinilo; Treprostinilum; Treprostinol; 15AU81; U-62840; UT-15. ({(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl}oxy)acetic acid.

Трепростинил

$C_{23}H_{34}O_5$ = 390.5.

CAS — 81846-19-7.

ATC — B01AC21.

ATC Vet — QB01AC21.

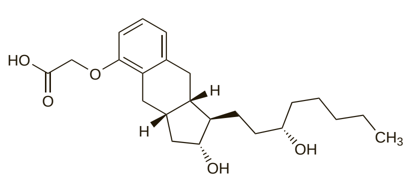

Treprostinil Sodium *(rINNM)*

Natrii Treprostinilum; Tréprostinil Sodique; Treprostinilo sódico.

Натрий Трепростинил

$C_{23}H_{33}NaO_5$ = 412.5.

CAS — 289480-64-4.

ATC — B01AC21.

ATC Vet — QB01AC21.

Adverse Effects and Precautions

Infusion site pain and reactions, including erythema, induration, and rash, are the most common adverse effects reported during subcutaneous infusion of treprostinil. Other effects include headache, nausea, diarrhoea, jaw pain, oedema, vasodilatation, dizziness, hypotension, and pruritus.

Abrupt cessation of the infusion should be avoided, because symptoms of pulmonary hypertension may worsen. Treprostinil should be used with caution in hepatic impairment.

Interactions

Since treprostinil is a vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants.

Pharmacokinetics

Treprostinil sodium is rapidly and completely absorbed after subcutaneous injection. It is metabolised by the liver and eliminated with a terminal half-life of about 4 hours. About 80% of a dose is excreted in the urine, mainly as metabolites.

◊ References.

1. Wade M, *et al.* Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. *J Clin Pharmacol* 2004; **44:** 83–8.
2. Wade M, *et al.* Pharmacokinetics of treprostinil sodium administered by 28-day chronic continuous subcutaneous infusion. *J Clin Pharmacol* 2004; **44:** 503–9.
3. Laliberte K, *et al.* Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharmacol* 2004; **44:** 209–14.
4. McSwain CS, *et al.* Dose proportionality of treprostinil sodium administered by continuous subcutaneous and intravenous infusion. *J Clin Pharmacol* 2008; **48:** 19–25.

Uses and Administration

Treprostinil, a vasodilator and platelet aggregation inhibitor, is an analogue of the prostaglandin epoprostenol (prostacyclin; p.1279). Treprostinil sodium is given by continuous subcutaneous infusion in the treatment of pulmonary hypertension (p.1179); if this route cannot be tolerated, treprostinil sodium may be given by continuous infusion through a central venous catheter. Doses are calculated in terms of treprostinil: treprostinil sodium 1.32 nanograms is equivalent to about 1.25 nanograms of treprostinil. The infusion is started with a dose equivalent to treprostinil 1.25 nanograms/kg per minute; if this is not tolerated the dose should be halved. The infusion rate can be increased according to patient response, by increments of up to 1.25 nanograms/kg per minute each week for the first 4 weeks, followed by increases of up to 2.5 nanograms/kg per minute each week. There is limited experience with doses above 40 nanograms/kg per minute. The dose of treprostinil should be reduced in hepatic impairment, see below.

Inhaled treprostinil is under investigation in pulmonary hypertension, and intravenous use has been investigated for intermittent claudication.

◊ References.

1. Moller ER, *et al.* Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. *Vasc Med* 2000; **5:** 231–7.
2. Simonneau G, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2002; **165:** 800–804.
3. Vachiéry J-L, *et al.* Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest* 2002; **121:** 1561–5.
4. Vachiéry JL, Naeije R. Treprostinil for pulmonary hypertension. *Expert Rev Cardiovasc Ther* 2004; **2:** 183–91.
5. Oudiz RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; **126:** 420–7.
6. Gomberg-Maitland M, *et al.* Efficacy and safety of sildenafil added to treprostinil in pulmonary hypertension. *Am J Cardiol* 2005; **96:** 1334–6.
7. Fernandez B, Strootman D. The prostacyclin analog, treprostinil sodium, provides symptom relief in severe Buerger's disease—a case report and review of literature. *Angiology* 2006; **57:** 99–102.
8. Voswinckel R, *et al.* Inhaled treprostinil for treatment of chronic pulmonary arterial hypertension. *Ann Intern Med* 2006; **144:** 149–50.
9. Channick RN, *et al.* Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol* 2006; **48:** 1433–7.

Administration in hepatic impairment. Clearance of treprostinil is reduced in patients with hepatic impairment. The manufacturers recommend that the initial dose should be 0.625 nanograms/kg per minute, and should be increased cautiously, in mild to moderate impairment. Treprostinil has not been studied in severe hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Remodulin; ***Chile:*** Remodulin; ***Cz.:*** Remodulin; ***Fr.:*** Remodulin; ***Gr.:*** Remodulin; ***Israel:*** Remodulin; ***Port.:*** Remodulin; ***Switz.:*** Remodulin; ***USA:*** Remodulin.

Triamterene *(BAN, USAN, rINN)* ⊗

NSC-77625; SKF-8542; Triamtereeni; Triamterén; Triamteren; Triamterenas; Triamtérène; Triamtereno; Triamterenum; Triantereno. 6-Phenylpteridine-2,4,7-triamine; 2,4,7-Triamino-6-phenylpteridine.

Триамтерен

$C_{12}H_{11}N_7$ = 253.3.

CAS — 396-01-0.

ATC — C03DB02.

ATC Vet — QC03DB02.

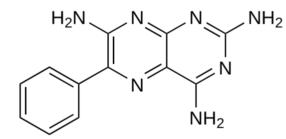

NOTE. Compounded preparations of triamterene may be represented by the following names:

- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Triamterene). A yellow, crystalline powder. Very slightly soluble in water and in alcohol. Protect from light.

USP 31 (Triamterene). A yellow, odourless, crystalline powder. Practically insoluble in water, in chloroform, in ether, in benzene, and in dilute alkali hydroxides; very slightly soluble in alcohol, in acetic acid, and in dilute mineral acids; soluble 1 in 30 of formic acid and 1 in 85 of 2-methoxyethanol. Store in airtight containers. Protect from light.

Adverse Effects

As for Amiloride Hydrochloride, p.1209. Triamterene has also been reported to cause photosensitivity reactions, increases in uric acid concentrations, and blood dyscrasias. Renal calculi may occur in susceptible patients, and megaloblastic anaemia has been reported in patients with depleted folic acid stores such as those with hepatic cirrhosis. Reversible renal failure, due either to acute interstitial nephritis or to an interaction with NSAIDs (see under Interactions, below) has occurred.

Incidence of adverse effects. In a postmarketing surveillance study of 70 898 patients[1] taking triamterene with hydrochlorothiazide the most common adverse effects were fatigue, dizziness, and nausea. Adverse effects necessitated withdrawal in 8.1% of patients. A subgroup analysis of 21 731 patients[2] indicated that hyperkalaemia was more common in elderly patients and in those with diabetes mellitus.

1. Hollenberg NK, Mickiewicz CW. Postmarketing surveillance in 70,898 patients treated with a triamterene/hydrochlorothiazide combination (Maxzide). *Am J Cardiol* 1989; **63:** 37B–41B.
2. Hollenberg NK, Mickiewicz CW. Hyperkalemia in diabetes mellitus: effect of a triamterene-hydrochlorothiazide combination. *Arch Intern Med* 1989; **149:** 1327–30.

Effects on the blood. There have been case reports of pancytopenia associated with triamterene therapy.[1,2] Some patients had hepatic cirrhosis and the antifolate activity of triamterene was considered responsible.[2]

1. Castellano G, *et al.* Pancitopenia aguda y megaloblastosis medular durante el tratemiento con triamterene de la ascitis causada por cirrosis hepática: aportación de dos casos. *Gastroenterol Hepatol* 1983; **6:** 540–4.
2. Remacha A, *et al.* Triamterene-induced megaloblastosis: report of two new cases, and review of the literature. *Biol Clin Hematol* 1983; **5:** 127–34.

Effects on the kidneys. There have been a number of reports[1-4] of renal calculi containing triamterene or its metabolites, generally in patients also taking hydrochlorothiazide. An abnormal urinary sediment was described which was thought to represent precipitated triamterene.[5] These observations were expanded in a crossover study:[6] abnormal urinary sediment was seen in 14 of 26 patients taking triamterene but in none taking amiloride. Triamterene and its metabolites were identified by others in 181 of 50 000 renal calculi.[7] Triamterene either formed the nucleus of the stone or was deposited with calcium oxalate or uric acid. One-third of the 181 stones were entirely or mainly composed of triamterene and its metabolites and it was suggested that supersaturation of the urine with these substances could provide suitable nuclei for the crystallisation of calcium oxalate.[8] However, other workers were unable to confirm this and suggested that triamterene and its metabolites could become incorporated into the protein matrix of existing stones.[9] In addition, an epidemiological study[10] found no evidence that triamterene use was associated with an increased incidence of renal stones. Some authors[11] have therefore considered that there was not enough evidence to contra-indicate the drug in patients with a history of recurrent renal calculi.

Deposition of triamterene in the urine may also play a part in the development of interstitial nephritis, which was diagnosed in 4 patients also taking hydrochlorothiazide, over a period of 4 years.[6]

Triamterene has also been associated with transient decline in renal function and the development of renal failure.[12,13] Several mechanisms may be responsible including interstitial nephritis, intrarenal obstruction by crystalline deposits, and an interaction with NSAIDs (see under Interactions, below).[13] Elderly patients may be particularly at risk.[12]

1. Ettinger B, *et al.* Triamterene-induced nephrolithiasis. *Ann Intern Med* 1979; **91:** 745–6.
2. Socolow EL. Triamterene-induced nephrolithiasis. *Ann Intern Med* 1980; **92:** 437.
3. Gault MH, *et al.* Triamterene urolithiasis. *Can Med Assoc J* 1981; **124:** 1556–7.
4. Grunberg RW, Silberg SJ. Triamterene-induced nephrolithiasis. *JAMA* 1981; **245:** 2494–5.
5. Fairley KF, *et al.* Abnormal urinary sediment in patients on triamterene. *Lancet* 1983; **i:** 421–2.
6. Spence JD, *et al.* Effects of triamterene and amiloride on urinary sediment in hypertensive patients taking hydrochlorothiazide. *Lancet* 1985; **ii:** 73–5.
7. Ettinger B, *et al.* Triamterene nephrolithiasis. *JAMA* 1980; **244:** 2443–5.
8. White DJ, Nancollas GH. Triamterene and renal stone formation. *J Urol (Baltimore)* 1982; **127:** 593–7.
9. Werness PG, *et al.* Triamterene urolithiasis: solubility, pK, effect on crystal formation, and matrix binding of triamterene and its metabolites. *J Lab Clin Med* 1982; **99:** 254–62.
10. Jick H, *et al.* Triamterene and renal stones. *J Urol (Baltimore)* 1982; **127:** 224–5.
11. Woolfson RG, Mansell MA. Does triamterene cause renal calculi? *BMJ* 1991; **303:** 1217–18.
12. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; **98:** 629–33.
13. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; **51:** 454–61.

Effects on the skin. Photodermatitis has been reported in a patient taking triamterene.[1] Pseudoporphyria, possibly associated with exposure to sunlight, occurred in a patient with vitiligo during treatment with triamterene and hydrochlorothiazide.[2]

1. Fernández de Corres L, *et al.* Photodermatitis from triamterene. *Contact Dermatitis* 1987; **17:** 114–15.
2. Motley RJ. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; **300:** 1468.

Precautions

As for Amiloride Hydrochloride, p.1209. Triamterene should also be given with caution to patients with hyperuricaemia or gout, or a history of renal calculi. Patients with depleted folic acid stores such as those with hepatic cirrhosis may be at increased risk of megaloblastic anaemia.

Triamterene may interfere with the fluorescent measurement of quinidine. It may slightly colour the urine blue.

Interactions

As for Amiloride Hydrochloride, p.1209.

Digoxin. For a report of the effect of triamterene on digoxin, see p.1262.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p.793.

NSAIDs. There have been several reports of renal failure in patients taking triamterene and NSAIDs.[1,2] Both types of drug are nephrotoxic and in combination the effect appears to be additive.[3-5] It has been suggested that the suppression of urinary prostaglandins by NSAIDs could potentiate the nephrotoxic effects of triamterene.[1]

NSAIDs may also antagonise the diuretic action of triamterene.[6]

1. Favre L, *et al.* Reversible acute renal failure from combined triamterene and indomethacin: a study in healthy subjects. *Ann Intern Med* 1982; **96:** 317–20.
2. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293:** 698–9.
3. Bailey RR. Adverse renal reactions to non-steroidal anti-inflammatory drugs and potassium-sparing diuretics. *Adverse Drug React Bull* 1988; (Aug.): 492–5.
4. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; **98:** 629–33.
5. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; **51:** 454–61.
6. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Pharmacokinetics

Triamterene is variably but fairly rapidly absorbed from the gastrointestinal tract. The bioavailability has been reported to be about 50%. The plasma half-life has been reported to be about 2 hours. It is estimated to be about 60% bound to plasma proteins. It is extensively metabolised and is mainly excreted in the urine in the form of metabolites with some unchanged triamterene. Triamterene crosses the placenta and may be distributed into breast milk.

◊ References.

1. Pruitt AW, *et al.* Variations in the fate of triamterene. *Clin Pharmacol Ther* 1977; **21:** 610–19.
2. Gundert-Remy U, *et al.* Plasma and urinary levels of triamterene and certain metabolites after oral administration to man. *Eur J Clin Pharmacol* 1979; **16:** 39–44.
3. Gilfrich HJ, *et al.* Pharmacokinetics of triamterene after iv administration to man: determination of bioavailability. *Eur J Clin Pharmacol* 1983; **25:** 237–41.
4. Sörgel F, *et al.* Oral triamterene disposition. *Clin Pharmacol Ther* 1985; **38:** 306–12.

Hepatic impairment. Triamterene clearance was markedly decreased in 7 patients with alcoholic cirrhosis and ascites.[1] The diuretic effect lasted for up to 48 hours in cirrhotic patients compared with 8 hours in healthy controls.

1. Villeneuve JP, *et al.* Triamterene kinetics and dynamics in cirrhosis. *Clin Pharmacol Ther* 1984; **35:** 831–7.

Renal impairment. Urinary excretion of triamterene and its metabolite, hydroxytriamterene sulfate, was significantly reduced in patients with renal impairment[1] and in the elderly whose renal function was reduced.[2] Accumulation of the active metabolite was possible in patients with renal impairment.[1]

1. Knauf H, *et al.* Delayed elimination of triamterene and its active metabolite in chronic renal failure. *Eur J Clin Pharmacol* 1983; **24:** 453–6.
2. Williams RL, *et al.* Absorption and disposition of two combination formulations of hydrochlorothiazide and triamterene: influence of age and renal function. *Clin Pharmacol Ther* 1986; **40:** 226–32.

Uses and Administration

Triamterene is a weak diuretic with potassium-sparing properties which has actions and uses similar to those of amiloride (p.1210). It produces a diuresis in about 2 to 4 hours, with a duration of 7 to 9 hours. The full therapeutic effect may be delayed until after several days of treatment.

Triamterene adds to the natriuretic but diminishes the kaliuretic effects of other diuretics. It is mainly used, as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the treatment of refractory oedema associated with hepatic cirrhosis, heart failure (p.1165), and the nephrotic syndrome. It is also used with other diuretics in the treatment of hypertension (p.1171).

When triamterene is given alone in the treatment of **oedema**, the oral dosage range is 150 to 250 mg daily, given in 2 divided doses, after breakfast and lunch. Doses may be given on alternate days for maintenance therapy. More than 300 mg daily should not be given.

Smaller doses are used initially when other diuretics are also given. When used with hydrochlorothiazide, for example, in the treatment of **hypertension**, an initial dose of 50 mg of triamterene daily may be used.

Potassium supplements should not be given.

Preparations

BP 2008: Co-triamterzide Tablets; Triamterene Capsules;
USP 31: Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Triamterene Capsules.

Proprietary Preparations (details are given in Part 3)
Belg.: Dytac; ***Canad.:*** Dyrenium†; ***Neth.:*** Dytac†; ***UK:*** Dytac; ***USA:*** Dyrenium.

Multi-ingredient: ***Austral.:*** Hydrene; ***Austria:*** Confit; Dytide H; Hydrotrix; Salodiur; Triamteren comp; Triastad HCT; Trioral/HCT; ***Belg.:*** Diucomb†; Dyta-Urese; Dytenzide; ***Braz.:*** Diurana; Iguassina; ***Canad.:*** Apo-Triazide; Novo-Triamzide; Nu-Triazide; ***Chile:*** Drinamil; Hidroronol T; Uren; ***Fin.:*** Furesis comp; Uretren Comp; ***Fr.:*** Isobar; Prestole; ***Ger.:*** Beta-Turfa; dehydro sanol tri; Diu Venostasin; Diucomb; Diuretikum Verla; Diutensat comp†; Diutensat†; Dociteren; duradiuret†; Dytide H; Haemiton compositum†; Hydrotrix; Jenateren comp†; Neotri; Nephral; Propra comp; Sali-Puren†; Thiazid-comp; Tri-Thiazid; Tri-Thiazid Reserpin†; Triampur Compositum; Triamteren comp; Triamteren HCT; Triamteren tri-comp; Triamteren-H†; Triarese; triazid†; Turfa; Veratide; ***Hong Kong:*** Apo-Triazide; Dyazide; Triam-Co†; ***India:*** Ditide; ***Irl.:*** Dyazide; ***Ital.:*** Fluss 40; ***Malaysia:*** Apo-Triazide†; ***Mex.:*** Dyazide; ***Neth.:*** Dyta-Urese; Dytenzide; ***NZ:*** Triamizide; ***Port.:*** Dyazide; Triam Tiazida R; ***Rus.:*** Apo-Triazide (Апо-триазид); Triam-Co (Триам-ко); Triampur Compositum (Триампур Композитум); ***S.Afr.:*** Dyazide; Renezide; ***Singapore:*** Apo-Triazide; ***Spain:*** Salidur; ***Switz.:*** Dyazide; Dyrenium compositum; t/h-basan; ***Thai.:*** Dazid†; Dinazide; Dyazide; Dyterene†; ***Turk.:*** Triamteril; ***UK:*** Dyazide; Dytide; Frusene; Kalspare; Triamaxco†; Triamco; ***USA:*** Dyazide; Maxzide.

Trichlormethiazide *(rINN)* ⊗

Trichlorméthiazide; Trichlormethiazidum; Triclormetiazida; Trikloorimetiatsidi; Triklormetiazid. 6-Chloro-3-dichloromethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Трихлорметиазид

$C_8H_8Cl_3N_3O_4S_2$ = 380.7.
CAS — 133-67-5.
ATC — C03AA06.
ATC Vet — QC03AA06.

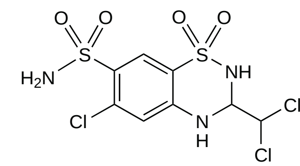

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Trichlormethiazide). A white or practically white, crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 1100 of water, 1 in 48 of alcohol, 1 in 5000 of chloroform, 1 in about 4 of dimethylformamide, 1 in about 9 of dioxan, and 1 in 1400 of ether; freely soluble in acetone; soluble in methyl alcohol.

Profile

Trichlormethiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis begins about 2 hours after an oral dose, and lasts about 24 hours.

In the treatment of oedema the usual dose is 1 to 4 mg daily or intermittently. In the treatment of hypertension the usual dose is 2 to 4 mg daily, either alone, or with other antihypertensives. In some patients 1 mg daily may be adequate. In children over 6 months of age a dose of 70 micrograms/kg daily in one or two doses has been used.

Preparations

USP 31: Trichlormethiazide Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Diurese†; Metahydrin†; Naqua†.

Multi-ingredient: ***Fin.:*** Uretren Comp; ***Ger.:*** Esmalorid†; ***Spain:*** Rulun; ***USA:*** Metatensin†.

Triflusal *(BAN, rINN)*

Triflusaali; Triflusalis; Triflusalum; Trifluzál; UR-1501. 2-Acetoxy-4-trifluoromethylbenzoic acid; *O*-Acetyl-4-(trifluoromethyl)salicylic acid.

Трифлусал

$C_{10}H_7F_3O_4$ = 248.2.
CAS — 322-79-2.
ATC — B01AC18.
ATC Vet — QB01AC18.

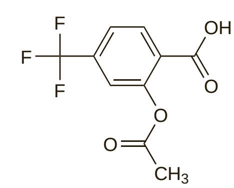

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Triflusal). A white or almost white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 25°.

Profile

Triflusal is an inhibitor of platelet aggregation used in the management of thromboembolic disorders (p.1187) in usual oral doses of 300 to 900 mg daily.

◊ References.

1. Murdoch D, Plosker GL. Triflusal: a review of its use in cerebral infarction and myocardial infarction, and as thromboprophylaxis in atrial fibrillation. *Drugs* 2006; **66:** 671–92.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Disgren; ***Braz.:*** Disgren; ***Chile:*** Logrosal†; ***Gr.:*** Aflen; Reoflen; ***Hung.:*** Disgren; ***Ital.:*** Triflux; ***Mex.:*** Disgren; ***Port.:*** Tecnosal; ***Spain:*** Anpeval; Disgren; ***Venez.:*** Disgren.

Trimetaphan Camsilate *(BAN, rINN)*

Cansilato de trimetafán; Méthioplégium; Trimetaphan Camphorsulfonate; Trimétaphan, Camsilate de; Trimetaphan Camsylate; Trimetaphani Camsilas; Trimetaphani Camsylas; Trimethaphan Camsylate. (+)-1,3-Dibenzylperhydro-2-oxothieno-[1′,2′:1,2]thieno[3,4-*d*]-imidazol-5-ium 2-oxobornane-10-sulfonate; 4,6-Dibenzyl-4,6-diaza-1-thioniatricyclo[$6.3.0.0^{3,7}$]undecan-5-one 2-oxobornane-10-sulfonate.

Триметафана Камзилат

$C_{22}H_{25}N_2OS,C_{10}H_{15}O_4S$ = 596.8.

CAS — 7187-66-8 (trimetaphan); 68-91-7 (trimetaphan camsilate).

ATC — C02BA01.

ATC Vet — QC02BA01.

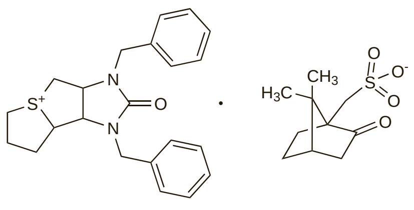

Incompatibility. Trimetaphan is incompatible with thiopental sodium, gallamine triethiodide, iodides, bromides, and strongly alkaline solutions.

Adverse Effects and Treatment

The adverse effects of trimetaphan are mainly due to ganglionic blockade. A reduction in gastrointestinal motility may cause constipation and, on prolonged use, paralytic ileus. Urinary retention, cycloplegia, mydriasis, tachycardia, precipitation of angina, and gastrointestinal disturbances such as anorexia, nausea, or vomiting, may occur. Orthostatic hypotension may be severe. Rapid intravenous infusion can result in respiratory arrest. Other adverse effects include raised intra-ocular pressure, dry mouth, hypoglycaemia, hypokalaemia, fluid retention, weakness, urticaria, and itching. Trimetaphan crosses the placenta and can cause paralytic or meconium ileus in the neonate.

If severe hypotension occurs, trimetaphan should be stopped and the patient positioned with the head lower than the feet. A vasopressor may be given cautiously if necessary.

Effects on the eyes. Although trimetaphan may increase intra-ocular pressure, a sudden and dramatic reduction of intra-ocular pressure to very low levels was noted in 5 patients undergoing surgery when the systolic blood pressure was reduced to 60 mmHg with trimetaphan infusion.[1]

1. Dias PLR, *et al.* Effect on the intraocular pressure of hypotensive anaesthesia with intravenous trimetaphan. *Br J Ophthalmol* 1982; **66:** 721–4.

Precautions

Trimetaphan should be avoided in patients with asphyxia or respiratory insufficiency, uncorrected anaemia, shock or hypovolaemia, severe arteriosclerosis, severe ischaemic heart disease, or pyloric stenosis and should only be used with extreme caution in those with hepatic or renal impairment, degenerative disease of the CNS, Addison's disease, prostatic hyperplasia, glaucoma, cerebral or coronary vascular insufficiency, and diabetes. It should be used with care in elderly or debilitated patients and should be avoided in pregnancy. Owing to a histamine-liberating effect it should be used with caution in allergic subjects.

Interactions

Trimetaphan should be used with caution in patients being treated with other antihypertensives, drugs that depress cardiac function, or muscle relaxants, and in those taking NSAIDs or corticosteroids. The hypotensive effect is enhanced by general and spinal anaesthetics. Adrenaline should not be infiltrated locally at the site of incision when trimetaphan is being given since this may antagonise the effect of trimetaphan.

Neuromuscular blockers. For a reference to possible potentiation of neuromuscular blockade by trimetaphan, see Ganglion Blockers, under Interactions of Atracurium, p.1904.

Uses and Administration

Trimetaphan is a ganglion blocker that inhibits the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. The sympathetic blockade produces peripheral vasodilatation. Trimetaphan also has a direct vasodilator effect on peripheral blood vessels. It has been used for inducing controlled hypotension during surgical procedures; it acts rapidly to produce a hypotensive response which persists for about 10 to 15 minutes. Trimetaphan has also been used for the emergency treatment of hypertensive crises (p.1171), especially in the presence of pulmonary oedema or acute dissecting aortic aneurysms. However, sodium nitroprusside is now preferred.

Trimetazidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimetazidina; Trimetatsidiinidihydrokloridi; Trimetazidin Hidroklorür; Trimetazidindihidroklorid; Trimetazidindihydrochlorid; Trimetazidindihydroklorid; Trimétazidine, Chlorhydrate de; Trimétazidine, dichlorhydrate de; Trimetazidine Dihydrochloride; Trimetazidini dihydrochloridum; Trimetazidini Hydrochloridum; Trimetazidino hidrochloridas; Trimetazine Hydrochloride. 1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride.

Триметазидина Гидрохлорид

$C_{14}H_{22}N_2O_3,2HCl$ = 339.3.

CAS — 5011-34-7 (trimetazidine); 13171-25-0 (trimetazidine hydrochloride).

ATC — C01EB15.

ATC Vet — QC01EB15.

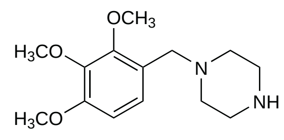

(trimetazidine)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Trimetazidine Dihydrochloride; Trimetazidine Hydrochloride BP 2008). A slightly hygroscopic, white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Trimetazidine hydrochloride is used in angina pectoris (p.1157) and in ischaemia of neurosensorial tissues as in Ménière's disease (p.564); 40 to 60 mg is given daily by mouth in divided doses.

◊ References.

1. McClellan KJ, Plosker GL. Trimetazidine: a review of its use in stable angina pectoris and other coronary conditions. *Drugs* 1999; **58:** 143–57.
2. Ciapponi A, *et al.* Trimetazidine for stable angina. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/06).
3. Danchin N. Clinical benefits of a metabolic approach with trimetazidine in revascularized patients with angina. *Am J Cardiol* 2006; **98** (suppl): 8J–13J.

Effects on the nervous system. Eight elderly patients aged between 72 and 94 years were reported[1] to have developed signs of parkinsonism while taking trimetazidine; the parkinsonism regressed completely when the drug was stopped. A retrospective study[2] found that adverse effects on motor function, including parkinsonism, gait disorders, and tremor, occurred in 56 of 130 patients taking trimetazidine and were more common in older patients.

1. Martí Massó JF. Parkinsonismo por trimetazidina. *Neurologia* 2004; **19:** 392–5.
2. Martí Massó J-F, *et al.* Trimetazidine induces parkinsonism, gait disorders and tremor. *Therapie* 2005; **60:** 419–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vastarel; ***Austria:*** Vastarel; ***Braz.:*** Vastarel; ***Chile:*** Vastarel; ***Cz.:*** Adexor; Preductal; ***Denm.:*** Vastarel; ***Fr.:*** Centrophene†; Vastarel; ***Gr.:*** Atanol; Imovexil; Intervein; Latrimet†; Liomagen; Novazidine; Trimedin; Trimedor; Trimevert; Vastarel; Zidin; ***Hong Kong:*** Vastarel; ***Hung.:*** Adexor; Preductal; ***India:*** Flavedon; Mayozest; Metacard; Metagard; Trivedon; ***Indon.:*** Trizedon; ***Irl.:*** Vastarel; ***Ital.:*** Vastarel; ***Malaysia:*** Metagard; Vastarel; ***Philipp.:*** Angirel; Vastarel; ***Pol.:*** Metazydyna; Preductal; Trimetaratio; ***Port.:*** Tacirel; Vastarel; ***Rus.:*** Deprenorm (Депренорм); Medarum (Медарум); Preductal (Предуктал); Rimecor (Римекор); Trimetazide (Триметазид); ***Singapore:*** Metagard; Vastarel; ***Spain:*** Idaptan; Vaso Rimal†; ***Thai.:*** Matenol; Trizidine; Vastarel; Vastinol; ***Turk.:*** Vastarel; ***Venez.:*** Vastarel.

Tripamide *(USAN, rINN)* ⊗

ADR-033; E-614; Tripamida; Tripamidum. 4-Chloro-*N*-(*endo*-hexahydro-4,7-methanoisoindolin-2-yl)-3-sulphamoylbenzamide.

Трипамид

$C_{16}H_{20}ClN_3O_3S$ = 369.9.

CAS — 73803-48-2.

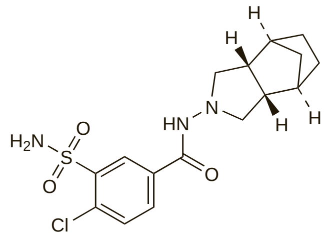

Profile

Tripamide is a diuretic structurally related to indapamide. It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Thai.: Normonal.

Urapidil *(BAN, rINN)*

B-66256M; Urapidiili; Urapidilum. 6-[3-(4-*o*-Methoxyphenylpiperazin-1-yl)propylamino]-1,3-dimethyluracil.

Урапидил

$C_{20}H_{29}N_5O_3$ = 387.5.

CAS — 34661-75-1.

ATC — C02CA06.

ATC Vet — QC02CA06.

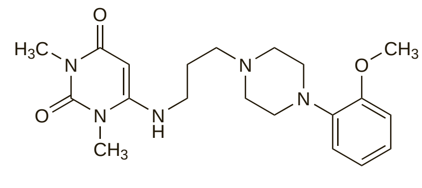

Pharmacopoeias. In *Jpn.*

Urapidil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de urapidil; Urapidil, Chlorhydrate d'; Urapidili Hydrochloridum.

Урапидила Гидрохлорид

$C_{20}H_{29}N_5O_3,HCl$ = 423.9.

CAS — 64887-14-5.

ATC — C02CA06.

ATC Vet — QC02CA06.

Adverse Effects and Precautions

Urapidil is reported to be well-tolerated, with adverse effects generally transient and most frequent at the beginning of therapy. Dizziness, nausea, headache, fatigue, orthostatic hypotension, palpitations, nervousness, pruritus, and allergic skin reactions have been reported.

It should be used with care in elderly patients and those with severe hepatic impairment. Intravenous urapidil should not be used in patients with aortic stenosis.

Urinary incontinence. Enuresis was reported[1] to be associated with the use of urapidil in 2 elderly patients.

1. Jonville A-P, *et al.* Urapidil and enuresis. *Lancet* 1992; **339:** 688.

Pharmacokinetics

After oral doses urapidil is rapidly absorbed with a reported bioavailability of 70 to 80%. It is reported to be about 80% bound to plasma proteins. Urapidil is extensively metabolised in the liver, mainly by hydroxylation, and excreted mostly in urine, as metabolites and 10 to 20% of unchanged drug. The elimination half-life is reported to be about 4.7 hours when given orally as capsules and about 2.7 hours after intravenous dosage.

◊ Reviews.

1. Kirsten R, *et al.* Clinical pharmacokinetics of urapidil. *Clin Pharmacokinet* 1988; **14:** 129–40.

Uses and Administration

Urapidil is an antihypertensive drug that is reported to block peripheral $alpha_1$ adrenoceptors (see Alpha Blockers, p.1153) and to have central actions. It produces a reduction in peripheral resistance and a fall in systolic and diastolic blood pressure, usually without reflex tachycardia.

Urapidil is used in the management of hypertension (p.1171), including hypertensive crises.

Urapidil is given orally as the base and intravenously as the hydrochloride, but doses are usually expressed in terms of the base. Urapidil hydrochloride 10.94 mg is equivalent to about 10 mg of urapidil. Urapidil fumarate has also been given orally.

In hypertension doses of 30 to 90 mg are given twice daily by mouth. In hypertensive crises a suggested regimen is to give an initial dose of 25 mg by slow intravenous injection over 20 seconds, repeated if necessary after 5 minutes. This may be followed by a dose of 50 mg after a further 5 minutes if the response is still inadequate. Treatment should continue with a maintenance infusion of 9 to 30 mg/hour once the blood pressure is sufficiently reduced.

◊ Reviews.

1. Dooley M, Goa KL. Urapidil: a reappraisal of its use in the management of hypertension. *Drugs* 1998; **56:** 929–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ebrantil; ***Belg.:*** Ebrantil; ***Cz.:*** Ebrantil; ***Fr.:*** Eupressyl; Mediatensyl; ***Ger.:*** Ebrantil; ***Hung.:*** Ebrantil; ***Ital.:*** Ebrantil; ***Neth.:*** Ebrantil; ***Pol.:*** Ebrantil; ***Port.:*** Ebrantil; ***Spain:*** Elgadil; ***Switz.:*** Ebrantil.

Urokinase *(BAN, USAN, rINN)*

Urokinaasi; Urokinas; Urokinasa; Urokinasum; Ürokinaz; Urokináz; Urokinazė; Uroquinasa.

Урокиназа

CAS — 9039-53-6.

ATC — B01AD04.

ATC Vet — QB01AD04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Urokinase). An enzyme isolated from human urine that activates plasminogen. It consists of a mixture of low (33 000) and high (54 000) molecular mass forms, the high molecular mass form being predominant. The potency is not less than 70 000 international units per mg of protein. A white or almost white, amorphous powder. Soluble in water. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. Solutions of urokinase containing 2500 to 25 000 units/mL were found to be stable in single-use syringes when stored at −30° for 30 days and also when stored frozen for 7 days, thawed, and refrozen for a further 23 days.[1]

1. Dedrick SC, Ramirez-Rico J. Potency and stability of frozen urokinase solutions in syringes. *Am J Health-Syst Pharm* 2004; **61:** 1586–9.

Units

The potency of urokinase is expressed in international units. Preparations are assayed using the first International Reference Preparation (1968), a mixture of low-molecular-weight and high-molecular-weight urokinases. The first International Standard for high-molecular-weight urokinase was established in 1989 for use with preparations of this type of urokinase.

Potency used to be expressed in Ploug or Plough units or in CTA units, but these now appear to be obsolete.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Serious allergic reactions may be less likely to occur with urokinase than with streptokinase.

Hypersensitivity. Allergic reactions are considered to be less frequent with urokinase than with streptokinase. However, in a series of 6 patients who had previously been treated with streptokinase,[1] thrombolytic therapy with urokinase for recurrent myocardial infarction was associated with rigors in 4 patients, 2 of whom also developed bronchospasm. None of the patients had any history of atopy.

1. Matsis P, Mann S. Rigors and bronchospasm with urokinase after streptokinase. *Lancet* 1992; **340:** 1552.

Transmission of infection. Some preparations of urokinase are produced in cultures of human cells and there is a risk of transmission of infection associated with their use.

Interactions

As for Streptokinase, p.1404.

Pharmacokinetics

After intravenous infusion urokinase is cleared rapidly from the circulation by the liver. A plasma half-life of up to 20 minutes has been reported.

Uses and Administration

Urokinase is a thrombolytic produced by the kidney and found in human urine. It directly converts plasminogen to plasmin, a proteolytic enzyme with fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Urokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p.1156).

Urokinase is used similarly to streptokinase (p.1404) in the management of thromboembolic disorders including venous thromboembolism (pulmonary embolism and deep-vein thrombosis; p.1189) and peripheral arterial thromboembolism (p.1178). It is also used to clear occluded catheters and cannulas. Urokinase has been used in myocardial infarction and for clearing clots after haemorrhage within the eye.

In the treatment of **venous thromboembolism**, urokinase is given by intravenous infusion in an initial dose of 4400 units/kg over 10 minutes. This is followed by 4400 units/kg per hour for 12 hours in pulmonary embolism, and for 12 to 24 hours in deep-vein thrombosis. Alternatively, patients with pulmonary embolism may be given a bolus injection of 15 000 units/kg into the pulmonary artery; the injection may be repeated, with the dose adjusted according to plasma-fibrinogen concentration, up to 3 times in 24 hours.

In the treatment of **peripheral arterial thromboembolism**, a solution containing urokinase 2000 units/mL is infused into the clot via a catheter at a rate of 4000 units/minute for 2 hours. Angiography should then be performed and, if flow has not resumed, the catheter should be advanced into the occluded vessel and the infusion continued at the same rate for a further 2 hours. The procedure may be repeated, if necessary, up to 4 times. Once blood flow is re-established, the catheter should be partially withdrawn and infusion continued at a rate of 1000 units/minute until the remaining clot has lysed; a dose of 500 000 units given over 8 hours is usually sufficient.

For **clearing occluded intravenous catheters or cannulas**, 5000 to 25 000 units of urokinase dissolved in 2 mL of sodium chloride 0.9% may be instilled into the device and clamped off for up to 4 hours; the lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5000 units of urokinase in 200 mL of sodium chloride 0.9% may be infused into the device over 30 minutes.

Catheters and cannulas. For reference to the use of urokinase to maintain patency of long-term venous access devices, see under Uses for Alteplase, p.1208.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Abbokinase; Actosolv; ***Belg.:*** Actosolv; ***Cz.:*** Rheotromb; ***Ger.:*** Corase; Rheotromb; ***Gr.:*** Ukidan†; Urochinasi; ***Hung.:*** Rheotromb; ***India:*** Solokinase; Ukidan†; Uni-Kinase; ***Israel:*** Abbokinase; ***Ital.:*** Actosolv†; Alfakinasi†; Kisolv†; Persolv Richter†; ***Jpn:*** Uronase; ***Neth.:*** Medacinase; ***Port.:*** Ukidan†; ***Spain:*** Uroquidan; ***Swed.:*** Abbokinase†; ***UK:*** Syner-Kinase; ***USA:*** Abbokinase.

Valsartan *(BAN, USAN, rINN)*

CGP-48933; Valsartaani; Valsartán; Valsartanum. *N*-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine; *N*-Pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine.

Вальзартан

$C_{24}H_{29}N_5O_3$ = 435.5.

CAS — 137862-53-4.

ATC — C09CA03.

ATC Vet — QC09CA03.

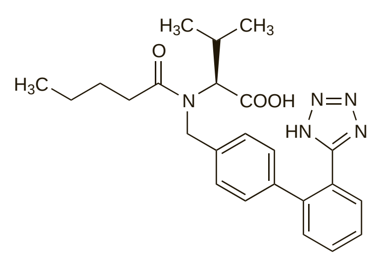

Pharmacopoeias. In *US.*

USP 31 (Valsartan). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Suspension. The US licensed product information provides the following method for making 160 mL of a suspension containing valsartan 4 mg/mL:

- add 80 mL of *Ora-Plus* (*Paddock, USA*) to an amber glass bottle containing eight 80-mg tablets (*Diovan, Novartis*) and shake for at least 2 minutes
- allow to stand for at least 1 hour then shake again for at least 1 minute
- add 80 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and shake for at least 10 seconds

The suspension can be stored for 30 days at or below 30° or for up to 75 days at 2° to 8°.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326. Valsartan should be used with caution in patients with hepatic impairment, cirrhosis, or biliary obstruction.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23%. Peak plasma concentrations of valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolised and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose about 83% is excreted in the faeces and 13% in urine.

◊ References.

1. Brookman LJ, *et al.* Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; **62:** 272–8.
2. Prasad PP, *et al.* Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *J Cardiovasc Pharmacol* 2002; **40:** 801–7.

Uses and Administration

Valsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171), to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction (p.1175), and in the management of heart failure (see under Losartan Potassium, p.1327).

Valsartan is given orally. After a dose the hypotensive effect occurs within 2 hours, reaches a peak within 4 to 6 hours, and persists for over 24 hours. The maximum hypotensive effect is achieved within 2 to 4 weeks.

In **hypertension**, valsartan is given in an initial dose of 80 mg once daily. This may be increased, if necessary, to 160 mg once daily; the maximum dose is 320 mg once daily. A lower initial dose of 40 mg once daily may be used in elderly patients over 75 years, and in those with intravascular volume depletion.

In **heart failure,** valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

In patients who have had **myocardial infarction**, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, in an initial dose of 20 mg twice daily; the dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated.

Valsartan should be used with caution in patients with hepatic or renal impairment and dose reduction may be required (see below).

◊ Reviews.

1. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54:** 299–311.
2. Ripley TL. Valsartan in chronic heart failure. *Ann Pharmacother* 2005; **39:** 460–9.
3. Mistry NB, *et al.* The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7:** 575–81.
4. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vasc Health Risk Manag* 2007; **3:** 425–30.

Administration in children. Valsartan may be used for hypertension in children aged 6 to 16 years. US licensed product information recommends an initial dose of 1.3 mg/kg once daily (up to a maximum of 40 mg). The dose should be adjusted according to response, but doses above 2.7 mg/kg daily have not been studied. A suspension formulation may be used (see Suspension, above) but exposure to valsartan may be higher with the suspension than with tablets. There is no experience with valsartan in children with renal impairment (creatinine clearance below 30 mL/minute per 1.73 m^2) and it should therefore not be used in such children.

Administration in hepatic or renal impairment. The elimination of valsartan may be reduced in patients with hepatic impairment or biliary obstruction and it should be used with caution, if at all, in such patients; dose reductions may be required. In the UK, valsartan is contra-indicated in patients with severe hepatic impairment, cirrhosis, or biliary obstruction. In mild to moderate hepatic impairment an initial dose of 40 mg once daily and a maximum dose of 80 mg once daily is recommended for hypertension, and the dose after myocardial infarction should not generally exceed 80 mg twice daily.

Lower doses of valsartan may also be considered in patients with renal impairment. In the UK, an initial dose of 40 mg once daily is recommended for the treatment of hypertension in patients with moderate or severe renal impairment (creatinine clearance less than 20 mL/minute). Doses may need to be reduced in patients with heart failure or after myocardial infarction if renal function deteriorates.

Preparations

USP 31: Valsartan and Hydrochlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alpertan; Diovan; Redutensil†; Sarval; Simultan; ***Austria:*** Angiosan; Diovan; ***Belg.:*** Diovane; ***Braz.:*** Diovan; Tareg†; ***Canad.:*** Diovan; ***Chile:*** Tareg; Valaplex; Vartalan; ***Cz.:*** Diovan; Sarton†; Valsacor; ***Denm.:*** Diovan; ***Fin.:*** Diovan; ***Fr.:*** Nisis; Tareg; ***Ger.:*** Cordinate; Diovan; Provas; ***Gr.:*** Dalzad; Diovan; ***Hong Kong:*** Diovan; ***Hung.:*** Diovan; Varexan; ***India:*** Diovan; Starval; ***Indon.:*** Diovan; ***Irl.:*** Diovan; ***Israel:*** Diovan; ***Ital.:*** Rixil; Tareg; Valpression; ***Jpn:*** Diovan; ***Malaysia:*** Diovan; ***Mex.:*** Diovan; ***Neth.:*** Diovan; ***Norw.:*** Diovan; ***Philipp.:*** Diovan; ***Pol.:*** Diovan; ***Port.:*** Diovan; Tareg; ***Rus.:*** Diovan (Диован); ***S.Afr.:*** Diovan; Tareg; ***Singapore:*** Diovan; ***Spain:*** Diovan; Kalpress; Miten; Vals; ***Swed.:*** Diovan; ***Switz.:*** Diovan; Provas; ***Thai.:*** Diovan; ***Turk.:*** Diovan; ***UK:*** Diovan; ***USA:*** Diovan; ***Venez.:*** Alsart; Diovan; Vasaten.

Multi-ingredient: ***Arg.:*** Diovan A; Diovan D; Diovan Triple; Simultan D; ***Austria:*** Co-Angiosan; Co-Diovan; Valsartan/HCTZ†; ***Belg.:*** Co-Diovane; ***Braz.:*** Cotareg†; Diocomb SI; Diovan Amlo; Diovan HCT; ***Canad.:*** Diovan HCT; ***Chile:*** Tareg-D; Valaplex-D; Vartalan D; ***Cz.:*** Co-Diovan; Copalia; Dafiro; Exforge; Imprida; ***Denm.:*** Diovan Comp; ***Fin.:*** Diovan Comp; ***Fr.:*** Cotareg; Nisisco; ***Ger.:*** Co-Diovan; Cordinate plus; Provas comp; ***Gr.:*** Co-Dalzad; Co-Diovan; Copalia; Dafiro; Exforge; ***Hong Kong:*** Co-Diovan; ***Hung.:*** Diovan HCT; Varexan HCT; ***Indon.:*** Co-Diovan; ***Irl.:*** Co-Diovan; ***Israel:*** Co-Diovan; ***Ital.:*** Combisartan; Corixil; Cotareg; ***Malaysia:*** Co-Diovan; ***Mex.:*** Co-Diovan; ***Neth.:*** Co-Diovan; Cotareg; ***Norw.:*** Diovan Comp; ***Philipp.:*** Co-Diovan; ***Pol.:*** Co-Diovan; ***Port.:*** Co-Diovan; Co-Tareg; Copalia; Dafiro; Imprida; ***Rus.:*** Co-Diovan (Ко-Диован); ***S.Afr.:*** Co-Diovan; ***Singapore:*** Co-Diovan; ***Spain:*** Co-Diovan; Co-Vals; Kalpress Plus; Miten Plus; ***Swed.:*** Diovan Comp; ***Switz.:*** Co-Diovan; Provas comp; Provas maxx; ***Thai.:*** Co-Diovan; ***Turk.:*** Co-Diovan; ***UK:*** Co-Diovan; Exforge; ***USA:*** Diovan HCT; Exforge; ***Venez.:*** Diovan HCT; Diovan/Amlibon; Vasaten HCT.

Verapamil Hydrochloride

(BANM, USAN, rINNM)

CP-16533-1 (verapamil); D-365 (verapamil); Hidrocloruro de verapamilo; Iproveratril Hydrochloride; Verapamiilihydrokloridi; Vérapamil, chlorhydrate de; Verapamil Hidroklorür; Verapamil-hidroklorid; Verapamil-hydrochlorid; Verapamilhydroklorid; Verapamili hydrochloridum; Verapamilio hidrochloridas. 5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

Верапамила Гидрохлорид

$C_{27}H_{38}N_2O_4,HCl = 491.1.$

CAS — 52-53-9 (verapamil); 152-11-4 (verapamil hydrochloride).

ATC — C08DA01.

ATC Vet — QC08DA01.

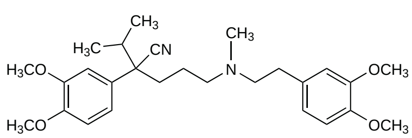

(verapamil)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Verapamil Hydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Verapamil Hydrochloride). A white or practically white, practically odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Verapamil hydrochloride will precipitate in alkaline solutions. There have been reports of incompatibility with solutions of aminophylline,[1] nafcillin sodium,[2] and sodium bicarbonate.[3]

1. Johnson CE, *et al.* Compatibility of aminophylline and verapamil in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 97–100.
2. Tucker R, Gentile JF. Precipitation of verapamil in an intravenous line. *Ann Intern Med* 1984; **101:** 880.
3. Cutie MR. Verapamil precipitation. *Ann Intern Med* 1983; **98:** 672.

Adverse Effects

Treatment with verapamil is generally well tolerated, but adverse effects connected with its pharmacological effects on cardiac conduction can arise and may be particularly severe in patients with previous myocardial damage or hypertrophic cardiomyopathies. Adverse effects on the heart include bradycardia, AV block, worsening heart failure, and transient asystole. These effects are more common with parenteral than with oral therapy.

The most troublesome non-cardiac adverse effect is constipation. Nausea may occur but is less frequently reported. Other adverse effects include hypotension, dizziness, flushing, headaches, fatigue, dyspnoea, and peripheral oedema. There have been reports of skin reactions and some cases of abnormal liver function and hepatotoxicity. Gingival hyperplasia has occurred. Gynaecomastia has been reported rarely.

In overdosage there may be severe cardiotoxicity and profound hypotension.

Carcinogenicity. See under Adverse Effects of Nifedipine, p.1350.

Effects on the cardiovascular system. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see Effects on Mortality, under Adverse Effects of Nifedipine, p.1350.

Verapamil has vasodilating properties and negative inotropic activity and may cause adverse cardiovascular effects with worsening of arrhythmias. As discussed under Precautions (below) certain cardiac disorders put the patient at risk of severe toxicity.

Some references.

1. Radford D. Side effects of verapamil in infants. *Arch Dis Child* 1983; **58:** 465–6.
2. Perrot B, *et al.* Verapamil: a cause of sudden death in a patient with hypertrophic cardiomyopathy. *Br Heart J* 1984; **51:** 352–4.
3. Kirk CR, *et al.* Cardiovascular collapse after verapamil in supraventricular tachycardia. *Arch Dis Child* 1987; **62:** 1265–6.
4. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure. *JAMA* 1989; **261:** 994.
5. Garratt C, *et al.* Degeneration of junctional tachycardia to pre-excited atrial fibrillation after intravenous verapamil. *Lancet* 1989; **ii:** 219.
6. Stajer D, *et al.* Cardiogenic shock following a single therapeutic oral dose of verapamil. *Int J Clin Pract* 2001; **55:** 69–70.
7. Shiraishi H, *et al.* Two cases of polymorphic ventricular tachycardia induced by the administration of verapamil against paroxysmal supraventricular tachycardia. *Intern Med* 2002; **41:** 445–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Effects on the endocrine system. Hyperprolactinaemia has been reported[1-4] in patients receiving verapamil, and in a few cases[2,3] patients have also had galactorrhoea.

Hyperglycaemia, metabolic acidosis, hyperkalaemia, and bradycardia have occurred[5] after a single dose of modified-release verapamil in a non-diabetic patient who had previously tolerated regular verapamil.

Verapamil has been reported not to affect the release of calcitonin,[6] thyroxine, tri-iodothyronine, thyrotrophin (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), or testosterone when given orally;[1] however, intravenous use has been reported to have an inhibitory effect on the release of FSH, LH, and TSH.[7]

1. Semple CG, *et al.* Calcium antagonists and endocrine status: lack of effect of oral verapamil on pituitary-testicular and pituitary-thyroid function. *Br J Clin Pharmacol* 1984; **17:** 179–82.
2. Gluskin LE, *et al.* Verapamil-induced hyperprolactinemia and galactorrhea. *Ann Intern Med* 1981; **95:** 66–7.
3. Fearrington EL, *et al.* Hyperprolactinemia-galactorrhea induced by verapamil. *Am J Cardiol* 1983; **51:** 1466–7.
4. Romeo JH, *et al.* Hyperprolactinaemia and verapamil: prevalence and potential association with hypogonadism in men. *Clin Endocrinol (Oxf)* 1996; **45:** 571–5.
5. Roth A, *et al.* Slow-release verapamil and hyperglycemic metabolic acidosis. *Ann Intern Med* 1989; **110:** 171–2.
6. Amado JA, *et al.* No effect of verapamil on calcium stimulated calcitonin release. *Postgrad Med J* 1987; **63:** 23–4.
7. Barbarino A, De Marinis L. Calcium antagonists and hormone release II: effects of verapamil on basal, gonadotrophin-releasing hormone- and thyrotrophin-releasing hormone-induced pituitary hormone release in normal subjects. *J Clin Endocrinol Metab* 1980; **51:** 749–53.

Effects on the gastrointestinal tract. For a report of intestinal pseudo-obstruction related to verapamil use, see under Adverse Effects of Diltiazem, p.1265.

Effects on the liver. Elevated serum concentrations of liver enzymes and bilirubin have been reported during verapamil therapy.[1-5] Clinical symptoms of hepatotoxicity such as abdominal pain, fever, darkened urine, and malaise have also occurred.[2-5] These reactions might have been due to a hypersensitivity reaction and were reversible on stopping verapamil.

1. Brodsky SJ, *et al.* Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981; **94:** 490–1.
2. Stern EH, *et al.* Possible hepatitis from verapamil. *N Engl J Med* 1982; **306:** 612–13.
3. Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983; **249:** 395–6.
4. Guarascio P, *et al.* Liver damage from verapamil. *BMJ* 1984; **288:** 362–3.
5. Kumar KL, Colley CA. Verapamil-induced hepatotoxicity. *West J Med* 1994; **160:** 485–6.

Effects on the mouth. Gingival hyperplasia[1] and oral mucosal injury[2] have been associated with verapamil therapy. A study involving 115 patients who had received nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[3]

1. Pernu HE, *et al.* Verapamil-induced gingival overgrowth: a clinical, histologic, and biochemic approach. *J Oral Pathol Med* 1989; **18:** 422–5.
2. Guttenberg SA. Chemical injury of the oral mucosa from verapamil. *N Engl J Med* 1990; **323:** 615.
3. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120:** 663–4.

Effects on the nervous system. There has been a report[1] of 3 patients who complained of unusual perceptual symptoms, described as painful coldness and numbness or bursting feelings, especially in the legs, while taking oral verapamil.

1. Kumana CR, Mahon WA. Bizarre perceptual disorder of extremities in patients taking verapamil. *Lancet* 1981; **i:** 1324–5.

Effects on the neuromuscular system. Movement disorders, including acute dystonia,[1] myoclonic dystonia,[2] myoclonus,[3,4] and parkinsonism,[5,6] have occurred in patients receiving verapamil. However, there have also been reports of the successful use of verapamil in refractory movement disorders (see below).

1. Pina MA, *et al.* Verapamil and acute dystonia. *J Clin Pharm Ther* 1998; **23:** 79–80.
2. Hicks CB, Abraham K. Verapamil and myoclonic dystonia. *Ann Intern Med* 1985; **103:** 154.
3. Maiteh M, Daoud AS. Myoclonic seizure following intravenous verapamil injection: case report and review of the literature. *Ann Trop Paediatr* 2001; **21:** 271–2.
4. Vadlamudi L, Wijdicks EFM. Multifocal myoclonus due to verapamil overdose. *Neurology* 2002; **58:** 984.
5. García-Albea E, *et al.* Parkinsonism unmasked by verapamil. *Clin Neuropharmacol* 1993; **16:** 263–5.
6. Padrell MD, *et al.* Verapamil-induced parkinsonism. *Am J Med* 1995; **99:** 436.

Effects on the peripheral circulation. Secondary erythermalgia, a vasospastic arterial disorder that may be caused by vasoactive drugs, has been reported[1,2] in patients taking verapamil. Symptoms included burning pain, swelling, and erythema of the hands[2] and feet,[1,2] and resolved when verapamil was stopped. Similar reactions have been reported with nifedipine and other calcium-channel blockers (see p.1351).

1. Drenth JPH, *et al.* Verapamil-induced secondary erythermalgia. *Br J Dermatol* 1992; **127:** 292–4.
2. Hart JJ. Painful, swollen, and erythematous hands and feet. *Arthritis Rheum* 1996; **39:** 1761–2.

Effects on the respiratory tract. A patient with a history of bronchial asthma developed symptoms of acute asthma after use of a modified-release verapamil preparation;[1] it was possible that excipients, notably alginate, may have been responsible for the reaction.

1. Ben-Noun L. Acute asthma associated with sustained-release verapamil. *Ann Pharmacother* 1997; **31:** 593–5.

Effects on sexual function. In a group of 14 men taking verapamil, 3 reported impotence;[1] in 1 patient normal sexual function returned when verapamil was stopped, but impotence recurred on rechallenge.

1. King BD, *et al.* Impotence during therapy with verapamil. *Arch Intern Med* 1983; **143:** 1248–9.

Effects on the skin and hair. The commonest skin reactions to verapamil have been rash, pruritus, alopecia, and urticaria;[1] there have been a few reports of erythema multiforme, the Stevens-Johnson syndrome, and exfoliative dermatitis.[1] Hypertrichosis, over many parts of the body, has been reported in a male patient within about 1 month of starting verapamil therapy.[2] In a female patient who had been prematurely grey for about 40 years use of verapamil caused portions of the hair to regrow in its original natural black colour.[3]

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149:** 829–32.
2. Sever PS. Hypertrichosis and verapamil. *Lancet* 1991; **338:** 1215–16.
3. Read GM. Verapamil and hair colour change. *Lancet* 1991; **338:** 1520.

Haemorrhage. See Effects on the Blood under Adverse Effects of Nifedipine, p.1350.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p.1352, but see also below.

Verapamil is not removed by dialysis.

Overdosage. The consequences and treatment of overdosage with verapamil are similar to those with other calcium-channel blockers (see Treatment of Adverse Effects under Nifedipine, p.1352), although death and life-threatening complications may be more common with non-dihydropyridines such as verapamil; a number of fatalities have occurred.[1]

Individual reports of overdosage with verapamil have included:

- A patient[2] who took 3.2 g of verapamil developed bradycardia and hypotension, which responded to intravenous calcium gluconate injection. A continuous infusion of calcium gluconate was given for 12 hours to maintain sinus rhythm. The blood-verapamil concentration measured 5 hours after ingestion was 4 micrograms/mL.

- A patient[3] presented with loss of consciousness, severe hypotension, and bradycardia up to 18 hours after taking at least 1.2 g of verapamil. Treatment with glucagon, prenalterol, and atropine was unsuccessful, and there was a minimal response to intravenous calcium gluconate. Dobutamine and isoprenaline were given to maintain the blood pressure and mechanical ventilation was required for 24 hours, during which time metabolic acidosis and hyperglycaemia developed. The patient survived with cerebral anoxic damage.
- A patient[4] who had taken an unknown amount of verapamil developed cyanosis, undetectable blood pressure, and complete heart block. There was some response to sympathomimetics and calcium gluconate, although pacing was necessary to reverse the bradycardia. However, hypotension unresponsive to sympathomimetics developed after an episode of asystole and the patient died 19 hours after admission. The serum-verapamil concentration 12 hours after admission was 3 micrograms/mL.
- Haematemesis occurred in a patient[5] who took 3.2 g of verapamil; gastric ulceration was found on gastroscopy 12 hours after admission.

Overdosage with modified-release preparations of verapamil may result in prolonged toxicity of delayed onset.[6] Conventional-release preparations may also produce prolonged toxicity; elimination half-life was reported to be prolonged to 15 hours and peak plasma concentrations delayed to 6 to 7 hours in a 59-year-old man after ingestion of 2.4 g of verapamil.[7] Rate-limiting absorption at high doses was considered to be the cause.

Although severe toxicity usually relates to acute verapamil overdosage, similar symptoms have also been reported with chronic toxicity. Long-term treatment with verapamil 240 mg daily[8] in a patient with cirrhosis of the liver led to loss of consciousness, cardiogenic shock, cyanosis, hypotension, severe acidosis, hyperkalaemia, hypothermia, and renal failure. The patient recovered after treatment with high doses of dopamine, noradrenaline, sodium bicarbonate, and sodium chloride.

1. Hofer CA, *et al.* Verapamil intoxication: a literature review of overdoses and discussions of therapeutic options. *Am J Med* 1993; **95:** 431–8.
2. Perkins CM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. *BMJ* 1978; **2:** 1127.
3. Crump BJ, *et al.* Lack of response to intravenous calcium in severe verapamil poisoning. *Lancet* 1982; **ii:** 939–40.
4. Orr GM, *et al.* Fatal verapamil overdose. *Lancet* 1982; **ii:** 1218–19.
5. Miller ARO, Ingamells CJ. Gastrointestinal haemorrhage associated with an overdose of verapamil. *BMJ* 1984; **288:** 1346.
6. Barrow PM, *et al.* Overdose of sustained-release verapamil. *Br J Anaesth* 1994; **72:** 361–5.
7. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. *Br J Clin Pharmacol* 1995; **39:** 680–3.
8. Stehle G, *et al.* Cardiogenic shock associated with verapamil in a patient with liver cirrhosis. *Lancet* 1990; **336:** 1079.

Precautions

Verapamil is contra-indicated in hypotension, cardiogenic shock, marked bradycardia, and uncompensated heart failure. It is also contra-indicated in second- or third-degree AV block, and in the sick-sinus syndrome, unless a pacemaker is fitted. There is an increased incidence of adverse cardiac effects in patients with hypertrophic cardiomyopathy. In patients with atrial flutter or fibrillation and an accessory pathway with anterograde conduction, for example Wolff-Parkinson-White syndrome, verapamil may induce severe ventricular tachycardia and it is usually contra-indicated in such patients.

Special care is required in using verapamil as an antiarrhythmic in infants as they may be more susceptible to verapamil-induced arrhythmias.

Doses of verapamil should be reduced in patients with hepatic impairment.

Sudden withdrawal of verapamil might be associated with exacerbation of angina.

Breast feeding. Verapamil concentrations in breast milk similar to those found in plasma have been reported[1] in a woman taking verapamil 80 mg four times daily. The maximum concentration measured in breast milk was 300 nanograms/mL. However, the average concentration in milk in another woman[2] taking 80 mg three times daily was 23% of that in serum. The serum concentration of verapamil in the breast-fed child was 2.1 nanograms/mL during treatment and undetectable 38 hours after the last maternal dose. In another patient[3] taking the same dose, the average steady-state concentrations of verapamil and norverapamil in milk were, respectively, 60% and 16% of the concentration in plasma, with the ratio between milk and plasma varying during a dosage interval. It was estimated that the infant received less than 0.01% of the mother's dose, and no verapamil or norverapamil could be detected in the plasma of the infant. No adverse effects have been seen in breast-feeding infants, and the American Academy of Pediatrics considers[4] that verapamil is therefore usually compatible with breast feeding.

1. Inoue H, *et al.* Level of verapamil in human milk. *Eur J Clin Pharmacol* 1984; **26:** 657–8.
2. Andersen HJ. Excretion of verapamil in human milk. *Eur J Clin Pharmacol* 1983; **25:** 279–80.
3. Anderson P, *et al.* Verapamil and norverapamil in plasma and breast milk during breast feeding. *Eur J Clin Pharmacol* 1987; **31:** 625–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Muscular disorders. Sudden respiratory failure was believed to have been precipitated by intravenous verapamil therapy in a patient with Duchenne's muscular dystrophy.[1]

1. Zalman F, *et al.* Acute respiratory failure following intravenous verapamil in Duchenne's muscular dystrophy. *Am Heart J* 1983; **105:** 510–11.

Porphyria. Verapamil has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Wolff-Parkinson-White Syndrome. Patients with atrial flutter or fibrillation and an accessory pathway, such as those with Wolff-Parkinson-White syndrome, may be at increased risk of developing ventricular tachycardia if AV-blocking drugs such as verapamil are used, since conduction across the anomalous pathway may be increased. Ventricular fibrillation and severe hypotension have been reported[1] after the use of intravenous verapamil 5 to 10 mg in patients with the Wolff-Parkinson-White syndrome.

1. McGovern B, *et al.* Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. *Ann Intern Med* 1986; **104:** 791–4.

Interactions

Verapamil should be used with caution with drugs that have antiarrhythmic or beta-blocking effects; the use of intravenous verapamil with a beta blocker is especially hazardous (see below). Verapamil is extensively metabolised in the liver and interactions may occur with drugs that inhibit or enhance hepatic metabolism. Grapefruit juice may cause increased plasma concentrations of verapamil. Verapamil can itself affect the pharmacokinetics of other drugs, particularly by inhibition of the cytochrome P450 isoenzyme CYP3A4 and by effects on P-glycoprotein. Drugs affected include carbamazepine, ciclosporin, digoxin, midazolam, simvastatin, and theophylline; the plasma concentration of alcohol may also be increased. For details of these interactions, see under the individual drug monographs.

Analgesics. For a possible interaction of verapamil with *aspirin*, see under Antiplatelets, below.

Antiarrhythmics. Verapamil may have pharmacodynamic and pharmacokinetic interactions with other antiarrhythmics. Cardiogenic shock and asystole occurred in 2 patients receiving *flecainide* when verapamil was added to their therapy.[1] Verapamil given intravenously has been reported to cause severe hypotension in patients also receiving oral *quinidine*;[2] both drugs block alpha-adrenoceptors and verapamil may also increase the plasma concentration of quinidine.

1. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; **340:** 546.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. *N Engl J Med* 1985; **312:** 167–70.

Antibacterials. Acute verapamil toxicity manifested by complete heart block has been reported in a patient after the use of *ceftriaxone* and *clindamycin*.[1] Displacement of verapamil from binding sites was postulated as the probable mechanism of action. *Rifampicin* is an enzyme-inducing drug and has been reported[2,3] to reduce plasma-verapamil concentrations. A verapamil dose of 1.92 g was required to control supraventricular tachycardia in a patient also taking rifampicin[3] and when rifampicin was withdrawn the plasma-verapamil concentration 9 days later was almost four times higher. A patient taking propranolol and verapamil developed symptomatic bradycardia a few days after starting treatment with *clarithromycin* and on another occasion after starting treatment with *erythromycin*.[4] Inhibition of verapamil metabolism by the antibacterials was proposed as the mechanism for the interaction. A further case of severe hypotension and bradycardia has also been reported[5] in a patient shortly after beginning therapy with clarithromycin and verapamil, and similar effects were seen[6] in a patient 2 days after starting *telithromycin*. A case of complete heart block has been reported[7] in a patient aged 79 taking verapamil, one week after erythromycin was added to her therapy, probably due to mutual inhibition of hepatic metabolism of both drugs.

1. Kishore K, *et al.* Acute verapamil toxicity in a patient with chronic toxicity: possible interaction with ceftriaxone and clindamycin. *Ann Pharmacother* 1993; **27:** 877–80.
2. Rahn KH, *et al.* Reduction of bioavailability of verapamil by rifampin. *N Engl J Med* 1985; **312:** 920–1.
3. Barbarash RA. Verapamil-rifampin interaction. *Drug Intell Clin Pharm* 1985; **19:** 559–60.
4. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* 1998; **32:** 387–8.
5. Kaeser YA, *et al.* Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health-Syst Pharm* 1998; **55:** 2417–18.
6. Reed M, *et al.* Verapamil toxicity resulting from a probable interaction with telithromycin. *Ann Pharmacother* 2005; **39:** 357–60.
7. Goldschmidt N, *et al.* Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* 2001; **35:** 1396–9.

Antiepileptics. *Phenobarbital* is a hepatic enzyme-inducing drug and has been reported[1] to increase the clearance of oral and intravenous verapamil and to reduce oral bioavailability in healthy subjects. Plasma protein binding of verapamil was also reduced. Dosage adjustment of verapamil may be needed in patients also taking phenobarbital. Marked reduction in verapamil concentrations has also occurred with *phenytoin*.[2]

For a report of neurotoxicity in patients given verapamil with *carbamazepine*, see Calcium-channel Blockers, under Interactions of Carbamazepine, p.475.

1. Rutledge DR, *et al.* Effects of chronic phenobarbital on verapamil disposition in humans. *J Pharmacol Exp Ther* 1988; **246:** 7–13.
2. Woodcock BG, *et al.* A reduction in verapamil concentrations with phenytoin. *N Engl J Med* 1991; **325:** 1179.

Antiplatelets. Calcium-channel blockers can inhibit platelet function (see Effects on the Blood under Adverse Effects of Nifedipine, p.1350). Use of verapamil and *aspirin* in an 85-year-old man was considered to be the cause of ecchymoses and retroperitoneal bleeding that developed about 3 weeks after starting treatment with the combination.[1]

1. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; **28:** 536–7.

Anxiolytics. For the effect of verapamil on plasma-*buspirone* concentrations, see p.966.

Benzodiazepines. For the effects of verapamil on the pharmacokinetics of *midazolam*, see Calcium-channel Blockers, p.990.

Beta blockers. Oral verapamil and beta blockers have been used together in the treatment of angina and hypertension but both drugs have cardiodepressant activity and the combination, if used at all, must be used with extreme caution; bradycardia, heart block, and left ventricular failure have been reported.[1-4] Bradycardia has also been reported[5] in a patient treated with *timolol* eye drops and oral verapamil. Patients with severe ischaemic heart disease or heart failure are particularly at risk.[6] The risks are increased with intravenous verapamil, and it has been suggested[6] that treatment with beta blockers should be stopped at least 24 hours before giving verapamil by this route; the interaction is particularly hazardous when both verapamil and beta blockers are given intravenously, and such combinations are not recommended.

Verapamil may also affect the pharmacokinetics of some beta blockers (see Calcium-channel Blockers, under Interactions of Beta Blockers, p.1229).

1. Eisenberg JNH, Oakley GDG. Probable adverse interaction between oral metoprolol and verapamil. *Postgrad Med J* 1984; **60:** 705–6.
2. Hutchison SJ, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 659–60.
3. Findlay IN, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1074.
4. McGourty JC, Silas JH. β blockers and verapamil: a cautionary tale. *BMJ* 1984; **289:** 1624.
5. Pringle SD, MacEwen CJ. Severe bradycardia due to interaction of timolol eye drops and verapamil. *BMJ* 1987; **294:** 155–6.
6. McInnes GT. Interactions that matter: calcium blockers. *Prescribers' J* 1988; **28:** 60–4.

Calcium salts. Calcium salts antagonise the pharmacological response to verapamil and other calcium-channel blockers and are given intravenously to treat their adverse effects (see Treatment of Adverse Effects under Nifedipine, p.1352). Recurrence of atrial fibrillation has occurred[1] during maintenance verapamil treatment when calcium adipinate and calciferol were given orally.

1. Bar-Or D, Yoel G. Calcium and calciferol antagonise effect of verapamil in atrial fibrillation. *BMJ* 1981; **282:** 1585–6.

Everolimus. For the effect of verapamil on everolimus, see p.1834.

Histamine H_2-antagonists. Studies in healthy subjects using single doses of verapamil after pretreatment with *cimetidine* for up to 8 days have produced conflicting results. The pharmacokinetics of intravenous verapamil were unaltered by cimetidine in some studies,[1,2] but a 21% reduction in clearance and a 50% increase in the elimination half-life were also reported.[3] The pharmacokinetics of oral verapamil were unchanged in one study[2] but two others[1,4] reported a significant increase in bioavailability. Although one of these studies[1] found the interaction had no clinical effects, the other[4] reported an increased clinical effect in 5 of 6 subjects. The interaction with cimetidine appears to be stereoselective since the oral bioavailability of the *S*-enantiomer increased by 35% and that of the *R*-enantiomer by 15%.[4] The clinical significance of this interaction in patients and during long-term verapamil treatment is unknown, but cimetidine should be used with caution in patients receiving verapamil.

1. Smith MS, *et al.* Influence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther* 1984; **36:** 551–4.
2. Abernethy DR, *et al.* Lack of interaction between verapamil and cimetidine. *Clin Pharmacol Ther* 1985; **38:** 342–9.
3. Loi C-M, *et al.* Effect of cimetidine on verapamil disposition. *Clin Pharmacol Ther* 1985; **37:** 654–7.
4. Mikus G, *et al.* Interaction of verapamil and cimetidine: stereochemical aspects of drug metabolism, drug disposition and drug action. *J Pharmacol Exp Ther* 1990; **253:** 1042–8.

Lithium. Verapamil may have effects on neuromuscular function (see under Adverse Effects, above) and neurotoxicity has occurred[1-4] in patients receiving lithium after the addition of verapamil to their therapy, despite serum-lithium concentrations (where reported[1,2,4]) remaining in the therapeutic range. Verapamil has also been reported to decrease serum-lithium concentrations.[5]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Price WA, Shalley JE. Lithium-verapamil toxicity in the elderly. *J Am Geriatr Soc* 1987; **35:** 177–8.
3. Helmuth D, *et al.* Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* 1989; **9:** 454–5.
4. Wright BA, Jarrett DB. Lithium and calcium channel blockers: possible neurotoxicity. *Biol Psychiatry* 1991; **30:** 635–6.
5. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.

St John's wort. A study in healthy subjects[1] found that repeated doses of St John's wort significantly reduced the plasma concentrations of both the *R*- and *S*-isomers of verapamil, probably due to induction of the cytochrome P450 isoenzyme CYP3A4.

1. Tannergren C, *et al.* St John's wort decreases the bioavailability of *R*- and *S*-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther* 2004; **75:** 298–309.

Theophylline. For the effects of verapamil on the pharmacokinetics of theophylline, see Calcium-channel Blockers, p.1144.

Pharmacokinetics

Verapamil is about 90% absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver and the bioavailability is only about 20%.

Verapamil exhibits bi- or tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hours after a single oral dose or after intravenous dosage. With repeated oral doses half-life increases to 4.5 to 12 hours. Verapamil acts within 5 minutes when given intravenously and within 1 to 2 hours when given orally; peak plasma concentrations occur 1 to 2 hours after an oral dose. There is considerable interindividual variation in plasma concentrations.

Verapamil is about 90% bound to plasma proteins. It is extensively metabolised in the liver to at least 12 metabolites of which norverapamil has been shown to have some activity. About 70% of a dose is excreted by the kidneys in the form of its metabolites but about 16% is excreted in the bile into the faeces. Less than 4% is excreted unchanged. Verapamil crosses the placenta and is distributed into breast milk.

◊ Reviews.

1. Hamann SR, *et al.* Clinical pharmacokinetics of verapamil. *Clin Pharmacokinet* 1984; **9:** 26–41.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; **22:** 416–33.
3. Kang D, *et al.* Population analyses of sustained-release verapamil in patients: effects of sex, race, and smoking. *Clin Pharmacol Ther* 2003; **73:** 31–40.

The elderly. Studies[1-3] comparing the pharmacokinetics and pharmacodynamics of verapamil in elderly (61 years and older) and young subjects have found that clearance and elimination half-life are increased in older subjects, and increased plasma concentrations have also been reported. However, there may also be changes in the response to verapamil in older subjects that are not directly related to the plasma concentration.

1. Abernethy DR, *et al.* Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: altered electrocardiographic and hypotensive responses. *Ann Intern Med* 1986; **105:** 329–36.
2. Gupta SK, *et al.* Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *Br J Clin Pharmacol* 1995; **40:** 325–31.
3. Abernethy DR, *et al.* Verapamil metabolite exposure in older and younger men during steady-state oral verapamil administration. *Drug Metab Dispos* 2000; **28:** 760–5.

Metabolism. Verapamil is extensively metabolised in the liver to a number of metabolites, and several cytochrome P450 isoenzymes appear to be involved. An *in-vitro* study[1] has suggested that the main isoenzymes responsible for the metabolism of both enantiomers of verapamil are CYP3A4, CYP3A5, and CYP2C8, and that the same isoenzymes are involved in the further metabolism of norverapamil. However, since CYP2C8 generally makes up only a small part of the cytochrome P450 content of the liver, it was considered that this would have little significance for potential drug interactions. In contrast to some previous reports, the isoenzymes CYP1A2 and CYP2C9 were not found to be involved to any great extent.

1. Tracy TS, *et al.* Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. *Br J Clin Pharmacol* 1999; **47:** 545–52.

Stereospecificity. Verapamil is used as a racemic mixture. It has been shown[1] that *S*-verapamil is 3.3 times more potent than the racemic mixture and 11 times more potent than *R*-verapamil. Thus it was concluded that the cardiac effects of verapamil are related not to the total plasma-verapamil concentration but to the concentration of the *S*-isomer, and conventional plasma concentration monitoring will be of little value in establishing therapeutic plasma concentrations during multiple oral dosing.

A series of studies have been carried out to determine whether differences in the pharmacokinetics of the *R*- and *S*-isomers of verapamil could account for observed differences in the plasma concentration-response curve after oral and intravenous doses. When given intravenously, there were pronounced differences in the pharmacokinetics and protein binding of the 2 isomers;[2] the volume of distribution and total systemic clearance of *S*-verapamil were much higher than those of the *R*-isomer although the terminal half-life was similar. After oral doses of a mixture of *R*- and *S*-verapamil, plasma concentrations of the *R*-isomer were found to be substantially higher than those of the more potent *S*-isomer,[3] suggesting stereospecific first-pass hepatic metabolism and accounting for the apparent lower potency of verapamil when given orally. The proportion of *S*-isomer also depends on the oral formulation; modified-release formulations produce lower proportions of *S*-isomer in plasma than conventional formulations.[4]

1. Echizen H, *et al.* Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. *Clin Pharmacol Ther* 1985; **38:** 71–6.
2. Eichelbaum M, *et al.* Pharmacokinetics of (+)-, (−)- and (±)-verapamil after intravenous administration. *Br J Clin Pharmacol* 1984; **17:** 453–8.
3. Vogelgesang B, *et al.* Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of - and - verapamil examined with a stable isotope technique. *Br J Clin Pharmacol* 1984; **18:** 733–40.
4. Karim A, Piergies A. Verapamil stereoisomerism: enantiomeric ratios in plasma dependent on peak concentrations, oral input rate, or both. *Clin Pharmacol Ther* 1995; **58:** 174–84.

Uses and Administration

Verapamil is a phenylalkylamine calcium-channel blocker (p.1154) and a class IV antiarrhythmic (p.1153). It slows conduction through the AV node, and thus slows the increased ventricular response rate that occurs in atrial fibrillation and flutter. Its anti-anginal effect is mainly due to coronary and peripheral vasodilatation, although it also inhibits coronary artery spasm; the decrease in peripheral vascular resistance reduces the work of the heart, which has a sparing effect on myocardial intracellular oxygen consumption. The decrease in peripheral vascular resistance may also explain its antihypertensive effect. Verapamil is used in the control of supraventricular arrhythmias and in the management of angina pectoris and hypertension. It may also be used in the management of myocardial infarction.

Verapamil may be given intravenously or orally, as the hydrochloride; doses are expressed in terms of verapamil hydrochloride.

In the acute management of supraventricular **arrhythmias** it is given intravenously, preferably under continuous ECG and blood pressure monitoring. The initial dose is 5 to 10 mg by slow intravenous injection over 2 to 3 minutes. If necessary, licensed product information in the UK allows a second dose of 5 mg to be given 5 to 10 minutes after the first; in the USA, a second dose of 10 mg may be given after 30 minutes.

Oral doses for the treatment of supraventricular arrhythmias are 120 to 480 mg daily in 3 or 4 divided doses, according to the severity of the condition and the patient's response.

In the management of **angina pectoris,** the usual oral dose is 120 mg three times daily; some patients with angina of effort may respond to 80 mg three times daily, but this lower dose is not likely to be effective in angina at rest or Prinzmetal's variant angina. Modified-release preparations may be given in doses of up to 480 mg daily.

In **hypertension** the usual initial oral dose is 240 mg daily, in 2 or 3 divided doses, adjusted according to response; doses of up to 480 mg daily have been used. Modified-release preparations may be given in similar daily doses.

In the secondary prevention of **myocardial infarction**, verapamil hydrochloride is given as a modified-release oral preparation, started at least 1 week after acute infarction (in patients without heart failure), in a dose of 360 mg daily in divided doses.

Doses of verapamil should be reduced in patients with hepatic impairment (see below).

For doses of verapamil in children with supraventricular arrhythmias or hypertension, see below.

◊ General reviews.

1. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. *Drugs* 1996; **51:** 792–819.
2. Prisant LM. Verapamil revisited: a transition in novel drug delivery systems and outcomes. *Heart Dis* 2001; **3:** 55–62.

Administration in children. Verapamil may be used for the treatment of supraventricular arrhythmias and hypertension in children, although great care is needed, especially in infants (see Precautions, above).

Intravenous doses of verapamil hydrochloride for supraventricular arrhythmias are as follows:

- children up to 1 year of age, 100 to 200 micrograms/kg
- 1 to 15 years, 100 to 300 micrograms/kg (to a maximum dose of 5 mg)

The dose should be given over at least 2 minutes and may be repeated after 30 minutes if necessary; doses at the lower end of the range may be adequate and the injection should be stopped when a response has been obtained.

Oral doses for supraventricular arrhythmias or for hypertension are:

- children up to 2 years of age, 20 mg two or three times daily
- 2 years and over, 40 to 120 mg two or three times daily according to age and response

Administration in the elderly. For a discussion of the effects of increasing age on verapamil, see under Pharmacokinetics, above.

Administration in hepatic impairment. Verapamil is extensively metabolised in the liver and should be used with caution in hepatic impairment; US licensed product information recommends that oral doses for patients with severe hepatic impairment should be reduced to about one-third of the usual dose (see above).

In a study[1] of patients with liver cirrhosis steady-state plasma concentrations of verapamil were double those seen in patients with normal liver function after intravenous doses and 5 times the normal concentration when given orally. The elimination half-life was prolonged about fourfold after oral or intravenous doses, suggesting that steady-state plasma concentration will not be reached in patients with liver cirrhosis until about 56 hours after therapy has started.

1. Somogyi A, *et al.* Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J Clin Pharmacol* 1981; **12:** 51–60.

Administration in renal impairment. The pharmacokinetics and pharmacodynamic effects of verapamil are not significantly altered by renal impairment[1] and dosage adjustment is not considered to be necessary. The elimination of verapamil is not altered by haemodialysis,[1,2] haemofiltration,[2] or peritoneal dialysis[2] and no dosage supplement is required in patients undergoing these procedures.

1. Mooy J, *et al.* Pharmacokinetics of verapamil in patients with renal failure. *Eur J Clin Pharmacol* 1985; **28:** 405–10.
2. Beyerlein C, *et al.* Verapamil in antihypertensive treatment of patients on renal replacement therapy—clinical implications and pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39** (suppl 1): S35–S37.

Amaurosis fugax. For a report of the use of verapamil in patients with amaurosis fugax, see under Uses and Administration of Nifedipine, p.1354.

Bipolar disorder. Although lithium and valproate are the mainstays of therapy in bipolar disorder (p.372) many other drugs have been tried, including verapamil.[1] Beneficial responses to verapamil at doses up to 480 mg daily have been reported,[2-4] although a review[5] concluded that there is limited support for its use. Verapamil has also been used with lithium, but there may be an increased risk of neurotoxicity (see under Interactions, above).

1. Höschl C. Do calcium antagonists have a place in the treatment of mood disorders? *Drugs* 1991; **42:** 721–29.
2. Dubovsky SL, *et al.* Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res* 1986; **18:** 309–20.
3. Giannini AJ, *et al.* Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol* 1987; **27:** 980–2.

4. Wisner KL, *et al.* Verapamil treatment for women with bipolar disorder. *Biol Psychiatry* 2002; **51:** 745–52.
5. Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. *Bipolar Disord* 2000; **2:** 108–19.

Box jellyfish sting. Stings by the box jellyfish (*Chironex fleckeri*) (p.2220) can be fatal because of the effects of the venom on the cardiovascular and respiratory systems and on the kidneys. Studies in *rodents* have reported a beneficial effect of intravenous verapamil in the treatment of box jellyfish envenomation, and use in patients with serious box-jellyfish stings has been recommended.[1] However, it has also been suggested[2] that the lack of evidence for benefit and the potential for adverse effects means that use of verapamil should be limited to extreme cases only.

1. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; **153:** 363.
2. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; **178:** 34–7.

Cardiac arrhythmias. Verapamil has an established role in the management of supraventricular cardiac arrhythmias (p.1160). It is used for rate control in atrial fibrillation and flutter, and may also be used in paroxysmal supraventricular tachycardia. It has been successfully used with digoxin for transplacental therapy in fetal atrial flutter or supraventricular tachycardia,[1,2] although caution is necessary if it is used in infants since they may be particularly susceptible to its adverse effects (see Precautions, above).

1. Maxwell DJ, *et al.* Obstetric importance, diagnosis, and management of fetal tachycardias. *BMJ* 1988; **297:** 107–10.
2. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; **79:** 576–81.

Cardiomyopathies. Verapamil has an established role as a negative inotrope in the management of patients with *hypertrophic cardiomyopathy*,[1,2] although it is usually reserved for patients in whom beta blockers either fail to control symptoms or are not tolerated. It may improve symptoms and exercise tolerance; although a crossover study[3] failed to show an improvement in exercise capacity with verapamil or the beta blocker nadolol, most patients preferred drug treatment to placebo and there was an apparent improvement in quality of life with verapamil. Verapamil may also be useful for rate control in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. However, there is no evidence that it reduces the incidence of sudden cardiac death, and serious adverse effects have been reported,[4] especially in patients with severe outflow obstruction. Patients with hypertrophic cardiomyopathy appear to be particularly susceptible to conduction disturbances associated with verapamil, and this may worsen hypotension and outflow obstruction.

Dilated cardiomyopathy is treated similarly to heart failure and calcium-channel blockers are not usually used, although some benefit has been reported with diltiazem (see p.1267).

For a discussion of the management of cardiomyopathies in general, see p.1163.

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; **287:** 1308–20.
2. Maron BJ, *et al.* American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; **42:** 1687–713. Also published in *Eur Heart J* 2003; **24:** 1965–91. Also available at: http://www.acc.org/qualityandscience/clinical/consensus/cardiomyopathy/index.pdf (accessed 14/08/08) and at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HCM-FT.pdf (accessed 14/08/08)
3. Gilligan DM, *et al.* A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993; **21:** 1672–9.
4. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circulation* 1981; **64:** 437–41.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p.1355), although studies with verapamil have suggested that it is less effective than the ACE inhibitor trandolapril in patients with non-diabetic renal disease,[1] and that it does not prevent the development of renal disease in type 2 diabetics.[2] There is some evidence that verapamil may reduce the nephrotoxicity associated with certain drugs, including ciclosporin (see Transplantation, below), and the aminoglycoside gentamicin.[3]

1. Hemmelder MH, *et al.* Antiproteinuric efficacy of verapamil in comparison to trandolapril in non-diabetic renal disease. *Nephrol Dial Transplant* 1999; **14:** 98–104.
2. Ruggenenti P, *et al.* for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; **351:** 1941–51.
3. Kazierad DJ, *et al.* The effect of verapamil on the nephrotoxic potential of gentamicin as measured by urinary enzyme excretion in healthy volunteers. *J Clin Pharmacol* 1995; **35:** 196–201.

Malignant neoplasms. Verapamil has been shown to reverse multidrug resistance to antineoplastics in cultured cells and in *animal* studies,[1] but studies in which verapamil was added to therapy for small cell lung cancer[2] or multiple myeloma[3] failed to show any benefit. See p.643 for a discussion of resistance to antineoplastics.

1. Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; **42:** 155–99.
2. Milroy R, *et al.* A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; **68:** 813–18.
3. Dalton WS, *et al.* A phase III randomized study of oral verapamil as a chemosensitizer to reverse drug resistance in patients with refractory myeloma: a Southwest Oncology Group Study. *Cancer* 1995; **75:** 815–20.

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including verapamil, in the management of migraine and cluster headache, see under Nifedipine, p.1355.

Movement disorders. Verapamil has been associated with the development of various movement disorders (see under Adverse Effects, above) but there have also been case reports[1,2] of its successful use in refractory movement disorders, including severe tardive dyskinesia. However, a systematic review[3] concluded that evidence for the use of verapamil or other calcium-channel blockers in tardive dyskinesia is limited and they are not generally recommended.

The usual management of tardive dyskinesia is discussed under the Adverse Effects of Chlorpromazine, p.971.

1. Abad V, Ovsiew F. Treatment of persistent myoclonic tardive dystonia with verapamil. *Br J Psychiatry* 1993; **162:** 554–6.
2. Ovsiew F, *et al.* Verapamil for severe hyperkinetic movement disorders. *Mov Disord* 1998; **13:** 341–4.
3. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/03/07).

Myocardial infarction. Calcium-channel blockers are not routinely used in either the acute or long-term treatment of myocardial infarction (p.1175), although some benefit has been reported with non-dihydropyridines. Diltiazem, started within 24 to 72 hours of the onset of infarction and continued for up to 14 days, has been reported to protect against re-infarction and refractory angina in patients recovering from acute non-Q-wave infarction.[1] A pilot study[2] of intravenous diltiazem as an adjunct to thrombolysis in acute myocardial infarction also suggested a reduction in recurrent ischaemia; diltiazem was given intravenously for 48 hours, beginning at the same time as the thrombolytic, then continued orally for 4 weeks. However, a study[3] with verapamil, started on admission to hospital, found no effect on mortality at 6 months, and there was a suggestion that very early use (within 6 hours of symptom onset) was detrimental. A later study[4] reported that early use of verapamil in patients receiving thrombolysis improved outcome at 90 days. Benefit has also been shown[5] with use of intracoronary verapamil to terminate post-reperfusion arrhythmias. For use of verapamil in patients receiving percutaneous coronary intervention see Reperfusion and Revascularisation Procedures, below.

Although they are not standard therapy, diltiazem and verapamil may be used for long-term management in selected patients without heart failure. In a study by the Multicenter Diltiazem Postinfarction Trial (MDPIT) research group,[6] diltiazem (target dose 240 mg daily) reduced 1-year mortality and re-infarction rates in patients without left ventricular dysfunction, but increased such adverse events in those with left ventricular dysfunction. Re-analysis of the study provided further evidence that diltiazem should be avoided in postinfarction patients with left ventricular dysfunction.[7] Another study[8] in patients with acute myocardial infarction treated with thrombolysis found no reduction in mortality with diltiazem started 36 to 96 hours after infarction and continued for up to 6 months, although the incidence of non-fatal cardiac events was reduced. Patients with heart failure were excluded from the trial. In the DAVIT II study[9] late intervention with verapamil (started in the second week after admission) reduced overall mortality, cardiac events, and re-infarction although another study[10] found only a benefit in re-infarction rate and not in overall mortality.

1. Gibson RS, *et al.* Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986; **315:** 423–9.
2. Théroux P, *et al.* Intravenous diltiazem in acute myocardial infarction: diltiazem as adjunctive therapy to activase (DATA) trial. *J Am Coll Cardiol* 1998; **32:** 620–8.
3. The Danish Study Group on Verapamil in Myocardial Infarction. The Danish studies on verapamil in acute myocardial infarction. *Br J Clin Pharmacol* 1986; **21:** 197S–204S.
4. Marangelli V, *et al.* Early administration of verapamil after thrombolysis in acute anterior myocardial infarction: effect on left ventricular remodeling and clinical outcome. *Ital Heart J* 2000; **1:** 336–43.
5. Kato M, *et al.* Intracoronary verapamil rapidly terminates reperfusion tachyarrhythmias in acute myocardial infarction. *Chest* 2004; **126:** 702–8.
6. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319:** 385–92.
7. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. *Circulation* 1991; **83:** 52–60.
8. Boden WE, *et al.* Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. *Lancet* 2000; **355:** 1751–6.
9. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II—DAVIT II). *Am J Cardiol* 1990; **66:** 779–85.
10. Rengo F, *et al.* A controlled trial of verapamil in patients after acute myocardial infarction: results of the calcium antagonist reinfarction Italian study (CRIS). *Am J Cardiol* 1996; **77:** 365–9.

Peyronie's disease. Verapamil has been used by intraplaque injection for the treatment of Peyronie's disease.[1,2] Pain, curvature, and erectile dysfunction were all improved. A systematic review[2] of 19 studies involving plaque injection therapy for Peyronie's disease, of which 4 used verapamil, noted that although the results of these suggested that injection was safe and effective in mild to moderate Peyronie's disease, the quality of studies was generally poor and its efficacy needed to be verified. Verapamil has also been given by iontophoresis, but again benefits remain unclear. A study[3] comparing verapamil and dexamethasone with lidocaine reported considerable improvement in plaque volume, penile curvature, and pain in the group given verapamil and dexamethasone, while patients given lidocaine had a transient improvement in pain but no change in plaque volume or curvature. However, a study[4] comparing verapamil with sodium chloride as placebo reported some improvement with both treatments, with no difference between the groups.

1. Levine LA, *et al.* Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol (Baltimore)* 2002; **168:** 621–5.
2. Russell S, *et al.* Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol* 2007; **51:** 640–7.
3. Di Stasi SM, *et al.* A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol (Baltimore)* 2004; **171:** 1605–8.
4. Greenfield JM, *et al.* Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol (Baltimore)* 2007; **177:** 972–5.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention is widely used in the management of patients with acute myocardial infarction and angina pectoris, and adjunctive drug treatment has an important role in reducing complications and improving outcome (see p.1181). Intracoronary verapamil may be used to treat vasospasm[1] and has also been used to treat[2,3] and prevent[4,5] the 'no-reflow' phenomenon. However, transient heart block occurred in some patients given verapamil prophylactically,[5] and this may limit its use.

There is also some evidence that verapamil may reduce the incidence of restenosis after coronary[6] or peripheral[7] percutaneous interventions.

1. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005; **26:** 804–47. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf (accessed 14/08/08)
2. Piana RN, *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; **89:** 2514–18.
3. Demir I, *et al.* Treatment of no-reflow phenomenon with verapamil after primary stent deployment during myocardial infarction. *Jpn Heart J* 2002; **43:** 573–80.
4. Hang C-L, *et al.* Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest* 2005; **128:** 2593–8.
5. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; **92:** 1278–84.
6. Bestehorn H-P, *et al.* Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: the randomized, double-blind, placebo-controlled, multicenter Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) Trial. *J Am Coll Cardiol* 2004; **43:** 2160–5.
7. Schweizer J, *et al.* Effect of high dose verapamil on restenosis after peripheral angioplasty. *J Am Coll Cardiol* 1998; **31:** 1299–1305.

Transplantation. Ciclosporin is widely used in transplantation to prevent rejection but its use is limited by its nephrotoxicity. Dihydropyridine calcium-channel blockers (see under Uses of Nifedipine, p.1356) and diltiazem (p.1267) have been reported to reduce ciclosporin-associated nephrotoxicity, and there is some evidence that verapamil may have a similar effect. Studies in renal[1,2] and heart or lung[3] transplant recipients suggested that verapamil can improve outcomes in patients receiving ciclosporin. Most studies have found that verapamil prevents ciclosporin-induced deterioration in renal function, despite increasing plasma-ciclosporin concentrations,[1,2] and there is also evidence[2] that graft survival may be improved. The beneficial effect of verapamil may be related to its ability to protect cells from ischaemia, selective vasodilatation of the afferent renal arterioles, or inherent immunosuppressive properties; its effect on plasma-ciclosporin concentrations may also be involved, either directly[1,2] or by allowing reduction of the ciclosporin dose.[3] However, one study[4] found that use of verapamil with ciclosporin resulted in higher serum-creatinine concentrations in patients given verapamil, with no reduction in the incidence of rejection, and careful monitoring is necessary if the drugs are used together. A higher incidence of severe infections has also been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; **90** (suppl 5A): 37S–41S.
2. Dawidson I, *et al.* Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2:** 983–90.
3. Chan C, *et al.* A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; **63:** 1435–40.
4. Pirsch JD, *et al.* A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; **21:** 189–95.
5. Nanni G, *et al.* Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; **32:** 551–3.

Preparations

BP 2008: Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;
USP 31: Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Isoptino; Veral; Verapal†; ***Austral.:*** Anpec; Cordilox; Isoptin; Veracaps; Verahexal; ***Austria:*** Isoptin; Verapabene; Verastad; ***Belg.:*** Isoptine; Lodixal; ***Braz.:*** Cordilat; Coronaril; Cronovera†; Dilacard†; Dilacor; Dilacoron; Multicor; Neo Verpamil; Vascord†; Vasoton; Veramil; Veraval; ***Canad.:*** Apo-Verap; Chronovera; Isoptin; Novo-Veramil; Nu-Verap; ***Chile:*** Cardiolen; Isoptina; Presocor; ***Cz.:*** Apo-Verap†; Isoptin; Lekoptin; Verahexal; Verogalid; ***Denm.:*** Geangin; Hexasoptin; Isoptin; Veraloc; ***Fin.:*** Isoptin; Vermin; Verpamil; ***Fr.:*** Isoptine; ***Ger.:*** Azupamil†; durasoptin†; Falicard; Isoptin; Jenapamil†; Vera; Vera-Lich; Verabeta; Veragamma; Verahexal; Veramex; Veranorm; Verasal; Veroptinstada; ***Gr.:*** Brovicarpine†; Elanver†; Isoptin; ***Hong Kong:*** Akilen†; Isoptin; ***Hung.:*** Chinopamil; Isoptin; Verogalid†; ***India:*** Calaptin; Veramil; ***Indon.:*** Cardiover; Isoptin; ***Irl.:*** Isoptin; Veramil; Verap; Verisop; ***Israel:*** Apoacor; Ikacor; Ikapress; Veracor; Verapress; ***Ital.:*** Cardinorm; Isoptin; Kata†; Quasar†; Veraptin; ***Malaysia:*** Akilen; Anpec†; Cintsu†; Isoptin; Verpamil; Viratin†; ***Mex.:*** Cronovera; Dilacoran; Euritmin†; Europave; Serriten; Vepiltax; Veraken; Verdilac; ***Neth.:*** Chronovera†; Geangin; Isoptin; ***Norw.:*** Isoptin; Verakard; ***NZ:*** Civicor†; Isoptin; Verpamil; ***Philipp.:*** Isoptin; Verelan; ***Pol.:*** Isoptin; Lekoptin; Novo-Veramil; Staveran; ***Port.:*** Fibrocard; Isoptin; ***Rus.:*** Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин); Verogalid (Верогалид); ***S.Afr.:*** Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; ***Singapore:*** Isoptin; Verpamil; ***Spain:*** Manidon; ***Swed.:*** Isoptin; ***Switz.:*** Corpamil†; Flamon; Isoptin; Verapam; ***Thai.:*** Caveril; Civicor†; Isopamil†; Isoptin; Verapin; Vermine; ***Turk.:*** Fibrocard; Isoptin; Ormil; Veroptin; ***UK:*** Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; ***USA:*** Calan; Covera; Isoptin; Verelan; ***Venez.:*** Cronovera; Manidon; Veracor.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Captocomp; Confit; Tarka; Veracapt; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Cordichin; Isoptin plus; Stenoptin†; Tarka; Udramil†; Veratide; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

Vernakalant Hydrochloride *(USAN, rINNM)*

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum. (3*R*)-1-{(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl}pyrrolidin-3-ol hydrochloride.

Вернакаланта Гидрохлорид

$C_{20}H_{31}NO_4,HCl = 385.9.$

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).

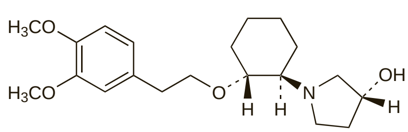

(vernakalant)

Profile

Vernakalant is an antiarrhythmic under investigation as the hydrochloride for the treatment of atrial arrhythmias.

◊ References.

1. Roy D, *et al.* A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; **44:** 2355–61.
2. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Invest Drugs* 2007; **16:** 519–32.
3. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; **42:** 533–42.

Vesnarinone *(USAN, rINN)*

OPC-8212; Vesnarinona; Vesnarinonum. 1-(1,2,3,4-Tetrahydro-2-oxo-6-quinolyl)-4-veratroylpiperazine.

Веснаринон

$C_{22}H_{25}N_3O_4 = 395.5.$

CAS — 81840-15-5.

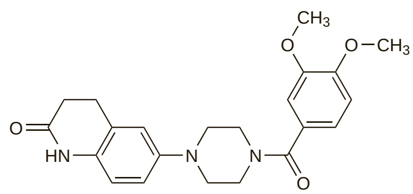

Profile

Vesnarinone is a phosphodiesterase inhibitor with positive inotropic activity that has been tried orally in the management of heart failure.

Adverse effects. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate. In a multicentre study of vesnarinone,[1] doses of 120 mg daily resulted in increased mortality whereas 60 mg daily for 6 months was associated with lower morbidity and mortality. Reversible neutropenia occurred in 2.5% of the patients given 60 mg daily. However, in a subsequent larger study,[2] increased mortality was also reported with doses of 30 and 60 mg daily.

1. Feldman AM, *et al.* Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993; **329:** 149–55.
2. Cohn JN, *et al.* A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998; **339:** 1810–16.

Warfarin Sodium *(BANM, rINNM)*

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin sodná sůl; Warfarina sódica; Warfarine sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum. The sodium salt of 4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin ; Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate.

Натрий Варфарин

$C_{19}H_{15}NaO_4 = 330.3.$

CAS — 81-81-2 (warfarin); 2610-86-8 (warfarin potassium); 129-06-6 (warfarin sodium).

ATC — B01AA03.

ATC Vet — QB01AA03.

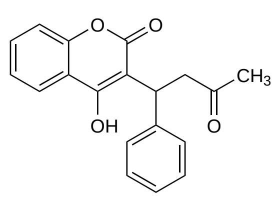

(warfarin)

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Chin., Int., and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).

Jpn includes Warfarin Potassium.

Ph. Eur. 6.2 (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

USP 31 (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] could demonstrate no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part i: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; **31:** 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Warfarin Sodium Clathrate *(BANM)*

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum natricum clathratum. The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.

ATC — B01AA03.

ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p.vii).

Chin., Int., and *US* permit either warfarin sodium or warfarin sodium clathrate.

Ph. Eur. 6.2 (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

Warfarin sodium clathrate contains about 92% of warfarin sodium.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied; one estimate is that if a coumarin anticoagulant is taken during pregnancy, one-sixth of pregnancies will result in an abnormal liveborn infant, and one-sixth will result in abortion or still-birth.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical trials[1,2] and in population-based studies.[1,3-7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to duration of anticoagulation therapy, risk may be highest early in the course.[2]

Withdrawal of warfarin therapy may lead to rebound hypercoagulability and it has been suggested[8] that warfarin should be withdrawn gradually, although there is no clinical evidence to support this.

1. Reynolds MW, *et al.* Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest* 2004; **126:** 1938–45.
2. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
3. Gitter MJ, *et al.* Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc* 1995; **70:** 725–33.
4. Fihn SD, *et al.* The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996; **124:** 970–9.
5. Palareti G, *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; **348:** 423–8.
6. Palareti G, *et al.* Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. *Arch Intern Med* 2000; **160:** 470–8.
7. Fang MC, *et al.* Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; **141:** 745–52.
8. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 1996; **30:** 300–13.

Effects on the bones. Vitamin K is involved in bone metabolism and vitamin K deficiency is associated with an increased risk of osteoporotic fractures. It has been suggested, therefore, that patients on long-term treatment with those oral anticoagulants that are vitamin K antagonists may be at increased risk of osteoporosis and fractures. However, two large observational studies in older women have produced conflicting results. A prospective study[1] of both users and nonusers of warfarin found that warfarin was not associated with decrease in bone density or increase in fracture rates. A retrospective study[2] reported an association between long-term anticoagulant use and increased risk of vertebral and rib fractures, compared with the general population. Overall, however, the risk of any fracture was not significantly increased.

1. Jamal SA, *et al.* Warfarin use and risk for osteoporosis in elderly women. *Ann Intern Med* 1998; **128:** 829–32.
2. Caraballo PJ, *et al.* Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med* 1999; **159:** 1750–6.

Effects on the fetus. Fetal complications of coumarin anticoagulants during pregnancy have been reviewed.[1-3]

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; **68:** 122–40.
2. Chan WS, *et al.* Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; **160:** 191–6.
3. Bates SM, *et al.* Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 844S–886S.

Effects on the liver. There have been a few isolated reports of cholestatic liver damage in patients taking warfarin sodium,[1-3] which resolved on withdrawal.

1. Rehnqvist N. Intrahepatic jaundice due to warfarin therapy. *Acta Med Scand* 1978; **204:** 335–6.
2. Jones DB, *et al.* Jaundice following warfarin therapy. *Postgrad Med J* 1980; **56:** 671.
3. Adler E, *et al.* Cholestatic hepatic injury related to warfarin exposure. *Arch Intern Med* 1986; **146:** 1837–9.

Effects on sexual function. There have been reports[1-3] of priapism in patients taking oral anticoagulants such as warfarin.

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
2. Daryanani S, Wilde JT. Priapism in a patient with protein C deficiency. *Clin Lab Haematol* 1997; **19:** 213–14.
3. Zimbelman J, *et al.* Unusual complications of warfarin therapy: skin necrosis and priapism. *J Pediatr* 2000; **137:** 266–8.

Effects on the skin and hair. Skin and soft-tissue necrosis is a rare but well-established adverse effect of coumarin anticoagulants.[1-4] It is characterised by a localised, painful skin lesion, initially erythematous or haemorrhagic in appearance, that becomes bullous and eventually culminates in gangrenous necrosis. Fatalities have occurred. Areas of increased subcutaneous fat such as breast, thigh, and buttocks have most often been involved. The aetiology appears to be thrombotic but the exact pathophysiology is not known. Patients with protein C deficiency appear to be at highest risk. Treatment with coumarin anticoagulants should be stopped if skin lesions appear and vitamin K should be given to reverse their effect. Heparin should be given to provide anticoagulation. Fresh frozen plasma or protein C concentrates may also have a role in reversing the condition. Surgical intervention is usually required if necrosis does develop.

Other skin reactions have also been reported with coumarins. Vasculitis affecting both legs developed in a 74-year-old woman a few weeks after starting treatment with acenocoumarol for deep-vein thrombosis and pulmonary embolism.[5] Acenocoumarol treatment was stopped and the skin lesions steadily improved over 15 days. However, the skin lesions reappeared a few hours after re-exposure to a single dose of acenocoumarol. The patient had also been taking amiodarone which may have contributed to the reaction. Henoch-Schönlein purpura was reported[6] in a 76-year-old woman 2 months after she started treatment with acenocoumarol; it resolved rapidly after the drug was withdrawn.

Increased shedding of telogen hair has been stated to occur in patients given coumarin anticoagulants.[7]

1. Cole MS, *et al.* Coumarin necrosis—a review of the literature. *Surgery* 1988; **103:** 271–7.
2. Comp PC. Coumarin-induced skin necrosis: incidence, mechanisms, management and avoidance. *Drug Safety* 1993; **8:** 128–35.
3. Chan YC, *et al.* Warfarin induced skin necrosis. *Br J Surg* 2000; **87:** 266–72.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Warfarin-induced skin necrosis. *Aust Adverse Drug React Bull* 2005; **24:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0512.pdf (accessed 10/03/08)
5. Susano R, *et al.* Hypersensitivity vasculitis related to nicoumalone. *BMJ* 1993; **306:** 973.
6. Borrás-Blasco J, *et al.* Acenocoumarol-induced Henoch-Schönlein purpura. *Ann Pharmacother* 2004; **38:** 261–4.
7. Smith AG. Drug-induced disorders of hair and nails. *Adverse Drug React Bull* 1995 (173); 655–8.

Treatment of Adverse Effects

The methods used to manage bleeding and/or excessive anticoagulation during warfarin therapy, or after warfarin overdosage, depend upon the degree of bleeding, the value of the international normalised ratio (INR), and the degree of thromboembolic risk.

For patients **over-anticoagulated** on warfarin, the *British Society for Haematology* recommends the following:

- in cases where the INR is 0.5 above the target value but less than 6.0, warfarin should be reduced in dose or withdrawn until the INR falls to below 5.0
- if the INR is greater than 6.0 but less than 8.0 and there is no bleeding or only minor bleeding, warfarin should be temporarily withheld until the INR falls to below 5.0
- for an INR greater than 8.0 use of phytomenadione (vitamin K_1) should also be considered if there are other risk factors for bleeding; typical doses of phytomenadione are 0.5 mg intravenously or up to 2.5 mg orally using the intravenous preparation. (The *BNF* allows 5 mg orally for more complete reversal of anticoagulation.)
- if there is any major bleeding warfarin should be stopped and phytomenadione given in a dose of 5 or 10 mg, preferably by slow intravenous injection. A concentrate of factors II, VII, IX, and X should also be given. The dose of concentrate should be calculated based on 50 units of factor IX/kg. If no concentrate is available fresh frozen plasma should be infused (about one litre for an adult), but may not be as effective. Higher doses of phytomenadione have been used (see Over-anticoagulation, p.1997); however phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.

US guidelines from the *American College of Chest Physicians* are as follows:

- if the INR is above therapeutic range but below 5.0, without significant bleeding, warfarin should be reduced in dose or stopped until the INR falls to therapeutic range
- for an INR of 5.0 or over but less than 9.0, warfarin should be stopped. If the patient is at increased risk of bleeding, phytomenadione 1 to 2.5 mg should be given orally, or up to 5 mg orally for more complete reversal of anticoagulation
- if the INR is 9.0 or above with no significant bleeding, warfarin should be stopped and phytomenadione 2.5 to 5 mg may be given orally
- if there is any major bleeding, warfarin should be stopped and phytomenadione 10 mg given by slow intravenous injection, with fresh plasma, concentrates of factors II, VII, IX, and X, or recombinant factor VIIa.

If bleeding occurs unexpectedly at therapeutic INR values, the possibility of an underlying cause such as renal or alimentary tract disease should be investigated.

See under Effects on the Skin and Hair, above, for the management of skin and soft tissue necrosis.

For **poisoning** in individuals not taking anticoagulant therapy, the *UK National Poisons Information Service* recommends that those who have ingested more than 250 micrograms/kg of warfarin or who have an INR greater than 6.0, should be given phytomenadione 10 to 20 mg orally or intravenously. If there is active bleeding, factor concentrate or fresh frozen plasma should also be given.

Precautions

Warfarin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, and bacterial endocarditis. Consideration should be given to stopping warfarin a few days before an invasive procedure and using an alternative form of antithrombotic therapy. Severe hepatic and renal impairment as well as severe hypertension are considered by some to be contra-indications. Pregnancy is also generally considered to be a contra-indication, especially in the first trimester and during the late stages of pregnancy (see Adverse Effects, above).

Many factors may affect anticoagulant control with warfarin. These include vitamin K status, thyroid status, renal function, bioavailability differences between warfarin preparations, factors affecting absorption of warfarin, genetic variation in warfarin metabolism (see below), and drug interactions. Such factors may be responsible for apparent resistance to warfarin and a few patients have displayed hereditary resistance. Dosage alterations should be guided by regular monitoring of oral anticoagulant therapy and clinical status. Patients should carry anticoagulant treatment booklets.

◊ A discussion of factors affecting the anticoagulant effect of warfarin sodium.[1]

1. Shetty HGM, *et al.* Clinical pharmacokinetic considerations in the control of oral anticoagulant therapy. *Clin Pharmacokinet* 1989; **16:** 238–53.

Breast feeding. Drug concentrations were measured[1] in the plasma and milk of 13 women receiving 2 to 12 mg of warfarin daily. Plasma concentrations varied from 1.6 to 8.5 micromoles/litre but none was detectable in the breast milk or in the plasma of the 7 infants who were breastfed (limit of detection 0.08 micromoles/litre). No anticoagulant effect was found in the 3 breast-fed infants tested. In another report[2] of 2 women (dose of warfarin not specified), no evidence of the drug was found in the milk of one mother, and no anticoagulant effect was found in either infant. The American Academy of Pediatrics considers[3] that warfarin is therefore usually compatible with breast feeding.

1. Orme ML'E, *et al.* May mothers given warfarin breast-feed their infants? *BMJ* 1977; **1:** 1564–5.
2. McKenna R, *et al.* Is warfarin sodium contraindicated in the lactating mother? *J Pediatr* 1983; **103:** 325–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Genetic variation. The response to warfarin and dosing requirements vary widely between individuals and between different racial groups.[1] Factors involved include age, indication for anticoagulation, diet, and use of interacting drugs, but much of the variability appears to be related to genetic polymorphism. Two genes appear to be particularly important: the gene for the cytochrome P450 isoenzyme CYP2C9, the major enzyme involved in warfarin metabolism; and the gene for vitamin K epoxide reductase (VKOR), which is involved in the synthesis of clotting factors and is the major target for warfarin and other coumarin anticoagulants.[2] Although polymorphisms in either gene may affect dose requirements, patients with variant alleles for both genes appear to be particularly sensitive to warfarin;[3] initial variability in response may be more strongly associated with VKOR.[4] Identification of affected patients by genetic testing may be used to guide initial warfarin dosage, and a dosage algorithm has been suggested, although it requires validation.[5] Similar effects have also been noted with other coumarins, including acenocoumarol[6] and phenprocoumon.[7]

1. Dang M-TN, *et al.* The influence of ethnicity on warfarin dosage requirement. *Ann Pharmacother* 2005; **39:** 1008–12.
2. Schwarz UI, Stein CM. Genetic determinants of dose and clinical outcomes in patients receiving oral anticoagulants. *Clin Pharmacol Ther* 2006; **80:** 7–12.

3. Aquilante CL, *et al.* Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. *Clin Pharmacol Ther* 2006; **79:** 291–302.
4. Schwarz UI, *et al.* Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008; **358:** 999–1008.
5. Millican EA, *et al.* Genetic-based dosing in orthopedic patients beginning warfarin therapy. *Blood* 2007; **110:** 1511–15.
6. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther* 2006; **80:** 13–22.
7. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. *Clin Pharmacol Ther* 2007; **81:** 185–93.

Macular degeneration. Intra-ocular haemorrhage leading to loss of vision has been reported[1,2] in patients with neovascular (wet) age-related macular degeneration receiving warfarin, and caution has been advised[3] in such patients.

1. Tilanus MAD, *et al.* Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2000; **238:** 482–5.
2. Ung T, *et al.* Long term warfarin associated with bilateral blindness in a patient with atrial fibrillation and macular degeneration. *Heart* 2003; **89:** 985.
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Interactions

Many compounds interact with warfarin and other oral anticoagulants. Details of these interactions are given below for all oral anticoagulants with different groups of drugs; if the anticoagulant is other than warfarin, then its identity is specified. The major interactions are summarised in the tables, below.

Drugs generally recognised as diminishing the effects of oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

acetomenaphthone	ethchlorvynol
alcohol (chronic ingestion without liver impairment)	glutethimide
aminoglutethimide	griseofulvin
barbiturates	nafcillin
bosentan	phytomenadione
carbamazepine	rifampicin
dichloralphenazone	St John's wort

Drugs recognised or generally reported as enhancing oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

alcohol (acute ingestion or chronic ingestion with liver impairment)	ethylestrenol
allopurinol	fluconazole
amiodarone	glucagon
aspirin	itraconazole
cefamandole	ketoconazole
chloramphenicol	metronidazole
cimetidine	miconazole
clofibrate	norethandrolone
cloral hydrate	NSAIDs
co-trimoxazole	oxymetholone
danazol	quinidine
dextropropoxyphene	stanozolol
dextrothyroxine	sulfinpyrazone
dipyridamole	tamoxifen
disulfiram	telithromycin
erythromycin	thyroid agents
etacrynic acid	tramadol
	triclofos sodium

Interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to another but this may not be the case with pharmacokinetic interactions. Many food and herbal preparations also have the potential to interact with oral anticoagulants; some are discussed below.

An interaction may be due to increased or decreased anticoagulant metabolism; with warfarin some interacting drugs such as cimetidine, co-trimoxazole, or phenylbutazone have a selective effect on its stereoisomers. Altered absorption may sometimes play a part, as with colestyramine. Displacement of oral anticoagulants from plasma protein binding sites has been reported with many drugs, including some analgesics. Not all reports that have recorded an alteration in the pharmacokinetics of the anticoagulant have, however, shown a corresponding change in clinical response.

Interference with the coagulation process may be responsible for the increased risk of haemorrhage when aspirin, clofibrate, or thyroid hormones are used with anticoagulants. Many other compounds, such as asparaginase, some contrast media, epoprostenol, streptokinase, and urokinase also carry this risk; while interactions between these compounds and anticoagulants are not discussed further below, the possibility of an increased risk of haemorrhage should be considered when they are used together.

Where there is a risk of serious haemorrhage from an interaction, then use of both drugs is best avoided. In other instances the anticoagulant activity should be carefully monitored so as to increase or decrease the anticoagulant dose as required. Critical periods are when patients stabilised on an anticoagulant start treatment with an interacting drug, or when patients stabilised on a regimen of an interacting drug and anticoagulant have the interacting drug withdrawn. Depending on the mechanism of the interaction, the clinical response to the interaction may be rapid or may take some days. Interactions involving displacement from plasma protein binding sites are often transient. Some interacting drugs do not produce predictable effects; there have for instance been reports of increased as well as decreased anticoagulant activity with disopyramide, phenytoin, quinidine, and oral contraceptives. Another problem occurs with dipyridamole; it can cause bleeding when given to patients taking anticoagulants but without any changes in the measures used for anticoagulant control.

◊ Reviews.

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Alcohol. Alcohol has a variable effect on warfarin. Heavy regular drinkers may have a diminished effect, perhaps through enzyme induction, although the effect of warfarin may be increased in the presence of liver impairment; acute ingestion has enhanced the effect of warfarin. A moderate alcohol intake is generally not considered to cause problems.

Analgesics and NSAIDs. All NSAIDs should be used with caution or not at all in patients on warfarin. Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinaemic effect of warfarin, possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein-binding sites. Many studies have compared the relative displacing action of a range of NSAIDs *in vitro*, but such studies cannot easily be extrapolated to the clinical situation. Changes in plasma concentration of unbound warfarin resulting from displacement from plasma protein-binding sites are usually transient and are most likely to occur in the first few weeks after an NSAID is added to or withdrawn from warfarin therapy; monitoring of anticoagulant therapy is, therefore, most critical during this period.

High doses of *aspirin* and some other *salicylates* enhance the hypoprothrombinaemic effect of warfarin and should generally be avoided in patients on oral anticoagulant therapy. Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. The possibility of an interaction with topical salicylates should also be considered.[1,2]

Use of *phenylbutazone* with warfarin has led to serious haemorrhage and should be avoided. Phenylbutazone affects the metabolism of the *R*- and *S*- isomers of warfarin in complex and different ways with the net effect of enhancing its anticoagulant activity.[3] Related drugs such as *oxyphenbutazone*, *azapropazone*,[4-6] and *feprazone*[7] behave similarly and should also be avoided.

For the following NSAIDs there are a few studies or isolated reports suggesting that they may enhance the hypoprothrombinaemic effect of warfarin or other specified oral anticoagulant: *diflunisal* (with acenocoumarol[8] or warfarin[9]), *flurbiprofen* (with acenocoumarol),[10] *indometacin*,[11,12] *ketoprofen*,[13] *meclofenamate sodium*,[14] *mefenamic acid*,[15] *piroxicam*, (with warfarin[16] or acenocoumarol[17]), *sulindac*,[18,19] *tiaprofenic acid* (with acenocoumarol),[20] and *tolmetin sodium*.[21] In many cases the result of concomitant therapy was an increased prothrombin time which may or may not be clinically significant; in other cases haemorrhage occurred. It should also be noted that for many of the above NSAIDs, perhaps particularly indometacin, there are studies (not cited) in which no enhancement of warfarin activity was found. NSAIDs with an apparently minimal effect on warfarin activity include *etodolac*, *ibuprofen*, and *naproxen*.

Interactions have also been reported with NSAIDs that are selective inhibitors of cyclo-oxygenase-2. As with other NSAIDs, some studies (not cited) have shown a lack of interaction between warfarin and *celecoxib*, but there have been several reports[22-25] of an increase in the INR with concomitant therapy and bleeding has occurred in some patients.[24] Increases in INR have also been reported in studies[25,26] of warfarin with *rofecoxib*; and there have also been reports of bleeding.[27] A small increase in INR was also reported[28] with *etoricoxib* in healthy subjects but was thought unlikely to be of clinical significance in most patients.

In view of the above considerations, *paracetamol* is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution should be observed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon)[29,30] and isolated reports[31] have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported[32] in a controlled study of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.

Opioid analgesics do not generally cause problems. However, there have been reports of enhanced anticoagulant activity in patients given *tramadol* with warfarin[33,34] including 2 deaths from haemorrhagic stroke,[34] and also with phenprocoumon,[35] although a randomised, double-blind, placebo-controlled study[36] in 19 patients failed to find evidence of an interaction between phenprocoumon and tramadol. *Co-proxamol*, a combination of *dextropropoxyphene* and paracetamol, has increased the effect of warfarin.[37-39] *Co-codamol*, a combination of *codeine* and paracetamol, has also enhanced warfarin activity.[40]

Amongst other analgesics, *glafenine* has been reported to possibly enhance the activity of phenprocoumon.[41] *Phenazone*, an inducer of enzyme metabolism, reduces plasma concentrations of warfarin and, in contrast with most other analgesics, may necessitate an increase in warfarin dosage.[42]

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19. Ross JRY, Beeley L. Sulindac, prothrombin time, and anticoagulants. *Lancet* 1979; **ii:** 1075.
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21. Koren JF, *et al.* Tolmetin-warfarin interaction. *Am J Med* 1987; **82:** 1278–9.
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42. Whitfield JB, *et al.* Changes in plasma γ-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; **1:** 316–18.

Antiarrhythmics. *Amiodarone* has been shown in several studies to increase the activity of warfarin[1-5] and acenocoumarol,[6,7] probably through inhibition of metabolism. The potentiating effect of amiodarone has been reported to persist for up to 4 months after its withdrawal.[1] Phenprocoumon has been reported to be either unaffected[8] or potentiated[9] by amiodarone. Isolated reports with *disopyramide*[10] and *quinidine*[11] have suggested that these drugs can enhance the anticoagulant effect of warfarin. In 7 patients on warfarin or dicoumarol treated with disopyramide or quinidine, however, all but one needed a small increase in the weekly anticoagulant dose suggesting that the antiarrhythmic had reduced the anticoagulant effect.[12] Since the effect was observed after conversion of atrial fibrillation to sinus rhythm an involvement of haemodynamic factors was postulated. Several studies (not cited) have failed to show an effect of quinidine on warfarin. There are also reports indicating that *propafenone*[13] and *moracizine*[14] can enhance warfarin.

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5. Kerin NZ, *et al.* The incidence, magnitude, and time course of the amiodarone-warfarin interaction. *Arch Intern Med* 1988; **148:** 1779–81.
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Antibacterials. Several antibacterials have been involved in interactions with warfarin. Only a few reports are of serious effects and it is unlikely that any of the drugs need to be contra-indicated with warfarin; careful control should suffice.

Most of the drugs enhance the effects of warfarin. Apart from possible effects on the metabolism or plasma-protein binding of warfarin, some antibacterials may interfere with platelet function or with the bacterial synthesis of vitamin K in the gastrointestinal tract and thus have an anticoagulant effect of their own. This is generally considered unlikely to be of clinical significance except, perhaps, in patients with an inadequate vitamin K intake. Fever itself may increase the catabolism of clotting factors and exaggerate a potential antibacterial-warfarin interaction.

There are several reports of an enhanced warfarin response with *co-trimoxazole*; stereospecific inhibition of warfarin metabolism is probably responsible.[1] The interaction is generally attributed to the *sulfamethoxazole* moiety and there are isolated reports suggesting that the activity of warfarin (or other specified oral anticoagulant) may be enhanced by other sulfonamides including *sulfafurazole*,[2] *sulfamethizole*,[3] and *sulfaphenazole* (with phenindione).[4]

There are several reports of potentiation of the effects of warfarin by *erythromycin* or its salts; inhibition of warfarin metabolism probably occurs. Although no clinically-significant increase in prothrombin time was found in 8 non-infected patients, the potential for an interaction was recognised.[5] An enhanced response to warfarin has also been reported with *azithromycin*,[6,7] with *roxithromycin*,[8] which included reports of spontaneous bleeding, and with *telithromycin*,[9,10] including a case of mild haemoptysis.[9] *Clarithromycin* may potentiate the effect of acenocoumarol[11] and of warfarin,[12] although other factors may also have been involved in this case.

Cefamandole has been reported to enhance the hypoprothrombinaemic response to warfarin.[13,14] Interference with vitamin K synthesis in the gastrointestinal tract and/or liver has been implicated. Related cephalosporins with an *N*-methylthiotetrazole side-chain such as *cefmetazole*, *cefmenoxime*, *cefoperazone*, and *latamoxef* may be expected to behave similarly although there appear to be no reports of an interaction. *Cefazolin*, which has a similar side-chain, may also enhance the effect of warfarin to some extent.[14]

There have been reports of increased activity of warfarin (or other specified oral anticoagulant) by quinolone antibacterials including *nalidixic acid* (with warfarin[15,16] or acenocoumarol[17]), *ciprofloxacin*,[18-20] *gatifloxacin*,[20,21] *levofloxacin*,[20,22] *moxifloxacin*,[20,23] *norfloxacin*,[20,24] and *ofloxacin*,[25,26] although for some of these there are also studies indicating no effect (not cited). *Enoxacin* has been reported to decrease the clearance of *R*-warfarin but not *S*-warfarin; no prolongation of prothrombin time occurred.[27]

There are isolated reports suggesting an enhanced effect of warfarin (or other specified oral anticoagulant) with *aminosalicylic acid*,[28] *benzylpenicillin*,[29] *chloramphenicol* (with dicoumarol),[30] *doxycycline*,[31] *isoniazid*,[32] and *neomycin*.[33] Prothrombin times might be prolonged by broad-spectrum antibacterials such as *ampicillin*, and there has been a report[34] of an increased INR and haematuria in a patient taking warfarin with amoxicillin and clavulanic acid. Manufacturers' warnings of potentiation of warfarin by *aztreonam*, *trimethoprim*, and *tetracyclines* other than doxycycline appear to have only a theoretical basis. *Metronidazole* is discussed under Antiprotozoals, below.

Rifampicin diminishes the effect of warfarin by induction of metabolising enzymes in the liver. There are several reports of a similar effect with *nafcillin*[35-37] and with *dicloxacillin sodium*.[38,39]

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8. Anonymous. Interaction of warfarin with macrolide antibiotics. *Aust Adverse Drug React Bull* 1995; **14:** 11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 19/08/08)
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18. Mott FE, *et al.* Ciprofloxacin and warfarin. *Ann Intern Med* 1989; **111:** 542–3.
19. Kamada AK. Possible interaction between ciprofloxacin and warfarin. *DICP Ann Pharmacother* 1990; **24:** 27–8.
20. Health Canada. Fluoroquinolones and warfarin: suspected interaction. *Can Adverse React News* 2004; **14** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n3_e.pdf (accessed 23/05/08)
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37. Davis RL, *et al.* Warfarin-nafcillin interaction. *J Pediatr* 1991; **118:** 300–3.
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39. Mailloux A, *et al.* Potential interaction between warfarin and dicloxacillin. *Ann Pharmacother* 1996; **30:** 1402–7.

Antidepressants. *Amitriptyline* and *nortriptyline* have been reported to prolong the half-life of dicoumarol in healthy subjects.[1,2] The few reports investigating the effect of tricyclic antidepressants on warfarin have not been able to conclude that a significant interaction exists. *Mianserin* and phenprocoumon have been reported not to interact.[3]

The *BNF* considers that there is a possible risk of increased warfarin activity with *SSRIs*; increased warfarin activity has been reported in a few patients taking *fluoxetine*,[4] in a patient taking *fluvoxamine*,[5] and another taking the SNRI *duloxetine*.[6] There has also been a report of increased anticoagulant activity in a patient taking acenocoumarol and *citalopram*.[7]

An increase in the dose of warfarin has been required by patients also taking *trazodone*.[8,9]

See also St John's Wort, p.1432.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Pond SM, *et al.* Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* 1975; **18:** 191–9.
3. Kopera H, *et al.* Phenprocoumon requirement, whole blood coagulation time, bleeding time and plasma γ-GT in patients receiving mianserin. *Eur J Clin Pharmacol* 1978; **13:** 351–6.
4. Woolfrey S, *et al.* Fluoxetine-warfarin interaction. *BMJ* 1993; **307:** 241.
5. Limke KK, *et al.* Fluvoxamine interaction with warfarin. *Ann Pharmacother* 2002; **36:** 1890–2.
6. Glueck CJ, *et al.* Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA* 2006; **295:** 1517–18.
7. Borrás-Blasco J, *et al.* Probable interaction between citalopram and acenocoumarol. *Ann Pharmacother* 2002; **36:** 345.
8. Hardy J-L, Sirois A. Reduction of prothrombin and partial thromboplastin times with trazodone. *Can Med Assoc J* 1986; **135:** 1372.
9. Small NL, Giamonna KA. Interaction between warfarin and trazodone. *Ann Pharmacother* 2000; **34:** 734–6.

Antidiabetics. There have been a few early instances of *tolbutamide* enhancing the activity of dicoumarol.[1] However, this effect has not been seen in later studies involving dicoumarol,[1-3] warfarin,[2] and phenprocoumon,[4] although one study did find altered dicoumarol pharmacokinetics.[3] An absence of effect has been documented for phenprocoumon and *insulin*, *glibenclamide*, or *glibornuride*,[4] but there is a report of glibenclamide enhancing the effect of warfarin.[5]

There has been an isolated report of bleeding in a patient taking *phenformin* and warfarin.[6] *Metformin* has been reported to diminish phenprocoumon activity.[7]

An enhanced response to warfarin has been reported in a patient receiving *troglitazone*.[8]

Coumarin anticoagulants may increase the hypoglycaemic effect of *sulfonylureas* (see p.462).

1. Chaplin H, Cassell M. Studies on the possible relationship of tolbutamide to dicumarol in anticoagulant therapy. *Am J Med Sci* 1958; **235:** 706–16.
2. Poucher RL, Vecchio TJ. Absence of tolbutamide effect on anticoagulant therapy. *JAMA* 1966; **197:** 1069–70.
3. Jähnchen E, *et al.* Pharmacokinetic analysis of the interaction between dicoumarol and tolbutamide in man. *Eur J Clin Pharmacol* 1976; **10:** 349–56.
4. Heine P, *et al.* The influence of hypoglycaemic sulphonylureas on elimination and efficacy of phenprocoumon following a single oral dose in diabetic patients. *Eur J Clin Pharmacol* 1976; **10:** 31–6.
5. Jassal SV. *BMJ* 1991; **303:** 789.
6. Hamblin TJ. Interaction between warfarin and phenformin. *Lancet* 1971; **ii:** 1323.
7. Ohnhaus EE, *et al.* The influence of dimethylbiguanide on phenprocoumon elimination and its mode of action: a drug interaction study. *Klin Wochenschr* 1983; **61:** 851–8.
8. Plowman BK, Morreale AP. Possible troglitazone—warfarin interaction. *Am J Health-Syst Pharm* 1998; **55:** 1071.

Antiepileptics. Barbiturates such as *phenobarbital* and *primidone* diminish the activity of warfarin and other coumarins through increased metabolism. *Carbamazepine* is reported to have a similar effect.[1,2] Reports of the effect of *phenytoin* on anticoagulants do not provide a clear picture. There are reports of phenytoin enhancing the effects of warfarin[3,4] and a report of initial enhancement followed by decreased anticoagulant action.[5] Phenytoin has been reported to diminish the effect of dicoumarol.[6] Addition of *felbamate* has been reported[7] to necessitate a reduction in warfarin dosage. In another patient there was a transient increase in response to warfarin when *valproic acid* was started.[8] Valproate also inhibits platelet function and caution is required with warfarin and other anticoagulants.

For the effect of oral anticoagulants on phenytoin, see p.498.

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; **12:** 539–43.
2. Ross JRY, Beeley L. Interaction between carbamazepine and warfarin. *BMJ* 1980; **280:** 1415–16.
3. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* 1979; **90:** 852.
4. Panegyres PK, Rischbieth RH. Fatal phenytoin warfarin interaction. *Postgrad Med J* 1991; **67:** 98.
5. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* 1984; **3:** 200–3.
6. Hansen JM, *et al.* Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* 1971; **189:** 15–19.
7. Tisdel KA, *et al.* Warfarin—felbamate interaction: first report. *Ann Pharmacother* 1994; **28:** 805.
8. Guthrie SK, *et al.* Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol* 1995; **15:** 138–9.

Antifungals. *Griseofulvin* has been reported to diminish the activity of warfarin.[1-3] There are several reports indicating that *miconazole*, given either systemically or topically as the oral gel, may enhance the activity of oral anticoagulants (warfarin, ethyl biscoumacetate, acenocoumarol, phenindione, and tioclomarol).[4-11] Absorption of miconazole after intravaginal use may have enhanced the activity of acenocoumarol in 2 patients;[12] it enhanced the activity of warfarin[13] in another. Studies in healthy subjects given a single warfarin dose[14,15] support case reports[16-18] suggesting that *fluconazole* may increase the anticoagulant activity of warfarin. There are isolated reports of the potentiation of warfarin by *itraconazole*[19] and *ketoconazole*,[20] and of unspecified coumarins by topical *bifonazole* or *econazole*.[21] There has been a case report of a reduction in the effect of warfarin by *terbinafine*,[22] although a study[23] in healthy subjects found no clinically significant interaction, and others[24] considered that no interaction usually occurs. A case of potentiation of warfarin by terbinafine has also been reported;[25] the authors speculate that concomitant cimetidine may have contributed to the interaction by increasing plasma-terbinafine concentrations.

1. Cullen SI, Catalano PM. Griseofulvin-warfarin antagonism. *JAMA* 1967; **199:** 582–3.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; **77** (Aug.): 20–5.
3. Okino K, Weibert RT. Warfarin-griseofulvin interaction. *Drug Intell Clin Pharm* 1986; **20:** 291–3.
4. Loupi E, *et al.* Interactions médicamenteuses et miconazole: a propos de 10 observations. *Therapie* 1982; **37:** 437–41.
5. Watson PG, *et al.* Drug interaction with coumarin derivative anticoagulants. *BMJ* 1982; **285:** 1045–6.
6. Colquhoun MC, *et al.* Interaction between warfarin and miconazole oral gel. *Lancet* 1987; **i:** 695–6.
7. Bailey GM, *et al.* Miconazole and warfarin interaction. *Pharm J* 1989; **242:** 183.
8. Ariyaratnam S, *et al.* Potentiation of warfarin anticoagulant activity by miconazole oral gel. *BMJ* 1997; **314:** 349.
9. Evans J, *et al.* Treating oral candidiasis: potentially fatal. *Br Dent J* 1997; **182:** 452.
10. Pemberton MN, *et al.* Derangement of warfarin anticoagulation by miconazole oral gel. *Br Dent J* 1998; **184:** 68–9.
11. Ortín M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; **33:** 175–7.
12. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; **47:** 225–6.
13. Thirion DJG, Farquhar Zanetti LA. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000; **20:** 98–9.
14. Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12** (suppl 3): S327–S333.
15. Black DJ, *et al.* Warfarin–fluconazole II: a metabolically based drug interaction: in vivo studies. *Drug Metab Dispos* 1996; **24:** 422–8.
16. Seaton TL, *et al.* Possible potentiation of warfarin by fluconazole. *DICP Ann Pharmacother* 1990; **24:** 1177–8.
17. Gericke KR. Possible interaction between warfarin and fluconazole. *Pharmacotherapy* 1993; **13:** 508–9.
18. Baciewicz AM, *et al.* Fluconazole—warfarin interaction. *Ann Pharmacother* 1994; **28:** 1111.
19. Yeh J, *et al.* Potentiation of action of warfarin by itraconazole. *BMJ* 1990; **301:** 669.
20. Smith AG. Potentiation of oral anticoagulants by ketoconazole. *BMJ* 1984; **288:** 188–9. Correction. *ibid.*; 608.
21. Alexandra J-F, *et al.* Overanticoagulation with coumarin and cutaneous azole therapy. *Ann Intern Med* 2008; **148:** 633–5.
22. Warwick JA, Corrall RJ. Serious interaction between warfarin and oral terbinafine. *BMJ* 1998; **316:** 440.
23. Guerret M, *et al.* Evaluation of effects of terbinafine on single oral dose pharmacokinetics and anticoagulant actions of warfarin in healthy volunteers. *Pharmacotherapy* 1997; **17:** 767–73.
24. Stockley IH. Terbinafine and warfarin mystery. *Pharm J* 1998; **260:** 408.
25. Gupta AK, Ross GS. Interaction between terbinafine and warfarin. *Dermatology* 1998; **196:** 266–7.

Antigout drugs. The two drugs in this group mostly implicated in interactions with anticoagulants are allopurinol and sulfinpyrazone.

With *allopurinol* there are conflicting reports of patients experiencing no interaction or an enhanced anticoagulant effect with dicoumarol,[1] phenprocoumon,[2] or warfarin.[3,4]

Interactions with *sulfinpyrazone* have usually involved warfarin and, apart from a case of a mixed response,[5] have involved increased anticoagulant activity, sometimes with haemorrhage, so calling for careful control. It is still not clear how sulfinpyrazone exerts its effect, but studies point to a stereoselective effect on warfarin metabolism where the *S*-isomer's metabolic clearance is inhibited;[6] sulfinpyrazone also affects platelets. Sulfinpyrazone has also enhanced the anticoagulant activity of acenocoumarol.[7] A significant interaction with phenprocoumon appears unlikely.[8]

Probenecid has accelerated the elimination of a single dose of phenprocoumon without effect on the prothrombin time.[9]

Benziodarone has been reported to enhance the effects of warfarin, diphenadione, ethyl biscoumacetate, and acenocoumarol, but not of dicoumarol, phenindione, or phenprocoumon.[10] A further study[11] confirmed that benziodarone could increase the half-life of ethyl biscoumacetate, but also found that the effect of phenprocoumon was enhanced. A study[12] of *benzbromarone*, which is structurally related to benziodarone, concluded that it enhanced the effect of warfarin by inhibition of the cytochrome P450 isoenzyme CYP2C9, leading to a stereoselective inhibition of the metabolism of warfarin.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; **283:** 1484–8.
2. Jähnchen E, *et al.* Interaction of allopurinol with phenprocoumon in man. *Klin Wochenschr* 1977; **55:** 759–61.
3. Rawlins MD, Smith SE. Influence of allopurinol on drug metabolism in man. *Br J Pharmacol* 1973; **48:** 693–8.
4. Pond SM, *et al.* The effects of allopurinol and clofibrate on the elimination of coumarin anticoagulants in man. *Aust N Z J Med* 1975; **5:** 324–8.
5. Nenci GG, *et al.* Biphasic sulphinpyrazone-warfarin interaction. *BMJ* 1981; **282:** 1361–2.
6. Toon S, *et al.* The warfarin-sulfinpyrazone interaction: stereochemical considerations. *Clin Pharmacol Ther* 1986; **39:** 15–24.
7. Michot F, *et al.* Über die Beeinflussung der gerinnungshemmenden Wirkung von Acenocoumarol durch Sulfinpyrazon. *Schweiz Med Wochenschr* 1981; **111:** 255–60.
8. Heimark LD, *et al.* The effect of sulfinpyrazone on the disposition of pseudoracemic phenprocoumon in humans. *Clin Pharmacol Ther* 1987; **42:** 312–19.
9. Mönig H, *et al.* The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon. *Eur J Clin Pharmacol* 1990; **39:** 261–5.
10. Pyörälä K, *et al.* Benziodarone (Amplivix) and anticoagulant therapy. *Acta Med Scand* 1963; **173:** 385–9.
11. Verstraete M, *et al.* Dissimilar effect of two anti-anginal drugs belonging to the benzofuran group on the action of coumarin derivatives. *Arch Int Pharmacodyn Ther* 1968; **176:** 33–41.
12. Takahashi H, *et al.* Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. *Clin Pharmacol Ther* 1999; **66:** 569–81.

Antihistamines. There has been a report[1] of a raised INR and severe epistaxis in a patient after the addition of *cetirizine* to long-term acenocoumarol.

1. Berod T, Mathiot I. Probable interaction between cetirizine and acenocoumarol. *Ann Pharmacother* 1997; **31:** 122.

Antimalarials. The ingestion of large amounts of tonic water by 2 patients necessitated a reduction in warfarin dosage. The enhanced effect was attributed to the *quinine* content of the tonic water.[1] A woman stabilised on warfarin developed haematuria and a high prothrombin ratio after taking *proguanil* for malaria prophylaxis.[2]

1. Clark DJ. Clinical curio: warfarin and tonic water. *BMJ* 1983; **286:** 1258.
2. Armstrong G, *et al.* Warfarin potentiated by proguanil. *BMJ* 1991; **303:** 789.

Antimuscarinics. There have been 2 cases reported[1] of *tolterodine* enhancing the effect of warfarin. It was stated that the manufacturers of tolterodine were aware of 6 reports of a possible interaction with warfarin.

1. Colucci VJ, Rivey MP. Tolterodine–warfarin drug interaction. *Ann Pharmacother* 1999; **33:** 1173–6.

Antineoplastics. There have been several reports of interactions between warfarin and antineoplastics. No clear picture emerges from these reports which is not surprising considering that antineoplastics are often given in combination and that they can exert their own haematological effects. *Cyclophosphamide* for instance has been associated with an increase in warfarin's activity when given with *methotrexate* and *fluorouracil*,[1] but with a decrease when given with non-antineoplastic drugs.[2] An increase in the activity of warfarin and mucous membrane bleeding occurred in a patient who had 4 courses of fluorouracil and folic acid at weekly intervals.[3] The patient was also taking indometacin. Warfarin dosage had to be reduced in 5 patients given fluorouracil-based antineoplastic regimens.[4] An increase in the effect of warfarin has been reported when given with fluorouracil and levamisole (see Levamisole, below). *Capecitabine* increases plasma-warfarin concentrations[5] and there have been reports of increased warfarin activity,[5-7] in 1 case resulting in gastrointestinal bleeding;[6] licensed product information for capecitabine states that altered coagulation parameters and bleeding have also occurred with phenprocoumon. There have been 2 cases reported[8] where *trastuzumab* enhanced the effect of warfarin. *Etoposide* with *vindesine*[9] or with *carboplatin*,[10] *ifosfamide* with *mesna*,[11] and *tamoxifen*[12-14] have all produced an increased anticoagulant effect. *Aminoglutethimide* has led to decreased activity of warfarin or acenocoumarol,[15,16] probably due to increased warfarin metabolism. Licensed product information for the antiandrogen *flutamide* states that increases in prothrombin time have been reported after starting flutamide therapy in patients on long-term warfarin. *In vitro* data indicate a similar reaction is likely with *bicalutamide*. *Mercaptopurine*[17] and *mitotane*[18] have also decreased warfarin activity. Licensed product information for *vorinostat* states that prolongation of prothrombin time has been seen when the drug is given with coumarin derivatives; prothrombin time and INR should be monitored in patients given both drugs.

1. Seifter EJ, *et al.* Possible interactions between warfarin and antineoplastic drugs. *Cancer Treat Rep* 1985; **69:** 244–5.
2. Tashima CK. Cyclophosphamide effect on coumarin anticoagulation. *South Med J* 1979; **72:** 633–4.
3. Brown MC. Multisite mucous membrane bleeding due to a possible interaction between warfarin and 5-fluorouracil. *Pharmacotherapy* 1997; **17:** 631–3.
4. Kolesar JM, *et al.* Warfarin–5-FU interaction—a consecutive case series. *Pharmacotherapy* 1999; **19:** 1445–9.
5. Camidge R, *et al.* Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer. *J Clin Oncol* 2005; **23:** 4719–25.
6. Copur MS, *et al.* An adverse interaction between warfarin and capecitabine: a case report and review of the literature. *Clin Colorectal Cancer* 2001; **1:** 182–4.
7. Janney LM, Waterbury NV. Capecitabine–warfarin interaction. *Ann Pharmacother* 2005; **39:** 1546–51.
8. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. *JAMA* 1999; **282:** 2299–2300.
9. Ward K, Bitran JD. Warfarin, etoposide, and vindesine interactions. *Cancer Treat Rep* 1984; **68:** 817–18.
10. Le AT, *et al.* Enhancement of warfarin response in a patient receiving etoposide and carboplatin chemotherapy. *Ann Pharmacother* 1997; **31:** 1006–8.
11. Hall G, *et al.* Intravenous infusions of ifosfamide/mesna and perturbation of warfarin anticoagulant control. *Postgrad Med J* 1990; **66:** 860–1.
12. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
13. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
14. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
15. Lønning PE, *et al.* The influence of a graded dose schedule of aminoglutethimide on the disposition of the optical enantiomers of warfarin in patients with breast cancer. *Cancer Chemother Pharmacol* 1986; **17:** 177–81.
16. Bruning PF, Bonfrèr JGM. Aminoglutethimide and oral anticoagulant therapy. *Lancet* 1983; **ii:** 582.
17. Spiers ASD, Mibashan RS. Increased warfarin requirement during mercaptopurine therapy: a new drug interaction. *Lancet* 1974: **ii:** 221–2.
18. Cuddy PG, *et al.* Influence of mitotane on the hypoprothrombinemic effect of warfarin. *South Med J* 1986; **79:** 387–8.

Antiplatelets. The interaction between anticoagulants and *dipyridamole* is unusual as bleeding can occur without any alteration in prothrombin times; special care is therefore required. This interaction has involved a small number of patients taking dipyridamole and warfarin or phenindione;[1] inhibition of platelet function by dipyridamole has been implicated. However, in general it does not appear to increase the risk of bleeding.[2]

Paradoxically, addition of *ticlopidine* was found to significantly increase acenocoumarol requirements.[3]

See also under Analgesics and NSAIDs (above).

1. Kalowski S, Kincaid-Smith P. Interaction of dipyridamole with anticoagulants in the treatment of glomerulonephritis. *Med J Aust* 1973; **2:** 164–6.
2. Levine MN, *et al.* Hemorrhagic complications of long-term anticoagulant therapy. *Chest* 1989; **95** (suppl): 26S–36S.
3. Salar A, *et al.* Ticlopidine antagonizes acenocoumarol treatment. *Thromb Haemost* 1997; **77:** 223–4.

Antiprotozoals. *Metronidazole* enhances the activity of warfarin[1,2] through selective inhibition of the metabolism of its *S*-isomer.[3]

1. Kazmier FJ. A significant interaction between metronidazole and warfarin. *Mayo Clin Proc* 1976; **51:** 782–4.

2. Dean RP, Talbert RL. Bleeding associated with concurrent warfarin and metronidazole therapy. *Drug Intell Clin Pharm* 1980; **14:** 864–6.
3. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med* 1976; **295:** 354–7.

Antithyroid drugs. See Thyroid and Antithyroid Drugs, below.

Antivirals. Reductions in dosage of either warfarin[1] or acenocoumarol[2] were necessary in 2 patients receiving *interferon alfa* for hepatitis C. The interactions may have been due to decreased metabolism of the anticoagulant. A similar need for a reduced warfarin dose had also been noted in other patients taking *interferon alfa-2b* or *interferon beta*.[1] However, in a patient taking interferon alfa-2b with *ribavirin*,[3] the warfarin dose needed to be increased, probably due to the interaction between ribavirin and warfarin.

An enhanced response to warfarin has been reported[4] in a patient taking *saquinavir.* The mechanism may involve competitive inhibition of warfarin metabolism and might also occur with other HIV-protease inhibitors. However, a decreased response to warfarin seemed to be caused by *ritonavir* when it was added to the multidrug therapy of a patient.[5] Ritonavir has also been reported to decrease the response to acenocoumarol.[6]

Up to October 2005 there had been 19 reports[7] received by the Canadian health authorities (Health Canada) of enhanced response to warfarin between 1 and 11 days after starting *oseltamivir.* The increased INR ranged from 3.2 to 10.9; however, there was not enough information to be certain of causality. In 3 other cases there was a decrease in INR on the addition of oseltamivir.

1. Adachi Y, *et al.* Potentiation of warfarin by interferon. *BMJ* 1995; **311:** 292.
2. Serratrice J, *et al.* Interferon-alpha 2b interaction with acenocoumarol. *Am J Hematol* 1998; **57:** 89.
3. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* 2002; **36:** 72–4.
4. Darlington MR. Hypoprothrombinemia during concomitant therapy with warfarin and saquinavir. *Ann Pharmacother* 1997; **31:** 647.
5. Knoell KR, *et al.* Potential interaction involving warfarin and ritonavir. *Ann Pharmacother* 1998; **32:** 1299–1302.
6. Llibre JM, *et al.* Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002; **36:** 621–3.
7. Health Canada. Oseltamivir (Tamiflu) and warfarin: suspected increase in INR. *Can Adverse React News* 2006; **16** (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v16n1-eng.pdf (accessed 19/08/08)

Anxiolytic sedatives, hypnotics, and antipsychotics. *Barbiturates*, by inducing liver metabolism, can reduce the activity of anticoagulants; *glutethimide* has a similar action. The *benzodiazepines* do not generally have any effect although there is the rare report of increased or decreased activity.

Although there is a report suggesting that *cloral hydrate* may decrease the effect of dicoumarol by enzyme induction,[1] other studies and experience indicate an increase in the anticoagulant activity of warfarin.[2-4] However, the increase is only transient and is probably the result of displacement of warfarin from plasma protein binding sites by the metabolite trichloroacetic acid.[2] *Triclofos sodium* appears to increase the activity of warfarin in a similar way.[5]

Reduced anticoagulant activity has been reported with *dichloralphenazone*,[6,7] *ethchlorvynol* (with dicoumarol),[8] and *haloperidol* (with phenindione).[9] Compounds such as *meprobamate* and *methaqualone* appear to have no effect.

1. Cucinell SA, *et al.* The effect of chloral hydrate on bishydroxycoumarin metabolism: a fatal outcome. *JAMA* 1966; **197:** 366–8.
2. Sellers EM, Koch-Weser J. Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. *Ann N Y Acad Sci* 1971; **179:** 213–25.
3. Boston Collaborative Drug Surveillance Program. Interaction between chloral hydrate and warfarin. *N Engl J Med* 1972; **286:** 53–5.
4. Udall JA. Warfarin-chloral hydrate interaction: pharmacological activity and clinical significance. *Ann Intern Med* 1974; **81:** 341–4.
5. Sellers EM, *et al.* Enhancement of warfarin-induced hypoprothrombinemia by triclofos. *Clin Pharmacol Ther* 1972; **13:** 911–15.
6. Breckenridge A, Orme M. Clinical implications of enzyme induction. *Ann N Y Acad Sci* 1971; **179:** 421–3.
7. Whitfield JB, *et al.* Changes in plasma α-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; **1:** 316–18.
8. Johansson S-A. Apparent resistance to oral anticoagulant therapy and influence of hypnotics on some coagulation factors. *Acta Med Scand* 1968; **184:** 297–300.
9. Oakley DP, Lautch H. Haloperidol and anticoagulant treatment. *Lancet* 1963; **ii:** 1231.

Beta blockers. Beta blockers, particularly those with a high lipid solubility such as propranolol, may inhibit the metabolism of warfarin.[1] Although a number of studies have shown pharmacokinetic interactions between some beta blockers and oral anticoagulants, no effect on anticoagulant activity has generally been found. However, possible potentiation of the effect of warfarin by *propranolol*[2] has been reported.

1. Mantero F, *et al.* Effect of atenolol and metoprolol on the anticoagulant activity of acenocoumarin. *Br J Clin Pharmacol* 1984; **17:** 94S–96S.
2. Bax NDS, *et al.* Inhibition of drug metabolism by β-adrenoceptor antagonists. *Drugs* 1983; **25** (suppl 2): 121–6.

Central stimulants. *Methylphenidate* has been reported both to increase the half-life of ethyl biscoumacetate,[1] and to have no effect on its half-life or anticoagulant activity.[2] *Prolintane* had no effect.[2]

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate: a new action of methylphenidate. *JAMA* 1969; **207:** 2053.
2. Hague DE, *et al.* The effect of methylphenidate and prolintane on the metabolism of ethyl biscoumacetate. *Clin Pharmacol Ther* 1971; **12:** 259–62.

Chamomile. A 70-year-old woman stabilised on warfarin developed multiple internal haemorrhages after she increased her use of chamomile lotion and consumption of chamomile tea to 4 or 5 times per day.[1] The interaction was considered to be due to the coumarin constituent of chamomile.

1. Segal R, Pilote L. Warfarin interaction with Matricaria chamomilla. *Can Med Assoc J* 2006; **174:** 1281–2.

Chinese herbal remedies. There have been a number of reports of increased anticoagulation in patients taking Chinese herbal remedies with warfarin.[1-6] The remedies have ranged from single ingredient herbal preparations to complex multi-ingredient products, sometimes sold under the same brand name but with very different compositions.

1. Yu CM, *et al.* Chinese herbs and warfarin potentiation by 'Danshen'. *J Intern Med* 1997; **241:** 337–9.
2. Izzat MB, *et al.* A taste of Chinese medicine! *Ann Thorac Surg* 1998; **66:** 941–2.
3. Page RL, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999; **19:** 870–6.
4. Chan TYK. Interaction between warfarin and danshen (Salvia miltiorrhiza). *Ann Pharmacother* 2001; **35:** 501–4.
5. Lam AY, *et al.* Possible interaction between warfarin and Lycium barbarum L. *Ann Pharmacother* 2001; **35:** 1199–1201.
6. Wong ALN, Chan TYK. Interaction between warfarin and the herbal product Quilinggao. *Ann Pharmacother* 2003; **37:** 836–8.

Corticosteroids and corticotropin. Corticosteroids are associated with an increase in blood coagulability, but their extensive use with anticoagulants, and very few reports of interaction, suggests that any problems are rare. However, there are some reports of corticosteroids or corticotropin either enhancing[1-3] or diminishing[4] the effects of anticoagulants. A retrospective study[5] in patients on long-term warfarin therapy given short courses of oral corticosteroids found that in most cases (29 of 32) there was an increase in INR, suggesting that careful monitoring is required.

1. Van Cauwenberge H, Jaques LB. Haemorrhagic effect of ACTH with anticoagulants. *Can Med Assoc J* 1958; **79:** 536–40.
2. Costedoat-Chalumeau N, *et al.* Potentiation of vitamin K antagonists by high-dose intravenous methylprednisolone. *Ann Intern Med* 2000; **132:** 631–5.
3. Stading JA, *et al.* Effects of prednisone on the international normalized ratio. *Am J Health-Syst Pharm* 2006; **63:** 2354–6. Correction. *ibid.* 2007; **64:** 130.
4. Chatterjea JB, Salomon L. Antagonistic effect of ACTH and cortisone on the anticoagulant activity of ethyl biscoumacetate. *BMJ* 1954; **2:** 790–2.
5. Hazlewood KA, *et al.* Effect of oral corticosteroids on chronic warfarin therapy. *Ann Pharmacother* 2006; **40:** 2101–6.

Cough suppressants. An increase in the activity of warfarin has been reported in patients taking *noscapine*[1,2] or *oxolamine*.[3] A subsequent study[3] suggested that the dose of warfarin should be reduced by 50% if oxolamine was started.

See also Menthol, below.

1. Scordo MG, *et al.* Warfarin–noscapine interaction: a series of four case reports. *Ann Pharmacother* 2008; **42:** 448–50.
2. Ohlsson S, *et al.* Noscapine may increase the effect of warfarin. *Br J Clin Pharmacol* 2008; **65:** 277–8.
3. Min KA, *et al.* Effect of oxolamine on anticoagulant effect of warfarin. *Am J Health-Syst Pharm* 2006; **63:** 153–6.

Cranberry. Between 1999 and 2003 the UK CSM[1] had received 5 reports suggesting an interaction between warfarin and cranberry juice. In 3 patients the activity of warfarin had been potentiated and one of them had died. In the other patients the INR was either reduced or unstable. By 2004 there had been 7 further reports of suspected interactions and the CSM advised[2] patients to avoid cranberry juice and other cranberry products while taking warfarin. However. despite case reports suggesting an increase in warfarin activity, the potential for a pharmacokinetic effect has been questioned,[3] and pharmacokinetic studies[4,5] have failed to confirm an interaction.

1. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Possible interaction between warfarin and cranberry juice. *Current Problems* 2003; **29:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
2. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Interaction between warfarin and cranberry juice: new advice. *Current Problems* 2004; **30:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. *Am J Health-Syst Pharm* 2007; **64:** 490–4.
4. Li Z, *et al.* Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc* 2006; **106:** 2057–61.
5. Lilja JJ, *et al.* Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam—probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther* 2007; **81:** 833–9.

Dermatological drugs. A patient's warfarin dose had to be increased when he started treatment with *etretinate*.[1]

1. Ostlere LS, *et al.* Reduced therapeutic effect of warfarin caused by etretinate. *Br J Dermatol* 1991; **124:** 505–10.

Dietary supplements. There have been reports of an increased INR in patients taking warfarin and dietary supplements containing *glucosamine* and *chondroitin*,[1,2] and the UK CHM advises[3] that patients on warfarin should not take glucosamine. A similar effect has been reported[4] with *poliglusam*.

1. Rozenfeld V, *et al.* Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health-Syst Pharm* 2004; **61:** 306–7.
2. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008; **28:** 540–8.
3. CHM/MHRA. Glucosamine adverse reactions and interactions. *Current Problems* 2006; **31:** 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
4. Huang S-S, *et al.* Chitosan potentiation of warfarin effect. *Ann Pharmacother* 2007; **41:** 1912–14.

Disulfiram. Two reports suggesting that disulfiram enhances the activity of warfarin[1,2] were confirmed by a study in 8 healthy subjects.[3] Although inhibition of liver enzymes by disulfiram was considered responsible,[3] a later study[4] suggested that disulfiram acts directly on the liver to increase hypoprothrombinaemia. This interaction is complicated by the variable effects of alcohol on warfarin (see above). Special care is therefore called for when these drugs are used together.

1. Rothstein E. Warfarin effect enhanced by disulfiram. *JAMA* 1968; **206:** 1574–5.
2. Rothstein E. Warfarin effect enhanced by disulfiram (Antabuse). *JAMA* 1972; **221:** 1052–3.
3. O'Reilly RA. Interaction of sodium warfarin and disulfiram (Antabuse) in man. *Ann Intern Med* 1973; **78:** 73–6.
4. O'Reilly RA. Dynamic interaction between disulfiram and separated enantiomorphs of racemic warfarin. *Clin Pharmacol Ther* 1981; **29:** 332–6.

Diuretics. *Etacrynic acid* has been reported to enhance the activity of warfarin.[1] *Chlortalidone*[2] and *spironolactone*[3] have both been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. However, *bumetanide*, *furosemide*, and the *thiazides* appear to have no effect on warfarin.

1. Petrick RJ, *et al.* Interaction between warfarin and ethacrynic acid. *JAMA* 1975; **231:** 843–4.
2. O'Reilly RA, *et al.* Impact of aspirin and chlorthalidone on the pharmacodynamics of oral anticoagulant drugs in man. *Ann N Y Acad Sci* 1971; **179:** 173–86.
3. O'Reilly RA. Spironolactone and warfarin interaction. *Clin Pharmacol Ther* 1980; **27:** 198–201.

Endothelin receptor antagonists. A study in healthy subjects[1] showed that *bosentan* decreased the anticoagulant effect of warfarin; a case report[2] confirmed this.

1. Weber C, *et al.* Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; **39:** 847–54.
2. Murphey LM, Hood EH. Bosentan and warfarin interaction. *Ann Pharmacother* 2003; **37:** 1028–31.

Gastrointestinal drugs. Antacids may or may not interact with warfarin. *Bismuth carbonate* and *magnesium trisilicate* for example have been reported to reduce warfarin's absorption,[1] but *aluminium hydroxide* has been observed to have no effect on warfarin or dicoumarol.[2] *Psyllium*[3] and *magnesium hydroxide*[2] have also been reported to have no effect on warfarin, but the latter has increased the plasma concentrations of dicoumarol.[2]

There have been occasional reports of *sucralfate* diminishing the effect of warfarin.[4-6]

Histamine H_2-antagonists have been widely studied. There are several reports indicating that *cimetidine* can enhance the anticoagulant effect of warfarin and haemorrhage has occurred. A number of studies show that cimetidine can increase the plasma concentration and half-life of warfarin and that there is a selective inhibitory effect on the metabolism of its *R*-isomer.[7-10] Not all these studies have, however, found an increase in prothrombin time. The effect of cimetidine on warfarin appears to be dose-dependent[7] and to be subject to interindividual variation;[9,10] careful monitoring is needed. Limited evidence suggests that cimetidine has a similar effect on the metabolism of acenocoumarol[11,12] and phenindione[11] but not of phenprocoumon.[13] Studies with *ranitidine* have generally been unable to show an effect on the metabolism of warfarin,[10,14] although in one study warfarin clearance was reduced.[7] There is a case report suggesting that potentiation of warfarin by ranitidine may occasionally occur.[15]

One study has suggested that *omeprazole* could inhibit the metabolism of *R*-warfarin although a clinically significant effect was unlikely.[16] No evidence of an interaction was found in a retrospective study[17] of patients on acenocoumarol and omeprazole. Similarly, *pantoprazole* appears to have no effect on the pharmacokinetics or pharmacodynamics of warfarin[18] or phenprocoumon.[19]

A marked increase in the effect of warfarin has been reported in a patient when *cisapride* was added.[20]

A study[21] in healthy subjects found that *aprepitant* caused a small decrease in plasma concentration of the more active *S*-isomer of warfarin and there was also a decrease in INR.

A reduction in the response to warfarin with development of venous thrombosis has been reported in a patient receiving *mesalazine*,[22] and in another patient receiving *sulfasalazine*.[23]

1. McElnay JC, *et al.* Interaction of warfarin with antacid constituents. *BMJ* 1978; **2:** 1166.
2. Ambre JJ, Fischer LJ. Effect of coadministration of aluminum and magnesium hydroxides on absorption of anticoagulants in man. *Clin Pharmacol Ther* 1973; **14:** 231–7.
3. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
4. Mungall D, *et al.* Sucralfate and warfarin. *Ann Intern Med* 1983; **98:** 557.
5. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; **25:** 745–6.
6. Parrish RH, *et al.* Sucralfate-warfarin interaction. *Ann Pharmacother* 1992; **26:** 1015–16.
7. Desmond PV, *et al.* Decreased oral warfarin clearance after ranitidine and cimetidine. *Clin Pharmacol Ther* 1984; **35:** 338–41.
8. Choonara IA, *et al.* Stereoselective interaction between the R enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; **21:** 271–7.
9. Sax MJ, *et al.* Effect of two cimetidine regimens on prothrombin time and warfarin pharmacokinetics during long-term warfarin therapy. *Clin Pharm* 1987; **6:** 492–5.
10. Toon S, *et al.* Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. *Eur J Clin Pharmacol* 1987; **32:** 165–72.
11. Serlin MJ, *et al.* Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979; **ii:** 317–19.
12. Gill TS, *et al.* Cimetidine-nicoumalone interaction in man: stereochemical considerations. *Br J Clin Pharmacol* 1989; **27:** 469–74.
13. Harenberg J, *et al.* Cimetidine does not increase the anticoagulant effect of phenprocoumon. *Br J Clin Pharmacol* 1982; **14:** 292–3.
14. Serlin MJ, *et al.* Lack of effect of ranitidine on warfarin action. *Br J Clin Pharmacol* 1981; **12:** 791–4.
15. Baciewicz AM, Morgan PJ. Ranitidine-warfarin interaction. *Ann Intern Med* 1990; **112:** 76–7.
16. Sutfin T, *et al.* Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther Drug Monit* 1989; **11:** 176–84.
17. Vreeburg EM, *et al.* Lack of effect of omeprazole on oral acenocoumarol anticoagulant therapy. *Scand J Gastroenterol* 1997; **32:** 991–4.
18. Duursema L, *et al.* Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1995; **39:** 700–3.
19. Ehrlich A, *et al.* Lack of pharmacodynamic and pharmacokinetic interaction between pantoprazole and phenprocoumon in man. *Eur J Clin Pharmacol* 1996; **51:** 277–81.
20. Darlington MR. Hypoprothrombinemia induced by warfarin sodium and cisapride. *Am J Health-Syst Pharm* 1997; **54:** 320–1.
21. Depré M, *et al.* Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Clin Pharmacol* 2005; **61:** 341–6.
22. Marinella MA. Mesalamine and warfarin therapy resulting in decreased warfarin effect. *Ann Pharmacother* 1998; **32:** 841–2.
23. Teefy AM, *et al.* Warfarin resistance due to sulfasalazine. *Ann Pharmacother* 2000; **34:** 1265–8.

Ginkgo biloba. There is a report[1] of a woman stabilised on warfarin for 5 years who suffered an intracerebral haemorrhage 2 months after starting *Ginkgo biloba*, possibly due to the additive effect of the latter's antiplatelet activity. However, a study[2] in healthy subjects found no evidence that ginkgo affected warfarin pharmacokinetics or coagulation.

1. Matthews MK. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology* 1998; **50:** 1933–4.
2. Jiang X, *et al.* Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 425–32.

Ginseng. A reduction in the response to warfarin was reported[1] in a patient after taking a ginseng preparation. A study[2] in healthy subjects also found a small reduction in response.

1. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health-Syst Pharm* 1997; **54:** 692–3.
2. Yuan C-S, *et al.* American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med* 2004; **141:** 23–7.

Glucagon. A dose-dependent enhancement of warfarin's anticoagulant activity has been reported with glucagon.[1]

1. Koch-Weser J. Potentiation by glucagon of the hypoprothrombinemic action of warfarin. *Ann Intern Med* 1970; **72:** 331–5.

Glucosamine. See Dietary Supplements, above.

Immunosuppressants. Severe bleeding occurred in a patient on long-term warfarin after stopping *azathioprine*,[1] while another patient[2] required an increased dose of warfarin when it was given with azathioprine.

There have been a few case reports of interaction between warfarin or acenocoumarol and *ciclosporin*, in which the dose of the anticoagulant or ciclosporin or both needed to be altered (see Anticoagulants under Interactions of Ciclosporin, p.1827).

There has been a report[3] of *leflunomide* enhancing the effects of warfarin, causing gross haematuria after the second dose; the patient's INR rose from 3.4 to 11. It was stated that the UK CSM had received 4 reports of increased INR with leflunomide up to the end of 2002.

1. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. *Am J Med* 1992; **92:** 217.
2. Rotenberg M, *et al.* Effect of azathioprine on the anticoagulant activity of warfarin. *Ann Pharmacother* 2000; **34:** 120–2.
3. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. *BMJ* 2002; **325:** 1333. Correction. *ibid.* 2003; **326:** 432.

Leukotriene antagonists. *Zafirlukast* is reported to decrease the clearance of *S*-warfarin.[1] Licensed product information for zafirlukast states that it probably inhibits the cytochrome P450 isoenzyme CYP2C9 which is involved in the metabolism of warfarin. Prothrombin time may be significantly prolonged when zafirlukast is added and warfarin dosage should be adjusted accordingly.

A study[2] of *montelukast* and warfarin found no significant interaction between the two drugs.

1. Suttle AB, *et al.* Effect of zafirlukast on the pharmacokinetics of R- and S-warfarin in healthy men. *Clin Pharmacol Ther* 1997; **61:** 186.
2. Van Hecken, *et al.* Effect of montelukast on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 495–500.

Levamisole. An increased INR has been reported[1] in a patient taking chronic warfarin therapy after addition of *levamisole* and fluorouracil, possibly due to inhibition of warfarin metabolism. Interactions between warfarin and other fluorouracil-containing regimens have been reported (see Antineoplastics, above) but levamisole might also be involved. In a second patient, a similar reaction was reported[2] after levamisole and fluorouracil and an episode of bleeding subsequently occurred after levamisole alone.

1. Scarfe MA, Israel MK. Possible drug interaction between warfarin and combination of levamisole and fluorouracil. *Ann Pharmacother* 1994; **28:** 464–7.
2. Wehbe TW, Warth JA. A case of bleeding requiring hospitalization that was likely caused by an interaction between warfarin and levamisole. *Clin Pharmacol Ther* 1996; **59:** 360–2.

Lipid regulating drugs. Fibrates have been reported to interact with coumarin anticoagulants. *Clofibrate* can enhance the activity of warfarin, sometimes to the point of haemorrhage. The mechanism of this interaction is not clear, but it does not appear to be a pharmacokinetic effect. Similar enhancement of activity has been reported with clofibrate and dicoumarol or phenindione. *Bezafibrate* has been reported to enhance the effect of phenprocoumon[1] and warfarin,[2] and *fenofibrate*[3] and *gemfibrozil*[4] have been reported to enhance the effect of warfarin, although a study[5] in healthy subjects found that gemfibrozil slightly decreased plasma-warfarin concentrations.

Interactions may also occur between statins and coumarin anticoagulants,[6] although there have been conflicting reports in some cases. Hypoprothrombinaemia and bleeding has been reported in 2 patients on warfarin given *lovastatin*.[7] An increased response to warfarin has also been reported[6,8,9] in a number of patients taking *fluvastatin*. A study[10] with *rosuvastatin* and warfarin reported an increased INR in healthy subjects and in patients on long-term warfarin therapy, although another study[11] found no effect. However, there have been reports of haematoma and raised INR in patients after addition of rosuvastatin to long-term therapy with warfarin[12] or acenocoumarol.[13] An increased response to warfarin has been observed with *simvastatin*,[14] including a fatal cerebral haemorrhage in a patient who was changed from atorvastatin to simvastatin,[15] and potentiation of the effect of acenocoumarol by simvastatin has also been reported.[16] However, the INR in another patient on long-term warfarin remained stable on the addition of simvastatin.[17] Licensed product information for *pravastatin* states that no change in warfarin activity has been seen in patients given both drugs, but there has been a report[18] of bleeding in a patient taking fluindione when pravastatin was added. In a study[19] of 46 patients on warfarin who had been converted from pravastatin to simvastatin, the mean INR increased, but the median weekly warfarin dose did not differ significantly and no episodes of bleeding were reported.

Dextrothyroxine increases the anticoagulant effect of warfarin sodium[20,21] and dicoumarol.[22]

Colestyramine has reduced warfarin's serum concentration[23] and half-life[24] as well as its activity.[23,24] The mechanisms of this interaction include binding of warfarin to colestyramine and reduced absorption;[23] the enterohepatic recycling of warfarin may also be interrupted.[24] Phenprocoumon's activity has also been reduced by colestyramine.[25] However, colestyramine can also reduce vitamin K absorption, and this may result in hypoprothrombinaemia and bleeding.

Use of *omega-3 fatty acids* (as fish oil preparations) in patients taking warfarin and other antithrombotics has been associated with INR elevation[26] and subdural haematoma.[27] However, controlled studies in patients taking fish oil and warfarin[28,29] have failed to show an effect on bleeding episodes or bleeding time.

Benfluorex[30] and *colestipol*[31] have been reported not to interact with phenprocoumon.

1. Zimmermann R, *et al.* The effect of bezafibrate on the fibrinolytic enzyme system and the drug interaction with racemic phenprocoumon. *Atherosclerosis* 1978; **29:** 477–85.
2. Beringer TRO. Warfarin potentiation with bezafibrate. *Postgrad Med J* 1997; **73:** 657–8.
3. Ascah KJ, *et al.* Interaction between fenofibrate and warfarin. *Ann Pharmacother* 1998; **32:** 765–8.
4. Ahmad S. Gemfibrozil interaction with warfarin sodium (Coumadin). *Chest* 1990; **98:** 1041–2.
5. Lilja JJ, *et al.* Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 433–9.
6. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy* 2004; **24:** 285–90.
7. Ahmad S. Lovastatin: warfarin interaction. *Arch Intern Med* 1990; **150:** 2407.
8. Trilli LE, *et al.* Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* 1996; **30:** 1399–1402.
9. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother* 1997; **31:** 790–1.
10. Simonson SG, *et al.* Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol* 2005; **45:** 927–34.
11. Jindal D, *et al.* Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. *Eur J Clin Pharmacol* 2005; **61:** 621–5.
12. Barry M. Rosuvastatin–warfarin drug interaction. *Lancet* 2004; **363:** 328.
13. Mondillo S, *et al.* Rosuvastatin–acenocoumarol interaction. *Clin Ther* 2005; **27:** 782–4.
14. Hickmott H, *et al.* The effect of simvastatin co-medication on warfarin anticoagulation response and dose requirements. *Thromb Haemost* 2003; **89:** 949–50.
15. Westergren T, *et al.* Probable warfarin–simvastatin interaction. *Ann Pharmacother* 2007; **41:** 1292–5.
16. Grau E, *et al.* Simvastatin-oral anticoagulant interaction. *Lancet* 1996; **347:** 405–6.
17. Gaw A, Wosornu D. Simvastatin during warfarin therapy in hyperlipoproteinaemia. *Lancet* 1992; **340:** 979–80.
18. Trenque T, *et al.* Pravastatin: interaction with oral anticoagulant? *BMJ* 1996; **312:** 886.
19. Lin JC, *et al.* The effect of converting from pravastatin to simvastatin on the pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; **39:** 86–90.
20. Owens JC, *et al.* Effect of sodium dextrothyroxine in patients receiving anticoagulants. *N Engl J Med* 1962; **266:** 76–9.
21. Solomon HM, Schrogie JJ. Change in receptor site affinity: a proposed explanation for the potentiating effect of D-thyroxine on the anticoagulant response to warfarin. *Clin Pharmacol Ther* 1967; **8:** 797–9.
22. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
23. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; **12:** 491–5.
24. Jähnchen E, *et al.* Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol* 1978; **5:** 437–40.
25. Meinertz T, *et al.* Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. *Clin Pharmacol Ther* 1977; **21:** 731–5.
26. Buckley MS, *et al.* Fish oil interaction with warfarin. *Ann Pharmacother* 2004; **38:** 50–3.
27. McClaskey EM, Michalets EL. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. *Pharmacotherapy* 2007; **27:** 152–60.
28. Eritsland J, *et al.* Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coag Fibrinol* 1995; **6:** 17–22.
29. Bender NK, *et al.* Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *J Thromb Thrombolysis* 1998; **5:** 257–61.
30. De Witte P, Brems HM. Co-administration of benfluorex with oral anticoagulant therapy. *Curr Med Res Opin* 1980; **6:** 478–80.
31. Harvengt C, Desager JP. Effect of colestipol, a new bile acid sequestrant, on the absorption of phenprocoumon in man. *Eur J Clin Pharmacol* 1973; **6:** 19–21.

Menthol. A significant decrease in INR was reported[1] in a patient stabilised on warfarin when he started using a menthol cough preparation.

1. Kassebaum PJ, *et al.* Possible warfarin interaction with menthol cough drops. *Ann Pharmacother* 2005; **39:** 365–7.

Pesticides. Chlorinated insecticides diminished the activity of warfarin in a patient.[1]

1. Jeffery WH, *et al.* Loss of warfarin effect after occupational insecticide exposure. *JAMA* 1976; **236:** 2881–2.

Piracetam. Piracetam caused an increase in prothrombin time in a patient who had been stabilised on warfarin.[1]

1. Pan HYM, Ng RP. The effect of Nootropil in a patient on warfarin. *Eur J Clin Pharmacol* 1983; **24:** 711.

Sex hormones. There have been reports of steroids with anabolic or androgenic properties enhancing the activity of anticoagulants to the point of haemorrhage. Reports have covered *oxymetholone* and warfarin[1-3] or acenocoumarol;[4] *stanozolol* and warfarin[5,6] or dicoumarol;[7] *ethylestrenol* and phenindione;[8] *norethandrolone* and dicoumarol;[9] *methyltestosterone* and phenprocoumon;[10] and *danazol* and warfarin.[11-13] The manufacturer of *oxandrolone* states that an 80 to 85% reduction in warfarin dose was needed when oxandrolone was added to treatment. The mechanism of this interaction is not clear although it is considered that it is not caused by altered pharmacokinetics. Steroids with a 17-α-alkyl substituent appear to be most involved, but there has been a report of topically applied testosterone, which does not have such a substituent, enhancing warfarin.[14]

A retrospective study[15] of women receiving anticoagulant therapy who were started on *HRT* found that *tibolone* enhanced the effect of warfarin and of phenindione, possibly due to its androgenic properties.

Oral contraceptives have also been implicated in interactions. However, while the effects of dicoumarol were diminished by a combined oral contraceptive,[16] those of acenocoumarol were enhanced by other preparations.[17] Combined oral contraceptives have increased the clearance of phenprocoumon without altering the anticoagulant effect.[18] There has also been a report[19] of a single course of *levonorgestrel* for emergency contraception increasing the effect of warfarin.

1. Robinson BHB, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **i:** 1356.
2. Longridge RGM, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 90.
3. Edwards MS, Curtis JR. Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; **ii:** 221.
4. de Oya JC, *et al.* Decreased anticoagulant tolerance with oxymetholone in paroxysmal nocturnal haemoglobinuria. *Lancet* 1971; **ii:** 259.
5. Acomb C, Shaw PW. A significant interaction between warfarin and stanozolol. *Pharm J* 1985; **234:** 73–4.
6. Shaw PW, Smith AM. Possible interaction of warfarin and stanozolol. *Clin Pharm* 1987; **6:** 500–2.
7. Howard W, *et al.* Anabolic steroids and anticoagulants. *BMJ* 1977; **1:** 1659–60.
8. Vere DW, Fearnley GR. Suspected interaction between phenindione and ethyloestrenol. *Lancet* 1968; **ii:** 281.
9. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; **8:** 70–7.
10. Husted S, *et al.* Increased sensitivity to phenprocoumon during methyltestosterone therapy. *Eur J Clin Pharmacol* 1976; **10:** 209–16.
11. Goulbourne IA, Macleod DAD. An interaction between danazol and warfarin: case report. *Br J Obstet Gynaecol* 1981; **88:** 950–1.
12. Meeks ML, *et al.* Danazol increases the anticoagulant effect of warfarin. *Ann Pharmacother* 1992; **26:** 641–2.
13. Booth CD. A drug interaction between danazol and warfarin. *Pharm J* 1993; **250:** 439–40.
14. Lorentz SMcQ, Weibert RT. Potentiation of warfarin anticoagulation by topical testosterone ointment. *Clin Pharm* 1985; **4:** 332–4.
15. McLintock LA, *et al.* Interaction between hormone replacement therapy preparations and oral anticoagulant therapy. *Br J Obstet Gynaecol* 2003; **110:** 777–9.
16. Schrogie JJ, *et al.* Effect of oral contraceptives on vitamin K-dependent clotting activity. *Clin Pharmacol Ther* 1967; **8:** 670–5.
17. de Teresa E, *et al.* Interaction between anticoagulants and contraceptives: an unsuspected finding. *BMJ* 1979; **2:** 1260–1.
18. Mönig H, *et al.* Effect of oral contraceptive steroids on the pharmacokinetics of phenprocoumon. *Br J Clin Pharmacol* 1990; **30:** 115–18.
19. Ellison J, *et al.* Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ* 2000; **321:** 1382.

St John's wort. St John's wort has been reported to reduce the anticoagulant effect of warfarin.[1]

1. Yue Q-Y, *et al.* Safety of St John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.

Thyroid and antithyroid drugs. Since response to oral anticoagulants is dependent on thyroid status an interaction between oral anticoagulants and thyroid or antithyroid drugs might be expected. Thyroid compounds do enhance the activity of oral anticoagulants possibly by increased metabolism of clotting factors. Dextrothyroxine is discussed under Lipid Regulating Drugs, above. Antithyroid compounds have not, however, been reported to diminish the effect of anticoagulants and paradoxically *propylthiouracil* has been reported to have caused hypoprothrombinaemia (see Effects on the Blood, under Carbimazole, p.2168). However, in a patient given *thiamazole* for Grave's disease, the response to warfarin varied depending on his thyroid status and thiamazole dose.[1]

1. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. *Ann Pharmacother* 2006; **40:** 1200–3.

Tobacco. Although tobacco smoking may increase warfarin clearance,[1] an appreciable effect on anticoagulant activity appears unlikely.[1,2] However, there has been a report[3] of an increase in INR in a patient receiving warfarin when he stopped smoking.

1. Bachmann K, *et al.* Smoking and warfarin disposition. *Clin Pharmacol Ther* 1979; **25:** 309–15.
2. Weiner B, *et al.* Warfarin dosage following prosthetic valve replacement: effect of smoking history. *Drug Intell Clin Pharm* 1984; **18:** 904–6.
3. Colucci VJ, Knapp JF. Increase in international normalized ratio associated with smoking cessation. *Ann Pharmacother* 2001; **35:** 385–6.

Ubidecarenone. Decreased INR values and reduced effect of warfarin has been reported[1] in 3 patients given ubidecarenone.

1. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; **344:** 1372–3.

Vaccines. There have been a few reports of increased prothrombin time and bleeding in warfarin-stabilised patients after *influenza vaccination*. Studies investigating this possible interaction have found only a small or inconsistent increase in warfarin activity[1,2] or no effect.[3-5] One study suggested that influenza vaccine decreases rather than increases the prothrombin time.[6] In a group of patients on long-term acenocoumarol therapy, influenza vaccination had no effect on acenocoumarol activity.[7]

1. Kramer P, *et al.* Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* 1984; **35:** 416–18.
2. Weibert RT, *et al.* Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm* 1986; **5:** 499–503.
3. Lipsky BA, *et al.* Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* 1984; **100:** 835–7.
4. Scott AK, *et al.* Lack of effect of influenza vaccination on warfarin in healthy volunteers. *Br J Clin Pharmacol* 1985; **19:** 144P–145P.
5. Gomolin IH. Lack of effect of influenza vaccine on warfarin anticoagulation in the elderly. *Can Med Assoc J* 1986; **135:** 39–41.
6. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm* 1988; **22:** 198–201.
7. Souto JC, *et al.* Lack of effect of influenza vaccine on anticoagulation by acenocoumarol. *Ann Pharmacother* 1993; **27:** 365–8.

Vitamins. Since vitamin K reverses the effects of oral anticoagulants, it is not surprising that there have been reports of *acetomenaphthone* and *phytomenadione* reducing anticoagulant activity, or of foods or nutritional preparations containing vitamin K compounds doing the same.

Occasional reports of *ascorbic acid* reducing the activity of warfarin[1,2] have not been confirmed in subsequent studies.[3,4] There have also been isolated reports suggesting that *vitamin E* may enhance the activity of warfarin[5] or dicoumarol,[6] although no effect was found in a study[7] of patients receiving warfarin and vitamin E.

1. Rosenthal G. Interaction of ascorbic acid and warfarin. *JAMA* 1971; **215:** 1671.
2. Smith EC, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **221:** 1166.
3. Hume R, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; **219:** 1479.
4. Feetam CL, *et al.* Lack of a clinically important interaction between warfarin and ascorbic acid. *Toxicol Appl Pharmacol* 1975; **31:** 544–7.
5. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974; **230:** 1300–1.
6. Schrogie JJ. Coagulopathy and fat-soluble vitamins. *JAMA* 1975; **232:** 19.
7. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* 1996; **77:** 545–6.

Pharmacokinetics

Warfarin sodium is readily absorbed from the gastrointestinal tract; it can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 37 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is used as a racemic mixture; the *S*-isomer is more potent. The *R*- and *S*-isomers are both metabolised in the liver. The *S*-isomer is metabolised more rapidly than the *R*-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes are also involved in the metabolism of the *R*-isomer. The stereoisomers may be affected differently by other drugs (see Interactions, above). Metabolites, with negligible or no anticoagulant activity, are excreted in the urine following reabsorption from the bile.

◊ References.

1. Mungall DR, *et al.* Population pharmacokinetics of racemic warfarin in adult patients. *J Pharmacokinet Biopharm* 1985; **13:** 213–27.
2. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose-effect relationship. *Clin Pharmacokinet* 1986; **11:** 483–504.
3. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 2001; **40:** 587–603.

Uses and Administration

Warfarin is a coumarin anticoagulant used in the treatment and prophylaxis of thromboembolic disorders (p.1187). It acts by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p.1045. Since warfarin acts indirectly, it has no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Warfarin is used in the prevention and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189). If an immediate effect on blood coagulation is required, heparin should be given intravenously or subcutaneously to cover the first 2 to 3 days. Warfarin therapy may be begun with, or shortly after, initial heparin treatment. Warfarin is also used for the prevention of systemic thromboembolism and ischaemic stroke in some patients with atrial fibrillation (p.1160), prosthetic heart valves (see Valvular Heart Disease, p.1187), or who have suffered a myocardial infarction (p.1175). It may also have a role in the prevention of myocardial infarction and in the management of stroke or transient ischaemic attacks (p.1185). Antiplatelet drugs may be given concomitantly.

Some patients may show a hereditary resistance to warfarin. Warfarin is a potent rodenticide although resistance has been reported in *rats*.

Administration and dosage. Warfarin is equally effective either orally or intravenously, but is usually given orally. Dosage must be determined individually as discussed below under Control of Anticoagulant Therapy. When rapid anticoagulation is required, an initial dose of warfarin sodium 10 mg may be given on the first day, although in many cases an initial dose of 5 mg daily is adequate; initial doses of less than 5 mg daily may be used in elderly patients and in those at increased risk of bleeding (see Precautions, above). Subsequent doses depend on the results of coagulation tests, but maintenance doses usually range from 3 to 9 mg daily. If necessary the same dose may be given by slow intravenous injection. Doses of warfarin sodium should be given at the same time each day. Theoretically, stopping warfarin abruptly may result in rebound hypercoagulability with risk of thrombosis. Therefore some clinicians tail off long-term treatment over several weeks but the need for this is unclear and the *British Society for Haematology* suggests that treatment may be stopped abruptly. Anticoagulant treatment booklets should be carried by patients.

Warfarin has also been given as the potassium salt; warfarin-deanol has been tried.

Control of oral anticoagulant therapy. Treatment with oral anticoagulants must be monitored to ensure that the dose is providing the required effect on the vitamin-K-dependent clotting factors; too small a dose provides inadequate anticoagulation, too large a dose puts the patient at risk of haemorrhage. This monitoring is commonly carried out by checking the clotting property of the patient's plasma using a suitable preparation of thromboplastin and a source of calcium. The time taken for the clot to form due to the effect of the thromboplastin preparation on prothrombin is known as the prothrombin time (PT). The prothrombin time ratio (PTR) is the prothrombin time of the patient's plasma divided by that for a standard plasma sample.

So that there is some consistency in prothrombin time ratios measured at different times or at different laboratories, it is now common practice for the manufacturer or control laboratory to calibrate their batches of thromboplastin against the international reference preparation. This calibration produces an international sensitivity index (ISI) appropriate to that thromboplastin. The laboratory measuring the clotting capacity of a sample of plasma is thus able to convert the prothrombin time ratio to an international normalised ratio (INR) using the sensitivity index through the formula

$$\text{INR} = \text{PTR}^{(\text{ISI})}$$

Thus a prothrombin time ratio of 2.0 obtained with a thromboplastin with a declared international sensitivity index of 1.5 would be converted to an international normalised ratio of 2.8. An international normalised ratio is therefore equivalent to a prothrombin time ratio carried out using the primary international reference preparation of thromboplastin.

This method of standardisation has taken over from methods involving use of a standard reagent such as the British or Manchester comparative thromboplastin. Preparations of thromboplastin derived from *rabbit* brain have superseded or are superseding those from human brain because of the dangers of viral transmission; a recombinant human form is also available.

Recommended target values or ranges of international normalised ratio for patients receiving anticoagulant treatment or cover for various conditions or procedures are given by the *British Society for Haematology* in the UK and the *American College of Chest Physicians*.

These are given in Table 6, below. An INR within 0.5 units of the target value in the UK is generally considered satisfactory. In the USA it is recommended that the INR be maintained at the mid-level of the range. An INR less than 2.0 generally represents inadequate anticoagulation and an INR above 4.5 represents greater risk of haemorrhage.

Measurements should be carried out before treatment and then daily or on alternate days in the early stages of treatment. Once the dose has been established and the patient well stabilised the measurement can be made at greater but regular intervals, for example every 8 weeks; allowances should be made for any events that might influence the activity of the anticoagulant. Self-monitoring may be appropriate in some patients.

◊ General references.

1. Harrington R, Ansell J. Risk-benefit assessment of anticoagulant therapy. *Drug Safety* 1991; **6:** 54–69.
2. Le DT, *et al.* The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. *Ann Intern Med* 1994; **120:** 552–8.
3. British Society for Haematology: British Committee for Standards in Haematology—Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation: third edition. *Br J Haematol* 1998; **101:** 374–87. Also available at: http://www.bcshguidelines.com/pdf/bjh715.pdf (accessed 25/02/05) Updated 2005 guidelines. Update: Baglin T, *et al*, for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition—2005 update. *Br J Haematol* 2006; **132:** 277–85. Also available at: http://www.bcshguidelines.com/pdf/oralanticoagulation.pdf (accessed 07/06/06)
4. Hardman SMC, Cowie MR. Anticoagulation in heart disease. *BMJ* 1999; **318:** 238–44.
5. Gage BF, *et al.* Management and dosing of warfarin therapy. *Am J Med* 2000; **109:** 481–8.
6. Hirsh J, *et al.* American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 2003; **107:** 1692–1711. Also available at: http://circ.ahajournals.org/cgi/reprint/107/12/1692.pdf (accessed 25/02/05)
7. Fitzmaurice DA, *et al.* British Society of Haematology Taskforce for Haemostasis and Thrombosis. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol* 2005; **131:** 156–65. Correction. *ibid.* 2006; **132:** 118. Also available at: http://www.bcshguidelines.com/pdf/fitzmaurice_100306.pdf (accessed 27/05/08)
8. Ansell J, *et al.* Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 160S–198S.

Administration and dosage. Algorithms and guidelines have been developed for beginning anticoagulant therapy, based on the method of Fennerty *et al.*[1] Although a loading dose of 10 mg daily for 2 days (depending on the INR) has been widely used, lower doses may be more appropriate, especially in hospitalised patients at greater risk of over-anticoagulation. Studies[2-4] comparing warfarin loading doses of 5 and 10 mg found that for both groups a therapeutic INR in the range of 2.0 to 3.0 was reached in most patients by day 5 of treatment. Although a study of outpatients with venous thromboembolism[5] found that a therapeutic INR was achieved 1.4 days sooner with the larger loading dose, the nomogram used was not designed for inpatients.

In situations where rapid anticoagulation is not necessary, loading doses may not be required and treatment should begin with the estimated maintenance dose. Studies[6,7] have found that the maintenance dose decreases with age and is lower in women than in men, and lower initial doses are therefore recommended in the elderly. Regimens that have been suggested include warfarin in a dose of 4 mg daily for 3 days, then adjusted according to the INR,[8] or, for patients requiring anticoagulation prophylaxis, 2 mg daily for 2 weeks followed by weekly adjustment using an algorithm until the target INR is reached.

1. Fennerty A, *et al.* Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ* 1984; **288:** 1268–70.
2. Harrison L, *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; **126:** 133–6.
3. Crowther MA, *et al.* Warfarin: less may be better. *Ann Intern Med* 1997; **127:** 333.
4. Crowther MA, *et al.* A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; **159:** 46–8.
5. Kovacs MJ, *et al.* Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003; **138:** 714–19.
6. Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. *Am J Health-Syst Pharm* 2005; **62:** 1062–6.
7. Garcia D, *et al.* Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005; **127:** 2049–56.
8. Siguret V, *et al.* Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005; **118:** 137–42.

Administration in infants and children. Increasing numbers of infants and children are receiving anticoagulants for prophylaxis and treatment of thromboembolism. Doses of warfarin and therapeutic INR ranges have been adapted from adult therapy but cohort studies[1,2] of paediatric patients have found that warfarin requirements may be affected by a number of factors including age, and the use of infant formulas supplemented with vitamin K. Recommendations[3] for the use of oral anticoagulants in children have been published.

1. Tait RC, *et al.* Oral anticoagulation in paediatric patients: dose requirements and complications. *Arch Dis Child* 1996; **74:** 228–31.
2. Streif W, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999; **94:** 3007–14.
3. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Catheters and cannulas. For mention of the use of oral anticoagulants to prevent thrombosis in patients with indwelling infusion devices, see Heparin Sodium, p.1304.

Connective tissue and muscular disorders. Warfarin has been proposed to treat subcutaneous calcium deposition (calcinosis cutis) in patients with dermatomyositis, but its value is disputed, see Polymyositis and Dermatomyositis, p.1510.

Table 6. Recommended International Normalised Ratios (INR).

	INR	Condition or procedure
UK	2.5	Pulmonary embolism; deep-vein thrombosis; recurrence of venous thromboembolism when no longer on warfarin; symptomatic inherited thrombophilia; venous thromboembolism associated with antiphospholipid syndrome; atrial fibrillation; mural thrombus; cardiomyopathy; bioprosthetic heart valves.
	2.5 or 3.0	Cardioversion (higher INR may be appropriate before procedure); some mechanical prosthetic heart valves.
	3.5	Recurrence of venous thromboembolism when on warfarin; some mechanical prosthetic heart valves.
US	2.0 to 3.0	Prophylaxis of venous thromboembolism in high-risk surgical patients; treatment of venous thrombosis and pulmonary embolism; prophylaxis of systemic embolism in patients with atrial fibrillation, valvular heart disease, bioprosthetic heart valves or some mechanical prosthetic heart valves; prevention of recurrent myocardial infarction in patients receiving aspirin.
	2.5 to 3.5	Prophylaxis in patients with some mechanical prosthetic heart valves.
	3.0 to 4.0	Prevention of recurrent myocardial infarction in patients not receiving aspirin; systemic embolism in patients with some mechanical heart valves.

Preparations

BP 2008: Warfarin Tablets;
USP 31: Warfarin Sodium for Injection; Warfarin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Circuvit; Coumadin; ***Austral.:*** Coumadin; Marevan; ***Belg.:*** Marevan; ***Braz.:*** Coumadin; Marevan; ***Canad.:*** Coumadin; ***Chile:*** Coumadin; ***Cz.:*** Lawarin; ***Denm.:*** Marevan; ***Fin.:*** Marevan; ***Fr.:*** Coumadine; ***Ger.:*** Coumadin; ***Gr.:*** Marevan; Panwarfin; ***Hung.:*** Marfarin; ***India:*** Uniwarfin; Warf; ***Indon.:*** Simarc-2; ***Irl.:*** Warfant; ***Israel:*** Coumadin; ***Ital.:*** Coumadin; ***Malaysia:*** Coumadin; Orfarin; ***Mex.:*** Coumadin; ***Norw.:*** Marevan; ***NZ:*** Coumadin; Marevan; ***Philipp.:*** Coumadin; ***Port.:*** Varfine; ***Rus.:*** Warfarex (Варфарекс); ***S.Afr.:*** Coumadin†; ***Singapore:*** Coumadin; Marevan; Orfarin; ***Spain:*** Aldocumar; Tedicumar; ***Swed.:*** Waran; ***Thai.:*** Befarin; Fargem; Maforan; Orfarin; ***Turk.:*** Coumadin; Orfarin; ***UK:*** Marevan; ***USA:*** Coumadin; Jantoven; ***Venez.:*** Anasmol; Coumadin; Cumar.

Xamoterol Fumarate *(BANM, USAN, rINNM)*

Fumarato de xamoterol; ICI-118587; Ksamoterolfumarat; Ksamoterolifumaraatti; Xamotérol, Fumarate de; Xamoteroli Fumaras. *N*-{2-[2-Hydroxy-3-(4-hydroxyphenoxy)propylamino]-ethyl}morpholine-4-carboxamide fumarate.

Ксамотерола Фумарат

$(C_{16}H_{25}N_3O_5)_2,C_4H_4O_4 = 794.8.$
CAS — 81801-12-9 (xamoterol); 90730-93-1 (xamoterol fumarate).
ATC — C01CX07.
ATC Vet — QC01CX07.

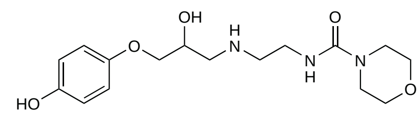

(xamoterol)

Profile

Xamoterol is a beta-adrenoceptor partial agonist with a selective action on beta$_1$ receptors. As a partial agonist it exerts mainly agonist activity at rest and under conditions of low sympathetic drive which results in improved ventricular function and increased cardiac output; during exercise and during conditions of increased sympathetic drive, such as that occurring in severe heart failure, xamoterol exerts beta-blocking activity. It therefore has the properties of both sympathomimetics (see p.1407) and beta blockers (see p.1225).

Xamoterol has been used in the management of chronic mild heart failure but was associated with deterioration and an excess of deaths in those with more severe disease. It has also been used in orthostatic hypotension secondary to autonomic failure.

◊ References.

1. Anonymous. Xamoterol—more trouble than it's worth? *Drug Ther Bull* 1990; **28:** 53–4.
2. Anonymous. New evidence on xamoterol. *Lancet* 1990; **336:** 24.
3. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990; **336:** 1–6.

Xantinol Nicotinate *(BAN, rINN)*

Ksantinolinikotinaatti; Ksantynolu nikotynian; Nicotinato de xantinol; SK-331A; Xanthinol Niacinate *(USAN)*; Xanthinol Nicotinate; Xanthinol nikotinát; Xantinol, Nicotinate de; Xantinoli Nicotinas; Xantinolnikotinat. 7-{2-Hydroxy-3-[(2-hydroxyethyl)methylamino]propyl}theophylline nicotinate.

Ксантинола Никотинат

$C_{13}H_{21}N_5O_4,C_6H_5NO_2 = 434.4.$
CAS — 437-74-1.
ATC — C04AD02.
ATC Vet — QC04AD02.

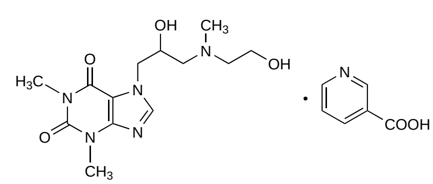

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Xantinol nicotinate is a vasodilator with general properties similar to those of nicotinic acid (p.1957), to which it is slowly hydrolysed. Xantinol nicotinate is used in the management of peripheral (p.1178) and cerebral vascular disorders (p.1165) and in hyperlipidaemias (p.1169). Oral doses of up to 3 g daily may be given. It has also been given by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Frigol; ***Cz.:*** Xanidil; ***Ger.:*** Complamin spezial; ***Hung.:*** Xavin; ***India:*** Complamina; ***Ital.:*** Complamin; Vedrin†; ***Neth.:*** Complamin; ***Pol.:*** Sadamin; ***Switz.:*** Complamin.

Multi-ingredient: ***Spain:*** Rulun.

Xemilofiban Hydrochloride *(USAN, rINNM)*

Hidrocloruro de xemilofibán; SC-54684A; Xémilofiban, Chlorhydrate de; Xemilofibani Hydrochloridum. Ethyl (3*S*)-3-{3-[(*p*-amidinophenyl)carbamoyl]propionamido}-4-pentynoate monohydrochloride.

Ксемилофибана Гидрохлорид

$C_{18}H_{22}N_4O_4,HCl = 394.9.$

CAS — 149820-74-6 (xemilofiban); 156586-91-3 (xemilofiban hydrochloride).

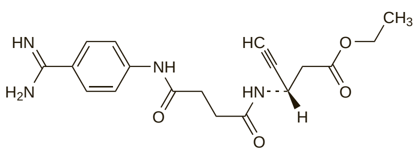

(xemilofiban)

Profile

Xemilofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug for the management of thromboembolic disorders such as unstable angina, and after angioplasty, but results have been disappointing.

◊ References.

1. O'Neill WW, *et al.* Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. *N Engl J Med* 2000; **342:** 1316–24.

Xipamide *(BAN, USAN, rINN)* ⊗

Be-1293; Ksipamidi; MJF-10938; Xipamid; Xipamida; Xipamidum. 4-Chloro-5-sulphamoylsalicylo-2′,6′-xylidide; 5-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxy-benzamide.

Ксипамид

$C_{15}H_{15}ClN_2O_4S = 354.8.$

CAS — 14293-44-8.

ATC — C03BA10.

ATC Vet — QC03BA10.

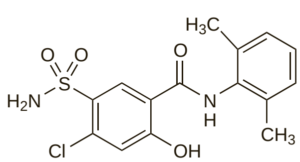

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Effects on electrolyte balance. Although reductions in plasma-potassium concentrations with xipamide have been shown to be on average comparable with those produced by thiazide and loop diuretics at equipotent doses,[1] there have been several reports of marked hypokalaemia in individual patients. Asymptomatic hypokalaemia was reported in 4 of 5 patients[2] (serum-potassium concentrations of less than 3.4 mmol/litre) and in 3 of 13 patients[3] (serum-potassium concentrations of less than 3.0 mmol/litre). Severe hypokalaemia resulting in ventricular arrhythmias has been reported after xipamide used alone[4] or with indapamide.[5] Profound electrolyte disturbances with altered consciousness and ventricular extrasystoles occurred in a patient taking digoxin after the addition of xipamide for 10 days.[6] A case of hypokalaemic periodic paralysis associated with xipamide use has also been reported.[7]

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.
2. Weissberg P, Kendall MJ. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
3. Raftery EB, *et al.* A study of the antihypertensive action of xipamide using ambulatory intra-arterial monitoring. *Br J Clin Pharmacol* 1981; **12:** 381–5.
4. Altmann P, Hamblin JJ. Ventricular fibrillation induced by xipamide. *BMJ* 1982; **284:** 494.
5. Boulton AJM, Hardisty CA. Ventricular arrhythmias precipitated by treatment with non-thiazide diuretics. *Practitioner* 1982; **226:** 125–8.
6. Bentley J. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
7. Boulton AJM, Hardisty CA. Hypokalaemic periodic paralysis precipitated by diuretic therapy and minor surgery. *Postgrad Med J* 1982; **58:** 106–7.

Hepatic impairment. For a recommendation that xipamide should be given with caution to patients with liver disease, see under Pharmacokinetics, below.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Xipamide has been reported to be well absorbed from the gastrointestinal tract. Absorption is fairly rapid with peak plasma concentrations occurring within 1 or 2 hours of oral doses. It is 99% bound to plasma proteins, and is excreted in the urine, partly unchanged and partly in the form of the glucuronide metabolite. It is reported to have a plasma half-life of about 5 to 8 hours. In patients with renal impairment excretion in the bile becomes more prominent.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Hepatic impairment. Xipamide was present in the plasma and in ascitic fluid in patients with liver cirrhosis in proportion to the protein content of the respective compartments.[1] The amount of drug excreted into the urine was much greater in patients with liver disease than in healthy control subjects. This was attributed to a diminution in hepatic elimination, which could result in significant effects on the clinical response to xipamide. Thus patients with cholestasis could have an enhanced response to xipamide. On the other hand cirrhotic patients with the hepatorenal syndrome may be resistant to diuretics. Xipamide should be used with caution in patients with liver disease.

1. Knauf H, *et al.* Xipamide disposition in liver cirrhosis. *Clin Pharmacol Ther* 1990; **48:** 628–32.

Renal impairment. After single oral and intravenous doses of xipamide 20 mg the drug appeared to be completely absorbed from the gastrointestinal tract.[1] The mean elimination half-life in healthy subjects was 7 hours and two-thirds of the clearance was by extrarenal routes. There was some accumulation in patients with chronic renal failure, with a calculated elimination half-life of 9 hours in end-stage renal disease.

1. Knauf H, Mutschler E. Pharmacodynamics and pharmacokinetics of xipamide in patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; **26:** 513–20.

Uses and Administration

Xipamide is a diuretic, structurally related to indapamide, with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis begins about 1 or 2 hours after an oral dose, reaches a peak at 4 to 6 hours, and lasts for about 12 hours.

In the treatment of **hypertension** the usual dose is 20 mg daily as a single morning dose, either alone, or with other antihypertensives. In some patients a dose of 10 mg daily may be adequate. In the treatment of **oedema** the usual initial dose is 40 mg daily, subsequently reduced to 20 mg daily, according to response; in resistant cases 80 mg daily may be required.

◊ References.

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Aquaphoril; ***Fr.:*** Lumitens†; ***Ger.:*** Aquaphor; Aquex; Xipa; Xipalsis; Xipagamma; ***India:*** Xipamid; ***Ital.:*** Aquafor†; ***Port.:*** Diurexan; ***S.Afr.:*** Diurexan†; ***Spain:*** Demiax†; Diurex; ***UK:*** Diurexan.

Multi-ingredient: ***Ger.:*** Durotan†; Neotri.

Zofenopril Calcium *(BANM, USAN, rINNM)*

Calcii Zofenoprilum; SQ-26991; Zofenopril cálcico; Zofénopril Calcique. Calcium salt of (4*S*)-1-[(2*S*)-3-(Benzylthio)-2-methylpropionyl]-4-(phenylthio)-L-proline.

Кальций Зофеноприл

$C_{44}H_{44}CaN_2O_8S_4 = 897.2.$

CAS — 81872-10-8 (zofenopril); 81938-43-4 (zofenopril calcium).

ATC — C09AA15.

ATC Vet — QC09AA15.

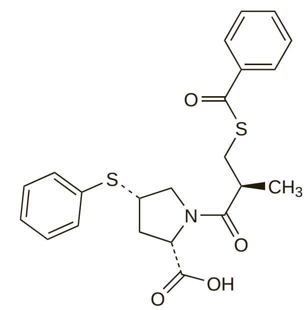

(zofenopril)

Profile

Zofenopril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171) and myocardial infarction (p.1175). It owes its activity to the active metabolite zofenoprilat (SQ-26333) to which it is converted after oral doses. It is given orally in a usual daily maintenance dose of 30 to 60 mg of the calcium salt, as a single dose or in two divided doses.

◊ References.

1. Ambrosioni E, *et al.* The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995; **332:** 80–5.
2. Borghi C, *et al.* Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension: SMILE study investigators: Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens* 1999; **12:** 665–72.
3. Borghi C, *et al.* A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. *Expert Opin Pharmacother* 2004; **5:** 1965–77.
4. Buikema H. Use of the ACE inhibitor zofenopril in the treatment of ischemic heart disease. *Expert Rev Cardiovasc Ther* 2006; **4:** 631–47.
5. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. *Am J Cardiovasc Drugs* 2007; **7:** 17–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Bifril; ***Fr.:*** Zofenil; ***Gr.:*** Zofepril; Zopranol; ***Irl.:*** Zofenil; ***Ital.:*** Bifril; Zantipres; Zopranol; ***Neth.:*** Zofil; Zopranol; ***Port.:*** Zofenil; Zopranol; ***Rus.:*** Zocardis (Зокардис); ***Spain:*** Zofenil; Zopranol; ***Swed.:*** Bifril†; ***Switz.:*** Zofenil; ***Turk.:*** Zoprotec.

Multi-ingredient: ***Fr.:*** Zofenilduo; ***Gr.:*** Zofepril Plus; Zopranol Plus; ***Ital.:*** Bifrizide; Zantipride; Zoprazide; ***Port.:*** Zofenil Plus.

Chelators Antidotes and Antagonists

The drugs included in this chapter act in a variety of ways to counter the toxic effects of exogenous and endogenous substances in the body. They are therefore used in the management of poisoning and overdosage, to protect against the toxicity of drugs such as antineoplastics, and in the management of metabolic disorders such as Wilson's disease where toxic substances accumulate.

The main groups of drugs used include:

- antagonists, such as the opioid antagonist naloxone, that compete with the poison for receptor sites. Other antagonists act by blocking substances that mediate the effects of the toxin; atropine (p.1219) acts in this way
- chelators and other drugs that form complexes with the toxin. This may reduce absorption of the toxin from the gastrointestinal tract, inactivate or reduce the activity of the toxin, or increase its elimination
- drugs that affect the metabolism of the toxin. Some antidotes, such as fomepizole in methyl alcohol poisoning, act by reducing the rate of metabolism to a toxic metabolite; alcohol (p.1625) has a similar action. Others, such as methionine and glutathione, promote the formation of inactive metabolites; acetylcysteine (p.1548) also acts in this way
- drugs that bypass the effect of the toxin. Calcium folinate (p.1943) is used for this purpose in methotrexate overdosage.

Acute poisoning

In the management of suspected acute poisoning it is often impossible to determine the identity of the poison or the size of the dose received with any certainty. Moreover, few poisons have specific antidotes or methods of elimination, and the mainstay of treatment for patients with suspected acute poisoning is therefore supportive and symptomatic therapy; in many cases nothing further is required. Symptoms of acute poisoning are frequently non-specific, particularly in the early stages. Maintenance of the airway and ventilation is the most important initial measure; other treatment, for example for cardiovascular or neurological symptoms, may be added as appropriate. Patients who are unconscious or who have respiratory depression may be given naloxone, particularly if opioid overdosage is a possibility. Some centres also recommend the routine administration of glucose to all unconscious patients since hypoglycaemia may be a cause of unconsciousness, although blood glucose measurements should be obtained first where facilities are immediately available; thiamine may be given in addition since glucose may precipitate Wernicke's encephalopathy.

Specific antidotes are available for a number of poisons and are the primary treatment where there is severe poisoning with a known toxin. They may be life-saving in such cases but their use is not without hazard and in many situations they are not necessary; their use does not preclude relevant supportive treatment.

Measures to reduce or prevent the absorption of the poison are widely advocated. For inhalational poisoning the victim is removed from the source of poisoning. Some toxins, in particular pesticides, may be absorbed through the skin, and clothing should be removed and the skin thoroughly washed to avoid continued absorption. Caustic substances are removed from the skin or eyes with copious irrigation. However, for orally ingested poisons the best method for gastrointestinal decontamination remains controversial.

Activated charcoal adsorbs a wide range of toxins and is often given to reduce absorption from the gastrointestinal tract. A single dose is generally effective, particularly if it is given within one hour of ingestion, although delayed use may be beneficial for modified-release preparations or for drugs that slow gastrointestinal transit time, such as those with antimuscarinic properties. Charcoal is generally well tolerated, although vomiting is common and there is a risk of aspiration if the airway is not adequately protected. Repeated doses may be of use to eliminate some substances even after systemic absorption has occurred.

Active removal of poisons from the stomach by induction of emesis or gastric lavage has been widely used, but there is little evidence to support its role (see under Ipecacuanha, p.1563). Induction of emesis with an emetic such as syrup of ipecacuanha has been used but is no longer recommended for either the home or hospital situation since there is no evidence that it improves outcomes and it may increase the risk of aspiration. If used at all, it should only be in fully conscious patients, where a potentially toxic amount has been ingested within the previous hour, and where other measures are unavailable or inappropriate. Emesis should not be induced if the poison is corrosive or petroleum based, nor if the poison is removable by treatment with activated charcoal. Gastric lavage may occasionally be indicated for ingestion of non-caustic poisons that are not absorbed by activated charcoal, but only if less than one hour has elapsed since ingestion; it should not be attempted if the airway is not adequately protected.

Whole-bowel irrigation using a non-absorbable osmotic agent such as a macrogol has also been used, particularly for substances that pass beyond the stomach before being absorbed, such as iron preparations or enteric-coated or modified-release formulations, but its role is not established.

Techniques intended to promote the elimination of poisons from the body, such as haemodialysis or haemoperfusion, are only of value for a limited number of poisons in a few severely poisoned patients. Forced diuresis is no longer recommended, although alkalinisation of the urine using sodium bicarbonate infusion may have a role for selected poisons. Repeated oral doses of activated charcoal may be as effective as these more invasive methods for some drugs that undergo enterohepatic or enteroenteric recycling.

Poisons Information Centres exist in many countries and should be consulted for more detailed information in specific situations.

Activated Charcoal

Aktif Kömür; Aktiivihiili; Aktivált szén; Aktyvintosios anglys; Carbo activatus; Carbo Medicinalis; Carbón activado; Charbon activé; Decolorising Charcoal; Kol, aktivt; Medicinal Charcoal; Uhlí aktivní; Węgiel leczniczy.

CAS — 16291-96-6 (charcoal).
ATC — A07BA01.
ATC Vet — QA07BA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Charcoal, Activated). It is obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power. A black, light powder free from grittiness. Practically insoluble in all usual solvents. It adsorbs not less than 40% of its own weight of phenazone, calculated with reference to the dried substance. Store in airtight containers.

USP 31 (Activated Charcoal). The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. A fine, black, odourless, tasteless powder, free from gritty matter. The USP 31 has tests for adsorptive power in respect of alkaloids and dyes.

Adverse Effects and Precautions

Activated charcoal is relatively non-toxic when given by mouth but gastrointestinal disturbances such as vomiting, constipation, or diarrhoea have been reported. It may colour the faeces black. Activated charcoal should be used with caution in patients at risk of gastrointestinal obstruction as it may reduce gastrointestinal motility.

Haemoperfusion with activated charcoal has produced various adverse effects including platelet aggregation, charcoal embolism, thrombocytopenia, haemorrhage, hypoglycaemia, hypocalcaemia, hypothermia, and hypotension.

Care is needed if activated charcoal is used in patients receiving specific oral antidotes such as methionine (see Interactions, below). As with any treatment given by mouth for poisoning the risk of aspiration should be considered in drowsy or comatose patients.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are the main complication of oral activated charcoal. Vomiting may occur and is a risk factor for pulmonary aspiration (see Effects on the Lungs, below). Although some preparations may cause diarrhoea, activated charcoal may reduce gastrointestinal motility and multiple doses have been associated with intestinal obstruction or faecal impaction,[1-4] in some cases leading to ulceration[5] or perforation;[6] overdosage with drugs that reduce gastrointestinal motility may increase the risk.[2,3,6] Two cases of pseudo-obstruction, one of which was fatal, have also been reported[7] after the use of activated charcoal and sorbitol with opioid sedation for theophylline poisoning. In another report,[8] severe peritonitis developed in a patient given oral activated charcoal following gastric lavage; charcoal was found in the peritoneum, although the site of perforation could not be detected. Acute appendicitis has also been reported after multiple doses of activated charcoal.[9]

1. Watson WA, *et al.* Gastrointestinal obstruction associated with multiple-dose activated charcoal. *J Emerg Med* 1986; **4:** 401–7.
2. Anderson IM, Ware C. Syrup of ipecacuanha. *BMJ* 1987; **294:** 578.
3. Ray MJ, *et al.* Charcoal bezoar: small-bowel obstruction secondary to amitriptyline overdose therapy. *Dig Dis Sci* 1988; **33:** 106–7.
4. Atkinson SW, *et al.* Treatment with activated charcoal complicated by gastrointestinal obstruction requiring surgery. *BMJ* 1992; **305:** 563.
5. Mizutani T, *et al.* Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning. *Hum Exp Toxicol* 1991; **10:** 385–6.
6. Gomez HF, *et al.* Charcoal stercolith with intestinal perforation in a patient treated for amitriptyline ingestion. *J Emerg Med* 1994; **12:** 57–60.
7. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7:** 74–7.
8. Mariani PJ, Pook N. Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. *Ann Emerg Med* 1993; **22:** 606–9.
9. Eroglu A, *et al.* Multiple dose-activated charcoal as a cause of acute appendicitis. *J Toxicol Clin Toxicol* 2003; **41:** 71–3.

Effects on the lungs. Vomiting after oral activated charcoal for acute poisoning has been associated with pulmonary aspiration of gastric contents, sometimes with fatal results.[1-3] Vomiting may be related to the formulation used and may be increased with sorbitol-containing preparations,[4] although a study in children[5] failed to confirm this. The use of a cuffed endotracheal tube has been recommended for any patient with impaired laryngeal reflexes to prevent aspiration;[3] however, there have been reports of aspiration despite a protected airway, including a case of obstructive laryngitis in a child.[6] Acute[7] and chronic[8] pulmonary toxicity has also been reported after accidental administration of charcoal into the lung due to misplacement of the nasogastric tube.

1. Harsch HH. Aspiration of activated charcoal. *N Engl J Med* 1986; **314:** 318.
2. Menzies DG, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 459–60.
3. Rau NR, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 918–19.
4. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; **27:** 358–61.
5. Osterhoudt KC, *et al.* Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics* 2004; **113:** 806–10.
6. Donoso A, *et al.* Activated charcoal laryngitis in an intubated patient. *Pediatr Emerg Care* 2003; **19:** 420–1.
7. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med* 1993; **22:** 1470–3.
8. Graff GR, *et al.* Chronic lung disease after activated charcoal aspiration. *Pediatrics* 2002; **109:** 959–61.

Interactions

Activated charcoal has the potential to reduce the absorption of many drugs from the gastrointestinal tract and simultaneous oral therapy should therefore be avoided. In the management of acute poisoning, concurrent medication should be given parenterally. Care is needed if a specific oral antidote such as methionine is given since adsorption of the antidote may decrease its effectiveness; it has been recommended that activated charcoal should be cleared from the stomach or avoided if oral antidotes are to be used.

Uses and Administration

Activated charcoal can adsorb a wide range of plant and inorganic poisons and many drugs including salicylates, paracetamol, barbiturates, and tricyclic antidepressants; when given orally it reduces their systemic absorption from the gastrointestinal tract and is therefore used in the treatment of acute oral poisoning. It is of no value for poisoning by strong acids, alkalis, or other corrosive substances and its adsorptive capacity is too low to be of use in poisoning with iron salts, cyanides, lithium, malathion, clofenotane, and some organic solvents such as methyl alcohol or ethylene glycol. Adsorption characteristics can be influenced by the charcoal's particle size, thus different responses may be obtained with different preparations.

Activated charcoal is given by mouth usually as a slurry in water. A usual adult dose for reduction of absorption is 50 g, but higher doses have been used. Children 1 to 12 years old may be given 25 to 50 g and infants under 1 year 1 g/kg. For maximum efficacy, activated charcoal should be given as soon as possible (within 1 hour) after ingestion of the toxic compound. However, it may be effective several hours after poisoning with certain drugs that slow gastric emptying. In the case of drugs that undergo enterohepatic or enteroenteric recycling (e.g. phenobarbital and theophylline) *repeated doses* of activated charcoal are of value in enhancing faecal elimination. Adult doses for repeated administration in active elimination have varied but typically 50 g may be given every 4 hours or 25 g every 2 hours. Doses in children and infants are similar to those used above for reduction of absorption and may be given every 4 to 6 hours. Administration may also be via a nasogastric tube.

Mixtures such as 'universal antidote' that contained activated charcoal, magnesium oxide, and tannic acid should not be used; activated charcoal alone is more effective and tannic acid may cause hepatotoxicity.

In treatment of poisoning using charcoal haemoperfusion, activated charcoal is used to remove drugs from the bloodstream. Where available, it may be of value in acute severe poisoning by drugs such as the barbiturates, glutethimide, or theophylline when other intensive measures fail to improve the condition of the patient.

Activated charcoal is used in dressings for ulcers and suppurating wounds (p.1585) to reduce malodour and may improve the rate of healing.

Activated charcoal has been used as a marker of intestinal transit and has also been tried in the treatment of flatulence. Both activated charcoal and vegetable charcoal (wood charcoal; carbo ligni) are included in preparations for various gastrointestinal disorders.

Technical grades of activated charcoal have been used as purifying and decolorising agents, for the removal of residual gases in low-pressure apparatus, and in respirators as a protection against toxic gases.

Administration. Activated charcoal is most commonly given as a slurry in water but this is often unpalatable because of the colour, gritty taste, lack of flavour, and difficulty in swallowing.[1] Flavourings and other excipients are often added in an attempt to improve palatability, although the effect of any additives on the adsorptive capacity of charcoal needs to be considered. Studies *in vitro* or in healthy subjects indicated that some foods such as ice cream, milk, and cocoa might inhibit the adsorptive capacity of activated charcoal, whereas starches and jams appeared to have no effect.[2,3] Carmellose has improved palatability although it might also reduce adsorptive capacity.[4-6] Saccharin sodium, sucrose, or sorbitol may be suitable additives,[7] although there may be problems associated with sorbitol-containing products (see under Poisoning, below). Chocolate syrup has also been used but the sweetness and flavour may disappear after a few minutes of contact with the activated charcoal.[1] A more recent study[8] of charcoal use in children with suspected poisoning found no evidence that use of flavourings improved the success of administration.

1. Scholtz EC, *et al.* Evaluation of five activated charcoal formulations for inhibition of aspirin absorption and palatability in man. *Am J Hosp Pharm* 1978; **35:** 1355–9.
2. Levy G, *et al.* Inhibition by ice cream of the antidotal efficacy of activated charcoal. *Am J Hosp Pharm* 1975; **32:** 289–91.
3. De Neve R. Antidotal efficacy of activated charcoal in presence of jam, starch and milk. *Am J Hosp Pharm* 1976; **33:** 965–6.
4. Mathur LK, *et al.* Activated charcoal–carboxymethylcellulose gel formulation as an antidotal agent for orally ingested aspirin. *Am J Hosp Pharm* 1976; **33:** 717–19.
5. Manes M. Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; **33:** 1120, 1122.
6. Mathur LK, *et al.* Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; **33:** 1122.
7. Cooney DO. Palatability of sucrose-, sorbitol-, and saccharin-sweetened activated charcoal formulations. *Am J Hosp Pharm* 1980; **37:** 237–9.
8. Osterhoudt KC, *et al.* Activated charcoal administration in a pediatric emergency department. *Pediatr Emerg Care* 2004; **20:** 493–8.

Poisoning. The management of acute poisoning is discussed on p.1435. The use of a *single oral dose* of activated charcoal has become a widespread method of preventing the absorption of ingested compounds and may be superior to gastric emptying. The American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) consider[1] that activated charcoal may be used if a patient presents within 1 hour of ingesting a potentially toxic amount of a poison known to be adsorbed by charcoal. There are insufficient data to support general use beyond 1 hour after ingestion.[1-3] In addition, *multiple oral doses* of activated charcoal have been found to enhance the elimination of some drugs and toxic substances even after systemic absorption. Mechanisms by which activated charcoal may increase drug elimination from the body include interruption of the enterohepatic circulation of drugs excreted into the bile, reduction of the reabsorption of drugs which diffuse or are actively secreted into the intestines, and increased elimination of the drug via the gastrointestinal tract when given with a laxative to decrease gastrointestinal transit time, although the practice of using charcoal with a laxative has been questioned.[4-6] Repeated oral doses of activated charcoal may therefore be considered for compounds that undergo enterohepatic or enteroenteric circulation, have a small volume of distribution, are not extensively bound to plasma proteins, and have a low endogenous clearance. Following a review of the literature[6] the AACT and EAPCCT recommended that multiple doses of charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Anecdotal reports and studies in acutely poisoned patients indicate that a technique of giving multiple doses of charcoal may offer an alternative to charcoal haemoperfusion or haemodialysis. However, while activated charcoal is generally well tolerated, major complications do occasionally occur, including pulmonary aspiration and bowel obstruction.[7] Also, use of multiple doses of charcoal preparations containing sorbitol or sodium bicarbonate can result in increased vomiting[8] or in electrolyte disturbances.[4,9,10]

1. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *J Toxicol Clin Toxicol* 2005; **43:** 61–87. Also available at: http://www.clintox.org/Pos_Statements/SingleDoseActivatedCharcoal.pdf (accessed 27/09/05)
2. Green R, *et al.* How long after drug ingestion is activated charcoal still effective? *J Toxicol Clin Toxicol* 2001; **39:** 601–5.
3. Cooper GM, *et al.* A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *QJM* 2005; **98:** 655–60.
4. Neuvonen PJ, Olkkola KT. Oral activated charcoal in the treatment of intoxications: role of single and repeated doses. *Med Toxicol* 1988; **3:** 33–58.
5. Neuvonen PJ, Olkkola KT. Effect of purgatives on antidotal efficacy of oral activated charcoal. *Hum Toxicol* 1986; **5:** 255–63.
6. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; **37:** 731–51. Also available at: http://www.clintox.org/Pos_Statements/MultipleDoseActivatedCharcoal.pdf (accessed 27/09/05)
7. Palatnick W, Tenenbein M. Activated charcoal in the treatment of drug overdose: an update. *Drug Safety* 1992; **7:** 3–7.
8. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; **27:** 358–61.
9. McLuckie A, *et al.* Role of repeated doses of oral activated charcoal in the treatment of acute intoxications. *Anaesth Intensive Care* 1990; **18:** 375–84.
10. Tenenbein M. Multiple doses of activated charcoal: time for reappraisal? *Ann Emerg Med* 1991; **20:** 529–31.

HAEMOPERFUSION. Haemoperfusion involves the passage of blood through an adsorbent material such as activated charcoal or synthetic hydrophobic polystyrene resins that can retain certain drugs and toxic agents. Early problems with charcoal haemoperfusion such as charcoal embolism, marked thrombocytopenia, fibrinogen loss, and pyrogen reactions have been largely overcome by purification procedures and by coating the carbon with biocompatible polymers. However, transient falls in platelet count, leucocyte count, and circulatory concentrations of clotting factors, calcium, glucose, urea, creatinine, and urate have been reported during haemoperfusion. While there is no substitute for supportive measures, haemoperfusion can significantly reduce the body burden of certain compounds with a low volume of distribution within 4 to 6 hours in some severely poisoned patients; haemoperfusion is not effective for drugs or poisons with very large volumes of distribution.

References.

1. Winchester JF. Dialysis and hemoperfusion in poisoning. *Adv Ren Replace Ther* 2002; **9:** 26–30.

Porphyria. Activated charcoal may be used as part of the management of erythropoietic protoporphyria, one of the non-acute porphyrias (p.1448). It acts as a sorbent in the gut lumen, interrupting the enterohepatic recycling of protoporphyrin. It may also have a role in congenital erythropoietic porphyria, a very rare porphyria. In a patient[1] with photomutilation due to this condition, activated charcoal 30 g given orally every 3 hours for 36 hours reduced the plasma-porphyrin concentration to normal values by 20 hours and was more effective than colestyramine or red cell transfusion. After discontinuation of activated charcoal, plasma-porphyrin concentrations rose rapidly to near pretreatment levels within 10 days. Long-term treatment with oral charcoal over a 9-month period produced a clinical remission with low concentrations of plasma and skin porphyrin and an absence of photocutaneous activity. The optimal dose was determined to be 60 g three times daily. However, exacerbation after an initial period of remission has been reported in another patient[2] and total lack of efficacy in a third.[3]

Activated charcoal has also been tried in variegate porphyria, but a study[4] in 8 patients found that oral charcoal led to clinical and biochemical deterioration with an increase in skin lesions and in urinary and plasma porphyrins.

1. Pimstone NR, *et al.* Therapeutic efficacy of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1987; **316:** 390–3.
2. Hift RJ, *et al.* The effect of oral activated charcoal on the course of congenital erythropoietic porphyria. *Br J Dermatol* 1993; **129:** 14–17.
3. Minder EI, *et al.* Lack of effect of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1994; **330:** 1092–4.
4. Hift RJ, *et al.* Administration of oral activated charcoal in variegate porphyria results in a paradoxical clinical and biochemical deterioration. *Br J Dermatol* 2003; **149:** 1266–9.

Pruritus. Activated charcoal has been tried in pruritus (p.1582) associated with renal failure. In a double-blind crossover study,[1] activated charcoal 6 g daily by mouth for 8 weeks was more effective than placebo in relieving generalised pruritus in 11 patients undergoing maintenance haemodialysis. Another study[2] found that activated charcoal completely relieved pruritus in 10 of 23 haemodialysis patients, with a partial response in a further 10; treatment was generally well tolerated.

1. Pederson JA, *et al.* Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980; **93:** 446–8.
2. Giovannetti S, *et al.* Oral activated charcoal in patients with uremic pruritus. *Nephron* 1995; **70:** 193–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mamograf; Minicam Carb; ***Austral.:*** Ad-Sorb; Carbosorb; Charcocaps; Karbons†; ***Austria:*** Norit; Norit-Carbomix; ***Belg.:*** Norit; Norit-Carbomix; ***Braz.:*** Neocarbon†; ***Canad.:*** Charac; Charcodote Aqueous; ***Cz.:*** Carbosorb; Norit; ***Fin.:*** Carbomix; ***Fr.:*** Alione Charbon; Carbactive; Carbomix; Carbonet; Charbon de Belloc; Colocarb; Formocarbine; Splenocarbine; Toxicarb; ***Ger.:*** Kohle-Compretten; Kohle-Hevert; Kohle-Pulvis; Kohle-Tabletten; Ultracarbon; ***Gr.:*** Carbomix†; Norit; Toxicarb; ***Hong Kong:*** Charcodote; ***Indon.:*** Bekarbon; ***Irl.:*** Carbomix; Carbonet; ***Israel:*** Norit; ***Ital.:*** Carbomix; ***Mex.:*** Carbotural; ***Neth.:*** Norit; ***Norw.:*** Kohle-Compretten; ***NZ:*** Carbosorb X; ***Port.:*** Askina Carbsorb†; Norit; ***Singapore:*** Aqueous Charcodote; Ultracarbon; ***Spain:*** Arkocapsulas Carbon Vegetal; Ultra Adsorb; ***Swed.:*** Carbomix; Kolsuspension; Medikol; ***Thai.:*** Ca-R-Bon; Ultracarbon; ***Turk.:*** Charflo Aqua; ***UK:*** Actidose-Aqua; Bragg's Medicinal Charcoal; Carbomix; Carbonet; Charcodote; Clinisorb; Legius; Lyofoam C; Modern Herbals Trapped Wind & Indigestion; Norit; ***USA:*** Actidose-Aqua; Charcoaid; Charcoal Plus; Charcocaps; Liqui-Char.

Multi-ingredient: ***Arg.:*** Carbogasol; Carbon Tabs; Diarrocalmol; Estreptocarbocaftiazol; Karbonetas; Lefa Enteril†; Opocarbon; ***Austral.:*** Carboflex†; Carbosorb S; No Gas†; ***Austria:*** Eucarbon; Eucarbon Herbal; Intestinol; Sabatif; ***Belg.:*** Carbobel; Carbolactanose; ***Canad.:*** Carboflex†; Charac Tol; Charcodote; ***Chile:*** Carbon Sulfaguanidina; ***Cz.:*** Carbocit; Carbotox; ***Fr.:*** Acticarbine; Actisorb Ag ; Carboflex; Carbolevure; Carbophos; Carbosylane; Carbosymag; Notgaz; ***Ger.:*** Actisorb Silver†; ***Gr.:*** Carbosylane; ***India:*** Distenil; Molzyme†; Nutrozyme; Papytazyme; Unienzyme; ***Irl.:*** Actisorb Silver; ***Israel:*** Carbosylane; Charcodote; Eucarbon; Kaltocarb; Novicarbon; ***Ital.:*** Actisorb Plus; Carbone Composto; Carbonesia; Carboyoghurt; Eucarbon; No-Gas; ***Malaysia:*** Eucarbon†; ***Mex.:*** Acilin; Dipecfur; ***NZ:*** Carbosorb S†; Carbosorb XS; ***Pol.:*** Rapacholin AC; Rapacholin C; ***Port.:*** Carboflex†; ***S.Afr.:*** Rubilax†; ***Switz.:*** Carbolevure; Carboticon; Carvon†; ***Thai.:*** Belacid; Bicobon†; Biodan†; Carbonpectate; Delta Charcoal; Papytazyme†; Pepsitase; Polyenzyme-I; ***Turk.:*** Charflo Sorbitol; Eucarbon; Intestinol; Karboseptin; ***UK:*** Acidosis; Actisorb Silver; Carbellon; ***USA:*** Actidose with Sorbitol; Flatulex; Poison Antidote Kit; ***Venez.:*** Carbargal; Carbargal con Atropina; Guanicar.

Amifostine *(BAN, USAN, rINN)*

Amifostiini; Amifostin; Amifostina; Amifostinum; Ethiofos; Gammaphos; NSC-296961; WR-2721. *S*-[2-(3-Aminopropylamino)ethyl] dihydrogen phosphorothioate.

Амифостин

$C_5H_{15}N_2O_3PS = 214.2.$

CAS — 20537-88-6 (amifostine); 63717-27-1 (amifostine monohydrate).

ATC — V03AF05.

ATC Vet — QV03AF05.

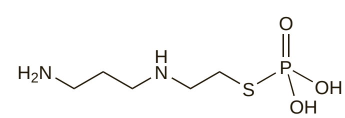

Pharmacopoeias. *US* includes the trihydrate.

USP 31 (Amifostine). The trihydrate is a white crystalline powder. Freely soluble in water. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Incompatibility. Amifostine has been reported[1] to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, chlorpromazine hydrochloride, cisplatin, ganciclovir sodium, hydroxyzine hydrochloride, miconazole, minocycline hydrochloride, and prochlorperazine edisilate during simulated Y-site administration.

1. Trissel LA, Martinez JF. Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2208–12.

Adverse Effects, Treatment, and Precautions

Amifostine may cause a transient reduction, usually in systolic, or, less frequently, in diastolic blood pressure. However, more pronounced reductions in blood pressure may occur and transient loss of consciousness has been reported very rarely. To minimise hypotension, patients should be adequately hydrated before treatment begins and should be in a supine position. Amifostine is contra-indicated in patients who are hypotensive or dehydrated. Patients taking antihypertensive drugs should discontinue treatment 24 hours before starting amifostine. Arterial blood pressure must be monitored during the amifostine infusion and if systolic blood pressure decreases significantly, the infusion must stop. It may be continued if blood pressure returns to normal within 5 minutes.

Nausea and vomiting are frequently reported and concurrent antiemetic therapy is recommended.

Amifostine reduces serum-calcium concentrations, although clinical hypocalcaemia has occurred only very rarely in patients who received multiple doses of amifostine within 24 hours. Serum-calcium concentrations should be monitored in patients at risk of hypocalcaemia.

Other adverse effects include flushing, chills, somnolence, hiccups, and sneezing. Hypersensitivity reactions and anaphylactoid reactions have been reported. Skin rashes may occur and there have been reports of more severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, in some cases resulting in fatality.

Administration of amifostine over a longer period than the recommended 15 minutes is associated with a higher incidence of adverse effects.

Effects on the skin. Amifostine has been associated with severe skin reactions, including Stevens-Johnson syndrome[1,2] and toxic epidermal necrolysis,[1,2] and fatalities have occurred.[2] The reactions appear to be more common in patients receiving radiotherapy.[2]

1. Lale Atahan I, *et al*. Two cases of Stevens-Johnson syndrome: toxic epidermal necrolysis possibly induced by amifostine during radiotherapy. *Br J Dermatol* 2000; **143:** 1072–3.
2. Boccia R, *et al*. Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004; **60:** 302–9.

Pharmacokinetics

Amifostine is rapidly cleared from the plasma after intravenous administration and is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065, a free thiol compound. The elimination half-life of amifostine after a 15-minute infusion is less than 10 minutes. About 6% or less of a dose is excreted in the urine.

Uses and Administration

Amifostine, an aminothiol compound, is a cytoprotective agent. It is converted in the body to its active metabolite WR-1065, which protects noncancerous cells against the toxic effects of antineoplastics and ionising radiation. It is used in patients with advanced ovarian cancer to reduce neutropenia-related infection associated with cyclophosphamide and cisplatin therapy and, in patients with advanced solid tumours of non-germ cell origin, to reduce the cumulative renal toxicity associated with repeated cisplatin use. It is also used to reduce the incidence of xerostomia (dry mouth) in patients undergoing radiation therapy for head and neck cancer. Amifostine is under investigation in ameliorating the adverse effects of other antineoplastics and in the treatment of myelodysplasia.

In chemotherapy, amifostine is given by intravenous infusion over 15 minutes starting no more than 30 minutes before the antineoplastic therapy. The dose in adults is 910 mg/m^2 once daily. Subsequent doses should be reduced to 740 mg/m^2 in patients unable to tolerate the full dose. A dose of 740 mg/m^2 is also recommended for the reduction of renal toxicity of cisplatin if doses of cisplatin of less than 100 mg/m^2 are used.

In the prevention of xerostomia, amifostine is given in a dose of 200 mg/m^2 daily as a 3-minute intravenous infusion started 15 to 30 minutes before radiotherapy.

Cytoprotection. WR-1065, the active metabolite of amifostine, readily enters non-malignant cells where it deactivates cytotoxics such as alkylating and platinum-containing antineoplastics and protects against the effects of ionising radiation.[1-3] The cytoprotective effects of amifostine are reported to be selective for normal cells and not to interfere with the cytotoxic effects of antineoplastics and radiation on malignant cells. Several factors contribute to this selectivity, including the lower alkaline phosphatase content of malignant cells compared with normal cells, and the lower pH of malignant tissues, both of which decrease the formation and uptake of WR-1065 by malignant cells.[2,3]

Benefit has been reported with amifostine in various malignancies and the American Society of Clinical Oncology currently recommends[4] that its use may be considered in patients receiving cisplatin- or alkylating agent-based chemotherapy, and in patients receiving radiation therapy in the head and neck region. Although it is usually given intravenously, there is some evidence[5,6] that the subcutaneous route may be effective and may be associated with fewer adverse effects.

1. Foster-Nora JA, Siden R. Amifostine for protection from antineoplastic drug toxicity. *Am J Health-Syst Pharm* 1997; **54:** 787–800.
2. Mabro M, *et al*. A risk-benefit assessment of amifostine in cytoprotection. *Drug Safety* 1999; **21:** 367–87.
3. Culy CR, Spencer CM. Amifostine: an update on its clinical status as a cytoprotectant in patients with cancer receiving chemotherapy or radiotherapy and its potential therapeutic application in myelodysplastic syndrome. *Drugs* 2001; **61:** 641–84.
4. Schuchter LM, *et al*. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002; **20:** 2895–903. Also available at: http://www.jco.org/cgi/reprint/20/12/2895.pdf (accessed 4/10/05)
5. Koukourakis MI, *et al*. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *J Clin Oncol* 2000; **18:** 2226–33.
6. Bonner HS, Shaw LM. New dosing regimens for amifostine: a pilot study to compare the relative bioavailability of oral and subcutaneous administration with intravenous infusion. *J Clin Pharmacol* 2002; **42:** 166–74.

Preparations

USP 31: Amifostine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Erifostine; Ethyol†; ***Austral.:*** Ethyol; ***Belg.:*** Ethyol; ***Braz.:*** Ethyol; ***Chile:*** Ethyol; ***Cz.:*** Ethyol; ***Denm.:*** Ethyol; ***Fin.:*** Ethyol; ***Fr.:*** Ethyol; ***Ger.:*** Ethyol; ***Gr.:*** Ethyol; ***Hong Kong:*** Ethyol†; ***Hung.:*** Ethyol†; ***India:*** Amiphos; ***Israel:*** Ethyol; ***Ital.:*** Ethyol; ***Malaysia:*** Ethyol†; ***Mex.:*** Ethyol; ***Neth.:*** Ethyol; ***NZ:*** Ethyol; ***Philipp.:*** Ethyol; ***Pol.:*** Ethyol; ***Port.:*** Ethyol; ***S.Afr.:*** Ethyol; ***Singapore:*** Ethyol†; ***Spain:*** Ethyol; ***Swed.:*** Ethyol; ***Switz.:*** Ethyol; ***Thai.:*** Cytofos; Ethyol; ***Turk.:*** Ethyol; ***UK:*** Ethyol†; ***USA:*** Ethyol; ***Venez.:*** Ethyol.

Ammonium Tetrathiomolybdate

Tetratiomolibdato de amonio.
$(NH_4)_2MoS_4$ = 260.3.
CAS — 15060-55-6.

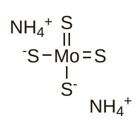

Profile

Ammonium tetrathiomolybdate is a chelator that aids the elimination of copper from the body. It is under investigation in the treatment of Wilson's disease.

Wilson's disease. Ammonium tetrathiomolybdate forms a complex with protein and copper. When it is taken with food it blocks the intestinal absorption of copper, and when given between meals it combines with albumin- and caeruloplasmin-bound copper. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels in patients with Wilson's disease (p.1459); it may be particularly suitable for patients with neurological symptoms.[1] Bone marrow depression[1,2] and raised liver enzymes[1] have been reported; both have responded to temporary withdrawal or dose reduction.

1. Brewer GJ, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate III: initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003; **60:** 379–85.
2. Harper PL, Walshe JM. Reversible pancytopenia secondary to treatment with tetrathiomolybdate. *Br J Haematol* 1986; **64:** 851–3.

Amyl Nitrite

Amyli Nitris; Amylis Nitris; Amylium Nitrosum; Amylnitrit; Amyylinitriitti; Azotito de Amilo; Isoamyl Nitrite; Isopentyl Nitrite; Nitrito de amilo; Pentanolis Nitris.
$C_5H_{11}NO_2$ = 117.1.
ATC — V03AB22.
ATC Vet — QV03AB22.

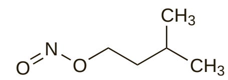

and

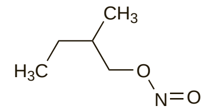

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amyl nitrite:
60 second trip; Aimes; Aimies; Ames; Amys; Boppers; Hard on; Pearls; Poppers; Sixty second trip; Snappers; Whiffenpoppers.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Amyl Nitrite). A mixture of the nitrite esters of 3-methyl-1-butanol and 2-methyl-1-butanol. A clear, yellowish liquid having a peculiar, ethereal, fruity odour. It is very flammable. It is volatile even at low temperatures. B.p. about 96°. Practically insoluble in water; miscible with alcohol and with ether. Store in a cool place in airtight containers. Protect from light.

Stability. Amyl nitrite is liable to decompose with evolution of nitrogen, particularly if it has become acid in reaction.

Adverse Effects, Treatment, and Precautions

Amyl nitrite inhalation commonly causes flushing, headache, and dizziness; nausea and vomiting, hypotension, restlessness, and tachycardia may also occur. Overdosage may result in cyanosis, syncope, dyspnoea, and muscular weakness, due to vasodilatation and methaemoglobinaemia. Methylthioninium chloride may be required for severe methaemoglobinaemia but should not be used if cyanide poisoning is suspected since cyanide may be displaced.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

Abuse. Volatile nitrites (commonly known as 'poppers'), including amyl, butyl, or isobutyl nitrite, have been abused in the belief that they expand creativity, stimulate music appreciation, promote a sense of abandon in dancing, and intensify sexual experience.[1,2]

Inhalation causes headache, tachycardia, syncope, acute psychosis, increased intra-ocular pressure, transient hemiparesis, methaemoglobinaemia, coma, and, rarely, sudden death. Haemolytic anaemia has also been reported;[3-5] in some subjects, Heinz body formation has been detected.[3] Methaemoglobinaemia may be severe,[6] and has also been reported after ingestion of volatile nitrites.[7-10] Symptoms are similar to those of hypoxia[9] and may be reversed by methylthioninium chloride.[6-10]

Amyl nitrite inhalation has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body.[11]

1. Sigell LT, *et al*. Popping and snorting volatile nitrites: a current fad for getting high. *Am J Psychiatry* 1978; **135:** 1216–18.
2. Lockwood B. Poppers: volatile nitrite inhalants. *Pharm J* 1996; **257:** 154–5.
3. Romeril KR, Concannon AJ. Heinz body haemolytic anaemia after sniffing volatile nitrites. *Med J Aust* 1981; **1:** 302–3.
4. Brandes JC, *et al*. Amyl nitrite-induced hemolytic anemia. *Am J Med* 1989; **86:** 252–4.
5. Graves TD, Mitchell S. Acute haemolytic anaemia after inhalation of amyl nitrite. *J R Soc Med* 2003; **96:** 594–5.
6. Modarai B, *et al*. Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 2002; **19:** 270–1.
7. Laaban JP, *et al*. Amyl nitrite poppers and methemoglobulinemia. *Ann Intern Med* 1985; **103:** 804–5.
8. Osterloh J, Olson K. Toxicities of alkyl nitrites. *Ann Intern Med* 1986; **104:** 727.
9. Pierce JMT, Nielsen MS. Acute acquired methaemoglobinaemia after amyl nitrite poisoning. *BMJ* 1989; **298:** 1566.
10. Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. *Arch Dis Child* 1991; **66:** 152.
11. Bos JD, *et al*. Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis* 1985; **12:** 109.

Handling and storage. Amyl nitrite is very flammable and must not be used where it may be ignited.

Uses and Administration

Amyl nitrite is rapidly absorbed on inhalation and has been used in the immediate treatment of patients with definite cyanide poisoning (p.2045) to induce the formation of methaemoglobin, which combines with the cyanide to form non-toxic cyanmethaemoglobin. The value of such treatment has been questioned since only low levels of methaemoglobin are formed, but other mechanisms may also be important. A suggested procedure has

The symbol † denotes a preparation no longer actively marketed

been to give amyl nitrite by inhalation for up to 30 seconds every minute until other measures can be instituted. It has also been suggested for use in the management of hydrogen sulfide poisoning (p.1690).

Amyl nitrite has an action similar to that of glyceryl trinitrate (p.1297) and used to be given by inhalation for the relief of acute attacks of angina pectoris but is seldom used now.

Homoeopathy. Amyl nitrite has been used in homoeopathic medicines under the following names: Amyl nitrosum; Am. nit.

Preparations

USP 31: Amyl Nitrite Inhalant.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Percucor†; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package; Emergent-Ez.

Asoxime Chloride

Asoxima, cloruro de; HI-6. 1-({[4-(Aminocarbonyl)pyridinio]methoxy}methyl)-2-[(hydroxyimino)methyl]pyridinium dichloride.

$C_{14}H_{16}Cl_2N_4O_3$ = 359.2.

CAS — 34433-31-3.

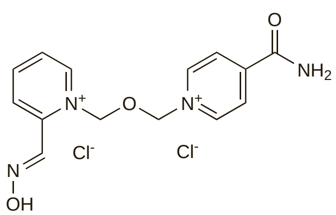

Profile

Asoxime chloride is a cholinesterase reactivator that has been tried in the treatment of poisoning by organophosphorus pesticides and related compounds, including nerve agents.

◊ References.

1. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; **9:** 49–51.
2. Kušić R, *et al.* HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 1991; **10:** 113–18.

AST-120

CAS — 90597-58-3.

Profile

AST-120 is an adsorbent consisting of spherical microcrystalline carbonaceous particles with oxygen complex including surface oxides. It is given orally to delay the progression of chronic renal failure by removing uraemic toxins and their precursors from the gastrointestinal tract. It is also under investigation in gastrointestinal disorders.

◊ References.

1. Takahashi N, *et al.* Therapeutic effects of long-term administration of an oral adsorbent in patients with chronic renal failure: two-year study. *Int J Urol* 2005; **12:** 7–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Kremezin.

Atipamezole *(BAN, USAN, rINN)*

Atipamezol; Atipamézole; Atipamezolum; MPV-1248. 4-(2-Ethyl-2-indanyl)imidazole.

Атипамезол

$C_{14}H_{16}N_2$ = 212.3.

CAS — 104054-27-5.

ATC Vet — QV03AB90.

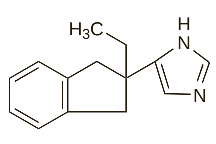

Atipamezole Hydrochloride *(BANM, rINNM)*

Atipametsolihydrokloridi; Atipamézole, Chlorhydrate d'; Atipamezolhydroklorid; Atipamezoli Hydrochloridum; Hidrocloruro de atipamezol.

Атипамезола Гидрохлорид

$C_{14}H_{16}N_2$,HCl = 248.8.

CAS — 104075-48-1.

Profile

Atipamezole is a selective alpha$_2$-adrenergic receptor antagonist that is used as the hydrochloride in veterinary medicine to reverse the sedative effects of medetomidine.

Calcium Polystyrene Sulfonate

Calcium Polystyrene Sulphonate; Poliestirenosulfonato cálcico; Polistiren Sülfonat Kalsiyum.

CAS — 37286-92-3.

ATC — V03AE01.

ATC Vet — QV03AE01.

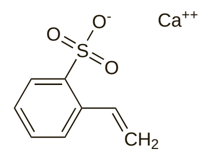

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2008 (Calcium Polystyrene Sulphonate). A cream to light brown, fine powder. The calcium content is not less than 6.5% and not more than 9.5%, calculated with reference to the dried substance. Each g exchanges not less than 1.3 mmol and not more than 2.0 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water and in alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Sodium Polystyrene Sulfonate, p.1465. Sodium overloading is not a problem with calcium polystyrene sulfonate, but calcium overloading and hypercalcaemia may occur. It should therefore be avoided in patients with conditions such as hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma who may present with renal failure together with hypercalcaemia. Patients should be monitored for electrolyte disturbances, especially hypokalaemia and hypercalcaemia.

Effects on the lungs. An elderly man who died from cardiac arrest was found at autopsy to have bronchopneumonia associated with inhalation of calcium polystyrene sulfonate;[1] the resin had been given by mouth to treat hyperkalaemia.

1. Chaplin AJ, Millard PR. Calcium polystyrene sulphonate: an unusual cause of inhalation pneumonia. *BMJ* 1975; **3:** 77–8.

Interactions

As for Sodium Polystyrene Sulfonate, p.1465. Calcium ions are released from the resin in the gastrointestinal tract and this may reduce the absorption of tetracycline given by mouth.

Uses and Administration

Calcium polystyrene sulfonate, the calcium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges calcium ions for potassium ions and other cations in the gastrointestinal tract. It is used similarly to sodium polystyrene sulfonate (p.1465) to enhance potassium excretion in the treatment of hyperkalaemia (p.1669) and may be preferred to the sodium resin in patients who cannot tolerate an increase in their sodium load. It is estimated that 1 g of calcium polystyrene sulfonate could bind 1.3 to 2 mmol of potassium but it is unlikely that such figures could be achieved in practice.

It is given orally, in a dose of 15 g three or four times daily, as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content. A dose for children is 1 g/kg daily in divided doses for acute hyperkalaemia, reduced to a maintenance dose of 500 mg/kg daily in divided doses; the oral route is not recommended for neonates.

When oral administration is difficult, calcium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 100 mL of 2% methylcellulose '450' and 100 mL of water and retained, if possible, for at least 9 hours. Initial therapy may involve both oral and rectal routes. Following retention of the enema the colon should be irrigated to remove the resin. Children and neonates may be given rectal doses similar to the oral doses suggested for children.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Resincalcio; RIC Calcio†; ***Austral.:*** Calcium Resonium; ***Austria:*** CPS Pulver; Sorbisterit; ***Belg.:*** Kayexalate; ***Braz.:*** Sorcal; ***Canad.:*** Resonium Calcium; ***Chile:*** Sorbisterit; ***Cz.:*** Calcium Resonium; Resical; Sorbisterit†; ***Denm.:*** Resonium Calcium; ***Ger.:*** Anti-Kalium; Calcium Resonium; CPS Pulver; Elutit-Calcium; Sorbisterit; ***Gr.:*** Calcium Resonium†; ***Hong Kong:*** Calcium Resonium; ***Indon.:*** Kalitake; ***Irl.:*** Calcium Resonium; ***Jpn:*** Kalimate; ***Malaysia:*** Kalimate; ***Neth.:*** Sorbisterit; ***Norw.:*** Resonium Calcium; ***NZ:*** Calcium Resonium; ***Philipp.:*** Kalimate; ***Pol.:*** Calcium Resonium; ***Port.:*** Resical; ***Spain:*** Resincalcio; ***Swed.:*** Resonium Calcium; ***Switz.:*** Sorbisterit; ***Thai.:*** Kalimate; Resincalcio; ***Turk.:*** Anti-potasium; ***UK:*** Calcium Resonium.

Deferasirox *(USAN, rINN)*

CGP-72670; Déférasirox; Deferasiroxum; ICL-670; ICL-670A. 4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.

Деферазирокс

$C_{21}H_{15}N_3O_4$ = 373.4.

CAS — 201530-41-8.

ATC — V03AC03.

ATC Vet — QV03AC03.

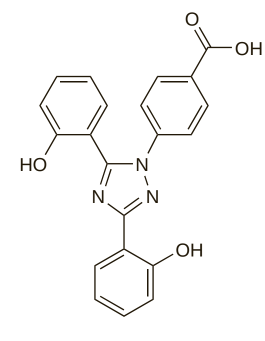

Adverse Effects and Precautions

The commonest adverse effects with deferasirox are dose-related gastrointestinal disorders, such as nausea, vomiting, diarrhoea, and abdominal pain; diarrhoea may be more common in young children. Skin rashes are also common and may respond to a reduction in dose. Other adverse effects include headache, pyrexia, and cough.

Dose-dependent increases in serum creatinine are common and proteinuria may also occur; there have been reports of acute renal failure, including fatalities. Serum creatinine should be measured before starting deferasirox, and renal function should be assessed weekly for the first month (particularly in patients with risk factors for renal disease) and for a month after dosage increases, then monthly thereafter; tests for proteinuria should also be performed monthly. The dose should be reduced or treatment stopped if persistent increases in serum creatinine occur.

Liver enzyme values may increase in patients receiving deferasirox, and cases of hepatitis have occurred; gallstones and related biliary disorders have also been reported. Liver enzymes should be monitored monthly and treatment should be stopped if persistent increases occur.

As with other iron chelators, hearing loss and visual disorders, including cataracts, have occurred. Audiological and ophthalmological tests should be performed before starting deferasirox and then every 12 months. Serum ferritin should be measured monthly. In children, annual assessment of growth and development is also recommended.

There have been rare reports of blood disorders, some of which have been fatal, including agranulocytosis, neutropenia, and thrombocytopenia, in patients taking deferasirox. Blood counts should be monitored regularly.

Interactions

Deferasirox should not be given with aluminium-containing antacids since there is a possibility that it may chelate aluminium.

Pharmacokinetics

Deferasirox is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.5 to 4 hours after ingestion. The absolute bioavailability is about 70% but is increased in the presence of food. Deferasirox is about 99% bound to plasma proteins, mainly albumin. It is metabolised by glucuronidation and is excreted mainly in the faeces via bile, as metabolites and as unchanged drug; there is a possibility that enterohepatic recycling may occur. About 8% of a dose is excreted in the urine. The mean elimination half-life is about 8 to 16 hours.

Uses and Administration

Deferasirox is an orally active iron chelator that is used in the management of chronic iron overload (p.1442) due to blood transfusion. It is available as tablets that are made into a suspension immediately before use. The usual initial dose in adults and children 2 years of age and older is 20 mg/kg once daily, taken on an empty stomach at least 30 minutes before food. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary. The maximum recommended dose is 30 mg/kg daily.

◊ References.

1. VanOrden HE, Hagemann TM. Deferasirox—an oral agent for chronic iron overload. *Ann Pharmacother* 2006; **40:** 1110–17.
2. Stumpf JL. Deferasirox. *Am J Health-Syst Pharm* 2007; **64:** 606–16.
3. Yang LPH, *et al*. Deferasirox: a review of its use in the management of transfusional chronic iron overload. *Drugs* 2007; **67:** 2211–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Exjade; ***Austral.:*** Exjade; ***Chile:*** Exjade; ***Cz.:*** Exjade; ***Fr.:*** Exjade; ***Gr.:*** Exjade; ***Hung.:*** Exjade; ***Indon.:*** Exjade; ***Malaysia:*** Exjade; ***NZ:*** Exjade; ***UK:*** Exjade; ***USA:*** Exjade.

Deferiprone *(BAN, rINN)*

CP-20; Deferipron; Deferiprona; Défériprone; Deferiproni; Deferipronum; Dimethylhydroxypyridone; L1. 1,2-Dimethyl-3-hydroxypyrid-4-one; 3-Hydroxy-1,2-dimethyl-4-pyridone.

Дефериприон

$C_7H_9NO_2$ = 139.2.
CAS — 30652-11-0.
ATC — V03AC02.
ATC Vet — QV03AC02.

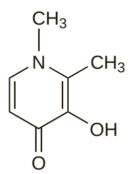

Adverse Effects and Precautions

Deferiprone has been shown to cause neutropenia and should not be used in neutropenic patients; the neutrophil count should be monitored weekly and treatment should be stopped if neutropenia develops. Agranulocytosis has also occurred. Patients should be advised to seek immediate medical attention if symptoms indicative of infection such as fever, sore throat, or flu-like symptoms occur.

Gastrointestinal disorders such as diarrhoea, nausea, vomiting, and abdominal pain are common during deferiprone treatment and may require a temporary reduction in dose. A reddish-brown discoloration of the urine is also common. Other adverse effects that have been reported include arthralgia and increased liver enzymes. Deferiprone may reduce plasma-zinc concentrations and zinc supplements may be required.

Deferiprone is teratogenic in *animals* and should not be used during pregnancy. Women of child-bearing potential should be advised to use contraceptive measures during treatment with deferiprone.

Caution is advised in patients with hepatic or renal impairment.

Effects on the blood. Agranulocytosis, in some cases fatal, has been reported in association with deferiprone use.[1,2]

1. Henter J-I, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007; **109:** 5157–9.
2. Anonymous. Deferiprone: agranulocytosis and neurological disorders. *Prescrire Int* 2007; **16:** 72.

Overdosage. Neurological disorders were reported by the manufacturer and the French pharmacovigilance authorities in 2 children aged 7 and 9 who had been treated with deferiprone doses at 2 ⁄ times the highest recommended dose of 100 mg/kg daily. The children were treated for 1 and 2 years, respectively, and developed nystagmus, gait disorders, ataxia, dystonia, and, in one case, psychomotor retardation. These disorders gradually improved after deferiprone was stopped.[1]

1. Agence française de sécurité sanitaire des produits de santé/Laboratoires Chiesi, France. Risque d'agranulocytoses fatales et de troubles neurologiques lors de l'utilisation de Ferriprox (défériprone) (issued 1st September, 2006). Available at: http://agmed.sante.gouv.fr/htm/10/filltrpsc/lp060901.pdf (accessed 27/09/07)

Interactions

Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations; it should not be given with aluminium-containing antacids. Due to the risk of additive toxicity, use with drugs that may cause neutropenia or agranulocytosis is not recommended.

Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring 45 to 60 minutes after an oral dose; absorption may be slowed in the presence of food and peak serum concentrations may be reduced. Deferiprone is metabolised to an inactive glucuronide metabolite and is excreted primarily in the urine, mainly as the metabolite and the iron-deferiprone complex, with a small amount of unchanged drug. The elimination half-life is about 2 to 3 hours.

Uses and Administration

Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. It may be given by mouth in doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended. For use in children, see Administration in Children, below.

◊ Reviews.

1. Barman Balfour JA, Foster RH. Deferiprone: a review of its clinical potential in iron overload in β-thalassaemia major and other transfusion-dependent diseases. *Drugs* 1999; **58:** 553–78.
2. Kontoghiorghes GJ, *et al*. Benefits and risks of deferiprone in iron overload in thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. *Drug Safety* 2003; **26:** 553–84.
3. Hoffbrand AV. Deferiprone therapy for transfusional iron overload. *Best Pract Res Clin Haematol* 2005; **18:** 299–317.
4. Piga A, *et al*. Deferiprone: new insight. *Ann N Y Acad Sci* 2005; **1054:** 169–74.

Administration in children. UK licensed product information states that there are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on use in children below 6. Australian licensed product information states that limited data exist for children between the ages of 2 and 10 but that the effects of deferiprone on growth are unknown. Licensed doses in children are calculated by weight on the same basis as adults (see Uses and Administration, above).

Thalassaemia. Patients with thalassaemia receiving regular blood transfusions commonly develop iron overload requiring use of iron chelators. Deferiprone was developed as an oral alternative to desferrioxamine, but its role has been controversial. See Thalassaemia under Uses of Desferrioxamine, p.1442, for further information.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferriprox; ***Austral.:*** Ferriprox; ***Belg.:*** Ferriprox; ***Braz.:*** Ferriprox; ***Cz.:*** Ferriprox; ***Denm.:*** Ferriprox; ***Fin.:*** Ferriprox; ***Fr.:*** Ferriprox; ***Ger.:*** Ferriprox; ***Gr.:*** Ferriprox; Kelfer; ***Hong Kong:*** Ferriprox; ***India:*** Kelfer; ***Irl.:*** Ferriprox†; ***Ital.:*** Ferriprox; ***Malaysia:*** Ferriprox; Kelfer; ***Neth.:*** Ferriprox; ***Port.:*** Ferriprox; ***Spain:*** Ferriprox; ***Swed.:*** Ferriprox; ***Switz.:*** Ferriprox; ***Turk.:*** Ferriprox; ***UK:*** Ferriprox.

Desferrioxamine Mesilate *(BANM)*

Deferoxamine Mesilate *(pINNM)*; Ba-33112; Ba-29837 (desferrioxamine hydrochloride); Deferoksamiinimesilaatti; Deferoksamin Mezilat; Deferoksamino mesilatas; Déféroxamine, Mésilate de; Deféroxamine, mésilate de; Deferoxamine Mesylate *(USAN)*; Deferoxamini mesilas; Deferoxaminmesilat; Deferoxamin-mesylát; Deferoxamin-mezilát; Desferrioksamin Mesilat; Desferrioxamine Mesylate; Desferrioxamine Methanesulphonate; Mesilato de deferoxamina; NSC-527604 (desferrioxamine). 30-Amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate; *N'*-{5-[(4-{[5-(Acetylhydroxyamino)pentyl]amino}-1,4-dioxobutyl)hydroxyamino]pentyl}-*N*-(5-aminopentyl)-*N*-hydroxy-butanediamide monomethanesulphonate.

Дефероксамина Мезилат

$C_{25}H_{48}N_6O_8,CH_3SO_3H$ = 656.8.
CAS — 70-51-9 (desferrioxamine); 138-14-7 (desferrioxamine mesilate); 1950-39-6 (desferrioxamine hydrochloride).
ATC — V03AC01.
ATC Vet — QV03AC01.

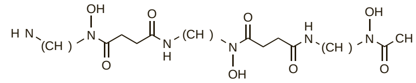

(desferrioxamine)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Deferoxamine Mesilate; Desferrioxamine Mesilate BP 2008). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol. A freshly prepared 10% solution in water has a pH of 3.7 to 5.5. Store at 2° to 8°. Protect from light.
USP 31 (Deferoxamine Mesylate). A white to off-white powder. Freely soluble in water; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Incompatibility. Licensed product information states that desferrioxamine solutions are incompatible with heparin.

Adverse Effects and Treatment

Rapid intravenous injection of desferrioxamine may cause flushing, urticaria, hypotension, and shock. Local pain may occur with subcutaneous or intramuscular injections and pruritus, erythema, and swelling have occurred after prolonged subcutaneous use. Gastrointestinal disorders, dysuria, fever, allergic skin rashes, tachycardia, cardiac arrhythmias, convulsions, and leg cramps have been reported. Visual disturbances, including retinal changes, and hearing loss may occur and may be reversible if desferrioxamine is withdrawn. Cataract formation has also been reported. Desferrioxamine therapy may retard growth in very young children.

The adverse effects of desferrioxamine generally respond to dosage reduction. In acute overdosage desferrioxamine may be removed by haemodialysis.

◊ Reviews of the adverse effects of desferrioxamine.

1. Bentur Y, *et al*. Deferoxamine (desferrioxamine): new toxicities for an old drug. *Drug Safety* 1991; **6:** 37–46.

Effects on the blood. A patient with end-stage renal disease developed reversible thrombocytopenia on 3 separate occasions after intravenous infusions of desferrioxamine for dialysis osteomalacia.[1] Acute fatal aplastic anaemia occurred in a 16-year-old girl with thalassaemia after high intravenous doses of desferrioxamine (80 mg/kg daily) for 20 days.[2]

1. Walker JA, *et al*. Thrombocytopenia associated with intravenous desferrioxamine. *Am J Kidney Dis* 1985; **6:** 254–6.
2. Sofroniadou K, *et al*. Acute bone marrow aplasia associated with intravenous administration of deferoxamine (desferrioxamine). *Drug Safety* 1990; **5:** 152–4.

Effects on the ears and eyes. Lens opacities, retinal pigmentary changes and other retinal abnormalities, and ocular disturbances including loss of colour vision, night blindness, decreased visual acuity, and field defects, have been reported in patients receiving long-term or high-dose treatment with desferrioxamine.[1-4] The incidence appears to be about 30%, although individual studies have reported widely differing rates; in 2 studies long-term use of desferrioxamine was associated with symptomatic or asymptomatic ocular changes in 4% (2 of 52)[5] and 66% (10 of 15)[6] of patients respectively.

Sensorineural hearing impairment has also been reported,[5,7-12] and in one study[13] was attributed to desferrioxamine in 29% of patients (22 of 75). Tinnitus has been reported in a few patients.[11,14]

The mechanism by which desferrioxamine causes neurotoxicity is unclear. Some studies[8,15] have found an association with dose, suggesting a direct toxic effect of desferrioxamine; other studies[6,16] have suggested that depletion of trace metals, particularly zinc or copper, may be involved. Both ophthalmic and auditory abnormalities can improve when desferrioxamine is withdrawn,[1,3,5-10] although sometimes the effects may be irreversible[17] or recovery may only be partial.[8,9] There has also been a report[18] of improvement following use of zinc supplements.

1. Davies SC, *et al*. Ocular toxicity of high-dose intravenous desferrioxamine. *Lancet* 1983; **ii:** 181–4.
2. Simon P, *et al*. Desferrioxamine, ocular toxicity, and trace metals. *Lancet* 1983; **ii:** 512–13.
3. Borgna-Pignatti C, *et al*. Visual loss in patient on high-dose subcutaneous desferrioxamine. *Lancet* 1984; **i:** 681.
4. Rubinstein M, *et al*. Ocular toxicity of desferrioxamine. *Lancet* 1985; **i:** 817–18.
5. Cohen A, *et al*. Vision and hearing during deferoxamine therapy. *J Pediatr* 1990; **117:** 326–30.
6. De Virgiliis S, *et al*. Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia. *Arch Dis Child* 1988; **63:** 250–5.
7. Guerin A, *et al*. Acute deafness and desferrioxamine. *Lancet* 1985; **ii:** 39.
8. Olivieri NF, *et al*. Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. *N Engl J Med* 1986; **314:** 869–73.
9. Barratt PS, Toogood IRG. Hearing loss attributed to desferrioxamine in patients with beta-thalassaemia major. *Med J Aust* 1987; **147:** 177–9.
10. Wonke B, *et al*. Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.
11. Porter JB, *et al*. Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Br J Haematol* 1989; **73:** 403–9.
12. Argiolu F, *et al*. Hearing impairment during deferoxamine therapy for thalassemia major. *J Pediatr* 1991; **118:** 826.
13. Chiodo AA, *et al*. Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26:** 116–22.
14. Marsh MN, *et al*. Tinnitus in a patient with beta-thalassaemia intermedia on long-term treatment with desferrioxamine. *Postgrad Med J* 1981; **57:** 582–4.

15. Bentur Y, *et al.* Comparison of deferoxamine pharmacokinetics between asymptomatic thalassemic children and those exhibiting severe neurotoxicity. *Clin Pharmacol Ther* 1990; **47:** 478–82.
16. Pall H, *et al.* Ocular toxicity of desferrioxamine – an example of copper promoted auto-oxidative damage? *Br J Ophthalmol* 1989; **73:** 42–7.
17. Bene C, *et al.* Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol* 1989; **31:** 45–8.
18. Pinna A, *et al.* Rapid recovery with oral zinc sulphate in deferoxamine-induced presumed optic neuropathy and hearing loss. *J Neuroophthalmol* 2001; **21:** 32–3.

Effects on growth rate. Growth retardation has been noted in thalassaemic children undergoing desferrioxamine therapy.[1,2] Growth retardation was related to dose[1,2] and inversely related to iron stores.[1] It was greater in those who started receiving desferrioxamine at the start of transfusion therapy at about 9 months old than in those who started desferrioxamine once iron accumulation was established, after about 3 years. A sharp increase in growth velocity was reported in 15 patients with low ferritin levels after a 50% reduction in desferrioxamine dose.[1]

1. Piga A, *et al.* High-dose desferrioxamine as a cause of growth failure in thalassaemic patients. *Eur J Haematol* 1988; **40:** 380–1.
2. De Virgiliis S, *et al.* Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr* 1988; **113:** 661–9.

Effects on the kidneys. Intensive treatment with intravenous infusions of desferrioxamine has been associated[1,2] with acute decreases in renal function, and it has been suggested[3] that nephrotoxicity could be related to the high doses used; acute renal failure has also been reported[4,5] after intravenous overdosage of desferrioxamine. However, other studies[6,7] have also found reductions in renal function associated with more usual subcutaneous dosage regimens.

1. Batey R, *et al.* Acute renal insufficiency occurring during intravenous desferrioxamine therapy. *Scand J Haematol* 1979; **22:** 277–9.
2. Koren G, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1989; **143:** 1077–80.
3. Li Volti S, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1990; **144:** 1069–70.
4. Cianciulli P, *et al.* Acute renal failure occurring during intravenous desferrioxamine therapy: recovery after haemodialysis. *Haematologica* 1992; **77:** 514–15.
5. Prasannan L, *et al.* Acute renal failure following deferoxamine overdose. *Pediatr Nephrol* 2003; **18:** 283–5.
6. Koren G, Bentur Y. Acute changes in renal function associated with deferoxamine. *Am J Dis Child* 1990; **144:** 1070.
7. Cianciulli P, *et al.* Early detection of nephrotoxic effects in thalassemic patients receiving desferrioxamine therapy. *Kidney Int* 1994; **46:** 467–70.

Effects on the lungs. Pulmonary complications, including fatal acute respiratory distress syndrome, have been reported in patients given prolonged or high-dose intravenous desferrioxamine. A pulmonary syndrome with tachypnoea, hypoxaemia, reduced pulmonary function, and evidence of diffuse interstitial fibrosis and inflammation, has been reported[1,2] with high doses, possibly associated with a hypersensitivity reaction. There has also been a report[3] of fatal acute respiratory distress syndrome in 4 patients given intravenous desferrioxamine for 65 to 92 hours; toxicity was attributed to the prolonged infusion since no pulmonary complications had been noted with desferrioxamine given for less than 24 hours. Subsequent correspondence, however, suggested alternative explanations for the pulmonary injury including the use of doses above the daily maximum,[4] as well as inadequate desferrioxamine therapy.[5]

1. Freedman MH, *et al.* Pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine infusions. *Am J Dis Child* 1990; **144:** 565–9.
2. Scanderbeg AC, *et al.* Pulmonary syndrome and intravenous high-dose desferrioxamine. *Lancet* 1990; **336:** 1511.
3. Tenenbein M, *et al.* Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; **339:** 699–701.
4. Macarol V, Yawalkar SJ. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.
5. Shannon M. Desferrioxamine in acute iron poisoning. *Lancet* 1992; **339:** 1601.

Effects on the skin. Desferrioxamine may be used in the management of porphyria cutanea tarda (see p.1448). However, lesions resembling porphyria cutanea tarda developed in 3 patients during long-term therapy with desferrioxamine for aluminium toxicity.[1] The lesions worsened on exposure to sun and resolved when treatment was completed. It was also possible that the lesions were associated with aluminium accumulation. Alopecia was noted in 1 patient but an association with desferrioxamine could not be established.

1. McCarthy JT, *et al.* Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; **74:** 257–76.

Hypersensitivity. Individual cases of anaphylactoid reactions have been reported with desferrioxamine given by various parenteral routes, and desensitisation has been carried out successfully in some patients.[1-4] Immunological studies have suggested that the reaction may be pseudo-allergic in nature;[2-4] 4 patients who were unable to tolerate subcutaneous desferrioxamine due to severe hypersensitivity reactions were successfully treated with high-dose intravenous therapy.[5]

Effects on the lungs have also been attributed to hypersensitivity (see above).

1. Miller KB, *et al.* Rapid desensitisation for desferrioxamine anaphylactic reaction. *Lancet* 1981; **i:** 1059.
2. Bousquet J, *et al.* Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983; **ii:** 859–60.
3. Patriarca G, *et al.* Successful desensitization of a child with desferrioxamine hypersensitivity. *J Investig Allergol Clin Immunol* 1995; **5:** 294–5.
4. La Rosa M, *et al.* Desensitization treatment for anaphylactoid reactions to desferrioxamine in a pediatric patient with thalassemia. *J Allergy Clin Immunol* 1996; **97:** 127–8.
5. Lombardo T, *et al.* High-dose intravenous desferrioxamine (DFO) delivery in four thalassemic patients allergic to subcutaneous DFO administration. *Am J Hematol* 1996; **51:** 90–2.

Precautions

Desferrioxamine should be used with caution in patients with renal impairment since the metal complexes are excreted by the kidneys; in those with severe renal impairment dialysis increases elimination. The desferrioxamine-iron complex may colour the urine reddish-brown.

Desferrioxamine may exacerbate aluminium-related encephalopathy and precipitate seizures. Prophylactic treatment with antiepileptics such as clonazepam has been suggested for patients judged to be at risk.

An increased susceptibility to infection, particularly with *Yersinia* species, has been reported in patients with iron overload treated with desferrioxamine. Severe fungal infections have also been reported, mainly in patients undergoing dialysis. If infection is suspected, treatment with desferrioxamine should be stopped and appropriate antimicrobial treatment given.

Skeletal fetal anomalies have occurred in *animals*.

The urinary excretion of iron should be regularly monitored during treatment and periodic ophthalmological and audiological examinations are recommended for patients on long-term therapy. Monitoring of cardiac function is also recommended for patients receiving combined treatment with ascorbic acid (see also under Interactions, below).

Inappropriately high dosage in children with low ferritin levels may retard growth and therefore regular checks on height and weight are recommended for children.

Aluminium encephalopathy. Desferrioxamine may be used in the management of aluminium-associated encephalopathy, but has also been associated with precipitation or exacerbation of dementia,[1-3] with some fatal outcomes,[1] in dialysis patients with aluminium overload. It has been suggested[2] that the effect could be dose related. Desferrioxamine mobilises stored aluminium and may therefore increase plasma-aluminium concentrations, leading to toxicity. Use of a low dose of desferrioxamine (for example, 10 mg/kg) shortly before dialysis, in addition to charcoal haemoperfusion, has been recommended.[1] However, exacerbation of aluminium encephalopathy has also been reported[3] after the low dose of 500 mg twice weekly.

1. Sherrard DJ, *et al.* Precipitation of dialysis dementia by deferoxamine treatment of aluminum related bone disease. *Am J Kidney Dis* 1988; **12:** 126–30.
2. McCauley J, Sorkin I. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 110–14.
3. Lillevang ST, Pedersen FB. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; **4:** 676.

Diagnostic tests. *In vitro* and *animal* studies[1] have suggested that desferrioxamine could interfere with estimations of total iron-binding capacity. It may also interfere with colorimetric iron assays.

Desferrioxamine also binds gallium and has been reported[2-4] to distort the results of gallium-67 imaging studies.

1. Bentur Y, *et al.* Misinterpretation of iron-binding capacity in the presence of deferoxamine. *J Pediatr* 1991; **118:** 139–42.
2. Nagamachi S, *et al.* Gallium-67 scintigraphy in patients with hemochromatosis treated by deferoxamine. *Ann Nucl Med* 1988; **2:** 35–9.
3. Baker DL, Manno CS. Rapid excretion of gallium-67 isotope in an iron-overloaded patient receiving high-dose intravenous deferoxamine. *Am J Hematol* 1988; **29:** 230–2.
4. Brown SJ, *et al.* Altered biodistribution of gallium-67 in a patient with aluminum toxicity treated with desferoxamine. *J Nucl Med* 1990; **31:** 115–17.

Infection susceptibility. *Yersinia enterocolitica* is one of the most iron-dependent of all microbes and the risk of infection is increased in patients with iron overload. Use of exogenous iron-binding compounds (siderophores) such as desferrioxamine, may increase the ability of *Y. enterocolitica* to take up iron and may contribute to the increased risk of infection. Infections due to *Y. enterocolitica* (p.174) have been reported in patients receiving desferrioxamine for acute iron overdosage[1] or for chronic iron overload.[2-5] Severe infection with *Y. pseudotuberculosis* has also been reported in a thalassaemic patient on long-term desferrioxamine therapy.[6]

Treatment with desferrioxamine may also increase susceptibility to mucormycosis. Infections have occurred both in patients with iron overload disorders[7,8] and in those who do not have excessive iron stores.[9-11] A review[8] of 26 cases of mucormycosis in patients undergoing treatment revealed that 23 patients died; in 19 cases the diagnosis was only made at necropsy and only 9 patients received potentially effective treatment (surgery and/or amphotericin B). The organisms responsible were *Rhizopus* species in 13 cases and *Cunninghamella bertholletiae* in 3. In another review of 24 cases of mucormycosis in patients on dialysis,[12] at least 21 were receiving desferrioxamine; infection was fatal in 21 of the 24 patients.

In view of the serious nature of these infections it is important that they should be recognised and treated promptly. It has been suggested that a short course of a suitable antibacterial could be given as prophylaxis to young children from areas with a high incidence of yersiniosis who require treatment with desferrioxamine.[13]

1. Melby K, *et al.* Septicaemia due to Yersinia enterocolitica after oral overdoses of iron. *BMJ* 1982; **285:** 467–8.
2. Scharnetzky M, *et al.* Prophylaxis of systemic yersinosis in thalassaemia major. *Lancet* 1984; **i:** 791.
3. Chiu HY, *et al.* Infection with Yersinia enterocolitica in patients with iron overload. *BMJ* 1986; **292:** 97.
4. Kelly D, *et al.* Yersinia and iron overload. *BMJ* 1986; **292:** 413.
5. Gallant T, *et al.* Yersinia sepsis in patients with iron overload treated with deferoxamine. *N Engl J Med* 1986; **314:** 1643.
6. Gordts B, *et al.* Yersinia pseudotuberculosis septicaemia in thalassaemia major. *Lancet* 1984; **i:** 41–2.
7. Sane A, *et al.* Deferoxamine treatment as a risk factor for zygomycete infection. *J Infect Dis* 1989; **159:** 151–2.
8. Daly AL, *et al.* Mucormycosis: association with deferoxamine therapy. *Am J Med* 1989; **87:** 468–71.
9. Goodill JJ, Abuelo JG. Mucormycosis–a new risk of deferoxamine therapy in dialysis patients with aluminum or iron overload? *N Engl J Med* 1987; **316:** 54.
10. Windus DW, *et al.* Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. *Ann Intern Med* 1987; **107:** 678–80.
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13. Hadjiminas JM. Yersiniosis in acutely iron-loaded children treated with desferrioxamine. *J Antimicrob Chemother* 1988; **21:** 680–1.

Pregnancy. Desferrioxamine has been associated with fetal abnormalities in *animals*, and is generally only recommended in pregnancy if the benefits are considered to outweigh the risks. A review[1] of pregnancy outcome following iron overdose found that of 66 patients reported to the UK Teratology Information Service, 35 of whom had received desferrioxamine, 7 gave birth to infants with malformations (severe in one). However, in each case overdosage had occurred after the first trimester and the malformations therefore could not be directly related to either iron or desferrioxamine. It was concluded that treatment of iron overdose with desferrioxamine should not be withheld solely on the grounds of pregnancy. Long-term use of desferrioxamine has also been reported in pregnant patients with thalassaemia; a case report[2] and review of the literature found no evidence of teratogenicity despite use at various stages of gestation, suggesting that desferrioxamine may be given to the mother if necessary.

1. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
2. Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999; **60:** 24–6.

Interactions

Desferrioxamine is usually given parenterally and thus drug interactions due to chelation with oral metal ions are not a problem.

Ascorbic acid. Ascorbic acid is often given in addition to desferrioxamine to patients with iron overload to achieve better iron excretion. However, early on in treatment when there is excess tissue iron there is some evidence that ascorbic acid may worsen the iron toxicity, particularly to the heart. Thus, ascorbic acid should not be given for the first month after starting desferrioxamine treatment.

Phenothiazines. Neurological symptoms including loss of consciousness occurred in 2 patients given *prochlorperazine* during desferrioxamine therapy,[1] possibly due to synergistic effects on iron mobilisation. UK licensed product information therefore advises that they should not be used together.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Pharmacokinetics

Desferrioxamine mesilate is poorly absorbed from the gastrointestinal tract. After parenteral administration, desferrioxamine forms chelates with metal ions, which are then excreted in the urine; it is also metabolised, primarily in the plasma. The iron-desferrioxamine chelate is excreted in the urine and bile. Desferrioxamine is absorbed during peritoneal dialysis if added to the dialysis fluid. It is also removed by dialysis.

◊ References.

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2. Allain P, *et al.* Pharmacokinetics and renal elimination of desferrioxamine and ferrioxamine in healthy subjects and patients with haemochromatosis. *Br J Clin Pharmacol* 1987; **24:** 207–12.
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Uses and Administration

Desferrioxamine is a chelator that has a high affinity for ferric iron. When given by injection it forms a stable water-soluble iron-complex (ferrioxamine) that is readily excreted in the urine and in bile. Desferrioxamine appears to remove both free iron and bound iron from haemosiderin and ferritin but not from haemoglobin, transferrin, or cytochromes. It is estimated that 100 mg of desferrioxamine mesilate could bind about 8.5 mg of iron but it is unlikely that such a figure could be achieved in practice. Desferrioxamine also has an affinity for other trivalent metal ions including aluminium and theoretically 100 mg of the mesilate could bind 4.1 mg of aluminium.

Desferrioxamine increases the excretion of iron from the body and is used in conditions associated with chronic iron overload (such as the iron storage disorders haemochromatosis and haemosiderosis and after repeated blood transfusions as in thalassaemia) and in acute iron poisoning. It has been used as eye drops in the management of ocular siderosis and corneal rust stains. It is also used to reduce aluminium overload in patients with end-stage renal failure on maintenance dialysis.

Desferrioxamine is used as the mesilate and may be given by subcutaneous or intravenous infusion, by intramuscular injection, or intraperitoneally. It has been given orally in acute iron poisoning but this is no longer generally recommended (see Iron Poisoning, below).

In the treatment of **chronic iron overload**, the dosage and route of administration should be determined for each patient by monitoring urinary iron excretion, with the aim of normalising serum-ferritin concentrations. Continuous subcutaneous infusions, preferably with the aid of a small portable infusion pump, are particularly convenient for ambulant patients and are more effective than intramuscular injections. Continuous intravenous infusion has been recommended for patients incapable of continuing subcutaneous infusions or for those with cardiac problems secondary to iron overload. An initial daily dose of desferrioxamine mesilate 500 mg may be given by subcutaneous infusion or intravenous infusion, increasing until a plateau of iron excretion is reached. The usual effective dose range is 20 to 60 mg/kg daily. Subcutaneous infusions are given 3 to 7 times a week depending on the degree of iron overload, usually over 8 to 12 hours, but infusion over 24 hours may be necessary in some patients. For intramuscular injection, an initial dose of 0.5 to 1 g daily as 1 or 2 injections has been used, with the maintenance dose determined by response. It has been suggested that in addition to intramuscular treatment, up to 2 g of desferrioxamine mesilate should be given by intravenous infusion for each unit of blood transfused, at a rate not more than 15 mg/kg per hour at the time of each blood transfusion. Desferrioxamine should be given separately from the blood. Ascorbic acid supplements can enhance the excretion of iron, but, to reduce the risk of toxicity, should not be started until 1 month after starting desferrioxamine treatment (see under Interactions, above). Ascorbic acid is given in doses of up to 200 mg daily for adults or 50 to 200 mg daily for children; it also enhances iron absorption and should therefore be given separately from food.

Desferrioxamine has been used as a *diagnostic test* for iron storage disease in patients with normal renal function by injecting 500 mg of the mesilate intramuscularly and estimating the excretion of iron in the urine collected over the next 6 hours; an excretion of more than 1 mg of iron is suggestive of iron storage disease and more than 1.5 mg can be regarded as pathological.

In the treatment of **acute iron poisoning**, desferrioxamine is usually given by intravenous infusion, particularly in patients who are symptomatic. However, US licensed product information advises intramuscular injection unless the patient is in shock, due to the risk of adverse effects with the intravenous route. The dose should be adjusted according to the severity of the poisoning, preferably as indicated by the serum-iron concentration and total iron binding capacity, if available, although chelation therapy should be started in patients with significant symptoms without waiting for the results of blood concentrations. In the UK, the usual initial dose of desferrioxamine mesilate is 15 mg/kg per hour by slow intravenous infusion, reducing after 4 to 6 hours to provide a total dose not exceeding 80 mg/kg in 24 hours, although larger doses may be tolerated. Alternatively, it may be given intramuscularly as a single dose of 2 g for adults or 1 g for children. In the USA, an initial dose of 1 g is given, either intravenously at a maximum rate of 15 mg/kg per hour, or by intramuscular injection; subsequent doses of 500 mg may be given, by infusion over 4 to 12 hours or intramuscularly at intervals of 4 to 12 hours, to a maximum of 6 g in 24 hours.

In the treatment of **aluminium overload** in patients with end-stage renal failure, those undergoing maintenance haemodialysis or haemofiltration may be given desferrioxamine mesilate 5 mg/kg once a week by slow intravenous infusion during the last hour of a dialysis session, or 5 hours before dialysis in patients with more severe overload. In patients on peritoneal dialysis (CAPD or CCPD), desferrioxamine mesilate 5 mg/kg may be given once a week, by slow intravenous infusion, subcutaneously, intramuscularly, or intraperitoneally (the recommended route) before the final exchange of the day. For the *diagnosis* of aluminium overload, desferrioxamine mesilate 5 mg/kg is given by slow intravenous infusion during the last hour of haemodialysis. An increase in serum-aluminium concentration above baseline of more than 150 nanograms/mL (measured at the start of the next dialysis session) suggests aluminium overload.

Eye drops containing desferrioxamine mesilate 10% have been used for the treatment of ocular siderosis and corneal rust stains.

Administration. Compliance may be a problem with standard parenteral desferrioxamine regimens in patients with chronic iron overload. The oral,[1-3] rectal,[4] and intranasal[5] routes have therefore been tried as alternatives, but results have generally been disappointing. Twice-daily subcutaneous bolus injection has also been reported,[6-9] although the volume of the injection may be a limiting factor.[9]

Intraperitoneal desferrioxamine may be used to reduce aluminium levels in patients receiving peritoneal dialysis for chronic renal failure. Good results have also been reported[10] in a patient with haemochromatosis complicated by cirrhosis and cardiomyopathy, in whom a chronic peritoneal dialysis catheter was used to control ascites and to give desferrioxamine.

1. Callender ST, Weatherall DJ. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii:** 689.
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Aluminium overload. Desferrioxamine is an effective aluminium chelator and may have a role in both acute and chronic aluminium toxicity.

Accumulation of aluminium may be a particular problem in patients with chronic renal failure and has been implicated in renal osteodystrophy and dialysis dementia, as well as in other conditions, see Aluminium p.2254. The main sources in patients with renal failure are aluminium-containing phosphate binders and the use of tap water with a high aluminium content in the preparation of dialysis fluids. Acute aluminium toxicity is less common, but may occur following exposure to soluble aluminium salts.

Use of alternative phosphate binders (see Renal Osteodystrophy, p.1086) and limits on the aluminium concentration of dialysis fluids reduce the exposure to aluminium in patients with chronic renal failure, but desferrioxamine may also be used to remove aluminium that has already accumulated. The desferrioxamine-aluminium chelate (aluminoxamine) is removed by haemoperfusion and by haemodialysis,[1] and also by peritoneal dialysis, although the amount removed may be much less, and desferrioxamine has been used successfully to treat aluminium overload in dialysis patients. It has also been used with dialysis in acute toxicity.

In patients with *dialysis encephalopathy*, increased aluminium excretion and clinical improvement has been reported[2,3] in patients given desferrioxamine in doses of up to 6 g once a week via the arterial line during the first 2 hours of haemodialysis.[2,3] A study[4] of 11 patients with dialysis encephalopathy found that 5 patients who were treated with deionised or reverse-osmosis water alone died, whereas of 6 who were also given desferrioxamine 6 to 10 g intravenously each week at dialysis, 4 showed clinical improvement. Substantial improvement in early aluminium encephalopathy has been achieved in a patient on continuous ambulatory peritoneal dialysis by using intraperitoneal desferrioxamine.[5] Another small study[6] found that desferrioxamine improved psychomotor function in haemodialysis patients with impaired cerebral function but no clinical encephalopathy, who had only mildly elevated plasma-aluminium concentrations; desferrioxamine was given 3 times weekly during dialysis. Improvement in acute encephalopathy related to alum bladder irrigation has also been reported.[7] However, use of desferrioxamine may also exacerbate encephalopathy and caution is required (see Aluminium Encephalopathy, under Precautions, above).

Desferrioxamine has produced rapid clinical improvement in patients with *dialysis-related bone disease*.[8-10] In some studies[9,10] this has been associated with a reduction in the aluminium content of bone; others[8] have reported clinical improvement with no apparent effect on bone aluminium. Diagnosis of aluminium-related bone disease may require bone biopsy, but some studies have suggested that measurement of plasma-aluminium concentrations after a desferrioxamine infusion may also be used. Some studies reporting positive results[9,11] have used relatively high doses of desferrioxamine (40 mg/kg) with plasma-aluminium measured 24 to 44 hours later; a study[10] using a lower dose of desferrioxamine (28.5 mg/kg) and measuring plasma aluminium 5 hours later found similar increases in patients both with and without bone-aluminium accumulation. However, others have reported[12] that lower doses of desferrioxamine (5 or 10 mg/kg) are adequate when combined with measurement of serum-parathyroid hormone concentrations.

Desferrioxamine therapy has also produced beneficial results in *dialysis patients with anaemia*[13-15] and has also been found to reverse aluminium-induced resistance to erythropoietin.[16,17]

Prurigo nodularis in chronic aluminium overload has responded to desferrioxamine, with resolution of itch and skin lesions.[18]

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3. Arze RS, *et al.* Reversal of aluminium dialysis encephalopathy after desferrioxamine treatment. *Lancet* 1981; **ii:** 1116.
4. Milne FJ, *et al.* Low aluminium water, desferrioxamine, and dialysis encephalopathy. *Lancet* 1982; **ii:** 502.
5. Payton CD, *et al.* Successful treatment of aluminium encephalopathy by intraperitoneal desferrioxamine. *Lancet* 1984; **i:** 1132–3.
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7. Nakamura H, *et al.* Acute encephalopathy due to aluminum toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; **40:** 296–300.
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10. Malluche HH, *et al.* The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* 1984; **311:** 140–4.
11. Milliner DS, *et al.* Use of deferoxamine infusion test in the diagnosis of aluminium-related osteodystrophy. *Ann Intern Med* 1984; **101:** 775–80.

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13. de la Serna F-J, *et al.* Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. *Lancet* 1988; **i:** 1009–11.
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16. Rosenlöf K, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 247–9.
17. Zachée P, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; **335:** 1038–9.
18. Brown MA, *et al.* Prurigo nodularis and aluminium overload in maintenance haemodialysis. *Lancet* 1992; **340:** 48.

Iron overload. Chronic iron overload can be caused by inappropriately increased gastrointestinal absorption, by grossly excessive oral intake over long periods, or by parenteral administration of iron, for example from transfused blood.[1,2] Excess iron is stored in the form of ferritin and haemosiderin. The term *haemosiderosis* is applied to the accumulation of haemosiderin in body tissues without associated tissue damage; *haemochromatosis* refers to a chronic disease state in which iron overload leads to tissue damage, mainly in the heart, liver, and pancreas. Primary or hereditary haemochromatosis is caused by a genetic defect in iron metabolism that results in excessive gastrointestinal absorption of iron. The treatment of choice for primary haemochromatosis is phlebotomy,[1-7] but chelation therapy may be needed in patients with anaemia, hypoproteinaemia, or severe cardiac disease. Neonatal haemochromatosis is a rare condition of unknown cause and results in fetal death or severe liver injury. Antoxidants and iron chelators may improve prognosis,[8] but many infants require liver transplantation. Maternal treatment with normal immunoglobulins has also been reported[9] to reduce the severity of recurrent neonatal haemochromatosis. Secondary or acquired haemochromatosis is commonly associated with chronic anaemias, in particular thalassaemia, in which excessive iron uptake due to disordered erythropoiesis and excess iron from repeated blood transfusions contribute to iron overload.[1,2] These patients generally require iron chelation, usually with parenteral desferrioxamine although oral iron chelators such as deferasirox and deferiprone have also been used (see below).

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4. Hall CJ, *et al.* Haemochromatosis: a time for guidelines? *Hosp Med* 1999; **60:** 884–90.
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THALASSAEMIA. Patients homozygous for β-thalassaemia (p.1045) have severe anaemia requiring regular blood transfusions. As a consequence of this treatment iron overload develops and the excessive deposition of iron in the myocardium usually results in these patients dying in their second or third decade from arrhythmias or cardiac failure. Iron chelators such as desferrioxamine are therefore used to retard the accumulation of iron.

Desferrioxamine has been shown to prevent complications and improve survival in thalassaemic patients given regular systemic therapy.[1-3] There is also some evidence that impaired organ function might improve with intensive therapy. The liver is the main site of iron accumulation in iron overload, and a reduction in liver-iron concentrations and improvement in liver function has been reported[4] in patients with transfusional iron overload treated with desferrioxamine 2 to 4 g by slow subcutaneous infusion over 12 hours on 6 nights a week. However, in another study[5] improvement in the degree of hepatic fibrosis was seen after 3 to 5 years in only 2 of 7 patients given desferrioxamine up to 85 mg/kg daily by subcutaneous injection, despite reductions in iron concentrations. Preservation or possibly improvement in cardiac function has also been reported,[6-8] although cardiac disease continues to be the main cause of death in patients with thalassaemia. Although initial studies used intramuscular treatment, increased iron excretion is seen with continuous subcutaneous infusion, and this is usually the preferred route. However, compliance may be a problem, and is a major determinant of the effectiveness of treatment.[2] Intensive intravenous therapy, using continuous infusion devices, has been used successfully[9] in patients inadequately treated with subcutaneous desferrioxamine, and good results have also been reported[10,11] with intermittent intravenous infusions. Subcutaneous bolus injection has also been used (see Administration, above) although it may not be tolerated in all patients. Better iron excretion may be achieved if patients are given ascorbic acid 100 to 200 mg daily in addition to desferrioxamine (but see under Interactions, above). The most appropriate time to start desferrioxamine is not clear. Beginning chelation therapy before puberty could help to ensure normal sexual development in patients with thalassaemia major.[12] Other studies[1,2] have reported that initiation of therapy before severe iron overload develops, and maintenance of low serum-ferritin concentrations, prevents cardiac disease and improves prognosis, suggesting that chelation therapy should be started as early as possible, to prevent organ damage developing. However, desferrioxamine has been associated with adverse effects on growth (see Effects on Growth Rate, above) and it is usual to delay therapy until children are about 3 years of age, when iron overload becomes significant, although earlier treatment may be required in some cases.[3]

Alternatives to desferrioxamine have also been investigated. Deferiprone, which is given orally, effectively reduces iron overload,[13] but its long-term benefits are controversial. A study[14] in patients with thalassaemia reported progression of hepatic fibrosis in patients given deferiprone, although another study[15] was unable to confirm these findings. Other studies[16,17] have suggested that deferiprone may be superior to desferrioxamine in reducing cardiac complications. A systematic review[18] found no evidence to change treatment recommendations that indicate deferiprone for use in those for whom desferrioxamine is contra-indicated or ineffective; the authors acknowledged that there is a need for more research. Good results have been reported[19] with a combination of desferrioxamine and deferiprone, but the safety and efficacy of this regimen remains to be confirmed. Deferasirox, another oral iron chelator, is also used.

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17. Piga A, *et al.* Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003; **88:** 489–96.
18. Roberts DJ, *et al.* Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/07).
19. Wonke B, *et al.* Combined therapy with deferiprone and desferrioxamine. *Br J Haematol* 1998; **103:** 361–4.

Iron poisoning. Despite the frequency of acute poisoning with iron preparations, no universally accepted treatment protocol exists. Diagnosis relies primarily on the history and clinical symptoms, although it is often difficult to determine the amount of iron ingested, and clinical assessment can be misleading since patients may exhibit mild symptoms despite having ingested potentially toxic quantities of iron. Measurement of the serum-iron concentration is useful in assessing the severity of poisoning but may not be immediately available, and does not always correlate with the severity of symptoms. Measurement of total iron binding capacity (TIBC) has been used but may be misleading and is no longer recommended.

Other tests that have been used include the desferrioxamine challenge test, in which desferrioxamine 50 mg/kg (to a maximum dose of 1 g) is given intramuscularly; if free iron is present, ferrioxamine will be excreted in the urine imparting a classic 'vin rosé' colour. However, interpretation is difficult and a negative result does not rule out toxicity; the test is no longer generally recommended.

The initial stage of treatment involves intravenous fluids and other supportive care as appropriate, and this may be sufficient in mild poisoning. Gastric lavage may be performed to remove any unabsorbed iron from the gastrointestinal tract, but may not remove tablets effectively; whole-bowel irrigation is an alternative, particularly in patients suspected of ingesting modified-release preparations or those with radiographic evidence of unabsorbed tablets remaining after gastric lavage. Addition of desferrioxamine to the lavage fluid has been suggested but there is little evidence of efficacy and some concern over possible toxic effects of ferrioxamine, and it is not routinely recommended. Activated charcoal is not effective in iron poisoning.

Chelation therapy with desferrioxamine is indicated in severe poisoning, including patients with impaired consciousness, shock, hypotension, or severe acidosis; other signs of severe poisoning include leucocytosis. A serum-iron concentration above 5 micrograms/mL indicates severe poisoning, and is usually an indication for chelation, but patients with shock or coma should be treated without waiting for the results of serum-iron tests; patients with moderate poisoning (serum-iron concentration 3 to 5 micrograms/mL) may be given chelation therapy if they are symptomatic. There is no general agreement on the duration of chelation therapy; among the suggested end-points are the resolution of severe symptoms, disappearance of the vin rosé coloration of the urine, 24 hours after the disappearance of coloration, and reduction of serum-iron concentrations to the normal range.

General references.

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4. Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30:** 71–90.

Malaria. Following the suggestion that iron-deficiency anaemia may offer some protection against infections (see Infections in the Precautions for Iron, p.1950), desferrioxamine was tried in a few patients with malaria.[1,2] Any antimalarial effect of desferrioxamine was thought to be as a result of chelation of parasite-associated iron rather than reduction in body-iron concentrations in the patient. Desferrioxamine given intravenously was reported[3] to shorten the time to regain consciousness in children with cerebral malaria receiving standard therapy with intravenous quinine and oral pyrimethamine-sulfadoxine. However, in another study[4] there was no evidence of a beneficial effect on mortality when desferrioxamine was added to an antimalarial treatment regimen that included a loading dose of quinine.

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2. Thompson DF. Deferoxamine treatment of malaria. *Ann Pharmacother* 1994; **28:** 602–3.
3. Gordeuk V, *et al.* Effect of iron chelation therapy on recovery from deep coma, in children with cerebral malaria. *N Engl J Med* 1992; **327:** 1473–7.
4. Thuma PE, *et al.* Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998; **92:** 214–18.

Porphyria. The management of various forms of porphyria is discussed on p.1448. Desferrioxamine has been used to reduce serum-iron concentrations in porphyria cutanea tarda and may have a role if phlebotomy is contra-indicated. In a study of 25 patients with porphyria cutanea tarda,[1] subcutaneous infusion of desferrioxamine was found to be as effective as repeated phlebotomies in normalising porphyrin excretion and iron storage. Desferrioxamine was also used successfully to treat haemodialysis-related porphyria cutanea tarda in a 22-year-old man in whom venesection therapy was contra-indicated because of severe anaemia requiring multiple blood transfusion.[2] Each course of intravenous desferrioxamine therapy after the end of 3 haemodialysis sessions was accompanied by a marked decrease in plasma porphyrins, a sharp increase in haematocrit values, and a simultaneous improvement in skin lesions.

1. Rocchi E, *et al.* Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion. *Br J Dermatol* 1986; **114:** 621–9.
2. Praga M, *et al.* Treatment of hemodialysis-related porphyria cutanea tarda with deferoxamine. *N Engl J Med* 1987; **316:** 547–8.

Preparations

BP 2008: Desferrioxamine Injection;
USP 31: Deferoxamine Mesylate for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Desferal; ***Austral.:*** Desferal; ***Austria:*** Desferal; ***Belg.:*** Desferal; ***Braz.:*** Desferal; ***Canad.:*** Desferal; ***Chile:*** Desferal; ***Cz.:*** Desferal; ***Denm.:*** Desferal; ***Fin.:*** Desferal; ***Fr.:*** Desferal; ***Ger.:*** Desferal; ***Gr.:*** Desferal; ***Hong Kong:*** Desferal; ***Hung.:*** Desferal; ***India:*** Desferal; ***Indon.:*** Desferal; ***Irl.:*** Desferal; ***Israel:*** Desferal; ***Ital.:*** Desferal; ***Malaysia:*** Desferal; ***Mex.:*** Desferal; ***Neth.:*** Desferal; ***Norw.:*** Desferal; ***NZ:*** Desferal†; ***Pol.:*** Desferal; ***Port.:*** Desferal; ***Rus.:*** Desferal (Десферал); ***S.Afr.:*** Desferal; ***Spain:*** Desferin; ***Swed.:*** Desferal; ***Switz.:*** Desferal; ***Thai.:*** Desferal; ***Turk.:*** Desferal; ***UK:*** Desferal; ***USA:*** Desferal; ***Venez.:*** Desferal.

Dexrazoxane *(BAN, USAN, rINN)*

ADR-529; Dexrazoxano; Dexrazoxanum; ICRF-187; NSC-169780. (+)-(S)-4,4′-Propylenebis(piperazine-2,6-dione).

Дексразоксан

$C_{11}H_{16}N_4O_4$ = 268.3.

CAS — 24584-09-6.

ATC — V03AF02.

ATC Vet — QV03AF02.

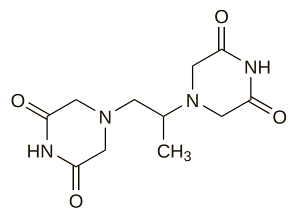

Adverse Effects and Precautions

Dexrazoxane may add to the bone-marrow depression caused by antineoplastics and frequent complete blood counts are recommended during therapy. Although dexrazoxane protects against the cardiotoxic effects of anthracyclines, cardiac function should continue to be monitored when dexrazoxane is used. Pain on injection has been reported.

When used to reduce the cardiotoxicity of doxorubicin, licensed product information in the USA recommends that dexrazoxane should only be given to patients who have received a cumulative dose of doxorubicin of 300 mg/m^2 and who require continued use, since there is some evidence that dexrazoxane may reduce the efficacy of some antineoplastic regimens.

Patients with known liver function disorders should have their liver function assessed before receiving dexrazoxane for anthracycline extravasation.

Effects on the skin. Severe cutaneous and subcutaneous necrosis has been reported[1] in a patient who received dexrazoxane by infusion into a peripheral forearm vein, followed by intravenous injection of doxorubicin at a different site in the same arm. Local pain occurred during the dexrazoxane infusion but there was no evidence of extravasation.

1. Lossos IS, Ben-Yehuda D. Cutaneous and subcutaneous necrosis following dexrazoxane-CHOP therapy. *Ann Pharmacother* 1999; **33:** 253–4.

Pharmacokinetics

Dexrazoxane is mainly excreted in the urine as unchanged drug and metabolites. The elimination half-life is reported to be about 2 hours.

Uses and Administration

Dexrazoxane is the (+)-enantiomorph of the antineoplastic drug razoxane (p.767) and is a cytoprotective agent that is used to reduce the cardiotoxicity of doxorubicin and other anthracyclines (see p.713); it is also used in the management of anthracycline extravasation. It is hydrolysed to an active metabolite that is similar to edetic acid. This chelates iron within the cells and appears to prevent the formation of the anthracycline-iron complex that is thought to be responsible for cardiotoxicity.

Dexrazoxane is used to reduce the incidence and severity of cardiomyopathy associated with doxorubicin or epirubicin in patients with advanced or metastatic cancer who have previously received anthracyclines; in the USA, it is only licensed for use in women with metastatic breast cancer who have received a cumulative dose of doxorubicin of 300 mg/m^2 and who require continued use. It is given as the hydrochloride, by slow intravenous injection or rapid intravenous infusion, starting within 30 minutes before the anthracycline. The dose is expressed as the base. In the USA, the dose is calculated on a 10:1 ratio with doxorubicin; typically, 500 mg/m^2 of dexrazoxane is given for every 50 mg/m^2 of doxorubicin. In the UK the dose is calculated on a 20:1 ratio with doxorubicin and a 10:1 ratio with epirubicin. A reduction in dose may be required in patients with renal impairment (see below).

In patients with anthracycline extravasation, dexrazoxane is given intravenously into a large vein in an area other than that affected by the extravasation. It is given once daily for 3 days, by intravenous infusion over 1 to 2 hours, starting within 6 hours of extravasation; the dose should be given at about the same time each day. The usual dose is 1000 mg/m^2 on the first and second days, and 500 mg/m^2 on the third day; the maximum single dose for patients with a body-surface greater than 2 m^2 is 2000 mg.

Dexrazoxane is also being investigated for use in various other malignancies.

◊ References.

1. Links M, Lewis C. Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. *Drugs* 1999; **57:** 293–308.
2. Schuchter LM, *et al.* 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002; **20:** 2895–903. Also available at: http://www.jco.org/cgi/reprint/20/12/2895.pdf (accessed 04/10/05)
3. Cvetković RS, Scott LJ. Dexrazoxane : a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; **65:** 1005–24.

Administration in children. Doxorubicin has been used in the treatment of acute lymphoblastic leukaemia in children but cardiotoxicity may be a problem. A randomised study[1] in 206 children found that those given dexrazoxane with doxorubicin had fewer elevations of cardiac troponin T, a marker of myocardial damage, than those given doxorubicin alone, but longer follow-up was needed to assess effects on cardiac function and survival. Another study[2] in children with Hodgkin's disease suggested that use of dexrazoxane might increase the risk of secondary malignancies, but further analysis of the leukaemia study[3] found no evidence of such an effect.

1. Lipshultz SE, *et al.* The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004; **351:** 145–53.
2. Tebbi CK, *et al.* Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007; **25:** 493–500.
3. Barry EV, *et al.* Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol* 2008; **26:** 1106–11.

Administration in renal impairment. Dexrazoxane is mainly excreted in the urine and the dose should be reduced in patients with renal impairment. A reduction of 50% is recommended for patients with a creatinine clearance below 40 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cardioxane; ***Braz.:*** Cardioxane; ***Canad.:*** Zinecard; ***Cz.:*** Cardioxane; Savene; ***Denm.:*** Cardioxane; ***Fr.:*** Cardioxane; ***Gr.:*** Savene; ***Hung.:*** Cardioxane; ***Irl.:*** Cardioxane; ***Israel:*** Cardioxane; ***Ital.:*** Cardioxane; ***Mex.:*** Cardioxane; ***Pol.:*** Cardioxane; ***UK:*** Cardioxane; Savene; ***USA:*** Totect; Zinecard; ***Venez.:*** Cardioxane.

Dicobalt Edetate *(BAN, rINN)*

Cobalt Edetate; Cobalt EDTA; Cobalt Tetracemate; Dicobalti Edetas; Dikobolt Edetat; Édétate Dicobaltique; Edetato de dicobalto; Edetato dicobaltio. Cobalt [ethylenediaminetetra-acetato(4−)-*N*,*N*′,*O*,*O*′]cobalt(II).

Дикобальта Эдетат

$C_{10}H_{12}Co_2N_2O_8$ = 406.1.

CAS — 36499-65-7.

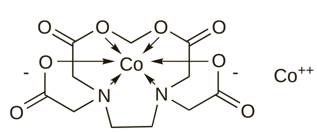

Adverse Effects and Precautions

Dicobalt edetate may cause hypotension, tachycardia, and vomiting. Anaphylactic reactions have occurred; oedema of the face and neck, sweating, chest pain, cardiac irregularities, and skin rashes have been reported. The adverse effects of dicobalt edetate are more severe in the absence of cyanide. Therefore, dicobalt edetate should not be given unless cyanide poisoning is definitely confirmed and poisoning is moderate or severe, that is, when consciousness is impaired.

Oedema. A patient with cyanide toxicity developed severe facial and pulmonary oedema after treatment with dicobalt edetate.[1] It has been suggested that when dicobalt edetate is used, facilities for intubation and resuscitation should be immediately available.

1. Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *BMJ* 1985; **291:** 785–6.

Uses and Administration

Dicobalt edetate is a chelator used in the treatment of acute cyanide poisoning (p.2045). Its use arises from the property of cobalt salts to form a relatively non-toxic stable ion-complex with cyanide. Owing to its toxicity, dicobalt edetate should be used only in confirmed cyanide poisoning and never as a precautionary measure. Cyanide poisoning must be treated as quickly as possible. A suggested dose is 300 mg given by intravenous injection over about 1 minute, repeated if the response is inadequate; a further dose of 300 mg of dicobalt edetate may be given 5 minutes later if required. For less severe poisoning the injection should be given over 5 minutes. Each injection of dicobalt edetate may be followed immediately by 50 mL of glucose 50% intravenously to reduce toxicity, though the value of giving glucose has been questioned.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Kelocyanor; ***Gr.:*** Kelocyanor.

Digoxin-specific Antibody Fragments

Digoxin Immune Fab (Ovine); F(ab); Fragmentos de anticuerpos específicos antidigoxina.

ATC — V03AB24.

ATC Vet — QV03AB24.

Adverse Effects and Precautions

Allergic reactions to digoxin-specific antibody fragments have been reported rarely. Patients known to be allergic to sheep protein and patients who have previously received digoxin-specific antibody fragments are likely to be at greater risk of developing an allergic reaction. Blood pressure, ECG, and potassium concentrations should be monitored closely during and after use.

Uses and Administration

Digoxin-specific antibody fragments are derived from antibodies produced in sheep immunised to digoxin. Digoxin has greater affinity for the antibodies than for tissue-binding sites, and the digoxin-antibody complex is then excreted in the urine. Digoxin-specific antibody fragments are generally restricted to the treatment of life-threatening digoxin or digitoxin intoxication in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

It is estimated that 38 mg of antibody fragments could bind about 500 micrograms of digoxin or digitoxin and the dose calculation is based on this estimate and the body-load of digoxin (based on the amount ingested or ideally from the steady-state plasma concentration). Administration is by intravenous infusion over a 30-minute period. If cardiac arrest is imminent the dose may be given as a bolus. In the case of incomplete reversal or recurrence of toxicity a further dose can be given. In patients considered to be at high risk of an allergic response an intradermal or skin scratch test may be performed.

◊ Clinical studies[1-3] and reviews[4] of the use of digoxin-specific antibody fragments have confirmed their effectiveness in the treatment of severe digitalis toxicity in the majority of patients. An initial response is usually seen within 30 minutes of the end of the infusion with a maximum response after 3 to 4 hours.[4] The main causes of treatment failure or partial response are incorrect diagnosis of digitalis intoxication, inadequate dosage of antibody fragments, and use in patients already moribund.[3,4] Few adverse reactions have been attributed to the use of digoxin-specific antibody fragments; a few cases of minor allergic reactions have been reported including erythema, facial swelling, urticaria, and rashes,[2,4] but no anaphylactic reactions have been reported.[1-4] Haemodynamic status normally improves, but withdrawal of the inotropic support provided by digoxin may produce a decline in cardiac function in some patients. There may be dramatic reductions in plasma potassium concentrations.

Treatment has been successful in patients with varying degrees of renal impairment.[2,4,5] Elimination of the antibody fragment-digoxin complex may be markedly delayed in severe renal impairment and prolonged monitoring may be required in such patients.[6] Measurement of free serum-digoxin concentrations may be useful.[7] Experience with digoxin-specific antibody fragments in a patient with chronic renal failure receiving haemodialysis has been reported.[8] The patient had a good clinical response but haemodialysis did not remove the antibody fragment-digoxin complex.

In patients with adequate renal function the half-life of the antibody fragment-digoxin complex has been reported[2] to be about 16 to 20 hours although longer half-lives have been reported.[9] It has been suggested[10] that giving digoxin-specific antibody fragments by infusion over 7 hours, after an initial loading dose, could be useful in ensuring adequate antibody concentrations are maintained to bind digoxin as it is released from tissue stores over a prolonged period.

Use of the antibody fragments has also been effective in children with severe digitalis intoxication.[11]

Digoxin-specific antibody fragments have also been used successfully in poisoning due to preparations containing toad venom,[12] or due to common or yellow oleander (see Oleander, p.2356).

1. Smith TW, *et al*. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. *N Engl J Med* 1982; **307:** 1357–62.
2. Wenger TL, *et al*. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol* 1985; **5:** 118A–123A.
3. Antman EM, *et al*. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. *Circulation* 1990; **81:** 1744–52.
4. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; **27:** 1115–33.
5. Allen NM, *et al*. Clinical and pharmacokinetic profiles of digoxin immune Fab in four patients with renal impairment. *DICP Ann Pharmacother* 1991; **25:** 1315–20.
6. Ujhelyi MR, *et al*. Disposition of digoxin immune Fab in patients with kidney failure. *Clin Pharmacol Ther* 1993; **54:** 388–94.
7. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; **28:** 483–93.
8. Clifton GD, *et al*. Free and total serum digoxin concentrations in a renal failure patient after treatment with digoxin immune Fab. *Clin Pharm* 1989; **8:** 441–5.
9. Gibb I, Parnham A. A star treatment for digoxin overdose? *BMJ* 1986; **293:** 1171–2.
10. Schaumann W, *et al*. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; **30:** 527–33.
11. Woolf AD, *et al*. The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med* 1992; **326:** 1739–44.
12. Brubacher JR, *et al*. Treatment of toad venom poisoning with digoxin-specific Fab fragments. *Chest* 1996; **110:** 1282–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Digibind; ***Austria:*** Digitalis Antidot†; ***Belg.:*** Digitalis Antidot; ***Canad.:*** Digibind; ***Fr.:*** Digidot†; ***Ger.:*** Digitalis Antidot; ***Gr.:*** Digibind†; DigiFab; ***Hong Kong:*** Digitalis Antidote; ***Swed.:*** Digitalis Antidot; ***Switz.:*** Digitalis Antidot; ***UK:*** Digibind; ***USA:*** Digibind; DigiFab.

Dimercaprol *(BAN, rINN)*

BAL; British Anti-Lewisite; Dimercaprolum; Dimerkaprol; Dimerkaproli; Dimerkaprolis. 2,3-Dimercaptopropan-1-ol.

Димеркапрол

$C_3H_8OS_2$ = 124.2.

CAS — 59-52-9.

ATC — V03AB09.

ATC Vet — QV03AB09.

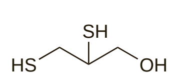

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Dimercaprol). A clear colourless or slightly yellow liquid. Soluble in water and in arachis oil; miscible with alcohol and with benzyl benzoate. Store at 2° to 8° in well-filled airtight containers. Protect from light.

USP 31 (Dimercaprol). A colourless or practically colourless liquid, having a disagreeable, mercaptan-like odour. Soluble 1 in 20 of water; soluble in alcohol, in benzyl benzoate, and in methyl alcohol. Store at a temperature not exceeding 8° in airtight containers. Protect from light.

Adverse Effects and Treatment

The most consistent adverse effects produced by dimercaprol are hypertension and tachycardia. Other adverse effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat, and eyes, lachrymation and salivation, tingling of the extremities, a sensation of constriction in the throat and chest, muscle pains and muscle spasm, rhinorrhoea, conjunctivitis, sweating, restlessness, and abdominal pain. Transient reductions in the leucocyte count have also been reported. Pain may occur at the injection site and sterile abscesses occasionally develop. In children, fever commonly occurs and persists during therapy.

Adverse effects are dose-related, relatively frequent, and usually reversible. It has been suggested that ephedrine sulfate 30 to 60 mg, given by mouth 30 minutes before each injection of dimercaprol, may reduce adverse effects; antihistamines may alleviate some of the symptoms.

Precautions

Dimercaprol should be used with care in patients with hypertension or renal impairment. It should be discontinued, or continued with extreme caution, if acute renal insufficiency develops during therapy. Alkalinisation of the urine may protect the kidney during therapy by stabilising the dimercaprol-metal complex. Dimercaprol should not be used in patients with hepatic impairment unless due to arsenic poisoning. It should not be used in the treatment of poisoning due to cadmium, iron, or selenium as the dimercaprol-metal complexes formed are more toxic than the metals themselves.

G6PD deficiency. Haemolysis has been reported[1] during chelation therapy with dimercaprol and sodium calcium edetate for high blood-lead concentrations in 2 children with a deficiency of G6PD.

1. Janakiraman N, *et al*. Hemolysis during BAL chelation therapy for high blood lead levels in two G6PD deficient children. *Clin Pediatr (Phila)* 1978; **17:** 485–7.

Interactions

Iron supplements should not be given during dimercaprol therapy as toxic dimercaprol-metal complexes are formed.

Pharmacokinetics

After intramuscular injection, maximum blood concentrations of dimercaprol may be attained within 30 to 60 minutes. Dimercaprol is rapidly metabolised and the metabolites and dimercaprol-metal chelates are excreted in the urine and bile. Elimination is essentially complete within 4 hours of a single dose.

Uses and Administration

Dimercaprol is a chelator used in the treatment of acute poisoning by arsenic (p.2261), gold (p.123), and mercury (p.2342); it may also be used in the treatment of poisoning by antimony, bismuth, and possibly thallium. It is also used, with sodium calcium edetate, in acute lead poisoning (p.2332).

The sulfhydryl groups on dimercaprol compete with endogenous sulfhydryl groups on proteins such as enzymes to combine with these metals; chelation by dimercaprol therefore prevents or reverses any inhibition of the sulfhydryl enzymes by the metal and the dimercaprol-metal complex formed is readily excreted by the kidney. Since the complex may dissociate, particularly at acid pH, or be oxidised, the aim of treatment is to provide an excess of dimercaprol in body fluids until the excretion of the metal is complete.

Dimercaprol should be given by deep intramuscular injection and the injections should be given at different sites. The usual initial dose is up to 18 mg/kg daily in divided doses on the first day, reducing the daily dose and the frequency of injections over the subsequent days; a minimum interval of 4 hours between doses appears to reduce adverse effects. The individual dose is determined by severity of symptoms and the causative agent. Single doses should not generally exceed 3 mg/kg but single doses of up to 5 mg/kg may be required initially in patients with severe acute poisoning. Various dosage schedules are in use.

In the UK, adults may be given doses of 400 to 800 mg on the first day of treatment, 200 to 400 mg on the second and third days, and 100 to 200 mg on the fourth and subsequent days, all in divided doses; children may be given a similar dose per kg as for adults. Alternatively, the *BNF* recommends a dose for both adults and children of 2.5 to 3 mg/kg every 4 hours for 2 days, 2 to 4 times daily on the third day, then 1 to 2 times daily for 10 days or until recovery.

In the USA, a recommended schedule for severe arsenical or gold poisoning is 3 mg/kg given at 4-hourly intervals throughout the first 2 days, 4 times on the third day, and twice on each of the next 10 days. In milder cases, 2.5 mg/kg is given 4 times daily on each of the first 2 days, twice daily on the third day, and once daily on subsequent days for 10 days or until recovery.

Dimercaprol is also used with sodium calcium edetate (p.1462) in the treatment of lead poisoning and can be of particular value in the treatment of acute lead encephalopathy. Dimercaprol is usually started first, since sodium calcium edetate may cause lead to shift into the CNS. A suggested procedure is to give dimercaprol intramuscularly in an initial dose of 4 mg/kg, followed at 4-hourly intervals by dimercaprol 3 to 4 mg/kg intramuscularly and sodium calcium edetate; the sodium calcium edetate may be given either intravenously, or intramuscularly at a different site from the dimercaprol. Treatment may be continued for 2 to 7 days depending on the clinical response.

Preparations

BP 2008: Dimercaprol Injection;
USP 31: Dimercaprol Injection.

Proprietary Preparations (details are given in Part 3)

Rus.: Zorex (Зорекс).

4-Dimethylaminophenol Hydrochloride

Dimetamfenol Hydrochloride; 4-Dimetilaminofenol, hidrocloruro de; 4-DMAP.

$C_8H_{11}NO,HCl$ = 173.6.

CAS — 619-60-3 (4-dimethylaminophenol); 5882-48-4 (4-dimethylaminophenol hydrochloride).

ATC — V03AB27.

ATC Vet — QV03AB27.

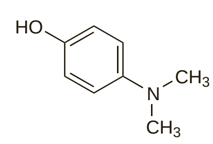

(4-dimethylaminophenol)

Profile

4-Dimethylaminophenol hydrochloride is reported to oxidise haemoglobin to methaemoglobin and has been used with sodium thiosulfate as an alternative to sodium nitrite (p.1464) in the treatment of cyanide poisoning. Doses of 3 to 4 mg/kg have been given intravenously.

◊ References.

1. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)–experimental and clinical overview. *Fundam Appl Toxicol* 1983; **3:** 387–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: 4-DMAP; ***Neth.:*** 4-DMAP.

Diprenorphine Hydrochloride *(BANM, rINNM)*

Diprénorphine, Chlorhydrate de; Diprenorphini Hydrochloridum; Hidrocloruro de diprenorfina; M-5050. (6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-(1-hydroxy-1-methylethyl)-6-*O*-methyl-6,14-ethano-17-normorphine hydrochloride; 2-[(−)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]propan-2-ol hydrochloride.

Дипренорфина Гидрохлорид

$C_{26}H_{35}NO_4,HCl = 462.0.$

CAS — 14357-78-9 (diprenorphine); 16808-86-9 (diprenorphine hydrochloride).

ATC Vet — QV03AB92.

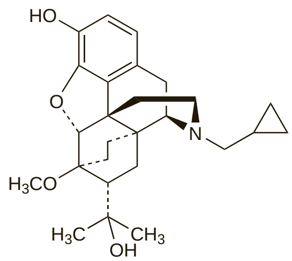

(diprenorphine)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Diprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Diprenorphine hydrochloride is an opioid antagonist used in veterinary medicine to reverse the effects of etorphine hydrochloride.

Ditiocarb Sodium *(rINN)*

DDTC; Dithiocarb Sodium; Ditiocarbe Sodique; Ditiocarbo sódico; Ditiocarbum Natricum; DTC; Sodium Diethyldithiocarbamate; Sodu dietyloditiokarbaminian; U-14624.

Дитиокарб Натрий

$C_5H_{10}NNaS_2 = 171.3.$

CAS — 148-18-5.

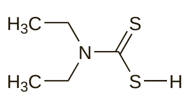

(ditiocarb)

Profile

Ditiocarb sodium is a chelator that has been used in nickel carbonyl poisoning. Disulfiram (p.2296), which is rapidly metabolised to ditiocarb, has been used as an alternative. Ditiocarb has also been used in the destruction of cisplatin wastes (see Handling and Disposal, p.699). It also has immunomodulating properties and has been investigated in HIV infection.

Edetic Acid *(BAN, rINN)*

Acide Édétique; Ácido edético; Acidum edeticum; Edathamil; Edetiinihappo; Edetinsyra; Edeto rūgštis; EDTA; Etiléndiamintetraecetsav; Kwas edetynowy; Kyselina edetová; Tetracemic Acid. Ethylenediaminetetra-acetic acid.

Эдетовая Кислота

$C_{10}H_{16}N_2O_8 = 292.2.$

CAS — 60-00-4.

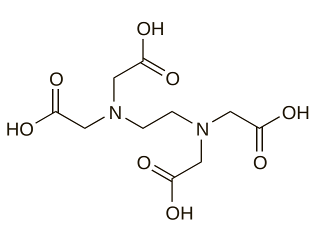

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Edetic Acid). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Edetic Acid). A white crystalline powder. Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Incompatibility. Edetic acid and its salts chelate bivalent and trivalent metals and may affect the activity of drugs such as zinc insulin that contain such ions. Although edetates may enhance the antimicrobial efficacy of some disinfectants (see Chloroxylenol, p.1640), other preservatives may be inactivated. For reference to the inactivation of phenylmercuric salts by disodium edetate, see Incompatibility, under Phenylmercuric Nitrate, p.1657. For a report of edetates reducing the antimicrobial efficacy of thiomersal, see Incompatibility, p.1664.

Adverse Effects and Precautions

Edetic acid, used as a pharmaceutical excipient, is generally well tolerated. Adverse effects have been reported after inhalation of solutions containing edetic acid.

Asthma. Inhalation of an ipratropium nebuliser solution that contained edetic acid as one of the preservatives caused bronchoconstriction in 6 of 22 patients with asthma.[1] Inhalation of edetic acid alone produced dose-related bronchoconstriction that persisted for more than 1 hour.

1. Beasley CRW, *et al*. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987; **294:** 1197–8.

Blood testing. Pseudothrombocytopenia due to platelet clumping is a recognised complication of the use of edetates as anticoagulants for blood sampling and may lead to diagnostic errors.[1] The mechanism appears to be antibody-mediated. Alternative anticoagulants have been suggested.[1,2]

1. Bizzaro N. EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10-year follow-up. *Am J Hematol* 1995; **50:** 103–9.
2. Lippi U, *et al*. EDTA-induced platelet aggregation can be avoided by a new anticoagulant also suitable for automated complete blood count. *Haematologica* 1990; **75:** 38–41.

Uses

Edetic acid and its salts are chelators and are used in pharmaceutical manufacturing as well as having other industrial applications. They are also used as anticoagulants for blood taken for haematological investigations. Salts of edetic acid that are used clinically include sodium edetate (p.1463), sodium calcium edetate (p.1462), dicobalt edetate (p.1443), and sodium feredetate (p.1962).

Gallstones. Edetic acid has been suggested as a possible solvent for non-cholesterol gallstones (p.2409).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Clear Eyes Contact Lens Relief; Summers Eve Post-Menstrual; Triv; Zonite.

Flumazenil *(BAN, USAN, rINN)*

Flumatseniili; Flumazénil; Flumazenilis; Flumazenilum; Flumazepil; Ro-15-1788; Ro-15-1788/000. Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

Флумазенил

$C_{15}H_{14}FN_3O_3 = 303.3.$

CAS — 78755-81-4.

ATC — V03AB25.

ATC Vet — QV03AB25.

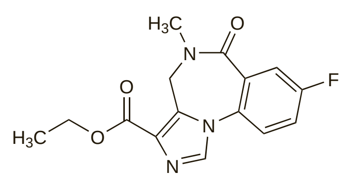

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Flumazenil). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in dichloromethane; sparingly soluble in methyl alcohol.

USP 31 (Flumazenil). A white to off-white powder. Practically insoluble in water; slightly soluble in acidic aqueous solutions. Store in airtight containers.

Adverse Effects and Precautions

The adverse effects experienced during use of flumazenil are generally due to the reversal of benzodiazepine effects and resemble benzodiazepine withdrawal symptoms (see p.987). Nausea, vomiting, dizziness, blurred vision, headache, and flushing may occur. Anxiety, fear, and agitation have been reported after too rapid reversal of sedation. There have been reports of seizures, especially in epileptics. Transient increases in blood pressure and heart rate have been observed. Hypersensitivity reactions have occurred rarely. Patients who have received benzodiazepines for prolonged periods are particularly at risk of experiencing withdrawal symptoms and rapid injection of flumazenil should be avoided in such patients.

Because of its short duration of action, patients given flumazenil to reverse benzodiazepine-induced sedation should be kept under close observation; further doses of flumazenil may be necessary. Flumazenil is contra-indicated in patients who are receiving benzodiazepines to control potentially life-threatening conditions and should not be given to epileptic patients who have been receiving benzodiazepines for a prolonged period to control seizures.

In cases of mixed overdose, flumazenil may unmask adverse effects of other psychotropic drugs. In particular, it should not be used in the presence of severe intoxication with tricyclic and related antidepressants.

Flumazenil should not be given to patients who have received neuromuscular blockers until the effects of neuromuscular blockade have fully cleared. Dosage should be adjusted individually; in high-risk or anxious patients, and after major surgery, it may be preferable to maintain some sedation during the early postoperative period. Flumazenil should be used with caution in patients with head injury since it may precipitate seizures or alter cerebral blood flow.

Careful titration of dosage is recommended in hepatic impairment.

◊ Cardiac arrhythmias,[1] sometimes preceded by tonic-clonic (grand mal) seizures[2,3] and occasionally fatal,[2] have been reported in several patients after the use of flumazenil for mixed overdoses with benzodiazepines and other psychotropics. Heart block has also been reported[4] after flumazenil use in a patient who had taken benzodiazepines, paracetamol, nifedipine, and atenolol. Death from refractory tonic-clonic seizures has been reported in a patient[5] after the use of flumazenil for a mixed overdose with a benzodiazepine and a tricyclic antidepressant.

Death from respiratory failure occurred in an 83-year-old woman after sedation with midazolam[6] despite use of flumazenil, although some[7] considered that this did not represent a failure by flumazenil to reverse the depressive effects on respiration of midazolam. Ventricular fibrillation followed by asystole and death has been reported in a patient given flumazenil during weaning from assisted ventilation (a period during which diazepam had been given).[8]

1. Short TG, *et al*. Ventricular arrhythmia precipitated by flumazenil. *BMJ* 1988; **296:** 1070–1.
2. Burr W, *et al*. Death after flumazenil. *BMJ* 1989; **298:** 1713.
3. Marchant B, *et al*. Flumazenil causing convulsions and ventricular tachycardia. *BMJ* 1989; **299:** 860.
4. Herd B, Clarke F. Complete heart block after flumazenil. *Hum Exp Toxicol* 1991; **10:** 289.
5. Haverkos GP, *et al*. Fatal seizures after flumazenil administration in a patient with mixed overdose. *Ann Pharmacother* 1994; **28:** 1347–9.
6. Lim AG. Death after flumazenil. *BMJ* 1989; **299:** 858–9. Correction. *ibid.*: 1531.
7. Birch BRP, Miller RA. Death after flumazenil? *BMJ* 1990; **300:** 467–8.
8. Katz Y, *et al*. Cardiac arrest associated with flumazenil. *BMJ* 1992; **304:** 1415.

Effects on mental function. Although flumazenil is considered to lack agonist properties, a study[1] in healthy subjects found that intravenous flumazenil resulted in impairment of some measures of cognition and alertness. A severe acute psychotic disorder, which developed during treatment with flumazenil in a patient with hepatic encephalopathy, resolved when flumazenil was discontinued.[2]

1. Neave N, *et al*. Dose-dependent effects of flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers. *Br Dent J* 2000; **189:** 668–74.
2. Seebach J, Jost R. Flumazenil-induced psychotic disorder in hepatic encephalopathy. *Lancet* 1992; **339:** 488–9.

Pharmacokinetics

Flumazenil is well absorbed from the gastrointestinal tract but undergoes extensive first-pass hepatic metabolism and has a systemic bioavailability of about 20%. It is about 50% bound to plasma proteins. After intravenous administration it is extensively metabolised in the liver to the inactive carboxylic acid form, which is excreted mainly in the urine. The elimination half-life is about 40 to 80 minutes. In patients with hepatic impairment the clearance of flumazenil is decreased with a resultant prolongation of half-life.

◊ References.

1. Klotz U, *et al.* Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *Eur J Clin Pharmacol* 1984; **27:** 115–17.
2. Roncari G, *et al.* Pharmacokinetics of the new benzodiazepine antagonist Ro 15-1788 in man following intravenous and oral administration. *Br J Clin Pharmacol* 1986; **22:** 421–8.
3. Breimer LTM, *et al.* Pharmacokinetics and EEG effects of flumazenil in volunteers. *Clin Pharmacokinet* 1991; **20:** 491–6.
4. Jones RDM, *et al.* Pharmacokinetics of flumazenil and midazolam. *Br J Anaesth* 1993; **70:** 286–92.
5. Roncari G, *et al.* Flumazenil kinetics in the elderly. *Eur J Clin Pharmacol* 1993; **45:** 585–7.

Uses and Administration

Flumazenil is a benzodiazepine antagonist that acts competitively at CNS benzodiazepine receptors. It is used in anaesthesia and intensive care to reverse benzodiazepine-induced sedation; it may also be used to treat benzodiazepine overdosage (but see warnings in Precautions, above, and under Benzodiazepine Antagonism: Overdosage, below).

Flumazenil should be given by slow intravenous injection or infusion.

The usual initial dose for the reversal of benzodiazepine-induced sedation is 200 micrograms, followed at intervals of 60 seconds by further doses of 100 to 200 micrograms if required, to a maximum total dose of 1 mg or occasionally 2 mg (usual range, 0.3 to 1 mg); each dose should be given over 15 seconds, and further doses should only be given if an adequate response has not occurred 45 seconds after completion of the injection. If drowsiness recurs an intravenous infusion may be used, at a rate of 100 to 400 micrograms/hour, adjusted according to response. Alternatively, further doses of up to 1 mg, in boluses of 200 micrograms as above, may be given at 20-minute intervals to a maximum of 3 mg in one hour. Patients at risk from the effects of benzodiazepine reversal, such as those dependent on benzodiazepines, should receive smaller bolus injections of 100 micrograms. The dose for children is 10 micrograms/kg, repeated at 60-second intervals up to a maximum of 50 micrograms/kg or 1 mg, whichever is lower; doses are given intravenously over 15 seconds, with further doses if an adequate response has not occurred 45 seconds after completion of the injection, as for adults.

The usual initial dose for the management of benzodiazepine overdose is 200 micrograms given intravenously over 30 seconds. A further dose of 300 micrograms can be given after another 30 seconds and can be followed by doses of 500 micrograms at one-minute intervals if required, to a total dose of 3 mg or occasionally 5 mg. If a dose of up to 5 mg produces no response then further doses are unlikely to be effective. If symptoms of intoxication recur, repeated doses may be given at 20-minute intervals; not more than 1 mg should be given at any one time and not more than 3 mg in one hour. As before a slower rate of administration may be used for 'at risk' patients.

If signs of overstimulation occur during the use of flumazenil, then diazepam or midazolam may be given by slow intravenous injection.

Flumazenil labelled with carbon-11 has been used for studying GABA receptors by positron emission tomography.

◊ General references.

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; **42:** 1061–89.
2. Hoffman EJ, Warren EW. Flumazenil: a benzodiazepine antagonist. *Clin Pharm* 1993; **12:** 641–56.
3. Krenzelok EP. Judicious use of flumazenil. *Clin Pharm* 1993; **12:** 691–2.
4. Seger DL. Flumazenil—treatment or toxin. *J Toxicol Clin Toxicol* 2004; **42:** 209–16.

Benzodiazepine antagonism. Flumazenil is a specific benzodiazepine antagonist that binds competitively with benzodiazepine receptors, reversing the centrally mediated effects of benzodiazepines. Its effects are evident within a few minutes of intravenous injection, even after substantial doses of benzodiazepines, and last for up to 3 hours depending on the dose and on the characteristics of the benzodiazepine intoxication. In patients who have received benzodiazepines for prolonged periods, flumazenil may precipitate withdrawal symptoms.

SEDATION. Flumazenil reduces sedation and amnesia following the use of benzodiazepines for induction or maintenance of general anaesthesia, and in patients undergoing minor surgery or diagnostic procedures who are given benzodiazepines for conscious sedation.[1] Sedation may recur, particularly if long-acting benzodiazepines have been used, and there have been reports of increased analgesic requirements and anxiety following the use of flumazenil. Although flumazenil may antagonise the obvious effects of sedation, higher cognitive functions may still be impaired[2,3] and the patient may be unfit to be discharged safely unaccompanied. Flumazenil is usually given intravenously but reversal of sedation has also been reported[4] with oral use. Although experience with flumazenil in children is limited, it appears to be well tolerated and effective when used to reverse conscious sedation.[5] Flumazenil has also been used in intensive care to reverse sedation and assist in weaning from mechanical ventilation, but is not routinely recommended.

OVERDOSAGE. Flumazenil may be used as an adjunct in the management of benzodiazepine overdose including overdose involving multiple agents. However, its use may unmask the effects of other intoxicants,[6] and since benzodiazepine overdose is rarely lethal and may even protect against the toxicity of other drugs, flumazenil should be used with great caution in mixed overdose, particularly when involving tricyclic antidepressants.[7] Repeated doses of flumazenil may be required to maintain consciousness depending on the benzodiazepine responsible and the magnitude of the overdose; continuous infusion has also been used.[8,9]

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; **42:** 1061–89.
2. Sanders LD, *et al.* Reversal of benzodiazepine sedation with the antagonist flumazenil. *Br J Anaesth* 1991; **66:** 445–53.
3. Girdler NM, *et al.* A randomised crossover trial of post-operative cognitive and psychomotor recovery from benzodiazepine sedation: effects of reversal with flumazenil over a prolonged recovery period. *Br Dent J* 2002; **192:** 335–9.
4. Girdler NM, *et al.* A randomised, controlled trial of cognitive and psychomotor recovery from midazolam sedation following reversal with oral flumazenil. *Anaesthesia* 2002; **57:** 868–76.
5. Shannon M, *et al.* Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. *J Pediatr* 1997; **131:** 582–6.
6. Weinbroum AA, *et al.* A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Safety* 1997; **17:** 181–96.
7. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness: controversies in the use of a 'coma cocktail'. *JAMA* 1995; **274:** 562–9.
8. Brammer G, *et al.* Continuous intravenous flumazenil infusion for benzodiazepine poisoning. *Vet Hum Toxicol* 2000; **42:** 280–1.
9. Chern C-H, *et al.* Continuous flumazenil infusion in preventing complications arising from severe benzodiazepine intoxication. *Am J Emerg Med* 1998; **16:** 238–41.

Hepatic encephalopathy. Flumazenil has been tried in hepatic encephalopathy (p.1697) because of the suspected role of benzodiazepine-like agonists in the pathogenesis of the disorder.[1,2] However, benefits have generally been modest, and a meta-analysis[3] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended.

1. Grimm G, *et al.* Improvement of hepatic encephalopathy treated with flumazenil. *Lancet* 1988; **ii:** 1392–4.
2. Basile AS, *et al.* The pathogenesis and treatment of hepatic encephalopathy: evidence for the involvement of benzodiazepine receptor ligands. *Pharmacol Rev* 1991; **43:** 27–71.
3. Als-Nielsen B, *et al.* Benzodiazepine receptor antagonists for hepatic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 04/10/05).

Non-benzodiazepine antagonism. Although flumazenil is a specific benzodiazepine antagonist, it may also block the effects of other drugs that act via the benzodiazepine receptor, such as zopiclone and zolpidem. In a double-blind study[1] in healthy subjects, flumazenil rapidly antagonised clinical sedation induced by zolpidem, and a rapid response to flumazenil has been reported[2] in a patient who presented in a coma following mixed overdosage with zolpidem, alcohol, and prothipendyl. There have also been reports of flumazenil reversing coma associated with antihistamines,[3] carisoprodol,[4] gabapentin,[5] and promethazine.[6] Although reversal of alcohol-induced sedation has also been suggested, a controlled study[7] found no effect with flumazenil at a dose comparable to that used for benzodiazepine overdosage.

1. Patat A, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther* 1994; **56:** 430–6.
2. Lheureux P, *et al.* Zolpidem intoxication mimicking narcotic overdose: response to flumazenil. *Hum Exp Toxicol* 1990; **9:** 105–7.
3. Lassaletta A, *et al.* Reversal of an antihistamine-induced coma with flumazenil. *Pediatr Emerg Care* 2004; **20:** 319–20.
4. Roberge RJ, *et al.* Flumazenil reversal of carisoprodol (Soma) intoxication. *J Emerg Med* 2000; **18:** 61–4.
5. Butler TC, *et al.* Flumazenil and dialysis for gabapentin-induced coma. *Ann Pharmacother* 2003; **37:** 74–6.
6. Plant JR, MacLeod DB. Response of a promethazine-induced coma to flumazenil. *Ann Emerg Med* 1994; **24:** 979–82.
7. Lheureux P, Askenasi R. Efficacy of flumazenil in acute alcohol intoxication: double blind placebo-controlled evaluation. *Hum Exp Toxicol* 1991; **10:** 235–9.

Preparations

USP 31: Flumazenil Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fadaflumaz; Flumage; Flumanovag; Flumazen; Fluxifarm; Lanexat†; ***Austral.:*** Anexate; ***Austria:*** Anexate; ***Belg.:*** Anexate; ***Braz.:*** Flumazen; Flumazil; Lanexat; ***Canad.:*** Anexate; ***Chile:*** Lanexat; ***Cz.:*** Anexate; ***Denm.:*** Lanexat; ***Fin.:*** Lanexat; ***Fr.:*** Anexate; ***Ger.:*** Anexate; ***Gr.:*** Anexate; Demoxate; Flumexate; ***Hong Kong:*** Anexate; ***Hung.:*** Anexate; ***Indon.:*** Anexate; ***Irl.:*** Anexate; ***Israel:*** Anexate; ***Ital.:*** Anexate; ***Malaysia:*** Anexate; ***Mex.:*** Lanexat; ***Neth.:*** Anexate; ***Norw.:*** Anexate; ***NZ:*** Anexate; ***Philipp.:*** Anexate; ***Pol.:*** Anexate; ***Port.:*** Anexate; ***S.Afr.:*** Anexate; ***Singapore:*** Anexate; ***Spain:*** Anexate; ***Swed.:*** Lanexat; ***Switz.:*** Anexate; ***Thai.:*** Anexate; ***Turk.:*** Anexate; ***UK:*** Anexate; ***USA:*** Romazicon; ***Venez.:*** Lanexat.

Fomepizole *(BAN, USAN, rINN)*

Fomepitsoli; Fomepizol; Fomépizole; Fomepizolum; 4-Methylpyrazole; 4-MP. 4-Methyl-1*H*-pyrazole.

Фомепизол

$C_4H_6N_2$ = 82.10.

CAS — 7554-65-6.

ATC — V03AB34.

ATC Vet — QV03AB34.

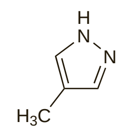

Adverse Effects

The most frequent adverse effects associated with fomepizole are headache, nausea, dizziness, drowsiness, and taste disturbances. Abdominal pain, vomiting, diarrhoea, hypotension, tachycardia, hypersensitivity reactions, and raised hepatic enzymes have also been reported.

Pharmacokinetics

Fomepizole is absorbed from the gastrointestinal tract but is usually given intravenously. It is metabolised in the liver, primarily to 4-carboxypyrazole; the metabolites are excreted in the urine, with only a small amount of unchanged drug. After multiple doses, fomepizole induces its own metabolism by the cytochrome P450 enzyme system, significantly increasing the rate of elimination. Fomepizole is removed by dialysis.

Uses and Administration

Fomepizole is a competitive inhibitor of alcohol dehydrogenase. It is used for the treatment of poisoning by ethylene glycol (p.2300) or methyl alcohol (p.2024), which are converted to toxic metabolites by alcohol dehydrogenase. Fomepizole is given in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 4 doses; the dose should then be increased to 15 mg/kg every 12 hours until serum concentrations of ethylene glycol or methyl alcohol are less than 20 mg/100 mL. All doses should be given by intravenous infusion over 30 minutes. In patients who also require haemodialysis, doses of fomepizole should be given every 4 hours during haemodialysis sessions.

Fomepizole has also been given similarly as the sulfate.

◊ References.

1. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; **106:** 1489–91.
2. Brent J, *et al.* Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; **344:** 424–9.
3. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; **36:** 1085–9.
4. Mycyk MB, Leikin JB. Antidote review: fomepizole for methanol poisoning. *Am J Ther* 2003; **10:** 68–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Antizol; ***Israel:*** Antizol; ***UK:*** Antizol; ***USA:*** Antizol.

Fuller's Earth

Terra Fullonica; Tierra de Fuller.

CAS — 8031-18-3.

Profile

Fuller's earth consists largely of montmorillonite, a native hydrated aluminium silicate, with which very finely divided calcite (calcium carbonate) may be associated. It is an adsorbent and has been used in dusting powders, toilet powders, and lotions. Fuller's earth of high adsorptive capacity has been used in industry as a clarifying and filtering medium.

It has been used in the treatment of paraquat poisoning (p.2047), usually as a 15% suspension given in an initial oral dose of about 100 g, followed by further doses of about 50 g every 2 hours for 3 doses. Purgatives such as magnesium sulfate or mannitol have been given at the same time to promote emptying of the gut, but some suggest they should only be given with the first dose.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Braz.:* Camomila.

Glucagon *(BAN, rINN)*

Gliukagonas; Glucagón; Glucagonum; Glukagon; Glukagoni; HGF.
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

Глюкагон

$C_{153}H_{225}N_{43}O_{49}S$ = 3482.7.

CAS — 16941-32-5.

ATC — H04AA01.

ATC Vet — QH04AA01.

Pharmacopoeias. In *US.*

USP 31 (Glucagon). A polypeptide hormone obtained from porcine and bovine pancreas glands. A fine, white or faintly coloured, practically odourless, crystalline powder. Soluble in dilute alkali and acid solutions; insoluble in most organic solvents. Store under nitrogen in airtight glass containers at a temperature of 2° to 8°.

Adverse Effects

Nausea and vomiting may occur after use of glucagon. Hypersensitivity reactions, abdominal pain, hypotension, tachycardia, and hypokalaemia have also been reported.

Precautions

Glucagon should generally not be given to patients with phaeochromocytoma since it can cause a release of catecholamines producing marked hypertension. Glucagon should be given with care to patients with insulinoma as it may induce hypoglycaemia due to its insulin-releasing effect. Glucagon was formerly used to diagnose phaeochromocytoma and insulinoma but this use has been largely abandoned. Caution is also required when it is being used as a diagnostic aid in diabetic patients or in elderly patients with heart disease.

Glucagon is not effective in patients with marked depletion of liver glycogen stores, as in starvation, adrenal insufficiency, alcohol-induced hypoglycaemia, or chronic hypoglycaemia. Oral carbohydrates should be given after glucagon to prevent the development of secondary hypoglycaemia.

Interactions

Warfarin. For a report of glucagon enhancing the anticoagulant effect of warfarin, see p.1431.

Pharmacokinetics

Glucagon has a plasma half-life of about 3 to 6 minutes but longer values have been reported in diabetics (see Bioavailability, below). It is inactivated in the liver, kidneys, and plasma.

Bioavailability. In a study[1] in healthy subjects and diabetic patients the bioavailability of glucagon given intranasally was about 30% of that after intramuscular injection. However, the mean value for the apparent half-life after intramuscular injection was 28.6 and 31.4 minutes respectively in the two groups, compared with 6.6 and 11.9 minutes for intravenous infusion, and 5.5 and 13.8 minutes when given intranasally, possibly due to slow release of glucagon from the injection site.

1. Pontiroli AE, *et al.* Pharmacokinetics of intranasal, intramuscular and intravenous glucagon in healthy subjects and diabetic patients. *Eur J Clin Pharmacol* 1993; **45:** 555–8.

Uses and Administration

Glucagon is an endogenous polypeptide hormone that is produced by the alpha cells of the pancreatic islets of Langerhans. It is a hyperglycaemic that mobilises glucose by activating hepatic glycogenolysis. It can to a lesser extent stimulate the secretion of pancreatic insulin. Glucagon for therapeutic use may be derived from animal sources but is now more commonly produced using recombinant DNA techniques. It is given as the hydrochloride, but doses are usually expressed as glucagon (note that 1 unit is equivalent to 1 mg of glucagon).

Glucagon is used in the treatment of severe hypoglycaemic reactions when the patient cannot take glucose by mouth and intravenous glucose is not feasible. It is given by subcutaneous, intramuscular, or intravenous injection in a dose of 1 mg (or 500 micrograms in patients under about 25 kg body-weight). If there is no response within 10 minutes, intravenous glucose should be given, although there is no contra-indication to repeating the dose of glucagon. Once the patient has responded sufficiently to take carbohydrate orally this should be given to restore liver glycogen stores and prevent secondary hypoglycaemia.

As glucagon reduces the motility of the gastrointestinal tract it is used as a diagnostic aid in gastrointestinal examinations. The route of administration and dose is dependent upon the diagnostic procedure. A dose of 1 to 2 mg intramuscularly has an onset of action of 4 to 15 minutes and a duration of effect of 10 to 40 minutes; 0.2 to 2 mg intravenously produces an effect within 1 minute that lasts for 5 to 25 minutes.

Glucagon possesses positive cardiac inotropic activity but is not generally considered suitable for heart failure. However, as it can bypass blocked beta receptors, it is used in the treatment of beta-blocker overdosage, see Cardiovascular Effects, below.

Intranasal preparations have been studied.

Cardiovascular effects. Glucagon has chronotropic and inotropic effects due to its ability to raise cyclic AMP concentrations independently of a response to catecholamines.[1] It is used in the management of beta-blocker overdosage (p.1227), although evidence of benefit is mainly anecdotal;[2] doses of 2 to 10 mg (or 50 to 150 micrograms/kg in children) by intravenous injection, followed by an infusion of 50 micrograms/kg per hour, have been suggested.

Glucagon may also have a role in anaphylactic shock (see under Adrenaline, p.1205), particularly in patients receiving beta blockers, in whom adrenaline may be less effective. A dramatic improvement in refractory hypotension during an anaphylactic reaction to contrast media was described in a 75-year-old man receiving beta blockers after intravenous glucagon.[3]

There has also been a report[4] of benefit with intravenous glucagon following calcium-channel blocker overdosage, but evidence from controlled studies is not available[2] and glucagon is not generally regarded as standard treatment for such patients.

1. White CM. A review of potential cardiovascular uses of intravenous glucagon administration. *J Clin Pharmacol* 1999; **39:** 442–7.
2. Bailey B. Glucagon in β-blocker and calcium channel blocker overdoses: a systematic review. *J Toxicol Clin Toxicol* 2003; **41:** 595–602.
3. Zaloga GP, *et al.* Glucagon reversal of hypotension in a case of anaphylactic shock. *Ann Intern Med* 1986; **105:** 65–6.
4. Walter FG, *et al.* Amelioration of nifedipine poisoning associated with glucagon therapy. *Ann Emerg Med* 1993; **22:** 1234–7.

Diagnosis and testing. Glucagon stimulates secretion of growth hormone and cortisol (hydrocortisone) and has been used as a test of pituitary function in adults,[1-3] and in children.[4,5] It may be particularly suitable when first-line tests such as the insulin-tolerance test are contra-indicated.[3] The glucagon stimulation test should be used with caution in young children;[5] severe secondary hypoglycaemia and death has been reported[6] in a 2-year-old child after a glucagon test for growth hormone secretion.

1. Gómez JM, *et al.* Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. *Clin Endocrinol (Oxf)* 2002; **56:** 329–34.
2. Abs R. Update on the diagnosis of GH deficiency in adults. *Eur J Endocrinol* 2003; **148:** S3–S8.
3. Ho KKY. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol* 2007; **157:** 695–700. Also available at: http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf (accessed 18/07/08)
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
5. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
6. Shah A, *et al.* Hazards of pharmacologic tests of growth hormone secretion in childhood. *BMJ* 1992; **304:** 173–4.

Gastrointestinal disorders. The relaxant effect of glucagon on smooth muscle has been used to facilitate passage of swallowed foreign bodies[1] and impacted food boluses[2] that have become lodged in the lower oesophagus. However, a controlled trial[3] in children with impacted oesophageal coins found that glucagon was not effective.

1. Cooke MW, Glucksman EE. Swallowed coins. *BMJ* 1991; **302:** 1607.
2. Farrugia M, *et al.* Radiological treatment of acute oesophageal food impaction. *Br J Hosp Med* 1995; **54:** 410–11.
3. Mehta D, *et al.* Glucagon use for esophageal coin dislodgment in children: a prospective, double-blind, placebo-controlled trial. *Acad Emerg Med* 2001; **8:** 200–3.

Hypoglycaemia. Hypoglycaemia most commonly occurs in diabetic patients, particularly those receiving insulin therapy. Other rare causes include alcohol ingestion and tumours such as insulinomas. Neonatal hypoglycaemia occurs in small-for-gestational-age infants or infants of diabetic mothers. Persistent or recurrent hypoglycaemia in neonates is usually due to an endocrine or metabolic disorder, such as nesidioblastosis.

Glucose is the treatment of choice for **acute** hypoglycaemia since it corrects the problem at source. In patients who are unconscious or unable to take glucose orally, it may need to be given intravenously. Glucagon is an alternative in such situations, and first-line use has been suggested[1] since it is more convenient and easier to give than parenteral glucose, particularly in emergency situations. However, glucagon has a slower onset and may not always be effective, particularly where hepatic glycogen stores are depleted, such as in patients with alcohol-induced hypoglycaemia or with insulinoma. Low doses of glucagon have also been given prophylactically[2] in diabetic children at risk of developing hypoglycaemia due to gastrointestinal disorders or reduced oral intake.

Hypoglycaemia in neonates is usually managed by adjusting the enteral feeds or by giving parenteral glucose in symptomatic infants. Glucagon may be used if parenteral glucose is not effective or cannot be given.[3,4] In infants with persistent hyperinsulinaemic hypoglycaemia,[5] continuous infusion of glucagon has been used, although oral treatments such as diazoxide or chlorothiazide are usually preferred.

Intractable hypoglycaemia (such as that resulting from excessive endogenous insulin production from islet cell tumours or hyperplasia) is usually treated with diazoxide, but continuous infusion of glucagon has been used in patients with tumour-associated hypoglycaemia.[6,7]

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306:** 600–1.
2. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001; **24:** 643–5.
3. Carter PE, *et al.* Glucagon for hypoglycaemia in infants small for gestational age. *Arch Dis Child* 1988; **63:** 1264.
4. Williams AF. Hypoglycaemia of the newborn: a review. *Bull WHO* 1997; **75:** 261–90.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.
6. Samaan NA, *et al.* Successful treatment of hypoglycemia using glucagon in a patient with an extrapancreatic tumor. *Ann Intern Med* 1990; **113:** 404–6.
7. Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. *Cancer* 1998; **82:** 1585–92.

Liver disorders. For references to the use of glucagon with insulin in the treatment of liver disorders, see under Insulin, p.452.

Preparations

USP 31: Glucagon for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: GlucaGen; ***Austral.:*** GlucaGen; ***Austria:*** GlucaGen; ***Belg.:*** GlucaGen; ***Braz.:*** GlucaGen; ***Cz.:*** GlucaGen; ***Denm.:*** GlucaGen; ***Fin.:*** GlucaGen; ***Fr.:*** GlucaGen; ***Ger.:*** GlucaGen; ***Gr.:*** GlucaGen; ***Hong Kong:*** GlucaGen; ***Hung.:*** GlucaGen; ***India:*** GlucaGen; ***Irl.:*** GlucaGen; ***Israel:*** GlucaGen; ***Ital.:*** GlucaGen; ***Malaysia:*** GlucaGen; ***Neth.:*** GlucaGen; ***NZ:*** GlucaGen; ***Pol.:*** GlucaGen; ***Port.:*** GlucaGen; ***Rus.:*** GlucaGen (Глюкаген); ***S.Afr.:*** GlucaGen; ***Singapore:*** GlucaGen; ***Spain:*** GlucaGen; ***Switz.:*** GlucaGen; ***Turk.:*** GlucaGen; ***UK:*** GlucaGen; ***USA:*** GlucaGen.

Glucarpidase *(rINN)*

Carboxypeptidase G_2; Glucarpidasa; Glucarpidasum.

Глюкарпидаз

CAS — 9074-87-7.

ATC — V03AF09.

ATC Vet — QV03AF09.

Profile

Glucarpidase is a recombinant glutamate carboxypeptidase that hydrolyses methotrexate to inactive metabolites; it is under investigation for the management of methotrexate toxicity.

◊ References.

1. Widemann BC, *et al.* Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. *J Clin Oncol* 1997; **15:** 2125–34.
2. Widemann BC, *et al.* Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. *J Natl Cancer Inst* 2004; **96:** 1557–9.
3. Buchen S, *et al.* Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 2005; **92:** 480–7.

Glutathione *(BAN)*

Glutathion; Glutathionum; Glutatión; Glutation; Glutationas; Glutationi; GSH. *N*-(*N*-L-γ-Glutamyl-L-cysteinyl)glycine.

$C_{10}H_{17}N_3O_6S$ = 307.3.

CAS — 70-18-8.

ATC — V03AB32.

ATC Vet — QV03AB32.

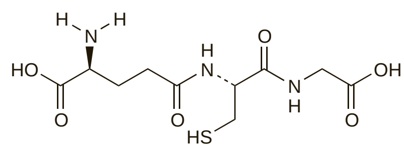

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*.

Ph. Eur. 6.2 (Glutathione). Fermentation product. A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Glutathione is an endogenous peptide with antoxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin or oxaliplatin; they have also been used to prevent other adverse effects of antineoplastic and radiation therapy, as well as in a wide range of other disorders including poisoning with heavy metals and other compounds, liver disorders, corneal disorders, and eczema. Glutathione has also been tried in idiopathic pulmonary fibrosis and peripheral vascular disorders.

Antineoplastic toxicity. Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomised trial[1] in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity. Similar benefit was observed in a randomised, double-blind, placebo-controlled trial involving 52 patients receiving oxaliplatin.[2]

1. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995; **13:** 26–32.
2. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2002; **20:** 3478–83.

Lung disorders. Glutathione is an important extracellular antoxidant in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulised glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis)[1] and in cystic fibrosis,[2] but the clinical effects of these changes are not clear. Another study in cystic fibrosis[3] found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function. Benefit has also been reported[4] in a patient with emphysema. However, in a study[5] of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.

1. Borok Z, *et al.* Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet* 1991; **338:** 215–16.
2. Roum JH, *et al.* Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. *J Appl Physiol* 1999; **87:** 438–43.
3. Griese M, *et al.* Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. *Am J Respir Crit Care Med* 2004; **169:** 822–8.
4. Lamson DW, Brignall MS. The use of nebulized glutathione in the treatment of emphysema: a case report. *Altern Med Rev* 2000; **5:** 429–31.
5. Marrades RM, *et al.* Nebulized glutathione induces bronchoconstriction in patients with mild asthma. *Am J Respir Crit Care Med* 1997; **156:** 425–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Glu-tathion; TAD; ***Ital.:*** Eudon†; Glutanil†; Gluthion; Ipatox†; Maglut†; Reglumax†; Ridutox; Rition; Scavenger†; TAD; Tationil; Thioxene†; ***Jpn:*** Glutathin; ***Rus.:*** Glutoxim (Глутоксим); ***USA:*** Cachexon.

Multi-ingredient: ***Austral.:*** BSS Plus; ***Austria:*** BSS Plus; ***Canad.:*** BSS Plus; ***Fr.:*** BSS Plus; ***Ger.:*** BSS Plus; ***Hong Kong:*** BSS Plus†; ***Hung.:*** BSS Plus; ***Israel:*** BSS Plus; ***Malaysia:*** BSS Plus; ***Philipp.:*** Illumina; ***S.Afr.:*** BSS Plus; ***Singapore:*** BSS Plus; ***Switz.:*** BSS Plus†; ***Thai.:*** BSS Plus; ***USA:*** BSS Plus; Sucrets Defense Kids Formula; ***Venez.:*** BSS Plus†.

Haem Derivatives

Heme Derivatives; Hemo, derivados del grupo.

ATC — B06AB01 (Haematin).

ATC Vet — QB06AB01 (haematin).

Profile

Haem is the iron protoporphyrin constituent of haemoglobin and is responsible for its colour and oxygen-carrying capacity. It is used in the management of porphyrias (below). Haem is given intravenously as its derivatives, although there is some confusion over their terminology. The names haematin (hematin) and haemin (hemin) have been used interchangeably although chemically haematin is the hydroxy derivative, formed by the reaction of haemin and sodium carbonate in solution. The arginine salt (haem arginate; haemin arginate; heme arginate) is reported to be more stable.

Haem arginate is used in the treatment of acute hepatic porphyrias, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria. It is given by slow intravenous infusion in a dose of 3 mg/kg daily for 4 days, infused over at least 30 minutes. The maximum recommended dose is 250 mg daily. The course may be repeated, with close monitoring, in patients with an inadequate response.

Haematin is used intravenously for the amelioration of acute intermittent porphyria associated with the menstrual cycle in patients unresponsive to other therapy. It is given in a usual dose of 1 to 4 mg/kg daily for 3 to 14 days as an intravenous infusion over 10 to 15 minutes. In severe cases the dose may be repeated after 12 hours, but no more than 6 mg/kg should be given in any 24 hour period.

Phlebitis may occur after infusion of haem derivatives and they should be given into a large arm vein or central vein. Use of a filter is recommended due to the colour of the infusion.

Porphyrias. The porphyrias are a group of inherited and acquired disorders of haem biosynthesis in which defects in specific enzymes lead to the accumulation of haem precursors, including aminolevulinic acid, porphobilinogen, and porphyrins.[1-11] They are generally classified as acute or non-acute, reflecting their clinical presentation, or as hepatic or erythropoietic, depending on the site of the enzyme defect. The three most common forms are acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria.

ACUTE PORPHYRIAS. These are inherited disorders characterised by the accumulation of porphyrin precursors, leading to acute attacks of neurovisceral symptoms. The most common form is *acute intermittent porphyria* (acute hepatic porphyria); *variegate porphyria* and *hereditary coproporphyria* are generally less common forms in which there is accumulation of both porphyrin precursors and porphyrins, leading to acute attacks with cutaneous symptoms similar to those seen in non-acute porphyrias (see below).

In acute porphyrias, some enzyme activity is present and the defect only becomes apparent when demand for hepatic haem is increased. Attacks are rare before puberty and the disorder may remain latent in many patients. The presenting symptom is most commonly severe abdominal pain; other gastrointestinal symptoms such as nausea and vomiting also occur, along with autonomic effects including hypertension, tachycardia, sweating, pallor, and pyrexia. Convulsions may occur at the peak of an attack and may persist between attacks. Neuropathy leads to weakness and paralysis and may progress rapidly to respiratory distress. Psychiatric symptoms are also common, particularly agitation, anxiety, and behavioural disturbances. Various factors can increase the demand for haem and attacks are usually precipitated by drugs, alcohol, steroid hormones, reduced caloric intake, or infection. They typically last for several days and are followed by complete recovery, although in some patients chronic abdominal pain may persist without other symptoms.

The primary management of an attack is to remove precipitants and to provide intensive support. *Symptomatic treatment* is complicated by the wide range of drugs that may precipitate porphyria. High doses of parenteral opioids may be required for pain; there is a danger of addiction occurring, but this is rare unless attacks are frequent or pain persists between attacks. Phenothiazines such as chlorpromazine are useful to control nausea and agitation and their sedative effect may also be beneficial. High doses of propranolol may be required for cardiovascular symptoms. Assisted ventilation may be necessary. Convulsions usually disappear as the attack resolves; management of patients who experience convulsions between attacks is a therapeutic problem since many antiepileptics are porphyrinogenic (see Porphyria, p.471). *Specific therapy* is aimed at suppressing the haem biosynthetic pathway, to prevent further accumulation of precursors. Haem, given as either haematin or haem arginate, is the most effective treatment and should be given as soon as possible after onset of the attack; it produces feedback suppression of the biosynthetic pathway. Tin-protoporphyrin, a haem oxygenase inhibitor, has been given with haem to prolong its action but is not commercially available. A high carbohydrate intake may also suppress haem precursor production and should be ensured in all patients, especially if haem is not immediately available; it is usually given orally to prevent fluid overload and exacerbation of hyponatraemia, but intravenous glucose may be required in patients who are vomiting. *Prevention* of attacks involves avoiding drugs that precipitate porphyria and maintaining an adequate carbohydrate intake. Gonadorelin analogues, such as buserelin, may have a role in preventing attacks related to the menstrual cycle. Long-term treatment with haem has been tried in patients with frequent attacks, although such use is not established.

NON-ACUTE PORPHYRIAS. These are characterised by the accumulation of porphyrins and usually present with cutaneous symptoms, although porphyrins also accumulate in the liver and liver damage commonly occurs. *Porphyria cutanea tarda* (cutaneous hepatic porphyria) is the most common form of porphyria. It is usually an acquired disorder and in most cases there is a history of moderate or heavy alcohol intake. There is usually a raised serum-iron concentration and use of oestrogen has also been implicated. The main clinical symptom is cutaneous photosensitivity leading to bullous dermatosis, pruritus, and skin fragility, in areas exposed to sunlight. *Management* involves protecting the skin from sunlight and trauma and avoiding causative agents such as alcohol and iron. Sunscreen preparations must be based on zinc oxide or titanium dioxide to be effective. Reduction of serum-iron concentrations by phlebotomy restores enzyme function and is effective in most patients; it should be carried out every 1 to 2 weeks until remission occurs, and may be required periodically for maintenance. Chloroquine and hydroxychloroquine have also been used and may be effective where phlebotomy is contra-indicated; they appear to act by complexing with porphyrins and increasing their excretion, but low doses are necessary to avoid exacerbating the condition. An alternative method of reducing serum-iron is with the iron chelator desferrioxamine, although it may be less effective than phlebotomy; it is usually reserved for patients unable to tolerate phlebotomy. In patients with renal failure who are too anaemic for phlebotomy and who cannot excrete chloroquine, erythropoietin may be used, and may be combined with desferrioxamine or low-volume phlebotomy.

Erythropoietic protoporphyria is a less common non-acute porphyria and is an inherited disorder leading to accumulation of protoporphyrin. Symptoms are cutaneous and there is an acute reaction to sunlight leading to urticaria, pruritus, swelling, redness, and a severe burning sensation; liver damage may also occur. *Management* involves protection of the skin, as for porphyria cutanea tarda. Betacarotene is widely used to increase tolerance to sunlight, although its efficacy is not established; canthaxanthin, another carotenoid, has also been used. Haem administration, as haematin or haem arginate, may be beneficial in suppressing protoporphyrin production. Colestyramine and activated charcoal reduce protoporphyrin levels by interrupting enterohepatic recycling; they also bind other porphyrins and may have a role in rare forms of porphyria such as *congenital erythropoietic porphyria*.

1. Murphy GM. The cutaneous porphyrias: a review. *Br J Dermatol* 1999; **140:** 573–81.
2. Thadani H, *et al.* Diagnosis and management of porphyria. *BMJ* 2000; **320:** 1647–51.
3. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; **26:** 225–32.
4. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002; **56:** 272–8.
5. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003; **16:** 57–64.
6. Lecha M, *et al.* Diagnosis and treatment of the hepatic porphyrias. *Dermatol Ther* 2003; **16:** 65–72.
7. Kauppinen R. Porphyrias. *Lancet* 2005; **365:** 241–52.
8. Anderson KE, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; **142:** 439–50. Correction. *ibid.*; **143:** 316.
9. European Porphyria Initiative. Information available at: http://www.porphyria-europe.com (accessed 04/10/05)
10. University of Cape Town Porphyria Service. Information available at: http://www.porphyria.uct.ac.za (accessed 04/10/05)
11. University of Queensland Porphyria Research Unit. Information available at: http://www.uq.edu.au/porphyria (accessed 04/10/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Panhematin†; ***Denm.:*** Normosang; ***Fin.:*** Normosang; ***Fr.:*** Normosang; ***Ger.:*** Normosang; ***Ital.:*** Normosang; ***Neth.:*** Normosang; ***Port.:*** Normosang; ***Spain:*** Normosang; ***Swed.:*** Normosang; ***Switz.:*** Normosang; ***UK:*** Normosang; ***USA:*** Panhematin.

Multi-ingredient: ***Cz.:*** Normosang.

Lanthanum Carbonate *(USAN)*

Lanthanum carbonate (2:3) hydrate.

$La_2(CO_3)_3,xH_2O$ = 457.8 (anhydrous lanthanum carbonate).
CAS — 54451-24-0.
ATC — V03AE03.
ATC Vet — QV03AE03.

Adverse Effects and Precautions

The most common adverse effects with lanthanum carbonate are gastrointestinal disturbances, including nausea, vomiting, constipation, diarrhoea, dyspepsia, and abdominal pain. Only small amounts of lanthanum are absorbed from the gastrointestinal tract but some accumulation of lanthanum in bone has been reported; the clinical significance of this is unknown.

Ingestion of lanthanum carbonate may produce a radio-opaque appearance on abdominal radiography.

Uses and Administration

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia (p.1669) in patients with chronic renal failure. It is given orally as the hydrate, but doses are expressed in terms of elemental lanthanum. The usual initial daily dose is 0.75 to 2.25 g of elemental lanthanum, given in divided doses with meals. The dose should be adjusted every 2 to 3 weeks until an acceptable serum-phosphate concentration is achieved; the usual maintenance dose is 1.5 to 3 g daily in divided doses, but up to 3.75 g daily has been given. The tablets should be chewed thoroughly before swallowing.

◊ Reviews.

1. Swainston Harrison T, Scott LJ. Lanthanum carbonate. *Drugs* 2004; **64:** 985–96.
2. Joy MS, *et al.* Lanthanum carbonate. *Ann Pharmacother* 2006; **40:** 234–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Fosrenol; ***Cz.:*** Fosrenol; ***Fr.:*** Fosrenol; ***Gr.:*** Fosrenol; ***Irl.:*** Foznol; ***Port.:*** Fosrenol; ***Swed.:*** Fosrenol; ***UK:*** Fosrenol; ***USA:*** Fosrenol.

Lofexidine Hydrochloride *(BANM, USAN, rINNM)*

Ba-168; Hidrocloruro de lofexidina; Lofeksidin Hidroklorür; Lofexidine, Chlorhydrate de; Lofexidini Hydrochloridum; MDL-14042; MDL-14042A; RMI-14042A. 2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride.

Лофексидина Гидрохлорид

$C_{11}H_{12}Cl_2N_2O,HCl$ = 295.6.
CAS — 31036-80-3 (lofexidine); 21498-08-8 (lofexidine hydrochloride).
ATC — N07BC04.
ATC Vet — QN07BC04.

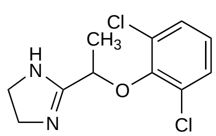

(lofexidine)

Pharmacopoeias. In *Chin.*

Adverse Effects

Lofexidine has central alpha-adrenergic effects and may cause drowsiness, dryness of the mouth, throat, and nose, hypotension, and bradycardia; prolongation of the QT interval has also been reported. Sedation may occur following overdosage.

Sudden withdrawal of lofexidine may produce rebound hypertension.

Precautions

Lofexidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including recent myocardial infarction, bradycardia, renal impairment, or a history of depression.

It may cause drowsiness and if affected, patients should not drive or operate machinery.

Withdrawal of lofexidine therapy should be gradual over 2 to 4 days or more to reduce the risk of rebound hypertension.

Interactions

Lofexidine may enhance the central depressant effects of sedatives, including alcohol. It may also enhance the effects of antihypertensives. Tricyclic antidepressants may reduce the efficacy of lofexidine.

Methadone. A 44-year-old opioid-dependent female receiving methadone had prolongation of the QT interval after a single 400-microgram dose of lofexidine.[1] The patient had previously had a normal QT while receiving methadone and it was suggested the effect might have been caused by the combination of the 2 drugs.

1. Schmittner J, *et al.* QT interval increased after single dose of lofexidine. *BMJ* 2004; **329:** 1075.

Pharmacokinetics

Lofexidine is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 3 hours. It is extensively metabolised in the liver and excreted mainly in the urine. The elimination half-life is 11 hours.

Uses and Administration

Lofexidine is an $alpha_2$-adrenoceptor agonist structurally related to clonidine (p.1247). It has antihypertensive activity, but is used mainly in the control of opioid withdrawal symptoms.

In opioid withdrawal, lofexidine is given as the hydrochloride in an initial oral dose of 800 micrograms daily in divided doses. The dose may be increased gradually by 400 to 800 micrograms daily to a maximum of 2.4 mg daily; the maximum single dose should not exceed 800 micrograms. After 7 to 10 days, or longer in some cases, treatment is withdrawn gradually over at least 2 to 4 days.

Opioid dependence. A systematic review[1] of the use of $alpha_2$-adrenoceptor agonists in the management of opioid dependence (p.101) concluded that they were as effective as methadone, although patients stayed in treatment for longer with methadone and there were fewer adverse effects with methadone than with clonidine. Lofexidine was associated with less hypotension than clonidine and may therefore be preferred, particularly for outpatient treatment.

1. Gowing L, *et al.* Alpha2 adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 04/10/05).

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Britlofex.

Mesna *(BAN, USAN, rINN)*

D-7093; Mesnum; NSC-113891; UCB-3983. Sodium 2-mercaptoethanesulphonate.

Месна

$C_2H_5NaO_3S_2$ = 164.2.
CAS — 19767-45-4.
ATC — R05CB05; V03AF01.
ATC Vet — QR05CB05; QV03AF01.

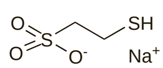

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Mesna). A white or slightly yellow, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility and stability. There was no evidence of degradation of mesna when stored in solution with ifosfamide in polyethylene infusion bags at room temperature for 7 hours[1] or in polypropylene syringes at room temperature or at 4° for 4 weeks.[2] However, in the latter study ifosfamide concentrations fell by about 3% after 7 days and 12% after 4 weeks at both temperatures. Another study[3] found that mixtures of mesna with cyclophosphamide in polyethylene infusion bags were stable for 48 hours at 4° and for 6 hours at room temperature.

Mesna has been reported to be incompatible with platinum compounds such as carboplatin and cisplatin.

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Menard C, *et al.* Stability of cyclophosphamide and mesna admixtures in polyethylene infusion bags. *Ann Pharmacother* 2003; **37:** 1789–92.

Adverse Effects and Precautions

Adverse effects that may occur after use of mesna include gastrointestinal effects, headache, fatigue, limb pains, depression, irritability, hypotension (but see below), tachycardia, and skin rash. Bronchospasm has been reported after nebulisation.

Mesna may produce a false positive result in diagnostic tests for urinary ketones and may produce a false positive or false negative result in diagnostic tests for urinary erythrocytes.

Effects on blood pressure. Hypotension may occur with mesna; however, severe hypertension has also been reported[1] after use of mesna, either alone or with ifosfamide.

1. Gilleece MH, Davies JM. Mesna therapy and hypertension. *DICP Ann Pharmacother* 1991; **25:** 867.

Effects on the nervous system. For reports of severe encephalopathy in patients receiving mesna and ifosfamide, see p.732.

Hypersensitivity. Hypersensitivity reactions including rash, fever, nausea, facial and periorbital oedema, ulceration of mucous membranes, and tachycardia have been attributed to mesna.[1-4] Reactions may be more common in patients with autoimmune disorders; drug eruptions developed in 7 of 16 patients receiving mesna and cyclophosphamide for auto-immune disorders.[5] Five of these patients had a rash, with angioedema in 2 cases, and a pseudo-hypersensitivity reaction was diagnosed.

1. Lang E, Goos M. Hypersensitivity to mesna. *Lancet* 1985; **ii:** 329.
2. Seidel A, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 381.
3. Gross WL, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 381–2.
4. D'Cruz D, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 705–6.
5. Zonzits E, *et al.* Drug eruptions from mesna: after cyclophosphamide treatment of patients with systemic lupus erythematosus and dermatomyositis. *Arch Dermatol* 1992; **128:** 80–2.

Pharmacokinetics

Mesna is absorbed from the gastrointestinal tract. It is rapidly metabolised after oral or intravenous dosage to mesna disulfide (dimesna) and is excreted in the urine as both metabolite and unchanged drug; dimesna is reduced back to mesna, which is the active form, in the kidney. The half-lives of mesna and dimesna are reported to be about 20 minutes and 70 minutes respectively. After intravenous use, most of the dose is excreted in the urine within 4 hours. Mesna is about 70% bound to plasma proteins.

◊ References.

1. Burkert H, *et al.* Bioavailability of orally administered mesna. *Arzneimittelforschung* 1984; **34:** 1597–1600.
2. James CA, *et al.* Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects. *Br J Clin Pharmacol* 1987; **23:** 561–8.
3. El-Yazigi A, *et al.* Pharmacokinetics of mesna and dimesna after simultaneous intravenous bolus and infusion administration in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1997; **37:** 618–24.

Uses and Administration

Mesna is used for the prevention of urothelial toxicity in patients being treated with the antineoplastics ifosfamide or cyclophosphamide. In the kidney, dimesna, the inactive metabolite of mesna, is reduced to free mesna. This has thiol groups that react with the metabolites of ifosfamide and cyclophosphamide, including acrolein, which are considered to be responsible for the toxic effects on the bladder.

The aim of mesna therapy is to ensure adequate levels of mesna in the urine throughout the period during which these toxic metabolites are present. The duration of mesna treatment should therefore equal that of the antineoplastic treatment plus the time taken for the concentration of antineoplastic metabolites in the urine to fall to non-toxic concentrations. Urinary output should be maintained and the urine monitored for haematuria and proteinuria throughout the treatment period. However, frequent emptying of the bladder should be avoided.

Mesna may be given intravenously or orally for the prevention of urothelial toxicity, the dosage and frequency depending on the antineoplastic regimen used. After oral use, availability of mesna in urine is about 50% of that after intravenous use and excretion in urine is delayed up to 2 hours and is more prolonged. The intravenous preparation may be given orally added to a flavoured drink; this mixture may be stored in a sealed container in a refrigerator for up to 24 hours. Alternatively, tablets are available.

Intravenous bolus antineoplastic regimens. If ifosfamide or cyclophosphamide is given as an intravenous bolus, the *intravenous dose of mesna* is 20% of the dose of the antineoplastic on a weight for weight basis given on 3 occasions over 15 to 30 minutes at intervals of 4 hours beginning at the same time as the antineoplastic injection; thus the total dose of mesna is equivalent to 60% of the antineoplastic given. This regimen is repeated each time the antineoplastic is used. Each individual dose of mesna may be increased to 40% of the dose of the antineoplastic and given 4 times at intervals of 3 hours for children and patients at high risk of urotoxicity; in such cases the total dose of mesna is equivalent to 160% of the antineoplastic given. The *oral dose of mesna* is 40% of the dose of the antineoplastic given on 3 occasions at intervals of 4 hours beginning 2 hours before the antineoplastic injection; thus a total dose of mesna equivalent to 120% of the antineoplastic is given. Alternatively, the initial dose of mesna may be given *intravenously* (20% of the dose of the antineoplastic), followed by two *oral doses* (each 40% of the dose of the antineoplastic) given 2 and 6 hours after the intravenous dose. Any of these regimens may be used if **cyclophosphamide** is given **orally**.

Intravenous infusion antineoplastic regimens. If the antineoplastic is given as an intravenous infusion over 24 hours, an initial *intravenous injection* of mesna as 20% of the total antineoplastic dose is followed by 100% of the total dose by intravenous infusion concurrently over 24 hours, followed by 60% by intravenous infusion over a further 12 hours (total dose 180% of the antineoplastic). The final 12-hour infusion may be replaced either by 3 intravenous injections each of 20% of the antineoplastic dose at intervals of 4 hours, the first injection being given 4 hours after the infusion has been stopped, or by *oral mesna* given in 3 doses each of 40% of the antineoplastic dose, the first dose being given when the 24-hour infusion is stopped, and the second and third doses being given 2 and 6 hours later.

Mesna is also used as a **mucolytic** in the management of some respiratory-tract disorders. The usual daily dose is 0.6 to 1.2 g given by a nebuliser; it may also be given by direct endotracheal instillation.

◊ General references.

1. Schoenike SE, Dana WJ. Ifosfamide and mesna. *Clin Pharm* 1990; **9:** 179–91.
2. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Delinar; Mesnex†; Mestian; Neper; Uromitexan†; Varimesna; ***Austral.:*** Uromitexan; ***Austria:*** Mistabron; Uromitexan; ***Belg.:*** Mistabron; Uromitexan; ***Braz.:*** Mitexan; ***Canad.:*** Uromitexan; ***Chile:*** Mucofluid; Uromitexan; Uroprot; ***Cz.:*** Mistabron; Uromitexan; ***Denm.:*** Uromitexan; ***Fin.:*** Uromitexan; ***Fr.:*** Mucofluid; Uromitexan; ***Ger.:*** Mistabronco†; Uromitexan; ***Gr.:*** Uromitexan; ***Hong Kong:*** Mistabron; Uromitexan; ***Hung.:*** Uromitexan; ***India:*** Uromitexan; ***Indon.:*** Uromitexan; ***Irl.:*** Uromitexan; ***Israel:*** Mexan; ***Ital.:*** Mucofluid†; Mucolene†; Uromitexan; ***Jpn:*** Uromitexan; ***Malaysia:*** Mistabron†; Uromitexan†; ***Mex.:*** Mesnil; Mesodal; Uromes; Uromitexan†; Uroprot; Ziken; ***Neth.:*** Mistabron; Uromitexan; ***Norw.:*** Uromitexan; ***NZ:*** Uromitexan; ***Philipp.:*** Mistabron; Uromitexan; ***Pol.:*** Anti-Uron; Mistabron; Mucofluid; Uromitexan; ***Port.:*** Uromitexan; ***S.Afr.:*** Mistabron; Uromitexan; ***Singapore:*** Mistabron; Uromitexan; ***Spain:*** Mucofluid; Uromitexan; ***Swed.:*** Uromitexan; ***Switz.:*** Mistabron†; Uromitexan; ***Thai.:*** Mistabron†; Uromitexan; ***Turk.:*** Uromitexan; ***UK:*** Uromitexan†; ***USA:*** Mesnex.

Multi-ingredient: ***India:*** Holoxan Uromitexan; Ifex-M; Ipamide with Mesna.

Methionine *(USAN, rINN)*

L-Metionina; M; Methionin; Méthionine; *S*-Methionine; L-Methionine; Methioninum; Metioniini; Metionin; Metionina; Metioninas. L-2-Amino-4-(methylthio)butyric acid.

Метионин

$C_5H_{11}NO_2S$ = 149.2.
CAS — 63-68-3.
ATC — V03AB26.
ATC Vet — QA05BA90; QG04BA90; QV03AB26.

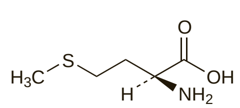

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Methionine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. A 2.5% solution in water has a pH of 5.5 to 6.5. Protect from light.
USP 31 (Methionine). White crystals having a characteristic odour. Soluble in water, in warm dilute alcohol, and in dilute mineral acids; insoluble in dehydrated alcohol, in acetone, in ether, and in benzene. pH of a 1% solution in water is between 5.6 and 6.1.

DL-Methionine

DL-Metionina; Methionin racemický; DL-Méthionine; DL-Methioninum; Methioninum Racemicum; DL-Metioniini; DL-Metionin; DL-Metionina; DL-Metioninas; Racemethionine *(USAN)*. DL-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$ = 149.2.
CAS — 59-51-8.
ATC — V03AB26.
ATC Vet — QV03AB26.

NOTE. The name methionine is often applied to DL-methionine.
Compounded preparations of DL-methionine may be represented by the following names:

- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol respectively.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Viet.*
Ph. Eur. 6.2 (DL-Methionine). An almost white crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol; dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 5.4 to 6.1. Protect from light.

Adverse Effects and Precautions

Methionine may cause nausea, vomiting, drowsiness, and irritability. It should not be used in patients with acidosis. Methionine may aggravate hepatic encephalopathy in patients with established liver damage; it should be used with caution in patients with severe liver disease.

Interactions

Methionine may be adsorbed by activated charcoal and the effect of oral methionine may be reduced if they are given together.

Dopaminergics. For reference to the antagonism of the antiparkinsonian effect of *levodopa* by methionine, see Nutritional Agents, under Interactions of Levodopa, p.808.

Pharmacokinetics

Methionine is absorbed from the gastrointestinal tract. It is extensively metabolised to *S*-adenosylmethionine (ademetionine, p.2247), homocysteine, and other metabolites, and is excreted in the urine as an inorganic sulfate.

Uses and Administration

L-Methionine is an essential amino acid and is therefore included in amino-acid solutions used for parenteral nutrition (p.1923).

Methionine also enhances the synthesis of glutathione and is used as an alternative to acetylcysteine in the treatment of paracetamol poisoning to prevent hepatotoxicity (see p.108). The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the usual dose of DL-methionine is 2.5 g by mouth every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. Children under 6 years old may be given 1 g every 4 hours for 4 doses. Methionine has also been given intravenously. Preparations containing both methionine and paracetamol have been formulated for use in situations where overdosage may occur. However, the issue of whether methionine should be routinely added to paracetamol preparations is contentious for medical and ethical reasons.

Methionine has also been given orally to lower urinary pH and as an adjunct in the treatment of liver disorders. It has also been used in the assessment of hyperhomocysteinaemia.

Acetylmethionine has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Neutrodor†; ***Austral.:*** Methnine; ***Austria:*** Acimethin; ***Ger.:*** Acimethin; Acimol; Methio; Methiotrans; Urol methin; Uromethin†; ***Switz.:*** Acimethin; ***USA:*** M-Caps; Pedameth†; Uracid.

Multi-ingredient: ***Austral.:*** Berberis Complex; Liv-Detox†; ***Braz.:*** Aminotox†; Anekron; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Extrato Hepatico Vitaminado†; Hecrosine B12†; Hepacitron†; Hepalin; Hepatogenol†; Hepatotris†; Hepatox; Hormo Hepatico†; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B-6; Panvitrop; Regenom; Silimalon; Xantina B12†; Xantinon B12; Xantinon Complex; ***Canad.:*** Amino-Cerv; Selenium Plus; ***Cz.:*** Lipovitan†; ***Fr.:*** Cysti-Z†; Lobamine-Cysteine; Nivabetol; Verrulyse-Methionine; ***Ger.:*** Lipovitan†; ***Hong Kong:*** Bilsan; Lipochol; ***India:*** Neutrosec; ***Indon.:*** BIO-EPL; Lipagent; Methicol; Methioson; Naturica DFM; Vionin NF; ***Irl.:*** Antox; ***Ital.:*** Agedin Plus; Detoxicon; Meziv†; ***Mex.:*** Lipovitasi-Or; ***S.Afr.:*** Hepavite; ***Spain:*** Dertrase; Epitelizante; ***Switz.:*** Mechovit; ***Thai.:*** Bio-Vitas†; Lipochol; Liporon; ***UK:*** Lipotropic Factors; Paradote; ***USA:*** Amino-Cerv.

Methylthioninium Chloride *(BAN, rINN)*

Azul de Metileno; Błękit metylenowy; Blu di Metilene; CI Basic Blue 9; Cloruro de metiltioninio; Colour Index No. 52015; Methylene Blue; Methylenii Caeruleum; Methylthioninii chloridum; Methylthioninii Chloridum Hydricum; Méthylthioninium, chlorure de; Methylthioninium-chlorid hydrát; Metilen Mavisi; Metiltioninio chloridas; Metiltioninio-klorid; Metylotioniniowy chlorek; Metyltioniniumklorid; Metyylitioniniumkloridi; Schultz No. 1038; Tetramethylthionine Chloride Trihydrate. 3,7-Bis(dimethylamino)phenazathionium chloride trihydrate.

Метилтиониния Хлорид

$C_{16}H_{18}ClN_3S,3H_2O$ = 373.9.
CAS — 61-73-4 (anhydrous methylthioninium chloride); 7220-79-3 (methylthioninium chloride trihydrate).
ATC — V03AB17; V04CG05.
ATC Vet — QV03AB17; QV04CG05.

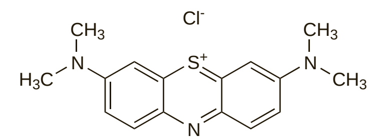

NOTE. *Commercial methylthioninium chloride may consist of the double chloride of tetramethylthionine and zinc, and is not suitable for medicinal use.*

Pharmacopoeias. In *Chin.* and *US*; in *Eur.* (see p.vii) (as xH_2O); in *Int.* (as anhydrous or $3H_2O$).
Ph. Eur. 6.2 (Methylthioninium Chloride). A dark blue, crystalline powder with a copper-coloured sheen, or green crystals with a bronze-coloured sheen. Soluble in water; slightly soluble in alcohol. Store in airtight containers. Protect from light.
USP 31 (Methylene Blue). Dark green crystals or crystalline powder with a bronze-like lustre. Is odourless or practically so. Solutions in water or alcohol are deep blue in colour. Soluble 1 in 25 of water and 1 in 65 of alcohol; soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

After high intravenous doses, methylthioninium chloride may cause nausea, vomiting, abdominal and chest pain, headache, dizziness, mental confusion, profuse sweating, dyspnoea, and hypertension; methaemoglobinaemia and haemolysis may occur. Haemolytic anaemia and hyperbilirubinaemia have been reported in neonates after intra-amniotic injection. Oral use may cause gastrointestinal disturbances and dysuria.

Methylthioninium chloride should not be injected subcutaneously as it has been associated with isolated cases of necrotic abscesses. It should not be given by intrathecal injection as neural damage has occurred. Methylthioninium chloride should be used with caution in patients with severe renal impairment and is contra-indicated in patients with G6PD deficiency (see Uses, below). Methylthioninium chloride is used to treat methaemoglobinaemia but in large doses it can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride should not be used to treat methaemoglobinaemia induced by sodium nitrite during the treatment of cyanide poisoning, since cyanide binding will be reduced with resultant increased toxicity. It has also been contra-indicated in methaemoglobinaemia due to chlorate poisoning because of the risk that the more toxic hypochlorite may be formed, although several authorities consider its use to treat methaemoglobinaemia in severe chlorate poisoning appropriate.

Methylthioninium chloride imparts a blue colour to saliva, urine, faeces, and skin, which may hinder a diagnosis of cyanosis.

Aniline poisoning. It has been suggested[1] that methylthioninium chloride should be used with caution in the treatment of aniline-induced methaemoglobinaemia since it may precipitate Heinz body formation and haemolytic anaemia. Methylthioninium chloride may reduce methaemoglobin concentrations, but repeated doses could aggravate haemolysis without further reducing methaemoglobinaemia.

1. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. *Br J Haematol* 1983; **54:** 29–41.

Pregnancy. Although intra-amniotic injection of methylthioninium chloride has been used to diagnose premature rupture of fetal membranes or to identify separate amniotic sacs in twin pregnancies, there have been several reports of haemolytic anaemia (Heinz-body anaemia) and hyperbilirubinaemia in neonates who had been exposed to methylthioninium chloride in the amniotic cavity.[1-5] In most cases, exchange transfusions and/or phototherapy were required to control the jaundice; in 1 case phototherapy led to a phototoxic reaction.[5] It has therefore been suggested[3,6] that the use of methylthioninium chloride for detecting premature rupture of the membranes should be avoided.

Multiple ileal occlusions have been reported in babies born to mothers who had twin pregnancies and who had received methylthioninium chloride by amniocentesis;[4,7,8] in some cases it was possible to determine that methylthioninium chloride had been injected into the amniotic sac of the affected twin. Analysis of data from the EUROCAT registries[9] for 1980 to 1988, which surveyed pregnancy outcomes in 11 countries, found a slightly higher risk of ileal and jejunal atresia or stenosis in twins regardless of whether they had received methylthioninium chloride, but the use of methylthioninium chloride was rare and no increased risk could be shown in babies exposed to it. A subsequent review[6] from the Centers for Disease Control and Prevention concluded that the epidemiological evidence for the teratogenicity of methylthioninium chloride was quite strong and advised that it should not be used for midtrimester amniocentesis.

A further difficulty in using methylthioninium chloride by amniocentesis for the diagnosis of premature rupture of the membranes is that the resultant staining of the skin and mucous membranes of the neonate hinders assessment of hypoxia, including the use of pulse oximetry.[10]

1. Cowett RM, *et al.* Untoward neonatal effect of intraamniotic administration of methylene blue. *Obstet Gynecol* 1976; **48** (suppl): 74s–75s.
2. Serota FT, *et al.* The methylene-blue baby. *Lancet* 1979; **ii:** 1142–3.
3. Crooks J. Haemolytic jaundice in a neonate after intra-amniotic injection of methylene blue. *Arch Dis Child* 1982; **57:** 872–3.
4. Nicolini V, Monni G. Intestinal obstruction in babies exposed in utero to methylene blue. *Lancet* 1990; **336:** 1258–9.
5. Porat R, *et al.* Methylene blue-induced phototoxicity: an unrecognized complication. *Pediatrics* 1996; **97:** 717–21.
6. Cragan JD. Teratogen update: methylene blue. *Teratology* 1999; **60:** 42–8.
7. van der Pol JG, *et al.* Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. *Br J Obstet Gynaecol* 1992; **99:** 141–3.
8. Lancaster PAL, *et al.* Intra-amniotic methylene blue and intestinal atresia in twins. *J Perinat Med* 1992; **20** (suppl 1): 262.
9. Dolk H. Methylene blue and atresia or stenosis of ileum and jejunum. *Lancet* 1991; **338:** 1021–2.
10. Troche BT. The methylene blue baby. *N Engl J Med* 1989; **320:** 1756–7.

Interactions

Serotonergic drugs. Methylthioninium chloride has been associated with CNS toxicity when given intravenously as a visualising agent for thyroid or parathyroid surgery in patients who had recently received serotonergic drugs such as *bupropion, buspirone, clomipramine, mirtazapine, SSRIs,* or *venlafaxine*.[1] The MHRA in the UK therefore recommends that methylthioninium chloride should be avoided in patients recently treated with such drugs.

1. MHRA/CHM. Methylthioninium chloride (methylene blue): CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; **1** (6): 5–6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 19/07/08)

Pharmacokinetics

Methylthioninium chloride is absorbed from the gastrointestinal tract. It is believed to be reduced in the tissues to leucomethylene blue, which is slowly excreted, mainly in the urine, with some unchanged drug.

◊ References.

1. Peter C, *et al.* Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; **56:** 247–50.

Uses and Administration

Methylthioninium chloride is a thiazine dye that is used in the treatment of methaemoglobinaemia; it is also used as an antiseptic and in diagnostic procedures.

In patients with methaemoglobinaemia, therapeutic doses of methylthioninium chloride can lower the levels of methaemoglobin in the red blood cells. It activates a normally dormant reductase enzyme system, which reduces the methylthioninium chloride to leucomethylene blue and in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses methylthioninium chloride can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency as these patients have a diminished capacity to reduce methylthioninium chloride to leucomethylene blue; it is also potentially harmful as patients with G6PD deficiency are particularly susceptible to the haemolytic anaemias induced by methylthioninium chloride.

In the treatment of acute methaemoglobinaemia, such as in nitrite poisoning, methylthioninium chloride is given intravenously as a 1% solution in doses of 1 to 2 mg/kg injected over a period of several minutes. A repeat dose may be given after one hour if required. It may be of some value in inherited methaemoglobinaemia; doses of up to 300 mg daily by mouth have been used.

Methylthioninium chloride has a mildly antiseptic action and has been given orally in doses of 65 to 130 mg three times daily in minor urinary-tract infections and to prevent the formation of urinary oxalate stones. It is also included in some preparations intended for application to the eye, mouth and pharynx, and skin.

Methylthioninium chloride is also used as a bacteriological stain, as a dye in diagnostic procedures such as fistula detection and the diagnosis of ruptured amniotic membranes (but see Pregnancy under Adverse Effects and Precautions, above), and for the delineation of certain body tissues during surgery, in particular the parathyroid glands. It is also used for viral photoinactivation in some plasma products. The blue colour can be removed from the skin with hypochlorite solution. Methylthioninium chloride was formerly used in a renal-function test.

Dementia. The aggregation of tau protein filaments in the brain is believed to be associated with the development of cognitive symptoms in Alzheimer's disease (see Dementia, p.362). Methylthioninium chloride, which is thought to dissolve and prevent such aggregations, is under investigation in the management of Alzheimer's disease.

Glutaric aciduria. Glutaric aciduria type II is a metabolic disorder associated with a deficiency of electron-transferring flavoproteins involved in the metabolism of amino acids and fatty acids. Treatment may involve diets low in fats and protein, and some success has been reported with riboflavin. Methylthioninium chloride may also be of benefit since it may act as an electron acceptor, and a response has been seen in an infant[1] with neonatal glutaric aciduria type II. An association has also been noted between encephalopathy due to ifosfamide neurotoxicity (see Effects on the Nervous System under Adverse Effects of Ifosfamide, p.732) and glutaric aciduria, possibly due to inhibition of electron transport by a metabolite of ifosfamide. Methylthioninium chloride has therefore been tried for both treatment and prevention of ifosfamide neurotoxicity, and successful results have been reported;[2-4] however, its role remains unclear.[5]

1. Harpey J-P, *et al.* Methylene-blue for riboflavine-unresponsive glutaricaciduria type II. *Lancet* 1986; **i:** 391.
2. Küpfer A, *et al.* Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet* 1994; **343:** 763–4.
3. Zulian GB, *et al.* Methylene blue for ifosfamide-associated encephalopathy. *N Engl J Med* 1995; **332**: 1239–40.
4. Pelgrims J, *et al.* Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer* 2000; **82:** 291–4.
5. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother* 2006; **40:** 299–303.

Hypotension. Excess nitric oxide production leading to peripheral vasodilatation may be involved in the pathogenesis of hypotension associated with a number of conditions and it has been suggested that methylthioninium chloride, which is a guanylate cyclase inhibitor, may block the effects of nitric oxide and increase blood pressure in such cases. Studies[1,2] in patients with septic shock, including 5 neonates[3] with refractory hypotension assumed to be due to sepsis, have suggested that methylthioninium chloride increases blood pressure and improves tissue oxygenation, although no mortality benefit has been demonstrated.

There have also been reports of the successful use of methylthioninium chloride in patients with anaphylactic shock,[4] hypotension associated with haemodialysis,[5] vasoplegia after cardiac surgery,[6] and severe hepatopulmonary syndrome,[7] all of which may involve increased nitric oxide production. However, the role of methylthioninium chloride in these conditions is not established.

The usual management of shock is discussed on p.1183; anaphylactic shock should be treated with adrenaline, as discussed on p.1205.

1. Preiser J-C, *et al.* Methylene blue administration in septic shock: a clinical trial. *Crit Care Med* 1995; **23:** 259–64.
2. Kirov MY, *et al.* Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001; **29:** 1860–7.
3. Driscoll W, *et al.* Effect of methylene blue on refractory neonatal hypotension. *J Pediatr* 1996; **129:** 904–8.
4. Oliviera Neto AM, *et al.* Methylene blue: an effective treatment for contrast medium-induced anaphylaxis. *Med Sci Monit* 2003; **9:** CS102–CS106.
5. Peer G, *et al.* Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. *Nephrol Dial Transplant* 2001; **16:** 1436–41.
6. Levin RL, *et al.* Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg* 2004; **77:** 496–9.
7. Schenk P, *et al.* Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; **133:** 701–6.

Ifosfamide encephalopathy. See Glutaric Aciduria, above.

Methaemoglobinaemia. Methaemoglobinaemia is a rare disorder of the blood in which there is an increase in the proportion of haemoglobin present in the oxidised form. Inherited methaemoglobinaemia may be due either to a deficiency of methaemoglobin reductase or to a structural abnormality of haemoglobin. Acquired methaemoglobinaemia may be caused by drugs[1] or chemicals that oxidise haemoglobin, including nitrates and nitrites, sodium nitroprusside, dapsone, sulfonamides, phenacetin, and some local anaesthetics such as prilocaine; it may occur as a result of direct administration or occupational[2] or environmental exposure. Exposure to low doses over long periods may lead to chronic methaemoglobinaemia whereas large doses may lead to an acute effect.

Methaemoglobinaemia has a profound effect on oxygen transport by the blood; there is an increase in oxygen affinity leading to reduced tissue delivery and varying degrees of cyanosis. The presence of symptoms depends upon the degree and rapidity of methaemoglobin formation. Chronic mild methaemoglobinaemia is generally well tolerated although patients may appear cyanotic. Acute methaemoglobinaemia, particularly where methaemoglobin levels exceed 20%, is associated with dyspnoea, headache, malaise, giddiness, and altered mental state; methaemoglobin levels above 50% may lead to vascular collapse, coma, and death.

Patients with inherited methaemoglobinaemia are usually asymptomatic but treatment may be given for cosmetic purposes to reduce the cyanotic skin colour. Patients with reductase deficiency generally respond to oral therapy with drugs that promote the reduction of methaemoglobin to haemoglobin, such as ascorbic acid, riboflavin, or methylthioninium chloride; methylthioninium chloride may also be given intravenously. Patients with structural abnormalities of haemoglobin do not respond. In acquired methaemoglobinaemia the causative agent should be identified and removed. Chronic or mild cases may not require treatment but acute symptomatic methaemoglobinaemia may be life-threatening and patients should be given intravenous methylthioninium chloride, along with oxygen and other supportive therapy as required. Toxicity is uncommon with methylthioninium chloride but it should not be used for methaemoglobinaemia due to the use of nitrites for cyanide poisoning since increased toxicity may result (for debate about its use after chlorate poisoning, see Adverse Effects and Precautions, above). Severe methaemoglobinaemia may require exchange transfusion; exchange transfusion with haemodialysis is the treatment of choice in patients with acute methaemoglobinaemia and haemolysis. Hyperbaric oxygen therapy has also been suggested in severe cases. Ascorbic acid is not useful in the acute situation since it acts too slowly but it may be of benefit where maintenance therapy is required.

1. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia: treatment issues. *Drug Safety* 1996; **14:** 394–405.
2. Bradberry SM. Occupational methaemoglobinaemia: mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev* 2003; **22:** 13–27.

ADMINISTRATION. In acute methaemoglobinaemia, methylthioninium chloride is usually given by intravenous bolus injection, but repeated doses may be needed and continuous intravenous infusion has also been used. Methylthioninium chloride was given at a dose of 7.5 to 10 mg/hour for 43 hours to control methaemoglobinaemia after dapsone poisoning.[1] The patient had responded to two bolus doses of 100 mg but methaemoglobinaemia had subsequently increased again owing to the long half-life of dapsone. Additional therapy included repeated doses of activated charcoal. A dosing schedule for methylthioninium chloride of 1 to 2 mg/kg as a bolus followed by a continuous infusion at an initial rate of 100 to 150 micrograms/kg per hour was suggested.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.

Priapism. Priapism is usually treated with corporal aspiration or intracavernosal vasoconstrictors (see under Uses of Metaraminol, p.1333). There have been reports[1-4] of the successful use of intracavernosal methylthioninium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred[5] after the use of methylthioninium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthioninium chloride about 5 minutes after injection has been suggested.[2,3]

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; **146:** 1361–3.
2. deHoll JD, *et al.* Alternative approaches to the management of priapism. *Int J Impot Res* 1998; **10:** 11–14.
3. Martínez Portillo FJ, *et al.* Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; **39:** 20–3.
4. Hübler J, *et al.* Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; **35:** 519–21.
5. Mejean A, *et al.* Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; **149:** 1149.

Preparations

BP 2008: Methylthioninium Injection;
USP 31: Methylene Blue Injection.

Proprietary Preparations (details are given in Part 3)
Hung.: Metilenkek; ***USA:*** Urolene Blue.

Multi-ingredient: ***Arg.:*** Lagrimas de Santa Lucia†; Mictasol Azul; Muelita; Visubril; ***Austria:*** Methyment; ***Braz.:*** Acridin; Cystex; Lisian†; Pilulas De Witt's†; Sepurin; Vislin; Visodin; Visolux†; ***Canad.:*** Collyre Bleu†; ***Fr.:*** Collyre Bleu; Pastilles Monleon; ***Hong Kong:*** Clear Blue; ***Israel:*** Pronestin; ***Ital.:*** Mictasol Bleu†; Visustrin; ***NZ:*** De Witts Pills†; ***Pol.:*** Ginjal; Mibalin; ***Rus.:*** Neo-Anusol (Нео-анузол); ***Spain:*** Argentofenol†; Centilux; Tivitis; ***Switz.:*** Collyre Bleu Laiter; ***Turk.:*** Buco Bleu; Helmobleu; ***USA:*** Atrosept; Dolsed†; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X†; UAA; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira.

Milk Thistle

Cardo mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainių vaisiai (milk-thistle fruit); Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Plod ostropestřece mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle.
CAS — 84604-20-6 (milk thistle extract).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug). Protect from light.

USP 31 (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin *(rINN)*

Silibinina; Silibinine; Silibininum; Silybin; Silybum Substance E_6; Silybinina. 3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.
Силибинин
$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 22888-70-6.

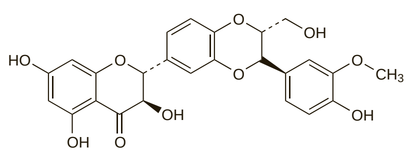

NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin *(rINN)*

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin. 2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuranyl]-3,5,7-trihydroxy-4-chromanone.
Силикристин
$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 33889-69-9.

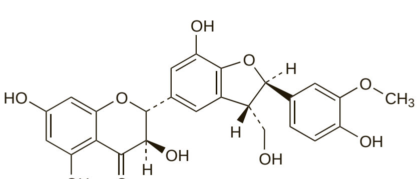

Silidianin *(rINN)*

Silidianina; Silidianine; Silidianinum; Silydianin. (+)-2,3α,3aα,7a-Tetrahydro-7aα-hydroxy-8(*R**)-(4-hydroxy-3-methoxyphenyl)-4-(3α,5,7-trihydroxy-4-oxo-2β-chromanyl)-3,6-methanobenzofuran-7(6α*H*)-one.
Силидианин
$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 29782-68-1.

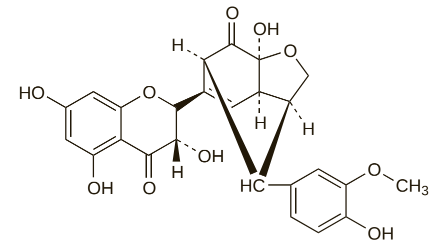

Silymarin

Silimarina; Silymarinum. A mixture of the isomers silibinin, silicristin, and silidianin.
CAS — 65666-07-1.
ATC — A05BA03.
ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum*; *Carduus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotectant properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* poisoning (p.2349) both silymarin and silibinin (as the disodium dihemisuccinate salt) have been used.

Milk thistle is usually given as a standardised extract containing mainly silymarin, although the herb and fruit have also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; the usual dose in *Amanita phalloides* poisoning is equivalent to silibinin 20 mg/kg daily, given by intravenous infusion in 4 divided doses.

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.[1-3]

1. Lorenz D. Über die anwending von silibinin bei der knollenblätterpilzvergiftung. *Dtsch Arzt* 1982; **79:** 43–5.
2. Hruby K, *et al.* Chemotherapy of Amanita phalloides poisoning with intravenous silibinin. *Hum Toxicol* 1983; **2:** 183–90.
3. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40:** 715–57.

Liver disorders. References to the use of milk thistle or silymarin in patients with liver disorders.

1. Saller R, *et al.* The use of silymarin in the treatment of liver diseases. *Drugs* 2001; **61:** 2035–63.
2. Jacobs BP, *et al.* Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002; **113:** 506–15.

Preparations

USP 31: Milk Thistle Capsules; Milk Thistle Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Benevolus†; Laragon; ***Austral.:*** Bioglan Liver-Vite; Herbal Liver Formula†; Prol†; Silymarin Phytosome†; ***Austria:*** Apihepar; Ardeyhepan; Legalon; Silyhexal; ***Belg.:*** Legalon; Legalon SIL; ***Braz.:*** Eleparon†; Legalon; Siliver; ***Chile:*** Legalon; ***Cz.:*** Flavobion; Lagosa; Legalon; Nat Cubetu Benediktu†; Silygal; ***Fr.:*** Legalon; ***Ger.:*** Alepa; Ardeyhepan; Cefasliymarin; durasilymarin; Hegrimarin; Hepa-Loges; Hepa-Merz Sil†; HepaBesch; Hepaduran V†; Hepar-Pasc; Heparsyx N†; Hepatos; Heplant; Lagosa; Legalon; Legalon SIL; Lomacholan†; Phytohepar; Poikicholan†; Silibene; Silicur; Silimarit; Silmar†; Silvaysan; Sily-Sabona†; ***Gr.:*** Legalon; ***Hong Kong:*** Legalon; ***Hung.:*** Hegrimarin; Legalon; Legalon SIL; Silegon; ***India:*** Limarin; Silybon; ***Ital.:*** Legalon; Silimarin; Silirex; Silliver†; ***Mex.:*** Etagerin; Legalon; ***Philipp.:*** Hepavit; Legalon; Liveraide; ***Pol.:*** Flexiderm; Lagosa; Legalon; Silimax; Sylicaps; Sylimarol; Syliverin; ***Port.:*** Legalon; Legalon SIL; ***Rus.:*** Carsil (Карсил); ***S.Afr.:*** Legalon; ***Spain:*** Legalon; Legalon SIL; Silarine; Silimazu†; ***Switz.:*** Legalon; Legalon SIL; ***Thai.:*** Legalon; Leveron; Marina; Samarin; Sivylar; ***Venez.:*** Legalon.

Multi-ingredient: ***Arg.:*** Bibol Leloup; Hepadigenor†; Quelodin F; ***Austral.:*** Antioxidant Forte Tablets; Bupleurum Complex; Bupleurum Compound; Digest; Extralife Liva-Care; Herbal Cleanse†; Lifesystem Herbal Formula 7 Liver Tonic†; Liver Tonic Herbal Formula 6†; Livstim†; Livton Complex†; Silybum Complex†; St Mary's Thistle Plus; ***Austria:*** Hepabene; ***Braz.:*** Silimalon; ***Canad.:*** Milk Thistle; Milk Thistle Extract Formula†; ***Cz.:*** Hepabene†; Iberogast; Naturland Grosser Swedenbitter†; Simepar; Ungolen†; ***Ger.:*** Bilisan Duo; Cheiranthol†; Cholhepan N; Cholosom-Tee; Gallexier; Galloselect M†; Hepaticum-Medice H†; Heumann Leber- und Gallentee Solu-Hepar S†; Heumann Verdauungstee Solu-Lipar; Heusin†; Iberogast; Marianon†; Pankreaplex Neu†; Pascopankreat novo†; Presselin Hepaticum P†; Schwohepan S†; Venacton†; ***Hong Kong:*** Hepatofalk Planta; Simepar; ***Hung.:*** Hepabene; ***India:*** Livosil-B; ***Indon.:*** Aptivium Liver Support; Curliv Plus; Hepa-Q; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta; Verona; Vionin NF; ***Ital.:*** Depatox; Epagest†; Liverton; Tarassaco (Specie Composta)†; Venoplus†; ***Malaysia:*** Hepavite; Simepar; ***Philipp.:*** Liverine; Livermin; ***Pol.:*** Artecholin; Artecholwex; Gastrobonisol; Sylicynar; Sylivit; Tabletki Przeciw Niestrawnosci; ***Port.:*** Cholagutt†; Synchrorose; ***Rus.:*** Hepabene (Гепабене); Sibectan (Сибектан); ***Singapore:*** Hepatofalk Planta; Hepavite; Noricaven†; Simepar; ***Switz.:*** Demonatur Gouttes pour le foie et la bile; Iberogast; Phytomed Hepato†; Simepar†; Tisane hepatique et biliaire.

Nalmefene *(BAN, USAN, rINN)*

6-Desoxy-6-methylene-naltrexone; JF-1; Nalméfène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676. 17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol.
Налмефен
$C_{21}H_{25}NO_3$ = 339.4.
CAS — 55096-26-9.

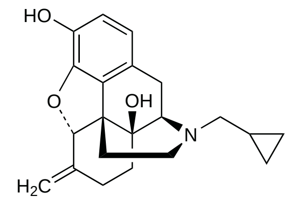

Nalmefene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalmefeno; Nalméfène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmetrene Hydrochloride.
Налмефена Гидрохлорид
$C_{21}H_{25}NO_3,HCl$ = 375.9.
CAS — 58895-64-0.

Adverse Effects

Nausea, vomiting, tachycardia, hypertension, fever, and dizziness have been reported with therapeutic doses of nalmefene. At higher doses or in patients later found to be physically dependent on opioids, symptoms suggestive of opioid withdrawal have been noted; these have included abdominal cramps, chills, dysphoria, myalgia, and joint pain.

Precautions

As for Naloxone, p.1453.

Incremental doses of nalmefene should be given slowly in patients with renal impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is not complete owing to significant first-pass metabolism. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The plasma elimination half-life is reported to be about 10 hours.

◊ References.

1. Dixon R, *et al.* Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39:** 49–53.
2. Dixon R, *et al.* Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; **27:** 233–9.
3. Frye RF, *et al.* The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; **42:** 301–6.
4. Frye RF, *et al.* Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; **61:** 15–23.

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions and uses similar to those of naloxone (p.1454), but with a longer duration of action. It is given as the hydrochloride but doses are expressed in terms of the base. Nalmefene hydrochloride 111 micrograms is equivalent to about 100 micrograms of nalmefene. It is usually given intravenously for a rapid onset of action; subcutaneous or intramuscular administration is also effective but has a slower onset. Nalmefene has also been given orally.

For the reversal of postoperative central depression due to the use of opioids, nalmefene is given intravenously, at a concentration of 100 micrograms/mL, in an initial dose of 250 nanograms/kg. Further doses of 250 nanograms/kg may be given at intervals of 2 to 5 minutes until the desired level of opioid reversal is reached; cumulative doses above 1 microgram/kg do not provide additional benefit. In patients with an increased cardiovascular risk a concentration of 50 micrograms/mL and doses and increments of 100 nanograms/kg are recommended.

In the management of known or suspected opioid overdosage, nalmefene is given intravenously at a concentration of 1 mg/mL. An initial dose of 500 micrograms per 70 kg is recommended, followed by a second dose of 1 mg per 70 kg after 2 to 5 minutes if necessary. If a total dose of 1.5 mg per 70 kg is not effective then additional doses are unlikely to have an effect. If the patient is suspected of being physically dependent on opioids an initial test dose of 100 micrograms per 70 kg is recommended; if there is no evidence of withdrawal symptoms within 2 minutes the usual dosage may be used.

Although nalmefene has a longer duration of action than naloxone, all patients should be closely observed and if respiratory depression does recur, the dose of nalmefene should be titrated as above to avoid over-reversal of opioid effects.

Alcohol withdrawal and abstinence. For mention of the use of nalmefene in the adjunctive management of patients with alcohol dependence, see under Naltrexone, p.1456.

Pruritus. It has been suggested that because central opioid receptors modulate itch, an opioid antagonist might be useful in pruritus (p.1582). A systematic review[1] found that opioid antagonists are effective in opioid-induced pruritus, and a number have also been reported to be of benefit in pruritus of other causes.

Rapid improvement of severe pruritus was reported after a single oral dose of *nalmefene* 10 or 20 mg in a double-blind study of 80 patients with either chronic urticaria or atopic dermatitis.[2] Pruritus was almost completely eliminated in up to 60% of patients receiving nalmefene. Adverse effects occurred in 67% of patients and included dizziness or lightheadedness, fatigue, and nausea. In another study,[3] 14 patients with resistant pruritus secondary to cholestatic liver disease were treated with oral nalmefene for 2 to 26 months. The initial dose was 2 mg twice daily and the dose was increased gradually as necessary. Although 13 of the patients reported some amelioration of pruritus, 5 found that increasing doses were required to produce any benefit, and in 3 tolerance appeared to develop.

Continuous infusion of *naloxone* 200 nanograms/kg per minute was reported to reduce perception of pruritus and scratching activity in a double-blind study of 29 patients with pruritus due to cholestasis,[4] although the role of continuous infusion in long-term management may be limited.

Benefit has been reported with oral *naltrexone* 50 mg daily in pruritus of various origins,[5] as well as in patients with cholestatic pruritus.[6,7] In uraemic pruritus, conflicting results have been reported;[8,9] a subsequent study[10] suggested that naltrexone might be of benefit in selected patients.

1. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18:** 346–57.
2. Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; **21:** 135–6.
3. Bergasa NV, *et al.* Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27:** 679–84.
4. Bergasa NV, *et al.* Effects of naloxone infusions in patients with the pruritus of cholestasis. *Ann Intern Med* 1995; **123:** 161–7.
5. Metze D, *et al.* Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; **41:** 533–9.
6. Wolfhagen FH, *et al.* Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; **113:** 1264–9.
7. Terg R, *et al.* Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol* 2002; **37:** 717–22.
8. Peer G, *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348:** 1552–4.
9. Pauli-Magnus C, *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11:** 514–9.
10. Legroux-Crespel E, *et al.* A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; **208:** 326–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Nocarex; ***USA:*** Revex.

Nalorphine *(BAN, rINN)*

Nalorfiini; Nalorfin; Nalorfina; Nalorphinum. (−)-(5*R*,6*S*)-9a-Allyl-4,5-epoxymorphin-7-en-3,6-diol; 17-Allyl-17-normorphine.

Налорфин

$C_{19}H_{21}NO_3$ = 311.4.
CAS — 62-67-9.
ATC — V03AB02.
ATC Vet — QV03AB02.

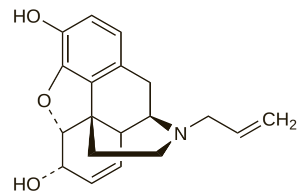

Nalorphine Hydrobromide *(BANM, rINNM)*

Hidrobromuro de nalorfina; Nalorphine, Bromhydrate de; Nalorphini Hydrobromidum.

Налорфина Гидробромид

$C_{19}H_{21}NO_3,HBr$ = 392.3.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *Chin.*

Nalorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalorfina; Nalorphine, Chlorhydrate de; Nalorphini Hydrochloridum; Nalorphinium Chloride.

Налорфина Гидрохлорид

$C_{19}H_{21}NO_3,HCl$ = 347.8.
CAS — 57-29-4.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *US.*
USP 31 (Nalorphine Hydrochloride). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

As for Naloxone (below). Nalorphine also has some opioid agonist properties and adverse effects such as drowsiness, respiratory depression, miosis, dysphoria, and lethargy may occur if it is given to patients who have not received opioids.

Uses and Administration

Nalorphine is an opioid antagonist with properties similar to those of naloxone (below); in addition it also possesses some agonist properties. It has been used as the hydrobromide or hydrochloride in the treatment of opioid-induced respiratory depression; it reverses severe opioid-induced respiratory depression but may exacerbate respiratory depression such as that induced by alcohol or other non-opioid central depressants.

Preparations

USP 31: Nalorphine Hydrochloride Injection.

Naloxone Hydrochloride

(BANM, USAN, rINNM)

N-Allylnoroxymorphone Hydrochloride; Cloridrato de Naloxona; EN-15304; Hidrocloruro de naloxona; Nalokson Hidroklorür; Naloksonihydrokloridi; Naloksono hidrochloridas; Naloksonu chlorowodorek dwuwodny; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydraté; Naloxon-hidroklorid; Naloxon-hydrochlorid; Naloxonhydroklorid; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum. 17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (−)-(5*R*,14*S*)-9a-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.

Налоксона Гидрохлорид

$C_{19}H_{21}NO_4,HCl,2H_2O$ = 399.9.
CAS — 465-65-6 (naloxone); 357-08-4 (anhydrous naloxone hydrochloride); 51481-60-8 (naloxone hydrochloride dihydrate).
ATC — V03AB15.
ATC Vet — QV03AB15.

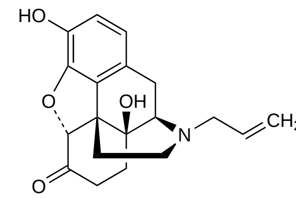

(naloxone)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.* Forms specified may be anhydrous, dihydrate, or both.
Ph. Eur. 6.2 (Naloxone Hydrochloride Dihydrate; Naloxone Hydrochloride BP 2008). It contains two molecules of water of hydration. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.
USP 31 (Naloxone Hydrochloride). It is anhydrous or contains two molecules of water of hydration. A white to slightly off-white powder. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its aqueous solution is acidic. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Infusions of naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or solutions with an alkaline pH.

Adverse Effects

Nausea and vomiting have occurred with naloxone. Some adverse effects may be associated with opioid withdrawal. There have been individual reports of hypotension, hypertension, cardiac arrhythmias, and pulmonary oedema, generally in patients given naloxone postoperatively. Seizures have also been reported infrequently.

◊ Hypertension,[1,2] pulmonary oedema,[3] and cardiac arrhythmias including ventricular tachycardia and fibrillation[4] have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients,[5,6] including some fatalities.[5]

Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke.[7]

Ventricular fibrillation has been observed in an opioid addict given naloxone to reverse the effects of diamorphine.[8] However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the National Poisons Information Service in London noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year.[9] In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication.[10] The effects were: asystole (1 case), generalised convulsions (3), pulmonary oedema (1), and violent behaviour (1).

1. Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; **228:** 25–6.
2. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; **58:** 524–5.
3. Flacke JW, *et al.* Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47:** 376–8.
4. Michaelis LL, *et al.* Ventricular irritability associated with the use of naloxone hydrochloride: two case reports and laboratory assessment of the effects of the drug on cardiac excitability. *Ann Thorac Surg* 1974; **18:** 608–14.
5. Wride SRN, *et al.* A fatal case of pulmonary oedema in a healthy young male following naloxone administration. *Anaesth Intensive Care* 1989; **17:** 374–7.
6. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59:** 576–7.
7. Barsan WG, *et al.* Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; **17:** 762–7.
8. Cuss FM, *et al.* Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; **288:** 363–4.
9. Barret L, *et al.* Cardiac arrest following naloxone. *BMJ* 1984; **288:** 936.
10. Osterwalder JJ. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; **34:** 409–16.

Precautions

Naloxone should be used with caution in patients physically dependent on opioids, or who have received large doses of opioids, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p.101). Naloxone crosses the placenta and a withdrawal syndrome may be precipitated in neonates of opioid-dependent mothers.

Caution is required in patients with cardiac disease or those receiving cardiotoxic drugs.

The duration of action of some opioids exceeds that of naloxone; patients should therefore be carefully observed after administration in case of relapse.

Pharmacokinetics

Naloxone is absorbed from the gastrointestinal tract but it is subject to considerable first-pass metabolism. It is metabolised in the liver, mainly by glucuronide conjugation, and excreted in the urine. It has a plasma half-life of about 1 hour after parenteral administration. Naloxone crosses the placenta.

Pregnancy and the neonate. A study in 30 mothers given a single intravenous dose of naloxone during the second stage of labour, indicated that naloxone rapidly crossed the placental barrier so that some therapeutic effect might be anticipated in most neonates.[1] Placental transfer in 7 further mothers given naloxone intramuscularly was considered to be too variable for therapeutic purposes.

In 12 neonates given naloxone hydrochloride 35 or 70 micrograms intravenously via the umbilical vein, the mean plasma half-life was 3.53 or 2.65 hours respectively.[2] These half-lives were 2 to 3 times longer than those reported for adults, possibly due to a diminished ability of the newborn to metabolise drugs by conjugation with glucuronic acid. Mean peak plasma concentrations of 8.2 nanograms/mL or 13.7 nanograms/mL in those given 35 or 70 micrograms respectively, were reached within 40 minutes but this time was very variable, and in 5 neonates peak concentrations were reached within 5 minutes. Naloxone hydrochloride 200 micrograms intramuscularly in 17 further neonates produced peak concentrations of 7.4 to 34.6 nanograms/mL at 0.5 to 2 hours.

1. Hibbard BM, *et al*. Placental transfer of naloxone. *Br J Anaesth* 1986; **58:** 45–8.
2. Moreland TA, *et al*. Naloxone pharmacokinetics in the newborn. *Br J Clin Pharmacol* 1980; **9:** 609–12.

Uses and Administration

Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is an effective antagonist of opioids that possess agonist or mixed agonist-antagonist activity although larger doses may be needed for compounds with the latter activity. It is used to reverse opioid central depression, including respiratory depression, induced by natural or synthetic opioids in the treatment of known or suspected opioid overdosage, postoperatively after the use of opioids during surgery, and in neonates when opioid analgesics have been given to the mother during labour.

Naloxone hydrochloride is usually given intravenously for a rapid onset of action, which occurs within 2 minutes. The onset of action is only slightly less rapid when it is given intramuscularly or subcutaneously. Other routes, including the endotracheal, have also been used. The duration of action of naloxone is dependent on the dose and route; it is usually reported to be several hours, but may be much shorter, in the region of 1 hour or less.

In the treatment of known or suspected **opioid overdosage**, the initial dose of naloxone hydrochloride is 0.4 to 2 mg given intravenously and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the patient is suspected of being physically dependent on opioids the dose may be reduced to 100 to 200 micrograms to avoid precipitating withdrawal symptoms. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used.

Naloxone hydrochloride may also be used **postoperatively** to reverse central depression resulting from the use of opioids during surgery. For adults, a dose of 100 to 200 micrograms may be given intravenously at intervals of 2 to 3 minutes, titrated for each patient in order to obtain an optimum respiratory response while maintaining adequate analgesia.

All patients receiving naloxone should be closely observed as the duration of action of many opioids exceeds that of naloxone and repeated doses may be required. Alternatively, to sustain opioid antagonism, an intravenous infusion may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response. Some have recommended an infusion of 60% of the initial dose per hour, diluted to a concentration of 200 micrograms/mL in glucose. Others have suggested an initial intravenous loading dose of 400 micrograms, followed by a continuous infusion at an initial rate of 400 micrograms/hour. Alternatively, an intravenous loading dose of 5 micrograms/kg has been suggested, followed by a continuous infusion of 2.5 micrograms/kg per hour.

For doses in children, see Administration in Children, below.

Some opioid analgesics have been formulated with naloxone hydrochloride to reduce their potential for parenteral abuse, or as a substitution treatment for opioid dependence. Naloxone hydrochloride has also been used cautiously in small doses to diagnose opioid dependence by precipitating the withdrawal syndrome (see below and under Naltrexone, p.1455).

Administration in children. In the treatment of known or suspected **opioid overdosage** in children, licensed product information recommends an initial dose of naloxone hydrochloride of 10 micrograms/kg intravenously, followed, if necessary, by a larger dose of 100 micrograms/kg. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used.

For **acute respiratory depression induced by opioids** the Committee on Drugs of the American Academy of Pediatrics has recommended a dose for naloxone of 100 micrograms/kg by the intramuscular, intravenous, or intratracheal routes for neonates, including premature infants, to the age of 5 years or 20 kg body-weight; absorption may be erratic after intramuscular use. They advocated that children over 5 years or 20 kg should be given a *minimum* of 2 mg. These doses may be repeated as necessary to maintain opioid reversal.[1,2] The Committee noted that these higher dose recommendations were based partly on the concern that 10 micrograms/kg might not provide optimal opiate reversal in some infants, and that it was felt that the higher doses posed no increased risk.[3] The American Heart Association guidelines for paediatric advanced life support gave the same doses as the Committee for children to the age of 5 years or 20 kg body-weight, but stated that those aged over 5 years or 20 kg be given a dose of 2 mg, without specifying this as a minimum.[4] The use of injections containing 20 micrograms/mL of naloxone hydrochloride is no longer recommended because of the fluid load involved at these doses, especially in small neonates.[1] It has been noted that specialists differ in their dosage of naloxone;[5] a study in the USA found that paediatric intensive care and emergency medicine physicians tended to use 100 micrograms/kg up to a *maximum* initial dose of 2 mg.

In contrast, anaesthesiologists have tended to use initial doses of 10 to 20 micrograms naloxone, regardless of body-weight;[5] the American Academy of Pediatrics states that lower initial doses of 10 micrograms/kg may be considered for other clinical situations such as **respiratory depression during pain management**.[2] Licensed product information states that for **postoperative use**, initial doses of 5 to 10 micrograms may be given intravenously at 2 to 3 minute intervals until the desired response is obtained.

Opioid-induced depression in **neonates** resulting from the use of opioid analgesics in the mother during labour may be reversed by giving naloxone hydrochloride 10 micrograms/kg to the infant by intravenous, intramuscular, or subcutaneous injection, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single intramuscular dose of about 60 micrograms/kg may be given at birth for a more prolonged action. Naloxone should be given with caution to the infants of opioid dependent mothers since withdrawal symptoms can result.

1. American Academy of Pediatrics. Emergency drug doses for infants and children and naloxone use in newborns: clarification. *Pediatrics* 1989; **83:** 803.
2. Committee on Drugs. Drugs for pediatric emergencies. Abstract: *Pediatrics* 1998; **101:** e13. Full version: http://pediatrics.aappublications.org/cgi/reprint/101/1/e13.pdf (accessed 30/06/06)
3. American Academy of Pediatrics. Naloxone dosage and route of administration for infants and children: addendum to emergency drug doses for infants and children. *Pediatrics* 1990; **86:** 484–5.
4. American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: Pediatric Advanced Life Support. *Circulation* 2005; **112** (suppl): IV-167–IV-187. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-1.pdf (accessed 05/02/08)
5. Hasan RA, *et al.* Cardiorespiratory effects of naloxone in children. *Ann Pharmacother* 2003; **37:** 1587–92.

Eating disorders. Endogenous opioids may have a role in the pathophysiology of eating disorders,[1] thus opioid antagonists such as naloxone and naltrexone have been tried in their management. However, their role appears to be limited and they do not form part of the usual management of these conditions.

1. de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. *J Clin Pharmacol* 1992; **32**; 1060–72.

Non-opioid overdosage. Naloxone antagonises the action of exogenous and endogenous opioids. This may explain the varying responses reported to naloxone used in the treatment of overdosage with non-opioids, some of which may modulate endogenous opioids.

Benefit has been reported[1] with naloxone in valproate overdosage, although the evidence is based on case reports. There have also been case reports suggesting benefit in overdosage with camylofin,[2] chlorpromazine,[3] and ibuprofen.[4] A study[5] with midazolam in healthy subjects found that naloxone did not reverse respiratory depression, although there had been earlier reports of benefit in coma due to benzodiazepines.

Naloxone has been used for clonidine intoxication, but retrospective reviews[6,7] have concluded that responses are inconsistent, and there have been reports of hypertension. A lack of response has also been reported[8] in brimonidine overdosage. There has been a report[9] of the successful use of naloxone after captopril overdosage.

Naloxone may also be of benefit in overdosage with drugs that are structurally related to opioids, including apomorphine,[10] dextromethorphan,[11] and loperamide.[12]

1. Roberge RJ, Francis EH. Use of naloxone in valproic acid overdose: case report and review. *J Emerg Med* 2002; **22:** 67–70.
2. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; **ii:** 1246.
3. Chandavasu O, Chatkupt S. Central nervous system depression from chlorpromazine poisoning: successful treatment with naloxone. *J Pediatr* 1985; **106:** 515–6.
4. Easley RB, Altemeier WA. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. *Pediatr Emerg Care* 2000; **16:** 39–41.
5. Forster A, *et al*. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. *Anesth Analg* 1983; **62:** 920–4.
6. Fiser DH, *et al.* Critical care for clonidine poisoning in toddlers. *Crit Care Med* 1990; **18:** 1124–8.
7. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
8. Sztajnbok J. Failure of naloxone to reverse brimonidine-induced coma in an infant. *J Pediatr* 2002; **140:** 485–6.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.
10. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.
11. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
12. Friedli G, Haenggeli C-A. Loperamide overdose managed by naloxone. *Lancet* 1980; **i:** 1413.

Pruritus. For reference to the use of opioid antagonists, including naloxone, in the management of pruritus, see under Nalmefene, p.1453

Reversal of opioid effects. Naloxone is used postoperatively to reverse central depression resulting from the use of opioids during surgery. However, the beneficial analgesic effects of the opioids may also be reversed, and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use.

In patients receiving longer-term opioids, naloxone has been reported to alleviate some of their adverse effects without loss of therapeutic efficacy. Naloxone reversed respiratory depression in a patient given intrathecal morphine,[1] and urinary retention in 3 patients after epidural morphine,[2] without reversing analgesia. However, a study[3] in patients receiving extradural fentanyl found that naloxone failed to relieve urinary retention whereas pain scores rapidly increased. Naloxone given intravenously has been shown to reverse the delay in gastric emptying induced by opioid analgesics in healthy subjects[4] and in women during labour.[5] Continuous intravenous infusion of naloxone reduced the incidence of adverse effects in patients receiving morphine by patient-controlled analgesia for postoperative pain.[6] Pain control was not compromised and the lower dose of naloxone used (250 nanograms/kg hourly as opposed to 1 microgram/kg hourly) appeared to have an opioid-sparing effect. In patients receiving long-term opioids, oral naloxone in a daily dose equivalent to 20 to 40% of the daily opioid dose relieved opioid-induced constipation without compromising analgesic control.[7,8] Doses equivalent to 10% or less of the opioid dose were ineffective.[9] However, other studies[10] have found adverse effects even at low doses of naloxone, and the optimum dose remains unclear. Methylnaltrexone, a related opioid antagonist is also used for the reversal of opioid-induced constipation (see p.1747).

1. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. *BMJ* 1980; **281:** 645–6.
2. Rawal N, *et al*. Naloxone reversal of urinary retention after epidural morphine. *Lancet* 1981; **ii:** 1411.

3. Wang J, *et al.* Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. *Br J Anaesth* 1998; **80:** 565–6.
4. Nimmo WS, *et al.* Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *BMJ* 1979; **2:** 1189.
5. Frame WT, *et al.* Effect of naloxone on gastric emptying during labour. *Br J Anaesth* 1984; **56:** 263–5.
6. Gan TJ, *et al.* Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997; **87:** 1075–81.
7. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **337:** 1475.
8. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 582.
9. Robinson BA, *et al.* Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 581–2.
10. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. *Am J Health-Syst Pharm* 2003; **60:** 1264–7.

DIAGNOSTIC USE. Naloxone is used to reverse opioid effects in the diagnosis of opioid overdose, although some workers have recommended that it should only be used in patients with clinical signs of opioid overdose.[1]

Naloxone has also been used in the diagnosis of opioid dependence. It has been given intravenously to precipitate withdrawal symptoms, but methods that do not induce acute withdrawal have also been investigated. Pupillary dilatation in response to topical naloxone solution (naloxone eye drops) has been suggested as a useful method, but varying results have been reported depending on the strength of the solution used. A study[2] using naloxone hydrochloride solution 1 mg/mL distinguished patients with a physical dependence from non-dependent patients who had received opioids on a single occasion as pre-operative medication, but this response was not confirmed in another study[3] using naloxone 400 micrograms/mL solution. Another study[4] reported that a 2 mg/mL solution of naloxone hydrochloride gave useful results in an outpatient setting. However, there has been a report[5] of withdrawal syndrome and pupillary dilatation in 4 opioid dependent subjects after instillation of naloxone solution 40 mg/mL.

1. Hoffman JR, *et al.* The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991; **20:** 246–52.
2. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; **i:** 748–50.
3. Loimer N, *et al.* Conjunctival naloxone is no decision aid in opioid addiction. *Lancet* 1990; **335:** 1107–8.
4. Ghodse AH, *et al.* Evaluation of the opioid addiction test in an out-patient drug dependency unit. *Br J Psychiatry* 1999; **175:** 158–62.
5. Sanchez-Ramos JR, Senay EC. Ophthalmic naloxone elicits abstinence in opioid-dependent subjects. *Br J Addict* 1987; **82:** 313–15.

OPIOID OVERDOSAGE. Naloxone is usually given intravenously in opioid overdosage but may also be given intramuscularly if intravenous access is not available. Alternative routes have also been tried; a study[1] using intranasal naloxone found that it was effective for prehospital management of suspected opioid overdosage, although response was slower than with intramuscular injection.

1. Kelly A-M, *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005; **182:** 24–7.

Shock. Endogenous opioids may have a role in the pathophysiology of shock but studies investigating naloxone for the treatment of shock have produced contradictory results. A systematic review[1] concluded that naloxone does increase blood pressure in various forms of shock, but no significant effect on mortality was shown. US licensed product information has noted that the optimal dose and duration of therapy with naloxone have not been established, and that caution should be exercised before its use, particularly in patients with underlying pain or who have previously received opioids and may have developed opioid tolerance.

1. Boeuf B, *et al.* Naloxone for shock. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 04/10/05).

Preparations

BP 2008: Naloxone Injection; Neonatal Naloxone Injection;
USP 31: Naloxone Hydrochloride Injection; Pentazocine and Naloxone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiopiaz; Grayxona; Narcanti; Narxona; ***Austral.:*** Narcan; ***Austria:*** Narcanti; ***Belg.:*** Narcan†; ***Braz.:*** Narcan; ***Canad.:*** Narcan†; ***Cz.:*** Intrenon; Narcanti†; ***Denm.:*** Narcanti; ***Fin.:*** Narcanti; ***Fr.:*** Nalone†; Narcan†; ***Ger.:*** Naloselect†; Narcanti; ***Gr.:*** Narcan; ***Hong Kong:*** Mapin; Narcan†; ***Hung.:*** Narcanti†; ***India:*** Narcotan; ***Indon.:*** Nokoba; ***Irl.:*** Narcan; ***Israel:*** Narcanti†; ***Ital.:*** Narcan; ***Malaysia:*** Mapin; Narcan†; ***Mex.:*** Narcanti†; ***Norw.:*** Narcanti; ***NZ:*** Narcan; ***Port.:*** Narcan†; Naxan; Naxolan; ***Rus.:*** Naloxon (Налоксон); ***S.Afr.:*** Narcan†; Zynox; ***Singapore:*** Narcan†; ***Swed.:*** Narcanti; ***Switz.:*** Narcan; ***Thai.:*** Narcan; ***UK:*** Narcan†; ***USA:*** Narcan†; ***Venez.:*** Narcan; Oxogina.

Used as an adjunct in: ***Belg.:*** Tinalox; Valtran; ***Cz.:*** Suboxone; ***Fr.:*** Suboxone; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura; Tiligetic†; Tilimerck†; Tilnalox; Valoron N; ***Israel:*** Talwin NX†; ***Malaysia:*** Suboxone; ***NZ:*** Suboxone; ***Port.:*** Suboxone; ***UK:*** Suboxone; ***USA:*** Suboxone; Talwin NX.

Naltrexone *(BAN, USAN, rINN)*

Naltrexona; Naltrexonum. (5*R*)-9a-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one; 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

Налтрексон

$C_{20}H_{23}NO_4$ = 341.4.
CAS — 16590-41-3.
ATC — N07BB04.
ATC Vet — QN07BB04; QV03AB30.

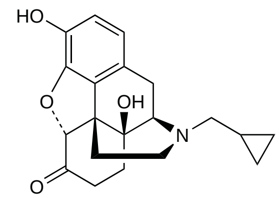

Naltrexone Hydrochloride *(BANM, rINNM)*

EN-1639A; Hidrocloruro de naltrexona; Naltreksonihydrokloridi; Naltreksono hidrochloridas; Naltrexone, chlorhydrate de; Naltrexon-hydrochlorid; Naltrexonhydroklorid; Naltrexoni hydrochloridum.

Налтрексона Гидрохлорид

$C_{20}H_{23}NO_4$,HCl = 377.9.
CAS — 16676-29-2.
ATC — N07BB04.
ATC Vet — QN07BB04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Naltrexone Hydrochloride). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Naltrexone Hydrochloride). Store in airtight containers.

Adverse Effects

Difficulty in sleeping, loss of energy, anxiety, dysphoria, abdominal pain, nausea, vomiting, reduction in appetite, joint and muscle pain, and headache may occur with naltrexone. Dizziness, constipation, diarrhoea, skin rashes, and reduced potency and ejaculatory difficulties have also been reported. Some adverse effects may be associated with opioid withdrawal. Thrombocytopenic purpura has occurred rarely. High doses may cause hepatocellular injury. Injection site reactions, including abscesses and tissue necrosis, have been reported with use of the intramuscular preparation.

Effects on the liver. Increased liver enzyme values were reported in 6 of 40 obese patients given naltrexone 50 or 100 mg daily for 8 weeks.[1] Five of the 6 patients had minimally abnormal liver function before naltrexone was given and liver function tests returned to baseline values or better on stopping naltrexone.

Raised transaminase levels were noted in 5 of 26 obese patients after 3 weeks of treatment with naltrexone 300 mg daily; transaminase activity returned to normal when treatment was stopped.[2]

1. Atkinson RL, *et al.* Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; **38:** 419–22.
2. Mitchell JE. Naltrexone and hepatotoxicity. *Lancet* 1986; **i:** 1215.

Effects on the muscles. Asymptomatic rhabdomyolysis has been reported[1] in a patient receiving naltrexone; the condition resolved when naltrexone was withdrawn.

1. Zaim S, *et al.* Rhabdomyolysis associated with naltrexone. *Ann Pharmacother* 1999; **33:** 312–3.

Precautions

Naltrexone should be avoided in patients receiving opioids therapeutically, or in those misusing them, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p.101). Withdrawal symptoms may develop within 5 minutes and last up to 48 hours. Naltrexone should be discontinued at least 48 hours before elective surgery involving opioid analgesia. For further precautions when using naltrexone as an adjunct in the treatment of opioid dependence, see Uses and Administration, below.

When analgesia is required, larger doses than usual of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects.

Naltrexone should be used with caution in patients with hepatic impairment and is contra-indicated in patients with acute hepatitis or hepatic failure. Regular monitoring of hepatic function has been recommended. Naltrexone should be given with caution to patients with renal impairment.

Pharmacokinetics

Naltrexone is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism and may undergo enterohepatic recycling. It is extensively metabolised in the liver and the major metabolite, 6-β-naltrexol, may also possess weak opioid antagonist activity. Maximum plasma concentrations of naltrexone and 6-β-naltrexol are achieved in about 1 hour and naltrexone is about 20% bound to plasma proteins at therapeutic doses. The elimination half-life of naltrexone is approximately 4 hours and that of 6-β-naltrexol about 13 hours. Naltrexone and its metabolites are excreted mainly in the urine. Less than 1% of an oral dose of naltrexone is excreted unchanged.

Hepatic impairment. A study[1] in 11 patients with hepatic cirrhosis found that the systemic availability of naltrexone was significantly increased, particularly in those with decompensated disease.

1. Bertolotti M, *et al.* Effect of liver cirrhosis on the systemic availability of naltrexone in humans. *J Hepatol* 1997; **27:** 505–511.

Uses and Administration

Naltrexone is a specific opioid antagonist with actions similar to those of naloxone (p.1454); however, it is more potent than naloxone and has a longer duration of action. It is used in the management of opioid dependence and alcohol dependence, and has also been investigated in other addictive disorders.

Naltrexone is used as the hydrochloride as an aid to maintaining abstinence after opioid withdrawal in detoxified, formerly **opioid-dependent** patients. Naltrexone treatment should not be started until the patient has been detoxified and abstinent from opioids for at least 7 to 10 days because of the risk of acute withdrawal; abstinence should be verified by analysis of the patient's urine. A *naloxone challenge test* should then be performed to confirm the absence of opioid dependence, as follows: naloxone hydrochloride 200 micrograms is given intravenously and the patient observed for 30 seconds for evidence of withdrawal symptoms; if none occur, a further dose of 600 micrograms is given and the patient observed for 30 minutes. A confirmatory rechallenge with naloxone hydrochloride 1.6 mg intravenously may be considered if results are ambiguous. Sources in the USA suggest a naloxone challenge test with a single dose of 800 micrograms given subcutaneously as an alternative to the intravenous route.

Once a negative naloxone challenge test has been obtained, naltrexone hydrochloride is given orally to maintain abstinence. Treatment may be initiated with a dose of 25 mg. If no signs of opioid withdrawal occur subsequent doses may be increased to 50 mg daily. The usual maintenance dose of naltrexone hydrochloride is 350 mg weekly given as 50 mg daily, but the dosing interval may be lengthened to improve compliance; for example, doses of 100 mg on Monday and Wednesday and 150 mg on Friday may be effective, and various other intermittent dosage regimens have been used. Patients should be carefully counselled and warned that attempts to overcome the opioid blockade with large doses of opioids could result in fatal opioid intoxication.

Naltrexone hydrochloride is also used as an adjunct in the management of **alcohol dependence** at a recommended oral dose of 50 mg daily. Alternatively, naltrexone (as the base) may be given as a modified-release intramuscular injection in a dose of 380 mg once every 4 weeks.

The symbol † denotes a preparation no longer actively marketed

Alcohol withdrawal and abstinence. Naltrexone may be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p.1626). Two systematic reviews[1,2] have concluded that oral naltrexone is safe and effective for the short-term treatment of alcohol dependence, although there is less evidence for long-term benefit. However, since the risk of relapse is particularly high early after alcohol withdrawal, treatment for at least 3 to 6 months has been recommended.[2,3] Compliance with oral naltrexone may be a problem,[1,2] and promising results[4,5] have been reported with a long-acting intramuscular injection given monthly.

Naltrexone appears to be more effective at reducing the amount of alcohol consumed than producing complete abstinence;[1] reports[6] from patients who continued to drink during therapy suggest that naltrexone may reduce the pleasure associated with drinking, possibly by blocking the effect of endorphins released as a result of alcohol consumption.

Although naltrexone does not appear to be hepatotoxic at the oral dosage of 50 mg daily used for alcohol dependence, caution is recommended in patients with liver disease;[3] careful monitoring is recommended if it is given with disulfiram since hepatotoxicity could potentially be increased.

Other opioid antagonists have also been studied. Preliminary results[7,8] suggest that nalmefene may also be effective, although there is insufficient evidence to recommend its use.[2]

1. Carmen B, *et al.* Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; **99:** 811–28.
2. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Berg BJ, *et al.* A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety* 1996; **15:** 274–82.
4. Garbutt JC, *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293:** 1617–25. Correction. *ibid.*: 1978.
5. Swainston Harrison T, *et al.* Extended-release intramuscular naltrexone. *Drugs* 2006; **66:** 1741–51.
6. Volpicelli JR, *et al.* Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995; **152:** 613–15.
7. Mason BJ, *et al.* A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 1994; **18:** 1162–7.
8. Mason BJ, *et al.* A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 1999; **56:** 719–24.

Autism. Autistic disorders have been linked with abnormalities in the endogenous opioid system and there is some evidence[1] that naltrexone may be of benefit in children with autism, especially in those with self-injurious behaviour.

1. ElChaar GM, *et al.* Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 2006; **40:** 1086–95.

Opioid dependence. *MAINTENANCE.* Naltrexone is a long-acting, non-addictive oral opioid antagonist. It can be effective in maintaining abstinence in opioid addicts after detoxification, but compliance with therapy is difficult to maintain because although it blocks the euphoriant effects of opioids it does not block the craving for narcotics. It is thus most effective in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids. Subcutaneous formulations have also been used but have been associated with serious complications (see Rapid Detoxification, below).

For a discussion of the management of opioid dependence, see p.101.

References.

1. Gonzalez JP, Brogden RN. Naltrexone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs* 1988; **35:** 192–213.
2. Minozzi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. NICE. Naltrexone for the management of opioid dependence: Technology Appraisal Guidance 115 (issued January 2007). Available at: http://guidance.nice.org.uk/TA115/guidance/pdf/English (accessed 02/05/07)
4. Lobmaier P, *et al.* Sustained-release naltrexone for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).

RAPID DETOXIFICATION. Naltrexone has been used in various regimens for rapid detoxification;[1,2] opioid withdrawal may be achieved in only a few days, although benefits for long-term outcome are not yet established. It has also been used for ultrarapid detoxification under anaesthesia, although a systematic review[3] concluded that the risks outweighed the benefits of using opioid antagonists in such procedures. A later study[4] also failed to support the use of such a regimen. After detoxification, patients may be given oral naltrexone for maintenance; subcutaneous formulations of naltrexone have also been used in an attempt to improve compliance, although serious complications, including deaths, have been reported[5-7] with their use.

1. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA* 1998; **279:** 229–34.
2. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 02/09/08).
4. Collins ED, *et al.* Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005; **294:** 903–13.
5. Hamilton RJ, *et al.* Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002; **9:** 63–8.
6. Gibson AE, *et al.* Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **186:** 152–3.
7. Lintzeris N, *et al.* Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust* 2008; **188:** 441–4.

Pruritus. For reference to the use of opioid antagonists, including naltrexone, in pruritus, see under Nalmefene, p.1453.

Preparations

USP 31: Naltrexone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Revez; ***Austral.:*** Revia; ***Austria:*** Dependex; Ethylex; Nalone†; Naltrexin; Nemexin; Revia; ***Belg.:*** Nalorex; ***Braz.:*** Revia; ***Canad.:*** Revia; ***Chile:*** Nalerona; ***Cz.:*** Nemexin; Revia; ***Denm.:*** Revia; ***Fin.:*** Revia; ***Fr.:*** Nalorex; Revia; ***Ger.:*** Nemexin; ***Gr.:*** Nalorex; ***Hong Kong:*** Revia; ***Hung.:*** Antaxon; Nemexin; Revia; ***India:*** Nodict; ***Indon.:*** Nutrexon; Phaltrexia; ***Irl.:*** Nalorex; Revia; ***Israel:*** Revia†; ***Ital.:*** Antaxone; Nalorex; Narcoral; ***Malaysia:*** Trexan†; ***Mex.:*** Revia; ***Neth.:*** Nalorex; Revia; ***Norw.:*** Revia; ***NZ:*** Revia; ***Port.:*** Antaxone; Basinal; Destoxican; Nalorex; ***Rus.:*** Antaxone (Антаксон); ***S.Afr.:*** Revia†; ***Singapore:*** Trexan†; ***Spain:*** Antaxone; Celupan; Revia; ***Swed.:*** Revia; ***Switz.:*** Naltrexin; Nemexin; ***Thai.:*** Revia; ***UK:*** Nalorex; Opizone; ***USA:*** Depade†; Revia; Trexan; Vivitrol.

Obidoxime Chloride *(USAN, rINN)*

Cloruro de obidoxima; LüH6; Obidoxime, Chlorure d'; Obidoximi Chloridum. 1,1′-[Oxybis(methylene)]bis[4-(hydroxyimino)methyl]pyridinium dichloride.

Обидоксима Хлорид

$C_{14}H_{16}Cl_2N_4O_3$ = 359.2.

CAS — 7683-36-5 (obidoxime); 114-90-9 (obidoxime chloride).

ATC — V03AB13.

ATC Vet — QV03AB13.

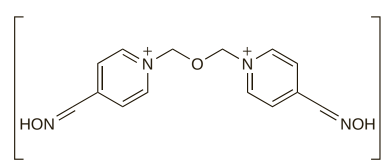

Profile

Obidoxime chloride is a cholinesterase reactivator with similar actions and uses to pralidoxime (p.1460). It is given with atropine in the treatment of organophosphorus poisoning in a usual initial dose of 250 mg (4 mg/kg) by slow intravenous injection. This may be followed by intravenous infusion of 750 mg over 24 hours, continued until the concentration of organophosphate is below critical levels; alternatively, repeated doses of 4 to 8 mg/kg may be given at intervals of 2 to 4 hours. It has also been given by intramuscular injection.

◊ References.

1. Thiermann H, *et al.* Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. *Hum Exp Toxicol* 1997; **16:** 473–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Toxogonin; ***Chile:*** Toxogonin; ***Cz.:*** Toxogonin; ***Ger.:*** Toxogonin; ***Neth.:*** Toxogonin; ***S.Afr.:*** Toxogonin; ***Swed.:*** Toxogonin; ***Switz.:*** Toxogonine.

Penicillamine *(BAN, USAN, rINN)*

Penicilamin; Penicilamina; Penicilaminas; Penicillamin; Pénicillamine; D-Penicillamine; Penicillaminum; Penicylamina; Penisilamin; Penisillamiini. D-3,3-Dimethylcysteine; D-3-Mercaptovaline.

Пеницилламин

$C_5H_{11}NO_2S$ = 149.2.

CAS — 52-67-5 (penicillamine); 2219-30-9 (penicillamine hydrochloride).

ATC — M01CC01.

ATC Vet — QM01CC01.

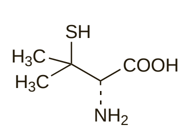

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Penicillamine). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 31 (Penicillamine). A white or practically white, crystalline powder having a slight characteristic odour. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store in airtight containers.

Adverse Effects and Treatment

Adverse effects of penicillamine are frequent. Gastrointestinal disturbances including anorexia, nausea, and vomiting may occur; oral ulceration and stomatitis have been reported and impaired taste sensitivity is common.

Skin rashes occurring early in treatment are commonly allergic and may be associated with pruritus, urticaria, and fever; they are usually transient but temporary drug withdrawal and use of corticosteroids or antihistamines may be required. Lupus erythematosus and pemphigus have been reported. A Stevens-Johnson-like syndrome has been observed during penicillamine treatment. Prolonged use of high doses may affect skin collagen and elastin, resulting in increased skin friability, eruptions resembling elastosis perforans serpiginosa, and a late rash or acquired epidermolysis bullosa (penicillamine dermatopathy) that may necessitate dosage reduction or discontinuation.

Haematological adverse effects have included thrombocytopenia and, less frequently, leucopenia; these are usually reversible, but agranulocytosis and aplastic anaemia have occurred and fatalities have been reported. Haemolytic anaemia has also occurred.

Proteinuria occurs frequently and in some patients may progress to glomerulonephritis or nephrotic syndrome. Penicillamine-induced haematuria is rare but normally requires immediate discontinuation.

Other adverse effects associated with penicillamine include Goodpasture's syndrome, bronchiolitis and pneumonitis, myasthenia gravis, polymyositis (rarely with cardiac involvement), intrahepatic cholestasis, and pancreatitis.

Incidence of adverse effects. References describing the range and incidence of adverse effects associated with of D-penicillamine.[1-3] The L- or DL-forms are much more toxic.[4]

1. Kean WF, *et al.* Efficacy and toxicity of -penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; **30:** 94–100.
2. Steen VD, *et al.* The toxicity of -penicillamine in systemic sclerosis. *Ann Intern Med* 1986; **104:** 699–705.
3. Munro R, Capell HA. Penicillamine. *Br J Rheumatol* 1997; **36:** 104–9.
4. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; **338:** 1565–8.

Effects on the blood. Of the 18 deaths ascribed to penicillamine reported to the UK CSM between January 1964 and December 1977, 14 were apparently due to blood disorders, at least 7 of them being marrow aplasias. The myelotoxicity of penicillamine was reviewed in 10 patients with confirmed or suspected marrow depression during penicillamine treatment for rheumatoid arthritis or scleroderma; 6 died.[1]

An incidence of 12 to 27% has been reported for penicillamine-induced thrombocytopenia in patients with rheumatoid arthritis, possibly due to bone-marrow suppression and a reduced platelet-production rate.[2]

There have been isolated reports[3-5] of thrombotic thrombocytopenic purpura attributed to the use of penicillamine, with some fatalities.

1. Kay AGL. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; **38:** 232–6.
2. Thomas D, *et al.* Thrombokinetics in patients with rheumatoid arthritis treated with D-penicillamine. *Ann Rheum Dis* 1984; **43:** 402–6.
3. Ahmed F, *et al.* Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; **138:** 1292–3.
4. Speth PAJ, *et al.* Thrombotic thrombocytopenic purpura associated with D-penicillamine treatment in rheumatoid arthritis. *J Rheumatol* 1982; **9:** 812–13.
5. Trice JM, *et al.* Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med* 1983; **143:** 1487–8.

Effects on the breasts. Breast enlargement has been reported both in women[1-5] and in men[6] taking penicillamine and may be a rare adverse effect. In some patients breast enlargement was prolonged with poor resolution and others required surgery.

Danazol has been used successfully to treat penicillamine-induced breast gigantism.[2-4]

1. Thew DCN, Stewart IM. D penicillamine and breast enlargement. *Ann Rheum Dis* 1980; **39:** 200.
2. Taylor PJ, *et al.* Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 362–3.
3. Rooney PJ, Cleland J. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 1627–8.
4. Craig HR. Penicillamine induced mammary hyperplasia: report of a case and review of the literature. *J Rheumatol* 1988; **15:** 1294–7.
5. Tchebiner JZ. Breast enlargement induced by D-penicillamine. *Ann Pharmacother* 2002; **36:** 444–5.
6. Reid DM, *et al.* Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *BMJ* 1982; **285:** 1083–4.

Effects on the gastrointestinal tract. There have been isolated reports of acute colitis in patients taking penicillamine.[1,2] Ileal ulceration and stenosis in a patient with Wilson's disease was considered to be related to elastosis probably resulting from long-term penicillamine therapy.[3]

1. Hickling P, Fuller J. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 367.
2. Grant GB. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 555.
3. Wassef M, *et al.* Unusual digestive lesions in a patient with Wilson's disease treated with long-term penicillamine. *N Engl J Med* 1985; **313:** 49.

Effects on the heart. For reports of heart block, Stokes-Adams syndrome, and fatal myocarditis in patients taking penicillamine, see Polymyositis under Effects on the Muscles and the Neuromuscular System, below.

Effects on the kidneys. Proteinuria associated with penicillamine[1] has usually occurred within 4 to 18 months of starting therapy, although onset can be later. A greater incidence has been found in patients with rheumatoid arthritis and cystinuria than in those with Wilson's disease. The severity varies; proteinuria of nephrotic proportions usually develops rapidly but resolves on drug withdrawal. Minimal change, mesangioproliferative, and membranous nephropathy have all been associated with penicillamine; progressive glomerulonephritis has been observed in a few patients with features of Goodpasture's syndrome (see Effects on the Respiratory System, below).

Although there is some evidence of a relationship between nephropathy and penicillamine dose and its rate of increase,[1] a study of 33 rheumatoid arthritis patients with penicillamine-induced nephropathy found no correlation with the dose or duration of treatment.[2] Appreciable proteinuria could still be detected 12 months after stopping penicillamine in 40% of these patients, but subsequently resolved in those whose proteinuria was solely related to penicillamine.

Penicillamine was successfully reintroduced and continued for at least 13 months in 5 patients with rheumatoid arthritis who had developed proteinuria during the first course of therapy. Proteinuria did not recur.[3] Another study[4] in 8 patients with proteinuria but no oedema suggested that penicillamine could be safely continued; proteinuria resolved in 5 of the patients during continued therapy.

Corticosteroids have been used in patients developing rapidly progressive glomerulonephritis[5] but may be unnecessary and potentially hazardous in patients who develop nephrotic syndrome.[2]

1. Anonymous. Penicillamine nephropathy. *BMJ* 1981; **282:** 761–2.
2. Hall CL, *et al.* Natural course of penicillamine nephropathy: a long term study of 33 patients. *BMJ* 1988; **296:** 1083–6.
3. Hill H, *et al.* Resumption of treatment with penicillamine after proteinuria. *Ann Rheum Dis* 1979; **38:** 229–31.
4. DeSilva RN, Eastmond CJ. Management of proteinuria secondary to penicillamine therapy in rheumatoid arthritis. *Clin Rheumatol* 1992; **11:** 216–9.
5. Ntoso KA, *et al.* Penicillamine-induced rapidly progressive glomerulonephritis in patients with progressive systemic sclerosis: successful treatment of two patients and a review of the literature. *Am J Kidney Dis* 1986; **8:** 159–63.

Effects on the liver. Penicillamine has been associated with hepatotoxicity. A case report and review of the literature[1] described 9 patients, all of whom had liver function profiles consistent with intrahepatic cholestasis; 1 patient died of acute renal failure but the others improved rapidly after drug withdrawal. In a later report,[2] a 72-year-old man with rheumatoid arthritis developed jaundice about 4 weeks after starting penicillamine therapy. Liver biopsy indicated a slight degree of cholangitis with eosinophils in the portal tracts and severe predominantly intrahepatocellular cholestasis. Jaundice cleared within 3 weeks of stopping penicillamine and liver enzyme values approached normal after 6 weeks. However, in another case[3] cholestasis persisted despite withdrawal of penicillamine and the patient died of sepsis 14 months later. Monitoring of liver function and eosinophil counts in the early weeks of penicillamine therapy has been recommended.[1]

1. Seibold JR, *et al.* Cholestasis associated with D-penicillamine therapy: case report and review of the literature. *Arthritis Rheum* 1981; **24:** 554–6.
2. Devogelaer JP, *et al.* A case of cholestatic hepatitis associated with D-penicillamine therapy for rheumatoid arthritis. *Int J Clin Pharmacol Res* 1985; **5:** 35–8.
3. Jacobs JWG, *et al.* Fatal cholestatic hepatitis caused by -penicillamine. *Br J Rheumatol* 1994; **33:** 770–3.

Effects on the muscles and the neuromuscular system. Neuromyotonia,[1] and profound sensory and motor neuropathy that responded to pyridoxine supplementation,[2] have occurred in patients taking penicillamine. Low back pain with fever and rash has also been reported;[3] back pain and fever recurred on rechallenge. It was suggested that an allergic mechanism was involved.

1. Reeback J, *et al.* Penicillamine-induced neuromyotonia. *BMJ* 1979; **1:** 1464–5.
2. Pool KD, *et al.* Penicillamine-induced neuropathy in rheumatoid arthritis. *Ann Intern Med* 1981; **95:** 457–8.
3. Bannwarth B, *et al.* Low back pain associated with penicillamine. *BMJ* 1991; **303:** 525.

Myasthenia. Myasthenia gravis is a well recognised, though uncommon, complication of long-term penicillamine therapy, particularly in patients with rheumatoid arthritis or other auto-immune disorders.[1-5] Symptoms are similar to those seen with spontaneous myasthenia gravis and include ptosis and diplopia, and generalised weakness, occasionally affecting the respiratory muscles. The onset of symptoms usually occurs within 6 to 7 months but may be delayed for a number of years. Myasthenic symptoms usually resolve spontaneously once penicillamine is withdrawn, but some patients require anticholinesterase therapy. Acetylcholine receptor antibodies have been reported in 75% or more of affected patients.[2,3] Several reports have suggested a genetic tendency to penicillamine-induced myasthenia, and an association with HLA antigens DR1 and Bw35 has been found in some studies,[1,4] although others[5] have not replicated these findings.

1. Delamere JP, *et al.* Penicillamine-induced myasthenia in rheumatoid arthritis: its clinical and genetic features. *Ann Rheum Dis* 1983; **42:** 500–4.
2. Carter H, *et al.* La myasthénie au cours du traitement de la polyarthrite rhumatoïde par la D-pénicillamine. *Therapie* 1984; **39:** 689–95.
3. Katz LJ, *et al.* Ocular myasthenia gravis after D-penicillamine administration. *Br J Ophthalmol* 1989; **73:** 1015–18.
4. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
5. Drosos AA, *et al.* D-penicillamine induced myasthenia gravis: clinical, serological and genetic findings. *Clin Exp Rheumatol* 1993; **11:** 387–91.

Polymyositis. Penicillamine therapy has been associated rarely with polymyositis and dermatomyositis.[1-5] Cardiac complications may occur: at least 2 deaths have resulted from myocarditis,[1] and complete heart block[1,3,6] and severe Stokes-Adams attacks[3] have been reported. It is possible that some patients may have a genetically determined susceptibility to this complication.[4]

1. Doyle DR, *et al.* Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; **98:** 327–30.
2. Renier JC, *et al.* Polymyosite induite par la D-pénicillamine. *Therapie* 1984; **39:** 697–703.
3. Christensen PD, Sørensen KE. Penicillamine-induced polymyositis with complete heart block. *Eur Heart J* 1989; **10:** 1041–4.
4. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
5. Aydintug AO, *et al.* Polymyositis complicating -penicillamine treatment. *Postgrad Med J* 1991; **67:** 1018–20.
6. Wright GD, *et al.* D-penicillamine induced polymyositis causing complete heart block. *Clin Rheumatol* 1994; **13:** 80–2.

Effects on the respiratory system. Pulmonary haemorrhage associated with progressive renal failure has been reported[1,2] with penicillamine and has generally been classified as Goodpasture's syndrome, although patients usually lack anti-glomerular basement membrane antibodies; an immune-complex mechanism has also been suggested.[1] There have been rare reports of obliterative bronchiolitis in patients with rheumatoid arthritis treated with penicillamine.[3-6]

Upper respiratory tract disorders have also been reported. A 76-year-old patient taking penicillamine developed rhinitis, bilateral blepharitis, and pemphigus foliaceus;[7] the rhinitis and blepharitis resolved when penicillamine was withdrawn. In addition, 2 patients with lower respiratory symptoms also developed persistent sinusitis,[6] which required surgery.

1. Turner-Warwick M. Adverse reactions affecting the lung: possible association with D-penicillamine. *J Rheumatol* 1981; **8** (suppl 7): 166–8.
2. Derk CT, Jimenez SA. Goodpasture-like syndrome induced by D-penicillamine in a patient with systemic sclerosis: report and review of the literature. *J Rheumatol* 2003; **30:** 1616–20.
3. Lyle WH. D-Penicillamine and fatal obliterative bronchiolitis. *BMJ* 1977; **1:** 105.
4. Epler GR, *et al.* Bronchiolitis and bronchitis in connective tissue disease: a possible relationship to the use of penicillamine. *JAMA* 1979; **242:** 528–32.
5. Murphy KC, *et al.* Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine. *Arthritis Rheum* 1981; **24:** 557–60.
6. Wolfe F, *et al.* Upper and lower airway disease in penicillamine treated patients with rheumatoid arthritis. *J Rheumatol* 1983; **10:** 406–10.
7. Presley AP. Penicillamine induced rhinitis. *BMJ* 1988; **296:** 1332.

Effects on the skin. Penicillamine-induced skin lesions have been reviewed.[1] Reactions include those resulting from interference with collagen and elastin (see below); those associated with auto-immune mechanisms such as pemphigus, pemphigoid, lupus erythematosus, and dermatomyositis; and those classified as acute sensitivity reactions including macular or papular eruptions and urticaria. The effects on collagen and elastin tend to occur only after prolonged use of high doses, as in patients with Wilson's disease or cystinuria, whereas patients with diseases characterised by altered immune systems, such as rheumatoid arthritis, are more prone to develop the antibody-related adverse skin reactions. Acute hypersensitivity reactions tend to occur early in treatment, usually within the first 7 to 10 days, and appear not to be dose-related. Lichenoid reactions, stomatitis, nail changes, and adverse effects on hair have also occurred.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.

Interference with collagen and elastin. Long-term, high-dose treatment with penicillamine can interfere with elastin and collagen production giving rise to increased skin friability, haemorrhagic lesions, miliary papules, and excessive wrinkling and laxity of the skin.[1] Penicillamine dermatopathy, characterised by wrinkling and purpura over bony prominences, has been described.[2] In addition, lesions resembling pseudoxanthoma elasticum have been reported.[3,4] Abnormal elastic tissue has also been reported in patients taking low doses of penicillamine (less than 1 g daily), not only in the skin but also in joint capsules,[5] and elastosis perforans serpiginosa has been reported[6,7] in 2 patients. In all these cases, histological findings generally show damage to elastic fibres giving them a typical appearance described as 'lumpy-bumpy' or 'bramble-bush'.

For reports of cutis laxa in neonates, see Pregnancy under Precautions, below.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.
2. Sternlieb I, Scheinberg IH. Penicillamine therapy for hepatolenticular degeneration. *JAMA* 1964; **189:** 748–54.
3. Thomas RHM, *et al.* Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1984; **77:** 794–8.
4. Bentley-Phillips B. Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1985; **78:** 787.
5. Dalziel KL, *et al.* Elastic fibre damage induced by low-dose D-penicillamine. *Br J Dermatol* 1990; **123:** 305–12.
6. Sahn EE, *et al.* D-Penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. *J Am Acad Dermatol* 1989; **20:** 979–88.
7. Hill VA, *et al.* Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; **142:** 560–1.

Lichen planus. There have been rare reports of lichen planus in patients with primary biliary cirrhosis taking penicillamine,[1,2] although the role of penicillamine has been questioned. Oral lichen planus associated with penicillamine has also been reported[3] in patients with rheumatoid arthritis.

1. Powell FC, Rogers RS. Primary biliary cirrhosis, penicillamine, and lichen planus. *Lancet* 1981; **ii:** 525.
2. Powell FC, *et al.* Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; **107:** 616.
3. Blasberg B, *et al.* Lichenoid lesions of the oral mucosa in rheumatoid arthritis patients treated with penicillamine. *J Rheumatol* 1984; **11:** 348–51.

Pemphigus. Bullous skin disorders are established adverse effects of penicillamine and appear to have an auto-immune basis.[1] Pemphigus-spectrum disorders have been most commonly reported, including pemphigus vulgaris, pemphigus foliaceus, herpetiform pemphigus, pemphigus erythematosus, benign mucous membrane pemphigoid, cicatricial pemphigoid, and combined pemphigus and pemphigoid features.

1. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35:** 732–42.

Psoriasiform eruptions. Two patients with rheumatoid arthritis developed psoriasiform eruptions during penicillamine treatment.[1] In 1 patient the eruption resolved when penicillamine was stopped but worsened when treatment was restarted.

1. Forgie JC, Highet AS. Psoriasiform eruptions associated with penicillamine. *BMJ* 1987; **294:** 1101.

Scleroderma. Penicillamine has been used in the treatment of scleroderma and systemic sclerosis (see under Uses, below). However, scleroderma, with evidence of pulmonary involvement, developed in a 14-year-old boy with Wilson's disease who had been treated with penicillamine for 11 years[1] and the suitability of penicillamine for this indication has therefore been questioned.

1. Miyagawa S, *et al.* Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; **116:** 95–100.

Toxic epidermal necrolysis. A 56-year-old woman developed agranulocytosis and toxic epidermal necrolysis 7 weeks after starting therapy with penicillamine 250 mg daily for primary biliary cirrhosis.[1] Severe toxic epidermal necrolysis has also been reported[2] in a woman taking penicillamine for Wilson's disease.

1. Ward K, Weir DG. Life threatening agranulocytosis and toxic epidermal necrolysis during low dose penicillamine therapy. *Ir J Med Sci* 1981; **150:** 252–3.
2. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol* 1984; **10:** 973–8.

Genetic factors. There is evidence that some patients may have a genetically determined increased susceptibility to the adverse effects of penicillamine. Several studies have suggested that rheumatoid arthritis patients with a poor capacity for producing sulfoxides may be more susceptible to the toxic effects of penicillamine.[1,2] Patients with primary biliary cirrhosis also appear to have poor sulfoxidation capacity,[3] and this may contribute to their high incidence of adverse reactions to penicillamine, although no association between penicillamine toxicity and sulfoxidation status was found in a study of 20 such patients.[4]

Several studies have also suggested that certain histocompatibility antigens may increase susceptibility to penicillamine toxicity. An increased incidence of adverse reactions was noted[2] in patients with HLA-DR3, while other studies have shown associations between proteinuria and HLA antigens B8 and DR3,[5,6] myasthenia gravis and Bw35 and DR1,[7] thrombocytopenia and HLA antigens DR4,[5,6] A1,[5] and C4BQO,[5] and polymyositis or dermatomyositis and HLA antigens B18, B35, and DR4.[8] However, not all studies have reported the same associations, and the clinical usefulness of sulfoxidation testing or HLA-typing is not established.[6,9]

1. Panayi GS, *et al.* Deficient sulphoxidation status and D-penicillamine toxicity. *Lancet* 1983; **i:** 414.
2. Emery P, *et al.* D-Penicillamine induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; **11:** 626–32.
3. Olomu A, *et al.* Poor sulphoxidation in primary biliary cirrhosis. *Lancet* 1985; **i:** 1504.
4. Mitchison HC, *et al.* D-penicillamine-induced toxicity in primary biliary cirrhosis (PBC): the role of sulphoxidation status. *Gut* 1986; **27:** A622.
5. Stockman A, *et al.* Genetic markers in rheumatoid arthritis: relationship to toxicity from D-penicillamine. *J Rheumatol* 1986; **13:** 269–73.
6. Moens HJB, *et al.* Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
7. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
8. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
9. Hall CL. Penicillamine nephropathy. *BMJ* 1988; **297:** 137.

Systemic lupus erythematosus. A syndrome resembling lupus erythematosus developed in 6 women with long-standing severe rheumatoid arthritis while being treated with penicillamine;[1] this represented a frequency of penicillamine-induced lupus erythematosus of about 2%. All 6 had developed previous cutaneous reactions to gold therapy. A case of bullous systemic lupus erythematosus associated with penicillamine has also been reported.[2]

1. Chalmers A, *et al*. Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97:** 659–63.
2. Condon C, *et al.* Penicillamine-induced type II bullous systemic lupus erythematosus. *Br J Dermatol* 1997; **136:** 474–5.

Precautions

Penicillamine is contra-indicated in patients with lupus erythematosus or a history of penicillamine-induced agranulocytosis, aplastic anaemia, or severe thrombocytopenia. It should be used with care in patients with mild renal impairment and is contra-indicated in patients with moderate or severe renal impairment.

Penicillamine should not be given with other drugs capable of causing similar serious haematological or renal adverse effects, for example gold salts, chloroquine or hydroxychloroquine, or immunosuppressive drugs. Penicillamine is a degradation product of penicillin and patients who are allergic to penicillin may show cross-sensitivity to penicillamine although this appears to be rare.

Patients need to be carefully monitored for adverse effects. In particular full blood counts and urinalysis should be carried out; one recommendation is to perform blood counts weekly or fortnightly, and urinalysis weekly, for the first 2 months of treatment and after any change in dosage, and monthly thereafter. Treatment should be withdrawn if there is a fall in white cell or platelet count, or if progressive or serious proteinuria or haematuria occur. Liver function tests at 6-monthly intervals have also been recommended and renal function should be monitored.

Pyridoxine 25 mg daily may be given to patients on long-term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

A reduced dose of penicillamine has been suggested for patients undergoing surgery (see Anaesthesia and Surgery, below).

Anaesthesia and surgery. Penicillamine may delay wound healing due to its effects on collagen and elastin and it has been suggested that the dose should be reduced to 250 mg daily for 6 weeks before surgery and during the postoperative period until healing has taken place.

The effects of penicillamine on muscle function should also be considered in patients requiring anaesthesia; a 57-year-old woman[1] with penicillamine-induced myasthenia developed prolonged postoperative apnoea, necessitating artificial ventilation.

1. Fried MJ, Protheroe DT. D-Penicillamine induced myasthenia gravis: its relevance for the anaesthetist. *Br J Anaesth* 1986; **58:** 1191–3.

Pregnancy. Penicillamine teratogenicity has been reviewed.[1] Evidence of the embryotoxicity of maternal penicillamine exposure in *animal* studies had been confirmed in humans by 5 reports of cutis laxa in neonates of mothers who had taken penicillamine during pregnancy; 3 further reports of intra-uterine brain injury were less characteristic. Nevertheless most pregnancy outcomes were normal. No birth defects had been reported when penicillamine was discontinued in early pregnancy. It is generally recommended that women receiving penicillamine for Wilson's disease should continue throughout pregnancy since the benefits outweigh the risks. However, in other conditions, particularly where there are safer alternatives, discontinuation of penicillamine is advised.

1. Rosa FW. Teratogen update: penicillamine. *Teratology* 1986; **33:** 127–31.

Interactions

Penicillamine forms chelates with metal ions and oral absorption may be reduced if it is given with iron or other metals, antacids, or food. Penicillamine should be taken on an empty stomach and it has been recommended that there should be an interval of at least 2 hours between taking penicillamine and iron supplements. Additive toxicity may occur if penicillamine is given with drugs that have adverse renal or haematological effects (see Precautions, above).

Antacids or food. In a single-dose study in 6 healthy subjects, penicillamine given orally immediately after food or a dose of an antacid mixture (aluminium hydroxide, magnesium hydroxide, and simeticone), resulted in plasma concentrations of penicillamine that were 52% and 66%, respectively, of those obtained in a fasting state. Results suggested that the reduction in plasma-penicillamine concentrations was associated with decreased absorption.[1] Another study[2] showed that the reduction of penicillamine plasma concentrations produced by aluminium- and magnesium-containing antacids did not occur with sodium bicarbonate, and thus the interaction was probably a result of chelation rather than a pH effect.

1. Osman MA, *et al*. Reduction in oral penicillamine absorption by food, antacid, and ferrous sulphate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Ifan A, Welling PG. Pharmacokinetics of oral 500 mg penicillamine: effect of antacids on absorption. *Biopharm Drug Dispos* 1986; **7:** 401–5.

Diazepam. For a report of exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine, see under Diazepam, p.991.

Gold. There have been conflicting reports on the effect of previous gold therapy on the subsequent development of penicillamine toxicity in patients with rheumatoid arthritis.

Some studies[1,2] have suggested that adverse effects with penicillamine may be more common in patients who have previously reacted adversely to gold, but others[3,4] have found no correlation. One study[5] found that although the overall incidence of adverse effects with penicillamine appeared unaffected by prior gold therapy, bone-marrow depression and rashes were more common in those previously treated with gold. It has been suggested[2] that the interaction occurs due to mobilisation of gold from the tissues by penicillamine, and an interval of at least 6 months between gold and penicillamine in patients with prior gold toxicity was recommended. However, another report[6] found that the interval between gold and penicillamine had no influence on the development of toxicity and suggested that there might be a common genetic susceptibility in certain patients. A patient who had experienced myasthenia with penicillamine had a recurrence with gold therapy,[7] but another study[4] found no evidence that the adverse effects of gold were increased in those with prior penicillamine toxicity.

1. Hill H. Penicillamine and previous treatment with gold. *BMJ* 1978; **2:** 961.
2. Dodd MJ, *et al.* Adverse reactions to D-penicillamine after gold toxicity. *BMJ* 1980; **280:** 1498–1500.
3. Multi-centre Trial Group. Absence of toxic or therapeutic interaction between penicillamine and previously administered gold in a trial of penicillamine in rheumatoid disease. *Postgrad Med J* 1974; **50** (suppl 2): 77–8.
4. Steven MM, *et al.* Does the order of second-line treatment in rheumatoid arthritis matter? *BMJ* 1982; **284:** 79–81.
5. Webley M, Coomes EN. Is penicillamine therapy in rheumatoid arthritis influenced by previous treatment with gold? *BMJ* 1978; **2:** 91.
6. Smith PJ, *et al.* Influence of previous gold toxicity on subsequent development of penicillamine toxicity. *BMJ* 1982; **285:** 595–6.
7. Moore AP, *et al.* Penicillamine induced myasthenia reactivated by gold. *BMJ* 1984; **288:** 192–3.

Insulin. Unexplained hypoglycaemia in 2 patients with type 1 diabetes occurred 6 to 8 weeks after penicillamine treatment for rheumatoid arthritis was started.[1] Both patients required a reduction in their insulin dose. A possible immunological mechanism has been proposed.[1,2]

1. Elling P, Elling H. Penicillamine, captopril, and hypoglycemia. *Ann Intern Med* 1985; **103:** 644–5.
2. Becker RC, Martin RG. Penicillamine-induced insulin antibodies. *Ann Intern Med* 1986; **104:** 127–8.

Iron. Plasma-penicillamine concentrations were reduced to 35% when penicillamine was given after a dose of ferrous sulfate in healthy subjects.[1] Patients stabilised on penicillamine while on oral iron therapy were considered unlikely to respond fully to penicillamine and would be exposed to a large increase in penicillamine absorption with possible adverse reactions if the iron was stopped.[2]

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* 1982; **ii:** 1368–9.

Probenecid. Probenecid may reduce the beneficial effects of penicillamine in cystinuria, and it has been suggested[1] that hyperuricaemic cystinuric patients should not be given both drugs.

1. Yu T-F, *et al*. Studies on the metabolism of D-penicillamine and its interaction with probenecid in cystinuria and rheumatoid arthritis. *J Rheumatol* 1984; **11:** 467–70.

Pharmacokinetics

Penicillamine is rapidly but variably absorbed from the gastrointestinal tract and reaches peak concentrations in the blood within 1 to 3 hours. It is reported to be more than 80% bound to plasma proteins. It undergoes some metabolism in the liver, to *S*-methyl penicillamine, and is excreted primarily in the urine, mainly as disulfides, along with some *S*-methyl penicillamine and unchanged drug; a small amount may be excreted in the faeces. Elimination is biphasic with an initial elimination half-life of about 1 to 3 hours followed by a slower phase, suggesting gradual release from tissues.

◊ Reviews.

1. Netter P, *et al.* Clinical pharmacokinetics of D-penicillamine. *Clin Pharmacokinet* 1987; **13:** 317–33.

Uses and Administration

Penicillamine is a chelator that aids the elimination from the body of certain heavy-metal ions, including copper, lead, and mercury, by forming stable soluble complexes with them that are readily excreted by the kidney. It is used in the treatment of Wilson's disease (to promote the excretion of copper), in heavy-metal poisoning such as lead poisoning, in cystinuria (to reduce urinary concentrations of cystine), in severe active rheumatoid arthritis, and in chronic active hepatitis.

Penicillamine is given orally and should be taken on an empty stomach. A low initial dose increased gradually to the minimum optimal maintenance dosage may reduce the incidence of adverse effects as well as provide closer control of the condition being treated.

In the treatment of **Wilson's disease**, a dose of 1.5 to 2 g daily in divided doses may be given initially. The optimal dosage to achieve a negative copper balance should be determined initially by regular analysis of 24-hour urinary copper excretion and subsequently by monitoring free copper in the serum. A maintenance dose of 0.75 to 1 g daily may be adequate once control is achieved and should be continued indefinitely; UK licensed product information recommends that a maintenance dose of 2 g daily should not be continued for more than a year. In children, a suggested dose is up to 20 mg/kg daily (minimum 500 mg daily) in divided doses. A dose of 20 mg/kg daily is suggested for the elderly.

In the management of **lead poisoning**, penicillamine may be given in doses of 1 to 1.5 g daily in divided doses until urinary lead is stabilised at less than 500 micrograms/day. Children and the elderly may be given 20 mg/kg daily in divided doses.

In **cystinuria**, doses of penicillamine are adjusted according to cystine concentrations in the urine. For the *treatment* of cystinuria and cystine calculi, the dose is usually in the range of 1 to 4 g daily in divided doses; a suggested dose for children is 30 mg/kg daily in divided doses. For the *prevention* of cystine calculi, lower doses of 0.5 to 1 g at bedtime may be given. An adequate fluid intake is essential to maintain urine flow when penicillamine is used for cystinuria.

In the treatment of **severe active rheumatoid arthritis**, an initial dose of penicillamine 125 to 250 mg daily is increased gradually by the same amount at intervals of 4 to 12 weeks. Remission is usually achieved with maintenance doses of 500 to 750 mg daily in divided doses, but up to 1.5 g daily may be required. Improvement may not occur for several months; US licensed product information suggests that penicillamine should be discontinued if there is no response after treatment for 3 to 4 months with 1 to 1.5 g daily; in the UK, a trial for 12 months is suggested. After remission has been sustained for 6 months an attempt may be made gradually to reduce the dose by 125 to 250 mg daily every 3 months but relapse may occur. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Initial doses of 125 mg daily are recommended, gradually increased to a maximum of 1 g daily if necessary. In children the maintenance dose is 15 to 20 mg/kg daily; a suggested initial dose is 2.5 to 5 mg/kg daily increased gradually at 4-week intervals.

In the management of **chronic active hepatitis**, penicillamine may be given after liver function tests have indicated that the disease has been controlled by corticosteroids. The initial dose is 500 mg daily in divided doses, increased gradually over 3 months to 1.25 g daily, while at the same time reducing the corticosteroid dose.

Acetylpenicillamine has been used in mercury poisoning.

Chronic active hepatitis. Penicillamine has been tried in chronic active hepatitis (p.1501) as an alternative to prolonged corticosteroid maintenance therapy once control of the disease is achieved. The dose of penicillamine is increased over several months to a suitable maintenance dose and, at the same time, the corticosteroid dose is decreased.

Cystinuria. Cystinuria is an inherited disorder of renal amino-acid excretion in which there is excessive excretion of cystine (cysteine disulfide), along with ornithine, lysine, and arginine. The low solubility of cystine leads to the formation of cystine stones in the kidney, resulting in pain, haematuria, renal obstruction, and infection. Treatment is primarily aimed at reducing the urinary concentration of cystine to below its solubility limit of 300 to 400 mg/litre at neutral pH. Patients with cystinuria excrete 400 to 1200 mg cystine daily and should be advised to drink at least 3 litres of water daily, including at night, to maintain a dilute urine. Cystine is more soluble in alkaline urine and urinary alkalinisers such as sodium bicarbonate, sodium citrate, or potassium citrate may be used; however, high doses are required and calcium stone formation may be promoted. Penicillamine may also be used, particularly in patients where these measures are ineffective or not tolerated; it complexes with cysteine to form a more soluble mixed disulfide, therefore reducing cystine excretion, preventing cystine stone formation, and promoting the gradual dissolution of existing stones. Adverse effects are common and tiopronin, which has a similar action, may be used as an alternative. Surgical removal may be necessary for established stones but lithotripsy is not very effective.

Lead poisoning. Penicillamine may be used to treat asymptomatic lead intoxication and to achieve desirable tissue-lead concentrations in patients with symptomatic lead poisoning once they have received treatment with sodium calcium edetate and dimercaprol (see p.2332).

Primary biliary cirrhosis. Copper accumulation in the liver has been noted in patients with primary biliary cirrhosis (see under Ursodeoxycholic Acid,p.2408) and therapy with penicillamine to reduce liver-copper concentrations has been studied. Despite good preliminary results, most studies have found it to be ineffective and any benefit appears to be offset by the high incidence of adverse effects.[1,2]

1. James OFW. -Penicillamine for primary biliary cirrhosis. *Gut* 1985; **26:** 109–13.
2. Gong Y, *et al.* D-penicillamine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 04/04/06).

Retinopathy of prematurity. Penicillamine has been investigated for the prophylaxis of retinopathy of prematurity (p.1994) in infants considered to be at risk, and a systematic review of 2 such studies considered that there was evidence for a reduced incidence of acute retinopathy.[1] Further studies were considered justified, with careful attention to possible adverse effects.

1. Phelps DL, *et al.* D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 04/10/05).

Rheumatoid arthritis. Penicillamine is one of a diverse group of disease-modifying antirheumatic drugs that have been used in rheumatoid arthritis (p.11) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease. However, early enthusiasm for penicillamine has been tempered by a high incidence of adverse effects.[1] During long-term therapy as many as 50% of patients taking penicillamine have been reported to stop treatment because of adverse effects.[2] Low doses of penicillamine to reduce the incidence of adverse effects have been tried and while doses as low as 125 mg daily have been claimed to be effective in some patients, a 36-week multicentre double-blind study[3] involving 225 patients concluded that a dose of penicillamine 500 mg daily was only slightly more effective than placebo. A dose of 125 mg daily was not significantly different from either the 500-mg dose or placebo. However, a 5-year open study[4] comparing penicillamine in doses up to 500 mg daily with hydroxychloroquine, sodium aurothiomalate, or auranofin found penicillamine to be as effective as the other drugs and well tolerated, with 53% of the patients randomised to penicillamine still receiving it at 5 years, as opposed to about 30 to 35% of those randomised to other drugs.

1. Suarez-Almazor ME, *et al.* Penicillamine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 04/10/05).
2. Moens HJB, *et al.* Longterm followup of treatment with -penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
3. Williams HJ, *et al.* Low-dose -penicillamine therapy in rheumatoid arthritis: a controlled, double-blind clinical trial. *Arthritis Rheum* 1983; **26:** 581–92.
4. Jessop JD, *et al.* A long-term five-year randomized controlled trial of hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine in the treatment of patients with rheumatoid arthritis. *Br J Rheumatol* 1998; **37:** 992–1002.

Scleroderma. Penicillamine affects the cross-linking of collagen,[1] and observational studies[2,3] have suggested that it may be of benefit in scleroderma (p.1817), and perhaps in some visceral manifestations of systemic sclerosis. A randomised study[4] comparing a conventional dose of penicillamine (up to 1 g daily) with a very low dose (125 mg on alternate days) found no difference in outcome, but there were more adverse effects with the higher dose. Although the lower dose was not expected to be effective, the skin score improved significantly in both groups; however, there was insufficient evidence to attribute this to use of penicillamine, and its role in scleroderma remains to be established.

For a report of sclerodermatous lesions in a patient taking penicillamine for Wilson's disease, see Scleroderma, under Effects on the Skin, above.

1. Herbert CM, *et al.* Biosynthesis and maturation of skin collagen in scleroderma, and effect of D-penicillamine. *Lancet* 1974; **i:** 187–92.
2. Steen VD, *et al.* -Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982; **97:** 652–9.
3. Derk CT, *et al.* A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. *Br J Dermatol* 2008; **158:** 1063–8.
4. Clements PJ, *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999; **42:** 1194–1203.

Wilson's disease. Wilson's disease, or hepatolenticular degeneration, is a rare autosomal disorder of copper accumulation.[1-5] Excretion of excess copper, which normally occurs via the bile, is impaired and total body copper progressively increases. The excess copper accumulates in the liver, brain, and other organs including the kidneys and corneas, and eventually causes tissue damage.

Effective treatment of Wilson's disease involves the use of copper-reducing drugs to establish a negative copper balance. This prevents deposition of more copper and also mobilises excess copper that has already been deposited making it available for excretion. Once negative copper balance has been achieved, maintenance treatment must be continued lifelong. Dietary restriction of copper is not generally considered to be an important part of the treatment of Wilson's disease, although patients may be advised to avoid copper-rich foods, such as liver and shellfish, during the first year of treatment and to restrict their consumption thereafter. Symptomatic recovery from copper overload occurs slowly, but is usually complete if treatment is started early enough, and a normal life expectancy can be achieved. However, once irreversible organ damage such as liver cirrhosis has occurred, treatment can only prevent further deterioration; those presenting with end-stage liver disease do not benefit from copper-reducing therapy, and liver transplantation is necessary (although successful medical treatment has been reported in children). The drugs used to reduce copper concentrations in the treatment of Wilson's disease are penicillamine, trientine, and zinc. Ammonium tetrathiomolybdate, an investigational drug, may also be used.

Penicillamine reduces copper concentrations in several ways. Its main action is to chelate circulating copper, which is then excreted in the urine. In addition, penicillamine reduces the affinity of copper for proteins and polypeptides, allowing removal of copper from tissues. It also induces hepatic synthesis of metallothionein, a protein that combines with copper to form a non-toxic product. *Trientine* is a less potent copper chelator than penicillamine; it competes for copper bound to serum albumin and increases copper excretion. *Zinc* induces synthesis of metallothionein in the intestine so that absorption of copper from the gastrointestinal tract is blocked. It is usually given as the acetate as this form is less irritating to the stomach than the sulfate. *Ammonium tetrathiomolybdate* forms a complex with protein and copper. When it is given with food it blocks the intestinal absorption of copper, and when taken between meals it combines with albumin- and caeruloplasmin-bound copper.

CHOICE OF DRUG. Penicillamine is generally regarded as the drug of choice for the initial management of Wilson's disease as it produces a rapid reduction in copper levels. However, it may initially exacerbate neurological symptoms (possibly due to transiently increased brain and blood copper concentrations) and some practitioners therefore suggest starting with zinc; zinc is less suitable in those requiring rapid reduction of copper levels as it has a slow onset of action. Trientine, which may also exacerbate neurological symptoms, is principally used in patients intolerant of penicillamine. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels; it may be particularly suitable for patients with neurological symptoms.

Once a negative copper balance is achieved, maintenance therapy must be continued for life. Penicillamine, trientine, and zinc are all used for maintenance treatment. Patients taking penicillamine are also given pyridoxine to prevent deficiency (see Precautions, above). The adverse effects of penicillamine may be a problem during long-term use and zinc, which has low toxicity, is often preferred. Zinc is also used in patients in the asymptomatic stage of the disease.

1. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000; **223:** 39–46.
2. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology* 2003; **37:** 1475–92.
3. El-Youssef M. Wilson disease. *Mayo Clin Proc* 2003; **78:** 1126–36.
4. Merle U, *et al.* Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut* 2007; **56:** 115–20.
5. Ala A, *et al.* Wilson's disease. *Lancet* 2007; **369:** 397–408.

Preparations

BP 2008: Penicillamine Tablets;
USP 31: Penicillamine Capsules; Penicillamine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cuprimine; Cupripen; ***Austral.:*** D-Penamine; ***Austria:*** Artamin; ***Belg.:*** Kelatin†; ***Braz.:*** Cuprimine; ***Canad.:*** Cuprimine; Depen†; ***Cz.:*** Metalcaptase; Trolovol†; ***Denm.:*** Atamir; ***Fr.:*** Trolovol; ***Ger.:*** Metalcaptase; Trisorcin†; ***Gr.:*** Cupripen†; ***Hong Kong:*** Cuprimine†; ***Hung.:*** Byanodine†; ***India:*** Cilamin; ***Irl.:*** Distamine; ***Israel:*** Cuprimine†; ***Ital.:*** Pemine; ***Jpn:*** Metalcaptase; ***Malaysia:*** Artamin; ***Mex.:*** Adalken; Sufortan; ***Neth.:*** Gerodyl; ***Norw.:*** Cuprimine†; ***NZ:*** D-Penamine; Distamine†; ***Pol.:*** Cuprenil; ***Port.:*** Kelatine; Trolovol; ***S.Afr.:*** Metalcaptase; ***Spain:*** Cupripen; ***Switz.:*** Mercaptyl; ***Thai.:*** Cuprimine; ***UK:*** Distamine; ***USA:*** Cuprimine; Depen.

Pentetic Acid *(BAN, USAN, rINN)*

Acide Pentétique; Ácido pentético; Acidum Penteticum; DTPA; ZK-43649. Diethylenetriamine-*NNN′N″N″*-penta-acetic acid.

Пентетовая Кислота

$C_{14}H_{23}N_3O_{10}$ = 393.3.

CAS — 67-43-6.

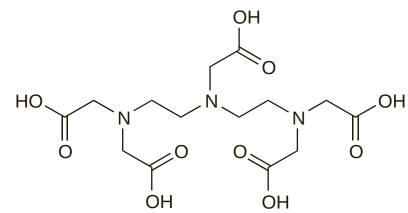

Pharmacopoeias. In *US.*

USP 31 (Pentetic Acid). A white odourless or almost odourless powder.

Calcium Trisodium Pentetate *(BAN, rINN)*

Ca-DTPA; Calcii Trinatrii Pentetas; Calcium Trisodium DTPA; NSC-34249; Pentetate Calcium Trisodium *(USAN)*; Pentétate de Calcium Trisodique; Pentetato calcio y trisodio; Trisodium Calcium Diethylenetriaminepentaacetate.

Кальция Тринатрия Пентетат

$C_{14}H_{18}CaN_3Na_3O_{10}$ = 497.4.

CAS — 12111-24-9.

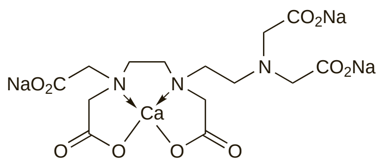

Zinc Trisodium Pentetate *(rINNM)*

Pentétate de Zinc Trisodique; Pentetate Zinc Trisodium; Pentetato zinc y trisodio; Trisodium Zinc Diethylenetriaminepentaacetate; Zinci Trinatrii Pentetas; Zn-DTPA (zinc pentetate or zinc trisodium pentetate).

Цинка Тринатрия Пентетат

$C_{14}H_{18}N_3Na_3O_{10}Zn$ = 522.7.

CAS — 65229-17-6 (zinc pentetate); 125833-02-5 (zinc trisodium pentetate).

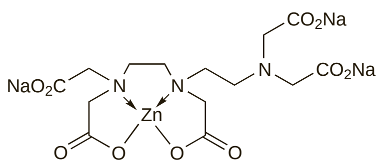

Adverse Effects and Precautions

Adverse effects that have been reported with calcium or zinc trisodium pentetate include headache, nausea and diarrhoea, and injection-site reactions. Bronchospasm has occurred after inhalation. Pentetates chelate trace metals and supplements may be needed with long-term use. Serum-electrolytes should be monitored during use. Pentetates should be used with caution in patients with haemochromatosis since fatalities have been reported.

Uses and Administration

Pentetic acid and its salts are chelators with the general properties of the edetates (see Edetic Acid, p.1445). Calcium trisodium pentetate is used in the treatment of poisoning by heavy metals; both calcium trisodium pentetate and zinc trisodium pentetate are used for poisoning with radioactive metals such as plutonium, americium, and curium.

In heavy-metal poisoning, calcium trisodium pentetate has been given in a dose of 1 g daily by intravenous infusion for 3 to 5 days, with further treatment, if necessary, after an interval of 3 days.

For poisoning with plutonium and similar radioactive metals, either calcium trisodium pentetate or zinc trisodium pentetate may be used. Calcium trisodium pentetate is more effective within the first 24 hours and is preferred for the initial dose; however, zinc depletion may occur and if further chelation is required treatment should be continued with zinc trisodium pentetate if possible. The usual dose is 1 g of either calcium or zinc trisodium pentetate once daily, by slow intravenous injection over 3 to 4 minutes or by intravenous infusion. Treatment is usually continued for 5 days and then modified depending on the estimated radioactive body burden. For patients with poisoning by inhalation only, the calcium trisodium pentetate or zinc trisodium pentetate may be given by nebulisation.

Pentetates, labelled with metallic radionuclides, are used in nuclear medicine (see Indium-111, p.2054, and Technetium-99m, p.2056).

Thalassaemia. Iron overload in patients with thalassaemia (p.1045) is usually treated with desferrioxamine, but auditory toxicity can result. Calcium pentetic acid has been used as an alternative. A study[1] in 5 patients in whom desferrioxamine had to be withdrawn because of high-tone deafness found that the pentetate was as effective as desferrioxamine and hearing improved during treatment. Oral zinc supplements were necessary to maintain adequate plasma-zinc concentrations.

1. Wonke B, *et al.* Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Ditripentat; ***Ger.:*** Ditripentat-Heyl.

Potassium Polystyrene Sulfonate

Poliestirenosulfonato potásico; Potassium Polystyrene Sulphonate.

CAS — 9011-99-8.

ATC — V03AE01.

ATC Vet — QV03AE01.

Profile

Potassium polystyrene sulfonate, the potassium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges potassium ions for calcium ions and other cations and has been used in the management of hypercalciuria and renal calculi.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Ujostabil†.

Pralidoxime *(BAN, rINNM)*

Pralidoksiimi; Pralidoxim; Pralidoxima; Pralidoximum. 2-Hydroxyiminomethyl-1-methylpyridinium.

Пралидоксим

$C_7H_9N_2O$ = 137.2.

CAS — 6735-59-7; 495-94-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pralidoxime Chloride *(BANM, USAN, rINNM)*

2-Formyl-1-methylpyridinium Chloride Oxime; 2-PAM; 2-PAM Chloride; 2-PAMCl; Pralidoxima, cloruro de; Pralidoxime, Chlorure de; Pralidoximi Chloridum; 2-Pyridine Aldoxime Methochloride.

Пралидоксима Хлорид

$C_7H_9ClN_2O$ = 172.6.

CAS — 51-15-0.

ATC — V03AB04.

ATC Vet — QV03AB04.

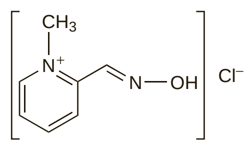

Pharmacopoeias. In *US.*

USP 31 (Pralidoxime Chloride). A white to pale yellow, odourless, crystalline powder. Freely soluble in water.

Pralidoxime Iodide *(BANM, USAN, rINN)*

Ioduro de pralidoxima; NSC-7760; 2-PAM Iodide; 2-PAMI; Pralidoxime, Iodure de; Pralidoximi Iodidum.

Пралидоксима Йодид

$C_7H_9IN_2O$ = 264.1.

CAS — 94-63-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pharmacopoeias. In *Chin.*

Pralidoxime Mesilate *(BANM, rINNM)*

Mesilato de pralidoxima; 2-PAMM; Pralidoksiimimesilaatti; Pralidoksim Mezilat; Pralidoxime, Mésilate de; Pralidoxime Mesylate *(USAN)*; Pralidoxime Methanesulphonate; Pralidoximi Mesilas; Pralidoximmesilat; P2S.

Пралидоксима Мезилат

$C_7H_9N_2O,CH_3O_3S$ = 232.3.

CAS — 154-97-2.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pralidoxime Metilsulfate *(BANM, rINNM)*

Pralidoxima, metilsulfato de; Pralidoxime Methylsulphate; Pralidoxime, Métilsulfate de; Pralidoximi Metilsulfas.

Пралидоксима Метилсульфат

$C_7H_9N_2O,CH_3SO_4$ = 248.3.

CAS — 1200-55-1.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pharmacopoeias. In *It.*

Adverse Effects

Use of pralidoxime may be associated with drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness. Tachycardia, laryngospasm, and muscle rigidity have been attributed to giving pralidoxime intravenously at too rapid a rate. Large doses of pralidoxime may cause transient neuromuscular blockade.

Precautions

Pralidoxime should be used cautiously in patients with renal impairment; a reduction in dosage may be necessary. Caution is also required in giving pralidoxime to patients with myasthenia gravis as it may precipitate a myasthenic crisis. Pralidoxime should not be used to treat poisoning by carbamate pesticides.

When atropine and pralidoxime are given together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

Pharmacokinetics

Pralidoxime is not bound to plasma proteins, does not readily pass into the CNS, and is rapidly excreted in the urine, partly unchanged and partly as a metabolite. The elimination half-life is about 1 to 3 hours.

◊ References.

1. Sidell FR, Groff WA. Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime methochloride to man. *J Pharm Sci* 1971; **60:** 1224–8.
2. Siddell FR, *et al.* Pralidoxime methanesulfonate: plasma levels and pharmacokinetics after oral administration to man. *J Pharm Sci* 1972; **61:** 1136–40.
3. Swartz RD, *et al.* Effects of heat and exercise on the elimination of pralidoxime in man. *Clin Pharmacol Ther* 1973; **14:** 83–9.
4. Schexnayder S, *et al.* The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *J Toxicol Clin Toxicol* 1998; **36:** 549–55.

Uses and Administration

Pralidoxime is a cholinesterase reactivator. It is used as an adjunct to, but *not* as a substitute for, atropine in the treatment of poisoning by certain cholinesterase inhibitors. Its main indication is in poisoning due to organophosphorus insecticides or related compounds (see p.2047). These compounds phosphorylate and consequently inactivate cholinesterase, causing acetylcholine accumulation and muscle paralysis. Pralidoxime acts principally to reactivate cholinesterase, restoring the enzymatic destruction of acetylcholine at the neuromuscular junction and relieving muscle paralysis. However, concomitant use of atropine is required to counteract directly the adverse effects of acetylcholine accumulation, particularly at the respiratory centre. Pralidoxime is not equally antagonistic to all organophosphorus anticholinesterases as reactivation is dependent on the nature of the phosphoryl group and the rate at which inhibition becomes irreversible. It is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates, or organophosphates without anticholinesterase activity. It has usually been contra-indicated in the treatment of poisoning by carbamate insecticides (including carbaryl poisoning) as it may increase toxicity (see p.2037). The use of pralidoxime has been suggested for the treatment of overdosage by anticholinesterase drugs, including those used to treat myasthenia gravis such as neostigmine; however, it is only slightly effective and its use is not generally recommended.

Pralidoxime is usually given as the chloride or mesilate but the iodide and metilsulfate salts have also been used. Doses are usually expressed in terms of the salts.

Pralidoxime may be given by slow intravenous injection over 5 to 10 minutes, by intravenous infusion over 15 to 30 minutes, or by subcutaneous or intramuscular injection; it has also been given orally.

In the treatment of **organophosphorus poisoning** pralidoxime should be given as soon as possible. After about 24 hours it becomes less effective since cholinesterase inactivation usually becomes irreversible after this time; however, patients with severe poisoning may occasionally respond up to 36 hours or longer after exposure, depending on the organophosphate involved. Injections of *atropine* should be given intravenously or intramuscularly and repeated as necessary until the patient shows signs of atropine toxicity; atropinisation should then be maintained for 48 hours or more. Large amounts of atropine may be required.

See under Atropine Sulfate, p.1221, for details of dosages. As soon as the effects of atropine become apparent, 1 to 2 g of *pralidoxime* chloride, iodide, or mesilate, should be given intramuscularly or intravenously and repeated after 1 hour and then every 8 to 12 hours if necessary. Alternatively, the *BNF* recommends pralidoxime chloride in an initial dose of 30 mg/kg given by intravenous infusion over 20 minutes, or by intravenous injection over at least 5 minutes if pulmonary oedema is present or infusion cannot be given; the initial dose is then followed by intravenous infusion at a rate of 8 mg/kg per hour. In some countries, auto-injectors are available for emergency use containing pralidoxime, either alone or combined with atropine and/or avizafone, a prodrug of diazepam. Typical doses are 600 mg of pralidoxime chloride or 500 mg of pralidoxime mesilate given intramuscularly up to 3 times, depending on symptoms. Another alternative, in severe poisoning, is the use of a continuous infusion of 200 to 500 mg/hour, titrated against response. A maximum dose of 12 g in 24 hours has been suggested. The dose of pralidoxime may need to be reduced in patients with renal impairment.

Treatment should preferably be monitored by the determination of blood-cholinesterase concentrations and clinical symptoms. Patients should be closely observed for at least 24 hours after resolution of symptoms.

Other oximes with cholinesterase-reactivating properties that have been used similarly include asoxime chloride (p.1438), obidoxime chloride (p.1456), and trimedoxime bromide (p.1467).

Organophosphorus poisoning. Oximes such as pralidoxime are widely used in poisoning with organophosphate *pesticides*. Although benefit has been shown in *animal* studies, reviews[1,2] have pointed out that there is little good evidence from human studies to support their use and that randomised controlled studies are needed to confirm their efficacy and safety, as well as the optimum regimens to use. A randomised study[3] in patients with moderately severe poisoning with organophosphorus pesticides found that a continuous infusion of pralidoxime iodide 1 g/hour for 48 hours was more effective than a dose of 1 g every 4 hours.

Cholinesterase reactivators such as the oximes have also been used for poisoning with organophosphate *nerve agents*. Studies in *animals* have suggested that the efficacy of the different oximes depends on the organophosphate involved; asoxime (p.1438) and HLö-7 may be more effective than pralidoxime or obidoxime for poisoning with nerve agents, particularly for soman poisoning.[4]

1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003; **22:** 165–90.
2. Buckley NA, *et al.* Oximes for acute organophosphate pesticide poisoning. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Pawar KS, *et al.* Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet* 2006; **368:** 2136–41.
4. Kassa J. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J Toxicol Clin Toxicol* 2002; **40:** 803–16.

Preparations

USP 31: Pralidoxime Chloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Contrathion; ***Braz.:*** Contrathion; ***Canad.:*** Protopam; ***Fr.:*** Contrathion; ***Gr.:*** Contrathion; ***India:*** Neopam; ***Ital.:*** Contrathion; ***Malaysia:*** Pampara; ***NZ:*** Pam†; ***Turk.:*** Contrathion; ***USA:*** Protopam.

Multi-ingredient: ***UK:*** Nerve Agent Antidote L4A1; ***USA:*** DuoDote.

Protamine *(rINNM)*

Protamina; Protaminum.

Протамин

CAS — 9012-00-4.
ATC — V03AB14.
ATC Vet — QV03AB14.

Protamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Protamina; Hidrocloruro de protamina; Protamiinihydrokloridi; Protamine, chlorhydrate de; Protamin-hidroklorid; Protamin-hydrochlorid; Protaminhydroklorid; Protamini hydrochloridum; Protamino hidrochloridas.

Протамина Гидрохлорид

ATC — V03AB14.
ATC Vet — QV03AB14.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Protamine Hydrochloride). A mixture of the hydrochlorides of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Protamine Sulfate *(rINN)*

Protamiinisulfaatti; Protamine, sulfate de; Protamine Sulphate *(BAN)*; Protamini sulfas; Protamino sulfatas; Protaminsulfat; Protamin-sulfát; Protamin-szulfát; Protaminy siarczan; Sulfato de protamina.

Протамина Сульфат

CAS — 9009-65-8.
ATC — V03AB14.
ATC Vet — QV03AB14.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Protamine Sulphate). A mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 31 (Protamine Sulfate). A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish. Store at 2° to 8° in airtight containers.

Adverse Effects and Precautions

Intravenous injections of protamine, particularly if given rapidly, may cause hypotension, bradycardia, and dyspnoea. A sensation of warmth, transitory flushing, nausea and vomiting, and lassitude may also occur.

Hypersensitivity reactions can occur; patients at risk include diabetics who have received protamine-insulin preparations, those who have previously received protamine (including those who have undergone procedures such as coronary angioplasty or cardiopulmonary bypass surgery where protamine is frequently used), and those allergic to fish. Protamine is a constituent of sperm and men who are infertile or who have had a vasectomy may also be at increased risk since they may have antibodies to protamine. Anaphylactoid reactions have been reported.

Protamine has an anticoagulant effect when given in the absence of heparin.

When repeated doses of protamine are used to neutralise large doses of heparin, rebound bleeding which responds to further doses of protamine, may occur. Clotting parameters should be closely monitored in patients receiving such prolonged therapy.

◊ In a report on 4 patients given protamine sulfate after cardiac surgery to neutralise the effect of heparin, severe adverse reactions including marked hypotension, vascular collapse, and pulmonary oedema were described.[1] Previous reports of similar reactions to protamine were reviewed. A total of 17 patients had immediate anaphylactic reactions; in 1 patient a complement-dependent IgG antibody-mediated reaction had been demonstrated and 3 patients tested for allergy to protamine had positive skin tests. In 15 of these 17 patients there was evidence of previous exposure to protamine; those with a high risk of sensitisation included leucapheresis donors who had received the drug, diabetics using insulin containing protamine, and patients with fish allergy. Suspected reactions to protamine occurred in a further 10 patients after cardiac surgery. However, these reactions were characterised by severe vascular damage, manifested as noncardiogenic pulmonary oedema or persistent hypotension, and onset was delayed for 30 minutes to several hours. Evidence suggested that these reactions were not antibody mediated; only 2 of 7 evaluable patients had previous exposure. All patients required aggressive therapy.

In a review of the toxicity of protamine,[2] adverse cardiovascular responses were considered to be of 3 types: transient hypotension related to rapid drug administration, occasional anaphylactoid responses, and rarely, catastrophic pulmonary vasoconstriction.

1. Holland CL, *et al.* Adverse reactions to protamine sulfate following cardiac surgery. *Clin Cardiol* 1984; **7:** 157–62.
2. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985; **64:** 348–61.

Uses and Administration

Protamine is a basic protein that combines with heparin to form a stable inactive complex. Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin or low-molecular-weight heparin overdosage. It is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulfate, although the hydrochloride may also be used.

Protamine sulfate is given by slow intravenous injection over a period of about 10 minutes. The dose is dependent on the amount of heparin to be neutralised and ideally should be titrated against the coagulability of the patient's blood. Protamine has weak anticoagulating properties and if given in gross excess its anticoagulant action could be significant. As heparin is being continuously excreted the dose should be reduced if more than 15 minutes have elapsed since intravenous heparin injection; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Alternative regimens may be necessary if heparin has been given subcutaneously or by continuous intravenous infusion. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required.

For *unfractionated heparin* the Ph. Eur. 6.2 specifies that 1 mg of either protamine hydrochloride or protamine sulfate precipitates not less than 100 units of heparin, assayed against a specific reference batch of heparin sodium. One UK manufacturer has stated that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous). In the USA stated values are that each mg of protamine sulfate neutralises about 90 USP units of heparin (lung) or about 115 USP units of heparin (mucous).

For *low-molecular-weight heparins*, protamine neutralises the anti-thrombin activity but only partially neutralises the anti-factor-Xa effect; 1 mg of protamine is stated to inhibit the effects of:

- 71 units of bemiparin sodium
- 80 to 120 units of certoparin sodium
- 100 units of dalteparin sodium
- 1 mg (100 units) of enoxaparin sodium
- 82 units of reviparin sodium
- 100 units of tinzaparin sodium

Haemorrhagic disorders. Endogenous production of heparin-like substances may, rarely, be responsible for some bleeding disorders. It has been suggested that protamine could be useful as a diagnostic aid *in vitro* and could be given intravenously for transient control of bleeding in such patients.[1,2]

1. Tefferi A, *et al.* Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med* 1990; **88:** 184–8.
2. Bayly PJM, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73:** 840–2.

Preparations

BP 2008: Protamine Sulphate Injection;
USP 31: Protamine Sulfate for Injection; Protamine Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Denpru; ***Hong Kong:*** Prosulf; ***India:*** Prota; ***Israel:*** Prosulf; ***UK:*** Prosulf.

Prussian Blue

Azul de Prusia; Berlin Blue; CI Pigment Blue 27; Colour Index No. 77510; Ferric Ferrocyanide; Ferric Hexacyanoferrate (II); Insoluble Prussian Blue; Prussian Blue Insoluble *(USAN)*.

$Fe_4[Fe(CN)_6]_3$ = 859.2.

CAS — 14038-43-8 (insoluble Prussian blue); 12240-15-2 (soluble Prussian blue); 25869-00-5 (soluble Prussian blue).
ATC — V03AB31.
ATC Vet — QV03AB31.

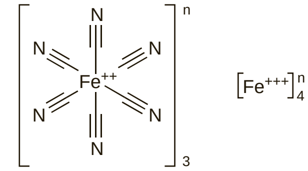

NOTE. Prussian blue is available in a number of forms and it is not always clear from the literature which form is being referred to. CI Pigment Blue 27 has been used for both insoluble ferric hexacyanoferrate (II) (Colour Index No. 77510) and the soluble potassium, sodium, or ammonium ferric hexacyanoferrate (II) salts

Profile

Prussian blue is used in the treatment of thallium poisoning (see p.2400) and for known or suspected internal contamination with radiocaesium. When given orally it forms a non-absorbable complex with thallium or caesium in the gastrointestinal tract and increases their elimination from the body; it may also bind other elements and patients should be monitored for electrolyte imbalances. Prussian blue may cause constipation and a fibre-based laxative is recommended.

The usual dose of Prussian blue is 250 to 300 mg/kg daily, or up to 20 g daily for an adult, given in divided doses either by mouth or by nasogastric or duodenal tube. In the USA, a lower dose of 3 g three times daily for adults, or 1 g three times daily for children, has been recommended. For thallium poisoning, treatment should continue until the urinary excretion of thallium falls to 500 micrograms or less per 24 hours, the urine or blood concentration is less than 10 micrograms/L, or no thallium can be detected in the faeces. For radiocaesium contamination, a minimum of 30 days treatment should be given.

◊ References.

1. Thompson DF, Church CO. Prussian blue for treatment of radiocesium poisoning. *Pharmacotherapy* 2001; **21:** 1364–7.
2. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
3. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Radiogardase-Cs; ***Ger.:*** Antidotum Thallii-Heyl; Radiogardase-Cs; ***USA:*** Radiogardase.

Sevelamer *(BAN, rINN)*

Sevelameeri; Sévélamer; Sevelámero; Sevelamerum. Allylamine polymer with 1-chloro-2,3-epoxypropane.

Севеламер

CAS — 52757-95-6.
ATC — V03AE02.
ATC Vet — QV03AE02.

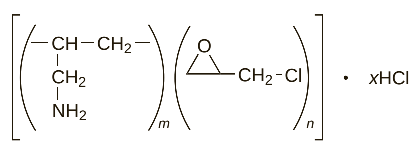

Sevelamer Carbonate *(BANM, USAN, rINNM)*

Carbonato de sevelámero; GT-335-012; Sévélamer Carbonate; Sevelameri Carbonas. Allylamine polymer with 1-chloro-2,3-epoxypropane carbonate.

Севеламера Карбонат

CAS — 845273-93-0.
ATC — V03AE02.
ATC Vet — QV03AE02.

Sevelamer Hydrochloride *(BANM, USAN, rINNM)*

GT16-026A; Hidrocloruro de sevelámero; Sévélamer, Chlorhydrate de; Sevelameri Hydrochloridum. Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride.

Севеламера Гидрохлорид

CAS — 182683-00-7.
ATC — V03AE02.
ATC Vet — QV03AE02.

NOTE. The name sevelamer has been used for both sevelamer and sevelamer hydrochloride.

Adverse Effects and Precautions

The most common adverse effects associated with sevelamer are diarrhoea, nausea and vomiting, constipation, headache, cough and other respiratory symptoms, dizziness, hypotension or hypertension, peripheral oedema, pain, and fever. Flatulence, pharyngitis, skin rashes, and pruritus have also occurred; intestinal obstruction and ileus have been reported.

Sevelamer is contra-indicated in patients with hypophosphataemia and in bowel obstruction. Patients with renal impairment may develop hypocalcaemia or hypercalcaemia, and serum-calcium concentrations should be monitored. Serum-chloride concentrations should also be monitored during treatment with sevelamer.

Interactions

Sevelamer has been reported to reduce the bioavailability of ciprofloxacin and should not be taken at the same time. It may also affect the bioavailability of other drugs and should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

Uses and Administration

Sevelamer is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure on haemodialysis. It is given orally as either the carbonate or the hydrochloride. The initial dose is 0.8 to 1.6 g of sevelamer carbonate or sevelamer hydrochloride three times daily with each meal, depending on the severity of hyperphosphataemia. Doses should then be adjusted according to plasma-phosphate concentrations; the usual maintenance dose is from 0.8 to 4 g with each meal.

◊ References.

1. Burke SK. Renagel: reducing serum phosphorus in haemodialysis patients. *Hosp Med* 2000; **61:** 622–7.
2. Qunibi WY, *et al.* Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). *Kidney Int* 2004; **65:** 1914–26.
3. Almirall J, *et al.* Safety and efficacy of sevelamer in the treatment of uncontrolled hyperphosphataemia of haemodialysis patients. *Nephron Clin Pract* 2004; **97:** c17–c22.
4. Duggal A, *et al.* Novel dosage forms and regimens for sevelamer-based phosphate binders. *J Ren Nutr* 2006; **16:** 248–52.
5. Fischer D, *et al.* Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. *Am J Kidney Dis* 2006; **48:** 437–44.
6. Suki WN, *et al.* Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007; **72:** 1130–7.
7. Tonelli M, *et al.* Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; **22:** 2856–66.
8. Ramos R, *et al.* The Catalano–Balear Peritoneal Dialysis Study Group. Sevelamer hydrochloride in peritoneal dialysis patients: results of a multicenter cross-sectional study. *Perit Dial Int* 2007; **27:** 697–701.
9. Delmez J, *et al.* A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol* 2007; **68:** 386–91.
10. Suki WN. Dialysis Clinical Outcomes Revisited Investigators. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. *J Ren Nutr* 2008; **18:** 91–8.
11. Goldsmith DR, *et al.* Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. *Drugs* 2008; **68:** 85–104.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Renagel; ***Belg.:*** Renagel; ***Canad.:*** Renagel; ***Cz.:*** Renagel; ***Denm.:*** Renagel; ***Fin.:*** Renagel; ***Fr.:*** Renagel; ***Ger.:*** Renagel; ***Gr.:*** Renagel; ***Hong Kong:*** Renagel; ***Hung.:*** Renagel; ***Irl.:*** Renagel; ***Israel:*** Renagel; ***Ital.:*** Renagel; ***Jpn:*** Renagel; ***Neth.:*** Renagel; ***Norw.:*** Renagel; ***Pol.:*** Renagel; ***Port.:*** Renagel; ***Spain:*** Renagel; ***Swed.:*** Renagel; ***Switz.:*** Renagel; ***Turk.:*** Renagel; ***UK:*** Renagel; ***USA:*** Renagel; Renvela.

Sodium Calcium Edetate *(BAN, rINN)*

Calcioedetato de sodio; Calcium Disodium Edathamil; Calcium Disodium Edetate; Calcium Disodium Ethylenediaminetetra-acetate; Calcium Disodium Versenate; Calcium édétate de sodium; Calcium EDTA; Disodium Calcium Tetracemate; E385; Edetan sodno-vápenatý hydrát; Edetate Calcium Disodium *(USAN)*; Kalcium-nátrium-edetát; Natrii calcii edetas; Natrii Calcii Edetas Hydricus; Natrio-kalcio edetatas; Natriumkalciumedetat; Natriumkalsiumedetaatti; Sodium, calcium édétate de; Sodium Calciumedetate; Sodu wapnia edetynian; Sodyum Kalsiyum Edetat; Wapniowo-disodowy edetynian. The calcium chelate of disodium ethylenediaminetetra-acetate; Disodium[(ethylenedinitrilo)tetraacetato]calciate(2–) hydrate.

Натрия Кальция Эдетат

$C_{10}H_{12}CaN_2Na_2O_8,xH_2O$ = 374.3 (anhydrous).

CAS — 62-33-9 (anhydrous sodium calcium edetate); 23411-34-9 (sodium calcium edetate hydrate).

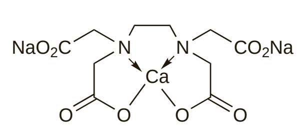

NOTE. Do not confuse with sodium edetate; see Inappropriate Administration under Sodium Edetate, p.1464.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Sodium Calcium Edetate). A white or almost white, hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 6.5 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Edetate Calcium Disodium). White, slightly hygroscopic, odourless, crystalline powder or granules. Freely soluble in water. pH of a 20% solution in water is between 6.5 and 8.0. Store in airtight containers.

Adverse Effects

Sodium calcium edetate is nephrotoxic and may cause renal tubular necrosis. Nausea, diarrhoea, and abdominal cramp may also occur. Thrombophlebitis has followed intravenous infusion and may be related to the concentration of the injection. Pain at the intramuscular injection site has been reported. Other adverse effects that have been reported include fever, malaise, headache, myalgia, histamine-like responses such as sneezing, nasal congestion, and lachrymation, skin eruptions, transient hypotension, and ECG abnormalities.

Sodium calcium edetate chelates zinc within the body and zinc deficiency has been reported. Displacement of calcium from sodium calcium edetate may lead to hypercalcaemia.

Effects on the kidneys. Of 130 children with lead poisoning who received chelation therapy with sodium calcium edetate (25 mg/kg intramuscularly every 12 hours) and dimercaprol (3 mg/kg intramuscularly every 4 hours) for a total of 5 days, 21 developed clinical evidence of nephrotoxicity and in 4 severe oliguric acute renal failure began 1 or 2 days after chelation therapy was discontinued.[1] Nephrotoxicity was probably attributable to the use of sodium calcium edetate.

1. Moel DI, Kumar K. Reversible nephrotic reactions to a combined 2,3-dimercapto-l-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics* 1982; **70:** 259–62.

Precautions

Sodium calcium edetate should be used with caution, if at all, in patients with renal impairment. Daily urinalysis to monitor proteinuria and haematuria and regular monitoring of renal and hepatic function has been recommended.

Sodium calcium edetate can chelate several endogenous metals, including zinc, and may increase their excretion; therapy should be intermittent to prevent severe deficiency developing and monitoring of zinc levels may be required (see below).

Sodium calcium edetate should not be given orally in the treatment of lead poisoning as it has been suggested that absorption of lead may be increased as a result.

◊ Sodium calcium edetate 500 mg/m^2 was given by deep intramuscular injection every 12 hours for 5 days to 10 children with asymptomatic lead poisoning.[1] Blood-lead concentrations decreased to about 58% of the pretreatment values after 5 days and were essentially unchanged for up to 60 hours after the last dose. Sodium calcium edetate also produced a marked fall in the mean plasma-zinc concentration but this rebounded rapidly after the end of treatment. Mean urinary-lead excretion increased about 21-fold during the first 24 hours of therapy and urinary-zinc excretion increased about 17-fold. Sodium calcium edetate had little effect on the plasma concentrations or urinary excretion of copper. The results suggested that careful monitoring of zinc was required during treatment with sodium calcium edetate.

1. Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium disodium ethylenediamine tetraacetate treatment of lead-poisoned children. *J Pharmacol Exp Ther* 1986; **239:** 829–35.

Pharmacokinetics

Sodium calcium edetate is poorly absorbed from the gastrointestinal tract. It distributes primarily to the extracellular fluid and does not penetrate cells. It is not significantly metabolised; after intravenous injection about 50% of a dose is excreted in the urine in 1 hour and over 95% in 24 hours.

Uses and Administration

Sodium calcium edetate is the calcium chelate of disodium edetate and is a chelator used in the treatment of lead poisoning (see Treatment of Adverse Effects under Lead, p.2332). It mobilises lead from bone and tissues and aids elimination from the body by forming a stable, water-soluble, lead complex which is readily excreted by the kidneys. It may be used as a diagnostic test for lead poisoning but measurement of blood-lead concentrations is generally preferred.

Sodium calcium edetate is also a chelator of other heavy-metal polyvalent ions, including chromium. A cream containing sodium calcium edetate 10% has been used in the treatment of chrome ulcers and skin sensitivity reactions due to contact with heavy metals.

Sodium calcium edetate is also used as a pharmaceutical excipient and as a food additive.

In the treatment of lead poisoning, sodium calcium edetate may be given by intramuscular injection or by intravenous infusion. The intramuscular route may be preferred in patients with lead encephalopathy and increased intracranial pressure in whom excess fluids must be avoided, and also in children, who have an increased risk of incipient encephalopathy. Sodium calcium edetate may initially aggravate the symptoms of lead toxicity due to mobilisation of stored lead and it has often been given with dimercaprol (p.1444) in patients who are symptomatic; the first dose of dimercaprol should preferably be given at least 4 hours before the sodium calcium edetate.

For intravenous infusion, 1 g of sodium calcium edetate should be diluted with 250 to 500 mL of glucose 5% or sodium chloride 0.9%; a concentration of 3% should not be exceeded. The infusion should be given over a period of at least 1 hour. In the UK, the usual dose is 60 to 80 mg/kg daily given in two divided doses. In the USA, a dose of 1000 mg/m^2 daily is suggested for asymptomatic adults and children; a daily dose of 1500 mg/m^2 may be used in patients with symptomatic poisoning. Treatment is given for up to 5 days, repeated if necessary after an interval of at least 2 days. Any further treatment with sodium calcium edetate should then not be given for at least 7 days.

Alternatively, the same daily dose of sodium calcium edetate may be given intramuscularly in 2 to 4 divided doses as a 20% solution. Intramuscular injection of sodium calcium edetate is painful and it is recommended that preservative-free procaine hydrochloride should be added to a concentration of 0.5 to 1.5% to minimise pain; alternatively, lidocaine may be added to a concentration of 0.5%.

As excretion is mainly renal, an adequate urinary flow must be established and maintained during treatment. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. The dose of sodium calcium edetate should be reduced in patients with renal impairment. It has been suggested that the dose is halved and given once daily in moderate impairment, and that smaller and less frequent doses are given if renal impairment is severe.

Preparations

BP 2008: Sodium Calcium Edetate Intravenous Infusion;
USP 31: Edetate Calcium Disodium Injection.

Proprietary Preparations (details are given in Part 3)
Ger.: Calcium Vitis†; ***Gr.:*** Ledclair; ***Irl.:*** Ledclair; ***Switz.:*** Chelintox†; ***Turk.:*** Libenta; ***UK:*** Ledclair.

Multi-ingredient: ***Arg.:*** Calcium C.

Sodium Cellulose Phosphate

Cellulose Sodium Phosphate *(USAN)*; Celulosa, fosfato sódico de.

CAS — 9038-41-9; 68444-58-6.

ATC — V03AG01.

ATC Vet — QV03AG01.

Pharmacopoeias. In *US.*

USP 31 (Cellulose Sodium Phosphate). It is prepared by the phosphorylation of alpha cellulose. A free-flowing, cream-coloured, odourless, powder. Insoluble in water, in dilute acids, and in most organic solvents. The pH of a filtrate of a 5% mixture in water is between 6.0 and 9.0. The inorganic bound phosphate content is not less than 31.0% and not more than 36.0%; the free phosphate content is not more than 3.5%; and the sodium content is not less than 9.5% and not more than 13.0%, all calculated on the dried basis. The calcium binding capacity, calculated on the dried basis, is not less than 1.8 mmol per g.

Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances have been reported.

Sodium cellulose phosphate should not be given to patients with primary or secondary hyperparathyroidism, hypomagnesaemia, hypocalcaemia, bone disease, or enteric hyperoxaluria. It should be used cautiously in pregnant women and children, since they have high calcium requirements.

Patients should be monitored for electrolyte disturbances. Uptake of sodium and phosphate may increase and sodium cellulose phosphate should not be given to patients with renal failure or conditions requiring a restricted sodium intake such as heart failure. Theoretically, long-term treatment could result in calcium deficiency; regular monitoring of calcium and parathyroid hormone has therefore been recommended. Sodium cellulose phosphate is not a totally selective exchange resin and the intestinal absorption of other dietary cations may be reduced; magnesium deficiency has been reported but may be corrected by dosage reduction or oral magnesium supplements. Urinary excretion of oxalate may increase and dietary restriction of oxalate intake may be necessary.

◊ Potential complications of long-term sodium cellulose phosphate therapy include secondary hyperparathyroidism and bone disease; deficiency of magnesium, copper, zinc, and iron; and hyperoxaluria. A study in 18 patients[1] with absorptive hypercalciuria and recurrent renal stones indicated that these complications could largely be avoided if use was confined to those with absorptive hypercalciuria (hypercalciuria, intestinal hyperabsorption of calcium, and normal or suppressed parathyroid function), if the dose was adjusted so as not to reduce intestinal calcium absorption or urinary calcium subnormally (the optimal maintenance dose in most patients was 10 g daily), if oral magnesium supplements were provided, and if a moderate dietary restriction of calcium and oxalate was imposed. There was no evidence of zinc, copper, or iron deficiency.

1. Pak CYC. Clinical pharmacology of sodium cellulose phosphate. *J Clin Pharmacol* 1979; **19:** 451–7.

Interactions

Sodium cellulose phosphate binds with calcium and other cations. Use with calcium or magnesium salts, including cation-donating antacids or laxatives, may reduce its efficacy. Magnesium supplements are often required in patients receiving sodium cellulose phosphate but should be given at least one hour before or after any dose of the resin since the absorption of the magnesium may otherwise be impaired.

Uses and Administration

Sodium cellulose phosphate, the sodium salt of the phosphate ester of cellulose, is a cation-exchange resin that exchanges sodium ions for calcium and other divalent cations. When given orally, it binds calcium ions within the stomach and intestine to form a non-absorbable complex which is excreted in the faeces. Theoretically a 5-g dose will bind about 350 mg calcium. It is used in the treatment of absorptive hypercalciuria type I with recurrent formation of calcium-containing renal calculi (p.2181), usually with a moderate dietary calcium restriction. Sodium cellulose phosphate is also used in the treatment of hypercalcaemia associated with osteopetrosis, sarcoidosis, and vitamin D intoxication, and in idiopathic hypercalcaemia of infancy, although other more effective agents are usually used (see Vitamin D-mediated Hypercalcaemia, p.1668).

The usual initial dose is 15 g daily by mouth in 3 divided doses with meals reducing to 10 g daily for maintenance. A suggested dose for children is 10 g daily (but see Adverse Effects and Precautions, above). The powder may be taken dispersed in water or sprinkled onto food. Oral magnesium supplements equivalent to about 60 or 90 mg (about 2.4 or 3.6 mmol) of elemental magnesium twice daily have been recommended for patients taking daily doses of sodium cellulose phosphate 10 or 15 g respectively. The magnesium supplement should not be given simultaneously with sodium cellulose phosphate.

Sodium cellulose phosphate has also been used for the investigation of calcium absorption.

Preparations

USP 31: Cellulose Sodium Phosphate for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Spain: Anacalcit; ***USA:*** Calcibind.

Sodium Edetate

Sodu edetynian.

Эдетат Натрия

CAS — 17421-79-3 (monosodium edetate).

ATC — S01XA05.

ATC Vet — QS01XA05.

NOTE. The name sodium edetate has been used in the literature for various sodium salts of edetic acid. Do not confuse with sodium calcium edetate (p.1462) or etomidate (p.1783); see also Inappropriate Administration, below.

Disodium Edetate *(BAN)*

Dinatrii edetas; Dinatrii Edetas Dihydricus; Dinatrio edetatas; Dinatriumedetaatti; Dinatriumedetat; Disodium Edathamil; Disodium EDTA; Disodium Tetracemate; Disodu edetynian; Edetan disodný dihydrát; Édétate disodique; Edetate Disodium; Edetato disódico; Edetynian disodu; Natrii Edetas; Nátrium-edetát; Sodium Versenate. Disodium dihydrogen ethylenediaminetetra-acetate dihydrate .

$C_{10}H_{14}N_2Na_2O_8,2H_2O$ = 372.2.

CAS — 139-33-3 (anhydrous disodium edetate); 6381-92-6 (disodium edetate dihydrate).

ATC — S01XA05.

ATC Vet — QS01XA05.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Disodium Edetate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 31 (Edetate Disodium). A white crystalline powder. Soluble in water. pH of a 5% solution in water is between 4.0 and 6.0.

Trisodium Edetate

Edetate Trisodium *(USAN)*; Edetato trisódico. Trisodium hydrogen ethylenediaminetetra-acetate .

$C_{10}H_{13}N_2Na_3O_8$ = 358.2.

CAS — 150-38-9.

ATC — S01XA05.

ATC Vet — QS01XA05.

Tetrasodium Edetate

Edetate Sodium *(USAN)*.

$C_{10}H_{12}N_2Na_4O_8$ = 380.2.

CAS — 64-02-8.

ATC — S01XA05.

ATC Vet — QS01XA05.

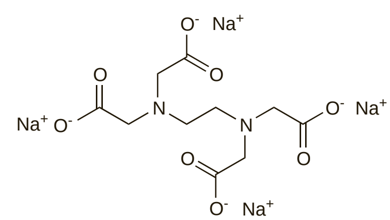

Incompatibility. See under Edetic Acid, p.1445.

Adverse Effects and Treatment

In common with other edetates (see Sodium Calcium Edetate, p.1462), sodium edetate may cause gastrointestinal effects such as nausea, vomiting, and diarrhoea. Pain at the site of injection and thrombophlebitis may also occur. Other adverse effects include fever, headache, skin rashes, hypotension, and hyperuricaemia; nephrotoxicity has also been reported, particularly following overdosage.

Hypocalcaemia can occur, particularly if sodium edetate is infused too rapidly or in too concentrated a solution and tetany, convulsions, respiratory arrest, and cardiac arrhythmias may result.

The rate of infusion should be decreased if signs of muscle reactivity occur. The infusion should be discontinued if tetany occurs and should only be restarted cautiously after plasma ionised and total calcium concentrations indicate a need for further treatment and tetany has stopped. Calcium supplements may be given intravenously for hypocalcaemia but should be used with extreme caution in patients with tetany, particularly in digitalised patients since the effect of the digitalis may be reversed.

◊ References.

1. Morgan BW, *et al.* Adverse effects in 5 patients receiving EDTA at an outpatient chelation clinic. *Vet Hum Toxicol* 2002; **44:** 274–6.
2. Prabha A, *et al.* Chelation therapy for coronary heart disease. *Am Heart J* 2002; **144:** E10.

Inappropriate administration. There have been fatalities in both children and adults when they were given sodium edetate instead of *sodium calcium edetate* (p.1462), which is a chelator used for the treatment of lead poisoning.[1,2] The FDA had received reports of 11 deaths associated with the use of sodium edetate over the period 1971 to 2007;[3] in 5 cases, sodium edetate was given instead of sodium calcium edetate, and in 2 cases, sodium edetate was given instead of *etomidate* (p.1783). In some cases, confusion had arisen due to the use of the term EDTA in prescribing the drug. The FDA has subsequently recommended that the full product name be used, and that prescribers should consider including the indication for use on the prescription.[2]

1. CDC. Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR* 2006; **55:** 204–7. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a3.htm (accessed 25/01/08)
2. FDA Public Health Advisory. Edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/cder/drug/advisory/edetate_disodium.htm (accessed 25/01/08)
3. FDA. Questions and answers on edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/cder/drug/infopage/edetate_disodium/QA.htm (accessed 25/01/08)

Precautions

Sodium edetate is contra-indicated in patients with renal impairment and should be used with caution in patients with hypokalaemia, tuberculosis, impaired cardiac function, diabetes mellitus, or a history of seizures. Plasma-electrolyte concentrations, particularly ionised calcium, and renal function should be monitored regularly; daily urinalysis is also recommended. Sodium edetate is irritant to the tissues and must be diluted before infusion; the recommended rate should not be exceeded.

Uses and Administration

Sodium edetate is a chelator with a high affinity for calcium, with which it forms a stable, soluble complex that is readily excreted by the kidneys. It has been given intravenously, as the disodium and trisodium salts, in the emergency treatment of hypercalcaemia (p.1668); it has also been used to control digitalis-induced cardiac arrhythmias, although less toxic agents are generally preferred (p.1260). It is also used topically to treat calcium deposits in the eye.

Sodium edetate also chelates other polyvalent metals but, unlike sodium calcium edetate, which is saturated with calcium, it is not used for the treatment of heavy metal poisoning since hypocalcaemia rapidly develops.

In the treatment of hypercalcaemia, injections containing varying amounts of disodium and trisodium edetate are used. In the UK, the trisodium salt is generally used. A dose of up to 70 mg/kg daily has been suggested for adults; children may be given up to 60 mg/kg daily. It should be given by slow intravenous infusion over 2 to 3 hours and each gram of trisodium edetate should be diluted with 100 mL of glucose 5% or sodium chloride 0.9%. In the USA, disodium edetate is given in an adult dose of 50 mg/kg in 24 hours by slow intravenous infusion; the maximum daily dose is 3 g. Children may be given 40 to 70 mg/kg in 24 hours. The injection should be diluted with 500 mL of sodium chloride 0.9% or glucose 5% for adults or to a concentration not greater than 3% for children, and infused over 3 hours or more, preferably 4 to 6 hours. The dosage may be repeated for a further 4 days followed by a two-day interval before subsequent courses of treatment. If necessary, up to fifteen doses may be given in total.

Sodium edetate is used in the treatment of calcium deposits from calcium oxide or calcium hydroxide burns of the eye and in the treatment of calcified corneal opacities, either by topical application after removing the appropriate area of corneal epithelium or by iontophoresis. Irrigation has also been suggested for zinc chloride injury to the eye, but treatment may be ineffective unless started within 2 minutes. In the UK, a 0.4% solution of the trisodium salt is used for topical application to the eye; in the USA, a 0.35 to 1.85% solution of the disodium salt has been suggested.

Sodium edetates are also used in cleaners for contact lenses and as antoxidant synergists in cosmetic and pharmaceutical preparations.

Atherosclerosis. Calcium is thought to be necessary for several steps in atherogenesis and removal of calcium from atherosclerotic plaques using a chelator such as disodium edetate has been tried in patients with atherosclerosis (p.1159). However, reports of beneficial clinical responses are largely anecdotal or from small, short-term, or uncontrolled clinical studies; a meta-analysis[1] of controlled trials concluded that there was insufficient evidence of benefit or harm, and a further randomised trial[2] in patients with coronary heart disease found no benefit with sodium edetate treatment. In addition, adverse effects are common with chelation therapy, and fatalities have been reported;[3] literature reviews[4,5] considering both uncontrolled and controlled studies have concluded that in view of the potential toxicity of such treatment it should be considered obsolete.

1. Villarruz MV, *et al.* Chelation therapy for atherosclerotic cardiovascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 04/10/05).
2. Knudtson ML, *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* 2002; **287:** 481–6.
3. Magee R. Chelation treatment of atherosclerosis. *Med J Aust* 1985; **142:** 514–15.
4. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. *Circulation* 1997; **96:** 1031–3.
5. Ernst E. Chelation therapy for coronary heart disease: an overview of all clinical investigations. *Am Heart J* 2000; **140:** 139–41.

Preparations

BP 2008: Trisodium Edetate Intravenous Infusion;
USP 31: Edetate Disodium Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Chelatran; ***Irl.:*** Limclair; ***UK:*** Limclair†; ***USA:*** Endrate; ***Venez.:*** Edetil.

Multi-ingredient: ***Mex.:*** Adapettes; ***NZ:*** Conditioning Solution†; ***UK:*** Uriflex G; Uriflex R.

Sodium Fytate *(rINNM)*

Fitato sódico; Fytate de Sodium; Natrii Fytas; Phytate Sodium *(USAN)*; Sodium Phytate; SQ-9343. The nonasodium salt of *myo*-inositol hexakis(dihydrogen phosphate); Sodium cyclohexanehexyl(hexaphosphate).

Натрий Фэитат

$C_6H_9Na_9O_{24}P_6$ = 857.9.

CAS — 83-86-3 (fytic acid); 7205-52-9 (sodium fytate).

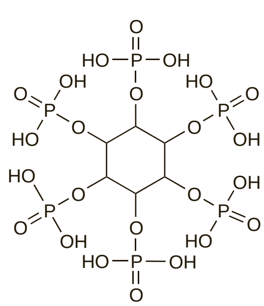

(fytic acid)

Profile

Sodium fytate reacts with calcium in the gastrointestinal tract to form non-absorbable calcium fytate which is excreted in the faeces. Sodium fytate has been used in a similar manner to sodium cellulose phosphate (p.1463) to reduce the absorption of calcium from the gut in the treatment of hypercalciuria. It also binds other metals; fytic acid has been used as an antoxidant, and as an adjunct in topical preparations for hyperpigmentation disorders.

Sodium fytate labelled with technetium-99m (p.2055) has been used intravenously for imaging of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Fyton.

Multi-ingredient: ***Ital.:*** Lightening; Phytic Acid.

Sodium Nitrite

Dusitan sodný; E250; Natrii nitris; Natrio nitritas; Natrium Nitrosum; Natriumnitriitti; Natriumnitrit; Nátrium-nitrit; Nitrito sódico; Sodium, nitrite de; Sodu azotyn; Sodyum Nitrit.

$NaNO_2$ = 69.00.

CAS — 7632-00-0.

ATC — V03AB08.

ATC Vet — QV03AB08.

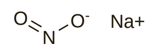

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Sodium Nitrite). Hygroscopic, colourless crystals or mass, or yellowish rods. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 31 (Sodium Nitrite). A white to slightly yellow granular powder, or white or practically white, opaque fused masses or sticks. It is deliquescent in air. Soluble 1 in 1.5 of water; sparingly soluble in alcohol. Its solutions are alkaline to litmus. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

Sodium nitrite may cause nausea and vomiting, abdominal pain, dizziness, headache, flushing, cyanosis, tachypnoea, and dyspnoea; vasodilatation resulting in syncope, hypotension, and tachycardia may occur. Overdosage may result in cardiovascular collapse, coma, convulsions, and death. Ionised nitrites readily oxidise haemoglobin to methaemoglobin, causing methaemoglobinaemia.

Sodium nitrite is a precursor for the formation of nitrosamines, many of which are carcinogenic in *animals*, but a relationship with human cancer has not been established.

Methaemoglobinaemia. Severe methaemoglobinaemia has been reported after the consumption of nitrite-contaminated meat,[1,2] as well as following inadvertent ingestion of sodium nitrite.[3,4]

1. Walley T, Flanagan M. Nitrite-induced methaemoglobinaemia. *Postgrad Med J* 1987; **63:** 643–44.
2. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; **76:** 367–8.
3. Finan A, *et al.* Methaemoglobinaemia associated with sodium nitrite in three siblings. *BMJ* 1998; **317:** 1138–9.
4. Anonymous. Methemoglobinemia following unintentional ingestion of sodium nitrite—New York, 2002. *MMWR* 2002; **51:** 639–42.

Treatment of Adverse Effects

When toxicity results from the ingestion of nitrites, treatment is supportive and symptomatic; oxygen and methylthioninium chloride may be required for methaemoglobinaemia although methylthioninium chloride should not be given if cyanide poisoning is suspected since cyanide may be displaced. Exchange transfusion may be considered when methaemoglobinaemia is severe.

Uses and Administration

Sodium nitrite is used with sodium thiosulfate in the treatment of cyanide poisoning (p.2045). Sodium nitrite produces methaemoglobinaemia and it is thought that cyanide ions combine with the methaemoglobin to produce cyanmethaemoglobin, thus protecting cytochrome oxidase from the cyanide ions; however, other mechanisms may have a significant role. As the cyanmethaemoglobin slowly dissociates, the cyanide is converted to relatively non-toxic thiocyanate and is excreted in the urine. Sodium thiosulfate provides an additional source of sulfur for this reaction and this accelerates the process.

The usual dosage regimen in adults is 300 mg of *sodium nitrite* (10 mL of a 3% solution) given intravenously over 5 to 20 minutes followed by 12.5 g of *sodium thiosulfate* (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over a period of about 10 minutes. A suggested dosage regimen in children is about 4 to 10 mg/kg of *sodium nitrite*, given as a 3% solution (0.13 to 0.33 mL/kg), to a maximum of 300 mg (10 mL), followed by about 400 mg/kg of *sodium thiosulfate*, as a 25 or 50% solution (1.65 mL/kg of a 25% solution) to a maximum of 12.5 g (50 mL of a 25% solution). The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses.

Sodium nitrite has also been suggested in the treatment of hydrogen sulfide poisoning (see p.1690).

Sodium nitrite has been used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats but should not be used in food for infants under the age of 3 months due to the risk of methaemoglobinaemia. Potassium nitrite is also used as a food preservative.

Preparations

USP 31: Sodium Nitrite Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: O A R†.

Multi-ingredient: ***Ital.:*** Citrosil Alcolico Azzuro; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package.

Sodium Polystyrene Sulfonate

Natrii polystyrenesulfonas; Natrii Polystyrensulfonas; Natrio polistirensulfonatas; Natriumpolystyreenisulfonaatti; Natriumpolystyrensulfonat; Natrium-polystyrensulfonát; Poliestirenosulfonato sódico; Polystyrène sulfonate sodique; Sodium Polystyrene Sulphonate.

CAS — 9003-59-2; 9080-79-9; 25704-18-1.

ATC — V03AE01.

ATC Vet — QV03AE01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Sodium Polystyrene Sulphonate). An almost white to light brown powder. It contains 9.4 to 11.0% of sodium, calculated with reference to the dried substance. Each g exchanges 2.8 mmol to 3.4 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 31 (Sodium Polystyrene Sulfonate). A golden brown, fine, odourless powder containing not more than 10% of water. The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis. Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis. Insoluble in water.

Adverse Effects

Anorexia, nausea, vomiting, constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate. Constipation may be severe; large doses in elderly patients and in children may result in faecal impaction and gastrointestinal concretions have occurred after oral use in neonates. If necessary a mild laxative may be used to prevent or treat constipation (but see Precautions, below, for laxatives that should be avoided).

Serious potassium deficiency can occur with sodium polystyrene sulfonate and signs of severe hypokalaemia may include irritability, confusion, ECG abnormalities, cardiac arrhythmias, and severe muscle weakness. Like other cation-exchange resins, sodium polystyrene sulfonate is not totally selective and its use may result in other electrolyte disturbances such as hypocalcaemia. Significant sodium retention may also occur, especially in patients with renal impairment, and may lead to heart failure.

Effects on the gastrointestinal tract. Colonic necrosis, including some fatalities, has been reported[1-3] after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in *animals*[1] suggested that use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested[4,5] as a possible cause. Both colonic[6] and upper gastrointestinal necrosis[7] have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there has also been a report[8] of colonic necrosis with oral sodium polystyrene sulfonate alone.

1. Lillemoe KD, *et al.* Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; **101:** 267–72.
2. Wootton FT, *et al.* Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; **111:** 947–9.
3. Rogers FB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* 2001; **51:** 395–7.
4. Burnett RJ. Sodium polystyrene-sorbitol enemas. *Ann Intern Med* 1990; **112:** 311–12.
5. Shepard KV. Cleansing enemas after sodium polystyrene sulfonate enemas. *Ann Intern Med* 1990; **112:** 711.
6. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997; **21:** 60–9.
7. Abraham SC, *et al.* Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; **25:** 637–44.
8. Cheng ES, *et al.* Colonic necrosis and perforation following oral sodium polystyrene sulfonate (Resonium A /Kayexelate) in a burn patient. *Burns* 2002; **28:** 189–90.

Effects on the lungs. Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of 3 patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in 2 and with early bronchitis in the third.[1] It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.

1. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; **142:** 379–81.

Precautions

Sodium polystyrene sulfonate should not be given orally to neonates, and is contra-indicated by any route in neonates with reduced gut motility or in any patient with obstructive bowel disease. Care is also needed with rectal use in neonates and children in order to avoid impaction of the resin. Treatment should be discontinued if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis in patients receiving this combination (see Effects on the Gastrointestinal Tract, above) and licensed product information advises against the use of sorbitol with polystyrene sulfonates. Magnesium-containing laxatives are also contra-indicated (see Interactions, below).

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Use of sodium polystyrene sulfonate can result in sodium overloading and it should be used cautiously in patients with renal failure or conditions requiring a restricted sodium intake, such as heart failure and severe hypertension; calcium polystyrene sulfonate (p.1438) may be preferred in these patients.

The possible effects of sodium polystyrene sulfonate on serum electrolytes should be considered when interpreting diagnostic measurements.

After use of sodium polystyrene sulfonate retention enemas, the colon should be irrigated to ensure removal of the resin.

Interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, particularly in patients with renal impairment, metabolic alkalosis may develop due to binding of the cation by the resin; this prevents neutralisation of bicarbonate ions in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine (see p.2173) and lithium salts.

Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

Uses and Administration

Sodium polystyrene sulfonate, the sodium salt of sulfonated styrene copolymer with divinylbenzene, is a cation-exchange resin that exchanges sodium ions for potassium ions and other cations in the gastrointestinal tract when given orally or rectally. The exchanged resin is then excreted in the faeces. Each gram of resin exchanges about 3 mmol of potassium *in vitro*, and about 1 mmol *in vivo*.

Sodium polystyrene sulfonate is used to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria (caution is required due to the sodium content). An effect may not be evident for several hours or longer, and in severe hyperkalaemia, where a rapid effect is required, other measures must also be considered (see p.1669).

Serum-electrolyte concentrations should be monitored throughout treatment and doses given according to response.

The usual oral dose is 15 g up to four times daily as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content. A suggested oral dose for children is 1 g/kg daily in divided doses for acute hyperkalaemia, reduced to a maintenance dose of 500 mg/kg daily; the oral route is not recommended for neonates.

When oral use is difficult, sodium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 100 mL of 2% methylcellulose '450' and 100 mL of water and retained, if possible, for at least 9 hours; higher doses, shorter retention times, and alternative vehicles have also been used. After retention of the enema the colon should be irrigated to remove the resin. Initial therapy may involve both oral and rectal routes. Children and neonates may be given rectal doses similar to the oral doses suggested for children; particular care is needed with rectal use in children as excessive dosage or inadequate dilution could result in impaction of resin.

Other polystyrene sulfonate resins include calcium polystyrene sulfonate (p.1438), which is used similarly to the sodium resin and potassium polystyrene sulfonate (p.1460), which has been used in the treatment of hypercalciuria. Aluminium polystyrene sulfonate, ammonium polystyrene sulfonate, and magnesium polystyrene sulfonate have all occasionally been used.

Preparations

USP 31: Sodium Polystyrene Sulfonate Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Resonium A; ***Austria:*** Resonium A; ***Belg.:*** Kayexalate; ***Canad.:*** K-Exit; Kayexalate; ***Denm.:*** Resonium; ***Fin.:*** Resonium; ***Fr.:*** Kayexalate; ***Ger.:*** Elutit-Natrium; Resonium A; ***Gr.:*** Kayexalate; ***Hong Kong:*** Resonium A; ***Hung.:*** Resonium A; ***Irl.:*** Resonium A†; ***Israel:*** Kayexalate; ***Ital.:*** Kayexalate; ***Malaysia:*** Resonium A†; ***Neth.:*** Resonium A; ***NZ:*** Resonium A; ***Pol.:*** Resonium A; ***Port.:*** Resonium; ***S.Afr.:*** Kexelate; ***Singapore:*** Resinsodio; ***Spain:*** Resinsodio; ***Swed.:*** Resonium; ***Switz.:*** Resonium A; ***Thai.:*** Kayexalate; Resinsodio; Resonium A; ***UK:*** Resonium A; ***USA:*** Kayexalate; Kionex; SPS; ***Venez.:*** Kayexalate.

Multi-ingredient: ***Ger.:*** Ujostabil†.

Sodium Thiosulfate

Disodium Thiosulfate Pentahydrate; Hiposulfito sódico; Natrii thiosulfas; Natrii Thiosulfas Pentahydricus; Natrio tiosulfatas; Natrium Thiosulfuricum; Natriumtiosulfaatti; Natriumtiosulfat; Nátrium-tioszulfát; Sodium Hyposulphite; Sodium, thiosulfate de; Sodium Thiosulphate; Sodu tiosiarczan; Sodyum Tiyosülfat; Thiosíran sodný pentahydrát; Tiosulfato sódico.

$Na_2S_2O_3,5H_2O$ = 248.2.

CAS — 7772-98-7 (anhydrous sodium thiosulfate); 10102-17-7 (sodium thiosulfate pentahydrate).

ATC — V03AB06.

ATC Vet — QV03AB06.

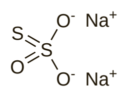

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Sodium Thiosulphate). Colourless transparent crystals; efflorescent in dry air. It dissolves in its own water of crystallisation at about 49°. Very soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH of 6.0 to 8.4. Store in airtight containers.

USP 31 (Sodium Thiosulfate). Large, colourless crystals, or a coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33°. Soluble 1 in 0.5 of water; insoluble in alcohol. Its solutions are neutral or faintly alkaline to litmus. Store in airtight containers.

Incompatibility. Sodium thiosulfate may reduce the activity of some preservatives, including bronopol (p.1633), phenylmercuric salts (see Phenylmercuric Nitrate, p.1657), and thiomersal (p.1664).

Stability. Solutions of sodium thiosulfate 50% stored in air developed cloudiness or a deposit after autoclaving.[1] Addition of sodium phosphate 0.5% or 1.2% improved stability but solutions became cloudy or developed a deposit after 12 and 6 weeks respectively at 25°. Solutions containing sodium bicarbonate 0.5% became cloudy or developed a deposit after 12 weeks at 25°. No significant improvement in stability was obtained when the concentration of sodium thiosulfate was reduced to 30% or 15%, or when the injection was sealed under nitrogen.

1. Anonymous. Sodium thiosulphate injection–effect of additives on stability. *PSGB Lab Rep* P/75/3 1975.

Adverse Effects

Apart from osmotic disturbances sodium thiosulfate is relatively non-toxic. Large oral doses have a cathartic action.

Pharmacokinetics

Sodium thiosulfate is poorly absorbed from the gastrointestinal tract. After intravenous injection it is distributed throughout the extracellular fluid and rapidly excreted in the urine.

◊ An intravenous infusion of sodium thiosulfate 12 g/m^2 was given over 6 hours to 8 patients receiving intraperitoneal antineoplastic therapy.[1] The thiosulfate was rapidly eliminated, 95% being excreted within 4 hours of stopping the infusion; on average only 28.5% of the dose was recovered unchanged in the urine. The mean plasma elimination half-life was 80 minutes.

1. Shea M, *et al.* Kinetics of sodium thiosulfate, a cisplatin neutralizer. *Clin Pharmacol Ther* 1984; **35:** 419–25.

Uses and Administration

Sodium thiosulfate is used in the treatment of cyanide poisoning (p.2045). Sodium thiosulfate may be effective alone in less severe cases of cyanide poisoning, but it is often used with sodium nitrite (p.1464).

Sodium thiosulfate acts as a sulfur-donating substrate for the enzyme rhodanese, which catalyses the conversion of cyanide to relatively non-toxic thiocyanate, and thus accelerates the detoxification of cyanide.

The usual dosage regimen in adults is 300 mg of *sodium nitrite* (10 mL of a 3% solution) given intravenously over 5 to 20 minutes followed by 12.5 g of *sodium thiosulfate* (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over a period of about 10 minutes. A suggested dosage regimen in children is about 4 to 10 mg/kg of *sodium nitrite*, given as a 3% solution (0.13 to 0.33 mL/kg) to a maximum of 300 mg (10 mL), followed by about 400 mg/kg of *sodium thiosulfate*, as a 25 or 50% solution (1.65 mL/kg of a 25% solution) to a maximum of 12.5 g (50 mL of a 25% solution). The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses.

Sodium thiosulfate is used as an isotonic 4% solution in the management of extravasation of chlormethine and has been tried in the management of extravasation of some other antineoplastics (but see below).

Sodium thiosulfate has been used for its antifungal properties. Sodium thiosulfate and magnesium thiosulfate are included in mixed preparations for a variety of disorders.

Antineoplastic toxicity. Sodium thiosulfate may be used in the management of extravasation of chlormethine and some other antineoplastics (although this is a contentious area, see p.640). It is also used to inactivate some antineoplastics before disposal.

Sodium thiosulfate, given by intravenous infusion, has also been investigated for reducing the systemic toxicity of some antineoplastics. It has been reported to reduce the incidence of nephrotoxicity associated with intraperitoneal cisplatin (see Prophylaxis under Effects on the Kidneys, p.699) and to reduce hearing loss associated with carboplatin (see Effects on the Ears, p.693).

Bromate poisoning. Sodium thiosulfate has been used in the treatment of bromate poisoning[1,2] although its clinical efficacy is unclear;[3] it is thought to act by reducing bromate to the less toxic bromide ion, but evidence is lacking.[3,4] Although it has been given orally, this is no longer recommended since toxic sulfide may be formed.[4] However, intravenous sodium thiosulfate may have a role in some clinical circumstances.[4,5]

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; **7:** 66–70.

2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; **114:** 891–4.

3. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 570, 572.

4. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.

5. Johnson CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 572.

Preparations

BP 2008: Sodium Thiosulphate Injection;
USP 31: Sodium Thiosulfate Injection.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Azufracid; ***Austria:*** Schwefelbad Dr Klopfer; ***Braz.:*** Dessensibilizante Chauvin†; ***Canad.:*** Adasept; ***Cz.:*** Carbotox; ***Fr.:*** Desintex; Desintex Infantile; Desintex-Choline; Rhino-Sulfuryl; Vagostabyl; ***Ger.:*** Corti Jaikal†; Jaikal†; Schwefelbad Dr Klopfer; Sulfuretten†; ***Hung.:*** Schwefelbad Dr Klopfer; ***Ital.:*** Antimicotica Solforata; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package; Tinver; Versiclear.

Succimer *(BAN, USAN, rINN)*

DIM-SA; DMSA; Succimère; Succímero; Succimero; Succimerum; Suksimeeri. *meso*-2,3-Dimercaptosuccinic acid; (R^*,S^*)-2,3-Dimercapto-butanedioic acid.

Сукцимер

$C_4H_6O_4S_2$ = 182.2.

CAS — 304-55-2.

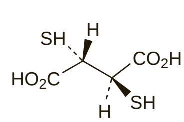

Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

Succimer may cause gastrointestinal disorders, skin rashes, increases in serum transaminase, flu-like symptoms, drowsiness, and dizziness. Mild to moderate neutropenia has been reported in some patients and regular full blood counts are recommended during therapy. Succimer should be used with caution in patients with renal impairment or a history of hepatic disease.

Pharmacokinetics

Succimer is rapidly but incompletely absorbed after oral doses. It undergoes rapid and extensive metabolism and is excreted mainly in the urine with small amounts excreted in the bile and via the lungs.

◊ References.

1. Dart RC, *et al.* Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; **125:** 309–16.

Uses and Administration

Succimer is a chelator structurally related to dimercaprol (p.1444). It forms water-soluble chelates with heavy metals and is used in the treatment of lead poisoning. It has also been used in the treatment of poisoning with arsenic or mercury.

Succimer, labelled with a radionuclide, is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given orally in a dose of 10 mg/kg or 350 mg/m^2 every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks.

Lead poisoning. Succimer is an effective lead chelator[1] and is used in the management of lead poisoning (see Treatment of Adverse Effects under Lead, p.2332). Succimer is also used in children with chronic lead exposure, and various dosage regimens have been studied.[2] It is generally only indicated if blood-lead concentrations are greater than 45 micrograms per 100 mL;[3] although short-term studies[4] in children with lower concentrations have shown effective reduction of blood lead, no effect on neurodevelopmental outcome has been shown in follow-up studies[5,6] and treatment of such children remains controversial.

1. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; **10:** 914–22.

2. Farrar HC, *et al.* A comparison of two dosing regimens of succimer in children with chronic lead poisoning. *J Clin Pharmacol* 1999; **39:** 180–3.

3. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; **116:** 1036–46. Also available at: http://pediatrics.aappublications.org/cgi/reprint/116/4/1036 (accessed 11/10/05)

4. Besunder JB, *et al.* Short-term efficacy of oral dimercaptosuccinic acid in children with low to moderate lead intoxication. *Pediatrics* 1995; **96:** 683–7.

5. Rogan WJ, *et al.* The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; **344:** 1421–6.

6. Dietrich KN, *et al.* Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. *Pediatrics* 2004; **114:** 19–26.

Mercury poisoning. Succimer, given orally, increases the renal excretion of mercury and may be used in mercury poisoning (see Treatment of Adverse Effects under Mercury, p.2342). In patients with renal impairment, the succimer-mercury chelate may accumulate, and alternative methods have been tried. Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.[1] Clearance was about ten times greater than that achieved with haemodialysis after intramuscular dimercaprol.

1. Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; **9:** 137–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Succicaptal; ***USA:*** Chemet.

Sugammadex Sodium *(USAN, rINNM)*

Natrii Sugammadexum; Org-25969; Sugammadex sódico; Sugammadex Sodique.

Натрий Сугаммадекс

$C_{72}H_{104}Na_8O_{48}S_8$ = 2178.0.

CAS — 343306-79-6.

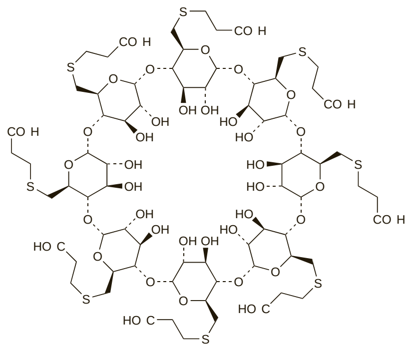

(sugammadex)

Profile

Sugammadex sodium is a modified gamma cyclodextrin under investigation as a selective relaxant binding agent for the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

◊ Reviews.

1. Nicholson WT, *et al.* Sugammadex: a novel agent for the reversal of neuromuscular blockade. *Pharmacotherapy* 2007; **27:** 1181–8.

Tiopronin *(rINN)*

Thiopronine; Thiopronınum; Tioproniini; Tiopronina; Tiopronine; Tiopronınum. *N*-(2-Mercaptopropionyl)glycine.

Тиопронин

$C_5H_9NO_3S$ = 163.2.

CAS — 1953-02-2.

ATC — R05CB12.

ATC Vet — QG04BC90; QR05CB12.

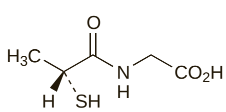

and enantiomer

Adverse Effects and Precautions

Tiopronin has similar adverse effects and precautions to those of penicillamine (p.1456).

Incidence of adverse effects. In a study of 140 patients[1] with rheumatoid arthritis receiving long-term treatment with tiopronin, adverse effects necessitated withdrawal of treatment in 56 patients (40%). The majority of adverse effects occurred within the first 6 months of treatment. The most common were those affecting the skin and mucous membranes (46 patients) including stomatitis, pruritus, erythema, and 1 case of pemphigus. Proteinuria developed in 5 patients and nephrotic syndrome in 3. Haematological disorders developed in 13 patients. Gastrointestinal disorders and ageusia were also reported.

In another study of 74 patients[2] with rheumatoid arthritis adverse effects were reported in 32 patients (43%) and necessitated withdrawal in 24%. The most common adverse effects were ageusia (21%), mucocutaneous lesions (16%), and gastrointestinal disturbances (14%). Haematological disorders occurred in 5 patients and proteinuria in 3 patients.

In a comparative study in 200 patients,[3] treatment was withdrawn due to toxicity in 27% of patients taking tiopronin and 21% of patients treated with gold.

1. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.
2. Ehrhart A, *et al.* Effets secondaires dus au traitement par la tiopronine de 74 polyarthrites rhumatoïdes. *Rev Rhum* 1991; **58:** 193–7.
3. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.

Effects on the blood. Haematological disorders including leucopenia or thrombocytopenia have been reported during long-term studies of tiopronin. Isolated cases of agranulocytosis[1] and bone marrow aplasia[2] have also occurred.

See also Incidence of Adverse Effects, above.

1. Corda C, *et al.* Thiopronin-induced agranulocytosis. *Therapie* 1990; **45:** 161.
2. Taillan B, *et al.* Aplasie médullaire au cours d'une polyarthrite rhumatoïde traitée par tiopronine. *Rev Rhum* 1990; **57:** 443–4.

Effects on the kidneys. Proteinuria developed in 3 patients 4 to 14 months after starting treatment with tiopronin for cystinuria.[1] None of the patients had clinical symptoms of nephrotic syndrome. Renal biopsies in 2 patients demonstrated membranous glomerulonephritis. Proteinuria disappeared in all 3 patients 4 to 5 months after tiopronin was discontinued. However, there was histological evidence of irreversible changes and signs of progressive glomerular lesions in 1 patient.

1. Lindell A, *et al.* Membranous glomerulonephritis induced by 2-mercaptopropionylglycine (2-MPG). *Clin Nephrol* 1990; **34:** 108–15.

Effects on the skin. Mucocutaneous lesions are among the most common adverse effects of tiopronin (see Incidence of Adverse Effects, above). Reversible lichenoid eruptions have been reported[1] in a patient after treatment with tiopronin for 2 years, and may have been due to an immunological reaction to the sulfhydryl group. Lesions resembling pemphigus have also been reported in a few patients[2,3] and may require treatment with a corticosteroid or other immunosuppressant.

1. Kurumaji Y, Miyazaki K. Tiopronin-induced lichenoid eruption in a patient with liver disease and positive patch test reaction to drugs with sulfhydryl group. *J Dermatol* 1990; **17:** 176–81.
2. Trotta F, *et al.* Thiopronine-induced pemphigus vulgaris in rheumatoid arthritis. *Scand J Rheumatol* 1984; **13:** 93–5.
3. Verdier-Sevrain S, *et al.* Thiopronine-induced herpetiform pemphigus: report of a case studied by immunoelectron microscopy and immunoblot analysis. *Br J Dermatol* 1994; **130:** 238–40.

Pharmacokinetics

Tiopronin is absorbed from the gastrointestinal tract. Up to 48% of the dose is reported to be excreted in the urine during the first 4 hours and up to 78% by 72 hours.

◊ References.

1. Carlsson SM, *et al.* Pharmacokinetics of intravenous 2-mercaptopropionylglycine in man. *Eur J Clin Pharmacol* 1990; **38:** 499–503.
2. Carlsson MS, *et al.* Pharmacokinetics of oral tiopronin. *Eur J Clin Pharmacol* 1993; **45:** 79–84.

Uses and Administration

Tiopronin is a sulfhydryl compound and chelator with properties similar to those of penicillamine (p.1458). It is given orally in the management of cystinuria, in conjunction with adequate hydration and alkalinisation of the urine, in usual doses of 0.8 to 1 g daily in divided doses. The dose should be adjusted according to the urinary cystine concentration; up to 2 g daily has been given. Tiopronin should be given on an empty stomach. Tiopronin is used in similar doses in rheumatoid arthritis. It has been used in hepatic disorders and heavy-metal poisoning, and has been given by inhalation as a mucolytic in respiratory disorders. It may also be given by intravenous or intramuscular injection.

The sodium salt has also been used.

Cystinuria. Tiopronin may be used as an alternative to penicillamine in the management of cystinuria (p.1459). A multicentre study[1] in 66 patients with cystine nephrolithiasis found that addition of tiopronin in doses of up to 2 g daily (mean 1.193 g) to standard alkali and fluid therapy significantly reduced urinary-cystine concentrations and the rate of new stone formation. Adverse effects were similar to those reported with penicillamine. In the 49 patients who had previously received penicillamine, 41 had adverse effects with penicillamine, requiring cessation of therapy in 34, whereas 37 had adverse effects with tiopronin, requiring drug withdrawal in 15. In the remaining 17 patients, 11 had adverse effects with tiopronin and 1 discontinued treatment because of proteinuria. However, of the 34 patients who had been unable to tolerate penicillamine, 22 were able to continue treatment with tiopronin.

1. Pak CYC, *et al.* Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol (Baltimore)* 1986; **136:** 1003–8.

Mucolytic activity. Studies on the mucolytic activity of tiopronin.

1. Costantini D, *et al.* Evaluation of the therapeutic effectiveness of thiopronine in children with cystic fibrosis. *Curr Ther Res* 1982; **31:** 714–17.
2. Carratù L, *et al.* Clinico-functional and rheological research on mucolytic activity of thiopronine in chronic broncho-pneumopathies. *Curr Ther Res* 1982; **32:** 529–43.

Rheumatoid arthritis. Tiopronin has been reported to have activity comparable to that of gold salts[1] and penicillamine[2] in patients with rheumatoid disease, and has been used to treat rheumatoid arthritis (p.11), particularly in patients intolerant of penicillamine.

1. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.
2. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Thiola†; ***Fr.:*** Acadione; ***Ger.:*** Captimer; ***Hong Kong:*** Thiola†; ***Ital.:*** Mucolysin†; Mucosyt†; Thiola; Thiosol; ***Switz.:*** Mucolysin†; ***USA:*** Thiola.

Trientine Dihydrochloride *(BAN, rINNM)*

Dihidrocloruro de trientina; MK-0681; Trien Hydrochloride; Trientin Dihidroklorür; Trientine, Dichlorhydrate de; Trientine Hydrochloride *(USAN)*; Trientini Dihydrochloridum; Triethylenetetramine Dihydrochloride. 2,2′-Ethylenedi-iminobis(ethylamine) dihydrochloride; *N,N′*-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

Триентина Дигидрохлорид

$C_6H_{18}N_4,2HCl$ = 219.2.

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).

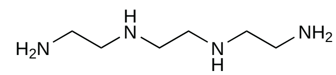

(trientine)

Pharmacopoeias. In *US.*

USP 31 (Trientine Hydrochloride). A white to pale yellow crystalline powder. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store under an inert gas in airtight containers at 2° to 8°. Protect from light.

Adverse Effects and Precautions

Trientine may cause nausea and skin rashes; duodenitis and colitis have also been reported. Iron deficiency may occur; if iron supplements are given an interval of at least 2 hours between the doses of trientine and iron has been recommended. Recurrence of symptoms of SLE has been reported in a patient who had previously reacted to penicillamine.

Interactions

Chelation of trientine with metal ions in the diet or in mineral supplements may impair the absorption of both. Trientine should not be taken with mineral supplements and should be taken at least 1 hour apart from food, other drugs, or milk, to reduce the likelihood of absorption being affected. Iron supplements should be taken at least 2 hours before or after trientine.

Uses and Administration

Trientine is a copper chelator used in a similar way to penicillamine in the treatment of Wilson's disease (p.1459). It tends to be used in patients intolerant of penicillamine.

Trientine dihydrochloride is given orally, preferably on an empty stomach. In the USA, the usual initial dose for adults is 0.75 to 1.25 g daily in 2 to 4 divided doses; this may be increased to a maximum of 2 g daily if required. In children, the usual initial dose is 500 to 750 mg daily, increased if necessary to a maximum dose of 1.5 g daily. In the UK, a dose of 1.2 to 2.4 g daily, in 2 to 4 divided doses, has been recommended for adults; children may be given an initial dose of 0.6 to 1.5 g daily.

Preparations

USP 31: Trientine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)

USA: Syprine.

Trimedoxime Bromide *(rINN)*

Bromuro de trimedoxima; Dipyroxime; TMB-4; Trimédoxime, Bromure de; Trimedoximi Bromidum. 1,1′-Trimethylenebis[4-formylpyridinium bromide]dioxime.

Тримедоксима Бромид

$C_{15}H_{18}Br_2N_4O_2$ = 446.1.

CAS — 56-97-3.

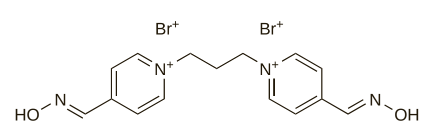

NOTE. Do not confuse with Trimedoxine, a range of veterinary antibacterial preparations.

Profile

Trimedoxime bromide is a cholinesterase reactivator given with atropine in the treatment of organophosphorus poisoning.

◊ References.

1. Kozer E, *et al.* Pediatric poisoning from trimedoxime (TMB4) and atropine automatic injectors. *J Pediatr* 2005; **146**: 41–4.

Unithiol

DMPS; Unithiolum; Unitiol; Unitioli. Sodium 2,3-dimercaptopropanesulfonate .

$C_3H_7NaO_3S_3$ = 210.3.

CAS — 4076-02-2.

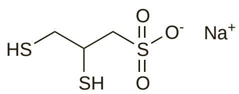

Profile

Unithiol is a chelator structurally related to dimercaprol (p.1444). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds; it has also been used in poisoning with chromium or cadmium, although its efficacy is not established.

Unithiol is given orally in doses of 100 mg three or four times daily in chronic poisoning. In acute poisoning, a dose of 1.2 to 2.4 g by mouth, in divided doses over 24 hours, has been suggested. It may also be given parenterally in patients with severe toxicity; a suggested intravenous dose is 3 to 5 mg/kg every 4 hours, reducing the frequency after 1 to 2 days and then changing to oral therapy.

◊ Reviews.

1. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; **2:** 317–23.
2. Aposhian HV, *et al.* Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology* 1995; **97:** 23–38.

Arsenic poisoning. Complete recovery, without renal or neurological sequelae, has been reported[1,2] following the use of unithiol in patients with potentially lethal acute arsenic poisoning; haemodialysis was also used in 1 patient.[2] Increased urinary arsenic excretion, with some improvement in clinical symptoms, has also been reported[3,4] with unithiol in chronic arsenic toxicity.

1. Moore DF, *et al.* Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). *J Neurol Neurosurg Psychiatry* 1994; **57:** 1133–5.
2. Kruszewska S, *et al.* The use of haemodialysis and 2,3 propanesulphonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide. *Int J Occup Med Environ Health* 1996; **9:** 111–115.
3. Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. *J Toxicol Clin Toxicol* 2000; **38:** 777–80.
4. Guha Mazumder DN, *et al.* Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *J Toxicol Clin Toxicol* 2001; **39:** 665–74.

Lead poisoning. Unithiol may be used in lead poisoning, although other chelators are generally preferred (see Treatment of Adverse Effects under Lead, p.2332). In a study of 12 children[1] it reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.

1. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; **235:** 665–9.

Mercury poisoning. Unithiol is used in poisoning with mercury and mercury salts (see Treatment of Adverse Effects under Mercury, p.2342) and has been given by various routes. In 7 patients with poisoning due to mercury vapour or mercuric oxide, unithiol 100 mg given twice daily by mouth for up to 15 days enhanced urinary elimination of mercury;[1] the urinary elimination of copper and zinc was also increased in most patients and 2 developed skin rashes. A dose of 5 mg/kg intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[2] A patient with severe mercuric chloride poisoning was treated successfully with unithiol given intravenously for 4 weeks, then orally for 3 weeks.[3] Unithiol has also been used with haemofiltration in patients with inorganic mercury poisoning and acute renal failure.[4,5]

1. Mant TGK. Clinical studies with dimercaptopropane sulphonate in mercury poisoning. *Hum Toxicol* 1985; **4:** 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; **218:** 74–83.
3. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13:** 11–16.
4. Pai P, *et al.* Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulphonate [sic]) and continuous haemofiltration. *Nephrol Dial Transplant* 2000; **15:** 1889–90.
5. Dargan PI, *et al.* Case report: severe mercuric sulphate poisoning treated with 2,3-dimercaptopropane-1-sulphonate and haemodiafiltration. *Crit Care* 2003; **7:** R1–R6.

Wilson's disease. Unithiol 200 mg twice daily[1] was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease (p.1459) after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride. Unithiol was started in 2 similar patients[1] but both withdrew from treatment, one because of fever and a fall in leucocyte count after a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *BMJ* 1985; **290:** 673–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dimaval; ***Ger.:*** Dimaval; Mercuval.

Colouring Agents

Colouring agents have long been used in foods and cosmetics in an attempt to improve the appearance of the product or subject. They are also used in medicinal preparations for several reasons. These include improving their acceptability to patients, giving drug formulations a distinctive appearance to help identification and prevent counterfeiting, and increasing the stability of light-sensitive drugs. This chapter describes colouring agents used in medicines and some used in foods, cosmetics, and some medical devices including contact lenses. Most countries restrict the nature and extent of colouring agents used for such purposes. Matters of concern that have received considerable publicity include sensitivity reactions (see Tartrazine, p.1473) and hyperactive behaviour in children (see below).

Colouring agents can be broadly categorised into synthetic dyes and into natural agents (such as canthaxanthin, caramel, carmine, chlorophyll, cochineal, saffron, and turmeric, all of which are described in this chapter). Other compounds that may be used as cosmetic colours or food colours (and which are themselves natural pigments of foodstuffs) are anthocyanins (E163) and carotenoids. In this latter group are included bixin and norbixin which are obtained from annatto, capsanthin (E160c) which is an extract of paprika, carotenes (E160a) (see Betacarotene, p.1930), lycopene (E160d), beta-apo-8′-carotenal (E160e), and the ethyl ester of beta-apo-8′-carotenoic acid (E160f); lutein (E161b), like canthaxanthin, can be classified either as a carotenoid or as a xanthophyll.

Other agents described elsewhere in *Martindale* that may be used as food colours include aluminium (p.2254), gold (p.2316), indigo carmine (p.2324), patent blue V (p.2363), riboflavin (p.1977), silver (p.2387), and titanium dioxide (p.1617).

Hyperactivity. The role of foods and food additives in hyperactive behaviour (p.2148) has been debated for many years.

A meta-analysis[1] sought to evaluate whether artificial food colours (including carmoisine, sunset yellow, and tartrazine) contribute to the symptomatology of childhood hyperactivity in children already diagnosed with hyperactive syndromes. For the primary analysis only double-blind placebo-controlled trials were evaluated. Overall, the results supported the hypothesis that such food colours promote hyperactivity in hyperactive children as measured on behavioural ratings. However, caution was advised about making any clinical recommendations. The restrictions needed for a colour-free diet may be too much of a burden on the children and their families. Also, there is a need to find out more about the biology of artificial food colours and to ascertain whether responses depend on an allergic or pharmacological mechanism. A further study[2] in a more general population of children also found that mixtures of food additives including food colourings were associated with an increase in hyperactivity, although the European Food Safety Authority considered[3] that the results of the study were not conclusive enough to necessitate a change in the approved daily intakes for the additives involved.

1. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004; **25:** 423–34.
2. McCann D, *et al.* Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; **370:** 1560–7. Correction. *ibid.*; 1542.
3. European Food Safety Authority. Assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children's behaviour: scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). Available at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_ej660_McCann_study_sum_en.pdf (accessed 04/07/08)

Allura Red AC

CI Food Red 17; Colour Index No. 16035; E129; FD & C Red No. 40; Rojo allura AC. Disodium 6-hydroxy-5-(6-methoxy-4-sulphonato-*m*-tolylazo)naphthalene-2-sulphonate.

Красный Очарователь

$C_{18}H_{14}N_2Na_2O_8S_2$ = 496.4.

CAS — 25956-17-6.

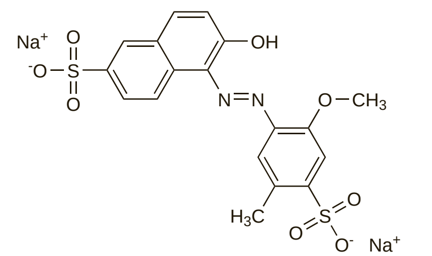

Profile

Allura red AC is used as a colouring agent in drugs, cosmetics, and foodstuffs.

Amaranth

Amarant; Amaranto; Bordeaux S; CI Acid Red 27; CI Food Red 9; Colour Index No. 16185; E123; formerly FD & C Red No. 2; Naphtol Rot S. It consists mainly of trisodium 3-hydroxy-4-(4-sulphonato-1-naphthylazo)naphthalene-2,7-disulphonate.

Амарант

$C_{20}H_{11}N_2Na_3O_{10}S_3$ = 604.5.

CAS — 915-67-3.

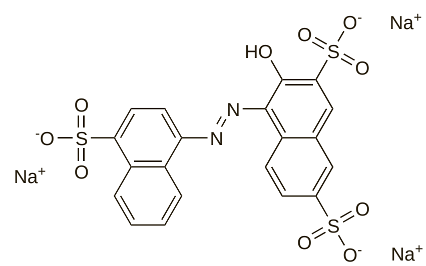

NOTE. The name amaranth is also used to refer to a number of species of plant in the genus *Amaranthus*, some of which have been used as a source of dyes.

Profile

Amaranth is used as a colouring agent in medicines, foodstuffs, and cosmetics.

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies, subsequent work failed to confirm these findings and in the UK amaranth is considered suitable for use as a food colour.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.

Annatto

CI Natural Orange 4; Colour Index No. 75120; E160(b).

Аннато

CAS — 1393-63-1.

Bixin

E160(b). Methyl (9-*cis*)-hydrogen-6,6′-diapo-ψ,ψ-carotenedioate.

Биксин

$C_{25}H_{30}O_4$ = 394.5.

CAS — 6983-79-5.

Norbixin

E160(b). 6,6′-Diapo-ψ,ψ-carotenedioic acid.

Норбиксин

$C_{24}H_{28}O_4$ = 380.5.

CAS — 542-40-5.

Profile

Annatto is a colouring agent extracted from the seeds of *Bixa orellana*. It and its derivatives, the carotenoids bixin and norbixin, are used to colour foods, drugs, and cosmetics.

Bixin and norbixin exist in both *cis-* and *trans-* forms, with the *cis-* forms being the major colouring components.

Hypersensitivity. Hypersensitivity reactions to annatto have been reported rarely. A single case of anaphylaxis has been reported in a male patient, after consumption of cereal coloured with annatto.[1] Sensitivity was confirmed with a skin test. The design of several oral challenge studies using annatto has been criticised in a literature review.[2] However, the authors of the review acknowledge that annatto may cause rare but severe reactions in some patients, and may worsen the symptoms of patients with recurrent urticaria.

1. Nish WA *et al.* Anaphylaxis to annatto dye: a case report. *Ann Allergy* 1991; **66:** 129–31.
2. Lucas CD *et al.* The role of natural color additives in food allergy. *Adv Food Nutr Res* 2001; **43:** 195–216.

Beetroot Red

Beet Red; E162; Rojo de remolacha.

Свекольный Красный

CAS — 7659-95-2 (betanine).

Profile

Beetroot red is obtained from the roots of red beets, *Beta vulgaris* var. *rubra* (Chenopodiaceae). The main colouring principle consists of betacyanins of which betanine is the main constituent. Beetroot red is used as a colouring agent for drugs, foodstuffs, and cosmetics.

Black PN

Brilliant Black BN; Brilliant Black PN; CI Food Black 1; Colour Index No. 28440; E151; Negro brillante BN; Negro PN; Noir Brillant BN. It consists mainly of tetrasodium 4-acetamido-5-hydroxy-6-[7-sulphonato-4-(4-sulphonatophenylazo)-1-naphthylazo]naphthalene-1,7-disulphonate.

Бриллиантовый Чёрный PN; Чёрный Блестящий PN

$C_{28}H_{17}N_5Na_4O_{14}S_4$ = 867.7.

CAS — 2519-30-4.

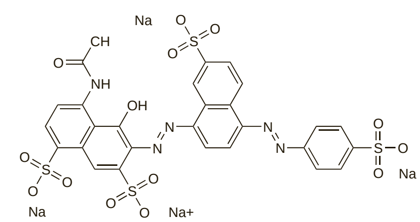

Profile

Black PN is used as a colouring agent in medicines, cosmetics, and foods.

Bordeaux B

Azorubrum; Burdeos B; CI Acid Red 17; Colour Index No. 16180. It consists mainly of disodium 3-hydroxy-4-(1-naphthylazo)naphthalene-2,7-disulphonate.

Кислотный Бордо

$C_{20}H_{12}N_2Na_2O_7S_2$ = 502.4.

CAS — 5858-33-3.

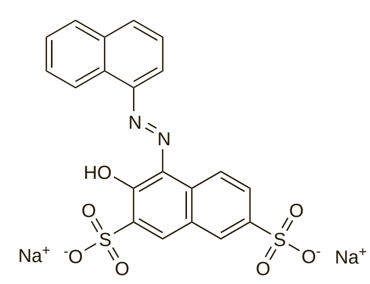

Profile

Bordeaux B was formerly used as a colouring agent for medicines and foods but has been replaced by other colours.

Brilliant Blue FCF

Azul brillante FCF; Blue EGS; CI Acid Blue 9; CI Food Blue 2; Colour Index No. 42090; E133; FD & C Blue No. 1; Patent Blue AC. Disodium 4′,4″-bis(*N*-ethyl-3-sulphonatobenzylamino)triphenylmethylium-2-sulphonate.

Бриллиантовый Голубой FCF; Синий Блестящий FCF

$C_{37}H_{34}N_2Na_2O_9S_3$ = 792.8.

CAS — 3844-45-9.

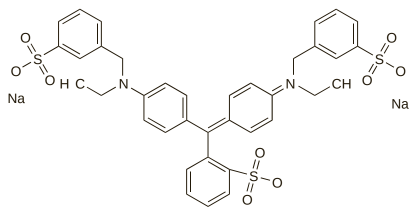

Profile

Brilliant blue FCF is used as a colouring agent in medicines, cosmetics, and foodstuffs. The parent compound, brilliant blue, is under investigation as a stain in ophthalmology.

Enteral feeds. Blue colourings such as brilliant blue FCF have been added to enteral feeds to aid the detection of pulmonary aspiration but such use has been associated with toxic effects. Blue discoloration of the skin, initially attributed to cyanosis, has been reported[1] in a child who received a large quantity of brilliant blue FCF as a colouring in an enteral feed. Abnormal systemic absorption of the dye has also been reported[2] in 2 critically ill patients, both of whom subsequently died. As of September 2003 the FDA was aware of 20 cases of blue discoloration of body fluids and skin associated with the use of blue dyes, including 12 fatalities.[3] Most cases occurred in patients with a history of sepsis, suggesting that altered intestinal permeability could be a factor.

1. Zillich AJ, *et al.* Skin discoloration with blue food colouring. *Ann Pharmacother* 2000; **34:** 868–70.
2. Lucarelli MR, *et al.* Toxicity of Food Drug and Cosmetic Blue No. 1 dye in critically ill patients. *Chest* 2004; **125:** 793–5.
3. Anonymous. Blue discoloration and death from FD&C Blue No. 1. *WHO Drug Inf* 2003; **17:** 239–40.

Brown FK

Chocolate Brown FK; CI Food Brown 1; E154; Marrón FK. A mixture of 6 azo dyes: sodium 2′,4′-diaminoazobenzene-4-sulphonate; sodium 2′,4′-diamino-5′-methylazobenzene-4-sulphonate; disodium 4,4′-(4,6-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4′-(2,4-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4′-(2,4-diamino-5-methyl-1,3-phenylenebisazo) dibenzenesulphonate; trisodium 4,4′,4″-(2,4-diaminobenzene-1,3,5-triazo)tribenzenesulphonate.

Коричневый FK

CAS — 8062-14-4.

Profile

Brown FK is used as a colouring agent for foodstuffs.

Brown HT

Chocolate Brown HT; CI Food Brown 3; Colour Index No. 20285; E155; Marrón HT. Disodium 4,4′-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylenebisazo)di(naphthalene-1-sulphonate).

Коричневый HT

$C_{27}H_{18}N_4Na_2O_9S_2$ = 652.6.

CAS — 4553-89-3.

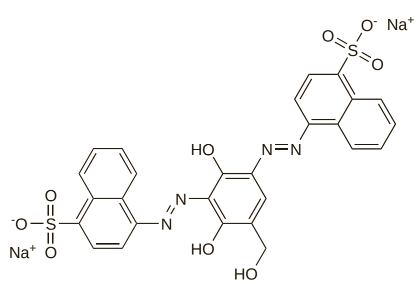

Profile

Brown HT is used as a colouring agent for drugs and foodstuffs.

Canthaxanthin

Cantaxantina; Canthaxanthinum; CI Food Orange 8; Colour Index No. 40850; E161(g); Kantaksantiini; Kantaxantin. β,β-Carotene-4,4′-dione.

Кантаксантин

$C_{40}H_{52}O_2$ = 564.8.

CAS — 514-78-3.

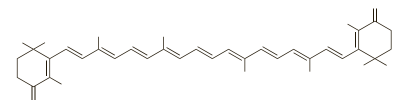

Profile

Canthaxanthin is a carotenoid but unlike betacarotene or β-apo-8′-carotenal it has no vitamin A activity. It has selected uses as a food colouring and is given to salmon, trout, and poultry to colour their flesh, and to laying hens to colour the yolks of their eggs. It is also used to colour drugs and cosmetics.

Canthaxanthin has also been given orally to produce an artificial suntan, and as an adjunct to betacarotene in the management of erythropoietic protoporphyria (see Porphyrias under Haem Derivatives, p.1448). Such use has led to retinal deposits and in some cases to impairment of vision.

Adverse effects. Canthaxanthin has been associated with retinal changes involving accumulation of bright yellow particles around the macula ('gold speck' maculopathy), and alterations in eye function and visual deterioration have occurred.[1,2] Although these reports have related to oral use either for the production of an artificial tan by means of pigment deposition in the skin or for the medical treatment of erythropoietic protoporphyria, there has been concern about the use of canthaxanthin as a food colouring, and it was suggested that it should be restricted to use as a feed additive for farmed salmon and trout in order to produce a coloration of the fish flesh.[1] The results of long-term toxicity studies in *animals* have led to concern[2] about the potential for hepatotoxicity. However, subsequent studies failed to confirm hepatotoxicity in humans and it is now allowed as a food colouring,[3] although its uses are restricted in some countries.

There has also been a report of fatal aplastic anaemia in a patient who took canthaxanthin in order to produce an artificial tan.[4]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 25/05/07)
3. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 859* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_859.pdf (accessed 25/05/07)
4. Bluhm R, *et al.* Aplastic anemia associated with canthaxanthin ingested for 'tanning' purposes. *JAMA* 1990; **264:** 1141–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bronzearte.

Multi-ingredient: ***Arg.:*** Bronsul; Sol Bronce Vital.

Caramel

Burnt Sugar; Caramelo; Sacch. Ust.; Saccharum Ustum.

Жжёный Сахар; Сахарный Колер

CAS — 8028-89-5.

Pharmacopoeias. In *USNF.*

USNF 26 (Caramel). A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali or of alkaline carbonate or a trace of mineral acid being added while heating. It is a thick, dark brown liquid, having the characteristic odour of burnt sugar, and a pleasant bitter taste. One part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish-orange colour. The colour of this solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. When spread as a thin layer on a glass plate, it appears homogeneous, reddish-brown, and transparent. Miscible with water; immiscible with ether, with chloroform, with acetone, with petroleum spirit, and with benzene; soluble in dilute alcohol up to 55%. Store in airtight containers.

Profile

Caramels are used in foods, drugs, and cosmetics to produce pale yellow to dark brown colours. They have no calorific value. They are complex mixtures of compounds prepared by heating carbohydrates (food-grade sweeteners consisting of glucose, fructose, or polymers of these) either alone or in the presence of acids or alkalis (food-grade citric or sulfuric acids or calcium, potassium, or sodium hydroxides, or mixtures of these). The caramels can be classified according to the reactants used in the manufacturing process:

Class I (E150a, plain caramel, spirit caramel, or caustic caramel); no ammonium or sulfite compounds are used.

Class II (E150b or caustic sulfite caramel); sulfite compounds used but not ammonium compounds.

Class III (E150c, ammonia caramel, or beer caramel); ammonium compounds used but not sulfite compounds

Class IV (E150d, sulfite ammonia caramel, or soft-drink caramel); both ammonium and sulfite compounds used.

Some caramels also have flavouring properties.

Carbazole Violet

Colour Index No. 51319; Pigment Violet 23. 8,18-Dichloro-5,15-diethyl-5,15-dihydrodiindolo(3,2-*b*:3′,2′-*m*)triphenodioxazine.

Фиолетовый Карбазол

$C_{34}H_{22}Cl_2N_4O_2$ = 589.5.

CAS — 6358-30-1.

Profile

Carbazole violet is a colouring agent used in cosmetics and contact lenses.

Carmine

Carmín; CI Natural Red 4; Cochineal Carmine; Colour Index No. 75470; E120.

Кармин

CAS — 1390-65-4.

Profile

Carmine is an aluminium lake of the colouring matter of cochineal (p.1471). It contains carminic acid, an anthraquinone glycoside. Unless precautions are taken during manufacture and transport to prevent contamination, carmine may be infected with salmonella micro-organisms.

Carmine and some of its salts are used as colouring agents in medicines, foodstuffs, and cosmetics.

Carmine passes through the gastrointestinal tract unchanged and has been used as a faecal 'marker'.

Hypersensitivity. By February 2004 the FDA was aware of 35 cases of hypersensitivity to carmine, carminic acid, or cochineal extract published in the scientific and medical literature and/or reported directly to the FDA. Hypersensitivity reactions to carmine, carminic acid, or cochineal extract included contact dermatitis (4 cases), urticaria/angioedema (9), occupational asthma (10), and systemic anaphylaxis (12). In more than half of these reports, there was evidence of an IgE-mediated diagnostic response. The adverse effects included allergic reactions to foods containing carmine and cochineal extract, occupational asthma from exposure to carmine, and allergic reactions to topically applied cosmetics containing carmine.

The FDA concluded that carmine and cochineal extract may cause potentially severe allergic responses and proposed that food and cosmetic labelling be enhanced; a declaration of inactive ingredients in drugs was already in force.[1]

1. *Fed Regist* 2006; **71:** 4839–51. Available at: http://www.cfsan.fda.gov/~lrd/fr060130.html (accessed 16/11/06)

Carmoisine

Azorrubina; Azorubine; Carmoisina; CI Food Red 3; Colour Index No. 14720; E122. It consists mainly of disodium 4-hydroxy-3-(4-sulphonato-1-naphthylazo)naphthalene-1-sulphonate.

Кармуазин

$C_{20}H_{12}N_2Na_2O_7S_2$ = 502.4.

CAS — 3567-69-9.

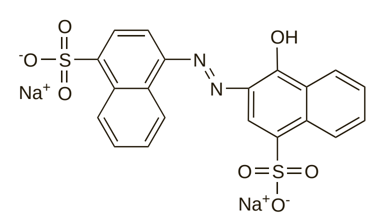

Profile

Carmoisine is used as a colouring agent in foods, medicines, and cosmetics. It has also been investigated clinically as a stain, to aid visualisation of malignant neoplasms of the skin during surgery.

Chlorophyll

CI Natural Green 3; Clorofila; Colour Index No. 75810; E140 (chlorophylls or chlorophyllins).

Хлорофилл

CAS — 479-61-8 (chlorophyll a); 519-62-0 (chlorophyll b).

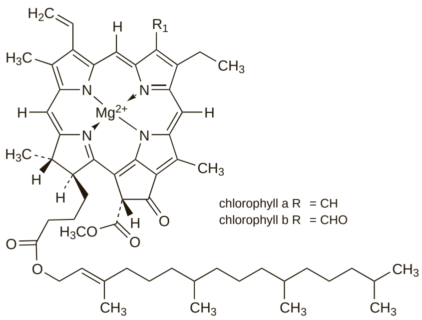

Chlorophyllin Copper Complex Sodium

Clorofilina cúprica, complejo sódico de.

Медного Комплекса Хлорофиллина Натриевая Соль

Pharmacopoeias. In *US.*

USP 31 (Chlorophyllin Copper Complex Sodium). It contains sodium salts of copper-chelated chlorophyll derivatives, but no artificial colouring. Store in airtight containers. Protect from light.

Profile

Chlorophyll is a green photosynthetic pigment found in plants, algae, and cyanobacteria (blue-green algae). There are four closely related forms of chlorophyll. Chlorophyll a ($C_{55}H_{72}MgN_4O_5$ = 893.5) and chlorophyll b ($C_{55}H_{70}MgN_4O_6$ = 907.5) are found in plants and some types of algae; chlorophyll c, further subdivided into chlorophyll c1 ($C_{35}H_{30}MgN_4O_5$ = 610.9) and chlorophyll c2 ($C_{35}H_{28}MgN_4O_5$ = 608.9), is found in some types of algae; and chlorophyll d ($C_{54}H_{70}MgN_4O_6$ = 895.5) is found in some types of algae and in cyanobacteria.

Oil-soluble chlorophyll derivatives. Replacement of the magnesium atom in the chlorophylls by 2 hydrogen atoms using dilute mineral acids produces olive-green water-insoluble phaeophytins. Copper phaeophytins (sometimes called copper chlorophyll complex; E141) can be formed; these are more stable to acids and to light than the chlorophylls.

Water-soluble chlorophyll derivatives. When the chlorophylls are hydrolysed with alkali, phytyl alcohol and methyl alcohol are split off and green water-soluble chlorophyllins are formed as the potassium or sodium salts. Similar water-soluble compounds can be prepared in which the magnesium is replaced by copper to give copper chlorophyllin complex (E141).

Chlorophylls and chlorophyllins, as well as the copper complexes of these compounds, are used mainly as colouring agents, in foods, medicines, and cosmetics.

Chlorophyll is used clinically, as an external application in the treatment of wounds and ulcers, and as a mouthwash. There is no clear evidence that it accelerates healing but it is considered to have a deodorant action. Chlorophyllin and copper chlorophyllin complex are used similarly. Chlorophyll is also used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Chloresium; Derifil; Pals.

Multi-ingredient: ***Arg.:*** Fanaletas; Notoxin; Palan†; ***Braz.:*** Broncopinol†; Emoform Clorofila; Eucaliptan†; Mentozil†; Salimetin†; ***Ger.:*** Chlorophyl liquid "Schuh"†; Chlorophyllin Salbe "Schuh"†; Ginseng-Complex "Schuh"†; Stomasal Med†; ***Hong Kong:*** Epilon; ***Indon.:*** Methaphyllin; ***Spain:*** Odontocromil c Sulfamida†; Vitavox Pastillas†; ***Thai.:*** Sanaco†; ***UK:*** Chlorophyll; ***USA:*** AllanEnzyme; AllanfillEnzyme; Fresh-N-Free; Gladase-C; Panafil; Prophyllin; Wound Cleanser; Ziox.

CI Solvent Yellow 18

CI Food Yellow 12; Colour Index No. 12740. 4-[(2,4-Dimethylphenyl)azo]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one.

$C_{18}H_{18}N_4O$ = 306.4.

CAS — 6407-78-9.

Profile

CI Solvent Yellow 18 is a colouring agent used in contact lenses.

CI Vat Orange 1

Colour Index No. 59105. Dibromo-dibenzo (b,def) chrysene-7,14-dione.

CI Кубовый Оранжевый 1

$C_{24}H_{10}Br_2O_2$ = 490.1.
CAS — 1324-11-4.

Profile

CI Vat Orange 1 is a colouring agent used in contact lenses.

Citranaxanthin

Citranaxantina; Elbli.

$C_{33}H_{44}O$ = 456.7.
CAS — 3604-90-8.

Profile

Citranaxanthin is a colouring agent used in animal feeds, to colour the fat of poultry and the egg-yolks of laying hens. It has vitamin A activity.

Citrus Red 2

CI Solvent Red 80; Colour Index No. 12156. 1-(2,5-Dimethoxyphenylazo)-2-naphthol.

Цитрусовый Красный 2

$C_{18}H_{16}N_2O_3$ = 308.3.
CAS — 6358-53-8.

Profile

Citrus Red 2 is a colouring agent used in foods.

Cochineal

CI Natural Red 4; Coccionella; Coccus; Coccus Cacti; Cochinilla; Colour Index No. 75470; E120.

Кошениль

CAS — 1343-78-8.

Pharmacopoeias. In *Br.*

BP 2008 (Cochineal). The dried female insect, *Dactylopius coccus* containing eggs and larvae. It has a characteristic odour. It complies with a test for contamination with *Escherichia coli* and salmonellae.

Profile

Cochineal, which is a source of carmine, is used as a red colouring agent in food, medicines, and cosmetics.

There have been reports of sensitivity reactions including anaphylaxis, after use of products containing cochineal (see Hypersensitivity in Carmine, p.1470).

Homoeopathy. Cochineal has been used in homoeopathic medicines under the following names: Coccus cacti; Dactylopius coccus; Coc. c.

Curcumin

Colour Index No. 75300; Curcumina; E100; Kurkum; Kurkumina; Turmeric Yellow. 1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione.

Куркумин

$C_{21}H_{20}O_6$ = 368.4.
CAS — 458-37-7.

Profile

Curcumin is the main colouring component of turmeric (p.1473). It is used as a colouring agent for drugs, foodstuffs, and cosmetics. It is also thought to be responsible for many of the pharmacological properties for which turmeric is under investigation (see p.1473).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***India:*** Well-Beeing†; ***Ital.:*** Depatox.

Eosin

CI Acid Red 87; Colour Index No. 45380; D & C Red No. 22; Eosin Y; Eosina; Éosine Disodique. The disodium salt of 2′,4′,5′,7′-tetrabromofluorescein .

Эозин

$C_{20}H_6Br_4Na_2O_5$ = 691.9.
CAS — 548-26-5; 17372-87-1.
ATC — D08AX02.
ATC Vet — QD08AX02.

Pharmacopoeias. In *Fr.*

Profile

Eosin has been incorporated in solution-tablets to give a distinctive colour to solutions prepared from them. It is also used in cosmetics.

Eosin has been used as a topical antiseptic in nappy rash, burns and other skin conditions, although other drugs are usually preferred.

Adverse effects. Contact dermatitis to eosin was seen relatively frequently between the 1920s and 1940s when it was a common colour in lipsticks. Fewer reports of hypersensitivity have occurred since then: changing fashions in cosmetic colours have reduced use of eosin and, if used, a purer grade and lower concentrations are now usually employed. However, cases of dermatitis after topical application of antiseptic preparations containing eosin were noted in the 1980s and 1990s. One report[1] suggested that an impurity might be responsible but another[2] implicated eosin itself after patch tests were performed with various products and pure tetrabromofluorescein.

1. Tomb RR. Allergic contact dermatitis from eosin. *Contact Dermatitis* 1991; **24:** 27–9.
2. Koch P, *et al.* Allergic contact dermatitis from purified eosin. *Contact Dermatitis* 1995; **32:** 92–5.

Erythrosine

CI Food Red 14; Colour Index No. 45430; E127; Eritrosin BS; Eritrosina; Erythrosine BS; Erythrosine Sodium; FD & C Red No. 3. The monohydrate of the disodium salt of 2′,4′,5′,7′-tetraiodofluorescein .

Эритрозин

$C_{20}H_6I_4Na_2O_5,H_2O$ = 897.9.
CAS — 568-63-8 (anhydrous erythrosine sodium); 16423-68-0 (anhydrous erythrosine sodium); 49746-10-3 (erythrosine sodium monohydrate).

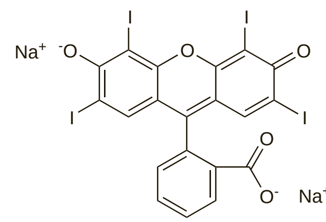

(anhydrous erythrosine sodium)

Profile

Erythrosine is used as a colouring agent for medicines, foods, and cosmetics. It is also used as a disclosing agent for plaque on teeth.

◊ Although early *animal* studies had indicated that erythrosine might have an adverse effect on the thyroid gland, a review[1] of the evidence and later studies, suggested that erythrosine was not genotoxic or mutagenic and was suitable for use as a food colour. Similarly, no evidence was found to support restricting its use in pharmaceutical products.[2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. European Commission. Opinion on toxicological data on colouring agents for medicinal products: erythrosin, adopted by the Scientific Committee on Medicinal Products and Medical Devices on 21 October 1998. Available at: http://ec.europa.eu/health/ph_risk/committees/scmp/docshtml/scmp_out08_en.htm (accessed 04/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Revelplac; ***Austral.:*** Disclo-Gel; Disclo-Tabs; ***UK:*** Ceplac.
Multi-ingredient: ***Arg.:*** Revelplac 2001.

Ferric Oxide

Demir Oksitler; E172 (iron oxides or hydroxides); Hierro, óxido de.

Оксид Железа

CAS — 51274-00-1; 1309-37-1.

Pharmacopoeias. *Chin.* includes red, black, brown, purple, and yellow ferric oxide. *It.* includes both red and yellow ferric oxide. *USNF* allows the basic colours of red or yellow ferric oxide or mixtures of these.

USNF 26 (Ferric Oxide). A powder exhibiting two basic colours (red and yellow), or other shades produced on blending the basic colours. Insoluble in water and in organic solvents; dissolves in hydrochloric acid upon warming, a small amount of insoluble residue usually remaining.

Profile

Ferric oxide is used for colouring medicines, contact lenses, cosmetics, and foodstuffs.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Port.:*** Filter Oil Free†.

Green S

Acid Brilliant Green BS; Acid Green S; CI Food Green 4; Colour Index No. 44090; E142; Lissamine Green; Verde Brillante BS; Verde Lisamina; Verde S; Wool Green B; Yeşil S. Sodium 1-[4-dimethylamino-α-(4-dimethyliminiocyclohexa-2,5-dienylidene)benzyl]-2-hydroxynaphthalene-3,6-disulphonate.

Зелёный S

$C_{27}H_{25}N_2NaO_7S_2 = 576.6.$

CAS — 3087-16-9.

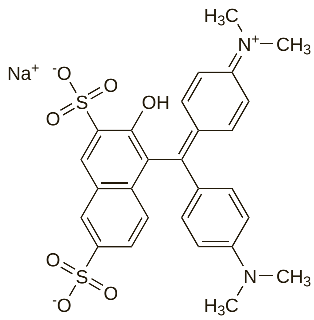

Profile

Green S is used as a colouring agent in medicines, cosmetics, and foodstuffs.

◊ Studies in *animals* indicated that there is some absorption of green S and caecal enlargement but it was considered that there is a very large margin of safety between the highest estimated human intake of green S of 130 micrograms daily and the level at which changes were seen in *animal* studies (500 mg/kg daily). It was recommended that the use of green S in food is acceptable.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.

Logwood

CI Natural Black 1; Colour Index No. 75290.

Кампешевое Дерево (*Haematoxylon campechianum*)

CAS — 8005-33-2.

Profile

Logwood extract is a colouring agent derived from the logwood tree, *Haematoxylum (Haematoxylon) campechianum*. The logwood extract haematoxylin is used mainly as a histological stain. It is also used for colouring non-absorbable sutures.

Orange B

CI Acid Orange 137; Colour Index No. 19235. The disodium salt of 1-(4-Sulfophenyl)-3-ethylcarboxyl-4-(4-sulfonaphthylazo)-5-hydroxypyrazole.

Оранжевый B

$C_{22}H_{16}N_4Na_2O_9S_2 = 590.5.$

CAS — 15139-76-1.

Profile

Orange B is a colouring agent used in foods.

Pigment Rubine

Brilliant Carmine 6B; Carmine 6B; CI Pigment Red 57; Colour Index No. 15850; E180; FD & C Red No. 7; Lithol Rubine BK; Litholrubine BK; Litholrubintoner BKL; Litolrubina BK; Permanent Rubin L6B; Pigmento rubí; Rubinpigment. Calcium 3-hydroxy-4-(4-methyl-2-sulfonatophenylazo)-2-naphthalene carboxylate.

Рубиновый Литол BK

$C_{18}H_{12}CaN_2O_6S = 424.4.$

CAS — 5281-04-9.

Profile

Pigment rubine is used as a colouring agent for foodstuffs and cosmetics.

Ponceau 4R

Brilliant Ponceau 4RC; Brilliant Scarlet; CI Food Red 7; Coccine Nouvelle; Cochineal Red A; Colour Index No. 16255; E124; Punzó 4R; Rojo de cochinilla A; Rouge Cochenille A. Trisodium 7-hydroxy-8-(4-sulphonato-1-naphthylazo)naphthalene-1,3-disulphonate.

Понсо 4R; Пунцовый 4R

$C_{20}H_{11}N_2Na_3O_{10}S_3 = 604.5.$

CAS — 2611-82-7.

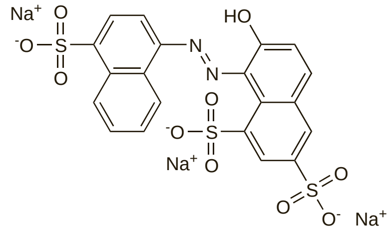

Profile

Ponceau 4R is used as a colouring agent in medicines, cosmetics, and foods. Sensitivity reactions have been reported.

Quinoline Yellow

Amarillo de quinoleína; Canary Yellow; CI Acid Yellow 3; CI Food Yellow 13; Colour Index No. 47005; E104; Jaune de Quinoléine; Kinolin Sarisi; Tartrazin. It consists essentially of sodium salts of a mixture of disulfonates (principally), monosulfonates, and trisulfonates of 2-(2-quinolyl)-1,3-indandione or a mixture containing about two-thirds of 2-(2-quinolyl)-1,3-indandione and one-third of 2-[2-(6-methyl-quinolyl)]1,3-indandione.

Жёлтый Хинолиновый

CAS — 8004-92-0 (unmethylated disulfonic acids).

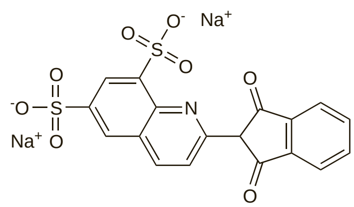

(disulfonate)

NOTE. D & C yellow No. 10 has been used as a synonym for quinoline yellow, but describes a mixture consisting mainly of a monosulfonate.

Profile

Quinoline yellow is used as a colouring agent in medicines, cosmetics, and foodstuffs.

Hypersensitivity. A severe urticarial reaction[1] in a patient has been attributed to quinoline yellow.

1. Bell T. Colourants and drug reactions. *Lancet* 1991; **338:** 55–6.

Raspberry

Framboise; Frambuesa; Fructus Rubi Idaei; Himbeer.

Малина

CAS — 8027-46-1.

Profile

Raspberry, the fresh ripe fruit of *Rubus idaeus* (Rosaceae), is used as a colouring and flavouring agent in medicines and foodstuffs.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** IgeE.

Red Cherry

Cerasus; Cerise Rouge; Rojo cereza; Sour Cherry.

Вишня Кислая

Pharmacopoeias. *USNF* includes cherry juice.
Fr. includes, under the title Griottier, cherry stalks from either the red (sour) cherry, *Prunus cerasus*, or from the sweet cherry, *P. avium*.
USNF 26 (Cherry Juice). The liquid expressed from the fresh ripe fruit of *Prunus cerasus* (Rosaceae). It contains not less than 1.0% of malic acid. pH 3.0 to 4.0. Store in airtight containers. Protect from light.

Profile

Red cherry is used as a colouring and flavouring agent.

Inflammation. A small placebo-controlled crossover study[1] indicated that some symptoms of muscle damage induced by eccentric exercise (pain and strength loss) could be reduced by drinking cherry juice. It was suggested that anthocyanins and flavonoids present in tart cherry juice might have anti-inflammatory properties.

1. Connolly DAJ, *et al.* Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br J Sports Med* 2006; **40:** 679–83.

Preparations

USNF 26: Cherry Syrup.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Vitamina C-Complex; ***Fr.:*** Evacrine; ***Switz.:*** Drosana Resiston avec vitamine C.

Red 2G

Acid Red 1; Azogeranina; Azogeranine; CI Food Red 10; Colour Index No. 18050; E128; Ext. D & C Red No. 11; Geranine 2G; Rojo 2G. Disodium 5-acetamido-4-hydroxy-3-phenylazonaphthalene-2,7-disulphonate.

Красный 2G

$C_{18}H_{13}N_3Na_2O_8S_2 = 509.4.$

CAS — 3734-67-6.

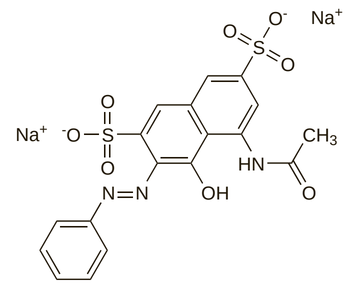

Profile

Red 2G may be used as a colouring agent in cosmetics. It has also been employed as a food colour but this use was suspended in the EU in 2007 on the basis that its main metabolite, aniline, has both genotoxic and carcinogenic effects in *rodents*.

Red-Poppy Petal

Aguonų birulių žiedai; Coquelicot; Coquelicot, pétales de; Corn Poppy Petal; Klatschrose; Kornvallmo, kronblad; Květ máku vlčího; Papaveris rhoeados flos; Pétalos de amapola; Rhoead. Pet.; Rhoeados Petalum; Unikonkukan terälehdet.

Мака Самосейки Лепестки

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Red Poppy Petals). The dried, whole or fragmented petals of *Papaver rhoeas*.

Profile

Red-poppy petal has been used as a colouring agent. It is also included in several herbal preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Nocvalene†; ***Ital.:*** Altuss; Gastrotuss; ***Switz.:*** Baume†; Pectosan N†; Pommade au Baume; Tisane pectorale et antitussive.

Red-Rose Petal

Fleur de Rose; Flos Rosae; Pétalos de rosa; Red Rose Petals; Ros. Pet.; Rosae Gallicae Petala; Rosae Petalum; Rose Rouge; Rosenblüte.

Лепестки Розы

Pharmacopoeias. In *Fr.*

Profile

Red-rose petal, the petals of the red or Provins rose, *Rosa gallica* (Rosaceae), has been used as a colouring agent and for its mild astringent properties.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Expectosan Hierbas y Miel; ***Fr.:*** Ophtalmine; ***Spain:*** Natusor Infenol†.

Saffron

Açafrão; Azafrán; CI Natural Yellow 6; Colour Index No. 75100; Croci stigma; Crocus; Estigmas de Azafrán; French Saffron; Keshar; Saffran; Safraan; Safran; Sahrami; Spanish Saffron.

Шафран

NOTE. Do not confuse with the meadow saffron (*Colchicum autumnale*), the source of colchicum (p.558) and colchicine (p.556), or Indian saffron, which is a name sometimes used for Turmeric (p.1473).

Pharmacopoeias. In *Chin.* and *Jpn.*
Eur. (see p.vii) includes Saffron for Homoeopathic Preparations.
Ph. Eur. 6.2 (Saffron for Homoeopathic Preparations). The dried stigmas of *Crocus sativus* usually joined by the base to a short style. It has a characteristic, aromatic odour. Protect from light.

Profile

Saffron consists of the dried stigmas and tops of the styles of *Crocus sativus* (Iridaceae), containing crocines, crocetins, and picrocrocine. Saffron is used to colour medicines, foods, and cosmetics. It is also used as a flavouring agent. Saffron has been included in preparations for teething pain. It is being investigated for the treatment of depression. There have been reports of poisoning with saffron, but in some cases these may have been due to meadow saffron, *Colchicum autumnale*.

Homoeopathy. Saffron has been used in homoeopathic medicines under the following names: Croci stigma; Crocus sativus; Crocus; Croc. s.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; ***Ger.:*** Infi-tract†; ***Rus.:*** Tentex (Тентекс); ***Spain:*** Dentol Topico; Dentomicin.

Sunset Yellow FCF

Amarillo anaranjado S; Amarillo ocaso FCF; CI Food Yellow 3; Colour Index No. 15985; Crelborange S; E110; FD & C Yellow No. 6; Günbatimi Sarisi FCF; Jaune Orangé S; Jaune Soleil; Orange Yellow S. Disodium 6-hydroxy-5-(4-sulphonatophenylazo)naphthalene-2-sulphonate.

Жёлтый Солнечный Закат

$C_{16}H_{10}N_2Na_2O_7S_2$ = 452.4.
CAS — 2783-94-0.

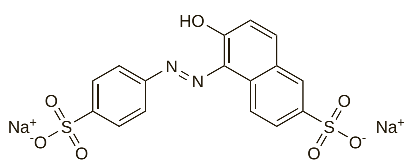

Profile

Sunset yellow FCF is used as a colouring agent in foods, medicines, and cosmetics. Sensitivity reactions have been reported.

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies subsequent work failed to confirm these findings and in the UK sunset yellow FCF is considered suitable for use as a food colour.[1]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London. HMSO, 1987.

Hypersensitivity. Hypersensitivity reactions including severe abdominal cramps[1] and Quincke's oedema[2] have been recorded in individual patients receiving medication that was coloured with sunset yellow FCF.

1. Gross PA, *et al.* Additive allergy: allergic gastroenteritis due to yellow dye #6. *Ann Intern Med* 1989; **111:** 87–8.
2. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338:** 393.

Tartrazine

CI Food Yellow 4; Colour Index No. 19140; E102; FD & C Yellow No. 5; Jaune Tartrique; Tartracina; Tartrazin.; Tartrazina; Tartrazol Yellow. It consists mainly of trisodium 5-hydroxy-1-(4-sulphonatophenyl)-4-(4-sulphonatophenylazo)pyrazole-3-carboxylate.

Тартразин

$C_{16}H_9N_4Na_3O_9S_2$ = 534.4.
CAS — 1934-21-0.

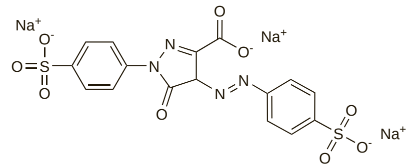

Profile

Tartrazine is used as a colouring agent in foods, cosmetics, and medicines. Some patients may experience sensitivity reactions.

Adverse Effects. There have been numerous reports of reactions to tartrazine including angioedema, asthma, urticaria, and anaphylactic shock. Some of the reports have dealt with cross-sensitivity, especially with aspirin, although the connection with aspirin has been questioned.[1] A suggested incidence[2] of tartrazine sensitivity is 1 in 10 000. The mechanism of the reactions may not necessarily be immunological.[3]

In considering the reports of tartrazine sensitivity or intolerance the Food Advisory Committee in the UK[1] reported that similar evidence of intolerance might well be obtained for a variety of natural food ingredients if as many studies were conducted on them as on tartrazine. The Committee considered that tartrazine posed no more problems than other colours or food ingredients and recommended that the continued use of tartrazine in food was acceptable. However, use of tartrazine in medicines appears to be diminishing.

A systematic review[4] noted that there was no evidence that tartrazine makes asthma worse, nor did avoiding it make asthma any better.

Tartrazine has often been implicated in the aggravation of hyperactive behaviour in children; for a discussion, see Hyperactivity, p.1469.

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. Anonymous. Tartrazine: a yellow hazard. *Drug Ther Bull* 1980; **18:** 53–5.
3. Murdoch RD, *et al.* Tartrazine induced histamine release in vivo in normal subjects. *J R Coll Physicians Lond* 1987; **21:** 257–61.
4. Ram FS, Ardern KD. Tartrazine exclusion for allergic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 18/04/07).

Turmeric

CI Natural Yellow 3; Cúrcuma; Indian Saffron.

Куркума; Турмерик
CAS — 458-37-7.

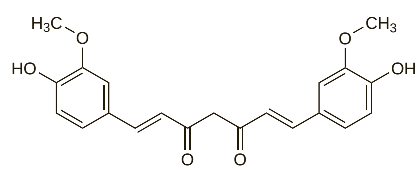

Pharmacopoeias. In *Chin.*

Profile

Turmeric, the dried rhizome of *Curcuma longa* (Zingiberaceae), is used principally as a constituent of curry powders and other condiments. Turmeric and its main ingredient curcumin (p.1471) are used as yellow colouring agents in foods. Turmeric has also been used as an ingredient of preparations indicated for biliary and gastrointestinal disorders and has been promoted as an anti-inflammatory. Turmeric is the source of turmeric oil. Turmeric is a commonly used ayurvedic medicine. Other species of *Curcuma* may be used similarly.

◊ Reviews of the properties of turmeric and curcumin.

1. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. *Planta Med* 1991; **57:** 1–7.
2. Grant KL, Schneider CD. Turmeric. *Am J Health-Syst Pharm* 2000; **57:** 1121–2.
3. Ringman JM, *et al.* A potential role of the curry spice curcumin in Alzheimer's disease. *Curr Alzheimer Res* 2005; **2:** 131–6.
4. Singh S, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem* 2006; **6:** 259–70.
5. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. *Adv Exp Med Biol* 2007; **595:** 105–25.
6. Sharma RA, *et al.* Pharmacokinetics and pharmacodynamics of curcumin. *Adv Exp Med Biol* 2007; **595:** 453–70.
7. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid Redox Signal* 2008; **10:** 511–45.
8. Hatcher H, *et al.* Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 2008; **65:** 1631–52.

Effects on the thyroid. There has been some concern about the safety of turmeric oleoresin, an extract of turmeric, after reports of adverse thyroid changes in *pigs*.[1,2]

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4.* London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 789* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 30/05/07)

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Turmerik; ***Ger.:*** Aristochol CC†; Choldestal†; Sergast†; ***Indon.:*** Rheumakur; ***Pol.:*** Solaren.

Multi-ingredient: ***Austral.:*** Arthriforte; Bioglan Joint Mobility; Extralife Arthri-Care; Extralife Liva-Care; Herbal Digestive Formula†; Vitanox; ***Austria:*** Apozema; Spasmo Claim; ***Canad.:*** Milk Thistle; ***Cz.:*** Cholagol; ***Fr.:*** Hepatoum; ***Ger.:*** Chol-Arbuz NF; Cholagogum F†; Cholagogum N†; Cholosom Phyto N; Digest-Merz†; Gallo Merz N†; Gastrol S†; Hepaticum-Medice H†; Horvilan N; Opobyl-phyto†; spasmo gallo sanol†; Ventracid N; ***Hong Kong:*** Hepatofalk Planta; ***Hung.:*** Cholagol; ***India:*** FN-T-Tus; ***Indon.:*** Aptivium Liver Support; Diapet; Entrodiar; Fitodiar; Heparviton; Heparviton NF; Hepasil; Hepatin; Lanagogum; Lecur; Procur Plus; Reliv; Tripid; ***Ital.:*** Cinarepa; Reumafort; ***Mex.:*** Ifuchol; Rodan; ***Pol.:*** Chelicur; Cholitol; ***Rus.:*** Cholagol (Холагол); Doktor Mom (Доктор Мом); Suprima-Broncho (Суприма-бронхо); ***S.Afr.:*** Lewensessens; ***Singapore:*** Artrex†; ***Switz.:*** Stago N†; ***UK:*** Arheumacare; BackOsamine.

Vegetable Carbon

Bitkisel Kömür; Carbon Black; Carbón vegetal; E153; Vegetable Black.

Уголь Растительный

NOTE. The name Carbon Black has also been used as a synonym for Channel Black, a colouring agent not used in food; care should be taken to avoid confusion between the two compounds.

Profile

Vegetable carbon, which consists essentially of finely divided carbon, is produced by the carbonisation of vegetable material such as peat or wood. It is used as a colouring agent for medicines, foodstuffs, and cosmetics.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Chile:*** Kordinol Compuesto†; ***Fr.:*** Stomargil.

Yellow 2G

107; Acid Light Yellow 2G; Acid Yellow 17; Amarillo 2G; CI Food Yellow 5; Colour Index No. 18965. Disodium 2,5-dichloro-4-[5-hydroxy-3-methyl-4-(4-sulphonatophenylazo)pyrazol-1-yl]benzenesulphonate.

Жёлтый 2G
$C_{16}H_{10}Cl_2N_4Na_2O_7S_2$ = 551.3.
CAS — 6359-98-4.

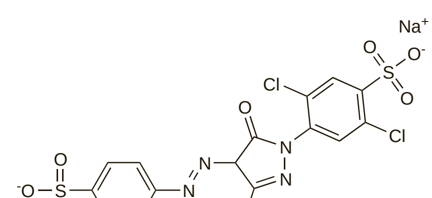

Profile

Yellow 2G is used as a colouring agent in cosmetics.

Contrast Media

Contrast media are widely used as adjuncts to diagnostic visualisation techniques such as radiography, magnetic resonance imaging, and ultrasound imaging. Although the techniques vary, they are all based on the fact that different tissues within the body have different physical properties, for example their ability to absorb radiation, or their density. These differences can be detected and used to produce images. Contrast media act in varying ways to accentuate the differences between tissues, and enhance the images obtained. There are different types of contrast medium, and choice depends upon the visualisation technique being used, as well as the properties of the individual media. The main groups described below are magnetic resonance contrast media, radiographic contrast media, and ultrasound contrast media.

Magnetic Resonance Contrast Media

Magnetic resonance imaging uses a combination of radiofrequency energy and magnetic fields to produce sectional images of the body. The technique is based on the property of hydrogen nuclei (protons) to absorb energy when aligned in a magnetic field; the energy is then released as the protons relax, generating a signal. Tissues differ in their proton content and factors affecting relaxation, and therefore produce different signals, which can be detected and analysed to produce an image.

Contrast media may be used to enhance magnetic resonance images. The media used are *paramagnetic* or *superparamagnetic* agents that develop magnetic properties when placed in a magnetic field. These properties affect the relaxation of adjacent protons during magnetic resonance imaging, and thus modify the signals produced. Paramagnetic compounds contain gadolinium or manganese and act by increasing relaxation and enhancing the signal. They are used as complexes or chelates to reduce their toxicity; gadopentetic acid is a typical gadolinium chelate, while mangafodipir is the only manganese chelate currently available. Superparamagnetic contrast media, such as ferucarbotran and ferumoxides, contain coated particles of iron compounds and act by interfering with the magnetic field to reduce the signal from proton relaxation.

◊ References.

1. Sands MJ, Levitin A. Basics of magnetic resonance imaging. *Semin Vasc Surg* 2004; **17:** 66–82.
2. Gibby WA. Basic principles of magnetic resonance imaging. *Neurosurg Clin N Am* 2005; **16:** 1–64.

Radiographic Contrast Media

Radiography (including X-ray imaging, computed tomography, and fluoroscopy) is based on the difference between tissues in the extent to which they absorb X-rays. This depends largely on the density of the tissue, and increasing the difference, or contrast, between specific tissues can enhance the images produced. In *positive contrast* imaging this is achieved by introducing a contrast medium into the area of interest to increase the density and enhance absorption of the X-rays. Alternatively, in *negative contrast* imaging, a gas (air, oxygen, or carbon dioxide) may be used to allow the X-rays to penetrate more easily. *Double contrast* uses both a gas and contrast medium together.

Radiographic contrast media are based on elements with high atomic numbers that absorb X-rays. The agents most commonly used are *iodinated organic compounds*, particularly tri-iodinated benzene compounds, and their degree of opacity or radiodensity is directly proportional to their iodine content. *Barium* is another element that absorbs X-rays, and barium sulfate has long been used in radiography. Other heavy atoms have been investigated but acute or chronic toxicity makes most of them unsuitable for use.

Iodinated contrast media may be classified as ionic or nonionic, and as monomeric or dimeric, and there are important differences between them that affect their use. The most important requirements for a contrast medium are that it absorbs X-rays efficiently, that it can be introduced into the area of the body to be visualised, and that it is safe. For iodinated contrast media, the radiodensity depends solely on the iodine concentration, whereas adverse effects are largely dependent on the osmolality of the solution (the number of particles present in a given weight of solution), with low-osmolality solutions being better tolerated. Distribution within the body depends on the pharmacokinetic and physical properties of the contrast medium.

Ionic monomeric media, such as the amidotrizoates, generally have a very high osmolality when given in concentrations suitable for radiographic visualisation, and therefore tend to be associated with a relatively high incidence of adverse effects. Osmolality may be reduced by using an *ionic dimeric* medium, such as adipiodone, which has twice the number of iodine atoms per molecule, or by using a *nonionic monomer*, such as iohexol, which does not dissociate into a cation and anion. *Nonionic dimeric* media, such as iodixanol, are also available and have the best ratio of radiodensity to osmolality; however, they also tend to be more viscous, and this may lead to problems with administration and distribution within the body.

◊ References.

1. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; **209:** 185–7.
2. Barrs TJ. X-rays and radiopaque drugs. *Am J Health-Syst Pharm* 2005; **62:** 2026–30.

Ultrasound Contrast Media

Ultrasound imaging uses the acoustic properties of different tissues to produce images. Reflection of sound waves (echo) occurs at the interface between tissues with different acoustic properties, particularly where this difference is large, and this can be detected and analysed to produce images. Contrast agents are generally used to enhance the echogenicity of blood and therefore to enable measurement of blood flow in different parts of the body.

Ultrasound contrast media increase echogenicity by providing an interface that reflects sound. Although usually referred to as ultrasound contrast media or *echocontrast* media, the increase in echogenicity may in fact reduce contrast between tissues, and *echoenhancers* may be a better term. Most ultrasound contrast media consist of microbubbles and provide a gas-liquid interface that reflects sound more effectively than blood alone, allowing blood flow to be more easily detected. The microbubbles may be air or another inert gas, such as perflutren or another perfluorocarbon, and may be either preformed or made at the time of injection. Agitated saline has been used as a simple ultrasound contrast medium, but is only suitable for cardiac imaging since the bubbles lack stability. Microbubbles of air formed during the dissolution of galactose are also used, and may be stabilised by addition of palmitic acid. Other stabilisers may be used, or the microbubbles may be encapsulated to increase the duration of their effect. Substances used for encapsulation include albumin (p.1052) and phospholipids; polycyanoacrylates have also been investigated.

◊ References.

1. Blomley MJK, *et al.* Microbubble contrast agents: a new era in ultrasound. *BMJ* 2001; **322:** 1222–5.
2. Liang H-D, Blomley MJK. The role of ultrasound in molecular imaging. *Br J Radiol* 2003; **76** (special issue): S140–S150.
3. Dijkmans PA, *et al.* Microbubbles and ultrasound: from diagnosis to therapy. *Eur J Echocardiogr* 2004; **5:** 245–56.
4. Dayton PA, Rychak JJ. Molecular ultrasound imaging using microbubble contrast agents. *Front Biosci* 2007; **12:** 5124–42.
5. Klibanov AL. Ultrasound molecular imaging with targeted microbubble contrast agents. *J Nucl Cardiol* 2007; **14:** 876–84.
6. Hauff P, *et al.* Ultrasound contrast agents for molecular imaging. *Handb Exp Pharmacol* 2008; 223–45.

Choice of Contrast Medium

Radiography, with and without the use of contrast, has been one of the most widely used diagnostic techniques and remains of great importance. However, concerns about the adverse effects of X-rays, and limitations of the images produced, have led to the increasing use of alternative methods such as ultrasound and magnetic resonance imaging. Choice of technique and use of contrast depends on the area to be visualised, the facilities available, and any patient characteristics affecting the likelihood of adverse effects, such as age and morbidity. Some imaging procedures and the factors affecting choice of technique and use of contrast, including adverse effects, are discussed below.

Uses of contrast media. For **urography** (visualisation of the kidneys and urinary tract) ultrasound is generally the most widely used technique, but radiography still has an important role. Contrast media that are excreted in the urine are used to enhance the images. Suitable media contain small, highly water-soluble molecules, with low protein-binding, that undergo rapid glomerular filtration and passage into the urinary tract. High plasma concentrations are needed to achieve adequate urinary concentrations for visualisation, so they are generally given intravenously. Most ionic iodinated media are suitable and the amidotrizoates have often been used, but lower-osmolality media are usually preferred since they have a lower incidence of adverse effects.

For **angiography** (visualisation of the circulatory system) radiography is still frequently used, particularly to produce dynamic images (fluoroscopy) during invasive procedures, although magnetic resonance angiography may be an alternative. Iodinated contrast media for angiography are similar to those used for urography; the main requirement is for a water-soluble molecule that will be rapidly distributed through the blood vessels. In addition, the solution should be of low viscosity to facilitate rapid injection and of high radiodensity to counteract the diluting effects of the blood. Low cardiotoxicity is particularly important for procedures that require a high concentration of contrast medium, such as angiocardiography or digital subtraction angiography, and low-osmolality media are now generally preferred for all angiographic procedures. Another widely used method for visualising the heart is echocardiography, which uses ultrasound imaging, and microbubble contrast media such as galactose or encapsulated gases (perfluorocarbons or sulfur hexafluoride) may be used to improve the images.

For **gastrointestinal imaging** endoscopy is often the preferred technique, but radiography also has a role. Positive, negative, and double contrast techniques are used. For positive contrast the contrast medium should not be absorbed but should form an even, homogeneous coat on the gastrointestinal mucosa, without interacting with gut secretions or producing misleading radiographic artefacts. The chief contrast medium for this purpose is barium sulfate, and much effort has been devoted to the production of suitable formulations to improve its coating properties and reduce the formation of bubbles, cracks, and other radiographic artefacts. Iodinated contrast media may be used as an alternative, but images tend to be inferior.

For **cholecystography** and **cholangiography** (visualisation of the gallbladder and biliary tract) ultrasound techniques have generally replaced radiography. Where radiography is used, choice of contrast medium depends on the intended procedure and the route. For intra-operative or endoscopic procedures, water-soluble contrast media may be used, but for non-invasive imaging the contrast medium used must be excreted in the bile. This requires a molecule with a free carboxy or other acidic group, since the biliary active transport mechanism is an anion transfer process; the molecule also needs to be large or highly protein-bound to prevent rapid excretion by the kidney. Suitable intravenous media include adipiodone and iotroxic acid. For oral use, absorption from the gastrointestinal tract is also required, and suitable media tend to be smaller molecules that are conjugated with glucuronic acid within the body before excretion in the bile, such as iopanoic acid. For visualisation of lesions within the liver itself, magnetic resonance imaging may be used; contrast media used to enhance the images include ferucarbotran and ferumoxides, as well as gadolinium or manganese chelates.

For **myelography** (visualisation of the structures of the spinal cord) and imaging of other parts of the CNS, magnetic resonance imaging is generally preferred, often with the use of gadolinium chelates such as gadopentetic acid as contrast media. Where radiography is used, the most important requirement for contrast media is low toxicity, and nonionic media are most common.

For **arthrography** (visualisation of the joint capsule) many radiographic contrast media are suitable provided they are well-diluted before use. Magnetic resonance imaging with gadolinium chelates may also have a role.

Bronchography (examination of the bronchial tree) has been performed with oily or aqueous media, such as iopydol or iopydone, instilled through a catheter or bronchoscope to coat the airways; however, other visualisation techniques are generally preferred.

For **hysterosalpingography** (visualisation of the uterus and fallopian tubes) ultrasound and endoscopic techniques are generally used, and microbubble contrast media such as galactose may be used to improve ultrasound images. If radiography is performed, water-soluble iodinated contrast media may be used.

For **lymphography** or **lymphangiography** (visualisation of the lymphatic system) a high radiodensity is required and the contrast medium must be retained within the lymphatic system for long enough to be visualised, requiring particulate, water-insoluble media, or very large molecules. Iodised oil has been most widely used, but adverse effects and limited distribution within the lymphatic system restrict its use.

Adverse effects of contrast media. Although contrast media are generally considered to be very safe, with most adverse effects being mild and transient, more severe and even life-threatening reactions are possible, and the risk of adverse effects may influence the choice of contrast medium or imaging technique in a particular patient.

Iodinated radiographic contrast media all have a similar range of adverse effects (see under Amidotrizoic Acid, p.1475) but the incidence and severity varies. Many of the adverse effects are related to the osmolality of the preparation, and the incidence tends to be lower with those that have low osmolality. Osmolality depends on the number of particles present in the solution; for a given iodine content, this is highest for the ionic monomers and lowest for nonionic dimers, and this is reflected in the incidence of adverse effects. Hypersensitivity reactions also tend to be less frequent with nonionic media (see under Amidotrizoic Acid, p.1476), although these reactions are not directly related to osmolality. However, low-osmolality media tend to be more expensive; while nonionics and dimers are preferred, ionic monomers may still have a role in patients at low risk of adverse effects. Ionic contrast media may also carry a lower risk of thromboembolism (see Effects on the Blood, p.1476).

Magnetic resonance contrast media tend to be safer than iodinated contrast media, although similar general effects may occur. Ionic and nonionic media are available, but this tends to have little influence on the incidence of adverse effects. All gadolinium chelates have similar adverse effects (see under Gadopentetic Acid, p.1479); there is a theoretical risk of gadolinium toxicity due to instability of the chelates and most preparations also contain free chelating agent to reduce this risk. The adverse effects of superparamagnetic iron compounds are described under ferumoxides (p.1478) and ferumoxsil (p.1478).

Ultrasound contrast media are generally safe; minor and transient adverse effects have been reported, but may be due to the procedure rather than to the contrast medium used.

References.

1. Thomsen HS, Bush WH. Adverse effects of contrast media: incidence, prevention and management. *Drug Safety* 1998; **19:** 313–24.
2. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; **12:** 205–13.
3. Maddox TG. Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician* 2002; **66:** 1229–34.
4. Kirchin MA, Runge VM. Contrast agents for magnetic resonance imaging: safety update. *Top Magn Reson Imaging* 2003; **14:** 426–35.
5. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; **209:** 185–7.
6. Jakobsen JÅ, *et al.* Safety of ultrasound contrast agents. *Eur Radiol* 2005; **15:** 941–5.
7. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; **78:** 686–93.
8. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. *Drug Safety* 2006; **29:** 133–41.
9. European Society of Urogenital Radiology. ESUR guidelines on contrast media (February 2007). Available at: http://www.esur.org/fileadmin/Guidelines/ESUR_2007_Guideline_6_Kern_Ubersicht.pdf (accessed 14/07/08)

Adipiodone *(BAN, rINN)*

Adipiodon; Adipiodona; Adipiodoni; Adipiodonum; Iodipamide. 3,3′-Adipoyldiaminobis(2,4,6-tri-iodobenzoic acid).

Адипиодон

$C_{20}H_{14}I_6N_2O_6$ = 1139.8.
CAS — 606-17-7.
ATC — V08AC04.
ATC Vet — QV08AC04.

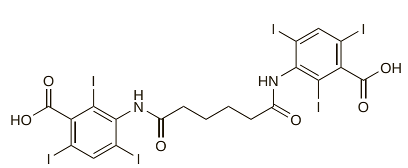

Description. Adipiodone contains about 66.8% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Iodipamide). A white, practically odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Meglumine Adipiodone *(rINNM)*

Adipiodona de meglumina; Adipiodone Méglumine; Adipiodone Meglumine *(BANM)*; Dimeglumine Iodipamide; Iodipamide Meglumine; Meglumine Iodipamide; Meglumini Adipiodonum. The di(*N*-methylglucamine) salt of adipiodone.

Меглумина Адипиодон

$C_{20}H_{14}I_6N_2O_6,(C_7H_{17}NO_5)_2$ = 1530.2.
CAS — 3521-84-4.
ATC — V08AC04.
ATC Vet — QV08AC04.

Description. Meglumine adipiodone contains about 49.8% of I.

Pharmacopoeias. *US* includes only as an injection.

Incompatibility. Incompatibilities have been reported between meglumine adipiodone and some antihistamines.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475. Rapid injection may increase the incidence of adverse effects.

Adipiodone may show some uricosuric activity.

Effects on the liver. Of 149 patients given the recommended dose of adipiodone, 13 developed elevated serum aspartate aminotransferase (SGOT) values; of 126 who received twice the dose, 23 developed elevated values.[1] Hepatotoxicity has also been reported[2-4] on isolated occasions in patients given meglumine adipiodone.

1. Scholz FJ, *et al.* Hepatotoxicity in cholangiography. *JAMA* 1974; **229:** 1724.
2. Stillman AE. Hepatotoxic reaction to iodipamide meglumine injection. *JAMA* 1974; **228:** 1420–1.
3. Sutherland LR, *et al.* Meglumine iodipamide (Cholografin) hepatotoxicity. *Ann Intern Med* 1977; **86:** 437–9.
4. Imoto S. Meglumine hepatotoxicity. *Ann Intern Med* 1978; **88:** 129.

Pharmacokinetics

Meglumine adipiodone is rapidly distributed in extracellular fluid after intravenous injection and is reported to be extensively bound to plasma proteins. It appears in the bile ducts within about 10 to 15 minutes after injection, with peak opacity at about 20 to 30 minutes, and reaches the gallbladder by about 1 hour, peak opacification occurring after about 2 hours. About 80 to 95% is excreted unchanged in the faeces; small amounts are excreted unchanged in urine. A terminal half-life of about 2 hours has been reported.

Uses and Administration

Adipiodone is an ionic dimeric iodinated radiographic contrast medium (see p.1474); it is taken up by the liver and excreted in bile, and is used in cholangiography and cholecystography.

Adipiodone is given intravenously as a solution containing 52% of the meglumine salt. The usual dose is about 10 g of meglumine adipiodone, given by slow intravenous injection over about 10 minutes.

A solution of meglumine adipiodone with meglumine diatrizoate is given by intra-uterine instillation for hysterosalpingography.

Preparations

BP 2008: Meglumine Iodipamide Injection;
USP 31: Iodipamide Meglumine Injection.

Proprietary Preparations (details are given in Part 3)
USA: Cholografin.

Multi-ingredient: ***USA:*** Sinografin.

Amidotrizoic Acid *(BAN, rINNM)*

Acide amidotrizoïque; Ácido amidotrizoico; Acidum amidotrizoicum; Acidum Diatrizoicum; Amidotritsoiinihappo; Amidotrizoesav; Amidotrizoinė rūgštis; Amidotrizoinsyra; Diatritsoiinihappo; Diatrizoic Acid *(USAN)*; Diatrizoinsyra; Kyselina amidotrizoová; NSC-262168. 3,5-Diacetamido-2,4,6-tri-iodobenzoic acid.

Амидотризоевая Кислота

$C_{11}H_9I_3N_2O_4,2H_2O$ = 649.9.
CAS — 117-96-4 (anhydrous amidotrizoic acid); 50978-11-5 (amidotrizoic acid dihydrate).
ATC — V08AA01.
ATC Vet — QV08AA01.

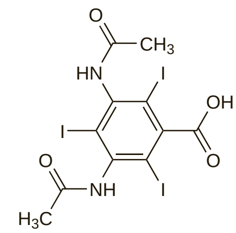

Description. Amidotrizoic acid contains about 62% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Amidotrizoic Acid Dihydrate). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Diatrizoic Acid). It is anhydrous or contains two molecules of water of hydration. A white, odourless, powder. Very slightly soluble in water and in alcohol; soluble in dimethylformamide and in alkali hydroxide solutions.

Meglumine Amidotrizoate *(BANM, rINNM)*

Amidotrizoate de Méglumine; Amidotrizoato de meglumina; Diatrizoate Meglumine; Meglumine Diatrizoate; Meglumini Amidotrizoas; Methylglucamine Diatrizoate. *N*-Methylglucamine 3,5-diacetamido-2,4,6-tri-iodobenzoate.

Меглумина Амидотризоат

$C_{11}H_9I_3N_2O_4,C_7H_{17}NO_5$ = 809.1.
CAS — 131-49-7.
ATC — V08AA01.
ATC Vet — QV08AA01.

Description. Meglumine amidotrizoate contains about 47.1% of I.

Pharmacopoeias. In *US.*

USP 31 (Diatrizoate Meglumine). A white, odourless, powder. Freely soluble in water. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Sodium Amidotrizoate *(BANM, rINN)*

Amidotrizoate de Sodium; Amidotrizoato de sodio; Diatrizoate Sodium; Natrii amidotrizoas; Natrio amidotrizoatas; Natriumamidotritsoaatti; Natriumamidotrizoat; Nátrium-amidotrizoát; Natrium-amidotrizoát; NSC-61815; Sodium, amidotrizoate de; Sodium Diatrizoate; Sodu amidotrizoat. Sodium 3,5-diacetamido-2,4,6-tri-iodobenzoate.

Натрия Амидотризоат

$C_{11}H_8I_3N_2NaO_4$ = 635.9.
CAS — 737-31-5.
ATC — V08AA01.
ATC Vet — QV08AA01.

Description. Sodium amidotrizoate contains about 59.9% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.,* and *US.*
Chin. includes the injection.

Ph. Eur. 6.2 (Sodium Amidotrizoate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 50% solution in water has a pH of 7.5 to 9.5. Protect from light.

USP 31 (Diatrizoate Sodium). A white, odourless, powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether.

Incompatibility. Incompatibilities of sodium amidotrizoate with some antihistamines have been reported.

Adverse Effects and Treatment

Amidotrizoates and other iodinated contrast media may cause adverse effects due to direct toxicity, which tends to be dose-related and predictable, but use often leads to unpredictable or anaphylactoid reactions. Most reactions occur within 5 to 10 minutes and are mild and transient; however, severe, life-threatening reactions may also occur, and delayed reactions have been reported.

Direct toxic effects of iodinated contrast media are related to the osmolality of the solutions used and are most common with the amidotrizoates and other ionic monomeric compounds, which have a high osmolality. The route, the speed with which it is given, and the volume, concentration, and viscosity of the solution, also affect the incidence of adverse effects. For ionic media, the cation is also important: meglumine salts are generally better tolerated, but sodium salts have a lower viscosity and may produce fewer arrhythmias, and preparations containing a mixture of the salts are therefore often used. Anaphylactoid reactions are also more common with high-osmolality, ionic contrast media.

The most frequent direct adverse reaction to iodinated contrast media is flushing or a sensation of heat and caused by vasodilatation in response to the osmolality of the solution. Pain at the injection site is also common and extravasation may lead to tissue damage or thrombophlebitis.

General symptoms such as nausea, vomiting, headache, and dizziness may be related to patient anxiety or similar factors, or may be due to a mild anaphylactoid reaction. Urticaria, pruritus, pallor, sweating, a metallic taste, weakness, coughing, rhinitis, sneezing, lachrymation, and visual disturbances may also occur. Cardiovascular effects may also be due to direct toxicity, notably after intracoronary injection, or anaphylactoid response; they include hypotension, tachycardia, bradycardia, transient ECG abnormalities, and haemodynamic disturbances. More severe anaphylactoid reactions may lead to dyspnoea, bronchospasm, angioedema, severe urticaria, and eventually to profound hypotension, pulmonary oedema, respiratory arrest, ventricular fibrillation, circulatory failure, and cardiac arrest; fatalities have occurred.

CNS effects may result from direct toxicity, particularly after intrathecal use of ionic media or use in patients with a compromised blood-brain barrier, and can lead to severe neurotoxicity. Convulsions are more common in patients with epilepsy or brain tumours, but may also result from anaphylactoid reactions; paraesthesia, paralysis, and coma have also been reported.

Acute renal failure is an established adverse effect of contrast media, particularly in patients with predisposing factors such as dehydration (see Effects on the Kidneys, and Precautions, below). It appears to be related to the osmolality of the solution and is usually reversible, but deaths have occurred.

Iodinated contrast media also have direct effects on the blood, inhibiting blood coagulation and platelet aggregation. However, thromboembolism may also occur (see below). Disseminated intravascular coagulation and thrombocytopenia have also been reported.

Hyperthyroidism has been reported with use of iodinated contrast media, particularly in patients with goitre, and thyroid storm may be precipitated in patients with thyrotoxicosis. This is probably due to the small amounts of iodine present as a contaminant or released by any breakdown of the medium in the body. For the effects of iodine on the thyroid gland, see p.2169.

Mild diarrhoea may follow the oral or rectal use of amidotrizoates for gastrointestinal examinations. Aspiration of oral solutions has caused fatal pulmonary oedema.

Adverse effects are treated symptomatically; adequate resuscitative facilities should be available when radiographic procedures are undertaken, and patients should be kept under observation for a suitable period after the procedure.

Effects on the blood. Iodinated contrast media affect blood coagulation to differing degrees.[1,2] Amidotrizoates and other ionic contrast media have inhibitory effects on blood coagulation and platelet aggregation, whereas nonionic media lack these effects. In procedures such as angiography, which are associated with a risk of thromboembolism, there may therefore be an advantage in using ionic media. However, the better overall tolerability of nonionic media means that they are still generally preferred to ionic media for angiography, particularly in patients at high risk of non-thromboembolic adverse effects.

Other effects on the blood that have been reported with amidotrizoates and other iodinated contrast media include disseminated intravascular coagulation,[3,4] haemolysis,[5] thrombocytopenia,[6,7] and thrombotic microangiopathy.[8]

1. Husted SE, Kanstrup H. Thrombotic complications in coronary angioplasty—ionic versus non-ionic low-osmolar contrast media. *Acta Radiol* 1998; **39:** 340–3.
2. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
3. Lucas LM, *et al.* Case report: multisystem failure following intravenous iopamidol. *Clin Radiol* 1992; **45:** 276–7.
4. Shigyo M, *et al.* A rare case of disseminated intravascular coagulation caused by the nonionic contrast medium iohexol. *J Urol (Baltimore)* 1995; **153:** 1901–3.
5. Catterall JR, *et al.* Intravascular haemolysis with acute renal failure after angiocardiography. *BMJ* 1981; **282:** 779–80.
6. Shojania AM. Immune-mediated thrombocytopenia due to an iodinated contrast medium (diatrizoate). *Can Med Assoc J* 1985; **133:** 123.
7. Ural AU, *et al.* Thrombocytopenia following intravenous iopamidol. *Eur J Clin Pharmacol* 1998; **54:** 575–6.
8. Fairley S, Ihle BU. Thrombotic microangiopathy and acute renal failure associated with arteriography. *BMJ* 1986; **293:** 922–3.

Effects on the kidneys. Contrast nephropathy or contrast-induced nephrotoxicity is a well-established adverse effect of iodinated contrast media.[1-9] Estimates of the incidence vary depending on the type and amount of contrast medium used, the definition of nephropathy, and the population of patients being studied, but is about 1 to 6% overall. In the majority of patients who develop contrast-medium-induced renal impairment the condition develops within about 24 hours of the procedure, is asymptomatic, and resolves completely within about 10 days. However, the condition may occasionally be severe, producing oliguria and renal failure that requires dialysis; fatalities have occurred.

The mechanism of nephrotoxicity is not certain, but is thought to involve both medullary hypoxia due to reduced renal blood flow, and direct toxicity. The osmolality of the contrast medium solution appears to be an important factor and most studies have shown that high-osmolality media increase the risk compared with low-osmolality media. There is also some evidence that use of media that are iso-osmolar with plasma may reduce the risk even further. The volume of contrast solution used is also important, and risk increases with higher volumes. The use of ionic or nonionic media appears to have less influence, except that nonionic media generally have a lower osmolality and may therefore be preferred.

The most important patient characteristic that increases the risk of nephrotoxicity is pre-existing renal impairment, especially in patients with diabetes mellitus. Other risk factors include conditions where there is reduced renal blood flow, such as heart failure and dehydration. Old age, repeated exposure (over a short period of time), multiple myeloma, and use with other nephrotoxic drugs, are also risk factors.

Various methods have been tried to prevent contrast medium-induced nephropathy.[1,3-12] All patients should be assessed for risk factors and those at high risk should be given a small volume of a low-osmolality or iso-osmolar nonionic medium if possible. Hydration before and after the procedure is of established benefit and is recommended in all patients, although the optimum route and fluid to use remains unclear. Oral hydration may be adequate in low risk patients, but most patients are given sodium chloride 0.45% or 0.9% intravenously. Sodium bicarbonate may be an alternative; a study[13] in patients with pre-existing stable renal impairment suggested that it was more effective than sodium chloride. However, a retrospective study[14] found an increased risk of nephropathy in patients given sodium bicarbonate compared with those who had no prophylaxis, and further studies are needed to confirm its role.

Antoxidants have been suggested as a way of reducing the direct toxicity of contrast media. Acetylcysteine is widely used,[15] but evidence of benefit is conflicting. Some studies have produced promising results, but others have been less positive and, although reviews and meta-analyses have shown benefit[16,17] or a trend towards benefit,[18-20] most have concluded[15,17-21] that the wide variation between the studies included means that the efficacy of acetylcysteine remains uncertain. Later randomised studies have also reported conflicting results.[22,23] An observational study[24] found that there was no difference in the incidence of contrast nephropathy before and after the introduction of acetylcysteine prophylaxis, while a follow-up study[25] found that acetylcysteine had no effect on overall outcomes over 9 months. However, some authors[4,7,15] recommend the use of acetylcysteine in particularly high-risk patients. Ascorbic acid has also been tried and showed benefit in one study,[26] and promising results have been reported with trimetazidine, an anti-anginal drug with antoxidant properties,[27] but further confirmation is needed.

Other approaches have generally produced disappointing results.[1,3-7,10] The use of diuretics may increase the risk of nephropathy and is not recommended. Vasodilators have been tried, including atrial natriuretic peptide, calcium-channel blockers, low-dose dopamine, and alprostadil, but benefit has not been established and they are not generally used. Although positive results have been reported[28] with fenoldopam, which has preferential effects on renal blood flow, a large randomised study[29] failed to confirm any benefit. Studies with theophylline have produced conflicting results, although a meta-analysis[30] concluded that it might be of benefit. Use of dialysis to remove contrast medium from the circulation has also been suggested; some benefit has also been found with haemofiltration started before the procedure,[31] but not with haemodialysis immediately after the procedure.[32]

1. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; **25:** 1079–98.
2. Rudnick MR, Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. *Rev Cardiovasc Med* 2003; **4** (suppl 5): S28–S33.
3. Cox CD, Tsikouris JP. Preventing contrast nephropathy: what is the best strategy? A review of the literature. *J Clin Pharmacol* 2004; **44:** 327–37.
4. Maeder M, *et al.* Contrast nephropathy: review focusing on prevention. *J Am Coll Cardiol* 2004; **44:** 1763–71.
5. Thomsen HS. How to avoid CIN: guidelines from the European Society of Urogenital Radiology. *Nephrol Dial Transplant* 2005; **20** (suppl 1): i18–i22. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/20/suppl_1/i18.pdf (accessed 27/03/06)
6. Itoh Y, *et al.* Clinical and experimental evidence for prevention of acute renal failure induced by radiographic contrast media. *J Pharmacol Sci* 2005; **97:** 473–88.
7. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. *Can Med Assoc J* 2005; **172:** 1461–71. Correction. *ibid.*; **173:** 1210.
8. Tepel M, *et al.* Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation* 2006; **113:** 1799–1806.
9. Pannu N, *et al.* Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006; **295:** 2765–79.
10. Lepor NE. A review of pharmacologic interventions to prevent contrast-induced nephropathy. *Rev Cardiovasc Med* 2003; **4** (suppl 5): S34–S42.
11. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006; **354:** 379–86.
12. Kelly AM, *et al.* Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; **148:** 284–94.
13. Merten GJ, *et al.* Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; **291:** 2328–34.
14. From AM, *et al.* Sodium bicarbonate is associated with an increased incidence of contrast nephropathy: a retrospective cohort study of 7977 patients at Mayo Clinic. *Clin J Am Soc Nephrol* 2008; **3:** 10–18.
15. Fishbane S, *et al.* N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004; **15:** 251–60.
16. Birck R, *et al.* Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; **362:** 598–603.
17. Bagshaw SM, Ghali WA. Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. *BMC Med* 2004; **2:** 38.
18. Pannu N, *et al.* Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; **65:** 1366–74.
19. Nallamothu BK, *et al.* Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004; **117:** 938–47.
20. Zagler A, *et al.* N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. *Am Heart J* 2006; **151:** 140–5.
21. Kshirsagar AV, *et al.* N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; **15:** 761–9.
22. Coyle LC, *et al.* Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J* 2006; **151:** 1032.e9–1032.e12.
23. Marenzi G, *et al.* N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; **354:** 2773–82.
24. Shah SJ, Hsu C-Y. Has acetylcysteine use changed the incidence of contrast nephropathy in hospitalized patients? A before-after study. *Am J Med* 2004; **117:** 948–52.
25. Miner SES, *et al.* N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J* 2004; **148:** 690–5.
26. Spargias K, *et al.* Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; **110:** 2837–42.
27. Onbasili AO, *et al.* Trimetazidine in the prevention of contrast-induced nephropathy after coronary procedures. *Heart* 2007; **93:** 698–702.
28. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; **35:** 1278–82. Correction. *ibid.*; 1677.
29. Stone GW, *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; **290:** 2284–91.
30. Bagshaw SM, Ghali WA. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Arch Intern Med* 2005; **165:** 1087–93.
31. Marenzi G, *et al.* The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; **349:** 1333–40.
32. Vogt B, *et al.* Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med* 2001; **111:** 692–8.

Hypersensitivity. Anaphylactoid reactions to iodinated contrast media are more common with the ionic agents than the nonionic media of lower osmolality. Patients at increased risk are those with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to a contrast medium, and those receiving beta blockers or interleukin-2 therapy. In such patients, nonionic media are preferred. Stopping treatment with beta blockers should be considered in patients with other risk factors.

Pretreatment with corticosteroids may be considered for preventing anaphylactoid reactions in high-risk patients, and an antihistamine may be given. However, reactions may still occur and the value of premedication remains controversial.

References.

1. Canter LM. Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 2005; **26:** 199–203.
2. Idée J-M, *et al.* Allergy-like reactions to iodinated contrast agents: a critical analysis. *Fundam Clin Pharmacol* 2005; **19:** 263–81.
3. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; **78:** 686–93.
4. Tramèr MR, *et al.* Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. Abridged version: *BMJ* 2006; **333:** 675–8. Full version: http://www.bmj.com/cgi/reprint/333/7570/675 (accessed 05/09/08)

Precautions

The risk of anaphylactoid reactions with amidotrizoates and other iodinated contrast media is increased in patients with asthma or a history of allergies and they should be used with great caution in such patients; they should not be used in patients with a previous reaction to contrast media or iodine. Test doses have been given but are not generally recommended since they do not predict hypersensitivity with certainty and may cause severe or fatal reactions. Pretreatment with corticosteroids may be considered in patients considered at high risk of reactions, but the value of this is uncertain (see Hypersensitivity, above). An antihistamine may be given with the corticosteroid.

Iodinated contrast media should be used with caution in patients with severe hepatic or renal impairment, diabetics with renal impairment, and others who may be at increased risk of renal failure. Dehydration should be avoided, and any fluid or electrolyte imbalance should be corrected before contrast media are given. Particular care is needed in patients with multiple myeloma since dehydration resulting from use of contrast media may cause precipitation of protein in the renal tubules, leading to anuria and fatal renal failure.

Caution is also necessary in patients with severe hypertension, advanced cardiac disease, phaeochromocytoma, sickle-cell disease, or hyperthyroidism or epilepsy, and in debilitated, severely ill, very old, or very young patients.

Amidotrizoates and other hypertonic contrast media are neurotoxic and should not be given intrathecally; patients with subarachnoid haemorrhage may be at risk with any intravascular use. Intravascular contrast media should also be used with caution in any patient with occlusive vascular disease. Iodinated contrast media should not be used for hysterosalpingography in the presence of infection or inflammation of the pelvic cavity, nor during menstruation or in pregnancy (although any abdominal radiography should be avoided during pregnancy because of the risks of radiation to the fetus).

Iodine-containing contrast media may interfere with thyroid function tests. There may also be interference with blood coagulation tests and certain urine tests.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving amidotrizoates and the American Academy of Pediatrics considers[1] that they are therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Neonates. Although amidotrizoates may be used in the management of some forms of intestinal obstruction (see below), meglumine amidotrizoate was considered[1] a possible contributory factor in the deaths of 2 infants who developed bowel necrosis, perforation, and peritonitis after its use for meconium ileus.

1. Leonidas JC, *et al.* Possible adverse effects of methylglucamine diatrizoate compounds on the bowel of newborn infants with meconium ileus. *Radiology* 1976; **121:** 693–6.

Pharmacokinetics

Amidotrizoates are very poorly absorbed from the gastrointestinal tract. Amidotrizoates in the circulation are not significantly bound to plasma proteins. If renal function is not impaired, unchanged amidotrizoate is rapidly excreted by glomerular filtration; over 95% of an intravascular dose is reported to be excreted in urine within 24 hours, and about 1 to 2% of a dose may be excreted in faeces. Trace amounts may be detected in other body fluids including tears and saliva. Faecal excretion may increase to 10 to 50% in severe renal impairment. The half-life of amidotrizoates has been reported to be 30 to 60 minutes, which can increase to 20 to 140 hours in severe renal impairment. They are removed by haemodialysis and peritoneal dialysis.

The amidotrizoates cross the placenta and are distributed into breast milk.

Uses and Administration

The amidotrizoates are ionic monomeric iodinated radiographic contrast media (p.1474). Both the sodium and the meglumine salt have been widely used in diagnostic radiography; however, adverse effects may be reduced by using a mixture of both salts, and this is often preferred. Preparations are available containing a wide range of strengths. Mixtures containing sodium amidotrizoate 10% w/v with meglumine amidotrizoate 66% w/v, or sodium amidotrizoate 4% with meglumine amidotrizoate 26%, are commonly used. For use alone, preparations containing sodium amidotrizoate 25 to 50% w/v, or meglumine amidotrizoate 60% w/v, may be appropriate.

The amidotrizoates are used in an extensive range of procedures, although in many cases lower osmolality contrast media are now preferred. The dose and route depend on the procedure and the degree and extent of contrast required. They are given intravenously for urography, for venography, and in computed tomography; for urography, they have also been given by intramuscular or subcutaneous injection, but these routes are not generally recommended. They may be given intra-arterially for angiography, by intra-articular injection for arthrography, or by intra-osseous injection for imaging of the vasculature of the bones. For other procedures they may be instilled into body cavities, or injected into the gallbladder, biliary ducts, or spleen. Amidotrizoates have also been given orally or rectally for imaging of the gastrointestinal tract.

Solutions of amidotrizoates have also been given as an enema in the treatment of uncomplicated meconium ileus.

Calcium amidotrizoate and lysine amidotrizoate have also been used as contrast media.

Gastrointestinal obstruction. Amidotrizoates and other water-soluble contrast media have been given rectally as osmotic agents in the management of gastrointestinal obstruction due to meconium ileus;[1] however, adverse effects have been reported in neonates (see above). They have also been used as an alternative to barium sulfate enemas in the management of intussusception (see below). Amidotrizoates given orally have been used in the management of adhesive small bowel obstruction;[2] they allow identification of patients who require surgery and, although they have not been shown to relieve obstruction, they may reduce length of hospital stay in patients treated without surgery.

1. Murshed R, *et al.* Meconium ileus: a ten-year review of thirty-six patients. *Eur J Pediatr Surg* 1997; **7:** 275–7.
2. Abbas S, *et al.* Oral water soluble contrast for the management of adhesive small bowel obstruction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 14/07/08).

Preparations

BP 2008: Meglumine Amidotrizoate Injection; Sodium Amidotrizoate Injection;
USP 31: Diatrizoate Meglumine and Diatrizoate Sodium Injection; Diatrizoate Meglumine and Diatrizoate Sodium Solution; Diatrizoate Meglumine Injection; Diatrizoate Sodium Injection; Diatrizoate Sodium Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Angiografina; Densopax; Hypaque 60%†; Hypaque 76%†; MD-76; MD-Gastroview; Plenigraf; Temistac; Tomoray; Triyosom; Urografina; Urovison; ***Austral.:*** Angiografin†; Gastrografin; MD-60†; MD-76; MD-Gastroview; Urografin; ***Austria:*** Gastrografin; Urografin†; ***Belg.:*** Gastrografin; Urografine†; ***Braz.:*** Hypaque; Hypaque-M; Urografina; ***Canad.:*** Hypaque-M†; Hypaque†; MD-76; ***Chile:*** Angiovist; Hypaque 60%†; Hypaque 76%†; Pielograf†; Reliev; Reliev 76%; ***Cz.:*** Urografin†; ***Denm.:*** Urografin; Urografin Meglumin; ***Fin.:*** Gastrografin; ***Fr.:*** Gastrografine; Radioselectan; ***Ger.:*** Ethibloc; Gastrografin; Gastrolux; Peritrast; Peritrast comp; Peritrast-Infusio 160/32%†; Peritrast-Infusio 180/31%; Peritrast-Oral CT; Peritrast-Oral-GI; Peritrast-RE; Urolux; Urolux Retro; Urovison†; ***Gr.:*** Gastrografin; ***Hung.:*** Gastrografin; Peritrast; ***India:*** Urografin; ***Israel:*** Urografin†; ***Ital.:*** Gastrografin; ***Neth.:*** Angiografin†; Gastrografin; Urografin; Urovison†; ***Norw.:*** Gastrografin; ***NZ:*** Gastrografin; Urografin; ***Port.:*** Gastrografina; Urografina; ***Rus.:*** Hypaque (Гипак)†; Trazograph (Тразограф); Urographin (Урографин); ***S.Afr.:*** Angiografin†; Gastrografin; Urografin; ***Spain:*** Gastrografin; Pielograf; Plenigraf; Radialar 280; Trazograf; Uro Angiografin; Urografin; ***Swed.:*** Gastrografin; Urografin; ***Switz.:*** Gastrografin; Urografin†; ***UK:*** Gastrografin; Hypaque; Urografin 150 and 370; ***USA:*** Cystografin; Gastrografin; Hypaque; Hypaque-M, Hypaque-76; MD-76; MD-Gastroview; Reno-M; Renografin; ***Venez.:*** Hypaque-M†.

Multi-ingredient: ***USA:*** Sinografin.

Barium Sulfate

Barii sulfas; Barii Sulphas; Bario sulfatas; Barium Sulfuricum; Barium Sulphate; Bariumsulfaatti; Bariumsulfat; Bárium-szulfát; Baru siarczan; Baryum (Sulfate de); Baryum, sulfate de; Síran barnatý; Sulfato de bario.

$BaSO_4$ = 233.4.
CAS — 7727-43-7.
ATC Vet — QV08BA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Barium Sulphate). A fine, white powder, free from gritty particles. Practically insoluble in water and in organic solvents; very slightly soluble in acids and in solutions of alkali hydroxides.

USP 31 (Barium Sulfate). A fine, white, odourless, bulky powder, free from grittiness. Practically insoluble in water, in organic solvents, and in solutions of acids and of alkalis. pH of a 10% w/w aqueous suspension is between 3.5 and 10.0.

Adverse Effects

Because barium sulfate is almost insoluble it lacks the severe toxicity characteristic of the barium ion; deaths have occurred in patients given the more soluble barium sulfide in error for the sulfate.

Constipation may occur after oral or rectal barium sulfate; impaction, obstruction, and appendicitis have occurred. Surgical removal of faecaliths has sometimes been necessary. Cramping or diarrhoea have also been reported. Venous intravasation has led to the formation of emboli; deaths have occurred. Perforation of the bowel has led to peritonitis, adhesions, granulomas, and a high mortality rate.

ECG abnormalities have occurred during the use of barium sulfate enemas.

Accidental aspiration into the lungs has led to pneumonitis or granuloma formation.

Hypersensitivity. A survey of hypersensitivity reactions to barium preparations found that although barium is inert many of the additives used in formulation have the potential to cause reactions.[1] Of 106 reactions reported or found in the literature, 61% involved the skin and only 8% the respiratory tract; unconsciousness was reported in 8% of cases. In view of the frequency of use of barium preparations, such adverse reactions must be very rare, but radiologists should be aware that they might be somewhat more common than was usually appreciated. A number of severe reactions associated with the use of barium enemas supplied with an inflatable latex cuff may have been due to leaching of components from the latex.[2]

1. Janower ML. Hypersensitivity reactions after barium studies of the upper and lower gastrointestinal tract. *Radiology* 1986; **161:** 139–40.
2. Nightingale SL. Severe adverse reactions to barium enema procedures. *JAMA* 1990; **264**: 2863.

Precautions

Barium sulfate should not be given to patients with intestinal obstruction and care is needed in those with conditions such as pyloric stenosis or lesions that may predispose to obstruction. Adequate hydration should be ensured after the procedure to prevent severe constipation.

It is contra-indicated in patients with gastrointestinal perforation, and should be avoided, particularly when given rectally, in those at risk of perforation, such as patients with acute ulcerative colitis or diverticulitis and after rectal or colonic biopsy, sigmoidoscopy, or radiotherapy.

Uses and Administration

Barium sulfate is used as a radiographic contrast medium (p.1474) for X-ray examination of the gastrointestinal tract involving single- or double-contrast techniques or computed tomography.

The dose of barium sulfate is dependent upon the type of examination and technique used. In the UK typical doses and concentrations used for examination are:

- oesophagus: up to 150 mL of a 50 to 200% w/v suspension given orally
- stomach and duodenum: up to 300 mL of a 30 to 200% w/v suspension given orally
- small intestine: 100 to 300 mL of a 30 to 150% w/v suspension given orally
- colon: 200 mL to 2 litres of a 20 to 130% w/v suspension given as an enema.

A suspension containing 1.6 to 2.2% may be used in gastrointestinal computed tomography.

In the USA, suspensions containing up to 230% w/v barium sulfate may be used; lower concentrations are available for use in computed tomography and usually contain about 1 to 2% w/v.

For double-contrast examination, gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide; separate gas-producing preparations based on sodium bicarbonate are also available. Air given via a tube may be used as an alternative to carbon dioxide.

◊ Reviews.

1. Nolan DJ, Traill ZC. The current role of the barium examination of the small intestine. *Clin Radiol* 1997; **52:** 809–20.
2. Mendelson RM. The role of the barium enema in the diagnosis of colorectal neoplasia. *Australas Radiol* 1998; **42:** 191–6.
3. de Zwart IM, *et al.* Barium enema and endoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. *Clin Radiol* 2001; **56:** 401–9.
4. Rubesin SE, Maglinte DD. Double-contrast barium enema technique. *Radiol Clin North Am* 2003; **41:** 365–76.
5. O'Connor SD, Summers RM. Revisiting oral barium sulfate contrast agents. *Acad Radiol* 2007; **14:** 72–80.

Intussusception. Contrast media enemas and ultrasound are both used in the diagnosis of intussusception, a condition in infants where part of the intestine prolapses into the lumen of an adjacent part causing an obstruction.[1,2] However, some consider ultrasound to be superior for diagnosis and reserve enemas for the therapeutic reduction of intussusception. Reduction is achieved as a result of the hydrostatic pressure of the enema pushing the intestine back into its natural position. Although there is extensive experience using barium enemas for reduction some centres prefer to use water-soluble contrast media so as to minimise the risk of chemical peritonitis if perforation of the bowel occurs. Other agents used instead of barium for reduction include air enemas or ultrasound guided saline enemas, both of which avoid or reduce radiographic exposure. Surgery is indicated when enema therapy fails or is considered unsuitable.

1. del-Pozo G, *et al.* Intussusception in children: current concepts in diagnosis and enema reduction. *Radiographics* 1999; **19:** 299–319.
2. Sorantin E, Lindbichler F. Management of intussusception. *Eur Radiol* 2004; **14** (suppl 4): L146–L154.

Preparations

BP 2008: Barium Sulphate for Suspension; Barium Sulphate Oral Suspension;
USP 31: Barium Sulfate for Suspension; Barium Sulfate Paste; Barium Sulfate Suspension; Barium Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Barigraf; Bario; Bariofarma; Barosperse; E-Z-Cat; Entero VU; Gastropaque; Novopacum; Opti-Up†; Scheribar; Tixobar; Top-Cat; ***Austral.:*** Medebar; Medescan; Tixobar†; ***Austria:*** Barilux; Prontobario; Scannotrast; ***Belg.:*** E-Z-Paque; Micropaque; Microtrast; Polibar; ***Braz.:*** Bariogel; Celobar†; ***Chile:*** Barigraf†; ***Cz.:*** E-Z-Cat; E-Z-HD; E-Z-Paque†; Micropaque; Microtrast; Polibar; Prontobario†; ***Denm.:*** Micropaque; Microtrast; Mixobar; ***Fin.:*** Mixobar; ***Fr.:*** Micropaque; Microtrast; ***Ger.:*** Barilux; Micropaque; Microtrast; ***Gr.:*** Barilux; Micropaque; Unibaryt-R; ***Hung.:*** E-Z-Cat; E-Z-HD; Micropaque; Microtrast; Polibar ACB; Polibar Rapid; ***Israel:*** E-Z-Cat; E-Z-HD; E-Z-Paque; Entero VU; Liquid Polibar Plus; Polibar ACB; ***Ital.:*** Mixobar†; Prontobario; TAC Esofago; ***Neth.:*** Baricol; E-Z-HD; Micropaque; Polibar; ***Norw.:*** Mixobar; ***NZ:*** Medebar†; ***Port.:*** E-Z-Cat; E-Z-HD; Gastrobario; Micropaque; Microtrast; Polibar; ***Spain:*** Barigraf; Bario Dif; Bario Llorente†; Disperbarium; Justebarin†; Micropaque†; ***Swed.:*** Mixobar; ***Switz.:*** CAT-Barium (E-Z-CAT); Microbar-HD (E-Z-HD); Micropaque; Polibar ACB; ***UK:*** Baritop; E-Z-Cat; E-Z-HD; E-Z-Paque; Polibar; Polibar Rapid; ***USA:*** Anatrast; Baricon; Baro-cat; Barobag; Barosperse; Bear-E-Yum; CheeTah; Enecat; Enemark; Enhancer; Entrobar; Epi-C; Flo-Coat; HD 200 Plus; HD 85; Intropaste; Liqui-Coat HD; Liquipake; Medebar; Medescan; Prepcat; Scan C; Tomocat; Tonojug; Tonopaque; ***Venez.:*** Barin; Bariogel†; Bariotin†; Sulfobarina†.

The symbol † denotes a preparation no longer actively marketed

Ferristene *(BAN, USAN)*

Ferristeno.

$C_8H_{11}NO_3S,(Fe_2O_3)_{0.725}$.

CAS — 155773-56-1.

ATC — V08CB02.

ATC Vet — QV08CB02.

Description. Ferristene contains about 23.4% of Fe.

Profile

Ferristene consists of iron ferrite crystals carried on monosized spheres of cross-linked poly(ammonium styrenesulfonate). It has superparamagnetic properties and has been used orally as a magnetic resonance contrast medium (p.1474) for imaging of the abdomen.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Abdoscan†.

Ferucarbotran *(BAN, USAN)*

Ferrixan; Ferucarbotrano; SHU-555A; ZK-132281.

Profile

Ferucarbotran is a colloidal aqueous suspension of iron oxide (magnetite and maghemite) particles coated with carboxydextran. It has superparamagnetic properties and is used similarly to ferumoxides (below) as a magnetic resonance contrast medium (p.1474) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is given intravenously as a solution containing 28 mg/mL of iron. The usual dose is 0.9 mL for patients weighing less than 60 kg and 1.4 mL for patients weighing 60 kg and over.

◊ References.

1. Reimer P, Balzer T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. *Eur Radiol* 2003; **13:** 1266–76.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Resovist†; ***Austria:*** Resovist; ***Belg.:*** Resovist; ***Cz.:*** Resovist; ***Denm.:*** Resovist; ***Fin.:*** Resovist†; ***Ger.:*** Resovist; ***Gr.:*** Resovist; ***Israel:*** Resovist†; ***Ital.:*** Resovist; ***Neth.:*** Resovist; ***Norw.:*** Resovist; ***Port.:*** Resovist; ***Spain:*** Resograf; Resovist; ***Swed.:*** Resovist; ***Switz.:*** Resovist.

Ferumoxides *(BAN, USAN)*

AMI-25; Ferumóxidos.

$(Fe_2O_3)_m(FeO)_n$.

CAS — 119683-68-0.

Adverse Effects and Precautions

The most common adverse effects with ferumoxides are pain, vasodilatation, and hypotension; paraesthesia may also occur. Hypersensitivity reactions have developed. Extravasation may lead to discoloration of the skin around the injection site. Ferumoxides should not be used in patients with known hypersensitivity to iron and should be used with caution in patients with iron overload disorders.

Uses and Administration

Ferumoxides consists of colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p.1474) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is available as a suspension containing 11.2 mg/mL of iron, which should be diluted in 100 mL of glucose 5% before use and given intravenously over at least 30 minutes. The dose is expressed in terms of iron. In Europe, the usual dose is 0.84 mg/kg; in the USA, a dose of 0.56 mg/kg is used.

◊ Reference to the use of ferumoxides followed by a gadolinium-based contrast medium.[1]

1. Qayyum A, *et al.* Detection of hepatocellular carcinoma by ferumoxides-enhanced MR imaging in cirrhosis: incremental value of dynamic gadolinium-enhancement. *J Magn Reson Imaging* 2006; **23:** 17–22.

Preparations

USP 31: Ferumoxides Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Feridex†; ***Austria:*** Endorem; ***Belg.:*** Endorem; ***Denm.:*** Endorem; ***Fin.:*** Endorem; ***Fr.:*** Endorem; ***Ger.:*** Endorem; ***Gr.:*** Endorem; ***Israel:*** Feridex†; ***Ital.:*** Endorem; ***Jpn:*** Feridex; ***Neth.:*** Endorem; ***Norw.:*** Endorem; ***Port.:*** Endorem; ***Spain:*** Endorem; ***Swed.:*** Endorem; ***Switz.:*** Endorem; ***USA:*** Feridex.

Ferumoxsil *(BAN, USAN)*

AMI-121; Ferumoksiili; Ferumoxil; Férumoxsil; Ferumoxsilum.

ATC — V08CB01.

ATC Vet — QV08CB01.

Adverse Effects and Precautions

The most common adverse effects with ferumoxsil are diarrhoea, nausea, vomiting, and abdominal pain; oral paraesthesia has also been reported. Ferumoxsil should be used with caution in patients with iron overload disorders.

Uses and Administration

Ferumoxsil consists of a silicone polymer bonded to colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p.1474) for imaging of the gastrointestinal tract; the particles remain in the stomach and intestine when given orally or rectally and provide contrast enhancement. It is given as a suspension containing 175 micrograms/mL of iron. The usual dose is 600 to 900 mL by mouth, or 300 to 600 mL rectally.

Preparations

USP 31: Ferumoxsil Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austria: Lumirem; ***Braz.:*** Lumirem†; ***Denm.:*** Lumirem; ***Fin.:*** Lumirem; ***Fr.:*** Lumirem; ***Ger.:*** Lumirem; ***Ital.:*** Lumirem; ***Neth.:*** Lumirem; ***Port.:*** Lumirem; ***Swed.:*** Lumirem; ***USA:*** Gastromark.

Ferumoxtran-10 *(USAN)*

AMI-227; BMS-180549; Code 7227.

CAS — 189047-99-2.

Profile

Ferumoxtran-10 consists of colloidal particles of magnetite (iron oxide) coated with a low-molecular-weight dextran. It has superparamagnetic properties and is under investigation as a magnetic resonance contrast medium for imaging of the lymphatic system.

Gadobenic Acid *(BAN, rINN)*

Acide Gadobénique; Ácido gadobénico; Acidum Gadobenicum; B-19036; Gd-BOPTA. Dihydrogen [(±)-4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5−)]gadolinate(2−).

Гадобеновая Кислота

$C_{22}H_{28}GdN_3O_{11}$ = 667.7.

CAS — 113662-23-0.

ATC — V08CA08.

ATC Vet — QV08CA08.

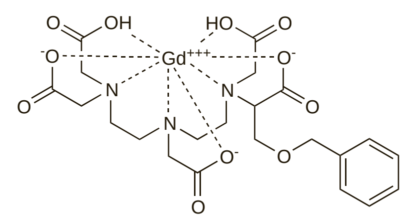

Meglumine Gadobenate *(BANM, rINNM)*

B-19036/7; Gadobenaattidimeglumiini; Gadobenatdimeglumin; Gadobénate de Méglumine; Gadobenate Dimeglumine *(USAN)*; Gadobenato de meglumina; Gadobenatum Dimegluminum; Meglumini Gadobenas.

Меглумина Гадобенат

$C_{22}H_{28}GdN_3O_{11},2C_7H_{17}NO_5$ = 1058.1.

CAS — 127000-20-8.

ATC — V08CA08.

ATC Vet — QV08CA08.

Adverse Effects and Precautions

As for Gadopentetic Acid, p.1479.

◊ References.

1. Kirchin MA, *et al.* Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. *J Magn Reson Imaging* 2001; **14:** 281–94.
2. Shellock FG, *et al.* Safety of gadobenate dimeglumine (MultiHance): summary of findings from clinical studies and postmarketing surveillance. *Invest Radiol* 2006; **41:** 500–9.

Pharmacokinetics

Gadobenate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of about 1.2 to 1.7 hours has been reported. It is not metabolised and about 78 to 94% of a dose is excreted in the urine within 24 hours; about 2 to 4% is excreted in the faeces.

Uses and Administration

Gadobenic acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the liver and CNS.

Gadobenic acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadobenate 529 mg/mL (0.5 mmol/mL). Usual doses for imaging are:

- liver: 0.1 mL/kg (0.05 mmol/kg) intravenously
- brain or spine: 0.2 mL/kg (0.1 mmol/kg) intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: MultiHance; ***Belg.:*** MultiHance; ***Cz.:*** MultiHance; ***Denm.:*** MultiHance; ***Fin.:*** MultiHance; ***Fr.:*** MultiHance; ***Ger.:*** MultiHance; ***Gr.:*** MultiHance; ***Hung.:*** MultiHance; ***Irl.:*** MultiHance†; ***Israel:*** MultiHance; ***Ital.:*** MultiHance; ***Neth.:*** MultiHance; ***Norw.:*** MultiHance; ***NZ:*** MultiHance; ***Port.:*** MultiHance; ***Spain:*** MultiHance; ***Swed.:*** MultiHance; ***Switz.:*** MultiHance; ***UK:*** MultiHance; ***USA:*** MultiHance.

Gadobutrol *(rINN)*

Gadobutrolum. {10-[(1*RS*,2*SR*)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato-(3−)}gadolinium.

Гадобутрол

$C_{18}H_{31}GdN_4O_9$ = 604.7.

CAS — 138071-82-6.

ATC — V08CA09.

ATC Vet — QV08CA09.

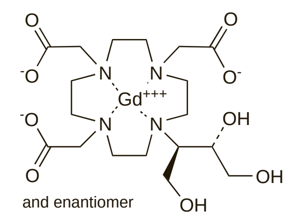

and enantiomer

Adverse Effects and Precautions

As for Gadopentetic Acid, p.1479. Gadobutrol may prolong cardiac repolarisation and should not be used in patients with uncorrected hypokalaemia. Caution is required in patients with severe cardiovascular disease, and in those with congenital long QT syndrome or a history of drug-induced arrhythmias.

Pharmacokinetics

Gadobutrol is rapidly distributed into the extracellular space following intravenous injection. It is not significantly bound to plasma proteins. An elimination half-life of about 1.8 hours has been reported. It is not metabolised and more than 90% of a dose is excreted in the urine within 12 hours; less than 0.1% is excreted in the faeces.

Uses and Administration

Gadobutrol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the CNS, kidneys, and liver, and in magnetic resonance angiography.

Gadobutrol is available as a solution containing 605 mg/mL (1 mmol/mL). Usual doses are:

- cranial and spinal imaging: 0.1 mL/kg (0.1 mmol/kg) intravenously. A second dose of up to 0.2 mL/kg (0.2 mmol/kg) may be given within 30 minutes if required
- kidneys and liver: 0.1 mL/kg (0.1 mmol/kg) intravenously
- angiography: 0.1 to 0.3 mL/kg (0.1 to 0.3 mmol/kg) intravenously

A solution containing 302.5 mg/mL (0.5 mmol/mL) has also been used.

◊ References.

1. Huppertz A, Rohrer M. Gadobutrol, a highly concentrated MR-imaging contrast agent: its physicochemical characteristics and the basis for its use in contrast-enhanced MR angiography and perfusion imaging. *Eur Radiol* 2004; **14** (suppl 5): M12–M18.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Gadovist; ***Austria:*** Gadovist; ***Belg.:*** Gadovist; ***Canad.:*** Gadovist; ***Cz.:*** Gadovist; ***Denm.:*** Gadovist; ***Fin.:*** Gadovist; ***Ger.:*** Gadovist; ***Gr.:*** Gadovist; ***Hung.:*** Gadovist; ***Ital.:*** Gadovist; ***Neth.:*** Gadovist; ***Norw.:*** Gadovist; ***NZ:*** Gadovist; ***Port.:*** Gadovist; ***Rus.:*** Gadovist (Гадовист); ***S.Afr.:*** Gadovist; ***Spain:*** Gadograf; Gadovist; ***Swed.:*** Gadovist; ***Switz.:*** Gadovist; ***UK:*** Gadovist.

Gadodiamide *(BAN, USAN, rINN)*

Gadodiamid; Gadodiamida; Gadodiamidi; Gadodiamidum; Gd-DTPA-BMA; S-041. [*N,N*-Bis(2-{(carboxymethyl)[(methylcarbamoyl)methyl]amino}ethyl)glycinato(3−)]gadolinium; a complex of gadolinium with diethylenetriamine penta-acetic acid bismethylamide.

Гадодиамид

$C_{16}H_{26}GdN_5O_8$ = 573.7.
CAS — 131410-48-5 (anhydrous gadodiamide); 122795-43-1 (gadodiamide hydrate).
ATC — V08CA03.
ATC Vet — QV08CA03.

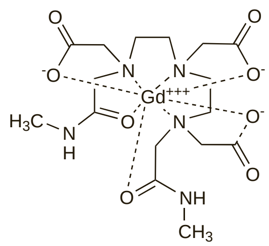

Pharmacopoeias. In *US.*

USP 31 (Gadodiamide). A white, odourless, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Store in airtight containers.

Adverse Effects and Precautions

As for Gadopentetic Acid, below.

Effects on the pancreas. Acute pancreatitis developed in a patient shortly after injection of gadodiamide for hepatic imaging.[1] Another patient[2] developed both acute pancreatitis and acute renal failure after use of gadodiamide for angiography.

1. Terzi C, Sökmen S. Acute pancreatitis induced by magnetic-resonance-imaging contrast agent. *Lancet* 1999; **354:** 1789–90. Correction. *ibid.* 2000; **355:** 660.
2. Schenker MP, *et al.* Gadolinium arteriography complicated by acute pancreatitis and acute renal failure. *J Vasc Interv Radiol* 2001; **12:** 393.

Interference with diagnostic tests. Gadodiamide may interfere with colorimetric methods for measuring serum calcium concentrations, resulting in falsely low measurements. Severe pseudohypocalcaemia has been reported[1-3] after the use of gadodiamide, particularly in patients with renal impairment.[2] There is also *in vitro* evidence that a similar interference may occur with gadoversetamide.[2]

1. Doorenbos CJ, *et al.* Severe pseudohypocalcemia after gadolinium-enhanced magnetic resonance angiography. *N Engl J Med* 2003; **349:** 817–18.
2. Prince MR, *et al.* Gadodiamide administration causes spurious hypocalcemia. *Radiology* 2003; **227** 639–46.
3. Williams SF, *et al.* Spurious hypocalcemia after gadodiamide administration. *Mayo Clin Proc* 2005; **80:** 1655–7.

Renal impairment. For the view that gadodiamide may carry a particular risk of the development of nephrogenic systemic sclerosis in patients with renal impairment, see p.1479.

Pharmacokinetics

Gadodiamide is rapidly distributed into extracellular fluid. About 96% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 70 minutes has been reported. Gadodiamide is not bound to plasma proteins. It is removed by haemodialysis.

Uses and Administration

Gadodiamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures, imaging of the whole body, angiography, and mammography.

Gadodiamide is available as a solution containing 287 mg/mL (0.5 mmol/mL). Usual doses are:

- cranial and spinal imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg). Adults may be given a second dose of 0.4 mL/kg (0.2 mmol/kg) within 20 minutes if required.
- whole body imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg)
- kidneys: 0.1 mL/kg (0.05 mmol/kg) may be adequate
- angiography: for adults, 0.2 mL/kg (0.1 mmol/kg)
- mammography: 0.2 to 0.4 mL/kg (0.1 to 0.2 mmol/kg).

Preparations

USP 31: Gadodiamide Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Omniscan†; ***Austral.:*** Omniscan; ***Austria:*** Omniscan; ***Belg.:*** Omniscan; ***Braz.:*** Omniscan†; ***Canad.:*** Omniscan; ***Chile:*** Omniscan; ***Cz.:*** Omniscan; ***Denm.:*** Omniscan; ***Fin.:*** Omniscan; ***Fr.:*** Omniscan; ***Ger.:*** Omniscan; ***Gr.:*** Omniscan; ***Hung.:*** Omniscan; ***Israel:*** Omniscan; ***Ital.:*** Omniscan; ***Jpn:*** Omniscan; ***Neth.:*** Omniscan; ***Norw.:*** Omniscan; ***NZ:*** Omniscan; ***Port.:*** Omniscan; ***Rus.:*** Omniscan (Омнискан)†; ***Spain:*** Omniscan; ***Swed.:*** Omniscan; ***Switz.:*** Omniscan; ***UK:*** Omniscan; ***USA:*** Omniscan; ***Venez.:*** Omniscan†.

Gadofosveset Trisodium *(USAN, rINNM)*

Gadofosveset trisódico; Gadofosvéset Trisodique; Gadofosvesetum Trinatricum; MS-32520; MS-325 (gadofosveset). Trisodium (*N*-{2-[bis(carboxymethyl)amino]ethyl}-*N*-{(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl}glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6−))gadolinate(3−).

Тринатрий Гадофосвезет

$C_{33}H_{38}GdN_3Na_3O_{14}P$ = 957.9.
CAS — 201688-00-8 (gadofosveset); 193901-90-5 (gadofosveset trisodium).
ATC — V08CA11.
ATC Vet — QV08CA11.

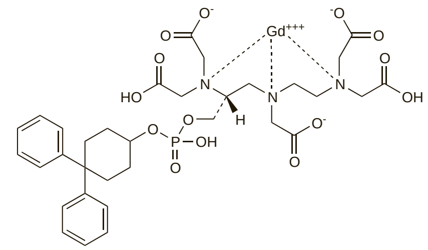

(gadofosveset)

Profile

Gadofosveset is a gadolinium chelate used as a paramagnetic contrast medium (p.1474) in magnetic resonance angiography. It binds to plasma proteins, particularly albumin, and therefore acts as a blood pool agent, allowing visualisation of the vasculature.

Gadofosveset is given intravenously as the trisodium salt. It is available as a solution containing gadofosveset trisodium 244 mg/mL (0.25 mmol/mL). The usual dose is 0.12 mL/kg (0.03 mmol/kg) by intravenous injection.

◊ References.

1. Henness S, Keating GM. Gadofosveset. *Drugs* 2006; **66:** 851–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Vasovist; ***Gr.:*** Vasovist; ***Hung.:*** Vasovist; ***Neth.:*** Vasovist; ***Port.:*** Vasovist; ***UK:*** Vasovist.

Gadopentetic Acid *(BAN, rINN)*

Acide Gadopentétique; Ácido gadopentético; Acidum Gadopenteticum; Gadolinium-DTPA. Dihydrogen (*N,N*-bis{2-[bis(carboxymethyl)amino]ethyl}glycinato(5−))gadolinate(2−); a complex of gadolinium with diethylenetriamine penta-acetic acid.

Гадопентетовая Кислота

$C_{14}H_{20}GdN_3O_{10}$ = 547.6.
CAS — 80529-93-7.
ATC — V08CA01.
ATC Vet — QV08CA01.

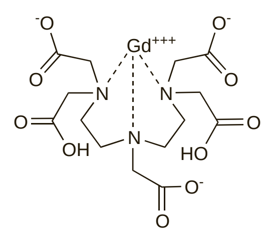

Meglumine Gadopentetate *(BANM, rINNM)*

Dimeglumine Gadopentetate; Gadopentétate de Méglumine; Gadopentetate Dimeglumine *(USAN)*; Gadopentetate Meglumine; Gadopentétate méglumine; Gadopentetato de meglumina; Meglumini gadopentetas; SH-L-451-A.

Меглумина Гадопентетат

$C_{14}H_{20}GdN_3O_{10},(C_7H_{17}NO_5)_2$ = 938.0.
CAS — 86050-77-3.
ATC — V08CA01.
ATC Vet — QV08CA01.

Pharmacopoeias. *Chin.* and *US* include only as an injection.

Adverse Effects

There may be headache, nausea, vomiting, and transient sensations of heat or cold or taste disturbances on injection of gadopentetate or other gadolinium chelates. Rarely, convulsions, hypotension, allergic or anaphylactoid reactions, and shock may occur. Paraesthesias, dizziness, and localised pain have also been reported. Transient elevations of serum iron and bilirubin values have been observed. Nephrogenic systemic fibrosis may occur rarely in patients with renal impairment (see under Precautions, below).

◊ General references.

1. Nelson KL, *et al.* Clinical safety of gadopentetate dimeglumine. *Radiology* 1995; **196:** 439–43.

Effects on the nervous system. Subacute encephalopathy has been reported[1] in a woman who was given repeated doses of a gadolinium chelate for magnetic resonance imaging. It was suggested that renal impairment may have contributed to retention of gadolinium, with subsequent diffusion into the CSF.

1. Maramattom BV, *et al.* Gadolinium encephalopathy in a patient with renal failure. *Neurology* 2005; **64:** 1276–8.

Hypersensitivity. Although rare, anaphylactoid reactions have occurred with a number of gadolinium chelates.[1] Severe reactions have been reported with gadopentetate,[2] gadoterate,[3,4] and gadoteridol,[5] including a fatal reaction with gadopentetate.[6] There has also been a report[7] of a severe reaction with gadoteridol in a patient who had previously tolerated gadopentetate. Reactions may occur despite premedication with antihistamines and corticosteroids.[8]

1. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; **12:** 205–13.
2. Tardy B, *et al.* Anaphylactic shock induced by intravenous gadopentetate dimeglumine. *Lancet* 1992; **339**: 494.
3. Meuli RA, Maeder P. Life-threatening anaphylactoid reaction after IV injection of gadoterate meglumine. *Am J Roentg* 1996; **166:** 729.
4. Beaudouin E, *et al.* Anaphylactic shock induced by gadoterate meglumine (DOTAREM). *Allerg Immunol (Paris)* 2003; **35:** 382–5.
5. Shellock FG, *et al.* Adverse reaction to intravenous gadoteridol. *Radiology* 1993; **189:** 151–2.
6. Jordan RM, Mintz RD. Fatal reaction to gadopentetate dimeglumine. *Am J Roentg* 1995; **164:** 743–4.
7. Witte RJ, Anzai LL. Life-threatening anaphylactoid reaction after intravenous gadoteridol administration in a patient who had previously received gadopentetate dimeglumine. *Am J Neuroradiol* 1994; **15:** 523–4.
8. Dillman JR, *et al.* Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *Am J Roentg* 2008; **190:** 187–90.

Precautions

Gadopentetate should not be used in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2) or with acute renal impairment associated with hepato-renal syndrome or liver transplantation (see Renal Impairment, below). It should be given with care to patients with moderate renal impairment, epilepsy, hypotension, or a history of hypersensitivity, asthma, or other allergic respiratory disorders. Care should be taken to avoid extravasation. Gadopentetate may interfere with tests of serum iron or bilirubin concentrations.

Breast feeding. Studies[1-3] have shown that gadopentetate is distributed into breast milk in very small amounts; the total amount excreted in the milk within 24 hours was less than 0.04% of the intravenous dose in all cases. No adverse effects have been seen in breast-feeding infants whose mothers were receiving gadopentetic acid and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Schmiedl U, *et al.* Excretion of gadopentetate dimeglumine in human breast milk. *Am J Roentg* 1990; **154:** 1305–6.
2. Rofsky NM, *et al.* Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. *J Magn Reson Imaging* 1993; **3:** 131–2.
3. Kubik-Huch RA, *et al.* Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology* 2000; **216:** 555–8.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Myasthenia gravis. Acute deterioration of myasthenia gravis has been reported[1] in a patient after imaging of the brain using gadopentetate.

1. Nordenbo AM, Somnier FE. Acute deterioration of myasthenia gravis after intravenous administration of gadolinium-DTPA. *Lancet* 1992; **340:** 1168.

Renal impairment. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) is a rare condition that has been reported in patients with renal impairment. Use of gadolinium-containing contrast media appears to be a risk factor;[1-3] most cases have occurred with gadodiamide given in high doses for magnetic resonance angiography, but there have also been reports with other gadolinium-containing contrast media and with lower doses. It has been suggested that the mechanism involves release of free gadolinium ions into the tissues, and that the potential for this varies between the different gadolinium-based contrast media available, with gadodiamide and gadoversetamide more likely to do so.[4] The macrocyclic structure of gadoteridol and gadoterate was thought to be less prone to this effect, but further research is needed. The FDA[5] and the MHRA[6] advise that use of gadolinium-containing contrast media should be restricted in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2). The MHRA contra-indicates the use of gadodiamide or gadopentetate in such patients (other gadolinium-containing contrast media are under review), whereas the FDA advises that all gadolinium-containing contrast media should be avoided unless the diagnostic information is essential and cannot be obtained another way. The FDA gives a similar warning for use in patients with acute renal failure associated with hepato-renal syndrome or around the time of liver transplantation. The value of haemodialysis to remove gadolinium-containing contrast media after use is unknown.

1. Perazella MA, Rodby RA. Gadolinium-induced nephrogenic systemic fibrosis in patients with kidney disease. *Am J Med* 2007; **120:** 561–2.
2. Health Canada. Gadolinium-containing contrast agents and nephrogenic systemic fibrosis: update. *Can Adverse React News* 2007; **17** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v17n4-eng.php#1 (accessed 14/07/08)
3. Moreno-Romero JA, *et al.* Nephrogenic systemic fibrosis: a case series suggesting gadolinium as a possible aetiological factor. *Br J Dermatol* 2007; **157:** 783–7.
4. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? *Semin Dial* 2008; **21:** 129–34.
5. FDA. Gadolinium-containing contrast agents for magnetic resonance imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance (issued 08/06/06, updated 22/12/06 and 23/05/07). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705.htm (accessed 14/07/08)
6. MHRA/CHM. Gadolinium-containing MRI contrast agents: nephrogenic systemic fibrosis. *Drug Safety Update* 2007; **1** (1): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2031801&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)

Pharmacokinetics

Gadopentetate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of 1.6 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours. It does not appear to bind to plasma proteins. A small amount is distributed into breast milk. Gadopentetate is removed by haemodialysis.

Uses and Administration

Gadopentetic acid is an ionic gadolinium chelate used as a contrast medium in magnetic resonance imaging (p.1474). Gadolinium has paramagnetic properties that affect the relaxivity of hydrogen ions, increasing the signal intensity and therefore enhancing the contrast between tissues. Chelation of gadolinium reduces its toxicity while retaining its paramagnetic properties; it also affects distribution within the body. Most gadolinium chelates distribute freely into extracellular fluid but do not cross the blood-brain barrier, and they are particularly useful for imaging the brain and associated structures.

Gadopentetic acid is given intravenously as meglumine gadopentetate for contrast enhancement in magnetic resonance imaging of cranial and spinal structures, and of the whole body, and may also be used for evaluation of renal function. It is given by intra-articular injection for arthrography, and has been used orally and rectally in imaging of the gastrointestinal tract.

For cranial, spinal, and whole body imaging, a solution containing meglumine gadopentetate 469.01 mg/mL (0.5 mmol/mL) is used. The usual dose in adults, children, and neonates is 0.2 mL/kg (0.1 mmol/kg) intravenously. For cranial and spinal imaging, a further dose of 0.2 mL/kg (0.1 mmol/kg) may be given within 30 minutes if necessary; in adults this second dose may be 0.4 mL/kg (0.2 mmol/kg). For whole body imaging in adults and children over 2 years, a dose of 0.4 mL/kg (0.2 mmol/kg) may be needed in some cases to produce adequate contrast and in special circumstances a dose of 0.6 mL/kg (0.3 mmol/kg) may be used in adults.

For arthrography a solution containing meglumine gadopentetate 1.876 mg/mL (0.002 mmol/mL) is given by intra-articular injection. The dose depends on the joint being imaged; the usual range is from 1 to 20 mL.

For imaging of the gastrointestinal tract a solution containing meglumine gadopentetate 9.38 mg/mL has been used, diluted further before use.

Preparations

USP 31: Gadopentetate Dimeglumine Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Magnevist; Opacite; Viewgam; ***Austral.:*** Magnevist; ***Austria:*** Magnevist; ***Belg.:*** Magnevist; ***Braz.:*** Magnevistan; ***Canad.:*** Magnevist; ***Chile:*** Magnevistan; ***Cz.:*** Magnegita; Magnevist; ***Denm.:*** Magnevist; ***Fin.:*** Magnevist; ***Fr.:*** Magnevist; ***Ger.:*** Magnevist; ***Gr.:*** Magnevist; ***Hung.:*** Magnevist; ***Ital.:*** Magnevist; ***Mex.:*** Viewgam; ***Neth.:*** Magnevist; ***Norw.:*** Magnevist; ***NZ:*** Magnevist; ***Port.:*** Magnevist; ***Rus.:*** Magnevist (Магневист); ***S.Afr.:*** Magnevist; ***Spain:*** Magnevist; Magnograf; ***Swed.:*** Magnevist; ***Switz.:*** Magnevist; ***UK:*** Magnevist; ***USA:*** Magnevist; ***Venez.:*** Magnevistan.

Gadoteric Acid *(BAN, rINN)*

Acide Gadotérique; Ácido gadotérico; Acidum Gadotericum; Gadoteerihappo; Gadotersyra; Gd-DOTA; ZK-112004. Hydrogen [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4−)]-gadolinate(1−); Hydrogen [1,4,7,10-tetrakis(carboxylatomethyl)-1,4,7,10-tetra-azacyclododecane-κ⁴N]gadolinate(1−).

Гадотеровая Кислота

$C_{16}H_{25}GdN_4O_8$ = 558.6.
CAS — 72573-82-1.
ATC — V08CA02.
ATC Vet — QV08CA02.

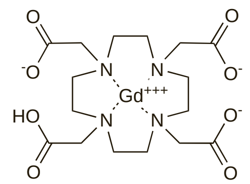

Meglumine Gadoterate *(BANM, rINNM)*

Gadotérate de Méglumine; Gadoterate Meglumine; Gadoterato de meglumina; Meglumini Gadoteras.

Меглумина Гадотерат

ATC — V08CA02.
ATC Vet — QV08CA02.

Adverse Effects and Precautions

As for Gadopentetic Acid, p.1479.

Hypersensitivity. For reports of anaphylactoid reactions with gadoterate, see under Adverse Effects of Gadopentetic Acid, p.1479.

Pharmacokinetics

Gadoterate is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. A plasma half-life of about 1.5 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours.

Uses and Administration

Gadoteric acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (above). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body, and in magnetic resonance angiography.

Gadoteric acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadoterate 376.9 mg/mL (0.5 mmol/mL). The usual dose in adults and children is 0.2 mL/kg (0.1 mmol/kg) by intravenous injection. A second dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given if necessary. For angiography, a dose of 0.1 to 0.2 mL/kg (0.05 to 0.1 mmol/kg) may be given, repeated if required.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dotarem; ***Austral.:*** Dotarem; ***Austria:*** Dotarem; ***Belg.:*** Artirem; Dotarem; ***Braz.:*** Dotarem†; ***Chile:*** Dotarem; ***Cz.:*** Dotarem; ***Denm.:*** Dotarem; ***Fin.:*** Dotarem; ***Fr.:*** Artirem; Dotarem; ***Ger.:*** Artirem; Dotarem; ***Gr.:*** Dotarem; ***Hung.:*** Dotarem; ***Israel:*** Dotarem; ***Ital.:*** Dotarem; ***Neth.:*** Artirem; Dotarem; ***Norw.:*** Dotarem; ***Port.:*** Dotarem; ***Spain:*** Dotarem; ***Swed.:*** Dotarem; ***Switz.:*** Artirem; Dotarem; ***Venez.:*** Dotarem.

Gadoteridol *(BAN, USAN, rINN)*

Gadotéridol; Gadoteridoli; Gadoteridolum; Gd-HP-DO3A; SQ-32692. (±)-[10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3−)]gadolinium.

Гадотеридол

$C_{17}H_{29}GdN_4O_7$ = 558.7.
CAS — 120066-54-8.
ATC — V08CA04.
ATC Vet — QV08CA04.

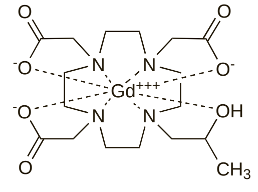

Pharmacopoeias. In *US.*

USP 31 (Gadoteridol). A white to off-white, odourless, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in isopropyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Gadopentetic Acid, above.

◊ Reviews.

1. Runge VM, Parker JR. Worldwide clinical safety assessment of gadoteridol injection: an update. *Eur Radiol* 1997; **7** (suppl 5): 243–5.

Hypersensitivity. For a report of an anaphylactoid reaction with gadoteridol, see under Adverse Effects of Gadopentetic Acid, p.1479.

Pharmacokinetics

Gadoteridol is distributed into extracellular fluid after intravenous injection. About 94% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 1.57 hours has been reported.

Uses and Administration

Gadoteridol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body.

Gadoteridol is available as a solution containing 279.3 mg/mL (0.5 mmol/mL). The usual adult dose is 0.2 mL/kg (0.1 mmol/kg) intravenously; for CNS imaging, an additional dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given up to 30 minutes after the first if necessary. A single dose of 0.2 mL/kg (0.1 mmol/kg) is used in children from 6 months of age.

Preparations

USP 31: Gadoteridol Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Prohance; ***Austria:*** Prohance; ***Belg.:*** Prohance; ***Cz.:*** Prohance; ***Denm.:*** Prohance; ***Fin.:*** Prohance; ***Fr.:*** Prohance; ***Ger.:*** Prohance; ***Irl.:*** Prohance†; ***Ital.:*** Prohance; ***Jpn:*** Prohance; ***Neth.:*** Prohance; ***Norw.:*** Prohance; ***Spain:*** Prohance; ***Swed.:*** Prohance; ***Switz.:*** Prohance; ***UK:*** Prohance; ***USA:*** Prohance.

Gadoversetamide *(BAN, USAN, rINN)*

Gadoversetamida; Gadoversétamide; Gadoversetamidum; MP-1177. {*N,N*-Bis[2-({(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl}amino)ethyl]glycinato(3−)}gadolinium.

Гадоверсетамид

$C_{20}H_{34}GdN_5O_{10}$ = 661.8.
CAS — 131069-91-5.
ATC — V08CA06.
ATC Vet — QV08CA06.

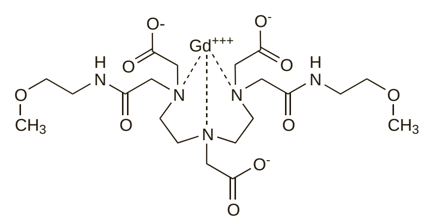

Pharmacopoeias. In *US.*

USP 31 (Gadoversetamide). A white odourless powder. Freely soluble in water. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Gadopentetic Acid, p.1479.

Interference with diagnostic tests. Like gadodiamide (see p.1479), gadoversetamide may interfere with colorimetric methods for measuring serum-calcium concentrations.

Gadoversetamide may also interfere with measurement of serum-copper, iron, and zinc concentrations.

Renal impairment. For the view that gadoversetamide may carry an increased risk of the development of nephrogenic systemic sclerosis in patients with renal impairment, see p.1479.

Pharmacokinetics

Gadoversetamide is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. An elimination half-life of about 1.7 hours has been reported. It is not metabolised and about 95.5% of a dose is excreted in the urine within 24 hours. Gadoversetamide is removed by haemodialysis.

Uses and Administration

Gadoversetamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body.

Gadoversetamide is available as a solution containing 330.9 mg/mL (0.5 mmol/mL). The usual dose is 0.2 mL/kg (0.1 mmol/kg) intravenously.

Preparations

USP 31: Gadoversetamide Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Optimark; ***Austral.:*** Optimark; ***Canad.:*** Optimark; ***Cz.:*** Optimark; ***Port.:*** Optimark; ***USA:*** Optimark.

Gadoxetic Acid *(rINN)*

Acide Gadoxétique; Ácido gadoxético; Acidum Gadoxeticum; Gd-EOB-DTPA. Dihydrogen [*N*-{(2*S*)-2-[bis(carboxymethyl)-amino]-3-(*p*-ethoxyphenyl)propyl}-*N*-{2-[bis(carboxymethyl)-amino]ethyl}glycinato(5−)]gadolinate(2−).

Гадоксетовая Кислота

$C_{23}H_{30}GdN_3O_{11}$ = 681.7.
CAS — 135326-11-3 (gadoxetic acid).
ATC — V08CA10.
ATC Vet — QV08CA10.

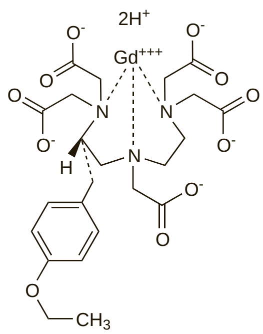

Sodium Gadoxetate *(rINNM)*

Gadoxétate de Sodium; Gadoxetate Disodium *(USAN)*; Gadoxetate Sodium; Gadoxetato de sodio; Natrii Gadoxetas; ZK-139834.

Натрий Гадоксетат

$C_{23}H_{28}GdN_3Na_2O_{11}$ = 725.7.
CAS — 135326-22-6.
ATC — V08CA10.
ATC Vet — QV08CA10.

Adverse Effects and Precautions

As for Gadopentetic Acid, p.1479.

Pharmacokinetics

Gadoxetate is distributed into the extracellular space after intravenous injection and is also taken up by the liver. It is less than 10% bound to plasma proteins. It is excreted in about equal amounts in the bile and in the urine. An elimination half-life of about 1 hour has been reported. Gadoxetate is removed by haemodialysis.

Uses and Administration

Gadoxetic acid is an ionic gadolinium chelate with actions similar to those of gadopentetic acid (p.1480). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p.1474). It is taken up by the liver and excreted in bile and is used in imaging of the liver.

Gadoxetic acid is given intravenously as the sodium salt. It is available as a solution containing sodium gadoxetate 181.4 mg/mL (0.25 mmol/mL). The usual dose is 0.1 mL/kg (0.025 mmol/kg).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Primovist; ***Cz.:*** Primovist; ***Fin.:*** Primovist; ***Gr.:*** Primovist; ***Hung.:*** Primovist; ***Neth.:*** Primovist; ***Norw.:*** Primovist; ***Swed.:*** Primovist; ***Switz.:*** Primovist; ***UK:*** Primovist.

Galactose *(USAN)*

D-Galactopyranose; α-D-Galactopyranose; Galactosa; D-Galactose; Galactosum; Galaktoosi; Galaktos; Galaktosa; Galaktóz; Galaktoza; Galaktozė.

$C_6H_{12}O_6$ = 180.2.
CAS — 59-23-4 (D-galactose); 3646-73-9 (α-D-galactose).
ATC — V04CE01; V08DA02 (microparticles of galactose).
ATC Vet — QV04CE01; QV08DA02 (microparticles of galactose).

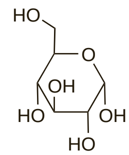

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Galactose). A white or almost white, crystalline or finely granulated powder. Freely soluble or soluble in water; very slightly soluble in alcohol.

USNF 26 (Galactose). A white, crystalline or finely granulated powder. Soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Profile

Galactose is a naturally occurring monosaccharide used as an ultrasound contrast medium (p.1474); dissolution of galactose microparticles releases microbubbles of air that provide echo-enhancement. Galactose is used to enhance ultrasound imaging of the female genital tract. It is given transcervically as a microbubble-microparticle suspension prepared immediately before use by suspending 3 g of galactose microparticles in 13.5 mL of a solution containing 200 mg/mL galactose. The usual dose is 2 to 5 mL, with additional doses of 1 to 2 mL as required, to a maximum of 30 mL. Similar suspensions of galactose, with palmitic acid to stabilise the microbubbles, have been used in echocardiography.

The clearance of galactose given intravenously has been used as a measure of liver function. Galactose labelled with carbon-13 (p.2277) has also been used.

Precautions. Preparations that contain, or are metabolised to, galactose may interfere with the results from glucose tests (p.2314). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/cber/safety/maltose110405.htm (accessed 01/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Levovist†; ***Austral.:*** Levovist; ***Austria:*** Echovist; Levovist†; Ombravist†; ***Canad.:*** Echovist†; Levovist†; ***Cz.:*** Levovist†; ***Denm.:*** Levovist†; ***Fin.:*** Echovist†; Levovist†; ***Fr.:*** Echovist; Levovist; ***Ger.:*** Echovist; Levovist; ***Hung.:*** Echovist; ***Israel:*** Echovist; ***Ital.:*** Levovist; ***Neth.:*** Echovist†; Levovist; ***Norw.:*** Levovist†; ***NZ:*** Levovist; ***Port.:*** Levovist; ***S.Afr.:*** Echovist†; ***Spain:*** Levograf; Levovist; ***Swed.:*** Echovist; Levovist†; ***Switz.:*** Levovist; ***UK:*** Echovist; Levovist†.

Multi-ingredient: ***Gr.:*** L-Vist.

Iobitridol *(BAN, rINN)*

Iobitridolum; Jobitridol; Jobitridoli. *N*,*N*′-Bis(2,3-dihydroxypropyl)-5-[2-(hydroxymethyl)hydracrylamido]-2,4,6-triiodo-*N*,*N*′-dimethylisophthalamide; .

Йобитридол

$C_{20}H_{28}I_3N_3O_9$ = 835.2.
CAS — 136949-58-1.
ATC — V08AB11.
ATC Vet — QV08AB11.

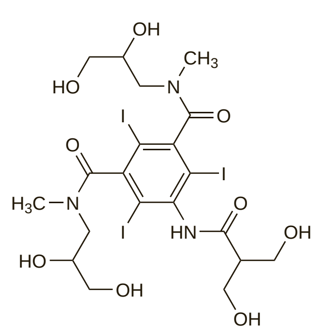

Profile

Iobitridol is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, or by instillation into body cavities and is used in a wide range of procedures including angiography, arthrography, cholangiopancreatography, and hysterosalpingography. It is also used for contrast enhancement in computed tomography.

It is usually available as solutions containing 54.84 to 76.78% of iobitridol (equivalent to 250 to 350 mg/mL of iodine). The dose and strength used varies depending on the procedure and route.

◊ References.

1. Petersein J, *et al.* Results of the safety and efficacy of iobitridol in more than 61,000 patients. *Eur Radiol* 2003; **13:** 2006–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Xenetic; Xenetix; ***Austria:*** Xenetix; ***Belg.:*** Xenetix; ***Braz.:*** Henetix†; ***Chile:*** Xenetix; ***Cz.:*** Xenetix; ***Denm.:*** Xenetix; ***Fin.:*** Xenetix; ***Fr.:*** Xenetix; ***Ger.:*** Xenetix; ***Gr.:*** Xenetix; ***Hung.:*** Xenetix; ***Israel:*** Xenetix; ***Ital.:*** Xenetix; ***Neth.:*** Xenetix; ***Norw.:*** Xenetix; ***Port.:*** Xenetix; ***Spain:*** Xenetix; ***Swed.:*** Xenetix; ***Switz.:*** Xenetix; ***Venez.:*** Xenetix.

Iocetamic Acid *(BAN, USAN, pINN)*

Acide Iocétamique; Ácido iocetámico; Acidum Iocetamicum; DRC-1201; Jocetamsyra; Josetaamihappo; MP-620. *N*-Acetyl-*N*-(3-amino-2,4,6-tri-iodophenyl)-2-methyl-β-alanine; 2-[*N*-(3-Amino-2,4,6-tri-iodophenyl)acetamidomethyl]-propionic acid.

Йоцетамовая Кислота

$C_{12}H_{13}I_3N_2O_3$ = 614.0.
CAS — 16034-77-8.
ATC — V08AC07.
ATC Vet — QV08AC07.

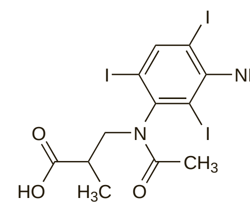

Description. Iocetamic acid contains about 62% of I.

Profile

Iocetamic acid is an ionic monomeric iodinated radiographic contrast medium with similar properties to iopanoic acid (p.1484). It is absorbed from the gastrointestinal tract and excreted in bile and has been given orally for cholecystography.

Preparations

Proprietary Preparations (details are given in Part 3)
Neth.: Cholebrine†.

Iodamide *(BAN, USAN, rINN)*

Ametriodinic Acid; B-4130; Iodamida; Iodamidum; Jodamid; Jodiamidi; SH-926. α,5-Diacetamido-2,4,6-tri-iodo-*m*-toluic acid; 3-Acetamido-5-acetamidomethyl-2,4,6-tri-iodobenzoic acid.

Йодамид

$C_{12}H_{11}I_3N_2O_4$ = 627.9.
CAS — 440-58-4.
ATC — V08AA03.
ATC Vet — QV08AA03.

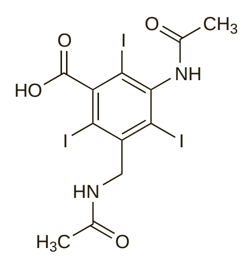

Description. Iodamide contains about 60.6% of I.

Pharmacopoeias. In *Jpn.*

Meglumine Iodamide *(BANM, rINNM)*

Iodamida de meglumina; Iodamide Meglumine *(USAN)*; Iodamide Méglumine; Meglumini Iodamidum. The *N*-methylglucamine salt of iodamide.

Меглумина Йодамид

$C_{12}H_{11}I_3N_2O_4,C_7H_{17}NO_5$ = 823.2.
CAS — 18656-21-8.
ATC — V08AA03.
ATC Vet — QV08AA03.

Description. Meglumine iodamide contains about 46.3% of I.

Sodium Iodamide *(BANM, rINNM)*

Iodamida sódica; Iodamide Sodique; Iodamide Sodium; Natrii Iodamidum.

Натрий Йодамид

$C_{12}H_{10}I_3N_2NaO_4$ = 649.9.
CAS — 10098-82-5.
ATC — V08AA03.
ATC Vet — QV08AA03.

Description. Sodium iodamide contains about 58.6% of I.

Profile

Iodamide is an ionic monomeric iodinated radiographic contrast medium (see p.1474). It is used in many procedures and may be given intravenously or by other routes, for example by instillation into the bladder or uterus; it has also been used for computed tomography.

It is usually given as a 24 to 65% solution of the meglumine salt, or as a mixture of the sodium and meglumine salts; solutions of the sodium salt have also been used. The dose varies according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Uromiro; ***Ital.:*** Isteropac ER; Opacist ER; Uromiro 24%, 36%, and 300†; Uromiro 300 Sodico†; Uromiro 340 and 420†; ***Switz.:*** Isteropac†; Opacist ER†; Uromiro†; ***Venez.:*** Angiomiron†; Uromiron.

Iodised Oil

Aceite yodado; Ethiodized Oil.

CAS — 8001-40-9 (iodised oil); 8008-53-5 (ethiodized oil injection).
ATC — V08AD01.
ATC Vet — QV08AD01.

Description. Iodised oil is an iodine addition product of the ethyl esters of the fatty acids obtained from poppy-seed oil. It contains about 35 to 39% of combined iodine.

Incompatibility. Because of its solvent action on polystyrene, iodised oil injection should not be given in syringes made with polystyrene.

Adverse Effects and Precautions

The risk of hypersensitivity reactions or iodism is greater after the use of iodised oil than after water-soluble iodinated contrast media such as the amidotrizoates. Pulmonary oil embolism is reported to be relatively frequent after lymphography but is not usually severe; however, hypotension, tachycardia, and pulmonary oedema and infarction may occur rarely and deaths have been reported in patients with pulmonary disease. Chemical pneumonitis, oedema, granuloma formation, and goitre have occurred.

Great care must be taken to avoid vascular structures, because of the danger of oil embolism; it should therefore not be used in areas affected by haemorrhage or local trauma. Iodised oil should be used with care in patients with thyroid dysfunction or a history of allergic reactions. Use may interfere with thyroid-function tests for several months.

Hysterosalpingography. The use of oily contrast media such as iodised oil for hysterosalpingography has been associated with serious adverse effects, including tubal occlusion,[1] and cerebral and pulmonary oil embolism,[2,3] and water-soluble contrast media are usually preferred. However, diagnostic hysterosalpingography using iodised oil has been associated with an increase in fertility[4] and randomised trials[5,6] using iodised oil for treatment in patients with unexplained infertility have found a similar effect.

1. Wright FW, Stallworthy J. Female sterility produced by investigation. *BMJ* 1973; **3:** 632.
2. Dan U, *et al.* Cerebral embolization and coma after hysterosalpingography with oil-soluble contrast medium. *Fertil Steril* 1990; **53:** 939–40.
3. Uzun O, *et al.* Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. *Respirology* 2004; **9:** 134–6.
4. Johnson NP. A review of the use of lipiodol flushing for unexplained infertility. *Treat Endocrinol* 2005; **4:** 233–43.
5. Nugent D, *et al.* A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. *Fertil Steril* 2002; **77:** 173–5.
6. Johnson NP, *et al.* The FLUSH trial—flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. *Hum Reprod* 2004; **19:** 2043–51.

Pharmacokinetics

Iodised oil may persist in the body for several weeks or months. It is only slowly absorbed from most body sites, although absorption from the peritoneal cavity is stated to be relatively rapid. It is reported to be slowly metabolised to fatty acids and iodine.

Uses and Administration

Iodised oil is an iodinated radiographic contrast medium (p.1474) that is used mainly for lymphography. It has been used for hysterosalpingography but water-soluble agents are preferred. Although some preparations have been used in bronchography, the fluid injection of iodised oil is unsuitable for such use. Doses are dependent upon the procedure.

Because it is slowly metabolised to release iodine, iodised oil is used in the management of iodine deficiency (p.2170).

Infertility. For reference to the use of iodised oil in the management of infertility, see Hysterosalpingography under Adverse Effects and Precautions, above.

Malignant neoplasms. Intra-arterial injection of iodised oil has been used in both the diagnosis and management of malignant neoplasms of the liver (p.667). After injection into the hepatic artery, iodised oil is selectively retained by hepatic carcinomas and may have a role as an adjunct to computed tomography for both diagnosis and monitoring.[1-3] It has also been used in the management of hepatic carcinoma,[2,4] either to increase the retention of antineoplastics (chemoembolisation),[5] or to provide targeted delivery of radioactive iodine.[6]

1. Dalla Palma L. Diagnostic imaging and interventional therapy of hepatocellular carcinoma. *Br J Radiol* 1998; **71:** 808–18.
2. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003; **52** (suppl): iii1–iii8. Also available at: http://www.bsg.org.uk/pdf_word_docs/hcc.pdf (accessed 27/03/06)
3. Zheng X-H, *et al.* Detection of hypervascular hepatocellular carcinoma: comparison of multi-detector CT with digital subtraction angiography and Lipiodol CT. *World J Gastroenterol* 2005; **11:** 200–203.
4. Trinchet JC, *et al.* Review article: intra-arterial treatments in patients with hepatocellular carcinoma *Aliment Pharmacol Ther* 2003; **17** (suppl 2): 111–118.
5. Group d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; **332:** 1256–61.
6. Lau WY, *et al.* Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353:** 797–801.

Preparations

BP 2008: Iodised Oil Fluid Injection;
USP 31: Ethiodized Oil Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Lipiodol; ***Austral.:*** Lipiodol; ***Austria:*** Lipiodol; ***Belg.:*** Lipiodol; ***Braz.:*** Lipiodol†; ***Chile:*** Lipiodol; ***Cz.:*** Lipiodol; ***Denm.:*** Lipiodol; ***Fr.:*** Lipiodol; ***Ger.:*** Lipiodol; ***Gr.:*** Lipiodol; ***Hung.:*** Lipiodol; ***Israel:*** Lipiodol; ***Ital.:*** Lipiodol; ***Neth.:*** Lipiodol; ***Norw.:*** Lipiodol†; ***NZ:*** Lipiodol; ***Port.:*** Lipiodol; ***Switz.:*** Lipiodol; ***UK:*** Lipiodol; ***USA:*** Ethiodol; ***Venez.:*** Lipiodol.

Iodixanol *(BAN, USAN, rINN)*

2-5410-3A; Iodixanolum; Jodiksanoli; Jodixanol. 5,5′-[(2-Hydroxytrimethylene)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide].

Йодиксанол

$C_{35}H_{44}I_6N_6O_{15}$ = 1550.2.
CAS — 92339-11-2.
ATC — V08AB09.
ATC Vet — QV08AB09.

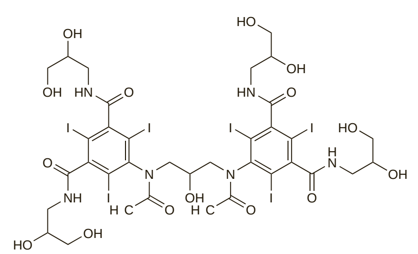

Description. Iodixanol contains about 49.1% of I.

Pharmacopoeias. In *US.*

USP 31 (Iodixanol). A white to off-white, amorphous, odourless, hygroscopic powder. Freely soluble in water. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475. For adverse effects relating to the use of nonionic contrast media such as iodixanol for myelography, see under Iohexol (p.1483).

Pharmacokinetics

Iodixanol is rapidly distributed into extracellular fluid after intravenous injection. It is not bound to plasma proteins. It is not metabolised and about 97% of a dose is excreted in the urine within 24 hours. A terminal elimination half-life of about 2 hours has been reported. Iodixanol is removed by dialysis.

Uses and Administration

Iodixanol is a nonionic dimeric iodinated radiographic contrast medium (see p.1474); it is iso-osmolar with blood. It may be given intravenously, intra-arterially, intrathecally, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, cholangiopancreatography, hysterosalpingography, myelography, and urography, as well as for imaging of the upper gastrointestinal tract and for contrast enhancement during computed tomography.

Iodixanol is usually available as a solution containing between 30.5 and 65.2% of iodixanol (equivalent to between 150 and 320 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

◊ References.

1. Spencer CM, Goa KL. Iodixanol: a review of its pharmacodynamic and pharmacokinetic properties and diagnostic use as an x-ray contrast medium. *Drugs* 1996; **52:** 899–927.

Preparations

USP 31: Iodixanol Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Visipaque; ***Austria:*** Visipaque; ***Belg.:*** Visipaque; ***Braz.:*** Visipaque†; ***Canad.:*** Visipaque; ***Chile:*** Visipaque; ***Cz.:*** Visipaque; ***Denm.:*** Visipaque; ***Fin.:*** Visipaque; ***Fr.:*** Visipaque; ***Ger.:*** Visipaque; ***Gr.:*** Visipaque; ***Hung.:*** Visipaque; ***Israel:*** Visipaque; ***Ital.:*** Visipaque; ***Neth.:*** Visipaque; ***Norw.:*** Visipaque; ***NZ:*** Visipaque; ***Port.:*** Visipaque; ***Rus.:*** Visipaque (Визипак)†; ***Spain:*** Visipaque; ***Swed.:*** Visipaque; ***Switz.:*** Visipaque; ***UK:*** Visipaque; ***USA:*** Visipaque.

Iodoxamic Acid *(BAN, USAN, rINN)*

Acide Iodoxamique; Ácido iodoxámico; Acidum Iodoxamicum; B-10610; Jodoksaamihappo; Jodoxamsyra; SQ-21982. 3,3′-(4,7,10,13-Tetraoxahexadecanedioyldiamino)bis(2,4,6-tri-iodobenzoic acid).

Йодоксамовая Кислота

$C_{26}H_{26}I_6N_2O_{10}$ = 1287.9.
CAS — 31127-82-9.
ATC — V08AC01.
ATC Vet — QV08AC01.

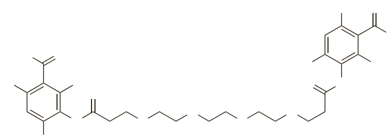

Description. Iodoxamic acid contains about 59.1% of I.

Meglumine Iodoxamate *(BANM, rINNM)*

Dimeglumine Iodoxamate; Iodoxamate de Méglumine; Iodoxamate Meglumine *(USAN)*; Iodoxamato de meglumina; Meglumini Iodoxamas. The di(*N*-methylglucamine) salt of iodoxamic acid.

Меглумина Йодоксамат

$C_{26}H_{26}I_6N_2O_{10},(C_7H_{17}NO_5)_2$ = 1678.3.
CAS — 51764-33-1.
ATC — V08AC01.
ATC Vet — QV08AC01.

Description. Meglumine iodoxamate contains about 45.4% of I.

Profile

Iodoxamic acid is an ionic dimeric iodinated radiographic contrast medium (p.1474) that has been used intravenously as the meglumine salt for cholecystography and cholangiography.

Iofendylate *(BAN, rINN)*

Ethyl Iodophenylundecylate; Iodophendylate; Iofendilato; Iofendylatum; Iophendylate; Jofendylaatti; Jofendylat. A mixture of stereoisomers of ethyl 10-(4-iodophenyl)undecanoate.

Йофендилат

$C_{19}H_{29}IO_2$ = 416.3.
CAS — 99-79-6; 1320-11-2.
ATC — V08AD04.
ATC Vet — QV08AD04.

Description. Iofendylate contains about 30.5% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Iophendylate). A colourless to pale yellow, viscous liquid, darkening on long exposure to air. Is odourless or has a faintly ethereal odour. Very slightly soluble in water; freely soluble in alcohol, in chloroform, in ether, and in benzene. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Iofendylate is an ionic monomeric iodinated radiographic contrast medium (p.1474). It was formerly used for myelography, but was associated with serious adverse effects, including allergy, arachnoiditis, and aseptic meningitis, and has now been superseded by nonionic media. Residues of iofendylate remaining years after myelography have been associated with adverse effects. Other former uses included ventriculography, and visualisation of the fetus in the amniotic sac.

Preparations

BP 2008: Iofendylate Injection;
USP 31: Iophendylate Injection.

Ioglicic Acid *(BAN, USAN, rINN)*

Acide Ioglicique; Ácido ioglícico; Acidum Ioglicicum; Joglicinsyra; Joglisiinihappo; SH-H-200-AB. 5-Acetamido-2,4,6-tri-iodo-*N*-(methylcarbamoylmethyl)isophthalamic acid.

Йоглициевая Кислота

$C_{13}H_{12}I_3N_3O_5$ = 671.0.
CAS — 49755-67-1.
ATC — V08AA06.
ATC Vet — QV08AA06.

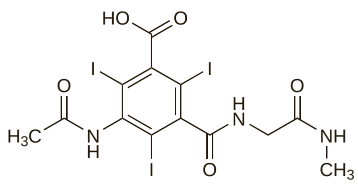

Description. Ioglicic acid contains about 56.7% of I.

Meglumine Ioglicate *(BANM, rINNM)*

Ioglicate de Méglumine; Ioglicate Meglumine; Ioglicato de meglumina; Meglumini Ioglicas. The *N*-methylglucamine salt of ioglicic acid.

Меглумина Йоглициат

$C_{13}H_{12}I_3N_3O_5,C_7H_{17}NO_5$ = 866.2.
ATC — V08AA06.
ATC Vet — QV08AA06.

Description. Meglumine ioglicate contains about 44.0% of I.

Sodium Ioglicate *(BANM, rINNM)*

Ioglicate de Sodium; Ioglicate Sodium; Ioglicato sódico; Natrii Ioglicas.

Натрий Йоглициат

$C_{13}H_{11}I_3N_3NaO_5$ = 692.9.
ATC — V08AA06.
ATC Vet — QV08AA06.

Description. Sodium ioglicate contains about 54.9% of I.

Profile

Ioglicic acid is an ionic monomeric iodinated radiographic contrast medium (p.1474) that has been used, as the meglumine and sodium salts, for diagnostic procedures.

Iohexol *(BAN, USAN, rINN)*

Iohexolum; Joheksoli; Joheksolis; Johexol; Win-39424. *N,N'*-Bis(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.

Йогексол

$C_{19}H_{26}I_3N_3O_9$ = 821.1.
CAS — 66108-95-0.
ATC — V08AB02.
ATC Vet — QV08AB02.

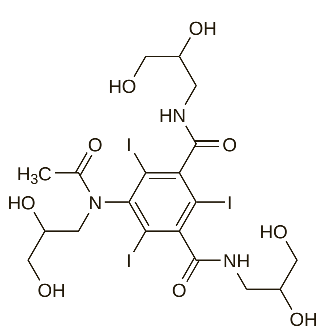

Description. Iohexol contains about 46.4% of I.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Iohexol). A white or greyish-white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Iohexol). A white to off-white, hygroscopic, odourless powder. Very soluble in water and in methyl alcohol; practically insoluble or insoluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

Iohexol and other nonionic iodinated contrast media have similar adverse effects and precautions to ionic media but the effects tend to be less severe and the incidence is generally lower; see under the amidotrizoates, p.1475 for details.

Additional neurological adverse effects may occur when nonionic media such as iohexol are used for myelography. These include severe headache, backache, neck stiffness, dizziness, and leg or sciatic-type pain. Convulsions, aseptic meningitis, and mild and transitory perceptual aberrations, such as visual and speech disturbances, and confusion, may occur occasionally; rarely, more severe mental disturbances have occurred. Urinary retention has also been reported.

Breast feeding. Iohexol is distributed into breast milk in very small quantities[1] but no adverse effects have been seen in breast-feeding infants whose mothers were receiving iohexol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Nielsen ST, *et al.* Excretion of iohexol and metrizoate in human breast milk. *Acta Radiol* 1987; **28:** 523–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Effects on the nervous system. Encephalopathy developed in a 48-year-old man with sciatica within 9 hours of iohexol for lumbar myelography but had largely resolved 48 hours after the myelogram; complete resolution took 4 days.[1] However, recovery was slow in a patient who developed paraplegia and areflexia in the legs after a similar procedure. Five months later the patient still complained of paraesthesia in her legs and could not stand without support.[2]

1. Donaghy M, *et al.* Encephalopathy after iohexol myelography. *Lancet* 1985; **ii:** 887.
2. Noda K, *et al.* Prolonged paraplegia after iohexol myelography. *Lancet* 1991; **337**: 681.

Pharmacokinetics

After intravascular use, 90% or more of a dose of iohexol is eliminated unchanged in the urine within 24 hours. An elimination half-life of about 2 hours in patients with normal renal function has been reported. Protein binding in blood is reported to be very low.

Pregnancy. Contrast material was detected[1] in the intestines of twin neonates who were born 17 hours after iohexol was given to their mother for angiography, suggesting that transplacental transfer had taken place.

1. Moon AJ, *et al.* Transplacental passage of iohexol. *J Pediatr* 2000; **136:** 548–9.

Uses and Administration

Iohexol is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, intrathecally, orally, rectally, or by instillation into body cavities and is used in diagnostic procedures including myelography, angiography, urography, arthrography, and visualisation of the gastrointestinal tract and body cavities. Iohexol is also used to produce contrast enhancement during computed tomography.

Iohexol is usually available as solutions containing 30.2 to 75.5% of iohexol (equivalent to 140 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

Preparations

USP 31: Iohexol Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Omnipaque†; ***Austral.:*** Omnipaque; ***Austria:*** Accupaque; Omnipaque; ***Belg.:*** Omnipaque; ***Braz.:*** Omnipaque†; ***Canad.:*** Omnipaque; ***Chile:*** Omnipaque; ***Cz.:*** Omnipaque; ***Denm.:*** Omnipaque; ***Fin.:*** Omnipaque; ***Fr.:*** Omnipaque; ***Ger.:*** Accupaque; Omnipaque; ***Gr.:*** Omnipaque; ***Hung.:*** Omnipaque; ***India:*** Radiopaque; ***Israel:*** Omnipaque; ***Ital.:*** Omnipaque; ***Neth.:*** Omnipaque; ***Norw.:*** Omnipaque; ***NZ:*** Omnipaque; ***Port.:*** Omnipaque; ***Rus.:*** Omnipaque (Омнипак); ***Spain:*** Omnigraf; Omnipaque; Omnitrast; ***Swed.:*** Omnipaque; ***Switz.:*** Accupaque; Omnipaque; ***UK:*** Omnipaque; ***USA:*** Omnipaque; ***Venez.:*** Omnipaque†.

Iomeprol *(BAN, USAN, rINN)*

Ioméprol; Iomeprolum; Jomeprol; Jomeproli. *N,N'*-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(*N*-methylglycolamido)-isophthalamide.

Йомепрол

$C_{17}H_{22}I_3N_3O_8$ = 777.1.
CAS — 78649-41-9.
ATC — V08AB10.
ATC Vet — QV08AB10.

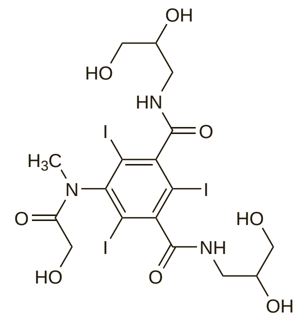

Description. Iomeprol contains about 49% of I.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates (p.1475). For adverse effects relating to the use of nonionic contrast media such as iomeprol for myelography, see under Iohexol (p.1483).

Pharmacokinetics

After intravascular use, iomeprol is rapidly eliminated unchanged in the urine, with a terminal elimination half-life of 1.9 hours. It is not significantly bound to plasma proteins.

Uses and Administration

Iomeprol is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, intrathecally, or by instillation into body cavities, and is used in radiographic procedures including myelography, angiography, urography, and arthrography. It is also used to produce contrast enhancement during computed tomography.

Iomeprol is usually available as solutions containing 30.62 to 81.65% of iomeprol (equivalent to 150 to 400 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

◊ Reviews.

1. Dooley M, Jarvis B. Iomeprol: a review of its use as a contrast medium. *Drugs* 2000; **59:** 1169–86.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Iomeron; ***Austria:*** Iomeron; ***Belg.:*** Iomeron; ***Cz.:*** Iomeron; ***Denm.:*** Iomeron; ***Fin.:*** Iomeron; ***Fr.:*** Iomeron; ***Ger.:*** Imeron; ***Gr.:*** Iomeron; ***Hung.:*** Iomeron; ***Irl.:*** Iomeron†; ***Israel:*** Iomeron; ***Ital.:*** Iomeron; ***Jpn:*** Iomeron; ***Neth.:*** Iomeron; ***Norw.:*** Iomeron; ***NZ:*** Iomeron; ***Port.:*** Iomeron; ***Spain:*** Iomeron; ***Swed.:*** Iomeron; ***Switz.:*** Iomeron; ***UK:*** Iomeron.

Iopamidol *(BAN, USAN, rINN)*

B-15000; Iopamidolum; Jopamidol; Jopamidoli; Jopamidolis; SQ-13396. (*S*)-*N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-tri-iodo-5-lactamidoisophthalamide.

Йопамидол

$C_{17}H_{22}I_3N_3O_8$ = 777.1.
CAS — 60166-93-0; 62883-00-5.
ATC — V08AB04.
ATC Vet — QV08AB04.

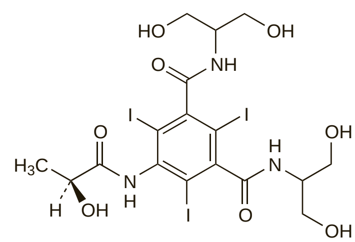

Description. Iopamidol contains about 49% of I.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Iopamidol). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane; very slightly soluble in methyl alcohol. Protect from light.

USP 31 (Iopamidol). A white to off-white, practically odourless, powder. Very soluble in water; practically insoluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p.1475. For the adverse effects relating to the use of nonionic contrast media such as iopamidol for myelography, see under Iohexol, p.1483; for specific references, see below.

Effects on the nervous system. Reports of serious neurological sequelae to lumbar myelography with iopamidol.

1. Wallers K, *et al.* Severe meningeal irritation after intrathecal injection of iopamidol. *BMJ* 1985; **291:** 1688.
2. Robinson C, Fon G. Adverse reaction to iopamidol. *Med J Aust* 1986; **144:** 553.
3. Bell JA, McIlwaine GG. Postmyelographic lateral rectus palsy associated with iopamidol. *BMJ* 1990; **300**: 1343–4.
4. Mallat Z, *et al.* Aseptic meningoencephalitis after iopamidol myelography. *Lancet* 1991; **338**: 252.
5. Bain PG, *et al.* Paraplegia after iopamidol myelography. *Lancet* 1991; **338**: 252–3.
6. Klein KM, *et al.* Status epilepticus and seizures induced by iopamidol myelography. *Seizure* 2004; **13:** 196–9.

Pharmacokinetics

On intravascular use, iopamidol is rapidly eliminated, with up to 50% of the dose recovered unchanged in the urine within 2 hours; the elimination half-life is about 2 hours. It is not significantly bound to plasma proteins.

Uses and Administration

Iopamidol is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, intrathecally, intra-articularly, orally, or rectally and is used in radiographic procedures including angiography, arthrography, myelography, urography, and imaging of the gastrointestinal tract. Iopamidol is also used for contrast enhancement during computed tomography.

Iopamidol is usually available as solutions containing 30.62 to 75.5% of iopamidol (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Preparations

USP 31: Iopamidol Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Hemoray; Iopamiron; Opacrile; ***Austral.:*** Isovue; ***Austria:*** Gastromiro; Jopamiro; Scanlux; ***Braz.:*** Iopamiron; ***Chile:*** Radiomiron; ***Cz.:*** Gastromiro†; Iopamiro†; Scanlux; ***Denm.:*** Iopamiro; ***Fr.:*** Iopamiron; ***Ger.:*** Solutrast; Unilux; ***Gr.:*** Iopamiro; Scanlux; ***Hung.:*** Gastromiro†; Iopamiro; Scanlux; ***Irl.:*** Gastromiro†; Niopam†; ***Israel:*** Gastromiro†; Iopamiro; ***Ital.:*** Gastromiro; Iopamiro; Iopasen; ***Mex.:*** Pamiray; ***Neth.:*** Gastromiro; Iopamiro; Scanlux; ***Norw.:*** Iopamiro; ***NZ:*** Iopamiro; Isovue; ***Port.:*** Gastromiro; Iopamiro; Scanlux; ***Spain:*** Iopamiro; ***Swed.:*** Iopamiro; ***Switz.:*** Iopamiro; Scanlux; ***UK:*** Gastromiro; Niopam; Scanlux; ***USA:*** Isovue; ***Venez.:*** Iopamiron.

Iopanoic Acid *(BAN, rINN)*

Acide iopanoïque; Ácido iopanoico; Acidum iopanoicum; Iodopanoic Acid; Jopaanihappo; Jopano rūgštis; Jopánsav; Jopansyra; Kyselina jopanoová. 2-(3-Amino-2,4,6-tri-iodobenzyl)butyric acid.

Йопаноевая Кислота

$C_{11}H_{12}I_3NO_2$ = 570.9.
CAS — 96-83-3.
ATC — V08AC06.
ATC Vet — QV08AC06.

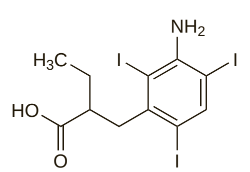

Description. Iopanoic acid contains about 66.7% of I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Iopanoic Acid). A white or yellowish-white powder. Practically insoluble in water; soluble in dehydrated alcohol and in methyl alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Iopanoic Acid). A cream-coloured powder, with a faint characteristic odour. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

Adverse Effects

Gastrointestinal disturbances such as nausea, vomiting, abdominal cramp, and diarrhoea are reported to occur in up to 40% of patients but are usually mild and transient. Mild stinging or burning on micturition, and skin rashes and flushing have occurred occasionally. Acute renal failure, thrombocytopenia, and hypersensitivity reactions have been reported.

Iopanoic acid has potent uricosuric and anticholinesterase effects.

Precautions

Iopanoic acid is contra-indicated in severe hepatic or renal disease; doses higher than 3 g should not be given to patients with renal impairment. It should not be used in the presence of acute gastrointestinal disorders that may impair absorption. It should be used with caution in patients with a history of hypersensitivity to iodine or to other contrast media, severe hyperthyroidism, hyperuricaemia, or cholangitis. Because of its cholinergic action, premedication with atropine has been suggested in some countries for patients with coronary heart disease. Iodine-containing contrast media may interfere with thyroid-function tests and with some blood and urine tests.

Breast feeding. No adverse effects have been observed in breast-feeding infants whose mothers were receiving iopanoic acid and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Pharmacokinetics

Iopanoic acid is variably absorbed from the gastrointestinal tract and is strongly and extensively bound to plasma proteins. It is conjugated in the liver to the glucuronide and excreted largely in the bile and the remainder (about one-third of the dose) in the urine. It appears in the gallbladder about 4 hours after a dose is taken and maximum concentrations occur after about 17 hours. About 50% of a dose is excreted in 24 hours, but elevated protein-bound iodine concentrations may persist for several months.

Uses and Administration

Iopanoic acid is an ionic monomeric iodinated radiographic contrast medium (p.1474). It has been given orally for cholecystography and cholangiography in usual doses of 3 g, given with plenty of water, about 10 to 14 hours before X-ray examination.

Iopanoic acid has also been used in the management of hyperthyroidism (see below).

Hyperthyroidism. Iopanoic acid and other iodinated oral cholecystographic agents reduce conversion of thyroxine to tri-iodothyronine, as well as inhibiting release of thyroid hormones from the thyroid gland,[1] and they have been used in the management of hyperthyroidism (p.2165). Iopanoic acid has been used successfully for pre-operative preparation in severe hyperthyroidism,[2-4] and for control of hyperthyroidism before radio-iodine treatment.[5] It has a rapid effect but rebound hyperthyroidism may occur and it is not generally suitable for long-term use.[1]

1. Braga M, Cooper DS. Oral cholecystographic agents and the thyroid. *J Clin Endocrinol Metab* 2001; **86:** 1853–60.
2. Pandey CK, *et al.* Rapid preparation of severe uncontrolled thyrotoxicosis due to Graves' disease with iopanoic acid—a case report. *Can J Anesth* 2004; **51:** 38–40.
3. Dhillon KS, *et al.* Treatment of hyperthyroidism associated with thyrotropin-secreting pituitary adenomas with iopanoic acid. *J Clin Endocrinol Metab* 2004; **89:** 708–11.
4. Panzer C, *et al.* Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab* 2004; **89:** 2142–4.
5. Bal CS, *et al.* Effect of iopanoic acid on radioiodine therapy of hyperthyroidism: long-term outcome of a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 6536–40.

Preparations

BP 2008: Iopanoic Acid Tablets;
USP 31: Iopanoic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Colesom†; ***Ital.:*** Cistobil†; ***Spain:*** Colegraf; ***Venez.:*** Colepak†.

Iopentol *(BAN, USAN, rINN)*

Compound 5411; Iopentolum; Jopentol; Jopentoli. *N,N'*-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxy-3-methoxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.

Йопентол

$C_{20}H_{28}I_3N_3O_9$ = 835.2.
CAS — 89797-00-2.
ATC — V08AB08.
ATC Vet — QV08AB08.

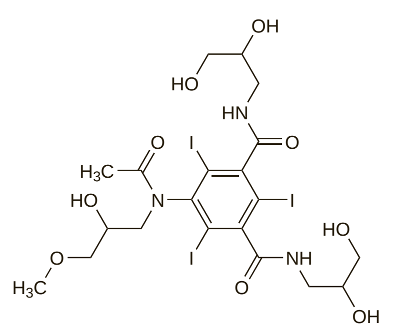

Description. Iopentol contains about 45.6% of I.

Profile

Iopentol is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, endoscopic retrograde cholangiopancreatography, hysterosalpingography, urography, and visualisation of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Iopentol is usually available as solutions containing 32.9 to 76.8% of iopentol (equivalent to 150 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Imagopaque; ***Fr.:*** Ivepaque; ***Ger.:*** Imagopaque; ***Gr.:*** Imagopaque; ***Ital.:*** Imagopaque; ***Spain:*** Imagopaque†; ***Switz.:*** Imagopaque†.

Iopodic Acid *(BANM, rINNM)*

Acide Iopodique; Ácido iopodico; Acidum Iopodicum; Ipodic Acid. 3-(3-Dimethylaminomethyleneamino-2,4,6-tri-iodophenyl)propionic acid.

Йоподовая Кислота

$C_{12}H_{13}I_3N_2O_2$ = 598.0.
CAS — 5587-89-3.
ATC — V08AC08; V08AC10.
ATC Vet — QV08AC08; QV08AC10.

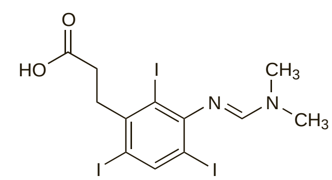

Calcium Iopodate *(BANM, rINNM)*

Calcii Iopodas; Calcium Ipodate; Iopodate Calcique; Iopodato cálcico; Ipodate Calcium; Kalciumjopodat; Kalsiumjopodaatti.

Кальций Йоподат

$(C_{12}H_{12}I_3N_2O_2)_2Ca$ = 1234.0.
CAS — 1151-11-7.
ATC — V08AC10.
ATC Vet — QV08AC10.

Description. Calcium iopodate contains about 61.7% of I.

Sodium Iopodate *(BAN, rINN)*

Iopodate de Sodium; Iopodato de sodio; Ipodate Sodium *(USAN)*; Natrii Iopodas; Natriumjopodaatti; Natriumjopodat; NSC-106962; Sodium Ipodate.

Натрий Йоподат

$C_{12}H_{12}I_3N_2NaO_2$ = 619.9.
CAS — 1221-56-3.
ATC — V08AC08.
ATC Vet — QV08AC08.

Description. Sodium iopodate contains about 61.4% of I.

Pharmacopoeias. In *US.*

USP 31 (Ipodate Sodium). A fine, white or off-white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 2 of dimethylacetamide, and 1 in 3.5 of dimethylformamide and of dimethyl sulfoxide; very slightly soluble in chloroform; freely soluble in methyl alcohol. Store in airtight containers.

Profile

Iopodic acid is an ionic monomeric iodinated radiographic contrast medium (see p.1474). It has similar properties to iopanoic acid (p.1484) and has been used orally as the sodium or calcium salt for cholecystography and cholangiography. It has also been tried in the management of hyperthyroidism.

Preparations

USP 31: Ipodate Sodium Capsules.

Proprietary Preparations (details are given in Part 3)
Gr.: Biloptin†; ***UK:*** Biloptin†; Solu-Biloptin†.

Iopromide *(BAN, USAN, rINN)*

Iopromida; Iopromidum; Jopromid; Jopromidi; ZK-35760. *N,N′*-Bis(2,3-dihydroxypropyl)-2,4,6-tri-iodo-5-(2-methoxyacetamido)-*N*-methylisophthalamide.

Йопромид

$C_{18}H_{24}I_3N_3O_8$ = 791.1.
CAS — 73334-07-3.
ATC — V08AB05.
ATC Vet — QV08AB05.

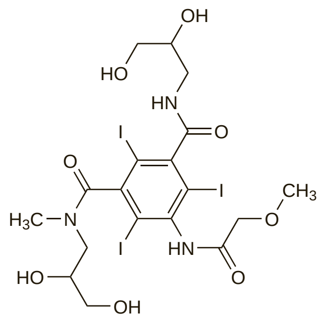

Description. Iopromide contains about 48.1% of I.

Pharmacopoeias. In *US*.

USP 31 (Iopromide). A white to slightly yellow powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol, in acetone, and in ether. Protect from light.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475.

Pharmacokinetics

On intravascular use, iopromide is rapidly distributed in the extracellular fluid. It is not metabolised and is eliminated unchanged in the urine; about 2% of a dose is excreted in faeces. An elimination half-life of about 2 hours has been reported; about 60% of a dose is excreted in urine within 3 hours and about 92% within 24 hours. Iopromide is not significantly bound to plasma proteins.

Uses and Administration

Iopromide is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It may be given intravenously, intra-arterially, or by instillation into body cavities, and is used in procedures including angiography, arthrography, hysterosalpingography, urography, and assessment of dialysis shunt patency. It is also used for contrast enhancement during computed tomography.

Iopromide is usually available as solutions containing 31.2 to 76.9% of iopromide (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Preparations

USP 31: Iopromide Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Clarograf; ***Austral.:*** Ultravist; ***Austria:*** Ultravist; ***Belg.:*** Ultravist; ***Canad.:*** Ultravist†; ***Cz.:*** Ultravist; ***Denm.:*** Ultravist; ***Fin.:*** Ultravist; ***Fr.:*** Ultravist; ***Ger.:*** Ultravist; ***Gr.:*** Ultravist; ***Hung.:*** Ultravist; ***Israel:*** Ultravist; ***Ital.:*** Ultravist; ***Jpn:*** Proscope; ***Neth.:*** Ultravist; ***Norw.:*** Ultravist; ***NZ:*** Ultravist; ***Port.:*** Ultravist; ***Rus.:*** Ultravist (Ультравист); ***S.Afr.:*** Ultravist; ***Spain:*** Clarograf; Ultravist; ***Swed.:*** Ultravist; ***Switz.:*** Ultravist; ***UK:*** Ultravist; ***USA:*** Ultravist.

Iopydol *(BAN, USAN, pINN)*

Iopidol; Iopydolum; Jopydol; Jopydoli. 1-(2,3-Dihydroxypropyl)-3,5-di-iodo-4-pyridone.

Йопидол

$C_8H_9I_2NO_3$ = 421.0.
CAS — 5579-92-0.
ATC — V08AD02.
ATC Vet — QV08AD02.

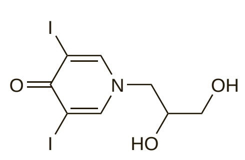

Description. Iopydol contains about 60.3% of I.

Profile

Iopydol is an iodinated radiographic contrast medium (p.1474) that has been used with iopydone for bronchography.

Iopydone *(BAN, USAN, rINN)*

Iopidona; Iopydonum. 3,5-Di-iodo-4-pyridone.

Йопидон

$C_5H_3I_2NO$ = 346.9.
CAS — 5579-93-1.

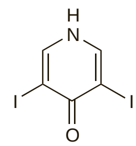

Description. Iopydone contains about 73.2% of I.

Profile

Iopydone is an iodinated radiographic contrast medium (p.1474) that has been used with iopydol for bronchography.

Iosarcol *(pINN)*

Iosarcolum. 3,5-Diacetamido-2,4,6-triiodo-*N*-methyl-*N*-{[methyl(D-*gluco*-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]methyl}-benzamide.

Йозаркол

$C_{21}H_{29}I_3N_4O_9$ = 862.2.
CAS — 97702-82-4.

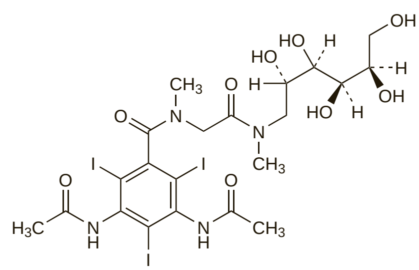

Description. Iosarcol contains about 44.2% of I.

Profile

Iosarcol is an iodinated nonionic monomeric contrast medium used for a wide range of radiographic imaging procedures.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Melitrast; ***Ger.:*** Melitrast.

Iotalamic Acid *(BAN, rINN)*

Acide iotalamique; Ácido iotalámico; Acidum iotalamicum; Iothalamic Acid *(USAN)*; Jotalaamihappo; Jotalaminsav; Jotalamo rūgštis; Jotalamsyra; Kyselina jotalamová; Methalamic Acid; MI-216. 5-Acetamido-2,4,6-tri-iodo-*N*-methylisophthalamic acid.

Йоталамовая Кислота

$C_{11}H_9I_3N_2O_4$ = 613.9.
CAS — 2276-90-6.
ATC — V08AA04.
ATC Vet — QV08AA04.

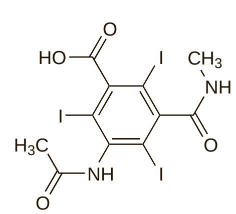

Description. Iotalamic acid contains about 62% of I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Iotalamic Acid). A white or almost white powder. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Iothalamic Acid). A white, odourless, powder. Slightly soluble in water and in alcohol; soluble in solutions of alkali hydroxides. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Meglumine Iotalamate *(BANM, rINNM)*

Iotalamate de Méglumine; Iotalamato de meglumina; Iothalamate Meglumine; Meglumine Iothalamate; Meglumini Iotalamas. The *N*-methylglucamine salt of iotalamic acid.

Меглумина Йоталамат

$C_{11}H_9I_3N_2O_4,C_7H_{17}NO_5$ = 809.1.
CAS — 13087-53-1.
ATC — V08AA04.
ATC Vet — QV08AA04.

Description. Meglumine iotalamate contains about 47.1% of I.

Pharmacopoeias. *US* includes only as various injections.

Sodium Iotalamate *(BANM, rINNM)*

Iotalamate de Sodium; Iotalamato de sodico; Iotalamato de sodio; Iothalamate Sodium; Natrii Iotalamas; Sodium Iothalamate.

Натрий Йоталамат

$C_{11}H_8I_3N_2NaO_4$ = 635.9.
CAS — 17692-74-9; 1225-20-3.
ATC — V08AA04.
ATC Vet — QV08AA04.

Description. Sodium iotalamate contains about 59.9% of I.

Pharmacopoeias. *US* includes only as various injections.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p.1475.

Incidence of adverse effects. In 40 patients who underwent phlebography with 60% meglumine iotalamate minor adverse reactions were common despite the use of saline flushing and muscle contraction to clear the veins after examination.[1] The commonest effect was pain at the site of injection, or in the calf and foot; 15 patients of those who had pain in the calf or foot were found to have venous thrombosis. Major complications of phlebography appear to be rare but can cause serious morbidity; examination of 200 case notes and a retrospective study involving 3060 patients revealed 4 cases of necrosis in the skin of the foot and gangrene of the foot in 2.

1. Thomas ML, MacDonald LM. Complications of ascending phlebography of the leg. *BMJ* 1978; **ii:** 317–18.

Pharmacokinetics

On intravascular use the iotalamates are rapidly distributed; suitable concentrations for urography reach the urinary tract within 3 to 8 minutes of a bolus intravenous injection. Protein binding is reported to be low. The iotalamates are eliminated by the kidneys. In patients with normal renal function more than 90% of the dose injected is excreted in urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Small amounts are reported to be excreted via the bile in the faeces. The iotalamates are removed by peritoneal dialysis and haemodialysis.

Uses and Administration

Iotalamic acid is an ionic monomeric iodinated radiographic contrast medium (p.1474) with actions similar to the amidotrizoates (p.1477). It may be given intravenously, intra-arterially, or by instillation into the bladder or uterus, and is used in procedures including angiography, arthrography, cholangiography, urography and hysterosalpingography. It is also used for contrast enhancement in computed tomography. Iotalamates have also been given orally or rectally for imaging of the gastrointestinal tract.

Iotalamic acid is usually available as solutions containing up to 66.8% of sodium iotalamate or up to 60% of meglumine iotalamate. The dose and strength used vary according to the procedure and route. A mixture of the two salts has been given to minimise adverse effects.

Preparations

USP 31: Iothalamate Meglumine and Iothalamate Sodium Injection; Iothalamate Meglumine Injection; Iothalamate Sodium Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Conray; Cysto-Conray; ***Austral.:*** Conray 280; ***Canad.:*** Conray; Cysto-Conray; ***Ger.:*** Conray 30†; Conray 60†; ***Ital.:*** Conray†; ***UK:*** Conray; ***USA:*** Conray; Cysto-Conray.

Iotrolan *(BAN, USAN, rINN)*

Iotrol; Iotrolán; Iotrolane; Iotrolanum; Iotrolum; Jotrolaani; Jotrolan; ZK-39482. *N,N′,N″,N‴*-Tetrakis(2,3-dihydroxy-1-hydroxymethylpropyl)-2,2′,4,4′,6,6′-hexaiodo-5,5′-(*N,N′*-dimethylmalonyldi-imino)di-isophthalamide.

Йотролан

$C_{37}H_{48}I_6N_6O_{18}$ = 1626.2.
CAS — 79770-24-4.
ATC — V08AB06.
ATC Vet — QV08AB06.

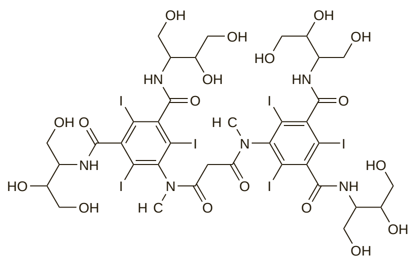

Description. Iotrolan contains about 46.8% of I.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Iotrolan). A white or yellowish-white, hygroscopic powder. Very soluble in water; practically insoluble in alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p.1475. For the adverse effects relating to the use of nonionic contrast media such as iotrolan for myelography, see under Iohexol, p.1483.

Pharmacokinetics

Iotrolan is excreted unchanged in the urine. After intrathecal injection, about 80% is excreted in the urine within 24 hours.

Uses and Administration

Iotrolan is a nonionic dimeric iodinated radiographic contrast medium (p.1474). It is given intrathecally for myelography and for contrast enhancement in computed tomography, and by instillation into body ducts or cavities for procedures including lymphography, arthrography, hysterosalpingography, cholangiopancreatography, and for visualisation of the mammary ducts. It may also be given orally for imaging of the gastrointestinal tract.

Iotrolan is usually available as solutions containing 51.3% or 64.1% of iotrolan (equivalent to 240 or 300 mg/mL of iodine, respectively) and the dose and strength used vary according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Isovist†; ***Austria:*** Isovist; ***Canad.:*** Osmovist†; ***Cz.:*** Isovist†; ***Denm.:*** Isovist; ***Fin.:*** Isovist†; ***Ger.:*** Isovist; ***Hung.:*** Isovist; ***Neth.:*** Isovist; ***NZ:*** Isovist; ***S.Afr.:*** Isovist; ***Switz.:*** Isovist; ***UK:*** Isovist.

Iotroxic Acid *(BAN, USAN, rINN)*

Acide Iotroxique; Ácido iotróxico; Acidum Iotroxicum; Jotroksihappo; Jotroxsyra; SH-213AB. 3,3′-(3,6,9-Trioxaundecanedioyldi-imino)bis(2,4,6-tri-iodobenzoic acid).

Йотроксовая Кислота

$C_{22}H_{18}I_6N_2O_9$ = 1215.8.
CAS — 51022-74-3.
ATC — V08AC02.
ATC Vet — QV08AC02.

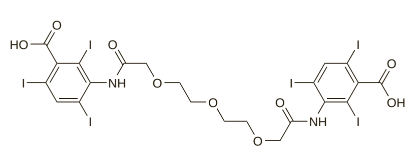

Description. Iotroxic acid contains about 62.6% of I.

Pharmacopoeias. In *Int.* and *Jpn.*

Meglumine Iotroxate *(BANM, rINNM)*

Dimeglumine Iotroxate; Iotroxate de Méglumine; Iotroxate Meglumine; Iotroxato de meglumina; Meglumine Iotroxinate; Meglumini Iotroxas. The di(*N*-methylglucamine)salt of iotroxic acid.

Меглумина Йотроксат

$C_{22}H_{18}I_6N_2O_9,2C_7H_{17}NO_5$ = 1606.2.
CAS — 68890-05-1.
ATC — V08AC02.
ATC Vet — QV08AC02.

Description. Meglumine iotroxate contains about 47.4% of I.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475.

Pharmacokinetics

After intravenous injection, iotroxic acid binds to plasma proteins and is taken up by the liver; plasma-protein binding is about 60 to 90%. It is excreted primarily unchanged in the bile; a small amount is metabolised and excreted in the urine.

Uses and Administration

Iotroxic acid is an ionic dimeric iodinated radiographic contrast medium (see p.1474); it is taken up by the liver and excreted in bile, and is used in cholecystography and cholangiography.

Iotroxic acid is given intravenously as a solution containing 10.5% of the meglumine salt. The usual dose is 10.5 g of meglumine iotroxate (equivalent to about 5 g of iodine), given by infusion over at least 15 minutes. Alternatively, a solution containing 22.8% of meglumine iotroxate may be used.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Biliscopin; ***Austria:*** Biliscopin; ***Ger.:*** Biliscopin; ***Gr.:*** Biliscopin; ***NZ:*** Biliscopin; ***Spain:*** Bilisegrol†; ***Swed.:*** Biliscopin†; ***Switz.:*** Biliscopin; ***UK:*** Biliscopin.

Ioversol *(BAN, USAN, rINN)*

Ioversolum; Joversol; Joversoli; MP-328. *N,N′*-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl)glycolamido]-2,4,6-tri-iodoisophthalamide.

Йоверсол

$C_{18}H_{24}I_3N_3O_9$ = 807.1.
CAS — 87771-40-2.
ATC — V08AB07.
ATC Vet — QV08AB07.

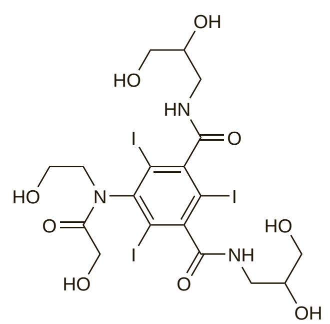

Description. Ioversol contains about 47.2% of I.

Pharmacopoeias. In *US.*

USP 31 (Ioversol). Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475.

Pharmacokinetics

When given intravascularly, ioversol is rapidly eliminated unchanged in the urine, with a half-life of about 1.5 hours; more than 95% of a dose is eliminated within 24 hours. Binding to plasma or serum proteins is very low.

Uses and Administration

Ioversol is a nonionic monomeric iodinated radiographic contrast medium (p.1474) that is given intra-arterially or intravenously for angiography and urography. It is also used for contrast enhancement during computed tomography. It is usually available as a solution containing 34 to 74% of ioversol (equivalent to 160 to 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

◊ References.

1. Floriani I, *et al.* Clinical profile of ioversol: a metaanalysis of 57 randomized, double-blind clinical trials. *Invest Radiol* 1996; **31:** 479–91.

Preparations

USP 31: Ioversol Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Optiray; ***Austral.:*** Optiray; ***Austria:*** Optiray; ***Belg.:*** Optiject; Optiray; ***Canad.:*** Optiray; ***Cz.:*** Optiray; ***Denm.:*** Optiray; ***Fin.:*** Optiray; ***Fr.:*** Optiject; Optiray; ***Ger.:*** Optiray†; ***Gr.:*** Optiray; ***Hung.:*** Optiray; ***Israel:*** Optiray; ***Ital.:*** Optiray; ***Neth.:*** Optiray; ***Norw.:*** Optiray; ***Port.:*** Optiray; ***Spain:*** Optiray; ***Swed.:*** Optiray; ***Switz.:*** Optiray; ***UK:*** Optiray; ***USA:*** Optiray.

Ioxaglic Acid *(BAN, USAN, rINN)*

Acide ioxaglique; Ácido ioxáglico; Acidum ioxaglicum; Joksagliinihappo; Joksagliko rūgštis; Joxaglinsav; Joxaglinsyra; Kyselina joxaglová; P-286. *N*-(2-Hydroxyethyl)-2,4,6-tri-iodo-5-[2′,4′,6′-tri-iodo-3′-(*N*-methylacetamido)-5′-methylcarbamoylhippuramido]-isophthalamic acid.

Йоксагловая Кислота

$C_{24}H_{21}I_6N_5O_8$ = 1268.9.
CAS — 59017-64-0.
ATC — V08AB03.
ATC Vet — QV08AB03.

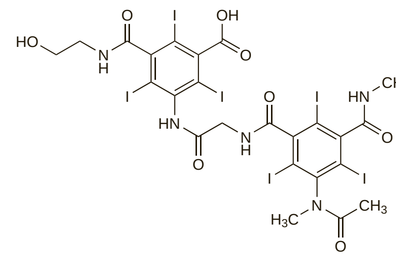

Description. Ioxaglic acid contains about 60% of I.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ioxaglic Acid). A white or almost white hygroscopic powder. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 31 (Ioxaglic Acid). Store at a temperature of 25°, excursions permitted between 15° and 30°.

Meglumine Ioxaglate *(BANM, rINNM)*

Ioxaglate de Méglumine; Ioxaglate Meglumine *(USAN)*; Ioxaglato de meglumina; Meglumini Ioxaglas; MP-302 (meglumine ioxaglate with sodium ioxaglate). The *N*-methylglucamine salt of ioxaglic acid.

Меглумина Йоксаглат

$C_{24}H_{21}I_6N_5O_8,C_7H_{17}NO_5$ = 1464.1.
CAS — 59018-13-2.
ATC — V08AB03.
ATC Vet — QV08AB03.

Description. Meglumine ioxaglate contains about 52% of I.

Sodium Ioxaglate *(BANM, rINNM)*

Ioxaglate de Sodium; Ioxaglate Sodium *(USAN)*; Ioxaglato sódico; MP-302 (sodium ioxaglate with meglumine ioxaglate); Natrii Ioxaglas; Natriumjoksaglaatti; Natriumjoxaglat.

Натрий Йоксаглат

$C_{24}H_{20}I_6N_5NaO_8$ = 1290.9.
CAS — 67992-58-9.
ATC — V08AB03.
ATC Vet — QV08AB03.

Description. Sodium ioxaglate contains about 59% of I.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475.

Pharmacokinetics

On intravascular use, ioxaglates are rapidly distributed throughout the extracellular fluid. Protein binding is reported to be very low. They are mainly excreted unchanged in the urine, although biliary excretion may predominate in renal impairment. With normal renal function, about 90% of a dose is excreted in the urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Ioxaglates cross the placenta and are distributed into breast milk. They are removed by haemodialysis and peritoneal dialysis.

Uses and Administration

Ioxaglic acid is an ionic dimeric iodinated radiographic contrast medium (p.1474). It is given intravenously, intra-arterially, intra-articularly, or by instillation into body ducts and cavities and is used in diagnostic procedures including angiography, arthrography, hysterosalpingography, and urography. It is also used for contrast enhancement during computed tomography.

Ioxaglic acid is usually available as solutions containing a mixture of the sodium and meglumine salts. Commonly used solutions contain 39.3% of meglumine ioxaglate and 19.6% of sodium ioxaglate (equivalent to 320 mg/mL of iodine) or 24.6% of meglumine ioxaglate and 12.3% of sodium ioxaglate (equivalent to 200 mg/mL of iodine). The dose and strength used depend upon the procedure and route.

Preparations

USP 31: Ioxaglate Meglumine and Ioxaglate Sodium Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Hexabrix; ***Austral.:*** Hexabrix; ***Austria:*** Hexabrix; ***Belg.:*** Hexabrix; ***Braz.:*** Hexabrix†; ***Canad.:*** Hexabrix; ***Chile:*** Hexabrix; ***Cz.:*** Hexabrix; ***Denm.:*** Hexabrix; ***Fin.:*** Hexabrix; ***Fr.:*** Hexabrix; ***Ger.:*** Hexabrix; ***Gr.:*** Hexabrix; ***Hung.:*** Hexabrix; ***Israel:*** Hexabrix; ***Ital.:*** Hexabrix; ***Neth.:***

Hexabrix; ***Norw.:*** Hexabrix; ***NZ:*** Hexabrix; ***Port.:*** Hexabrix; ***Spain:*** Hexabrix; ***Swed.:*** Hexabrix; ***Switz.:*** Hexabrix; ***UK:*** Hexabrix; ***USA:*** Hexabrix; ***Venez.:*** Hexabrix.

Ioxilan *(USAN, rINN)*

Ioxilán; Ioxilane; Ioxilanum. *N*-(2,3-Dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-*N'*-(2-hydroxyethyl)-2,4,6-triidoisophthalamide.

Йоксилан

$C_{18}H_{24}I_3N_3O_8$ = 791.1.

CAS — 107793-72-6.

ATC — V08AB12.

ATC Vet — QV08AB12.

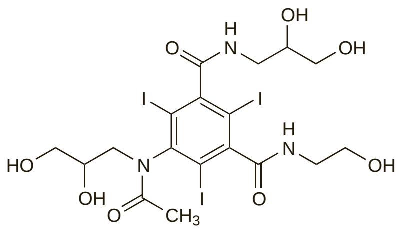

Description. Ioxilan contains about 48.1% of I.

Pharmacopoeias. In *US.*

USP 31 (Ioxilan). A white to off-white, practically odourless, powder. Soluble in water and in methyl alcohol. pH of a 10% solution in water is between 5.0 and 7.5. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p.1475.

Pharmacokinetics

After intravascular use, ioxilan is rapidly eliminated unchanged in the urine; about 94% of a dose is excreted within 24 hours. Protein binding is reported to be very low. Ioxilan is dialysable.

Uses and Administration

Ioxilan is a nonionic monomeric iodinated radiographic contrast medium (see p.1474). It is given intra-arterially or intravenously for procedures including angiography and urography; it is also used for contrast enhancement during computed tomography.

Ioxilan is usually available as solutions containing 62.3 or 72.7% of ioxilan (equivalent to 300 or 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

Preparations

USP 31: Ioxilan Injection.

Proprietary Preparations (details are given in Part 3)
Jpn: Imagenil; ***USA:*** Oxilan.

Ioxitalamic Acid *(rINN)*

Acide Ioxitalamique; Ácido ioxitalámico; Acidum Ioxitalamicum; AG-58107; Ioxithalamic Acid; Joksitalaamihappo; Joxitalamsyra. 5-Acetamido-*N*-(2-hydroxyethyl)-2,4,6-tri-iodoisophthalamic acid.

Йокситаламовая Кислота

$C_{12}H_{11}I_3N_2O_5$ = 643.9.

CAS — 28179-44-4.

ATC — V08AA05.

ATC Vet — QV08AA05.

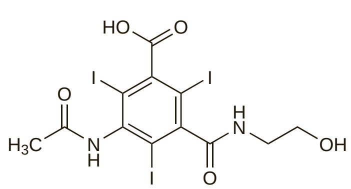

Description. Ioxitalamic acid contains about 59.1% of I.

Pharmacopoeias. In *Fr.*

Meglumine Ioxitalamate *(rINNM)*

Ioxitalamate de Méglumine; Ioxitalamate Meglumine; Ioxitalamato de meglumina; Meglumini Ioxitalamas. The *N*-methylglucamine salt of ioxitalamic acid.

Меглумина Йокситаламат

$C_{12}H_{11}I_3N_2O_5,C_7H_{17}NO_5$ = 839.2.

CAS — 29288-99-1.

ATC — V08AA05.

ATC Vet — QV08AA05.

Description. Meglumine ioxitalamate contains about 45.4% of I.

Sodium Ioxitalamate *(rINNM)*

Ioxitalamate de Sodium; Ioxitalamate Sodium; Ioxitalamato sódico; Natrii Ioxitalamas.

Натрий Йокситаламат

$C_{12}H_{10}I_3N_2NaO_5$ = 665.9.

CAS — 33954-26-6.

ATC — V08AA05.

ATC Vet — QV08AA05.

Description. Sodium ioxitalamate contains about 57.2% of I.

Profile

Ioxitalamic acid is an ionic monomeric iodinated radiographic contrast medium (p.1474) with actions similar to those of the amidotrizoates (p.1475). It is given intravenously or by instillation into body cavities for procedures including angiography, cholangiography, cystography, hysterosalpingography, and urography; it may be given orally or rectally for imaging of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Ioxitalamic acid is usually available as a solution containing 21% of the sodium salt (equivalent to 120 mg/mL of iodine), 55.1 to 66% of the meglumine salt (equivalent to 250 to 300 mg/mL of iodine), or as a mixture of both salts. The dose and strength used vary according to the procedure and route.

Monoethanolamine ioxitalamate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Telebrix 30; Telebrix 38; Telebrix Coronario; Telebrix Hystero; ***Belg.:*** Telebrix; Telebrix Gastro; Telebrix Hystero; ***Braz.:*** Telebrix†; ***Canad.:*** Telebrix; ***Chile:*** Telebrix 30; Telebrix 35; ***Cz.:*** Telebrix 30; Telebrix 35; Telebrix Gastro; ***Fr.:*** Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Ger.:*** Telebrix Gastro; Telebrix N 180 and 300; ***Gr.:*** Telebrix Gastro; Telebrix Hystero†; ***Hung.:*** Telebrix; Telebrix Gastro; ***Israel:*** Telebrix; Telebrix Gastro; ***Mex.:*** Telebrix; ***Neth.:*** Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Port.:*** Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Switz.:*** Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; ***Venez.:*** Telebrix 30; Telebrix 35; Telebrix Hystero.

Mangafodipir Trisodium *(BANM, USAN, rINNM)*

Mangafodipir trisódico; Mangafodipir Trisodique; Mangafodipirum Trinatricum; MnDPDP (mangafodipir); S-095 (mangafodipir); Win-59010; Win-59010-2 (mangafodipir). Trisodium trihydrogen (*OC*-6-13)-{[*N*,*N'*-ethylenebis(*N*-{[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl}glycine) 5,5'-bis(phosphato)](8-)} manganate(6-); Trisodium trihydrogen (*OC*-6-13)-*N*,*N'*-ethane-1,2-diylbis{N-[2-methyl-3-oxido-κ*O*-5-(phosphonatooxymethyl)-4-pyridylmethyl]glycinato(*O*,*N*)}manganate(II).

Тринатрий Мангафодипир

$C_{22}H_{27}MnN_4Na_3O_{14}P_2$ = 757.3.

CAS — 155319-91-8 (mangafodipir); 140678-14-4 (mangafodipir trisodium).

ATC — V08CA05.

ATC Vet — QV08CA05.

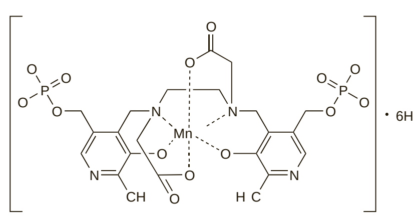

(mangafodipir)

Pharmacopoeias. In *US.*

USP 31 (Mangafodipir Trisodium). Pale yellow crystals or crystalline powder. Freely soluble in water; slightly soluble in alcohol and in acetone; slightly soluble in chloroform; sparingly soluble in methyl alcohol. pH of a 1% solution in water is between 5.5 and 7.0. Store at a temperature not exceeding 8°.

Adverse Effects and Precautions

The most common adverse effects of mangafodipir are injection site discomfort, feelings of warmth or flushing, headache, nausea, vomiting, abdominal pain, and taste disturbances. Hypersensitivity reactions, including anaphylactoid reactions, may occur. Transient increases in bilirubin and liver transaminase concentrations and decreases in plasma-zinc concentrations have been reported.

Mangafodipir should be used with caution in patients with hepatic or renal impairment and should be avoided if impairment is severe. It should not be given to patients with phaeochromocytoma.

◊ References.

1. Federle MP, *et al.* Safety and efficacy of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: results of the U.S. multicenter phase III clinical trials (safety). *J Magn Reson Imaging* 2000; **12:** 186–97.

Pharmacokinetics

After intravenous injection, mangafodipir is dephosphorylated and manganese is exchanged for zinc leading to the release of free manganese ions and the formation of 2 inactive metabolites. Manganese is rapidly taken up by the liver, pancreas, kidney and spleen; about 15 to 20% is excreted in the urine within 24 hours, with most of the remainder excreted in the faeces over about 4 days. The metabolites are almost entirely excreted in the urine within 24 hours.

Uses and Administration

Mangafodipir is a manganese chelate that is used as a magnetic resonance contrast medium (p.1474) for imaging of the liver and pancreas. Manganese has paramagnetic properties that increase the relaxivity of hydrogen ions, leading to signal enhancement. Free manganese is released from mangafodipir in the body and is taken up by normal liver and pancreatic tissue, increasing the degree of contrast.

Mangafodipir is given intravenously as the trisodium salt.

In the UK, a solution containing mangafodipir trisodium 7.57 mg/mL (10 micromol/mL) is used. Usual doses for imaging are:

- liver: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 2 to 3 mL/minute
- pancreas: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 4 to 6 mL/minute

In the USA, a more concentrated preparation is used, containing mangafodipir trisodium 37.9 mg/mL (50 micromol/mL). Usual doses are:

- liver: 0.1 mL/kg (5 micromol/kg), given by slow intravenous injection to a maximum dose of 15 mL

Preparations

USP 31: Mangafodipir Trisodium Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Teslascan; ***Belg.:*** Teslascan; ***Cz.:*** Teslascan; ***Denm.:*** Teslascan†; ***Fin.:*** Teslascan†; ***Fr.:*** Teslascan; ***Ger.:*** Teslascan; ***Gr.:*** Teslascan; ***Hung.:*** Teslascan; ***Ital.:*** Teslascan; ***Neth.:*** Teslascan; ***Norw.:*** Teslascan; ***NZ:*** Teslascan; ***Port.:*** Teslascan; ***Spain:*** Teslascan; ***Swed.:*** Teslascan; ***Switz.:*** Teslascan; ***UK:*** Teslascan; ***USA:*** Teslascan.

Metrizamide *(BAN, USAN, rINN)*

Metritsamidi; Metrizamid; Metrizamida; Métrizamide; Metrizamidum; Win-39103. 2-[3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzamido]-2-deoxy-D-glucose.

Метризамид

$C_{18}H_{22}I_3N_3O_8$ = 789.1.

CAS — 31112-62-6 (metrizamide); 55134-11-7 (metrizamide, glucopyranose form).

ATC — V08AB01.

ATC Vet — QV08AB01.

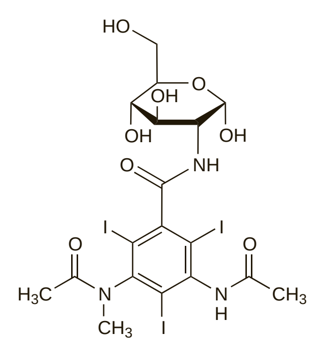

Description. Metrizamide contains about 48.2% of I.

Profile

Metrizamide is a nonionic monomeric iodinated radiographic contrast medium (p.1474) that has been used in myelography, angiography, intravenous urography, and arthrography, and also for contrast enhancement during computed tomography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizamide and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

The symbol † denotes a preparation no longer actively marketed

Metrizoic Acid *(BANM, rINNM)*

Acide Métrizoïque; Ácido metrizoico; Acidum Metrizoicum; Metritsoiinihappo; Metrizoinsyra. 3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzoic acid.

Метризоевая Кислота

$C_{12}H_{11}I_3N_2O_4$ = 627.9.
CAS — 1949-45-7.
ATC — V08AA02.
ATC Vet — QV08AA02.

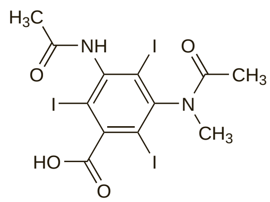

Description. Metrizoic acid contains about 60.6% of I.

Meglumine Metrizoate *(BANM, rINNM)*

Meglumini Metrizoas; Métrizoate de Méglumine; Metrizoate Meglumine; Metrizoato de meglumina. The *N*-methylglucamine salt of metrizoic acid.

Меглумина Метризоат

$C_{12}H_{11}I_3N_2O_4,C_7H_{17}NO_5$ = 823.2.
CAS — 7241-11-4.
ATC — V08AA02.
ATC Vet — QV08AA02.

Description. Meglumine metrizoate contains about 46.3% of I.

Sodium Metrizoate *(BAN, rINN)*

Métrizoate de Sodium; Metrizoate Sodium *(USAN)*; Metrizoato de sodio; Natrii Metrizoas; NSC-107431.

Натрия Метризоат

$C_{12}H_{10}I_3N_2NaO_4$ = 649.9.
CAS — 7225-61-8.
ATC — V08AA02.
ATC Vet — QV08AA02.

Description. Sodium metrizoate contains about 58.6% of I.

Profile

Metrizoic acid is an ionic monomeric iodinated radiographic contrast medium (p.1474) with actions similar to those of the amidotrizoates (p.1475). It has been used as the meglumine and sodium salts, often with calcium metrizoate and magnesium metrizoate, for a variety of diagnostic procedures including angiography, cholangiography, and hysterosalpingography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizoate and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Isopaque Cysto†.

Perflenapent *(USAN, rINN)*

Dodecafluoropentanum; Dodekafluoropentaani; Dodekafluoropentan; Perflénapent; Perflenapentum. Dodecafluoropentane.

Перфленапент

C_5F_{12} = 288.0.
CAS — 678-26-2.
ATC — V08DA03.
ATC Vet — QV08DA03.

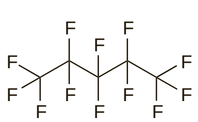

Profile

Perflenapent is a liquid perfluorocarbon that has been used as an ultrasound contrast medium (p.1474) for echocardiography. It has been given intravenously as an emulsion containing droplets of perflenapent; on warming to body temperature the droplets form microbubbles of perflenapent gas that provide echo-enhancement. A small amount of perflisopent (below) was also included in the formulation.

◊ References.

1. Robbin ML, Eisenfeld AJ. Perflenapent emulsion: a US contrast agent for diagnostic radiology—multicenter, double-blind comparison with a placebo. *Radiology* 1998; **207:** 717–22.
2. Kitzman DW, Wesley DJ. Safety assessment of perflenapent emulsion for echocardiographic contrast enhancement in patients with congestive heart failure or chronic obstructive pulmonary disease. *Am Heart J* 2000; **139:** 1077–80.

Perflexane *(USAN, rINN)*

Perflexano; Perflexanum. Tetradecafluorohexane.

Перфлексан

C_6F_{14} = 338.0.
CAS — 355-42-0.

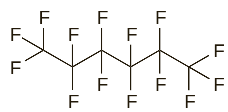

Profile

Perflexane is a perfluorocarbon gas that has been used as an ultrasound contrast medium (p.1474) for echocardiography. Dry microspheres containing the gas are reconstituted immediately before use, leading to the formation of microbubbles of perflexane that provide echo-enhancement; lipids are included in the microspheres to stabilise the bubbles when they form.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Imagent.

Perflisopent *(USAN, rINN)*

Perflisopentum. Nonafluoro-2-(trifluoromethyl)butane.

Перфлизопент

C_5F_{12} = 288.0.
CAS — 594-91-2.

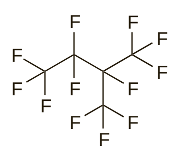

Profile

Perflisopent is a perfluorocarbon that has been used as an ultrasound contrast medium (p.1474) with perflenapent (above) for echocardiography.

Perflutren *(USAN, rINN)*

DMP-115; FS-069; MRX-115; Octafluoropropanum; Oktafluoropropaani; Oktafluoropropan; Perfluoropropane; Perflutrène; Perflutreno; Perflutrenum. Octafluoropropane.

Перфлутрен

C_3F_8 = 188.0.
CAS — 76-19-7.

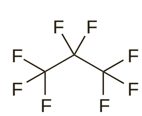

Profile

Perflutren is a perfluorocarbon gas used as either albumin- or lipid-coated microspheres as an ultrasound contrast medium (p.1474) for echocardiography.

The albumin-coated microspheres are suspended in 1% albumin solution immediately before use and are given in a dose of 0.5 to 3 mL by intravenous injection, repeated if necessary up to a total dose of 8.7 mL.

The lipid-coated microsphere suspension is formed by agitating the gas with a lipid solution immediately before use and is given in a dose of 10 microlitre/kg by intravenous injection, repeated once after 30 minutes if required, or as intravenous injections of 100 to 400 microlitres repeated as required up to a maximum total dose of 1.6 mL. Alternatively, 1.3 mL of the suspension may be diluted in 50 mL of sodium chloride 0.9% and given by intravenous infusion at an initial rate of 4 mL/minute, adjusted as required, to a maximum rate of 10 mL/minute.

Serious cardiopulmonary reactions, including fatalities, have been reported with perflutren and it should be used with extreme caution in patients with pulmonary hypertension or unstable cardiopulmonary conditions. The safety of perflutren has not been established in patients with right-to-left cardiac shunts; it should also be used with extreme caution or avoided in such patients.

Perflutren has also been given by intra-ocular injection to provide tamponade in the management of retinal detachment.

Adverse effects. References.

1. Herzog CA. Incidence of adverse events associated with use of perflutren contrast agents for echocardiography. *JAMA* 2008; **299:** 2023–5.

Preparations

USP 31: Perflutren Protein-Type A Microspheres Injectable Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Optison†; ***Austria:*** Optison; ***Canad.:*** Definity; ***Chile:*** Definity; ***Cz.:*** Luminity; Optison; ***Denm.:*** Optison; ***Fr.:*** Luminity; ***Ger.:*** Optison; ***Gr.:*** Optison; ***Hung.:*** Optison; ***Israel:*** Definity; ***Ital.:*** Optison; ***Neth.:*** Optison; ***Port.:*** Luminity; Optison; ***Spain:*** Optison; ***Swed.:*** Optison; ***Switz.:*** Optison; ***UK:*** Luminity; Optison; ***USA:*** Definity; Luminity; Optison.

Propyliodone *(rINN)*

Propiliodona; Propyliodonum; Propyljodon; Propyylijodoni. Propyl 1,4-dihydro-3,5-di-iodo-4-oxo-1-pyridylacetate.

Пропилиодон

$C_{10}H_{11}I_2NO_3$ = 447.0.
CAS — 587-61-1.
ATC — V08AD03.
ATC Vet — QV08AD03.

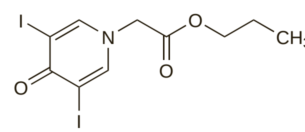

Description. Propyliodone contains about 56.8% of I.

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Propyliodone). A white or almost white, crystalline powder. Is odourless or has a faint odour. Practically insoluble in water; soluble in alcohol, in acetone, and in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Propyliodone is an iodinated radiographic contrast medium (p.1474) that has been used for bronchography as either an aqueous or oily suspension.

Preparations

USP 31: Propyliodone Injectable Oil Suspension.

Proprietary Preparations (details are given in Part 3)
Israel: Dionosil†.

Sodium Tyropanoate *(BAN, rINN)*

Natrii Tyropanoas; NSC-107434; Tiropanoato de sodio; Tyropanoate de Sodium; Tyropanoate Sodium *(USAN)*; Win-8851-2. Sodium 2-(3-butyramido-2,4,6-tri-iodobenzyl)butyrate.

Натрия Тиропаноат

$C_{15}H_{17}I_3NNaO_3$ = 663.0.
CAS — 27293-82-9 (tyropanoic acid); 7246-21-1 (sodium tyropanoate).
ATC — V08AC09.
ATC Vet — QV08AC09.

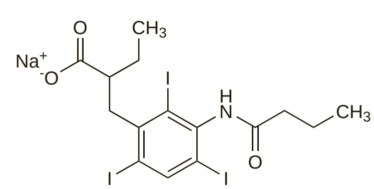

Description. Sodium tyropanoate contains about 57.4% of I.

Profile

Sodium tyropanoate is an ionic monomeric iodinated radiographic contrast medium (p.1474) with actions similar to those of iopanoic acid (p.1484) and has been used for cholecystography and cholangiography.

Sulfur Hexafluoride *(USAN)*

BRI; Hexafluouro de azufre; Sulphur Fluoride; Sulphur Hexafluoride.

F_6S = 146.1.
CAS — 2551-62-4.
ATC — V08DA05.
ATC Vet — QV08DA05.

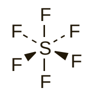

Profile

Sulfur hexafluoride is a gas with little biological activity that is used as an ultrasound contrast medium (p.1474) for imaging of the blood vessels and for echocardiography. Microbubbles of sulfur hexafluoride are formed on reconstitution of the preparation and provide echo-enhancement; phospholipids and surfactants are included to stabilise the microbubbles. It is given intravenously as a suspension containing 45 micrograms/mL, in a usual dose of 2 mL for echocardiography, or 2.4 mL for imaging blood vessels; the dose may be repeated once if necessary.

Sulfur hexafluoride has been associated with hypersensitivity reactions; patients should be monitored for at least 30 minutes after use, and resuscitation equipment should be available. Particular care is advised in patients with ischaemic heart disease, in whom serious and occasionally fatal cardiac events have occurred: sulfur hexafluoride is contra-indicated in patients with recent acute coronary syndrome or clinically unstable ischaemic heart disease. It should also not be given to patients with severe pulmonary hypertension, uncontrolled hypertension, acute respiratory distress syndrome, or right-to-left shunts. Care is advised in patients with lung disorders.

Sulfur hexafluoride has also been used as an adjunct in eye surgery for retinal detachment.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: SonoVue; ***Belg.:*** SonoVue; ***Cz.:*** SonoVue; ***Denm.:*** SonoVue; ***Fin.:*** SonoVue; ***Fr.:*** SonoVue; ***Gr.:*** SonoVue; ***Ital.:*** SonoVue; ***Neth.:*** SonoVue; ***Norw.:*** SonoVue; ***Port.:*** SonoVue; ***Swed.:*** SonoVue; ***Switz.:*** SonoVue; ***UK:*** SonoVue.

Corticosteroids

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The adrenal cortex synthesises both corticosteroids, based on a 21-carbon nucleus, and some sex hormones, primarily androgens, based on a 19-carbon nucleus. The corticosteroids are traditionally divided into those with mainly glucocorticoid actions, of which cortisol (hydrocortisone) is the most important endogenous example, and those that are primarily mineralocorticoid, of which aldosterone is much the most important.

The endogenous glucocorticoids are under regulatory control from the hypothalamus and pituitary, via the releasing hormones corticorelin (p.1523) and corticotropin or ACTH (p.1523). In return the glucocorticoids act to inhibit production and release of these releasing hormones by a negative feedback mechanism. The system is known collectively as the hypothalamic-pituitary-adrenal (HPA) axis. Aldosterone secretion, by contrast, is under the control of the renin-angiotensin system.

The main **mineralocorticoid** actions are on fluid and electrolyte balance. They enhance sodium reabsorption in the kidney and hence expand the extracellular fluid volume, and they enhance renal excretion of potassium and H^+.

The **glucocorticoid** actions are wide-ranging. They have potent anti-inflammatory and immunosuppressive effects, at least partly through inhibition of the release of various cytokines, and it is primarily these that are made use of clinically (see p.1495). They also have profound metabolic effects: blood glucose concentrations are maintained or increased by a decrease in peripheral glucose utilization and an increase in gluconeogenesis; glycogen deposition, protein breakdown, and lipolysis are increased, and effects on calcium uptake and excretion lead to a decrease in body calcium stores. Glucocorticoids facilitate the action of many other active endogenous substances, and affect the function of cardiovascular system, kidneys, skeletal muscle and CNS.

Many synthetic congeners and derivatives of the corticosteroids are available. The main corticosteroids used systemically are hydroxy compounds (alcohols). They are relatively insoluble in water and the sodium salt of the phosphate or succinate ester is generally used to provide water-soluble forms for injections or solutions. Such esters are readily hydrolysed in the body.

Various structure-activity relationships are understood for the corticosteroids and have been made use of in the development of new compounds. The presence of a hydroxyl group at position 11 seems to be essential for glucocorticoid activity, while a hydroxyl at position 21 is required for mineralocorticoid activity. Fluorination at position 9 enhances both mineralocorticoid and glucocorticoid activity. Substitution at carbon 16 (as in betamethasone, dexamethasone, or triamcinolone) virtually eliminates mineralocorticoid activity. Esterification of corticosteroids at the 17 or 21 positions with fatty acids generally increases the topical activity. The formation of cyclic acetonides at the 16 and 17 positions further increases topical anti-inflammatory activity, usually without increasing systemic glucocorticoid activity.

In the medical and pharmacological literature the names of unesterified corticosteroids have frequently been used indiscriminately for both the unesterified and esterified forms and it is not always apparent to which form reference is being made. The unesterified form is sometimes qualified by the phrase 'free alcohol'.

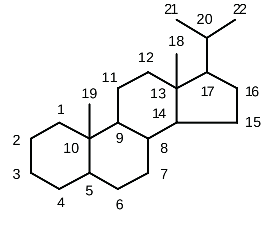

steroidal skeleton

Adverse Effects of Corticosteroids and their Treatment

The adverse effects of corticosteroids may result from unwanted mineralocorticoid or glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis.

Mineralocorticoid adverse effects are manifest in the retention of sodium and water, with oedema and hypertension, and in the increased excretion of potassium with the possibility of hypokalaemic alkalosis. In susceptible patients, cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticosteroids, such as cortisone and hydrocortisone, but are less frequent with many synthetic glucocorticoids, which have little or no mineralocorticoid activity.

Adverse **glucocorticoid** effects lead to mobilisation of calcium and phosphorus, with osteoporosis and spontaneous fractures; muscle wasting and nitrogen depletion; and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased. Increased appetite is often reported.

Impaired tissue repair and immune function can lead to delayed wound healing, and increased susceptibility to infection. Increased susceptibility to all kinds of infection, including septicaemia, tuberculosis, fungal infections, and viral infections, has been reported in patients on corticosteroid therapy. Infections may also be masked by the anti-inflammatory, analgesic, and antipyretic effects of glucocorticoids. The increased severity of varicella and measles may lead to a fatal outcome in non-immune patients receiving systemic corticosteroid therapy.

Other adverse effects include menstrual irregularities, amenorrhoea, hyperhidrosis, skin thinning, ocular changes including development of glaucoma and cataract, mental and neurological disturbances, benign intracranial hypertension, acute pancreatitis, and avascular necrosis of bone. An increase in the coagulability of the blood may lead to thromboembolic complications. Peptic ulceration has been reported but reviews of the literature do not always agree that corticosteroids are responsible for an increased incidence.

The negative feedback effects of glucocorticoids on the hypothalamic-pituitary-adrenal (HPA) axis may lead to adrenal atrophy, in some cases after therapy for as little as 7 days. This produces secondary adrenocortical insufficiency, which may become manifest after overly rapid withdrawal of treatment or be precipitated by some stress such as infection or trauma. Patients vary considerably in the degree and duration of adrenal suppression after a given course of corticosteroid, but adrenal atrophy may persist for months or years, and withdrawal should be gradual in those who have been treated for any length of time (see also Withdrawal, below). High doses of corticosteroids given during pregnancy may cause fetal or neonatal adrenal suppression. Although the precise mechanism is uncertain, growth retardation may follow the use of even relatively small doses of corticosteroids in children.

Large doses of corticosteroids, or of corticotropin, may produce Cushingoid symptoms typical of hyperactivity of the adrenal cortex, with moon-face, sometimes with hirsutism, buffalo hump, flushing, increased bruising, ecchymoses, striae, and acne (see also Cushing's Syndrome, p.2344). Giving large intravenous doses of corticosteroids too rapidly may cause cardiovascular collapse.

Hypersensitivity reactions have occurred with corticosteroids, mainly when applied topically.

Adverse effects occur, in general, fairly equally with all systemic corticosteroid preparations and their incidence rises steeply if dosage increases much above physiological values, traditionally considered to be about 7.5 mg daily of prednisolone or its equivalent (see Uses and Administration, below, for equivalent doses of other corticosteroids). Short courses at high dosage for emergencies appear to cause fewer adverse effects than prolonged courses with lower doses.

Most topically applied (including inhaled) corticosteroids may, under certain circumstances, be absorbed in sufficient amounts to produce systemic effects. The topical application of corticosteroid preparations to the eyes has produced corneal ulcers, raised intra-ocular pressure, and reduced visual function. Application of corticosteroids to the skin has led to loss of skin collagen and subcutaneous atrophy; local hypopigmentation of deeply pigmented skins has been reported after both the intradermal injection and topical application of potent corticosteroids. Dryness, irritation, epistaxis, and rarely ulceration or perforation of the nasal septum have followed intranasal use; smell and taste disturbances may also occur. Hoarseness and candidiasis of the mouth or throat may occur in patients receiving inhaled corticosteroids.

Intrathecal dosage (including inadvertent intrathecal dosage after attempted epidural injection) has been associated with arachnoiditis.

Adverse effects should be treated symptomatically, with the corticosteroid dosage reduced or slowly withdrawn where possible.

Adrenal suppression. The inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use may persist for a year or more after treatment is withdrawn and may cause acute adrenocortical insufficiency with circulatory collapse during stress. The degree of suppression depends on a number of factors, including length of treatment, time of day treatment is given, type of corticosteroid preparation used, route, dose used, and dosing interval. In general, suppression of secretion of adrenocorticotrophic hormone and atrophy of the adrenal gland become progressively more definite as doses of corticosteroid exceed physiological amounts (see Uses and Administration, below), and as the duration of therapy increases (significant suppression is likely in patients receiving more than 3 weeks of therapy). It is less when the corticosteroid is given as a single dose in the morning, and even less if this morning dose is given on alternate days or less frequently. In patients taking high enough doses of corticosteroids to suppress the adrenals the dose should be increased during any form of stress (for example, illness or surgery); similarly those treated with such doses within the last 2 or 3 months should be restarted on therapy. Where the interval since treatment is greater than 3 months, resumption of treatment depends on clinical assessment of signs of adrenocortical insufficiency.

To avoid precipitating acute adrenocortical insufficiency, withdrawal of corticosteroid treatment should be carried out gradually, differing regimens being used according to the disease being treated and the duration of therapy. Examples of withdrawal regimens that have been used are described under Withdrawal, below.

Adrenal suppression may occur after very short courses of high-dose therapy and since many patients undergoing such therapy will be under continuing stress when the drugs are stopped, gradual withdrawal of corticosteroids over 5 to 7 days is preferable.

It should also be remembered that corticosteroid-induced adrenal suppression has been associated not only with systemic therapy, but has followed topical application of corticosteroid preparations, particularly those containing potent corticosteroids. Some degree of adrenal suppression is also associated with the use of high dose inhalants and nasal preparations, and has followed the topical application of eye drops and eye ointments.

Effects on the bones and joints. Corticosteroid-induced **avascular necrosis** of bone is an uncommon but disabling complication of therapy.[1-3] The incidence may vary in patients with different disease states; alcoholics, and patients with connective tissue disease (especially SLE) may have increased susceptibility.[3,4] There may be a relationship with corticosteroid dose: even short courses of high-dose corticosteroids may be associated with its development.[1-3] Avascular necrosis has also been associated with topical application of corticosteroids.[5]

Corticosteroids may also produce **osteoporosis.** A review[6] of data obtained from studies published between 1970 and 1990 established that osteoporosis is a common consequence of long-term treatment with corticosteroids, occurring in about 50% of patients. Bone loss is more rapid during the early stages of therapy and is most rapid in areas of the skeleton containing the greatest proportion of trabecular bone such as the spine, hip, distal radius, pelvis, and ribs.

Reviews and guidelines[7-11] on the prevention and management of corticosteroid-induced osteoporosis suggest that the dose should be minimised, as oral doses above 7.5 mg of prednisolone or prednisone (or the equivalent) daily are associated with more significant bone loss and increased fracture risk.[12] Alternate-day therapy, although desirable for its reduced effect on the hypothalamic-pituitary-adrenal axis, does not reduce the risk of bone loss. It should be borne in mind that long-term use of inhaled corticosteroids may also reduce bone mineral density. Patients should maintain an adequate intake of calcium and vitamin D (prophylactic therapy with both has been advocated in all patients starting corticosteroids[13]), should take regular exercise, and avoid smoking and excessive alcohol intake. HRT has been advocated in postmenopausal women but recent re-evaluation of the risks and benefits of HRT may render this option unattractive. Bisphosphonates may be used in high-risk patients as they are effective at preventing and treating corticosteroid-induced bone loss[14] and may reduce fracture rates.[8-10] There is some evidence to suggest that calcitonin has a beneficial effect on bone mass, and it may be considered as an alternative when bisphosphonates cannot be used. Fluoride has been studied in corticosteroid-induced osteoporosis, but although it was found to increase bone density, there is concern about the resultant bone structure and a possible increase in fracture rates. There are reports of benefit from anabolic therapy, but evidence is limited. A thiazide diuretic may be helpful in controlling hypercalciuria in patients not receiving calcitriol.[8] Whether some corticosteroids have reduced effects on the bone is unclear.[9]

There is a risk of **tendinopathies** with the use of corticosteroids, especially of the Achilles and patellar tendons; ruptures have been reported.[15] Most reports have concerned oral or intra-articular use, but there have been occasional cases in patients receiving inhaled or topical corticosteroids.

1. Nixon JE. Early diagnosis and treatment of steroid induced avascular necrosis of bone. *BMJ* 1984; **288:** 741–4.
2. Anonymous. Transplant osteonecrosis. *Lancet* 1985; **i:** 965–6.
3. Capell H. Selected side-effects: 5. steroid therapy and osteonecrosis. *Prescribers' J* 1992; **32:** 32–4.
4. Knight A. Images in clinical medicine: corticosteroid osteonecrosis. *N Engl J Med* 1995; **333:** 130.
5. McLean CJ, *et al.* Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet* 1995; **345:** 330.
6. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112:** 352–64.
7. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum* 2001; **44:** 1496–1503.
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10. Cohen D, Adachi JD. The treatment of glucocorticoid-induced osteoporosis. *J Steroid Biochem Mol Biol* 2004; **88:** 337–49.
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12. van Staa TP, *et al.* Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)* 2000; **39:** 1383–9.
13. Homik J, *et al.* Calcium and vitamin D for corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 12/05/05).
14. Homik J, *et al.* Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 12/05/05).
15. Blanco I, *et al.* Corticosteroid-associated tendinopathies: an analysis of the published literature and spontaneous pharmacovigilance data. *Drug Safety* 2005; **28:** 633–43.

Effects on carbohydrate and protein metabolism. Corticosteroids produce glucose intolerance[1-4] and protein catabolism.[5,6] Although mainly associated with systemic use, there is a report of deterioration in diabetic control associated with high-dose inhaled corticosteroid treatment.[7]

1. Landy HJ, *et al.* The effect of chronic steroid therapy on glucose tolerance in pregnancy. *Am J Obstet Gynecol* 1988; **159:** 612–15.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; **40:** 6–18.
3. Bruno A, *et al.* Serum glucose, insulin and C-peptide response to oral glucose after intravenous administration of hydrocortisone and methylprednisolone in man. *Eur J Clin Pharmacol* 1994; **46:** 411–5.
4. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
5. Brownlee KG, *et al.* Catabolic effect of dexamethasone in the preterm baby. *Arch Dis Child* 1992; **67:** 1–4.
6. Van Goudoever JB, *et al.* Effect of dexamethasone on protein metabolism in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; **124:** 112–18.
7. Faul JL, *et al.* High dose inhaled corticosteroids and dose dependent loss of diabetic control *BMJ* 1998; **317:** 1491.

Effects on the cardiovascular system. Adverse effects of glucocorticoids include hypertension, hyperglycaemia, obesity, and dyslipidaemia,[1-3] which are independent risk factors for cardiovascular disease. However, glucocorticoids also have anti-inflammatory effects[1,2] which may exert an anti-atherosclerotic effect. Cohort studies[2,3] established that oral glucocorticoid use was associated with an increased risk for heart failure, and that high-dose therapy was associated with an increased risk for cardiovascular disease, including myocardial infarction.

1. Ng MKC, Celermajer DS. Glucocorticoid treatment and cardiovascular disease. *Heart* 2004; **90:** 829–30.
2. Souverein PC, *et al.* Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart* 2004; **90:** 859–65.
3. Wei L, *et al.* Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; **141:** 764–70.

Effects on the cerebrovascular system. Despite being used in high doses to treat benign intracranial hypertension, corticosteroids may also occasionally cause this disorder. Children receiving long-term therapy are mainly affected, an increase in dosage often being responsible. Symptoms usually subside when dosage is reduced.[1]

1. Gibberd B. Drug-induced benign intracranial hypertension. *Prescribers' J* 1991; **31:** 118–21.

Effects on the eyes. During ophthalmic use of corticosteroids about one-third of patients will develop **raised intra-ocular pressure**, usually within a few weeks of treatment with potent corticosteroids, or within months with weaker ones.[1] The effects on children are variable, but they may be at risk of a greater and more rapid response to ophthalmic corticosteroids.[1] Raised intra-ocular pressure and glaucoma can also be caused by topical use of corticosteroids on the face, particularly with prolonged use.[2] There is evidence of an increased risk in patients receiving prolonged high-dose inhaled corticosteroids.[3] Increases in intra-ocular pressure appear to be less common with systemic corticosteroids,[4] but a study in elderly patients showed that the risk of raised intra-ocular pressure or open-angle glaucoma increased with the dose and duration of oral use.[5]

Topical application of corticosteroids in patients with bacterial, fungal, or viral **eye infection** can alleviate the symptoms but allow the infection to develop.[1,6] In ocular herpes simplex infection there is the risk of corneal ulceration and scarring that may lead to loss of vision.

Cataract formation is associated with systemic corticosteroid use. It has also been reported after ophthalmic[1,4] and topical[2,7] use. There is evidence that cataract formation may also be associated with prolonged use of high-dose inhaled corticosteroids.[8-10] The intranasal use of corticosteroids, however, does not appear to increase the risk.[11] It has been suggested that the lens in children might be more sensitive than in adults, but this may be due to the large doses of corticosteroids, relative to body size, given orally in these cases. Evidence of an increased risk in children from inhaled corticosteroids is limited, but is probably outweighed by the benefits of asthma control.[12]

Systemic corticosteroid use has also been associated with damage to the retinal pigment epithelial barrier, predisposing the patient to serous **retinal detachment**.[13]

1. McGhee CNJ, *et al.* Locally administered ocular corticosteroids: benefits and risks. *Drug Safety* 2002; **25:** 33–55.
2. McLean CJ, *et al.* Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet* 1995; **345:** 330.
3. Garbe E, *et al.* Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997; **277:** 722–7.
4. Butcher JM, *et al.* Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 1994; **309:** 43.

5. Garbe E, *et al.* Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet* 1997; **350:** 979–82.
6. Baratz KH, Hattenhauer MG. Indiscriminate use of corticosteroid-containing eyedrops. *Mayo Clin Proc* 1999; **74:** 362–6.
7. Costagliola C, *et al.* Cataracts associated with long-term topical steroids. *Br J Dermatol* 1989; **120:** 472–3.
8. Cumming RG, *et al.* Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997; **337:** 8–14.
9. Garbe E, *et al.* Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA* 1998; **280:** 539–43. Correction. *ibid.*; 1830.
10. Smeeth L, *et al.* A population based case-control study of cataract and inhaled corticosteroids. *Br J Ophthalmol* 2003; **87:** 1247–51.
11. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. *J Allergy Clin Immunol* 2000; **105:** 912–16.
12. Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. *Drug Safety* 1999; **20:** 77–84.
13. Polak BCP, *et al.* Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol* 1995; **79:** 922–5.

Effects on the gastrointestinal tract. It has long been considered that treatment with corticosteroids might lead to peptic ulcers. Some years ago a review of the data then available suggested that since an ulcer developed in 1% of control patients not receiving corticosteroids, the 2% incidence for patients receiving corticosteroids did not warrant the prophylactic use of anti-ulcer drugs in all patients.[1] Others have found little evidence of an increased risk of peptic ulcer produced by corticosteroids alone although there is some increased risk when using them with NSAIDs.[2] A later cohort study[3] found a modest increase in risk of gastrointestinal bleeding with current use of corticosteroids, which increased when NSAIDs were also used. It has been suggested that it might be prudent to avoid such combination therapy whenever possible.[4]

Doubt has therefore been cast on the prophylactic value of anti-ulcer therapy given with corticosteroids.[1,5] If an ulcer does develop and there is good reason to continue treatment then corticosteroids may be continued along with some form of ulcer therapy.[1]

There have been several reports of corticosteroids being associated with gastrointestinal perforation.[6-9] There is a risk that the anti-inflammatory properties of corticosteroids may mask the signs of perforation and delay diagnosis with potentially fatal results.

1. Spiro HM. Is the steroid ulcer a myth? *N Engl J Med* 1983; **309:** 45–7.
2. Piper JM, *et al.* Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; **114:** 735–40.
3. Nielsen GL, *et al.* Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med* 2001; **111:** 541–5.
4. Guslandi M, Tittobello A. Steroid ulcers: a myth revisited. *BMJ* 1992; **304:** 655–6.
5. Marcus P, McCauley DL. Steroid therapy and H -receptor antagonists: pharmacoeconomic implications. *Clin Pharmacol Ther* 1997; **61:** 503–8.
6. Arsura EL. Corticosteroid-associated perforation of colonic diverticula. *Arch Intern Med* 1990; **150:** 1337–8.
7. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66:** 1164–6.
8. O'Neil EA, *et al.* Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. *Arch Dis Child* 1992; **67:** 10–11.
9. Epstein A, *et al.* Perforation of colon diverticula during corticosteroid therapy for pemphigus vulgaris. *Ann Pharmacother* 1993; **27:** 979–80.

Effects on growth. Corticosteroids impair normal growth in children when given systemically,[1-3] and although alternate-day therapy may reduce the effect on growth it does not abolish it. There has been some concern about possible effects of inhaled corticosteroids on growth.[1,4] Some studies have not found an effect of inhaled corticosteroids on growth if doses are modest, even when treatment is prolonged.[1,5,6] Others have found that inhaled corticosteroids, particularly in high doses, do have some effect on growth parameters,[5,7-10] but it is unclear whether this has long-term effects on the child's ultimate height, and the alternative in children requiring such high-dose therapy is likely to be an oral corticosteroid, with its consequent effects. Some studies,[11,12] in children with mild to moderate asthma, have suggested that a small reduction in growth velocity may occur in the first year of treatment, but that it then normalises and adult height is not adversely affected. Nonetheless, in the light of the increasing number of studies suggesting some effects of inhaled or intranasal corticosteroids on growth the FDA has required the inclusion of a warning in US labelling that such products may slow growth rates. For a suggestion that inhalation of a single dose of budesonide in the morning had less effect on growth than twice daily dosage, see Administration, p.1521.

1. Allen DB, *et al.* A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994; **93:** 967–76.
2. Lai H-C, *et al.* Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med* 2000; **342:** 851–9.
3. Mushtaq T, Ahmed SF. The impact of corticosteroids on growth and bone health. *Arch Dis Child* 2002; **87:** 93–6.
4. Hanania NA, *et al.* Adverse effects of inhaled corticosteroids. *Am J Med* 1995; **98:** 196–208.
5. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992; **89:** 839–42.
6. Volovitz B, *et al.* Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993; **329:** 1703–8.
7. Wolthers OD, Pedersen S. Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; **68:** 673–6.
8. Todd G, *et al.* Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; **348:** 27–9.
9. McCowan C, *et al.* Effect of asthma and its treatment on growth: four year follow up of cohort of children from general practices in Tayside, Scotland. *BMJ* 1998; **316:** 668–72.
10. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Abstract: *Pediatrics* 2000; **106:** 129. Full version: http://pediatrics.aappublications.org/cgi/content/full/106/1/e8 (accessed 27/04/04)
11. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343:** 1054–63.
12. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; **343:** 1064–9.

Effects on immune response. Owing to their immunosuppressant effect, giving corticosteroids in doses greater than those required for physiological replacement therapy is associated with increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. An additional problem is that the anti-inflammatory effect of corticosteroids may mask symptoms until the infection has progressed to an advanced stage; the altered response of the body may also permit the bizarre spread of infections, frequently in aberrant forms, such as disseminated parasitic infections. The risk is greater in patients receiving high doses, or associated therapy with other immunosuppressants such as cytotoxic drugs, and in those who are already debilitated. Children receiving high doses of corticosteroids are at special risk from childhood diseases, such as chickenpox, but vaccination with living organisms is contra-indicated since infection may be induced (killed vaccines or toxoids can be given but the response may be reduced).

This increased susceptibility to infection and masking of symptoms may also be caused by topical or local corticosteroid therapy. Thus, topical application to the skin has led to unusual changes such as atypical ringworm infection. Fungal infections (particularly candidiasis), generally restricted to the mouth and throat, are associated with corticosteroid inhalations. Severe damage to the eye has followed the ocular use of corticosteroids in herpetic infections, and a generalised spread of herpes infection may follow application to the mouth in the presence of herpes infection.

Conversely, the effect of corticosteroids on the symptoms and course of some infections may be life-saving (see Infections, under Uses and Administration, below). Before embarking on a long-term course of corticosteroid therapy general measures for the reduction of risk of infection include a diligent search for active or quiescent infection and, where appropriate, prevention or eradication of the infection before starting, or giving chemoprophylaxis during corticosteroid treatment.

Effects on lipid metabolism. Glucocorticoids have potent effects on lipid metabolism, facilitating the effects of growth hormone and endogenous stimulants of lipolysis. As a result they increase both high- and low-density lipoprotein cholesterol concentrations in the blood.

On prolonged use glucocorticoids also have a dramatic effect on body fat distribution, resulting in the characteristic Cushingoid appearance of moon face, and increased fat at the back of the neck and supraclavicular area.

Effects on mental state. Mental disturbances caused by corticosteroids include depression, mania, euphoria, and delirium.[1] Psychotic symptoms, insomnia, and hyperactivity have also been reported in children and adolescents treated with inhaled,[2,3] oral, and intravenous corticosteroids.[2] The risk of adverse effects appears to be dose-related, but there are reports of cases associated with very low dosages. Reversible impairment of memory has been associated with intravenous methylprednisolone.[4,5]

1. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Safety* 2000; **22:** 111–22.
2. Stuart FA, *et al.* Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child* 2005; **90:** 500–506.
3. de Vries TW, *et al.* Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur J Clin Pharmacol* 2006; **62:** 343–6.
4. Oliveri RL, *et al.* Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 1998; **97:** 366–9.
5. Brunner R, *et al.* Effect of corticosteroids on short-term and long-term memory. *Neurology* 2005; **64:** 335–7.

Effects on the neonate. Various adverse effects have been reported in premature neonates given corticosteroids, see under Dexamethasone, p.1526.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with intravenous use of dexamethasone sodium phosphate[1-4] and hydrocortisone sodium phosphate,[5] but not with hydrocortisone sodium succinate.[5] Descriptions of this reaction include itching, burning, tingling, and severe pain. It can begin within seconds of giving the injection, and clear within minutes of stopping. This reaction appears to be caused by the corticosteroid phosphate ester itself, and clears in the time it takes for the drug to be hydrolysed. It has been suggested that the reaction can be abolished or avoided by giving the drug as a dilute solution, over at least 5 to 15 minutes.[2-4]

Epidural lipomatosis (fat deposition around the spinal cord) is a rare complication of systemic corticosteroids.[6] It has been associated with both high daily doses (more than 30 mg prednisone daily) and lower doses given over several years. The onset of symptoms is usually gradual, ranging from 6 months to more than 20 years after beginning corticosteroid use. Spinal cord compression causes back pain radiating to the lower limbs, and severe neurological complications can develop. The lipomatosis may regress or disappear after the corticosteroid is withdrawn or the dose is lowered, but patients with myelopathy or rapidly progressive neurological deficit may need emergency surgery.

1. Czerwinski AW, *et al.* Effects of a single, large, intravenous injection of dexamethasone. *Clin Pharmacol Ther* 1972; **13:** 638–42.
2. Allan SG, Leonard RCF. Dexamethasone antiemesis and side-effects. *Lancet* 1986; **i:** 1035.
3. Neff SPW, *et al.* Excruciating perineal pain after intravenous dexamethasone. *Anaesth Intensive Care* 2002; **30:** 370–1.
4. Perron G, *et al.* Perineal pruritus after iv dexamethasone administration. *Can J Anesth* 2003; **50:** 749–50.
5. Novak E, *et al.* Anorectal pruritus after intravenous hydrocortisone sodium succinate and sodium phosphate. *Clin Pharmacol Ther* 1976; **20:** 109–12.
6. Hierholzer J, *et al.* Epidural lipomatosis: case report and literature review. *Neuroradiology* 1996; **38:** 343–8.

Effects on the pancreas. Acute pancreatitis has been associated with corticosteroid use,[1-3] although evidence supporting the association has been challenged on a number of grounds, both clinical and experimental.[2]

1. Nakashima Y, Howard JM. Drug-induced acute pancreatitis. *Surg Gynecol Obstet* 1977; **145:** 105–9.
2. Banerjee AK, *et al.* Drug-induced acute pancreatitis: a critical review. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
3. Felig DM, Topazian M. Corticosteroid-induced pancreatitis. *Ann Intern Med* 1996; **124:** 1016.

Effects on the skin. Topical corticosteroids are associated with a number of local adverse effects on the skin, principally due to their antiproliferative effects on keratinocytes and fibroblasts (leading to skin thinning and atrophy), and to possible interference with the skin flora (leading to increased risk of superinfection or opportunistic infection).[1] Skin thinning is more likely if corticosteroids are applied under occlusion (this is especially true of halogenated corticosteroids, which are more resistant to inactivation by enzymes in the epidermis). Striae, which occur usually in intertriginous areas such as axillae and groin where skin is thin, moist, and occluded, are the most readily appreciable manifestation of skin atrophy, and are irreversible, unlike more minor degrees of atrophy. Other local adverse effects include telangiectasias and purpura.[1] Acneform pustules at the site of application have occurred.

The balance between benefit and the likelihood of local or systemic adverse effects on topical application of corticosteroids will depend on the chemical structure of the drug (i.e. its lipophilicity and resistance to enzymic degradation), the formulation of the vehicle, the way in which it is applied, and the nature of the skin to be treated.[1]

Skin thinning, bruising, and purpura have also been reported in patients receiving inhaled corticosteroids.[2-4] There have been a few case reports of eczematous and erythematous lesions of the face and body, and urticaria, following inhalation or intranasal use.[5]

The adverse skin effects arising from systemic corticosteroids also include striae and skin thinning as well as acneform eruptions. Somewhat counter-intuitively a case-control study has suggested an increased risk of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients receiving corticosteroids, particularly in the period shortly after beginning therapy.[6]

1. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; **10:** 406–12.
2. Shuttleworth D, *et al.* Inhaled corticosteroids and skin thinning. *Br J Dermatol* 1990; **122:** 268.
3. Capewell S, *et al.* Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990; **300:** 1548–51.
4. Tashkin DP, *et al.* Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest* 2004; **126:** 1123–33.
5. Isaksson M. Skin reactions to inhaled corticosteroids: incidence, avoidance and management. *Drug Safety* 2001; **24:** 369–73.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

Effects on the voice. Dysphonia is associated with inhaled corticosteroids.[1] Although oropharyngeal candidiasis and dysphonia may occur at the same time, many patients with dysphonia do not have candidiasis, and the two conditions do not appear to be directly related. The cause of this dysphonia has not been fully explained, but clinical investigations have found changes including bowing of the vocal cords due to bilateral adductor myopathy, mucosal changes, and supraglottic hyperfunction.

1. Lavy JA, *et al.* Dysphonia associated with inhaled steroids. *J Voice* 2000; **14:** 581–8.

Hypersensitivity and anaphylaxis. There have been occasional reports of hypersensitivity reactions, and sometimes anaphylaxis, caused by corticosteroids.[1] Reactions have occurred with any route, although the topical route is mainly involved. It has been observed that the incidence of hypersensitivity is increasing[2] and it has been suggested that a lack of response in chronic eczema might be due to a reaction to the corticosteroid treatment.[2] Fluorinated corticosteroids may be less likely to induce a contact hypersensitivity reaction than non-fluorinated compounds.[3]

1. Kamm GL, Hagmeyer KO. Allergic-type reactions to corticosteroids. *Ann Pharmacother* 1999; **33:** 451–60.
2. Dooms-Goossens A. Sensitivity to corticosteroids: consequences for anti-inflammatory therapy. *Drug Safety* 1995; **13:** 123–9.
3. Thomson KF, *et al.* The prevalence of corticosteroid allergy in two U.K. centres: prescribing implications. *Br J Dermatol* 1999; **141:** 863–6.

Tumour lysis syndrome. There have been reports of corticosteroid-induced tumour lysis syndrome.[1-3]

1. Sparano J, *et al.* Increasing recognition of corticosteroid-induced tumour lysis syndrome in non-Hodgkin's lymphoma. *Cancer* 1990; **65:** 1072–3.
2. Smith RE, Stoiber TR. Acute tumor lysis syndrome in prolymphocytic leukemia. *Am J Med* 1990; **88:** 547–8.
3. Haller C, Dhadly M. The tumor lysis syndrome. *Ann Intern Med* 1991; **114:** 808–9.

Withdrawal of Corticosteroids

The use of pharmacological doses of corticosteroids suppresses the endogenous secretion of corticotropin by the anterior pituitary, with the result that the adrenal cortex becomes atrophied. Sudden withdrawal or reduction in dosage, or an increase in corticosteroid requirements associated with the stress of infection or accidental or surgical trauma, may then precipitate acute adrenocortical insufficiency; deaths have followed the abrupt withdrawal of corticosteroids. Adrenocortical insufficiency has also occurred after the effective reduction in systemic corticosteroid concentrations produced by overly rapid transfer from oral to inhaled corticosteroid therapy. For the emergency treatment of acute adrenocortical insufficiency caused by abrupt withdrawal of corticosteroids, see Adrenocortical Insufficiency, p.1498.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment. Other effects that may occur during withdrawal or change of corticosteroid therapy include fever, myalgia, arthralgia, weight loss, benign intracranial hypertension with headache and vomiting, and papilloedema caused by cerebral oedema. Latent rhinitis or eczema may be unmasked.

Duration of treatment and dosage are important factors in determining suppression of the pituitary-adrenal response to stress on cessation of corticosteroid treatment, and individual liability to suppression is also important.

After short courses at moderate doses it may be appropriate to withdraw corticosteroids without tapering the dose (see below). However, after high-dose or prolonged therapy, withdrawal should be gradual, the rate depending upon the individual patient's response, the dose, the disease being treated, and the duration of therapy. Recommendations for initial reduction, stated in terms of prednisolone, have varied from as little as steps of 1 mg monthly to 2.5 to 5 mg every 2 to 7 days. Provided the disease is unlikely to relapse the dose of systemic corticosteroid may be reduced rapidly to physiological values; dose reduction should then be slower to allow recovery of pituitary-adrenal function. Symptoms attributable to over-rapid withdrawal should be countered by resuming a higher dose and continuing the reduction at a slower rate. Giving corticotropin does not help to re-establish adrenal responsiveness.

This gradual withdrawal of corticosteroid therapy permits a return of adrenal function adequate for daily needs, but years may sometimes be required for the return of function necessary to meet the stress of infection, surgery, or trauma. On such occasions patients with a history of recent corticosteroid withdrawal should be protected by means of supplementary corticosteroid therapy as described under Precautions, below.

◊ The UK CSM recommends that moderate dosage with corticosteroids (up to 40 mg daily of prednisolone, or equivalent), for up to 3 weeks, may be stopped without tapering provided that the original disease is unlikely to relapse, although prophylactic cover may be required for any stress within a week of finishing the course.[1] However, it should be borne in mind that individuals vary widely in their response to corticosteroids and their ability to tolerate withdrawal. Gradual withdrawal should be considered, even after shorter courses, if higher doses are given, or in patients with other risk factors for adrenocortical insufficiency, including those who have had repeated courses of systemic corticosteroids, those who receive a course within one year of finishing long-term corticosteroid therapy, or those who regularly take doses in the evening, when their suppressive effect is greater. Withdrawal should not be abrupt in any patient who receives systemic corticosteroids for more than 3 weeks.[1]

How dose reduction is carried out depends largely on the likelihood of relapse of the original disease. If this is unlikely, the dose of systemic corticosteroid may be reduced rapidly to physiological values (traditionally considered to be 7.5 mg of prednisolone daily or equivalent). It should then be reduced more slowly to allow the hypothalamic-pituitary-adrenal axis to recover.[1] Where disease relapse is a possibility even the initial reduction may need to be more cautious. Long-term treatment may require withdrawal over many months (such as a reduction of 1 mg in the daily dose of prednisolone every 3 to 4 weeks).

In reviews of the inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use, further regimens for corticosteroid withdrawal are described.[2-4] For example, patients who have been treated for weeks or months may have their daily dose of prednisolone reduced by 2.5 to 5 mg every 2 or 3 days, or, for those on longer-term treatment, the reduction may be more gradual at a rate of 2.5 mg every 1 to 3 weeks and possibly less. When the dose has reached 10 mg daily decrements may be made with 1-mg tablets. Another approach may be to convert daily therapy gradually into alternate-day therapy by progressively reducing the amount of corticosteroid received on every second day, and once alternate-day therapy is established the dose may be further reduced until, for example, a dose of 1 mg on alternate days for one week is attained.

1. CSM/MCA. Withdrawal of systemic corticosteroids. *Current Problems* 1998; **24:** 5–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
2. Anonymous. Corticosteroids and hypothalamic-pituitary-adrenocortical function. *BMJ* 1980; **280:** 813–14.
3. Helfer EL, Rose LI. Corticosteroids and adrenal suppression: characterising and avoiding the problem. *Drugs* 1989; **38:** 838–45.
4. Page RC. How to wean a patient off corticosteroids. *Prescribers' J* 1997; **37:** 11–16.

Precautions for Corticosteroids

Systemic corticosteroids should be used with great caution in the presence of heart failure, recent myocardial infarction, or hypertension, in patients with diabetes mellitus, epilepsy (but see below for use in infantile seizures), glaucoma, hypothyroidism, hepatic failure, osteoporosis, peptic ulceration, psychoses or severe affective disorders, and renal impairment. Children may be at increased risk of some adverse effects; in addition, corticosteroids may cause growth retardation, and prolonged use is rarely justified. The elderly too may be at greater risk from adverse effects.

Corticosteroids are usually contra-indicated in the presence of acute infections uncontrolled by appropriate antimicrobial therapy. Similarly, patients already receiving corticosteroids are more susceptible to infection, the symptoms of which, moreover, may be masked until an advanced stage has been reached. Patients with active or doubtfully quiescent tuberculosis should not be given corticosteroids except, very rarely, as adjuncts to treatment with antitubercular drugs. Patients with quiescent tuberculosis should be observed closely and should receive chemoprophylaxis if corticosteroid therapy is prolonged.

The risks of chickenpox and probably of severe herpes zoster are increased in non-immune patients receiving therapeutic doses of systemic corticosteroids, and patients should avoid close personal contact with either infection. Passive immunisation is recommended for non-immune patients who do come into contact with chickenpox. Similar precautions apply to measles. Live vaccines should not be given to patients receiving high-dose systemic corticosteroid therapy nor for at least 3 months afterwards; killed vaccines or toxoids may be given although the response may be attenuated.

During prolonged courses of corticosteroid therapy, patients should be examined regularly. Sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of the fluid intake and output, and daily weight records may give early warning of fluid retention. Back pain may signify osteoporosis. Children are at special risk from raised intracranial pressure. Patients should carry cards (and preferably also wear bracelets) giving full details of their corticosteroid therapy; they and their relatives should be fully conversant with the implications of their therapy and the precautions to be taken.

Measures to compensate for the adrenals' inability to respond to stress (see Withdrawal, above) include increasing the dose to cover minor intercurrent illnesses or trauma such as surgery (with intramuscular doses to cover vomiting). For details of dosages used, see Uses and Administration, below.

Rapid intravenous injection of massive doses of corticosteroids may sometimes cause cardiovascular collapse and injections should therefore be given slowly or by infusion.

Many drugs have been reported to interfere with certain assay procedures for corticosteroids in body fluids and corticosteroids themselves may interfere with or alter the results of assays for some endogenous substances or drugs.

The risk of systemic absorption should always be considered when applying corticosteroids topically. They should not be applied with an occlusive dressing to large areas of the body. Long-term topical use is best avoided, especially in children. Also they should not be used for the treatment of ulcerative conditions, nor of rosacea, and should not be used indiscriminately for pruritus. Occasionally they may be used with the addition of a suitable antimicrobial substance in the treatment of infected skin but there is a risk of sensitivity reactions occurring.

Height should be monitored in children receiving prolonged therapy with inhaled or nasal corticosteroids. High doses of inhaled corticosteroids should preferably be inhaled using large-volume spacer devices to reduce oropharyngeal deposition and hence the incidence of candidiasis; rinsing the mouth with water after inhalation may also be helpful. In addition the use of spacer devices may reduce systemic absorption (see also Inhalation Therapy, under Uses and Administration, below). Paradoxical bronchospasm has occurred with inhaled corticosteroids and may require therapy to be stopped, although if mild it may be prevented by inhalation of a $beta_2$ adrenoceptor agonist, or by transfer from an aerosol to a dry powder formulation.

Caution is required when corticosteroids are used locally to treat eye disorders (see below).

Contraception. There are some isolated case reports of contraceptive failure in women using intra-uterine devices and receiving corticosteroid therapy.[1-3]

1. Zerner J, *et al.* Failure of an intrauterine device concurrent with administration of corticosteroids. *Fertil Steril* 1976; **27:** 1467–8.
2. Inkeles DM, Hansen RI. Unexpected pregnancy in a woman using an intrauterine device and receiving steroid therapy. *Ann Ophthalmol* 1982; **14:** 975.
3. Buhler M, Papiernik E. Successive pregnancies in women fitted with intrauterine devices who take anti-inflammatory drugs. *Lancet* 1983; **i:** 483.

Eye disorders. Topical corticosteroids have transformed the management of inflammatory disease of the anterior segment of the eye and it should be noted that while their proper use may be sight-saving their inappropriate use is potentially blinding.[1] The dangers include the conversion of a simple dendritic herpes simplex epithelial lesion into an extensive amoeboid ulcer with the likelihood of permanent corneal scarring and loss of vision and also the risk of potentiation of bacterial and fungal infections. Other dangers include the development of open-angle glaucoma and cataracts. Topical corticosteroids are used by ophthalmologists in herpes simplex keratitis but always under appropriate antiviral cover and their use requires considerable experience. They should never be given for an undiagnosed red eye and many consultant ophthalmic surgeons believe that general practitioners should never begin therapy without an ophthalmic opinion.

Further studies and discussions on the inappropriate use of corticosteroids to treat eye disorders are listed below.[2-10]

1. St Clair Roberts D. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1414–15.
2. Lavin MJ, Rose GE. Use of steroid eye drops in general practice. *BMJ* 1986; **292:** 1448–50.
3. Claoué CMP, Stevenson KE. Incidence of inappropriate treatment of herpes simplex keratitis with topical steroids. *BMJ* 1986; **292:** 1450–1.
4. Livingstone A. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1737.
5. Lawrence M. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1737–8.
6. Trevor-Roper P. Steroids, the eye, and general practitioners. *BMJ* 1986; **292:** 1738.
7. Jay B. Steroids, the eye, and general practitioners. *BMJ* 1986; **293:** 205.
8. Rose GE, Lavin MJ. Steroids, the eye, and general practitioners. *BMJ* 1986; **293:** 205.
9. O'Day DM. Corticosteroids: an unresolved debate. *Ophthalmology* 1991; **98:** 845–6.
10. Stern GA, Buttross M. Use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease. *Ophthalmology* 1991; **98:** 847–53.

Intranasal administration. Local adverse effects from intranasal corticosteroids include irritation, epistaxis, and smell and taste disturbances (see also above). Ulceration, septal perforation, and hypersensitivity reactions have occurred.[1]

There have been cases of Cushing's syndrome associated with inappropriately prolonged use of corticosteroid nasal drops in children.[2,3] Such drops should not be prescribed on a repeat prescription basis; where treatment is contemplated for more than 6 weeks appropriate monitoring has been recommended. See also Adrenal Suppression, under Adverse Effects, above.

1. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Safety* 2003; **26:** 863–93.
2. Findlay CA, *et al.* Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions. *BMJ* 1998; **317:** 739–40.
3. Perry RJ, *et al.* Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids. *Arch Dis Child* 2002; **87:** 45–8.

Porphyria. Corticosteroids are generally considered to be safe in patients with porphyria although there is conflicting evidence of porphyrinogenicity. In a review[1] of drug-induced porphyrias it was noted that a report suggesting that corticosteroids may have a role in treating the acute attack together with many reports attesting to their safety, contrasted with their repeated incrimination as the offending agent in producing such episodes. It was considered that as corticosteroids may be life-saving, they should be used if really indicated.

1. Moore MR, Disler PB. Drug-induction of the acute porphyrias. *Adverse Drug React Acute Poisoning Rev* 1983; **2:** 149–89.

Pregnancy. Studies have shown that corticosteroid use in pregnant women did not have adverse effects on the fetus in terms of psychological development[1] or growth and general health factors.[2] However, in an isolated report[3] the topical use of triamcinolone in a pregnant woman for treatment of eczema was considered to have caused fetal growth retardation. In another study[4] of 11 women with placenta praevia given intramuscular betamethasone 12 mg repeated 24 hours later, there were 2 cases of constriction of the ductus arteriosus; neither case was severe.

Early studies in *animals* showed an increase in fetal cleft palate after maternal ingestion of high corticosteroid doses, and cortisone has been used widely as a tool for the investigation of mechanisms responsible for cleft lip and palate. With doses used in clinical practice, however, the risk appears to be low. In an analysis of several hundred cases reported in the literature[5] it was concluded that the incidence of cleft palate in exposed children was slightly higher than in a random sample, but that in the small selected group studied, this higher incidence might be fallacious. Although an increased incidence of malformations in the children of asthmatic mothers given prednisolone 2.5 to 30 mg daily during pregnancy was noted,[6] others[7] have suggested that the outcome might have been worse in untreated asthmatic mothers. Moreover, no significant increase in the risk of fetal or maternal complications was found in a study of asthmatic mothers given prednisolone 2.5 to 20 mg daily.[8] Subsequently, no evidence of a teratogenic effect for corticosteroids was noted in a comparison of the maternal drug histories of the mothers of 764 infants born with anomalies of the CNS and 764 controls,[9] and in another study[10] there were no striking differences in birth-weight and frequency of 'small for dates' infants born to mothers who received systemic corticosteroids during pregnancy for pemphigoid gestationis and those who did not.

Fears concerning the use of corticosteroids during late pregnancy relate to their direct adverse effects on the fetus. These involve the known adverse effects of corticosteroids, such as increased risk of infection and adrenal insufficiency. No such adverse effects were noted in the infants of 70 exposed pregnancies,[8] although there have been individual reports.[11,12] The potential dangers of maternal diabetogenic effects have been demonstrated in a study of metabolic changes induced in diabetic women by salbutamol (used in the prevention of premature labour) which could be exacerbated by use of dexamethasone (to promote maturation of the fetal lung) with consequent danger to the fetus.[13]

A review[14] by the UK CSM concluded that there was no convincing evidence that corticosteroids caused an increased incidence of congenital abnormality. Prolonged or repeated use during pregnancy did increase the risk of intra-uterine growth retardation but this did not seem to be a problem following short-term treatment. It was noted that the ability of different corticosteroids to cross the placenta varied very markedly.

1. Schmand B, *et al.* Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. *Pediatrics* 1990; **86:** 58–64.
2. Doyle LW, *et al.* Antenatal steroid therapy and 5-year outcome of extremely low birth weight infants. *Obstet Gynecol* 1989; **73:** 743–6.
3. Katz VL, *et al.* Severe symmetric intrauterine growth retardation associated with the topical use of triamcinolone. *Am J Obstet Gynecol* 1990; **162:** 396–7.
4. Wasserstrum N, *et al.* Betamethasone and the human fetal ductus arteriosus. *Obstet Gynecol* 1989; **74:** 897–900.
5. Popert AJ. Pregnancy and adrenocortical hormones: some aspects of their interaction in rheumatic diseases. *BMJ* 1962; **1:** 967–72.
6. Warrell DW, Taylor R. Outcome for the foetus of mothers receiving prednisolone during pregnancy. *Lancet* 1968; **i:** 117–18.
7. Scott JK. Foetal risk with maternal prednisolone. *Lancet* 1968; **i:** 208.
8. Schatz M, *et al.* Corticosteroid therapy for the pregnant asthmatic patient. *JAMA* 1975; **233:** 804–7.
9. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
10. Holmes RC, Black MM. The fetal prognosis in pemphigoid gestationis (herpes gestationis). *Br J Dermatol* 1984; **110:** 67–72.
11. Grajwer LA, *et al.* Neonatal subclinical adrenal insufficiency: result of maternal steroid therapy. *JAMA* 1977; **238:** 1279–80.
12. Evans TJ, *et al.* Congenital cytomegalovirus infection after maternal renal transplantation. *Lancet* 1975; **i:** 1359–60.
13. Gündoğdu AS, *et al.* Comparison of hormonal and metabolic effects of salbutamol infusion in normal subjects and insulin-requiring diabetics. *Lancet* 1979; **ii:** 1317–21.
14. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; **24:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Septic shock. Some manufacturers recommend that corticosteroids should not be given to patients with septic shock and references to the controversial use of high-dose corticosteroids are given under Septic Shock, in Uses and Administration, below.

Sickle-cell disease. Sickle-cell crisis was reported to have been precipitated by corticosteroids in 2 patients with sickle C disease.[1] The crises in these patients were considered to have started with ischaemic necrosis of the bone marrow leading to fat embolism, cerebral hypoxia, and coma.

For mention of the use of corticosteroids in sickle-cell crisis, see under Sickle-cell Disease, in Uses and Administration, below.

1. Huang JC, *et al.* Sickling crisis, fat embolism, and coma after steroids. *Lancet* 1994; **344:** 951–2.

Tooth erosion. The increased incidence of tooth erosion seen in patients with asthma might be related to the pH of inhaled powder (but not aerosol) formulations.[1] Beclometasone dipropionate and fluticasone had pHs of 4.76 as powder formulations, whereas the pHs of the aerosols were well above the pH of 5.5 at which tooth substance begins to dissolve. Budesonide was less acidic in its powder formulation (pH 6.47).

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; **317:** 820.

Varicella. A number of cases of fatal or near fatal chickenpox have been reported in patients receiving corticosteroids.[1-3] Although mostly associated with systemic use, severe disseminated varicella and staphylococcal pericarditis have been reported in an infant following a single application of a potent topical corticosteroid cream.[4] Guidelines issued by the UK CSM state that all patients taking systemic corticosteroids for purposes other than replacement, and who have not had chickenpox, should be regarded as being at risk of severe chickenpox, irrespective of the dose or duration of treatment.[2,5] Passive immunisation with varicella-zoster immunoglobulin should be given to non-immune patients who are receiving corticosteroids, or who have received them within the last 3 months, if they are exposed to chickenpox. Passive immunisation should preferably be given within 3 days and not later than 10 days from exposure.[2] The CSM considered that there was no good evidence that topical, inhaled, or rectal corticosteroids were associated with an increased risk of severe chickenpox.

1. Rice P, *et al.* Near fatal chickenpox during prednisolone treatment. *BMJ* 1994; **309:** 1069–70.
2. CSM/MCA. Severe chickenpox associated with systemic corticosteroids. *Current Problems* 1994; **20:** 1–2.
3. Dowell SF, Breese JS. Severe varicella associated with steroid use. *Pediatrics* 1993; **92:** 223–8.
4. Brumund MR, *et al.* Disseminated varicella and staphylococcal pericarditis after topical steroids. *J Pediatr* 1997; **131:** 162–3.
5. Ellender D, *et al.* Severe chickenpox during treatment with corticosteroids. *BMJ* 1995; **310:** 327.

Interactions of Corticosteroids

Concurrent use of barbiturates, carbamazepine, phenytoin, primidone, or rifampicin may enhance the metabolism and reduce the effects of systemic corticosteroids. Conversely oral contraceptives or ritonavir may increase plasma concentrations of corticosteroids. Use of corticosteroids with potassium-depleting diuretics, such as thiazides or furosemide, may cause excessive potassium loss. There is also an increased risk of hypokalaemia with concurrent amphotericin B or bronchodilator therapy with xanthines or beta$_2$ agonists. There may be an increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Response to anticoagulants may be altered by corticosteroids and requirements of antidiabetic drugs and antihypertensives may be increased. Corticosteroids may decrease serum concentrations of salicylates and may decrease the effect of anticholinesterases in myasthenia gravis.

Analgesics. For the effect of corticosteroids on *salicylates*, see Aspirin, Interactions, p.23.

Antibacterials. *Rifampicin* reduces the activity of corticosteroids[1-8] by accelerating their metabolism, and a similar effect would be expected with other rifamycins. There is limited evidence that the macrolide antibacterials *troleandomycin*,[9-11] and perhaps *erythromycin*,[12] may inhibit the metabolism of methylprednisolone, but not of prednisolone.[10] Dosage reduction should be made as necessary if troleandomycin and methylprednisolone are used together. There is no evidence of a clinically significant interaction between these macrolides and other corticosteroids.

For reference to corticosteroids lowering plasma concentrations of *isoniazid* and enhancing its renal clearance, see p.290.

1. Edwards OM, *et al.* Changes in cortisol metabolism following rifampicin therapy. *Lancet* 1974; **ii:** 549–51.
2. Maisey DN, *et al.* Rifampicin and cortisone replacement therapy. *Lancet* 1974; **ii:** 896–7.
3. Steenbergen GJ, Pfaltzgraff RE. Treatment of neuritis in borderline leprosy with rifampicin and corticosteroids—a pilot trial. *Lepr Rev* 1975; **46:** 115–18.
4. Buffington GA, *et al.* Interaction of rifampin and glucocorticoids: adverse effect on renal allograft function. *JAMA* 1976; **236:** 1958–60.
5. Hendrickse W, *et al.* Rifampicin-induced non-responsiveness to corticosteroid treatment in nephrotic syndrome. *BMJ* 1979; **1:** 306.
6. van Marle W, *et al.* Concurrent steroid and rifampicin therapy. *BMJ* 1979; **1:** 1020.
7. Jopline WH, Pettit JHS. Interaction between rifampicin, steroids and oral contraceptives. *Lepr Rev* 1979; **50:** 331–2.
8. McAllister WAC, *et al.* Rifampicin reduces effectiveness and bioavailability of prednisolone. *BMJ* 1983; **286:** 923–5.
9. Szefler SJ, *et al.* The effect of troleandomycin on methylprednisolone elimination. *J Allergy Clin Immunol* 1980; **66:** 447–51.
10. Szefler SJ, *et al.* Steroid-specific and anticonvulsant interaction aspects of troleandomycin-steroid therapy. *J Allergy Clin Immunol* 1982; **69:** 455–60.
11. Kamada AK, *et al.* Glucocorticoid reduction with troleandomycin in chronic severe asthmatic children: implication for future trials and clinical application. *J Allergy Clin Immunol* 1992; **89:** 285.
12. LaForce CF, *et al.* Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. *J Allergy Clin Immunol* 1983; **72:** 34–9.

Anticoagulants. For the various effects of corticosteroids on anticoagulants, see under Warfarin Sodium, p.1430.

Antiepileptics. Reduced efficacy of corticosteroids has been noted in asthmatic, arthritic, renal transplant, and other patients who also received *phenytoin* or *phenobarbital*,[1-3] and the clearance of corticosteroids has also been reported to be markedly increased by *carbamazepine*.[3] Induction of microsomal liver enzymes by the antiepileptic, resulting in enhanced metabolism of the corticosteroid is believed to be the underlying mechanism. Different corticosteroids appear to be affected to different degrees, but the disease state, doses, and other determinants such as diet, sex, and other drugs used may also be contributory factors. An increase in the dosage of the corticosteroids may be necessary in order to maintain the desired therapeutic response.[1]

1. Brooks SM, *et al.* Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N Engl J Med* 1972; **286:** 1125–8.
2. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.
3. Bartoszek M, *et al.* Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy. *Clin Pharmacol Ther* 1987; **42:** 424–32.

Antifungals. *Ketoconazole*[1,2] and *itraconazole*[3,4] increase serum-methylprednisolone concentrations and enhance methylprednisolone's adrenal suppressive effects. A 50% reduction in intravenous methylprednisolone dose was suggested during ketoconazole therapy.[2] A similar effect was not evident with oral prednisone[4,5] although some workers[6] found that ketoconazole reduced the total clearance of prednisolone given intravenously and of prednisone given by mouth. Itraconazole can also reduce the clearance of dexamethasone; in a study[7] of 8 healthy subjects, the area under the concentration-time curve (AUC) for both intravenous and oral dexamethasone was increased about 3.5-fold, and the morning plasma-cortisol concentration was suppressed for at least 2 days longer. A study[8] of healthy subjects found that ketoconazole increased the AUC for oral budesonide more than sixfold when they were given together, but only about fourfold when the doses were given 12 hours apart. Systemic exposure to inhaled budesonide is increased by itraconazole, which probably reduces the metabolism of budesonide.[9] Adrenal suppression was found in 11 of 25 patients with cystic fibrosis who were treated with this combination; one patient developed Cushing's syndrome.[10] A similar interaction may have been the cause of significant adrenal suppression in a patient with cystic fibrosis who was treated with itraconazole and inhaled fluticasone propionate.[11]

1. Glynn AM, *et al.* Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. *Clin Pharmacol Ther* 1986; **39:** 654–9.
2. Kandrotas RJ, *et al.* Ketoconazole effects on methylprednisolone disposition and their joint suppression of endogenous cortisol. *Clin Pharmacol Ther* 1987; **42:** 465–70.
3. Varis T, *et al.* Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; **64:** 363–8.
4. Lebrun-Vignes B, *et al.* Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; **51:** 443–50.
5. Ludwig EA, *et al.* Steroid-specific effects of ketoconazole on corticosteroid disposition: unaltered prednisolone elimination. *DICP Ann Pharmacother* 1989; **23:** 858–61.
6. Zürcher RM, *et al.* Impact of ketoconazole on the metabolism of prednisolone. *Clin Pharmacol Ther* 1989; **45:** 366–72.
7. Varis T, *et al.* The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; **68:** 487–94.
8. Seidegård J. Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics by separation of their time of administration. *Clin Pharmacol Ther* 2000; **68:** 13–17.
9. Raaska K, *et al.* Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002; **72:** 362–9.
10. Skov M, *et al.* Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *Eur Respir J* 2002; **20:** 127–33.
11. Parmar JS, *et al.* Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002; **57:** 749–50.

Antineoplastics. For reference to single doses of prednisone inhibiting the activation of *cyclophosphamide* (but longer-term treatment increasing its activation), see Cyclophosphamide, p.703.

Antivirals. For a possible effect of corticosteroids on the metabolism of HIV-protease inhibitors, see p.883.

Ritonavir can greatly increase plasma concentrations of fluticasone, through inhibition of cytochrome P450 isoenzyme CYP3A4, leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.[1-3] There have been reports of osteoporosis, with fractures in one case, associated with Cushing's syndrome due to this interaction.[2] Similar interactions are expected with other HIV-protease inhibitors.

1. GlaxoSmithKline, Canada. Important safety information regarding a drug interaction between fluticasone propionate (Flonase /Flovent /Advair) and ritonavir (Norvir /Kaletra), issued 22 January, 2004. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/fluticasone_ritonavir_hpc-cps-eng.pdf (accessed 22/08/08)
2. Samaras K, *et al.* Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005; **90:** 4394–8.
3. Johnson SR, *et al.* Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006; **148:** 386–8.

Calcium-channel blockers. Studies in healthy subjects have found that *diltiazem* reduces the clearance of methylprednisolone.[1,2]

1. Varis T, *et al.* Diltiazem and mibefradil increase the plasma concentrations and greatly enhance the adrenal-suppressant effect of oral methylprednisolone. *Clin Pharmacol Ther* 2000; **67:** 215–21.
2. Booker BM, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and methylprednisolone in healthy volunteers. *Clin Pharmacol Ther* 2002; **72:** 370–82.

Gastrointestinal drugs. *Aprepitant* increased plasma concentrations of dexamethasone and methylprednisolone in a pharmacokinetic study.[1] Licensed product information for aprepitant recommends that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. For the appropriate regimen when these drugs are given together for nausea and vomiting, see Administration under Aprepitant, p.1709.

1. McCrea JB, *et al.* Effects of the neurokinin receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; **74:** 17–24.

Immunosuppressants. It has been suggested that mutual inhibition of metabolism occurs between *ciclosporin* and corticosteroids, and may increase the plasma concentrations of either drug.[1,2] A review[3] cited studies supporting this conclusion but also mentioned studies that showed that ciclosporin did not significantly decrease clearance of prednisolone[4] and that corticosteroids either did not change, or decreased, ciclosporin concentrations.[5,6] Some of these conflicting results may be due to differences in the methods used to measure ciclosporin concentrations.

1. Ost L. Effects of cyclosporin on prednisolone metabolism. *Lancet* 1984; **i:** 451.
2. Klintmalm G, Säwe J. High dose methylprednisolone increases plasma cyclosporin levels in renal transplant recipients. *Lancet* 1984; **i:** 731.
3. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (part II). *Clin Pharmacokinet* 1990; **19:** 400–15.
4. Frey FJ, *et al.* Evidence that cyclosporine does not affect the metabolism of prednisolone after renal transplantation. *Transplantation* 1987; **43:** 494–8.
5. Ptachcinski RJ, *et al.* Cyclosporine - high-dose steroid interaction in renal transplant recipients: assessment by HPLC. *Transplant Proc* 1987; **19:** 1728–9.
6. Hricik DE, *et al.* Association of the absence of steroid therapy with increased cyclosporine blood levels in renal transplant recipients. *Transplantation* 1990; **49:** 221–3.

Leukotriene antagonists. Severe peripheral oedema occurred in a patient treated with *montelukast* and prednisone for asthma, but not when either drug was used alone.[1] Montelukast may have potentiated sodium and fluid retention caused by the corticosteroid.

1. Geller M. Marked peripheral edema associated with montelukast and prednisone. *Ann Intern Med* 2000; **132:** 924.

Lipid regulating drugs. Giving *colestipol* to a patient with hypopituitarism taking oral hydrocortisone maintenance therapy resulted in headaches, ataxia, and lethargy.[1] Mental status returned to normal within hours of an intravenous dose of hydrocortisone 100 mg, and colestipol was subsequently withdrawn uneventfully.

1. Nekl KE, Aron DC. Hydrocortisone-colestipol interaction. *Ann Pharmacother* 1993; **27:** 980–1.

Neuromuscular blockers. For reference to corticosteroids antagonising the effects of *competitive neuromuscular blockers*, see under Atracurium, p.1904.

Sex hormones. There have been reviews[1,2] discussing several reports of an enhanced effect of corticosteroids in women also receiving *oestrogens* or *oral contraceptives* and commenting that the dose of corticosteroids in some cases may need to be reduced. There is some evidence that budesonide may be less affected by use with oral contraceptives than prednisolone.[3]

1. Shenfield GM. Drug interactions with oral contraceptive preparations. *Med J Aust* 1986; **144:** 205–10.
2. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; **18:** 472–84.
3. Seidegård J, *et al.* Effect of an oral contraceptive on the plasma levels of budesonide and prednisolone and the influence on plasma cortisol. *Clin Pharmacol Ther* 2000; **67:** 373–81.

Smoking. There was a report of an appreciable and consistent increase in plasma corticosteroids after cigarette smoking.[1] However, a review concerning the clinical importance of smoking and drug interactions[2] concluded that in the majority of examples, including corticosteroids, there was little evidence of a recognisable hazard from the interaction.

1. Kershbaum A, *et al.* Effect of smoking and nicotine on adrenocortical secretion. *JAMA* 1968; **203:** 275–8.
2. D'Arcy PF. Tobacco smoking and drugs: a clinically important interaction? *Drug Intell Clin Pharm* 1984; **18:** 302–7.

Sympathomimetics. Studies in 21 asthmatic patients suggested that the plasma half-life of dexamethasone was decreased by *ephedrine*.[1] More importantly use of corticosteroids with *beta$_2$ agonists* may potentiate any hypokalaemic effects.[2]

1. Brooks SM, *et al.* The effects of ephedrine and theophylline on dexamethasone metabolism in bronchial asthma. *J Clin Pharmacol* 1977; **17:** 308–18.
2. Committee on Safety of Medicines. β agonists, xanthines and hypokalaemia. *Current Problems 28* 1990.

Thalidomide. In a double-blind crossover study of thalidomide in the treatment of severe chronic erythema nodosum leprosum,[1] the dose of prednisolone necessary to suppress symptoms was considerably reduced in 9 of 10 patients while they were receiving thalidomide; there has been a comment[2] that prednisolone should not be given with thalidomide.

For reference to a possible interaction between thalidomide and dexamethasone, see Effects on the Skin under Adverse Effects of Thalidomide, p.2397.

1. Waters MFR. An internally-controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev* 1971; **42:** 26–42.
2. WHO, Regional Office for the Western Pacific. Final report on the first regional working group on leprosy, Manila, Philippines, 7–12 December, 1978. *Lepr Rev* 1979; **50:** 326–9.

Xanthines. For the effect of corticosteroids on *aminophylline* and *theophylline*, see p.1144.

Pharmacokinetics of Corticosteroids

Corticosteroids are, in general, readily absorbed from the gastrointestinal tract. They are also absorbed when given locally. After topical use, particularly under an occlusive dressing or when the skin is broken, or use rectally as an enema, sufficient corticosteroid may be absorbed to give systemic effects; this is also a possibility with other local routes such as inhalation. Water-soluble forms of corticosteroids are given by intravenous injection for a rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.

Corticosteroids are rapidly distributed to all body tissues. They cross the placenta to varying degrees and may be distributed in small amounts into breast milk.

Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin (transcortin) has high affinity but low binding capacity, while albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.

Corticosteroids are metabolised mainly in the liver but also in other tissues, and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

◊ Reviews.

1. Begg EJ, *et al.* The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; **146:** 37–41.
2. McGhee CNJ. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol* 1992; **76:** 681–4.
3. Jusko WJ. Pharmacokinetics and receptor-mediated pharmacodynamics of corticosteroids. *Toxicology* 1995; **102:** 189–96.
4. Derendorf H, *et al.* Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; **101** (suppl 2): S440–6.
5. Czock D, *et al.* Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* 2005; **44:** 61–98.

Uses and Administration of Corticosteroids

The corticosteroids are used in physiological doses for replacement therapy in adrenal insufficiency. Pharmacological doses are used when palliative anti-inflammatory or immunosuppressant effects are required. Before instituting therapy the benefits and risks of corticosteroids should be considered; where appropriate, local rather than systemic therapy should be used. The lowest effective dose should be used for the shortest possible time; high doses may be needed for life-threatening situations.

The effects of different corticosteroids vary qualitatively as well as quantitatively, and it may not be possible to substitute one for another in equal therapeutic amounts without provoking adverse effects. Thus, whereas cortisone and hydrocortisone have very appreciable mineralocorticoid (or sodium-retaining) properties relative to their glucocorticoid (or anti-inflammatory) properties, prednisolone and prednisone have considerably less, and others, such as betamethasone and dexamethasone, have none or virtually none. In contrast, the mineralocorticoid properties of fludrocortisone are so pronounced that its glucocorticoid effects are considered to have no clinical significance.

As a rough guide, the approximate **equivalent doses** of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties alone, are:

- betamethasone 0.75 mg
- cortisone acetate 25 mg
- dexamethasone 0.75 mg
- hydrocortisone 20 mg
- methylprednisolone 4 mg
- prednisolone 5 mg
- prednisone 5 mg
- triamcinolone 4 mg

The mineralocorticoid properties of corticosteroids (see p.1490) are rarely used. Exceptions include the treatment of primary adrenocortical insufficiency, in which both mineralocorticoid and glucocorticoid replacement is necessary, usually in the form of fludrocortisone with hydrocortisone (for details, see p.1498). The mineralocorticoid properties of fludrocortisone are also used to maintain blood pressure in patients with orthostatic hypotension (see p.1530).

The anti-inflammatory and immunosuppressant glucocorticoid properties of corticosteroids (see p.1490) are used to suppress the clinical manifestations of disease in a wide range of disorders considered to have inflammatory or immunological components. For these purposes, the synthetic analogues with their considerably reduced mineralocorticoid properties linked with enhanced glucocorticoid properties, are preferred.

Despite the existence of very powerful synthetic glucocorticoids with virtually no mineralocorticoid activity, the hazards of inappropriately high glucocorticoid therapy are such that the less powerful prednisolone and prednisone are the glucocorticoids of choice for most conditions, since they allow for a greater margin of safety. There is little to choose between prednisolone and prednisone; prednisolone is usually recommended in the UK since it exists in a metabolically active form, whereas prednisone is inactive and must be converted into its active form by the liver; hence, particularly in some liver disorders, bioavailability of prednisone is less reliable (but see Hepatic Impairment under Precautions of Prednisolone, p.1541).

Because the therapeutic effects of corticosteroids seem to be of longer duration than the metabolic effects, intermittent treatment with corticosteroids has been used to allow the metabolic rhythm of the body to become re-established while maintaining the therapeutic effects. Regimens of intermittent therapy have usually consisted of short courses of treatment or of the use of single doses on alternate days. Such alternate-day therapy, however, is only appropriate for corticosteroids with a relatively short duration of action and small mineralocorticoid effect, such as prednisolone, and only in certain disease states. Corticosteroids are also given in single daily doses at times coinciding with maximum or minimum output of the adrenal cortex in order to obtain the desired effect on the adrenals (see Administration, below).

Doses of corticosteroids higher than those required for physiological replacement will eventually lead to some degree of adrenal suppression, the extent depending on the dose given, and the route, frequency, time, and duration of treatment. The adrenal glands are traditionally considered to have a daily output equivalent to about 20 mg of hydrocortisone (cortisol), but individual blood-cortisol concentrations may vary widely, and can increase up to tenfold or more during stress. Therefore, during periods of stress or trauma, such as during and after surgery and when suffering from infections, the corticosteroid dosage of patients must be increased. In patients on long-term corticosteroid therapy undergoing surgery this is usually provided by parenteral hydrocortisone; graduated regimens tailored to the severity of surgery (see p.1536) are now preferred to the former high-dose standard regimens tapered over 5 days, whose use has been questioned (see Surgery, under Administration, below).

Although the empirical use of a corticosteroid is appropriate in a life-threatening situation, generally it is advisable not to begin corticosteroid therapy until a definite diagnosis has been made, for otherwise symptoms may be masked to such an extent that a true diagnosis becomes extremely difficult to make and the disease may reach an advanced stage before detection.

Systemic therapy is indicated in a wide variety of conditions. Where possible the oral route is preferred but parenteral doses may be used if the disease is severe or an emergency arises. Intravenous therapy is generally used for intensive emergency treatment as the onset of action is relatively fast although intramuscular injections, often formulated as longer-acting depot preparations, may also be used to provide subsequent cover. Examples of conditions treated with systemic corticosteroids include:

- as an adjunct to adrenaline in life-threatening allergic reactions such as angioedema or anaphylaxis (see p.1205)
- some blood disorders, including auto-immune haemolytic anaemia (p.1043) and idiopathic thrombocytopenic purpura (p.1505)
- selected connective tissue and muscle disorders, such as Behçet's syndrome (p.1499), polymyalgia rheumatica (p.1510), polymyositis (p.1510), SLE (p.1513), and the vasculitic syndromes (p.1515)
- some inflammatory eye disorders, particularly those affecting the posterior chamber
- inflammatory gastrointestinal disorders, such as Crohn's disease and ulcerative colitis, although local administration by the rectal route may be preferred in some circumstances (see p.1697)
- infections accompanied by a severe inflammatory component provided that appropriate anti-infective drugs are also given and that the benefits of corticosteroid therapy outweigh the possible risk of disseminated infection; examples of conditions where corticosteroid may be considered include helminthic infections, the Jarisch-Herxheimer reaction, and tuberculous meningitis (p.1514)
- selected kidney disorders including lupus nephritis (see Systemic Lupus Erythematosus, p.1513) and various glomerular disorders (p.1504)
- selected liver disorders, including auto-immune chronic active hepatitis (p.1501)
- some neurological disorders such as infantile seizures and subacute demyelinating polyneuropathy; also in cerebral oedema (p.1501), including that associated with malignancy
- some respiratory disorders, such as asthma (see p.1108, although inhaled corticosteroids are preferred to oral therapy for prophylaxis), diffuse parenchymal lung disease (p.1502), pulmonary sarcoid (p.1512), and neonatal respiratory distress syndrome (p.1508)
- some cases of rheumatoid arthritis, where recent evidence suggests there may be value in early treatment of active disease (see p.1511)
- severe skin disorders such as pemphigus and pemphigoid (p.1582)

Glucocorticoids are also used with antineoplastics in regimens for the management of malignant disease. They are also given to reduce immune responses after organ transplantations, often with other immunosuppressants (see p.1810).

Corticosteroids are not now considered useful in patients with aspiration syndromes, stroke, or septic shock.

Intra-articular injection, in the absence of infection and with full aseptic precautions, may be used, for example, in the treatment of rheumatoid arthritis (p.11), osteoarthritis (p.11), and ankylosing spondylitis (see Spondyloarthropathies, p.13). Either hydrocortisone acetate or one of the esters of the synthetic corticosteroids is used. It should be noted that there have been several reports of joint damage after the intra-articular injection of corticosteroids into load-bearing joints.

Topical application often produces dramatic suppression of skin diseases in which inflammation is a prominent feature, such as eczema (p.1579), seborrhoeic dermatitis (p.1584), and some forms of psoriasis (p.1583). However, the disease may return or be exacerbated when corticosteroids are withdrawn and this appears to be a particular problem in some of the forms of psoriasis. Occasionally, corticosteroids may be used with the addition of a suitable antimicrobial, such as neomycin, in the treatment of infected skin. For comments on the topical application of preparations containing a corticosteroid and neomycin, see Adverse Effects of Neomycin, p.305.

Intralesional injection sometimes hastens the resolution of chronic skin lesions such as lichen planus (p.1580), alopecia areata (p.1577), and keloids.

Topical application to the eye in inflammatory and traumatic disorders has led to dramatic results, but the occurrence of herpetic and fungal infections of the cornea and other serious complications are considerable obstacles, and eye drops containing corticosteroids should be used under strict ophthalmic supervision with regular checks of intra-ocular pressure. Care is also required when corticosteroids are given by **subconjunctival injection** in inflammatory eye disorders.

Ear drops containing corticosteroids are used in the treatment of otitis externa (see p.182).

Inhalational therapy is widely used in the prophylaxis of asthma (see p.1108).

Nasal application is used in the prophylaxis and treatment of allergic and non-allergic rhinitis (see p.565) and nasal polyps (p.1508).

Rectal administration, by either suppository or enema, may be used for some corticosteroids, notably in the treatment of inflammatory bowel disease (p.1697).

Administration

Diurnal effect. The diurnal rhythm of the adrenal cortex leads to about 70% of the daily secretion being made between midnight and 9 am.[1] In the treatment of adrenal cortical hyperplasia a dose of hydrocortisone given at night will be nearly twice as suppressive as the same dose given during the day. However, in treating allergic or collagen disease when suppression of adrenal cortical activity is best avoided a dose of hydrocortisone at about 8 am is indicated. When reducing corticosteroid dosage after treatment, a single dose given at 8 am will be most beneficial and will not inhibit corticotropin secretion. Also, for similar reasons,[2] when used for replacement therapy corticosteroids are given in unequal doses during the day (two-thirds of the daily dose in the morning, and one-third at night).

1. Demos CH, *et al*. A modified (once a day) corticosteroid dosage regimen. *Clin Pharmacol Ther* 1964; **5:** 721–7.
2. Aronson JK. Chronopharmacology: reflections on time and a new text. *Lancet* 1990; **335:** 1515–16.

Epidural route. Reviews[1,2] of the epidural use of corticosteroids in sciatica concluded that reported clinical complications were uncommon but that their role is unclear. Another study[3] suggested that although epidural injection of methylprednisolone acetate produced short-term improvement in pain and sensory deficit, treatment resulted in no functional benefit and did not reduce the need for surgery.

It should be noted that inadvertent intrathecal injection of corticosteroids has resulted in severe neurological complications.

1. Bogduk N, Cherry D. Epidural corticosteroid agents for sciatica. *Med J Aust* 1985; **143:** 402–6.
2. Tonkovich-Quaranta LA, Winkler SR. Use of epidural corticosteroids in low back pain. *Ann Pharmacother* 2000; **34:** 1165–72. Correction. *ibid.*; 1489.
3. Carette S, *et al*. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; **336:** 1634–40.

Inhalational therapy. Corticosteroids are given by inhalation, particularly in the maintenance therapy of asthma, in order to deliver the drug directly to the lungs, at smaller doses than are needed orally, and minimise systemic adverse effects. Different inhaled corticosteroids differ in their potency, though there is little evidence of a difference in efficacy at recommended doses.[1] Of those widely available by inhalation, flunisolide is less potent than beclometasone while budesonide is considered more potent, and fluticasone more potent still. (However, a general practice study in New Zealand has suggested that budesonide is less potent than beclometasone.[2]) The ability to use fewer inhalations with more potent drugs might enhance compliance.[1] For inhaled corticosteroids to be effective in the prophylaxis of asthma they must be taken regularly and patient compliance is important.

Efficient delivery to the bronchial tree is crucial and a number of different devices are available, including pressurised aerosol inhalers, breath-actuated aerosol inhalers, and dry powder inhalers. These devices appear to be equally effective for the delivery of corticosteroids.[3] However, many patients, especially children, find that inhalation is made much easier by fitting a spacer device to the inhaler.[4] Such a device is recommended when high doses are to be inhaled, to prevent oropharyngeal deposition and subsequent systemic absorption. However, the type of spacer used and the method of use may dramatically alter the amount of drug available for inhalation. The drug should be introduced into the spacer by single actuations, each followed by inhalation, with the delay between actuation of the inhaler and inhalation from the spacer kept to a minimum. In some spacers static electricity accumulates, and the build up of charge reduces drug delivery: this can be controlled by washing and drying the spacer in air once a month. Considerable differences in the dose delivered to the airways may also be seen between different types of nebuliser, and between nebulisers and spacer devices.[5]

Changes in formulation of the propellant, to remove chlorofluorocarbons, may also affect drug availability; it is reported to be increased, requiring dose reduction with some formulations.[6,7]

It should be borne in mind that apparent differences in the dose supplied from inhaler devices in different countries may in some cases be artefacts, due to variations in the way the dose is measured or expressed. In the UK, for example, the dose supplied from a metered-dose inhaler is generally quoted as the amount released into the mouthpiece from the valve. In the USA, however, doses may be stated in terms of the amount of drug emitted from the mouthpiece, which due to drug deposition will be slightly less than the amount released from the valve.

1. Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998; **32:** 220–32.
2. Pethica BD, *et al.* Comparison of potency of inhaled beclometasone and budesonide in New Zealand: retrospective study of computerised general practice records. *BMJ* 1998; **317:** 986–90.
3. Brocklebank D, *et al.* Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. *BMJ* 2001; **323:** 896–900.
4. O'Callaghan C, Barry PW. How to choose delivery devices for asthma. *Arch Dis Child* 2000; **82:** 185–7.
5. O'Callaghan C, Barry P. Delivering inhaled corticosteroids to patients. *BMJ* 1999; **318:** 410–11.
6. Newman SP. Deposition and effects of inhaled corticosteroids. *Clin Pharmacokinet* 2003; **42:** 529–44.
7. MHRA/CHM. Inhaled products that contain corticosteroids. *Drug Safety Update* 2008; **1** (12): 6–7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)

Intra-articular route. Intra-articular and periarticular injection of corticosteroids is an established treatment for a variety of joint and soft-tissue lesions.[1-3] Pain and inflammation associated with rheumatoid and juvenile idiopathic arthritis, crystal arthropathies such as gout, and osteoarthritis can be alleviated by injection of a suitable corticosteroid, and in some cases the benefits may be quite prolonged. The longer-acting esters methylprednisolone acetate, triamcinolone acetonide, and triamcinolone hexacetonide are generally preferred. In some cases these may be combined with a local anaesthetic and a short-acting soluble corticosteroid for more rapid relief and to reduce the risk of a post-injection flare.

The risks associated with this technique have been reviewed.[4] Accurate injection technique is essential, and vigorous skin cleansing and an aseptic technique are required to avoid the introduction of infection into the joint; pre-existing joint infection is a contra-indication to corticosteroid injection. Intra-articular injections may be repeated if necessary but it has been suggested that a single joint should not be injected more than 3 or 4 times a year.

Periarticular injection is also used in various soft tissue disorders such as bursitis, capsulitis (painful shoulder syndromes), epicondylitis, tenosynovitis, and carpal tunnel syndrome. Particular care is required to avoid injection directly into a tendon, as this may cause the tendon to rupture. A shorter-acting corticosteroid such as hydrocortisone acetate may be more suitable for extra-articular lesions.

1. Anonymous. Articular and periarticular corticosteroid injections. *Drug Ther Bull* 1995; **33:** 67–70.
2. Caldwell JR. Intra-articular corticosteroids: guide to selection and indications for use. *Drugs* 1996; **52:** 507–14.
3. Pullar T. Routes of drug administration: intra-articular route. *Prescribers' J* 1998; **38:** 123–6.
4. Hunter JA, Blyth TH. A risk-benefit assessment of intra-articular corticosteroids in rheumatic disorders. *Drug Safety* 1999; **21:** 353–65.

Intranasal route. In the management of allergic rhinitis corticosteroids are given intranasally in order to deliver the drug directly to the affected area, to use lower doses than are needed orally, and reduce the risk of systemic adverse effects. They are usually given by metered dose pump spray. The extent of local effect versus systemic effect may be influenced by the drug's molecular weight, lipophilicity, metabolism in nasal tissue, and type of delivery device.[1] In practice, however, when intranasal corticosteroid sprays are used as recommended there is little evidence that they have a significant systemic effect, and their local adverse effects are similar.[2,3] For details of systemic effects associated with inappropriately prolonged use of corticosteroid nasal drops, see Intranasal Administration under Precautions, p.1494.

1. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Safety* 2000; **23:**11–33.
2. Waddell AN, *et al.* Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J Laryngol Otol* 2003; **117:** 843–5.
3. Meltzer EO. Intranasal steroids: managing allergic rhinitis and tailoring treatment to patient preference. *Allergy Asthma Proc* 2005; **26:** 445–51.

Surgery. In the light of what was known in 1994 about the adrenal stress response to surgery, a discussion on the appropriate glucocorticoid supplementation for patients receiving corticosteroids who undergo surgery concluded that some recommendations were excessive.[1] (At this time in the UK recommended regimens consisted of the equivalent of 100 mg of hydrocortisone, usually as the sodium succinate, intravenously or intramuscularly before surgery, repeated every 8 hours, with the dose being tapered over 5 days to 20 or 30 mg daily.) It was suggested that for minor surgery 25 mg of hydrocortisone or its equivalent pre-operatively was adequate; where surgical stress was likely to be moderate, 50 to 75 mg of hydrocortisone or its equivalent daily in divided doses for 1 to 2 days was suggested. For major surgical stress, a target of 100 to 150 mg of hydrocortisone or its equivalent should be given daily in divided doses for 2 to 3 days, although less might be given if the patient's pre-operative glucocorticoid dose was low. It was also considered that the practice of gradually reducing postoperative coverage over several days was not supported by evidence except in cases of high-dose glucocorticoid use for prolonged periods.

Another review[2] of this subject also concluded that for minor surgery, 25 mg of hydrocortisone, or the patient's usual dose of corticosteroid, given pre-operatively, was appropriate. However, the authors argued that for surgery causing greater stress, it was preferable to avoid the increases in plasma-cortisol associated with intermittent bolus doses. They suggested that for moderate surgery an intravenous dose of hydrocortisone 25 mg at induction should be followed by an infusion of 100 mg over 24 hours; for major surgery the infusion should be continued for 48 to 72 hours after surgery. The usual oral corticosteroid dose may be resumed once these infusions have been completed, providing the postoperative course is uncomplicated and gastrointestinal function has returned.

For currently recommended regimens see Uses and Administration of Hydrocortisone, p.1536.

1. Salem M, *et al.* Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg* 1994; **219:** 416–25.
2. Nicholson G, *et al.* Peri-operative steroid supplementation. *Anaesthesia* 1998; **53:** 1091–1104.

Topical application. Guidelines[1,2] for the correct use of topical corticosteroids recommend that an appropriately potent preparation to bring the skin disorder under control should be used. Some recommend use of the lowest potency that will control the disorder, while others have advocated starting treatment with a more potent preparation, treatment may then be continued with a less potent preparation and with less frequent application, once control is obtained. The most potent topical corticosteroids are generally reserved for recalcitrant dermatoses. Once the skin has healed, treatment should be tailed off. Particular care is necessary in the use of topical corticosteroids in children, and the more potent preparations are contra-indicated in infants under 1 year of age, although potent preparations may be needed briefly in older children. It has been suggested that a 'steroid holiday' of at least 2 weeks be considered in children after each 2 or 3 weeks of daily topical therapy to allow thinned epidermis to restore itself and maintain its barrier function.[3]

Care is also necessary in applying corticosteroids to certain anatomical sites such as the face and flexures; some advocate using only hydrocortisone 0.5 or 1% on the face. Advice should be given that topical corticosteroids should be applied sparingly in thin layers, by smoothing gently into the skin preferably after a bath, and that no benefit is gained from more frequent than twice daily application or by vigorous rubbing.

In a study to determine the requirement of topical corticosteroids,[4] 16 adult patients with eczema were treated with a variety of topical preparations until substantial clearing had occurred (up to 10 days). Results indicated that the mean requirement of preparation, regardless of potency or vehicle, was 6.86 g/m^2. Using this value the calculated quantities of topical corticosteroid to the nearest 5 g required for twice daily application for one week for the whole body, arms and legs only, and trunk only respectively were as follows:

- 6 months of age, 35 g, 20 g, and 15 g
- 1 year, 45 g, 25 g, and 15 g
- 4 years, 60 g, 35 g, and 20 g
- 8 years, 90 g, 50 g, and 35 g
- 12 years, 120 g, 65 g, and 45 g
- 16 years, 155 g, 85 g, and 55 g
- adult (70-kg male), 170 g, 90 g, and 60 g

Calculated quantities for the same application schedule for an adult (70-kg male) for individual portions of the body were:

- face and neck, 10 g
- one arm, 15 g
- one leg, 30 g
- hands and feet, 10 g

Table 1, below, is a guide to the potency of topical corticosteroids. There may be some degree of overlap between these groups and, not surprisingly, there are minor varia-

Table 1. Guide to potencies of topical corticosteroids.

Very potent	Potent	Moderately potent	Mild
Clobetasol propionate 0.05%	Amcinonide 0.1%	Alclometasone dipropionate 0.05%	Fluocinolone acetonide 0.0025%
Diflucortolone valerate 0.3%	Beclometasone dipropionate 0.025%	Betamethasone valerate 0.025%	Hydrocortisone 0.5% and 1%
Fluocinolone acetonide 0.2%	Betamethasone benzoate 0.025%	Clobetasone butyrate 0.05%	Hydrocortisone acetate 1%
Halcinonide 0.1%	Betamethasone dipropionate 0.05%	Desoximetasone 0.05%	Methylprednisolone acetate 0.25%
Ulobetasol propionate 0.05%	Betamethasone valerate 0.1%	Fludroxycortide 0.0125%	
	Budesonide 0.025%	Flumetasone pivalate 0.02%	
	Desonide 0.05%	Fluocinolone acetonide 0.00625% and 0.01%	
	Desoximetasone 0.25%	Fluocortin butyl 0.75%	
	Diflorasone diacetate 0.05%	Fluocortolone preparations (caproate with pivalate, each 0.1% and caproate with either free alcohol or pivalate, each 0.25%)	
	Diflucortolone valerate 0.1%	Hydrocortisone aceponate 0.1%	
	Fluclorolone acetonide 0.025%	Hydrocortisone buteprate 0.1%	
	Fluocinolone acetonide 0.025%	Prednicarbate 0.25%	
	Fluocinonide 0.05%		
	Fluprednidene acetate 0.1%		
	Fluticasone propionate 0.005% and 0.05%		
	Hydrocortisone butyrate 0.1%		
	Methyprednisolone aceponate 0.1%		
	Mometasone furoate 0.1%		
	Triamcinolone acetonide 0.1%		

tions to this classification. For example, some authorities consider fluocinolone acetonide 0.2% to be potent rather than very potent and halcinonide 0.1% to be potent rather than very potent.

It has been suggested, however, that the advent of non-fluorinated double esters such as hydrocortisone and methylprednisolone aceponates, or prednicarbate, has resulted in corticosteroids whose topical anti-inflammatory potency is not as closely related to their potential atrophic effects on skin, and that a classification taking both into account would be desirable.[5,6]

1. Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 1980; **19:** 119–34.
2. Savin JA. Some guidelines to the use of topical corticosteroids. *BMJ* 1985; **290:** 1607–8.
3. Hepburn D, *et al.* Topical steroid holiday. *Pediatrics* 1995; **95:** 455.
4. Maurice PDL, Saihan EM. Topical steroid requirement in inflammatory skin conditions. *Br J Clin Pract* 1985; **39:** 441–2.
5. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; **10:** 406–12.
6. Schäfer-Korting M, *et al.* Topical glucocorticoids with improved risk-benefit ratio: rationale of a new concept. *Drug Safety* 1996; **14:** 375–85.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is characterised by areas of lung damage leading to decreased pulmonary compliance, pulmonary oedema associated with increased capillary and alveolar permeability, and refractory hypoxaemia. Diffuse pulmonary infiltrates are seen on radiography, and patients exhibit dyspnoea, tachypnoea, or both. Diagnosis is primarily clinical, and there has been some disagreement as to what should be included in the syndrome;[1] it is now seen as forming the most severe end of a spectrum of symptoms due to lung inflammation and increased permeability known as acute lung injury.[1-3] ARDS is sometimes considered to refer to 'adult respiratory distress syndrome' but it is not confined to adult patients.[1,2]

ARDS may be caused by a variety of pulmonary or systemic insults but is particularly frequent in patients with sepsis;[4] because of an association with failure of other organs it has been suggested that it represents the pulmonary component of multiple organ failure syndrome.[5] A wide variety of inflammatory mediators have been implicated in its pathogenesis but evidence suggests that recruitment of neutrophils by interleukins plays an important role.[1]

Management. Therapy for ARDS is essentially supportive. Mechanical ventilation is necessary in most cases, and circulatory support may require fluids, cardiac inotropes, and vasodilators. Optimum management may include diuretics and fluid restriction provided that cardiac output and oxygen delivery are maintained.[6] Because of the association with sepsis antibacterial therapy may be important, but studies of anti-endotoxin antibodies have produced disappointing results.[3] Improvements in supportive care and mechanical ventilation are considered to have reduced the mortality rate.[1,7] Partial liquid ventilation with perfluorocarbons has been tried, but good evidence to support this intervention is not available.[8]

Numerous drugs have been proposed for the management of ARDS, but, although case reports are often encouraging, none has been conclusively shown to improve mortality in controlled trials,[9] or in systematic review.[10] Corticosteroids do not appear to reduce acute mortality,[3,5] although they may be tried in the later phases of the syndrome (5 or more days from onset) to try to prevent fibroproliferative lung changes.[1,11,12] Good results have been reported with inhaled epoprostenol,[13,14] but these results await confirmation from larger controlled studies.

There is evidence that ketoconazole may prevent development of ARDS in patients considered at risk,[15,16] but it does not appear to be effective as a treatment for ARDS or acute lung injury.[17] Among the drugs that have proved disappointing are acetylcysteine,[18,19] alprostadil,[20,21] and nitric oxide[22] (which may, however, improve oxygenation to some degree). Studies[23,24] of pulmonary surfactants in ARDS have generally shown no survival benefit; however, calfactant significantly decreased mortality when given to infants, children, and adolescents.[25]

A high-fat, low-carbohydrate diet has been advocated for patients with ARDS. Supplementation with eicosapentaenoic acid and gamolenic acid has been reported to benefit oxygenation, but with no significant effect on mortality.[7,12]

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1334–49. Correction. *ibid.*; **343:** 520.
2. Bernard GR, *et al.* The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149:** 818–24.
3. Bigatello LM, Zapol WM. New approaches to acute lung injury. *Br J Anaesth* 1996; **77:** 99–109.
4. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med* 2004; **141:** 460–70.
5. Weinberger SE. Recent advances in pulmonary medicine (part 2). *N Engl J Med* 1993; **328:** 1462–70.
6. Elsasser S, *et al.* Adjunctive drug treatment in severe hypoxic respiratory failure. *Drugs* 1999; **58:** 429–46.
7. Hite RD, Morris PE. Acute respiratory distress syndrome: pharmacological treatment options in development. *Drugs* 2001; **61:** 897–907.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
9. Jain R, DalNogare A. Pharmacological therapy for acute respiratory distress syndrome. *Mayo Clin Proc* 2006; **81:** 205–12.
10. Adhikari N, *et al.* Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
11. Meduri GU, *et al.* Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998; **280:** 159–65.
12. Cranshaw J, *et al.* The pulmonary physician in critical care 9: non-ventilatory strategies in ARDS. *Thorax* 2002; **57:** 823–9.
13. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342:** 961–2.
14. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153:** 991–6.
15. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21:** 1635–42.
16. Sinuff T, *et al.* Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14:** 1–6.
17. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283:** 1995–2002.
18. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; **20:** 918–23.
19. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; **12:** 177–82.
20. Bone RC, *et al.* Randomized double-blind, multicenter study of prostaglandin E in patients with the adult respiratory distress syndrome. *Chest* 1989; **96:** 114–19.
21. Abraham E, *et al.* Liposomal prostaglandin E , in acute respiratory distress syndrome: a placebo-controlled, randomized, double-blind, multicenter clinical trial. *Crit Care Med* 1996; **24:** 10–15.
22. Sokol J, *et al.* Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 05/05/05).
23. Anzueto A, *et al.* Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996; **334:** 1417–21.
24. Spragg RG, *et al.* Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; **351:** 884–92.
25. Willson DF, *et al.* Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA* 2005; **293:** 470–6. Correction. *ibid.*; **294:** 900.

Adrenal hyperplasia, congenital

See Congenital Adrenal Hyperplasia, below.

Adrenocortical insufficiency

The major function of the adrenal cortex is the production of glucocorticoid and mineralocorticoid hormones, of which cortisol (hydrocortisone) and aldosterone respectively are the most important. Glucocorticoid production is regulated by the hypothalamic-pituitary-adrenal axis, being stimulated by the release of ACTH (adrenocorticotrophic hormone; corticotropin) from the pituitary, while mineralocorticoid production is primarily controlled by the renin-angiotensin system.

Adrenocortical insufficiency is defined as inadequate production of endogenous corticosteroids. It may be primary (Addison's disease), due to destruction of the adrenal cortex; or secondary, due to hypothalamic or pituitary disease, or corticosteroid therapy which suppresses ACTH release.[1] Diagnosis can be difficult, even with the aid of hormone tests such as the tetracosactide stimulation test.[2]

Clinical manifestations of adrenocortical insufficiency are usually seen once about 90% of the adrenal cortex is destroyed. Weight loss, anorexia, weakness, and fatigue may be accompanied by gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhoea, as well as electrolyte abnormalities (hyponatraemia, hyperkalaemia), salt craving, and orthostatic hypotension. In acute cases, abdominal pain and rigidity, fever, volume depletion, hypotension, and shock may occur. Hyperpigmentation, especially of skin creases, exposed areas, and scars is a distinguishing feature of primary, but not secondary, insufficiency. Hypoglycaemia is more likely in secondary deficiency due to lack of growth hormone, and failure of other pituitary hormones usually accompanies secondary adrenocortical insufficiency.

Treatment for acute insufficiency should be with intravenous hydrocortisone as the sodium succinate, sodium phosphate or other readily soluble ester: the usual dose is the equivalent of 100 mg every 6 to 8 hours for 24 hours. Volume depletion, dehydration, hypotension and hypoglycaemia should be corrected with intravenous saline and glucose, and precipitating factors, such as infection, should be dealt with appropriately. Provided no complications occur, the dosage of hydrocortisone can be tapered over 4 or 5 days to oral maintenance therapy.

For chronic insufficiency the usual oral dosage of **maintenance** or **replacement therapy** is hydrocortisone 20 to 30 mg, preferably divided unequally, e.g. 30 mg as 20 mg in the morning and 10 mg in the evening, in an attempt to mimic the natural pattern of secretion. Other corticosteroids have been used, including cortisone acetate, prednisolone, prednisone, and dexamethasone, but offer no advantage over hydrocortisone. Patients with primary insufficiency also require additional mineralocorticoid replacement with fludrocortisone, usually in a dose of 100 micrograms daily. Mineralocorticoid replacement is not usually necessary in secondary insufficiency. There has been some evidence of benefit from studies of adjunctive oral use of prasterone, another steroidal compound secreted by the adrenal glands, in patients with primary or secondary adrenal insufficiency.

Corticosteroid cover. An increase in replacement therapy is required during periods of stress. In mild infection, a doubling of the maintenance dose of hydrocortisone may be appropriate but for major infection, or severe stress such as surgery, parenteral therapy is required. It is generally considered safer to overestimate rather than underestimate the appropriate cover. For regimens used to provide cover in patients with secondary insufficiency due to corticosteroid therapy see Uses and Administration of Hydrocortisone, p.1536.

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AIDS

For the use of corticosteroids in AIDS patients with pneumocystis pneumonia, see p.1510.

Alopecia

The management of alopecia (p.1577) is often difficult. In alopecia areata intralesional corticosteroids, most commonly triamcinolone, will induce hair growth although they are not suitable when more than 50% of the scalp is involved.[1] Regrowth is confined to the site of injection and therefore patchy, although soon concealed by spontaneous growth from uninjected regions. Some atrophy of the scalp is inevitable. Topical corticosteroids are mostly reported to be ineffective although some consider them beneficial; the use of systemic corticosteroids is controversial, given their adverse effects and a lack of evidence that they alter the long-term prognosis.

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Anaemias

For the use of corticosteroids in haemolytic anaemias, including cold haemagglutinin disease, see p.1043.

Anaphylaxis

For the use of corticosteroids in the management of anaphylaxis, see p.1205. Intravenous corticosteroids are given after initial treatment with adrenaline as part of the management of anaphylaxis; their effects are delayed, and they are not suited for immediate relief, but early use may help prevent deterioration after primary treatment has been given.

Aspiration syndromes

For a review of the management of aspiration syndromes, including reference to the probable lack of value of corticosteroids, see p.1693.

Asthma

The cornerstones of current asthma therapy, as discussed in more detail on p.1108, are the beta$_2$-adrenoceptor agonists and the corticosteroids. Drug therapy for **chronic asthma** is managed by a stepwise approach. Patients requiring only occasional relief from symptoms may be managed with an inhaled short-acting beta$_2$ agonist as required. An inhaled corticosteroid such as beclometasone dipropionate, budesonide, or fluticasone may be added to therapy if symptomatic relief is needed more than two or three times a week but regular use is important since corticosteroids take several hours to exert an effect in asthma. If control is still inadequate, a long-acting beta$_2$ agonist is added. The dose of inhaled corticosteroid may be increased if further control is needed, and other additional therapies include anti-leukotrienes or theophylline. Severe asthma requires regular bronchodilator therapy as well as high-dose inhaled corticosteroids, while in the most severe cases, regular oral corticosteroids may also be required. A short 'rescue' course of oral corticosteroid may be needed at any stage for an acute exacerbation. Corticosteroids should be used cautiously in children because of possible adverse effects on growth.

Guidelines vary slightly in their definition of low, moderate and high inhaled corticosteroid doses. ***UK*** guidelines use beclometasone dipropionate (p.1516) given via a chlorofluorocarbon (CFC)-containing metered-dose inhaler (MDI) as the reference inhaled corticosteroid. Although now almost phased out, this is the formulation used in most of the evidence-base that supports current asthma management. Adjustments to doses will be required for other formulations and corticosteroids. Differences in CFC-free beclometasone dipropionate formulations available in the UK mean they are not dose equivalent (see Reformulation, under Beclometasone Dipropionate, p.1517).

- For **adults**, doses in the range 200 to 800 micrograms daily of beclometasone dipropionate via a CFC-containing MDI are considered *low* initial doses, with 400 micrograms daily being an appropriate starting dose for most patients
- a dose of 800 micrograms daily is considered *moderate*
- doses greater than 800 up to 2000 micrograms daily are *high*
- For **children** under 12 years, doses in the range 200 to 400 micrograms daily are considered *low* initial doses, with 200 micrograms daily being an appropriate starting dose for most patients
- a dose of 400 micrograms daily is considered *moderate*
- doses of more than 400 up to 800 microgram daily are *high*

The definition in ***global*** guidelines vary slightly.

- For **adults**, doses in the range 200 to 500 micrograms daily of beclometasone dipropionate via a CFC-containing MDI are considered *low* initial doses
- 500 to 1000 micrograms daily are considered *moderate*
- 1000 to 2000 microgram daily doses are *high*
- For **children**, doses in the range 100 to 200 micrograms daily are considered *low* initial doses
- doses from over 200 up to 400 micrograms daily are considered *moderate*
- doses more than 400 micrograms are *high*

In the ***USA*** CFC-containing beclometasone dipropionate MDIs have been phased out and replaced with MDIs containing hydrofluoroalkane (HFA). The recommended US dose of beclometasone dipropionate HFA MDI, relative to a CFC-containing MDI formulation, is lower due to differences in delivery characteristics between the products; however, a definitive comparative therapeutic ratio has not been demonstrated. In addition, doses are given as the amount delivered *from* the mouthpiece in the USA, instead of the amount delivered *into* the mouthpiece. For one product, Qvar (*Teva, USA*), each 100 micrograms of beclometasone dipropionate delivered *into* the mouthpiece equates to 80 micrograms delivered *from* the mouthpiece. Doses in the US guidelines will therefore seem somewhat lower, although in practical terms there is probably little difference.

- For **adults**, US guidelines consider doses in the range 80 to 240 micrograms daily of beclometasone dipropionate via a HFA-containing MDI to be *low* initial doses
- doses greater than 240 up to 480 micrograms daily are considered *moderate*
- doses above 480 micrograms daily are *high*
- For **children** 5 years and over, doses in the range 80 to 160 micrograms daily are considered *low* initial doses
- doses greater than 160 up to 320 micrograms are considered *moderate*
- doses above 320 micrograms are considered *high*

Acute severe asthma (status asthmaticus) is potentially life-threatening and is treated with inhaled oxygen and beta$_2$ agonists, as well as systemic corticosteroids; inhaled ipratropium bromide, and intravenous magnesium sulfate, xanthine, or beta$_2$ agonist may need to be added. Once lung function is stabilised the patient can be discharged on a regimen of oral and inhaled corticosteroids, and bronchodilators.

Behçet's syndrome

Behçet's syndrome (or Behçet's disease) is a recurrent multifocal disorder most prevalent in the Far East and countries of the Mediterranean and Middle East.

The clinical features include oral and genital ulceration, skin lesions, arthritis, vasculitis leading to thromboembolic disorders and aneurysms, ocular lesions (including uveitis, hypopyon, and iridocyclitis leading eventually to blindness), and CNS involvement (meningomyelitis, dementia, extrapyramidal symptoms, and paralysis, sometimes fatal). Gastrointestinal disturbances and involvement of other body systems have been reported. However, the complete gamut of symptoms is unlikely in a single patient, and the disease has been classified into mucocutaneous, arthritic, neurological, and ocular forms depending on the predominant symptoms. Diagnosis can be difficult, but oral ulceration, with recurrent genital ulceration, ocular involvement, and skin lesions or a positive pathergy test are considered the major diagnostic criteria.[1,2]

Treatment of Behçet's syndrome is essentially symptomatic and empirical. Controlled studies are mostly lacking, which has hindered meta-analysis.[3] Where possible, topical treatment of **mucocutaneous** lesions should be attempted before embarking on systemic therapy. Topical application of a potent corticosteroid, such as triamcinolone acetonide, or a tetracycline solution may be tried for oral ulceration.[1,2] Genital ulcers can be treated topically with betamethasone ointment.[2] Sucralfate suspension used topically has also been reported to be effective in oral and genital ulceration,[4] and topical mesalazine has been tried.[5] Systemically, colchicine is reportedly beneficial in the treatment of mucocutaneous lesions,[1,2] although a review failed to find any evidence of benefit from colchicine treatment.[3] Systemic corticosteroids are advocated for severe mucocutaneous disease;[4] oral prednisolone has been given for erythema nodosum.[1,2] Thalidomide is also effective for mucocutaneous symptoms,[2,4] although relapses occur on cessation of therapy. Other drugs with reported efficacy for mucocutaneous symptoms include azathioprine,[4] benzathine benzylpenicillin (sometimes with colchicine),[4] dapsone,[1,2,4,6] interferon alfa,[4,6] levamisole,[4] pentoxifylline,[1] and rebamipide.[4,6]

The use of NSAIDs in the treatment of **arthritis** in patients with Behçet's disease is controversial,[4] although indometacin is used.[2] Colchicine is also used,[2,4] and sulfasalazine may be beneficial in patients who do not respond to NSAIDs.[1] Corticosteroids used with azathioprine are effective,[2,4] as are interferon alfa,[1,2,4] and benzathine benzylpenicillin.[3]

Short courses of intravenous methylprednisolone or high-dose oral prednisolone with subsequent tapering are used in the acute phase of **neurological** involvement, and may be followed by chlorambucil, cyclophosphamide, or methotrexate.[2] Chronic CNS disease is generally resistant to therapy.[2]

Ocular involvement in Behçet's disease leads to blindness in about a quarter of patients.[1,2] For acute attacks of anterior uveitis, topical mydriatics such as tropicamide, or corticosteroid drops may be sufficient. Local injections of corticosteroids are used to treat acute attacks of posterior uveitis, and systemic use may also be required.[2] Oral corticosteroid therapy does not improve visual prognosis, however, and may lead to secondary retinal thrombosis or cataracts;[2] good evidence of its benefit is lacking.[3] Colchicine is used for prophylaxis of both anterior and posterior uveitis;[2] ciclosporin is considered more effective at controlling acute ocular attacks[1] but its efficacy appears to gradually decline.[2,4] Other drugs deemed effective in preventing ocular inflammation include azathioprine,[1-4] chlorambucil,[2,4] and cyclophosphamide.[2,4] There are reports of benefit with benzathine benzylpenicillin, interferon alfa, levamisole, methotrexate, pentoxifylline, sulfasalazine, and thalidomide.[4] Tacrolimus has also been beneficial in cases of refractory uveitis.[1,4] Combinations of the above drugs are also used, such as corticosteroids with immunosuppressants, or corticosteroids with cytotoxics.[4]

In patients with **vasculitis**, arteritis is treated with systemic corticosteroids and cyclophosphamide, either orally or pulsed monthly boluses.[1,2] Deep-vein thrombosis has been treated with anticoagulants, such as warfarin or heparin, but caution is advised in those with pulmonary arteritis because of the risk of potentially fatal haemoptysis,[2] and their use is generally not recommended.[1,4] Aspirin is used with immunosuppressants, particularly azathioprine.[4] Stanozolol has also been used to treat the vascular symptoms of Behçet's disease.

Corticosteroids and sulfasalazine are the main drugs used for **gastrointestinal** lesions;[2] thalidomide has also been beneficial.[1]

Infliximab has been found to reduce acute ocular inflammation,[7] and heal gastrointestinal ulceration;[8] it has also proved effective in controlling neurological manifestations of the disease.[9]

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Bell's palsy

Bell's palsy is a condition that may be caused[1,2] by herpes simplex virus 1. It affects the facial nerves and results in facial muscle weakness and paralysis. It is often accompanied by pain and lachrymation. Untreated, over 80% of all patients recover completely or almost so, while in a smaller number facial weakness persists; complete failure of motor recovery is very rare.

Corticosteroids dramatically relieve pain associated with Bell's palsy,[3] and their use in treatment is widely accepted.[4] The suggested oral dose of prednisone for adults is 1 mg/kg daily in divided doses morning and evening; if the paralysis remains incomplete after 5 or 6 days the prednisone is gradually withdrawn over the next 5 days but if the paralysis is complete the initial dosage should be continued for another 10 days and then gradually withdrawn.[3] While a review of 4 studies in 1996 suggested an increased rate of complete recovery with corticosteroid treatment,[5] and others consider treatment to decrease the incidence of permanent facial paralysis,[2] not all studies have shown such benefits.[2,6] The original review included a study in which a large number of patients were lost to follow-up, and a more recent review concluded that available evidence does not show significant benefit from corticosteroid therapy,[6] although their anti-inflammatory effects might prevent nerve damage. There is some suggestion that addition of aciclovir or valaciclovir to corticosteroid treatment may improve outcome,[4,7] although again substantive evidence is lacking.[2,8]

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Bites and stings

Corticosteroids (prednisone 100 mg daily) have been recommended for the stabilisation of erythrocyte membranes in the management of systemic envenomation by the brown recluse spider (*Loxosceles reclusa*).[1] They have also been given after stings by some species of scorpion, although their value is not certain.[1] Corticosteroids are considered to have no place in snake venom poisoning.[2] Topical corticosteroids may be useful for mild itching of healing skin after some types of jelly fish sting, while systemic corticosteroids have been used for delayed hypersensitivity reactions.[3]

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Bone cysts

Intralesional corticosteroid injection (usually methylprednisolone) has been used as an alternative to surgical or other methods for the treatment of bone cysts.[1-6] An early report indicated that methylprednisolone acetate 40 to 200 mg injected into unicameral bone cysts under brief general anaesthesia stimulated bone formation to obliterate the cyst or promoted sufficient healing to prevent further fractures.[1] A single injection was sufficient for healing in 10 to 25% of cysts; only rarely were more than 4 injections needed. Treatment of an aneurysmal bone cyst with methylprednisolone and calcitonin has also been reported.[7] (Systemic corticosteroids are, of course, generally associated with bone loss rather than bone formation—see Effects on the Bones and Joints, p.1491).

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Brain injury

See Spinal Cord and Head Injury, p.1513.

Bronchiolitis

Acute bronchiolitis is usually caused by RSV infection (p.860) in infants and young children, and may contribute to the subsequent development of asthma. Supportive therapy, where necessary, may involve the use of oxygen and bronchodilators (see also p.1134). Numerous studies have failed to show a benefit from corticosteroid therapy, and it has generally been considered that corticosteroids have no role in the management of the condition.[1] Although one study did find that oral prednisolone might be of benefit,[2] it was suggested that the results might be due to inclusion of children with asthma among the study population.[3] A systematic review[4] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. However, a study[5] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms. Inhaled corticosteroids seem to be of little value[6] and a systematic review concluded that they did not prevent post-bronchiolitic wheezing when given during the initial acute phase of bronchiolitis.[7]

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Bronchopulmonary dysplasia

Bronchopulmonary dysplasia is the major cause of chronic lung disease (defined as the need for supplementary oxygen more than 28 days after birth) in neonates. It has also been defined as oxygen dependency beyond a corrected gestational age of 36 weeks.[1] It is considered to comprise 4 radiographically distinct stages, of which stage 1 is effectively indistinguishable from neonatal respiratory distress syndrome (see p.1508), with which it is usually associated. A 'bubbly' appearance of the lung is seen in radiographs of advanced disease. Bronchopulmonary dysplasia is invariably associated with prolonged mechanical ventilation, but it is uncertain whether it plays a causative role, or whether the disease develops anyway in infants with respiratory failure severe enough to need prolonged ventilation.[2] Other risk factors include prematurity, low birthweight, pulmonary oedema, inflammation due to infection or other causes, and adrenal insufficiency.[1]

Treatment. Corticosteroids, usually in the form of systemic dexamethasone, have been widely used in premature infants with bronchopulmonary dysplasia,[1] or who are considered to be at high risk of it (the borderline between treatment and prophylaxis in studies in these mechanically ventilated infants is not always clear[3]). Dexamethasone has been reported to improve pulmonary outcome, allowing more rapid weaning from mechanical ventilation, and in some studies was reported to improve neurological outcome as well.[4] However, some investigators consider its benefits in the long term inadequately established.[3,5,6]

There also remains some concern about possible adverse effects of dexamethasone, especially on long-term development.[1,7,8] One meta-analysis suggested that use was associated with a high incidence of cerebral palsy and neurodevelopmental impairment, and should be abandoned.[9] Infants requiring mechanical ventilation and given intravenous dexamethasone or placebo in a trial were followed up about 8 years later. Children in the dexamethasone group were shorter, had smaller head circumferences, poorer motor skills and coordination, lower IQ scores, and a higher frequency of clinically significant disabilities.[10] However, a 15-year follow-up of preterm infants given dexamethasone at 2 weeks of age, showed that those given a 42-day course had significantly better neurological outcomes than those given an 18-day course, or saline placebo.[11]

Many studies have favoured an initial dexamethasone dose of 500 micrograms/kg daily intravenously, tapered over a period of days to weeks, but it is not always clear if this is expressed in terms of the base or one of its esters,[12] and in any case regimens have varied between studies. Despite suggestions that beginning therapy shortly after birth might minimise lung injury, evidence suggests that early therapy offers no advantage,[6,13] and may be more hazardous.[6,8,14-16] Meta-analysis has suggested that while beginning dexamethasone at any time between birth and 14 days of age reduced the risk of chronic lung disease, mortality was only reduced in the group who began treatment between 7 and 14 days of age.[17] However, a subsequent systematic review concluded that the benefits of therapy started between 7 to 14 days may not outweigh the adverse effects.[15]

In an attempt to propose guidelines, a review of the available evidence concluded that there was no role for corticosteroid use in the first 4 days of life and that use should be limited to exceptional clinical circumstances such as ventilator dependency in an infant after the second week of life. When used, the lowest effective dose was recommended for the shortest possible duration; dexamethasone 200 micrograms/kg daily (in two divided doses) for 3 days, then 100 micrograms/kg daily for 3 days, then 50 micrograms/kg daily for 3 days was suggested.[1]

Inhaled corticosteroids have also been investigated. A systematic review did not demonstrate any reduction in the incidence of chronic lung disease or the need for systemic corticosteroids.[18] Another systematic review of controlled studies found that inhaled corticosteroids may improve the rate of extubation in infants.[19]

Additional therapy is essentially supportive, including fluid restriction, nutritional supplementation, bronchodilators, and diuretics. Routine use of bronchodilators for prevention of bronchopulmonary dysplasia is not recommended, and studies of use in treatment are limited.[2] UK guidelines (issued in 1998 but not subsequently updated) considered that diuretics were indicated for episodes of associated cardiac failure but their long-term value was uncertain; if used, consideration should be given to a calcium-sparing regimen.[20] Improved pulmonary status has been reported with furosemide in established dysplasia,[21,22] although routine or sustained use cannot be recommended at present. Results with hydrochlorothiazide and spironolactone are more ambiguous.[23,24] Anaemia in infants with bronchopulmonary dysplasia has benefited from erythropoietin.[25] Although vitamin A deficiency has been implicated in the pathogenesis of bronchopulmonary dysplasia, trials of vitamin A supplementation have produced conflicting results. However, differences in patient population, postnatal therapies, and dosage of vitamin A could explain these results,[26] and some recommend supplementation to reduce the incidence of chronic lung disease.[2,26] Despite promising preliminary results,[27] treatment with alpha$_1$-proteinase inhibitor has not been shown to reduce the incidence of chronic lung disease.[2] Similarly, although there is evidence suggesting that early use of sudismase may reduce development of chronic lung disease (but not bronchopulmonary dysplasia),[28] routine use is not recommended.[2]

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Cachexia

For mention of the use of corticosteroids in cancer-related cachexia see under Uses and Administration of Megestrol, p.2115.

Cardiac arrhythmias

Atrial fibrillation (see Cardiac Arrhythmias, p.1160) is common after cardiothoracic surgery, and although it is usually self-limiting, it may be associated with increased morbidity and mortality. Cardiopulmonary bypass used during surgery provokes an inflammatory response that may contribute to atrial fibrillation, and there has been some investigation of the effect of prophylactic corticosteroids. Dexamethasone, hydrocortisone, methylprednisolone, and prednisolone have been tried, in single doses or short courses; studies have been small and results mixed.[1-3] A systematic review[3] of 9 studies found that corticosteroids may reduce the incidence of atrial fibrillation and shorten hospital stay, but the effect may depend on the dose, and larger studies are required.

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Cerebral oedema

Corticosteroids (usually dexamethasone) play an important role in the treatment of cerebral oedema caused by malignancy and dexamethasone is advocated for the cerebral oedema associated with high-altitude disorders (see p.1168). The management of raised intracranial pressure and the usual drugs used to treat it are discussed on p.1181.

Corticosteroids have also been used for the management of raised intracranial pressure in patients with head injuries or stroke, but despite earlier small studies showing them to be beneficial in some patients, current opinion is that corticosteroids are not useful in head injuries (see Spinal Cord and Head Injury, p.1513) or stroke, and that their adverse effects may outweigh any possible benefit.

Chronic active hepatitis

Chronic hepatitis is characterised by liver cell necrosis and inflammation that persists for more than 6 to 12 months. Probably the most serious form is chronic active hepatitis in which inflammatory infiltrates (mononuclear and plasma cells) are found within and around the portal areas, with piecemeal necrosis of adjacent liver cells, and in severe cases bands of necrotic tissue between portal tracts or to the central vein (bridging necrosis). Symptoms are essentially non-specific and include fatigue, malaise, fever, anorexia, jaundice, and raised serum aminotransferase values; biopsy is required for accurate diagnosis. The causes of chronic active hepatitis vary and may include: infection with hepatitis viruses; adverse effects of drugs such as isoniazid, methyldopa, or nitrofurantoin; or, particularly in women, an apparently idiopathic form, auto-immune hepatitis.

Treatment with corticosteroids is widely used in patients with auto-immune hepatitis.[1,2] A moderate initial oral dose of 20 to 30 mg of prednisolone or prednisone daily or a higher dose of 60 mg daily may be used,[3-5] and is then slowly tapered over several months to the minimum required for maintenance. Daily maintenance therapy appears more effective than alternate-day regimens. Patients who respond (as shown by a return of serum aminotransferase values to the normal or near normal range and a reduction in the inflammatory processes on biopsy) usually require prolonged treatment; although some patients remain in remission for months to years after withdrawal, relapse generally occurs, and therapy should be reinstated when the disease becomes active again.[1]

Combined treatment including azathioprine is frequently given and may be the preferred initial treatment in some patients;[4,5] such treatment is at least as effective as a corticosteroid alone,[2] can produce[6,7] and maintain[8,9] remission, and permits a reduction in corticosteroid dosage in a group of patients who will require long-term drug treatment.[1] There has been some dispute about the value of azathioprine alone, but combined therapy has generally been found to be superior.[6] However, azathioprine has been used alone in high doses to maintain remission.[5,9]

In contrast to the fairly extensive experience with azathioprine, ciclosporin is little used in this condition; once started it appears to be required indefinitely.[4] It may be an alternative in severe disease where corticosteroids alone or with azathioprine cannot suffice. Mycophenolate mofetil may offer an alternative to azathioprine.[5] Some investigators have also used cyclophosphamide successfully,[3] and tacrolimus has been reported to be of benefit.[10]

Penicillamine has been tried as an alternative to prolonged use of corticosteroid maintenance therapy, the dose of penicillamine being gradually increased over several months to a suitable maintenance dose as the dosage of corticosteroid is tapered off.

It is generally agreed that immunosuppression is not suitable in patients with viral chronic active hepatitis.[11] However, combination therapy has been reported to produce benefit in patients positive for HBsAg,[6] and it has been reported[12] that patients with chronic active hepatitis of unknown cause, at least some of whom may have hepatitis C,[11] respond as well to corticosteroids or combined therapy as patients with proven auto-immune disease. Liver transplantation (p.1815) may be necessary in patients who are refractory to or intolerant of immunosuppressive therapy, and in whom end-stage liver disease develops.[1]

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Chronic obstructive pulmonary disease

Corticosteroids play some part in the symptomatic and palliative management of chronic obstructive pulmonary disease (COPD—p.1112), although there is controversy as to their value. It remains to be confirmed whether corticosteroids slow the deterioration rate and improve long-term outcome in COPD, regardless of corticosteroid responsiveness. Some studies have suggested that inhaled corticosteroids might reduce the number of acute exacerbations and slow the decline in lung function,[1-3] whereas others found no, or limited, benefit.[4-7] Some commentators have therefore cautioned against the routine use of corticosteroids in patients with COPD;[8] certain subgroups of patients, however, may benefit from corticosteroid therapy,[8,9] and reviews[10,11] have concluded that inhaled corticosteroids were beneficial in reducing COPD exacerbation rates. Official guidelines generally recommend the use of inhaled corticosteroids in patients with severe disease and repeated exacerbations (see p.1112).

A large randomised study[12] found that combination therapy with fluticasone and salmeterol reduced exacerbation rate compared with placebo, and improved lung function significantly more than treatment with either drug alone. However, there is some uncertainty as to the degree of clinical benefit.[13]

Short courses of systemic corticosteroids are commonly used for acute exacerbations of COPD, despite limited evidence of clinical benefit. However, a systematic review[14] concluded that the benefit from corticosteroid therapy is evident within the first day and lasts for at least 5 days of therapy, although there is no evidence suggesting advantage to courses for longer than 2 weeks. Dose-dependent deleterious effects on bone mineral density may occur.

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Churg-Strauss syndrome

The Churg-Strauss syndrome is sometimes classified with polyarteritis nodosa (see p.1510), although, unlike the latter, pulmonary manifestations are relatively common in Churg-Strauss syndrome. Patients commonly have a history of allergic disease (rhinitis, sinusitis, and asthma); intractable asthma and eosinophilia with granulomatous vasculitis characterise the syndrome.

Treatment is similar to that of polyarteritis nodosa, being based on systemic corticosteroids and, where necessary, cyclophosphamide.[1-4] When cyclophosphamide is used, intravenous pulse therapy is often preferred to continuous oral dosage,[2,4] as it has been shown to reduce adverse effects and allows for a lower total dose.[3,4] Substitution of cyclophosphamide with azathioprine or mycophenolate mofetil after 4 to 6 months can also allow for reduced overall doses of cyclophosphamide to be given,[3,4] although azathioprine is not as effective as cyclophosphamide for primary treatment.[3] In patients with haemorrhagic cystitis, there is some suggestion that mycophenolate mofetil may be more effective than azathioprine.[3] Interferon alfa may also be of benefit.[4,5] In patients refractory to corticosteroids and cyclophosphamide, there are reports of benefit with antilymphocyte immunoglobulins or intravenous immunoglobulins.[3]

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Cogan's syndrome

Corticosteroids are useful in the treatment of Cogan's syndrome, a condition characterised by non-syphilitic interstitial keratitis and audiovestibular symptoms including deafness.[1-3] The deafness, although often irreversible, may respond to systemic corticosteroids begun within 2 weeks of onset of symptoms (prednisolone or prednisone, at least 1.5 mg/kg daily for 2 weeks is advised) and ocular involvement benefits from topical corticosteroid therapy (e.g. prednisolone 1% at a rate of 1 drop every hour for 1 to 2 weeks).[3] Improvement in ocular symptoms has also been seen with sodium cromoglicate eye drops.[4] For patients with severe Cogan's syndrome including large-vessel vasculitis, corticosteroids have been used with other immunosuppressants such as azathioprine, ciclosporin and cyclophosphamide.[5] Methotrexate has also been tried.[6]

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Congenital adrenal hyperplasia

Congenital adrenal hyperplasia comprises a heterogeneous group of disorders due to inherited defects of steroid synthesis in the adrenal gland, the most frequent of which are defects involving 21-hydroxylase or 11-β-hydroxylase. Defective enzyme production blocks the formation of cortisol and aldosterone; the pituitary produces increased amounts of ACTH in an attempt to compensate, but this results in excessive adrenal androgen production. Presentation varies from virilisation and abnormal genital formation at birth to mild cryptic forms that may be detected only later in life. Salt-losing forms (due to lack of aldosterone or the accumulation of precursors with antagonist activity) may lead to hyperkalaemia, acidosis, and dehydration. Patients with 11-β-hydroxylase defect are also prone to hypertension.

Neonates with **salt-losing forms** of congenital adrenal hyperplasia require urgent treatment. Treatment usually consists of a mineralocorticoid, fludrocortisone, and a glucocorticoid (usually hydrocortisone) in regimens similar to those for adrenocortical insufficiency (see p.1498).[1-5] Saline infusion or addition of salt to the feed is required initially.

Even where salt-losing symptoms are not overt or marked, control is reportedly better with a mineralocorticoid added to therapy, rather than with hydrocortisone alone,[4] and it has been recommended that children with salt-losing congenital adrenal hyperplasia should continue to receive combined therapy at least until adult life.[1] Careful titration of dosage is important to avoid growth retardation and toxicity, and potent synthetic glucocorticoids such as betamethasone and dexamethasone may be inappropriate in infants and children with the condition, even in the non-salt-losing form. An alternative approach is the use of flutamide and testolactone to block androgenic effects, with a reduced dose of hydrocortisone.[4,6] However, studies suggest that normal growth is possible with regular glucocorticoid therapy.[7,8]

Patients with **non-salt-losing congenital adrenal hyperplasia** may be adequately managed with glucocorticoids alone, and in mild late-onset forms a single dose daily in the late evening (when its suppressive effect on ACTH production is greatest) may be sufficient. In adults who do not require mineralocorticoid treatment betamethasone or dexamethasone may be useful because of their lack of mineralocorticoid actions.

Surgical correction may be necessary in females with masculinised external genitalia. Giving a glucocorticoid to pregnant women whose offspring are considered at risk has been tried in an attempt to prevent virilisation:[3] dexamethasone is preferred to hydrocortisone because of a lack of placental degradation.[4]

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Corneal graft rejection

Corticosteroids are the mainstay of postoperative prophylaxis and treatment of corneal graft rejection.[1] Topical and subconjunctival corticosteroids are widely used, but in acute rejection episodes involving the endothelium systemic therapy is usually necessary. A single 500-mg intravenous pulse of methylprednisolone appears to be as effective as up to 2 weeks of treatment with oral prednisolone 60 to 80 mg daily for the management of severe endothelial rejection.[2] However, another study found that addition of a single intravenous pulse of 500 mg methylprednisolone to local corticosteroid treatment with betamethasone and dexamethasone gave no benefit over local therapy alone.[3]

In high-risk patients corticosteroids alone provide insufficient immunosuppression and systemic immunosuppression has been tried, although the evidence base is limited,[1] mainly relating to the use of ciclosporin, and with inconsistent results. Mycophenolate mofetil has also been tried,[1,4] and has been reported to be as effective as ciclosporin in preventing acute rejection after high-risk corneal transplantation.[4] However, because most patients are healthy and transplantation is not life-saving, the risks of systemic immunosuppression may be hard to justify.[1] Topical ciclosporin has also been investigated.[5]

Corticosteroids have also been used to reduce inflammation after corneal reconstruction using tissue engineered from autologous oral mucosal epithelium.[6]

For discussions of the role of corticosteroids in other forms of organ and tissue grafting, see Organ and Tissue Transplantation, p.1810.

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Croup

Croup is an acute childhood syndrome of upper respiratory tract inflammation (laryngotracheobronchitis) associated with viral infection, usually by parainfluenza virus although other viruses may also produce the syndrome. It is characterised by harsh, barking cough, stridor, and hoarseness, most usually occurring at night.[1-3]

Traditional home management has revolved around the inhalation of steam, despite a lack of evidence for effectiveness, but symptoms may be sufficiently alarming to result in presentation to a hospital.

In severe croup there is clear evidence that treatment with a systemic corticosteroid reduces symptoms and decreases the need for intubation.[4-6] Oral dexamethasone is as effective as intramuscular,[7] and while dexamethasone 600 micrograms/kg is commonly prescribed, lower doses of 300 micrograms/kg and 150 micrograms/kg appear to be equally effective.[2] Nebulised budesonide has also been reported to be effective,[8-10] and of similar efficacy to inhalation of nebulised adrenaline.[11] However despite the theoretical attraction of this route, studies have failed to find any significant difference in effectiveness between nebulised budesonide 2 mg and oral dexamethasone 600 micrograms/kg,[12] or combination therapy with both,[13] and another study found 600 micrograms/kg of dexamethasone given intramuscularly to be more effective than 4 mg of nebulised budesonide.[14] In contrast, others have found that addition of nebulised budesonide to oral dexamethasone produced more rapid improvement than the latter alone.[15] Studies have also shown a significant benefit from corticosteroids in children with mild to moderate croup,[12,16-18] and although the use of such potent drugs in children with a mild, largely self-limiting condition has been questioned,[19] a review of the risks and benefits concluded that oral dexamethasone 150 micrograms/kg, or nebulised budesonide 2 mg were the treatment of choice in mild to moderate croup while oral prednisolone 1 mg/kg should be given for croup requiring intubation.[1] However, nebulised adrenaline is probably the initial drug of choice where rapid relief of obstructive symptoms is required.[2,3] Oxygen is given to those children with upper airway obstruction and significant oxygen desaturation.[3] Heliox, a mixture of helium and oxygen, may be used as adjunctive therapy to glucocorticoids, for short-term treatment of refractory croup.[2]

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Cystic fibrosis

Corticosteroids have been used orally or by inhalation in the management of the inflammatory response of the lungs in cystic fibrosis (see p.166) but do not form part of standard management.

Deafness

For references to the use of corticosteroids in the treatment of deafness associated with Cogan's syndrome, see above.

Dermatomyositis

For references to the treatment of dermatomyositis with corticosteroids, see Polymyositis and Dermatomyositis, p.1510.

Diffuse parenchymal lung disease

Diffuse parenchymal lung disease (DPLD; interstitial lung disease) represents a large and heterogeneous group of inflammatory disorders that have in common a thickening of the interstitial walls between alveoli. In some cases, particularly in the early stages, this is due to accumulation of inflammatory cells in the interstitium, and control of inflammation can reverse the changes; however, when fibrotic changes to the alveolar walls take place these are usually irreversible. The causes of chronic DPLD are numerous and include pneumoconioses due to inhalation of inorganic dusts (as in asbestosis and silicosis); extrinsic allergic alveolitis due to inhalation of, usually, organic antigens (as in farmers' lung, bird fanciers' lung, and many similar occupational disorders); cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis); adverse effects of drugs such as bleomycin; sarcoidosis; lung disease associated with collagen vascular disorders such as rheumatoid arthritis and SLE, or with the vasculitides; histiocytic syndromes; and pulmonary eosinophilic syndromes. Cryptogenic fibrosing alveolitis (below) and sarcoidosis (p.1512) are probably the most common chronic DPLDs.[1]

The symptoms of DPLD are usually insidious and non-specific, and may include dyspnoea of varying severity, usually first noticed on exertion, cough, and fatigue; fine crackling sounds (rales) on breathing and finger clubbing occur in some forms. If the disease progresses, respiratory failure becomes more severe, and eventually may prove fatal.

Where a causative agent can be identified, initial treatment is to prevent exposure but where inflammation persists, or where the causation is uncertain, corticosteroids are the mainstay of treatment (despite a lack of controlled trials for efficacy),[2] in an attempt to control inflammation and preserve as much normal tissue as possible. The management of cryptogenic fibrosing alveolitis is discussed in more detail below.

Cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) is a form of DPLD of uncertain origin, associated with alveolitis and thickening of the interstitial walls by oedema, cellular exudate, and fibrosis. The clinical course is variable but the mean survival is only 3 to 5 years.[3] Cryptogenic fibrosing alveolitis itself appears to represent a spectrum of disorders; some have advocated that usual interstitial pneumonia (the most common form) should be distinguished from forms such as non-specific, or desquamative interstitial pneumonia, or cryptogenic organising pneumonia (bronchiolitis obliterans organising pneumonia), which differ in prognosis and may respond better to corticosteroid therapy.[4-9]

Treatment of cryptogenic fibrosing alveolitis is highly controversial, with no proven benefit from conventional therapy with corticosteroids, immunosuppressants, and cytotoxics.[9] The British[1] and American[8] Thoracic Societies have recommended that where therapy is considered appropriate initial treatment should be with oral prednisone or prednisolone 500 micrograms/kg daily plus azathioprine. Azathioprine may be used alone where corticosteroid therapy is problematic, or cyclophosphamide may be given with the corticosteroid if azathioprine is not tolerated. About 50% of patients with cryptogenic fibrosing alveolitis show a symptomatic response to corticosteroids and about 25% show an improvement in lung function.[1] However, in the absence of placebo-controlled trials there is no clear evidence that treatment improves survival.[1,7,9] Survival does seem to be improved after treatment with corticosteroids plus azathioprine, compared with corticosteroids alone.[1] It should also be borne in mind that patients defined as having cryptogenic fibrosing alveolitis are a heterogeneous group, with some forms appearing to respond better to treatment than others, which makes comparison of studies difficult.[5] If the condition stabilises, the dose of corticosteroid may be reduced gradually for maintenance. Corticosteroid therapy is usually continued lifelong; attempts at withdrawal should be gradual and cautious. Relapse or clinical deterioration may warrant an increased dose of corticosteroid, or addition of an immunosuppressant.[8]

Many other drugs have been tried in patients with cryptogenic fibrosing alveolitis.[1,5,8-11] Ciclosporin has been used adjunctively and also as a corticosteroid-sparing treatment;[11] some benefit has been reported,[1] but data are too limited to support its use.[8,9,11] Colchicine has been suggested to be as effective as corticosteroids, and some consider it for first-line therapy or for patients refractory to corticosteroids, either alone or with immunosuppressants.[8] However, studies have generally shown no evidence of survival benefit, and others do not recommend its use.[9] There are reports of response to penicillamine, but controlled studies are lacking, and in view of its adverse effects, its use is generally not recommended.[8,9,11] Toxicity has limited the use of chlorambucil and methotrexate,[8] and there is no evidence to support the use of vincristine or mercaptopurine.[11] Despite promising preliminary results, a controlled trial of interferon gamma found no significant effects on mortality compared with placebo.[9] Early trials of pirfenidone have shown improvements in pulmonary function;[9] further studies are underway. Acetylcysteine is also under investigation.[9,12] Experimental strategies include the use of relaxin, suramin, endothelin-1 inhibitors, angiotensin II receptor antagonists, and gene therapy.[8,9,11]

In patients in whom other options fail, lung transplantation (p.1815) should be considered.[1,5,8,10,11]

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Eaton-Lambert myasthenic syndrome

Corticosteroids have been tried in the treatment of Eaton-Lambert myasthenic syndrome (p.629).

Eczema

Topical corticosteroids have an important role in the management of atopic eczema (p.1579). The least potent preparation that is effective should be used, combined with regular use of an emollient; in mild to moderate disease the topical corticosteroid is only given for 1 to 2 weeks at a time. Most patients with mild to moderate eczema respond to treatment with a mildly potent preparation such as 1% hydrocortisone ointment. For older children and adults with refractory disease, a more potent topical corticosteroid should be considered for long enough to bring the disease under control, followed by a weaker preparation as the condition improves.

The use of systemic corticosteroids is a treatment of last resort in resistant severe eczema, usually for short periods to control the disease, and very rarely for maintenance.

Epidermolysis bullosa

High-dose oral corticosteroids may be tried to control blistering in severe forms of epidermolysis bullosa (p.1579).

Epilepsy

Corticosteroids and corticotropin have been commonly used to treat **infantile spasms,** which are generally unresponsive to conventional antiepileptics. There is, however, limited evidence for the efficacy of oral corticosteroids.[1] Corticotropin appears to be effective for short-term treatment, and one study[2] indicated that high-dose corticotropin was preferable to prednisone, but the optimum dose and duration of therapy have not been determined.[1,3] In addition, corticotropin and corticosteroids are associated with frequent and severe adverse effects, and as discussed on p.465, some now prefer newer antiepileptics such as vigabatrin. A short-term study of infants with spasms of non-tuberous sclerosis origin found that tetracosactide or prednisolone were superior to vigabatrin.[4] However, vigabatrin is preferred for the treatment of spasms due to tuberous sclerosis,[3,4] and data are insufficient for recommendations regarding the use of any drug to improve the long-term outcome of children with infantile spasms.[1,3]

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Erythema multiforme

In the management of erythema multiforme (p.1580) systemic corticosteroids may be considered in severe reactions but there has been controversy about their value.

Giant cell arteritis

Giant cell arteritis (temporal arteritis; cranial arteritis) is a vasculitic disorder that is frequently associated with polymyalgia rheumatica (p.1510). It occurs mainly in persons over 50 years of age of European, particularly Scandinavian, extraction and is more common in women than men. It is characterised by inflammatory, granulomatous lesions with giant mononuclear cell infiltrates affecting large and medium sized arteries, particularly those supplying the neck and extracranial structures of head and arms. Symptoms vary but may include headache, scalp tenderness, claudication of the jaw, swelling and absence of pulse in the temporal artery, fever, weight loss, malaise, anaemia, visual disturbances, and irreversible blindness. About a third of all patients also exhibit polymyalgia rheumatica.

Treatment is with corticosteroids,[1-8] and early diagnosis and treatment is desirable to reduce the risk of sudden blindness. Most regimens have involved high initial doses of corticosteroid to control the disease followed by reduction to a maintenance dose, but both initial and maintenance doses have varied considerably. Prednisone or prednisolone 40 to 60 mg daily by mouth initially is generally considered adequate in uncomplicated cases without visual symptoms;[1,4-6] this can then be reduced gradually according to the patient's response. Some, however, recommend[3] lower initial doses of about 20 mg daily.

While it is suggested that patients presenting with visual symptoms should receive 80 mg daily or 1 mg/kg daily of prednisone or prednisolone,[3,7,8] some ophthalmologists[9] recommend that all patients with giant cell arteritis receive these doses, as visual loss may be sudden and profound. Initial 1-g doses of pulsed intravenous methylprednisolone have also been used.[2,5,8,9]

Maintenance treatment is usually required and while a small number require indefinite treatment, most patients should be able to stop treatment within 5 years; however, relapses are not uncommon.[7]

Because of the need for prolonged corticosteroid therapy, adverse effects are common,[7] and their management difficult. Azathioprine has been added to corticosteroid therapy for its modest 'steroid-sparing' effect,[10] whereas results with methotrexate have been conflicting.[4,6,11] Other immunosuppressants have been tried,[4,6] but are not routinely used. Dapsone has been reported to be of benefit, but its use is limited by haematological toxicity.[4] Infliximab has been tried.[8]

The prognosis is excellent in adequately-treated patients, as the life expectancy of patients with giant cell arteritis is the same as the general population.[12]

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Glomerular kidney disease

Glomerular disease accounts for a considerable proportion of all kidney disease. Various forms of primary glomerular disease (glomerulopathy) are known, and are discussed below; in addition, numerous systemic diseases (connective tissue disorders such as SLE as well as malignancy and conditions such as diabetes), may result in secondary glomerular disorders. Despite the various potential causes it is thought that many of these diseases act by common immunological mechanisms to damage the glomerulus, either by accumulation of antigen-antibody complexes (immune-complex nephritis) or more rarely by the formation of antibodies to the glomerular basement membrane (anti-GBM nephritis).[1]

Since the kidney can respond in only a limited number of ways to glomerular damage, certain common presentations are seen regardless of aetiology, including **acute glomerulonephritis** (acute nephritis syndrome), which is marked by haematuria and proteinuria of abrupt onset, usually with renal impairment (a decrease in glomerular filtration rate), salt and water retention, and hypertension; and the **nephrotic syndrome**, which is marked by severe proteinuria, hypoalbuminaemia, and oedema. Other, less dramatic presentations of glomerular disease are asymptomatic proteinuria or microscopic haematuria; alternatively, glomerular disease may be one of the many potential causes of chronic renal failure. Appropriate management of these conditions depends to a considerable extent on the underlying disease.

• MANAGEMENT OF PRIMARY GLOMERULAR DISEASE.

Minimal change nephropathy (MCN; minimal change disease). This condition occurs mainly in children, the highest incidence being at 2 to 4 years, and is the main cause of childhood nephrotic syndrome. It also accounts for about 20% of adult cases of nephrotic syndrome.[2] It is treated with a corticosteroid. Regimens vary somewhat but a suggested oral regimen for adults has been 60 mg prednisolone daily for 4 days, reduced to 40 mg daily until remission occurs (which in 90% of patients will be within 3 weeks) and then tapered off.[2] In children, initial doses of 60 mg/m^2 of prednisolone or prednisone daily have been used,[3] which may be given for 4 weeks before switching to 40 mg/m^2 given on alternate days for a further 4 weeks, and then tapered off.[4] Lower relapse rates have been reported with 60 mg/m^2 prednisone given daily for 6 weeks, followed by 40 mg/m^2 on alternate days for 6 weeks; this 12-week course may be preferable to the standard 8-week course.[3] A modification to the children's dose is to give 60 mg/m^2 of prednisolone daily until there is a response when the dose is reduced to 40 mg/m^2 on alternate days for the next 4 weeks. If there is no response within 4 weeks of treatment with the 60 mg/m^2 dose then the drug should be withdrawn and the child considered to be corticosteroid resistant.[5] A systematic review of treatment regimens found that children with their first episode of nephropathy should be treated with prednisone for at least 3 months, and possibly up to 7, to reduce the risk of relapse.[6]

Relapse is common and occurs in about 60% of cases; relapses usually respond to a further course of corticosteroids, but if a third relapse occurs cyclophosphamide 2 to 3 mg/kg daily for 8 to 12 weeks may be added to a course of corticosteroid therapy.[2,3] Deflazacort may also be effective in corticosteroid-sensitive patients who do not respond to prednisone.[6] Cytotoxics or immunosuppressants are reserved for frequently relapsing or corticosteroid-dependent cases because of their potential for severe toxicity, including carcinogenesis; cyclophosphamide appears to be preferred to chlorambucil because it is perceived as entailing a somewhat lower risk, although both are effective.[3,7] Ciclosporin has been used long-term to achieve and maintain remission, although renal biopsies are advised to screen for nephrotoxicity.[3,7] Levamisole has also been reported to be of benefit.[3,7]

Focal glomerulosclerosis. Focal glomerulosclerosis is a sclerosing lesion affecting parts of the glomeruli which occurs in some patients who otherwise have symptoms characteristic of minimal change nephropathy, and some authorities do not regard it as a distinct disease. It is common in abusers of diamorphine and has also been linked with the nephropathy that can occur in patients with AIDS. Treatment is similar to that for minimal change nephropathy but only about 20% of cases respond to corticosteroids; addition of a cytotoxic immunosuppressant such as cyclophosphamide may improve the prospect of remission. Responses to ciclosporin have been seen in both adults and children with corticosteroid-resistant disease.[3,8] Prolonged treatment may be necessary and relapse is common when ciclosporin is stopped.[7] Tacrolimus has been reported to be successful after ciclosporin failure,[3,8] and mycophenolate mofetil has been tried with conflicting results.[8] High-dose pulsed methylprednisolone, given in a tapering schedule over 6 years, has been reported to show high response rates in focal glomerulosclerosis.[3] In patients who fail to respond, progression to renal failure may occur over several years, but renal transplantation may not be helpful as disease can recur in the transplanted kidney.

Membranous nephropathy (membranous glomerulonephritis). This is a disease mainly of adults, in whom it is the single most important cause of the nephrotic syndrome, accounting for about 50% of cases. It is characterised by diffuse thickening of the glomerular basement membrane after subepithelial deposition of immune complexes. The course of disease is variable and often slow, with some spontaneous remissions, which makes the benefits of treatment difficult to demonstrate and the use of potentially toxic drugs difficult to justify. Cyclophosphamide or chlorambucil combined with a corticosteroid appear to produce some clinical improvement, and stabilisation of progressive disease, but corticosteroids alone do not appear to be of benefit.[9-11] Cyclophosphamide may be preferred as it seems to be better tolerated.[11] Ciclosporin is an alternative but therapy may need to be continued for 6 months or more before remission occurs[9,10] and a systematic review found it to be no better than placebo.[11] Other immunosuppressants under investigation in this condition include mycophenolate mofetil[10] and rituximab. Recent studies have also emphasised the control of blood pressure and proteinuria using ACE inhibitors and angiotensin II receptor antagonists.[10]

Mesangiocapillary glomerulonephritis (MCGN; membranoproliferative glomerulonephritis; MPGN). Mesangiocapillary glomerulonephritis comprises 2 separate diseases, known as type I and type II, which both occur in children and young adults and usually result in nephrotic syndrome, although about 20% of cases present with acute glomerulonephritis. Both forms show proliferation of mesangial cells and thickening of glomerular walls with formation of deposits (in type I disease due to immune complexes) in capillary walls and basement membranes. There is no established treatment regimen: some improvement or stabilisation of renal function may occur with corticosteroids and cytotoxic immunosuppressants, but about half of all patients develop end-stage renal failure within 15 to 20 years (type I disease) or 6 to 10 years (type II disease). Antiplatelet drugs and anticoagulants have also been tried but as with other therapies there is little evidence of benefit, and some centres do not recommend any specific therapy, although prednisolone and cyclophosphamide may be offered to those with a rapidly progressive course.[12]

IgA nephropathy (Berger's disease) is the commonest cause of primary glomerular disease, and is most common in young men. It results in focal, segmental proliferative glomerulonephritis associated with mesangial formation of immune deposits largely composed of IgA. The usual presentation is acute glomerulonephritis with gross haematuria, often during or just after viral upper-respiratory-tract infection. Some patients develop rapidly progressive disease similar to idiopathic rapidly progressive glomerulonephritis, with renal failure within 6 months, but in many others the syndrome is benign, and requires only observation. No form of therapy has been unequivocally shown to be of value, but control of associated hypertension, usually with ACE inhibitors, is considered important. Corticosteroids and cytotoxic immunosuppressants may be tried in severe rapidly progressive disease.[13-17] Promising results have been seen with the use of n-3 fatty acids from fish oil, and there are also reports of benefit with normal immunoglobulin, and mycophenolate mofetil.[16]

Idiopathic rapidly progressive glomerulonephritis (RPGN). Although rapidly progressive glomerulonephritis (crescentic glomerulonephritis) may be a feature of other forms of glomerular disease such as IgA nephropathy (see above) or Goodpasture's syndrome (see below) it also occurs in an idiopathic form. The disease is characterised by the formation of glomerular crescents associated with leakage of fibrin from damaged capillaries, and loss of renal function is very rapid, sometimes with renal failure within weeks. Oral corticosteroids are of little value alone, but pulsed intravenous methylprednisolone followed by oral prednisone or prednisone and cyclophosphamide over several months has produced some impressive responses;[18,19] an alternative is the use of intensive plasma exchange with a corticosteroid and cytotoxic immunosuppressants.[20] Controlled trials of these therapies are mostly lacking, although a small prospective study[21] found lymphocytapheresis to be more effective than pulsed methylprednisolone as an addition to prednisolone and cyclophosphamide therapy for reduction of glomerular injury.

Goodpasture's syndrome. Goodpasture's syndrome is a form of anti-GBM nephritis in which rapidly progressive glomerulonephritis is accompanied by pulmonary haemorrhage (because the antibody responsible for the renal symptoms also reacts with the membranes of the alveoli). It is a disease mainly of young males. Pulmonary haemorrhage responds to high dose oral prednisolone or prednisone, or pulsed intravenous methylprednisolone, but corticosteroids are of little value in controlling renal lesions, which requires vigorous plasma exchange therapy with corticosteroids and cyclophosphamide on a daily or alternate-day basis for several weeks, until antibody is no longer detectable and disease progression has halted; it is important to begin therapy before renal damage becomes irreversible.[22]

• MANAGEMENT OF SECONDARY GLOMERULAR DISEASE.

Post-infectious glomerulonephritis. The classical form of post-infectious glomerulonephritis is post-streptococcal glomerulonephritis, which produces an immune-complex-mediated acute glomerulonephritis, but glomerular disease may follow other bacterial infections, as well as protozoal infections such as malaria (malaria-associated nephrotic syndrome is familiar in endemic regions) and viral infections such as AIDS (see Focal Glomerulosclerosis, above). In most cases no additional treatment beyond appropriate management of infection and general supportive care is warranted, and corticosteroids and cytotoxic immunosuppressants are not generally used and may in some cases be harmful.[23] Nonetheless, delayed progressive renal disease may occur in a minority of patients, and has prompted efforts to treat.[22]

Other secondary glomerulopathies. Where glomerular disease is secondary to other diseases (connective tissue disorders such as SLE, the vasculitides, Henoch-Schönlein purpura, thrombotic thrombocytopenic purpura, or others such as rheumatoid arthritis, amyloidosis, neoplasia, sickle-cell disease, gout, or diabetes mellitus) most treatment is directed at the underlying disease. In addition, symptomatic management such as the use of sodium restriction for the oedema of nephrotic syndrome may be appropriate; diuretics should be used cautiously because of the risk of hypovolaemia.[24] Proteinuria of various causes may respond to the use of ACE inhibitors or NSAIDs,[2,24] although care is required in patients with renal artery stenosis or renal failure respectively. Associated hypertension and hypercholesterolaemia should be treated, and anticoagulants such as heparin may be required for associated coagulation disorders.[24] Renal toxicity can arise from various drug treatments and this should also be treated symptomatically.

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Graves' ophthalmopathy

Patients with moderate to severe ophthalmopathy as a result of hyperthyroidism (p.2165) may be treated with corticosteroids or with orbital radiotherapy. There is evidence of a synergistic effect when these therapies are combined. If orbital radiotherapy is contra-indicated, glucocorticoids may be combined with ciclosporin. There is some suggestion that intravenous pulse therapy is more effective than oral glucocorticoids.[1] Giving a corticosteroid with radioiodine therapy may prevent transient exacerbation of Graves' ophthalmopathy.[2]

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Haemangioma

Haemangiomas are benign vascular neoplasms of the skin that may enlarge dramatically before regressing spontaneously. Although no treatment is normally required, occasional complications due to ocular or visceral involvement, or associated thrombocytopenia due to platelet trapping (the Kasabach-Merritt syndrome), may merit treatment, generally with corticosteroids. Oral prednisone or prednisolone is usually given; intravenous high-dose methylprednisolone has been used for life-threatening haemangiomas.[1] Response is variable.[1-3] Another common technique is intralesional injection of a mixture of triamcinolone with betamethasone.[4] There has been a report of 2 infants responding to vincristine after corticosteroids had failed.[5] Interferon alfa has been used for corticosteroid-refractory lesions.[1] Phototherapy with a pulsed dye laser has also been reported to be effective;[6] a randomised study of this method found no benefit compared with observation only,[7] but treatment is still recommended by some[8] for problematic lesions.

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Headache

Corticosteroids have a limited role in the management of some types of headache. Although their long-term use is not considered desirable, short courses of prednisolone or prednisone in doses of 20 to 40 mg daily can be an effective alternative to standard drugs such as ergotamine in the prevention of cluster headache attacks during cluster periods (p.616). Corticosteroids have also been used for the emergency treatment of prolonged severe attacks of migraine (status migrainosus) (p.616) refractory to other drugs.

Herpes infections

Although corticosteroids alone are contra-indicated for most forms of ocular herpes simplex infection (p.854), which should be treated with a topical antiviral, a combination of corticosteroid and antiviral may be indicated for herpes simplex stromal keratitis. For discussion of the use of corticosteroids in Bell's palsy, which may be associated with herpes simplex virus, see p.1499, and for discussion of their role in postherpetic neuralgia, see p.9.

Hypercalcaemia

For a description of the treatment of hypercalcaemia, including the specific role of corticosteroids, see p.1668, and p.1083.

Hypersensitivity vasculitis

Hypersensitivity vasculitis is usually associated with an antigenic stimulus, either exogenous (e.g. a drug[1] or microbe), or endogenous (e.g. an immune complex associated with connective tissue disease). The term covers a heterogeneous group of disorders, many of which are associated with some underlying disease process (including infections, malignant neoplasms and disorders such as rheumatoid arthritis or SLE), as well as vasculitis of less clear aetiology such as Henoch-Schönlein purpura, a disease typically seen in prepubertal males. There is a suggestion that such a broad grouping is inappropriate, and that the term 'hypersensitivity vasculitis' should not be used;[2] however, it continues to be found in the literature.

Hypersensitivity vasculitis is characterised by small vessel involvement (arterioles and venules), particularly of the skin, and skin manifestations such as purpura, rashes, and urticaria predominate. Neutrophil debris is typically present around the vessel (**leucocytoclastic vasculitis**). However other organ systems may also be involved: in **Henoch-Schönlein purpura**, the skin lesions are associated with arthralgia, abdominal pain and other gastrointestinal symptoms, and glomerulonephritis.[3] Although not always immediately apparent, renal impairment may be delayed, and progress to end-stage renal failure.[4]

The prognosis is typically much better in hypersensitivity vasculitis than in the other major vasculitic syndromes, and most cases resolve spontaneously. Where a recognised antigenic stimulus is present it should be removed if possible, e.g. by withdrawal of a drug[1] or by appropriate therapy of infection. Hypersensitivity vasculitis generally responds less well to conventional drug therapy than other vasculitic syndromes. Nonetheless, where disease persists or results in organ dysfunction, a corticosteroid should be given, typically oral prednisone or prednisolone 60 mg, or 1 mg/kg daily, tapered rapidly until therapy can be stopped. Plasmapheresis has also been used, but the use of cytotoxic immunosuppressants is less well established. However azathioprine[4] and cyclophosphamide[5] have been used successfully with corticosteroids. Anecdotal reports of excellent responses to dapsone in Henoch-Schönlein purpura exist.[6] Other drugs that have been tried include danazol,[7] pentoxifylline,[8] the latter sometimes with dapsone,[8] and normal immunoglobulin.[9]

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Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP; sometimes referred to as auto-immune thrombocytopenic purpura[1]) is an auto-immune bleeding disorder characterised by the development of antibodies to the body's own platelets, with consequent sequestration and destruction of platelets. Both acute and chronic forms are seen; the acute form, which is usually self-limiting and follows viral or other infection, is the usual form in children, whereas chronic and sometimes more serious disease is more likely in adults, particularly young or middle-aged women. Patients develop petechiae, ecchymoses, and epistaxis, and women may develop menorrhagia; death due to haemorrhage is not unknown.

Treatment. For both adults and children with mild thrombocytopenia (counts of 20 000 to 30 000 cells/mm^3 or more) and no severe bruising or haemorrhage, no treatment is required.[2-8] American guidelines[7] recommend treatment for children with platelet counts below 10 000 cells/mm^3 and minor bruising; British guidelines[6] recommend that clinical severity also be considered before treating, as even pronounced bruising does not necessarily indicate a serious bleeding risk. In many cases the platelet count will return to normal or remain in a safe range despite the lack of therapy, and spontaneous remission can occur, even after a period of years.[9]

Where treatment is required in chronic disease, corticosteroids are the mainstay of therapy in adults.[8,10,11] Prednisolone or prednisone 1 mg/kg daily is used, usually for 2 to 4 weeks,[6,7] and then tapered down.[6,8] Most responses occur within the first 3 weeks, but there is no consensus as to appropriate duration of treatment.[5,11] Response rates vary widely, but most patients will relapse when the drug is withdrawn.[6] Good responses have also been reported with the use of high-dose oral or intravenous methylprednisolone for 3 to 7 days.[12-15] This has also been tried in children with the acute form[16] although controlled studies in children[17] and adults[18] found intravenous normal immunoglobulin to be more effective. Pulsed high-dose dexamethasone at 40 mg daily for 4 days has produced promising results,[3,19,20] although it is not clear how great the benefits will be in children.[21-23]

Use of corticosteroids for acute or chronic ITP in children is in any case controversial. Some consider low daily doses of prednisolone (250 micrograms/kg daily for 21 days) to be effective, while others have used high doses (prednisone 4 mg/kg daily for 7 days, then tapered).[6,7] Generally, lower doses of prednisone or prednisolone 1 to 2 mg/kg daily should not be used for longer than 2 to 3 weeks in children with ITP, and higher doses of 4 mg/kg daily are to be used for a maximum of 4 to 7 days, and tapered off as necessary.[6,7] Some centres consider that corticosteroids are of at best temporary benefit in children.[24]

In patients with chronic disease and symptoms of bleeding who fail to respond to first-line therapy, splenectomy should be considered.[2,3,5-8,10,24] About 70% of patients will respond but the operative and postoperative risks (notably of sepsis) must be considered, particularly in children.

Responses can also be achieved with intravenous normal immunoglobulin, which in practice is often preferred to corticosteroids for initial drug therapy of acute ITP in children,[4,25] and appears to be more effective in increasing platelet counts.[26] Although the effect may be transient, an increase in platelet count is achievable with doses of 400 mg/kg daily for 5 days;[6,7] single doses of 800 mg/kg or 1 g/kg are equally effective. Response is often achievable even in patients refractory to other therapies,[2,3] but treatment must be repeated periodically. It is perhaps most useful when acute symptoms supervene, because of its rapid activity, and it is recommended that it be reserved for patients with acute severe bleeding, as pre-operative prophylaxis in patients with severe thrombocytopenia, or for patients with bleeding symptoms refractory to corticosteroids.[2,3,6-8] A response to normal immunoglobulin has been reported to be a good predictor of benefit from splenectomy.[27,28] An alternative to normal immunoglobulin in rhesus-positive patients may be the use of anti-D immunoglobulin,[4,5,8,29] although there are conflicting views as to its effectiveness,[10,29-33] and it has been associated with haemoglobinuria and haemoglobinaemia.[34]

Other second-line drugs have been tried in the minority of patients with refractory chronic disease, but few have been well evaluated. Generally,[35-39] but not universally,[8,40] good results have been reported with danazol, particularly in older patients. Since response may be delayed, therapy should be continued for at least 6 months, and preferably for 1 year if no adverse effects occur.[8]It may have advantages for long-term maintenance, and is a potential alternative to splenectomy, at least in selected patients.[37,38] It can be used as a 'steroid-sparing' drug, permitting reduction in corticosteroid maintenance doses.[5,37] Dapsone may also elicit responses in patients with chronic ITP,[41] but is less effective in severe cases.[6]

Antineoplastic and immunosuppressive drugs have been tried in refractory disease, but their potential toxicity has meant that they have often been reserved for older patients, as a treatment of last resort. Oral cyclophosphamide 1 to 2 mg/kg or azathioprine 1 to 4 mg/kg have been given daily[5,8] to adults; responses to cyclophosphamide generally occur within 8 weeks but for azathioprine several months of treatment is generally necessary before response can be assessed.[3,6] High-dose cyclophosphamide has also been tried in refractory, life-threatening disease.[3] Although some patients have responded to intravenous injection of vincristine, responses have tended to be partial and inadequate, and somewhat better results have been achieved with infusions of platelets incubated with vinblastine or vincristine to encourage binding and permit selective drug delivery to the macrophages responsible for platelet destruction.[42-44] Although the developers of this technique have reported long-lasting remission in 38% of patients,[44] enthusiasm elsewhere appears to be muted.[5,45] Combination chemotherapy (cyclophosphamide and prednisone plus vincristine, vincristine and procarbazine, or etoposide) has produced prolonged remission in a few patients,[3,8,46,47] but such aggressive treatment would be difficult to justify in most cases. Ciclosporin may be a reasonable salvage treatment in refractory ITP,[8,48] and mycophenolate mofetil has been reported to be of benefit in small numbers of patients.[6] Rituximab[49,50] may also be a useful alternative, and alemtuzumab has been well tolerated.[6]

Other reports of benefit exist for colchicine,[51-53] heparin,[54] and ascorbic acid,[55] the latter having at least the advantage that it is relatively non-toxic, but such therapies remain experimental.

Thrombopoietin may offer a future new approach to treatment.[5,8,56] Other compounds that stimulate platelet production are also under investigation, including eltrombopag[57] and romiplostim,[58] which act on the thrombopoietin receptor.

Tranexamic acid may be helpful in the symptomatic management of menorrhagia, although hysterectomy is occasionally necessary.

In pregnancy. Particular problems arise in the management of ITP in pregnancy, since antiplatelet antibodies can cross the placenta and produce thrombocytopenia in the fetus. The risk is greater when disease exists before pregnancy than when it develops in the course of pregnancy.

If therapy is considered necessary the mother may be given corticosteroids or normal immunoglobulin, with platelet infusions for more serious, unresponsive symptoms.[6,7] Treatment may be required for the neonate[5] if there are complications or the platelet count falls below 30 000 cells/mm^3. The risk of intracranial haemorrhage is not necessarily reduced by caesarean section,[5] and the mode of delivery should be determined by obstetric indications.[6]

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Infections

Although long-term corticosteroid therapy has an adverse effect on the body's response to infection (see Effects on Immune Response, under Adverse Effects, p.1492), the judicious use of corticosteroids, usually on a short-term basis, with appropriate anti-infective drugs, may have a beneficial effect on the symptoms of selected acute infections, and may on occasions be life-saving. Guidelines have been published concerning a number of infections and whether corticosteroids should be used or not.[1]

For further comment on the use of corticosteroids in ocular herpes infections, infectious mononucleosis, leishmaniasis, leprosy, meningitis, pneumocystis pneumonia in AIDS patients, septic shock, and tuberculosis, see under the relevant headings in this section.

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Infectious mononucleosis

Discussions on the use of corticosteroids in infectious mononucleosis (glandular fever—see Epstein-Barr Virus Infections, p.854) usually consider that although all cases would respond promptly to therapy, only patients with an unduly prolonged infection and those with an exceptionally severe sore throat that interferes with respiratory function should be treated with a corticosteroid.[1,2] Some may consider using corticosteroids in patients with aplastic anaemia, thrombocytopenia, haemolytic anaemia, encephalitis, pericarditis, or myocarditis associated with infection by the Epstein-Barr virus. The corticosteroid used, dosage, route, and duration of treatment is variable. Dexamethasone, methylprednisolone, and prednisolone have all been tried in infectious mononucleosis. While corticosteroid treatment is considered relatively safe in infectious mononucleosis, impaired immunity might theoretically increase the risk of Epstein-Barr virus-related tumours in later life.

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Inflammatory bowel disease

Corticosteroids with aminosalicylates form the mainstay of treatment for active ulcerative colitis and Crohn's disease (see Inflammatory Bowel Disease, p.1697). In moderate to severe acute disease systemic corticosteroids are indicated for initial management, either orally or in the most severe cases intravenously. Doses are high initially and are gradually reduced as symptoms resolve. In patients with disease confined to the distal colon or rectum, local topical therapy with suppositories, rectal foams, or enemas of corticosteroids may be appropriate. Oral or rectal formulations of poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol have been developed in the hope of producing local improvement without systemic effects.

Leishmaniasis

Corticosteroids may be required to control severe inflammation in patients with mucocutaneous leishmaniasis (p.824), although pentavalent antimony is usually the drug used for initial treatment.

Leprosy

Type I lepra (reversal) reactions in patients with leprosy (p.176) frequently respond to high-dose corticosteroids (for example 40 to 60 mg of prednisolone daily) started immediately and given for several days.[1] Doses may be reduced over several weeks or months. Corticosteroids may also be used for type II reactions.

It has been considered that corticosteroid treatment of nerve function impairment should be started within 6 months of onset, as the earlier that treatment was started, the more likely it was that function would be restored. A standardised regimen in which the usual adult dose was 40 mg daily of prednisolone for 4 weeks, tapered over the next 12 weeks, has been reported to be successful in the field management of acute nerve function impairment,[2] as has a regimen consisting of 30 mg of prednisone for 2 weeks tapered down with a minimum duration of 10 weeks.[3] However, a subsequent study[4] in patients with mild nerve impairment for less than 6 months, and another in patients with established sensory impairment[5] both failed to show any benefit from a tapered corticosteroid regimen. There was evidence that sensory impairment may undergo some degree of spontaneous recovery, which casts doubt on previous reports of benefit from uncontrolled studies of corticosteroids. The use of a lower dose prophylactic regimen has also been studied, starting with prednisolone 20 mg daily for 3 months then tapering in the fourth month.[6] Although the incidence of new leprosy-related reactions and associated nerve function impairment in all patients was reduced during corticosteroid treatment, there appeared to be a rebound after this was stopped and the initial beneficial effect was not sustained at 1 year. Interestingly, however, subgroup analysis suggested that existing nerve function impairment at diagnosis may affect the outcome; after 4 months of prophylaxis, a significant reduction in acute reactions or new nerve function impairment was seen only in those without initial evidence of impairment although, as before, this was not sustained.

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Lichen

Lichen planus (p.1580) is generally controlled with corticosteroids applied topically or, occasionally, injected intralesionally; systemic corticosteroids (usually prednisone or prednisolone) are used for severe erosive lichen planus, generalised cutaneous disease, and acute exacerbations.[1,2] Prednisone has generally been used in oral doses of 30 to 60 mg daily, for courses of 4 to 6 weeks.[1] Shorter courses may be of value: prednisolone (30 mg daily for 10 days) was reported to be effective and safe for mild or moderately severe lichen planus.[3]

The use of topically applied corticosteroids in the treatment of lichen sclerosus (p.1580) has been discussed.[4,5] Relief from vulvar pruritus is obtained in most cases with a potent corticosteroid preparation, such as clobetasol propionate, applied twice daily for up to 3 months before tapering the dose.[4]

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Liver disorders

Corticosteroids are considered to be useful in chronic active hepatitis (p.1501). There is some disagreement over the benefit from corticosteroid therapy in alcoholic liver disease with hepatic encephalopathy,[1-4] and they do not appear to be of benefit in acute hepatic failure.[5] Corticosteroid therapy may however be of benefit in sclerosing cholangitis.[6]

No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p.2408). Corticosteroids are one of a number of drugs for which reports of benefit exist, but their use has been restricted as they may exacerbate bone disease.

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Male infertility

Immunosuppressive treatment with corticosteroids has been given for male infertility (p.2080) due to low-grade auto-immune orchitis.[1] Corticosteroids have also been used in men with autoantibodies to spermatozoa. Various regimens have been tried, such as giving the man a corticosteroid for a set number of days during the partner's menstrual cycle, or giving a continuous low-dose for several months.[2] However, there is a lack of evidence of benefit from substantial controlled trials and the use of corticosteroids is not generally recommended. They might, however, be considered for men with autoantibodies who have failed assisted reproductive techniques.[1]

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Malignant neoplasms

Corticosteroids are extensively prescribed in malignant disease for the relief of pain, nerve compression, or raised intracranial pressure; to alleviate dyspnoea, effusion, or hypercalcaemia; to counteract adverse effects of other therapies such as antineoplastic-induced nausea and vomiting or radiation-induced inflammation; and in the management of cachexia and to improve mood and sense of well-being.[1] In addition they form an important part of multidrug anticancer regimens used for various haematological malignancies such as acute lymphoblastic leukaemia (p.651) and Hodgkin's disease (p.655). In contrast, it has been postulated that the use of corticosteroids in patients with solid, non-haematological tumours might induce resistance in cancer cells to cytotoxic therapy, and increase the risk of treatment failure, although clinical evidence for this is lacking.[2]

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Meningitis

Corticosteroids may be given as adjuncts to antibacterial therapy in bacterial meningitis (p.178), in the hope of moderating any neurological sequelae; there is some evidence that dexamethasone, especially if given early, may reduce the risk of deafness in children and reduce mortality in adults.

Mouth ulceration

Local treatment of mouth ulcers (p.1700) often involves a topical corticosteroid for symptomatic relief. Systemic corticosteroids have occasionally been given where there is severe underlying disease.

Multiple sclerosis

Corticosteroids are often used in the management of multiple sclerosis (p.892). Corticosteroid therapy reduces the duration of the relapse and accelerates recovery, but it is not known whether it alters the course of the disease in the long term.[1,2] Methylprednisolone has superseded corticotropin and prednisolone as the drug of choice. Methylprednisolone is usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days, sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g of methylprednisolone daily have been tried.[3] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis[4] although the effect was not sustained beyond 2 years.[5] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[6] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[7]

In patients with primary progressive disease, the benefits of short-course methylprednisolone lasted no longer than 3 months[8] although, in patients with secondary progressive disease, a preliminary study has suggested that progression may be delayed by intermittent high-dose methylprednisolone therapy.[9]

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Muscular dystrophies

Muscular dystrophies are a range of inherited myopathies in which there is progressive degeneration of muscle fibres and associated muscle weakness. They may be classified according to the mode of inheritance. The most common type is the fatal recessive X-linked **Duchenne muscular dystrophy** (DMD) in which there is a deficiency in the structural muscle protein dystrophin. There is no effective therapy that affects the ultimate outcome of the various muscular dystrophies. Management is mainly through the use of physiotherapy, supports, and surgery. Drug treatment has been tried for symptomatic management, but generally the number of patients studied has been small. However, corticosteroids have been shown to be effective in increasing muscle strength and function in children for 6 months to 2 years;[1] prednisone or prednisolone 750 micrograms/kg daily is considered to be the most effective dose,[1-3] with gradual tapering to doses as low as 300 micrograms/kg daily if necessary.[2] Improvement does not appear to be sustained to the same degree with alternate-day therapy;[4] some benefit in terms of motor function preservation has been reported with intermittent prednisone (750 micrograms/kg daily for 10 days of each month).[5] Benefit has also been seen with deflazacort[1-3,6] in doses of 900 micrograms/kg daily. It has been suggested that the failure of azathioprine to produce any beneficial effect when used alone or added to prednisone treatment might indicate that prednisone's effectiveness is not due to immunosuppression.[7] There have also been reports of benefit in small numbers of patients given ciclosporin or oxandrolone; evidence to support the use of most other drugs (e.g. allopurinol) is either conflicting or unconvincing. A small trial found that supplementation with creatine monohydrate (100 micrograms/kg daily) significantly increased handgrip strength in the dominant hand compared with placebo; results were independent of corticosteroid use.[8] Future prospects for treatment include gene therapy, haematopoietic stem-cell therapy, or upregulation of the protein utrophin (related to dystrophin) to try to ameliorate the dystrophy.[9,10]

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2. Moxley RT, *et al.* Practice parameter: corticosteroid treatment of Duchenne dystrophy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2005; **64:** 13–20. Also available at: http://www.aan.com/professionals/practice/guidelines/pda/Duchenne_Muscular_Dystrophy.pdf (accessed 26/08/08)
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Myasthenia gravis

Corticosteroids are the main immunosuppressants used in the management of myasthenia gravis (p.629).

Nasal polyps

Nasal polyps[1-3] are outgrowths of the nasal mucosa, typically pale, smooth, translucent, and round or pear-shaped. They are often associated with a history of rhinitis or asthma; the triad of nasal polyps, asthma, and hypersensitivity to aspirin may occur. Patients typically present with obstruction, loss of smell, and often rhinorrhoea and postnasal drip.

Corticosteroids are extremely effective in reducing polyp size, either by the intranasal[4,5] or systemic route.[5] In the former case beginning with betamethasone sodium phosphate nasal drops, and then maintaining the reduction with an intranasal spray such as beclometasone, budesonide, or fluticasone, has been suggested.[1] Alternatively prednisone, prednisolone, or dexamethasone can be given orally: suggested regimens have included prednisone 60 mg daily, tapered over 10 or 14 days and followed by intranasal corticosteroids,[2] or dexamethasone 12, 8, and 4 mg daily, each for 3 days.[1] Surgery may be necessary where there is marked obstruction, and most patients require it at some point,[1] although polyps usually recur. Pre-operative use of systemic corticosteroids may help reduce recurrence.[2] Continued use of topical corticosteroids may reduce the frequency of relapses.[4] Antibacterials may be indicated for superimposed bacterial infection. Antihistamines, although not extensively studied, have been reported to be of benefit in nasal obstruction. Leukotriene antagonists have shown promising results, although large-scale trials are lacking; they may be indicated in patients with aspirin hypersensitivity.[5]

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Nausea and vomiting

Corticosteroids, usually in the form of dexamethasone, play an important role in antiemetic regimens (see p.1700) used to combat the effects of moderately to severely emetogenic cancer chemotherapy: they have been shown to enhance the effects of both metoclopramide- and 5-HT_3 antagonist-based regimens. Dexamethasone is a well-established treatment for delayed emesis. It is also used in palliative care and in the prophylaxis of postoperative nausea and vomiting. A study of corticosteroid treatment in refractory hyperemesis gravidarum showed improvements in appetite, weight gain, and well-being, and suggested that corticosteroids might improve nausea and vomiting but was too small to provide conclusive evidence.[1]

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Neonatal intraventricular haemorrhage

For the suggestion that antenatal corticosteroids may reduce the incidence of intraventricular haemorrhage in neonates, see p.1050.

Neonatal respiratory distress syndrome

Neonatal respiratory distress syndrome is a condition of increasing respiratory distress occurring at, or shortly after, birth. It is marked by cyanosis, tachypnoea, expiratory grunting and sternal retraction. Symptoms increase in severity with progressive collapse of the lung (atelectasis), leakage of plasma into alveolar spaces, and the formation of hyaline membranes, until death occurs or slow recovery takes place from about the 2nd to 4th day. The syndrome affects primarily premature infants and its incidence increases with the degree of prematurity; severe problems are most likely in those delivered before 30 weeks of gestation. Symptoms are thought to be at least partly due to inadequate amounts of surfactant in the premature lung resulting in high internal surface tension and increased risk of alveolar collapse, but in very immature infants other factors, possibly including impaired sodium and fluid absorption from the lung, may play a role.[1]

Treatment. The optimum treatment is prevention, and previous[2] and more recent[3] UK guidelines recommend betamethasone 12 mg daily by intramuscular injection for 2 days in women in whom delivery before 34 weeks of gestation is likely. Similar recommendations apply elsewhere. In the USA, for example, antenatal corticosteroid treatment (with betamethasone or dexamethasone) is recommended for women between 24 and 34 weeks of pregnancy who show signs of premature delivery.[4] Results from a large trial suggest that babies born after 37 weeks by elective caesarean section also benefit from antenatal betamethasone.[5] Betamethasone may be preferable to dexamethasone, as the latter appears to have a deleterious effect on neurodevelopment.[6] Long-term follow-up of those exposed antenatally to betamethasone showed no deleterious effects on psychological functioning[7] or on cardiovascular risk factors;[8] however, small increases in insulin resistance, albeit clinically insignificant, were noted in those exposed to the glucocorticoid. An overview of studies of antenatal corticosteroid therapy suggests that it may reduce the risk of respiratory distress syndrome by about 50% overall;[9] the risk of death, and of periventricular haemorrhage and necrotising enterocolitis is also reduced. Whether repeat courses should be considered is uncertain, although the practice has become widespread. A systematic review[10] indicated that repeat doses did reduce the occurrence and severity of neonatal lung disease and risk of serious health problems in the first few weeks of life. However, these benefits were associated with a reduction in some measures of weight and head circumference at birth and there was insufficient evidence on the long-term benefits and risks. Some have recommended that repeat doses be restricted to patients in clinical studies.[6,11] While repeat doses of corticosteroids may reduce the development of severe respiratory distress syndrome, especially among neonates of less than 28 weeks of gestation, weekly courses of betamethasone or dexamethasone did not reduce neonatal morbidity compared with a single course of treatment.[12] Delaying delivery with a tocolytic (see Premature Labour, p.2003) may be considered to increase the time available for management with antenatal corticosteroids.[2,3] Reported benefit from adding protirelin to antenatal corticosteroids has not been borne out by 2 large multicentre studies.[13-15] The earlier of these studies actually found neonatal outcome and maternal morbidity to be worse in those who also received protirelin,[13,14] but this conclusion has been questioned.[16,17]

In infants born with the syndrome rapid supportive care is required, which may include correction of metabolic acidosis, circulatory support, oxygen supplementation, and assisted ventilation, although there has been a lack of consensus about the most appropriate method for these.[2] Ventilation using a helium-oxygen mixture may give better results than a nitrogen-oxygen mix.[18] Another alternative is the use of partial liquid ventilation with the fluorocarbon compound perflubron.[19] Meta-analysis suggests that inhaled nitric oxide improves outcomes in infants born at or near term who are hypoxaemic,[20] but evidence of benefit in preterm infants has not been shown.[21] The majority of infants survive the acute episode with careful management, although associated complications may subsequently develop, including bronchopulmonary dysplasia (p.1500), retinopathy of prematurity (p.1994), and cerebral palsy. There is evidence that supplementation with inositol can significantly reduce the incidence of adverse outcomes in preterm infants.[22]

Since deficiency of surfactant is considered to play an important role in the neonatal respiratory distress syndrome, the use of surfactant replacement therapy has been intensively investigated, and is now accepted as reducing the risk of death from the disease and the development of pneumothorax and other lung complications.[2,23,24] Both natural and synthetic surfactants have been used and although both are effective results have tended to be better with the preparations of natural origin.[25-27] Natural surfactants of differing origins may also vary in their properties: poractant,[28] or calfactant,[29] have both been reported to give better responses than beractant. Surfactant is given as a suspension by endotracheal tube directly into the infant's lung, although other devices, such as nebulisers, have been investigated. Most surfactants are given in recommended doses of 100 to 200 mg/kg phospholipids. Repeat doses may be given if necessary, and a meta-analysis[30] of data from two randomised controlled trials using preparations of natural surfactant extract in neonates with established disease found a more favourable clinical outcome, including a decreased risk of pneumothorax, with multiple rather than single doses. However, in clinical practice the number of doses and the dosage interval varies. One large study[31] found that a dose of 100 mg/kg, repeated twice, was as effective as 200 mg/kg followed by up to four further doses of 100 mg/kg. Another found that 3 doses, given at 12-hour intervals with the first dose shortly after birth were more effective than the first dose alone in improving physiological findings and mortality rates in low birth-weight infants.[32] One large multicentre randomised controlled trial[33] investigated the difference between giving repeat doses of a surfactant (calfactant) at a low threshold of respiratory support, as recommended by the manufacturer, versus a higher threshold. The conclusion was that efficacy was not compromised by delaying surfactant re-treatment in infants with uncomplicated respiratory distress syndrome until they had reached a higher level of respiratory support than is currently recommended, but infants with complications should continue to be treated by the currently recommended low-threshold strategy.

There has been debate whether 'prophylactic' early therapy, given immediately after birth to all infants deemed at risk of the syndrome, or delayed therapy given 2 or more hours after birth to intubated infants who have developed symptoms, is the more appropriate,[34] but the large OSIRIS study,[35] and later systematic reviews,[36-38] found in favour of early intervention, and this strategy is recommended in the UK guidelines.[2,3]

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Optic neuropathies

Causes of optic neuropathies are diverse, and they may be classified by their aetiology.[1,2] Ischaemic optic neuropathies, of which the acute anterior form is most common, may be caused by vasculitic syndromes (p.1515) such as giant cell arteritis (p.1503).[3] Inflammatory optic neuropathies (optic neuritis) may be caused by infectious disease, immune-mediated disorders such as Behçet's disease (p.1499), sarcoidosis (p.1512), or demyelination of the optic nerve such as occurs with multiple sclerosis (p.892).[4,5] Other causes include hereditary disorders, trauma, or compression. Vitamin or nutritional deficiency (often due to alcohol abuse) or toxicity (due to drugs such as amiodarone, digoxin, or isoniazid) may also lead to optic neuropathy.[1,2] Clinical features such as pattern of visual field loss and pain can aid diagnosis.[2]

Management will depend on the type of neuropathy and any underlying disease. Individual studies have reported benefit with corticosteroids. Improvement in vision was reported in patients with auto-immune optic neuropathy after 5 to 7 days of treatment with high doses of intravenous methylprednisolone (1 to 2 g daily) or oral prednisolone (80 to 400 mg daily).[6] In some patients, recurrent visual loss required repeated high-dose intravenous methylprednisolone, an increase in oral prednisolone dosage, or additional immunosuppressants, but in many patients visual benefits were maintained even when treatment was withdrawn. Visual recovery has also been reported in patients with optic neuritis of unknown aetiology given intravenous methylprednisolone 250 or 500 mg every 6 hours for 3 to 7 days.[7] Another study found oral prednisone alone (1 mg/kg daily for 14 days) to be ineffective whereas intravenous methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days) was beneficial in the treatment of acute optic neuritis.[8] A review of corticosteroid use in optic neuritis concluded that high-dose oral or parenteral methylprednisolone, or corticotropin, were of value in the treatment of acute disease. However, their long-term benefit could not be determined.[9] In contrast, a systematic review of 5 studies found no evidence of benefit from intravenous or oral corticosteroid therapy at the doses used.[10]

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Organ and tissue transplantation

For a discussion of organ and tissue transplantation, including the role of corticosteroids, see p.1810.

Osteoarthritis

Systemic corticosteroids are not considered to have a place in the management of osteoarthritis (p.11); however, intra-articular injection may be useful for acute exacerbations of joint pain and inflammation. Such injections should be given only infrequently and as adjunctive therapy.

Osteopetrosis

Osteopetrosis is a rare set of heterogeneous disorders characterised by an increase in bone density, generally due to a failure of the osteoclasts to resorb mineralised bone. In the severe infantile malignant form there is reduction in the bone marrow space, leading to anaemia, hepatosplenomegaly, and nerve compression that may produce blindness and deafness; early death often results. The adult form is benign; patients typically present with fractures, back and bone pain, but no haematological abnormalities, and generally have a full life expectancy.[1]

Bone marrow transplantation may be curative for the infantile malignant form if a suitable donor can be found.[1,2] Corticosteroids are used palliatively. Benefit has been reported in 3 of 4 children treated with oral prednisone 1 mg/kg daily, with phosphate supplements and a low-calcium diet.[3] Some patients have also benefited from the use of high-dose calcitriol, again with a low-calcium diet.[4]

Another study, in 14 patients, found that treatment with interferon gamma-1b increased bone resorption.[5] In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

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Pain

Corticosteroids have produced improvement, often substantial, in neuropathic pain, including pain due to nerve damage and sympathetically maintained pain, and are widely used in conditions such as cancer pain. Dexamethasone, methylprednisolone, and prednisolone have been used for pain management, sometimes in the form of long-acting depot injections administered locally. The exact mechanism of action of corticosteroids in analgesia is not clear but may involve relief of pressure on nervous tissue by reduction of inflammation and oedema.

For discussions of pain and its management, see p.2.

Pancreatitis

Corticosteroids are generally ineffective for pancreatitis (p.2361), but a response has been reported[1,2] in patients with acute episodes caused by sarcoidosis (p.1512).

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Pemphigus and pemphigoid

Systemic corticosteroids are the mainstay of management of pemphigus and pemphigoid (p.1582). Initially, high doses are used to control blistering, which may take weeks. The optimum dose has not yet been established and suggestions have varied enormously; very high doses of oral prednisolone have been used in the past. The usual starting dose for widespread disease is about 1 mg/kg daily of prednisolone, continued until new blisters stop forming, then gradually decreased. However, doses above 750 micrograms/kg daily may have no additional benefit in bullous pemphigoid, and lower starting doses have been suggested for some patients: 300 micrograms/kg daily in localised or mild disease, 600 micrograms/kg daily in moderate disease, and 0.75 to 1 mg/kg daily in severe disease.[1] Doses of 40 to 60 mg daily for mild pemphigus vulgaris and 60 to 100 mg daily for more severe disease have been recommended.[2] Pulsed intravenous corticosteroids such as methylprednisolone (250 to 1000 mg given for up to 5 consecutive days) may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2] Other immunosuppressants may be added once remission is achieved and the condition has stabilised, with the aim of tapering the corticosteroid and eventually withdrawing treatment. Maintenance treatment must be individualised; one suggested regimen for tapering the corticosteroid is to reduce the dose of prednisolone by 50% every 2 weeks; alternatively, the dose is reduced by 5 to 10 mg weekly then more slowly below 20 mg daily.[2]

A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid, and can be a useful adjunct to systemic treatment in pemphigus and pemphigoid.[1,2] A large randomised study[3] found that topical application of 40 g of clobetasol propionate cream 0.05% daily to the entire body had a similar efficacy to oral prednisone 500 micrograms/kg daily for moderate bullous pemphigoid and was better than 1 mg/kg daily for severe disease. Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations such as mouthwashes, adhesive pastes, lozenges, or aerosols.[2,4] Intralesional injections have also been used for isolated lesions of the oral mucosa.[4] Topical corticosteroids do not control ocular disease on their own but may be added to initial systemic therapy to control acute ocular inflammation; they should not be used as long-term therapy.[5]

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Pneumocystis pneumonia

The management of pneumocystis pneumonia (p.521) is primarily with co-trimoxazole. In patients with severe infection who are hypoxic, adjuvant therapy with high-dose oral or intravenous corticosteroids reduces both the risk of respiratory failure and the risk of death.[1,2] Concerns about the potential for further immunosuppression with such adjuvant therapy in patients with HIV infection[3] do not seem to have been borne out: a comparative study noted no increase in mortality or the risk of developing other opportunistic infections.[4]

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Polyarteritis nodosa and microscopic polyangiitis

Polyarteritis nodosa is considered the prototype of systemic necrotising vasculitis. It may occur at any age but is more common in white patients and in men. It is characterised by inflammation throughout the arterial wall with fibrinoid necrosis of the arterial media, particularly in medium-sized vessels, partial occlusion of the vessel due to proliferation of the intima (possibly leading to thrombosis and infarction), fibrosis, and the formation of aneurysms. Microscopic polyangiitis, in which small vessels are primarily involved, with frequent renal and pulmonary involvement, has been seen as part of the spectrum of polyarteritis nodosa but is now considered an entity in its own right, although patients may have features of both. Antineutrophil cytoplasmic antibodies (ANCA) are common in patients with microscopic polyangiitis, which has many similarities to Wegener's granulomatosis (p.1515), but not in classic polyarteritis nodosa.

Symptoms depend on the vessels affected but most patients have fever, weight loss, myalgia, and arthralgia. Those associated with gastrointestinal involvement include mouth ulceration, diarrhoea, visceral pain, haemorrhage, or sometimes infarction of the bowel, while involvement of liver can lead to hepatomegaly or hepatic necrosis and pancreatic involvement may simulate pancreatitis. Renal involvement may present as acute glomerulonephritis and renal failure or as nephrotic syndrome; like pulmonary involvement it is a feature particularly of microscopic polyangiitis, and associated with a poor prognosis. Skin lesions, peripheral neuropathies, alterations in mental function, convulsions, episcleritis or scleritis and retinal vasculitis, ischaemic heart disease, heart failure, Raynaud's phenomenon, and hypertension are among other potential symptoms. If untreated, death, usually due to renal or cardiac involvement, occurs in about 90% of patients within 5 years.

Classic polyarteritis nodosa may respond to treatment with a corticosteroid given alone, typically prednisone or prednisolone in a dose of 40 to 60 mg daily; however, although the benefits of adding a cytotoxic to the regimen have been queried,[1,2] a combined regimen with cyclophosphamide is often preferred.[1,3-5] Some reserve combined therapy for patients with evidence of more severe disease.[6] In patients with microscopic polyangiitis a combined regimen is recommended.[6,7] One suggested oral regimen is prednisone or prednisolone 1 mg/kg with cyclophosphamide 2 mg/kg, both daily, for initial induction of remission.[8] Pulsed intravenous methylprednisolone has also been used, followed by a tapering dose of corticosteroid. There is a trend towards giving shorter courses of cyclophosphamide, and to using intravenous pulsed cyclophosphamide rather than oral dosage, in an attempt to reduce adverse effects.[5,8,9] Treatment with corticosteroids and cyclophosphamide should not exceed 1 year.[9] Azathioprine has been substituted for cyclophosphamide to maintain remission, and mycophenolate mofetil has been tried in a few patients as an alternative to cyclophosphamide in combination therapy after initial induction.[6,10]

Polyarteritis nodosa may be associated with hepatitis B infection; the vasculitis responds in most cases to treatment with antiviral drugs and plasma exchange.[3,9] Prolonged treatment with corticosteroids and cyclophosphamide should be avoided in these patients because of the risks of enhanced viral replication. However, corticosteroids may be given initially to rapidly control severe life-threatening vasculitis. The corticosteroid is stopped abruptly after 2 weeks to enhance immunological clearance of hepatocytes infected by hepatitis B virus and to favour seroconversion, and plasma exchange and antiviral drug therapy are started.[5]

Plasma exchange with cyclophosphamide may also be useful in patients with microscopic polyangiitis, particularly those with acute renal failure or severe pulmonary haemorrhage.[7] Another therapy that has been tried in this group, but with ambiguous results, is high dose intravenous normal immunoglobulin.[8]

Vasodilators such as calcium-channel blockers, inhibitors of platelet activation, or drugs that improve blood flow may be useful to improve local ischaemia.[11] Skin lesions in a patient with cutaneous polyarteritis nodosa have reportedly responded to oral pentoxifylline.[12]

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Polychondritis

Relapsing polychondritis is a rare systemic disease that results in inflammation and destruction of cartilage in various parts of the body, most seriously in the respiratory system (e.g. nose, larynx, and trachea). Airway narrowing and obstruction due to loss of cartilaginous support results, and may be complicated by pneumonia; fatalities have resulted. Cardiovascular involvement, ocular manifestations, skin disorders, and renal disease may occur; it may also be associated with other diseases such as the vasculitic syndromes. Mild inflammation is usually treated with dapsone, colchicine, or NSAIDs. Relatively high doses of corticosteroid may improve symptoms in active disease, but do not appear to retard progression. Acute airway obstruction may be treated with high-dose intravenous pulse corticosteroids.[1,2] Methotrexate,[3] azathioprine,[1] or ciclosporin[2] may be of value in reducing corticosteroid requirements. CD4 antibodies have also been tried in refractory disease but did not prove particularly useful in clinical practice.[2] Newer biological therapies such as infliximab or etanercept have been reported to be of benefit in a few cases, but their role in the management of the disease remains to be determined.[2]

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3. Trentham DE, Le CH. Relapsing polychondritis. *Ann Intern Med* 1998; **129:** 114–22.

Polymyalgia rheumatica

Polymyalgia rheumatica is a rheumatic disorder of uncertain aetiology. It occurs mainly in persons over 50 years of age of European, especially Scandinavian, extraction and is more common in women than in men. The disease is characterised by myalgia and severe morning stiffness in the neck and shoulder girdle and in the hips and pelvic girdle, which may spread in more advanced cases to the muscles of the thighs, chest, and arms. Stiffness and pain are worse after periods of inactivity. There may be some joint involvement; other symptoms include fatigue, weight loss, and fever, and anaemia and raised erythrocyte sedimentation rate are seen. In some patients polymyalgia rheumatica is associated with giant cell arteritis (p.1503).

Treatment. Although NSAIDs may improve the symptoms of polymyalgia rheumatica they do not control the disease process, and corticosteroids are preferred;[1-5] in particular, corticosteroid therapy is essential where giant cell arteritis is present.

The usual initial oral dose is prednisolone or prednisone 10 to 20 mg daily, depending on the severity of symptoms; higher doses are needed where giant cell arteritis is also present, particularly if there are ophthalmic symptoms.[4,6] After 1 to 2 months a reduction in dosage is usually possible provided symptoms are well controlled. Dosage reduction should be gradual;[4,5] mean maintenance dose at one year is about 6 mg daily.[1,5]

Maintenance therapy may need to be prolonged. Although about a third to a half of all patients may be able to have corticosteroids withdrawn within about 2 years,[2] maintenance can be required for considerably longer periods.[5] Intramuscular methylprednisolone has also been found to be effective in polymyalgia rheumatica; because the cumulative dose with prolonged therapy is lower it has been suggested that this has advantages over the use of oral corticosteroids.[7] Intravenous pulse methylprednisolone has also been used.[5] Relapse is not uncommon and is most likely within one year of corticosteroid withdrawal.[2,3,5] It may be associated with arteritic symptoms, but arteritic relapses are unusual in patients whose original presentation was pure polymyalgia.[2] Methotrexate or azathioprine may be used for their corticosteroid-sparing effect in patients in whom withdrawal is difficult.[2-4]

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Polymyositis and dermatomyositis

The term polymyositis has been used to describe several types of rare idiopathic inflammatory muscle disorders (myopathies).

The cardinal symptom of polymyositis is symmetrical progressive muscle weakness, usually starting in the shoulder girdle and neck, and pelvic girdle. Onset is usually gradual over a period of months, and accompanied by mild pain and tenderness, although more rapidly evolving disease with intense muscle pain is known. With progression, weakness may prevent the patient from moving their limbs, and muscle atrophy and contracture can develop. Dysphagia, pulmonary aspiration, and hypoventilation may occur, and some patients develop fibrosing alveolitis; pulmonary involvement, especially aspiration pneumonia, can be fatal. ECG abnormalities, usually asymptomatic, are common, and some patients develop Raynaud's syndrome. Primary disease may be associated with skin rashes, in which case it is known as dermatomyositis. Purplish scaly rashes on knees, elbows, and knuckles, and a characteristic purplish ('heliotrope') coloration and oedema of the eyelids may occur. A childhood form known as juvenile dermatomyositis exists, in which additional signs include vasculitis and subcutaneous calcium deposition (calcinosis cutis), and gastrointestinal haemorrhage and perforation may occur.

Treatment. Patients with active disease require bed rest, with the head elevated in patients at risk of aspiration. Physiotherapy to maintain muscle tone and avoid the development of contractures may be required.

Initial drug therapy is based on corticosteroids.[1-5] The usual choice is oral prednisone or prednisolone 40 to 60 mg or more, or 1 to 2 mg/kg daily. This usually produces improvement within 1 to 2 months. The dose may then be gradually tapered off to the minimum required for disease control;[1-3] some patients with well controlled disease may be satisfactorily maintained on an alternate-day regimen.[2,3] In patients with severe disease or extramuscular manifestations such as lung involvement, pulse intravenous methylprednisolone may be preferred initially, to gain more rapid disease control.[1,2,4] Maintenance therapy may need to be prolonged and a reduction in corticosteroid dosage to the minimum is therefore desirable, but too early or too rapid a reduction may lead to relapse.

Up to 30% of patients do not respond to corticosteroids,[2] or develop unacceptable adverse effects, and in these cases the second-line drugs are cytotoxic immunosuppressants.[1-3] There is considerable experience with the use of methotrexate, by mouth, subcutaneously, intramuscularly, or intravenously, usually at weekly intervals; it may be used with corticosteroids, permitting a reduction in their dose. Azathioprine may also be given with corticosteroids, again permitting a reduction in corticosteroid dosage, and the combination has also been shown to be superior to a corticosteroid alone for long-term maintenance (although this was only apparent after more than a year of therapy).[6] There is some evidence that methotrexate may be superior to azathioprine in patients unresponsive to prednisone alone.[7] Combining methotrexate and azathioprine has also been suggested.[2,4]

Some consider that corticosteroid therapy should be combined with a cytotoxic immunosuppressant such as azathioprine or methotrexate from the outset of treatment.

The role of other drugs is less well defined. Cyclophosphamide may be of use in patients with lung disease,[1,3,5] while chlorambucil and tacrolimus have produced benefit in individual cases but have not been formally assessed.[4] There have been reports of ciclosporin producing a response in refractory disease.[2,4] Normal immunoglobulin has also produced responses; it is usually reserved for refractory cases, or as an add-on therapy in patients inadequately controlled on corticosteroids and immunosuppressants, or for whom immunosuppressants are contra-indicated.[2,3] Promising results have been obtained with fludarabine[1] and mycophenolate mofetil;[2,3] there are preliminary reports of success with etanercept, and infliximab, and interferon beta has been investigated.[2]

Cutaneous symptoms in patients with dermatomyositis do not always respond satisfactorily to corticosteroids, but hydroxychloroquine is reputed to be of benefit in patients with rash,[8] probably due to a photoprotective effect.[9] Calcinosis, which can cause considerable morbidity, is particularly difficult to treat but some cases have responded to treatment with aluminium hydroxide, alendronate, diltiazem, or magnesium sulfate.[4] Warfarin therapy has been used,[10,11] but its value for calcinosis is disputed.[12]

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Polyneuropathies

Ten patients with subacute demyelinating polyneuropathy obtained a beneficial response to corticosteroid therapy.[1] In one patient the response was initially slight, but became dramatic when azathioprine was added. Prednisone was given in initial single daily doses of 40 to 150 mg, until definite clinical improvement was obtained, and followed by a single-dose alternate-day regimen. Corticosteroids are generally considered to be of little use in Guillain-Barré syndrome (p.2228), which usually occurs due to an acute inflammatory polyradiculoneuropathy.[2] In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), corticosteroids are reported to be beneficial,[1,3] although a review[3] found weak evidence to support this. Subacute demyelinating neuropathy appeared to be a distinct and clinically identifiable entity in which corticosteroid therapy is indicated.[1]

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Postoperative ocular inflammation

Corticosteroid eye drops are used to control the inflammatory response commonly seen after cataract surgery; prednisolone is usually used but dexamethasone may be necessary if the inflammation is severe.

Corticosteroids should only be used with care and for short periods for topical control of postoperative ocular inflammation, as discussed on p.100.

Pregnancy

Although some adverse effects have been recorded and certain precautions need to be observed, the use of corticosteroids during pregnancy (see under Precautions, p.1494) is appropriate to promote fetal maturation where there is a risk of premature delivery (see Neonatal Respiratory Distress Syndrome, above). In addition, in those maternal conditions serious enough to require systemic corticosteroids the risk to both mother and offspring of discontinuing therapy is often greater than that of corticosteroid use during pregnancy.

Psoriasis

Reviews of psoriasis (p.1583) and its management[1-3] include topical corticosteroids among first-line treatments. Combination therapy using corticosteroids with other topical treatments, such as calcipotriol or tazarotene, may be used to reduce adverse effects and improve efficacy of both drugs.[4]

Intralesional injection of corticosteroids has been used for small, localised, recalcitrant plaques of psoriasis but caution is required to avoid skin atrophy or depigmentation.[1] Systemic corticosteroids are not generally recommended, but have been used for short periods in extreme or rare cases; there is a risk of systemic adverse effects and of rebound psoriasis occurring on stopping therapy.

Topical corticosteroids remain the mainstay of treatment in scalp psoriasis, although long-term treatment is not recommended; the more potent corticosteroids are reserved for adult use.[5]

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Pyoderma gangrenosum

A systemic corticosteroid is one of the treatments that is usually tried in pyoderma gangrenosum (p.1583). High-dose oral treatment or intravenous pulse therapy may be needed initially to induce remission.[1,2] Response is usually rapid, but maintenance doses vary considerably. Healing of superficial granulomatous pyoderma has occurred after intralesional injection of triamcinolone,[3,4] oral doses of prednisolone,[3,4] and after long-term topical corticosteroids.[4]

1. Reichrath J, *et al.* Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53:** 273–83.
2. Brooklyn T, *et al.* Diagnosis and treatment of pyoderma gangrenosum. *BMJ* 2006; **333:** 181–4.
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Respiratory disorders

Although corticosteroids have been used in the management of many forms of respiratory disorder, this use has frequently been on an empirical and uncontrolled basis, and evidence of benefit is often somewhat mixed. Thus, while an established role exists for corticosteroids in the management of asthma (p.1108), the antenatal prevention of neonatal respiratory distress syndrome (p.1508), and probably in croup (p.1502) they are no longer used in aspiration syndromes (p.1693) and their role in diffuse parenchymal lung disorders (see p.1502 and under Sarcoidosis, below) and in acute respiratory distress syndrome (p.1498) is uncertain. Other disorders in which they have been tried with varying success include bronchiolitis (p.1500), chronic obstructive pulmonary disease (see p.1501), fat embolism syndrome,[1] acute eosinophilic pneumonia[2] and pulmonary eosinophilia,[3] diffuse alveolar haemorrhage,[4] and 'ice hockey lung' (due to nitrogen dioxide).[5]

1. Van Besouw J-P, Hinds CJ. Fat embolism syndrome. *Br J Hosp Med* 1989; **42:** 304–11.
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3. Anonymous. Pulmonary eosinophilia. *Lancet* 1990; **335:** 512.
4. Metcalf JP, *et al.* Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. *Am J Med* 1994; **96:** 327–34.
5. Anonymous. Ice hockey lung: NO poisoning. *Lancet* 1990; **335:** 1191.

Retinal vasculitis

Inflammation of the retinal blood vessels (retinal vasculitis) usually occurs as a feature of ocular disorders such as Eales disease; systemic inflammatory conditions such as Behçet's disease (p.1499), sarcoidosis (p.1512), and multiple sclerosis (p.892); or infections such as herpes (p.854), tuberculosis (p.196), syphilis (p.192), and toxoplasmosis (p.826). Vascular sheathing, occlusion, macular oedema, and retinal haemorrhage can occur, and symptoms of retinal vasculitis include painless loss of vision, blurred vision, floaters, and scotoma.[1,2]

In the treatment of non-infectious retinal vasculitis, corticosteroids are used to control inflammation and prevent long-term vision loss. Local treatment by periocular injection may be used in unilateral disease or moderate inflammation; improvement usually occurs in 2 to 3 weeks and may last for up to 3 months. Oral corticosteroids may be required for moderate to severe bilateral disease with a marked reduction in visual acuity, and improvement may take 3 to 4 weeks to appear.[1] Other immunosuppressants may be needed for vasculitis that is unresponsive or inadequately controlled by corticosteroids, and may be used for their corticosteroid-sparing effect when long-term therapy is required. Azathioprine and ciclosporin are most commonly used, but cyclophosphamide, methotrexate, and mycophenolate have also been tried.[1,2] Appropriate anti-infective therapy can clear retinal vasculitis associated with infection, but corticosteroids may be needed where there is residual vasculitis.[1]

1. Walton RC, Ashmore ED. Retinal vasculitis. *Curr Opin Ophthalmol* 2003; **14:** 413–19.
2. Levy-Clarke GA, Nussenblatt R. Retinal vasculitis. *Int Ophthalmol Clin* 2005; **45** (2): 99–113.

Rheumatoid arthritis

Systemic corticosteroids can play an important role in the management of juvenile idiopathic arthritis (p.10); they may be given by intra-articular injection in oligoarthritis, and to control disease flares, or systemically in more widespread and severe disease.

Similarly, in adult rheumatoid arthritis (p.11). corticosteroids may be added to DMARD therapy to control synovitis or provide cover when changing therapies, since they provide rapid symptomatic control. They have been shown to reduce the development of joint erosions, and in the short-term this beneficial effect outweighs their adverse effects on bone. Short- to moderate-term use of systemic corticosteroids (in doses not exceeding the equivalent of 15 mg of prednisolone daily) is therefore considered valuable. However, their adverse effects mean that longer term use cannot be justified. Intra-articular injection is recommended for acute disease flares, particularly when combined with aggressive DMARD therapy.

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3. Cleary AG, *et al.* Intra-articular corticosteroid injections in juvenile idiopathic arthritis. *Arch Dis Child* 2003; **88:** 192–6.

4. Luqmani R, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). *Rheumatology (Oxford)* 2006; **45:** 1167–9. Full guideline available at: http://rheumatology.oxfordjournals.org/cgi/data/kel215a/DC1/1 (accessed 15/02/08)
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Rhinitis

For a brief description of rhinitis and a discussion of its management including the use of corticosteroids, see p.565. Reviews[1,2] including a systematic review,[1] found that intranasal corticosteroids produced greater relief of the nasal symptoms of allergic rhinitis than oral antihistamines, and there was no difference between the two treatments in relief of eye symptoms. Commonly used nasal sprays appear to have similar efficacy and adverse effect profiles,[3] and choice of therapy is probably influenced by other factors including cost[3] and patient preference.[4]

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Sarcoidosis

Sarcoidosis is a disorder involving the development of multiple granulomas in a variety of organs, which may subsequently resolve or progress to chronic fibrosis.[1] The disease is frequently asymptomatic, and since it usually regresses spontaneously estimating the incidence is difficult, but it appears to vary considerably in different countries. It is most often seen in young adults and is slightly more common in female than male and in black than white patients.

Almost any organ can be affected, but manifestations in lymph nodes, lungs, skin, joints, and eyes are common. Lymphadenopathy, some decrease in pulmonary function, dyspnoea, and cough may mark lung and lymph node involvement. Skin manifestations include erythema nodosum, macular or papular lesions due to granuloma formation in the skin, and violaceous plaques on fingers, nose, ears, and cheeks known as lupus pernio. Arthropathy, with painful joint swellings, may be associated with erythema nodosum and fever in acute presentations; bone lesions are most common in fingers and toes. Involvement of the nervous system may be particularly difficult to diagnose because of its protean manifestations. Involvement of the eyes is usually manifest as uveitis although other symptoms include keratoconjunctivitis sicca. Symptomatic disease involving the gastrointestinal tract, liver, pancreas, heart, or kidneys is rare, although asymptomatic involvement may occur.

In addition to symptoms directly due to the disease, sarcoidosis is often associated with hypercalcaemia (p.1668) and hypersensitivity to the effects of vitamin D. Other biochemical abnormalities include raised serum concentrations of angiotensin-converting enzyme (ACE), and there are abnormalities of some aspects of immune function.

Diagnosis of sarcoidosis is problematic because of its multiple manifestations and the fact that it is so often clinically silent. It is often detected by accident, when radiography is performed for other reasons, but biopsy is often needed to help confirm the disease. The Kveim test, in which an antigen derived from patients with sarcoidosis (see p.2329) is given intradermally and produces a delayed reaction in patients with the disease, is now rarely used because of its perceived lack of precision, although some still consider it useful.[2]

Treatment. Asymptomatic disease requires no therapy, and since spontaneous remission can occur, corticosteroids, which are the usual therapy,[1] are generally reserved for patients in whom the disease affects the function of a vital organ or for patients with hypercalcaemia. NSAIDs alone may be adequate to control the fever and arthropathy of acute disease. Where corticosteroids are called for a typical oral regimen is prednisolone or prednisone 30 to 40 mg daily, the dose being reduced after several weeks as the patient improves.[3-5] Therapy should be continued (at the minimum effective maintenance dose) for 12 to 18 months before any attempt is made to withdraw it.[3] Alternate-day dosage has been suggested, with 40 mg every other day as initial therapy,[6] and 5 to 10 mg every other day as maintenance.[7] There is some evidence[8] that relapse may be more likely after withdrawal of corticosteroids than in patients who do not receive corticosteroid therapy, but this may simply reflect the natural course of disease in this group. Higher initial doses of 60 to 80 mg daily of prednisone are generally used in cardiac sarcoidosis, although controversy exists as to the clinical efficacy and optimal dose and duration of corticosteroids. Treatment halts progression and improves survival, but it does not reduce the incidence of ventricular arrhythmias.[9] There also remains some dispute about the value of oral corticosteroids in pulmonary disease: although they are useful in the short term their long-term benefits are more uncertain.[10] Inhaled corticosteroids have also been investigated in pulmonary sarcoidosis; they appear less reliable than oral therapy for primary treatment, but may have a role as maintenance therapy.[5,11] In patients with ocular disease corticosteroid drops and ointment are used for anterior uveitis; resistant cases, or patients with posterior uveitis, require systemic corticosteroids.[1] Skin lesions usually respond to corticosteroids but the high doses that may be required for suppression of lupus pernio may produce changes in appearance as disfiguring as the disease.[3]

Other drugs have occasionally been used in sarcoidosis but are very much second-line. In patients in whom corticosteroids are not effective or not tolerated cytotoxic immunosuppressants have been given, with variable results.[1,3,5,7] Methotrexate has perhaps been most useful, having been found to be effective in low oral doses (up to 15 mg weekly) in refractory disease;[1,12] corticosteroid-sparing effects may be evident after 6 months.[7] Azathioprine has been used for severe refractory cases.[5] Results with ciclosporin have been variable,[7] although there are reports of response in refractory skin lesions and optic neuropathy.[1] Toxicity and concerns about carcinogenesis limit the use of chlorambucil and cyclophosphamide.[1,5] The antimalarials have also been tried as adjuncts or alternatives to corticosteroid therapy,[5] and may be useful for skin disease and hypercalcaemia.[7] Potential ocular toxicity is a concern, however, and although hydroxychloroquine may be less oculotoxic than chloroquine,[7] regular ophthalmological assessment is recommended.[5] Other reports of benefit in cutaneous sarcoidosis have involved allopurinol,[13] thalidomide,[14] and tranilast,[15] while there is report of response to melatonin in 2 patients with refractory sarcoidosis.[16] Infliximab and pentoxifylline have also shown promising results.[7]

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Sciatica

For mention of the use of epidural corticosteroid injections to treat sciatica, and doubts about the extent of benefit, see Administration, Epidural Route, p.1496.

Scleritis

Scleritis and episcleritis are inflammatory diseases of the sclera often associated with various systemic diseases. Episcleritis tends to be a benign superficial condition but treatment can be difficult and it tends to recur. The use of topical corticosteroids and topical NSAIDs are sometimes of temporary benefit. Scleritis is a rarer more deep-seated inflammation. Initial treatment of non-necrotising scleritis is with NSAIDs; high dose systemic corticosteroids (usually oral prednisone or prednisolone 60 to 80 mg daily) have been used successfully in many patients unresponsive to NSAIDs.[1,2] If necessary, to reduce any attendant adverse effects, corticosteroids have been given by orbital floor injection (methylprednisolone acetate 40 mg)[1] or at a reduced systemic dosage with an additional immunosuppressant such as ciclosporin, methotrexate, cyclophosphamide, or azathioprine.[3] Immunosuppressants may also be of value alone in severe or unresponsive disease.[4] It has been suggested that immunosuppressant therapy should be the initial choice in necrotising scleritis, as therapeutic failure is very common with less aggressive regimens.[4]

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Scleroderma

Corticosteroids may be useful for the management of scleroderma (p.1817), but must be used with care because of the risk of exacerbating renal and other problems.

Seborrhoeic dermatitis

Topical corticosteroids are used with an imidazole antifungal in the management of seborrhoeic dermatitis (p.1584).

Septic shock

The role of corticosteroids in septic shock (see under Septicaemia, p.190) has been controversial. Early studies reported both beneficial[1] and detrimental[2] effects, but corticosteroids were considered ineffective[2,3] and likely to worsen secondary infection.[4-7] More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency.[8] However, their routine use in septic shock is not recommended[9] and a systematic review[10] concluded that short-course high-dose corticosteroids did not alter mortality rates in severe sepsis and septic shock, and that current evidence did not support their use. However, meta-analyses[10,11] and a review[12] suggest that longer courses (5 to 11 days) of low-dose corticosteroids might reduce mortality especially in those with vasopressor-dependent septic shock.

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Sickle-cell disease

A study[1] has suggested that a short course of high-dose methylprednisolone might be a useful adjunct in controlling pain in sickle-cell crisis (p.9). However, the use of corticosteroids in sickle-cell disease is problematic; apart from the usual adverse effects, including the risk of exacerbating underlying infection, corticosteroid therapy has been reported to provoke sickle-cell crisis in patients with sickle C disease—see under Precautions, p.1494.

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Skin disorders

For some guidelines to the use of topical application of corticosteroids in skin disorders, see under Administration, p.1497. For discussion of the use of corticosteroids in individual skin disorders see under the relevant headings in this section.

Soft-tissue rheumatism

Soft-tissue rheumatism (p.13) includes a number of conditions affecting tendons, ligaments, muscles, fascia, and joint capsules; some lesions may respond to local injections of corticosteroid, often given with a local anaesthetic. In the treatment of shoulder pain, intra-articular injection of triamcinolone acetonide was considered to be superior to physiotherapy for reducing pain in the short-term.[1] Injection of corticosteroids below the point where the clavicle joins the shoulder blade (subacromial injection) may be superior to placebo for rotator cuff disease, as may intra-articular injection for adhesive capsulitis.[2] One meta-analysis[3] found that subacromial injection produced dose dependent benefit for up to 9 months in shoulder pain associated with rotator cuff tendinitis, with a number-needed-to-treat of between 1.4 and 2.2; there was some evidence that higher doses (50 mg equivalent of prednisone or greater) were more effective. However, there has been concern over accuracy of needle placement, and the scanty evidence to guide treatment.[2,4] There is also limited evidence that oral corticosteroids may produce improvement in pain and mobility in patients with adhesive capsulitis (frozen shoulder), but this improvement may not last beyond 6 weeks.[5] In lateral epicondylitis (tennis elbow), local injections of triamcinolone acetonide with local anaesthetic improved short-term outcomes such as pain and disability, although long-term results favoured physiotherapy.[6] Another study found that short-term benefit with corticosteroid injection for epicondylitis was paradoxically reversed after 6 weeks, implying the need for caution.[7] Evidence appears to support the use of corticosteroids such as betamethasone and methylprednisolone, with local anaesthetic, in trigger finger.[4] In contrast, no benefit has been found in Achilles' tendinopathy.[4] In carpal tunnel syndrome, injection of corticosteroids produces short term benefit but has not been shown to produce better results than other treatments such as splinting in the longer term.[8] Concerns have been expressed about the lack of good studies to support the use of corticosteroids,[2,4] and some have suggested that in tendinopathies, they be reserved for chronic injuries, and that short- or moderate-acting, soluble preparations be used.[4] Tendon rupture after local corticosteroid injection may occur.[4]

See also Administration, Intra-articular Route, p.1497

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Spinal cord and head injury

Spinal cord injury usually causes significant disability arising from either partial or total paralysis. The degree of disability and organ dysfunction is determined by the spinal level of the injury, and whether severance of the cord is complete or not. Patients with lesions at the level of the fourth cervical vertebra and above will almost certainly have respiratory problems or diaphragm paralysis, requiring ventilation. Spinal shock occurs almost invariably, resulting in hypotension and reduced renal perfusion, which may cause renal failure. Patients are also at risk for acute respiratory distress syndrome (p.1498) and thromboembolism (p.1187). Lesions above the fifth thoracic vertebra may cause autonomic dysreflexia which results in a potentially life-threatening rise in blood pressure, requiring the use of antihypertensives.[1]

Neural tissue in the spinal cord cannot regenerate and damage is considered permanent; however, some lessening of disability is possible with rehabilitation. One of the main aims in the management of spinal cord injuries is to minimise secondary damage from hypoxia, hypoperfusion and inflammation. Results of a multicentre placebo-controlled study in the USA[2] indicated that high-dose intravenous corticosteroids resulted in improvements in neurological function if given within 8 hours of spinal cord injury. Methylprednisolone was given in an initial dose of 30 mg/kg followed by 5.4 mg/kg per hour for 23 hours. A subsequent study found that although this regimen was adequate if begun within 3 hours of injury, better results were obtained by continuing methylprednisolone for 48 hours in patients in whom therapy commenced 3 to 8 hours after injury.[3,4] The lazaroid tirilazad, given for 48 hours, had some benefit in this study, although it was less effective than 48 hours of treatment with methylprednisolone in the doses used. In contrast, a systematic review found that high-dose methylprednisolone did not improve neurological function in patients, and might potentially have a deleterious effect.[5] Another review failed to find any benefit from the use of gangliosides.[6]

The longer-term management of spinal cord injuries has been reviewed.[7]

Management of traumatic head injury poses similar problems and risks to those of spinal cord trauma. The effects of corticosteroids on mortality in acute traumatic head injury had been unclear, until an international randomised trial in 10 008 adults found that the risk of death from all causes within 2 weeks[8] or 6 months[9] of significant head injury was higher in the group given methylprednisolone compared with placebo. There is little evidence that tirilazad is of any value in acute traumatic brain injury,[10,11] nor for other interventions that have been suggested for this, including barbiturates,[12] calcium-channel blockers such as nimodipine (other than perhaps in a subgroup of patients with subarachnoid haemorrhage—see also p.1357),[13] central stimulants such as methylphenidate or the amfetamines,[14] inhibitors of glutamate neurotransmission,[15] or hyperventilation or hyperbaric oxygen therapy.[16,17] Mannitol is widely used after severe head injury to reduce intracranial pressure (p.1181), but evidence from randomised studies is limited and it is unclear whether mannitol therapy has any effect on death or disability.[18]

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Spondyloarthropathies

Intra-articular injections of corticosteroids have been given in ankylosing spondylitis (see Spondyloarthropathies, p.13).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an auto-immune disease of complex aetiology characterised by autoantibodies that participate in the mediation of tissue damage affecting joints, skin, kidney, CNS, and other organs. It is far more common in women than in men, the evidence suggesting that male hormones have a protective effect, and peak onset is usually in women in their 20s and 30s.

The commonest symptom in patients with SLE is arthralgia or arthritis; fatigue, fever, weight loss, rashes (characteristically a so-called 'butterfly rash' on the cheeks and bridge of the nose), CNS involvement including personality changes, anaemia, nephritis, and pulmonary symptoms (notably pleurisy) are also frequent, while other symptoms include myalgia, alopecia, Raynaud's syndrome, convulsions, coma, stroke, pneumonitis, pericarditis, myocarditis with tachycardia, leucopenia, thrombocytopenia, coagulation disorders (both thrombosis and haemorrhage), hepatomegaly, splenomegaly, and lymphadenopathy. Thrombotic symptoms and recurrent miscarriage may represent an 'antiphospholipid antibody syndrome' due to antibodies against phospholipids, which occurs in about a third of all patients with SLE but may also occur independently.[1]

Management. SLE is characterised by exacerbation and remission so individualised management with careful monitoring and appropriate and timely symptomatic treatment is required. Treatment is largely empirical and there have been few controlled studies.

In addition to any specific treatment, patients require emotional support, extensive rest, and avoidance where possible of stimuli that may provoke disease exacerbation, including ultraviolet light, certain drugs or foods rich in psoralens, infections, and psychological stress.

Mild disease may require no treatment, or may be managed simply with NSAIDs for muscular and joint symptoms.[2] In more severe, but non-life-threatening disease chloroquine or, more often, hydroxychloroquine is effective, particularly for cutaneous and joint manifestations,[3-5] although disease flare may occur on withdrawal.[6] Retinoids such as acitretin have also been shown to be of use in some patients.[7]

Many patients require treatment with corticosteroids at some point, although in such patients they can be a major cause of morbidity.[3,8] It is usual to use a corticosteroid when treatment with NSAIDs or antimalarials has failed, or when life or vital organs are threatened.[2] They are usually given in high doses (1 mg/kg or more of prednisone or prednisolone daily, sometimes preceded by a course of intravenous methylprednisolone)[2] for life-threatening manifestations such as high fever, severe thrombocytopenia, coma, seizures, or involvement of a major organ such as the kidney (see also Lupus Nephritis, below). Non-life-threatening symptoms that fail to respond to other measures will usually respond to lower corticosteroid doses (not more than 500 micrograms/kg daily of prednisolone or prednisone).[2] Once a response is achieved the dose should be tapered to the lowest required to control symptoms, sometimes in the form of alternate-day dosage, although disease may relapse.[2] Complete withdrawal is optimal, although some patients may need long-term maintenance on about 5 mg daily.[2] One study found that raising the maintenance corticosteroid dose temporarily to counteract any increases in the concentration of antibodies to double-stranded DNA may reduce the number of relapses,[9] but the design and conclusions of this study are open to criticism.

Prolonged corticosteroid therapy, particularly at the higher doses, is associated with adverse effects such as aseptic bone necrosis and an increased susceptibility to infection, and other drugs have been added to corticosteroid therapy in an attempt to lower the corticosteroid dose but maintain disease control. In particular the immunosuppressant azathioprine has been used for its corticosteroid-sparing effect.[2] Oral or intravenous pulse cyclophosphamide has been used with some success to treat severe organ involvement although toxicity may be of concern.[2,3] Low-dose weekly methotrexate may also be helpful in patients with cutaneous or joint involvement.[10] The antimalarials may also be combined with corticosteroid therapy, and in addition to a corticosteroid-sparing effect there is a suggestion that hydroxychloroquine may counter the adverse effects of corticosteroids on serum-lipid profiles.[2,11] Prasterone is under investigation for the treatment of severe disease.[12] Thalidomide has been investigated for treating cutaneous manifestations of SLE.[13] Remission has been reported in a few patients with refractory disease given rituximab.[5]

Thrombotic symptoms due to antiphospholipid antibodies require adequate long-term anticoagulation with warfarin or low-dose aspirin, and it should be borne in mind that stroke and related CNS symptoms will not respond to corticosteroids. In patients with other severe CNS symptoms that fail to respond to corticosteroids intravenous cyclophosphamide may be helpful,[14,15] but response is unpredictable. Intravenous immunoglobulin has been used as an adjunct in CNS lupus,[5] although its role is unclear; it may also be used in the management of thrombocytopenic symptoms.[16]

In patients with severe and potentially fatal symptoms plasma exchange may provide temporary benefit by removing circulating antibodies.

Lupus nephritis. Renal disease is probably the best studied symptom of SLE. Almost all patients develop some renal involvement,[17] with clinical nephritis in up to 50%.[18,19] Usual manifestations of renal disease include hypertension, oedema, proteinuria or frank nephrotic syndrome, and oliguria; more severe disease is usually associated with focal or diffuse proliferative glomerulonephritis on biopsy.[18,19]

Patients with active disease (worsening renal function, proteinuria, and urinary sediment) require aggressive treatment to prevent irreversible renal damage. It is generally accepted that the use of a cytotoxic immunosuppressant with a corticosteroid is more effective than the use of corticosteroids alone in controlling nephritis and the risk of end-stage renal failure,[17,18] although corticosteroids alone may be used for less severe disease.[16]

One suggested outline for treatment in severe active disease is to begin with pulsed intravenous methylprednisolone as 3 doses of 1g daily, or prednisone or prednisolone orally (initially 0.5 to 1 mg/kg daily, gradually reduced) accompanied if necessary by cyclophosphamide or azathioprine.[19] An alternative approach is to begin therapy with intermittent intravenous cyclophosphamide,[20] which appears to be more effective than pulsed methylprednisolone[21,22] and then to maintain patients with low-dose oral prednisone plus pulsed intravenous cyclophosphamide. Azathioprine may be a useful alternative for patients who cannot tolerate cyclophosphamide;[18,19] it may be used as maintenance after cyclophosphamide induction in an attempt to reduce toxicity.[17,19] Ciclosporin has also been investigated, with preliminary results suggestive of benefit,[23,24] but has been viewed with caution because of its nephrotoxicity.[18,19] Mycophenolate mofetil has shown promising results;[25,26] some suggest it may come to replace cyclophosphamide.[5] Abetimus is under investigation,[18] and other drugs that have been reported to be of benefit include intravenous immunoglobulins,[18] cladribine, and fludarabine.[17] Autologous haematopoietic stem-cell transplantation (p.1811) is considered feasible in SLE.[18,27]

Pregnancy. Although symptoms of SLE do not appear to be exacerbated in most patients during pregnancy,[28,29] it is considered advisable that pregnancy be deferred until the disease is in remission or controlled by therapy, since complications are more likely in active disease.[13,28] Cyclophosphamide or methotrexate are contra-indicated in pregnancy because of the risk of teratogenesis but corticosteroids, azathioprine, and hydroxychloroquine may be used if necessary:[2-4,30] the risks of miscarriage, still-birth, growth retardation, or preterm delivery due to the disease are considered greater than the risks to the fetus of continued therapy. The use of low-dose aspirin (75 mg daily) has been recommended in women with renal involvement or a history of pre-eclampsia or fetal growth retardation;[30] in women with antiphospholipid antibodies, low-dose aspirin with subcutaneous heparin or low-molecular-weight heparin markedly improves the live birth rate.[1,13,31] The use of high-dose prednisone, with or without aspirin, to suppress antiphospholipid antibodies, while reportedly effective in some women with bad obstetric histories,[32,33] has been found by others to be of no benefit,[34] and is associated with unacceptable maternal morbidity.[35] Warfarin prophylaxis, which appears effective in other patients with the antiphospholipid antibody syndrome,[36] is unsuited to pregnant women because of the teratogenic effects of warfarin.[37]

Postpartum exacerbation is well recognised,[28,30] and some workers favour prophylactic corticosteroid cover during the puerperium. A small proportion of neonates born to mothers with lupus exhibit a neonatal lupus syndrome,[38] manifesting most seriously as heart block which may require a permanent pacemaker.

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Takayasu's arteritis

Takayasu's arteritis is a vasculitis of the aorta and its branches seen particularly in young women and in Oriental patients. It is characterised by vasculitis followed by fibrosis, leading to stenosis or occlusion of the vessel. Symptoms vary depending on the anatomical site, but include constitutional symptoms such as fever, malaise, and arthralgia, syncope, dyspnoea, palpitations, loss of pulses, intermittent claudication, and visual disturbances.

Active inflammatory disease may respond to corticosteroids: doses of 1 mg/kg daily of prednisone or prednisolone, tapered after one month in patients who respond, have been suggested.[1,2] In patients who do not respond, azathioprine, cyclophosphamide, or methotrexate have been added, although opinions vary as to the necessity of cytotoxic agents in these patients.[1-3] Ciclosporin[4] and mycophenolate mofetil[5] have also been used. A preliminary report[6] suggests that the use of etanercept or infliximab to inhibit the actions of tumour necrosis factor may be useful in patients who are refractory to other treatments. Widely varying estimates of mortality and aggressiveness exist for Takayasu's arteritis, and in the absence of large controlled studies it is difficult to assess the benefits of drug therapy. The course may be very prolonged, and minimising the maintenance dosage (e.g. by alternate-day corticosteroid therapy) is important to avoid adverse effects.[7]

Surgical reconstruction of affected vessels has been carried out in patients at risk of ischaemic compromise.[8] Angioplasty has been tried.

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Tuberculosis

The use of corticosteroids in tuberculosis (p.196) is controversial.[1-3] They should never be given to patients with active disease without protective chemotherapy cover, and must be used with caution in patients with dormant disease as it may be reactivated. Use of corticosteroids in pulmonary tuberculosis is to be avoided except in life-threatening disease. WHO suggests that corticosteroids may be useful adjuvants to antituberculous therapy in selected conditions including tuberculous meningitis, pericarditis, pleural effusion, or laryngitis, or tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuberculosis, massive lymph node enlargement, or to control drug hypersensitivity. They are also likely to be of benefit in patients with HIV infection and the above conditions.[4] Similar recommendations have been made by NICE with regard to tuberculous meningitis and pericarditis.[5] However, systematic reviews of tuberculous pleurisy[6] and pericarditis[7] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions.

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Urticaria and angioedema

Oral antihistamines are the mainstay of treatment for urticaria (p.1584). Severe attacks refractory to standard therapy may require a short course of oral corticosteroid therapy.

When angioedema affecting the larynx (laryngeal oedema) is present, the patients should be treated with adrenaline as an allergic emergency (see Anaphylaxis and Anaphylactic Shock, p.1205).

Uveitis

Uveitis is inflammation of the uveal tract of the eye, which comprises the choroid, ciliary body, and the iris. It is usually idiopathic but may be secondary to infection, allergy, or inflammatory disorders with an auto-immune component.

In anterior uveitis, also referred to as iridocyclitis, there is inflammation of the iris (iritis) and the ciliary body (cyclitis). It tends to be acute and self-limiting and is likely to be associated with infection. The iris becomes spongy and hyperaemic and exudates may result in adhesions between the iris and the lens (posterior synechiae). Chronic anterior uveitis is associated with formation of cataracts and glaucoma. Posterior uveitis can be acute or chronic and may just affect the choroid (choroiditis) or may also involve the retina (chorioretinitis). It is more likely to be an auto-immune condition.

The treatment of uveitis has been reviewed.[1-4]

Corticosteroids given topically and, when necessary, systemically are the mainstay of treatment for acute anterior uveitis.[5] Cycloplegics and mydriatics such as atropine, cyclopentolate, and homatropine are used adjunctively to rest the ciliary body and iris, diminish hyperaemia, and to prevent the formation of posterior synechiae. Antibacterials should be used to treat any infection. In children with chronic anterior uveitis associated with juvenile idiopathic arthritis, corticosteroids are supplemented with chronic use of an oral NSAID if inflammation persists after 90 days of treatment and attempted corticosteroid withdrawal.[6] In the 30% or so of cases that do not respond to corticosteroids and NSAIDs, low-dose weekly methotrexate (with folic acid supplements daily) is advocated, with other immunosuppressants being substituted or used adjunctively when methotrexate fails or is not tolerated.

Treatment of posterior uveitis is less satisfactory than that of acute anterior uveitis since gross damage to the retina often occurs before the condition can be controlled. Corticosteroids are usually required given either as periocular injections or as high-dose systemic therapy.[5] A suggested protocol[2] involves the use of high-dose systemic corticosteroids to control active disease; long-term control is then maintained primarily with low-dose ciclosporin, corticosteroids being tapered to a low dose or eventually withdrawn. Certain patients may require an additional immunosuppressant, usually azathioprine, although methotrexate, cyclophosphamide, ciclosporin, or chlorambucil may be considered. Other immunosuppressants being studied include tacrolimus, and there are reports of improvement with mycophenolate mofetil.[4,5]

Visual impairment in chronic uveitis is often the result of macular oedema and is not necessarily prevented by immunosuppressants. Short-term treatment with acetazolamide is considered to have produced some encouraging results in reducing chronic uveitic macular oedema but its long-term efficacy or efficacy with low-dose corticosteroids remains to be determined.[7] Although systemic and topical NSAIDs have been shown to reduce cystoid macular oedema in post cataract extraction (see Postoperative Inflammatory Ocular Disorders, p.100) their role in the treatment of macular oedema associated with uveitis is less clear.

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Vasculitic syndromes

Vasculitis may be defined as inflammation of the blood vessel wall, and the term has been applied in describing a wide range of diseases involving blood vessels of various sizes and types. Vasculitis may occur as part of a systemic disease such as rheumatoid arthritis or SLE, or may itself be the primary disorder, and symptoms may vary from superficial cutaneous disease, with purpura and urticaria, to progressive and fatal systemic vasculitides such as Wegener's granulomatosis. In some forms of vasculitis, such as giant cell arteritis, mononuclear giant cells may be seen, while in granulomatous vasculitis the mononuclear cells form granulomata adjacent to the damaged vessel wall. Necrotising vasculitis is used to describe inflammation associated with necrosis of the media, the middle part of the vessel wall, while polyarteritis implies inflammation of the full thickness of an arterial wall.

Because of the heterogeneous nature of this group of diseases and the degree of overlap which exists between some of them, and between them and other diseases, classification has been difficult. Classification has often been based on the size of the affected vessel, as well as the presence or absence of granulomata and antineutrophil cytoplasmic antibodies (ANCA), and whether the vasculitis is primary or secondary. Of the major primary vasculitic syndromes, giant cell arteritis (p.1503) and Takayasu's arteritis (p.1514) are examples of large vessel disease; classic polyarteritis nodosa (p.1510) affects medium-sized vessels; Churg-Strauss syndrome (p.1501), microscopic polyangiitis (p.1510), and Wegener's granulomatosis (below) are diseases of small or medium-sized vessels; the so-called 'hypersensitivity vasculitides' (p.1505), including Henoch-Schönlein purpura, are small vessel diseases, though usually limited in extent.

Treatment depends on the type of vasculitis, its severity, and prognosis. Treatment of the systemic vasculitides has revolved around corticosteroids and cyclophosphamide; other cytotoxic immunosuppressants, normal immunoglobulins, NSAIDs, anticoagulants, dapsone, and colchicine have been tried in various forms of disease.

Vitiligo

Topical corticosteroids are sometimes effective in inducing repigmentation in patients with vitiligo (p.1582 under Pigmentation Disorders).

Wegener's granulomatosis

Wegener's granulomatosis is a form of granulomatous vasculitis that occurs more frequently in men and in white patients. It is characterised by necrotising vasculitis of small arteries and veins, accompanied by granuloma formation, and affecting particularly the respiratory tract and kidneys. It is usually associated with antineutrophil cytoplasmic antibodies (ANCA). Symptoms include rhinorrhoea, sinusitis, cough and dyspnoea (signs of pulmonary infiltration which is seen in the majority of patients at presentation); renal manifestations include haematuria, proteinuria, uraemia, and oedema of the lower limbs due to a focal glomerulonephritis which can progress to crescentic glomerulonephritis and rapidly progressive renal failure. Other organ systems may be involved, with effects similar to those of microscopic polyangiitis (see p.1510). If untreated, the disease is fatal.

Treatment is with a combination regimen based on cyclophosphamide with a corticosteroid. A standard regimen has been low-dose (1 to 2 mg/kg daily) oral cyclophosphamide, with prednisolone or prednisone 1 mg/kg daily by mouth initially, subsequently tapered to an alternate-day regimen and eventually stopped.[1-3] Cyclophosphamide is usually continued for at least a year before considering gradual withdrawal but there is a trend in Europe towards the use of shorter courses of cyclophosphamide.[4] Standard treatment regimens produce improvement or remissions in about 90% of patients.[1,5] Relapses may subsequently occur in about half, and require re-treatment; prompt intensification of treatment when serum ANCA concentrations begin to rise may avert relapse.[6] There is evidence from one controlled study that addition of co-trimoxazole to maintenance regimens reduces the incidence of relapse,[7] although another suggested that it might actually increase the risk of relapse.[8]

Despite the success of regimens based on low-dose oral cyclophosphamide there is considerable concern about their toxicity, particularly since prolonged use may be necessary. Intermittent high-dose intravenous ('pulse') cyclophosphamide has been suggested as an alternative to the oral regimen with fewer adverse effects,[9] but results in practice seem to have been variable.[10,11] Regimens similar to the standard regimen, but substituting azathioprine for cyclophosphamide once remission is achieved (usually after 3 to 6 months) and continuing with low-dose corticosteroids concomitantly have been used.[12] Other drugs, such as methotrexate, have been tried and addition of low-dose weekly methotrexate to a corticosteroid may be a possible treatment option.[8,13-15] Ciclosporin has been reported to reverse acute renal failure in 2 patients with Wegener's granulomatosis, as well as controlling fulminant symptoms unresponsive to cyclophosphamide and corticosteroids in one of them,[16] but others have found ciclosporin plus a corticosteroid to be ineffective in suppressing disease activity.[17] Etoposide[18] and infliximab[19] have also been successfully used to induce remission in cyclophosphamide-resistant disease, but etanercept has proved ineffective in maintaining remission.[20] Other drugs that have been investigated include high-dose intravenous immunoglobulin,[21] mycophenolate mofetil,[22] and rituximab,[23] while anti-CD4 monoclonal antibodies have proved useful in patients with microscopic polyangiitis, which has some similarities to Wegener's granulomatosis, but the role of such investigational regimens remains to be determined.

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Alclometasone Dipropionate *(BANM, USAN, rINNM)* ⊗

Alclométasone, Dipropionate d'; Alclometasoni Dipropionas; Alklometasondipropionat; Alklometasonidipropionaatti; Dipropionato de alclometasona; Sch-22219. 7α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

Альклометазона Дипропионат

$C_{28}H_{37}ClO_7$ = 521.0.

CAS — 67452-97-5 (alclometasone); 66734-13-2 (alclometasone dipropionate).

ATC — D07AB10; S01BA10.

ATC Vet — QD07AB10; QS01BA10.

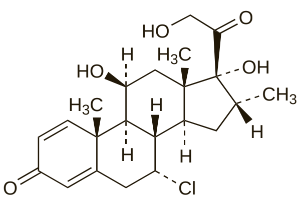

(alclometasone)

Pharmacopoeias. In *US.*

USP 31 (Alclometasone Dipropionate). Store in airtight containers.

Profile

Alclometasone dipropionate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see Topical Application, p.1497.

Preparations

USP 31: Alclometasone Dipropionate Cream; Alclometasone Dipropionate Ointment.

Proprietary Preparations (details are given in Part 3)
Austral.: Logoderm†; ***Chile:*** Logoderm†; ***Cz.:*** Afloderm; ***Denm.:*** Legederm†; ***Fin.:*** Legederm†; ***Ger.:*** Delonal; ***Gr.:*** Lomesone; ***Hong Kong:*** Perderm; ***Hung.:*** Perderm†; ***Indon.:*** Cloderm; Perderm; ***Irl.:*** Modrasone; ***Ital.:*** Legederm; ***Malaysia:*** Perderm†; ***Mex.:*** Logoderm; ***Neth.:*** Aclosone; ***NZ:*** Logoderm†; ***Port.:*** Miloderme; ***Rus.:*** Afloderm (Афлодерм); ***Singapore:*** Perderm†; ***Swed.:*** Legederm†; ***Switz.:*** Delonal†; ***UK:*** Modrasone; ***USA:*** Aclovate; ***Venez.:*** Demiderm.

Aldosterone *(BAN, rINN)*

Aldosteron; Aldosterona; Aldostérone; Aldosteroni; Aldosteronum; Electrocortin. 11β,18-Epoxy-18,21-dihydroxypregn-4-ene-3,20-dione.

Альдостерон

$C_{21}H_{28}O_5$ = 360.4.

CAS — 52-39-1.

ATC — H02AA01.

ATC Vet — QH02AA01.

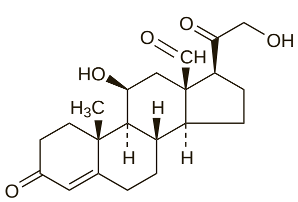

Adverse Effects

Aldosterone has very pronounced mineralocorticoid actions and little effect on carbohydrate metabolism. It may therefore exhibit the mineralocorticoid adverse effects described for the corticosteroids in general (p.1490).

Uses and Administration

Aldosterone is the main mineralocorticoid (p.1490) secreted by the adrenal cortex. It has no significant glucocorticoid (anti-inflammatory) properties.

Aldosterone has been given by intramuscular or intravenous injection, with a glucocorticoid, in the treatment of primary adrenocortical insufficiency (p.1498) but synthetic mineralocorticoids such as fludrocortisone (p.1530), which can be given orally, are usually preferred. It has also been used as the sodium succinate.

Amcinonide *(BAN, USAN, rINN)* ⊗

Amcinónida; Amcinonidum; Amcinopol; CL-34699. 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

Амцинонид

$C_{28}H_{35}FO_7$ = 502.6.

CAS — 51022-69-6.

ATC — D07AC11.

ATC Vet — QD07AC11.

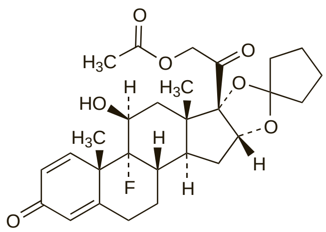

Pharmacopoeias. In *US.*

Profile

Amcinonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

USP 31: Amcinonide Cream; Amcinonide Ointment.

Proprietary Preparations (details are given in Part 3)
Belg.: Amicla; ***Canad.:*** Amcort; Cyclocort; ***Fr.:*** Penticort†; ***Ger.:*** Amciderm; ***Mex.:*** Visderm H; ***Thai.:*** Amciderm; Visderm†; ***USA:*** Cyclocort†.

Beclometasone Dipropionate

(BANM, rINNM) ⊗

Béclométasone, dipropionate de; Beclometasoni dipropionas; Beclometasoni Dipropionas; Beclomethasone Dipropionate *(USAN)*; Beklometasondipropionat; Beklometason-dipropionát; Beklometasonidipropionaatti; Beklometazon Dipropiyonat; Beklometazon-dipropriónát; Beklometazono dipropionatas; Beklometazonu dipropionian; 9α-Chloro-16β-methylprednisolone Dipropionate; Dipropionato de beclometasona; Sch-18020W. 9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

Беклометазона Дипропионат

$C_{28}H_{37}ClO_7$ = 521.0.

CAS — 4419-39-0 (beclometasone); 5534-09-8 (beclometasone dipropionate).

ATC — A07EA07; D07AC15; R01AD01; R03BA01.

ATC Vet — QA07EA07; QD07AC15; QR01AD01; QR03BA01.

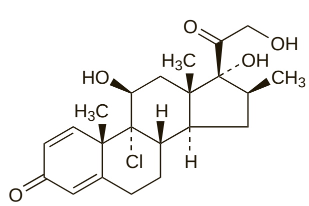

(beclometasone)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *Jpn. US* allows either the anhydrous or monohydrate form. *Eur.* also includes a separate monograph for the monohydrate.

Ph. Eur. 6.2 (Beclometasone Dipropionate, Anhydrous). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

Ph. Eur. 6.2 (Beclometasone Dipropionate Monohydrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 31 (Beclomethasone Dipropionate). It is anhydrous or contains one molecule of water of hydration. A white to cream white, odourless powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; very soluble in chloroform.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (p.1490).

Adrenal suppression may occur in some patients treated with high-dose long-term inhalation therapy for asthma. It has been stated that in the majority of patients no significant suppression is likely to occur when total daily doses of less than 1.5 mg are used (but see Adrenal Suppression, below).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Systemic absorption may also follow nasal use, particularly after high doses or prolonged treatment.

Adrenal suppression. The problem of adrenal suppression with corticosteroids is discussed on p.1491. Listed below are some references and correspondence concerning adrenal suppression due to beclometasone inhalation therapy,[1-8] in some cases occurring with doses below 1.5 mg daily.[6] However, one study found that function of the hypothalamic-pituitary-adrenal axis remained normal in most patients at beclometasone doses below 3 mg daily.[9]

1. Grant IWB, Crompton GK. Becloforte inhaler. *BMJ* 1983; **286:** 644–5.
2. Slessor IM. Becloforte inhaler. *BMJ* 1983; **286:** 645.
3. Ebden P, Davies BH. High-dose corticosteroid inhalers for asthma. *Lancet* 1984; **ii:** 576.
4. Law CM, *et al.* Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. *Lancet* 1986; **i:** 942–4.
5. Brown HM. Nocturnal adrenal suppression in children inhaling beclomethasone dipropionate. *Lancet* 1986; **i:** 1269.
6. Maxwell DL, Webb J. Adverse effects of inhaled corticosteroids. *BMJ* 1989; **298:** 827–8.
7. Priftis K, *et al.* Adrenal function in asthma. *Arch Dis Child* 1990; **65:** 838–40.
8. Tabachnik E, Zadik Z. Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. *J Pediatr* 1991; **118:** 294–7.
9. Brown PH, *et al.* Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax* 1993; **48:** 233–8.

Candidiasis. Results of a study involving 229 asthmatic children indicated that the presence of a sore throat or a hoarse voice was not related to the presence of *Candida* or to treatment with inhaled beclometasone.[1] The occurrence of only one clinical case of oral candidiasis in 129 of the children receiving beclometasone confirmed previous observations that it is an uncommon finding in children compared with the reported incidence of between 4.5 and 13% in adults. The incidence of colonisation with *Candida* was greater in those children who received corticosteroids than in those who did not but was not affected by either the dose or type of inhaler used.

1. Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986; **61:** 788–90.

Effects on the bones. The adverse effects of corticosteroids in general on bones are discussed on p.1491.

Studies in healthy subjects have shown that inhaled beclometasone dipropionate can suppress bone metabolism.[1-3] These studies measured biochemical markers such as serum-osteocalcin concentrations, serum alkaline phosphatase activity, and urinary hydroxyproline-creatinine ratio, over short periods of time. Another study found that markers of collagen turnover, but not osteocalcin, were reduced by beclometasone or budesonide 800 micrograms daily in mildly asthmatic children.[4] Results are difficult to interpret since osteocalcin concentrations are reduced in patients with asthma regardless of treatment,[5] and it is uncertain whether significant bone loss does occur in practice. One 12-month study[6] in adults with asthma found that biochemical markers showed suppressed bone formation from inhaled beclometasone, and that there was some loss of bone mineral density from the hip. This study also found that inhaled fluticasone, in equivalent therapeutic doses, may have less adverse effect on bone. Another, smaller, study[7] found no adverse effects from beclometasone or fluticasone on bone mass or metabolism. In a study[8] of asthmatic children, comparing those treated with inhaled budesonide with those who received no corticosteroids, an average daily dose of about 500 micrograms budesonide for 3 to 6 years did not adversely affect bone density and mineral measures.

1. Pouw EM, *et al.* Beclomethasone inhalation decreases serum osteocalcin concentrations. *BMJ* 1991; **302:** 627–8.

2. Ali N, *et al.* Beclomethasone and osteocalcin. *BMJ* 1991; **302:** 1080.
3. Teelucksingh S, *et al.* Inhaled corticosteroids, bone formation and osteocalcin. *Lancet* 1991; **338:** 60–1.
4. Birkebæk NH, *et al.* Bone and collagen turnover during treatment with inhaled dry powder budesonide and beclomethasone dipropionate. *Arch Dis Child* 1995; **73:** 524–7.
5. König P, *et al.* Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993; **122:** 219–26.
6. Pauwels RA, *et al.* Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. *Am J Respir Crit Care Med* 1998; **157:** 827–32.
7. Medici TC, *et al.* Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000; **55:** 375–82.
8. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998; **157:** 178–83.

Effects on growth. Meta-analysis of 3 eligible studies (out of 92 examined) concluded that inhaled beclometasone therapy at a dose of 400 micrograms daily may cause a 1.54 cm/year decrease in growth in children with mild to moderate asthma.[1] The long-term effects of treatment are unknown, and therefore it is not clear whether catch-up growth will occur on stopping therapy. The lowest possible dose of corticosteroid therapy should be used in asthma, and growth should be monitored.[1] There is also evidence[2] that long-term intranasal beclometasone for the treatment of allergic rhinitis can slow growth in children; the effect on final height is unknown. For further details of the effects of corticosteroids on growth, see p.1492.

1. Sharek PJ, *et al.* Beclomethasone for asthma in children: effects on linear growth. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).
2. Skoner DP, *et al.* Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Abstract: *Pediatrics* 2000; **105:** 415–16. Full version: http://pediatrics.aappublications.org/cgi/content/full/105/2/e23 (accessed 27/04/04)

Effects on the lungs. Pulmonary eosinophilia has occurred in patients treated with inhaled beclometasone.[1-4]

1. Paterson IC, *et al.* Pulmonary eosinophilia after substitution of aerosol for oral corticosteroid therapy. *Br J Dis Chest* 1975; **69:** 217–22.
2. Hudgel DW, Spector SL. Pulmonary infiltration with eosinophilia: recurrence in an asthmatic patient treated with beclomethasone dipropionate. *Chest* 1977; **72:** 359–60.
3. Klotz LR, *et al.* The use of beclomethasone dipropionate inhaler complicated by the development of an eosinophilic pneumonia reaction. *Ann Allergy* 1977; **39:** 133–6.
4. Mollura JL, *et al.* Pulmonary eosinophilia in a patient receiving beclomethasone dipropionate aerosol. *Ann Allergy* 1979; **42:** 326–9.

Hypersensitivity. There have been reports of asthmatic reactions to beclometasone dipropionate inhalations, possibly associated with materials used in their formulation, or with the containers.[1-4]

1. Maddern PJ, *et al*. Adverse reaction after aerosol inhalation. *Med J Aust* 1978; **1:** 274.
2. Godin J, Malo JL. Acute bronchoconstriction caused by Becovent and not Vanceril. *Clin Allergy* 1979; **9:** 585–9.
3. Clark RJ. Exacerbation of asthma after nebulised beclomethasone dipropionate. *Lancet* 1986; **ii:** 574–5.
4. Beasley R, *et al.* Benzalkonium chloride and bronchoconstriction. *Lancet* 1986; **ii:** 1227.

Reformulation. Reformulation of some metered-dose inhalers to use a chlorofluorocarbon (CFC)-free propellant has resulted in a change of efficacy. One CFC-free product (*Qvar, UK*) is reported to be effective at about half the dose[1] required with the standard product (see Uses and Administration, below) and the UK CSM has issued a reminder of the need for dosage reduction when converting from the conventional formulation to this product.[2] An open-label, crossover study in healthy subjects also found higher beclometasone plasma concentrations after use of another brand (*Beclozone, Eire*) of CFC-free product.[3] However, this dose reduction does not apply to all CFC-free formulations of beclometasone. A review[4] concluded that good studies on the bioequivalence between the reference beclometasone preparation and the newer CFC-free formulations are not available.

1. Davies RJ, *et al.* Hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol provides equivalent asthma control to chlorofluorocarbon beclomethasone dipropionate at approximately half the total daily dose. *Respir Med* 1998; **92** (suppl): 23–31.
2. CSM/MCA. Dose of CFC-free inhaled beclomethasone (Qvar). *Current Problems* 1999; **25:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 06/07/06)
3. Lipworth BJ, Jackson CM. Pharmacokinetics of chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclomethasone dipropionate. *Br J Clin Pharmacol* 1999; **48:** 866–8.
4. Derom E, Pauwels RA. Pharmacokinetic and pharmacodynamic properties of inhaled beclometasone dipropionate delivered via hydrofluoroalkane-containing devices. *Clin Pharmacokinet* 2005; **44:** 815–36.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495. Beclometasone is stated to be readily absorbed from sites of local application, and rapidly distributed to all body tissues. It is metabolised principally in the liver, but also in other tissues including gastrointestinal tract and lung; enzymatic hydrolysis rapidly produces the monopropionate (which has some glucocorticoid activity), and, more slowly, the free alcohol, which is virtually devoid of activity. Only a small proportion of an absorbed dose is excreted in urine, the remainder being excreted in the faeces mainly as metabolites.

Uses and Administration

Beclometasone dipropionate is a corticosteroid with mainly glucocorticoid activity (p.1490) that is stated to exert a topical effect on the lungs without significant systemic activity at recommended doses (but see Adrenal Suppression under Adverse Effects, above). It is used by inhalation, generally from a metered-dose aerosol, for the prophylaxis of asthma (see below).

Many formulations are now available, with differing dosage regimens, and the appropriate product literature should be consulted before starting therapy or changing to another formulation. Furthermore in the UK the doses of beclometasone dipropionate for asthma and rhinitis are expressed in units of 50 micrograms or multiples thereof (dose supplied into the mouthpiece per actuation) whereas in the USA the dose-unit is 42 micrograms or multiples thereof (dose emitted from the mouthpiece); recommended doses therefore appear somewhat lower in the USA than the UK doses given below, although in practical terms there is probably no difference.

In the UK the adult dosage of the **conventional aerosol** and some dry powder inhalers is usually 400 micrograms daily, inhaled in 2 to 4 divided doses for maintenance treatment; if necessary, 600 to 800 micrograms may be inhaled daily initially, subsequently adjusted according to the patient's response. In patients with severe asthma or in those showing only a partial response to standard inhalation doses, high-dose inhalation therapy may be considered; doses of 1 mg daily (250 micrograms four times daily or 500 micrograms twice daily) may be used and may be increased to 1.5 to 2 mg daily (500 micrograms three or four times daily) if necessary; a maximum of 2 mg daily should not be exceeded. In children, 50 or 100 micrograms may be inhaled 2 to 4 times daily according to the response or alternatively, 100 or 200 micrograms may be inhaled twice daily.

Although beclometasone dipropionate is generally inhaled in aerosol form, **inhalation capsules** or **discs** containing powder for inhalation are available for patients who experience difficulty in using the aerosol. Owing to differences in the relative bioavailability to the lungs a 100-microgram dose from an inhalation capsule or disc is approximately equivalent in activity to a 50-microgram dose from a conventional aerosol. Recommended maintenance doses of beclometasone dipropionate from inhalation capsules or discs are therefore *higher*: 200 micrograms inhaled 3 or 4 times daily or 400 micrograms inhaled twice daily for adults, and 100 micrograms inhaled 2 to 4 times daily or 200 micrograms inhaled twice daily for children. Up to 800 micrograms twice daily may be inhaled if necessary in adults requiring high-dose therapy.

In some countries beclometasone dipropionate is now available as a **CFC-free aerosol**. Because of changes in particle size the dose required from some such inhalers may be *lower* than that from a conventional aerosol: typical UK doses for one product (*Qvar*) range from 100 to 200 micrograms daily in mild asthma to 400 to 800 micrograms daily in severe asthma, given as 2 divided doses.

Inhalation of **nebulised** beclometasone dipropionate has also been used in the management of asthma in children.

Beclometasone dipropionate is also used as a **nasal spray** in the prophylaxis and treatment of allergic and non-allergic rhinitis (p.565). Usual doses are 100 micrograms in each nostril twice daily or 50 micrograms in each nostril 3 or 4 times daily; a total of 400 micrograms daily should not generally be exceeded. A dose of 50 micrograms in each nostril twice daily may be sufficient for prophylaxis. The nasal spray is also used to prevent recurrence of nasal polyps after surgical removal (p.1508).

Beclometasone dipropionate is also used **topically** in the treatment of various skin disorders. It is generally applied as a cream or ointment containing 0.025%. Beclometasone salicylate has also been used topically. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Adenoidal hypertrophy. Although normally managed by surgery (or if less severe simply by symptomatic relief) adenoidal hypertrophy in children was reported to respond to aqueous nasal beclometasone 336 micrograms daily in an 8-week crossover study.[1] Improvements in adenoidal obstruction and symptom scores were enhanced in a subsequent 16-week follow-on study using 168 micrograms daily. Another similar study,[2] of an initial 4-week crossover period followed by 24 weeks of open-label treatment, found symptomatic improvements in about half of the patients, and at 100 weeks there was a decrease in the rate of adenotonsillectomy in children who had responded to beclometasone compared with nonresponders.

1. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. *Pediatrics* 1995; **95:** 355–64.
2. Criscuoli G, *et al.* Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. Abstract: *Pediatrics* 2003; **111:** 663. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/3/e236 (accessed 27/04/04)

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (p.1108). Patients requiring only occasional relief from symptoms may be managed with an inhaled short-acting beta$_2$ agonist, and an inhaled corticosteroid such as beclometasone is added if symptomatic relief is needed more than once daily. In more severe asthma other drugs may be added (combination with a long-acting beta$_2$ agonist may have synergistic benefits), or the dose of inhaled corticosteroid may be increased.

High-dose regimens may pose problems of compliance if beclometasone must be inhaled several times daily. However, one study[1] found once-daily inhalation to be as effective as the same dose divided into 2 daily inhalations in short-term control of moderate asthma. Also there have been doubts that increasing the dose of inhaled beclometasone brings about increased benefits,[2] but guidelines and clinical practice suggest that improved control can often be achieved by increasing the dose. A systematic review[3] noted that while there was little evidence of an effect of dose titration above 400 micrograms daily in those with mild to moderate asthma, evidence was lacking in patients with more severe disease (who are more likely to be given high-dose therapy), and studies were needed to resolve the question.

Inhalation of beclometasone dipropionate as a nebulised solution has been found to be useful in the management of severe asthma in children aged 2 years or under previously unresponsive to other drugs.[4] Nebulised beclometasone dipropionate was also effective in the management of recurrent episodes of bronchopulmonary obstruction following bronchiolitis in children under 2 years of age.[5] However, in other reports nebulised beclometasone dipropionate, although more effective than saline in pre-school children, produced a response less than that usually observed with inhalation of beclometasone from an aerosol or capsules,[6] or no benefit at all.[7] This may have been due to beclometasone somehow failing to reach the lungs.[8] In pre-school children able to use a spacer device with a metered aerosol, intermittent therapy with high-dose beclometasone dipropionate, given at the first sign of symptoms, reduced the severity of acute episodic asthma.[9]

1. Gagnon M, *et al.* Comparative safety and efficacy of single or twice daily administration of inhaled beclomethasone in moderate asthma. *Chest* 1994; **105:** 1732–7.
2. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal axis. *Eur Respir J* 1994; **7:** 2179–84.
3. Adams NP, *et al.* Beclomethasone versus placebo for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 22/08/08).
4. Pedersen W, Prahl P. Jet-nebulized beclomethasone dipropionate in the management of bronchial asthma: topical steroids for asthmatic children younger than 4 years. *Allergy* 1987; **42:** 272–5.

5. Carlsen KH, *et al.* Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988; **63:** 1428–33.
6. Storr J, *et al.* Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986; **61:** 270–3.
7. Webb MSC, *et al.* Nebulised beclomethasone dipropionate suspension. *Arch Dis Child* 1986; **61:** 1108–10.
8. Clarke SW. Nebulised beclomethasone dipropionate suspension: commentary. *Arch Dis Child* 1986; **61:** 1110.
9. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; **65:** 407–10.

Chronic obstructive pulmonary disease. For discussion of the value of inhaled corticosteroids in chronic obstructive pulmonary disease, see p.1501.

Cough. In children with recurrent cough inhalation of beclometasone 200 micrograms twice daily from a conventional aerosol or salbutamol 200 micrograms twice daily had no effect on cough frequency or severity.[1] However, in another study of 200 adults, use of beclometasone, salbutamol, or sodium cromoglicate (all in aerosol formulation) given 15 minutes before anaesthesia, significantly decreased coughing caused by fentanyl when compared with placebo. Of the 50 patients given beclometasone, none experienced coughing.[2]

1. Chang AB, *et al.* A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch Dis Child* 1998; **79:** 6–11.
2. Agarwal A, *et al.* Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. *Can J Anesth* 2003; **50:** 297–300.

Graft-versus-host disease. Beclometasone is under investigation for its topical effect in the treatment of intestinal graft-versus-host disease (GVHD). A study[1] in patients with acute intestinal GVHD after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811) found that addition of oral beclometasone to prednisolone therapy was associated with a greater proportion of durable responses after 30 days. Repeated courses may be needed in some patients to achieve and maintain response, but prolonged therapy appears to be feasible.[2]

1. McDonald GB, *et al.* Oral beclomethasone dipropionate for treatment of intestinal graft-versus-host disease: a randomized, controlled trial. *Gastroenterology* 1998; **115:** 28–35.
2. Iyer RV, *et al.* Long-term use of oral beclomethasone dipropionate for the treatment of gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant* 2005; **11:** 587–92.

Inflammatory bowel disease. Beclometasone 500 micrograms given nightly as an enema was as effective as betamethasone 5 mg enemas in the treatment of acute attacks of distal ulcerative colitis.[1] Although betamethasone produced slightly superior histological improvement and faster disappearance of blood from the stools, systemic adverse effects observed with betamethasone therapy were absent in patients treated with beclometasone.

Comparisons of beclometasone dipropionate enemas (3 mg) with prednisolone sodium phosphate enemas[2] (30 mg) or mesalazine enemas[3] (1 g) found them to be equally effective. Treatment was well tolerated. Beclometasone dipropionate has also been investigated for the oral treatment of ulcerative colitis.[4,5]

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p.1697.

1. Halpern Z, *et al.* A controlled trial of beclomethasone versus betamethasone enemas in distal ulcerative colitis. *J Clin Gastroenterol* 1991; **13:** 38–41.
2. Campieri M, *et al.* Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. *Aliment Pharmacol Ther* 1998; **121:** 361–6.
3. Gionchetti P, *et al.* Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005; **39:** 291–7.
4. Rizzello F, *et al.* Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002; **16:** 1109–16.
5. Campieri M, *et al.* Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; **17:** 1471–80.

Preparations

BP 2008: Beclometasone Cream; Beclometasone Nasal Spray; Beclometasone Ointment; Beclometasone Powder for Inhalation; Beclometasone Pressurised Inhalation.

Proprietary Preparations (details are given in Part 3)
Arg.: Airbeclosona; Egosona†; Menaderm Simple; Propavent; Qvar†; Rectomenaderm; Rinosol; ***Austral.:*** Aldecin†; Becloforte†; Beconase; Beconase Hayfever; Becotide; Qvar; ***Austria:*** Aerocortin; Beclomet; Beconase; Becotide; Clenil; ***Belg.:*** Beclometatop; Beclophar; Beconase; Becotide†; Qvar; ***Braz.:*** Alerfin; Beclosol; Clenil; Miflasona; ***Canad.:*** Gen-Beclo; Propaderm; Qvar; Rivanase; ***Chile:*** Beclosema; Beclovent†; Beconase†; Destap; Filair; Flumates; Xiten†; ***Cz.:*** Aldecin; Beclazone†; Becloforte; Beclomet; Becodisks; Beconase; Becotide; Clenil; Ecobec; Miflason†; Nasobec; ***Denm.:*** AeroBec; Beclomet; Beconase; ***Fin.:*** AeroBec; Beclomet; Beclonasal; Beconase; Becotide†; ***Fr.:*** Asmabec; Beclo-Rhino; Beclojet; Beclone; Beclospin; Becotide; Bemedrex; Ecobec; Humex Rhume des Foins; Miflasone; Nexxair; Prolair; Qvar; Spir†; ***Ger.:*** AeroBec; Beclo; Beclo Sioz-wo†; Beclobreathe; Beclohexal; Beclomet; Beclorhinol; Becloturmant; Beconase Aquosum; Bronchocort; Junik; ratioAllerg; Rhinivict; Sanasthmax; Sanasthmyl; Ventolair; Viarox†; ***Gr.:*** Beclomet†; Becolex; Becotide†; Bidiclin; Clenil Forte Jet; Clenil Rino; Clenil†; Qvar; Respocort; Rinosol; ***Hong Kong:*** Aldecin†; Beclate; Beclazone; Beclo Asma†; Becloforte†; Becodisks; Beconase; Becotide; Cycloson; Nasobec; Qvar; ***Hung.:*** Aldecin†; Beclomet†; Beclonasal; Ecobec†; ***India:*** Beclate; ***Indon.:*** Beclomet; Beconase; Becotide; Cleniderm; ***Irl.:*** AeroBec†; Asmabec; Beclazone; Beclo-Rhino; Becodisks†; Beconase; Becotide; Nasobec; Qvar; ***Israel:*** Becloforte; Beconase†; Becotide†; Rhinocort; Viarex; ***Ital.:*** Becotide; Becotide A†; Bronco-Turbinal†; Clenil; Clenilexx; Clipper; Klostenal; Menaderm Simplex; Prontinal; Rino Clenil; Topster; Turbinal; ***Jpn:*** Propaderm; Rhinocort; Salcoat; ***Malaysia:*** Atomase†; Beclate; Beclazone; Becloforte†; Beclomet; Beconase; Becotide†; Clenil; Qvar; ***Mex.:*** Beclazone; Beconase; Becotide; Dobipro; Riferina; ***Neth.:*** AeroBec†; Aldecin; Beclodin; Becloforte; Beconase; Becotide; Clenil; Qvar; Viarin; ***Norw.:*** AeroBec; Beclomet; Becotide; ***NZ:*** Alanase; Atomase; Atomide†; Beclazone; Beconase Hayfever; Miflasone†; Qvar; Respocort; ***Philipp.:*** Qvar; ***Pol.:*** Becodisk; Cortare; Nasobec; ***Port.:*** Aldecina†; Beclotaide; Beconase; Clenil; Ecobec; ***Rus.:*** Aldecin (Альдецин); Beclazone (Беклазон); Becloforte (Беклофорте); Beclojet (Беклоджет); Becodisk (Бекодиск); Beconase (Беконазе)†; Becotide (Бекотид); Clenil (Кленил); Nasobec (Насобек); ***S.Afr.:*** AeroBec†; Anceron†; Beceze†; Beclate; Becloforte; Becodisks†; Beconase; Becotide; Clenil†; Cycloson†; Nobec†; Qvar; Ventnaze; Viarox†; ***Singapore:*** Atomase†; Beclazone†; Beclo Asma; Becloforte†; Beclomet; Becotide†; Clenil†; Decomit; Qvar†; Rino Clenil†; ***Spain:*** Asmabec†; Beclo Asma; Beclo Rino; Becloenema; Beclofort; Beclomet; Beclosona; Beconase; Becotide; Betsuril†; Broncivent†; Decasona†; Dereme; Menaderm Simple; Qvar†; Recto Menaderm NF; ***Swed.:*** AeroBec; Beclomet; Becotide; ***Switz.:*** AeroBec†; BECeco; Becloforte†; Beclomet†; Beclonarin; Becodisk; Beconase; Beconasol; Becotide†; ***Thai.:*** Atomase; Becloforte†; Beclomet; Becodisk†; Beconase; Becotide†; Bemase; Clenil; Rino Clenil; ***Turk.:*** Becloforte; Becodisks; Beklamet; Beklazon; Filair; ***UAE:*** Beclohale; ***UK:*** AeroBec; Asmabec; Beceze; Beclazone; Becloforte†; Beclogen; Becodisks; Beconase; Becotide†; Clenil; Clipper; Filair; Hayfever Relief; Nasal-Bec†; Nasobec; Pollenase Nasal; Propaderm†; Pulvinal Beclometasone Dipropionate; Qvar; Vivabec; ***USA:*** Beclovent; Beconase; Qvar; Vancenase†; ***Venez.:*** Aldecina†; Beclofortil; Beclomet†; Beclorino; Beclosil; Beconase; Biobeclasona; Biobeclod; Genbeclo; Nasair; Rinoclenil†.

Multi-ingredient: ***Arg.:*** Beclasma; Biotaer Gamma†; Biotaer Nebulizable; Butocort; Butosol; Menaderm N; Salbutol Beclo; Ventide; ***Austria:*** Ventide; ***Braz.:*** Aerotide; Clenil Compositum; ***Chile:*** Aero-Plus; Aerosoma; Asmavent-B; Beclasma†; Belomet; Broncoterol-B†; Butotal B; Herolan Aerosol; Ventide; ***Cz.:*** Clenigen†; Combair; Formodual; ***Fr.:*** Innovair; ***Hong Kong:*** Ventide; ***India:*** Aerocort; Anovate; Beclate-C; Beclate-N; Candibiotic; Candid B; Candiderma +; Candiderma†; Globen-G; Clocip B; Clocip NB; Cutinorm†; Ecodax†; NC-Derm; Otek-AC+; Pilovate; Sigmaderm; Stecort-NM; Translipo-Triple; ***Indon.:*** Ventide; ***Ital.:*** Clenil Compositum; Menaderm; Ventolin Flogo†; ***Mex.:*** Ventide; ***Philipp.:*** Candibec; ***Port.:*** Formodual; Foster; ***Rus.:*** Candibiotic (Кандибиотик); Candid B (Кандид Б); ***Singapore:*** Clenil Compositum†; Ventide†; ***Spain:*** Butosol; Menaderm Clio; Menaderm Neomicina; Menaderm Otologico; ***Thai.:*** Clenil Compositum; Ventide†; ***Turk.:*** Ventide; ***UK:*** Fostair; ***Venez.:*** Aerocort; Beclomet Compositum†; Beclosal; Butosol; Salbutide†; Venticort; Ventide.

Betamethasone *(BAN, USAN, rINN)* ⊗

Beetametasoni; Betadexamethasone; Betametason; Betametasona; Betametazon; Betametazonas; Betamethason; Bétaméthasone; Betamethasonum; Flubenisolone; Flubenisolonum; 9α-Fluoro-16β-methylprednisolone; β-Methasone; NSC-39470; Sch-4831. 9α-Fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione.

Бетаметазон

$C_{22}H_{29}FO_5$ = 392.5.

CAS — 378-44-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QD07XC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS01CB04; QS02BA07; QS03BA03.

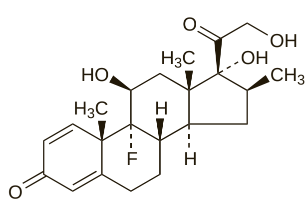

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Betamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 31 (Betamethasone). A white to practically white, odourless, crystalline powder. Soluble 1 in 5300 of water, 1 in 65 of alcohol, 1 in 15 of warm alcohol, 1 in 325 of chloroform, and 1 in 3 of methyl alcohol; sparingly soluble in acetone and in dioxan; very slightly soluble in ether. Store in airtight containers at a temperature between 2° and 30°.

Betamethasone Acetate *(BANM, rINNM)* ⊗

Acetato de betametasona; Beetametasoniasetaatti; Betametasonacetat; Betametazon Asetat; Betametazon-acetát; Betametazono acetatas; Betamethason-acetát; Bétaméthasone, acétate de; Betamethasoni acetas. Betamethasone 21-acetate.

Бетаметазона Ацетат

$C_{24}H_{31}FO_6$ = 434.5.

CAS — 987-24-6.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Betamethasone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane; freely soluble in acetone. It shows polymorphism. Protect from light.

USP 31 (Betamethasone Acetate). A white to creamy-white, odourless powder. Soluble 1 in 2000 of water, 1 in 9 of alcohol, and 1 in 16 of chloroform; freely soluble in acetone. Store in airtight containers at a temperature between 2° and 30°.

Betamethasone Benzoate *(BANM, USAN, rINNM)* ⊗

Benzoato de betametasona; Bétaméthasone, Benzoate de; Betamethasoni Benzoas; W-5975. Betamethasone 17α-benzoate.

Бетаметазона Бензоат

$C_{29}H_{33}FO_6$ = 496.6.

CAS — 22298-29-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

Pharmacopoeias. In *US.*

USP 31 (Betamethasone Benzoate). A white to practically white, practically odourless, powder. Insoluble in water; soluble in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers at a temperature between 2° and 30°.

Betamethasone Dipropionate

(BANM, USAN, rINNM) ⊗

Beetametasonidipropionaatti; Betametasondipropionat; Betametazon Dipropiyonat; Betametazon-dipropionát; Betametazono dipropionatas; Betametazonu dipropionian; Betamethason-dipropionát; Bétaméthasone, dipropionate de; Betamethasoni dipropionas; Dipropionato de betametasona; Sch-11460. Betamethasone 17α,21-dipropionate.

Бетаметазона Дипропионат

$C_{28}H_{37}FO_7$ = 504.6.

CAS — 5593-20-4.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

NOTE. Compounded preparations of betamethasone dipropionate may be represented by the following names:

- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Betamethasone Dipropionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 31 (Betamethasone Dipropionate). A white to cream-white, odourless powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Betamethasone Sodium Phosphate

(BANM, rINNM) ⊗

Beetametasoninatriumfosfaatti; Betametasonnatrifosfatum; Betametazon Disodyum Fosfat; Betametazon-nátrium-foszfát; Betametazono natrio fosfatas; Betamethasone Disodium Phosphate; Bétaméthasone, phosphate sodique de; Betamethason-fosfát sodná sůl; Betamethasoni natrii phosphas; Fosfato sódico de betametasona; Natrii Betamethasoni Phosphas. Betamethasone 21-(disodium phosphate).

Натрия Бетаметазона Фосфат

$C_{22}H_{28}FNa_2O_8P$ = 516.4.

CAS — 360-63-4 (betamethasone phosphate); 151-73-5 (betamethasone sodium phosphate).

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

NOTE. BET is a code approved by the BP 2008 for use on single unit doses of eye drops containing betamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Betamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.0. Store in airtight containers. Protect from light.

USP 31 (Betamethasone Sodium Phosphate). A white to practically white, odourless, hygroscopic, powder. Soluble 1 in 2 of water and 1 in 470 of alcohol; freely soluble in methyl alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers.

Betamethasone Valerate (*BANM, USAN, rINNM*) ⊗

Beetametasonivaleraatti; Betametasonvalerat; Betametazon Valerat; Betametazono valeratas; Betametazonu walerianian; Betametazon-valerát; Bétaméthasone, valérate de; Betamethasoni valeras; Betamethason-valerát; Valerato de betametasona. Betamethasone 17α-valerate.

Бетаметазона Валерат

$C_{27}H_{37}FO_6$ = 476.6.

CAS — 2152-44-5.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Betamethasone Valerate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 31 (Betamethasone Valerate). A white to practically white, odourless, powder. Practically insoluble in water; soluble 1 in 16 of alcohol, 1 in less than 10 of chloroform, and 1 in 400 of ether; freely soluble in acetone; slightly soluble in benzene. Store in airtight containers.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Betamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Anosmia. Complete anosmia was reported in 2 patients after the use of nasal drops containing betamethasone and neomycin sulfate[1] and, in one patient, showed no sign of resolving 1 year later. The reaction was thought to be due to the preservative thiomersal present in the drops, although it was noted that neomycin could exert a toxic effect on the olfactory mucosa and that there have been several reports of anosmia associated with the use of betamethasone alone.

1. Whittet HB, *et al.* Anosmia due to nasal administration of corticosteroid. *BMJ* 1991; **303:** 651.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495. Betamethasone crosses the placenta.

Uses and Administration

Betamethasone is a corticosteroid with mainly glucocorticoid activity (p.1490); the anti-inflammatory activity of 750 micrograms of betamethasone is equivalent to about 5 mg of prednisolone. It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p.1495), except adrenal-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. Its virtual lack of mineralocorticoid properties makes betamethasone particularly suitable for treating conditions in which water retention would be a disadvantage.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 1 mg of betamethasone:

- betamethasone acetate 1.1 mg
- betamethasone benzoate 1.3 mg
- betamethasone dipropionate 1.3 mg
- betamethasone sodium phosphate 1.3 mg
- betamethasone valerate 1.2 mg

When given orally betamethasone or betamethasone sodium phosphate are used; the usual dose, expressed in terms of betamethasone, ranges from 0.5 to 5 mg daily.

For parenteral use the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection in doses equivalent to 4 to 20 mg of betamethasone. It may also be given by local injection into soft tissues in doses equivalent to 4 to 8 mg of betamethasone. Doses in children, as a slow intravenous injection, are:

- infants aged up to 1 year: the equivalent of 1 mg of betamethasone
- 1 to 5 years: 2 mg
- 6 to 12 years: 4 mg

Doses may be repeated 3 or 4 times in 24 hours if necessary, depending on the condition being treated and the clinical response. The sodium phosphate ester is also sometimes used with the acetate or dipropionate esters, which have a slower and more prolonged action.

Betamethasone sodium phosphate is also used in the topical treatment of allergic and inflammatory conditions of the eyes, ears, or nose, usually as drops or ointment containing 0.1%.

For topical application in the treatment of various skin disorders the dipropionate and valerate esters of betamethasone are extensively used; the usual concentrations available are the equivalent of 0.05% of betamethasone as the dipropionate, and 0.025 or 0.1% as the valerate. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Betamethasone valerate has also been used by inhalation for the prophylaxis of asthma.

Other esters of betamethasone which have occasionally been used include the benzoate, butyrate propionate, phosphate, salicylate (cortobenzolone), and valeroacetate.

Betamethasone adamantoate has been used in veterinary practice.

Haemangioma. For reference to the use of a mixture of betamethasone and triamcinolone for the intralesional injection of haemangiomas, see p.1505.

Inflammatory bowel disease. For a comparison of betamethasone and beclometasone enemas in the treatment of ulcerative colitis, see under Beclometasone, p.1518. Corticosteroids are one of the mainstays of treatment of inflammatory bowel disease, the general management of which is discussed on p.1697.

Neonatal respiratory distress syndrome. For a discussion on the antenatal use of betamethasone to prevent neonatal respiratory distress syndrome, see p.1508.

Preparations

BP 2008: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Betamethasone Eye Drops; Betamethasone Injection; Betamethasone Sodium Phosphate Tablets; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Betamethasone Valerate Scalp Application;

USP 31: Betamethasone Benzoate Gel; Betamethasone Cream; Betamethasone Dipropionate Cream; Betamethasone Dipropionate Lotion; Betamethasone Dipropionate Ointment; Betamethasone Dipropionate Topical Aerosol; Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension; Betamethasone Sodium Phosphate Injection; Betamethasone Syrup; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Clotrimazole and Betamethasone Dipropionate Cream.

Proprietary Preparations (details are given in Part 3)

Arg.: Beta Adenil†; Betacort; Betasone-G; Betasone-G 12 Horas; Betatopic; Betnovate; Betnovate Capilar; Blacor; Butasona; Butasona RL; Celestone; Celestone Cronodose; Cevicort; Cevicort NC; Coid; Corteroid; Corteroid Retard; Cortiderma; Cortimar; Cronocorteroid; Cronolevel; Deltalaf; Dermizol; Difenac Forte; Diprocel†; Diprosone; Lazar-Cort; Maxisona†; Metamar; Micosep B; Quiacort; Transderma B; Valederm; ***Austral.:*** Antroquoril; Betnovate; Celestone Chronodose; Celestone M; Celestone V†; Cortival; Diprosone; Eleuphrat; ***Austria:*** Betnesol; Betnovate; Celestan; Diproderm; Diproforte; Diprophos; Solu-Celestan; ***Belg.:*** Betnelan-V; Celestone; Celestone Chronodose; Diprolene; Diprosone; ***Braz.:*** Alersan†; Beclonato; Benevat; Beta Long; Betaderm; Betametagen; Betaprospan; Betaspan; Betatrinta; Betnelan; Betnolon; Betnovate; Betrat B; Betrospam; Betsona; Celestan†; Celestone; Celestone Soluspan; Dermobet†; Dermonil†; Dermoval†; Dermovat†; Dibetam†; Diprobeta; Diprocort; Diprosen; Diprosone; Diprospan; Duoflam; Koide; Sensitex; Valbet; ***Canad.:*** Betaderm; Betaject; Betnesol; Celestoderm†; Celestone Soluspan; Diprolene Glycol; Diprosone; Prevex B; ratio-Ectosone; ratio-Topilene; ratio-Topisone; Taro-Sone; Topisone†; Valisone; ***Chile:*** Betnovate†; Cidoten; Cidoten Rapilento; Cidoten V; Coritex; Cremirit; Cronolevel; Dacam; Dacam RL; Diprolene; Diprospan; Disopranil; Konicortil; Labosona; Oftasona P; Spel; ***Cz.:*** Beloderm; Beta†; Betesil; Betnovate; Celestoderm-V†; Diprophos; Diprosone; Kuterid; ***Denm.:*** Betnovat; Bettamousse; Celeston; Diproderm; Diprolen; Diprospan; ***Fin.:*** Bemetson; Betapred; Betnovat; Bettamousse; Celestoderm; Celeston Chronodose; Diproderm; Diprolen; ***Fr.:*** Betesil; Betnesol; Betneval; Celestene; Celestene Chronodose; Celestoderm; Diprolene; Diprosone; ***Ger.:*** Bemon; Beta-Stulln†; Beta-Wolff†; BetaCreme; Betagalen; Betam-Ophtal†; BetaSalbe; Betnesalic mono; Betnesol; Betnesol-V; Celestamine N; Celestan Depot; Celestan solubile; Celestan-V; Cordes Beta; Deflatop; Diprosis; Diprosone; Diprosone Depot; Linola Cort Beta; Pentacort†; Soderm; ***Gr.:*** Betamatic†; Betnesol; Betnovate; Celestene; Celestoderm-V; Celestone; Celestone Chronodose; Flogozyme; Galinocort; Locason-N; Locason†; Movithiol; Osmoran; Propiochrone; Propioform; Sanorvil; ***Hong Kong:*** Betaderma; Betasone; Betazone; Betnovate; Celestoderm-V†; Celestone†; Derzid; Diprocel; Diprosone; Diprospan; Ectosone†; Synmethasone; ***Hung.:*** Betesil; Celestone†; Diprophos; ***India:*** Betafoam; Betnecip; Betnecort; Betnederm; Betnelan; Betnesol; Betnovate; Topicasone; Valbet; Walacort; ***Indon.:*** Benoson; Betam-Ophtal; Betason; Betnovate; Betodermin; Betopic; Celestoderm-V; Celestone; Corsaderm; Diprosone-OV; Exabet; Mesonta; Metonate; Molason; Oviskin; Proson; Scanderma; Skizon; Vason; ***Irl.:*** Betacap; Betnelan; Betnesol; Betnovate; Bettamousse; Diprosone; ***Israel:*** Betacorten; Betnesol; Betnovate; Bettamousse; Celestone Chronodose; Diprolene; Diprosone; Diprospan; ***Ital.:*** Beben; Bentelan; Beta 21; Betamesol; Betesil; Bettamousse; Celestoderm-V†; Celestone; Celestone Cronodose; Diprosone; Ecoval; ***Malaysia:*** Beavate; Beprogel; Beprosone; Besone; Beta; Betasone; Betnesol†; Betnosone; Betnovate; Bufencon; Celestoderm-V†; Celestone†; Daivobet; Dermasole DP†; Dermasole†; Dibetasol; Diprocel; Diprosone; Diprospan; Setrosone†; Uniflex†; ***Mex.:*** Betnovate; Celestoderm-V†; Celestone; Celestone Soluspan; Cronolevel; Dermoval; Diprofast; Dipronova; Diprosone; Diprospan; Disons Dex; Erispan; Reubaxona; ***Neth.:*** Betnelan; Betnesol; Celestoderm; Celestone; Celestone Chronodose; Diprolene; Diprosone; ***Norw.:*** Betnovat; Bettamousse; Celeston; Diproderm; ***NZ:*** Beta; Betnesol; Betnovate; Bivate; Celestone Chronodose; Diprolene; Diprosone; ***Philipp.:*** Beta; Betnelan; Betnovate; Celestone; Diprolene; Diprosone; Diprospan; Steroderm; ***Pol.:*** Celestone; Diprolene; Diprophos; Diprosone; Kuterid; ***Port.:*** Betnasol; Betnovate; Celesdepot; Celestone; Cilestoderme; Dibetop†; Diprofos; Diprosone; Soluderme; Vabeta; ***Rus.:*** Akriderm (Акридерм); Beloderm (Белодерм); Betasone (Бетазон); Celestoderm-V (Целестодерм-В); Diprospan (Дипроспан); ***S.Afr.:*** Betanoid; Betnesol; Betnovate; Celestoderm-V†; Celestone; Celestone Soluspan; Diprolene†; Diprosone; Lenasone; Lenovate; Persivate; Repivate; Steromien†; Topivate; ***Singapore:*** Beprogel; Beprosone; Besone; Betacorten; Betasone; Betnovate; Camnovate; Celestoderm-V†; Celestone†; Dermasone; Derzid; Dibetasol; Diprocel; Diprosone; Diprospan; Uniflex†; ***Spain:*** Betnovate; Bettamousse; Celestoderm; Celestoderm-V; Celestone; Celestone Cronodose; Diproderm; ***Swed.:*** Betapred; Betnovat; Bettamousse; Celeston; Celeston bifas; Celeston valerat; Diproderm; Diprolen; ***Switz.:*** Betnesol; Betnovate; Celestoderm-V; Celestone; Celestone Chronodose; Diprolene; Diprosone; ***Thai.:*** Bennasone†; Beprogel; Bepronate; Beprosone; Besone; Bessasone; Beta; Betameth; Bethasone; Betnovate; Betosone; Bipro; Clinivate; Derzid; Diprobet†; Diprosone; Diprospan; Diprotop; Polynovate; Prevex B†; Sebo; Valbet; Valerbet†; ***Turk.:*** Betnovate; Celestoderm-V; Celestone Chronodose; Diprolene; Diprospan; Seroderm; ***UAE:*** Betasone; ***UK:*** Betacap; Betnelan; Betnesol; Betnovate; Betnovate RD (Ready Diluted); Bettamousse; Diprosone; Vista-Methasone; ***USA:*** Alphatrex†; Beta-Val; Cel-U-Jec; Celestone; Celestone Soluspan; Diprolene; Diprosone; Luxiq; Maxivate; Teladar†; Valisone; ***Venez.:*** Beprospen; Betacort; Betaderm; Betagen; Betagen Solspen; Betnovate; Celestoderm; Celestone; Celestone Soluspan; Detarmon†; Diprocel; Diprosone; Diprospan; Itisona.

Multi-ingredient: ***Arg.:*** Adenil; Algio Nervomax Fuerte; Antiflogol; Antihemorroidal; Bacticort; Bacticort Complex; Becortin; Betacort Plus; Betametasona B12; Betasalic; Betasone-G Compuesto; Betnovate Antihemorroidal†; Betnovate-C; Betnovate-N; Blamy; Blokium B12; Calmurid; Celestamine; Celestamine-L; Cevaderm; Ciprocort L; Clarityne Cort; Confor-Tar†; Corteroid Gesic; Cortispec; Cortistamin L; Cortistamin NF†; Cuta Crema; Denvercrem; Dermizol G; Dermizol Trio; Dermosona; Dermovit†; Diclogesic Plus B12; Dioxaflex B12; Diprogenta; Diprosalic; Doxtran B12; Drum B; Eubetal Biotic†; Factor Dermico; Fucicort; Fusimed B; Gelbiotic Plus; Gentasol; Hifamonil Crema; Histamino Corteroid L; Ingemet; Lazar-Cort Complex; Lisaler Beta; Lotricomb; Macril; Maxisalic; Mencogrin; Micomazol B; Miklogen; Monizol Cort Crema; Negalerg†; Neo-Mudapenil†; Nularef Cort; Oxa B12; Procto-Metadyne; Quadriderm; Quiacort G; Quiacort G Plus; Rodinac B12; Salicort; Sinaler B; Sirotamicin BG; Sorsis Beta; Toflam; Tribiocort; Triliver; Triplex; Vesalion B12; Virobron B12 NF; Vitacortil; Vixidone LB; Xedenol B12; ***Austral.:*** Celestone VG†; Daivobet; ***Austria:*** Betnesol-N; Betnovate-C; Betnovate-N; Celestamin; Diprogenta; Diprosalic; Fucicort; Psorcutan Beta; ***Belg.:*** Betnelan-VC†; Diprophos; Diprosalic; Dovobet; Fucicort; Garasone†; Lotriderm; ***Braz.:*** Betaderm N; Betazol Cort; Betnovate-N; Betnovate-Q; Candicort; Celerg; Celestamil†; Celestamine; Celestrat; Celetil; Celocort; Cetobeta; Cetocort; Cetocorten; Cimecort; Cremederme; Daivobet; Dermosalic; Dextamine; Dipro AS; Diprogenta; Diprosalic; Emscort; Garasone; Gentacort; Histamed; Koide D; Lestamil; Microbiogen†; Naderm; Novacort; Oto Betnovate; Permut; Poliderms; Postec; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Reumix†; Tetraderm; Trok; Trok-N; Verutex B; ***Canad.:*** Diprogen†; Diprosalic; Dovobet; Garasone; Lotriderm; Pentasone; ratio-Topisalic; Valisone-G; ***Chile:*** B-Laboterol; Betnovate-N†; Cam; Celestamine; Cestop B†; Clofexan; Clotrimin-B; Cobefen; Contralmor; Creminem-B; Deucoaler; Diproquin; Diprosalic; Diprospan G; Donomix; Fucicort; Gentasone; Gotalgic; Labosalic; Labosona G; Labosona N†; Locrim; Lotriderm; Mixgen; Novadrel; Novarnela; Oftagen Compuesto; Oftasona N; Otandrol; Otazol†; Oticum; Otolisan; Plexus; Prodel B; Vilterm†; ***Cz.:*** Belogent; Belosalic; Betabioptal†; Daivobet; Diprosalic; Fucicort; Garasone; Lotriderm†; ***Denm.:*** Betnovat med Chinoform; Betnovat Rektal†; Celeston med Chinoform; Clotrason; Daivobet; Diprosalic; Fucicort; ***Fin.:*** Bemetson-K; Betnovat Comp†; Betnovat-C; Celestoderm cum Chinoform†; Celestoderm cum Garamycin; Daivobet; Diprosalic; Fucicort; ***Fr.:*** Betnesalic†; Betneval-Neomycine†; Celestamine; Daivobet; Diprosalic; Diprosept†; Diprosone Neomycine; Diprostene; ***Ger.:*** Betadermic; Betagentam; Betamethason comp; Betamethason Plus†; Celestamine†; Daivobet; Dermobeta†; Diprogenta; Diprosalic; Fucicort; Lotricomb; Lygal E Tinktur†; Psorcutan Beta; Soderm Plus; Sulmycin mit Celestan-V; Terracortril N; ***Gr.:*** Alpider; Befucil; Betacort; Betafusin; Betasid; Betfu; Betnovate-C; Betnovate-N; Celestoderm-V/GA; Dovobet; Fubecot; Fucicort; Fucicream; Fusibet; Garamat; Propiogenta; Propiosalic; Roseti; Sensibio; Staficort; ***Hong Kong:*** Allersan; Aristobet-N; Bechlomin; Beclomin†; Becogem; Betnesalic†; Betnovate-C†; Betnovate-N; Bonjedex; Celestamine; Celestoderm-V with Garamycin; Clobeta-G; Conazole; Daivobet; Dermafacte; Derzid-C; Derzid-N†; Dexmin†; Dextrosone; Diprogenta; Diprosalic; Fucicort; Garasone; Lozopin; Lycobeta-G; Quadriderm; Synbetamine; Triderm; ***Hung.:*** Daivobet; Diprosalic; Fucicort; Garasone; Gentason; Vipsogal†; ***India:*** Betamil-GM; Betamil-M; Betasalic; Betnederm C; Betnederm GM; Betnederm N; Betnesol-N; Betnesol-N Nasal; Betnor; Betnovate-C; Betnovate-GM; Betnovate-M; Betnovate-N; Betnovate-S; Fourderm; Fourderm AF; Genticyn B Eye/Ear†; Quiss; Supirocin-B; Surfaz-SN; Topicasone with Neomycin; Valbet; ***Indon.:*** Benoson G; Benoson M; Benoson N; Benoson V; Berloson-N; Betagentam; Betasin; Betason-N; Betnovate-N; Bevalex; Biocort; Celestamine; Celestoderm-V with Garamycin; Colergis; Daivobet; Digenta; Diprogenta; Diprosalic; Diprosta; Exabetin; Fucicort; Garasone; Heltiskin; Isotic Betaracin; Krimbeson; Lotriderm; Mastroson; Metaskin-N; Mytaderm; Nilacelin; Ocuson; Polacel; Proson N; Salgen Plus; Scanderma Plus; Skilone; Skinal; Sonigen; Tuderm-N; Zestam; ***Irl.:*** Betnesol-N; Betnovate-C; Betnovate-N; Diprosalic; Dovobet; Fucibet; Lotriderm; ***Israel:*** Betacorten-G; Betnesol-N; Betnovate-C; Betnovate-N; Clotrisone; Daivobet; Diprogenta; Diprosalic; Fucicort; Triderm; ***Ital.:*** Alfaflor; Batasalgin; Beben Clorossina; Betabioptal; Betacream; Betafloroto; Biorinil; Brumeton Colloidale S; Deltavagin; Dermabiolene; Dermatar; Diproform; Diprosalic; Dovobet; Ecoval con Neomicina; Egerian; Eubetal Antibiotico; Fidagenbeta; Fluororinil; Fucicort; Gentalyn Beta; Kamelyn; Micutrin Beta†; Psorinase†; Rinojet†; Sterozinil; Stranoval; Token; Visublefarite; Visumetazone Antibiotico; ***Malaysia:*** Axcel Fusi-Corte; B-Mycin; Beavate N; Beprogent; Beprosalic; Besone-N; Betacin; Betagen; Betamethasone Clo; Betamethasone G; Betamethasone N; Betamethasone SA; Betnesol-N†; Betnosone N; Betnovate-N; Celestoderm-V with Garamycin†; Diprogenta; Diprosalic; Fobancort; Fucicort; Fusidic B; Garasone; Joysun; Triderm-C; Uniflex-N†; ***Mex.:*** Artridol; Barmicil Compuesto; Beclogen; Betrigen; Celestamine NS; Celestamine-F†; Celestamine†; Claricort†; Clio-Betnovate; Clotricina; Daivobet; Diprosalic†; Diprosone G; Diprosone Y; Farmalor; Fucicort; Garamicina-V; Garasone; Gelmicin; Miclobet; Prubagen; Quadriderm NF; Tamex; Triderm; ***Neth.:*** Diprosalic; Dovobet; ***Norw.:*** Betnovat med Chinoform; Daivobet; Diprosalic; ***NZ:*** Betnesol Aqueous; Betnovate-C; Daivobet; Diprosalic†; Fucicort; Lotricomb†; ***Philipp.:*** Betneton; Betnovate-C; Betnovate-N; Celestamine; Claricort; Clotrasone; Daivobet; Diproform; Diprogenta; Diprosalic; Fucicort; Garasone; Hoebedic; Ophtasone; Quadriderm; Quadrotopic; Triderm; ***Pol.:*** Bedicort G; Betnovate-C; Betnovate-N; Daivobet; Diprogenta; Diprosalic; Lotriderm; Triderm; ***Port.:*** Beta-Micoter; Betnovate-C; Betnovate-N; Daivobet; Dibetop Q†; Diprogenta; Diprosalic; Epione; Flotiran; Fucicort; Psodermil; Quadriderme; ***Rus.:*** Akriderm Genta (Акридерм Гента); Akriderm GK (Акридерм ГК); Akriderm SK (Акридерм СК); Belogent (Белогент); Belosalic (Белосалик); Betagenot (Бетагенот); Celestoderm-V with Garamycin (Целестодерм-В с Гарамицином); Daivobet (Дайвобет); Diprosalic (Дипросалик); Fucicort (Фуцикорт); Triderm (Тридерм); ***S.Afr.:*** Betanoid N†; Betnesol-N; Betnovate-C; Betnovate-N; Celestamine; Celestoderm-V with Garamycin†; Diprogenta; Diprosalic; Garasone†; Lotriderm; Quadriderm; ***Singapore:*** B-Tasone-G; Beprogent; Beprosalic; Besone-N; Bufencon; Celestoderm-V with Garamycin†; Celestoderm-V with Neomycin†; Clotrasone†; Combiderm; Conazole; Daivobet; Dermanol-C; Diprogenta; Diprosalic; Fobancort; Fucicort; Garasone; Gentriderm; Gentrisone; Modaderm; Neoderm; Quadriderm†; Tri-Micon; Triderm; ***Spain:*** Alergical; Beta Micoter; Betamida†; Bronsal; Celesemine; Celestoderm Gentamicina; Celestone S; Clotrasone; Cuatroderm; Daivobet; Diprogenta; Diprosalic; Fucibet; Resorborina†; ***Swed.:*** Betnovat med Chinoform; Betnovat med Neomycin; Celeston valerat comp†; Celeston valerat med chinoform; Celeston valerat med gentamicin; Daivobet; Diprosalic; ***Switz.:*** Betnesalic; Betnovate-C; Betnovate-N; Celestamine; Daivobet; Diprogenta; Diprophos; Diprosalic; Fucicort; Ophtasone; Quadriderm; Triderm; ***Thai.:*** Bacda-B; Beprogent; Beprogenta; Beprolic; Besone-N; Beta-C; Beta-Dipo†; Beta-N; Beta-S; Betama-EN†; Betameth-N; Bethasone-N; Betnesalic†; Betnovate-C; Betnovate-N; Betosalic; Betosone-CE; Canasone†; Canazol-BE; Clinivate-N; Clotrasone†; Daivobet; Derzid-C; Derzid-N; Diprogenta†; Diprosalic; Fango-B; Fucicort; Fungiderm-B; Gynesten-B; Myda-B; Myrazole-B; Topaben-N; Twina; Valbet-N; ***Turk.:*** Betnovate-C; ***UAE:*** Futasone; Supraproct-S; ***UK:*** Betnesol-N; Betnovate-C; Betnovate-N; Diprosalic; Dovobet; Fucibet; Vipsogal; Vista-Methasone N; ***USA:*** Lotrisone; Taclonex; ***Venez.:*** Betaderm con Gentamicina; Celestamincort; Celestamine; Celestoderm con Gentalyn; Claricort; Diproformo; Diprogenta; Diprosalic; Garabet; Garasone; Lotricomb; Lotrisone; Propioformo†; Propiogenta†; Propiosalic†; Quadriderm; Triderm; Tridetarmon; Urisalic†; Vio Celestoderm†.

Budesonide *(BAN, USAN, rINN)* ⊗

Budesonid; Budesónida; Budésonide; Budesonidi; Budesonidum; Budezonid; Budezonidas; S-1320. An epimeric mixture of the α- and β-propyl forms of 16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

Будезонид

$C_{25}H_{34}O_6$ = 430.5.

CAS — 51333-22-3 (11β,16α); 51372-29-3 (11β,16α(R)); 51372-28-2 (11β,16α(S)).

ATC — A07EA06; D07AC09; H02AB16; R01AD05; R03BA02.

ATC Vet — QA07EA06; QD07AC09; QR01AD05; QR03BA02.

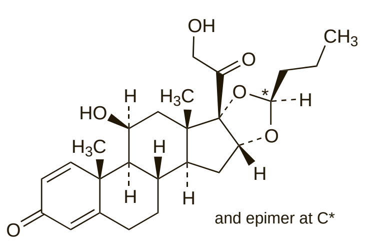

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Budesonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

USP 31 (Budesonide). A white to off-white, odourless, crystalline powder. Practically insoluble in water and in heptane; sparingly soluble in alcohol; freely soluble in chloroform. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Inhalation of high doses of budesonide is associated with some adrenal suppression. Systemic absorption may follow nasal use, particularly after high doses or prolonged treatment. The dose of oral budesonide may need to be reduced in hepatic impairment (see also Administration in Hepatic Impairment, below).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Effects on the bones. For mention of the effects of inhaled budesonide on markers of collagen turnover and bone density in asthmatic children, see under Adverse Effects of Beclometasone, p.1516. For the suggestion that inhalation once-daily in the morning may have less marked effects on growth and collagen turnover than twice-daily inhalation, see Administration, below.

Effects on the nervous system. Psychotic behaviour has been reported after use of inhaled budesonide.[1-3]

1. Lewis LD, Cochrane GM. Psychosis in a child inhaling budesonide. *Lancet* 1983; **ii:** 634.
2. Meyboom RHB, de Graff-Breederveld N. Budesonide and psychic side effects. *Ann Intern Med* 1988; **109:** 683.
3. Connett G, Lenney W. Inhaled budesonide and behavioural disturbances. *Lancet* 1991; **338:** 634–5.

Hypersensitivity. Contact dermatitis has been reported to topical or intranasal budesonide.[1] An anaphylactoid reaction occurred 5 minutes after the first dose of oral budesonide in a patient who had previously reacted in a similar way to mesalazine.[2]

1. Quintiliani R. Hypersensitivity and adverse reactions associated with the use of newer intranasal corticosteroids for allergic rhinitis. *Curr Ther Res* 1996; **57:** 478–88.
2. Heeringa M, *et al.* Anaphylactic-like reaction associated with oral budesonide. *BMJ* 2000; **321:** 927.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495. Budesonide is rapidly and almost completely absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone have less than 1% of the glucocorticoid activity of unchanged budesonide. Budesonide is reported to have a terminal half-life of about 2 to 4 hours.

◊ Reviews.

1. Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinet* 2001; **40:** 427–40.
2. Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin Pharmacokinet* 2004; **43:** 803–21.
3. Kraft WK, *et al.* The pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 67–72.
4. Lähelmä S, *et al.* Equivalent lung deposition of budesonide in vivo: a comparison of dry powder inhalers using a pharmacokinetic method. *Br J Clin Pharmacol* 2005; **59:** 167–73.

Uses and Administration

Budesonide is a corticosteroid with mainly glucocorticoid activity (p.1490). It is used by inhalation in the management of **asthma**, in usual doses of 400 micrograms daily in 2 divided doses from a metered-dose aerosol; in severe asthma the dosage may be increased up to a total of 1.6 mg daily, and guidelines for the management of asthma permit up to 2 mg daily (see p.1108). Maintenance doses may be less than 400 micrograms daily but should not be below 200 micrograms daily. A dose for children is 50 to 400 micrograms inhaled twice daily. Budesonide is also available for the management of asthma in the form of a dry powder inhaler; doses are 200 to 800 micrograms daily, as 2 divided doses or a single daily dose; up to 800 micrograms twice daily may be given to adults if necessary. Patients for whom budesonide from a pressurised inhaler or dry powder formulation is unsatisfactory may use a nebulised solution. The usual adult dosage by this method is 1 to 2 mg inhaled twice daily. This may be increased if asthma is severe. Maintenance doses are 0.5 to 1 mg inhaled twice daily. For children between 3 months and 12 years of age, an initial dose is 0.5 to 1 mg twice daily with a maintenance dose of 0.25 to 0.5 mg twice daily.

Budesonide is also given by inhalation as a nebulised solution in the management of childhood **croup** (p.1502). The usual dose is 2 mg, as a single inhaled dose or 2 doses of 1 mg, given 30 minutes apart.

Budesonide is used topically in the treatment of various **skin disorders**, as a cream, lotion, or ointment containing 0.025%. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Budesonide is also used intranasally for the prophylaxis and treatment of **rhinitis** (p.565). In the UK, two nasal spray preparations are available, one containing 100 micrograms per metered spray, and one containing 64 micrograms per metered spray. The initial recommended dose for adults and children over 12 years is either 2 sprays into each nostril once daily in the morning, or 1 spray into each nostril twice daily. This may be subsequently reduced to 1 spray into each nostril once daily; treatment can be continued for up to 3 months. In the USA and some other countries, a nasal spray and a nasal inhaler are available. The intranasal dose may be expressed in multiples of 32 micrograms, which is the quantity of budesonide delivered from the nasal adaptor. When given from a nasal inhaler, the recommended initial dose for adults and children over 6 years is 4 sprays into each nostril in the morning, or 2 sprays into each nostril twice daily, to give a total daily dose of 256 micrograms daily. This is reduced to the lowest dose adequate to control symptoms. If no benefit is seen after 3 weeks of treatment, budesonide should be stopped. When given as an aqueous nasal spray, the recommended initial dose for adults and children over 6 years is 1 spray into each nostril once daily (64 micrograms daily), increasing as necessary up to a maximum of 256 micrograms daily for adults and 128 micrograms daily for children aged less than 12 years. Budesonide is also used as a nasal spray in the management of **nasal polyps** (p.1508). In the UK, for adults and children over 12 years, 1 spray (containing 64 or 100 micrograms, as above) is given into each nostril twice daily for up to 3 months.

Local formulations of budesonide are used in the management of **inflammatory bowel disease** (see below). In mild to moderate Crohn's disease affecting the ileum or ascending colon it is given orally as modified-release capsules intended for a topical effect on the gastrointestinal tract. The recommended dose is 9 mg daily for active disease, as either a single dose before breakfast or in 3 divided doses about 30 minutes before meals, depending on the preparation. Treatment is given for up to 8 weeks, and the dosage should be reduced 2 to 4 weeks before discontinuing therapy. For recurring episodes of active Crohn's disease, an 8-week course may be repeated. After an 8-week course for active disease, budesonide 6 mg once daily is recommended for maintenance of clinical remission, for up to 3 months; thereafter, doses are tapered and therapy stopped, as continued treatment has not shown substantial clinical benefit. There is some absorption of budesonide from the gastrointestinal tract, and the dose may need to be reduced in patients with hepatic impairment, especially those with cirrhosis (see also Administration in Hepatic Impairment, below). Ulcerative colitis affecting the rectum and sigmoid colon may be treated locally with budesonide. A retention enema providing a dose of 2 mg in 100 mL is given daily at bedtime for 4 weeks, which may be extended to 8 weeks if the patient is not in remission after the initial 4-week course. Alternatively, a rectal foam can be used in a dose of 2 mg once daily, usually for 6 to 8 weeks. The dose may be given in the morning or the evening, but treatment is more effective if the bowel is emptied before a dose is given.

Local formulations of budesonide are also used in the management of **collagenous colitis** (see below). It is given orally as modified-release capsules in a dose of 3 mg three times daily for up to 8 weeks. The dosage should be reduced gradually during the last 2 weeks of therapy.

◊ General references.

1. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 1992; **44:** 375–407 and 1012.
2. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000; **60:** 1141–78.
3. Stanaland BE. Once-daily budesonide aqueous nasal spray for allergic rhinitis: a review. *Clin Ther* 2004; **26:** 473–92.

Administration. *INHALATIONAL ROUTE.* One study in 6 children aged up to 30 months found that about 75% of the nominal dose of nebulised budesonide was deposited in the nebuliser system,[1] while a study in 126 older children indicated that maintenance doses of budesonide could be halved when the dose was given by dry powder inhaler rather than nebuliser, without any loss of asthma control.[2] Although oropharyngeal deposition is thought to play a role in the systemic effects of inhaled corticosteroids, another study[3] indicated that only about 20% of the systemically available drug appeared to be derived from oropharyngeal deposition after inhalation from a dry powder inhaler.

There is evidence that the timing of inhaled therapy might influence some systemic effects. A study[4] in children with mild asthma found that 800 micrograms of budesonide inhaled in the morning had less effect on measurements of short-term growth and collagen turnover than inhalation of 400 micrograms twice daily.

1. Carlsen KCL, *et al.* How much nebulised budesonide reaches infants and toddlers? *Arch Dis Child* 1992; **67:** 1077–9.
2. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993; **69:** 130–3.
3. Pedersen S, *et al.* The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler. *Br J Clin Pharmacol* 1993; **36:** 211–14.
4. Heuck C, *et al.* Adverse effects of inhaled budesonide (800 micrograms) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. *J Pediatr* 1998; **133:** 608–12.

Administration in hepatic impairment. In a study[1] of patients with primary biliary cirrhosis the clearance of oral budesonide was significantly reduced in those with cirrhosis (stage IV) compared with milder disease (stage I/II). Elevated budesonide concentrations were sufficient to suppress cortisol production, and believed to be associated with the development of portal vein thrombosis in 2 cirrhotic patients.

1. Hempfling W, *et al.* Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. *Hepatology* 2003; **38:** 196–202.

Asthma. References to the use of budesonide in asthma.[1-7] Its use as a fixed-dose combination with formoterol has also been reviewed.[8,9]

1. Baker JW, *et al.* A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999; **103:** 414–21.
2. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343:** 1054–63.
3. Leflein JG, *et al.* Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. *Pediatrics* 2002; **109:** 866–72.
4. Pauwels RA, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; **361:** 1071–6.
5. FitzGerald JM, *et al.* Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004; **59:** 550–6.
6. Berger WE, *et al.* Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. *J Pediatr* 2005; **146:** 91–5.
7. Berger WE. Budesonide inhalation suspension for the treatment of asthma in infants and children. *Drugs* 2005; **65:** 1973–89.
8. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; **64:** 1597–1618.
9. O'Byrne PM, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; **171:** 129–36.

Chronic obstructive pulmonary disease. For discussion of the value of inhaled corticosteroids in chronic obstructive pulmonary disease, including reference to the use of budesonide, see p.1501. The use of a fixed-dose combination of budesonide and formoterol in chronic obstructive pulmonary disease has been reviewed.[1]

1. Reynolds NA, *et al.* Budesonide/formoterol: in chronic obstructive pulmonary disease. *Drugs* 2004; **64:** 431–41.

Collagenous colitis. Budesonide has been used in a few small controlled studies[1-5] of the management of collagenous colitis (see Microscopic Colitis, p.1700). Treatment courses given orally for 6 or 8 weeks were found to improve symptoms and histology, and the short-term benefits have been confirmed by meta-analysis,[6] although high rates of relapse after stopping treatment have been reported.[3,5]

1. Baert F, *et al.* Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002; **122:** 20–5.
2. Miehlke S, *et al.* Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002; **123:** 978–84.
3. Bonderup OK, *et al.* Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 2003; **52:** 248–51.
4. Madisch A, *et al.* Oral budesonide therapy improves quality of life in patients with collagenous colitis. *Int J Colorectal Dis* 2005; **20:** 312–16.
5. Miehlke S, *et al.* Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. *Aliment Pharmacol Ther* 2005; **22:** 1115–19.
6. Feyen B, *et al.* Meta-analysis: budesonide treatment for collagenous colitis. *Aliment Pharmacol Ther* 2004; **20:** 745–9.

Cystic fibrosis. Cystic fibrosis (p.166) is associated with bronchial hyper-responsiveness; a small study[1] has suggested that inhalation of budesonide 1.6 mg daily for 6 weeks improves hyper-responsiveness slightly and leads to improvement in cough and dyspnoea. A larger study[2] of budesonide given for two successive 3-month treatment periods found improved hyper-responsiveness and a trend towards slower decline in lung function.

1. Van Haren EHJ, *et al.* The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995; **89:** 209–14.
2. Bisgaard H, *et al.* Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med* 1997; **156:** 1190–6.

Inflammatory bowel disease. Budesonide has been given as an enema for the treatment of distal ulcerative colitis, in which context its potency and low systemic availability are advantageous.[1] A rectal foam has also been developed, which may be easier to use, and retain in the bowel, than an enema.[2] Budesonide is available as a modified-release oral dosage form for the management of active Crohn's disease.[1,3] Ileal-release preparations of budesonide have been indicated as first-line therapy in the treatment of mild to moderate ileal and right-sided colonic Crohn's disease.[4] Systematic review[5] has suggested that it is slightly less effective than conventional corticosteroid therapy, but is associated with fewer adverse effects. Budesonide has also been effective in delaying relapse in quiescent disease.[6-8] However, the benefit appears to be short-term (3 months)[4] and it has been concluded that oral modified-release budesonide is not effective in long-term (12 months) maintenance of remission.[4,9] Similarly, oral budesonide was ineffective in preventing postoperative recurrence after resection for Crohn's disease.[10]

For a discussion of inflammatory bowel disease, see p.1697.

1. Spencer CM, McTavish D. Budesonide: a review of its pharmacological properties and therapeutic efficacy in inflammatory bowel disease. *Drugs* 1995; **50:** 854–72.
2. Gross V, *et al.* Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; **23:** 303–12.
3. McKeage K, Goa KL. Budesonide (Entocort EC capsules): a review of its therapeutic use in the management of active Crohn's disease in adults. *Drugs* 2002; **62:** 2263–82.
4. Lichtenstein GR, *et al.* American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; **130:** 935–9. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508506000734.pdf (accessed 22/09/06)
5. Seow CH, *et al.* Budesonide for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 22/08/08).
6. Greenberg GR, *et al.* Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled dose-ranging study. *Gastroenterology* 1996; **110:** 45–51.
7. Löfberg R, *et al.* Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease: a placebo controlled one year study. *Gut* 1996; **39:** 82–6.
8. Gross V, *et al.* Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. *Gut* 1998; **42:** 493–6.
9. Simms L, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 12/05/05).
10. Hellers G, *et al.* Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. *Gastroenterology* 1999; **116:** 294–300.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aerovent; Airbude; Budefarma†; Budeson; Cuteral; Despex†; Entocort; Hypersol B; Inflammide; Infliplus; Kerpet†; Nastizol Hidrospray; Neumocort; Neumotex; Proetzonide; Pulmo Lisoflam; Rino-B; Spirocort; ***Austral.:*** Budamax; Entocort; Pulmicort; Rhinocort; ***Austria:*** Budiair; Budosan; Entocort; Miflonide; Novolizer; Pulmicort; Rhinocort; ***Belg.:*** Budenofalk; Docbudeso; Entocort; Merckrhinobudesonide; Miflonide; Pulmicort; Rhinocort; ***Braz.:*** Budecort; Budiair; Busonid; Entocort; Miflonide; Noex; Novopulmon†; Pulmicort; ***Canad.:*** Entocort; Pulmicort; Rhinocort; ***Chile:*** Aero-Bud; Aerovial; Budasmal; Budenofalk; Clebudan; Entocort†; Inflammide; Neumocort; Pulmicort; Rhinocort; ***Cz.:*** Apulein†; Budenofalk; Budiair; Easi-Cort†; Entocort; Giona; Inflammide†; Miflonid; Pulmax; Pulmicort; Rhinocort; Ribuspir; Tafen; Tinkair; ***Denm.:*** Budenofalk; Entocort; Giona; Miflonide; Pulairmax; Rhinocort; Rhinosol; Spirocort; ***Fin.:*** Budenofalk; Cortivent†; Entocort; Pulmicort; Rhinocort; ***Fr.:*** Entocort; Miflonil; Novopulmon; Pulmicort; Rafton; Rhinocort; ***Ger.:*** Aquacort; Benosid†; Budapp†; Budecort; Budefat†; Budenofalk; Budes; Budiair; Budon†; Entocort; Miflonide; Novopulmon; Pulmicort; Respicort†; ***Gr.:*** Arsicort; Astrocast; Aurid; Axelovert; Beysonit; Biosonide; Budecol; Budemar; Budenite; Budenofalk; Budeprol; Buderen; Budesan; Budesoderm; Budesonal; Budiair; Busonal; Butekont; Dedostryl; Dexalocal; Esonide; Etrafonil; Farlidone; Ixor; Lisobron; Lydenal†; Miflonide; Minalerg; Nalator; Obecirol; Obusonid; Olfosonide; Olyspal; Pimoftal†; Pulmicort; Pulmiver; Pulmovance; Resata; Rhinobros; Rhinoside; Ribuspir; Rinoster; Serbo; Sonidal; Talgan; Therasound; Udesogel; Udesospray; Velorium; Vericort; Vinecort; Zefecort; Zymacter; Zyolaif; Zytual; ***Hong Kong:*** Budenase; Budenofalk; Cycortide; Entocort; Pulmicort; Rhinocort; ***Hung.:*** Aerox; Apulein†; Budenofalk; Budesogen; Entocort; Miflonide; Neplit; Pulmax; Pulmicort; Rhinocort; ***India:*** Budecort†; Budenase†; Pulmicort; Rhinocort; ***Indon.:*** Budenofalk; Inflammide; Pulmicort; Rhinocort; ***Irl.:*** Budenofalk; Entocort; Pulmicort; Rhinocort; ***Israel:*** Budeson; Budicort; Entocort; Miflonide; Nasocort; Pulmotide†; ***Ital.:*** Aircort; Bidien; Desonax; Eltair; Enterocir†; Entocir; Kesol; Miflo; Miflonide; Preferid; Pulmaxan; Rhinocort; Spirocort; Xavin; ***Malaysia:*** Budecort; Budenase; Budiair; Butacort; Eltair; Giona; Inflammide; Pulmicort; Rhinocort; ***Mex.:*** Aerosial; Budosan; Entocort; Miflonide; Numark; Pulmicort; Rhinocort; ***Neth.:*** Budenofalk; Entocort; Pulmicort; Rhinocort; ***Norw.:*** Entocort; Giona; Pulmicort; Rhinocort; ***NZ:*** Butacort; Eltair; Entocort; Pulmicort; ***Philipp.:*** Asmavent; Budecort; Budenofalk; Primavent; ***Pol.:*** Budenofalk; Buderhin; Entocort; Horacort; Miflonide; Neplit; Pulmicort; Rhinocort; Tafen; ***Port.:*** Aeromax; Budo-san; Entocort; Miflonide; Neo Rinactive; Pulmax; Pulmicort; ***Rus.:*** Benacort (Бенакорт); Benarin (Бенарин); Pulmicort (Пульмикорт); Tafen (Тафен); ***S.Afr.:*** Budeflam; Entocord; Inflacor†; Inflammide; Inflanaze; Pulmicort; Rhinocort; ***Singapore:*** Budenofalk; Eltair; Entocort†; Esonide; Giona; Inflammide; Pulmicort; Rhinocort; ***Spain:*** Budenofalk; Demotest; Entocord; Miflonide; Neo Rinactive; Novopulm; Olfex; Pulmicort; Pulmictan; Rhinocort; Ribujet; ***Swed.:*** Budenofalk; Entocort; Giona; Pulmicort; Rhinocort; ***Switz.:*** Budenofalk; Cortinasal; Entocort; Miflonide; Pulmicort; Rhinocort; ***Thai.:*** Budecort; Bunase; Eltair; Giona; Inflammide†; Pulmicort; Rhinocort; ***Turk.:*** Budenofalk; Entocort; Inflacort; Miflonid; Pulmicort; Rhinocort; ***UAE:*** Sonidar; ***UK:*** Budenofalk; Entocort; Pulmicort; Rhinocort; ***USA:*** Entocort; Pulmicort; Rhinocort; ***Venez.:*** Biosonida; Bronklast; Budecort; Budenas; Miflonide; Pulmicort; Pulmolet; Rhinocort; Rinaqua†; Rinolet.

Multi-ingredient: ***Arg.:*** Neumoterol; Symbicort; ***Austral.:*** Symbicort; ***Austria:*** Symbicort; ***Belg.:*** Symbicort; ***Braz.:*** Alenia; Foraseq; Symbicort; ***Canad.:*** Symbicort; ***Chile:*** Symbicort; ***Cz.:*** Symbicort; ***Denm.:*** Symbicort; ***Fin.:*** Symbicort; ***Fr.:*** Symbicort; ***Ger.:*** Symbicort; ***Gr.:*** Symbicort; ***Hong Kong:*** Symbicort; ***Hung.:*** Symbicort; ***India:*** Budesal†; Foracort; ***Indon.:*** Symbicort; ***Irl.:*** Symbicort; ***Israel:*** Symbicort; ***Ital.:*** Assieme; Sinestic; Symbicort; ***Malaysia:*** Foracort; Symbicort; ***Mex.:*** Symbicort; ***Neth.:*** Assieme; Sinestic; Symbicort; ***Norw.:*** Symbicort; ***NZ:*** Symbicort; ***Philipp.:*** Symbicort; ***Pol.:*** Symbicort; ***Port.:*** Assieme; Symbicort; ***Rus.:*** Biasten (Биастен); Simbicort (Симбикорт); ***S.Afr.:*** Symbicord; ***Singapore:*** Symbicort; ***Spain:*** Rilast; Symbicort; ***Swed.:*** Symbicort; ***Switz.:*** Symbicort; ***Thai.:*** Symbicort; ***Turk.:*** Symbicort; ***UK:*** Symbicort; ***USA:*** Symbicort; ***Venez.:*** Foraseq; Symbicort.

Ciclesonide *(USAN, rINN)* ⊗

BY-9010; Ciclesonida; Ciclésonide; Ciclesonidum; RPR-251526. (*R*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate.

Циклезонид

$C_{32}H_{44}O_7$ = 540.7.

CAS — 126544-47-6; 141845-82-1.

ATC — R03BA08.

ATC Vet — QR03BA08.

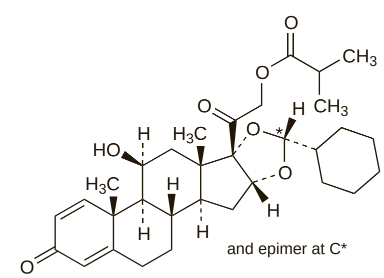

and epimer at C*

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Systemic absorption may follow inhalation of ciclesonide, particularly if high doses are used for prolonged periods.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495. Ciclesonide is hydrolysed to its biologically active metabolite by esterase enzymes in the lung and nasal mucosa; the systemic bioavailability for the active metabolite is reported to be more than 50% when ciclesonide is given by metered-dose inhaler.

Oral bioavailability is less than 1%. Ciclesonide and its active metabolite are extensively bound to plasma proteins. It is further metabolised to inactive metabolites via the cytochrome P450 isoenzyme CYP3A4. After oral or intravenous dosage, ciclesonide is mainly excreted via the faeces.

◊ References.

1. Rohatagi S, *et al.* Population pharmacokinetics and pharmacodynamics of ciclesonide. *J Clin Pharmacol* 2003; **43:** 365–78.
2. Nave R, *et al.* Pharmacokinetics of [C]ciclesonide after oral and intravenous administration to healthy subjects. *Clin Pharmacokinet* 2004; **43:** 479–86.
3. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. *J Clin Pharmacol* 2007; **47:** 782–9.

Uses and Administration

Ciclesonide is a corticosteroid with glucocorticoid activity (p.1490). It is used by inhalation in the management of asthma (p.1108) in adults and adolescents aged 12 years and older. The usual dose is 160 micrograms once daily from a metered-dose aerosol; the dose may be reduced to 80 micrograms once daily for maintenance. It is preferably given in the evening. Ciclesonide is given intranasally for the treatment of seasonal and perennial allergic rhinitis (p.565) in adults and adolescents 12 years of age and older; children 6 years of age and older may be treated for seasonal allergic rhinitis. A dose of 200 micrograms once daily is given as 2 sprays of 50 micrograms into each nostril.

◊ References.

1. Postma DS, *et al.* Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. *Eur Respir J* 2001; **17:** 1083–8.
2. Reynolds NA, Scott LJ. Ciclesonide. *Drugs* 2004; **64:** 511–19.
3. Christie P. Ciclesonide: a novel inhaled corticosteroid for asthma. *Drugs Today* 2004; **40:** 569–76.
4. Chapman KR, *et al.* Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. *Allergy* 2005; **60:** 330–7.
5. Dhillon S, Wagstaff AJ. Ciclesonide nasal spray: in allergic rhinitis. *Drugs* 2008; **68:** 875–83.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alvesco; Cicletex; ***Austral.:*** Alvesco; ***Braz.:*** Alvesco; ***Chile:*** Alvesco; ***Cz.:*** Alvesco; ***Gr.:*** Alvesco; Amavio; Freathe; ***Hong Kong:*** Alvesco; ***Hung.:*** Alvesco; ***India:*** Osonide; ***Irl.:*** Alvesco; ***Malaysia:*** Alvesco; ***Mex.:*** Alvesco; ***Neth.:*** Alvesco; ***Pol.:*** Alvesco; ***S.Afr.:*** Alvesco; ***UK:*** Alvesco; ***USA:*** Alvesco; Omnaris; ***Venez.:*** Alvesco.

Ciprocinonide *(USAN, rINN)* ⊗

Ciprocinonida; Ciprocinonidum; RS-2386. (6α,11β,16α)-21-[(cyclopropylcarbonyl)oxy]-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)-bis(oxy)]-pregna-1,4-diene-3,20-dione.

Ципроцинонид

$C_{28}H_{34}F_2O_7$ = 520.6.

CAS — 58524-83-7.

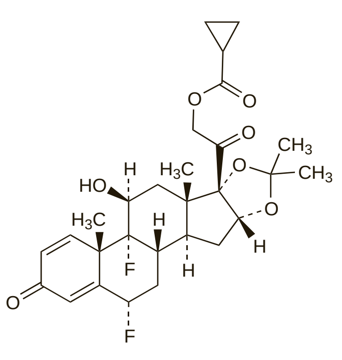

Profile

Ciprocinonide is a derivative of fluocinolone acetonide (p.1531) that has been applied topically with fluocinonide and procinonide in the management of various skin disorders.

Clobetasol Propionate *(BANM, USAN, rINNM)* ⊗

CCI-4725; Clobétasol, propionate de; Clobetasoli propionas; GR-2/925; Klobetasol-propionát; Klobetazol Propiyonat; Klobetazolu propionian; Propionato de clobetasol. 21-Chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

Клобетазола Пропионат

$C_{25}H_{32}ClFO_5$ = 467.0.

CAS — 25122-41-2 (clobetasol); 25122-46-7 (clobetasol propionate).

ATC — D07AD01.

ATC Vet — QD07AD01.

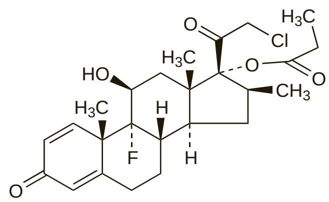

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Clobetasol Propionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 31 (Clobetasol Propionate). A white to cream crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone, in chloroform, in dimethyl sulfoxide, in dioxan, and in methyl alcohol; slightly soluble in benzene and in ether. Store in airtight containers. Protect from light.

Profile

Clobetasol propionate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, ointment, gel, scalp application, or foam containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

◊ References.

1. Campisi G, *et al.* A new delivery system of clobetasol-17-propionate (lipid-loaded microspheres 0.025%) compared with a conventional formulation (lipophilic ointment in a hydrophilic phase 0.025%) in topical treatment of atrophic/erosive oral lichen planus: a phase IV, randomized, observer-blinded, parallel group clinical trial. *Br J Dermatol* 2004; **150:** 984–90.
2. Jarratt M, *et al.* Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol* 2004; **3:** 367–73.
3. Reygagne P, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; **16:** 31–6.
4. Breneman D, *et al.* Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. *J Drugs Dermatol* 2005; **4:** 330–6.
5. Lowe N, *et al.* Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. *J Dermatol Treat* 2005; **16:** 158–64.
6. Reid DC, Kimball AB. Clobetasol propionate foam in the treatment of psoriasis. *Expert Opin Pharmacother* 2005; **6:** 1735–40.
7. Sanchez Regana M, *et al.* Treatment of nail psoriasis with 8% clobetasol nail lacquer: positive experience in 10 patients. *J Eur Acad Dermatol Venereol* 2005; **19:** 573–7.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154:** 139–45.
9. Vena GA, *et al.* Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006; **154:** 353–6.

Preparations

BP 2008: Clobetasol Cream; Clobetasol Ointment;
USP 31: Clobetasol Propionate Cream; Clobetasol Propionate Ointment; Clobetasol Propionate Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cantril†; Clobesol; Clobex; Dermaclob; Dermadex; Dermexane; Perfracort; Ribatra; Salac; ***Austria:*** Dermovate; ***Belg.:*** Dermovate; ***Braz.:*** Clob-X; Clobesol; Cortalen C; Dermacare; Propiosol; Psorex; Psorin; Therapsor; ***Canad.:*** Clobex; Dermasone†; Dermovate; ***Chile:*** Alticort; Clob-X; Clodavan; Cortopic; Dermovate; Koniderm; Lobevat†; Xinder; ***Cz.:*** Clobex; Dermovate; ***Denm.:*** Dermovat; ***Fin.:*** Dermovat; ***Fr.:*** Dermoval; ***Ger.:*** Clobegalen; Dermoxin; Dermoxinale; Karison; ***Gr.:*** Butavate; Clarelux; Rubocort; ***Hong Kong:*** Clobasol; Clobesol; Clobex; Dermasone†; Dermo; Dermovate; Dhabesol; Eurobetsol; Medodermone; Uniderm; ***Hung.:*** Closanasol; Dermovate; ***India:*** Cloderm; Lobate; Tenovate; Topifort; ***Indon.:*** Bersol; Closol; Dermovate; Elopro; Forderm; Ikaderm; Kloderma; Klonat; Lamodex; Lotasbat; Primaderm; Psoriderm; ***Irl.:*** Dermovate; ***Israel:*** Dermovate; ***Ital.:*** Clobesol; ***Malaysia:*** Betasol†; Clobet; Cloderm; Dermapro†; Dermosol; Dermovate; Dhabesol; Lobesol†; Uniderm; Univate†; ***Mex.:*** Clobesol; Dermatovate; Lobevat; ***Neth.:*** Clarelux; Clobex; Dermovate; Olux†; ***Norw.:*** Dermovat; ***NZ:*** Dermol; ***Philipp.:*** Clonate; Closderm; Dermovate; Glevate; ***Pol.:*** Clobederm; Dermklobal; Dermovate; Novate; ***Port.:*** Clarelux; Dermovate; Etrivex; ***Rus.:*** Dermovate (Дермовейт); ***S.Afr.:*** Dermovate; Dovate; Xenovate; ***Singapore:*** Clobeson†; Cloderm; Dermosol; Dermovate; Dhabesol; Medodermone; Powercort; Uniderm; Univate; ***Spain:*** Clovate; Decloban; ***Swed.:*** Dermovat; ***Switz.:*** Dermovate; ***Thai.:*** Betasol; Clinoderm; Clobasone; Clobet; Clobetate; Cloderm; Clonovate; Cotaso; Dermasil†; Dermovate; Medodermone†; P-Vate; Stivate; Uniderm; ***Turk.:*** Dermovate; Psoderm; Psovate; ***UAE:*** Gamavate; ***UK:*** Clarelux; Dermovate; Etrivex; ***USA:*** Clobex; Cormax; Embeline†; Olux; Temovate; ***Venez.:*** Dermovate.

Multi-ingredient: ***Arg.:*** Clobeplus; Clobesol LA; Dermadex NN; ***India:*** Cloderm GM; Lobate-G; Lobate-GM; Lobate-M; Tenovate G; Tenovate M; ***Philipp.:*** Dermovate-NN; ***Port.:*** Dermovate-NN†; ***Switz.:*** Dermovate-NN; ***UK:*** Dermovate-NN.

Clobetasone Butyrate *(BANM, USAN, rINNM)* ⊗

Butirato de clobetasona; CCI-5537; Clobétasone, butyrate de; Clobetasoni Butiras; Clobetasoni butyras; GR-2/1214; Klobetasonbutyrat; Klobetason-butyrát; Klobetasonibutyraatti; Klobetazon Bütirat; Klobetazon-butirát; Klobetazono butiratas. 21-Chloro-9α-fluoro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione 17-butyrate.

Клобетазона Бутират

$C_{26}H_{32}ClFO_5$ = 479.0.

CAS — 54063-32-0 (clobetasone); 25122-57-0 (clobetasone butyrate).

ATC — D07AB01; S01BA09.

ATC Vet — QD07AB01; QS01BA09.

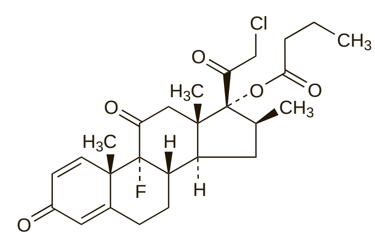

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clobetasone Butyrate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Profile

Clobetasone butyrate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Clobetasone butyrate is also used for inflammatory eye disorders, as eye drops containing 0.1%. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intraocular pressure and reduced visual function.

Preparations

BP 2008: Clobetasone Cream; Clobetasone Ointment.

Proprietary Preparations (details are given in Part 3)

Arg.: Eumovate; ***Austria:*** Emovate; ***Belg.:*** Eumovate; ***Braz.:*** Eumovate; ***Canad.:*** Eumovate; ***Chile:*** Eumovate†; ***Denm.:*** Emovat; ***Fin.:*** Emovat; ***Ger.:*** Emovate; ***Gr.:*** Rettavate; ***Hong Kong:*** Eumovate; ***India:*** Eumosone; ***Irl.:*** Eumovate; ***Israel:*** Eumovate; ***Ital.:*** Clobet; Eumovate; Visucloben; ***Malaysia:*** Cortoftal†; Eumovate; Euvaderm†; U-Closone; ***Neth.:*** Emovate; ***Norw.:*** Cloptison†; ***NZ:*** Eumovate; ***Port.:*** Emovate; ***S.Afr.:*** Eumovate; ***Singapore:*** Amisol; Eumovate; ***Spain:*** Cortoftal†; Emovate; ***Swed.:*** Emovat; ***Switz.:*** Emovate; ***Thai.:*** Eumovate†; ***Turk.:*** Eumovate; ***UK:*** Eumovate; ***Venez.:*** Eumovate.

Multi-ingredient: ***Arg.:*** Cloptison-N†; ***India:*** Eumosone-G; Eumosone-M; ***Israel:*** Cicloderm-C; ***Ital.:*** Visucloben Antibiotico; Visucloben Decongestionante; ***UK:*** Trimovate.

Clocortolone Pivalate (USAN, rINNM) ⊗

CL-68; Clocortolone, Pivalate de; Clocortoloni Pivalas; Pivalato de clocortolona; SH-863. 9α-Chloro-6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-pivalate.

Клокортолона Пивалат

$C_{27}H_{36}ClFO_5$ = 495.0.
CAS — 4828-27-7 (clocortolone); 34097-16-0 (clocortolone pivalate).
ATC — D07AB21.
ATC Vet — QD07AB21.

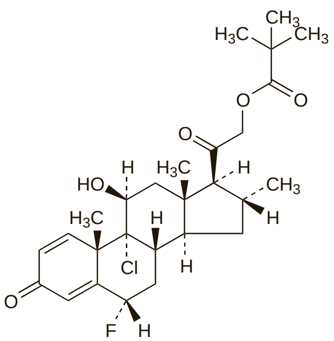

Pharmacopoeias. In *US.*

USP 31 (Clocortolone Pivalate). A white to yellowish-white, odourless powder. Sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform and in dioxan; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clocortolone pivalate is a corticosteroid used topically for its glucocorticoid activity (p.1490), as a 0.1% cream or ointment, in the treatment of various skin disorders. Clocortolone caproate has been used with the pivalate.

When applied topically, particularly to large areas, where the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

USP 31: Clocortolone Pivalate Cream.

Proprietary Preparations (details are given in Part 3)
Austria: Glimbal; ***Ger.:*** Kaban; Kabanimat; ***USA:*** Cloderm.

Multi-ingredient: ***Ger.:*** Corto-Tavegil†; Crino-Kaban N†; Procto-Kaban†.

Cloprednol (BAN, USAN, rINN) ⊗

Cloprednolum; RS-4691. 6-Chloro-11β,17α,21-trihydroxypregna-1,4,6-triene-3,20-dione.

Клопреднол

$C_{21}H_{25}ClO_5$ = 392.9.
CAS — 5251-34-3.
ATC — H02AB14.
ATC Vet — QH02AB14.

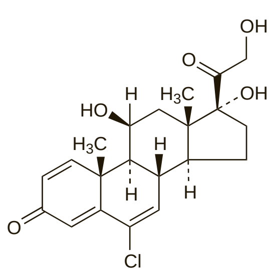

Profile

Cloprednol is a corticosteroid with mainly glucocorticoid activity (p.1490); the anti-inflammatory activity of 2.5 mg of clopredнol is equivalent to about 5 mg of prednisolone. Cloprednol is given orally in various disorders for which corticosteroid therapy is helpful (p.1495), in usual doses ranging from 1.25 to 12.5 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Syntestan.

Corticorelin (rINN) ⊗

Corticoliberin; Corticorelina; Corticoréline; Corticorelinum; Corticotrophin-releasing Hormone; Corticotropin-releasing Factor; CRF; CRH; HLC; Hormona liberadora de corticotropina.

Кортикорелин

$C_{208}H_{344}N_{60}O_{63}S_2$ = 4757.5 (human); $C_{205}H_{339}N_{59}O_{63}S$ = 4670.3 (ovine).
CAS — 86784-80-7 (corticorelin (human)); 79804-71-0 (corticorelin (ovine)).
ATC — V04CD04.
ATC Vet — QV04CD04.

Corticorelin Triflutate (rINNM) ⊗

Corticorelin Trifluoroacetate; Corticoréline, Triflutate de; Corticorelini Triflutas; Triflutato de corticorelina.

Кортикорелина Трифлутат

$C_{205}H_{339}N_{59}O_{63}S,xC_2HF_3O_2$ (ovine).
CAS — 121249-14-7 (corticorelin ovine triflutate).
ATC — V04CD04.
ATC Vet — QV04CD04.

NOTE. Corticorelin Ovine Triflutate is *USAN.*

Adverse Effects

Flushing of the face, neck, and upper chest, and mild dyspnoea may follow intravenous injection of corticorelin, and last for about 3 to 5 minutes. Prolonged flushing, tachycardia, hypotension, and chest tightness have been reported after large doses.

Effects on the cardiovascular system. Loss of consciousness, lasting for 10 seconds to 5 minutes, occurred in 3 patients, 2 of whom had Cushing's disease and one who had secondary adrenal insufficiency, after intravenous injection of corticorelin 200 micrograms.[1] The 2 patients with Cushing's disease had a slight accompanying fall in blood pressure. In a fourth patient, receiving corticosteroid and thyroid hormone replacement therapy, injection of corticorelin was associated with a sharp fall in systolic blood pressure and subsequent asystole. These serious adverse effects were not noted by others[2,3] and were variously attributed to impurities,[2] high dosage,[2] vasovagal syncope,[3] or to the fact that the corticorelin used in the study was of ovine rather than human origin.[3] The authors of the original study[1] have since stated[4] that lowering of the dose from 200 micrograms given intravenously over 10 seconds to 100 micrograms over 60 seconds has stopped serious adverse effects but that ovine corticorelin was still preferred because of its longer duration of action and lower incidence of hypotensive adverse effects. There has, however, been a further report of chest pain accompanied by a fall in blood pressure in a patient receiving corticorelin at a dose of 100 micrograms.[5]

1. Hermus A, *et al.* Serious reactions to corticotropin-releasing factor. *Lancet* 1983; **i:** 776.
2. Schulte HM, *et al.* Safety of corticotropin-releasing factor. *Lancet* 1983; **i:** 1222.
3. Oppermann D. Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1031–2.
4. Hermus ARMM, *et al.* Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; **ii:** 1032–3.
5. Paloma VC, *et al.* Chest pain after intravenous corticotropin-releasing hormone. *Lancet* 1989; **i:** 222.

Uses and Administration

Corticorelin is a polypeptide hypothalamic releasing hormone that stimulates the release of corticotropin (p.1523) from the anterior pituitary. It is used in the differential diagnosis of Cushing's syndrome (p.2344) and other adrenal disorders. Corticorelin is usually given as the triflutate, but doses are expressed in terms of corticorelin (human or ovine). A single dose of 100 micrograms, or of 1 microgram/kg, is given by intravenous injection over 30 seconds. Higher and more rapid doses have been used but may be associated with an increased risk of adverse effects (see above).

Corticorelin acetate is under investigation in cerebral oedema.

Administration. Corticorelin was well absorbed after subcutaneous injection and bioavailability was calculated to be about 60 to 70%; absorption was slower with high doses, suggesting that it may be a saturable process. Given the retention of bioactivity, the subcutaneous route was considered an attractive alternative to intravenous use.[1]

1. Angst MS, *et al.* Pharmacokinetics, cortisol release, and hemodynamics after intravenous and subcutaneous injection of human corticotropin-releasing factor in humans. *Clin Pharmacol Ther* 1998; **64:** 499–510.

Diagnosis and testing. Corticorelin may be used in the diagnosis of adrenal disorders including Cushing's syndrome (p.2344). In the initial diagnosis of Cushing's syndrome, a dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism in patients with mild hypercortisolism and equivocal results on other diagnostic tests. This combination is reportedly more accurate than either alone,[1] but it is cumbersome and difficult to carry out on an ambulatory basis.[2]

When a diagnosis of ACTH-dependent Cushing's syndrome has been established, corticorelin may be used for differential diagnosis of the subtype. Patients with pituitary Cushing's syndrome have an exaggerated increase in plasma-corticotropin and plasma-cortisol concentrations in response to corticorelin, whereas those with adrenal or ectopic syndrome generally have no response.[3,4] The corticorelin stimulation test is of comparable diagnostic efficacy to the dexamethasone suppression test,[5,6] although false results have been obtained with both tests.[2,5,7] Again, a combination of the dexamethasone and corticorelin tests is reportedly more accurate than either alone.[6] The most reliable test to distinguish between pituitary and nonpituitary forms of Cushing's syndrome is to measure the difference between central and peripheral concentrations of ACTH after giving corticorelin.[2] However, this requires sampling of central (petrosal) venous blood, an invasive procedure needing considerable expertise.

1. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269:** 2232–8.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
3. Chrousos GP, *et al.* The corticotropin-releasing factor stimulation test: an aid in the evaluation of patients with Cushing's syndrome. *N Engl J Med* 1984; **310:** 622–6.
4. Newell-Price J, *et al.* Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2002; **87:** 1640–5.
5. Hermus AR, *et al.* The corticotropin-releasing-hormone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. *Lancet* 1986; **ii:** 540–4.
6. Nieman LK, *et al.* The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **105:** 862–7.
7. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: CRH; ***Fr.:*** Stimu-ACTH; ***Ger.:*** Cortirel; CRH; ***Neth.:*** CRH; ***USA:*** Acthrel.

Corticotropin (BAN, rINN) ⊗

ACTH; Adrenocorticotrophic Hormone; Adrenocorticotrophin; Corticotrophin; Corticotropina; Corticotropine; Corticotropinum; Kortikotropiini; Kortikotropin.

Кортикотропин

CAS — 9002-60-2 (corticotropin); 9050-75-3 (corticotropin zinc hydroxide); 8049-55-6 (corticotropin zinc hydroxide).
ATC — H01AA01.
ATC Vet — QH01AA01.

Pharmacopoeias. In *US* as preparations for injection.

Units

5 units of porcine corticotropin for bioassay are contained in about 50 micrograms (with lactose 5 mg) in one ampoule of the third International Standard (1962).

Adverse Effects

Corticotropin stimulates the adrenals to produce cortisol (hydrocortisone) and mineralocorticoids; it therefore has the potential to produce similar adverse glucocorticoid and mineralocorticoid effects to those of the corticosteroids (see p.1490). In particular, its mineralocorticoid properties can produce marked sodium and water retention; considerable potassium loss may also occur.

Corticotropin can induce sensitisation, and severe hypersensitivity reactions, including anaphylaxis, may occur. This is generally considered to be due to the porcine component of the peptide.

Whereas corticosteroids replace endogenous cortisol (hydrocortisone) and thereby induce adrenal atrophy, corticotropin's stimulant effect induces hypertrophy. Nevertheless, the ability of the hypothalamic-pituitary-adrenal axis to respond to stress is still reduced, and abrupt withdrawal of corticotropin may result in symptoms of adrenal insufficiency (see Withdrawal, below).

◊ Reports of adverse effects in children given corticotropin for infantile spasms.

1. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980; **55:** 664–72.
2. Hanefeld F, *et al.* Renal and pancreatic calcification during treatment of infantile spasms with ACTH. *Lancet* 1984; **i:** 901.
3. Riikonen R, *et al.* Disturbed calcium and phosphate homeostasis during treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 671–6.
4. Perheentupa J, *et al.* Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; **61:** 750–3.

Withdrawal

Corticotropin use may depress the hypothalamic-pituitary-adrenal axis. Abrupt withdrawal of corticotropin may therefore produce adrenocortical and pituitary unresponsiveness, and therapy should be stopped gradually. An increase in corticosteroid requirements associated with the stress of infection, or accidental or surgical trauma, may also precipitate acute adrenocortical insufficiency. See also Withdrawal under Corticosteroids, p.1493.

Precautions

As for Corticosteroids, p.1493.

Phaeochromocytoma. A hypertensive crisis in a patient given intravenous tetracosactide led to the discovery of an adrenaline-secreting phaeochromocytoma in a patient.[1] It was suggested that caution should be observed when using corticotropin in patients with orthostatic hypotension in whom the diagnosis of phaeochromocytoma has not been excluded.

1. Jan T, *et al.* Epinephrine-producing pheochromocytoma with hypertensive crisis after corticotropin injection. *Am J Med* 1990; **89:** 824–5.

Interactions

Interactions seen with corticotropin are liable to be similar to those with corticosteroids (p.1494).

Uses and Administration

Corticotropin is a naturally occurring hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal glands to secrete adrenocortical hormones, especially cortisol (hydrocortisone), some mineralocorticoids such as corticosterone, and, to a lesser extent, androgens. It has little effect on aldosterone secretion, which proceeds independently.

Secretion of corticotropin by the functioning pituitary gland is controlled by the release of corticorelin from the hypothalamus and is also regulated by a negative feedback mechanism involving concentrations of circulating glucocorticoids. Conditions of stress may also stimulate secretion.

Corticotropin may be used diagnostically to investigate adrenocortical insufficiency. It has also been used therapeutically in most of the conditions (with the exception of the adrenal deficiency states and adrenocortical overactivity) for which systemic corticosteroid therapy is indicated (p.1495). Such use is now fairly limited. However, corticotropin may be used in certain neurological disorders such as infantile spasms and multiple sclerosis. The synthetic polypeptide tetracosactide (p.1543), which has the same amino-acid sequence as the first 24 residues of human corticotropin, may be used as an alternative. Tosactide is another polypeptide analogue of corticotropin; it has the same sequence as the first 28 residues.

Corticotropin has been available for injection in two forms. One form is a plain injection that may be given by the subcutaneous, intramuscular, or intravenous routes. The other form is a long-acting depot preparation in which the viscosity is increased by the addition of gelatin, and which is given subcutaneously or intramuscularly; it must not be given intravenously. Individual responses to therapeutic corticotropin vary considerably and doses must be adjusted accordingly.

For *diagnostic purposes* the corticotropin test is based on the measurement of plasma-cortisol concentrations before and after injection. The plain preparation is used in doses of 10 to 25 units in 500 mL of glucose 5% infused intravenously over 8 hours.

For *therapeutic purposes* typical initial doses for the depot preparation have been about 20 to 80 units every 24 to 72 hours by the subcutaneous or the intramuscular route. As soon as possible the dosage should be reduced gradually to the minimum necessary to control symptoms.

A depot preparation of corticotropin combined with zinc hydroxide for intramuscular injection has been used in the past.

Epilepsy. The use of corticotropin in the management of infantile spasms is referred to under Epilepsy in Corticosteroids, p.1503.

Multiple sclerosis. Short-term courses of corticotropin have been used to speed recovery from acute exacerbations of multiple sclerosis (p.892) but corticosteroids, usually methylprednisolone, are now preferred.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or tetracosactide, but a controlled study of tetracosactide use found no benefit (see p.1544).

Preparations

USP 31: Corticotropin for Injection; Corticotropin Injection; Corticotropin Zinc Hydroxide Injectable Suspension; Repository Corticotropin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Acthelea; ***Irl.:*** Acthar†; ***USA:*** Acthar.

Cortisone Acetate *(BANM, rINNM)* ⊗

Acetato de cortisona; Compound E Acetate; Cortisone, acétate de; Cortisoni acetas; 11-Dehydro-17-hydroxycorticosterone Acetate; Kortisonacetat; Kortison-acetát; Kortisoniasetaatti; Kortizon-acetát; Kortizono acetatas; Kortyzonu octan. 17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-acetate.

Кортизона Ацетат

$C_{23}H_{30}O_6$ = 402.5.
CAS — 53-06-5 (cortisone); 50-04-4 (cortisone acetate).
ATC — H02AB10; S01BA03.
ATC Vet — QH02AB10; QS01BA03.

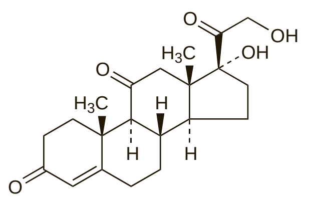

(cortisone)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Cortisone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; freely soluble in dichloromethane; soluble in dioxan. Protect from light.

USP 31 (Cortisone Acetate). A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 350 of alcohol, 1 in 75 of acetone, 1 in 4 of chloroform, and 1 in 30 of dioxan. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Cortisone acetate is readily absorbed from the gastrointestinal tract and the cortisone is rapidly converted in the liver to its active metabolite, hydrocortisone (cortisol). The biological half-life of cortisone itself is only about 30 minutes. Absorption of cortisone acetate from intramuscular sites is considerably slower than after oral doses.

Uses and Administration

Cortisone is a corticosteroid secreted by the adrenal cortex. It has glucocorticoid activity (p.1490), as well as appreciable mineralocorticoid activity; 25 mg of cortisone acetate is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

Cortisone acetate is rapidly effective when given orally, and more slowly by intramuscular injection.

Cortisone acetate has been used mainly for replacement therapy in adrenocortical insufficiency (p.1498), but hydrocortisone (p.1535) is generally preferred since cortisone itself is inactive and must be converted by the liver to hydrocortisone, its active metabolite; hence, in some liver disorders the activity of cortisone may be less reliable. Doses of cortisone acetate for oral replacement therapy are 12.5 to 37.5 mg daily in divided doses, with fludrocortisone if additional mineralocorticoid activity is required.

Cortisone acetate has been used in the treatment of many of the allergic and inflammatory disorders for which corticosteroid therapy is helpful (p.1495) but prednisolone or other synthetic glucocorticoids are generally preferred. Doses of cortisone acetate employed have generally ranged from about 25 to 300 mg daily by mouth or by intramuscular injection.

Preparations

BP 2008: Cortisone Tablets;
USP 31: Cortisone Acetate Injectable Suspension; Cortisone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Cortate; ***Belg.:*** Adreson†; ***Canad.:*** Cortone†; ***Ital.:*** Cortone; ***Neth.:*** Adreson†; ***S.Afr.:*** Cortogen†; ***UK:*** Cortisyl; ***USA:*** Cortone.

Multi-ingredient: ***Braz.:*** Corciclen; ***Spain:*** Blefarida; Gingilone.

Cortivazol *(USAN, pINN)* ⊗

Cortivazolum; H-3625; MK-650; NSC-80998. 11β,17α,21-Trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-c]pyrazol-20-one 21-acetate.

Кортивазол

$C_{32}H_{38}N_2O_5$ = 530.7.
CAS — 1110-40-3.
ATC — H02AB17.
ATC Vet — QH02AB17.

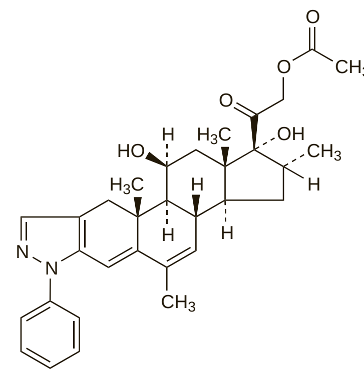

Profile

Cortivazol is a corticosteroid with mainly glucocorticoid activity (p.1490); 300 micrograms of cortivazol is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is given in the treatment of musculoskeletal and joint disorders by intra-articular, periarticular, or epidural injection in doses of about 1.25 to 3.75 mg, according to the size of the joint, usually at intervals of 1 to 3 weeks. It has also been given by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Altim.

Deflazacort *(BAN, USAN, rINN)* ⊗

Azacort; Deflatsakorti; Déflazacort; Deflazacortum; Deflazakort; DL-458-IT; L-5458; MDL-458; Oxazacort. 11β,21-Dihydroxy-2′-methyl-5′β*H*-pregna-1,4-dieno[17,16-*d*]oxazole-3,20-dione 21-acetate.

Дефлазакорт

$C_{25}H_{31}NO_6$ = 441.5.
CAS — 14484-47-0.
ATC — H02AB13.
ATC Vet — QH02AB13.

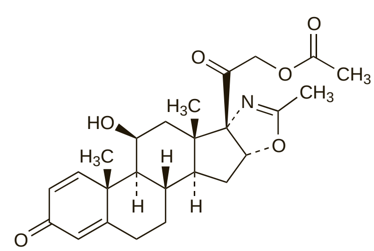

Profile

Deflazacort is a corticosteroid with mainly glucocorticoid activity (p.1490); 6 mg of deflazacort is reportedly equivalent in anti-inflammatory activity to about 5 mg of prednisolone (but see Action, below).

Deflazacort is used for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy (p.1495). It is given in initial oral doses of up to 120 mg daily; usual maintenance doses are 3 to 18 mg daily. Doses of 0.25 to 1.5 mg/kg daily have been used in children.

◊ References.

1. Markham A, Bryson HM. Deflazacort: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; **50:** 317–33.
2. Mignogna MD, *et al.* Oral pemphigus: long term behaviour and clinical response to treatment with deflazacort in sixteen cases. *J Oral Pathol Med* 2000; **29:** 145–52.
3. Campbell C, Jacob P. Deflazacort for the treatment of Duchenne dystrophy: a systematic review. *BMC Neurol* 2003; **3:** 7. Available at: http://www.biomedcentral.com/1471-2377/3/7 (accessed 20/06/06)
4. Biggar WD, *et al.* Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscul Disord* 2006; **16:** 249–55.

Action. Although it has been suggested that deflazacort produces fewer adverse effects than some conventional corticosteroids such as prednisolone, a study in healthy subjects found that the ratio of efficacy for deflazacort compared with prednisolone was higher than the 1.2 : 1 previously assumed,[1] implying that lower effective doses of deflazacort had been used in such comparisons. A review[2] of clinical studies of patients treated with deflazacort concluded that it was slightly less potent than prednisolone, and that many of the data on adverse effects were inconsistent. All systemic corticosteroids may produce clinically significant adverse reactions (see also p.1490) which are primarily dependent on dose and duration of use.

1. Babadjanova G, *et al.* Comparison of the pharmacodynamic effects of deflazacort and prednisolone in healthy subjects. *Eur J Clin Pharmacol* 1996; **51:** 53–7.
2. Anonymous. Deflazacort – an alternative to prednisolone? *Drug Ther Bull* 1999; **37:** 57–8.

Renal calculi. Deflazacort has been given with nifedipine to ease the spontaneous passage of renal calculi and stone fragments (see Renal Calculi under Nifedipine, p.1356).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Azacortid; Defas; Flamirex; ***Braz.:*** Calcort; Cortax; Deflaimmun; Deflanil; Denacen; Flaz-Cort; Flazal; ***Chile:*** Azacortid; Dezartal; ***Ger.:*** Calcort; ***Irl.:*** Calcort; ***Ital.:*** Deflan; Flantadin; ***Mex.:*** Calcort; Setatrep; ***Port.:*** Rosilan; ***Spain:*** Dezacor; Tobolacer; Zamene; ***Switz.:*** Calcort; ***Turk.:*** Flantadin; ***UK:*** Calcort; ***Venez.:*** Calcort.

Deprodone *(BAN, rINN)* ⊗

Deprodona; Déprodone; Deprodonum; Desolone; RD-20000 (propionate). 11β,17α-Dihydroxypregna-1,4-diene-3,20-dione.

Депродон

$C_{21}H_{28}O_4$ = 344.4.
CAS — 20423-99-8 (deprodone); 20424-00-4 (deprodone propionate).

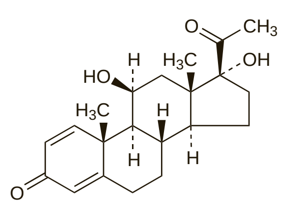

Profile

Deprodone is a corticosteroid that has been used topically as the propionate.

Desonide *(BAN, USAN, rINN)* ⊗

D-2083; Desfluorotriamcinolone Acetonide; Desonid; Desonida; Désonide; Desonidi; Desonidum; 16-Hydroxyprednisolone 16,17-Acetonide; Prednacinolone Acetonide. 11β,21-Dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

Дезонид

$C_{24}H_{32}O_6$ = 416.5.
CAS — 638-94-8.
ATC — D07AB08; S01BA11.
ATC Vet — QD07AB08; QS01BA11.

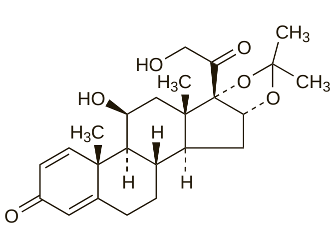

Profile

Desonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, ointment, or lotion containing 0.05%. The pivalate and the sodium phosphate esters have also been used.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Desoplus; DesOwen; Esteronide†; Locatop; Prenacid†; ***Austral.:*** DesOwen; ***Belg.:*** Sterax†; ***Braz.:*** Desonol; DesOwen†; Steronide†; ***Canad.:*** Desocort; ***Chile:*** DesOwen; Sterax†; ***Cz.:*** Locatop; ***Fin.:*** Apolar; ***Fr.:*** Locapred; Locatop; Tridesonit; ***Hong Kong:*** DesOwen; ***India:*** DesOwen; ***Indon.:*** Apolar; Dermades; Dermanide; Desolex; Nufapolar; ***Israel:*** Locatop; ***Ital.:*** Prenacid; Reticus; Sterades; ***Mex.:*** DesOwen; ***Norw.:*** Apolar; ***NZ:*** DesOwen†; ***Philipp.:*** DesOwen; ***Pol.:*** Locatop; ***Port.:*** Locapred; Zotinar; ***Rus.:*** Prenacid (Пренацид); ***Singapore:*** DesOwen; ***Swed.:*** Apolar†; ***Switz.:*** Locapred; Locatop; Sterax†; ***Turk.:*** Prenacid; ***USA:*** DesOwen; LoKara; Tridesilon†; Verdeso; ***Venez.:*** Dermosupril; DesOwen; Erilon.

Multi-ingredient: ***Fr.:*** Cirkan a la Prednacinolone; ***Indon.:*** Apolar-N; Desolex-N; ***Norw.:*** Apolar med dekvalin; ***Port.:*** Zotinar-N; ***USA:*** Tridesilon†; ***Venez.:*** Dermosupril C.

Desoximetasone *(BAN, USAN, rINN)* ⊗

A-41-304; Desoksimetasoni; Desoximetason; Desoximetasona; Désoximétasone; Desoximetasonum; Desoxymethasone; Hoe-304; R-2113. 9α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Дезоксиметазон

$C_{22}H_{29}FO_4$ = 376.5.
CAS — 382-67-2.
ATC — D07AC03.
ATC Vet — QD07AC03; QD07XC02.

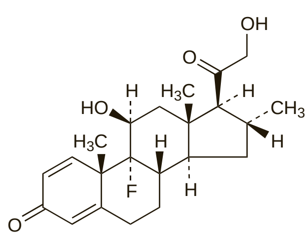

Pharmacopoeias. In *US.*

USP 31 (Desoximetasone). A white to practically white, odourless, crystalline powder. Insoluble in water; freely soluble in alcohol, in acetone, and in chloroform.

Profile

Desoximetasone is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, or ointment; concentrations used range from 0.05 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Adverse effects. A photosensitivity reaction occurred in a patient treated for psoriasis with topical desoximetasone; rechallenge led to a recurrence.[1] The patient was also receiving propranolol hydrochloride.

1. Stierstorfer MB, Baughman RD. Photosensitivity to desoximetasone emollient cream. *Arch Dermatol* 1988; **124:** 1870–1.

Preparations

USP 31: Desoximetasone Cream; Desoximetasone Gel; Desoximetasone Ointment.

Proprietary Preparations (details are given in Part 3)

Austria: Topisolon; ***Braz.:*** Esperson; ***Canad.:*** Desoxi†; Topicort; ***Denm.:*** Ibaril; ***Fin.:*** Ibaril; ***Ger.:*** Topisolon; ***Indon.:*** Dercason; Desomex; Dexocort; Esperson; Inerson; Lerskin; Pyderma; Soderma; Topcort; ***Irl.:*** Topisolon†; ***Israel:*** Desicort; ***Ital.:*** Flubason; ***Neth.:*** Ibaril; Topicorte; ***Norw.:*** Ibaril; ***Spain:*** Flubason; ***Swed.:*** Ibaril†; ***Switz.:*** Topisolon; ***Thai.:*** Cendexsone; Esperson; Topicorte; ***UK:*** Stiedex LP†; ***USA:*** Topicort.

Multi-ingredient: ***Austria:*** Topisolon mit Salicylsaure; ***Braz.:*** Esperson N; ***Denm.:*** Ibaril med salicylsyre†; ***Ger.:*** Topisolon†; ***Indon.:*** Denomix; ***Norw.:*** Ibaril med salicylsyre†; ***Swed.:*** Ibaril med salicylsyra†; ***Thai.:*** Topifram; ***UK:*** Stiedex†.

Desoxycortone *(BAN, rINN)*

Decortone; Deoxycortone; Desoksikortoni; Desoxicortona; Desoxikorton; Desoxycorticosterone; Désoxycortone; Desoxycortonum. 21-Hydroxypregn-4-ene-3,20-dione.

Дезоксикортон

$C_{21}H_{30}O_2$ = 314.5.
CAS — 64-85-7.
ATC — H02AA03.
ATC Vet — QH02AA03.

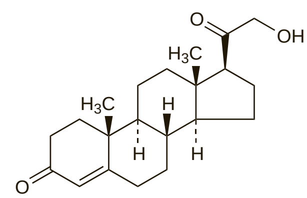

Desoxycortone Acetate *(BANM, rINNM)*

Acetato de desoxicortona; Cortin; Decortone Acetate; 11-Deoxycorticosterone Acetate; Deoxycortone Acetate; Desoksikortoniasetaatti; Desoxikortonacetat; Desoxycorticosterone Acetate; Désoxycortone, acétate de; Desoxycortoni acetas; Desoxykorton-acetát; Dezoksikortono acetatas; Dezoksykortonu octan; Dezoxikorton-acetát. Desoxycortone 21-acetate.

Дезоксикортона Ацетат

$C_{23}H_{32}O_4$ = 372.5.
CAS — 56-47-3.
ATC — H02AA03.
ATC Vet — QH02AA03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Desoxycortone Acetate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; slightly soluble in propylene glycol and in fatty oils. Protect from light.

USP 31 (Desoxycorticosterone Acetate). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in dioxan; slightly soluble in vegetable oils. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Desoxycortone Pivalate *(BANM, rINNM)*

Deoxycorticosterone Pivalate; Deoxycorticosterone Trimethylacetate; Deoxycortone Pivalate; Deoxycortone Trimethylacetate; Desoxycorticosterone Pivalate; Desoxycorticosterone Trimethylacetate; Désoxycortone, Pivalate de; Desoxycortoni Pivalas; Pivalato de desoxicortona. Desoxycortone 21-pivalate.

Дезоксикортона Пивалат

$C_{26}H_{38}O_4$ = 414.6.
CAS — 808-48-0.
ATC — H02AA03.
ATC Vet — QH02AA03.

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Desoxycorticosterone Pivalate). Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Desoxycortone is a corticosteroid secreted by the adrenal cortex and has primarily mineralocorticoid activity (p.1490). It has no significant glucocorticoid action.

Desoxycortone acetate has been used in the treatment of adrenocortical insufficiency (p.1498) as an adjunct to cortisone or hydrocortisone. For this purpose, however, fludrocortisone given orally is now usually preferred.

Desoxycortone acetate is given by intramuscular injection as an oily solution, in doses of up to 10 mg once or twice daily.

Desoxycortone has also been used as its enantate, phenylpropionate, and sodium hemisuccinate esters. Desoxycortone pivalate is used in veterinary medicine.

Preparations

USP 31: Desoxycorticosterone Acetate Injection; Desoxycorticosterone Acetate Pellets.

Proprietary Preparations (details are given in Part 3)

Fr.: Syncortyl; ***Ital.:*** Cortiron; ***Switz.:*** Cortisteron.

Dexamethasone *(BAN, rINN)* ⊗

Deksametasoni; Deksametazon; Deksametazonas; Desamethasone; Dexametason; Dexametasona; Dexametasone; Dexametazon; Dexamethason; Dexaméthasone; Dexamethasonum; 9α-Fluoro-16α-methylprednisolone; Hexadecadrol. 9α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Дексаметазон

$C_{22}H_{29}FO_5$ = 392.5.

CAS — 50-02-2.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QD07XB05; QD10AA03; QH02AB02; QR01AD03; QS01BA01; QS01CB01; QS02BA06; QS03BA01.

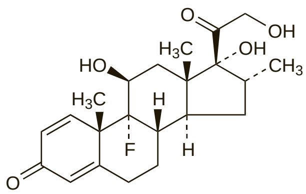

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Dexamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Protect from light.

USP 31 (Dexamethasone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, in dioxan, and in methyl alcohol; slightly soluble in chloroform; very slightly soluble in ether.

Dexamethasone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de dexametasona; Deksametasoniasetaatti; Deksametazono acetatas; Dexametasonacetat; Dexametazon-acetát; Dexamethason-acetát; Dexaméthasone, acétate de; Dexamethasoni acetas. Dexamethasone 21-acetate.

Дексаметазона Ацетат

$C_{24}H_{31}FO_6$ = 434.5.

CAS — 1177-87-3 (anhydrous dexamethasone acetate); 55812-90-3 (dexamethasone acetate monohydrate).

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Viet.*

Int. and *US* allow the anhydrous form or the monohydrate.

Ph. Eur. 6.2 (Dexamethasone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol and in acetone; slightly soluble in dichloromethane. Protect from light.

USP 31 (Dexamethasone Acetate). It contains one molecule of water of hydration or is anhydrous. A clear, white to off-white, odourless powder. Practically insoluble in water; freely soluble in acetone, in dioxan, and in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Dexamethasone Isonicotinate *(BANM, rINNM)* ⊗

Deksametasoniisonikotinaatti; Deksametazonu izonikotynian; Dexametasonisonikotinat; Dexaméthasone, isonicotinate de; Dexamethasoni isonicotinas; Dexamethason-isonikotinát; Isonicotinato de dexametasona. Dexamethasone 21-isonicotinate.

Дексаметазона Изоникотинат

$C_{28}H_{32}FNO_6$ = 497.6.

CAS — 2265-64-7.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dexamethasone Isonicotinate). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone.

Dexamethasone Phosphate *(BANM, rINNM)* ⊗

Dexaméthasone, Phosphate de; Dexamethasoni Phosphas; Fosfato de dexametasona. Dexamethasone 21-(dihydrogen phosphate).

Дексаметазона Фосфат

$C_{22}H_{30}FO_8P$ = 472.4.

CAS — 312-93-6.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

Dexamethasone Sodium Metasulfobenzoate *(rINNM)* ⊗

Dexaméthasone Métasulfobenzoate Sodique; Dexamethasone Sodium Metasulphobenzoate *(BANM)*; Metasulfobenzoato sódico de dexametasona; Natrii Dexamethasoni Metasulfobenzoas. Dexamethasone 21-(sodium *m*-sulphobenzoate).

Натрий Метасульфобензоат Дексаметазон

$C_{29}H_{32}FNaO_9S$ = 598.6.

CAS — 3936-02-5.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

Dexamethasone Sodium Phosphate *(BANM, rINNM)* ⊗

Deksametasoninatriumfosfaatti; Deksametazon Sodyum Fosfat; Deksametazono natrio fosfatas; Dexametasonnatriumfosfat; Dexametazon-nátrium-foszfát; Dexaméthasone, phosphate sodique de; Dexamethasone Phosphate Sodium; Dexamethason-fosfát sodná sůl; Dexamethasoni natrii phosphas; Fosfato sódico de dexametasona; Natrii Dexamethasoni Phosphas; Sodium Dexamethasone Phosphate. Dexamethasone 21-(disodium orthophosphate).

Натрия Дексаметазона Фосфат

$C_{22}H_{28}FNa_2O_8P$ = 516.4.

CAS — 2392-39-4.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

NOTE. DSP is a code approved by the BP 2008 for use on single unit doses of eye drops containing dexamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Dexamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.5. Store in airtight containers. Protect from light.

USP 31 (Dexamethasone Sodium Phosphate). A white or slightly yellow, crystalline powder. Is odourless or has a slight odour of alcohol, and is exceedingly hygroscopic. Soluble 1 in 2 of water; slightly soluble in alcohol; insoluble in chloroform and in ether; very slightly soluble in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Dexamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on the neonate. The adverse effects of corticosteroids on the fetus are discussed under Pregnancy on p.1494.

Adverse effects noted in premature neonates with bronchopulmonary dysplasia (p.1500) receiving dexamethasone treatment to enable weaning from assisted ventilation have included hypertension[1-4] often accompanied by bradycardia,[1,2] gastroduodenal perforation,[4-6] ulceration and thinning of the gastric wall,[5] development of a catabolic state,[4,7] renal calcification,[8,9] and transient myocardial hypertrophy.[10-13] There is some evidence of a suppressive effect on motor activity and spontaneous movement.[14] It has been postulated that neonatal dexamethasone may both increase[15] and decrease[16] retinopathy of prematurity; its true effect is uncertain.[17]

There is also a concern that longer term development of the child may be adversely affected.[18,19] Although data are scanty, a meta-analysis[20] has concluded that postnatal use of corticosteroids to treat or prevent bronchopulmonary dysplasia is associated with dramatic increases in the incidence of cerebral palsy and neurodevelopmental impairment, and suggested that such use should be abandoned.

Pulsed dosage may reduce the adverse effects but may also reduce efficacy.[21]

1. Ohlsson A, Heyman E. Dexamethasone-induced bradycardia. *Lancet* 1988; **ii:** 1074.
2. Puntis JWL, *et al.* Dexamethasone-induced bradycardia. *Lancet* 1988; **ii:** 1372.
3. Marinelli KA, *et al.* Effects of dexamethasone on blood pressure in premature infants with bronchopulmonary dysplasia. *J Pediatr* 1997; **130:** 594–602.
4. Stark AR, *et al.* Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 95–101.
5. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66:** 1164–6.
6. Smith H, Sinha S. Gastrointestinal complications associated with dexamethasone treatment. *Arch Dis Child* 1992; **67:** 667.
7. Macdonald PD, *et al.* A catabolic state in dexamethasone treatment of bronchopulmonary dysplasia. *Arch Dis Child* 1990; **65:** 560–1.
8. Kamitsuka MD, Peloquin D. Renal calcification after dexamethasone in infants with bronchopulmonary dysplasia. *Lancet* 1991; **337:** 626.
9. Narendra A, *et al.* Nephrocalcinosis in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F207–F213.
10. Werner JC, *et al.* Hypertrophic cardiomyopathy associated with dexamethasone therapy for bronchopulmonary dysplasia. *J Pediatr* 1992; **120:** 286–91.
11. Bensky AS, *et al.* Cardiac effects of dexamethasone in very low birth weight infants. *Pediatrics* 1996; **97:** 818–21.
12. Skelton R, *et al.* Cardiac effects of short course dexamethasone in preterm infants. *Arch Dis Child* 1998; **78:** F133–F137.
13. Zecca E, *et al.* Cardiac adverse effects of early dexamethasone treatment in preterm infants: a randomized clinical trial. *J Clin Pharmacol* 2001; **41:** 1075–81.
14. Bos AF, *et al.* Qualitative assessment of general movements in high-risk preterm infants with chronic lung-disease requiring dexamethasone therapy. *J Pediatr* 1998; **132:** 300–6.
15. Batton DG, *et al.* Severe retinopathy of prematurity and steroid exposure. *Pediatrics* 1992; **90:** 534–6.
16. Sobel DB, Philip AGS. Prolonged dexamethasone therapy reduces the incidence of cryotherapy for retinopathy of prematurity in infants of less than 1 kilogram birth weight with bronchopulmonary dysplasia. *Pediatrics* 1992; **90:** 529–33.
17. Ehrenkranz RA. Steroids, chronic lung disease, and retinopathy of prematurity. *Pediatrics* 1992; **90:** 646–7.
18. Greenough A. Gains and losses from dexamethasone for neonatal chronic lung disease. *Lancet* 1998; **352:** 835–6.
19. Shinwell ES, *et al.* Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed* 2000; **83:** F177–F181.
20. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr* 2001; **1:** 1. Available at: http://www.biomedcentral.com/1471-2431/1/1 (accessed 27/04/04)
21. Bloomfield FH, *et al.* Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial. *J Pediatr* 1998; **133:** 395–400.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with the intravenous use of dexamethasone sodium phosphate (see p.1492).

Interactions

The interactions of corticosteroids in general are described on p.1494. Various drugs may interfere with the dexamethasone suppression test.

Antiepileptics. As mentioned on p.499, dexamethasone may decrease or increase plasma concentrations of *phenytoin*. Like other enzyme-inducing drugs, phenytoin also has the potential to increase the metabolism of dexamethasone. There have been reports of false positive dexamethasone suppression tests (see Diagnosis and Testing, below) in patients taking *carbamazepine*.[1]

1. Ma RCW, *et al.* Carbamazepine and false positive dexamethasone suppression tests for Cushing's syndrome. *BMJ* 2005; **330:** 299–300.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Dexamethasone is readily absorbed from the gastrointestinal tract. Its biological half-life in plasma is about 190 minutes. Binding of dexamethasone to plasma proteins is about 77%, which is less than for most other corticosteroids. Up to 65% of a dose is excreted in urine within 24 hours. Clearance in premature neonates is reported to be proportional to gestational age, with a reduced elimination rate in the most premature. It readily crosses the placenta with minimal inactivation.

Uses and Administration

Dexamethasone is a corticosteroid with mainly glucocorticoid activity (p.1490); 750 micrograms of dexamethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p.1495), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred. Its lack of mineralocorticoid properties makes dexamethasone particularly suitable for treating conditions where water retention would be a disadvantage.

The dose may be expressed in terms of the base, and the following are each equivalent to about 1 mg of dexamethasone:

- dexamethasone acetate 1.1 mg
- dexamethasone isonicotinate 1.3 mg
- dexamethasone phosphate 1.2 mg
- dexamethasone sodium metasulfobenzoate 1.5 mg
- dexamethasone sodium phosphate 1.3 mg

Dexamethasone sodium phosphate 1.1 mg is equivalent to about 1 mg of dexamethasone phosphate.

For **oral** administration dexamethasone is given in usual doses of 0.5 to 10 mg daily. Dexamethasone is also used orally in the dexamethasone suppression tests for the diagnosis of Cushing's syndrome (for further details see under Diagnosis and Testing, below).

For **parenteral administration** in **intensive therapy** or in **emergencies**, the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection; doses are sometimes expressed in terms of the free alcohol, the phosphate, or the sodium phosphate and confusion has sometimes arisen in the literature because of these variations. Initial doses used, expressed in terms of dexamethasone phosphate, range from about 0.5 to 24 mg daily (about 0.4 to 20 mg of dexamethasone). Intravenous doses equivalent to 2 to 6 mg/kg of dexamethasone phosphate given slowly over a minimum period of several minutes have been suggested for the treatment of severe shock. These high doses may be repeated within 2 to 6 hours and this treatment should be continued only until the patient's condition is stable and usually for no longer than 48 to 72 hours. Alternatively, the initial intravenous injection may be followed by a continuous intravenous infusion of 3 mg/kg per 24 hours.

Dexamethasone sodium phosphate is also used in the treatment of **cerebral oedema** caused by malignancy. An initial intravenous dose equivalent to 10 mg of dexamethasone phosphate is usually given followed by 4 mg intramuscularly every 6 hours; a response is usually obtained after 12 to 24 hours and dosage may be reduced after 2 to 4 days, and gradually stopped over 5 to 7 days. A much higher dosage schedule has also been suggested for use in acute life-threatening cerebral oedema; initial doses equivalent to 50 mg of dexamethasone phosphate have been given intravenously on the first day together with 8 mg intravenously every 2 hours reduced gradually over 7 to 13 days. A maintenance dose of 2 mg two or three times daily has been used in patients with recurrent or inoperable neoplasms.

The sodium phosphate ester is given by **intra-articular, intralesional**, or **soft-tissue injection**. For intra-articular injection doses equivalent to 0.8 to 4 mg of dexamethasone phosphate are used depending upon the size of the joint. For soft-tissue injection doses of 2 to 6 mg are used. Injections are repeated every 3 to 5 days to every 2 to 3 weeks.

Dexamethasone acetate may be given by **intramuscular injection** in conditions where corticosteroid treatment is indicated but a prompt response of short duration is not required; doses are equivalent to 8 to 16 mg of dexamethasone, repeated, if necessary, every 1 to 3 weeks. The acetate may also be given locally by **intra-articular** or **soft-tissue injection** in doses equivalent to 4 to 16 mg of dexamethasone, repeated, if necessary, every 1 to 3 weeks, or by **intralesional injection** in doses equivalent to 0.8 to 1.6 mg.

For **ophthalmic disorders** or for topical application in the treatment of various skin disorders, either dexamethasone or its esters may be used; concentrations are often expressed in terms of dexamethasone or dexamethasone phosphate and are commonly 0.05 to 0.1% for eye or ear drops and ointments and 0.1% for topical skin preparations. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

For allergic rhinitis (p.565) and other allergic or inflammatory **nasal conditions**, a nasal spray containing dexamethasone isonicotinate is available; the acetate, phosphate, sodium phosphate, and sodium metasulfobenzoate have also been used.

Dexamethasone is given intravenously and orally for the prevention of **nausea and vomiting** induced by cancer chemotherapy (see below).

Other esters of dexamethasone that have occasionally been used include the hemisuccinate, linoleate, palmitate, pivalate, propionate, sodium succinate, tebutate, and valerate.

The phenpropionate and troxundate esters have been used in veterinary medicine.

Dexamethasone-releasing stents may be used to reduce restenosis after coronary artery stent placement.

Alcohol withdrawal syndrome. Dexamethasone was reported to be effective in a patient with benzodiazepine-resistant delirium tremens[1] and resolved symptoms of alcohol withdrawal syndrome resistant to other treatments in another 110 patients.[2] However, a subsequent small study found no evidence that dexamethasone was effective.[3]

1. Fischer DK, *et al.* Efficacy of dexamethasone in benzodiazepine-resistant delirium tremens. *Lancet* 1988; **i:** 1340–1.
2. Pol S, *et al.* Dexamethasone for alcohol withdrawal. *Ann Intern Med* 1991; **114:** 705–6.
3. Adinoff B, Pols B. Dexamethasone in the treatment of the alcohol withdrawal syndrome. *Am J Drug Alcohol Abuse* 1997; **23:** 615–22.

Amyloidosis. For mention of the use of dexamethasone in patients with amyloidosis, see p.743.

Blood disorders. High-dose pulsed dexamethasone therapy has been found useful in some patients with idiopathic thrombocytopenic purpura (p.1505), although results have been variable in children.

Cerebral oedema. Corticosteroids, usually dexamethasone, play an important role in the treatment of cerebral oedema in malignancy (see Raised Intracranial Pressure, p.1181), and dexamethasone is advocated for the cerebral oedema associated with high-altitude disorders (see below).

Congenital adrenal hyperplasia. Because of its lack of mineralocorticoid properties, dexamethasone has little advantage in the salt-losing form of congenital adrenal hyperplasia (p.1502), in which mineralocorticoid therapy must be given, and its potency means that dose titration to avoid toxicity can be difficult in infants and children, even with the non-salt-losing form. However, it may be useful in adults with forms of the syndrome that do not require mineralocorticoid replacement. It has also been given antenatally to the mother to prevent virilisation of female fetuses.

Diagnosis and testing. *CUSHING'S SYNDROME.* Dexamethasone has been used to differentiate Cushing's disease (adrenal hyperplasia caused by defects of pituitary origin) from other forms of Cushing's syndrome (caused by ectopic ACTH secretion from non-pituitary tumours or by cortisol secretion from adrenal tumours). The dexamethasone suppression test as first proposed[1] involved giving oral dexamethasone in low doses of 500 micrograms four times daily for 8 doses followed by higher doses of 2 mg four times daily for 8 doses. In the low-dose tests the urinary excretion of cortisol and 17-hydroxycorticosteroids is suppressed in healthy persons but not in patients and in the high-dose tests the excretion is still not suppressed in those with Cushing's syndrome but is partially suppressed in those with Cushing's disease. Because this test usually involves patients being admitted to hospital for urine collection over a number of days and because false-negative responses are reported to be fairly frequent, more rapid and reliable tests have been sought. The low-dose test plus measurement of serum-cortisol concentrations and the excretion of free cortisol in urine over 24 hours has been suggested[2] to be a reliable method for screening for Cushing's syndrome. In the UK a single dose of 1 mg of dexamethasone given at night is often used and is considered sufficient to inhibit corticotropin secretion for 24 hours in most subjects. In another variation[3] a single dose of dexamethasone 8 mg has been given at night and plasma-cortisol concentrations measured the next day; this test (known as the overnight high-dose dexamethasone suppression test) has again been said to be a practical and reliable alternative for the differential diagnosis of Cushing's syndrome.

Further variations in the dexamethasone suppression test have included giving a continuous intravenous infusion of dexamethasone at a rate of 1 mg/hour for 7 hours, with hourly measurement of blood-cortisol concentrations.[4] Initial results indicate that this variation produces a lower number of false-positive diagnoses than the test using oral dexamethasone. Other alternatives are a combined low-dose dexamethasone suppression test and corticotropin-releasing hormone (corticorelin) test,[5] or combination of a dexamethasone suppression test with a metyrapone test.[6]

Reviews[7,8] of diagnostic tests for Cushing's syndrome have outlined both the advantages and disadvantages of tests using dexamethasone. These suggested that where there is suspicion of Cushing's syndrome, the overnight low-dose dexamethasone suppression test may be used as part of a range of measures, and that the dexamethasone-corticorelin test may be useful when there are equivocal results from initial screening. In a study to assess the effectiveness of low-dose dexamethasone, some patients were found to suppress plasma or urinary steroid concentrations to levels previously thought to exclude a diagnosis of Cushing's syndrome. The authors concluded that these low-dose tests should not be used as the sole criterion for diagnosis, and that a much lower value for serum cortisol should be used to achieve adequate sensitivity.[9] In the differentiation of ACTH-dependent and ACTH-independent forms of Cushing's syndrome, one review[7] suggested that the high-dose dexamethasone suppression test cannot be recommended because of poor specificity.

For further discussion of the various methods used for the diagnosis of Cushing's syndrome and details of its management, see p.2344. Various drugs may interfere with the dexamethasone suppression test.

1. Liddle GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1960; **20:** 1539–60.
2. Kennedy L, *et al.* Serum cortisol concentrations during low dose dexamethasone suppression test to screen for Cushing's syndrome. *BMJ* 1984; **289:** 1188–91.
3. Tyrrell JB, *et al.* An overnight high-dose dexamethasone suppression test for rapid differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **104:** 180–6.
4. Biemond P, *et al.* Continuous dexamethasone infusion for seven hours in patients with the Cushing syndrome: a superior differential diagnostic test. *Ann Intern Med* 1990; **112:** 738–42.
5. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269:** 2232–8.
6. Avgerinos PC, *et al.* The metyrapone and dexamethasone suppression tests for the differential diagnosis of the adrenocorticotropin-dependent Cushing syndrome: a comparison. *Ann Intern Med* 1994; **121:** 318–27.
7. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
8. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.
9. Findling JW, *et al.* The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. *J Clin Endocrinol Metab* 2004; **89:** 1222–6.

DEPRESSION. The Health and Public Policy Committee of the American College of Physicians noted that the dexamethasone suppression test for depression (p.373) was based on the premise that endogenously depressed patients have shown pituitary-adrenal axis abnormalities but had been found to have a low sensitivity for detecting depression. It was of unproven value and was not recommended as a screening test.[1] Nonetheless, interest remains; studies[2-6] have shown conflicting results.

1. Young M, Schwartz JS. The dexamethasone suppression test for the detection, diagnosis, and management of depression. *Ann Intern Med* 1984; **100:** 307–8.
2. Coryell W. DST abnormality as a predictor of course in major depression. *J Affect Disord* 1990; **19:** 163–9.
3. Plocka-Lewandowska M, *et al.* Dexamethasone suppression test and suicide attempts in schizophrenic patients. *Eur Psychiatry* 2001; **16:** 428–31.
4. Coryell W, Schlesser M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry* 2001; **158:** 748–53.
5. Black DW, *et al.* The relationship between DST results and suicidal behavior. *Ann Clin Psychiatry* 2002; **14:** 83–8.
6. Yerevanian BI, *et al.* The dexamethasone suppression test as a predictor of suicidal behavior in unipolar depression. *J Affect Disord* 2004; **83:** 103–8.

High-altitude disorders. Dexamethasone is effective in the prevention of symptoms of acute mountain sickness (p.1168), for which mild cerebral oedema may be a contributing factor, but it is not generally considered suitable for routine prophylaxis because of concern about its adverse effects. In the treatment of acute severe mountain sickness, which may involve the development of pulmonary and cerebral oedema, the mandatory treatment is immediate descent, and drug therapy is primarily adjunctive, to facilitate descent or maintain the patient until descent is possible. Under these circumstances dexamethasone and oxygen form the mainstays of treatment.

References.

1. Ferrazzini G, *et al*. Successful treatment of acute mountain sickness with dexamethasone. *BMJ* 1987; **294:** 1380–2.
2. Ellsworth AJ, *et al*. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med* 1987; **83:** 1024–30.
3. Montgomery AB, *et al*. Effects of dexamethasone on the incidence of acute mountain sickness at two intermediate altitudes. *JAMA* 1989; **261:** 734–6.
4. Levine BD, *et al*. Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 1989; **321:** 1707–13.
5. Keller H-R, *et al*. Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ* 1995; **310:** 1232–5.
6. Dumont L, *et al*. Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321:** 267–72.

Hirsutism. Unbound testosterone concentrations were consistently elevated in 32 hirsute women; when concentrations were suppressed to normal by dexamethasone 0.5 to 1 mg at night hirsutism was generally improved or ceased to progress after 8 to 10 months of treatment.[1] Other studies have shown only a modest improvement[2] or no improvement at all[3] in hirsutism when treated with dexamethasone. Addition of dexamethasone to anti-androgen therapy appeared to prolong the duration of remission in a later study.[4]

The mainstay of drug treatment for hirsutism tends to be an anti-androgen such as cyproterone or spironolactone (p.2089). Although low dose corticosteroids can suppress adrenal androgen production, careful consideration of the risks and benefits is advisable, especially since therapy for hirsutism may have to be given long-term.

1. Paulson JD, *et al*. Free testosterone concentration in serum: elevation is the hallmark of hirsutism. *Am J Obstet Gynecol* 1977; **128:** 851–7.
2. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 1991; **78:** 845.
3. Rittmaster RS, Thompson DL. Effect of leuprolide and dexamethasone on hair growth and hormone levels in hirsute women: the relative importance of the ovary and the adrenal in the pathogenesis of hirsutism. *J Clin Endocrinol Metab* 1990; **70:** 1096–1102.
4. Carmina E, Lobo RA. The addition of dexamethasone to antiandrogen therapy for hirsutism prolongs the duration of remission. *Fertil Steril* 1998; **69:** 1075–9.

Malaria. Corticosteroids, especially dexamethasone, have been used in cerebral malaria (p.594) in the belief that their anti-inflammatory effect would reduce cerebral oedema. However, studies have shown that cerebral oedema does not play a significant role in the pathophysiology of cerebral malaria and, indeed, double-blind studies using both moderate doses (2 mg/kg) and high doses (11 mg/kg) of dexamethasone intravenously over 48 hours found no reduction in death rates. Thus it is now considered that corticosteroids have no place in the treatment of cerebral malaria.[1]

1. Prasad K, Garner P. Steroids for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).

Malignant neoplasms. Dexamethasone has been used in some regimens for the treatment of malignancy, for example in acute lymphoblastic leukaemia (p.651) and multiple myeloma (p.658).

Meningitis. The role of corticosteroids in the adjuvant treatment of bacterial meningitis (p.178) has been the subject of considerable debate. Studies have shown conflicting results.[1-3] However, a systematic review[4] concluded that there was evidence of benefit, particularly in reducing deafness in children in high-income countries, and in reducing mortality in adults. It has been suggested[4] that a 4-day regimen of dexamethasone be given to adults and in children in high-income countries, preferably before or with the first dose of antibacterial.

1. Molyneux EM, *et al*. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002; **360:** 211–18.
2. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347:** 1549–56.
3. Thwaites GE, *et al*. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351:** 1741–51.
4. van de Beek D, *et al*. Corticosteroids for acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/08/08).

Nausea and vomiting. Dexamethasone has antiemetic properties, particularly against acute and delayed vomiting induced by cancer chemotherapy[1] (p.1700). It may be used alone for prevention of acute symptoms associated with moderately-emetogenic treatment and is combined with a 5-HT_3 antagonist for highly-emetogenic treatment. Typical dosage regimens have been dexamethasone 4 to 8 mg orally immediately before moderately-emetogenic chemotherapy and 20 mg by intravenous injection for more severely emetogenic chemotherapy. Dexamethasone is the drug of choice for prevention of delayed symptoms, given alone or with other antiemetics. A typical oral dose is 8 mg twice daily for 2 to 4 days. Dexamethasone is also effective for the prevention of postoperative nausea and vomiting,[2] and may be used to manage nausea and vomiting in palliative care.

1. Ioannidis JPA, *et al*. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol* 2000; **18:** 3409–22.
2. Henzi I, *et al*. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000; **90:** 186–94.

Opportunistic mycobacterial infections. Dexamethasone in doses of 1 to 4 mg daily was associated with weight gain, reduction in fever, and an improved sense of well-being in 5 patients with HIV and disseminated *Mycobacterium avium* complex infection.[1] Combination antimycobacterial therapy for nontuberculous mycobacterial infections (p.181) was also given. Similar results have been noted by others.[2]

1. Wormser GP, *et al*. Low-dose dexamethasone as adjunctive therapy for disseminated Mycobacterium avium complex infections in AIDS patients. *Antimicrob Agents Chemother* 1994; **38:** 2215–17.
2. Dorman SE, *et al*. Adjunctive corticosteroid therapy for patients whose treatment for disseminated Mycobacterium avium complex infection has failed. *Clin Infect Dis* 1998; **26:** 682–6.

Respiratory disorders. Corticosteroids such as dexamethasone have been given antenatally to mothers at risk of premature delivery in order to hasten fetal lung maturation and help prevent *neonatal respiratory distress syndrome* (p.1508) and *bronchopulmonary dysplasia* (p.1500). Neonatal dexamethasone has been reported to improve pulmonary outcome and assist weaning from mechanical ventilation in infants that have developed bronchopulmonary dysplasia.

Dexamethasone is also one of the drugs of choice for the management of severe *croup* (see p.1502). However, as with other corticosteroids (p.1500) it appears to be of little value in *bronchiolitis*.[1,2]

1. Roosevelt G, *et al*. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996; **348:** 292–5.
2. Klassen TP, *et al*. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized controlled trial. *J Pediatr* 1997; **130:** 191–6.

Retinopathy of prematurity. For a suggestion that antenatal dexamethasone might be helpful in the prophylaxis of retinopathy of prematurity, see p.1994. For mention of the uncertain effect of neonatal dexamethasone on retinopathy of prematurity, see Effects on the Neonate, under Adverse Effects above.

Preparations

BP 2008: Dexamethasone and Neomycin Ear Spray; Dexamethasone Sodium Phosphate Injection; Dexamethasone Tablets;
USP 31: Ciprofloxacin and Dexamethasone Otic Suspension; Dexamethasone Acetate Injectable Suspension; Dexamethasone Elixir; Dexamethasone Gel; Dexamethasone Ophthalmic Suspension; Dexamethasone Oral Solution; Dexamethasone Sodium Phosphate Cream; Dexamethasone Sodium Phosphate Inhalation Aerosol; Dexamethasone Sodium Phosphate Injection; Dexamethasone Sodium Phosphate Ophthalmic Ointment; Dexamethasone Sodium Phosphate Ophthalmic Solution; Dexamethasone Tablets; Dexamethasone Topical Aerosol; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Decadron; Degabina; Dexafarm†; Dexalaf; Dexalergin; Dexameral; Dexatotal; Duo Decadron; Fadametasona†; Gotabiotic D; Ingedex; Isopto Maxidex; Lormine; Nexadron; Rupedex; Sedesterol; Trofinan; ***Austral.:*** Dexmethsone; Maxidex; ***Austria:*** Dexabene; Fortecortin; ***Belg.:*** Aacidexam; Decadron†; Dexa-Sine; Maxidex; Oradexon; ***Braz.:*** Cortidex†; Corti-top; Decadron; Decadronal; Deflaren; Dexacilin; Dexaden; Dexadermil; Dexaflan†; Dexagreen; Dexameson; Dexametax†; Dexametonal†; Dexametrat†; Dexamex†; Dexaminor; Dexanil; Dexason; Dexazen†; Dexazona; Dexmene†; Dextasona†; Maxidex; Metaxon; Minidex; Neodex; Netazon†; Topidexa; Uni Dexa; ***Canad.:*** Decadron†; Dexasone; Diodex†; Hexadrol†; Maxidex; ***Chile:*** Maxidex; Oradexon; ***Cz.:*** Baycuten; Dexa†; Dexaltin; Dexamed; Dexapos†; Dexason†; Dexona†; Fortecortin; ***Denm.:*** Decadron†; Maxidex; ***Fin.:*** Decadron†; Kaarmepakkaus; Oftan Dexa; Oradexon; ***Fr.:*** Dectancyl; Desocort†; Maxidex; ***Ger.:*** afpred-DEXA; Auxiloson†; Cortidexason†; Cortisumman†; Dexa; Dexa Loscon mono; Dexa-Allvoran; dexa-clinit; Dexa-Effekton; Dexa-ratiopharm; Dexa-Rhinospray Mono; Dexa-sine; Dexabene; Dexabeta; DexaEDO; Dexaflam; Dexagalen; Dexagel; Dexahexal; Dexamonozon; Dexamonozon N†; Dexapos; Fortecortin; Isopto Dex; Lipotalon; Solupen N; Solutio Cordes Dexa N; Spersadex; Totocortin; Tuttozem N; ***Gr.:*** Decadron; Dexacollyre; Dexaton; Iriniozol; Maxidex; Oradexon; Soldesanil; Thilodexine; Thiloxedine†; ***Hong Kong:*** Dexaltin; Dexamed; Dexasone; Dexmetha; Dexmethsone; Maxidex; Spersadex†; ***Hung.:*** Dexa; Maxidex; Oradexon; ***India:*** Decdan; Dexacip; Dexasone; Dexona; Millicortenol; Wymesone; ***Indon.:*** Cetadexon; Cortidex; Danasone; Decilone; Dellamethasone; Dexa-M; Etason; Fortecortin; Indexon; Inthesa-5; Kalmethasone; Lanadexon; Licodexon; Molacort; Nufadex; Oradexon; Prodexon; Pycameth; Pyradexon; Scandexon; ***Irl.:*** Decadron†; Maxidex; ***Israel:*** Dexacort; Maxidex; Sterodex; ***Ital.:*** Decadron; Dermadex; Etacortilen; Luxazone; Megacort; Soldesam; Visumetazone; ***Jpn:*** Limethason; Methaderm; ***Malaysia:*** Cortidax†; Decadron†; Decan; Dexalone; Dexaltin; Dexasone; Limethason†; Maxidex; ***Mex.:*** Adrecort; Alin; Azona; Baycuten; Beminex; Cortidex; Cryometasona; Decadron; Decadronal; Decorex; Dexafrin; Dexagrin; Dexal; Dexamilan; Dexicar; Dexona; Dibasona; Examsa; Indarzona-N; Lergosin; Maxidex; Metax; Migradexan†; Pardex; Reusan; Taprodex; Taxyl; ***Neth.:*** Decadron†; Dexa-POS; Oradexon; ***Norw.:*** Decadron†; Isopto Maxidex; Spersadex; ***NZ:*** Maxidex; ***Philipp.:*** Cordex; Dabrin; Decan; Decilone; Drenex; Isodexam; Maxidex; Midexone; Oradexon; Penodex; Santeson; Scancortin; Vexamet; ***Pol.:*** Dexafree; Dexapolcort; Dexaven; ***Port.:*** Decadron; Dexaval; Oradexon; Ronic; ***Rus.:*** Detametazon (Детаметажон)†; Dexamed (Дексамед); Dexapos (Дексапос); Dexaven (Дексавен); Dexona (Дексона Д); Maxidex (Максидекс); Oftan Dexamethason (Офтан Дексаметазон); ***S.Afr.:*** Decadron; Decasone; Maxidex; Oradexon†; Spersadex; ***Singapore:*** Decan; Decordex; Dexaltin; Dexamed; Dexasone; Erladexone†; Limethason†; Maxidex; Mexasone†; ***Spain:*** Dalamon Inyectable; Fortecortin; Maxidex; ***Swed.:*** Decadron†; Dexacortal; Isopto Maxidex; Opnol; ***Switz.:*** Decadron†; Dexacortin; Dexacortin-K†; Dexalocal; Fortecortin; Maxidex; Mephamesone; Millicortene†; Spersadex; ***Thai.:*** B Dexol; Decadron; Dexa ANB; Dexa-P†; Dexa†; Dexaltin; Dexano; Dexasone; Dexion; Dexon; Dexthasol; Dexton; Limethason†; Oradexon; Phenodex; ***Turk.:*** Cebedex; Dekort; Deksalon; Deksamet; Dexa-Sine; Maxidex; Onadron; Spersadex; ***UK:*** Decadron†; Dexsol; Maxidex; ***USA:*** Aeroseb-Dex; Dalalone; Decadron; Decaspray; Dexameth†; Dexasone; Dexone; DexPak; Hexadrol; Maxidex; Solurex†; ***Venez.:*** Decadron†; Decalona; Decobel; Dexacort; Dexamin; Maradex; Metalexina†.

Multi-ingredient: ***Arg.:*** Alergi; Belbar; Bicrinol; Bio Cabal†; Biocort; Bioptic DX; Biotaer Ultrason Nebulizable†; Ciloxadex; Ciprocort; Cortaler Novo†; Decadron con Ciprofloxina; Decadron con Neomicina; Decadron con Tobramicina; Dexa Aminofilin; Dexa Teosona; Dexa-Rhinospray N; Dexabion; Dexafurazon†; Dexalergin; Dexamytrex; Dexaprof D; Dexatopic†; Empecid Cort; Exudrol con Dexametasona; Factioneye; Flexicamin B12; Flogiatrin B12; Fluoropoen; Fotadex; Gotabiotic F; Hongal; Isoptomax; Klonamicin Compuesto; Larsen; Linfol; Mefenix Relax†; Melasmax; Naxo TV; Neodexa Plus; Neoftalm Dexa; Neolag; Neosona; Nexadron Compuesto; Nexadron Plus; Nipiol†; Paraflex Plus; Polioftal; Polyplex; Proetztotal; Provisual Compuesto; Quidex; Radina Dex; Sincerum Biotic; Sincerum Biotic L; Sindrolen†; Solocalm Plus; Tacines; Tobrabiotic D; Tobracort; Tobradex; Tobragan D; Toflamixina Plus; Tratomax; Trimepol D; Vixalerg; Vixidone; Vixidone T†; Xao-Dex†; Xibradex; ***Austral.:*** Otodex; Sofradex; ***Austria:*** Ambene; Dexagenta; Dexasalyl†; Multodrin; Rheumesser; Tobradex; Uromont; ***Belg.:*** De Icin†; De Icol; Dexa-Polyspectran New; Dexa-Rhinospray; Dexagenta-POS; Frakidex; Maxitrol; Percutalgine; Polydexa; Tobradex; ***Braz.:*** Baycuten; Biamotil-D; Cianotrat-Dexa; Cilodex; Cylocort; Decadron Colirio; Decadron Nasal; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacilin; Dexaclor†; Dexacobal; Dexacort†; Dexador; Dexadoze; Dexafenicol; Dexagil; Dexalgen; Dexamytrex†; Dexaneurin; Dexanevral†; Dexanil; Dexavison; Dexazona; Duo-Decadron; Emistin; Fenidex; Gynax-N; Hidrocin; Maxiflox D; Maxitrol; Metcort; Neocortin; Neodex; Nepodex; Otofenicol-D†; Rinosbon†; Tobracin D; Tobracort; Tobradex; Trivagel N; Vagitrin-N; Vitatonus Dexa; ***Canad.:*** Ciprodex; Dioptrol†; Maxitrol; Opticort; Sofracort; Tobradex; ***Chile:*** Baycuten; Cilodex; Ciprodex; Dexagin; Grifoftal-D; Maxitrol; Oflono-D; Poentobral Plus; Spersadex Comp†; Telugren Plus; Tobradex; Tobragan D; Tobrin-D; Todexona; Tribesona; Xolof D; ***Cz.:*** Dexa-Gentamicin; Doxiproct Plus; Maxitrol; Otobacid N; Pulpomixine; Sofradex†; Spersadex Compositum; Tobradex; ***Denm.:*** Decadron med Neomycin†; Sofradex; Spersadex Comp; ***Fin.:*** Maxitrol; Oftan Dexa-Chlora; Sofradex; ***Fr.:*** Auricularum; Cebedexacol; Chibro-Cadron; Corticetine; Dexagrane; Frakidex; Framyxone; Maxidrol; Percutalgine; Polydexa; Ster-Dex; Tobradex; ***Ger.:*** Baycuten†; Corti Biciron N; Cortidexason comp; Corto-Tavegil†; Dexa Biciron; Dexa Polyspectran; Dexa-Gentamicin; Dexa-Phlogont L†; Dexa-Siozwo; Dexamytrex; Dispadex comp; Duodexa N†; Ell-Cranell dexa; Isopto Max; Lokalison-antimikrobiell Creme N; Nystalocal; Otobacid N; Rheumasit†; Rhinoguttae Dexamethasoni cum Naphazolino†; Spersadex Comp†; Spersadexolin†; Supertendin; Supertendin 2000 N†; Ultra-Demoplas†; Uro-Stilloson†; ***Gr.:*** Afacort; Antilerg-F†; Chlorapred; Dexa-Rhinaspray-N; Dexachlor; Dexamycin; Dexamytrex; Dispersadron-C; Ekzegamma†; Eyebrex-Dexa†; Fluoscin†; Genefacort†; Gentadex; Isopto Maxitrol; Lofoto; Nezefib; O-Biotic; Otocort; Otomize; Saocin-D; Spersadexoline†; Thilomicine Dex; Tobradex; Urecortin; ***Hong Kong:*** Chloram-D; Dexoph; Dextracin; Eurodron; Frakidex; Maxitrol; Neo-Dex (Improved); Parasone; Polydex-N; Polydexa; Sofradex; Sonexa-C; Spersadex Comp; Spersadexoline†; Tobradex; ***Hung.:*** Dexapolcort N; Doxiproct Plus; Spersadex Comp†; Tobradex; ***India:*** Ciplox D; Decdan-N; Dexona Eye/Ear; Dexosyn Plus; Dexosyn-C; Dexosyn-N; Gentacip D; Millicorten-Vioform; Mycidex†; Obrasone; Ocupol-D; Ocutob-D; Oflox D; Pyrimon; Sofracort; Sofradex; Sofradex-F; Tobazon DM; ***Indon.:*** Alegi; Alerdex; Baycuten-N; Blecidex; Bralifex Plus; Dexatopic; Dextafen; Dextamine; Inmatrol; Isotic Neolyson; Isotic Tobrizon; Kloramixin D; Lorson; Lotharson; Maxitrol; Oregan; Osatrol; Polidemisin; Pritacort; Sofradex; Soldextam; Spersadex Comp; Tobradex; Trodex; Ximex Optixitrol; ***Irl.:*** Dexa-Rhinaspray Duo; Maxitrol; Otomize; Sofradex; ***Israel:*** Adexone; Auricularum; Desoren; Dethamycin; Dethaphrine; Dex-Otic; Dexamycin; Dexefrin; Maxitrol; Otomize†; Polycutan; Tarocidin D; Tevacutan; ***Ital.:*** Cloradex; Corti-Arscolloid; Desalfa; Desamix Effe; Desamix-Neomicina; Dexoline; Doxiproct; Eta Biocortilen; Eta Biocortilen VC; Luxazone Eparina; Neo Cortofen; Netildex; Tobradex; Visumetazone Antistaminico; Visumetazone Decongestionante; ***Jpn:*** Una A Gel; ***Malaysia:*** Baycuten N; De Icol; Dexa-Gentamicin†; Dexamytrex†; Dextracin; Gentadexa; Maxitrol; Neo-Deca; Sofradex; Spersadex Comp†; Spersadexoline; Tobradex; ***Mex.:*** Alin Nasal; Alin Oftalmico; Baycuten N; Bexine; Biodexan; Butisel; Cilodex; Cloxona-O; Decadron con Neomicina; Decadron con Nistatina; Dexabion; Dexadutil; Dexamicin; Dexne; Dexsul; Dextone; Dibutasona; Dinill-D; Doxiproct Plus; Exafenil; Gotadex†; Innobion; Kodakon†; Lergosin A; Levodexan; Levofenil; Maxitrol; Mildex; Neobacigrin; Neuralin; Nispil; Obrydex; Odexan; Ofodex; Polideltaxin NF; Rinadex Compuesto; Rinidyl DN; Soldrin; Sondex-Of; Tiamidexal; Timpacil; Tobracort; Tobradex; Trazidex; Trineurovita Compuesto; UV IX†; Vengesic†; Zolidime†; ***Neth.:*** Dexagenta-POS; Dexamytrex; Dexatopic†; Maxitrol; Sofradex; Tobradex; ***Norw.:*** Maxitrol; Sofradex; Spersadex med kloramfenikol; ***NZ:*** Maxitrol; Sofradex; Tobradex; ***Philipp.:*** Baycuten; Dexamytrex; Dexanicol; Maxirap; Maxitrol; Maxoptic; Postop; Postotic; Spersadex Compound; Syntemax; Tobradex; ***Pol.:*** Dexadent; Dexamytrex; Dexapolcort N; Maxitrol; Tobradex; ***Port.:*** Baycuten; Decadron com Neomicina; Dexamytrex; Dexaval A; Dexaval N; Dexaval O; Dexaval V; Doxiproct Plus; Frakidex; Gentadexa; Otomize†; Polydexa; ***Rus.:*** Ambene (Амбене); Dexa-Gentamicin (Декса-Гентамицин); Dexona (Дексона); Maxitrol (Макситрол); Percutalgine (Перкуталжин)†; Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Tobradex (Тобрадекс); Tobrasone (Тобразон); ***S.Afr.:*** Covomycin-D; Maxitrol; Sofradex; Spersadex Comp; Spersadexoline; Tobradex; ***Singapore:*** Dexamytrex; Dextracin; Frakidex†; Maxitrol; Polydexa; Sofradex; Spersadex Comp†; Spersadexoline†; Tobradex; ***Spain:*** Amplidermis; Broncoformo Muco Dexa; Cloran Hemidex; Cresophene; Dalamon†; Decadran Neomicina†; Dexa Tavegil; Dexam Constric†; Gentadexa; Hem Anth; Hongosan; Icol; Inzitan; Liquipom Dexa Antib; Maxitrol; Neodexa; Neurocatavin Dexa†; Neurodavur Plus; Oftalmotrim Dexa†; Otix; Oto Vitna†; Phonal; Resorborina; Rino Dexa; Sabanotropico; Sedofarin; Tobradex; Vasodexa; ***Swed.:*** Decadron cum neomycin†; ***Switz.:*** Antikeloides Creme; Chronocorte; Corticetine†; Cresophene†; Dexalocal-F; Dexasalyl; Dexolan; Doxiproct Plus; Frakidex; Maxitrol; Nystalocal; Otospray†; Pigmanorm; Polydexa; Sebo-Psor; Sofradex; Spersadex Comp; Spersadexoline†; Tobradex; ***Thai.:*** Archidex; Cadexcin-N†; Decadron with Neomycin†; Dexacin; Dexamytrex; Dexasil†; Dexoph; Dexylin; Eyedex; Maxitrol; Neo-Optal; Neodex; Opsardex†; Percutalgine†; Sofradex; Spersadexoline; Tobradex; Trabit†; Vesoph;

UK: Dexa-Rhinaspray Duo†; Maxitrol; Otomize; Sofradex; Tobradex; ***USA:*** Ak-Neo-Dex; Ak-Trol†; Ciprodex; Dexacidin†; Dexacine†; Dexasporin; Maxitrol; Neo-Dexameth†; NeoDecadron†; Neodexasone; Neopolydex; Ocu-Trol; Poly-Dex; Tobradex; ***Venez.:*** Baycuten N; Cipromet†; Cyprodex; Decadron†; Decaven; Deicol†; Dexaneol†; Dexapostafen; Gentidexa; Kanasone†; Maxicort; Maxitrol; Otocort; Poentobral Plus; Poli-Otico; Quinocort; Tobracort; Tobradex; Tobragan D; Todex; Trazidex.

Dichlorisone Acetate *(rINNM)* ⊗

Acetato de diclorisona; Dichlorisone, Acétate de; Dichlorisoni Acetas; Diclorisone Acetate. 9α,11β-Dichloro-17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

Дихлоризона Ацетат

$C_{23}H_{28}Cl_2O_5$ = 455.4.

CAS — 7008-26-6 (dichlorisone); 79-61-8 (dichlorisone acetate).

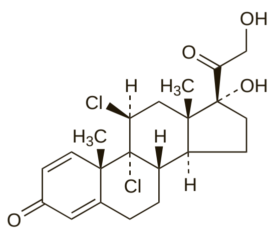

(dichlorisone)

Profile

Dichlorisone acetate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream containing 0.25 or 1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Dermaren; Dicloderm Forte.

Diflorasone Diacetate *(BANM, USAN, rINNM)* ⊗

Diacetato de diflorasona; Diflorasone, Diacetate de; Diflorasoni Diacetas; U-34865. 6α,9α-Difluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate.

Дифлоразона Диацетат

$C_{26}H_{32}F_2O_7$ = 494.5.

CAS — 2557-49-5 (diflorasone); 33564-31-7 (diflorasone diacetate).

ATC — D07AC10.

ATC Vet — QD07AC10.

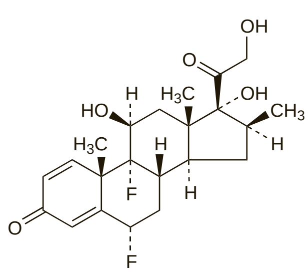

(diflorasone)

Pharmacopoeias. In *US.*

USP 31 (Diflorasone Diacetate). A white to pale yellow, crystalline powder. Insoluble in water; soluble in acetone and in methyl alcohol; very slightly soluble in ether; sparingly soluble in ethyl acetate; slightly soluble in toluene. Store in airtight containers.

Profile

Diflorasone diacetate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

USP 31: Diflorasone Diacetate Cream; Diflorasone Diacetate Ointment.

Proprietary Preparations (details are given in Part 3)
Ger.: Florone; ***Ital.:*** Dermaflor†; ***Mex.:*** Diasorane; ***Spain:*** Murode; ***USA:*** ApexiCon; Florone; Maxiflor; Psorcon.

Multi-ingredient: ***Arg.:*** Filoderma; Filoderma Plus; Griseocrem; Novo Bacticort Complex†; Novo Bacticort†.

Diflucortolone *(BAN, USAN, rINN)* ⊗

Diflucortolona; Diflucortolonum; Diflukortolon; Diflukortoloni. 6α,9α-Difluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Дифлукортолон

$C_{22}H_{28}F_2O_4$ = 394.5.

CAS — 2607-06-9.

ATC — D07AC06.

ATC Vet — QD07AC06; QD07XC04.

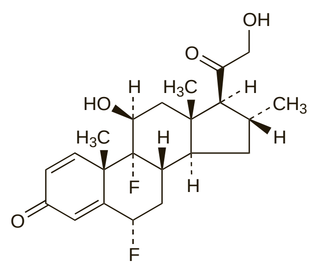

Diflucortolone Pivalate *(BANM, USAN, rINNM)* ⊗

Diflucortolone, Pivalate de; Diflucortoloni Pivalas; Pivalato de diflucortolona; SH-968. Diflucortolone 21-pivalate.

Дифлукортолона Пивалат

$C_{27}H_{36}F_2O_5$ = 478.6.

CAS — 15845-96-2.

ATC — D07AC06.

ATC Vet — QD07AC06.

Diflucortolone Valerate *(BANM, rINNM)* ⊗

Diflucortolone, Valérate de; Diflucortoloni Valeras; Diflukortolon Valerat; Valerato de diflucortolona. Diflucortolone 21-valerate.

Дифлукортолона Валерат

$C_{27}H_{36}F_2O_5$ = 478.6.

CAS — 59198-70-8.

ATC — D07AC06.

ATC Vet — QD07AC06.

Pharmacopoeias. In *Br.*

BP 2008 (Diflucortolone Valerate). A white to creamy white crystalline powder. Practically insoluble in water; freely soluble in dichloromethane and in dioxan; sparingly soluble in ether; slightly soluble in methyl alcohol. Protect from light.

Profile

Diflucortolone is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.1 or 0.3% of the valerate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

BP 2008: Diflucortolone Cream; Diflucortolone Oily Cream; Diflucortolone Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Nerisona; ***Austria:*** Neriforte; Nerisona; ***Belg.:*** Nerisona; ***Braz.:*** Nerisona; ***Canad.:*** Nerisone; ***Denm.:*** Nerisona; ***Fr.:*** Nerisone; ***Ger.:*** Nerisona; ***Hong Kong:*** Nerisone; ***Indon.:*** Nerilon; Nerisona; Valeron; ***Israel:*** Neriderm; ***Ital.:*** Cortical; Dermaval; Dervin; Dicortal†; Flu-Cortanest; Nerisona; Temetex; ***Malaysia:*** Nerisone†; ***Mex.:*** Nerisona; ***Neth.:*** Nerisona; ***NZ:*** Nerisone; ***Philipp.:*** Nerisona; ***Port.:*** Nerisona; ***S.Afr.:*** Nerisone; ***Singapore:*** Nerisone†; ***Spain:*** Claral; ***Switz.:*** Nerisona†; ***Turk.:*** Temetex; ***UK:*** Nerisone.

Multi-ingredient: ***Arg.:*** Diflunazol†; Nerisona C; Scheriderm; ***Austria:*** Travocort; ***Belg.:*** Travocort; ***Braz.:*** Bi-Nerisona; ***Canad.:*** Nerisalic; ***Chile:*** Bi-Nerisona; ***Fr.:*** Nerisalic; Nerisone C; ***Ger.:*** Nerisona C†; Travocort; ***Gr.:*** Travocort; ***Hong Kong:*** Nerisone C; Travocort; ***Indon.:*** Nerisona Combi; Travocort; ***Irl.:*** Travocort; ***Israel:*** Isocort; Multiderm; Tevaderm; ***Ital.:*** Corti-Fluoral; Dermaflogil; Impetex; Nerisalic; Nerisona C; Travocort; ***Malaysia:*** Isoradin; Travocort; ***Mex.:*** Bi-Nerisona; Scheriderm; ***NZ:*** Nerisone C; ***Philipp.:*** Nerisona Combi; Travocort; ***Pol.:*** Travocort; ***Port.:*** Nerisona C; Travocort; ***Rus.:*** Travocort (Травокорт); ***S.Afr.:*** Travocort; ***Singapore:*** Nerisone C†; Travocort; ***Spain:*** Claral Plus; ***Switz.:*** Travocort; ***Thai.:*** Travocort; ***Turk.:*** Impetex; Nerisona C; Travazol; Travocort; ***Venez.:*** Binerisona.

Difluprednate *(USAN, rINN)* ⊗

CM-9155; Difluprednato; Difluprednatum; W-6309. 6α,9α-Difluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate.

Дифлупреднат

$C_{27}H_{34}F_2O_7$ = 508.6.

CAS — 23674-86-4.

ATC — D07AC19.

ATC Vet — QD07AC19.

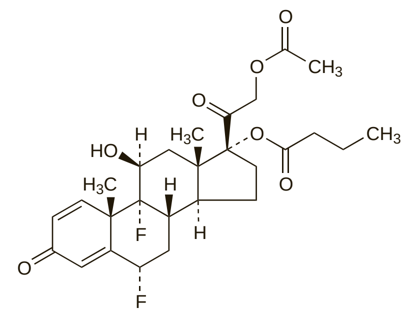

Profile

Difluprednate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or gel; concentrations used are 0.02 or 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Difluprednate is under investigation as a 0.05% ophthalmic emulsion for the treatment of inflammation following ocular surgery and uveitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Epitopic; ***Jpn:*** Myser†.

Fluclorolone Acetonide *(BAN, rINN)* ⊗

Acetónido de fluclorolona; Fluclorolone, Acétonide de; Flucloroloni Acetonidum; Flucloronide *(USAN)*; Fluklorolonacetonid; Fluklorolonіasetonidi; RS-2252. 9α,11β-Dichloro-6α-fluoro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

Флуклоролона Ацетонид

$C_{24}H_{29}Cl_2FO_5$ = 487.4.

CAS — 3693-39-8.

ATC — D07AC02.

ATC Vet — QD07AC02.

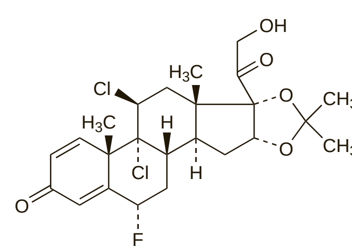

Profile

Fluclorolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream containing 0.2%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Cutanit.

Fludrocortisone Acetate *(BANM, rINNM)*

Acetato de fludrocortisona; Fludrocortisone, acétate de; Fludrocortisoni acetas; Fludrokortison acetát; Fludrokortisonacetat; Fludrokortisoniasetaatti; Fludrokortizon-acetát; Fludrokortizono acetatas; Fludrokortyzonu octan; 9α-Fluorohydrocortisone 21-Acetate. 9α-Fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate.

Флудрокортизона Ацетат

$C_{23}H_{31}FO_6$ = 422.5.

CAS — 127-31-1 (fludrocortisone); 514-36-3 (fludrocortisone acetate).

ATC — H02AA02.

ATC Vet — QH02AA02.

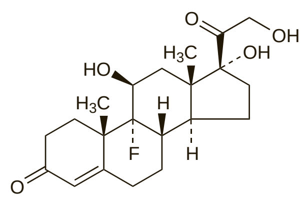

(fludrocortisone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Fludrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

USP 31 (Fludrocortisone Acetate). White to pale yellow, odourless or practically odourless, hygroscopic, crystals or crystalline powder. Insoluble in water; sparingly soluble in alcohol and in chloroform; slightly soluble in ether. Protect from light.

Adverse Effects, Treatment, Withdrawal, and Precautions

Fludrocortisone acetate has glucocorticoid actions about 10 times as potent as hydrocortisone and mineralocorticoid effects more than 100 times as potent. Adverse effects are mainly those due to mineralocorticoid activity, as described on p.1490.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Fludrocortisone is readily absorbed from the gastrointestinal tract. The plasma half-life is about 3.5 hours or more, but fludrocortisone exhibits a more prolonged biological half-life of 18 to 36 hours.

Uses and Administration

Fludrocortisone is a corticosteroid with glucocorticoid and highly potent mineralocorticoid activity (p.1490).

Fludrocortisone acetate is given orally to provide mineralocorticoid replacement in primary adrenocortical insufficiency (p.1498), with glucocorticoids. It is used in a dose range of 50 to 300 micrograms daily.

Fludrocortisone acetate may also be given with glucocorticoid therapy in doses of up to 200 micrograms daily in the salt-losing form of congenital adrenal hyperplasia (p.1502).

It is also given in the management of severe orthostatic hypotension (see below).

Fludrocortisone acetate is applied topically for its glucocorticoid actions in the treatment of various disorders. It is used as an ingredient of eye ointment or ear drops, usually in a concentration of 0.1%. Fludrocortisone acetate has also been included in topical preparations used for skin disorders. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Administration. A study of fludrocortisone requirements in 10 patients with Addison's disease indicated that dosage was often inadequate.[1] Nine were initially on fludrocortisone 50 to 100 micrograms daily in addition to cortisone or hydrocortisone; 5 were also taking levothyroxine for an associated auto-immune thyroid disease; one, who had detectable levels of aldosterone, was not initially receiving fludrocortisone. All the patients had evidence of sodium and water depletion and fludrocortisone was started at 300 micrograms daily, with downwards adjustments. Most patients required 200 micrograms daily; 2 patients elected to remain on 300 micrograms daily, but in most this dose caused pronounced sodium and water retention. The patient with detectable aldosterone levels required 50 micrograms daily. Eight of the 10 patients felt better on the higher fludrocortisone doses while 2 felt no change.

1. Smith SJ, *et al.* Evidence that patients with Addison's disease are undertreated with fludrocortisone. *Lancet* 1984; **i:** 11–14.

Neurally mediated hypotension. Fludrocortisone may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p.1174) but there is limited evidence to support its use.

Orthostatic hypotension. Orthostatic (postural) hypotension[1-8] is a fall in blood pressure that occurs upon rising abruptly to an erect position, although it may also occur after a period of prolonged standing. Characteristic symptoms include lightheadedness, dizziness, blurred vision, weakness in the limbs, and syncope.

The causes of orthostatic hypotension are wide-ranging and include autonomic dysfunction, such as in the Shy-Drager syndrome, diabetes mellitus, and Parkinson's disease, circulating volume depletion, phaeochromocytoma, and Addison's disease. Orthostatic hypotension may also occur following a period of prolonged bed rest or after meals.

Orthostatic hypotension may result from the adverse effects of a range of drugs, such as antihypertensives, diuretics, tricyclic antidepressants, phenothiazines, and MAOIs.

In mild cases **nonpharmacological treatment** alone may be adequate. This includes increasing salt intake if not contra-indicated, maintaining adequate hydration, the use of elastic stockings to improve venous return and increase cardiac output, and elevating the head of the bed to reduce early morning symptoms. Drug-induced orthostatic hypotension should be treated by withdrawing the drug or by dose reduction.

Pharmacological treatment. No pharmacological treatment is entirely satisfactory: responses and tolerance vary greatly between patients. Fludrocortisone acetate is usually tried first; it increases sodium retention and thus plasma volume. Most reports indicate some response in about 80% of patients, but hypokalaemia, fluid retention, and supine hypertension may limit its use. In patients who fail to respond adequately an NSAID (usually indometacin) may be tried, alone or with fludrocortisone. In patients with overt autonomic failure a beta blocker with some partial agonist activity, such as pindolol, may be tried although they are potentially dangerous.

Sympathomimetics may be useful in some patients with autonomic failure; the direct acting drugs such as phenylephrine or midodrine are usually more consistently effective than the indirect such as ephedrine, but even so, responses tend to vary with the degree of denervation. Ambulatory noradrenaline infusion therapy is under investigation for severe refractory orthostatic hypotension. Patients with central neurological abnormalities may respond to desmopressin, while drugs such as ergotamine or dihydroergotamine may be useful for resistant disease.

Other drugs that have been tried include metoclopramide, which may be useful for autonomic symptoms in patients with diabetes mellitus, fluoxetine, octreotide, yohimbine, clonidine, and in patients with concurrent anaemia, erythropoietin. Caffeine has been tried in postprandial hypotension but its value in all but the mildest cases is dubious.[5] The use of MAOIs (which given alone can induce orthostatic hypotension) with a sympathomimetic to induce a pressor reaction is controversial. Most of these drugs have potentially serious adverse effects and few are well evaluated.

1. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39:** 74–85.
2. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153:** 474–85.
3. Schoenberger JA. Drug-induced orthostatic hypotension. *Drug Safety* 1991; **6:** 402–7.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51:** 648–60.
5. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.
6. Frishman WH, *et al.* Drug treatment of orthostatic hypotension and vasovagal syncope. *Heart Dis* 2003; **5:** 49–64.
7. Freeman R. Treatment of orthostatic hypotension. *Semin Neurol* 2003; **23:** 435–42.
8. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; **120:** 841–7.

Preparations

BP 2008: Fludrocortisone Tablets;
USP 31: Fludrocortisone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lonikan; ***Austral.:*** Florinef; ***Austria:*** Astonin H; ***Braz.:*** Florinefe; ***Canad.:*** Florinef; ***Chile:*** Florinef; ***Denm.:*** Florinef; ***Fin.:*** Florinef; ***Ger.:*** Astonin H; ***Gr.:*** Florinef; ***Hong Kong:*** Florinef; ***Hung.:*** Astonin H; ***Irl.:*** Florinef; ***Israel:*** Florinef†; ***Malaysia:*** Florinef; ***Mex.:*** Florinef; ***Neth.:*** Florinef; ***Norw.:*** Florinef; ***NZ:*** Florinef; ***Pol.:*** Cortineff; ***Rus.:*** Cortineff (Кортинефф); ***S.Afr.:*** Florinef; ***Singapore:*** Florinef; ***Spain:*** Astonin; ***Swed.:*** Florinef; ***Switz.:*** Florinef; ***Thai.:*** Florinef; ***UK:*** Florinef; ***USA:*** Florinef; ***Venez.:*** Florinefe†.

Multi-ingredient: ***Belg.:*** Panotile; ***Braz.:*** Otodol†; Panotil; ***Fr.:*** Panotile; ***Ger.:*** Panotile N†; ***Gr.:*** Paroticin; ***Indon.:*** Nelicort; Otopain; Otopraf; Otozambon; ***Neth.:*** Panotile; ***Pol.:*** Dicortineff; ***Spain:*** Fludronef; Panotile; ***Switz.:*** Panotile; ***Thai.:*** Otosamthong.

Fludroxycortide *(BAN, rINN)* ⊗

33379; Fludroksikortidi; Fludroxicortida; Fludroxikortid; Fludroxycortidum; Fluorandrenolone; 6α-Fluoro-16α-hydroxyhydrocortisone 16,17-Acetonide; Flurandrenolide *(USAN)*; Flurandrenolone. 6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

Флудроксикортид

$C_{24}H_{33}FO_6$ = 436.5.

CAS — 1524-88-5.

ATC — D07AC07.

ATC Vet — QD07AC07.

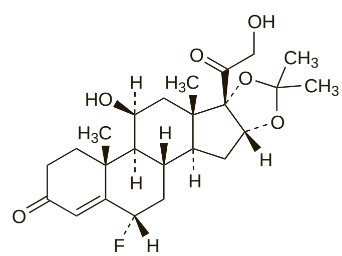

Pharmacopoeias. In *US.*

USP 31 (Flurandrenolide). A white to off-white, fluffy, odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 72 of alcohol, 1 in 10 of chloroform, and 1 in 25 of methyl alcohol. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Profile

Fludroxycortide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.0125% or 0.05%. It is also used as an adhesive polyethylene tape impregnated with fludroxycortide 4 micrograms/cm^2.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

USP 31: Flurandrenolide Cream; Flurandrenolide Lotion; Flurandrenolide Ointment; Flurandrenolide Tape; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment.

Proprietary Preparations (details are given in Part 3)
Braz.: Drenison; ***UK:*** Haelan; ***USA:*** Cordran.

Multi-ingredient: ***Braz.:*** Dreniformio; Drenison N.

Flumetasone Pivalate *(BANM, rINNM)* ⊗

Flumetason pivalát; Flumétasone, pivalate de; Flumetasoni pivalas; Flumetasonipivalaatti; Flumetasonpivalat; Flumetasonum Pivalas; Flumetazon Pivalat; Flumetazono pivalatas; Flumetazon-pivalát; Flumetazonu piwalan; Flumethasone Pivalate *(USAN)*; Flumethasone Trimethylacetate; NSC-107680; Pivalato de flumetasona. Flumethasone 21-pivalate.

Флуметазона Пивалат

$C_{27}H_{36}F_2O_6$ = 494.6.

CAS — 2002-29-1.

ATC — D07AB03.

ATC Vet — QD07AB03.

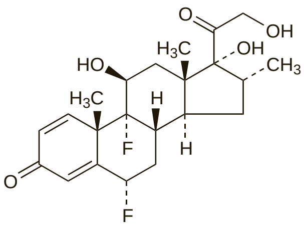

(flumetasone)

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Flumetasone Pivalate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in acetone. Protect from light.

USP 31 (Flumethasone Pivalate). A white to off-white crystalline powder. Insoluble in water; soluble 1 in 89 of alcohol, 1 in 350 of chloroform, and 1 in 2800 of ether; slightly soluble in methyl alcohol; very slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flumetasone pivalate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a 0.02% cream, ointment, or lotion. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Flumetasone pivalate is also used in ear drops in a concentration of 0.02% with clioquinol 1%.

Preparations

USP 31: Flumethasone Pivalate Cream.

Proprietary Preparations (details are given in Part 3)

Belg.: Locacortene; ***Ger.:*** Cerson; Locacorten; ***Ital.:*** Locorten†; ***Neth.:*** Locacorten; ***Pol.:*** Lorinden; ***Switz.:*** Locacorten; ***Venez.:*** Lexifal†; Locorten†.

Multi-ingredient: ***Arg.:*** Locorten Vioformo†; Salena†; Tresite F; ***Austral.:*** Locacorten Vioform; ***Austria:*** Locacorten mit Neomycin; Locacorten Tar; Locacorten Vioform; Locasalen; ***Belg.:*** Locacortene Tar†; Locacortene Vioforme†; Locasalen; ***Braz.:*** Locorten Vioformio; Locorten†; Losalen; ***Canad.:*** Locacorten Vioform; ***Cz.:*** Locacorten Tar†; Lorinden A†; Lorinden C†; ***Denm.:*** Locacorten Vioform; ***Fin.:*** Locacorten Vioform; ***Fr.:*** Locacortene Vioforme; Locacortene†; Locasalene; Psocortene; ***Ger.:*** Locacorten Vioform; Locasalen; Lorinden T†; ***Gr.:*** Locacorten Neomycin†; Locasalene; ***Hong Kong:*** Locacorten Tar†; Locasalen; ***Hung.:*** Lorinden A; Lorinden C; ***Indon.:*** Locasalen; ***Israel:*** Locacorten with Neomycin†; Topicorten V; Topicorten-Tar; Topisalen; ***Ital.:*** Locorten; Locorten Vioformio; Losalen; Vasosterone Oto; ***Neth.:*** Locacorten Vioform; Locasalen; ***NZ:*** Locorten Vioform; ***Philipp.:*** Locasalen; ***Pol.:*** Lorinden A; Lorinden C; Lorinden N; ***Port.:*** Locorten Vioformio†; Losalen†; ***Rus.:*** Lorinden A (Лоринден А); Lorinden C (Лоринден С); ***S.Afr.:*** Locacorten Vioform; ***Spain:*** Losalen; ***Swed.:*** Locacorten Vioform; ***Switz.:*** Locasalen; ***Thai.:*** Flumasalen; Locasalen; ***Turk.:*** Locacorten Vioform; Locasalene; ***UK:*** Locorten Vioform; ***Venez.:*** Flutalon†; Locasalen; Locorten Vioformo.

Flunisolide *(BAN, USAN, rINN)* ⊗

Flunisolid; Flunisolida; Flunisolidi; Flunisolidum; RS-3999; RS-1320 (flunisolide acetate). 6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

Флунизолид

$C_{24}H_{31}FO_6$ = 434.5.

CAS — 3385-03-3 (flunisolide); 77326-96-6 (flunisolide hemihydrate); 4533-89-5 (flunisolide acetate).

ATC — R01AD04; R03BA03.

ATC Vet — QR01AD04; QR03BA03.

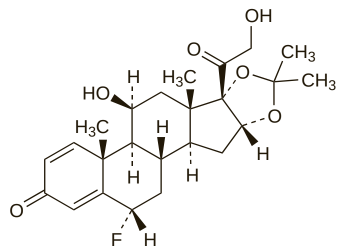

Pharmacopoeias. In *US* which specifies the hemihydrate.

USP 31 (Flunisolide). A white to creamy-white crystalline powder. Practically insoluble in water; soluble in acetone; sparingly soluble in chloroform; slightly soluble in methyl alcohol.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495. Flunisolide is reported to undergo extensive first-pass metabolism, with only 20% of the dose available systemically if it is given by mouth. The major metabolite, 6β-hydroxyflunisolide has some glucocorticoid activity; it has a half-life of about 4 hours. Only small amounts of flunisolide are absorbed after intranasal doses.

◊ References.

1. Chaplin MD, *et al.* Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980; **27:** 402–13.
2. Möllmann H, *et al.* Pharmacokinetic/pharmacodynamic evaluation of systemic effects of flunisolide after inhalation. *J Clin Pharmacol* 1997; **37:** 893–903.

Uses and Administration

Flunisolide is a corticosteroid with glucocorticoid activity (p.1490) used as a nasal spray for the prophylaxis and treatment of allergic rhinitis (p.565). In the UK a formulation containing 25 micrograms per metered spray is available, whereas in the USA each metered spray contains 29 micrograms flunisolide. In adults, the recommended starting dose is 2 sprays into each nostril twice daily, increased if necessary to three times daily, and then reduced for maintenance. In the USA a maximum dose of 8 sprays into each nostril daily has been established. For children aged from about 5 to 14 years, 1 spray into each nostril may be given up to 3 times daily; the USA also allows for an initial 2 sprays into each nostril twice daily (this is the recommended maximum of 4 sprays into each nostril daily).

Flunisolide is also used by inhalation from metered-dose aerosols in the management of asthma (p.1108). The usual adult dosage of flunisolide from an aerosol using chlorofluorocarbon (CFC) propellants is 500 micrograms inhaled twice daily. In severe asthma the dosage may be increased but should not exceed a total of 2 mg daily. A dose for children of 6 to 15 years of age is 500 micrograms inhaled twice daily, which should not be exceeded. A hydrofluoroalkane (CFC-free) aerosol, which is also available in some countries, has a lower dose because of different delivery characteristics. The usual adult dose, expressed as flunisolide hemihydrate, is 160 micrograms twice daily, which may be increased after 3 to 4 weeks but should not exceed 320 micrograms twice daily. In children aged 6 to 11 years of age a dose of 80 micrograms twice daily may be used, increased to a maximum of 160 micrograms twice daily if necessary.

Preparations

USP 31: Flunisolide Nasal Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Flunitec†; ***Austria:*** Pulmilide; ***Belg.:*** Syntaris; ***Canad.:*** Rhinalar†; ***Cz.:*** Bronilide†; Syntaris; ***Denm.:*** Locasyn†; ***Fr.:*** Nasalide; ***Ger.:*** Inhacort†; Syntaris; ***Gr.:*** Bronalide†; ***Irl.:*** Syntaris†; ***Ital.:*** Aerflu; Aerolid; Asmaflu; Assolid; Careflu; Charlyn; Citiflux; Desaflu; Doricoflu; Eliosid; Euroflu; Fluminex; Flunigar†; Flunitop; Gibiflu; Givair; Inalcort; Kaimil; Levonis; Lunibron; Lunis; Nebulcort; Nereflun; Nisolid; Nisoran; Pantasol†; Plaudit; Pulmist; Syntaris; Turm; Ventoflu; ***Neth.:*** Syntaris; ***Norw.:*** Lokilan; ***Switz.:*** Broncort†; Syntaris†; ***UK:*** Syntaris; ***USA:*** AeroBid; AeroSpan; Nasalide†; Nasarel.

Multi-ingredient: ***Ital.:*** Plenaer.

Fluocinolone Acetonide *(BANM, USAN, rINN)* ⊗

Acetónido de fluocinolona; 6α,9α-Difluoro-16α-hydroxyprednisolone Acetonide; Fluocinolon acetonid; Fluocinolonacetonid; Fluocinolon-acetonid; Fluocinolone, acétonide de; Fluocinoloni acetonidum; Fluocinolono acetonidas; Fluocynolonu acetonid; Fluosinoloniasetonidi; NSC-92339. 6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

Флуоцинолона Ацетонид

$C_{24}H_{30}F_2O_6$ = 452.5.

CAS — 67-73-2.

ATC — C05AA10; D07AC04; S01BA15.

ATC Vet — QC05AA10; QD07AC04; QS01BA15.

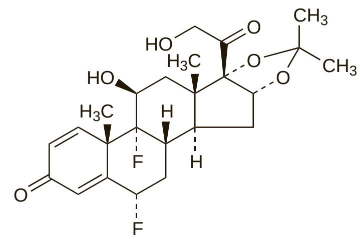

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *Viet. Br.* and *Viet.* have a separate monograph for the dihydrate; *US* allows either the anhydrous form or the dihydrate.

Ph. Eur. 6.2 (Fluocinolone Acetonide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol and in acetone. Protect from light.

BP 2008 (Fluocinolone Acetonide Dihydrate). A white or almost white, crystalline powder. Practically insoluble in water and in hexane; soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 31 (Fluocinolone Acetonide). It is anhydrous or contains two molecules of water of hydration. A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 45 of alcohol, 1 in 25 of chloroform, and 1 in 350 of ether; soluble in methyl alcohol.

Profile

Fluocinolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application; concentrations normally range from 0.0025 to 0.025% although higher-strength preparations may be available. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Fluocinolone acetonide is also used topically with an antibacterial in the treatment of infective inflammatory eye, ear, and nose disorders.

A sterile implant of fluocinolone acetonide is used intravitreally for the treatment of chronic non-infectious posterior uveitis.

Formulation. The potency of fluocinolone acetonide varied with the formulation in a study[1] involving different *Synalar* topical preparations, the gel, ointment, and cream. The cream was the most potent followed by the gel, and then the ointment. A comparison of topical vasoconstrictor activity (used as an index of potency) unexpectedly found that the commercial dilutions of the cream (containing 0.00625% and 0.0025%) were indistinguishable in their effects from the full-strength (0.025%) cream.

1. Gao HY, Li Wan Po A. Topical formulations of fluocinolone acetonide: are creams, gels and ointments bioequivalent and does dilution affect activity? *Eur J Clin Pharmacol* 1994; **46:** 71–5.

Preparations

BP 2008: Fluocinolone Cream; Fluocinolone Ointment;
USP 31: Fluocinolone Acetonide Cream; Fluocinolone Acetonide Ointment; Fluocinolone Acetonide Topical Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream.

Proprietary Preparations (details are given in Part 3)

Arg.: Duoflu; Flulone; ***Austria:*** Synalar; ***Belg.:*** Synalar; ***Canad.:*** Capex; Derma-Smoothe/FS; Fluoderm†; Synalar; ***Chile:*** Adermina; ***Cz.:*** Flucinar; Gelargin; Synalar†; ***Denm.:*** Synalar; ***Fr.:*** Synalar†; ***Ger.:*** Flucinar; Jellin; Jellisoft; ***Gr.:*** Synalar; ***Hong Kong:*** Cinotec†; Flunolone-V†; Synalar; ***Hung.:*** Flucinar; Synalar†; ***India:*** Flucort; Flucort-H; Luci; ***Indon.:*** Cinolon; Dermasolon; Esinol; Inoderm; Licosolon; ***Irl.:*** Synalar†; ***Israel:*** Dermalar; ***Ital.:*** Atoactive; Cortamide†; Dermobeta; Dermolin; Esacinone†; Fluocit; Fluomix Same; Fluovitef; Fluvean†; Localyn; Localyn SV; Omniderm; Sterolone; Ultraderm; ***Malaysia:*** Synalar†; ***Mex.:*** Cortifung-S; Cortilona; Cremisona; Farmacorti; Flumicin; Fluomex; Fusalar; Lonason; Synalar; ***Norw.:*** Synalar; ***NZ:*** Synalar; ***Philipp.:*** Aplosyn; Cynozet; Synalar; Syntopic; ***Pol.:*** Flucinar; ***Port.:*** Oto-Synalar N; Synalar; ***Rus.:*** Flucinar (Флуцинар); Sinaflan (Синафлан); ***S.Afr.:*** Cortoderm; Fluoderm; Synalar; ***Singapore:*** Flunolone-V; ***Spain:*** Co Fluocin Fuerte; Cortiespec; Fluocid Forte; Fluodermo Fuerte; Flusolgen; Gelidina; Intradermo Corticosteroi†; Synalar; Synalar Rectal Simple; ***Swed.:*** Synalar; ***Switz.:*** Synalar; ***Thai.:*** Cervicum; Fluciderm†; Flunolone-V; Fulone; Supralan; Synalar; ***UK:*** Synalar; ***USA:*** Capex; Derma-Smoothe/FS; DermOtic; Fluonid; Flurosyn†; Retisert; Synalar; Synemol; ***Venez.:*** Bratofil; Fluquinol Simple†; Neo-Synalar; Neoflu†.

Multi-ingredient: ***Arg.:*** Adop-Tar†; Tri-Luma; ***Austria:*** Myco-Synalar; Procto-Synalar; Synalar N; ***Belg.:*** Procto-Synalar; Synalar Bi-Otic; ***Braz.:*** Dermobel†; Dermoxin; Elotin; Fluo-Vaso; Neocinolon; Otauril†; Otocort†; Otomixyn; Otosynalar; Tri-Luma; Vitacid Plus; ***Chile:*** Otoseptil; Tri-Luma; ***Denm.:*** Synalar med Chinoform; ***Fr.:*** Antibio-Synalar; ***Ger.:*** Jellin polyvalent†; Jellin-Neomycin; Procto-Jellin†; ***Gr.:*** Myco-Synalar; Procto Synalar†; Procto-Synalar N; ***Hong Kong:*** Aplosyn-Otic; Flunolone; Fluonid-N; Synalar N; Synco-CFN; Syneolona; Tri-Luma; ***Hung.:*** Eczil†; Flucinar N; Synalar N†; ***India:*** Eczo-Wokadine; Flucort-C; Flucort-MZ; Flucort-N; Flucreme NM; Luci-N; Micogel F; Neocip FC; Zole-F; ***Indon.:*** Cinogenta; Cinolon-N; Fasolon; Genolon; Gentasolon; Kalcinol-N; Neosinol; Ociderm-N; Sinobiotik; Zumaderm-N; ***Irl.:*** Synalar C†; Synalar N†; ***Ital.:*** Cortanest Plus; Doricum; Lauromicina; Localyn; Localyn-Neomicina; Mecloderm F; Meclutin†; Nefluan; Proctolyn; ***Malaysia:*** Flumicin; Fluonid-N†; Synalar N†; Tri-Luma; ***Mex.:*** Acenil; Bentix; Cetoquina Y; Cortifung-N; Cortifung-Y; Cortilona Compuesta; Farmacorti YC; Fluccinol C†; Fluccinol N; Flunal-Neo†; Flunal†; Fluo Grin; Gynoclin-V; Lasalar-Y; Luzolona Y; Neoderm-F; Nysmosons-V; Promibasol-Plus; Synalar C; Synalar N; Synalar Neo; Synalar O; Synalar Oftalmico; Tri-Luma; Vagitrol-V; Yderm; ***Neth.:*** Synalar Bi-Otic†; ***Norw.:*** Synalar med Chinoform; ***Philipp.:*** Aplosyn C; Aplosyn N; Aplosyn-Otic; Neo-Synalar; Synalar Otic; Tri-Luma; ***Pol.:*** Flucinar N; ***Port.:*** Synalar N; Synalar Rectal; ***Rus.:*** Flucinar N (Флуцинар Н); Simetrid (Симетрид); ***S.Afr.:*** Cortoderm-C; Synalar C; Synalar N; ***Singapore:*** Flunolone; Tri-Luma; ***Spain:*** Abrasone; Abrasone Rectal; Aceoto Plus; Alergical; Artrodesmol Extra; Bazalin; Cetraxal Plus; Cexidal Otico†; Creanolona; Flodermol; Fluo Fenic; Intradermo Cort Ant Fung†; Midacina; Neo Analsona; Otomidrin; Synalar Nasal; Synalar Neomicina; Synalar Otico; Synalar Rectal; Synalotic; Synobel†; Ultramicina Plus†; Vinciseptil Otico; ***Switz.:*** Myco-Synalar†; Procto-Synalar N; Synalar N; ***Thai.:*** Fluciderm-N†; Flunolone; Fluonid-N; Gental-F; Supralan-N; Synalar N; Tri-Luma; ***UK:*** Synalar C; Synalar N; ***USA:*** Tri-Luma; ***Venez.:*** Bratofil c Neomicina; Fluquinol†; Neo-Synalar con Neomicina; Neo-Synalar con Yodoclorohidroxiquina†; Neo-Synalar†; Neoflu con Neomicina†; Tri-Luma.

Fluocinonide *(BAN, USAN, rINN)* ⊗

Fluocinolide; Fluocinolone Acetonide 21-Acetate; Fluocinonid; Fluocinónida; Fluocinonidum; Fluosinonidi; NSC-101791. 6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate.

Флуоцинонид

$C_{26}H_{32}F_2O_7$ = 494.5.

CAS — 356-12-7.

ATC — C05AA11; D07AC08.

ATC Vet — QC05AA11; QD07AC08.

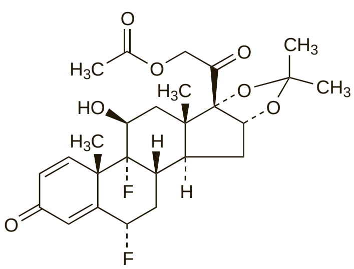

Pharmacopoeias. In *Br.*, *Chin.*, *Jpn*, and *US.*

BP 2008 (Fluocinonide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in chloroform. Protect from light.

USP 31 (Fluocinonide). A white to cream-coloured, crystalline powder having not more than a slight odour. Practically insoluble in water; slightly soluble in alcohol, in methyl alcohol, and in dioxan; sparingly soluble in acetone and in chloroform; very slightly soluble in ether.

Profile

Fluocinonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application containing 0.05%. A cream containing 0.1% may also be available.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

BP 2008: Fluocinonide Cream; Fluocinonide Ointment;
USP 31: Fluocinonide Cream; Fluocinonide Gel; Fluocinonide Ointment; Fluocinonide Topical Solution.

Proprietary Preparations (details are given in Part 3)
Austria: Topsym; Topsymin F; ***Belg.:*** Lidex†; ***Canad.:*** Lidemol; Lidex; Lyderm; Lydonide†; Tiamol; Topsyn; ***Denm.:*** Metosyn; ***Ger.:*** Topsym; ***Gr.:*** Lidex; ***Ital.:*** Flu-21†; Topsyn; ***Mex.:*** Topsyn; ***Norw.:*** Metosyn; ***Philipp.:*** Lidemol; Lidex; ***Singapore:*** Lidex†; ***Spain:*** Klariderm†; Novoter; ***Switz.:*** Topsym; Topsymin; ***UK:*** Metosyn; ***USA:*** Lidex; Vanos.

Multi-ingredient: ***Austria:*** Topsym polyvalent; ***Ger.:*** Jelliproct; Topsym polyvalent; ***Hung.:*** Vipsogal†; ***Israel:*** Comagis; ***Mex.:*** Topsyn-Y; ***Philipp.:*** Lidex NGN; ***Spain:*** Novoter Gentamicina; ***Switz.:*** Mycolog N; Topsym polyvalent; ***UK:*** Vipsogal.

Fluocortin Butyl *(BAN, USAN, rINNM)* ⊗

Butil éster de la fluocortina; Butylis Fluocortinas; Fluocortine Butyle; SH-K-203. Butyl 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-oate.

Флуокортин Бутил

$C_{26}H_{35}FO_5$ = 446.6.

CAS — 33124-50-4 (fluocortin); 41767-29-7 (fluocortin butyl).

ATC — D07AB04.

ATC Vet — QD07AB04.

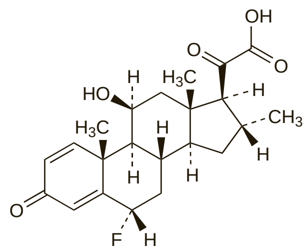

(fluocortin)

Profile

Fluocortin butyl is a corticosteroid that has been used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.75%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Fluocortin butyl has also been used in the form of a dry powder nasal inhalation for the management of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Varlane†; ***Ger.:*** Vaspit†; ***Ital.:*** Vaspit; ***Spain:*** Vaspit.

Multi-ingredient: ***Ger.:*** Bi-Vaspit†.

Fluocortolone *(BAN, USAN, rINN)* ⊗

Fluocortolona; Fluocortolonum; Fluokortolon; Fluokortoloni; 6α-Fluoro-16α-methyl-1-dehydrocorticosterone; SH-742. 6α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Флуокортолон

$C_{22}H_{29}FO_4$ = 376.5.

CAS — 152-97-6.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

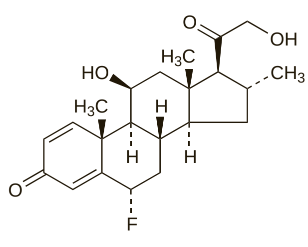

Fluocortolone Caproate *(USAN, rINNM)* ⊗

Caproato de fluocortolona; Fluocortolone, Caproate de; Fluocortolone Hexanoate *(BANM)*; Fluocortoloni Caproas; Fluokortolon Kaproat; Fluokortolon Kapronat; SH-770. Fluocortolone 21-hexanoate.

Флуокортолона Капроат

$C_{28}H_{39}FO_5$ = 474.6.

CAS — 303-40-2.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

Pharmacopoeias. In *Br.*

BP 2008 (Fluocortolone Hexanoate). A white or creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water and in ether; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone and in dioxan; sparingly soluble in chloroform. Protect from light.

Fluocortolone Pivalate *(BANM, rINNM)* ⊗

Fluocortolone, pivalate de; Fluocortolone Trimethylacetate; Fluocortoloni pivalas; Fluokortolon Pivalat; Fluokortolonipivalaatti; Fluokortolono pivalatas; Fluokortolonpivalat; Fluokortolon-pivalát; Pivalato de fluocortolona. Fluocortolone 21-pivalate.

Флуокортолона Пивалат

$C_{27}H_{37}FO_5$ = 460.6.

CAS — 29205-06-9.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fluocortolone Pivalate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dioxan. Protect from light.

Profile

Fluocortolone and its esters are corticosteroids mainly used topically for their glucocorticoid activity (p.1490) in the treatment of various skin disorders. They are usually used as a cream or ointment; concentrations usually used are 0.25% of the caproate with 0.25% of either the free alcohol or pivalate ester. The pivalate and caproate esters have also been used together in ointments or suppositories for the treatment of anorectal disorders.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Fluocortolone free alcohol is sometimes given orally for its systemic effects in conditions for which corticosteroids are indicated (p.1495), in usual doses of 5 to 100 mg daily.

Preparations

BP 2008: Fluocortolone Cream.

Proprietary Preparations (details are given in Part 3)
Arg.: Ultracur S; ***Austria:*** Ultralan; ***Chile:*** Ultralan†; ***Ger.:*** Ultralan; ***Hong Kong:*** Ultralan; ***Israel:*** Ultralan; ***Ital.:*** Ultralan; ***Mex.:*** Ultralan†; ***Philipp.:*** Ultralan; ***Spain:*** Ultralan M; ***Turk.:*** Ultralan.

Multi-ingredient: ***Arg.:*** Ultraproct; ***Austral.:*** Ultraproct; ***Austria:*** Pilison; Ultraproct; ***Belg.:*** Ultraproct; ***Braz.:*** Ultraproct; ***Chile:*** Ultraproct; ***Denm.:*** Doloproct; Doloproct Comp; ***Fin.:*** Neoproct; ***Fr.:*** Ultralan; Ultraproct; ***Ger.:*** Doloproct; Ultralan†; Ultraproct†; ***Gr.:*** Doloproct; ***Hong Kong:*** Ultraproct N; Ultraproct†; ***Indon.:*** Ultraproct; Ultraproct N; ***Irl.:*** Ultraproct; ***Ital.:*** Doloproct; Ultraproct; ***Mex.:*** Ultraproct; ***NZ:*** Ultraproct; ***Philipp.:*** Ultraproct; ***Port.:*** Ultraproct; ***Rus.:*** Ultraproct (Ультрапрокт); ***Thai.:*** Scheriproct N; ***Turk.:*** Ultralan Crilane; Ultraproct; ***UK:*** Ultralanum Plain; Ultraproct.

Fluorometholone *(BAN, rINN)* ⊗

Fluorométholone; Fluorometholonum; Fluorometolon; Fluorometolona; Fluorometoloni. 9α-Fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

Флуорометолон

$C_{22}H_{29}FO_4$ = 376.5.

CAS — 426-13-1.

ATC — C05AA06; D07AB06; S01BA07.

ATC Vet — QC05AA06; QD07AB06; QD07XB04; QD10AA01; QS01BA07; QS01CB05.

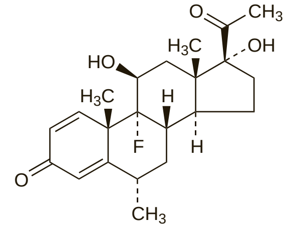

Pharmacopoeias. In *Br.*, *Jpn*, and *US.*

BP 2008 (Fluorometholone). A white to yellowish white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in ether.

USP 31 (Fluorometholone). A white to yellowish-white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 2200 of chloroform; very slightly soluble in ether. Store in airtight containers. Protect from light.

Fluorometholone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de fluorometolona; Fluorométholone, Acétate de; Fluorometholoni Acetas; Fluorometolon Asetat; U-17323. Fluorometholone 17-acetate.

Флуорометолона Ацетат

$C_{24}H_{31}FO_5$ = 418.5.
CAS — 3801-06-7.
ATC — C05AA06; D07AB06; S01BA07.
ATC Vet — QC05AA06; QD07AB06; QS01BA07.

Pharmacopoeias. In *US.*

USP 31 (Fluorometholone Acetate).

Profile

Fluorometholone is a corticosteroid used for its glucocorticoid activity (p.1490), usually as eye drops containing 0.1%, in the treatment of allergic and inflammatory conditions of the eye. Fluorometholone acetate is used similarly.

Fluorometholone is also used topically in the treatment of various skin disorders.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

BP 2008: Fluorometholone Eye Drops;
USP 31: Fluorometholone Cream; Fluorometholone Ophthalmic Suspension; Neomycin Sulfate and Fluorometholone Ointment; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Flarex; FML; ***Austral.:*** Flarex; Flucon; FML; ***Austria:*** Flarex†; ***Belg.:*** Fluacort; Flucon; FML; ***Braz.:*** Florate; Flumex; Flutinol; ***Canad.:*** Flarex; FML; ***Chile:*** Aflarex; Fluforte; ***Cz.:*** Efflumidex; Flarex; Flucon; Flumetol S†; Fluoropos; ***Denm.:*** Flurolon; ***Fin.:*** FML; ***Fr.:*** Flucon; ***Ger.:*** Efflumidex; Fluoro-Ophtal; Fluoropos; Isopto Flucon†; ***Gr.:*** Flucon; Fluxinam; FML; Talirax†; ***Hong Kong:*** Flarex; Flucon; Flumetholon; FML; ***Hung.:*** Efflumidex; Flarex; Flucon; ***India:*** Flomex; Flosef; ***Indon.:*** Flumetholon; ***Irl.:*** FML; ***Israel:*** Flarex; FML; ***Ital.:*** Flarex; Fluaton; Flumetol; Flumetol Semplice†; ***Malaysia:*** Flarex; FML†; ***Mex.:*** Flarex; Fluforte; Flumetol NF; ***Neth.:*** Flarex; FML; ***NZ:*** Flarex†; Flucon; FML; ***Philipp.:*** Flarex; Flulon; FML; ***Pol.:*** Flarex; Flucon; ***Port.:*** Flurop; FML; ***Rus.:*** Flarex (Фларекс); ***S.Afr.:*** Flucon; FML; ***Singapore:*** FML; ***Spain:*** FML; Isopto Flucon; ***Switz.:*** FML; ***Thai.:*** Flarex; Flu Oph; Flucon; FML; ***Turk.:*** Flarex; FML; ***UK:*** FML; ***USA:*** Eflone; Flarex; Fluor-Op†; FML; ***Venez.:*** Aflarex; Flumetol.

Multi-ingredient: ***Arg.:*** Delisan; Efemolina; FML Neo; Larsimal; Nesbiler†; ***Belg.:*** Infectoflam; ***Braz.:*** Flumex N; ***Chile:*** Fluforte N†; ***Cz.:*** Infectoflam†; ***Ger.:*** Cibaflam; Efemolin; Efflumycin†; ***Gr.:*** Efemoline; FML Neo; Indocort†; Luzin; ***Hong Kong:*** Efemoline; ***India:*** Flomex N; ***Ital.:*** Efemoline; Flumeciclina; Flumetol Antibiotico†; Flumezina; Gentacort; ***Malaysia:*** Efemoline†; Infectoflam†; ***Mex.:*** Fluforte N; Fluorometil; ***Philipp.:*** Efemoline; Infectoflam; ***Port.:*** FML Neo; Neo-Preocil; ***S.Afr.:*** Efemoline; FML Neo; ***Singapore:*** Efemoline; Infectoflam; ***Spain:*** Bexicortil; Cortisdin Urea; Flugen; Fluorvas; ***Switz.:*** Efemoline; FML Neo; Infectoflam; ***Thai.:*** Efemoline; FML Neo†; Infectoflam; ***Turk.:*** Efemoline; Flumetol; ***USA:*** FML-S.

Fluprednidene Acetate *(BANM, rINNM)* ⊗

Acetato de fluprednideno; Fluprednidène, Acétate de; Fluprednideni Acetas; Fluprednylidene 21-Acetate. 9α-Fluoro-11β,17α,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione 21-acetate.

Флупреднидена Ацетат

$C_{24}H_{29}FO_6$ = 432.5.
CAS — 2193-87-5 (fluprednidene); 1255-35-2 (fluprednidene acetate).
ATC — D07AB07.
ATC Vet — QD07AB07.

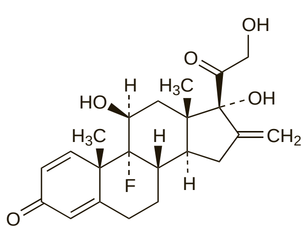

(fluprednidene)

Profile

Fluprednidene acetate is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a 0.1% cream, or as an ointment containing 0.05% or 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Decoderm; ***Belg.:*** Decoderm; ***Ger.:*** Decoderm; ***Indon.:*** Decoderm; ***Port.:*** Crinohermal; ***Swed.:*** Corticoderm†; ***Switz.:*** Decoderm.

Multi-ingredient: ***Arg.:*** Tri-Emcortina†; ***Austria:*** Decoderm Compositum; Decoderm trivalent; ***Belg.:*** Decoderm Compositum; ***Braz.:*** Emecort†; Pan-Emecort†; ***Ger.:*** Candio-Hermal Plus; Crinohermal fem; Decoderm Comp; Decoderm tri; Sali-Decoderm; Vobaderm; ***Gr.:*** Antimycotic; Catrigel; Combi; Conazol; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Fluniprol; Flunovon; Fosemyk; Fumicon; Micoflup; Micogen; Mifler; Oxigon; Panderm; Panmyk; Sarmel; Verdal; ***Indon.:*** Decoderm 3; Gentacortin; ***Switz.:*** Decoderm bivalent; ***Thai.:*** Supracortin 3†; ***UK:*** Acorvio Plus.

Fluticasone *(BAN, rINN)* ⊗

Fluticasona; Fluticasonum. S-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate.

Флутиказон

$C_{22}H_{27}F_3O_4S$ = 444.5.
CAS — 90566-53-3.
ATC — D07AC17; R01AD08; R03BA05.
ATC Vet — QD07AC17; QR01AD08; QR03BA05.

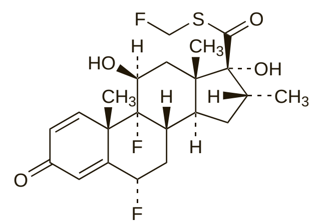

Fluticasone Furoate *(BANM, USAN, rINN)* ⊗

Fluticasonum Furoas; Furoate de Fluticasone; Furoato de Fluticasona; GW-685698X. 6α,9-Difluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate.

Флутиказон Фуроат

$C_{27}H_{29}F_3O_6S$ = 538.6.
CAS — 397864-44-7.
ATC — D07AC17; R01AD08; R01AD12; R03BA05.
ATC Vet — QD07AC17; QR01AD08; QR01AD12; QR03BA05.

Fluticasone Propionate *(BANM, USAN, rINNM)* ⊗

CCI-18781; Fluticasone, propionate de; Fluticasoni propionas; Flutikasonipropionaatti; Flutikasonpropionat; Flutikason-propionát; Flutikazon Propiyonat; Flutikazono propionatas; Propionato de fluticasona. S-Fluoromethyl 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate 17-propionate.

Флутиказона Пропионат

$C_{25}H_{31}F_3O_5S$ = 500.6.
CAS — 80474-14-2.
ATC — D07AC17; R01AD08; R03BA05.
ATC Vet — QD07AC17; QR01AD08; QR03BA05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluticasone Propionate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Fluticasone Propionate). Micronised fluticasone propionate is a fine white powder. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490). Hypersensitivity reactions have occurred. Eosinophilic conditions, including Churg-Strauss syndrome, have been reported rarely, in most cases after a transfer from oral corticosteroid therapy.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Inhalation or nasal use of large amounts of fluticasone may produce systemic effects also (see below).

Adrenal suppression. Despite the fact that inhaled fluticasone is generally thought to lack systemic effects at therapeutic doses, a study in 25 healthy subjects[1] indicated that fluticasone propionate as single inhaled doses of 250, 500, and 1000 micrograms did produce a reduction in plasma cortisol, indicating suppression of the hypothalamic-pituitary-adrenal axis to some degree. Others have also found evidence of adrenal suppression with fluticasone,[2-5] particularly at high doses and in children,[6] and the effect may be more marked with repeated than with single doses.[4,6-8] A number of cases of adrenal crisis have been associated with high-dose inhaled fluticasone,[9,10] including at least one fatality.[6] It has been recommended that children using inhaled fluticasone at doses above 400 micrograms daily should have adrenal function monitoring and a written plan for emergency corticosteroid replacement therapy.[6]

1. Grahnén A, *et al.* An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994; **38:** 521–5.
2. Clark DJ, *et al.* Comparative systemic bioactivity of inhaled budesonide and fluticasone propionate in asthmatic children. *Br J Clin Pharmacol* 1996; **42:** 264P.
3. Rohatagi S, *et al.* Dynamic modeling of cortisol reduction after inhaled administration of fluticasone propionate. *J Clin Pharmacol* 1996; **36:** 938–41.
4. Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997; **52:** 55–8.
5. Eid N, *et al.* Decreased morning serum cortisol levels in children with asthma treated with inhaled fluticasone propionate. *Pediatrics* 2002; **109:** 217–21.
6. Paton J, *et al.* Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch Dis Child* 2006; **91:** 808–13.
7. Lönnebo A, *et al.* An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur J Clin Pharmacol* 1996; **49:** 459–63.
8. Wilson AM, *et al.* Adrenal suppression with high doses of inhaled fluticasone propionate and triamcinolone acetonide in healthy voluteers. *Eur J Clin Pharmacol* 1997; **53:** 33–7.
9. Todd GRG, *et al.* Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; **87:** 457–61.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Fluticasone and adrenal crisis. *Aust Adverse Drug React Bull* 2003; **22:** 6. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0304.htm (accessed 06/05/04)

Aspergillosis. The fungal infection aspergillosis has been reported in patients receiving inhaled[1,2] and intranasal[3] fluticasone.

1. Fairfax AJ, *et al.* Laryngeal aspergillosis following high dose inhaled fluticasone therapy for asthma. *Thorax* 1999; **54:** 860–1.
2. Leav BA, *et al.* Invasive pulmonary aspergillosis associated with high-dose inhaled fluticasone. *N Engl J Med* 2000; **343:** 586.
3. Bratton RL, *et al.* Aspergillosis related to long-term nasal corticosteroid use. *Mayo Clin Proc* 2002; **77:** 1353–7.

Effects on the bones. For studies of the effects on bone of inhaled fluticasone, compared with beclometasone, see p.1516.

Effects on the muscles. Proximal myopathy has been reported in children receiving high-dose inhaled fluticasone;[1] the patients recovered after replacement of fluticasone with alternative corticosteroid therapy.

1. De Swert LF, *et al.* Myopathy in children receiving high-dose inhaled fluticasone. *N Engl J Med* 2004; **350:** 1157–9.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Fluticasone propionate is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism; oral bioavailability is reported to be only about 1%.

◊ References.

1. Mackie AE, *et al.* Pharmacokinetics of intravenous fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 539–42.
2. van Boxtel CJ, Sheffer AL, eds. The pharmacokinetics of fluticasone propionate. *Clin Pharmacokinet* 2000; **39** (suppl): 1–54.
3. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol* 2001; **51:** 103–5.
4. Allen A, *et al.* Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin Ther* 2007; **29:** 1415–20.

Uses and Administration

Fluticasone is a corticosteroid with mainly glucocorticoid activity (p.1490).

Fluticasone propionate is stated to exert a topical effect on the lungs without significant systemic effects at usual doses, due to its low systemic bioavailability (but see Adrenal Suppression, above). It is used by powder or aerosol inhalation for the prophylaxis of **asthma**. Typical initial doses in the UK range from 100 to 250 micrograms twice daily in mild asthma up to 1 mg twice daily in severe asthma, adjusted according to response. Children over 4 years of age may be given initial doses of 50 to 100 micrograms twice daily, increased to 200 micrograms twice daily if necessary.

The drug may also be given via a nebuliser in severe chronic asthma. Usual adult doses are 0.5 to 2 mg twice daily. Children aged 4 to 16 years may be given 1 mg twice daily. In the USA, doses by powder inhalation are similar to that in the UK. The aerosol inhalation formulations contain 50, 125, or 250 micrograms of fluticasone propionate in each metered spray, which delivers 44, 110, or 220 micrograms, respectively from the actuator. Doses are therefore expressed in these units; dosage ranges from 88 micrograms twice daily to 880 micrograms twice daily, depending on previous therapy. Children aged 4 to 11 years are given 88 micrograms twice daily.

Fluticasone propionate is also available in some countries as a powder or aerosol inhalation for the treatment of **chronic obstructive pulmonary disease**, when it is given in doses of 500 micrograms twice daily.

Fluticasone is administered by nasal spray in the prophylaxis and treatment of **allergic rhinitis**. The usual dose of fluticasone propionate is 100 micrograms into each nostril once daily, increased if necessary to 100 micrograms into each nostril twice daily. Children over 4 years of age may be given half these doses. Fluticasone furoate is also used in the management of allergic rhinitis. This salt has enhanced affinity for the glucocorticoid receptor, and is given in a starting dose of 55 micrograms into each nostril once daily. When the maximum benefit has been achieved and symptoms controlled, the dose should be gradually reduced to the minimum effective dose; 27.5 micrograms into each nostril once daily may be sufficient to maintain control of symptoms. Children aged 2 years and over may be started on 27.5 micrograms into each nostril once daily, which may be increased to 55 micrograms into each nostril once daily if necessary to control symptoms.

Fluticasone propionate drops are used in the treatment of **nasal polyps**, 200 micrograms should be instilled into each nostril once or twice daily for at least 4 to 6 weeks.

Fluticasone propionate is applied topically in the treatment of various **skin disorders**. Creams and ointments containing 0.05% and 0.005%, respectively are available. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (p.1108). Patients requiring only occasional relief from symptoms may be managed with an inhaled short-acting beta$_2$ agonist, and an inhaled corticosteroid such as fluticasone is added if symptomatic relief is needed more than once daily. In more severe asthma other drugs may be added (combination with a long-acting beta$_2$ agonist may have synergistic benefits), or the dose of inhaled corticosteroid may be increased.

Some references to the use of fluticasone propionate for asthma are given below,[1-15] including one to a study indicating that increasing the dose of inhaled fluticasone did not produce increased benefit.[1]

1. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. *Eur Respir J* 1994; **7:** 2179–84.
2. Jarvis B, Faulds D. Inhaled fluticasone propionate: a review of its therapeutic efficacy at dosages ≤ 500 micrograms/day in adults and adolescents with mild to moderate asthma. *Drugs* 1999; **57:** 769–803.
3. Bisgaard H, *et al.* The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999; **160:** 126–31.
4. Markham A, Jarvis B. Inhaled salmeterol/fluticasone propionate combination: a review of its use in persistent asthma. *Drugs* 2000; **60:** 1207–33.
5. ZuWallack R, *et al.* Long-term efficacy and safety of fluticasone propionate powder administered once or twice daily via inhaler to patients with moderate asthma. *Chest* 2000; **118:** 303–312.
6. Holt S, *et al.* Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001; **323:** 253–6.
7. Purucker ME, *et al.* Inhaled fluticasone propionate by diskus in the treatment of asthma: a comparison of the efficacy of the same nominal dose given either once or twice a day. *Chest* 2003; **124:** 1584–93.
8. Masoli M, *et al.* Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax* 2004; **59:** 16–20.
9. Masoli M, *et al.* Systematic review of the dose-response relation of inhaled fluticasone propionate. *Arch Dis Child* 2004; **89:** 902–7.
10. Adams NP, *et al.* Fluticasone at different doses for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 12/05/06).
11. Adams NP, *et al.* Fluticasone versus placebo for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).
12. Reynolds NA, *et al.* Inhaled salmeterol/fluticasone propionate: a review of its use in asthma. *Drugs* 2005; **65:** 1715–34.
13. Lasserson TJ, *et al.* Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 12/05/06).
14. Guilbert TW, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; **354:** 1985–97.
15. Adams N, *et al.* Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 22/08/08).

Chronic obstructive pulmonary disease. For discussion of the value of inhaled corticosteroids in chronic obstructive pulmonary disease, including reference to the use of fluticasone, see p.1501.

Reviews.

1. Fenton C, Keating GM. Inhaled salmeterol/fluticasone propionate: a review of its use in chronic obstructive pulmonary disease. *Drugs* 2004; **64:** 1975–96.
2. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; **67:** 2383–2405.

Cough. A small study in children with persistent nocturnal cough compared fluticasone propionate 1 mg twice daily for 3 nights, followed by 500 micrograms twice daily for 11 nights, given by metered-dose inhaler, with placebo. Coughs reduced significantly by nights 15 and 16 in the children given the corticosteroid. However, both groups improved significantly compared to baseline, leading the authors to conclude that inhaled corticosteroids should not be given at the time of presentation of persistent nocturnal cough. If they are given, then a 2-week course of high dose corticosteroids may benefit some children.[1] In a controlled crossover study in adult patients with chronic cough, inhaled fluticasone 500 micrograms twice daily for 14 days significantly improved certain measurements of cough, although overall reduction in cough severity was modest.[2] In adults with a cough lasting more than 2 weeks, fluticasone 500 micrograms twice daily for 2 weeks decreased cough scores from day 5 onwards in non-smokers.[3]

1. Davies MJ, *et al.* Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. *Arch Dis Child* 1999; **81:** 38–44.
2. Chaudhuri R, *et al.* Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *J Allergy Clin Immunol* 2004; **113:** 1063–70.
3. Ponsioen BP, *et al.* Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J* 2005; **25:** 147–52.

Eczema. In a study in patients with moderate to severe eczema (p.1579), fluticasone propionate 0.05% cream or 0.005% ointment was applied once or twice daily for 4 weeks; if eczema stabilised, either the cream, the ointment, or an emollient placebo was then applied on 2 days per week, for up to 16 weeks. Fluticasone cream reduced the risk of relapse to about one-sixth of that of placebo, whereas the ointment formulation reduced the risk to about half; median times to relapse were similar for both fluticasone formulations. The formulations were originally expected to be of similar potency.[1] Others have commented[2] that caution should be exercised in generalising these results to primary care settings where most cases of eczema are likely to be mild, and relapses infrequent.

1. Berth-Jones J, *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; **326:** 1367.
2. Williams HC. Twice-weekly topical corticosteroid therapy may reduce atopic dermatitis relapses. *Arch Dermatol* 2004; **140:** 1151–2.

Inflammatory bowel disease. Fluticasone propionate, given orally, has produced variable results in the treatment of Crohn's disease[1] and ulcerative colitis;[2,3] some benefit was also reported in coeliac disease.[4] The dose was 5 mg four times daily but some consider[2] higher doses necessary.

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p.1697.

1. Carpani de Kaski M, *et al.* Fluticasone propionate in Crohn's disease. *Gut* 1991; **32:** 657–61.
2. Hawthorne AB, *et al.* Double blind trial of oral fluticasone propionate v prednisolone in the treatment of active ulcerative colitis. *Gut* 1993; **34:** 125–8.
3. Angus P, *et al.* Oral fluticasone propionate in active distal ulcerative colitis. *Gut* 1992; **33:** 711–14.
4. Mitchison HC, *et al.* A pilot study of fluticasone propionate in untreated coeliac disease. *Gut* 1991; **32:** 260–5.

Nasal polyps. For discussion of the value of corticosteroids in the treatment of nasal polyps, including reference to the use of fluticasone, see p.1508.

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p.565. Some further references to the use of fluticasone in rhinitis are given below.

1. Wiseman LR, Benfield P. Intranasal fluticasone propionate: a reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs* 1997; **53:** 885–907.
2. McCormack PL, Scott LJ. Fluticasone furoate: intranasal use in allergic rhinitis. *Drugs* 2007; **67:** 1905–15.

Preparations

BP 2008: Fluticasone Cream; Fluticasone Nasal Spray; Fluticasone Ointment;
USP 31: Fluticasone Propionate Nasal Spray.

Proprietary Preparations (details are given in Part 3)
Arg.: Cutivate; Flixonase; Flixotide; Fluti-K; Fluticort; Lidil Cort; Proair; Rinisona; ***Austral.:*** Avamys; Beconase Allergy; Flixonase; Flixotide; ***Austria:*** Cutivate; Flixonase; Flixotide; ***Belg.:*** Cutivate; Flixonase; Flixotide; ***Braz.:*** Flixonase; Flixotide; Fluticaps; Flutivate; Plurair; ***Canad.:*** Cutivate; Flonase; Flovent; ***Chile:*** Albeoler; Brexonase; Brexovent; Flixonase; Flixotide; Flusona; Flutivate; Nebulex; Raffonin; ***Cz.:*** Alergonase; Avamys; Cutivate; Flixonase; Flixotide; Nasofan; ***Denm.:*** Cutivat; Flixonase; Flixotide; ***Fin.:*** Flixonase; Flixotide; ***Fr.:*** Flixonase; Flixotide; Flixovate; ***Ger.:*** Atemur; Flutide; Flutivate; ***Gr.:*** Alerxem; Cortixide; Dermocort; Flicazen; Flihaler; Flixocort; Flixoderm; Flixonase†; Flixotide; Flucortis; Flutinasal; Flutizal; Ybecor; ***Hong Kong:*** Cutivate; Flixonase; Flixotide; ***Hung.:*** Cutivate; Flixonase; Flixotide; Flutirin; ***India:*** Flohale; Flomist; Zoflut; ***Indon.:*** Cutivate; Flixonase; Flixotide; Medicort; ***Irl.:*** Flixonase; Flixotide; Nasofan; ***Israel:*** Allegro; Cutivate†; Flixonase; Flixotide; ***Ital.:*** Flixoderm; Flixonase; Flixotide; Fluspiral; Ticavent; ***Jpn:*** Flonase; ***Malaysia:*** Cutivate; Flixonase; Flixotide; ***Mex.:*** Cutivate; Flixonase; Flixotide; ***Neth.:*** Cutivate; Flixonase; Flixotide; Flutide; ***Norw.:*** Flutide; Flutivate; ***NZ:*** Flixonase; Flixotide; Nasaclear; ***Philipp.:*** Cutivate; Flixotide; ***Pol.:*** Cutivate; Flixonase; Flixotide; ***Port.:*** Asmatil; Asmo-Lavi; Brisovent; Cutivate; Eustidil; Flixotaide; Flutaide; Rontilona; Ubizol; ***Rus.:*** Cutivate (Кутивейт); Flixonase (Фликсоназе); Flixotide (Фликсотид); Seretide (Серетид); ***S.Afr.:*** Cutivate; Flixonase; Flixotide; Flohale DP; Flomist; ***Singapore:*** Cutivate; Flixonase; Flixotide; ***Spain:*** Drolasona†; Flixonase; Flixotide; Fluinol; Flusonal; Inalacor; Rinosone; Rontilona; Trialona; ***Swed.:*** Flutide; Flutivate; ***Switz.:*** Axotide; Cutivate; Flutinase; ***Thai.:*** Flixonase; Flixotide; ***Turk.:*** Brethal; Cutivate; Flixonase; Flixotide; ***UAE:*** Potencort; ***UK:*** Cutivate; Flixonase; Flixotide; Nasofan; ***USA:*** Cutivate; Flonase; Flovent; Veramyst; ***Venez.:*** Cutivate; Flixonase; Flixotide; Fluticort.

Multi-ingredient: ***Arg.:*** Flutivent; Neumotide; Seretide; ***Austral.:*** Seretide; ***Austria:*** Seretide; Viani; ***Belg.:*** Seretide; ***Braz.:*** Seretide; ***Canad.:*** Advair; ***Chile:*** Aerometrol Plus; Aurituss; Brexotide; Seretide; ***Cz.:*** Duaspir; Seretide; ***Denm.:*** Seretide; ***Fin.:*** Seretide; ***Fr.:*** Seretide; ***Ger.:*** Atmadisc; Viani; ***Gr.:*** Seretide; Viani†; ***Hong Kong:*** Seretide; ***Hung.:*** Seretide; Thoreus; ***India:*** Duonase; Forair; Seretide; Seroflo; ***Indon.:*** Seretide; ***Irl.:*** Seretide; ***Israel:*** Seretide; ***Ital.:*** Aliflus; Seretide; ***Malaysia:*** Seretide; ***Mex.:*** Seretide; ***Neth.:*** Seretide; Viani; ***Norw.:*** Seretide; ***NZ:*** Seretide; ***Philipp.:*** Seretide; ***Pol.:*** Seretide; ***Port.:*** Brisomax; Maizar; Seretaide; Veraspir; ***S.Afr.:*** Seretide; ***Singapore:*** Seretide; ***Spain:*** Anasma; Brisair; Inaladuo; Plusvent; Seretide; ***Swed.:*** Seretide; ***Switz.:*** Seretide; ***Thai.:*** Seretide; ***Turk.:*** Seretide; ***UK:*** Seretide; ***USA:*** Advair; ***Venez.:*** Seretide.

Formocortal *(BAN, USAN, rINN)* ⊗

Fl-6341; Fluoroformylon; Formocortalum. 3-(2-Chloroethoxy)-9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-20-oxopregna-3,5-diene-6-carbaldehyde 21-acetate.

Формокортал

$C_{29}H_{38}ClFO_8$ = 569.1.
CAS — 2825-60-7.
ATC — S01BA12.
ATC Vet — QS01BA12.

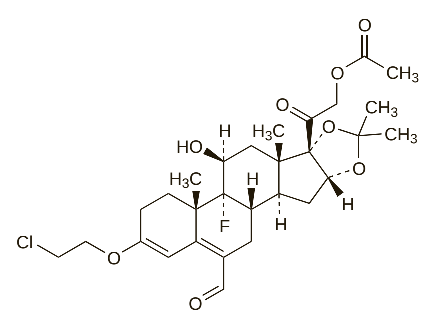

Profile

Formocortal is a corticosteroid that is used for its glucocorticoid activity (see p.1490) in the treatment of inflammatory eye disorders as eye drops and eye ointments containing 0.05%.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Formoftil.

Multi-ingredient: ***Ital.:*** Formomicin.

Halcinonide *(BAN, USAN, rINN)* ⊗

Alcinonide; Halcinonid; Halcinónida; Halcinonidum; Halsinonid; Halsinonidi; SQ-18566. 21-Chloro-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

Гальцинонид

$C_{24}H_{32}ClFO_5$ = 455.0.

CAS — 3093-35-4.

ATC — D07AD02.

ATC Vet — QD07AD02.

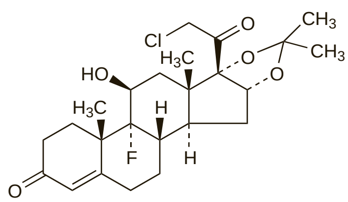

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Halcinonide). A white to off-white, odourless, crystalline powder. Insoluble in water and in hexanes; slightly soluble in alcohol and in ether; soluble in acetone and in chloroform.

Profile

Halcinonide is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a 0.1% cream, lotion, or ointment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

USP 31: Halcinonide Cream; Halcinonide Ointment; Halcinonide Topical Solution.

Proprietary Preparations (details are given in Part 3)

Austria: Halog; ***Braz.:*** Halog; ***Canad.:*** Halog; ***Cz.:*** Betacorton; ***Ger.:*** Halog†; ***Hong Kong:*** Halog; ***India:*** Cortilate; ***Indon.:*** Halog; ***Ital.:*** Halciderm; ***Mex.:*** Dermalog; ***Spain:*** Halog; ***Switz.:*** Betacortone; ***Turk.:*** Volog; ***UK:*** Halciderm†; ***USA:*** Halog; ***Venez.:*** Halog.

Multi-ingredient: ***Cz.:*** Betacorton S; Betacorton U; ***Ger.:*** Halog Tri†; ***India:*** Cobederm-H; Cortilate-S; ***Ital.:*** Anfocort; Halciderm; Halciderm Combi; ***Mex.:*** Dermalog-C; ***Switz.:*** Betacortone; Betacortone S; ***Turk.:*** Betacorton; ***Venez.:*** Halcicomb; Halog.

Halometasone *(rINN)* ⊗

C-48401-Ba; Halometason; Halometasona; Halométasone; Halometasoni; Halometasonum; Halometazon; Halomethasone. 2-Chloro-6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Галометазон

$C_{22}H_{27}ClF_2O_5$ = 444.9.

CAS — 50629-82-8.

ATC — D07AC12.

ATC Vet — QD07AC12.

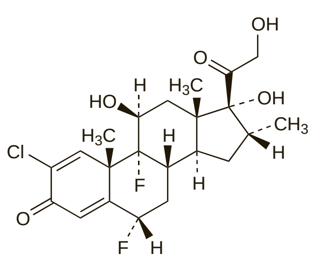

Profile

Halometasone is a corticosteroid used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream containing 0.05% of halometasone monohydrate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Sicorten; ***Belg.:*** Sicorten†; ***Ger.:*** Sicorten†; ***Hong Kong:*** Sicorten; ***Neth.:*** Sicorten†; ***Port.:*** Sicorten†; ***Spain:*** Sicorten; ***Switz.:*** Sicorten; ***Turk.:*** Sicorten.

Multi-ingredient: ***Ger.:*** Sicorten Plus; ***Hong Kong:*** Sicorten Plus†; ***Israel:*** Sicorten Plus†; ***Port.:*** Sicorten Plus†; ***Spain:*** Sicorten Plus; ***Switz.:*** Sicorten Plus; ***Venez.:*** Sicorten Plus†.

Hydrocortisone *(BAN, rINN)* ⊗

Anti-inflammatory Hormone; Compound F; Cortisol; Hidrocortisona; Hidrokortizon; Hidrokortizonas; Hydrocortisonum; Hydrokortison; Hydrokortisoni; Hydrokortyzon; 17-Hydroxycorticosterone; NSC-10483. 11β,17α,21-Trihydroxypregn-4-ene-3,20-dione.

Гидрокортизон

$C_{21}H_{30}O_5$ = 362.5.

CAS — 50-23-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QD07XA01; QH02AB09; QS01BA02; QS01CB03; QS02BA01.

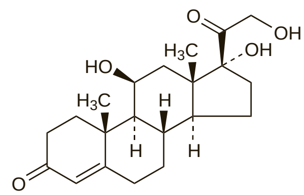

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Hydrocortisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; slightly soluble in dichloromethane. Protect from light.

USP 31 (Hydrocortisone). A white to practically white, odourless, crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 40 of alcohol and 1 in 80 of acetone; slightly soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Hydrocortisone Acetate *(BANM, rINNM)* ⊗

Acetato de hidrocortisona; Cortisol Acetate; Hidrokortizon Asetat; Hidrokortizon-acetát; Hidrokortizono acetatas; Hydrocortisone, acétate d'; Hydrocortisoni acetas; Hydrokortisonacetat; Hydrokortison-acetát; Hydrokortisoniasetaatti; Hydrokortyzonu octan. Hydrocortisone 21-acetate.

Гидрокортизона Ацетат

$C_{23}H_{32}O_6$ = 404.5.

CAS — 50-03-3.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

NOTE. HCOR is a code approved by the BP 2008 for use on single unit doses of eye drops containing hydrocortisone acetate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Hydrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 31 (Hydrocortisone Acetate). A white to practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 230 of alcohol and 1 in 200 of chloroform.

Hydrocortisone Buteprate *(BANM, rINNM)* ⊗

Buteprato de hidrocortisona; Hydrocortisone, Butéprate d'; Hydrocortisone Butyrate Propionate; Hydrocortisone Probutate *(USAN)*; Hydrocortisoni Butepras; TS-408. Hydrocortisone 17-butyrate 21-propionate.

Гидрокортизона Бутепрат

$C_{28}H_{40}O_7$ = 488.6.

CAS — 72590-77-3.

ATC — D07AB11.

ATC Vet — QD07AB11.

Hydrocortisone Butyrate *(BANM, USAN, rINNM)* ⊗

Butirato de hidrocortisona; Cortisol Butyrate; Hidrokortizon Bütirat; Hydrocortisone, Butyrate d'; Hydrocortisoni Butiras. Hydrocortisone 17α-butyrate.

Гидрокортизона Бутират

$C_{25}H_{36}O_6$ = 432.5.

CAS — 13609-67-1.

ATC — D07AB02.

ATC Vet — QD07AB02.

Pharmacopoeias. In *Chin., Jpn,* and *US.*

USP 31 (Hydrocortisone Butyrate). A white to practically white, practically odourless crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; freely soluble in chloroform; slightly soluble in ether.

Hydrocortisone Cipionate *(BANM, rINNM)* ⊗

Cipionato de hidrocortisona; Cortisol Cypionate; Hydrocortisone, Cipionate d'; Hydrocortisone Cyclopentylpropionate; Hydrocortisone Cypionate; Hydrocortisoni Cipionas. Hydrocortisone 21-(3-cyclopentylpropionate).

Гидрокортизона Ципионат

$C_{29}H_{42}O_6$ = 486.6.

CAS — 508-99-6.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

Hydrocortisone Hydrogen Succinate *(BANM, rINNM)* ⊗

Cortisol Hemisuccinate; Hidrogenosuccinato de hidrocortisona; Hidrokortizon-hidrogén-szukcinát; Hidrokortizono hemisukcinatas; Hydrocortisone Hemisuccinate; Hydrocortisone, Hémisuccinate d'; Hydrocortisone, hydrogénosuccinate d'; Hydrocortisone Succinate; Hydrocortisoni Hemisuccinas; Hydrocortisoni hydrogenosuccinas; Hydrokortison-hydrogen-sukcinát; Hydrokortisonivetysuksinaatti; Hydrokortisonvätesuccinat. Hydrocortisone 21-(hydrogen succinate).

Гидрокортизона Гемисукцинат

$C_{25}H_{34}O_8$ = 462.5.

CAS — 2203-97-6 (anhydrous hydrocortisone hydrogen succinate); 83784-20-7 (hydrocortisone hydrogen succinate monohydrate).

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. US* allows the anhydrous form or the monohydrate.

Ph. Eur. 6.2 (Hydrocortisone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali carbonates and alkali hydroxides. Store in airtight containers. Protect from light.

USP 31 (Hydrocortisone Hemisuccinate). It contains one molecule of water of hydration or is anhydrous. Store in airtight containers.

Hydrocortisone Sodium Phosphate *(BANM, rINNM)* ⊗

Cortisol Sodium Phosphate; Fosfato sódico de hidrocortisona; Hydrocortisone, Phosphate Sodique d'; Natrii Hydrocortisoni Phosphas. Hydrocortisone 21-(disodium orthophosphate).

Натрия Гидрокортизона Фосфат

$C_{21}H_{29}Na_2O_8P$ = 486.4.

CAS — 6000-74-4.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Hydrocortisone Sodium Phosphate). A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 31 (Hydrocortisone Sodium Phosphate). A white to light yellow, odourless or practically odourless, exceedingly hygroscopic, powder. Soluble 1 in 1.5 of water; slightly soluble in alcohol; practically insoluble in chloroform, in dioxan, and in ether. Store in airtight containers.

Hydrocortisone Sodium Succinate

(BANM, rINNM) ⊗

Cortisol Sodium Succinate; Hydrocortisone, Succinate Sodique d'; Hydrocortisoni Natrii Succinas; Hydrokortyzonu bursztynianu sól sodowa; Succinato sódico de hidrocortisona. Hydrocortisone 21-(sodium succinate).

Гидрокортизона Натрия Сукцинат

$C_{25}H_{33}NaO_8$ = 484.5.

CAS — 125-04-2.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

Pharmacopoeias. In *Chin., Int., It., Jpn., Pol.,* and *US.*

USP 31 (Hydrocortisone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform. Store in airtight containers. Protect from light.

Hydrocortisone Valerate *(BANM, USAN, rINNM)* ⊗

Cortisol Valerate; Hydrocortisone, Valérate d'; Hydrocortisoni Valeras; Valerato de hidrocortisona. Hydrocortisone 17-valerate.

Гидрокортизона Валерат

$C_{26}H_{38}O_6$ = 446.6.

CAS — 57524-89-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

Pharmacopoeias. In *US.*

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on fluid and electrolyte balance. A report of marked hypokalaemia and hypomagnesaemia associated with high-dose intravenous hydrocortisone therapy in an alcoholic patient with suspected immune thrombocytopenia.[1] Cardiac arrhythmias developed, and prolonged infusion of magnesium and potassium was required to restore normal plasma concentrations.

1. Ramsahoye BH, *et al.* The mineralocorticoid effects of high dose hydrocortisone. *BMJ* 1995; **310:** 656–7.

Effects on the nervous system. For reports and comments on paraesthesia or perineal irritation associated with hydrocortisone sodium phosphate given intravenously, see p.1492.

Hypersensitivity and anaphylaxis. References to hypersensitivity reactions and anaphylaxis associated with the intravenous use of hydrocortisone;[1-7] topical application can also result in hypersensitivity.[8]

1. Chan CS, *et al.* Hydrocortisone-induced anaphylaxis. *Med J Aust* 1984; **141:** 444–6.
2. Seale JP. Anaphylactoid reaction to hydrocortisone. *Med J Aust* 1984; **141:** 446.
3. Corallo CE, Sosnin M. Bronchospasm, tachycardia following intravenous hydrocortisone. *Aust J Hosp Pharm* 1985; **15:** 103–4.
4. Al Mahdy H, Hall M. Anaphylaxis and hydrocortisone. *Ann Intern Med* 1988; **108:** 487–8.
5. Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust* 1991; **154:** 210–14.
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Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief account of the pharmacokinetics of corticosteroids, see p.1495.

Hydrocortisone is readily absorbed from the gastrointestinal tract and peak blood concentrations are attained in about an hour. The plasma half-life is about 100 minutes. It is more than 90% bound to plasma proteins. Following intramuscular injection, the absorption of the water-soluble sodium phosphate and sodium succinate esters is rapid, while absorption of hydrocortisone free alcohol and its lipid-soluble esters is slower. Absorption of hydrocortisone acetate after intra-articular or soft-tissue injection is also slow. Hydrocortisone is absorbed through the skin, particularly in denuded areas.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in the urine, mainly conjugated as glucuronides, with a very small proportion of unchanged hydrocortisone. Hydrocortisone readily crosses the placenta.

Uses and Administration

Hydrocortisone is a corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity (p.1490). As cortisol it is the most important of the predominantly glucocorticoid steroids secreted by the adrenal cortex. Hydrocortisone is used, usually with a more potent mineralocorticoid, for replacement therapy in adrenocortical insufficiency (p.1498). It may also be used for its glucocorticoid properties in other conditions for which corticosteroid therapy is indicated (p.1495) but drugs with fewer mineralocorticoid effects tend to be preferred for the long-term systemic therapy of auto-immune and inflammatory disease.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of hydrocortisone:

- hydrocortisone acetate 112 mg
- hydrocortisone buteprate 135 mg
- hydrocortisone butyrate 119 mg
- hydrocortisone cipionate 134 mg
- hydrocortisone hydrogen succinate 128 mg
- hydrocortisone sodium phosphate 134 mg
- hydrocortisone sodium succinate 134 mg
- hydrocortisone valerate 123 mg

However, esterification generally alters potency and compounds with equivalent hydrocortisone content may not have equivalent clinical effect.

When given **orally** hydrocortisone free alcohol is usually used; the cipionate ester is used in some formulations. For **replacement therapy** in acute or chronic adrenocortical insufficiency the normal requirement is 20 to 30 mg daily (usually taken in 2 doses, the larger in the morning and the smaller in the early evening, to mimic the circadian rhythm of the body). Children may be given 400 to 800 micrograms/kg daily in 2 or 3 divided doses, adjusted as needed. Additional sodium chloride may be required if there is defective aldosterone secretion, but mineralocorticoid activity is usually supplemented by fludrocortisone acetate orally. Similar regimens have also been used to correct glucocorticoid deficiency in the salt-losing form of congenital adrenal hyperplasia (p.1502).

Hydrocortisone may be given **intravenously**, by slow injection or infusion, in the form of a water-soluble derivative such as hydrocortisone sodium succinate or hydrocortisone sodium phosphate when a rapid effect is required in **emergencies**: such conditions are acute adrenocortical insufficiency caused by Addisonian or post-adrenalectomy crises, by the abrupt accidental withdrawal of therapy in corticosteroid-treated patients, or by the inability of the adrenal glands to cope with increased stress in such patients; certain allergic emergencies such as anaphylaxis; acute severe asthma (status asthmaticus—see also p.1108); and shock. The usual dose is the equivalent of 100 to 500 mg of hydrocortisone, repeated 3 or 4 times in 24 hours, according to the severity of the condition and the patient's response. Children up to 1 year of age may be given 25 mg, those aged 1 to 5 years 50 mg, and those aged 6 to 12 years 100 mg. Fluids and electrolytes should be given as necessary to correct any associated metabolic disorder. Similar doses to those specified above may also be given **intramuscularly** but the response is likely to be less rapid than that observed after intravenous doses. Corticosteroids are considered to be of secondary value in anaphylactic shock because of their relatively slow onset of action, but intravenous hydrocortisone may be a useful adjunct to adrenaline to prevent further deterioration in severely affected patients.

In patients with adrenal deficiency states supplementary corticosteroid therapy may be necessary during some **surgical operations** and hydrocortisone sodium succinate or sodium phosphate may be given intramuscularly or intravenously before surgery. Various regimens have been proposed (see also Surgery, p.1497). In patients taking more than 10 mg of oral prednisolone or its equivalent daily, the *BNF* recommends the following regimen:

- *minor surgery under general anaesthesia*, either the usual oral corticosteroid dose on the morning of surgery *or* hydrocortisone 25 to 50 mg (usually as the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is resumed after surgery
- *moderate or major surgery*, the usual oral corticosteroid dose on the morning of surgery, *plus* hydrocortisone 25 to 50 mg intravenously at induction, and followed by similar doses of hydrocortisone 3 times daily, for 24 hours after moderate surgery and 48 to 72 hours after major surgery; the usual corticosteroid dose is resumed once hydrocortisone injections are stopped.

For **local injection** into soft tissues hydrocortisone is usually used in the form of the sodium phosphate or sodium succinate esters; doses in terms of hydrocortisone are usually 100 to 200 mg. For intra-articular injection hydrocortisone acetate is usually used in doses of 5 to 50 mg depending upon the size of the joint.

For **topical application** in the treatment of various skin disorders hydrocortisone and the acetate, buteprate, butyrate, and valerate esters are normally employed in creams, ointments, or lotions. Concentrations usually used have ranged from 0.1 to 2.5%. Although it is considered that hydrocortisone has fewer adverse effects on the skin and is less liable to cause adrenal suppression than the more potent topical corticosteroids (see p.1497 for a rough guide to the clinical potencies of topical corticosteroids), it should be borne in mind that this property may be considerably modified both by the type of formulation or vehicle used and by the type of esterification present; other factors that may also influence the degree of absorption include the site of application, use of an occlusive dressing, the degree of skin damage, and the size of the area to which the preparation is applied.

Hydrocortisone or its esters are also available in a variety of other dosage forms including those for ophthalmic, aural, dental, and rectal application, for use in allergic and inflammatory disorders.

Other esters of hydrocortisone that have occasionally been used include the aceponate, glycyrrhetinate, and propionate. Esters such as the aceponate may show modified topical activity.

Preparations

BP 2008: Gentamicin and Hydrocortisone Acetate Ear Drops; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injection; Hydrocortisone Acetate Ointment; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment; Hydrocortisone and Neomycin Cream; Hydrocortisone Cream; Hydrocortisone Ointment; Hydrocortisone Oromucosal Tablets; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate Injection; Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment;

USP 31: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone Ointment; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injectable Suspension; Hydrocortisone Acetate Lotion; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Ophthalmic Ointment; Hydrocortisone Acetate Ophthalmic Suspension; Hydrocortisone and Acetic Acid Otic Solution; Hydrocortisone Butyrate Cream; Hydrocortisone Cream; Hydrocortisone Gel; Hydrocortisone Injectable Suspension; Hydrocortisone Lotion; Hydrocortisone Ointment; Hydrocortisone Rectal Suspension; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate for Injection;

Hydrocortisone Tablets; Hydrocortisone Valerate Cream; Hydrocortisone Valerate Ointment; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Polymyxin B Sulfate and Hydrocortisone Otic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Alfacort; Anusol-HC; Azuthirona; Cortenem†; Demacort; Efficort†; Fridalit; Hidrotisona; Idenona†; Lactid HC; Locoid; Medrocil; Microsona; Oralsone; Schericur; Sirotamicin HC; Stiefcortil; Transderma H; ***Austral.:*** Colifoam; Cortaid†; Cortef; Cortic; Derm-Aid; Egocort; Hycor; Hysone; Sigmacort; Siguent Hycor; Solu-Cortef; ***Austria:*** Colifoam; Ekzemsalbe F; Hydoftal sine neomycino; Hydrocortone; Hydroderm; Locoidon; Retef; ***Belg.:*** Azacortine; Buccalsone†; Cortril†; Cremicort-H; Locoid; Nozema; Pannocort; Solu-Cortef; ***Braz.:*** Berlison; Cortisonal; Cortiston; Cortizol; Cortizon; Hidrocortex; Hidyn H; Locoid; Nutracort; Solu-Cortef†; Stiefcortil; Therasona; Westcort; ***Canad.:*** A-Hydrocort†; Barriere-HC; Claritin Skin Itch Relief; Cortate; Cortef; Cortenema; Cortifoam; Cortoderm; Dermaflex HC; Dermarest Dricort Anti-Itch; Emo-Cort; Hycort; Hyderm; Hydrosone; HydroVal; Novo-Hydrocort; Prevex HC; Sarna HC; Solu-Cortef; Westcort; ***Chile:*** Aquanil HC; Calmurid; Cortisol; Efficort; Hipoge; Lacticare-HC†; Locoid; Nutracort; Nutralona†; Pandel; Solu-Cortef; Vitulpas†; ***Cz.:*** Laticort†; Locoid; Solu-Cortef†; ***Denm.:*** Colifoam; Locoid; Mildison; Solu-Cortef; Uniderm; ***Fin.:*** Ampikyy; Apocort; Bucort; Colifoam; Kyppakkaus; Locoid; Nutracort†; Solu-Cortef; ***Fr.:*** Aphilan; Calmicort†; Colofoam; Cortapaisyl; Cortisedermyl; Dermaspraid Demangeaison; Dermofenac†; Efficort; Hydracort; Locoid; Mitocortyl; Proctocort†; ***Ger.:*** Alfason; Colifoam; Dermallerg†; Dermo Posterisan†; Ebenol; Fenistil Hydrocort; Ficortril; Glycocortison†; Hydro-Wolff†; Hydrocort†; Hydrocutan; Hydrocutan mild; Hydroderm HC; Hydrogalen; Laticort; Linola Cort Hydro; Munitren; Pandel; Posterine Corte†; Posterisan cort; ratioAllerg†; Remederm HC; Sanatison Mono; Soventol HC; Systral Hydrocort; velopural†; ***Gr.:*** Colifoam; Filocot; Lyo-Cortin†; Nutracort†; Rolak; Solu-Cortef; ***Hong Kong:*** Cortef; Derm-Aid; Dhacort; Efficort†; Egocort; Hycortin†; Hydrosone; Hytisone; Lacticare-HC†; Sigmacort; Solu-Cortef; ***Hung.:*** Cortef; Laticort; Locoid; Solu-Cortef; ***India:*** Cipcorlin; Cutisoft; Entofoam; Wycort; ***Indon.:*** Berlicort; Calacort; Enkacort; Lexacorton; Locoid; Steroderm; ***Irl.:*** Colifoam; Corlan; Cortopin; Dioderm; Hc45; Hydrocortisyl; Hydrocortone; Locoid; Mildison†; Solu-Cortef; ***Israel:*** Cortifoam; Cortizone; Efficort; Lanacort; Solu-Cortef; ***Ital.:*** Colifoam; Cortaid†; Cortidro; Cortop; Dermirit; Dermocortal; Efficort†; Flebocortid; Foille Insetti; Idracemi; Lanacort; Lenirit; Locoidon; Sintotrat; Solu-Cortef; ***Jpn:*** Pandel; ***Malaysia:*** Derm-Aid; Dhacort†; Efficort; Egocort; H-Cort; Hydrocort; Solu-Cortef; ***Mex.:*** Aquanil HC; Collicort; Efficort; Fadol; Flebocortid; Flemex; Icorsan; Lacticare-HC; Locoid; Microsona; Nositrol; Nutracort; Solhidrol; Westcort; ***Neth.:*** Buccalsone; Cremicort; Locoid; Mildison; Solu-Cortef; ***Norw.:*** Colifoam; Locoid; Mildison; Solu-Cortef; ***NZ:*** BK HC; Ciprobay HC; Derm-Aid; DP Hydrocortisone; Egocort; Lemnis Fatty Cream HC; Lipocort; Locoid; Mildison; Skincalm; Solu-Cortef; ***Philipp.:*** Cortizan; Droxiderm; Efficort; Hycortil; Hydrotopic; Lacticare-HC; Pharmacort; Solu-Cortef; ***Pol.:*** Corhydron; Laticort; Locoid; Procortin; ***Port.:*** Colifoam; Dermimade Hidrocortisona†; Hidalone; Hydrocortone; Lactisona; Locoid; Pandel; Pandermil; Rapicort; Solu-Cortef; ***Rus.:*** Cortef (Кортеф); Laticort (Латикорт); Locoid (Локоид); Solu-Cortef (Солу-кортеф)†; Sopolcort N (Сополькорт Н); ***S.Afr.:*** Biocort; Colifoam†; Covocort; Cutaderm†; Dilucort; Locoid; Mylocort; Procutan; Solu-Cortef; Stopitch; ***Singapore:*** Derm-Aid; Dhacort; Efficort; Egocort; Hydrocort; Hydroderm; Solu-Cortef; ***Spain:*** Actocortina; Aftasone; Ceneo; Dermosa Hidrocortisona; Hemodren; Hemorrane; Hidroaltesona; Hidrocisdin; Isdinium; Lactisona; Oralsone; Scalpicin Capilar; Schericur; Suniderma; ***Swed.:*** Colifoam; Ficortril; Locoid; Mildison; Solu-Cortef; Uniderm; ***Switz.:*** Alfacortone; Glycocortisone H†; Hydrocortone; Locoid; Sanadermil; Solu-Cortef; ***Thai.:*** Hytisone; Prevex HC; Solu-Cortef; ***Turk.:*** Cortimycine; Hipokort; Locoid; ***UAE:*** Alfacort; ***UK:*** Colifoam; Corlan; Cortopin; Cortropin; Dermacort; Dioderm; Efcortelan; Efcortesol; Exe-Cort; Hc45; Hydrocortistab; Hydrocortone; Lanacort; Locoid; Mildison; Solu-Cortef; Zenoxone; ***USA:*** A-Hydrocort; Acticort; Ala-Cort; Anucort-HC; Aquanil HC; Bactine; CaldeCort; Carmol HC; Cetacort; Colocort; Cort-Dome; Cortaid; Cortef; Cortef Feminine Itch; Cortenema†; Corticaine; Cortifoam; Cortizone; Dermarest Dri-Cort; Dermol HC; Dermolate; EarSol-HC; Gynecort; Hemril-HC; Hi-Cor; Hydrocortone; HydroSkin; Hytone; Lacticare-HC; Lanacort; Locoid; Massengill Medicated; Neutrogena T/Scalp; Nutracort; Orabase HCA; Pandel; Penecort; Procort; Proctocort; Proctocream HC 2.5%; Recort Plus; Solu-Cortef; Synacort; Tegrin-HC; Texacort; U-Cort; Westcort; ***Venez.:*** Corticina; Efficort; Hidrocort; Hidrozona; Histasona†; Lacticare-HC†; Liocort; Nutracort; Pantocort†; Solu-Cortef; Stricort.

Multi-ingredient: ***Arg.:*** Aeromicrosona C†; Alercortil†; Antibiocort†; Anusol Duo; Anusol Duo S; Atomoderma Plus; Bactisona; Bexon; Biocortin†; Cipro HC; Ciprocort; Ciproflox-Otic; Ciriax Otic; Ciriax Otic L; Colirio Antibiotico CNH; Cristalomicina; Delos Otic; Dercotex; Derivoco†; Dermoperative; Disel Hidrocortisona; Epiprocto; Gentacler; Gramicortil†; Griseoplus; Hidrocortin†; Hipoglos con Hidrocortisona; Irigal; Lactiderm HC†; Lidocort Proct; Linfol Dermico; Masivol Urea; Micozol Compuesto†; Microsona C; Microsona Otica; Monizol Cort; Neo Pelvicillin; Otex HC; Oto Biotaer; Otobiotic; Otocipro; Otoseptil; Otosporin; Otosporin C; Otosporin L; Procto-Ikatral; Proctocrem; Prootocipro; Prurisedan Biotic†; Quemicetina con Hidrocortisona; Reacur†; Start NP†; Terra-Cortril; Terra-Cortril Nistatina†; Tocorectal; Tricur; Tridermal; Triefect†; Vagicural; Xilocler; Xyloprocto; ***Austral.:*** Ciproxin HC; Hydroform; Hydrozole; Proctosedyl; Rectinol HC; Resolve Plus; Xyloproct; ***Austria:*** C-Bildz; Calmurid HC; Cortison Kemicetin; Hydoftal; Hydrocortimycin; Ichtho-Cortin; Otosporin; Tropoderm; ***Belg.:*** Daktacort; Eoline†; Fucidin Hydrocortisone; Onctose a l'Hydrocortisone; Otosporin†; Terra-Cortril; Terra-Cortril + Polymyxine B; ***Braz.:*** Anusol-HC; Cipro HC; Gingilone; Hemodotti; Hidrocorte; Hidroneo†; Nitrolerg†; Otociriax; Otosporin; Terra-Cortril; Vioformio-Hidrocortisona; Xyloproct; ***Canad.:*** Anodan-HC; Anugesic-HC; Anusol-HC; Anuzinc HC; Anuzinc HC Plus; Cipro HC; Cortimyxin; Cortisporin; Egozinc-HC; Fucidin H; Neo-Cortef†; Pentamycetin-HC; Pramox HC; Proctodan-HC; Proctofoam-HC; Proctol; Proctomyxin HC; Proctosedyl; ratio-Hemcort-HC; ratio-Proctosone; Rectogel HC; Rivasol HC; Sterex Plus; Uremol-HC; Vioform-Hydrocortisone; VoSoL HC†; ***Chile:*** Cortifenol H†; Fucidin H; Otex HC; ***Cz.:*** Ciprobay HC Otic; Dobexil Plus†; Fucidin H; Ophthalmo-Framykoin Compositum; Otosporin; Pimafucort; Proctosedyl†; Septomixine; ***Denm.:*** Brentacort; Ciflox; Fucidin-Hydrocortison; Hydrocortison med Terramycin; Hydrocortison med Terramycin og Polymyxin-B; Locoidol; Proctosedyl; ***Fin.:*** Ciproxin-Hydrocortison; Daktacort; Duocort; Fucidin-Hydrocortison; Locoidol†; Pantyson; Pimafucort; Proctosedyl; Sibicort; Terra-Cortril; Terra-Cortril P; Trosycort; Xyloproct†; ***Fr.:*** Bacicoline; Madecassol Neomycine Hydrocortisone†; ***Ger.:*** Antiprurit†; Baycuten HC; Canesten HC†; Corti Jaikal†; Farco-Tril†; Fucidine plus†; Hydrodexan; Ichthocortin; Novifort†; Nystaderm comp; Pigmanorm; Polyspectran HC; Posterisan Forte†; Terracortril†; ***Gr.:*** Ciprofloxacin HY†; Cortiphenol H; Daktodor; Fucidin H; Hydrofusin; Terra-Cortril; ***Hong Kong:*** Anusol-HC†; Canesten HC; Cipro HC; Corticin†; Cortiphenol H; Daktacort; Fucidin H; Hemcort HC†; Hydro-Funga; Micosone; Otosporin; Posterisan Forte; Proctosedyl†; Proctosone†; Xyloproct; ***Hung.:*** Chlorocid-H†; Ciprobay†; Fucidin H; Otosporin; Oxycort; Pimafucort; Posterisan Forte; Tetran-Hydrocortison; ***India:*** Bell Diono Resolvent; Bell Resolvent; Belmycetin-C; Cortison Kemicetine†; Cortola-m; Cortoquinol; Crotorax-HC; Daktacort; Efcorlin; Furacin-S; Genticyn HC†; Keralin; Medithane; Multifungin H†; Neosporin-H; Pino-Cort; Proctosedyl; Shield; Wycort c Neomycin; ***Indon.:*** Anusol-HC; Brentan; Chloramphecort; Dermacort; Enpicortyn; Haemocaine; Indoson; Kemiderm; Nufacort; Particol; Ramicort; Sancortmycin; Terra-Cortril; Thecort; Viohydrocort; Visancort; Zolacort; ***Irl.:*** Alphaderm; Alphosyl HC†; Anugesic-HC; Anusol-HC; Calmurid HC; Canesten HC; Daktacort; Eurax-Hydrocortisone; Fucidin H; Gentisone HC; Locoid C; Nystaform-HC†; Otosporin; Perinal; Proctofoam-HC; Proctosedyl; Quinocort†; Timodine; Vioform-Hydrocortisone; Xyloproct; ***Israel:*** Alphosyl HC†; Benzantine H; Calmurid HC†; Ciproxin HC; Daktacort; Epifoam; Fucidin H†; Hycocin; Hycomycin; Hydroagisten; Panthisone; Perinal; Procto-Glyvenol; Proctofoam-HC; Proctozorin-N; Xyloproct†; ***Ital.:*** Argisone; Cort-Inal; Cortison Chemicetina; Emorril; Fucidin H; Idracemi; Idracemi Eparina; Idrocet†; Idroneomicil†; Kinogen; Mictasone; Mixotone; Mobilat; Nasomixin; Nevacort; Prepacort H; Preparazione Antiemorroidaria†; Proctidol; Proctofoam-HC; Proctosedyl; Proctosoll; Reumacort; Scalpicin; Sedalen Cort†; Vasosterone; Vasosterone Antibiotico; Vasosterone Collirio; ***Malaysia:*** Becacort†; Candacort; Cipro HC†; Crotamiton H; Daktacort; Decocort; Foban-Hydro; Fucidin H; Miconazole H†; Neo-Hydro†; Pocin H; Proctosedyl; Proctosone†; Setarin H†; Ucort; Xyloproct; Zaricort†; ***Mex.:*** Angenovag; Biotarson N; Ciproxina HC; Clioderm-H; Cortisporin; Daktacort; Dermanol; Hidrofenil; Hidropolicin; Litiset; Ofodex; Orecil NF; Otifar; Oto Eni; Otolone†; Poral; Soldrin; Sulfa Hidro; Ultracortin; Vioformo-Cort; Xyloderm; Xyloproct Plus; ***Neth.:*** Bacicoline-B; Calmurid HC; Daktacort; Otosporin; Pimafucort; Proctosedyl; Terra-Cortril Gel Steraject met polymyxine-B†; Terra-Cortril met polymyxine-B; ***Norw.:*** Daktacort; Fucidin-Hydrocortison; Locoidol; Proctosedyl; Terra-Cortril; Terra-Cortril Polymyxin B; Xyloproct; ***NZ:*** Ciproxin HC; Daktacort; DP Lotion-HC; Fungocort†; Locoid C; Micreme H; Pimafucort; Proctosedyl; Xyloproct; ***Philipp.:*** Cortisporin; Daktacort; Fucidin H; Hydrospor; Isonep H; Proctosedyl; Trimycin-H; ***Pol.:*** Atecortin; Chlorchinaldin H; Daktacort†; Hemcort HC; Laticort-CH; Oxycort; Pimafucort; Posterisan H; Proctosone; ***Port.:*** Anucet; Clorcorticil†; Corticil T; Daktacort; Davimicina†; Fucidine H; Leuco Hubber†; Locoid C†; Otosporin; Pimafucort; Proctonostrum†; ***Rus.:*** Cortomycetin (Кортомицетин); Fucidin H (Фуцидин Г); Gioxyson (Гиоксизон); Oxycort (Оксикорт); Pimafucort (Пимафукорт); Posterisan Forte (Постеризан Форте); Relief Ultra (Релиф Ультра); ***S.Afr.:*** Calmurid HC†; Ciprobay HC; Daktacort; Fucidin H; Nasomixin†; Neoderm; Otosporin; Proctofoam†; Proctosedyl; Terra-Cortril; Viocort; ***Singapore:*** Candacort; Canesten HC; Ciprobay HC; Cortaid with Aloe†; Daktacort; Decocort; Fucidin H; Hydroderm-C; Micon-H; Neo-Hydro; Proctosedyl; Zaricort; ***Spain:*** Aftajuventus; Aftasone B C; Anginovag; Antihemorroidal; Bacisporin; Brentan; Cilinafosal Hidrocortisona; Ciproxina; Cohortan; Cortenema; Cortison Chemicet Topica; Dermo Hubber; Detraine; Edifaringen; Fucidine H; Grietalgen Hidrocort†; Halibut Hidrocortisona; Hemodren Compuesto†; Hepro; Leuco Hubber; Milrosina Nistatina; Neo Hubber; Oto Difusor†; Oto Vitna†; Otosporin; Roberfarin; Terra-Cortril; Tisuderma; ***Swed.:*** Cortimyk; Daktacort; Fenuril-Hydrokortison; Fucidin-Hydrocortison; Proctosedyl†; Terracortril; Terracortril med polymyxin B; Xyloproct; ***Switz.:*** Calmurid HC†; Ciproxin HC; Cortifluid N; Cortimycine; Daktacort; Dermacalm-d; Fucidin H; Haemocortin; Hydrocortisone compositum; Neo-Hydro; Otosporin; Septomixine; Terracortril†; ***Thai.:*** Antergan†; Candacort; Daktacort; Decocort; Dermasol; Doproct; Fucidin H; Ladocort; Otosporin†; Proctosedyl; ***Turk.:*** Cormisin; Kortos; Ma-Ka-Ta; Ureacort; ***UK:*** Actinac; Alphaderm; Alphosyl HC; Anugesic-HC; Anusol-HC; Plus HC; Calmurid HC; Canesten HC; Daktacort; Daktacort HC; Econacort; Eurax-Hydrocortisone; Fucidin H; Gentisone HC; Germoloids HC; Gregoderm†; Locoid C; Nystaform-HC; Otosporin; Perinal; Proctofoam-HC; Proctosedyl; Terra-Cortril†; Timodine; Uniroid-HC; Vioform-Hydrocortisone; Xyloproct; ***USA:*** 1 + 1-F; Acetasol HC; Alcortin; Analpram-HC; AnaMantle HC; Anumed HC; Cipro HC; Coly-Mycin S Otic; Corque; Cortane-B; Cortatrigen; Cortic ND; Corticaine; Cortimycin; Cortisporin; Cortisporin-TC; Cortisporin†; Cyotic; Dermtex HC with Aloe; Ear-Eze; Emergent-Ez; Enzone; Epifoam; Fungoid HC; HC Derma-Pax; HC Pramoxine; Hysone; LazerSporin-C; LidaMantle HC; Mediotic-HC; Neotricin HC; Novacort; Octicair†; Oti-Med†; Otic-Care; OtiTricin; Otobiotic; Otocort; Otomar-HC; Otomycin-HPN; Otosporin; Pediotic; Pramosone; Proctofoam-HC; Terra-Cortril; Tri-Otic†; UAD-Otic; Vanoxide-HC; VoSoL HC†; Vytone; Xyralid; Zone-A; Zoto-HC; ***Venez.:*** Hipoglos con Hidrocortisona†; Otalex; Quinotic HC; Terra-Cortril†.

Isoflupredone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de isoflupredona; 9α-Fluoroprednisolone Acetate; Isoflupredone, Acétate d'; Isoflupredoni Acetas; U-6013. 9α-Fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate.

Изофлупредона Ацетат

$C_{23}H_{29}FO_6$ = 420.5.

CAS — 338-95-4 (isoflupredone); 338-98-7 (isoflupredone acetate).

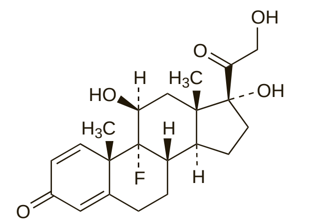

(isoflupredone)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Isoflupredone Acetate). Protect from light.

Profile

Isoflupredone acetate is a corticosteroid that has been used for its topical glucocorticoid activity (p.1490) in allergic rhinitis.

Isoflupredone is also employed in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Israel:*** Proaf.

Loteprednol Etabonate *(BANM, USAN, rINNM)* ⊗

CDDD-5604; Etabonato de loteprednol; HGP-1; Lotéprednol, Etabonate de; Loteprednol Ethyl Carbonate; Loteprednoli Etabonas; P-5604. (11β,17α)-17-[(Ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester.

Лотепреднола Этабонат

$C_{24}H_{31}ClO_7$ = 467.0.

CAS — 129260-79-3 (loteprednol); 82034-46-6 (loteprednol etabonate).

ATC — S01BA14.

ATC Vet — QS01BA14.

Profile

Loteprednol etabonate is a corticosteroid used for its glucocorticoid activity (p.1490) in the topical management of inflammatory and allergic disorders of the eye. It is usually used as eye drops containing 0.2 or 0.5%.

Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

◊ References.

1. Noble S, Goa KL. Loteprednol etabonate: clinical potential in the management of ocular inflammation. *BioDrugs* 1998; **10:** 329–39.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alrex; Lopred; Lotemax; Lotesoft; ***Braz.:*** Alrex†; ***Ger.:*** Lotemax; ***Gr.:*** Lotemax; ***Hong Kong:*** Lotemax; ***India:*** Loteflam; ***Ital.:*** Lotemax; ***Mex.:*** Loterex; ***Singapore:*** Lotemax; ***UK:*** Lotemax; ***USA:*** Alrex; Lotemax; ***Venez.:*** Lotesoft.

Multi-ingredient: ***Arg.:*** Lotemicin.

Mazipredone *(rINN)* ⊗

Mazipredona; Mazipredone; Mazipredonum. 11β,17-Dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione.

Мазипредон

$C_{26}H_{38}N_2O_4$ = 442.6.

CAS — 13085-08-0.

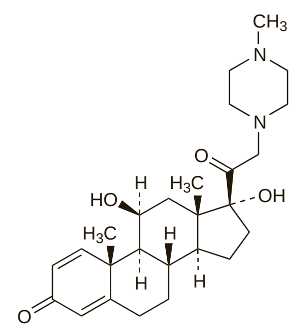

Profile

Mazipredone is a corticosteroid used topically for its glucocorticoid activity (p.1490). It is used as the hydrochloride with miconazole in the treatment of fungal infections of the skin.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Depersolon†; ***Hung.:*** Depersolon†.
Multi-ingredient: ***Cz.:*** Mycosolon†; ***Hung.:*** Mycosolon; ***Pol.:*** Mycosolon; ***Rus.:*** Mycosolon (Микозолон).

Medrysone *(USAN, pINN)* ⊗

11β-Hydroxy-6α-methylprogesterone; Medrisona; Médrysone; Medrysonum; NSC-63278; U-8471. 11β-Hydroxy-6α-methylpregn-4-ene-3,20-dione.

Медризон

$C_{22}H_{32}O_3$ = 344.5.
CAS — 2668-66-8.
ATC — S01BA08.
ATC Vet — QS01BA08.

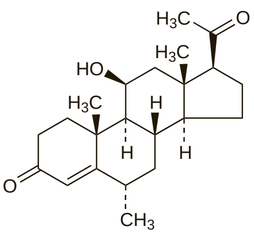

Profile

Medrysone is a corticosteroid used for its glucocorticoid activity (see p.1490) in the topical treatment of allergic and inflammatory conditions of the eye. It is usually given as 1% eye drops.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: HMS†; ***Port.:*** Medrisocil†; ***USA:*** HMS†.

Meprednisone *(USAN, rINN)* ⊗

Meprednisona; Méprednisone; Meprednisonum; 16β-Methylprednisone; NSC-527579; Sch-4358. 17α,21-Dihydroxy-16β-methylpregna-1,4-diene-3,11,20-trione.

Мепреднизон

$C_{22}H_{28}O_5$ = 372.5.
CAS — 1247-42-3.
ATC — H02AB15.
ATC Vet — QH02AB15.

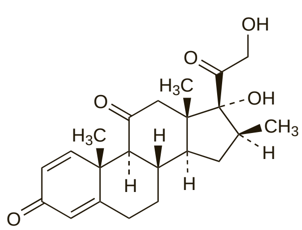

Pharmacopoeias. In *US.*

USP 31 (Meprednisone). Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Meprednisone is a corticosteroid with mainly glucocorticoid activity (p.1490). It has been given orally as either the free alcohol or the acetate and by injection as the sodium hemisuccinate.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cortipyren B; Deltisona B; Latisona B; Prednisonal; Prenolone; Rupesona B; ***Mex.:*** Lectan.

Methylprednisolone *(BAN, rINN)* ⊗

Meilprednizolon; Methylprednisolon; Méthylprednisolone; 6α-Methylprednisolone; Methylprednisolonum; Metilprednisolona; Metilprednizolon; Metilprednizolonas; Metylprednisolon; Metyyliprednisoloni; NSC-19987. 11β,17α,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

Метилпреднизолон

$C_{22}H_{30}O_5$ = 374.5.
CAS — 83-43-2.
ATC — D07AA01; H02AB04.
ATC Vet — QD07AA01; QD10AA02; QH02AB04.

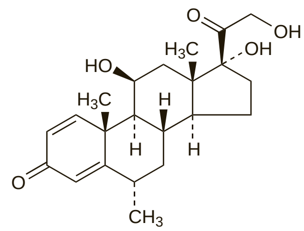

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Methylprednisolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in acetone and in dichloromethane. Protect from light.

USP 31 (Methylprednisolone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 100 of alcohol, and in 1 in 800 of chloroform and of ether; slightly soluble in acetone; sparingly soluble in dioxan and in methyl alcohol. Store in airtight containers. Protect from light.

Methylprednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de metilprednisolona; Methylprednisolon-acetát; Méthylprednisolone, acétate de; Methylprednisoloni acetas; Metilprednizolon Asetat; Metilprednizolon-acetát; Metilprednizolono acetatas; Metylprednisolonacetat; Metyyliprednisoloniasetaatti. Methylprednisolone 21-acetate.

Метилпреднизолона Ацетат

$C_{24}H_{32}O_6$ = 416.5.
CAS — 53-36-1.
ATC — D07AA01; H02AB04.
ATC Vet — QD07AA01; QH02AB04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Methylprednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

USP 31 (Methylprednisolone Acetate). A white or practically white, odourless, crystalline powder. Soluble 1 in 1500 of water, 1 in 400 of alcohol, 1 in 250 of chloroform, and 1 in 1500 of ether; sparingly soluble in acetone and in methyl alcohol; soluble in dioxan. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Methylprednisolone Hydrogen Succinate *(BANM, rINNM)* ⊗

Hidrogenosuccinato de metilprednisolona; Methylprednisolone Hemisuccinate; Méthylprednisolone, Hémisuccinate de; Méthylprednisolone, Hydrogénosuccinate de; Methylprednisolon-hydrogen-sukcinát; Methylprednisoloni Hemisuccinas; Methylprednisoloni hydrogenosuccinas; Metilprednizolon-hidrogén-szukcinát; Metilprednizolono-vandenilio sukcinatas; Metylprednisolonvätesuccinat; Metyyliprednisolonivetysuksinaatti. Methylprednisolone 21-(hydrogen succinate).

Метилпреднизолона Гемисукцинат

$C_{26}H_{34}O_8$ = 474.5.
CAS — 2921-57-5.
ATC — D07AA01; H02AB04.
ATC Vet — QD07AA01; QH02AB04.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Methylprednisolone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 31 (Methylprednisolone Hemisuccinate). A white or nearly white, odourless or nearly odourless, hygroscopic solid. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone. Store in airtight containers.

Methylprednisolone Sodium Succinate *(BANM, rINNM)* ⊗

Methylprednisolone Sodium Hemisuccinate; Méthylprednisolone, Succinate Sodique de; Methylprednisoloni Natrii Succinas; Metilprednizolon Sodyum Süksinat; Succinato sódico de metilprednisolona. Methylprednisolone 21-(sodium succinate).

Метилпреднизолона Натрия Сукцинат

$C_{26}H_{33}NaO_8$ = 496.5.
CAS — 2375-03-3.
ATC — D07AA01; H02AB04.
ATC Vet — QD07AA01; QH02AB04.

Pharmacopoeias. In *US.*

USP 31 (Methylprednisolone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Soluble 1 in 1.5 of water and 1 in 12 of alcohol; very slightly soluble in acetone; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Methylprednisolone sodium succinate injection (*Solu-Medrol, USA*) was considered to be stable for 7 days when diluted in water for injection and stored in glass vials at 4°. When stored under similar conditions at 22°, it was considered to be stable for 24 hours.[1] The manufacturers state that the prepared solution should be stored at 20 to 25° and used within 48 hours of mixing.

1. Nahata MC, *et al.* Stability of diluted methylprednisolone sodium succinate injection at two temperatures. *Am J Hosp Pharm* 1994; **51:** 2157–9.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490). Rapid intravenous injection of large doses has been associated with cardiovascular collapse.

Methylprednisolone may be slightly less likely than prednisolone to cause sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

◊ References to various adverse effects associated with intravenous methylprednisolone in high-dose pulse therapy[1-11] and to adverse effects after intra-articular[12,13] and intranasal injection.[14] Epidural dosage (or more particularly inadvertent intrathecal dosage during attempted epidural placement) may be associated with serious adverse effects including arachnoiditis and aseptic meningitis, although the degree of risk is uncertain.[15]

1. Newmark KJ, *et al.* Acute arthralgia following high-dose intravenous methylprednisolone therapy. *Lancet* 1974; **ii:** 229.
2. Bailey RR, Armour P. Acute arthralgia after high-dose intravenous methylprednisolone. *Lancet* 1974; **ii:** 1014.
3. Bennett WM, Strong D. Arthralgia after high-dose steroids. *Lancet* 1975; **i:** 332.
4. Moses RE, *et al.* Fatal arrhythmia after pulse methylprednisolone therapy. *Ann Intern Med* 1981; **95:** 781–2.
5. Oto A, *et al.* Methylprednisolone pulse therapy and peritonitis. *Ann Intern Med* 1983; **99:** 282.
6. Suchman AL, *et al.* Seizure after pulse therapy with methyl prednisolone. *Arthritis Rheum* 1983; **26:** 117.
7. Ayoub WT, *et al.* Central nervous system manifestations after pulse therapy for systemic lupus erythematosus. *Arthritis Rheum* 1983; **26:** 809–10.
8. Williams AJ, *et al.* Disseminated aspergillosis in high dose steroid therapy. *Lancet* 1983; **i:** 1222.
9. Barrett DF. Pulse methylprednisolone therapy. *Lancet* 1983; **ii:** 800.
10. Baethge BA, Lidsky MD. Intractable hiccups associated with high-dose intravenous methylprednisolone therapy. *Ann Intern Med* 1986; **104:** 58–9.
11. Gardiner PVG, Griffiths ID. Sudden death after treatment with pulsed methylprednisolone. *BMJ* 1990; **300:** 125.
12. Black DM, Filak AT. Hyperglycemia with non-insulin-dependent diabetes following intraarticular steroid injection. *J Fam Pract* 1989; **28:** 462–3.
13. Pollock B, *et al.* Chronic urticaria associated with intra-articular methylprednisolone. *Br J Dermatol* 2001; **144:** 1228–30.
14. Johns KJ, Chandra SR. Visual loss following intranasal corticosteroid injection. *JAMA* 1989; **261:** 2413.
15. Rodgers PT, Connelly JF. Epidural administration of methylprednisolone for back pain. *Am J Hosp Pharm* 1994; **51:** 2789–90.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Methylprednisolone is fairly rapidly distributed after oral doses, with a plasma half-life of 3.5 hours or more. The tissue half-life is reported to range from 18 to 36 hours.

Methylprednisolone acetate is absorbed from joints over a week but is more slowly absorbed following deep intramuscular injection. The sodium succinate ester is rapidly absorbed after intramuscular doses, with peak plasma concentrations obtained in 2 hours.

Methylprednisolone crosses the placenta.

◊ References.

1. Tornatore KM, *et al.* Repeated assessment of methylprednisolone pharmacokinetics during chronic immunosuppression in renal transplant recipients. *Ann Pharmacother* 1995; **29:** 120–4.
2. Rohatagi S, *et al.* Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; **37:** 916–25.
3. Tornatore KM, *et al.* Pharmacokinetics and pharmacodynamic response of methylprednisolone in premenopausal renal transplant recipients. *J Clin Pharmacol* 2004; **44:** 1003–11.

Uses and Administration

Methylprednisolone is a corticosteroid with mainly glucocorticoid activity (p.1490); 4 mg of methylprednisolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p.1495) except adrenocortical-deficiency states, for which hydrocortisone with supplementary fludrocortisone is preferred.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 40 mg of methylprednisolone:

- methylprednisolone acetate 44 mg
- methylprednisolone hydrogen succinate 51 mg
- methylprednisolone sodium succinate 53 mg

When given **orally**, methylprednisolone usually has an initial dosage range of 4 to 48 mg daily but higher initial doses of up to 100 mg or more daily may be used in acute severe disease.

For **parenteral use** in **intensive** or **emergency therapy**, methylprednisolone sodium succinate may be given by intramuscular or intravenous injection or by intravenous infusion. The intravenous route is preferred for its more rapid effect in emergency therapy. The usual initial intramuscular or intravenous dose ranges from the equivalent of 10 to 500 mg of methylprednisolone daily. Large intravenous doses (over 250 mg) should normally be given slowly over at least 30 minutes; doses up to 250 mg should be given over at least 5 minutes. High doses should generally not be given for prolonged periods; emergency treatment should only be used until the patient is stabilised. High doses given intermittently for a limited period have sometimes been known as 'pulse therapy' (see Administration, below) and in graft rejection (see Organ and Tissue Transplantation, p.1810) up to 1 g has been given daily for up to 3 days. In intensive therapy of acute spinal cord injury (p.1513) initial doses of the equivalent of up to 30 mg/kg of methylprednisolone have been given by bolus intravenous injection over 15 minutes and followed, after a 45-minute pause, by intravenous infusion of 5.4 mg/kg per hour over 24 hours or longer. For slow intravenous infusion methylprednisolone sodium succinate is dissolved in an appropriate volume of glucose 5% or sodium chloride 0.9% or sodium chloride 0.9% and glucose 5%.

Parenteral doses in children have varied considerably, depending on the condition: a range of 1 to 30 mg/kg of methylprednisolone daily has been given by the intravenous or intramuscular routes. A total dose of 1 g daily should not normally be exceeded.

Methylprednisolone acetate may be given by intramuscular injection for a prolonged systemic effect, the dose varying from 40 mg every 2 weeks to 120 mg weekly.

For **intra-articular injection** and for **injection into soft tissues** methylprednisolone acetate as an aqueous suspension is used. The dose by intra-articular injection varies from 4 to 80 mg according to the size of the affected joint. The acetate may also be given by intralesional injection in doses of 20 to 60 mg.

For use in the treatment of various skin disorders methylprednisolone acetate may be applied **topically**, usually in concentrations of 0.25%. The aceponate, which may exhibit modified topical activity, has also been applied as a 0.1% cream, lotion, or ointment. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Other esters of methylprednisolone that have occasionally been used include the cipionate and the suleptanate.

◊ General references.

1. Cronstein BN. Clinical use of methylprednisolone sodium succinate: a review. *Curr Ther Res* 1995; **56:** 1–15.

Administration. For short-term intensive corticosteroid therapy or in certain emergency situations a technique known as 'pulse therapy' has been used. Methylprednisolone has often been used in this manner. Typically, high doses of about 1 g intravenously have been given, daily or on alternate days or weekly, for a limited number of doses; the most common regimen appears to be 1 g daily for 3 days.

Blood disorders. Methylprednisolone is one of the corticosteroids that have been used in the management of haemangioma (p.1505) and the Kasabach-Merritt syndrome.[1] There are also reports of benefit from very high-dose therapy in a few patients with refractory primary acquired pure red cell aplasia,[2] or aplasia due to Blackfan-Diamond anaemia.[3]

1. Özsoylu Ş, *et al.* Megadose methylprednisolone therapy for Kasabach-Merritt syndrome. *J Pediatr* 1996; **129:** 947.
2. Kadikoylu G, *et al.* High-dose methylprednisolone therapy in pure red cell aplasia. *Ann Pharmacother* 2002; **36:** 55–8.
3. Bernini JC, *et al.* High-dose intravenous methylprednisolone therapy for patients with Diamond-Blackfan anemia refractory to conventional doses of prednisone. *J Pediatr* 1995; **127:** 654–9.

IDIOPATHIC THROMBOCYTOPENIC PURPURA. High-dose intravenous methylprednisolone may be used as part of the emergency management of acute idiopathic thrombocytopenic purpura (p.1505), for example when major acute bleeding or intracranial haemorrhage supervene. There is some evidence that methylprednisolone is less effective than normal immunoglobulins. Methylprednisolone has also been used by mouth or intravenously in the management of the chronic form, although prednisolone or prednisone are more frequently used for oral therapy and good controlled trials are scanty.

References.

1. von dem Borne AEGKR, *et al.* High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *BMJ* 1988; **296:** 249–50.
2. Özsoylu S, *et al.* Megadose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1990; **336:** 1078–9.
3. Akoğlu T, *et al.* Megadose methylprednisolone pulse therapy in adult idiopathic thrombocytopenic purpura. *Lancet* 1991; **337:** 56.
4. Özsoylu S. Mega-dose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1991; **337:** 1611–12.
5. Rosthøj S, *et al.* Randomized trial comparing intravenous immunoglobulin with methylprednisolone pulse therapy in acute idiopathic thrombocytopenic purpura. *Acta Paediatr* 1996; **85:** 910–15.
6. Alpdoğan Ö, *et al.* Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. *Br J Haematol* 1998; **103:** 1061–3.
7. Godeau B, *et al.* Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; **359:** 23–9.

Rheumatoid arthritis. Methylprednisolone given in intravenous pulses has been reported[1-7] to be effective in the treatment of rheumatoid arthritis (p.11) including juvenile idiopathic arthritis. Some studies have shown this treatment to be of greatest benefit when given with a disease-modifying antirheumatic drug (DMARD),[1,2,4] although others showed the addition of methylprednisolone to existing therapy to have no extra benefit.[6] A comparatively low dose of 100 mg was found to be as effective as 1000 mg in one study.[3] Monthly doses of methylprednisolone by deep intramuscular injection were also an effective adjunct to gold therapy.[8]

A preliminary study in children has found intravenous pulses of methylprednisolone 30 mg/kg to be effective treatment for systemic flares of juvenile idiopathic arthritis.[7]

1. Walters HT, Cawley MID. Combined suppressive drug treatment in severe refractory rheumatoid disease: an analysis of the relative effects of parenteral methylprednisolone, cyclophosphamide and sodium aurothiomalate. *Ann Rheum Dis* 1988; **47:** 924–9.
2. Smith MD, *et al.* The clinical and immunological effects of pulse methylprednisolone therapy in rheumatoid arthritis I: clinical effects. *J Rheumatol* 1988; **15:** 229–32.
3. Igelhart IW, *et al.* Intravenous pulsed steroids in rheumatoid arthritis: a comparative dose study. *J Rheumatol* 1990; **17:** 159–62.
4. Smith MD, *et al.* Pulse methylprednisolone therapy in rheumatoid arthritis: unproved therapy, unjustified therapy, or effective adjunctive treatment? *Ann Rheum Dis* 1990; **49:** 265–7.
5. Kapisinszky N, Keszthelyi B. High dose intravenous methylprednisolone pulse therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 1990; **49:** 567–8.
6. Hansen TM, *et al.* Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. *BMJ* 1990; **301:** 268–70.
7. Adebajo AO, Hall MA. The use of intravenous pulsed methylprednisolone in the treatment of systemic-onset juvenile chronic arthritis. *Br J Rheumatol* 1998; **37:** 1240–2.
8. Corkill MM, *et al.* Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. *Br J Rheumatol* 1990; **29:** 274–9.

Systemic lupus erythematosus. Methylprednisolone has been widely used to treat disease flares or severe manifestations of SLE (p.1513).

References.

1. Badsha H, Edwards CJ. Intravenous pulses of methylprednisolone for systemic lupus erythematosus. *Semin Arthritis Rheum* 2003; **32:** 370–7.
2. Danowski A, *et al.* Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone. *J Rheumatol* 2006; **33:** 57–60.
3. Trevisani VF, *et al.* Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 20/06/06).

Preparations

BP 2008: Methylprednisolone Acetate Injection; Methylprednisolone Tablets;
USP 31: Methylprednisolone Acetate Cream; Methylprednisolone Acetate Injectable Suspension; Methylprednisolone Sodium Succinate for Injection; Methylprednisolone Tablets; Neomycin Sulfate and Methylprednisolone Acetate Cream.

Proprietary Preparations (details are given in Part 3)
Arg.: Advantan; Cipridanol; Corticel†; Cortisolona†; Solu-Medrol; ***Austral.:*** Advantan; Depo-Medrol; Depo-Nisolone; Medrol†; Solu-Medrol; ***Austria:*** Advantan; Depo-Medrol; Solu-Medrol; Urbason; ***Belg.:*** Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Braz.:*** Advantan; Alergolon; Depo-Medrol; Predmetil; Solu-Medrol; Solu-Pred†; Solupren; Unimedrol; ***Canad.:*** Depo-Medrol; Medrol; Solu-Medrol; ***Chile:*** Depo-Medrol; Medrol; Solu-Medrol; ***Cz.:*** Advantan; Depo-Medrol; Medrol; Metypred†; Solu-Medrol; Urbason†; ***Denm.:*** Depo-Medrol; Medrol; Solu-Medrol; ***Fin.:*** Advantan; Depo-Medrol; Medrol; Solomet; Solu-Medrol; ***Fr.:*** Depo-Medrol; Medrol; Solu-Medrol; ***Ger.:*** Advantan; Depo-Medrate†; M-PredniHexal; Medrate; Metypred; Metysolon; Predni M; Urbason; ***Gr.:*** Advantan; Depo-Medrol; Depo-Medrone†; Lyo-drol†; Medrol; Solu-Medrol; ***Hong Kong:*** Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Hung.:*** Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***India:*** Depo-Medrol; Solu-Medrol; Unidrol†; ***Indon.:*** Advantan; Depo-Medrol; Flason; Hexilon; Intidrol; Lameson; Lexcomet; Medixon; Medrol; Meprilon; Meproson; Mesol; Methylon; Metidrol; Metisol; Nichomedson; Prednicort; Prednox; Pretilon; Sanexon; Solu-Medrol; Somerol; Sonicor; Stenirol; Thimelon; Tison; Tropidrol; Urbason; Yalone; ***Irl.:*** Depo-Medrone; Solu-Medrone; ***Israel:*** A-Methapred†; Depo-Medrol; Medrol; Solu-Medrol; Vanderm†; ***Ital.:*** Advantan; Asmacortone; Avancort; Depo-Medrol; Esametone†; Medrol; Metilbetasone Solubile; Solu-Medrol; Supresol; Urbason; ***Malaysia:*** Depo-Medrol; Solu-Medrol; ***Mex.:*** Advantan; Cryosolona; Depo-Medrol; Metisona; Prednilem; Radilem; Solipred; Solu-Medrol; ***Neth.:*** Depo-Medrol; Metypresol†; Solu-Medrol; ***Norw.:*** Depo-Medrol; Medrol; Solu-Medrol; ***NZ:*** Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Philipp.:*** Adrena; Advantan; Depo-Medrol; Medixon; Medrol; Solu-Medrol; ***Pol.:*** Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***Port.:*** Advantan; Depo-Medrol; Medrol; Metilpren; Solu-Medrol; ***Rus.:*** Advantan (Адвантан); Depo-Medrol (Депо-медрол)†; Medrol (Медрол); Metypred (Метипред); Solu-Medrol (Солу-медрол); ***S.Afr.:*** Advantan; Depo-Medrol; Medrol; Metypresol; Solu-Medrol; ***Singapore:*** Solu-Medrol; ***Spain:*** Adventan; Depo Moderin†; Lexxema; Solu-Moderin; Urbason; ***Swed.:*** Depo-Medrol; Medrol; Solu-Medrol; ***Switz.:*** Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Thai.:*** Depo-Medrol; Solu-Medrol; ***Turk.:*** Advantan; Depo-Medrol; Prednol; ***UK:*** Depo-Medrone; Medrone; Solu-Medrone; ***USA:*** A-Methapred; depMedalone; Depo-Medrol; Depopred†; Medrol; Solu-Medrol; ***Venez.:*** Advantan; Depo-Medrol; Medrol; Prednicort; Solu-Medrol.

Multi-ingredient: ***Austral.:*** Neo-Medrol; ***Austria:*** Depo-Medrol mit Lidocain; ***Belg.:*** Depo-Medrol + Lidocaine; ***Canad.:*** Depo-Medrol with Lidocaine; Medrol Acne Lotion; Neo-Medrol Acne; Neo-Medrol Veriderm†; ***Fin.:*** Depo-Medrol cum Lidocain; Neo-Medrol comp†; Solomet c bupivacain hydrochlorid; ***Hong Kong:*** Depo-Medrol with Lidocaine; Neo-Medrol Acne; ***Irl.:*** Depo-Medrone with Lidocaine; ***Israel:*** Depo-Medrol with Lidocaine; Neo-Medrol; ***Ital.:*** Depo-Medrol + Lidocaina; Medrol Lozione Antiacne†; Neo-Medrol Veriderm†; ***Malaysia:*** Neo-Medrol; ***Neth.:*** Depo-Medrol + Lidocaine; ***Norw.:*** Depo-Medrol cum Lidocain; ***NZ:*** Depo-Medrol with Lidocaine; ***Pol.:*** Depo-Medrol z Lidokaina; ***Port.:*** Depo-Medrol com Lidocaina; ***S.Afr.:*** Depo-Medrol with Lidocaine; Neo-Medrol; ***Singapore:*** Neo-Medrol; ***Spain:*** Moderin Acne†; ***Swed.:*** Depo-Medrol cum Lidocain; ***Switz.:*** Depo-Medrol Lidocaine; ***Thai.:*** Depo-Medrol with Lidocaine†; Neo-Medrol; ***UK:*** Depo-Medrone with Lidocaine.

Mometasone Furoate *(BANM, USAN, rINNM)* ⊗

Furoato de mometasona; Mométasone, furoate de; Mometasonfuroat; Mometason-furoát; Mometasoni furoas; Mometasonifuroaatti; Mometazon Furoat; Mometazon-furoát; Mometazono furoatas; Mometazonu furoinian; Sch-32088. 9α,21-Dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate).

Мометазона Фуроат

$C_{27}H_{30}Cl_2O_6$ = 521.4.
CAS — 105102-22-5 (mometasone); 83919-23-7 (mometasone furoate).
ATC — D07AC13; R01AD09; R03BA07.
ATC Vet — QD07AC13; QR01AD09; QR03BA07.

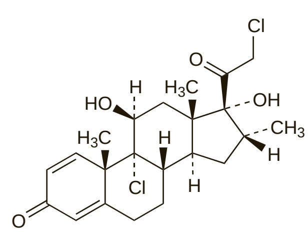

(mometasone)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mometasone Furoate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone and in dichloromethane.

USP 31 (Mometasone Furoate). A white to off-white powder. Soluble in acetone and in dichloromethane.

Profile

Mometasone furoate is a corticosteroid used topically for its glucocorticoid activity (see p.1490) in the treatment of various **skin disorders**. It is usually used as a cream, ointment, or lotion containing 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

A nasal suspension of mometasone furoate 0.05%, as the monohydrate, is given in the treatment and prophylaxis of the symptoms of **allergic rhinitis** (p.565). The usual adult dose is the equivalent of 100 micrograms of mometasone furoate in each nostril once daily, increased if necessary to 200 micrograms in each nostril daily. Once symptoms are controlled a dose of 50 micrograms in each nostril daily may be effective for maintenance. In the UK, the dose for children aged between 6 and 11 years is the equivalent of 50 micrograms in each nostril once daily. In the USA, similar doses may be given to treat allergic rhinitis in children from 2 years of age.

The nasal suspension is also given for the treatment of **nasal polyps** in patients 18 years and older; the recommended initial dose in the UK is 100 micrograms into each nostril once daily, increased after 5 to 6 weeks to twice daily if needed. In the USA the recommended initial dose is 100 micrograms in each nostril twice daily, although once daily administration may be sufficient in some patients.

Mometasone furoate is used by dry powder inhaler for the prophylaxis of **asthma** (p.1108). Doses may differ between countries and dosage units may be expressed differently, as either the amount of drug released per actuation or the amount delivered from the mouthpiece. UK licensed product information includes an initial dose of 400 micrograms inhaled once daily in the evening for mild to moderate asthma in adults and adolescents aged 12 years and older. This may be adjusted to a maintenance dose of 200 micrograms once or twice daily. In severe asthma, an initial dose of 400 micrograms twice daily is used, then titrated to the lowest effective dose once symptoms are controlled. US doses are provided in terms of the amount of drug released per actuation (an actuation that releases 110 micrograms delivers 100 micrograms from the mouthpiece). An initial dose of 220 micrograms once daily in the evening is used in adults and adolescents, aged 12 years and older, who have been treated with inhaled therapy only (bronchodilators or corticosteroids); this may be increased to a maximum of 440 micrograms daily as a single dose or 2 divided doses. Patients receiving oral corticosteroids may be started on 440 micrograms twice daily. Children aged 4 to 11 years may be given 110 micrograms once daily in the evening, regardless of prior therapy; this is the maximum recommended daily dose.

◊ References.

1. Prakash A, Benfield P. Topical mometasone: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. *Drugs* 1998; **55:** 145–63.
2. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 1998; **56:** 725–45.
3. Meltzer EO, *et al.* A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; **104:** 107–14.
4. Meltzer EO, *et al.* Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. *J Allergy Clin Immunol* 2000; **106:** 630–7.
5. Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. *Drugs* 2001; **61:** 1325–50.
6. O'Connor B, *et al.* Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. *Ann Allergy Asthma Immunol* 2001; **86:** 397–404.
7. Lundblad L, *et al.* Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2001; **121:** 505–9.
8. Schenkel E. Features of mometasone furoate nasal spray and its utility in the management of allergic rhinitis. *Expert Opin Pharmacother* 2003; **4:** 1579–91.
9. van Drunen C, *et al.* Nasal allergies and beyond: a clinical review of the pharmacology, efficacy, and safety of mometasone furoate. *Allergy* 2005; **60** (suppl 80): 5–19. Correction. *ibid.*; 1335.
10. Stjarne P, *et al.* A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006; **132:** 179–85.
11. McCormack PL, Plosker GL. Inhaled mometasone furoate: a review of its use in persistent asthma in adults and adolescents. *Drugs* 2006; **66:** 1151–68.
12. Zitt M, *et al.* Mometasone furoate nasal spray: a review of safety and systemic effects. *Drug Safety* 2007; **30:** 317–26.

Preparations

BP 2008: Mometasone Aqueous Nasal Spray; Mometasone Cream; Mometasone Ointment; Mometasone Scalp Application;
USP 31: Mometasone Furoate Cream; Mometasone Furoate Ointment; Mometasone Furoate Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Elocon; Fenisona; Metason; Momeplus; Nasonex; Novasone; Uniclar; ***Austral.:*** AllerMax†; Elocon; Nasonex; Novasone; ***Austria:*** Asmanex; Elocon; Elovent; Nasonex; ***Belg.:*** Elocom; Nasonex; ***Braz.:*** Asmanex†; Elocom; Nasonex; Topison; ***Canad.:*** Elocom; Nasonex; ***Chile:*** Dermenet†; Dermosona; Elocom; Flogocort; Lisoder; Momelab; Nasonex; Rinoval†; Uniclar; ***Cz.:*** Asmanex; Elocom; Nasonex; ***Denm.:*** Asmanex; Elocon; Nasonex; ***Fin.:*** Asmanex†; Elocon; Nasonex; ***Fr.:*** Nasonex; ***Ger.:*** Asmanex; Ecural; Nasonex; ***Gr.:*** Asmanex; Bioelementa; Ecelecort; Elocon; Elovent†; Esine; F-Din; Fremomet; Makiren; Metason; Mofur; Molken; Momecort; Movesan; Mozeton; Nasamet; Nasonex; Pharmecort; Yperod; ***Hong Kong:*** Elomet; Nasonex; Topcort; ***Hung.:*** Elocom; Nasonex; ***India:*** Elocon; Metaspray; Momate; Topcort; ***Indon.:*** Dermovel; Elocon; Eloskin; Elox; Intercon; Mefurosan; Mesone; Mofacort; Mofulex; Momet; Motaderm; Moteson; Nasonex; ***Irl.:*** Asmanex; Elocon; Nasonex; ***Israel:*** Elocom; Nasonex; ***Ital.:*** Altosone; Elocon; Nasonex; Rinelon; Uniclar†; ***Malaysia:*** Elomet; Momate; Nasonex; ***Mex.:*** Elica; Elomet; Elovent; Rinelon; Uniclar; ***Neth.:*** Asmanex; Elocon; Elovent; Nasonex; ***Norw.:*** Elocon; Nasonex; ***NZ:*** Asmanex; Bronconex; Elocon; ***Philipp.:*** Elica; Elocon; Momate; Nasonex; Rinelon; ***Pol.:*** Elocom; Elosone; Nasonex; ***Port.:*** Asmanex; Elocom; Elomet; Elovent; Nasomet; Prospiril; ***Rus.:*** Elocom (Элоком); Nasonex (Назонекс); ***S.Afr.:*** Elica†; Elocon; Nasonex; Rinelon†; ***Singapore:*** Elomet; Nasonex; ***Spain:*** Asmanex†; Elica; Elocom; Nasonex; Rinelon; ***Swed.:*** Asmanex; Elocon; Nasonex; ***Switz.:*** Asmanex; Elocom; Nasonex; ***Thai.:*** Elomet; Nasonex; Rinelon†; ***Turk.:*** Elocon; M-Furo; Nasonex; ***UK:*** Asmanex; Elocon; Nasonex; ***USA:*** Asmanex; Elocon; Nasonex; ***Venez.:*** Asmanex; Cortynase; Dergentil; Elocon; Eloconex†; Elomet; Nasonex; Uniclar†.

Multi-ingredient: ***Arg.:*** Elosalic†; ***Austria:*** Elosalic; ***Chile:*** Velosalic; ***Cz.:*** Momesalic; Monsalic†; ***Ger.:*** Elosalic; ***Hong Kong:*** Elosalic; ***India:*** Momate-S; ***Indon.:*** Elosalic; ***Pol.:*** Elosalic; ***Port.:*** Monsalic; ***Rus.:*** Elocom-S (Элоком-С); ***S.Afr.:*** Elosalic; ***Swed.:*** Elosalic; ***Thai.:*** Elosalic†; ***Turk.:*** Elosalic; ***Venez.:*** Elosalic.

Paramethasone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de parametasona; 6α-Fluoro-16α-methylprednisolone 21-Acetate; Parametazon Asetat; Paraméthasone, Acétate de; Paramethasoni Acetas. 6α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate.

Параметазона Ацетат

$C_{24}H_{31}FO_6$ = 434.5.

CAS — 53-33-8 (paramethasone); 1597-82-6 (paramethasone acetate).

ATC — H02AB05.

ATC Vet — QH02AB05.

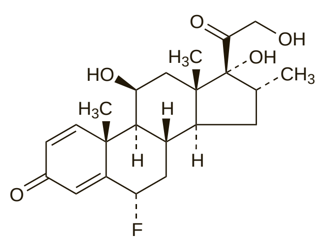

(paramethasone)

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Paramethasone Acetate). A white to creamy-white, fluffy, odourless, crystalline powder. Insoluble in water; soluble 1 in 50 of chloroform and 1 in 40 of methyl alcohol; soluble in ether. Store in airtight containers.

Profile

Paramethasone acetate is a corticosteroid that has been used systemically for its predominantly glucocorticoid activity (p.1490); 2 mg of paramethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. The disodium phosphate has also been used.

Preparations

USP 31: Paramethasone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)

Mex.: Dilar; ***Spain:*** Cortidene; ***Turk.:*** Depo-Dilar.

Multi-ingredient: ***Mex.:*** Dilarmine.

Prednicarbate *(BAN, USAN, rINN)* ⊗

Hoe-777; Prednicarbato; Prednicarbatum; Prednikarbaatti; Prednikarbát; Prednikarbat; Prednikarbatas; S-77-0777. 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 17-(ethyl carbonate) 21-propionate.

Предникарбат

$C_{27}H_{36}O_8$ = 488.6.

CAS — 73771-04-7.

ATC — D07AC18.

ATC Vet — QD07AC18.

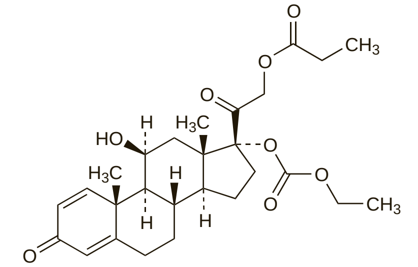

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Prednicarbate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

USP 31 (Prednicarbate). A white to almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

Profile

Prednicarbate is a corticosteroid used topically for its glucocorticoid activity (see p.1490) in the treatment of various skin disorders. It has usually been used as a cream, ointment, or lotion, containing 0.1 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

◊ References.

1. Schäfer-Korting M, *et al.* Prednicarbate activity and benefit/risk ratio in relation to other topical glucocorticoids. *Clin Pharmacol Ther* 1993; **54:** 448–56.

Preparations

USP 31: Prednicarbate Cream; Prednicarbate Ointment.

Proprietary Preparations (details are given in Part 3)

Arg.: Primaderm†; ***Austria:*** Prednitop; ***Braz.:*** Dermatop; Invex; ***Canad.:*** Dermatop; ***Chile:*** Dermatop; ***Cz.:*** Dermatop; ***Ger.:*** Dermatop; Prednitop; ***Indon.:*** Dermatop; ***Ital.:*** Dermatop; ***Mex.:*** Alisyd; ***Spain:*** Batmen; Peitel; ***Switz.:*** Prednitop; ***Thai.:*** Dermatop; ***Turk.:*** Dermatop; ***USA:*** Dermatop.

Prednisolone *(BAN, rINN)* ⊗

1,2-Dehydrohydrocortisone; Deltahydrocortisone; Δ^1-Hydrocortisone; Metacortandralone; NSC-9120; Prednisolon; Prednisolona; Prednisoloni; Prednisolonum; Prednizolon; Prednizolonas. 11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione.

Преднизолон

$C_{21}H_{28}O_5$ = 360.4.

CAS — 50-24-8 (anhydrous prednisolone); 52438-85-4 (prednisolone sesquihydrate).

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QD07XA02; QH02AB06; QR01AD02; QS01BA04; QS01CB02; QS02BA03; QS03BA02.

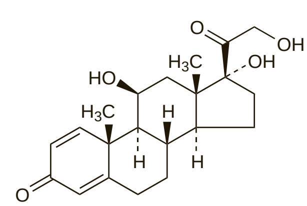

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *Viet.*

US allows the anhydrous form or the sesquihydrate.

Ph. Eur. 6.2 (Prednisolone). A white or almost white, hygroscopic, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Prednisolone). It is anhydrous or contains one and one-half molecules of water of hydration. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 30 of alcohol, 1 in 50 of acetone, and 1 in 180 of chloroform; soluble in dioxan and in methyl alcohol.

Prednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisolona; Prednisolonacetat; Prednisolon-acetát; Prednisolone, acétate de; Prednisoloni acetas; Prednisoloniasetaatti; Prednizolon Asetat; Prednizolon-acetát; Prednizolono acetatas; Prednizolonu octan. Prednisolone 21-acetate.

Преднизолона Ацетат

$C_{23}H_{30}O_6$ = 402.5.

CAS — 52-21-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Prednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Prednisolone Acetate). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 120 of alcohol; slightly soluble in acetone and in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Prednisolone Caproate *(rINNM)* ⊗

Caproato de prednisolona; Prednisolone, Caproate de; Prednisolone Hexanoate *(BANM)*; Prednisoloni Caproas. Prednisolone 21-hexanoate.

Преднизолона Капроат

$C_{27}H_{38}O_6$ = 458.6.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Prednisolone Hydrogen Succinate *(BANM, rINNM)* ⊗

Hidrogenosuccinato de prednisolona; Prednisolone Hemisuccinate; Prednisolone, Hémisuccinate de; Prednisoloni Hemisuccinas. Prednisolone 21-(hydrogen succinate).

Преднизолона Гемисукцинат

$C_{25}H_{32}O_8$ = 460.5.

CAS — 2920-86-7.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Prednisolone Hemisuccinate). A fine, creamy-white, practically odourless, powder with friable lumps. Soluble 1 in 4170 of water, 1 in 6.3 of alcohol, 1 in 1064 of chloroform, and 1 in 248 of ether; soluble in acetone. Store in airtight containers.

Prednisolone Metasulfobenzoate Sodium *(rINNM)* ⊗

Metasulfobenzoato sódico de prednisolona; Natrii Prednisoloni Metasulfobenzoas; Prednisolone Métasulfobenzoate Sodique; Prednisolone Metasulphobenzoate Sodium *(BANM)*; Prednisolone Sodium Metasulphobenzoate; R-812. Prednisolone 21-(sodium *m*-sulphobenzoate).

Натрий Метасульфобензоат Преднизолон

$C_{28}H_{31}NaO_9S$ = 566.6.

CAS — 630-67-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Prednisolone Pivalate *(BANM, rINNM)* ⊗

Pivalato de prednisolona; Prednisolone, pivalate de; Prednisolone Trimethylacetate; Prednisoloni pivalas; Prednisolonipivalaatti; Prednisolonpivalat; Prednisolon-pivalát; Prednizolono pivalatas; Prednizolon-pivalát; Prednizolonu piwalan. Prednisolone 21-pivalate.

Преднизолона Пивалат

$C_{26}H_{36}O_6$ = 444.6.

CAS — 1107-99-9.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Prednisolone Pivalate). A white, or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Prednisolone Sodium Phosphate *(BANM, rINNM)* ⊗

Fosfato sódico de prednisolona; Natrii Prednisoloni Phosphas; Prednisolone, phosphate sodique de; Prednisolonfosfát sodná sůl; Prednisoloni natrii phosphas; Prednisoloninatriumfosfaatti; Prednisolonnatriumfosfat; Prednizolon Sodyum Fosfat; Prednizolon-nárium-foszfát; Prednizolono natrio fosfatas. Prednisolone 21-(disodium orthophosphate).

Натрия Преднизолона Фосфат

$C_{21}H_{27}Na_2O_8P$ = 484.4.

CAS — 125-02-0.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

NOTE. PRED is a code approved by the BP 2008 for use on single unit doses of eye drops containing prednisolone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Prednisolone Sodium Phosphate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 31 (Prednisolone Sodium Phosphate). A white or slightly yellow friable granules or powder. Is odourless or has a slight odour. Is slightly hygroscopic. Soluble 1 in 4 of water and 1 in 13 of methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone and in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Prednisolone Sodium Succinate *(BANM, rINNM)* ⊗

Prednisolone Sodium Hemisuccinate; Prednisolone, Succinate Sodique de; Prednisoloni Natrii Succinas; Succinato sódico de prednisolona. 11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(sodium succinate).

Преднизолона Натрия Сукцинат

$C_{25}H_{31}NaO_8$ = 482.5.

CAS — 1715-33-9.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Pharmacopoeias. *US* includes Prednisolone Sodium Succinate for Injection.

USP 31 (Prednisolone Sodium Succinate for Injection). A creamy white powder with friable lumps, having a slight odour.

Prednisolone Steaglate *(BAN, rINN)* ⊗

Esteaglato de prednisolona; Prednisolone, Stéaglate de; Prednisoloni Steaglas. Prednisolone 21-stearoylglycolate.

Преднизолона Стеаглат

$C_{41}H_{64}O_8$ = 684.9.

CAS — 5060-55-9.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Prednisolone Tebutate *(BANM, rINNM)* ⊗

Prednisolone Butylacetate; Prednisolone 21-*tert*-Butylacetate; Prednisolone, Tébutate de; Prednisolone Tertiary-butylacetate; Prednisoloni Tebutas; Tebutato de prednisolona. Prednisolone 21-(3,3-dimethylbutyrate).

Преднизолона Тебутат

$C_{27}H_{38}O_6,H_2O$ = 476.6.

CAS — 7681-14-3 (anhydrous prednisolone tebutate).

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Pharmacopoeias. In *US.*

USP 31 (Prednisolone Tebutate). A white to slightly yellow, hygroscopic, free-flowing powder, which may show some soft lumps. Is odourless or has not more than a moderate characteristic odour. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in chloroform and in dioxan. Store in airtight containers sealed under nitrogen at a temperature not exceeding 8°.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490).

Owing to its less pronounced mineralocorticoid activity prednisolone is less likely than cortisone or hydrocortisone to cause sodium retention, electrolyte imbalance, and oedema. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Breast feeding. Concentrations of prednisone and prednisolone in breast milk from one woman 120 minutes after prednisone 10 mg by mouth were found to be 26.7 nanograms and 1.6 nanograms/mL respectively.[1] In 7 similar women given a single 5-mg oral dose of tritium-labelled prednisolone, a mean of 0.14% of the radioactivity from the dose was recovered per litre of milk in the following 48 to 61 hours.[2] In a study of 3 women, only about 0.025% of a single intravenous dose of prednisolone phosphate 50 mg was recovered in breast milk over 6 hours.[3] During maintenance therapy with prednisolone in daily doses of 10 to 80 mg in 6 women, the milk to serum concentration ratio of prednisolone ranged from 0.2, for doses of 30 mg or more, to 0.1 for lower doses.[4] The authors estimated that the breast-fed infant would receive less than 0.1% of the maternal dose of prednisolone, and that this would be a negligible addition to the infant's endogenous cortisol production. They also concluded that exposure could be minimised by breast feeding at least 4 hours after the dose.

A review[5] by the UK CSM remarked that prednisolone was distributed into breast milk in small amounts and recommended that infants of mothers receiving 40 mg or more daily should be monitored for signs of adrenal suppression. The American Academy of Pediatrics considers[6] that the use of prednisone or prednisolone is usually compatible with breast feeding.

1. Katz FH, Duncan BE. Entry of prednisone into human milk. *N Engl J Med* 1975; **293:** 1154.
2. McKenzie SA, *et al.* Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; **50:** 894–6.
3. Greenberger PA, *et al.* Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993; **53:** 324–8.
4. Öst L, *et al.* Prednisolone excretion in human milk. *J Pediatr* 1985; **106:** 1008–11.
5. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; **24:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)
6. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/04)

Hepatic impairment. Conversion of prednisone to prednisolone has been reported to be impaired in chronic active liver disease.[1,2] However, although plasma-prednisolone concentrations were found to be more predictable after prednisolone than prednisone in a group of healthy subjects,[3] no difference was noted in patients with chronic active hepatitis, in whom impaired elimination of prednisolone compensated for any impaired conversion of prednisone. A review of the pharmacokinetics of prednisone and prednisolone[4] concluded that fear of inadequate conversion of prednisone into prednisolone was not justified.

1. Powell LW, Axelsen E. Corticosteroids in liver disease: studies on the biological conversion of prednisone to prednisolone and plasma protein binding. *Gut* 1972; **13:** 690–6.
2. Madsbad S, *et al.* Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis. *Gut* 1980; **21:** 52–6.
3. Davis M, *et al.* Prednisone or prednisolone for the treatment of chronic active hepatitis? A comparison of plasma availability. *Br J Clin Pharmacol* 1978; **5:** 501–5.
4. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; **19:** 126–46.

Inflammatory bowel disease. Symptoms recurred in a patient with Crohn's disease on changing from conventional to enteric-coated tablets of prednisolone.[1] This was not an isolated occurrence in the authors' unit, and it was advocated that only non-enteric-coated prednisolone tablets should be used in Crohn's disease, and that the enteric-coated form be used with caution in any condition characterised by diarrhoea or a rapid transit time.

1. Beattie RM, Walker-Smith JA. Use of enteric coated prednisolone in Crohn's disease. *Arch Dis Child* 1994; **71:** 282.

Interactions

The interactions of corticosteroids in general are described on p.1494.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Prednisolone and prednisone are both readily absorbed from the gastrointestinal tract, but whereas prednisolone already exists in a metabolically active form, prednisone must be converted in the liver to its active metabolite, prednisolone. In general, this conversion is rapid so this difference is of little consequence when seen in the light of intersubject variation in the pharmacokinetics of prednisolone itself; bioavailability also depends on the dissolution rates of the tablet formulations. As discussed under Hepatic Impairment, above, reduced corticosteroid concentrations when giving prednisone to patients with liver disease do not seem to be a problem in practice. After intramuscular doses the sodium phosphate ester of prednisolone is rapidly absorbed whereas the acetate, in the suspension form, is only slowly absorbed.

Peak plasma concentrations of prednisolone are obtained 1 or 2 hours after an oral dose, and it has a usual plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food.

Prednisolone is extensively bound to plasma proteins, although less so than hydrocortisone (cortisol). The volume of distribution, and also the clearance are reported to increase with an increase from low to moderate doses; at very high doses, clearance appears to become saturated.

Prednisolone is excreted in the urine as free and conjugated metabolites, with an appreciable proportion of unchanged prednisolone. Prednisolone is largely inactivated as it crosses the placenta; small amounts are excreted in breast milk.

Prednisolone has a biological half-life lasting several hours, intermediate between those of hydrocortisone (cortisol) and the longer-acting glucocorticoids, such as dexamethasone. It is this intermediate duration of action that makes it suitable for the alternate-day dosage regimens which have been found to reduce the risk of adrenocortical insufficiency, yet provide adequate corticosteroid coverage in some disorders.

◊ General reviews of the pharmacokinetics of prednisolone[1,2] and some references to its pharmacokinetics in healthy subjects[3] and in various disease states.[4-8]

1. Begg EJ, *et al.* The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; **146:** 37–41.
2. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; **19:** 126–46.
3. Rohatagi S, *et al.* Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; **37:** 916–25.
4. Berghouse LM, *et al.* Plasma prednisolone levels during intravenous therapy in acute colitis. *Gut* 1982; **23:** 980–3.
5. Shaffer JA, *et al.* Absorption of prednisolone in patients with Crohn's disease. *Gut* 1983; **24:** 182–6.
6. Reece PA, *et al.* Prednisolone protein binding in renal transplant patients. *Br J Clin Pharmacol* 1985; **20:** 159–62.
7. Frey FJ, *et al.* Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin Pharmacol Ther* 1988; **44:** 510–21.
8. Miller PFW, *et al.* Pharmacokinetics of prednisolone in children with nephrosis. *Arch Dis Child* 1990; **65:** 196–200.

Uses and Administration

Prednisolone is a corticosteroid with mainly glucocorticoid activity (p.1490); 5 mg of prednisolone is equivalent in anti-inflammatory activity to about 25 mg of cortisone acetate. In general, prednisolone, either in the form of the free alcohol or in one of the esterified forms, is the drug of choice in the UK for conditions in which routine systemic corticosteroid therapy is indicated (see p.1495), except adrenocortical-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. The more potent pituitary-suppressant properties of a glucocorticoid such as dexamethasone may, however, be required for the diagnosis and management of conditions associated with adrenal hyperplasia.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of prednisolone:

- prednisolone acetate 110 mg
- prednisolone caproate 127 mg
- prednisolone hydrogen succinate 128 mg
- prednisolone metasulfobenzoate sodium 157 mg
- prednisolone pivalate 123 mg
- prednisolone sodium phosphate 135 mg
- prednisolone sodium succinate 134 mg
- prednisolone steaglate 190 mg
- prednisolone tebutate 132 mg

When given **orally** prednisolone is usually used although prednisolone sodium phosphate or prednisolone steaglate are also given; the usual dose, expressed in terms of prednisolone, is about 2.5 to 60 mg daily in divided doses, as a single daily dose after breakfast, or as a double dose on alternate days. Alternate-day early-morning dosage regimens produce less suppression of the hypothalamic-pituitary axis but may not always provide adequate control. Enteric-coated tablets of prednisolone are also available (for the view that these should not be used in patients with inflammatory bowel disease, see above).

For **parenteral use** the sodium phosphate ester is normally given, either intravenously by injection or infusion or intramuscularly by injection; doses appear to have been variously expressed in terms of prednisolone, prednisolone phosphate, or prednisolone sodium phosphate but are generally within the range of 4 to 60 mg daily. An aqueous suspension of prednisolone acetate is also used intramuscularly for a prolonged effect, in doses of 25 to 100 mg once or twice weekly. The sodium succinate ester has also been given parenterally.

For **intra-articular injection** the acetate, sodium phosphate, and tebutate esters are used. Suggested doses are 5 to 25 mg of prednisolone acetate, 2 to 30 mg of prednisolone phosphate (for the sodium phosphate ester), and 4 to 40 mg of prednisolone tebutate. The sodium phosphate and tebutate esters are also given by intralesional injection and by injection into soft tissue.

Prednisolone acetate and prednisolone sodium phosphate are also used in the **topical treatment** of allergic and inflammatory conditions of the eyes or ears, usually as drops containing 0.5 or 1%. Prednisolone has also been used topically as the free alcohol and as the hemisuccinate, pivalate, and metasulfobenzoate sodium esters.

For **rectal use** prednisolone metasulfobenzoate sodium or prednisolone sodium phosphate are often given. Retention enemas containing the equivalent of 20 mg of prednisolone per 100 mL, rectal foam containing the equivalent of 20 mg of prednisolone per dose, or suppositories containing the equivalent of 5 mg of prednisolone are available. Prednisolone has also been used rectally as the free alcohol and as the acetate and caproate esters.

Other esters of prednisolone that have occasionally been used include the farnesil, palmitate, sodium tetrahydrophthalate, and valeroacetate.

Preparations

BP 2008: Gastro-resistant Prednisolone Tablets; Prednisolone Enema; Prednisolone Sodium Phosphate Eye Drops; Prednisolone Tablets;
USP 31: Chloramphenicol and Prednisolone Ophthalmic Ointment; Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Prednisolone Acetate Injectable Suspension; Prednisolone Acetate Ophthalmic Suspension; Prednisolone Cream; Prednisolone Sodium Phosphate Injection; Prednisolone Sodium Phosphate Ophthalmic Solution; Prednisolone Sodium Succinate for Injection; Prednisolone Syrup; Prednisolone Tablets; Prednisolone Tebutate Injectable Suspension; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Cortizul; Ultracortenol; ***Austral.:*** Panafcortelone; Predmix; Predsol; Predsolone; Redipred; Solone; Sterofrin; ***Austria:*** Aprednislon; Kuhlprednon; Prednihexal; Rectopred; Solu-Dacortin; Ultracortenol; ***Belg.:*** Deltacortril†; Pred Forte; Prednicortelone†; Solu-Dacortine†; Ultracortenol; ***Braz.:*** Oftpred; Pred Fort; Pred Mild; Predsim; Prelone; ***Canad.:*** Ak-Tate; Diopred†; Inflamase†; Ophtho-Tate†; Pediapred; Pred Forte; Pred Mild; SAB-Prednase†; ***Chile:*** Pred Forte; Pred Mild†; Predsolets; Preventan†; ***Cz.:*** Inflanefran†; Linola-H N†; Linola-H-Fett N; Predni-POS; Solu-Decortin H†; Ultracortenol; ***Denm.:*** Pred-Clysma; Ultracortenol; ***Fin.:*** Di-Adreson-F; Pred Forte; Ultracortenol; ***Fr.:*** Hydrocortancyl; Solupred; ***Ger.:*** Decortin H; Dermosolon; Dontisolon D; duraprednisolon; hefasolon; Infectocortikrupp; Inflanefran; Klismacort; Linola-H N; Linola-H-Fett N; Lygal Kopftinktur N; Prectal†; Prednabene; Predni; Predni H; Predni-Ophtal; Predni-POS; Prednigalen; Prednihexal; Prednisolut; Solu-Decortin H; Ultracortenol; ***Gr.:*** Adelcort; Adelone; Deltacortril; Prezolon; ***Hong Kong:*** Dhasolone; Di-Adreson-F; Panafcortelone; Pred Forte; Pred Mild; Predenema; Predfoam; Prelone†; Redipred; Ultracortenol; ***Hung.:*** Di-Adreson-F; Klismacort†; Linola-H N; Linola-H-Fett N; Ultracortenol; ***India:*** Predone; Wysolone; ***Irl.:*** Deltacortril; Pred Forte†; Pred Mild; Predenema; Predfoam; Prednesol; Predsol; ***Israel:*** Pred Forte; Prelone†; Ultracortenol; ***Ital.:*** Meticortelone†; Soludacortin†; ***Jpn:*** Farnerate; Farnezone; Lidomex; Livimex; ***Malaysia:*** Dhasolone; Pred Forte; Pred Mild; Predon; Setsolone†; Sterosone†; ***Mex.:*** Cetapred; Delta-Diona; Fisopred; Meticortelone; Pred; Pred-NF; Prednefrin SF; Sophipren; ***Neth.:*** Di-Adreson-F; Pred Forte; Ultracortenol; ***Norw.:*** Pred-Clysma; Ultracortenol; ***NZ:*** Pred Forte; Pred Mild; Redipred; ***Philipp.:*** Histacort; Inflastat; Liquipred; Optipred; Pred Forte; Predisyr; Prednecort; Syrupred; ***Pol.:*** Encortolon; Fenicort; Mecortolon; ***Port.:*** Frisolona; Lepicortinolo; Predniocil; Sintisone†; Solu-Dacortina; ***Rus.:*** Medopred (Медопред); ***S.Afr.:*** Capsoid; Lenisolone; Meticortelone†; Pred Mild; Predsol†; Preflam; Prelone; ***Singapore:*** Dhasolone; Econopred; Pred; Walesolone; Xepasone†; ***Spain:*** Dacortin H†; Estilsona; Pred Forte; ***Swed.:*** Precortalon aquosum; Pred-Clysma; Ultracortenol; ***Switz.:*** Corti-Clyss†; Hexacortone; Pred Forte; Pred Mild; Solu-Dacortine†; Spiricort; Ultracortene H†; Ultracortenol; ***Thai.:*** Di-Adreson-F; Inf-Oph; Opredsone; Polypred; Pred Forte; Pred Mild; Predisole†; Prednersone; Prednisil; ***Turk.:*** Codelsol; Codelton; Deltacortril; Hexacorton; Neocorten; Norsol; Pred Forte; Prednol; ***UAE:*** Gupisone; ***UK:*** Deltacortril; Deltastab; Precortisyl; Pred Forte; Predenema; Predfoam; Predsol; ***USA:*** Ak-Pred†; Delta-Cortef†; Econopred†; Flo-Pred; Hydeltrasol†; Inflamase†; Key-Pred-SP; Key-Pred†; Millipred; Orapred; Pediapred; Pred; Pred Forte; Pred Mild; Pred-Phosphate; Predalone†; Predcor; Prednisol; Prelone; ***Venez.:*** Meticortelone; Ocupred; Prednefrin†; Sintisone; Sophipren.

Multi-ingredient: ***Arg.:*** Bactio Rhin Prednisolona; Blefamide; Cortizul; Delta Tomanil B12; Deltar; Efecoryl Forte; Esodar; Fenipred; Itro†; Neocortizul; Oftalmoflogol†; Otidrops; Prednefrin; Prednifarma; Procto Venart; Relefrina; Rucaten Prednisolona; Scheriproct; Solupred; ***Austral.:*** Prednefrin; Scheriproct; ***Austria:*** Alpicort; Delta-Hadensa; Phoscortil; Scheriproct; ***Belg.:*** Hemosedan; Predmycin P; Scheriproct; Sofrasolone; ***Braz.:*** Colutoide; Fonergin; Isopto Cetapred; Polipred; Predmicin; Reumazine†; Rifocort; Rinisone; ***Canad.:*** Blephamide; Dioptimyd†; Vasocidin†; ***Chile:*** Banedif Oftalmico con Prednisolona; Blefamide; Deltamid; Gemitin con Prednisolona; Pred G†; Scheriproct; Sintoftona; ***Cz.:*** Alpicort; Alpicort F; Imacort; Isopto Cetapred†; Linola-H-compositum N†; Linoladiol-H N†; Prednisolon J†; ***Fin.:*** Scheriproct; Septison; ***Fr.:*** Cortisal; Deliproct; Derinox; Deturgylone; ***Ger.:*** Alferm†; Alpicort; Alpicort F; Anumedin†; Aquapred; Berlicetin; Bismolan H Corti; Blephamide; Corti-Dynexan†; Dexa-Phlogont L†; Imazol comp; Inflanegent; Leioderm P; Linola-H-compositum N†; Linoladiol-H N; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Scheriproct†; Ultra-Demoplas†; Virunguent P†; ***Gr.:*** Blephamide†; Dermol; Isopto Cetapred; Precortivit†; Scheriproct Neo; ***Hong Kong:*** Blephamide; Chlomy-P†; Pilelife; Prednitracin†; ***Hung.:*** Alpicort; Alpicort F; Aurobin; Linoladiol-H N†; Prednisolon J; Rheosolon; ***India:*** Atrisolon; Otek-AC†; Perfocyn; Polyderm†; ***Indon.:*** Borraginol-S; Chloramphecort-H; Klorfeson; ***Irl.:*** Scheriproct; ***Israel:*** Aflumycin; Blephamide; Threolone; ***Ital.:*** Bio-Delta Cortilen; Deltamidrina; Solprene; ***Malaysia:*** Blephamide†; ***Mex.:*** Artrilan; Blefamide; Blefamide-F; Dartrizon; Deltamid; Deltron; Isopto Cetapred; Metimyd†; Obrypre; Otalgan; Premid; Scheriproct; ***Norw.:*** Scheriproct; ***NZ:*** Blephamide; ***Philipp.:*** Cetapred; Histacort; Isopto Cetapred; Predmycin-P; ***Pol.:*** Alpicort; Alpicort E; Mecortolon N; ***Port.:*** Anacal; Ciclobiotico†; Conjunctilone-S; Flogiftalmina†; Meocil; Neo-Davisolona; Prednierma†; Predniftalmina; Scheriproct; Vitasma†; ***Rus.:*** Aurobin (Ауробин); Dermosolon (Дермозолон); Hepatrombin H (Гепатромбин Г); Tergynan (Тержинан); ***S.Afr.:*** Scheriproct; ***Singapore:*** Blephamide; Predmycin-P†; ***Spain:*** Alergical; Antigrietun; Kanapomada; Nasopomada; Otonina†; Poly Pred; Predni Azuleno; Proctium; Rinobanedif; Rinovel; Ruscus; Scheriproct; Teolixir Compositum; ***Swed.:*** Scheriproct N; ***Switz.:*** Alpicort F; Blephamide; Calpred; Imacort; Locaseptil-Neo; Mycinopred; Nystacortone†; Prednitracin†; Premandol; Scheriproct; ***Thai.:*** Denson; Farakil; Levoptin; Mysolone-N; Neopred†; Neozolone; Pred Oph; Predex†; Predmycin†; Prednisil-N; Prednisil†; Scheriproct†; Unipred; ***Turk.:*** Blephamid; Otimisin; Prednol-A; Suprenil; ***UK:*** Predsol-N; Scheriproct; ***USA:*** Blephamide; Metimyd; Poly-Pred; Pred G; Sulfamide; Vasocidin; Vasocine; ***Venez.:*** Clorasona; Permucal; Scheriproct; Sulfacort.

Prednisone *(BAN, rINN)* ⊗

Δ[1]-Cortisone; 1,2-Dehydrocortisone; Deltacortisone; Deltadehydrocortisone; Metacortandracin; NSC-10023; Prednison; Prednisona; Prednisoni; Prednisonum; Prednizon; Prednizonas. 17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione.

Преднизон

$C_{21}H_{26}O_5$ = 358.4.

CAS — 53-03-2.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

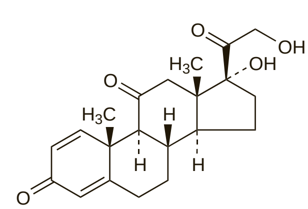

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows the anhydrous form or the monohydrate.

Ph. Eur. 6.2 (Prednisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Prednisone). It contains one molecule of water of hydration or is anhydrous. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 150 of alcohol and 1 in 200 of chloroform; slightly soluble in dioxan and in methyl alcohol.

Prednisone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisona; Prednisone, Acétate de; Prednisoni Acetas; Prednizonu octan. Prednisone 21-acetate.

Преднизона Ацетат

$C_{23}H_{28}O_6$ = 400.5.

CAS — 125-10-0.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Prednisone is a biologically inert corticosteroid that is converted in the liver to the mainly glucocorticoid corticosteroid prednisolone. It has the same chemical relationship to prednisolone as cortisone has to hydrocortisone. The indications and dosage of prednisone for oral use are exactly the same as those for prednisolone (see p.1542, and the chapter introduction, p.1495).

In the UK prednisolone has historically been preferred to prednisone, on the grounds that it does not require conversion to the active substance, but in practice this is rarely significant (see Hepatic Impairment, under Prednisolone, p.1541), and in some countries, such as the USA, prednisone is the drug of choice for many of the conditions in which routine systemic corticosteroid therapy is indicated.

Preparations

USP 31: Prednisone Oral Solution; Prednisone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Meticorten; Metilpres; Prednipirine; Prenisonal†; ***Austral.:*** Panafcort; Predsone; Sone; ***Belg.:*** Prednicort†; ***Braz.:*** Artinizona; Becortem; Corticorten; Meticorten; Metilen†; Precortil; Predicorten†; Predison; Prednax; Predval; ***Canad.:*** Winpred; ***Chile:*** Bersen; Cortiprex; Meticorten; Procion; ***Cz.:*** Rectodelt; ***Fr.:*** Cortancyl; ***Ger.:*** Decortin; Predni Tablinen; Rectodelt; ***Hung.:*** Rectodelt; ***Indon.:*** Inflason; ***Ital.:*** Deltacortene; ***Mex.:*** Ednapron; Meprosona-F; Meticorten; Norapred; Nosipren†; Ofisolona†; Predicor†; Prednidib; Premagnol†; ***Philipp.:*** Bioster; Oracort; Orasone; Pred; Prolix; Steerometz; ***Pol.:*** Encorton; ***Port.:*** Meticorten; ***S.Afr.:*** Meticorten; Panafcort; Predeltin; Pulmison; ***Spain:*** Dacortin; ***Swed.:*** Deltison; ***USA:*** Deltasone; Liquid Pred; Meticorten; Panasol-S; Sterapred; ***Venez.:*** Corticorp†; Meticorten; Vitazon†.

Multi-ingredient: ***Arg.:*** Peganix; ***Austria:*** Fluorex Plus; Oleomycetin-Prednison; ***Chile:*** Alerzona; ***Ger.:*** Oleomycetin-Prednison†; ***Mex.:*** Barigesic; Pre Clor; ***Spain:*** Coliriocilina Prednisona; Fiacin; Kanafosal Predni; Prednisona Neomicina.

Prednylidene *(BAN, rINN)* ⊗

16-Methyleneprednisolone; Prednilideeni; Prednilideno; Prednyliden; Prednylidène; Prednylidenum. 11β,17α,21-Trihydroxy-16-methylenepregna-1,4-diene-3,20-dione.

Преднилиден

$C_{22}H_{28}O_5$ = 372.5.

CAS — 599-33-7.

ATC — H02AB11.

ATC Vet — QH02AB11.

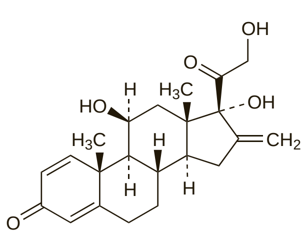

Profile

Prednylidene is a corticosteroid that has been used for its glucocorticoid activity similarly to prednisolone (see p.1540). It has been given orally as the free alcohol and by injection as the diethylaminoacetate hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Decortilen†.

Procinonide *(USAN, rINN)* ⊗

Procinonida; Procinonidum; RS-2362. (6α,11β,16α)-6,9-Difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-21-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Процинонид

$C_{27}H_{34}F_2O_7$ = 508.6.

CAS — 58497-00-0.

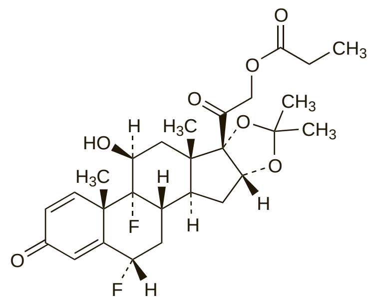

Profile

Procinonide is a derivative of fluocinolone acetonide (p.1531) that has been applied topically with fluocinonide and ciprocinonide in the management of various skin disorders.

Resocortol Butyrate *(USAN, rINNM)* ⊗

ALO-2184; Butirato de resocortol; Org-7417; Résocortol, Butyrate de; Resocortoli Butiras; Resocortoli Butyras; Resokortolbutyrat; Resokortolibutyraatti. 11β,17α-Dihydroxy-17-propionylandrost-4-en-3-one 17-butyrate.

Резокортола Бутират

$C_{26}H_{38}O_5$ = 430.6.

CAS — 76675-97-3 (resocortol); 76738-96-0 (resocortol butyrate).

ATC Vet — QD07AC90.

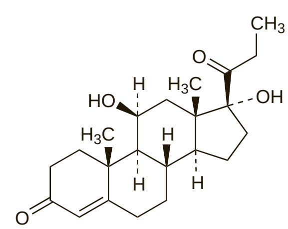

(resocortol)

Profile

Resocortol butyrate is a corticosteroid that is used topically in veterinary medicine.

Rimexolone *(BAN, USAN, rINN)* ⊗

Org-6216; Rimeksolon; Rimeksoloni; Rimexolon; Rimexolona; Rimexolonum; Trimexolone. 11β-Hydroxy-16α,17α-dimethyl-17β-propionylandrosta-1,4-dien-3-one.

Римексолон

$C_{24}H_{34}O_3$ = 370.5.

CAS — 49697-38-3.

ATC — H02AB12; S01BA13.

ATC Vet — QH02AB12; QS01BA13.

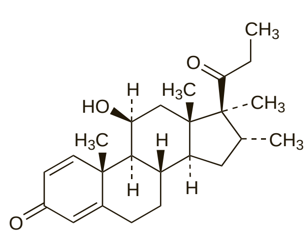

Pharmacopoeias. In *US.*

USP 31 (Rimexolone). A white to off-white powder. Freely soluble in chloroform; sparingly soluble in methyl alcohol.

Profile

Rimexolone is a corticosteroid applied topically to the eye for its glucocorticoid activity (see p.1490) in the treatment of inflammatory eye disorders including uveitis (p.1515) and postoperative inflammation. It is used as a 1% suspension.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Preparations

USP 31: Rimexolone Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)
Austria: Vexol; ***Belg.:*** Vexolon; ***Braz.:*** Vexol; ***Canad.:*** Vexol; ***Cz.:*** Vexol†; ***Denm.:*** Vexol; ***Fin.:*** Vexol; ***Fr.:*** Vexol; ***Ger.:*** Rimexel; Vexol; ***Gr.:*** Vexol; ***Hong Kong:*** Vexol; ***Hung.:*** Vexol†; ***Irl.:*** Vexol; ***Ital.:*** Vexol; ***Mex.:*** Vexol; ***Neth.:*** Vexol; ***Norw.:*** Vexol; ***Port.:*** Vexol; ***Spain:*** Vexol; ***Swed.:*** Vexol; ***Switz.:*** Vexol; ***Turk.:*** Vexol; ***UK:*** Vexol; ***USA:*** Vexol.

Suprarenal Cortex ⊗

Corteza suprarrenal.

Profile

Suprarenal cortex contains a number of steroid compounds the most active of which are corticosterone, dehydrocorticosterone, hydrocortisone, cortisone, and aldosterone. It has been prepared from the adrenal glands of oxen. Suprarenal cortex was formerly used intramuscularly for the treatment of adrenocortical insufficiency but it has been superseded by hydrocortisone and other corticosteroids (see p.1498).

Suprarenal cortex is an ingredient of a wide range of preparations, often with other organ extracts or vitamins, promoted for indications ranging from asthenia to liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Mobilat; ***Belg.:*** Mobilat; ***Braz.:*** Broncopinol†; Mobilat; Suprasten†; ***Canad.:*** ratio-Heracline; ***Chile:*** Mobilat; ***Cz.:*** Mobilat; ***Fin.:*** Mobilat; ***Ger.:*** Arthrodeformat P†; Mobilat†; ***Hong Kong:*** Mobilat†; ***Philipp.:*** Mobilat; ***Pol.:*** Mobilat; ***Singapore:*** Mobilat†; ***Spain:*** Neurocatavin Dexa†; Pleocortex B6†; Rubrocortin†; ***Thai.:*** Mobilat.

Tetracosactide *(BAN, rINN)* ⊗

α^{1-24}-Corticotrophin; β^{1-24}-Corticotrophin; Cosyntropin *(USAN)*; Tetracosactida; Tétracosactide; Tetracosactido; Tetracosactidum; Tetracosactrin; Tetrakosaktid; Tetrakosaktidi; Tetrakosaktrin; Tetrakozaktidas. Corticotrophin-(1–24)-tetracosapeptide; Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro.

Тетракозактид

$C_{136}H_{210}N_{40}O_{31}S$ = 2933.4.

CAS — 16960-16-0 (tetracosactide); 22633-88-1 (tetracosactide hexaacetate); 60189-34-6 (tetracosactide x acetate).

ATC — H01AA02.

ATC Vet — QH01AA02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tetracosactide). A synthetic tetracosapeptide in which the sequence of amino acids is the same as that of the first 24 residues of human corticotropin. It is available as an acetate and contains water. It increases the rate at which corticoid hormones are secreted by the adrenal gland. The potency is not less than 800 units/mg. A white or yellow, amorphous powder. Sparingly soluble in water. Store under nitrogen at a temperature of 2° to 8°. Protect from light.

Adverse Effects, Withdrawal, and Precautions

As for Corticotropin, p.1523. Although hypersensitivity reactions, including anaphylaxis, may occur with the use of tetracosactide, it is reported to be less immunogenic than corticotropin; US licensed product information suggests that patients with a history of hypersensitivity to corticotropin may tolerate tetracosactide. In the UK, however, previous hypersensitivity to corticotropin or to tetracosactide is considered a contra-indication to tetracosactide use. Tetracosactide is also contra-indicated in patients with a history of allergic disorders such as asthma.

Since hypersensitivity reactions may occur up to 1 hour after injection, sufficient time should be allowed for recovery after use at the hospital or surgery. Self-administration is not recommended.

Interactions

As for Corticosteroids, p.1494.

Pharmacokinetics

On intravenous injection tetracosactide exhibits triphasic pharmacokinetics. It is rapidly eliminated from plasma, mostly by distribution to the adrenal glands and kidneys. It is metabolised by serum endopeptidases into inactive oligopeptides, and then by aminopeptidases into free amino acids. Most of a dose is excreted in urine within 24 hours. The terminal half-life of tetracosactide is about 3 hours.

Uses and Administration

Tetracosactide is a synthetic polypeptide with general properties similar to those of corticotropin (p.1524). Tetracosactide is used diagnostically to investigate adrenocortical insufficiency (p.1498).

Although tetracosactide, like corticotropin, has also been used therapeutically for most of the conditions in which systemic corticosteroid therapy is indicated, it is now rarely used for such indications.

Tetracosactide is usually used in the form of the acetate although doses are often expressed in terms of tetracosactide itself.

For diagnostic purposes tetracosactide acetate is used intramuscularly or intravenously as a plain injection in the first instance then, if results are inconclusive, intramuscularly as a long-acting depot injection. The initial test using the plain injection is based on the measurement of plasma-cortisol concentrations immediately before and exactly 30 minutes after an intramuscular or intravenous injection equivalent to 250 micrograms of tetracosactide; adrenocortical function may be regarded as normal if there is a rise in the cortisol concentration of at least 200 nanomoles/litre (70 micrograms/litre). A suggested intravenous dose in children has been 250 micrograms per 1.73 m^2.

If the results of this test are equivocal the long-acting depot preparation may be used, the adult dose being 1 mg of tetracosactide acetate given intramuscularly. Adrenocortical function is regarded as normal if plasma-cortisol concentrations have steadily increased to 1000 to 1800 nanomoles/litre 5 hours after the injection. A 3-day test, for example with 1 mg of the depot preparation given each morning, is also used to differentiate between primary and secondary adrenocortical insufficiency; this is preceded on the first day and followed on the fourth day by the test using the plain injection. A marked improvement in the second assessment suggests secondary adrenocortical insufficiency.

For therapeutic purposes tetracosactide acetate has been given by intramuscular injection as the long-acting depot preparation. The usual initial adult dose of tetracosactide acetate has been 1 mg daily (or 1 mg every 12 hours in acute cases), reduced after the acute symptoms have been controlled to 0.5 to 1 mg every 2 or 3 days or 1 mg weekly. For children aged 3 to 5 years, a dose of 250 to 500 micrograms intramuscularly has been given daily initially, and then every 2 to 8 days for maintenance. A dose of 0.25 to 1 mg has been used similarly in children aged 5 to 12 years.

Tetracosactide has also been used in children aged 1 month and older to manage infantile spasms in a dose of 500 micrograms by intramuscular injection given on alternate days and adjusted to response.

◊ Reviews.

1. Dorin RI, *et al*. Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; **139:** 194–204.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or, more recently, tetracosactide.[1-5] Intramuscular injection and intravenous infusion have both been used, but a controlled study[6] in 18 women found that a single intramuscular dose of tetracosactide 1 mg was no more beneficial than sodium chloride 0.9%. As discussed on p.1851, many patients respond to conservative measures.

1. Collier BB. Treatment for post dural puncture headache. *Br J Anaesth* 1994; **72:** 366–7.
2. Foster P. ACTH treatment for post-lumbar puncture headache. *Br J Anaesth* 1994; **73:** 429.
3. Kshatri AM, Foster PA. Adrenocorticotropic hormone infusion as a novel treatment for postdural puncture headache. *Reg Anesth* 1997; **22:** 432–4.
4. Carter BL, Pasupuleti R. Use of intravenous cosyntropin in the treatment of postdural puncture headache. *Anesthesiology* 2000; **92:** 272–4.
5. Cánovas L, *et al*. Use of intravenous tetracosactin in the treatment of postdural puncture headache: our experience in forty cases. *Anesth Analg* 2002; **94:** 1369.
6. Rucklidge MWM, *et al*. Synacthen Depot for the treatment of postdural puncture headache. *Anaesthesia* 2004; **59:** 138–41.

Preparations

BP 2008: Tetracosactide Injection; Tetracosactide Zinc Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Synacthen; ***Austria:*** Synacthen; ***Belg.:*** Synacthen; ***Canad.:*** Cortrosyn; Synacthen Depot; ***Chile:*** Synacthen; ***Cz.:*** Synacthen†; ***Denm.:*** Synacthen; ***Fr.:*** Synacthene; ***Ger.:*** Synacthen; Synacthen Depot; ***Gr.:*** Cortrosyn; Nuvacthen; Synacthene; ***Hong Kong:*** Cortrosyn; ***Irl.:*** Synacthen; ***Israel:*** Cortrosyn†; Synacthen; ***Ital.:*** Cortrosyn†; Synacthen; ***Neth.:*** Cortrosyn†; Synacthen; ***NZ:*** Synacthen; ***Port.:*** Synacthen; ***Rus.:*** Synacthen (Синактен); Synacthen Depot (Синактен Депо); ***S.Afr.:*** Synacthen Depot; ***Spain:*** Nuvacthen Depot; ***Swed.:*** Synacthen; ***Switz.:*** Synacthen; Synacthen Depot; ***Thai.:*** Cortrosyn; ***Turk.:*** Synacthen Depot; ***UK:*** Synacthen; Synacthen Depot; ***USA:*** Cortrosyn; ***Venez.:*** Synacthen.

Tixocortol Pivalate *(BANM, USAN, rINNM)* ⊗

JO-1016; Pivalato de tixocortol; Tixocortol, Pivalate de; Tixocortoli Pivalas. 11β,17α-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione 21-pivalate.

Тиксокортола Пивалат

$C_{26}H_{38}O_5S$ = 462.6.

CAS — 61951-99-3 (tixocortol); 55560-96-8 (tixocortol pivalate).

ATC — A07EA05; R01AD07.

ATC Vet — QA07EA05; QR01AD07.

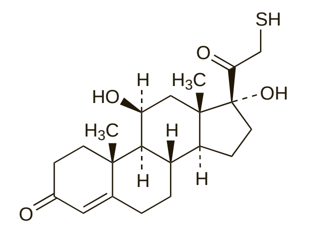

(tixocortol)

Profile

Tixocortol pivalate is a corticosteroid with mainly glucocorticoid activity (p.1490). It is used as buccal, nasal, throat, and rectal preparations. It is reported to undergo rapid first-pass metabolism, primarily in the liver, and to have minimal systemic effect.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Rhinovalon†; ***Fr.:*** Pivalone; ***Neth.:*** Pivalone†; Rectovalone†; ***Singapore:*** Pivalone; ***Spain:*** Tiovalone†; ***Switz.:*** Pivalone.

Multi-ingredient: ***Belg.:*** Rhinovalon Neomycine†; ***Fr.:*** Oropivalone Bacitracine†; Thiovalone; ***Singapore:*** Pivalone Neomycin†; ***Switz.:*** Oro-Pivalone; Pivalone compositum.

Triamcinolone *(BAN, rINN)* ⊗

9α-Fluoro-16α-hydroxyprednisolone; Fluoxiprednisolonum; Triamcinolon; Triamcinolona; Triamcinolonas; Triamcinolonum; Triamcynolon; Triamsinoloni. 9α-Fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione.

Триамцинолон

$C_{21}H_{27}FO_6$ = 394.4.

CAS — 124-94-7.

ATC — A01AC01; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.

ATC Vet — QA01AC01; QD07AB09; QD07XB02; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

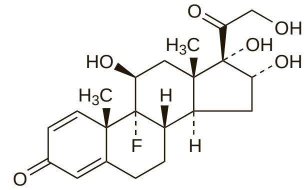

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Triamcinolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water and in dichloromethane; slightly soluble in methyl alcohol. Protect from light.

USP 31 (Triamcinolone). A white or practically white, odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol.

Triamcinolone Acetonide *(BANM, rINNM)* ⊗

Acetónido de triamcinolona; Triamcinolon acetonid; Triamcinolonacetonid; Triamcinolone, acétonide de; Triamcinoloni acetonidum; Triamcinolono acetonidas; Triamcynolonu acetonid; Triamsinolon Asetonid; Triamsinoloniasetonidi. 9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

Триамцинолона Ацетонид

$C_{24}H_{31}FO_6$ = 434.5.

CAS — 76-25-5.

ATC — A01AC01; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.

ATC Vet — QA01AC01; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Chin. also includes Triamcinolone Acetonide Acetate.

Ph. Eur. 6.2 (Triamcinolone Acetonide). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Triamcinolone Acetonide). A white to cream-coloured crystalline powder, having not more than a slight odour. Practically insoluble in water; sparingly soluble in dehydrated alcohol, in chloroform, and in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Triamcinolone Acetonide Sodium Phosphate *(BANM, USAN, rINNM)* ⊗

CL-61965; CL-106359; Fosfato de sodio del acetónido de triamcinolona; Triamcinolone Acétonide, Phosphate Sodique de; Triamcinoloni Acetonidi Natrici Phosphas. Triamcinolone acetonide 21-disodium phosphate.

Триамцинолона Ацетонида Натрия Фосфат

$C_{24}H_{30}FNa_2O_9P$ = 558.4.

CAS — 1997-15-5.

ATC — A01AC01; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.

ATC Vet — QA01AC01; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Triamcinolone Diacetate *(BANM, rINNM)* ⊗

Diacetato de triamcinolona; Triamcinolone, Diacetate de; Triamcinoloni Diacetas. Triamcinolone 16α,21-diacetate.

Триамцинолона Диацетат

$C_{25}H_{31}FO_8$ = 478.5.

CAS — 67-78-7.

ATC — A01AC01; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.

ATC Vet — QA01AC01; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Pharmacopoeias. In *US.*

USP 31 (Triamcinolone Diacetate). A fine, white to off-white, crystalline powder, having not more than a slight odour. Practically insoluble in water; soluble 1 in 13 of alcohol, 1 in 80 of chloroform, and 1 in 40 of methyl alcohol; slightly soluble in ether.

Triamcinolone Hexacetonide *(BAN, USAN, rINN)* ⊗

CL-34433; Hexacetónido de triamcinolona; TATBA; Triamcinolone Acetonide 21-(3,3-Dimethylbutyrate); Triamcinolone, hexacétonide de; Triamcinolonhexacetonid; Triamcinolon-hexacetonid; Triamcinoloni hexacetonidum; Triamcinolono heksacetonidas; Triamsinoloniheksasetonidi. 9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-(3,3-dimethylbutyrate).

Триамцинолона Гексасетонид

$C_{30}H_{41}FO_7$ = 532.6.

CAS — 5611-51-8.

ATC — A01AC01; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.

ATC Vet — QA01AC01; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Triamcinolone Hexacetonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol. Protect from light.

USP 31 (Triamcinolone Hexacetonide). A white to cream-coloured powder. Practically insoluble in water; soluble in chloroform; slightly soluble in methyl alcohol.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p.1490). High doses of triamcinolone may have a greater tendency to produce proximal myopathy. Its effects on sodium and water retention are less than those of prednisolone.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Effects on the eye. For complications and precautions associated with intravitreal use of triamcinolone see under Eye Disorders, below.

Hypersensitivity. Local reactions to topical triamcinolone preparations have been attributed to the content of ethylenediamine.[1,2] However, there have also been reports of anaphylactic shock after intra-articular[3] or intramuscular[4] injection of triamcinolone acetonide.

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; **287:** 463–4.
2. Freeman S. Allergy to Kenacomb cream. *Med J Aust* 1986; **145:** 361.
3. Larsson L. Anaphylactic shock after ia administration of triamcinolone acetonide in a 35-year-old female. *Scand J Rheumatol* 1989; **18:** 441–2.
4. Gonzalo FE, *et al.* Anaphylactic shock caused by triamcinolone acetonide. *Ann Pharmacother* 1994; **28:** 1310.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p.1495.

Triamcinolone is reported to have a half-life in plasma of about 2 to over 5 hours. It is bound to plasma albumin to a much smaller extent than hydrocortisone.

The acetonide, diacetate, and hexacetonide esters of triamcinolone are only very slowly absorbed from injection sites.

Triamcinolone crosses the placenta.

◊ References to the pharmacokinetics of triamcinolone and its esters.

1. Möllmann H, *et al*. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985; **29:** 85–9.
2. Derendorf H, *et al.*. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther* 1986; **39:** 313–17.
3. Derendorf H, *et al.* Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. *J Clin Pharmacol* 1995; **35:** 302–5.
4. Argenti D, *et al.* A mass balance study to evaluate the biotransformation and excretion of [C]-triamcinolone acetonide following oral administration. *J Clin Pharmacol* 2000; **40:** 770–80.

Uses and Administration

Triamcinolone is a corticosteroid with mainly glucocorticoid activity (p.1490); 4 mg of triamcinolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p.1495), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred.

For **oral dosage** triamcinolone is used in doses ranging from 4 to 48 mg daily.

For **parenteral use** the acetonide or diacetate esters are given in doses of about 40 mg by intramuscular injection. They are usually given as suspensions to provide a prolonged systemic effect. A dose of 40 to 100 mg of the acetonide may provide symptomatic control throughout the pollen season for hay fever sufferers (but see Rhinitis, below); for the diacetate, a 40-mg dose is given weekly.

For **intra-articular injection** triamcinolone acetonide, diacetate, and hexacetonide have all been used. Doses for these esters have typically been in the range of 2.5 to 40 mg, 3 to 48 mg, and 2 to 30 mg respectively, depending upon the size of the joint injected.

For **topical application** in the treatment of various skin disorders triamcinolone acetonide is used, usually in creams, lotions, or ointments containing 0.1% although concentrations ranging from 0.025 to 0.5% have been employed. Several topical preparations also contain an antimicrobial drug. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Triamcinolone esters are also commonly used by **intralesional** or **intradermal injection** in the treatment of some inflammatory skin disorders such as keloids. Suggested doses for the various esters have been:

- acetonide: 1 to 3 mg per site with no more than 5 mg injected into any one site or not more than 30 mg in total if several sites of injection are used
- diacetate: a total of 5 mg in divided doses into small lesions or up to a total of 48 mg in divided doses into large lesions with no more than 12.5 mg injected into any one site or 25 mg injected into any one lesion
- hexacetonide: up to 500 micrograms per square inch (about 80 micrograms/cm^2) of affected skin.

Triamcinolone acetonide is also used **by inhalation** for the control of asthma in a usual dose of about 150 micrograms by metered-dose inhaler three or four times daily, or 300 micrograms twice daily; the dose should not exceed 1200 micrograms daily. Children aged 6 to 12 years may be given 75 or 150 micrograms three or four times daily, or 150 to 300 micrograms twice daily; the daily dose should not exceed 900 micrograms.

In the prophylaxis and treatment of allergic rhinitis triamcinolone acetonide may be given by a **nasal spray** in a usual initial dose of 2 sprays (110 micrograms) into each nostril once daily, reduced to 1 spray (55 micrograms) when control is achieved. Children aged 6 to 12 years may be given 1 spray (55 micrograms) into each nostril once daily; in severe symptoms this may be increased to 220 micrograms daily.

A preservative-free suspension of triamcinolone acetonide 40 mg/mL is available for **intravitreal injection**. A dose of 4 mg is used for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions that are unresponsive to topical corticosteroids. Further doses may be given as needed during the course of treatment. A dose of 1 to 4 mg may be used for visualisation during vitrectomy.

Other esters of triamcinolone that have occasionally been used include the acetonide dipotassium phosphate, acetonide hemisuccinate, aminobenzal benzamidoisobutyrate, and benetonide. Flupamesone (triamcinolone acetonide metembonate) has also been used.

Asthma. Intramuscular triamcinolone acetonide has been reported to be more effective than oral low-dose prednisone in controlling exacerbations in patients with severe, chronic, life-threatening asthma,[1] although this conclusion is controversial.[2-7]

Corticosteroids and $beta_2$-adrenoceptor agonists form the cornerstone of the management of asthma (p.1108). Inhaled corticosteroids are added to therapy with a short-acting $beta_2$ agonist if symptom relief with the latter is needed more than once daily, although corticosteroids with reduced systemic activity are generally preferred to triamcinolone. Systemic corticosteroids are reserved for the most severe cases, and for the management of acute severe asthma attacks (status asthmaticus).

1. Ogirala RG, *et al.* High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N Engl J Med* 1991; **324:** 589–9. Correction. *ibid.*; 1380.
2. Salmeron S, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 429–30.
3. Nicholas SS. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
4. Kidney JC, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
5. Capewell S, McLeod DT. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 430.
6. Ogirala RG, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325:** 431.
7. Capewell S, McLeod D. Injected corticosteroids in refractory asthma. *Lancet* 1991; **338:** 1075–6.

Chronic obstructive pulmonary disease. For discussion of the value of inhaled corticosteroids in chronic obstructive pulmonary disease, including reference to the use of triamcinolone acetonide, see p.1501.

Eye disorders. Intravitreal injection of triamcinolone acetonide has been tried in the management of eye disorders characterised by oedema and the abnormal proliferation of intra-ocular cells. Promising results have been reported in diabetic macular oedema,[1,2] cystoid macular oedema, and oedema associated with retinal vein occlusion.[2-5] It has also been used in age-related macular degeneration (p.785; better results being seen when it is combined with photodynamic therapy), in proliferative diabetic retinopathy, and in the management of some forms of cataract and non-infectious uveitis.[2,3] Complications of treatment may include raised intra-ocular pressure (IOP)[6] and both infectious and non-infectious endophthalmitis.[2] Patients with a baseline IOP greater than 16 mmHg or receiving a second injection should be carefully monitored, as they may be at greater risk of an increase; monitoring should continue beyond 6 months.[6]

Dissolved drugs are not retained in the eye for prolonged periods, and early studies and off-label treatment have used injectable suspensions to achieve long-lasting concentrations of triamcinolone in the vitreous body.[7] However, these commercial products were intended for intramuscular and intra-articular use and not licensed for intravitreal injection, and there has been concern about the potential ocular toxicity of their preservative, benzyl alcohol.[2,7] Various techniques, such as sedimentation, centrifugation, and filtration, have been used extemporaneously to reduce the benzyl alcohol content of such products, but the quantity of triamcinolone in the final preparation may be altered depending on the technique used.[8] More recently, a preservative-free product has been licensed in the USA for intravitreal use (*Triesence; Alcon, USA*—see Uses and Administration, above).

1. Ip MS. Intravitreal injection of triamcinolone: an emerging treatment for diabetic macular edema. *Diabetes Care* 2004; **27:** 1794–7.
2. Jonas JB. Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand* 2005; **83:** 645–63.
3. van Kooij B, *et al.* The pros and cons of intravitreal triamcinolone injections for uveitis and inflammatory cystoid macular edema. *Ocul Immunol Inflamm* 2006; **14:** 73–85.
4. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. *Ophthalmic Res* 2006; **38:** 218–45.
5. Sivaprasad S, *et al.* Intravitreal steroids in the management of macular oedema. *Acta Ophthalmol Scand* 2006; **84:** 722–33.
6. Rhee DJ, *et al.* Intraocular pressure alterations following intravitreal triamcinolone acetonide. *Br J Ophthalmol* 2006; **90:** 999–1003.
7. Jonas JB. Effects of triamcinolone acetonide injections with and without preservative. *Br J Ophthalmol* 2007; **91:** 1099–1101.
8. García-Arumí J, *et al.* Comparison of different techniques for purification of triamcinolone acetonide suspension for intravitreal use. *Br J Ophthalmol* 2005; **89:** 1112–14.

Haemangioma. For reference to the use of a mixture of triamcinolone and betamethasone for intralesional injection of haemangioma, see p.1505.

Rhinitis. Triamcinolone is used[1,2] in the management of allergic rhinitis (p.565). However, the use of depot injections of triamcinolone to manage seasonal allergic rhinitis has been deemed unacceptable by some.[3]

1. Jeal W, Faulds D. Triamcinolone acetonide: a review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinitis. *Drugs* 1997; **53:** 257–80.
2. Gawchik SM, Saccar CL. A risk-benefit assessment of intranasal triamcinolone acetonide in allergic rhinitis. *Drug Safety* 2000; **23:** 309–22.
3. Anonymous. Any place for depot triamcinolone in hay fever? *Drug Ther Bull* 1999; **37:** 17–18.

Preparations

BP 2008: Triamcinolone Acetonide Injection; Triamcinolone Cream; Triamcinolone Hexacetonide Injection; Triamcinolone Ointment; Triamcinolone Oromucosal Paste; Triamcinolone Tablets;

USP 31: Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Cream; Triamcinolone Acetonide Dental Paste; Triamcinolone Acetonide Injectable Suspension; Triamcinolone Acetonide Lotion; Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Topical Aerosol; Triamcinolone Diacetate Injectable Suspension; Triamcinolone Diacetate Syrup; Triamcinolone Hexacetonide Injectable Suspension; Triamcinolone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Fortcinolona; Glytop; Kenacort; Kenacort-A; Ledercort; Nasacort; Rezamid D, Rezamid F, Rezamid M†; Triamciterap; Triampoen; ***Austral.:*** Aristocort; Kenacort-A; Kenalog in Orabase; Telnase; Tricortone; ***Austria:*** Delphicort; Nasacort; Solu-Volon A; Triamhexal; Volon; Volon A; ***Belg.:*** Albicort; Delphi; Kenacort-A; Kenacort†; Ledercort†; ***Braz.:*** Airclin; Azmacort; Nasacort; Omcilon A Orabase; Theracort; Triancil; ***Canad.:*** Aristocort; Aristospan; Kenalog; Kenalog in Orabase; Nasacort; Oracort; Triaderm; ***Chile:*** Kenacort-A; Nasacort; ***Cz.:*** Azmacort†; Kenalog†; Nasacort; Triamcinolon-Ivax; ***Denm.:*** Kenalog; Lederspan; Nasacort; ***Fin.:*** Aftab; Kenacort-T; Lederspan; Nasacort; ***Fr.:*** Hexatrione; Kenacort; Nasacort; ***Ger.:*** Aftab; Arutrin†; Berlicort†; Delphicort; Delphimix†; Kenalog†; Kortikoid-ratiopharm; Lederlon; Linola Cort Triam; Nasacort; Rhinisan; Triam; Triam-Creme; Triamgalen; Triamhexal; TriamSalbe; Volon; Volon A; Volonimat; Volonimat N; ***Gr.:*** Forlion; Kenacort-A; Nasacort; Nasatrim; Triamcinal; ***Hong Kong:*** Aftach; Aristo; Aristocort†; Denkacort†; Dermacort; Kemzid†; Kenacort-A; Kenalog in Orabase; Nasacort; Triam; ***Hung.:*** Ftorocort; Kenalog; Polcortolone; ***India:*** Kenacort; Ledercort; Tess; Tricort; ***Indon.:*** Flamicort; Kenacort; Kenacort-A; Kenalog in Orabase; Ketricin; Nasacort; Triamcort; Tridez; Trilac; Trinolon; ***Irl.:*** Adcortyl; Adcortyl in Orabase; Kenalog; Nasacort; ***Israel:*** Adcortyl†; Kenalog in Orabase†; Kenalog†; Oracort; Sterocort; Steronase Aq; ***Ital.:*** Aftab; Ipercortis; Kenacort; Ledercort†; Nasacort; Triacort; Triamvirgi; ***Jpn:*** Aftach; ***Malaysia:*** Dermacort; Kenacort-A†; Kenaderm†; Kenalog in Orabase; Metoral; Nasacort AQ; Orrepaste; Shincort; Tramsone; Trim†; ***Mex.:*** Azucort; Intralon; Kenacort; Kenalog

Dental; Nasacort; Triamsicort; Zamacort; ***Neth.:*** Albicort†; Kenacort-A; Nasacort; ***Norw.:*** Kenacort-T; Lederspan; Nasacort; ***NZ:*** Aristocort; Kenacort-A; Kenalog in Orabase; Oracort; Telnase; ***Philipp.:*** Kenacort; Kenacort-A; ***Pol.:*** Polcortolon; ***Port.:*** Aftach; ***Rus.:*** Berlicort (Берликорт); Ftorocort (Фторокорт); Kenalog (Кеналог); Polcortolon (Полькортолон); Polcortolon TC (Полькортолон ТС); Triacort (Триакорт); ***S.Afr.:*** Kenalog in Orabase; Nasacor; ***Singapore:*** Dermacort; Kemzid†; Kenacort-A; Kenalog in Orabase; Nasacort; Oramedy; Orrepaste; Shincort; Triam†; Trinolone; ***Spain:*** Flutenal; Kenalog in Orabase; Nasacort; Proctosteroid; Trigon Depot; ***Swed.:*** Kenacort-T; Lederspan; Nasacort; ***Switz.:*** Kenacort; Kenacort-A; Kenacort-A Solubile; Ledercort†; Nasacort; Triamcort; ***Thai.:*** Aristocort; Centocort; Facort; Ftorocort; Generlog; Kanolone; Kela; Kemzid; Kena-Lite; Kenacort; Kenalog in Orabase; Keno; Laver; Manolone; Metoral; Milanolone; Nasacort; Oral-T; Oralog; Orcilone; Risto; Shincort; Simacort; T-1; TA Osoth; Tacinol; Topilone; Tramsilone; Triama†; Trilosil†; Trim; Unif; V-Nolone; Vacinolone; Zyno; ***Turk.:*** Kenacort-A; Nasacort; Sinakort-A; ***UK:*** Adcortyl; Adcortyl in Orabase; Kenalog; Nasacort; ***USA:*** Amcort†; Aristocort†; Aristospan; Atolone; Azmacort; Delta-Tritex†; Flutex; Kenalog; Kenalog in Orabase; Kenonel; Nasacort; Oralone Dental; Tac; Tri-Kort; Tri-Nasal; Triacet; Triam-A; Triam†; Triamonide; Triderm; Triesence; Trilog; Trilone†; ***Venez.:*** Kenacort; Nasacort.

Multi-ingredient: ***Arg.:*** Bagovit A Plus; Biotaer Nasal; Domtisona†; Exfolium†; Kenacomb; Ledercort con Neomicina†; Mantus; Rezamid†; Sorsis; ***Austral.:*** Kenacomb; Otocomb Otic; ***Austria:*** Aureocort; Ledermix; Mycostatin V; Neo-Delphicort; Pevisone; Steros-Anal; Volon A antibiotikahaltig; Volon A Tinktur; Volon A-Zinklotion; ***Belg.:*** Mycolog; Pevisone; Trianal; ***Braz.:*** Londern-N; Mud; Neolon-D; Omcilon A M; Onciplus; ***Canad.:*** Kenacomb†; ratio-Triacomb; Triacomb†; Viaderm-KC; ***Cz.:*** Triaderm; Triamcinolon Compositum†; Triamcinolon E; Triamcinolon S; Triamcinolon-Galena†; Triamcinolon-Ivax; ***Denm.:*** Kenacutan; Kenalog Comp med Mycostatin; Kenalog med Salicylsyre; Ledermix†; Pevisone; ***Fin.:*** Pevisone; ***Fr.:*** Cidermex; Corticotulle Lumiere†; Kenalcol; Localone; Mycolog†; Pevisone; ***Ger.:*** Aureodelf†; Corticotulle Lumiere†; Epipevisone; Extracort Tinktur†; Ledermix; Moronal V; Mykoproct sine; Polcortolon TC; Steros-Anal†; Volon A antibiotikahaltig N†; Volon A Tinktur N; Volon A-Rhin†; Volon A-Schuttelmix; Volonimat Plus N; ***Gr.:*** Kenacomb; Olamyc; Pevison; ***Hong Kong:*** Anso; Clotrinolon; Kenacomb; Oragesic; Pevisone; Tri-Gel; Triacomb; Triconazole; Triditol-G; ***Hung.:*** Alkcema; Polcortolon TC; ***India:*** Kenacomb; Kenalog-S; Ledercort-N; ***Indon.:*** Kenantist; New Kenacomb; ***Irl.:*** Audicort†; Kenacomb; ***Israel:*** Dermacombin; Kenacomb†; Ledermix; Oracort E; Pevisone; ***Ital.:*** Assocort; Aureocort; Dirahist; Kataval; Pevisone; ***Malaysia:*** Ecocort; Econazine; Kenacomb; Oral-Aid; Pevisone†; ***Mex.:*** Bidrozil; Biotriamin; Kenacomb; ***Neth.:*** Albicort Compositum†; Mycolog; Trianal; Will-Anal; ***Norw.:*** Kenacort-T comp; Kenacutan; Pevisone; ***NZ:*** Kenacomb; Viaderm-KC; ***Philipp.:*** Kenacomb; Nizolex; Pevisone; ***Pol.:*** Pevisone; Polcortolon TC; Triacomb; ***Port.:*** Kenacomb; Localone; Pevisone; ***S.Afr.:*** Kenacomb; Pevisone; Trialone; ***Singapore:*** Ecocort; Econazine; Kenacomb†; Oral-Aid; Pevisone†; ***Spain:*** Aldo Otico†; Aldoderma; Anasilpiel; Anso; Cemalyt; Cremsol; Flutenal Gentamicina; Flutenal Sali; Interderm; Nesfare; Positon; Trigon Rectal; Trigon Topico; ***Swed.:*** Kenacombin Novum; Kenacort-T comp; Kenacutan; Pevisone; ***Switz.:*** Kenacort-A; Ledermix; Mycolog†; Pevisone; ***Thai.:*** Dermacombin; Ecocort; Ecoderm; Fungisil-T; KA-Cilone; Kelaplus; Kenacomb; Pevisone†; Tara-Plus; Timi; Tricozole; Trimicon; ***UAE:*** Panderm; ***UK:*** Audicort†; Aureocort; Ledermix; Tri-Adcortyl; ***USA:*** Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; Mytrex†; NGT; Tri-Statin II; ***Venez.:*** Kenacomb; Kenalog.

Ulobetasol Propionate *(rINNM)* ⊗

BMY-30056; CGP-14458; 6-α-Fluoroclobetasol Propionate; Halobetasol Propionate *(USAN)*; Propionato de ulobetasol; Ulobétasol, Propionate d'; Ulobetasoli Propionas. 21-Chloro-6α,9-difluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

Улобетазола Пропионат

$C_{25}H_{31}ClF_2O_5$ = 485.0.

CAS — 98651-66-2 (ulobetasol); 66852-54-8 (ulobetasol propionate).

ATC — D07AC21.

ATC Vet — QD07AC21.

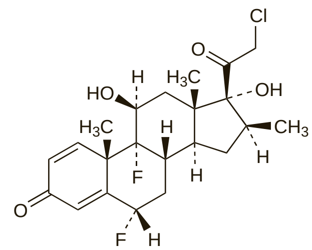

(ulobetasol)

Profile

Ulobetasol propionate is a corticosteroid that is used topically for its glucocorticoid activity (p.1490) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p.1490). The effects of topical corticosteroids on the skin are described on p.1492. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p.1497.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Ultravate; ***USA:*** Ultravate.

Cough Suppressants Expectorants Mucolytics and Nasal Decongestants

This chapter describes drugs that are used mainly as cough suppressants, expectorants, or mucolytics, and also those sympathomimetics primarily used for the relief of nasal congestion. Other drugs used in cough include antihistamines (p.561), bronchodilators (p.1108), and local anaesthetics (p.1850). Compounds with a demulcent action such as glycerol (p.2314) and sucrose (p.1969) are also used, as are various hydrating inhalations.

Cough suppressants

Cough suppressants have either a central or a peripheral action on the cough reflex or a combination of both. Centrally acting cough suppressants increase the threshold of the cough centre in the brain to incoming stimuli whereas those acting peripherally decrease the sensitivity of the receptors in the respiratory tract. Some drugs have an indirect peripheral mechanism of action and may alter mucociliary factors, exert a local analgesic or anaesthetic action on the receptors, protect the receptors from irritant stimuli, or act as bronchodilators.

Those centrally acting cough suppressants structurally related to morphine that are included in this chapter, such as dextromethorphan, have little or no analgesic action. Those that also have an important analgesic action, such as codeine or diamorphine, are described in the chapter on Analgesics, p.1.

Described in this chapter are

Acetyldihydrocodeine, p.1550	Helicidine, p.1562
Alloclamide, p.1550	Isoaminile, p.1563
Benproperine, p.1552	Menglytate, p.1564
Benzonatate, p.1552	Morclofone, p.1565
Bibenzonium, p.1552	Nepinalone, p.1566
Butamirate, p.1553	Nicocodine, p.1566
Butetamate, p.1553	Normethadone, p.1566
Caramiphen, p.1553	Noscapine, p.1566
Clobutinol, p.1554	Oxeladin, p.1567
Clofedanol, p.1554	Oxolamine, p.1567
Cloperastine, p.1554	Pentoxyverine, p.1567
Dextromethorphan, p.1555	Pholcodine, p.1570
Dimemorfan, p.1557	Pipazetate, p.1570
Dimethoxanate, p.1557	Poppy Capsule, p.1571
Dropropizine, p.1557	Prenoxdiazine, p.1571
Elecampane, p.1558	Promolate, p.1571
Ethyl Orthoformate, p.1560	Sodium Dibunate, p.1573
Fedrilate, p.1560	Thebacon, p.1574
Fominoben, p.1561	Tipepidine, p.1574
Glaucine, p.1561	Zipeprol, p.1575

Expectorants

Expectorants are considered to increase the volume of secretions in the respiratory tract thereby facilitating their removal by ciliary action and coughing. Many traditional expectorants, including ipecacuanha, squill, ammonium salts, some volatile oils, and various iodide compounds, have been considered to achieve this by a reflex irritant effect on the gastric mucosa.

Described in this chapter are

Ammonium Salts, p.1551	Guaietolin, p.1561
Calcium Iodide, p.1553	Guaifenesin, p.1561
Cocillana, p.1554	Guaimesal, p.1562
Coltsfoot, p.1555	Iodinated Glycerol, p.1562
Creosote, p.1555	Ipecacuanha, p.1562
Elecampane, p.1558	Marrubium, p.1564
Eprazinone, p.1559	Senega Root, p.1572
Eprozinol, p.1560	Squill, p.1573
Eriodictyon, p.1560	Sulfogaiacol, p.1573
Fudosteine, p.1561	Terpin, p.1573
Guacetisal, p.1561	Tolu Balsam, p.1574
Guaiacol, p.1561	

Mucolytics

Mucolytics alter the structure of mucus to decrease its viscosity thereby facilitating its removal by ciliary action or expectoration.

Acetylcysteine, carbocisteine, and mecysteine all have thiol groups; if this group is free, as in acetylcysteine, it may be substituted for disulfide bonds in mucus and therefore break the mucus chains. However, drugs such as carbocisteine with 'protected' thiol groups cannot act by this mechanism and their exact mode of action is unclear. Thiol groups are also involved in the mechanism of action of some of these drugs when they are used in the treatment of poisoning.

Deoxyribonucleases such as dornase alfa act as mucolytics by hydrolysing the accumulated extracellular DNA from decaying neutrophils that contributes to the viscous respiratory secretions of cystic fibrosis.

Drugs with **mucoregulatory** actions, typically affecting mucin and chloride secretion by acting on ion channels in the respiratory tract, are also being developed; examples under investigation include denufosol and talniflumate.

Described in this chapter are

Acetylcysteine, p.1548	Erdosteine, p.1560
Ambroxol, p.1550	Ethyl Cysteine Hydrochloride, p.1560
Bromhexine, p.1552	Letosteine, p.1563
Brovanexine, p.1553	Mecysteine, p.1564
Carbocisteine, p.1553	Methyl Dacisteine, p.1564
Dembrexine, p.1555	Neltenexine, p.1566
Denufosol, p.1555	Sobrerol, p.1572
Dornase Alfa, p.1557	Talniflumate, p.1573
Eprazinone, p.1559	Telmesteine, p.1573
Eprozinol, p.1560	

Sympathomimetics

Sympathomimetics described in this chapter may be used systemically (such as phenylephrine) or locally (such as naphazoline), for their alpha agonist actions to produce vasoconstriction of the nasal mucosa, thus relieving congestion. Others such as ephedrine have both alpha and beta agonist actions. The beta agonist actions confer upon them bronchodilating properties, but they have been superseded as bronchodilators by the more selective beta$_2$ agonists such as salbutamol. The value of bronchodilators in non-asthmatic cough has not been confirmed.

Described in this chapter are

Amidefrine, p.1551	Naphazoline, p.1565
Clonazoline, p.1554	Oxymetazoline, p.1567
Ephedra, p.1558	Phenylephrine, p.1568
Ephedrine, p.1558	Phenylpropanolamine, p.1569
Etafedrine, p.1560	Pseudoephedrine, p.1571
Fenoxazoline, p.1560	Tetryzoline, p.1574
Indanazoline, p.1562	Tramazoline, p.1574
Levmetamfetamine, p.1564	Tuaminoheptane, p.1575
Methoxyphenamine, p.1564	Tymazoline, p.1575
Methylephedrine, p.1564	Xylometazoline, p.1575
Metizoline, p.1565	

Cough

Cough is an important physiological protective mechanism, but may also occur as a symptom of an underlying disorder such as asthma, gastro-oesophageal reflux disease, and postnasal drip. Treatment of the disorder often alleviates the cough, but there are times when symptomatic treatment is appropriate. The treatment chosen depends on whether the cough is productive or non-productive.[1-11]

A **non-productive cough** such as that often seen with the common cold serves no useful purpose for the patient, and cough suppressants may provide some relief, particularly if given at night.

- Of the commonly used *cough suppressants*, pholcodine and dextromethorphan are considered to have fewer adverse effects than codeine. However, there is little evidence that these drugs are effective in severe cough. Codeine or similar opioids are not generally recommended as cough suppressants in children, and should be avoided altogether in those under 1 year of age.
- Sedating *antihistamines* such as diphenhydramine are frequently used as cough suppressants in compound preparations. Suggested mechanisms of action have included reduction in cholinergic nerve transmission, or cough suppression as a result of their sedative effects. Antihistamines reduce nasal secretions and may be of value in treating cough caused by postnasal drip, particularly if associated with allergic rhinitis (see p.565). However, they should not be used to treat a productive cough because they may cause formation of viscid mucus plugs. Their sedative effects are a disadvantage for daytime use but may be a short-term advantage for night coughs.
- *Demulcents* probably act as indirect peripherally acting cough suppressants by providing a protective coating over sensory receptors in the pharynx. Demulcents include glycerol, honey, liquorice, and sucrose syrups.

A potent cough suppressant such as morphine is needed for the relief of **intractable cough** in terminal illness. The use of such a potent opioid is not otherwise considered appropriate for cough.

- *Local anaesthetics* such as lidocaine or bupivacaine have been inhaled in severe intractable cough, including cough caused by malignant neoplasms. Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, such treatment should be used with care. There may also be temporary loss of the swallowing reflex.

A **productive cough** is characterised by the presence of sputum and may be associated with conditions such as chronic bronchitis, bronchiectasis, or cystic fibrosis. Cough suppressants are inappropriate, since the cough serves the purpose of clearing the airways, but expectorants have been used on the grounds that increasing the volume of secretions in the respiratory tract facilitates removal by ciliary action and coughing. However, clinical evidence of efficacy is lacking, and many authorities consider expectorants to be of no value other than as a placebo.

- Commonly used *expectorants* include ammonium salts, guaifenesin, ipecacuanha, and sodium citrate. Iodides have also been used but there has been concern over their safety for prolonged use in respiratory disorders and because of their potential for thyroid suppression; in particular, it has been recommended that they should not be given to children, adolescents, pregnant women, or patients with goitre.
- *Mucolytics* have been shown to affect sputum viscosity and structure and patients have reported alleviation of their symptoms, but no consistent improvement in lung function has been found. Commonly used mucolytics include acetylcysteine, bromhexine, carbocisteine, and mecysteine. Dornase alfa is also available, in particular for patients with cystic fibrosis. In theory mucolytics may disrupt the gastric mucosal barrier and caution has been recommended in patients with a history of peptic ulcer disease.
- *Hydrating agents* liquefy mucus and also have a demulcent effect. Hydration may be achieved simply by inhaled warm moist air. The addition of substances such as menthol, benzoin, or volatile oils is unlikely to provide any additional benefit but may encourage the use of such inhalations. Inhaled aerosols of water, sodium bicarbonate, sodium chloride, surfactants such as tyloxapol, and proteolytic enzymes such as chymotrypsin and trypsin, have also been used for their reported hydrating or mucolytic effects on respiratory secretions.

Cough may sometimes be associated with **bronchospasm** in patients with asthma.

- *Bronchodilators* such as salbutamol (a beta$_2$ agonist) or ipratropium (an antimuscarinic) alleviate cough associated with bronchospasm. However, they are not generally considered of benefit in other forms of cough, and hence are not recommended other than in asthma or selected patients with chronic obstructive pulmonary disease.

Cough and cold preparations containing various combinations of cough suppressants and/or expectorants, with sympathomimetics, antihistamines, or analgesics are available. Some combinations, such as a cough suppressant and an expectorant, seem illogical and have little evidence to support their efficacy. As with many combinations, doses of individual drugs may be inadequate or inappropriate, and the large number of ingredients may expose the patient to unnecessary adverse effects. In particular, concern has been expressed about the safety in *children* of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[12] has found no good evidence for or against the effectiveness of over-the-counter preparations in acute cough. The British Thoracic Society considers that over-the-counter medications are as effective as placebo for acute cough with head colds in children.[13] In early 2008, the FDA[14] and MHRA[15] both advised that over-the-counter cough and cold preparations should not be given to children under 2 years of age. They warn of the potential for serious and potentially life-threatening adverse effects and that such preparations provide only symptomatic relief, at best. If these products are used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing.

To alleviate symptoms of coughs and colds in children aged under 2 years, the MHRA recommends using single-constituent paracetamol or ibuprofen, simple cough preparations (such as those containing glycerol or honey and lemon), vapour rubs and inhalant decongestants (that can be applied to clothing), and, particularly in infants, sodium chloride nasal drops.

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14. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01778.html (accessed 15/04/08)
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Nasal congestion

Nasal congestion is frequently a symptom of conditions such as rhinitis (p.565), treatment of which can include the use of antihistamines, sympathomimetics, corticosteroids, antimuscarinics, and cromoglicate or nedocromil.

Sympathomimetics are also widely used as nasal decongestants to provide symptomatic relief of the common cold (p.850). They are used for the vasoconstriction produced by their alpha-adrenergic effects; redistribution of local blood flow reduces oedema of the nasal mucosa, thus improving ventilation, drainage, and nasal stuffiness. Sympathomimetics such as ephedrine, phenylephrine, naphazoline, oxymetazoline, and xylometazoline can be used topically as nasal drops or sprays. Those such as pseudoephedrine are given orally. Over-the-counter cough and cold preparations containing sympathomimetic decongestants should be used with caution in children and generally avoided in those under 2 years of age (see above). However, the *BNFC* suggests that, in certain circumstances, specialists may prescribe ephedrine or xylometazoline nasal drops for children under 2 years in the short-term treatment of severe nasal congestion that has not responded to sodium chloride nasal drops or inhalation of warm moist air (see below).

Topical use, particularly if prolonged, may lead to rebound congestion as vasodilatation becomes prominent and the effects of vasoconstriction subside. Use is therefore restricted to periods of not more than 7 consecutive days. Oral use is not associated with such rebound congestion, but is more likely to be associated with systemic adverse effects and a higher risk of drug interactions. A systematic review found no difference in efficacy between oral and topical decongestants from the limited evidence available.[1]

The benefits of *antihistamines* in nasal congestion other than that associated with allergic rhinitis are doubtful, particularly by topical application.

Inhalations of warm moist air are also useful in the treatment of nasal congestion associated with the common cold. As in the case of cough (see above) the addition of substances such as menthol, benzoin, or volatile oils may encourage the use of such inhalations. Sodium chloride nasal drops may also be effective, particularly in infants and young children.

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Acetylcysteine *(BAN, USAN, rINN)*

5052; Acetilcisteína; Acetilcisteinas; Acetilcisztein; Acetylcystein; Acétylcystéine; Acetylcysteinum; Asetilsistein; Asetyylikysteiini; NSC-111180. *N*-Acetyl-L-cysteine.

Ацетилцистеин

$C_5H_9NO_3S$ = 163.2.

CAS — 616-91-1.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

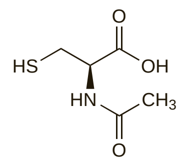

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Acetylcysteine). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 2.8. Protect from light.

USP 31 (Acetylcysteine). A white crystalline powder having a slight acetic odour. Soluble 1 in 5 of water and 1 in 4 of alcohol; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 2.8. Store in airtight containers.

Incompatibility. Acetylcysteine is incompatible with some metals, including iron and copper, with rubber, and with oxygen and oxidising substances. Some antimicrobials including amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with, acetylcysteine.

Stability. A change in colour of solutions of acetylcysteine to light purple does not indicate significant impairment of safety or efficacy.

Acetylcysteine Sodium *(BANM, rINNM)*

Acetilcisteína sódica; Acétylcystéine Sodique; Natrii Acetylcysteinum.

Натрий Ацетилцистеин

$C_5H_8NNaO_3S$ = 185.2.

CAS — 19542-74-6.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

Adverse Effects

Hypersensitivity reactions have been reported in patients receiving acetylcysteine, including bronchospasm, angioedema, rashes and pruritus; hypotension, or occasionally hypertension, may occur. Other adverse effects reported with acetylcysteine include flushing, nausea and vomiting, fever, syncope, sweating, arthralgia, blurred vision, disturbances of liver function, acidosis, convulsions, and cardiac or respiratory arrest. Haemoptysis, rhinorrhoea, and stomatitis have been associated with inhalation of acetylcysteine.

Hypersensitivity. The most common symptoms of patients experiencing **anaphylactoid** reactions after the intravenous use of acetylcysteine in the treatment of paracetamol poisoning are rash and pruritus; other features have included flushing, nausea or vomiting, angioedema, tachycardia, bronchospasm, hypotension, and hypertension;[1-3] ECG abnormalities associated with an anaphylactoid reaction have also been reported in a patient.[4] Anaphylactoid reactions to intravenous acetylcysteine appear to be dose-related.[5] One group estimated that when acetylcysteine was given correctly the **frequency** of the anaphylactoid response was between 0.3 and 3%, whereas 11 of 15 patients who had received an overdose had an anaphylactoid reaction.[6] Intradermal testing and study of plasma-acetylcysteine concentrations in patients who developed reactions to acetylcysteine suggests a 'pseudo-allergic' rather than an immunological reaction,[7,8] although symptoms consistent with a serum sickness-like illness developed after exposure to acetylcysteine in one patient.[9] It has been suggested that generalised reactions to acetylcysteine can be **treated** with intravenous injection of an antihistamine;[5,10] infusion of acetylcysteine should be temporarily stopped but can usually be restarted at a slower rate without further reaction.[3]

Symptoms after **overdosage** with acetylcysteine have been more severe. Hypotension appears to be especially prominent;[6] additional symptoms have included respiratory depression, haemolysis, disseminated intravascular coagulation, and renal failure, but some of these may have been due to paracetamol poisoning.[1] Death occurred in 3 patients who received an overdose of acetylcysteine while being treated for paracetamol poisoning,[1,11] but in 2 of them the role of acetylcysteine in this outcome was unclear.

1. Mant TGK, *et al.* Adverse reactions to acetylcysteine and effects of overdose. *BMJ* 1984; **289:** 217–19.
2. Dawson AH, *et al.* Adverse reactions to N-acetylcysteine during treatment for paracetamol poisoning. *Med J Aust* 1989; **150:** 329–31.
3. Pizon AF, LoVecchio F. Adverse reaction from use of intravenous N-acetylcysteine. *J Emerg Med* 2006; **31:** 434–5.
4. Bonfiglio MF, *et al.* Anaphylactoid reaction to intravenous acetylcysteine associated with electrocardiographic abnormalities. *Ann Pharmacother* 1992; **26:** 22–5.
5. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; **31:** 710–15.
6. Sunman W, *et al.* Anaphylactoid response to intravenous acetylcysteine. *Lancet* 1992; **339:** 1231–2.
7. Bateman DN, *et al.* Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; **3:** 393–8.
8. Donovan JW, *et al.* Adverse reactions of N-acetylcysteine and their relation to plasma levels. *Vet Hum Toxicol* 1987; **29:** 470.
9. Mohammed S, *et al.* Serum sickness-like illness associated with N-acetylcysteine therapy. *Ann Pharmacother* 1994; **28:** 285.
10. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; (Dec.): 496–9.
11. Anonymous. Death after N-acetylcysteine. *Lancet* 1984; **i:** 1421.

Precautions

Acetylcysteine should be used with caution in asthmatic patients. It should also be used with caution in patients with a history of peptic ulcer disease, both because drug-induced nausea and vomiting may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition, and because of a theoretical risk that mucolytics may disrupt the gastric mucosal barrier.

Asthma. Bronchospasm precipitated in 2 asthmatic patients[1] and severe asthma and respiratory arrest in another[2] have been reported after intravenous treatment with acetylcysteine. There is also a report of a patient with brittle asthma who had a similar reaction and subsequently died after receiving intravenous treatment with acetylcysteine.[3] The increased risk does not justify delaying or witholding acetylcysteine in asthmatic patients with paracetamol poisoning, but consideration might be given to initial intravenous infusion over 30 to 60 minutes rather than the conventional 15 minutes.[4] However, a large multicentre study found no benefit from the more prolonged infusion—see Paracetamol under Poisoning and Toxicity, below.

1. Ho SW-C, Beilin LJ. Asthma associated with N-acetylcysteine infusion and paracetamol poisoning: report of two cases. *BMJ* 1983; **287:** 876–7.
2. Reynard K, *et al.* Respiratory arrest after N-acetylcysteine for paracetamol overdose. *Lancet* 1992; **340:** 675.
3. Appelboam AV, *et al.* Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. *Emerg Med J* 2002; **19:** 594–5.
4. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2001; **51:** 87–91.

Hepatic impairment. The total clearance of acetylcysteine in patients with cirrhosis was found to be markedly impaired, and the elimination half-life almost twice that of healthy controls.[1] Since some of the more serious adverse effects of acetylcysteine occur when plasma concentrations are high, the authors considered that increased vigilance for untoward anaphylactoid reactions and other adverse effects was necessary in patients with cirrhosis receiving acetylcysteine, and further studies to determine the optimum dosage regimen in such patients were required.

1. Jones AL, *et al.* Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease. *Aliment Pharmacol Ther* 1997; **11:** 787–91.

Pharmacokinetics

◊ Acetylcysteine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5 to 1 hour after oral doses of 200 to 600 mg.[1] Some studies indicate dose-dependent pharmacokinetics with peak concentrations, the time taken to reach peak concentrations, and bioavailability increasing with increasing doses.[2] Acetylcysteine may be present in plasma as the parent compound or as various oxidised metabolites such as *N*-acetylcystine, *N*,*N*-diacetylcystine, and cysteine either free or bound to plasma proteins by labile disulfide bonds or as a fraction incorporated into protein peptide chains.[3] In a study about 50% was in a covalently protein-bound form 4 hours after a dose.[4] Oral bioavailability is low and mean values have ranged from 4 to 10% depending on whether total acetylcysteine or just the reduced forms are measured.[4,5] It has been suggested that acetylcysteine's low oral bioavailability may be due to metabolism in the gut wall and first-pass metabolism in the liver.[4,5] Renal clearance may account for about 30% of total body clearance.[5] On intravenous dosage mean terminal half-lives have been calculated to be 1.95 and 5.58 hours for reduced and total acetylcysteine, respectively; the terminal half-life of total acetylcysteine was 6.25 hours after oral doses.[4]

For reference to altered pharmacokinetics in patients with hepatic impairment, see above.

1. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. *Clin Pharmacokinet* 1991; **20:** 123–34.
2. Borgström L, Kågedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. *Biopharm Drug Dispos* 1990; **11:** 131–6.
3. De Caro L, *et al.* Pharmacokinetics and bioavailability of oral acetylcysteine in healthy volunteers. *Arzneimittelforschung* 1989; **39:** 383–6.
4. Olsson B, *et al.* Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. *Eur J Clin Pharmacol* 1988; **34:** 77–82.
5. Borgström L, *et al.* Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986; **31:** 217–22.

Uses and Administration

Acetylcysteine is a mucolytic that reduces the viscosity of secretions probably by the splitting of disulfide bonds in mucoproteins. This action is greatest at a pH of 7 to 9 and the pH may have been adjusted in commercial preparations with sodium hydroxide. It is sometimes stated that acetylcysteine sodium is used, although the dose is expressed in terms of acetylcysteine.

Acetylcysteine is also able to promote the detoxification of an intermediate paracetamol metabolite, and has a key role in the management of paracetamol overdosage.

Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. It can be given by nebulisation of 3 to 5 mL of a 20% solution or 6 to 10 mL of a 10% solution through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution or 2 to 20 mL of a 10% solution may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour. Mechanical suction of the liquefied secretions may be necessary, and nebulisers containing iron, copper, or rubber components should not be used.

Acetylcysteine as a mucolytic is also given orally, as lozenges, or as granules or effervescent tablets dissolved in water, in a usual dose of 600 mg daily as a single dose or in 3 divided doses.

In the treatment of **dry eye** (p.2140) associated with abnormal mucus production, acetylcysteine, usually as a 5% solution with hypromellose, is given topically 3 or 4 times daily. Higher concentrations have been used in some centres.

Acetylcysteine is given by intravenous infusion or by mouth in the treatment of **paracetamol poisoning**.

- If given intravenously: 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given initially over 15 minutes, followed by infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre of glucose 5% over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable.
- If given orally: an initial dose of 140 mg/kg as a 5% solution is followed by 70 mg/kg every 4 hours for an additional 17 doses.

Acetylcysteine is reported to be most effective when given within 8 hours of paracetamol overdosage, with the protective effect diminishing after this time. However, starting treatment with acetylcysteine later (up to and beyond 24 hours) may still be of benefit (see also below).

Acetylcysteine is under investigation for the treatment of idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, below).

For administration in children, see below.

◊ Reviews.

1. Atkinson MC. The use of N-acetylcysteine in intensive care. *Crit Care Resusc* 2002; **4:** 21–7.
2. Dekhuijzen PNR. Antioxidant properties of *N*-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease. *Eur Respir J* 2004; **23:** 629–36.
3. Guerin J-C, *et al.* Le stress oxydatif en pathologie broncho-pulmonaire : apport de la N-acétyl-cystéine (NAC). *Rev Pneumol Clin* 2005; **61:** 16–21.
4. Aitio M-L. N-acetylcysteine—passe-partout or much ado about nothing? *Br J Clin Pharmacol* 2006; **61:** 5–15.
5. Dekhuijzen PN. Acetylcysteine in de behandeling van ernstige COPD. *Ned Tijdschr Geneeskd* 2006; **150:** 1222–6.

Administration in children. Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. Doses in children are similar to adults; 3 to 5 mL of a 20% solution, or 6 to 10 mL of a 10% solution, may be nebulised through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution, or 2 to 20 mL of a 10% solution, may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour.

Acetylcysteine has also been given orally in a variety of dosage forms. Licensed doses and age ranges vary somewhat from country to country and even from preparation to preparation. For example, in France, children may be given the following doses:

- 1 month to 2 years: 100 mg twice daily
- 2 to 7 years: 200 mg twice daily
- 7 years and over: 200 mg 3 times daily (adult dose)

In Germany and Switzerland, however, a more typical dose for children under 2 years of age is 50 mg two or three times daily.

Acetylcysteine has been used to treat meconium ileus in neonates and distal obstruction syndrome in children with **cystic fibrosis**, although the *BNFC* states that evidence of its efficacy is lacking. Such use is not licensed in the UK, but if it is to be used the *BNFC* suggests an oral dose of acetylcysteine 200 to 400 mg up to 3 times daily for meconium ileus in neonates. For the *treatment* of distal intestinal obstruction syndrome in children with cystic fibrosis, a single oral dose is recommended as follows:

- 1 month to 2 years: 400 mg to 3 g
- 2 to 7 years: 2 to 3 g
- 7 to 18 years: 4 to 6 g

For the *prevention* of distal intestinal obstruction syndrome, it is recommended to be given orally as follows:

- 1 month to 2 years: 100 to 200 mg 3 times daily
- 2 to 12 years: 200 mg 3 times daily
- 12 to 18 years: 200 to 400 mg 3 times daily

The injection may be used orally, diluted to a concentration of 50 mg/mL; orange or black currant juice or cola may be used as diluents to mask the bitter taste.

In the treatment of **dry eye** associated with impaired or abnormal mucus production, acetylcysteine 5% eye drops with hypromellose may be applied, as in adults, 3 or 4 times daily.

Acetylcysteine is given by intravenous infusion or by mouth in the treatment of **paracetamol poisoning**. Doses for children are similar to adults (see also above and on p.108), although the volume of intravenous fluid is modified. The *BNFC* suggests the following *intravenous* doses:

- neonates to 5 years (or body-weight under 20 kg): initially 150 mg/kg in 3 mL/kg glucose 5% given over 15 minutes, followed by 50 mg/kg in 7 mL/kg glucose 5% given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% given over 16 hours
- 5 to 12 years (or body-weight over 20 kg): initially 150 mg/kg in 100 mL glucose 5% given over 15 minutes, followed by 50 mg/kg in 250 mL glucose 5% given over 4 hours, then 100 mg/kg in 500 mL glucose 5% given over 16 hours
- 12 to 18 years: adult dose

In the USA, the following *oral* dose has also been suggested for children: 140 mg/kg initially, followed by 70 mg/kg every 4 hours for an additional 17 doses.

Aspergillosis. Although it is not one of the standard therapies discussed on p.517, local instillation of acetylcysteine into the cavity containing the fungus ball has been used to treat aspergilloma.[1] There is some evidence *in vitro* that acetylcysteine has inhibitory properties against *Aspergillus* and *Fusarium* spp.[2]

1. Kauffman CA. Quandary about treatment of aspergillomas persists. *Lancet* 1996; **347:** 1640.
2. De Lucca AJ, *et al.* N-Acetylcysteine inhibits germination of conidia and growth of Aspergillus spp. and Fusarium spp. *Antimicrob Agents Chemother* 1996; **40:** 1274–6.

Burns. Children with inhalation injury (see Burns, p.1578) who were treated with aerosolised heparin 5000 units alternating with 3 mL of 20% acetylcysteine solution, inhaled every 2 hours for the first 7 days after injury, appeared to have significantly reduced mortality and reintubation rates compared with historical controls.[1]

1. Desai MH, *et al.* Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [sic] therapy. *J Burn Care Rehabil* 1998; **19:** 210–12. Correction. *ibid.* 1999; **20:** 49.

Cystic fibrosis. Mucolytics such as acetylcysteine are generally not considered[1] to be effective in treating the pulmonary manifestations of cystic fibrosis (p.166).

Meconium ileus equivalent (bowel obstruction due to abnormally viscid contents of the terminal ileum and right colon[2]) in patients with cystic fibrosis has largely disappeared with the use of pancreatic enzymes but may occur when insufficient doses are given;[3] mild cases may be treated with acetylcysteine.[3] Doses of 10 mL of a 20% solution of acetylcysteine have been given orally 4 times daily with 100 mL of a 10% solution of acetylcysteine given as an enema up to 4 times daily depending on the degree of the obstruction.[2]

For suggested children's doses in meconium ileus and distal obstruction syndrome, see Administration in Children, above.

1. Duijvestijn YC, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999; **88:** 38–41.
2. Hanly JG, Fitzgerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *BMJ* 1983; **286:** 1411–13.
3. David TJ. Cystic fibrosis. *Arch Dis Child* 1990; **65:** 152–7.

Diffuse parenchymal lung disease. Acetylcysteine is under investigation for the treatment of idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, p.1502). In a randomised controlled study, adjunctive treatment with acetylcysteine 600 mg three times daily by mouth slowed the loss of vital lung capacity compared with standard therapy with azathioprine and prednisone.[1]

1. Demedts M, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; **353:** 2229–42.

HIV infection and AIDS. The cysteine-containing peptide glutathione is involved in intracellular defence mechanisms, and it has been shown that low glutathione concentrations are associated with poorer survival in HIV-infected patients.[1] Since acetylcysteine can replenish glutathione, it has been suggested[2,3] that it may have a role in the treatment of AIDS (p.856). *In-vitro* studies indicate that acetylcysteine can suppress HIV expression,[4,5] and there has been a suggestion from observational data that acetylcysteine supplements can improve survival in HIV-infected individuals.[1] However, an attempt to use acetylcysteine supplementation to reduce the frequency of adverse reactions to co-trimoxazole in HIV-infected patients was not successful.[6] Nonetheless, reviews of preliminary studies[7,8] have concluded that acetylcysteine may be a beneficial supplementary therapy in HIV-infected patients.

1. Herzenberg LA, *et al.* Glutathione deficiency is associated with impaired survival in HIV disease. *Proc Natl Acad Sci U S A* 1997; **94:** 1967–72.
2. Staal FJT, *et al.* Glutathione deficiency and human immunodeficiency virus infection. *Lancet* 1992; **339:** 909–12.
3. Roederer M, *et al.* N-acetylcysteine: potential for AIDS therapy. *Pharmacology* 1993; **46:** 121–9.
4. Roederer M, *et al.* Cytokine-stimulated human immunodeficiency virus replication is inhibited by N-acetyl-L-cysteine. *Proc Natl Acad Sci U S A* 1990; **87:** 4884–8.
5. Kalebic T, *et al.* Suppression of human immunodeficiency virus expression in chronically infected monocytic cells by glutathione, glutathione ester, and N-acetylcysteine. *Proc Natl Acad Sci U S A* 1991; **88:** 986–90.
6. Åkerlund B, *et al.* N-acetylcysteine treatment and the risk of toxic reactions to trimethoprim-sulphamethoxazole in primary Pneumocystis carinii prophylaxis in HIV-infected patients. *J Infect* 1997; **35:** 143–7.
7. Dröge W, Breitkreutz R. N-acetyl-cysteine in the therapy of HIV-positive patients. *Curr Opin Clin Nutr Metab Care* 1999; **2:** 493–8.
8. Patrick L. Nutrients and HIV: Part Three—N-acetylcysteine, alpha-lipoic acid, L-glutamine, and L-carnitine. *Altern Med Rev* 2000; **5:** 290–305.

Kidney disorders. Acetylcysteine has been reported to improve kidney function in patients with the hepatorenal syndrome and may offer a potential bridging therapy in such patients awaiting liver transplantation.[1] It has also been used in the prevention of contrast media-induced nephrotoxicity in patients with chronic renal impairment, but evidence of benefit is conflicting and its role remains to be established; see Effects on the Kidney under Adverse Effects of Amidotrizoic Acid (p.1476) for further details.

1. Holt S, *et al.* Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999; **353:** 294–5.

Liver disorders. Although benefit has been reported from studies of acetylcysteine in acute liver failure,[1] and some have suggested that it may be useful in preventing tissue hypoxia in patients with acute liver failure receiving vasopressors,[2] studies have mainly been small and clinical outcomes are not well studied.[1] It does not appear to be of benefit in patients undergoing orthotopic liver transplantation.[3,4]

For reference to use in the hepatorenal syndrome, see Kidney Disorders, above. For use in paracetamol-induced liver damage see Overdosage, under Paracetamol, p.108.

1. Sklar GE, Subramaniam M. Acetylcysteine treatment for non-acetaminophen-induced acute liver failure. *Ann Pharmacother* 2004; **38:** 498–501.
2. Caraceni P, Van Thiel DH. Acute liver failure. *Lancet* 1995; **345:** 163–9.
3. Bromley PN, *et al.* Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation. *Br J Anaesth* 1995; **75:** 352–4.
4. Steib A, *et al.* Does N-acetylcysteine improve hemodynamics and graft function in liver transplantation? *Liver Transpl Surg* 1998; **4:** 152–7.

Meconium ileus. For the use of acetylcysteine in infants with meconium ileus see Cystic Fibrosis, above.

Myocardial infarction. Some studies suggest that addition of intravenous acetylcysteine to thrombolytic therapy in patients with acute myocardial infarction (p.1175) may be of benefit.[1,2] The value of acetylcysteine as an adjunct in patients with or at risk of myocardial infarction has been reviewed.[3,4]

1. Arstall MA, *et al.* N-Acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction: safety and biochemical effects. *Circulation* 1995; **92:** 2855–62.
2. Šochman J, *et al.* Infarct size limitation: acute N-acetylcysteine defense (ISLAND trial): preliminary analysis and report after the first 30 patients. *Clin Cardiol* 1996; **19:** 94–100.

3. Marchetti G, *et al.* Use of N-acetylcysteine in the management of coronary artery diseases. *Cardiologia* 1999; **44:** 633–7.
4. Sochman J. N-acetylcysteine in acute cardiology: 10 years later: what do we know and what would we like to know?! *J Am Coll Cardiol* 2002; **39:** 1422–8.

Nitrate tolerance. Acetylcysteine appears to be able to potentiate the peripheral and coronary effects of glyceryl trinitrate.[1] While some studies[2-5] have suggested that acetylcysteine can reverse tolerance to nitrates in patients with coronary heart disease or heart failure, others have failed to find any benefit,[6] although there may be a specific subgroup of responders.[5] The various attempts at overcoming nitrate tolerance are discussed on p.1297.

1. Horowitz JD, *et al.* Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris. *Circulation* 1988; **77:** 787–94.
2. Packer M, *et al.* Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med* 1987; **317:** 799–804.
3. May DC, *et al.* In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. *N Engl J Med* 1987; **317:** 805–9.
4. Boesgaard S, *et al.* Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992; **85:** 143–9.
5. Pizzulli L, *et al.* N-acetylcysteine attenuates nitroglycerin tolerance in patients with angina pectoris and normal left ventricular function. *Am J Cardiol* 1997; **79:** 28–33.
6. Hogan JC, *et al.* Chronic administration of N-acetylcysteine fails to prevent nitrate tolerance in patients with stable angina pectoris. *Br J Clin Pharmacol* 1990; **30:** 573–7.

Poisoning and toxicity. Acetylcysteine has been studied for the potential treatment of many forms of toxicity,[1] but only treatment of acute paracetamol poisoning is widely accepted.

1. Chyka PA, *et al.* Utility of acetylcysteine in treating poisonings and adverse drug reactions. *Drug Safety* 2000; **22:** 123–48.

CARBON TETRACHLORIDE. The treatment of carbon tetrachloride poisoning is discussed on p.2021. Reports suggest that prompt intravenous therapy with acetylcysteine may help to minimise hepatorenal damage in acute poisoning with carbon tetrachloride.[1,2] When added to supportive therapy the initial dosage regimen should be the same as that used for paracetamol poisoning but as carbon tetrachloride has a much longer half-life than paracetamol, the duration of treatment may need to be increased.[3]

1. Ruprah M, *et al.* Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. *Lancet* 1985; **i:** 1027–9.
2. Mathieson PW, *et al.* Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. *Hum Toxicol* 1985; **4:** 627–31.
3. Meredith TJ, *et al.* Diagnosis and treatment of acute poisoning with volatile substances. *Hum Toxicol* 1989; **8:** 277–86.

PARACETAMOL. Acetylcysteine is usually the antidote of choice for paracetamol overdose (see p.108). The intravenous route is favoured in the UK, despite possible anaphylactic reaction, mainly because of concerns over the effects of vomiting and activated charcoal on oral absorption.[1] In the USA the oral route has conventionally been used, despite the unpleasant odour and taste of acetylcysteine solutions, with no evident reduction in effect by charcoal.[2] The intravenous route is now also licensed in the USA. Oral and intravenous formulations appear to be equally effective.[3] A disadvantage of the oral route is therapeutic failure in those patients who develop nausea and vomiting, which occurs in most patients with severe poisoning; delays in absorption may also be of concern especially when the end of the critical 8-hour interval is approaching. However, with oral doses, the whole absorbed dose passes through the liver, producing high local concentrations at the site of toxicity.[4] Some consider the intravenous route to be more reliable, and to require fewer doses and a shorter duration of treatment.[5] The major disadvantage of intravenous use is possible anaphylactic reaction. Although these reactions are considered uncommon in patients with paracetamol poisoning, rare fatalities have been reported, and patients with asthma appear to be at particular risk (see also above).[4] Some infuse the first dose of acetylcysteine over 60 minutes instead of the recommended 15 minutes[5] in order to reduce the incidence and severity of reactions. However, a multicentre, randomised study found no reduction in adverse outcomes with a 60-minute infusion compared to the standard infusion period of 15 minutes.[6] It has been suggested that intravenous acetylcysteine may be preferred in those patients with severe poisoning, who present late, who have nausea and vomiting, or who have problems with absorption. Oral use might be preferred in those who present early with uncomplicated mild to moderate poisoning, or who have asthma.[4,7] Whichever route is given, the interval is considered the single most important factor for the prevention of severe hepatic damage.[3,4]

1. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; **346:** 547–52.
2. Bowden CA, Krenzelok EP. Clinical applications of commonly used contemporary antidotes: a US perspective. *Drug Safety* 1997; **16:** 9–47.
3. Brok J, *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/10/06).
4. Prescott L. Oral or intravenous *N*-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005; **45:** 409–13.
5. Anonymous. Acetylcysteine (Acetadote) for acetaminophen overdosage. *Med Lett Drugs Ther* 2005; **47:** 70–1.
6. Kerr F, *et al.* The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005; **45:** 402–8.
7. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; **63:** 1821–7.

Respiratory disorders. Acetylcysteine has been used as a mucolytic in a variety of respiratory disorders associated with productive cough (p.1547). Although there is controversy over the benefits of mucolytics in treating chronic bronchitis or chronic obstructive pulmonary disease (COPD), there is some evidence that they may reduce exacerbations (see p.1112). However, a double-blind multicentre study in patients with COPD failed to find evidence that acetylcysteine 600 mg daily by mouth reduced exacerbations;[1] like most other interventions in this condition, it could also not be shown to reduce the rate of decline in lung function.

For the use of aerosolised heparin and acetylcysteine to treat inhalation injury see Burns, above. It has been suggested that intravenous acetylcysteine might also be of use in acute respiratory distress syndrome (ARDS—p.1498),[2] possibly due to its action as a free radical scavenger,[2,3] but controlled studies in established ARDS failed to show benefit.[4,5]

Acetylcysteine has been investigated in idiopathic pulmonary fibrosis (see Diffuse Parenchymal Lung Disease, above). See also above for the use of acetylcysteine in the management of cystic fibrosis.

1. Decramer M, *et al.* Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; **365:** 1552–60.
2. Bernard GR. Potential of N-acetylcysteine as treatment for the adult respiratory distress syndrome. *Eur Respir J* 1990; **3** (suppl 11): 496S–498S.
3. Skolnick A. Inflammation-mediator blockers may be weapons against sepsis syndrome. *JAMA* 1990; **263:** 930–1.
4. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; **20:** 918–23.
5. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; **12:** 177–82.

Scleroderma. Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome resulting from scleroderma (see p.1817).

Preparations

BP 2008: Acetylcysteine Injection;
USP 31: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Acetylcysteine Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: AC Lan; ACC†; Acemuk; Fluimucil†; Lubrisec†; ***Austral.:*** Mucomyst; Parvolex; ***Austria:*** ACC; Aeromuc; Aerosolv; Bronchohexal; Bronchoplus; Cimelin; Cimexyl; Fluimucil; Husten ACC; Hustenloser; Mucobene; Mucomyst; NAC; Pulmovent†; Siccoral; ***Belg.:*** Docacetyl; Lysodrop†; Lysomucil; Lysox; Mucomyst; Pectomucil; ***Braz.:*** Bromuc; Flucistein; Fluimucil; Fluimucil Solucao Nasal; NAC; ***Canad.:*** Mucomyst; Parvolex; ***Chile:*** Mucolitico; ***Cz.:*** ACC; Broncholysin†; Fluimucil; L-Cimexyl†; Mucobene; NAC; Solmucol; ***Denm.:*** Alcur†; Granon; Mucolysin; Mucomyst; ***Fin.:*** Mucomyst; Mucoporetta; ***Fr.:*** Broncoclar; Codotussyl Expectorant; Exomuc; Fluimucil; Genac; Humex Expectorant; Mucolator; Mucomyst; Mucomystendo; Mucospire; Solmucol; Tixair; ***Ger.:*** ACC; Acemuc; Acetabs; Acetyst; Atse†; Azubronchin†; Bromuc†; Durabronchal†; Fluimucil; Muciteran†; Muco Sanigen†; Mucocedyl†; Mucret; Myxofat; NAC; Phamuc†; Pulmicret†; Siran†; ***Gr.:*** Chricetyl; Elicor†; Flumil Antidoto; Flustaren†; Kantrenol; Mucomyst; Neocof; Ovoctil†; Parvolex; Saloril†; Spacyl†; Trebon; Vaden†; Vlenolys; ***Hong Kong:*** Exomuc; Fluimucil; Hidonac; Mucolator†; Mutamso; Parvolex; Solmucol; ***Hung.:*** Ac-Pulmin†; ACC; Fluimucil; NAC; Solmucol; Solv-Ac T†; Sputopur; ***India:*** Mucomix; ***Indon.:*** Hidonac; ***Irl.:*** Parvolex; ***Israel:*** Mucomyst†; Reolin; Siran; ***Ital.:*** Altersol; Brunac; Fluimucil; Hidonac; Mucisol; Mucofial; Mucofrin; Mucoxan; Solmucol; Tirocular; Ultraflu; ***Malaysia:*** Acypront†; Fluimucil; Hidonac; Mucolator; Parvolex; ***Mex.:*** ACC; ***Neth.:*** Bisolbruis; Fluimucil; Mucomyst; Solmucol; ***Norw.:*** Bronkyl; Mucomyst; ***NZ:*** Parvolex; ***Philipp.:*** Fluimucil; Hidonac; Solmucol; ***Pol.:*** ACC; Fluimucil; Syntemucol; Tussicom; ***Port.:*** Fluimucil; Flumil; Mucolator; Pulmosal; Tirocular; ***Rus.:*** ACC (АЦЦ); Exomuc (Экзомюк); Fluimucil (Флуимуцил); Muconex (Муконекс); ***S.Afr.:*** ACC; Parvolex; Solmucol; ***Singapore:*** Fluimucil†; Mucoza†; Solmucol†; Spatam; ***Spain:*** Fluimucil; Flumil; Flumil Antidoto; Flumonac; Frenacil; Locomucil†; Mucoaliv; Mucolibex; Solmucol†; ***Swed.:*** Mucomyst; Viskoferm; ***Switz.:*** ACC; Acemucol; Bisolapid†; Demolibral; Dynamucil; Ecomucyl; Fluimucil; L-Cimexyl; Muco-Mepha; Mucofluid; Mucostop; NeoCitran Expectorant; Robitussin Expectorant; Secresol; Solmucol; ***Thai.:*** Acetin; Flemex-AC; Flucil; Fluimucil; Hidonac; Mucil; Mucocil; Mucotic; Mucoza; Mysoven; NAC; Simucin; ***Turk.:*** Asist; Brunac; Mentopin; Muconex; NAC; Oxxa; ***UK:*** Parvolex; ***USA:*** Acetadote; Mucomyst; Mucosil†.

Multi-ingredient: ***Arg.:*** Acemuk Biotic; Fluimucil Biotic†; ***Braz.:*** Rinofluimucil; ***Fr.:*** Rhinofluimucil; ***Ger.:*** Rinofluimucil-S†; ***Hong Kong:*** Rinofluimucil; ***Hung.:*** Rinofluimucil; ***Indon.:*** Dorbigot; Fluimucil; Sistenol; ***Irl.:*** Ilube; ***Ital.:*** Migel; Rinofluimucil; ***Port.:*** Rinofluimucil; ***Rus.:*** Rinofluimucil (Ринофлуимуцил); ***Spain:*** Flumil Antibiotico; Rinoflumil; ***Switz.:*** Rinofluimucil; Solmucaine; Solmucalm; ***Thai.:*** Fluimucil Antibiotic; Rinofluimucil; ***UK:*** Ilube.

Acetyldihydrocodeine Hydrochloride

Acetildihidrocodeína, hidrocloruro de. 4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-yl acetate hydrochloride.

Ацетилдигидрокодеина Гидрохлорид

$C_{20}H_{25}NO_4$,HCl = 379.9.
CAS — 3861-72-1 (acetyldihydrocodeine).
ATC — R05DA12.
ATC Vet — QR05DA12.

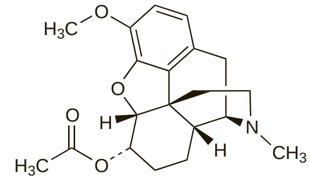

(acetyldihydrocodeine)

Profile

Acetyldihydrocodeine hydrochloride is an opioid derivative related to dihydrocodeine (p.48). It is used as a centrally acting cough suppressant for non-productive cough (p.1547) and has been given in a usual oral daily dose of 20 to 50 mg; no more than 20 mg should be taken as a single dose.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Acetylcodone.

Alloclamide Hydrochloride *(rINNM)*

Alloclamide, Chlorhydrate d'; Alloclamidi Hydrochloridum; CE-264; Hidrocloruro de aloclamida. 2-Allyloxy-4-chloro-*N*-(2-diethylaminoethyl)benzamide hydrochloride.

Аллокламида Гидрохлорид

$C_{16}H_{23}ClN_2O_2$,HCl = 347.3.
CAS — 5486-77-1 (alloclamide); 5107-01-7 (alloclamide hydrochloride).

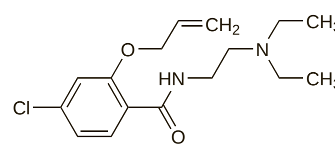

(alloclamide)

Profile

Alloclamide hydrochloride is a cough suppressant.

Ambroxol Hydrochloride *(BANM, rINNM)*

Ambroksolihydrokloridi; Ambroksolio hidrochloridas; Ambroxol, chlorhydrate d'; Ambroxol hydrochlorid; Ambroxol-hidroklorid; Ambroxolhydroklorid; Ambroxoli hydrochloridum; Hidrocloruro de ambroxol; NA-872 (ambroxol). *trans*-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol hydrochloride.

Амброксола Гидрохлорид

$C_{13}H_{18}Br_2N_2O$,HCl = 414.6.
CAS — 18683-91-5 (ambroxol); 15942-05-9 (ambroxol hydrochloride); 23828-92-4 (ambroxol hydrochloride).
ATC — R05CB06.
ATC Vet — QR05CB06.

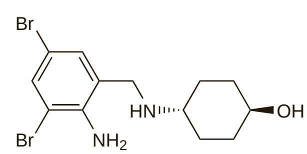

(ambroxol)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ambroxol Hydrochloride). A white or yellowish crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Ambroxol is a metabolite of bromhexine (p.1552) and is used similarly as a mucolytic. It is given in a usual oral daily dose of

60 to 120 mg of the hydrochloride in 2 divided doses. Ambroxol has also been given by inhalation, injection, or rectally.

Adverse effects. HYPERSENSITIVITY. A report[1] of contact allergy to ambroxol, but not bromhexine.

1. Mancuso G, Berdondini RM. Contact allergy to ambroxol. *Contact Dermatitis* 1989; **20:** 154.

Pharmacokinetics. References to pharmacokinetic studies of ambroxol.

1. Hammer R, *et al.* Speziesvergleich in Pharmakokinetik und Metabolismus von NA 872 Cl Ambroxol bei Ratte, Kaninchen, Hund und Mensch. *Arzneimittelforschung* 1978; **28:** 899–903.
2. Jauch R, *et al.* Ambroxol, Untersuchungen zum Stoffwechsel beim Menschen und zum quantitativen Nachweis in biologischen Proben. *Arzneimittelforschung* 1978; **28:** 904–11.
3. Vergin H, *et al.* Untersuchungen zur Pharmakokinetik und Bioäquivalenz unterscheidlicher Darreichungsformen von Ambroxol. *Arzneimittelforschung* 1985; **35:** 1591–5.

Respiratory disorders. Mixed results[1-3] were obtained when ambroxol was used in chronic bronchitis or chronic obstructive pulmonary disease (COPD—p.1112); in a randomised study, it was no better than placebo in preventing acute exacerbations of COPD; however, in a subset of patients with more severe disease, ambroxol therapy reduced the number of exacerbations.[4] It was ineffective[5] when given to mothers for the prophylaxis of neonatal respiratory distress syndrome (p.1508), although it may be of modest benefit in the early treatment of established disease in infants.[6,7]

Inhalation of ambroxol aerosol has also produced beneficial effects in a patient with alveolar proteinosis who refused alveolar lavage.[8]

For the use of mucolytics in productive cough see p.1547.

1. Olivieri D, *et al.* Ambroxol for the prevention of chronic exacerbations: long-term multicenter trial: protective effect of ambroxol against winter semester exacerbations: a double-blind study versus placebo. *Respiration* 1987; **51** (suppl 1): 42–51.
2. Guyatt GH, *et al.* A controlled trial of ambroxol in chronic bronchitis. *Chest* 1987; **92:** 618–20.
3. Alcozer G, *et al.* Prevention of chronic bronchitis exacerbations with ambroxol (Mucosolvan Retard): an open, long-term, multicenter study in 5,635 patients. *Respiration* 1989; **55** (suppl 1): 84–96.
4. Malerba M, *et al.* Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD: double-blind, randomized, multicenter, placebo-controlled study (the AMETHIST Trial). *Pulm Pharmacol Ther* 2004; **17:** 27–34.
5. Dani C, *et al.* Antenatal ambroxol treatment does not prevent the respiratory distress syndrome in premature infants. *Eur J Pediatr* 1997; **156:** 392–3.
6. Wauer RR, *et al.* Randomized double blind trial of Ambroxol for the treatment of respiratory distress syndrome. *Eur J Pediatr* 1992; **151:** 357–63.
7. Schmalisch G, *et al.* Changes in pulmonary function in preterm infants recovering from RDS following early treatment with ambroxol: results of a randomized trial. *Pediatr Pulmonol* 1999; **27:** 104–12.
8. Diaz JP, *et al.* Response to surfactant activator (ambroxol) in alveolar proteinosis. *Lancet* 1984; **i:** 1023.

Uricosuric action. A study[1] was carried out in 48 young male healthy subjects to examine the uricosuric effect of ambroxol. The minimum effective dose for lowering plasma-uric acid concentrations was found to be between 250 and 500 mg daily given in 2 divided doses. Although these doses are much higher than those used to treat bronchopulmonary disease, doses as high as 1 g daily were well tolerated.

1. Oosterhuis B, *et al.* Dose-dependent uricosuric effect of ambroxol. *Eur J Clin Pharmacol* 1993; **44:** 237–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Ambril; Apracur Expectorante; Cortos; Graneodin Expectorante†; Mucosolvon; Tabcin Expectorante†; Tavinex Expectorante; Tavinex Expectotabs; Tosambrex; ***Austria:*** Ambrobene; Ambrohexal; Ambrolan; Ambrolos†; Ambronorm; Bisolangin†; Bisolaryn; Broxol; Mucoangin; Mucosolvan; Sekretovit; ***Belg.:*** Mucoangin; Surbronc; ***Braz.:*** Ambrizol†; Ambrol†; Ambroten; Ambrox†; Anabron; Broncoflux; Bronxol; Expectuss; Fluibron; Fluidin; Fluxol†; Mucibron; Mucoclean†; Mucolin; Mucosolvan; Mucoxolan; Neossolvan; Probec†; Pulmosolvan†; Surfactil†; ***Chile:*** Bronchopront†; Broncot; Fluibron; Fluomit; Milbron†; Mintamox; Mucosolvan; Muxol; Tocalm; ***Cz.:*** Ambex; Ambrobene; Ambrosan; Ambrospray; Bronchopront†; Dignobroxol†; Dr Rentschler Hustenloser; Fervex†; Flavamed; Halixol; Mucosin; Mucosolvan; Neo-Bronchol; Solvolan; ***Denm.:*** Mucoangin; ***Fr.:*** Lysopadol; Muxol; Surbronc; ***Ger.:*** Ambril; Ambro; Ambro-Puren†; Ambrobeta; Ambrodoc; Ambrohexal; Ambroinfant†; Ambrolos†; Ambropp†; Bronchopront; Bronchowern; duramucal†; Expit; frenopect; Frubizin akut; Larylin Husten-Loser Pastillen; Larylin Husten-Loser Saft†; Lindoxyl; Muco-Aspecton†; Mucoangin; Mucobroxol†; Mucophlogat†; Mucosolvan; Neo-Bronchol†; Padiamuc; Pulmotin Hustenloser; Sigabroxol†; stas-Hustenloser†; tuss†; ***Gr.:*** Abrobion; Abrolen; Afrodor; Amboral; Ambrobion†; Ambromyc; Anavix; Aprinol; Auroxidol; Bunafon; Celibron; Dolcevin; Ebertuss; Effercet; Erosil; Fluibrox; Grenovix; Hivotex; Kriolen; Lextarol; Mavixan; Mucolin; Mucosolvan; Mucovix; Nibren; Olbenorm; Provixen-N; Puntol; Respirol; Saribal; Stefolant; Strubelin; Tevoril; Tosse; Tussefar; Zyrantol; ***Hong Kong:*** Amxol; Bronchopront; Marbroxol; Max; Medovent†; Mucosolvan; Qualisolvon; ***Hung.:*** Ambrobene; Ambrohexal; Bronchopront†; Halixol; Mucoangin; Solvolan; ***India:*** Acocontin; Acolyt; Ambrodil; Inhalex; ***Indon.:*** Ambril; Brommer; Bronchopront; Broncozol; Broxal; Epexol; Extropect; Gunapect; Interpec; Lapimuc; Molapect; Mucera; Mucolica; Mucopect; Mucos; Mucoxol; Nufanibrox; Silopect; Sohopect; Transbroncho; Transmuco; ***Ital.:*** Ambrotus; Amobronc; Atus; Broxol; Fluibron; Fluixol; Lintos; Lisopulm†; Muciclar; Mucoaricodil; Mucobron; Mucosolvan; Secretil; Surfactal; Tauxolo; Viscomucil; ***Jpn:*** Mucosal; Mucosolvan; ***Malaysia:*** Amxol; Axol; Mucosolvan; Shinoxol; Strepsils Chesty Cough; ***Mex.:*** Ambrofur; Amocrol; Axol; Balsibron; Bionoxol; Boxolam; Brogal; Bronolban; Brosolan; Broxaquim; Broxofar; Broxoffler; Broxol; Broxolim; Cloxan; Ebromin; Euroxol; Exabrol†; Expeflen; Fantrodol†; Ital-Ultra; Loexom; Loxibrin; Mucibron; Mucoangin; Mucosolvan; Mucovibrol; Mucovibrol T†; Mucoxol; Musalten; Musvan; Muxol†; Oxolvan; Prospec; Protitus; Randex; Rimoxol†; Sekretovit; Septacin; Seraxol-S; Softixol†; Solpat; Tobrin; Tradexol†; Trimexine; Tunitol-BX; Tusibron; Ulax-F; Viaxol; Weiscal; ***Neth.:*** Mucoangin; ***Philipp.:*** Ambrolex; Atrivex; Brocof; Bromace; Bromacef; Broxan; Broxifil; Broxil-M; Broxitrol; Broxolvan; Exolpen; Expel; Medibron; Mepebrox; Mucosolin; Mucosolvan; Mucovis; Phlemasol; Pontef; Pulmobrol; Venteze; Voxoll; Zobrixol; ***Pol.:*** Aflegan; Ambro; Ambrohexal; Ambroksol; Ambrosan; Ambrosol; Deflegmin; Flavamed; Mucoangin; Mucosolvan; Mukobron; Tussal Expectorans; ***Port.:*** Benflux; Bromax; Bronchopront†; Broncoliber; Bronxol; Drenoxol; Fluidox; Fluidrenol; Hipotosse; Mucodrenol; Mucosolvan; Mucotosse; ***Rus.:*** Ambrobene (Амбробене); Ambrohexal (Амброгексал); Ambrosan (Амбросан); Ambrosol (Амбросол); Bronchowern (Бронховерн); Halixol (Халиксол); Lasolvan (Лазолван); Medovent (Медовент); Suprima-Kof (Суприма-Коф); ***Singapore:*** Amxol; Axol; Bronchopront†; Max; Mucosolvan; Shinoxol; ***Spain:*** Ambrolitic; Dinobroxol; Motosol; Mucibron; Mucosan; Naxpa; ***Swed.:*** Mucoangin; ***Switz.:*** Fluibron†; Mucabrox; Mucoangin; Mucosolvon; ***Thai.:*** Ambrol†; Ambrolytic†; Ambrox†; Ambroxan; Ampromed; Amtuss; Amxol; Bronchopront†; Broncol; Broxol; Broxsa†; Max; Medovent; Misovan; Movent†; Mucodic; Mucolan; Mucolid; Mucomed; Mucopec; Mucosolvan; Mucoxine-F; Mucozan; Musocan; Nucobrox; Polibroxol; Simusol; Strepsils Chesty Cough; Streptuss-AX; ***Turk.:*** Ambreks; Fluibron; Mukoral; Pulmor; Sekrol; Tusilin; ***UAE:*** Mucum; ***Venez.:*** Ambril; Ambromuco; Ambrox; Benflux; Brocantol; Bronchopront; Litusix; Misulvan; Mucoangin; Mucorama; Mucosolvan; Muxen; Xolvax.

Multi-ingredient: ***Arg.:*** Amoxi Respiratorio†; Amoxidal Respiratorio; Amoxidal Respiratorio Duo; Amoxigrand Bronquial; Amoxipenil Bronquial; Amoxitenk Respiratorio†; Aseptobron Respiratorio; Bronco Biotaer†; Bronquisedan; Bronquisedan Mucolitico; Cefacar Mucolitico†; Cefacilina Bronquial; Gentiabron†; Letondal; Muco Cortos†; Muco Dosodos; Muco Dosodos Biotic; Mucoprednibron; Mucosolvon Compositum; No-Tos Biotic; Nobactam Bronquial; Oxibron NF; Oximar Respiratorio; Pulmonix Plus; Toraxan; Trexirol NF†; Trifamox Bronquial Duo; ***Austria:*** Mucospas; ***Braz.:*** Penetro†; ***Chile:*** Ambrotos; ***Cz.:*** Doxycyclin Al Comp; ***Ger.:*** Ambrodoxy; Ambroxol AL comp; Ambroxol comp; Amdox-Puren†; Azudoxat comp†; Broncho-Euphyllin; Doxam; Doximucol; Doxy Comp; Doxy Lindoxyl; Doxy Plus; Doxy-Wolff Mucolyt†; Doxysolvat†; Jenabroxol comp†; Sigamuc†; Spasmo-Mucosolvan; Terelit†; ***India:*** Ambrodil Plus; Ambrodil-S; Amcof; Amcold; Asthalin AX; Axalin-AX; Axalin†; Kofarest; Mucaryl-AX†; Novamox AX; Resproxin-ME; Suprivent-A; ***Mex.:*** Acimox-Ex; Aeroflux; Alerfin Ex; Alexing; Ambodil-C; Aminoefedrison; Balsibron-C; Biovicam Ex; Bisincof; Bolbamox†; Brogal Compositum; Brogal-T; Brogamax; Brominol-C; Bronar; Bronolban-M; Broquixol; Brosolan C; Broxofar Compuesto; Broxol Air; Broxol Plus; Broxolim-AM†; Broxolim-C; Brumax; Cefabroxil; Cibronal; Cobadex; Coricidin Expec; Dexol; Dexoltryn; Dofaxil; Doralan-Ax; Ebromin P; Epicol NF†; Faribrox; Ferlex; Flamebin; Fludexol-CL; Fluvicil; Fluxibit; Fluxol; Fultac; Gimabrol; Histiacil NF; Laritol Ex; Linfarden; Loexom FC; Loexom FS; Loxorol; Mucoflux; Mucosolvan Compositum; Mucovibrol Amoxi; Mucovibrol C; Musaldox; Neumyn-AS; Pentibroxil; Plexus; Ravotaf; Removil; Rezplen; Rombox; Salamflux; Sekretovit Amoxi; Sekretovit Ex; Sensibit XP; Septacin Amoxi; Septacin Ex; Seraxol; Serbol; Sermoxol; Sibilex; Solcibrol; Tadinar-C; Tavexyl; TheraFlu Tenalif; Torva; Toxol; Ulax-C; Vanmoxol; ***Port.:*** Clembroxol; Lactucol; Mucospas; Ventoliber; ***Rus.:*** Coldact Broncho (Колдакт Бронхо)†; Rinicold-Broncho (Риниколд Бронхо); ***Venez.:*** Aeroflux; Ambroclar; Ambromuco Compositum; Arbixil; Clenbuxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Amidefrine Mesilate *(BANM, rINN)* ⊗

5190; Amidéfrine, Mésilate d'; Amidefrini Mesilas; Amidephrine Mesylate *(USAN)*; Mesilato de amidefrina; MJ-5190. 3-(1-Hydroxy-2-methylaminoethyl)methanesulphonanilide methanesulphonate.

Амидефрина Мезилат

$C_{10}H_{16}N_2O_3S,CH_4O_3S = 340.4.$

CAS — 3354-67-4 (amidefrine); 1421-68-7 (amidefrine mesilate).

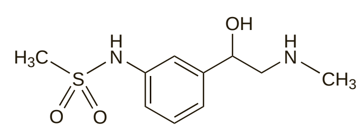

(amidefrine)

Profile

Amidefrine mesilate is a sympathomimetic with alpha-adrenergic activity similar to that of phenylephrine (p.1568). It is used for its vasoconstrictor properties in the local treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Fentrinol.

Ammonium Acetate

Amonio, acetato de; Amonowy octan.

Ацетат Аммония; Уксуснокислый Аммоний

$CH_3CO_2NH_4 = 77.08.$

CAS — 631-61-8 (ammonium acetate); 8013-61-4 (ammonium acetate solution).

Pharmacopoeias. *Br.* includes Strong Ammonium Acetate Solution.

Ammonium Bicarbonate *(BAN)*

Ammonii hydrogenocarbonas; Ammonium, bicarbonate d'; Ammónium-hidrogén-karbonát; Ammoniumvätekarbonat; Ammoniumvetykarbonaatti; Amonio, bicarbonato de; Amonio-vandenilio karbonatas; E503; Hydrogenuhličitan amonný. Ammonium hydrogen carbonate.

Бикарбонат Аммония; Гидрокарбонат Аммония; Двууглекислый Аммоний

$NH_4HCO_3 = 79.06.$

CAS — 1066-33-7.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ammonium Hydrogen Carbonate; Ammonium Bicarbonate BP 2008). A fine, white or almost white, slightly hygroscopic, crystalline powder or white or almost white crystals. It volatilises rapidly at 60°; volatilisation takes place slowly at ambient temperatures if slightly moist. It is in a state of equilibrium with ammonium carbamate. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

The BP 2008 directs that when Ammonium Carbonate is prescribed or demanded Ammonium Bicarbonate shall be dispensed or supplied.

Ammonium Carbonate

Amonio, carbonato de; Amonowy węglan; Carbonato de Amonio; E503.

Карбонат Аммония; Углекислый Аммоний

CAS — 8000-73-5.

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 26 (Ammonium Carbonate). A white powder, or hard, white or translucent masses having a strong odour of ammonia, without empyreuma. It consists of ammonium bicarbonate and ammonium carbamate, in varying proportions. It yields 30 to 34% of NH_3. On exposure to air it loses ammonia and carbon dioxide, becoming opaque, and is finally converted into friable porous lumps or a white powder of ammonium bicarbonate. Soluble 1 in 4 of water. It is decomposed by hot water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

NOTE. The **BP 2008** directs that Ammonium Bicarbonate shall be dispensed or supplied when Ammonium Carbonate is prescribed or demanded.

Ammonium Chloride

510; Ammonii chloridum; Ammonium Chloratum; Ammonium, chlorure d'; Ammoniumklorid; Ammónium-klorid; Ammoniumkloridi; Amonio chloridas; Amonio, cloruro de; Amonowy chlorek; Chlorid amonný; Cloruro de Amonio; Muriate of Ammonia; Sal Ammoniac.

Хлорид Аммония; Хлористый Аммоний

$NH_4Cl = 53.49.$

CAS — 12125-02-9.

ATC — B05XA04; G04BA01.

ATC Vet — QB05XA04; QG04BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *US*, and *Viet.*

Ph. Eur. 6.2 (Ammonium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water.

USP 31 (Ammonium Chloride). Colourless crystals or white, fine or course, crystalline powder. Is somewhat hygroscopic. Freely soluble in water and in glycerol, and even more so in boiling water; sparingly soluble in alcohol. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers.

Adverse Effects and Treatment

Ammonium salts are irritant to the gastric mucosa and may produce nausea and vomiting particularly in large doses. Large doses of ammonium chloride may cause a profound acidosis and hypokalaemia which should be treated symptomatically. Intravenous ammonium chloride can cause pain and irritation at the site of injection, which may be decreased by slowing the rate of infusion.

Excessive doses of ammonium salts, particularly if given by rapid intravenous injection, may give rise to hepatic encephalopathy due to the inability of the liver to convert the increased load of ammonium ions to urea.

Precautions

Ammonium salts are contra-indicated in patients with hepatic or renal impairment.

Pharmacokinetics

Ammonium chloride is absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the blood and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine; this is followed by transient diuresis.

Uses and Administration

Ammonium chloride is used as an expectorant in productive cough (p.1547). Other ammonium salts that have been used similarly include the acetate, bicarbonate, camphorate, carbonate, citrate (p.2256), and glycyrrhizate (p.2316).

Giving ammonium chloride produces a transient diuresis and acidosis. It may be used in the treatment of severe metabolic alkalosis (p.1667). Each g of ammonium chloride represents 18.69 mmol of chloride. It is usually given as a 1 to 2% solution by slow intravenous infusion, in a dosage depending on the severity of the alkalosis. A concentrated solution of ammonium chloride may be diluted by sodium chloride injection.

Ammonium chloride may also be used to maintain the urine at an acid pH in the treatment of some urinary-tract disorders. It is usually given orally, often as enteric-coated tablets, in a dose of 1 to 2 g every four to six hours. Higher doses were sometimes used in forced acid diuresis procedures to aid the excretion of basic drugs, such as amfetamines, in severe cases of overdosage (but see p.2153).

Ammonium chloride has been promoted for self administration as a diuretic, for example in premenstrual water retention; an oral dose of 650 mg three times daily for up to 6 days has been suggested, but such use is generally considered inappropriate.

Preparations

BP 2008: Ammonium Chloride Mixture; Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment;
USP 31: Ammonium Chloride Delayed-release Tablets; Ammonium Chloride Injection; Aromatic Ammonia Spirit; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Nyal Bronchitis; ***Fr.:*** Chlorammonic†; ***Ger.:*** Extin N; ***Switz.:*** Chloramon.

Multi-ingredient: numerous preparations are listed in Part 3.

Benproperine *(rINN)*

ASA-158/5 (benproperine phosphate); Benproperiini; Benproperin; Benproperina; Benpropérine; Benproperinum. 1-[2-(2-Benzylphenoxy)-1-methylethyl]piperidine.

Бенпроперин

$C_{21}H_{27}NO = 309.4$.
CAS — 2156-27-6.
ATC — R05DB02.
ATC Vet — QR05DB02.

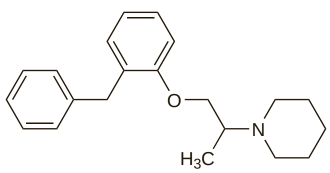

Pharmacopoeias. *Chin.* includes the phosphate.

Profile

Benproperine is used as a cough suppressant in non-productive cough (p.1547). It is reported to have a peripheral and central action and has been given in usual oral doses of 25 to 50 mg two to four times daily as the phosphate. Benproperine embonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Tussafug; ***Hong Kong:*** Cofrel; ***Jpn:*** Flaveric.

Benzonatate *(BAN, rINN)*

Bensonatat; Bentsonataatti; Benzonatato; Benzonatatum; Benzononatine; KM-65. 3,6,9,12,15,18,21,24,27-Nonaoxaoctacosyl 4-butylaminobenzoate.

Бензонатат

$C_{13}H_{18}NO_2(OCH_2CH_2)_nOCH_3$, where *n* has an average value of 8.
CAS — 104-31-4 (where n = 8).
ATC — R05DB01.
ATC Vet — QR05DB01.

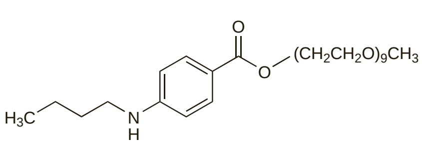

Pharmacopoeias. In *US.*

USP 31 (Benzonatate). A clear, pale yellow, viscous liquid having a faint characteristic odour. Soluble 1 in less than 1 of water, of alcohol, of chloroform, and of ether; freely soluble in benzene. Store in airtight containers. Protect from light.

Adverse Effects

Headache, dizziness, gastrointestinal disturbances, nasal congestion, hypersensitivity, pruritus, and skin rash have been reported. There may be drowsiness. Benzonatate has local anaesthetic properties and can produce numbness of the mouth, tongue, and pharynx. CNS stimulation and convulsions, followed by CNS depression, may occur in overdosage.

Uses and Administration

Benzonatate is a cough suppressant used in non-productive cough (p.1547); it is stated to act peripherally. It is related to tetracaine (p.1871) and has a local anaesthetic action on mucosa. It is given to adults and children over the age of 10 years in an oral dose of 100 mg three times daily; up to 600 mg daily in divided doses may be given if necessary. Benzonatate is reported to act within about 20 minutes and its effects are reported to last for 3 to 8 hours.

Preparations

USP 31: Benzonatate Capsules.

Proprietary Preparations (details are given in Part 3)
Mex.: Alzomed-F†; Beknol; Benzonal; Bronpax; Capsicof; D-Tato; Lemtosid; Nactol†; Novapsyl; Parven†; Pebegal; Pharben; Supracof; Tesalon; Tesopen; Texoven; Tusical; Tusitato; Tuzzil; Velpro; ***USA:*** Tessalon.

Bibenzonium Bromide *(BAN, rINN)*

Bibenzonii Bromidum; Bibenzonium, Bromure de; Bromuro de bibenzonio; Diphenetholine Bromide; ES-132. [2-(1,2-Diphenylethoxy)ethyl]trimethylammonium bromide.

Бибензония Бромид

$C_{19}H_{26}BrNO = 364.3$.
CAS — 59866-76-1 (bibenzonium); 15585-70-3 (bibenzonium bromide).
ATC — R05DB12.
ATC Vet — QR05DB12.

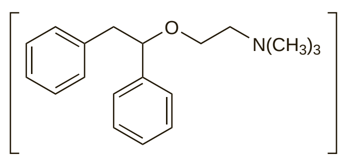

Profile

Bibenzonium bromide is a cough suppressant used in non-productive cough (p.1547) which is stated to have a central action. It has been given in a usual oral dose of 30 to 60 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Lysbex.

Bromhexine *(BAN, rINN)*

Bromexina; Bromhexin; Bromhexina; Bromhexinum; Bromiheksiini; Butamirat. 2-Amino-3,5-dibromobenzyl(cyclohexyl)methylamine.

Бромгексин

$C_{14}H_{20}Br_2N_2 = 376.1$.
CAS — 3572-43-8.
ATC — R05CB02.
ATC Vet — QR05CB02.

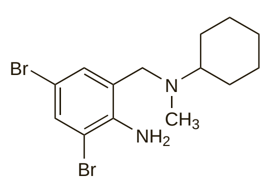

Bromhexine Hydrochloride *(BANM, USAN, rINNM)*

Bromheksino hidrochloridas; Bromhexine, chlorhydrate de; Brómhexin-hidroklorid; Bromhexin-hydrochlorid; Bromhexinhydroklorid; Bromhexini hydrochloridum; Bromiheksiinihydrokloridi; Bromoheksyny chlorowodorek; Cloridrato de Bromexina; Hidrocloruro de bromhexina; NA-274.

Бромгексина Гидрохлорид

$C_{14}H_{20}Br_2N_2,HCl = 412.6$.
CAS — 611-75-6.
ATC — R05CB02.
ATC Vet — QR05CB02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Bromhexine Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Adverse Effects

Gastrointestinal adverse effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported. Other reported adverse effects include headache, dizziness, sweating, and skin rashes. Inhalation of bromhexine has occasionally produced cough or bronchospasm in susceptible subjects.

Precautions

Since mucolytics may disrupt the gastric mucosal barrier bromhexine should be used with care in patients with a history of peptic ulcer disease. Care is also advisable in asthmatic patients. Clearance of bromhexine or its metabolites may be reduced in patients with severe hepatic or renal impairment.

Pharmacokinetics

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations occur after about 1 hour. Bromhexine undergoes extensive first-pass metabolism in the liver: its oral bioavailability is stated to be only about 20%. It is widely distributed to body tissues. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. Ambroxol (p.1550) is a metabolite of bromhexine. Bromhexine is highly bound to plasma proteins. It has a terminal elimination half-life of 13 to 40 hours. Bromhexine crosses the blood-brain barrier and small amounts cross the placenta.

Uses and Administration

Bromhexine is a mucolytic used in the treatment of respiratory disorders associated with productive cough (p.1547). Bromhexine is usually given orally in a dose of 8 to 16 mg of the hydrochloride three times daily. It has also been given by deep intramuscular or slow intravenous injection or inhaled as an aerosol solution.

Bromhexine has also been used orally and topically in the treatment of dry eye syndromes associated with abnormal mucus production (see below).

Dry eye. Bromhexine has been used orally in the treatment of dry eye (p.2140) in Sjögren's syndrome but results have been conflicting; it appears to have no effect on tear secretion in healthy subjects.[1] It has also been tried topically.

1. Avisar R, *et al.* Oral bromhexine has no effect on tear secretion in healthy subjects. *Ann Pharmacother* 1996; **30:** 1498.

Respiratory-tract infection. *USE WITH AN ANTIBACTERIAL.* Bromhexine has been shown to enhance the penetration of erythromycin into bronchial secretions.[1] Although bromhexine is used as an adjuvant in the treatment of respiratory infections, few controlled studies appear to have been conducted to determine if any additional benefit is obtained. However, some studies have found improved responses with cefalexin[2] and amoxicillin.[3]

1. Bergogne-Berezin E, *et al.* Etude de l'influence d'un agent mucolytique (bromhexine) sur le passage de l'érythromycine dans les sécrétions bronchiques. *Therapie* 1979; **34:** 705–11.
2. Boraldi F, Palmieri B. Antibiotic and mucolytic therapy in elderly patients with different cases of bronchopulmonary diseases. *Curr Ther Res* 1983; **33:** 686–91.
3. Roa CC, Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection: a randomized controlled trial. *Arzneimittelforschung* 1995; **45:** 267–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Amiorel; Aseptobron Expectorante; Balsasulf; Bisolvon; Brometos; Bromexidryl; Broncocalmine; Brondilax; Bronquisedan Elixir; Bronquisedan Paediatrico; Catarrosine; Expectosan Extra Forte; Funciobron B; Jarabe Medex; Lisi-Tos; Lorbi; Lorbi-Bis; Namir; Nastizol Expectorante; No-Tos Mucolitico; Pectoral Pagliano†; Pulmonix; Pulmosan; Qura Plus; Sandival; Toscalmin; Tostop; ***Austral.:*** Bisolvon Chesty; Duro-Tuss Mucolytic Cough Liquid; ***Austria:*** Bisolvon; ***Belg.:*** Bisolvon; Bromex; Bronchi-Mereprine; ***Braz.:*** Bisolvon; Clarus†; ***Chile:*** Bisolvon; Flumed; ***Cz.:*** Bisolvon†; Flegamina†; Mucohex; Paxirasol; ***Denm.:*** Bisolvon; Viscolyt†; ***Fin.:*** Bisolvon; Medipekt; Mucovin; ***Fr.:*** Bisolvon; ***Ger.:*** Aparsonin N†; Bisolvon; Hustentabs†; Omniapharm†; ***Gr.:*** Bisolvon; Bolisegna†; Bromiramin†; Bronchotussine; ***Hong Kong:*** Asthmaxine; Bisolvon; Bromoson; Bromxine; Duro-Tuss Mucolytic; Exolit; Vasican; ***Hung.:*** Paxirasol; ***India:*** Bromex; ***Indon.:*** Bisolvon; Bromika; Dexolut; Ethisolvan; Exovon; Farmavon; Hexon; Lexavon; Mucobron; Mucohexin; Mucosolvan; Poncosolvon; Solvinex; Thephidron; Yavon; ***Irl.:*** Bisolvon; ***Israel:*** Movex; Solvex; ***Ital.:*** Bisolvon; Broncokin†; ***Jpn:*** Bisolvon; ***Malaysia:*** Beacolytic; Bislan; Bisolvon†; Bromxine; Disol; Ekxine†; Hexolvon†; Vasican; ***Mex.:*** Bisolvon; Bromicof; Dibroxin†; Dizolvin†; Meroxan; Nastizol Ex; Normoflex; Tesacof; Toridran-N; ***Neth.:*** Bisolvon; Darolan Slijmoplossende; Famel Broomhexine†; Kruidvat Hoestelixer; Kruidvat Hoesttabletten; Streptuss vastzittende hoest†; Trekpleister Hoesttabletten†; ***Norw.:*** Bisolvon; ***NZ:*** Bisolvon; Duro-Tuss Mucolytic†; ***Philipp.:*** Bisolvon; Dur-Elix; Easepex; Fleminate; Mucolyptus; Xinebrom; ***Pol.:*** Flegamina; ***Port.:*** Bisolvon; Bromocal; Lisomucin; Tosseque; ***Rus.:*** Flegamin (Флегамин); ***S.Afr.:*** Bisolvon; Bronkese; ***Singapore:*** Bislan; Bisolvon; Bromxine; Broxine†; Duro-Tuss Mucolytic; Mucosol†; Vasican; ***Spain:*** Bisolvon; ***Swed.:*** Bisolvon; ***Switz.:*** Bisolvon; Hustosol†; Solvolin; ***Thai.:*** Asovon; Axistal; Behexine†; Bisoltab; Bisolvon; Bomexin; Bromex†; Bromoson; Bromso; Bromxin†; Bromxine; Bronclear; Disol; Dutross†; Exolit†; Ida; Manovon; Mihexine; Mucine†; Mucola†; Mucoxin; Ohexine; Romulin; Tromadil; ***Turk.:*** Bromek; Bromeksin; Viscol; ***UAE:*** Mucolyte; ***Venez.:*** Bedena; Bexilon; Bisectron; Bisolvon; Bromedrina; Brometix†; Bromexol; Bromox; Bronacim†; Drometox†; Inquixol; Kecnitril; Lisomucin; Mucobrol; Reosil; Teraflem; Tolmix†.

Multi-ingredient: numerous preparations are listed in Part 3.

Brovanexine Hydrochloride *(rINNM)*

Brovanexine, Chlorhydrate de; Brovanexini Hydrochloridum; Hidrocloruro de brovanexina. 4-(Acetyloxy)-*N*-[2,4-dibromo-6-[(cyclohexylmethylamino)methyl]phenyl]-3-methoxybenzamide monohydrochloride.

Брованексина Гидрохлорид

$C_{24}H_{29}Br_2ClN_2O_4$ = 604.8.
CAS — 54340-61-3 (brovanexine); 54340-60-2 (brovanexine hydrochloride).

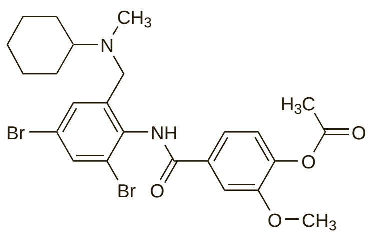

(brovanexine)

Profile

Brovanexine is a derivative of bromhexine (above) and is given orally as the hydrochloride, usually as an adjunct to antibacterials in preparations for the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Bronquimucil; ***Port.:*** Bronquimucil†; Pulmo-San†; ***Spain:*** Broncimucil.

Multi-ingredient: ***Arg.:*** Trifamox Bronquial; ***Spain:*** Bronquimucil†; Eupen Bronquial.

Butamirate Citrate *(BANM, USAN, rINNM)*

Abbott-36581; Butamirát-citrát; Butamirate, Citrate de; Butamirati Citras; Butamyrate Citrate; Citrato de butamirato; HH-197. 2-(2-Diethylaminoethoxy)ethyl 2-phenylbutyrate dihydrogen citrate.

Бутамирата Цитрат

$C_{18}H_{29}NO_3,C_6H_8O_7$ = 499.6.
CAS — 18109-80-3 (butamirate); 18109-81-4 (butamirate citrate).
ATC — R05DB13.
ATC Vet — QR05DB13.

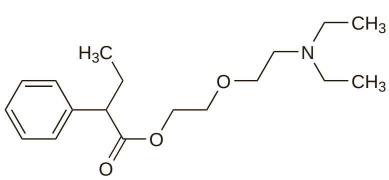

(butamirate)

Profile

Butamirate citrate is a cough suppressant used in non-productive cough (p.1547) and stated to have a central action. The usual oral dose is up to 30 mg daily in 3 or 4 divided doses; some countries permit up to 90 mg daily in divided doses. Modified-release tablets containing 50 mg have been given 2 or 3 times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dosodos; Talasa NF; Tossec; ***Belg.:*** Quintex†; Sinecod; ***Braz.:*** Besedan†; ***Cz.:*** Sinecod; Tussin; ***Gr.:*** Antis; Antitoss; Betavix; Boutavixal; Bronchofyl; Butacodin; Butagan; Butamir; Butrin; Buvastin; Chemisolv; Chributan; Codexine-R; Codimin; Cyne†; Devix; Doctamine; Drosten; Ellisek-S; Gertotus; Leogumil; Mebronol; Minatuss; Nontoss; Novamir; Oaxen; Pandigal; Pintal; Roctylan; Rondover; Safarol; Sinecod; Siroflex; Stilex; Velkacet; Verocod; Vilvom; Zeleven; Zestapron†; Zetapron; ***Hung.:*** NeoCitran Antitussive; Sinecod; ***Ital.:*** Butiran; Lenistar; Lexosedin; Sinecod Tosse Sedativo; ***Neth.:*** Sinecod; ***Philipp.:*** Sinecod; ***Pol.:*** Sinecod; Supremin; ***Port.:*** Sinecod; ***Rus.:*** Sinecod (Синекод); ***Switz.:*** DemoTussol; NeoCitran Antitussif; Sinecod; ***Thai.:*** Sinecod; ***Turk.:*** Kreval; Sinecod.

Multi-ingredient: ***Arg.:*** Muco Dosodos; ***Braz.:*** Novotussan†; ***Cz.:*** Stoptussin; ***Rus.:*** Stoptussin (Стоптуссин); ***Switz.:*** Hicoseen.

Butetamate Citrate *(BANM, rINNM)*

Butétamate, Citrate de; Butetamati Citras; Butethamate Citrate; Butethamate Dihydrogen Citrate; Citrato de butetamato. 2-Diethylaminoethyl 2-phenylbutyrate citrate.

Бутетамата Цитрат

$C_{16}H_{25}NO_2,C_6H_8O_7$ = 455.5.
CAS — 14007-64-8 (butetamate); 13900-12-4 (butetamate citrate).

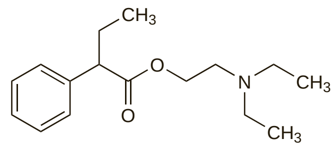

(butetamate)

Profile

Butetamate citrate is reported to be an antispasmodic and bronchodilator and has been used alone or in combination preparations for the symptomatic treatment of coughs and other associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Heliphenicol.

Multi-ingredient: ***Arg.:*** Febrigrip; Fugafebril; Kiper; Mejoral Grip; Muco Cortos†; Mucoprednibron; Piritos; Pulmocler; Refenax Jarabe; Tavinex Antigripal; ***Austria:*** Coldadolin; Influbene; ***Switz.:*** Bronchotussine.

Calcium Iodide

Calcii Iodidum; Calciumjodid; Ioduro de calcio; Kalcio jodidas; Kalsiumjodidi.

Йодид Кальция

CaI_2 = 293.9.
CAS — 10102-68-8.

Pharmacopoeias. *Eur.* (see p.vii) includes the tetrahydrate for homoeopathic preparations.

Ph. Eur. 6.2 (Calcium Iodide Tetrahydrate for Homoeopathic Preparations; Calcii Iodidi Tetrahydricum ad Praeparationes Homoeopathicas). A white or almost white, very hygroscopic, powder. Very soluble to freely soluble in water and in alcohol. Store in airtight containers.

Profile

Calcium iodide has been used orally in expectorant mixtures. The limitations of iodides as expectorants are discussed under Cough, p.1547. The actions of the iodides are discussed under Iodine (p.2169).

Homoeopathy. Calcium iodide has been used in homoeopathic medicines under the following names: Calcium iodatum; Calcium jodatum; Calcarea iodata; Cal. iod.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Zantril†; ***Gr.:*** Vitreolent; ***USA:*** Calcidrine; Norisodrine with Calcium Iodide.

Caramiphen Edisilate *(BANM, rINNM)*

Caramiphen Edisylate; Caramiphène, Edisilate de; Caramipheni Edisilas; Edisilato de caramifeno. 2-Diethylaminoethyl 1-phenylcyclopentane-1-carboxylate ethane-1,2-disulphonate.

Карамифена Эдизилат

$C_{38}H_{60}N_2O_{10}S_2$ = 769.0.
CAS — 77-22-5 (caramiphen); 125-86-0 (caramiphen edisilate); 125-85-9 (caramiphen hydrochloride).

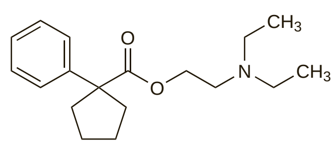

(caramiphen)

Profile

Caramiphen is a centrally acting cough suppressant that has been used as the edisilate in combination preparations for coughs (p.1547). Caramiphen hydrochloride was originally used similarly to trihexyphenidyl (p.820) for its antimuscarinic actions.

Carbocisteine *(BAN, rINN)*

AHR-3053; Carbocisteína; Carbocistéine; Carbocisteinum; Carbocysteine *(USAN)*; Karbocistein; Karbocisteinas; Karbociszteín; Karbocystein; Karbocysteina; Karbosisteiini; Karbosistein; LJ-206. *S*-Carboxymethyl-L-cysteine.

Карбоцистеин

$C_5H_9NO_4S$ = 179.2.
CAS — 2387-59-9; 638-23-3 (carbocisteine, L-form).
ATC — R05CB03.
ATC Vet — QR05CB03.

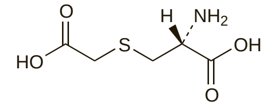

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Carbocisteine). A white or almost white, crystalline powder. Practically insoluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. A 1% suspension in water has a pH of 2.8 to 3.0. Protect from light.

Incompatibility. UK licensed product information states that mixing carbocisteine with pholcodine linctus causes precipitation of carbocisteine from solution but no information is given on whether this incompatibility is with the pholcodine or some component of the formulation used.

Carbocisteine Lysine *(BANM, rINNM)*

Carbocisteína lisina; Carbocistéine Lysine; Carbocisteinum Lysinum; Carbocysteine Lysine.

Карбоцистеина Лизин

CAS — 49673-81-6.
ATC — R05CB03.
ATC Vet — QR05CB03.

Carbocisteine Sodium *(BANM, rINNM)*

Carbocisteína sódica; Carbocistéine Sodique; Carbocysteine Sodium; Natrii Carbocisteinum.

Натрий Карбоцистеин

CAS — 49673-84-9 (carbocisteine sodium, L-form).
ATC — R05CB03.
ATC Vet — QR05CB03.

Adverse Effects and Precautions

Nausea and gastric discomfort, and gastrointestinal bleeding have occasionally occurred with carbocisteine. Skin rashes have also been reported.

Carbocisteine should be used with caution in patients with a history of peptic ulcer disease because of the risk that mucolytics may disrupt the gastric mucosal barrier.

Effects on endocrine function. Transient hypothyroidism associated with the use of carbocisteine developed in a patient with compromised thyroid function.[1]

1. Wiersinga WM. Antithyroid action of carbocisteine. *BMJ* 1986; **293:** 106.

Pharmacokinetics

Carbocisteine is rapidly and well absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 2 hours after an oral dose. It appears to penetrate into lung tissue and respiratory mucus. Carbocisteine is excreted in the urine as unchanged drug and metabolites. Acetylation, decarboxylation, and sulfoxidation have been identified as the major metabolic pathways. Sulfoxidation may be governed by genetic polymorphism.

◊ References.

1. Karim EFIA, *et al.* An investigation of the metabolism of S-carboxymethyl-L-cysteine in man using a novel HPLC-ECD method. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 253–6.
2. Brockmoller J, *et al.* Evaluation of proposed sulphoxidation pathways of carbocysteine in man by HPLC quantification. *Eur J Clin Pharmacol* 1991; **40:** 387–92.
3. Steventon GB. Diurnal variation in the metabolism of S-carboxymethyl-L-cysteine in humans. *Drug Metab Dispos* 1999; **27:** 1092–7.
4. Jovanovic D, *et al.* A comparative bioavailability study of a generic capsule formulation containing carbocysteine. *Pharmazie* 2006; **61:** 446–9.

Uses and Administration

Carbocisteine is used for its mucolytic activity in respiratory disorders associated with productive cough (p.1547). It is given orally in a dose of 750 mg three times daily, reduced by one-third when a response is obtained. Carbocisteine is also given orally as the sodium or lysine salts.

For children's doses, see Administration in Children, below.

Administration in children. Children from 2 to 5 years may be given oral carbocisteine 62.5 to 125 mg four times daily and those aged 5 to 12 years 250 mg three times daily.

Chronic obstructive pulmonary disease. The value of mucolytic therapy in chronic obstructive pulmonary disease (COPD—p.1112) is controversial. Two studies have reported some improvements in lung function in patients with chronic bronchitis given carbocisteine for up to 6 months,[1,2] but it appeared to have no effect on the number of acute exacerbations.[1] However, later studies[3,4] have reported reductions in the number of acute exacerbations; the number of common colds was also lower in the carbocisteine group in one of the studies.[4] Carbocisteine may also produce some beneficial effects on sputum rheology.[2,5]

1. Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis: a double blind trial with placebo control. *Br J Clin Pract* 1985; **39:** 395–8.
2. Aylward M, *et al*. Clinical evaluation of carbocisteine (Mucolex) in the treatment of patients with chronic bronchitis: a double-blind trial with placebo control. *Clin Trials J* 1985; **22:** 36–44.
3. Allegra L, *et al*. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. *Respiration* 1996; **63:** 174–80.
4. Yasuda H, *et al*. Carbocisteine reduces frequency of common colds and exacerbations in patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc* 2006; **54:** 378–80.
5. Braga PC, *et al*. Identification of subpopulations of bronchitic patients for suitable therapy by a dynamic rheological test. *Int J Clin Pharmacol Res* 1989; **IX:** 175–82.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mucolitic; Salvitos; ***Belg.:*** Bronchathiol†; Muco Rhinathiol; Mucosteine†; Romilar Mucolyticum; Siroxyl; Soludril Expectorans; ***Braz.:*** Carbocin; Carbofan; Carbotoss; Carboxil†; Certuss; Fluitoss; Fluizan†; Mucocis; Mucocistein; Mucofan; Mucoflux; Mucolab; Mucolisil; Mucolitic; Mucolix; Mucotoss; ***Chile:*** Coldin; ***Cz.:*** Fenorin; Mucopront†; Pectodrill; Rhinathiol†; ***Fin.:*** Reodyn; Toclapekt†; ***Fr.:*** Actifed Expectorant†; Bronchathiol; Bronchokod; Broncoclar; Broncorinol Expectorant†; Bronkirex†; Codotussyl Expectorant; Dimotapp Expectorant†; Drill Expectorant; Ergix; Exotoux; Fluditec; Fluvic; Humex Expectorant; Muciclar; Pectosan Expectorant; Pharmakod expectorant; Rhinathiol; Sirop des Vosges Expectorant†; Solutricine Expectorant†; Toclase Expectorant†; Tussilene†; ***Ger.:*** Mucopront†; Sedotussin muco†; Transbronchin; ***Gr.:*** Allstam; Bronchiole†; Ceflavit†; Chilvax; Divalio†; Duxil; Ectofus; Estival; Mucorem†; Mucothiol; Pneumol; Pulmoclase; Santamex-Expectorant†; Santamex†; Trusil; ***Hong Kong:*** Fluifort; Mucospect; Purasol; Rhinathiol; Solmux; ***Hung.:*** Drill Expectorant; Fenorin; Mucopront; NeoCitran Expectorant; Rhinathiol; Solucis; ***Indon.:*** Broncholit; Mucocil; Solmux; ***Irl.:*** Benylin Clear Action; Exputex; Mucodyne; Mucogen; Mucolex; Pulmoclase; Viscolex; ***Israel:*** Mical; Mucolit; Mucomed; ***Ital.:*** Broncomucil; Bronx†; Carbocit; Fluifort; Lisomucil; Mucocis; Mucojet†; Mucolase; Mucostar; Mucotreis; Polifluidil†; Polimucil; Reomucil†; Sinecod Tosse Fluidificante; Solucis; Tossefluid†; ***Jpn:*** Mucodyne; ***Malaysia:*** Fluifort; Kastipron; Mucopront†; Pabron Cough; Rhinathiol; SCMC; ***Mex.:*** Arbistin; Mucolin; ***Neth.:*** Dampo Solvopect; Mucodyne; Pectocold; Rami Slijmoplossende; Rhinathiol; ***Philipp.:*** Abluent; Aflem; Ameustyn; Bromycil; Broncocent; Broxytone; Carboflem; Carbosol; Cysdexpel; Emuxel; Esboxyl; Fayerex; Fluralex; Genecar; Lofenin; Loviscol; Mediphlegm; Pertussin; Phlegmol; Solmux; Solplem; Trimulex; Westcarbox; Zylotin; Zymelytic; ***Pol.:*** Mukolina; PectoDrill; ***Port.:*** Drill Mucolitico; Finatux; Mucolex; Mucorespiral; Mucorhinathiol Infantil; Mucorhinathiol Mucoral; Pulmiben; Pulmoclase†; ***Rus.:*** Bronchobos (Бронхобос); Fluditec (Флюдитек); Fluifort (Флуифорт); Mucodin (Мукодин); ***S.Afr.:*** Acuphlem; Betaphlem; Bronchette; Co-Flem; Flemex; Flemgo; Flemlite; Lessmusec; Medphlem; Mucocaps†; Mucoflem; Mucoless; Mucolinct; Mucosirop†; Mucospect; ***Singapore:*** Mucopront†; Rhinathiol; SCMC; ***Spain:*** Actithiol; Anatac; Fluidin Mucolitico; Iniston Mucolitico; Mucovital; Pectodrill; Pectox; Viscoteina; ***Switz.:*** Mephathiol; Mucogeran†; Mucoseptal†; Pectox; Rhinathiol; Tussantiol; ***Thai.:*** Amicof; Bocytin; Carbocter; Carbomed; Cisteine†; Exflem; Flemex; Fluifort; I-Cof; Mucolex; Mucomex; Mucopront†; Muflex; Murhinal; Rhinathiol; Rhinex; Siflex; Solmux; Throatsil-CBS; ***Turk.:*** Mucocis; Mukoliz; Mukotik; ***UK:*** Mucodyne; ***Venez.:*** Broxolflem; Cisteinol†; Gulaper; Loganil; Loviscol; Mucofar; Mucopront.

Multi-ingredient: ***Arg.:*** Mucolitic Antitusivo†; Polimucil†; ***Fr.:*** Rhinathiol Promethazine; ***Gr.:*** Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Vanesin; ***Hong Kong:*** Mucosin; Rhinathiol Promethazine; ***India:*** Caceff; Carbomox; Moxycarb-DT†; ***Ital.:*** Broncofluid; Keraflex; Libexin Mucolitico; ***Malaysia:*** Mucoease Plus; Rhinathiol Promethazine; SCMC Promethazine†; ***Mex.:*** Mucolin A; ***Philipp.:*** Solmux-Broncho (Reformulated); ***Port.:*** Bronquial; Niflux; ***Singapore:*** Rhinathiol Promethazine; ***Spain:*** Actithiol Antihist; Bronquicisteina; Eduprim Mucolitico; ***Switz.:*** Rhinathiol Promethazine; Triofan.

Clobutinol Hydrochloride *(rINNM)*

Clobutinol, Chlorhydrate de; Clobutinoli Hydrochloridum; Hidrocloruro de clobutinol; KAT-256. 2-(4-Chlorobenzyl)-3-(dimethylaminomethyl)butan-2-ol hydrochloride.

Клобутинола Гидрохлорид

$C_{14}H_{22}ClNO,HCl = 292.2.$
CAS — 14860-49-2 (clobutinol); 1215-83-4 (clobutinol hydrochloride).
ATC — R05DB03.
ATC Vet — QR05DB03.

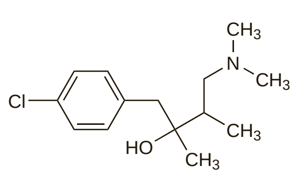

(clobutinol)

Profile

Clobutinol hydrochloride is a centrally acting cough suppressant for non-productive cough (p.1547) that has been given orally in doses of 40 to 80 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection. However, the EMEA has recommended for its withdrawal due to the risk of QT interval prolongation.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Proking; Silomat†; ***Austria:*** Silomat†; ***Belg.:*** Silomat†; ***Braz.:*** Silomat†; ***Chile:*** Broncodual; Calfetos; Clobatos†; Cloval; Pulbronc Simple; Silomat†; ***Cz.:*** Silomat†; ***Fin.:*** Mixtus; Silomat†; ***Fr.:*** Silomat†; ***Ger.:*** Hustenstiller†; Nullatuss†; Rofatuss†; Silomat†; stas-Hustenstiller N†; Tussed†; ***Gr.:*** Silomat†; ***Ital.:*** Silomat-Fher†; ***Malaysia:*** Silomat†; ***Port.:*** Silomat†; ***Singapore:*** Silomat†; ***Thai.:*** Silomat†; ***Venez.:*** Silomat†.

Multi-ingredient: ***Arg.:*** Bronquisedan; Bronquisedan Mucolitico; ***Braz.:*** Hytos Plus; Silomat Plus†; ***Chile:*** Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron; Vapoflu; ***Fr.:*** Silomat†; ***Indon.:*** Silomat Compositum; ***S.Afr.:*** Silomat DA†; ***UAE:*** Orcinol; ***Venez.:*** Silomat Compositum†.

Clofedanol Hydrochloride *(BANM, rINNM)*

Chlophedianol Hydrochloride *(USAN)*; Clofédanol, Chlorhydrate de; Clofedanoli Hydrochloridum; Hidrocloruro de clofedanol; SL-501. 2-Chloro-α-(2-dimethylaminoethyl)benzyl alcohol hydrochloride.

Клофеданола Гидрохлорид

$C_{17}H_{20}ClNO,HCl = 326.3.$
CAS — 791-35-5 (clofedanol); 511-13-7 (clofedanol hydrochloride).
ATC — R05DB10.
ATC Vet — QR05DB10.

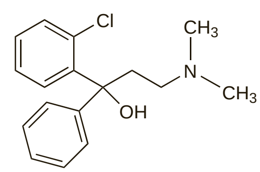

(clofedanol)

Pharmacopoeias. In *Jpn.*

Profile

Clofedanol hydrochloride is a centrally acting cough suppressant for non-productive cough (p.1547) that has been given in oral doses of 25 mg three or four times daily. For children's doses, see Administration in Children, below.

Administration in children. The following oral doses of clofedanol hydrochloride have been recommended for children:

- 2 to 6 years: 12.5 mg 3 or 4 times daily
- 6 to 12 years: 12.5 to 25 mg 3 or 4 times daily

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Ulone; ***Hong Kong:*** Coldrin†; ***Singapore:*** Coldrin†; ***Spain:*** Gentos†.

Multi-ingredient: ***Arg.:*** Bronco Biotaer†; Causalon Bronquial; Cofron; Gentiabron†; Neo-Tosel†; Notozen; Pectoral Hebert; Selectus FN; Torfan H†; Toxam†; Toxambay; ***Chile:*** Bauxol; Brontal; Cofron†; Diadicon; Kolibel; Mucobrol.

Clonazoline Hydrochloride *(rINNM)* ⊗

Clonazoline, Chlorhydrate de; Clonazolini Hydrochloridum; Hidrocloruro de clonazolina. 2-[(4-Chloro-1-naphthyl)methyl]-2-imidazoline hydrochloride.

Клоназолина Гидрохлорид

$C_{14}H_{13}ClN_2,HCl = 281.2.$
CAS — 17692-28-3 (clonazoline); 23593-08-0 (clonazoline hydrochloride).

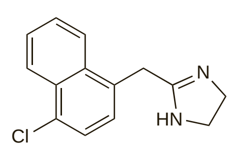

(clonazoline)

Profile

Clonazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p.1565) used for its vasoconstrictor activity in the local treatment of nasal congestion (p.1548).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Localyn.

Cloperastine *(rINN)*

Cloperastina; Clopérastine; Cloperastinum; HT-11. 1-{2-[(*p*-Chloro-α-phenylbenzyl)oxy]ethyl}piperidine.

Клоперастин

$C_{20}H_{24}ClNO = 329.9.$
CAS — 3703-76-2 (cloperastine); 132301-89-4 (levocloperastine).
ATC — R05DB21.
ATC Vet — QR05DB21.

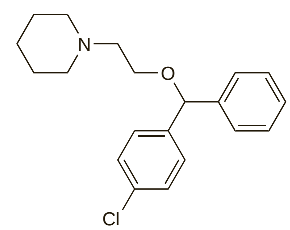

Cloperastine Fendizoate *(rINNM)*

Clopérastine, Fendizoate de; Cloperastine Hydroxyphenylbenzoyl Benzoic Acid; Cloperastine Phendizoate; Cloperastini Fendizoas; Fendizoato de cloperastina.

Клоперастина Фендизоат

$C_{20}H_{24}ClNO,C_{20}H_{14}O_4 = 648.2.$
CAS — 85187-37-7 (cloperastine fendizoate); 220329-19-1 (levocloperastine fendizoate).
ATC — R05DB21.
ATC Vet — QR05DB21.

Cloperastine Hydrochloride *(rINNM)*

Clopérastine, Chlorhydrate de; Cloperastini Hydrochloridum; Hidrocloruro de cloperastina.

Клоперастина Гидрохлорид

$C_{20}H_{24}ClNO,HCl = 366.3.$
CAS — 14984-68-0.
ATC — R05DB21.
ATC Vet — QR05DB21.

Pharmacopoeias. In *Jpn.*

Profile

Cloperastine is primarily a centrally acting cough suppressant used for non-productive cough (p.1547). It also has some antihistaminic action. The hydrochloride has been given orally as tablets in usual doses of 10 to 20 mg three times daily. Cloperastine fendizoate is used in oral liquid preparations in equivalent doses. Cloperastine fendizoate 17.7 mg is equivalent to about 10 mg of cloperastine hydrochloride. Levocloperastine fendizoate has been used similarly.

◊ References.

1. Aliprandi P, *et al*. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. *Drugs Exp Clin Res* 2004; **30:** 133–41.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Lysotossil; Novotossil†; Sekin; ***Braz.:*** Seki; ***Hong Kong:*** Uncough; ***Ital.:*** Cloel; Clofend; Mitituss; Nitossil; Politosse; Privituss; Quik; Seki; ***Jpn:*** Hustazol; ***Malaysia:*** Copastin; ***Mex.:*** Privituss; ***Port.:*** Tecnofox; ***Spain:*** Flutox; Sekisan.

Multi-ingredient: ***Thai.:*** Hustazol-C†.

Cocillana

Grape Bark; Guapi Bark; Huapi Bark.

Коккилана

CAS — 1398-77-2.

Profile

Cocillana is the dried bark of *Guarea guidonia* (*G. rusbyi*, *Sycocarpus rusbyi*, *G. trichilioides*; Meliaceae), a South American tree. It is used as an expectorant similarly to ipecacuanha (p.1562). It has been used in large doses as an emetic.

Preparations

Proprietary Preparations (details are given in Part 3)
Fin.: Codetabs.

Multi-ingredient: ***Braz.:*** Elixir de Marinheiro†; ***Canad.:*** Alsidrine†; Sirop Cocillana Codeine; Sirop Cocillana Compose; ***Fin.:*** Codesan Comp; Codesan N†; ***Hong Kong:*** Coci-Fedra; Coci-Fedra-C; Cocillana Christo; Cocillana Compound; Dextrocilla; Eurocilana; Mefedra-N†; ***Ital.:*** Broncosedina; ***S.Afr.:*** Cocillana Co; Corbar; ***Swed.:*** Cocillana-Etyfin; ***Venez.:*** Cerylana.

Coltsfoot

Coughwort; Fárfara; Huflattich; Tusílago; Tussilage.

Камчужная Трава

Pharmacopoeias. *Chin.* and *Fr.* include Coltsfoot Flower.

Profile

The leaves and flowers of coltsfoot (*Tussilago farfara*) have been used for their demulcent and supposed expectorant properties in the treatment of cough and other mild respiratory disorders. However, there has been some concern about potential hepatotoxicity and carcinogenicity due to the content of pyrrolizidine alkaloids.

◊ A review[1] of the actions and uses of coltsfoot pointed out that given the potential risks of its use long-term or in pregnancy, and the availability of other demulcent herbs, the use of coltsfoot preparations to treat throat irritations can no longer be considered appropriate.

1. Berry M. Coltsfoot. *Pharm J* 1996; **256:** 234–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Arceligasol; Negacne; ***Cz.:*** Perospir†; Species Pectorales Planta; ***Ital.:*** Lozione Same Urto; ***Pol.:*** Mucosit; Pyrosal; ***Spain:*** Llantusil†; ***UK:*** Antibron; Chesty Cough Relief.

Creosote

Creasote; Creosota; Creosotal (creosote carbonate); Wood Creosote.

Древесный Креозот

CAS — 8021-39-4 (creosote); 8001-59-0 (creosote carbonate).
ATC — R05CA08.
ATC Vet — QR05CA08.

Pharmacopoeias. In *Jpn.*

Profile

Creosote is a liquid consisting of a mixture of guaiacol, cresol, and other phenols obtained from wood tar. It possesses disinfectant properties and has been used as an expectorant. It has also been used as the carbonate and as lactocreosote.

Adverse effects are similar to those of Phenol, p.1656.

Commercial creosote used for timber preservation is obtained from coal tar.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Compound Inhalation of Menthol; ***Austria:*** Famel cum Codein; Famel cum Ephedrin; ***Braz.:*** Rhum Creosotado; ***Hung.:*** Fagifor†; ***India:*** Pulmo-Cod (C & G); ***Ital.:*** Creosoto Composto; Famel†; ***Switz.:*** Famel; ***UK:*** Famel Original.

Dembrexine *(BAN, rINN)*

Dembreksiini; Dembrexin; Dembrexina; Dembrexinum; Dembroxol. *trans*-4-[(3,5-Dibromosalicyl)amino]cyclohexanol.

Дембрексин

$C_{13}H_{17}Br_2NO_2$ = 379.1.
CAS — 83200-09-3 (dembrexine); 52702-51-9 (dembrexine hydrochloride).

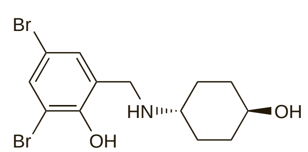

Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Dembrexine Hydrochloride Monohydrate for Veterinary Use; Dembrexine Hydrochloride Monohydrate BP(Vet) 2008). A white or almost white, crystalline powder. Slightly soluble in water and in anhydrous ethanol; freely soluble in methyl alcohol.

Profile

Dembrexine is a mucolytic used as the hydrochloride in veterinary medicine.

Denufosol Tetrasodium *(USAN, rINNM)*

Denufosol tetrasódico; Dénufosol tetrasodique; Denufosolum tetranatricum; INS-37217. 2′-Deoxycytidine(5′)tetraphospho(5′)uridine tetrasodium.

Денуфозол Тетранатрий

$C_{18}H_{23}N_5Na_4O_{21}P_4$ = 861.3.
CAS — 211448-85-0 (denufosol); 318250-11-2 (denufosol tetrasodium).

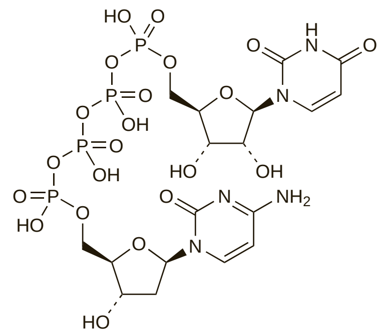

(denufosol)

Profile

Denufosol tetrasodium is a selective $P2Y_2$-receptor agonist that stimulates chloride and water secretion from respiratory tract epithelial cells, and increases mucosal hydration and mucociliary clearance. An inhaled preparation is under investigation for the treatment of cystic fibrosis.

Dextromethorphan *(BAN, pINN)*

Dekstrometorfaani; Dextrométhorphane; Dextromethorphanum; Dextrometorfán; Dextrometorfano. (+)-3-Methoxy-9a-methylmorphinan; (9*S*,13*S*,14*S*)-6,18-Dideoxy-7,8-dihydro-3-*O*-methylmorphine.

Декстрометорфан

$C_{18}H_{25}NO$ = 271.4.
CAS — 125-71-3.
ATC — R05DA09.
ATC Vet — QR05DA09.

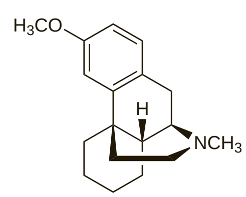

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextromethorphan: Bromage; Brome; Candy; CCC; C-C-C; Dex; Dextro; DM; Drex; DXM; Red Devils; Robo; Rojo; Skittles; Triple C; Triple C's; Tussin; Velvet; Vitamin D.

Pharmacopoeias. In *US.*

USP 31 (Dextromethorphan). A practically white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; freely soluble in chloroform. Store in airtight containers.

Dextromethorphan Hydrobromide *(BANM, pINNM)*

Dekstrometorfaanihydrobromidi; Dekstrometorfan Hidrobromür; Dekstrometorfano hidrobromidas; Dekstrometorfanu bromowodorek; Dextromethorfan-hydrobromid monohydrát; Dextrométhorphane, bromhydrate de; Dextromethorphani hydrobromidum; Dextromethorphani Hydrobromidum Monohydricum; Dextrometorfán-hidrobromid; Dextrometorfanhydrobromid; Hidrobromuro de dextrometorfano. Dextromethorphan hydrobromide monohydrate.

Декстрометорфана Гидробромид

$C_{18}H_{25}NO,HBr,H_2O$ = 370.3.
CAS — 125-69-9 (anhydrous dextromethorphan hydrobromide); 6700-34-1 (dextromethorphan hydrobromide monohydrate).
ATC — R05DA09.
ATC Vet — QR05DA09.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Dextromethorphan Hydrobromide). An almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Dextromethorphan Hydrobromide). Practically white crystals or crystalline powder having a faint odour. Soluble 1 in 65 of water; freely soluble in alcohol and in chloroform; insoluble in ether. pH of a 1% solution in water is between 5.2 and 6.5. Store in airtight containers.

Adverse Effects and Treatment

Adverse effects with dextromethorphan appear to be rare and may include dizziness and gastrointestinal disturbances. Excitation, confusion, and respiratory depression may occur after overdosage. Dextromethorphan has been subject to abuse, but there is little evidence of dependence of the morphine type.

◊ General references.

1. Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Safety* 1992; **7:** 190–9.

Hypersensitivity. A fixed-drug reaction developed in a patient after ingestion of dextromethorphan 30 mg.[1] Oral provocation with dextromethorphan produced a positive reaction but the results of topical application tests were negative. Urticaria, angioedema, and shortness of breath were reported in another patient;[2] symptoms recurred on oral challenge, but no skin test was performed. Similar symptoms were reported in a third patient;[3] skin testing provoked a positive reaction. On oral rechallenge, the patient developed urticaria initially, followed by generalised erythema and pruritus and decreased blood pressure after a second dose.

1. Stubb S, Reitamo S. Fixed-drug eruption due to dextromethorphan. *Arch Dermatol* 1990; **126:** 970–1.
2. Knowles SR, Weber E. Dextromethorphan anaphylaxis. *J Allergy Clin Immunol* 1998; **102:** 316–17.
3. Robledo T, *et al.* Adverse reaction to dextromethorphan. *Allergy* 2004; **59:** 890.

Overdosage. There have been reports[1-7] of overdosage or accidental poisoning (usually in children) due to dextromethorphan, including rare fatalities. Naloxone may be effective in reversing toxicity. Extrapyramidal reactions were seen in a child who ingested dextromethorphan.[6] Overdosage has also been associated with abuse (see below).

1. Shaul WL, *et al.* Dextromethorphan toxicity: reversal by naloxone. *Pediatrics* 1977; **59:** 117–19.
2. Katona B, Wason S. Dextromethorphan danger. *N Engl J Med* 1986; **314:** 993.
3. Rammer L, *et al.* Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988; **37:** 233–6.
4. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
5. Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. *Pediatr Emerg Care* 1991; **7:** 163–5.
6. Warden CR, *et al.* Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997; **13:** 214–15.
7. Roberge RJ, *et al.* Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; **17:** 285–8.

Precautions

Dextromethorphan should not be given to patients at risk of developing respiratory failure. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs.

Abuse. Dextromethorphan has been abused,[1-12] alone or with other drugs in over-the-counter preparations or as a powder sold under the name DXM. There have been a few reports of dependence,[1,2,11] but evidence of classical opioid dependence is generally considered to be lacking.

1. Fleming PM. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 597.
2. Orrell MW, Campbell PG. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; **293:** 1242–3.
3. Walker J, Yatham LN. Benylin (dextromethorphan) abuse and mania. *BMJ* 1993; **306:** 896.
4. Wolfe TR, Caravati EM. Massive dextromethorphan ingestion and abuse. *Am J Emerg Med* 1995; **13:** 174–6.
5. Nordt SP. DXM: a new drug of abuse? *Ann Emerg Med* 1998; **31:** 794–5.
6. Cranston JW, Yoast R. Abuse of dextromethorphan. *Arch Fam Med* 1999; **8:** 99–100.
7. Price LH, Lebel J. Dextromethorphan-induced psychosis. *Am J Psychiatry* 2000; **157:** 304.
8. Noonan WC, *et al.* Dextromethorphan abuse among youth. *Arch Fam Med* 2000; **9:** 791–2.
9. Banerji S, Anderson IB. Abuse of Coricidin HBP cough and cold tablets: episodes recorded by a poison center. *Am J Health-Syst Pharm* 2001; **58:** 1811–14.
10. Food and Drug Administration. FDA warns against abuse of dextromethorphan (DXM) (issued 20 May 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html (accessed 16/05/07)
11. Desai S, *et al.* Chronic addiction to dextromethorphan cough syrup: a case report. *J Am Board Fam Med* 2006; **19:** 320–3.
12. Bryner JK, *et al.* Dextromethorphan abuse in adolescence: an increasing trend: 1999-2004. *Arch Pediatr Adolesc Med* 2006; **160:** 1217–22.

Children. For doubts about the use of dextromethorphan as an antitussive in children see Cough, under Uses and Administration, below.

Interactions

Severe and sometimes fatal reactions have been reported after use of dextromethorphan in patients receiving

MAOIs. Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6; the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine, SSRIs, and thioridazine, should be borne in mind.

Antiarrhythmics. *Quinidine* can increase serum concentrations of dextromethorphan markedly, and some patients have experienced symptoms of dextromethorphan toxicity when the two drugs have been used together.[1,2] Based on this interaction, the combination has been studied for its therapeutic effect in amyotrophic lateral sclerosis (see Neurological Disorders, below). *Amiodarone* also appears to be able to increase serum concentrations of dextromethorphan.[3]

1. Zhang Y, *et al.* Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther* 1992; **51:** 647–55.
2. Pope LE, *et al.* Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* 2004; **44:** 1132–42.
3. Funck-Brentano C, *et al.* Influence of amiodarone on genetically determined drug metabolism in humans. *Clin Pharmacol Ther* 1991; **50:** 259–66.

Antibacterials. Serotonin syndrome-like symptoms have occurred when dextromethorphan has been taken with *linezolid*.

Antidepressants. A patient receiving *fluoxetine* experienced visual hallucinations after she began taking dextromethorphan.[1] The hallucinations were similar to those she had had 12 years earlier with lysergide. She had previously taken dextromethorphan alone without any adverse reactions. A serotonin syndrome (p.416) has been reported in a patient who took a cold-remedy containing dextromethorphan while receiving *paroxetine*.[2]

1. Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan. *Am J Psychiatry* 1992; **149:** 1406.
2. Skop BP, *et al.* The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 1994; **12:** 642–4.

Pharmacokinetics

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan (p.2293), which has some cough suppressant activity.

Genetic polymorphism. The *O*-demethylation of dextromethorphan and the hydroxylation of debrisoquine are under common polymorphic control, involving the cytochrome P450 isoenzyme CYP2D6, and dextromethorphan has been used as an alternative to debrisoquine (p.1256) for the phenotyping of oxidative metabolism.[1,2] Non-invasive determinations can be made using samples of urine or saliva.[3,4] Dextromethorphan has also been suggested as a tool to investigate *N*-demethylation, an alternate metabolic pathway for this drug.[5]

1. Belec L, *et al.* Extensive oxidative metabolism of dextromethorphan in patients with almitrine neuropathy. *Br J Clin Pharmacol* 1989; **27:** 387–90.
2. Streetman DS, *et al.* Dose dependency of dextromethorphan for cytochrome P450 2D6 (CYP2D6) phenotyping. *Clin Pharmacol Ther* 1999; **66:** 535–41.
3. Hildebrand M, *et al.* Determination of dextromethorphan metabolizer phenotype in healthy volunteers. *Eur J Clin Pharmacol* 1989; **36:** 315–18.
4. Hou Z-Y, *et al.* Salivary analysis for determination of dextromethorphan metabolic phenotype. *Clin Pharmacol Ther* 1991; **49:** 410–19.
5. Jones DR, *et al.* Determination of cytochrome P450 3A4/5 activity in vivo with dextromethorphan N-demethylation. *Clin Pharmacol Ther* 1996; **60:** 374–84.

Uses and Administration

Dextromethorphan hydrobromide is a cough suppressant used for the relief of non-productive cough; it has a central action on the cough centre in the medulla. It is also an antagonist of *N*-methyl-D-aspartate (NMDA) receptors. Although structurally related to morphine, dextromethorphan has no classical analgesic properties (but see Pain below) and little sedative activity.

Dextromethorphan hydrobromide is reported to act within half an hour of an oral dose and to exert an effect for up to 6 hours. It is given orally in doses of 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24 hours.

Dextromethorphan polistirex (a dextromethorphan and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release oral preparations. The dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, is the equivalent of 60 mg every 12 hours.

Dextrorphan (p.2293), the *O*-demethylated metabolite of dextromethorphan, also has cough suppressant properties.

For dosage of dextromethorphan in children, see Administration in Children, below.

Administration in children. Although dextromethorphan hydrobromide is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547 and also Cough, below).

In the USA, the following oral doses have been used:

- 2 to 6 years: 2.5 to 5 mg every 4 hours, or 7.5 mg every 6 to 8 hours, to a maximum of 30 mg in 24 hours
- 6 to 12 years: 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours to a maximum of 60 mg in 24 hours

Dextromethorphan polistirex is used in modified-release oral preparations. The following dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, has been given to children:

- 2 to 6 years: 15 mg every 12 hours
- 6 to 12 years: 30 mg every 12 hours

Cough. Equal doses of dextromethorphan hydrobromide and codeine phosphate were of similar efficacy in reducing the frequency of chronic cough (p.1547) in a double-blind crossover study in adults, but dextromethorphan had a greater effect than codeine on cough intensity.[1] However, these drugs were little more effective than placebo in suppressing night-time cough in children.[2-4] The American Academy of Pediatrics has commented[5] that there is no good evidence for the antitussive efficacy of dextromethorphan in children, that dosage guidelines are derived from (possibly inappropriate) extrapolation from effects in adults, and that adverse effects have been reported. Furthermore, in 2008, the FDA and the MHRA advised that over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

There is also some evidence that genetic polymorphism in the cytochrome P450 isoenzyme CYP2D6, and hence variations in metabolism, may have a significant influence on the antitussive efficacy of dextromethorphan.[6]

1. Matthys H, *et al.* Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; **11:** 92–100.
2. Gadomski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics* 1992; **89:** 774–6.
3. Taylor JA, *et al.* Efficacy of cough suppressants in children. *J Pediatr* 1993; **122:** 799–802.
4. Paul IM, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; **114:** e85–e90.
5. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997; **99:** 918–20. [Re-affirmed October 2006] Also available at: http://pediatrics.aappublications.org/cgi/reprint/99/6/918.pdf (accessed 11/05/07)
6. Wright CE, *et al.* CYP2D6 polymorphism and the anti-tussive effect of dextromethorphan in man. *Thorax* 1997; **52** (suppl 6): A73.

Neurological disorders. Dextromethorphan appears to have anticonvulsant activity and may have neuroprotective effects in cerebral ischaemia.[1] These effects may be related to its activity as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors or to interaction with σ-receptors. It has been studied in Parkinson's disease for treatment[2] or for management of levodopa-induced dyskinesias,[3] and for its potential protective action in stroke and acute brain injury. Dextromethorphan has also been studied for the management of amyotrophic lateral sclerosis (see Motor Neurone Disease, p.2380) but has not been found to be of benefit.[4-6] A study[7] in which quinidine was given to inhibit the metabolism of dextromethorphan did find the combination to be more effective in controlling pseudobulbar affect (emotional lability) than either drug alone, but also associated with more adverse effects. In the treatment of pseudobulbar affect in multiple sclerosis patients the dextromethorphan and quinidine combination was found to be well tolerated and more effective than placebo.[8] The NMDA-antagonist properties of dextromethorphan have also been investigated for the treatment[9,10] of nonketotic hyperglycinaemia (p.2393).

1. Tortella FC, *et al.* Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol Sci* 1989; **10:** 501–7.
2. Bonuccelli U, *et al.* Dextromethorphan and parkinsonism. *Lancet* 1992; **340:** 53.
3. Verhagen Metman L, *et al.* Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. *Neurology* 1998; **51:** 203–6.
4. Askmark H, *et al.* A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1993; **56:** 197–200.
5. Blin O, *et al.* A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. *Clin Neuropharmacol* 1996; **19:** 189–92.
6. Gredal O, *et al.* A clinical trial of dextromethorphan in amyotrophic lateral sclerosis. *Acta Neurol Scand* 1997; **96:** 8–13.
7. Brooks BR, *et al.* Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology* 2004; **63:** 1364–70.
8. Panitch HS, *et al.* Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol* 2006; **59:** 780–7.
9. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
10. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.

Pain. Dextromethorphan has a potential role in the blockade of pain. It has been investigated[1-3] in the management of neuropathic pain with promising results in diabetic neuropathy (p.6), although pain was not reduced in postherpetic neuralgia (p.9). High doses of dextromethorphan may be needed for an effect, or combination with quinidine, which inhibits dextromethorphan metabolism.[4] However, the use of dextromethorphan in diabetic neuropathy remains investigational, and further well-controlled trials are needed.[5]

A systematic review[6] of 28 studies of dextromethorphan as an adjunct for postoperative pain found that despite a tendency for patients to report less pain than with placebo, and to use less opioid analgesia postoperatively, the differences tended to be inconsistent and of questionable clinical significance. There was some suggestion that parenteral dextromethorphan was more effective than oral.

1. Nelson KA, *et al.* High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; **48:** 1212–18.
2. Sang CN, *et al.* Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology* 2002; **96:** 1053–61.
3. Carlsson KC, *et al.* Analgesic effect of dextromethorphan in neuropathic pain. *Acta Anaesthesiol Scand* 2004; **48:** 328–36.
4. Thisted RA, *et al.* Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. *Clin Ther* 2006; **28:** 1607–18.
5. Criner TM, Perdun CS. Dextromethorphan and diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 1221–3.
6. Duedahl TH, *et al.* A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006; **50:** 1–13.

Preparations

USP 31: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Dextromethorphan Hydrobromide Syrup; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Dextrotos; Romilar; ***Austral.:*** Benadryl for the Family Dry Forte; Bisolvon Dry; Dexi-Tuss†; Nucosef DM†; Robitussin DX; Robitussin Honey Cough Syrup†; Strepsils Cough Relief; Strepsils Dry Cough†; Tussinol for Dry Coughs†; ***Austria:*** Prontodex; Wick Formel 44; Wick Formel 44 plus Husten-Pastillen; Wick Formel 44 Plus Hustenstiller; ***Belg.:*** Actifed New; Bronchosedal; Dexir; Humex; Nortussine Mono; Notuxal; Romilar Antitussivum; Soludril Antiussivum; Toux-San; Touxium Antitussivum; Tussipect; Tusso Rhinathiol; Vicks Vaposyrup Antitussif; ***Canad.:*** Balminil DM; Benylin DM; Bronchophan DM; Buckley's DM; Calmylin No 1†; Cough Syrup DM; Delsym; DM Children's Cough Syrup; DM Cough Syrup; DM Sans Sucre; Jack & Jill Thin Strips Cough; Koffex DM; Neo Citran Cough; Pharmilin-DM†; Pharminil DM; Robitussin Childrens Cough DM; Robitussin DM CoughGels; Sedatuss DM; Sucrets Cough Control; Syrup DM; Triaminic Cough; Triaminic DM; Triaminic Long Acting Cough; Tussin Antitussive†; Vicks Formula 44; ***Chile:*** Pectobronc; Tusminal; ***Cz.:*** Dr Rentschler Hustenstiller; Humex Pro Deti; Robitussin Antitussicum; Robitussin Junior; Tussidrill; ***Denm.:*** Dexofan; ***Fin.:*** Lagun†; Resilar; ***Fr.:*** Codotussyl Toux Seche; Dexir; Drill toux seche; Ergix; Ergix Toux Seche; Fluditec toux seche; Humex Toux Seche Dextromethorphane; Nodex; Pulmodexane; Tussidane; Tuxium†; Vicks Toux Seche; ***Ger.:*** Arpha Hustensirup†; Em-medical forte†; Hustenstiller; NeoTussan; Silomat DMP; Tuss Hustenstiller†; Wick Formel 44 Husten-Stiller; Wick Formel 44 plus Husten-Pastillen S; ***Gr.:*** Vaposyrup†; ***Hong Kong:*** Balminil DM†; Dextrome; Pusiran; Robitussin Maximum Strength Cough; Robitussin Paediatric Cough; Tussils; ***Hung.:*** Drill; Methor; Rhinathiol; Robitussin Antitussicum; Robitussin Junior; Wick Formula 44 kohogescillapito†; ***India:*** Alex Cough; Lastuss; Lexcof; ***Indon.:*** Bisoltussin; ***Irl.:*** Benylin Non-Drowsy Dry Cough; Delsym; Robitussin Dry Cough; Robitussin Junior; ***Israel:*** Tarodex; ***Ital.:*** Aricodiltosse; Bechilar; Bronchenolo; Broncofama; Formitrol; Honeytuss; Lisomucil Tosse Sedativo; Metorfan; Neo Borocillina Tosse Sciroppo; Sanabronchiol†; Tossoral; Tussycalm; Vicks Tosse Pastiglie; Vicks Tosse Sedativo; ***Malaysia:*** Dexcophan; Metofen Forte†; Nospan; Pusiran; Tussidex Forte†; Tussils; Upha Dextrophan; ***Mex.:*** Atassol; Athos; Balbek; Balsedrina; Bekesina-S; Bekidiba Dex; Bioquidan; Brocolan; Bromelip; Debequin; Dontuxin; Flex Metak; Jarabe Garde; Megal Simple†; Neo-Ulcoid; Numonyl D†; Protan; Quimofan; Romilar; Tosifan; ***Neth.:*** Bisoltussin; Dampo bij droge hoest; Darolan Hoestprikkeldempende; Daromefan; Pectofree; Rami-Dextromethorfan; Romilar; Tussipect; Vicks Hoestsiroop; Vicks Vaposiroop; Vicks Vapotab; ***NZ:*** Benadryl Dry Forte; Robitussin DX; Strepsils Cough; Strepsils Dry Cough; ***Philipp.:*** Cofles; Extendryl DM; Mytusan DM; Pulmodex; Streptuss; Suprekof DM; ***Pol.:*** Acodin; Dexatussin; Robitussin Antitussicum; Robitussin Junior; Tussal Antitussicum; Tussidex; TussiDrill; ***Port.:*** Bisoltussin; Diacol; Drill Tosse Seca; Rhinathiol; Tussilene; Vicks Pastihas; Vicks Xarope Antitussico; ***S.Afr.:*** Benylin Dry Cough; ***Singapore:*** Beathorphan; Dexcophan; Metophan; Nospan; Pusiran; Tussidex†; Tussils; ***Spain:*** Aquitos; Benylin Antitusivo†; Bexatus; Bisolvon Antitusivo; Cinfatos; Formulatus; Frenatus; Ilvitus; Iniston Antitusivo; Parlatos; Pastillas Dr Andreu; Robitussin DM Antitusivo; Romilar; Serratos; Streptuss; Tosrhimatiol†; Tusitinas†; Tusorama; Tussidrill; ***Switz.:*** Astho-Med; Bexine; Calmerphan-L; Calmesine; Emedrin N; Pharmacard Family Toux seche†; Pulmofor; Tussalpront; Vicks Formule 44 Calmine; ***Thai.:*** Cortuss; Dec†; Depan-F; Dex†; Dextramet; Dextroral; Eicof; Icolid; Icolid Plus; Manodextro; MLM-Dex; Polydex; Potussan; Pusiran; Romilar; Strepsils Dry Cough; Throatsil-DEX; Tusco; Tussils; ***UAE:*** Exedexe; Sedofan P; ***UK:*** Adult Dry Cough; Benylin Dry Coughs Non-Drowsy; Dry Cough Syrup; Robitussin for Dry Coughs; Vicks Cough Lozenges with Honey; Vicks Cough Syrup with Honey for Dry Coughs; Vicks Vaposyrup for Dry Coughs; ***USA:*** AeroTuss 12; Benylin Adult†; Benylin Pediatric†; Buckleys

Cough; Creo-Terpin; Creomulsion; Delsym; DexAlone; Diabe-Tuss DM; ElixSure Childrens Cough; Hold DM; Little Colds Cough Formula; PediaCare Childrens Long-Acting Cough; PediaCare Infants Long-Acting Cough; Robitussin Pediatric; Scot-Tussin DM Cough Chasers; Silphen DM; Simply Cough; Sucrets DM; Theraflu Cough; Triaminic Long Acting Cough; Trocal; Vicks 44 Cough Relief; ***Venez.:*** Bromodel†; Detofan†; Hidrofan†; Libolar; Metordex†; Mexobron†; Promedin; Tilodrin.

Multi-ingredient: numerous preparations are listed in Part 3.

Dimemorfan Phosphate *(rINNM)*

AT-17; Dimémorfane, Phosphate de; Dimemorfani Phosphas; Fosfato de dimemorfano. (+)-3,9a-Dimethylmorphinan phosphate.

Димеморфана Фосфат

$C_{18}H_{25}N,H_3PO_4$ = 353.4.
CAS — 36309-01-0 (dimemorfan); 36304-84-4 (dimemorfan phosphate).
ATC — R05DA11.
ATC Vet — QR05DA11.

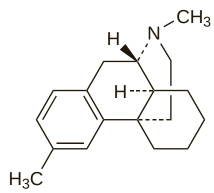

(dimemorfan)

Pharmacopoeias. In *Jpn.*

Profile

Dimemorfan phosphate is a centrally acting cough suppressant used for non-productive cough (p.1547). It is given orally in doses of 10 to 20 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tusben; ***Spain:*** Dastosin.

Dimethoxanate Hydrochloride *(BANM, rINNM)*

Diméthoxanate, Chlorhydrate de; Dimethoxanati Hydrochloridum; Hidrocloruro de dimetoxanato. 2-(2-Dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate hydrochloride.

Диметоксаната Гидрохлорид

$C_{19}H_{22}N_2O_3S,HCl$ = 394.9.
CAS — 477-93-0 (dimethoxanate); 518-63-8 (dimethoxanate hydrochloride).
ATC — R05DB28.
ATC Vet — QR05DB28.

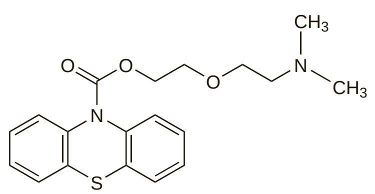

(dimethoxanate)

Profile

Dimethoxanate hydrochloride is a centrally acting cough suppressant used for non-productive cough (p.1547). It is given orally in usual doses of 37.5 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cotrane.

Dornase Alfa *(BAN, USAN, rINN)*

Deoxyribonuclease; Desoxyribonuclease; DNase I; Dornasa alfa; Dornasum Alfa; Dornaz Alfa; rhDNase. Deoxyribonuclease I (human recombinant).

Дорназа Альфа

$C_{1321}H_{1995}N_{339}O_{396}S_9$ = 29249.6.
CAS — 143831-71-4; 132053-08-8.
ATC — B06AA10; R05CB13.
ATC Vet — QB06AA10; QR05CB13.

Description. Dornase alfa is a recombinant enzyme having the same amino acid sequence and glycosylation pattern as human deoxyribonuclease I.

Adverse Effects

Common adverse effects with dornase alfa aerosol include pharyngitis, hoarseness of the voice, and chest pain. Occasionally laryngitis, conjunctivitis, and skin rashes and urticaria have been reported. There may be a transient decline in pulmonary function on beginning therapy with dornase alfa.

Uses and Administration

Dornase alfa acts as a mucolytic by hydrolysing DNA that has accumulated in sputum from decaying neutrophils. It is used as a nebulised solution in patients with cystic fibrosis; in the UK its indication is limited to patients with a forced vital capacity (FVC) greater than 40% of predicted value and to patients over 5 years of age, but in the USA it may also be given for advanced disease (FVC less than 40%) and to younger children. The usual dose is 2500 units (2.5 mg) of dornase alfa given once daily via a jet nebuliser. This dose may be given twice daily to patients over 21 years of age.

Bovine deoxyribonuclease has been used similarly. It has also been used topically, often with fibrinolysin, as a debriding agent for inflammatory and infected lesions. Bovine deoxyribonuclease has also been given by injection.

Administration in children. Although in some countries dornase alfa is not recommended for use in children under 5 years of age, a study[1] to assess the delivery of dornase alfa to the lungs of children with cystic fibrosis aged between 3 months and 5 years, showed that the amounts present in the lower airways were comparable to those in older children. It also appeared to be safe in these younger patients during the 2-week study period.

1. Wagener JS, *et al.* Aerosol delivery and safety of recombinant human deoxyribonuclease in young children with cystic fibrosis: a bronchoscopic study. *J Pediatr* 1998; **133:** 486–91.

Asthma. There are reports of the use of dornase alfa to liquefy mucus plugs and relieve an attack of acute severe asthma (p.1108) in children.[1-3] However, a randomised controlled study[4] found that adding a single dose of nebulised dornase alfa to standard emergency treatment has no benefits in children with moderate to severe acute asthma.

1. Greally P. Human recombinant DNase for mucus plugging in status asthmaticus. *Lancet* 1995; **346:** 1423–4.
2. Patel A, *et al.* Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment. *Br J Anaesth* 2000; **84:** 505–7.
3. Durward A, *et al.* Resolution of mucus plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000; **28:** 560–2.
4. Boogaard R, *et al.* Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax* 2008; **63:** 141–6.

Chronic obstructive pulmonary disease. A large phase III study in patients hospitalised for acute exacerbations of chronic bronchitis (p.1112) was halted prematurely because of a non-significant trend to increased mortality in patients given dornase alfa.[1]

1. Hudson TJ. Dornase in treatment of chronic bronchitis. *Ann Pharmacother* 1996; **30:** 674–5.

Cystic fibrosis. There is good evidence that inhalation therapy with dornase alfa can produce modest but useful improvement in lung function in some patients with cystic fibrosis (p.166). Most studies have concentrated on patients with mild or moderate disease (forced vital capacity at least 40% of the predicted value) in whom FEV_1 and forced vital capacity have shown improvements generally of the order of 5 to 10%,[1-3] and in whom more prolonged therapy (24 weeks) has been shown to reduce the risk of exacerbations of respiratory infections, and hence the need for intravenous antibacterial therapy.[3] There is also evidence that benefit may occur in patients with more severe disease.[4] A systematic review[5] of studies concluded that there is evidence to show that dornase alfa therapy over a 1-month period is associated with improved lung function. Furthermore, a randomised, multicentre, placebo-controlled study[6] in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a period of 96 weeks. However, only a minority of patients, perhaps about one-third,[7] benefit from the drug, and at present there is no way of identifying those who will respond other than by a therapeutic trial.[8,9]

Given the high cost of therapy, which is not entirely recouped by savings in acute care, there has been some controversy about the appropriate use of dornase alfa:[10-13] it seems to be generally felt that it should be reserved for specialist use in cystic fibrosis clinics, but that patients should not be denied a trial where appropriate. Most responders with mild to moderate impairment of lung function will show improvements within 2 weeks, although in more severely affected patients a 6-week trial is advocated.[8] A review of the use of dornase alfa in cystic fibrosis concluded that dosing on alternate days would be as effective as daily dosing, and would reduce costs and treatment time.[14]

1. Ramsey BW, *et al.* Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993; **148:** 145–51.
2. Ranasinha C, *et al.* Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993; **342:** 199–202.
3. Fuchs H, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994; **331:** 637–42.
4. McCoy K, *et al.* Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996; **110:** 889–95.
5. Jones AP, *et al.* Dornase alpha for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/07/08).
6. Quan JM, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; **139:** 813–20.
7. Davis PB. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994; **331:** 672–3.
8. Conway SP, Littlewood JM. rhDNase in cystic fibrosis. *Br J Hosp Med* 1997; **57:** 371–2.
9. Ledson MJ, *et al.* Targeting of dornase alpha therapy in adult cystic fibrosis. *J R Soc Med* 1998; **91:** 360–4.
10. Anonymous. Dornase alfa for cystic fibrosis. *Drug Ther Bull* 1995; **33:** 15–16.
11. Spencer D, Weller P. Dornase-alfa for cystic fibrosis. *Lancet* 1995; **345:** 1307.
12. Bush A, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **310:** 1533.
13. Robert G, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; **311:** 813.
14. Suri R. The use of human deoxyribonuclease (rhDNase) in the management of cystic fibrosis. *BioDrugs* 2005; **19:** 135–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pulmozyme; ***Austral.:*** Pulmozyme; ***Austria:*** Pulmozyme; ***Belg.:*** Pulmozyme; ***Braz.:*** Pulmozyme; ***Canad.:*** Pulmozyme; ***Chile:*** Viscozyme; ***Cz.:*** Pulmozyme; ***Denm.:*** Pulmozyme; ***Fin.:*** Pulmozyme; ***Fr.:*** Pulmozyme; ***Ger.:*** Pulmozyme; ***Gr.:*** Pulmozyme; ***Hung.:*** Pulmozyme; ***Irl.:*** Pulmozyme; ***Israel:*** Pulmozyme; ***Ital.:*** Pulmozyme; ***Mex.:*** DNSM; Pulmozyme; ***Neth.:*** Pulmozyme; ***Norw.:*** Pulmozyme; ***NZ:*** Pulmozyme; ***Pol.:*** Pulmozyme; ***Port.:*** Pulmozyme; ***Rus.:*** Pulmozyme (Пульмозим); ***S.Afr.:*** Pulmozyme; ***Spain:*** Pulmozyme; ***Swed.:*** Pulmozyme; ***Switz.:*** Pulmozyme; ***Turk.:*** Pulmozyme; ***UK:*** Pulmozyme; ***USA:*** Pulmozyme.

Multi-ingredient: ***Arg.:*** Clorfibrase; ***Austria:*** Fibrolan; ***Braz.:*** Cauterex; Dermofibrin C†; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino-Cauterex; Gino-Fibrase; Procutan†; ***Chile:*** Elase; ***Cz.:*** Fibrolan; ***Fr.:*** Elase; ***Ger.:*** Fibrolan†; ***Hung.:*** Fibrolan; ***Ital.:*** Elase†; ***Malaysia:*** Elase; ***Mex.:*** Fibrase; Fibrase SA; Ridasa; ***Pol.:*** Fibrolan; ***Switz.:*** Fibrolan.

Dropropizine *(BAN, rINN)*

Dropropitsiini; Dropropizin; Dropropizina; Dropropizinum; UCB-1967. 3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.

Дропропизин

$C_{13}H_{20}N_2O_2$ = 236.3.
CAS — 17692-31-8.
ATC — R05DB19.
ATC Vet — QR05DB19.

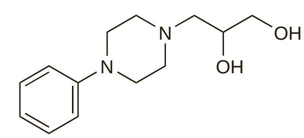

Levodropropizine *(BAN, rINN)*

DF-526; Levdropropizine; Levodropropitsiini; Levodropropizin; Levodropropizina; Levodropropizinas; Lévodropropizine; Levodropropizinum. The (−)-(*S*)-isomer of dropropizine.

Леводропропизин

$C_{13}H_{20}N_2O_2$ = 236.3.
CAS — 99291-25-5.
ATC — R05DB27.
ATC Vet — QR05DB27.

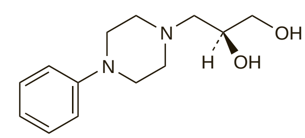

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Levodropropizine). A white or almost white powder. Slightly soluble in water and in alcohol; freely soluble in dilute acetic acid and in methyl alcohol. A 2.5% solution in water has a pH of 9.2 to 10.2. Protect from light.

Profile

Dropropizine is a cough suppressant reported to have a peripheral action in non-productive cough (p.1547). It is given orally usually in a dose of 30 mg three or four times daily. Levodropropizine, the (−)-(*S*)-isomer of dropropizine, is claimed to produce fewer CNS effects and is used similarly in an oral dose of 60 mg up to three times daily.

◊ References.

1. Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough: comparison with dextromethorphan. *Pulm Pharmacol Ther* 1997; **10:** 89–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Perlatos; ***Belg.:*** Catabex; Levotuss; ***Braz.:*** Antux; Atossion; Ecos; Eritos; Flextoss; Neotoss; Percof; Tussiflex D; Vibral; Zyplo; ***Chile:*** Broncard; ***Cz.:*** Ditustat; Levopront; ***Ger.:*** Larylin Husten-Stiller; ***Gr.:*** Dropavix; Levotuss; ***Hung.:*** Levopront; ***Indon.:*** Levopront; ***Ital.:*** Danka; Domutussina; Levotuss; Rapitux†; Ribex Tosse; Salvituss; Tau-Tux; ***Mex.:*** Levocof; Troferit; Zyplo; ***Neth.:*** Levotuss; ***Philipp.:*** Levopront; ***Pol.:*** Levopront; ***Port.:*** Catabina; Levotuss; ***Singapore:*** Levopront†; ***Spain:*** Levotuss; Tautoss; ***Thai.:*** Levopront; ***Turk.:*** Levopront; ***Venez.:*** Antux; Levopront.

Multi-ingredient: ***Belg.:*** Catabex Expectorans†; ***Braz.:*** Notuss; ***Ital.:*** Elisir Terpina; Guaiacalcium Complex; Ribexen con Espettorante; Tiocalmina; Tussamag Complex; ***Port.:*** Catabina Expectorante.

Elecampane

Ala; Alant; Aunée; Énula; Énula campana; Helenio; Ínula; Inula.

Девясил Высокий

CAS — 97676-35-2 (elecampane oil).

Pharmacopoeias. In *Chin.* (which also includes various other species of *Inula*) and *Fr.*

Profile

Elecampane is the root of *Inula helenium* (Compositae). It has been used in herbal preparations for the treatment of cough for its supposed expectorant and cough suppressant properties. It is also used as a flavouring in foods and alcoholic beverages.

Elecampane contains sesquiterpene lactones including alantolactone (alant camphor; elecampane camphor; inula camphor; helenin), which was formerly used in the treatment of worm infections, and has also been an ingredient of some cough preparations.

Elecampane oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Brust- und Hustentee St Severin; ***Cz.:*** Klosterfrau Melisana; Species Cholagogae Planta; ***Fr.:*** Mediflor Tisane Digestive No 3; Mediflor Tisane Hepatique No 5; ***Ger.:*** Leber-Galle-Tropfen 83†; ***Pol.:*** Pectosol; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Wonderkroonessens; ***Spain:*** Bronpul†; Natusor Asmaten†; Natusor Broncopul†; ***Switz.:*** Hederix; Padmed Laxan; ***UK:*** Catarrh-eeze; Cough-eeze; Horehound and Aniseed Cough Mixture; Vegetable Cough Remover.

Ephedra ⊗

Efedra; Ma-huang.

Хвойник; Эфедра хвощевая (*Ephedra equisetina*)

Pharmacopoeias. In *Chin., Ger.,* and *Jpn.*

Chin. also includes the roots of *Ephedra sinica* or *E. intermedia*.

Profile

Ephedra consists of the dried young branches of *Ephedra sinica*, *E. equisetina*, and *E. gerardiana* (including *E. nebrodensis*) (Ephedraceae), containing not less than 1.25% of alkaloids, calculated as ephedrine.

The action of ephedra is due to the presence of ephedrine (below) and pseudoephedrine (p.1571). It has been used chiefly as a source of these alkaloids. The FDA states that ephedra-containing dietary supplements are unsafe and the sale of these products is banned in the USA. Other countries have also banned the sale of ephedra-containing dietary supplements.

◊ For reference to the adverse effects of herbal products containing ephedra see Abuse under Ephedrine, below.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Herbal Cold Relief†; ***Ger.:*** Cardibisana†; Cefadrin.

Ephedrine *(BAN)* ⊗

Efedriini; Efedrin; Efedrina; Efedrinas; Ephedrina; Éphédrine; (−)-Ephedrine; Ephedrinum. (1*R*,2*S*)-2-Methylamino-1-phenylpropan-1-ol.

Эфедрин

$C_{10}H_{15}NO$ = 165.2.

CAS — 299-42-3 (anhydrous ephedrine); 50906-05-3 (ephedrine hemihydrate).

ATC — R01AA03; R01AB05; R03CA02; S01FB02.

ATC Vet — QG04BX90; QR01AA03; QR01AB05; QR03CA02; QS01FB02.

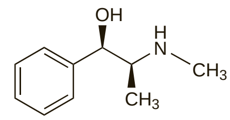

Description. Ephedrine is an alkaloid obtained from species of *Ephedra*, or prepared synthetically. It may exist in a hemihydrate form or as the anhydrous substance.

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of ephedrine:

Trucker's Speed.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*, which have specifications, in either the same monograph or in separate monographs, for the anhydrous form and for the hemihydrate.

Ph. Eur. 6.2 (Ephedrine, Anhydrous). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 36°. Protect from light.

Ph. Eur. 6.2 (Ephedrine Hemihydrate; Ephedrine BP 2008). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 42°, determined without previous drying. Protect from light.

USP 31 (Ephedrine). It is anhydrous or contains not more than one-half molecule of water of hydration. It is an unctuous, practically colourless solid or white crystals or granules. It gradually decomposes on exposure to light. M.p. between 33° and 40°, the variability being the result of differences in the moisture content, anhydrous ephedrine having a lower melting-point than the hemihydrate. Soluble 1 in 20 of water and 1 in 0.2 of alcohol; soluble in chloroform and in ether; moderately and slowly soluble in liquid paraffin, the solution becoming turbid if the ephedrine contains more than about 1% of water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Ephedrine Hydrochloride *(BANM)* ⊗

Efedriinihydrokloridi; Efedrin Hidroklorür; Efedrin hydrochlorid; Efedrina, hidrocloruro de; Efedrin-hidroklorid; Efedrinhydroklorid; Efedrino hidrochloridas; Efedryny chlorowodorek; Ephedrinae Hydrochloridum; Éphédrine, chlorhydrate d'; Ephedrine Chloride; Ephedrini hydrochloridum; Ephedrinium Chloratum; *l*-Ephedrinum Hydrochloricum.

Эфедрина Гидрохлорид

$C_{10}H_{15}NO,HCl$ = 201.7.

CAS — 50-98-6.

ATC — R01AA03; R01AB05; R03CA02; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Ephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. It melts at about 219°. Protect from light.

USP 31 (Ephedrine Hydrochloride). Fine, white, odourless crystals or powder. Soluble 1 in 3 of water and 1 in 14 of alcohol; insoluble in ether. Protect from light.

Ephedrine Sulfate ⊗

Efedrina, sulfato de; Ephedrine Sulphate *(BANM)*.

Эфедрина Сульфат

$(C_{10}H_{15}NO)_2,H_2SO_4$ = 428.5.

CAS — 134-72-5.

ATC — R01AA03; R01AB05; R03CA02; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Ephedrine Sulfate). Fine, white, odourless crystals or powder. It darkens on exposure to light. Soluble 1 in 1.3 of water and 1 in 90 of alcohol. Protect from light.

Racephedrine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Efedriinihydrokloridi, raseeminen; Efedrinhydroklorid, racemisk; Efedrino (raceminio) hidrochloridas; Éphédrine (chlorhydrate d') racémique; *dl*-Ephedrine Hydrochloride; Ephedrini racemici hydrochloridum; *dl*-Ephedrinium Chloride; Hidrocloruro de racefedrina; Racém efedrin-hidroklorid; Racemic Ephedrine Hydrochloride; Racéphédrine, Chlorhydrate de; Racephedrini Hydrochloridum. (±)-2-Methylamino-1-phenylpropan-1-ol hydrochloride.

Рацефедрина Гидрохлорид

$C_{10}H_{15}NO,HCl$ = 201.7.

CAS — 90-81-3 (racephedrine); 134-71-4 (racephedrine hydrochloride).

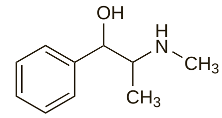

(racephedrine)

Pharmacopoeias. In *Eur.*

Ph. Eur. 6.2 (Ephedrine Hydrochloride, Racemic; Racephedrine Hydrochloride BP 2008). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in ether. It melts at about 188°. Protect from light.

Adverse Effects

As for Sympathomimetics, p.1407. Ephedrine has both alpha- and beta-agonist effects and its commonest adverse effects are tachycardia, anxiety, restlessness, and insomnia. Tremor, dry mouth, impaired circulation to the extremities, hypertension, and cardiac arrhythmias may also occur.

Ephedrine may be used in labour to maintain blood pressure during spinal anaesthesia but can cause fetal tachycardia.

Paranoid psychosis, delusions, and hallucinations may also follow ephedrine overdosage. Prolonged use has no cumulative effect, but tolerance with dependence has been reported.

◊ For a discussion of the toxicity reported from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, see Abuse, below.

Precautions

As for Sympathomimetics, p.1407. Ephedrine should be given with care to patients with hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, renal impairment, or angle-closure glaucoma. In patients with prostatic enlargement, ephedrine may increase difficulty with micturition.

Irritability and disturbed sleep have been reported in breast-fed infants.

Abuse. Although illicit use of ephedrine is primarily in the manufacture of street stimulants such as metamfetamine (p.2158), there is increasing evidence of the abuse of ephedrine preparations in some countries,[1] and the public health and social problems associated with its abuse appear to be significant, particularly in certain African countries. Ephedrine is also sold as a street substitute for 'Ecstasy' (Methylenedioxymethamfetamine, p.2159).

Adverse effects reported with illicit ephedrine use include cardiovascular toxicity[2,3] and chest pain.[4]

There is controversy over the abuse liability of over-the-counter (OTC) stimulants such as ephedrine:[5] some studies have indicated that ephedrine is, overall, a relatively weak reinforcer whereas others have suggested that the abuse potential may be high. Examination of the characteristics of 5 patients who had been taking ephedrine-containing OTC preparations in high doses for periods ranging from 8 months to 2 years, emphasised the reinforcing and, therefore, addictive potential of ephedrine; similar observations were made for 2 patients who had ingested phenylpropanolamine long term, combined with pseudoephedrine in one of these cases. The authors suggested that, for most people, OTC preparations containing weaker sympathomimetics will not be reinforcing at the recommended doses. However, these cases strengthen the research findings that high-dose use of an OTC stimulant increases its potency, and thus its effects become more like amfetamine (p.2150).

Toxicity has also been reported[6-8] from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, usually based on ephedra (ma-huang) and marketed for a variety of purposes including weight loss and as an alternative to illegal drugs of abuse. Not all cases of ephedrine toxicity have arisen as a result of overt abuse but rather because of inadequate labelling of content and dosage instructions on some unlicensed products. A small study found that combinations of herbal caffeine and ephedra alkaloids taken in recommended amounts resulted in plasma ephedrine concentrations that exceeded the usual therapeutic range. Significant increases occurred in blood pressure and heart rate, and unfavourable effects on glucose and potassium homoeostasis were noted.[9] The use of ephedra-containing dietary supplements is now banned in the USA and some other countries.

Adverse effects from ingestion of ephedrine-containing OTC preparations, including herbal products (usually in high doses and/or long term) have included coronary artery thrombosis,[10] myocardial infarction, seizures,[11] psychotic reactions,[12] nephrolithiasis,[13-15] and myocarditis;[16] a number of fatalities have been reported. Frank dependence has been reported in female weight-lifters following long-term use of high doses.[17]

For a report of urinary calculi developing in a patient who had ingested a preparation containing guaifenesin and ephedrine, see Abuse, under Guaifenesin, p.1561.

1. WHO. Recommendations from the Expert Committee on Drug Dependence. *WHO Drug Inf* 1998; **12:** 227–9.
2. Cockings JGL, Brown MA. Ephedrine abuse causing acute myocardial infarction. *Med J Aust* 1997; **167:** 199–200.
3. Zahn KA, *et al.* Cardiovascular toxicity after ingestion of "herbal ecstacy" [sic]. *J Emerg Med* 1999; **17:** 289–91.
4. James LP, *et al.* Sympathomimetic drug use in adolescents presenting to a pediatric emergency department with chest pain. *J Toxicol Clin Toxicol* 1998; **36:** 321–8.
5. Tinsley JA, Watkins DD. Over-the-counter stimulants: abuse and addiction. *Mayo Clin Proc* 1998; **73:** 977–82.
6. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; **343:** 1833–8.
7. Dennehy CE, *et al.* Dietary supplement-related adverse events reported to the California Poison Control System. *Am J Health-Syst Pharm* 2005; **62:** 1476–82.
8. Samenuk D, *et al.* Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002; **77:** 12–16.
9. Haller CA, *et al.* Short-term metabolic and hemodynamic effects of ephedra and guarana combinations. *Clin Pharmacol Ther* 2005; **77:** 560–71.
10. Sola S, *et al.* Coronary dissection and thrombosis after ingestion of ephedra. *Am J Med* 2004; **116:** 645–6.
11. Anonymous. Adverse events associated with ephedrine-containing products—Texas, December 1993-September 1995. *JAMA* 1996; **276:** 1711–12.
12. Doyle H, Kargin M. Herbal stimulant containing ephedrine has also caused psychosis. *BMJ* 1996; **313:** 756.
13. Powell T, *et al.* Ma-huang strikes again: ephedrine nephrolithiasis. *Am J Kidney Dis* 1998; **32:** 153–9.
14. Blau JJ. Ephedrine nephrolithiasis associated with chronic ephedrine abuse. *J Urol (Baltimore)* 1998; **160:** 825.
15. Hoffman N, *et al.* Resolution of ephedrine stones with dissolution therapy. *Urology* 2003; **61:** 1035.
16. Zaacks SM, *et al.* Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol* 1999; **37:** 485–9.
17. Gruber AJ, Pope HG. Ephedrine abuse among 36 female weightlifters. *Am J Addict* 1998; **7:** 256–61.

Interactions

As for Sympathomimetics, p.1407. Ephedrine has direct and indirect actions and may cause a hypertensive crisis in patients receiving an MAOI (including a RIMA); the possibility of such an interaction after intranasal use of ephedrine should also be borne in mind. See also under Phenelzine (p.418) and Moclobemide (p.411). Since ephedrine has both alpha- and beta-agonist properties it should be avoided or used with care in patients undergoing anaesthesia with cyclopropane, halothane, or other volatile anaesthetics. An increased risk of arrhythmias may occur if given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants, and there is an increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids or oxytocin. The rate of metabolism of some other drugs is increased by ephedrine. For mention of the potential additive stimulant effects seen with caffeine and ephedrine, see Sympathomimetics, under Caffeine, p.1118.

Pharmacokinetics

Ephedrine is readily and completely absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine, with small amounts of metabolites produced by hepatic metabolism. Ephedrine has been variously reported to have a plasma half-life ranging from 3 to 6 hours depending on urinary pH; elimination is enhanced and half-life accordingly shorter in acid urine.

◊ References.

1. Welling PG, *et al.* Urinary excretion of ephedrine in man without pH control following oral administration of three commercial ephedrine sulfate preparations. *J Pharm Sci* 1971; **60:** 1629–34.
2. Sever PS, *et al.* The metabolism of (–)-ephedrine in man. *Eur J Clin Pharmacol* 1975; **9:** 193–8.
3. Pickup ME, *et al.* The pharmacokinetics of ephedrine after oral dosage in asthmatics receiving acute and chronic treatment. *Br J Clin Pharmacol* 1976; **3:** 123–34.

Uses and Administration

Ephedrine is a sympathomimetic (p.1408) with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity and has pronounced stimulating effects on the CNS. It has a more prolonged though less potent action than adrenaline. In therapeutic doses it raises the blood pressure by increasing cardiac output and also by inducing peripheral vasoconstriction. Tachycardia may occur but is less frequent than with adrenaline. Ephedrine also causes bronchodilatation, reduces intestinal tone and motility, relaxes the bladder wall while contracting the sphincter muscle but relaxes the detrusor muscle of the bladder and usually reduces the activity of the uterus. It has a stimulant action on the respiratory centre. It dilates the pupil but does not affect the light reflexes. After ephedrine has been used for a short while, tachyphylaxis may develop.

Ephedrine salts are used, either alone or in combination preparations, in the symptomatic relief of nasal congestion (p.1548). They may be given orally, or topically as nasal drops or sprays. Ephedrine salts have sometimes been used in motion sickness in combination preparations with hyoscine or an antihistamine and have been tried for postoperative nausea and vomiting (p.1700).

Ephedrine salts have been given parenterally to combat a fall in blood pressure during spinal or epidural anaesthesia. Ephedrine is of little value in hypotensive crises due to shock, circulatory collapse, or haemorrhage. It is no longer generally advocated for orthostatic hypotension.

Ephedrine salts have been used as bronchodilators, but the more $beta_2$-selective sympathomimetics, such as salbutamol, are now preferred.

Other uses of ephedrine salts include diabetic neuropathic oedema, in which they may provide marked relief. They have also been used in micturition disorders.

Nasal drops or sprays usually containing ephedrine 0.5 or 1% are used in the treatment of **nasal congestion**. Ephedrine salts have also been given by oral inhalation.

To reverse **hypotension** induced by spinal or epidural anaesthesia, a solution containing ephedrine hydrochloride 3 mg/mL is given by slow intravenous injection in doses of 3 to 6 mg (or at most 9 mg) repeated every 3 to 4 minutes as required; the maximum total dose is 30 mg. Ephedrine salts have also been given by intramuscular or subcutaneous injection.

The *BNF* suggests an oral dose of 30 to 60 mg of ephedrine hydrochloride three times daily in the treatment of **diabetic neuropathic oedema**.

Several other salts of ephedrine have been given including the camsilate, the levulinate, and the tannate. Racephedrine hydrochloride has also been used.

For children's doses, see Administration in Children, below.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including ephedrine) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547). However, the *BNFC* suggests that, in certain circumstances, specialists may prescribe ephedrine nasal drops for children under 2 years in the short-term treatment of severe **nasal congestion** that has not responded to sodium chloride nasal drops or inhalation of warm moist air. Nasal drops or sprays containing ephedrine hydrochloride 0.5% are licensed to treat nasal congestion in young children over 3 months of age. Although not licensed for such use, the *BNFC* recommends a strength of 0.25% for use in children aged 1 to 3 months.

Ephedrine is rarely needed in children for reversal of **hypotension** induced by spinal or epidural anaesthesia, but if it is used the *BNFC* suggests the following doses of a solution containing ephedrine hydrochloride 3 mg/mL, given by slow intravenous injection via a central line:

- 1 to 12 years: 500 to 750 micrograms/kg or 17 to 25 mg/m^2 every 3 to 4 minutes according to response up to a maximum total dose of 30 mg
- 12 to 18 years: 3 to 7.5 mg (maximum 9 mg) repeated every 3 to 4 minutes according to response up to a maximum total dose of 30 mg

Micturition disorders. Ephedrine salts have been used in nocturnal enuresis, although other treatments are usually preferred, and have been tried in patients with stress incontinence but the value of such treatment is not clear.

Spinal anaesthesia. Parenteral sympathomimetics such as ephedrine and phenylephrine have been advocated for the correction of hypotension associated with local anaesthesia. The risk of hypotension with spinal or epidural block is greater than many other forms of nerve block (see Adverse Effects of Central Block, p.1850). Ephedrine has been used[1,2] although not always successfully[3] for the correction of such hypotension. It has also been used prophylactically,[4,5] although prophylactic use during labour has been associated with fetal tachycardia,[5] and adequate hydration of the patient beforehand is more important in minimising hypotension.

1. Hall PA, *et al.* Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. *Br J Anaesth* 1994; **73:** 471–4.
2. Thomas DG, *et al.* Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. *Br J Anaesth* 1996; **76:** 61–5.
3. Critchley LAH, *et al.* Hypotension during subarachnoid anaesthesia: haemodynamic effects of ephedrine. *Br J Anaesth* 1995; **74:** 373–8.
4. Sternlo J-E, *et al.* Prophylactic im ephedrine in bupivacaine spinal anaesthesia. *Br J Anaesth* 1995; **74:** 517–20.
5. Cleary-Goldman J, *et al.* Prophylactic ephedrine and combined spinal epidural: maternal blood pressure and fetal heart rate patterns. *Obstet Gynecol* 2005; **106:** 466–72.

Preparations

BP 2008: Ephedrine Elixir; Ephedrine Hydrochloride Tablets; Ephedrine Nasal Drops;
USP 31: Ephedrine Sulfate Capsules; Ephedrine Sulfate Injection; Ephedrine Sulfate Nasal Solution; Ephedrine Sulfate Syrup; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Muchan; ***Belg.:*** Ephedronguent; ***Braz.:*** Unifedrine; ***Chile:*** Efedrosan; ***Gr.:*** Neo Rhinovit; Rhinolex; ***Hung.:*** Epherit; ***Mex.:*** Tendrin; ***Pol.:*** Efrinol; ***Port.:*** Spinefe; ***Turk.:*** Rinitalmit; ***UK:*** CAM; ***USA:*** Kondon's Nasal; ***Venez.:*** Boref†; Colirio Iris.

Multi-ingredient: Numerous preparations are listed in Part 3.

Eprazinone Hydrochloride *(rINNM)*

CE-746; Éprazinone, Chlorhydrate d'; Eprazinoni Hydrochloridum; Hidrocloruro de eprazinona. 3-[4-(β-Ethoxyphenethyl)piperazin-1-yl]-2-methylpropiophenone dihydrochloride.

Эпразинона Гидрохлорид

$C_{24}H_{32}N_2O_2,2HCl = 453.4.$

CAS — 10402-90-1 (eprazinone); 10402-53-6 (eprazinone hydrochloride).

ATC — R05CB04.

ATC Vet — QR05CB04.

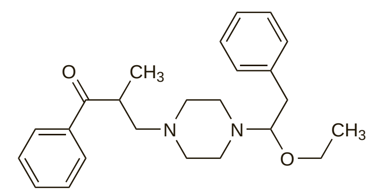

(eprazinone)

Profile

Eprazinone hydrochloride has been variously described as having mucolytic or expectorant properties (p.1547) as well as a direct relaxant action on bronchial smooth muscle. It is given in oral doses of 50 to 100 mg three times daily. It has also been given rectally.

Effects on the skin. Skin eruptions have been associated with the oral use of eprazinone.[1,2]

1. Faber M, *et al.* Eprazinonexanthem mit subkornealer Pustelbildung. *Hautarzt* 1984; **35:** 200–3.
2. Tanabe K, *et al.* Non-pigmented fixed drug eruption induced by eprazinone hydrochloride. *Dermatol Online J* 2005; **11:** 25.

Overdosage. Symptoms in two 22-month-old children who received an overdose of 800 mg of eprazinone included somnolence, ataxia, and seizures.[1]

1. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitutés de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Eftapan; ***Belg.:*** Isilung; ***Ger.:*** Eftapan.

Multi-ingredient: ***Austria:*** Eftapan Tetra.

Eprozinol Hydrochloride *(rINNM)*

Éprozinol, Chlorhydrate d'; Eprozinoli Hydrochloridum; Hidrocloruro de eprozinol. 3-[4-(β-Methoxyphenethyl)piperazin-1-yl]-1-phenylpropan-1-ol dihydrochloride.

Эпрозинола Гидрохлорид

$C_{22}H_{30}N_2O_2,2HCl$ = 427.4.

CAS — 32665-36-4 (eprozinol).

ATC — R03DX02.

ATC Vet — QR03DX02.

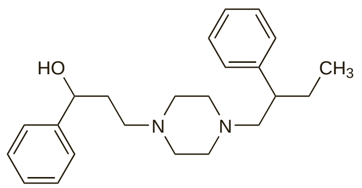

(eprozinol)

Profile

Eprozinol hydrochloride has been given orally for its mucolytic or expectorant properties.

Adverse effects. Convulsions and coma were reported in a 19-year-old patient after taking eprozinol.[1]

1. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Eupneron†.

Erdosteine *(rINN)*

Erdosteiini; Erdostein; Erdosteína; Erdostéine; Erdosteinum. (±)-({[(Tetrahydro-2-oxo-3-thienyl)carbamoyl]methyl}thio)acetic acid.

Эрдостеин

$C_8H_{11}NO_4S_2$ = 249.3.

CAS — 84611-23-4.

ATC — R05CB15.

ATC Vet — QR05CB15.

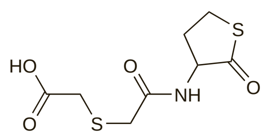

Adverse Effects and Precautions

Gastrointestinal disturbances may occur with erdosteine. Headache, dyspnoea, taste alterations, urticaria, erythema, and dermatitis have been reported rarely. Licensed product information for erdosteine suggests that it should not be used in patients with active peptic ulcer disease.

Pharmacokinetics

Erdosteine is rapidly absorbed after oral use; absorption is unaffected by food. Peak plasma concentrations are reached after about an hour. Erdosteine undergoes first-pass metabolism to an active metabolite, *N*-thiodiglycolyl-homocysteine. Plasma protein binding is about 64.5%. The elimination half-life is about 1.46 hours for erdosteine, and about 1.62 hours for the metabolite. Excretion is mainly via the urine, as metabolites; faecal elimination is negligible.

Uses and Administration

Erdosteine is a mucolytic that is used in the treatment of disorders of the respiratory tract characterised by productive cough (p.1547). It is given in usual oral doses of 300 mg twice daily for a maximum of 10 days.

Administration in hepatic and renal impairment. Exposure to erdosteine is increased in patients with hepatic impairment. UK licensed product information states that no increase in adverse effects has been observed in patients with mild liver failure, but restricts the dose in these patients to a maximum of 300 mg daily by mouth. Erdosteine is contra-indicated in severe hepatic impairment.

Although no difference in absorption or elimination has been seen in patients with moderate renal impairment, the risk of accumulation of metabolites cannot be excluded. For this reason, use of erdosteine is contra-indicated in patients with a creatinine clearance of less than 25 mL/minute.

Chronic obstructive pulmonary disease. Erdosteine has been used[1-3] in the management of chronic obstructive pulmonary disease (p.1112) but the value of mucolytics in this disorder is controversial.

1. Dechant KL, Noble S. Erdosteine. *Drugs* 1996; **52:** 875–81.
2. Marchioni CF, *et al.* Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study). *Int J Clin Pharmacol Ther* 1995; **33:** 612–18.
3. Moretti M, *et al.* The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: the EQUALIFE Study. *Drugs Exp Clin Res* 2004; **30:** 143–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Amuctol†; Fluidasa; ***Austria:*** Erdomed; ***Belg.:*** Mucothera†; ***Braz.:*** Erdotin†; Flusten; ***Chile:*** Biopulmin; ***Cz.:*** Erdomed; ***Denm.:*** Erdotin; ***Fin.:*** Erdopect; ***Fr.:*** Edirel†; Vectrine; ***Gr.:*** Theovix; Tusselin; ***Hung.:*** Erdomed; ***Indon.:*** Vectrine; ***Ital.:*** Erdotin; ***Mex.:*** Dostein; Esteclin; ***Philipp.:*** Ectrin; ***Port.:*** Erdotin; ***Switz.:*** Mucofor; ***Turk.:*** Erdostin; ***UK:*** Erdotin.

Multi-ingredient: ***Mex.:*** Esteclin Bac.

Eriodictyon

Hierba santa; Mountain Balm; Yerba Santa.

Эриодиктион калифорнийский

CAS — 8013-08-9.

Profile

Eriodictyon consists of the dried leaves of *Eriodictyon californicum* (Hydrophyllaceae). It has been used as an expectorant. It has also been used in the treatment of dry mouth and to mask the taste of bitter drugs.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Mouth Kote; ***Hong Kong:*** Pretz†.

Multi-ingredient: ***Ital.:*** Broncosedina; ***UK:*** Saliva Natura; ***USA:*** Feminease; ***Venez.:*** Yerba Santa.

Etafedrine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Étafédrine, Chlorhydrate d'; Etafedrini Hydrochloridum; Ethylephedrine Hydrochloride; Hidrocloruro de etafedrina. (−)-2-(Ethylmethylamino)-1-phenylpropan-1-ol hydrochloride.

Этафедрина Гидрохлорид

$C_{12}H_{19}NO,HCl$ = 229.7.

CAS — 7681-79-0 (etafedrine); 48141-64-6 ((−)-etafedrine); 5591-29-7 (etafedrine hydrochloride).

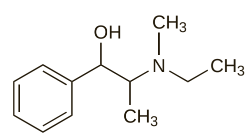

(etafedrine)

Profile

Etafedrine hydrochloride is a sympathomimetic related to ephedrine (p.1558). It is used for its bronchodilator effects in combination preparations for the relief of cough and associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Broncolex†; EMS Expectorante; Revenil; Revenil Dospan; Revenil Expectorante; ***Canad.:*** Dalmacol; ratio-Calmydone; ***Indon.:*** Decolsin; ***S.Afr.:*** Nethaprin Dospan; Nethaprin Expectorant; ***Thai.:*** Brondil.

Ethyl Cysteine Hydrochloride

Etilcisteína, hidrocloruro de. Ethyl L-2-amino-3-mercaptopropionate hydrochloride.

Этиловый Эфир Цистеина Гидрохлорида

$C_5H_{11}NO_2S,HCl$ = 185.7.

CAS — 3411-58-3 (ethyl cysteine); 868-59-7 (ethyl cysteine hydrochloride).

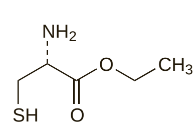

(ethyl cysteine)

Pharmacopoeias. In *Jpn.*

Profile

Ethyl cysteine hydrochloride is a mucolytic that has been used in the treatment of disorders of the respiratory tract associated with productive cough.

Ethyl Orthoformate

Ether de Kay; Triethoxymethane; Trietoximetano. Triethyl orthoformate.

Этиловый Эфир Ортомуравьиной Кислоты

$C_7H_{16}O_3$ = 148.2.

CAS — 122-51-0.

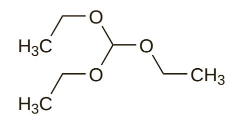

Pharmacopoeias. In *Fr.*

Profile

Ethyl orthoformate is a cough suppressant (see p.1547). It is reported to be a respiratory antispasmodic and has been given by mouth or rectally.

Fedrilate *(rINN)*

Fédrilate; Fedrilato; Fedrilatum; UCB-3928. 1-Methyl-3-morpholinopropyl perhydro-4-phenylpyran-4-carboxylate.

Федрилат

$C_{20}H_{29}NO_4$ = 347.4.

CAS — 23271-74-1.

ATC — R05DB14.

ATC Vet — QR05DB14.

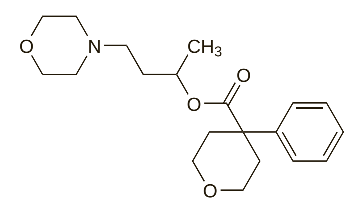

Profile

Fedrilate is a cough suppressant used orally for non-productive cough.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Gotas Binelli.

Fenoxazoline Hydrochloride *(rINNM)* ⊗

Fénoxazoline, Chlorhydrate de; Fenoxazolini Hydrochloridum; Hidrocloruro de fenoxazolina. 2-(2-Isopropylphenoxymethyl)-2-imidazoline hydrochloride.

Феноксазолина Гидрохлорид

$C_{13}H_{18}N_2O,HCl$ = 254.8.

CAS — 4846-91-7 (fenoxazoline); 21370-21-8 (fenoxazoline hydrochloride).

ATC — R01AA12.

ATC Vet — QR01AA12.

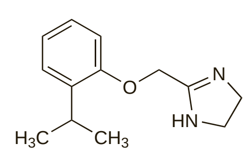

(fenoxazoline)

Profile

Fenoxazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p.1565) that has been used topically for its vasoconstrictor properties in the symptomatic treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nebulicina; ***Braz.:*** Aturgyl†; Nasofelin.

Fominoben Hydrochloride *(rINNM)*

Fominobène, Chlorhydrate de; Fominobeni Hydrochloridum; Hidrocloruro de fominobén; PB-89. 3′-Chloro-2′-[*N*-methyl-*N*-(morpholinocarbonylmethyl)aminomethyl]benzanilide hydrochloride.

Фоминобена Гидрохлорид

$C_{21}H_{24}ClN_3O_3,HCl$ = 438.3.

CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben hydrochloride).

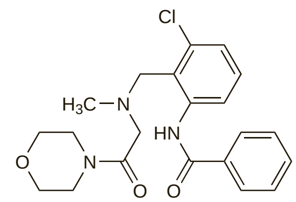

(fominoben)

Profile

Fominoben hydrochloride is a centrally acting cough suppressant (see p.1547) that is also reported to have respiratory stimulant properties. It is given in oral doses of 160 mg up to three times daily; it has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Noleptan; ***Mex.:*** Noleptan; ***Spain:*** Tosifar.

Fudosteine *(rINN)*

Fudosteína; Fudostéine; Fudosteinum; SS-320A. (−)-3-[(3-Hydroxypropyl)thio]-L-alanine.

Фудостеин

$C_6H_{13}NO_3S$ = 179.2.

CAS — 13189-98-5.

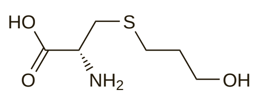

Profile

Fudosteine is an expectorant given orally in a dose of 400 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cleanal.

Glaucine

Boldine Dimethyl Ether; DL-832 (*dl*-glaucine phosphate); Glaucina; *dl*-Glaucine; MDL-832 (*dl*-glaucine phosphate). DL-1,2,9,10-Tetramethoxyaporphine.

Глауцин

$C_{21}H_{25}NO_4$ = 355.4.

CAS — 5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glaucine hydrobromide).

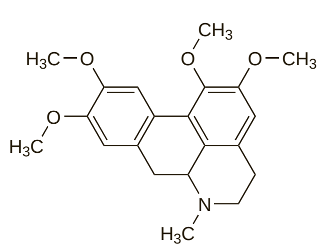

(dl-glaucine)

Profile

Glaucine is a centrally acting cough suppressant used in non-productive cough (p.1547); it has been given as the phosphate.

d-Glaucine has also been used, as the hydrobromide and the hydrochloride. It has been obtained from *Glaucium flavum* (Papaveraceae).

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Glauvent (Глаувент)†.

Multi-ingredient: ***Rus.:*** Bronchitussin (Бронхитусен); Bronchocin (Бронхоцин); Broncholytin (Бронхолитин).

Guacetisal *(rINN)*

Acetylsalicylic Acid Guaiacol Ester; Guacétisal; Guacetisalum. *o*-Methoxyphenyl salicylate acetate.

Гуацетисал

$C_{16}H_{14}O_5$ = 286.3.

CAS — 55482-89-8.
ATC — N02BA14.
ATC Vet — QN02BA14.

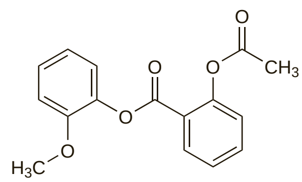

Profile

Guacetisal has been used in respiratory disorders as an expectorant (see p.1547). It has also been used as an antipyretic to reduce fever (p.10). It has been given by mouth and rectally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Prontomucil.

Guaiacol

Gaïacol; Guaiacolum; Guajacol; Guayacol; Gwajakol; Methyl Catechol. 2-Methoxyphenol.

Гваякол

$C_7H_8O_2$ = 124.1.

CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbonate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-4 (guaiacol phenylacetate).

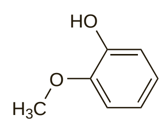

Pharmacopoeias. In *Eur.* (see p.vii). *Fr.* also includes guaiacol carbonate.

Ph. Eur. 6.2 (Guaiacol). A crystalline mass or colourless or yellowish hygroscopic liquid. Sparingly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Guaiacol has disinfectant properties and has been used in dentistry and as an expectorant for productive cough (p.1547).

In high concentrations, adverse effects are similar to, but less severe than, those of phenol (p.1656).

A wide range of salts and derivatives of guaiacol have been used similarly including the carbonate, cinnamate, ethylglycolate, calcium and sodium glycolates, phenylacetate, and phenylbutyrate. See also Guaifenesin, p.1561 and Sulfogaiacol, p.1573.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Eucaliptine.

Multi-ingredient: ***Arg.:*** Aseptobron; Atomo Desinflamante; Atomo Desinflamante Familiar; ***Belg.:*** Eucalyptine; Eucalyptine Pholcodine; Inopectol; ***Braz.:*** Canfomenol†; Egotussano†; Ozonyl; Transpulmin; Transpulmin Balsamo; Tripulmin Balsamico†; ***Canad.:*** Creo-Rectal; Demo-Cineol; Omni-Tuss†; Valda; ***Cz.:*** Biocalyptol S†; ***Fr.:*** Bronchorectine au Citral; Essence Algerienne; Pulmo Bailly; Pulmoserum; Valda; ***Ger.:*** Dalet Med Balsam†; ***Gr.:*** Gulamyl; ***Hong Kong:*** Biocalyptol†; Valda†; ***Irl.:*** Valda†; ***Ital.:*** Eugenol-Guaiacolo Composto; Fosfoguaiacol; Lactocol; Lipobalsamo; ***Mex.:*** Eucalin†; Guayalin; Guayalin-Plus†; ***Port.:*** Algina; Analgil; Valda†; ***Spain:*** Bronco Aseptilex Fuerte; Eucalyptospirine†; Tos Mai; ***UK:*** Dragon Balm; Pulmo Bailly; ***USA:*** Methagual; ***Venez.:*** Derpinol†.

Guaietolin *(rINN)*

Glycerylguethol; Glyguetol; Guaietolina; Guaïétoline; Guaietolinum; Guayetolina. 3-(2-Ethoxyphenoxy)propane-1,2-diol.

Гвайэтолин

$C_{11}H_{16}O_4$ = 212.2.

CAS — 63834-83-3.

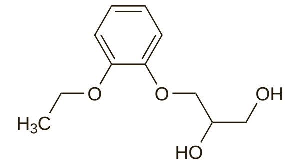

Profile

Guaietolin is an analogue of guaifenesin which is used as an expectorant (see p.1547). It has been given in oral doses of 300 to 600 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Guethural.

Guaifenesin *(BAN, USAN, rINN)*

Glyceryl Guaiacolate; Glycerylguayacolum; Guaiacol Glycerol Ether; Guaiacyl Glyceryl Ether; Guaifenesiini; Guaifenesina; Guaïfénésine; Guaifénésine; Guaifenesinum; Guaiphenesin; Guajacolum Glycerolatum; Gvajfenezin; Gvajfenezinas. (*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol.

Гвайфенезин

$C_{10}H_{14}O_4$ = 198.2.

CAS — 93-14-1.
ATC — R05CA03.
ATC Vet — QM03BX90; QR05CA03.

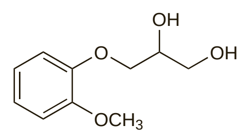

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Guaifenesin). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol.

USP 31 (Guaifenesin). A white to slightly grey crystalline powder. May have a slight characteristic odour. Soluble 1 in 60 to 70 of water; soluble in alcohol, in chloroform, and in propylene glycol; sparingly soluble in glycerol. Store in airtight containers.

Adverse Effects and Precautions

Gastrointestinal discomfort, nausea, and vomiting have occasionally been reported with guaifenesin, particularly in very large doses.

Abuse. Urinary calculi have been reported in patients consuming large quantities of over-the-counter preparations containing guaifenesin.[1,2] Spectroscopic analysis[1] revealed that the stones were composed of a calcium salt of beta-(2-methoxyphenoxy)-lactic acid, which is a metabolite of guaifenesin. Small quantities of ephedrine were also present in the stones of one of several patients who had ingested preparations containing a combination of guaifenesin and ephedrine.[2]

1. Pickens CL, *et al.* Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. *Urology* 1999; **54:** 23–7.
2. Assimos DG, *et al.* Guaifenesin- and ephedrine-induced stones. *J Endourol* 1999; **13:** 665–7.

Porphyria. Guaifenesin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pharmacokinetics

Guaifenesin is well absorbed from the gastrointestinal tract. It is metabolised and then excreted in the urine.

Uses and Administration

Guaifenesin is reported to increase the volume and reduce the viscosity of tenacious sputum and is used as an expectorant for productive cough. It is given in oral doses of 200 to 400 mg every 4 hours. Modified-release preparations, given every 12 hours, are also available. For doses in children see Administration in Children, below.

Guaifenesin has been used similarly as the calcium salt.

Guaifenesin is used as an adjunct to anaesthesia in veterinary medicine.

Administration in children. Guaifenesin is licensed for use as an expectorant in children; however, over-the-counter cough and cold preparations containing expectorants (including guaifenesin) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547). Typical licensed oral doses, given every 4 hours, are:

- 6 months to 2 years, 25 to 50 mg
- 2 to 6 years, 50 to 100 mg
- 6 to 12 years, 100 to 200 mg

UK preparations suggest that these doses be given up to a maximum of 4 times daily, although in other countries higher total doses may be given.

Respiratory disorders. An FDA review of preparations available over-the-counter concluded that guaifenesin was an effective expectorant.[1] The use of expectorants for productive cough is discussed on p.1547. A small study[2] found that guaifenesin also appeared to reduce cough reflex sensitivity in patients with upper respiratory-tract infections, which produce a transient increase in sensitivity, although it had no effect on cough reflex in healthy subjects. The mechanism for this effect was unclear.

Guaifenesin has been given to patients with altered nasal mucociliary clearance associated with HIV infection.[3]

1. Thomas J. Guaiphenesin—an old drug now found to be effective. *Aust J Pharm* 1990; **71:** 101–3.
2. Dicpinigaitis PV, Gayle YE. Effect of guaifenesin on cough reflex sensitivity. *Chest* 2003; **124:** 2178–81.
3. Rosen EJ, Calhoun KH. Alterations of nasal mucociliary clearance in association with HIV infection and the effect of guaifenesin therapy. *Laryngoscope* 2005; **115:** 27–30.

Preparations

USP 31: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Guaifenesin and Codeine Phosphate Syrup; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin Capsules; Guaifenesin Syrup; Guaifenesin Tablets; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Guaifen; Omega 100 Bronquial; Plenum; Robitussin†; Vick 44 Exp; Vickmiel; ***Austral.:*** Actifed CC Chesty; Robitussin Chesty Cough; Robitussin EX; Strepsils Chesty Cough†; Vicks Cough Syrup for Chesty Coughs†; ***Austria:*** Resyl; Waldheim Husten; ***Belg.:*** Vicks Vaposyrup Expectorant; ***Braz.:*** Broncofenil; Dimetapp Expectorante; Transpulmin; Vick Xarope; ***Canad.:*** Balminil Expectorant; Benylin E; Bronchophan Expectorant; Cough Syrup Expectorant; Expectorant; Expectorant Cough Formula; Expectorant Cough Syrup†; Expectorant Syrup; Extra Strength Cough Syrup Expectorant†; Koffex Expectorant†; Robitussin; Sirop Expectorant†; Tussin Expectorant†; Vicks Chest Congestion Relief; ***Cz.:*** Coldrex Broncho; Guajacuran; Robitussin Expectorans; ***Fin.:*** Tintus; ***Fr.:*** Vicks Expectorant; ***Ger.:*** Fagusan; Wick Formel 44 Husten-Loser; ***Gr.:*** VP-Syrup†; ***Hong Kong:*** Breacol; Excough†; Gufensin; Mucolex; Robitussin Expectorant; Uni-Colex; ***Hung.:*** Relaxil-G; Robitussin Expectorans; Wick Formula 44 kopteto†; ***Indon.:*** Probat; ***Irl.:*** Benylin Childrens Chesty Coughs; Robitussin Chesty Cough; Tixylix Chesty Cough; ***Israel:*** Resyl; Robitussin; Vitussin; ***Ital.:*** Broncovanil; Resyl; Vicks Tosse Fluidificante; ***Malaysia:*** Fuston†; Robitussin Expectorant†; ***Mex.:*** Robitussin; Tukol; Vick 44 Exp; ***NZ:*** Actifed CC Chesty†; Lemsip Chesty Cough†; Robitussin EX; ***Philipp.:*** Bena; Benadryl Expectorant; Guais; Robitussin Expectorant; Suprekof; Transpulmin G; ***Pol.:*** Guajazyl; Robitussin Expectorans; ***Rus.:*** Novo-Passit (Ново-Пассит); Theraflu KV (Терафлю КВ); Tussin (Туссин); ***S.Afr.:*** Actospect; Benylin Wet Cough; Borstol Linctus; Chamberlains Cough Remedy Honey and Liquorice; Chamberlains Cough Remedy Peppermint; Dilinct Junior; Expelinct; Flemmi-Ped; Med-Lemon Cough Syrup; Vicks Acta Plus Expectorant; ***Singapore:*** Breacol; Cofen; Robitussin; ***Spain:*** Formulaexpec; Robitussin; Serraspec; ***Swed.:*** Resyl; ***Switz.:*** Bronchol; Nicobrevin N†; Resyl; Vicks Formule 44 Expectine; ***Thai.:*** Glycolate; Glyryl; Mulade; Robitussin; Tussa; ***Turk.:*** Vicks VapoSyrup; ***UK:*** Adult Chesty Cough Non Drowsy; Benylin Childrens Chesty Coughs; Boots Chesty Cough Syrup 1 Year Plus; CalCough Chesty; Expectorant Cough Syrup; Hill's Balsam Chesty Cough; Jackson's All Fours; Jackson's Bronchial Balsam; Robitussin for Chesty Coughs; Tixylix Chesty Cough; Venos for Kids; Vicks Cough Syrup for Chesty Coughs; Vicks Vaposyrup for Chesty Coughs; ***USA:*** Allfen; Anti-Tuss†; Buckleys Chest Congestion; Duratuss G†; Fenesin†; Ganidin NR; Glycotuss; Guaifenex G†; Guaifenex LA†; Guiatuss; Halotussin†; Humavent; Humibid Maximum Strength; Hytuss†; Liquibid; Mucinex; Muco-Fen†; Naldecon Senior EX; Organidin NR; Refenesen; Respa-GF†; Robitussin; Scot-Tussin Expectorant; Siltussin; Touro Ex†; Tusibron; Xpect; ***Venez.:*** Alivetos Pediatrico; Robitessin; Robitessin Kit Tos†.

Multi-ingredient: Numerous preparations are listed in Part 3.

Guaimesal *(rINN)*

Guaïmésal; Guaimesalum. (±)-2-(*o*-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-one.

Гваймесал

$C_{16}H_{14}O_5$ = 286.3.
CAS — 81674-79-5.

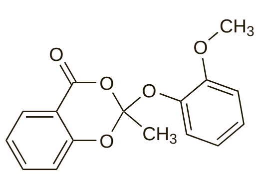

Profile

Guaimesal is reported to have expectorant and antipyretic properties and has been given orally as an adjunct in the treatment of respiratory-tract disorders. It has also been given rectally in suppositories.

Helicidine

Helicidina; Helixinum.

Гелицидин

Profile

Helicidine is a mucoglycoprotein from the snail *Helix pomatia* that has been used as a cough suppressant.

◊ References.

1. Pons F, *et al.* L'effect bronchorelaxant de l'helicidine, un extrait d'Helix pomatia, fait intervenir une liberation de prostaglandine E2. *Pathol Biol (Paris)* 1999; **47:** 73–80.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Original Schneckensirup†.

Indanazoline Hydrochloride *(rINNM)* ⊗

Hidrocloruro de indanazolina; Indanazolin Hidroklorür; Indanazoline, Chlorhydrate d'; Indanazolini Hydrochloridum.

Инданазолина Гидрохлорид

$C_{12}H_{15}N_3,HCl$ = 237.7.
CAS — 56601-85-5.

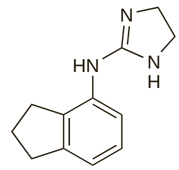

(indanazoline)

Profile

Indanazoline is a sympathomimetic with effects similar to those of naphazoline (p.1565). It has been used as the hydrochloride for its vasoconstrictor effect in the management of nasal congestion (p.1548). It has been given as nasal drops, a nasal gel, or a nasal spray in a concentration equivalent to indanazoline 0.1%.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Farial; ***Turk.:*** Farial.

Iodinated Glycerol *(BAN, USAN)*

Glicerol yodado; Iodopropylidene Glycerol.

Глицерин Йодированный

$C_6H_{11}IO_3$ = 258.1.
CAS — 5634-39-9.

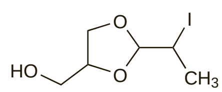

Profile

Iodinated glycerol, a methyl derivative of domiodol, is an isomeric mixture of iodinated dimers of glycerol. It has been used as an expectorant. The limitations of iodides as expectorants are discussed in Cough on p.1547. The actions of iodides and iodine compounds are discussed under Iodine p.2169. Prolonged use of iodinated glycerol has been associated with thyroid dysfunction (see Effects on the Thyroid Gland, below) and severe skin eruptions; gastrointestinal disturbances and hypersensitivity reactions have also occurred. Malignant neoplasms have developed in *animals* given iodinated glycerol.

Chronic obstructive pulmonary disease. Studies[1-3] of the use of iodinated glycerol in patients with chronic bronchitis have produced conflicting results. The use of mucolytics or expectorants in chronic obstructive pulmonary disease (p.1112) is controversial.

1. Petty TL. The National Mucolytic Study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990; **97:** 75–83.
2. Repsher LH. Treatment of stable chronic bronchitis with iodinated glycerol: a double-blind, placebo-controlled trial. *J Clin Pharmacol* 1993; **33:** 856–60.
3. Rubin BK, *et al.* Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996; **109:** 348–52.

Effects on the thyroid gland. Thyroid dysfunction (both hyperthyroidism and hypothyroidism) has developed after giving iodinated glycerol to previously euthyroid patients. It was recommended that baseline thyroid function tests should be carried out before starting treatment with iodinated glycerol;[1] it should be withdrawn if abnormal results are obtained during use.

1. Gittoes NJL, Franklyn JA. Drug-induced thyroid disorders. *Drug Safety* 1995; **13:** 46–55.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Iophen; Par Glycerol; R-Gen.

Ipecacuanha

Hlavěnkový kořen; Ipecac; Ipecacuana; Ipécacuanha, racine d'; Ipecacuanha Root; Ipecacuanhae radix; Ipekakuána-gyökér; Ipekakuananjuuri (ipecacuanha root); Ipekakuanarot (ipecacuanha root); Ipekakuanų šaknys; Korzeń ipekakuany; Raíz de ipecacuana.

Ипекакуана

CAS — 8012-96-2.
ATC — R05CA04; V03AB01.
ATC Vet — QR05CA04; QV03AB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Eur., *Jpn*, and *US* also include a monograph for Prepared Ipecacuanha or a similar standardised form.

Ph. Eur. 6.2 (Ipecacuanha Root; Ipecacuanha BP 2008). It consists of the fragmented and dried underground organs of *Cephaelis ipecacuanha* known as Matto Grosso ipecacuanha, or of *C. acuminata* known as Costa Rica ipecacuanha, or a mixture of both species. It contains not less than 2.0% of total alkaloids, calculated as emetine. It has a slight odour. Store in airtight containers. Protect from light.

The BP 2008 directs that when Ipecacuanha, Ipecacuanha Root, or Powdered Ipecacuanha is prescribed or demanded, Prepared Ipecacuanha shall be dispensed or supplied.

Ph. Eur. 6.2 (Ipecacuanha, Prepared; Ipecacuanhae Pulvis Normatus). It is ipecacuanha root powder adjusted to an alkaloidal content of 1.9 to 2.1% of total alkaloids, calculated as emetine. Store in airtight containers. Protect from light.

USP 31 (Ipecac). The dried rhizome and roots of *Cephaelis acuminata* or of *C. ipecacuanha* (Rubiaceae). It yields not less than 2% of ether-soluble alkaloids of which not less than 90% is emetine and cephaeline; the content of cephaeline varies from an amount equal to, to an amount not more than 2.5 times, that of emetine.

USP 31 (Powdered Ipecac). It contains 1.9 to 2.1% of ether-soluble alkaloids, with emetine and cephaeline content as for Ipecacuanha. It is pale brown, weak yellow, or light olive-grey powder that should be stored in airtight containers.

Adverse Effects

Large doses of ipecacuanha have an irritant effect on the gastrointestinal tract, and persistent bloody vomiting or bloody diarrhoea may occur. Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which is most likely if vomiting does not occur after emetic doses of ipecacuanha, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, combined with dehydration due to vomiting may cause vasomotor collapse followed by death.

There have been several reports of chronic abuse of ipecacuanha to induce vomiting in eating disorders; cardiotoxicity and myopathy have occurred and may be a result of accumulation of emetine.

There have also been several reports of ipecacuanha poisoning due to the unwitting substitution of Ipecac Fluidextract (a former USP preparation) for Ipecac Syrup (USP); the fluidextract was about 14 times the strength of the syrup.

◊ References.

1. Manno BR, Manno JE. Toxicology of ipecac: a review. *Clin Toxicol* 1977; **10:** 221–42.

Hypersensitivity. Allergy, characterised by rhinitis, conjunctivitis, and chest tightness, has occurred due to inhalation of ipecacuanha dust in packers of ipecacuanha tablets.[1]

1. Luczynska CM, *et al.* Occupational allergy due to inhalation of ipecacuanha dust. *Clin Allergy* 1984; **14:** 169–75.

Vomiting. Prolonged vomiting has been reported in 17% of patients given ipecacuanha in the treatment of poisoning and may lead to gastric rupture, Mallory-Weiss tears of the oesophagogastric junction, cerebrovascular events, and pneumomediastinum and pneumoperitoneum.[1]

1. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; **133:** (Dec.): 496–9.

Treatment of Adverse Effects

After acute overdose of ipecacuanha, activated charcoal is given to delay absorption followed if necessary by gastric lavage. Prolonged vomiting may be controlled by the injection of antiemetics. Fluid and electrolyte imbalance should be corrected and facilities should be available to correct any cardiac effects and subsequent shock.

When ipecacuanha is withdrawn after chronic abuse, recovery may be prolonged due to the slow elimination of emetine.

Precautions

The use of emetics is now rarely favoured; in particular, ipecacuanha should not be used as an emetic in patients who are unconscious or whose condition otherwise increases the risk of aspiration, nor in patients who have taken substances, such as corrosive compounds or petroleum products, that might be especially dangerous if aspirated. Ipecacuanha should not be given to patients in shock or to those at risk from seizures either as a result of their condition or from compounds, such as strychnine, that have been ingested. Patients with cardiovascular disorders are at risk if ipecacuanha is absorbed.

Abuse. Ipecac syrup has been abused by patients with eating disorders to induce vomiting.[1] Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations (the Mallory-Weiss syndrome) may be observed. Cardiotoxicity may occur and fatalities have been reported including one patient who had ingested 90 to 120 mL of ipecac syrup daily for 3 months.[2] It has been suggested that cardiac effects and myopathy following the prolonged abuse of ipecac syrup may be due to the long-term accumulation of emetine[3,4] but some have expressed doubts.[5]

Cardiomyopathy has also been reported in children given ipecacuanha to produce factitious illness (Munchausen's syndrome by proxy);[6-8] fatalities have occurred.

1. Harris RT. Bulimarexia and related serious eating disorders with medical complications. *Ann Intern Med* 1983; **99:** 800–7.
2. Adler AG, *et al.* Death resulting from ipecac syrup poisoning. *JAMA* 1980; **243:** 1927–8.
3. Palmer EP, Guay AT. Reversible myopathy secondary to abuse of ipecac in patients with major eating disorders. *N Engl J Med* 1985; **313:** 1457–9.
4. Pope HG, *et al.* The epidemiology of ipecac abuse. *N Engl J Med* 1986; **314:** 245–6.
5. Isner JM. Effects of ipecac on the heart. *N Engl J Med* 1986; **314:** 1253.
6. Goebel J, *et al.* Cardiomyopathy from ipecac administration in Munchausen syndrome by proxy. *Pediatrics* 1993; **92:** 601–3.
7. Schneider DJ, *et al.* Clinical and pathologic aspects of cardiomyopathy from ipecac administration in Munchausen's syndrome by proxy. *Pediatrics* 1996; **97:** 902–6.
8. Carter KE, *et al.* Munchausen syndrome by proxy caused by ipecac poisoning. *Pediatr Emerg Care* 2006; **22:** 655–6.

Interactions

The action of ipecacuanha may be delayed or diminished if it is given with or after charcoal; antiemetics may also reduce its effect.

Food. Milk had been believed to impair the emetic efficacy of ipecacuanha but there was no significant difference in the time to onset of vomiting, the duration of vomiting, or the number of episodes in 250 children who were given ipecac syrup with milk compared with 250 given ipecac syrup with clear fluids.[1]

1. Klein-Schwartz W, *et al.* The effect of milk on ipecac-induced emesis. *J Toxicol Clin Toxicol* 1991; **29:** 505–11.

Uses and Administration

Ipecacuanha has been used as an **expectorant** in productive cough (p.1547) in doses of up to about 1.4 mg of total alkaloids.

Ipecacuanha may also be used in larger doses as an **emetic** but is of very limited value (see Emesis Induction in Acute Poisoning, below). Vomiting usually occurs within 30 minutes of an oral emetic dose, due to an irritant effect on the gastrointestinal tract and a central action on the chemoreceptor trigger zone. Doses are usually followed by a copious drink of water or fruit juice. Adults have been given doses of about 21 to 42 mg of total alkaloids; each 5 mL of Ipecac Syrup (USP 31) supplies about 7 mg of total alkaloids. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred. For children's doses, see Administration in Children, below.

Homoeopathy. Ipecacuanha has been used in homoeopathic medicines under the following names: Ipeca; Cephaelis ipecacuanha; Ipecac.

Administration in children. Over-the-counter cough and cold preparations containing expectorants (including ipecacuanha) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

In the UK, induction of emesis with ipecacuanha is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration (see also Emesis Induction in Acute Poisoning, below).

In the USA, children aged 6 months to 1 year have been given about 7 to 14 mg of total alkaloids and older children about 21 mg. Each 5 mL of Ipecac Syrup (USP 31) supplies about 7 mg of total alkaloids. Doses are usually followed by a copious drink of water or fruit juice; in young children this may be given before the dose. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred.

Emesis induction in acute poisoning. Standard practice in the management of acute poisoning (p.1435) has varied widely, with different procedures favoured at different times and in different countries. However, measures to reduce absorption of the toxic substance, such as stomach emptying, have often been advocated.

Two techniques of stomach emptying have been very widely used: gastric lavage; and emesis induction, with ipecacuanha as the emetic of choice. Neither technique is without hazard and the dangers of attempting to empty the stomach have to be balanced against the toxicity of the ingested poison. If the patient presents late or the risk of toxicity is small, then gastric emptying is unnecessary.

- **Gastric lavage** is not recommended in the routine management of poisoned patients[1] because there is little evidence from experimental studies that it improves the clinical outcome and it may cause significant morbidity. *It should only be considered if a potentially life-threatening amount of toxic substance has been ingested within the preceding hour.* There is significant danger of aspiration of stomach contents associated with the procedure and it should only be attempted in fully conscious patients with good airway protective reflexes, unless other means are undertaken to protect the airway. Gastric lavage is also contra-indicated if corrosive or petroleum products have been ingested. Another risk that has been suggested with gastric lavage is that the procedure may propel stomach contents beyond the pylorus and thus enhance absorption,[2] but this conclusion has been challenged[3] and the evidence appears to be limited.
- Induction of **emesis** with ipecacuanha has often been advocated for use in children, in whom gastric lavage may be particularly traumatic; it has also been used in adults. However, like gastric lavage, its routine use is not recommended in the management of poisoned patients[4] because there is no clear evidence from clinical studies that it improves the outcome; clinically significant absorption may not be prevented even if it is given within 1 hour of the ingested poison. It may also delay the use or reduce the effectiveness of activated charcoal or oral antidotes. Ipecacuanha should not be given to patients with compromised airway reflexes, nor following ingestion of corrosive or petroleum products. In addition it should be avoided in debilitated or elderly patients, or those with medical conditions that may be compromised by induction of emesis. *It may be considered in alert, conscious patients, if a potentially life-threatening amount of toxic substance has been ingested within the preceding hour, and if gastric lavage or activated charcoal are deemed inappropriate.*

Because of the limitations of both methods of gastric emptying, a number of studies have addressed the question of whether either is appropriate. Such studies have indicated that the use of activated charcoal alone to prevent absorption, without gastric emptying, is as effective as a combination of both methods.[5-7]

1. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. *J Toxicol Clin Toxicol* 2004; **42:** 933–43. Also available at: http://www.clintox.org/Pos_Statements/GastricLavage.pdf (accessed 5/12/06)
2. Saetta JP, *et al.* Gastric emptying procedures in the self-poisoned patient: are we forcing gastric content beyond the pylorus? *J R Soc Med* 1991; **84:** 274–6.
3. Eddleston M, *et al.* Does gastric lavage really push poisons beyond the pylorus? A systematic review of the evidence. *Ann Emerg Med* 2003; **42:** 359–64.
4. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position statement: ipecac syrup. *J Toxicol Clin Toxicol* 2004; **42:** 133–43. Also available at: http://www.clintox.org/Pos_Statements/IpecacSyrup.pdf (accessed 5/12/06)
5. Albertson TE, *et al.* Superiority of activated charcoal alone compared with ipecac and activated charcoal in the treatment of acute toxic ingestions. *Ann Emerg Med* 1989; **18:** 56–9.
6. Merigian KS, *et al.* Prospective evaluation of gastric emptying in the self-poisoned patient. *Am J Emerg Med* 1990; **8:** 479–83.
7. Pond SM, *et al.* Gastric emptying in acute overdose: a prospective randomised controlled trial. *Med J Aust* 1995; **163:** 345–9.

Preparations

BP 2008: Paediatric Ipecacuanha Emetic Mixture;
Ph. Eur.: Ipecacuanha Liquid Extract, Standardised; Ipecacuanha Tincture, Standardised;
USP 31: Ipecac Syrup.

Proprietary Preparations (details are given in Part 3)
Fin.: Ipeca†; ***Gr.:*** Ipecavom; ***UK:*** Fennings Little Healers.

Multi-ingredient: ***Arg.:*** Cobenzil Compuesto†; No-Tos Infantil; ***Braz.:*** Agrimel†; Expec; Expectomel; Fenergan Expectorante; Iodesin; Iodopulmin†; Ipecol†; Kl-Expectorante; Melagriao; Pilulas Ross; Tussol†; Tussucalman†; ***Fr.:*** Humex†; ***Hong Kong:*** Pectoral†; ***Hung.:*** Artin†; ***Indon.:*** Andonex; Koffex for Children; Prome; Promedex; Promethazine Ikapharmindo; ***Irl.:*** Venos Honey & Lemon; ***Israel:*** Doveri; Laxative Comp; Promethazine Expectorants; Prothiazine Expectorant; ***Neth.:*** Buckleys Kinderhoestsiroop; ***Rus.:*** Prothiazine Expectorant (Протиазин Экспекторант); ***S.Afr.:*** Chamberlains Cough Remedy Regular; Cough Elixir; Linctus Tussi Infans; SB Cirogin Cough Mixture; ***Singapore:*** Beacons Cough; ***Spain:*** Alofedina; Buco Regis; Encialina†; Fenergan Expectorante; ***Switz.:*** Bromocod N; Demo Elixir pectoral N; Gouttes contre la toux "S"; Neo-Codion N; Pastilles pectorales Demo N; ***UK:*** Allens Dry Tickly Cough; Allens Pine & Honey; Asthma & Catarrh Relief; Beehive Balsam; Buttercup Infant Cough Syrup; Buttercup Syrup (Blackcurrant flavour); Buttercup Syrup (Honey and Lemon flavour); Cough-eeze; Galloway's Cough Syrup; Hill's Balsam Chesty Cough for Children; Hill's Balsam Chesty Cough Pastilles; Hill's Balsam Extra Strong; Honey & Molasses; Jackson's Troublesome Coughs; Kilkof; Lockets Medicated Linctus; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Vegetable Cough Remover; ***USA:*** Poison Antidote Kit; Quelidrine; ***Venez.:*** Tabonuco; Tessamag con Codeina.

Isoaminile *(BAN, rINN)*

Isoaminiili; Isoaminil; Isoaminilo; Isoaminilum. 4-Dimethylamino-2-isopropyl-2-phenylpentanonitrile.

Изоаминил

$C_{16}H_{24}N_2$ = 244.4.
CAS — 77-51-0.
ATC — R05DB04.
ATC Vet — QR05DB04.

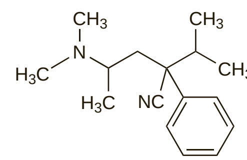

Isoaminile Citrate *(BANM, rINNM)*

Citrato de isoaminilo; Isoaminile, Citrate d'; Isoaminili Citras. 4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile dihydrogen citrate.

Изоаминила Цитрат

$C_{16}H_{24}N_2,C_6H_8O_7$ = 436.5.
CAS — 126-10-3; 28416-66-2.
ATC — R05DB04.
ATC Vet — QR05DB04.

Isoaminile Cyclamate *(rINNM)*

Ciclamato de isoaminilo; Isoaminile, Cyclamate d'; Isoaminili Cyclamas. 4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile cyclohexanesulfamate.

Изоаминила Цикламат

$C_{16}H_{24}N_2,C_6H_{13}NO_3S$ = 423.6.
CAS — 10075-36-2.
ATC — R05DB04.
ATC Vet — QR05DB04.

Profile

Isoaminile is a centrally acting cough suppressant. Isoaminile cyclamate has been given orally in doses of 40 to 80 mg up to 5 times daily. For children's doses, see Administration in Children, below. The citrate has also been used.

Administration in children. Isoaminile cyclamate has been given orally in the following doses:
- 1 to 6 years: 20 mg 2 or 3 times daily
- over 6 years: 40 mg 2 or 3 times daily

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Peracon†; ***Indon.:*** Peracon; ***S.Afr.:*** Peracon†.

Multi-ingredient: ***S.Afr.:*** Peracon Expectorant†.

Letosteine *(pINN)*

Letosteína; Létostéine; Letosteinum. 2-[2-(Ethoxycarbonylmethylthio)ethyl]thiazolidine-4-carboxylic acid.

Летостеин

$C_{10}H_{17}NO_4S_2$ = 279.4.
CAS — 53943-88-7.
ATC — R05CB09.
ATC Vet — QR05CB09.

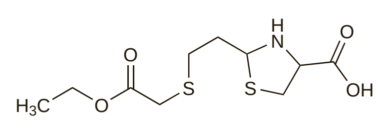

Profile

Letosteine is a mucolytic that has been used in the treatment of respiratory disorders associated with productive cough (p.1547).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Viscotiol†; ***Spain:*** Broluidan†.

Levmetamfetamine (USAN, rINN) ⊗

l-Deoxyephedrine; L-Desoxiefedrina; L-Desoxyephedrine; Lesoxyephedrine; Levmétamfétamine; Levmetamfetaminum; Levmetanfetamina; Levometanfetamina; *l*-Methamphetamine; *l*-Methylamphetamine. (*R*)-*N*,α-Dimethylbenzeneethanamine; (−)-(*R*)-*N*,α-Dimethylphenethylamine.

Левметамфетамин

$C_{10}H_{15}N$ = 149.2.

CAS — 33817-09-3.

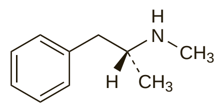

Pharmacopoeias. In *US.*

USP 31 (Levmetamfetamine). A clear, practically colourless, liquid. Store in airtight containers. Protect from light.

Profile

Levmetamfetamine is the *laevo* isomer of metamfetamine (p.2158) and is used topically in the treatment of nasal congestion (p.1548).

Abuse. Levmetamfetamine is a less potent central stimulant than metamfetamine, but it has been subject to occasional abuse.[1,2] In addition, as a stimulant its use is prohibited in sport during competition. However, it is classed by the World Anti-Doping Agency as one of the specified substances particularly susceptible to unintentional anti-doping rule violations because of general availability in medicinal products or which are less likely to be successfully abused as doping agents.[3]

1. Halle AB, *et al.* Drug abuse with Vicks nasal inhaler. *South Med J* 1985; **78:** 761–2.
2. Ferrando RL, *et al.* Bizarre behavior following the ingestion of levo-desoxyephedrine. *Drug Intell Clin Pharm* 1988; **22:** 214–17.
3. World Anti-Doping Agency. The World Anti-Doping Code: 2007 Prohibited List International Standard (issued 16 September, 2006). Available at: http://www.wada-ama.org/rtecontent/document/2007_List_En.pdf (accessed 04/04/07)

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Vicks Vapor Inhaler.

Marrubium

Andornkraut; Herba Marrubii; Hurtanminttu; Jablečníková nať; Juanrubio; Kransborre; Malva de sapo; Malvarrubia; Marrube blanc, parties aériennes fleuries de; Marrubii herba; Marrubio; Šantrų žolė; White Horehound.

Шандра Обыкновенная

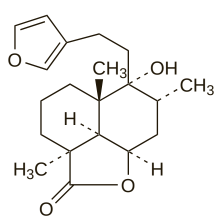

(marrubiin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (White Horehound). The whole or fragmented dried flowering aerial parts of *Marrubium vulgare*. It contains a minimum 0.7% of marrubiin ($C_{20}H_{28}O_4$ = 332.4), calculated as the dried drug.

Profile

Marrubium is the flower or leaf of *Marrubium vulgare* (Labiatae). It has been used for its supposed expectorant properties in herbal preparations for the treatment of cough. It has also been used as a flavouring.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Angocin Bronchialtropfen.

Multi-ingredient: ***Austral.:*** Broncafect; Verbascum Complex†; ***Austria:*** Asthmatee EF-EM-ES; Gallen- und Lebertee St Severin; ***Canad.:*** Herbal Throat†; Original Herb Cough Drops; Swiss Herb Cough Drops; ***Chile:*** Fucus Compuesto†; ***Cz.:*** Original Schwedenbitter; Species Cholagogae Planta; The Salvat; Zlucnikova Cajova Smes; ***Ital.:*** Altuss; Broncosedina; ***Pol.:*** Amarosal; ***S.Afr.:*** Cough Elixir; ***Spain:*** Natusor Asmaten†; Natusor Broncopul†; ***Switz.:*** Hederix; ***UK:*** Allens Chesty Cough; Asthma & Catarrh Relief; Catarrh-eeze; Chest Mixture; Cough-eeze; Herb and Honey Cough Elixir; Honey & Molasses; Horehound and Aniseed Cough Mixture; Modern Herbals Cough Mixture; Vegetable Cough Remover.

Mecysteine Hydrochloride (BANM, rINNM)

Hidrocloruro de mecisteína; Mécystéine, Chlorhydrate de; Mecysteini Hydrochloridum; Methyl Cysteine Hydrochloride; Methylcysteine Hydrochloride. Methyl L-2-amino-3-mercaptopropionate hydrochloride.

Мецистеина Гидрохлорид

$C_4H_9NO_2S,HCl$ = 171.6.

CAS — 2485-62-3 (mecysteine); 18598-63-5 (mecysteine hydrochloride); 5714-80-7 (mecysteine hydrochloride).

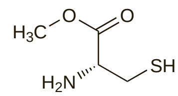

(mecysteine)

Adverse Effects and Precautions

Nausea and heartburn have occasionally been reported. Since mucolytics may disrupt the gastric mucosal barrier mecysteine hydrochloride should be used with caution in patients with a history of peptic ulcer disease.

Uses and Administration

Mecysteine hydrochloride is used as a mucolytic in respiratory disorders associated with productive cough (p.1547). It is given orally in a usual dose of 200 mg three times daily before meals reduced to 200 mg twice daily after 6 weeks. A rapid clinical effect can be achieved by giving 200 mg four times daily for the first 2 days. For children's doses, see Administration in Children, below. Mecysteine has also been given by inhalation.

Administration in children. The recommended oral dose of mecysteine hydrochloride in children aged 5 to 12 years is 100 mg 3 times daily.

Respiratory disorders. Mecysteine hydrochloride given orally has reduced symptoms of cough in patients with chronic bronchitis or other respiratory disorders, but its effect on sputum production and pulmonary function has been variable.[1,2] The use of mucolytics in chronic obstructive pulmonary disease (p.1112) is controversial.

1. Aylward M, *et al.* Clinical therapeutic evaluation of methylcysteine hydrochloride in patients with chronic obstructive bronchitis: a balanced double-blind trial with placebo control. *Curr Med Res Opin* 1978; **5:** 461–71.
2. Sahay JN, *et al.* The effect of methyl cysteine (Visclair) in respiratory diseases: a pilot study. *Clin Trials J* 1982; **19:** 137–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Irl.: Visclair; ***UK:*** Visclair.

Multi-ingredient: ***Ital.:*** Donatiol.

Menglytate (rINN)

Menglitato; Menglytatum; Menthol Ethylglycolate. *p*-Menth-3-yl ethoxyacetate.

Менглитат

$C_{14}H_{26}O_3$ = 242.4.

CAS — 579-94-2.

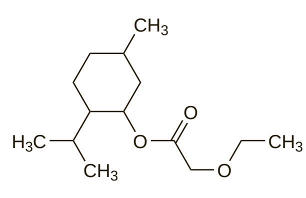

Profile

Menglytate is an ingredient of a number of preparations promoted for the treatment of cough.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Coryfin C; Neo Borocillina Balsamica.

Methoxyphenamine Hydrochloride (BANM, rINNM) ⊗

Hidrocloruro de metoxifenamina; Methoxiphenadrin Hydrochloride; Méthoxyphénamine, Chlorhydrate de; Methoxyphenamini Hydrochloridum; Mexyphamine Hydrochloride. 2-Methoxy-*N*α-dimethylphenethylamine hydrochloride.

Метоксифенамина Гидрохлорид

$C_{11}H_{17}NO,HCl$ = 215.7.

CAS — 93-30-1 (methoxyphenamine); 5588-10-3 (methoxyphenamine hydrochloride).
ATC — R03CB02.
ATC Vet — QR03CB02.

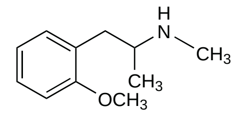

(methoxyphenamine)

Profile

Methoxyphenamine is a sympathomimetic with effects similar to those of ephedrine (p.1558), given orally as the hydrochloride. It has been used as a bronchodilator mainly in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Cheracol; ***Hong Kong:*** Asmeton; ***Irl.:*** Casacol; ***Thai.:*** Asmeton†; ***Venez.:*** Metoxifilin.

Methyl Dacisteine (rINNM)

Dacisteína de metilo; Dacistéine Méthyle; Dacisteinum Methylis; EL-1035 (dacisteine); Methyl Diacetylcysteinate. Methyl *N*,*S*-diacetyl-L-cysteinate.

Дацистеин Метил

$C_8H_{13}NO_4S$ = 219.3.

CAS — 18725-37-6 (dacisteine); 19547-88-7 (methyl dacisteine).

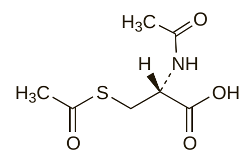

(dacisteine)

Profile

Like acetylcysteine (p.1548), methyl dacisteine has been used as a mucolytic in respiratory disorders associated with productive cough (p.1547). It has been given orally in a usual dose of 600 mg daily, divided into 3 or 4 doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Mucothiol; ***Hung.:*** Mucothiol†; ***Ital.:*** Mucothiol.

Methylephedrine Hydrochloride (BANM) ⊗

dl-Methylephedrine Hydrochloride; *dl*-*N*-Methylephedrine Hydrochloride; Metilefedrina, hidrocloruro de. (1*RS*,2*RS*)-2-Dimethylamino-1-phenylpropan-1-ol hydrochloride.

Метилэфедрина Гидрохлорид

$C_{11}H_{17}NO,HCl$ = 215.7.

CAS — 552-79-4 ((−)-methylephedrine); 1201-56-5 ((±)-methylephedrine); 38455-90-2 ((−)-methylephedrine hydrochloride); 942-46-1 ((±)-methylephedrine hydrochloride); 18760-80-0 ((±)-methylephedrine hydrochloride).

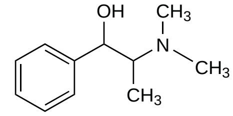

(methylephedrine)

Pharmacopoeias. In *Jpn.*

Profile

Methylephedrine hydrochloride is a sympathomimetic with effects similar to those of ephedrine (p.1558). It has been used as a bronchodilator and is given orally in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Tussoretardin; ***Hong Kong:*** Codaewon; ***Jpn:*** Colgen Kowa IB Toumei; Sin Colgen Kowa Kaze; ***S.Afr.:*** Ilvico; ***Switz.:*** Tossamine plus; ***Thai.:*** Coughmin†; Hustazol-C†; Methorcon; ***Venez.:*** Ilvico.

Metizoline Hydrochloride *(BANM, USAN, rINNM)* ⊗

EX-10-781; Hidrocloruro de metizolina; Métizoline, Chlorhydrate de; Metizolini Hydrochloridum; Metyzoline Hydrochloride; RMI-10482A. 2-(2-Methylbenzo[*b*]thienylmethyl)-2-imidazoline hydrochloride.

Метизолина Гидрохлорид

$C_{13}H_{14}N_2S,HCl = 266.8.$

CAS — 17692-22-7 (metizoline); 5090-37-9 (metizoline hydrochloride).

ATC — R01AA10.

ATC Vet — QR01AA10.

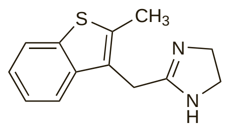

(metizoline)

NOTE. The name benazoline has been used as a synonym for metizoline. Care should be taken to distinguish it from benazolin (4-chloro-2,3-dihydro-2-oxo-1,3-benzothiazol-3-ylacetic acid, $C_9H_6ClNO_3S = 243.7$), which is a herbicide. Also do not confuse with benzazoline (see Tolazoline, p.1415), which is a vasodilator.

Profile

Metizoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p.1565) that has been used for its vasoconstrictor activity in the treatment of nasal congestion.

Morclofone *(rINN)*

Dimeclofenone; Morclofona; Morclofonum; Morclophon. 4′-Chloro-3,5-dimethoxy-4-(2-morpholinoethoxy)benzophenone.

Морклофон

$C_{21}H_{24}ClNO_5 = 405.9.$

CAS — 31848-01-8 (morclofone); 31848-02-9 (morclofone hydrochloride).

ATC — R05DB25.

ATC Vet — QR05DB25.

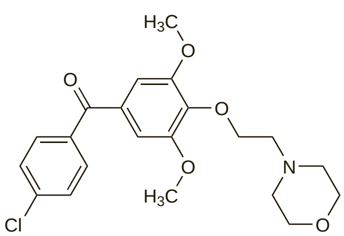

Profile

Morclofone is a centrally acting cough suppressant used for non-productive cough (p.1547); it is given orally in usual doses of 150 mg four or five times daily. It has also been given as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Plausitin; ***Switz.:*** Nitux.

Naphazoline *(BAN, rINN)* ⊗

Nafatsoliini; Nafazolin; Nafazolina; Naphazolinum. 2-(1-Naphthylmethyl)-2-imidazoline.

Нафазолин

$C_{14}H_{14}N_2 = 210.3.$

CAS — 835-31-4.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

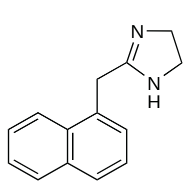

Naphazoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de nafazolina; Nafatsoliinihydrokloridi; Nafazolin Hidroklorür; Nafazolin-hidroklorid; Nafazolin-hydrochlorid; Nafazolinhydroklorid; Nafazolino hidrochloridas; Naphazoline, chlorhydrate de; Naphazolini hydrochloridum.

Нафазолина Гидрохлорид

$C_{14}H_{14}N_2,HCl = 246.7.$

CAS — 550-99-2.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Naphazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 31 (Naphazoline Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Naphazoline Nitrate *(BANM, rINNM)* ⊗

Nafatsoliininitraatti; Nafazolin Nitrat; Nafazolinnitrat; Nafazolin-nitrát; Nafazolino nitratas; Nafazoliny azotan; Naphazoline, nitrate de; Naphazolini nitras; Naphazolinium Nitricum; Naphthizinum; Nitrato de nafazolina.

Нафазолина Нитрат

$C_{14}H_{14}N_2,HNO_3 = 273.3.$

CAS — 5144-52-5.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *Viet.*

Ph. Eur. 6.2 (Naphazoline Nitrate). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p.1407; naphazoline has mainly alpha-agonist effects. After local use, transient irritation may occur. Rebound congestion may occur after frequent or prolonged use. Systemic effects, including nausea, headache, and dizziness have occurred after topical use. Overdosage or accidental dosage by mouth may cause CNS depression with marked reduction of body temperature and bradycardia, sweating, drowsiness, and coma, particularly in children; it should be used with great caution, if at all, in infants and young children. Use of naphazoline in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Hypertension may be followed by rebound hypotension. Treatment of adverse effects is symptomatic.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing naphazoline, see under Phenylephrine, p.1568.

Intraoperative use. A report[1] of 2 cases of toxicity associated with intraoperative use of a naphazoline-soaked sponge to control excessive bleeding after adenoidectomy. Both patients experienced hypertension and reflex bradycardia, which evolved in one case into marked hypotension. There was evidence of CNS depression with a reduced respiration rate and prolonged recovery from anaesthesia.

1. Wenzel S, *et al.* Course and therapy of intoxication with imidazoline derivate naphazoline. *Int J Pediatr Otorhinolaryngol* 2004; **68:** 979–83.

Interactions

Since naphazoline is absorbed through the nasal mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p.1407.

Pharmacokinetics

Systemic absorption has been reported after topical use of solutions of naphazoline. It is not given systemically, but it is readily absorbed from the gastrointestinal tract. Naphazoline instilled into the eye causes conjunctival vasoconstriction within 10 minutes and effects can last for up to 6 hours.

Uses and Administration

Naphazoline is a sympathomimetic (p.1408) with marked alpha-adrenergic activity. It is a vasoconstrictor with a rapid and prolonged action in reducing swelling and congestion when applied to mucous membranes.

Naphazoline and its salts are used for the symptomatic relief of nasal congestion (p.1548). Solutions containing 0.05 to 0.1% of the hydrochloride or the nitrate may be applied topically as nasal drops or a spray usually up to once every 6 hours. Children aged 7 years and over have used a preparation containing 0.05%.

Solutions containing up to 0.1% of naphazoline hydrochloride have been instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p.564).

Naphazoline has been used as a vasoconstrictor with local anaesthetics.

Naphazoline acetate has also been used in nasal preparations.

Preparations

USP 31: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution; Naphazoline Hydrochloride Nasal Solution; Naphazoline Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Actifedrin Nasal; Bactio Rhin; Bano Ocular Agrand; Dazolin; Disel; Gotabiotic D; Gotinal; Let-Nasal; Mirasan; Mirus-S; Nafazolex; Nasalex; Privina; Rhinal; ***Austral.:*** Albalon; Clear Eyes†; Naphcon; Optazine†; ***Austria:*** Aconex; Coldan; Isoftal; Mertan; Privin; Rhinon; Rhinoperd; ***Belg.:*** Albalon†; Deltarhinol-Mono; Naphcon; Neusinol; Priciasol; Vasocedine; ***Braz.:*** Clarivit†; Claroft; Multisoro; Narial†; Narix; Nazicol; Neosoro; Privina; Rino Resfenol†; Rinos-A; ***Canad.:*** Ak-Con; Albalon; Allergy Drops; Clear Eyes; Diopticon; Naphcon Forte; Red Away†; Vasocon†; ***Chile:*** Albasol†; Clarimir; Red Off; Vi-Claro†; ***Cz.:*** Proculin†; Sanorin; ***Ger.:*** Idril N sine†; Piniol Nasenspray†; Privin; Proculin; Rhinex mit Naphazolin; Telestulln; ***Gr.:*** Coldan; Naphcon; ***Hong Kong:*** Albalon; All Clear; ***Hung.:*** Naphcon†; Proculin†; ***India:*** Clearine; Ocustress; ***Indon.:*** Optrine; ***Israel:*** Naphasal; Naphcon Forte; ***Ital.:*** Collirio Alfa; Desamin Same; Imidazyl; Iridina Due; Naftazolina; Pupilla; Rinazina; Rino Naftazolina; Video-Mill; Virginiana Gocce Verdi†; ***Malaysia:*** Albalon; ***Mex.:*** Afazol; Alphadinal; Celunaf; Fazolin; Gotinal; Nazil; ***Neth.:*** Albalon; ***NZ:*** Albalon†; Clear Eyes; Naphcon; ***Philipp.:*** Cosooth; ***Pol.:*** Rhinazin; ***Rus.:*** Naphthyzin (Нафтизина)†; Sanorin (Санорин); ***S.Afr.:*** Murine Clear Eyes†; Safyr Bleu; ***Spain:*** Alfa; Euboral; Miraclar; Vasoconstrictor Pensa; ***Swed.:*** Rimidol†; ***Switz.:*** Albalon; Minha†; ***Thai.:*** Albalon; Naphcon; ***Turk.:*** Deltarhinol; Enflucide; ***UK:*** Murine; ***USA:*** Ak-Con; Albalon; All Clear; Allerest†; Allergy Drops†; Clear Eyes; Clear Eyes Plus Redness Relief; Comfort Eye Drops†; Degest†; Nafazair†; Napha Forte; Naphcon; Privine; Vasocon†; ***Venez.:*** Clarasol; Clearize; Fanasal†; Fazolan; Fazonil†; Gotinal; Nafin†; Naphcon; Nas; Niazol; Ninazo.

Multi-ingredient: ***Arg.:*** Alercortil†; Alvo Nasal†; Antibiocort†; Bactio Rhin Prednisolona; Bideon; Biotaer Nasal; Dexafurazon†; Dexalergin; Disel Hidrocortisona; Drynisan; Factioneye; Fadanasal; Gramicortil†; Hyalcrom; Mira Klonal; Mirus; Nasojol†; Nasomicina; Neo-Currino; Neodexa Plus; Neoefodil†; Neosona; Nexadron Compuesto; Nexadron Plus; Panoptic; Provacsin Nasal; Refenax Colirio; Refenax Gotas Nasales; Rinoflax AG M; Rinogel; Suavithiol; Vistacloran†; ***Austral.:*** Albalon-A; Antistine-Privine; In A Wink†; Naphcon-A; Optrex; Visine Allergy with Antihistamine; ***Austria:*** Coldistan; Coldophthal; Histophtal; Luuf-Nasenspray; Ophtaguttal; Rhinodrin; Rhinon; Rhinoperd comp; ***Belg.:*** Diphenhydramine Constrictor†; Minhavez; Naphcon-A; Neofenox; Sofraline; Sofrasolone; Zincfrin Antihistaminicum†; ***Braz.:*** Alergotox Nasal†; Claril; Colirio Legrand; Colirio Moura Brasil; Colirio Teuto; Conidrin; Fluo-Vaso; Hemodotti; Hidrocin; Inhadrina†; Lerin; Maxibell; Mentodrin†; Naridrin; Nariflux; Naso-Josp†; Nazobel†; Nazobio†; Neo Quimica Colirio; Nitrileno; Novo Rino; Rhinosept; Rinisone; Rinosite†; Sinustrat Vasoconstritor; Sorine Adulto; Stilux; Visazul; Visiplex; Visolon; Visual†; Zincolok; ***Canad.:*** Albalon-A; Clear Eyes Allergy; Collyre Bleu†; Diopticon A; Naphcon-A; Onrectal; Opcon-A; Vasocon-A†; Visine Advance Allergy; Zincfrin-A; ***Chile:*** Albasol A†; Clarimir F; Dessolets; Miral; Mirus†; Naphcon-A; Naphtears; Nico Drops; Novo-Tears; Oculosan; Oftalirio; Red Off Aqua; Red Off Plus; ***Cz.:*** Sanorin-Analergin; ***Denm.:*** Ansal; Antistina-Privin; Sesal; ***Fin.:*** Antistin-Privin†; Zincfrin-A†; ***Fr.:*** Collyre Bleu; Derinox; ***Ger.:*** Antistin-Privin; Diabenyl-Rhinex†; duraultra; Konjunktival Thilo†; Oculosan N; Rhinoguttae Dexamethasoni cum Naphazolino†; Rhinosovil†; Siozwo; Stipo†; ***Gr.:*** Neo-Priphen; Oculosan; Septobore; Zabysept; ***Hong Kong:*** Clear Blue; Frazoline; Konjunktival†; Naphcon-A; Nazin; Oculosan; Opcon-A; ***Hung.:*** Coldistan†; ***India:*** Andre; Andre-I-Kul; Betnesol-N Nasal; Efcorlin; Fenox; Ocurest; Ocurest-AH; Ocurest-Z; Proto-Boric; ***Indon.:*** Flamergi; Indofrin-A; Isotic Azora; Naphcon-A; Oculosan; Zincopto; ***Israel:*** Alnase; Antistin-Privin†; Nodryl†; Optryl; Phenyphrine-Azol†; Proaf; ***Ital.:*** Alfaflor; Antisettico Astringente Sedativo; Antistin-Privina; Collirio Alfa Antistaminico; Corizzina†; Deltarinolo; Fotofil; Genalfa; Idroneomicil†; Imidazyl Antistaminico; Indaco; Iristamina; Nafcon A†; Oftalmil; Pupilla Antistaminico; Rinocidina; Rinofomentil†; Zinc-Imizol; ***Malaysia:*** Alergoftal; Napha A; Naphcon-A; Oculosan†; ***Mex.:*** Afazol Z; Biofrin; Biotarson O; Eyrasil; Istasol; Midazol Ofteno; Mirus; Naphacel; Naphtears; Oftalirio†; Opcon-A; Soltrictor con Lagrifilm; Solutina; Sulvi; Zincfrin-A; ***NZ:*** Albalon-A†; Betnesol Aqueous; Clear Eyes ACR†; Degest 2†; Naphcon-A; Optrex Red-Eye Relief; Visine Allergy; ***Philipp.:*** Decocon A; Moisturizing All Clear; Naphcon-A; Oculosan; Optaphen; ***Pol.:*** Betadrin; Cincol; Dermophenazol; Mibalin; Oculosan; Oftophenazol; Rhinophenazol; Sulfarinol; ***Port.:*** Alergiftalmina; Colircusi Anestesico; Naso-Prieulina†; ***Rus.:*** Betadrin (Бетадрин); Polynadim (Полинадим); Sanorin (Санорин); Sanorin-Analergin (Санорин-аналергин); ***S.Afr.:*** Albalon-A†; Antistin-Privin; Covomycin; Covosan; ENT; Nasdro; Oculosan; Universal Nasal Drops; Zincfrin-A; ***Singapore:*** Antistin-Privin; Flucur†; Naphcon-A; Opcon-A; ***Spain:*** Alergoftal; Centilux; Cloram Zinc; Coliriocilina Adren Astr; Epistaxol; Kanafosal; Kanafosal Predni; Oftalmol Ocular; Ojosbel; Rinovel; Zolina; ***Swed.:*** Antasten-Privin; ***Switz.:*** Antistin-Privin; Collyre Alpha†; Collyre Bleu Laiter; Gouttes nasales N†; Oculosan; Spray nasal comp pour adultes; ***Thai.:*** Levoptin; Naphcon-A; Oculosan; ***Turk.:*** Alergoftal; Sulfarhin; ***UK:*** Eye Dew; Optrex Red Eyes; ***USA:*** 4-Way Fast Acting; Antazoline-V; Clear Eyes Seasonal Relief; Maximum Strength Allergy Drops; Nafazair A†; Naphazoline Plus; Naphcon-A;

Naphoptic-A; Ocuhist; Opcon-A; VasoClear A; VasoClear†; Vasocon-A; Visine-A; ***Venez.:*** Camolyn Plus; Fesanol†; Pinazo; Soltin; Soluclear.
Used as an adjunct in: ***Fr.:*** Xylocaine; ***Spain:*** Anestesico.

Neltenexine *(rINN)*

Neltenexina; Nelténexine; Neltenexinum. 4′,6′-Dibromo-α-[(*trans*-4-hydroxycyclohexyl)amino]-2-thiophene-carboxy-*o*-toluidide.

Нелтенексин

$C_{18}H_{20}Br_2N_2O_2S$ = 488.2.
CAS — 99453-84-6.
ATC — R05CB14.
ATC Vet — QR05CB14.

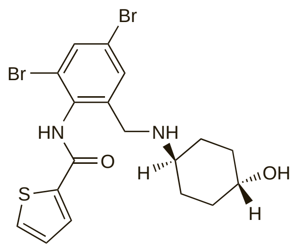

Profile

Neltenexine is a mucolytic that has been used in respiratory disorders associated with productive cough (p.1547). It has been given orally as the monohydrate, in usual doses of 37.4 mg three times daily. Neltenexine has also been given rectally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Alveoten; Muco4; Tenoxol.

Nepinalone *(rINN)*

Nepinalona; Népinalone; Nepinalonum. (±)-3,4-Dihydro-1-methyl-1-(2-piperidinoethyl)-2(1*H*)-napthalenone.

Непиналон

$C_{18}H_{25}NO$ = 271.4.
CAS — 22443-11-4.
ATC — R05DB26.
ATC Vet — QR05DB26.

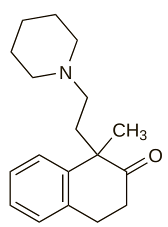

Profile

Nepinalone has been used as the hydrochloride as a cough suppressant in non-productive cough (p.1547). Oral doses of nepinalone hydrochloride 10 mg have been given three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Nepituss; Placatus; Tussolvina.

Nicocodine *(BAN, rINN)*

Nicocodina; Nicocodinum. 6-Nicotinoylcodeine; 3-*O*-Methyl-6-*O*-nicotinoylmorphine.

Никокодин

$C_{24}H_{24}N_2O_4$ = 404.5.
CAS — 3688-66-2.

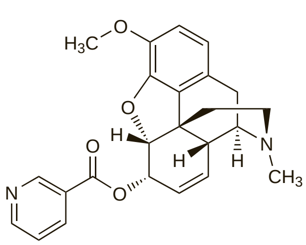

Profile

Nicocodine is an opioid related to codeine (p.37). It has been used as the hydrochloride for its central cough suppressant effects in non-productive cough (p.1547). Nicocodine hydrochloride is given orally in doses of 5 to 7.5 mg up to three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Tusscodin.

Normethadone Hydrochloride *(BANM, rINNM)*

Desmethylmethadone Hydrochloride; Hidrocloruro de normetadona; Hoechst-10582 (normethadone); Norméthadone, Chlorhydrate de; Normethadoni Hydrochloridum; Phenyldimazone Hydrochloride. 6-Dimethylamino-4,4-diphenylhexan-3-one hydrochloride.

Норметадона Гидрохлорид

$C_{20}H_{25}NO,HCl$ = 331.9.
CAS — 467-85-6 (normethadone); 847-84-7 (normethadone hydrochloride).
ATC — R05DA06.
ATC Vet — QR05DA06.

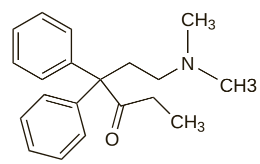

(normethadone)

Profile

Normethadone is closely related to methadone (p.82). The hydrochloride is given orally as a cough suppressant in preparations for non-productive cough.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Canad.:*** Cophylac.

Noscapine *(BAN, rINN)*

Narcotine; L-α-Narcotine; Noscapina; Noscapinum; Noskapiini; Noskapin; Noskapinas; Noszkapin; NSC-5366. (3*S*)-6,7-Dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide.

Носкапин

$C_{22}H_{23}NO_7$ = 413.4.
CAS — 128-62-1.
ATC — R05DA07.
ATC Vet — QR05DA07.

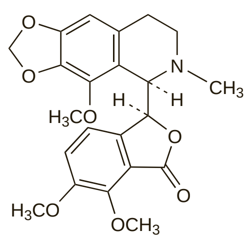

Description. Noscapine is an alkaloid obtained from opium.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Noscapine). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water at 20°, very slightly soluble at 100°; slightly soluble in alcohol; soluble in acetone; dissolves in strong acids although the base may be precipitated on dilution with water. Protect from light.

USP 31 (Noscapine). A fine, white or practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in ether; soluble in acetone; freely soluble in chloroform.

Noscapine Camsilate *(BANM, rINNM)*

Camphoscapine; Camsilato de noscapina; Noscapine, Camsilate de; Noscapine Camsylate; Noscapini Camsilas. Noscapine camphor-10-sulphonate.

Носкапина Камзилат

$C_{22}H_{23}NO_7, C_{10}H_{16}O_4S$ = 645.7.
CAS — 25333-79-3.
ATC — R05DA07.
ATC Vet — QR05DA07.

Noscapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de noscapina; Narcotine Hydrochloride; Noscapine, chlorhydrate de; Noscapini hydrochloridum; Noscapini Hydrochloridum Monohydricum; Noscapinium Chloride; Noskapiinihydrokloridi; Noskapin hydrochlorid monohydrát; Noskapinhydroklorid; Noskapino hidrochloridas; Noskapiny chlorowodorek; Noszkapin-hidroklorid.

Носкапина Гидрохлорид

$C_{22}H_{23}NO_7,HCl,H_2O$ = 467.9.
CAS — 912-60-7 (anhydrous noscapine hydrochloride).
ATC — R05DA07.
ATC Vet — QR05DA07.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* (both with H_2O); in *Jpn* (with xH_2O).

Ph. Eur. 6.2 (Noscapine Hydrochloride). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water and in alcohol. Aqueous solutions are faintly acid; the base may be precipitated when the solutions are allowed to stand. A 2% solution in water has a pH of not less than 3.0. Protect from light.

Adverse Effects and Precautions

As for Dextromethorphan, p.1555. Hypersensitivity reactions have been reported.

Breast feeding. Maximum concentrations of noscapine in the breast milk of 8 women given 100 or 150 mg of noscapine ranged[1] from 11 to 83 nanograms/mL. It was estimated that breast-fed infants of mothers receiving noscapine 50 mg three times daily would ingest at most 300 nanograms/kg of noscapine, an amount considered unlikely to be a hazard. No adverse effects have been seen in breast-fed infants whose mothers were given noscapine, and the American Academy of Pediatrics[2] considers that it is therefore usually compatible with breast feeding.

1. Olsson B, *et al.* Excretion of noscapine in human breast milk. *Eur J Clin Pharmacol* 1986; **30:** 213–15.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/12/06)

Pregnancy. The UK CSM stood by their recommendation[1] that products containing noscapine should be contra-indicated in women of child-bearing potential (because of potential mutagenic effects[2]), after criticism that the decision was based solely on the results of *in-vitro* work.[3]

1. Asscher AW, Fowler LK. Papaveretum in women of childbearing potential. *BMJ* 1991; **303:** 648.
2. Committee on Safety of Medicines. Genotoxicity of papaveretum and noscapine. *Current Problems 31* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 21/03/07)
3. Allen S, *et al.* Papaveretum in women of child bearing potential. *BMJ* 1991; **303:** 647.

Interactions

Noscapine should not be given with alcohol or other CNS depressants.

Anticoagulants. For mention of a possible interaction between noscapine and *warfarin,* see Cough Suppressants, p.1430.

Pharmacokinetics

◊ References.

1. Karlsson MO, *et al.* Pharmacokinetics of oral noscapine. *Eur J Clin Pharmacol* 1990; **39:** 275–9.
2. Karlsson MO, Dahlstrom B. Serum protein binding of noscapine: influence of a reversible hydrolysis. *J Pharm Pharmacol* 1990; **42:** 140–3.

Uses and Administration

Noscapine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p.1556). It is given in an oral dose of up to 50 mg three times daily. It is also used rectally. Noscapine has also been given as the ascorbate, camsilate, embonate, and the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Nosca-Mereprine; Noscaflex; Noscafex†; ***Chile:*** Factoss†; ***Ger.:*** Capval; ***Hong Kong:*** Recoma; ***Indon.:*** Longatin; Mercotin; ***Neth.:*** Roter Noscapect; Streptuss kriebelhoest†; ***S.Afr.:*** Nitepax; ***Spain:*** Tuscalman; ***Swed.:*** Nipaxon; ***Switz.:*** Tussanil N.

Multi-ingredient: ***Arg.:*** Funciobron; Graneodin N; Jarabe Bago†; No-Tos Pocket; Saltos Infantil†; Saltos†; Tosedrin Compuesto; Vi-Balsabron†; ***Austria:*** Pneumopect; Tuscalman; ***Belg.:*** Noscaflex; Rosils†; ***Braz.:*** Expectussin†; Ipecol†; ***Chile:*** AB Antitusivo; Captus; Congestex; Cotibin Flu†; Freshmel Tos; Graneodin N†; Graneodin-Tos; Gripexin Limonada Caliente; Gripexin Nueva Formula Compuesto†; Kitadol Flu Noche†; Kitadol Flu†; Pectoserum†; Tapsin Compuesto; Tapsin Compuesto con Clorfenamina; Tapsin Compuesto Dia/Noche Plus; Tapsin Compuesto DN; Tapsin Limonada D.N.†; Tapsin Limonada Dia†; Tapsin Limonada Noche†; ***Fin.:*** Codesan N†; Posivil†; ***Fr.:*** Tussisedal; ***Hong Kong:*** Asmeton; Coldcap-A; Coldrex†; Coldtab-2; Mefedra-N†; Panadol Cold & Flu Extra; ***India:*** Coscopin; Coscopin Plus; ***Indon.:*** Flunadin; Noscapax; Paratusin; Tilomix; ***Swed.:*** Spasmofen; ***Switz.:*** Brosoline-Rectocaps†; DemoTussil; Hederix; Noscorex; Spasmosol; Tossamine; Tossamine plus; Tuscalman; Tussanil Compositum†; ***Thai.:*** Asmeton†; ***Turk.:*** Coldeks.

Oxeladin Citrate *(BANM, rINNM)*

Citrato de oxeladina; Okseladiinivetysitraatti; Okseladino-vandenilio citratas; Oxeladin-citrát; Oxéladine, Citrate d'; Oxéladine, hydrogénocitrate d'; Oxeladini Citras; Oxeladini hydrogenocitras; Oxeladinvätecitrat. 2-(2-Diethylaminoethoxy)ethyl 2-ethyl-2-phenylbutyrate dihydrogen citrate.

Окселадина Цитрат

$C_{20}H_{33}NO_3,C_6H_8O_7$ = 527.6.
CAS — 468-61-1 (oxeladin); 52432-72-1 (oxeladin citrate).
ATC — R05DB09.
ATC Vet — QR05DB09.

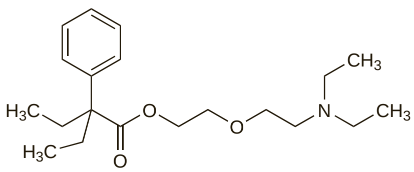

(oxeladin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oxeladin Hydrogen Citrate). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly to very slightly soluble in ethyl acetate.

Profile

Oxeladin citrate has been given orally as a centrally acting cough suppressant for non-productive cough (p.1547). Up to 50 mg daily in divided doses has been given orally. Higher doses of up to 120 mg daily have been given as a modified-release preparation.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Elitos; Frenotos; Nadetos; Plardox; ***Fr.:*** Paxeladine.

Multi-ingredient: ***Arg.:*** Aseptobron Bromexina; Aseptobron C; Frenotos Muc; Pectoral Lafedar; ***Braz.:*** Novotussan†; Tossivitan†; Tripulmin†; ***Mex.:*** Fluxedan; TheraFlu Tenalif.

Oxolamine *(rINN)*

683-M; Oksolamiini; Oksolamin; Oxolamin; Oxolamina; Oxolaminum. 5-[2-(Diethylamino)ethyl]-3-phenyl-1,2,4-oxadiazole.

Оксоламин

$C_{14}H_{19}N_3O$ = 245.3.
CAS — 959-14-8.
ATC — R05DB07.
ATC Vet — QR05DB07.

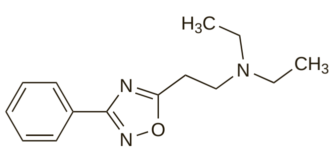

Oxolamine Citrate *(rINNM)*

AF-438; Citrato de oxolamina; Oxolamine, Citrate d'; Oxolamini Citras; SKF-9976.

Оксоламина Цитрат

$C_{14}H_{19}N_3O,C_6H_8O_7$ = 437.4.
CAS — 1949-20-8.
ATC — R05DB07.
ATC Vet — QR05DB07.

Oxolamine Phosphate *(rINNM)*

Fosfato de oxolamina; Oxolamine, Phosphate d'; Oxolamini Phosphas.

Оксоламина Фосфат

CAS — 1949-19-5.
ATC — R05DB07.
ATC Vet — QR05DB07.

Profile

Oxolamine is a cough suppressant with a mainly peripheral action that has been used for non-productive cough (p.1547). It has been given as the citrate in usual oral doses of 100 to 200 mg three times daily. The phosphate has been used similarly. It has also been given as the tannate.

Hallucinations in children have been reported after oxolamine use.

◊ References.

1. McEwen J, *et al.* Hallucinations in children caused by oxolamine citrate. *Med J Aust* 1989; **150:** 449–52.

Interactions. *ANTICOAGULANTS.* For mention of a possible interaction between oxolamine and *warfarin*, see Cough Suppressants, p.1430.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Numosol; Perebron; Respibron; Tulox; ***Israel:*** Symphocal; ***Ital.:*** Gantrimex†; Perebron; Tussibron; ***Mex.:*** Aledron; Bredon; Contuxin; Eumol; Expecmin; Fartoxol†; Kentosanil†; Oxathos; Oxobron; Oxomar; Oxomifer; Oxotus; Oxotusin; Toxal†; Tukson†; ***Turk.:*** Kalamin; Oksabron; Perbrons; Perebron; Sekodin; Subitol; ***Venez.:*** Broxol; Cafox; Calcimonio; Citralamina; Exeton†; Lexo; Opilina; Oxalcor; Oxolam†; Oxotil; Perebron; Toxolen†.

Multi-ingredient: ***Ital.:*** Uniplus; ***Mex.:*** Caltusine; Caobe; ***Turk.:*** Forza; Katarin; Katarin Forte; Oledro; ***Venez.:*** Broxamel†; Opilina Compuesta; Oxolavin Compuesto; Perebron con Miel†.

Oxymetazoline Hydrochloride

(BANM, USAN, rINNM) ⊗

H-990; Hidrocloruro de oximetazolina; Oksimetatsoliinihydrokloridi; Oksimetazolin Hidroklorür; Oksimetazolino hidrochloridas; Oximetazolin-hidroklorid; Oximetazolinhydroklorid; Oxymetazolin hydrochlorid; Oxymétazoline, chlorhydrate d'; Oxymetazolini hydrochloridum; Sch-9384.

Оксиметазолина Гидрохлорид

$C_{16}H_{24}N_2O,HCl$ = 296.8.
CAS — 2315-02-8.
ATC — R01AA05; R01AB07; S01GA04.
ATC Vet — QR01AA05; QR01AB07; QS01GA04.

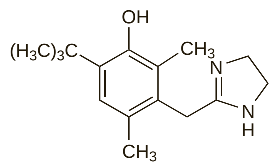

(oxymetazoline)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Oxymetazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 31 (Oxymetazoline Hydrochloride). A white to practically white, fine, hygroscopic, crystalline powder. Soluble 1 in 6.7 of water, 1 in 3.6 of alcohol, and 1 in 862 of chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 4.0 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Naphazoline, p.1565.

Porphyria. Oxymetazoline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Since oxymetazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p.1407.

Uses and Administration

Oxymetazoline is a direct-acting sympathomimetic (p.1408) with marked alpha-adrenergic activity. It is a vasoconstrictor and reduces swelling and congestion when applied to mucous membranes. It acts within a few minutes and the effect lasts for up to 12 hours. It is used as the hydrochloride for the symptomatic relief of nasal congestion (p.1548). In adults and children over 6 years, a 0.05% solution of oxymetazoline hydrochloride is applied topically as nasal drops or a spray, usually 2 or 3 times daily to each nostril as required. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including oxymetazoline) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

A 0.025% solution of oxymetazoline hydrochloride may be instilled into the eye every 6 hours when necessary as a conjunctival decongestant in adults and children over 6 years (see Conjunctivitis, p.564).

Preparations

USP 31: Oxymetazoline Hydrochloride Nasal Solution; Oxymetazoline Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Apracur Nasal; Dristan Nasal†; Isly†; Lidil; Newclar; Rinox VX; Vick Sinex†; Visine D; Yusin; ***Austral.:*** Chemists Own Decongestant Nasal Spray†; Dimetapp 12 Hour Nasal; Drixine Nasal; Logicin Rapid Relief; Ordov Sinudec†; ***Austria:*** Nasivin; ***Belg.:*** Nesivine; Rhino Humex; Vicks Sinex; ***Braz.:*** Afrin; Aturgyl; Desfrin; Freenal; Nasivin; ***Canad.:*** Claritin Allergic Congestion Relief; Claritin Eye Allergy Relief; Decongestant Nasal Mist; Dristan; Drixoral; Long Lasting Nasal Mist; Nafrine†; Vicks Sinex; Visine Workplace; ***Chile:*** Facimin; Iliadin; Isly†; Oxilin; ***Cz.:*** Iversal†; Nasivin; Oxamet; ***Denm.:*** Drixin; Iliadin; ***Fin.:*** Vicks Sinex; ***Fr.:*** Aturgyl; ***Ger.:*** Em-medical Mono†; Nasivin; Nasivin gegen Schnupfen†; Nasivin Sanft; Nasivinetten gegen Schnupfen†; Vistoxyn; Wick Sinex; ***Gr.:*** Narol; Ronal; ***Hong Kong:*** Afrin; Duration; Iliadin; Logicin Rapid Relief; Long Lasting Decongestant Nasal Mist; Nezeril†; Oxylin†; ***Hung.:*** Afrin; Nasivin; ***India:*** Naselin; Nasivion; Sinarest; Sinarest-PD; ***Indon.:*** Afrin; Iliadin; Visine LR; ***Irl.:*** Dristan†; ***Israel:*** Af-Tipa; Alrin; Nasivin†; Rhinoclir; Sinulen; ***Ital.:*** Actifed Nasale; Coricidin†; Oxilin; Rino Calyptol; ***Jpn:*** Nasivin; ***Malaysia:*** Afrin; Iliadin; Oxynase†; ***Mex.:*** Afrin; Fracidin†; Iliadin; Naztril; Ocuclear†; Oxylin; Sinex; Visine AD; ***Neth.:*** Nasivin; Oxylin; Vicks Sinex; ***Norw.:*** Iliadin; Rhinox; ***NZ:*** At-Eze; Dimetapp 12 Hour Nasal; Drixine†; ***Philipp.:*** Drixine; Nasivin; ***Pol.:*** Acatar; Afrin; Nasivin; Nosox; Oxalin; Resoxym; ***Port.:*** Alerjon; Bisolspray; Nasarox; Nasex; Nasorhinathiol; Neozine†; Oxylin; Rinerge; Sinexsensi; Vicks Vapospray; ***Rus.:*** Nasivin (Називин); Nazol (Назол); Sanorinchik (Саноринчик); ***S.Afr.:*** Dristan; Drixine; Iliadin; Merck-P Nasal†; Oxylin; Sparkling White Eye Drops; Vicks Decongestant; ***Singapore:*** Afrin; Iliadin; Nazolin; Oxy-Nase; Utabon; ***Spain:*** Alerfrin; Antirrinum; Corilisina; Couldespir; Idasal Nebulizador†; Ilvinax; Nasolina; Nebulicina; Oftinal; Respibien; Respir; Serranasal; Utabon; ***Swed.:*** Iliadin; Nasin; Nezeril; Zolin†; ***Switz.:*** Nasivine; Nasivinettes†; Vistoxyn†; ***Thai.:*** Iliadin; Oxymet; ***Turk.:*** Iliadin; Oksinazal; ***UAE:*** Nasivin; ***UK:*** Afrazine; Nasivin; Vicks Sinex; ***USA:*** 4-Way Long Lasting; Afrin; Allerest 12 Hour Nasal; Chlorphed-LA; Dristan 12-hr Nasal Decongestant Spray; Dristan Long Lasting; Duramist Plus; Duration; Genasal; Nasal Relief; Nasal Spray; Neo-Synephrine 12 Hour; Nostrilla; NTZ Long Acting Nasal; Ocuclear†; Twice-A-Day; Vicks Sinex 12-Hour; Visine LR; ***Venez.:*** Afrin; Airfen; Clarix; Drixine; Nasin; Solarsal†.

Multi-ingredient: ***Arg.:*** Panoxi; ***Austral.:*** Nasex; Vasylox†; Vicks Sinex; ***Austria:*** Wick Sinex; ***Fr.:*** Deturgylone; ***Hong Kong:*** Bonjedex; ***Hung.:*** Nasopax; ***Israel:*** Sinaf; ***Ital.:*** Triaminic; Vicks Sinex; ***Mex.:*** Grimal; Hyalox; ***NZ:*** Vicks Sinex; ***Rus.:*** Nazol Advance (Назол Адванс); ***S.Afr.:*** Nazene Z; ***Spain:*** Egarone†; Seniospray; Vicks Spray; ***Switz.:*** Vicks Sinex.

Pentoxyverine *(BAN, rINN)*

Carbetapentane; Pentoksiveriini; Pentoxiverin; Pentoxiverina; Pentoxyvérine; Pentoxyverinum. 2-[2-(Diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate.

Пентоксиверин

$C_{20}H_{31}NO_3$ = 333.5.
CAS — 77-23-6.
ATC — R05DB05.
ATC Vet — QR05DB05.

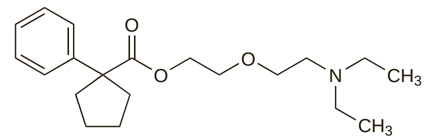

Pentoxyverine Citrate *(BANM, rINNM)*

Carbetapentane Citrate; Citrato de pentoxiverina; Pentoksiveriinivetysitraatti; Pentoksiverino-vandenilio citratas; Pentoxiverin-hidrogén-citrát; Pentoxiverinvätecitrat; Pentoxyverin-citrát; Pentoxyvérine, Citrate de; Pentoxyverine Hydrogen Citrate; Pentoxyvérine, hydrogénocitrate de; Pentoxyverini Citras; Pentoxyverini hydrogenocitras; UCB-2543.

Пентоксиверина Цитрат

$C_{20}H_{31}NO_3,C_6H_8O_7$ = 525.6.
CAS — 23142-01-0.
ATC — R05DB05.
ATC Vet — QR05DB05.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Pentoxyverine Hydrogen Citrate; Pentoxyverine Citrate BP 2008). A white or almost white crystalline powder. M.p. about 93°. Freely soluble in water and in methyl alcohol; soluble in alcohol and in dichloromethane; very soluble in glacial acetic acid. A 10% solution in water has a pH of 3.3 to 3.7. Protect from light.

Pentoxyverine Hydrochloride *(BANM)*

Pentoksiverin Hidroklorür; Pentoxiverina, hidrocloruro de.

Пентоксиверина Гидрохлорид

$C_{20}H_{31}NO_3,HCl$ = 369.9.
CAS — 1045-21-2.
ATC — R05DB05.
ATC Vet — QR05DB05.

Profile

Pentoxyverine is a centrally acting cough suppressant used for non-productive cough (p.1547). Usual doses of up to 180 mg daily of the citrate or hydrochloride have been given orally in divided doses. The tannate is also given orally and the base has been given rectally.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Nyal Dry Cough†; ***Austria:*** Atenos; Sedotussin; ***Belg.:*** Balsoclase Antitussivum; Tuclase; ***Cz.:*** Sedotussin†; ***Denm.:*** Toclase†; ***Fin.:*** Toclase; ***Fr.:*** Pectosan Toux Seche; Toclase Toux Seche; Vicks Pectoral; ***Ger.:*** Pertix-Solo-N, Pertix-T, Pertix-Z, and Pertix-L†; Sedotussin; ***Gr.:*** Tuclase; ***Hong Kong:*** Toclase; ***Hung.:*** Sedotussin; ***Ital.:*** Tuclase; ***Neth.:*** Balsoclase; Tuclase; ***Norw.:*** Toclase; ***Philipp.:*** Toclase; ***Swed.:*** Toclase; ***Thai.:*** Toclase; ***Turk.:*** Toclase; ***USA:*** Solotuss; ***Venez.:*** Carbin†.

Multi-ingredient: ***Arg.:*** Bio Grip Plus; Rynatus†; Wilpan Antigripal; Wilpan C†; ***Austral.:*** Vicks Cough Syrup; ***Austria:*** Tussoretardin; ***Belg.:*** Balsoclase Expectorans; ***Braz.:*** Alergo Glucalbet†; Coldrin; Gegrip†; Resprin; ***Fin.:*** Toclase Expectorant; ***Ger.:*** Sedotussin plus†; ***Hong Kong:*** Coci-Fedra; Marflu-X; Vida Cough; ***Neth.:*** Balsoclase Compositum; Balsoclase-E; ***S.Afr.:*** Vicks Acta Plus; ***Switz.:*** Sedotussin†; ***Turk.:*** Gayaben; ***USA:*** AMBI 1000/5; Aridex; BetaVent; C-Tanna 12D; Carb Pseudo-Tan; Carbatab; Diphen Tann/ PE Tann/ CT Tann; Duratuss CS; Dynex VR; Dytan-AT; Dytan-CD; Dytan-CS; Exratuss; Extendryl GCP; Levall; Levall 12; Oratuss; Pyrlex CB; Re-Tann; Rentamine Pediatric; Respi-Tann G; Ry-Tuss†; Rynatuss; Tannic-12; Tri-Tannate Plus Pediatric; Tuss-Tan; Tussi-12; Tussi-12 D; Tussi-12 S; Tussizone; Vazotan; XiraTuss; Xpect-AT; ***Venez.:*** Resprin; Tolmex; Yerba Santa.

Phenylephrine *(BAN, rINN)*

Fenilefrin; Fenilefrina; Fenilefrinas; Fenylefrin; Fenyyliefriini; Phényléphrine; Phenylephrinum; *m*-Synephrine. (1*R*)-1-(3-Hydroxyphenyl)-2-methylaminoethanol.

Фенилэфрин

$C_9H_{13}NO_2$ = 167.2.

CAS — 59-42-7.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

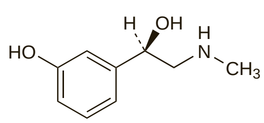

NOTE. Synephrine has been used as a synonym for oxedrine (p.1364). Care should be taken to avoid confusion with phenylephrine (*m*-synephrine).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Phenylephrine). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. It dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Phenylephrine Acid Tartrate

Phenylephrine Bitartrate *(rINNM)*; Bitartrato de fenilefrina; Phényléphrine, Bitartrate de; Phenylephrine Tartrate *(BANM)*; Phenylephrini Bitartras; Tartrato ácido de fenilefrina.

Фенилэфрина Битартрат

$C_9H_{13}NO_2,C_4H_6O_6$ = 317.3.

CAS — 13998-27-1.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

Pharmacopoeias. In *US.*

USP 31 (Phenylephrine Bitartrate). A white or almost white powder or colourless crystals. Freely soluble in water. pH of a 10% solution in water is between 3.0 and 4.0. Store in airtight containers. Protect from light.

Phenylephrine Hydrochloride *(BANM, rINNM)*

Fenilefrin Hidroklorür; Fenilefrin-hidroklorid; Fenilefrino hidrochloridas; Fenylefrin hydrochlorid; Fenylefrinhydroklorid; Fenylefryny chlorowodorek; Fenyyliefriinihydrokloridi; Hidrocloruro de fenilefrina; Mesatonum; Metaoxedrini Chloridum; Phényléphrine, chlorhydrate de; Phenylephrini hydrochloridum.

Фенилэфрина Гидрохлорид

$C_9H_{13}NO_2,HCl$ = 203.7.

CAS — 61-76-7.

ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.

ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.

NOTE. PHNL is a code approved by the BP 2008 for use on single unit doses of eye drops containing phenylephrine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Phenylephrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 31 (Phenylephrine Hydrochloride). White or practically white, odourless, crystals. Freely soluble in water and in alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Phenylephrine is stated to be incompatible with the local anaesthetic butacaine.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407; phenylephrine has mainly alpha-agonist effects. It has a longer duration of action than noradrenaline and an excessive vasopressor response may cause a prolonged rise in blood pressure. It induces tachycardia or reflex bradycardia and should therefore be avoided in severe hyperthyroidism and used with caution in severe ischaemic heart disease. Patients with diabetes mellitus or prostatic hyperplasia should also avoid phenylephrine.

Since phenylephrine is absorbed through the mucosa systemic effects may follow application to the eyes or the nasal mucosa. In particular, phenylephrine 10% eye drops can have powerful systemic effects. They should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis. Fatalities have been reported in patients with pre-existing cardiovascular disease.

Use of phenylephrine in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Ophthalmic solutions of phenylephrine are contra-indicated in patients with angle-closure glaucoma. Corneal clouding may occur if corneal epithelium has been denuded or damaged.

Excessive or prolonged use of phenylephrine nasal drops can lead to rebound congestion.

Phenylephrine hydrochloride is irritant and may cause local discomfort at the site of application; extravasation of the injection may even cause local tissue necrosis.

Effects on the cardiovascular system. Systemic adverse effects have occurred after the use of phenylephrine as eye drops (particularly at a strength of 10%), or nasal drops.

Hypertension[1] and hypertension with pulmonary oedema[2] have been described in infants and children after the use of phenylephrine 10% eye drops. Hypertension with arrhythmias has also been reported in an 8-year-old child[3] and in an adult[4] after phenylephrine 10% eye drops had been used. Details have also been published on a series of 32 patients who had systemic cardiovascular reactions, including fatal myocardial infarctions, after the use of phenylephrine 10% solutions in the eye.[5] Severe cardiovascular adverse reactions have also been reported to the use of phenylephrine as topical 10% ocular[6] or 0.25% nasal[7] pledgets. Although the incidence of such reactions seems low,[8] the use of lower concentrations[1,5] and caution in susceptible patients such as those with cardiovascular disorders or the elderly,[5] have been advocated. A reduction in the eye-drop volume has been found to produce adequate mydriasis and may reduce systemic absorption and the risk of adverse cardiovascular effects.[9,10]

1. Borromeo-McGrail V, *et al.* Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. *Pediatrics* 1973; **51:** 1032–6.
2. Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. *Br J Anaesth* 2002; **88:** 440–2.
3. Vaughan RW. Ventricular arrhythmias after topical vasoconstrictors. *Anesth Analg* 1973; **52:** 161–5.
4. Lai Y-K. Adverse effect of intraoperative phenylephrine 10%: case report. *Br J Ophthalmol* 1989; **73:** 468–9.
5. Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; **85:** 447–53.
6. Fraunfelder FW, *et al.* Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol* 2002; **134:** 624–5.
7. Hecker RB, *et al.* Myocardial ischemia and stunning induced by topical intranasal phenylephrine pledgets. *Mil Med* 1997; **162:** 832–5.
8. Brown MM, *et al.* Lack of side effects from topically administered 10% phenylephrine eyedrops: a controlled study. *Arch Ophthalmol* 1980; **98:** 487–9.
9. Craig EW, Griffiths PG. Effect on mydriasis of modifying the volume of phenylephrine drops. *Br J Ophthalmol* 1991; **75:** 222–3.
10. Wheatcroft S, *et al.* Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol* 1993; **77:** 364–5.

Effects on the eyes. Acute and chronic conjunctivitis has been reported[1] after use of over-the-counter ophthalmic decongestant preparations of phenylephrine, naphazoline, or tetryzoline. The conjunctival inflammation took several weeks to resolve in some cases. Dermatoconjunctivitis[2] has also been reported after use of phenylephrine eye drops.

1. Soparkar CN, *et al.* Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol* 1997; **115:** 34–8.
2. Moreno-Ancillo A, *et al.* Allergic contact reactions due to phenylephrine hydrochloride in eyedrops. *Ann Allergy Asthma Immunol* 1997; **78:** 569–72.

Effects on mental function. Hallucinations and paranoid delusions have been reported[1] in a patient after excessive use of a nasal spray containing phenylephrine 0.5%. Mania has also followed the use of large oral doses.[2]

1. Snow SS, *et al.* Nasal spray 'addiction' and psychosis: a case report. *Br J Psychiatry* 1980; **136:** 297–9.
2. Waters BGH, Lapierre YD. Secondary mania associated with sympathomimetic drug use. *Am J Psychiatry* 1981; **138:** 837–40.

Hypersensitivity. Cross-sensitivity to phenylephrine has been reported in a patient hypersensitive to pseudoephedrine.[1] See also Effects on the Eyes, above.

1. Buzo-Sanchez G, *et al.* Stereoisomeric cutaneous hypersensitivity. *Ann Pharmacother* 1997; **31:** 1091.

Interactions

As for Sympathomimetics, p.1407. Phenylephrine has mainly direct alpha-agonist properties and is less liable than adrenaline or noradrenaline to induce ventricular fibrillation if used as a pressor agent during anaesthesia with inhalational anaesthetics such as cyclopropane and halothane; nevertheless, caution is necessary. Since phenylephrine is absorbed through the mucosa, interactions may also follow topical application, particularly in patients receiving an MAOI (including a RIMA). See also under Phenelzine (p.418) and Moclobemide (p.411).

Cardiovascular drugs. Hypertensive reactions have been reported in a patient stabilised on *debrisoquine* when given phenylephrine orally,[1] in patients receiving *reserpine* or *guanethidine* when given phenylephrine eye drops,[2] and a fatal reaction occurred in a patient receiving *propranolol* and *hydrochlorothiazide* also after the instillation of phenylephrine eye drops.[3]

1. Aminu J, *et al.* Interaction between debrisoquine and phenylephrine. *Lancet* 1970; **ii:** 935–6.
2. Kim JM, *et al.* Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervation. *Am J Ophthalmol* 1978; **85:** 862–8.
3. Cass E, *et al.* Hazards of phenylephrine topical medication in persons taking propranolol. *Can Med Assoc J* 1979; **120:** 1261–2.

Pharmacokinetics

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about 1 hour and up to about 2 hours, respectively. Intravenous injections are effective for about 20 minutes.

Systemic absorption follows topical application.

Uses and Administration

Phenylephrine hydrochloride is a sympathomimetic (p.1408) with mainly direct effects on adrenergic receptors. It has mainly alpha-adrenergic activity and is without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline (p.1360) but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys.

Phenylephrine and its salts are most commonly used, either topically or by mouth, for the symptomatic relief of **nasal congestion** (p.1548). They are frequently included in preparations intended for the relief of cough and cold symptoms. For nasal congestion, a 0.25 to 1% solution may be instilled as nasal drops or a spray into each nostril every 4 hours as required, or phenylephrine hydrochloride may be given in usual oral doses of 10 mg every four hours (up to a maximum of 60 mg daily) or 12 mg up to four times daily.

In ophthalmology, phenylephrine hydrochloride is used as a **mydriatic** (p.1874) in concentrations of up to 10%; generally solutions containing 2.5 or 10% are used but systemic absorption can occur (see Effects on the Cardiovascular System, above) and the 10% strength, in particular, should be used with caution. The mydriatic effect can last several hours. Solutions containing 2.5% or more may cause intense irritation and a local anaesthetic other than butacaine (which is incompatible) should be instilled into the eye a few minutes beforehand.

Ocular solutions containing lower concentrations (usually 0.12% phenylephrine hydrochloride) are used as a **conjunctival decongestant** (see Conjunctivitis, p.564).

Phenylephrine has been used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure or spinal anaesthesia. Phenylephrine has also been used in orthostatic hypotension (see under Fludrocortisone, p.1530). For **hypotension**, an initial dose of phenylephrine hydrochloride 2 to 5 mg may be given as a 1% solution subcutaneously or intramuscularly with further doses of 1 to 10 mg if necessary, according to response. A dose of 100 to 500 micrograms by slow intravenous injection as a 0.1% solution, repeated as necessary after at least 15 minutes, has also been used. In severe hypotensive states, 10 mg in 500 mL of glucose 5% or sodium chloride 0.9% has been infused intravenously, initially at a rate of up to 180 micrograms/minute, reduced, according to the response, to 30 to 60 micrograms/minute.

For children's doses, see Administration in Children, below.

Phenylephrine hydrochloride has been given by intravenous injection to stop **paroxysmal supraventricular tachycardia** but other drugs are preferred (see Cardiac Arrhythmias, p.1160). The initial dose is usually not greater than 500 micrograms given as a 0.1% solution with subsequent doses gradually increased in increments of 100 to 200 micrograms up to 1 mg if necessary.

Phenylephrine hydrochloride has been used for its vasoconstrictor action as an **adjunct** to local anaesthetics.

Phenylephrine has also been used as the acid tartrate to prolong the bronchodilator effects of isoprenaline when given by inhalation. However, isoprenaline is now little used by this route.

Phenylephrine tannate has also been used.

Administration in children. Phenylephrine hydrochloride is used for the symptomatic relief of **nasal congestion**; however, over-the-counter cough and cold preparations containing sympathomimetic decongestants (including phenylephrine) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547). In the USA, the following doses have been used in children:

- 2 to 6 years: 2 or 3 drops of a 0.125% or 0.16% solution into each nostril every four hours as needed
- 6 to 12 years: 2 or 3 drops, or 1 or 2 sprays, of a 0.25% solution may be instilled into each nostril every four hours as needed.

In the UK, oral preparations for nasal congestion associated with colds and hay fever are not licensed in children under 12 years of age.

Phenylephrine is used for **mydriasis** in diagnostic or therapeutic procedures. Solutions containing 2.5% are used in children as the 10% strength is contra-indicated owing to the risk of systemic effects.

For acute **hypotension**, the *BNFC* states that phenylephrine hydrochloride may be given subcutaneously or intramuscularly in the following doses:

- 1 to 12 years: 100 micrograms/kg every 1 to 2 hours as needed (to a maximum dose of 5 mg)
- 12 to 18 years: 2 to 5 mg, followed if necessary by further doses of 1 to 10 mg (maximum initial dose 5 mg)

Although the intravenous route is not licensed in the UK for such use in children, intravenous injection is preferred to the other parenteral routes; the *BNFC* recommends the following doses given as a 0.1% solution:

- 1 to 12 years: 5 to 20 micrograms/kg (maximum 500 micrograms), repeated as needed after at least 15 minutes.
- 12 to 18 years: 100 to 500 micrograms, repeated as needed after at least 15 minutes

For intravenous infusion, the solution is diluted with glucose 5% or sodium chloride 0.9% to a concentration of 20 micrograms/mL and given as a continuous infusion via a central venous catheter. The *BNFC* gives the following doses:

- 1 to 16 years: 100 to 500 nanograms/kg per minute, adjusted according to response
- 16 to 18 years: initially up to 180 micrograms/minute, reduced to 30 to 60 micrograms/minute according to response

Faecal incontinence. Topical application of phenylephrine gel has been shown to increase resting anal tone[1] and has been investigated in patients with faecal incontinence.[2] Although application of a 10% gel did not appear to be of clinical benefit in a double-blind crossover study in 36 patients with faecal incontinence caused by internal sphincter dysfunction,[3] continence was improved in another small study in patients with ileoanal pouches.[4]

1. Cheetham MJ, *et al.* Topical phenylephrine increases anal canal resting pressure in patients with faecal incontinence. *Gut* 2001; **48:** 356–9.
2. Cheetham M, *et al.* Drug treatment for faecal incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 04/01/07).
3. Carapeti EA, *et al.* Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence. *Br J Surg* 2000; **87:** 38–42.
4. Carapeti EA, *et al.* Randomized, controlled trial of topical phenylephrine for fecal incontinence in patients after ileoanal pouch construction. *Dis Colon Rectum* 2000; **43:** 1059–63.

Nasal congestion. A meta-analysis concluded that there was insufficient evidence that phenylephrine 10 mg was an effective oral decongestant.[1]

1. Hatton RC, *et al* Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. *Ann Pharmacother* 2007; **41:** 381–90.

Priapism. Alpha agonists, including phenylephrine, may be used in the management of priapism (see under Metaraminol, p.1333). For reference to phenylephrine in low dosage and dilute solution being given by intracavernosal injection to reverse priapism, see under Alprostadil, p.2184.

Preparations

BP 2008: Phenylephrine Eye Drops; Phenylephrine Injection;
USP 31: Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Phenylephrine Hydrochloride Injection; Phenylephrine Hydrochloride Nasal Jelly; Phenylephrine Hydrochloride Nasal Solution; Phenylephrine Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Fadalefrina; Mydfrin†; Poen Efrina; Prefrin; Qura Nasal; ***Austral.:*** Actifed PE; Albalon Relief; Isopto Frin†; Neo-Synephrine; Nyal Decongestant; Nyal Sinus Relief†; Prefrin; Sudafed PE; Visopt†; ***Austria:*** Visadron; ***Belg.:*** Spraydil; Visadron; ***Braz.:*** Denason; ***Canad.:*** Ak-Dilate†; Dionephrine; Mydfrin; Neo-Synephrine; Prefrin; Triaminic Thin Strips Nasal Congestion; Triaminic Toddler Congestion; ***Chile:*** Mydfrin; ***Cz.:*** Humex Nosni; Neo-Synephrine; Visadron†; ***Fin.:*** Oftan Metaoksedrin†; ***Fr.:*** Auristan†; Neosynephrine; ***Ger.:*** Neo-Mydrial†; Neosynephrin-POS; Otriven Baby; Visadron; ***Hong Kong:*** Mydfrin; Prefrin; ***India:*** Drosyn; Pupiletto†; ***Irl.:*** Isopto Frin†; ***Israel:*** Af-Taf; Efrin; Neo-Synephrine; Prefrin†; ***Ital.:*** Isonefrine; Neo-Synephrine; Ribex Nasale†; Visadron†; ***Malaysia:*** Analux†; Isopto Frin†; Mydfrin; Prefrin†; ***Mex.:*** Dilufrin; Lefrine; Nefrin; Rinolan; Weiscalina†; ***Neth.:*** Boradrine; Visadron; ***NZ:*** Albalon Relief†; Isopto Frin†; Neosynephrine; Prefrin; ***Philipp.:*** Mydfrin; ***Port.:*** Davinefrina; Neo-Sinefrina; VibrocilFen; Visadron; ***Rus.:*** Irifrin (Ирифрин); Nazol Baby (Назол Бэби); Nazol Kids (Назол Кидс); ***S.Afr.:*** I-Glo; Naphensyl; Prefrin; ***Singapore:*** Isopto Frin†; Mydfrin; Prefrin†; ***Spain:*** ADA; Analux†; Boraline; Disneumon Mentol; Disneumon Pernasal; Mirazul; Rin Up†; Visadron; Vistafrin; ***Switz.:*** Gouttes nasales†; Rexophtal N; Spray nasal pour enfants; ***Turk.:*** Mydfrin; ***UK:*** Boots Decongestant Capsules; Fenox; Non-Drowsy Sudafed Congestion Relief; ***USA:*** AH-chew D; Ak-Dilate; Children's Nostril; Lusonal; Medicone†; Mydfrin; Nasop; Neo-Synephrine; Neofrin; Nostril; Ocu-Phrin; Pedia Care Childrens Decongestant; Phenoptic†; Phenyl-T; Prefrin†; Pretz-D†; Rectacaine; Relief; Rhinall; Sinex; Sudafed PE; Triaminic Infant Thin Strips Decongestant; Triaminic Thin Strips Cold; Tronolane.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Braz.:*** Anestesico.

Phenylpropanolamine *(BAN, rINN)*

Fenilpropanolamina; Fennylpropanolamin; Fenyylipropanoliamiini; (±)-Norephedrine; Phénylpropanolamine; Phenylpropanolaminum. (1*RS*,2*SR*)-2-Amino-1-phenylpropan-1-ol.

Фенилпропаноламин

$C_9H_{13}NO$ = 151.2.

CAS — 14838-15-4.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

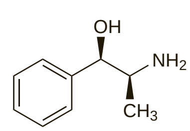

(+)-Form

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phenylpropanolamine: Pseudocaine.

Phenylpropanolamine Hydrochloride

(BANM, rINNM)

Fenilpropanolamin-hidroklorid; Fenilpropanolamino hidrochloridas; Fenylpropanolamin hydrochlorid; Fenylpropanolaminhydroklorid; Fenyylipropanoliamiinihydrokloridi; Hidrocloruro de fenilpropanolamina; Mydriatin; Phénylpropanolamine, chlorhydrate de; Phenylpropanolamini Hydrochloridum; Phenylpropanolamini hydrochloridum.

Фенилпропаноламина Гидрохлорид

$C_9H_{13}NO,HCl$ = 187.7.

CAS — 154-41-6.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

US also includes phenylpropanolamine bitartrate.

Ph. Eur. 6.2 (Phenylpropanolamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane.

USP 31 (Phenylpropanolamine Hydrochloride). A white crystalline powder, having a slight aromatic odour. Soluble 1 in 1.1 of water, 1 in 7.4 of alcohol, and 1 in 4100 of chloroform; insoluble in ether. pH of a 3% solution in water is between 4.2 and 5.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Ephedrine, p.1558.

Severe hypertensive episodes have followed phenylpropanolamine ingestion (see below). As with other indirect-acting sympathomimetics, tolerance to the therapeutic effects of phenylpropanolamine has been reported with prolonged use.

◊ An extensive and detailed review[1] of adverse effects attributed to phenylpropanolamine noted in 1990 that many of the adverse drug reactions reported in Europe described an alteration of mental status whereas those in North America were more often compatible with hypertension. The author suggested that this might be due to a difference in the isomers present in phenylpropanolamine preparations, based on earlier reports that *d*-norpseudoephedrine, the most potent of several isomeric forms as a stimulant of the CNS, was present in European preparations of phenylpropanolamine. However, later investigation suggests that currently the racemic mixture (±)-norephedrine (*d*,*l*-norephedrine) is the isomeric form present in commercial preparations in both Europe and the USA.[2]

The original review[1] concentrated on North American cases. The majority of products available were decongestants or cough or cold remedies; a small number were promoted as diet aids.

The data suggested that over-the-counter (OTC) products were more likely to be associated with an adverse reaction than a prescription medication; this may be because such OTC products were more likely to be overused and to be considered innocuous by the patient. It was also likely that drug interactions (below) rather than 'true overdosages' were involved in many of the adverse events, particularly as many OTC preparations contain other ingredients. (See also Abuse under Ephedrine, p.1558, for further discussion about the consequences of use of OTC preparations containing sympathomimetics, including phenylpropanolamine.)

The adverse reactions varied widely ranging from headache and elevated blood pressure to cardiopulmonary arrest, intracranial haemorrhage, and death. Mild reactions included blurred vision, dizziness, anxiety, agitation, tremor, confusion, and hypersensitivity reaction. Severe reactions included hypertensive crisis with hypertensive encephalopathy, seizures, arrhythmias, psychosis, and acute tubular necrosis. One unifying theme of many of the severe cases was that high blood pressure or symptoms suggestive of this were the presenting feature; an acute, persistent, severe headache was also noted in many cases.

It was pointed out that overall phenylpropanolamine was relatively safe. Although billions of doses were consumed annually, few cases of adverse drug reactions had been reported.

It was believed that certain groups may be at particular risk of adverse reactions to phenylpropanolamine: persons with elevated blood pressure, overweight persons (who are likely to be both hypertensive and to use diet aids), patients with eating disorders (who tend to abuse substances including diet aids), and the elderly (who may be multiple drug takers and likely to be hypertensive and at risk already of a stroke).

Subsequently, after a large case-control study in the USA which found an increased risk of haemorrhagic stroke associated with the use of preparations containing phenylpropanolamine (and in particular in women who used phenylpropanolamine as an appetite suppressant),[3] the FDA took steps to remove phenylpropanolamine from all drug products in the USA and requested that it no longer be marketed. Products containing phenylpropanolamine have also been withdrawn in some other countries. However, this study and the FDA decision have been criticised[4-6] notably on the basis that there was no evidence of an increased risk with the amount of phenylpropanolamine normally present in decongestant preparations and the study may have been subject to confounding. The UK CSM[7] considered that the evidence of a link between UK products containing phenylpropanolamine and haemorrhagic stroke was weak (phenylpropanolamine is not licensed as an appetite suppressant in the UK and the maximum recommended dose of 100 mg daily was lower than the 150 mg daily recommended in the USA). It was therefore suggested by UK commentators that use of licensed doses, with appropriate precautions, posed no additional risk.[2] However, subsequently, UK preparations containing phenylpropanolamine have either been reformulated (mainly with pseudoephedrine) or withdrawn by the manufacturers.

1. Lake CR, *et al.* Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990; **89:** 195–208.
2. Moffatt T, *et al.* Phenylpropanolamine: putting the record straight. *Pharm J* 2000; **265:** 817.
3. Kernan WN, *et al.* Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000; **343:** 1826–32.
4. Ernst ME, Hartz A. Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094.
5. Wolowich WR, *et al.* Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094–5.
6. Stier BG, Hennekens CH. Phenylpropanolamine and hemorrhagic stroke in the Hemorrhagic Stroke Project: a reappraisal in the context of science, the Food and Drug Administration, and the law. *Ann Epidemiol* 2006; **16:** 49–52.
7. Committee on Safety of Medicines/Medicines Control Agency. Phenylpropanolamine and haemorrhagic stroke. *Current Problems* 2001; **27:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 04/01/07)

Interactions

As for Sympathomimetics, p.1407. For a comment that drug interactions were likely to have been involved in many adverse events associated with phenylpropanolamine see under Adverse Effects and Precautions, above. Due to its indirect action, hypertensive crisis is a particular risk in patients receiving MAOIs.

Amantadine. Severe psychosis has been reported[1] in a woman taking amantadine with phenylpropanolamine. In another report,[2] a 39-year-old man had intense and recurrent *déjà vu* experiences after taking amantadine with phenylpropanolamine for viral influenza. The effect ceased when he stopped both drugs. The authors suggested that his symptoms were due to increased dopamine activity caused by the combination.

1. Stroe AE, *et al.* Psychotic episode related to phenylpropanolamine and amantadine in a healthy female. *Gen Hosp Psychiatry* 1995; **17:** 457–8.
2. Taiminen T, Jääskeläinen SK. Intense and recurrent déjà vu experiences related to amantadine and phenylpropanolamine in a healthy male. *J Clin Neurosci* 2001; **8:** 460–2.

Antipsychotics. A 27-year-old woman with schizophrenia and T-wave abnormality of the heart, who had responded to *thioridazine* 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with phenylpropanolamine hydrochloride 50 mg (*Contac C*), concurrently with thioridazine.[1]

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Antivirals. A patient taking an over-the-counter nasal decongestant preparation containing phenylpropanolamine and clemastine as well as a triple-drug HIV prophylactic regimen, had a hypertensive crisis 3 days after *stavudine* was substituted for *zidovudine*;[1] the other antivirals in the regimen were *indinavir* and *lamivudine*.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Bromocriptine. For a report of hypertension and life-threatening complications after use of phenylpropanolamine with bromocriptine, see Sympathomimetics, p.800.

NSAIDs. A 27-year-old woman who had been taking D-phenylpropanolamine [sic] 85 mg daily for some months, experienced severe hypertension when she also took *indometacin* 25 mg. It was considered that the inhibition of prostaglandin synthesis by indometacin might have caused enhancement of the sympathomimetic effect of phenylpropanolamine.[1]

1. Lee KY, *et al.* Severe hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. *Lancet* 1979; **i:** 1110–11.

Pharmacokinetics

Phenylpropanolamine is readily and completely absorbed from the gastrointestinal tract, peak plasma concentrations being achieved about 1 or 2 hours after oral doses. It undergoes some metabolism in the liver, to an active hydroxylated metabolite, but up to 80 to 90% of a dose is excreted unchanged in the urine within 24 hours. The half-life has been reported to be about 3 to 5 hours.

◊ References.

1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; **129:** 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57:** 62–7.

Uses and Administration

Phenylpropanolamine is a mainly indirect-acting sympathomimetic (p.1408) with an action similar to that of ephedrine (p.1559) but less active as a CNS stimulant.

Phenylpropanolamine has been given orally as the hydrochloride for the symptomatic treatment of **nasal congestion** (p.1548). It has frequently been used in combination preparations for the relief of cough and cold symptoms.

In the management of nasal congestion, phenylpropanolamine hydrochloride has been given in oral doses of up to 50 mg twice daily as modified-release preparations.

Other uses of phenylpropanolamine have included the control of urinary incontinence in some patients (see p.2180). It has also been given in the management of some forms of priapism (see under Metaraminol, p.1333). Phenylpropanolamine has been used to suppress appetite in the management of obesity (p.2149) but the use of stimulants is no longer recommended.

Phenylpropanolamine polistirex (a phenylpropanolamine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as have phenylpropanolamine bitartrate, phenylpropanolamine maleate, and phenylpropanolamine sulfate.

Preparations

USP 31: Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Capsules; Phenylpropanolamine Hydrochloride Extended-release Capsules; Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Oral Solution; Phenylpropanolamine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Fin.: Rinexin; ***Ger.:*** Boxogetten S; Recatol mono; ***Norw.:*** Rinexin; ***Philipp.:*** Decolgen; Desotap; Disudrin; Naldec; Nasadec; Nasaphen; Nasathera P; Neo-Coldan; ***S.Afr.:*** Restaslim†; ***Swed.:*** Rinexin; ***Switz.:*** Kontexin†; Merex†; Slim Caps.

Multi-ingredient: numerous preparations are listed in Part 3.

Pholcodine *(BAN, rINN)*

Folcodina; Folkodiini; Folkodin; Folkodin monohydrát; Folkodinas; Pholcodinum; Pholcodinum Monohydricum. 3-*O*-(2-Morpholinoethyl)morphine monohydrate.

Фолкодин

$C_{23}H_{30}N_2O_4,H_2O = 416.5.$
CAS — 509-67-1 (anhydrous pholcodine).
ATC — R05DA08.
ATC Vet — QR05DA08.

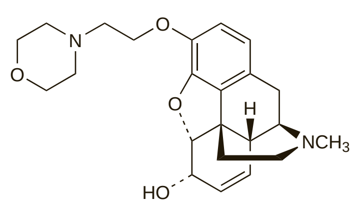

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Pholcodine). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; freely soluble in alcohol and in acetone; dissolves in dilute mineral acids.

Adverse Effects and Precautions

As for Dextromethorphan, p.1555. Constipation, drowsiness, and skin rashes have been reported occasionally.

Interactions

Use of pholcodine with alcohol or other CNS depressants may increase the effects on the CNS.

Uses and Administration

Pholcodine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p.1556). It is given orally in a usual dose of 5 to 10 mg three or four times daily. For children's doses, see Administration in Children, below. The citrate has also been used. Pholcodine polistirex (a pholcodine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has been used in modified-release preparations.

Administration in children. Although pholcodine is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including pholcodine) should be used with caution and generally avoided in those under 2 years of age (see p.1547). The following oral doses of pholcodine are given in the *BNFC* for use in children:

- 2 to 5 years: 2 mg three times daily
- 5 to 12 years: 2 to 5 mg three or four times daily

Preparations

BP 2008: Pholcodine Linctus; Strong Pholcodine Linctus.

Proprietary Preparations (details are given in Part 3)
Austral.: Actifed CC Dry; Actuss†; Duro-Tuss; Logicin Cough Suppressant†; Nyal Plus+ Dry Cough†; Ordov Dry Tickly Cough†; Pholtrate†; Tussinol; ***Cz.:*** Neocodin†; ***Fin.:*** Tuxi; ***Fr.:*** Biocalyptol; Broncorinol toux seche†; Codotussyl Toux Seche; Dimetane; Humex; Pharmakod toux seche; Respilene; Rhinathiol Toux Seche Pholcodine; Sirop des Vosges Toux Seche; ***Hong Kong:*** Duro-Tuss; Uni-Pholco; ***Irl.:*** Expulin Dry Cough; Pholcodex; Pholcolin; ***Malaysia:*** Dhacodine; Duro-Tuss; ***Norw.:*** Tuxi; ***NZ:*** Actifed CC Dry†; Duro-Tuss; ***S.Afr.:*** Pholcolinct; Pholtex; ***Singapore:*** Duro-Tuss; ***Spain:*** Trophires†; ***UK:*** Benylin Childrens Dry Coughs; Boots Dry Cough Syrup 1 Year Plus; Galenphol; Hill's Balsam Dry Cough; Pavacol-D; Tixylix Daytime.

Multi-ingredient: ***Austral.:*** Chemists Own Kiddicol; Demazin Cough & Cold; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant; Duro-Tuss Dry Cough Plus Nasal Decongestant; Duro-Tuss Expectorant; Phensedyl†; Tixylix Nightime; ***Belg.:*** Broncho-pectoralis Pholcodine; Eucalyptine Pholcodine; Eucalyptine Pholcodine Le Brun†; Folex†; Norhitis; Pectorhinyl; Pholco-Mereprine; ***Cz.:*** Biocalyptol S†; ***Fr.:*** Atouxx; Broncalene; Clarix; Denoral†; Hexapneumine; Isomyrtine†; Polery; Trophires; ***Hong Kong:*** Biocalyptol†; Duro-Tuss Decongestant; Duro-Tuss Expectorant; Hexapneumine; Tripe P; ***India:*** Tixylix; ***Irl.:*** Day Nurse; Expulin; Expulin Childrens Cough; ***Malaysia:*** Difflam Anti-Inflammatory Lozenges (with cough suppressant); Duro-Tuss Expectorant; Phensedyl Dry Cough; Promedyl Plus; Rhynacol; Russedyl Plus; Tixylix†; ***NZ:*** Difflam Cough; Duro-Tuss Cough; Duro-Tuss Expectorant; Duro-Tuss Lozenges; Phensedyl Dry Family Cough†; Tixylix; ***S.Afr.:*** Contra-Coff; Docsed; Folcofen; Pholtex Linctus; Procof; Respinol Compound; Tixylix; ***Singapore:*** 3P†; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant; Duro-Tuss Expectorant; ***Spain:*** Caltoson Balsamico; ***Switz.:*** Pecto-Baby; Phol-Tussil; Phol-Tux; Tussiplex†; ***UK:*** Boots Nightime Cough Syrup 1 Year Plus; Cough Nurse; Day & Night Nurse; Day Nurse; Expulin Childrens Cough†; Nirolex Day Cold & Flu; Nirolex Night Cold & Flu; Tixylix Cough & Cold; Tixylix Night-Time.

Pipazetate *(BAN, rINN)*

D-254; Pipazétate; Pipazetato; Pipazetatum; Pipazethate *(USAN)*; SKF-70230-A; SQ-15874. 2-(2-Piperidinoethoxy)ethyl pyrido[3,2-*b*][1,4]benzothiazine-10-carboxylate.

Пипазетат

$C_{21}H_{25}N_3O_3S = 399.5.$
CAS — 2167-85-3.
ATC — R05DB11.
ATC Vet — QR05DB11.

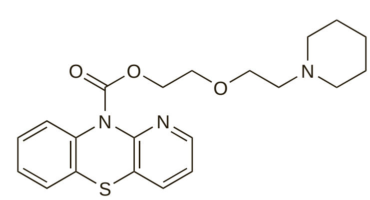

Pipazetate Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipazetato; Pipazétate, Chlorhydrate de; Pipazetati Hydrochloridum; Pipazethate Hydrochloride; Piperestazine Hydrochloride.

Пипазетата Гидрохлорид

$C_{21}H_{25}N_3O_3S,HCl = 436.0.$
CAS — 6056-11-7.
ATC — R05DB11.
ATC Vet — QR05DB11.

Profile
Pipazetate hydrochloride is a centrally acting cough suppressant that also has some peripheral actions in non-productive cough (p.1547). It has been given by mouth and rectally.

Overdosage. A healthy 4-year-old child became somnolent and agitated, with convulsions, followed by coma, after swallowing an unknown number of tablets containing pipazetate; cardiac arrhythmias also developed.[1] Fatal toxicity has also been reported in children.[2,3]

1. da Silva OA, Lopez M. Pipazethate—acute childhood poisoning. *Clin Toxicol* 1977; **11:** 455–8.
2. Bonavita V, *et al.* Accidental lethal pipazethate poisoning in a child. *Z Rechtsmed* 1982; **89:** 145–8.
3. Soto E, *et al.* Pipazethate lethality in a baby. *Vet Hum Toxicol* 1993; **35:** 41.

Preparations
Proprietary Preparations (details are given in Part 3)
Braz.: Selvigon; ***Ital.:*** Selvjgon; ***Mex.:*** Selvigon; ***Thai.:*** Transpulmin†.

Poppy Capsule
Dormideiras; Fruit du Pavot; Fruto de adormidera; Mohnfrucht; Papaveris Capsula; Poppy Heads.

Маковая Коробочка

Pharmacopoeias. In *Chin.*

Profile
Poppy capsule consists of dried fruits of *Papaver somniferum* (Papaveraceae), collected before dehiscence has occurred, containing very small amounts of morphine with traces of other opium alkaloids. It is mildly sedative and has been used as a liquid extract or syrup in cough mixtures.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Sedemol; Sulfa-Sedemol; ***Braz.:*** Malvodon.

Prenoxdiazine Hydrochloride *(rINNM)*
Hidrocloruro de prenoxdiazina; HK-256; Prenoxdiazin Hydrochloride; Prénoxdiazine, Chlorhydrate de; Prenoxdiazini Hydrochloridum. 3-(2,2-Diphenylethyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole hydrochloride.

Преноксдиазина Гидрохлорид

$C_{23}H_{27}N_3O,HCl = 397.9.$

CAS — 47543-65-7 (prenoxdiazine); 37671-82-2 (prenoxdiazine hibenzate); 982-43-4 (prenoxdiazine hydrochloride).

ATC — R05DB18.

ATC Vet — QR05DB18.

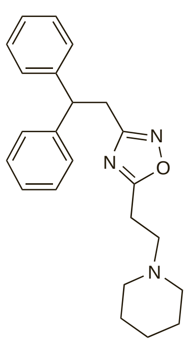

(prenoxdiazine)

Profile
Prenoxdiazine hydrochloride is a peripherally acting cough suppressant for non-productive cough (p.1547) that has been given orally. Prenoxdiazine hibenzate has also been used.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Libexin†; ***Hung.:*** Libexin; Rhinathiol Tusso; ***India:*** Libexin; ***Rus.:*** Libexin (Либексин).

Multi-ingredient: ***Ital.:*** Broncofluid; Libexin Mucolitico.

Promolate *(rINN)*
Morphethylbutyne; Promolato; Promolatum. 2-Morpholinoethyl 2-methyl-2-phenoxypropionate.

Промолат

$C_{16}H_{23}NO_4 = 293.4.$

CAS — 3615-74-5.

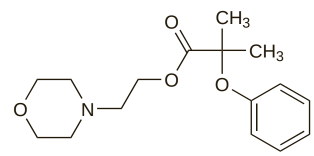

Profile
Promolate is a cough suppressant that has been given rectally to infants.

Preparations
Proprietary Preparations (details are given in Part 3)
Chile: Atusil.

Pseudoephedrine *(BAN, rINN)*
d-Ψ-Ephedrine; *d*-Isoephedrine; Pseudoefedriini; Pseudoefedrin; Pseudoefedrina; Pseudoéphédrine; Pseudoephedrinum. (+)-(1S,2S)-2-Methylamino-1-phenylpropan-1-ol.

Псевдоэфедрин

$C_{10}H_{15}NO = 165.2.$

CAS — 90-82-4.

ATC — R01BA02.

ATC Vet — QR01BA02.

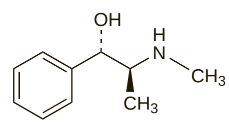

Description. Pseudoephedrine is an alkaloid obtained from *Ephedra* spp.

Pseudoephedrine Hydrochloride
(BANM, USAN, rINNM)

Hidrocloruro de pseudoefedrina; Pseudoefedriinihydrokloridi; Pseudoefedrin-hydrochlorid; Pseudoefedrinhydroklorid; Pseudoefedrino hidrochloridas; Pseudoéphédrine, chlorhydrate de; Pseudoephedrini hydrochloridum; Psödoefedrin Hidroklorür; Pszeudoefedrin-hidroklorid.

Псевдоэфедрина Гидрохлорид

$C_{10}H_{15}NO,HCl = 201.7.$

CAS — 345-78-8.

ATC — R01BA02.

ATC Vet — QR01BA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Pseudoephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Pseudoephedrine Hydrochloride). A fine, white to off-white crystalline powder, having a faint characteristic odour. Soluble 1 in 0.5 of water, 1 in 3.6 of alcohol, 1 in 91 of chloroform, and 1 in 7000 of ether. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers. Protect from light.

Pseudoephedrine Sulfate *(USAN, rINNM)*
Pseudoéphédrine, Sulfate de; Pseudoephedrine Sulphate *(BANM)*; Pseudoephedrini Sulfas; Sch-4855; Sulfato de pseudoefedrina.

Псевдоэфедрина Сульфат

$(C_{10}H_{15}NO)_2,H_2SO_4 = 428.5.$

CAS — 7460-12-0.

ATC — R01BA02.

ATC Vet — QR01BA02.

Pharmacopoeias. In *US.*

USP 31 (Pseudoephedrine Sulfate). Odourless, white crystals or crystalline powder. Freely soluble in alcohol. pH of a 5% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions
As for Ephedrine, p.1558. The commonest adverse effects of pseudoephedrine include tachycardia, anxiety, restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred. Hallucinations have been reported rarely, particularly in children.

◊ In response to reports in the USA of overdosages associated with cough and cold medications, the CDC and the National Association of Medical Examiners investigated deaths in infants aged under 12 months associated with such use; 3 cases were identified. All 3 infants had high concentrations of pseudoephedrine in postmortem blood samples, 2 had detectable blood concentrations of dextromethorphan and paracetamol, and 1 was also found to have detectable concentrations of doxylamine. None of the deaths were determined to be intentional. Two infants had evidence of respiratory infection upon autopsy; no cardiac abnormalities were found in any of the infants.[1]

1. CDC. Infant deaths associated with cough and cold medications—two States, 2005. *MMWR* 2007; **56:** 1–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm (accessed 19/04/07)

Abuse. Acute psychosis and visual and tactile hallucinations have been reported[1] in an 18-year-old male after intravenous misuse of pseudoephedrine hydrochloride. Pseudoephedrine has also been used for the illicit manufacture of street stimulants such as metamfetamine (p.2158).

For reference to toxic effects after long-term use of over-the-counter preparations containing sympathomimetics, such as pseudoephedrine, see under Ephedrine, p.1558.

1. Sullivan G. Acute psychosis following intravenous abuse of pseudoephedrine: a case report. *J Psychopharmacol* 1996; **10:** 324–5.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers that contain pseudoephedrine with dexbrompheniramine maleate have resulted in crying, irritability, and poor sleep patterns in the infant.

The concentrations of pseudoephedrine and triprolidine in plasma and breast milk of 3 mothers for up to 48 hours after ingestion of a preparation containing pseudoephedrine hydrochloride 60 mg with triprolidine hydrochloride 2.5 mg have been studied.[2] Concentrations of pseudoephedrine in milk were consistently higher than in plasma; the half-life in both fluids was between 4.2 and 7.0 hours. Assuming a generous milk secretion of 500 mL over 12 hours it was calculated that the excreted dose was the equivalent of 250 to 330 micrograms of pseudoephedrine base, or 0.5 to 0.7% of the dose ingested by the mothers. Triprolidine did not appear to be concentrated in breast milk. The amounts of pseudoephedrine and triprolidine distributed into breast milk were probably not high enough to warrant cessation of breast feeding.

A small, randomised, crossover study concluded that a single dose of 60 mg pseudoephedrine hydrochloride decreased 24-hour milk production by 24%. The authors of the study suggested that pseudoephedrine might be of benefit for suppressing excess milk production.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/01/07)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; **18:** 901–6.
3. Aljazaf K, *et al.* Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *Br J Clin Pharmacol* 2003; **56:** 18–24.

Convulsions. A child who suffered a generalised seizure after ingesting a large quantity of pseudoephedrine hydrochloride tablets was believed to be the first report of convulsions associated with overdose of a preparation containing the drug as a single ingredient.[1]

1. Clark RF, Curry SC. Pseudoephedrine dangers. *Pediatrics* 1990; **85:** 389–90.

Effects on the gastrointestinal tract. Ischaemic colitis has been reported[1-3] after acute or chronic use of pseudoephedrine in combination cold and allergy preparations. In one case[3] the authors suggested that use with tramadol may have contributed to adrenergic vasoconstriction by inhibition of noradrenaline reuptake.

1. Dowd J, *et al.* Ischemic colitis associated with pseudoephedrine: four cases. *Am J Gastroenterol* 1999; **94:** 2430–4.
2. Lichtenstein GR, Yee NS. Ischemic colitis associated with decongestant use. *Ann Intern Med* 2000; **132:** 682.
3. Traino AA, *et al.* Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. *Ann Pharmacother* 2004; **38:** 2068–70.

Effects on mental function. Adverse mental effects (particularly in children) have been associated with combination preparations containing pseudoephedrine.[1-5] See also Abuse, above.

1. Leighton KM. Paranoid psychosis after abuse of Actifed. *BMJ* 1982; **284:** 789–90.
2. Sankey RJ, *et al.* Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288:** 1369.
3. Stokes MA. Visual hallucinations in children receiving decongestants. *BMJ* 1984; **288:** 1540.

4. Roberge RJ, *et al.* Dextromethorphan and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; **17:** 285–8.
5. Soutullo CA, *et al.* Psychosis associated with pseudoephedrine and dextromethorphan. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 1471–2.

Effects on the skin. Recurrent pseudo-scarlatina has been described in a female patient and attributed, on some occasions at least, to ingestion of pseudoephedrine.[1] Further fixed drug eruptions associated with pseudoephedrine have been reported.[2-4] In another woman, an erythematous macular rash developed 5⁄ hours after an oral challenge with pseudoephedrine 60 mg; other symptoms, which mimicked the effects of toxic shock syndrome, included nausea and vomiting, fever, orthostatic hypotension, light-headedness, fatigue, and desquamation of the skin on her palms and soles.[3] However, considering the frequent use of pseudoephedrine in over-the-counter medications, associated drug eruptions generally appear to be rare.[2]

1. Taylor BJ, Duffill MB. *Br J Dermatol* 1988; **118:** 827–9.
2. Camisa C. Fixed drug reactions to pseudoephedrine hydrochloride. *Br J Dermatol* 1989; **120:** 857–8.
3. Cavanah DK, Ballas ZK. Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. *Ann Intern Med* 1993; **119:** 302–3.
4. Hauken M. Fixed drug eruption and pseudoephedrine. *Ann Intern Med* 1994; **120:** 442.

Pregnancy. During pregnancy taking pseudoephedrine with paracetamol has been suggested to increase the risk of gastroschisis (defective closure of the abdominal wall) in newborns.[1] Although the evidence for this is weak, it is advisable that pseudoephedrine should be avoided during pregnancy because of the severity of the abnormality and the availability of alternatives to pseudoephedrine.

1. Werler MM, *et al.* Maternal medication use and risks of gastroschisis and small intestinal atresia.*Am J Epidemiol* 2002; **155:** 26–31.

Tolerance. In 34 healthy males given pseudoephedrine 120 or 150 mg twice daily for 7 days, as a modified-release preparation, mean plasma concentrations were about 450 or 510 nanograms/mL, respectively. Adverse effects (dry mouth, anorexia, insomnia, anxiety, tension, restlessness, tachycardia, palpitations) were common; there was some evidence of tachyphylaxis.[1]

1. Dickerson J, *et al*. Dose tolerance and pharmacokinetic studies of L(+) pseudoephedrine capsules in man. *Eur J Clin Pharmacol* 1978; **14:** 253–9.

Interactions

As for Ephedrine, p.1559. Pseudoephedrine may cause a hypertensive crisis in patients receiving a MAOI (including a RIMA). For additional warnings see under phenelzine (p.418) and moclobemide (p.411). For mention of a possible interaction between pseudoephedrine and tramadol, see Effects on the Gastrointestinal Tract, above.

Antacids. The absorption rate of pseudoephedrine hydrochloride was increased by *aluminium hydroxide* mixture but was decreased by *kaolin*; in the latter case adsorption may have competed with absorption.[1]

1. Lucarotti RL, *et al.* Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J Pharm Sci* 1972; **61:** 903–5.

Vaccines. A 21-year-old mildly obese man taking pseudoephedrine in an over-the-counter formulation for weight loss collapsed and died with a core temperature of 42.2° while exercising, shortly after inoculation with *Japanese encephalitis vaccine* and *typhoid vaccine*.[1] The combined effects of the pseudoephedrine, activity, and the pyrogenic action of the vaccines appeared to have contributed to failure of the thermoregulatory system.

1. Franklin QJ. Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine. *Mil Med* 1999; **164:** 157–9.

Pharmacokinetics

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine with small amounts of its hepatic metabolite. It has a half-life of about 5 to 8 hours; elimination is enhanced and half-life accordingly shorter in acid urine. Small amounts are distributed into breast milk.

◊ References.

1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; **129:** 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57:** 62–7.

Uses and Administration

Pseudoephedrine is a direct- and indirect-acting sympathomimetic (p.1408). It is a stereoisomer of ephedrine (p.1558) and has a similar action, but has been stated to have less pressor activity and fewer CNS effects.

Pseudoephedrine and its salts are given orally for the symptomatic relief of nasal congestion (p.1548). They are commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms.

Pseudoephedrine hydrochloride or sulfate are generally given orally in doses of 60 mg every 4 to 6 hours up to a maximum of 4 doses in 24 hours. For children's doses, see Administration in Children, below. Modified-release preparations are also available; a usual adult dose is 120 mg every 12 hours or 240 mg every 24 hours.

Other uses of pseudoephedrine include the control of urinary incontinence (p.2180) in some patients. It has also been given in the management of some forms of priapism (see under Metaraminol, p.1333).

Pseudoephedrine polistirex (a pseudoephedrine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as has pseudoephedrine tannate.

Administration in children. The *BNFC* states there is little evidence to support the use of systemic decongestants in children. However, the following oral doses of pseudoephedrine hydrochloride are suggested for children in the management of mucosal congestion of the upper respiratory tract:

- 2 to 6 years: 15 mg 3 or 4 times daily
- 6 to 12 years: 30 mg 3 or 4 times daily

Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including pseudoephedrine) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547).

Barotrauma. Results from a controlled study[1] suggest that pseudoephedrine given to adults at least 30 minutes before flying appears to decrease the incidence of ear pain associated with pressure changes.[1] However, a similar decrease in risk was not noted in children.[2]

1. Jones JS, *et al.* A double-blind comparison between oral pseudoephedrine and topical oxymetazoline in the prevention of barotrauma during air travel. *Am J Emerg Med* 1998; **16:** 262–4.
2. Buchanan BJ, *et al.* Pseudoephedrine and air travel-associated ear pain in children. *Arch Pediatr Adolesc Med* 1999; **153:** 466–8.

Preparations

BP 2008: Pseudoephedrine Tablets;
USP 31: Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution; Diphenhydramine and Pseudoephedrine Capsules; Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride Extended-Release Capsules; Pseudoephedrine Hydrochloride Extended-release Tablets; Pseudoephedrine Hydrochloride Syrup; Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution; Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aseptobron Descongestivo; Mex; Qura Plus; ***Austral.:*** Chemists Own Sinus Relief; Demazin Sinus†; Dimetapp Sinus; Logicin Sinus; Nyal Plus+ Decongestant†; Sudafed; Sudafed Sinus & Nasal Decongestant; ***Belg.:*** Rinomar; Vasocedine Pseudoephedrine; ***Canad.:*** Benylin D; Congest Aid; Contac Cold Nasal Congestion Nondrowsy; Decongestant Tablets†; Drixoral ND; Eltor; Nasal & Sinus Relief†; Pseudofrin; Sudafed Decongestant; Tantafed; Triaminic Allergy Congestion†; Triaminic Pediatric Drops; ***Chile:*** Asafen Nueva Formula†; Dexan; ***Cz.:*** Nurofen Stopgrip; ***Fr.:*** Ephedroides†; Sudafed; ***Hong Kong:*** Logicin Sinus; Vidadrine; ***India:*** Sudafed; ***Indon.:*** Alco; Disudrin; Neo Triaminic; Sudafed; ***Irl.:*** Sudafed; ***Israel:*** Afalpi Tiptipot; Otrinol†; Sinufed; Sinufed Kid Day†; Tarophed; ***Ital.:*** Narixan†; ***Mex.:*** Dofedrin; Suboffen†; Sudafed; ***NZ:*** Dimetapp Sinus†; Sudafed 12 Hour Relief; Sudafed for Children†; Sudafed Sinus & Nasal Decongestant; Sudomyl; ***Pol.:*** Sudafed; ***Port.:*** Sudafed; ***S.Afr.:*** Acunaso; Adco-Sufedrin; Demazin Decongestant†; Drilix; Drinasal S; Flutex Decon-S†; Monofed†; Sinumed; Sudafed Sinus; Symptofed; ***Singapore:*** Sudafed; ***Spain:*** Neodurasina†; Reactine Plus; ***Switz.:*** Otrinol; ***Thai.:*** Sudosian†; ***Turk.:*** Eksofed; Rinogest; Sudafed; ***UAE:*** Sedofan II; ***UK:*** Contac Non Drowsy; Galsud; Meltus Decongestant; Non-Drowsy Sudafed Decongestant; ***USA:*** Afrin; Allermed; Cenafed; Childrens Sudafed Nasal Decongestant; Congestaid; Decofed; DeFed; Dimetapp Decongestant; Dorcol Children's Decongestant; Drixoral Non-Drowsy Formula; Efidac 24 Pseudoepehdrine; ElixSure Childrens Congestion; Genaphed; Halofed; Kid Kare Pediatric Nasal Decongestant; Medi-First Sinus Decongestant; Mini Pseudo; Nasofed; PediaCare Infant's Decongestant; Pseudo; Pseudo-Gest; Seudotabs; Silfedrine; Simply Stuffy; Sinustop Pro; Sudafed; Triaminic Allergy Congestion; Triaminic AM Decongestant Formula†; Triaminic Infant Oral Decongestant†; Unifed.

Multi-ingredient: numerous preparations are listed in Part 3.

Senega Root

Észak-amerikai-szenegagyökér; Polígala Raíz; Polygala, racine de; Polygalae radix; Putokšlių šaknys; Raíz de polígala; Rattlesnake Root; Seneca Snakeroot; Senega; Seneganjuuri; Senegarot; Vítodový kořen.

Истод Сенега

ATC — R05CA06.
ATC Vet — QR05CA06.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Jpn also describes the powdered root.
Ph. Eur. 6.2 (Senega Root). The dried and usually fragmented root and root crown of *Polygala senega* or certain closely related species of *Polygala* or a mixture of these. It has a faint, sweet odour, slightly rancid or reminiscent of methyl salicylate. Protect from light and humidity.

Profile

Senega root has been used as an expectorant in oral preparations for respiratory-tract disorders.

Polygala amara is a related species that is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Antitos†; Hebert Caramelos; Ixana; No-Tos Adultos; No-Tos Infantil; Pectobron; ***Austral.:*** Asa Tones; Senagar†; Senega and Ammonia; ***Austria:*** Eicebaer; Tussimont; ***Belg.:*** Saintbois; Tux†; ***Braz.:*** Expectomel; Limao Bravo†; Melagriao; Pectal†; ***Canad.:*** Bronchial; Bronchial Cough; Sirop Cocillana Codeine; Sirop Cocillana Compose; Wampole Bronchial Cough Syrup†; ***Cz.:*** Stodal; ***Fr.:*** Neo-Codion; ***Ger.:*** Asthma 6-N†; ***Hong Kong:*** Coci-Fedra; Coci-Fedra-C; Cocillana Christo; Cocillana Compound; Dextrocilla; Eurocilana; Mefedra-N†; Mist Expect Stim; Pectoral†; ***Ital.:*** Altuss; ***Port.:*** Calmarum†; Stodal; ***Rus.:*** Neo-Codion Babies (Нео-Кодион Для Младенцев); ***S.Afr.:*** Borstol Cough Remedy; ***Spain:*** Broncovital†; Pastillas Pectoral Kely; Pulmofasa; ***Swed.:*** Cocillana-Etyfin; ***Switz.:*** Bronchofluid N†; Expectoran Codein†; Expectoran†; Foral†; Hederix; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives; Makaphyt Sirop; Pectocalmine; Pectoral N; Phol-Tux; ***UK:*** Antibron; Chest Mixture; Chesty Cough Relief; Tickly Cough & Sore Throat Relief; ***Venez.:*** Acetoben; Corsaben†; Dromil Sauco; Isacol†; Novacodin; Yerba Santa.

Sobrerol

Ciclidrol; Cyclidrol; Sobreroli; Sobrerolo; Sobrerolum. *p*-Menth-6-ene-2,8-diol.

Собрерол

$C_{10}H_{18}O_2$ = 170.2.
CAS — 498-71-5.
ATC — R05CB07.
ATC Vet — QR05CB07.

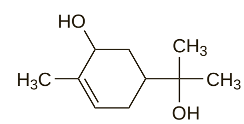

Pharmacopoeias. In *It.*

Profile

Sobrerol is a mucolytic that has been used in respiratory disorders characterised by productive cough (p.1547). Oral doses of up to 800 mg have been given daily in divided doses. Sobrerol has also been given by injection, inhalation, or rectally.

Pharmacokinetics. The pharmacokinetics of sobrerol after oral or intravenous doses has been studied in patients with acute exacerbations of chronic bronchitis.[1] Sobrerol was rapidly absorbed from the gastrointestinal tract and rapidly distributed. After intravenous and oral dosage, 13 and 23% of the dose respectively was excreted in the urine as unchanged drug, glucuronidated sobrerol, and hydrated carvone. Sobrerol was shown to accumulate in bronchial mucus.

1. Braga PC, *et al*. Pharmacokinetics of sobrerol in chronic bronchitis: comparison of serum and bronchial mucus levels. *Eur J Clin Pharmacol* 1983; **24:** 209–15.

Respiratory disorders. References.

1. Bellussi L, *et al.* Evaluation of the efficacy and safety of sobrerol granules in patients suffering from chronic rhinosinusitis. *J Int Med Res* 1990; **18:** 454–9.
2. Azzollini E, *et al.* Sobrerol (Sobrepim®) administered dropwise to children with acute hypersecretory bronchopulmonary disease: a controlled trial v bromhexine. *Clin Trials J* 1990; **27:** 241–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Sobrepin; ***Hong Kong:*** Mucoflux; ***Ital.:*** Sobrepin; Sopulmin; ***Malaysia:*** Mucoflux; ***Philipp.:*** Mucoflux; ***Port.:*** Broncopulmo†; Mucodox; Mucolavi†; Pulmus; ***Singapore:*** Mucoflux; ***Spain:*** Sobrepin; ***Thai.:*** Mucoflux.

Multi-ingredient: ***Arg.:*** Polimucil†; ***Gr.:*** Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Vanesin; ***Ital.:*** Fluental; ***Port.:*** Bronquial; Niflux.

Sodium Dibunate *(BAN, rINN)*

Dibunate de Sodium; Dibunato de sodio; L-1633; Natrii Dibunas. Sodium 2,6-di-*tert*-butylnaphthalene-1-sulphonate.

Натрий Дибунат

$C_{18}H_{23}NaO_3S$ = 342.4.

CAS — 14992-59-7 (sodium dibunate).
ATC — R05DB16.
ATC Vet — QR05DB16.

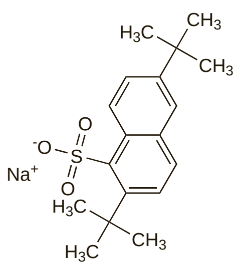

Profile

Sodium dibunate is a cough suppressant given by mouth and rectally in non-productive cough (p.1547). It is claimed to have central and peripheral actions. Chlorcyclizine dibunate (naftoclizine) has also been given by mouth or rectally.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Dibunafon; ***Port.:*** Becantex; ***Thai.:*** Becantex†.

Multi-ingredient: *Belg.:* Nobroncit; ***Braz.:*** Becantosse†; Beclase; Cessatosse†; Coquevit†; Gotas Nican†; Naquinto†; Pectal†; Pulmoverina†; Tussodina†; ***Canad.:*** Balminil Suppositories; ***Ger.:*** Cito-Guakalin†; Ephepect-Blocker-Pastillen N; ***Hong Kong:*** Ephepect Blocker; ***Mex.:*** Broend; Neo-Brontyl; Tasakal†; ***Thai.:*** Coughmin†.

Squill

Bulbo de Escila; Cebolla Albarrana; Cila; Escila; Meerzwiebel; Scilla; Scillae bulbus; Scille; Scille, bulbe de; White Squill.

Морской Лук

Pharmacopoeias. In *Br.* and *Ger.*

BP 2008 (Squill). The dried sliced bulb of *Drimia maritima* with the membranous outer scales removed, and containing not less than 68% of alcohol (60%)-soluble extractive. Store at a temperature not exceeding 25° in a dry place.

Indian Squill

Escila india; Urginea.

Морской Лук Индийский

Pharmacopoeias. In *Br.*

BP 2008 (Indian Squill). The bulb of *Drimia indica*, with the outer membranous scales removed, usually sliced and dried. Store at a temperature not exceeding 25° in a dry place.

Adverse Effects, Treatment, and Precautions

The adverse effects of squill and Indian squill in large doses include nausea, vomiting, and diarrhoea. As squill and Indian squill contain cardiac glycosides they can cause similar adverse effects to digoxin (p.1259).

Abuse. Reports of cardiac glycoside toxicity and myopathy associated with the abuse of linctuses which have contained opiates and squill.[1-5]

1. Kennedy M. Cardiac glycoside toxicity: an unusual manifestation of drug addiction. *Med J Aust* 1981; **2:** 686–9.
2. Kilpatrick C, *et al.* Myopathy with myasthenic features possibly induced by codeine linctus. *Med J Aust* 1982; **2:** 410.
3. Seow SSW. Abuse of APF linctus codeine and cardiac glycoside toxicity. *Med J Aust* 1984; **140:** 54.
4. Thurston D, Taylor K. Gee's Linctus. *Pharm J* 1984; **233:** 63.
5. Smith W, *et al.* Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; **292:** 868.

Uses and Administration

Squill and Indian squill are used as expectorants in productive cough (p.1547) and have been given as the oxymel, elixir, tincture, or vinegar. Preparations containing squill are used in some countries in the treatment of cardiovascular disorders.

Red squill has been used as a rodenticide (p.2050).

◊ The historical use of squill has been reviewed.[1]

1. Aliotta G, *et al.* The diuretic use of Scilla from Dioscorides to the end of the 18th century. *J Nephrol* 2004; **17:** 342–7.

Preparations

BP 2008: Squill Liquid Extract; Squill Oxymel.

Proprietary Preparations (details are given in Part 3)
Ger.: Digitalysat Scilla-Digitaloid†; Scillase N†.

Multi-ingredient: *Canad.:* Bronco Asmol; Sirop Cocillana Codeine; Sirop Cocillana Compose; ***Ger.:*** Miroton; Miroton N†; Nephrisan P†; ***Hong Kong:*** Coci-Fedra; Coci-Fedra-C; Cocillana Christo; Cocillana Compound; Dextrocilla; Eurocilana; Mefedra-N†; Mist Expect Stim; ***S.Afr.:*** Cocillana Co; Contra-Coff; Linctus Tussi Infans; ***UK:*** Allens Chesty Cough; Balm of Gilead; Buttercup Syrup; Chest Mixture; Covonia Mentholated; Galloway's Cough Syrup; Honey & Molasses; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Potters Gees Linctus; Sanderson's Throat Specific.

Sulfogaiacol *(rINN)*

Kalii Sulfoguajacolas; Kalium Guajacolsulfonicum; Kaliumsulfoguajakolaatti; Kaliumsulfoguajakolat; Potassium Guaiacolsulfonate; Potassium Guaiacolsulphonate; Sulfogaïacol; Sulfogaiacolum; Sulfoguayacol; Sulfogwajakol; Thiocol; Tiocol. Potassium hydroxymethoxybenzenesulphonate hemihydrate.

Сульфогайякол

$C_7H_7KO_5S,\frac{1}{2}H_2O$ = 251.3.

CAS — 1321-14-8 (anhydrous sulfogaiacol); 78247-49-1 (sulfogaiacol hemihydrate).
ATC — R05CA09.
ATC Vet — QR05CA09.

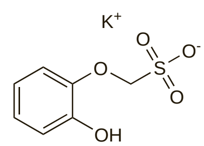

Pharmacopoeias. In *Pol.* and *US*. Also in *Fr.* and *Jpn*, both of which do not specify the hemihydrate.

USP 31 (Potassium Guaiacolsulfonate). Protect from light.

Profile

Sulfogaiacol is used as an expectorant for productive cough (p.1547). Calcium guaiacolsulfonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pectoral Lafedar Ninos; ***Austria:*** Pectosorin; ***Israel:*** Guaiacol; ***Ital.:*** Tioguaialina; ***Mex.:*** Broncoserum; ***Pol.:*** Apitussic; Diabetussic.

Multi-ingredient: *Arg.:* Antitos†; Medex Rub; No-Tos Infantil; Pastillas De Ambay; Pectobron; Pectoral Lafedar; Polipectol†; ***Austria:*** Asthma-Hilfe; Pneumopan; ***Belg.:*** Broncho-pectoralis Pholcodine; Eucalyptine Pholcodine Le Brun†; Eucalytux; Nobroncit; Pholco-Mereprine; Saintbois; ***Braz.:*** Benzomel†; Broncatar; Broncofisin†; Bronkotrat†; Cessatosse†; Expectil; Fenergan Expectorante; Frenotossil†; Iodetal; Iodeto de Potassio†; Ipecol†; Pulmonix†; Pulmoverina†; Trifedrin; Tussodina†; Tussucalman†; Xarope Sao Joao†; Xpe SPC†; ***Fr.:*** Camphodionyl; Ephydion; Eucalyptine Le Brun; Germose†; Neo-Codion; Passedyl; ***Hong Kong:*** Bendracol; Chrisracol; ***Hung.:*** Erigon; ***India:*** Neogadine SG; Pulmo-Cod (C & G); ***Indon.:*** Benacol DTM; Benacol Expectorant; Fludexin; Phenadex; Prome; Promethazine Ikapharmindo; Sanadryl; ***Israel:*** Cod-Guaiacol; Oxacatin; Pertussol; Promethazine Expectorants; Shiulon; Tussophedrine New Formula; ***Ital.:*** Balsamina Kroner; Balsatux†; Broncal†; Bronchenolo; Bronchiase; Donalg; Guaiacalcium Complex; Polised; Pulmarin; Sciroppo Berta; Stenobronchial; Tauglicolo; Tiocalmina; Tiocosol; Tionamil†; Tussanyl; ***Mex.:*** Eucaliptine; Exofil; Oxin; Pulmovital; ***Pol.:*** Apipulmol; Gwajatussin; Herbapect; Pastylki Wykrztusne; Thiocodin; ***Port.:*** Calmarum†; Codol; Lesil; Xarope Antigripal†; ***Rus.:*** Neo-Codion (Нео-Кодион); ***Spain:*** Bronco Medical; Broncovir; Broncovital†; Brota Rectal Balsamico; Fenergan Expectorante; Pastillas Pectoral Kely; Pazbronquial; Pulmofasa; ***Switz.:*** Neo-Codion N; Phol-Tux; Saintbois; ***Thai.:*** Bisolvon EX; Bromso-Ex; Dutross-P200†; Hustazol-C†; Med-Mucolo†; ***Turk.:*** Antibeksin; Artu; Fenokodin; Gayabeksin; Gayaben; Latusin; Pektodin; ***USA:*** Cypex; De-Chlor NX; Entuss Expectorant; Humibid DM; Humibid DM; Hy-KXP; Hydron EX; Hydron KGS; KGS-PE; Lemotussin-DM; Marcof; Protuss-D†; Protuss†.

Talniflumate *(USAN, rINN)*

BA-7602-06; Talniflumato; Talniflumatum. Phthalidyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

Тальнифлумат

$C_{21}H_{13}F_3N_2O_4$ = 414.3.

CAS — 66898-62-2.

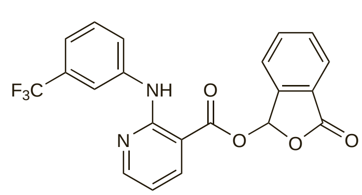

Profile

Talniflumate inhibits the human calcium-activated chloride channel protein hCLCA1, which is overexpressed in the lungs of patients with certain pulmonary diseases associated with excessive or abnormal mucus production. Talniflumate is under investigation for the management of cystic fibrosis, chronic obstructive pulmonary disease, and asthma. Talniflumate has also been used to treat inflammation.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Somalgen.

Telmesteine *(rINN)*

Telmesteína; Telmestéine; Telmesteinum. (−)-3-Ethyl hydrogen (*R*)-3,4-thiazolidinedicarboxylate.

Тельместеин

$C_7H_{11}NO_4S$ = 205.2.

CAS — 122946-43-4.

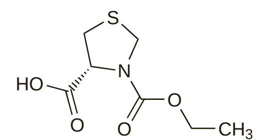

Profile

Telmesteine has been used as a mucolytic (p.1547) in the treatment of respiratory-tract disorders in oral doses of 300 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Muconorm†; Reolase.

Multi-ingredient: *UK:* Atopiclair; Xclair; ***USA:*** Atopiclair.

Terpin Hydrate *(BANM)*

Terpene Hydrate; Terpiinihydraatti; Terpina, hidrato de; Terpinhydrat; Terpini Hydras; Terpinol. *p*-Menthane-1,8-diol monohydrate; 4-Hydroxy-α,α,4-trimethylcyclohexanemethanol monohydrate.

Терпингидрат

$C_{10}H_{20}O_2,H_2O$ = 190.3.

CAS — 80-53-5 (anhydrous terpin); 2451-01-6 (terpin monohydrate).

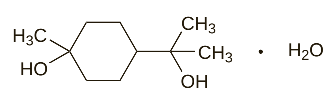

Pharmacopoeias. In *Fr.*, *Swiss*, *US*, and *Viet.*

USP 31 (Terpin Hydrate). Colourless lustrous crystals or white powder with a slight odour. It effloresces in dry air. Soluble 1 in 200 of water, 1 in 35 of boiling water, 1 in 13 of alcohol, 1 in 3 of boiling alcohol, and 1 in 140 of chloroform and of ether. A hot 1% solution is neutral to litmus. Store in airtight containers.

Stability. If crystals form in terpin hydrate elixir, they may be redissolved by warming the closed container of solution in warm water and then gently shaking it.

Profile

Terpin hydrate has been stated to increase bronchial secretion directly and has been given orally as an expectorant in productive cough (p.1547).

Nausea, vomiting, or abdominal pain may follow the ingestion of terpin hydrate on an empty stomach.

Terpin hydrochloride has also been used.

Preparations

USP 31: Terpin Hydrate and Codeine Elixir; Terpin Hydrate Elixir.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Braz.:* Ozonyl; Tetrapulmo; ***Canad.:*** Valda; ***Chile:*** Broncodeina; ***Cz.:*** Coldrex; ***Fin.:*** Toclase Expectorant; ***Fr.:*** Bronchorectine au Citral; Pates Pectorales; Pulmofluide Simple; Pulmoll; Terpone; ***Ger.:*** Ozothin†; ***Hong Kong:*** Bendracol; Chrisracol; Codoplex; Coldcap-A; Coldrex†; Coldtab-2; Panadol Cold & Flu Day; Panadol Cold & Flu Extra; Panadol Cold and Flu; ***Hung.:*** Coldrex; ***Ital.:*** Elisir Terpina; Neo Borocillina Balsamica; Tionamil†; ***Neth.:*** Balsoclase Compositum; ***Pol.:*** Coldrex MaxGrip C; ***Rus.:*** Alex Plus (Алекс Плюс); Glycodin (Гликодин); ***Spain:*** Pastillas Pectoral Kely; Terponil; ***Switz.:*** Bromocod N; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; Sedotussin†; ***Thai.:*** Antust; D-Coate; Dexpin; Dextro BS; Fartussin; Med-Guaiphan†; Mila-Tercon; Muco-DX; Rocal; Seco; Stocof; Terco-C; Terco-D; ***UK:*** Original Cabdrivers Expectorant; ***Venez.:*** Codoformo†; Derpinol†.

Tetryzoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tetrizolina; Tetrahydrozoline Hydrochloride; Tetrazolin Hidroklorür; Tetrizolino hidrochloridas; Tetrytsoliinihydrokloridi; Tétryzoline, chlorhydrate de; Tetryzolin-hydrochlorid; Tetryzolinhydroklorid; Tetryzolini hydrochloridum. 2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline hydrochloride.

Тетризолина Гидрохлорид

$C_{13}H_{16}N_2$,HCl = 236.7.

CAS — 84-22-0 (tetryzoline); 522-48-5 (tetryzoline hydrochloride).

ATC — R01AA06; R01AB03; S01GA02.

ATC Vet — QR01AA06; QR01AB03; QS01GA02.

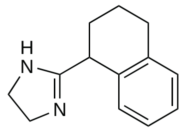

(tetryzoline)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Tetryzoline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dehydrated alcohol; practically insoluble in acetone.

USP 31 (Tetrahydrozoline Hydrochloride). A white odourless solid. Soluble 1 in 3.5 of water and 1 in 7.5 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Store in airtight containers.

Profile

Tetryzoline is a sympathomimetic with effects similar to those of naphazoline (p.1565). It is used as the hydrochloride for its vasoconstrictor effect in the symptomatic relief of nasal congestion (p.1548). A 0.1% solution is instilled into each nostril as nasal drops or a spray as necessary, although not more often than every 3 hours. Children aged 2 to 6 years of age may be given 2 or 3 drops of a 0.05% solution in each nostril as necessary, although again not more often than every 3 hours.

Solutions of tetryzoline hydrochloride containing 0.05% are used as a conjunctival decongestant (see Conjunctivitis, p.564).

Other salts of tetryzoline including the nitrate, phosphate, and sulfate have been used similarly.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing tetryzoline, see under Phenylephrine, p.1568.

Preparations

USP 31: Tetrahydrozoline Hydrochloride Nasal Solution; Tetrahydrozoline Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Bano Ocular; Chiosan; Octilia†; Ocudiafan†; Piam; ***Austral.:*** Murine Sore Eyes; Optazine Fresh†; Visine Original; ***Belg.:*** Visine; ***Canad.:*** Eye Drops†; Visine Original; ***Chile:*** Murine Plus†; Visional Gotas; ***Cz.:*** Rhinal; Tyzine†; Vasopos N; Visine; ***Denm.:*** Tyzine; ***Fin.:*** Oftan Starine; Visine; ***Fr.:*** Constrilia; ***Ger.:*** Caltheon†; Diabenyl T†; Ophtalmin N; Rhinex mit Tetryzolin; Rhinopront†; Sanopinwern T†; Tetrilin; Tyzine†; Vasopos N; Visine Yxin; Yxin†; ***Gr.:*** Ursa-Fin; Visine; ***Hong Kong:*** Optizoline; Visine Original; ***Hung.:*** Tyzine; Visine; ***India:*** Visine; ***Indon.:*** Braito; Insto; Isotic Clearin; Visine; Visolin; Visto; ***Israel:*** Azoline; Stilla; V-Zoline; Visine; ***Ital.:*** Demetil; Octilia; Stilla Decongestionante; Vasorinil; Visine; ***Malaysia:*** Visine; ***Mex.:*** Eye-Mo; Tetrazol; ***NZ:*** Visine; ***Philipp.:*** Eye-Mo; Sinutab NS; Visine; Visine Advanced Relief; Visine Cool; ***Pol.:*** Berberil; Starazolin; Tetryvil; Visine; ***Port.:*** Visine; ***Rus.:*** Octilia (Октилия); Tyzine (Тизин); Visine (Визин); ***S.Afr.:*** Visine; ***Singapore:*** Octilia†; Visine; ***Spain:*** Azulina; Vispring; ***Switz.:*** Rhinopront Top; Visine; ***Thai.:*** Visine; ***Turk.:*** Burnil; Eye-Visol; Visine; Zenkain; ***USA:*** Eye Drops; Eye-Zine; Geneye Extra†; Mallazine†; Optigene 3; Tetrasine†; Tyzine; Visine Original; ***Venez.:*** Cusibel†.

Multi-ingredient: ***Arg.:*** Antiflogol; Biocortin†; Efemolina; Larsimal; Provisual Compuesto; Toflam; Visine Plus; Visubril; ***Austral.:*** In A Wink Allergy†; Visine Advanced Relief; Visine Allergy†; Visine Revive†; ***Braz.:*** Fenidex; Mirabel; Vislin; Visodin; Visolux†; ***Canad.:*** Visine Advance Triple Action; Visine Allergy; Visine Cool; ***Chile:*** Spersallerg; ***Cz.:*** Spersallerg; ***Ger.:*** Allergopos N; Berberil N; Efemolin; Spersadexolin†; Spersallerg; ***Gr.:*** Spersadexoline†; Spersallerg; ***Hong Kong:*** Efemoline; Spersadexoline†; Spersallerg; Visine AC; Visine Moisturizing; ***Hung.:*** Spersallerg; ***Indon.:*** Visine Extra; ***Israel:*** Visine AC; ***Ital.:*** Biorinil; Cromozil; Dexoline; Efemoline; Eta Biocortilen VC; Flumezina; Ischemol A; Stillerg; Tetramil; Vasosterone; Vasosterone Antibiotico; Vasosterone Collirio; Visublefarite; Visucloben Decongestionante; Visumetazone Antibiotico; Visumetazone Decongestionante; Visustrin; ***Malaysia:*** Efemoline†; Gentadexa; Murine Plus†; Spersadexoline; Spersallerg; ***Mex.:*** Fluorometil; Visine Extra; ***Norw.:*** Spersallerg; ***NZ:*** Visine Advanced Relief; ***Philipp.:*** Efemoline; Spersallerg; ***Pol.:*** Spersallerg; ***Port.:*** Gentadexa; Medrivas Antibiotico; ***Rus.:*** Spersallerg (Сперсаллерг); ***S.Afr.:*** Efemoline; Gemini; Oculerge; Oculoforte†; Safyr Bleu Antihistamine†; Spersadexoline; Spersallerg; ***Singapore:*** Efemoline; Spersadexoline†; Spersallerg; ***Spain:*** Dexam Constric†; Fluorvas; Gentadexa; Medrivas; Medrivas Antib; Tivitis; Vasodexa; ***Switz.:*** Collypan; Efemoline; Spersadexoline†; Spersallerg; ***Thai.:*** Antazallerge; Efemoline; Histaoph; Mano; Opsa-His†; Opsil-A; Spersadexoline; Spersallerg; ***Turk.:*** Efemoline; Flumetol; ***USA:*** Advanced Relief Visine; Collyrium Fresh†; Murine Plus; Tetrasine Extra†; Visine Allergy Relief; Visine Moisturizing†; ***Venez.:*** Gentidexa; Gentisor†.

Thebacon Hydrochloride *(BANM, rINNM)*

Acethydrocodone Hydrochloride; Acetyldihydrocodeinone Hydrochloride; Dihydrocodeinone Enol Acetate Hydrochloride; Hidrocloruro de tebacón; Thébacone, Chlorhydrate de; Thebaconi Hydrochloridum. 6-*O*-Acetyl-7,8-dihydro-3-*O*-methyl-6,7-didehydromorphine hydrochloride; (−)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphin-6-en-6-yl acetate hydrochloride.

Тебакона Гидрохлорид

$C_{20}H_{23}NO_4$,HCl = 377.9.

CAS — 466-90-0 (thebacon); 20236-82-2 (thebacon hydrochloride).

ATC — R05DA10.

ATC Vet — QR05DA10.

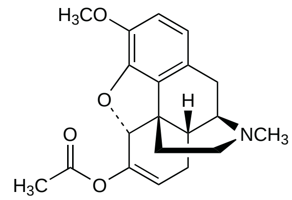

(thebacon)

Profile

Thebacon hydrochloride is a centrally acting cough suppressant used for non-productive cough (p.1547). It has actions similar to those of codeine (p.37) but is stated to be about 4 times more potent. It is given orally in a usual daily dose of 10 mg in divided doses; the maximum daily dose should not exceed 20 mg.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Acedicon.

Tipepidine Hibenzate *(rINNM)*

AT-327 (tipepidine); CR-662 (tipepidine); Hibenzato de tipepidina; Tipépidine, Hibenzate de; Tipepidine Hybenzate; Tipepidini Hibenzas. 3-[Di(2-thienyl)methylene]-1-methylpiperidine 2-(4-hydroxybenzoyl)benzoate.

Типепидина Гибензат

$C_{15}H_{17}NS_2$,$C_{14}H_{10}O_4$ = 517.7.

CAS — 5169-78-8 (tipepidine); 31139-87-4 (tipepidine hibenzate).

ATC — R05DB24.

ATC Vet — QR05DB24.

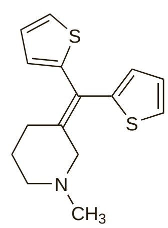

(tipepidine)

Pharmacopoeias. In *Jpn.*

Profile

Tipepidine hibenzate is a cough suppressant used for non-productive cough (p.1547) which is claimed also to have an expectorant action. It is given orally as the hibenzate but doses are expressed as the citrate; tipepidine hibenzate 22.2 mg is equivalent to about 20 mg of tipepidine citrate. A usual dose is the equivalent of 20 to 40 mg of the citrate 3 times daily.

Epileptogenic effect. Generalised convulsions associated with therapeutic oral doses of tipepidine hibenzate have occurred in some patients.[1]

1. Cuomo RM. On the possible convulsive activity of an antitussive piperidinic derivative ('tipepidina ibenzato') in man. *Acta Neurol (Napoli)* 1982; **37:** 110–16.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Asvex; ***Jpn:*** Asverin.

Multi-ingredient: ***Arg.:*** Di-Neumobron; ***Indon.:*** Neo Novapon; Neo Novapon Plus; ***Jpn:*** Sin Colgen Kowa Kaze.

Tolu Balsam

Bálsamo de tolú; Balsamum tolutanum; Baume de tolu; Tolu balzamas; Toluánský balzám; Tolubalsam; Tolubalzsam; Tolupalsami.

Толуанский Бальзам

CAS — 9000-64-0; 8017-09-2.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Tolu Balsam). Oleoresin obtained from the trunk of *Myroxylon balsamum* var. *balsamum*. It contains 25 to 50% of free or combined acids, expressed as cinnamic acid, calculated with reference to the dried drug. It occurs as a hard, friable, brownish to reddish-brown mass; thin fragments are brownish-yellow when examined against the light. It has an odour reminiscent of vanillin. Practically insoluble in water and in petroleum spirit; very soluble or freely soluble in alcohol. Do not store in powdered form.

USP 31 (Tolu Balsam). A balsam obtained from *Myroxylon balsamum* (Leguminosae). It is a brown or yellowish-brown plastic solid transparent in thin layers and brittle when old, dried, or exposed to cold temperatures. It has a pleasant aromatic odour, resembling that of vanilla. Practically insoluble in water and in petroleum spirit; soluble in alcohol, in chloroform, and in ether, sometimes with slight residue or turbidity. Store at a temperature not exceeding 40° in airtight containers.

Profile

Tolu balsam is considered to have very mild antiseptic properties and some expectorant action but is mainly used in the form of a syrup to flavour cough mixtures. However, Tolu Syrup (BP 2008) no longer contains tolu balsam but is based on cinnamic acid (p.1640).

Preparations

BPC 1954: Compound Iodoform Paint;
USNF 26: Tolu Balsam Syrup; Tolu Balsam Tincture;
USP 31: Compound Benzoin Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cobenzil Compuesto†; No-Tos Adultos; No-Tos Infantil; Pastillas Medex; Pectobron; Polipectol†; Refenax Caramelos Expectorantes; ***Austral.:*** Camphor Linctus Compound; ***Belg.:*** Saintbois; Tux†; ***Braz.:*** Agrimel†; Broncofisin†; Calmatoss†; Expectomel; Frenotosse; Frenotossil†; Glycon; Infantoss†; Inhalante Yatropan; Iodetal; Ipecol†; Melagriao; Peitoral Angico Pelotense†; Pulmonix†; Tossanil†; Vick Pastilhas; Xarope de Caraguata†; Xarope Sao Joao†; ***Canad.:*** Bronco Asmol; Rophelin†; ***Chile:*** Elitos ET; Fitotos; Flemex Jat; Jarabe Palto Compuesto con Miel Adulto; Notosil†; Pulmosina; Sedotus†; ***Cz.:*** Solutan†; Stodal; ***Fr.:*** Broncalene Nourisson; Dinacode avec codeine†; Dinacode†; Hexapneumine; Pastilles Medicinales Vicks; Pastilles Monleon; Pates Pectorales; Phytotux; Theralene Pectoral Nourrisson†; Tussipax; ***Hong Kong:*** Baby Cough with Antihistamine; Hexapneumine; ***Ital.:*** Stenobronchial; ***Mex.:*** Citos; Epicol†; Fen-y-Tos; ***Port.:*** Broncodiazina; Lesil; Stodal; ***Rus.:*** Solutan (Солутан); ***S.Afr.:*** Choats Extract of Lettuce Cough Mixture; Linctus Tussi Infans; Puma Cough Balsam; Turlington Tincture; ***Spain:*** Bactopumon; Bronquidiazina CR; Pastillas Antisep Garg M; Pulmofasa; Tosdiazina†; ***Switz.:*** Baume†; Dinacode N†; Euphon N; Ipeca†; Neo-Codion N; Neo-DP†; Pastilles pectorales Demo N; Pectocalmine Junior N; Pectosan N†; Phol-Tussil; Pommade au Baume; Saintbois; Sano Tuss; ***Thai.:*** Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; ***UK:*** Allens Chesty Cough; Chesty Cough Relief; Modern Herbals Cold & Congestion; Sanderson's Throat Specific; ***USA:*** Tonsiline; Vicks Menthol Cough Drops; ***Venez.:*** Yerba Santa.

Tramazoline Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de tramazolina; Tramazoline, chlorhydrate de; Tramazolin-hidroklorid; Tramazolin-hydrochlorid; Tramazolini hydrochloridum; Tramazolino hidrochloridas; Tramazoliny chlorowodorek. 2-(5,6,7,8-Tetrahydro-1-naphthylamino)-2-imidazoline hydrochloride monohydrate.

Трамазолина Гидрохлорид

$C_{13}H_{17}N_3$,HCl,H_2O = 269.8.

CAS — 1082-57-1 (tramazoline); 3715-90-0 (tramazoline hydrochloride).

ATC — R01AA09.

ATC Vet — QR01AA09.

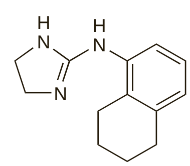

(tramazoline)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tramazoline Hydrochloride Monohydrate). A white or almost white crystalline powder. Soluble in water and in alcohol. A 5% solution in water has a pH of 4.9 to 6.3.

Profile

Tramazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p.1565). It is used to provide symptomatic relief of nasal congestion (p.1548). Tramazoline hydrochloride is given as a solution containing about 0.12%, instilled into each nostril as nasal drops or a spray three or four times daily.

Solutions of tramazoline hydrochloride containing about 0.06% have also been used in eye drops as a conjunctival decongestant (see Conjunctivitis, p.564).

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Spray-Tish; ***Austria:*** Rinorix; ***Belg.:*** Rhinospray; ***Cz.:*** Muconasal Plus; ***Ger.:*** Biciron; Ellatun; Rhinospray; ***Ital.:*** Ringoutt Spray-Fher; ***Neth.:*** Bisolnasal; ***Port.:*** Rhinospray; ***Spain:*** Rhinospray.

Multi-ingredient: ***Arg.:*** Dexa-Rhinospray N; ***Austral.:*** Spray-Tish Menthol; ***Austria:*** Rhinospray Plus; ***Belg.:*** Dexa-Rhinospray; ***Ger.:*** Dexa Biciron; Oxy Biciron; Rhinospray Plus; Rhinospray sensitiv; ***Gr.:*** Dexa-Rhinaspray-N; ***Hung.:*** Rhinospray Plus; ***Irl.:*** Dexa-Rhinaspray Duo; ***Ital.:*** Rinogutt Antiallergico Spray; Ringoutt Eucalipto-Fher; ***Neth.:*** Rhinospray met menthol; ***Rus.:*** Adrianol (Адрианол); ***Spain:*** Rhinospray Antialergico; ***UK:*** Dexa-Rhinaspray Duo†.

Tuaminoheptane Sulfate *(rINNM)* ⊗

Sulfato de tuaminoheptano; Tuaminoheptane, Sulfate de; Tuaminoheptane Sulphate *(BANM)*; Tuaminoheptani Sulfas.

Туаминогептана Сульфат

$(C_7H_{17}N)_2,H_2SO_4$ = 328.5.

CAS — 6411-75-2.

ATC — R01AA11; R01AB08.

ATC Vet — QR01AA11; QR01AB08.

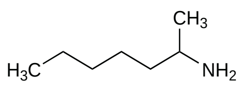

(tuaminoheptane)

Profile

Tuaminoheptane is a volatile sympathomimetic (p.1407) that has been used as the sulfate for the symptomatic relief of nasal congestion. Tuaminoheptane has also been used in the form of the carbonate.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Rinofluimucil; ***Fr.:*** Rhinofluimucil; ***Ger.:*** Rinofluimucil-S†; ***Hong Kong:*** Rinofluimucil; ***Hung.:*** Rinofluimucil; ***Ital.:*** Rinofluimucil; ***Port.:*** Rinofluimucil; ***Rus.:*** Rinofluimucil (Ринофлуимуцил); ***Spain:*** Rinoflumil; ***Switz.:*** Rinofluimucil; ***Thai.:*** Rinofluimucil.

Tymazoline Hydrochloride *(BANM)* ⊗

2-Thymyloxymethyl-2-imidazoline Hydrochloride; Timazolina, hidrocloruro de; Tymazolini Hydrochloridum; Tymazoliny chlorowodorek. 2-(2-Isopropyl-5-methylphenoxymethyl)-2-imidazoline hydrochloride.

Тимазолина Гидрохлорид

$C_{14}H_{20}N_2O,HCl$ = 268.8.

CAS — 24243-97-8 (tymazoline); 28120-03-8 (tymazoline hydrochloride).

ATC — R01AA13.

ATC Vet — QR01AA13.

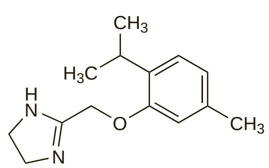

(tymazoline)

Pharmacopoeias. In *Pol.*

Profile

Tymazoline is a sympathomimetic that has been used as the hydrochloride similarly to naphazoline (p.1565) for its local vasoconstrictor effect in the symptomatic relief of nasal congestion (p.1548).

Preparations

Proprietary Preparations (details are given in Part 3)

Pol.: Thymazen; ***Thai.:*** Pernazene.

Xylometazoline Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de xilometazolina; Ksilometazolin Hidroklorür; Ksilometazolino hidrochloridas; Ksylometatsoliinihydrokloridi; Ksylometazoliny chlorowodorek; Xilometazolinhidroklorid; Xylométazoline, chlorhydrate de; Xylometazolinhydro; Xylometazolin-hydrochlorid; Xylometazolini hydrochloridum. 2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-2-imidazoline hydrochloride.

Ксилометазолина Гидрохлорид

$C_{16}H_{24}N_2,HCl$ = 280.8.

CAS — 526-36-3 (xylometazoline); 1218-35-5 (xylometazoline hydrochloride).

ATC — R01AA07; R01AB06; S01GA03.

ATC Vet — QR01AA07; QR01AB06; QS01GA03.

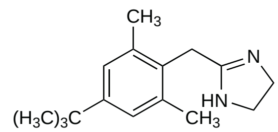

(xylometazoline)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Xylometazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 31 (Xylometazoline Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 35 of water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Naphazoline, p.1565.

Interactions

Since xylometazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p.1407.

Uses and Administration

Xylometazoline is a direct-acting sympathomimetic (p.1408) with marked alpha-adrenergic activity. It is a vasoconstrictor which reduces swelling and congestion when applied to mucous membranes. The effect begins within 5 to 10 minutes of application and lasts for up to 10 hours.

Xylometazoline is used as the hydrochloride for the short-term symptomatic relief of nasal congestion (p.1548). A 0.1% solution of xylometazoline hydrochloride is applied topically as nasal drops or a spray into each nostril two or three times daily. For children's doses, see Administration in Children, below.

Xylometazoline hydrochloride solution is instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p.564). Preparations containing 0.05% xylometazoline hydrochloride with 0.5% antazoline sulfate are typical; 0.1% xylometazoline hydrochloride has also been used.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including xylometazoline) should be used with caution in children and generally avoided in those under 2 years of age (see p.1547). However, the *BNFC* suggests that, in certain circumstances, specialists may prescribe xylometazoline nasal drops for children under 2 years in the short-term treatment of severe nasal congestion which has not responded to sodium chloride nasal drops or inhalation of warm moist air. A 0.05% solution of xylometazoline hydrochloride is licensed for use in children aged from 2 to 12 years; 1 or 2 drops are instilled into each nostril once or twice daily, for a maximum of 7 days. The *BNFC* suggests that younger children aged 3 months and over may be given similar doses.

Preparations

BP 2008: Xylometazoline Nasal Drops;
USP 31: Xylometazoline Hydrochloride Nasal Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Nastizol; Otrivina; ***Austral.:*** Otrivin; ***Austria:*** Olynth; Otrivin; Ratio-Soft; Xylo-COMOD; ***Belg.:*** Nasa Rhinathiol; Nasasinutab; Nuso-San; Otrivine Anti-Rhinitis; Rhinidine†; ***Braz.:*** Orlaxyl†; Otrivina; ***Canad.:*** Balminil Nasal Decongestant; Certified Decongestant; Decongest†; Decongestant Nasal Spray; Decongestant Nose Drops; Nasal Decongestant; Otrivin; ***Cz.:*** Dr Rentschler Snupfenspray†; Dr Rentschler Snupfentropfen†; Mar Rhino; Nasenspray AL; Nasentropfen AL; Olynth; Otrivin; Rhino-Stas; Xylo-COMOD; ***Denm.:*** Otrivin; Passagen; Zymelin; ***Fin.:*** Naso-Ratiopharm; Nasolin; Otrivin; Zymelin†; ***Ger.:*** Balkis; Gelonasal; Imidin K†; Imidin N; Mentopin Nasenspray†; Nasan; Nasengel; Nasengel AL; Nasenspray; Nasenspray AL; Nasenspray E; Nasenspray K; Nasenspray-CT; Nasentropfen AL; Nasentropfen E; Nasentropfen K; Nasentropfen Stada; Olynth; Otriven; Otriven gegen Schnupfen; Rapako xylo; Rhinex mit Xylometazolin; schnupfen endrine; Siozwo Akut†; Snup; stas Nasentropfen, Nasenspray†; Tussamag Nasenspray; Xylo; Xylo Siozwo†; Xylo-COMOD†; Xylo-POS; ***Gr.:*** Otrivin; Otrivin-Menthol; ***Hong Kong:*** Decongestant Nasal Spray; Otrivin; Xyloma; ***Hung.:*** Nasan; Novorin; Otrivin; Rhinathiol; Rhino-Stas; ***India:*** Decon; Nazalin; Otrivin; ***Indon.:*** Otrivin; ***Irl.:*** Otrivine; ***Israel:*** Nazalet; Otrivin; Xylovit; ***Ital.:*** Neo Rinoleina; Otrivin; Respiro; ***Malaysia:*** Otrivin; ***Neth.:*** Kruidvat Neusdruppels; Kruidvat Neusspray; Mucorhinyl; Otrivin; Xylo-COMOD; ***Norw.:*** Naso; Nazaren; Otrivin; Xolin; Zymelin; ***NZ:*** Otrivine; ***Philipp.:*** Otrivin; ***Pol.:*** Otrivin; Xylogel; Xylorin; ***Port.:*** Otrivina; ***Rus.:*** Dlianos (Длянос); Grippostad Rhino (Гриппостад Рино); Halazolin (Галазолин); Olynth (Олинт); Otrivin (Отривин); Rhinonorm (Ринонорм); Rhinostop (Риностоп); Suprima-Nos (Суприма-Ноз); Tyzine Xylo (Тизин Ксило); Xymelin (Ксимелин); ***S.Afr.:*** Otrivin; ***Singapore:*** Otrivin; ***Spain:*** Amidrin; Idasal; Otrivin; Rinoblanco; ***Swed.:*** Nasoferm; Otrivin; Zymelin; ***Switz.:*** Nasben; Nasobol Xylo; Olynth; Otrivin; Rhinostop; Rhume†; Rinosedin; Xylo-Mepha; ***Thai.:*** Otrivin; ***Turk.:*** Naze; Otrivine; Rinizol; Xylo-COMOD; ***UAE:*** Xylolin; ***UK:*** Non-Drowsy Sudafed Decongestant Nasal Spray; Otradrops; Otraspray; Otrivine; Tixycolds Cold and Allergy; ***USA:*** 4-Way Moisturizing Relief; Otrivin.

Multi-ingredient: ***Chile:*** Bacitopic Compuesto; Nasomin; Rinobanedif; ***Denm.:*** Otrivin Menthol; ***Fin.:*** Otrivin Menthol; ***Ger.:*** Lomupren compositum†; Nasic; ***Irl.:*** Otrivine-Antistin; ***Israel:*** Aforinol; ***Ital.:*** Inalar; ***Malaysia:*** Rynacrom Compound†; ***Mex.:*** Rinadex Compuesto; ***Neth.:*** Otrivin Menthol; ***NZ:*** Otrivine Menthol; Otrivine-Antistin; ***Swed.:*** Otrivin Menthol; ***Switz.:*** Lomusol-X†; Muco-Trin†; Triofan; ***Thai.:*** Rynacrom Compound†; ***Turk.:*** Rynacrom Compound; ***UK:*** Otrivine-Antistin; Rynacrom Compound†.

Zipeprol Hydrochloride *(rINNM)*

CERM-3024; Hidrocloruro de zipeprol; Zipéprol, Chlorhydrate de; Zipeproli Hydrochloridum. α-(α-Methoxybenzyl)-4-(β-methoxyphenethyl)-1-piperazineethanol dihydrochloride.

Зипепрола Гидрохлорид

$C_{23}H_{32}N_2O_3,2HCl$ = 457.4.

CAS — 34758-83-3 (zipeprol); 34758-84-4 (zipeprol hydrochloride).

ATC — R05DB15.

ATC Vet — QR05DB15.

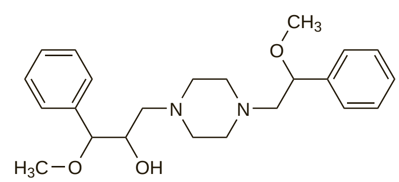

(zipeprol)

Profile

Zipeprol is a centrally acting cough suppressant that is stated to have a peripheral action on bronchial spasm. It has been given as the hydrochloride, typically in an oral dose of 150 to 300 mg daily in divided doses. There have been reports of abuse and overdosage producing neurological symptoms.

Abuse and overdosage. Severe neurological symptoms have been reported in young adults after habitual abuse of zipeprol for euphoria. Patients have presented with generalised seizures, followed by coma.[1] One patient who ingested 750 mg of zipeprol [over twice the maximum daily dose] had several opisthotonic crises and developed cerebral oedema.[2] Symptoms of overdosage in children have included restlessness, somnolence, ataxia, choreic movements, forced deviation of the head and eyes, generalised seizures, respiratory depression, and coma.[1,3] Fatalities have been reported.

Dependence and withdrawal symptoms similar to those produced by opioids have been reported.[4] WHO has assessed zipeprol to have a moderate potential for dependence and liability for abuse.[5] Although zipeprol is a weak opioid agonist at high doses its toxicity and hallucinogenic and other psychotropic effects constitute a significant element in its abuse, and the public health and social problems associated with such abuse were considered substantial.

1. Moroni C, *et al*. Overdosage of zipeprol, a non-opioid antitussive agent. *Lancet* 1984; **i:** 45.
2. Perraro F, Beorchia A. Convulsions and cerebral oedema associated with zipeprol abuse. *Lancet* 1984; **i:** 45–6.
3. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués dé la pipérazine (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; **32:** 504–11.
4. Mallaret MP, *et al.* Zipeprol: primary dependence in an unaddicted patient. *Ann Pharmacother* 1995; **29:** 540.
5. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_856.pdf (accessed 11/05/07)

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Frenotos; ***Gr.:*** Dovavixin†; Duo-Extolen†; Jactuss†; ***Mex.:*** Respilene†; Tusigen; ***Venez.:*** Coloplex†.

Dermatological Drugs and Sunscreens

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The skin is subject to a very wide range of lesions. Some may be characteristic of specific systemic diseases and fade as the disease regresses. Some are caused by specific local infections and are best treated by the appropriate antimicrobial (see Skin Infections in the chapters Antibacterials, p.194, and Antifungals, p.521). The skin is also subject to damage from environmental hazards. Excessive or prolonged exposure to solar radiation is associated with degenerative changes in the skin (premature ageing of the skin or photoageing, p.1581), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), and malignant neoplasms of the skin (p.672). Some skin disorders are adverse effects of therapeutic and other agents, ranging from mild hypersensitivity to the life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis (see Drug-induced Skin Reactions, p.1578, and Drug-induced Photosensitivity, p.1581). There also remain skin disorders whose aetiology is poorly understood.

The distribution and morphological description of the skin lesion (its shape, colour, and surface characteristics) are important in the diagnosis of skin disorders. There are many terms used to describe skin lesions:

- abscess–a collection of pus in a cavity
- bulla (or blister)–a fluid-filled circumscribed lesion larger than 0.5 cm in diameter
- comedo–a plug of keratin and sebum in a pilosebaceous follicle
- ecchymosis (bruise)–an extravasation of blood into the skin
- erythema–red coloration due to vascular dilatation
- fissure–a slit through the whole thickness of the skin
- horn–a thickening of the skin that is taller than it is broad
- keratosis–a horny thickening of the skin
- lichenification–hard, thickened skin with increased markings
- macule–an area of altered colour or texture with no elevation above the surface of the surrounding skin
- nodule–a dome-shaped or spherical-shaped, solid lesion, usually more than 0.5 cm in diameter and depth
- papilloma–a nipple-like mass
- papule–a raised solid lesion, usually less than 0.5 cm in diameter
- petechia–a pinhead-sized macule of blood in the skin
- plaque–a raised, flat-topped, circumscribed lesion, usually larger than 2 cm in diameter but with no substantial depth
- purpura–a macule of blood in the skin, larger than a petechia
- pustule–an accumulation of pus in the skin
- scale–a flat plate or flake of stratum corneum
- stria–a streak-like, linear, atrophic lesion, pink, purple, or white in colour
- telangiectasia–a visible permanent dilatation of small cutaneous blood vessels
- ulcer–a loss of the whole thickness of dermis and epidermis produced by sloughing of necrotic tissue; healing results in a scar
- vesicle–a fluid-filled circumscribed lesion less than 0.5 cm in diameter
- wheal–an elevated, white, compressible area of oedema often surrounded by a red flare

Dermatological Drug Groups

Treatment of skin disorders may include topical and/or systemic drug therapy, although the pharmacology of many of the drugs used in dermatology is poorly understood. Physical methods such as cryotherapy, UV radiation, radiotherapy, and surgery also have a role. Some of the main drug groups used in dermatology are described below.

Antidandruff Drugs

Antidandruff drugs have antibacterial and antifungal properties and are used particularly in shampoos to manage dandruff and seborrhoeic dermatitis of the scalp.

Described in this chapter are
Dipyrithione, p.1595
Piroctone Olamine, p.1610
Pyrithione Zinc, p.1611
Selenium Sulfide, p.1613

Corticosteroids

Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) and immunosuppressant properties in the management of various skin conditions. Topical preparations are commonly used, but systemic treatment may be required for severe conditions or to control acute exacerbations. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p.1490. See also below for other immunosuppressants used in dermatology.

Immune System Modifiers

Some immunosuppressants are used specifically in psoriasis or eczema, and are included in this chapter. Other immunosuppressants and antineoplastics with immunosuppressant properties that are used in dermatology and covered in other chapters include azathioprine (p.1818), ciclosporin (p.1822), methotrexate (p.745), and tacrolimus (p.1843). Corticosteroids are also widely used for their anti-inflammatory and immunosuppressant effects (see above). Adalimumab (p.15), etanercept (p.50), and infliximab (p.69) are immunomodulators also used in the management of psoriasis.

Described in this chapter are
Alefacept, p.1587
Efalizumab, p.1596
Pimecrolimus, p.1609

Keratolytics

Keratolytics help to soften and ease exfoliation of the horny layer of the epidermis, and are used in conditions such as acne, seborrhoeic dermatitis and dandruff, and hyperkeratotic disorders.

Described in this chapter are
Alcloxa, p.1587
Aldioxa, p.1587
Allantoin, p.1588
Benzoyl Peroxide, p.1590
Glycolic Acid, p.1598
Keluamid, p.1603
Resorcinol, p.1612
Salicylic Acid, p.1612
Salnacedin, p.1613
Sulfur, p.1614
Urea, p.1620

Photosensitisers

Psoralen photosensitisers markedly increase the skin's sensitivity to UVA light, and are used in photochemotherapy (PUVA) for the management of disorders such as psoriasis, vitiligo, cutaneous T-cell lymphoma, and polymorphic light eruption. For a discussion of photodynamic therapy, a form of light-activated treatment used in the management of malignant neoplasms, see under Porfimer Sodium, p.764.

Described in this chapter are
5-Methoxypsoralen, p.1607
Methoxsalen, p.1605
Trioxysalen, p.1620

Pigment Modifiers

Drugs such as hydroquinone that reduce pigmentation are used to lighten skin in hyperpigmentation conditions such as chloasma. Dihydroxyacetone is used to darken skin in vitiligo, and monobenzone is used to permanently depigment normal skin in extensive vitiligo. Erythrulose is used to darken skin, either alone or with dihydroxyacetone, in artificial suntan preparations. Photosensitisers (above) are also used in vitiligo.

Described in this chapter are
Arbutin, p.1589
Dihydroxyacetone, p.1594
Erythrulose, p.1597
Hydroquinone, p.1598
Mequinol, p.1604
Monobenzone, p.1607

Retinoids

Retinoids, and the retinoid analogue adapalene, are vitamin A analogues used in the management of various skin conditions including acne, psoriasis, and keratinisation disorders.

Described in this chapter are
Acitretin, p.1586
Adapalene, p.1587
Etretinate, p.1597
Isotretinoin, p.1599
Motretinide, p.1608
Retinaldehyde, p.1612
Tazarotene, p.1617
Tretinoin, p.1618

Sunscreens

Sunscreens are used to protect the skin against sunlight. There are 2 types: *physical* (reflective or inorganic) agents that are opaque and reflect both UVA and UVB radiation and *chemical* (absorbent or organic) agents that because of their chromophore groups absorb a particular range of wavelengths within the UV spectrum (for definitions, see Light-induced Skin Reactions, p.1580). Physical sunscreens include titanium dioxide and zinc oxide. A classification of the chemical sunscreens included in this chapter is given in Table 1, below. Many products combine sunscreens from different groups in order to widen the protection afforded.

Table 1. Chemical sunscreens.

UVA absorbers	UVB absorbers
Anthranilates	**Aminobenzoates**
Meradimate	Aminobenzoic acid
Camphorsulfonic acid derivatives	Lisadimate
Ecamsule	Padimate
Dibenzoylmethanes	Padimate O
Avobenzone	**Camphor derivatives**
Dibenzoylmethane	Enzacamene
Isopropyldibenzoylmethane	**Cinnamates**
UVA and UVB absorbers	Amiloxate
Benzophenones	Cinoxate
Dioxybenzone	Diolamine methoxycinnamate
Mexenone	Octinoxate
Oxybenzone	Octocrilene
Sulisobenzone	**Salicylates**
	Homosalate
	Octisalate

Trolamine salicylate (p.132) and salol (p.122) are salicylic acid derivatives that have analgesic properties, but have also been used as sunscreens.

Described in this chapter are
Amiloxate, p.1589
Aminobenzoic Acid, p.1589
Avobenzone, p.1589
Bemotrizinol, p.1590
Bisoctrizole, p.1591
Cinoxate, p.1593
Dibenzoylmethane, p.1594
Diolamine Methoxycinnamate, p.1594
Dioxybenzone, p.1594
Drometrizole, p.1596
Ecamsule, p.1596
Ensulizole, p.1597
Enzacamene, p.1597
Homosalate, p.1598
Iscotrizinol, p.1599
Isopropyldibenzoylmethane, p.1599
Lisadimate, p.1604
Melanin, p.1604
Meradimate, p.1604
Methyl Anthranilate, p.1607
Mexenone, p.1607
Octil Triazone, p.1608
Octinoxate, p.1608
Octisalate, p.1608
Octocrilene, p.1608
Oxybenzone, p.1608
Padimate, p.1609
Padimate O, p.1609
Sulisobenzone, p.1614
Titanium Dioxide, p.1617
Zinc Oxide, p.1621

Vitamin D Derivatives

Some vitamin D derivatives are used in the treatment of psoriasis because they appear to induce differentiation and suppress proliferation of keratinocytes. Mention of other vitamin D derivatives that have been studied in psoriasis can be found under Vitamin D Substances, p.1986.

Described in this chapter are

Calcipotriol, p.1591	Tacalcitol, p.1615

Wound Management Agents

Many compounds and dressings are used in the management of wounds and ulcers. Although some are included in this chapter, others can be found throughout *Martindale*, including white and yellow soft paraffins (p.2031), alginates such as calcium alginate (p.1058), proteolytic enzymes such as collagenase (p.2286) and fibrinolysin (p.1287), and fibrin glue (p.1069).

Described in this chapter are

Becaplermin, p.1590	Polyphloroglucinol Phosphate, p.1611
Centella, p.1592	Polyurethane Foam, p.1611
Cerous Nitrate, p.1593	Prezatide Copper Acetate, p.1611
Crilanomer, p.1593	Skin Substitutes, p.1613
Dextranomer, p.1593	
Maggots, p.1604	

Topical Drug Administration

For drugs that are applied topically, the vehicle and formulation may be as important as the active drug. Indeed, some cream and ointment bases are used alone for their protective or emollient properties, while adverse effects of topical preparations are sometimes attributed to constituents of the vehicle such as stabilisers and preservatives. The choice of formulation depends on the skin condition being treated and the area affected. Lotions and gels are useful for hairy areas. Creams (oil-in-water emulsions) have cooling and emollient effects, are readily absorbed by the skin, and are used for acute and exudative conditions. Ointments (water-in-oil emulsions) are more occlusive than creams and are particularly suitable for dry lesions. Pastes (powder incorporated in an ointment basis) are also occlusive and are useful for their protective properties and for their use on circumscribed lesions. Less frequently used formulations include applications, collodions, and dusting powders. Typical quantities of preparations required per week for twice daily application to specific areas of an adult are given in Table 2, below.

Table 2. Typical quantities of preparations required per week for twice daily application to an adult.

	Creams and Ointments	Lotions
Face	15 to 30 g	100 mL
Both hands	25 to 50 g	200 mL
Scalp	50 to 100 g	200 mL
Both arms or both legs	100 to 200 g	200 mL
Trunk	400 g	500 mL
Groins and genitalia	15 to 25 g	100 mL

NOTE. These quantities do *not* apply to corticosteroid preparations.

Management of Dermatological Disorders

The management of some of the commoner skin conditions is discussed below.

Acne

Acne is a disorder of the pilosebaceous follicle; common features include increased sebum production, follicular keratinisation, colonisation by *Propionibacterium acnes*, and localised inflammation. Mild acne is characterised by open or closed comedones (blackheads and whiteheads), some of the latter developing into inflamed lesions such as papules and pustules. In moderate acne, the papules and pustules are more widespread, and there may be mild scarring. Severe acne is characterised by the presence of nodular abscesses or cysts in addition to widespread pustules and papules, and may lead to extensive scarring.

The most common form of acne is acne vulgaris. It is common in teenagers and while by their mid-20s the majority of cases have resolved, a few people still require treatment in their 30s and 40s. Skin areas typically affected are the face, shoulders, upper chest, and back. Acne may also occur in late middle age and in the elderly (late onset acne) and in infants (infantile acne). Certain drugs, including androgens, corticosteroids, corticotropin, hormonal contraceptives containing androgenic progestogens such as levonorgestrel, isoniazid, lithium, methoxsalen, and some antiepileptics may produce an acneform rash, as may substances such as tars, oils, and oily cosmetics.

Treatment aims to reduce the bacterial population of the pilosebaceous follicles, reduce the rate of sebum production, reduce inflammation, and remove the keratinised layer blocking the follicles. Drugs used include keratolytics, retinoids, and antibacterials. If topical preparations are not effective, oral preparations may be required. Response to therapy is commonly slow and long-term treatment is usually necessary.

Mild acne is treated topically, in particular with benzoyl peroxide, retinoids, and antibacterials. Abrasives have been used but their effectiveness is doubtful, and preparations based on sulfur or salicylic acid are considered by some to be obsolete; irritating astringents, harsh cleansers, and antibacterial soaps should be avoided. Topical corticosteroids, despite their presence in some compound preparations, should not be used.

Benzoyl peroxide has an antimicrobial action and mild keratolytic properties, and both comedones and inflammation generally respond well. It is probably the most widely used drug in mild acne because of its ready availability. Azelaic acid is an alternative to benzoyl peroxide that may cause less local irritation, but be less effective. Topical retinoids are effective in both comedonal and inflammatory acne; tretinoin is widely used but isotretinoin and tazarotene are considered to be equally effective. Adapalene, a naphthoic acid derivative with retinoid activity, also has similar efficacy, but may be better tolerated. Topical antibacterials can be used particularly for inflammatory acne. Tetracycline, clindamycin, and erythromycin are generally used, and appear to be roughly equivalent in efficacy. However, development of resistance by the skin flora is an increasing problem. Nicotinamide has also been used topically in mild to moderate inflammatory acne.

Generally, benzoyl peroxide is used alone as a first-line therapy for mild inflammatory acne, and topical retinoids can be used when comedones predominate.[1,2] Topical antibacterials may be used in inflammatory acne but should not be used alone; the addition of a topical retinoid or benzoyl peroxide improves efficacy and reduces the risk of developing resistance. However, many patients have both comedonal and inflammatory acne to some degree, and a retinoid with benzoyl peroxide, or a retinoid with benzoyl peroxide and a topical antibacterial, can be used.[3] Once there is clinical improvement and inflammatory lesions are under control, which may take 8 to 12 weeks,[4] the antibacterial can be stopped and the retinoid continued as maintenance therapy.[3] If there is no improvement within 6 to 8 weeks with antibacterial therapy, treatment should be stopped.[5] Further courses of topical antibacterial may be needed for flare-ups.[3]

Moderate acne is best treated with oral rather than topical antibacterials, of which tetracyclines appear to be the drugs of first choice. Tetracycline, doxycycline, lymecycline, or oxytetracycline may be used. Minocycline has also been reported to be effective; however, it can cause skin pigmentation and may be associated rarely with immunologically mediated reactions. Alternatives to the tetracyclines include erythromycin, co-trimoxazole, and trimethoprim. Resistance is an important problem, especially with erythromycin, and benzoyl peroxide is therefore also used.[3,6] To further limit the development of resistance, antibacterials should be used for no longer than necessary, the same antibacterial should be used for subsequent courses if the patient relapses,[3,6] and oral and topical antibacterials should not be used together.[6] Oral antibacterials have to be used for at least 3 months.[3,6] A total course of up to 6 months may be needed; longer treatment should generally be avoided but may be warranted in some cases.[6] If there is no response after 6 to 8 weeks, the antibacterial should be changed.[3] A topical retinoid may also be used for additional comedolytic activity. After the course of antibacterial has finished, a topical retinoid alone or with benzoyl peroxide is continued as maintenance therapy.[3,6] Women with moderate acne who also require oral contraception may be treated additionally with a combined oral contraceptive containing a non-androgenic progestogen.[2,4]

Severe acne is usually treated with oral isotretinoin;[3] there are also reports of oral isotretinoin being used outside this licensed indication for less severe acne that is resistant to treatment or that is causing physical scarring or psychological distress.[1] Where it cannot be used, high doses of oral antibacterials with a topical retinoid and benzoyl peroxide may be considered.[6] In women with signs of hyperandrogenism,[2-4] adjunctive use of the combination of anti-androgenic cyproterone with ethinylestradiol may be considered (this is available as a combination preparation that also provides contraception). A combined (non-androgenic) contraceptive is an alternative. Spironolactone has been used for its anti-androgenic properties in women when oestrogens are contra-indicated.

There is evidence to suggest that photodynamic therapy with a photosensitiser, such as 5-aminolevulinic acid, may be beneficial in acne.

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Alopecia

Alopecia (hair loss) has many causes but androgenetic alopecia is the most common form. Alopecia may also be congenital, be associated with systemic disorders, severe emotional and physical stress, or skin disorders, or be due to nutritional deficiencies. Some drugs may cause alopecia; examples include antineoplastics (see p.639), beta blockers, diazoxide, heparin, verapamil, and warfarin. In cicatricial alopecia there is destruction of the hair follicles (scarring) resulting in permanent hair loss. Drug treatment may be tried in alopecia areata and androgenetic alopecia but it is often unsuccessful or has only a modest effect. Treatment of any other associated underlying condition causing alopecia, or removal of a suspected drug, may produce hair regrowth. Some treatments have also been tried in cicatricial alopecia in an attempt to stop the scarring process and permanent hair loss. Non-drug options include the use of wigs and hairpieces, cosmetic hair products, or hair transplantation surgery.

Alopecia areata is an auto-immune disorder in which there is a loss of hair in sharply defined areas of skin that normally bear hair. The affected area can vary in size from about 1 cm^2 to the whole scalp (alopecia totalis) or all body hair (alopecia universalis).

Small or isolated patches of alopecia areata may not need treatment and in many patients hair regrows within a few months. If loss of hair becomes a problem cosmetically, treatment may be offered but is often not totally satisfactory. Several treatment options have been tried.[1-3] Intralesional corticosteroids stimulate hair regrowth at the site of injection and may be of benefit for limited patchy hair loss. Oral pulsed or continuous corticosteroids may be used in severe progressive cases. Potent topical corticosteroids, topical dithranol, and minoxidil lotion may also be used, although their efficacy is debatable. Contact immunotherapy with diphencyprone has shown benefit in patients with extensive patchy hair loss, alopecia totalis and universalis. Photochemotherapy with ultraviolet A radiation (PUVA) with either systemic or topical psoralens such as methoxsalen has been tried, but potentially serious adverse effects and limited efficacy restrict its use.

Androgenetic alopecia is hereditary thinning of the hair induced by androgens in genetically susceptible men and women.[1] Over time, the growth phase of the hair cycle becomes shorter and hair follicles become smaller, producing shorter, finer hairs that cover the scalp poorly. *Male-pattern alopecia* (male-pattern baldness)[1,3,4] involves recession of the hairline in the frontal region of the scalp or loss of hair at the vertex. It is usually associated with increasing age in men. Topical minoxidil is more effective in male-pattern alopecia than it is in the areata forms of alopecia, but is still, at best, only modestly effective. Because of the role of androgens in this condition anti-androgens and 5α-reductase inhibitors may also be tried. The 5α-reductase inhibitor finasteride has been shown to be of benefit in men with male-pattern alopecia, but is restricted to use in males. Alfatradiol, another 5α-reductase inhibitor, is available in some countries for topical use. To maintain effectiveness, minoxidil or finasteride must be used continuously as any benefit will be lost within months of stopping treatment. Androgenetic alopecia also occurs in women (*female-pattern alopecia*);[5] there is a similar pattern of hair loss although the thinning may be more diffuse and milder in women than men. Most women with androgenetic alopecia do not have elevated androgen concentrations and are treated with topical minoxidil. However, an anti-androgen such as cyproterone acetate or spironolactone might be considered for women with accompanying signs of hyperandrogenism such as hirsutism (p.2089).

Cicatricial alopecia involves inflammation and replacement of the hair follicles by fibrous tissue and the aim of treatment is to stop this process before hair loss is permanent. As well as hair loss, there can be pustules, crusting, scaling, and itching. There are a number of different types of cicatricial alopecia and many treatments have been tried, but there is no standard therapy.[6,7] In those where the scalp biopsy shows mainly lymphocytic infiltration, topical and/or intralesional corticosteroids can be used alone for limited disease or added to systemic therapy. Systemic corticosteroids may be used and other oral treatments that have been tried for more extensive or progressive disease include hydroxychloroquine, isotretinoin, mycophenolate mofetil, and ciclosporin. There are also reports of benefit from other topical therapies such as pimecrolimus, tacrolimus, and tazarotene. In neutrophilic cicatricial alopecia, oral antibacterials are used to control follicular infection and suppuration. Oral isotretinoin has been used in patients with neutrophilic dissecting cellulitis.

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Burns

Burns may be caused by chemicals or heat. Initial treatment of burns is irrigation with cold or tepid water for at least 20 minutes; hypothermia should be avoided. This limits the skin damage in burns caused by heat and removes the causative agent in chemical burns. Sodium bicarbonate solution is then used on acid burns and acetic acid solution on alkaline burns. The extent of a burn injury is described by area and depth. The affected body-surface can be calculated, and the depth of the burn may be classified as superficial (first-degree); partial thickness (second-degree), which may be further classified as superficial or deep partial thickness; or full thickness (third-degree). The major problems associated with burns are hypovolaemic shock, inhalation injury, metabolic abnormalities, and infection. For burns affecting the eye, see p.1674.

- After a burn, fluid accumulates rapidly in the wound area due to increased permeability of the microcirculation and this loss of fluid from the circulation may produce hypovolaemic shock (p.1183) if burns involve at least 15 to 20% of the body-surface.
- Inhalation injury producing airway oedema is mainly a result of exposure to toxic gases. Endotracheal intubation is required until the oedema subsides. Oxygen therapy is used, and nebulised beta$_2$ agonists may be given to treat bronchospasm. Inhalation of heparin and acetylcysteine may be of benefit in reducing pulmonary failure.
- Hypermetabolism and marked catabolism can result from major burn injury. Protein breakdown and loss causes muscle wasting and weakness, impaired wound healing and skin breakdown, and impaired immunity. Other effects of metabolic disturbances include an increase in liver fat and hepatomegaly, osteopenia, tachycardia and increased myocardial oxygen consumption. Enteral feeding (p.1923) to match nutrient requirements is essential for metabolic management. Other treatments that have been tried to reduce net catabolism include the amino acids arginine and glutamine, drugs with anabolic effects including insulin, oxandrolone, and somatropin (for concerns about the latter use see p.1802), and catecholamine antagonism using beta blockers such as propranolol.
- Prevention of infection is an important part of burn wound management. Micro-organisms proliferate rapidly in burn wounds, especially those severe enough to impair immune function, and sepsis remains the major fatal complication of burns. Burn wounds should be cleansed with normal saline (see Wounds and Ulcers, below). This may be all that is required for very minor burn wounds; a non-adherent dressing, such as paraffin tulle, may be used if necessary. Topical antibacterials, such as chlorhexidine, sulfadiazine silver, silver nitrate, and mafenide acetate, may be applied as required. Sodium hypochlorite (Dakin's solution) may also be of value, although opinions differ as to its usefulness. Removal of devitalised tissue is also an essential element of management. Infections require aggressive systemic treatment (see under Skin Infections, p.194).

Full thickness burn wounds require skin grafting. This is performed as soon as possible after stabilisation of the patient. Skin grafting may also be considered for deep partial thickness wounds. If the area to be grafted is very extensive, the grafting procedure may have to be in stages (at intervals of about a week) as sufficient autologous skin becomes available. Alternatively, temporary skin substitutes may be used to supplement autologous skin and allow wound closure in one stage.

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Darier's disease

Darier's disease (keratosis follicularis) is an uncommon inherited keratinisation disorder (see below) and is characterised by groups of horny papules over the body. These may become irritated and/or infected, exudative, and crusted. Involvement of the nails is characteristic. Severity varies greatly; emollients, use of soap substitutes, and wearing cool clothing are important in controlling irritation in all patients, and may be sufficient in the mildest cases. More severe cases are treated by topical application of keratolytics such as salicylic acid or topical retinoids such as isotretinoin, tretinoin, or tazarotene. Topical corticosteroids are helpful in some patients to alleviate retinoid-induced irritation. Treatment with oral retinoids (acitretin, etretinate, or isotretinoin) is needed in more extensive disease, and has been combined with topical retinoids. Ciclosporin and topical fluorouracil have also been tried; some patients have been reported to respond to dietary supplementation with essential fatty acids. There is only anecdotal evidence to support the use of surgery or laser therapy, although these may be tried in refractory cases.

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Dermatitis herpetiformis

Dermatitis herpetiformis is a rare blistering disorder of the subepidermal tissue in which the vesicles and papules are intensely irritant and pruritic. The knees, elbows, buttocks, shoulders, and scalp are areas typically affected. The disease presents usually during early to middle adult life and is a chronic condition, although there may be periods of remission that last several months. In most patients there is also a mild gastrointestinal absorptive defect characterised by gluten hypersensitivity (gluten enteropathy or coeliac disease, see p.1922). Skin lesions can be suppressed by dapsone; the sulfonamides sulfamethoxypyridazine or sulfapyridine have been used as alternatives to dapsone.[1-5] A gluten-free diet may improve both gastrointestinal symptoms and the skin disorder.[2,4-6]

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Drug-induced skin reactions

Drugs are a frequent cause of adverse skin reactions. The skin reaction may mimic a spontaneously occurring skin disorder and is therefore included in the differential diagnosis of most skin diseases. Alternatively, the drug may produce quite specific changes. The reaction can develop after the first dose or after a period of sensitisation. Pigmentation changes or effects on hair may take some months to become apparent. Drug-induced nail changes have also been reported.

Reactions range from mild rashes to severe life-threatening reactions including angioedema with urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Other serious skin reactions include hypersensitivity syndromes, serum sickness, and vasculitis.

Stevens-Johnson syndrome (see also Erythema Multiforme, below) is a severe, blistering skin reaction also affecting the mucous membranes of the oropharynx, eyes, and genitalia and accompanied sometimes by fever, pain, and malaise. **Toxic epidermal necrolysis** (Lyell's syndrome or scalded skin syndrome) as described on p.1584, is a more severe form of the reaction where considerable amounts of the epidermis may be shed. Sulfonamides, carbamazepine, and allopurinol are among the many drugs that have been associated with both these reactions.

Hypersensitivity syndrome is a severe, idiosyncratic reaction which includes rash and fever, and often hepatitis, arthralgias, lymphadenopathy, and haematological abnormalities. It tends to have a relatively late and slow onset. Some antiepileptics and sulfonamides cause this syndrome, as well as allopurinol, dapsone, and gold salts. **Serum sickness** is manifest as rash, fever, arthralgia and arthritis and typically develops 8 to 14 days after doses of serum preparations and vaccines. **Vasculitic reactions** may occur 7 to 21 days after beginning therapy with drugs such as allopurinol, penicillins, and sulfonamides (see Hypersensitivity Vasculitis, p.1505). The vasculitis usually affects small vessels of the lower extremities producing purpura, although it can also affect vessels in the kidney, liver, and gastrointestinal tract, in which case it may be life-threatening.

Maculopapular exanthematic eruptions are probably the most frequent drug-induced skin reaction. Drugs commonly causing these rashes include carbamazepine, chlorpromazine, nitrofurantoin, penicillins, and sulfonamides. **Urticaria** (p.1584) is also frequently drug-induced. **Photosensitivity** rashes where the skin reaction is confined to light-exposed areas may be phototoxic or photoallergic in nature (see Drug-induced Photosensitivity, p.1581). Amiodarone produces a phototoxic reaction in many patients. Some drugs cause **pigmentary changes** (see Pigmentation Disorders, p.1582). Chlorpromazine can cause both photosensitivity and pigmentary changes. **Acneform eruptions** may be produced by a number of drugs (see Acne, above). Some drugs produce skin reactions resembling **pemphigus** and **pemphigoid** (see p.1582). Most of the drugs implicated contain a thiol group or metabolism of the drug generates a thiol group. Examples include captopril, penicillamine, penicillins, piroxicam, and rifampicin. **Fixed-drug eruptions** are inflammatory patches that appear at the same sites each time the drug is taken, and may occur with many drugs including dapsone, sulfonamides, and tetracycline.

Drug-induced **nail changes** include onychomadesis, nail fragility, onycholysis, paronychia, pigmentation, and vascular changes. The effect is usually transient and disappears with drug withdrawal. Drugs reported to cause nail changes include antineoplastics, psoralens, retinoids, tetracyclines, and zidovudine.

The majority of drug-induced adverse skin reactions are mild. However, in severe reactions rapid withdrawal of the suspected drug is needed. In some cases, this may mean stopping several drugs. In most cases the skin reaction will be resolved by symptomatic treatment. Another dose of the offending drug may establish whether the skin eruption is drug-induced, although reactions may be more severe and therefore rechallenge should not be performed after a serious reaction.

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Eczema

Eczema (often used synonymously with the term dermatitis) refers to a variety of skin conditions characterised by epidermal inflammation and itching. The areas of skin affected vary in the different types of eczema, but the skin lesions share certain common features. In acute eczema the skin is typically red and inflamed with papules, vesicles, and blisters. In chronic eczema the skin may show the same features but be more dry, scaly, pigmented, and thickened. Eczema may be categorised as exogenous (including allergic, irritant, and photosensitivity eczema) or endogenous (such as atopic, discoid/nummular, gravitational, and seborrhoeic eczema), but there may be multiple causes of eczema, both endogenous and exogenous, in an individual patient. Two of the most common forms of eczema are atopic eczema (see below) and seborrhoeic dermatitis (p.1584).

Atopic eczema mainly affects infants and children although adults may also suffer. The skin is itchy and there is a chronic or relapsing dermatitis in which the face and neck and flexures of the elbows and knees are involved most often and are excoriated and lichenified.

General principles for the management of **atopic eczema** may also be applied to other eczematous skin disorders. Cure of atopic eczema is said to be unrealistic, but good control can be achieved with proper management. The objective of treatment should be to reduce signs and symptoms, to prevent or reduce recurrences, and to provide long-term management by preventing exacerbation. Guidelines have been issued by, among others, the Primary Care Dermatology Society with the British Association of Dermatologists,[1] the American Academy of Dermatology,[2] and the International Consensus Conference on Atopic Dermatitis (ICCAD II).[3] The management of eczema is also frequently reviewed.[4-6]

First-line treatment.

- Regular bathing using soap substitutes is important to *cleanse and hydrate* the skin; soaps and detergents should be avoided as these remove the natural lipid from the skin. Suitable bath oils should be used to maintain skin hydration. Emollients should be applied liberally to the whole body at least twice daily, especially after bathing, and more frequently throughout the day to hands and face.
- Patients should be educated on the *avoidance of trigger factors*. These may include irritants, microbes, and psychological or allergic factors.

Acute control of pruritus and inflammation.

- Intermittent topical *corticosteroids* are the mainstay of treatment and are used for up to a week to manage acute flares of atopic eczema. Treatment for up to 6 weeks may be needed for initial control of chronic eczema. To minimise potential adverse effects the minimum strength preparation to control the disease should be used, and the age of patient, site of eczema, and extent of disease should be considered when selecting the appropriate preparation. Very potent preparations should be used in children only under specialist supervision.
- Topical *calcineurin inhibitors* (pimecrolimus or tacrolimus) may be used as alternative therapy when corticosteroids are contra-indicated, or as second-line therapy in patients who have not responded adequately to topical corticosteroids. Pimecrolimus is indicated for mild to moderate disease and tacrolimus for moderate to severe eczema. The main adverse effect is burning at the site of application. Once the condition settles the patient should revert to treatment with emollients.

Maintenance therapy.

- Topical corticosteroids may be used intermittently for acute exacerbations. Once the patient is back in remission emollients should be continued.
- For persistent disease or frequent flares, topical calcineurin inhibitors are effective and may be used at the earliest sign of recurrence. While these drugs prevent disease progression they do not have the adverse effects of corticosteroids and consequently may be used on all body areas (including sensitive areas like the face, eyelids, and neck) for extended periods. Studies so far suggest that these new drugs are safe in the short term. However, they do suppress T lymphocytes and although systemic absorption is minimal there may be a possibility of immunosuppression, skin cancers, or bacterial infection. There has been considerable debate about the possible risk of cancer associated with topical calcineurin inhibitors (see Carcinogenicity, under Tacrolimus, p.1843). These concerns in particular prompted licensing authorities in Europe and the USA in 2006 to remind prescribers that these drugs should only be used intermittently as second-line treatments, and should not be used in children less than 2 years of age.[7-9]
- *Coal tar* preparations may be used occasionally for chronic atopic eczema, and *ichthammol* may be used as an ointment or paste bandages for chronic lichenified eczema.

Adjunctive therapy.

- Overt bacterial, fungal, or viral infections should be treated with an appropriate systemic drug (see Skin Infections under Antibacterials, p.194, and under Antifungals, p.521). Topical preparations are generally not used as they should be restricted to limited areas and patients with eczema often have widespread infections.
- A sedating *antihistamine* may be used short term for severe pruritus associated with relapse or at night-time if scratching disturbs sleep or occurs while asleep. Non-sedating antihistamines are generally ineffective in eczema but may be of benefit in atopic dermatitis and concomitant urticaria. Topical *doxepin* may provide short-term relief from pruritus, but drowsiness and contact dermatitis can occur.

Patients whose eczema fails to respond to these first-line treatments, even under specialist supervision, require further measures.

Severe refractory disease.

- *Phototherapy* with ultraviolet A or B, or in combination, may be useful, and photochemotherapy using a psoralen (generally methoxsalen) with ultraviolet A (PUVA) may be used in severe, widespread disease. However, potential long term effects such as premature ageing of the skin and skin malignancy need to be considered.
- Therapy with *more potent topical and oral corticosteroids* may be considered for short periods of time. In general, only mild corticosteroids (such as 1% hydrocortisone) should be used on the face and in flexures as absorption is increased in these areas.
- *Wet-wrap dressings* are sometimes used intermittently, particularly in children, for hydration and anti-inflammatory effects.[10,11] Different techniques have been described: wet bandages or dressings may be applied to skin already covered with an emollient or diluted corticosteroid cream, alternatively the dressing may be soaked in warm diluted cream before use; a dry outer dressing may be added. Dressings may be used only on affected parts of the body, or a whole-body suit may be used for extensive eczema, and left in place for up to 24 hours. Treatment can continue for several weeks, but should probably be limited to 1 week when corticosteroids are used because of the risk of adverse effects from systemic absorption.[10] Wet-wrapping may not be appropriate in patients whose eczema has become infected.
- Various *other drugs* have been tried in resistant eczema. Azathioprine, ciclosporin, or methotrexate may be tried in selected patients.

Evening primrose oil and borage oil have also been tried although evidence in favour of a useful therapeutic effect is poor. Other drugs at an experimental stage include interferons, mycophenolate mofetil, and thymopentin. There has been much interest in the use of complementary and alternative therapies and herbal medicines, but serious adverse effects have occasionally occurred and although encouraging results have been reported the degree of benefit is still uncertain.[12,13]

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Epidermolysis bullosa

Epidermolysis bullosa consists of a group of similar congenital disorders characterised by severe blistering of the skin.[1,2] Sometimes the mucosae, especially of the mouth and oesophagus, are also affected. The blistering may be caused by various structural and metabolic defects and occurs at different levels in the skin in the different forms (simple, junctional, and dystrophic). Blistering can follow even minor trauma or can arise spontaneously. In some patients blistering and scarring can cause marked tissue loss of the affected areas and the most severe forms are fatal in early infancy because of infection of the blisters. Milder forms may be managed by avoiding trauma and keeping blisters clean and dry, but there is no truly effective treatment for the severe forms. High-dose oral corticosteroids may be needed. Phenytoin has been tried, but was unsuccessful in a controlled study. Thalidomide has also been tried, and oral tetracycline has reduced the number of lesions in a few cases.

There is also an acquired form of the disease, epidermolysis bullosa acquisita, and it too is difficult to treat;[3] corticosteroids and other immunosuppressants may be tried. Individual patients have responded to high-dose intravenous immunoglobulins or extracorporeal photochemotherapy (oral methoxsalen followed by removal of blood and UV irradiation of leucocytes outside the body before reinfusion).[4,5] There are individual case reports of successful treatment with monoclonal antibodies such as basiliximab (an interleukin-2 receptor antibody)[6] and rituximab (an anti-CD20 antibody).[7]

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Erythema multiforme

Erythema multiforme is an inflammatory reaction of the skin characterised by maculopapular lesions that may become annular and blister. Areas typically affected are the hands, forearms, elbows, knees, and feet. It is usually associated with a precipitating trigger such as infection (notably herpes simplex infection); it may also be associated with drug use, neoplastic disease, or collagen or inflammatory diseases. In severe forms there is also blistering of the mucous membranes (usually of the mouth). There is some overlap in the descriptions of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and attempts have been made to classify them into distinct categories.[1-3] Erythema multiforme occurs mainly after infections, whereas the Stevens-Johnson syndrome is mainly a drug-induced reaction and seems to be part of a spectrum of skin reactions, with life-threatening toxic epidermal necrolysis being the more severe form (see Drug-induced Skin Reactions, above).

As erythema multiforme is usually an acute reaction of relatively short duration, symptomatic treatment as for burns (see above) may be all that is required. If severe reactions occur systemic corticosteroids may be considered, although there has been controversy about their value. Erythema multiforme may become a recurrent disorder in some patients and various drugs have been tried for treatment and prophylaxis.[4] Aciclovir, given in short courses or continuously, has been used particularly when herpes simplex infection appeared to be a trigger factor. Other drugs that have been tried for recurrent erythema multiforme include dapsone, hydroxychloroquine, mepacrine, azathioprine, mycophenolate, and thalidomide.

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Hyperhidrosis

Hyperhidrosis (excessive sweating) can be generalised or focal, affecting the palms of the hands, soles of the feet, axillae, or less commonly the craniofacial region. No cause can usually be established although it may be secondary to an underlying endocrinological, neurological, or neoplastic disorder;[1,2] in some cases, it may be drug-induced.[3]

Drug therapy should be tried initially but is often ineffective in severe cases. Aluminium salts, such as aluminium chloride or aluminium chlorohydrate in alcoholic solvents applied topically, may be successful in milder forms of focal hyperhidrosis.[1,2,4] Topical antimuscarinics such as diphemanil metilsulfate, glycopyrronium bromide, or hyoscine hydrobromide may also provide some relief, particularly in craniofacial sweating.[2] Adverse effects of oral antimuscarinics generally preclude such use, although oral propantheline bromide has been used successfully to control excessive sweating in a few patients with spinal cord injuries. An intravenous infusion of phentolamine mesilate may be effective in some patients with generalised hyperhidrosis.[5] Tap water iontophoresis is an alternative first-line option for palmar or plantar hyperhidrosis.[1,2,4] Intradermal injection of botulinum A toxin is used for focal hyperhidrosis when topical therapies are insufficient, although injections are painful and local or regional anaesthesia may be needed, especially for treatment of the hands and feet.[1,2,4] Formaldehyde and glutaral solutions have been used topically for hyperhidrosis affecting the feet but are not very effective and are not usually recommended.

When drug therapy fails to provide adequate relief surgery may be attempted.[1,2,4] Subcutaneous curettage or excision of skin bearing the eccrine glands has been used but minimally invasive techniques, notably endoscopic thoracic sympathectomy, are now available; the latter offers a simple and effective management for severe localised upper limb hyperhidrosis.

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Ichthyosis

Ichthyosis is a term used for generalised noninflammatory dry scaling or keratinisation disorders (see below). There are several different forms of ichthyosis and severity and incidence varies. They are generally inherited disorders. Emollients, including urea, are used to provide relief to the dry skin by coating the skin surface with an oily film thus preventing evaporation of water. If scaling is more severe topical keratolytics such as salicylic acid or urea are used. Topical retinoids such as tazarotene may be tried. In the severest forms of ichthyosis oral retinoids may be necessary. Acitretin, etretinate, and isotretinoin have all been used. A few patients have responded to topical calcipotriol or tacrolimus, but systemic absorption may be a problem. Liarozole, an oral inhibitor of retinoic acid catabolism, is under investigation.

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Keratinisation disorders

Keratinisation is the process whereby basal epidermal cells are transformed into dead cells of the stratum corneum from where they are shed. The process takes about 14 days and shedding normally balances production so that the thickness of the stratum corneum does not alter. Keratinisation disorders (keratoses) are characterised by reduced shedding and the formation of scale at the skin surface. A scale is an aggregate of horn cells that have failed to separate horizontally and hyperkeratosis is an exaggeration of this failure in which there is also a vertical build up of the horn cells. Keratinisation disorders include Darier's disease and ichthyosis (see above). Certain inflammatory skin disorders, such as psoriasis (see p.1583), also show enhanced epidermal proliferation.

Lichen planus

Lichen planus is an inflammatory skin disorder with itchy papular lesions arising usually on the extremities. The nails and oral or buccal mucosa, and rarely the genital mucosa, may also be affected. Its cause is uncertain although sufferers have a higher incidence of auto-immune disease than normal. Some drugs can produce lichenoid reactions; examples include mepacrine, methyldopa, penicillamine, and sodium aurothiomalate.

Evidence for the efficacy of the various treatments that have been tried is mostly scanty.[1,2] In most patients lichen planus remits spontaneously and, if mild and localised, little or no treatment is needed. Potent topical corticosteroids are often used for localised cutaneous disease when treatment is needed, and occlusive dressings may be used to enhance efficacy.[1,3] However, less potent corticosteroids should generally be used on the face, axillae, groin, or genitals. Intralesional corticosteroids, such as triamcinolone acetonide, can be used for hyperkeratotic or resistant localised plaques. Symptomatic mucosal disease is also treated with topical corticosteroids;[1,3,4] various dosage forms have been used including ointments, adhesive bases, pastes, lozenges, and mouthwashes. Other drugs that have been used topically, with variable results, include ciclosporin and the retinoids isotretinoin and tretinoin. Intralesional corticosteroids have also been used for resistant or erosive mucosal lesions.[1,4]

Systemic corticosteroids may be used in generalised cutaneous lichen planus and acute exacerbations of mucosal disease.[1,3,4] If the condition becomes resistant to corticosteroid therapy, an oral retinoid such as acitretin, etretinate, or isotretinoin, may be tried. Other oral treatments for which there are reports of benefit in small numbers of patients include ciclosporin, griseofulvin, chloroquine and hydroxychloroquine, and photochemotherapy using a psoralen with UVA (PUVA).[1,4] Topical tacrolimus and pimecrolimus have also been tried.

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Lichen sclerosus

Lichen sclerosus is a chronic inflammatory skin condition that most commonly occurs in women, but is also seen in men and children.[1-5] It affects the anogenital area, causing itching, soreness, and urinary and sexual problems. Extragenital lesions may occur, but do not usually itch, and some patients may show no symptoms at all.[1,2,5] Lichen sclerosus runs a relapsing and remitting course and complications include secondary infection, most commonly with *Candida*, physical scarring, and vulvodynia. The most common complication seen in male patients is phimosis. Although the exact cause of the disease is unknown, there appears to be a strong association with auto-immune disorders and genetic factors have also been implicated. There is also an association between lichen sclerosus and squamous cell and verrucous carcinoma.[2,3,5]

Management of lichen sclerosus includes the control of symptoms, prevention and treatment of complications, and the early detection of malignancies.[3,5] Topical potent corticosteroids such as clobetasol propionate or betamethasone dipropionate 0.05% have been shown to be safe and effective for both genital and extragenital disease. Intralesional triamcinolone was found to be effective in a small trial. The benefit and safety of other topical treatments, such as pimecrolimus, tacrolimus, retinoids, testosterone, and progesterone are not clear. Systemic retinoids may be useful in complicated disease that is not responding to topical corticosteroids. There have been reports of benefit for treatment with stanozolol, photochemotherapy using a psoralen with UVA (PUVA), photodynamic therapy using topical 5-aminolevulinic acid, and laser therapy. Surgical intervention is only indicated for complications of scarring or the development of malignancy.[2,3,5]

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Light-induced skin reactions

Light, although essential for many biological functions, may cause a variety of disorders, particularly due to the ultraviolet portion of the solar spectrum.

Ultraviolet (UV) light has different properties according to its wavelength.

- **UVA** (wavelengths 320 to 400 nm) produces immediate direct tanning of the skin with little erythema although it does contribute to the long-term harmful effects of photoageing and cancers. UVA has also been subdivided into UVA-I (340 to 400 nm) and UVA-II (320 to 340 nm); the effects of UVA-II are more like those of UVB.
- **UVB** (wavelengths 290 to 320 nm) is about 1000 times stronger than UVA in producing erythema and is that part of the sun's spectrum that is responsible for producing sunburn and it too contributes to long-term effects. UVB also produces tanning by indirect pigmentation.
- **UVC** (wavelengths 200 to 290 nm) produces erythema without tanning. The earth's surface is usually screened by the ozone layer from UVC radiation although UVC may be emitted by artificial sources such as bactericidal lamps and industrial welding arcs.

In normal healthy individuals **exposure to sunlight** (including reflected light from snow, white sand, or water) causes an increase in pigmentation (tanning). This is an adaptive mechanism to protect the skin from UV radiation. Immediate tanning results from the oxidation of melanin precursors in the uppermost layers of the skin. There may also be a delayed and indirect pigmentation due to the formation of new melanin. The ability of an individual to form a tan is genetically predetermined. Melanin provides some protection against further exposure, but the main protection is provided by thickening of the corneous layer. However, excessive exposure to strong sunlight causes erythema and sunburn, which is an inflammatory response to the damage caused by UV radiation.

Excessive and prolonged exposure to intense sunlight may lead to degenerative changes in the skin (premature ageing of the skin or photoageing, below), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), immunosuppression, and some skin cancers such as basal cell or squamous cell carcinomas and malignant melanomas (see Malignant Neoplasms of the Skin, p.672). Some patient groups are also at higher risk of adverse effects from sunlight exposure. Even brief exposure to sunlight can trigger a reaction in those with photosensitivity disorders (below), patients with hypopigmentation disorders such as vitiligo and albinism (see Pigmentation Disorders, p.1582) are more susceptible to sunburn, and transplant patients receiving systemic immunosuppressants are at increased risk of skin cancers (see under Organ and Tissue Transplantation, p.1810). Many drugs can cause a phototoxic or photoallergic reaction (see Drug-induced Photosensitivity, below).

Protection against sunlight is therefore beneficial, both in healthy people to prevent skin damage, and in patients at increased risk of adverse effects from sunlight exposure. Medical and scientific personnel exposed to ultraviolet lamps may need protection against the whole of the UV spectrum. This may be achieved by appropriate dress and through the use of **sunscreens** applied to the skin. Sunscreens may be of chemical or physical types (see p.1576) and many products combine sunscreens of different types to maximise protection. A broad-spectrum sunscreen should be effective against both UVA and UVB, but UVA coverage can be variable. It may be difficult to formulate physical sunscreens in cosmetically acceptable ways.

The efficacy of a particular sunscreen preparation is often expressed as its **sun protection factor (SPF)**. This is a ratio of the time required for irradiation to produce minimal perceptible erythema (minimal erythemal dose; MED) with the skin protected with the sunscreen compared with the MED without protection, for a standard 2 mg/cm^2 dose of sunscreen. Thus the SPF is mainly an indication of efficacy against UVB light. Various systems have been suggested for classifying the relative efficacies of sunscreens against UVA light but none appears, as yet, to be universally accepted. The efficacy of a sunscreen is also highly dependent upon its correct application and studies have found that, in general, sunscreen preparations are applied haphazardly and in insufficient quantities to provide optimal protection.

Governmental authorities and dermatologists in many countries issue guidance to the public on sun protection, including sunscreen use. General measures include avoiding sunlight exposure when UV radiation is strongest (usually between 10 a.m. and 3 p.m.), seeking shade when outdoors in strong sunlight, using wrap-around sunglasses that conform to appropriate standards, and wearing a broad-brimmed hat and clothing that protect against sunlight. Sunscreens should be applied liberally and evenly to all exposed areas of skin at least 15 to 30 minutes before sunlight exposure, and re-applied at least every 2 hours and after swimming or perspiring. Broad-spectrum products are recommended; dermatologists in some countries such as the UK and USA advocate the use of preparations with at least SPF 15 (SPF 15+), while in Australia SPF 30+ is recommended.

Many treatments have been tried in the management of acute *sunburn*, but studies have been small and results often conflicting. There is a lack of strong evidence to show that any specific treatment reduces epidermal damage or the time to healing once the signs and symptoms of sunburn have developed. Emollients, cool compresses, paracetamol, and NSAIDs, are often used for symptomatic relief of erythema, pain, and pruritus; oral antihistamines, topical hydrocortisone, and topical anaesthetics might also be considered.

Reviews.

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Drug-induced photosensitivity. Photosensitivity can be produced by drugs either given systemically or applied topically, and the reaction can be phototoxic or photoallergic in nature.[1] In *phototoxicity,* a direct toxic effect on tissues occurs when the drug is energised by absorbing radiation. The reaction has a rapid onset (usually within 24 hours) and occurs on exposed skin areas. Resembling an exaggerated sunburn, the reaction can include erythema, oedema, hyperpigmentation causing a darker red than sunburn, pruritus, and urticaria. The response is dependent on the dose of the photosensitiser and the intensity of sunlight exposure. In *photoallergy,* the hypersensitivity reaction has an immunological basis requiring previous exposure to the photosensitising drug. The onset may be delayed until several days after exposure to sunlight and present as a papulovesicular eruption, pruritus, and eczematous dermatitis. Photoallergic reactions are less common than phototoxicity.

Systemic drug groups that have been reported to cause photosensitivity include:

- antibacterials (fluoroquinolones, sulfonamides, and tetracyclines)
- antidepressants (tricyclic antidepressants and St John's wort)
- antiepileptics (carbamazepine, lamotrigine, phenobarbital, and phenytoin)
- antihistamines (including cyproheptadine, diphenhydramine, and loratadine)
- antimalarials (chloroquine, quinine, pyrimethamine, and mefloquine)
- antineoplastics (including fluorouracil, methotrexate, and vinblastine)
- cardiovascular drugs (including ACE inhibitors, amiodarone, quinidine, thiazide diuretics, and simvastatin)
- corticosteroids
- NSAIDs
- phenothiazine antipsychotics
- sex hormones (oestrogens and progestogens)
- sulfonylurea antidiabetic drugs
- retinoids (isotretinoin)

Photocontact dermatitis occurs from the interaction between sunlight and topically applied substances, and can be either a phototoxic or photoallergic reaction. Implicated drugs have included antiseptics, antifungals, coal tar, corticosteroids, local anaesthetics, and retinoids.[1] Photosensitivity reactions have also occurred to the topical sunscreens intended to prevent them.[1,2] Photoallergic reactions have been reported for chemical sunscreens, particularly aminobenzoic acid and benzophenones (dioxybenzone, mexenone, oxybenzone, and sulisobenzone). Reactions to cinnamates seem to be less frequent.

Photosensitivity reactions are managed symptomatically as for sunburn (see Light-induced Skin Reactions, above); antihistamines and corticosteroids may be needed to treat photoallergic reactions. If the offending drug cannot be withdrawn or substituted, sun exposure should be minimised with appropriate clothing and sunscreens.[1]

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Photoageing. Exposure to sunlight induces changes in the skin in addition to the normal ageing process. This photoageing, or photodamage, can manifest as wrinkles, skin roughness and dryness, irregular pigmentation, telangiectasia, sallowness, and lentigines (sun or liver spots). Photoageing is also associated with increased risks of actinic keratoses and skin cancers (see Malignant Neoplasms of the Skin, p.672).

Cosmetic treatments and procedures for the effects of photoageing have been extensively and widely promoted, but few have undergone rigorous scientific evaluation and there is a lack of data in general.[1] Measures to limit sunlight exposure, including the use of sunscreens, reduce the progression of photoageing.[2,3] Topical retinoids, such as isotretinoin, tazarotene, and tretinoin, can improve fine wrinkles, irregular pigmentation, roughness, and lentigines. However, the effect is dose-related and these drugs can cause irritation and photosensitivity.[1-4] Hydroxyacid keratolytics such as glycolic acid are also widely promoted for the reduction of photoageing effects. Low concentrations are used in nonprescription cosmetic preparations, and higher concentrations may be used as chemical peels. Overall, however, their effects are limited.[1,2] Local injection of botulinum A toxin to cause muscle paralysis is used for the cosmetic reduction of lines and wrinkles.[2,3] Injectable skin fillers such as bovine collagen and hyaluronic acid are also available to reduce lines and deep wrinkles.[2] Other procedures in use include dermabrasion to reduce wrinkles, and cryosurgery or electrosurgery for discrete pigmented lesions; lasers or other light therapies are also used for wrinkles, pigmented lesions, and benign vascular proliferations such as telangiectasia and angiomas.[2] Oral and topical antioxidants have also been promoted for the treatment and prevention of photoageing, but there is a lack of data to support such claims.[2,3]

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Photosensitivity disorders. In some persons even brief exposure to sunlight can result in light-induced disorders of the skin.

Polymorphic light eruption is a common hypersensitivity reaction characterised by pruritic erythematous papulovesicular lesions that develop several hours after exposure to sunlight. The condition usually begins in adulthood and affects more women than men. For many patients the susceptibility to eruption starts in early spring and resolves by late summer as the skin becomes more tolerant to sunlight, but patients with severe forms may also be symptomatic in the winter. Mild forms can settle without scarring within days, by sun avoidance and use of a broad-spectrum sunscreen. Potent topical corticosteroids or a short course of oral prednisolone may be useful to control the acute rash. A gradual increase in exposure to sunlight may be sufficient for desensitisation in mild cases, but patients with more severe disease may need to undergo artificial hardening of the skin by UVB phototherapy or photochemotherapy using a psoralen with UVA (PUVA). However, this effect is temporary and usually needs to be repeated each spring.[1-3] Azathioprine may be considered in patients who are very sensitive to sunlight, for whom sunscreens are ineffective, and who cannot tolerate phototherapy.[2]

Chronic actinic dermatitis is manifested by a persistent, often lichenified, eczematous eruption that usually only affects the exposed areas although in a small number of patients larger areas can be affected. It mainly affects older men, and many patients may be unaware of the role that sunlight plays in the condition. These patients may also show clinically relevant allergy to many naturally occurring substances, as well as drugs and sunscreens.[3-5] Management is based on sunlight and allergen avoidance and the use of sunscreens, emollients, and topical or oral corticosteroids. Phototherapy or photochemotherapy may also be useful. Systemic immunosuppressants including azathioprine, ciclosporin, and mycophenolate mofetil have been used in resistant disease.[1,4,5] Interferon alfa and topical tacrolimus have also been used successfully in a few cases.[1]

Actinic prurigo is similar to polymorphic light eruption but less common, and is characterised by persistent pruritic papules on areas exposed to sunlight, often with extension to covered areas. Other features include scarring, cheilitis, and eye involvement. It is managed similarly with sunscreens, topical or oral corticosteroids, and phototherapy or photochemotherapy. Thalidomide has been used, but relapse frequently occurs when treatment is stopped.[1]

Solar urticaria is an uncommon condition that can often be managed with sunscreens alone, but non-sedating antihistamines such as loratadine may also be helpful. Phototherapy and photochemotherapy have also been used.[1]

Xeroderma pigmentosum is a rare autosomal recessive condition in which a defective DNA-repair system fails to repair UV-induced DNA damage.[6] The skin is hypersensitive to sunlight, resulting in serious sunburn after minimal exposure. From a very early age patients start to develop lentigines (sun or liver spots), spotty hypopigmentation, telangiectasias, calloused thickening, atrophy, scabbing, and scarring. Numerous actinic keratoses, precancerous lesions, and malignant neoplasms of the skin (p.672) develop in childhood and many patients die before reaching adulthood. Other effects of the disease include motor impairment, mental retardation, ocular damage, leukaemia, and dental caries. Management involves strict avoidance of sunlight and use of broad-spectrum sunscreens. There is some evidence that systemic retinoids, such as acitretin and isotretinoin, may be useful in preventing the development of skin cancers, although adverse effects from long-term use may be of concern. Topical fluorouracil may be used on actinic keratoses and malignant skin cancers. A topical preparation containing recombinant T4 endonuclease V, a DNA-repair enzyme, is under investigation to reduce the incidence of actinic keratoses and skin cancers.

Other conditions that can be exacerbated by sunlight include the cutaneous porphyrias (p.1448), lupus erythematosus (p.1513), and sometimes herpes labialis (p.854).

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Pemphigus and pemphigoid

Pemphigus and pemphigoid are rare, disabling, and severe or potentially fatal blistering skin diseases. They are distinct disorders although both have an auto-immune basis. Some drugs might also trigger pemphigus or pemphigoid; implicated drugs have included penicillamine and ACE inhibitors.

- There are several types of pemphigus. In pemphigus vulgaris, the most common type, the blistering is intra-epidermal and can occur anywhere on the skin surface or present as ulceration of the mucous membranes. It is a chronic, progressive disorder requiring prolonged treatment.
- Pemphigoid is also known as bullous pemphigoid and occurs mainly in elderly persons. The blistering is sub-epidermal and affects the skin; mucous membranes can be affected in up to a half of all patients but it may be mild and not noticed by the patient. Pemphigoid is usually a self-limiting disorder and treatment can often be stopped after a couple of years.
- Mucous membrane pemphigoid (cicatricial pemphigoid) is a rare form that affects mainly the oral mucosa and conjunctiva, and may affect other mucosae, causing scarring.

The treatment of the blistering in both pemphigus and pemphigoid follows a similar pattern. Wet dressings and general treatment as for burns (see p.1578) are commonly used. Corticosteroids are used initially to induce remission. Maintenance treatment often includes adjunctive therapies aimed at keeping control of the disease while tapering the corticosteroid dose, with the ultimate aim of complete treatment withdrawal.

High doses of systemic corticosteroids may be required to control the blistering, which may take weeks.[1-3] The optimum dose has not been established and suggestions have varied enormously (for more detail see Pemphigus and Pemphigoid, under Corticosteroids, p.1509); very high doses of oral prednisolone have been used in the past.[2] Pulsed intravenous corticosteroids such as methylprednisolone may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2,3] A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid.[1,3-5] Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations.[2,3,6] Intralesional injections have also been used for isolated lesions of the skin[3] and oral mucosa.[3,6] Topical corticosteroids may need to be added to initial systemic therapy to control acute ocular inflammation.[7]

Various therapies have been used as adjuncts or occasionally as alternatives to treatment with corticosteroids. However, given the rarity of the diseases, few controlled studies have been performed. Immunosuppressive therapy, usually with azathioprine, may be added to improve disease control and permit a reduction in corticosteroid dosage.[1,2,4,6] Cyclophosphamide and methotrexate have been used similarly although there is less information published about their use.[1,2,4] Oral or intravenous cyclophosphamide with a corticosteroid may be useful in severe or rapidly progressing mucous membrane pemphigoid.[6] Chlorambucil might be considered if other immunosuppressants cannot be used, but there is very limited evidence to support this.[1,2] Mycophenolate mofetil and ciclosporin have also been used in small numbers of patients with some reports of success.[1,2,4,6] Some patients with bullous pemphigoid respond to dapsone,[1,4] and it may be adequate for first-line treatment in mild to moderate inflammation in mucous membrane pemphigoid.[6,7] There have also been a number of reports suggesting that a tetracycline alone or with nicotinamide, may be useful in controlling the lesions of various types of pemphigus and pemphigoid. They may be tried in patients with mild to moderate disease.[1,2,4] Intramuscular gold therapy has also been used for pemphigus vulgaris, and might be considered when other adjunctive drugs cannot be used.[2] High-dose intravenous immunoglobulin has been given to permit reduction of corticosteroid therapy in pemphigus and pemphigoid, and in some patients has produced prolonged remission.[8] It is usually reserved for severe disease that has not responded to other therapies.[2,4] There have been a few reports of rituximab inducing remission in previously unresponsive pemphigus.[3] Plasmapheresis (plasma exchange) may be tried in severe, unresponsive disease,[1,2] but there is little evidence of benefit and its use can be limited by cost and adverse effects.[4]

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Pigmentation disorders

The pigment melanin is produced in melanocytes in the basal layer of the epidermis. It is a complex polymer synthesised from the amino acid, dihydroxyphenylalanine. Melanin production is under pituitary control but is also influenced by other endocrine secretions.

Decreased pigmentation (hypopigmentation) and excessive pigmentation (hyperpigmentation) can occur and may be either generalised or localised.

Albinism is a rare inherited disorder that can cause generalised **hypopigmentation**. Affected individuals are extremely sensitive to solar irradiation and must use sunscreens regularly.

A common form of localised hypopigmentation is **vitiligo**. Sharply defined areas of depigmentation are seen and may remain localised or spread so that total depigmentation eventually occurs. Depigmented areas are more susceptible to sunburn and all exposed areas, both normal and depigmented, should be protected from sunlight with clothing or sunscreens. Cosmetic camouflage of the depigmented area is commonly used, and may be sufficient for patients when only small affected areas are visible.[1] Dihydroxyacetone produces a brown staining of the skin that may be cosmetically acceptable. There is no totally effective repigmentation treatment, although some therapies may offer a degree of benefit.[2] Oral or topical photochemotherapy with psoralens (PUVA) is currently considered to be the best treatment.[1,3] Topical corticosteroids are sometimes effective at inducing repigmentation.[4,5] Experimental drug therapy for re-inducing pigment has included UVA light therapy with either khellin or phenylalanine; oral levamisole, alone or with topical corticosteroids, has also been reported to be of benefit. UVB phototherapy has also been tried and some consider it to be superior to the use of UVA,[4,5] and the initial treatment of choice in moderate to severe disease.[6] There are a few small studies and case reports of benefit with the use of topical tacrolimus or pimecrolimus[6,7] and combinations of topical calcipotriol with either UV light therapy or a corticosteroid.[6] Transplantation of autologous cultured melanocytes, ultrathin epidermal sheets, or basal cell layer suspension may be beneficial in some forms of vitiligo. Transplantation is not suitable for progressive, widespread vitiligo vulgaris.[5,8] If the vitiligo affects a large proportion of the body (more than 50%), and if PUVA is ineffective at inducing repigmentation, an option is to consider inducing depigmentation in the remaining normal skin in order to match the lighter vitiligous areas. Permanent depigmentation may be induced by monobenzone, but patients must subsequently use topical sunscreens in order to avoid damage caused by solar exposure.[1]

Hyperpigmentation can be caused by increased amounts of melanin, or by other substances such as iron in the skin. Generalised hyperpigmentation may be seen in Addison's disease, acanthosis nigricans, and primary haemochromatosis; other causes may include cirrhosis, chronic renal failure, and glycogen storage disease. Darkening of the skin can also occur in patients taking certain drugs due to a deposition of the drug-melanin complex in the skin. Notable examples include amiodarone, minocycline, and phenothiazines. Localised hyperpigmentation is seen in chloasma (melasma) in which there is facial involvement and is encountered most commonly in pregnancy; it may also be associated with hormonal contraceptive use. A number of compounds have been used basically as bleaching agents in hyperpigmentary disorders, and of these hydroquinone has been used most often;[9,10] monobenzone is not recommended. A beneficial response to topical tretinoin and azelaic acid in patients with chloasma has been described. Combination preparations containing hydroquinone, tretinoin, and a corticosteroid are available in some countries. Laser therapy, or the use of chemical peels, has also been tried.[9,10]

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Pruritus

Pruritus (itching) is a common and distressing symptom of many skin disorders but may also have a systemic cause such as obstructive jaundice, chronic renal disease, endocrine disease, certain malignancies, or a drug hypersensitivity reaction. The exact pathophysiology of itching is unclear, and different inflammatory mediators may be associated with itching in different disorders; the CNS is also thought to play a role in the perception of itch.

Pruritus should be considered as symptomatic of the underlying disorder and treatment should focus on the removal of the offending trigger. However, symptomatic treatment of pruritus may also be necessary.

Emollients may be useful where dry skin is a contributory factor, and may be applied for **topical** management of pruritus. Calamine and crotamiton are often used topically, despite some uncertainty about their value, as are preparations containing phenol or agents such as menthol that cause capillary dilatation with a subsequent sensation of cold and analgesia. Topical capsaicin has also been used and topical corticosteroids may be used to relieve pruritus when there is associated inflammation. Local anaesthetics or antihistamines are only marginally effective for topical use and can very occasionally cause sensitisation. However, lauromacrogol 400 has proved of benefit. Doxepin, a tricyclic antidepressant with very potent antihistaminic activity, has been used topically for the relief of pruritus associated with dermatitis, but adverse effects from systemic absorption can limit its use.

Sedating antihistamines given **by mouth** are commonly used to relieve more generalised pruritus and are used to control the severe itching associated with dermatoses such as atopic eczema (see p.1579). Mirtazapine, a noradrenergic and serotonergic antidepressant with a potent antihistamine effect, has been tried in various types of pruritus with reports of success. Bile-acid binding resins, such as colestyramine, are used to relieve pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction, primary biliary cirrhosis, or intrahepatic cholestasis of pregnancy. There are reports of cholestatic pruritus also responding to ondansetron although results from controlled trials have been mixed. Pruritus caused by obstetric cholestasis has been treated with ursodeoxycholic acid, which also corrects the associated biochemical abnormalities. Central opioid receptors modulate itch and opioid antagonists such as nalmefene and naltrexone have been reported to relieve pruritus. Many other drugs, including cimetidine and propofol, have been of benefit in some patients. Paroxetine has been useful in some patients with cancer-related pruritus, but the effect tended to wear off after several weeks. PUVA (see under Methoxsalen, p.1606) may be helpful in some pruritic skin conditions including aquagenic pruritus.

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Psoriasis

Psoriasis is a chronic inflammatory skin disorder characterised by enhanced epidermal proliferation leading to erythema, scaling, and thickening of the skin. It appears to be a T-cell mediated auto-immune disease. There are several types of psoriasis including guttate, flexural, pustular, and erythrodermic, but chronic plaque psoriasis (psoriasis vulgaris) is the most common form. In chronic plaque psoriasis the areas most commonly affected are the extensor sides of the knees, elbows, and hands, and the scalp and sacrum. There is no cure and treatment is designed to induce a remission or suppress disease to a tolerable level.

The treatment of psoriasis has been the subject of a number of reviews.[1-9]

Topical drugs are the treatment of first choice for chronic plaque psoriasis. Mild conditions may be managed with the use of emollients alone but dithranol, coal tar, calcipotriol, or tazarotene are the usual active treatments for mild to moderate forms. Patients unresponsive to one topical drug may respond to another and alternatives should be tried before considering more aggressive management. Topical drugs are often used in combination.

- Although effective, dithranol stains the skin and clothes and as it is irritant careful adjustment of the strength and duration of application needs to be made. It has traditionally been applied overnight in the form of ointments or pastes but newer short-contact regimens and creams are more suitable for home therapy.
- Coal tar is used either as crude extracts or refined products and although the refined products may be more aesthetically acceptable they may also be less effective.
- Salicylic acid enhances the rate of loss of surface scale and is included in many combination preparations with dithranol or coal tar.
- Calcipotriol and tacalcitol are vitamin D analogues, that have the advantage of being odourless and nonstaining. Maxacalcitol is another vitamin D analogue under investigation.
- Tazarotene, a retinoid, is also effective in psoriasis but significant irritation can limit its use and it should be avoided in pruritic psoriasis.
- Topical corticosteroids are also effective but they may lead to dermal atrophy, tachyphylaxis, systemic toxicity, and may precipitate unstable and pustular psoriasis. They are reported to be the most widely used treatment in the USA.[2]

Guttate psoriasis is strongly associated with streptococcal infection and patients may require antimicrobial treatment but firm evidence of a beneficial effect on the skin lesions[10] (or indeed of any intervention for guttate psoriasis[11]) is lacking.

Phototherapy with UVB light (290 to 320 nm) is effective when used alone for chronic plaque or guttate psoriasis but also enhances the effectiveness of calcipotriol, coal tar, or dithranol. Studies have indicated that the therapeutic wavelengths are in the region of 311 to 313 nm. Consequently, narrowband UVB lamps (TL-01) have been developed to emit a spectrum that peaks at 311 nm.[12]

Photochemotherapy (PUVA) involves the use of oral or topical psoralens such as methoxsalen with UVA light and is generally considered to be the treatment of first choice for psoriasis that is resistant to topical therapies. Guidelines for PUVA have been published.[13,14] Psoralens have also been used with UVB light. Commercially available sunbeds, which emit UVA light, are not recommended as they are rarely effective and induce skin ageing and fragility.

Psoriasis refractory to topical therapy and PUVA may respond to **systemic drugs**. Systemic treatment may also be indicated for extensive chronic plaque psoriasis in elderly or infirm patients, for generalised pustular or erythrodermic psoriasis, or for severe psoriatic arthritis (see Spondyloarthropathies, p.13).

- Immunosuppressants such as methotrexate are useful for severe refractory psoriasis, the aim of treatment being to bring psoriasis under control, enabling a return to other modes of treatment rather than to induce remission. Ciclosporin is also used in severe refractory psoriasis and may be used either to induce a remission or in low-dose maintenance therapy to prevent relapse. Tacrolimus, sirolimus, and mycophenolate are under investigation for both oral and topical use, and azathioprine has been tried.
- With the recognition that psoriasis is an auto-immune disease, immunomodulating drugs have been developed with an aim to provide selective immunotherapy, by either targeting T-cells or by cytokine modulation. Alefacept and efalizumab inhibit T-cell activation and show similar efficacy in the treatment of psoriasis. Cytokine modulating therapy includes blocking the action of tumour necrosis factor with adalimumab, etanercept, or infliximab, which have been found to be effective for psoriasis skin lesions and psoriatic arthritis.

  The British Association of Dermatologists recommends[15] that in chronic plaque psoriasis the biological therapies (efalizumab, etanercept, and infliximab) should be reserved for patients with severe disease that is unresponsive or refractory to standard therapies such as acitretin, ciclosporin, methotrexate, UVB, and PUVA, or when such therapies cannot be used. Etanercept is considered to be the first choice in stable disease, infliximab may be useful when rapid disease control is needed such as in unstable erythrodermic or pustular psoriasis, and efalizumab should be used in patients with a high risk of latent tuberculosis or evidence of demyelinating disease, as the other 2 drugs are contra-indicated in these patients.
- Systemic retinoids such as acitretin are also effective, and use with PUVA may allow a reduction in doses and associated toxicity for each therapy. Generalised pustular and palmoplantar pustular psoriasis are particularly responsive to acitretin. UVB therapy may also be used with acitretin.
- Hydroxycarbamide, fumarates, tioguanine, and sulfasalazine have also been tried. Many anecdotal reports note improvement of psoriasis when patients are given drug therapy for co-existing disease. The value of such drugs can be particularly difficult to establish because of the chronic relapsing and recurring nature of psoriasis.

The chronic nature of psoriasis has resulted in a number of different strategies being tried in order to maximise treatment efficacy and minimise toxicity.[5,6] Combinations of established drugs at lower doses can include methotrexate with either ciclosporin or acitretin, or acitretin with UV therapy. Sequential therapy uses a rapidly acting, potentially more toxic, drug to bring the condition under control initially, followed by a less toxic drug for maintenance; examples include using methotrexate or ciclosporin followed by acitretin. Rotational therapy may be used to minimise long-term toxicity by using each treatment for 1 to 2 years; methotrexate, acitretin, and UV therapy have been used in this way.[6] However, ciclosporin should not follow PUVA therapy in this way because of an increased risk of cutaneous squamous cell carcinoma.[5] There is limited experience with the use of newer immunomodulating drugs in these regimens.[6]

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Pyoderma gangrenosum

Pyoderma gangrenosum is a rare serious ulcerative skin disorder often associated with systemic diseases such as inflammatory bowel disease, rheumatoid arthritis, or myeloproliferative disorders. Initially an acutely inflamed nodule is present which progresses very rapidly to large painful ulcers. Any area of the body may be involved, but the face, legs, and buttocks are frequent sites.

Treatment essentially consists of cleansing and dressings for the ulcers and appropriate therapy for any underlying disease. When necessary high doses of systemic corticosteroids or treatment with ciclosporin may be given. There have also been reports in small numbers of patients of benefit with sulfasalazine, dapsone, azathioprine, tacrolimus, thalidomide, infliximab, colchicine, and nicotine chewing gum.

A related but less severe form of the disease, superficial granulomatous pyoderma, has responded to intralesional or oral corticosteroids.

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Rosacea

Rosacea is a chronic condition affecting the face; rarely, the trunk and limbs may be affected. Phases of this disorder include flushing episodes, persistent erythema and telangiectasia, an inflammatory papulopustular phase, and in advanced cases rhinophyma (nasal hypertrophy and deformity). Ocular involvement is also common and can cause conjunctivitis, keratitis, styes, and chalazia.[1-4] The precise cause of rosacea remains unclear. It has been suggested that *Helicobacter pylori* in the gastrointestinal tract may cause flushing by inducing the production of endogenous vasodilators, and that *Demodex folliculorum*, a mite found in human follicles, may have a role in papulopustular rosacea.[3]

The inflammatory episodes of rosacea (papules, swelling, and pustules) are responsive to treatment, but the underlying erythema and telangiectasia usually persist.

- Episodes of flushing may be limited by avoiding trigger factors such as alcoholic and hot drinks, and spicy foods.[1,4,5] Patients should use soap-free cleansers and high factor sunscreens.[1,3] In severe cases clonidine or a beta blocker such as atenolol, has been used.[3]
- Persistent erythema may be improved by *H. pylori* eradication (see Peptic Ulcer Disease, p.1702) but the effectiveness of such therapy has not been established.[3]

- Papulopustular rosacea is usually controlled effectively by oral antibacterials.[1,3-6] Tetracyclines (doxycycline, minocycline, oxytetracycline, tetracycline) have been widely used, but clarithromycin, erythromycin, and metronidazole are suitable alternatives. Improvement occurs over several weeks, and long-term treatment may be necessary. Systemic isotretinoin is also effective, but it is generally reserved for severe or resistant cases of rosacea.

  Topical therapies, particularly metronidazole and azelaic acid,[3-5,7,8] provide effective alternatives to oral drugs. Other topical therapies that may be useful include tetracyclines, clindamycin, erythromycin, retinoids, or a combination of sulfacetamide sodium with sulfur. Where infestations of *D. folliculorum* are suspected of aggravating the condition, topical treatments such as benzyl benzoate, crotamiton, or permethrin may be tried. There are also anecdotal reports of the successful treatment of demodicidosis with oral ivermectin. Topical corticosteroids should not be used because they exacerbate rosacea.
- Ocular rosacea symptoms are managed with eyelid hygiene and artificial tears. Metronidazole gel can be applied to the eyelids but systemic antibacterials may be needed for more severe disease.[4,5]
- Rhinophyma requires conventional or laser surgery;[1,3-5] isotretinoin may be used for a few months pre-operatively to shrink the bulbous portions.[1]

Non-drug therapies that have been advocated include facial massage;[1] however, as for many of the drug therapies[7] controlled studies are lacking. Laser therapy has been used to obliterate telangiectasia.[1,3,5]

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Seborrhoeic dermatitis

Seborrhoeic dermatitis is a common eczematous skin disorder (see Eczema p.1579) in which erythematous pruritic patches of skin may become either scaly or exudative and crusted. Scaling lesions are the type most commonly observed. In some cases, known as seborrhoeic folliculitis, there may also be follicular papules or pustules. Seborrhoeic dermatitis occurs in regions of the body where sebaceous glands are plentiful, such as the scalp, face, and chest, although the condition is not associated with increased sebum production. The cause of seborrhoeic dermatitis is unknown, although it might be related to overgrowth with *Malassezia ovalis* (*Pityrosporum ovale*), a normal commensal yeast.

Treatment is suppressive rather than curative. Topical preparations containing antifungals such as ciclopirox olamine, terbinafine, or an imidazole (bifonazole, ketoconazole, miconazole), usually with hydrocortisone, are the main drugs used. If unsuccessful, keratolytics such as salicylic acid or tars may be used. Topical macrolactam immunosuppressants such as pimecrolimus and tacrolimus are being investigated as alternate therapy. Shampoos containing ketoconazole, pyrithione zinc, or selenium sulfide are commonly used for scalp involvement. Topical lithium succinate has been tried.

Dandruff due to normal shedding of scalp skin (pityriasis capitis) is treated similarly to seborrhoeic dermatitis of the scalp.

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Toxic epidermal necrolysis

Toxic epidermal necrolysis (Lyell's syndrome or scalded skin syndrome) is usually a drug-induced skin reaction. It has been described as a severe form of Stevens-Johnson syndrome, or as the most severe form of erythema multiforme (p.1580), although such classifications have been debated. It generally begins with lesions of the mucous membranes of the oropharynx, eyes, and genitalia, and fever and pain. Subsequently, a macular rash, blisters, or diffuse erythema develop, and affected skin may detach irregularly, sometimes in large sheets. Toxic epidermal necrolysis is managed similarly to burns (p.1578), but specific treatments have not been established. The use of systemic corticosteroids is controversial because of a higher risk of infection. Other treatments that have been tried with some reports of benefit include plasmapheresis, intravenous immunoglobulin, cyclophosphamide, ciclosporin, and infliximab.

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Urticaria and angioedema

Urticaria and angioedema are conditions caused by the release of inflammatory mediators from mast cells and basophils. **Urticaria** (also known as nettlerash or hives) is characterised by circumscribed, elevated, erythematous, and usually pruritic areas of oedema (wheals) involving the superficial portion of the dermis. Individual lesions arise suddenly, often within a few minutes, and may last up to 24 hours. In severe, acute urticaria, wheals may cover most of the skin surface. In chronic urticaria (continuous or recurrent lesions over at least 6 weeks) only a few wheals may develop each day. When subcutaneous or submucosal tissues are involved, causing swelling of the eyelids, lips, tongue, larynx, or genitalia, the condition is called **angioedema**. For hereditary angioedema, caused by complement C1 esterase inhibitor deficiency, see p.1081.

Although urticaria may be caused by an allergy, it often has a non-allergic mechanism. Urticaria occurs as an adverse effect of many drugs, for example aspirin and many antibacterials. Other types of urticaria include dermographism (linear wheal formation on scratching or stroking) and cholinergic urticaria (evoked by such triggers as exercise, heat, and emotion and characterised by small papulous wheals surrounded by an erythematous flare). In **idiopathic anaphylaxis**, patients experience attacks of urticaria or angioedema, sometimes with bronchospasm, hypotension, or syncope.

The **management** of urticaria and angioedema has been reviewed.[1-5] Avoidance of unnecessary exposure to known allergens or triggers is of prime importance in the management of urticaria, although in many chronic cases no trigger factor can be found. Severe, acute urticaria or angioedema requires urgent treatment as for anaphylaxis (p.1205).

- Topical treatment of urticaria is rarely effective except for mild cases. Calamine, menthol, and crotamiton have cooling or antipruritic effects. Topical corticosteroids are of no value; topical antihistamines are not very effective and carry a slight risk of sensitisation.
- Most patients with urticaria derive some benefit from oral antihistamines (H_1-antagonists), especially in the relief of pruritus. A non-sedating antihistamine is the first line of treatment. Sedating antihistamines are useful at bedtime. If such antihistamines are only partly successful, combination with an H_2-antagonist, such as cimetidine or ranitidine, may be tried. The tricyclic antidepressant doxepin has H_1- and H_2-antagonist properties and has sometimes been effective in patients with urticaria.
- Leukotriene antagonists such as montelukast and zafirlukast and the leukotriene inhibitor zileuton have been tried alone and with antihistamines in the management of urticaria. Montelukast may add benefit to an antihistamine in chronic urticaria associated with hypersensitivity to aspirin or food additives, and in patients with evidence of histamine-releasing autoantibodies, but not in chronic idiopathic urticaria. There is some anecdotal evidence that antileukotrienes might be useful in primary cold urticaria, delayed pressure urticaria, and dermographism.[6]
- Addition of a sympathomimetic such as terbutaline or a calcium-channel blocker such as nifedipine has also been suggested for patients unresponsive to treatment with an H_1-antagonist alone, but results have varied.
- A short course of an oral corticosteroid may be indicated for control of acute urticaria in patients refractory to other measures.

It has been suggested that chronic urticaria may be associated with thyroid auto-immunity and that levothyroxine therapy may be of benefit in patients with antithyroid antibodies. A number of other drugs including danazol, stanozolol, dapsone, sulfasalazine, ciclosporin, and intravenous immunoglobulin have reportedly produced benefit in limited numbers of patients, but such therapies are largely used empirically.

Patients with frequent attacks of idiopathic anaphylaxis have benefited from prophylaxis with a corticosteroid and antihistamine; once the condition is controlled the corticosteroid, and then the antihistamine, may be tapered and gradually withdrawn. Adjuvant ketotifen, cromoglicate, salbutamol, or montelukast may be helpful in permitting corticosteroid tapering in dependent patients. Adrenaline should be available for acute attacks.[7]

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Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Plantar warts on the soles of the feet are sometimes called verrucas. Anogenital warts are known as condylomata acuminata. Warts do disappear spontaneously but as they may not do so for months or years patients often seek treatment.

There is no specific antiviral therapy against the human papillomavirus,[1-6] although cidofovir has been tried (see below). Treatment usually relies on some form of local tissue destruction.

- Non-pharmacological techniques include surgical excision, electrocauterisation, or laser therapy. Photodynamic therapy using 5-aminolevulinic acid has also been investigated. Cryotherapy (tissue freezing) may be performed with liquid nitrogen or solid carbon dioxide.
- Chemical destruction with acids (acetic acid, lactic acid, nitric acid, salicylic acid, or trichloroacetic acid), silver nitrate, formaldehyde or glutaral, or podophyllum resin or its derivatives (podophyllotoxin) is another option. Podophyllum resin and podophyllotoxin are often used for anogenital warts.
- Intralesional injection of cytotoxics such as bleomycin or fluorouracil also destroys the wart and may be used in severe or resistant cases. Fluorouracil may also be applied topically.

Other treatments based on less destructive mechanisms have also been used.

- Tretinoin has been tried topically for its effect on epidermal growth.
- Imiquimod is an immune response modifier that is used topically to treat anogenital warts. There is also some evidence to suggest that it is effective for other cutaneous warts. Other drugs with immunomodulatory effects, such as cimetidine, have been tried in a few patients. There are also small studies of treatment with diphencyprone, a contact sensitiser.

- Interferons have antiviral, antiproliferative, and immunomodulatory actions and have thus been investigated in the management of warts; some studies, especially those involving intralesional administration, have showed benefit. Other routes of administration are under investigation; topical interferon alfa for anogenital warts, and an oral formulation for warts in the oral cavity of patients with HIV infection.
- Cidofovir is an antiviral that has activity against human papillomavirus. Investigational intravenous or topical use has been successful in a small number of patients with cutaneous or anogenital warts.
- Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, it is used in the treatment of external genital and perianal warts.

A quadrivalent recombinant human papillomavirus vaccine has recently been developed and is used to prevent anogenital warts, cervical cancer, and other pre-cancerous lesions caused by human papillomavirus types 6, 11, 16, and 18.

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Wounds and ulcers

Wounds (physical injuries of the skin and underlying structures) may be the result of mechanical trauma, burns, or chemical injury. Ulcers are often the result of various underlying disorders. Among the commonest types, *decubitus ulcers* (bedsores, pressure sores) occur in patients with extended immobility when prolonged pressure on the skin over a bony prominence produces localised ischaemia. *Leg ulcers* may result from venous incompetence (venous ulcers) or be ischaemic in origin (arterial ulcers), while patients with peripheral neuropathy, such as diabetics or those with leprosy, may develop *neuropathic ulcers* due to repetitive inadvertent injury. Wounds or ulcers may be described as superficial, partial thickness, or full thickness. Superficial wounds are limited to epithelial tissue and heal rapidly by regeneration of epithelial cells. Partial thickness wounds involve the dermis and include some blood vessel damage, and therefore wound repair is a longer process. Full thickness wounds extend at least to subcutaneous fat, and healing requires synthesis of new connective tissue.

Healing mechanisms are essentially the same regardless of the cause of the damage:

- immediate haemostatic processes involve formation of a platelet plug and fibrin clot, as described under Haemostasis and Fibrinolysis, p.1045
- the early granulation and re-epithelialisation phase takes place up to about 21 days after injury depending on wound size and site. Platelet-derived growth factors stimulate fibroblasts to produce granulation tissue, comprising a collagen matrix well-supplied with capillary vessels, and growth of epidermal cells leading to re-epithelialisation of the wound surface
- during the final dermal repair and remodelling phase the collagen matrix undergoes strengthening and there is a reduction in vascularity. This phase can continue for up to 2 years after injury.

Several factors are important for efficient wound healing. Adequate supplies of nutrients, especially vitamin C and zinc (which are often given as supplements) and oxygen are needed. A good blood supply is thus essential. Clinical infection, either systemic or local, due to contamination by environmental microbes, causes tissue damage and delays healing. The process of wound repair requires many cellular and acellular factors, such as platelets and growth factors, and deficiencies in these may also be responsible for delayed healing. Thus, the patient's age, systemic conditions, concomitant drugs, nutritional status, and congenital deficiencies all influence the rate of healing.

Local **wound management** includes cleansing, removal of exudate, and prevention of microbial contamination. Choice of wound treatment preparation will depend on the size, location, type, and cause of the wound, on the presence of infection, and on the particular stage of healing.

Wound **cleansing** is required to remove any dirt or foreign bodies and to **remove exudate** and slough (pus and necrotic tissue). This helps to prevent infection and aids healing. Commonly used cleansing solutions are sodium chloride 0.9%, hypochlorite, hydrogen peroxide, povidone-iodine, and chlorhexidine. However, some antiseptics and hypochlorites might be associated with delayed wound healing, especially with prolonged use, as they delay collagen production and cause inflammation. Also, many antiseptics are inactivated by organic material. Sodium chloride solution may be all that is required for routine cleansing of non-infected wounds.

Many of the cleansing solutions also help to remove slough. Other wound management preparations more specifically directed at removing slough include dextranomer, hydrogels, hydrocolloids, and enzyme preparations such as a mixture of streptokinase and streptodornase. Dextranomer, hydrogels, and hydrocolloids cause debridement by their occlusive, rehydrating properties. Surgical debridement is a fast and efficient way of removing necrotic tissue. Larval therapy (the use of live sterile maggots of *Lucilia sericata*, the common greenbottle fly) has also been effective for debridement of infected or necrotic wounds, including diabetic foot ulceration.

Wounds may produce large volumes of exudate as a result of inflammatory reactions, especially during the first few days. Hydrocolloid and alginate preparations and foam dressings are effective moisture absorbers.

All wounds are colonised by bacteria to some extent and there is no evidence that this superficial **infection** affects healing. However, infection with *Pseudomonas aeruginosa* may delay healing and sulfadiazine silver is used especially in burns. Acetic acid has also been used. Infections are treated systemically if there are indications of clinical infection such as sudden pain, cellulitis, and increased discharge; systemic management of bacterial skin infections is described on p.194.

Wound **dressings** and packing preparations help to protect the wound and provide the correct environment for wound healing. Some also help by absorbing exudate. Superficial wounds usually only require a low-adherent dressing. Alginates may be used for exuding wounds. Traditional dry dressings such as cotton wool, gauze, and lint are not used for partial or full thickness cavity wounds since they shed fibres, adhere to the wound, and cause wound dehydration. Hydrogels, hydrocolloids, polysaccharides, cadexomer-iodine, alginates, and foam dressings are all effective cavity wound preparations. Hyaluronic acid is incorporated into some dressings to promote wound healing.

Activated charcoal is very effective at reducing offensive odours from **malodorous wounds**, as are sugar (sucrose) pastes. Sucrose may exert its antibacterial effect by competing for water present in the cells of bacteria. Metronidazole is active against anaerobic bacteria that are associated with the pungent smell and is used topically for deodorising malodorous tumours. Metronidazole is not generally used on wounds because of the risk of inducing resistance but it is sometimes used to deodorise malodorous venous leg ulcers or decubitus ulcers.

In addition to the use of wound preparations, there may be other measures that aid healing of specific wounds or ulcers. Some wounds may require skin grafting. Skin substitutes, and growth factors, such as becaplermin, molgramostim, trafermin, and urogastrone, are being used or developed for non-healing ulcers and wounds. Topical phenytoin has produced some encouraging results in promoting the healing of various types of ulcers. Measures that aid the return of fluid from the leg, such as flexing the ankles, elevation, and use of compression bandages are beneficial in **venous ulcers**. There is insufficient evidence to recommend one type of dressing in preference to another, including the use of hydrocolloid dressings instead of simple low adherent dressings. The bioflavonoids, given orally, may improve venous insufficiency and therefore also aid healing. Systemic drugs that improve the supply of oxygen to tissues, for example pentoxifylline, may be useful in ischaemic and venous ulcers. Topical and systemic ketanserin has been investigated in a few patients and may be beneficial in wounds and ulcers where there is impaired blood flow. Hyperbaric oxygen therapy has been tried in a range of chronic wounds; it might be useful in reducing amputation in patients with chronic diabetic foot ulcers. Vascular surgery may be necessary in the management of some ulcers caused by ischaemia or chronic venous insufficiency. In **decubitus ulcers**, relief of pressure is the most important measure in management. The management of **burns** and **chemical burns** is described on p.1578.

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Abrasive Agents

Abrasivos.

Абразивные Вещества; Шлифовальные Средства

Aluminium Oxide

Aliuminio oksidas; Alumiinioksidi; Aluminii Oxidum; Aluminio, óxido de; Aluminiumoxid; Alumínium-oxid; Glinu tlenek.

Алюминия Оксид

Al_2O_3 = 102.0.

CAS — 1344-28-1.

ATC — D10AX04.

ATC Vet — QD10AX04.

Pharmacopoeias. *Eur.* (see p.vii) includes the hydrated form (see Aluminium Hydroxide, p.1706).

Pumice

Lapis Pumicis; Piedra pómez; Pierre Ponce Granulée; Pumex; Pumex Granulatus; Pumice Stone.

Пемза

CAS — 1332-09-8.

Pharmacopoeias. In *US.*

USP 31 (Pumice). Pumice is a substance of volcanic origin consisting chiefly of complex silicates of aluminium, potassium, and sodium. Odourless, very light, hard, rough, porous greyish masses or gritty, greyish powder. It is stable in air. Practically insoluble in water and not attacked by acids. Three grades of powdered pumice are recognised:

- superfine (=pumice flour)—not less than 97% passes through a No. 200 [US] sieve
- fine—not less than 95% passes through a No. 150 sieve and not more than 75% through a No. 200 sieve
- coarse—not less than 95% passes through a No. 60 sieve and not more than 5% through a No. 200 sieve

Profile

Abrasive agents such as fused synthetic aluminium oxide or powdered pumice have been used either as adjuncts in the treatment of acne (despite doubts about their value—see p.1577) or for the removal of hard skin. Pumice has also been used as a dental abrasive and as a filtering medium. Other agents used as abrasives for acne include polyethylene granules.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Abralux; Ionax Scrub; ***Austral.:*** Brasivol; Ionax Scrub†; ***Braz.:*** Ionax Scrub; ***Chile:*** Ionax Scrub; ***Fr.:*** Brasivol; Ionax Scrub; ***Hong Kong:*** Brasivol†; Ionax Scrub†; ***Irl.:*** Brasivol; Ionax Scrub†; ***Malaysia:*** Ionax Scrub;

Mex.: Betagranulos; ***S.Afr.:*** Brasivol; ***Singapore:*** Ionax Scrub; ***UK:*** Brasivol; ***USA:*** Ionax Scrub; ***Venez.:*** Betagranulos; Ionax Scrub.

Multi-ingredient: ***Canad.:*** Pernox; ***Indon.:*** Aludonna; ***Ital.:*** Gastrodue†; ***Malaysia:*** Belcid†; ***Mex.:*** Dermobras; Ionax Scrub; ***Philipp.:*** Ionax Scrub; ***S.Afr.:*** Pedimed; ***Switz.:*** Cliniderm; ***USA:*** Pernox; Zanfel; ***Venez.:*** Exfoliderm.

Acitretin *(BAN, USAN, rINN)*

Acitretina; Acitretinas; Acitrétine; Acitretinum; Asitretiini; Asitretin; Etretin; Ro-10-1670; Ro-10-1670/000. (*all-trans*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid; (2*E*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid.

Ацитретин

$C_{21}H_{26}O_3$ = 326.4.

CAS — 55079-83-9.

ATC — D05BB02.

ATC Vet — QD05BB02.

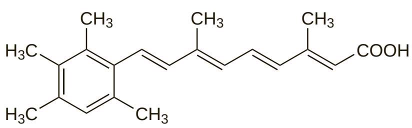

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Acitretin). A yellow or greenish-yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. It is sensitive to air, heat, and light, especially in solution. Store at 2° to 8° in airtight containers. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

USP 31 (Acitretin). A yellow or greenish, crystalline powder. Practically insoluble in water; slightly soluble in acetone and in alcohol; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. Store in airtight containers at 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

As for Isotretinoin, p.1599.

Acitretin has a relatively short half-life, but etretinate, which has a very prolonged half-life, has been detected in the plasma of some patients receiving acitretin. Recommendations vary slightly in different countries but pregnancy should be avoided for at least 2 to 3 years after treatment has been withdrawn (see also Pregnancy, below) and patients should not donate blood for at least 1 to 3 years after stopping therapy. Female patients should avoid alcohol during treatment with acitretin and for 2 months after stopping treatment (see under Interactions, below).

Breast feeding. Acitretin was distributed into the breast milk of a woman treated with oral acitretin for psoriasis. Although the estimated amount of acitretin that would be consumed by a breast-fed infant was only 1.5% of the maternal dose, the authors considered that the toxic potential of acitretin to the infant justified its avoidance. In this case, the infant was not breast-fed during acitretin therapy.[1] Licensed product information also recommends that breast-feeding women should not be given acitretin. The American Academy of Pediatrics, however, has found no mention of clinical effect on the infant, and considers the maternal use of acitretin to be usually compatible with breast feeding.[2]

1. Rollman O, Pihl-Lundin I. Acitretin excretion into human breast milk. *Acta Derm Venereol (Stockh)* 1990; **70:** 487–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/09/07)

Capillary leak syndrome. There are rare reports of capillary leak syndrome associated with acitretin. In one case, generalised oedema and weight gain, haemorrhagic lesions, and evidence of rhabdomyolysis were seen.[1] In another, there was oedema and weight gain, dyspnoea, pulmonary infiltrates, pleural effusion, hypotension, and oliguria.[2] These reactions may be related to the retinoic acid syndrome that can occur with tretinoin (see p.1618). Generalised oedema has also been reported with etretinate (p.1597).

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Effects on the blood. For reports of adverse effects on the blood by oral retinoids, including agranulocytosis associated with acitretin, see under Isotretinoin, p.1599.

Effects on the eyes. For reference to maculopathy occurring during therapy with acitretin, and the ocular effects of benign intracranial hypertension caused by retinoids, see under Isotretinoin, p.1600.

Effects on the musculoskeletal system. For reference to myopathy occurring during therapy with acitretin, and a discussion of hyperostosis and calcinosis that can occur with oral retinoid therapy, see under Isotretinoin, p.1600.

Effects on the skin. For mention of the exacerbation of erythroderma by acitretin, see under Isotretinoin, p.1601.

Pregnancy. The risks of spontaneous abortion and malformations similar to those associated with isotretinoin (p.1601) are high when acitretin or etretinate are given during pregnancy, particularly the first trimester.[1,2] Although the risks might be lower after stopping treatment, malformations have still been reported in infants and aborted fetuses conceived within 2 years of stopping acitretin[1,3] and up to 45 months after stopping etretinate.[1] In the UK licensed product information for acitretin recommends that pregnancy should be avoided for at least 2 years (3 years is recommended in the USA) after withdrawal of therapy because etretinate, which has a much longer half-life than acitretin, has been detected in the plasma of some patients given acitretin. It has been pointed out that plasma-etretinate concentrations are a poor indication of total body stores; a study[4] has indicated that there may be substantial concentrations of etretinate in the fatty tissues of women who have received acitretin.

For information on contraceptive choice in women taking oral retinoids, see under Isotretinoin, p.1601.

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4. Sturkenboom MCJM, *et al.* Inability to detect plasma etretinate and acitretin is a poor predictor of the absence of these teratogens in tissue after stopping acitretin treatment. *Br J Clin Pharmacol* 1994; **38:** 229–35.

Interactions

As for Isotretinoin, p.1602.

Etretinate has been detected in the plasma of some patients receiving acitretin and acitretin is also a metabolite of etretinate; therefore interactions associated with etretinate (see p.1597) may also apply to acitretin. Taking acitretin with alcohol has been associated with etretinate formation.

For discussion of the potential interactions of retinoids with hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p.2068.

Alcohol. The consumption of alcohol has been associated with the formation of etretinate in patients taking acitretin.[1,2] One study[2] found a trend suggesting that a higher alcohol intake was associated with a higher risk of etretinate formation and higher etretinate concentrations. However, the presence of alcohol is not essential for this transformation to take place and etretinate has also been detected in a patient taking acitretin who did not drink alcohol.[3] Consequently, licensed product information warns that alcohol must not be consumed by female patients during acitretin therapy and for 2 months after stopping, to avoid the formation of etretinate and associated prolonged risks of teratogenicity (see Pregnancy, above).

1. Larsen FG, *et al.* Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol* 1993; **100:** 623–7.
2. Larsen FG, *et al.* Acitretin is converted to etretinate only during concomitant alcohol intake. *Br J Dermatol* 2000; **143:** 1164–9.
3. Maier H, Hönigsmann H. Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 1996; **348:** 1107.

Pharmacokinetics

Acitretin is absorbed from the gastrointestinal tract and peak plasma concentrations have been obtained 1 to 5 hours after oral doses. Bioavailability after a single dose is about 60 to 70%, but this can vary considerably; bioavailability may be increased by dosage with food. Acitretin is highly bound to plasma proteins. It is metabolised to 13-*cis*-acitretin. Etretinate (p.1597) has also been detected in the plasma of some patients after doses of acitretin. The elimination half-life of acitretin is about 2 days but account should always be taken of the fact that the half-life of etretinate is much longer, being about 120 days. Acitretin is excreted as metabolites in bile and urine, and is distributed into breast milk.

◊ General references.

1. Larsen FG, *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; **23:** 42–61.
2. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **190** (suppl): 1–33.
3. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; **39** (suppl): S25–S33.

Renal impairment. The pharmacokinetics of acitretin are reported to be altered in patients with chronic renal failure but neither acitretin nor its 13-*cis* metabolite are removed by haemodialysis.[1]

1. Stuck AE, *et al.* Pharmacokinetics of acitretin and its 13-cis metabolite in patients on haemodialysis. *Br J Clin Pharmacol* 1989; **27:** 301–4.

Uses and Administration

Acitretin is a retinoid and is a metabolite of etretinate (p.1597). It is used orally in the treatment of severe psoriasis resistant to other forms of therapy, palmoplantar pustular psoriasis, severe congenital ichthyosis and Darier's disease (keratosis follicularis), and in severe lichen planus.

In the UK, acitretin is given in an initial daily dose of 25 or 30 mg with food for 2 to 4 weeks; in the USA (where it is licensed only for use in psoriasis) initial doses up to 50 mg daily are permitted. The daily dosage is adjusted thereafter according to clinical response and adverse effects; optimal results are usually obtained with 25 to 50 mg given daily for a further 6 to 8 weeks but some patients may require up to 75 mg daily. For the treatment of Darier's disease a starting dose of 10 mg may be appropriate, adjusted thereafter according to response. In Darier's disease and congenital ichthyosis treatment may be required for more than 3 months but a daily dosage of 50 mg should not be exceeded. In the UK, licensed product information recommends that continuous treatment should not last longer than 6 months for any indication because of limited clinical data. For lichen planus, doses are similar to those used in the UK (see above).

For doses in children, see below.

Administration in children. Acitretin is not generally considered suitable for use in children. However, a review of its use in 29 children with severe inherited disorders of keratinisation[1] reported that acitretin was an effective and safe treatment provided that the minimal effective dose was used and that adverse effects were carefully monitored. UK licensed product information contra-indicates acitretin use in children unless the benefits significantly outweigh the risks, particularly premature epiphyseal closure and other skeletal effects associated with retinoids. However, if deemed necessary an oral dose of 500 micrograms/kg once daily (occasionally up to 1 mg/kg daily for limited periods) has been suggested, but the maximum daily dose should not exceed 35 mg. The *BNFC* suggests that these doses may be used under expert supervision for children aged 1 month to 12 years for the treatment of severe extensive psoriasis resistant to other forms of therapy, palmo-plantar pustular psoriasis, severe congenital ichthyosis, and Darier's disease. The adult dose (see above) is considered suitable for children from 12 years of age. The *BNFC* also includes a dose of 500 micrograms/kg daily (occasionally up to 1 mg/kg daily) for the management of harlequin ichthyosis in neonates.

1. Lacour M, *et al.* An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol* 1996; **134:** 1023–9.

Eye disorders. A case report indicated that acitretin, given for psoriasis at an initial dose of 30 mg daily for one month and then reduced to 20 mg daily, improved corneal opacities in a patient with chronic tuberculosis-related interstitial keratitis.[1]

1. Labetoulle M, *et al.* Rapid improvement of chronic interstitial keratitis with acitretin. *Br J Ophthalmol* 2002; **86:** 1445–6.

Malignant neoplasms. Acitretin may be useful in preventing the development of skin neoplasms in high-risk individuals, such as solid organ transplant recipients.[1,2] However, long-term therapy is needed to maintain the effect and adverse effects can limit its use[2] (see also Malignant Neoplasms under Isotretinoin, p.1603). Gradual dose escalation may help to minimise mucocutaneous effects, and one proposed schedule for oral acitretin starts with 10 mg on alternate days for 2 weeks, 10 mg daily for the next 2 weeks, then 20 mg daily for a month; the dose is then adjusted as tolerated. Maintenance regimens of 25 mg daily, or alternating daily doses of 10 mg and 20 mg, have been used.[3]

1. Chen K, *et al.* Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; **152:** 518–23.
2. Kovach BT, *et al.* Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; **19:** 726–34.
3. Otley CC, *et al.* Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; **32:** 562–8.

Skin disorders. Acitretin is used alone or with PUVA (a psoralen with UVA irradiation) or UVB in psoriasis[1-4] (p.1583). Studies have shown that use with PUVA or UVB light may increase efficacy and allow a reduction in the exposure to radiation required. It is also used in keratinisation disorders such as severe forms of ichthyosis[1,5-7] (p.1580) and Darier's disease (keratosis follicularis)[1,8] (p.1578). Benefit has been reported in various other skin disorders including lichen planus (p.1580), lichen sclerosus (p.1580), and cutaneous lupus erythematosus (p.1513).[1]

1. Berbis P. Acitretin. *Ann Dermatol Venereol* 2001; **128:** 737–45.
2. Lebwohl M, *et al.* Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol* 2001; **45:** 544–53.
3. Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother* 2005; **6:** 1725–34.
4. British Association of Dermatologists. Psoriasis guideline 2006. Available at: http://www.bad.org.uk/healthcare/guidelines/psoriasis_guideline_(Final_update)_280906.pdf (accessed 27/09/07)
5. Bruckner-Tuderman L, *et al.* Acitretin in the symptomatic therapy for severe recessive X-linked ichthyosis. *Arch Dermatol* 1988; **124:** 529–32.
6. Steijlen PM, *et al.* Acitretin in the treatment of lamellar ichthyosis. *Br J Dermatol* 1994; **130:** 211–14.
7. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; **154:** 267–76.
8. van Dooren-Greebe RJ, *et al.* Acitretin monotherapy in Darier's disease. *Br J Dermatol* 1989; **121:** 375–9.

Preparations

USP 31: Acitretin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Neotigason; ***Austral.:*** Neotigason; ***Austria:*** Neotigason; ***Belg.:*** Neotigason; ***Braz.:*** Neotigason; ***Canad.:*** Soriatane; ***Chile:*** Neotigason; ***Cz.:*** Neotigason; ***Denm.:*** Neotigason; ***Fin.:*** Neotigason; ***Fr.:*** Soriatane; ***Ger.:*** Neotigason; ***Gr.:*** Neotigason; ***Hong Kong:*** Neotigason†; ***Hung.:*** Neotigason; ***Irl.:*** Neotigason; ***Israel:*** Neotigason; ***Ital.:*** Neotigason; ***Malaysia:*** Neotigason; ***Mex.:*** Neotigason; ***Neth.:*** Neotigason; ***Norw.:*** Neotigason; ***NZ:*** Neotigason; ***Philipp.:*** Neotigason; ***Pol.:*** Neotigason; ***Port.:*** Neotigason; ***S.Afr.:*** Neotigason; ***Singapore:*** Neotigason†; ***Spain:*** Neotigason; ***Swed.:*** Neotigason; ***Switz.:*** Neotigason; ***Thai.:*** Neotigason; ***Turk.:*** Neotigason; ***UK:*** Neotigason; ***USA:*** Soriatane; ***Venez.:*** Neotigason.

Adapalene *(BAN, USAN, rINN)*

Adapaleeni; Adapalen; Adapalène; Adapaleno; Adapalenum; CD-271. 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Адапален

$C_{28}H_{28}O_3$ = 412.5.

CAS — 106685-40-9.

ATC — D10AD03.

ATC Vet — QD10AD03.

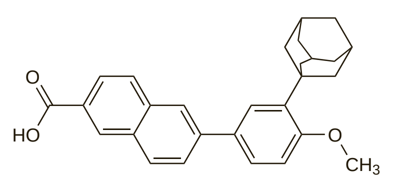

Adverse Effects and Precautions

As for Tretinoin, p.1618.

Pregnancy. Anophthalmia and agenesis of the optic chiasma were found in a fetus after termination of pregnancy in a woman who had applied adapalene 0.1% topically from the month before pregnancy until 13 weeks of gestation.[1]

1. Autret E, *et al.* Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet* 1997; **350:** 339.

Uses and Administration

Adapalene is a naphthoic acid derivative and retinoid analogue with actions similar to those of tretinoin (p.1619). Adapalene is used in topical treatment of mild to moderate acne (p.1577) where comedones, papules, and pustules predominate.

Adapalene is usually applied once daily at night as a 0.1% solution, cream, or gel to skin that has been cleansed and dried; a 0.3% gel is also available. Some patients may require less frequent applications. Other topical preparations that may cause irritation should not be used concurrently. If treatment with topical antibacterials or benzoyl peroxide is required, these should be applied in the morning and adapalene applied at night.

There may be apparent exacerbations of the acne during early treatment and a consistent therapeutic response may not be evident for at least 8 weeks. However, if there is no response after 12 weeks, therapy should be reassessed.

For use in young children, see below.

◊ References.

1. Brogden RN, Goa KL. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs* 1997; **53:** 511–19.
2. Waugh J, *et al.* Adapalene: a review of its use in the treatment of acne vulgaris. *Drugs* 2004; **64:** 1465–78.
3. Pariser DM, *et al.* Adapalene Study Group. The efficacy and safety of adapalene gel 0.3% in the treatment of acne vulgaris: a randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. *Cutis* 2005; **76:** 145–51.
4. Thiboutot D, *et al.* Adapalene Study Group. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol* 2006; **54:** 242–50.
5. Thiboutot DM, *et al.* Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol* 2006; **142:** 597–602.

Administration in children. Although not licensed for young children in the UK the *BNFC* includes adapalene 0.1% cream and gel, applied thinly once daily at night, for neonatal and infantile acne.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Adapne; Differin; Panalene; Sinac; ***Austral.:*** Differin; ***Austria:*** Differin; ***Belg.:*** Differin; ***Braz.:*** Dalap; Differin; ***Canad.:*** Differin; ***Chile:*** Adiamil; Differin; ***Cz.:*** Differine; ***Denm.:*** Redap; ***Fin.:*** Differin; ***Fr.:*** Differine; ***Ger.:*** Differin; ***Gr.:*** Adaferin; ***Hong Kong:*** Differin; ***Hung.:*** Differin; ***India:*** Aclene; Adaferin; Adiff; Deriva; ***Indon.:*** Evalen; ***Irl.:*** Differin; ***Israel:*** Adaferin; ***Ital.:*** Differin; ***Malaysia:*** Differin; ***Mex.:*** Adaferin; ***Neth.:*** Differin; ***Norw.:*** Differin; ***NZ:*** Differin; ***Philipp.:*** Differin; Klenzit; ***Pol.:*** Differin; ***Port.:*** Differin; ***Rus.:*** Differin (Дифферин); ***S.Afr.:*** Differin; ***Singapore:*** Differin; ***Spain:*** Differine; ***Swed.:*** Differin; ***Switz.:*** Differin; ***Thai.:*** Differin; ***Turk.:*** Differin; ***UK:*** Differin; ***USA:*** Differin; ***Venez.:*** Differin.

Multi-ingredient: ***Fr.:*** Epiduo; ***India:*** Deriva-C.

Alcloxa *(USAN, rINN)*

ALCA; Alcloxum; Aluminium Chlorhydroxyallantoinate; RC-173. Chlorotetrahydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl)ureato]-dialuminium.

Альклокса

$C_4H_9Al_2ClN_4O_7$ = 314.6.

CAS — 1317-25-5.

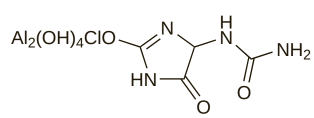

Profile

Alcloxa is an astringent and keratolytic related to allantoin (below). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Babysan Powder.

Multi-ingredient: ***Hong Kong:*** Pilelife; ***Malaysia:*** Neo-Medrol; ***NZ:*** Acnederm†; ***Singapore:*** Neo-Medrol; ***Thai.:*** Neo-Medrol; ***UK:*** Dermidex.

Aldioxa *(USAN, rINN)*

ALDA; Aldioxum; Aluminium Dihydroxyallantoinate; Dihydroxyaluminum Allantoinate; RC-172. Dihydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl)ureato]aluminium.

Альдиокса

$C_4H_7AlN_4O_5$ = 218.1.

CAS — 5579-81-7.

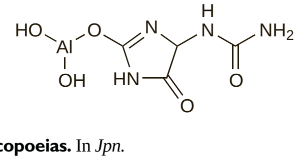

Pharmacopoeias. In *Jpn.*

Profile

Aldioxa is an astringent and keratolytic related to allantoin (below). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** ZeaSorb; ***Austral.:*** ZeaSorb; ***Canad.:*** ZeaSorb; ***Chile:*** ZeaSorb†; ***Fr.:*** ZeaSorb; ***Indon.:*** ZeaSorb; ***Irl.:*** ZeaSorb; ***Israel:*** Aronal Forte; ***Ital.:*** Rikospray; ***Malaysia:*** ZeaSorb†; ***Mex.:*** Dentsiblen; ***Philipp.:*** ZeaSorb; ***S.Afr.:*** ZeaSorb; ***Singapore:*** ZeaSorb; ***Thai.:*** ZeaSorb; ***UK:*** Cetanorm; ZeaSorb.

Alefacept *(BAN, USAN, rINN)*

Aléfacept; Alefaceptum; BG-9273; BG-9712; LFA3TIP; Recombinant Human LFA-3/IgG$_1$ Fusion Protein. A dimer of 1-92 antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C$_H$2-C$_H$3 γ1-chain).

Алефацепт

CAS — 222535-22-0.

ATC — L04AA15.

ATC Vet — QL04AA15.

Adverse Effects and Precautions

Chills are common on intravenous dosage of alefacept. Other adverse effects are cough, dizziness, headache, injection site pain and inflammation, myalgia, nausea, pharyngitis, and pruritus. More serious adverse reactions are cardiovascular events (including coronary artery disorder and myocardial infarction), hypersensitivity reactions, lymphopenia, and serious infections requiring hospitalisation. Cases of hepatotoxicity including asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, and acute liver failure have occurred. Like other drugs with immunosuppressant actions, alefacept may increase the risk of malignancies, particularly basal or squamous cell cancers of the skin. It should not be given to patients with a history of malignancy.

Alefacept should also not be given to patients with pre-existing serious infections, and should be stopped if these develop. Its use should be considered carefully in patients with chronic infections or a history of recurrent infection.

Alefacept induces a dose-dependent reduction in circulating CD4+ and CD8+ T-lymphocyte counts. It is therefore also contra-indicated in patients with HIV infection as the reduction in CD4+ T-lymphocytes could accelerate disease progression or increase complications of HIV infection. CD4+ T-lymphocyte counts should be monitored before starting alefacept therapy and then every 2 weeks during the 12-week treatment period. Treatment should not be started in patients with a CD4+ T-lymphocyte count below normal. Doses should be withheld and weekly monitoring started if the counts fall below 250 cells/microlitre, and treatment stopped if the counts remain below this level for one month.

Therapy should be stopped immediately, and appropriate treatment given, in patients who experience anaphylaxis or serious hypersensitivity; it should not be restarted.

◊ References.

1. Goffe B, *et al.* An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther* 2005; **27:** 1912–21.

Pharmacokinetics

Alefacept has a bioavailability of about 63% after intramuscular injection. After an intravenous dose it has an elimination half-life of about 11 to 12 days.

◊ References.

1. Vaishnaw AK, TenHoor CN. Pharmacokinetics, biologic activity, and tolerability of alefacept by intravenous and intramuscular administration. *J Pharmacokinet Pharmacodyn* 2002; **29:** 415–26.

Uses and Administration

Alefacept is a recombinant human fusion protein that binds to CD2 on memory T-lymphocytes, preventing their activation and reducing their number. It is used in the management of moderate to severe chronic plaque psoriasis (p.1583) and is given in a dose of 7.5 mg once weekly by intravenous injection, or 15 mg once weekly by intramuscular injection, for 12 weeks. A second 12-week course may be given if necessary, starting not less than 12 weeks after the completion of the first.

◊ General references.

1. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; **345:** 248–55.
2. Krueger GG, *et al.* A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; **47:** 821–33.
3. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. *Br J Dermatol* 2003; **148:** 784–8.

4. Lebwohl M, *et al.* An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003; **139:** 719–27.
5. Korman NJ, Moul DK. Alefacept for the treatment of psoriasis: a review of the current literature and practical suggestions for everyday clinical use. *Semin Cutan Med Surg* 2005; **24:** 10–18.
6. Ortonne JP, *et al.* An open-label study of alefacept plus ultraviolet B light as combination therapy for chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2005; **19:** 556–63.
7. Mease PJ, *et al.* Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006; **54:** 1638–45.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Amevive; ***Canad.:*** Amevive; ***Israel:*** Amevive; ***Switz.:*** Amevive; ***USA:*** Amevive.

Allantoin *(BAN, USAN)*

Alantoin; Alantoína; Alantoinas; Allantoiini; Allantoïne; Allantoinum; Glyoxyldiureide. 5-Ureidohydantoin; 5-Ureidoimidazolidine-2,4-dione; 2,5-Dioxoimidazolidin-4-ylurea.

Аллантоин; Кордианин

$C_4H_6N_4O_3$ = 158.1.
CAS — 97-59-6.

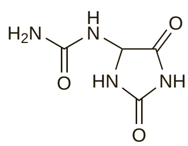

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Allantoin). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.
USP 31 (Allantoin). A white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.

Profile

Allantoin is an astringent and keratolytic. It is present in multi-ingredient preparations intended for various skin disorders and is also used for its astringent properties in preparations for the treatment of haemorrhoids and other anorectal disorders.

Psoriasis. In the USA the FDA decided that allantoin should be removed from lotions indicated for psoriasis as it was considered to be ineffective.[1]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; **5:** 62.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Soothex†; ***India:*** Masse; ***Pol.:*** Alantan.

Multi-ingredient: ***Arg.:*** Abanta; Afonisan; Atomoderma A-E; Bushi; Contractubex; Crema Para Paspaduras; Cremsor N; Dermaloe†; Esmedent con Fluor; Euroderm-A; Factor Vit AE; Glossderm†; Lactocrem Bebe; Lociherp Liposomas Vitaminado; Medic†; Mencogrin; Mencogrin AP; Mencogrin†; Pastillas Lorbi; Pastillas Medex; Quem Plus†; ***Austral.:*** Acne & Pimple Gel†; Alphosyl; Blistex Medicated Lip Ointment; ER Cream†; Hemocane; Macro Natural Vitamin E Cream; Medi Creme; Medi Pulv; Paxyl; SoloSite; Solyptol†; VR†; ***Austria:*** Alphosyl; Contractubex; Rheumex; Ulcurilen; ***Braz.:*** Contractubex; Lactrex; Senol†; Vitaderme; ***Canad.:*** Blistex Medicated Lip Ointment; Phenoris; Tanac†; ***Chile:*** Dermaglos; Dermaglos Plus†; Lactrex†; Nenegloss; Pancrit; Queratopil; Sanoderm; Ureadin 30; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; ***Cz.:*** Brand- und Wundgel†; Contractubex; Jox; Panlid; ***Fr.:*** Alpha 5 DS†; Alphosyl†; Cicatryl; Erygine; Hydracuivre; Prebutix; Provictol†; Purif-Ac Emulsion; Purif-Ac Gel; Seborheane; Spirial; Topialyse Fluide; Topialyse Plus; ***Ger.:*** Brand- und Wund-Gel Eu Rho†; Contractubex; Ellsurex; Essaven Tri-Complex†; Haemo-Exhirud†; Hydro Cordes; Leukona-Wundsalbe†; Lipo Cordes; Psoriasis-Salbe S†; Ulcurilen N†; ***Hong Kong:*** Blistex Lip Ointment†; Burn Cream†; Contractubex; Egoderm; Egopsoryl TA; Medipulv†; Pyodontyl; ***Hung.:*** Contractubex; Jox†; ***India:*** Contractubex; New Eye Lotion; Shield; ***Indon.:*** Mederma; Verile; ***Israel:*** Alphosyl HC†; Alphosyl†; Comfrey Plus; Pitrisan; Proctozorin-N; Rekasitin; ***Ital.:*** Alphosyle†; Angstrom Viso; Balta-Crin Tar†; Centella Complex; Cerosteril; Cerox†; Ginoxil Ecoschiuma; Keraflex; Sensigel; Sensiquell; Tial-Z; Xerial; ***Malaysia:*** Egoderm; Egopsoryl TA; ***Mex.:*** Antaderm; Dealan; Glossderm; Hipoglos; Hipoglos Cremoso; Lactrex; Sebryl; Sebryl Plus; Sebstopp; Unguento de la Madre; ***NZ:*** Egoderm; Egopsoryl TA; Medipulv; ***Philipp.:*** Contractubex; ***Pol.:*** Alantan-Plus; Alantavit; Cepan; Contractubex; Dernilan; Mucosit; Pupilek; Septalan; Tointex; ***Port.:*** Hidratoderme†; ***Rus.:*** Contractubex (Контрактубекс); Hepatrombin (Гепатромбин); Jox (Йокс); ***S.Afr.:*** Alphosyl; Arola Rosebalm; Blistex; Clearasil Medicated Facial Cleanser; ***Singapore:*** Egoderm; Egopsoryl TA; Erase; ***Spain:*** Alphosyl; Amplidermis; Antigrietun; Cortenema; Egarone†; Hepro; Polaramine Topico; ***Swed.:*** Alphosyl†; ***Switz.:*** Alphastria; Alphosyl†; Alumagall†; Carmol Plus†; Contractubex; Gorgonium; Hepathrombine†; Keli-med; Leniderm†; Lyman; Optrex compresses; Sportium; Unatol; Wulnasin; ***Thai.:*** Opplin†; ***UK:*** Actinac; Alphosyl HC; Anodesyn; Atopiclair; Vesagex Heelbalm; ***USA:*** Alasulf; Anbesol Cold Sore Therapy; Atopiclair; Blistex; Blistex Lip Balm; Deltavac; DIT1-2; Dr Dermi-Heal; Ionax Astringent; Orabase Lip; Tanac; Tanac Dual Core; ***Venez.:*** Alantamida; Lactrex.

Aloe Vera

Aloe.

Алоэ Вера; Алоэ Древовидное

Profile

Aloe vera gel is a mucilaginous preparation obtained from the leaves of *Aloe vera* (*A. barbadensis*). It does not include the sap of *Aloe vera*, which contains anthraquinones, and should not be confused with aloes (p.1705).

◊ Aloe vera is widely used in cosmetics and toiletries for a reported moisturising and revitalising action. There are also claims for the beneficial and even curative properties of aloe vera gel in the treatment of conditions such as acne, psoriasis, burns, wounds, arthritis, diabetes, hyperlipidaemia, peptic ulcer, and genital herpes.[1,2] Evidence to support these claims is lacking. There is also no strong evidence to support the use of aloe vera gel in the prevention or treatment of radiation-induced skin reactions in cancer patients.[3]

1. Marshall JM. Aloe vera gel: what is the evidence? *Pharm J* 1990; **244:** 360–2.
2. Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. *Br J Gen Pract* 1999; **49:** 823–8.
3. Richardson J, *et al.* Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)* 2005; **17:** 478–84.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Biorevit Gel†; Capson; Puraloe Post Solar; ***Braz.:*** Probeks†; Soapelle; ***Fr.:*** Veraskin; ***Ital.:*** Epitaloe; ***NZ:*** Solarcaine Aloe Vera; ***Singapore:*** Curacao.

Multi-ingredient: ***Arg.:*** Abanta; Acuaderm; Aloebel; Aristaloe; Brunavera; Controlacne; Crema De Ordene; Dermaloe†; Dermvien†; Eurocolor Post Solar; Europrotec Post Solar†; Galenic Restaurador Capilar; Herbaccion Nutriderm†; KW; Mucobase; Negacne; Odontobiotic†; Olamine; Pedicrem; Puraloe; Puraloe Nutritivo; Refrane P; Refrane Plus; Sadeltan F†; Snella Vag; Solenil Post Solar; Talowin; Yuyo; ***Austral.:*** Aloe Vera Plus; Lipz Lip Ointment; Percutane; Psor-Asist; Rapaid Rash-Relief; ***Braz.:*** Actine; Derm'attive Solaire†; Malvatricin Natural Soft; ***Chile:*** Ac-Sal; Fray Romano; Nenegloss; Solarcaine Aloe Vera Gel; Ureadin Rx DB; Ureadin Rx RD; ***Cz.:*** After Burn†; ***Fr.:*** Alkagin; Alra†; Cicatridine; Postopyl†; Rhinodoron; ***Ger.:*** Rhinodoron; ***Hong Kong:*** Apaisac; Pregnacare; ***India:*** Elovera; Elovera-SPF; Sofderm; ***Indon.:*** Jointfit; Velostin; ***Israel:*** Agisten with Aloe Vera; Aphtagone; Aptha-X; ***Ital.:*** Capso; Ektrofil; Ginoxil Ecoschiuma; Ninfagin; Vicks Baby Balsam†; Vulnopur; ***Malaysia:*** Boots Antenatal Massage Cream†; Elovera; Lorasil Feminine Hygeine†; Neo-Healar; ***Mex.:*** Gelconordin; Hipoglos Cremoso; ***NZ:*** Chap Stick; Lamisil Odor Eze; Vicks Baby Balsam; ***Philipp.:*** Elovera; Intima; ***Port.:*** Alkagin; Antiacneicos Ac-Sal†; Multi-Mam Compressas†; ***Singapore:*** Cortaid with Aloe†; Desitin Creamy†; ***UK:*** Antiac; Don't Bug Me; Sinose; Solarcaine†; ***USA:*** Aloe Grande; Biotene with Calcium; Bodi Kleen; Dermtex HC with Aloe; Entertainer's Secret; Geri-Lav Free; Gold Bond Medicated Triple Action Relief; Hawaiian Tropic Cool Aloe with I.C.E.; Hemorid For Women; Maximum Strength Flexall 454; Nasal-Ease; OraMagicRx; RadiaPlex Rx; Solarcaine Aloe Extra Burn Relief; ***Venez.:*** Andantol Jalea; Flucirac; Gelsem; Jengimiel; Jengimiel Sabila.

Aluminium Chloride

Aliuminio chloridas heksahidratas; Alumiinikloridiheksahydraatti; Aluminii chloridum hexahydricum; Aluminio, cloruro de; Aluminium Chloratum; Aluminium (chlorure d') hexahydraté; Alumínium-klorid-hexahidrát; Aluminiumkloridhexahydrat; Aluminum Chloride; Chlorid hlinitý hexahydrát; Cloreto de Alumínio; Cloruro de Aluminio; Glinu chlorek. Aluminium chloride hexahydrate.

Алюминия Хлорид

$AlCl_3,6H_2O$ = 241.4.
CAS — 7446-70-0 (anhydrous aluminium chloride); 7784-13-6 (aluminium chloride hexahydrate).
ATC — D10AX01.
ATC Vet — QD10AX01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Aluminium Chloride Hexahydrate). A deliquescent, white or slightly yellow, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; soluble in glycerol. Store in airtight containers.
USP 31 (Aluminium Chloride). Deliquescent, white or yellowish-white, practically odourless, crystalline powder. Its solutions are acid to litmus. Soluble 1 in 0.9 of water and 1 in 4 alcohol; soluble in glycerol. Store in airtight containers.

Adverse Effects

Aluminium chloride may cause irritation especially if applied to damp skin; this is attributed to the formation of hydrochloric acid.

Uses and Administration

Aluminium chloride has astringent properties and is used in a 20% alcoholic solution as an antiperspirant in the treatment of hyperhidrosis (p.1580). It is applied to dry skin, usually at bedtime, and is washed off in the morning before the sweat glands are fully active. Initially, it may be applied each night until sweating improves, then less frequently, as required, to maintain efficacy.

◊ References.

1. Scholes KT, *et al.* Axillary hyperhidrosis treated with alcoholic solution of aluminium chloride hexahydrate. *BMJ* 1978; **2:** 84–5.
2. Ellis H, Scurr JH. Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. *Postgrad Med J* 1979; **55:** 868–9.

Preparations

BP 2008: Aluminium Chloride Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Alumpak; Anhidrot†; Drysol; ***Austral.:*** Driclor; Odaban†; ***Chile:*** Drysol; Xerac AC; ***Fr.:*** Driclor; Etiaxil; ***Ger.:*** Gargarisma zum Gurgeln; Mallebrin Konzentrat; ***Hong Kong:*** Driclor; ***Irl.:*** Anhydrol Forte; Driclor; ***Israel:*** Anhydrol Forte; Driclor†; ***Malaysia:*** Driclor†; ***Mex.:*** Drysol; ***NZ:*** Hidrosol; ***Philipp.:*** Driclor; ***Pol.:*** Antidral; ***S.Afr.:*** Driclor; ***Singapore:*** Driclor; ***Switz.:*** Etiaxil; Racestyptine; ***UK:*** Anhydrol Forte; Driclor; Odaban; ***USA:*** Drysol; Xerac AC.

Multi-ingredient: ***Arg.:*** Carnot Topico; ***Chile:*** Hidrofugal; Hidrofugal Forte; ***Mex.:*** Prespir; ***Switz.:*** Sansilla; ***USA:*** Stypto-Caine.

Aluminium Chlorohydrate

Aluminio, clorohidróxido de; Aluminium Chlorhydrate; Aluminium Chloride Hydroxide Hydrate; Aluminum Chlorhydroxide; Aluminum Chloride Hydroxide Hydrate; Aluminum Chlorohydrate *(USAN)*; Aluminum Hydroxychloride; Alüminyum Hidroksiklorür; Basic Aluminium Chloride.

Алюминия Хлорогидрат

$Al_2(OH)_5Cl,xH_2O$.
CAS — 1327-41-9 (anhydrous aluminium chlorohydrate).
ATC — D09AA08; M05BX02.
ATC Vet — QD09AA08; QM05BX02.

Pharmacopoeias. In *US.*
US also includes a range of compounds based on aluminium chlorohydrate. These are:

- aluminium dichlorohydrate and sesquichlorohydrate
- the polyethylene glycol (macrogol) complexes and propylene glycol complexes of aluminium chlorohydrex, aluminium dichlorohydrex, and aluminium sesquichlorohydrex
- the tri-, tetra-, penta-, and octachlorohydrates of aluminium zirconium and their respective glycine derivatives.

USP 31 (Aluminum Chlorohydrate). A 15% w/w solution in water has a pH of 3.0 to 5.0

Profile

Aluminium chlorohydrate is used similarly to aluminium chloride in hyperhidrosis (p.1580). Single-ingredient products for hyperhidrosis generally have a concentration in the range of 10 to 25%.

Aluminium chlorohydrate is also included in a variety of dermatological preparations for its astringent and antiperspirant properties.

Aluminium toxicity. Bone pain, extreme fatigue, and raised aluminium concentrations in a woman with normal renal function were attributed to the use of an antiperspirant cream containing aluminium chlorohydrate 20%. She had been applying about 1 g of cream to each underarm daily for 4 years. Within 8 months of stopping the antiperspirant, plasma-aluminium concentrations had returned to normal and symptoms had resolved.[1]

1. Guillard O, *et al.* Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. *Am J Med* 2004; **117:** 956–9.

Preparations

USP 31: Aluminum Chlorohydrate Solution; Aluminum Dichlorohydrate Solution; Aluminum Sesquichlorohydrate Solution; Aluminum Zirconium Octachlorohydrex Gly Solution; Aluminum Zirconium Pentachlorohydrate Solution; Aluminum Zirconium Pentachlorohydrex Gly Solution; Aluminum Zirconium Tetrachlorohydrate Solution; Aluminum Zirconium Tetrachlorohydrex Gly Solution; Aluminum Zirconium Trichlorohydrate Solution; Aluminum Zirconium Trichlorohydrex Gly Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Bromhistop; Daewo†; Normoskin†; Sodorant; ***Canad.:*** Roll-On†; Scholl Dry Antiperspirant Foot Spray†; ***Chile:*** Hansaplast Footcare; Hidrofugal; ***Fr.:*** pM; Spirial; ***Ger.:*** Phosphonorm; ***Israel:*** Aloxan Derma; ***Ital.:*** Spirial; ***Mex.:*** Skin Dry; ***NZ:*** Neat Effect; Neat Feat; Neat One; Neat Touch; ***Port.:*** Dermagor-Antitranspirante; Lambda; ***Switz.:*** Alopon†; Gelsica; Phosphonorm; Sansudor; ***Turk.:*** Kursept; Terkur; ***UK:*** Chiron Barrier Cream; ***USA:*** Bromi-Lotion.

Multi-ingredient: ***Arg.:*** Neobitiol; Sodorant; Ublosid†; ***Austral.:*** Nappy-Mate†; Neo-Medrol; ***Austria:*** Sulgan 99; ***Canad.:*** Medrol Acne Lotion; Neo-Medrol Acne; ***Chile:*** Hidrofugal; Hidrofugal Forte; Lady Fittig†; Uriage Desodorante Tri-Actif; ***Fin.:*** Neo-Medrol comp†; ***Fr.:*** Spirial; ***Ger.:*** Ansudor†; Epipak†; ***Hong Kong:*** Neo-Medrol Acne; ***Indon.:*** Betiga; ***Israel:*** Fungimon; Neo-Medrol; Pedisol; ***Ital.:*** Medrol Lozione Antiacne†; ***S.Afr.:*** Neo-Medrol; ***Spain:*** Hongosan; Moderin Acne†; ***USA:*** Breezee Mist Foot Powder; Ostiderm.

Amiloxate *(USAN, rINN)*

Amiloxato; Amiloxatum; E-1000; Isoamyl *p*-Methoxycinnamate. Isopentyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 3-methylbutyl ester.

Амилоксат

$C_{15}H_{20}O_3$ = 248.3.
CAS — 71617-10-2.

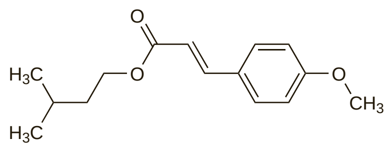

NOTE. Neo-Heliopan E 1000 is a trade name that has been used for amiloxate.

Pharmacopoeias. In *US.*

USP 31 (Amiloxate). Store in airtight containers.

Profile

Amiloxate, a substituted cinnamate, is a sunscreen (p.1576) with actions similar to those of octinoxate (p.1608). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Aminobenzoic Acid

Acide 4-Aminobenzoïque; Acidum 4-aminobenzoicum; Amben; 4-Aminobensoesyra; 4-Aminobentsoehappo; 4-aminobenzoesav; Aminobenzoico, ácido; 4-Aminobenzoinė rūgštis; Kwas 4-aminobenzoesowy; Kyselina 4-aminobenzoová; PAB; PABA; Pabacidum; Para-aminobenzoic Acid; Vitamin Bx; Vitamin H′. 4-Aminobenzoic acid.

Аминобензойная Кислота

$C_7H_7NO_2$ = 137.1.
CAS — 150-13-0.
ATC — D02BA01.
ATC Vet — QD02BA01.

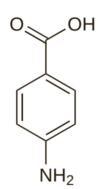

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (4-Aminobenzoic Acid; Aminobenzoic Acid BP 2008). White or slightly yellow crystalline powder. Slightly soluble in water; freely soluble in alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Aminobenzoic Acid). White or slightly yellow, odourless crystals or crystalline powder. It discolours on exposure to air or light. Slightly soluble in water and in chloroform; freely soluble in alcohol and in solutions of alkali hydroxides or carbonates; sparingly soluble in ether. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse skin reactions such as local irritation and contact dermatitis have been reported after the topical use of aminobenzoate sunscreens. Aminobenzoate sunscreens should not be used by those with a history of photosensitivity or hypersensitivity reactions to structurally related drugs such as sulfonamides, thiazide diuretics, and ester-type local anaesthetics.

Aminobenzoic acid may stain clothing.

◊ Allergic and photoallergic contact dermatitis have been reported after topical use of aminobenzoic acid or its esters.[1] Early reports of such reactions led to the removal of these compounds from sunscreen preparations (many are now described as 'PABA-free'), although padimate O still appears to be widely used.[2] Patients allergic to aminobenzoic acid may also react to structurally related allergens such as para-aminobenzoic acid ester anaesthetics, sulfonamides, and paraphenylenediamine in hair dyes.[1,2]

Skin reactions (vitiligo) have also been reported with oral aminobenzoic acid[3] and the adverse effects associated with the former use of high oral doses for various conditions have been highlighted.[4]

1. Scheuer E, Warshaw E. Sunscreen allergy: A review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis* 2006; **17:** 3–11. Correction. *ibid.*; 162.
2. Mackie BS, Mackie LE. The PABA story. *Australas J Dermatol* 1999; **40:** 51–3.
3. Hughes CG. Oral PABA and vitiligo. *J Am Acad Dermatol* 1983; **9:** 770.
4. Worobec S, LaChine A. Dangers of orally administered para-aminobenzoic acid. *JAMA* 1984; **251:** 2348.

Pharmacokinetics

If given orally, aminobenzoic acid is absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged drug and metabolites.

Uses and Administration

Aminobenzoic acid is applied topically as a sunscreen (p.1576). Aminobenzoic acid and its derivatives effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p.1580). Aminobenzoate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity.

Aminobenzoic acid has sometimes been included as a member of the vitamin-B group, but deficiency of aminobenzoic acid in man or *animals* has not been found.

Aminobenzoic acid has been used with bentiromide (p.2264) in the PABA or BTPABA test of pancreatic function.

Preparations

USP 31: Aminobenzoic Acid Gel; Aminobenzoic Acid Topical Solution.

Proprietary Preparations some preparations are listed in Part 3.

Ammonium Lactate *(USAN)*

Amonio, lactato de; BMS-186091.

Аммония Лактат

$C_3H_9NO_3$ = 107.1.
CAS — 52003-58-4.
ATC Vet — QA16QA04.

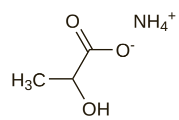

Profile

Ammonium lactate is a humectant applied as a cream or lotion containing 12% lactic acid neutralised with ammonium hydroxide. It is used in the treatment of dry scaly conditions of the skin including ichthyosis. Adverse effects of topical ammonium lactate preparations include transient erythema, burning, and stinging. Treated areas may be more sensitive to sunlight and exposure should be minimised.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lacto-Cev; Lactrex; ***Braz.:*** Lac-Hydrin; ***Canad.:*** Lac-Hydrin; ***Chile:*** Kerapil†; Topilact 12†; ***Fr.:*** Kerapil†; ***Malaysia:*** Lanate; ***Mex.:*** Lac-Hydrin; ***NZ:*** Lac-Hydrin; Lanate; ***Singapore:*** Lac-Hydrin; Lanate; ***USA:*** Amlactin; Geri-Hydrolac; Kerasal AL; Lac-Hydrin; LAC-Lotion.

Multi-ingredient: ***Arg.:*** Clobeplus; Clobesol LA; Lactiderm; Lactiderm HC†; Lacto-Cev Zn; Urecrem Hidro; ***Braz.:*** Lactrex; ***Chile:*** Ichtyosoft†; KPL†; Lactrex†; Queratopil; ***Fr.:*** I-Soft†; Ichtyosoft†; Keralac Plus†; Zeniac LP Fort†; Zeniac LP†; Zeniac†; ***Indon.:*** Exfoliac; ***Ital.:*** Alfa Acid; Ipso Urea; ***Mex.:*** Lactrex; ***Port.:*** Lactonico†; ***Venez.:*** Lactrex.

Arbutin

Arbutoside; Arbutyna; Beta-arbutin; Ursin. 4-Hydroxyphenyl-β-D-glucopyranoside.

Арбутин

$C_{12}H_{16}O_7$ = 272.3.
CAS — 497-76-7 (beta-arbutin); 84380-01-8 (alpha-arbutin).

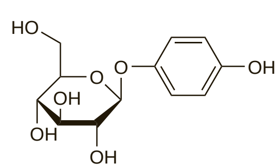

Profile

Arbutin is a glycosylated derivative of hydroquinone (p.1598) extracted from bearberry (p.2263) and similar plants. It is used topically in concentrations of 1 to 5% as a depigmenting agent for the skin in hyperpigmentation disorders. The higher concentrations may lead to a paradoxical hyperpigmentation.

Alpha-arbutin has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cellskinlab Phyto Spot; Melasoft†; ***Chile:*** Phyto Corrective Gel; Phyto Spot; ***Port.:*** Despigmentante.

Avobenzone *(USAN, rINN)*

Avobenzona; Avobenzonum; Butylmethoxydibenzoylmethane; 4-*tert*-Butyl-4′-methoxydibenzoylmethane. 1-(*p*-*tert*-Butylphenyl)-3-(*p*-methoxyphenyl)-1,3-propanedione; 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-1,3-propanedione.

Авобензон

$C_{20}H_{22}O_3$ = 310.4.
CAS — 70356-09-1.

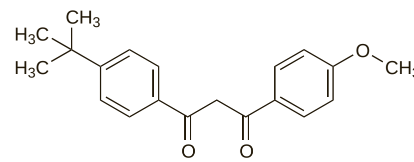

NOTE. Escalol 517, Eusolex 9020, Neo-Heliopan 357, and Parsol 1789 are trade names that have been used for avobenzone.

Pharmacopoeias. In *US.*

USP 31 (Avobenzone). M.p. 81° to 86°. Store in airtight containers. Protect from light.

Profile

Avobenzone is a substituted dibenzoylmethane used by topical application as a sunscreen (p.1576). Dibenzoylmethanes absorb light in the UVA range (for definitions, see p.1580) and may therefore be used with other sunscreens that absorb UVB light to prevent sunburn; they will also provide some protection against drug-related or other photosensitivity reactions associated with UVA light.

Contact and photocontact allergic dermatitis has occasionally been reported with the topical use of dibenzoylmethane sunscreens.

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Azelaic Acid *(USAN, rINN)*

Acide azélaïque; Ácido azelaico; Acidum azelaicum; Anchoic acid; Atselaiinihappo; Azelaik Asit; Azelainsyra; Lepargylic acid; ZK-62498. Nonanedioic acid; Heptane-1,7-dicarboxylic acid.

Азелаиновая Кислота

$C_9H_{16}O_4$ = 188.2.
CAS — 123-99-9.
ATC — D10AX03.
ATC Vet — QD10AX03.

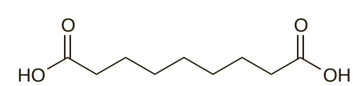

Adverse Effects and Precautions

Topical application of azelaic acid may produce a transient skin irritation such as burning, stinging, pruritus, dryness, and scaling. It is usually mild and disappears on continued treatment, but in a few patients the irritation may persist, requiring reduced frequency of application or temporary suspension of treatment. There have been rare reports of hypopigmentation, rash, and photosensitivity. Azelaic acid should not be applied to the eyes, mouth, or other mucous membranes.

Uses and Administration

Azelaic acid inhibits the growth of *Propionibacterium* spp. and reduces keratinisation. It is used in the topical treatment of mild to moderate inflammatory acne (p.1577) and for the inflammatory papules and pustules of mild to moderate rosacea (p.1583). It has also been tried in hyperpigmentary skin disorders such as melasma, and in malignant melanoma.

In the treatment of **acne** azelaic acid is applied twice daily for up to 6 months as a 20% cream or 15% gel. Improvement usually occurs within four weeks.

For the treatment of mild to moderate **rosacea**, a 15% gel should be applied to the affected area twice daily for a period of up to 12 weeks. Improvement usually occurs in 4 to 8 weeks.

◊ References.

1. Fitton A, Goa KL. Azelaic acid: a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs* 1991; **41:** 780–98.
2. Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. *Cutis* 1996; **57** (suppl): 36–45.
3. Elewski B, Thiboutot D. A clinical overview of azelaic acid. *Cutis* 2006; **77** (suppl): 12–16.
4. Del Rosso JQ. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. *Cutis* 2006; **77** (suppl): 22–4.
5. Liu RH, *et al.* Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. *Arch Dermatol* 2006; **142:** 1047–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cutacelan; ***Austral.:*** Finacea; Skinoren; ***Austria:*** Skinoren; ***Belg.:*** Skinoren; ***Braz.:*** Azelan; Dermizan; ***Cz.:*** Aknoren; Skinoren; ***Denm.:*** Finacea; Skinoren; ***Fin.:*** Skinoren; ***Fr.:*** Finacea; Skinoren; ***Ger.:*** Skinoren; ***Gr.:*** Alenzantyl; Azedose; Azelac; Azelaxine; Azelderm; Cevigen; Chemilaic†; Exazen; Forcilen†; Kenedril; Noreskin; Opilet; Prevolac†; Skinoren; Sonalent; Zelicrema; Zorkenil; Zumilin; ***Hong Kong:*** Qualicren; Qualilaic; Skinoren; ***Hung.:*** Skinoren; ***Indon.:*** Aza 20; Skinoren; Zelface; Zeliris; ***Irl.:*** Skinoren; ***Israel:*** Skinoderm; ***Ital.:*** Acnezaic†; Finacea; Neocutis; Skinoren; ***Malaysia:*** Skinoren; ***Mex.:*** Cutacelan†; Finacea; ***Norw.:*** Finacea; Skinoren; ***NZ:*** Skinoren; ***Philipp.:*** Skinoren; ***Pol.:*** Acne-Derm; Hascoderm; Skinoren; ***Port.:*** Dermazil; Finacea; Skinoren; ***Rus.:*** Skinoren (Скинорен); ***S.Afr.:*** Skinoren; ***Singapore:*** Skinoren; ***Spain:*** Finacea; Skinoren; Zeliderm; ***Swed.:*** Finacea; Skinoren; ***Switz.:*** Skinoren; ***Thai.:*** Skinoren; ***Turk.:*** Azelderm; Skinoren; ***UK:*** Finacea; Skinoren; ***USA:*** Azelex; Finacea; Finevin; ***Venez.:*** Cutacelan.

Multi-ingredient: *Austral.:* Acnederm Medicated; ***Hong Kong:*** Acnederm; ***Ital.:*** Zeroac; ***Malaysia:*** Acnederm Lotion; ***NZ:*** Acnederm; ***Singapore:*** Acnederm.

Becaplermin *(BAN, USAN, rINN)*

Becaplermina; Bécaplermine; Becaplerminum; Bekaplermiini; Bekaplermin; RWJ-60235. Recombinant human platelet-derived growth factor B.

Бекаплермин

CAS — 165101-51-9.
ATC — D03AX06.
ATC Vet — QD03AX06.

Profile

Becaplermin is a recombinant human platelet-derived growth factor (rhPDGF-BB) that enhances the formation of granulation tissue and promotes wound healing (p.1585). Becaplermin is applied topically as a 0.01% gel in the management of full thickness neuropathic diabetic skin ulcers (see Diabetic Complications, p.433). It is applied once daily, covered by a moist saline gauze dressing, for up to 20 weeks. If no meaningful healing process (decrease in ulcer size of about 30%) is evident after 10 weeks of therapy, treatment should be re-assessed.

Becaplermin should not be applied to ulcers where neoplasms are present or to clinically infected ulcers. If the ulcer becomes infected during therapy, becaplermin should be stopped until the infection has cleared. US licensed product information warns that an increased rate of death from all cancers has been seen in patients treated with 3 or more tubes of becaplermin gel (tube size not specified).

Becaplermin is used with a resorbable synthetic calcium phosphate matrix to promote bone and tissue growth in the treatment of periodontal disease. It is also under investigation in the treatment of osteonecrosis of the jaw, fractures, and osteoporosis, and in the repair of cartilage, ligament, and tendon injuries.

◊ References.

1. Wieman TJ, *et al.* Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; **21:** 822–7.
2. Smiell JM, *et al.* Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair Regen* 1999; **7:** 335–46.
3. Guzman-Gardearzabal E, *et al.* Treatment of chronic ulcers in the lower extremities with topical becaplermin gel .01%: a multicenter open-label study. *Adv Therapy* 2000; **17:** 184–9.
4. Mandracchia VJ, *et al.* The use of becaplermin (rhPDGF-BB) gel for chronic nonhealing ulcers: a retrospective analysis. *Clin Podiatr Med Surg* 2001; **18:** 189–209.
5. Nagai MK, Embil JM. Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. *Expert Opin Biol Ther* 2002; **2:** 211–18.
6. Nevins M, *et al.* Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. *J Periodontol* 2005; **76:** 2205–15.
7. McGuire MK, *et al.* rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. *Int J Periodontics Restorative Dent* 2006; **26:** 223–31. Correction. *ibid.* 2007; **27:** 88.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Regranex; ***Canad.:*** Regranex; ***Cz.:*** Regranex; ***Fr.:*** Regranex; ***Ger.:*** Regranex; ***Gr.:*** Regranex; ***Israel:*** Regranex; ***Mex.:*** Regranex; ***Neth.:*** Regranex; ***Port.:*** Regranex; ***Spain:*** Regranex; ***Switz.:*** Regranex; ***UK:*** Regranex; ***USA:*** Regranex.

Multi-ingredient: *USA:* GEM 21S.

Bemotrizinol *(USAN, rINN)*

Bémotrizinol; Bemotrizinolum; BEMT; Bis-ethylhexyloxyphenol Methoxyphenol Triazine; FAT-70884. 2,2′-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis{5-[(2-ethylhexyl)oxy]phenol}.

Бемотризинол

$C_{38}H_{49}N_3O_5$ = 627.8.
CAS — 187393-00-6.

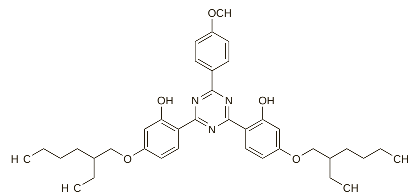

NOTE. Tinosorb S is a trade name that has been used for bemotrizinol.

Profile

Bemotrizinol is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Bentoquatam *(USAN)*

Quaternium 18-bentonite.

Бентокватам

CAS — 1340-69-8.

Profile

Bentoquatam, described as an organoclay compound, is a barrier preparation that is applied topically as a 5% lotion to prevent allergic contact dermatitis caused by poison ivy, poison oak, or poison sumac. The lotion is applied in a sufficient quantity to form a visible coating 15 minutes before possible contact with the plants. If continued protection is required the lotion may be re-applied every 4 hours or at any time if the visible coating is removed.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ivy Block.

Benzoyl Peroxide *(USAN)*

Bensoylperoxid; Bentsoyyliperoksidi; Benzoilo peroksidas; Benzoil-peroxid; Benzoyil Peroksit; Benzoylis peroxidum; Benzoylperoxid; NSC-675; Peróxido de benzoilo; Peroxyde de benzoyle. Dibenzoyl peroxide.

Бензоил Пероксид; Пероксид Бензоила

$C_{14}H_{10}O_4$ = 242.2.
CAS — 94-36-0 (anhydrous benzoyl peroxide).
ATC — D10AE01.
ATC Vet — QD10AE01; QD11AX90.

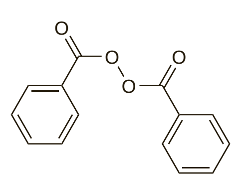

(anhydrous benzoyl peroxide)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Benzoyl Peroxide, Hydrous). It contains not less than 70% and not more than 77% of anhydrous benzoyl peroxide and not less than 20% of water. It rapidly loses water on exposure to air and may explode if the water content is too low. A white or almost white, amorphous or granular powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; soluble in dichloromethane with separation of water. Store at 2° to 8° in a container that has been treated to reduce static charges and that has a device for the release of excess pressure. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine after acidification with dilute hydrochloric acid. Protect from light.

USP 31 (Hydrous Benzoyl Peroxide). It contains not less than 65% and not more than 82% of anhydrous benzoyl peroxide with a water content of about 26%. The hydrous form is a white granular powder with a characteristic odour. Sparingly soluble in water and in alcohol; soluble in acetone, in chloroform, and in ether. Store in the original container, treated to reduce static charges. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine.

Adverse Effects and Precautions

Topical application of benzoyl peroxide may produce skin irritation, particularly at the start of treatment. In some patients the irritation may require reduced frequency of application or temporary suspension of treatment. Skin dryness, peeling, rash, and transient local oedema may also occur. Contact sensitisation has been reported in some patients using preparations containing benzoyl peroxide. Caution is required when applying it near the eyes, the mouth and other mucous membranes, and to the neck and other sensitive areas. Patients should be alerted to benzoyl peroxide's bleaching property.

Body odour. An unusual unpleasant body odour in a patient was attributed to the topical use of benzoyl peroxide.[1]

1. Molberg P. Body odor from topical benzoyl peroxide. *N Engl J Med* 1981; **304:** 1366.

Carcinogenicity. There has been concern at the implications of some *animal* studies showing benzoyl peroxide to possess some tumour-promoting activity.[1] However, a retrospective survey in Canada concluded that there was no indication that the normal use of benzoyl peroxide in the treatment of acne was associated with an increased risk of facial cancer.[2] A comprehensive review[3] that included *in-vitro* and *animal* studies, as well as human data, also concluded that there was no evidence to associate the topical use of benzoyl peroxide with the development of skin cancer in humans. However, the International Agency for Research on Cancer[4] considers that there is inadequate evidence in humans and its overall evaluation is that benzoyl peroxide is not classifiable as to its carcinogenicity to humans.

1. Jones GRN. Skin cancer: risk to individuals using the tumour promoter benzoyl peroxide for acne treatment. *Hum Toxicol* 1985; **4:** 75–8.
2. Hogan DJ, *et al.* A study of acne treatments as risk factors for skin cancer of the head and neck. *Br J Dermatol* 1991; **125:** 343–8.
3. Kraus AL, *et al.* Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. *Regul Toxicol Pharmacol* 1995; **21:** 87–107.
4. IARC/WHO. Benzoyl peroxide. *IARC monographs on the evaluation of carcinogenic risks to humans volume 71* 1999. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 27/09/07)

Handling. Benzoyl peroxide powder may explode if subjected to grinding, percussion, or heat. Hydrous benzoyl peroxide containing water to reduce the risk of explosion may still explode if exposed to temperatures higher than 60° or cause fires in the presence of reducing substances.

Hypersensitivity. Benzoyl peroxide appears to induce contact hypersensitivity quite often when used to treat leg ulcers,[1] but it is unclear how often this occurs when used in the treatment of acne.[2] Patch testing[3,4] in some studies suggests that up to 76% of patients may be hypersensitive to benzoyl peroxide but this does not appear to correlate either with the clinical irritation produced during treatment, which usually resolves on continued use, or with the reported incidence of hypersensitivity.[2,4] In one study 25% of patients were considered to be hypersensitive from patch testing but only 2 of 44 patients developed clinical hypersensitivity.[4] Another study involving 204 patients with acne found that the incidence of false-positive irritant skin reactions to benzoyl peroxide was about 15% but only 1% of the patients had true allergic reactions to the drug on further testing.[5] However, there has been concern that hypersensitivity to benzoyl peroxide may be mistaken for irritation or worsening of the acne.[3]

1. Vena GA, *et al.* Contact dermatitis to benzoyl peroxide. *Contact Dermatitis* 1982; **8:** 338.
2. Cunliffe WJ, Burke B. Benzoyl peroxide: lack of sensitization. *Acta Derm Venereol (Stockh)* 1982; **62:** 458–9.
3. Leyden JJ, Kligman AM. Contact sensitization to benzoyl peroxide. *Contact Dermatitis* 1977; **3:** 273–5.
4. Rietschel RL, Duncan SH. Benzoyl peroxide reactions in an acne study group. *Contact Dermatitis* 1982; **8:** 323–6.
5. Balato N, *et al.* Acne and allergic contact dermatitis. *Contact Dermatitis* 1996; **34:** 68–9.

Pharmacokinetics

◊ Work *in vitro* and in *animals*[1] suggests that although there is some absorption of benzoyl peroxide after topical application, any absorbed drug appears to be metabolised in the skin to benzoic acid and rapidly excreted in the urine.

1. Yeung D, *et al.* Benzoyl peroxide: percutaneous penetration and metabolic disposition II: effect of concentration. *J Am Acad Dermatol* 1983; **9:** 920–4.

Uses and Administration

Benzoyl peroxide has mild keratolytic properties. Its antimicrobial action is probably due to its oxidising effect and activity has been reported against *Staphylococcus epidermidis* and *Propionibacterium acnes*. It is used mainly in the treatment of acne (below), applied once or twice daily in topical preparations usually containing 2.5 to 10%, sometimes with other antimicrobials. For use in young children, see below. It has been used similarly in the treatment of fungal skin infections (p.521), such as tinea pedis although other drugs are usually preferred. A 20% lotion has been applied every 8 to 12 hours in the treatment of decubitus or stasis ulcers. Strengths are expressed as anhydrous benzoyl peroxide although it is used in a hydrous form for safety (see Pharmacopoeias, above).

Benzoyl peroxide is also used as a bleaching agent in the food industry and as a catalyst in the plastics industry.

Acne. Benzoyl peroxide applied topically in concentrations of up to 10% is probably the most widely used first-line drug in the management of mild acne (p.1577). Early studies in *animals* found benzoyl peroxide to be sebosuppressive[1] but later studies demonstrated that sebum excretion rises during the first few months of treatment,[2,3] probably due to the comedolytic action of benzoyl peroxide, and remains at a stable level thereafter. Benzoyl peroxide has been shown to have a significant inhibitory effect on skin microflora, with reductions in surface and follicular micro-organisms within 48 hours of beginning treatment, but clinical improvement took several more days to appear.[4] The combined use of benzoyl peroxide with topical clindamycin or erythromycin can inhibit the development of antibacterial resistance and bring about clinical improvement when resistance already exists.[5]

1. Gloor M, *et al.* Cytokinetic studies on the sebo-suppressive effect of drugs using the example of benzoyl peroxide. *Arch Dermatol Res* 1980; **267:** 97–9.
2. Cunliffe WJ, *et al.* Topical benzoyl peroxide increases the sebum excretion rate in patients with acne. *Br J Dermatol* 1983; **109:** 577–9.
3. Pierard-Franchimont C, *et al.* Topical benzoyl peroxide increases the sebum excretion rate. *Br J Dermatol* 1984; **110:** 506.
4. Bojar RA, *et al.* The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* 1995; **132:** 204–8.
5. Taylor GA, Shalita AR. Benzoyl peroxide-based combination therapies for acne vulgaris: a comparative review. *Am J Clin Dermatol* 2004; **5:** 261–5.

Administration in children. Benzoyl peroxide has been used topically in the treatment of neonatal and infantile acne, applied once or twice daily starting with lower strength preparations of 2.5%.

Preparations

BP 2008: Benzoyl Peroxide Cream; Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream;
USP 31: Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Erythromycin and Benzoyl Peroxide Topical Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Acnepas; Acnesan; Benzihex; Clidan B; Eclaran; Ecnagel PB; Paracne; PB Gel; Solugel; Tiltis; Vixiderm E; ***Austral.:*** Benzac; Brevoxyl; Clearasil Ultra; Neutrogena Acne Mask†; Oxy; PanOxyl; ***Austria:*** Akneroxid; Benzaknen; Brevoxyl; PanOxyl; Scherogel; ***Belg.:*** Akneroxid; Benzac; Brevoxyl; Pangel; ***Braz.:*** Acnase; Benzac AC; PanOxyl; Solugel; ***Canad.:*** Acetoxyl; Benoxyl; Benzac; Benzagel†; Clean & Clear Continuous Control; Clean & Clear Persa Gel; Clearasil B.P. Plus; Dermance†; Dermoxyl†; Desquam-X; Neo Strata Astringent Acne Treatment†; Neo Strata Blemish Spot†; Neutrogena Acne Mask†; Neutrogena On The Spot Acne Treatment†; Oxy; Oxyderm; PanOxyl; Solugel; ***Chile:*** Benzac; Pansulfox; Peroxiben Plus; Pirobac; Solugel; ***Cz.:*** Aknecide†; Aknefug-oxid†; Akneroxid; Antopar†; Basiron AC; Eclaran; Inoxitan†; Oxy; ***Fin.:*** Basiron; Brevoxyl; ***Fr.:*** Brevoxyl; Cutacnyl; Eclaran; Effacne; Pannogel; PanOxyl; ***Ger.:*** Aknederm Oxid†; Aknefug-oxid; Akneroxid; Benzaknen; Benzoyt; Benzperox; Brevoxyl; Cordes BPO; Dercome; Klinoxid; Marduk; PanOxyl; Sanoxit; Scherogel†; ***Gr.:*** Benzac-W; Brevoxyl; ***Hong Kong:*** Acnacyl†; Acneclear; Benzac AC; Brevoxyl; Oxy; PanOxyl; ***Hung.:*** Acne-Med†; Aknefug-oxid; Akneroxid; Lubexyl; ***India:*** Benzac AC; Persol; ***Indon.:*** Benzolac; Pimplex; ***Irl.:*** Acnecide; Brevoxyl; PanOxyl; ***Israel:*** Acne Derm; Acne Mask†; Benzac AC; Clearex Cover Up; Oxy; Oxy Sensitive; PanOxyl; ***Ital.:*** Benoxid; Benzac; PanOxyl; Reloxyl; ***Malaysia:*** Akneroxid; Benzac AC; Brevoxyl; PanOxyl; ***Mex.:*** Akeprul; Benoxyl; Benzac AC; Benzaderm; Oxy†; Solugel; ***Neth.:*** Akneroxid; Benzac; Clearamed†; Oxy; Tendox; ***Norw.:*** Basiron; Brevoxyl; PanOxyl; ***NZ:*** Benzac; Brevoxyl; Clearasil Ultra; PanOxyl; ***Philipp.:*** Benoxyl; Benzac AC; Brevoxyl; PanOxyl; Ultra Clearasil; ***Pol.:*** Akneroxid; Benzacne; Benzapur; Brevoxyl; Clearasil Ultra†; Lubexyl; ***Port.:*** Benacne; Benoxygel; Benzac; Eclaran; Lutsimed; PanOxyl; Peroxiben; ***Rus.:*** Basiron (Базирон); ***S.Afr.:*** Benoxyl; Benzac AC; Brevoxyl; Clearasil Benzoyl P; Dry & Clear; PanOxyl; ***Singapore:*** Acnacyl†; Akneroxid; Benzac; Brevoxyl; PanOxyl; ***Spain:*** Benoxygel; Oxiderma; PanOxyl; Peroxacne; Peroxiben; Solucel; Stop Espinilla Normaderm; ***Swed.:*** Basiron; Bexid†; Brevoxyl; Stioxyl†; ***Switz.:*** Acnefuge†; Akneroxid; Aknex; Basiron†; Benzac; Effacne†; Lubexyl; PanOxyl†; ***Thai.:*** Acnexyl†; Benzac; Brevoxyl; PanOxyl; ***Turk.:*** Aknefug BP; Aksil; Benzac AC; ***UK:*** Acnecide; Brevoxyl; Oxy; PanOxyl; ***USA:*** Acne Clear; Ambi 10; Benzac; Benziq; Brevoxyl; Clearasil; Clinac BPO; Del Aqua; Desquam; Fostex; NeoBenz; Oxy; PanOxyl; Triaz; Zaclir; ***Venez.:*** Acnex; Benoxyl†; Benzac AC; Ecuaderm; PanOxyl†; Solugel†.

Multi-ingredient: ***Arg.:*** Acnepas E; Benzamycin†; Clindacur; Clindoxyl; CP-Acne; Dermaclean; Duo Clindacin; Erimicin; Kitacne PB†; Pentoclave Combi; Perclin; Peroximicina; ***Austral.:*** Duac; ***Austria:*** Acne Plus; Clindoxyl; ***Belg.:*** Acneplus; Benzamycin; ***Braz.:*** Acnase; Akirol†; Benzac Eritromicina†; Clindoxyl; ***Canad.:*** Benzaclin; Benzamycin; Clindoxyl; ***Chile:*** Benzac Plus; Benzamycin†; Erimicin; Indoxyl; Klina; ***Cz.:*** Duac; ***Fr.:*** Epiduo; ***Ger.:*** Acne Plus; ***Gr.:*** Benzamycin†; Indoxyl; ***Hong Kong:*** Benzamycin; Duac; ***India:*** Persol Forte; ***Indon.:*** Benzolac Cl; Feldixid; ***Irl.:*** Benzamycin; Duac; Quinoderm; ***Israel:*** Benzamycin; ***Ital.:*** Acnidazil; Delta 80; Delta 80 Plus; Katoxyn; ***Mex.:*** Benzac Plus; Benzaclin; Benzamycin; Clindapack; Indoxyl; ***Neth.:*** Acnecare; Acnecure†; Acnidazil†; Duac; ***NZ:*** Duac; ***Philipp.:*** Acne Plus; ***Pol.:*** Duac; ***Port.:*** Duac; Zacne; ***S.Afr.:*** Acneclear; Acnidazil; Benzamycine†; Quinoderm; ***Singapore:*** Benzamycin; ***Spain:*** Duac; ***Swed.:*** Duac; ***Switz.:*** Acne Creme Plus; ***Turk.:*** Benzamycin; ***UK:*** Benzamycin†; Duac Once Daily; Quinoderm; ***USA:*** Benzaclin; Benzamycin; Duac; Sulfoxyl; Vanoxide-HC; Zacare Kit; Zoderm.

Bisoctrizole *(USAN, rINN)*

Bisoctrizol; Bisoctrizolum; FAT-75634; MBBT; Methylene Bis-Benzotriazolyl Tetramethylbutylphenol. 2,2′-Methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol].

Бизоктризол

$C_{41}H_{50}N_6O_2$ = 658.9.

CAS — 103597-45-1.

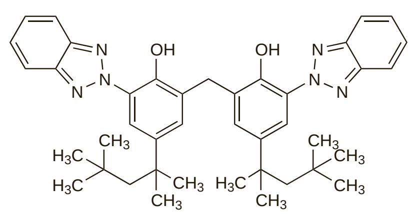

NOTE. Tinosorb M is a trade name that has been used for bisoctrizole.

Pharmacopoeias. In *US.*

USP 31 (Bisoctrizole). Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Profile

Bisoctrizole is used as a sunscreen (p.1576). It is effective against UVB and UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Calamine

Calamina; Kalamin; Prepared Calamine.

Каламин

Pharmacopoeias. In *Br., Chin., Int.,* and *US.*

BP 2008 (Calamine). It is a basic zinc carbonate coloured with ferric oxide. It is an amorphous, impalpable, pink or reddish-brown powder, the colour depending on the variety and amount of ferric oxide present and the process by which it is incorporated. Practically insoluble in water; it dissolves with effervescence in hydrochloric acid.

USP 31 (Calamine). It is zinc oxide with a small proportion of ferric oxide. A pink, odourless, fine powder. Insoluble in water; practically completely soluble in mineral acids.

Profile

Calamine has mild astringent and antipruritic actions and is used as a dusting powder, cream, lotion, or ointment in a variety of skin conditions although its value is uncertain.

Preparations

BP 2008: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Calamine Ointment;
USP 31: Calamine Topical Suspension; Phenolated Calamine Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Braz.: Calaphyl†; Ducilamina; ***Spain:*** Talquistina.

Multi-ingredient: ***Arg.:*** Acuaderm; Caladryl; Calcusan; Dermithan; Irricutan; Northicalm; Pinklot; Piracalamina; Pruripelen†; Prurisedan; Prurisedan Rosa; Urtikalma; ***Austral.:*** Animine; Calaband; Calamine Lotion; Dermalife Plus; Quinaband†; ***Belg.:*** Caladryl; ***Braz.:*** Caladerm†; Caladryl; Calamed; Calamina; Calamyn; Dermamina; Dermdryl†; Solardril Composto; ***Canad.:*** Aveeno Anti-Itch; Caladryl; Calamine Antihistamine; ***Chile:*** Ivarest; Pruriced; ***Fr.:*** Gel de Calamine; Pruriced; ***Hong Kong:*** Cadramine-V; Caladryl; Calamine-D†; ***India:*** Caladryl; Siloderm; ***Indon.:*** Caladine; Caladryl; Calamec; Calarex; Minos; Regata; ***Irl.:*** Benadryl; RBC; Vasogen; ***Israel:*** Baby Paste + Chamomile; Calamine Lotion; Calatrim cum Sulphur†; Calatrim†; ***Ital.:*** Mavipiu†; ***Malaysia:*** Dermoplex Calamine; Twinkle Calamine; ***Mex.:*** Caladryl; Dermocare; Procicar; ***NZ:*** Am-O-Lin; Lacto Calamine†; ***Philipp.:*** Caladryl; Calmoseptine; ***Port.:*** Benaderma com Calamina; Benaderma Pruridermase†; Caladryl; Pruridermase†; Solpic†; ***S.Afr.:*** Biohist; Caladryl; Calasthetic; Histamed; Lacto Calamine†; ***Singapore:*** Acne Clear; ***Thai.:*** Ancamin†; Cadinyl; Cadramine; Caladerm†; Caladryl; Calanol; Calapro; Hista; Lanol; M-D; ***Turk.:*** Caladryl; Diyenil; Kalmosan; Tanol; ***UK:*** Calaband; Lacto Calamine; Quinaband†; RBC; Swarm; Vasogen; ***USA:*** Caladryl; Calamycin; Dome-Paste; Ivarest; RA Lotion; ***Venez.:*** Borocanfor; Caladryl†; Calaminol; Calaminol Simple†; Calasyl Original; Micofeet.

Calcipotriol *(BAN, rINN)*

Calcipotriene *(USAN)*; Calcipotriolum; Kalcipotriol; Kalcypotriol; Kalsipotriol; Kalsipotrioli; MC-903. (5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol.

Кальципотриол

$C_{27}H_{40}O_3$ = 412.6.

CAS — 112828-00-9; 112965-21-6.

ATC — D05AX02.

ATC Vet — QD05AX02.

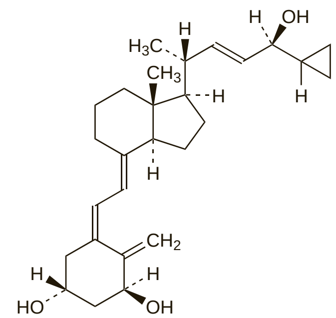

Pharmacopoeias. In *Eur.* (see p.vii), which also includes the monohydrate.

Ph. Eur. 6.2 (Calcipotriol, Anhydrous; Calcipotriolum Anhydricum). A white or almost white, crystalline powder. It is sensitive to heat and light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers at a temperature of −20° or below. Protect from light.

Ph. Eur. 6.2 (Calcipotriol Monohydrate; Calcipotriolum Monohydricum). A white or almost white, crystalline powder. It is sensitive to light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

The most frequent adverse effect associated with calcipotriol is skin irritation and it should not therefore be applied to the facial area. Symptoms may include burning, itching, erythema, and dry skin, but stopping therapy is seldom necessary. Aggravation of psoriasis may occur. Hypercalcaemia has occurred during treatment with calcipotriol and although rapidly reversible on withdrawal, it should not be used in patients with disorders of calcium metabolism. Other rare adverse effects may include skin atrophy, hyperpigmentation, and photosensitivity. Patients should limit or avoid excessive exposure to both natural and artificial sunlight, because *animal* studies have suggested that topical calcipotriol may enhance the effect of UV radiation to induce skin tumours.

Effects on calcium homoeostasis. Calcipotriol is a vitamin D derivative and therefore has the potential to cause hypercalcaemia and hypercalciuria. Up to December 1993, when about 150 000 patients in the UK had been treated with calcipotriol, the UK CSM had received 6 reports of hypercalcaemia and 2 of hypercalciuria.[1] Three of the patients with hypercalcaemia either had used doses in excess of the recommended maximum (see Uses and Administration, below) or had pustular or exfoliative psoriasis. Hypercalcaemia and hypercalciuria were reversible on withdrawal of calcipotriol. A study[2] investigating the effect of calcipotriol on urine calcium excretion found that use of the maximum recommended dose for 4 weeks produced increased urine calcium excretion, and the authors suggested that patients requiring the maximum dose of calcipotriol should be monitored for hypercalciuria before and during treatment. A review[3] of the effects of vitamin D analogues on calcium homoeostasis concluded that patients with unstable psoriasis are at particular risk of

The symbol † denotes a preparation no longer actively marketed

toxicity from calcipotriol and that measurement of urine calcium excretion is a more sensitive indicator of toxicity than serum-calcium concentrations.

1. Committee on Safety of Medicines/Medicines Control Agency. Dovonex ointment (calcipotriol). *Current Problems* 1994; **20:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
2. Berth-Jones J, *et al.* Urine calcium excretion during treatment of psoriasis with topical calcipotriol. *Br J Dermatol* 1993; **129:** 411–14.
3. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135:** 347–54.

Hyperpigmentation. Hyperpigmentation occurred at the site of calcipotriol application in 2 patients after use with PUVA-bath therapy (a topical psoralen with UVA irradiation) for psoriasis.[1] The effect persisted for at least 4 months in these patients. Hyperpigmentation of psoriatic plaques was also reported in a patient treated with topical calcipotriol and UVB phototherapy.[2] Abnormal lentiginous pigmentation of psoriatic plaques occurred in a patient treated with topical calcipotriol for psoriasis, which had worsened during chemotherapy for melanoma, and was still present 2 years after stopping chemotherapy and calcipotriol.[3] The authors also noted that melanoma can cause pigment changes and may have played a role in this case.

There has been some interest in the hyperpigmentary effects of calcipotriol for the possible treatment of vitiligo (see Skin Disorders, below).

1. Gläser R, *et al.* Hyperpigmentation due to topical calcipotriol and photochemotherapy in two psoriatic patients. *Br J Dermatol* 1998; **139:** 148–51.
2. Rütter A, Schwarz T. Ausgeprägte Hyperpigmentierung in psoriatischen Plaques als Folge einer Kombinationsbehandlung mit UVB-311 nm und Calcipotriol. *Hautarzt* 2000; **51:** 431–3.
3. Oláh J, *et al.* Pigment anomaly caused by calcipotriol in a subject with melanoma. *J Eur Acad Dermatol Venereol* 2004; **18:** 113–15.

Uses and Administration

Calcipotriol is a vitamin D_3 derivative. *In vitro* it appears to induce differentiation and to suppress proliferation of keratinocytes.

Calcipotriol is used in a cream or ointment for the management of plaque psoriasis and as a solution in the management of scalp psoriasis; the concentration of calcipotriol used is 0.005%. Applications should be made once or twice daily. No more than 100 g of cream or ointment, or 60 mL of scalp solution, should be applied in one week. If both are used, the limit is 60 g of cream or ointment with 30 mL of scalp solution, or 30 g of cream or ointment with 60 mL of scalp solution.

For the use of calcipotriol in children, see below.

Administration in children. Topical calcipotriol may be used in the management of plaque psoriasis in children. In the UK, the cream or ointment (0.005%) may be applied twice daily. The maximum applied in one week should be 50 g in children aged 6 to 12 years, and 75 g in children more than 12 years of age. The *BNFC* also suggests that under specialist supervision the scalp solution (0.005%) may be applied twice daily to children aged 6 years and over for the treatment of scalp psoriasis; no more than 30 mL of the solution should be applied in one week to those aged 6 to 12 years, with older children receiving a maximum of 45 mL in one week. When preparations are used together, the *BNFC* recommends a maximum total calcipotriol dose of 2.5 mg in any one week for children aged 6 to 12 years (e.g. 20 mL of the scalp solution with 30 g of the cream or ointment); in older children, the maximum is 3.75 mg in any one week (e.g. 30 mL of the scalp solution with 45 g of the cream or ointment). In the UK, the scalp solution is not licensed for use in children and the cream and ointment are not licensed for use in children under 6 years; however, safety and efficacy have been reported in small 8-week studies that have included children as young as 2 years old.[1-3] There are also a few case reports of topical calcipotriol use in infants with psoriasis, aged 3 months[4] and 6 months.[5]

1. Darley CR, *et al.* Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; **135:** 390–3.
2. Oranje AP, *et al.* Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; **36:** 203–8.
3. Patrizi A, *et al.* Topical calcipotriol in childhood psoriasis. *Acta Derm Venereol* 1999; **79:** 477.
4. Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; **68:** 341–4.
5. Choi YJ, *et al.* Infantile psoriasis: successful treatment with topical calcipotriol. *Pediatr Dermatol* 2000; **17:** 242–4.

Skin disorders. Topical drugs are the treatment of first choice for *chronic plaque psoriasis* (p.1583). Calcipotriol, dithranol, and coal tar are commonly used for mild to moderate forms of the disorder. Calcipotriol inhibits cell proliferation and increases cell differentiation by binding to vitamin D receptors, thus inhibiting epidermal growth and returning some normality to the skin's structure. It is also possible that calcipotriol affects immunological and inflammatory processes in the skin.[1] Topical calcipotriol has been shown to be effective in mild to moderate chronic plaque psoriasis; it is at least as effective as dithranol, coal tar, and corticosteroids, and has been reported to be superior in a number of studies.[1,2] Calcipotriol is also more cosmetically acceptable than dithranol, which can stain, and coal tar, which can have an unpleasant smell. Benefits have been maintained with long-term use, and repeat courses are effective for the management of relapse. Although there are fewer studies in children, calcipotriol has been reported to be safe and effective in studies including children aged 2 to 15 years[1] (see also Administration in Children, above). Calcipotriol, applied as a topical solution, is also effective for *scalp psoriasis*.[3] When solutions of calcipotriol and betamethasone were compared for mild to moderate scalp psoriasis,[4] calcipotriol produced a satisfactory response, but betamethasone was more effective and was associated with less irritation of the scalp and face. Similar results were reported in a study comparing calcipotriol with clobetasol propionate in moderate to severe scalp psoriasis.[5] In a study of patients with *nail psoriasis* about half received benefit from calcipotriol ointment over a 3 to 5 month treatment period.[6] This result was similar to that found for patients treated with betamethasone and salicylic acid ointment.

Use of calcipotriol with other antipsoriatic drugs may be beneficial. The combination of calcipotriol with a topical corticosteroid is more effective than monotherapy with either of these.[1,7,8] Treatment for up to 4 weeks is usually effective and may be followed by maintenance calcipotriol monotherapy.[9] Topical calcipotriol with systemic therapies has also been tried. There is evidence that the response to oral ciclosporin or acitretin can be improved,[1] as can the response to phototherapy (UVB) or photochemotherapy (PUVA).[1,10] Combination therapy may also reduce the cumulative dose of acitretin, UVB, or PUVA required to achieve clearance or marked improvement of psoriasis, potentially reducing the risk of long-term adverse effects from these treatments.[1,10,11] However, because of the potential for the vehicle of topical calcipotriol preparations to block UV irradiation, they should be applied at least 2 hours before irradiation.[12] Despite promising reports from combination therapy using topical calcipotriol with systemic treatment, phototherapy, or photochemotherapy, a systematic review[13] found that although there can be a measurable additive effect, it may not be clinically significant in patients' own assessments.

A 2-week course of high-dose calcipotriol (up to 360 g of 0.005% ointment weekly) has been used for inpatient treatment of extensive psoriasis, followed by the usual recommended dose (up to 100 g weekly) for residual psoriasis.[14] Asymptomatic hypercalcaemia and hypercalciuria occurred in some patients, and the authors suggested that the monitoring of calcium homoeostasis is mandatory with this regimen (see also Effects on Calcium Homoeostasis, above). Relapse occurred in most patients within one year.

Beneficial results with calcipotriol have also been reported in small numbers of patients with various skin disorders[15] including *acrodermatitis continua of Hallopeau*, *confluent and reticulated papillomatosis*, *congenital ichthyosis*, *inflammatory linear verrucous epidermal nevus*, *lichen amyloidosis*, *morphea or linear scleroderma*, *pityriasis rubra pilaris*, *prurigo nodularis*, and *seborrhoeic dermatitis*. A small open study[16] has indicated that topical calcipotriol may be effective in the treatment of oral *leucoplakia* (see under Bleomycin, p.688). It has also been tried, alone or with UVA or UVB, or a topical corticosteroid, in the treatment of *vitiligo*[17-21] (see Pigmentation Disorders, p.1582), but results have been mixed.

1. Scott LJ, *et al.* Calcipotriol ointment: a review of its use in the management of psoriasis. *Am J Clin Dermatol* 2001; **2:** 95–120.
2. Ashcroft DM, *et al.* Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; **320:** 963–7.
3. Thaçi D, *et al.* Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology* 2001; **203:** 153–6.
4. Klaber MR, *et al.* Comparative effects of calcipotriol solution (50 micrograms/mL) and betamethasone 17-valerate solution (1 mg/mL) in the treatment of scalp psoriasis. *Br J Dermatol* 1994; **131:** 678–83.
5. Reygagne P, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; **16:** 31–6.
6. Tosti A, *et al.* Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998; **139:** 655–9.
7. Fenton C, Plosker GL. Calcipotriol/betamethasone dipropionate: a review of its use in the treatment of psoriasis vulgaris. *Am J Clin Dermatol* 2004; **5:** 463–78.
8. Kragballe K, van de Kerkhof PCM. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20:** 39–44.
9. White S, *et al.* Use of calcipotriene cream (Dovonex cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex): a randomized, parallel-group clinical trial. *Am J Clin Dermatol* 2006; **7:** 177–84.
10. Torras H, *et al.* A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *J Dermatol Treat* 2004; **15:** 98–103.
11. Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol* 2003; **149:** 146–50.
12. De Rie MA, *et al.* Calcipotriol ointment and cream or their vehicles applied immediately before irradiation inhibit ultraviolet B-induced erythema. *Br J Dermatol* 2000; **142:** 1160–5.
13. Ashcroft DM, *et al.* Combination regimens of topical calcipotriene in chronic plaque psoriasis: systematic review of efficacy and tolerability. *Arch Dermatol* 2000; **136:** 1536–43.
14. Bleiker TO, *et al.* Long-term outcome of severe chronic plaque psoriasis following treatment with high-dose topical calcipotriol. *Br J Dermatol* 1998; **139:** 285–6.
15. Holm EA, Jemec GBE. The therapeutic potential of calcipotriol in diseases other than psoriasis. *Int J Dermatol* 2002; **41:** 38–43.
16. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30:** 402–6.
17. Ameen M, *et al.* Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. *Br J Dermatol* 2001; **145:** 476–9.
18. Chiaverini C, *et al.* Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venereol* 2002; **16:** 137–8.
19. Kumaran MS, *et al.* Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20:** 269–73.
20. Goktas E, *et al.* Combination of narrow band UVB and topical calcipotriol for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20:** 553–7.
21. Arca E, *et al.* Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *J Dermatol* 2006; **33:** 338–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Daivonex; Dermocal†; ***Austral.:*** Daivonex; ***Austria:*** Psorcutan; ***Belg.:*** Daivonex; ***Braz.:*** Daivonex; ***Canad.:*** Dovonex; ***Chile:*** Daivonex; ***Cz.:*** Daivonex; Psorcutan†; ***Denm.:*** Daivonex; ***Fin.:*** Daivonex; ***Fr.:*** Daivonex; ***Ger.:*** Daivonex; Psorcutan; ***Gr.:*** Cipocal; Dovonex; F-Psorin; Psoraffect; ***Hong Kong:*** Daivonex; ***Hung.:*** Daivonex; ***India:*** Daivonex; ***Indon.:*** Daivonex; ***Irl.:*** Dovonex; ***Israel:*** Daivonex; ***Ital.:*** Daivonex; Psorcutan; ***Jpn:*** Dovonex; ***Malaysia:*** Daivobet; Daivonex; ***Mex.:*** Daivonex; Eukadar; ***Neth.:*** Daivonex; ***Norw.:*** Daivonex; ***NZ:*** Daivonex; ***Philipp.:*** Daivonex; ***Pol.:*** Daivonex; ***Port.:*** Daivonex; ***Rus.:*** Daivonex (Дайвонекс); ***S.Afr.:*** Dovonex; ***Singapore:*** Daivonex; ***Spain:*** Daivonex; ***Swed.:*** Daivonex; ***Switz.:*** Daivonex; ***Thai.:*** Daivonex; ***Turk.:*** Psorcutan; ***UK:*** Dovonex; ***USA:*** Dovonex; ***Venez.:*** Daivonex†.

Multi-ingredient: ***Austral.:*** Daivobet; ***Austria:*** Psorcutan Beta; ***Belg.:*** Dovobet; ***Braz.:*** Daivobet; ***Canad.:*** Dovobet; ***Cz.:*** Daivobet; ***Denm.:*** Daivobet; ***Fin.:*** Daivobet; ***Fr.:*** Daivobet; ***Ger.:*** Daivobet; Psorcutan Beta; ***Gr.:*** Dovobet; ***Hong Kong:*** Daivobet; ***Hung.:*** Daivobet; ***Indon.:*** Daivobet; ***Irl.:*** Dovobet; ***Israel:*** Daivobet; ***Ital.:*** Dovobet; Token; ***Mex.:*** Daivobet; ***Neth.:*** Dovobet; ***Norw.:*** Daivobet; ***NZ:*** Daivobet; ***Philipp.:*** Daivobet; ***Pol.:*** Daivobet; ***Port.:*** Daivobet; ***Rus.:*** Daivobet (Дайвобет); ***Singapore:*** Daivobet; ***Spain:*** Daivobet; ***Swed.:*** Daivobet; ***Switz.:*** Daivobet; ***Thai.:*** Daivobet; ***UK:*** Dovobet; ***USA:*** Taclonex.

Centella

Azijinės centelės žolė; Ázsiai gázlófű; Centellae asiaticae herba; Herba Centellae; Hidrocótilo; Hydrocotyle; Indian Pennywort; Nať centely asijské; Rohtosammakonputki; Sallatsspikblad.

Центелла Азиатская (*Centella asiatica*)

CAS — 18449-41-7 (madecassic acid); 464-92-6 (asiatic acid); 16830-15-2 (asiaticoside).

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Centella). The dried, fragmented aerial parts of *Centella asiatica*. It contains not less than 6% of total triterpenoid derivatives, expressed as asiaticoside, calculated with reference to dried drug. Protect from light.

Profile

Centella contains madecassic acid, asiatic acid, and asiaticoside. It has been used topically and orally in the management of wounds, ulcers, and keloid scars.

The names gotu kola, gotu cola, and gota kola are used for *Centella asiatica* (=*Hydrocotyle asiatica*) in herbal medicine. Centella is also used in homoeopathic medicine.

Adverse effects. Contact dermatitis has been reported with the topical use of centella.[1] There is also a report of 3 cases of hepatotoxicity associated with ingestion of centella, all presenting with jaundice, painful hepatomegaly, and granulomatous hepatitis with areas of necrosis.[2]

1. Gonzalo Garijo MA, *et al.* Allergic contact dermatitis due to Centella asiatica: a new case. *Allergol Immunopathol (Madr)* 1996; **24:** 132–4.
2. Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. *Rev Esp Enferm Dig* 2005; **97:** 115–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gotu Kola†; Pertusan†; Remiderm†; ***Austria:*** Madecassol; ***Belg.:*** Madecassol; ***Braz.:*** Centelax; Centella-Vit; ***Chile:*** Celulase; Celulase Plus; Centabel; Escar T; Madecassol; ***Fr.:*** Madecassol; ***Gr.:*** Madecassol; ***Hong Kong:*** Madecassol; ***Indon.:*** Fitocassol; Lanakeloid; Madecassol; ***Ital.:*** Centellase; ***Malaysia:*** Lanakeloid; ***Mex.:*** Madecassol; ***Port.:*** Madecassol; ***Singapore:*** Centellase; Centica; ***Spain:*** Blastoestimulina; ***Thai.:*** Madecassol†; ***Turk.:*** Madecassol; ***Venez.:*** Litonate; Madecassol; Triffadiane†.

Multi-ingredient: ***Arg.:*** Celu-Atlas; Centella Asiatica Compuesta; Centella Asiatica Diates; Centella Asiatica Vital; Centella Incaico; Centella Queen Complex; Centella Queen Reductora; Centellacrom; Centellase de Centella Queen; Centellase Gel; Clevosan; Enlinea†; Estri-Atlas; Garcinol Max; Ginal Cent; Ginkan; Herbaccion Celfin; Lidersoft†; Linfol Cicatrizante; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Mailen; Moragen; Nio Marine; No-Gras; Ovumix; Pentol; Redudiet; Septigyn; Vagicural Plus; Venoful; VNS 45; ***Austral.:*** Extralife Leg-Care; ***Braz.:*** Composto Anticelulítico†; Composto Emagrecedor†; Derm'attive 10†; Emagrevit†;

Chile: Celulase Con Neomicina; Cicapost; Dermaglos Plus†; Escar T-Neomicina; Madecassol Neomicina†; Ureadin Rx DB; ***Fr.:*** Calmiphase†; Cicatridine; Fadiamone; Madecassol Neomycine Hydrocortisone†; ***Indon.:*** Lanakeloid-E; Venos; ***Ital.:*** Angiorex Complex; Angioton; Angiovein; Capill; Capill Venogel; Centella Complex; Centeril H; Dermilia Flebozin; Emmenoiasi; Flebo-Si; Flebofort; Flebolider; Gelovis; Levital Plus; Neomyrt Plus; Osmogel; Pik Gel; Varicofit; Venactive; ***Malaysia:*** Total Man†; ***Mex.:*** Madecassol C; Madecassol N; ***Philipp.:*** Memori Plus; Memory DD; Ruflex; ***Port.:*** Antiestrias; ***Spain:*** Blastoestimulina; Cemalyt; Nesfare; ***Venez.:*** Celyth's.

Cerous Nitrate

Cerio, nitrato de; Cerium Nitrate; Ceru(III) azotan.

Церия Нитрат

$Ce(NO_3)_3$ = 326.1.

CAS — 10108-73-3.

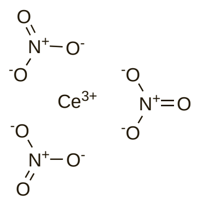

Profile

Cerous nitrate has been used topically, mainly with sulfadiazine silver, in the treatment of burns.

◊ References.

1. Garner JP, Heppell PS. Cerium nitrate in the management of burns. *Burns* 2005; **31:** 539–47.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Sulfatral-Cerio†; ***Belg.:*** Flammacerium; ***Braz.:*** Dermacerium; ***Cz.:*** Flammacerium†; ***Fr.:*** Flammacerium; ***Gr.:*** Flammacerium; ***Neth.:*** Flammacerium; ***Philipp.:*** Flammacerium; ***Pol.:*** Flammacerium; ***UK:*** Flammacerium.

Cinoxate *(USAN, rINN)*

Cinoxato; Cinoxatum. 2-Ethoxyethyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 2-ethoxyethyl ester.

Циноксат

$C_{14}H_{18}O_4$ = 250.3.

CAS — 104-28-9.

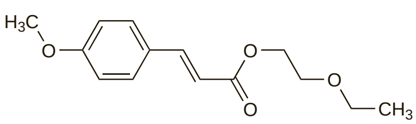

Profile

Cinoxate, a substituted cinnamate, is a sunscreen (p.1576) with actions similar to those of octinoxate (p.1608). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Crilanomer *(rINN)*

Acrylonitrile-starch Copolymer; Crilanomère; Crilanómero; Crilanomerum; ZK-94006. A starch polymer with acrylonitrile.

Криланомер

CAS — 37291-07-9.

ATC — D03AX09.

ATC Vet — QD03AX09.

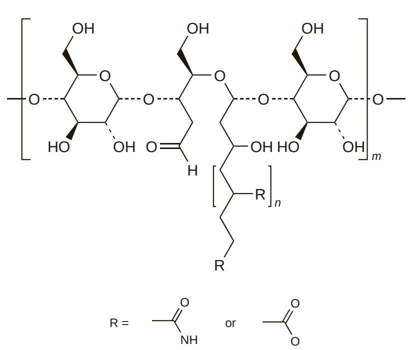

Profile

Crilanomer is a starch copolymer used as a hydrogel wound dressing in the management of wounds.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Intrasite; ***S.Afr.:*** Intrasite.

Crotamiton *(BAN, rINN)*

Crotam; Crotamitón; Crotamitonum; Krotamiton; Krotamitonas; Krotamitoni. *N*-Ethyl-*N*-*o*-tolylcrotonamide; *N*-Ethylcrotono-*o*-toluidide; *N*-Ethyl-*N*-(2-methylphenyl)-2-butenamide.

Кротамитон

$C_{13}H_{17}NO$ = 203.3.

CAS — 483-63-6.

ATC Vet — QP53AX04.

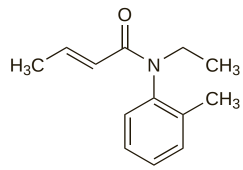

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Crotamiton). A colourless or pale yellow oily liquid. It solidifies partly or completely at low temperatures. It is mainly the (*E*)-isomer, with not more than 15% of the (*Z*)-isomer. Slightly soluble in water; miscible with alcohol. Protect from light.

USP 31 (Crotamiton). A colourless to slightly yellowish oil with a faint amine-like odour. It is a mixture of *cis*- and *trans*-isomers. Soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Topical use of crotamiton occasionally causes irritation. There have been rare reports of hypersensitivity reactions. Crotamiton should not be used in patients with acute exudative dermatitis. It should not be applied near the eyes, mouth, or other mucous membranes or on excoriated skin.

Ingestion of crotamiton may cause burning and irritation of oral, oesophageal, and gastric mucosa with nausea, vomiting, and abdominal pain.

Overdosage. A 23-year-old woman developed tonic-clonic seizures, requiring treatment with diazepam, after ingestion of a crotamiton emulsion.[1] Other hospital treatment included gastric lavage, activated charcoal, and metoclopramide. Crotamiton was detected in serum at a concentration of 34 micrograms/mL and was also detectable with several metabolites in the urine. Reference was also made to a report of a 2½-month-old child who had developed pallor and cyanosis after excessive dermal application of a crotamiton cream.

1. Meredith TJ, *et al.* Crotamiton overdose. *Hum Exp Toxicol* 1990; **9:** 57.

Uses and Administration

Crotamiton is used as an antipruritic (p.1582), although its value is considered uncertain (see also below). It is applied as a 10% cream or lotion 2 or 3 times daily; children aged less than 3 years may receive one application daily.

Crotamiton has also been used as an acaricide in the treatment of scabies but other more effective drugs are usually preferred (p.2035). The 10% cream or lotion is applied, after first bathing and drying, to the whole of the body-surface below the chin, particular attention being paid to body folds and creases. A second application should be applied 24 hours later but it may need to be used once daily up to a total of 5 days to be effective.

Pruritus. A double-blind study in 31 patients[1] found that 10% crotamiton lotion was no more effective an antipruritic than its vehicle.

1. Smith EB, *et al.* Crotamiton lotion in pruritus. *Int J Dermatol* 1984; **23:** 684–5.

Preparations

BP 2008: Crotamiton Cream; Crotamiton Lotion;
USP 31: Crotamiton Cream.

Proprietary Preparations (details are given in Part 3)

Austral.: Eurax; ***Austria:*** Eurax; ***Belg.:*** Eurax; ***Canad.:*** Eurax; ***Chile:*** Eurax; ***Fr.:*** Eurax; ***Ger.:*** Crotamitex; Eraxil; ***Hong Kong:*** Eurax; Eurosin; Marax; ***India:*** Crotorax; ***Irl.:*** Eurax; ***Israel:*** Eurax; Scabicin; ***Ital.:*** Eurax; ***Malaysia:*** Crotorax; Eurax; Moz-Bite; ***Mex.:*** Eurax; ***Norw.:*** Eurax; ***NZ:*** Eurax; ***Philipp.:*** Congen; Eurax; Scabirax; ***Port.:*** Eurax; Scabicin; ***S.Afr.:*** Eurax; ***Singapore:*** Eurax; Moz-Bite; ***Spain:*** Euraxil; ***Switz.:*** Eurax; ***UK:*** Eurax; ***USA:*** Eurax; ***Venez.:*** Crotanol.

Multi-ingredient: ***Arg.:*** Anastim con RTH; Empecid Pie; ***Fr.:*** Acarcid†; Kelual DS; Triazol†; ***India:*** Crotorax-HC; ***Irl.:*** Eurax-Hydrocortisone; ***Israel:*** Duo-Scabil; ***Jpn:*** Una A Gel; ***Malaysia:*** Crotamiton H; ***UK:*** Eurax-Hydrocortisone; ***Venez.:*** Kertyol.

Dextranomer *(BAN, rINN)*

Dekstranomeeri; Dextranomère; Dextranómero; Dextranomerum. Dextran cross-linked with epichlorohydrin (1-chloro-2,3-epoxypropane); Dextran 2,3-dihydroxypropyl 2-hydroxy-1,3-propanediyl ether.

Декстраномер

CAS — 56087-11-7.

ATC — D03AX02.

ATC Vet — QD03AX02.

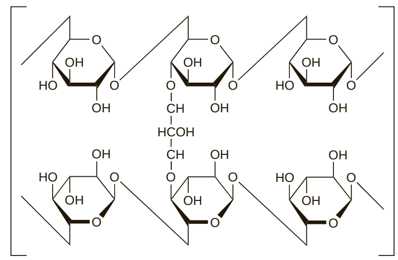

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dextranomer). White or almost white, spherical beads. Practically insoluble in water. It swells in water and electrolyte solutions

Adverse Effects and Precautions

Dextranomer can cause pain during dressing changes in some patients, and bleeding, blistering, and erythema have been reported occasionally. It should not be used in deep wounds or cavities from which it cannot be easily removed, nor should it be used on dry wounds. Care should be exercised when paste formulations of dextranomer are used near the eyes.

Spillage may render surfaces very slippery.

Viscous gel implants containing dextranomer, injected submucosally around the urethra, can cause transient urinary retention. Injection site reactions including mass, abscess, and pseudocyst formation have been reported.

Uses and Administration

The action of dextranomer as a wound dressing depends upon its ability to absorb up to 4 times its weight of fluid, including dissolved and suspended material of molecular weight up to about 5000.

Dextranomer is used for the cleansing of exudative and infected burns (p.1578), wounds and ulcers (p.1585), and for preparation for skin grafting.

The wound is cleansed with sterile water or saline and allowed to remain wet; dextranomer in the form of spherical beads is sprinkled on to a depth of at least 3 to 6 mm and covered with a sterile dressing. Occlusive dressings are not recommended as they may lead to maceration around the wound. The dextranomer can be renewed up to 5 times daily (usually once or twice daily) when the layer has become saturated with exudate; the old layer is washed off with a stream of sterile water or saline before renewal. All dextranomer must be removed before skin grafting. Dextranomer may also be applied as a paste (either ready-made or prepared by mixing dextranomer beads with glycerol).

Implants containing dextranomer microspheres in a stabilised hyaluronic acid carrier gel (NASHA/Dx) are available for injection. In female stress urinary incontinence (p.2180), 4 injections each containing 35 mg of dextranomer are injected into the submucosa of the urethra. Connective tissue gradually surrounds the microspheres, and the resulting augmented tissue helps to restore urinary continence. A second implantation may be performed if necessary, but no sooner than 6 weeks after the first. In vesicoureteral reflux in children, up to 50 mg may be injected into the submucosa of the ureter, creating a bulge close to the ureteral orifice. The procedure may be repeated after 3 months if necessary.

◊ References.

1. Stenberg ÅM, *et al.* Urethral injection for stress urinary incontinence: long-term results with dextranomer/hyaluronic acid copolymer. *Int Urogynecol J* 2003; **14:** 335–8.
2. van Kerrebroeck P, *et al.* Efficacy and safety of a novel system (NASHA/Dx copolymer using the Implacer device) for treatment of stress urinary incontinence. *Urology* 2004; **64:** 276–81.
3. Chapple CR, *et al.* An open, multicentre study of NASHA/Dx Gel (Zuidex) for the treatment of stress urinary incontinence. *Eur Urol* 2005; **48:** 488–94.
4. Dean GE, Doumanian LR. The extended use of Deflux (dextranomer/hyaluronic acid) in pediatric urology. *Curr Urol Rep* 2006; **7:** 143–8.
5. Routh JC, *et al.* Single center experience with endoscopic management of vesicoureteral reflux in children. *J Urol (Baltimore)* 2006; **175:** 1889–93.
6. Yu RN, Roth DR. Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics* 2006; **118:** 698–703.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Debrisan†; ***Ger.:*** Debrisorb†; ***Hong Kong:*** Debrisan†; ***Hung.:*** Crupodex†; ***Irl.:*** Debrisan†; ***Ital.:*** Debrisan; ***Mex.:*** Debrisan†; ***Pol.:*** Acudex; ***S.Afr.:*** Debrisan; ***UK:*** Debrisan†; ***USA:*** Debrisan.

Multi-ingredient: *UK:* Zuidex; ***USA:*** Deflux.

Dibenzoylmethane

Dibenzoilmetano. 1,3-Diphenyl-1,3-propanedione.

Дибензоилметан

$C_{15}H_{12}O_2$ = 224.3.

CAS — 120-46-7.

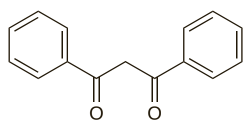

Profile

Dibenzoylmethane is a sunscreen (p.1576) with actions similar to those of avobenzone (p.1589). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Dihydroxyacetone

DHA; Dihidroxiacetona; Ketotriose. 1,3-Dihydroxypropan-2-one.

Дигидроксиацетон

$C_3H_6O_3$ = 90.08.

CAS — 96-26-4.

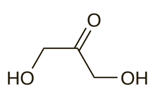

NOTE. DHA is also used as a synonym for docosahexaenoic acid (p.1362).

Pharmacopoeias. In *US.*

USP 31 (Dihydroxyacetone). A white to off-white crystalline powder. The monomeric form is freely soluble in water, in alcohol, and in ether; the dimeric form is freely soluble in water, soluble in alcohol, and sparingly soluble in ether. A 5% solution in water has a pH between 4.0 and 6.0. Store at a temperature of 8° to 15° in airtight containers.

Adverse Effects and Precautions

Skin irritation from dihydroxyacetone occurs rarely; rashes and allergic dermatitis have been reported. Contact with eyes, abraded skin, and clothing should be avoided.

Uses and Administration

Application to the skin of preparations containing dihydroxyacetone slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin.

A single application may give rise to a patchy appearance; progressive darkening of the skin results from repeated use until a point is reached when the maximum effect is achieved. If the treatment is stopped the colour starts to fade after about 2 days and disappears completely within 8 to 14 days as the external epidermal cells are lost by normal attrition.

Preparations usually contain 5% of dihydroxyacetone and have been used to camouflage vitiligo (see Pigmentation Disorders, p.1582) or to produce an artificial suntan. Some preparations include sunscreens since the pigmentation produced gives no protection against sunburn.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Autohelios†; Eurocolor Sin Sol; Ikx Autobronceante; Leche Autobronceadora†; Lelco sin Sol; ***Austral.:*** Le Tan Fast Extra Dark†; Le Tan Fast Self Tan†; Vitadye; ***Braz.:*** Autohelios; ***Chile:*** Fotoprotectores; Leche Autobronceadora Cara Y Cuerpo; Neutrogena Bronceador; ROC Minesol Bronze; Sans Soleil Skin Ceuticals†; ***Malaysia:*** Vitadye†; ***Mex.:*** Dermacrom; ***USA:*** Chromelin Complexion Blender.

Multi-ingredient: *Arg.:* Fotosol Ultra Autobronceante; Polysianes Autobronceante; ***Austral.:*** Le Tan Fast Plus†; ***Braz.:*** Sunmax Autobronzeador; ***UK:*** ViTicolor; ***USA:*** QT.

Diolamine Methoxycinnamate

Diolamine *p*-Methoxycinnamate *(pINNM)*; DEA-Methoxycinnamate; Diethanolamine Methoxycinnamate; Diolamina metoxicinnamato; Diolamine Méthoxycinnamate; Diolaminum Metoxicinnamatum. *p*-Methoxycinnamic acid compound with 2,2′-iminodiethanol (1:1).

Диоламин Метоксисинамат

$C_{10}H_{10}O_3,C_4H_{11}NO_2$ = 283.3.

CAS — 56265-46-4.

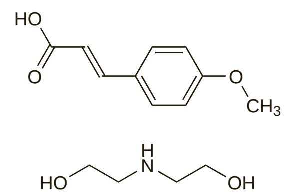

Profile

Diolamine methoxycinnamate, a compounded substituted cinnamate, is a sunscreen (p.1576) with actions similar to those of octinoxate (p.1608). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Dioxybenzone *(USAN, rINN)*

Benzofenon-8; Benzophenone-8; Dioxibenzona; Dioxybenzonum; NSC-56769. 2,2′-Dihydroxy-4-methoxybenzophenone.

Диоксибензон

$C_{14}H_{12}O_4$ = 244.2.

CAS — 131-53-3.

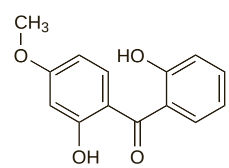

Pharmacopoeias. In *US.*

USP 31 (Dioxybenzone). A yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Dioxybenzone, a substituted benzophenone, is a sunscreen (p.1576) with actions similar to those of oxybenzone (p.1608). It is effective against UVB and some UVA light (for definitions, see p.1580).

Preparations

USP 31: Dioxybenzone and Oxybenzone Cream.

Proprietary Preparations some preparations are listed in Part 3.

Diphencyprone

Difenciprona. 2,3-Diphenylcyclopropenone-1.

Дифенципрон

$C_{15}H_{10}O$ = 206.2.

CAS — 886-38-4.

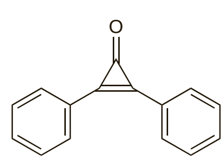

Profile

Diphencyprone has been applied as a contact sensitiser for the treatment of alopecia. It has also been tried in warts.

Adverse effects. Diphencyprone is considered to lack serious adverse effects but some patients may not be able to tolerate the induced hypersensitivity reaction. There have been reports of generalised urticaria and dermographism, sometimes severe, following the use of diphencyprone.[1-5] In another case, a severe reaction of urticaria and dermographism, which lasted several months, occurred after the initial sensitisation dose.[6] Allergy to diphencyprone has been reported in medical and nursing staff in spite of taking protective precautions during its application.[7] A patient who received diphencyprone treatment for warts developed a widespread pruritic rash and palpitations due to ventricular extrasystoles.[1] Vitiligo has also been reported in patients treated with diphencyprone[8-10] and it has been suggested that this might be due to unmasking of subclinical vitiligo.[8,9] Erythema multiforme-like eruptions have been associated with the topical application of diphencyprone.[11,12]

1. Lane PR, Hogan DJ. Diphencyprone. *J Am Acad Dermatol* 1988; **19:** 364–5.
2. Tosti A, *et al.* Contact urticaria during topical immunotherapy. *Contact Dermatitis* 1989; **21:** 196–7.
3. Skrebova N, *et al.* Severe dermographism after topical therapy with diphenylcyclopropenone for alopecia universalis. *Contact Dermatitis* 2000; **42:** 212–15.
4. Francomano M, Seidenari S. Urticaria after topical immunotherapy with diphenylcyclopropenone. *Contact Dermatitis* 2002; **47:** 310–11.
5. Short KA, Higgins EM. Urticaria as a side-effect of diphencyprone therapy for resistant viral warts. *Br J Dermatol* 2005; **152:** 583–5.
6. Alam M, *et al.* Severe urticarial reaction to diphenylcyclopropenone therapy for alopecia areata. *J Am Acad Dermatol* 1999; **40:** 110–12.
7. Shah M, *et al.* Hazards in the use of diphencyprone. *Br J Dermatol* 1996; **134:** 1153.
8. Hatzis J, *et al.* Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica* 1988; **177:** 146–8.
9. Duhra P, Foulds IS. Persistent vitiligo induced by diphencyprone. *Br J Dermatol* 1990; **123:** 415–16.
10. Henderson CA, Ilchyshyn A. Vitiligo complicating diphencyprone sensitization therapy for alopecia universalis. *Br J Dermatol* 1995; **133:** 496–7.
11. Perret CM, *et al.* Erythema multiforme-like eruptions: a rare side effect of topical immunotherapy with diphenylcyclopropenone. *Dermatologica* 1990; **180:** 5–7.
12. Oh C-W, *et al.* Bullous erythema multiforme following topical diphenylcyclopropenone application. *Contact Dermatitis* 1998; **38:** 220–1.

Alopecia. Diphencyprone has been used as a contact sensitiser in the treatment of various forms of alopecia (p.1577) including areata, totalis, and universalis. Case series reports generally describe treatment of adults, but some groups have also included adolescents and children, and some have reported solely on treatment in children.[1,2]

Initial sensitisation is usually achieved by applying a 2% solution of diphencyprone in acetone to a small area of scalp, which may be repeated if necessary beneath plastic occlusion if adequate sensitisation is not produced. Thereafter, weaker concentrations are applied once weekly and gradually increased in strength to produce erythema and pruritus for 36 to 48 hours post-therapy. Concentrations that have been used vary between reports and the first treatment application may be as dilute as 0.00001%, with further applications gradually increased to up to 2%. Only one side of the scalp is treated until the optimum concentration is found, in order to prevent a widespread adverse reaction. Once hair regrowth has started on the treated side the applications may be extended to the entire scalp.[1-8] As well as erythema and pruritus, patients usually experience transient eczema and regional lymph node swelling.[2,5,7,8]

Hair regrowth may not start for several months,[4,6,8] and the required duration of therapy can vary considerably; at least 8 months of treatment may be required,[3,6] and up to 12 months[1,2] or more[4,6] has been reported. Not all patients will respond to treatment and reported response rates vary, although these have probably been influenced by the different definitions used for complete, partial, and no response. Overall, however, regrowth of hair can occur in up to about 70% of patients, with around half of these having complete regrowth.[1,4,6-8] Some reports have attempted to determine which factors might be associated with clinical response to diphencyprone. There is disagreement between studies but some possible unfavourable prognostic factors include extensive involvement,[4,6,8] younger age at onset,[8] longer disease duration before treatment,[5,7] and a history of atopic eczema.[4,7] The need for high diphencyprone concentrations and prolonged therapy have also been associated with a less favourable outcome.[8]

Despite these rates of response a significant number of patients will relapse, either during or after stopping treatment, and retreatment may be considered.[4,6,7] The time to relapse can be variable. Remission in a small group of complete responders ranged from 1 month to 2 years after stopping therapy.[4] Another group of patients who achieved total regrowth of hair were able to stop treatment with diphencyprone for a mean of 15 months without relapse[9] while a further group maintained satisfactory hair growth for a mean follow-up period of 19.8 months.[5]

1. MacDonald Hull S, *et al.* Alopecia areata in children: response to treatment with diphencyprone. *Br J Dermatol* 1991; **125:** 164–8.
2. Schuttelaar M-L, *et al.* Alopecia areata in children: treatment with diphencyprone. *Br J Dermatol* 1996; **135:** 581–5.
3. MacDonald Hull S, Cunliffe WJ. Successful treatment of alopecia areata using the contact allergen diphencyprone. *Br J Dermatol* 1991; **124:** 212–13.
4. Hoting E, Boehm A. Therapy of alopecia areata with diphencyprone. *Br J Dermatol* 1992; **127:** 625–9.
5. Gordon PM, *et al.* Topical diphencyprone for alopecia areata: evaluation of 48 cases after 30 months' follow-up. *Br J Dermatol* 1996; **134:** 869–71.

6. Pericin M, Trüeb RM. Topical immunotherapy of severe alopecia areata with diphenylcyclopropenone: evaluation of 68 cases. *Dermatology* 1998; **196:** 418–21.
7. Cotellessa C, *et al.* The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *J Am Acad Dermatol* 2001; **44:** 73–6.
8. Wiseman MC, *et al.* Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; **137:** 1063–8.
9. van der Steen PHM, *et al.* Topical immunotherapy for alopecia areata: re-evaluation of 139 cases after an additional follow-up period of 19 months. *Dermatology* 1992; **184:** 198–201.

Warts. Diphencyprone has been tried in the treatment of recalcitrant warts. The successful treatment of digital or plantar warts in 42 of 60 patients has been described.[1] The patients were initially sensitised with a 2% topical solution of diphencyprone in acetone, then the warts treated every 1 to 4 weeks with solutions ranging from 0.01 to 6%. In another series,[2] diphencyprone in a paraffin ointment was effective in the clearance of palmar, plantar, palmoplantar, and periungual warts in 135 of 154 patients. A concentration of diphencyprone 2% was used for the initial sensitisation, and concentrations of 0.5 to 4% were used for treatment once every 3 weeks. After initial sensitisation with diphencyprone 2% in acetone, a preparation of diphencyprone with salicylic acid in white soft paraffin applied every night as tolerated was reported to be successful in 44 of 50 patients treated for palmoplantar warts.[3] The concentration of diphencyprone in the ointment ranged from 0.01 to 0.2%, and the concentration of salicylic acid was 15%.

1. Buckley DA, *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141:** 292–6.
2. Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. *J Cutan Med Surg* 2002; **6:** 214–17.
3. Armour K, Orchard D. Treatment of palmoplantar warts with a diphencyprone and salicylic acid ointment. *Australas J Dermatol* 2006; **47:** 182–5.

Dipyrithione *(USAN, rINN)*

Bispiriyon; Bispyrithione; Dipiritiona; Dipyrithionum; OMDS; Piriyon Disülfit; Pyrithione Disulfide. 2,2′-Dithiodipyridine 1,1′-dioxide.

Дипиритион

$C_{10}H_8N_2O_2S_2$ = 252.3.

CAS — 3696-28-4.

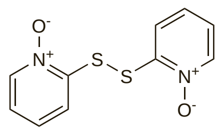

Profile

Dipyrithione is reported to have antibacterial and antifungal properties and is included in preparations for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Part 3)

Turk.: Perkapil.

Multi-ingredient: ***Canad.:*** Dan-Tar Plus; Polytar AF; ***Switz.:*** Crimanex.

Dithiosalicylic Acid

Ditiosalicílico, ácido. 2-Hydroxybenzenecarbodithioic acid.

Дитиосалициловая Кислота

$C_7H_6OS_2$ = 170.3.

CAS — 527-89-9.

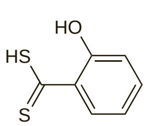

Profile

Dithiosalicylic acid has been used in multi-ingredient preparations used topically for the treatment of acne and seborrhoeic dermatitis.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Sacnel.

Dithranol *(BAN, rINN)*

Anthralin; Antralin; Dioxyanthranol; Dithranolum; Ditranol; Ditranoli; Ditranolis. 1,8-Dihydroxyanthrone; 1,8-Dihydroxy-9(10*H*)-anthracenone.

Дитранол

$C_{14}H_{10}O_3$ = 226.2.

CAS — 1143-38-0 (dithranol); 16203-97-7 (dithranol triacetate).

ATC — D05AC01.

ATC Vet — QD05AC01.

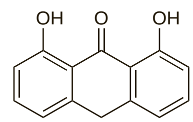

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Dithranol). A yellow or brownish-yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Anthralin). A yellowish-brown, odourless, crystalline powder. Insoluble in water; slightly soluble in alcohol, in ether, and in glacial acetic acid; soluble in acetone, in chloroform, in benzene, and in solutions of alkali hydroxides. The filtrate from a suspension in water is neutral to litmus. Store at a temperature of 8° to 15° in airtight containers. Protect from light.

Stability. The stability of dithranol has been studied in a number of bases and vehicles.[1-4] The weaker preparations of dithranol may be less stable.[1,3,4] Salicylic acid is included in dithranol preparations as an antioxidant and its inclusion in pastes also containing zinc oxide prevents their discoloration due to the inactivation of dithranol by zinc oxide.[5] However, zinc oxide or starch can be omitted from dithranol pastes without loss of effectiveness provided stiffness is maintained.[5] Addition of ascorbic or oxalic acid may improve dithranol's stability in '*Unguentum Merck*' but salicylic acid appears to be ineffective.[1] The effect of salicylic acid on the instability of dithranol in yellow soft paraffin is variable[1,2] and its inclusion has been questioned as it can be irritant and percutaneous absorption can be significant.[1] Dithranol is relatively stable in white soft paraffin.[1]

The application of any type of heat and contact with metal spatulas should be avoided during the manufacture of dithranol pastes[6] and if milling facilities are not available dithranol can be incorporated into Lassar's paste by dissolving it first in chloroform.[5]

1. Green PG, *et al.* The stability of dithranol in various bases. *Br J Dermatol* 1985; **113** (suppl 29): 26.
2. Lee RLH. Stability of dithranol (anthralin) in various vehicles. *Aust J Hosp Pharm* 1987; **17:** 254–8.
3. Hiller C, *et al.* How stable is dithranol? An investigation into the degradation of different dithranol formulations. *Pharm Pract* 1995; **5:** 428–31.
4. Thoma K, Holzmann C. Stabilization of dithranol in topical formulations. *Acta Pharm Hung* 1998; **68:** 313–21.
5. Comaish S, *et al.* Factors affecting the clearance of psoriasis with dithranol (anthralin). *Br J Dermatol* 1971; **84:** 282–9.
6. *PSGB Lab Report P/79/1* 1979.

Adverse Effects and Precautions

Dithranol may cause a burning sensation especially on perilesional skin. Patients with fair skin may be more sensitive than those with dark skin. It is irritant to the eyes and mucous membranes. Use on the face, skin flexures, and genitals should be avoided. Hands should be washed after use.

Dithranol should not be used for acute or pustular psoriasis or on inflamed skin. It stains skin, hair, some fabrics, plastics, and enamel. Staining of bathroom ware may be less of a problem with creams than ointments. Stains on skin and hair slowly disappear on cessation of treatment.

Handling. Dithranol is a powerful irritant and should be kept away from the eyes and tender parts of the skin.

Uses and Administration

Dithranol is used in the treatment of subacute and chronic psoriasis, usually in one of two ways.

Conventional treatment is commonly started with an ointment or paste containing 0.1% dithranol (0.05% in very fair patients) applied for a few hours; the strength is gradually increased as necessary to 0.5%, occasionally to 1%, and the duration of contact extended to overnight periods or longer. The preparation is sparingly and accurately applied to the lesions only. If, on initial treatment, lesions spread or excessive irritation occurs, the concentration of dithranol or the frequency of application should be reduced; if necessary, treatment should be stopped. After each treatment period the patient should bathe or shower to remove any residual dithranol.

For *short-contact therapy* dithranol is usually applied in a soft basis to the lesions for up to 60 minutes daily, before being washed off. As with conventional treatment the strength used is gradually increased from 0.1 to 2% but strengths up to 5% have been used. Surrounding unaffected skin may be protected by white soft paraffin.

Treatment for psoriasis should be continued until the skin is entirely clear. Intermittent courses may be needed to maintain the response. Treatment schedules often involve coal tar and UV irradiation (preferably UVB) before the application of dithranol (see below). Salicylic acid is included in many topical preparations of dithranol.

A cream containing dithranol triacetate has been used similarly to dithranol in conventional treatment of psoriasis.

Alopecia. Dithranol cream (0.5 to 1%) applied for 20 to 60 minutes to the scalp and then washed off, has been found to be of benefit in the treatment of alopecia areata (p.1577). However, at least 6 months of treatment may be required for a cosmetically acceptable result.[1] The response rate has, however, been difficult to evaluate because of the small number of reports, and although it has been widely prescribed for limited patchy alopecia areata, some guidelines conclude that there is no convincing evidence of efficacy.[2]

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; **61:** 53–69.
2. MacDonald Hull SP, *et al.* British Association of Dermatologists. Guidelines for the management of alopecia areata. *Br J Dermatol* 2003; **149:** 692–9. Also available at: http://www.bad.org.uk/healthcare/guidelines/Alopecia_Areata.pdf (accessed 27/09/07)

Psoriasis. Dithranol used alone or with coal tar, (with or without ultraviolet light), continues to be one of the drugs of first-line treatment for psoriasis (p.1583). It is particularly suited to the treatment of stable chronic plaque psoriasis but unlike coal tar, is irritant to healthy skin and care is required to ensure that it is only applied to lesions. Treatment with dithranol is therefore more feasible when the plaques are large, or few in number. Use with coal tar may help to reduce the irritant effects of dithranol without affecting efficacy. Traditional treatment with dithranol is time consuming and more suitable for use on hospital inpatients. Dithranol formulated in stiff preparations such as Lassar's paste to minimise spreading to perilesional skin is left on overnight covered with a suitable dressing and washed off the next day. Treatment is usually started with a concentration of 0.1% (0.05% in fair-skinned patients) and gradually increased according to the response and irritation produced. Cream formulations may be less effective but are more suitable for domestic use. Short-contact therapy in which concentrations of up to 5% of dithranol are applied daily for up to 1 hour is more suitable for use on an outpatient basis and there appears to be little reduction in efficacy; irritation and staining may also be reduced.

Dithranol is also used with UVB phototherapy and there have been many modifications of the original Ingram's regimen in which dithranol is applied after bathing in a tar bath and exposure to ultraviolet light. Inpatient stays of up to 3 weeks may be required but long periods of remission can be obtained.

Reviews.

1. Mahrle G. Dithranol. *Clin Dermatol* 1997; **15:** 723–37.

Preparations

BP 2008: Dithranol Cream; Dithranol Ointment; Dithranol Paste;
USP 31: Anthralin Cream; Anthralin Ointment.

Proprietary Preparations (details are given in Part 3)

Austral.: Dithrocream†; Micanol†; ***Austria:*** Micanol; ***Belg.:*** Micanol†; ***Canad.:*** Anthraforte; Anthranol; Anthrascalp; Micanol†; ***Denm.:*** Micanol†; ***Fin.:*** Micanol†; ***Ger.:*** Micanol; ***Hong Kong:*** Micanol†; ***India:*** Psorinol; ***Indon.:*** Anthramed; ***Irl.:*** Dithrocream; Micanol†; ***Israel:*** Dithrocream; Micanol; ***Ital.:*** Psoriderm; Timicolid†; ***Neth.:*** Psoricreme; Psoristick; ***Norw.:*** Micanol; ***NZ:*** Micanol; ***Port.:*** Micanol; ***S.Afr.:*** Anthranol; ***Spain:*** Micanol; ***Swed.:*** Micanol; ***Thai.:*** Micanol†; ***UK:*** Dithrocream; Micanol; ***USA:*** Anthra-Derm†; Dritho-Scalp; Drithocreme†; Psoriatec.

Multi-ingredient: ***Austral.:*** Dithrasal; ***Fr.:*** Anaxeryl; ***Ger.:*** Psoradexan; Psoralon MT; ***Hong Kong:*** Dithrasal; ***India:*** Derobin Skin; ***Singapore:*** Dithrasal; ***Spain:*** Lapices Epiderm Metadier; ***Turk.:*** Psoraks; ***UK:*** Psorin.

Drometrizole *(USAN, rINN)*

Drométrizol; Drometrizol; Drometrizolum. 2-(2*H*-Benzotriazol-2-yl)-*p*-cresol.

Дрометризол

$C_{13}H_{11}N_3O$ = 225.2.

CAS — 2440-22-4.

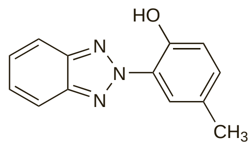

Drometrizole Trisiloxane

2-(2*H*-Benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-{1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]-1-disiloxanyl}propyl)phenol.

Дрометризола Трисилоксан

$C_{24}H_{39}N_3O_3Si_3$ = 501.8.

CAS — 155633-54-8.

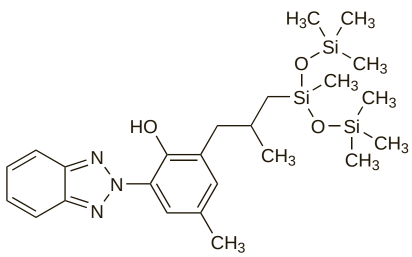

NOTE. Mexoryl XL and Silatrizole are trade names that have been used for drometrizole trisiloxane.

Profile

Drometrizole trisiloxane is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Ecamsule *(USAN, rINN)*

Ecamsul; Écamsule; Ecamsulum. (±)-(3*E*,3′*E*)-3,3′-(*p*-Phenylenedimethylidyne)bis[2-oxo-10-bornanesulfonic acid]; Terephthalylidene-3,3′-dicamphor-10,10′-disulfonic acid.

Экамсул

$C_{28}H_{34}O_8S_2$ = 562.7.

CAS — 92761-26-7.

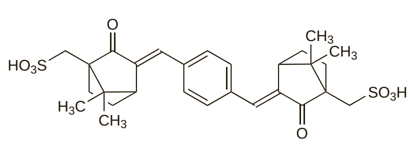

NOTE. Mexoryl SX is a trade name that has been used for ecamsule.

Profile

Ecamsule, a camphorsulfonic acid derivative, is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Efalizumab *(USAN, rINN)*

Anti-CD11a; Éfalizumab; Efalizumabum; Hu-1124. Immunoglobulin G1, anti-(human antigen CD11a)(human-mouse monoclonal hu1124 γ1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer.

Эфализумаб

CAS — 214745-43-4.

ATC — L04AA21.

ATC Vet — QL04AA21.

Adverse Effects and Precautions

The most common adverse affects associated with efalizumab are flu-like symptoms including chills, fever, headache, myalgia, and nausea. These reactions are dose-related in both incidence and severity and usually occur within two days after the first two injections. Other adverse effects include acne, back pain, and an elevation in alkaline phosphatase concentrations. More serious adverse effects of efalizumab include arthritis, interstitial pneumonitis, hypersensitivity reactions, inflammatory polyradiculoneuropathy, and thrombocytopenia. Treatment should be stopped in patients who develop such reactions. Severe haemolytic anaemia, diagnosed 4 to 6 months after the start of efalizumab treatment, has been reported. Treatment should be stopped immediately if haemolytic anaemia occurs. Asymptomatic leucocytosis or lymphocytosis commonly occurs during treatment. Worsening of psoriasis or development of variant forms (pustular, erythrodermic, or guttate) have been reported during and after stopping efalizumab therapy.

As a result of immunosuppression, patients given efalizumab are at increased risk of infection, and might be at increased risk of developing malignancies. It should not be given to patients with pre-existing serious infection and should be used with care in patients with a history of recurring infection or malignancy. Response to vaccines may also be reduced and acellular, live, and live-attenuated vaccines should not be given during efalizumab treatment.

Assessment of the platelet count is advised before starting therapy and monthly during early treatment. Frequency of monitoring may be decreased with ongoing treatment.

Incidence of adverse effects. The safety data from 13 controlled and open-label studies of efalizumab in psoriasis have been analysed.[1] During the first 12 weeks of therapy the most common events in patients treated with efalizumab were headache, fever, chills, nausea, vomiting, or myalgia, starting within 48 hours of dosing. In 4 controlled studies that included 1620 patients treated with efalizumab and 715 with placebo, about a third of efalizumab-treated patients reported headache, while chills, nausea, and pain occurred in around 10%, and fever and myalgia in about 8%. These events usually occurred with the first 1 or 2 doses of efalizumab but by the third and subsequent doses the incidence was similar to that in the placebo group. Atypical or unusual worsening of psoriasis, and the development of variant forms, particularly guttate psoriasis, were reported in 3.2% of patients treated with efalizumab; other forms included psoriatic erythroderma, inverse psoriasis, palmoplantar psoriasis, and pustular psoriasis. In 5 studies of extended therapy for 13 to 60 weeks (1115 patients treated for 13 to 24 weeks and 228 for 60 weeks) the rate of adverse effects remained low, there was no new pattern of serious adverse effects, and there was no evidence of cumulative toxicity. An analysis of infection risk found similar rates of mild to moderate and serious infections in patients treated with either efalizumab or placebo. Nevertheless, efalizumab should not be used in patients with pre-existing serious infection. Anti-efalizumab antibodies were found in 67 of 1063 patients, but there was no apparent effect on efficacy, safety, or pharmacodynamics.

There have been infrequent reports of new onset or recurrent severe arthritis, including psoriatic arthritis, in patients treated with efalizumab. Separate analyses[1,2] of pooled study data both found that the incidence of arthropathy events was low (less than 4%) and similar for patients treated with either efalizumab or placebo. However, there was some suggestion[2] that patients with a history of arthropathy and those who have a poor clinical response to efalizumab may be at higher risk.

1. Papp KA, *et al.* Safety of efalizumab in patients with moderate to severe chronic plaque psoriasis: review of clinical data. *J Cutan Med Surg* 2005; **9:** 313–23.
2. Pincelli C, *et al.* The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long-term treatment: pooled analysis of data from phase III clinical trials of efalizumab. *Arch Dermatol Res* 2006; **298:** 329–38.

Carcinogenicity. Efalizumab is an immunosuppressant and as such might increase the risk of malignancy. An analysis[1] of pooled data from clinical studies that included 2980 patients given efalizumab found 51 patients (1.7%) with 67 malignancies. Most cases were of non-melanoma skin cancer (51 cases in 35 patients) and it was found that many had risk factors for skin cancer. Other cases included 3 lymphomas, 12 solid tumours at various sites, and 1 malignant melanoma. However, when compared with patients given placebo and data from 2 external cohorts of psoriasis patients (to allow for the increased risk of skin cancers seen in psoriasis patients compared with the general population) there was no evidence that efalizumab increased the risk of developing a malignancy. Nevertheless, further data are needed to determine whether efalizumab has any long-term effect on the development of malignancies.

1. Leonardi CL, *et al.* A review of malignancies observed during efalizumab (Raptiva) clinical trials for plaque psoriasis. *Dermatology* 2006; **213:** 204–14.

Effects on the blood. Thrombocytopenia has been described in 6 patients given efalizumab.[1] In 5 cases it started 8 to 12 weeks after starting weekly efalizumab. In all cases the platelet counts recovered quickly after efalizumab was stopped; in 5 cases corticosteroids were also given. In another case a woman presented with pancytopenia 4 weeks after starting efalizumab therapy.[2] Efalizumab was stopped and the patient treated with granulocyte colony-stimulating factor, normal immunoglobulin, oral prednisone, platelet transfusion, and darbepoetin alfa. Cell counts returned to normal limits within 4 weeks.

1. Warkentin TE, Kwon P. Immune thrombocytopenia associated with efalizumab therapy for psoriasis. *Ann Intern Med* 2005; **143:** 761–3.
2. Tom WL, *et al.* Efalizumab-induced autoimmune pancytopenia. *Br J Dermatol* 2006; **155:** 1045–7.

Interactions

For a warning concerning the use of live vaccines in patients receiving efalizumab see Adverse Effects and Precautions, above.

Pharmacokinetics

Peak plasma concentrations of efalizumab are reached about 1 to 2 days after subcutaneous injection, with a bioavailability of about 50%. Steady state is reached at week 4 of weekly dosing. Efalizumab is metabolised by intracellular degradation. It is cleared by non-linear saturable elimination and the time to elimination after the last dose is about 25 days.

◊ References.

1. Mortensen DL, *et al.* Pharmacokinetics and pharmacodynamics of multiple weekly subcutaneous efalizumab doses in patients with plaque psoriasis. *J Clin Pharmacol* 2005; **45:** 286–98.
2. Sun Y-N, *et al.* Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol* 2005; **45:** 468–76.
3. Joshi A, *et al.* An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. *J Clin Pharmacol* 2006; **46:** 10–20.

Uses and Administration

Efalizumab is a humanised monoclonal antibody that binds to human CD11a on leucocytes to inhibit the activation of T-lymphocytes. It is used for the treatment of chronic moderate to severe plaque psoriasis (p.1583) in patients aged 18 years and over. Efalizumab is given by subcutaneous injection. The initial dose is 700 micrograms/kg, followed by a weekly dose of 1 mg/kg; a single dose should not exceed 200 mg. Treatment is given for 12 weeks, then continued in those who have responded.

◊ References.

1. Lebwohl M, *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003; **349:** 2004–13.
2. Gordon KB, *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; **290:** 3073–80. Correction. *ibid.* 2004; **291:** 1070.
3. Menter A, *et al.* Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; **141:** 31–8.
4. Leonardi CL, *et al.* Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol* 2005; **52:** 425–33.
5. Wellington K, Perry CM. Efalizumab. *Am J Clin Dermatol* 2005; **6:** 113–20.
6. Jordan JK. Efalizumab for the treatment of moderate to severe plaque psoriasis. *Ann Pharmacother* 2005; **39:** 1476–82.
7. Menter A, *et al.* Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol* 2006; **54** (suppl 1): S182–S188.
8. Dubertret L, *et al.* Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006; **155:** 170–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Raptiva; ***Austral.:*** Raptiva; ***Braz.:*** Raptiva; ***Canad.:*** Raptiva; ***Cz.:*** Raptiva; ***Denm.:*** Raptiva; ***Fin.:*** Raptiva; ***Fr.:*** Raptiva; ***Ger.:*** Raptiva; ***Gr.:*** Raptiva; ***Hong Kong:*** Raptiva; ***Irl.:*** Raptiva; ***Ital.:*** Raptiva; ***Malaysia:*** Raptiva; ***Mex.:*** Raptiva; ***Neth.:*** Raptiva; ***Norw.:*** Raptiva; ***NZ:*** Raptiva; ***Port.:*** Raptiva; ***Singapore:*** Raptiva; ***Spain:*** Raptiva; ***Swed.:*** Raptiva; ***Switz.:*** Raptiva; ***UK:*** Raptiva; ***USA:*** Raptiva.

Ensulizole *(USAN, rINN)*

Ensulizol; Ensulizolum; Phenylbenzimidazole Sulphonic Acid. 2-Phenyl-1*H*-benzimidazole-5-sulphonic acid.

Энсулизол

$C_{13}H_{10}N_2O_3S$ = 274.3.

CAS — 27503-81-7.

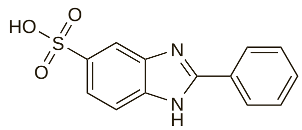

NOTE. Eusolex 232 and Neo-Heliopan Hydro are trade names that have been used for ensulizole.

Pharmacopoeias. In *US.*

USP 31 (Ensulizole). A white to ivory-coloured, odourless powder. Practically insoluble in water and in oily solvents; soluble in alcohol; its salts are freely soluble in water. Store in airtight containers at a temperature of 8° to 15°.

Profile

Ensulizole is used topically as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Enzacamene *(USAN, rINN)*

Enzacamène; Enzacameno; Enzacamenum; Methyl Benzylidene Camphor; 3-(4-Methylbenzylidene)bornan-2-one; 3-(4-Methylbenzylidene)camphor. 1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one.

Энзакамен

$C_{18}H_{22}O$ = 254.4.

CAS — 36861-47-9 (DL-form); 38102-62-4 (form unspecified).

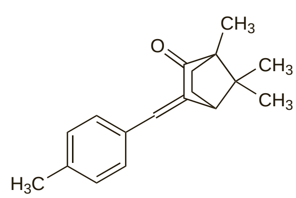

NOTE. Eusolex 6300, Neo-Heliopan MBC, and Parsol 5000 are trade names that have been used for enzacamene.

Pharmacopoeias. In *US.*

USP 31 (Enzacamene). A white, fine crystalline powder. M.p. between 66° and 68°. Practically insoluble in water; freely soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Enzacamene is a camphor derivative used as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Erythrulose

DL-Glycero-tetrulose. 1,3,4-Trihydroxy-2-butanone.

Эритрулаза

$C_4H_8O_4$ = 120.1.

CAS — 40031-31-0 (DL-erythrulose); 496-55-9 (D-erythrulose); 533-50-6 (L-erythrulose).

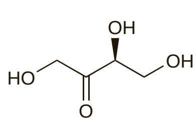

Profile

Application to the skin of preparations containing L-erythrulose slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin. It is often used with dihydroxyacetone (p.1594) in artificial suntan preparations. Recommended concentrations are up to 5% when used alone or up to 4% with dihydroxyacetone.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Sunmax Autobronzeador; ***UK:*** ViTicolor.

Etretinate *(BAN, USAN, rINN)*

Etretinaatti; Etretinat; Étrétinate; Etretinato; Etretinatum; Ro-10-9359. Ethyl 3-methoxy-15-apo-ϕ-caroten-15-oate; Ethyl (*all-trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate.

Этретинат

$C_{23}H_{30}O_3$ = 354.5.

CAS — 54350-48-0.

ATC — D05BB01.

ATC Vet — QD05BB01.

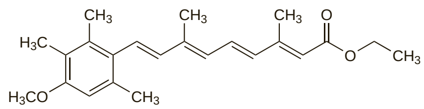

Adverse Effects and Precautions

As for Isotretinoin, p.1599.

Donation of blood should be avoided for at least 2 years after cessation of treatment. The period of time during which pregnancy must be avoided after stopping treatment has not been determined; detectable plasma-etretinate concentrations have been reported nearly 3 years after the last dose.

◊ In addition to the references cited below, further references to the adverse effects of etretinate can be found in Isotretinoin, p.1599, under Effects on the Blood, Cardiovascular System, Eyes, Liver, Musculoskeletal System, Serum Lipids, and the Skin, as well as under Vasculitic Syndromes.

Carcinogenicity. A report of 2 patients who developed lymphomas while receiving etretinate[1] prompted a report of 3 other malignancies in patients taking etretinate.[2]

1. Woll PJ, *et al.* Lymphoma in patients taking etretinate. *Lancet* 1987; **ii:** 563–4.
2. Harrison PV. Retinoids and malignancy. *Lancet* 1987; **ii:** 801.

Effects on the kidneys. Rare cases of impaired renal function associated with etretinate have been described.[1,2] In one report[1] it was also noted that in manufacturer-sponsored studies the mean serum-creatinine concentration had been raised in patients receiving etretinate.

1. Horber FF, *et al*. Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
2. Cribier B, *et al.* Renal impairment probably induced by etretinate. *Dermatology* 1992; **185:** 266–8.

Oedema. A report of generalised oedema after treatment with etretinate.[1] Five other cases had been reported in the literature and rechallenge in 4 patients had provoked a recurrence. Generalised oedema as part of the capillary leak syndrome has been reported with acitretin (p.1586).

1. Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; **19:** 140.

Pregnancy. For further information on the teratogenicity of etretinate, see under Acitretin, p.1586.

Interactions

As for Isotretinoin, p.1602.

Anticoagulants. Etretinate has been reported to reduce the therapeutic efficacy of *warfarin* (see p.1430).

Antiepileptics. Etretinate was ineffective and none of its characteristic mucocutaneous adverse effects occurred in a patient with pityriasis rubra pilaris who was already taking *carbamazepine* and *valproate* for epilepsy. However, there was a clinical response after the carbamazepine had been withdrawn, suggesting that it may have reduced the bioavailability or increased the metabolism of etretinate.[1]

1. Mohammed KN. Unresponsiveness to etretinate during anticonvulsant therapy. *Dermatology* 1992; **185:** 79.

Antineoplastics. The risk of developing hepatotoxicity may be increased when etretinate is used with *methotrexate* (see Retinoids, p.748).

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p.2068.

Pharmacokinetics

The mean bioavailability of etretinate is about 40% after oral doses but there is a large interindividual variation. Absorption can be increased if taken with milk or fatty food. Etretinate undergoes significant first-pass metabolism and plasma concentrations of the active carboxylic acid metabolite, acitretin (p.1586), may be detected before those of the parent drug; acitretin may itself be metabolised to etretinate (see p.1586). Both etretinate and acitretin are extensively bound to plasma protein. Etretinate appears to accumulate in adipose tissue after repeated dosing and has a prolonged elimination half-life of about 120 days; detectable serum concentrations have been observed up to 3 years after stopping therapy. Up to 75% of a dose is excreted in the faeces mainly as unchanged drug. Etretinate is also excreted in the urine as metabolites. Etretinate crosses the placenta. Although it is not known whether etretinate is distributed into breast milk, this would be expected because of its lipophilicity; acitretin, a metabolite of etretinate, has been found in breast milk when it was given to a lactating woman (see p.1586).

◊ References.

1. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10:** 38–62.
2. DiGiovanna JJ, *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; **125:** 246–51.
3. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; **190** (suppl): 1–33.
4. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; **39** (suppl): S25–S33.

Uses and Administration

Etretinate is a retinoid and is a derivative of tretinoin (p.1618). It has been given orally for the treatment of severe, extensive psoriasis that has not responded to other treatment, especially generalised and palmo-plantar pustular psoriasis. It has also been used in severe congenital ichthyosis, severe Darier's disease (keratosis follicularis) as well as other disorders of keratinisation, and oral lichen planus. Acitretin (p.1586) is now preferred to etretinate.

Therapy is generally started at doses of 0.75 to 1 mg/kg daily in divided oral doses. A maximum dose of 1.5 mg/kg daily should not be exceeded (some licensed product information has suggested a maximum of 75 mg daily). Erythrodermic psoriasis may respond to lower initial doses of 250 micrograms/kg daily, increased at weekly intervals by 250 micrograms/kg daily until optimal response occurs. After the initial response, generally after 8 to 16 weeks of therapy, maintenance doses of 500 to 750 micrograms/kg daily have been given. Therapy should be stopped once lesions have sufficiently resolved.

◊ References.

1. Magis NLJ, *et al.* The treatment of psoriasis with etretinate and acitretin: a follow up of actual use. *Eur J Dermatol* 2000; **10:** 517–21.
2. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; **154:** 267–76.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Tigason.

Fumaric Acid

Acidum Fumaricum; Allomalenic Acid; Boletic Acid; E297; Fumárico, ácido; Kwas fumarowy. *trans*-Butenedioic acid.

Фумаровая Кислота

$C_2H_2(CO_2H)_2$ = 116.1.

CAS — 110-17-8 (fumaric acid); 624-49-7 (dimethyl fumarate).

ATC — D05AX01.

ATC Vet — QD05AX01.

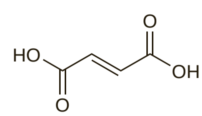

Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 26 (Fumaric Acid). White, odourless granules or crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform.

Profile

Fumaric acid and some of its derivatives have been used in the treatment of psoriasis and other skin disorders.

Fumaric acid is also used as an acidifier and flavouring agent in foods.

Skin disorders. Fumaric acid, its sodium salts, and derivatives such as dimethyl fumarate, monoethyl fumarate (ethyl hydrogen fumarate), and octil hydrogen fumarate have been used, both topically and systemically, in the treatment of psoriasis (p.1583) and other skin disorders. Dimethyl fumarate appears to be the most active compound given orally but combination with various salts of monoethyl fumarate has been claimed to improve efficacy.[1-6] However, there have been reports of acute renal failure associated with treatment and the German Federal Office of Health has expressed the opinion that the available evidence did not establish the value of fumaric acid derivatives in psoriasis or other skin disorders.[7] A subsequent retrospective analysis of 41 patients who received fumaric acid esters orally, for between 1 and 14 years, suggested that these drugs might be effective,[8] and a later review suggested that they may be of value in refractory psoriasis.[9] Reported adverse effects in the earlier analysis[8] were generally mild, with only 1 case of elevated serum creatinine; however, lymphocytopenia was noted in 76% of patients and treatment consequently stopped in 4 patients. Other adverse effects with oral therapy have included disturbances of liver function,[3,10] gastrointestinal effects,[2-4,10,11] and flushing.[2-4,10,11] There has been a report of exanthema in a patient receiving dimethyl fumarate for lichen planus.[12]

1. van Loenen AC, *et al.* Fumaarzuurtherapie: van fictie tot werkelijkheid? *Pharm Weekbl* 1989; **124:** 894–900.
2. Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: a long-term retrospective study on the effect of fumaric acid combination (FAC-EC) therapy and dimethyl-fumaric acid ester (DMFAE) monotherapy. *Br J Dermatol* 1990; **123:** 534–5.
3. Nugteren-Huying WM, *et al.* Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; **22:** 311–12.
4. Altmeyer PJ, *et al.* Antipsoriatic effect of fumaric acid derivatives: results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994; **30:** 977–81.
5. Mrowietz U, *et al.* Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. *Br J Dermatol* 1999; **141:** 424–9.
6. Ständer H, *et al.* Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris. *Br J Dermatol* 2003; **149:** 220–2.
7. Anonymous. Fumaric acid derivatives and nephrotoxicity. *WHO Drug Inf* 1990; **4:** 28.
8. Hoefnagel JJ, *et al.* Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149:** 363–9.
9. Harries MJ, *et al.* Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; **153:** 549–51.
10. Nieboer C, *et al.* Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989; **20:** 601–8.
11. Mrowietz U, *et al.* Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. *Br J Dermatol* 1998; **138:** 456–60.
12. Guenther CH, *et al.* Macular exanthema due to fumaric acid esters. *Ann Pharmacother* 2003; **37:** 234–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Ingepsor; ***Ger.:*** Psoriasis-Solution†; Psoriasis-Tabletten†.

Multi-ingredient: *Arg.:* Noquerat†; ***Austral.:*** Pro-PS†; ***Ger.:*** Fumaderm; Psoriasis-Bad†; Psoriasis-Salbe S†.

Glycolic Acid

Glicólico, ácido; Hydroxyacetic Acid. Hydroxyethanoic acid.

Гидроксиуксусная Кислота; Гликолевая Кислота

$C_2H_4O_3 = 76.05.$

CAS — 79-14-1.

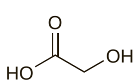

Profile

Glycolic acid is an alpha hydroxy organic acid that has been used in topical preparations for hyperpigmentation (see Pigmentation Disorders, p.1582) and photodamaged skin (see Photoageing, p.1581).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alfabase 8; Geloforte†; Glicoisdin; Gligel; Lactrime†; Lipomax†; Loxidil; Vansame G; ***Canad.:*** Reversa; ***Chile:*** Alastik†; Neosolets; Teen Derm†; ***Hong Kong:*** Glyderm; ***Indon.:*** Exfoliac; Glycare; ***Ital.:*** Neostrata; Revitalizing†; ***Malaysia:*** Glyderm†; ***Mex.:*** Glicoderm; Glicolic; Nova Derm; ***Philipp.:*** Teranex; ***Singapore:*** Glyderm; Sunsense Anti-Ageing; ***Venez.:*** Glyco-A†; Teen Derm†.

Multi-ingredient: *Arg.:* Cellskinlab C + AHA; Controlacne; Diacneal; Effalpha†; Hidroskin; Hydragenic†; Keracnyl; Melacler†; Negacne; Neoquin; Neoquin Forte; Neostrata; Neostrata Gel Despigmentante; Purasoft; Revital; Vansame GS; Vansame Plus; ***Austral.:*** Neostrata; ***Braz.:*** Glyquin; ***Canad.:*** Biobase-G; Dilusol AHA†; Glyquin XM; Neostrata; NeoStrata Blemish Spot Gel; NeoStrata Daytime; NeoStrata HQ; Reversa UV; Viquin Forte†; ***Chile:*** Alastik†; D 4†; Diacneal; Neostrata; Neutrogena Healthy Skin; Neutrogena Limpiadora; Primacy C+AHA†; Ureadin Forte; ***Fr.:*** Alpha 5 DS†; Aniospray 29; Body Peel; Cleanance K; Correcteur Anti-Taches; Cosmodex Uniwhite†; Day Peel; Hyfac soin keratolytique†; Item Alphakeptol; Kelual DS; Keracnyl; Keracnyl eau nettoyante; Keracnyl stop bouton; Kertyol-S; Night Peel; Photakne†; Seborheane; ***Hong Kong:*** Glyquin; ***Indon.:*** Exfoliac; Interquin Plus; ***Ital.:*** Acnesan†; Biophase Shampoo; Lightening; Neoceuticals Spot Treatment; Phytic Acid; Same-Seb Beta; Sebacnol†; ***Mex.:*** Nova Derm; ***Port.:*** Bioclin Sebo Care; Ureadin; Ureadin Forte; ***Singapore:*** Glyquin; Glyquin XM; Percutalfa; ***USA:*** Glyquin XM; ***Venez.:*** Diacneal; Photoderm AKN.

Homosalate *(USAN, rINN)*

Homomenthyl Salicylate; Homosalato; Homosalatum. 3,3,5-Trimethylcyclohexyl salicylate.

Гомосалат

$C_{16}H_{22}O_3 = 262.3.$

CAS — 118-56-9.

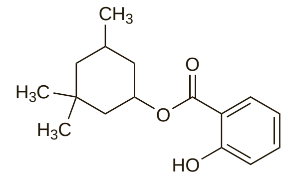

NOTE. Eusolex HMS and Neo-Heliopan HMS are trade names that have been used for homosalate.

Pharmacopoeias. In *US.*

USP 31 (Homosalate). Store in airtight containers.

Profile

Homosalate, a substituted salicylate, is a sunscreen (p.1576) with actions similar to those of octisalate (p.1608). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Hydroquinone

Hidrokinon; Hidroquinona; Hydrochinon; Hydrochinonum; Quinol. 1,4-Benzenediol.

Гидрохинон

$C_6H_6O_2 = 110.1.$

CAS — 123-31-9.

ATC — D11AX11.

ATC Vet — QD11AX11.

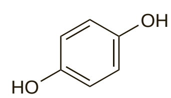

NOTE. Do not confuse with Hydroquinine (p.2322).

Pharmacopoeias. In *US.*

USP 31 (Hydroquinone). Fine white needles which darken on exposure to light and air. Soluble 1 in 17 of water, 1 in 4 of alcohol, 1 in 51 of chloroform, and 1 in 16.5 of ether. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Topical hydroquinone may cause transient erythema and a mild burning sensation. Occasionally hypersensitivity has occurred and US licensed product information recommends skin testing before use. Hydroquinone should not be applied to abraded or sunburnt skin. It should not be used to bleach eyelashes or eyebrows and contact with the eyes should be avoided as it may produce staining and corneal opacities. High concentrations or prolonged use may produce a blue-black hyperpigmentation (ochronosis) or pigmented colloid milium. The systemic effects of hydroquinone and their treatment are similar to those of phenol (see p.1656) but tremors and convulsions may also occur.

Carcinogenicity. There is some evidence from *animal* studies that hydroquinone might be carcinogenic (see Effects on the Skin, below).

Effects on the liver. Toxic hepatitis in a radiographer was attributed to occupational exposure to hydroquinone fumes from the developing medium used in the darkroom.[1] However, it has been pointed out[2] that hydroquinone is not volatile under normal conditions of use and that surveillance of 879 people engaged in the manufacture and use of hydroquinone from 1942 to 1990 found no association between toxic hepatitis and hydroquinone exposure.

1. Nowak AK, *et al.* Darkroom hepatitis after exposure to hydroquinone. *Lancet* 1995; **345:** 1187.
2. O'Donaghue JL, *et al.* Hydroquinone and hepatitis. *Lancet* 1995; **346:** 1427–8.

Effects on the skin. The incidence of exogenous ochronosis (blue-black hyperpigmentation) in a survey of black South African patients was found to be 15% in males and 42% in females with 69% of affected individuals admitting to using hydroquinone-containing preparations.[1] This was considered to be more consistent with a toxic effect of a drug with a low therapeutic index, rather than an idiosyncratic reaction. The data revealed that even preparations with hydroquinone 2% or less with a sunscreen produced ochronosis. Ochronosis usually became apparent after about 6 months of use and, once established, was probably irreversible. Patients may initially use skin lighteners for cosmetic purposes but once ochronosis develops they may fall into the 'skin lightener trap' as they use other hydroquinone preparations to remove the disfigurement.[1] Treatment of exogenous ochronosis is based on stopping the use of hydroquinone, but it may take years for any improvement to be apparent. There are a few reports of benefit from topical tretinoin, dermabrasion, and laser therapy, but these are far from established therapies.[2] Reversible brown discoloration of the nails has also been reported after the use of skin lighteners containing hydroquinone.[3-5]

In addition to the risk of ochronosis it has been suggested that, based on *animal* studies, long-term use of hydroquinone might be carcinogenic.[6] In the USA, preparations containing up to 2% hydroquinone may be sold without prescription, but in 2006, based on data regarding potential carcinogenicity and reports of ochronosis, the FDA proposed to reclassify these products as drugs and make them available by prescription only.[7] In Europe the use of hydroquinone in cosmetic preparations for skin lightening is already banned, but it is still available for prescription as a medicine.[6]

1. Hardwick N, *et al.* Exogenous ochronosis: an epidemiological study. *Br J Dermatol* 1989; **120:** 229–38.
2. Levin CY, Maibach H. Exogenous ochronosis: an update on clinical features, causative agents and treatment options. *Am J Clin Dermatol* 2001; **2:** 213–17.
3. Mann RJ, Harman RRM. Nail staining due to hydroquinone skin-lightening creams. *Br J Dermatol* 1983; **108:** 363–5.
4. Ozluer SM, Muir J. Nail staining from hydroquinone cream. *Australas J Dermatol* 2000; **41:** 255–6.
5. Parlak AH, *et al.* Discolouration of the fingernails from using hydroquinone skin-lightening cream. *J Cosmet Dermatol* 2003; **2:** 199–201.
6. Kooyers TJ, Westerhof W. Toxicology and health risks of hydroquinone in skin lightening formulations. *J Eur Acad Dermatol Venereol* 2006; **20:** 777–80.
7. FDA. Skin bleaching drug products for over-the-counter human use: proposed rule. *Fed Regist* 2006; **71:** 51146–55. Available at: http://a257.g.akamaitech.net/7/257/2422/01jan20061800/edocket.access.gpo.gov/2006/pdf/E6-14263.pdf (accessed 27/09/07)

Uses and Administration

Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. Hydroquinone is used topically as a depigmenting agent for the skin in hyperpigmentation conditions (p.1582) such as chloasma (melasma), freckles, and lentigines (liver spots). Concentrations of 2 to 4% are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis. It may be several weeks before any effect is apparent but depigmentation may last for 2 to 6 months after stopping. Application of hydroquinone should stop if there is no improvement after 2 months. Hydroquinone should be applied twice daily only to intact skin which should be protected from sunlight to reduce repigmentation. A preparation containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% may be applied once daily at night in the treatment of chloasma (melasma). Hydroquinone preparations often include a sunscreen or a sunblocking basis.

Hydroquinone is also used as an antoxidant in topical preparations and in photographic developers.

Preparations

USP 31: Hydroquinone Cream; Hydroquinone Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Claripel; ***Braz.:*** Claripel; Solaquin; ***Canad.:*** African Gold†; Banishing Cream; Eldopaque; Eldoquin; Esoterica Regular; Esoterica Unscented; Lustra; Nadinola†; NeoStrata Canada HQ Plus; Porcelana Nighttime Formula†; Ultraquin Plain; ***Chile:*** Etnoderm; Unitone 4; ***Hong Kong:*** Derma-Rx Lightener; Eldopaque; Eldoquin; Solaquin; ***Indon.:*** Bioquin; Mediquin; Melanox; Melaskin; Pigmet; Pylaquin; Qutifar; Vitaquin; ***Israel:*** Esomed; ***Malaysia:*** Eldopaque; Eldoquin; ***Mex.:*** Crema Blanca; Eldopaque; Eldoquin; Hidroquin; Melanex; Quinoret Forte; ***NZ:*** Eldoquin; ***Singapore:*** Eldopaque; Eldoquin; Polyquin; Solaquin; ***Spain:*** Hidroquilaude; Licostrata; Melanasa; Nadona; Pigmentasa; ***Thai.:*** Clariderm; ***Turk.:*** Expigment; ***UK:*** Eldopaque; Eldoquin; Solaquin; ***USA:*** Aclaro; Claripel; Eldopaque; Eldoquin; EpiQuin; Esoterica Regular; Lustra; Solaquin; ***Venez.:*** Pharquinon†.

Multi-ingredient: *Arg.:* Melacler†; Melasmax; Neoceuticals Crema Despigmentante de Dia†; Neoquin; Neoquin Forte; Neostrata Gel Despigmentante; Solaquin Forte; Tri-Luma; ***Austral.:*** Superfade; ***Braz.:*** Glyquin; Tri-Luma; Vitacid Plus; ***Canad.:*** Esoterica; Glyquin XM; Lustra-AF; NeoStrata Canada HQ Plus; NeoStrata HQ; Porcelana Daytime Formula†; Solaquin Forte†; Ultraquin; Viquin Forte†; ***Chile:*** Alastik†; Clasifel; D 4†; Neostrata; Tri-Luma; Trio-D†; ***Ger.:*** Pigmanorm; ***Hong Kong:*** Glyquin; Superfade; Tri-Luma; ***India:*** Melalite 15; ***Indon.:*** Hidrogel; Interquin; Interquin Plus; Nu-Derm Sunblock; ***Malaysia:*** Solaquin Forte; Tri-Luma; ***Mex.:*** Clasifel; Nova Derm; Quinoret; Solaquin; Tri-Luma; ***Philipp.:*** Tri-Luma; ***Singapore:*** Glyquin; Glyquin XM; Tri-Luma; ***Switz.:*** Pigmanorm; ***Thai.:*** Tri-Luma; ***Turk.:*** Metamorfoz; ***USA:*** Esoterica Facial and Sunscreen; Glyquin XM; Solaquin Forte; Tri-Luma; ***Venez.:*** Tri-Luma.

Ichthammol (BAN)

Ammonii Bituminosulfonas; Ammonii Sulfogyrodalas; Ammonio Sulfoittiolato; Ammonium Bithiolicum; Ammonium Bitumenosulfonicum; Ammonium Bituminosulphonate; Ammonium Ichthosulphonate; Ammonium Sulfobituminosum; Ammonium Sulpho-Ichthyolate; Amonowy sulfobituminian; Bithiolate Ammonique; Bithyol; Bitiol; Bitiolato amónico; Bitomol; Bituminol; Ichtammol; Ichtamolis; Ichthammolum; Ichthamol; Ichthosulphol; Ichthyol; Ichthyolammonium; Ictamol; Ictiolsulfonato amónico; Ihtamol; Iktammol; Iktammoli; Sulfobituminato amónico; Sulfoictiolato amónico.

Ихтаммол; Ихтиол

CAS — 8029-68-3.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Ichthammol). A dense blackish-brown liquid. It is obtained by distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with ammonia. It contains not less than 4.5% and not more than 7.0% of total ammonia, not less than 10.5% of organically combined sulfur, calculated with reference to the dried substance, and not more than 20% of the total sulfur in the form of sulfates.

Miscible with water and with glycerol; slightly soluble in alcohol, in fatty oils, and in liquid paraffin; forms homogeneous mixtures with wool fat and soft paraffin.

USP 31 (Ichthammol). A reddish-brown to brownish-black viscous fluid with a strong characteristic empyreumatic odour. It is obtained by the destructive distillation of a bituminous schist, sulfonation of the distillate, and neutralisation of the product with ammonia. It yields not less than 10.0% of total sulfur and not less than 2.5% of ammonia. Miscible with water, with glycerol, and with fixed oils and fats. Partially soluble in alcohol and in ether.

Incompatibility. Ichthammol is incompatible with wool alcohols.

Profile

Ichthammol has slight bacteriostatic properties and is used in a wide range of topical preparations, for a variety of skin disorders; it has also been used in suppositories for anorectal disorders. Ichthammol is often used with zinc oxide in medicated bandages for chronic lichenified eczema (p.1579). Ichthammol may be slightly irritant to the skin and there have been rare reports of hypersensitivity.

Light Ammonium Bituminosulfonate (Ammoniumbituminosulfonat Hell) is produced from the light distillate fraction of shale oil.

Ammoniumsulfobitol, an ammonium bituminosulfonate similar to ichthammol but with a low sulfur content, was commercially available as Tumenol Ammonium.

Preparations

BP 2008: Zinc and Ichthammol Cream;
USP 31: Ichthammol Ointment.

Proprietary Preparations (details are given in Part 3)
Austral.: Egoderm; ***Austria:*** Ichtho-Bad; Ichtholan; Ichtopur; ***Belg.:*** Bithiol; Poudre Velours; ***Cz.:*** Ichtoxyl; ***Fr.:*** Gelictar†; ***Ger.:*** Ichtho-Bad; Ichtholan; Ichtholan spezial; Ichthyol; Thiobitum; ***Neth.:*** Daroderm Trekzalf; Trekzalf; ***Switz.:*** Ichtho-Bad; Ichtholan; ***Turk.:*** Ihtiyol; Pomat Ichthyole; Pommade Ichthyole.

Multi-ingredient: ***Arg.:*** Cicatrina; ***Austral.:*** Egoderm; Icthaband†; ***Austria:*** Aknemycin compositum; Delta-Hadensa; Hadensa; Ichth-Oestren; Inotyol; ***Belg.:*** Antipiol; Inotyol; ***Canad.:*** Boil Ease†; ***Cz.:*** Pityol; Saloxyl; ***Denm.:*** Inotyol; ***Fin.:*** Hadensa; ***Fr.:*** Anaxeryl; Gelictar Fort; Inotyol†; Node DS; Novophane S; Oxythyol; Phytheol; Phytolithe†; Provictol†; Selegel; Squaphane Masque-Creme; ***Ger.:*** Aknemycin; ***Hong Kong:*** Acnederm; Egoderm; ***Israel:*** Aknemycin; Inotyol; ***Ital.:*** Antiemorroidali; Dermatar; Ichthopaste; Inotyol†; Tricoderm F; ***Malaysia:*** Acnederm†; Egoderm; ***Norw.:*** Inotyol; ***NZ:*** Acnederm†; Egoderm; ***Pol.:*** Neo-Tormentil; Tormentile Forte; Tormentiol; ***Port.:*** Efluvium Anti-caspa; Efluvium Anti-seborreico; Oleoban Composto†; Pansebase Composto; Secpel Composto; ***Rus.:*** Bethiol (Бетиол); ***S.Afr.:*** Antipeol; ***Singapore:*** Egoderm; ***Spain:*** Hadensa; Ictiomen; Lamnotyl†; ***Swed.:*** Inotyol; ***Switz.:*** Aknemycin; Bain extra-doux dermatologique; Epithelial†; Furodermal; Leucen; Radix; Riccovitan†; ***Turk.:*** Hedensa; ***UK:*** Antipeol; Ichthopaste; Icthaband; St James Balm; ***USA:*** Boil Ease; Boyol Salve; Medicone Derma†; ***Venez.:*** Node DS.

Ictasol (USAN)

Ichtasol; Ichthyol-Natrium Hell; Light Sodium Bituminosulphonate; Natrium Sulfobituminosum Decoloratum; Sulfobituminato sódico; Sulfobituminato sódico decolorado.

$C_{28}H_{36}Na_2O_6S_3$ = 610.8.
CAS — 12542-33-5; 1340-06-3.
ATC — D10BX01.
ATC Vet — QD10BX01.

Profile

Ictasol is a sodium bituminosulfonate produced from the light distillate fraction of shale oil. Sodium bituminosulfonate is obtained by the destructive distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with sodium hydroxide.

Ictasol has similar properties to ichthammol (above) and is used in a wide range of preparations for a variety of skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Crino Cordes; Ichthraletten; Lavichthol; ***Ger.:*** Aknichthol Creme; Crino Cordes N†; Dermichthol†; Ichthoderm; Ichtholan T; Ichthosin; Ichthraletten; Leukichtan; Solutio Cordes.

Multi-ingredient: ***Arg.:*** Selegel; ***Austria:*** Aknichthol; Ichthalgan forte; Ichtho-Bellol; Ichtho-Cortin; Leukichtan; ***Chile:*** Ichtyosoft†; ***Fr.:*** I-Soft†; Ichtyosoft†; Sebosquam; ***Ger.:*** Aknederm Neu; Aknichthol N; Ichthalgan†; Ichtho-Bellol compositum S†; Ichtho-Bellol†; Ichthocortin; Ichthoseptal; Pelvichthol N; ***Switz.:*** Aknichthol N.

Iscotrizinol (USAN)

Diethylhexyl Butamido Triazone; Diethylhexylbutamido Triazone; Dioctylbutamidotriazone. Bis(2-ethylhexyl) 4,4′-[(6-{[4-(*tert*-butylcarbamoyl)phenyl]amino}-1,3,5-triazine-2,4-diyl)diimino]dibenzoate.

$C_{44}H_{59}N_7O_5$ = 766.0.
CAS — 154702-15-5.

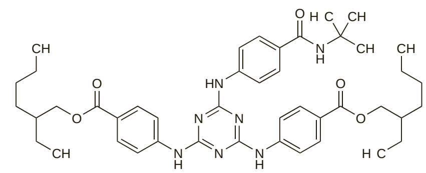

NOTE. Uvasorb HEB is a trade name that has been used for iscotrizinol.

Profile

Iscotrizinol is used as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Isopropyldibenzoylmethane

Isopropildibenzoilmetano. 1-[4-(1-Methylethyl)phenyl]-3-phenyl-1,3-propanedione.

Изопропилдибензоилметан

$C_{18}H_{18}O_2$ = 266.3.
CAS — 63250-25-9.

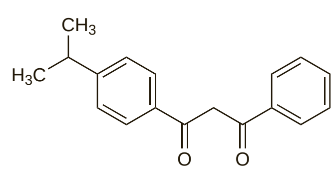

Profile

Isopropyldibenzoylmethane, a substituted dibenzoylmethane, is a sunscreen (p.1576) with actions similar to those of avobenzone (p.1589). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Isotretinoin (BAN, USAN, rINN)

Isotretinoiini; Isotretinoína; Isotrétinoïne; Isotretinoinum; Izotretinoin; Izotretinoinas; Izotretynoina; 13-*cis*-Retinoic Acid; Ro-4-3780. (13*Z*)-15-Apo-β-caroten-15-oic acid; (2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid.

Изотретиноин

$C_{20}H_{28}O_2$ = 300.4.
CAS — 4759-48-2.
ATC — D10AD04; D10BA01.
ATC Vet — QD10AD04; QD10BA01.

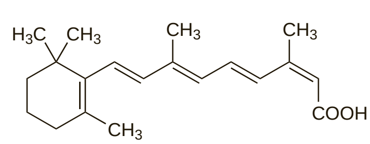

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Isotretinoin). A yellow or light orange, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. It is sensitive to air, heat, and light, especially in solution. Store in airtight containers at a temperature not exceeding 25°. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and that any unused part be protected by an atmosphere of an inert gas.

USP 31 (Isotretinoin). Yellow crystals. Practically insoluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in macrogol 400; soluble in chloroform. Store in airtight containers under an atmosphere of an inert gas. Protect from light.

Adverse Effects

The adverse effects of isotretinoin and other oral retinoids are similar to those of vitamin A (see p.1971) and are generally reversible and dose-related. The most common are dryness of the mucous membranes and skin, which can often progress to cheilitis, epistaxis, conjunctivitis, localised exfoliation including palmoplantar exfoliation, pruritus, erythematous rash, and skin fragility. Less common effects have included hair thinning (occasionally irreversible), hirsutism, photosensitivity, changes in skin pigmentation, paronychia, nail dystrophy, pyogenic granuloma, and increased sweating. Acne can be exacerbated at the beginning of isotretinoin treatment, and there are very rare reports of acne fulminans occurring. Less common adverse effects on the eyes include corneal opacities, visual disturbances such as blurred vision and colour vision disorders, impaired night vision that may persist, photophobia, and keratitis. Papilloedema, visual disturbances, headache, and nausea and vomiting can be signs and symptoms of benign intracranial hypertension. Arthralgia, myalgia, and back pain are commonly reported, and there have been rare reports of arthritis, osteoporosis, and tendinitis. Hyperostosis and calcinosis have also occurred, particularly in patients treated with high doses of isotretinoin over long periods for keratinisation disorders. Premature closure of the epiphyses has occurred in children treated with isotretinoin. Elevation of serum triglycerides is common, and pancreatitis has occurred in patients with high concentrations; cholesterol concentrations may also be increased. Increases in hepatic enzymes, erythrocyte sedimentation rate, and blood glucose can also occur. Alterations in haematological measures are common; there have also been reports of anaemia, thrombocytopenia, and neutropenia, and very rare reports of agranulocytosis. Other effects that have been reported rarely include gastrointestinal symptoms, hepatitis, hearing impairment, drowsiness, seizures, vasculitis, and hypersensitivity reactions including anaphylaxis. Mood changes, psychotic symptoms, depression, and suicidal behaviour have occurred in patients treated with oral isotretinoin. There may also be an association with skin infections and an inflammatory bowel syndrome.

Isotretinoin and other retinoids are teratogenic.

When isotretinoin is applied topically the adverse effects are similar to those of tretinoin (see p.1618).

◊ General references.

1. Mills CM, Marks R. Adverse reactions to oral retinoids: an update. *Drug Safety* 1993; **9:** 280–90.
2. Keefe M. Adverse reactions profile: retinoids. *Prescribers' J* 1995; **35:** 71–6.
3. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol* 2001; **45:** S188–S194.
4. British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne (2003). Available at: http://www.bad.org.uk/healthcare/guidelines/acne.asp (accessed 27/09/07)
5. Charakida A, *et al.* Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Saf* 2004; **3:** 119–29.
6. Goldsmith LA, *et al.* American Academy of Dermatology consensus conference on the safe and optimal use of isotretinoin: summary and recommendations. *J Am Acad Dermatol* 2004; **50:** 900–906. Correction. *ibid.*; **51:** 348. [dose]

Effects on the blood. Serious adverse effects on the blood have been reported rarely with oral retinoids, and are thought to be idiosyncratic in nature. There have been reports of thrombocytopenia in patients taking isotretinoin[1] and etretinate.[2,3] A few cases of agranulocytosis have involved isotretinoin[4] and acitretin.[5] In contrast, there are also reports of transient and asymptomatic thrombocytosis associated with isotretinoin[6] and tretinoin.[7,8] Leucocytosis is often associated with the retinoic acid syndrome caused by tretinoin (p.1618).

1. Moeller KE, Touma SC. Prolonged thrombocytopenia associated with isotretinoin. *Ann Pharmacother* 2003; **37:** 1622–4.
2. Naldi L, *et al.* Etretinate therapy and thrombocytopenia. *Br J Dermatol* 1991; **124:** 395.

3. Seishima M, *et al.* Thrombocytopenia possibly induced by etretinate in a psoriatic patient. *J Dermatol* 2005; **32:** 917–20.
4. Waisman M. Agranulocytosis from isotretinoin. *J Am Acad Dermatol* 1988; **18:** 395–6.
5. Chave TA, *et al.* Agranulocytosis and total scalp alopecia following acitretin. *Br J Dermatol* 2003; **148:** 1063–4.
6. Jansen T, Altmeyer P. Thrombocytosis induced by low-dose isotretinoin. *Int J Dermatol* 2000; **39:** 956–7.
7. Losada R, *et al.* Thrombocytosis in patients with acute promyelocytic leukaemia during all-trans retinoic acid treatment. *Br J Haematol* 1996; **95:** 704–5.
8. Kentos A, *et al.* All-trans retinoic acid induced thrombocytosis in a patient with acute promyelocytic leukaemia. *Br J Haematol* 1997; **97:** 685.

Effects on the cardiovascular system. From 1983 to the end of 2005, Health Canada had received 29 reports of adverse cardiovascular effects in patients treated with isotretinoin, including myocardial infarction, stroke, and pulmonary embolism.[1] Thrombotic stroke has also been attributed to the use of acitretin in a woman treated for psoriasis,[2] and rare cases of myocardial ischaemia and infarction have been reported with etretinate.[3] Thromboembolic disorders have also occurred in patients given tretinoin for remission induction in acute promyelocytic leukaemia (see p.1618).

There are rare reports of isotretinoin causing cardiac arrhythmias, such as sinus tachycardia with right branch bundle block[4] and atrial tachycardia.[5]

1. Springuel P, Roy G. Health Canada. Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders. *Can Adverse React News* 2006; **16:** 3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n2-eng.php (accessed 28/07/08)
2. Royer B, *et al.* Acitretin-associated thrombotic stroke. *Ann Pharmacother* 2002; **36:** 1879–82.
3. Anonymous. Reports from regulatory agencies: etretinate. *WHO Drug Inf* 1987; **1:** 29.
4. Charalabopoulos K, *et al.* Two new adverse effects of isotretinoin. *Br J Dermatol* 2003; **148:** 593.
5. Hasdemir C, *et al.* Isotretinoin (13-cis-retinoic acid) associated atrial tachycardia. *Pacing Clin Electrophysiol* 2005; **28:** 348–9.

Effects on the eyes. A number of ocular adverse effects have been reported with oral isotretinoin, and these have been reviewed.[1,2] Using the WHO Causality Assessment Guide of Suspected Adverse Reactions, an analysis[3] of 2449 spontaneous reports found that decreased dark adaptation, ocular sicca, and the ocular signs and symptoms of intracranial hypertension, accounted for most of the reports that were certainly associated with isotretinoin. In some cases of intracranial hypertension the patient had also been taking other drugs, such as tetracyclines, that have also been associated with this effect. There was also a certain association between isotretinoin and abnormal meibomian gland secretion and gland atrophy, blepharoconjunctivitis, corneal opacities, decreased vision, increased tear osmolarity, keratitis, myopia, ocular discomfort and decreased tolerance to contact lenses, and photophobia. There was a probable association with reversible decreased colour vision and permanent loss of dark adaptation. Other effects that had been reported, but only possibly associated with isotretinoin, included corneal ulcers, diplopia, eyelid oedema, optic neuritis, permanent sicca, and subconjunctival haemorrhage.

There are fewer reports of ocular adverse effects with other oral retinoids. Intracranial hypertension with papilloedema, blurred vision, and headache, has been reported with acitretin, etretinate, and tretinoin.[4-6] A 1-year follow-up failed to find any evidence of ocular toxicity attributable to etretinate in 4 patients who had received long-term treatment, including 1 patient who had toxic optic neuropathy due to methotrexate and who was able to continue treatment with etretinate.[7] Ectropion has been associated with etretinate therapy in a patient.[8] Maculopathy occurred in a patient after a year of treatment with acitretin for psoriasis.[9]

1. Fraunfelder FT, *et al.* Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985; **100:** 534–7.
2. Fraunfelder FT, *et al.* Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol* 2001; **132:** 299–305.
3. Fraunfelder FW. Ocular side effects associated with isotretinoin. *Drugs Today* 2004; **40:** 23–7.
4. Colucciello M. Pseudotumor cerebri induced by all-trans retinoic acid treatment of acute promyelocytic leukemia. *Arch Ophthalmol* 2003; **121:** 1064–5.
5. Guirgis MF, Lueder GT. Intracranial hypertension secondary to all-trans retinoic acid treatment for leukemia: diagnosis and management. *J AAPOS* 2003; **7:** 432–4.
6. Fraunfelder FW, Fraunfelder FT. Evidence for a probable causal relationship between tretinoin, acitretin, and etretinate and intracranial hypertension. *J Neuroophthalmol* 2004; **24:** 214–16.
7. Pitts JF, *et al.* Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol* 1991; **125:** 53–5.
8. Brenner S, *et al.* Ectropion: an adverse effect of etretinate therapy for psoriasis. *DICP Ann Pharmacother* 1990; **24:** 1007.
9. Lois N, White M. Acitretin-associated maculopathy. *Arch Ophthalmol* 2004; **122:** 928–30.

Effects on the gastrointestinal tract. A causal association has been suggested in cases of inflammatory bowel disease developing in patients taking oral isotretinoin.[1,2] Between 1997 and 2002 the FDA received 85 reports of Crohn's disease, ulcerative colitis, colitis, or haemorrhagic colitis attributed to isotretinoin;[3] the association was judged probable in 62 cases and possible in 23. Specific treatment, in addition to drug withdrawal, was required in 35 patients, 11 were hospitalised, and 7 underwent surgery. Rechallenge was positive in the 3 reported cases. The mechanism of this adverse effect is unknown, and because young adulthood is the most common age for both the onset of inflammatory bowel disease and the use of isotretinoin, a coincidence could not be ruled out. The authors of this review suggested that isotretinoin should be used with caution in patients with a history of inflammatory bowel disease or symptoms suggestive of the condition and those who might be at increased risk because of a family history. Although there have been patients with inflammatory bowel disease who have received isotretinoin without adverse effect, there are some cases in which the condition was apparently exacerbated by isotretinoin.[1,4]

1. Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. *Ann Pharmacother* 2001; **35:** 1214–16.
2. Passier JLM, *et al.* Isotretinoin-induced inflammatory bowel disease. *Neth J Med* 2006; **64:** 52–4.
3. Reddy D, *et al.* Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol* 2006; **101:** 1569–73.
4. Godfrey KM, James MP. Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. *Br J Dermatol* 1990; **123:** 653–5.

Effects on the liver. Transient slight elevations of serum concentrations of liver enzymes are common with etretinate, but there have been few reports of acute hepatitis[1,2] or cholestatic jaundice.[3] Acute hepatitis may progress to chronic active hepatitis, despite stopping etretinate therapy[4] but studies of serial liver biopsies from patients receiving long-term etretinate have failed to show any significant chronic liver damage.[5-7] Licensed product information has included reports of hepatic fibrosis, necrosis, and/or cirrhosis.

An overview considered that some form of hepatotoxicity may be seen in up to 20% of patients treated with etretinate and significant liver disease in 1%.[8]

Isotretinoin may also cause mild elevations of liver enzymes and licensed product information states that hepatitis has occurred rarely. There is also a report of fatty liver.[9]

1. Foged EK, Jacobsen FK. Side effects due to RO 10-9359 (Tigason). *Dermatologica* 1982; **164:** 395–403.
2. Weiss VC, *et al.* Hepatotoxic reactions in a patient treated with etretinate. *Arch Dermatol* 1984; **120:** 104–6.
3. Gavish D, *et al.* Cholestatic jaundice, an unusual side effect of etretinate. *J Am Acad Dermatol* 1985; **13:** 669–70.
4. Weiss VC, *et al.* Chronic active hepatitis associated with etretinate therapy. *Br J Dermatol* 1985; **112:** 591–7.
5. Glazer SD, *et al.* Ultrastructural survey and tissue analysis of human livers after a 6-month course of etretinate. *J Am Acad Dermatol* 1984; **10:** 632–8.
6. Foged E, *et al.* Histologic changes in the liver during etretinate treatment. *J Am Acad Dermatol* 1984; **11:** 580–3.
7. Roenigk HH, *et al.* Serial liver biopsies in psoriatic patients receiving long-term etretinate. *Br J Dermatol* 1985; **112:** 77–81.
8. Boyd AS. An overview of the retinoids. *Am J Med* 1989; **86:** 568–74.
9. Taylor AEM, Mitchison H. Fatty liver following isotretinoin therapy. *Br J Dermatol* 1991; **124:** 505–6.

Effects on mental function. Case reports provide evidence of depression, psychotic symptoms, suicide, and suicide attempts occurring as idiosyncratic adverse effects of isotretinoin. However, the high background prevalence of psychiatric illness among adolescents in general, and among patients with acne, are potentially confounding factors. Retrospective studies have not shown a clear cause and effect mechanism and prospective studies have been limited by sample size. Systematic reviews have found no strong evidence for an association between isotretinoin use and depression or suicidal behaviour, but noted that the evidence was not sufficiently compelling to rule out a weak association,[1,2] although other factors were probably more important.[1] In the absence of better evidence, monitoring for depression and other psychiatric effects has been advised for all patients receiving isotretinoin.[3-5]

Two cases of sustained dreaming have also been reported. After 2 to 3 weeks of oral isotretinoin, both patients reported changes in their dreaming pattern with a feeling that they had been 'dreaming all night'. The dreams persisted for 4 to 5 weeks after which they subsided despite continued isotretinoin therapy.[6]

1. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2005; **24:** 92–102.
2. Strahan JE, Raimer S. Isotretinoin and the controversy of psychiatric adverse effects. *Int J Dermatol* 2006; **45:** 789–99.
3. Ng CH, Schweitzer I. The association between depression and isotretinoin use in acne. *Aust N Z J Psychiatry* 2003; **37:** 78–84.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Acne, isotretinoin and suicidality. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0506.htm (accessed 27/09/07)
5. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Isotretinoin (Roaccutane): psychiatric adverse reactions. *Current Problems* 2006; **31:** 8–9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
6. Gupta MA, Gupta AK. Isotretinoin use and reports of sustained dreaming. *Br J Dermatol* 2001; **144:** 919–20.

Effects on the musculoskeletal system. Hyperostotic changes (bone spurs) or calcification of tendons and ligaments, resembling *diffuse idiopathic skeletal hyperostosis* (DISH), have been reported with systemic retinoid therapy.[1,2] DISH-like hyperostotic changes are common in the general population and are associated with ageing; the use of chronic retinoid therapy may increase the risk of developing these changes. Reports have particularly involved patients with keratinisation disorders being treated with large doses of retinoids for prolonged periods, and radiographic changes can be found in most patients after long-term treatment. However, minimal bone changes have also been found in radiographic studies of patients treated with isotretinoin in the dose range usually used to treat acne. Changes were also reported in a study of very low doses of isotretinoin used over 3 years to investigate skin cancer prevention. There have been few reports on the skeletal adverse effects of chronic low-dose etretinate and acitretin and results so far have been equivocal;[2] further studies are needed to clarify any effects. *Premature closure of the epiphyses* in children treated with retinoids has also been described.[1] Again, high doses or prolonged therapy were often used. There is limited evidence to suggest that children might also be at increased risk of slender long bones. There have been rare reports of changes in bone mineral density and *osteoporosis* from retinoid therapy, but there is limited evidence to confirm this association.[1] Ongoing clinical surveillance and periodic radiographic skeletal surveys have been recommended during long-term therapy; symptomatic bone spurs may be treated surgically.[1]

There have also been individual reports of *hypercalciuria*[3] or *hypercalcaemia*[4-6] associated with oral retinoid therapy.

Muscular disorders such as myalgia are not uncommon in patients treated with oral isotretinoin. Reversible myopathy with muscle pain, weakness, and raised creatine kinase concentrations has been described in a few patients treated with isotretinoin,[7] etretinate,[8] and acitretin.[9] Asymptomatic muscle damage has also been found in a study of patients given etretinate for at least a year.[10] Rhabdomyolysis and myoglobinuria have been described in a patient given isotretinoin for acne.[11] Myositis, often affecting the lower limbs, has occurred in a few patients given tretinoin for remission induction in acute promyelocytic leukaemia.[12-15] In one case, cardiac myositis also occurred.[14] Symptoms usually had an onset of 2 to 4 weeks and responded to stopping tretinoin and being treated with a corticosteroid. In a few cases, subsequent courses of tretinoin were given without recurrence of symptoms.[14,15] A review[15] suggested that some cases of myositis might have been associated with the retinoic acid syndrome (see under Tretinoin, p.1618) or Sweet's syndrome (see Effects on the Skin, under Tretinoin, p.1618).

1. DiGiovanna JJ. Isotretinoin effects on bone. *J Am Acad Dermatol* 2001; **45:** S176–S182.
2. Halverstam CP, *et al.* Lack of significant skeletal changes after long-term, low-dose retinoid therapy: case report and review of the literature. *J Cutan Med Surg* 2006; **10:** 291–9.
3. Wilson DJ, *et al.* Skeletal hyperostosis and extraosseous calcification in patients receiving long-term etretinate (Tigason). *Br J Dermatol* 1988; **119:** 597–607.
4. Valentic JP, *et al.* Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. *JAMA* 1983; **250:** 1899–1900.
5. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; **ii:** 1093.
6. Akiyama H, *et al.* Hypercalcaemia due to all-trans retinoic acid. *Lancet* 1992; **339:** 308–9.
7. Hodak E, *et al.* Muscle damage induced by isotretinoin. *BMJ* 1986; **293:** 425–6.
8. Hodak E, *et al.* Etretinate-induced skeletal muscle damage. *Br J Dermatol* 1987; **116:** 623–6.
9. Lister RK, *et al.* Acitretin-induced myopathy. *Br J Dermatol* 1996; **134:** 989–90.
10. David M, *et al.* Electromyographic abnormalities in patients undergoing long-term therapy with etretinate. *J Am Acad Dermatol* 1988; **19:** 273–5.
11. Guttman-Yassky E, *et al.* Acute rhabdomyolysis and myoglobinuria associated with isotretinoin treatment. *Int J Dermatol* 2003; **42:** 499–500.
12. Miranda N, *et al.* Myositis with tretinoin. *Lancet* 1994; **334:** 1096.
13. Martínez-Chamorro C, *et al.* ATRA-induced myositis in induction therapy of acute promyelocytic leukemia. *Haematologica* 2002; **87:** ECR08.
14. Fabbiano F, *et al.* All-trans retinoic acid induced cardiac and skeletal myositis in induction therapy of acute promyelocytic leukaemia. *Br J Haematol* 2005; **129:** 444–5.
15. Chan KH, *et al.* A case of all-trans retinoic acid-induced myositis in the treatment of acute promyelocytic leukaemia. *Clin Lab Haematol* 2005; **27:** 399–401.

Effects on the nervous system. There has been a report[1] of Guillain-Barré syndrome in 2 patients taking oral isotretinoin; both patients required ventilatory support and recovered slowly after treatment with intravenous immunoglobulins. There had been 1 case reported previously to the UK CSM. Intracranial hypertension, causing headaches and papilloedema, can occur with retinoids, including isotretinoin (see Effects on the Eyes, above).

1. Pritchard J, *et al.* Guillain-Barré syndrome seen in users of isotretinoin. *BMJ* 2004; **328:** 1537.

Effects on the respiratory system. There have been reports of exercise-induced wheezing,[1] eosinophilic pleural effusion,[2] and worsening asthma[3,4] associated with isotretinoin therapy. The US manufacturers have records of adverse effects on the lung including worsening asthma, recurrent pneumothorax, interstitial fibrosis, and pulmonary granuloma.[5] A study of healthy subjects confirmed that lung function tests could deteriorate after treatment with isotretinoin.[5]

1. Fisher DA. Exercise-induced bronchoconstriction related to isotretinoin therapy. *J Am Acad Dermatol* 1985; **13:** 524.
2. Bunker CB, *et al.* Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989; **i:** 435–6.

3. Sabroe RA, *et al.* Bronchospasm induced by isotretinoin. *BMJ* 1996; **312:** 886.
4. Kapur N, *et al.* Exacerbation of asthma by isotretinoin. *Br J Dermatol* 2000; **142:** 388–9.
5. Bunker CB, *et al.* Isotretinoin and the lung. *Br J Dermatol* 1991; **125** (suppl 38): 29.

Effects on serum lipids. The oral retinoids induce dose-dependent changes in serum lipids. There can be increases in very-low-density-lipoprotein cholesterol with smaller increases in low-density-lipoprotein cholesterol and reductions in high-density-lipoprotein cholesterol.[1,2] These effects appear to be unrelated to age or sex. They occur early during treatment and are usually reversible within a few weeks of withdrawal. Overall, the effect of isotretinoin is much greater than that of etretinate. Although the total cholesterol and triglyceride concentrations may remain within normal limits, types IIb and IV hyperlipidaemias are not uncommon among patients receiving oral retinoids. A large retrospective study[3] of patients treated with isotretinoin for acne found that of those who had normal concentrations before treatment, there was an increase in triglycerides in 44% and in total cholesterol in 31% of patients. Pancreatitis may be associated with hypertriglyceridaemia in patients treated with isotretinoin.[4-7]

Retinoids should be used with caution in patients with pre-existing hypertriglyceridaemia or in those at risk of developing hypertriglyceridaemia.[1] Use of fish oil containing eicosapentaenoic acid has been reported to attenuate retinoid-induced increases in serum-cholesterol and serum-triglyceride concentrations.[2,8]

1. Henkin Y, *et al.* Secondary dyslipidemia: inadvertent effects of drugs in clinical practice. *JAMA* 1992; **267:** 961–8.
2. Mantel-Teeuwisse AK, *et al.* Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Safety* 2001; **24:** 443–56.
3. Zane LT, *et al.* A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. *Arch Dermatol* 2006; **142:** 1016–22.
4. Flynn WJ, *et al.* Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. *Ann Intern Med* 1987; **107:** 63.
5. McCarter TL, Chen YK. Marked hyperlipidemia and pancreatitis associated with isotretinoin therapy. *Am J Gastroenterol* 1992; **87:** 1855–8.
6. Jamshidi M, *et al.* Acute pancreatitis secondary to isotretinoin-induced hyperlipidemia. *J Okla State Med Assoc* 2002; **95:** 79–80.
7. Greene JP. An adolescent with abdominal pain taking isotretinoin for severe acne. *South Med J* 2006; **99:** 992–4.
8. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. *Hum Toxicol* 1987; **6:** 219–22.

Effects on sexual function. Ejaculatory failure has been reported in 3 men to be associated with isotretinoin treatment.[1] A possible mechanism could be an effect on the goblet cells of the seminal vesicles, an effect similar to the general reduction in body secretions which leads to dry mucous membranes.

1. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. *Lancet* 1994; **344:** 198.

Effects on the skin, hair, and nails. Apart from the more common effects of oral retinoids on the skin and hair (see Adverse Effects, above), there have been isolated reports of various other reactions. Stickiness of the skin, particularly of the palms and soles, has been described with etretinate.[1,2] It has also occurred in a patient using topical tretinoin,[3] but not when he had previously taken a course of oral isotretinoin. Papules and pustules on the palms and soles have also been described with etretinate use.[4] In a series of 5 patients being treated for psoriasis, the lesions appeared 5 to 9 days after starting therapy and cleared spontaneously within a few weeks leaving a desquamation, despite continuing etretinate.

Granulomatous nodules or pyogenic granulomas have been reported with isotretinoin,[5,6] etretinate,[7,8] topical tretinoin,[9,10] and topical tazarotene.[11] Pyoderma gangrenosum has occurred in patients treated with isotretinoin.[12-14] Prurigo-like eruptions have been reported with etretinate.[15] Precipitation or exacerbation of erythroderma has been reported with isotretinoin,[16] etretinate,[17] and acitretin.[18]

Reversible chloasma (melasma) has been reported with isotretinoin.[19]

Acne fulminans is an uncommon complication of acne, developing as a sudden onset of ulcerative crusting acne with fever, weight loss, and musculoskeletal pain. Although isotretinoin may be used to treat this condition,[20] there have been reports of acne fulminans being precipitated by isotretinoin.[21,22] In some cases erythema nodosum has also developed,[23,24] but it has been suggested that this might be a manifestation of acne fulminans rather than an adverse effect of isotretinoin.[24] Erythema nodosum has also occurred in patients given oral tretinoin for remission induction in acute promyelocytic leukaemia. In a series of 4 cases, patients were successfully managed with a 5-day course of oral corticosteroid allowing the tretinoin course to be completed.[25] There has been a report of fatal toxic epidermal necrolysis associated with etretinate.[26]

For other reports of eruptions associated with vasculitic syndromes, see below. Painful scrotal ulcers and Sweet's syndrome (acute febrile neutrophilic dermatosis) are other reactions that have been reported with oral tretinoin (see p.1618). Skin erosion after wax depilation has been reported in patients receiving retinoids (see Skin Fragility under Precautions, below).

Curling hair has been described in transplant recipients taking isotretinoin and azathioprine.[27] Oral retinoids have been associated with nail fragility, onycholysis,[28] paronychia, and other forms of nail dystrophy.[29,30]

1. Penneys NS, Hernandez D. A sticky problem with etretinate. *N Engl J Med* 1991; **325:** 521.
2. Higgins EM, Pembroke AC. Sticky palms—an unusual side-effect of etretinate therapy. *Clin Exp Dermatol* 1993; **18:** 389–90.
3. Lockridge J, *et al.* Tretinoin-induced sticky skin: a case report and review of the literature. *Cutis* 1999; **63:** 142–4.
4. David M, *et al.* Palmoplantar eruption associated with etretinate therapy. *Acta Derm Venereol (Stockh)* 1986; **66:** 87–9.
5. Lane PR, Hogan DJ. Granulomatous lesions appearing during isotretinoin therapy. *Can Med Assoc J* 1984; **130:** 550.
6. Türel A, *et al.* A rare side-effect of systemic isotretinoin treatment: pyogenic granuloma. *J Eur Acad Dermatol Venereol* 2003; **17:** 609–11.
7. Williamson DM, Greenwood R. Multiple pyogenic granulomata occurring during etretinate therapy. *Br J Dermatol* 1983; **109:** 615–17.
8. Kanoh H, *et al.* Granulomatous nodule on vocal cord possibly induced by etretinate therapy. *Br J Dermatol* 2000; **142:** 1258–60.
9. MacKenzie-Wood AR, Wood G. Pyogenic granuloma-like lesions in a patient using topical tretinoin. *Australas J Dermatol* 1998; **39:** 248–50.
10. Teknetzis A, *et al.* Pyogenic granulomas following topical application of tretinoin. *J Eur Acad Dermatol Venereol* 2004; **18:** 337–9.
11. Dawkins MA, *et al.* Pyogenic granuloma-like lesion associated with topical tazarotene therapy. *J Am Acad Dermatol* 2000; **43:** 154–5.
12. Hughes BR, Cunliffe WJ. Development of folliculitis and pyoderma gangrenosum in association with abdominal pain in a patient following treatment with isotretinoin. *Br J Dermatol* 1990; **122:** 683–7.
13. Gangaram HB, *et al.* Pyoderma gangrenosum following treatment with isotretinoin. *Br J Dermatol* 1997; **136:** 636–7.
14. Freiman A, Brassard A. Pyoderma gangrenosum associated with isotretinoin therapy. *J Am Acad Dermatol* 2006; **55** (suppl): S107–S108.
15. Boer J, Smeenk G. Nodular prurigo-like eruptions induced by etretinate. *Br J Dermatol* 1987; **116:** 271–4.
16. Wantzin GL, Thomsen K. A new cutaneous side effect of isotretinoin. *J Am Acad Dermatol* 1985; **13:** 665.
17. Levin J, Almeyda J. Erythroderma due to etretinate. *Br J Dermatol* 1985; **112:** 373.
18. Mahé E, *et al.* Acitretin-induced erythroderma in a psoriatic patient. *J Eur Acad Dermatol Venereol* 2006; **20:** 1133–4.
19. Burke H, Carmichael AJ. Reversible melasma associated with isotretinoin. *Br J Dermatol* 1996; **135:** 862.
20. Seukeran DC, Cunliffe WJ. The treatment of acne fulminans: a review of 25 cases. *Br J Dermatol* 1999; **141:** 307–9.
21. Huston NR, Mules R. Acne fulminans with severe myalgia precipitated by isotretinoin therapy. *N Z Med J* 1985; **36:** 821.
22. Choi EH, Bang D. Acne fulminans and 13-cis-retinoic acid. *J Dermatol* 1992; **19:** 378–83.
23. Kellett JK, *et al.* Erythema nodosum and circulating immune complexes in acne fulminans after treatment with isotretinoin. *BMJ* 1985; **290:** 820.
24. Tan BB, *et al.* Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; **22:** 26–7.
25. Kuo MC, *et al.* All-trans-retinoic acid-induced erythema nodosum in patients with acute promyelocytic leukemia. *Ann Hematol* 2004; **83:** 376–80.
26. McIvor A. Fatal toxic epidermal necrolysis associated with etretinate. *BMJ* 1992; **304:** 548.
27. van der Pijl JW, *et al.* Isotretinoin and azathioprine: a synergy that makes hair curl? *Lancet* 1996; **348:** 622–3.
28. Önder M, *et al.* Isotretinoin-induced nail fragility and onycholysis. *J Dermatol Treat* 2001; **12:** 115–16.
29. Dharmagunawardena B, Charles-Holmes R. Median canaliform dystrophy following isotretinoin therapy. *Br J Dermatol* 1997; **137:** 658–9.
30. Yung A, *et al.* Isotretinoin-induced elkonyxis. *Br J Dermatol* 2005; **153:** 671–2.

Effects on taste. Almost complete loss of taste has been reported in a patient given oral isotretinoin 600 micrograms/kg daily for 20 weeks.[1] Sense of taste returned about 6 months after isotretinoin was stopped. Up to September 1994 the UK CSM knew of 5 cases of taste changes, including 4 reports of loss of taste.

1. Halpern SM, *et al.* Loss of taste associated with isotretinoin. *Br J Dermatol* 1996; **134:** 378.

Overdosage. Apart from vague abdominal discomfort there were no other symptoms or significant abnormalities in a 15-year-old who was treated with gastric lavage 1.5 hours after ingestion of 350 mg of isotretinoin.[1] The authors noted a similar outcome in 2 other cases of isotretinoin overdosage reported in the literature at that time. In a subsequent report, mild headache, skin that was dry and peeling, and cheilitis occurred in a 29-year-old who ingested 900 mg of isotretinoin.[2]

1. Hepburn NC. Deliberate self-poisoning with isotretinoin. *Br J Dermatol* 1990; **122:** 840–1.
2. Aubin S, *et al.* Massive isotretinoin intoxication. *Clin Exp Dermatol* 1995; **20:** 348–50.

Vasculitic syndromes. The manufacturer of isotretinoin and etretinate has received isolated reports of vasculitis associated with the use of these oral retinoids; Wegener's granulomatosis has also been reported after the use of isotretinoin.[1,2] The precise mechanism underlying these effects is unknown; in some patients there may have been a direct toxic effect as symptoms developed shortly after the start of treatment, in other patients the onset was long-delayed and may have been triggered by the incidental use of antibacterials. Vasculitis, manifesting as fever and skin lesions, has been reported in patients given oral tretinoin for acute promyelocytic leukaemia.[3]

1. Dwyer JM, *et al.* Vasculitis and retinoids. *Lancet* 1989; **ii:** 494–6.
2. Anonymous. Retinoids and necrotizing vasculitis. *WHO Drug Inf* 1989; **3:** 187.
3. Paydas S, *et al.* Vasculitis associated with all trans retinoic acid (ATRA) in a case with acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 547–8.

Precautions

Isotretinoin and other oral retinoids are teratogenic and therefore contra-indicated in pregnant patients. It is advisable for female patients to begin using contraceptive measures 1 month before starting isotretinoin treatment. Pregnancy should be excluded before starting therapy and avoided during treatment and for 1 month after stopping treatment. Patients receiving isotretinoin should not donate blood during, or for 1 month after stopping therapy, because of the potential risk to the fetus of a pregnant transfusion recipient. *Pregnancy or blood donation must be avoided for much longer periods in patients taking acitretin or etretinate.* Isotretinoin is contra-indicated in patients with hepatic impairment, hyperlipidaemias, and hypervitaminosis A. Renal impairment does not affect the pharmacokinetics of isotretinoin but a lower starting dose has been suggested in severe impairment. It is not known whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely; isotretinoin use in breast-feeding women is therefore contra-indicated because of the potential for adverse effects in the infant. Isotretinoin should be used with care in patients with a history of depression and patients taking isotretinoin should be monitored for signs of depressive illness.

Liver function and fasting blood lipids should be measured at the start of therapy, after the first month (or every 1 to 2 weeks for the first 2 months for acitretin), and thereafter as appropriate. Blood glucose should be monitored throughout treatment in patients who either have, or are predisposed to, diabetes mellitus. Some recommend routine radiological evaluation in patients receiving long-term therapy (see under Effects on the Musculoskeletal System, above). Patients may have a reduced tolerance to contact lenses.

Excessive exposure to sunlight and UV light should be avoided.

Dizziness, drowsiness, and visual disturbances may occur rarely, and could affect the performance of skilled tasks such as driving.

When applied topically the precautions described under tretinoin (see p.1618) should be considered.

Pregnancy. The problem of prescribing oral retinoids to women of child-bearing potential has been discussed.[1,2] Intra-uterine exposure to isotretinoin has caused spontaneous abortion and a characteristic pattern of fetal malformations involving craniofacial, cardiac, thymic, and CNS structures.[3,4] Some infants have also shown subnormal intelligence and other neuropsychological impairments.[5] The risk of malformation appears to be high at all therapeutic doses of isotretinoin even when the duration of exposure is short.[6] Despite warnings on the use of retinoids during pregnancy and the need for adequate contraception in women of child-bearing potential, and other strict guidelines on their use, intra-uterine exposure to retinoids has still occurred.[7-10]

Isotretinoin has a relatively short half-life and it has been recommended that conception should be avoided for at least one month after the end of treatment. A survey of women who conceived after the use of isotretinoin (64% within one month of stopping treatment) suggested that the incidence of spontaneous abortion or congenital malformations was no greater than in the general population.[11]

Warnings to avoid conception are similar for oral tretinoin (see p.1618). However, patients taking oral retinoids with longer half-lives must avoid conception for much longer periods; at least 2 years (3 years in the USA) is recommended if patients are taking acitretin although the period of time for patients taking etretinate has not been established (see also Pregnancy under Acitretin, p.1586).

Unless otherwise contra-indicated, oral combined contraceptives have been recommended as the contraceptive method of choice for women undergoing retinoid treatment.[12] Use of an additional form of contraception, such as a barrier method, is also recommended.[2,7] For further information on the use of hormonal contraceptives with retinoids, see p.2068.

1. Mitchell AA. Oral retinoids: what should the prescriber know about their teratogenic hazards among women of child-bearing potential? *Drug Safety* 1992; **7:** 79–85.
2. Chan A, *et al.* Oral retinoids and pregnancy. *Med J Aust* 1996; **165:** 164–7.
3. Lammer EJ, *et al.* Retinoic acid embryopathy. *N Engl J Med* 1985; **313:** 837–41.
4. Rosa F. Isotretinoin dose and teratogenicity. *Lancet* 1987; **ii:** 1154.
5. Adams J. High incidence of intellectual deficits in 5-year-old children exposed to isotretinoin 'in utero'. *Teratology* 1990; **41:** 614.
6. Dai WS, *et al.* Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol* 1992; **26:** 599–606.
7. Atanackovic G, Koren G. Fetal exposure to oral isotretinoin: failure to comply with the Pregnancy Prevention Program. *Can Med Assoc J* 1999; **160:** 1719–20.
8. CDC. Accutane -exposed pregnancies—California, 1999. *MMWR* 2000; **49:** 28–31.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Avoiding fetal abnormalities with isotretinoin.*Aust Adverse Drug React Bull* 2005; **24:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.htm (accessed 27/09/07)
10. Abroms L, *et al.* What is the best approach to reducing birth defects associated with isotretinoin? *PLoS Med* 2006; **3:** e483. Available at: http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0030483 (accessed 27/09/07)
11. Dai WS, *et al.* Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol* 1989; **125:** 362–5.
12. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; **184:** 161–70.

Skin fragility. Wax depilation should be avoided in patients receiving retinoids since they cause increased skin fragility and facial and leg erosions have occurred.[1-3] Licensed UK product information also recommends that wax depilation should be avoided for at least 6 months after isotretinoin treatment because of the risk of epidermal stripping. Aggressive chemical dermabrasion and cutaneous laser treatment should also be avoided for a period of 5 to 6 months after treatment because of the risk of hypertrophic scarring in atypical areas and, more rarely, post-inflammatory hypo- or hyperpigmentation in treated areas.

1. Egido Romo M. Isotretinoin and wax epilation. *Br J Dermatol* 1991; **124:** 393.
2. Holmes SC, Thomson J. Isotretinoin and skin fragility. *Br J Dermatol* 1995; **132:** 165.
3. Woollons A, Price ML. Roaccutane and wax epilation: a cautionary tale. *Br J Dermatol* 1997; **137:** 839–40.

Interactions

Use of isotretinoin with vitamin A (including dietary supplements) should be avoided because of additive toxic effects. Tetracyclines should be avoided as their use with isotretinoin has been associated with the development of benign intracranial hypertension. Skin irritation may be increased if isotretinoin is given with topical keratolytic or exfoliative anti-acne treatments; such use should be avoided.

Antiepileptics. For the effect of isotretinoin on *carbamazepine*, see p.475.

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p.2068.

Pharmacokinetics

Isotretinoin is absorbed from the gastrointestinal tract and absorption may be increased by food. Minimal systemic absorption occurs after topical application. Peak plasma concentrations occur 1 to 4 hours after oral doses. Oral bioavailability is low, possibly due to metabolism in the gut wall and first-pass metabolism in the liver. Isotretinoin is highly bound to plasma proteins. It is metabolised in the liver to its major metabolite 4-oxo-isotretinoin; there is also some isomerisation of isotretinoin to tretinoin. Several cytochrome P450 isoenzymes are involved in isotretinoin metabolism, including CYP2C8, CYP2C9, CYP3A4, and CYP2B6. Isotretinoin, tretinoin, and their metabolites undergo enterohepatic recycling. The terminal elimination half-life of isotretinoin is 10 to 20 hours, while that of the 4-oxo metabolite may be up to 50 hours; return to physiological levels of retinoids takes about 2 weeks after stopping therapy. Equal amounts of a dose appear in the faeces, mainly as unchanged drug, and in the urine as metabolites.

Isotretinoin crosses the placenta. It is not known whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely.

◊ References.

1. Colburn WA, *et al.* Food increases the bioavailability of isotretinoin. *J Clin Pharmacol* 1983; **23:** 534–9.
2. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; **10:** 38–62.
3. Kraft JC, *et al.* Embryonic retinoid concentrations after maternal intake of isotretinoin. *N Engl J Med* 1989; **321:** 262.
4. Larsen FG, *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; **23:** 42–61.
5. Chen C, *et al.* Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol* 1997; **37:** 279–84.
6. Nulman I, *et al.* Steady-state pharmacokinetics of isotretinoin and its 4-oxo metabolite: implications for fetal safety. *J Clin Pharmacol* 1998; **38:** 926–30.

Uses and Administration

Isotretinoin is a retinoid. It is the *cis* configuration of tretinoin (p.1618), which is the acid form of vitamin A (p.1971). Isotretinoin is given orally for the treatment of severe acne (below) that has not responded to other measures; it is also applied topically in milder forms of acne. It is not indicated for uncomplicated adolescent acne, and is not licensed for prepubertal acne (but see also Administration in Children, below, for use in infantile acne). Isotretinoin has also been tried in a number of other skin disorders and in some forms of neoplastic disease.

In the UK and a number of other countries the initial oral dose of isotretinoin for acne is 500 micrograms/kg daily, although in the USA initial doses of up to 1 mg/kg daily are permitted. The dose is given with food once daily or in two divided doses and adjusted if necessary up to 1 mg/kg daily according to response and adverse effects. Patients intolerant to the initial dose may be able to continue treatment at a lower dose, but there is a higher risk of relapse. Doses up to 2 mg/kg daily are permitted in the USA and some other countries for patients whose disease is very severe or primarily on the body instead of the face. A lower starting dose has been recommended in the UK for patients with severe renal impairment (see below).

Acute exacerbation of acne is occasionally seen during the initial period, but usually subsides within 7 to 10 days on continued treatment. Treatment should continue for 15 to 24 weeks or until the total cyst count has decreased by over 70%. Long-term remission and relapse rates are related to total dose, and additional benefit is not expected beyond a cumulative dose of 120 to 150 mg/kg. Improvement may continue for several months after stopping treatment; prolonged remissions can occur.

Repeat courses are not normally recommended but occasionally they may be required. However, since acne may continue to improve after stopping isotretinoin, there must be at least a 2-month drug-free period before starting repeat treatment.

For the topical treatment of acne a gel containing 0.05% of isotretinoin is applied sparingly once or twice daily. A therapeutic response may not be evident for 6 to 8 weeks.

◊ General reviews.

1. DiGiovanna JJ. Systemic retinoid therapy. *Dermatol Clin* 2001; **19:** 161–7.
2. Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; **45** (suppl): S150–S157.
3. Vivat-Hannah V, Zusi FC. Retinoids as therapeutic agents: today and tomorrow. *Mini Rev Med Chem* 2005; **5:** 755–60.
4. Njar VC, *et al.* Retinoids in clinical use. *Med Chem* 2006; **2:** 431–8.

Acne. The retinoids play an important role in the treatment of acne (p.1577). Isotretinoin reduces sebum excretion with a subsequent reduction in growth of *Propionibacterium acnes*; it also normalises the differentiation of keratinocytes, which has a comedolytic effect, and appears to have a direct anti-inflammatory effect.[1-3] The main indication for oral isotretinoin therapy is severe forms of acne (such as conglobate or nodulocystic acne or acne at risk of permanent scarring) that is unresponsive to other therapy including systemic antibacterials. Some argue,[4,5] however, that oral isotretinoin should be considered for first-line treatment in other cases, such as less severe acne that has the potential to cause scarring or acne that is causing severe psychological distress. Most patients remain free of their disease after a single course of isotretinoin, or have a mild recurrence that responds to other treatments to which it was previously resistant. A minority will relapse and those at higher risk include patients less than 16 years of age, those with severe acne on the trunk, and adult women.[2] Cumulative dose, rather than daily dose, appears to be an important factor in achieving stable remission.[4] To avoid relapse, a course of therapy to a cumulative dose of 120 to 150 mg/kg is required.[2] This usually equates to a course of 5 to 6 months using daily doses of 0.5 to 1 mg/kg. One group suggests[4] that treatment should be continued for 2 months after complete clearing of acne to avoid recurrence, and that higher cumulative doses (up to 200 mg/kg) might be needed in some cases, such as those showing clear signs of ongoing improvement when a cumulative dose of 150 mg/kg has been reached. In patients who do relapse, repeat courses may be indicated.[2,3] However, improvement may continue for several months after withdrawal and at least 2 months should elapse before determining whether further treatment is necessary. There is evidence to suggest that patients who repeatedly relapse after stopping standard isotretinoin therapy may benefit from continuous use of very low doses of isotretinoin, such as 250 or 500 micrograms/kg daily taken every 4th week for 6 months, 100 micrograms/kg daily, or a single dose of 20 mg once or twice a week.[6] Low-dose regimens have also been tried instead of standard isotretinoin doses for persistent moderate or severe acne. A dose of 20 mg daily for 6 months has produced significant improvement or complete remission in moderate acne.[7] However, prolonged use of low-dose regimens is needed to achieve a cumulative dose of 120 mg/kg and reduce the risk of relapse.[8] Isotretinoin has also been used for the treatment of acne associated with immunosuppressive therapy in transplant recipients.[9,10]

Isotretinoin is also used topically for acne. Although it has no sebosuppressive effect and only a weak direct anti-inflammatory effect by this route[1] its comedolytic effect makes unplugged follicles less anaerobic, reducing *P. acnes* growth and associated inflammation.[11] Topical isotretinoin appears to have a similar efficacy to tretinoin, but may be better tolerated.[3]

Isotretinoin is not licensed for the treatment of prepubertal acne because of the risk of adverse effects including early epiphyseal closure, but see also Administration in Children, below.

1. Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. *Drugs* 2003; **63:** 1579–96.
2. James WD. Acne. *N Engl J Med* 2005; **352:** 1463–72.
3. Chivot M. Retinoid therapy for acne: a comparative review. *Am J Clin Dermatol* 2005; **6:** 13–19.
4. Cooper AJ. The Australian Roaccutane Advisory Board. Treatment of acne with isotretinoin: recommendations based on Australian experience. *Australas J Dermatol* 2003; **44:** 97–105.
5. Dréno B, *et al.* An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. *Eur J Dermatol* 2006; **16:** 565–71.
6. Palmer RA, *et al.* 'Microdose' isotretinoin. *Br J Dermatol* 2000; **143:** 205–6.
7. Amichai B, *et al.* Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol* 2006; **54:** 644–6.
8. Mandekou-Lefaki I, *et al.* Low-dose schema of isotretinoin in acne vulgaris. *Int J Clin Pharmacol Res* 2003; **23:** 41–6.
9. Tam M, Cooper A. The use of isotretinoin in a renal transplant patient with acne. *Br J Dermatol* 1987; **116:** 463.
10. Bunker CB, *et al.* Isotretinoin treatment of severe acne in post-transplant patients taking cyclosporine. *J Am Acad Dermatol* 1990; **22:** 693–4.
11. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Pediatr Drugs* 2003; **5:** 301–13.

Administration in children. Oral isotretinoin is licensed in most countries for use from 12 years of age where appropriate, but it is not licensed for the treatment of prepubertal acne because of the risk of adverse effects including early epiphyseal closure. However, it has been used orally with some success in nodulocystic infantile acne when topical preparations and antibacterial therapies have not been effective.[1-4] A range of doses have been used, sometimes influenced by the dosage form available, but in general doses have been similar to those used in older patients, that is, 0.5 to 1 mg/kg daily to cumulative doses of 120 to 150 mg/kg. As there are no suitable licensed oral products for children, isotretinoin liquid capsules have been opened and the contents mixed with a drink[1,2] or soft food[3] immediately before use to make administration easier. One report[3] described freezing the capsule so that it could be cut more easily to the required dose, which could then be concealed in food.

For mention of the investigation of isotretinoin in children with neuroblastoma, see Malignant Neoplasms, below.

1. Mengesha YM, Hansen RC. Toddler-age nodulocystic acne. *J Pediatr* 1999; **134:** 644–8.
2. Sarazin F, *et al.* Treatment of an infantile acne with oral isotretinoin. *Eur J Dermatol* 2004; **14:** 71–2.
3. Barnes CJ, *et al.* A practical approach for the use of oral isotretinoin for infantile acne. *Pediatr Dermatol* 2005; **22:** 166–9.
4. Torrelo A, *et al.* Severe acne infantum successfully treated with isotretinoin. *Pediatr Dermatol* 2005; **22:** 357–9.

Administration in renal impairment. Although renal impairment does not affect the pharmacokinetics of isotretinoin, licensed UK product information suggests that patients with severe renal impairment being treated with oral isotretinoin for acne should be started at a lower dose, such as 10 mg daily. It may be gradually increased up to 1 mg/kg daily as tolerated.

Malignant neoplasms. Retinoids such as isotretinoin have been studied in the treatment of various neoplastic or preneoplastic disorders. Although oral tretinoin is used for remission induction in acute promyelocytic leukaemia (see p.1619), other retinoids do not have an established role in the treatment of cancer. There may, however, be a place for the use of retinoids in the chemoprevention of some malignancies.

There has been particular interest in the potential for retinoids to prevent the formation of *skin cancers* (p.672) in patients at increased risk. Maintenance immunosuppression may increase the incidence of pre-malignant and malignant skin lesions in solid organ transplant recipients; large numbers of lesions can develop and tend to be more aggressive than those in the general population.[1] Although there has been some investigation in cardiac transplant recipients, most case reports and some small studies have involved renal transplant patients. Oral acitretin has been reported to reduce the number of actinic keratoses and reduce the development of new basal and squamous cell carcinomas in these patients.[1-4] Other patients at increased risk of skin cancers who may benefit from prophylactic retinoid therapy include those with xeroderma pigmentosum and naevoid basal cell carcinoma syndrome; oral isotretinoin, rather than acitretin, has been tried in such patients.[5] Retinoids might also be considered in others who have already developed nonmelanoma skin cancers, such as those with conditions requiring maintenance immunosuppression, chronic lymphocytic leukaemia or non-Hodgkin's lymphoma, severe photodamage of the skin, and those with squamous cell carcinoma at high risk of metastasis or that has already metastasised.[5]

Since retinoids suppress rather than cure skin cancer, rebound occurs when the retinoid is stopped and long-term therapy is needed. There is some concern about the risks of such long-term use, particularly on plasma lipids and bone, and monitoring has been recommended.[1,4,5] The mucocutaneous adverse effects that commonly occur can affect patient acceptance during long-term use; mucocutaneous effects may be more severe with isotretinoin, but hair loss may be more extensive with acitretin.[4,5] Gradual dose escalation to an effective dose can be used to minimise these mucocutaneous effects. One example using isotretinoin starts with a dose of 250 micrograms/kg on alternate days for a month, increased to 250 micrograms/kg daily for the second month, then to 500 micrograms/kg daily for the third month; the dose is then adjusted as tolerated.[5] As there are risks of teratogenicity with retinoids, isotretinoin is preferred for women of child-bearing potential because of its shorter half-life.[4,5] For acitretin doses that have been used, see p.1586.

Topical application of retinoids has also been tried for chemoprevention of skin cancers. Topical tretinoin has been used on actinic keratoses in organ transplant recipients, but results have been mixed and may depend on dose. If squamous cell carcinomas are present, however, systemic retinoids should be considered.[3]

Retinoids have been studied in the chemoprevention of primary disease recurrence and second primary tumours after treatment for *squamous cell carcinoma of the head and neck* (p.666) but results have been mixed and limited by resistance and toxicity.[6] A large placebo-controlled study[7] has also reported that low-dose oral isotretinoin (30 mg daily for 3 years with an additional 4 years of follow-up) did not reduce the rate of second primary tumours or death in patients who had been treated for early stage head and neck squamous cell carcinoma. There has also been some interest in the use of retinoids, given orally (isotretinoin) or topically (isotretinoin or tretinoin), in the management of *oral leucoplakia*, which can be pre-malignant (see under Bleomycin, p.688). However, despite reports of beneficial response, relapse frequently occurs on stopping retinoid therapy.[6,8]

Oral isotretinoin has been studied as continuation therapy in children with high-risk *neuroblastoma* that had responded to intensive chemotherapy. One study[9] found improved survival with 6 cycles of isotretinoin given for 14 days of each 28-day cycle. However, another study[10] using a lower dose given daily for 4 years or until relapse found no additional benefit from isotretinoin.

1. Kovach BT, *et al.* Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; **19:** 726–34.
2. Chen K, *et al.* Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; **152:** 518–23.
3. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. *Dermatol Ther* 2005; **18:** 28–33.
4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19:** 306–14.
5. Otley CC, *et al.* Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; **32:** 562–8.
6. Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Crit Rev Oncol Hematol* 2005; **55:** 143–52.
7. Khuri FR, *et al.* Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006; **98:** 441–50.
8. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; **95:** 1258–64.
9. Matthay KK, *et al.* Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; **341:** 1165–73.
10. Kohler JA, *et al.* A randomized trial of 13-cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. *Br J Cancer* 2000; **83:** 1124–7.

Skin disorders. Apart from its established role in the treatment of acne (above), isotretinoin has been tried in many other skin disorders not responding to usual therapy.[1,2] Clinical responses to oral isotretinoin have been reported[1] in small numbers of patients with anogenital warts (p.1584), rosacea (p.1583), and lichen planus (p.1580). Benefit has also been reported for keratinisation disorders such as Darier's disease[2] (p.1578), ichthyosis[1,2] (p.1580), and pityriasis rubra pilaris.[1,2] Isotretinoin is less effective than other retinoids for psoriasis[1] (p.1583). Oral isotretinoin may be used for chemoprevention of skin cancers (see Malignant Neoplasms, above).

Topical isotretinoin has been used to reduce some of the signs of photoageing[3] (p.1581).

1. Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. *Am J Clin Dermatol* 2005; **6:** 175–84.
2. Sehgal VN, *et al.* Isotretinoin – unapproved indications/uses and dosage: a physician's reference. *Int J Dermatol* 2006; **45:** 772–7.
3. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.

Preparations

BP 2008: Isotretinoin Capsules; Isotretinoin Gel;
USP 31: Isotretinoin Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Atlacne; Curacne; Isotrex; Retinide; Roaccutan; Scheritonin†; Zonatian; ***Austral.:*** Accure; Isohexal; Isotrex; Oratane; Roaccutane; ***Austria:*** Ciscutan; Isocutan†; Isosol; Lurantal; Roaccutan; ***Belg.:*** Isosupra Lidose; Roaccutane; ***Braz.:*** Acnil; Cecnoin; Isoacne†; Isoface; Isotrex; Lurantal; Roacutan; ***Canad.:*** Accutane; Clarus; Isotrex†; ***Chile:*** Acnotin; Isotrex; Lisacne†; Piplex; Roacnetan; ***Cz.:*** Aknenormin; Curacne; Isotretin; Isotrex†; Roaccutane; Stiefel Acne Gel; ***Denm.:*** Accutin; Dermaoral†; Isotrex; Roaccutan; ***Fin.:*** Roaccutan; ***Fr.:*** Contracne; Curacne; Procuta; Roaccutane; ***Ger.:*** Aknefug Iso; Aknenormin; Isoderm; Isotret; Isotrex; Roaccutan; ***Gr.:*** A-Cnotren; Accuran; Acnogen; Aknesil; Curacne; Derminoin†; Flitrion; Inotrin; Isodermal; Isogeril†; Isoskin; Isotroin; Lyotret; Noitron; Noroseptan; Novacne; Opridan; Policano; Reducar; Roaccutane; Stiefotrex; Trecifan; Tretin; ***Hong Kong:*** Acnotin; Isotrex; Oratane†; Roaccutane; ***Hung.:*** Aknenormin; Isotrex; Roaccutan; Sotret; Tretinak; ***India:*** Acutret†; Isotroin; ***Irl.:*** Isotrex; Roaccutane; ***Israel:*** Curatane; Isotrex; Roaccutane; ***Ital.:*** Aisoskin; Isotrex; Roaccutan; ***Malaysia:*** Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Mex.:*** Isoface; Isotrex; Neotrex; Oratane; Roaccutan; Sotrexe; ***Neth.:*** Roaccutane; ***NZ:*** Isotane; Isotrex; Oratane; Roaccutane†; ***Philipp.:*** Acnetrex; Isotrex; Roaccutane; ***Pol.:*** Aknenormin; Curacne; Isotrex; Izotek; Roaccutane; Tretinex; ***Port.:*** Isdiben; Isoprotil; Isotrex; Orotrex; Roaccutan†; ***S.Afr.:*** Acnetane; Isotrex; Oratane; Roaccutane; ***Singapore:*** Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Spain:*** Acnemin; Dercutane; Farmacne; Flexresan; Isdiben; Iso Estedi†; Isotrex; Roacutan; ***Switz.:*** Curakne; Liderma; Roaccutane; Tretinac; ***Thai.:*** Acnotin; Isotane; Isotrex; Proacne; Roaccutane; Sotret; ***Turk.:*** Roaccutane; ***UK:*** Isotrex; Roaccutane; ***USA:*** Accutane; Amnesteem; Claravis; Sotret; ***Venez.:*** Cuticlin; Isoface; Isotrex†; Roaccutan.

Multi-ingredient: ***Austria:*** Isotrex; Isotrexin; ***Braz.:*** Isotrexin; Isotrexol; ***Cz.:*** Isotrexin; ***Fr.:*** Antibiotrex; ***Ger.:*** Isotrexin; ***Hung.:*** Isotrexin; ***Irl.:*** Isotrexin; ***Ital.:*** Isotrexin; ***Pol.:*** Isotrexin; ***Port.:*** Isotrexin; ***Singapore:*** Isotrexin; ***Spain:*** Isotrex Eritromicina; ***Thai.:*** Isotrexin; ***UK:*** Isotrexin.

Keluamid

Keluamida.

Келуамид

Profile

Keluamid has keratolytic properties and has been used in topical preparations for the treatment of seborrhoeic dermatitis and other scaling skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Kelual; ***Fr.:*** Kelual.

Multi-ingredient: ***Arg.:*** Kelual Zinc; ***Fr.:*** Kelual DS; Kelual Zinc; Kertyol-S.

Kinetin

N^6-Furfuryladenine; 6-Furfurylaminopurine.

Кинетин

$C_{10}H_9N_5O = 215.2.$

CAS — 525-79-1.

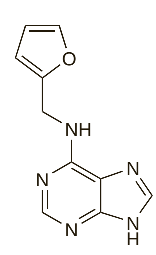

NOTE. The name kinetin has also been used as a proprietary name for hyaluronidase (p.2321).

Profile

Kinetin is a plant growth hormone that has been promoted in products for the management of photodamaged skin and hyperpigmentation but good evidence of efficacy appears to be lacking.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Kinerase†; ***Braz.:*** Kinerase; ***Hong Kong:*** Kinerase; ***Malaysia:*** Kinerase†; ***Mex.:*** Kinerase; ***Singapore:*** Kinerase; ***USA:*** Kinerase.

Kojic Acid

Kójico, ácido. 5-Hydroxy-2-hydroxymethyl-4-pyrone.

Койевая Кислота

$C_6H_6O_4 = 142.1.$

CAS — 501-30-4.

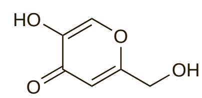

Profile

Kojic acid is reported to inhibit melanin production and is used in topical preparations for the treatment of hyperpigmentation disorders (p.1582). Kojic acid is also used as a food additive.

◊ References.

1. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg* 1999; **25:** 282–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Unitone 4.

Multi-ingredient: ***Arg.:*** Cellskinlab Phyto Spot; Melasoft†; Neoquin; ***Braz.:*** Melani-D Maos; ***Chile:*** Alastik†; D 4†; Neostrata; Phyto Spot; Primacy Phyto +†; ***Mex.:*** Nova Derm; ***Port.:*** Despigmentante; Fade Cream†.

Liarozole *(BAN, rINN)*

Liarozol; Liarozolum. (±)-5-(*m*-Chloro-α-imidazol-1-ylbenzyl)benzimidazole.

Лиарозол

$C_{17}H_{13}ClN_4 = 308.8.$

CAS — 115575-11-6; 145858-51-1.

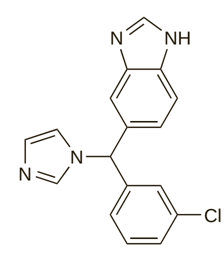

Liarozole Fumarate *(BANM, USAN, rINNM)*

Fumarato de liarozol; Liarozole, Fumarate de; Liarozoli Fumaras; R-85246.

Лиарозола Фумарат

$2C_{17}H_{13}ClN_4,3C_4H_4O_4 = 965.7.$

CAS — 145858-52-2.

Liarozole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de liarozol; Liarozole, Chlorhydrate de; Liarozoli Hydrochloridum; R-75251.

Лиарозола Гидрохлорид

$C_{17}H_{13}ClN_4, HCl = 345.2.$

CAS — 145858-50-0.

Profile

Liarozole, an imidazole analogue, increases plasma and cutaneous retinoic acid concentrations through inhibition of cytochrome P450 isoenzymes involved in retinoic acid catabolism. It is under investigation for the management of ichthyoses and psoriasis.

◊ References.

1. Bhushan M, *et al.* Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145:** 546–53.
2. Lucker GPH, *et al.* Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. *Br J Dermatol* 2005; **152:** 566–9.
3. Verfaille CJ, *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; **156:** 965–73.

Lisadimate *(USAN, rINN)*

Glyceryl Aminobenzoate; Glyceryl PABA; Lisadimato; Lisadimatum. Glyceryl 1-(4-aminobenzoate).

Лизадимат

$C_{10}H_{13}NO_4$ = 211.2.

CAS — 136-44-7.

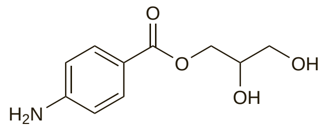

Profile

Lisadimate, a substituted aminobenzoate, is a sunscreen (see p.1576) with actions similar to those of aminobenzoic acid (p.1589). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Lithium Succinate

Litio, succinato de.

Лития Сукцинат

$C_4H_6O_4.xLi$.

CAS — 16090-09-8.

ATC — D11AX04.

ATC Vet — QD11AX04.

Profile

Lithium succinate is reported to have anti-inflammatory properties and is used as an 8% cream or ointment, usually with zinc sulfate. It is applied twice daily initially in the treatment of seborrhoeic dermatitis (p.1584). It should be used with caution in patients with psoriasis as it may exacerbate their condition.

◊ References.

1. Gould DJ, *et al.* A double-blind, placebo-controlled, multicenter trial of lithium succinate ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 1992; **26:** 452–7.
2. Cuelenaere C, *et al.* Use of topical lithium succinate in the treatment of seborrhoeic dermatitis. *Dermatology* 1992; **184:** 194–7.
3. Langtry JA, *et al.* Topical lithium succinate ointment (Efalith) in the treatment of AIDS-related seborrhoeic dermatitis. *Clin Exp Dermatol* 1997; **22:** 216–19.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Litiofarm†; ***Austria:*** Efalith; ***Belg.:*** Efalith; ***Ger.:*** Efadermin; ***Irl.:*** Efalith; ***Switz.:*** Efalith.

Maggots

Larvas; Sterile Larvae.

Личинки

Profile

Maggots used in wound management are the live sterile larvae of *Lucilia sericata*, the common greenbottle fly. Larval therapy (sometimes called biosurgery) may be used for debridement of infected or necrotic wounds (p.1585), including diabetic foot ulcers. Maggots produce a mixture of proteolytic enzymes that breaks down the necrotic tissue while leaving the healthy tissue unharmed, and kill or prevent the growth of micro-organisms, particularly Gram-positive bacteria. The movement of the maggots also appears to stimulate the growth of granulation tissue.

The maggots are applied to the surface of the wound and kept in place with dressings for up to 3 days. They are removed with the dressing, and the wound is irrigated with sodium chloride solution; any remaining maggots are removed with forceps.

Maggots should not be applied to wounds that have a tendency to bleed easily, or that communicate with a body cavity or any internal organ. Pain has been reported with larval therapy and some patients may require analgesics.

◊ References.

1. Courtenay M, *et al.* Larva therapy in wound management. *J R Soc Med* 2000; **93:** 72–4.
2. Jukema GN, *et al.* Amputation-sparing treatment by nature: "surgical" maggots revisited. *Clin Infect Dis* 2002; **35:** 1566–71.
3. Sherman RA, Shimoda KJ. Presurgical maggot debridement of soft tissue wounds is associated with decreased rates of postoperative infection. *Clin Infect Dis* 2004; **39:** 1067–70.
4. Armstrong DG, *et al.* Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc* 2005; **95:** 254–7.
5. Steenvoorde P, *et al.* Maggot debridement therapy: free-range or contained? An in-vivo study. *Adv Skin Wound Care* 2005; **18:** 430–5.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: LarvE.

Melanin

Меланин

Profile

Melanin is a group of natural pigments found in many plants and animals; they are present in human skin and hair. Natural and synthetic forms of melanin have been used in sunscreen preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Fotobloc.

Multi-ingredient: ***Arg.:*** Fotocrem Ultra; ***Chile:*** ProZone Face; ProZone Gel; ***Mex.:*** ProZone Body; ProZone Face; ProZone Gel; ProZone Ultra; ProZone Ultra Fluido.

Mequinol *(USAN, rINN)*

BMS-181158; *p*-Guaiacol; 4-HA; 4-Hidroxianisol; HQMME; Hydroquinone Monomethyl Ether; *p*-Hydroxyanisole; Hydroxyquinone Methyl Ether; Méquinol; Mequinolum; Metoxifenol; *p*-Metoxifenol. 4-Methoxyphenol.

Мехвинол

$C_7H_8O_2$ = 124.1.

CAS — 150-76-5.

ATC — D11AX06.

ATC Vet — QD11AX06.

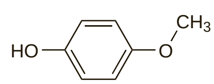

Profile

Mequinol is used similarly to hydroquinone (p.1598), in concentrations of up to 20%, in the treatment of hyperpigmentation (see Pigmentation Disorders, p.1582). A preparation containing mequinol 2% with tretinoin 0.01% is used for the treatment of solar lentigines (liver spots).

Adverse effects. A report of severe reversible irregular hypopigmentation of the hands, arms, neck, and legs in a West Indian woman who applied a bleaching wax containing mequinol for 2 to 3 months to lighten the colour of her skin.[1]

1. Boyle J, Kennedy CTC. British cosmetic regulations inadequate. *BMJ* 1984; **288:** 1998–9.

Pigmentation disorders. References.

1. Fleischer AB, *et al.* The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42:** 459–67.
2. Njoo MD, *et al.* Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; **42:** 760–9.
3. Ortonne JP, *et al.* Safety and efficacy of combined use of 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% solution and sunscreen in solar lentigines. *Cutis* 2004; **74:** 261–4.
4. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis* 2004; **74:** 319–22.
5. Draelos ZD. The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin effectively improves the appearance of solar lentigines in ethnic groups. *J Cosmet Dermatol* 2006; **5:** 239–44.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Leucobasal; ***Braz.:*** Leucodin; ***Fr.:*** Any; Leucodinine B; ***Gr.:*** Leucodinine-M; ***Spain:*** Novo Dermoquinona.

Multi-ingredient: ***Canad.:*** Solage†; ***USA:*** Solage.

Meradimate *(USAN, rINN)*

Menthyl *O*-Aminobenzoate; Menthyl Anthranilate; Méradimate; Meradimato; Meradimatum. 5-Methyl-2-(1-methylethyl)-cyclohexyl 2-aminobenzoate.

Мерадимат

$C_{17}H_{25}NO_2$ = 275.4.

CAS — 134-09-8.

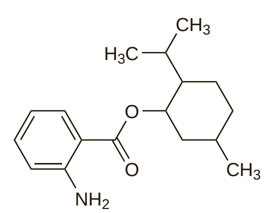

NOTE. Do not confuse with methyl anthranilate (p.1607). Neo-Heliopan MA is a trade name that has been used for meradimate.

Pharmacopoeias. In *US.*

USP 31 (Meradimate). Store in airtight containers.

Profile

Meradimate is used as a sunscreen (p.1576). It is effective against UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Ammoniated Mercury

Aminomercuric Chloride; Hydrargyri Aminochloridum; Hydrargyrum Amidochloratum; Hydrargyrum Ammoniatum; Hydrargyrum Praecipitatum Album; Mercuric Amidochloride; Mercuric Ammonium Chloride; Mercurio amoniacal; Mercury Amide Chloride; Mercury Aminochloride; Precipitado blanco (de mercurio); White Precipitate.

Хлористый Меркураммоний

NH_2HgCl = 252.1.

CAS — 10124-48-8.

ATC — D08AK01.

ATC Vet — QD08AK01.

NOTE. 'White Precipitate' has also been used as a name for Precipitated Mercurous Chloride.

Pharmacopoeias. In *US.*

USP 31 (Ammoniated Mercury). A white amorphous powder or pulverulent pieces; odourless. It is stable in air, but darkens on exposure to light. Insoluble in water and in alcohol; readily soluble in warm hydrochloric, nitric, and acetic acids. Protect from light.

Profile

Ammoniated mercury was formerly used topically in the treatment of skin infections and psoriasis but the use of such mercurial preparations is generally deprecated. Frequent or prolonged application to large areas or to broken skin or mucous membranes can cause mercury poisoning (see p.2341) and use on infants has produced acrodynia (pink disease). Ammoniated mercury is also a potent sensitiser and can produce allergic reactions.

Effects on the kidneys. Of 60 patients who were found to have nephrotic syndrome, 32 had used skin-lightening creams containing 5 to 10% of ammoniated mercury.[1] Concentrations of mercury in the urine of these patients were up to 250 nanograms/mL compared with a usual upper limit of 80 nanograms/mL. Of 26 patients followed up for up to 2 years, 13 had no remission or response to treatment; 6 of these had used skin lighteners.

1. Barr RD, *et al.* Nephrotic syndrome in adult Africans in Nairobi. *BMJ* 1972; **2:** 131–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Homeovox; ***Hung.:*** Dermaforine†.

Mesulphen *(BAN)*

Mesulfen *(pINN)*; Dimethyldiphenylene Disulphide; Dimethylthianthrene; Mesulfeeni; Mésulfène; Mesulfeno; Mesulfenum. It consists mainly of 2,7-dimethylthianthrene.

Месульфен

$C_{14}H_{12}S_2$ = 244.4.

CAS — 135-58-0.

ATC — D10AB05; P03AA03.

ATC Vet — QD10AB05; QP53AA01.

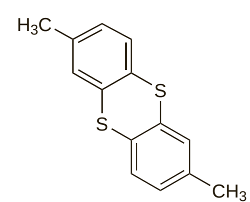

Pharmacopoeias. *Jpn* includes thianthol, a mixture of 2,7-dimethylthianthrene and ditolyl disulfide.

Profile

Mesulphen has been used as a parasiticide and antipruritic in a range of skin disorders including acne, scabies, and seborrhoea. Sensitivity to mesulphen has occasionally been reported.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Citemul S†; ***Switz.:*** Soufrol.

Multi-ingredient: ***India:*** Polyderm†.

Methoxsalen (BAN)

Ammoidin; Amoidina; Methoxalenum; 8-Methoxypsoralen; Metoksaleeni; Metoksalen; Metoxalen; Metoxaleno; Metoxipsoraleno; 8-MOP; Xanthotoxin; Xantotoxina. 9-Methoxyfuro[3,2-g]chromen-7-one; 9-Methoxy-7H-furo[3,2-g][1]benzopyran-7-one.

Метоксален

$C_{12}H_8O_4$ = 216.2.

CAS — 298-81-7.

ATC — D05AD02; D05BA02.

ATC Vet — QD05AD02; QD05BA02.

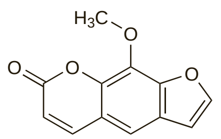

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Methoxsalen). White to cream-coloured, odourless, fluffy, needle-like crystals. Practically insoluble in water; sparingly soluble in boiling water and in ether; soluble in boiling alcohol, in acetone, in acetic acid, in propylene glycol, and in benzene; freely soluble in chloroform. Protect from light.

Adverse Effects

Methoxsalen given orally commonly causes nausea and less frequently mental effects including insomnia, nervousness, and depression.

Photochemotherapy or PUVA (see under Uses and Administration, below) may cause pruritus and mild transient erythema. Other effects include oedema, dizziness, headache, vesiculation, bulla formation, acneform eruption, and severe skin pain. Overexposure to sunlight or UVA radiation may produce severe burns in patients being treated with psoralens. Hypertrichosis, pigmentation alterations of skin or nails, and onycholysis, have also been reported. PUVA can produce premature ageing of the skin, and may be associated with an increased risk of malignant cutaneous neoplasms.

Carcinogenicity. See under Effects on the Skin, below.

There has been concern about a possible increased risk of noncutaneous malignancies associated with PUVA. However, a long-term study of 1380 patients followed for 20 years reported no overall increase in solid malignancies, lymphoma, or leukaemia.[1]

1. Stern RS, Väkevä LH. PUVA Follow-up Study. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; **108:** 897–900.

Effects on the eyes. Free methoxsalen has been detected in the lens of the eye for at least 12 hours after oral doses.[1] It may become integrated into the structure of the lens if there is exposure to UV light, promoting cataract formation in patients who fail to wear suitable eye protection for 12 to 24 hours after methoxsalen ingestion.[2] However, provided that eye protection is used there appears to be no significant dose-dependent increase in the risk of cataract formation,[3] although a higher risk of developing nuclear sclerosis and posterior subcapsular opacities has been noted in patients who have received more than 100 treatments.[4] Other ocular effects include dose-related transient visual-field defects reported in 3 patients receiving PUVA therapy.[5] Psoralens may also increase the sensitivity of the retina to visible light.[6]

1. Lerman S, *et al.* Potential ocular complications from PUVA therapy and their prevention. *J Invest Dermatol* 1980; **74:** 197–9.
2. Woo TY, *et al.* Lenticular psoralen photoproducts and cataracts of a PUVA-treated psoriatic patient. *Arch Dermatol* 1985; **121:** 1307–8.
3. See J-A, Weller P. Ocular complications of PUVA therapy. *Australas J Dermatol* 1993; **34:** 1–4.
4. Stern RS, *et al.* Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; **85:** 269–73.
5. Fenton DA, Wilkinson JD. Dose-related visual-field defects in patients receiving PUVA therapy. *Lancet* 1983; **i:** 1106.
6. Souêtre E, *et al.* 5-Methoxypsoralen increases the sensitivity of the retina to light in humans. *Eur J Clin Pharmacol* 1989; **36:** 59–61.

Effects on the hair. Hypertrichosis was noticed in 15 of 23 female patients receiving PUVA therapy compared with 2 of 14 patients treated with UVA alone.[1]

1. Rampen FHJ. Hypertrichosis in PUVA-treated patients. *Br J Dermatol* 1983; **109:** 657–60.

Effects on the immune system. PUVA therapy appears to have immunosuppressive effects and inhibits lymphocytes, polymorphonuclear leucocytes, and Langerhans' cells.[1-3] It is capable of inducing antinuclear antibody formation and a syndrome similar to systemic lupus syndrome has developed during treatment.[4,5] An immunological basis has also been suspected for the development of nephrotic syndrome in one patient who received PUVA therapy.[6]

See also Hypersensitivity, below.

1. Farber EM, *et al.* Long-term risks of psoralen and UV-A therapy for psoriasis. *Arch Dermatol* 1983; **119:** 426–31.
2. Morison WL, *et al.* Abnormal lymphocyte function following long-term PUVA therapy for psoriasis. *Br J Dermatol* 1983; **108:** 445–50.
3. Chang A, *et al.* PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. *Br J Dermatol* 1988; **119:** 281–7.
4. Bruze M, *et al.* Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol (Stockh)* 1984; **64:** 157–60.
5. Bruze M, Ljunggren B. Antinuclear antibodies appearing during PUVA therapy. *Acta Derm Venereol (Stockh)* 1985; **65:** 31–6.
6. Lam Thuon Mine LTK, *et al.* Nephrotic syndrome after treatment with psoralens and ultraviolet A. *BMJ* 1983; **287:** 94–5.

Effects on the skin. *MALIGNANT NEOPLASMS.* Squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, actinic keratosis, Bowen's disease, and malignant melanoma have all been reported during or after cessation of PUVA.[1-3] There have been several large long-term follow-up studies to assess the risk of **non-melanoma** skin cancer in patients receiving PUVA therapy. Early studies from Europe found no clear evidence that PUVA was independently carcinogenic but did find that previous treatment with arsenic, methotrexate, or ionising radiation increased the incidence of skin tumours.[4] Studies from the USA have found an increase in the incidence of basal cell carcinoma and squamous cell carcinoma independent of other treatment,[5] which was dose-related in some studies.[6] Male genitalia appeared to be particularly susceptible.[7] It has been suggested that the differences between the findings might be due to the fact that in Europe higher and fewer doses are used and the median total dose employed may be only 29% of that used in the USA.[8] However, further studies from northern Europe also found a dose-related increase in the risk of developing squamous cell carcinomas.[9-11] One small series suggested that about 50% of the recipients of high-dose PUVA went on to develop squamous cell carcinomas or premalignant lesions.[12] While some European workers have findings that confirm the increased susceptibility of the male genitalia[13] others have failed to find any such evidence.[14,15] Ongoing surveillance of patients is encouraged as US data[16,17] show the risk of skin cancers and genital tumours to persist long-term after stopping PUVA therapy. A few patients have gone on to develop metastatic disease.[18,19]

There are anecdotal reports of **malignant melanomas** occurring in patients who had received PUVA. A prospective study[20] in 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976 found that the risk of melanoma increases about 15 years after the first treatment with PUVA and that the risk was increased especially in patients who had received 250 treatments or more. The authors suggested that long-term PUVA should therefore be used with caution, especially in younger patients. Further follow-up of this group[21] found the incidence of melanoma to increase over time. However, a similar follow-up study[11] of 4799 patients treated with PUVA found no increase in the risk for malignant melanoma. Comparing their findings with the earlier study, the authors suggested that the results might differ because one-fifth of their cohort had received bath PUVA in which lower UVA doses are used. The comment has also been made[22] that patients receiving long-term therapy should be followed up carefully and that such therapy should not be used in patients at risk for melanoma.

A study[23] of follow-up data on patients who had received trioxysalen bath PUVA did not find an increase in risk of developing either squamous cell carcinoma or malignant melanoma, but the authors suggested that further study is needed to determine the carcinogenicity of trioxysalen PUVA.

1. Reshad H, *et al.* Cutaneous carcinoma in psoriatic patients treated with PUVA. *Br J Dermatol* 1984; **110:** 299–305.
2. Kemmett D, *et al.* Nodular malignant melanoma and multiple squamous cell carcinomas in a patient treated by photochemotherapy for psoriasis. *BMJ* 1984; **289:** 1498.
3. Suurmond D, *et al.* Skin cancer and PUVA maintenance therapy for psoriasis. *Br J Dermatol* 1985; **113:** 485–6.
4. Henseler T, *et al.* Skin tumors in the European PUVA study. *J Am Acad Dermatol* 1987; **16:** 108–16.
5. Forman AB, *et al.* Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 1989; **125:** 515–19.
6. Stern RS, *et al.* Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; **91:** 120–4.
7. Stern RS, *et al.* Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322:** 1093–7.
8. Moseley H, Ferguson J. Photochemotherapy: a reappraisal of its use in dermatology. *Drugs* 1989; **38:** 822–37.
9. Bruynzeel I, *et al.* 'High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 1991; **124:** 49–55.
10. Lindelöf B, *et al.* PUVA and cancer: a large-scale epidemiological study. *Lancet* 1991; **338:** 91–3.
11. Lindelöf B, *et al.* PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141:** 108–12.
12. Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; **131:** 215–19.
13. Perkins W, *et al.* Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336:** 1248.
14. Wolff K, Hönigsmann H. Genital carcinomas in psoriasis patients treated with photochemotherapy. *Lancet* 1991; **337:** 439.
15. Aubin F, *et al.* Genital squamous cell carcinoma in men treated by photochemotherapy: a cancer registry-based study from 1978 to 1998. *Br J Dermatol* 2001; **144:** 1204–6.
16. Stern RS, *et al.* The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002; **47:** 33–9.
17. Nijsten TEC, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 2003; **121:** 252–8.
18. Lewis FM, *et al.* Metastatic squamous-cell carcinoma in patient receiving PUVA. *Lancet* 1994; **344:** 1157.
19. Stern RS. Metastatic squamous cell cancer after psoralen photochemotherapy. *Lancet* 1994; **344:** 1644–5.
20. Stern RS, *et al.* Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; **336:** 1041–5.
21. Stern RS. The PUVA Follow Up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44:** 755–61.
22. Wolff K. Should PUVA be abandoned? *N Engl J Med* 1997; **336:** 1090–1.
23. Hannuksela-Svahn A, *et al.* Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *Br J Dermatol* 1999; **141:** 497–501.

NON-MALIGNANT SKIN DISORDERS. Toxic pustuloderma, marked by erythema and superficial pustular lesions, has been reported in a patient given PUVA therapy for mycosis fungoides.[1] There have been a number of reports of bullous pemphigoid occurring, or recurring, in patients treated with PUVA, usually for psoriasis.[2] A case of lichen planus pemphigoides has also been described in a woman treated with topical PUVA.[3] Another effect sometimes associated with PUVA is severe skin pain;[4,5] the pain may respond to treatment with topical capsaicin.[5] Long-term PUVA treatment accelerates ageing of the skin.[6]

1. Yip J, *et al.* Toxic pustuloderma due to PUVA treatment. *Br J Dermatol* 1991; **125:** 401–2.
2. Barnadas MA, *et al.* Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. *Int J Dermatol* 2006; **45:** 1089–92.
3. Kuramoto N, *et al.* PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; **142:** 509–12.
4. Burrows NP, *et al.* PUVA-induced skin pain. *Br J Dermatol* 1993; **129:** 504.
5. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
6. Sator P-G, *et al.* Objective assessment of photoageing effects using high-frequency ultrasound in PUVA-treated psoriasis patients. *Br J Dermatol* 2002; **147:** 291–8.

Hypersensitivity. Hypersensitivity reactions to methoxsalen and PUVA therapy occur rarely but there have been reports of drug-induced fever,[1] bronchoconstriction,[2] and contact dermatitis.[3] Cases of anaphylaxis have also been attributed to methoxsalen[4] and 5-methoxypsoralen.[5]

1. Tóth Kása I, Dobozy A. Drug fever caused by PUVA treatment. *Acta Derm Venereol (Stockh)* 1985; **65:** 557–8.
2. Ramsay B, Marks JM. Bronchoconstriction due to 8-methoxypsoralen. *Br J Dermatol* 1988; **119:** 83–6.
3. Takashima A, *et al.* Allergic contact and photocontact dermatitis due to psoralens in patients with psoriasis treated with topical PUVA. *Br J Dermatol* 1991; **124:** 37–42.
4. Park JY, *et al.* Anaphylaxis to 8-methoxypsoralen during photochemotherapy. *Photodermatol Photoimmunol Photomed* 2003; **19:** 37–8.
5. Legat FJ, *et al.* Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol* 2001; **145:** 821–2.

Precautions

Methoxsalen should not generally be given to patients with diseases associated with light sensitivity such as porphyria, although it may be used with care in some photosensitivity disorders to decrease sensitivity to sunlight. Other contra-indications include aphakia, melanoma or a history of melanoma, and invasive squamous cell carcinoma. It is generally recommended that PUVA therapy should not be used in children. Methoxsalen should be used with caution in patients with hepatic impairment.

Patients should not sunbathe for 24 hours before and 48 hours after PUVA treatment. They should avoid exposure to sunlight, even through glass or cloud cover for at least 8 hours after methoxsalen ingestion and should wear wrap-around UVA absorbing glasses for 24 hours after ingestion. Photosensitivity is more prolonged after topical application and treated skin should be protected from exposure to sunlight for at least 12 to 48 hours, and possibly for up to a week. Unless specific treatment is required male genitalia should be shielded during PUVA therapy. It has been recommended that patients undergo an ophthalmic examination before starting therapy and at regular intervals thereafter, especially those at increased risk of cataracts. Patients should also receive regular examinations for signs of premalignant or malignant skin lesions. Anti-nuclear antibody titre may be tested before starting therapy, particularly if there is a suggestion of connective tissue disease; frequent evaluation during treatment is probably not necessary for patients with uncomplicated psoriasis, an initial negative test, and no symptoms of connective tissue disease.

Porphyria. Methoxsalen should not be given to patients with porphyria.

Interactions

Methoxsalen should be used with caution with other drugs also known to cause photosensitivity. It inhibits the action of cytochrome P450 isoenzyme CYP2A6, and may increase plasma concentrations of drugs metabolised via this enzyme.

Antiepileptics. Failure of PUVA treatment due to abnormally low serum concentrations of methoxsalen in a patient with epilepsy was probably a result of induction of hepatic enzymes by *phenytoin*.[1]

1. Staberg B, Hueg B. Interaction between 8-methoxypsoralen and phenytoin. *Acta Derm Venereol (Stockh)* 1985; **65:** 553–5.

Emollients. Some emollient preparations may have a photoprotective effect, and if applied immediately before UVA irradiation could interfere with the efficacy of PUVA therapy.[1,2]

1. Hudson-Peacock MJ, *et al.* Photoprotective action of emollients in ultraviolet therapy of psoriasis. *Br J Dermatol* 1994; **130:** 361–5.
2. Otman SGH, *et al.* Modulation of ultraviolet (UV) transmission by emollients: relevance to narrowband UVB phototherapy and psoralen plus UVA photochemotherapy. *Br J Dermatol* 2006; **154:** 963–8.

Food. Some foods, for example, celery, parsnip, and parsley, contain psoralens and eating large quantities may increase the risk of phototoxicity with methoxsalen. A patient[1] who ate a large quantity of celery soup the evening before and 2 hours before undergoing PUVA therapy for atopic eczema developed severe phototoxicity after treatment, which was attributed to the additive effects of methoxsalen and psoralens contained in the celery.

1. Boffa MJ, *et al.* Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* 1996; **135:** 334.

Xanthines. For mention of the effect of systemic methoxsalen on the metabolism of theophylline, see Methoxsalen, under Interactions of Theophylline, p.1145.

Pharmacokinetics

When taken orally methoxsalen is well but variably absorbed from the gastrointestinal tract and there is considerable interindividual variation in peak serum concentrations. Depending on the oral formulation used increased photosensitivity is present 1 hour after a dose, reaches a peak at about 1 to 4 hours, and disappears after about 8 hours. Methoxsalen is highly protein bound. It appears to be preferentially taken up by epidermal cells. It also diffuses into the lens of the eye. Methoxsalen is almost completely metabolised. About 95% of a dose is excreted in the urine within 24 hours. The photosensitising action of methoxsalen may persist for several days after topical application. The erythema induced by oral or topical PUVA is usually delayed and peaks after 2 to 3 days.

◊ References.

1. de Wolff FA, Thomas TV. Clinical pharmacokinetics of methoxsalen and other psoralens. *Clin Pharmacokinet* 1986; **11:** 62–75.

Uses and Administration

Methoxsalen, a psoralen, is a constituent of the seeds of *Ammi majus* and the roots of *Heracleum candicans*. It is a photosensitiser that markedly increases skin reactivity to long-wavelength ultraviolet radiation (320 to 400 nm), an effect used in photochemotherapy or PUVA [psoralen (P) and high-intensity long-wavelength UVA irradiation]. In the presence of UVA methoxsalen bonds with DNA, inhibiting DNA synthesis and cell division, and can lead to cell injury. Recovery from the cell injury may be followed by increased melanisation of the epidermis and thickening of the stratum corneum. Methoxsalen may also increase pigmentation by an action on melanocytes.

PUVA is used to treat idiopathic vitiligo and severe, recalcitrant, disabling psoriasis not adequately responsive to conventional topical therapy. It may also be useful in selected cases of atopic eczema and polymorphic light eruptions and may be used in T-cell lymphomas such as mycosis fungoides.

Methoxsalen is given orally or applied topically in PUVA regimens. *Differing oral dosage forms of methoxsalen may exhibit significantly varying bioavailabilities and times to onset of photosensitisation.* The UVA exposure dose should generally be based on prior measurement of the minimal phototoxic dose although it can be calculated with regard to the skin type of the patient if phototoxic dose testing cannot be carried out.

- To repigment **vitiliginous** areas, methoxsalen is given in a dose of 20 mg or up to 600 micrograms/kg *orally* 2 to 4 hours before measured periods of exposure to UVA, depending on the preparation. Treatment is usually given twice a week or on alternate days, but always at least 48 hours apart.
- Methoxsalen may also be applied *topically* to repigment small, well-defined vitiliginous lesions. Preparations containing up to 1% have been used but dilution to 0.1 or 0.01% may be necessary to avoid adverse cutaneous effects. The surrounding skin should be protected by an opaque sunscreen. Some suggest that the treated area should be exposed to UVA soon after application while others recommend waiting up to 2 hours. After exposure the lesions should be washed and protected from light; protection may be necessary for up to 48 hours or longer. Treatment is repeated usually once weekly. Significant repigmentation may not appear until after 6 to 9 months of treatment.
- For the treatment of **psoriasis** a dose of up to about 600 micrograms/kg *orally* is given 1.5 to 3 hours before UVA, depending on the preparation. Treatment is usually given twice a week although increased frequencies, but with at least 48-hour intervals between doses, have been suggested. If there is no response or only minimal response after the fifteenth PUVA treatment some suggest that the dosage may be increased by 10 mg and that this higher dose be used for the remainder of the course of treatment.
- Methoxsalen may also be used *topically* with UVA exposure for the treatment of psoriasis. For direct application to affected areas of skin a preparation containing approximately 0.15% (or diluted to 0.015% if necessary to avoid adverse cutaneous effects) is applied 15 minutes before UVA exposure. Alternatively the patient may take a whole body bath for 15 minutes in a methoxsalen solution, followed immediately by UVA exposure. UK guidelines (see also Skin Disorders, below) suggest a typical concentration of methoxsalen 2.6 mg/litre for such solutions although higher concentrations (up to about 3.7 mg/litre) have been used. Hand and foot soaks may be used to treat only those affected areas; a solution containing methoxsalen 3 mg/litre may be used with the affected areas immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. Baths or soaks are generally given twice a week.

Psoralen itself has also been used.

Administration. The dose of methoxsalen is usually calculated on the basis of body-weight. This method of dose calculation produces a considerable difference between the doses received by heavy and light patients. A study in 41 patients with psoriasis[1] suggested that using methoxsalen 25 mg/m^2 gave more consistent plasma concentrations and may reduce the potential for burning in heavy patients and prevent underdosing in light patients undergoing PUVA therapy.

1. Sakuntabhai A, *et al.* Calculation of 8-methoxypsoralen dose according to body surface area in PUVA treatment. *Br J Dermatol* 1995; **133:** 919–23.

PUVA. PUVA combines psoralens with UVA irradiation. The psoralens may be given directly to the patient, either orally or topically, and the patient is then exposed to UVA. In extracorporeal PUVA (extracorporeal photochemotherapy; photopheresis), an oral dose of a psoralen is given, after which the patient's leucocytes are isolated, exposed to UVA extracorporeally, and then reinfused. In another method of extracorporeal photopheresis methoxsalen is added directly to leucocytes that have already been removed from the patient. The mixture is then treated with UVA after which it is returned to the patient; the total dose of methoxsalen used by this method is lower than that used orally. PUVA has been used in a wide range of disorders including skin disorders, mycosis fungoides, and organ and tissue transplant rejection (below).

MYCOSIS FUNGOIDES. PUVA therapy is used in the treatment of the manifestations of cutaneous mycosis fungoides and Sèzary syndrome, two forms of cutaneous T-cell lymphoma (see p.657). Extracorporeal PUVA therapy (photopheresis; see above) has also been used,[1-6] particularly for disease with erythrodermic features. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests a usual treatment cycle of 2 consecutive days, which is repeated every 2 to 4 weeks. More frequent treatment may be given to symptomatic patients and those with a high peripheral blood tumour burden. Response is assessed every 3 months and then, when complete or maximal response has occurred, treatment is tapered to every 6 to 12 weeks before stopping. Relapse may be treated with the same schedule. After the first 3 months of therapy, treatment should generally be continued for a further 3 months in patients with stable disease (no response). However, consideration should be given to stopping treatment, or using combination therapy (photopheresis with interferon alfa and/or bexarotene), if there is disease progression. At 6 months and beyond, treatment should be stopped, or combination therapy considered, in patients with stable or progressive disease, but for those already receiving combination therapy, photopheresis should be stopped.

1. Duvic M, *et al.* Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35:** 573–9.
2. Zic JA, *et al.* Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; **35:** 935–45.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Rubegni P, *et al.* Extracorporeal photochemotherapy in long-term treatment of early stage cutaneous T-cell lymphoma. *Br J Dermatol* 2000; **143:** 894–6.
5. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003; **16:** 337–46.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.

ORGAN AND TISSUE TRANSPLANTATION. PUVA[1,2] and extracorporeal PUVA therapy[3-6] (photopheresis; see above) have been tried in both acute and chronic graft-versus-host disease (GVHD) that is unresponsive to usual treatment (see Haematopoietic Stem Cell Transplantation, p.1811). As well as improvements in GVHD, particularly cutaneous manifestations, PUVA therapies have enabled the doses of corticosteroids and other immunosuppressants to be reduced. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests, for chronic GVHD, a usual treatment cycle of 2 consecutive days, repeated every 2 weeks. Response is assessed after 3 months and treatment reduced to once every 4 weeks if there has been a complete or partial response. Treatment is then reassessed every 3 months and tapered or stopped when a complete or maximal response has occurred. It should be stopped if there is no response or disease progression.

Photopheresis has also been tried in treating rejection of solid organ transplants,[3,6,8] particularly after heart transplantation (p.1812). It has also shown promise in a study[9] of the prevention of heart transplant rejection.

1. Bonanomi S, *et al.* Bath PUVA therapy in pediatric patients with drug-resistant cutaneous graft-versus-host disease. *Bone Marrow Transplant* 2001; **28:** 631–2.
2. Furlong T, *et al.* Psoralen and ultraviolet A irradiation (PUVA) as therapy for steroid-resistant cutaneous acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; **8:** 206–12.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
4. Foss FM, *et al.* Extracorporeal photopheresis in chronic graft-versus-host disease. *Bone Marrow Transplant* 2002; **29:** 719–25.
5. Kanold J, *et al.* Extracorporeal photochemotherapy for graft versus host disease in pediatric patients. *Transfus Apheresis Sci* 2003; **28:** 71–80.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; **154:** 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158:** 659–78.
8. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. *Transfus Apheresis Sci* 2002; **26:** 197–204.
9. Barr ML, *et al.* Photopheresis for the prevention of rejection in cardiac transplantation. *N Engl J Med* 1998; **339:** 1744–51.

SKIN DISORDERS. PUVA has been used in a wide range of skin disorders and guidelines have been published by the British Photodermatology Group,[1,2] which are summarised as follows:

- Indications for PUVA in chronic plaque **psoriasis** include severe extensive psoriasis unresponsive to conventional topical therapies, relapse within 3 to 6 months of successful topical treatment, or patient refusal of topical treatment if UVB phototherapy has failed (see p.1583 for a discussion of the various treatments of psoriasis). Initial UVA exposure should preferably be determined on the basis of prior measurement of the minimal phototoxic dose rather than on the skin type. Increases in UVA irradiation are then calculated as a percentage of previous doses.

  Methoxsalen in an oral dose of 600 micrograms/kg given 2 hours before UVA exposure is the widely accepted standard regimen. Alternatively, 5-methoxypsoralen 1.2 mg/kg, again 2 hours before UVA exposure, can be given and appears to be almost free of the adverse reactions such as nausea, pruritus, and erythema induced by methoxsalen. However, until the clinical efficacy of 5-methoxypsoralen has been clearly shown, methoxsalen should remain the psoralen of choice for most clinical situations.

  Alternatives to oral PUVA are baths or soaks using methoxsalen or trioxysalen. For whole body bathing a concentration of methoxsalen 2.6 mg/litre is typically utilised with the patient bathing for 15 minutes followed by immediate exposure to UVA. For hand and foot soaks a concentration of methoxsalen 3 mg/litre is used with the affected area immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. For trioxysalen a concentration of about 330 micrograms/litre is used for a 15-minute whole body bath or hand and foot soak followed by immediate UVA exposure for whole body therapy, or a 30 minute delay before hand and foot UVA exposure. Whole body baths or hand and foot soaks are given twice each week.

  Methoxsalen may also be applied topically to the affected areas. A concentration of about 0.15% (or 0.015% if erythema occurs) is used in an emulsion, or 0.005% in an aqueous gel, and applied 15 minutes before UVA exposure.

  PUVA treatment should be stopped as soon as disease clearance is achieved; maintenance PUVA should be avoided to minimise cumulative UVA exposure, but may be considered if there is rapid relapse. A combination of PUVA with acitretin (300 to 700 micrograms/kg orally) or etretinate (0.5 to 1 mg/kg orally) may be considered in patients who have reached 50 treatment sessions or relapsed within 6 months of PUVA. PUVA and methotrexate are also effective for severe psoriasis but should be reserved for such cases because of the possible increased risk of skin cancer
- Oral PUVA twice weekly with methoxsalen 600 micrograms/kg or 5-methoxypsoralen 1.2 mg/kg has been effective in many patients with **vitiligo** (see Pigmentation Disorders, p.1582). If patches are well demarcated topical application of methoxsalen 0.15% may be preferable
- In **mycosis fungoides** PUVA is an effective symptomatic treatment for early disease and a useful adjunct for late-stage disease but optimal regimens have not been established (see above)
- PUVA is effective for atopic **eczema** (p.1579) but clearance is less certain than for psoriasis, twice the number of treatments may be needed, and relapse is more frequent. It should therefore be reserved for severe disease unresponsive to conventional treatments. Optimal regimens have not been established
- In **polymorphic light eruptions** (see Photosensitivity Disorders, p.1581) PUVA is effective in up to 90% of patients but is only indicated in those who are frequently or severely affected despite the regular use of high-protection broad-spectrum sunscreens. Several arbitrary regimens are in use
- Variable results have also been reported in a variety of other disorders but data has been insufficient to establish precise guidelines. Such disorders include actinic prurigo, alopecia areata, aquagenic pruritus, chronic actinic dermatitis, granuloma annulare, lichen planus, nodular prurigo, pityriasis lichenoides, localised scleroderma, solar urticaria, and urticaria pigmentosa. In most cases relapse occurs in the absence of maintenance therapy and PUVA should usually only be tried as a last resort.

Extracorporeal PUVA has been tried in patients with severe epidermolysis bullosa acquisita,[3,4] lichen planus,[5] and scleroderma.[6,7]

1. British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; **130:** 246–55.
2. Halpern SM, *et al.* Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; **142:** 22–31. Also available at: http://www.bad.org.uk/healthcare/guidelines/Topical_PUVA_Therapy.pdf (accessed 27/09/07)
3. Miller JL, *et al.* Remission of severe epidermolysis bullosa acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 1995; **133:** 467–71.
4. Gordon KB, *et al.* Treatment of refractory epidermolysis bullosa acquisita with extracorporeal photochemotherapy. *Br J Dermatol* 1997; **136:** 415–20.
5. Guyot AD, *et al.* Treatment of refractory erosive oral lichen planus with extracorporeal photochemotherapy: 12 cases. *Br J Dermatol* 2007; **156:** 553–6.
6. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; **3:** 50–62.
7. Knobler RM, *et al.* A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J Am Acad Dermatol* 2006; **54:** 793–9.

Preparations

USP 31: Methoxsalen Capsules; Methoxsalen Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Oxsoralen Ultra; ***Austral.:*** Oxsoralen; ***Austria:*** Oxsoralen; ***Belg.:*** Mopsoralen; ***Braz.:*** Oxsoralen; ***Canad.:*** Oxsoralen; Ultramop; ***Chile:*** Oxsoralen; ***Cz.:*** Oxsoralen; Uvadex; ***Denm.:*** Geroxalen†; ***Fr.:*** Meladinine; Uvadex; ***Ger.:*** Meladinine; ***Gr.:*** Melaoline; ***Hong Kong:*** Oxsoralen; ***Hung.:*** Geroxalen†; Oxsoralen; ***India:*** Macsoralen†; Manaderm; Melanocyl; ***Indon.:*** Delsoralen; Oxsoralen; ***Irl.:*** Deltasoralen; ***Ital.:*** Oxsoralen†; ***Jpn:*** Oxsoralen; ***Malaysia:*** Meladinine†; Oxsoralen; ***Mex.:*** Dermox; Meladinina; Oxsoralen; ***Neth.:*** Geroxalen; Meladinine; Oxsoralen†; ***Norw.:*** Geroxalen†; ***NZ:*** Oxsoralen; ***Pol.:*** Geralen; Oxsoralen; ***Rus.:*** Oxsoralen (Оксорален); ***S.Afr.:*** Oxsoralen; ***Singapore:*** Oxsoralen; ***Spain:*** Oxsoralen; ***Switz.:*** Meladinine; ***Thai.:*** Meladinine†; ***Turk.:*** Geroxalen; Vitspo; ***UK:*** Puvasoralen; ***USA:*** Oxsoralen; Uvadex.

Multi-ingredient: ***India:*** Melanocyl.

5-Methoxypsoralen

Bergapteeni; Bergapten; Bergapteno; Bergaptenum; 5-Metoxipsoraleno; 5-MOP. 4-Methoxy-7*H*-furo[3,2-g]chromen-7-one.

5-Метоксипсорален

$C_{12}H_8O_4$ = 216.2.
CAS — 484-20-8.
ATC — D05BA03.
ATC Vet — QD05BA03.

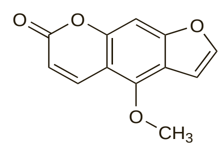

Profile

5-Methoxypsoralen is a photosensitiser with actions similar to those of methoxsalen (above). It may be given orally in the PUVA therapy (see under Methoxsalen, above) of psoriasis and vitiligo.

5-Methoxypsoralen is included in some cosmetic suntan preparations to enhance tanning but because of its potential phototoxicity this is considered unwise by authorities in Europe and the USA. Photosensitivity caused by 5-methoxypsoralen is sometimes known as Berloque dermatitis.

5-Methoxypsoralen is an ingredient of bergamot oil (p.2265).

◊ References.

1. McNeely W, Goa KL. 5-Methoxypsoralen: a review of its effects in psoriasis and vitiligo. *Drugs* 1998; **56:** 667–90.

Hypersensitivity. For mention of anaphylaxis associated with the use of 5-methoxypsoralen, see Hypersensitivity, under Adverse Effects of Methoxsalen, p.1605.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Pentaderm†; ***Austria:*** Geralen; ***Fr.:*** Psoraderm 5†; ***UK:*** Pentaderm.

Methyl Anthranilate

Metilo, antranilato de; Metylu antranilan. Methyl 2-aminobenzoate.

Метилантранилат

$C_8H_9NO_2$ = 151.2.
CAS — 134-20-3.

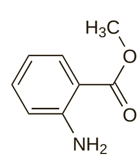

NOTE. Do not confuse with menthyl anthranilate (see Meradimate, p.1604).

Profile

Methyl anthranilate has been used in sunscreen preparations. It is a constituent of several essential oils.

Mexenone *(BAN, pINN)*

Benzofenon-10; Benzophenone-10; Mexenona; Mexénone; Mexenonum. 2-Hydroxy-4-methoxy-4′-methylbenzophenone.

Мексенон

$C_{15}H_{14}O_3$ = 242.3.
CAS — 1641-17-4.

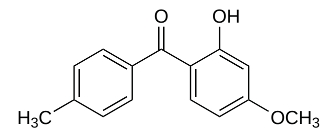

Pharmacopoeias. In *Br.*

BP 2008 (Mexenone). A pale yellow odourless or almost odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone.

Profile

Mexenone, a substituted benzophenone, is a sunscreen (p.1576) with actions similar to those of oxybenzone (p.1608). It is effective against UVB and some UVA light (for definitions, see p.1580)

Preparations

BP 2008: Mexenone Cream.

Monobenzone *(rINN)*

Benoquina; Hydroquinone Monobenzyl Ether; Monobenzona; Monobenzonum. 4-Benzyloxyphenol.

Монобензон

$C_{13}H_{12}O_2$ = 200.2.
CAS — 103-16-2.
ATC — D11AX13.
ATC Vet — QD11AX13.

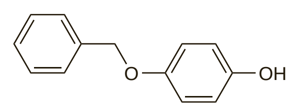

Pharmacopoeias. In *US.*

USP 31 (Monobenzone). Store at a temperature not exceeding 30° in airtight containers. Protect from light.

Adverse Effects and Precautions

Monobenzone may cause skin irritation and sensitisation. In some patients this is transient and the drug need not be withdrawn. In others, an eczematous sensitisation may occur. Excessive depigmentation may occur even beyond the areas under treatment and may produce unsightly patches.

Monobenzone frequently produces permanent depigmentation and should not be used as a substitute for hydroquinone.

Interactions

Agalsidase. For the recommendation that monobenzone not be used with agalsidase alfa or beta, see p.2252.

Uses and Administration

Monobenzone has actions similar to those of hydroquinone (p.1598) but in some patients it also produces extensive and selective destruction of melanocytes. It is used locally for final, permanent depigmentation of normal skin in extensive vitiligo (see Pigmentation Disorders, p.1582). Monobenzone is not recommended for freckling, chloasma, or hyperpigmentation following skin inflammation or due to photosensitisation after the use of certain perfumes. It has no effect on melanomas or pigmented naevi.

For vitiligo a cream containing monobenzone 20% is applied to the affected areas two or three times daily until a satisfactory response is obtained, and thereafter as necessary, usually about twice weekly. Depigmentation only becomes apparent when the preformed melanin pigments have been lost with the normal sloughing of the stratum corneum and this may take several months. If, however, no improvement is noted after 4 months, treatment should be stopped. Excessive exposure to sunlight should be avoided during treatment. After depigmentation the skin will be sensitive for the rest of the patient's life and a sunscreen must be used during sun exposure.

Preparations

USP 31: Monobenzone Cream.

Proprietary Preparations (details are given in Part 3)
Canad.: Benoquin; ***India:*** Benoquin†; ***USA:*** Benoquin.

Monochloroacetic Acid

Chloroacetic Acid; Kwas chlorooctowy; Monocloroacético, ácido.

Монохлоруксусная Кислота

$C_2H_3O_2Cl$ = 94.5.

CAS — 79-11-8.

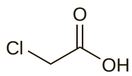

Profile

Preparations containing 50% of monochloroacetic acid are used as a caustic for the removal of plantar warts (p.1584).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Warzenmittel; ***Ger.:*** Acetocaustin; ***Switz.:*** Acetocaustine.
Multi-ingredient: ***Turk.:*** IL-33.

Motretinide *(USAN, rINN)*

Motretinid; Motretinida; Motrétinide; Motretinidi; Motretinidum; Ro-11-1430. (*all-trans*)-*N*-Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide.

Мотретинид

$C_{23}H_{31}NO_2$ = 353.5.

CAS — 56281-36-8.
ATC — D10AD05.
ATC Vet — QD10AD05.

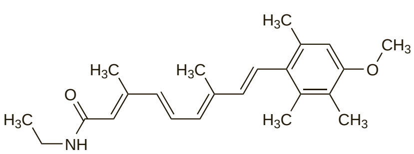

Profile

Motretinide is a retinoid structurally related to acitretin (p.1586). Motretinide is used topically in the treatment of acne (p.1577). It is applied in preparations containing 0.1%.

Preparations

Proprietary Preparations (details are given in Part 3)
Switz.: Tasmaderm.

Naphthalan Liquid

Naftalan; Naphthalanic Oil; Naphthalanum Liquidum.

Нафталановое Масло

CAS — 37229-16-6.

Profile

Naphthalan liquid is an oil-like complex mixture of naphthene hydrocarbons and tars obtained from the oil fields of Azerbaijan and Croatia. It has analgesic, anti-inflammatory, and emollient properties and is used in the treatment of conditions such as psoriasis and in various musculoskeletal disorders. It is usually applied locally in the form of the oil or as an ointment or alternatively patients may bath in the oil.

◊ References.

1. Vržogić P, *et al.* Naphthalan – a natural medicinal product. *Acta Dermatovenerol Croat* 2003; **11:** 178–84.

Octil Triazone

Octiltriazona; Octyl Triazone. 2,4,6-Trianilino-*p*-(carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine.

Октилтриазон

$C_{48}H_{66}N_6O_6$ = 823.1.

CAS — 88122-99-0.

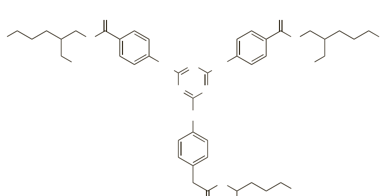

NOTE. Uvinul T 150 is a trade name that has been used for octil triazone.

Profile

Octil triazone is used as a sunscreen (p.1576). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Octinoxate *(USAN, rINN)*

Octinoxato; Octinoxatum; Octyl methoxycinnamate. 2-Ethylhexyl-*p*-methoxycinnamate; 3-(4-Methoxylphenyl)-2-propenoic acid 2-ethylhexyl ester.

Оциноксат

$C_{18}H_{26}O_3$ = 290.4.

CAS — 5466-77-3.
ATC — D02BA02.
ATC Vet — QD02BA02.

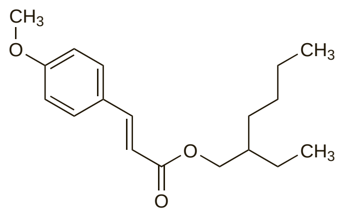

NOTE. Escalol 557, Eusolex 2292, Neo-Heliopan AV, Parsol MCX, Tinosorb OMC, Uvinul MC 80, and Uvinul MC 80 N are trade names that have been used for octinoxate.

Pharmacopoeias. In *US.*

USP 31 (Octinoxate). Pale yellow oil. Insoluble in water. Store in airtight containers at a temperature of 8° to 15°.

Profile

Octinoxate, a substituted cinnamate, is used by topical application as a sunscreen (p.1576). Cinnamate sunscreens effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p.1580). Cinnamate sunscreens may therefore be used to prevent sunburn but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity. Cinnamates may occasionally produce photosensitivity reactions.

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Octisalate *(USAN, rINN)*

Octisalato; Octisalatum; Octyl Salicylate. 2-Ethylhexyl salicylate; 2-Hydroxybenzoic acid 2-ethylhexyl ester.

Октисалат

$C_{15}H_{22}O_3$ = 250.3.

CAS — 118-60-5.

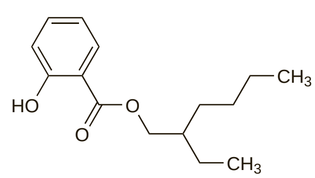

NOTE. Escalol 587, Eusolex OS, and Neo-Heliopan OS are trade names that have been used for octisalate.

Pharmacopoeias. In *US.*

USP 31 (Octisalate). Store in airtight containers.

Profile

Octisalate is a substituted salicylate used topically as a sunscreen (p.1576). Salicylates effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p.1580). Salicylate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection.

Salicylates may occasionally produce photosensitivity reactions or contact dermatitis.

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Octocrilene *(rINN)*

2-Ethylhexyl α-cyano-β-phenylcinnamate; Octocrilène; Octocrileno; Octocrilenum; Octocrylene *(USAN)*. 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate.

Октокрилен

$C_{24}H_{27}NO_2$ = 361.5.

CAS — 6197-30-4.

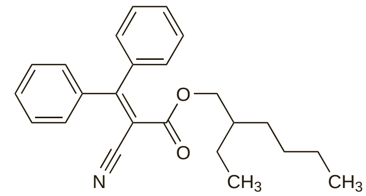

NOTE. Escalol 597, Eusolex OCR, Neo-Heliopan 303, Parsol 340, and Uvinul N 539 T are trade names that have been used for octocrilene.

Pharmacopoeias. In *US.*

USP 31 (Octocrylene). Store in airtight containers.

Profile

Octocrilene, a substituted cinnamate, is a sunscreen (p.1576) with actions similar to those of octinoxate (above). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations numerous preparations are listed in Part 3.

Oxybenzone *(USAN, rINN)*

Benzofenon-3; Benzophenone-3; Oxibenzona; Oxybenzonum. 2-Hydroxy-4-methoxybenzophenone.

Оксибензон

$C_{14}H_{12}O_3$ = 228.2.

CAS — 131-57-7.

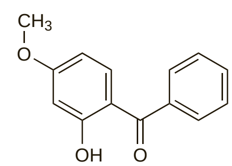

NOTE. Escalol 567, Eusolex 4360, Neo-Heliopan BB, Tinosorb B3, and Uvinul M 40 are trade names that have been used for oxybenzone.

Pharmacopoeias. In *US.*

USP 31 (Oxybenzone). A pale yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Oxybenzone is a substituted benzophenone used topically as a sunscreen (p.1576). Benzophenones effectively absorb light throughout the UVB range (wavelengths 290 to 320 nm) and also absorb some UVA light with wavelengths of 320 to about 360 nm and some UVC light with wavelengths of about 250 to 290 nm (for definitions, see p.1580). Benzophenones may therefore be used to prevent sunburn and may also provide some protection against drug-related or other photosensitivity reactions associated with UVA light; in practice they are usually combined with a sunscreen from another group.

Photocontact allergic dermatitis can be caused by topical application of benzophenone sunscreens. Oxybenzone is widely used and often found to be a photo-allergen in patients with these reactions. Contact allergy reactions occur less frequently.

Hypersensitivity. Chemical sunscreens are known to cause photosensitivity and contact allergy reactions. Oxybenzone is widely used and reported to be the sunscreen photo-allergen most commonly detected in photopatch testing.[1,2] In a group of 5800 patients with suspected allergic contact dermatitis who were tested for contact allergens,[3] a positive reaction to oxybenzone was recorded in 0.6%. There have also been rare reports of severe allergic reactions to oxybenzone including anaphylaxis; sensitivity was confirmed by patch testing.[4,5] A history of atopy may predispose patients to such reactions.

1. Berne B, Ros A-M. 7 years experience of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 1998; **38:** 61–4.
2. Bryden AM, *et al.* Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 2006; **155:** 737–47.

3. Marks JG, *et al.* North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am J Contact Dermat* 2003; **14:** 59–62.
4. Emonet S, *et al.* Anaphylaxis to oxybenzone, a frequent constituent of sunscreens. *J Allergy Clin Immunol* 2001; **107:** 556–7.
5. Yesudian PD, King CM. Severe contact urticaria and anaphylaxis from benzophenone-3 (2-hydroxy 4-methoxy benzophenone). *Contact Dermatitis* 2002; **46:** 55–6.

Preparations

USP 31: Dioxybenzone and Oxybenzone Cream.

Proprietary Preparations numerous preparations are listed in Part 3.

Arg.: Biorevit Labial; Lelco; ***Braz.:*** Solaquin.

Padimate *(BAN, rINN)*

Amyl Dimethylaminobenzoate; Isoamyl Dimethylaminobenzoate; Padimate A *(USAN)*; Padimato; Padimatum. A mixture of pentyl, isopentyl, and 2-methylbutyl 4-dimethylaminobenzoates.

Падимат

$C_{14}H_{21}NO_2$ = 235.3.

CAS — 14779-78-3 (pentyl 4-dimethylaminobenzoate); 21245-01-2 (isopentyl 4-dimethylaminobenzoate).

Profile

Padimate, a substituted aminobenzoate, is a sunscreen (p.1576) with actions similar to those of aminobenzoic acid (p.1589). It is effective against UVB light (for definitions, see p.1580).

Preparations

Proprietary Preparations some preparations are listed in Part 3.

Padimate O *(BANM, USAN)*

Ethylhexyl Dimethyl PABA; Octyl Dimethyl PABA; Padimato O. 2-Ethylhexyl 4-(dimethylamino)benzoate.

Падимат O

$C_{17}H_{27}NO_2$ = 277.4.

CAS — 21245-02-3.

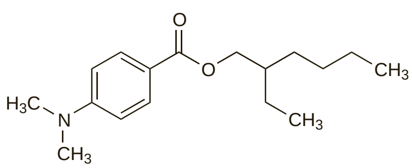

NOTE. Escalol 507 and Eusolex 6007 are trade names that have been used for padimate O.

Pharmacopoeias. In *US.*

USP 31 (Padimate O). A light yellow, mobile liquid with a faint aromatic odour. Practically insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin. Store in airtight containers. Protect from light.

Profile

Padimate O, a substituted aminobenzoate, is a sunscreen (p.1576) with actions similar to those of aminobenzoic acid (p.1589). It is effective against UVB light (for definitions, see p.1580).

Preparations

USP 31: Padimate O Lotion.

Proprietary Preparations some preparations are listed in Part 3.

Pimecrolimus *(BAN, USAN, rINN)*

ASM-981; Pimécrolimus; Pimecrolimús; Pimecrolimusum; Pimekrolimus; Pimekrolimuusi; SDZ-ASM-981. (3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-3-{(*E*)-2-[(1*R*,3*R*,4*S*)-4-Chloro-3-methoxycyclohexyl]-1-methylvinyl}-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone.

Пимекролимус

$C_{43}H_{68}ClNO_{11}$ = 810.5.

CAS — 137071-32-0.

ATC — D11AX15.

ATC Vet — QD11AX15.

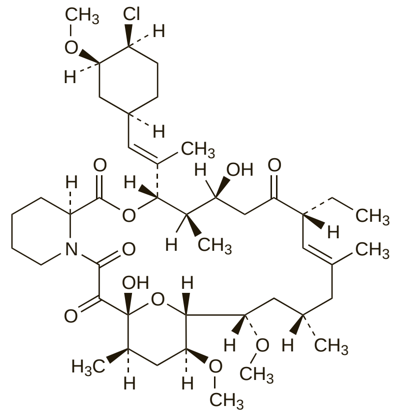

Adverse Effects and Precautions

As for topical tacrolimus (p.1843).

The most frequent adverse effects of topical pimecrolimus are a burning sensation, irritation, pruritus, erythema, and skin infections at the application site. Rarely anaphylactic reactions, sometimes severe, have been reported.

Cases of lymphadenopathy have been reported in patients using pimecrolimus cream. Treatment with pimecrolimus should be stopped in patients who develop lymphadenopathy in the absence of a clear aetiology or in the presence of acute infectious mononucleosis. All patients should be monitored to ensure that the condition resolves.

Carcinogenicity. Carcinogenicity studies in *animals* and reports of malignancies in patients treated with topical calcineurin inhibitors prompted the FDA to issue an alert about the possible risk and to make recommendations about the appropriate use of pimecrolimus and tacrolimus (see under Tacrolimus, p.1843).

Interactions

Alcohol intolerance, described as flushing, rash, burning, itching, or swelling, has occurred rarely after the consumption of alcohol by patients using topical pimecrolimus.

Pharmacokinetics

There is minimal systemic absorption and no accumulation from topical use of pimecrolimus. Studies in *animals* and *in vitro* have found no evidence of metabolism in the skin.

Pimecrolimus is absorbed from the gastrointestinal tract after oral doses, and is about 74 to 87% bound to plasma proteins. It is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A subfamily. About 78% of a single dose is eliminated in the faeces as metabolites and less than 1% as unchanged pimecrolimus. Only about 2.5% of a dose is eliminated in the urine, as metabolites.

◊ References.

1. Van Leent EJM, *et al.* Low systemic exposure after repeated topical application of pimecrolimus (Elidel , SD Z ASM 981) in patients with atopic dermatitis. *Dermatology* 2002; **204:** 63–8.
2. Scott G, *et al.* Pharmacokinetics of pimecrolimus, a novel nonsteroid anti-inflammatory drug, after single and multiple oral administration. *Clin Pharmacokinet* 2003; **42:** 1305–14.
3. Zollinger M, *et al.* Pimecrolimus: absorption, distribution, metabolism, and excretion in healthy volunteers after a single oral dose and supplementary investigations in vitro. *Drug Metab Dispos* 2006; **34:** 765–74.

Uses and Administration

Pimecrolimus is a macrolactam ascomycin derivative related to tacrolimus (p.1846) that acts as a calcineurin inhibitor and has similar anti-inflammatory and immunosuppressant actions. It is used for short-term and intermittent long-term treatment of mild to moderate atopic eczema (p.1579) in non-immunocompromised patients over the age of 2 years when conventional therapies are ineffective or unsuitable. Pimecrolimus is applied twice daily as a 1% cream until signs and symptoms clear. Treatment should be stopped if there is no improvement after 6 weeks or if eczema is exacerbated.

Oral forms of pimecrolimus are also being investigated for the treatment of psoriasis and atopic eczema.

◊ References.

1. Wellington K, Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. *Drugs* 2002; **62:** 817–40.
2. Anonymous. Topical pimecrolimus (Elidel) for treatment of atopic dermatitis. *Med Lett Drugs Ther* 2002; **44:** 48–50.
3. Anonymous. Pimecrolimus cream for atopic dermatitis. *Drug Ther Bull* 2003; **41:** 33–6.
4. Papp K, *et al.* Effect of pimecrolimus cream 1% on the long-term course of pediatric atopic dermatitis. *Int J Dermatol* 2004; **43:** 978–83.
5. Meurer M, *et al.* Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. *Dermatology* 2004; **208:** 365–72.
6. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330:** 516–22.
7. Papp KA, *et al.* Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. *J Am Acad Dermatol* 2005; **52:** 240–6.
8. Wolff K, *et al.* Efficacy and tolerability of three different doses of oral pimecrolimus in the treatment of moderate to severe atopic dermatitis: a randomized controlled trial. *Br J Dermatol* 2005; **152:** 1296–1303.

Administration in infants. A 6-week, double-blind, randomised study of 186 infants between the age of 3 and 23 months, followed by a 20-week open-label phase, showed that 1% pimecrolimus cream, applied twice daily was both safe and effective in mild to moderate atopic eczema.[1] A review[2] of data from 10 studies that included 1133 infants between 3 and 23 months of age who were treated for up to 2 years found that the level of systemic exposure to pimecrolimus was very low and comparable to that observed in older children and adults. Treatment was reported to be effective and there was no evidence of immunosuppression or an increase in the rate of infections. Licensed product information, however, does not recommend its use in patients under 2 years of age as the effect of pimecrolimus cream on the developing immune system in infants is unknown (for concerns about possible carcinogenicity see above).

1. Ho VC, *et al.* Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *J Pediatr* 2003; **142:** 155–62.
2. Paul C, *et al.* Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Abstract: *Pediatrics* 2006; **117:** 202–3. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/1/e118 (accessed 27/09/07)

Lichen. There are a few case reports[1,2] of benefit from pimecrolimus 1% cream in the management of oral *lichen planus* (p.1580). In most cases it was applied twice daily, and in some cases adhesive gel or paste was also used. Improvement in oral lesions occurred within 2 to 4 weeks in 3 cases.[1] In a placebo-controlled study[3] of 20 patients with oral erosive lichen planus, pimecrolimus 1% cream was applied twice daily for 4 weeks. Although pain scores were reduced with pimecrolimus, the reduction in erythema was not maintained. There was also a trend towards an improvement in ulceration but changes in scores were not statistically significant. Topical pimecrolimus has also been tried in the management of genital lichen planus. In a series[4] of 11 women, 9 experienced benefit after 4 to 6 weeks of treatment; with follow-up of up to 10 months, 6 of them had experienced a complete response and 3 a partial response.

The resolution of signs and symptoms of *lichen sclerosus* (p.1580) has been reported in 7 female patients (aged 4 to 48 years) with the use of topical pimecrolimus 1% cream twice daily for 3 to 4 months.[5,6] A poor response was reported in a 62-year-old woman who used the cream less frequently because of burning and stinging.[5]

1. Esquivel-Pedraza L, *et al.* Treatment of oral lichen planus with topical pimecrolimus 1% cream. *Br J Dermatol* 2004; **150:** 771–3.
2. Dissemond J, *et al.* Pimecrolimus in an adhesive ointment as a new treatment option for oral lichen planus. *Br J Dermatol* 2004; **150:** 782–4.
3. Swift JC, *et al.* The effectiveness of 1% pimecrolimus cream in the treatment of oral erosive lichen planus. *J Periodontol* 2005; **76:** 627–35.
4. Lonsdale-Eccles AA, Velangi S. Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series. *Br J Dermatol* 2005; **153:** 390–4.
5. Goldstein AT, *et al.* Pimecrolimus for the treatment of vulvar lichen sclerosus: a report of 4 cases. *J Reprod Med* 2004; **49:** 778–80.
6. Boms S, *et al.* Pimecrolimus 1% cream for anogenital lichen sclerosus in childhood. *BMC Dermatol* 2004; **4:** 14. Available at: http://www.biomedcentral.com/1471-5945/4/14 (accessed 27/09/07)

Psoriasis. Topical pimecrolimus may have some benefit[1] in the treatment of psoriasis (p.1583). Although studies have generally found it to be less effective than topical corticosteroids or topical calcipotriol,[2-4] one study[2] in patients with chronic plaque psoriasis did report that pimecrolimus 1% ointment applied under occlusion had a similar efficacy to clobetasol propionate 0.05% ointment.

Oral pimecrolimus is also under investigation and has reduced disease severity in dose-finding studies in patients with chronic plaque psoriasis.[5,6]

1. Gribetz C, *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004; **51:** 731–8.
2. Mrowietz U, *et al.* The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol* 1998; **139:** 992–6.
3. Mrowietz U, *et al.* An experimental ointment formulation of pimecrolimus is effective in psoriasis without occlusion. *Acta Derm Venereol* 2003; **83:** 351–3.
4. Kreuter A, *et al.* 1% Pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol* 2006; **142:** 1138–43.
5. Rappersberger K, *et al.* Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol* 2002; **119:** 876–87.
6. Gottlieb AB, *et al.* Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol* 2005; **152:** 1219–27.

Seborrhoeic dermatitis. Small studies[1,2] suggest that topical pimecrolimus has a similar efficacy to topical corticosteroids in the treatment of seborrhoeic dermatitis (p.1584). It has also been effective in a few cases that had not responded to topical corticosteroids.[3]

1. Rigopoulos D, *et al.* Pimecrolimus cream 1% vs. betamethasone 17-valerate 0.1% cream in the treatment of seborrhoeic dermatitis: a randomized open-label clinical trial. *Br J Dermatol* 2004; **151:** 1071–5.
2. Firooz A, *et al.* Pimecrolimus cream, 1%, vs hydrocortisone acetate cream, 1%, in the treatment of facial seborrheic dermatitis: a randomized, investigator-blind, clinical trial. *Arch Dermatol* 2006; **142:** 1066–7.
3. Cunha PR. Pimecrolimus cream 1% is effective in seborrhoeic dermatitis refractory to treatment with topical corticosteroids. *Acta Derm Venereol* 2006; **86:** 69–70.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Elidel; ***Austral.:*** Elidel; ***Austria:*** Elidel; ***Belg.:*** Elidel; ***Braz.:*** Elidel; ***Canad.:*** Elidel; ***Chile:*** Elidel; ***Cz.:*** Elidel; ***Denm.:*** Elidel; ***Fin.:*** Elidel; ***Fr.:*** Elidel; ***Ger.:*** Douglan; Elidel; ***Gr.:*** Aregen; Elidel; ***Hong Kong:*** Elidel; ***Hung.:*** Elidel; ***Indon.:*** Elidel; ***Israel:*** Elidel; ***Ital.:*** Elidel; ***Malaysia:*** Elidel; ***Mex.:*** Elidel; ***Neth.:*** Elidel; ***Norw.:*** Elidel; ***NZ:*** Elidel; ***Philipp.:*** Elidel; ***Pol.:*** Elidel; ***Port.:*** Aregen; Elidel; ***Rus.:*** Elidel (Элидел); ***S.Afr.:*** Elidel; ***Singapore:*** Elidel; ***Spain:*** Elidel; Isaplic; Rizan; ***Swed.:*** Elidel; ***Switz.:*** Elidel; ***Thai.:*** Elidel; ***Turk.:*** Elidel; ***UK:*** Elidel; ***USA:*** Elidel; ***Venez.:*** Elidel.

Piroctone Olamine *(USAN, rINNM)*

Piroctona olamina; Piroctoni Olaminum. 1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1*H*)-pyridone compound with 2-aminoethanol (1:1).

Пироктон Оламин

$C_{14}H_{23}NO_2,C_2H_7NO$ = 298.4.

CAS — 50650-76-5 (piroctone); 68890-66-4 (piroctone olamine).

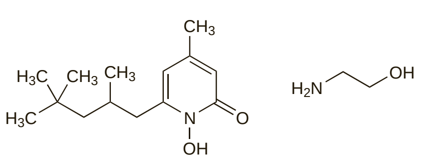

Profile

Piroctone olamine has been used in shampoos for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lovilia†; Megacistin G†; Octopil†; Plusgel; ***Austral.:*** Neoceuticals Therapeutic Shampoo†; ***Braz.:*** Soapex; ***Fr.:*** Charlieu Antipelliculaire; Cystel Antipelliculaire†; Evolith DS; Topicrem Traitement PV; Traitement PV; ***Irl.:*** Saliker†; ***Ital.:*** Olamin P; ***Mex.:*** Betapirox; ***Venez.:*** Betapirox; Hair Stabil†; Sante Vite†.

Multi-ingredient: ***Arg.:*** Aspergun†; Micocert; Micodual; Pitiriax; Pityval†; Saliker†; Tersoderm Anticaspa†; ***Braz.:*** Ortosol P; Pityval; Saliker; ***Chile:*** Eucerin Shampoo Anticaspa; Foltene Research Anticaspa; KPL†; Neostrata; Node DS; Shampoo Anticaspa; ***Fr.:*** Alpha 5 DS†; Epiphane†; Hyfac soin keratolytique†; Ionax P; Item Alphakeptol; Kelual DS; Kerium Intensive; Liperol; Mela'aura; Node DS; Node P; Phytheol; Phytosquame; Pityker†; Pityval; PSO; Saliker†; Seborheane; T/Gel; ***Irl.:*** Effaclar AI; ***Ital.:*** Biophase Shampoo; Biothymus DS; Genisol; Nonak; Prurex; Shamday Antiforfora†; Tricoderm F; ***Port.:*** Alpha Septol; Alphakeptol†; Bioclin Sebo Care; Ionil P†; ***Spain:*** Ionax P†; ***UK:*** Atopiclair; ***USA:*** Atopiclair; ***Venez.:*** Kertyol; Node DS; Sensibio DS.

Podophyllum

American Mandrake; May Apple Root; Podófilo; Podofilum; Podoph.; Podophyllum Rhizome; Rizoma de podófilo.

Подофилл щитовидный (*Podophyllum peltatum*)

Pharmacopoeias. In *US.*

USP 31 (Podophyllum). The dried rhizomes and roots of *Podophyllum peltatum* (Berberidaceae). It yields not less than 5% of resin. It has a slight odour.

Indian Podophyllum

Ind. Podoph.; Indian Podophyllum Rhizome; Podófilo indio.

Подофилл гималайский (*Podophyllum emodi*)

Description. The dried fruits or rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*) (Berberidaceae).

Podophyllum Resin

Podofilino; Podoph. Resin; Podophylli Resina; Podophyllin; Resina de podófilo.

Подофиллин

CAS — 8050-60-0.

Pharmacopoeias. In *Int.* and *US* (both from podophyllum only). In *Br.* from Indian podophyllum.

BP 2008 (Podophyllum Resin). The resin obtained from the rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*). It contains not less than 50% of total aryltetralin lignans, calculated as podophyllotoxin.

An amorphous powder, varying in colour from light brown to greenish-yellow or brownish-grey masses, with a characteristic odour; caustic. On exposure to light or to temperatures above 25° it becomes darker in colour.

Partly soluble in hot water but precipitated again on cooling; partly soluble in chloroform, in ether, and in dilute ammonia solution. Protect from light.

USP 31 (Podophyllum Resin). The powdered mixture of resins extracted from podophyllum (the rhizomes and roots of *Podophyllum peltatum*) by percolation with alcohol and subsequent precipitation with acidified water. It contains not less than 40% and not more than 50% of hexane-insoluble matter.

An amorphous caustic powder, varying in colour from light brown to greenish-yellow. On exposure to light or to temperatures above 25° it becomes darker in colour.

Soluble in alcohol with a slight opalescence; partially soluble in chloroform and in ether. A solution in alcohol is acid to litmus. Store in airtight containers. Protect from light.

Podophyllotoxin *(BAN)*

Podofilotoxina; Podofilox *(USAN)*; Podofyllotoksiini; Podofyllotoxin; Podophyllotoxinum. (5*R*,5a*R*,8a*R*,9*R*)-5,5a,6,8,8a,9-Hexahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one.

Подофиллотоксин

$C_{22}H_{22}O_8$ = 414.4.

CAS — 518-28-5.

ATC — D06BB04.

ATC Vet — QD06BB04.

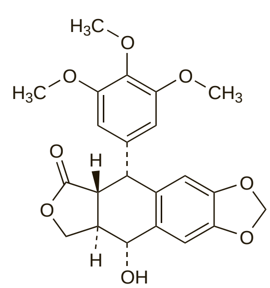

Adverse Effects

Podophyllum is very irritant, especially to the eyes and mucous membranes. It can also cause severe systemic toxicity after ingestion or topical application, which is usually reversible but has been fatal. Symptoms of toxicity include nausea, vomiting, abdominal pain, and diarrhoea; there may be thrombocytopenia, leucopenia, renal failure, and hepatotoxicity. Central effects are delayed in onset and prolonged in duration and include acute psychotic reactions, hallucinations, confusion, dizziness, stupor, ataxia, hypotonia, seizures, and coma. EEG changes may persist for several days. Peripheral and autonomic neuropathies develop later and may result in paraesthesias, reduced reflexes, muscle weakness, tachycardia, apnoea, orthostatic hypotension, paralytic ileus, and urinary retention. Neuropathy may persist for several months.

Poisoning. Reports and reviews of podophyllum toxicity.[1-7] A few of the cases followed consumption of herbal preparations containing podophyllum or the related plant bajiaolian (*Dysosma pleianthum*). Death has occurred after ingestion of 10 g of podophyllum.

1. Cassidy DE, *et al.* Podophyllum toxicity: a report of a fatal case and a review of the literature. *J Toxicol Clin Toxicol* 1982; **19:** 35–44.
2. Dobb GJ, Edis RH. Coma and neuropathy after ingestion of herbal laxative containing podophyllin. *Med J Aust* 1984; **140:** 495–6.
3. Holdright DR, Jahangiri M. Accidental poisoning with podophyllin. *Hum Exp Toxicol* 1990; **9:** 55–6.
4. Tomczak RL, Hake DH. Near fatal systemic toxicity from local injection of podophyllin for pedal verrucae treatment. *J Foot Surg* 1992; **31:** 36–42.
5. Kao W-F, *et al.* Podophyllotoxin intoxication: toxic effect of bajiaolian in herbal therapeutics. *Hum Exp Toxicol* 1992; **11:** 480–7.
6. Chan TYK, Critchley JAJH. Usage and adverse effects of Chinese herbal medicines. *Hum Exp Toxicol* 1996; **15:** 5–12.
7. Chu CC, *et al.* Sensory neuropathy due to bajiaolian (podophyllotoxin) intoxication. *Eur Neurol* 2000; **44:** 121–3.

Precautions

The risk of systemic toxicity after topical application of podophyllum is increased by the treatment of large areas with excessive amounts for prolonged periods, by the treatment of friable, bleeding, or recently biopsied warts, and by inadvertent application to normal skin or mucous membranes.

Podophyllum should not be used during pregnancy or breast feeding. There are few reports of use during pregnancy and a teratogenic risk cannot be ruled out. Adverse systemic effects in the mother would also be undesirable during pregnancy, and there are other non-drug treatments available for the treatment of anogenital warts. It is not known whether podophyllum is distributed into breast milk.

Handling. Podophyllum resin is strongly irritant to the skin, eyes, and mucous membranes and requires careful handling.

Uses and Administration

Podophyllum resin and podophyllotoxin have an antimitotic action and are used principally as topical treatments for anogenital warts (condylomata acuminata). Podophyllum resin and podophyllotoxin may be used on external genital and perianal warts; podophyllum resin may also be used on urethral meatus warts. However, neither of these compounds should be used to treat warts on mucous membranes, including vaginal, cervical, intra-urethral, intra-anal, and rectal warts.

Podophyllum resin is usually formulated in compound benzoin tincture in strengths of 15% Indian podophyllum resin or 10 to 25% American podophyllum resin. Lower concentrations of American podophyllum resin in alcoholic solutions have been used. The solution is left on the warts for 1 to 6 hours, and then washed off. Only a small area or number of warts should be treated at any one time and care must be taken to avoid application to healthy tissue. This procedure is carried out once a week for up to 3 to 6 weeks. Preparations containing podophyllotoxin 0.5% in alcohol or alcoholic gel or podophyllotoxin 0.15% cream are used similarly. They are applied twice daily for 3 days but not washed off. Treatment may be repeated at weekly intervals for up to a total of 4 or 5 weeks of treatment. Podophyllum resin is also used with other keratolytics for the removal of plantar warts.

Although podophyllum resin and podophyllotoxin preparations are generally not used in children, see below.

When taken orally podophyllum resin is highly irritant to the intestinal mucosa and produces violent peristalsis resulting in a drastic purging action. It has been superseded by less toxic laxatives.

Podophyllum has been used in homoeopathic medicine.

Administration in children. The use of podophyllum resin and podophyllotoxin preparations in children is generally avoided because of the potential for severe local irritation and systemic toxicity. Nonetheless, podophyllotoxin has been used for the treatment of symptomatic, persistent anogenital warts in children.[1] The *BNFC* suggests that, although not licensed for use in children, podophyllum resin and podophyllotoxin preparations may be used in regimens similar to those used in adults (see above) in children 2 years of age and older who are able to cooperate with treatment.

1. Bellew SG, *et al*. Childhood warts: an update. *Cutis* 2004; **73:** 379–84.

Anogenital warts. Podophyllum preparations are one of the treatment choices for anogenital warts caused by human papillomavirus infection (condylomata acuminata) (p.1584). Podophyllum resin preparations have traditionally been applied by a healthcare provider because of the potential local and systemic toxicity associated with inappropriate or excessive use.[1] However, podophyllotoxin may be more effective[2,3] and less toxic[2] than podophyllum resin, and is suitable for self-treatment by the patient.[1,4]

1. CDC. Sexually transmitted diseases treatment guidelines, 2006. *MMWR* 2006; **55** (RR-11): 1–94. Correction. *ibid.*; 997. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5511.pdf (accessed 27/09/07)
2. von Krogh G, Longstaff E. Podophyllin office therapy against condyloma should be abandoned. *Sex Transm Infect* 2001; **77:** 409–12.
3. Lacey CJN, *et al*. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; **79:** 270–5.
4. von Krogh G, *et al*. European Course on HPV Associated Pathology (ECHPV). European guideline for the management of anogenital warts. *Int J STD AIDS* 2001; **12** (suppl 3): 40–7. Also available at: http://www.iusti.org/sti-information/pdf/guidelines.pdf (accessed 27/09/07)

Preparations

BP 2008: Compound Podophyllin Paint;
USP 31: Podophyllum Resin Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Podoxin; ***Austral.:*** Condyline; Wartec; ***Austria:*** Condylox; ***Belg.:*** Wartec; ***Braz.:*** Wartec; ***Canad.:*** Condyline; Podofilm; Wartec; ***Chile:*** Wartec†; ***Cz.:*** Wartec; ***Denm.:*** Condyline; Wartec; ***Fin.:*** Condyline; Wartec; ***Fr.:*** Condyline; Wartec†; ***Ger.:*** Condylox; Wartec; ***Gr.:*** Podofilox†; Wartec; ***Hong Kong:*** Podofilm; Wartec; ***Hung.:*** Condyline; Wartec; ***Irl.:*** Condyline; Warticon; ***Israel:*** Condylox; ***Ital.:*** Condyline; Wartec; ***Mex.:*** Podofilia; Vipodo; Wartec; ***Neth.:*** Condyline; Wartec; ***Norw.:*** Condyline; Wartec; ***NZ:*** Condyline; Wartec; ***Pol.:*** Condyline; Wartec; ***Port.:*** Condyline; ***Rus.:*** Condyline (Кондилин); ***S.Afr.:*** Wartec; ***Singapore:*** Wartec; ***Spain:*** Wartec; ***Swed.:*** Condyline; Wartec; ***Switz.:*** Condyline; Warix; ***UK:*** Condyline; Warticon; ***USA:*** Condylox; Pod-Ben-25; Podocon; Podofin.

Multi-ingredient: ***Arg.:*** Calculina†; ***Austral.:*** Posalfilin; ***Canad.:*** Canthacur-PS; Cantharone Plus; ***Ger.:*** Unguentum lymphaticum; ***Hong Kong:*** Posalfilin†; ***Irl.:*** Posalfilin; ***Malaysia:*** Posalfilin†; ***NZ:*** Posalfilin; ***Port.:*** Cholagutt†; ***S.Afr.:*** Posalfilin; ***Singapore:*** Posalfilin†; ***Spain:*** Alofedina; ***UK:*** Posalfilin; ***Venez.:*** Linfoderm; Podoben†.

Polyphloroglucinol Phosphate

Polifloroglucinol, fosfato de; Polyphloroglucin Phosphate. Poly[benzene-1,3,5-triol mono(dihydrogen phosphate)].

Полифлороглюцина Фосфат

$(C_6H_7O_6P)_n$.

CAS — 51202-77-8.

Profile

Polyphloroglucinol phosphate has an inhibitory effect on hyaluronidase and has been applied topically in the treatment of wounds and pruritic skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Dealyd.

Polyurethane Foam *(USAN)*

Пенополиуретан; Полиуретановая Пена

CAS — 9009-54-5.

Profile

Polyurethane foam is a urethane polymer that is used in wound dressings.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Allevyn; Opsite; ***Fr.:*** Allevyn; Clip Blessures; Clip Derm; Clip Strip; Opsite; Optiskin; Permafoam; Suprasorb; Tielle; ***Ger.:*** Allevyn†; Opsite†; ***Irl.:*** Allevyn†; ***Ital.:*** Allevyn; Bioclusive; Cutinova Hydro; Opsite Flexigrid; ***S.Afr.:*** Opsite; ***UK:*** Allevyn; Cutinova; Lyofoam; Opsite.

Multi-ingredient: ***Ital.:*** Biopatch; Silverdres.

Prezatide Copper Acetate *(USAN, rINN)*

Acetato de prezatida cúprica; Acetato de prezatida de cobre; PC-1020 (prezatide copper); Prézatide Cuprique, Acétate de; Prezatidi Cuprici Acetas. Hydrogen [N^2-(*N*-glycyl-L-histidyl)-L-lysinato][N^2-(*N*-glycyl-L-histidyl)-L-lysinato(2–)]cuprate(1–) diacetate.

Презатида Меди Ацетат

$C_{28}H_{46}CuN_{12}O_8,2C_2H_4O_2 = 862.4.$

CAS — 130120-57-9.

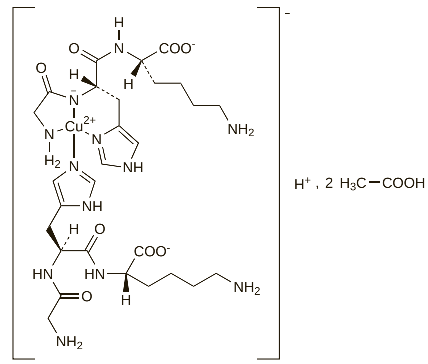

Profile

Prezatide copper acetate is a copper-containing tripeptide that is used topically as a wound-healing agent.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Prezatim†; ***Mex.:*** Iamin; ***USA:*** Iamin Hydrating Gel.

Pyrithione Zinc *(BAN, USAN, rINN)*

Çinko Pirition; Piritiona cíncica; Piritiona de zinc; Pyrithione Zincique; Pyrithionum Zincicum; Zinc 2-Pyridinethiol 1-Oxide; Zinc Pyridinethione. Bis[1-hydroxypyridine-2(1*H*)-thionato]zinc.

Пиритион Цинк

$C_{10}H_8N_2O_2S_2Zn = 317.7.$

CAS — 13463-41-7.
ATC — D11AX12.
ATC Vet — QD11AX12.

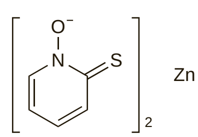

Profile

Pyrithione zinc has bacteriostatic and fungistatic properties. It is used similarly to selenium sulfide (p.1613) in usual concentrations of 1 to 2% in the control of seborrhoeic dermatitis and dandruff (p.1584). It is an ingredient of some proprietary shampoos. It has also been used in the treatment of pityriasis versicolor.

Pyrithione magnesium has also been used.

Effects on the nervous system. Peripheral neuritis with paraesthesia and muscle weakness in a patient was associated with the prolonged use of a shampoo containing pyrithione zinc 2%.[1] The muscle weakness had disappeared 3 months after stopping the shampoo and 2 years later the paraesthesia had improved by about 75%.

Studies in *animals* had found signs of neurotoxicity after oral doses of pyrithione zinc but whereas absorption after topical application was found to be 13% for pyrithione sodium it was less than 1% for pyrithione zinc.[2]

1. Beck JE. Zinc pyrithione and peripheral neuritis. *Lancet* 1978; **i:** 444.
2. Parekh CK. Zinc pyrithione and peripheral neuritis. *Lancet* 1978, **i:** 940.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aeroseb; Amenite Cap†; Antiminth; Dermazinc; Hairplus; Min Huil; Skin-Cap; ZNP†; ***Austral.:*** Dan-Gard; Dandruff Control Pert 2 in 1; ***Austria:*** Desquaman; ***Canad.:*** Advance†; Brylcreem Anti-Dandruff; Dan-Gard; Dandruff Shampoo plus Conditioner†; Denorex Everyday; Hair & Scalp†; Head & Shoulders; Lander Dandruff Control†; Out of Africa; Pert Plus; Satinique Anti-Dandruff†; Scott Dandruff Shampoo; Shaklee Dandruff Control†; Shampooing Anti-Pelliculaire; Solve Dandruff; Techniques Anti-Dandruff†; ZNP; ZP 11†; ***Chile:*** Biolane; DHS Zinc; Skin Cap; ZNP; ***Denm.:*** Skaelud; ***Fr.:*** Ducray Antipelliculaire†; Provegol; Shampooing Traitant Antipelliculaire†; ZNP; ***Ger.:*** De-squaman N†; ***Gr.:*** Daohair-S; ***Israel:*** Desquaman; ***Ital.:*** Rivescal ZPT; Shampoo SDE Zinc†; ZNP; ***Mex.:*** Pirimed; ZNP; ***Port.:*** ZP Dermil; ***Rus.:*** Freederm Zinc (Фридерм Цинк); Skin-Cap (Скин-Кап); ***Spain:*** Zincation; ***Turk.:*** Zetion; Zintion; ***USA:*** DHS Zinc; Head & Shoulders; Skin Cure; Zincon; ZNP; ***Venez.:*** Albepir; Blue Caps; Caduzinc†; Denorex Original†; Pirimed.

Multi-ingredient: ***Arg.:*** Aeroseb; Molnia; Neo Moldava†; ***Austral.:*** Fongitar; ***Braz.:*** Fisohex II; ***Canad.:*** Multi-Tar Plus; X-Seb Plus; Z-Plus; ***Chile:*** Node DS; ***Cz.:*** Polytar AF; ***Fr.:*** Item Alphakeptol; Kelual DS; Klorane Shampooing Antipelliculaire; Node DS; Node P; ***Hong Kong:*** Fongitar; Multi-Tar; ***Hung.:*** Polytar AF; Squa-med; ***India:*** Hyphoral; Scalpe; ***Ital.:*** Biothymus DS; Derman-Shampoo AF†; Keto Z; Ketomousse; Kevis; ***Malaysia:*** Ketoplus; ***NZ:*** Fongitar†; ***Philipp.:*** Fongitar; Scalpex; ***Pol.:*** Polytar AF; ***Port.:*** All Pecium†; Alpha Septol; Alphakeptol†; Fongitar; ***Rus.:*** Keto Plus (Кето Плюс); ***S.Afr.:*** Fongitar; ***Singapore:*** Fongitar; pHisoHex Reformulated†; ***Spain:*** Zincation Plus; ***Switz.:*** Sebo Shampooing; Sebo-Soufrol; Squa-med; ***Thai.:*** Fongitar; ***Turk.:*** Pirdolin; Seboreks; Sedolin; ***UK:*** Polytar AF; ***USA:*** X-Seb Plus; Xolegel Duo; ***Venez.:*** Node DS; Pelset Plus.

Pyrogallol

1,2,3-Bencenotriol; Pirogálico, ácido; Pirogalol; Pyrogallic Acid; Pyrogallolum. Benzene-1,2,3-triol.

Пирогаллол

$C_6H_6O_3 = 126.1.$

CAS — 87-66-1.

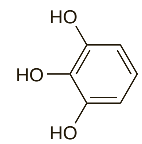

Pharmacopoeias. In *Fr.* and *Pol.*

Profile

Pyrogallol was formerly used topically in the treatment of psoriasis and parasitic skin diseases, but application over large areas or denuded surfaces is dangerous and may produce systemic effects similar to phenol poisoning (see p.1656); methaemoglobinaemia, haemolysis, and kidney damage may also occur.

Pyrogallol stains the skin and hair black.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Pyrogallic.

Pyroxylin *(rINN)*

Algodão-Polvora; Algodón pólvora; Cellulose Nitrate; Celulosa decanítrica; Colloxylinum; Fulmicoton; Gossypium Collodium; Kollodiumwolle; Nitrato de celulosa; Piroxilina; Pyroxyline; Pyroxylinum; Soluble Guncotton.

Пироксилин

CAS — 9004-70-0.

Pharmacopoeias. In *Br.*, *Jpn*, *Pol.*, and *US.*

BP 2008 (Pyroxylin). A nitrated cellulose obtained by the action of a mixture of nitric and sulfuric acids on wood pulp or cotton linters that have been freed from fatty matter. It must be damped with not less than 25% of isopropyl alcohol or of industrial methylated spirit. White or almost white cuboid granules or fine material resembling absorbent cotton but harsher to the touch and more powdery. It is highly flammable. Soluble in acetone and in glacial acetic acid. Store in well-closed containers, loosely packed, protected from light, and at a temperature not exceeding 15°, remote from fire. The container should be suitably designed to disrupt should the internal pressure reach or exceed 1400 kPa. The amount of damping fluid must not be allowed to fall below 25% w/w; should this happen, the material should be either rewetted or used immediately for the preparation of Collodion.

USP 31 (Pyroxylin). Pyroxylin is obtained by the action of a mixture of nitric and sulfuric acids on cotton and consists chiefly of cellulose tetranitrate $(C_{12}H_{16}N_4O_{18})_n$. It occurs as a light yellow, matted mass of filaments resembling raw cotton but harsher to the touch. It is highly flammable. Store loosely packed, protected from light. When kept in well-closed containers and exposed to light, it decomposes with the evolution of nitrous vapours, leaving a carbonaceous residue.

Profile

Pyroxylin is used in the preparation of collodions which are applied to the skin for the protection of small cuts and abrasions. Collodions are also used as vehicles for the application of drugs when prolonged local action is required.

Handling. Dry pyroxylin is explosive and sensitive to ignition by impact or friction and should be handled carefully.

Preparations

BP 2008: Collodion; Flexible Collodion.
USP 31: Collodion; Flexible Collodion.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Dispello.

Resorcinol

m-Dihidroxibenceno; *m*-Dihydroxybenzene; Dioxybenzolum; Resorcin; Resorcina; Résorcinol; Resorcinolum; Resorsinoli; Rezorcin; Rezorcinolis; Rezorcynol. Benzene-1,3-diol.

Резорцинол

$C_6H_6O_2$ = 110.1.
CAS — 108-46-3.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.

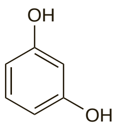

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Resorcinol). Colourless or slightly pinkish-grey crystals or crystalline powder. M.p. 109° to 112°. It becomes red on exposure to air and light. Very soluble in water and in alcohol. Protect from light.

USP 31 (Resorcinol). White or practically white, needle-shaped crystals or powder with a faint characteristic odour. M.p. 109° to 111°. It acquires a pink tint on exposure to air and light. Soluble 1 in 1 of water and of alcohol; slightly soluble in chloroform; freely soluble in ether and in glycerol. A 5% solution in water is neutral or acid to litmus. Protect from light.

Incompatibility. Resorcinol is incompatible with ferric salts.

Resorcinol Monoacetate

Acetato de resorcina; Resorcin Acetate; Resorcinol, monoacetato de. 3-Acetoxyphenol.

Резорцинола Моноацетат

$C_8H_8O_3$ = 152.1.
CAS — 102-29-4.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.

Pharmacopoeias. In *US.*

USP 31 (Resorcinol Monoacetate). A pale yellow or amber, viscous liquid with a faint characteristic odour. Sparingly soluble in water; soluble in alcohol and in most organic solvents. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Resorcinol is a mild irritant and may result in skin sensitisation. It should not be applied to large areas of the body, for prolonged periods, or in high concentrations, especially in children, as it is absorbed through intact skin as well as broken skin and may interfere with thyroid function or produce methaemoglobinaemia. Resorcinol may produce hyperpigmentation in patients with dark skins and may darken light-coloured hair. Systemic toxic effects of resorcinol are similar to those of phenol and are treated accordingly (see p.1656) but convulsions may occur more frequently.

Abnormal coloration. Resorcinol could cause green discoloration of the urine.[1]

1. Karlstrand J. The pharmacist and the ostomate. *J Am Pharm Assoc* 1977; **NS17:** 735–8.

Uses and Administration

Resorcinol has keratolytic properties and has been used, usually with sulfur, in topical preparations for the treatment of acne (p.1577) and seborrhoeic skin conditions (p.1584), although other treatments are generally preferred.

Resorcinol has also been used in preparations for the treatment of anorectal disorders often complexed with bismuth compounds (see Haemorrhoids, p.1697).

Resorcinol monoacetate has been used similarly but may provide a milder action with a longer duration.

Dentistry. Resorcinol powder added incrementally to a few drops of formaldehyde 40% solution to saturation and polymerised using 1 or 2 drops of sodium hydroxide 10% solution produces a hard red material, known as "Russian Red". This resin has been used in dentistry in eastern Europe, Russia, and China. Zinc oxide or barium sulfate is often added to the mixture before polymerisation to make it radio-opaque.[1]

1. Schwandt NW, Gound TG. Resorcinol-formaldehyde resin "Russian Red" endodontic therapy. *J Endod* 2003; **29:** 435–7.

Preparations

BPC 1973: Magenta Paint;
USP 31: Carbol-Fuchsin Topical Solution; Compound Resorcinol Ointment; Resorcinol and Sulfur Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Chile: Dermobarrina; ***USA:*** Castel.

Multi-ingredient: ***Arg.:*** Acnomel†; Acnoxin; Bifena; Callicida†; Coltix†; Controlacne; Cutidermin†; Dermo Vagisil Crema; Ecnagel; Ecnagel E; Farmigras; Histidanol†; Nemegel†; Pinklot; Suffisance; ***Austral.:*** Acne & Pimple Gel†; Eskamel; Seborrol†; ***Austria:*** Wisamt†; ***Belg.:*** Synthol; ***Braz.:*** Pantevit; ***Canad.:*** Clearasil Acne Control; Clearasil Acne Cream; Lanacane Medicated Cream; Mazon Medicated Cream; Vagisil; ***Chile:*** Acnaid†; Antiacne†; Dermac Crema; ***Fr.:*** Anaxeryl; Bain de Bouche Lipha; Gelictar Fort; Nestosyl; Osmotol; Squaphane S; Synthol; ***Ger.:*** Jaikal†; Wisamt N†; ***Hong Kong:*** Acne-Aid; ***Hung.:*** Glycosept; ***Indon.:*** Bioacne; Rosal; Verile; ***Irl.:*** Anugesic-HC; Anusol-HC; ***Israel:*** Acnex†; Pitrisan; ***Ital.:*** Anusol; Blefarolin; Fucsina Fenica; Labocaina; Rinantipiol†; ***Malaysia:*** Acne-Aid; ***Mex.:*** Crema Axel†; Dermac; Dermocare; Dermoscalp; Jabon del Tio Nacho; Shampoo del Tio Nacho; ***NZ:*** Egomycol†; Lanacane; Seborrol†; ***Pol.:*** Afronis; Hemorectal; Pigmentum Castellani; ***Port.:*** Edoltar†; Resodermil; ***Rus.:*** Neo-Anusol (Нео-анузол); ***S.Afr.:*** Anugesic; Eskamel; ***Singapore:*** Acne Clear; Acne-Aid; ***Spain:*** Acnisdin; Dermomycose Liquido; Milrosina; Resorborina; ***Switz.:*** Clabin; Euproctol; Lotio decapans; ***Thai.:*** Anusol; Zema; ***Turk.:*** Buco Bleu; ***UK:*** Eskamel; ***USA:*** Acnomel; Bensulfoid; Bicozene; Castaderm; Dermarest; Fungi-Nail; Heal Aid Plus; RA Lotion; Rezamid; Sulforcin; Unguentine Maximum Strength; Vagisil; ***Venez.:*** Alderil†; Klenyl.

Retinaldehyde

Retinal; Retinene; Vitamin A Aldehyde.

Ретинальдегид

$C_{20}H_{28}O$ = 284.4.
CAS — 116-31-4.

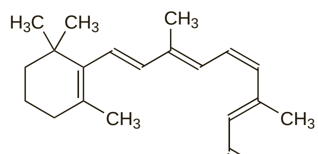

11-*cis* Retinaldehyde

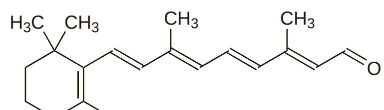

all-*trans* Retinaldehyde

Profile

Retinaldehyde is a derivative of vitamin A (p.1971) that has been used in preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ystheal; ***Chile:*** Ystheal.

Multi-ingredient: ***Arg.:*** Diacneal; Diroseal; ***Chile:*** Diacneal; Diroseal; ***Fr.:*** Diroseal; ***Venez.:*** Diacneal.

Salicylic Acid

Acide salicylique; Acido Ortóxibenzoico; Acidum salicylicum; Kwas salicylowy; Kyselina salicylová; Salicílico, ácido; Salicilo rūgštis; Salicylsyra; Salisilik Asit; Salisyylihappo; Salizylsäure; Szalicilsav. 2-Hydroxybenzoic acid.

Салициловая Кислота

$C_7H_6O_3$ = 138.1.
CAS — 69-72-7.
ATC — D01AE12; S01BC08.
ATC Vet — QD01AE12; QS01BC08.

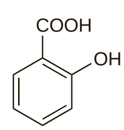

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Salicylic Acid). White or colourless acicular crystals or a white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Salicylic Acid). White crystals, usually in fine needles or a white, fluffy, crystalline powder. The synthetic form is white and odourless but if prepared from natural methyl salicylate it may have a slightly yellow or pink tint, and a faint, mint-like odour. Soluble 1 in 460 of water, 1 in 15 of boiling water, 1 in 3 of alcohol, 1 in 45 of chloroform, 1 in 3 of ether, and 1 in 135 of benzene.

Adverse Effects and Precautions

Salicylic acid is a mild irritant and application of salicylic acid preparations to the skin may cause dermatitis. Preparations containing high concentrations of salicylic acid can cause skin ulceration or erosion; healthy skin surrounding warts, corns, and calluses should be protected with soft paraffin or specially designed plasters when such preparations are being used. Salicylic acid should be used with care on the extremities of patients with impaired peripheral circulation or diabetes; caution has also been suggested if caustic preparations are used in patients with significant peripheral neuropathy. The drug is readily absorbed through the skin, and symptoms of acute systemic salicylate poisoning (see Aspirin, p.20) have been reported after excessive use; deaths have occurred, mainly in children. To minimise absorption after topical application salicylic acid should not be used for prolonged periods, in high concentrations, on large areas of the body, or on inflamed or broken skin. Contact with mouth, eyes, and other mucous membranes should be avoided.

Uses and Administration

Salicylic acid has **keratolytic** properties and is applied topically in the treatment of hyperkeratotic and scaling skin conditions such as dandruff and seborrhoeic dermatitis (p.1584), ichthyosis (p.1580), psoriasis (p.1583), and acne (p.1577). Preparations usually contain between 2 and 6% salicylic acid, but a wider range of concentrations has been used. It is often used with other drugs, notably coal tar.

Preparations containing up to 60% salicylic acid have been used as a **caustic** for the removal of plantar warts (p.1584), corns, or calluses; surrounding healthy skin should be protected (see above).

Salicylic acid also possesses **fungicidal** properties and is used topically in the treatment of dermatophyte skin infections (see p.521); propyl salicylate and bromosalicylic acid have been used similarly.

Zinc salicylate has been used similarly to salicylic acid in the treatment of seborrhoeic dermatitis and acne.

Preparations

BP 2008: Coal Tar and Salicylic Acid Ointment; Compound Benzoic Acid Ointment; Dithranol Paste; Salicylic Acid Collodion; Salicylic Acid Ointment; Zinc and Salicylic Acid Paste;
BPC 1973: Salicylic Acid and Sulphur Ointment;
USP 31: Benzoic and Salicylic Acids Ointment; Salicylic Acid Collodion; Salicylic Acid Gel; Salicylic Acid Plaster; Salicylic Acid Topical Foam; Zinc Oxide and Salicylic Acid Paste.

Proprietary Preparations (details are given in Part 3)
Arg.: Callicida; Desconphar†; Duofilm; Duoforte; Koal; Neo A-V; Renovate†; Salpad; Verrutopic AS; Verrutrix; Verruxane†; ***Austral.:*** Clear Away†; Clearasil Medicated Wipes; Duofilm; Egozite Cradle Cap; Ionil; John Plunketts Sunspot Cream; Johnsons Clean & Clear Skin Balancing Moisturiser; Sunspot; ***Austria:*** Squamasol; ***Belg.:*** Anticors Diable Vert; Compeedmed; Duofilm; Sicombyl; ***Braz.:*** A Curitybina; Clean & Clear Gel Secativo; Clean & Clear Hidratante; Clean & Clear Locao Adstringente; Clean & Clear Sabonete Liquido Refrecante†; Denorex Daily†; Denorex Plus†; Duoforte†; Ionil; Neutrogena Antiacne; Salipads†; Verrux; ***Canad.:*** Acne Solutions; Acnex†; Anti-Acne Control Formula†; Blemish Control; Carnation; Clean & Clear Blackhead Clearing Astringent; Clean & Clear Continuous Control Acne Wash; Clean & Clear Deep Cleaning Astringent†; Clean & Clear Invisible Blemish Treatment; Clearasil Cleanser; Clearasil Clearstick†; Clearasil Pads†; Clearasil Stayclear†; Clearskin Acne Defense Stick†; Clearskin Cleansing; Clearskin Medicated Wash†; Clearskin Overnight Acne Treatment†; Clearskin Targeted Blemish Remover; Compound W; Compound W Plus; Dermarest; Duofilm; Duoforte; Fixo†; Freezone; Herbal Essences Anti-Dandruff; Johnsons Clean & Clear Dual Action Moisturizer†; Johnsons Clean & Clear Pore Prep†; NeoStrata Astringent Acne Treatment†; Neutrogena Acne Wash; Neutrogena Clear Pore; Neutrogena Healthy Scalp Anti-Dandruff†; Neutrogena Skin Cleaning†; Neutrogena Soothing Gel Astringent†; Occlusal†; Off-Ezy; Oxy Daily Cleaning Pads; Oxy Daily Facial Cleanser Deep Pore; Oxy Finishing Toner†; Oxy Medicated Pads†; Propa PH†; Scholl 2-Drop Corn Remedy; Scholl Callus Remover; Scholl Clear Away†; Scholl Corn Remover; Scholl One Step†; Scholl Zino†; Sebcur; Soluver; Soluver Plus; Trans-Plantar; Trans-Ver-Sal; X-Seb; ***Chile:*** DHS Sal; Duoplant Gel; Eucerin Piel Grasa; Mediklin; Neutrogena Acondicionador Neutar Gel; Neutrogena Gel Control Brillo; Neutrogena Linea Acne; Quitacallos; Trans-Plantar†; Trans-Ver-Sal†; ***Cz.:*** Bukosan†; Callous; Seal & Heal†; Sophtal-POS N; Spofaplast; Urgocor; Verruca Removal; ***Denm.:*** Psorimed; Salicyl; ***Fr.:*** A-Derma Pain Salicylique†; Antalyre; Ciella; Coricide le Diable; Disques Coricides; Feuille de Saule; Kertyol; Optrex; Pansements Coricides†; Pommade Mo Cochon; Sanitos; Sophtal; Transvercid; ***Ger.:*** Aknefug-liquid; Gehwol Huhneraugen-Pflaster extra stark; Gehwol Schalpaste; Guttaplast†; Hansaplast Hornhaut-Pflaster†; Hansaplast Huhneraugen-Pflaster†; Humopin N†; Lygal Kopfsalbe N; Psorimed; Schrundensalbe Dermi-cyl; Sophtal-POS N; Squamasol; Urgo Activ Huhneraugenpflaster†; Verrucid; ***Gr.:*** 2-Drop; Adaptoplast; Apsoderm; Callifugo; Gallifugo†; Hansaplast Callous; Psorimed†; Salicyd; Salipsor; Solimed; Zino; ***Hong Kong:*** Duofilm; Egozite Cradle Cap; ***Hung.:*** Hansaplast; ***Indon.:*** Topix; Yodsaben; ***Irl.:*** Acnisal; Compound W; Occlusal; Psorimed†; Saliker†; Vericaps; ***Israel:*** Clearex; Clearex for Sensitive Skin; Salikaren; Scholl Corn/Callous Removers; ***Ital.:*** Keranon; Salicil; Trans-Ver-Sal; ***Malaysia:*** Clearasil 3 in 1 Deep Cleansing Wash; Clearasil Ice Wash; Clearasil Ultra Deep Pore; Egozite Cradle Cap; Palmer's Skin Success Acne Medication; ***Mex.:*** Duoplant; Excelsior†; Ionil Plus; Ionil†; Trans-Ver-Sal; ***Neth.:*** Formule W; Psorimed; ***NZ:*** Duofilm; Egozite Cradle Cap; ***Philipp.:*** Ionil; Wart-Off; ***Pol.:*** Callous; Corn; Corn and Callous; Keratolysin; Masc przeciw Odciskom i Zgrubieniom Skory; Saliderm; Seal & Heal; Soft Corn; Urgo Cor; ***Port.:*** Psorimed; Transvercid; Urgocor; Verrufilm; Verucid†; ***S.Afr.:*** Compound W; Cross Brand Corn Plasters; Emzaclear; Freezone; Jiffy Medi+ Plus; Piccadilly Foot Ointment; SB Unola Corn Remover; Yalta Corn Salve; ***Singapore:*** Clearasil 3 in 1; Clearasil Ice Wash; Duofilm; ***Spain:*** Callicida Gras; Callicida Salve; Callofin; Cornina†; Unguento Morry; Urgocall†; Verrupatch; Verruplan; ***Swed.:*** Salsyvase; ***Switz.:*** Scholl Warzenfilm; Verrufilm†; ***Turk.:*** Nasiral; Salsil; Scholl Callous; ***UK:*** Acnisal; Carnation; Clearasil Double Action Pads; Compound W; Occlusal; Pickles Foot Ointment; Scholl Callus Removal; Scholl Corn Removal; Scholl Verucca Removal; SCR; Snufflebabe Cradle Cap; Verrugon; Wartex; ***USA:*** Clearasil Clearstick; Compound W;

Dr Scholl's Callus Removers; Dr Scholl's Clear Away; Dr Scholl's Corn Removers; Dr Scholl's Corn/Callus Remover; Dr Scholl's Wart Remover; Duofilm; Duoplant; Fostex Acne Medication Cleansing; Freezone; Gordofilm; Hydrisalic; Ionil; Ionil Plus; Keralyt; Mediplast; MG217 Sal-Acid; Mosco; Occlusal; Off-Ezy; Oxy Night Watch; P & S; Panscol; PropapH; Psor-a-set; Sal-Acid; Sal-Plant; Salac; Salactic Film; Salex; Salkera; Sebucare†; Stri-Dex Clear; Trans-Ver-Sal AdultPatch; Trans-Ver-Sal PediaPatch; Trans-Ver-Sal PlantarPatch; Wart Remover; Wart-Off; X-Seb; ***Venez.:*** Acnil; Ven Hex†.

Multi-ingredient: numerous preparations are listed in Part 3.

Salnacedin *(USAN, rINN)*

G-201; Salnacedina; Salnacédine; Salnacedinum; SCY. *N*-Acetyl-L-cysteine salicylate.

Сальнацедин

$C_{12}H_{13}NO_5S$ = 283.3.

CAS — 87573-01-1.

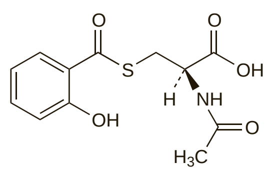

Profile

Salnacedin has anti-inflammatory and keratolytic properties and is applied topically in the treatment of seborrhoeic dermatitis and acne.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Encaskin Creme†; Encaskin Detergente†; ***Switz.:*** Encaskin Cream; Encaskin Liquid Detergent.

Sebacic Acid

Ácido decanodioico; Sebácico, ácido. Decanedioic acid; Octane-1,8-dicarboxylic acid.

Себациновая Кислота

$C_{10}H_{18}O_4$ = 202.2.

CAS — 111-20-6.

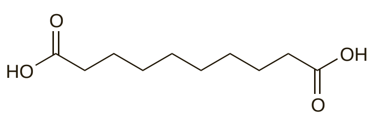

Profile

Sebacic acid may be used as a buffering agent in cosmetic preparations. Some of its esters, such as diethyl sebacate ($C_{14}H_{26}O_4$ = 258.4) and diisopropyl sebacate ($C_{16}H_{30}O_4$ = 286.4) may be used as emollients.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Port.:*** Pirrolfungin†.

Selenium Sulfide

Seleenidisulfidi; Selendisulfid; Seleni Disulfidum; Selenii disulfidum; Selenio, sulfuro de; Sélénium, disulfure de; Selenium Disulphide; Selenium Sulphide; Seleno disulfidas; Sulfid seleničitý; Szelén-diszulfid.

Сульфид Селения

SeS_2 = 143.1.

CAS — 7488-56-4.

ATC — D01AE13.

ATC Vet — QD01AE13.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Selenium Disulphide; Selenium Sulphide BP 2008). A bright orange to reddish-brown powder. Practically insoluble in water.

USP 31 (Selenium Sulfide). A bright orange to reddish-brown powder with not more than a faint odour. Practically insoluble in water and in organic solvents; soluble 1 in 161 of chloroform and 1 in 1667 of ether.

Adverse Effects, Treatment, and Precautions

Topical application of selenium sulfide can produce irritation of the scalp and skin, especially in the genital area and skin folds. Treated areas should be rinsed thoroughly to reduce inflammation, and contact with the eyes should be avoided. Oiliness or dryness of the scalp or hair, hair discoloration, and hair loss have been reported. Selenium sulfide shampoos should not be used within 48 hours of applying hair colours or straightening or waving preparations. Selenium sulfide may discolour metals.

Only traces of selenium sulfide are absorbed through intact skin but prolonged use on broken skin has resulted in systemic toxicity. To minimise absorption it should not be applied to mucous membranes or to skin that is inflamed or damaged. Toxicity is expected to be low from the ingestion of shampoos containing selenium sulfide. Nausea, vomiting, and diarrhoea may occur and gastrointestinal decontamination is generally considered unnecessary, but systemic absorption and toxicity, particularly neurological effects, might develop if large amounts are retained in the gut.

Systemic toxicity. A woman with excoriated eruptions on her scalp developed weakness, anorexia, abdominal pain, vomiting, tremors, sweating, a metallic taste in her mouth, and a garlic-like smell on her breath after using a shampoo containing selenium sulfide 2 or 3 times weekly for 8 months.[1] All symptoms subsided 10 days after the shampoo was stopped.

1. Ransone JW, *et al.* Selenium sulfide intoxication. *N Engl J Med* 1961; **264:** 384–5.

Uses and Administration

Selenium sulfide has antifungal and antiseborrhoeic properties. It is used topically in the treatment of dandruff (pityriasis capitis) and seborrhoeic dermatitis of the scalp (p.1584). Five to 10 mL of a lotion or shampoo containing 2.5% of selenium sulfide is applied to the wet scalp; the hair is rinsed and the application repeated; the preparation should remain in contact with the scalp for 2 to 3 minutes each time. The hair should be well rinsed after the treatment and all traces of the preparation removed from the hands and nails. Applications are usually made twice weekly for 2 weeks, then once weekly for 2 weeks and then only when necessary. Shampoos and lotions containing 1% are also used.

Selenium sulfide is also used as a 2.5% lotion in the treatment of pityriasis versicolor (see Skin Infections, p.521). The lotion may be applied to the affected areas with a small amount of water and allowed to remain for 10 minutes before thorough rinsing. This procedure is repeated once daily for about 7 days. Alternatively undiluted 2.5% lotion has been applied at bedtime and washed off in the morning on 3 separate occasions at 3-day intervals.

Selenium sulfide has also been used as an adjunct to the systemic treatment of tinea capitis (see Dermatophytoses under Skin Infections, p.521).

Preparations

BP 2008: Selenium Sulphide Scalp Application;
USP 31: Selenium Sulfide Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Selsun†; ***Austral.:*** Selsun; ***Austria:*** Selsun; STOI-X; ***Belg.:*** Selsun; ***Braz.:*** Caspacil; Selsun; ***Canad.:*** Head & Shoulders Intensive Treatment; Selsun; Versel; ***Chile:*** Selsun; ***Denm.:*** Selenol; Selsun†; ***Fin.:*** Selsun; Selukos; ***Fr.:*** Selsun; ***Ger.:*** Selsun; Selukos†; ***Gr.:*** Selsun; ***Hong Kong:*** Selsun; ***Indon.:*** Selsun; Topisel; ***Irl.:*** Selsun; ***Israel:*** Sebosel; Selsun; ***Ital.:*** Selsun Blu; ***Malaysia:*** Sellon; Selsun†; ***Neth.:*** Selsun; ***Norw.:*** Selsun; Selukos; ***NZ:*** Selsun; ***Philipp.:*** Selsun Blue; ***Pol.:*** Selsun; ***Port.:*** Finitor; Selenix; ***S.Afr.:*** Selsun†; ***Singapore:*** Seldron; ***Spain:*** Abbottselsun; Bioselenium; Caspiselenio; ***Swed.:*** Selsun; Selukos; ***Switz.:*** Selsun; ***Thai.:*** Sebosel; Selfide; Selsun; ***UK:*** Selsun; ***USA:*** Exsel†; Head & Shoulders Intensive Treatment; Selsun; ***Venez.:*** Selegel; Seltrex†.

Multi-ingredient: ***Arg.:*** Selegel; ***Canad.:*** Selsun with Provitamin B †; ***Fr.:*** Selegel; Vichy Dercos Shampooing Antipelliculaire; ***Ger.:*** Ellsurex; ***India:*** Candid-TV; ***Ital.:*** Selsun Plus†; ***Spain:*** Sebumselen; ***Switz.:*** Ektoselene; ***Venez.:*** Selenil.

Sinecatechins *(USAN)*

Kunecatechins. A mixture whose major constituents are (−)-epicatechin, (−)-epigallocatechin, the corresponding 3-gallate esters, and their corresponding epimers.

CAS — 811420-59-4 (sinecatechins); 490-46-0 ((−)-epicatechin); 1257-08-5 ((−)-epicatechin 3-O-gallate); 970-74-1 ((−)-epigallocatechin); 989-51-5 ((−)-epigallocatechin 3-O-gallate).

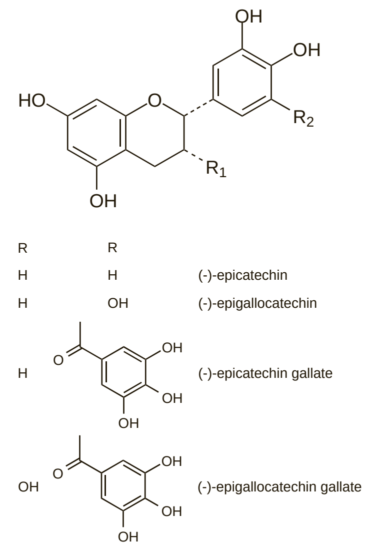

Profile

Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, sinecatechins is used in the treatment of external genital and perianal warts (p.1584). A 15% ointment is applied 3 times daily until complete clearance of all warts, but for no longer than 16 weeks. Local adverse effects are common with the topical application of sinecatechins and include erythema, pruritus, burning, pain or discomfort, erosion or ulceration, oedema, induration, and vesicular rash. Less common effects include urethritis, pigmentation changes, and hyperaesthesia.

◊ References.

1. Gross G, *et al.* A randomized, double-blind, four-arm parallel-group, placebo-controlled phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol* 2007; **21:** 1404–12.
2. Anonymous. Veregen: a botanical for treatment of genital warts. *Med Lett Drugs Ther* 2008; **50:** 15–16.
3. Gross G. Polyphenon E: Eine neue topische Therapie für Condylomata acuminata. *Hautarzt* 2008; **59:** 31–5.
4. Stockfleth E, *et al.* Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol* 2008; **158:** 1329–38.
5. Tatti S, *et al.* Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol* 2008; **111:** 1371–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Epinerve; ***USA:*** Veregen.

Skin Substitutes

Sustitutos de la piel.

Profile

Biological and semisynthetic materials have been developed for use as temporary dressings in burns, ulcers, and other injuries associated with skin loss. The rationale is to prevent fluid and heat loss, to reduce infection, to protect exposed structures, to reduce pain, and to prepare the site for grafting (see Burns, p.1578, and Wounds and Ulcers, p.1585).

Denatured porcine and bovine skin, consisting of the dermal and/or epidermal layers, have been used. More recently bioengineered human skin equivalents have been produced which more closely mimic human skin, as well as human, living dermal replacement products.

◊ Reviews.

1. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol* 2005; **23:** 403–12.
2. Braye F, *et al.* Les substituts cutanés reconstruits en laboratoire: application au traitement des brûlés. *Pathol Biol (Paris)* 2005; **53:** 613–17.
3. Bar-Meir E, *et al.* Skin substitutes. *Isr Med Assoc J* 2006; **8:** 188–91.
4. Hrabchak C, *et al.* Biological skin substitutes for wound cover and closure. *Expert Rev Med Devices* 2006; **3:** 373–85.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Kytinon Lamina†; Kytinon Membrana†; Pel Cupron†; ***S.Afr.:*** Dermagraft; ***UK:*** Dermagraft; Myskin; TransCyte; ***USA:*** Apligraf; Dermagraft; Orcel; TransCyte.

Multi-ingredient: ***Arg.:*** Kytinon ABC†; Kytinon ARHI†; Kytinon ATM†.

Sodium Pidolate *(pINNM)*

NaPCA; Natrii Pidolas; Pidolate de Sodium; Pidolato sódico; Piroglutamato sódico; Pirrolidona carboxilato de sodio; Sodium Pyroglutamate; Sodium Pyrrolidone Carboxylate. Sodium 5-oxopyrrolidine-2-carboxylate.

Натрий Пидолат

$C_5H_7NNaO_3$ = 152.1.

CAS — 28874-51-3 (DL-sodium pidolate); 54571-67-4 (L-sodium pidolate).

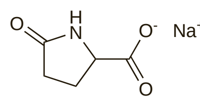

Profile

Sodium pidolate is used as a humectant. It is applied topically as a cream or lotion, often in multi-ingredient preparations, in the treatment of dry skin disorders.

Copper and zinc pidolate are used similarly; they have also been used as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Effaclar†; ***Hong Kong:*** DermaVeen.

Multi-ingredient: ***Arg.:*** Effalpha†; Lacticare; Sabal†; ***Austral.:*** Dermadrate; DermaVeen Moisturising; DermaVeen Shower & Bath; ***Braz.:*** Effaclar; Lacticare; ***Chile:*** Lacticare†; ***Fr.:*** BiaZinc†; Cu-Zn; DS Emulsion; Effaclar; Hydracuivre; Hyseke; Lacticare; Mycogel; ***Hong Kong:*** Dermadrate; DS Emulsion; Lacticare†; Mycogel; ***India:*** Efaderm; ***Indon.:*** Lacticare; ***Irl.:*** Effaclar; Effaclar K; Hydromol†; Lacticare; ***Ital.:*** Angstrom Viso; ***Malaysia:*** Lacticare; ***Mex.:*** Lacticare; ***NZ:*** Dermadrate; ***Philipp.:*** Lacticare; ***S.Afr.:*** Lacticare; ***Singapore:*** Dermadrate; DermaVeen Shower & Bath; Effaclar K; Lacticare; Stop-Itch Plus; ***Thai.:*** Lacticare; ***UK:*** Hydromol; Lacticare†.

Squaric Acid Dibutylester

Éster dibutílico del ácido escuárico; Quadratic Acid Dibutylester; SADBE. The dibutyl ester of 3,4-dihydroxy-3-cyclobutene-1,2-dione; 3,4-Dibutoxy-3-cyclobutene-1,2-dione; .

Дибутиловый Эфир Скварииковой Кислоты

$C_{12}H_{18}O_4$ = 226.3.

CAS — 2892-62-8 (squaric acid dibutylester); 2892-51-5 (squaric acid).

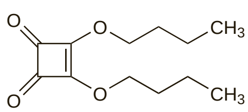

Profile

Squaric acid dibutylester has been tried similarly to diphencyprone (p.1594) as a contact sensitiser in the treatment of alopecia. It has also been tried in warts.

◊ References.

1. Tosti A, *et al.* Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis. *J Am Acad Dermatol* 1996; **35:** 199–201.
2. Micali G, *et al.* Treatment of alopecia areata with squaric acid dibutylester. *Int J Dermatol* 1996; **35:** 52–6.
3. Lee AN, Mallory SB. Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant warts. *J Am Acad Dermatol* 1999; **41:** 595–9.
4. Silverberg NB, *et al.* Squaric acid immunotherapy for warts in children. *J Am Acad Dermatol* 2000; **42:** 803–8.
5. Micali G, *et al.* Use of squaric acid dibutylester (SADBE) for cutaneous warts in children. *Pediatr Dermatol* 2000; **17:** 315–18.
6. Dall'Oglio F, *et al.* Adult and paediatric contact immunotherapy with squaric acid dibutylester (SADBE) for recurrent, multiple, resistant, mucocutaneous anogenital warts. *Sex Transm Infect* 2002; **78:** 309–10.
7. Dall'Oglio F, *et al.* Topical immunomodulator therapy with squaric acid dibutylester (SADBE) is effective treatment for severe alopecia areata (AA): results of an open-label, paired-comparison, clinical trial. *J Dermatol Treat* 2005; **16:** 10–14.
8. Ajith C, *et al.* Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in alopecia areata and factors influencing the outcome. *J Drugs Dermatol* 2006; **5:** 262–6.

Sulfur

Azufre; Enxôfre; Kén; Kükürt; Rikki; Schwefel; Siarka; Síra; Soufre; Sulphur; Sulphurium; Svavel.

Сера

S = 32.065.

CAS — 7704-34-9.
ATC — D10AB02.
ATC Vet — QD10AB02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.* Some have monographs for Precipitated Sulfur (Milk of Sulfur), Sublimed Sulfur (Flowers of Sulfur), or both. Some specify it is only for external use.

Ph. Eur. 6.2 (Sulphur for External Use). A yellow powder. The size of most of the particles is not greater than 20 micrometres and that of almost all the particles is not greater than 40 micrometres. Practically insoluble in water; soluble in carbon disulfide; slightly soluble in vegetable oils. Protect from light.

USP 31 (Precipitated Sulfur). A very fine, pale yellow, odourless, amorphous or microcrystalline powder. Practically insoluble in water; very slightly soluble in alcohol; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; soluble 1 in 100 of olive oil.

USP 31 (Sublimed Sulfur). A fine, yellow, crystalline powder with a faint odour. Practically insoluble in water and in alcohol; sparingly soluble in olive oil.

Adverse Effects and Precautions

Topical application of sulfur can cause skin irritation and dermatitis has been reported after repeated application. Contact with the eyes, mouth, and other mucous membranes should be avoided. Contact with sulfur can discolour certain metals such as silver, and application of sulfur with topical mercurial compounds can lead to the generation of hydrogen sulfide which has a foul odour and may stain the skin black.

Handling. Sulfur has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Uses and Administration

Sulfur is a keratolytic, a mild antiseptic, a mild antifungal, and a parasiticide.

Colloidal sulfur has a smaller particle size than either precipitated or sublimed sulfur. It is sulfur in an aqueous medium containing a colloid such as albumin or gelatin.

Sulfur has been widely used in lotions, creams, or ointments, usually combined with other agents, in concentrations of up to 10% in the treatment of acne, dandruff, seborrhoeic conditions, scabies, and superficial fungal infections, although there are more convenient and effective preparations.

Lotions of precipitated sulfur with lead acetate have been used to darken grey hair.

Sulfur was also formerly used as a mild irritant laxative.

Sulfur is used in homoeopathic medicine.

◊ General references.

1. Lin AN, *et al.* Sulfur revisited. *J Am Acad Dermatol* 1988; **18:** 553–8.
2. Gupta AK, Nicol K. The use of sulfur in dermatology. *J Drugs Dermatol* 2004; **3:** 427–31.

Preparations

BPC 1973: Salicylic Acid and Sulphur Ointment;
USP 31: Resorcinol and Sulfur Topical Suspension; Sulfur Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Macbirs; Macbirs Sulphur; Merbenloc; Suldiamin†; ***Braz.:*** Sabonete Sulfuroso†; ***Canad.:*** Postacne†; ***Cz.:*** Aknepur†; ***Ger.:*** Sulfopino†; ***Indon.:*** Acne Feldin; JF Sulfur; ***Ital.:*** Acqua di Sirmione†; Misurid; Sapol; ***Malaysia:*** JF Sulfur; ***Philipp.:*** Erasul; Sulderm; ***Turk.:*** Capila Savon; ***USA:*** Acne Lotion 10; Liquimat; Sulfoam; Sulmasque.

Multi-ingredient: ***Arg.:*** Acnomel†; Azufracid; Bentophyto; Bifena; C-G†; Farmigras; Medicatex; Molnia; Nemegel†; Onelacne†; Pinklot; Sastid; Suffisance; Tersoderm Cabellos Grasos†; ***Austral.:*** Acne & Pimple Gel†; Clearasil Acne Treatment Cream; Egopsoryl TA; Eskamel; Neo-Medrol; Psor-Asist; ***Austria:*** Aknichthol; Alpicort; Eucarbon; Herposicc; Leukona-Sulfomoor-Bad†; Sabatif; Salvyl; Schwefelbad Dr Klopfer; Sulfo-Schwefelbad; Wisamt†; ***Braz.:*** Acnase; Actine; Akirol†; Circanetten†; Dermax; Dermic; Polvilho Antisseptico†; Salder S; Salisoap; Sastid; Talco Alivio†; Varicell†; ***Canad.:*** Boil Ease†; Clearasil Acne Control; Clearasil Acne Cream; Mazon Medicated Shampoo; Medrol Acne Lotion; Meted; Neo-Medrol Acne; Pernox; Sebulex; Sebutone†; Sterex; Sterex Plus; Sulfacet-R; ***Chile:*** Acnaid†; Antiacne†; Dermac Crema; Sastid Jabon; ***Cz.:*** Acne Cream†; ***Fin.:*** Neo-Medrol comp†; Wicne; Wicnecarb; ***Fr.:*** Dermo-Sulfuryl; Paps; Selso; Solacy; Sulfuryl; Zeniac†; ***Ger.:*** Antihydral M†; Ellsurex; Fango-Rubriment; Schwefelbad Dr Klopfer; Sulfredox†; Sulfuretten†; Wisamt N†; ***Hong Kong:*** 2-4-2†; Acne-Aid; Acnederm; Antihydral M†; Cocois†; Egopsoryl TA; Neo-Medrol Acne; Sastid; ***Hung.:*** Bolus Laxans; Schwefelbad Dr Klopfer; ***India:*** Persol Forte; ***Indon.:*** Bioacne; Feldixid; Sastid; ***Irl.:*** Cocois; Meted; Pragmatar; ***Israel:*** Acnex†; Caltrim cum Sulphur†; Duo-Scabil; Eucarbon; Neo-Medrol; Sulfo-Salicyl; ***Ital.:*** Acnesan†; Anti-Acne; Eucarbon; Geroderm Zolfo†; Lenirose†; Medrol Lozione Antiacne†; Sacnel; Same-Seb; Saugella Solido Zolfo; Troca Flu Spray Nasale; ***Malaysia:*** Acne-Aid; Acnederm†; Clearasil Pimple Treatment; Cocois†; Egopsoryl TA; Eucarbon†; Neo-Medrol; Nixoderm; Sastid; ***Mex.:*** Crema Axel†; Dermac; Jabon del Tio Nacho; Locion Axel†; Sastid; ***NZ:*** Acnederm†; Clearasil; Coco-Scalp; Cocois†; Egopsoryl TA; ***Philipp.:*** Dermalin; Sastid; ***Pol.:*** Acne Sulf; Bals-Sulphur; Cocois; Dermaknel; Zdroj; ***Port.:*** All Pecium†; Resodermil; Sucadermil; ***Rus.:*** Olimetin (Олиметин)†; ***S.Afr.:*** Balsem Sulphuris; Clearasil T; Cuticura†; Eskamel; Haarlemensis; Neo-Medrol; Sastid; ***Singapore:*** Acne Clear; Acne-Aid; Clearasil Pimple Treatment; Egopsoryl TA; Neo-Medrol; Sastid; ***Spain:*** Acnisdin; Crislaxo; Laxante Sanatorium; Moderin Acne†; Sastid†; ***Swed.:*** Sevorex; ***Switz.:*** Acne Creme; Acne Gel; Ektoselene; Sebo-Soufrol; Soufrol TP†; ***Thai.:*** Circanetten; Neo-Medrol; Sastid; ***Turk.:*** Eucarbon; Karboseptin; Wilkinson; ***UK:*** Actinac; Balto Foot Balm; Clearasil Active Treatment Cream; Cocois; Eskamel; Herbheal Ointment; Meted; Pragmatar†; Psorasolv; Sebco; Simpsons; Skin Clear; TCP; ***USA:*** Acno; Acnomel; Acnotex; Avar; Aveeno Cleansing Bar; Bensulfoid; Boil Ease; Clenia; Finac; Fostex Medicated; Fostril†; Meted; MG217 Medicated Tar-Free; MG400; Nicosyn; Novacet; Pernox; Plexion; Rezamid; Rosac; Rosanil; Rosula; Sastid; Seale's Lotion; Sebasorb; Sebex; Sebex-T; Sebulex; Sulfacet-R; Sulforcin; Sulfoxyl; Sulpho-Lac; Suphera; Therac†; Zetacet; ***Venez.:*** Acnil†; Alderil†; Bori-Zinc†; Klenyl; Niosilin; Sastid†; Selenil.

Sulfurated Lime

Cal sulfurada; Calcium Sulphide; Calx Sulphurata; Sulfuro cálcico; Sulphurated Lime.

Сернистый Кальций (calcium sulfide); Сульфид Кальция (calcium sulfide)

CAS — 8028-82-8 (sulfurated lime solution).

Profile

Sulfurated lime is a mixture containing calcium sulfate and not less than 50% of calcium sulfide (CaS), prepared by heating calcium sulfate with carbonaceous matter. Sulfurated lime solution (Vleminckx's solution) is an aqueous solution containing calcium polysulfides and calcium thiosulfate prepared by boiling sublimed sulfur with calcium hydroxide in water.

Sulfurated lime has been used topically as sulfurated lime solution for acne, scabies, seborrhoeic dermatitis, and pustular infections such as boils and carbuncles. A similar solution known as 'lime-sulphur' is used as a fungicide in horticulture.

An impure grade of calcium sulfide (Hepar Sulphuris; Hepar Sulph.) is used in homoeopathic medicine.

NOTE. The title Hepar Sulfuris is also applied to Sulfurated Potash (see below).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Cz.:*** Homeovox.

Sulfurated Potash

Foie de Soufre; Hepar Sulfuris; Hígado de azufre; Kalii Sulfidum; Liver of Sulphur; Potasa sulfurada; Potassa Sulphurata; Schwefelleber; Sulphurated Potash.

Серная Печень

CAS — 39365-88-3.

NOTE. The title Hepar Sulphuris is used in homoeopathic medicine for an impure grade of calcium sulfide—see Sulfurated Lime, above.

Pharmacopoeias. In *US.*

USP 31 (Sulfurated Potash). A mixture composed chiefly of potassium polysulfides and potassium thiosulfate, containing not less than 12.8% of sulfur as sulfide. Irregular, liver-brown pieces when freshly made, changing to greenish-yellow. It has an odour of hydrogen sulfide. Soluble 1 in 2 of water, usually leaving a slight residue. Alcohol dissolves only the sulfides. A 10% solution is light brown in colour and alkaline to litmus. Store in small, airtight containers.

Incompatibility. Sulfurated potash is incompatible with acids.

Profile

Sulfurated potash has been used in the treatment of acne and other skin disorders usually in the form of a lotion with zinc sulfate.

Preparations

USP 31: Zinc Sulfide Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Leukona-Sulfomoor-Bad†.

Sulisobenzone *(USAN, rINN)*

Benzofenon-4; Benzophenone-4; NSC-60584; Sulisobenzona; Sulisobenzonum. 5-Benzoyl-4-hydroxy-2-methoxybenzenesulphonic acid.

Сулизобензон

$C_{14}H_{12}O_6S$ = 308.3.

CAS — 4065-45-6.

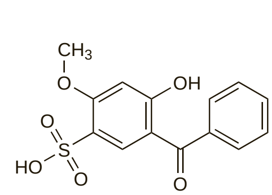

NOTE. Escalol 577 and Uvinul MS 40 are trade names that have been used for sulisobenzone.

Pharmacopoeias. In *US.*

USP 31 (Sulisobenzone). Light tan powder. M.p. about 145°. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Profile

Sulisobenzone, a substituted benzophenone, is a sunscreen (p.1576) with actions similar to those of oxybenzone (p.1608). It is effective against UVB and some UVA light (for definitions, see p.1580).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Nubevital BB; Nubevital Sunblock Ultra; Refrane Plus; ***Braz.:*** Sunmax Acqua; ***Canad.:*** Hawaiian Tropic Herbal†; ***Chile:*** Hidrafil; Spectraban 55; ***Mex.:*** Spectraban 55; ***USA:*** Hawaiian Tropic Protective Tanning Dry.

T4 Endonuclease V

Bacteriophage T4 Endodeoxyribonuclease V; T4N5. Coliphage T4 endodeoxyribonuclease V.

T4 Эндонуклеаза V

CAS — 52227-85-7.

Profile

T4 endonuclease V is a DNA-repair enzyme that is reported to remove DNA damaged by UV radiation. It is under investigation to reduce the incidence of actinic keratosis and basal cell carcinoma in patients with xeroderma pigmentosum (see Photosensitivity Disorders, p.1581).

◊ References.

1. Wolf P, *et al.* Topical treatment with liposomes containing T4 endonuclease V protects human skin in vivo from ultraviolet-induced upregulation of interleukin-10 and tumor necrosis factor-α. *J Invest Dermatol* 2000; **114:** 149–56.
2. Yarosh D, *et al.* Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001; **357:** 926–9.

Tacalcitol *(BAN, rINN)*

1α,24-Dihydroxycholecalciferol; 1α,24-Dihydroxyvitamin D_3; Tacalcitolum; Takalsitol. (+)-(5*Z*,7*E*,24*R*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,24-triol monohydrate.

Такальцитол

$C_{27}H_{44}O_3,H_2O$ = 434.7.

CAS — 57333-96-7 (anhydrous tacalcitol); 93129-94-3 (tacalcitol monohydrate).

ATC — D05AX04.

ATC Vet — QD05AX04.

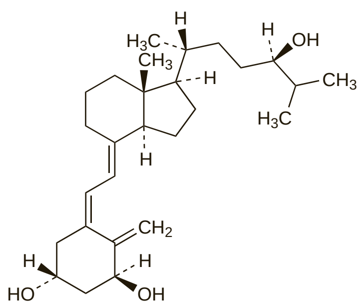

Adverse Effects and Precautions

As for Calcipotriol, p.1591. Paraesthesia may also occur. Tacalcitol may be applied to the face, but care should be taken to avoid the eyes. Tacalcitol may be degraded by UV radiation (see Uses and Administration, below).

Uses and Administration

Tacalcitol is a vitamin D_3 derivative, with actions and uses similar to those of calcipotriol (p.1592).

Tacalcitol is applied topically in the management of plaque psoriasis (p.1583). It is used as the monohydrate, but the concentration is expressed in terms of anhydrous tacalcitol; 4.17 micrograms of tacalcitol monohydrate is equivalent to about 4 micrograms of tacalcitol. It is applied as an ointment containing the equivalent of tacalcitol 4 micrograms/g (0.0004%). Applications are made once daily, preferably at bedtime, and no more than 10 g of ointment should be applied each day. Duration of treatment depends on the severity of the lesions; continuous and intermittent treatments for up to 12 months have been used.

Tacalcitol may be degraded by UV radiation and therefore if combined with UV therapy, the radiation should be given in the morning and tacalcitol applied at bedtime.

◊ References.

1. Peters DC, Balfour JA. Tacalcitol. *Drugs* 1997; **54:** 265–71.
2. Gollnick H, Menke T. Current experience with tacalcitol ointment in the treatment of psoriasis. *Curr Med Res Opin* 1998; **14:** 213–18.
3. Harrison PV. Topical tacalcitol treatment for psoriasis. *Hosp Med* 2000; **61:** 402–5.
4. Van de Kerkhof PCM, *et al.* Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. *Br J Dermatol* 2002; **146:** 414–22.
5. Lecha M, *et al.* Tacalcitol in the treatment of psoriasis vulgaris: the Spanish experience. *J Eur Acad Dermatol Venereol* 2005; **19:** 414–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bonalfa†; ***Austria:*** Curatoderm; ***Belg.:*** Curatoderm; ***Chile:*** Bonalfa; ***Cz.:*** Curatoderm; ***Fr.:*** Apsor; ***Ger.:*** Curatoderm; ***Hung.:*** Curatoderm; ***Israel:*** Curatoderm; ***Ital.:*** Ticlapsor; Vellutan; ***Jpn:*** Bonalfa; ***Mex.:*** Bonalfa; ***Pol.:*** Curatoderm; ***Port.:*** Bonalfa; ***Spain:*** Bonalfa; ***Switz.:*** Curatoderm; ***UK:*** Curatoderm; ***Venez.:*** Bonalfa†.

Purified Talc

E553(b); Mastek; Powdered Talc; Purified French Chalk; Talc; Talco (esteatita); Talco purificado; Talcum; Talcum Purificatum; Talk; Talkas; Talkki; Talkum.

Очищенный Тальк

CAS — 14807-96-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Talc; Purified Talc BP 2008). A powdered, selected, natural, hydrated, magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$; it may contain varying amounts of associated minerals. A light, homogeneous, white or almost white powder, greasy to the touch (non-abrasive). It should be free from asbestos. Practically insoluble in water, in alcohol, and in dilute solutions of acids and of alkali hydroxides.

USP 31 (Talc). A powdered, selected, natural, hydrated magnesium silicate. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminium and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant. A very fine, white or greyish-white, unctuous crystalline powder, which adheres readily to the skin, and is free from grittiness.

Adverse Effects and Precautions

Contamination of wounds or body cavities with talc is liable to cause granulomas and it should not be used for dusting surgical gloves.

Inhalation of talc can cause respiratory irritation; prolonged exposure may produce pneumoconiosis.

The most common adverse effects of talc pleurodesis are chest pain and fever. More serious complications that can occur include empyema, pneumonitis, dyspnoea, hypoxaemia, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome, and respiratory failure. Cardiovascular complications such as tachycardia, myocardial infarction, hypotension, hypovolaemia, and asystolic arrest have also occurred in patients treated with talc pleurodesis. However, the role of talc in serious complications is not always clear as the underlying condition of patients with malignant pleural effusion and the procedure itself are likely to be contributing factors.

Talc is liable to be heavily contaminated with bacteria, including *Clostridium tetani, Cl. welchii,* and *Bacillus anthracis.* When used in dusting powders or to treat pneumothorax and pleural effusions, it should be sterilised.

Abuse. Adverse pulmonary and ocular effects have been associated with the presence of talc in abused substances. It may be present as an excipient in oral medications that are crushed then dissolved and injected, or it may have been purposely added as a filler to the abused substance. When injected intravenously, the insoluble talc particles can embolise in small pulmonary vessels causing occlusion and pulmonary hypertension. The particles may also then migrate into the pulmonary interstitium, inducing a foreign-body reaction and fibrosis. Irregular nodules can develop in the lungs, which may coalesce to form conglomerate masses.[1] Talc retinopathy is described as deposits of crystalline talc embolising in the retinal microvasculature after intravenous injection.[2-4] Pulmonary granulomas[5] and talc retinopathy[6] have also been described after nasal inhalation of abused substances containing talc.

1. Gotway MB, *et al.* Thoracic complications of illicit drug use: an organ system approach. *Radiographics* 2002; **22** (suppl): S119–S135.
2. Martidis A, *et al.* Talc embolism: a static retinopathy. *Am J Ophthalmol* 1997; **124:** 841–3.
3. Fraser-Bell S, Capon M. Talc retinopathy. *Clin Experiment Ophthalmol* 2002; **30:** 432–3.
4. El-Jabali F, Cohen S. Talc retinopathy. *N Engl J Med* 2006; **354:** e11. Available at: http://content.nejm.org/cgi/reprint/354/12/e11.pdf (accessed 27/09/07)
5. Johnson DC, *et al.* Foreign body pulmonary granulomas in an abuser of nasally inhaled drugs. *Pediatrics* 1991; **88:** 159–61.
6. Kumar RL, *et al.* Crystalline retinopathy from nasal ingestion of methamphetamine. *Retina* 2006; **26:** 823–4.

Carcinogenicity. A review by a working group of the International Agency for Research on Cancer concluded that there was inadequate evidence to confirm whether purified talc was carcinogenic in humans but there was sufficient evidence to confirm that talc containing asbestiform fibres was carcinogenic to man.[1] There have been suggestions of a link between the use of talc and ovarian cancer[2] but although a case-controlled study suggested an approximate doubling of the risk among women after perineal use of talc the working group noted that information was not available on the asbestos content of the talcs.[1] Further case-controlled studies have also reported a positive association between perineal talc use and ovarian cancer, although others have found no association. A large prospective cohort study[3] that included 78 630 women found little support for an association overall, although from an analysis by histological subtype there appeared to be a modest increase in the risk for serous invasive cancer. A meta-analysis[4] that included this cohort study and 15 case-controlled studies did find a positive association between any exposure to perineal talc and the risk of developing ovarian cancer (relative risk 1.33; 95% confidence interval 1.16 to 1.45). However, the authors highlighted possible selection bias and confounding factors that may have resulted in a false-positive association. There was a lack of a clear dose-response relationship, different results for hospital-based and population-based patients, and the timing of exposure to talc in relation to cancer diagnosis was not always known.

An analysis of epidemiological studies in workers involved in milling the raw mineral (not containing asbestos-like fibres) found no evidence of an increased risk of lung cancer; there was some evidence of an excess among miners or other industrial workers exposed to talc, but these populations were also exposed to other potential carcinogens.[5]

1. IARC/WHO. Silica and some silicates. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 42* 1987. Available at: http://monographs.iarc.fr/ENG/Monographs/vol42/volume42.pdf (accessed 27/09/07)
2. Longo DL, Young RC. Cosmetic talc and ovarian cancer. *Lancet* 1979; **ii:** 349–51.
3. Gertig DM, *et al.* Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; **92:** 249–52.
4. Huncharek M, *et al.* Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res* 2003; **23:** 1955–60.
5. Wild P. Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. *Occup Environ Med* 2006; **63:** 4–9.

Effects on the lungs. Acute respiratory failure has occurred in patients treated with talc pleurodesis, given either as a slurry or by insufflation. In a series of 338 patients treated with insufflation, 4 developed acute respiratory failure and 3 of them died.[1] In another series[2] of 78 patients who underwent 89 procedures using slurry or insufflation, respiratory complications developed after 24 procedures including acute respiratory distress syndrome after 8 procedures in 7 patients of whom 1 died. In a debate based on these and other reports, including some series in which there were no respiratory complications, it was argued[3] that although the risk of acute respiratory distress is small the use of talc for pleurodesis should be abandoned in favour of other drugs such as tetracyclines or bleomycin, or mechanical abrasion of the pleura. The opposing view[4] was that there were many possible causes for acute respiratory distress in these cases, and that talc was still the best pleurodesis agent available. In a prospective randomised comparison in patients with malignant pleural effusion,[5] respiratory complications were more common with insufflation than slurry. The authors noted that the role of talc in causing acute respiratory complications of pleurodesis is unclear and further study is needed.

It has been suggested that acute respiratory distress syndrome after talc pleurodesis may be related to the talc particle size. There were no such reactions in a study[6] of 558 patients given large-particle (mean size 24.5 μm) talc insufflation, and the authors suggested that reported cases appeared to occur in countries where talc products contained higher concentrations of small particles (less than 5 μm).

For other effects on the lungs, see under Abuse, above and Infant Skin Care, below.

1. Campos JRM, *et al.* Respiratory failure due to insufflated talc. *Lancet* 1997; **349:** 251–2.
2. Rehse DH, *et al.* Respiratory failure following talc pleurodesis. *Am J Surg* 1999; **177:** 437–40.
3. Light RW. Talc should not be used for pleurodesis. *Am J Respir Crit Care Med* 2000; **162:** 2024–6.
4. Sahn SA. Talc should be used for pleurodesis. *Am J Respir Crit Care Med* 2000; **162:** 2023–4.
5. Dresler CM, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; **127:** 909–15.
6. Janssen JP, *et al.* Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007; **369:** 1535–9.

Infant skin care. The routine use of non-medicated powders in the skin care of infants can be hazardous and their use should be discouraged.[1,2] Talc acts as a pulmonary irritant and inhalation of baby-powders by infants has caused severe respiratory difficulties and several deaths have been reported. Careful respiratory monitoring is indicated in children suspected of inhaling talcum powder as the onset of symptoms may be delayed for several hours.[1] There have also been reports of umbilical granulomas resulting from contamination of umbilical stumps with talcum powder used for skin care.[2]

1. Pairaudeau PW, *et al.* Inhalation of baby powder: an unappreciated hazard. *BMJ* 1991; **302:** 1200–1.
2. Sparrow SA, Hallam LA. Talc granulomas. *BMJ* 1991; **303:** 58.

Uses and Administration

Purified talc is used in massage and as a dusting powder to allay irritation and prevent chafing. It is usually mixed with starch, to increase absorption of moisture, and zinc oxide. Talc used in dusting powders should be sterilised. Purified talc is used as a lubricant and diluent in making tablets and capsules and to clarify liquids.

Sterile purified talc is also used as a sclerosant after drainage of malignant pleural effusion and for recurrent spontaneous pneumothorax. It is administered into the pleural cavity as a slurry or by aerosol (insufflation). Doses of about 5 g may be used for pleural effusion and 2 g for pneumothorax.

Pleural effusions. Talc is used as a sclerosant to achieve pleurodesis in the management of benign and malignant pleural effusions (p.659) and recurrent spontaneous pneumothorax.[1-4] It is generally given into the pleural space as a slurry via intercostal tube, or by insufflation (talc poudrage) at thoracoscopy. Most reports have used a dose of 2 to 5 g, but doses have ranged from 1 to 10 g. A study[5] of talc pleurodesis in patients with malignant pleural effusion found both slurry and insufflation to be equally effective. The most common adverse effects associated with this use of talc are pain and fever. Other reported effects have included local infection and empyema, cardiovascular complications, and respiratory failure (see also Effects on the Lungs, above).

1. Kennedy L, Sahn SA. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. *Chest* 1994; **106:** 1215–22.
2. de Campos JRM, *et al.* Thoracoscopy talc poudrage: a 15 year experience. *Chest* 2001; **119:** 801–6.
3. Antunes G, *et al.* British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; **58** (suppl 2): ii29–ii38. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseMalignantPE.pdf (accessed 28/07/08)
4. Henry M, *et al.* British Thoracic Society. BTS guidelines for the management of spontaneous pneumothorax. *Thorax* 2003; **58** (suppl 2): ii39–ii52. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseSpontaneous.pdf (accessed 28/07/08)
5. Dresler CM, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; **127:** 909–15.

Preparations

BP 2008: Talc Dusting Powder.

Proprietary Preparations (details are given in Part 3)
USA: Sclerosol.

Multi-ingredient: ***Arg.:*** Dr Selby; ***Austral.:*** ZSC; ***Austria:*** Cutimix; Herposicc; Prurimix; Rombay; ***Belg.:*** Aloplastine; ***Braz.:*** Pasta d'Agua†; Pomaderme; Talco Alivio†; ***Chile:*** Hansaplast Footcare; ***Cz.:*** Cutimix†; Prurimix†; ***Fr.:*** Aloplastine; Eryange†; Poudre du Marcheur; ***Indon.:*** Minos; Yanthi Baby & Bath Powder; ***Israel:*** Pedisol; ***Malaysia:*** Rowarolan; ***Mex.:*** Hipoglos; ***NZ:*** Grans Remedy; Lamisil Odor Eze; ***Philipp.:*** Johnson's Baby Double Protection Powder; ***Pol.:*** Pedipur; ***Port.:*** Cuidaderma; ***Spain:*** Amniolina; Ictiomen; Pomada Infantil Vera†; ***Switz.:*** Tanno-Hermal; ***Turk.:*** Cinkos; ***USA:*** Columbia Antiseptic Powder; ***Venez.:*** Hipoglos con Hidrocortisona†; Hipoglos†.

Tars and Tar Oils

Breas y aceites de brea.

Birch Tar Oil

Aceite de abedul; Aceite de brea de abedul; Birkenteer; Goudron de Bouleau; Oleum Betulae Albae; Oleum Betulae Empyreumaticum; Oleum Betulae Pyroligneum; Oleum Rusci; Pix Betulae; Pyroleum Betulae.

Масло Берестового Дёгтя

Description. Birch tar oil is obtained by the destructive distillation of the wood and bark of the silver birch, *Betula verrucosa* (*B. pendula*; *B. alba*), and the birch, *B. pubescens* (Betulaceae); the distillate is allowed to stand and the oily upper layer separated from the residual tar.

Cade Oil

Alquitrán de Enebro; Ardıç Katranı; Brea de enebro; Goudron de Cade; Juniper Tar; Juniper Tar Oil; Kad Yağı; Kadeöl; Oleum Cadinum; Oleum Juniperi Empyreumaticum; Pix Cadi; Pix Juniperi; Pix Oxycedri; Pyroleum Juniperi; Pyroleum Oxycedri; Wacholderteer.

Можжевеловое Масло

Description. Cade oil contains guaiacol, ethylguaiacol, creosol, and cadinene.

Pharmacopoeias. In *US.*

USP 31 (Juniper Tar). The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* (Pinaceae). It is a dark brown, clear, thick liquid with a tarry odour. Very slightly soluble in water; soluble 1 in 9 of alcohol; soluble 1 in 3 of ether leaving only a slight flocculent residue; partially soluble in petroleum spirit; miscible with amyl alcohol, with chloroform, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Coal Tar

Alcatrão Mineral; Alquitrán de hulla; Brea de hulla; Crude Coal Tar; Goudron de Houille; Kamenouhelný dehet; Katran; Oleum Lithanthracis; Pix Carbon.; Pix Carbonis; Pix Lithanthracis; Pix Mineralis; Pyroleum Lithanthracis; Steinkohlenteer.

Каменноугольная Смола

Description. Prepared coal tar is commercial coal tar heated at 50° for 1 hour.

Alcoholic solutions of coal tar or prepared coal tar prepared with the aid of polysorbate have been referred to as Liquor Picis Carbonis and Liquor Carbonis Detergens.

Pharmacopoeias. In *Br., Fr., Int.,* and *US.*

BP 2008 (Coal Tar). A product obtained by the destructive distillation of bituminous coal at a temperature of about 1000°. A nearly black, viscous liquid with a strong characteristic penetrating odour. On exposure to air it gradually becomes more viscous. It burns in air with a luminous sooty flame. Slightly soluble in water; partly soluble in absolute alcohol, in chloroform, in ether, and in volatile oils. A saturated solution is alkaline to litmus.

USP 31 (Coal Tar). The tar obtained by the destructive distillation of bituminous coal at temperatures in the range of 900° to 1100°. It may be processed further either by extraction with alcohol and suitable dispersing agents and maceration times or by fractional distillation with or without the use of suitable organic solvents.

A nearly black, viscous liquid with a characteristic naphthalene-like odour. Slightly soluble in water to which it imparts an alkaline reaction; partially soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in ether, in methyl alcohol, and in petroleum spirit; more soluble in benzene; almost completely soluble in nitrobenzene. Store in airtight containers.

Tar

Alquitrán vegetal; Brea; Brea de pino; Brea vegetal; Goudron Végétal; Nadelholzteer; Pine Tar; Pix Abietinarum; Pix Liquida; Pix Pini; Pyroleum Pini; Wood Tar.

Древесная Смола; Древесный Дёготь

Pharmacopoeias. In *Br.*

BP 2008 (Tar). A bituminous liquid obtained from the wood of various trees of the family Pinaceae by destructive distillation. It is known in commerce as Stockholm Tar. A dark brown or nearly black semi-liquid with a characteristic empyreumatic odour; it is heavier than water. Soluble in alcohol (90%), in chloroform, in ether, and in fixed and volatile oils. The aqueous liquid obtained by shaking 1 g with 20 mL of water for 5 minutes is acidic to litmus paper.

Storage. When stored for some time tar separates into a layer which is granular in character due to minute crystallisation of catechol, resin acids, etc. and a surface layer of a syrupy consistence.

Adverse Effects and Precautions

Tars and tar oils may cause irritation and acne-like eruptions of the skin and should not be applied to inflamed or broken skin, mucosa, or the anogenital area. They should be used with caution on the face and skin flexures. Hypersensitivity reactions are rare but wood tars are more likely to cause sensitisation than coal tar. However, unlike wood tars, coal tar has a photosensitising action. Preparations of refined tar products appear to be less likely than crude tars to stain the skin, hair, and clothing.

Depending on their composition the systemic effects of tars and tar oils are similar to those for phenol (see p.1656).

Carcinogenicity. Coal tar and coal tar distillates contain a number of known and potential carcinogens including benzene, naphthalene, and other polycyclic aromatic hydrocarbons.[1] Studies of occupational exposure (for example, during coke production, coal gasification, and aluminium production) have found systemic absorption of significant amounts of polycyclic aromatic hydrocarbons,[2] and increases in the risks of developing a range of cancers.[1,2] Systemic absorption of polycyclic aromatic hydrocarbons has also been measured after the application of coal tar preparations used in the treatment of skin conditions.[2] However, although an increased risk of skin carcinoma was found[3] in 59 patients with psoriasis who had had very high exposures to tar and/or UV radiation, other cohort studies[4-6] found no increase in the risk of developing cancers from coal tar, even after long-term use.

1. National Toxicology Program. Coal tars and coal tar pitches. *Rep Carcinog* 2002; **10:** 68–70.
2. van Schooten F-J, Godschalk R. Coal tar therapy: is it carcinogenic? *Drug Safety* 1996; **15:** 374–7.
3. Stern RS, *et al.* Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1980; **i:** 732–5.
4. Pittelkow MR, *et al.* Skin cancer in patients with psoriasis treated with coal tar. *Arch Dermatol* 1981; **117:** 465–8.
5. Jones SK, *et al.* Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 1985; **113:** 97–101.
6. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73:** 2759–64.

Extemporaneous preparation. Concern about the possible carcinogenic potential of coal tar (see above) led the Health and Safety Executive in the UK to recommend that gloves for chemical protection, as opposed to disposable surgeon's gloves, should be worn during the extemporaneous preparation of formulations containing coal tar.[1]

1. Anonymous. Chemical protection gloves recommended for coal tar ointments. *Pharm J* 1997; **259:** 757.

Uses and Administration

Tars and tar oils can reduce the thickness of the epidermis. They are antipruritic and may be weakly antiseptic. They are used topically in eczema (p.1579), psoriasis (below), dandruff, seborrhoeic dermatitis (p.1584), and other skin disorders. Coal tar preparations have largely replaced the use of wood tars. Ultraviolet (UVB) light increases the efficacy of coal tar in the treatment of psoriasis.

Some wood tars, including creosote (p.1555) have been used in expectorant preparations.

Nonprescription use. After a review of products for safety and efficacy the FDA ruled that cade oil or tar should not be used in nonprescription shampoos[1] and that tar should no longer be included in nonprescription expectorants.[2]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; **5:** 62.
2. Anonymous. FDA announces standards for nonprescription sleep-aid products and expectorants. *Clin Pharm* 1989; **8:** 388.

Psoriasis. Coal tar has long been employed in the treatment of psoriasis (p.1583), and used alone or with dithranol and/or ultraviolet light it continues to be a first-line option, although its use is declining. It is particularly suited to the treatment of stable chronic plaque psoriasis. Its mode of action is unknown but it is considered to have antiproliferative and anti-inflammatory activity, producing a reduction in the thickness of viable epidermis. Crude tar preparations are rather messy and unpleasant; refined products may be more aesthetically acceptable and less likely to stain skin, hair, and clothing although some consider them to be less effective.

Treatments usually start with concentrations equivalent to 0.5 to 1% of crude coal tar with the concentration being increased as necessary every few days up to a maximum of 10%. The higher strength preparations may be required for the management of thicker patches of psoriasis but the British Association of Dermatologists considers that coal tar preparations of between 1 and 5% in white or yellow soft paraffin are as effective as higher concentrations, and that the use of higher concentrations, which has been traditionally advocated, has no evidence-based foundation and is best avoided, especially as it restricts outpatient use.

Coal tar may not clear psoriasis as fast as other agents but extended periods of remission can be obtained with its use. The Goeckerman regimen utilises the enhanced efficacy obtained when coal tar is applied before exposure to ultraviolet (UVB) light. The mechanism for this effect is not known but it does not appear to be due to the photosensitising action of coal tar. In most regimens the coal tar is applied 2 hours before exposure to UVB light. In Ingram's regimen and its modifications the use of coal tar and UVB light is followed by topical treatment with dithranol. It has been suggested that the irritant effects of dithranol treatment can be reduced without loss of efficacy if coal tar is also used.

References.

1. Rotstein H, Baker C. The treatment of psoriasis. *Med J Aust* 1990; **152:** 153–64.
2. Arnold WP. Tar. *Clin Dermatol* 1997; **15:** 739–44.
3. Thami GP, Sarkar R. Coal tar: past, present and future. *Clin Exp Dermatol* 2002; **27:** 99–103.
4. British Association of Dermatologists. Psoriasis guideline 2006. Available at: http://www.bad.org.uk/healthcare/guidelines/psoriasis_guideline_(Final_update)_280906.pdf (accessed 27/09/07)

Preparations

BP 2008: Calamine and Coal Tar Ointment; Coal Tar and Salicylic Acid Ointment; Coal Tar and Zinc Ointment; Coal Tar Paste; Coal Tar Solution; Strong Coal Tar Solution; Zinc and Coal Tar Paste;
USP 31: Coal Tar Ointment; Coal Tar Topical Solution; Compound Resorcinol Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Alcoderm; Alcontar†; Fijacid; Ingeshamp; Ionil-T Plus†; Soriacur†; Sorial; Supertar†; Sutrico Tar; Targel; ***Austral.:*** Alphosyl; Exorex†; Ionil-T Plus†; Linotar; Neutrogena T/Gel; Pinetarsol; Polytar Plus; Psorigel†;

Austria: Exorex; ***Braz.:*** Ionil-T Plus†; Tarflex; Theratar; ***Canad.:*** Balnetar; Doak-Oil; Estar†; Mazon Medicated Soap; Neutrogena T/Gel; Neutrogena T/Gel Therapeutic; Pentrax; Spectro Tar†; Targel; Tersa-Tar; ***Chile:*** DHS Tar Gel; Neutrogena Shampoo Neutar; Psorigel†; Tarmed; Tigel IRM; ***Cz.:*** Delatar; Teer-Linola-Fett N†; ***Denm.:*** Basotar†; ***Fr.:*** Caditar; ***Ger.:*** Basiter†; Berniter; Hoepixin Bad N†; Lorinden Teersalbe; Tarmed; Teer-Linola-Fett; ***Gr.:*** Exorex; Ionil; Tarmed; ***Hong Kong:*** Pinetarsol; Zetar; ***Irl.:*** Alphosyl†; Exorex; Pentrax; Psoriderm; ***Israel:*** Alphosyl 2 in 1; Denorex†; T/Gel; ***Ital.:*** Konor; Shampoo SDE Tar†; ***Malaysia:*** Pin-Xol; Pinetarsol; ***Mex.:*** Ionil-T Plus; Shampoo Tersa-Tar†; Tarmed; ***Neth.:*** Exorex; ***Norw.:*** Soraderm†; ***NZ:*** Pinetarsol; Psorigel†; ***Pol.:*** Delatar; Freederm Tar; Polytar; ***Port.:*** Neutar; Tarmed; ***Rus.:*** Freederm Tar (Фридерм Деготь); ***S.Afr.:*** Alphosyl; Denorex; Exarex†; Linotar; ***Singapore:*** Pinetarsol; ***Spain:*** Alfitar; Alphosyl; Piroxgel; Psoriasdin; Tar Isdin Champu; Tarmed; Tejel; ***UK:*** Alphosyl 2 in 1; Carbo-Dome; Clinitar; Exorex; Pentrax; Pinetarsol; Psoriderm; T/Gel; ***USA:*** Balnetar; Creamy Tar; DHS Tar; Estar†; Fototar; Ionil-T Plus; MG217 Medicated; Neutrogena T/Gel; Oxipor VHC; PC-Tar; Pentrax; Polytar; Psorigel†; Taraphilic; Tegrin; Tera-Gel; Zetar; ***Venez.:*** Alma-Tar†.

Multi-ingredient: ***Arg.:*** Acnetrol; Adop-Tar†; Aeroseb; Champuacid; Cicatrol; Confor-Tar†; Cremsor N; Domtisona†; Eurocoal; Farm-X; Hyaluron; Ingemet; Ionil-T; Laurinol Plus; Medic†; Mencogrin; Mencogrin AP; Oilalfo; Sequals G; Sorsis; Sorsis Beta; ***Austral.:*** Alphosyl; Eczema Cream; Egopsoryl TA; ER Cream†; Fongitar; Hamilton Pine Tar with Menthol; Ionil-T; Neutrogena T/Sal†; Pinetarsol; Polytar; Psor-Asist; Sebitar; Tarband†; ***Austria:*** Alphosyl; Alpicort; Locacorten Tar; ***Belg.:*** Locacortene Tar†; ***Braz.:*** Hebrin; Ionil-T; Polytar; Xarope Sao Joao†; ***Canad.:*** Boil Ease†; Dan-Tar Plus; Denorex Medicated; Mazon Medicated Cream; Mazon Medicated Shampoo; Medi-Dan; Multi-Tar Plus; Oxipor; P & S Plus; Polytar; Polytar AF; Sebcur/T; Sebutone†; SJ Liniment; Spectro Tar†; Sterex; Sterex Plus; Tardan; Targel SA; X-Seb T; X-Seb T Plus; X-Tar; ***Chile:*** Denorex Herbal†; Ionil-T; Tarytar†; ***Cz.:*** Locacorten Tar†; Polytar; Polytar AF; Suspensio Visnevski cum Pice Liquida Herbacos; ***Fr.:*** Alphosyl†; Cystel Shampooing Antiseborrheique†; Epiphane†; Item Alphacade; Laccoderme a l'huile de cade; Node DS; Node K; Node P; Novophane; Novophane S; Phytolithe†; Psocortene; Sebosquam; Squaphane; Squaphane E; Squaphane Masque-Creme; Squaphane P; Squaphane S; ***Ger.:*** Lorinden T†; Psorigerb N†; ***Hong Kong:*** 2-4-2†; Cocois†; Egopsoryl TA; Fongitar; Ionil-T; Locacorten Tar†; Multi-Tar; Polytar; Polytar Emollient; Sebitar; ***Hung.:*** Aknefug-liquid N†; Polytar; Polytar AF; ***India:*** Derobin Skin; Ionax T; ***Indon.:*** Polytar; ***Irl.:*** Alphosyl HC†; Capasal; Cocois; Denorex; Gelcotar†; Ionil-T†; Polytar; Polytar Emollient†; Pragmatar; ***Israel:*** Alphosyl HC†; Alphosyl†; Capasal; CT Ointment†; CT Pommade†; CT Shampoo†; Polytar; Topicorten-Tar; ***Ital.:*** Alphosyle†; Balta-Crin Tar†; Rivescal Tar; ***Malaysia:*** Cocois†; Egopsoryl TA; Mentar; Polytar; Sebitar; ***Mex.:*** Antaderm; Dariseb; Dealan; Dermoscalp; Ionil-T; Jabon del Tio Nacho; Polytar; Sebryl; Sebryl Plus; Sebstopp; Shampoo del Tio Nacho; ***Neth.:*** Denorex; ***NZ:*** Coco-Scalp; Cocois†; Egopsoryl TA; Fongitar†; Ionil-T; Polytar; Polytar Emollient; Polytar Plus; Sebitar; ***Philipp.:*** Fongitar; Ionil-T; Polytar; ***Pol.:*** Cocois; Polytar AF; Psorisan; ***Port.:*** Alpha Cade; Banholeum Composto; Betacade†; Edoltar†; Fongitar; Polytar; Sucadermil; ***S.Afr.:*** Alphosyl; Fongitar; Haarlemensis; Oxipor VHC; Polytar; SB Universal Ointment; ***Singapore:*** Denorex†; Egopsoryl TA; Fongitar; Ionil-T; Polytar; Sebitar; ***Spain:*** Alphosyl; Bazalin; Emolytar; Ionil Champu; Ionil†; Polytar; Quinortar†; Tar Isdin Plus†; Zincation Plus; ***Swed.:*** Alphosyl†; ***Switz.:*** Alphosyl†; ***Thai.:*** Fongitar; Ionil-T†; Polytar; ***Turk.:*** Kadolin; Wilkinson; ***UK:*** Alphosyl HC; Capasal; Cocois; Polytar AF; Polytar Emollient; Polytar Liquid; Polytar Plus; Pragmatar†; Psorin; Sebco; Snowfire; Varicose Ointment; ***USA:*** Boil Ease; Ionil-T; Medotar; Neutrogena T/Sal; Sal-Oil-T; Sebex-T; SLT†; Tarlene; Tarsum; X-Seb T; X-Seb T Plus; ***Venez.:*** Vitar†.

Tazarotene *(BAN, USAN, rINN)*

AGN-190168; Tatsaroteeni; Tazaroten; Tazarotène; Tazaroteno; Tazarotenum. Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate.

Тазаротен

$C_{21}H_{21}NO_2S$ = 351.5.

CAS — 118292-40-3.

ATC — D05AX05.

ATC Vet — QD05AX05.

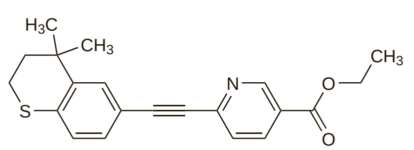

Adverse Effects and Precautions

As for Tretinoin, p.1618.

Systemic absorption from tazarotene applied topically is low, and the most frequent adverse effects are on the skin; the incidence of adverse events appears to be concentration related.

Animal studies have indicated that tazarotene is fetotoxic and teratogenic, and licensed product information recommends that tazarotene should not be used during pregnancy or in women planning a pregnancy. Similarly, tazarotene should not be used, or used with caution, during breast feeding, as *animal* data indicate that it may be distributed into breast milk.

Effects on the skin. A 57-year-old man with diabetes and recalcitrant psoriasis on the trunk and limbs developed acute dermatitis[1] in the genital area 2 weeks after starting treatment with topical tazarotene 0.1%. The affected areas became ulcerated over the next few days. It was suspected that accidental contact with the tazarotene that had been applied to the truncal psoriasis was responsible. Pyogenic granuloma has been associated with topical tazarotene and other retinoids given orally or applied topically (see Effects on the Skin, Hair, and Nails, under Isotretinoin, p.1601).

1. Wollina U. Genital ulcers in a psoriasis patient using topical tazarotene. *Br J Dermatol* 1998; **138:** 713–14.

Uses and Administration

Tazarotene is a retinoid used for the topical treatment of mild to moderate acne and plaque psoriasis, and to treat signs of photoageing. Tazarotene is a prodrug that is de-esterified in the skin to its active form, tazarotenic acid. The mode of action is unknown but it appears to modulate cell proliferation and differentiation.

In the treatment of **psoriasis**, tazarotene 0.05% cream or gel is used initially and increased to 0.1% if necessary. It is applied once daily in the evening. In the UK tazarotene is licensed for use in patients with psoriasis affecting up to 10% of the body-surface; in the USA, it may be used on psoriasis involving up to 20% of the body-surface.

In the treatment of **acne**, tazarotene is applied as a 0.1% gel or cream once daily in the evening.

There may be exacerbation of acne during early treatment or of psoriasis at any time during treatment. The treatment period is usually up to 12 weeks, although tazarotene has been used for up to 12 months in the treatment of psoriasis.

A 0.1% cream is used in the topical treatment of certain signs of **photoageing** (facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines). It is applied once daily at bedtime to lightly cover the entire face.

◊ Reviews.

1. Foster RH, *et al.* Tazarotene. *Drugs* 1998; **55:** 705–11.
2. Tang-Liu DD-S, *et al.* Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. *Clin Pharmacokinet* 1999; **37:** 273–87.
3. Guenther LC. Optimizing treatment with topical tazarotene. *Am J Clin Dermatol* 2003; **4:** 197–202.

Malignant neoplasms. There has been some interest in the use of topical tazarotene in the treatment of neoplasms affecting the skin. Preliminary studies have reported some lesion regression or clearance in basal cell[1] and squamous cell carcinomas[2] (p.673), and mycosis fungoides[3] (p.657).

1. Bianchi L, *et al.* Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. *Br J Dermatol* 2004; **151:** 148–56.
2. Bardazzi F, *et al.* A pilot study on the use of topical tazarotene to treat squamous cell carcinoma in situ. *J Am Acad Dermatol* 2005; **52:** 1102–4.
3. Apisarnthanarax N, *et al.* Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. *J Am Acad Dermatol* 2004; **50:** 600–607.

Skin disorders. Tazarotene is used for the topical treatment of mild to moderate acne[1,2] (p.1577) and plaque psoriasis[3,4] (p.1583); benefit has also been reported for psoriasis of the nails.[5,6] Improvement has been reported too in keratinisation disorders such as Darier's disease[7,8] (p.1578) and congenital ichthyosis[9-11] (p.1580). Topical tazarotene can also improve some signs of photoageing (p.1581), including fine wrinkling, mottled hyperpigmentation, and lentigines (liver spots).[12-14]

1. Leyden JJ. Meta-analysis of topical tazarotene in the treatment of mild to moderate acne. *Cutis* 2004; **74** (4 suppl): 9–15.
2. Shalita AR, *et al.* Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther* 2004; **26:** 1865–73.
3. Weinstein GD, *et al.* Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003; **48:** 760–7.
4. Dando TM, Wellington K. Topical tazarotene: a review of its use in the treatment of plaque psoriasis. *Am J Clin Dermatol* 2005; **6:** 255–72.
5. Scher RK, *et al.* Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001; **68:** 355–8.
6. Bianchi L, *et al.* Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: an open, prospective study. *Br J Dermatol* 2003; **149:** 207–9.
7. Oster-Schmidt C. The treatment of Darier's disease with topical tazarotene. *Br J Dermatol* 1999; **141:** 603–4.
8. Brazzelli V, *et al.* Linear Darier's disease successfully treated with 0.1% tazarotene gel "short-contact" therapy. *Eur J Dermatol* 2006; **16:** 59–61.
9. Hofmann B, *et al.* Effect of topical tazarotene in the treatment of congenital ichthyosis. *Br J Dermatol* 1999; **141:** 642–6.
10. Marulli GC, *et al.* Type I lamellar ichthyosis improved by tazarotene 0.1% gel. *Clin Exp Dermatol* 2003; **28:** 391–3.
11. Kundu RV, *et al.* Lamellar ichthyosis treated with tazarotene 0.1% gel. *J Am Acad Dermatol* 2006; **55** (suppl 5): S94–S95.
12. Phillips TJ, *et al.* Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol* 2002; **138:** 1486–93.
13. Machtinger LA, *et al.* Histological effects of tazarotene 0.1% cream vs. vehicle on photodamaged skin: a 6-month, multicentre, double-blind, randomized, vehicle-controlled study in patients with photodamaged facial skin. *Br J Dermatol* 2004; **151:** 1245–52.
14. Kang S, *et al.* A multicenter, randomized, double-blind trial of tazarotene 0.1% cream in the treatment of photodamage. *J Am Acad Dermatol* 2005; **52:** 268–74.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Zorac; ***Belg.:*** Zorac; ***Braz.:*** Zorac†; ***Canad.:*** Tazorac; ***Cz.:*** Tazorac; ***Fin.:*** Zorac†; ***Fr.:*** Zorac; ***Ger.:*** Zorac; ***Gr.:*** Zorac; ***India:*** La Tez; Tazret†; ***Irl.:*** Zorac; ***Israel:*** Zorac; ***Ital.:*** Zorac; ***Mex.:*** Suretin; ***Pol.:*** Zorac; ***S.Afr.:*** Zorak; ***Spain:*** Zorac; ***Swed.:*** Zorac†; ***Switz.:*** Zorac; ***UK:*** Zorac; ***USA:*** Avage; Tazorac.

Thioglycollic Acid

Kwas tioglikolowy; Tioglicólico, ácido. Mercaptoacetic acid.

Тиогликолевая Кислота

$C_2H_4O_2S$ = 92.12.

CAS — 68-11-1.

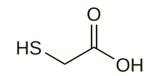

Calcium Thioglycollate

Calcium Mercaptoacetate; Tioglicolato cálcico. Calcium mercaptoacetate trihydrate.

Тиогликолят Кальция

$C_2H_2CaO_2S,3H_2O$ = 184.2.

CAS — 814-71-1.

Profile

Thioglycollic acid is used, usually as the calcium salt, in depilatory preparations. Thioglycollates are also used in hair waving or straightening products with potassium bromate as the neutraliser. There have been reports of skin reactions associated with the use of thioglycollates.

Tioxolone *(BAN, rINN)*

OL-110; Thioxolone; Tioksolon; Tioksoloni; Tioxolon; Tioxolona; Tioxolonum. 6-Hydroxy-1,3-benzoxathiol-2-one; .

Тиоксолон

$C_7H_4O_3S$ = 168.2.

CAS — 4991-65-5.

ATC — D10AB03.

ATC Vet — QD10AB03.

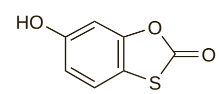

Pharmacopoeias. In *Pol.*

Profile

Tioxolone has astringent and keratolytic effects, and has been used topically in the treatment of various skin and scalp disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Loscon†.

Titanium Dioxide

CI Pigment White 6; Colour Index No. 77891; E171; Oxid titaničitý; Titaanidioksidi; Titandioxid; Titán-dioxid; Titane, dioxyde de; Titanii dioxidum; Titanio, dióxido de; Titanium Oxide; Titano dioksidas; Titanyum Dioksit; Tytanu(IV) tlenek.

Двуокись Титана; Диоксид Титана

TiO_2 = 79.87.

CAS — 13463-67-7.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Titanium Dioxide). A white or almost white powder. Practically insoluble in water; it does not dissolve in dilute mineral acids but dissolves slowly in hot concentrated sulfuric acid.

USP 31 (Titanium Dioxide). A white odourless powder. Insoluble in water, in hydrochloric acid, in nitric acid, and in 2N sulfuric acid; dissolves in hot sulfuric acid and in hydrofluoric acid; it is rendered soluble by fusion with potassium bisulfate or with alkali hydroxides or carbonates. A 10% suspension in water is neutral to litmus.

Profile

Titanium dioxide has an action on the skin similar to that of zinc oxide (p.1621) and has similar uses. Titanium peroxide and titanium salicylate are used with titanium dioxide for nappy rash. Titanium dioxide reflects ultraviolet light and is used as a physical sunscreen (p.1576). It is also an ingredient of some cosmetics. It is used to pigment and opacify hard gelatin capsules and tablet coatings and as a delustring agent for regenerated cellulose and other man-made fibres. Specially purified grades may be used in food colours.

Preparations

BP 2008: Titanium Ointment.

Proprietary Preparations numerous preparations are listed in Part 3.

Trafermin *(USAN, rINN)*

CAB-2001; Trafermina; Trafermine; Traferminum. 2-155-Basic fibroblast growth factor (human clone λKB7/λHFL1 precursor reduced).

Трафермин

CAS — 131094-16-1.

Profile

Trafermin is a human recombinant basic fibroblast growth factor (b-FGF) that promotes tissue granulation and the formation of new blood vessels. It is used as a topical liquid spray for the treatment of burns and intractable skin ulcers.

◊ References.

1. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–11.
2. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
3. Ichioka S, *et al.* The positive experience of using a growth factor product on deep wounds with exposed bone. *J Wound Care* 2005; **14:** 105–9.
4. Motomura H, *et al.* Aggressive conservative therapy for refractory ulcer with diabetes and/or arteriosclerosis. *J Dermatol* 2006; **33:** 353–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Fiblast.

Tretinoin *(BAN, USAN, rINN)*

Ácido retinoico; NSC-122758; Retinoic Acid; Tretinoiini; Tretinoína; Tretinoinas; Trétinoïne; Tretinoinum; Tretynoina; Vitamin A Acid; Vitamina A ácida. *all-trans*-Retinoic acid; 15-Apo-β-caroten-15-oic acid; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-*all-trans*-tetraenoic acid.

Третиноин

$C_{20}H_{28}O_2$ = 300.4.

CAS — 302-79-4.

ATC — D10AD01; L01XX14.

ATC Vet — QD10AD01; QL01XX14.

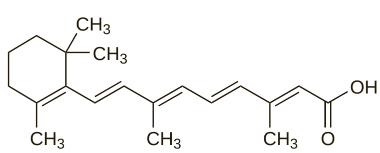

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Tretinoin). A yellow or light orange crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. It is sensitive to light, heat, and air, especially in solution. Store in airtight containers at a temperature not exceeding 25°. Protect from light. The contents of an opened container should be used as soon as possible and any unused portion should be protected by an atmosphere of an inert gas.

USP 31 (Tretinoin). A yellow to light-orange crystalline powder. Insoluble in water; slightly soluble in alcohol and in chloroform. Store in airtight containers, preferably under an atmosphere of an inert gas. Protect from light.

Adverse Effects

Tretinoin is a skin irritant. Topical application may cause transitory stinging and a feeling of warmth, and in normal use it produces some erythema, dryness, pruritus, and peeling similar to that of mild sunburn. Sensitive individuals may experience oedema, blistering, and crusting of the skin. Excessive application can cause severe erythema, peeling, and discomfort with no increase in efficacy. Photosensitivity may occur. Temporary hypopigmentation and hyperpigmentation have been reported.

Oral doses of tretinoin may produce similar adverse effects to those of isotretinoin (see p.1599). Adverse cardiovascular effects have also been reported; the most common were arrhythmias, flushing, hypotension, hypertension, and heart failure. Less common events were cardiac arrest, myocardial infarction, cardiomegaly, heart murmur, ischaemia, stroke, myocarditis, pericarditis, pulmonary hypertension, and secondary cardiomyopathy. A potentially life-threatening 'retinoic acid syndrome' (see below) has been described after oral use.

Carcinogenicity. Studies in *mice* suggested that tretinoin could enhance photocarcinogenesis.[1] However, other studies refuted this[2] and evidence indicates that topical tretinoin is not carcinogenic in humans.

1. Epstein JH. Chemicals and photocarcinogenesis. *Australas J Dermatol* 1977; **18:** 57–61.
2. Epstein JH. All-trans-retinoic acid and cutaneous cancers. *J Am Acad Dermatol* 1986; **15:** 772–8.

Effects on the blood. Transient and asymptomatic thrombocytosis has been reported with the use of oral tretinoin, see under Isotretinoin, p.1599.

Effects on the cardiovascular system. Tretinoin given for induction remission rapidly improves the coagulopathy associated with acute promyelocytic leukaemia, but there are associated reports of arterial and venous thromboembolism. In a number of cases the combination of tretinoin with an antifibrinolytic drug such as tranexamic acid may have increased the risk of thrombosis.[1-3] In other cases,[2,4] thrombosis occurred in the absence of tranexamic acid and appeared to be related to the retinoic acid syndrome (below). An assessment of 124 patients, including 11 who developed thrombosis, found that the expression of particular phenotypic and genotypic features of leukaemic cells may indicate an increased risk of thrombotic events in patients given tretinoin.[5]

For reports associated with other retinoids, see under Isotretinoin, p.1600.

1. Brown JE, *et al.* All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. *Br J Haematol* 2000; **110:** 1010–12.
2. Goldschmidt N, *et al.* Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 1433–7.
3. Levin M-D, *et al.* Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia. *Haematologica* 2003; **88:** ECR21. Available at: http://www.haematologica.org/cgi/reprint/88/6/ECR21.pdf (accessed 28/07/08)
4. Torromeo C, *et al.* Intraventricular thrombosis during all-trans retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 2001; **15:** 1311–13.
5. Breccia M, *et al.* Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia* 2007; **21:** 79–83.

Effects on the eyes. Papilloedema, retinal haemorrhage and visual changes as a result of benign intracranial hypertension have been associated with oral tretinoin;[1] children appear to be particularly sensitive. For further information about oral retinoids, including tretinoin, causing benign intracranial hypertension, see Effects on the Eyes under Isotretinoin, p.1600.

1. Mahmoud HH, *et al.* Tretinoin toxicity in children with acute promyelocytic leukaemia. *Lancet* 1993; **342:** 1394–5.

Effects on the musculoskeletal system. For reports of myositis occurring in patients receiving oral tretinoin, see under Isotretinoin, p.1600.

Effects on the nervous system. Neurotoxicity (ataxia, dysarthria, and headache) has been reported in a woman with liver impairment using topical tretinoin 0.025% for acne.[1]

1. Bernstein AL, Leventhal-Rochon JL. Neurotoxicity related to the use of topical tretinoin (Retin-A). *Ann Intern Med* 1996; **124:** 227–8.

Effects on the skin. Painful scrotal ulcers, often accompanied by fever, have occurred in men receiving oral tretinoin for acute promyelocytic leukaemia.[1-5] The appearance of the ulcers ranged from days 9 to 30 of the tretinoin course and improved after it was stopped (either at complete remission or because of the ulceration or other adverse effects). Management of the ulcers often included an intravenous or topical corticosteroid and in some cases an antibacterial ointment. Genital ulcers have also been reported in 2 women;[3] an 8-year-old girl developed ulcers 5 days after finishing a course of tretinoin.[6]

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in at least 12 patients treated with oral tretinoin for acute promyelocytic leukaemia.[7] In some cases there was also systemic involvement affecting muscle, kidneys, and lungs, and in a few cases patients also had retinoic acid syndrome (below). Most patients responded to systemic corticosteroid treatment and in some cases the course of tretinoin therapy could be continued as a result. There has also been a report[8] of Sweet's syndrome with myalgia and arthralgia in a child treated with oral tretinoin for acute myeloid leukaemia.

Details of other skin reactions to oral and topical retinoids, including tretinoin, are described under Isotretinoin, p.1601.

1. Mori A, *et al.* Scrotal ulcer occurring in patients with acute promyelocytic leukemia during treatment with all-trans retinoic acid. *Oncol Rep* 1999; **6:** 55–8.
2. Charles KS, *et al.* Scrotal ulceration during all-trans retinoic (ATRA) therapy for acute promyelocytic leukaemia. *Clin Lab Haematol* 2000; **22:** 171–4.
3. Fukuno K, *et al.* Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; **44:** 2009–13.
4. Gettinger S, *et al.* Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. *J Clin Oncol* 2004; **22:** 4648–9.
5. Shimizu D, *et al.* Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. *Intern Med* 2005; **44:** 480–3.
6. Ünal S, *et al.* Genital ulcers after treatment with all-trans-retinoic acid in a child with acute promyelocytic leukemia. *Pediatr Hematol Oncol* 2005; **22:** 357–9.
7. Astudillo L, *et al.* Sweet's syndrome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. *Ann Hematol* 2002; **81:** 111–14.
8. Al-Saad K, *et al.* Sweet syndrome developing during treatment with all-trans retinoic acid in a child with acute myelogenous leukemia. *J Pediatr Hematol Oncol* 2004; **26:** 197–9.

Retinoic acid syndrome. A syndrome consisting primarily of fever and respiratory distress developed in 9 of 35 patients between 2 and 21 days after starting induction therapy with oral tretinoin for suspected acute promyelocytic leukaemia.[1] Other symptoms included weight gain, oedema of the lower extremities, pleural or pericardial effusions, and episodic hypotension. Symptoms were life-threatening in 5 patients, 3 of whom subsequently died of multi-system failure. Leucocytosis was frequently, although not invariably, associated with development of the syndrome. Experience showed that early treatment with high-dose corticosteroids should be given to these patients irrespective of the leucocyte count. There have also been a few reports of thrombosis occurring with the retinoic acid syndrome (see Effects on the Cardiovascular System, above).

Reviews[2,3] of this syndrome, known as the 'retinoic acid syndrome', reported that it occurs in about 25% of patients with acute promyelocytic leukaemia treated with tretinoin and that the median time to onset is 10 to 12 days after the start of treatment; the severity of the syndrome varies greatly. A high leucocyte count at diagnosis or a rapidly-increasing count on initiation of therapy appears to increase the likelihood of the syndrome occurring. Close monitoring of leucocyte counts and clinical signs is recommended; high-dose intravenous corticosteroids, and possibly antineoplastic drugs, should be given if symptoms appear or the leucocyte count increases rapidly.

A similar syndrome has been reported in patients with acute promyelocytic leukaemia treated with arsenic trioxide (see p.2260). A capillary leak syndrome, similar to retinoic acid syndrome, has also been described with acitretin (see p.1586).

1. Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; **117:** 292–6.
2. Fenaux P, De Botton S. Retinoic acid syndrome: recognition, prevention and management. *Drug Safety* 1998; **18:** 273–9.
3. Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best Pract Res Clin Haematol* 2003; **16:** 453–61.

Vasculitic syndromes. For a report of vasculitis associated with oral tretinoin, see under Isotretinoin, p.1601.

Precautions

Contact of tretinoin with the eyes, mouth, or other mucous surfaces should be avoided. It should not be applied to eczematous, sunburnt, or abraded skin and the effects of other topical treatment, especially with keratolytics, should be allowed to subside before topical use of tretinoin. Exposure to UV light and excessive exposure to sunlight should be avoided.

Absorption does not seem to occur to any great extent with topical use. Nevertheless, because of teratogenicity in *animal* studies and isolated cases of congenital abnormalities (see below), licensed product information suggests that the use of topical tretinoin should be avoided during pregnancy. It is not known whether tretinoin is distributed into breast milk, and it should therefore be used topically with caution in breast-feeding mothers.

When tretinoin is given by mouth the precautions described under isotretinoin (see p.1601) should be adopted. Oral tretinoin is contra-indicated in pregnancy and in breast-feeding mothers.

Pregnancy. Although there have been isolated reports[1-4] of congenital abnormalities in infants born to mothers who used tretinoin topically before and during pregnancy, studies involving a total of 415 women[5-7] showed no increased risk for major congenital disorders in infants who had been exposed in the first trimester.

As a characteristic pattern of fetal malformation has been described with the use of oral retinoids, particularly isotretinoin (see p.1601), licensed product information warns that oral tretinoin is contra-indicated during pregnancy and that conception should be avoided for at least one month after the end of treatment. Nevertheless, the outcomes of up to 20 cases have been reviewed,[8,9] in which a course of tretinoin was generally given in the second or third trimester for promyelocytic leukaemia; some women were also given cytotoxic chemotherapy. There were reports of transient pulmonary and cardiac complications in some infants, but no congenital malformations were described. In one case[10] tretinoin was started in the first trimester and continued throughout the pregnancy to avoid the use of cytotoxic chemotherapy. The small-for-date infant was born by caesarean section at week 32 with jaundice and respiratory distress syndrome, which both resolved within 11 days. At 15 months of age the infant had normal growth and development.

1. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992; **339:** 687.
2. Lipson AH, *et al.* Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993; **341:** 1352–3.
3. Navarre-Belhassen C, *et al.* Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother* 1998; **32:** 505–6.
4. Colley SMJ, *et al.* Topical tretinoin and fetal malformations. *Med J Aust* 1998; **168:** 467.
5. Jick SS, *et al.* First trimester topical tretinoin and congenital disorders. *Lancet* 1993; **341:** 1181–2.
6. Shapiro L, *et al.* Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997; **350:** 1143–4.
7. Loureiro KD, *et al.* Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet* 2005; **136A:** 117–21.
8. Giagounidis AAN, *et al.* Acute promyelocytic leukemia and pregnancy. *Eur J Haematol* 2000; **64:** 267–71.
9. Consoli U, *et al.* Acute promyelocytic leukemia during pregnancy: report of 3 cases. *Int J Hematol* 2004; **79:** 31–6.
10. Simone MD, *et al.* All-trans retinoic acid (ATRA) administration during pregnancy in relapsed acute promyelocytic leukemia. *Leukemia* 1995; **9:** 1412–13.

Skin fragility. As with other retinoids (see under Isotretinoin, p.1602) the use of depilatory products should be avoided in patients treated with tretinoin. Erosions of the skin occurred in 2 patients after the use of wax depilation on facial areas also being treated topically with tretinoin.[1]

1. Goldberg NS, Zalka AD. Retin-A and wax epilation. *Arch Dermatol* 1989; **125:** 1717.

Interactions

As for Isotretinoin, p.1602.

Tretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, therefore there is a potential for interaction between oral tretinoin and inhibitors or inducers of these enzymes.

Antifibrinolytics. Thrombotic events have occurred in patients being treated with tretinoin and *tranexamic acid* (see Effects on the Cardiovascular System, above). Licensed product information for tretinoin used in the treatment of acute promyelocytic leukaemia advises caution when it is given with drugs such as *aminocaproic acid*, *aprotinin*, and tranexamic acid, particularly in the first month of treatment.

Minoxidil. For the effect of tretinoin on the percutaneous absorption of minoxidil, see p.1342.

Pharmacokinetics

After oral doses tretinoin is well absorbed from the gastrointestinal tract, and peak plasma concentrations are obtained after 1 to 2 hours. Oral bioavailability is about 50%. Minimal systemic absorption occurs after topical application. Tretinoin is highly bound to plasma proteins. It undergoes metabolism in the liver by the cytochrome P450 isoenzyme system. Metabolites include isotretinoin, 4-oxo-*trans*-retinoic acid, and 4-oxo-*cis*-retinoic acid. The terminal elimination half-life of tretinoin is 0.5 to 2 hours. Tretinoin is excreted in the bile and the urine. There is some evidence that tretinoin induces its own metabolism.

◊ References.

1. Regazzi MB, *et al.* Clinical pharmacokinetics of tretinoin. *Clin Pharmacokinet* 1997; **32:** 382–402.

Uses and Administration

Tretinoin is a retinoid and is the acid form of vitamin A (p.1971).

Tretinoin is used primarily in the topical treatment of **acne vulgaris** when comedones, papules, and pustules predominate. It appears to stimulate mitosis and turnover of follicular epithelial cells and reduce their cohesiveness thereby facilitating the extrusion of existing comedones and preventing the formation of new ones. It also appears to have a thinning effect on the stratum corneum. Tretinoin is applied as a cream, gel, or alcoholic solution, usually containing 0.01 to 0.1%. The skin should be cleansed to remove excessive oiliness and dried before applying tretinoin lightly, once or twice daily according to response and irritation; some patients may require less frequent applications. Other topical preparations (including skin moisturisers) should not be applied at the same time as tretinoin is applied, and caution is required if other local irritants are used concurrently. There may be apparent exacerbations of the acne during early treatment and a therapeutic response may not be evident for 6 to 8 weeks. When the condition has resolved maintenance therapy should be less frequent.

Preparations containing 0.02 or 0.05% tretinoin are available for the treatment of mottled hyperpigmentation, roughness, and fine wrinkling of **photodamaged skin**. It is applied once daily at night. Effects may not be seen until about 6 months after starting treatment.

Tretinoin is also used to induce remission in acute promyelocytic **leukaemia**. A daily dose of 45 mg/m^2 is given orally in 2 divided doses with food. Treatment is continued until 30 days after complete remission or 90 days of treatment have been given, whichever occurs first. Dose reduction has been recommended in hepatic or renal impairment (see below).

For the use of tretinoin in children, see below.

A liposomal formulation of tretinoin for intravenous use is under investigation in T-cell non-Hodgkin's lymphoma, and acute and chronic leukaemia.

Administration in children. Although topical tretinoin is not licensed for infantile acne in the UK, the *BNFC* suggests that it may be used under specialist supervision.

The use of oral tretinoin to induce remission in acute promyelocytic leukaemia (see Malignant Neoplasms, below) in children has been studied.[1-3] Although there is less experience than in adults, a similar dosage regimen of 45 mg/m^2 daily (see also above) has been used in children ranging in age from 1 to 16 years. Dose reduction should be considered if severe toxicity, particularly intractable headache, occurs. Although a lower dose of 25 mg/m^2 daily might reduce neurotoxicity[2,3] the two doses have not been directly compared.

1. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
2. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.

Administration in hepatic and renal impairment. Although dosage adjustment has not been studied in patients with hepatic or renal impairment, licensed UK product information suggests that oral doses of tretinoin for acute promyelocytic leukaemia should be reduced to 25 mg/m^2 daily.

There is a report[1] of 2 patients who required dialysis during tretinoin treatment for acute promyelocytic leukaemia and who achieved remission; one was given a dose of 20 mg/m^2 daily in 2 divided doses and the other received 35 mg/m^2 daily in 3 divided doses.

1. Takitani K, *et al.* Pharmacokinetics of all-trans retinoic acid in acute promyelocytic leukemia patients on dialysis. *Am J Hematol* 2003; **74:** 147–8.

Malignant neoplasms. Tretinoin differentiation therapy has become the established treatment for acute promyelocytic leukaemia (APL), a subtype of acute myeloid leukaemia (p.652). Tretinoin is effective in APL because the characteristic chromosomal abnormalities result in an abnormal retinoic acid receptor. When given *orally*, it has produced complete remissions in more than 90% of patients.[1-4] However, the duration of remission is short unless consolidation, usually with an anthracycline- and cytarabine-based regimen, is given concurrently or subsequently. The combination of tretinoin and chemotherapy has been shown to result in improved survival compared with chemotherapy alone.[1,5,6] Prolonged maintenance therapy including intermittent tretinoin also appears to reduce the rate of relapse.[6] Although benefit has been reported with continuous tretinoin maintenance[7] this is generally considered to lead to resistance.[8] A life-threatening syndrome has developed in some patients who have received oral tretinoin for APL (see Retinoic Acid Syndrome, under Adverse Effects, above). Children seem particularly sensitive to the adverse effects of oral tretinoin on the CNS (see also Effects on the Eyes, and Administration in Children, above). A lipid-based *intravenous* formulation of tretinoin is under investigation for the treatment of APL.

Tretinoin has also been tried for *topical* chemoprevention in patients at increased risk of skin cancers, and in the management of oral leucoplakia (see Malignant Neoplasms under Isotretinoin, p.1603).

1. Avvisati G, Tallman MS. All-trans retinoic acid in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol* 2003; **16:** 419–32.
2. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; **22:** 1404–12.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; **23:** 7632–40.
4. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; **106:** 447–53.
5. Tallman MS, *et al.* Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; **99:** 759–67.
6. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. *Curr Oncol Rep* 2002; **4:** 381–9.
7. Tallman MS, *et al.* All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood* 2002; **100:** 4298–4302.
8. Fenaux P, *et al.* A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999; **94:** 1192–1200.

Skin disorders. Topical treatment with tretinoin has been tried with varying success in a wide range of cutaneous conditions. Its use in acne (p.1577) is well established. Some benefit has also been reported in rosacea[1] (p.1583), in keratinisation disorders such as Darier's disease (p.1578), and in pigmentation disorders (p.1582) such as chloasma.[2] Healing of diabetic foot ulcers (see Diabetic Complications, p.433) was improved in a small placebo-controlled study of topical tretinoin.[3] The 0.05% solution was applied topically for 10 minutes of every day for 4 weeks.

Topical tretinoin is used to improve some of the signs of photoageing (p.1581). Studies have found that tretinoin can improve fine facial wrinkling, with some reduction in coarse wrinkles, tactile roughness, sallowness, irregular pigmentation, and actinic lentigines.[4-6] Tretinoin appears to prevent and repair collagen damage and reduce epidermal melanin content; there is also increased epidermal proliferation and thickening, compaction of the stratum corneum, and deposition of mucinous material.[5] The previous suggestion that skin irritation might be the mechanism behind tretinoin's effects on photodamaged skin has not been supported by clinical study.[4,5] It can take up to 4 months of treatment for a response to develop and the maximum response can be reached between 8 and 12 months. Continued use is necessary to maintain the effect of tretinoin, although it may be used less often.[5,6]

1. Ertl GA, *et al.* A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; **130:** 319–24.
2. Griffiths CEM, *et al.* Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* 1993; **129:** 415–21.
3. Tom WL, *et al.* The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes. *Arch Dermatol* 2005; **141:** 1373–7.
4. Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001; **26:** 613–18.
5. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; **65:** 1061–72.
6. Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; **19:** 297–305.

Preparations

BP 2008: Tretinoin Gel; Tretinoin Solution;
USP 31: Tretinoin Cream; Tretinoin Gel; Tretinoin Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: A Acido; Dorpiel; Eurotretin; Locacid; Lotioblanc; Neotretin; Niterey; Retacnyl; Reticne; Retin-A; Tretinoderm; Vesanoid; Vitanol-A†; ***Austral.:*** Retin-A; ReTrieve; Stieva-A; Vesanoid; ***Austria:*** Eudyna; Retin-A; Vesanoid; ***Belg.:*** Retinova†; Vesanoid; ***Braz.:*** Retacnyl†; Retin-A; Retinova; Vesanoid; Vitacid; Vitanol-A; ***Canad.:*** Rejuva-A; Renova; Retin-A; Retisol-A; Stieva-A; Vesanoid; ***Chile:*** Dermodan; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Cz.:*** Airol; Locacid; Retin-A; Vesanoid; ***Denm.:*** Retinova; ***Fin.:*** Avitcid; Vesanoid; ***Fr.:*** Effederm; Ketrel; Locacid; Retacnyl; Retin-A; Retinova†; Retitop†; Vesanoid; ***Ger.:*** Airol; Cordes VAS; Vesanoid; ***Gr.:*** Airol; Vesanoid; ***Hong Kong:*** Acta; Alten†; Locacid†; Quali-A; Retacnyl†; Retin-A; ReTrieve; Stieva-A; Vesanoid; Vitamin A Acid; ***Hung.:*** Vesanoid†; ***India:*** Eudyna; ***Indon.:*** Eudyna; Jeraklin; Melavita; Nuface; Retin-A; Skinovit; Tracne; Trentin; Vitacid; ***Irl.:*** Retin-A; Vesanoid; ***Israel:*** Airol; Locacid; Retavit; Retin-A; Vesanoid; ***Ital.:*** Airol; Retin-A; Vesanoid; ***Malaysia:*** Alten; Renova†; Retacnyl; Retin-A; Stieva-A; T3 Actin; Tretinon; ***Mex.:*** Acnil; Arretin; Biovitol-C; Epitrel; Queratal; Reacel-A; Ret-A-Pres; Retacnyl; Retin-A; Stieva-A; Tocoderm; Vesanoid; ***Neth.:*** Acid A Vit; Vesanoid; ***Norw.:*** Aberela; ***NZ:*** Retin-A; Retinova; Vesanoid; ***Philipp.:*** Airol; Derm A; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Pol.:*** Arretin; Atrederm; Locacid; Retin-A; Vesanoid; ***Port.:*** Ketrel; Locacid; Retin-A; Vesanoid; Vitacid†; ***Rus.:*** Vesanoid (Веcаноид); ***S.Afr.:*** Ilotycin-A; Renova; Retacnyl; Retin-A; Vesanoid; ***Singapore:*** Alten; Retacnyl; Retin-A; Retinova; ReTrieve; Stieva-A; Vesanoid†; ***Spain:*** Dermojuventus; Retinova†; Retirides; Vesanoid; Vitanol; ***Swed.:*** Aberela; Retinova; ***Switz.:*** Airol; Retin-A; Vesanoid; ***Thai.:*** A-Tinic†; Renova; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***Turk.:*** Acnelyse; Retino; Vesanoid; ***UK:*** Retin-A; Retinova†; Vesanoid; ***USA:*** Atralin; Avita; Renova; Retin-A; Tretin-X; Vesanoid; ***Venez.:*** Betarretin; Retacnyl; Retinei†; Tretinax; Vesanoid.

Multi-ingredient: *Arg.:* Acneout; Hidrosam T; Kitacne AR†; Melasmax; Puraloe; Stievamycin; Tratacne; Tri-Luma; Verrugard; ***Austria:*** Keratosis forte; ***Braz.:*** Tri-Luma; Vitacid Plus; ***Canad.:*** Solage†; Stievamycin; ***Chile:***

Dermodan Plus; Erylik; Stievamycin; Tri-Luma; ***Cz.:*** Aknemycin Plus; ***Fin.:*** Wicaran; ***Fr.:*** Erylik; ***Ger.:*** Aknemycin Plus; Balisa VAS; Carbamid + VAS; Clinesfar†; Pigmanorm; Ureotop + VAS; ***Hong Kong:*** Dermabaz†; Erylik; Tri-Luma; ***Hung.:*** Verra-med; ***Indon.:*** Medi-Klin TR; ***Israel:*** Aknemycin Plus; ***Ital.:*** Psorinase†; ***Malaysia:*** Aknemycin Plus; Tri-Luma; ***Mex.:*** Stievamycin; Tri-Luma; ***Philipp.:*** Tri-Luma; ***Pol.:*** Aknemycin Plus; ***Singapore:*** Aknemycin Plus; Tri-Luma; ***Spain:*** Acnisdin Retinoico; Loderm Retinoico; ***Switz.:*** Carbamide + VAS; Pigmanorm; Sebo-Psor; Verra-med; ***Thai.:*** Tri-Luma; ***UK:*** Aknemycin Plus; ***USA:*** Solage; Tri-Luma; Ziana; ***Venez.:*** Tri-Luma.

Trichloroacetic Acid

Acide Trichloracétique; Acidum trichloraceticum; Acidum Trichloroaceticum; Kwas trichlorooctowy; Kyselina trichloroctová; Trichloracetic Acid; Trichloracto rūgštis; Trichloressigsäure; Tricloroacético, ácido; Trikloorietikkahappo; Triklorättiksyra; Triklórecetsav.

Трихлоруксусная Кислота

$C_2HCl_3O_2$ = 163.4.

CAS — 76-03-9.

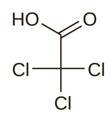

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Trichloroacetic Acid). A very deliquescent white or almost white crystalline mass or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322.

Uses and Administration

Trichloroacetic acid is caustic and astringent. When used as an escharotic for warts it is applied as a strong solution; a range of concentrations have been used including 50% and 80%. The surrounding areas of skin should be protected. Trichloroacetic acid has also been used for the removal of tattoos and in cosmetic surgery for chemical peeling of the skin.

Tattoo removal. References to the use of trichloroacetic acid in the removal of tattoos.

1. Hall-Smith P, Bennett J. Tattoos: a lasting regret. *BMJ* 1991; **303:** 397.

Warts. References to the use of trichloroacetic acid in the treatment of genital warts (p.1584).

1. Godley MJ, *et al.* Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; **63:** 390–2.
2. Davis AJ, Emans SJ. Human papilloma virus infection in the pediatric and adolescent patient. *J Pediatr* 1989; **115:** 1–9.
3. Boothby RA, *et al.* Single application treatment of human papillomavirus infection of the cervix and vagina with trichloroacetic acid: a randomized trial. *Obstet Gynecol* 1990; **76:** 278–80.
4. Abdullah AN, *et al.* Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* 1993; **20:** 344–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: AccuPeel†; ***Ital.:*** CL tre; Verrupor; ***Singapore:*** AccuPeel†; ***USA:*** Tri-Chlor.

Multi-ingredient: *Spain:* Callicida Brum†; ***Turk.:*** IL-33.

Trioxysalen *(rINN)*

NSC-71047; 4,5′,8-Trimethylpsoralen; Trioksisaleeni; Trioxisalen; Trioxisaleno; Trioxsalen *(USAN)*; Trioxysalène; Trioxysalenum. 2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one.

Триоксизален

$C_{14}H_{12}O_3$ = 228.2.

CAS — 3902-71-4.

ATC — D05AD01; D05BA01.

ATC Vet — QD05AD01; QD05BA01.

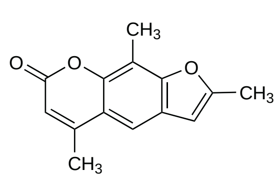

Pharmacopoeias. In *US.*

USP 31 (Trioxsalen). A white to off-white or greyish, odourless, crystalline solid. Practically insoluble in water; soluble 1 in 1150 of alcohol, 1 in 84 of chloroform, 1 in 43 of dichloromethane, and 1 in 100 of methyl isobutyl ketone. Protect from light.

Profile

Trioxysalen, a psoralen, is a photosensitiser used similarly to methoxsalen in photochemotherapy or PUVA therapy (p.1606).

Trioxysalen is used in idiopathic vitiligo to enhance pigmentation or increase the tolerance to sunlight in selected patients. In vitiligo an oral dose of 10 mg daily is given 2 to 4 hours before exposure to sunlight or ultraviolet radiation; prolonged therapy may be necessary. To increase tolerance to sunlight a dose of 10 mg daily is given 2 hours before exposure; treatment should not be continued for longer than 14 days.

Trioxysalen may also be used topically in the PUVA treatment of psoriasis.

◊ References.

1. Snellman E, Rantanen T. Concentration-dependent phototoxicity in trimethylpsoralen bath psoralen ultraviolet A. *Br J Dermatol* 2001; **144:** 490–4.

Preparations

USP 31: Trioxsalen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Trisoralen†; ***Fin.:*** Tripsor; ***Gr.:*** Trisolaren; ***Hong Kong:*** Puvadin†; ***India:*** Neosoralen†; ***Malaysia:*** Puvadin†.

Urea ⊗

Carbamida; Carbamide; E927b; Karbamid; Karbamidi; Močovina; Mocznik; Üre; Urée; Ureia; Urėja; Ureum. Carbonic acid diamide.

Карбамид; Мочевина

$NH_2.CO.NH_2$ = 60.06.

CAS — 57-13-6.

ATC — B05BC02; D02AE01.

ATC Vet — QB05BC02; QD02AE01.

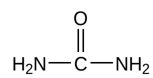

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Urea). Transparent, slightly hygroscopic, crystals or a white or almost white, crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 31 (Urea). Colourless or white, practically odourless, prismatic crystals, or white crystalline powder or pellets. May gradually develop a slight odour of ammonia on prolonged standing. Soluble 1 in 1.5 of water, 1 in 10 of alcohol, and 1 in 1 of boiling alcohol; practically insoluble in chloroform and in ether. Solutions are neutral to litmus. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Urea can cause haemolysis when mixed with blood and should never be added to whole blood for transfusion or given through the same set by which blood is being infused.

Adverse Effects and Precautions

As for Mannitol, p.1330. Urea should also be used with caution in liver impairment as blood-ammonia concentrations can rise, and should be avoided in liver failure.

Urea is reported to be more irritant than mannitol, and intravenous use may cause venous thrombosis or phlebitis at the site of injection; extravasation may cause sloughing or necrosis. Only large veins should be used for infusion, and urea should not be infused into veins of the lower limbs of elderly patients. Extreme care is essential to prevent accidental extravasation of urea infusions.

Rapid intravenous injection of solutions of urea can cause haemolysis; the risk is reduced by using glucose or invert sugar solutions as diluent. Urea should not be mixed with whole blood.

Topical applications may be irritant to sensitive skin.

Infants and neonates. High plasma-urea concentrations have been reported[1,2] in neonates after topical application of emollient creams containing urea. Since there was no evidence of dehydration[2,3] absorption of urea through the skin was the likely cause. Raised plasma-urea concentrations have been reported[4] in infants with erythematous skin conditions who had not been treated with urea cream and this was attributed to dehydration due to increased insensible water loss through the damaged skin.

1. Beverley DW, Wheeler D. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1986; **61:** 696–8.
2. Oudesluys-Murphy AM, van Leeuwen M. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1987; **62:** 212.
3. Beverley DW, Wheeler D. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245–6.
4. Garty BZ. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; **61:** 1245.

Pregnancy. There have been reports of women suffering coagulopathy associated with urea treatment given for termination of pregnancy.[1,2]

1. Grundy MFB, Craven ER. Consumption coagulopathy after intra-amniotic urea. *BMJ* 1976; **2:** 677–8.
2. Burkman RT, *et al.* Coagulopathy with midtrimester induced abortion: association with hyperosmolar urea administration. *Am J Obstet Gynecol* 1977; **127:** 533–6.

Pharmacokinetics

Urea is fairly rapidly absorbed from the gastrointestinal tract but causes gastrointestinal irritation. Urea is distributed into extracellular and intracellular fluids including lymph, bile, CSF, and blood. It is reported to cross the placenta, and penetrate the eye. It is excreted unchanged in the urine.

Uses and Administration

Urea promotes hydration and is mainly applied topically in the treatment of ichthyosis and hyperkeratotic skin disorders (p.1580). Used intravenously it has osmotic diuretic properties similar to mannitol (p.1331) and has been used in the treatment of acute increases in intracranial pressure (p.1181), due to cerebral oedema, and to decrease intra-ocular pressure in acute glaucoma (p.1873), but has been largely superseded by mannitol. Urea has also been given intra-amniotically for the termination of pregnancy (p.2004).

When applied topically urea has hydrating and keratolytic properties. In the management of ichthyosis and other dry skin disorders it is applied in creams or lotions containing 5 to 25% urea; higher concentrations of 30% and 40% have also been used in severe cases. A preparation containing 40% may be used for nail destruction.

For the reduction of raised intracranial or intra-ocular pressure, urea is given intravenously, as an infusion of a 30% solution in glucose 5 or 10% or invert sugar 10%, at a rate not exceeding 4 mL/minute, in a dose of 0.5 to 1.5 g/kg to a maximum of 120 g daily. Doses used in children are based on the same regimen, but see also below. Rebound increases in intracranial and intra-ocular pressure may occur after about 12 hours.

Solutions of urea 40 to 50% have been given by intra-amniotic injection for the termination of pregnancy.

Urea labelled with carbon-13 (p.2277) is used in the *in vivo* diagnosis of *Helicobacter pylori* infection (see Peptic Ulcer Disease, p.1702). The test involves collecting a breath sample before and after oral ingestion of a single dose of ^{13}C-urea. *H. pylori* produces urease which hydrolyses the urea to carbon dioxide and ammonia; therefore, an excess of carbon-13-labelled carbon dioxide in the sample, compared with a baseline sample, indicates infection. Doses of ^{13}C-urea include 50 mg, 75 mg, or 100 mg depending on the kit being used. Urea labelled with the radionuclide carbon-14 (p.2053) is also used in a urea breath test for *H. pylori* detection.

Administration in children. For the reduction of raised intracranial or intra-ocular pressure in children, urea is given intravenously in dosage regimens similar to those used in adults (see above). However, for children under 2 years of age, a dose of 100 mg/kg may be adequate.

Breath test kits containing ^{13}C-urea for the diagnosis of *Helicobacter pylori* infection are available for children. However, the *BNFC* states that the appropriateness of testing in children has not been established, and that endoscopy with biopsy is more accurate than *in vivo* breath testing, which is frequently unreliable in children.

Preparations

BP 2008: Urea Cream;
USP 31: Urea for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Hidroplus; Keratopic; Lociherp; Nutralcon; Optiwhite†; Ureadin; Urecrem; Uremol; Xerobase; ***Austral.:*** Aquacare; Hamilton Skin Therapy; Nutraplus; Urecare; Urederm; ***Austria:*** Nubral; ***Braz.:*** Emoderm; Hidrapel Plus; Nutraplus; Ureadin; ***Canad.:*** Dermaflex; Ultra Mide; Uree; Uremol; Urisec; ***Chile:*** Ayr con urea; Ayr-5; Hyderm; Nutraplus†; Uramol; Ureadin 10 and 20; ***Cz.:*** Elacutan; Excipial U; Linola Urea; ***Fin.:*** Fenuril; ***Fr.:*** Anti-Dessechement; Charlieu Topic†; Ictyoderm†; Nutraplus; Sedagel; ***Ger.:*** Balisa; Basodexan; Elacutan; Eucerin Salbe†; Hyanit N; Linola Urea; Nubral; Onychomal; Sebexol cum urea; Ureotop; ***Hong Kong:*** Balneum Intensiv; Carmol; Caruderma; Euderm; Nutraplus†; Urecare; Urederm; ***Hung.:*** Linola Urea; ***Indon.:*** Calmuderm; Carmed; Moisderm; Soft U Derm; Urederm; ***Irl.:*** Aquadrate; Nutraplus; ***Ital.:*** Dermal Care; ***Jpn:*** Keratinamin; ***Malaysia:*** Balneum Intensiv; Euderm†; Nutraplus; UO; Urecare†; ***Mex.:***

Derma-Keri; Dermoplast; Karmosan; Nutraplus; Uramol; ***NZ:*** Aquacare; Nutraplus; ***Philipp.:*** Nutraplus; ***Port.:*** Eucerin Pele Seca†; Rebladerm†; Ureadin 10 and 20; ***Singapore:*** Aqurea; Balneum Intensiv; Euderm†; Excipial U; Nutraplus; UO; Urecare†; ***Spain:*** Nutraplus†; ***Swed.:*** Calmuril; Canoderm; Caress; Fenuril; Karbaderm†; Karbasal; Monilen; ***Switz.:*** Carbamide Emulsion; Eucerin peau seche; Excipial U; Linola Uree; Nutraplus; Vita-Merfen Soins dermatologiques†; ***Thai.:*** Balneum Intensiv†; Nutraplus; ***Turk.:*** Excipial; Nutraplus; Urederm; ***UK:*** Aquadrate; Nutraplus; ***USA:*** Aquacare; Carmol; Gormel; Hydro 40; Kerafoam; Keralac; Kerol; Lanaphilic; Nutraplus; Rinnovi; Ultra Mide; Umecta; Ureacin; Ureaphil; Vanamide; ***Venez.:*** Aquaphar; Dermisol; Uricrim.

Multi-ingredient: ***Arg.:*** Acilac; Akerat; Aloebel; Cremisona†; Cremsor N; Hidrolac; Lactiderm; Lactiderm HC†; Lactocrem; Masivol Urea; Onixol†; Oxidermos; Sadeltan F†; Turgent Colageno; Turgent Emulsion; Ureadin Facial; Urecrem Hidro; Vansame; ***Austral.:*** Aussie Tan Skin Moisturiser; Calmurid; Curaderm†; Dermadrate; Psor-Asist; SP Cream†; ***Austria:*** Aleot; Calmurid; Calmurid HC; Canesten Bifonazol comp; Fungiderm comp†; Ichth-Oestren; Keratosis; Keratosis forte; Mirfulan; Optiderm; ***Belg.:*** Calmurid†; ***Braz.:*** Donnagel; Oticerim; Oto-Biotic†; Tricolpex; Tricomax; Vagi Biotic; Vagi-Sulfa; ***Canad.:*** Amino-Cerv; Hydrophil; Kerasal; Uremol-HC; ***Chile:*** Akerat; Mycosporan Onycoset†; Ureadin 30; Ureadin Facial; Ureadin Forte; Ureadin Pediatrics; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; ***Cz.:*** Betacorton U; Kerasal; Mycospor Sada na Nehty; ***Fin.:*** Calmuril; Wicaran; Wicarba; Wicnecarb; Wicnevit; ***Fr.:*** Akerat; Amycor Onychoset; Body Peel; Charlieu Topicrem; Day Peel; Liperol; Night Peel; Pedi-Relax Anti-callosites†; Provictol†; PSO; Topic 10; ***Ger.:*** Balisa VAS; Brand- u. Wundgel-Medice N; Calmurid†; Canesten Extra Nagelset; Carbamid + VAS; Fungidexan; Hydrodexan; Kelofibrase†; Mirfulan; Mycospor Nagelset†; Nubral 4†; Nubral Forte†; Oestrugol N†; Optiderm; Psoradexan; Psorigerb N†; Remederm; Ureata S†; Ureotop + VAS; ***Gr.:*** Lyoderm; Urecortin; ***Hong Kong:*** Balneum Intensiv Plus; Dermadrate; ***Hung.:*** Reseptyl-Urea; Squa-med; ***India:*** Cotaryl; ***Indon.:*** Foothy; ***Irl.:*** Alphaderm; Calmurid; Calmurid HC; ***Israel:*** Agispor Onychoset; Calmurid; Calmurid HC†; Derma-Care; Keratospor; U-Lactin Foot Cream; U-Lactin Forte; ***Ital.:*** Altadrine; Eudermico†; Ipso Urea; Keraflex; Optiderm; Verunec; Xerial; ***Malaysia:*** Balneum Intensiv Plus; Ucort; ***Mex.:*** Eucerin Piel Seca/Reseca†; Hidribet 5†; Hidribet†; Lowila; Mycospor Onicoset; Suavene; Urader Lactato; Ureaderm Lactato; ***Neth.:*** Calmurid; Calmurid HC; Symbial; ***NZ:*** Calmurid†; Dermadrate; ***Philipp.:*** Remederm; ***Pol.:*** Hasceral; Keratolit; Mycospor Onychoset; Optiderm; SolcoKerasal; Sterovag; ***Port.:*** Calmurid; Carmitol; Creme Laser Hidrante; Hidratoderme†; Mycospor†; U Lactin; Ureadin; Ureadin 10 Plus; Ureadin Facial; Ureadin Forte; Ureadin Maos; ***Rus.:*** Mycospor (Микоспор); ***S.Afr.:*** Calmurid HC†; Covancaine; Mycospor Onycho-set; ***Singapore:*** Balneum Intensiv Plus; Dermadrate; Topicrem; U-Lactin; ***Spain:*** Cortisdin Urea; Kanapomada; Mycospor Onicoset; ***Swed.:*** Fenuril-Hydrokortison; ***Switz.:*** Acne Gel; Antikeloides Creme; Betacortone; Calmurid; Calmurid HC†; Carbamide + VAS; Carbamide Creme; Kerasal; Klyx Magnum; Optiderm; Sebo Creme; Sebo-Psor; Turexan Capilla; Turexan Lotion; ***Thai.:*** Balneum Intensiv Plus†; Gynestin; ***Turk.:*** Betacorton; Kerasal; Mycospor; Ureacort; ***UK:*** Alphaderm; Antipeol; Balneum Plus; Calmurid; Calmurid HC; Cymex; E45 Itch Relief; St James Balm; Vesagex Heelbalm; ***USA:*** Accuzyme; AllanEnzyme; AllanfillEnzyme; Amino-Cerv; Ethezyme; Gladase; Gladase-C; Hydrocerin Plus; Kovia; Panafil; Panafil-White; Pap-Urea; Rosula; Rosula NS; Ziox; Zoderm; ***Venez.:*** Akerat; Caduril; Hidribet; Hidribet 5/5; Mycospor Onicoset; Pantonic; Pelset Plus; Ureaderm Lactato; Urimet†; Urisalic†.

Ustekinumab *(USAN, pINN)*

CNTO-1275; Ustékinumab; Ustekinumabum. Immunoglobulin G1, anti-(human interleukin-12 subunit beta (IL-12B, CLMF p40, NKSF2))(human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer.

Устекинумаб

CAS — 815610-63-0.

Profile

Ustekinumab is a human monoclonal antibody that binds to interleukins 12 and 23. It is under investigation in the treatment of psoriasis.

◊ References.

1. Krueger GG, *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; **356:** 580–92.
2. Leonardi CL, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371:** 1665–74. Correction. *ibid.*; 1838.
3. Papp KA, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371:** 1675–84.

Zinc Carbonate *(USAN)*

Zinc, carbonato de.

Карбонат Цинка; Углекислый Цинк

$ZnCO_3$ = 125.4.

CAS — 3486-35-9.

Basic Zinc Carbonate

Zinc, carbonato básico de.

Основный Карбонат Цинка; Основный Углекислый Цинк

NOTE. The names zinc carbonate, hydrated zinc carbonate, zinc subcarbonate, and zinc carbonate hydroxide have all been applied to basic zinc carbonate of varying composition occurring naturally or produced by the reaction of a soluble zinc salt with sodium carbonate.

Pharmacopoeias. In *US.*

USP 31 (Zinc Carbonate). It corresponds to $3Zn(OH)_2.2ZnCO_3$ containing the equivalent of not less than 70% ZnO. Store in airtight containers.

Profile

Zinc carbonate is mildly astringent and protective to the skin and is used topically, mainly in the form of calamine (p.1591), in a variety of skin conditions. In the USA the name calamine is used for zinc oxide (rather than zinc carbonate) with a small proportion of ferric oxide.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Pygmal†.

Zinc Oxide

Blanc de Zinc; Blanco de zinc; Cinko oksidas; Çinko Oksit; Cinkoxid; Cynku tlenek; Flores de zinc; Flowers of Zinc; Oxid zinečnatý; Sinkkioksidi; Zinc, óxido de; Zinc, oxyde de; Zinci oxidum; Zinci Oxydum; Zincum Oxydatum; Zinkoxid.

Окись Цинка; Цинк Оксид

ZnO = 81.38.

CAS — 1314-13-2.

NOTE. 'Zinc White' is a commercial form of zinc oxide used as a pigment.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

US also includes a neutral zinc oxide.

Ph. Eur. 6.2 (Zinc Oxide). A white or faintly yellowish-white, soft, amorphous powder, free from gritty particles. Practically insoluble in water and in alcohol; it dissolves in dilute mineral acids.

USP 31 (Zinc Oxide). A white or yellowish-white, odourless, amorphous, very fine powder, free from grittiness. It gradually absorbs carbon dioxide from air. Insoluble in water and in alcohol; soluble in dilute acids.

USP 31 (Zinc Oxide, Neutral). It is for use in sunscreen preparations only.

Incompatibility. Black discoloration has been reported when zinc oxide and glycerol are in contact in the presence of light.

Profile

Zinc oxide is mildly astringent and is used topically as a soothing and protective application in eczema and slight excoriations, in wounds, and for haemorrhoids. It is also used with coal tar (p.1616) or ichthammol (p.1599) in the treatment of eczema. Zinc oxide reflects ultraviolet radiation and is used as a physical sunscreen (see p.1576).

In the USA the name calamine is used for zinc oxide with a small proportion of ferric oxide.

Zinc oxide is used as the basis for the production of a number of dental cements. Mixed with phosphoric acid it forms a hard material composed largely of zinc phosphate; mixed with clove oil or eugenol, it is used as temporary dental filling.

For further details of zinc and its salts, see p.1999.

Complications of dental use. Solitary aspergillosis of the maxillary sinus in 29 of 30 patients was associated with zinc oxide from overfilled teeth.[1] Treatment consisted of removal of the fungal ball containing the zinc oxide; no antifungal treatment was necessary. Zinc oxide has been shown to accelerate the growth of *Aspergillus fumigatus*. Further cases have been reported, and adjunctive systemic antifungal treatment has been used.[2]

1. Beck-Mannagetta J, *et al.* Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* 1983; **ii:** 1260.
2. Martins WD, Ribeiro Rosa EA. Aspergillosis of the maxillary sinus: review and case report. *Scand J Infect Dis* 2004; **36:** 758–61.

Preparations

BP 2008: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Coal Tar and Zinc Ointment; Coal Tar Paste; Compound Aluminium Paste; Compound Zinc Paste; Dithranol Paste; Hexachlorophene Dusting Powder; Zinc and Castor Oil Ointment; Zinc and Coal Tar Paste; Zinc and Ichthammol Cream; Zinc and Salicylic Acid Paste; Zinc Cream; Zinc Ointment;

USP 31: Calamine Topical Suspension; Coal Tar Ointment; Compound Resorcinol Ointment; Zinc Oxide and Salicylic Acid Paste; Zinc Oxide Ointment; Zinc Oxide Paste.

Proprietary Preparations (details are given in Part 3)

Arg.: Balmex†; Caladaryl Panal†; Dermic; Pasta Dermic†; Sinamida-D†; Zincoxid; ***Austral.:*** Curash Anti-Rash; Prickly Heat Powder; Rectogesic; Ungvita†; Zinc Cream White; Zincaband†; Zink'N'Swim†; ***Canad.:*** Aveeno Diaper Rash; Babys Own Ointment†; Egozinc; Infazinc; Johnson's Diaper Rash; Johnson's Medicated†; Triple Care Cream†; Woodward's Diaper Rash; Zincoderm; Zincofax; ***Chile:*** Nenegloss Z; ***Denm.:*** Zipzoc; ***Fin.:*** Zipzoc; ***Fr.:*** Babygella; Filorga Soin Ecran Solaire; Mylange Creme†; Oxyplastine; Senophile†; Veinopress A3 and A4; ***Ger.:*** Cutaninfant†; Desitin†; Fissan-Zinkschuttelmixtur†; Labiosan; Pantederm N; Pinal S†; Retterspitz Heilsalbe ST; Robuvalen†; St. Jakobs-Balsam; Zinkpaste; Zinksalbe Dialon†; Zinksalbe Lichtenstein; ***Hong Kong:*** Desitin Daily Care†; ***India:*** Belle Cream†; ***Irl.:*** Viscopaste; Zipzoc; ***Israel:*** Dyprotex; Lotio Zinc; Lotio Zinci; Zinc Lotion; ***Ital.:*** Ceroxmed Tex; Delicate Skin Pasta; Gelocast; Gelostretch; Milsana; Oz; Scherilan Crema; Sicura3 Fisionorm; Tayderm; Tendigrip; Triderm Crema; Triderm Zeta; Varicex; Viscopaste PB7; Zinco All' Acqua†; Zincoderm; ***Mex.:*** Pasta de Lassar; Rosatil BB†; Saniderm; ***Neth.:*** Daroderm Zinkzalf; Zinkolie; Zinkzalf; Zipzoc; ***Philipp.:*** Curash; Desitin; Spectraban 19; ***Port.:*** Lassadermil; Oleo Dermosina Simples†; Zincoderma; Zipzoc; ***Rus.:*** Desitin (Деситин); ***S.Afr.:*** Clocktower; Johnson's Baby Nappy Rash Ointment; Vernleigh Baby Cream; Viscopaste PB7; ***Singapore:*** Desitin†; ***Spain:*** Anticongestiva; ***Swed.:*** Zipzoc Salvstrumpa; ***Switz.:*** Oxyplastine; Pelsano; Pommade Congo†; ZinCream; ***Thai.:*** Nappy-Hippo; Spectraban; ***UAE:*** Proskin; ***UK:*** Steripaste; Viscopaste PB7; Zincaband; Zipzoc; ***USA:*** Borofax; Delazinc; Diaparene Diaper Rash; Dr Smiths; Nupercainal†; Triple Paste; ***Venez.:*** Lanol-Zinc; Oxyphar.

Multi-ingredient: numerous preparations are listed in Part 3.

Zinc Phenolsulfonate

4-Hidroxibencenosulfonato de zinc; Phenozin; Zinc, fenosulfonato de; Zinc 4-Hydroxybenzenesulphonate; Zinc Phenolsulphonate. Zinc *p*-hydroxybenzenesulphonate.

Сульфофенолят Цинка; Фенолсульфонат Цинка

$C_{12}H_{10}O_8S_2Zn$ = 411.7.

CAS — 127-82-2.

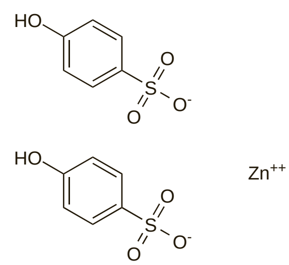

Profile

Zinc phenolsulfonate has astringent properties and has been used in multi-ingredient preparations applied topically for the treatment of a variety of disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Gineseptina†; ***Braz.:*** Lerin; Neo Quimica Colirio; Visazul; ***Ital.:*** Antisettico Astringente Sedativo; Oftalmil; ***USA:*** BFI.

Disinfectants and Preservatives

Contact lens care, p.1622
Disinfection in Creutzfeldt-Jakob disease, p.1622
Disinfection in dental practice, p.1623
Disinfection of endoscopes, p.1623
Disinfection in hepatitis and HIV infection, p.1623
Disinfection of water, p.1623
Hand hygiene, p.1624
Injection site and catheter care, p.1624
Pre-operative skin disinfection, p.1624
Wound disinfection, p.1624

This chapter describes those antimicrobial agents that are used for chemical methods of disinfection, antisepsis, preservation, and sterilisation. There is some overlap between these procedures and some agents may be used as both disinfectants and preservatives. Iodine (p.2169), not in this chapter, is also used for its disinfectant properties.

Definition of terms. There is often confusion between the terms disinfectant and antiseptic.

- The term **disinfectant** is applied to a chemical agent that destroys or inhibits the growth of pathogenic micro-organisms in the non-sporing or vegetative state; disinfectants do not necessarily kill all micro-organisms, but reduce them to a level that is harmful neither to health nor the quality of perishable goods. The term is applicable to agents used to treat inanimate objects and materials and may also be applied to agents used to treat the skin and other body membranes and cavities
- An **antiseptic** is a disinfectant that is used on skin and other living tissues thereby limiting or preventing infection
- **Sterilisation** is the total removal or destruction of all living micro-organisms; a few disinfectants (such as ethylene oxide) are capable of producing sterility under suitable conditions but, in general, sterility is produced by heat or radiation methods, with filtration being used for some heat-labile materials. Sterilisation by heating with a bactericide is no longer a recommended practice
- A **preservative** is one of a number of chemical agents that are included in preparations to prevent deterioration from oxidation **(antoxidants)** or to kill or inhibit the growth of micro-organisms inadvertently introduced during manufacture or use **(antimicrobial preservatives)**.

Use of disinfectants. Disinfectants are used in hospitals, industrial establishments, public buildings, on farms, and in the home for control and prevention of infection.

The choice of disinfectant depends on the purpose for which it is used and the likely contaminating organisms. In addition to vegetative bacteria, many common disinfectants could be expected to kill some fungi and lipid-containing viruses. Gram-negative bacteria, mycobacteria, and bacterial spores are generally more resistant to disinfectants, and some disinfectants are less effective against non-lipid enveloped viruses, for example the enteroviruses including polio and coxsackie. Prions are generally resistant to many disinfectants (see Disinfection in Creutzfeldt-Jakob Disease, below). Other factors affecting the effectiveness of disinfectants include the contact time, concentration of the disinfectant, the pH of the system, the number and accessibility of the contaminating micro-organisms, and the presence of interfering substances including lipids, organic matter, rubber, and plastics. Aqueous solutions of disinfectants, particularly quaternary ammonium compounds (such as benzalkonium chloride and cetrimide), chlorhexidine, and phenols, may be susceptible to contamination with micro-organisms. To reduce this risk many preparations are provided for clinical use in a sterile form for single use.

Use of preservatives. Antimicrobial preservatives are used in sterile preparations such as eye drops and multidose injections to maintain sterility during use. They may also be added to aqueous injections that cannot be sterilised in their final containers and have to be prepared using aseptic precautions, unless the volume to be injected as a single dose exceeds 15 mL. Antimicrobial preservatives are also used in cosmetics, foods, and non-sterile pharmaceutical products such as oral liquids and creams to prevent microbial spoilage. They should not be used indiscriminately. Preparations that should *not* contain preservatives include those for injection into the CSF, eye, or heart. Generally, the antimicrobial preservatives that may be added to foods, animal feeding stuffs, and cosmetics are controlled.

Preservatives used as antoxidants may be classified in 3 groups:

- ***true antoxidants***, or anti-oxygens, which probably inhibit oxidation by reacting with free radicals blocking the chain reaction. Examples are the alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, nordihydroguaiaretic acid, and the tocopherols (see Vitamin E Substances, p.1992)
- ***reducing agents***, which are substances having a lower redox potential than the drug or adjuvants that they are intended to protect and are therefore more readily oxidised. Reducing agents may act also by reacting with free radicals. Examples are ascorbic acid (p.1983) and the potassium and sodium salts of sulfurous acid (see Sulfites and Sulfur Dioxide)
- ***antoxidant synergists***, which usually have little antoxidant effect themselves but probably enhance the action of antoxidants in the first group by reacting with heavy-metal ions which catalyse oxidation. Examples of synergists are citric acid (p.2284), edetic acid and its salts (p.1445), lecithin (p.2332), and tartaric acid (p.2395)

◊ General references and guidelines for the use of disinfectants.

1. Ayliffe GAJ, *et al. Chemical disinfection in hospitals*. 2nd ed. London: PHLS, 1993.
2. Rutala WA. APIC guideline for selection and use of disinfectants. *Am J Infect Control* 1996; **24:** 313–42. Also available at: http://www.apic.org/AM/Template.cfm?Section=Search&section=Infection_Control&template=/CM/ContentDisplay.cfm&ContentFileID=319 (accessed 09/03/06)
3. Ayliffe GAJ, *et al. Hospital-acquired infection: principles and prevention*. 3rd ed. Oxford: Butterworth - Heinemann, 1999.
4. Mayhall CG, ed. *Hospital epidemiology and infection control.* 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999.
5. DoH. Standard principles for preventing hospital-acquired infections. *J Hosp Infect* 2001; **47** (suppl): S21–S37. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005481?IdcService=GET_FILE&dID=14080&Rendition=Web (accessed 27/08/08)
6. Block SS, ed. *Disinfection, sterilization, and preservation.* 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2001.
7. Ayliffe GAJ, English MP. *Hospital infection: from Miasmas to MRSA.* Cambridge: Cambridge University Press, 2003.
8. Fraise AP, *et al.*, eds. *Russel, Hugo and Ayliffe's principles and practice of disinfection, preservation, and sterilization*. 4th ed. Oxford: Blackwell Science, 2005.

Contact lens care

Wearers of contact lenses are at increased risk of corneal infections. Factors that predispose the cornea to infection include surface abrasions that may occur during normal wear, extended wear of soft (hydrogel) lenses, accidental trauma during insertion of a lens, and anoxia. In addition, the lens may provide a medium for introducing pathogens into the eye, especially if handling, cleaning, and disinfecting procedures are not followed. The most common pathogens are bacteria, in particular *Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Staph. epidermidis,* and *Streptococcus pneumoniae.* Fungi rarely cause lens-related keratitis, although contamination of soft lenses has been reported. *Acanthamoeba* can cause rare but serious corneal infections (p.822) mainly associated with soft contact lens wear; these protozoa are resistant to some commonly used disinfection systems and can colonise lens storage cases.

Lens care systems for **rigid** (hard or gas-permeable) lenses typically entail cleansing and disinfection stages.

- Daily cleansing with solutions containing surfactants and sometimes mild abrasives can substantially reduce microbial contamination as well as removing organic material which can compromise the activity of the disinfection stage. Cleansing solutions frequently contain substances that are irritant to the eye and should be removed by rinsing and soaking the lens.
- Soaking solutions also maintain lens hydration, disinfect the lens, and prevent contamination during storage. Although not intended for use in the eye, soaking solutions should be non-irritant.
- Commonly used disinfectants include benzalkonium chloride and chlorhexidine. Thiomersal is also used but has been associated with a high incidence of hypersensitivity reactions.
- Wetting or rewetting solutions are used to improve the comfort of the lens and, since they are applied to the eye, must be non-irritant. They commonly contain hypromellose, hyetellose, polyvinyl alcohol, or povidone, although a simple sodium chloride 0.9% solution may be used.

Initially chemical disinfection for **soft** contact lenses required 4 steps; cleaning, rinsing, soaking in a disinfectant, and final rinsing. The introduction of multipurpose solutions containing small amounts of surfactant cleaner and disinfectant have reduced the number of steps required.

- Soft contact lenses contain a high proportion of water and are liable to absorb substances from solution. For this reason some disinfectants, notably benzalkonium chloride, are not suitable for inclusion in solutions for soft lenses. Soft lenses may be disinfected by heating in a suitable unit, usually in isotonic saline solution, but this can shorten the life of the lens by denaturing the polymer or causing deposits of denatured protein, minerals, or preservatives from the saline solution. Stabilised hydrogen peroxide is suitable for cold disinfection of soft lenses and is particularly useful for preventing *Acanthamoeba* infections. However, it is irritant to the cornea and must be neutralised before the lens is inserted into the eye. Other disinfectants for soft lenses may include chlorhexidine and polihexanide.
- Cleansers for soft lenses may contain surfactants or enzymes, such as papain or pancreatin, that remove protein deposits.
- Wetting solutions may be used similarly to rigid lenses.

Reviews.

1. Rakow PL. Current contact lens care systems. *Ophthalmol Clin North Am* 2003; **16:** 415–32.

Disinfection in Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. The agent causing Creutzfeldt-Jakob disease (CJD) is resistant to many disinfection procedures including dry heat, ultraviolet irradiation, alcohols, ethylene oxide, eusol, formaldehyde, glutaral, hydrogen peroxide, iodine or iodophores, peracetic acid, phenolics, and propiolactone. Furthermore, aldehyde-type disinfectants have fixative proprieties and could anchor prion and other proteins to equipment and make them more difficult to remove by other means.[1] No sterilisation procedure can be guaranteed to be completely effective under all circumstances and for disposable instruments and materials the safest method is to destroy them by incineration.[2] Neurosurgical and ophthalmic instruments should also be destroyed by incineration if used in patients with confirmed or suspected CJD. WHO[2] has developed guidelines for control of transmissible spongiform encephalopathies which include measures for the decontamination and cleaning of instruments and materials designed for re-use. They recommend that contaminated instruments and material should be kept moist between the time of use and decontamination and that one of the following methods of decontamination be used for heat-resistant instruments (listed in increasing order of severity):

- immerse in 1N sodium hydroxide and heat in a gravity displacement autoclave at 121° for 30 minutes then clean, rinse in water, and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then transfer the instruments to water, heat in a gravity displacement autoclave at 121° for 1 hour, then clean and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then remove and rinse in water, transfer to an open pan and heat in a gravity displacement (121°) or porous load (134°) autoclave for 1 hour, then clean and continue with routine sterilisation processes

- immerse in 1N sodium hydroxide and boil for 10 minutes at atmospheric pressure then clean, rinse in water, and continue with routine sterilisation processes
- immerse in sodium hypochlorite (providing 20 000 ppm available chlorine) (preferred) or 1N sodium hydroxide (alternative) at ambient temperature for 1 hour then clean, rinse in water, and continue with routine sterilisation processes
- autoclave at 134° for 18 minutes

Heat sensitive instruments and surfaces should be decontaminated by flooding with 2N sodium hydroxide or undiluted sodium hypochlorite and left to stand for 1 hour, then mopped up and rinsed with water. If these agents cannot be tolerated then thorough cleaning with a diluted solution or other partially effective agent is advised.[2] In the UK, it is recommended[1] that if it is the intention to reuse an endoscope that has been employed in patients with suspected or confirmed CJD or has been used for invasive procedures in those at risk of CJD (e.g. haemophiliacs), then the endoscope should be disinfected with a non-aldehyde disinfectant (preferably single use) separately from other endoscopes and quarantined for use only in those with confirmed CJD.

Recommendations for disinfection and sterilisation in CJD have also been published in the UK[3] and USA.[4]

1. British Society of Gastroenterology. BSG Working Party Report 2003 (updated 2005). BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/pdf_word_docs/disinfection06.doc (accessed 09/03/06)
2. WHO. *WHO infection control guidelines for transmissible spongiform encephalopathies: report of a WHO consultation*. Geneva: WHO, 1999. Available at: http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.3.pdf (accessed 15/03/06)
3. Advisory Committee on Dangerous Pathogens, Spongiform Encephalopathy Advisory Committee. *Transmissible spongiform encephalopathy agents: safe working and the prevention of infection*. London: Department of Health, 2003. Also available at: http://www.dh.gov.uk/en/Publichealth/communicablediseases/CJD/CJDGeneralInformation/DH_4031067 (accessed 27/08/08)
4. Rutala WA, Weber DJ. Creutzfeldt-Jakob disease: recommendations for disinfection and sterilization. *Clin Infect Dis* 2001; **32:** 1348–56.

Disinfection in dental practice

Dental patients and healthcare staff can be exposed to viruses and bacteria that are present in blood or colonise or infect the oral cavity and respiratory tract, such as CMV, hepatitis B and C viruses, herpes simplex virus types 1 and 2, HIV, *Mycobacterium tuberculosis*, staphylococci, and streptococci. For information on endocarditis prophylaxis, see p.168. These organisms can be transmitted in dental settings through direct or indirect contact with blood, oral fluids, or other body matter; by indirect contact with contaminated objects (e.g. instruments, equipment, or environmental surfaces), or inhalation of airborne micro-organisms (which can remain suspended in the air for long periods).

Guidelines have been developed in the USA for preventing and controlling infectious diseases and managing personnel health and safety concerns related to infection control in dental settings.[1] **Hand hygiene** (see below) substantially reduces potential pathogens on the hands and is considered a critical measure for reducing the risk of transmitting organisms to patients and healthcare workers. For routine dental examinations and nonsurgical procedures, handwashing and hand antisepsis is achieved by using a plain or antimicrobial soap and water. If the hands are not visibly soiled, an alcohol-based hand rub may be used. Before surgical procedures an antimicrobial soap or alcohol hand rub with persistent activity should be used. This extended antimicrobial activity is needed to prevent the introduction of organisms, which can colonise the hands underneath gloves and enter the wound if gloves become punctured or torn.

Patient-care items such as dental instruments, devices, and equipment should be **cleaned** to remove debris as well as organic and inorganic contamination, before proceeding with disinfection and sterilisation. If manual cleaning cannot be done immediately, the instruments should be placed in a puncture-resistant container and soaked in a detergent, a disinfectant/detergent, or an enzymatic cleaner. Use of a liquid chemical sterilant/high-level disinfectant (e.g. glutaral) as a holding solution is not recommended.

Heat-tolerant dental instruments usually are **sterilised** by autoclaving, dry heat, or unsaturated chemical vapour. Three levels of **disinfection** are used for patient-care devices that do not require sterility:

- high (e.g. glutaral, hydrogen peroxide, hydrogen peroxide with peracetic acid, *o*-phthaldialdehyde, peracetic acid, and phenol with glutaral)
- intermediate (e.g. chlorine-containing products, iodophores, phenolics, and quaternary ammonium compounds with alcohol)
- low (e.g. quaternary ammonium compounds, some phenolics, and some iodophores)

Patient-care items are categorised as critical, semicritical, or noncritical, depending on the potential risk for infection associated with their intended use. Heat sterilisation is used for critical items (used to penetrate soft tissue or bone) also for semicritical items that touch mucous membranes or non-intact skin. Semicritical items that are heat-sensitive should be processed with high-level disinfection. Noncritical patient-care items, contacting only intact skin, just require cleaning, or if visibly soiled, cleaning followed by disinfection. When the item is visibly contaminated with blood or other potentially infectious material a disinfectant thought to be effective against tubercle bacilli (intermediate-level disinfectant) should be used.

Clinical contact surfaces can become contaminated from patient materials either by direct spray or spatter generated during dental procedures or by contact with dental healthcare workers' gloved hands. Two levels of disinfection, intermediate and low, are used for environmental surfaces. If protective barriers are not used, surfaces should be cleaned and disinfected between patients by using disinfectants effective against HIV or hepatitis B virus (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant) if the surface is visibly contaminated with blood or other potentially infectious material. General cleaning and disinfection are recommended for clinical contact surfaces, dental unit surfaces, and countertops at the end of daily work activities and are required if surfaces have become contaminated since their last cleaning. Spills of blood and other body fluids should be removed with absorbent material (e.g. disposable paper towels). Nonporous surfaces should be cleaned and then decontaminated with disinfectant effective against hepatitis B virus and HIV (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant).

1. Kohn WG, *et al.* CDC guidelines for infection control in dental health-care settings—2003. *MMWR* 2003; **52** (RR-17): 1–61. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5217.pdf (accessed 17/03/06)

Disinfection of endoscopes

Whenever possible, medical equipment that comes into intimate contact with the body should be heat sterilised, but some equipment, notably endoscopes, will not withstand high temperatures. Low-temperature steam and formaldehyde or ethylene oxide will achieve sterilisation, but may not be practical in a clinical setting. Satisfactory chemical disinfection of endoscopes and other heat-sensitive instruments relies on initial thorough cleansing of the instrument and choice of an appropriate high-level disinfectant which should be rapidly active against a wide range of pathogens including vegetative bacteria, bacterial spores, mycobacteria, and viruses. The disinfectant should not damage the instrument or discolour the optical components, and it should not leave a toxic residue. Instruments should be rinsed after disinfection with water or alcohols, such as isopropyl alcohol,[1] and dried with forced air.[2,3]

Glutaral 2% is commonly used.[2] To achieve sterilisation, immersion in glutaral 2% for 3 hours is necessary, but high-level disinfection, achieved by immersion for 20 minutes, is usually considered adequate for most endoscopes.[1,2,4,5] Immersion for a minimum of 20 minutes is required for elimination of tubercle bacilli, but immersion for 4 minutes may be adequate for gastroscopes, except those for use on immunocompromised patients. For specific information relating to hepatitis and HIV viruses, see below.

A disadvantage of glutaral is that it is irritant and may cause sensitisation. In addition, longer contact times are needed to eliminate atypical mycobacteria and glutaral-resistant strains of *M. chelonae* have been isolated from endoscope disinfecting equipment.[6,7] It should also be noted that in the UK it is recommended that units should move away from the use of aldehyde-based disinfectants because of their fixative properties, which in theory could anchor prion and other protein within endoscopes.[1] The use of aldehydes as the primary disinfectant should also be avoided in units serving groups at risk of CJD, such as haemophilia centres (see also Disinfection in Creutzfeldt-Jakob Disease, above). Alternative disinfectants include peracetic acid, chlorine dioxide, *o*-phthaldialdehyde, and superoxidised water (hypochlorous acid).[1,5,7] Other alternatives include peroxygen compounds, quaternary ammonium compounds, glucoprotamine, electrolysed acid water, succinic dialdehyde, and alcohol 70%.[1,2,5,7] However, peracetic acid and chlorine dioxide produce irritant fumes, peroxygen-containing compounds and quaternary ammonium compounds have questionable activity against mycobacteria and viruses, and alcohol has a number of practical limitations.[1,5,7]

1. British Society of Gastroenterology. BSG Working Party Report 2003 (updated 2005). BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/pdf_word_docs/disinfection06.doc (accessed 15/03/06)
2. Ayliffe GAJ, *et al. Chemical disinfection in hospitals*. 2nd ed. London: PHLS, 1993.
3. Rutala WA, Weber DJ. Disinfection and sterilization in health care facilities: what clinicians need to know. *Clin Infect Dis* 2004; **39:** 702–9.
4. American Society for Gastrointestinal Endoscopy. Multi-society guideline for reprocessing flexible gastrointestinal endoscopes. *Gastrointest Endosc* 2003; **58:** 1–8. Also available at: http://www.askasge.org/pages/safety/multisocietyguideline.pdf (accessed 06/03/06) Also published in: Nelson DB *et al.* Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 2003; **24:** 532–7. Also available at: http://www.askasge.org/WorkArea/showcontent.aspx?id=3376 (accessed 27/08/08)
5. Alvarado CJ, *et al.* Association for Professionals in Infection Control. APIC guideline for infection prevention and control in flexible endoscopy. *Am J Infect Control* 2000; **28:** 138–55.
6. Griffiths PA, *et al.* Glutaraldehyde-resistant Mycobacterium chelonae from endoscope washer disinfectors. *J Appl Microbiol* 1997; **82:** 519–26.
7. Rey J-F, *et al.* ESGE (European Society of Gastrointestinal Endoscopy); ESGENA (European Society of Gastrointestinal Endoscopy Nurses and Associates). ESGE/ESGENA technical note on cleaning and disinfection. *Endoscopy* 2003; **35:** 869–77. Also available at: http://www.esge.com/downloads/pdfs/guidelines/technical_note_on_cleaning_and_disinfection.pdf (accessed 15/03/06)

Disinfection in hepatitis and HIV infection

Hepatitis viruses and HIV are susceptible to heat and the methods recommended for sterilisation of equipment in the UK[1] are conventional procedures using moist or dry heat. Heat-labile articles and surfaces may undergo chemical disinfection but only in the absence of a satisfactory alternative. Although various publications have claimed efficacy against HIV for a wide range of disinfectants and detergents, the evidence for some claims is equivocal.

Fresh aqueous solutions of sodium hypochlorite or troclosene sodium are recommended for general surface disinfection. If contaminated by blood, the concentration must be equivalent to 10 000 ppm of available chlorine. For non-corrosive disinfection of delicate items such as fibreoptic endoscopes, freshly activated alkaline glutaral 2% may be used following thorough washing (but see also Disinfection of Endoscopes, above). If a sterile body cavity will be entered the endoscope must be immersed for a minimum of 3 hours; otherwise a minimum of 30 minutes is sufficient, or 1 hour if the presence of *Mycobacterium tuberculosis* is suspected.

1. DoH. *UK Health Departments guidance for clinical health care workers: protection against infection with blood-borne viruses: recommendations of the expert advisory group on AIDS and the advisory group on hepatitis* [undated]. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/04.00dh/04.00en/documents/digitalasset/dh_4014474.pdf (accessed 27/08/08)

Disinfection of water

Travellers to regions of the world where water is not disinfected at source should be advised to boil or chemically sterilise water for drinking, cleaning teeth, and washing fruit and vegetables.[1] Chlorine and chlorine-releasing disinfectants including tosylchloramide sodium, halazone, sodium hypochlorite, and troclosene sodium are commonly used to sterilise **drinking water**. Iodine-releasing disinfectants such as tetraglycine hydroperiodide, or iodine itself may be useful for short-term or emergency disinfection of small volumes of water.[2] Organic material suspended in the water may reduce the available halogen concentration, and cloudy water should be filtered or allowed to settle and decanted before treatment. Emergency treatment of drinking water with lemon juice has been suggested during epidemics of waterborne gastro-enteritis.[3]

Chlorine and chlorine-releasing disinfectants are also used for recreational and therapeutic **bathing** pools, often with ozone.[4,5] Bromine-based disinfectants and ultraviolet radiation may also be used.

Legionnaires' disease (p.176) is commonly transmitted via cooling water in **air conditioning** systems or **hot water** supplies. Hyperchlorination has been attempted to eradicate the organism from contaminated water sources but has been largely ineffective[6,7] and is no longer recommended. Other disadvantages of using chlorine-based systems at these temperatures and concentrations are corrosion of the plumbing system[7] and the production of potentially carcinogenic byproducts.[8] Effective disinfection can be achieved by raising and maintaining the water temperature above 50°, ultraviolet light, and copper-silver ionisation.

Haemodialysis patients are exposed to large quantities of municipal drinking water as it is used for the production of **dialysis** fluids and may also be used for dialyser rinsing and reuse. Many of the chemical substances in the water, such as calcium, sodium, aluminium, chloramines, fluoride, copper, zinc, sulfates, and nitrates are potentially dangerous for dialysis patients, and can lead to acute or chronic poisoning. There is also a microbiological risk associated with the control of bacterial growth in the water treatment and distribution system. Contaminants are therefore removed by water purification systems. Water is pretreated with activated carbon filters to remove chlorine and its derivatives and other suspended particles, and the hardness of the water is decreased with sodium exchange cationic resins, which remove calcium and magnesium. The final purification process then involves the removal of dissolved salts, bacteria, and endotoxins by reverse osmosis. Reverse osmosis membranes need to be regularly disinfected with chemical agents (such as hypochlorite and peracetic acid), heat, or ozone.[9]

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5. WHO. Guidelines for safe recreational waters: volume 2— swimming pools, spas, and similar recreational environments (draft August 2000). Geneva: WHO, 2000.
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Hand hygiene

Hospital-acquired infections, including those due to multidrug-resistant pathogens, such as meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staph. aureus*, and vancomycin-resistant enterococci, are a major problem in health care facilities.[1] Hand hygiene is one of the most important factors in preventing such infections, as it prevents transmission of pathogens by contact and the faecal-oral route. However, healthcare workers frequently do not wash their hands, and compliance rarely exceeds 40%.[2] A randomised study[3] to compare the efficacy of an alcohol-based solution for hand rubbing with hand washing with a medicated soap in reducing bacterial hand contamination during routine patient care found that the alcohol-based solution was significantly more effective (83% reduction versus 58%). The authors considered that the difference in efficacy might have been due to the duration of hand washing. Participants rubbed or washed their hands for about 30 seconds, but the recommended duration for hand washing is 30 seconds to 1 minute, a time that was adhered to in less than 35% of instances.

Authorities recommend[1,2] that alcohol-based hand rubs should replace hand washing as the standard for hand hygiene in all situations in which the hands are not visibly soiled. The basis for this is that hand rubbing requires less time, is microbiologically more effective, and is less irritating to skin than traditional hand washing with soap and water. The CDC in the USA advises[4] hand washing with a non-antimicrobial or antimicrobial soap and water when hands are visibly dirty or contaminated with proteinaceous material, blood, or other body fluids and if exposure to *Bacillus anthracis* is suspected or proven. Alcohols, chlorhexidine, iodophores, and other antiseptic agents are not recommended for *B. anthracis* contamination as they have poor activity against the spores. If hands are not visibly soiled, an alcohol-based hand rub may be used. Decontamination of the hands with an antiseptic hand rub or hand wash should occur before direct contact with patients, and before putting on sterile gloves when inserting catheters or other invasive devices that do not require a surgical procedure. Decontamination of the hands should also occur after contact with a patient's intact or non-intact skin, body fluids, mucous membranes, and wound dressings if hands are not visibly soiled. Hands should be decontaminated if moving from a contaminated body site to a clean body site during patient care, after contact with inanimate objects (including medical equipment) in the immediate vicinity of the patient, and after removing gloves. When performing surgical procedures hand hygiene with either an antimicrobial soap or an alcohol-based hand rub with persistent activity is recommended before putting on sterile gloves.

The CDC[4] considers that the best antimicrobial efficacy can be achieved with alcohol (ethanol), isopropyl alcohol, and propyl alcohol, as their activity is broad and they are fast acting. Ethanol at high concentrations is the most effective treatment against non-enveloped viruses, whereas propyl alcohol seems to be more effective against the resident bacterial flora. Combinations of alcohols may have a synergistic effect. The antimicrobial efficacy of chlorhexidine (2 to 4%) and triclosan (1 to 2%) is both lower and slower. Bacterial resistance may occur, although the risk is higher for chlorhexidine than triclosan. Even if used in conjunction with hand washing, they are still less effective than the alcohols. Plain soap and water has the lowest efficacy of all.

1. Trampuz A, Widmer AF. Hand hygiene: a frequently missed lifesaving opportunity during patient care. *Mayo Clin Proc* 2004; **79:** 109–16.
2. Widmer AF. Replace hand washing with use of a waterless alcohol hand rub? *Clin Infect Dis* 2000; **31:** 136–43.
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4. CDC. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 2002; **51** (RR-16): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf (accessed 15/03/06)

Injection site and catheter care

The need to disinfect the skin before injection is controversial.[1] Routine skin preparation of the injection site by swabbing with antiseptic has been reported to be both ineffective and unnecessary.[2,3] Central venous and arterial catheters, however, require the application of strict aseptic technique and injection site antisepsis to reduce the chance of infection.[4] Disinfection of catheter insertion sites with aqueous chlorhexidine 2% has been reported to be associated with fewer local and systemic infections than site preparation with either 10% povidone-iodine solution or 70% isopropyl alcohol,[5] although this has been challenged.[6] A subsequent study reported lower rates of catheter colonisation and catheter-related infection with an alcoholic solution of chlorhexidine 0.25% and benzalkonium chloride 0.025% than with povidone-iodine 10%.[7] In a study in preterm infants, technique had greater influence on bacterial counts at injection sites than the antiseptic used; chlorhexidine 0.5% in isopropyl alcohol and aqueous povidone-iodine 10% were equally effective, but cleansing with alcoholic chlorhexidine for 30 seconds or for two 10-second periods was more effective than cleansing for 5 or 10 seconds.[8]

The use of catheters impregnated with antiseptics or antibacterials has also been studied. Catheters impregnated with chlorhexidine and sulfadiazine silver on the external luminal surface, appear to be effective in reducing both catheter colonisation and related bloodstream infection in high-risk patients when used within 14 days.[9] Central venous catheters impregnated with minocycline and rifampicin have been reported to be associated with a lower infection rate than standard silicone catheters[10] and those impregnated with chlorhexidine and sulfadiazine silver.[11]

Guidelines have been produced for the prevention of infection associated with both peripheral intravascular and central venous catheterisation.[12-14]

1. Ayliffe GAJ, *et al. Chemical disinfection in hospitals.* 2nd ed. London: PHLS, 1993.
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3. Liauw J, Archer GJ. Swabaholics? *Lancet* 1995; **345:** 1648.
4. Shepherd A, Williams N. Care of long-term central venous catheters. *Br J Hosp Med* 1994; **51:** 598–602.
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6. Segura M, Sitges-Serra A. Intravenous catheter sites and sepsis. *Lancet* 1991; **338:** 1218.
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8. Malathi I, *et al.* Skin disinfection in preterm infants. *Arch Dis Child* 1993; **69:** 312–16.
9. Veenstra DL, *et al.* Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999; **281:** 261–7.
10. Hanna H, *et al.* Long-term silicone central venous catheters impregnated with minocycline and rifampin decrease rates of catheter-related bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol* 2004; **22:** 3163–71.
11. Darouiche RO, *et al.* A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999; **340:** 1–8.
12. DoH. Guidelines for preventing infections associated with the insertion and maintenance of central venous catheters. *J Hosp Infect* 2001; **47**(suppl): S47–S67. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005481?IdcService=GET_FILE&dID=14080&Rendition=Web (accessed 27/08/08)
13. O'Grady NP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *MMWR* 2002; **51** (RR-10): 1–29. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf (accessed 15/03/06)
14. NICE. Infection control: prevention of healthcare-associated infections in primary and community care (June 2003). Section 5: central venous catheterisation. Available at: http://www.nice.org.uk/nicemedia/pdf/Infection_control_fullguideline.pdf (accessed 27/08/08)

Pre-operative skin disinfection

Skin preparation with antiseptics before surgery is generally carried out in an attempt to reduce the risks of surgical infection (see p.195), but the evidence base for the practice is conflicting. The CDC recommends[1] pre-operative cleaning of skin at the incision site with either iodophores (e.g. povidone-iodine), alcohol-containing products, or chlorhexidine gluconate. While alcohol is considered to be the most effective and rapidly acting skin antiseptic, there are no appropriate studies to assess comparative efficacy. Furthermore, an analysis[2] of randomised studies comparing the use of pre-operative skin antiseptics with no antiseptics and studies comparing different skin antiseptics, found that there was insufficient evidence to conclude whether pre-operative skin antiseptics were effective in preventing postoperative surgical wound infection.

1. Mangram AJ, *et al.* CDC Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. *Am J Infect Control* 1999; **27:** 97–132. Also available at: http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf (accessed 15/03/06)
2. Edwards PS, *et al.* Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 15/03/06).

Wound disinfection

Antiseptic preparations are widely used to treat or prevent superficial infections and wounds, but their usefulness on broken skin and wounds has been questioned.[1] For further information on wound care, see p.1585. Chlorine-releasing antiseptic solutions are generally regarded as irritant and although there is little direct evidence in patients there is concern that they may delay wound healing. Cetrimide,[2] tosylchloramide sodium,[3] hydrogen peroxide 3%,[4] iodophores,[4] and sodium hypochlorite solutions[2] are all reported to be cytotoxic *in vitro* or in *animal* models. Long-term or repeated use of these antiseptics for wound cleaning should probably be avoided. Chlorhexidine is relatively non-toxic.[2,3]

1. Brown CD, Zitelli JA. A review of topical agents for wounds and methods of wounding: guidelines for wound management. *J Dermatol Surg Oncol* 1993; **19:** 732–7.
2. Thomas S, Hay NP. Wound cleansing. *Pharm J* 1985; **2:** 206.
3. Brennan SS, *et al.* Antiseptic toxicity in wounds healing by secondary intention. *J Hosp Infect* 1986; **8:** 263–7.
4. Lineweaver W, *et al.* Topical antimicrobial toxicity. *Arch Surg* 1985; **120:** 267–70.

Acridine Derivatives

Acridina, derivados.

Description. Acridine derivatives are a group of quinoline antimicrobial dyes structurally related to acridine.

Acriflavinium Chloride *(rINN)*

Acriflavine; Acriflavine Hydrochloride; Acriflavinii Chloridum; Acriflavinii Dichloridum; Acriflavinium, Chlorure d'; Akriflavinium-chlorid; Cloruro de acriflavinio. A mixture of 3,6-diamino-10-methylacridinium chloride hydrochloride and 3,6-diaminoacridine dihydrochloride.

Акрифлавиния Хлорид

CAS — 8063-24-9; 65589-70-0.
ATC — R02AA13.
ATC Vet — QG01AC90; QR02AA13.

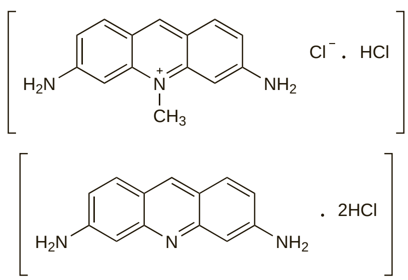

NOTE. The nomenclature is confusing. Acriflavinium Chloride is *rINN* but also the *BP* name for Acriflavinium Monochloride (see below).

Acriflavinium Monochloride

Acriflavinii monochloridum; Acriflavinio, monocloruro de; Acriflavinium, monochlorure d'; Akriflavinio monochloridas; Akriflaviniummonoklorid; Akriflaviniummonokloridi; Euflaviini; Euflavin; Euflavine; Euflavinum; Neutral Acriflavine; Neutroflavin. A mixture of 3,6-diamino-10-methylacridinium chloride and 3,6-diaminoacridine monohydrochloride. The latter is usually present to the extent of between 30 and 40%.

CAS — 68518-47-8.
ATC — D08AA03.
ATC Vet — QD08AA03.

NOTE. The nomenclature is confusing. Although the *BP* name was Acriflavinium Chloride this is also *rINN* for a related compound (see above).

Aminoacridine Hydrochloride *(BANM, rINNM)*

Aminacrine Hydrochloride *(USAN)*; Aminoacridine, Chlorhydrate d'; Aminoacridini Hydrochloridum; Hidrocloruro de aminoacridina; NSC-7571. 9-Aminoacridine hydrochloride monohydrate.

Аминоакридина Гидрохлорид

$C_{13}H_{10}N_2,HCl,H_2O$ = 248.7.
CAS — 90-45-9 (aminoacridine); 134-50-9 (anhydrous aminoacridine hydrochloride).
ATC — D08AA02.
ATC Vet — QD08AA02.

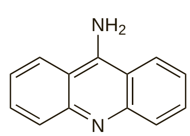

(aminoacridine)

Ethacridine Lactate *(BANM, rINNM)*

Acrinol; Aethacridinium Lacticum; Etakridiinilaktaatti; Etakridinlaktat; Etakridin-laktát; Etakridino laktatas; Etakrydyny mleczan; Éthacridine, lactate d'; Ethacridini lactas; Ethakridin-laktát; Lactato de etacridina; Lactoacridine. 6,9-Diamino-2-ethoxyacridine lactate.

Этакридина Лактат

$C_{15}H_{15}N_3O,C_3H_6O_3$ = 343.4.
CAS — 442-16-0 (ethacridine); 1837-57-6 (ethacridine lactate); 6402-23-9 (ethacridine lactate monohydrate).
ATC — B05CA08; D08AA01.
ATC Vet — QB05CA08; QD08AA01.

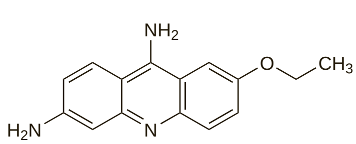

(ethacridine)

Pharmacopoeias. *Chin.*, *Eur.* (see p.vii), and *Jpn* describe the monohydrate.

Ph. Eur. 6.2 (Ethacridine Lactate Monohydrate). A yellow crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 5.5 to 7.0. Protect from light.

Proflavine Hemisulfate

Proflavine Hemisulphate *(pINNM)*; Hemisulfato de proflavina; Neutral Proflavine Sulphate; Proflavine, Hémisulfate de; Proflavini Hemisulfas. 3,6-Diaminoacridine sulphate dihydrate.

Профлавина Гемисульфат

$(C_{13}H_{11}N_3)_2,H_2SO_4,2H_2O$ = 552.6.
CAS — 92-62-6 (proflavine).

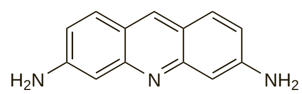

(proflavine)

Profile

The acridine derivatives are slow-acting antiseptics. They are bacteriostatic against many Gram-positive bacteria but less effective against Gram-negative bacteria. They are ineffective against spores. Their activity is increased in alkaline solutions and is not reduced by tissue fluids.

The acridine derivatives have been used for the treatment of infected wounds or burns and for skin disinfection, although they have been largely superseded by other antiseptics or suitable antibacterials. Prolonged treatment may delay healing. They have also been used for the local treatment of ear, oropharyngeal, and genito-urinary infections.

Aminoacridine is reported to be non-staining and is used as the hydrochloride as eye drops in the treatment and prophylaxis of superficial eye infections.

Ethacridine lactate is included in some preparations for the treatment of diarrhoea. It has also been given by extra-amniotic injection for the termination of pregnancy (p.2004) but other methods are usually preferred.

Other acridine derivatives covered elsewhere in *Martindale* include mepacrine (p.836), which is used in the treatment of giardiasis, and pyronaridine (p.612), which is used to treat malaria. Amsacrine (p.681) is a 9-anilinoacridine drug that is used in the treatment of adult leukaemias. Other acridine derivatives are also under investigation as anticancer drugs because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes.

Hypersensitivity to acridine derivatives has been reported.

◊ References.

1. Wainwright M. Acridine—a neglected antibacterial chromophore. *J Antimicrob Chemother.* 2001; **47:** 1–13.
2. Denny WA. Acridine derivatives as chemotherapeutic agents. *Curr Med Chem* 2002; **9:** 1655–65.

Preparations

BPC 1973: Proflavine Cream.

Proprietary Preparations (details are given in Part 3)
Austral.: Aminopt; ***Ger.:*** Metifex; Neochinosol; Rivanol; Uroseptol†; ***India:*** Emcredil; Vecredil; ***Pol.:*** Rivanol; Rivanolum; Rivel; Rywanol; ***Turk.:*** Rivanol.

Multi-ingredient: ***Arg.:*** Carnot Topico; Nene Dent; Otocuril; ***Austral.:*** Medijel; ***Austria:*** Dermowund; ***Braz.:*** Acridin; Cystex; Senol†; ***Chile:*** Molca; ***Cz.:*** Tannacomp†; ***Fr.:*** Chromargon; Pyorex; ***Ger.:*** Anaesthesin-Rivanol; Nordapanin N†; Otolitan N mit Rivanol†; Tannacomp; ***Hong Kong:*** Burn Cream†; Medijel; ***Hung.:*** Glycosept; ***India:*** Anaebell†; Emscab; ***Israel:*** Medijel; ***Malaysia:*** Burnol Plus; Medijel; ***NZ:*** Medijel; ***Pol.:*** Septalan; ***S.Afr.:*** Achromide; Daromide; Vagarsol; ***Singapore:*** Burnol Plus; Medijel; ***Spain:*** Antigrietun; Hepro; ***Switz.:*** Euproctol N; Flavangin†; Haemocortin; Haemolan; Tyrothricin; ***Thai.:*** Burnol Plus; Flavinol; ***UK:*** Iglu; Medijel; ***USA:*** Alasulf; Deltavac; DIT1-2.

Alcohol ⊗

Aethanolum; Alcool; Alkol; Etanol; Etanol (96%); Etanol bezwodny; Etanoli; Etanolis; Éthanol; Ethanol; Ethanolum; Ethyl Alcohol.

Алкоголь; Этанол

C_2H_5OH = 46.07.
CAS — 64-17-5.
ATC — D08AX08; V03AB16; V03AZ01.
ATC Vet — QD08AX08; QV03AB16; QV03AZ01.

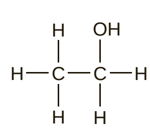

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of alcohol:

Booze; Drinks; Grog; Juice; Jungle juice; Liq; Liquor; Lunch head; Moonshine; Piss; Sauce; Schwillins.

Pharmacopoeias. Various strengths are included in *Br.*, *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Also in *USNF.*

In *Martindale* the term alcohol is used for alcohol 95 or 96% v/v.

Ph. Eur. 6.2 (Ethanol, Anhydrous; Ethanolum Anhydricum; Ethanol BP 2008). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH at 20°. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78°. Miscible with water and with dichloromethane. Protect from light.

The BP 2008 gives Absolute Alcohol and Dehydrated Alcohol as approved synonyms.

Ph. Eur. 6.2 (Ethanol (96 per cent)). It contains not less than 95.1% v/v or 92.6% w/w and not more than 96.9% v/v or 95.2% w/w of C_2H_5OH at 20°, and water. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78°. Miscible with water and with dichloromethane. Protect from light.

The BP 2008 gives Alcohol (96 per cent) as an approved synonym.

BP 2008 (Dilute Ethanols). The monograph describes several dilute alcohols containing between 20 and 90% v/v of C_2H_5OH, and one of these, ethanol (90%), is also known as rectified spirit.

USP 31 (Alcohol). It contains not less than 92.3% w/w or 94.9% w/v and not more than 93.8% w/w or 96.0% w/v of C_2H_5OH at 15.56°. A clear, colourless, mobile, volatile liquid with a characteristic odour and burning taste; it is flammable. B.p. about 78°. Miscible with water and with almost all other organic solvents. Store in airtight containers. Protect from light.

USP 31 (Dehydrated Alcohol). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH (sp. gr. not more than 0.7962 at 15.56°). Store in airtight containers. Protect from light.

USNF 26 (Diluted Alcohol). It contains 48.4 to 49.5% v/v or 41 to 42% w/w of C_2H_5OH. Store away from fire in airtight containers.

Alcoholic strength. This is expressed as a percentage by volume of alcohol. It was previously often expressed in terms of *proof spirit*. Proof spirit contained about 57.1% v/v or 49.2% w/w of C_2H_5OH, and was defined as 'that which at the temperature of 51°F weighs exactly twelve-thirteenths of an equal measure of distilled water'. Spirit of such a strength that 100 volumes contained as much ethyl alcohol as 160 volumes of proof spirit was described as '60 OP' (over proof). Spirit of which 100 volumes contained as much alcohol as 40 volumes of proof spirit was described as '60 UP' (under proof).

An alternative method of indicating spirit strength was used on the labels of alcoholic beverages in the UK when the strength was given as a number of degrees, proof spirit being taken as 100°. In the USA alcoholic strength is expressed in degrees, the value of which is equal to twice the percentage by volume. Thus 70° proof (old UK system) is equivalent to 40% v/v, and therefore to 80° proof (USA system).

Adverse Effects

Adverse effects of alcohol arise chiefly from the intake of alcoholic beverages. The concentration of alcohol in the blood producing a state of intoxication varies between individuals.

- Low concentrations (up to 180 mg per 100 mL) of alcohol may result in impaired vision, reaction time, and coordination and emotional lability.
- At low to moderate concentrations (180 to 350 mg per 100 mL), alcohol acts as an apparent stimulant; depression of cortical function causes loss of judgement, slurred speech, diplopia, blurred vision, ataxia, lack of coordination, blackouts, sweating, tachycardia, nausea, vomiting, and incontinence. Alcohol inhibits the release of antidiuretic hormone resulting in enhanced diuresis. Acidosis (especially in children), hypoglycaemia, and hypokalaemia may occur.
- High concentrations (350 to 450 mg per 100 mL) of alcohol result in cold clammy skin, hypothermia, hypotension, stupor, coma, dilated pupils, and depressed or absent tendon reflexes. Severe hypoglycaemia, convulsions, respiratory depression, and metabolic acidosis may occur. Cardiac arrhythmias such as atrial fibrillation and AV block have been recorded.

The median lethal blood-alcohol concentration is generally estimated to be about 400 to 500 mg per 100 mL. Death may occur at lower blood-alcohol concentrations due to inhalation of vomit during unconsciousness.

Chronic excessive consumption of alcohol may cause damage to many organs, particularly the brain and the liver. Possible direct toxic effects of alcohol on the brain, as well as thiamine deficiency, may lead to Wernicke-Korsakoff syndrome. Fat deposits may occur in the liver and there may be a reduction in various blood-cell counts. Nutritional diseases may occur due to inadequate diet. High alcohol consumption has been associated with pancreatitis, and an increased risk of cardiovascular disease, although some consider that moderate consumption might have a protective effect against ischaemic heart disease.

Alcohol consumption has also been associated with an increased risk of some types of cancer.

The term '**alcoholism**' may be used to denote dependence on alcohol, which is of the barbiturate-alcohol type (see Amobarbital, p.962) and usually involves tolerance to other sedatives and anaesthetics. After prolonged periods of excessive alcohol consumption, a drop in blood-alcohol concentration may precipitate a withdrawal syndrome characterised by tremor, agitation, feelings of dread, nausea, vomiting, and sweating; hallucinations, seizures, and delirium tremens may also develop.

A **fetal alcohol syndrome** has been identified in some infants born to some alcoholic mothers; such infants have a distinctive set of facial anomalies, growth retardation, and significant learning and/or behavioural problems. There have been some reports of the syndrome and other adverse effects on the fetus being associated with moderate alcohol intake in pregnancy. It is therefore generally suggested that alcohol is avoided, or at least intake limited, during pregnancy (see Pregnancy, below).

Frequent application of alcohol to the skin produces irritation and dry skin.

Effects on the skin. A 70% solution of alcohol, containing povidone-iodine, caused partial thickness chemical burns beneath tourniquets in 3 young children.[1] Other adverse effects on the skin reported with the topical application of alcohols have included necrosis after skin cleansing of preterm neonates with methylated spirits[2,3] and haemorrhagic skin necrosis due to the alcohol content of chlorhexidine in spirit used as a disinfectant in umbilical artery catheterisation in preterm infants.[4]

See also Children, under Adverse Effects of Isopropyl Alcohol, p.1651.

1. Dickinson JC, Bailey BN. Chemical burns beneath tourniquets. *BMJ* 1988; **297:** 1513.
2. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; **57:** 477–9.
3. Murch S, Costelloe K. Hyperosmolality related to propylene glycol in an infant. *BMJ* 1990; **301:** 389.
4. Al-Jawad ST. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1983; **58:** 395–6.

Treatment of Adverse Effects

Treatment of acute poisoning with alcohol should include hydration with intravenous fluids, control of nausea and vomiting, and correction of electrolyte imbalances, such as hypomagnesaemia. Protection of the airway is crucial and ventilation may be required in cases of respiratory depression. Glucose is indicated for patients with hypoglycaemia, while thiamine supplementation should be considered for chronic alcoholics. Hypothermia and hypotension should be corrected. Convulsions may be controlled with intravenous benzodiazepines or phenytoin. Haemodialysis is of value in severe alcohol poisoning. Gut decontamination and activated charcoal are unlikely to be of benefit due to the rapid absorption of alcohol through intestinal mucosa. The use of intravenous infusions of fructose to treat severe alcohol poisoning is not recommended.

The management of the alcohol withdrawal syndrome and long-term abstinence following withdrawal are discussed below.

Alcohol withdrawal and abstinence. The alcohol withdrawal syndrome presents in the early stages as a classical hyperadrenergic state with tremor, tachycardia, sweating, and hypertension. Sometimes this is accompanied by mild disorientation, anxiety, impaired concentration, depression, agitation, and gastrointestinal symptoms. Insomnia, nightmares, and transient hallucinations can also be present. The condition may be self-limiting without the need for therapeutic intervention or it may progress to the severe and potentially fatal condition of delirium tremens (DTs), often characterised by delirium, disorientation, and hallucinations. In some cases generalised tonic-clonic seizures occur within 24 hours of alcohol withdrawal and are followed by delirium tremens.

The general management of the alcohol **withdrawal** syndrome and maintenance of abstinence have been the subject of many reviews and discussions.[1-15] In most cases symptoms do not require treatment and disappear within a few days, but more severe cases may require managed withdrawal from alcohol to avoid complications.

Benzodiazepines are usually the drugs of first choice because of their sedative, anxiolytic and anticonvulsant properties. If given promptly, benzodiazepines can prevent progression to seizures and delirium tremens. Longer-acting drugs such as chlordiazepoxide or diazepam may be more effective against withdrawal seizures and provide smoother withdrawal, while shorter-acting ones such as lorazepam or oxazepam have a smaller risk of producing oversedation and may be more suitable for use in the elderly and, since they do not rely on hepatic enzymes for their metabolism, for patients with liver disease. Because of the risk of dependence benzodiazepines should only be given in short courses. Some advocate that benzodiazepine dosage should be adjusted according to the severity of symptoms with special care being paid to patients with a history of withdrawal seizures, comorbid conditions, or those using sedative or hypnotic medication. This reduces the amount of drug required and the duration of treatment but entails regular monitoring by trained nursing staff. For mild to moderate symptoms, standard anxiolytic or muscle-relaxing oral doses of benzodiazepines may be sufficient. For severe symptoms, or for the treatment of delirium tremens, higher doses and use of the intravenous route may be required. *Clomethiazole* appears to be an effective alternative to the benzodiazepines (but see under Interactions of Clomethiazole, p.978); although widely used in Europe, it is not available in the USA. Some centres use phenobarbital but *barbiturates* are generally not recommended for the treatment of alcohol withdrawal syndrome.

Antipsychotics are not usually recommended for use in the control of symptoms of alcohol withdrawal since they do not reduce delirium tremens and some may reduce the seizure threshold. However, they might be considered for use as adjuncts in patients requiring treatment of marked agitation or hallucinations.

The generalised tonic-clonic seizures associated with alcohol withdrawal are usually self-limiting and patients who experience only one or two seizures do not usually require any specific treatment beyond continuing therapy with benzodiazepines or clomethiazole. For recurrent seizures or status epilepticus (p.469) a benzodiazepine may be given intravenously. Other types of seizure may be associated with head trauma or pre-existing seizure disorders (p.465) and should be treated accordingly. Other *antiepileptics* such as carbamazepine have been tried in the treatment of alcohol withdrawal seizures and may be of use as adjuncts in controlling other symptoms of alcohol withdrawal syndrome. As benzodiazepines are effective in preventing withdrawal seizures, other prophylactic drugs are not usually indicated.

Beta blockers can reduce symptoms of autonomic overactivity such as tachycardia, hypertension, tremor, and agitation but because they can mask these symptoms of withdrawal and do not prevent the development of more serious complications they should not be used alone. Some beta blockers such as propranolol that penetrate the CNS may produce CNS effects that complicate therapy. The $alpha_2$-adrenoceptor agonist *clonidine* may be of similar benefit as an adjunct.

Other drugs that have been reported to be of benefit in alcohol withdrawal syndrome include nitrous oxide and gamma-hydroxybutyric acid.

It is essential that in all cases of alcohol withdrawal syndrome hypoglycaemia, dehydration, electrolyte disturbances (in particular magnesium), and vitamin deficiencies be corrected. However, hydration should be undertaken with care as alcoholics may be more prone to develop cerebral oedema, the management of which is discussed under Raised Intracranial Pressure on p.1181. It is usually recommended that all patients should be given thiamine because of their increased risk of developing Wernicke-Korsakoff syndrome (p.1977). It should be noted that giving intravenous glucose before thiamine may precipitate Wernicke's encephalopathy in thiamine-deficient patients.

Abstinence. Once the initial acute withdrawal of alcohol is achieved treatment may be required to maintain long-term abstinence. Pharmacotherapy should only be used as an adjunct to psychotherapy and supportive care. Drugs used to modify alcohol seeking behaviour either sensitise the patient to alcohol (aversive drugs) or reduce or alleviate the craving for alcohol. The main ones used for aversive therapy have historically been *disulfiram* and *calcium carbimide*. A patient who ingests alcohol after taking an adequate dose of one of these drugs will experience a severe and unpleasant reaction (see Adverse Effects of Disulfiram, p.2296). However, the deterrent value of aversive drugs, and their potential toxicity, has long been a matter of debate. Such treatment is likely to be of little use unless it is undertaken with the willing cooperation of the patient and is used with psychotherapy, and even then there is no evidence that it has any effect on the long-term course of alcoholism.

Of those drugs that have been reported to reduce alcohol craving *acamprosate* and *naltrexone* have been the most promising as adjuncts for management of alcohol dependence and have been shown to improve abstinence and reduce relapse rates. Whether benefit is maintained long-term after treatment is stopped is unclear. *Other drugs* tried with varying benefit include aripiprazole, tiapride, gamma-hydroxybutyric acid, bromocriptine, nalmefene, and topiramate. Experimental evidence suggests that serotonin plays a role in the impulsivity and craving and is partly responsible for alcohol dependence. However, studies with SSRIs in alcohol dependence have been disappointing and it would appear that the benefit is in treating underlying depression rather than influencing drinking behaviour. Similar results have been noted with other drugs acting at serotonin receptors such as buspirone, ritanserin, and nefazodone. However, studies with ondansetron have shown some efficacy on drinking frequency and intake.

1. Mayo-Smith MF. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278:** 144–51.
2. O'Connor PG, Schottenfeld RS. Patients with alcohol problems. *N Engl J Med* 1998; **338:** 592–602.
3. Tinsley JA, *et al.* Developments in the treatment of alcoholism. *Mayo Clin Proc* 1998; **73:** 857–63.
4. Schaffer A, Naraiyo CA. Recommended drug treatment strategies for the alcoholic patient. *Drugs* 1998; **56:** 571–85.
5. Naik PC, Brownell LW. Treatment of psychiatric aspects of alcohol misuse. *Hosp Med* 1999; **60:** 173–7.
6. Garbutt JC, *et al.* Pharmacological treatment of alcohol dependence: a review of the evidence. *JAMA* 1999; **281:** 1318–25.
7. Swift RM. Drug therapy for alcohol dependence. *N Engl J Med* 1999; **340:** 1482–90.
8. Kraemer KL, *et al.* Managing alcohol withdrawal in the elderly. *Drugs Aging* 1999; **14:** 409–25.
9. Myrick H, *et al.* New developments in the pharmacotherapy of alcohol dependence. *Am J Addict* 2001; **10** (suppl): 3–15.
10. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003; **348:** 1786–95.
11. Mayo-Smith MF, *et al.* Management of alcohol withdrawal delirium: an evidence-based practice guideline. *Arch Intern Med* 2004; **164:** 1405–12.
12. Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* 2004; **18:** 485–504.
13. Kenna GA, *et al.* Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 1. *Am J Health-Syst Pharm* 2004; **61:** 2272–9.
14. Kenna GA, *et al.* Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 2. *Am J Health-Syst Pharm* 2004; **61:** 2380–8.
15. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systemic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 15/03/06).

Precautions

Excessive alcohol intake should be avoided. In the UK, the Department of Health advises that men should not drink more than 3 to 4 units of alcohol per day, and women not more than 2 to 3 units of alcohol per day, regardless of whether one drinks every day, once or twice a week, or occasionally. A unit of alcohol is defined as 10 mL of pure alcohol. A normal measure of spirits in a public house contains about 1 unit of alcohol. A pint of ordinary strength lager or cider, a pint of bitter, or 175 mL glass of wine contain about 2 units of alcohol, while a pint of strong lager contains about 3 units of alcohol. Women and the elderly may be more susceptible to the adverse effects of alcohol ingestion.

Alcohol may aggravate peptic ulcer disease or hepatic impairment and impair control of diabetes mellitus or epilepsy. Ingestion of alcohol during pregnancy or breast feeding is not advisable. In chronic alcoholics there may be tolerance to the effects of other CNS depressants including general anaesthetics.

All processes requiring judgement and coordination are affected by alcohol and these include the driving of any form of transport and the operating of machinery. It is an offence in many countries for motorists to drive when the blood-alcohol concentration is above a stated value while in some countries any detectable concentration is an offence. The alcohol concentration in urine and expired air can be used to estimate the blood-alcohol concentration.

It should be remembered that alcohol may be present in a number of pharmaceutical preparations such as elixirs and mouthwashes, and that children may be particularly susceptible to its hypoglycaemic effects.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, ingestion of large amounts of alcohol by a breast-feeding mother may cause drowsiness, diaphoresis, deep sleep, weakness, decrease in linear growth, and abnormal weight gain in the infant; maternal ingestion of 1 g/kg or more daily decreases the milk ejection reflex.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Driving. In addition to the legal maximum blood-alcohol concentration permitted for motorists, in the UK there are restrictions on holding a driving licence for those who persistently misuse alcohol, have alcohol dependency, have had an alcohol-related seizure, or have an alcohol-related disorder.[1]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

Porphyria. Alcohol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Alcohol crosses the placenta and is both teratogenic and fetotoxic in humans.[1,2] Binge drinking or excessive alcohol intake is associated with low birth-weight, behavioural and intellectual difficulties later in life, and fetal alcohol syndrome (see Adverse Effects, above). It is therefore generally agreed that pregnant women should avoid or limit their intake of alcohol although guidance from professional bodies is slightly inconsistent. In the UK, the Royal College of Obstetricians and Gynaecologists[2] states that while the safest approach may be to avoid any alcohol intake during pregnancy, there is no evidence of harm from infrequent or low levels of alcohol intake (no more than one or two units once or twice a week) particularly after the first trimester. NICE[1] suggests limiting alcohol intake to no more than one unit per day. However, in the USA, the Surgeon General's Office[3] and the American Academy of Pediatrics[4] advise women who are pregnant or women who are planning a pregnancy to avoid alcohol use.

1. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman (issued October 2003). Available at: http://www.rcog.org.uk/resources/Public/pdf/Antenatal_Care.pdf (accessed 19/09/06)
2. Royal College of Obstetricians and Gynaecologists. RCOG Statement no. 5: alcohol consumption and the outcomes of pregnancy (issued March 2006).
Available at: http://www.rcog.org.uk/resources/Public/pdf/alcohol_pregnancy_rcog_statement5a.pdf (accessed 19/09/06)
3. United States Department of Health and Human Services. News release: U.S. Surgeon General releases advisory on alcohol use in pregnancy (issued 21st February 2005). Available at: http://www.hhs.gov/surgeongeneral/pressreleases/sg02222005.html (accessed 19/09/06)
4. American Academy of Pediatrics: Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics* 2000; **106:** 358–61. Also available at: http://www.pediatrics.org/cgi/content/full/106/2/358 (accessed 19/09/06)

Interactions

Reports of interactions between alcohol and other drugs are not consistent, possibly because acute alcohol intake may inhibit drug metabolism while chronic alcohol intake can enhance the induction of drug-metabolising enzymes in the liver.

Alcohol can enhance the acute effects of CNS depressants, such as hypnotics, antihistamines, opioid analgesics, antiepileptics, antidepressants, antipsychotics, and sedatives. In addition 'dose dumping', rapid and potentially fatal release of high doses from modified-release formulations, has occurred when some opioid preparations were taken with alcohol.

Unpleasant reactions, similar to those occurring with disulfiram (p.2296), may occur when alcohol is taken with chlorpropamide, griseofulvin, mepacrine, metronidazole and other nitroimidazoles, the nitrofuran derivatives furazolidone and nifuratel, procarbazine, or some cephalosporins. Alcoholic beverages containing tyramine may cause reactions when taken by patients receiving MAOIs.

Alcohol can cause hypoglycaemic reactions in patients receiving sulfonylurea antidiabetics or insulin, and orthostatic hypotension in patients taking drugs with a vasodilator action. It may enhance the hypotensive effects of antihypertensives and has also increased the sedative effect of indoramin. Alcohol may increase gastric bleeding caused by analgesics and can have a variable effect on oral anticoagulants. It may decrease the antidiuretic effect of vasopressin.

◊ Reviews.

1. McInnes GT. Interactions that matter: alcohol. *Prescribers' J* 1985; **25:** 87–90.
2. Lieber CS. Interaction of alcohol with other drugs and nutrients: implications for the therapy of alcoholic liver disease. *Drugs* 1990; **40** (suppl 3): 23–44.
3. Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet* 1997; **33:** 79–90.
4. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health* 1999; **23:** 40–54.

Cycloserine. Increased blood-alcohol concentrations have been reported in patients receiving cycloserine.[1]

1. Glass F, *et al.* Beobachtungen und untersuchungen über die gemeinsame wirkung von alkohol und D-cycloserin. *Arzneimittelforschung* 1965; **15:** 684–8.

H_2-antagonists. The existence of an interaction between H_2-antagonists and alcohol is controversial and has not been established. While some studies suggest that *cimetidine*[1-3] and *nizatidine*[3] can increase peak blood-alcohol concentrations the effects of *ranitidine*[2,4] have been variable; *famotidine* appears to have no significant effect.[2] Later studies report that any interaction between H_2-antagonists and alcohol is minor and unlikely to be of clinical importance.[5-8]

1. Caballeria J, *et al.* Effects of cimetidine on gastric alcohol dehydrogenase activity and blood ethanol levels. *Gastroenterology* 1989; **96:** 388–92.
2. DiPadova C, *et al.* Effects of ranitidine on blood alcohol levels after ethanol ingestion: comparison with other H -receptor antagonists. *JAMA* 1992; **267:** 83–6.
3. Holt S, *et al.* Evidence for an interaction between alcohol and certain H receptor antagonists. *Gut* 1991; **32:** A1220.
4. Toon S, *et al.* Lack of effect of high dose ranitidine on the postprandial pharmacokinetics of alcohol. *Gut* 1992; **33** (suppl): S10.
5. Raufman J-P, *et al.* Histamine-2 receptor antagonists do not alter serum ethanol levels in fed, nonalcoholic men. *Ann Intern Med* 1993; **118:** 488–94.
6. Levitt MD. Do histamine-2 receptor antagonists influence the metabolism of ethanol? *Ann Intern Med* 1993; **118:** 564–5.
7. Kleine M-W, Ertl D. Comparative trial in volunteers to investigate possible ethanol-ranitidine interaction. *Ann Pharmacother* 1993; **27:** 841–5.
8. Gugler R. H -antagonists and alcohol: do they interact? *Drug Safety* 1994; **10:** 271–80.

Paracetamol. The effects of paracetamol poisoning may be exacerbated by chronic alcohol consumption (see p.108).

Verapamil. When verapamil has been taken with alcohol there has been a reported increase in peak blood-alcohol concentrations of about 17%.[1] Such an interaction may extend the toxic effects of alcohol and raise its blood concentration above the legal limit for driving.[2]

1. Schumock G, *et al.* Verapamil inhibits ethanol elimination. *Pharmacotherapy* 1989; **9:** 184–5.
2. Anonymous. Does verapamil increase the effects of alcohol? *Pharm J* 1990; **244:** 14.

Pharmacokinetics

Alcohol is rapidly absorbed from the gastrointestinal tract and is distributed throughout the body fluids. It readily crosses the placenta. Alcohol vapour can be absorbed through the lungs. Absorption through intact skin is said to be negligible.

The rate of absorption of alcohol from the gastrointestinal tract may be modified by such factors as the presence of food, the concentration of alcohol, carbonation of the alcoholic beverage, and the period of time during which it is ingested.

Alcohol is mainly metabolised in the liver; it is converted by alcohol dehydrogenase to acetaldehyde and is then further oxidised to acetate. A hepatic microsomal oxidising system is also involved. About 90 to 98% of alcohol is oxidised and the remainder is excreted unchanged by the kidneys and the lungs. It also appears in breast milk, sweat, and other secretions.

The rate of metabolism may be accelerated after repeated excessive intake and by certain substances including insulin.

◊ Reviews.

1. Holford NHG. Clinical pharmacokinetics of ethanol. *Clin Pharmacokinet* 1987; **13:** 273–92.
2. Lotsof J. A revised pharmacokinetic model for alcohol. *Clin Pharmacokinet* 2003; **42:** 585–7.
3. Paton A. Alcohol in the body. *BMJ* 2005; **330:** 85–7.

Uses and Administration

Alcohol has been used and abused for many thousands of years, in the form of alcoholic beverages, for its effects on the CNS. However, it also has pharmaceutical applications.

Alcohol is bacteriostatic at low concentrations but has bactericidal activity at higher concentrations; it does not, however, destroy bacterial spores. The mechanism of action appears to be denaturation of proteins. In the total absence of water, proteins are not denatured as rapidly as when water is present. Its bactericidal activity drops sharply when diluted below a 50% concentration and the optimal bactericidal concentration is 60 to 90% by volume. Alcohol also exhibits some fungicidal and virucidal activity. It is used to disinfect skin before injection, venepuncture, or surgical procedures. It is also used to disinfect hands and clean surfaces. A concentration of 70%, often as methylated spirits (p.1652), is commonly used for disinfection. Alcohol should not be used for disinfection of surgical or dental instruments because of its low efficacy against bacterial spores and inability to penetrate protein-rich materials.

Alcohol also has anhidrotic, rubefacient, and astringent and haemostatic properties. It is sometimes used for its skin-cooling properties and to harden the skin. It is an ingredient of several topical preparations used for skin disorders.

Alcohol is widely used as a solvent and preservative in pharmaceutical preparations.

Alcohol may be used as a neurolytic in the management of severe and chronic pain.

Alcohol is given intravenously in the treatment of acute poisoning from ethylene glycol (p.2300) and methyl alcohol (p.2024).

Alcohol is also used in sclerotherapy.

Pain. The use of alcohol as a neurolytic to produce destructive nerve block (see under Pain, p.1852) has produced variable results, and some consider the risk of complications outweighs the benefits. However, alcohol has been injected into the pituitary gland for relief of severe pain of the head and neck;[1,2] doses of 1 mL of absolute alcohol have been used.[1] It may be useful in coeliac plexus block, and has been injected into the muscle sheath to relieve painful muscle spasms in patients with multiple sclerosis.[1] Alcohol 50 to 100% may be used for peripheral or central nerve block in terminally ill patients with pain that does not respond to drug therapy;[3,4] the block produced by alcohol may occasionally last up to 2 years, even longer than that produced by phenol. However, larger volumes of alcohol than phenol are required, which means that blockade may be less precise due to leakage to proximal sites;[4] in addition, alcohol may exacerbate local pain on injection, because of its irritant effect on the tissues, and injection of a local anaesthetic beforehand, or giving the alcohol combined with a local anaesthetic, may be necessary.[4,5]

Intrathecal injection of alcohol has also been used for the intractable pain of spasticity (p.1887); early use, as soon as spasticity becomes painful and disabling, has been advocated.[6]

1. Lloyd JW. Use of anaesthesia: the anaesthetist and the pain clinic. *BMJ* 1980; **281:** 432–4.
2. Lipton S. Pain relief in active patients with cancer: the early use of nerve blocks improves the quality of life. *BMJ* 1989; **298:** 37–8.
3. Hardy, PAJ. The role of the pain clinic in the management of the terminally ill. *Br J Hosp Med* 1990; **43:** 142–6.
4. Gordin V, *et al.* Acute and chronic pain management in palliative care. *Best Pract Res Clin Obstet Gynaecol* 2001; **15:** 203–34.
5. Kongsgaard UE, *et al.* Nevrolytisk blokade hos kreftpasienter–fortsatt en nyttig behandling. *Tidsskr Nor Laegeforen* 2004; **124:** 481–3.
6. Viel E, *et al.* Spasticité: intérêt du testing par anesthésie locorégionale et blocs thérapeutiques. *Ann Fr Anesth Reanim* 2005; **24:** 667–72.

Sclerotherapy. Alcohol has been used successfully as a sclerosant in a variety of conditions including aldosterone-producing adenoma,[1] parathyroid adenomas,[2] thyroid nodules,[3,4] advanced rectal cancer,[5] hepatocellular carcinoma,[6,7] dysphagia associated with oesophogastric cancer,[8,9] hepatic[10] or renal[11] cysts, and gallbladder obstruction.[12] It has also been used in the sclerotherapy of oesophageal varices,[13,14] although the safety of this procedure has been questioned after a report of complications developing in 13 of 17 patients, 2 of whom died.[15] Other conditions in which alcohol has been used as a sclerosant include bleeding from ruptured hepatomas[16] and in peptic ulcer disease,[17] vascular malformations,[18] and obstructive cardiomyopathies[19] resistant to usual treatment.

Other sclerosants used in oesophageal varices are discussed on p.2346.

1. Hokotate H, *et al.* Aldosteronomas: experience with superselective adrenal arterial embolization in 33 cases. *Radiology* 2003; **227:** 401–6.
2. Vergès B, *et al.* Traitement des adénomes parathyroïdiens par alcoolisation sous contrôle échographique. *Ann Chir* 2000; **125:** 457–60.
3. Monzani F, *et al.* Autonomous thyroid nodule and percutaneous ethanol injection. *Lancet* 1991; **337:** 743.
4. Bennedbaek FN, Hegedüs L. Alcohol sclerotherapy for benign solitary solid cold thyroid nodules. *Lancet* 1995; **346:** 1227.
5. Payne-James J, *et al.* Advanced rectal cancer. *BMJ* 1990; **300:** 746.
6. Lencioni R, *et al.* Alcoolizzazione percutanea dell'epatocarcinoma: risultati a lungo termine. *Radiol Med (Torino)* 1997; **94:** 8–13.

7. Ebara M, *et al.* Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005; **43:** 458–64.
8. Payne-James JJ, *et al.* Use of ethanol-induced tumor necrosis to palliate dysphagia in patients with esophagogastric cancer. *Gastrointest Endosc* 1990; **36:** 43–6.
9. Stanners AJ, *et al.* Alcohol injection for palliation of malignant oesophageal disease. *Lancet* 1993; **341:** 767.
10. Larsen TB, *et al.* Single-session alcohol sclerotherapy in symptomatic benign hepatic cysts: long-term results. *Acta Radiol* 1999; **40:** 636–8.
11. Mohsen T, Gomha MA. Treatment of symptomatic simple renal cysts by percutaneous aspiration and ethanol sclerotherapy. *BJU Int* 2005; **96:** 1369–72.
12. Asfar S, *et al.* Percutaneous sclerosis of gallbladder. *Lancet* 1989; **ii:** 387.
13. Meirelles-Santos JO, *et al.* Absolute ethanol and 5% ethanolamine oleate are comparable for sclerotherapy of esophageal varices. *Gastrointest Endosc* 2000; **51:** 573 6.
14. Ferrari AP, *et al.* Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. *Arq Gastroenterol* 2005; **42:** 72–6.
15. Bhargava DK, *et al.* Endoscopic sclerotherapy using absolute alcohol. *Gut* 1986; **27:** 1518.
16. Chung SCS, *et al.* Injection of alcohol to control bleeding from ruptured hepatomas. *BMJ* 1990; **301:** 421.
17. Lin HJ, *et al.* Heat probe thermocoagulation and pure alcohol injection in massive peptic ulcer haemorrhage: a prospective, randomised controlled trial. *Gut* 1990; **31:** 753–7.
18. Deveikis JP. Percutaneous ethanol sclerotherapy for vascular malformations in the head and neck. *Arch Facial Plast Surg* 2005; **7:** 322–5.
19. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet* 1995; **346:** 211–14.

Preparations

USP 31: Alcohol in Dextrose Injection; Dehydrated Alcohol Injection; Rubbing Alcohol.

Proprietary Preparations (details are given in Part 3)
Austral.: Microshield Antimicrobial Hand Gel; ***Canad.:*** Avagard D; Biobase; Dial†; Duonalc-E Mild; Instant Hand Sanitizer; One Step Hand Sanitizer; President's Choice Hand Sanitizer; Purell; ***Fr.:*** Curethyl; Optrex; Pharmadose alcool; ***Ger.:*** AHD 2000; Amphisept E; Fugaten; Klosterfrau Franzbranntwein Menthol; Manusept HD†; Sterillium Virugard; ***Hung.:*** Saletanol D†; ***Indon.:*** Handy Clean; ***Malaysia:*** QuickLean; ***Philipp.:*** AHD 2000; ***Switz.:*** Amphisept†; ***USA:*** Alcare; Bodi Line Action; Gel-Stat; Kleen-Handz†.

Multi-ingredient: ***Austral.:*** Dermatech Liquid; Johnsons Clean & Clear Invisible Blemish Treatment†; Johnsons Clean & Clear Oil Controlling Toner; Microshield Handrub; Microshield Tincture; ***Austria:*** Dodesept; Dodesept Gefarbt; Dodesept N; Skinsept; Skinsept mucosa; ***Belg.:*** Sabenyl; Solution Antiseptique Stella†; ***Canad.:*** Avagard CHG; Biobase-G; Chase Kolik Gripe Water; Dilusol AHA†; Dilusol†; Duonalc-E; Franzbranns†; Green Antiseptic Mouthwash & Gargle; Mouthwash Antiseptic & Gargle†; MRX†; Sans-Acne†; ***Chile:*** Abboderm†; Acnoxyl Locion Tonica; Alcolex; Listerine; Listermint Con Fluor; Oralfresh Citrus; Oralfresh Clasico; Oralfresh Menta; ***Cz.:*** Promanum N; Skinsept mucosa†; Softa-Man; ***Fin.:*** Otiborin; Somanol + Ethanol; ***Fr.:*** Alco-Aloe; Aniospray 29; Chlorispray†; Parogencyl gencives fragilisees†; ***Ger.:*** Aerodesin; Autoderm Extra; Bacillol; Bacillol AF; Betaseptic; Desderman N†; Franzbranntwein mit Fichtennadelol†; Freka-Derm; Freka-Nol; Freka-Sept 80; Hospidermin; Hospisept; Incidin; Incidin Spezial; Incidur Spray†; Klosterfrau Franzbranntwein; Klosterfrau Franzbranntwein Latschenkiefer; Mucasept-A; Promanum N; Riwa Franzbranntwein; Skinsept G; Skinsept mucosa; Softa Man; Softasept N; Spitacid; ***Gr.:*** Faragel-Forte; ***Hong Kong:*** Listerine; Listerine Tartar Control; ***Hung.:*** Fructosol E†; ***India:*** Daslin; Dettolin; ***Indon.:*** Allerin; Benadryl CM; Berlifed; Chlorphemin; Coricidin; Dactylen; Domeryl; Eksedryl Expectorant; Inadryl; Inadryl Plus; Koffex; Listerine; Listerine Coolmint; Neo Novapon; Nichodryl; OBH; Paradryl; ***Israel:*** Alcosept; Oxy Clean Medicated; Salisol; Septadine; Spirit Salicyl; V-Tabur; ***Ital.:*** Bemonalcool; Citroclorex; Citromed 80 and 85; Citromed Chirurgico; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosteril Strumenti; Clorexan Ferri; Eso Ferri Alcolico; Esoalcolico Incolore; Esoform Alcolico; Forbrand; Formedico; Incidin Spezial; Incidur Spray; Jodieci; Melsept Spray; Neomedil; Panseptil; Sekumatic; Simpottantacinque; Softa Man; ***Neth.:*** Softa-Man; ***Philipp.:*** BSI Medicated Spray; Dermablend Clarifying; Listerine Coolmint; Listerine Original; Zilactin; Zildent; ***Port.:*** Promanum; Softasept; ***S.Afr.:*** Clearasil Medicated Facial Cleanser; Dry & Clear Medicated Skin Cleanser; Listerine Antiseptic; Oxipor VHC; Specific Nerve Pain Remedy; ***Singapore:*** Hexodane Handrub; Listerine; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; Tri-Cidal†; ***Spain:*** Alcohocel; Alcohol Benzalconio; Alcohol Cetil†; Alcohol Cetilpi Cuve†; Alcohol CL Benz; Alcohol Poten; Alcohol Potenciado; Beta Alcanforado; Beta Romero; Embrocacion Gras; Farmalcohol; Linimento Naion; Menalcol; Mercrotona; ***Switz.:*** Betaseptic; Desitur†; Frekaderm†; Promanum N; Sclerovein; Softasept N; ***Thai.:*** Hand Joy; ***UK:*** Brushtox; Clearasil Pore Cleansing Lotion; Medi-Wipe; Oxy Cleanser; Oxy Duo Pads; Spectrum; ***USA:*** Banadyne-3; Clearasil Double Clear; Clearasil Double Textured Pads; Lipmagik; Maximum Strength Anbesol; Orasol; Stri-Dex Pads; ***Venez.:*** Frixonil.

Alkyl Gallates

Galatos de alquilo.

Dodecyl Gallate

Dodecilo galatas; Dodécyle, gallate de; Dodecylgallat; Dodecylgallát; Dodecylis gallas; Dodekyyligallaatti; E312; Galato de dodecilo; Lauryl Gallate; Laurylum Gallicum. Dodecyl 3,4,5-trihydroxybenzoate.

$C_{19}H_{30}O_5$ = 338.4.
CAS — 1166-52-5.

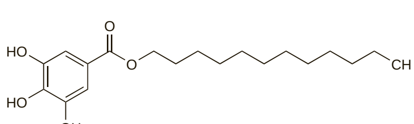

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dodecyl Gallate). A white or almost white crystalline powder. M.p. about 96°. Very slightly soluble or practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in nonmetallic containers. Protect from light.

Ethyl Gallate

Galato de etilo. Ethyl 3,4,5-trihydroxybenzoate.

$C_9H_{10}O_5$ = 198.2.
CAS — 831-61-8.

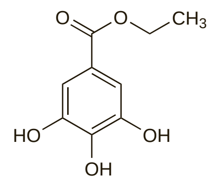

Pharmacopoeias. In *Br.*
BP 2008 (Ethyl Gallate). A white to creamy-white, odourless or almost odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in ether; practically insoluble in arachis oil. Protect from light. Avoid contact with metals.

Octil Gallate

E311; Galato de octilo; Octyl Gallate; Octyle, gallate d'; Octylis gallas; Oktilo galatas; Oktylgallat; Oktyl-gallát; Oktyyligallaatti. Octyl 3,4,5-trihydroxybenzoate.

$C_{15}H_{22}O_5$ = 282.3.
CAS — 1034-01-1.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Octyl Gallate). A white or almost white crystalline powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol. Store in nonmetallic containers. Protect from light.

Propyl Gallate

E310; Galato de propilo; Propil-gallát; Propilo galatas; Propyle, gallate de; Propylgallat; Propyl-gallát; Propylis gallas; Propylu galusan; Propylum Gallicum; Propyyligallaatti. Propyl 3,4,5-trihydroxybenzoate.

$C_{10}H_{12}O_5$ = 212.2.
CAS — 121-79-9.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Propyl Gallate). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.
USNF 26 (Propyl Gallate). A white crystalline powder with a slight characteristic odour. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers. Avoid contact with metals. Protect from light.

Adverse Effects and Precautions

The alkyl gallates may cause contact sensitivity and skin reactions.

Effects on the blood. Methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula has been reported.[1] Propyl gallate was suspected of being the most likely cause because its chemical structure is similar to pyrogallol (p.1611), a methaemoglobinaemia inducer.

1. Nitzan M, *et al.* Infantile methemoglobinemia caused by food additives. *Clin Toxicol* 1979; **15:** 273–80.

Uses

The alkyl esters of gallic acid (3,4,5-trihydroxybenzoic acid) have antoxidant properties and are used as preservatives in pharmaceuticals and cosmetics. Alkyl gallates are also used as antoxidants in foods and are useful in preventing deterioration and rancidity of fats and oils. They are used in concentrations of 0.001 to 0.1%.

To improve acceptability and efficacy, the alkyl gallates are frequently used with other antoxidants such as butylated hydroxyanisole or butylated hydroxytoluene and with sequestrants and synergists such as citric acid and zinc salts.

The alkyl gallates have also been reported to have limited antibacterial and antifungal activity.

Ambazone *(BAN, rINN)*

Ambatsoni; Ambazon; Ambazona; Ambazonum. 4-Amidinohydrazonocyclohexa-1,4-dien-3-one thiosemicarbazone monohydrate.

Амбазон

$C_8H_{11}N_7S,H_2O$ = 255.3.
CAS — 539-21-9 (anhydrous ambazone); 6011-12-7 (ambazone monohydrate).
ATC — R02AA01.
ATC Vet — QR02AA01.

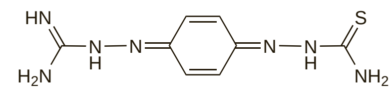

Profile

Ambazone is an antiseptic that is used in the form of lozenges for minor infections of the mouth and pharynx.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Faringosept†; ***Hung.:*** Faringosept†; ***Pol.:*** Faringosept; ***Rus.:*** Faringosept (Фарингосепт).

Aminoquinuride Hydrochloride *(rINNM)*

Aminoquinuride, Chlorhydrate d'; Aminoquinuridi Hydrochloridum; Hidrocloruro de aminoquinurida. 1,3-Bis(4-amino-2-methyl-6-quinolyl)urea dihydrochloride.

Аминохинурида Гидрохлорид

$C_{21}H_{20}N_6O,2HCl$ = 445.3.
CAS — 3811-56-1 (aminoquinuride); 5424-37-3 (aminoquinuride hydrochloride).

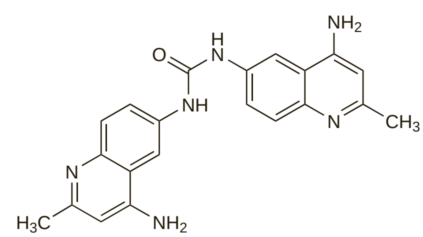

(aminoquinuride)

Profile

Aminoquinuride hydrochloride is an antiseptic that has been used in topical preparations for the treatment of mouth and skin disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Herviros; ***Ger.:*** Herviros†.

Amylmetacresol *(BAN, rINN)*

Amilmetacresol; Amilmetakrezol; Amylmétacrésol; Amylmetacresolum; Amylmetakresol; Amyylimetakresoli. 6-Pentyl-*m*-cresol; 5-Methyl-2-pentylphenol.

Амилметакрезол

$C_{12}H_{18}O$ = 178.3.
CAS — 1300-94-3.

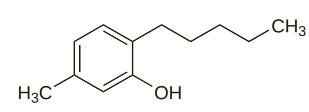

Pharmacopoeias. In *Br.*
BP 2008 (Amylmetacresol). A clear or almost clear liquid or a solid crystalline mass with a characteristic odour, colourless or slightly yellow when freshly prepared; it darkens on keeping. F.p. about 22°. Practically insoluble in water; soluble in alcohol, in ether, and in fixed and volatile oils. Protect from light.

Profile

Amylmetacresol is a phenolic antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Antiseptic Throat Lozenges; Throaties Anti-Bacterial Pastilles.

Multi-ingredient: ***Austral.:*** Sore Throat Chewing Gum†; Strepsils; Strepsils Plus; ***Austria:*** Coldangin; Neo-Angin; ***Belg.:*** Strepsils; Strepsils + Lidocaine; Strepsils Menthol; Strepsils Vit C; ***Canad.:*** Strepsils; Strepsils Cherry†; ***Cz.:*** Neo-Angin; Strepsils; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; ***Denm.:*** Strepsils; ***Fin.:*** Strepsils; Strepsils Menthol;

Fr.: Strepsils; Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsilspray Lidocaine; ***Ger.:*** Dobendan Synergie; Neo-Angin; ***Gr.:*** Strepsils; ***Hong Kong:*** Strepsils; Strepsils Dual Action; ***Hung.:*** Neo-Angin; Strepsils; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; ***India:*** Cof Q; Cofsils†; ***Irl.:*** Strepsils; Strepsils +Plus Anaesthetic; Strepsils Dual Action; Strepsils Vitamin C; ***Israel:*** Strepsils; Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; ***Ital.:*** Benagol; Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; ***Malaysia:*** Chericof; Strepsils; Strepsils Dual Action; ***Neth.:*** Strepsils; Strepsils Menthol en Eucalyptus; Strepsils Sinaasappel en Vitamine C; ***NZ:*** Strepsils; Strepsils Plus Anaesthetic; Strepsils with Vitamin C; ***Philipp.:*** Strepsils; ***Pol.:*** Neo-Angin; Strepsils; ***Rus.:*** Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс)†; Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Suprima-Lor (Суприма-Лор); ***S.Afr.:*** Strepsils; Strepsils Eucalyptus Menthol; Strepsils Orange-C; Strepsils Plus; Strepsils Soothing Honey & Lemon; ***Singapore:*** Strepsils; Strepsils Dual Action; ***Spain:*** Strepsils; Strepsils con Vitamina C; Strepsils Lidocaina; ***Swed.:*** Strepsils; ***Switz.:*** Neo-Angin au miel et citron; Neo-Angin avec vitamin C sans sucre; Neo-Angin sans sucre; ***Thai.:*** Strepsils Butter Menthol Capsicum; Strepsils Plus Anaesthetic; Strepsils Plus Vit C; Strepsils Sugar Free; Throatsil; ***Turk.:*** Strepsils; Strepsils C; Strepsils Mentollu; ***UK:*** Strepsils; Strepsils with Vitamin C.

Ascorbyl Palmitate

Ascorbilo, palmitato de; Ascorbyle, palmitate d'; Ascorbylis palmitas; Askorbilo palmitatas; Askorbylpalmitat; Askorbylpalmitát; Askorbylu palmitynian; Askorbyylipalmitaatti; Aszkorbilpalmitát; Vitamin C Palmitate. L-Ascorbic acid 6-hexadecanoate; L-Ascorbic acid 6-palmitate; 3-Oxo-L-gulofuranolactone 6-palmitate.

$C_{22}H_{38}O_7$ = 414.5.

CAS — 137-66-6.

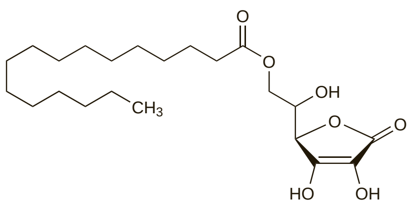

NOTE. The code E304 is used for fatty acid esters of ascorbic acid, which include ascorbyl palmitate.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Ascorbyl Palmitate). A white or yellowish-white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; practically insoluble in dichloromethane and in fatty oils. Store in airtight containers. Protect from light.

USNF 26 (Ascorbyl Palmitate). A white to yellowish-white powder with a characteristic odour. Very slightly soluble in water, in chloroform, in ether, and in vegetable oils; soluble 1 in 125 of alcohol. Store at 8° to 15° in airtight containers.

Profile

Ascorbyl palmitate is an antoxidant used as a preservative in pharmaceutical products and foods. It is often used with alpha tocopherol (p.1992), and this combination shows marked synergy. As it is a fat-soluble derivative of vitamin C (ascorbic acid, p.1983), ascorbyl palmitate is sometimes used as a source of vitamin C in nutritional supplements.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Neolucid-C.

Multi-ingredient: ***Hong Kong:*** Proflavanol†; ***Malaysia:*** Proflavanol; ***Port.:*** Thiospot; ***Singapore:*** Proflavanol.

Benzalkonium Chloride *(BAN, rINN)*

Bensalkoniumklorid; Bentsalkoniumkloridi; Benzalconio Cloruro; Benzalkonii chloridum; Benzalkonio chloridas; Benzalkoniowy chlorek; Benzalkonium Chloratum; Benzalkonium, chlorure de; Benzalkonium-chlorid; Benzalkónium-klorid; Benzalkonyum Klorür; Cloreto de Benzalconio; Cloruro de benzalconio.

Бензалкония Хлорид

CAS — 8001-54-5.

ATC — D08AJ01; D09AA11; R02AA16.

ATC Vet — QD08AJ01; QD09AA11; QR02AA16.

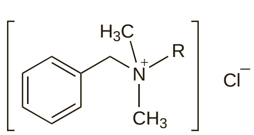

R = C_8H_{17} to $C_{18}H_{37}$

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *Jpn.* Also in *USNF.* Some pharmacopoeias also have a monograph for a solution.

Chin. also includes benzalkonium bromide.

Ph. Eur. 6.2 (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups having chain lengths of C_8 to C_{18}. It contains not less than 95% and not more than 104% of alkylbenzyldimethylammonium chlorides, calculated as $C_{22}H_{40}ClN$ with reference to the anhydrous substance.

A white or yellowish-white powder, or gelatinous yellowish-white pieces, hygroscopic and soapy to the touch. It forms a clear molten mass on heating. It contains not more than 10% of water. Very soluble in water and in alcohol. An aqueous solution froths copiously when shaken.

USNF 26 (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5.CH_2.N(CH_3)_2.R]Cl$, in which R represents a mixture of the alkyls having chain lengths from C_8 to C_{16}. It contains not less than 40% of the $C_{12}H_{25}$ compound, calculated on the anhydrous substance, not less than 20% of the $C_{14}H_{29}$ compound, and not less than 70% of the 2 compounds together.

A white or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic odour. It contains not more than 15% of water. Very soluble in water and in alcohol; the anhydrous form is soluble 1 in 100 of ether and 1 in 6 of benzene. A solution in water is usually slightly alkaline and foams strongly when shaken. Store in airtight containers.

Incompatibility. Benzalkonium chloride is incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, and zinc oxide and sulfate. Incompatibilities have been demonstrated with ingredients of some commercial rubber mixes or plastics. Incompatibilities have also been reported with other substances including aluminium, cotton dressings, fluorescein sodium, hydrogen peroxide, hypromellose, kaolin, hydrous wool fat, and some sulfonamides.

Adverse Effects, Treatment, and Precautions

As for Cetrimide, p.1634. Because some rubbers are incompatible with benzalkonium chloride silicone rubber teats should be used on eye drop containers unless the suitability has been established.

Catheters and cannulas. For reference to benzalkonium chloride used in the manufacturing process of heparin-bonded catheters interfering with determination of serum concentrations of sodium and potassium, see under Precautions for Heparin, p.1303.

Effects on the eyes. Benzalkonium chloride is one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes;[1] toxicity studies have tended to be carried out using relatively high concentrations of benzalkonium chloride[2] but damage to the tear film and corneoconjunctival surface have been noted in patients receiving regular long-term treatment for glaucoma with eye drops preserved with benzalkonium chloride in usual concentrations.[3,4]

Corneal toxicity has also been reported in patients inadvertently exposed to benzalkonium chloride as a preservative in viscoelastic material during cataract surgery.[5] The use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable.[1,2] Benzalkonium chloride is not suitable for use in solutions for storing and washing hydrophilic soft contact lenses, as it can bind to the lenses and may later produce ocular toxicity when the lenses are worn.[6] Similarly, benzalkonium chloride use in anaesthetic eye drops is discouraged, as the anaesthetic component reduces the blink reflex and increases the contact time with the eye drops which may consequently result in increased toxicity due to the preservative. Patients with dry eye syndrome are also at increased risk of toxicity as the corneal epithelium is exposed to the full strength of the eye drops, in addition to which these patients do not produce enough tears to dilute the preservative in the eye drops.

1. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc U K* 1985; **104:** 402–9.
2. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 1980; **25:** 15–30.
3. Herreras JM, *et al.* Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 1992; **99:** 1082–8.
4. Kuppens EVMJ, *et al.* Effect of timolol with and without preservative on the basal tear turnover in glaucoma. *Br J Ophthalmol* 1995; **79:** 339–42.
5. Eleftheriadis H, *et al.* Corneal toxicity secondary to inadvertent use of benzalkonium chloride preserved viscoelastic material in cataract surgery. *Br J Ophthalmol* 2002; **86:** 299–305.
6. Gasset AR. Benzalkonium chloride toxicity to the human cornea. *Am J Ophthalmol* 1977; **84:** 169–71.

Effects on the respiratory tract. Hypersensitivity to benzalkonium chloride, used as a preservative in nasal drops, was confirmed in a patient by a challenge that produced nasal congestion and irritation of the eyes and throat lasting 48 hours.[1] A review[2] of 18 studies (14 *in vivo*, 4 *in vitro*) where benzalkonium chloride was used as the preservative in multidose nasal products found that 8 studies (all *in vivo*) found no toxic effects, while 10 reported degenerative changes to the nasal epithelia or exacerbation of rhinitis medicamentosa. However, in only 2 of these 10 studies were the differences between benzalkonium chloride and control groups found to be significant, and both of these included the use of oxymetazoline, which is known to cause rhinitis medicamentosa.

Benzalkonium chloride used as a preservative in nebulised solutions of anti-asthma drugs has been reported to cause dose-related bronchoconstriction especially in asthmatic patients,[3] and has been associated with the precipitation of respiratory arrest.[4]

1. Hillerdal G. Adverse reaction to locally applied preservatives in nose drops. *ORL J Otorhinolaryngol Relat Spec* 1985; **47:** 278–9.
2. Marple B, *et al.* Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. *Otolaryngol Head Neck Surg* 2004; **130:** 131–41.
3. Committee on Drugs, American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99:** 268–78.
4. Boucher M, *et al.* Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; **26:** 772–4.

Interactions

Benzalkonium chloride is not suitable for use in eye drops containing local anaesthetics (see Effects on the Eyes, above).

Uses and Administration

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of the other cationic surfactants (see Cetrimide, p.1634). It is also used as an antimicrobial preservative for pharmaceutical products. Benzalkonium bromide and benzalkonium saccharinate have also been used.

Solutions of benzalkonium chloride 0.01 to 0.1% are used for cleansing skin, mucous membranes, and wounds. More dilute solutions of 0.005% are suitable for irrigation of deep wounds. A 0.02 to 0.05% solution has been used as a vaginal douche. An aqueous solution containing 0.005 to 0.02% has been used for irrigation of the bladder and urethra and a 0.0025 to 0.005% solution for retention lavage of the bladder.

Creams containing benzalkonium chloride are used in the treatment of napkin rash and other dermatoses.

A 0.2 to 0.5% solution has been used as a shampoo in seborrhoeic dermatitis.

Lozenges containing benzalkonium chloride are used for the treatment of superficial infections of the mouth and throat.

Benzalkonium chloride is used as a preservative in ophthalmic solutions at a concentration of 0.01 to 0.02%, and in nasal and otic solutions at a concentration of 0.002 to 0.02%. Benzalkonium chloride is used for disinfecting rigid contact lenses (p.1622) but is unsuitable as a preservative in solutions for washing and storing hydrophilic soft contact lenses (see also Effects on the Eyes, above).

Benzalkonium chloride is also used as a spermicide.

Solutions of 0.13% are used for disinfection and storage of surgical instruments, sometimes with the addition of sodium nitrite to inhibit rust.

Action. The antibacterial effect of benzalkonium chloride 0.003% was enhanced by 0.175% of benzyl alcohol, phenylpropanol, or phenethyl alcohol.[1] For the use of phenethyl alcohol with benzalkonium chloride as a preservative for ophthalmic solutions, see Antimicrobial Action, under Phenethyl Alcohol, p.1655.

1. Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against Pseudomonas aeruginosa by aromatic alcohols. *J Pharm Sci* 1973; **62:** 2035–7.

Catheter-related sepsis. Benzalkonium chloride has been investigated[1,2] for incorporation into catheters to reduce catheter-related sepsis (p.1624).

1. Tebbs SE, Elliott TSJ. A novel, antimicrobial central venous catheter impregnated with benzalkonium chloride. *J Antimicrob Chemother* 1993; **31:** 261–71.
2. Moss HA, *et al.* A central venous catheter coated with benzalkonium chloride for the prevention of catheter-related microbial colonization. *Eur J Anaesthesiol* 2000; **17:** 680–7.

Preparations

USNF 26: Benzalkonium Chloride Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Benzalcream†; Hidratant; Pharmatex; Usnicon†; ***Austral.:*** Bepanthen; Dettol Fresh; ***Belg.:*** Cedium; ***Braz.:*** Bacterian†; Fluimucil Solucao Nasal; ***Canad.:*** Antiseptic Skin Cream†; ***Chile:*** Germosept; ***Cz.:*** Pharmatex; ***Fr.:*** Humex; Pharmatex; Sparaplaie; ***Ger.:*** Baktonium†; Killavon; Laudamonium; Lysoform Killavon†; ***Hong Kong:*** Pharmatex; ***Hung.:*** Pharmatex; ***Irl.:*** Dettol Fresh; ***Israel:*** Pharmatex†; ***Ital.:*** Alfa C; Amuclean; Benalcon; Bergagyn; Bluesteril; Citrosil; Citrosteril Ambiente; Citrosteril Deterferri; Detergil; Dimanin R†; DiMill; Diseptil; Disigien; Disintyl; Display; Distasil; Disteril; Eso Deterferri; Eso Ferri; Esosan Casa; Esosan Soap; Germicidin; Germozero Clean; Helis; Hygienist Pavimenti e Piastrelle†; Iridina Light; Lacribase; Lozione Vittoria; Maxisteril; Neo-Desogen; Norica†; Polisan; Sanaform; Sangen†; SaniSteril Deterferri; Saquat; Sguardi; Sirigen; Steramin†; Steramina G; Stilla Delicato; Streptosil L PMC; Ten-Quat; Video-Light; ***Mex.:*** Derman Talco; Lubrizal†; Merthiolate†; ***NZ:*** Dettol; Dettol Fresh; Virasolve; ***Port.:*** Pharmatex; ***Rus.:*** Pharmatex (Фарматекс); Spermatex (Сперматекс); ***Spain:*** Armil†; Crema Contracepti Lanzas; Mini Ovulo Lanzas; ***Switz.:*** Benzaltex†; ***Thai.:*** Pose-Bac; ***Turk.:*** Zefan; Zefiran; Zefol; Zefort; Zefsolin; Zenfektol; Zentan; ***UK:*** Bradosol; Dermax Therapeutic Shampoo; Dettol Antiseptic Wash; Dettol Fresh; ***USA:*** Bacti-Cleanse; Benza; Mycocide NS; Ony-Clear†; Zephiran; ***Venez.:*** Decomed.

Multi-ingredient: ***Arg.:*** Antisepthic Plus; Crema de Ordene; Eurocoal; Hexil Antiseptico; Merthiolate NF; Muelita; Neo Coltirot; Oilalfo; Polviderm NF; Soquette; ***Austral.:*** Animine; Clean Skin Face Wash; Gum-Ese†; Mycil Healthy Feet†; Oilatum Plus; Paxyl; Solyptol†; TAGG†; Virasolve; ***Austria:*** Aleot; Dequonal; Dermaspray; Dorithricin; Limexx; Tyrothricin comp; ***Belg.:*** Akinspray; Dermaspray†; ***Braz.:*** Belagin; Cetrilan; Colpatrin; Colpist; Colpistar; Colpistatin; Dermol†; Dinill; Donnagel; Drapolene; Ginestatin; Higicler; Nasolin; Oxizinco; Pomada Minancora; Rinotil†; Tricomax; Vagi Biotic; Visolon; ***Canad.:*** Bactine; Family Medic First Aid Treatment; Medi-Dan; Protectaid; Tanac; ***Chile:*** Dermobarrina; Dexagin; Medisept†; Orajel Compuesto†; ***Cz.:*** Coldrex Laryplus; Dr Rentschler Halstabletten†; Oilatum Plus; Septolete; ***Fr.:*** Acarcid†; Biseptine; Dermaspraid Antiseptique; Dermobacter; Humex†; Kenalcol; Mercryl; Mercrylsoins; Pharmatex; Rhinofluimucil; ***Ger.:*** Baccalin†; Bacillocid rasant†; Cutasept; Dequonal; Dorithricin Original; Dynexan Mundgel; Freka-Derm; Freka-Sept 80; Gingicain D; Hexaquart L†; Hexaquart S; Incidin; Incidin extra N; Incidin Extra†; Incidin perfekt; Incidur Spray†; Inova†; Kohrsolin FF; Korsolex Extra; Korsolex FF; Lysetol Med†; Mikrobac; Quatohex; Sekusept Extra N; Sekusept forte†; Septolit†; Skinman Soft; Ultrasol-F; ***Gr.:*** Beta Opthiole; Cutasept; Olamyc; ***Hong Kong:*** Dermobacter; Dermojela; Drapolene†; Mycil; Oilatum Plus; Protectaid; Virasolve†; ***Hung.:*** Coldrex Laryplus†; Dorithricin; ***India:*** Rashfree; ***Indon.:*** Mexochrome; Oilatum Plus; ***Irl.:*** Conotrane†; Drapolene; Emulsiderm; Mycil; Oilatum Junior Flare-Up; Oilatum Plus; Torbetol; ***Israel:*** Aphtagone; Aptha-X; Emulsiderm; Garonsept; ***Ital.:*** Agipiu†; AZ 15; Barrycidal; Bemonalcool; Cerosteril; Cerox†; Citromed 80 and 85; Citromed Chirurgico; Citromedics Pronto; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosil Nubesan; Citrosteril Impronte; Citrosteril Pronto; Citrosteril Strumenti; Collyria†; Eso Ferri Alcolico; Eso Ferri Alcolico Plus; Eso S 80; Esoalcolico Incolore; Esoform 92; Esoform Alcolico; Esosan Pronto; Germozero Dermo; Germozero Plus; Hamamilla†; Herbe†; Incidin Spezial; Incidur Spray; Indulfan; Ipragocce†; Linea F; Lycia Luminique; Mediplus; Neo Emocicatrol; Neomedil; Norica; Odongi; Pupilla Light; Rexichlor; Sangen Casa; SaniSteril Strumenti Alcolico†; Sekusept Extra N†; Sicura3 Medical; Simp; Simpottantacinque; Sterosan; Tirs; Zincometil; ***Malaysia:*** Drapolene; Oilatum Plus Antibacterial; QV Flare Up; ***Mex.:*** Dermacid; Glossderm; Novageon; Sutin†; ***NZ:*** Oilatum Plus; ***Philipp.:*** Drapolene; Oilatum Plus; ***Pol.:*** Coldrex; Oilatum Plus; Septolete; ***Rus.:*** Drapolene (Драполен); Septogal (Септогал); Septolete (Септолете); ***S.Afr.:*** Oilatum Plus; ***Singapore:*** Dorithricin; Drapolene; Napitol†; Oilatum Plus; QV Flare Up; ***Spain:*** Aftajuventus; Alcohol Benzalconio; Alcohol CL Benz; Alcohol Potenciado; Avril; Curine†; Dermo Hali-but; Desinvag; Egarone†; Ginejuvent; Gradin Del D Andreu†; Lindemil; Mercryl Plus; Odamida; Otogen Calmante; Pental Forte†; Phonal; Pomada Heridas†; Resorborina; Sebumselen; Tulgrasum Cicatrizante; Vaselatum; ***Switz.:*** Cutasept; Dequonal; Frekaderm†; Leucen; Parapic; ***Thai.:*** Drapolene; Gynecon; Gynecon-T; Gynoco; Gynova; Gyracon; Napilene; Nystin; Oilatum Plus; Sanaco†; ***Turk.:*** Drapolene; Kortos; ***UK:*** Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus; Cetanorm; Conotrane; Dermol; Dettol; Drapolene; Emulsiderm; Germolene†; Germoloids†; Mycil; Neo Baby Cream; Oilatum Junior Flare-Up†; Oilatum Plus; Protectaid; ***USA:*** Bactine Antiseptic; Bactine Pain Relieving Cleansing; Cetylcide II; Cortic ND; Medi-Quik; Mediotic-HC; Orajel Mouth Aid; Oxyzal; Pedi-Pro; Tanac; Tanac Dual Core; Vagi-Gard Medicated Cream; Vi Rid-Ready; Zonite; ***Venez.:*** Gynovit; Pedi-Lotion.

Benzethonium Chloride *(BAN, rINN)*

Bensetoniumklorid; Bentsetoniumkloridi; Benzethonii chloridum; Benzéthonium, chlorure de; Benzethonium-chlorid; Benzetonio chloridas; Benzetoniowy chlorek; Benzetónium-klorid; Cloruro de bencetonio; Diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride. Benzyldimethyl(2-{2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy}ethyl)ammonium chloride.

Бензетония Хлорид

$C_{27}H_{42}ClNO_2$ = 448.1.
CAS — 121-54-0.
ATC — R02AA09.
ATC Vet — QR02AA09.

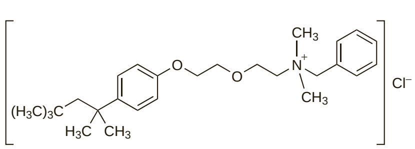

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Benzethonium Chloride). A white or yellowish-white powder. Very soluble in water and in alcohol; freely soluble in dichloromethane. An aqueous solution froths copiously when shaken. Protect from light.

USP 31 (Benzethonium Chloride). White crystals with a mild odour. Soluble 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in 6000 of ether. A 1% solution in water is slightly alkaline to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzethonium chloride is incompatible with soaps and other anionic surfactants.

Profile

Benzethonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used as a preservative in pharmaceutical and cosmetic products. It has also been used as a vaginal spermicide.

◊ Benzethonium chloride, which produced mild skin irritation at a concentration of 5% but not lower, was not considered to be a sensitiser, and was considered to be safe at a concentration of 0.5% in cosmetics applied to the skin and at a maximum concentration of 0.02% in cosmetics used in the eye area.[1]

1. The Expert Panel of the American College of Toxicology. Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. *J Am Coll Toxicol* 1985; **4:** 65–106.

Preparations

USP 31: Benzethonium Chloride Concentrate; Benzethonium Chloride Tincture; Benzethonium Chloride Topical Solution.

Proprietary Preparations (details are given in Part 3)

Canad.: Clearskin Antibacterial; Neutrogena Antiseptic Cleanser†; Skin Cleanser & Deodorizer†; ***S.Afr.:*** Johnson's Antiseptic Powder; ***USA:*** Antiseptic Wound & Skin Cleanser.

Multi-ingredient: ***Arg.:*** Butimerin; Solumerin; ***Austral.:*** Summers Eve Feminine; ***Belg.:*** Neo-Golaseptine; ***Braz.:*** Andolba; Hipodex; Solemil†; Spray Anti-Septico; ***Canad.:*** Antiseptic Skin Cream†; Lipsorex Plus; Lipsorex†; MRX†; Protecto†; VoSoL HC†; ***Chile:*** Aucusik; Dermaglos Plus†; Lerfimin; Molca; ***Cz.:*** Cemaquin†; ***Ger.:*** Brand- u. Wundgel-Medice N; ***Hong Kong:*** Cemaquin†; ***Ital.:*** Barrycidal; Sangen Casa; ***NZ:*** VoSoL; ***S.Afr.:*** Dry & Clear Medicated Skin Cleanser; ***Spain:*** Alcohol Poten; Eupnol; Halibut; Halibut Hidrocortisona; Isdinex†; ***Switz.:*** Angidine; Cemaquin; Rhinocure; Rhinocure simplex; Tyrocombine; Tyrothricine + Gramicidine; ***Thai.:*** Iwazin; Sigatricin; ***USA:*** Acetasol; Acetasol HC; Aerocaine†; Americaine First Aid†; Dermoplast Antibacterial; Skin Shield; Vagisil; VoSoL HC†; VoSoL†.

Benzoates

Benzoatos.

Benzoic Acid

Acide benzoïque; Acidum benzoicum; Bensoesyra; Bentsoehappo; Benzoesäure; Benzoesav; Benzoico, ácido; Benzoinė rūgštis; Dracylic Acid; E210; Kwas benzoesowy; Kyselina benzoová.

$C_6H_5.CO_2H$ = 122.1.
CAS — 65-85-0.

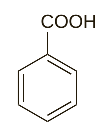

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Benzoic Acid). A white or almost white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour. Slightly soluble in water; soluble in boiling water; freely soluble in alcohol and in fatty oils. M.p. 121° to 124°.

USP 31 (Benzoic Acid). White crystals, scales, or needles, with a slight characteristic odour. Soluble 1 in 300 of water, 1 in 3 of alcohol, 1 in 5 of chloroform, and 1 in 3 of ether; freely volatile in steam. Congealing range 121° to 123°.

Incompatibility. The incompatibilities of benzoic acid are described under Sodium Benzoate, below.

Sodium Benzoate

Benzoan sodný; Benzoato sódico; E211; Natrii benzoas; Natrio benzoatas; Natrium Benzoicum; Natriumbensoat; Natriumbentsoaatti; Nátrium-benzoát; Sodii Benzoas; Sodium, benzoate de; Sodu benzoesan; Sodyum Benzoat.

$C_6H_5.CO_2Na$ = 144.1.
CAS — 532-32-1.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Sodium Benzoate). A white or almost white, slightly hygroscopic, crystalline or granular powder or flakes. Freely soluble in water; sparingly soluble in alcohol (90% v/v).

USNF 26 (Sodium Benzoate). A white, odourless or practically odourless, granular or crystalline powder. Soluble 1 in 2 of water, 1 in 75 of alcohol, and 1 in 50 of alcohol 90%.

Incompatibility. Benzoic acid and its salts are incompatible with quaternary compounds, calcium salts, ferric salts, and salts of heavy metals. Their activity is also diminished by nonionic surfactants or due to absorption by kaolin. They are relatively inactive above a pH of about 5.

Adverse Effects and Precautions

The benzoates can cause hypersensitivity reactions, but there have also been reports of non-immunological contact urticaria. The acid can be irritant to skin, eyes, and mucous membranes.

Infants given large doses of sodium benzoate have suffered vomiting. Symptoms of overdosage reported in this group have included vomiting, irritability and, in more severe cases, renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis.

Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

Hypersensitivity. Respiratory reactions to benzoates may occur, especially in patients susceptible to aspirin-induced asthma.[1,2] Urticarial reactions have also been associated with these compounds,[3,4] though at a lower incidence[5] and they can be non-immunological.[6] However, these reports have to be balanced against a controlled study[7] that showed no difference in the incidence of urticaria or atopic symptoms between patients given benzoic acid and those given lactose placebo. A retrospective study[8] of 47 patients who had previously shown a hypersensitivity reaction after ingesting food or products containing benzoate sodium found that the incidence of a repeat episode of acute urticaria or angioedema on re-challenge was very low (2%).

Anaphylactoid reactions have been reported in 2 patients.[9,10]

Erythema multiforme has been observed in several patients.[11]

1. Rosenhall L. Evaluation of intolerance to analgesics, preservatives and food colorants with challenge tests. *Eur J Respir Dis* 1982; **63:** 410–19.
2. Settipane GA. Aspirin and allergic diseases: a review. *Am J Med* 1983; **74** (suppl): 102–9.
3. Michaëlsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973; **88:** 525–32.
4. Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; **94:** 401–6.
5. Wüthrich B, Fabro L. Acetysalicylsäure-und lebensmitteladditiva-intoleranz bei urtikaria, asthma bronchiale und chronischer rhinopathie. *Schweiz Med Wochenschr* 1981; **III:** 1445–50.
6. Nethercott JR, *et al.* Airborne contact urticaria due to sodium benzoate in a pharmaceutical manufacturing plant. *J Occup Med* 1984; **26:** 734–6.
7. Lahti A, Hannuksela M. Is Benzoic acid really harmful in cases of atopy and urticaria? *Lancet* 1981; **ii:** 1055.
8. Nettis E, *et al.* Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. *Br J Dermatol* 2004; **151:** 898–902.
9. Moneret-Vautrin DA, *et al.* Anaphylactoid reaction to general anaesthesia: a case of intolerance to sodium benzoate. *Anaesth Intensive Care* 1982; **10:** 156–7.
10. Michils A, *et al.* Anaphylaxis with sodium benzoate. *Lancet* 1991; **337:** 1424–5.
11. Lewis MAO, *et al.* Recurrent erythema multiforme: a possible role of foodstuffs. *Br Dent J* 1989; **166:** 371–3.

Neonates. Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol as a preservative have been attributed to the accumulation of benzoic acid, a metabolite of benzyl alcohol (see p.1632). This risk led to the recommendation that Caffeine and Sodium Benzoate Injection (USP), which has been given as a respiratory stimulant, should not be used in neonates.[1]

Sodium benzoate has been tried in the treatment of some neonatal metabolic disorders (see Uses and Administration, below). However, benzoates can also displace bound bilirubin from albumin putting neonates at risk of kernicterus.[2] Three cases of toxicity have been reported after accidental high doses of intravenous sodium benzoate and sodium phenylacetate were given to children with hyperammonaemia.[3] All the children initially became agitated and confused, had Kussmaul respiration (rapid, deep breathing) and developed a partial metabolic acidosis with an increased anion gap. Two patients subsequently developed cerebral oedema and hypotension and died while the third survived after haemodialysis.

1. Edwards RC, Voegeli CJ. Inadvisability of using caffeine and sodium benzoate in neonates. *Am J Hosp Pharm* 1984; **41:** 658.
2. Schiff D, *et al.* Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 1971: **48:** 139–41.
3. Praphanphoj V, *et al.* Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. *J Inherit Metab Dis* 2000; **23:** 129–36.

Pharmacokinetics

The benzoates are absorbed from the gastrointestinal tract and conjugated with glycine in the liver to form hippuric acid, which is rapidly excreted in the urine.

Neonates. References.

1. Green TP, *et al.* Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr* 1983; **102:** 785–90.

Uses and Administration

Benzoates have antibacterial and antifungal properties. Their antimicrobial activity is due to the undissociated benzoic acid and is therefore pH-dependent. They are relatively inactive above a pH of about 5.

Benzoates are used as preservatives in pharmaceutical formulations including oral preparations; benzoic acid and sodium benzoate are typically used in concentrations of up to 0.2% and 0.5%, respectively. They are used as preservatives in foods, (and are also present naturally in some foods), and at similar concentrations in cosmetics.

Benzoic acid 6% with salicylic acid 3%, as Compound Benzoic Acid Ointment (BP 2008) (Whitfield's Ointment) has a long history of use as an antifungal (see Skin Infections, p.521). Benzoic acid has also been used in desloughing preparations and has been given as a urinary antiseptic.

An injection of caffeine and sodium benzoate has been used as a CNS stimulant, but see Neonates, under Adverse Effects and Precautions, above for a caution against its use in neonates.

Sodium benzoate is used as part of the treatment of hyperammonaemia that occurs in inborn errors of the urea cycle. It has also been reported to be effective in reducing plasma-glycine concentrations in nonketotic hyperglycinaemia (p.2393), although it may not be effective in preventing mental retardation.

Sodium benzoate is a common ingredient of cough preparations.

Hyperammonaemia. Sodium benzoate is used for treatment of hyperammonaemia (p.1929).[1-3] It is given with sodium phenylacetate (see p.2390 for doses) and a combined preparation is available in some countries.

1. Maestri NE, *et al.* Long-term survival of patients with argininosuccinate synthetase deficiency. *J Pediatr* 1995; **127:** 929–35.
2. Maestri NE, *et al.* Long-term treatment of girls with ornithine transcarbamylase deficiency. *N Engl J Med* 1996; **335:** 855–9.
3. Zammarchi E, *et al.* Neonatal onset of hyperornithinemia-hyperammonemia-homocitrullinuria syndrome with favorable outcome. *J Pediatr* 1997; **131:** 440–3.

Preparations

BP 2008: Benzoic Acid Solution; Compound Benzoic Acid Ointment; Toluflavour Solution;
USP 31: Benzoic and Salicylic Acids Ointment; Caffeine and Sodium Benzoate Injection.

Proprietary Preparations (details are given in Part 3)
Indon.: Topix; Yodsaben; ***Mex.:*** Colufase†.

Multi-ingredient: ***Arg.:*** Expectosan Hierbas y Miel; Fungicida†; Ixana; No-Tos Adultos; No-Tos Infantil; Pectobron; Refenax Jarabe; Solvex Liquido Fungicida†; Torfan H†; ***Austral.:*** Whitfields (Benzoic Acid Compound) Ointment; ***Austria:*** Acerbine; Mycopol; ***Belg.:*** Colimax†; Kamfeine†; Pholco-Mereprine; Toplexil; Tux†; ***Braz.:*** ABC Solucao†; Antimicon†; Benzomel†; Bronquidex; Bronquiogem; Cessatosse†; Dermicon; Dermycose†; Eaca Balsamico; Egotussano†; Expec; Expectobron†; Frenotosse; Fungolab; Gotas Nican†; Iodesin; Iodeto de Potassio†; Iodopulmin†; Iol†; Ipecol†; Kl-Expectorante; Limao Bravo†; Micotiazol; Micotox†; Micoz†; Peitoral Angico Pelotense†; Penetro; Po Antisseptico; Pulmoforte†; Pulmoverina†; Rhum Creosotado; Tiratosse†; Toplexil; Tossanil†; Tussodina†; Tussol†; Tussucalman†; Xarope de Caraguata†; Xarope Peitoral de Ameixa Composto†; Xarope Sao Joao†; Xpe SPC†; ***Canad.:*** Bronco Asmol; MRX†; Plax; ***Chile:*** Broncodeina; Caristop; Gotas Nican†; Gruben; Listerine; Pectoral Pasteur; Pectoserum†; Pulmagol; Summer's Eve Hierbas†; Summer's Eve Vinagre y Agua†; ***Denm.:*** Pectyl; ***Fr.:*** Broncalene; Broncalene Nourisson; Codotussyl Maux de Gorge; Dermacide; Dimetane Expectorant Enfant†; Dinacode avec codeine†; Dinacode†; Ephydion; Fluocaril blancheur; Germose†; Listerine; Neo-Codion; Ozothine; Paregorique; Passedyl; Pulmofluide Simple; Quintopan†; Rhinamide; Silomat†; ***Ger.:*** Sagrosept†; ***Hong Kong:*** Fungifax†; Gly Thymol; Listerine; Listerine Tartar Control; Listerine Teeth and Gum Defence; ***Hung.:*** Glycosept; ***India:*** Keralin; Mycoderm; Pragmatar; Zoderm; ***Indon.:*** Kalpanax; Kopamex; Listerine Coolmint; Mikorex; Sapona; ***Israel:*** Oxacatin; Pertussol; Phytoderm Compositum; Pitrisan; Shiulon; Spirit Whitfield; Toplexil; Tussophedrine New Formula; ***Ital.:*** Borocaina; Dentinale; Neo Borocillina; Paracodina; Sedocalcio; Tiocosol; Tionamil†; ***Malaysia:*** Nixoderm; ***Mex.:*** Pulmovital; ***NZ:*** Egomycol†; Listerine; Listerine Tartar Control; ***Philipp.:*** Dermalin; Listerine Coolmint; Listerine Freshburst; Listerine Original; Listerine Teeth & Gum Defense; United Home Whitfield's Ointment; ***Port.:*** Broncodiazina; Bronquiasmol†; Calmarum†; Codol; Drenoflux; Micaveen; ***Rus.:*** Neo-Codion Babies (Нео-Кодион Для Младенцев); ***S.Afr.:*** Aserbine; Dry & Clear Medicated Skin Cleanser; ***Singapore:*** Listerine; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; Whitfield†; ***Spain:*** Acerbiol; Broncoformo Muco Dexa; Broncovital†; Bronquidiazina CR; Bronquimar; Etermol Antitusivo; Neumopectolina†; Pastillas Pectoral Kely; Pazbronquial; Pulmo Menal†; Pulmofasa; Tos Mai; ***Switz.:*** Acerbine†; Dinacode N†; Foral†; Gem; Nasobol†; Neo-DP†; Nican; Onguent aux herbes Keller; Phol-Tussil; Phol-Tux; Saintbois; Toplexil; ***Turk.:*** Artu; Gayabeksin; Latusin; Nesgarin; ***UK:*** Aserbine†; Eczema Ointment; Hemocane; Potters Gees Linctus; Sanderson's Throat Specific; Toepedo; ***USA:*** Ammonul; Atrosept; Bensal HP; Cystex; Dolsed†; MHP-A; Prosed/DS; Trac Tabs 2X†; UAA; Ucephan; Uridon Modified†; Urised; Uriseptic; Uritact; ***Venez.:*** Acetoben; Amodion; Boramint†; Corsaben†; Dromil Sauco; Fedratal†; Isacol†; Kantol†; Metilfedrin†; Niosilin; Photoderm AKN; Pi-Fedrin; Tabonuco; Yerba Santa; Yodalmina†.

Benzododecinium Bromide

Benzododecinio, bromuro de. Benzyldodecyldimethylammonium bromide.

$C_{21}H_{38}BrN$ = 384.4.
CAS — 10328-35-5 (benzododecinium); 7281-04-1 (benzododecinium bromide).
ATC — D09AA05.
ATC Vet — QD09AA05.

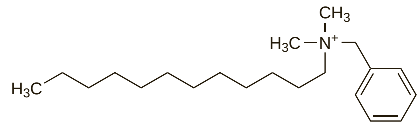

(benzododecinium)

Pharmacopoeias. In *Fr.*

Benzododecinium Chloride *(rINN)*

Benzododecinii Chloridum; Benzododécinium, Chlorure de; Cloruro de benzododecinio; Lauralkonium Chloride. Benzyldodecyldimethylammonium chloride.

Бензододециния Хлорид
$C_{21}H_{38}ClN$ = 340.0.
CAS — 139-07-1.
ATC — D09AA05.
ATC Vet — QD09AA05.

NOTE. The name Lauralkonium Chloride is also a *rINN* for another quaternary ammonium compound ($C_{29}H_{44}ClNO_2$; CAS – 19486-61-4).

Profile

Benzododecinium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in mouthwashes, eye preparations, and nasal sprays and solutions for the treatment of minor infections. It has also been used as a spermicide. Benzododecinium chloride has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ajatin; ***Fr.:*** Rhinedrine.

Multi-ingredient: ***Cz.:*** Ophtal; ***Fr.:*** Prorhinel; Sedacollyre; ***Switz.:*** Kemerhinose; Prorhinel.

Benzoxiquine *(USAN, rINN)*

Benzoxiquina; Benzoxiquinum; NSC-3951. 8-Quinolinol benzoate (ester).

Бензоксихин
$C_{16}H_{11}NO_2$ = 249.3.
CAS — 86-75-9.

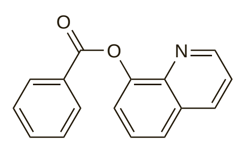

Profile

Benzoxiquine is an antiseptic that has been included in cosmetic products and multi-ingredient preparations used topically for the treatment of fungal infections. The salicylate has also been used.

Benzoxonium Chloride *(rINN)*

Benzoxonii Chloridum; Benzoxonium, Chlorure de; Cloruro de benzoxonio. Benzyldodecylbis(2-hydroxyethyl)ammonium chloride.

Бензоксония Хлорид
$C_{23}H_{42}ClNO_2$ = 400.0.
CAS — 19379-90-9.
ATC — A01AB14; D08AJ05.
ATC Vet — QA01AB14; QD08AJ05.

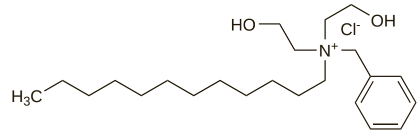

Profile

Benzoxonium chloride is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also used for instrument disinfection. Allergic contact dermatitis from benzoxonium chloride has been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Orofar; ***Chile:*** Bialcol; ***Gr.:*** Orocil; ***Ital.:*** Bactofen; Bialcol.

Multi-ingredient: ***Belg.:*** Orofar Lidocaine; ***Chile:*** Alcolex; ***Cz.:*** Orofar; ***Ger.:*** Loscon†; ***Gr.:*** Orocil Lido; ***Hung.:*** Mebucain; Vita-Merfen†; ***Israel:*** Merfen; Vita-Merfen NF; ***Philipp.:*** Orofar-L; ***Pol.:*** Orofar; ***Port.:*** Orofar†; ***Rus.:*** Theraflu Lar (Терафлю Лар); ***Switz.:*** Mebucalets f; Merfen; Orofar; Vita-Merfen.

Benzyl Alcohol *(rINN)*

Alcohol bencílico; Alcohol benzylicus; Alcoholum Benzylicum; Alcool Benzylique; Alkohol benzylowy; Bensylalkohol; Bentsyylialkoholi; Benzenemethanol; Benzil-alkohol; Benzilo alkoholis; Benzylalkohol; Benzylique, alcool; Fenilmetanol; Phenylcarbinol; Phenylmethanol.

Бензиловый Спирт
$C_6H_5.CH_2OH$ = 108.1.
CAS — 100-51-6.

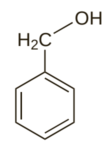

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Benzyl Alcohol). A clear colourless, oily liquid. Soluble in water; miscible with alcohol, and with fatty and essential oils. Store under nitrogen in airtight containers at a temperature of 2° to 8°. Protect from light.

USNF 26 (Benzyl Alcohol). A clear, colourless, oily liquid. Sparingly soluble in water; freely soluble in alcohol (50%); miscible with alcohol, with chloroform, and with ether. It is neutral to litmus.

Incompatibility. Benzyl alcohol is incompatible with oxidising agents and strong acids. The antimicrobial activity may be reduced by nonionic surfactants and benzyl alcohol may be lost from solutions stored in polyethylene containers.

Stability. Benzyl alcohol oxidises to produce benzaldehyde and benzoic acid and oxidation may take place slowly on exposure to air. Benzaldehyde may also be produced on autoclaving.

Adverse Effects and Precautions

There have been a few reports of hypersensitivity reactions to benzyl alcohol when used as a preservative.

The pure alcohol is irritant and requires handling with care; ingestion or inhalation can cause nausea, vomiting, diarrhoea, headache, and vertigo. Overexposure results in respiratory failure and CNS depression. However, concentrations of benzyl alcohol normally used for preservation are not associated with such effects.

There have been some instances of neurotoxic effects in patients given intrathecal injections that contained benzyl alcohol.

A fatal toxic syndrome in premature infants was attributed to benzyl alcohol present as a preservative in solutions used to flush intravenous catheters. This has led to restriction on the use of benzyl alcohol in neonates and young children, (see below).

Effects on the lungs. Severe bronchitis and haemoptysis was reported in a patient with obstructive pulmonary disease who, over a period of 2 years, had inhaled salbutamol nebuliser solution diluted with a bacteriostatic sodium chloride solution containing benzyl alcohol.[1]

1. Reynolds RD. Nebulizer bronchitis induced by bacteriostatic saline. *JAMA* 1990; **264:** 35.

Effects on the nervous system. Rapid development of flaccid areflexic paraplegia, total anaesthesia below the groin, and radicular abdominal pain occurred in a 64-year-old man after a lumbar intrathecal injection of cytarabine that contained 1.5% benzyl alcohol.[1] The patient recovered fully after 100 mL of CSF was replaced with sodium chloride 0.9% and 40 mg of methylprednisolone. Intrathecal injections of cytarabine dissolved in sterile distilled water before and after the episode of paraplegia caused no neurologic symptoms. On reviewing 20 other cases of paraparesis associated with methotrexate or cytarabine intrathecal injections, benzyl alcohol had been used as a preservative in

7. Of these, 4 developed neurotoxicity immediately; in the other 3 it did not develop for between 6 and 48 hours. The duration varied. One patient did not improve, one made a partial recovery, a third took 6 weeks to recover, another took 5 days; yet 2 patients recovered within 1 ⁄ to 2 ⁄ hours while the final patient experienced only transient effects.

1. Hahn AF, *et al.* Paraparesis following intrathecal chemotherapy. *Neurology* 1983; **33:** 1032–8.

Hypersensitivity. Hypersensitivity reactions to benzyl alcohol have been reported.[1-3]

1. Grant JA, *et al.* Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med* 1982; **306:** 108.
2. Shmunes E. Allergic dermatitis to benzyl alcohol in an injectable solution. *Arch Dermatol* 1984; **120:** 1200–1.
3. Wilson JP, *et al.* Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm* 1986; **20:** 689–91.

Neonates. During 1981 and 1982 reports were published from 2 centres in the USA[1-3] of 20 deaths in low-birth-weight neonates attributed to the use of benzyl alcohol as a preservative in solutions used to flush their umbilical catheters and in some cases also to dilute their medication. The neonates suffered a toxic syndrome whose features included metabolic acidosis, symptoms of progressive encephalopathy, intracranial haemorrhage, and respiratory depression with gasping.

These deaths prompted the FDA[4] to recommend that benzyl alcohol should not be used in such flushing solutions; sodium chloride injection 0.9% without preservative should be used instead. The FDA had also advised against the use of benzyl alcohol or any preservative in fluids being used for the dilution or reconstitution of medicines for the newborn.

Those reporting the deaths[2,3] considered that the toxic syndrome could have been caused by the accumulation of the benzoic acid metabolite of benzyl alcohol, which could not be handled effectively by the immature liver; given the very low weight of the neonates they would have been receiving a comparatively high dose of benzyl alcohol. In commenting on the problem, the American Academy of Pediatrics[5] agreed that the FDA's warning was warranted, but pointed out that there was no evidence from controlled studies to confirm that benzyl alcohol was responsible.

1. Gershanik JJ, *et al.* The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; **29:** 895A.
2. Brown WJ, *et al.* Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982; **i:** 1250.
3. Gershanik J, *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; **307:** 1384–8.
4. Anonymous. Benzyl alcohol may be toxic to newborns. *FDA Drug Bull* 1982; **12:** 10–11.
5. American Academy of Pediatrics. Benzyl alcohol: toxic agent in neonatal use. *Pediatrics* 1983; **72:** 356–7.

Pharmacokinetics

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

Uses

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%.

In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Babys Own Teething Gel†; Zilactin Cold Sore Gel; ***USA:*** Zilactin.

Multi-ingredient: ***Arg.:*** Standard XXI; ***Austral.:*** Coso; Soothe'n Heal; ***Austria:*** Dermaspray; ***Belg.:*** Dermaspray†; Purigel Crisp; Purigel NF; ***Chile:*** Aucusik; Medikem†; Medisept†; ***Denm.:*** Doloproct Comp; ***Fr.:*** Biseptine; Codotussyl Maux de Gorge; Dermaspraid Antiseptique; Pastilles Medicinales Vicks; ***Ger.:*** Autoderm Extra; Gelipur; Spitacid; ***India:*** Dicloran MS; ***Israel:*** Otomycin; ***Ital.:*** Borocaina; Foille Scottature; Foille Sole; Pitiren; Prurex; Skab 2; ***Singapore:*** Saak†; ***Spain:*** Acerbiol; Pastillas Antisep Garg M; ***UK:*** Sudocrem; ***USA:*** Itch-X; MouthKote O/R; Oragesic; Super Ivy Dry; Topic; Tucks.

Used as an adjunct in: ***Jpn:*** Panpurol†.

Biclotymol *(rINN)*

Biclotimol; Biclotymolum. 2,2′-Methylenebis(6-chlorothymole).

Биклотимол

$C_{21}H_{26}Cl_2O_2$ = 381.3.
CAS — 15686-33-6.

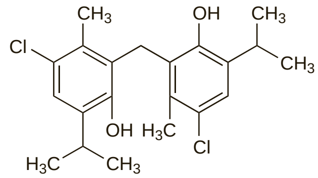

Profile

Biclotymol is a phenolic antiseptic that is used in lozenges and sprays for mouth and throat infections. It is also an ingredient of cough preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Hexaspray†; ***Fr.:*** Hexaspray; Humex; Rhinathiol maux de gorge†; Sagadreps†; Sagaspray; Solutricine Maux de Gorge; ***Hong Kong:*** Hexaspray; ***Port.:*** Hexaspray; ***Rus.:*** Hexaspray (Гексаспрей).

Multi-ingredient: ***Fr.:*** Hexalyse; Hexapneumine; Hexarhume; ***Hong Kong:*** Hexalyse; Hexapneumine; ***Rus.:*** Hexalyse (Гексализ).

Brilliant Green

CI Basic Green 1; Colour Index No. 42040; Diamond Green G; Emerald Green; Ethyl Green; Malachite Green G; Solid Green; Verde brillante; Viride Nitens. 4-(4-Diethylaminobenzhydrylidene)cyclohexa-2,5-dien-1-ylidenediethylammonium hydrogen sulphate.

$C_{27}H_{34}N_2O_4S$ = 482.6.
CAS — 633-03-4.

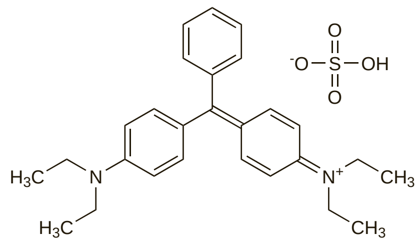

NOTE. The name Emerald Green has also been used for copper acetoarsenite.

Profile

Brilliant green is a triphenylmethane antiseptic dye with actions similar to those of methylrosanilinium chloride (p.1653). Its activity is greatly reduced in the presence of serum.

A gel containing brilliant green 0.5% with lactic acid was formerly used in the treatment of skin ulcers.

An alcoholic solution of brilliant green 0.5% and methylrosanilinium chloride 0.5% (Bonney's Blue) was formerly used for disinfecting the skin, but concern over evidence of *animal* carcinogenicity with methylrosanilinium chloride has led to a decline in its use. A solution of the two disinfectants has been used for marking incisions before surgery.

There have been occasional reports of sensitivity to brilliant green.

Adverse effects. For a report of necrotic skin reactions after application of a 1% solution of brilliant green to stripped skin, see under the Adverse Effects of Methylrosanilinium Chloride, p.1653.

Bromchlorophen

Bromchlorophene; Bromochlorophane; Bromoclorofeno. 2,2′-Methylenebis[6-bromo-4-chlorophenol].

$C_{13}H_8Br_2Cl_2O_2$ = 426.9.
CAS — 15435-29-7.

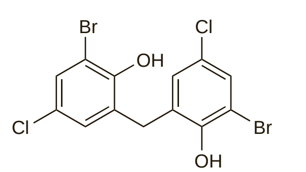

Profile

Bromchlorophen is a halogenated bisphenol antiseptic more active against Gram-positive than Gram-negative bacteria. It is used for disinfection of the hands and skin. It has also been used in deodorants and toothpastes.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Dibromol.

Bromsalans

Bromosalicilanilidas.
CAS — 55830-61-0.

Description. Bromsalans are a series of brominated salicylanilides that possess antimicrobial activity.

Dibromsalan *(USAN, pINN)*

Dibromsalán; Dibromsalanum; NSC-20527. 4′,5-Dibromosalicylanilide; 5-Bromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.

Дибромсалан

$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 87-12-7.

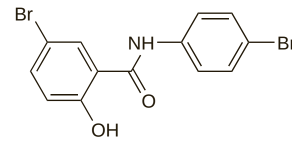

Metabromsalan *(USAN, pINN)*

Métabromsalan; Metabromsalán; Metabromsalanum; NSC-526280. 3,5-Dibromosalicylanilide; 3,5-Dibromo-2-hydroxy-*N*-phenylbenzamide.

Метабромсалан

$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 2577-72-2.

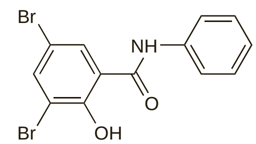

Tribromsalan *(BAN, USAN, rINN)*

ET-394; NSC-20526; TBS; Tribromsalán; Tribromsalanum. 3,4′,5-Tribromosalicylanilide; 3,5-Dibromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.

Трибромсалан

$C_{13}H_8Br_3NO_2$ = 449.9.
CAS — 87-10-5.

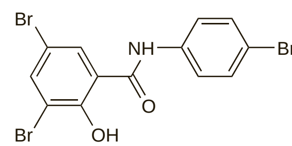

Profile

Bromsalans have antibacterial and antifungal activity and have been used in medicated soaps, but there have been many reports of photosensitivity arising from this use.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bergamon Sapone.

Bronopol *(BAN, rINN)*

Bronopolum. 2-Bromo-2-nitropropane-1,3-diol.

Бронопол

$C_3H_6BrNO_4$ = 200.0.
CAS — 52-51-7.
ATC Vet — QD01AE91.

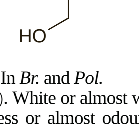

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Bronopol). White or almost white crystals or crystalline powder, odourless or almost odourless. Freely soluble in water and in alcohol; slightly soluble in glycerol and in liquid paraffin. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Incompatibility. The activity of bronopol can be reduced by sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride, and compounds with a thiol group. Incompatibility with unprotected aluminium affects packaging.

Stability. The stability of bronopol is affected by increases in temperature and by increases in pH above 8.

Creams and shampoos containing bronopol 0.01% as a preservative were found to contain free nitrite and, as a result of amines present in the preparations, nitrosamines.[1] It was recommended that nitrosamine formation could be reduced in preparations containing amines and bronopol by limiting the bronopol concentration to 0.01% and inclusion of alpha tocopherol 0.2% or butylated hydroxytoluene 0.05%.

1. Dunnett PC, Telling GM. Study of the fate of bronopol and the effects of antioxidants on N-nitrosamine formation in shampoos and skin creams. *Int J Cosmet Sci* 1984; **6:** 241–7.

Adverse Effects

Bronopol may be irritant when applied topically and cases of contact dermatitis have been reported.

Pharmacokinetics

Bronopol is absorbed following topical use.

Uses

Bronopol is active against a wide range of bacteria, including *Pseudomonas aeruginosa*, but is less active against moulds and yeasts. Bronopol is used as a preservative in shampoos, cosmetics, and both topical and oral pharmaceutical preparations; concentrations in pharmaceutical preparations range from 0.01 to 0.1%, with the usual concentration being 0.02%. It is also used for its antimicrobial properties in various industrial applications, including in air conditioning systems.

Butylated Hydroxyanisole *(BAN)*

BHA; Butilhidroksianizolas; Butilhidroxianisol; Butil-hidroxianizol; Butilidrossianisolo; Butylhydroxianisol; Butylhydroxyanisol; Butylhydroxyanisole; Butylhydroxyanisolum; Butylohydroksyanizol; Butyylihydroksianisoli; E320. 2-*tert*-Butyl-4-methoxyphenol; 2-(1,1-dimethylethyl)-4-methoxyphenol.

$C_{11}H_{16}O_2$ = 180.2.

CAS — 25013-16-5.

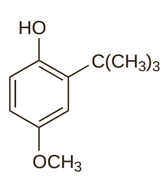

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Butylhydroxyanisole; Butylated Hydroxyanisole BP 2008). A white, yellowish, or slightly pinkish, crystalline powder. It contains not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol. Practically insoluble in water; freely soluble in alcohol and in fatty oils; very soluble in dichloromethane; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Butylated Hydroxyanisole). A white, or slightly yellow, waxy solid with a faint characteristic odour. Insoluble in water; soluble 1 in 4 of alcohol, 1 in 2 of chloroform, and 1 in 1.2 of ether; freely soluble in propylene glycol.

Incompatibility. Butylated hydroxyanisole is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Adverse Effects

Butylated hydroxyanisole can be irritant to the eyes, skin, and mucous membranes and can cause depigmentation. There are also reports of contact urticaria.

Carcinogenicity. There has been concern as to whether butylated hydroxyanisole may be a carcinogen.[1,2] These concerns stem from a study in which *rodents* given food containing 1 to 2% butylated hydroxyanisole developed squamous cell carcinoma of the forestomach. No similar malignancies were found in studies with *animals* that do not have a forestomach. The International Agency for Research on Cancer has concluded[2] that there is sufficient evidence for the carcinogenicity of butylated hydroxyanisole in *animals* but that there is no data on its carcinogenicity in humans.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 27/08/08)
2. IARC/WHO. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 40* 1986. Available at: http://monographs.iarc.fr/ENG/Monographs/vol40/volume40.pdf (accessed 23/05/06)

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed, see under Adverse Effects in Alkyl Gallates (p.1628).

Pharmacokinetics

Butylated hydroxyanisole is absorbed from the gastrointestinal tract, then metabolised and conjugated, and excreted in the urine; less than 1% is excreted in the urine as unchanged drug within 24 hours of ingestion.

Uses

Butylated hydroxyanisole is an antoxidant with some antimicrobial activity. It is used as a preservative in cosmetics and foods as well as pharmaceutical preparations, particularly to delay or prevent oxidative rancidity of fats and oils in concentrations of up to 0.02%; higher concentrations have been used for essential oils. It is also used to prevent the loss of activity of oil-soluble vitamins. To improve efficacy, butylated hydroxyanisole is frequently used with other antoxidants such as butylated hydroxytoluene or an alkyl gallate and with sequestrants or synergists such as citric acid.

Commercial supplies of butylated hydroxyanisole used in food technology consist of mixtures of the 2-*tert* and 3-*tert* isomers.

Use in food. In the UK the Food Advisory Committee has recommended that the use of butylated hydroxyanisole and butylated hydroxytoluene should no longer be permitted as additives for infant formulas as they are no longer required for the economic manufacture of vitamin A and vitamin A esters.[1]

1. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. *FdAC/REP/12.* London: HMSO, 1992.

Butylated Hydroxytoluene *(BAN)*

BHT; Butilhidroksitoluenas; Butilhidroxitolueno; Butil-hidroxitoluol; Butylhydroxitoluen; Butylhydroxitoluenum; Butylhydroxytoluen; Butylhydroxytoluène; Butylhydroxytoluene; Butylhydroxytoluenum; Butylohydroksytoluen; Butyylihydroksitolueeni; E321. 2,6-Di-*tert*-butyl-*p*-cresol.

$C_{15}H_{24}O$ = 220.4.

CAS — 128-37-0.

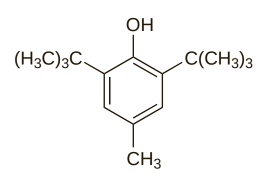

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Butylhydroxytoluene; Butylated Hydroxytoluene BP 2008). A white or yellowish-white, crystalline powder. F.p. 69° to 70°. Practically insoluble in water; freely soluble in alcohol and in vegetable oils; very soluble in acetone.

USNF 26 (Butylated Hydroxytoluene). A white crystalline solid with a faint characteristic odour. Insoluble in water and in propylene glycol; soluble 1 in 4 of alcohol and 1 in 1.1 of chloroform and of ether.

Incompatibility. Butylated hydroxytoluene is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Adverse Effects

As for Butylated Hydroxyanisole, p.1633.

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula, see under Adverse Effects in Alkyl Gallates, p.1628.

Poisoning. A 22-year-old woman experienced severe epigastric cramping, nausea and vomiting, and generalised weakness, followed by dizziness, confusion, and a brief loss of consciousness after ingesting 4 g of butylated hydroxytoluene. She recovered after conservative treatment, which was given 2 days later. The antoxidant had been taken as an unauthorised remedy for genital herpes simplex.[1]

1. Shlian DM, Goldstone J. Toxicity of butylated hydroxytoluene. *N Engl J Med* 1986; **314:** 648–9.

Pharmacokinetics

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract. It is excreted in the urine mainly as glucuronide conjugates of oxidation products.

Uses

Butylated hydroxytoluene is an antoxidant with uses similar to those of Butylated Hydroxyanisole, p.1633.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Proseptine-Plus.

Multi-ingredient: *Fr.:* Cinq sur Cinq.

Cadexomer-Iodine *(BAN)*

Cadexomer Iodine *(USAN)*; Cadexomerjod; Cadexómero yodado; Cadexomerum Iodum; Kadeksomeerijodi. 2-Hydroxymethylene cross-linked (1→4)-α-D-glucan carboxymethyl ether containing iodine.

CAS — 94820-09-4.
ATC — D03AX01.
ATC Vet — QD03AX01.

Adverse Effects and Precautions

As for Povidone-Iodine, p.1659. Some patients have experienced stinging and erythema on application of cadexomer-iodine to their ulcers. Free iodine is released during exposure of cadexomer-iodine preparations to wound exudate and absorption of iodine may occur. Prolonged treatment with cadexomer-iodine should be given with caution in patients with thyroid disorders.

Uses and Administration

Cadexomer-iodine, like povidone-iodine (p.1659), is an iodophore that releases iodine. It is used for its absorbent and antiseptic properties in the management of venous leg ulcers and pressure sores. It is applied as a powder, ointment, or paste containing iodine 0.9%; sufficient powder or ointment should be applied to form a layer about 3 mm thick. Treatment should not usually be continued for more than 3 months.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Iodosorb†; ***Austria:*** Iodosorb; ***Canad.:*** Iodosorb; ***Denm.:*** Iodosorb; ***Fin.:*** Iodosorb; ***Fr.:*** Iodosorb†; ***Ger.:*** Iodosorb†; ***Gr.:*** Iodosorb; ***Irl.:*** Iodoflex; ***Ital.:*** Iodosorb; ***Neth.:*** Iodosorb; ***Singapore:*** Iodoflex; Iodosorb; ***Spain:*** Iodosorb†; ***Swed.:*** Iodosorb; ***Switz.:*** Iodosorb; ***UK:*** Iodoflex; Iodosorb.

Calcium Peroxide

Calcium Dioxide; E930.

Пероксид Кальция

CaO_2 = 72.08.

CAS — 1305-79-9;.

Profile

The action of calcium peroxide is similar to that of hydrogen peroxide (p.1647). Calcium peroxide is used in dental products for tooth whitening. It is also used as a flour bleaching and improving agent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Arg.:* Hexiben.

Carbaethopendecinium Bromide

Carbethopendecinii Bromidum; Carbethoxypentadecyltrimethylammonium Bromide; Karbethopendecinium bromid. 1-Ethoxy-*N,N,N*-trimethyl-1-oxo-2-hexadecanaminium bromide.

$C_{21}H_{44}NO_2Br$ = 422.5.

CAS — 10567-02-9.

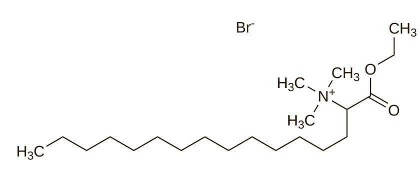

Profile

Carbaethopendecinium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in topical preparations for disinfection of skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mukoseptonex; Ophthalmo-Septonex; Septonex.

Multi-ingredient: *Cz.:* Mesocain; Mukoseptonex E; N-Septonex†; Ophthalmo-Septonex; Paradentol†; Septonex; Septonex Plus; Triamcinolon-Ivax.

Cetalkonium Chloride *(BAN, USAN, rINN)*

Cetalkonii Chloridum; Cétalkonium, Chlorure de; Cloruro de cetalconio; NSC-32942. Benzylhexadecyldimethylammonium chloride.

Цеталкония Хлорид

$C_{25}H_{46}ClN$ = 396.1.

CAS — 122-18-9.

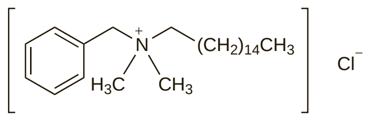

Profile

Cetalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in a variety of topical preparations in the treatment of minor infections of the mouth and throat. It has also been used in the treatment of eye infections. Cetalkonium bromide has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Pansoral; ***Austral.:*** Bonjela; ***Austria:*** Mundisal; ***Braz.:*** Pondicilina; ***Canad.:*** Bionet; ***Cz.:*** Mundisal; ***Fr.:*** Pansoral; ***Ger.:*** Mundisal†; ***Gr.:*** Mundisal; ***Hong Kong:*** Bonjela; ***Hung.:*** Mundisal; ***Irl.:*** Bonjela; ***Israel:*** Baby Gum; Bonjela; ***Malaysia:*** Bonjela; ***NZ:*** Bonjela; ***Pol.:*** Sachol zel Stomatologiczny; ***Rus.:*** Cholisal (Холисал); Pansoral (Пансорал); ***S.Afr.:*** AAA†; Bonjela; ***Singapore:*** Bonjela; ***Switz.:*** Mundisal; Pansoral; Tenderdol; ***Thai.:*** Bonjela; ***UK:*** Bonjela; Bonjela Teething Gel; ***USA:*** Babee.

Cethexonium Bromide

Cetexonio, bromuro de. Hexadecyl(2-hydroxycyclohexyl)dimethylammonium bromide.

$C_{24}H_{50}BrNO$ = 448.6.

CAS — 6810-42-0 (cethexonium); 1794-74-7 (cethexonium bromide); 58703-78-9 (cethexonium chloride).

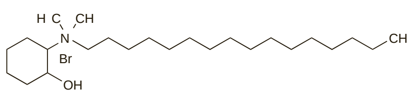

NOTE. Cethexonium Chloride is *rINN*.

Profile

Cethexonium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in preparations for the local treatment of minor infections of the eye, nose, and throat.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Biocidan.

Multi-ingredient: ***Fr.:*** Biocidan.

Cetrimide *(BAN, rINN)*

Cetrimid; Cetrimida; Cetrimidas; Cétrimide; Cetrimidum; Cetrymid; Setrimid; Setrimidi.

Цетримид

CAS — 1119-97-7 (trimethyltetradecylammonium bromide); 1119-94-4 (dodecyltrimethylammonium bromide); 8044-71-1 (cetrimide).

ATC — D08AJ04; D11AC01.

ATC Vet — QD08AJ04; QD11AC01.

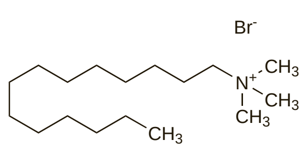

(trimethyltetradecylammonium bromide)

NOTE. The name cetrimonium bromide was often formerly used for cetrimide. Cetrimonium bromide (see below) is hexadecyltrimethylammonium bromide.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Br. also includes strong cetrimide solution.

Ph. Eur. 6.2 (Cetrimide). It consists of trimethyltetradecylammonium bromide (=tetradonium bromide (*rINN*)) and may contain smaller amounts of dodecyltrimethylammonium bromide and hexadecyltrimethylammonium bromide (=cetrimonium bromide, p.1635). A white or almost white, voluminous, free-flowing powder. Freely soluble in water and in alcohol. A 2.0% solution in water froths copiously when shaken.

BP 2008 (Strong Cetrimide Solution). It is an aqueous solution of cetrimide. It contains 20 to 40% w/v of cetrimide, calculated as $C_{17}H_{38}BrN$ and up to 10% alcohol or isopropyl alcohol, or both; alcohol may be replaced by industrial methylated spirit. It may be perfumed and may contain colouring matter. Store at a temperature above 15°.

Incompatibility. Cetrimide is incompatible with soaps and other anionic surfactants, bentonite, iodine, phenylmercuric nitrate, and alkali hydroxides. Aqueous solutions react with metals.

Adverse Effects and Treatment

At the concentrations used on the skin, solutions of cetrimide and other quaternary compounds do not generally cause irritation, but some patients become hypersensitive to cetrimide after repeated applications. Cetrimide powder is reported to be irritant. There have been rare reports of burns with concentrated solutions of cetrimide.

If ingested, cetrimide and other quaternary ammonium compounds cause nausea and vomiting; strong solutions may cause oesophageal damage and necrosis. They have depolarising muscle relaxant properties and toxic symptoms include dyspnoea and cyanosis due to paralysis of the respiratory muscles, possibly leading to asphyxia. CNS depression (sometimes preceded by excitement and convulsions), hypotension, coma, and death may also occur. Accidental intra-uterine or intravenous administration may cause haemolysis and pulmonary embolism.

Treatment of poisoning is symptomatic; demulcents and diluents may be given if necessary but emesis and lavage should be avoided, particularly if concentrated solutions have been ingested. Activated charcoal may be considered if the patient presents within an hour of ingestion. CNS stimulants and cholinesterase inhibitors are reported not to reverse paralysis due to cetrimide intoxication although sympathomimetics have been tried. Corticosteroids may reduce oropharyngeal oedema.

Effects after cyst irrigation. Adverse effects after irrigation with cetrimide solutions in the treatment of hydatid cysts have included chemical peritonitis,[1] methaemoglobinaemia with cyanosis,[2] and metabolic acidosis.[3]

1. Gilchrist DS. Chemical peritonitis after cetrimide washout in hydatid-cyst surgery. *Lancet* 1979; **ii:** 1374.
2. Baraka A, *et al.* Cetrimide-induced methaemoglobinaemia after surgical excision of hydatid cyst. *Lancet* 1980; **ii:** 88–9.
3. Momblano P, *et al.* Metabolic acidosis induced by cetrimonium bromide. *Lancet* 1984; **ii:** 1045.

Poisoning. The fatal dose of quaternary ammonium compounds was estimated to be 1 to 3 g.[1]

1. Arena JM. Poisonings and other health hazards associated with use of detergents. *JAMA* 1964; **190:** 56–8.

Precautions

Prolonged and repeated applications of cetrimide to the skin are inadvisable as hypersensitivity may occur. Contact with the eyes, brain, meninges, and middle ear should be avoided. Cetrimide is for external use only and should not be used in body cavities or as an enema.

Quaternary ammonium compounds are not reliable for sterilising surgical instruments and heat-labile articles. The antimicrobial activity of quaternary ammonium compounds may be reduced through absorption, or through combination with organic matter, or by reducing pH.

Solutions of quaternary ammonium compounds should not be used for disinfection of soft contact lenses.

Aqueous solutions of cetrimide or other quaternary ammonium disinfectants may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Handling. Cetrimide powder is irritant; it has been recommended that the nose and mouth should be protected by a mask when working with the powder[1] and eyes should be protected by goggles.

1. Jacobs JY. Work hazards from drug handling. *Pharm J* 1984; **233:** 195–6.

Uses and Administration

Cetrimide is a quaternary ammonium antiseptic with actions and uses typical of cationic surfactants. These surfactants dissociate in aqueous solution into a relatively large and complex cation that is responsible for the surface activity and a smaller inactive anion. In addition to emulsifying and detergent properties, quaternary ammonium compounds have bactericidal activity against Gram-positive and, at a higher concentration, against some Gram-negative bacteria. Some *Pseudomonas* spp. are particularly resistant as are strains of *Mycobacterium tuberculosis*. They are ineffective against bacterial spores, have variable antifungal activity, and are effective against some viruses.

Quaternary ammonium compounds are most effective in neutral or slightly alkaline solution and their bactericidal activity is appreciably reduced in acid media; their activity is enhanced by alcohols.

Like other quaternary ammonium compounds, notably benzalkonium chloride (p.1629), cetrimide has been employed for cleansing skin, wounds (but see under Wound Disinfection, p.1624), and burns. For these purposes it has been used as a 0.1 to 1.0% aqueous solution, generally prepared by dilution of a more concentrated solution, or as a cream or spray containing 0.5%. However, a mixture of cetrimide with chlorhexidine (p.1635) has often been preferred to cetrimide alone. This combination is also used in a lotion for acne (p.1577).

Solutions containing up to 10% of cetrimide have been used as shampoos to remove the scales in seborrhoeic dermatitis (p.1584).

Cetrimide solution 0.5 or 1% has been used as a scolicide to irrigate hydatid cysts during surgery (see Echinococcosis, p.136) but systemic adverse effects have been reported (see above).

Cetrimide and benzalkonium chloride are also used as preservatives in cosmetics and pharmaceutical formulations including eye drops and in disinfecting solutions for hard contact lenses; neither compound should be used for disinfection of soft contact lenses.

Cetrimide is also present in some emulsifying preparations such as Cetrimide Emulsifying Ointment (BP 2008).

Preparations

BP 2008: Cetrimide Cream; Cetrimide Emulsifying Ointment; Cetrimide Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Boucren; Sorbicet; ***Fr.:*** Cetavlon; Sterilene; ***Gr.:*** Cetavlon; ***Irl.:*** Cetavlex†; Vesagex; ***Malaysia:*** Cetavlex†; Dermoplex Antiseptic; ***Port.:*** Cetavlex; ***Singapore:*** Acnederm Wash; ***Spain:*** Cetavlon†; ***Turk.:*** Cetyl; ***UK:*** Bansor†; Cetavlex; Medi-Prep; Medicaid; Richmond Antiseptic Cream; Vesagex.

Multi-ingredient: ***Arg.:*** Cerosporin GS†; Jabonacid; Otidrops; Otocalmia Biotic; Sincerum; ***Austral.:*** Acnederm Foaming Wash; Curacleanse†; Dimethicream; Hamilton Pine Tar with Menthol; Hamilton Skin Repair†; Medi Creme; Microshield Antiseptic; Pro-PS†; Savlon Antiseptic; Soov Bite; Soov Burn; Soov Cream; ***Austria:*** Lemocin; Xylonor; ***Belg.:*** Lemocin; ***Braz.:*** Cetrilan; ***Canad.:*** Savlodil; ***Cz.:*** Hibicet Hospital Concentrate†; ***Fr.:*** Broncorinol rhinites†; Lysocalmspray; Rectoquotane; ***Gr.:*** Hibicet; ***Hong Kong:*** Acnederm Wash; B-Gel; Borraginol-N; Drapolene†; Hamilton Skin Repair; Hibicet Hospital Concentrate†; Medicreme; Soov Bite; Soov Cream; Tri-Gel; Zinsomine; ***India:*** Iteol-3; Scabine; Scarab; Siloderm; ***Indon.:*** Benzomid; Bioacne; Borraginol-N; Borraginol-S; Neo Resiguard; Pravlon; ***Irl.:*** Ceanel†; Drapolene; Hibicet; RBC; Savlon; Siopel†; Torbetol; ***Israel:*** Cetrin; Savior; Septacare†; Tisept; Travasept; ***Ital.:*** Baxidin; Cetrexidin; Cetrisan; Clotramid†; Cuprosodio; Farvicett; Hibizene; Lidocaina Spray; Panseptil; Steridol†; ***Malaysia:*** Acnederm Foaming Wash; Burnol Plus; Drapolene; Hibicet†; Soov Bite; ***Neth.:*** Hibicet concentraat; Hibicet verdunning; ***NZ:*** Acnederm Foaming Wash; Acnederm Wash†; Hairscience Conditioner†; Karicare Barrier Cream†; Medicreme; Savlon; Soov Bite; Soov Burn; Soov Cream; Soov Gel; ***Philipp.:*** Drapolene; ***Rus.:*** Drapolene (Драполен); ***S.Afr.:*** Benzet†; Germolene; Hibicet†; Medituss†; Siopel; Trochain; Virobis†; ***Singapore:*** Burnol Plus; Drapolene; Napitol†; Savlon†; Soov Bite; Soov Cream; ***Switz.:*** Gem; ***Thai.:*** Bacard; Burnol Plus; Chlorhex-C; Dekka; Drapolene; Frebac; Hibicet†; Inhibac; Napilene; Sepdine†; Septone†; ***Turk.:*** Drapolene; Savlex; Savonol; Savrolin; Setilin; ***UK:*** Ceanel; Cetanorm; Cymex; Dermidex; Drapolene; Hibicet†; Lypsyl Cold Sore Gel; Neo Baby Cream; Quinoderm Antibacterial Face Wash; Savlon Antiseptic Cream; Savlon Antiseptic Liquid; Siopel; Steripod Chlorhexidine Gluconate with Cetrimide†; Tisept; Torbetol; Travasept; ***USA:*** Scadan.

Cetrimonium Bromide *(BAN, rINN)*

Bromuro de cetrimonio; Cetrimonii Bromidum; Cétrimonium, Bromure de; Cetylotrimetyloamoniowy bromek; Cetyltrimethylammonium Bromide; CTAB. Hexadecyltrimethylammonium bromide.

Цетримония Бромид

$C_{19}H_{42}BrN = 364.4.$

CAS — 6899-10-1 (cetrimonium); 57-09-0 (cetrimonium bromide).

ATC — D08AJ02; R02AA17.

ATC Vet — QD08AJ02; QR02AA17.

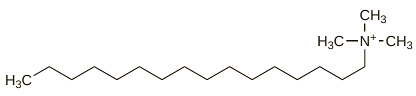

(cetrimonium)

NOTE. The name cetrimonium bromide was formerly applied to cetrimide (see above).

Pharmacopoeias. In *USNF.*

USNF 26 (Cetrimonium Bromide). A white to creamy white, voluminous, free-flowing powder, with a characteristic faint odour. Freely soluble in water and in alcohol; practically insoluble in ether.

Cetrimonium Chloride *(BAN)*

Cetrimonio, cloruro de. Hexadecyltrimethylammonium chloride.

$C_{19}H_{42}ClN = 320.0.$

CAS — 112-02-7.

Profile

Cetrimonium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). Cetrimonium chloride and cetrimonium tosilate are also used.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Tiracaspa†; ***Ital.:*** Golaval†; Senol; Sterilene; ***Switz.:*** Aknex Cleaning; Turisan.

Multi-ingredient: ***Arg.:*** Bagociletas sin Anestesia†; Bagoderm; Eryteal; Klorane Bebe Eryteal; Salvicutan†; ***Austria:*** Xylestesin; ***Belg.:*** Cetavlex; HAC; Hacdil-S; ***Braz.:*** Amigdalol; Drapolene; Leucocida†; ***Fr.:*** Eryteal†; Nostril; ***Ger.:*** Lemocin; Xylestesin Pumpspray†; ***Indon.:*** Lemocin; ***Israel:*** Lemocin; ***Ital.:*** Golamixin; Xylonor; ***Mex.:*** Dermatolona; ***Pol.:*** Cetriscabin; ***Spain:*** Diformiltricina; Hongosan; Xylonor; ***Switz.:*** Desitur†; Lemocin; Septivon N; Turexan Capilla; Xylestesin†; Xylonor; ***Venez.:*** Kertyol.

Cetylpyridinium Chloride *(BAN, rINN)*

Cetilpiridinio chloridas; Cetilpiridinium-klorid; Cetylpyridinii chloridum; Cetylpyridinii Chloridum Monohydricum; Cétylpyridinium, chlorure de; Cetylpyridinium-chlorid monohydrát; Cetylpyridiniumklorid; Cloruro de cetilpiridinio; Setilpiridinyum Klorür; Setyylipyridiniumkloridi. 1-Hexadecylpyridinium chloride monohydrate.

Цетилпиридиния Хлорид

$C_{21}H_{38}ClN,H_2O = 358.0.$

CAS — 7773-52-6 (cetylpyridinium); 123-03-5 (anhydrous cetylpyridinium chloride); 6004-24-6 (cetylpyridinium chloride, monohydrate).

ATC — B05CA01; D08AJ03; D09AA07; R02AA06.

ATC Vet — QB05CA01; QD08AJ03; QD09AA07; QR02AA06.

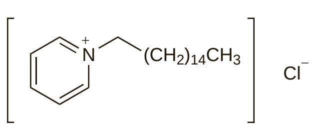

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cetylpyridinium Chloride). A white or almost white powder, slightly soapy to the touch. Soluble in water, frothing copiously when shaken; soluble in alcohol.

USP 31 (Cetylpyridinium Chloride). A white powder with a slight characteristic odour. Soluble 1 in 4.5 of water and of chloroform, and 1 in 2.5 of alcohol; slightly soluble in ether and in benzene.

Incompatibility. Cetylpyridinium chloride is incompatible with soaps and other anionic surfactants.

Profile

Cetylpyridinium chloride is a quaternary pyridinium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used chiefly as lozenges or solutions for the treatment of minor infections of the mouth and throat. It is also used topically for the treatment of skin and eye infections.

Cetylpyridinium bromide is used similarly for minor mouth and throat disorders.

Preparations

USP 31: Cetylpyridinium Chloride Lozenges; Cetylpyridinium Chloride Topical Solution.

Proprietary Preparations (details are given in Part 3)

Austral.: Cepacol Antibacterial; Cepacol Antiseptic Throat Lozenges; Cepacol Mint; Cepacol Regular; Lemsip Lozenges; ***Austria:*** Dobendan; Halset; ***Braz.:*** Gargocetil; Laringex; ***Canad.:*** Cepacol; Mouthwash†; Rince Bouche Antiseptique; Throat Lozenges; ***Chile:*** Freesept; ***Cz.:*** Halset; ***Fr.:*** Cetylyre†; Novoptine†; ***Ger.:*** Dobendan; Halstabletten akute; ***Hong Kong:*** Cepacol; Cetocomp; ***Hung.:*** Halset; ***Irl.:*** Merocets; ***Ital.:*** Bat; Borocaina Gola; Bronchenolo†; Cetilsan; Citromed Soap; Exil; Farin Gola; Golacetin; Golafair; Honeygola; Neo Cepacol Pastiglie; Neo Coricidin Gola†; Neo Formitrol; Periogard Plus; Ragaden; Stomygen; ***Mex.:*** Trociletas; ***Norw.:*** Pyrisept; ***NZ:*** Cepacol; Lemsip Throat Lozenges; ***Pol.:*** Halset; Menthosept; ***Port.:*** Septus; ***S.Afr.:*** Cepacol; Universal Throat Lollies; ***Singapore:*** Cepacol; ***Spain:*** Angifonil†; ***Thai.:*** Cepacol; Orasept; ***Turk.:*** Aseptol; Penipastil; ***UK:*** Listermint; Merocets; ***USA:*** Cepacol Mouthwash; Cepacol Throat; Choice DM Gentle Care; Scope; ***Venez.:*** Cepacol; Tablibut†.

Multi-ingredient: ***Arg.:*** Desenfriol Caramelos†; Ernex Duo; Oral-B Enjuague Bucal†; Periodil; Solumerin; ***Austral.:*** Cepacaine; Cepacol Anaesthetic; Cepacol Antibacterial; Cepacol Cough & Sore Throat; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Duro-Tuss Cough Lozenges; Gentlees; Seda-Gel†; ***Austria:*** Coldistan; Dentinox; Gurfix; Paididont; Tetesept; ***Braz.:*** Cepacaina; Cepacol Menta; Cetildrops†; Dentalivio†; Fenotricin†; Lima C; Limao Bravo com Vitamina C†; Limao Bravo†; Malvona†; Neopiridin; Pondicilina; Proplax†; Psiu; Sanilin; ***Canad.:*** Cepacol Extra Strength; Cepacol with Fluoride; Green Antiseptic Mouthwash & Gargle; Kank-A; Oral Plan†; Oral-B Anti-Bacterial with Fluoride; Throat Lozenges; ***Chile:*** Halita; Kank-Eze; Oralfresh Menta; Pancrit; Perio-Aid c Cloruro de Cetilpiridinio; Vitis Encias Colutorio; Vitis Encias Pasta; ***Cz.:*** Brand- und Wundgel†; Calgel; Neoseptolete; Panlid; Stas†; Tetesept Angidin†; ***Fin.:*** Bafucin; ***Fr.:*** Alodont; Broncorinol maux de gorge†; Lysopaine; Parogencyl prevention gencives; ***Ger.:*** Biogelt†; Brand- und Wund-Gel Eu Rho†; Broncho-Tyrosolvetten†; Dolo-Dobendan; Emmedical†; Frubienzym; Frubizin Forte†; Nordathricin N†; Trachiform†; Tyrosolvetten-C†; Tyrosolvetten†; Tyrosur; Wick Sulagil; ***Hong Kong:*** Dentinox Teething Gel; Difflam Anti-inflammatory Lozenges; Difflam Mouth Gel; Pharynx; Setronges†; ***Hung.:*** Mebucain; Tyrosur; ***Indon.:*** Sentril; ***Irl.:*** Anbesol; Merocaine; ***Israel:*** Cepadont; Kank-A; ***Ital.:*** Delta 80; Delta 80 Plus; Farmagola†; Ginvapast; Gola Action; Neo-Stomygen; Oral-B Collutorio per la Protezione di Denti e Gengive; Orosanyl†; Ridiodent; Rikospray; Stomygen; ***Malaysia:*** Cetylpyridinium B; Dentinox Teething Gel; Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Orregel; Pharynx; Setronges†; ***Mex.:*** Cepacaina; Mentalgina; Trociletas B; ***Neth.:*** Agre-Gola; ***Norw.:*** Aselli; ***NZ:*** Cepacaine; Cepacol Anaesthetic; Cepacol Cough Discs; Difflam Cough; Difflam Mouth Gel; Duro-Tuss Lozenges; ***Philipp.:*** Xylorinse; ***Pol.:*** Calgel; Lidodent; Septolete Plus; Tetesept; Undofen; ***Port.:*** Anbegele†; Biofluor Ortodoncia†; Biofluor Sensitive†; Dropcina; Mebocaina; ***Rus.:*** Calgel (Калгель); Septolete Plus (Септолете Плюс); ***S.Afr.:*** Anbesol; Andolex-C; Cepacaine; Cepacol; Cepacol Cough Discs; Cetoxol; Colphen; Endcol Lozenges; Medi-Kain†; Medi-Keel A; Prodol; Vagarsol; Vicks Acta Plus; Vicks Cough Syrup; ***Singapore:*** Dentinox Teething Gel; Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Mouth Gel; Duro-Tuss Cough Lozenges; Pharynx; Soragel; ***Spain:*** Alcohocel; Alcohol Cetil†; Alcohol Cetilpi Cuve†; Babysiton; Farmalcohol; Pastillas Antisep Garg L; Pastillas Antisep Garg M; Silidermil†; Vicks Formula 44†; ***Swed.:*** Bafucin; ***Switz.:*** Alodont†; Angina MCC; Anginazol; Desaquick forte†; Flavangin†; Hextriletten; Hextrimint; Lidazon; Mebucaine; Nasex†; Neo-Angin Lido; Otothricinol; Pharmacard Family Maux de gorge†; Wulnasin; ***Thai.:*** Sentril; Sore Mouth Gel; ***Turk.:*** Calgel; Nesgarin; ***UAE:*** B-Cool; New B-Cool; ***UK:*** Adult Meltus for Chesty Coughs & Catarrh; Allens Dry Tickly Cough; Anbesol; Calgel; Dentinox Teething Gel; Kilkof; Listermint with Fluoride; Macleans Mouthguard; Meltus Expectorant; Meltus Junior Expectorant; Merocaine; Merocets Plus; Rinstead; Rinstead Teething Gel†; Woodwards Teething Gel; ***USA:*** Cepacol Anesthetic; Cepacol Maximum Strength Sore Throat; Cepacol Regular Strength; Cylex; MouthKote O/R; MouthKote P/R†; Orajel Mouth Aid; ***Venez.:*** Borogin; Calgel†; Cepacol-BE; Isospray; Lafarcaina; Solunovar Compuesto.

Chlorhexidine *(BAN, rINN)*

Chlorhexidinum; Clorhexidina; Klooriheksidiini; Klorheksidin; Klorhexidin.

Хлоргексидин

CAS — 55-56-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

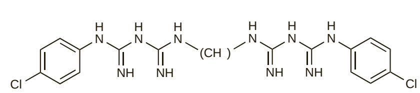

Chlorhexidine Acetate *(BANM, rINNM)*

Acetato de clorhexidina; Chlorheksidino diacetatas; Chlorhexidin-diacetát; Chlorhexidine, Acétate de; Chlorhexidine Diacetate; Chlorhexidine, diacétate de; Chlorhexidini Acetas; Chlorhexidini diacetas; Chloroheksydyny octan; Klooriheksidiinidiasetaatti; Klorhexidindiacetat; Klórhexidin-diacetát. 1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] diacetate.

Хлоргексидина Ацетат

$C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2 = 625.6.$

CAS — 56-95-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Int.*

Ph. Eur. 6.2 (Chlorhexidine Diacetate). A white or almost white, microcrystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycol.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, below.

Chlorhexidine Gluconate *(BANM, USAN, rINNM)*

Chlorheksidino digliukonato tirpalas; Chlorhexidin-diglukonát; Chlorhexidine Digluconate; Chlorhexidine, digluconate de; Chlorhexidine, Gluconate de; Chlorhexidini digluconas; Chlorhexidini Digluconatis Solutio; Chlorhexidini Gluconas; Chloroheksydyny diglukonianu roztwór; Gluconato de clorhexidina; Klooriheksidiinidiglukonaattiliuos; Klorheksidin Glukonat; Klorhexidindiglukonatlösning; Klórhexidin-diglükonát-oldat. 1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] digluconate.

Хлоргексидина Глюконат

$C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7 = 897.8.$

CAS — 18472-51-0.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

Pharmacopoeias. *Chin.*, *Eur.* (see p.vii), and *US* include a solution which contains 19 to 21% of chlorhexidine gluconate.

Ph. Eur. 6.2 (Chlorhexidine Digluconate Solution; Chlorhexidini Digluconatis Solutio; Chlorhexidine Gluconate Solution BP 2008). An aqueous solution which contains not less than 190 g/litre and not more than 210 g/litre of chlorhexidine gluconate. An almost colourless or pale-yellowish liquid. Miscible with water, with not more than 5 parts of alcohol, and with not more than 3 parts of acetone. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Protect from light.

USP 31 (Chlorhexidine Gluconate Solution). An aqueous solution which contains not less than 19% and not more than 21% of chlorhexidine gluconate. An almost colourless or pale yellow, clear liquid. Miscible with water and with glacial acetic acid; miscible with five times its volume of dehydrated alcohol and with three times its volume of acetone; further addition of dehydrated alcohol or of acetone yields a white turbidity. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, below.

Sterilisation. Dilutions of commercial concentrated solutions may be sterilised by autoclaving.

Chlorhexidine Hydrochloride *(BANM, USAN, rINNM)*

AY-5312; Chlorheksidino dihidrochloridas; Chlorhexidin-dihydrochlorid; Chlorhexidine, Chlorhydrate de; Chlorhexidine, dichlorhydrate de; Chlorhexidine Dihydrochloride; Chlorhexidini dihydrochloridum; Chlorhexidini Hydrochloridum; Hidrocloruro de clorhexidina; Klooriheksidiinidihydrokloridi; Klorheksidin Hidroklorür; Klórhexidin-dihidroklorid; Klorhexidindihydroklorid. 1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] dihydrochloride.

Хлоргексидина Гидрохлорид

$C_{22}H_{30}Cl_2N_{10},2HCl = 578.4.$

CAS — 3697-42-5.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.*

Ph. Eur. 6.2 (Chlorhexidine Dihydrochloride; Chlorhexidine Hydrochloride BP 2008). A white or almost white, crystalline powder. Sparingly soluble in water and in propylene glycol; very slightly soluble in alcohol.

Incompatibility. Chlorhexidine salts are incompatible with soaps and other anionic materials. Activity may be reduced in the presence of suspending agents such as alginates and tragacanth, insoluble powders such as kaolin, and insoluble compounds of calcium, magnesium, and zinc. Chlorhexidine acetate is incompatible with potassium iodide. At a concentration of 0.05%, chlorhexidine salts are incompatible with borates, bicarbonates, carbonates, chlorides, citrates, nitrates, phosphates, and sulfates, forming salts of low solubility which may precipitate out of solution. At dilutions of 0.01% or more, these salts are generally soluble. Insoluble salts may form in hard water. Chlorhexidine salts are inactivated by cork.

References to incompatibilities of chlorhexidine with suspending agents and insoluble solids.[1-3]

1. McCarthy TJ. The influence of insoluble powders on preservatives in solution. *J Mond Pharm* 1969; **12:** 321–8.
2. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
3. McCarthy TJ, Myburgh JA. The effect of tragacanth gel on preservative activity. *Pharm Weekbl* 1974; **109:** 265–8.

Stability. Chlorhexidine and its salts are stable at normal storage temperatures but when heated may decompose with the production of trace amounts of 4-chloroaniline. Chlorhexidine hydrochloride is less readily decomposed than chlorhexidine acetate and may be heated at 150° for 1 hour without appreciable production of 4-chloroaniline. Aqueous solutions of chlorhexidine salts decompose with the formation of trace amounts of 4-chloroaniline. This decomposition is increased by heating and alkaline pH.

Adverse Effects and Treatment

Skin sensitivity to chlorhexidine has occasionally been reported. Severe hypersensitivity reactions, including anaphylactic shock, have been reported rarely after topical use of chlorhexidine. Strong solutions may cause irritation of the conjunctiva and mucous membranes. The use of chlorhexidine dental gel and mouthwash has been associated with reversible discoloration of the tongue, teeth, and silicate or composite dental restorations. Transient taste disturbances and a burning sensation of the tongue may occur on initial use. Oral desquamation and occasional parotid gland swelling have been reported with the mouthwash. If desquamation occurs, 50% dilution of the mouthwash with water and less vigorous rinsing may allow continued use.

The main consequence of ingestion is mucosal irritation and systemic toxicity is rare due to minimal absorption from the gastrointestinal tract (see Poisoning, below). Haemolysis has been reported after accidental intravenous administration. Gastric lavage with demulcents has been suggested for acute ingestion.

Effects on the eyes. Corneal damage was reported in 4 patients after use of chlorhexidine gluconate for pre-operative preparation of facial skin.[1] Severe corneal endothelium damage occurred in a further 3 patients[2] when chlorhexidine was inadvertently used as an intra-ocular irrigating solution and 2 of the patients subsequently required penetrating keratoplasty. Other adverse effects included pronounced iris atrophy, anterior chamber flattening, and a retrocorneal membrane; one patient developed raised intra-ocular pressure. In another case progressive ulcerative keratitis and almost total loss of the corneal epithelium was reported[3] after use of chlorhexidine gluconate 0.02% and propamidine 0.1% eye drops for 8 weeks for *Acanthamoeba* keratitis. In 2 patients[4] treated similarly for 4 to 6 months, deep marginal ulceration of the cornea developed, in each case requiring a penetrating graft; a mature cataract and an atrophic iris were seen in each patient after removal of the cornea. Due to the similarity of both cases, it was suggested that these complications were caused by the drugs rather than by amoeba-induced inflammation.

1. Tabor E, *et al.* Corneal damage due to eye contact with chlorhexidine gluconate. *JAMA* 1989; **261:** 557–8.
2. Anders N, Wollensak J. Inadvertent use of chlorhexidine instead of balanced salt solution for intraocular irrigation. *J Cataract Refract Surg* 1997; **23:** 959–62.
3. Murthy S, *et al.* Progressive ulcerative keratitis related to the use of topical chlorhexidine gluconate (0.02%). *Cornea* 2002; **21:** 237–9.
4. Ehlers N, Hjortdal J. Are cataract and iris atrophy toxic complications of medical treatment of acanthamoeba keratitis? *Acta Ophthalmol Scand* 2004; **82:** 228–31.

Effects on the nose. Temporary hyposmia (reduced sense of smell) in some patients after transsphenoidal pituitary adenoma operation was assumed to be caused by pre-operative disinfection of the nasal cavity with chlorhexidine gluconate solution.[1]

1. Yamagishi M, *et al.* Impairment of olfactory epithelium treated with chlorhexidine digluconate (Hibitane). *Pract Otol* 1985; **78:** 399–409.

Hypersensitivity. Both immediate and delayed hypersensitivity reactions have been reported after topical use of chlorhexidine[1] and from the use of chlorhexidine-containing urethral lubricants.[2] However, the incidence is low given the frequent use of chlorhexidine. Delayed hypersensitivity reactions such as contact dermatitis, fixed drug eruptions, and photosensitivity reactions are more common than immediate hypersensitivity reactions (acute urticaria, angioedema, and bronchospasm which may progress to anaphylactic shock).[1,3]

Immediate hypersensitivity reactions have also occurred with surgical disinfection. Signs appear 15 to 45 minutes after the start of surgery and include hypotension, urticaria, tachycardia, bronchospasm, and sometimes anaphylactic shock, cardiovascular collapse, or cardiac arrest.[3,4] In 1998 the FDA issued a public notice[5] warning of potential hypersensitivity reactions to chlorhexidine-impregnated intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh, based on reports of adverse events that had occurred in the USA and other countries.

Occupational asthma has been attributed to an alcoholic chlorhexidine spray.[6]

1. Krautheim AB, *et al.* Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004; **50:** 113–16.
2. Jayathillake A, *et al.* Allergy to chlorhexidine gluconate in urethral gel: report of four cases and review of the literature. *Urology* 2003; **61:** 837iv–837vi.
3. Beaudouin E, *et al.* Immediate hypersensitivity to chlorhexidine: literature review. *Allerg Immunol (Paris)* 2004; **36:** 123–6.
4. Chisholm DG, *et al.* Intranasal chlorhexidine resulting in an anaphylactic circulatory arrest. *BMJ* 1997; **315:** 785.
5. FDA. FDA Public Health notice potential hypersensitivity reactions to chlorhexidine-impregnated medical devices (issued 11/03/98). Available at: http://www.fda.gov/cdrh/chlorhex.html (accessed 15/03/06)
6. Waclawski ER, *et al.* Occupational asthma in nurses caused by chlorhexidine and alcohol aerosols. *BMJ* 1989; **298:** 929–30.

Poisoning. Reports of adverse effects after ***ingestion*** of chlorhexidine salts include a neonate who developed multiple episodes of cyanosis and bradycardia;[1] the infant's mother had sprayed chlorhexidine onto her breasts to prevent mastitis. In contrast an 89-year-old woman only experienced mild giddiness, unusual laughter, and an increased appetite after mistakenly drinking 30 mL of a solution containing chlorhexidine gluconate 4% and isopropyl alcohol 4%.[2] A review[3] of 7 adult cases of deliberate ingestion of a commercially available mixture of cetrimide 3% and chlorhexidine gluconate 0.3%, concluded that symptoms were generally mild and included nausea, vomiting, sore throat, and abdominal pain. There has also been a report of a patient who developed gastritis after ingesting a pre-operative skin preparation containing chlorhexidine gluconate 4% when using it as a mouthwash.[4]

Another person had much more serious effects after drinking about 150 mL of chlorhexidine gluconate solution, corresponding to about 30 g of the pure substance.[5] Besides pharyngeal oedema and necrotic oesophageal lesions, the patient had aminotransferase concentrations that rose to 30 times normal 5 days after ingestion and were still 8 times normal one week later. After one month the serum aspartate aminotransferase was returning to normal while the serum alanine aminotransferase was still 3 times normal. Six months after ingestion the aminotransferase levels were normal. A liver biopsy performed soon after the peak in aminotransferase levels showed diffuse fatty degeneration and lobular hepatitis suggesting that chlorhexidine was absorbed from the gastrointestinal tract in a concentration high enough to produce liver necrosis. An 80-year-old woman had spontaneous vomiting and aspiration followed by acute respiratory distress syndrome within 5 hours of accidental ingestion of 200 mL of a chlorhexidine gluconate 5% solution .[6] Despite supportive treatment, the patient's condition continued to deteriorate and she developed shock and metabolic acidosis and died from cardiac arrest 12 hours after ingestion.

Accidental ***intravenous*** administration of 4 mL of a 20% chlorhexidine gluconate solution in a 67-year-old man undergoing a colectomy resulted in the sudden development of acute respiratory distress syndrome.[7] Respiratory failure progressed despite plasma exchange therapy over 3 consecutive days. Veno-arterial extracorporeal membrane oxygenation was started on the third day and after 72 hours improvement was noted and the patient subsequently recovered completely.

1. Quinn MW, Bini RM. Bradycardia associated with chlorhexidine spray. *Arch Dis Child* 1989; **64:** 892–3.
2. Emerson D, Pierce C. A case of a single ingestion of 4% Hibiclens. *Vet Hum Toxicol* 1988; **30:** 583.
3. Chan TYK. Poisoning due to Savlon (cetrimide) liquid. *Hum Exp Toxicol* 1994; **13:** 681–2.
4. Roche S, *et al.* Chlorhexidine-induced gastritis. *Postgrad Med J* 1991; **67:** 210–11.
5. Massano G, *et al.* Striking aminotransferase rise after chlorhexidine self-poisoning. *Lancet* 1982; **i:** 289.
6. Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. *Vet Hum Toxicol* 2002; **44:** 89–91.
7. Ishigami S, *et al.* Intravenous chlorhexidine gluconate causing acute respiratory distress syndrome. *J Toxicol Clin Toxicol* 2001; **39:** 77–80.

Precautions

Since chlorhexidine is irritant it is recommended that it should not be used on the brain, meninges, middle ear, or other sensitive tissues. Contact with the eye should be avoided except for dilute solutions expressly for use in the eyes. Chlorhexidine may be adsorbed by some soft contact lenses and cause eye irritation, although it may be suitable for use with others (see Contact Lens Care, p.1622). Syringes and needles that have been immersed in chlorhexidine solutions should be thoroughly rinsed with sterile water or saline before use.

Aqueous solutions of chlorhexidine salts may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Aqueous solutions of chlorhexidine used for instrument storage should contain sodium nitrite 0.1% to inhibit metal corrosion, and should be changed every 7 days. Commercial 5% concentrate contains a nonionic surfactant to prevent precipitation on dilution with hard water and is not suitable for use in body cavities or for disinfection of instruments containing cemented glass components; dilutions of the 20% concentrate should be used for this purpose.

Contamination. *Ralstonia pickettii* (*Burkholderia pickettii*; *Pseudomonas pickettii*) septicaemia developed in 6 patients after the use of aqueous chlorhexidine 0.05%, prepared with contaminated twice-distilled water, for skin disinfection before venepuncture and it was considered that unsterilised 0.05% solutions should not be used for such skin preparation.[1] Positive blood cultures of *Burkholderia cepacia* (*Pseudomonas cepacia*) were found in 2 patients after inappropriate use of a chlorhexidine handwash for the same purpose.[2] Further studies showed that the handwash supported pseudomonal growth only when diluted.[3]

1. Kahan A, *et al.* Is chlorhexidine an essential drug? *Lancet* 1984; **ii:** 759–60.
2. Gosden PE, Norman P. Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1985; **ii** 671–2.
3. Norman P, *et al.* Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1986; **i:** 209.

Neonates. Haemorrhagic skin necrosis associated with umbilical artery catheterisation in a premature infant was attributed to damage by the alcohol from the use of chlorhexidine 0.5% in spirit 70% as a disinfectant.[1]

For reference to the percutaneous absorption of chlorhexidine following topical use in neonates and infants, see Pharmacokinetics, below.

1. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; **57:** 477–9.

Oral hygiene. As toothpastes may contain anionic surfactants such as sodium laurilsulfate, which are incompatible with chlorhexidine, it has been recommended that at least 30 minutes should be allowed to elapse between the use of toothpaste and oral chlorhexidine preparations.[1]

1. Barkvoll P, *et al.* Interaction between chlorhexidine digluconate and sodium lauryl sulfate in vivo. *J Clin Periodontol* 1989; **16:** 593–5.

Washing precautions. Fabrics that have been in contact with chlorhexidine solution may develop a brown stain if bleached with a hypochlorite. A peroxide bleach may be used instead.

Pharmacokinetics

Chlorhexidine is poorly absorbed from the gastrointestinal tract and skin.

Neonates. Occasional reports of the percutaneous absorption of chlorhexidine in neonates and infants include a study in which chlorhexidine was detected in low concentrations in the venous blood of 5 of 24 infants after washing them with a preparation containing chlorhexidine gluconate 4% (*Hibiscrub*); no adverse effects were observed.[1] Low concentrations have been found[2] in the venous blood of neonates following the topical use of a powder containing chlorhexidine 1%. Percutaneous absorption of chlorhexidine was reported in preterm neonates (but not full-term infants) treated with chlorhexidine 1% in alcohol for neonatal cord care; no such absorption occurred when a dusting powder containing chlorhexidine 1% and zinc oxide 3% was used.[3]

1. Cowen J, *et al.* Absorption of chlorhexidine from the intact skin of newborn infants. *Arch Dis Child* 1979; **54:** 379–83.
2. Alder VG, *et al.* Comparison of hexachlorophane and chlorhexidine powders in prevention of neonatal infection. *Arch Dis Child* 1980; **55:** 277–80.
3. Aggett PJ, *et al.* Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981; **56:** 878–91.

Uses and Administration

Chlorhexidine is a bisbiguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of Gram-positive and Gram-negative bacteria. It is more effective against Gram-positive than Gram-negative bacteria, and some species of *Pseudomonas* and *Proteus* have low susceptibility. It is relatively ineffective against mycobacteria. Chlorhexidine inhibits some viruses and is active against some fungi. It is inactive against bacterial spores at room temperature. Chlorhexidine is most active at a neutral or slightly acid pH. Combinations of chlorhexidine with cetrimide (p.1634) or in alcoholic solution are used to enhance efficacy.

Chlorhexidine is formulated as lotions, washes, and creams for disinfection and cleansing of skin and wounds (p.1585), and as oral gels, sprays, and mouthwashes for mouth infections including candidiasis and to reduce dental plaque accumulation. It has also been used with neomycin to eliminate nasal carriage of staphylococci (p.195) and for disinfection of some contact lenses (but see Precautions, above). It has been suggested for use with propamidine isetionate for the treatment of Acanthamoeba keratitis and in spermicides to prevent transmission of HIV infection (p.858).

For pre-operative skin disinfection and hand-washing, chlorhexidine is used as a 0.5% solution of the acetate or gluconate in alcohol (70%) or as a 2 or 4% detergent solution of the gluconate. For disinfection of wounds, burns, or other skin damage or disorders chlorhexidine is used as a 0.05% aqueous solution of the acetate or gluconate, as a tulle dressing impregnated with chlorhexidine acetate 0.5%, or as a cream or powder containing chlorhexidine acetate or gluconate 1%. Preparations containing chlorhexidine acetate or gluconate 0.015% and cetrimide 0.15% are also used for cleansing and disinfection of skin and wounds. In obstetrics, chlorhexidine gluconate is used as a 0.05% aqueous solution or a 1% cream. The cream is also used as a barrier against bacterial hand infection.

Chlorhexidine gluconate is used in a 1% dental gel, 0.2% oral spray, and 0.1 to 0.2% mouthwash for the prevention of plaque and the prevention and treatment of gingivitis and in the treatment of oral candidiasis. A slow-release formulation containing 2.5 mg of chlorhexidine gluconate for insertion into periodontal pockets is also available.

A 0.02% solution may be used as a bladder irrigation in some urinary-tract infections. A gel containing 0.25% chlorhexidine gluconate solution and lidocaine hydrochloride has been used in catheterisation and cystoscopy.

For the emergency disinfection of clean instruments, a 2-minute immersion in chlorhexidine acetate or gluconate 0.5% in alcohol (70%) is used; for the storage and disinfection of clean instruments a 30-minute immersion in a 0.05% aqueous solution containing 0.1% sodium nitrite to inhibit metal corrosion is used.

As an antimicrobial preservative, chlorhexidine is used at a concentration of 0.01% of the acetate or gluconate in eye drops. Solutions containing 0.002 to 0.006% of chlorhexidine gluconate have also been used for disinfection of hydrophilic contact lenses.

Acanthamoeba infections. As discussed on p.822, the optimal antiamoebic therapy for *Acanthamoeba* keratitis has yet to be determined. Propamidine isetionate is commonly used, usually in combinations including a biguanide. A multicentre study[1] evaluated the efficacy of a combination of topical chlorhexidine 0.02% and propamidine 0.1% in 12 contact lens-wearing patients with confirmed *Acanthamoeba* keratitis. Patients were treated for between 2 to 6 months and resolution of signs occurred gradually over 5 to 28 weeks (mean 11 weeks). Resolution of symptoms occurred within 1 to 7 weeks (mean 3 weeks); patients noted a reduction of pain, photophobia and lid oedema after 3 weeks of treatment. No drug toxicity was noted in any of the patients. However, concern has been expressed over the possible toxicity of chlorhexidine at this concentration on the cornea (see Adverse Effects and Treatment, above).

Chlorhexidine is also an effective disinfectant against *Acanthamoeba* cysts and most bacteria found in contact lens storage cases.[2]

Chlorhexidine has also been used to treat skin lesions associated with disseminated *Acanthamoeba* infection[3] as an adjunct to systemic therapy (see p.822).

1. Seal D, *et al*. Successful medical therapy of Acanthamoeba keratitis with topical chlorhexidine and propamidine. *Eye* 1996; **10:** 413–21.
2. Seal DV. Acanthamoeba keratitis. *BMJ* 1994; **308:** 1116–17.
3. Slater CA, *et al*. Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; **331:** 85–7.

Contraception. Bisbiguanides of the chlorhexidine type are reported to have the ability to diffuse into cervical mucus and render it impenetrable to sperm at concentrations as low as 1 mg/mL.[1] Higher concentrations of chlorhexidine structurally modify the mucus, producing a barrier to both the entry of sperm and chlorhexidine. The potency[1] of chlorhexidine in inhibiting sperm motility *in vitro* is identical to that of nonoxinol 9, but unlike spermicides containing nonoxinol 9, which tend to trickle out, the clearance of chlorhexidine from the vagina is delayed.[2] Chlorhexidine also has potential for reducing transmission of HIV infection as it does not disrupt the vaginal epithelium and has activity *in vitro* against the HIV virus in low concentrations.[2]

For a review of contraception, including the view that spermicides are not a particularly effective method unless used with other means of contraception, see p.2070.

1. Pearson RM. Update on vaginal spermicides. *Pharm J* 1985; **234:** 686–7.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; **340:** 211–13.

Disinfection. Viable bacterial counts on the hands were reduced by a mean of 97.9% by the application of chlorhexidine gluconate 0.5% in alcohol 95%.[1] The reduction was not so substantial with a 0.5% chlorhexidine aqueous solution (65.1% reduction in bacterial count) or a 4% detergent solution (86.7%). Hand disinfection with chlorhexidine gluconate 4% appeared to be more effective than the use of isopropyl alcohol 60% and soap in preventing nosocomial infections in a study conducted in intensive care units but this may have been partly due to better compliance with hand-washing instructions when using chlorhexidine.[2] In another study,[3] pre-operative total body bathing with a 4% detergent did not decrease the risk of wound infection in patients compared with bathing in detergent alone.

Chlorhexidine 1% nasal cream failed to control an epidemic of meticillin-resistant *Staphylococcus aureus* in a neurosurgical ward[4] and handwashing with chlorhexidine soap failed to control an outbreak of infection with *Staph. aureus* resistant to meticillin and gentamicin in a neonatal intensive care unit.[5] The organisms were subsequently eradicated by the use of nasal mupirocin and hexachlorophene handwashing, respectively.

1. Lowbury EJL, *et al*. Preoperative disinfection of surgeons' hands: use of alcoholic solutions and effects of gloves on skin flora. *BMJ* 1974; **4:** 369–72.
2. Doebbeling BN, *et al*. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992; **327:** 88–93.
3. The European Working Party on Control of Hospital Infections. A comparison of the effects of preoperative whole-body bathing with detergent alone and with detergent containing chlorhexidine gluconate on the frequency of wound infections after clean surgery. *J Hosp Infect* 1988; **11:** 310–20.
4. Duckworth G. New method for typing Staphylococcus aureus resistant to methicillin. *BMJ* 1986; **293:** 885.
5. Reboli AC, *et al*. Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; **143:** 34–9.

INJECTION SITE AND CATHETER CARE. See p.1624.

Endocarditis. Antiseptics applied immediately before dental procedures may reduce postextraction bacteraemia. Chlorhexidine mouthwash or gel may be used as an adjunct to antibacterial prophylaxis in dental patients at risk of bacterial endocarditis.[1,2] The protective cover required for such patients is discussed on p.168.

1. Dajani AS, *et al*. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997; **277:** 1794–1801. Also available at: http://circ.ahajournals.org/cgi/content/full/96/1/358 (accessed 07/03/06)
2. Simmons NA, *et al*. Antibiotic prophylaxis and infective endocarditis. *Lancet* 1992; **339:** 1292–3.

Mouth disorders. Chlorhexidine mouthwashes, sprays, and gels are used to prevent accumulation of dental plaque (see Mouth Infections, p.180). Early studies[1-4] generally showed chlorhexidine mouthwash 0.1 to 0.2% used 2 or 3 times daily to be effective in reducing plaque accumulation and gingivitis and provided limited evidence of effectiveness in preventing caries in permanent teeth of children and adolescents. A retrospective review[5] of 22 controlled studies of chlorhexidine for caries prevention, found the evidence inconclusive in schoolchildren and adolescents with active caries and regular fluoride exposure; there was also no good evidence that it arrested root caries in patients with dry mouth and in frail elderly subjects. However, chlorhexidine varnishes showed a preventative effect for fissure caries compared with no treatment in children with low fluoride exposure. Other studies have shown that chlorhexidine reduces gingivitis by 60 to 90% but its use is limited by its unpleasant taste and staining properties; special circumstances in which chlorhexidine is helpful include management of acute gingivitis, control of periodontal involvement in immunocompromised patients, and promotion of healing after periodontal treatment.[6]

Chlorhexidine gluconate may be useful in controlling secondary bacterial infections of aphthous ulcers (see Mouth Ulceration, p.1700). Local application of chlorhexidine has been reported to reduce the incidence[7] and duration and severity[8] of recurrent ulcers, although one study showed no benefit compared with placebo.[9] However, a retrospective review[10] of 7 studies comparing chlorhexidine with placebo or no treatment found no evidence that chlorhexidine prevents oral mucositis in patients receiving cancer treatment.

Chlorhexidine may be a useful adjunct to antifungal treatment of oral candidiasis[11] (p.518).

For the need for a delay when using chlorhexidine with other oral hygiene preparations, see under Precautions, above.

1. Flötra L, *et al*. A 4-month study on the effect of chlorhexidine mouth washes on 50 soldiers. *Scand J Dent Res* 1972; **80:** 10–17.
2. O'Neil TCA, Figures KH. The effects of chlorhexidine and mechanical methods of plaque control on the recurrence of gingival hyperplasia in young patients taking phenytoin. *Br Dent J* 1982; **152:** 130–3.
3. de la Rosa M, *et al*. The use of chlorhexidine in the management of gingivitis in children. *J Periodontol* 1988; **59:** 387–9.
4. O'Neil TCA. The use of chlorhexidine mouthwash in the control of gingival inflammation. *Br Dent J* 1976; **141:** 276–80.
5. Twetman S. Antimicrobials in future caries control: a review with special reference to chlorhexidine treatment. *Caries Res* 2004; **38:** 223–9.
6. Greene JC, *et al*. Preventive dentistry II: periodontal diseases, malocclusion, trauma, and oral cancer. *JAMA* 1990; **263:** 421–5.
7. Hunter L, Addy M. Chlorhexidine gluconate mouthwash in the management of minor aphthous ulceration. *Br Dent J* 1987; **162:** 106–10.
8. Addy M, *et al*. Management of recurrent aphthous ulceration: a trial of chlorhexidine gluconate gel. *Br Dent J* 1976; **141:** 118–20.
9. Matthews RW, *et al*. Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; **63:** 189–91.
10. Worthington HV, *et al*. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/08/08).
11. WHO. *WHO model prescribing information: drugs used in skin diseases*. Geneva: WHO, 1997.

Obstetric use. Disinfection of the birth canal with chlorhexidine gluconate 0.05 to 0.4% during labour has been investigated as a method for reducing mother-to-child transmission of infections, including early-onset group B streptococcal infection and HIV.[1-6] Studies have shown that it has not reduced perinatal transmission of HIV except when membranes were ruptured for more than 4 hours before delivery[1] or if used before the membranes rupture and at higher concentrations.[4] A systematic review of 5 studies[5] to determine the efficacy of chlorhexidine vaginal disinfection for preventing early-onset group B streptococcal infection concluded that, although there was a statistically significant reduction in colonisation there was no significant reduction in early-onset infection, morbidity or mortality. Comparable results have been reported with the use of chlorhexidine gluconate 1% obstetric cream at each examination during labour.[3] A systematic review of 3 studies[6] to determine the efficacy of chlorhexidine vaginal disinfection for preventing perinatal transmission of infections other than group B streptococcal infection and HIV found no evidence to support its use. However, a study[2] conducted in Malawi reported a reduction in neonatal morbidity and mortality from other neonatal infections.

1. Biggar RJ, *et al*. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. *Lancet* 1996; **347:** 1647–50.
2. Taha TE, *et al*. Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *BMJ* 1997; **315:** 216–20.
3. Lindemann R, *et al*. Vaginal chlorhexidine disinfection during labour. *Lancet* 1992; **340:** 792.
4. Gaillard P, *et al*. Vaginal lavage with chlorhexidine during labour to reduce mother-to-child HIV transmission: clinical trial in Mombasa, Kenya. *AIDS* 2001; **15:** 389–96.
5. Stade B, *et al*. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 15/03/06).
6. Lumbiganon P, *et al*. Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding group B streptococcal and HIV). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 15/03/06).

Urinary catheter-related infection. Chlorhexidine solutions have been used in the management of catheter-related bladder infections and for urinary catheter maintenance. Twice-daily bladder irrigation with chlorhexidine acetate 0.02% did not produce a reduction in urinary bacterial counts in geriatric patients with indwelling catheters, and there was a tendency for overgrowth of *Proteus* spp. in patients given chlorhexidine.[1] In patients undergoing prostatectomy, intermittent pre-operative bladder irrigation with chlorhexidine gluconate 0.05% reduced the incidence of bacteraemia and severe wound infection, although urinary infections were eradicated in only 3 of the 13 patients treated.[2]

Addition of chlorhexidine to catheter drainage bags was not shown to reduce the frequency of urinary infections,[3] but infection rates were reduced by combining this technique with the use of a catheter lubricant containing chlorhexidine, disinfection of the urethral meatus, and aseptic nursing procedures.[4] The use of lubricating gel containing chlorhexidine did not reduce the risk of urinary-tract infections associated with short-term catheterisation,[5] and in general external disinfection of the periurethral area alone does not seem to be of benefit in reducing the rate of catheter-related bacteriuria.[6,7]

The treatment of urinary-tract infections is discussed on p.199.

1. Davies AJ, *et al*. Does instillation of chlorhexidine into the bladder of catheterized geriatric patients help reduce bacteriuria? *J Hosp Infect* 1987; **9:** 72–5.
2. Adesanya AA, *et al*. The use of intermittent chlorhexidine bladder irrigation in the prevention of post-prostatectomy infective complications. *Int Urol Nephrol* 1993; **25:** 359–67.
3. Gillespie WA, *et al*. Does the addition of disinfectant to urine drainage bags prevent infection in catheterised patients? *Lancet* 1983; **i:** 1037–9.
4. Southampton Infection Control Team. Evaluation of aseptic techniques and chlorhexidine on the rate of catheter-associated urinary-tract infection. *Lancet* 1982; **i:** 89–91.

5. Schiøtz HA. Antiseptic catheter gel and urinary tract infection after short-term postoperative catheterization in women. *Arch Gynecol Obstet* 1996; **258:** 97–100.
6. Webster J, *et al.* Water or antiseptic for periurethral cleaning before urinary catheterization: a randomized controlled trial. *Am J Infect Control* 2001; **29:** 389–94.
7. Koskeroglu N, *et al.* The role of meatal disinfection in preventing catheter-related bacteriuria in an intensive care unit: a pilot study in Turkey. *J Hosp Infect* 2004; **56:** 236–8.

Preparations

BP 2008: Chlorhexidine Irrigation Solution; Chlorhexidine Mouthwash; Lidocaine and Chlorhexidine Gel;
USP 31: Chlorhexidine Gluconate Oral Rinse.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiminth; Biguanex; Bucogel; Elugel; Finaplac; Hexidin; Hexil; Hexil-P; Hibiscrub; Hiboquad†; Laclorhex; Periodil; Pervinox Clorhexidina; Pervinox Incoloro; Plac Out; Strictus†; ***Austral.:*** Anti-Plaque Chewing Gum†; Bactigras; Bush Formula†; Catheter Preparation; Clorhexitulle†; Hexol†; Microshield 2, 4, and 5; Periogard Chlorohex†; Plaqacide†; Savacol Mouth and Throat Rinse; ***Austria:*** Chlorhexamed; Plak Out; ***Belg.:*** Astrexine; Baxil; Cedium Chlorhexidine; Corsodyl; Golaseptine; Hansamedic; Hibidil; Hibiguard; Hibiscrub; Hibitane; Medisepta; Mefren; Nolargin; Pixidin; Sterilon; Uro-Tainer†; ***Braz.:*** Asseptic; Glucohex†; Hibitane; Marclorhex; Merthiolate†; Noplak; ***Canad.:*** Bactigras; Baxedin; Hibidil; Hibitane; Peridex†; Spectro Gram; Stanhexidine; ***Chile:*** AB; Agermin†; Bucoseptil; Freshmel; Garonsept; Graneodin; Hibicrick†; Hibiscrub†; Oralgene; Ortoxine; Perident†; Perio-Aid; Periokin; Perioxidin†; ***Cz.:*** Corsodyl; Hibiscrub†; Septofort; ***Denm.:*** Hibitane; Periochip; ***Fin.:*** Corsodyl; Klorhexol; Travahex; ***Fr.:*** Biorgasept; Collunovar; Corsodyl; Dermachrome; Diaseptyl; Dosiseptine; Elgydium; Elugel; Euraxsepti; Exoseptoplix†; Hibidil; Hibiscrub; Hibisprint; Hibitane; Paroex; Plurexid; Prexidine; Septeal; Septiapaisyl; Septivon; ***Ger.:*** Bactigras†; Cathejell S; Chlorhexamed; CHX Dental Gel; Cidegol C; Dentosmin P; Frubilurgyl†; Gurgellosung Chauvin†; Hansamed Spray†; Lemocin CX; Nur 1 Tropfen Chlorhexidin; Periogard Chlorohex†; Trachisan N†; ***Gr.:*** Hibitane; Periochip; ***Hong Kong:*** Bactigras†; Corsodyl; Hexol†; Hibiscrub†; Hibitane†; Hydrex; Qualikin; Scanlin; ***Hung.:*** Septofort; ***India:*** Orinse; ***Indon.:*** Mediscrub; ***Irl.:*** Corsodyl; Hibiscrub; Hibitane; ***Israel:*** Alcoxidine; Bactoscrub; Bactosept; Cleardent; Corsodyl; Medident; Periochip; Pharma-Dentix; Septadine Scrub; Septal; Septalone; Septol; Tarodent; Uniscrub†; Unisept†; ***Ital.:*** Benodent; Benodent CLX; Broxodin; Clarifex; Clomirex; Clorosan; Corsodyl; Dempol; Dentosan Clorexidina; Dentosan Parodontale; Eburos; Ekuba; Esoform Mani; Golasan; Iodosan Clorexidina; Lenil; Master-Aid; Neo Perginol†; Neo-Destomygen; Neomercurocromo; Neoxene; Neoxinal; Parodontax; Periogard Chlorohex; Plak Out; Sicura 3; Triseptil; ***Malaysia:*** Antibex†; Antisol†; Baby Shield Plus; Bactigras; Hibiscrub†; Hibisol†; Hibitane†; Oradex†; Sepsol†; ***Mex.:*** Hibiscrub†; Perioxidin; ***Neth.:*** Chlorhexamed; Corsodyl; Hibiscrub; Hibitane; Hydrex; Irrisol; Lifo-Scrub; Periochip; Sterilon; Urogliss-S; ***Norw.:*** Corsodyl; Hibiscrub; Hibitane; Periochip; ***NZ:*** DP Hand Rub; Hibitane; Riotane; ***Philipp.:*** Bactigras; Orahex; ***Pol.:*** Septofervex; ***Port.:*** Bexident; Cloraldin; Corsodyl; Dialens; Handscrub; Hibitane; Lifo-Scrub; Periochip; Plak Out†; ***Rus.:*** Elgydium (Эльгидиум); Elugel (Элюгель); Hexicon (Гексикон); Intim (Интим)†; ***S.Afr.:*** Bactigras; Corsodyl; D-Germ; Hexidin; Hibidil†; Hibiscrub; Hibitane; Orosept; ***Singapore:*** Acnederm Wash; Baby Shield Plus; Chlorohex; Elgydium; Elugel; Hexodane Mouthwash; Hexoscrub; Pfizer Obstetric Lotion†; ***Spain:*** Clorxil†; Cristalcrom; Cristalmina; Curafil; Cuvefilm; Deratin; Hibimax; Hibiscrub; Menalmina; Septisan; ***Swed.:*** Cervitec†; Corsodyl; Descutan; Hexident; Hibiscrub; Hibitane; Periochip; ***Switz.:*** Chlorhexamed; Chlorohex†; Corsodyl; Dentohexine; Hibidil; Hibiscrub; Hibitane; Lifo-Scrub; Periochip; Plak Out; ***Thai.:*** Bacard Antiseptic; Bactigras; C-20; Chlorhex; Desmanol G†; Hexene; Hexide; Hexol†; Hibiscrub†; Hibitane†; Hidine†; Hydrex; Q-Bac; ***Turk.:*** Cloder; Disinfecting; Klorheksol; Klorhex; Mediscrub; Oroheks; ***UAE:*** Zordyl; ***UK:*** Acriflex; Bactigras; Cepton; Chlorohex; Corsodyl; Curasept; CX Powder; Elgydium; Hibiscrub; Hibitane; Hydrex; Savlon Antiseptic Wound Wash; Serotulle; Spotoway; Steripod Chlorhexidine Gluconate; Unisept; Uriflex C; ***USA:*** Betasept; Dyna-Hex; Exidine; Hibiclens; Hibistat; Peridex; Periochip; Periogard; ***Venez.:*** Peridont.

Multi-ingredient: *Arg.:* Antisepthic Plus; Buclorhex; Consil; Dexatopic†; Drill; Elgydium; Elgydium Dientes Sensibles; Elgyfluor†; Eludril; Fluorexidina†; Hexil Antiseptico; Instillagel; Merthiolate NF; Odontobiotic†; Parodium; Periobacter; Periobacter Prof Avio; Periodent; Periodil; ***Austral.:*** Acnederm Foaming Wash; Curacleanse†; Difflam-C; Hamilton Body Lotion†; Hamilton Cleansing Lotion†; Hemocane; Medi Creme; Medi Pulv; Microshield Antiseptic; Microshield Handrub; Microshield Tincture; Mycil Healthy Feet; Nasalate; Oralife Peppermint; Paraderm Plus; Pro-PS†; Savlon Antiseptic; Seda-Gel†; Silvazine; Soov Cream; Xylocaine Jelly with Chlorhexidine; ***Austria:*** Bepanthen Plus; Cathejell; Cathejell mit Lidocain; Dermaspray; Endosgel; Instillagel; Skinsept mucosa; Uromont; Vitawund; ***Belg.:*** Angiocine; Cathejell; Cetavlex; Dermaspray†; Eludril; HAC; Hacdil-S; Hibitane; Instillagel; Medica; Neo-Cutigenol; Neo-Golaseptine; Nestosyl; Sabenyl; Vita-Mefren†; ***Braz.:*** Effaclar; ***Canad.:*** Avagard CHG; Baxedin 2% - 70%; Flamazine C†; Savlodil; Spectro Tar†; ***Chile:*** AB Antitusivo; Cariax; Endogel Esteril; Freshmel Tos; Graneodin N†; Graneodin-Tos; Halita; Medisept†; Oralgene; Orthokin; Perio-Aid c Cloruro de Cetilpiridinio; ***Cz.:*** Bepanthen Plus; Cyteal; Drill; Hexoral; Hexoraletten N; Hibicet Hospital Concentrate†; Instillagel; N-Septonex†; Skinsept mucosa†; ***Denm.:*** Hexokain; Instillagel; ***Fin.:*** Duocort; Sibicort; Toncils; ***Fr.:*** Alco-Aloe; Aphtoral; Biseptine; Cantalene; Chlorispray†; Collu-Blache†; Collustan†; Cyteal; Dacryne; Dermaspraid Antiseptique; Dermobacter; Drill; Elgydium Dents Sensibiles; Elgyfluor†; Eludril; Instillagel; Mercryl; Mercrylsoins; Nostril; Parodium; Parogencyl sensibilite gencives; Paroplak; Posine†; Spitaderm†; Thiovalone; ***Ger.:*** Bepanthen Antiseptische; Cathejell mit Lidocain; Desmanol†; Endosgel; Hermalind†; Hexoraletten N; Instillagel; Nystalocal; Skinsept F; Skinsept mucosa; Trachisan†; Uro-Stilloson†; ***Gr.:*** Hibicet; Instillagel; Octrene; Trachisan; ***Hong Kong:*** Acnederm Wash; Dermobacter; Difflam-C; Hibicet Hospital Concentrate†; Hibisol†; Instillagel; Medicreme; Medipulv†; Mycil; Oragesic; Pilelife; Soov Cream; Trachisan†; ***Hung.:*** Alkcema; Alksebor; Bepanthen Plus; Drill; Instillagel; Vita-Merfen†; ***India:*** Argisept†; Burnheal†; Iteol-3; Silverex; ***Indon.:*** Dexatopic; Neo Resiguard; Pravlon; Spitaderm; ***Irl.:*** Alltracel S†; Hibicet; Hibisol; Instillagel; Mycil; Naseptin; Nystaform-HC†; Nystaform†; Savlon; ***Israel:*** Alcosept; Bepanthen Plus; Cathejell; Cetrin; Instillagel†; Merfen; Neocutan Silver; Savior; Septacare†; Septadine; Sterets H; Tisept; Travasept; V-Tabur; Vita-Merfen NF; ***Ital.:*** Bactigras; Baxidin; Benodent; Benodent Gel Gengivale†; Biopatch; Cetrexidin; Cetrisan; Citroclorex; Citromed; Citromed 80 and 85; Citromed Chirurgico; Citromedics Pronto; Citrosteril Pronto; Clorexan; Clorexan Ferri; Clotramid†; Cuprosodio Plus; Decon Lavanda; Dentaton; Dentosan Azione Intensiva; Dentosan Mese; Dentosan Placca & Carie; Disinfene; Eso Ferri Plus; Eso S 80; Esosan Pronto; Farvicett; Handexin; Hibizene; Neo-Stomygen; Neogyn; Ninfagin; Panseptil; Parogencyl Gengive Delicate; Rexichlor; Sicura3 Medical; Simp; Simpottantacinque; Spitaderm; Steridol†; Videorelax†; ***Malaysia:*** Acnederm Foaming Wash; Cathejell with Lidocaine; Difflam-C; Elan-Forte; Hibicet†; Horf; Oral-Aid; Trachisan†; ***Mex.:*** Instillagel†; Perioxidin; ***Neth.:*** Dexatopic†; Endosgel; Hibicet concentraat; Hibicet verdunning; Hibisol; Instillagel; Spitaderm; Urogliss; ***Norw.:*** Bacimycin; ***NZ:*** Acnederm Foaming Wash; Acnederm Wash†; Conditioning Solution†; Difflam-C; Egomycol†; Medicreme; Medipulv; Oralife Peppermint; Paraderm Plus; Savlon; Silvazine; Soov Cream; Xylocaine with Chlorhexidine†; ***Philipp.:*** Cathejell; ***Pol.:*** Bepanthen Plus; Sebidin; ***Port.:*** Alkagin; Alphacedre; Bepanthene; Bepanthene Plus; Biofluor Plus†; Biofluor Prevencao†; Cathejell; Cyteal; Drill; Eludril; Hibitane Menta†; Hibitane†; Instillagel; Lactigriet; Lubrificante Anestesico; ***Rus.:*** Bepanthen Plus (Бепантен Плюс); Cathejell with Lidocaine (Катеджель С Лидокаином)†; Cyteal (Цитеал); Drill (Дрилл); Elgyfluor (Эльгифлуор); Eludril (Элюдрил); Lysoplac (Лизоплак); Metrogyl Denta (Метрогил Дента); Parodium (Пародиум); Sebidin (Себидин); ***S.Afr.:*** Andolex-C; Cathejell with Lidocaine; Germolene; Hibicet†; Naseptin; Orochlor; ***Singapore:*** Cyteal; Difflam-C; Elgyfluor; Eludril; Hexodane Handrub; Oral-Aid; Savlon†; Silvazine; Silvin; Soov Cream; Trachisan; ***Spain:*** Angileptol; Bucodrin; Bucometasana; Bucospray; Drill; Eludril; Faringesic; Gargaril; Garydol; Hibitane; Mastiol; Menalcol; Mercryl Plus; ***Swed.:*** Instillagel; ***Switz.:*** Antebor N; Bepanthene Plus; Collu-Blache; Collunosol-N; Eludril; Eubucal†; Galamila; Gleitmittel†; Hibital; Hibitane Teinture; Lidohex†; Merfen; Nystacortone†; Nystalocal; Trachisan†; Vita-Hexin; Vita-Merfen; ***Thai.:*** Bacard; Cathejell with Lidocaine; Chlorhex-C; Dekka; Frebac; Hibicet†; Inhibac; Sepdine†; Septone†; ***Turk.:*** Bepanthene Plus; Dervanol; Gleitgelen; Hemoralgine; Kloroben; Pantenol Plus; Savlex; Savonol; Savrolin; Setilin; ***UK:*** Cathejell with Lidocaine; ChloraPrep; Clearasil Pore Cleansing Lotion; Covonia Throat Spray; Cyteal; Dermol; Eludril; Germolene; Germoloids†; Hibicet†; Hibisol; Instillagel; Medi-Swab H; Medi-Wipe; Mycil; Naseptin; Nystaform; Nystaform-HC; Quinoderm Antibacterial Face Wash; Savlon Antiseptic Cream; Savlon Antiseptic Liquid; Sterets H; Steripod Chlorhexidine Gluconate with Cetrimide†; Tisept; Torbetol; Travasept; ***USA:*** BactoShield; Fresh-N-Free.

Chlorinated Lime

Bleaching Powder; Cal clorada; Calcaria Chlorata; Calcii Hypochloris; Calcium Hypochlorite; Calcium Hypochlorosum; Calx Chlorata; Calx Chlorinata; Chloride of Lime; Chlorkalk; Chlorure de Chaux; Cloruro de Cal; Desmanche.

CAS — 7778-54-3.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2008 (Chlorinated Lime). A dull white powder with a characteristic odour, containing not less than 30.0% w/w of 'available chlorine'. It becomes moist and gradually decomposes on exposure to air, carbon dioxide being absorbed and chlorine evolved. Partly soluble in water and in alcohol.

Adverse Effects, Treatment, and Precautions

As for Sodium Hypochlorite, p.1661.

Uses and Administration

Chlorinated lime is a disinfectant and antiseptic with the general properties of chlorine (p.1638).

Its action is rapid but brief, the 'available chlorine' soon being exhausted by combination with organic material. It is used to disinfect faeces, urine, and other organic material, and as a cleansing agent for lavatories, drains, and effluents.

Chlorinated lime is used in the preparation of Surgical Chlorinated Soda Solution (BPC 1973) (Dakin's Solution) which has been employed as a wound disinfectant, and Chlorinated Lime and Boric Acid Solution (BP 1993), (Eusol), which has been used as a disinfectant lotion and wet dressing, sometimes with equal parts of liquid paraffin. However, such solutions are irritant when applied undiluted, and are no longer recommended for use in this way. In addition, there is some evidence that such chlorine-releasing solutions may delay wound healing (see Disinfection, Wounds under Uses and Administration of Sodium Hypochlorite, p.1662).

Preparations

BPC 1973: Surgical Chlorinated Soda Solution.

Chlorine

925; Chlor; Chlore; Chlorium; Cloro; Klor.

Хлор

Cl_2 = 70.906.

CAS — 7782-50-5.

Description. Chlorine is a greenish-yellow gas with a suffocating odour; commonly available as a pressurised liquid.

Adverse Effects and Treatment

Chlorine gas is irritant and corrosive producing inflammation, burns, and necrosis. Inhalation may result in coughing, choking, headache, dyspnoea, dizziness, expectoration of frothy white sputum (which may be blood stained), a burning chest pain, and nausea. Bronchospasm, laryngeal oedema, acute pulmonary oedema with cyanosis, and hypoxia may occur. There may be vomiting and development of acidosis. Death may result from hypoxia.

Some of the toxicity of chlorine may be due to its dissolution in tissue water to produce hydrochloric acid and hypochlorite. After exposure to chlorine, conjunctivitis may require a topical anaesthetic and frequent irrigations of water or saline. Respiratory distress should be treated with inhalations of humidified oxygen and bronchodilators; mechanical ventilation may be required. Corticosteroids have been given in an attempt to minimise pulmonary damage but their benefit is unproven. Acidosis may require the intravenous use of sodium bicarbonate or other suitable alkalising agent.

◊ Experience gained from 186 cases of acute chlorine exposure indicated that medical support was required for only a short time even when exposure was repeated;[1] late sequelae were not seen, even in patients with abnormal respiratory function tests or blood gases on admission. Thirteen children who were accidentally exposed to chlorine products and gas at a community swimming pool complained of eye and throat irritation, chest pain and tightness, shortness of breath, wheezing, and anxiety and 5 children with hypoxia required hospital admission. These children received humidified oxygen, salbutamol, and, in 4 patients, methylprednisolone, and all were discharged 1 to 2 days later.[2] Another report on 76 children with chlorine poisoning revealed that the longest period of hospitalisation was 12 hours after treatment with oxygen and corticosteroids.[3] A 14-year-old boy with a history of asthma exposed to chlorine gas developed acute respiratory distress syndrome and required intubation, ventilatory support, salbutamol, and corticosteroids. He was extubated after 19 days and recovered well.[4] There have been reports of deliberate inhalation of chlorine,[5,6] in one instance for pleasure,[5] leading to severe adverse effects. Some individuals may be unduly insensitive to chlorine-induced irritation and workers should be warned that concentrations of chlorine which can be tolerated for short periods without undue discomfort can still cause serious injury which may not be immediately apparent.[6]

Guidelines[7,8] have been issued for the management of chlorine exposure.

1. Barret L, Faure J. Chlorine poisoning. *Lancet* 1984; **i:** 561–2.
2. Sexton JD, Pronchik DJ. Chlorine inhalation: the big picture. *Clin Toxicol* 1998; **36:** 87–93.
3. Fleta J, *et al.* Intoxication of 76 children by chlorine gas. *Hum Toxicol* 1986; **5:** 99–100.
4. Traub SJ, *et al.* Case report and literature review of chlorine gas toxicity. *Vet Hum Toxicol* 2002; **44:** 235–9.
5. Rafferty P. Voluntary chlorine inhalation: a new form of self-abuse? *BMJ* 1980; **281:** 1178–9.
6. Dewhurst F. Voluntary chlorine inhalation. *BMJ* 1981; **282:** 565–6.
7. Department of Health. Chlorine: guidelines for action in the event of a deliberate release (issued February 2004). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947362398 (accessed 27/08/08)
8. Agency for Toxic Substances and Disease Registry. Medical management guidelines (MMGs) for chlorine (Cl). Available at: http://www.atsdr.cdc.gov/MHMI/mmg172.html (accessed 15/03/06)

Effects on the eyes. Eye examinations of 50 subjects immediately before and after swimming in a chlorinated pool (chlorine range 1.0 to 1.5 ppm) showed that 68% had symptoms of corneal oedema and 94% had corneal epithelial erosions. No subject had a measurable decrease in visual acuity.[1]

1. Haag JR, Gieser RG. Effects of swimming pool water on the cornea. *JAMA* 1983; **249:** 2507–8.

Precautions

The antimicrobial activity of chlorine disinfectants is reduced by the presence of organic material and by increasing pH. Hypochlorite solutions may delay wound healing (see Disinfection: Wounds under Uses and Administration of Sodium Hypochlorite, p.1662).

Uses and Administration

Chlorine is a disinfectant with a rapid potent brief bactericidal action. It is capable of killing most bacteria, and some fungi, yeasts, algae, viruses, and protozoa. It is slowly active against spores.

It is used for the treatment of water (p.1623), but for most other purposes it is used in the form of hypochlorites, organic and inorganic chloramines, chlorinated hydantoins, chlorinated isocyanurates, and similar oxidising compounds capable of releasing chlorine. In the presence of water these compounds produce hypochlorous acid (HOCl) and hypochlorite ion (OCl^-) and it is generally considered that the lethal action on micro-organisms is due to chlorination of cell protein or enzyme systems by nonionised hypochlorous acid, although the hypochlorite ion may also contribute.

The activity of most of the compounds decreases with increase of pH, the activity of solutions of pH 4 to 7 being greater than those of higher pH values. However, stability is usually greater at an alkaline pH.

The potency of chlorine disinfectants is expressed in terms of **available chlorine**. This is based on the concept of chlorine gas (Cl_2) as the reference substance. Two atoms of chlorine (2 × Cl) yield in water only one molecule of hypochlorous acid (on which activity is based), while hypochlorites and chloramines yield one molecule of hypochlorous acid for each atom of chlorine as shown in the following equations:

$$Cl_2 + H_2O \leftrightarrow HOCl + H^+ + Cl^-$$
$$NaOCl + H_2O \leftrightarrow HOCl + NaOH$$

Thus the assayed chlorine in such compounds has to be multiplied by 2 to produce 'available chlorine'. The term 'active chlorine' has been used confusingly for either 'available chlorine' (Cl_2) or 'combined chlorine' (Cl).

Because they have relatively low residual toxicity, chlorine compounds are useful for the disinfection of relatively clean impervious surfaces, such as babies' feeding bottles, baths, and food and dairy equipment. A concentration of 100 to 300 ppm of 'available chlorine' is used; a detergent may be added to ensure wetting of the surface. Solutions containing 1000 ppm 'available chlorine' are recommended for minor surface contamination and as part of general good hygiene practice. Solutions containing 10 000 ppm 'available chlorine' are used to disinfect surfaces contaminated with spilled blood or body fluids; this strength is effective against viruses including human immunodeficiency virus (HIV) and hepatitis B virus (p.1623). A concentration providing 20 000 ppm 'available chlorine' is used for material from patients with Creutzfeldt-Jakob disease (p.1622).

On a large scale, chlorine gas is used to disinfect public water supplies. On a smaller scale, the use of chlorine compounds is more convenient and sodium hypochlorite, tosylchloramide sodium, chlorinated lime, chlorine dioxide, or halazone are used. After satisfying the chlorine demand (the amount of chlorine needed to react with organic matter and other substances), a free-residual content of 0.2 to 0.4 ppm 'available chlorine' should be maintained, though more is required for alkaline waters with a pH of 9 or more. For the disinfection of potentially contaminated water a concentration of 1 ppm is recommended. Excessive residual chlorine may be removed by adding a little citric acid or sodium thiosulfate.

For use in small swimming pools, sodium or calcium hypochlorite may be added daily to maintain a free-residual 'available chlorine' concentration of 1 to 3 ppm. Tosylchloramide sodium, chlorinated lime, and the isocyanurates (see Troclosene, p.1665) may also be used. To minimise irritation of the eyes, maintain disinfectant activity, prevent precipitation of salts, and prevent metal corrosion, a pH of 7.2 to 7.8 should be maintained.

Solutions of chlorine-releasing compounds are also used in wound desloughing and disinfection (but see Disinfection: Wounds, under Sodium Hypochlorite, p.1662).

Chlorine Dioxide

926; Cloro, dióxido de.

ClO_2 = 67.45.

CAS — 10049-04-4.

Profile

Chlorine dioxide is a strong oxidising agent with the general properties of chlorine (p.1638). It is rapidly active against vegetative bacteria, including mycobacteria, and viruses and is also sporicidal. It is used for disinfection of medical equipment either in gaseous form or in a solution that requires activation before use and yields 700 to 1100 ppm 'available chlorine' (see p.1638). Chlorine dioxide is irritant to the skin, eyes, and respiratory tract and should be stored in sealed containers. It is potentially corrosive to many materials and solutions may contain corrosion inhibitors.

Chlorine dioxide is also used for treatment and disinfection of water supplies.

◊ General references.

1. WHO. Chlorine dioxide (gas). *Concise International Chemical Assessment Document 37* Geneva: WHO, 2002. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad37.pdf (accessed 14/03/06)

Disinfection of endoscopes. Chlorine dioxide solutions are used as an alternative to glutaral for the disinfection of endoscopes (p.1623).

Halitosis. Chlorine dioxide has been used in mouthwashes for the control of halitosis.[1]

1. Frascella J, *et al.* Odor reduction potential of a chlorine dioxide mouthrinse. *J Clin Dent* 1998; **9:** 39–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Retardex; ***Philipp.:*** Oracare; ***UK:*** Retardex.

Chloroacetamide

Chloracetamide; Cloroacetamida. 2-Chloroacetamide.

C_2H_4ClNO = 93.51.

CAS — 79-07-2.

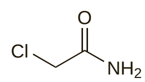

Profile

Chloroacetamide is a preservative that has been used in topical pharmaceutical preparations and cosmetics.

N-(3-Chloroallyl)hexaminium Chloride

N-(3-Cloroalil)hexaminio, cloruro de; Quaternium-15. 1-(3-Chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride.

$C_9H_{16}Cl_2N_4$ = 251.2.

CAS — 4080-31-3.

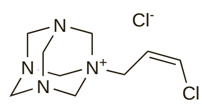

Profile

N-(3-Chloroallyl)hexaminium chloride is an antimicrobial preservative used in pharmaceutical preparations and cosmetics. Skin reactions have been reported.

Chlorobutanol *(BAN, rINN)*

Acetone-Chloroforme; Alcohol Trichlorisobutylicus; Chlorbutanol; Chlorbutanolum; Chlorbutol; Chloretone; Chlorobutanolis; Chlorobutanolum; Clorobutanol; Klooributanoli; Klorbutanol; Klorobutanol; Trichlorbutanolum. 1,1,1-Trichloro-2-methylpropan-2-ol.

Хлоробутанол

$C_4H_7Cl_3O$ = 177.5.

CAS — 57-15-8 (anhydrous chlorobutanol); 6001-64-5 (chlorobutanol hemihydrate).

ATC — A04AD04.

ATC Vet — QA04AD04.

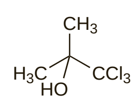

Pharmacopoeias. *Eur.* (see p.vii), *Int.*, and *USNF* allow either the anhydrous form or the hemihydrate; *Eur.* includes them as separate monographs. *Chin.* specifies the hemihydrate. *Jpn* permits up to 6% of water.

Ph. Eur. 6.2 (Chlorobutanol Hemihydrate; Chlorobutanol BP 2008). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 78°. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

Ph. Eur. 6.2 (Chlorobutanol, Anhydrous). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 95°. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

USNF 26 (Chlorobutanol). It is anhydrous or contains not more than one-half molecule of water of hydration. Colourless or white crystals with a characteristic, somewhat camphoraceous odour. M.p. about 76° for the hemihydrate and about 95° for the anhydrous form. Soluble 1 in 125 of water, 1 in 1 of alcohol, and 1 in 10 of glycerol; freely soluble in chloroform, in ether, and in volatile oils. Store in airtight containers.

Incompatibility and stability. The activity of chlorobutanol can be adversely affected by the presence of other compounds as well as by the packaging material. There may be sorption onto substances like magnesium trisilicate, bentonite, carmellose,[1] polyethylene,[2,3] or polyhydroxy-ethylmethacrylate that has been used in soft contact lenses.[4] Increasing heat[2,3] or pH[5,6] can reduce stability and activity.

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Friesen WT, Plein EM. The antibacterial stability of chlorobutanol stored in polyethylene bottles. *Am J Hosp Pharm* 1971; **28:** 507–12.
3. Holdsworth DG, *et al.* Fate of chlorbutol during storage in polyethylene dropper containers and simulated patient use. *J Clin Hosp Pharm* 1984; **9:** 29–39.
4. Richardson NE, *et al.* The interaction of preservatives with polyhydroxy-ethylmethacrylate (polyHEMA). *J Pharm Pharmacol* 1978; **30:** 469–75.
5. Nair AD, Lach JL. The kinetics of degradation of chlorobutanol. *J Am Pharm Assoc (Sci)* 1959; **48:** 390–5.
6. Patwa NV, Huyck CL. Stability of chlorobutanol. *J Am Pharm Assoc* 1966; **NS6:** 372–3.

Adverse Effects

Acute poisoning with chlorobutanol may produce CNS depression with weakness, loss of consciousness, and depressed respiration. Delayed (type IV) hypersensitivity reactions have been reported rarely.

◊ References.

1. Nordt SP. Chlorobutanol toxicity. *Ann Pharmacother* 1996; **30:** 1179–80.

Effects on the cardiovascular system. Rapid falls in arterial blood pressure were observed after injections of heparin containing chlorobutanol in patients undergoing coronary bypass.[1] No fall in blood pressure was seen in patients who received preservative-free heparin injection.

1. Bowler GMR, *et al.* Sharp fall in blood pressure after injection of heparin containing chlorbutol. *Lancet* 1986; **i:** 848–9.

Effects on mental function. The sedative effects of chlorobutanol have been reported to be a problem in a patient dependent on large doses (0.9 to 1.5 g daily with salicylamide 1.8 to 3.0 g daily)[1] and in another patient given high doses of morphine in an infusion preserved with chlorobutanol.[2]

1. Borody T, *et al.* Chlorbutol toxicity and dependence. *Med J Aust* 1979; **i:** 288.
2. DeChristoforo R, *et al.* High-dose morphine infusion complicated by chlorobutanol-induced somnolence. *Ann Intern Med* 1983; **98:** 335–6.

Hypersensitivity. A delayed, cellular type of hypersensitivity reaction to chlorobutanol used to preserve heparin injection after subcutaneous injection has been reported.[1] Pruritus from intranasal desmopressin has been attributed to the chlorobutanol preservative.[2]

1. Dux S, *et al.* Hypersensitivity reaction to chlorbutanol-preserved heparin. *Lancet* 1981; **i:** 149.
2. Itabashi A, *et al.* Hypersensitivity to chlorobutanol in DDAVP solution. *Lancet* 1982; **i:** 108.

Uses and Administration

Chlorobutanol has antibacterial and antifungal properties and it is used at a concentration of 0.5% as a preservative in injections and in eye drops as well as cosmetics.

Chlorobutanol has been used as a mild sedative and local analgesic but other compounds are preferred. It has been used in preparations for inflammatory and painful conditions of the ear and oropharynx.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Optrex; ***Port.:*** Vizoptal†.

Multi-ingredient: ***Arg.:*** Eludril; Otocalmia; ***Austral.:*** Cerumol; ***Austria:*** Aleot; ***Belg.:*** Eludril; Givalex; Prurisedine; ***Braz.:*** Auritricin; Lavolho†; ***Canad.:*** Cerumol; ***Fr.:*** Alodont; Balsamorhinol; Eludril; Givalex; ***Ger.:*** Givalex†; ***Hong Kong:*** Fungifax†; ***India:*** Andre; Clearwax; Waxolve; ***Irl.:*** Cerumol; Karvol; ***Israel:*** Cepadont; Cerumol; Dentin; Karvol; Pitrisan; ***Ital.:*** Fialetta Odontalgica Dr Knapp; Odontalgiche (Dentali)†; ***Malaysia:*** Cerumol; ***NZ:*** Frador; ***Port.:*** Eludril; Otoceril; ***Rus.:*** Eludril (Элюдрил); ***S.Afr.:*** Aurone Forte; Cerumol; Chamberlains Traditional Colic Remedy; Karvol; ***Singapore:*** Cerumol; Eludril; Karvol; ***Spain:*** Eludril; Otocerum; ***Switz.:*** Alodont†; Cerumenol; Eludril; ***Thai.:*** Opplin†; Optal; Optic; ***Turk.:*** Disinol; ***UK:*** Cerumol; Cetanorm; DDD; Dermidex; Eludril; Frador; Karvol; Monphytol†; ***USA:*** Outgro.

Chlorocarvacrol

5-Chlorocarvacrol; Clorcarvacrol; Clorcarvacrolum; Kloorikarvakroli; Klorkarvakrol; Monochloroisothymol. 4-Chloro-5-isopropyl-2-methylphenol.

$C_{10}H_{13}ClO$ = 184.7.

CAS — 5665-94-1.

Profile

Chlorocarvacrol is a phenolic antiseptic that is used as an ingredient of preparations for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Delta-Hadensa; Hadensa; Haemanal; ***Chile:*** Vatanal; ***Fin.:*** Hadensa; ***Ger.:*** Alcos-Anal†; ***Neth.:*** Epianal; ***Norw.:*** Alcos-Anal; ***Spain:*** Hadensa; ***Turk.:*** Hedensa.

The symbol † denotes a preparation no longer actively marketed

Chlorocresol *(USAN, rINN)*

Chlorkresol; Chlorkresolum; Chlorocrésol; Chlorocresolum; Chlorokrezolis; Clorocresol; Kloorikresoli; Klorkresol; Klorokrezol; Parachlorometacresol; PCMC. *p*-Chloro-*m*-cresol; 4-Chloro-3-methylphenol.

Хлорокрезол

C_7H_7ClO = 142.6.

CAS — 59-50-7.

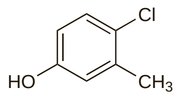

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Chlorocresol). A white or almost white, crystalline powder or compacted crystalline masses supplied as pellets or colourless or white crystals. M.p. 64° to 67°. Slightly soluble in water; very soluble in alcohol; freely soluble in fatty oils. It dissolves in solutions of alkali hydroxides. Protect from light.

USNF 26 (Chlorocresol). Colourless or practically colourless crystals or crystalline powder with a characteristic nontarry odour; it is volatile in steam. M.p. 63° to 66°. Soluble 1 in 260 of water; more soluble in hot water; soluble 1 in 0.4 of alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. Chlorocresol has long been recognised to be incompatible with a range of compounds including: calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, quinine hydrochloride,[1] methylcellulose,[2] and nonionic surfactants[3,4] such as cetomacrogol 1000 and polysorbate 80.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; **158:** 260–2.
2. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; **42:** 583–8.
3. *PSGB Lab Report P/70/15* 1970.
4. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.

Adverse Effects, Treatment, and Precautions

As for Phenol, p.1656. The antimicrobial activity of chlorocresol may be reduced by incompatibility (see above), adsorption, increasing pH, or through combination with organic matter (including oils and fats) or nonionic surfactants.

Chlorocresol is less toxic than phenol. Sensitisation reactions may follow application to the skin and hypersensitivity has occurred after systemic use of injections containing chlorocresol as a preservative.

Uses and Administration

Chlorocresol is a potent chlorinated phenolic disinfectant and antiseptic. It has bactericidal activity against Gram-positive and Gram-negative bacteria and is effective against fungi but has little activity against bacterial spores except at high temperatures. It is more active in acid than in alkaline solution.

Chlorocresol is used in preparations for disinfection of the skin and wounds. It is also used as a preservative in cosmetics and in creams and other preparations for external use that contain water.

Chlorocresol is used as a preservative in aqueous injections issued in multidose containers. It may also be added to aqueous preparations that cannot be sterilised in their final containers and have to be prepared using aseptic precautions. Concentrations of 0.1% have generally been used. Injections prepared with chlorocresol should not be injected into the CSF, the eye, or the heart. Also such injections should generally not be given in volumes greater than 15 mL. Sterilisation by heating with a bactericide such as chlorocresol is no longer a recommended practice.

Preparations

BPC 1973: Proflavine Cream.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Perfungol†; ***Austria:*** Ulcurilen; ***Chile:*** Perfungol; ***Cz.:*** Cyteal; ***Fr.:*** Cicatryl; Cyteal; ***Ger.:*** Bomix; Helipur; Ulcurilen N†; ***Gr.:*** Lyoderm; Octrene; ***Irl.:*** Anbesol; Valderma†; ***Ital.:*** Helipur; Hygienist†; ***Port.:*** Anbegele†; Cyteal; ***Rus.:*** Cyteal (Цитеал); ***S.Afr.:*** Anbesol; ***Singapore:*** Cyteal; ***UK:*** Anbesol; Cymex; Cyteal; Valderma.

Chlorothymol

Clorotimol; Monochlorothymol. 6-Chlorothymol; 4-Chloro-2-isopropyl-5-methylphenol.

$C_{10}H_{13}ClO$ = 184.7.

CAS — 89-68-9.

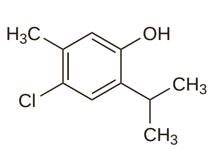

Profile

Chlorothymol is a chlorinated phenolic antiseptic used as an ingredient of preparations for hand and skin disinfection and topical treatment of fungal infections. It has also been used in preparations for anorectal disorders, cold symptoms, and mouth disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Pioral Pasta.

Multi-ingredient: ***Arg.:*** Solvex Liquido Fungicida†; ***India:*** Easi Breathe; Karvol Plus; Sinarest Vapocaps; ***Ital.:*** Labocaina; Traumicid†; Vagisil; ***Philipp.:*** Calmoseptine.

Chloroxylenol *(BAN, USAN, rINN)*

Chloroxylénol; Chloroxylenolum; Cloroxilenol; Parachlorometaxylenol; PCMX. 4-Chloro-3,5-xylenol; 4-Chloro-3,5-dimethylphenol.

Хлороксиленол

C_8H_9ClO = 156.6.

CAS — 88-04-0.

ATC — D08AE05.

ATC Vet — QD08AE05.

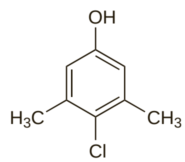

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Chloroxylenol). White or cream crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

USP 31 (Chloroxylenol). White crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol, in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

Incompatibility. Chloroxylenol has been reported to be incompatible with nonionic surfactants and methylcellulose.

Adverse Effects and Precautions

Chloroxylenol in the recommended dilutions is generally non-irritant but skin sensitivity has occurred. There have been isolated reports of poisoning. Symptoms include corrosion of the oral mucosa, larynx, and the gastrointestinal tract, bradycardia, hypotension, and renal failure. Large amounts may cause CNS depression. Pulmonary aspiration of chloroxylenol-based disinfectants may result in pneumonia, acute respiratory distress syndrome, and cardiorespiratory arrest.

The antimicrobial activity of chloroxylenol may be diminished through combination with organic matter. Aqueous solutions of chloroxylenol may be susceptible to contamination with micro-organisms. To reduce this risk, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Poisoning. Reports of fatal or severe self-poisoning with chloroxylenol solution.[1-5]

1. Meek D, *et al.* Fatal self-poisoning with Dettol. *Postgrad Med J* 1977; **53:** 229–31.
2. Joubert P, *et al.* Severe Dettol (chloroxylenol and terpineol) poisoning. *BMJ* 1978; **1:** 890.
3. Chan TYK, *et al.* Chemical gastro-oesophagitis, upper gastrointestinal haemorrhage and gastroscopic findings following Dettol poisoning. *Hum Exp Toxicol* 1995; **14:** 18–19.
4. Chan TY, Critchley JA. Pulmonary aspiration following Dettol poisoning: the scope for prevention. *Hum Exp Toxicol* 1996; **15:** 843–6.
5. Joynt GM, *et al.* Delayed upper airway obstruction: a life-threatening complication of Dettol poisoning. *Anaesthesia* 1997; **52:** 261–3.

Uses and Administration

Chloroxylenol is a chlorinated phenolic antiseptic that is bactericidal against most Gram-positive bacteria but less active against staphylococci and Gram-negative bacteria, and is often inactive against *Pseudomonas* spp. Its activity against *Ps. aeruginosa* appears to be increased by the addition of edetic acid. It is inactive against bacterial spores.

Chloroxylenol Solution (BP 2008) is used for skin and wound disinfection, and chloroxylenol is used as a preservative in a variety of other topical formulations.

Preparations

BP 2008: Chloroxylenol Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Espadol†; Previnfec†; Talowin; ***Austral.:*** Dettol Classic; ***Belg.:*** Dettol; ***Canad.:*** Antiseptic Ointment†; ***Gr.:*** Dettol; ***Hong Kong:*** Dettol; ***Irl.:*** Dettol; ***Ital.:*** Neomercurocromo; ***Malaysia:*** Dettol; ***Neth.:*** Dettol; ***NZ:*** Dettol; ***Singapore:*** Dettol; ***Thai.:*** Dettol; ***UK:*** Dettol.

Multi-ingredient: ***Arg.:*** Jabonacid; Kytinon ATM†; ZeaSorb; ***Austral.:*** Dettol Cream; Solyptol†; ZeaSorb; ***Canad.:*** ZeaSorb; ***Chile:*** Acnaid†; Dermac Crema; ZeaSorb†; ***Ger.:*** Gehwol Fungizid†; ***Hong Kong:*** Acne-Aid; Dettol†; ***India:*** Dettol Obstetric; Dettolin; ***Indon.:*** ZeaSorb; ***Irl.:*** Dettol; ZeaSorb; ***Israel:*** Gargol; Hemo; Rexitol; ***Ital.:*** Foille Scottature; Foille Sole; ***Malaysia:*** Acne-Aid; Dettol; ZeaSorb†; ***NZ:*** Dettol; ***Philipp.:*** Strepsils; ZeaSorb; ***Pol.:*** Sterovag; ***S.Afr.:*** Respisniffers; Woodwards Inhalant; ZeaSorb; ***Singapore:*** Acne-Aid; Dettol; ZeaSorb; ***Thai.:*** Dettol; Johnson's Baby Prickly Heat Powder†; ZeaSorb; ***UK:*** Dettol; Rinstead; Skintex; TCP; Waxwane†; ZeaSorb; ***USA:*** Calamycin; Cortane-B; Cortic ND; Cyotic; Dermacoat; Foille; Fungi-Nail; Geri-Lav Free; Gordochom; Lobana Peri-Garde; Mediotic-HC; Otomar-HC; PramOtic; Tri-Otic†; Unguentine Plus; Zoto-HC.

Cicliomenol *(rINN)*

Ciclioménol; Cicliomenolum. 2-Cyclohexyl-4-iodo-3,5-xylenol.

Циклиоменол

$C_{14}H_{19}IO$ = 330.2.

CAS — 10572-34-6.

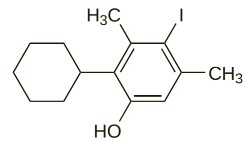

Profile

Cicliomenol is an antiseptic included in preparations intended for the topical treatment of mouth and throat infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Golamed†.

Multi-ingredient: ***Ital.:*** Golamed Due†; Pastiglie Valda†.

Cinnamic Acid

Cinámico, ácido; Cinnamylic Acid. *trans*-3-Phenylpropenoic acid.

$C_6H_5.CH{:}CH.CO_2H$ = 148.2.

CAS — 621-82-9.

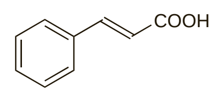

Pharmacopoeias. In *Br.*

BP 2008 (Cinnamic Acid). Colourless crystals with a faint balsamic odour. Very slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether.

Profile

Cinnamic acid has preservative properties. It is used with benzoic acid and other substances to simulate the flavour of tolu.

Preparations

BP 2008: Tolu-flavour Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Hemocane; Potters Gees Linctus; Sanderson's Throat Specific.

Cloponone *(BAN, rINN)*

Clopona; Clopononum. (*RS*)-2,2-Dichloro-*N*-[4-chloro-α-(chloromethyl)phenacyl]acetamide.

Клопонон

$C_{11}H_9Cl_4NO_2$ = 329.0.

CAS — 15301-50-5.

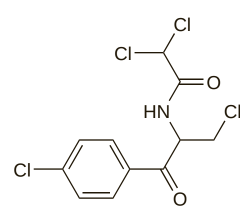

Profile

Cloponone is an antiseptic included in multi-ingredient preparations intended for the topical treatment of vaginal infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Ginetris†.

Clorophene *(USAN)*

Clorofene *(pINN)*; Clorfene; Clorofène; Clorofeno; Clorofenum; NSC-59989; Septiphene. 2-Benzyl-4-chlorophenol.

Клорофен

$C_{13}H_{11}ClO = 218.7$.

CAS — 120-32-1.

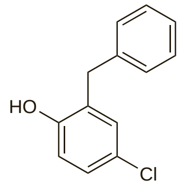

Profile

Clorophene is a chlorinated phenolic antiseptic stated to be active against a wide range of bacteria, fungi, protozoa, and viruses. It is used as a skin disinfectant and for surface and instrument disinfection. Clorophene sodium has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Neo-Sabenyl; ***Ger.:*** Bomix; Freka-Derm; Freka-Sept 80; Helipur; ***Ital.:*** Helipur; Hygienist†; ***Switz.:*** Frekaderm†; ***UAE:*** Radol; ***USA:*** BTK-Plus.

Cresol

Crésol brut (cresol, crude); Cresolum; Cresolum crudum (cresol, crude); Cresylic Acid; Kresol; Kresol, rå (cresol, crude); Kresoli, raaka (cresol, crude); Kresolum Venale; Krezol; Krezolis, negrynintas (cresol, crude); Metacresol *(BAN)*; Tricresol; Trikresolum. Methylphenol.

Крезол

$C_7H_8O = 108.1$.

CAS — 1319-77-3; 95-48-7 (o-cresol); 108-39-4 (m-cresol); 106-44-5 (p-cresol).

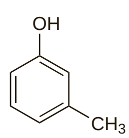

NOTE. Some grades of mixed cresols may be equivalent to Tar Acids (p.1663).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Eur. also includes metacresol.

Ph. Eur. 6.2 (Cresol, Crude; Cresolum Crudum). A mixture of *o*-, *m*-, and *p*-methylphenol. A colourless or pale brown liquid. Relative density 1.029 to 1.044. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Protect from light.

Ph. Eur. 6.2 (Metacresol; Metacresolum). A colourless or yellowish liquid. Relative density about 1.03. M.p. about 11°. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.

USNF 26 (Cresol). A mixture of cresol isomers obtained from coal tar or petroleum. A colourless, yellowish to brownish-yellow, or pinkish, highly refractive liquid, becoming darker with age or on exposure to light, with a phenol-like, sometimes empyreumatic odour. Specific gravity 1.030 to 1.038. Sparingly soluble in water, usually forming a cloudy solution; miscible with alcohol, with ether, and with glycerol; dissolves in solutions of fixed alkali hydroxides. A saturated solution in water is neutral or slightly acid to litmus. Store in airtight containers. Protect from light.

Profile

Cresol is a disinfectant with a similar action to phenol (p.1656); suitable precautions should be taken to prevent absorption through the skin.

It has been used as Cresol and Soap Solution (BP 1968) (Lysol) as a general disinfectant but it has been largely superseded by other, less irritant, phenolic disinfectants. Cresol has been used in dentistry, alone or with formaldehyde, but is caustic to the skin and unsuitable for skin and wound disinfection. The cresols have been widely used in disinfectants for domestic and hospital use. Cresol is also used as an antimicrobial preservative in parenteral pharmaceutical preparations and in some topical formulations.

Poisoning. References to poisoning with cresol solutions.[1-7]

1. Côté M-A, *et al.* Acute Heinz-body anaemia due to severe cresol poisoning: successful treatment with erythrocytapheresis. *Can Med Assoc J* 1984; **130:** 1319–22.
2. Wu ML, *et al.* Concentrated cresol intoxication. *Vet Hum Toxicol* 1998; **40:** 341–3.
3. Hashimoto T, *et al.* Marked increases of aminotransferase levels after cresol ingestion. *Am J Emerg Med* 1998; **16:** 667–8.
4. Sakai Y, *et al.* Chemical burn with systemic cresol intoxication. *Pediatr Int* 1999; **41:** 174–6.
5. Monma-Ohtaki J, *et al.* An autopsy case of poisoning by massive absorption of cresol a short time before death. *Forensic Sci Int* 2002; **126:** 77–81.
6. Hayakawa M. Severe hepatic dysfunction following cresol poisoning. *Intensive Care Med* 2002; **28:** 1190–1.
7. Kamijo Y, *et al.* Hepatocellular injury with hyperaminotransferasemia after cresol ingestion. *Arch Pathol Lab Med* 2003; **127:** 364–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Creolina.

Multi-ingredient: ***Arg.:*** Algiodent; Sulfanoral T; ***Austral.:*** Formo-Cresol Mitis; ***Canad.:*** Gernel; ***Spain:*** Tifell†; ***USA:*** Cresylate.

Decamethoxine

Dekametoksin. *N,N,N′,N′*-Tetramethyl-*N,N′*-bis(2-{[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy}-2-oxoethyl)-1,10-decanediaminium dichloride.

Декаметоксин

$C_{38}H_{74}Cl_2N_2O_4 = 693.9$.

CAS — 38146-42-8.

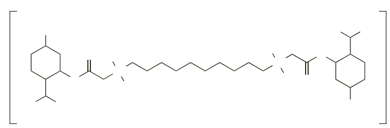

Profile

Decamethoxine is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used topically for disinfection of the skin and mucous membranes and for disinfection of equipment. Decamethoxine is also used as a gargle for infections of the oral cavity and has been used topically or as an irrigation for infections of the skin and various body cavities.

Dehydroacetic Acid

Deshidroacético, ácido; Methylacetopyronone. 3-Acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione (keto form); 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (enol form).

$C_8H_8O_4 = 168.1$.

CAS — 520-45-6 (keto form); 771-03-9 (enol form).

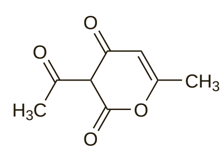

(keto form)

Pharmacopoeias. In *USNF.*

USNF 26 (Dehydroacetic Acid). A white or nearly white, crystalline powder. Very slightly soluble in water; soluble in aqueous solutions of alkalis. One g dissolves in about 35 mL of alcohol and in 5 mL of acetone.

Sodium Dehydroacetate

Deshidroacetato sódico. The sodium salt of 3-acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione.

$C_8H_7NaO_4 = 190.1$.

CAS — 4418-26-2.

Pharmacopoeias. In *USNF.*

USNF 26 (Sodium Dehydroacetate). A white or practically white, odourless powder. Freely soluble in water, in glycerol, and in propylene glycol.

Incompatibility. The activity of sodium dehydroacetate may be reduced by alkaline pH or interaction with nonionic surfactants.

Profile

Dehydroacetic acid and sodium dehydroacetate have some antifungal activity and have been used in the preservation of cosmetics and oral preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Venez.:*** Photoderm AKN.

Dequalinium Chloride *(BAN, rINN)*

BAQD-10; Cloruro de decualinio; Decalinium Chloride; Decaminum; Dekalinyum Klorür; Dekvalinio chloridas; Dekvalinium dichlorid; Dekvaliniumklorid; Dekvalinium-klorid; Dekvaliniumkloridi; Dequalinii chloridum; Dequalinii Dichloridum; Déqualinium, chlorure de. *N,N*-Decamethylenebis(4-amino-2-methylquinolinium chloride).

Деквалиния Хлорид

$C_{30}H_{40}Cl_2N_4 = 527.6$.

CAS — 6707-58-0 (dequalinium); 522-51-0 (dequalinium chloride); 4028-98-2 (dequalinium acetate); 16022-70-1 (dequalinium salicylate).

ATC — D08AH01; G01AC05; R02AA02.

ATC Vet — QD08AH01; QG01AC05; QR02AA02.

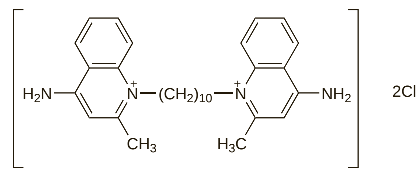

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dequalinium Chloride). A white or yellowish-white, hygroscopic powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Incompatibility. Dequalinium chloride is incompatible with soaps and other anionic surfactants, with phenol, and with chlorocresol.

Profile

Dequalinium chloride is a bisquaternary quinolinium antiseptic, bactericidal against many Gram-positive and Gram-negative bacteria, and effective against fungi. It is mainly used in the form of lozenges in the treatment of minor infections of the mouth and throat. It has been applied topically in the treatment of skin and vaginal infections.

Dequalinium salicylate and undecenoate have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Dequavagyn; Evazol; Sorot; Tonsillol; ***Belg.:*** Anginol; Laryngarsol; ***Canad.:*** Dequadin; ***Chile:*** Larylin†; ***Ger.:*** Evazol; Fluomycin N; Gurgellosung-ratiopharm; Maltyl†; Sorot; Stada Gurgellosung†; ***Hong Kong:*** Delin; Dequadin; Roxine; ***Indon.:*** Decamedin; Degirol; SP Troches; ***Irl.:*** Dequadin; ***Ital.:*** Dequadin; Dequosangola; Faringina; Goladin; Osangin; Pumilsan; ***Malaysia:*** Delin; Denium†; DQM; SP Troches; Synti†; Uphadeq†; ***Mex.:*** Apocatil†; ***Neth.:*** Gargilon; Natterman Streptofree; ***Philipp.:*** Dequadin; ***S.Afr.:*** Dequadin†; ***Singapore:*** Beacons DQ; Dequa-loz; Dequadin; SP Troches; ***Spain:*** Dequadin†; ***Switz.:*** Decatylene; Fluomizin; Pastilles pour la gorge formule 535†; ***Thai.:*** Decho; Deo; Dequadin; V Day Lozenges†; ***Turk.:*** Dequadin; ***UK:*** Dequadin; Labosept; ***Venez.:*** Dequadin; Laimolin.

Multi-ingredient: ***Austria:*** Dequafungan; Dequalinetten; Dequonal; Eucillin; Fluorex Plus; Tetesept; ***Belg.:*** Angin-San; Anginol-Lidocaine; Buccosan†; Dequalid; Ororhinathiol; Tricidine Dequalinium†; ***Braz.:*** Dequadin; ***Cz.:*** Larypront†; Stas†; Tetesept Angidin†; ***Fin.:*** Septison; ***Fr.:*** Humex Mal de Gorge sans sucre; ***Ger.:*** Corti-Dynexan†; Dequonal; Ephepect-Blocker-Pastillen N; Inspirol Halsschmerztabletten†; Jasimenth CN; Mycatox†; Otolitan N farblos†; Wick Sulagil; ***Hong Kong:*** Decatylen; Deq; Ephepect Blocker; Quadezyme; ***Indon.:*** Sentril; ***Irl.:*** Dequacaine; ***Ital.:*** Lisomucil Gola; Transpulmina Gola; ***Malaysia:*** Decatylen; Deq; Upha Lozenges; ***Mex.:*** Angenovag; ***Norw.:*** Apolar med dekvalin; ***Pol.:*** Tetesept; ***Port.:*** Anginova; Decatyleno; Dek; Medifon; ***S.Afr.:*** Dequadin Mouth Paint; ***Singapore:*** Decatylen; Deq; ***Spain:*** Anginovag; Roberfarin; Sedofarin; ***Switz.:*** Anginova†; Arbid-top; Decasept N; Decatylene Neo; Dequonal; Gramipan†; Neo-Bucosin†; Tyroqualine; ***Thai.:*** Deq; Detoch†; Sentril; ***UK:*** Dequacaine; ***Venez.:*** Alantamida; Benzodiazol; Laimoqualin.

Diacetylaminoazotoluene

Diacetazotol; Diacetilaminoazotoluene; Pellidol. 4-Diacetylamino-2′,3-dimethylazobenzene.

$C_{18}H_{19}N_3O_2 = 309.4$.

CAS — 83-63-6.

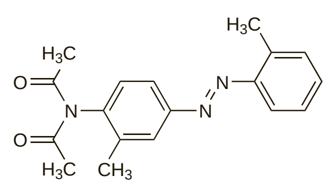

Profile

Diacetylaminoazotoluene is an antiseptic that has been used topically to promote wound healing.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Dermowund.

Dibrompropamidine Isetionate *(BANM, rINNM)*

Dibromipropamidiinidi-isetionaatti; Dibromopropamidine Isethionate; Dibromopropamidyny diizetionian; Dibrompropamidindiisetionat; Dibrompropamidin-diisetionát; Dibrompropamidine Diisetionate; Dibrompropamidine, diisétionate de; Dibrompropamidine, Isétionate de; Dibrompropamidini diisetionas; Dibrompropamidini Isetionas; Isetionato de dibrompropamidina. 3,3′-Dibromo-4,4′-trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).

Дибромпропамидина Изетионат

$C_{17}H_{18}Br_2N_4O_2,2C_2H_6O_4S$ = 722.4.

CAS — 496-00-4 (dibrompropamidine); 614-87-9 (dibrompropamidine isetionate).

ATC — D08AC01; S01AX14.

ATC Vet — QD08AC01; QS01AX14.

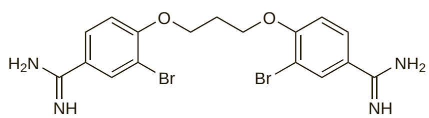

(dibrompropamidine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dibrompropamidine Diisetionate). A white or almost white, crystalline powder. Freely soluble or soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 5.0 to 6.0.

Profile

Dibrompropamidine isetionate is an aromatic diamidine antiseptic similar to propamidine (p.1660). It is bactericidal against Gram-positive bacteria but is less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties. It is available as topical preparations for the local treatment of minor eye and skin infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Brolene; Brulidine; ***Irl.:*** Brolene; ***Norw.:*** Brulidine; ***NZ:*** Brolene; ***UK:*** Brolene; Brulidine; Golden Eye Ointment; Pickles Antiseptic Cream.

Multi-ingredient: ***UK:*** Healthy Feet; No-Sor Nose Balm; RBC; Swarm.

Dichlordimethylhydantoin

Diclorodimetilhidantoína. 1,3-Dichloro-5,5-dimethylhydantoin; 1,3-Dichloro-5,5-dimethylimidazolidine-2,4-dione.

$C_5H_6Cl_2N_2O_2$ = 197.0.

CAS — 118-52-5.

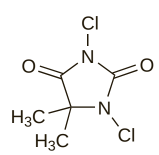

Profile

Dichlordimethylhydantoin is a disinfectant used as a source of chlorine, for sterilising food and dairy equipment and as a bleach. It contains about 72% w/w of 'available chlorine' (see p.1638).

Bromochlorodimethylhydantoin ($C_5H_6N_2O_2BrCl$ = 241.5) is a closely related bromine-releasing compound used for the disinfection of swimming-pool water.

Dichlorobenzyl Alcohol

Alcohol diclorobencílico; 2,4-Dichlorbenzyl-alcoholum; Dichlorophenylcarbinol; 2,4-Diklooribentsyyli-alkoholi; 2,4-Diklorbensylalkohol; Diklorobenzil Alkol. 2,4-Dichlorobenzyl alcohol.

$C_7H_6Cl_2O$ = 177.0.

CAS — 1777-82-8.

ATC — R02AA03.

ATC Vet — QR02AA03.

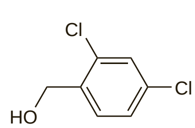

Profile

Dichlorobenzyl alcohol is an antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Neo Borocillina Collutorio; Neo Borocillina Spray.

Multi-ingredient: ***Austral.:*** Ayrton's Antiseptic; Logicin Rapid Relief; Sore Throat Chewing Gum†; Strepsils; Strepsils Plus; ***Austria:*** Coldangin; Neo-Angin; Sulgan 99; ***Belg.:*** Neofenox; Strepsils; Strepsils + Lidocaine; Strepsils Menthol; Strepsils Vit C; ***Canad.:*** Strepsils; Strepsils Cherry†; ***Chile:*** Cornina†; Hansaplast Antimicotico; ***Cz.:*** Neo-Angin; Strepsils; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; ***Denm.:*** Strepsils; ***Fin.:*** Bafucin; Strepsils; Strepsils Menthol; ***Fr.:*** Strepsils; Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsilspray Lidocaine; ***Ger.:*** Dobendan Synergie; Neo-Angin; ***Gr.:*** Strepsils; ***Hong Kong:*** Logicin Rapid Relief; Strepsils; Strepsils Dual Action; ***Hung.:*** Neo-Angin; Strepsils; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; ***India:*** Cofsils†; ***Irl.:*** Strepsils; Strepsils +Plus Anaesthetic; Strepsils Dual Action; Strepsils Vitamin C; ***Israel:*** Strepsils; Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; ***Ital.:*** Arscolloid; Benagol; Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; Bio-Arscolloid; Corti-Arscolloid; Farmagola†; Neo Borocillina; Neo Borocillina Balsamica; Neo Borocillina C; Neo Borocillina Tosse Compresse; ***Malaysia:*** Chericof; Strepsils; Strepsils Dual Action; ***Neth.:*** Strepsils; Strepsils Menthol en Eucalyptus; Strepsils Sinaasappel en Vitamine C; ***NZ:*** Strepsils; Strepsils Plus Anaesthetic; Strepsils with Vitamin C; ***Philipp.:*** Strepsils; ***Pol.:*** Neo-Angin; Strepsils; ***Port.:*** Benoral; Dropcina; ***Rus.:*** Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс)†; Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Suprima-Lor (Суприма-Лор); ***S.Afr.:*** Strepsils; Strepsils Eucalyptus Menthol; Strepsils Orange-C; Strepsils Plus; Strepsils Soothing Honey & Lemon; ***Singapore:*** Strepsils; Strepsils Dual Action; ***Spain:*** Strepsils; Strepsils con Vitamina C; Strepsils Lidocaina; ***Swed.:*** Bafucin; Strepsils; ***Switz.:*** Anginazol; Hextriletten; Lidazon; Neo-Angin au miel et citron; Neo-Angin avec vitamin C sans sucre; Neo-Angin sans sucre; Sulgan N; ***Thai.:*** Strepsils Butter Menthol Capsicum; Strepsils Plus Anaesthetic; Strepsils Plus Vit C; Strepsils Sugar Free; Throatsil; ***Turk.:*** Strepsils; Strepsils C; Strepsils Mentollu; ***UK:*** Strepsils; Strepsils with Vitamin C.

Dichloroxylenol *(BAN, rINN)*

DCMX; Dichlorometaxylenol; Dichloroxylénol; Dichloroxylenolum; Dicloroxilenol. 2,4-Dichloro-3,5-xylenol; 2,4-Dichloro-3,5-dimethylphenol.

Дихлороксиленол

$C_8H_8Cl_2O$ = 191.1.

CAS — 133-53-9.

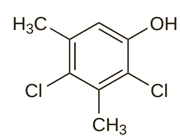

Profile

Dichloroxylenol is a chlorinated phenolic antiseptic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Fairgenol†; ***UAE:*** Radol.

Didecyldimethylammonium Chloride

DideciIdimetilamonio, cloruro de; Didecyldimonium Chloride. *N*-Decyl-*N*,*N*-demethyl-l-decanaminium chloride.

$C_{22}H_{48}ClN$ = 362.1.

CAS — 7173-51-5.

ATC — D08AJ06.

ATC Vet — QD08AJ06.

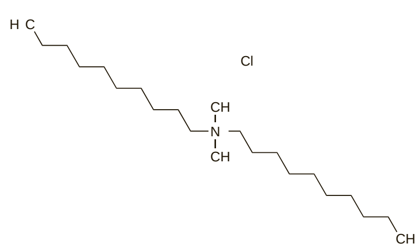

Profile

Didecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of the skin and mucous membranes. It is also used to disinfect instruments and surfaces.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Amosept; Fungisept; ***Ital.:*** Alfa; Farmasept; ***Thai.:*** Deconex 50FF†.

Multi-ingredient: ***Fr.:*** Aniospray 29; Aniospray 41; Aniosyme; Bacterianos D†; Chlorispray†; Hexanios G+R; Oxitou; Sanytol†; Surfanios; ***Ger.:*** Almyrol; Baccalin†; Bacillocid rasant†; Desoform†; Freka-Nol; Fugisept†; Gercid forte†; Gigasept Med†; Hexaquart L†; Hexaquart plus; Hexaquart S; Inova†; Kohrsolin FF; Korsolex Extra; Korsolex FF; Korsolex Plus; Lysoformin 3000; Lysoformin spezial; Meliseptol Rapid; Melsept SF; Melsitt; Quatohex; Teta Extra; ***Ital.:*** Melsept SF; ***Switz.:*** Desamon; ***Thai.:*** Deconex 53IN†; ***USA:*** Vi Rid-Ready.

1,6-Dihydroxy-2,5-dioxahexane

Ethylene Glycol Bis(semiformal); (Ethylenedioxy)dimethanol. [1,2-Ethanediylbis(oxy)]bismethanol.

$C_4H_{10}O_4$ = 122.1.

CAS — 3586-55-8.

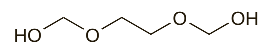

Profile

1,6-Dihydroxy-2,5,-dioxahexane is an aldehyde that slowly releases formaldehyde. It is used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Bacillol; Kohrsolin; Korsolex basic; Korsolex Extra.

Dioctyldimethylammonium Chloride

Dimethyldioctylammonium Chloride; Dioctyl Dimethyl Ammonium Chloride. *N*,*N*-Dimethyl-*N*-octyl-1-octanaminium chloride.

Диоктилдиметиламмония Хлорид

$C_{18}H_{40}ClN$ = 306.0.

CAS — 5538-94-3.

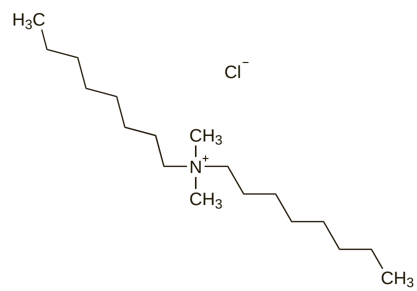

Profile

Dioctyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of surfaces.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Vi Rid-Ready.

Dodeclonium Bromide *(rINN)*

Bromuro de dodeclonio; Dodeclonii Bromidum; Dodéclonium, Bromure de; GR-412. [2-(*p*-Chlorophenoxy)ethyl]dodecyldimethylammonium bromide.

Додеклония Бромид

$C_{22}H_{39}BrClNO$ = 448.9.

CAS — 15687-13-5.

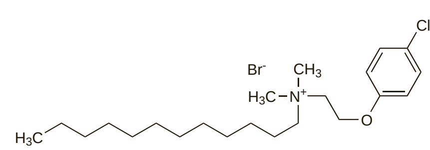

Profile

Dodeclonium bromide is an antiseptic that has been included in multi-ingredient preparations intended for the treatment of skin and anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Biogaze; ***Fr.:*** Sedorrhoide.

Domiphen Bromide *(BAN, USAN, rINN)*

Bromuro de domifeno; Domifeenibromidi; Domifenbromid; Domiphène, Bromure de; Domipheni Bromidum; NSC-39415; PDDB; Phenododecinium Bromide. Dodecyldimethyl-2-phenoxyethylammonium bromide.

Домифена Бромид

$C_{22}H_{40}BrNO = 414.5.$

CAS — 13900-14-6 (domiphen); 538-71-6 (domiphen bromide).

ATC — A01AB06.

ATC Vet — QA01AB06.

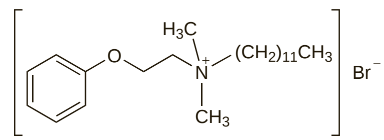

Pharmacopoeias. In *Br. Chin.* includes the monohydrate.

BP 2008 (Domiphen Bromide). Colourless or faintly yellow, crystalline flakes. Freely soluble in water and in alcohol; soluble in acetone.

Incompatibility. Domiphen bromide is incompatible with soaps and other anionic surfactants.

Profile

Domiphen bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). Preparations containing domiphen bromide are used in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Antiseptique Pastilles; Bronchodex Pastilles; ***Ital.:*** Bradoral; ***Malaysia:*** Domidin; ***Port.:*** Neobradoral.

Multi-ingredient: ***Austria:*** Bepanthen; Bradosol; ***Canad.:*** Nupercainal; ***Chile:*** Oralfresh Menta; ***Fr.:*** Fluoselgine; ***Ital.:*** Inalar; ***Pol.:*** Viosept.

Ethoxyquin

Etoxiquina. 6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline.

$C_{14}H_{19}NO = 217.3.$

CAS — 91-53-2.

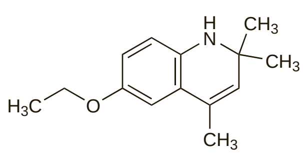

Profile

Ethoxyquin has been used as an antoxidant for the prevention of common scald of apples and pears during storage and as an additive to animal feeds. Concern has been expressed over the toxicity of ethoxyquin and its residues on foodstuffs and its use is limited or restricted in some countries.

Ethylene Oxide

Dimethylene oxide; Epoxietano; 1,2-Epoxyethane; Etylenu tlenek; Óxido de etileno; Oxirane; Oxirano; Oxirano.

Окись Этилена; Этиленоксид

$C_2H_4O = 44.05.$

CAS — 75-21-8.

Description. Ethylene oxide is a colourless flammable gas at room temperature and atmospheric pressure.

Stability. Mixtures of ethylene oxide with oxygen or air are explosive but the risk can be reduced by the addition of carbon dioxide or fluorocarbons.

Adverse Effects and Precautions

Ethylene oxide irritates the eyes and respiratory tract and may also cause nausea and vomiting, diarrhoea, headache, vertigo, CNS depression, dyspnoea, and pulmonary oedema. Liver and kidney damage and haemolysis may occur. Fatalities have occurred. Excessive exposure of the skin to liquid or solution causes burns, blistering, irritation, and dermatitis; percutaneous absorption may lead to systemic effects.

Many materials including plastics and rubber adsorb ethylene oxide. If such materials are being sterilised with ethylene oxide all traces of the gas must be removed before the materials can be used; removal may be by ventilation or more active means. Hypersensitivity reactions, including anaphylaxis, have been associated with ethylene oxide-contaminated materials. Ethylene oxide may also react with materials being sterilised to produce substances such as ethylene chlorohydrin (with chloride) or ethylene glycol (with water); these may contribute to any toxicity.

Pharmaceutical manufacturers within the EU have been advised to use ethylene oxide only when there is no alternative. Ethylene oxide has been shown to have carcinogenic and mutagenic properties and there is evidence of increased risk of neoplasms following occupational exposure.

◊ Reviews.

1. WHO. Ethylene oxide. *Environmental Health Criteria 55*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc55.htm (accessed 15/03/06)
2. WHO. Ethylene oxide health and safety guide. *IPCS Health and Safety Guide 16*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg016.htm (accessed 15/03/06)
3. WHO. Ethylene oxide. *Concise International Chemical Assessment Document 54* Geneva: WHO, 2003. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad54.pdf (accessed 15/03/06)

Carcinogenicity. Exposure of workers to ethylene oxide has been associated with the development of lymphatic and haematopoietic cancer and there is concern that it may be linked to breast cancer. In order to evaluate the carcinogenicity of ethylene oxide the National Institute for Occupational Safety and Health (NIOSH), in the mid 1980s, assembled a cohort of about 18 000 workers exposed to ethylene oxide.[1-3] Results of the initial cohort followed up to 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess of non-Hodgkin's lymphoma among men.[1] Based on limited clinical evidence from humans and from significant evidence in *animal* studies, the International Agency for Research on Cancer concluded in 1994 that there was sufficient evidence to classify ethylene oxide as a definite human carcinogen.[4] A later evaluation[3] of the NIOSH cohort from 1987 to 1998 indicated that, despite 2852 deaths as opposed to 1177 deaths in the earlier study, there was little evidence of cancer excesses for ethylene oxide exposed workers versus the general population, with the exception of bone cancer (6 deaths), and no conclusion could be drawn from this small number. However, exposure-response analyses found statistically significant evidence of an association between increased exposure and some types of haematopoietic cancer (non-Hodgkin's lymphoma and lymphocytic leukaemia), particularly for males.[2,3] There was also some evidence for a positive exposure-response for breast cancer. Follow-up of a cohort of 2876 workers exposed to ethylene oxide in the UK[5] found no statistically significant increase in mortality from cancer overall, or from any specific category of tumour. A study[6] of a cohort of 7576 female workers exposed to ethylene oxide suggested that ethylene oxide was associated with breast cancer. However, the authors indicated weaknesses in the study that could have influenced the findings.

1. Steenland K, *et al.* Mortality among workers exposed to ethylene oxide. *N Engl J Med* 1991; **324:** 1402–7.
2. Stayner L, *et al.* Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol* 1993; **138:** 787–98.
3. Steenland K, *et al.* Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occup Environ Med* 2004; **61:** 2–7.
4. IARC/WHO. Some industrial chemicals. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 60* 1994. Available at: http://monographs.iarc.fr/ENG/Monographs/vol60/volume60.pdf (accessed 23/05/06)
5. Coggon D, *et al.* Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. *Occup Environ Med* 2004; **61:** 358–62.
6. Steenland K, *et al.* Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control* 2003; **14:** 531–9.

Effects on the nervous system. Four men exposed to ethylene oxide at a concentration of greater than 700 ppm developed neurological disorders. One experienced headaches, nausea, vomiting, and lethargy followed by major motor seizures. The others had headaches, limb numbness and weakness, increased fatigue, trouble with memory and thought processes, and slurred speech. Three also developed cataracts, and one required bilateral cataract extractions.[1] Rash, followed a few months later by hand numbness and weakness, headaches, and cognitive impairment, has been reported[2] in a cluster of 12 surgical nurses and technicians after exposure for 5 months to ethylene oxide-contaminated surgical gowns. Several patients showed signs of peripheral and CNS dysfunction and one patient had signs of axonal injury.

1. Jay WM, *et al.* Possible relationship of ethylene oxide exposure to cataract formation. *Am J Ophthalmol* 1982; **93:** 727–32.
2. Brashear A, *et al.* Ethylene oxide neurotoxicity: a cluster of 12 nurses with peripheral and central nervous system toxicity. *Neurology* 1996; **46:** 992–8.

Hypersensitivity. Anaphylactoid reactions in dialysis patients have resulted from the use of dialysis equipment sterilised with ethylene oxide.[1-3] There have also been reports of hypersensitivity[4] and anaphylactoid[5] reactions in plateletpheresis donors caused by residues of ethylene oxide in components of apheresis kits. The most common adverse reactions reported have been dyspnoea, wheezing, urticaria, flushing, headache, and hypotension, but acute severe bronchospasm, circulatory collapse, cardiac arrest, and death have also occurred. It was noted[6] that where severe, sometimes fatal, anaphylactoid reactions have occurred at the beginning of dialysis, ethylene oxide has almost universally been implicated, although exposure to cuprammonium cellulose (cuprophane) dialysis membranes may also have been involved.

It has been reported that there may be an increased risk of ethylene oxide-induced anaphylactic shock in children undergoing surgery for spina bifida.[7] Such children might be at increased risk of sensitisation and anaphylaxis, and came into frequent contact with ethylene oxide through multiple operations and catheterisations.

Occupational asthma and contact dermatitis have been attributed to residual ethylene oxide in surgical gloves.[8]

1. Bommer J, *et al.* Anaphylactoid reactions in dialysis patients: role of ethylene-oxide. *Lancet* 1985; **ii:** 1382–5.
2. Rumpf KW, *et al.* Association of ethylene-oxide-induced IgE antibodies with symptoms in dialysis patients. *Lancet* 1985; **ii:** 1385–7.
3. Röckel A, *et al.* Ethylene oxide hypersensitivity in dialysis patients. *Lancet* 1986; **i:** 382–3.
4. Leitman SF, *et al.* Allergic reactions in healthy plateletpheresis donors caused by sensitization to ethylene oxide gas. *N Engl J Med* 1986; **315:** 1192–6.
5. Muylle L, *et al.* Anaphylactoid reaction in platelet-pheresis donor with IgE antibodies to ethylene oxide. *Lancet* 1986; **ii:** 1225.
6. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. *BMJ* 1986; **292:** 1221–2.
7. Moneret-Vautrin DA, *et al.* High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; **335:** 865–6.
8. Verraes S, Michel O. Occupational asthma induced by ethylene oxide. *Lancet* 1995; **346:** 1434–5.

Pregnancy. A study[1] of female staff responsible for sterilising instruments was carried out in all general hospitals in Finland. The incidence of spontaneous abortion (analysed according to employment at the time of conception and corrected for maternal age, parity, decade of pregnancy, smoking, and consumption of alcohol and coffee) was significantly increased in those exposed to ethylene oxide during pregnancy compared with those not so exposed. This study provoked criticism,[2,3] and the authors conceded that the study was not large enough to compare abortion rates and known ethylene oxide concentrations.[4] A retrospective analysis[5] of 32 dental assistants who had been exposed to ethylene oxide during pregnancy suggested that, after adjusting for age, the risk of spontaneous abortions and preterm or post-term births may have been more than doubled.

1. Hemminki K, *et al.* Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. *BMJ* 1982; **285:** 1461–3.
2. Gordon JE, Meinhardt TJ. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
3. Austin SG. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
4. Hemminki K, *et al.* Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976–7.
5. Rowland AS, *et al.* Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. *Epidemiology* 1996; **7:** 363–8.

Pharmacokinetics

Ethylene oxide gas is rapidly absorbed through the lungs and distributed throughout the body. Percutaneous absorption can occur from aqueous solutions. It is rapidly metabolised by hydrolysis or conjugation with glutathione.

Uses

Ethylene oxide is a bactericidal and fungicidal gaseous disinfectant that is effective against most micro-organisms, including viruses. It is also sporicidal. It is used for the gaseous sterilisation of heat-labile pharmaceutical and surgical materials that cannot be sterilised by other means.

Ethylene oxide forms explosive mixtures with air; this may be overcome by using mixtures containing 10% ethylene oxide in carbon dioxide, or by removing at least 95% of the air from the apparatus before admitting either ethylene oxide or a mixture of 90% ethylene oxide in carbon dioxide. Alternatively, non-flammable mixtures of dichlorodifluoromethane and trichlorofluoromethane with 9 to 12% w/w of ethylene oxide have been employed, but restrictions on the release of fluorocarbons or CFCs limit their use.

Effective sterilisation by ethylene oxide depends on exposure time, temperature, humidity, the amount and type of microbial contamination, and the partial pressure of the ethylene oxide in the exposure chamber. Concentrations of between 400 and 1000 mg/litre are usually used for sterilisation and the process time may vary from 30 minutes to 10 hours. The material being sterilised must be permeable to ethylene oxide if occluded micro-organisms are present. The bactericidal action is accelerated by increase of temperature; the average temperature used is between 40° and 50°.

Moisture is essential for sterilisation by ethylene oxide. In practice, dry micro-organisms need to be rehydrated before ethylene oxide can be effective; humidification is normally carried out under vacuum prior to introduction of ethylene oxide. Relative humidities of 40 to 60% are used.

Control of physical factors does not assure sterility, and the process should be monitored usually by using standardised suspensions of aerobic spores such as those of *Bacillus subtilis* var. *niger.*

Ethylhexanal

2-Ethylcaproaldehyde; 2-Ethylhexylaldehyde; Octylaldehyde. 2-Ethylhexanal.

$C_8H_{16}O = 128.2.$

CAS — 123-05-7.

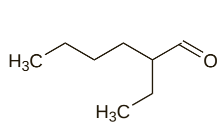

Profile

Ethylhexanal is an aldehyde disinfectant used for instrument disinfection.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Buraton 10 F; Helipur H plus N; Lysetol FF†; Sekucid konz†.

Ethylhexylglycerin

Octoxyglycerin. 3-[(2-Ethylhexyl)oxy]-1,2-propanediol.

Этилгексилглицерин

$C_{11}H_{24}O_3 = 204.3.$

CAS — 70445-33-9.

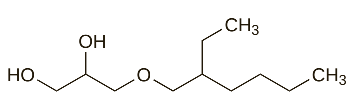

Profile

Ethylhexylglycerin is a disinfectant used in a concentration of 0.3% in topical deodorant preparations. It is also used in products for disinfection of the hands.

◊ References.

1. Stausbøl-Grøn B, Andersen KE. Allergic contact dermatitis to ethylhexylglycerin in a cream. *Contact Dermatitis* 2007; **57:** 193–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Effidrate†; ***Chile:*** Uriage Desodorante Tri-Actif.

Formaldehyde

Formaldehid; Formaldehído; Formaldehyd.

Формальдегид

$CH_2O = 30.03.$

CAS — 50-00-0.

ATC Vet — QP53AX19.

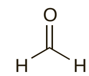

Formaldehyde Solution

Formaldehído, solución de; Formaldehido tirpalas; Formaldehidoldat; Formaldehyd roztok; Formaldéhyde, solution de; Formaldehydi solutio; Formaldehydiliuos; Formaldehydlösning; Formaldehydu roztwór.

NOTE. The names formalin and formol have been used for formaldehyde solution but in some countries they are trade marks.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Formaldehyde Solution (35 per cent); Formaldehyde Solution BP 2008). It contains 34.5 to 38.0% w/w of formaldehyde with methyl alcohol as a stabiliser. It is a clear, colourless, liquid. Miscible with water and with alcohol. It may be cloudy after storage. Store at a temperature between 15° and 25°. Protect from light.

USP 31 (Formaldehyde Solution). It contains not less than 34.5% w/w of formaldehyde with 9 to 15% methyl alcohol added to prevent polymerisation. It is a clear, colourless, or practically colourless liquid with a pungent, irritating odour. Miscible with water and with alcohol. Store at a temperature above 15° in airtight containers. It may become cloudy on standing due to the separation of paraformaldehyde, especially if the solution is kept in a cold place; the cloudiness disappears on warming.

Strength of solutions. Formaldehyde solution is sometimes known simply as formaldehyde and this has led to confusion in interpreting the strength and the form in which formaldehyde is being used. In practice formaldehyde is available as formaldehyde solution which is diluted before use, the percentage strength being expressed in terms of formaldehyde solution rather than formaldehyde. For example, in the UK, formaldehyde solution 3% consists of 3 volumes of Formaldehyde Solution (35 Per Cent) (Ph. Eur. 6.2) diluted to 100 volumes with water and thus contains 1.04 to 1.14% w/w of formaldehyde; it is ***not*** prepared by diluting Formaldehyde Solution (35 Per Cent) (Ph. Eur. 6.2) to arrive at a solution containing 3% w/w of formaldehyde.

Incompatibility. Formaldehyde reacts with protein and this may diminish its antimicrobial activity.

Adverse Effects and Precautions

Concentrated formaldehyde solutions applied to the skin cause whitening and hardening. Contact dermatitis and sensitivity reactions have occurred after the use of conventional concentrations and after contact with residual formaldehyde in resins.

Ingestion of formaldehyde solution causes intense burning pain in the mouth, throat, chest, and stomach, with inflammation, ulceration, and necrosis of mucous membranes. There may be nausea, vomiting, haematemesis, blood-stained diarrhoea, haematuria, and anuria; metabolic acidosis, vertigo, convulsions, loss of consciousness, and circulatory and respiratory failure may occur. Death has occurred after the ingestion of the equivalent of about 30 mL of formaldehyde solution. If the patient survives 48 hours, recovery is probable. Formaldehyde vapour is irritant to the eyes, nose, and upper respiratory tract, and may cause coughing, dysphagia, spasm and oedema of the larynx, bronchitis, pneumonia, and rarely, pulmonary oedema. Asthma-like symptoms have been reported after repeated exposure.

◊ General references.

1. Health and Safety Executive. Formaldehyde. *Toxicity Review 2.* London: HMSO, 1981.
2. WHO. Formaldehyde. *Environmental Health Criteria 89.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc89.htm (accessed 15/03/06)
3. WHO. Formaldehyde health and safety guide. *IPCS Health and Safety Guide 57.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg057.htm (accessed 15/03/06)
4. WHO. Formaldehyde. *Concise International Chemical Assessment Document 40* Geneva: WHO, 2002. Available at: http://whqlibdoc.who.int/hq/2002/a73769.pdf (accessed 15/03/06)

Abuse. References to the abuse of embalming fluid (the primary ingredient of which is formaldehyde), usually in the form of marijuana treated with embalming fluid and in some cases phencyclidine, a mixture known as 'fry'.[1-4]

1. Holland JA, *et al.* Embalming fluid-soaked marijuana: new high or new guise for PCP? *J Psychoactive Drugs* 1998; **30:** 215–9.
2. Peters RJ, *et al.* Beliefs and social norms about cigarettes or marijuana sticks laced with embalming fluid and phencyclidine (PCP): why youth use "fry". *Subst Use Misuse* 2005; **40:** 563–71.
3. Singer M, *et al.* Dust in the wind: the growing use of embalming fluid among youth in Hartford, CT. *Subst Use Misuse* 2005; **40:** 1035–50.
4. Singer M, *et al.* When the drug of choice is a drug of confusion: embalming fluid use in inner city Hartford, CT. *J Ethn Subst Abuse* 2005; **4:** 73–96.

Carcinogenicity. There is controversy as to the risk formaldehyde presents as a carcinogen. Studies on the occupational exposure of medical personnel and industrial workers[1-3] to formaldehyde have generally concluded that although the risk is small or non-existent, the possibility that formaldehyde is a human carcinogen cannot be excluded. Reanalyses of some studies have led to different interpretations of the results, with some workers concluding that the risk of cancer from formaldehyde is greater than originally thought.[4] Analysis of mortality data[5] for a cohort of 25619 workers exposed to formaldehyde in the USA found some evidence of an association with nasopharyngeal cancer and possibly cancers at other upper respiratory-tract sites. Based on the results of this large cohort study and supported by evidence from other epidemiological and *animal* studies, the International Agency for Research on Cancer (IARC) concluded,[6] in 2004, that occupational exposure to formaldehyde does cause nasopharyngeal cancer. Furthermore, they found strong, but not sufficient, evidence to establish a causal link with leukaemia and limited evidence to suggest it causes sinonasal cancer. IARC has concluded that formaldehyde is a definite human carcinogen.[6]

1. Gérin M, *et al.* Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montreal. *Int J Cancer* 1989; **44:** 53–8.
2. Blair A, *et al.* Mortality from lung cancer among workers employed in formaldehyde industries. *Am J Ind Med* 1990; **17:** 683–99.
3. Coggon D, *et al.* Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 2003; **95:** 1608–15.
4. Sterling TD, Weinkam JJ. Mortality from respiratory cancers (including lung cancer) among workers employed in formaldehyde industries. *Am J Ind Med* 1994; **25:** 593–602.
5. Hauptmann M, *et al.* Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 2004; **159:** 1117–30.
6. IARC/WHO. Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol. *IARC monographs on the evaluation of carcinogenic risks to humans volume 88* 2004. Available at: http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf (accessed 23/05/06)

Effects on the blood. Haemolysis during chronic haemodialysis was due to formaldehyde eluted from filters.[1]

1. Orringer EP, Mattern WD. Formaldehyde-induced hemolysis during chronic hemodialysis. *N Engl J Med* 1976; **294:** 1416–20.

Effects on the urinary tract. Adverse effects have resulted from intravesical instillation of formaldehyde solutions, ranging in strength from 1 to 10%, in the treatment of haemorrhagic cystitis. They include dysuria, suprapubic pain, ureteric and bladder fibrosis, hydronephrosis, vesicoureteral reflux, bilateral ureteral obstruction, papillary necrosis, bladder rupture, and acute tubular necrosis. Intraperitoneal spillage through a fistula, leading to adverse systemic effects, has also occurred.[1] Fatalities have resulted from cardiac arrest and acute renal failure.[1-3] See also Haemorrhagic Cystitis under Uses, below.

There has also been a report[4] of 4 patients exposed to high levels of atmospheric formaldehyde who developed membranous nephropathy, suggesting that there may be genetic susceptibility for this effect.

1. Capen CV, *et al.* Intraperitoneal spillage of formalin after intravesical instillation. *Urology* 1982; **19:** 599–601.
2. Melekos M, Lalos J. Intravesical instillation of formalin and its complications. *Urology* 1983; **21:** 331–2.
3. Sarnak MJ, *et al.* Intravesicular formaldehyde instillation and renal complications. *Clin Nephrol* 1999; **51:** 122–5.
4. Breysse P, *et al.* Membranous nephropathy and formaldehyde exposure. *Ann Intern Med* 1994; **120:** 396–7.

Hypersensitivity. Hypersensitivity to formaldehyde has had several manifestations. Effects on the skin have included acute exacerbation of eczema after injection of hepatitis B vaccine containing formaldehyde up to 20 micrograms/mL.[1] In another case, formaldehyde sensitivity was characterised by pruritus, burning, and redness within minutes of exposure to sunlight.[2] Painful, enlarged, and haemorrhagic gingival margins have occurred after the use of a toothpaste containing a solution of formaldehyde.[3] There is conflicting evidence of the respiratory effects of formaldehyde: although a low concentration has been reported not to trigger an asthma attack in patients with severe bronchial hyperresponsiveness,[4] occupational asthma has been documented.[5] More severe manifestations of hypersensitivity include 7 cases of shock of possible toxic or anaphylactic aetiology that occurred after the use of formaldehyde solutions during surgical removal of hydatid cysts.[6]

For mention of an allergic response to root canal paste containing paraformaldehyde, see p.1655.

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patients. *Lancet* 1986; **ii:** 522–3.
2. Shelley WB. Immediate sunburn-like reaction in a patient with formaldehyde photosensitivity. *Arch Dermatol* 1982; **118:** 117–18.
3. Laws IM. Toothpaste formulations. *Br Dent J* 1984; **156:** 240.
4. Harving H, *et al.* Low concentrations of formaldehyde in bronchial asthma: a study of exposure under controlled conditions. *BMJ* 1986; **293:** 310.

5. Heard BE. Low concentrations of formaldehyde in bronchial asthma. *BMJ* 1986; **293:** 821.
6. Galland MC, *et al.* Risques thérapeutiques de l'utilisation des solutions de formol dans le traitement chirurgical des kystes hydatiques du foie. *Therapie* 1980; **35:** 443–6.

Treatment of Adverse Effects

Contaminated skin should be washed with soap and water. After ingestion water, milk, charcoal, and/or demulcents should be given; emesis should be avoided. Assisted ventilation may be required and shock should be alleviated appropriately. Convulsions should be controlled with diazepam and pain with morphine. Acidosis, resulting from metabolism of formaldehyde to formic acid, may require intravenous sodium bicarbonate or sodium lactate. The use of haemodialysis has been suggested.

Uses and Administration

Formaldehyde solution is a bactericidal disinfectant also effective against fungi and many viruses. It is slowly effective against bacterial spores but its sporicidal effect is greatly increased by increase in temperature.

Formaldehyde solution is usually used diluted and it is important to note that the strength of preparations is given in terms of the content of formaldehyde solution and not in terms of the final concentration of formaldehyde (see under Strength of Solutions, above).

Formaldehyde solution is used in the disinfection of blankets and bedding and in the disinfection of the membranes in dialysis equipment. It is important to ensure that there are no traces of formaldehyde on any equipment before it is used. Formaldehyde solution is also used with succinic dialdehyde for instrument disinfection.

When applied to the unbroken skin, formaldehyde solution hardens the epidermis, renders it tough and whitish, and produces a local anaesthetic effect. Formaldehyde solution 3% v/v has been used for the treatment of warts on the palms of the hands and soles of the feet. It is used similarly as a water-miscible gel containing formaldehyde 0.75% w/w. Sweating of the feet may be treated by the application of formaldehyde solution in glycerol or alcohol but such applications are liable to produce sensitisation reactions and other treatments are regarded as more effective (see Hyperhidrosis, p.1580).

After surgical removal of hydatid cysts, diluted formaldehyde solution has been used for irrigating the cavities to destroy scolices but other larvicides are preferred (see Echinococcosis, p.136). It is generally too irritant for use on mucous membranes but it has been used in mouthwashes and pastes as an antiseptic and hardening agent for the gums. In dentistry it has been used in endodontic treatment.

Formaldehyde solution in concentrations of up to 10% v/v in saline is used as a preservative for pathological specimens. It is not suitable for preserving urine for subsequent examination. Formaldehyde solution is used for the inactivation of viruses in vaccine production.

Formaldehyde gas has little penetrating power and readily polymerises and condenses on surfaces and its effectiveness depends on it dissolving in a film of moisture before acting on micro-organisms; in practice a relative humidity of 80 to 90% is necessary. Formaldehyde gas is used for the disinfection of rooms and cabinets. The gas may be produced from 500 mL of undiluted formaldehyde solution by boiling with 1 litre of water or by addition of potassium permanganate or by heating a formaldehyde-containing solid such as paraformaldehyde (p.1655). Formaldehyde gas is used with low-temperature steam for the sterilisation of heat-sensitive items.

Other compounds which are thought to act by releasing formaldehyde include noxytiolin (p.1654) and methenamine (p.298).

Haemorrhagic cystitis. Formaldehyde has been used for local therapy of haemorrhagic cystitis (p.2178), although there has been debate about the most appropriate regimen. The Fair regimen[1] for the intravesical use of formaldehyde solution in haemorrhagic cystitis involves passive irrigation of the bladder with 500 to 1000 mL of formaldehyde solution 1% v/v for a total of 10 minutes, the bladder subsequently being emptied and washed out with 1 litre of distilled water. Stronger concentrations of formaldehyde solution and other methods can be used if bleeding does not stop.[2] In a review of 118 patients treated with solutions of formaldehyde for intractable haematuria, the authors felt that this was probably the most effective treatment, but also probably the most dangerous.[3] More concentrated instillations, containing formaldehyde solution 5 to 10% seem to be generally viewed as unnecessary, and associated with an increased risk of complications which precludes their use.[4-7]

1. Fair WR. Formalin in the treatment of massive bladder hemorrhage: techniques, results, and complications. *Urology* 1974; **3:** 573–6.
2. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; **i:** 304–6.
3. Godec CJ, Gleich P. Intractable hematuria and formalin. *J Urol (Baltimore)* 1983; **130:** 688–91.
4. Bullock N, Whitaker RH. Massive bladder haemorrhage. *BMJ* 1985; **291:** 1522–3.
5. Donahue LA, Frank IN. Intravesical formalin for haemorrhagic cystitis: analysis of therapy. *J Urol (Baltimore)* 1989; **141:** 809–12.
6. Murray JA, *et al.* Massive bladder haemorrhage. *BMJ* 1986; **292:** 57.
7. Smith PJB, *et al.* Massive bladder haemorrhage. *BMJ* 1986; **292:** 412.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Formol; ***Ger.:*** Lysoform; ***UK:*** Veracur; ***USA:*** Formadon; Formalaz; Formalyde; Lazerformaldehyde.

Multi-ingredient: ***Arg.:*** Cistimax Ungueal; Parodium; ***Austral.:*** Formo-Cresol Mitis; ***Canad.:*** British Army Foot Powder†; Duoplant; ***Fr.:*** Aniospray 41; Bacterianos D†; Chlorispray†; Ephydrol; Incidine†; Parodium; Veybirol-Tyrothyricine†; ***Ger.:*** Aseptisol†; Buraton 10 F; Desoform†; Incidin perfekt; Incidin Spezial; Lysoformin; Melsept†; Melsitt; Minutil†; Prontocid N†; Sekusept forte S; Sekusept forte†; Sporcid; Ultrasol-F; ***Indon.:*** Skintex; ***Ital.:*** Melsept; ***Rus.:*** Parodium (Пародиум); ***Spain:*** Tifell†; Viberol Tirotricina.

Glucoprotamine

Glucoprotamina. Reaction product of L-glutamic acid and cocopropylene-1,3-diamine.

Profile

Glucoprotamine is used as a disinfectant for surfaces and medical equipment.

◊ References.

1. Disch K. Glucoprotamine—a new antimicrobial substance. *Zentralbl Hyg Umweltmed* 1994; **195:** 357–65.
2. Meyer B, Kluin C. Efficacy of glucoprotamin containing disinfectants against different species of atypical mycobacteria. *J Hosp Infect* 1999; **42:** 151–4.
3. Widmer AE, Frei R. Antimicrobial activity of glucoprotamin: a clinical study of a new disinfectant for instruments. *Infect Control Hosp Epidemiol* 2003; **24:** 762–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Incidin Plus; Sekusept Plus.

Multi-ingredient: ***Ger.:*** Incidin; Incidin extra N; Sekumatic FDR†.

Glutaral *(USAN, rINN)*

Adehyd glutarowy; Glutaraldehid; Glutaraldehyde; Glutaralum; Glutaric Dialdehyde; Pentanedial. Pentane-1,5-dial.

Глутарал

$C_5H_8O_2$ = 100.1.

CAS — 111-30-8.

ATC — D08AX09.

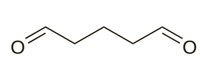

Pharmacopoeias. Solutions of glutaral are included in *Br.*, *Chin.*, and *US.* A solution is also in *USNF.*

BP 2008: (Strong Glutaraldehyde Solution). It contains 47 to 53% w/w of glutaral. Store at a temperature not exceeding 15°.

USP 31 (Glutaral Concentrate). It contains 50 to 52% w/w of glutaral and has a pH between 3.7 and 4.5. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

USNF 26 (Glutaral Disinfectant Solution). It has a pH between 2.7 and 3.7. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adverse Effects

As for Formaldehyde Solution, p.1644.

Effects on the gastrointestinal tract. Insufficient rinsing of a glutaral 2% solution from flexible endoscopes after disinfection appears to be responsible for outbreaks of glutaral-induced colitis in patients undergoing colonoscopy and sigmoidoscopy.[1-4] Symptoms may occur within minutes or up to 48 hours after endoscopy and are usually abdominal pain, mucous diarrhoea, and rectal bleeding. Fever, nausea, vomiting and leucocytosis have also been reported. A case of glutaral-induced colitis has also been attributed to inadequate flushing and drying of the endoscope channels.[2]

1. Durante L, *et al.* Investigation of an outbreak of bloody diarrhea: association with endoscopic cleaning solution and demonstration of lesions in an animal model. *Am J Med* 1992; **92:** 476–80.
2. West AB, *et al.* Glutaraldehyde colitis following endoscopy: clinical and pathological features and investigation of an outbreak. *Gastroenterology* 1995; **108:** 1250–5.
3. Fukunaga K, Khatibi A. Glutaraldehyde colitis: a complication of screening flexible sigmoidoscopy in the primary care setting. *Ann Intern Med* 2000; **133:** 315.
4. Stein BL, *et al.* Glutaraldehyde-induced colitis. *Can J Surg* 2001; **44:** 113–16.

Occupational exposure. Reviews[1,2] of the occupational hazards of glutaral have noted that several studies showed adverse effects, including nausea, headache, airway obstruction, asthma, rhinitis, eye irritation, and dermatitis, occurring among medical personnel exposed to glutaral, generally at concentrations below the recommended limits. Skin reactions were due to hypersensitivity or a direct irritant effect. It was concluded that, when using glutaral, workers should take suitable precautions to protect the skin and eyes and should avoid inhaling the vapour. Appropriate procedures should also be followed for disposal and clean-up of spills.

The risk of occupational exposure to glutaral vapour may be higher in warm climates.[3]

There has also been a report of accidental ocular contact with glutaral due to leakage of glutaral solution retained in an anaesthesia mask; moderate chemical conjunctivitis ensued.[4]

1. Burge PS. Occupational risks of glutaraldehyde. *BMJ* 1989; **299:** 342.
2. Ballantyne B, Jordan SL. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. *J Appl Toxicol* 2001; **21:** 131–51.
3. Mwaniki DL, Guthua SW. Occupational exposure to glutaraldehyde in tropical climates. *Lancet* 1992; **340:** 1476–7.
4. Murray WJ, Ruddy MP. Toxic eye injury during induction of anaesthesia. *South Med J* 1985; **78:** 1012–13.

Uses and Administration

Glutaral is a bactericidal disinfectant that is rapidly effective against Gram-positive and Gram-negative bacteria. It is also effective against *Mycobacterium tuberculosis*, some fungi, and viruses, including hepatitis B virus and HIV, and is slowly effective against bacterial spores. Aqueous solutions show optimum activity between pH 7.5 and 8.5; such solutions are chemically stable for about 14 days. Solutions at lower pH values are more stable.

A 2% aqueous solution buffered to a pH of about 8 (activated glutaral; alkaline glutaral) may be used for the sterilisation of endoscopic and dental instruments, rubber or plastic equipment, and for other equipment which cannot be sterilised by heat. Glutaral is non-corrosive towards most materials. Complete immersion in the solution for 10 to 20 minutes is sufficient for rapid disinfection of thoroughly cleansed instruments but exposure for up to 10 hours may be necessary for sterilisation. For further details, see Disinfection of Endoscopes, p.1623, and Disinfection in Hepatitis and HIV Infection, p.1623.

A 10% solution is applied twice daily for the treatment of warts (p.1584); a 5% solution and a 10% gel have also been used. Glutaral should not be used for facial or anogenital warts. Glutaral has also been used topically for treating hyperhidrosis of the palms and soles, although other agents are generally preferred (see p.1580).

Preparations

BP 2008: Glutaraldehyde Solution; Strong Glutaraldehyde Solution;
USNF 26: Glutaral Disinfectant Solution;
USP 31: Glutaral Concentrate.

Proprietary Preparations (details are given in Part 3)
Arg.: Asepto-Glutaral†; ***Austral.:*** Diswart; ***Fr.:*** Cidex†; Sekucid†; Steranios; ***Ger.:*** Cidex†; Korsolex-Endo-Disinfectant; Sekumatic FD†; ***India:*** Glutrex†; ***Irl.:*** Glutarol; ***Ital.:*** Citrosteril Sterilferri; Diba; Eso Cem; Eso H1, HP, and HP1; Esoxid; Ferriseptil; SaniSteril Sterilferri; Sporacid†; Sporex†; Sporicidin; T5†; ***S.Afr.:*** Virogerm; ***Thai.:*** Deconex 50FF†; ***UK:*** ASEP; Glutarol; ***USA:*** Cetylcide-G; Cidex.

Multi-ingredient: ***Fr.:*** Aniospray 41; Bacterianos D†; Chlorispray†; Incidine†; ***Ger.:*** Aerodesin; Aseptisol†; Bacillocid rasant†; Bacillol plus; Buraton 10 F; Desoform†; Helipur H plus N; Incidin perfekt; Incidin Spezial; Incidur; Incidur Spray†; Kohrsolin; Kohrsolin FF; Korsolex basic; Korsolex Extra; Korsolex FF; Lysetol FF†; Lysoformin; Lysoformin 3000; Melsept SF; Melsept†;

Melsitt; Minutil†; Prontocid N†; Sekucid konz†; Sekusept Extra N; Sekusept forte S; Sekusept forte†; Sporcid; Ultrasol-F; ***Ital.:*** Bergon†; Citrosteril Impronte; Diaril†; Eso Din; Esoform 92; Incidin Spezial; Melsept; Melsept SF; Sekucid; Sekumatic; Sekusept Extra N†; ***Thai.:*** Posequat with GA.

Glyoxal

Biformilo; Ethanedial; Glioxal; Oxalaldehyde. 1,2-Ethanedione.

$C_2H_2O_2$ = 58.04.
CAS — 107-22-2.

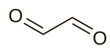

Profile

Glyoxal is an aldehyde used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Part 3)
Thai.: Deconex 50FF†.

Multi-ingredient: ***Fr.:*** Aniospray 41; Bacterianos D†; Incidine†; ***Ger.:*** Buraton 10 F; Desoform†; Freka-Nol; Fugisept†; Incidin perfekt; Incidin Spezial; Incidur; Lysoformin 3000; Meliseptol; Melsept SF; Melsept†; Minutil†; Sekusept forte†; Ultrasol-F; ***Ital.:*** Incidin Spezial; Indulfan; Melsept; Melsept SF; Melsept Spray.

Halazone *(rINN)*

Halazona; Halazonum; Pantocide. 4-(Dichlorosulphamoyl)benzoic acid.

Галазон

$C_7H_5Cl_2NO_4S$ = 270.1.
CAS — 80-13-7.

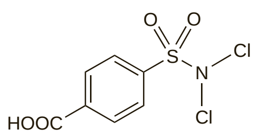

Pharmacopoeias. In *US.*

USP 31 (Halazone). A white crystalline powder with a characteristic odour of chlorine. Soluble 1 in more than 1000 of water and of chloroform, 1 in 140 of alcohol, and 1 in more than 2000 of ether; soluble in glacial acetic acid. It dissolves in solutions of alkali hydroxides and carbonates with the formation of a salt. Store in airtight containers. Protect from light.

Profile

Halazone is a disinfectant with the general properties of chlorine (p.1638) in aqueous solution and is used for the disinfection of drinking water (p.1623). It contains about 52% of 'available chlorine' (see p.1638). One tablet containing 4 mg of halazone, stabilised with sodium carbonate and sodium chloride, may be sufficient to treat about 1 litre of water in about 30 minutes to 1 hour. The taste of residual chlorine may be removed by adding sodium thiosulfate.

Preparations

USP 31: Halazone Tablets for Solution.

Proprietary Preparations (details are given in Part 3)
Ital.: Steridrolo a rapida idrolisi†; ***Port.:*** Speton†.

Hexachlorophene *(BAN, rINN)*

G-11; Heksaklorofeeni; Hexachlorofen; Hexachlorophane; Hexachlorophène; Hexachlorophenum; Hexaclorofeno; Hexaklorofen. 2,2′-Methylenebis(3,4,6-trichlorophenol).

Гексахлорофен

$C_{13}H_6Cl_6O_2$ = 406.9.
CAS — 70-30-4.
ATC — D08AE01.
ATC Vet — QD08AE01; QP52AG02.

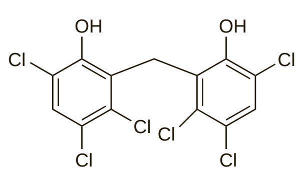

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Hexachlorophene). A white or pale buff, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in acetone and in ether. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Hexachlorophene). A white or light tan, crystalline powder which is odourless or has a slight phenolic odour. Insoluble in water; freely soluble in alcohol, in acetone, and in ether; soluble in chloroform and in dilute solutions of fixed alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. The activity of hexachlorophene may be reduced in the presence of blood or other organic material. It retains some activity in the presence of soap.

The activity has been reported[1] to be reduced by alkaline media and by nonionic surfactants such as polysorbate 80. It is extremely sensitive to iron, and to avoid discoloration due to traces of this metal in hexachlorophene detergent solutions, it is advisable to incorporate a sequestrant such as disodium edetate.[2]

1. Walter G, Gump W. Effect of pH on hexachlorophene. *Soap Chem Spec* 1963; **39:** 55–6.
2. Bell M. Hexachlorophene-based skin cleansers. *Specialities* 1965; **1:** 16–18.

Adverse Effects and Treatment

After ingestion, anorexia, nausea, vomiting, diarrhoea, abdominal cramps, dehydration, shock, and confusion may occur. Convulsions and death may follow. CNS stimulation, convulsions, and death have also occurred after absorption of hexachlorophene from burns and damaged skin. There have been reports showing that hexachlorophene can be absorbed through the skin of infants in amounts sufficient to produce spongy lesions of the brain, sometimes fatal.

Photosensitivity and skin sensitisation have occasionally occurred after repeated use of hexachlorophene.

Treatment of adverse effects is as for Phenol, p.1656.

Effects on the respiratory system. Asthma developed in a 43-year-old nurse after long-term exposure to hexachlorophene powder.[1]

1. Nagy L, Orosz M. Occupational asthma due to hexachlorophene. *Thorax* 1984; **39:** 630–1.

Precautions

Hexachlorophene should not be applied to mucous membranes, large areas of skin, or to burnt, damaged, or denuded skin and should not be used vaginally, applied under occlusive dressings, or applied to areas affected by dermatoses. It should be used with caution on infants, especially premature and low birth-weight neonates. Its use is not advised in pregnancy.

Preparations of hexachlorophene are liable to contamination, especially with Gram-negative bacteria.

Breast feeding. The American Academy of Pediatrics[1] considers that, while no effects on the infant have been reported, there is a possibility of contamination of breast milk with hexachlorophene used by breast-feeding mothers for nipple washing.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Neonates. Spongiform encephalopathy has occurred in neonates who were treated topically with hexachlorophene.[1] Neonates with a birth-weight of 1.4 kg or less appeared to be most susceptible, whereas those weighing over 2 kg were not considered to be at risk.[1,2] Also most of the reports involved hexachlorophene applied in a concentration of 3%.

1. Anonymous. Hexachlorophene today. *Lancet* 1982; **i:** 87–8.
2. Plueckhahn VD, Collins RB. Hexachlorophene emulsions and antiseptic skin care of newborn infants. *Med J Aust* 1976; **1:** 815–19.

Pregnancy. Hexachlorophene is absorbed from the skin and crosses the placenta, but whether it has produced teratogenic effects is subject to debate.[1,2] However, it is considered best to avoid its use during pregnancy.

1. Halling H. Suspected link between exposure to hexachlorophene and malformed infants. *Ann N Y Acad Sci* 1979; **320:** 426–35.
2. Baltzar B, *et al.* Pregnancy outcome among women working in Swedish hospitals. *N Engl J Med* 1979; **300:** 627–8.

Pharmacokinetics

Hexachlorophene is absorbed from the gastrointestinal tract after accidental ingestion, and through intact and denuded skin. Percutaneous absorption may be significant in premature infants and through damaged skin. Hexachlorophene crosses the placenta.

Uses and Administration

Hexachlorophene is a chlorinated bisphenol antiseptic with a bacteriostatic action against Gram-positive organisms, but much less effective against Gram-negative organisms. It is most active at pH 5 to 6.

Hexachlorophene is mainly used in soaps and creams in a concentration of 0.23 to 3% and is an ingredient of various preparations used for skin disorders. After repeated use of these preparations for several days there is a marked diminution of the bacterial flora due to accumulation of hexachlorophene in the skin. This residual effect is rapidly lost after washing with unmedicated soap or alcohol.

A preparation containing 3% is used for the disinfection of the hands of surgeons and other health-care personnel. Thorough rinsing is recommended before drying. Hexachlorophene has been applied as a 0.33% dusting powder to the umbilical cord stump for the control of staphylococcal infection in the newborn. However, care is necessary when using hexachlorophene in neonates (see above).

Hexachlorophene sodium has also been used.

Disinfection. Eradication of an outbreak of infection with meticillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit was achieved by use of hexachlorophene soap for hand washing. Previous infection-control measures including the use of chlorhexidine had failed.[1] For a discussion of staphylococcal infections and their treatment, see p.195.

1. Reboli AC, *et al.* Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; **143:** 34–9.

Preparations

BP 2008: Hexachlorophene Dusting Powder;
USP 31: Hexachlorophene Cleansing Emulsion; Hexachlorophene Liquid Soap.

Proprietary Preparations (details are given in Part 3)
Cz.: Aknefug-Simplex†; ***Ger.:*** Aknefug simplex†; ***Indon.:*** Dermisan; ***Switz.:*** Acne-Med Wolff Simplex†; ***UK:*** Ster-Zac†; ***USA:*** Septisol†; ***Venez.:*** Solu-Hex.

Multi-ingredient: ***Braz.:*** Micosan†; ***Canad.:*** pHisoHex; ***Cz.:*** Aknefug†; Hexadecyl†; Septonex; ***Ger.:*** Aknefug-Emulsion†; ***Hung.:*** Phlogosol; ***Indon.:*** Topicide; ***Irl.:*** Torbetol; ***Israel:*** Acnex†; ***Port.:*** Anacal; ***Spain:*** Cresophene; ***Switz.:*** Acerbine†; ***Thai.:*** Cibis; ***USA:*** pHisoHex; ***Venez.:*** Permucal.

Hexamidine Isetionate *(BANM, rINNM)*

Heksamidino diizetionatas; Hexamidin-diisetionát; Hexamidin-diizetionát; Hexamidine Diisetionate; Hexamidine, diisétionate d'; Hexamidine Isethionate; Hexamidine, Isétionate d'; Hexamidini diisetionas; Hexamidini Isetionas; Isetionato de hexamidina. 4,4′-(Hexamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).

Гексамидина Изетионат

$C_{20}H_{26}N_4O_2,2C_2H_6O_4S$ = 606.7.
CAS — 3811-75-4 (hexamidine); 659-40-5 (hexamidine isetionate).
ATC — D08AC04; R01AX07; R02AA18; S01AX08; S03AA05.
ATC Vet — QD08AC04; QR01AX07; QR02AA18; QS01AX08; QS03AA05.

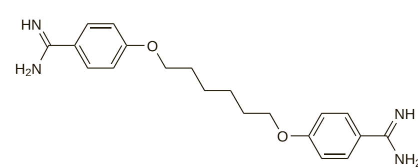

(hexamidine)

NOTE. The name Hexamidinum has been used for primidone (p.503).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hexamidine Diisetionate; Hexamidine Isetionate BP 2008). A white or slightly yellow hygroscopic powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

Profile

Hexamidine isetionate has antibacterial and antifungal properties and is available in preparations for the local treatment of minor infections.

Acanthamoeba keratitis. Hexamidine was suggested[1] as a possible alternative to propamidine for the treatment of *Acanthamoeba* keratitis (p.822) due to the poor cysticidal activity, chronic conjunctival infection, and resistance of some *Acanthamoeba* strains seen with propamidine.[1,2] Cures have been reported with 0.1% hexamidine used either as monotherapy[2,3] or with polihexanide.[2]

1. Perrine D, *et al.* Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; **39:** 339–42.

2. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; **26:** 231–6.
3. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; **17:** 893–905.

Adverse effects. A systemic allergic reaction in a patient after use of a topical antiseptic cream was confirmed, by skin prick tests, to be caused by hexamidine.[1]

1. Mullins RJ. Systemic allergy to topical hexamidine. *Med J Aust* 2006; **185:** 177.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Desomedine†; ***Belg.:*** Hexomedine; Ophtamedine; ***Fr.:*** Desomedine; Hexaseptine; Hexomedine; ***Ger.:*** Hexomedin N†; Laryngomedin N; ***Singapore:*** Desomedine; ***Spain:*** Hexomedin; ***Switz.:*** Desomedine; ***Venez.:*** Hexomedine.

Multi-ingredient: ***Austral.:*** Medi Creme; Medi Pulv; ***Belg.:*** Colludol; ***Braz.:*** Hexomedine; ***Cz.:*** Cyteal; Imacort; Imazol Plus; ***Fr.:*** Aurigoutte; Colludol; Cyteal; Hexomedine†; Oromedine; Otomide; Pulvo 47†; Solutricine Maux de Gorge; ***Ger.:*** Imazol; Imazol comp; Pulvo; ***Gr.:*** Octrene; ***Hong Kong:*** Medicreme; Medipulv†; ***NZ:*** Medicreme; Medipulv; ***Port.:*** Cyteal; ***Rus.:*** Cyteal (Цитеал); ***Singapore:*** Cyteal; ***Spain:*** Tantum; ***Switz.:*** Imacort; Imazol; ***Thai.:*** Pulvo 47; ***Turk.:*** Imazol; Pulvo 47; ***UK:*** Cyteal.

Hexetidine *(BAN, rINN)*

Heksetidiini; Heksetidin; Heksetidinas; Hexetidin; Hexetidina; Hexétidine; Hexetidinum. 5-Amino-1,3-bis(2-ethylhexyl)hexahydro-5-methylpyrimidine.

Гекcэтидин

$C_{21}H_{45}N_3$ = 339.6.

CAS — 141-94-6.

ATC — A01AB12.

ATC Vet — QA01AB12.

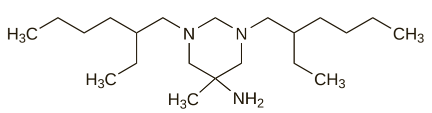

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hexetidine). An oily, colourless or slightly yellow liquid. Very slightly soluble in water; very soluble in alcohol, in acetone, and in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Adverse Effects

Allergic contact dermatitis, alterations in taste, and transient anaesthesia have occasionally been reported.

Uses and Administration

Hexetidine is a bactericidal and fungicidal antiseptic. It is used for minor infections of mucous membranes, and in particular as a 0.1% mouthwash for local infections and oral hygiene.

Oral hygiene. A mouthwash containing 0.1% hexetidine was no more effective than placebo in the management of patients with aphthous ulceration (see Mouth Ulceration, p.1700) and provided no additional benefits to oral hygiene or gingival health.[1] However, such a mouthwash does appear to be of benefit in reducing supragingival plaque and gingival inflammation.[2]

1. Chadwick B, *et al.* Hexetidine mouthrinse in the management of minor aphthous ulceration and as an adjunct to oral hygiene. *Br Dent J* 1991; **171:** 83–7.
2. Sharma NC, *et al.* Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash. *J Clin Periodontol* 2003; **30:** 590–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Duranil; ***Austria:*** Hexoral; Isozid-H; ***Belg.:*** Hextril; ***Canad.:*** Steri/Sol; ***Chile:*** Duranil; Muramyl†; ***Cz.:*** Dr Rentschler Rachenspray†; Dr Rentschler Rachenspulung†; ***Fr.:*** Collu-Hextril; Hextril; ***Ger.:*** Doreperol N†; Hexoral; Vagi-Hex; ***Gr.:*** Hexalen; Irin; ***Hong Kong:*** Bactidol; ***Indon.:*** Bactidol; Hexadol; ***Irl.:*** Oraldene; ***Ital.:*** Oraseptic; ***Malaysia:*** Bactidol†; ***Neth.:*** Hextril; ***Philipp.:*** Bactidol; ***Port.:*** Collu-Hextril; Hextril; ***Rus.:*** Hexoral (Гексорал); Stomatidine (Стоматидин); ***S.Afr.:*** Oraldine; ***Singapore:*** Bactidol; ***Spain:*** Hextril; ***Switz.:*** Drossadin; Hextril; Vagi-Hex; ***Turk.:*** Heksoral; Hekzoton; ***UK:*** Oraldene; ***Venez.:*** Oraldine†.

Multi-ingredient: ***Arg.:*** Buchex; Mantus; Pentadent†; ***Austria:*** Gurfix; ***Belg.:*** Givalex; ***Cz.:*** Stopangin; ***Fr.:*** Givalex; ***Ger.:*** Givalex†; ***Hong Kong:*** Anso; ***Rus.:*** Stopangin (Стопангин); ***Spain:*** Abrasone Rectal; Mentamida.

Hexylresorcinol *(BAN)*

Esilresorcina; Heksilrezorcinolis; Heksyyliresorsinoli; Hexilresorcinol; Hexilrezorcin; Hexylresocinolum; Hexylresorc; Hexylrésorcinol; Hexylresorcinolum. 4-Hexylbenzene-1,3-diol.

$C_{12}H_{18}O_2$ = 194.3.

CAS — 136-77-6.

ATC — R02AA12.

ATC Vet — QR02AA12.

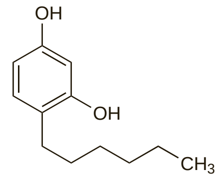

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Hexylresorcinol). A colourless, yellowish or reddish crystalline powder or needles, turning brownish-pink on exposure to light or air. It exhibits polymorphism. M.p. 66° to 68°; melting may occur at about 60° followed by solidification and a second melting at 66° to 68°. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Hexylresorcinol). M.p. 62° to 67°. Store in airtight containers. Protect from light.

Incompatibility. Hexylresorcinol is incompatible with alkalis and oxidising agents.

Profile

Hexylresorcinol is a phenolic antiseptic that is used topically for the treatment of minor infections of the skin and mucous membranes, and in the form of lozenges for the treatment of sore throat. It has also been used in vaginal spermicidal preparations.

High concentrations of hexylresorcinol are irritant and corrosive to skin and mucous membranes. Alcoholic solutions are vesicant.

It was formerly used as an anthelmintic.

Preparations

USP 31: Hexylresorcinol Lozenges.

Proprietary Preparations (details are given in Part 3)

Austral.: Nyal Medithroat Anaesthetic Lozenges†; Strepsils Extra; ***Canad.:*** Antiseptic Throat Lozenges; Bradosol; Bronchodex Pastilles Antiseptiques; Soothe Aid; Strepsils Anesthetic Formula; Sucrets Extra Strength; ***Cz.:*** Strepsinol; ***Irl.:*** Strepsils Extra; ***Israel:*** Sucrets†; ***Malaysia:*** Strepsils Pain Relief; ***Singapore:*** Strepsils Pain Relief; ***UK:*** Benylin Sore Throat Lozenge†; Halls Soothers Triple Action; Lemsip Sore Throat; Soothers Triple Action; Strepsils Extra; TCP; ***USA:*** ST 37; Sucrets Original Formula Sore Throat Original Mint.

Multi-ingredient: ***Arg.:*** Algiodent; Apracur Bucofaringeo†; Bagociletas sin Anestesia†; Balsamina; Caramelos Antibioticos; Caramelos Antibioticos Bucoangin†; Caramelos Antibioticos Lefmar; Caramelos Oriental; Collubiazol; Dotrin; Fanaletas; Fungicida†; Ixana; No-Tos Adultos; No-Tos Pocket; Pastillas Medex; Refenax Caramelos Expectorantes; Suavisan N; Suavisan†; ***Braz.:*** Andriodermol; Micoz†; ***Chile:*** Fittig; Lady Fittig†; ***Cz.:*** Coldrex Laryplus; ***Ger.:*** Hexamon; Mycatox†; ***Hung.:*** Coldrex Laryplus†; ***India:*** Tytin; ***Ital.:*** Golamed Due†; ***Pol.:*** Coldrex; ***UK:*** Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus.

Hydrargaphen *(BAN, rINN)*

Hidrargafeno; Hydraphen; Hydrargaphène; Hydrargaphenum; Hygraphen; Phenylmercuric Dinaphthylmethanedisulfonate. μ-(2,2′-Binaphthalene-3-sulphonyloxy)bis(phenylmercury).

Гидраргафен

$C_{33}H_{24}Hg_2O_6S_2$ = 981.9.

CAS — 14235-86-0.

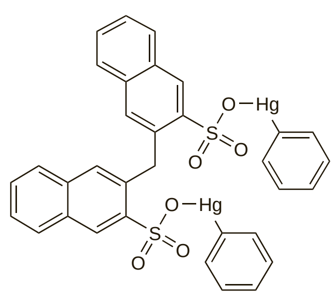

Profile

Hydrargaphen is a mercurial antiseptic with antibacterial and antifungal properties. It has been used in the treatment of vaginitis, wounds, burns, and infections of the skin.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Penotran†.

Hydrogen Peroxide

Hidrojen Peroksit; Hydrogène, peroxyde d'; Hydrogenii peroxidum; Peróxido de hidrógeno.

Перекись Водорода

H_2O_2 = 34.01.

CAS — 7722-84-1.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

NOTE. The BP 2008 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Incompatibility. Hydrogen peroxide solutions are incompatible with reducing agents, including organic matter and oxidisable substances, and with some metals, metallic salts, alkalis, iodides, permanganates, and other stronger oxidising agents.

Stability. Aqueous solutions of hydrogen peroxide gradually decompose on standing and if allowed to become alkaline. Decomposition is increased by light, agitation, and heat. Incompatibility may also produce decomposition. Solutions are comparatively stable in the presence of a slight excess of acid. Strong solutions are considered to be more stable than weak solutions.

Storage. Solutions of hydrogen peroxide should be stored in airtight containers at 15° to 30° (but see Hydrogen Peroxide Solution (30 per cent), below). Solutions should not be stored for long periods. Those not containing a stabiliser should be stored at a temperature not exceeding 15°. Protect from light.

Hydrogen Peroxide Solution (3 per cent)

3 %-os hidrogén-peroxid-oldat; Dilute Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (10-volume); Hydrogen Peroxide Topical Solution; Hydrogenii Peroxidum 3%; Hydrogenii Peroxidum 3 Per Centum; Oxydol; Peroxid vodíku 3%; Peróxido de hidrógeno, solución al 3%; Vandenilio peroksido 3% tirpalas; Väteperoxid 3%; Vetyperoksidi 3%; Wodoru nadtlenek 3%.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Hydrogen Peroxide Solution (3 per cent)). A clear colourless liquid containing 2.5 to 3.5% w/w of H_2O_2 corresponding to about 10 times its volume of oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15°. Protect from light.

The BP 2008 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

USP 31 (Hydrogen Peroxide Topical Solution). It contains 2.5 to 3.5% w/v of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Hydrogen Peroxide Solution (6 per cent)

Hydrog. Perox. Soln; Hydrogen Dioxide Solution; Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (20-volume); Liq. Hydrog. Perox.; Liquor Hydrogenii Peroxidi; Peróxido de hidrógeno, solución al 6%; Solución de Bióxido de Hidrogeno; Soluté Officinal d'Eau Oxygénée; Wasserstoffsuperoxydlösung.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Br.*

BP 2008 (Hydrogen Peroxide Solution (6 per cent)). A clear colourless aqueous liquid containing 5.0 to 7.0% w/v of H_2O_2 corresponding to about 20 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. It should not be stored for long periods. Solutions not containing a stabilising agent should be stored at a temperature below 15°. Protect from light.

The BP directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (27 per cent)

Hydrogenii Peroxidum; Perossido D'Idrogeno Soluzione; Peróxido de hidrógeno, solución al 27%; Solutio Hydrogenii Peroxydati; Strong Hydrog. Perox. Soln; Strong Hydrogen Peroxide Solution.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Description. Hydrogen peroxide solution (27 per cent) is a clear, colourless aqueous solution containing 26 to 28% w/w of H_2O_2, corresponding to about 100 times its volume of available oxygen. It may contain a suitable stabilising agent.

The symbol † denotes a preparation no longer actively marketed

The BP 2008 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (30 per cent)

30 %-os hidrogén-peroxid-oldat; Hydrogen Peroxide Concentrate; Hydrogen Peroxide Solution (100-volume); Hydrogenii Peroxidum 30%; Hydrogenii Peroxidum 30 Per Centum; Peroxid vodíku 30%; Peróxido de hidrógeno, solución al 30%; Vandenilio peroksido 30% tirpalas; Väteperoxid 30%; Vetyperoksidi 30%; Wodoru nadtlenek 30%.

ATC — A01AB02; D08AX01; S02AA06.
ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Eur.* (see p.vii).
Chin. specifies 26 to 28%.
US and *Viet.* specify 29 to 32%.
Ph. Eur. 6.2 (Hydrogen Peroxide Solution (30 per cent)). A clear colourless liquid containing 29.0 to 31.0% w/w of H_2O_2 corresponding to about 110 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15°. Protect from light.
The BP 2008 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.
USP 31 (Hydrogen Peroxide Concentrate). A clear, colourless liquid containing 29 to 32% w/w of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. It is acid to litmus. It slowly decomposes and is affected by light. Store in partially-filled containers having a small vent in the closure, at a temperature of 8° to 15°.

Adverse Effects and Precautions

Strong solutions of hydrogen peroxide produce irritating 'burns' on the skin and mucous membranes with a white eschar, but the pain disappears in about an hour. Continued use of hydrogen peroxide as a mouthwash may cause reversible hypertrophy of the papillae of the tongue.

It is dangerous to inject or instil hydrogen peroxide into closed body cavities from which the released oxygen has no free exit. Colonic lavage with solutions of hydrogen peroxide has been followed by gas embolism, rupture of the colon, proctitis, ulcerative colitis, and gangrene of the intestine.

Closed body cavities. Liberation of oxygen during the use of hydrogen peroxide in surgical procedures has resulted in oxygen embolism and local emphysema.[1-3] Gas embolism has also been reported after accidental ingestion of hydrogen peroxide solution.[4] Local damage to the colonic and rectal mucosa has followed the use of hydrogen peroxide 3% as an enema[5,6] and from residual hydrogen peroxide after disinfection of endoscopes.[7]

1. Sleigh JW, Linter SPK. Hazards of hydrogen peroxide. *BMJ* 1985; **291:** 1706.
2. Saïssy JM, *et al.* Risques de l'irrigation au peroxyde d'hydrogène en chirurgie de guerre. *Ann Fr Anesth Reanim* 1994; **13:** 749–53.
3. Konrad C, *et al.* Pulmonary embolism and hydrogen peroxide. *Can J Anaesth* 1997; **44:** 338–9.
4. Rackoff WR, Merton DF. Gas embolism after ingestion of hydrogen peroxide. *Pediatrics* 1990; **85:** 593–4.
5. Auroux J, *et al.* Rectocolite aiguë iatrogène après lavement à l'eau oxygénée. *Rev Geriatr* 1997; **22:** 21–4.
6. Gan SI, Price LM. Waiting-list induced proctitis: the hydrogen peroxide enema. *Can J Gastroenterol* 2003; **17:** 727–9.
7. Ryan CK, Potter GD. Disinfectant colitis: rinse as well as you wash. *J Clin Gastroenterol* 1995; **21:** 6–9.

Effects on the mouth. Use of hydrogen peroxide 3% as a mouthwash has been reported to cause mouth ulceration. A review[1] on the safety of hydrogen peroxide in dentistry concluded that low concentrations of hydrogen peroxide (1.5 to 3%) used long-term in mouthwashes and dentifrices, resulted in no adverse changes to the hard or soft tissues in the mouth. However, irritation may occur with low concentrations in patients with a thin or ulcerated oral mucosa. Short-term exposure to higher concentrations (30 to 35%), such as those used in teeth bleaching products and procedures, have resulted in mucosal erythema and sloughing, while long-term exposure may cause inflammation or hyperplasia.

1. Walsh LJ. Safety issues relating to the use of hydrogen peroxide in dentistry. *Aust Dent J* 2000; **45:** 257–69.

Intravascular administration. Intravenous injection of hydrogen peroxide solutions as unconventional therapy for AIDS or cancer has resulted in severe acute haemolysis.[1,2] Haemolysis and methaemoglobinaemia have been reported due to contamination of haemodialysis fluid with hydrogen peroxide.[3,4]

1. Jordan KS, *et al.* A 39-year-old man with acute hemolytic crisis secondary to intravenous injection of hydrogen peroxide. *J Emerg Nurs* 1991; **17:** 8–10.
2. Hirschtick RE, *et al.* Death from an unconventional therapy for AIDS. *Ann Intern Med* 1994; **120:** 694.
3. Gordon SM, *et al.* Hemolysis associated with hydrogen peroxide at a pediatric dialysis center. *Am J Nephrol* 1990; **10:** 123–7.
4. Davidovits M, *et al.* Methaemoglobinaemia and haemolysis associated with hydrogen peroxide in a paediatric haemodialysis centre: a warning note. *Nephrol Dial Transplant* 2003; **18:** 2354–8.

Poisoning. Ingestion of small quantities of hydrogen peroxide 3% generally results in only mild gastrointestinal effects. Ingestion of solutions of 10% or greater or large quantities of 3% solutions have been associated with severe morbidity and mortality. Irritation of the gastrointestinal tract with nausea, vomiting, foaming at the mouth, and haematemesis may occur. Blistering of the mucosa or oropharyngeal burns are common with solutions of 30% or greater. Large volumes of oxygen gas are produced in the stomach and this may result in painful gastric distension and belching. Apnoea, coma, convulsions, confusion, cyanosis, lethargy, stridor, and cardiorespiratory arrest have also been reported. Oxygen gas embolism is particularly dangerous. Immediate and permanent neurological damage has been reported after ingestion of hydrogen peroxide 35% and deaths have been reported in children and adults. Inhalation of high concentrations of hydrogen peroxide may cause irritation of the mucous membranes causing coughing and dyspnoea. Shock, convulsions, pulmonary oedema, and coma may follow. Exposure of the skin to concentrated solutions of hydrogen peroxide has resulted in blistering, erythema, focal epidermal necrosis, and purpura. Concentrations above 10% may result in ulceration or perforation of the cornea if they enter the eyes.[1]

1. Watt BE, *et al.* Hydrogen peroxide poisoning. *Toxicol Rev* 2004; **23:** 51–7.

Uses and Administration

Hydrogen peroxide is an oxidising agent used as an antiseptic, disinfectant, and deodorant. It has weak antibacterial activity and is also effective against viruses, including HIV. It also has a mild haemostatic action. It owes its antiseptic action to its ready release of oxygen when applied to tissues, but the effect lasts only as long as the oxygen is being released and is of short duration; in addition the antimicrobial effect of the liberated oxygen is reduced in the presence of organic matter. The mechanical effect of effervescence is probably more useful for wound cleansing (p.1624) than the antimicrobial action.

Hydrogen peroxide solutions are used to cleanse wounds and ulcers in concentrations of up to 6%; creams containing 1 or 1.5% stabilised hydrogen peroxide are also used. Although hydrogen peroxide alone is not considered effective on intact skin, it is used with other antiseptics for the disinfection of hands, skin, and mucous membranes. Injection into closed body cavities is dangerous (see above). Adhering and blood-soaked dressings may be released by the application of a solution of hydrogen peroxide.

A 1.5% solution of hydrogen peroxide has been used as a mouthwash in the treatment of acute stomatitis and as a deodorant gargle. A suitable solution can be prepared by diluting 15 mL of hydrogen peroxide 6% in half a tumblerful of warm water. An oral gel has also been used.

Hydrogen peroxide ear drops have been used for the removal of wax. Such ear drops were prepared by diluting a 6% solution of hydrogen peroxide with 3 parts of water preferably just before use.

Hydrogen peroxide 3% is used for disinfecting soft contact lenses.

Immersion for 30 minutes in hydrogen peroxide 6% has been suggested for disinfecting cleaned equipment.

For bleaching hair and delicate fabrics hydrogen peroxide 6% should be diluted with an equal volume of water.

Strong solutions (27 per cent and 30 per cent) of hydrogen peroxide are used for the preparation of weaker solutions and should not be applied to tissues undiluted.

Hydrogen peroxide and other peroxides have many industrial uses as bleaching and oxidising agents.

Disinfection. *CONTACT LENSES.* Hydrogen peroxide 3% is particularly useful for disinfecting soft contact lenses (p.1622) and lens storage cases since it is effective against *Acanthamoeba* spp. However, it is irritant to the cornea and requires inactivating with sodium pyruvate, catalase, or sodium thiosulfate, or with a platinum catalyst, before the lenses are used.

DIALYSIS EQUIPMENT. A disinfectant containing hydrogen peroxide and peracetic acid (*Renalin*) was not completely effective in killing *Mycobacterium chelonae* in high-flux dialysers. This possibly led to infection of 5 dialysis patients.[1] For a report of haemolysis and methaemoglobinaemia after inadvertent contamination of dialysis fluid with hydrogen peroxide, see Intravascular Administration under Adverse Effects and Precautions, above.

1. Lowry PW, *et al.* Mycobacterium chelonae infection among patients receiving high-flux dialysis in a hemodialysis clinic in California. *J Infect Dis* 1990; **161:** 85–90.

ENDOSCOPES. Peroxygen compounds have been suggested for disinfection of endoscopes as an alternative to glutaral (p.1623). In the USA, a product containing 7.5% hydrogen peroxide is available as a high level disinfectant for processing of reusable medical devices.[1] Products containing varying concentrations of hydrogen peroxide with peracetic acid have also been approved by the FDA.

Hydrogen peroxide damages external surfaces, particularly rubbers and plastics of the insertion tubes and can corrode aluminium, nickel-silver alloy, and chrome.[2,3] Other peroxygen-containing compounds have been assessed for disinfecting endoscopes, but they appear to be less active against enteroviruses[4] and mycobacteria.[5] The Working Party of the British Society of Gastroenterology does not recommend peroxygen disinfectants for gastrointestinal endoscopes.[3]

Residual hydrogen peroxide solution can cause mucosal damage (see Closed Body Cavities, under Adverse Effects, above) and endoscopes should be thoroughly rinsed before use.

1. FDA. FDA-cleared sterilants and high level disinfectants with general claims for processing reusable medical and dental devices (issued May 13, 2005). Available at: http://www.fda.gov/cdrh/ode/germlab.html (accessed 15/03/06)
2. Society of Gastroenterology Nurses and Associates, Inc. Guideline for the use of high-level disinfectants and sterilants for reprocessing of flexible gastrointestinal endoscopes. *Gastroenterol Nurs* 2000 **23:** 180–7. Also available at: http://www.sgna.org/Resources/guidelines/guideline6.cfm (accessed 08/03/06)
3. BSG Working Party. Cleaning and disinfection of equipment for gastrointestinal endoscopy: the report of a working party of the British Society of Gastroenterology Endoscopy Committee, 1997. Available at: http://www.bsg.org.uk/pdf_word_docs/glutaraldehyde.doc (accessed 15/03/06)
4. Tyler R, *et al.* Virucidal activity of disinfectants: studies with the poliovirus. *J Hosp Infect* 1990; **15:** 339–45.
5. Broadley SJ, *et al.* Antimycobacterial activity of 'Virkon'. *J Hosp Infect* 1993; **23:** 189–97.

Mouth ulceration and infection. The use of antiseptic mouthwashes may be helpful in the management of mouth ulcers (p.1700), although the use of high concentrations of hydrogen peroxide is not advisable (see Adverse Effects on the Mouth, above). Application of a 1.5% solution to individual ulcers with a topical corticosteroid may be useful. A randomised placebo-controlled study[1] to test the efficacy of a 1.5% hydrogen peroxide and 0.05% sodium fluoride-based mouthwash on gingivitis and tooth whitening, over a 6-month period found that it effectively whitened teeth and significantly reduced gingival redness. However, a review of the literature with practice guidelines pertaining to oral care of the critically ill[2] concluded that hydrogen peroxide could not be recommended as a mouthwash in this group, due to lack of evidence regarding its safety and efficacy in critically ill patients. A hydrogen peroxide denture cleaner was not effective in either preventing re-infection or in reducing mucosal inflammation in a study of 49 patients.[3] For oral candidal infections, specific antifungals are recommended (see p.518).

1. Hasturk H, *et al.* Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomized clinical trial. *J Periodontol* 2004; **75:** 57–65.
2. O'Reilly M. Oral care of the critically ill: a review of the literature and guidelines for practice. *Aust Crit Care* 2003; **16:** 101–10.
3. Walker DM, *et al.* The treatment of denture-induced stomatitis: evaluation of two agents. *Br Dent J* 1981; **151:** 416–19.

Preparations

BP 2008: Hydrogen Peroxide Mouthwash;
USP 31: Hydrogen Peroxide Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Aosept Plus; ***Austral.:*** Aosept; Focus Care One Step; Peroxyl; ***Belg.:*** Confosept Zuurstofwater; Crystacide†; ***Braz.:*** Aosept†; Oxysept; ***Canad.:*** Aosept; Orajel Perioseptic; ***Denm.:*** Brintoverilte; Microcid; ***Fr.:*** Dentex; Dosoxygenee; ***Ger.:*** Crystacide; ***Gr.:*** Peroxyl; ***Hong Kong:*** Crystacide†; ***Hung.:*** Microcid†; ***Irl.:*** Crystacide†; Hioxyl; ***Israel:*** Crystacide†; ***Ital.:*** Crystacide; Oragard; ***Neth.:*** Peroxyl; ***Norw.:*** Microcid; ***NZ:*** Aosept; Crystacide; Focus Care One Step†; ***Pol.:*** Peroxy-Dental; Peroxygel; ***Port.:*** Crystacide; ***Spain:*** Crystacide†; ***Swed.:*** Microcid; ***UK:*** Crystacide; Hioxyl†; Peroxyl; ***USA:*** Oxysept; Peroxyl.

Multi-ingredient: ***Arg.:*** One Step†; Oxysept Comfort; Plus & White†; ***Austral.:*** Omnicare 1 Step; Oxysept†; ***Austria:*** Kodan; Skinsept mucosa; ***Braz.:*** Malvatricin Branqueador; ***Canad.:*** UltraCare; ***Cz.:*** Skinsept mucosa†; ***Fr.:*** Anioxyde; Spitaderm†; ***Ger.:*** Peresal†; Skinsept F; Skinsept mucosa; ***Indon.:*** Spitaderm; ***Ital.:*** Eso 70; Esoform 7 mc; Esoform 70 mc; Peresal; Spitaderm; ***Neth.:*** Spitaderm; ***NZ:*** Omnicare 1 Step; ***Spain:*** Oximen; ***USA:*** Aosept; MiraSept; Soft Mate Consept; UltraCare.

Hydroxybenzoates

Parabenos; Parabens.

Benzyl Hydroxybenzoate

Benzyl Parahydroxybenzoate; Benzylparaben; Parahidroxibenzoato de bencilo. Benzyl 4-hydroxybenzoate.

$C_{14}H_{12}O_3$ = 228.2.
CAS — 94-18-8.

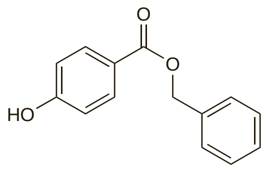

Pharmacopoeias. In *Br.* and *Int.*
BP 2008 (Benzyl Hydroxybenzoate). A white to creamy-white, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in ether. It dissolves in solutions of alkali hydroxides. M.p. about 112°.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Butyl Hydroxybenzoate

Butilo parahidroksibenzoatas; Butilparabeno; Butil-parahidroxibenzoát; Butyl Parahydroxybenzoate; Butyle, parahydroxybenzoate de; Butylis parahydroxybenzoas; Butylis Paraoxybenzoas; Butylparaben; Butylparabenum; Butylparahydroxibensoat; Butylu parahydroksybenzoesan; Butyyliparahydroksibentsoaatti. Butyl 4-hydroxybenzoate.

$C_{11}H_{14}O_3$ = 194.2.
CAS — 94-26-8.

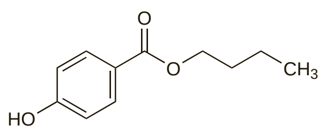

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Butyl Parahydroxybenzoate; Butyl Hydroxybenzoate BP 2008). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 68° to 71°.
USNF 26 (Butylparaben). Small colourless crystals or a white powder. Very slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol. M.p. 68° to 71°.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Ethyl Hydroxybenzoate

Aethylum Hydroxybenzoicum; E214; Ethyl Parahydroxybenzoate; Éthyle, parahydroxybenzoate d'; Ethylis parahydroxybenzoas; Ethylis Paraoxybenzoas; Ethylparaben; Ethylparabenum; Etilo parahidroksibenzoatas; Etilparabeno; Etil-parahidroxibenzoát; Etylparahydroxibensoat; Etylu parahydroksybenzoesan; Etyylipararahydroksibentsoaatti. Ethyl 4-hydroxybenzoate.

$C_9H_{10}O_3$ = 166.2.
CAS — 120-47-8.
ATC — D01AE10.
ATC Vet — QD01AE10.

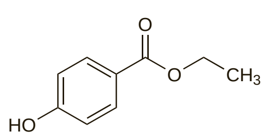

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Ethyl Parahydroxybenzoate; Ethyl Hydroxybenzoate BP 2008). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol.
USNF 26 (Ethylparaben). Small colourless crystals or a white powder. Slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Methyl Hydroxybenzoate

E218; Metagin; Methyl Parahydroxybenzoate; Méthyle, parahydroxybenzoate de; Methylis Oxybenzoas; Methylis parahydroxybenzoas; Methylis Paraoxibenzoas; Methylparaben *(USAN)*; Methylparabenum; Metilo parahidroksibenzoatas; Metilparabeno; Metil-parahidroxibenzoát; Metylparahydroxibensoat; Metylu parahydroksybenzoesan; Metyyliparahydroksibentsoaatti. Methyl 4-hydroxybenzoate.

$C_8H_8O_3$ = 152.1.
CAS — 99-76-3.

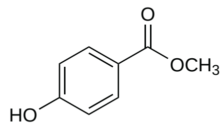

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Methyl Parahydroxybenzoate; Methyl Hydroxybenzoate BP 2008). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 125° to 128°.
USNF 26 (Methylparaben). Colourless crystals or a white crystalline powder. Soluble 1 in 400 of water, 1 in 50 of water at 80°, 1 in 3 of alcohol, and 1 in 10 of ether; freely soluble in methyl alcohol. M.p. 125° to 128°.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Propyl Hydroxybenzoate

E216; Propagin; Propilo parahidroksibenzoatas; Propilparabeno; Propil-parahidroxibenzoát; Propyl Parahydroxybenzoate; Propyle, parahydroxybenzoate de; Propylis Oxybenzoas; Propylis parahydroxybenzoas; Propylis Paraoxibenzoas; Propylparaben *(USAN)*; Propylparabenum; Propylparahydroxibensoat; Propylu parahydrobenzoesan; Propylu parahydroksybenzoesan; Propyyliparahydroksibentsoaatti. Propyl 4-hydroxybenzoate.

$C_{10}H_{12}O_3$ = 180.2.
CAS — 94-13-3.

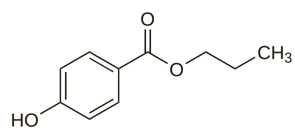

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Propyl Parahydroxybenzoate; Propyl Hydroxybenzoate BP 2008). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 96° to 99°.
USNF 26 (Propylparaben). Small colourless crystals or a white powder. Soluble 1 in 2500 of water, 1 in 400 of boiling water, 1 in 1.5 of alcohol, and 1 in 3 of ether. M.p. 96° to 99°.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Butyl Hydroxybenzoate

Butilparabeno sódico; Sodium Butyl Parahydroxybenzoate; Sodium Butylparaben.

$C_{11}H_{13}NaO_3$ = 216.2.
CAS — 36457-20-2.

Pharmacopoeias. In *Br.*
BP 2008 (Sodium Butyl Hydroxybenzoate). A white, odourless or almost odourless, hygroscopic powder. Freely soluble in water and in alcohol. A 0.1% solution in water has a pH of 9.5 to 10.5.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Ethyl Hydroxybenzoate

E215; Ethyl parahydroxybenzoate sodium; Éthyle (parahydroxybenzoate d') sodique; Ethylis Parahydroxybenzoas Natricum; Ethylis parahydroxybenzoas natricus; Ethylparaben sodná sůl; Etilo parahidroksibenzoato natrio druska; Etilparabeno sódico; Etylparahydroxibensoatnatrium; Etyyliparahydroksibentsoaattinatrium.

$C_9H_9NaO_3$ = 188.2.
CAS — 35285-68-8.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ethyl Parahydroxybenzoate Sodium; Ethyl Hydroxybenzoate Sodium BP 2008). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

The BP 2008 gives Ethylparaben Sodium as an approved synonym.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Methyl Hydroxybenzoate

E219; Méthyle (parahydroxybenzoate de) sodique; Methylis Parahydroxybenzoas Natricum; Methylis parahydroxybenzoas natricus; Methylparaben Sodium *(USAN)*; Methylparaben sodná sůl; Methylparabenum Natricum; Metilo parahidroksibenzoato natrio druska; Metilparabeno sódico; Metil-parahidroxibenzoátnátrium; Natriummetylparahydroxibensoat; Natriummetyyliparahydroksibentsoaatti; Sodium Methyl Parahydroxybenzoate; Sodium Methylparaben; Soluble Methyl Hydroxybenzoate.

$C_8H_7NaO_3$ = 174.1.
CAS — 5026-62-0.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sodium Methyl Parahydroxybenzoate; Sodium Methyl Hydroxybenzoate BP 2008). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5.
USNF 26 (Methylparaben Sodium). A white, hygroscopic, powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Propyl Hydroxybenzoate

E217; Natriumpropylparahydroxibensoat; Natriumpropyyliparahydroksibentsoaatti; Propilo parahidroksibenzoato natrio druska; Propilparabeno sódico; Propil-parahidroxibenzoátnátrium; Propyle (parahydroxybenzoate de) sodique; Propylis Parahydroxybenzoas Natricum; Propylis parahydroxybenzoas natricus; Propylparaben Sodium *(USAN)*; Propylparaben sodná sůl; Propylparabenum Natricum; Sodium Propyl Parahydroxybenzoate; Sodium Propylparaben; Soluble Propyl Hydroxybenzoate.

$C_{10}H_{11}NaO_3$ = 202.2.
CAS — 35285-69-9.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sodium Propyl Parahydroxybenzoate; Sodium Propyl Hydroxybenzoate BP 2008). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5.
USNF 26 (Propylparaben Sodium). A white, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The activity of hydroxybenzoates can be adversely affected by the presence of other excipients or active ingredients. There may be adsorption onto substances like magnesium trisilicate, aluminium magnesium silicate, talc, polysorbate 80,[1,2] carmellose sodium,[3] or plastics.[4] Nonionic surfactants can reduce hydroxybenzoate activity,[5] as may essential oils.[6] Other incompatibilities that have been reported include atropine,[7] iron,[4] sorbitol,[8] weak alkalis,[4] and strong acids.[4] Syrup preserved with hydroxybenzoates is incompatible with a range of compounds.[9,10] Methyl hydroxybenzoate 0.1% was reported[11] to be a poor preservative in insulin preparations, especially soluble insulin preparations. Increasing heat or pH can reduce stability and activity;[12] freeze-drying may also lead to a loss of activity.[13]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Allwood MC. The adsorption of esters of p-hydroxybenzoic acid by magnesium trisilicate. *Int J Pharmaceutics* 1982; **11:** 101–7.
3. Fawcett JP, *et al.* Binding of parabens to sodium carboxymethylcellulose in oral liquid formulations. *Aust J Hosp Pharm* 1996; **26:** 552–4.
4. Johnson R, Steer R. Methylparaben. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients*. 5th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2006: 466–70.
5. Yamaguchi M, *et al.* Antimicrobial activity of butylparaben in relation to its solubilization behavior by nonionic surfactants. *J Soc Cosmet Chem* 1982; **33:** 297–307.
6. Chemburkar PB, Joslin RS. Effect of flavoring oils on preservative concentrations in oral liquid dosage forms. *J Pharm Sci* 1975; **64:** 414–17.
7. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230:** 481.
8. Runesson B, Gustavii K. Stability of parabens in the presence of polyols. *Acta Pharm Suec* 1986; **23:** 151–62.
9. *PSGB Lab Report P/79/2* 1979.
10. *PSGB Lab Report P/80/1* 1980.

11. Allwood MC. The effectiveness of preservatives in insulin injections. *Pharm J* 1982; **229:** 340.
12. Sunderland VB, Watts DW. Kinetics of the degradation of methyl, ethyl and n-propyl 4-hydroxybenzoate esters in aqueous solution. *Int J Pharmaceutics* 1984; **19:** 1–15.
13. Flora KP, *et al.* The loss of paraben preservatives during freeze drying. *J Pharm Pharmacol* 1980; **32:** 577–80.

Adverse Effects and Precautions

Hypersensitivity reactions occur with the hydroxybenzoates. Generally these are of the delayed type, appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely.

Breast cancer. Some researchers[1] have questioned whether *p*-hydroxybenzoic acid esters, the most common preservatives found in body care cosmetic products, could increase the incidence of breast cancer in women. The esters have been shown to be oestrogenic *in vitro* and *in vivo* and have been detected in human breast tumour tissue, although a causal association cannot be confirmed.

1. Harvey PW, Darbre P. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? *J Appl Toxicol* 2004; **24:** 167–76.

Hypersensitivity. Immediate hypersensitivity reactions such as urticaria and bronchospasm with generalised pruritus, have been reported rarely on injection of preparations containing hydroxybenzoates.[1,2] Delayed contact dermatitis occurs more frequently, usually after use of topical medications, but has also occurred after use of an ester or of *p*-hydroxybenzoic acid in oral preparations.[3] Hypersensitivity reactions have also been reported in patients given local anaesthetics containing hydroxybenzoates[1,4] and cross-reactions with other para-amino compounds including benzocaine, paraphenylenediamine, and sulfonamides have occurred rarely.[5]

The incidence of sensitisation to hydroxybenzoates ranges from 0 to 3.5% but has tended to stay relatively constant over time.[5] A report from the North American Contact Dermatitis Group[6] in 1972 provided an incidence of 3%, while another later review[7] of a large number of patients gave an incidence of 2.2%. The Swiss Contact Dermatitis Research Group reported[8] a sensitisation rate of 1.7% based on a one-year study from 1989 to 1990 in 2295 patients.

Subjects with healthy skin exposed to hydroxybenzoates, for example in cosmetics, are considered to have a much lower incidence of reactions than patients with eczema or skin trauma. Unusually, patients who have reacted to a hydroxybenzoate with a contact dermatitis appear to be able to apply that preservative to another unaffected site and yet not suffer a reaction; this has been termed the 'paraben paradox'.[9]

1. Aldrete JA, Johnson DA. Allergy to local anaesthetics. *JAMA* 1969; **207:** 356–7.
2. Nagel JE, *et al.* Paraben allergy. *JAMA* 1977; **237:** 1594–5.
3. Kaminer Y, *et al.* Delayed hypersensitivity reaction to orally administered methylparaben. *Clin Pharm* 1982; **1:** 469–70.
4. Lederman DA, *et al.* An unusual skin reaction following local anesthetic injection: review of the literature and report of four cases. *Oral Surg* 1980; **49:** 28–33.
5. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; **17:** 251–63.
6. North American Contact Dermatitis Group. Epidemiology of contact dermatitis in North America 1972. *Arch Dermatol* 1973; **108:** 537–40.
7. Moore J. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. *J Am Coll Toxicol* 1984; **3:** 147–209.
8. Perrenoud D, *et al.* Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; **30:** 276–9.
9. Fisher AA. Cortaid cream dermatitis and the "paraben paradox". *J Am Acad Dermatol* 1982; **6:** 116–7.

Neonates. An *in-vitro* study on serum from neonates with hyperbilirubinaemia indicated that methyl hydroxybenzoate at a concentration of 200 micrograms/mL of serum increased the concentration of free unconjugated bilirubin and interfered with the binding of bilirubin to serum proteins. Methyl hydroxybenzoate was present in an injection of gentamicin sulfate at a concentration of 1.3 to 1.8 mg/mL. Neither gentamicin nor propyl hydroxybenzoate had a significant effect on bilirubin.[1]

1. Loria CJ, *et al.* Effect of antibiotic formulations in serum protein: bilirubin interaction of newborn infants. *J Pediatr* 1976; **89:** 479–82.

Pharmacokinetics

Neonates. After intramuscular injection, methyl hydroxybenzoate present in a gentamicin preparation was excreted in the urine of preterm infants to a variable extent and mainly in the conjugated form.[1] *p*-Hydroxybenzoic acid was detected as a metabolite. The injection contained methyl hydroxybenzoate 3.6 mg, propyl hydroxybenzoate 400 micrograms, and gentamicin 80 mg. Propyl hydroxybenzoate was also detected in the urine samples.

1. Hindmarsh KW, *et al.* Urinary excretion of methylparaben and its metabolites in preterm infants. *J Pharm Sci* 1983; **72:** 1039–41.

Uses

The hydroxybenzoate preservatives are alkyl esters of *p*-hydroxybenzoic acid with antibacterial and antifungal properties. They are more active against Gram-positive than against Gram-negative bacteria. They are active over a broad pH range (4 to 8), though are generally more active in acidic solutions. Activity increases with increasing alkyl chain length but aqueous solubility decreases, although this may be overcome by employing the more soluble sodium salts as long as the pH of the preparation is not increased. Activity may also be increased by combining two hydroxybenzoates with short alkyl chains. Another way of increasing activity is to use a hydroxybenzoate with propylene glycol.

Hydroxybenzoates are used as preservatives in pharmaceutical preparations in usual concentrations of up to 0.25%. Methyl hydroxybenzoate and propyl hydroxybenzoate are used together in some preparations. There have been reports of the hydroxybenzoates not being satisfactory preservatives for ophthalmic preparations because of their relative lack of efficacy against some Gram-negative bacteria, particularly *Pseudomonas aeruginosa*. The hydroxybenzoate preservatives are widely used in cosmetics and are also used for food preservation.

Hydroxybenzoates have been used in preparations promoted for the management of skin infections or pruritus.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nisapulvol; Nisaseptol; Nisasol; ***Malaysia:*** Nisapulvol.

Multi-ingredient: ***Austral.:*** Mycoderm; ***Hong Kong:*** Mycoderm†; ***Malaysia:*** Mycoderm; ***Neth.:*** Trachitol; ***UK:*** Brushtox; ***Venez.:*** Glizigen.

Imidurea

N,N″-Methylenebis{*N′*-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea}.

$C_{11}H_{16}N_8O_8$ = 388.3.

CAS — 39236-46-9.

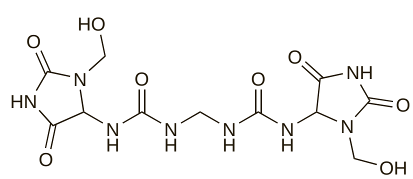

Pharmacopoeias. In *USNF.*

USNF 26 (Imidurea). A white odourless powder. Soluble in water and in glycerol; sparingly soluble in propylene glycol; insoluble in most organic solvents. A 1% solution in water has a pH of 6.0 to 7.5. Store in airtight containers.

Profile

Imidurea is used as an antimicrobial preservative in topical pharmaceutical and cosmetic preparations.

Iodoform

Iodoformo. Tri-iodomethane.

CHI_3 = 393.7.

CAS — 75-47-8.

ATC — D09AA13.

ATC Vet — QD09AA13.

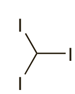

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Iodoform). A lustrous greenish-yellow powder or lustrous crystals. It is slightly volatile at ordinary temperatures and distils slowly with steam. It decomposes at high temperatures emitting vapours of iodine. Practically insoluble in water; sparingly soluble in alcohol, in glycerol, and in olive oil; soluble in boiling alcohol; freely soluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Iodoform slowly releases iodine (p.2169) when applied to the tissues and is used for its mild antiseptic action. Bismuth Subnitrate and Iodoform Paste (BPC 1954) (BIPP) has been applied to wounds and abscesses. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Adverse effects on the nervous system. Encephalopathy has been associated with the use of bismuth subnitrate and iodoform paste (BIPP) for the packing of wound cavities after ear, nose, and throat, oral, and maxillofacial surgery,[1,2] although there is some debate as to whether the bismuth or the iodoform component is responsible.[1-3] However, encephalopathy has been reported after application of iodoform gauze without bismuth.[4,5] CNS toxicity due to both iodine and bismuth has been reported[6] in an 86-year-old woman from an intra-oral plug of BIPP following partial maxillectomy. Five days after surgery the patient started to experience loss of appetite and lightheadedness, and by day 11 was suffering from fainting episodes, confusion, and paranoid ideation and was becoming increasingly aggressive. On day 14 the BIPP pack was removed; 7 days later the patient's condition improved and when discharged 5 days later she was alert and cooperative.

1. Wilson APR. The dangers of BIPP. *Lancet* 1994; **344:** 1313–14.
2. Youngman L, Harris S. BIPP madness; an iatrogenic cause of acute confusion. *Age Ageing* 2004; **33:** 406–7.
3. Farrell RWR. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1637–8.
4. Roy P-M, *et al.* Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; **344:** 1708.
5. Yamasaki K, *et al.* Delirium and a subclavian abscess. *Lancet* 1997; **350:** 1294.
6. Harris RA, Poole A. Beware of bismuth: post maxillectomy delirium. *Aust N Z J Surg* 2002; **72:** 846–7.

Hypersensitivity. A retrospective analysis of 185 patients[1] who were treated with a bismuth-iodoform-paraffin paste (BIPP) impregnated ribbon gauze pack after ear surgery found the incidence of allergic reactions to be 5.9%. A fivefold increase risk of developing allergic reactions was also found in those with previous exposure to BIPP. Three cases of allergic contact otitis externa have been reported following the use of bismuth subnitrate and iodoform paste to pack the ear after surgery.[2]

1. Lim PVH, *et al.* Hypersensitive allergic reactions to bismuth-iodoform-paraffin paste following ear surgery. *J Laryngol Otol* 1998; **112:** 335–7.
2. Roest MAB, *et al.* Allergic contact otitis externa due to iodoform in BIPP cavity dressings. *Contact Dermatitis* 2002; **46:** 360.

Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste; Compound Iodoform Paint.

Proprietary Preparations (details are given in Part 3)
Ger.: Iodoform†; Opraclean.

Multi-ingredient: ***Arg.:*** Aseptobron; ***Ital.:*** Pasta Iodoformica Radiopaca; ***Spain:*** Alvogil; ***Switz.:*** Alvogyl; ***UK:*** OxBipp.

Isopropyl Alcohol

Alcohol isopropílico; Alcohol isopropylicus; Alkohol izopropylowy; Dimethyl Carbinol; Isopropanol; Isopropylalkohol; Isopropylique, alcool; Isopropyylialkoholi; Izopropil Alkol; Izopropil-alkohol; Izopropilo alkoholis; 2-Propanol; Secondary Propyl Alcohol. Propan-2-ol.

Изопропиловый Спирт

$(CH_3)_2CHOH$ = 60.10.

CAS — 67-63-0.

ATC — D08AX05.

ATC Vet — QD08AX05.

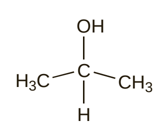

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Isopropyl Alcohol). A clear colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 31 (Isopropyl Alcohol). A transparent, colourless, mobile, volatile, flammable liquid with a characteristic odour. Miscible with water, with alcohol, with chloroform, and with ether. Store in airtight containers remote from heat.

Adverse Effects, Treatment, and Precautions

Isopropyl alcohol is considered to be more toxic than ethyl alcohol (p.1625), and the symptoms of intoxication appear to be similar, except that isopropyl alcohol has no initial euphoric action and gastritis, haemorrhage, pain, nausea, and vomiting are more prominent.

The lethal oral dose is reported to be about 120 to 240 mL in adults; however, toxic symptoms may be produced by as little as 20 mL. Ketoacidosis and ketonuria commonly occur due to the presence of the major metabolite, acetone, in the circulation. Inhalation of isopropyl alcohol vapour has been reported to produce coma.

Application of isopropyl alcohol to the skin may cause dryness and irritation; suitable precautions should be taken to prevent absorption through the skin, particularly in infants.

Treatment of adverse effects is as for Alcohol, p.1626.

◊ General references.

1. WHO. 2-Propanol. *Environmental Health Criteria 103*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc103.htm (accessed 15/03/06)

Children. Reports of chemical skin burns caused by the topical application of isopropyl alcohol in premature infants.[1,2]

Haemorrhagic gastritis in a 2-year-old febrile child was attributed to topical absorption of isopropyl alcohol that had been used for sponge bathing and followed by wrapping the child tightly in a blanket.[3]

1. Schick JB, Milstein JM. Burn hazard of isopropyl alcohol in the neonate. *Pediatrics* 1981; **68:** 587–8.
2. Weintraub Z, Iancu TC. Isopropyl alcohol burns. *Pediatrics* 1982; **69:** 506.
3. Dyer S, *et al.* Hemorrhagic gastritis from topical isopropanol exposure. *Ann Pharmacother* 2002; **36:** 1733–5.

Rectal absorption. Intoxication and raised serum-creatinine concentrations due to absorption of isopropyl alcohol followed its use as a rectal douche.[1] An 85-year-old woman who accidentally received an isopropyl alcohol enema developed rapid CNS depression, renal failure, and metabolic acidosis. She became comatose within 15 minutes and died 12 hours later after a cardiac arrest. Post-mortem examination showed necrosis of the colon.[2]

1. Barnett JM, *et al.* Intoxication after an isopropyl alcohol enema. *Ann Intern Med* 1990; **113:** 638–9.
2. Haviv YS, *et al.* Accidental isopropyl alcohol enema leading to coma and death. *Am J Gastroenterol* 1998; **93:** 850–1.

Pharmacokinetics

Isopropyl alcohol is readily absorbed from the gastrointestinal tract but there appears to be little absorption through intact skin. The vapour may be absorbed through the lungs. Isopropyl alcohol is metabolised more slowly than ethyl alcohol and about 15% of an ingested dose is metabolised to acetone.

◊ For reports of rectal absorption of isopropyl alcohol, see above.

Uses and Administration

Isopropyl alcohol is an antiseptic with bactericidal properties similar to those of alcohol (p.1627). It is used for pre-operative skin cleansing in concentrations of about 60 to 70%, and is an ingredient of preparations used for disinfection of hands and surfaces. Its marked degreasing properties may limit its usefulness in preparations used repeatedly. It is also used as a solvent, especially in cosmetics, perfumes and pharmaceutical preparations, and as a vehicle for other disinfectant compounds.

Propyl alcohol (p.1660) is also used as an antiseptic.

Preparations

USP 31: Azeotropic Isopropyl Alcohol; Isopropyl Rubbing Alcohol.

Proprietary Preparations (details are given in Part 3)

Canad.: Alcojel†; Auro-Dri; Duonalc; ***Ger.:*** Aktivin; ***S.Afr.:*** Medi-Swab; ***Switz.:*** Avitracid†; ***Turk.:*** Opak; ***UK:*** Alcowipe; Medi-Swab; Sterets; Steriwipe; ***USA:*** Auro-Dri; ***Venez.:*** Gel Secante†.

Multi-ingredient: ***Arg.:*** Sincerum Dry; ***Austral.:*** Aqua Ear; Ear Clear for Swimmer's Ear; Unisolve†; ***Austria:*** Braunoderm; Dodesept; Dodesept Gefarbt; Dodesept N; Kodan; Marcocid; Mycopol; Octeniderm; Skinsept; ***Belg.:*** Braunoderm; ***Canad.:*** Baxedin 2% - 70%; Duonalc-E; Swim-Ear†; ***Chile:*** NP-27; Solarcaine Spray Aerosol; ***Cz.:*** Promanum N; Softa-Man; ***Fr.:*** Clinogel; Manugel; Spitaderm†; Sterillium†; ***Ger.:*** Autoderm Extra; Bacillol; Bacillol AF; Bacillol plus; Betaseptic; Braunoderm; Cutasept; Desmanol†; Dibromol; Freka-Steril; Gercid forte†; Helipur H plus N; Incidin; Incidin M Spray Extra†; Kodan Tinktur Forte†; Mucasept-A; Neo Kodan†; Olbas; Poly-Alkohol; Primasept Med†; Promanum N; Rutisept extra; Sagrosept†; Sekucid konz†; Skinman Soft; Skinsept F; Skinsept G; Softasept N; Spitacid; St-Tissues; Sterillium; ***Gr.:*** Chiro Des; Cutasept; Octeniderm; Sterillium; ***Hong Kong:*** Hibisol†; ***Indon.:*** Mexochrome; Spitaderm; ***Irl.:*** Biofreeze; Hibisol; ***Israel:*** Dryears; Monorapid; Skin Des; Sterets H; ***Ital.:*** Bergon†; Braunoderm; Citromed; Clorexan; Eso Ferri Alcolico Plus; Eso Ferri Plus; Esocetic Plus; Esocetic†; Panseptil; SaniSteril Strumenti Alcolico†; Sekucid; Spitaderm; ***Neth.:*** Hibisol; Spitaderm; Sterillium; ***NZ:*** Aqua Ear†; ***Port.:*** Braunoderm; Promanum; Softasept; ***Singapore:*** Tri-Cidal†; ***Switz.:*** Betaseptic; Braunoderm; Cutasept; Desamon; Dolo-Arthrosenex sine Heparino†; Ederphyt†; Hibital; Hibitane Teinture; Kodan Teinture forte; Octeniderm; Promanum N; Softa-Man; Softasept N; Sterillium†; ***UK:*** ChloraPrep; Hibisol; Manusept; Medi-Swab H; Sterets H; Swim-Ear; ***USA:*** BactoShield; Blue Ice Gel; Cresylate; Dri/Ear; Ear-Dry; Fungi-Nail; Klout; Swim-Ear; Tinver.

Isothiazolinones

Isotiazolinonas.

Methylchloroisothiazolinone

Metilcloroisotiazolinona. 5-Chloro-2-methyl-3(2*H*)-isothiazolone; 5-Chloro-2-methyl-4-isothiazolin-3-one.

CAS — 26172-55-4.

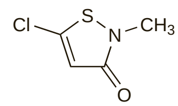

Methylisothiazolinone

Metilisotiazolinona. 2-Methyl-3(2*H*)-isothiazolone; 2-Methyl-4-isothiazolin-3-one.

CAS — 2682-20-4.

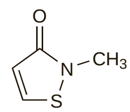

Profile

A mixture of isothiazolinones consisting of methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) in a ratio of about 3:1 is used as a preservative in industry and in cosmetic and household products. It is effective at very low concentrations against a wide spectrum of Gram-positive and -negative bacteria, yeasts, and fungi. The mixture is often referred to as Kathon CG, one of its proprietary names.

Isothiazolinones may cause contact dermatitis and local irritation.

Hypersensitivity. There have been reports of sensitisation and allergic contact dermatitis arising from the use of isothiazolinones in cosmetics, paints and from industrial exposure.[1-11] The incidence of allergy to methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) is reported be dose-related and ranges from less than 1% to 8.4%.[4,8] A study[6] conducted in 4713 patients at 22 European contact dermatitis clinics over a 12 month period from 1988 to 1989 reported the frequency of positive reactions to 100 ppm MCI/MI to be 3%.

Most hypersensitivity reports are related to use in cosmetics, especially 'leave-on' products such as moisturising creams, while the risk attributed to their use in 'rinse-off' products such as shampoos is considered to be minimal.[4,7] A review[7] of such rinse-off products found that they were even well tolerated in MCI/MI sensitised people. Airborne contact dermatitis has been reported in people exposed to MCI/MI in paints.[9,10] Occupational contact allergy and dermatitis due to MCI/MI have also been reported,[11] and there has been a case report of occupational asthma developing in a worker 5 months after starting work in an isothiazolinone manufacturing plant.[5]

1. Björkner B, *et al.* Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986; **14:** 85–90.
2. De Groot AC, Bos JD. Preservatives in the European standard series for epicutaneous testing. *Br J Dermatol* 1987; **116:** 289–92.
3. Fransway AF. Sensitivity to Kathon CG: findings in 365 consecutive patients. *Contact Dermatitis* 1988; **19:** 342–7.
4. De Groot AC, Herxheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *Lancet* 1989; **i:** 314–16.
5. Bourke SJ, *et al.* Occupational asthma in an isothiazolinone manufacturing plant. *Thorax* 1997; **52:** 746–8.
6. Menné T, *et al.* Contact sensitization to 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (MCI/MI): a European multicentre study. *Contact Dermatitis* 1991; **24:** 334–41.
7. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; **41:** 1–13.
8. Mowad CM. Methylchloro-isothiazolinone revisited. *Am J Contact Dermat* 2000; **11:** 115–18.
9. Bohn S, *et al.* Airborne contact dermatitis from methylchloroisothiazolinone in wall paint: abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; **42:** 196–201.
10. Reinhard E, *et al.* Preservation of products with MCI/MI in Switzerland. *Contact Dermatitis* 2001; **45:** 257–64.
11. Isaksson M, *et al.* Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; **15:** 201–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Switz.:*** Saltrates†.

Magenta

Aniline Red; Basic Fuchsin; Basic Magenta; CI Basic Violet 14; Colour Index No. 42510; Fuchsine; Fucsina.

CAS — 569-61-9 (pararosaniline hydrochloride); 632-99-5 (rosaniline hydrochloride).

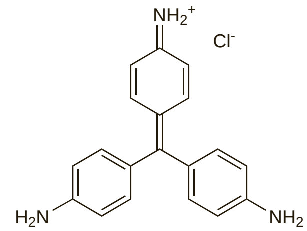

(pararosaniline hydrochloride)

Description. Magenta is a mixture of the hydrochlorides of pararosaniline {4-[(4-aminophenyl)(4-iminocyclohexa-2,5-dien-1-ylidene)-methyl]aniline} and rosaniline {4-[(4-aminophenyl)-(4-iminocyclohexa-2,5-dien-1-ylidene)methyl]-2-methylaniline}.

Pharmacopoeias. In *US.*

USP 31 (Basic Fuchsin). A mixture of rosaniline and pararosaniline hydrochlorides. It contains the equivalent of not less than 88% of rosaniline hydrochloride ($C_{20}H_{20}ClN_3$ = 337.8), calculated on the dried basis. A dark green powder or greenish glistening crystalline fragments with a bronze-like lustre and not more than a faint odour. Soluble in water, in alcohol, and in amyl alcohol; insoluble in ether.

Profile

Magenta is a triphenylmethane antiseptic dye effective against Gram-positive bacteria and some fungi. Magenta Paint (BPC 1973) (Castellani's Paint) was formerly used in the treatment of superficial dermatophytoses.

Decolorised magenta solution (Schiff reagent) is used as a test for the presence of aldehydes.

Concerns about possible carcinogenicity have restricted the use of magenta.

Carcinogenicity. The handling of magenta was not thought to induce carcinogenesis but its actual manufacture may produce tumours. The International Agency for Research on Cancer has concluded that the manufacturing process of magenta involves exposure to substances that are considered to be definite human carcinogens. Pararosaniline hydrochloride (Basic Red 9), and magenta containing it, are considered possibly carcinogenic to humans.[1] Magenta was also considered to be unsafe for use in food.[2]

1. IARC/WHO. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC monographs on the evaluation of carcinogenic risks to humans volume 57* 1993. Available at: http://monographs.iarc.fr/ENG/Monographs/vol57/volume57.pdf (accessed 23/05/06)
2. FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antoxidants: eighth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 309* 1965. Also available at: http://libdoc.who.int/trs/WHO_TRS_309.pdf (accessed 28/08/08)

Preparations

BPC 1973: Magenta Paint;
USP 31: Carbol-Fuchsin Topical Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Fucsina Fenica; ***Pol.:*** Pigmentum Castellani.

Magnesium Peroxide

Magnesii peroxidum; Magnesium Perhydrolum; Magnésium, peroxyde de; Magnesiumperoksidi; Magnesiumperoxid; Magnézium-peroxid; Magnio peroksidas; Peroxid hořečnatý; Peróxido de magnesio.

CAS — 1335-26-8; 14452-57-4.

ATC — A02AA03; A06AD03.

ATC Vet — QA02AA03; QA06AD03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Magnesium Peroxide). A mixture of magnesium peroxide and magnesium oxide. It contains not less than 22% and not more than 28% of MgO_2. A white or slightly yellow, amorphous, light powder. Practically insoluble in water and in alcohol; dissolves in mineral acids. Protect from light.

Profile
Magnesium peroxide is used as an antiseptic. It is also an ingredient of preparations for gastrointestinal disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Ozovit†.
Multi-ingredient: ***Israel:*** Digestif-Ara†; ***Ital.:*** Carbonesia; Ektogan; ***Switz.:*** Desaquick extra fresh†; Desaquick fresh†; Magenpulver Hafter†.

Malachite Green
Aniline Green; China Green; CI Basic Green 4; Colour Index No. 42000; Diamond Green B; Verde de malaquita; Viride Malachitum; Zieleń malachitowa. [4-(4-Dimethylaminobenzhydrylidene)cyclohexa-2,5-dienylidene]dimethylammonium chloride.

CAS — 569-64-2.

ATC Vet — QP53AX16.

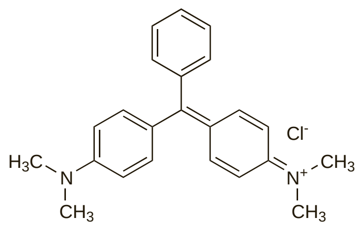

Profile
Malachite green is a triphenylmethane antiseptic dye with actions similar to those of brilliant green (p.1632). It has been used for skin disinfection.

Mecetronium Etilsulfate *(BAN, rINN)*
Etilsulfato de mecetronio; Mecetronii Etilsulfas; Mecetronium Ethylsulfate *(USAN)*; Mecetronium Ethylsulphate; Mécétronium, Étilsulfate de. Ethylhexadecyldimethylammonium ethyl sulphate.

Мецетрония Этилсульфат

$C_{22}H_{49}NO_4S$ = 423.7.

CAS — 3006-10-8.

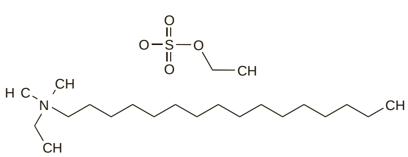

Profile
Mecetronium etilsulfate is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is active against bacteria, including mycobacteria, fungi, and viruses, including hepatitis B virus. It is used in alcoholic solution for disinfection of the skin and hard surfaces.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Sterillium†; ***Ger.:*** Bacillol; St-Tissues; Sterillium; ***Gr.:*** Sterillium; ***Neth.:*** Sterillium; ***Switz.:*** Sterillium†.

Merbromin *(rINN)*
Disodium 2,7-dibromo-4-hydroxymercurifluorescein; Merbromina; Merbromine; Merbrominum; Mercurescéine Sodique; Mercurochrome; Mercurodibromofluorescein; Merkürokrom. The disodium salt of [2,7-dibromo-9-(2-carboxyphenyl)-6-hydroxy-3-oxo-3*H*-xanthen-5-yl]hydroxymercury.

Мербромин

$C_{20}H_8Br_2HgNa_2O_6$ = 750.7.

CAS — 129-16-8.

ATC — D08AK04.

ATC Vet — QD08AK04.

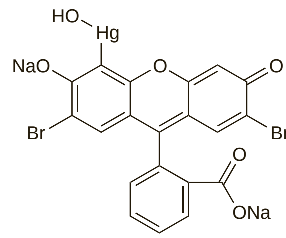

NOTE. The use of the name Merbromin is limited; in some countries it is a trade-mark.

Pharmacopoeias. In *Fr., It., Jpn,* and *Viet.*

Incompatibility. Merbromin is incompatible with acids, most alkaloidal salts, many local anaesthetics, metals, and sulfides. Activity may be reduced in the presence of organic material.

Adverse Effects and Treatment
As for Mercury, p.2341.

◊ General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; **18:** 109–60.

Toxicity. Reports of merbromin toxicity have included contact dermatitis[1] and epidermal cell toxicity.[2] A fatality has occurred after transcutaneous absorption of merbromin during treatment of infected omphalocele (umbilical hernia)[3,4] and death due to shock, with aplastic anaemia, has followed application to surgical wounds and decubitus areas.[5] Anaphylaxis has also occurred.[6] Extensive absorption after ingestion has also been reported.[7] There has also been a case report[8] of severe encephalopathy and meningitis within 24 hours of an accidental intrathecal application into a CSF fistula.

1. Camarasa G. Contact dermatitis from mercurochrome. *Contact Dermatitis* 1976; **2:** 120.
2. Anonymous. Topical antiseptics and antibiotics. *Med Lett Drugs Ther* 1977; **19:** 83–4.
3. Yeh T-F, *et al.* Mercury poisoning from mercurochrome therapy of infected omphalocele. *Lancet* 1978; **i:** 210.
4. Yeh TF, *et al.* Mercury poisoning from mercurochrome therapy of an infected omphalocele. *Clin Toxicol* 1978; **13:** 463–7.
5. Slee PHTJ, *et al.* A case of Merbromin (mercurochrome) intoxication possibly resulting in aplastic anemia. *Acta Med Scand* 1979; **205:** 463–6.
6. Galindo PA, *et al.* Mercurochrome allergy: immediate and delayed hypersensitivity. *Allergy* 1997; **52:** 1138–41.
7. Magarey JA. Absorption of mercurochrome. *Lancet* 1993; **342:** 1424.
8. Stark AM, *et al.* Accidental intrathecal mercury application. *Eur Spine J* 2004; **13:** 241–3.

Uses and Administration
Merbromin is a mercurial antiseptic that has been used for disinfection of skin and wounds.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Rojobacter†; ***Belg.:*** Medichrom; ***Braz.:*** Mercurio Cromo†; ***Fr.:*** Pharmadose mercuresceine†; Soluchrom; ***Ger.:*** Mercuchrom†; ***Gr.:*** Merbromin; Mercurochrome; ***Ital.:*** Cromocur†; ***S.Afr.:*** Red Seal; ***Spain:*** Cinfacromin; Cromer Orto; Mercromina; Mercurin; Mercurobromo; Mercutina Brota; Super Cromer Orto; ***Turk.:*** Mersol.
Multi-ingredient: ***S.Afr.:*** Achromide; Daromide; Ung Vernleigh; ***Spain:*** Argentocromo†; Mercrotona; ***Venez.:*** Thimerfesa†.

Mercurobutol *(rINN)*
L-542; Mercurobutolum. 4-*tert*-Butyl-2-chloro-mercuriphenol.

Меркуробутол

$C_{10}H_{13}ClHgO$ = 385.3.

CAS — 498-73-7.

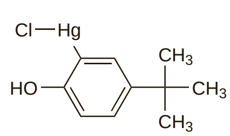

Pharmacopoeias. In *Fr.*

Profile
Mercurobutol is an organic mercurial antiseptic with antifungal properties. It has been used in the treatment of infections of the skin and mucous membranes.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Gr.:*** Sabenyl†.

Metalkonium Chloride *(rINN)*
Cloruro de metalconio; Dodecarbonium Chloride; Metalkonii Chloridum; Métalkonium, Chlorure de. Benzyl(dodecylcarbamoylmethyl)dimethylammonium chloride.

Металкония Хлорид

$C_{23}H_{41}ClN_2O$ = 397.0.

CAS — 100-95-8.

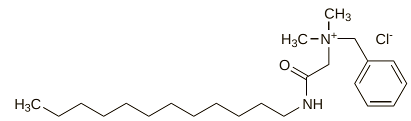

Profile
Metalkonium chloride is an antiseptic used for skin disinfection.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Theotex.

Methylated Spirits
Alcoholes desnaturalizados.

CAS — 8013-52-3 (ethyl alcohol-methyl alcohol mixture; industrial methylated spirit).

Description. Three classes of methylated spirits are listed under the Methylated Spirits Regulations, 1987 (SI 1987: No. 2009): industrial methylated spirits, mineralised methylated spirits, and denatured ethanol (denatured alcohol).
Industrial Methylated Spirits is defined as 95 parts by volume of spirits mixed with wood naphtha (mostly methyl alcohol—p.2024) 5 parts by volume. **Mineralised methylated spirits** is spirits mixed with wood naphtha 9.5 parts by volume and crude pyridine 0.5 parts by volume, and to every 2000 litres of this mixture is added 7.5 litres of mineral naphtha (petroleum oil) and 3 g of synthetic organic dyestuff (methyl violet). This is the only variety that may be sold in Great Britain for general use. **Denatured ethanol** is 999 parts by volume of spirits (of a strength not less than 85%) mixed with 1 part by volume of tertiary butyl alcohol, and to this mixture is added Bitrex (denatonium benzoate) 10 mg/litre.
As Industrial Methylated Spirit may contain small amounts of acetone it should not be used for the preparation of iodine solutions, since an irritating compound is formed by reaction between iodine and acetone; for such preparations Industrial Methylated Spirit (Ketone-free) should be used.

Pharmacopoeias. *Br.* includes Industrial Methylated Spirit and Industrial Methylated Spirit (Ketone-free).
BP 2008 (Industrial Methylated Spirit). A mixture of 19 volumes of ethyl alcohol of an appropriate strength with 1 volume of approved wood naphtha. Two strengths are available containing 99% and 95% v/v alcohol (also known as 74 OP and 66 OP respectively). It is a colourless, clear, mobile, volatile liquid with an odour which is spirituous and of wood naphtha. B.p. is about 78°.
The BP 2008 gives Industrial Methylated Spirits and IMS as approved synonyms.
BP 2008 (Industrial Methylated Spirit (Ketone-free)). A mixture of the same strength as Industrial Methylated Spirit, but it is substantially free from ketones, containing not more than the equivalent of 500 ppm of acetone.

Adverse Effects
As for Alcohol, p.1625, and Methyl Alcohol, p.2024. Adverse effects are due chiefly to consumption of methylated spirits rather than its topical use as a disinfectant.

Uses and Administration
Industrial methylated spirit, in a concentration of about 70%, is the usual form in which alcohol (p.1625) is used for disinfection. It is applied externally for its astringent action, but mucous membranes and excoriated skin surfaces must be protected. It may be used for skin preparation before injection.

Methylated spirits may be used in the form of Surgical Spirit (BP 2008), a mixture of methyl salicylate (0.5% v/v), diethyl phthalate (2% v/v), and castor oil (2.5% v/v) in industrial methylated spirit.

Preparations
BP 2008: Surgical Spirit.
Proprietary Preparations (details are given in Part 3)
Ital.: Esosan Gel.

Methylbenzethonium Chloride *(BAN, rINN)*

Cloruro de metilbencetonio; Methylbenzethonii Chloridum; Méthylbenzéthonium, Chlorure de. Benzyldimethyl-2-{2-[4-(1,1,3,3-tetramethylbutyl)-*o*-tolyloxy]ethoxy}ethylammonium chloride monohydrate.

Метилбензетония Хлорид

$C_{28}H_{44}ClNO_2,H_2O$ = 480.1.

CAS — 25155-18-4 (anhydrous methylbenzethonium chloride); 1320-44-1 (methylbenzethonium chloride monohydrate).

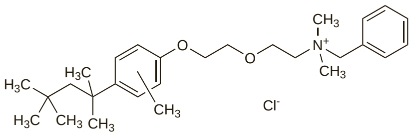

Pharmacopoeias. In *US.*

USP 31 (Methylbenzethonium Chloride). White hygroscopic crystals with a mild odour. Soluble 1 in 0.8 of water, 1 in 0.9 of alcohol, 1 in more than 10 000 of chloroform, and 1 in 0.7 of ether. Solutions are neutral or slightly alkaline to litmus. Store in airtight containers.

Profile

Methylbenzethonium chloride is a quaternary ammonium disinfectant and antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used topically for minor infections or irritation of the skin.

Leishmaniasis. Topical treatment of cutaneous leishmaniasis (p.824) with methylbenzethonium chloride 5 or 12% and paromomycin sulfate has proved beneficial.

Preparations

USP 31: Methylbenzethonium Chloride Lotion; Methylbenzethonium Chloride Ointment; Methylbenzethonium Chloride Topical Powder.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Israel:*** Leshcutan; ***Ital.:*** Traumicid†; ***Mex.:*** Norforms†; ***USA:*** Acnotex; Dermasept Antifungal; Drytex; Finac; Orasept.

Methylrosanilinium Chloride *(BAN, rINN)*

CI Basic Violet 3; Cloruro de metilrosanilina; Colour Index No. 42555; Crystal Violet; Fiolet krystaliczny; Gentian Violet; Hexamethylpararosaniline Chloride; Jansiyen Moru; Kristal Viyole; Kristallviolett; Methylrosaniline Chloride; Methylrosanilinii chloridum; Méthylrosanilinium, chlorure de; Methylrosanilinium-chlorid; Metilrozanilinio chloridas; Metilrozanilinyum Klorür; Metylrosaniliniumklorid; Metyylirosaniliniumkloridi; Pyoctaninum Caeruleum; Viola Crystallina. 4-[4,4′Bis(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidenedimethylammonium chloride.

Метилрозанилиния Хлорид

$C_{25}H_{30}ClN_3$ = 408.0.

CAS — 548-62-9.

ATC — D01AE02; G01AX09.

ATC Vet — QD01AE02; QG01AX09.

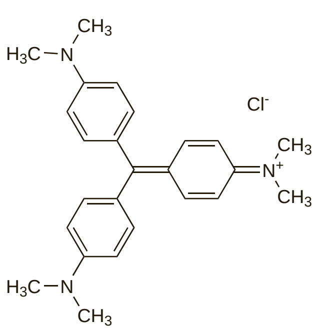

NOTE. The name methyl violet—CI Basic Violet 1; Colour Index No. 42535—has been used as a synonym for methylrosanilinium chloride, but is applied to a mixture of the hydrochlorides of the higher methylated pararosanilines consisting principally of the tetramethyl-, pentamethyl-, and hexamethyl- compounds.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Jpn includes a mixture of hexamethylpararosaniline hydrochloride with the tetramethyl- and pentamethyl- compounds.

Ph. Eur. 6.2 (Methylrosanilinium Chloride). A dark green, hygroscopic, shiny powder. It contains not more than 10% of pentamethyl-*p*-rosanilinium chloride. It is also known as crystal violet and gentian violet. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 31 (Gentian Violet). A dark green powder or greenish, glistening pieces with a metallic lustre, and with not more than a faint odour. Sparingly soluble in water; soluble 1 in 10 of alcohol and 1 in 15 of glycerol; soluble in chloroform; insoluble in ether.

Incompatibility. The antimicrobial activity of methylrosanilinium chloride may be reduced through incompatibilities, decreasing pH, or through combination with organic matter.

The antibacterial activity of methylrosanilinium chloride was inhibited in suspensions of bentonite with which it formed a stable complex.[1]

1. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; **42:** 583–8.

Adverse Effects and Precautions

Topical application of methylrosanilinium chloride can produce irritation and ulceration of mucous membranes. Ingestion of methylrosanilinium chloride during prolonged or frequent treatment for oral candidiasis has resulted in oesophagitis, laryngitis, and tracheitis; ingestion may also cause nausea, vomiting, diarrhoea, and abdominal pain. In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds. Contact with the eyes or broken skin should be avoided. Methylrosanilinium chloride may stain skin and clothing.

Animal carcinogenicity has restricted its use.

Carcinogenicity. Methylrosanilinium chloride has been shown *in vitro* to be capable of interacting with DNA of living cells,[1] and has demonstrable carcinogenicity in *mice*.[2]

1. Rosenkranz HS, Carr HS. Possible hazard in use of gentian violet. *BMJ* 1971; **3:** 702–3.
2. MAFF Food Advisory Committee. Final report on the review of the Colouring Matter in Food Regulations 1973: FdAC/REP/4. London: HMSO, 1987.

Effects on the skin and mucous membranes. Necrotic skin reactions have been reported after the use of topical 1% aqueous solutions of methylrosanilinium chloride;[1] areas affected include the submammary folds, gluteal fold, genitalia, and toe-webs. Similar reactions were observed in 2 patients after use of 1% methylrosanilinium chloride or brilliant green on stripped skin.[1] Oral ulceration developed in all of 6 neonates treated with aqueous methylrosanilinium chloride 0.5 or 1% for oral candidiasis.[2]

In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds.

1. Björnberg A, Mobacken H. Necrotic skin reactions caused by 1% gentian violet and brilliant green. *Acta Derm Venereol (Stockh)* 1972; **52:** 55–60.
2. Horsfield P, *et al.* Oral irritation with gentian violet. *BMJ* 1976; **2:** 529.

Effects on the urinary tract. Severe haemorrhagic cystitis rapidly occurred in a 32-year-old woman after accidental injection through the urethra of a solution of methylrosanilinium chloride 1% and alcohol 2%.[1] Two cases of severe cystitis were also reported after instillation into the bladder of an undiluted solution containing methylrosanilinium chloride and brilliant green 1:1 (Bonney's blue).[2] Haemorrhagic cystitis has also been reported in a 16-month-old boy after a diluted solution of methylrosanilinium chloride 1% was instilled into his bladder during an inguinal herniorrhaphy.[3]

1. Walsh C, Walsh A. Haemorrhagic cystitis due to gentian violet. *BMJ* 1986; **293:** 732.
2. Christmas TJ, *et al.* Bonney's blue. *Lancet* 1988; **ii:** 459–60.
3. Kim SJ, *et al.* Hemorrhagic cystitis due to intravesical instillation of gentian violet completely recovered with conservative therapy. *Yonsei Med J* 2003; **44:** 163–5.

Porphyria. Methylrosanilinium chloride has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Uses and Administration

Methylrosanilinium chloride is a triphenylmethane antiseptic dye effective against some Gram-positive bacteria, particularly *Staphylococcus* spp., and some pathogenic fungi such as *Candida* spp. It is much less active against Gram-negative bacteria and ineffective against acid-fast bacteria and bacterial spores. Its activity increases as pH increases.

Methylrosanilinium chloride has been applied topically as a 0.25 to 2.0% aqueous solution or as a cream for the treatment of bacterial and fungal infections, but in the UK its use is now restricted to application to unbroken skin because of concern over *animal* carcinogenicity. It has also been used as a 0.5% solution with brilliant green 0.5% (Bonney's blue) for skin marking before surgery.

Preparations

USP 31: Gentian Violet Cream; Gentian Violet Topical Solution.

Proprietary Preparations (details are given in Part 3)

Pol.: Pioktanina; ***Spain:*** Vigencial; ***Turk.:*** Viojen.

Multi-ingredient: ***Chile:*** Calmante de Aftas†; Faxet; ***Hung.:*** Dermaforine†.

Miramistin

Myramistin. Alkylamidopropylmethylbenzylammonium chloride.

Мирамистин

$C_{26}H_{47}N_2OCl$ = 439.1.

CAS — 126338-77-0; 15809-19-5.

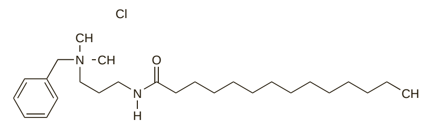

Profile

Miramistin is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also included in topical preparations for skin disorders when prone to infection.

Miripirium Chloride *(rINN)*

Cloruro de miripirio; Miripirii Chloridum; Miripirium, Chlorure de; Myristyl-gamma-picolinium Chloride. 4-Methyl-1-tetradecylpyridinium chloride.

Мирипирия Хлорид

$C_{20}H_{36}ClN$ = 326.0.

CAS — 7631-49-4 (miripirium); 2748-88-1 (miripirium chloride).

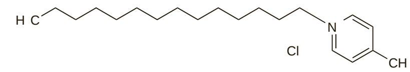

Profile

Miripirium chloride is used as an antimicrobial preservative in some pharmaceutical products.

Hypersensitivity. Two patients who had a delayed hypersensitivity reaction to retrobulbar injection of methylprednisolone acetate suspension (*Depo-Medrol*)[1] were found on intradermal testing to be sensitive to methylprednisolone and to miripirium chloride, included as a preservative in the formulation. A similar case of contact allergy has been reported[2] in a 56-year-old woman who received an intra-articular injection of methylprednisolone acetate. Patch testing showed allergy to the preservative miripirium chloride.

1. Mathias CGT, Robertson DB. Delayed hypersensitivity to a corticosteroid suspension containing methylprednisolone. *Arch Dermatol* 1985; **121:** 258–61.
2. Färm G, Eriksson I. Contact allergy to miripirium chloride in Depo-Medrol. *Contact Dermatitis* 2001; **44:** 127.

Miristalkonium Chloride *(BAN, rINN)*

Cloruro de miristalconio; Miristalkonii Chloridum; Miristalkonium, Chlorure de; Myristylbenzalkonium Chloride. Benzyldimethyltetradecylammonium chloride.

Миристалкония Хлорид

$C_{23}H_{42}ClN$ = 368.0.

CAS — 139-08-2.

ATC — R02AA10.

ATC Vet — QR02AA10.

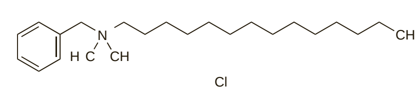

Profile

Miristalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It has been used in creams and lotions for disinfection of the skin and has been an ingredient of sprays used for the treatment of minor infections of the mouth and throat. It is also used as a vaginal spermicide.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Alpagelle.

Multi-ingredient: ***Fr.:*** Sterlane; ***Ital.:*** Eburdent F.

Monothioglycerol

α-Monothioglycerol; Monotioglicerol; Thioglycerol. 3-Mercaptopropane-1,2-diol.

$C_3H_8O_2S$ = 108.2.

CAS — 96-27-5.

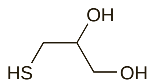

Pharmacopoeias. In *USNF.*

USNF 26 (Monothioglycerol). A colourless or pale yellow, viscous, hygroscopic liquid with a slight odour of sulfide. Freely soluble in water; miscible with alcohol; insoluble in ether. A 10% solution in water has a pH of 3.5 to 7.0. Store in airtight containers.

Profile

Monothioglycerol is used as an antoxidant preservative in pharmaceutical preparations. It has some antimicrobial activity.

Myralact *(BAN, pINN)*

Miralacto; Myralactum. (2-Hydroxyethyl)tetradecylammonium lactate.

Миралакт

$C_{19}H_{41}NO_4$ = 347.5.

CAS — 15518-87-3.

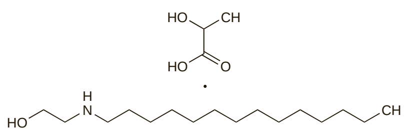

Profile

Myralact is an antiseptic included in multi-ingredient preparations intended for the topical treatment of vaginal infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Ginetris†.

Nitromersol

5-Methyl-2-nitro-7-oxa-8-mercurabicyclo[4.2.0]octa-1,3,5-triene.

$C_7H_5HgNO_3$ = 351.7.

CAS — 133-58-4.

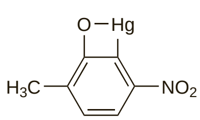

Pharmacopoeias. In *US.*

USP 31 (Nitromersol). A brownish-yellow to yellow odourless powder or granules. Very slightly soluble in water, in alcohol, in acetone, and in ether; soluble in solutions of alkalis and of ammonia with the formation of salts. Store in airtight containers. Protect from light.

Incompatibility. Nitromersol is incompatible with metals and sulfides. Its antimicrobial activity may be diminished in the presence of organic material.

Adverse Effects and Treatment

As for Mercury, p.2341.

Uses and Administration

Nitromersol is a mercurial antiseptic effective against some bacteria. It is not effective against spores or acid-fast bacteria. It has been used for superficial skin infections and for disinfection of the skin prior to surgical treatment.

Preparations

USP 31: Nitromersol Topical Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Butesin Picrate†; ***Chile:*** Butesin.

Nordihydroguaiaretic Acid

Acidum Nordihydroguaiareticum; NDGA; Nordihidroguayarético, ácido; Nordihydroguajareettiha ppo; Nordihydroguajaretsyra. 4,4′-(2,3-Dimethyltetramethylene)bis(benzene-1,2-diol).

$C_{18}H_{22}O_4$ = 302.4.

CAS — 500-38-9.

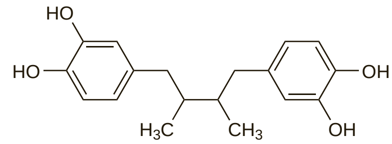

Profile

Nordihydroguaiaretic acid has been used as an antoxidant preservative. Allergic contact dermatitis has been reported.

Noxytiolin *(BAN, rINN)*

Noxitiolina; Noxythiolin; Noxytioline; Noxytiolinum. 1-Hydroxymethyl-3-methyl-2-thiourea.

Нокситиолин

$C_3H_8N_2OS$ = 120.2.

CAS — 15599-39-0.

ATC — B05CA07.

ATC Vet — QB05CA07.

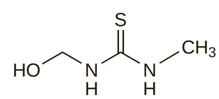

Adverse Effects and Treatment

When noxytiolin is given initially by irrigation for the treatment of the purulent infected bladder there may be an intense reaction with a burning sensation and the passage of large fibrin clumps. Giving it with a local anaesthetic such as tetracaine hydrochloride may control the pain.

Breath odour. A pervasive sweet breath odour characteristic of decaying vegetables has been noted in patients treated with peritoneal dialysis fluid containing noxytiolin.[1] The odour was attributed to unidentified sulfur metabolites.

1. Stewart WK, Fleming LW. Use your nose. *Lancet* 1983; **i:** 426.

Uses and Administration

Noxytiolin is an antiseptic with wide antibacterial and antifungal actions. It may act by slowly releasing formaldehyde in solution.

For instillation into, or irrigation of, the peritoneal cavity or other body cavities, a 1 or 2.5% solution is used. Solutions of noxytiolin should be warmed to 37° before instillation or irrigation. Treatment is usually for 3 to 7 days. The normal total daily amount used in adults should not exceed 5 g for instillation or 10 g for continuous irrigation.

Action. Although noxytiolin has generally been thought to act, at least in part, by slowly releasing formaldehyde into solution, it has been reported[1] that much smaller amounts are released than have previously been thought and that the antimicrobial effects of noxytiolin solutions cannot be attributed solely to the presence of formaldehyde. There is evidence *in vitro* that noxytiolin might reduce the adherence of micro-organisms to epithelial surfaces.[2]

1. Gorman SP, *et al.* Formaldehyde release from noxythiolin solutions. *Pharm J* 1984; **234:** 62–3.
2. Anderson L, *et al.* Clinical implications of the microbial antiadherence properties of noxythiolin. *J Pharm Pharmacol* 1985; **37** (suppl): 64P.

Infections of the pleural cavity. Three patients with pleural empyema or pneumonectomy space infection were treated by irrigation of the cavity with noxytiolin 1% in normal saline for 3 hours, followed by drainage for 1 hour, the cycle being repeated 4-hourly. Infection was eradicated within 21 days in all 3 patients.[1]

1. Rosenfeldt FL, *et al.* Comparison between irrigation and conventional treatment for empyema and pneumonectomy space infection. *Thorax* 1981; **36:** 272–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Noxyflex; ***Irl.:*** Noxyflex S; ***UK:*** Noxyflex S.

Octafonium Chloride *(BAN, rINN)*

Cloruro de octafonio; Octafonii Chloridum; Octafonium, Chlorure d'; Octaphonium Chloride; Phenoctide. Benzyldiethyl-2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethylammonium chloride monohydrate.

Октафония Хлорид

$C_{27}H_{42}ClNO,H_2O$ = 450.1.

CAS — 15687-40-8 (anhydrous octafonium chloride); 78-05-7 (anhydrous octafonium chloride).

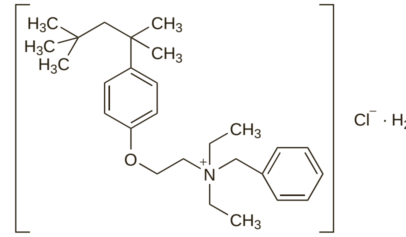

Profile

Octafonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in topical preparations for skin disinfection.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Germolene; ***UK:*** Germolene.

Octenidine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de octenidina; Octénidine, Chlorhydrate d'; Octenidini Hydrochloridum; Win-41464 (octenidine); Win-41464-2 (octenidine hydrochloride); Win-41464-6 (octenidine saccharin). 1,1′,4,4′-Tetrahydro-*N,N*′-dioctyl-1,1′-decamethylenedi-(4-pyridylideneamine) dihydrochloride.

Октенидина Гидрохлорид

$C_{36}H_{62}N_4,2HCl$ = 623.8.

CAS — 71251-02-0 (octenidine); 70775-75-6 (octenidine hydrochloride).

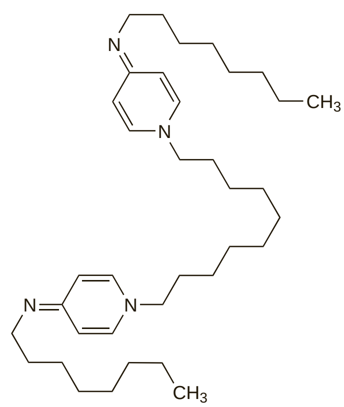

(octenidine)

Profile

Octenidine is a bispyridine bactericidal antiseptic with some antiviral and antifungal activity. It has been used as the hydrochloride for skin and mucous membrane disinfection.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Phisomain.

Multi-ingredient: ***Austria:*** Octeniderm; Octenisept; ***Ger.:*** Neo Kodan†; Octenisept; ***Gr.:*** Octeniderm; Octenisept; ***Switz.:*** Octeniderm; Octenisept.

Octyldecyldimethylammonium Chloride

Decyldimethyloctylammonium Chloride; Decyloctyldimethylammonium Chloride; Octyl Decyl Dimethyl Ammonium Chloride. *N,N*-Dimethyl-*N*-octyl-1-decanaminium chloride.

Октилдецилдиметиламмоний Хлорид

$C_{20}H_{44}ClN$ = 334.0.

CAS — 32426-11-2.

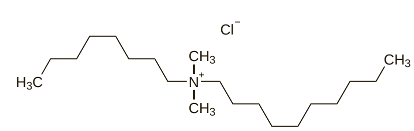

Profile

Octyldecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of hard surfaces and the skin.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***USA:*** Vi Rid-Ready.

Orthophenylphenol

2-Biphenylol; E231; E232 (sodium-*o*-phenylphenol); 2-Hydroxybiphenyl; *o*-Hydroxydiphenyl; Ortofenilfenol. (1,1′-Biphenyl)-2-ol.
$C_{12}H_{10}O$ = 170.2.
CAS — 90-43-7.
ATC — D08AE06.
ATC Vet — QD08AE06.

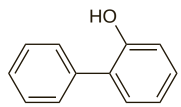

Profile

Orthophenylphenol is a phenolic disinfectant with antimicrobial properties similar to those of chloroxylenol (p.1640). It is used for disinfection of skin, hands, instruments, and hard surfaces. It also has many industrial and agricultural uses as a preservative for a wide range of materials, particularly against moulds and rots. Sodium-*o*-phenylphenol has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Amocid; ***Ital.:*** Citromedics Disinfettante; Citrosteril Aspiratori; Crescom; Esofenol 60; Germozero Clean; Helix I; Higesan; Neo Esoformolo; Vcanalare†; ***Switz.:*** Manusept†.

Multi-ingredient: ***Austria:*** Dodesept; Dodesept Gefarbt; Kodan; ***Ger.:*** Bomix; Desderman N†; Freka-Derm; Freka-Sept 80; Helipur; Incidin Extra†; Kodan Tinktur Forte†; Primasept Med†; ***Ital.:*** Bergon†; Diaril†; Esofenol Ferri; Germozero Dermo; Germozero Plus; Helipur; Hygienist†; Norica; Sangen Casa; Sterosan; ***Switz.:*** Frekaderm†; Kodan Teinture forte; ***USA:*** BTK-Plus.

Oxychlorosene *(USAN)*

Monoxychlorosene; Oxicloroseno.
$C_{20}H_{34}O_3S,HOCl$ = 407.0.
CAS — 8031-14-9.

Oxychlorosene Sodium *(USAN)*

Oxicloroseno sódico; Sodium Oxychlorosene.
CAS — 52906-84-0.

Profile

Oxychlorosene is the hypochlorous acid complex of a mixture of the phenyl sulfonate derivatives of aliphatic hydrocarbons. It is a chlorine-releasing antiseptic with the general properties of chlorine, p.1638.

A 0.4% solution of oxychlorosene sodium has been used for cleansing wounds (although chlorine-releasing antiseptics are generally regarded as too irritant for this purpose—see Disinfection, Wounds, under Uses and Administration of Sodium Hypochlorite, p.1662) and for pre-operative skin preparation; a 0.1 or 0.2% solution has been used in urological and ophthalmological disinfection.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Clorpactin WCS-90.

Oxymethurea

Carbamol; *N,N′*-di(hydroksimetyyli)karbamidi; *N,N′*-di(hydroximetyl)-karbamid; Dihydroxymethyl Carbamide; *N,N′*-di(hydroxymethyl)carbamidum; Oximeturea. *N,N′*-Bis(hydroxymethyl)urea.
$C_3H_8N_2O_3$ = 120.1.
CAS — 140-95-4.

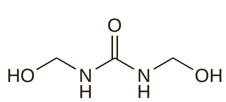

Profile

Oxymethurea is an antiseptic included in multi-ingredient preparations intended for the topical treatment of ear infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Ciloprin cum Anaesthetico†; ***Fin.:*** Ciloprin cum Anaesthetico†; ***India:*** Otogesic; ***Switz.:*** Ciloprin ca†.

Parachlorophenol

Paraclorofenol. 4-Chlorophenol.
C_6H_5ClO = 128.6.
CAS — 106-48-9.

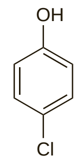

Pharmacopoeias. In *US.*
US also includes camphorated parachlorophenol.
USP 31 (Parachlorophenol). It consists of white or pink crystals with a characteristic phenolic odour. M.p. about 42°; congealing temperature between 42° and 44°. Sparingly soluble in water and in liquid paraffin; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble in soft paraffin. A 1% solution in water is acid to litmus. Store in airtight containers. Protect from light.
USP 31 (Camphorated Parachlorophenol). It contains not less than 33% and not more than 37% of parachlorophenol and not less than 63% and not more than 67% of camphor, with the sum of the percentages of parachlorophenol and camphor not less than 97% and not more than 103%. Store in airtight containers. Protect from light.

Profile

Parachlorophenol is a chlorinated phenolic disinfectant and antiseptic with similar properties to phenol (p.1656). Camphorated parachlorophenol has been used in dentistry in the treatment of infected root canals.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Esofenol Ferri; Pasta Iodoformica Radiopaca; ***Spain:*** Cresophene; ***Switz.:*** Cresophene†.

Paraformaldehyde

Paraform; Paraformaldehído; Paraformic Aldehyde; Polymerised Formaldehyde; Polyoxymethylene; Trioxyméthylène.
$(CH_2O)_n$.
CAS — 30525-89-4.

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Formaldehyde Solution, p.1644. There have been reports of allergic reactions and nerve damage associated with the dental use of paraformaldehyde as a root canal sealant; it should not extrude beyond the apex.

Uses and Administration

Paraformaldehyde is a disinfectant and antiseptic with the properties and uses of formaldehyde (p.1645) and is used as a source of formaldehyde. To disinfect rooms it has been vapourised by heating. Tablets prepared for this purpose should be coloured by the addition of a suitable blue dye.

Paraformaldehyde has been used in lozenges for the treatment of minor throat infections. In dentistry, it has been used as an obtundent for sensitive dentine and as an antiseptic in mummifying pastes and for root canals. Paraformaldehyde may also be used for the decontamination of equipment thought to be contaminated with the spores of *Bacillus anthracis.*

Preparations

Proprietary Preparations (details are given in Part 3)
Israel: Formalin.

Multi-ingredient: ***Ital.:*** Eso 70; Esoform 7 mc; Esoform 70 mc; Pasta Devitalizzante; ***Switz.:*** Asphaline†; Caustinerf forte†.

Peracetic Acid

Acetyl Hydroperoxide; Acidum Peraceticum; Kyselina peroctová; Peracético, ácido; Peroxyacetic Acid.
$C_2H_4O_3$ = 76.05.
CAS — 79-21-0.

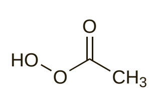

Adverse Effects and Precautions

Concentrated peracetic acid is corrosive to the skin. Inhalation may produce respiratory symptoms, including pulmonary oedema, although commercial solutions are claimed to have low vapour activity.

Occupational exposure. Although corrosive and highly irritating to skin, eyes, mucous membranes and respiratory tract, solutions of peracetic acid (with hydrogen peroxide) were thought unlikely to cause sensitisation leading to hypersensitivity reactions in healthcare workers who were occupationally exposed. In contrast, *o*-phthaldialdehyde, although its sensitising potential was much lower than that of glutaral, might cause respiratory and dermal sensitisation.[1]

1. Rideout K, *et al.* Considering risks to healthcare workers from glutaraldehyde alternatives in high-level disinfection. *J Hosp Infect* 2005; **59:** 4–11.

Uses

Peracetic acid is a strong oxidising disinfectant. It is active against many micro-organisms including bacteria, spores, fungi, and viruses. It is used for disinfecting medical equipment including dialysers and endoscopes. It is used in the food industry and for disinfecting sewage sludge, and has been used as a spray for sterilisation of laboratories.

◊ Reviews.

1. Kitis M. Disinfection of wastewater with peracetic acid: a review. *Environ Int* 2004; **30:** 47–55.

Disinfection of dialysis equipment. For use of peracetic acid with hydrogen peroxide in the disinfection of dialysis equipment, see under Hydrogen Peroxide, p.1648.

Disinfection of endoscopes. Peracetic acid has been used to disinfect endoscopes;[1,2] it is a possible alternative to glutaral (see p.1623).

1. Bradley CR, *et al.* Evaluation of the Steris system 1 peracetic acid endoscope processor. *J Hosp Infect* 1995; **29:** 143–51.
2. Middleton AM, *et al.* Disinfection of bronchoscopes, contaminated in vitro with Mycobacterium tuberculosis, Mycobacterium avium-intracellulare and Mycobacterium chelonae in sputum, using stabilized, buffered peracetic acid solution ('Nu-Cidex'). *J Hosp Infect* 1997; **37:** 137–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Dynacide; Nu-Cidex†; ***Ger.:*** Sekusept; ***Ital.:*** Esodrox; Ferrister; Renaxid; SaniDrox; Sekusept; Sporidox Plus; ***Singapore:*** Perasafe.

Multi-ingredient: ***Fr.:*** Anioxyde; ***Ger.:*** Peresal†; ***Ital.:*** Adaspor; Esocetic Plus; Esocetic†; Peresal; ***Singapore:*** Virkon.

Phenethyl Alcohol *(BAN)*

Alcohol feniletílico; Alcohol Phenylethylicus; Alkohol fenyloetylowy; Benzyl Carbinol; Phenethanolum; Phenylethyl alcohol. 2-Phenylethanol.
$C_6H_5.CH_2.CH_2OH$ = 122.2.
CAS — 60-12-8.

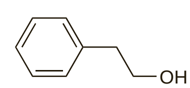

Pharmacopoeias. In *Pol.* and *US.*
USP 31 (Phenylethyl Alcohol). A colourless liquid with a rose-like odour. Soluble 1 in 60 of water, 1 in less than 1 of alcohol, of chloroform, of ether, of benzyl benzoate, and of diethyl phthalate, and 1 in 2 of alcohol 50%; very soluble in glycerol, in propylene glycol, and in fixed oils; slightly soluble in liquid paraffin. Store in airtight containers in a cool, dry place. Protect from light.

Incompatibility. Phenethyl alcohol is incompatible with oxidising agents and proteins. Activity may be reduced by nonionic surfactants or by adsorption onto low density polyethylene containers.

Profile

Phenethyl alcohol is more active against Gram-negative than Gram-positive bacteria. It is used as a preservative in ophthalmic, nasal, and otic solutions at a concentration of 0.25 to 0.5%, with another bactericide, and up to 1% in topical preparations. It is also used as an antiseptic in topical products in concentrations of up to 7.5%. It is also used as a component of flavouring essences and perfumes.

Phenethyl alcohol may cause eye irritation.

Antimicrobial action. Antimicrobial activity may be enhanced by the addition of phenethyl alcohol to solutions preserved with benzalkonium chloride, chlorhexidine acetate, phenylmercuric nitrate, chlorocresol, or chlorobutanol.[1]

1. Richards RME, McBride RJ. The preservation of ophthalmic solutions with antibacterial combinations. *J Pharm Pharmacol* 1972; **24:** 145–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Resolve Tinea; Sebirinse; ***Canad.:*** Sclerodex; ***Ger.:*** Imazol; ***Irl.:*** Ceanel†; ***NZ:*** Sebirinse; ***UK:*** Ceanel.

Phenol

Carbolic Acid; Fenol; Fenoli; Fenolis; Phenic Acid; Phénol; Phenolum; Phenyl Hydrate; Phenylic Acid. Hydroxybenzene.

Оксибензол; Фенол

$C_6H_5.OH$ = 94.11.

CAS — 108-95-2.

ATC — C05BB05; D08AE03; N01BX03; R02AA19.

ATC Vet — QC05BB05; QD08AE03; QN01BX03; QR02AA19.

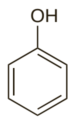

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*
Br., *Swiss*, and *US* also include a monograph for Liquefied Phenol.

Ph. Eur. 6.2 (Phenol). Colourless or faintly pink or faintly yellow deliquescent crystals or crystalline masses. F.p. not less than 39.5°. Soluble in water; very soluble in alcohol, in dichloromethane, and in glycerol. Store in airtight containers. Protect from light.

BP 2008 (Liquified Phenol). An aqueous mixture containing phenol 77.0 to 81.5% w/w in purified water. A colourless to faintly coloured, caustic liquid with a characteristic and not tarry odour. Soluble in water; miscible with alcohol, with ether, and with glycerol. Protect from light. It may congeal or deposit crystals if stored at a temperature below 4°. It should be completely melted before use.

When phenol is to be mixed with collodion, fixed oils, or paraffins, melted phenol should be used, and not Liquefied Phenol.

USP 31 (Phenol). Colourless to light pink, interlaced or separate, needle-shaped crystals, or a white to light pink crystalline mass, with a characteristic odour. It gradually darkens on exposure to light and air. Soluble 1 in 15 of water; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble 1 in 70 of liquid paraffin. A solution of 1 g in 15 mL water is clear and is neutral or acid to litmus. Store in airtight containers. Protect from light.

USP 31 (Liquefied Phenol). Phenol maintained in a liquid condition by the presence of about 10% of water; it contains not less than 89% by weight of phenol. It may contain a suitable stabiliser. A colourless to pink liquid which may develop a red tint upon exposure to air or light, and with a characteristic, somewhat aromatic odour. Miscible with alcohol, with ether, and with glycerol. Store in airtight glass containers. Protect from light.

When phenol is to be mixed with a fixed oil, liquid paraffin, or white soft paraffin, crystalline Phenol and not Liquefied Phenol should be used.

Incompatibility. Phenol is incompatible with alkaline salts and nonionic surfactants. The antimicrobial activity of phenol may be diminished through increasing pH or through combination with blood and other organic matter.

Use for preservation. NOTE. Phenol should not be used to preserve preparations that are to be freeze-dried.

Adverse Effects

When ingested, phenol causes extensive local corrosion, with pain, nausea, vomiting, sweating, and diarrhoea. Excitation may occur initially but it is quickly followed by unconsciousness. There is depression of the CNS, with cardiac arrhythmias, and circulatory and respiratory failure, which may lead to death. Acidosis may develop and occasionally there is haemolysis and methaemoglobinaemia with cyanosis. The urine may become dark brown or green. Pulmonary oedema and myocardial damage may develop, and damage to the liver and kidneys may lead to organ failure.

Severe or fatal poisoning may occur from the absorption of phenol from unbroken skin or wounds and suitable precautions should be taken to prevent absorption. Applied to skin, phenol causes blanching and corrosion, sometimes with little pain. Aqueous solutions as dilute as 10% may be corrosive.

Toxic symptoms may also arise through absorption of phenol vapour by the skin or lungs. Phenol throat spray may cause local oedema.

Cresols and other phenolic substances have similar effects.

Effects on the heart. A 10-year-old boy developed life-threatening premature ventricular complexes during the application of a solution of phenol 40% and croton oil 0.8% in hexachlorophene soap and water for chemical peeling of a giant hairy naevus.[1] Cardiac arrhythmias have been reported after the use of phenol for chemical face peeling.[2] They were also seen in 3 of 16 children who received phenol 5% as a neurolytic.[3]

1. Warner MA, Harper JV. Cardiac dysrhythmias associated with chemical peeling with phenol. *Anesthesiology* 1985; **62:** 366–7.
2. Botta SA, *et al.* Cardiac arrhythmias in phenol face peeling: a suggested protocol for prevention. *Aesthetic Plast Surg* 1988; **12:** 115–17.
3. Morrison JE, *et al.* Phenol motor point blocks in children: plasma concentrations and cardiac dysrhythmias. *Anesthesiology* 1991; **75:** 359–62.

Effects on the kidneys. A 41-year-old man developed acute renal failure due to cutaneous absorption of phenol after falling into a shallow vat of industrial solvent containing 40% phenol in dichloromethane. No ingestion occurred. Other symptoms included 50% body-surface burns, cold extremities, nausea, vomiting, and respiratory distress. The patient required haemodialysis for 3 weeks; some abnormalities of renal function remained one year later.[1]

1. Foxall PJD, *et al.* Acute renal failure following accidental cutaneous absorption of phenol: application of NMR urinalysis to monitor the disease process. *Hum Toxicol* 1989; **9:** 491–6.

Effects on the liver. Phenol-induced hepatotoxicity has been reported[1] in a 43-year-old man after injection sclerotherapy for haemorrhoids with 5% phenol in arachis oil. During treatment the patient experienced pain radiating to the penis, then later developed backache and haematuria, and 6 days later was admitted to hospital with jaundice. He recovered well and his liver enzymes returned to normal levels after 6 months.

1. Suppiah A, Perry EP. Jaundice as a presentation of phenol induced hepatotoxocity [sic] following injection sclerotherapy for haemorrhoids. *Surgeon* 2005; **3:** 43–4.

Effects on sexual function. Three patients developed urinary symptoms and impotence which lasted up to one year after each receiving phenol 5% in arachis oil sclerotherapy for haemorrhoids.[1]

1. Bullock N. Impotence after sclerotherapy of haemorrhoids: case reports. *BMJ* 1997; **314:** 419.

Effects on the throat. Acute life-threatening epiglottitis occurred in a 49-year-old woman after the use of a throat spray containing the equivalent of 1.4% phenol. The reaction may have been anaphylactic or due to a direct toxic effect of the spray.[1] The UK CSM[2] reported in 1990 that it had received 4 reports of oedema of the epiglottis and/or larynx leading to respiratory difficulties. While the condition was rare, the effects were severe; 1 patient died and 2 survived only after emergency hospital treatment.

1. Ho S-L, Hollinrake K. Acute epiglottitis and Chloraseptic. *BMJ* 1989; **298:** 1584.
2. Committee on Safety of Medicines. Chloraseptic throat spray and oedema of the epiglottis and larynx. *Current Problems 28* 1990.

Treatment of Adverse Effects

If phenol has been swallowed, activated charcoal may be useful. Some sources suggest the cautious use of gastric lavage although this is generally inappropriate after ingestion of corrosive substances.

If phenol has been spilled on the skin removal of contaminated clothing and excess phenol should be followed by washing of the skin with glycerol or, alternatively, with copious amounts of water. Macrogol 300 and vegetable oils have also been used.

Contamination of the eyes should be treated by flooding with water or sodium chloride 0.9% only for at least 10 to 15 minutes.

The patient should be kept warm and given supportive treatment. Intravenous sodium bicarbonate should be given where there is metabolic acidosis.

Precautions

Solutions containing phenol should not be applied to large areas of skin or large wounds since sufficient phenol may be absorbed to give rise to toxic symptoms. Phenol should not be used as a throat spray in patients with epiglottitis, or in children aged under 6 years.

Pharmacokinetics

Phenol is absorbed from the gastrointestinal tract and through skin and mucous membranes. It is metabolised to phenylglucuronide and phenyl sulfate, and small amounts are oxidised to catechol and quinol which are mainly conjugated. The metabolites are excreted in the urine; on oxidation to quinones they may tint the urine dark brown or green.

Uses and Administration

Phenol is an antiseptic and disinfectant effective against vegetative Gram-positive and Gram-negative bacteria, mycobacteria, and some fungi, but only very slowly effective against spores. It is also active against certain viruses. Phenol is more active in acid solution.

Aqueous solutions up to 1% are bacteriostatic while stronger solutions are bactericidal.

A 0.5 to 1% solution has been used for its local anaesthetic effect to relieve itching.

A 1.4% solution is used for pain or irritation of the mouth and throat. Weak concentrations (up to 2%) have also been used topically for disinfection. A 5% solution has been used as a disinfectant for excreta.

Oily Phenol Injection (BP 2008), up to 10 mL, has been injected into the tissues around internal haemorrhoids as an analgesic sclerosing agent, but alternative procedures may be preferred. Aqueous phenol has also been used as a sclerosant in the treatment of hydroceles.

Solutions of phenol in glycerol have been given intrathecally for the alleviation of spasticity (p.1887) or injected intrathecally or into soft-tissue structures for the treatment of chronic low back pain. Other types of severe intractable pain may be relieved by injecting aqueous phenol close to motor nerves. Aqueous phenol has been used for chemical sympathectomy in peripheral vascular disorders and for the treatment of urinary incontinence.

Liquefied phenol has been used in the treatment of ingrowing toenails.

Dystonias. Phenol appears to produce a decrease in muscle tone without profound weakness and is considered to be an effective agent in treating focal dystonias.[1] Intramuscular phenol was reported[2] to have produced improvement in 2 adult patients with moderately severe spasmodic torticollis (p.1892) who had not responded adequately to intramuscular injections of botulinum A toxin. Response was maintained by re-injection every 6 months. Following this case report, an open trial[3] was conducted on 3 patients with spasmodic torticollis who had not responded to botulinum toxin A and other drug treatments. After 10 intramuscular injections of phenol, given weekly and then monthly, 2 of the patients showed improvement; one reached partial remission while the other had improvement that lasted for 3 months. The third patient did not respond to treatment with phenol. A study[4] to determine the effectiveness and adverse effects of a 2% phenol block in patients with spasmodic torticollis was conducted in 16 patients, all of whom were refractory to oral drug and rehabilitation therapies. Results showed significant improvement in neck movement and position. However, 4 patients developed reversible sensory disturbance of the transverse cutaneous nerve of the neck area. A patient who developed a focal dystonic contraction of the foot responded to single intramuscular injection of 5% aqueous phenol, after initial treatment with botulinum toxin A had shown no benefit.[5]

1. Zafonte RD, Munin MC. Phenol and alcohol blocks for the treatment of spasticity. *Phys Med Rehabil Clin N Am* 2001; **12:** 817–32.
2. Massey JM. Treatment of spasmodic torticollis with intramuscular phenol injection. *J Neurol Neurosurg Psychiatry* 1995; **58:** 258–9.
3. García Ruiz PJ, Sanchez Bernardos V. Intramuscular phenol injection for severe cervical dystonia. *J Neurol* 2000; **247:** 146–7.
4. Takeuchi N, *et al.* Phenol block for cervical dystonia: effects and side effects. *Arch Phys Med Rehabil* 2004; **85:** 1117–20.
5. Kim J-S, *et al.* Idiopathic foot dystonia treated with intramuscular phenol injection. *Parkinsonism Relat Disord* 2003; **9:** 355–9.

Haemorrhoids. Sclerotherapy with oily phenol injection has been used[1] to treat haemorrhoids (p.1697). The technique for preventing mucosal prolapse is to inject small volumes (about 2 or 3 mL) of a 5% solution of phenol in arachis oil into the submucous space above each of the 3 principal haemorrhoids. Rather than causing the haemorrhoidal veins to thrombose, the injection works by producing submucosal fibrosis, fixing the mucosa to the underlying muscle. However, other techniques for mucosal fixation such as rubber band ligation or perhaps infra-red coagulation are more effective and associated with fewer complications.[2-5]

1. Alexander-Williams J. The management of piles. *BMJ* 1982; **285:** 1137–9.
2. Gartell PC, *et al.* A randomised clinical trial to compare rubber band ligation with phenol injection in the treatment of haemorrhoids. *Gut* 1984; **25:** A563.
3. Ambrose NS, *et al.* Prospective randomised trial of injection therapy against photocoagulation therapy in first and second degree haemorrhoids. *Gut* 1984; **25:** A563–4.
4. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. *Am J Gastroenterol* 1992; **87:** 1601–6.
5. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities: a meta-analysis. *Dis Colon Rectum* 1995; **38:** 687–94.

Ingrowing toenails. Liquefied phenol (88%) ablation has been performed as an alternative to surgical avulsion in the treatment of ingrowing toenails.[1,2] A systematic review[3] concluded that simple nail avulsion combined with treating the nail-bed with phenol was more effective at preventing symptomatic recurrence of ingrowing toenails than cutting out the nail-bed. However, there was a significant increase in postoperative infections when phenol was used.

1. Bostanci S, *et al.* Chemical matricectomy with phenol for the treatment of ingrowing toenail: a review of the literature and follow-up of 172 treated patients. *Acta Derm Venereol* 2001; **81:** 181–3.
2. Andreassi A, *et al.* Segmental phenolization for the treatment of ingrowing toenails: a review of 6 years experience. *J Dermatol Treat* 2004; **15:** 179–81.
3. Rounding C, Bloomfield S. Surgical treatments for ingrowing toenails. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/03/06).

Pain. The neurolytic use of phenol to produce destructive nerve block (see under Pain, p.1852) has produced variable results, and some consider the risk of complications outweighs the benefits. However, it may have the advantage over alcohol that it is painless on injection, and smaller volumes can be used, potentially allowing greater precision (see p.1627).

Urinary incontinence. Although injection of phenol into the pelvic plexus to produce partial denervation has been used in the management of severe intractable urge incontinence, its use has been largely abandoned. Some patients, especially those with detrusor hyperreflexia, have derived benefit[1,2] but overall efficacy can be poor and benefits short-lived.[3]

1. Ewing R, *et al.* Subtrigonal phenol injection therapy for incontinence in female patients with multiple sclerosis. *Lancet* 1983; **i:** 1304–5.
2. Blackford HN, *et al.* Results of transvesical infiltration of the pelvic plexuses with phenol in 116 patients. *Br J Urol* 1984; **56:** 647–9.
3. Rosenbaum TP, *et al.* Trans-trigonal phenol failed the test of time. *Br J Urol* 1990; **66:** 164–9.

Preparations

BP 2008: Aqueous Phenol Injection; Liquefied Phenol; Oily Phenol Injection; Phenol and Glycerol Injection;
BPC 1973: Magenta Paint;
USP 31: Camphorated Phenol Topical Gel; Carbol-Fuchsin Topical Solution; Liquefied Phenol; Phenolated Calamine Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Summers Eve Disposable†; ***Canad.:*** Chloraseptic Spray; P & S; ***Chile:*** Metapio; ***S.Afr.:*** Medi-Keel A; SB Aurico Ear Drops; Septosol; ***Thai.:*** Pose-Cresol; ***UK:*** Ultra Chloraseptic; ***USA:*** Cheracol Sore Throat; Chloraseptic Kids Sore Throat Spray; Chloraseptic Sore Throat; Green Throat Spray; P & S; Phenaseptic; Red Throat Spray; Triaminic Sore Throat Spray; Ulcerease.

Multi-ingredient: ***Arg.:*** Aceite Esmeralda Moone; Callicida; Dermithan; Manzan; Piracalamina; Prurisedan; Prurisedan Rosa; ***Austral.:*** Ayrton's Chilblain; Calamine Lotion; Egopsoryl TA; Nyal Toothache Drops; Sarna; ***Austria:*** Herposicc; ***Belg.:*** Eucalyptine Pholcodine; Sedemol; Sulfa-Sedemol; ***Braz.:*** Algidente†; Cloraseptic; Dentisan; Otoloide; Pradente†; Timpanol†; Um Instante†; Usedent†; ***Canad.:*** Anbesol Maximum Strength; Blistex DCT Lip Balm; Blistex Lip Medex; Blistex Medicated Lip Conditioner Jar†; Blistex Medicated Lip Ointment; Boil Ease†; Cepastat; Chapstick Medicated Lip Balm†; Lip Medex†; Mecca; Ozonol; Phenoris; ***Chile:*** Blistex; Chapstick Medicated; ***Fr.:*** Brulex; ***Hong Kong:*** Blistex Lip Ointment†; Cepastat; Doans†; Egopsoryl TA; ***Hung.:*** Reparon; ***Ital.:*** Creosoto Composto; Diaril†; Eso Din; Fucsina Fenica; Lavanda Sofar; Ondroly-A†; Pinselina Knapp; ***Malaysia:*** Egopsoryl TA; Sarna; ***Mex.:*** Forcremol; ***Neth.:*** Agre-Gola; ***NZ:*** Egopsoryl TA; Toothache Drops†; ***Philipp.:*** Calmoseptine; Sarna; ***Pol.:*** Pigmentum Castellani; ***Port.:*** Calicida Indiano; ***S.Afr.:*** Alpha Toothache Essence; Biohist; Blistex; Calasthetic; Cuticura†; Germolene; Lacto Calamine†; Prep; SB Universal Ointment; TCP; ***Singapore:*** Cepastat; Egopsoryl TA; Sarna; ***Spain:*** Argentofenol†; Carbocaina†; Dermomycose Liquido; Odontocromil c Sulfamida†; Otocerum; Otogen Calmante; Sabanotropico; ***Switz.:*** Caustinerf forte†; ***Thai.:*** Con Con; Lanol; Sarna; Zema; ***Turk.:*** Disinol; ***UK:*** Blistex Relief Cream; Chymol; Colsor; Dermacreme; Germolene; Lacto Calamine; TCP; ***USA:*** Anbesol; Blistex; Blistex Lip Balm; Boil Ease; Campho-Phenique; Castaderm; Cepastat; Cepastat Cherry; Chapstick Medicated Lip Balm; Columbia Antiseptic Powder; Debacterol; Heal Aid Plus; Lip Medex; Lipmagik; Massengill; Mycinette; Nasal Jelly; Orabase Lip; Orasol; Phylorinol; Skeeter Stik; Sting-Eze; Unguentine; Unguentine Plus.

Phenoxyethanol

Ethylene Glycol 2-Monophenyl Ether; Ethyleneglycol Monophenylether; Fenoksietanoli; Fenoksietanolis; Fenoksyetanol; Fenoxietanol; Fenoxyethanol; Phenoxyaethanol; Phénoxyéthanol; Phenoxyethanolum; β-Phenoxyethyl Alcohol; 2-Phenoxyethyl Alcohol. 2-Phenoxyethanol.

$C_8H_{10}O_2$ = 138.2.
CAS — 122-99-6.

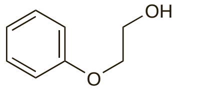

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Phenoxyethanol). A colourless slightly viscous liquid. Slightly soluble in water, in arachis oil and in olive oil; miscible with alcohol, with acetone, and with glycerol.

USNF 26 (Phenoxyethanol). A colourless, slightly viscous liquid. Specific gravity 1.105 to 1.110 at 20°. Slightly soluble in water; miscible with alcohol, with acetone, and with glycerol; slightly soluble in arachis oil and in olive oil. Store in a dry place, in airtight containers at a temperature of 8° to 15°. Protect from light.

Incompatibility. The activity of phenoxyethanol may be reduced by interaction with nonionic surfactants and possibly by adsorption onto PVC.

Profile

Phenoxyethanol is effective against strains of *Pseudomonas aeruginosa* but less so against other Gram-negative and Gram-positive bacteria. It has been used as a preservative in cosmetics and topical pharmaceuticals at a concentration of 0.5 to 1%. It is often used with other preservatives, commonly hydroxybenzoates, to obtain a wider spectrum of antimicrobial activity.

Phenoxyethanol is used in concentrations of about 2% as an antiseptic for minor infections of skin, wounds, and mucous membranes. Aqueous solutions may be prepared by shaking the phenoxyethanol with hot water until dissolved, then adjusting to final volume when cool. Preparation of the solution can be aided by propylene glycol.

Phenoxypropanol and chlorophenoxyethanol are related compounds used in topical preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Singapore: Acnederm Wash; ***UK:*** Biactol Liquid.

Multi-ingredient: ***Arg.:*** Cicatul; Polviderm NF; ***Austral.:*** Acnederm Foaming Wash; Acnederm Medicated; ***Austria:*** Octenisept; ***Chile:*** Eucerin Piel Grasa; ***Fr.:*** Alco-Aloe; Manugel; ***Ger.:*** Gigasept Med†; Lysetol Med†; Octenisept; ***Gr.:*** Octenisept; ***Ital.:*** Decon Ovuli; Fitostimoline; ***Malaysia:*** Acnederm Foaming Wash; Acnederm Lotion; ***Mex.:*** Fitoestimulina; Italdermol; ***NZ:*** Acnederm; Acnederm Foaming Wash; ***Singapore:*** Acnederm; ***Switz.:*** Ederphyt†; Octenisept; ***USA:*** Bodi Kleen; ***Venez.:*** Glizigen; Photoderm AKN.

Phenoxyisopropanol

Fenoxiisopropanol; Phenoxyisopropyl Alcohol. 1-phenoxypropan-2-ol.

$C_9H_{12}O_2$ = 152.2.
CAS — 770-35-4.

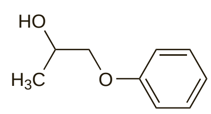

Profile

Phenoxyisopropanol is used as a preservative and as an antiseptic in preparations for the treatment of acne, insect bites, and minor abrasions to the skin.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Clearasil Daily Face Wash.

Phenylmercuric Salts

Fenilmercurio, sales.

Phenylmercuric Acetate

Fenilgyvsidabrio acetatas; Fenil-higany-acetát; Fenilmercurio, acetato de; Fenylhydrargyriumacetát; Fenylkvicksilveracetat; Fenylortęciowy octan; Fenyylimerkuriasetaatti; Phenylhydrargyni acetas; Phenylhydrargyri Acetas; Phénylmercure, acétate de; PMA. (Acetato)phenylmercury.

$C_8H_8HgO_2$ = 336.7.
CAS — 62-38-4.

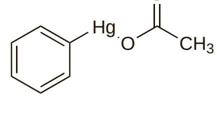

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Phenylmercuric Acetate). A white or yellowish crystalline powder or small, colourless crystals. Slightly soluble in water; soluble in alcohol and in acetone. Protect from light.

USNF 26 (Phenylmercuric Acetate). A white to creamy-white, odourless, crystalline powder or small white prisms or leaflets. Soluble 1 in 180 of water, 1 in 225 of alcohol, 1 in 6.8 of chloroform, and 1 in 200 of ether; soluble in acetone. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Borate *(rINN)*

Borato de fenilmercurio; Fenilgyvsidabrio boratas; Fenil-higany-borát; Fenylhydrargyriumborát; Fenylkvicksilverborat; Fenylortęciowy boran; Fenyylimerkuriboraatti; Hydrargyrum Phenyloboricum; Phenomerborum; Phenylhydrargyri boras; Phénylmercure, borate de.

Фенилмеркурборат

$C_6H_5HgOH,C_6H_5HgOB(OH)_2$ = 633.2 or $C_6H_5HgOH,C_6H_5HgBO_2$ = 615.2.
CAS — 8017-88-7 ($C_{12}H_{13}BHg_2O_4$); 6273-99-0 ($C_{12}H_{11}BHg_2O_3$); 102-98-7 ($C_6H_7BHgO_3$).
ATC — D08AK02.
ATC Vet — QD08AK02.

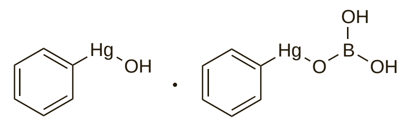

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Phenylmercuric Borate). A compound consisting of equimolecular proportions of phenylmercuric orthoborate and phenylmercuric hydroxide ($C_{12}H_{13}BHg_2O_4$) or of the dehydrated form (metaborate, $C_{12}H_{11}BHg_2O_3$) or a mixture of the two compounds. Colourless shiny crystals or a white or slightly yellowish crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Nitrate

Basic Phenylmercury Nitrate; Fenilgyvsidabrio nitratas; Fenil-higany-nitrát; Fenilmercurio, nitrato de; Fenylhydrargyriumnitrát; Fenylkvicksilvernitrat; Fenylortęci(II) azotan; Fenyylimerkurinitraatti; Phenylhydrargyri nitras; Phénylmercure, nitrate de; PMN. Nitratophenylmercury.

$C_6H_5HgOH,C_6H_5HgNO_3$ = 634.4.
CAS — 8003-05-2 ($C_6H_5HgOH,C_6H_5HgNO_3$); 55-68-5 ($C_6H_5HgNO_3$).
ATC — D09AA04.
ATC Vet — QD09AA04.

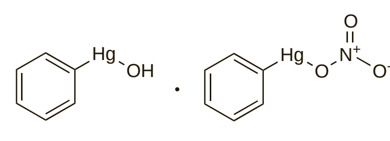

($C_6H_5HgOH,C_6H_5HgNO_3$)

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white or pale yellow powder. Very slightly soluble in water and in alcohol; slightly soluble in hot water; dissolves in glycerol and in fatty oils. Protect from light.

USNF 26 (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white crystalline powder. Soluble 1 in 600 of water; slightly soluble in alcohol and in glycerol; more soluble in the presence of nitric acid or alkali hydroxides. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. The activity of phenylmercuric salts may be reduced by interaction with compounds such as kaolin, magnesium trisilicate, starch, and talc.[1,2] Disodium edetate and sodium thiosulfate can also produce inactivation.[3] Sodium metabisulfite can lead to precipitation,[3] or chemical destruction,[4] but it can also produce increased activity.[3] Other incompatibilities include bromides, iodides (chlorides to a lesser extent), metals, and ammonia and its salts.[5] There can be adsorption onto rubber and some plastics[5,6] although sorption by low density polyethylene can be inhibited by phosphate ions.[7] Some filters, though not membrane filters, used for sterilisation removed considerable amounts of phenylmercuric nitrate from solution.[8] The pH may also affect activity.[9]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; **8:** 54–6.
2. Horn NR, *et al.* Interactions between powder suspensions and selected quaternary ammonium and organomercurial preservatives. *Cosmet Toilet* 1980; **95:** 69–73.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; **37** (suppl): 123P.

5. Hepburn SE. Phenylmercuric nitrate. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 5th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2006: 526–9.
6. Aspinall JA, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations. *J Clin Hosp Pharm* 1980; **5:** 21–9.
7. Aspinall JE, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations II. Inhibition of the sorption of phenylmercuric acetate. *J Clin Hosp Pharm* 1983; **8:** 233–40.
8. Naido NT, *et al.* Preservative loss from ophthalmic solutions during filtration sterilisation. *Aust J Pharm Sci* 1972; **NS1:** 16–18.
9. Wessels JMC, Adema DMM. Some data on the relationship between fungicidal protection and pH. In: Walters AH, Elphick JJ, eds. *Biodeterioration of materials.* Amsterdam: Elsevier, 1968: 517–23.

Adverse Effects and Precautions

While the adverse effects of inorganic mercury (p.2341) should be taken into account when considering the adverse effects of phenylmercuric compounds, there is little evidence of systemic toxicity arising from their use. They are irritant to the skin and may give rise to erythema and blistering. Hypersensitivity reactions have been reported. Topical application to eyes has been associated with mercurialentis and atypical band keratopathy; prolonged use of eye drops containing phenylmercuric preservatives is not recommended.

Effects on the eyes. References to primary atypical band keratopathy and pigmentation of the anterior capsule of the lens (mercurialentis) associated with the prolonged use of eye drops containing phenylmercuric preservative.

1. Kennedy RE, *et al.* Further observations on atypical band keratopathy in glaucoma patients. *Trans Am Ophthalmol Soc* 1974; **72:** 107–22.
2. Garron LK, *et al.* A clinical pathologic study of mercurialentis medicamentosus. *Trans Am Ophthalmol Soc* 1976; **74:** 295–320.
3. Brazier DJ, Hitchings RA. Atypical band keratopathy following long-term pilocarpine treatment. *Br J Ophthalmol* 1989; **73:** 294–6.

Uses

Phenylmercuric salts have antibacterial and antifungal properties. They are primarily bacteriostatic compounds although they also have a slow bactericidal action. Their activity has been reported to be pH dependent.

Phenylmercuric compounds are used as preservatives in cosmetic, ophthalmic, or pharmaceutical preparations and as antiseptics. They have also been used as spermicides.

As a preservative in eye drops, a concentration of 0.002% is usually used; in injection solutions, the concentration is usually 0.001%.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Panto Liquid; ***USA:*** Hem-Prep.

o-Phthaldialdehyde

o-Ftaldialdehído; *o*-Phthalaldehyde. 1,2-Benzenedicarboxaldehyde.
$C_8H_6O_2$ = 134.1.
CAS — 643-79-8.

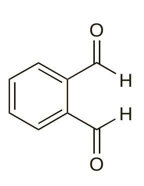

Adverse Effects and Precautions

As for Formaldehyde Solution, p.1644.

The manufacturer warns that *o*-phthaldialdehyde should not be used to process equipment used to treat patients with a history of bladder cancer as there have been associated rare reports of anaphylactoid reactions in such patients.

Occupational exposure. For mention of the potential of *o*-phthaldialdehyde to cause sensitisation in those occupationally exposed, see under Peracetic Acid, p.1655.

Uses and Administration

o-Phthaldialdehyde is a bactericidal disinfectant with similar actions to those of glutaral (p.1645) but it is reported to be more active against mycobacteria and to be stable at a wider pH range of 3 to 9. Unlike glutaral it requires no activation before use.

A 0.55% aqueous solution of *o*-phthaldialdehyde is used for high-level disinfection of medical equipment that cannot be sterilised by heat. It is non-corrosive towards most materials. Complete immersion in the solution for a minimum of 12 minutes at 20° or 5 minutes at 25° or higher is recommended. For further details, see Disinfection of Endoscopes, p.1623.

◊ References.

1. Cooke RPD, *et al.* An evaluation of Cidex OPA (0.55% ortho-phthalaldehyde) as an alternative to 2% glutaraldehyde for high-level disinfection of endoscopes. *J Hosp Infect* 2003; **54:** 226–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cidex OPA†; ***Ger.:*** Cidex OPA; ***USA:*** Cidex OPA.

Picloxydine Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de picloxidina; Picloxydine, Dichlorhydrate de; Picloxydini Dihydrochloridum. 1,1′-[Piperazine-1,4-diylbis(formimidoyl)]bis[3-(4-chlorophenyl)guanidine] dihydrochloride.
Пиклоксидина Дигидрохлорид
$C_{20}H_{24}Cl_2N_{10}$,2HCl = 548.3.
CAS — 5636-92-0 (picloxydine); 19803-62-4 (picloxydine dihydrochloride).
ATC — S01AX16.
ATC Vet — QS01AX16.

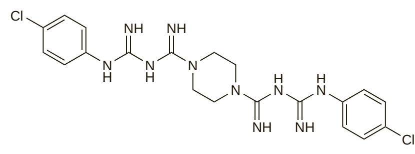

(picloxydine)

Profile

Picloxydine is a biguanide disinfectant with properties similar to those of chlorhexidine (p.1635). It is used in eye drops containing 0.05% of the dihydrochloride for the treatment of superficial infections of the eye. It has also been used as a surface disinfectant with quaternary ammonium compounds.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Vitabact; ***Hung.:*** Vitabact†; ***Rus.:*** Vitabact (Витабакт); ***Switz.:*** Vitabact†.

Polihexanide *(BAN, rINN)*

ICI-9073; Polihexanida; Polihexanidum; Polyhexamethylene Biguanide Hydrochloride; Polyhexanide. Poly(1-hexamethylenebiguanide hydrochloride).
Полигексанид
$(C_8H_{17}N_5,HCl)_n$.
CAS — 32289-58-0.
ATC — D08AC05.
ATC Vet — QD08AC05.

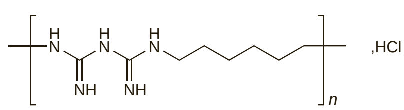

Profile

Polihexanide has antibacterial and antiamoebic activity. It is used as a surface disinfectant and for disinfecting soft contact lenses (p.1622). It is also used in the treatment of *Acanthamoeba* keratitis (p.822) and has also been tried as a mouthwash in dental care.

Bacterial vaginosis. A study[1] of the efficacy of a 2% polihexanide vaginal gel in the treatment of bacterial vaginosis found that a single application was comparable to that of a 2% clindamycin gel applied once daily for 7 consecutive days.

1. Gerli S, *et al.* A new approach for the treatment of bacterial vaginosis: use of polyhexamethylene biguanide: a prospective, randomized study. *Eur Rev Med Pharmacol Sci* 2003; **7:** 127–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Lavasept (Лавасепт); ***Switz.:*** Lavasept.

Multi-ingredient: ***Fr.:*** Aniospray 29; Hexanios G+R; ***Ger.:*** Teta Extra; Teta-S.

Polynoxylin *(BAN, rINN)*

Polinoxilina; Polynoksyliini; Polynoxyline; Polynoxylinum. Poly{[bis(hydroxymethyl)ureylene]methylene}.
Полиноксилин
$(C_4H_8N_2O_3)_n$.
CAS — 9011-05-6.
ATC — A01AB05; D01AE05.
ATC Vet — QA01AB05; QD01AE05.

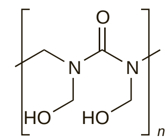

Profile

Polynoxylin is a condensation product of formaldehyde and urea. It is an antiseptic with antibacterial and antifungal actions and, like noxytiolin (p.1654), may act by the release of formaldehyde. It is used topically for the local treatment of minor infections, usually at a concentration of 10%.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Anaflex†; ***NZ:*** Ponoxylan†; ***Singapore:*** Anaflex; ***UK:*** Anaflex.

Potassium Nitrate ⊗

Dusičnan draselný; E252; Kalii nitras; Kalio nitratas; Kalium Nitricum; Kaliumnitraatti; Kaliumnitrat; Kálium-nitrát; Nitrato potásico; Nitre; Potassium, nitrate de; Potasu azotan; Saltpetre.
KNO_3 = 101.1.
CAS — 7757-79-1.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Potassium Nitrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.

USP 31 (Potassium Nitrate). Colourless crystals or a white crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. Store in airtight containers.

Nomenclature. The name saltpetre has been used as a generic term for a number of potassium- and sodium-based preservatives used in food manufacture. For a report of poisoning when a mixture of sodium nitrate and sodium nitrite was supplied for saltpetre, see p.1662.

Adverse Effects and Precautions

After ingestion potassium nitrate may be reduced to nitrite in the gastrointestinal tract by the action of bacteria and ingestion of large amounts can therefore cause methaemoglobinaemia. Gastrointestinal disturbances, vertigo, headache, flushing of the skin, hypotension, irregular pulse, cyanosis, convulsions, and collapse may occur. The toxic dose varies greatly; 15 g may prove fatal but much larger doses have been taken without serious effects. Poisoning has frequently been reported in infants given water from wells contaminated with nitrates.

Nitrites are precursors of nitrosamines, which are *animal* carcinogens, but a relationship with human cancer has not been established.

Concern has been expressed regarding the concentrations of nitrates and nitrites in the public drinking water supply. National limits are often set for permissible concentrations in drinking water.

Handling. Potassium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Uses and Administration

Potassium nitrate is used as a preservative in foods. It is also included in dentrifices to reduce the pain of hypersensitive teeth. When taken by mouth in dilute solution, it acts as a diuretic and was formerly used for this purpose.

Preparations

USP 31: Potassium Nitrate Solution.

Proprietary Preparations (details are given in Part 3)
Chile: Crowne; ***USA:*** Denquel; Original Sensodyne.

Multi-ingredient: ***Arg.:*** Esmedent Dientes Sens Blanq + Ctrol Sarro; Esmedent Dientes Sensibles; Fluorogel 2001 para Dientes Sensibles; Hyper Sensitive; Oral-B Dientes Sensibles con Fluor†; Sebulex; Sens-Out†; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Proteccion Total; Sensodyne-F; ***Austral.:*** Oral-B Sensitive†; ***Braz.:*** Malvatricin Dentes Sensiveis; Pilulas De Witt's†; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool; Sensodyne Fresh Mint; Sensodyne Protecao Total; Sensodyne-F; ***Canad.:*** Oral-B Sensitive†; Sensodyne-F; ***Chile:*** Sensaid; Sensilacer†; ***Fr.:*** Emoform Dents Sensibles; Emoform Gencives; Fluocaril dents sensibles; Sensigel; ***Ital.:*** Actisens†; Benodent Gel Gengivale†; Dentosan Sensibile; Emoform Actisens†; Fluocaril; Oral-B Sensitive; ***Mex.:*** Dentsiblen; ***Port.:*** Biofluor Sensitive†; ***Rus.:*** Sensigel (Сенсигель); ***Singapore:*** 2Sensitive†; Sensigel; ***Turk.:*** Sensodyne-F Gel; ***UK:*** Avoca; ***USA:*** Fluoridex Daily Defense Sensitivity Relief; Sensitivity Protection Crest; Sensodyne-F; ***Venez.:*** Sensident†; Sensodyne.

Potassium Permanganate

Kalii permanganas; Kalio permanganatas; Kalium Hypermanganicum; Kalium Permanganicum; Kaliumpermanganaatti; Kaliumpermanganat; Kálium-permanganát; Manganistan draselný; Permanganato potásico; Pot. Permang.; Potassium, permanganate de; Potasu nadmanganian; Potasyum Permanganat.

$KMnO_4$ = 158.0.

CAS — 7722-64-7.

ATC — D08AX06; V03AB18.

ATC Vet — QD08AX06; QV03AB18.

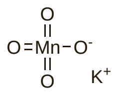

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Potassium Permanganate). Dark purple or almost black crystals or a dark purple or brownish-black granular powder, usually with a metallic lustre. It decomposes in contact with certain organic substances. Soluble in cold water and freely soluble in boiling water.

USP 31 (Potassium Permanganate). Dark purple crystals, almost opaque by transmitted light and with a blue metallic lustre by reflected light; its colour is sometimes modified by a dark bronze-like appearance. Soluble 1 in 15 of water and 1 in 3.5 of boiling water.

Incompatibility. Potassium permanganate is incompatible with iodides, reducing agents, and most organic substances.

Adverse Effects, Treatment, and Precautions

The dry crystals or concentrated solutions of potassium permanganate are highly corrosive to tissue, while dilute solutions are mildly irritant. Contact with the skin causes irritation, redness, pain and burns, and even dilute solutions cause hardening of the outer layer of the skin and leave a brown stain on the skin. Exposure of the eye to dry crystals (including crystal dust) or concentrated solutions causes irritation, blurred vision, redness, brown staining of the conjunctiva, swelling of the eyelids, and corneal and conjunctival burns. For the effects of ingestion, see below.

The insertion into the vagina of potassium permanganate for its supposed abortifacient action causes corrosive burns, severe vaginal haemorrhage, and perforation of the vaginal wall, leading to peritonitis. Vascular collapse may occur.

Handling and storage. Potassium permanganate may be explosive if it is brought into contact with organic or other readily oxidisable substances. It has been used for the illicit preparation of fireworks; care is required with its supply.

Poisoning. Ingestion of dilute solutions of potassium permanganate may result in the mouth and throat being stained brown, sore throat, dysphagia, abdominal pain, diarrhoea, and vomiting. Ingestion of dry crystals and concentrated solutions causes oedema and necrosis of the mouth, larynx, gastrointestinal tract, and upper respiratory tract. In severe cases, acute respiratory distress syndrome, coagulopathy, hypotension, methaemoglobinaemia, hepatic necrosis, pancreatitis, and acute renal failure may develop. Oesophageal strictures and pyloric stenosis are possible long-term consequences. The fatal dose is probably about 10 g and death is usually as a result of pharyngeal oedema and cardiovascular collapse, although multiple organ failure may occur. Inhalation of potassium permanganate causes sore throat, coughing, and shortness of breath. Chronic ingestion or inhalation of potassium permanganate has resulted in CNS symptoms such as sluggishness, sleepiness, weakness of the legs, tremor, spastic gait, and falling.

Symptoms of poisoning after ingestion of potassium permanganate should be treated symptomatically. Gut neutralisation and emesis are contra-indicated. Dilution with large quantities of water or milk is cautiously recommended, while the role of activated charcoal is unclear as it is not known whether it binds potassium permanganate. Similarly, the role of corticosteroids is controversial and the efficacy of *N*-acetylcysteine for potassium permanganate hepatotoxicity is unproven. Eyes and skin contaminated with potassium permanganate should be thoroughly washed.

Uses and Administration

Potassium permanganate possesses oxidising properties which in turn confer disinfectant and deodorising properties. It is also astringent. Though bactericidal *in vitro* its clinical value as a bactericide is minimised by its rapid reduction in the presence of body fluids.

Solutions are used as cleansing applications to wounds, ulcers, or abscesses and as wet dressings and in baths in eczematous conditions and acute dermatoses especially where there is secondary infection. It is often prepared as a concentrated 0.1% solution in water to be diluted 1 in 10 before use to provide a 0.01% (1 in 10 000) solution. Solutions have also been used in bromhidrosis, in mycotic infections such as athlete's foot, and in poison ivy dermatitis.

Potassium permanganate is added to formaldehyde solution to produce formaldehyde vapour for the disinfection of rooms and cabinets (see p.1645).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Permaton†; ***Turk.:*** Permasol; ***UK:*** Permitabs.

Povidone-Iodine *(BAN)*

Iodinated Povidone; Jodowany powidon; Polyvidone-Iodine; Polyvinylpyrrolidone-Iodine Complex; Povidon, joderad; Povidon jodovaný; Povidona yodada; Povidonas, joduotas; Povidone iodée; Povidoni, jodattu; Povidon-Iyot; Povidon-jód; Povidonum iodinatum; Propylèneglycol, monostéarate de; PVP-Iodine; PVP-Iodine.

Повидон-йод

CAS — 25655-41-8.

ATC — D08AG02; D09AA09; D11AC06; G01AX11; R02AA15; S01AX18.

ATC Vet — QD08AG02; QD09AA09; QD11AC06; QG01AX11; QG51AD01; QR02AA15; QS01AX18.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Povidone, Iodinated). A complex of iodine with povidone containing 9 to 12% of available iodine calculated with reference to the dried substance. Yellowish-brown or reddish-brown amorphous powder. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 1.5 to 5.0. Protect from light.

USP 31 (Povidone-Iodine). A complex of iodine with povidone containing 9 to 12% of available iodine calculated on the dried basis. A yellowish-brown to reddish-brown amorphous powder with a slight characteristic odour. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone, in carbon tetrachloride, in chloroform, in ether, and in petroleum spirit. Its solutions are acid to litmus. Store in airtight containers.

Incompatibility. Antimicrobial activity may be reduced at high pH.

Dermatological reactions, described as second- and third-degree burns, were observed in 4 patients in whom wounds were covered with a povidone-iodine soaked bandage secured to the skin by compound benzoin tincture. It was suggested that an interaction had occurred resulting in a more acidic pH.[1]

A mixture of povidone-iodine solution and hydrogen peroxide [brown bubbly] has caused explosions.[2]

1. Schillaci LJ, *et al.* Reduced pH associated with mixture of povidone-iodine and compound tincture of benzoin. *Am J Hosp Pharm* 1983; **40:** 1694–5.
2. Dannenberg E, Peebles J. Betadine-hydrogen peroxide irrigation solution incompatibility. *Am J Hosp Pharm* 1978; **35:** 525.

Adverse Effects and Precautions

Povidone-iodine can cause hypersensitivity reactions and irritation of the skin and mucous membranes, although severe reactions are rare and povidone-iodine is considered to be less irritant than iodine.

The application of povidone-iodine to severe burns or to large areas otherwise denuded of skin may produce the systemic adverse effects associated with iodine (p.2169) and metabolic acidosis, hypernatraemia, and renal impairment. Hyperthyroidism or hypothyroidism may occur after ingestion or absorption of large quantities. Hypothyroidism has occurred in neonates both as a result of absorption of iodine from povidone-iodine applied to the neonate and also to the mother during pregnancy or breast feeding. Povidone-iodine application is contra-indicated in premature neonates or those weighing less than 1.5 kg.

Regular or prolonged use should be avoided in patients with thyroid disorders or those receiving lithium therapy.

Acidosis. There have been reports of acidosis in patients whose burns were treated topically with povidone-iodine.[1,2] Fatal metabolic acidosis[3] and seizures[4] have been reported after mediastinal irrigation with povidone-iodine.

1. Pietsch J, Meakins JL. Complications of povidone-iodine absorption in topically treated burn patients. *Lancet* 1976; **i:** 280–2.
2. Scoggin C, *et al.* Hypernatraemia and acidosis in association with topical treatment of burns. *Lancet* 1977; **i:** 959.
3. Glick PL, *et al.* Iodine toxicity in a patient treated by continuous povidone-iodine mediastinal irrigation. *Ann Thorac Surg* 1985; **39:** 478–80.
4. Zec N, *et al.* Seizures in a patient treated with continuous povidone-iodine mediastinal irrigation. *N Engl J Med* 1992; **326:** 1784.

Breast feeding. Use of povidone-iodine in a vaginal gel by a breast-feeding woman resulted in elevated iodine concentrations in the breast milk and an odour of iodine on the infant's skin.[1] The American Academy of Pediatrics considers however that the use of povidone-iodine is usually compatible with breast feeding.[2]

For more on precautions in breast feeding when treated with iodine compounds see p.2170.

1. Pastellon DC, Aranow R. Iodine in mother's milk. *JAMA* 1982; **247:** 463.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Hypersensitivity. Immediate type I hypersensitivity reactions have been reported after topical disinfection with povidone-iodine; anaphylaxis has been reported after vaginal application[1,2] and after wound disinfection during surgery.[3] In some cases[2,3] skin tests showed that the reactions were caused by the povidone component.

Contact dermatitis has been reported[4] in a 36-year-old man who received a compress with 10% povidone-iodine aqueous solution under an occlusive bandage. The patient experienced mild itching, erythema, exudation, and a bullous reaction, limited to the area of the compress, 48 hours after application. He responded to topical corticosteroids within 5 to 6 days, but an area of sharply demarcated brown hyperpigmentation persisted for a month. While this was considered to be suggestive of an irritant effect, a positive patch test supported an allergic mechanism. A study to evaluate the incidence of contact dermatitis associated with povidone-iodine[5] found that 14 of 500 patients (2.8%) had a positive patch test with 10% povidone-iodine aqueous solution. On retesting with the same solution using a repeated open application test only 2 of the 14 (0.4%) were found to have true contact dermatitis to povidone-iodine.

1. Waran KD, Munsick RA. Anaphylaxis from povidone-iodine. *Lancet* 1995; **345:** 1506.
2. Adachi A, *et al.* Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermatitis* 2003; **48:** 133–6.
3. Le Pabic F, *et al.* First case of anaphylaxis to iodinated povidone. *Allergy* 2003; **58:** 826–7.
4. Borja JM, *et al.* Contact dermatitis due to povidone-iodine: allergic or irritant? *J Investig Allergol Clin Immunol* 2003; **13:** 131–2.
5. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: a re-evaluation study. *Contact Dermatitis* 2005; **52:** 9–10.

Neonates. Hypothyroidism has been reported in premature and very low birth-weight infants after the use of povidone-iodine for routine antisepsis,[1,2] and hyperthyroidism in a full-term infant following mediastinal lavage.[3]

Perinatal vaginal use of povidone-iodine may also cause neonatal thyroid dysfunction.[4]

1. Parravicini E, *et al.* Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996; **98:** 730–4.
2. Linder N, *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
3. Bryant WP, Zimmerman D. Iodine-induced hyperthyroidism in a newborn. *Pediatrics* 1995; **95:** 434–6. Correction. *ibid.*; **96:** 779.
4. l'Allemand D, *et al.* Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. *J Pediatr* 1983; **102:** 935–8.

Uses and Administration

Povidone-iodine is an iodophore that is used as a disinfectant and antiseptic mainly for the treatment of contaminated wounds and pre-operative preparation of the skin and mucous membranes as well as for the disinfection of equipment.

Iodophores are loose complexes of iodine and carrier polymers. Solutions of povidone-iodine gradually release iodine to exert an effect against bacteria, fungi, viruses, protozoa, cysts, and spores; povidone-iodine is thus less potent than preparations containing free iodine but it is less toxic.

A wide variety of topical formulations is available, the majority containing about 4 to 10% of povidone-iodine; a 1% mouthwash has been used for oral infections including candidiasis and topical powders containing up to 2.5% povidone-iodine have been tried in the treatment and prevention of wound infection. For vaginal application povidone-iodine has also been used as pessaries containing 200 mg or as a 10% gel or solution.

Preparations

BP 2008: Povidone-Iodine Mouthwash; Povidone-Iodine Solution;
USP 31: Povidone-Iodine Cleansing Solution; Povidone-Iodine Ointment; Povidone-Iodine Topical Aerosol; Povidone-Iodine Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiseptico; Clivasol†; DG-6 Iodopovidona†; Dovidox†; Extraleci; Iodep; Iodoasept†; Iodomax; Iodomine†; Iopox; IPV†; Nu-Gel Hidrogel en Placa; Pervinox; Povi Complex; Povibac; Povicler; Povitiol; Salguer†; Tycoytycoy; ***Austral.:*** Betadine; Isodine†; Logicin Sore Throat†; Microshield PVP; Microshield PVP-S; Minidine†; Nyal Medithroat Gargle†; PI Antiseptic Ointment†; Savlon Antiseptic; Viodine†; ***Austria:*** Betadona; Betaisodona; Betas-

an; Betaseptic; Braunol; Braunovidon; Wundesin; ***Belg.:*** Braunol; Iodex; Iso-Betadine; ***Braz.:*** Asteriodine†; Laboriodine; Marcodine; PVPI†; Sabofen†; ***Canad.:*** Betadine; Proviodine; ***Chile:*** Difexon; Neoyod†; ***Cz.:*** Betadine; Braunol; Braunovidon; Jodisol; Jodobac†; ***Fin.:*** Betadine; ***Fr.:*** Betadine; Poliodine; ***Ger.:*** Betaisodona; Braunol; Braunovidon; Freka-cid; Inadine†; Jodobac†; Mercuchrom-Jod; Polydona; Polysept; Sepso J; Traumasept; ***Gr.:*** Betadine; Drapix; Eva Povi†; Lombocid†; Oxisept; Tinsole; ***Hong Kong:*** Betadine; Freka-cid; Proviodine; Videne; ***Hung.:*** Betadine; Colpo-Cleaner; Gyneiod†; ***India:*** Alphadine†; Betadine; Betadine-AD; Cipladine; Povidine; Wokadine; ***Indon.:*** Abodine; Asepta; Betadine; Corsasep; Duvodine; Forinfec; Isodine; Molexdine; Mugisept; Neo Iodine; Scansepta; Septadine; Vidisep; ***Irl.:*** Betadine; Inadine; Savlon Dry; ***Israel:*** Idovit; Iodiflor; Iodispray; Iodo-Vit; Massengill Medicated†; Polydine; Polysept; Yodon; ***Ital.:*** Asepsan; Betadine; Betaseptic; Braunol; Citro Jod; Destrobac; Eso-Jod; Esoform Jod 35 and 75; Gammadin; Golasept; Inadine; Iodosteril; Iodoten; Jodocur†; Jodogard; Oftasteril; Paniodal†; Paniodine†; Poviderm; ***Jpn:*** Finish; ***Malaysia:*** Betadine; Freka-cid; Poviderm; Septi-Aid; Summers Eve Medicated; ***Mex.:*** Isodine; Solvin†; Yodacua; Yodine; ***Neth.:*** Betadine; Braunol; ***NZ:*** Betadine; Biocil; Riodine; Viodine†; ***Philipp.:*** Bacticide; Betadine; Povidine; Zigmadone; ***Pol.:*** Betadine; Braunovidon; Jodi; Polodina-R; Polseptol; PV Jod; ***Port.:*** Betadine; Braunol; Dinasepte†; Ginoseptil; Iodolab; Isodine; Septil; ***Rus.:*** Betadine (Бетадин); Iodoxyd (Йодоксид); Wokadine (Вокадин); ***S.Afr.:*** Betadine; Dermadine; Drygel; Podine; Septadine; Septisooth; Steridine; Zedchem PVP-I; ***Singapore:*** Betadine; ***Spain:*** Acydona; Betadine; Betatul; Curadona; Iodina; Orto Dermo P; Sanoyodo; Topionic; ***Switz.:*** Betadine; Braunol; Braunosan; Braunosan H Plus; Braunovidon; Destrobac; Intersept; Jodoplex; ***Thai.:*** Annadine; Bactedene; Bernadine†; Betadine; Cavodine†; Eprodine†; Freka-cid; Isodine; Movidone; P-Vidine†; Povadine; Sepfadine†; Septidine; Upodine; Videne; X-Tardine; ***Turk.:*** Batticon; Betakon; Biokadin; Isosol; Polyod; Poviseptin; ***UK:*** Betadine; Inadine; Savlon Dry; Videne; ***USA:*** ACU-dyne; Betadine; Biodine; Efodine; Iodex; Massengill Medicated; Minidyne; Operand; Polydine; Summers Eve Medicated; ***Venez.:*** Betadine; Etiyodix†; Intradine; Intradyn; Iopovidona†; Jabodine†; Norlidine; Podival†; Povidine†; Yodasep†.

Multi-ingredient: *Arg.:* Merthiolate Iodopovidona; Pervinox D; ***Austria:*** Braunoderm; ***Belg.:*** Braunoderm; ***Braz.:*** Iodocaine†; ***Cz.:*** Jox; ***Ger.:*** Betaseptic; Braunoderm; Repithel; ***Hung.:*** Eczil†; Jox†; ***India:*** Eczo-Wokadine; ***Indon.:*** Kalpanax; Kopamex; ***Ital.:*** Braunoderm; Jodieci; ***Jpn:*** U-Pasta; ***Mex.:*** Bano Coloide; Riban; ***Port.:*** Braunoderm; ***Rus.:*** Jox (Йокс); ***Switz.:*** Betaseptic; Braunoderm; ***Turk.:*** Batiodin; ***USA:*** Anbesol; Orasol; ProTech.

Propamidine Isetionate *(BANM, rINNM)*

Isetionato de propamidina; M&B-782; Propamidine Isethionate; Propamidine, Isétionate de; Propamidini Isetionas. 4,4′-Trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).

Пропамидина Изетионат

$C_{17}H_{20}N_4O_2,2C_2H_6O_4S$ = 564.6.

CAS — 104-32-5 (propamidine); 140-63-6 (propamidine isetionate).

ATC — D08AC03; S01AX15.

ATC Vet — QD08AC03; QS01AX15.

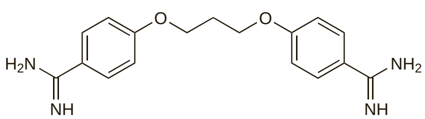

Profile

Propamidine isetionate is an aromatic diamidine antiseptic that is active against Gram-positive bacteria, but less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties and is active against *Acanthamoeba*. Ophthalmic solutions containing 0.1% of propamidine isetionate are used for the treatment of conjunctivitis and blepharitis.

Acanthamoeba keratitis. The optimal regimen for the treatment of *Acanthamoeba* keratitis (p.822) has yet to be determined. Propamidine isetionate applied topically was the first drug used with some success.[1,2] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. Due to surface toxicity and poor *in-vitro* sensitivity of neomycin, propamidine was later used with chlorhexidine or polihexanide. However, poor cysticidal activity, chronic conjunctival infection, and resistance of some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine.[3]

1. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; **26:** 231–6.
2. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; **17:** 893–905.
3. Perrine D, *et al.* Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; **39:** 339–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Brolene; ***Irl.:*** Brolene; ***NZ:*** Brolene; ***S.Afr.:*** Brolene; ***UK:*** Brolene; Golden Eye Drops.

Propiolactone *(BAN, USAN, rINN)*

BPL; NSC-21626; 2-Oxetanone; Propanolide; Propiolactona; β-Propiolactone; Propiolactonum. Propiono-3-lactone.

Пропиолактон

$C_3H_4O_2$ = 72.06.

CAS — 57-57-8.

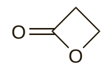

Profile

Propiolactone vapour is an irritant, mutagenic, possibly carcinogenic, disinfectant which is very active against most micro-organisms including viruses. It is rather less effective against bacterial spores.

Propiolactone vapour has been used for the gaseous sterilisation of pharmaceutical and surgical materials and for disinfecting large enclosed areas. It has low penetrating power. Propiolactone liquid has also been used.

Propyl Alcohol

Alcohol propílico; Normal Propyl Alcohol; Primary Propyl Alcohol; Propanol; Propanoli; Propanolis; Propanolum. Propan-1-ol.

$CH_3.CH_2.CH_2OH$ = 60.10.

CAS — 71-23-8.

ATC — D08AX03.

ATC Vet — QD08AX03.

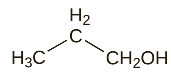

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Propanol). A clear colourless liquid. Miscible with water and with dehydrated alcohol. Protect from light.

Adverse Effects and Treatment

As for Alcohol, p.1625; propyl alcohol is considered more toxic.

◊ References.

1. WHO. 1-Propanol. *Environmental Health Criteria 102.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc102.htm (accessed 15/03/06)

Uses and Administration

Propyl alcohol, an antiseptic with properties similar to those of alcohol (p.1627), is used in preparations for disinfection of the hands, skin, surfaces, and instruments.

Isopropyl alcohol (p.1651) is also used as an antiseptic.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Skinman Asept.

Multi-ingredient: *Austria:* Dodesept; Kodan; Marcocid; Octeniderm; ***Fr.:*** Anios DD; Sterillium†; ***Ger.:*** Aerodesin; Bacillol; Bacillol AF; Bacillol plus; Desmanol†; Freka-Steril; Hospisept; Incidin; Incidur Spray†; Kodan Tinktur Forte†; Meliseptol; Meliseptol Rapid; Neo Kodan†; Primasept Med†; Sagrosept†; Softa Man; St-Tissues; Sterillium; ***Gr.:*** Chiro Des; Octeniderm; Sterillium; ***Ital.:*** Softa Man; ***Neth.:*** Softa-Man; Sterillium; ***Singapore:*** Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; ***Switz.:*** Kodan Teinture forte; Octeniderm; Softa-Man; Sterillium†.

Ritiometan *(rINN)*

Ritiométan; Ritiometán; Ritiometanum. (Methylidynetrithio)-triacetic acid.

Ритиометан

$C_7H_{10}O_6S_3$ = 286.3.

CAS — 34914-39-1.

ATC — R01AX05.

ATC Vet — QR01AX05.

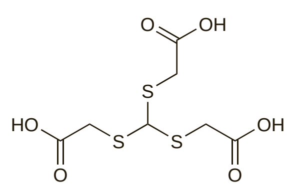

Profile

Ritiometan is used as the magnesium salt in an aerosol preparation for the treatment of infections of the nose and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Necyrane.

Scarlet Red

Biebrich Scarlet R Medicinal; CI Solvent Red 24; Colour Index No. 26105; Fat Ponceau R; Rojo escarlata; Rubrum Scarlatinum; Scharlachrot; Sudan IV. 1-[4-(*o*-Tolylazo)-*o*-tolylazo]naphth-2-ol.

$C_{24}H_{20}N_4O$ = 380.4.

CAS — 85-83-6.

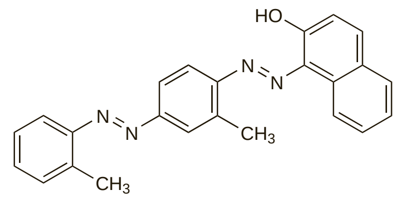

Profile

Scarlet red is an antiseptic dye that has been used topically. It can be irritant. Scarlet red is not permitted as a food colour in the EU, as it is thought to be a genotoxic carcinogen.

Sodium Azide

Azida sódica; Sodu azydek.

N_3Na = 65.01.

CAS — 26628-22-8.

$$Na^+$$
$$^-N{=}N^+{=}N^-$$

Adverse Effects and Precautions

Sodium azide is a potent vasodilator and the most common adverse effect, regardless of the route of exposure, is hypotension. Hypotension developing more than an hour after exposure is associated with more severe toxicity and fatality. Other severe symptoms include seizure, coma, arrhythmia, tachypnoea, pulmonary oedema, metabolic acidosis, and cardiorespiratory arrest. Milder symptoms include nausea, vomiting, diarrhoea, headache, dizziness, temporary loss of vision, palpitations, dyspnoea, temporary loss of consciousness, or decreased mental status. There is no specific antidote for sodium azide intoxication.

Solutions containing sodium azide must not be disposed of into drain pipelines containing copper, lead, or brass since highly explosive heavy metal azides may be produced.

◊ References to acute poisoning with sodium azide.

1. Edmonds OP, Bourne MS. Sodium azide poisoning in five laboratory technicians. *Br J Ind Med* 1982; **39:** 308–9.
2. Klein-Schwartz W, *et al.* Three fatal sodium azide poisonings. *Med Toxicol Adverse Drug Exp* 1989; **4:** 219–27.
3. Anonymous. Sodium azide contamination of hemodialysis water supplies. *JAMA* 1989; **261:** 2603.
4. Chang S, Lamm SH. Human health effects of sodium azide exposure: a literature review and analysis. *Int J Toxicol* 2003; **22:** 175–86.

Airbag deployment. Chemical and thermal burns have occurred after accidental perforation of airbags in motor vehicles and the release of sodium azide and other byproducts. Irritant contact dermatitis usually affecting the upper chest, arms, and face, and blunt trauma have also been reported.[1,2]

1. Corazza M, *et al.* Effects of airbag deployment: lesions, epidemiology, and management. *Am J Clin Dermatol* 2004; **5:** 295–300.
2. Suhr M, Kreusch T. Burn injuries resulting from (accidental) airbag inflation. *J Craniomaxillofac Surg* 2004; **32:** 35–7.

Effects on the nervous system. A study[1] to evaluate occupational neurotoxicity to sodium azide over a period of 3 years found that the only significant chronic symptom was trembling of the hands, occurring in 15 of 41 exposed workers compared with none of 42 controls. There was no difference between the 2 groups for other psychological or neuropsychological tests. Acute adverse effects most commonly reported by the exposed workers were heart palpitations, fatigue, nausea, vertigo, and irritated or red eyes.

1. Miljours S, Braun CMJ. A neuropsychotoxicological assessment of workers in a sodium azide production plant. *Int Arch Occup Environ Health* 2003; **76:** 225–32.

Haemodialysis. Of 10 investigations by the CDC[1] into outbreaks of disease caused by chemicals in haemodialysis facilities between 1979 and 1999, one was due to sodium azide. Inadequate rinsing of water filters resulted in the exposure of 9 patients to sodium azide in a dialysis centre. Patients experienced sudden hypotension, blurred vision, headache, nausea, vomiting, syncope, and 1 patient experienced cramps.

1. Arduino MJ. CDC investigations of noninfectious outbreaks of adverse events in hemodialysis facilities, 1979-1999. *Semin Dial* 2000; **13:** 86–91.

Uses

Sodium azide has been used as an antimicrobial preservative in laboratory reagents, serum samples, and dialysis equipment. It is also used in car airbags; sudden impact triggers an electrical charge causing the sodium azide to explode and nitrogen gas is released.

Sodium Diacetate

Diacetato de sodio; E262. Sodium hydrogen diacetate.

$CH_3COONa,CH_3COOH(+xH_2O)$.

CAS — 126-96-5 (anhydrous sodium diacetate).

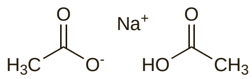

Profile

Sodium diacetate is used as a preservative in foods, particularly as an inhibitor of moulds and rope-forming micro-organisms in bread.

Sodium Formaldehyde Sulfoxylate

Formaldehído sulfoxilato sódico; Natrii Formaldehydosulfoxylas; Sodium Formaldehyde Sulphoxylate; Sodu formaldehydosulfoksylan. Sodium hydroxymethanesulphinate dihydrate.

$CH_3NaO_3S,2H_2O = 154.1$.

CAS — 149-44-0 (anhydrous sodium formaldehyde sulfoxylate); 6035-47-8 (sodium formaldehyde sulfoxylate, dihydrate).

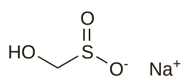

Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 26 (Sodium Formaldehyde Sulfoxylate). White crystals or hard white masses with the characteristic odour of garlic. Soluble 1 in 3.4 of water, 1 in 510 of alcohol, 1 in 175 of chloroform, and 1 in 180 of ether; slightly soluble in benzene. A 2% solution in water has a pH of 9.5 to 10.5. Store at 15° to 30°. Protect from light.

Profile

Sodium formaldehyde sulfoxylate is an antoxidant used as a preservative in pharmaceuticals. It has been used in the treatment of acute mercury poisoning (p.2342).

Sodium Hypochlorite

Hipoclorito sódico.

Гипохлорит Натрия

$NaOCl,5H_2O = 164.5$.

CAS — 7681-52-9.

ATC — D08AX07.

ATC Vet — QD08AX07.

NOTE. The term ‘liquid chlorine’ has been used for solutions of sodium hypochlorite. These should not be confused with the pressurised form of chlorine gas (p.1638) which is also liquid and has been referred to similarly.

Pharmacopoeias. *Br., Fr.,* and *US* include sodium hypochlorite solutions.

BP 2008 (Dilute Sodium Hypochlorite Solution). It contains 1% of available chlorine. Store away from acids at a temperature not exceeding 20°. Protect from light.

BP 2008 (Strong Sodium Hypochlorite Solution). It contains not less than 8% of available chlorine. It should be diluted before use. Store away from acids at a temperature not exceeding 20°. Protect from light.

USP 31 (Sodium Hypochlorite Solution). It contains not less than 4% and not more than 6% w/w of anhydrous sodium hypochlorite. It is not suitable for application to wounds. Store in airtight containers. Protect from light.

USP 31 (Sodium Hypochlorite Topical Solution). It contains 0.025% sodium hypochlorite. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of hypochlorites is rapidly reduced in the presence of organic material; it is also pH dependent being greater in acid pH although hypochlorites are more stable at alkaline pH.

Sodium hypochlorite solutions should not be mixed with solutions of strong acids or ammonia; the subsequent reactions release chlorine gas and tosylchloramide sodium gas, respectively.

Stability. The stability of sodium hypochlorite solutions increases with pH, solutions of pH 10 or more being most stable.[1] Stability studies have shown that solutions providing 0.04 to 0.12% ‘available chlorine’ stored in amber glass bottles at room temperature could carry a 23-month expiry date.[2]

1. Bloomfield SF, Sizer TJ. Eusol BPC and other hypochlorite formulations used in hospitals. *Pharm J* 1985; **235:** 153–5 and 157.
2. Fabian TM, Walker SE. Stability of sodium hypochlorite solutions. *Am J Hosp Pharm* 1982; **39:** 1016–17.

Adverse Effects

Hypochlorite solutions release hypochlorous acid upon contact with gastric juice and acids. Most patients ingesting hypochlorites will develop only mild gastrointestinal irritation. However, ingestion of small amounts of 3 to 5% hypochlorite solutions may result in irritation of the oropharynx, a burning sensation in the mouth and throat, and thirst. Nausea, vomiting, and haematemesis may occur. Ingestion of large amounts or more concentrated solutions causes irritation and corrosion of mucous membranes with chest and abdominal pain and tenderness, vomiting, haematemesis, watery diarrhoea and sometimes melaena. Ingestion of extremely large volumes may rarely cause hypernatraemia, hyperchloraemia, hypotension, and changes in mental status. In very severe cases ulceration or perforation of the oesophagus or stomach may occur leading to haemorrhage and shock.

Inhalation of the fumes is irritant to the eyes, nose, and respiratory tract. Sore throat, cough, bronchoconstriction, headache, ataxia, and confusion may develop. In severe cases dyspnoea and stridor due to laryngeal oedema may develop with breathlessness, wheeze, hypoxia, cyanosis, pneumonitis, and pulmonary oedema.

Hypochlorite solutions may be irritating to the skin and allergic contact dermatitis has been reported. Hypochlorite solutions may cause an alkali-type burn when splashed into the eye.

◊ General references.

1. Racioppi F, *et al.* Household bleaches based on sodium hypochlorite: review of acute toxicology and Poison Control Center experience. *Food Chem Toxicol* 1994; **32:** 845–61.

Effects on the blood. A child with G6PD deficiency had an acute haemolytic crisis after swimming for about 4 hours in an indoor pool containing very high concentrations of sodium hypochlorite.[1]

1. Ong SJ, Kearney B. Local swimming pool and G-6-PD deficiency. *Med J Aust* 1994; **161:** 226–7.

Effects on wound healing. For comment on the adverse effects of hypochlorite solutions on wound healing, see Disinfection: Wounds under Uses and Administration below.

Toxicity from mixing cleaning agents. Mixing the household cleaning agents bleach (5.25% sodium hypochlorite solution) and 4% phosphoric acid (p.2367) causes chlorine gas and water to be released. The chlorine in turn reacts with the water to form hydrochloric and hypochlorous acids. There have been case reports[1] of patients and hospital staff who have been accidentally exposed to chlorine gas as a result of mixing of these two cleaning agents. They had temporary illness and symptoms typical of chlorine toxicity; irritation of the eyes, nose and throat, headache, dizziness, nausea, cough, and chest pain or tightness. One patient had an acute exacerbation of asthma.

Tosylchloramide sodium gas is produced when common household cleaning agents containing sodium hypochlorite and ammonia (p.2256) are mixed together. On inhalation the water in the respiratory tract reacts with the tosylchloramide sodium gas to release ammonia, hydrochloric acid and oxygen free radicals. Numerous case reports have described the symptoms resulting from inhalation of these gases. A 12-month review[2] of 216 patients who reported to a regional poison information centre after exposure to tosylchloramide sodium gas as a result of mixing cleaning products found that only 1 patient, with a pre-existing respiratory-tract infection, required hospital admission for ongoing respiratory distress. The most frequent symptoms were cough and shortness of breath and other symptoms experienced were those commonly associated with exposure to chlorine gas (p.1638). Most (200) of the patients’ symptoms resolved within 6 hours and 145 patients were treated at home, while 71 were referred for further medical care. Oxygen was given to 62 patients, bronchodilators to 9 patients and 3 patients received corticosteroids. Similar symptoms and findings were reported[3] when 2 groups of 36 soldiers were exposed to tosylchloramide sodium gas as a result of mixing sodium hypochlorite and ammonia containing cleaning agents. Only 2 soldiers required hospital admission for persistent respiratory symptoms, with one of them requiring a few days of treatment in intensive care. Another case report[4] described a previously healthy 53-year-old woman who experienced shortness of breath progressing to pneumonitis and requiring emergency tracheostomy after a similar exposure to tosylchloramide sodium gas.

1. CDC. Epidemiologic notes and reports: chlorine gas toxicity from mixture of bleach with other cleaning products—California. *MMWR* 1991; **40:** 619–21, 627–9. Corrections. *ibid.*; 646, 819.
2. Mrvos R, *et al.* Home exposures to chlorine/chloramine gas: review of 216 cases. *South Med J* 1993; **86:** 654–7.
3. Pascuzzi TA, Storrow AB. Mass casualties from acute inhalation of chloramine gas. *Mil Med* 1998; **163:** 102–4.
4. Tanen DA, *et al.* Severe lung injury after exposure to chloramine gas from household cleaners. *N Engl J Med* 1999; **341:** 848–9.

Toxicity during root canal irrigation. A review of case reports[1] where sodium hypochlorite had been inadvertently injected into the periapical tissues during root canal irrigation reported that most patients experienced immediate severe pain and swelling of the neighbouring soft tissue, which could possibly spread over the injured side of the face, upper lip and infra-orbital region. Other symptoms included bleeding from the root canal, interstitial bleeding with haemorrhage of the skin and mucosa, a chlorine taste, irritation of the throat, and reversible anaesthesia or paraesthesia.

1. Hülsmann M, Hahn W. Complications during root canal irrigation—literature review and case reports. *Int Endod J* 2000; **33:** 186–93.

Treatment of Adverse Effects

If sodium hypochlorite solution is ingested symptomatic care, including dilution with water, milk, or other demulcents should be given; opinion over the use of antacids is divided. Sodium thiosulfate 1 to 2.5% solution has been used but is of little or no value. If spilled on skin or eyes, washing with copious amounts of water is recommended.

Poisoning. A patient who accidentally received an intravenous infusion of 150 mL of a 1% solution of sodium hypochlorite experienced a slow heart rate, mild hypotension, and increased respiratory rate. The slow heart rate persisted for 3 days but other parameters returned to normal after symptomatic treatment.[1]

1. Marroni M, Menichetti F. Accidental intravenous infusion of sodium hypochlorite. *DICP Ann Pharmacother* 1991; **25:** 1008–9.

Precautions

Topically applied hypochlorites may dissolve blood clots and cause bleeding.

Uses and Administration

Sodium hypochlorite is a disinfectant and antiseptic with the brief and rapid actions of chlorine (see p.1638). Sodium hypochlorite pentahydrate contains about 43% of ‘available chlorine’ (see p.1638); anhydrous sodium hypochlorite contains about 95%. Powders and solutions are commonly used for the rapid disinfection of hard surfaces (see Disinfection in Creutzfeldt-Jakob Disease, p.1622 and in Hepatitis and HIV Infection, p.1623), food and dairy equipment, babies’ feeding bottles, excreta, and water (p.1623). Solutions for use as domestic bleaches contain up to 5.25% of hypochlorite. Only diluted solutions containing up to 0.5% of ‘available chlorine’ are suitable for use on the skin and in wounds (but see Wound Disinfection, p.1624). Sodium hypochlorite solutions ranging from 0.5 to 5.25% are used in dentistry for root canal irrigation.

Solutions of hypochlorites used as disinfectants have included Labarraque’s Solution containing sodium hypochlorite with an alkali, and Eau de Javel, containing sodium or potassium hypochlorite.

Disinfection. *INSTRUMENTS.* Needles and syringes should not usually be sterilised chemically. However, cleaning of injection equipment with hypochlorite has been suggested as a last resort in the absence of sterile equipment, to reduce the risk of HIV transmission associated with the enforced re-use of injection equipment by injection drug users.[1] Use of full-strength domestic bleach (about 5% sodium hypochlorite, about 2% of ‘available chlorine’) was reported to be effective for the cleaning of intravenous drug users’ equipment; a 30-second contact time was required.[1,2] A 1 in 10 dilution of bleach was not effective after exposure for 5 minutes.[2] Despite rinsing with water, a low residual concentration of hypochlorite and microaggregates of blood are likely to remain on the cleaned instruments. Free chlorine is a potent oxidant and low concentrations of oxidants have been shown to enhance tissue inflammation *in vivo* as well as HIV-1 replication *in vitro*. This has led some researchers to suggest that there may be an increased possibility of an injection drug user contracting HIV-1 through the sharing of a bleach-cleaned blood-contaminated syringe as a consequence of the concomitant transmission of residual bleach; however, there is no epidemiological evidence to confirm this.[3]

1. Donoghoe MC, Power R. Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; **341:** 1658.
2. Watters JK, *et al.* Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; **342:** 742–3.
3. Contoreggi C, *et al.* Effects of varying concentrations of bleach on in vitro HIV-1 replication and the relevance to injection drug use. *Intervirology* 2000; **43:** 1–5.

WORMS. Sodium hypochlorite in aqueous solution at a concentration of 3.75% (or greater) is an effective ovicide for *Echinococcus* and may be used on hard surfaces, glassware, and sinks.[1]

1. Craig PS, Macpherson CNL. Sodium hypochlorite as an ovicide for Echinococcus. *Ann Trop Med Parasitol* 1988; **82:** 211–13.

WOUNDS. Hypochlorite solutions are now generally considered to be too irritant for use in the management of wounds (p.1585). Studies suggest that they may delay wound healing if repeatedly applied to open wounds.[1,2] It has been suggested that they may be of use in debriding burns (p.1578) or necrotic chronic wounds,[3] but also that any benefit that might be seen from the desloughing of necrotic tissue might be produced by damage of the superficial cell layer leading to separation[4] or from tissue hydration produced by wet dressing packs.[5] However, some burns units have found that hypochlorite as Dakin's solution (see Chlorinated Lime, p.1638) produces better healing than other antibacterials.[6]

See also p.1624.

1. Thomas S, Hay NP. Wound healing. *Pharm J* 1985; **235:** 206.
2. Lineweaver W, *et al.* Topical antimicrobial toxicity. *Arch Surg* 1985; **120:** 267–70.
3. Leaper DJ. Eusol. *BMJ* 1992; **304:** 930–1.
4. Anonymous. Local applications to wounds—I: cleansers, antibacterials, debriders. *Drug Ther Bull* 1991; **29:** 93–5.
5. Thomas S. Milton and the treatment of burns. *Pharm J* 1986; **236:** 128–9.
6. Murphy KD, *et al.* Current pharmacotherapy for the treatment of severe burns. *Expert Opin Pharmacother* 2003; **4:** 369–84.

Preparations

BP 2008: Dilute Sodium Hypochlorite Solution; Strong Sodium Hypochlorite Solution;
USP 31: Sodium Hypochlorite Solution; Sodium Hypochlorite Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Antibacter†; ***Austral.:*** Milton; ***Belg.:*** Dakincooper; ***Braz.:*** Liquido de Dakin†; ***Canad.:*** Dakin's Solution; Hygeol; ***Fr.:*** Dakin; ***Ger.:*** Maranon H†; ***Israel:*** Chlorasol; ***Ital.:*** Amukine Med; Milton; ***Singapore:*** Milton Anti-Bacterial; ***UK:*** Chlorasol†; Milton.

Multi-ingredient: ***Fr.:*** Amukine; ***Mex.:*** Amuchina†; ***Switz.:*** Amuchina Med.

Sodium Nitrate

E251; Natrii Nitras; Natrium Nitricum; Nitrato sódico; Sodu azotan.
$NaNO_3$ = 84.99.
CAS — 7631-99-4.

NOTE. Crude sodium nitrate is known as Chile Saltpetre.

Profile

Sodium nitrate has similar actions to potassium nitrate (p.1658) and is used as a preservative in foods, particularly in meat products.

Crude sodium nitrate is used as a fertiliser.

Handling. Sodium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Poisoning. Cyanosis and methaemoglobinaemia has been reported[1] in 3 patients after eating sausages that had been preserved mistakenly with a mixture of sodium nitrate and sodium nitrite rather than with potassium nitrate (saltpetre). The name saltpetre is used as a generic term for a number of potassium- or sodium-based preservatives used in food manufacture.

1. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; **76:** 367–8.

Sodium Perborate Monohydrate *(USAN)*

$NaBO_3,H_2O$ = 99.81.
CAS — 7632-04-4 (anhydrous sodium perborate); 10332-33-9 (sodium perborate monohydrate).
ATC — A01AB19.
ATC Vet — QA01AB19.

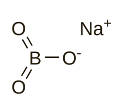

(anhydrous)

Sodium Perborate

Natrii perboras; Natrio perboratas; Natriumperboraatti; Natriumperborat; Nátrium-perborát; Perborato sódico; Perboritan sodný; Sod. Perbor.; Sodium, perborate de; Sodium Perborate Tetrahydrate.
$NaBO_3,4H_2O$ = 153.9.
CAS — 10042-94-1.
ATC — A01AB19.
ATC Vet — QA01AB19.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Sodium Perborate, Hydrated; Sodium Perborate BP 2008). Colourless prismatic crystals or a white or almost white powder, stable in crystalline form. Sparingly soluble in water, with slow decomposition. It dissolves in dilute mineral acids. Store in airtight containers.

Adverse Effects

Frequent use of toothpowders containing sodium perborate may cause blistering and oedema. Hypertrophy of the papillae of the tongue has also been reported. The effects of swallowed sodium perborate are similar to those of boric acid (p.2268).

Uses and Administration

Sodium perborate is a mild disinfectant and deodorant. It readily releases oxygen in contact with oxidisable matter and has been used in aqueous solutions for purposes similar to weak solutions of hydrogen peroxide.

Sodium perborate is used for tooth whitening and has also been used, with calcium carbonate, as a toothpowder. A freshly prepared solution is used as a mouthwash.

The monohydrate is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Hifamonil; ***Canad.:*** Amosan; ***India:*** Steradent; ***Ital.:*** Kavosan†; ***Neth.:*** Bocasan; ***USA:*** Amosan.

Multi-ingredient: ***Arg.:*** Oral-B Enjuague Bucal Amosan†; ***Austral.:*** Amosan; ***Belg.:*** Amosan; ***Braz.:*** Anginotricin; Malvatricin Branqueador; Oticerim; ***Fr.:*** Bactident; Hydralin; ***Hong Kong:*** Hydralin; ***Spain:*** Lema C; ***Switz.:*** Saltrates Rodell†; ***USA:*** Trichotine; ***Venez.:*** Novafix.

Sodium Percarbonate

Percarbonato sódico; Sodium Carbonate Peroxide.
$Na_2CO_3,1\frac{1}{2}H_2O_2$ = 157.0.
CAS — 15630-89-4.

Profile

Sodium percarbonate has similar uses to sodium perborate (above).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Ascoxal†; ***Austral.:*** Ascoxal; ***Fin.:*** Ascoxal†; ***Mex.:*** Ascoxal; ***Norw.:*** Ascoxal†; ***Swed.:*** Ascoxal†; ***Switz.:*** Desaquick forte†.

Sorbates

Sorbatos.

Sorbic Acid

Acide sorbique; Acidum sorbicum; E200; Kwas sorbowy; Kyselina sorbová; Sórbico, ácido; Sorbiinihappo; Sorbinsyra; Sorbo rūgštis; Szorbinsav. (*E,E*)-Hexa-2,4-dienoic acid.
$C_6H_8O_2$ = 112.1.
CAS — 22500-92-1.

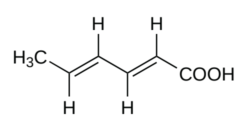

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sorbic Acid). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol. Protect from light.
USNF 26 (Sorbic Acid). A free-flowing white crystalline powder with a characteristic odour. Soluble 1 in 1000 of water, 1 in 10 of alcohol, 1 in 8 of dehydrated alcohol, 1 in 15 of chloroform, 1 in 30 of ether, 1 in 8 of methyl alcohol, and 1 in 19 of propylene glycol. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Incompatibility. The incompatibility of sorbates is discussed under Potassium Sorbate, below.

Potassium Sorbate

E202; Kalii sorbas; Kalio sorbatas; Kaliumsorbaatti; Kaliumsorbat; Kalium-sorbát; Kálium-szorbát; Potassium, sorbate de; Sorbato potásico. Potassium (*E,E*)-hexa-2,4-dienoate.
$C_6H_7KO_2$ = 150.2.
CAS — 590-00-1; 24634-61-5.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Potassium Sorbate). White or almost white granules or powder. Very soluble in water; slightly soluble in alcohol. Protect from light.
USNF 26 (Potassium Sorbate). White crystals or powder with a characteristic odour. Soluble 1 in 4.5 of water, 1 in 35 of alcohol, and 1 in more than 1000 of chloroform and of ether. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Incompatibility. Sorbic acid can be inactivated by oxidation and to some extent by nonionic surfactants and plastics. Activity of the sorbates may be reduced by increases in pH.[1]

1. Cook W. Sorbic acid. In: Rowe RC, *et al.*, eds. *Handbook of pharmaceutical excipients.* 5th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2006: 710–12.

Adverse Effects and Precautions

The sorbates can be irritant and have caused contact dermatitis.

Hypersensitivity. References to allergic-type skin reactions[1] and non-allergic irritant-type reactions[2,3] with potassium sorbate or sorbic acid.

1. Saihan EM, Harman RRM. Contact sensitivity to sorbic acid in 'Unguentum Merck'. *Br J Dermatol* 1978; **99:** 583–4.
2. Soschin D, Leyden JJ. Sorbic acid-induced erythema and edema. *J Am Acad Dermatol* 1986; **14:** 234–41.
3. Fisher AA. Erythema limited to the face due to sorbic acid. *Cutis* 1987; **40:** 395–7.

Uses

Potassium sorbate and sorbic acid possess antifungal, and to a lesser extent antibacterial, activity. They are relatively ineffective above a pH of about 6. They are used as preservatives in pharmaceutical preparations in concentrations of up to 0.2%, in enteral formulas, foods, and in cosmetic preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Caprilate; ***Ger.:*** Klysma Sorbit; Saseem; ***Ital.:*** Evasen Dischetti; Evasen Liquido; ***Mex.:*** Adapettes; ***UK:*** Relaxit; ***USA:*** Clear Eyes Contact Lens Relief; ***Venez.:*** Saxacid.

Sulfites and Sulfur Dioxide

Sulfitos y dióxido de azufre.

Potassium Bisulfite

Bisulfito potásico; E228; Potassium Bisulphite; Potassium Hydrogen Sulphite.
$KHSO_3$ = 120.2.
CAS — 7773-03-7.

Potassium Metabisulfite

Dipotassium Pyrosulphite; Disiřičitan draselný; E224; Kalii Disulfis; Kalii metabisulfis; Kalio metabisulfitas; Kaliummetabisulfiitti; Kaliummetabisulfit; Metabisulfito potásico; Potassium, métabisulfite de; Potassium Metabisulphite; Potassium Pyrosulphite; Potasu pirosiarczyn.
$K_2S_2O_5$ = 222.3.
CAS — 16731-55-8.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Potassium Metabisulphite). A white or almost white powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.5. Store in airtight containers. Protect from light.
USNF 26 (Potassium Metabisulfite). White or colourless, free-flowing crystals, crystalline powder, or granules, usually with an odour of sulfur dioxide. Gradually oxidises in air to the sulfate. Soluble in water; insoluble in alcohol. Its solutions are acid to litmus. Store in well-filled airtight containers at a temperature not exceeding 40°.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

Sodium Bisulfite

Bisulfito sódico; E222; Sodium Bisulphite; Sodium Hydrogen Sulphite.
$NaHSO_3$ = 104.1.
CAS — 7631-90-5.

Pharmacopoeias. In *Chin.* and *Jpn*, described in both as consisting of a mixture of sodium bisulfite and sodium metabisulfite.

Sodium Metabisulfite

Disiřičitan sodný; Disodium Pyrosulphite; E223; Metabisulfito sódico; Natrii Disulfis; Natrii metabisulfis; Natrii Pyrosulfis; Natrio metabisulfitas; Nátrium-diszulfit; Natriummetabisulfiitti; Natriummetabisulfit; Sodium Disulphite; Sodium, métabisulfite de; Sodium Metabisulphite; Sodium Pyrosulphite; Sodu pirosiarczyn.
$Na_2S_2O_5$ = 190.1.
CAS — 7681-57-4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Sodium Metabisulphite). Colourless crystals or a white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 5.0. Protect from light.
USNF 26 (Sodium Metabisulfite). White crystals or a white to yellowish crystalline powder with an odour of sulfur dioxide. Freely soluble in water and in glycerol; slightly soluble in alcohol. Store in well-filled airtight containers at a temperature not exceeding 40°.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

Sodium Sulfite

Anhydrous Sodium Sulphite; E221; Exsiccated Sodium Sulphite; Natrii Sulfis; Natrii sulfis anhydricus; Natrii Sulfis Siccatus; Natrii Sulphis; Natrio sulfitas, bevandenis; Natriumsulfiitti, vedetön; Natriumsulfit, vattenfritt; Siřičitan sodný; Sodium (sulfite de) anhydre; Sodium Sulphite; Sodu siarczyn; Sulfito sódico; Vízmentes nátrium-szulfit.

Na_2SO_3 = 126.0.
CAS — 7757-83-7.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.* Also in *USNF.*
Eur. also includes the heptahydrate.

Ph. Eur. 6.2 (Sodium Sulphite, Anhydrous; Natrii Sulfis Anhydricus). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Ph. Eur. 6.2 (Sodium Sulphite Heptahydrate; Natrii Sulfis Heptahydricus). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol.

USNF 26 (Sodium Sulfite). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

Sulfur Dioxide

Dióxido de azufre; E220; Kükürt Dioksit; Siarki dwutlenek; Sulphur Dioxide.

SO_2 = 64.06.
CAS — 7446-09-5.

Pharmacopoeias. In *USNF.*

USNF 26 (Sulfur Dioxide). A colourless non-flammable gas with a strong suffocating odour characteristic of burning sulfur. It condenses readily under pressure to a colourless liquid that boils at –10° and has a wt per mL of about 1.5 g. Soluble 36 in 1 of water and 114 in 1 of alcohol by vol. at 20° and standard pressure. Soluble in chloroform and in ether. Store in cylinders. It is usually packaged under pressure in liquid form.

Incompatibility and stability. Sulfite antoxidants can react with and inactivate sympathomimetics such as adrenaline.[1] Measures need to be taken to prevent such a reaction if sulfites have to be used. Cisplatin is another compound that can be inactivated.[2] Phenylmercuric nitrate may be inactivated or its activity enhanced.[3,4] Sulfites are reported to react with chloramphenicol.[1] Hydrogen peroxide generation has been reported on exposure to light of amino acid solutions containing sulfites.[5] When used in foods there can be a noticeable taste and a reduction in thiamine content.[6] Stability is affected by air and moisture,[7] and there is decomposition at very low pH.[7] There can be adsorption on to rubber closures.[8]

1. Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; **48:** 535–40.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; **37** (suppl): 123P.
5. Brawley V, *et al.* Effect of sodium metabisulfite on hydrogen peroxide production in light-exposed pediatric parenteral amino acid solutions. *Am J Health-Syst Pharm* 1998; **55:** 1288–92.
6. FAO/WHO. Evaluation of the toxicity of a number of antimicrobials and antioxidants: sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 228* 1962.
7. Stewart JT. Sodium metabisulfite. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 5th ed. London and Chicago: The Pharmaceutical Press, and the American Pharmaceutical Association 2006: 690–2.
8. Schroeter LC. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; **50:** 891–901.

Adverse Effects and Precautions

Gastric irritation due to liberation of sulfurous acid can follow ingestion of sodium metabisulfite and other sulfites. Large doses of sulfites may cause gastrointestinal upsets, respiratory or circulatory failure, and CNS disturbances.

Concentrated solutions of salts of sulfurous acid are irritant to skin and mucous membranes.

Sulfur dioxide is highly irritant to the eyes, skin, and mucous membranes. Inhalation results in irritation of the respiratory tract which may lead to bronchoconstriction and pulmonary oedema; very high concentrations may cause respiratory arrest and asphyxia. Contact with liquid sulfur dioxide results in acid burns.

Allergic reactions including anaphylaxis and deaths have been reported.

Hypersensitivity. Hypersensitivity reactions including bronchospasm, anaphylaxis, and some deaths have occurred in subjects, especially those with a history of asthma or atopic allergy, exposed to sulfites used as preservatives in foods.[1] These reactions have led to restrictions by the FDA on such use.[2] There have been case reports of reactions to sulfites in medicines;[3-9] such reports are considered to be few in number and the FDA has not extended the restriction on sulfites in foods to apply to their use in drugs since it was felt that in certain cases there was no suitable alternative to a sulfite.[2] It was even accepted that adrenaline recommended for use in treating allergic reactions could itself contain sulfite and that its presence should not preclude use of the adrenaline preparation even in sulfite-sensitive patients.[2]

1. Anonymous. Sulfites in drugs and food. *Med Lett Drugs Ther* 1986; **28:** 74–5.
2. Anonymous. Warning for prescription drugs containing sulfites. *FDA Drug Bull* 1987; **17:** 2–3.
3. Baker GJ, *et al.* Bronchospasm induced by metabisulphite-containing foods and drugs. *Med J Aust* 1981; **ii:** 614–17.
4. Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA* 1982; **248:** 2030–1.
5. Koepke JW, *et al.* Dose-dependent bronchospasm from sulfites in isoetharine. *JAMA* 1984; **251:** 2982–3.
6. Mikolich DJ, McCloskey WW. Suspected gentamicin allergy could be sulfite sensitivity. *Clin Pharm* 1988; **7:** 269.
7. Deziel-Evans LM, Hussey WC. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; **23:** 1032–3.
8. Campbell JR, *et al.* Allergic response to metabisulfite in lidocaine anesthetic solution. *Anesth Prog* 2001; **48:** 21–6.
9. Riemersma WA, *et al.* Type IV hypersensitivity to sodium metabisulfite in local anaesthetic. *Contact Dermatitis* 2004; **51:** 148.

Pharmacokinetics

Sulfites and metabisulfites are oxidised in the body to sulfate and excreted in the urine. Any sulfurous acid or sulfur dioxide is also converted to sulfate.

Uses

Sulfur dioxide and the sulfites that produce sulfur dioxide and sulfurous acid are strong reducing agents and are used as antoxidants. Concentrations of the sulfites in pharmaceutical preparations have ranged from 0.01 to 1.0%. At higher concentrations and preferably at an acid pH sulfur dioxide and the sulfites exhibit antimicrobial activity.

Sulfur dioxide and the sulfites are used in the food industry as antoxidants, antimicrobial preservatives, and anti-browning agents. They are used in wine making where tabletted sodium metabisulfite is commonly known as Campden Tablets. Concentrations of sulfites above 500 ppm impart a noticeable unpleasant taste to preparations. There is concern over the risk of severe allergic reactions arising from the use of sulfites in foods (see Hypersensitivity, above).

Tar Acids

Alquitrán, ácidos de.

Description. Tar acids are phenolic substances derived from the distillation of coal tar or petroleum fractions. The lowest boiling fraction of coal tar, distilling at 188° to 205°, consists of mixed cresol isomers. The middle fraction, known as 'cresylic acids', distils at 205° to 230° and consists of cresols and xylenols. The 'high-boiling tar acids', distilling at 230° to 290°, consist mainly of alkyl homologues of phenol, with naphthalenes and other hydrocarbons. Cresol is described on p.1641.

- **Black Fluids** are homogeneous solutions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons and with a suitable emulsifying agent.
- **White Fluids** are finely dispersed emulsions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons.
- **Modified Black Fluids** and **Modified White Fluids** may contain, as an addition, any other active ingredients, but if these are used, the type and amount must be disclosed, if required.

Adverse Effects and Treatment

As for Phenol, p.1656.

Tar acids are generally very irritant and corrosive to the skin, even when diluted to concentrations used for disinfection.

Poisoning. A report of fatal self-poisoning in a 59-year-old man after the ingestion of about 250 mL of a xylenol-containing disinfectant (*Stericol Hospital Disinfectant*).[1]

1. Watson ID, *et al.* Fatal xylenol self-poisoning. *Postgrad Med J* 1986; **62:** 411–12.

Uses

Tar acids are the phenolic components of coal tar and are used in the preparation of a range of fluids of varied activity used for household and general disinfection purposes.

Hydrocarbons are often used to enhance the activity of the tar acids in disinfectant fluids; they also help to reduce crystallisation of phenols.

Tertiary Butylhydroquinone

Butilhidroquinona terciaria; TBHQ. 2-*tert*-butylhydroquinone.

$C_{10}H_{14}O_2$ = 166.2.
CAS — 1948-33-0.

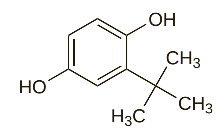

Profile

Tertiary butylhydroquinone is an antoxidant preservative used in foods. It has some antimicrobial activity.

Tetrabromocresol

3,4,5,6-Tetrabromo-*o*-cresol.

$C_7H_4Br_4O$ = 423.7.
CAS — 576-55-6.

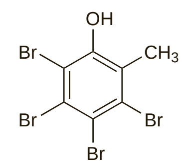

Profile

Tetrabromocresol is a brominated phenolic antiseptic. It has been used for hand disinfection and is applied topically in preparations for the treatment of fungal infections of the skin and bromhidrosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Pedoz; ***Ger.:*** Gehwol Fungizid†.

Tetraglycine Hydroperiodide

Tetraglicina, hidroperioduro de.

Гидропериодид Тетраглицина

$C_{16}H_{42}I_7N_8O_{16}$ = 1490.9.
CAS — 7097-60-1.

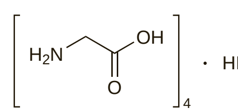

Profile

Tetraglycine hydroperiodide is an iodine-based disinfectant that is used in the emergency treatment of drinking water (p.1623).

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Potable Aqua; ***USA:*** Potable Aqua.

Thiomersal *(BAN, rINN)*

Mercurothiolate; Mercurothiolate Sodique; Sodium Ethyl Mercurithiosalicylate; Thimerosal; Thiomersalate; Thiomersalum; Tiomersaali; Tiomersal; Tiomersalis; Tiomerzál. Sodium (2-carboxyphenylthio)ethylmercury.

Тиомерсал

$C_9H_9HgNaO_2S$ = 404.8.
CAS — 54-64-8.
ATC — D08AK06.
ATC Vet — QD08AK06.

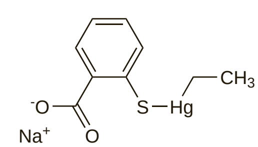

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Thiomersal). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble or soluble in alcohol; practically insoluble in dichloromethane. A 0.8% solution in water has a pH of 6.0 to 8.0. Protect from light.

USP 31 (Thimerosal). A light cream-coloured crystalline powder with a slight characteristic odour. Soluble 1 in 1 of water and 1 in 12 of alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 6.7. Store in airtight containers. Protect from light.

Incompatibility. Thiomersal is incompatible with acids, metal ions, and iodine. It forms precipitates with many alkaloids. The rate of oxidation of thiomersal in solution is greatly increased by traces of copper ions. In slightly acid solution thiomersal may be precipitated as the corresponding acid which undergoes slow decomposition with the formation of insoluble products. The activity of thiomersal may also be reduced by boric acid, edetic acid, or sodium thiosulfate or by the presence of blood or organic matter. Thiomersal may be adsorbed by plastic or rubber packaging materials.

References.

1. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
2. Reader MJ. Influence of isotonic agents on the stability of thimerosal in ophthalmic formulations. *J Pharm Sci* 1984; **73:** 840–1.
3. Morton DJ. EDTA reduces antimicrobial efficacy of thiomersal. *Int J Pharmaceutics* 1985; **23:** 357–8.

Adverse Effects, Treatment, and Precautions

As for Mercury, p.2341.

Hypersensitivity reactions occasionally occur. Allergic conjunctivitis has been reported.

◊ General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; **18:** 109–60.

Hypersensitivity. Both delayed (allergic contact) and immediate (including anaphylaxis and immune complex mediated disorders) hypersensitivity reactions have been associated with thiomersal.[1] The frequency of positive patch tests varies, with a Canadian centre reporting[2] an average incidence of 4.53% and a centre in the USA an incidence of 8.7%.[3] Most reactions are local and mild, involving application sites or blepharoconjunctivitis from ocular preparations,[1,4] although there has been a report of acute laryngeal obstruction in a patient previously sensitised to the substance who used a throat spray preserved with thiomersal.[5] A case of occupational allergic contact dermatitis has been reported in a nurse as a result of contact with thiomersal as a preservative in childhood vaccines.[6] A generalised maculopapular eruption from an influenza vaccine containing thiomersal has also been reported.[7] The main source of sensitisation is thought to be thiomersal-preserved vaccines. Most people with patch tests positive to thiomersal are able to tolerate thiomersal-containing vaccines, although some individuals may experience reactions ranging from mild to serious.[1] If there is a definite history of anaphylaxis to thiomersal in any product, vaccines containing thiomersal should not be given. However, while anaphylaxis has not been shown to occur as a result of thiomersal in vaccines, it remains a theoretical risk.[1]

1. National Advisory Committee on Immunization (NACI). Statement on thimerosal. *Can Commun Dis Rep* 2003; **29:** 1–10.
2. Freiman A, *et al.* Patch testing with thimerosal in a Canadian center: an 11-year experience. *Am J Contact Dermat* 2003; **14:** 138–43.
3. Suneja T, Belsito DV. Thimerosal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001; **45:** 23–7.
4. Wilson LA, *et al.* Delayed hypersensitivity to thiomersal in soft contact lens wearers. *Ophthalmology* 1981; **88:** 804–9.
5. Maibach H. Acute laryngeal obstruction presumed secondary to thiomersal (merthiolate) delayed hypersensitivity. *Contact Dermatitis* 1975; **1:** 221–2.
6. Kiec-Swierczynska M, *et al.* Occupational allergic contact dermatitis due to thimerosal. *Contact Dermatitis* 2003; **48:** 337–8.
7. Lee-Wong M, *et al.* A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol* 2005; **94:** 90–4.

Poisoning. Serious adverse effects have followed parenteral and topical use of thiomersal.

Six poisonings (5 fatal) resulted from the use of 1000 times the normal concentration of thiomersal in a preparation of chloramphenicol for intramuscular injection.[1] There has also been a case report[2] of mercury poisoning associated with the intravenous use of high-dose hepatitis B immunoglobulin, preserved with thiomersal, after liver transplantation. Initial symptoms were paranoia, which rapidly progressed to severe dysarthria, static tremor, chorea, and decreased motor strength, as well as haemorrhagic gastritis. The patient responded well to chelation therapy.

Thiomersal used in topical antiseptic preparations was found to be toxic to epidermal cells.[3] After the death of 10 of 13 children as a result of treatment of omphaloceles (umbilical hernia) with a tincture of thiomersal, it was recommended that organic mercurial disinfectants be heavily restricted or withdrawn from hospital use as absorption occurred readily through intact membranes.[4]

A 44 year-old man who drank 83 mg/kg of a thiomersal-containing solution in an attempted suicide, spontaneously vomited after 15 minutes.[5] On admission to hospital a gastric lavage was performed and chelating drugs given. Despite this he developed gastritis, renal failure, dermatitis, gingivitis, delirium, polyneuropathy, respiratory failure, and coma. The patient was treated symptomatically, and 148 days after ingestion had recovered fully, except for sensory defects in two toes.

1. Axton JHM. Six cases of poisoning after a parenteral organic mercurial compound (Merthiolate). *Postgrad Med J* 1972; **48:** 417–21.
2. Lowell JA, *et al.* Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B. *Liver Transpl Surg* 1996; **2:** 475–8.
3. Anonymous. Topical antiseptics and antibiotics: organic mercurials. *Med Lett Drugs Ther* 1977; **19:** 83.
4. Fagan DG, *et al.* Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch Dis Child* 1977; **52:** 962–4.
5. Pfab R, *et al.* Clinical course of severe poisoning with thiomersal. *J Toxicol Clin Toxicol* 1996; **34:** 453–60.

Vaccines. The use of thiomersal as a preservative in vaccines and its role as a possible cause of autism and neurodevelopmental disorders has been a controversial topic since 1999[1] when the regulatory authorities in both Europe[2] and the USA[3] issued statements recommending that the use of thiomersal in vaccines be phased out. This was based on the fact that the cumulative amount of mercury in the infant immunisation schedule potentially exceeds the recommended maximum level set by the US government for methyl mercury. More recently, however, a number of studies[4] have indicated a lack of association between thiomersal-containing vaccines and neurodevelopmental disorders such as autism and speech disorders. These findings were supported by the fact that thiomersal is metabolised to ethylmercury, which has substantially different pharmacokinetics to methylmercury. Ethylmercury is more rapidly excreted and does not accumulate in the body. The EMEA has issued a further statement[5] in which it confirmed that thiomersal could be used as a preservative when no alternative was available, subject to certain labelling requirements regarding hypersensitivity. The UK CSM[6] and the US FDA[7] have similarly concluded that there is no evidence of neurological adverse effects caused by the small amounts of thiomersal present in some vaccines; despite this, both endorse the view that the use of vaccines without thiomersal would be a prudent precautionary measure. WHO states[8,9] that there is no compelling scientific evidence of safety problems and advises that thiomersal-containing vaccines may continue to be used for global immunisation programmes because the benefit outweighs any theoretical risk of toxicity.

1. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28:** 89–101.
2. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal containing medicinal products (July 1999). EMEA publication no. 20962/99. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/2096299EN.pdf (accessed 27/08/08)
3. American Academy of Pediatrics, United States Public Health Service. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999; **48:** 563–5.
4. Parker SK, *et al.* Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004; **114:** 793–804.
5. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal in vaccines for human use—recent evidence supports safety of thiomersal-containing vaccines (March 2004). EMEA publication no. 1194/04. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/119404en.pdf (accessed 27/08/08)
6. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Safety of thiomersal-containing vaccines. *Current Problems* 2003; **29:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/03/06)
7. FDA. Thimerosal in vaccines (updated June 2008). Available at: http://www.fda.gov/cber/vaccine/thimerosal.htm (accessed 11/08/08)
8. WHO. Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. *WHO Tech Rep Ser 926* 2004. Available at: http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%204%20(95-102)TRS926thiomersal.pdf (accessed 16/03/06)
9. WHO. Statement on thiomersal (issued July 2006). Available at: http://www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/print (accessed 11/08/08)

Interactions

Tetracyclines. Nine patients using a contact lens solution containing 0.004% thiomersal developed varying degrees of ocular irritation after taking oral *tetracyclines* concurrently. Exposure to either the tetracyclines or thiomersal alone did not cause the response.[1]

1. Crook TG, Freeman JJ. Reactions induced by the concurrent use of thimerosal and tetracycline. *Am J Optom Physiol Opt* 1983; **60:** 759–61.

Uses and Administration

Thiomersal is a bacteriostatic and fungistatic mercurial antiseptic that has been applied topically usually in a concentration of 0.1%. Its antibacterial action results from the release of ethylmercury after breakdown to thiosalicylate and ethylmercury.

Thiomersal, 0.001 to 0.01%, is used as a preservative in biological and pharmaceutical products. It has also been used to preserve solutions used in the care of contact lenses (p.1622).

Preparations

USP 31: Thimerosal Tincture; Thimerosal Topical Aerosol; Thimerosal Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Lithiorsan; Merthiolate; ***Chile:*** Intrasept; ***Mon.:*** Vitaseptol; ***S.Afr.:*** Merthiolate; Thiomersalate; ***Thai.:*** Merthiolate†; ***USA:*** Aeroaid; Mersol; ***Venez.:*** Merthiolate.

Multi-ingredient: ***Spain:*** Proskin; ***Venez.:*** Thimerfesa†.

Thymol

Acido Timico; Isopropylmetacresol; Thymolum; Timol; Timolis; Tymol; Tymoli. 2-Isopropyl-5-methylphenol.

$C_{10}H_{14}O = 150.2.$

CAS — 89-83-8.

ATC Vet — QP53AX22.

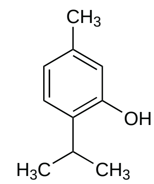

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Thymol). Colourless crystals. The melting range is 48° to 52°. Very slightly soluble in water; very soluble in alcohol; freely soluble in volatile and in fixed oils; sparingly soluble in glycerol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Thymol). Colourless, often large, crystals or a white crystalline powder with an aromatic thyme-like odour. The melting range is 48° to 51°; when melted it remains liquid at a considerably lower temperature. Soluble 1 in 1000 of water, 1 in 1 of alcohol and of chloroform, 1 in 1.5 of ether, and 1 in 2 of olive oil; soluble in glacial acetic acid and in fixed and volatile oils. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of thymol is reduced by combination with protein.

Adverse Effects, Treatment, and Precautions

As for Phenol, p.1656.

When ingested, thymol is less toxic than phenol. It is irritant to the gastric mucosa. Fats and alcohol increase absorption and aggravate the toxic symptoms.

Hypersensitivity. Contact allergy to a heparinoid cream was due to an allergen formed by the reaction between thymol and the degradation products of a triazine derivative, both present as preservatives.[1]

1. Smeenk G, *et al.* Contact allergy to a reaction product in Hirudoid cream: an example of compound allergy. *Br J Dermatol* 1987; **116:** 223–31.

Uses and Administration

Thymol is a phenolic antiseptic with antibacterial and antifungal activity. It is more powerful than phenol but its use is limited by its low solubility in water, irritancy, and susceptibility to protein.

Thymol is used chiefly as a deodorant in mouthwashes and gargles such as Compound Thymol Glycerin (BP 1988), an aqueous mixture of thymol 0.05% and glycerol 10% with colouring and flavouring, which may be used diluted with about 3 times its volume of warm water before use. Thymol has been used topically in the treatment of skin disorders and is also inhaled, with other volatile substances, for colds, coughs, and associated respiratory disorders.

Thymol 0.01% is added as an antoxidant to halothane, trichloroethylene, and tetrachloroethylene.

Thymol iodide is used in preparations for dental hygiene.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Medophyll†; ***S.Afr.:*** Cool Mint Listerine; Freshburst Listerine.

Multi-ingredient: ***Arg.:*** Fungicida†; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; Manzan; Novobroncol†; Periobacter Prof Avio; Vagicural; ***Austral.:*** SM-33; Vicks Vaporub; ***Austria:*** Alpicort; Criniton; DDD; Gingivan; Kinder Luuf; Luuf Balsam; Pe-Ce; Spasmo Claim; Thrombocid; Wick Vaporub; ***Belg.:*** Borostyrol; Dentophar; Perubore; Vicks Vaporub; ***Braz.:*** Anestesiol†; Angino-Rub; Cloraseptic; Cutisanol; Fluomint; Frixodon†; Gargotan†; Gyrol†; Lenidor†; Passaja†; Relampago†; Tabletes Valda†; Valda†; Vick Vaporub; ***Canad.:*** Antiseptic Mouthwash; Boil Ease†; Buckley's White Rub†; Carboseptol†; Lipsorex Plus; Lipsorex†; Listerine; Listerine Antiseptic Tartar Control; Mouthwash Antiseptic & Gargle†; Nasal Jelly†; Thermo-Gel; Valda; Vaporisateur Medicamente; Vaporizing Ointment; ***Chile:*** Balsamo Leon†; Galutec†; Hansaplast Descongestionante; Listerine; Listermint Con Fluor; Oralfresh Citrus; Oralfresh Clasico; Polisep†; ***Cz.:*** Parodontal F5†; Pinosol; Septolete; ***Fin.:*** Vicks Vaporub; ***Fr.:*** Borostyrol; Listerine; Listerine protection dents et gencives; Moustidose; Nisacalm; Pastilles Medicinales Vicks; Perubore; Valda; Vicks Vaporub; ***Ger.:*** Alferm†; Criniton†; Em-medical†; Nasentropfen-ratiopharm†; Oestrugol N†; Pulmotin; Retterspitz Ausserlich; Retterspitz Quick; Salviathymol N; Thrombocid; ***Gr.:*** Oulogram; ***Hong Kong:*** Burn Cream†; Cool Mint Listerine; Gly Thymol; Kamistad; Listerine; Listerine Tartar Control; Listerine Teeth and

Gum Defence; Salomethyl; Valda†; ***India:*** Anaebell†; ***Indon.:*** Dactylen; Listerine; Listerine Coolmint; Skintex; Vital Ear Oil; ***Irl.:*** Karvol; Valda†; ***Israel:*** Gargol; Garonsept; Karvol; Pronestin; Rectozorin; ***Ital.:*** Eucalipto Composto†; Eugenol-Guaiacolo Composto; Listerine Fresh Citrus; Listerine Tartar Control; Pinselina Knapp; Rinostil; ***Malaysia:*** Listerine†; Salonpas; ***Mex.:*** Dermacid; Listerine; ***Neth.:*** Vicks Vaporub; ***NZ:*** Listerine; Listerine Tartar Control; Thymol Mouthwash Red†; Vicks Vaporub; ***Philipp.:*** Calmoseptine; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar Control; Listerine Teeth & Gum Defense; Mentopas; ***Pol.:*** Afronis; Bronchosol; Derhotill; Icy Rub; Pinosol; Pulmonil; Rub-Arom; Septolete; Sonol; Wick Vaporub; ***Port.:*** Edoltar†; Freimax†; Listerine†; Thrombocid; Valda†; ***Rus.:*** Bioprost (Биопрост); Doktor Mom (Доктор Мом); Efcamon (Эфкамон); Pinosol (Пиносол); Septogal (Септогал); Septolete (Септолете); Suprima-Plus (Суприма-Плюс); ***S.Afr.:*** Karvol; Listerine Antiseptic; Prep; Tartar Control Listerine Antiseptic; Vicks Vaporub; ***Singapore:*** Kamistad; Karvol; Listerine; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; ***Spain:*** Balsamo Kneipp†; Co Bucal; Mentobox; Pastillas Antisep Garg M; Piorlis; Vicks Vaporub; ***Swed.:*** Vicks Vaporub†; ***Switz.:*** Asphaline†; Borostyrol N†; Butaparin; Cresophene†; Ederphyt; Furodermal; GU Eau†; Huile analgesique "Temple of Heaven" contre les maux de tete†; Penta; Perubare†; Rapura; Sedasept†; Sedotussin†; Thrombocid; Vicks Vaporub N; ***Thai.:*** Burnol Plus; Flavinol; Kamistad; Stopain; ***Turk.:*** Kataljin; Mentimol; Mentolin; Otaci Meyanbali; Otaci Oka Mentol; Otaci Salvia; Vicks Vaporub; ***UK:*** Antiseptic Mouthwash; DDD; Dragon Balm; Karvol; Listerine Antiseptic Mouthwash; No-Sor Vapour Rub; Potter's Catarrh Pastilles; ***USA:*** BFI; Boil Ease; Listerine; Massengill; Vicks Menthol Cough Drops; Zonite; ***Venez.:*** Amicets; Lafarcaina.

Tosylchloramide Sodium *(BAN, rINN)*

Chloramidum; Chloramina; Chloramine; Chloramine T; Chloraminum; Cloramina; Klóramin; Mianin; Natrium Sulfaminochloratum; Tosilchloramido natrio druska; Tosilcloramida sódica; Tosylchloramid sodná sůl trihydrát; Tosylchloramide sodique; Tosylchloramidum natricum; Tosylchloramidum Natricum Trihydricum; Tosylkloramidnatrium; Tosyylikloramidinatrium. Sodium *N*-chlorotoluene-*p*-sulphonimidate trihydrate.

Тозилхлорамид Натрий

$C_7H_7ClNNaO_2S,3H_2O$ = 281.7.

CAS — 144-86-5 (tosylchloramide); 127-65-1 (tosylchloramide sodium).

ATC — D08AX04.

ATC Vet — QD08AX04.

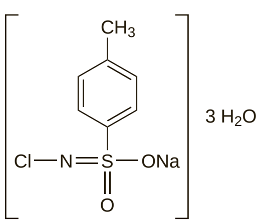

NOTE. The name Chloramin has also been formerly used for a preparation of chlorphenamine maleate (p.571).

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.*

Ph. Eur. 6.2 (Tosylchloramide Sodium). A white or slightly yellow, crystalline powder. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 8.0 to 10.0. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Vomiting, cyanosis, circulatory collapse, frothing at the mouth, and respiratory failure can occur within a few minutes of tosylchloramide sodium ingestion. Fatalities have occurred. Tosylchloramide sodium in tap water has caused methaemoglobinaemia and haemolysis in patients undergoing dialysis. Bronchospasm has occurred after inhalation.

Treatment of adverse effects is similar to that for Sodium Hypochlorite, p.1661.

Effects on the lungs. A study in Finland in dental staff who had reported occupational respiratory hypersensitivity between 1990 and 1998 found that 1 of 28 cases of rhinitis and 3 of 28 cases of asthma could be attributed to tosylchloramide sodium.[1] For further reference to respiratory effects associated with tosylchloramide sodium gas, see under Sodium Hypochlorite: Toxicity from mixing cleaning agents, p.1661.

1. Piirilä P, *et al.* Occupational respiratory hypersensitivity in dental personnel. *Int Arch Occup Environ Health* 2002; **75:** 209–16.

Uses and Administration

Tosylchloramide sodium is an organic chlorine-releasing compound. It has general properties similar to those of chlorine (p.1638) but is more stable. It contains about 25% w/w of 'available chlorine' (see p.1638). It is stable at an alkaline pH although it is much more active in acid media. It is more slowly active than hypochlorite solutions.

Tosylchloramide sodium is used for the treatment of minor wound infections and as a skin and hard surface disinfectant. It is also used for the treatment of drinking water (p.1623). It was formerly used as a spermicide.

Tosylchloramide sodium B (chlorogenium; sodium *N*-chlorobenzenesulphonimidate sesquihydrate) has been used similarly to tosylchloramide sodium.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Chloraseptine; Chlorazol; Chloronguent; Clonazone; ***Fr.:*** Hydroclonazone; ***Ger.:*** Chloramin T; Clorina; Trichlorol; ***Hung.:*** Neomagnol; ***Ital.:*** Amuclor Med; Citromed Chlor; Dermedal; Euclorina; Minachlor; Ottoclor†; Steridrolo; ***Spain:*** Clorina.

Triclocarban *(USAN, rINN)*

NSC-72005; TCC; 3,4,4′-Trichlorocarbanilide; Triclocarbán; Triclocarbanum. 1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea.

Триклокарбан

$C_{13}H_9Cl_3N_2O$ = 315.6.

CAS — 101-20-2.

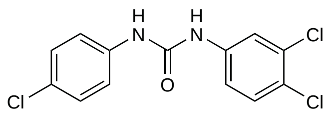

Adverse Effects and Precautions

When subjected to prolonged high temperatures triclocarban can decompose to form toxic chloroanilines, which can be absorbed through the skin and cause methaemoglobinaemia. Mild photosensitivity has been seen in patch testing.

Uses and Administration

Triclocarban is an anilide antiseptic. It is bacteriostatic against Gram-positive organisms but is not effective against Gram-negative organisms. It inhibits growth of some fungi. It is used in antiperspirants and soaps for disinfection of skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Jabobip†; Sodorant; Ungel; ***Braz.:*** Derso TCC†; ***Fr.:*** Cutisan; Nobacter; Solubacter; ***Gr.:*** Antibacter Forte; ***Ital.:*** Citrosil Sapone; Sangen Sapone Disinfettante; ***Mex.:*** Nutegen A†; ***UK:*** Valderma; ***USA:*** Cuticura†.

Multi-ingredient: ***Arg.:*** Bacteroskin†; LB Jabon con Purcelin†; Sodorant; ***Braz.:*** Soapex; ***Fr.:*** Septosan; Spray du Marcheur; ***Ger.:*** Ansudor†; ***Mex.:*** Septosan; ***Switz.:*** Septivon N.

Triclosan *(BAN, USAN, rINN)*

CH-3565; Cloxifenol; Triclosán; Triclosanum. 5-Chloro-2-(2,4-dichlorophenoxy)phenol; 2,4,4′-Trichloro-2′-hydroxydiphenyl ether.

Триклозан

$C_{12}H_7Cl_3O_2$ = 289.5.

CAS — 3380-34-5.

ATC — D08AE04; D09AA06.

ATC Vet — QD08AE04; QD09AA06.

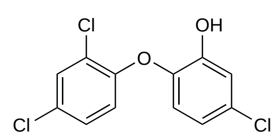

Pharmacopoeias. In *US.*

USP 31 (Triclosan). A fine whitish crystalline powder. M.p. about 57°. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; slightly soluble in petroleum spirit. Store in airtight containers. Protect from light.

Profile

Triclosan is a chlorinated bisphenol antiseptic, effective against Gram-positive and most Gram-negative bacteria but with variable or poor activity against *Pseudomonas* spp. It is also active against fungi. It is used in soaps, creams, and solutions in concentrations of up to 2% for disinfection of the hands and wounds and for disinfection of the skin prior to surgery, injections, or venepuncture. It is also used in oral hygiene products and in preparations for acne. There have been isolated reports of contact dermatitis.

MRSA control. Control of meticillin-resistant *Staphylococcus aureus* (MRSA) infection in surgical units has been achieved by procedures including handwashing and bathing with triclosan.[1-3] In the UK, guidelines on the control of MRSA recommend it as one of several alternatives for such purposes,[4] although alcohol hand rubs (also mentioned in the guidelines) are currently preferred for general hand hygiene (see p.1624). However, triclosan resistance has been reported.[5-7]

1. Bartzokas CA, *et al.* Control and eradication of methicillin-resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1984; **311:** 1422–5.
2. Bartzokas CA. Eradication of resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1985; **312:** 858–9.
3. Brady LM, *et al.* Successful control of endemic MRSA in a cardiothoracic surgical unit. *Med J Aust* 1990; **152:** 240–5.
4. Coia JE, *et al.* Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in hospitals (draft June 05). For the Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Available at: http://www.bsac.org.uk/_db/_documents/mrsa_INFECTION_JUNE_05.pdf (accessed 08/03/06)
5. Cookson BD, *et al.* Transferable resistance to triclosan in MRSA. *Lancet* 1991; **337:** 1548–9.
6. Sasatsu M, *et al.* Triclosan-resistant Staphylococcus aureus. *Lancet* 1993; **341:** 756. Correction. *ibid.*; **342:** 248.
7. Suller MT, Russell AD. Triclosan and antibiotic resistance in Staphylococcus aureus. *J Antimicrob Chemother* 2000; **46:** 11–18.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Daewo; ***Austral.:*** Dettol Liquid Wash; Gamophen; Johnsons Clean & Clear Facial Cleansing Bar†; Johnsons Clean & Clear Foaming Facial Wash; Liquid Soap Pre-Op†; Microshield T; Neutrogena Acne Skin Cleanser; Oxy Skin Wash; pHisoHex Face Wash; Sapoderm; Solyptol†; ***Braz.:*** Clean & Clear Sabonete Liquido Facial; Fisohex†; Hygine; Johnson's Sabonete Liquido Anti-Septico; Soapelle; Soapex; Theracne; ***Canad.:*** Adasept; Clean & Clear Foaming Facial Cleanser; Clearasil Face Wash†; Clearskin Antibacterial†; Clearskin Medicated Cleanser†; Dermance†; Dial Complete; Noxzema Triple Clean; Oxy Daily Facial Cleanser Regular†; Oxy Medicated Soap†; Skin So Soft Antibacterial†; Tersaseptic; Trisan†; ***Chile:*** Antiseptin; Lavasept; Sanigermin; ***Cz.:*** Lipo Sol†; ***Fr.:*** Nobacter; ***Gr.:*** Ampitasol; ***Hong Kong:*** Oxy Daily Wash; pHisoHex Reformulated†; ***Indon.:*** pHisoHex Reformulated; ***Israel:*** Dermax; ***Ital.:*** Cetriderm con Triclosan; Derman Plus; Geroderm; Ippi Verde; Irgaman; Lactacyd Antibatterico; Oilatum AD†; Till; ***Malaysia:*** pHisoHex†; ***Mex.:*** Septosan†; ***NZ:*** Dalacin T Prewash; Liquid Soap Pre-Op; Oxy Daily Skin Wash†; ***Philipp.:*** Lipo Sol; ***S.Afr.:*** Acneclear; ***Singapore:*** Clearasil Facial Cleansing; ***Switz.:*** Cliniderm; Lipo Sol; Procoutol; Shampooing extra-doux; ***Thai.:*** Virulex; ***UK:*** Aquasept; Gamophen; Oxy Facial Wash; Ster-Zac; ***USA:*** Ambi 10; ASC; Clearasil Daily Face Wash; Oxy Medicated Soap; Septi-Soft†; Septisol†; Stri-Dex Antibacterial Cleansing; Stri-Dex Face Wash.

Multi-ingredient: ***Arg.:*** Bentophyto; Dettonjab; Emoform Total; Esmedent con Fluor; Esmedent Dientes Sensibles; Heduline; Hekabetol; Hydragenic†; Neoceuticals Gel de Limpieza Facial; Odol Med Antiplaca†; Odol Tratamiento de Encias†; Prurigel; Sebulex; Tersoderm Cabellos Grasos†; Ublosid†; ***Austral.:*** Clearasil Acne Treatment Cream; Dettol Cream; Oilatum Plus; ***Braz.:*** Fisohex II; Malvatricin Antiplaca; Malvatricin Branqueador; Malvatricin Dentes Sensiveis; Malvatricin Plus; Salisoap; Soapex; Suavederm; ***Canad.:*** Adasept; Oral Plan†; PanOxyl Clear Acne; Solarcaine; ***Chile:*** Ac-Sal; Cariamyl; Cornina†; Gingilacer†; Hansaplast Antimicotico; Hansaplast Footcare; Kariax†; Ortodent†; Solarcaine Spray Aerosol; ***Cz.:*** Acne Cream†; Acne Lotio†; Oilatum Plus; ***Fin.:*** Wicne; Wicnecarb; Wicnelact; Wicnevit; ***Fr.:*** Clinogel; Delabarre Bio-adhesif; Oilatum AD†; Poudre du Marcheur; Sanytol†; Septiane; Septosan; Spray du Marcheur; ***Ger.:*** Rutisept extra; Sicorten Plus; ***Hong Kong:*** Dettol†; Oilatum Plus; Sicorten Plus†; ***Hung.:*** Aurobin; ***Indon.:*** Betiga; Oilatum Plus; Verile; ***Irl.:*** Dettol; Oilatum Junior Flare-Up; Oilatum Plus; ***Israel:*** Pedisol; Sicorten Plus†; ***Ital.:*** Aknicare Cleanser; Angstrom Viso; AZ Protezione Gengive; Colgate Total; Dopo Pik; Geroderm Zolfo†; Plax†; Steril Zeta; ***Malaysia:*** Clearasil Pimple Treatment; Dettol; Oilatum Plus Antibacterial; QV Flare Up; T3 Acne; ***Mex.:*** Cetaphil Antibacterial; Crema Axel†; Dermobras; Periodentyl; Prespir; Sebryl Plus; Septosan; ***NZ:*** Clearasil; Dettol; Oilatum Plus; Solarcaine; ***Philipp.:*** Oilatum Plus; Sebo Fluid; ***Pol.:*** Oilatum Plus; ***Port.:*** Aknicare; Alkagin; Antiacneicos Ac-Sal†; Bexident; Lambda; Sicorten Plus†; ***Rus.:*** Aurobin (Ауробин); ***S.Afr.:*** Clearasil T; Oilatum Plus; ***Singapore:*** Burnaid; Clearasil Overnight Defence; Clearasil Pimple Treatment; Dettol; Oilatum Plus; pHisoHex Reformulated†; QV Flare Up; T3; Tinasolve†; Tri-Cidal†; ***Spain:*** Doctodermis; Sicorten Plus; Vaselatum; ***Switz.:*** Acne Creme; Acne Gel; Acne Lotion; Antebor N; Keroderm†; Pixor Stick Anti-acne N; Saltrates†; Sebo Creme; Sebo Shampooing; Sicorten Plus; Sulgan N; Turexan Emulsion†; ***Thai.:*** Dettol; Hand Joy; Oilatum Plus; ***UK:*** Clearasil Active Treatment Cream; Dentyl pH; Dettol; Manusept; Oilatum Junior Flare-Up†; Oilatum Plus; Oxy Clean Facial Scrub; Oxy Cleanser; Oxy Dots; Oxy Duo Pads; Sensodyne-F; Solarcaine; TCP; ***USA:*** Clearasil Antibacterial; Solarcaine; ***Venez.:*** Exfoliderm; Sicorten Plus†.

Troclosene *(rINNM)*

Dichloroisocyanuric Acid; Troclosène; Trocloseno; Troclosenum. 1,3-Dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.

Троклозен

$C_3HCl_2N_3O_3$ = 198.0.

CAS — 2782-57-2.

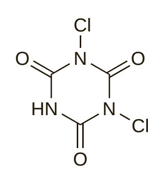

Troclosene Potassium *(USAN, rINN)*

Potassium Dichloroisocyanurate; Potassium Troclosene; Troclosène Potassique; Trocloseno de potasio; Troclosenum Kalicum.

Троклозен Калий

$C_3Cl_2KN_3O_3$ = 236.1.

CAS — 2244-21-5.

Troclosene Sodium *(rINNM)*

Sodium Dichloroisocyanurate; Sodium Dichloro-s-triazinetrione; Sodium Troclosene; Troclosène Sodique; Trocloseno sódico; Troclosenum Natricum.

Троклозен Натрий

$C_3Cl_2N_3NaO_3$ = 219.9.

CAS — 2893-78-9.

Profile

Troclosene sodium is a disinfectant with the general properties of chlorine (p.1638) and sodium hypochlorite (above) but it remains active as pH increases from 6 to 10 and is reported to be less susceptible to inactivation by organic material. It contains about 56 to 65% of 'available chlorine' (see p.1638).

Troclosene sodium is used for disinfecting hard surfaces (see Disinfection in Hepatitis and HIV Infection, p.1623), babies' feeding bottles, and food and dairy equipment, for treating water (p.1623), for rapid disinfection of swimming pools, for soft contact lens care (p.1622), and in various commercial bleach detergents and scouring powders as a relatively stable source of chlorine.

Troclosene, troclosene potassium, and symclosene (trichloroisocyanuric acid $C_3Cl_3N_3O_3$ = 232.4) are similarly used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Aquatabs (Puritabs); Milton; ***Fr.:*** Aquatabs; ***Hong Kong:*** Actichlor; ***Israel:*** Klor-De; Klorsept; Taharmayim; Taharsept; Tahartaf; ***Ital.:*** Dialster; Dicloraster; ***NZ:*** Puritabs; ***S.Afr.:*** Softab; ***Singapore:*** Milton Anti-Bacterial; ***UK:*** Milton; Presept.

Multi-ingredient: ***Fr.:*** Micropur Forte DCCNa.

Undebenzophene

Parahydroxybenzoate Phenoxyethanol; Undebenzofeno. 2-Phenoxyethyl *p*-hydroxybenzoate.
$C_{15}H_{14}O_4$ = 258.3.
CAS — 55468-88-7.

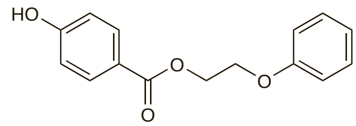

Profile

Undebenzophene is an antiseptic that has been included in preparations intended for wound and burn disinfection.

Urea Hydrogen Peroxide

Carbamide Peroxide; Hydroperite; Peróxido de hidrógeno y urea; Urea Peroxide.
$NH_2.CO.NH_2,H_2O_2$ = 94.07.
CAS — 124-43-6.

Pharmacopoeias. In *US.*

USP 31 (Carbamide Peroxide). Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Urea hydrogen peroxide consists of hydrogen peroxide and urea in equimolecular proportions. It is used for the extemporaneous preparation of hydrogen peroxide. It is used for tooth whitening, and has been used for infections of the ear, mouth, skin, and mucous membranes and for softening ear wax.

Preparations

USP 31: Carbamide Peroxide Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Blanc Dient; Yadid; ***Austral.:*** Ear Clear; ***Braz.:*** Aceratun; ***Canad.:*** Murine; ***Ger.:*** Elawox; ***Hung.:*** Hyperol; ***Irl.:*** Exterol; ***Israel:*** Exterol; ***Ital.:*** Debrox; Dermoxyl; Ginoxil; ***NZ:*** Earclear; ***UK:*** Exterol; Otex; ***USA:*** Auraphene-B; Auro; Debrox; ERO; Gly-Oxide; Mollifene; Murine; Orajel Perioseptic.

Multi-ingredient: ***Arg.:*** Hexiben Plus†.

Zinc Peroxide

Peróxido de zinc; Zinc Dioxide; Zinc Superoxide; ZPO.
ZnO_2 = 97.38.
CAS — 1314-22-3.

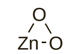

Profile

The action of zinc peroxide is similar to that of hydrogen peroxide (p.1647). Applied locally it has been used for disinfecting and deodorising burns, wounds, and various ulcers and lesions.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Anaseptil; ***Fr.:*** Bioxyol; ***Ital.:*** Ektogan.

Electrolytes

Acid–base Balance, p.1667
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Electrolytes are used to correct disturbances in fluid and electrolyte homoeostasis or acid–base balance and to re-establish osmotic equilibrium of specific ions. The osmotic effects of solutions may be expressed in terms of

- osmolality, which is defined as the 'molal' concentration in moles (or osmoles) per kg of solvent

or

- osmolarity, which is the 'molar' concentration in moles (or osmoles) per litre of solution

In clinical practice, solute concentrations are measured per litre of solution and are expressed as millimoles (mmol) per litre or sometimes as milliequivalents (mEq) per litre. Milliequivalents are converted to millimoles by dividing by the valency of the ion.

Positively charged ions are known as *cations* and include calcium, magnesium, potassium, and sodium ions. Negatively charged ions are known as *anions* and include bicarbonate, chloride, and phosphate ions. The ions principally involved in fluid and electrolyte homoeostasis and acid–base balance are sodium, chloride, bicarbonate, and potassium. Calcium, phosphate, and magnesium have a central role in the formation of bone mineral.

Acid–base Balance

Within the body, acid is mostly produced during cellular respiration in the form of carbon dioxide. Small amounts of various non-volatile acids are generated via metabolism, including lactic acid, uric acid, keto acids, and some inorganic acids such as sulfuric and phosphoric acids. For normal tissue function, the pH of the body needs to be held within a narrow range. The pH of arterial blood is normally maintained between about 7.38 and 7.42 by means of compensatory respiratory, renal, and buffering mechanisms.

The most important buffer system in the extracellular fluid is the bicarbonate-carbonic acid system. Bicarbonate and hydrogen ions are in equilibrium with carbonic acid which is in turn in equilibrium with carbon dioxide in the body fluid, as expressed by:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

A normal plasma-bicarbonate concentration in adults is in the range of 20 to 30 mmol/litre and arterial partial pressure of carbon dioxide (P_aCO_2) is normally 4.7 to 5.7 kPa (35 to 43 mmHg).

Ultimately, excess acid must be removed from the body and base regenerated. P_aCO_2 is under respiratory control with carbon dioxide being excreted by the lungs. Plasma-bicarbonate concentrations are regulated by the kidneys, where bicarbonate is actively regenerated or reabsorbed. Organic acids such as lactic acid may be eliminated by metabolism; and other non-volatile acids, such as the inorganic acids of phosphate and sulfate, are excreted via the kidneys with simultaneous regeneration of bicarbonate.

The relationship between plasma pH, P_aCO_2, and bicarbonate is defined by the Henderson-Hasselbalch equation which is used to assess acid–base balance.

For clinical purposes, this equation becomes

$$\mathrm{pH} = \mathrm{pK}_{CO_2} + \log\left(\frac{C_{HCO_3}}{\alpha \times P_aCO_2}\right)$$

where pH is the plasma pH, pK_{CO_2} is the carbonic acid dissociation constant (6.1), C_{HCO_3} is the plasma-bicarbonate concentration, α is a value representing carbon dioxide solubility, and P_aCO_2 is the arterial partial pressure of carbon dioxide. Disorders of acid–base balance may be due to a change in plasma-bicarbonate concentrations (metabolic) or to a change in P_aCO_2 (respiratory), although mixed disorders do occur.

The 4 major acid–base disturbances are:

- metabolic acidosis—a decrease in the plasma-bicarbonate concentration
- metabolic alkalosis—an increase in the plasma-bicarbonate concentration
- respiratory acidosis—hypoventilation and a raised P_aCO_2
- respiratory alkalosis—hyperventilation and a reduced P_aCO_2

A further measure that may provide useful information in the assessment of metabolic acidosis is the plasma anion gap. This is the difference in ionic charge between the principal plasma cation (sodium) and anions (chloride and bicarbonate), and provides an estimation of unmeasured serum anions, which include inorganic and organic acids.

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Metabolic acidosis. Metabolic acidosis, characterised by a low plasma-bicarbonate concentration and a tendency towards a fall in arterial pH, is the most frequent acid–base abnormality.

Metabolic acidosis with a *normal anion gap* is usually caused by excessive losses of bicarbonate from the gastrointestinal tract (as in severe diarrhoeas) or failure of the kidneys to reabsorb or regenerate adequate bicarbonate (as in the renal tubular acidoses). Ingestion of acidifying salts such as ammonium chloride, which generate hydrochloric acid, can also result in this type of acidosis. Metabolic acidosis characterised by an *increased anion gap* is often due to a reduction in the renal excretion of inorganic acids such as phosphates and sulfates as in renal failure (uraemic acidosis), or to the net accumulation of organic acids as, for example, in lactic acidosis or diabetic ketoacidosis.

Metabolic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH, and P_aCO_2. There is often hyperventilation with reduced cardiac function, constriction of peripheral veins, inhibition of the hepatic metabolism of lactate, and impairment of consciousness.

The main aim of **treatment** is to manage any underlying disorder,[1,2] and in some cases this will be sufficient to enable the body's homoeostatic mechanisms to correct the acid–base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over-alkalinisation, and in consequence such therapy tends to be reserved for more persistent or severe cases.

The usual alkalinising agent is sodium bicarbonate. It may be given orally to replace bicarbonate losses in various chronic metabolic acidoses such as uraemic acidosis or renal tubular acidosis. Potassium bicarbonate may be preferred if the acidosis is associated with potassium deficiency. Potassium citrate and sodium citrate have also been used. More severe and acute cases (particularly where arterial pH is below 7.1) may require intravenous sodium bicarbonate therapy. Intravenous sodium bicarbonate has a role in acute metabolic acidoses attributable to severe renal failure, severe secretory diarrhoeas, and renal tubular acidosis. Although hypertonic solutions have been used, for example, in patients with circulatory overload, roughly isotonic bicarbonate solutions are otherwise preferred; arterial pH and plasma bicarbonate should be raised a little at a time and the patient's response monitored.

Although the role of bicarbonate is accepted in the forms of metabolic acidosis mentioned, its use in the treatment of metabolic acidosis with concomitant tissue hypoxia, particularly lactic acidosis, is controversial.[1-4] The administration of bicarbonate generates carbon dioxide which, if not appropriately eliminated, due to poor tissue perfusion or impaired ventilation or both, diffuses rapidly into the cells exacerbating intracellular acidosis. In addition, in metabolic acidosis associated with organic acids such as lactic acid, there is a risk of over-alkalinisation due to the metabolism of the acid after correction of the arterial pH. For similar reasons, the use of sodium bicarbonate in advanced cardiac life support (p.1156) is no longer routine, although current guidelines permit consideration of its use to correct acidosis if the resuscitation effort is prolonged.

The role of bicarbonate in the management of diabetic ketoacidosis is also limited, although it may be appropriate in certain situations—see Diabetic Emergencies, p.435.

Because of concerns about the effects of bicarbonate, other agents have been investigated for the treatment of metabolic acidosis, including trometamol (THAM) and sodium dichloroacetate.[1-4] Alkalinising agents that have to be metabolised to bicarbonate before they have an effect, such as sodium lactate, are not generally used as many patients with acute acidosis have impaired metabolic activity, particularly of lactate.

Peritoneal dialysis, haemodialysis, or haemofiltration is required for refractory metabolic acidosis associated with acute renal failure (p.1672).

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Metabolic alkalosis. Metabolic alkalosis with an increased plasma-bicarbonate concentration and a sustained elevation in arterial pH results from excessive renal reabsorption and/or regeneration of bicarbonate. It is commonly seen with volume contraction (chloride depletion), potassium depletion, or mineralocorticoid excess, and may occur with excessive alkali intake as in the milk-alkali syndrome. If the metabolic alkalosis is severe, cardiac arrhythmias and hypoventilation may develop and there can be symptoms of concomitant hypokalaemia such as muscle weakness.

Treatment is generally aimed at the underlying disturbances.[1-3] Correcting volume depletion by giving a chloride salt often obviates the need for other treatment; sodium chloride is normally used. However, potassium chloride may also be required if there is potassium depletion, particularly if this is severe. Rarely, direct acidification with ammonium chloride, dilute hydrochloric acid, or acidifying salts such as lysine hydrochloride or arginine hydrochloride may be required if the alkalosis is severe.

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Calcium Homoeostasis

The adult body contains about 1.2 kg of calcium, of which about 99% is incorporated into the skeleton where its primary role is structural. The remaining 1% is found in body tissues and fluids and is essential for normal nerve conduction, muscle activity, and blood coagulation.

The concentration of calcium in plasma is normally kept within a narrow range (total calcium about 2.15 to 2.60 mmol/litre) by homoeostatic mechanisms involving parathyroid hormone, calcitonin, and vitamin D. Normally about 50% of calcium in plasma is in the ionised physiologically active form (giving a usual range of about 1.1 to 1.3 mmol/litre), about 10% is complexed with anions such as phosphate or citrate, and the remainder is bound to proteins, principally albumin. If the plasma-albumin concentration is raised (as in dehydration) or reduced (as is common in malignancy) it will affect the proportion of ionised calcium. Thus, the total plasma-calcium concentration is commonly adjusted for plasma albumin.

Hypercalcaemia. Hypercalcaemia, an increase in plasma-calcium concentration above the normal range, is most commonly due to primary hyperparathyroidism (p.1087) or malignant disease.[1-4] Less common causes of hypercalcaemia include vitamin D intoxication, granulomatous diseases such as sarcoidosis, familial benign hypercalcaemia, renal failure, thyrotoxicosis, and excess calcium carbonate ingestion (milk-alkali or calcium-alkali syndrome).[1-4]

Mild asymptomatic hypercalcaemia is often associated with a plasma-concentration elevated above the normal but below 3.00 mmol/litre. Severe symptomatic hypercalcaemia is broadly correlated with a plasma-calcium concentration of more than 3.50 mmol/litre.

Symptoms of hypercalcaemia include thirst, polyuria, anorexia, constipation, muscle weakness, fatigue, and confusion. In severe cases, there may be nausea and vomiting; cardiac arrhythmias may develop but are rare. Extreme hypercalcaemia may result in coma and death. Chronic hypercalcaemia can lead to interstitial nephritis and calcium renal calculi.[3]

Mild asymptomatic hypercalcaemia is best corrected by increasing oral fluid intake and treating any identified underlying disease. Patients with more severe hypercalcaemia, and/or significant symptoms, need prompt **treatment** to reduce plasma-calcium concentrations independent of the cause.[2,3]

The first step is rehydration with intravenous sodium chloride 0.9% to restore the intravascular volume and to promote renal excretion of calcium. Loop diuretics will enhance calcium excretion, but are usually only given to prevent fluid overload or heart failure.[1-4] Thiazide diuretics should be avoided[2] as they increase the renal tubular reabsorption of calcium. Peritoneal dialysis or haemodialysis with calcium-free dialysate should be considered[2,4,5] in patients with renal failure for whom urinary excretion of calcium is inadequate.

In life-threatening hypercalcaemia, more specific immediate therapy is generally required in addition to saline.[2,3] Most experience has been gained in the treatment of hypercalcaemia of malignancy (p.1083) using drugs that inhibit bone resorption, notably bisphosphonates.[1-5] Calcitonins have a rapid onset of action, but their effect is moderate and generally short-lived. Thus, they are seldom used alone, or as first-line agents; they may be given with bisphosphonates to rapidly lower serum calcium.[2,4] Plicamycin lowers serum calcium quickly but toxicity has limited its use.[2,3] Gallium nitrate is also effective when given continuously over several days; adverse effects such as nephrotoxicity are frequent and severe.[2,4] Corticosteroids are particularly effective for hypercalcaemia secondary to haematological malignancy, or associated with vitamin D toxicity, such as sarcoidosis.[1-5] They have been used to prolong the efficacy of calcitonin. Intravenous phosphates rapidly lower plasma-calcium concentrations but can cause soft tissue calcification (resulting in serious adverse effects such as irreversible renal damage and hypotension), and are best avoided.[2,3] Where intestinal calcium absorption is increased, dietary calcium and vitamin D intake should be restricted,[4,5] although some consider this unnecessary and ineffective.[1]

Choice of subsequent therapy is likely to depend on the specific cause.

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HYPERCALCAEMIA OF MALIGNANCY. About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive. Bisphosphonates are the preferred drugs for treating hypercalcaemia once the patient has been adequately rehydrated (see Hypercalcaemia of Malignancy, p.1083).

HYPERPARATHYROIDISM. Excess secretion of parathyroid hormone in primary hyperparathyroidism (p.1087) is characterised by hypercalcaemia, which is most frequently asymptomatic, and by hypophosphataemia. Oral phosphates and bisphosphonates have been used to control hypercalcaemia. However, in the long term, hypercalcaemia associated with primary hyperparathyroidism appears to be best managed by parathyroidectomy. Symptomatic hypocalcaemia may occur after surgery, requiring short-term treatment with calcium supplements and vitamin D.

VITAMIN D-MEDIATED HYPERCALCAEMIA. Hypercalcaemia can occur because of increased gastrointestinal absorption of calcium mediated by the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol). This may be a feature of diseases associated with increased vitamin D sensitivity or increased vitamin D production, or may occur due to overdose of vitamin D. For example, granulomatous diseases such as sarcoidosis (p.1512) are associated with unregulated production of 1,25-dihydroxycholecalciferol. Hypercalcaemia due to vitamin D is most commonly seen in patients with renal failure receiving vitamin D analogues such as ergocalciferol.

Treatment of severe hypercalcaemia requires prompt rehydration regardless of the cause (see Hypercalcaemia, above). Where hypercalcaemia is due to excessive doses of a vitamin D analogue, it should be discontinued until normocalcaemia is achieved. Corticosteroids effectively reduce gastrointestinal absorption of calcium, and these may be used intravenously as adjuncts to rehydration in severe hypercalcaemia, and orally for milder hypercalcaemia or longer term therapy. Oral sodium cellulose phosphate, which binds calcium in the gastrointestinal tract, and a low-calcium diet may also be considered. Oral chloroquine or hydroxychloroquine have been used in hypercalcaemia associated with sarcoidosis. Ketoconazole may be useful as an alternative to corticosteroids.

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Hypocalcaemia. Hypocalcaemia, a decrease in plasma-calcium concentration below the normal range, may be due to impaired or reduced absorption of calcium from the gastrointestinal tract, as with vitamin D deficiency disorders (see Osteomalacia and Rickets, p.1084) and chronic renal failure (see Renal Osteodystrophy, p.1086). Alternatively, it may be due to deficient parathyroid hormone secretion and/or action as in hypoparathyroidism (p.1087) and hypomagnesaemia (see below). Excessive phosphate administration is also a cause of hypocalcaemia (see Hyperphosphataemia, below). Rarely, hypocalcaemia may follow repeated infusions of citrate ions, for example, during transfusions utilising citrated blood, as the citrate complexes with the calcium ion. Respiratory alkalosis due to hyperventilation can also lead to depression of ionised plasma-calcium concentrations.

Where symptoms of hypocalcaemia occur, they are typically associated with increased neuromuscular excitability; paraesthesias can occur and in more severe cases, carpopedal spasm, muscle cramps, tetany, and convulsions may develop.[1-3] Other symptoms include ECG changes and mental disturbances such as irritability and depression. Prolonged hypocalcaemia can lead to dental defects, cataract formation, and in children can result in mental retardation.

In patients with hypocalcaemia due to an underlying disease, long-term management should be aimed at **treating** this disease. Vitamin D supplements are widely used to enhance calcium absorption and correct vitamin D deficiency disorders and hypoparathyroidism. Oral supplements of calcium salts are often also given. Acute hypocalcaemia or hypocalcaemic tetany require emergency treatment with intravenous calcium salts.

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Magnesium Homoeostasis

Magnesium is an essential body cation that is involved in numerous enzymatic reactions and physiological processes including energy transfer and storage, skeletal development, nerve conduction, and muscle contraction. Over half of the magnesium in the body is found in bone, about 40% is present in muscle and soft tissue, and only about 1% is present in the extracellular fluid. A normal concentration for magnesium in plasma is from about 0.7 to 1.0 mmol/litre.

Magnesium homoeostasis appears to be primarily regulated by the kidney where magnesium is extensively reabsorbed. Bone may act as a magnesium reservoir to reduce plasma-magnesium fluctuations. Magnesium is actively absorbed from the gastrointestinal tract and this is enhanced to some extent by 1,25-dihydroxycholecalciferol (calcitriol).

Hypermagnesaemia. Hypermagnesaemia is an increase in the plasma concentration of magnesium above the normal range, as may follow excessive parenteral doses of salts such as magnesium sulfate. Hypermagnesaemia due to oral intake is uncommon as the kidneys are able to excrete a relatively large magnesium load. However, it may occur in patients with impaired renal function taking large amounts of magnesium, for example, in antacids or laxatives.

Symptoms of hypermagnesaemia include nausea, vomiting, CNS and respiratory depression, hyporeflexia, muscle weakness, and cardiovascular effects including peripheral vasodilatation, hypotension, bradycardia, and cardiac arrest.

Treatment of mild hypermagnesaemia is usually limited to restricting magnesium intake. In severe hypermagnesaemia, ventilatory and circulatory support may be required. Slow intravenous injection of 10 to 20 mL of calcium gluconate 10% is recommended to reverse the effects on cardiovascular and respiratory systems. If renal function is normal, adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of furosemide. Haemodialysis using a magnesium-free dialysis solution effectively removes magnesium, and this may be necessary in patients with renal impairment, or for whom other methods prove ineffective.

Hypomagnesaemia. Hypomagnesaemia, a plasma-magnesium concentration below the normal range, may result from a reduced magnesium intake as in dietary deficiency or malabsorption syndromes. Alternatively, it may be due to excessive magnesium loss, either via the kidney because of inadequate reabsorption, or more often from the gut, for example during chronic diarrhoea. Drugs that may cause renal magnesium wasting include aminoglycosides, amphotericin B, ciclosporin, cisplatin (see Effects on Electrolytes, p.699), and diuretics.[1]

Hypomagnesaemia is closely associated with other electrolyte disturbances, especially hypocalcaemia (see above) and hypokalaemia (see below), and rarely occurs alone. Specific symptoms are therefore difficult to determine but may include anorexia, nausea, weakness, neuromuscular dysfunction such as tetany, tremor, and muscle fasciculations, and rarely seizures. Cardiac arrhythmias may occur, but the relative contribution of hypomagnesaemia and hypokalaemia to these is uncertain.

Magnesium salts can be given by mouth for the **treatment** of chronic or asymptomatic magnesium deficiency.[2,3] Parenteral therapy may be preferred in patients with poor gastrointestinal absorption of magnesium or who are unable to tolerate oral supplements (usually because they cause diarrhoea); magnesium sulfate can be given by intravenous or intramuscular injection. In acute symptomatic hypomagnesaemia, rapid replacement therapy with intravenous magnesium salts may be necessary. Renal function and plasma-magnesium concentrations should be monitored.

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Phosphate Homoeostasis

Phosphate is an essential bone mineral; about 80% of phosphorus in an adult body is incorporated into the skeleton as a calcium salt where it is required to give rigidity. The remainder is present in the soft tissues and is involved in several metabolic and enzymatic reactions including energy storage and transfer.

Phosphate exists in body fluids mainly as the divalent HPO_4^{2-} ion (about 80%) or monovalent $H_2PO_4^-$ ion (about 20%). Phosphate measurements are usually expressed as inorganic phosphorus to avoid confusion with the anion content. A normal range for phosphorus in plasma in adults is about 0.85 to 1.45 mmol/litre, but as only a small proportion of body phosphate is found in the extracellular fluid, plasma-phosphorus levels may not always reflect total body stores or predict replacement needs.

Phosphate concentrations in plasma are primarily regulated by renal excretion; parathyroid hormone reduces the renal tubular reabsorption of phosphate. Intestinal absorption of phosphate is enhanced by the vitamin D metabolite, 1,25-dihydroxycholecalciferol.

Hyperphosphataemia. Hyperphosphataemia, an abnormally raised plasma-phosphorus concentration, is usually associated with renal failure and may lead to renal osteodystrophy (p.1086). Hyperphosphataemia may also be a consequence of release of phosphate from cells; this can occur in conditions of cell breakdown such as haemolysis or rhabdomyolysis, during chemotherapy (when it may be part of the tumour lysis syndrome), or as a result of acidoses. Hypoparathyroidism may also lead to hyperphosphataemia due to decreased levels of parathyroid hormone (see Hypoparathyroidism, p.1087). Other causes include excessive phosphate doses during treatment of hypophosphataemia, overuse of phosphate enemas or oral phosphate bowel preparations, and excessive vitamin D intake.

Hyperphosphataemic symptoms include those of associated hypocalcaemia (see above). Complexation with calcium may lead to metastatic calcification.

The **treatment** of hyperphosphataemia[1,2] usually involves control of the relevant underlying condition, and the use of low-phosphate diets, and if necessary oral phosphate-binding agents, such as calcium acetate or carbonate or aluminium hydroxide. Sevelamer, a polymer capable of binding phosphate, may also be given.[2,3] Lanthanum carbonate has also been used.[2-4] Haemodialysis has been used to correct hyperphosphataemia in renal failure.[4]

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Hypophosphataemia. Hypophosphataemia, a reduction in plasma-phosphorus concentrations below the normal range, may be due to insufficient absorption of phosphate or increased renal clearance as in primary hyperparathyroidism, vitamin D deficiency, or X-linked familial hypophosphataemia. An increased cell uptake of phosphate can also result in hypophosphataemia, for example in chronic respiratory alkalosis and related disorders including alcoholism, hepatic failure, and septicaemia. As phosphate is widely available in foods, dietary deficiency is rare though it may occur in infants of low birth-weight fed exclusively on human breast milk (see Rickets of Prematurity, p.1684). The absorption of phosphate from the gastrointestinal tract can be reduced if phosphate-binding antacids are taken in large amounts.

Hypophosphataemia is usually asymptomatic but clinical symptoms become apparent when plasma-phosphorus concentrations fall below 0.3 mmol/litre.[1-4] Symptoms include neuromuscular dysfunction such as muscle weakness and paraesthesias, convulsions, cardiomyopathy, respiratory failure, and haematological abnormalities. Prolonged hypophosphataemia can result in rickets or osteomalacia (p.1084).

Treatment of hypophosphataemia primarily involves correction of any underlying disease.[4] Milk or oral phosphate supplements may be appropriate if a phosphate deficiency is identified or in certain disorders such as X-linked hypophosphataemic rickets. Intravenous phosphate may be required for severe hypophosphataemia (see p.1683), but this should be used cautiously to avoid hypocalcaemia and metastatic calcification.[2,3] Consideration should be given to correcting concomitant electrolyte disturbances such as hypomagnesaemia.

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Potassium Homoeostasis

Potassium is mainly an intracellular cation, primarily found in muscle; only about 2% is present in the extracellular fluid. It is essential for numerous metabolic and physiological processes including nerve conduction, muscle contraction, and acid–base regulation. A normal concentration of potassium in plasma is about 3.5 to 5.0 mmol/litre, but factors influencing transfer between intracellular and extracellular fluids such as acid–base disturbances can distort the relationship between plasma concentrations and total body stores. The body content of potassium is primarily regulated by renal glomerular filtration and tubular secretion. Aldosterone enhances the renal secretion of potassium and other factors such as sodium excretion, dietary potassium intake, and plasma pH can modulate the excretion of potassium by the kidney. Insulin, $beta_2$ agonists, and aldosterone, and increases in plasma pH, can promote the cellular uptake of potassium. The passage of potassium into the cells and retention against the concentration gradient requires active transport via the Na^+/K^+ ATPase enzyme.

Hyperkalaemia. Hyperkalaemia, an abnormally raised plasma-potassium concentration, can occur if the potassium intake is increased, if the renal excretion decreases (as in renal failure or adrenocortical insufficiency), or if there is a sudden efflux of potassium from intracellular stores, (as in acidosis, or cell destruction due to tissue trauma, burns, haemolysis, or rhabdomyolysis). Renal failure is the commonest cause of severe hyperkalaemia.[1] Hyperkalaemia may also be induced by drugs such as the potassium-sparing diuretics, ciclosporin, tacrolimus, NSAIDs, or ACE inhibitors.[2,3] Usually the renal mechanisms for potassium excretion adapt readily to an increased potassium load, and hyperkalaemia due to increased dietary intake is rare unless renal function is also impaired.

Hyperkalaemia mainly affects the heart, but skeletal muscle function may also be affected. Symptoms include ECG abnormalities, ventricular arrhythmias, cardiac arrest, and also neuromuscular dysfunction such as muscle weakness and paralysis.[3,4]

Treatment involves giving calcium to counteract the negative effects of hyperkalaemia on cardiac excitability, drugs such as insulin or sodium bicarbonate to promote the transfer of potassium from the extracellular to the intracellular fluid compartment, and enhancing potassium excretion with exchange resins or dialysis.[3,4] The methods used depend largely on the severity of the hyperkalaemia and critically, any associated ECG changes. Hyperkalaemia associated with a plasma concentration of potassium above 6.0 to 7.0 mmol/litre or with ECG changes is usually considered a medical emergency.

If effects on the heart are present, then first-line therapy should be with a calcium salt given intravenously; typically 10 to 20 mL of calcium gluconate 10% is given by slow intravenous injection, the dosage being titrated and adjusted based on ECG improvement.

Calcium will not, however, reduce the plasma-potassium concentration. In moderate to severe hyperkalaemia, insulin, together with glucose to prevent hypoglycaemia, is given intravenously in order to reduce the potassium concentration by stimulating the uptake of potassium by cells.[1,5] Insulin is given as a rapid-acting soluble insulin and typical doses are 5 to 10 units with 50 mL of glucose 50% given slowly over 5 to 15 minutes. Doses may need to be repeated as necessary. Alternatively or additionally, intravenous sodium bicarbonate may be used to correct acidosis and promote cellular uptake of potassium (but see Metabolic Acidosis above). Opinions vary on its value[5] and on the appropriate dose and concentration, but it may be indicated where there is severe associated acidosis (pH less than 7.2).[1]

The $beta_2$ agonist, salbutamol, given intravenously or by a nebuliser, has also been found to enhance the cellular uptake of potassium and reduce plasma-potassium concentrations.[3-6] However, its effect may be inconsistent,[6] and some clinicians prefer to avoid $beta_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7] Some consider that it should only ever be used in conjunction with insulin, as up to 40% of patients may not respond.[1]

After the plasma-potassium concentration has been reduced in the immediate term by enhancing cellular potassium uptake, treatments are often required that will remove excess potassium from the body over the longer term. Cation exchange resins such as calcium or sodium polystyrene sulfonate can be given orally or rectally and, after about 1 to 2 hours, will begin to remove potassium from the body, although the evidence to support their use is lacking.[5] Haemodialysis removes potassium from the body very effectively[5] and is particularly useful in patients with acute renal failure, hypervolaemia, hypernatraemia, or severe hyperkalaemia. Peritoneal dialysis is effective in some patients.

1. Ahee P, Crowe AV. The management of hyperkalaemia in the emergency department. *J Accid Emerg Med* 2000; **17:** 188–91.
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6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; **33:** 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; **352:** 135–40.

HYPERKALAEMIC PERIODIC PARALYSIS. Hyperkalaemic periodic paralysis is an inherited disorder in which sudden increases in plasma-potassium concentrations cause muscle paralysis, sometimes followed by myotonia. An acute attack may require intravenous calcium gluconate and insulin with glucose (see above). Inhalation of a $beta_2$ agonist such as salbutamol has been used to treat or abort attacks.[1,2] Diuretics such as acetazolamide or the thiazides are used prophylactically to reduce the frequency of attacks.[2,3]

1. Hanna MG, *et al.* Salbutamol treatment in a patient with hyperkalaemic periodic paralysis due to a mutation in the skeletal muscle sodium channel gene (SCN4A). *J Neurol Neurosurg Psychiatry* 1998; **65:** 248–50.
2. Bond EF. Channelopathies: potassium-related periodic paralyses and similar disorders. *AACN Clin Issues* 2000; **11:** 261–70.
3. Meola G, Sansone V. Therapy in myotonic disorders and in muscle channelopathies. *Neurol Sci* 2000; **21** (suppl): S953–61.

Hypokalaemia. Chronic hypokalaemia, a prolonged reduction of the plasma concentration of potassium, usually indicates a reduction in total body potassium. It may result from an inadequate intake, or gastrointestinal losses, for example in patients with secretory diarrhoeas, or from excessive renal losses as in hyperaldosteronism, Cushing's syndrome, or chronic metabolic alkalosis. Thiazides or loop diuretics increase urinary-potassium losses. Other drugs, notably corticosteroids and some antibacterials such as gentamicin, also have this effect. Hypokalaemia can also be caused by an increased cellular uptake of potassium rather than excess body losses. This may occur with drugs such as $beta_2$ agonists or xanthines, during insulin therapy, acute alkalosis, or possibly be induced by catecholamines after myocardial infarction. Hypokalaemia secondary to hypomagnesaemia (see above) can occur.

Hypokalaemia results in neuromuscular disturbances ranging from muscle weakness to paralysis and respiratory insufficiency and can also cause rhabdomyolysis, ECG abnormalities, and ileus. Chronic hypokalaemia may lead to renal tubular damage (hypokalaemic nephropathy). Hypokalaemia increases the risk of digoxin toxicity.

Treatment involves correcting any underlying disorder and replacement therapy with potassium salts. Oral potassium supplements are generally preferred but in severe hypokalaemia associated with cardiac arrhythmias, paralysis or diabetic ketoacidosis, parenteral therapy may be necessary. Potassium salts, usually potassium chloride, may be given by intravenous infusion but must be administered slowly to avoid causing hyperkalaemia and associated cardiac toxicity; plasma-potassium concentrations should be closely monitored and ECG monitoring may be required. The choice of salt for oral potassium replacement depends on co-existing acid–base and electrolyte disturbances. Potassium chloride is generally the drug of choice for the treatment of hypokalaemia in patients with metabolic alkalosis with hypochloraemia, whereas a salt such as the bicarbonate may be preferred in patients with hyperchloraemic acidosis as in some renal tubular acidoses. Hypokalaemia secondary to hypomagnesaemia requires magnesium replacement therapy.

References.

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2. Gennari FJ. Hypokalemia. *N Engl J Med* 1998; **339:** 451–8.
3. Cohn JN, *et al.* New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000; **160:** 2429–36.

BARTTER'S SYNDROME. Bartter's syndrome is a set of closely related disorders thought to result from inherited defects in ion transport in various sections of the renal tubule.[1,2] Patients exhibit hyperplasia of the juxtaglomerular cells, hypokalaemia and metabolic alkalosis, and excess aldosterone, prostaglandin, and renin production. Symptoms are primarily those of the hypokalaemia, including muscle weakness; polyuria and enuresis, and growth retardation in children, can occur. In contrast to other hyperreninaemic states, patients do not have hypertension or oedema.

Treatment rarely completely corrects hypokalaemia. Potassium supplementation may be given, while a cyclo-oxygenase inhibitor such as indometacin, or an ACE inhibitor such as captopril, can produce benefit.[2] Spironolactone and propranolol have also been tried and magnesium salts may be given if there is hypomagnesaemia.[2]

1. Guay-Woodford LM. Bartter syndrome: unraveling the pathophysiologic enigma. *Am J Med* 1998; **105:** 151–61.
2. Amirlak I, Dawson KP. Bartter syndrome: an overview. *Q J Med* 2000; **93:** 207–15.

DIURETIC-INDUCED HYPOKALAEMIA. Reduced potassium concentrations may result from the use of potassium-losing diuretics, particularly thiazides and loop diuretics. Clinically significant hypokalaemia is unlikely at the doses used in hypertension and the routine use of potassium supplements is no longer recommended. However, the concomitant use of a potassium-sparing diuretic such as amiloride or, less usually, a potassium supplement, may be necessary in patients at risk of hypokalaemia (see also Hydrochlorothiazide, Effects on Electrolyte Balance, p.1308).

HYPOKALAEMIC PERIODIC PARALYSIS. Hypokalaemic periodic paralysis is an inherited disorder in which episodes of hypokalaemia with muscle weakness or paralysis appear to be associated with a shift in potassium from the extracellular to the intracellular fluid. Acute attacks are treated with potassium, given orally or intravenously. Prophylaxis with acetazolamide has been found to reduce the frequency and severity of attacks.[1,2]

1. Ahlawat SK, Sachdev A. Hypokalaemic paralysis. *Postgrad Med J* 1999; **75:** 193–7.
2. Bond EF. Channelopathies: potassium-related periodic paralyses and similar disorders. *AACN Clin Issues* 2000; **11:** 261–70.

Sodium Homoeostasis

Sodium is the principal cation in the extracellular fluid and is responsible for the maintenance of the extracellular fluid volume and osmolality. In addition, sodium is also involved in nerve conduction, muscle contraction, acid–base balance, and cell nutrient uptake. A usual plasma concentration of sodium would be expected to be within 135 to 145 mmol/litre.

Sodium homoeostasis is complex and closely associated with fluid balance. The osmolality and volume of the extracellular fluid are tightly regulated. Small changes in osmolality (plasma-sodium concentrations) are corrected by alteration of extracellular volume. This balance of plasma osmolality is achieved by the secretion or suppression of antidiuretic hormone (ADH; vasopressin), which primarily controls water excretion by the kidney. A tendency towards hyponatraemia suppresses ADH secretion and promotes renal loss of water; an increase in ADH secretion increases water reabsorption by the renal distal tubules. Changes in extracellular volume will also affect ADH release independently of osmolality. In addition, changes in extracellular volume result in modulation of the renal excretion of sodium.

Total body sodium content is regulated by renal sodium excretion, which can vary widely depending on dietary intake. Various mechanisms are involved in controlling renal sodium excretion including the renin-angiotensin system, glomerular filtration rate, and natriuretic factors. A reduction in extracellular fluid volume leads to the production of angiotensin II which stimulates the secretion of aldosterone. Aldosterone promotes the reabsorption of sodium ions by the distal tubules. There may be significant effects on sodium homoeostasis if adrenal insufficiency or mineralocorticoid excess disturb this mechanism.

Hypernatraemia. Hypernatraemia is an abnormal rise in the plasma-sodium concentration with a simultaneous rise in plasma osmolality. It is generally associated with volume depletion when water intake is less than water losses through renal or extrarenal routes. The causes include impaired thirst, as in coma or essential hypernatraemia, osmotic diuresis (solute diuresis), as in diabetic ketoacidosis (see Diabetic Emergencies, p.435) or after drugs such as mannitol, and excessive water losses, either from the kidney, as in diabetes insipidus (p.2179), or extrarenally, for example because of excessive sweating or diarrhoea.

Hypernatraemia can also occur after excessive oral sodium intake (but this is uncommon) and after inappropriate use of intravenous sodium chloride.

The clinical manifestations of hypernatraemia are caused by the effect of increased plasma osmolality on the brain and include somnolence, confusion, respiratory paralysis, and coma. CNS symptoms are more severe when hypernatraemia develops rapidly. If there is volume depletion, other symptoms such as hypotension, tachycardia, and symptoms of circulatory insufficiency may occur as well. A high volume of dilute urine is seen in patients with abnormal renal water conservation, whereas a low volume of concentrated urine is expected in patients with impaired thirst or excessive extrarenal water loss.

Treatment of hypernatraemia usually requires water replacement, and drinking water may be sufficient for some patients. In more severe conditions, glucose 5% may be given by slow intravenous infusion. Alternatively, some recommend the use of sodium chloride 0.9% if volume depletion is severe. Care is required, as too rapid correction can induce cerebral oedema, particularly in chronic conditions.

If the total body sodium is too high, loop diuretics may be used to increase sodium excretion, with fluid losses being replaced by an infusion of glucose 5% and potassium chloride. It has also been suggested that dialysis may be necessary if there is significant renal impairment, if the patient is moribund, or if the serum-sodium concentration is greater than 200 mmol/litre.

References.

1. Adrogué HJ, Madias NE. Hypernatremia. *N Engl J Med* 2000; **342:** 1493–9.
2. Kang S-K, *et al.* Pathogenesis and treatment of hypernatremia. *Nephron* 2002; **92** (suppl): 14–17.
3. Reynolds RM, *et al.* Disorders of sodium balance. *BMJ* 2006; **332:** 702–5.

Hyponatraemia. Hyponatraemia, an abnormal fall in the plasma-sodium concentration, usually with a simultaneous fall in the plasma osmolality, is not uncommon, and may occur in diseases as diverse as heart failure, cirrhosis, adrenocortical insufficiency, hyperglycaemia, and AIDS.

The kidney is able to conserve sodium, and sodium depletion due to low salt intake is rare. Sodium depletion may occur if there are abnormal losses, either from the gut as a consequence of repeated diarrhoea and/or vomiting or from the kidney, for example, due to various renal disorders or the overuse of diuretics (see under Hydrochlorothiazide, Effects on Electrolyte Balance, p.1308).

The most common cause of hyponatraemia is dilution. This may result from excessive fluid intake, for example the ingestion of large volumes of water in patients with primary polydipsia (psychogenic polydipsia). More often, however, it is a result of reduced water excretion, as in renal impairment or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH—p.2182). Postoperative hyponatraemia is a frequent complication which can be exacerbated by the inappropriate intravenous use of hypotonic,[1] or even isotonic,[2] fluids.

Hyponatraemia due to sodium depletion in the presence of volume contraction may cause orthostatic hypotension and circulatory insufficiency. Dilutional hyponatraemia can be asymptomatic but headache, confusion, nausea, vomiting, somnolence, and weakness may occur. If severe, cerebral oedema may lead to respiratory arrest, convulsions, and coma. CNS symptoms are more common when the condition is acute.

Therapy is guided by the rate of development and degree of hyponatraemia, accompanying symptoms, and the state of water balance, and should also take into account the underlying cause. Mild asymptomatic hyponatraemia does not usually require specific therapy. Chronic mild to moderate sodium depletion, such as occurs in salt-losing bowel or renal disease, may be treated with oral sodium chloride supplements while ensuring adequate fluid intake.

When there is substantial volume depletion, volume replacement is necessary and intravenous sodium chloride 0.9% is often used.[3-5]

Chronic dilutional hyponatraemia, which is often asymptomatic, can generally be managed by correcting the underlying disease; water restriction may also be necessary and drugs that interfere with the action of ADH such as demeclocycline or lithium carbonate may be useful in SIADH.[3-6] Furosemide plus oral sodium chloride supplements have also been used.[7]

Acute symptomatic hyponatraemia (water intoxication) is generally associated with plasma-sodium concentrations below 120 mmol/litre and requires more aggressive therapy. This involves giving hypertonic or isotonic sodium chloride intravenously, often with a loop diuretic such as furosemide, especially if fluid overload is likely to be a problem.[4,6,7] The aim is to render the patient asymptomatic, with a plasma-sodium concentration of 120 to 130 mmol/litre; the plasma-sodium concentration should not be corrected to normal values nor should hypernatraemia be allowed to develop.[1,6,7] Plasma-sodium concentrations and the total body-water volume should be monitored throughout.

A rare neurological syndrome known as central pontine myelinolysis (osmotic demyelination) has been associated with the over-rapid correction of symptomatic hyponatraemia, particularly if the condition is well established. However, there is no consensus about the optimal administration of intravenous sodium chloride, and a number of regimens have been suggested. Generally, it has been recommended that the rate of correction of plasma-sodium should be 0.5 to 1 mmol/litre per hour, and not exceeding 2 mmol/litre per hour; maximum corrections have included 8 mmol/litre per 24 hours,[7] 12 mmol/litre per 24 hours or 18 mmol/litre over the first 48 hours,[6] and 20 mmol/litre in the first 48 hours.[1] Some[1,5] have given more specific recommendations depending on the severity of symptoms, suggesting that patients with severe symptoms, such as seizures, respiratory arrest, or neurogenic pulmonary oedema, require rapid correction in the first few hours, aiming for an initial increase in plasma-sodium of 2 to 4 mmol/litre, followed by a continuous infusion.

More recently, the vasopressin receptor antagonist conivaptan has become available for the management of euvolaemic and hypervolaemic hyponatraemia. It must be given intravenously, and other vasopressin receptor antagonists that are orally active are under investigation.[5,6]

1. Moritz ML, Ayus JC. Hospital-acquired hyponatremia—why are hypotonic parenteral fluids still being used? *Nat Clin Pract Nephrol* 2007; **3:** 374–82.
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3. Yeates KE, *et al.* Salt and water: a simple approach to hyponatremia. *CMAJ* 2004; **170:** 365–9.
4. Reynolds RM, *et al.* Disorders of sodium balance. *BMJ* 2006; **332:** 702–5.
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Dialysis Solutions

Soluciones para diálisis.

Pharmacopoeias. In *Eur.* (see p.vii), which includes separate monographs for solutions for haemodialysis, haemofiltration and haemodiafiltration, and peritoneal dialysis.

Dialysis and Haemofiltration

Dialysis and filtration solutions are solutions of electrolytes formulated in concentrations similar to those of extracellular fluid or plasma. They always contain sodium and chloride and bicarbonate or a bicarbonate precursor. In addition, they often contain calcium and magnesium, and rarely potassium. Glucose may be added as an osmotic agent. These solutions allow the removal of water and metabolites and the replacement of electrolytes.

In *haemodialysis*, the exchange of ions between the solution and the patient's blood is made across a semi-permeable membrane, primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by a pressure gradient. Membranes are either derived from cellulose (e.g. cuprophane) or are synthetic. Bicarbonate rather than a bicarbonate precursor is increasingly preferred as the bicarbonate source in haemodialysis since the problems of precipitation of calcium and magnesium have been overcome by changes in dialysis technique. Acetate is still used in some dialysers, but is thought to have vasodilator and cardiodepressant actions, and may not be converted to bicarbonate fast enough for high-flux haemodialysis or in patients with liver disease. Haemodialysis solutions are provided in a sterile concentrated form for dilution with water before use; this water need not be sterile.

In *peritoneal dialysis*, the exchange is made across the membranes of the peritoneal cavity primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by the use of osmotic agents such as glucose. The problems of calcium bicarbonate precipitation have not yet been overcome, and lactate is generally used as the bicarbonate precursor. Peritoneal dialysis solutions must be sterile and apyrogenic.

In *haemofiltration*, blood is filtered rather than dialysed. Metabolites are removed by convective transport, and excess water by hydrostatic ultrafiltration. Fluid and electrolytes are replaced by direct intravenous infusion. Most haemofiltration solutions use acetate or lactate as the bicarbonate source. Haemofiltration solutions must be sterile and apyrogenic.

Adverse Effects

Adverse effects occurring during *haemodialysis* include nausea, vomiting, hypotension, muscle cramps, and air embolus. Effects related to vascular access include infection, thrombosis, and haemorrhage. Adverse effects occurring during *haemofiltration* are similar to those for haemodialysis.

The most common adverse effects associated with *peritoneal dialysis* include peritonitis, hernias, hyperglycaemia, protein malnutrition, and catheter complications.

Long-term complications in dialysed patients, some of which may relate to renal failure itself, include haemodialysis-related amyloidosis, acquired cystic kidney disease, and accelerated atherosclerosis. Dialysis dementia is a special hazard of aluminium overload. Long-term peritoneal dialysis results in progressive structural changes to the peritoneal membrane ultimately resulting in dialysis failure.

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1. Himmelfarb J. Hemodialysis complications. *Am J Kidney Dis* 2005; **45:** 1122–31.

Aluminium overload. Accumulation of aluminium in patients on dialysis may result in dialysis dementia, anaemia, and aluminium-related bone disease (see also p.2254). Sources of aluminium include the water used for preparation of dialysis fluids and aluminium-containing phosphate binders used in treating renal osteodystrophy (p.1086). It is therefore important that water used for the preparation of dialysis fluids has a low aluminium concentration; Ph. Eur. 6.2 specifies a limit for aluminium of 10 micrograms/litre. Non-aluminium-containing phosphate binders such as calcium acetate or calcium carbonate may be preferred for long-term therapy. Aluminium overload in patients on dialysis has been treated with desferrioxamine (p.1441).

Copper toxicity. Liver and haematological toxicity has occurred as a result of absorption of copper from dialysis fluids (see Adverse Effects of Copper, p.1935).

Haemodialysis-induced cramp. Muscle cramps (see Muscle Spasms, p.1887) commonly occur during haemodialysis procedures and between sessions. Cramping usually affects the lower extremities, causing severe pain, and is a common reason for avoiding or stopping haemodialysis. The aetiology is not clear but possibly related to hypovolaemia, hypotension, changes in plasma osmolality, and hyponatraemia.[1]

Non-pharmacological measures to treat cramp during haemodialysis include the local application of moist heat and massage, and stretching the affected muscle. Hypotension should be corrected, by slowing or stopping ultrafiltration, and possibly giving isotonic or hypertonic sodium chloride infusion.[1] Adjustment of the dialysate sodium concentration during dialysis, or the use of a dialysate containing bicarbonate instead of one containing acetate, are other measures that may be used to reduce hypotension and cramp. Midodrine has also been recommended for the management of hypotension.[2] Hypertonic solutions of sodium chloride or glucose may be used to raise plasma osmolality; mannitol has also been used but may accumulate in the extracellular space.[1]

Quinine has been widely used for the prevention of haemodialysis-induced cramp, but it can cause serious adverse effects and such use has been discouraged.[1] Other treatments that have been tried as prophylaxis include carnitine, creatine, and vitamins C and E. However, information on these is limited and data on long-term efficacy and safety are lacking.[1] There is also limited evidence that a traditional herbal medicine, shao-yao-gan-cao-tang (shakuyaku-kanzo-to), comprising extracts of peony and liquorice roots, may be of benefit for both prevention and treatment of haemodialysis-induced cramp.[1]

1. Kobrin SM, Berns JS. Quinine—a tonic too bitter for hemodialysis-associated muscle cramps? *Semin Dial* 2007; **20:** 396–401.
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Hypersensitivity. For anaphylactic reactions associated with the use of ethylene oxide for the disinfection of dialysis equipment, see p.1643.

Infections. Patients undergoing haemodialysis are at risk of infections from microbial contamination of dialysis fluid, and from inadequate care of vascular access sites. Maximum microbial counts and limits for endotoxins have been specified for water used in dialysis fluids. Bicarbonate-based dialysis solutions are more susceptible to microbial growth than acetate-based solutions.

Peritonitis is common in patients receiving peritoneal dialysis. The risk of infection may be minimised by using disconnect systems, good aseptic technique, and by good care of catheters. Treatment of bacterial peritonitis requires intraperitoneal antibacterials, which are usually added to the dialysis fluid (see p.184).

Dialysis equipment should be regularly disinfected with agents such as formaldehyde (p.1645) or ethylene oxide (p.1643), but for mention of ethylene oxide anaphylactoid reactions, see p.1643.

Metabolic complications. The high concentrations of glucose in peritoneal dialysis solutions required to form an osmotic gradient can lead to weight gain, hyperglycaemia, hyperlipidaemia, and increased protein loss. Alternative osmotic agents such as icodextrin (p.1937) can be used, and amino acid-based solutions are also available.

References.

1. Burkart J. Metabolic consequences of peritoneal dialysis. *Semin Dial* 2004; **17:** 498–504.

Precautions

Peritoneal dialysis is not appropriate for patients with abdominal sepsis, previous abdominal surgery, or severe inflammatory bowel disease.

Haemodialysis should be used with caution in patients with unstable cardiovascular disease or active bleeding. During haemodialysis and haemofiltration, heparin (see Extracorporeal Circulation, p.1304) or epoprostenol (Uses, p.1280) are required to prevent clotting of the blood in the extracorporeal circuit.

Dialysis solutions should be warmed to body temperature with dry heat because wet heat carries a risk of microbial contamination.

Interactions

The effects of dialysis and filtration procedures on drug concentrations in the body can be complex. More drug may be removed by one dialysis technique than another. In general, drugs of low molecular weight, high water solubility, low volume of distribution, low protein binding, and high renal clearance are most extensively removed by dialysis. For example, aminoglycosides are extensively removed by dialysis procedures, and extra doses may be needed to replace losses. Specific drug dosage adjustments for dialysis procedures may be used where these are known. For drugs where the effect of dialysis is unknown, it is usual to give maintenance doses after dialysis. Dialysis has been used to remove some drugs in the treatment of overdosage and poisoning (see below).

Dialysis-induced changes in fluids and electrolytes have the potential to alter the effects of some drugs. For example, hypokalaemia predisposes to digoxin toxicity.

In patients undergoing peritoneal dialysis, drugs such as insulin and antibacterials may be added to the dialysis fluid. Consideration should be given to the possibility of adsorption of drugs onto the PVC bags.

◊ References.

1. Aronson JK. The principles of prescribing in renal failure. *Prescribers' J* 1992; **32:** 220–31.
2. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. *J Antimicrob Chemother* 1995; **36:** 773–80.
3. Aronoff GR, *et al.* *Drug prescribing in renal failure: dosing guidelines for adults*. 4th ed. Philadelphia: American College of Physicians, 1999.

Uses and Administration

Dialysis and filtration procedures are used in renal failure to correct electrolyte imbalance, correct fluid overload, and remove metabolites. They also have a limited role in the treatment of overdosage and poisoning. The two main techniques are haemodialysis and peritoneal dialysis; haemofiltration is used less frequently. The choice of technique will depend on the condition to be treated, the clinical state of the patient, patient preference, and availability.

Haemodialysis is more efficient than peritoneal dialysis at clearing small molecules such as urea, whereas peritoneal dialysis may be better at clearing larger molecules. Haemodialysis is considered to be less physiological as it alternates periods of high clearance with periods of no clearance.

Haemodialysis is usually performed intermittently (often 3 times a week); a typical session takes 3 to 5 hours. More recently high-flux dialysers have been developed which have reduced the time required for dialysis sessions.

Peritoneal dialysis may be performed continuously or intermittently. Continuous ambulatory peritoneal dialysis (CAPD) is the most commonly used technique. Patients remain mobile, except during exchanges, and can carry out the procedure themselves. There is always dialysis solution in the peritoneal cavity, and this is drained and replaced 3 to 5 times daily. Continuous cycle peritoneal dialysis (CCPD) is similar, except that exchanges are carried out automatically overnight, and patients do not have to carry out any exchanges during the day. Intermittent peritoneal dialysis (IPD) requires the patient to be connected to a dialysis machine for 12 to 24 hours 2 to 4 times a week. During this time, dialysis solution is pumped into and out of the peritoneal cavity, with a dwell time of about 10 to 20 minutes.

Haemofiltration is usually performed as a continuous technique and, as it is not portable, its principal use is in intensive care units. It may also be used intermittently as an adjunct to haemodialysis in patients with excess fluid weight gain. Continuous arteriovenous or venovenous haemodiafiltration (CAVHD or CVVHD) combines dialysis and filtration.

Assessing serum concentrations of urea or creatinine before the next dialysis session is not a good measure of the adequacy of the dialysis, so various other measures have been developed including the urea reduction ratio and urea kinetic modelling. The use of such measures is more established for haemodialysis than for peritoneal dialysis.

◊ References.

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15. Saxena R. Peritoneal dialysis: a viable renal replacement therapy option. *Am J Med Sci* 2005; **330:** 36–47. Correction. *ibid.*; 110.
16. Ikizler TA, Schulman G. Hemodialysis: techniques and prescription. *Am J Kidney Dis* 2005; **46:** 976–81.

Acute renal failure. Acute renal failure is characterised by a rapid decline in kidney function, and has a variety of causes.[1-7] It is often classified by origin as *prerenal* (e.g. due to hypovolaemia such as that associated with shock, burns, or dehydration; congestive heart failure; or renal artery obstruction), *renal* (such as acute tubular necrosis or interstitial nephritis of various causes, including nephrotoxic drugs and infections), or *postrenal* (acute urinary tract obstruction). The prognosis depends on the underlying disease, which should be identified and treated if possible, but the mortality may still be as high as 60%, particularly after surgery or trauma and in patients who become oliguric. Management is essentially supportive in the hope that renal function will recover. Complications of acute renal failure include extracellular volume overload and hyponatraemia, hyperkalaemia, metabolic acidosis, hyperphosphataemia and hypocalcaemia. Those complications requiring urgent treatment, often including the use of dialysis, are severe hyperkalaemia (p.1669), pulmonary oedema, pericarditis, and severe metabolic acidosis (p.1667). The use of dialysis before clinical signs of uraemia is a matter of debate since it does not appear to hasten recovery *per se*,[1] but all save the shortest episodes of acute renal failure will require some form of renal replacement therapy with dialysis or filtration. Intermittent haemodialysis and peritoneal dialysis are both used, but the newer haemofiltration techniques have theoretical advantages in terms of volume control and cardiovascular stability, and are increasingly preferred.[2,8,9]

Numerous drugs have been tried in attempts to attenuate renal injury or hasten recovery in patients with acute tubular necrosis due to ischaemia or nephrotoxins.[1,5,10,11] These include drugs to increase renal blood flow (e.g. low-dose dopamine, atrial natriuretic peptide, or prostaglandins), drugs to increase urine flow and protect the epithelial cells (mannitol and loop diuretics, calcium-channel blockers), or the use of chelating agents or antidotes against specific nephrotoxins. Consistent clinical benefit has not, however, been shown.

Acute renal failure is reversible in about 95% of patients who survive the complications. A few patients who survive acute renal failure will require long-term dialysis or kidney transplantation (p.1813).

1. Brady HR, Singer GG. Acute renal failure. *Lancet* 1995; **346:** 1533–40.
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7. Lameire N, *et al.* Acute renal failure. *Lancet* 2005; **365:** 417–30.
8. McCarthy JT. Renal replacement therapy in acute renal failure. *Curr Opin Nephrol Hypertens* 1996; **5:** 480–4.
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10. Albright RC. Acute renal failure: a practical update. *Mayo Clin Proc* 2001; **76:** 67–74.
11. Pruchnicki MC, Dasta JF. Acute renal failure in hospitalized patients: part II. *Ann Pharmacother* 2002; **36:** 1430–42.

Chronic renal failure. Chronic renal failure is the irreversible, usually progressive, loss of renal function that eventually results in end-stage renal disease (ESRD) and the need for renal replacement therapy (dialysis or renal transplantation). The rate of decline in renal function is generally constant for each patient and is usually monitored by measuring serum-creatinine concentrations as an indirect index of the glomerular filtration rate (GFR). In its early stages when the patient is asymptomatic, progressive loss of renal function is described as diminished renal reserve or chronic renal insufficiency. When the limits of renal reserve have been exceeded and symptoms become apparent, it is termed chronic renal failure or overt renal failure. When renal function is diminished to such an extent that life is no longer sustainable (GFR less than 5 mL/minute), the condition is termed ESRD or uraemia. Many diseases can lead to ESRD, the most common being diabetes (p.433), glomerulonephritis (p.1504), and hypertension (p.1171).

The management of patients with chronic renal failure prior to ESRD involves measures to conserve renal function and compensate for renal insufficiency. Methods to slow the progression of renal failure include the treatment of hypertension (p.1171), reduction of proteinuria, and the reduction of hyperlipidaemia (p.1169). ACE inhibitors (p.1199) or angiotensin II receptor antagonists (see Losartan, p.1328) are used for the reduction of proteinuria and the control of hypertension. Dietary protein restriction (see Renal Failure, p.1923) has also been used for control of proteinuria, but conclusive evidence for a renal protective effect is lacking. Anaemia (p.1063), hyperphosphataemia (p.1669), secondary hyperparathyroidism (p.1087), and renal osteodystrophy (p.1086) often require active treatment. Nephrotoxic drugs, including NSAIDs, should be avoided.

The choice between haemodialysis, peritoneal dialysis, and organ transplantation is considered, and the patient prepared, before it is actually required. In patients for whom transplantation is the preferred option, dialysis may still be required while waiting for a kidney. Kidney transplantation is discussed on p.1813. There are differences between countries in the choice of dialysis technique for patients with ESRD. For example, in-centre haemodialysis is used in about 80% of patients in the USA, whereas CAPD is used in over 50% of patients in the UK. Overall survival appears to be similar between the 2 techniques, but more patients on CAPD will eventually require a change to another dialysis method because of treatment failure.

Unlike renal transplant patients, dialysis patients still require replacement therapy with hormones that are usually produced by the kidney. Thus, recombinant erythropoietin and hydroxylated vitamin D analogues are commonly given.

References.

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3. Steinman TI. Kidney protection: how to prevent or delay chronic renal failure. *Geriatrics* 1996; **51:** 28–35.
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11. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005; **365:** 331–40.

Electrolyte disturbances. Haemodialysis with magnesium-free dialysis solution has been used to remove magnesium from the body in severe hypermagnesaemia (p.1668). Similarly, haemodialysis, and sometimes peritoneal dialysis, has been used in treating hypercalcaemia (p.1668), hyperkalaemia (p.1669), hypernatraemia (p.1670), and hyperphosphataemia (p.1669).

Overdosage and poisoning. Haemodialysis, or less often peritoneal dialysis, can be used to remove some substances from the body after overdosage or poisoning. Substances most readily removed have a low molecular weight, low volume of distribution, low protein binding, high water solubility, and high renal clearance. Examples of agents for which haemodialysis may have a role in the treatment of severe overdosage include alcohol (p.1626), ethylene glycol (p.2300), methyl alcohol (p.2024), lithium (p.403), and salicylates such as aspirin (p.20). Dialysis may be particularly important when poisoning with these agents is complicated by renal failure.

Preparations

Ph. Eur.: Solutions for Haemodialysis; Solutions for Haemofiltration and for Haemodiafiltration; Solutions for Peritoneal Dialysis.

Proprietary Preparations: some preparations are listed in Part 3.

Oral Rehydration Solutions

Soluciones de rehidratación oral.

Oral rehydration solutions have 4 main constituents:

- electrolytes—typically sodium chloride and potassium chloride
- a bicarbonate source to correct or prevent metabolic acidosis, such as sodium bicarbonate or sodium citrate
- water to replace fluid losses
- a carbohydrate source to maximise absorption of fluid and electrolytes—typically glucose, although cereal-based formulations may also be used.

They are most commonly available as oral powders (oral rehydration salts) that are reconstituted with water before use, but effervescent tablets and ready-to-use oral solutions are also available.

Adverse Effects

Vomiting can occur after taking oral rehydration solution, and may be an indication that it was given too quickly. If vomiting occurs, administration should be halted for 10 minutes then resumed in smaller, more frequent, amounts.

The risk of hypernatraemia or overhydration with oral rehydration solutions is low in patients with normal renal function. Overdosage of oral rehydration solutions in patients with renal impairment may lead to hypernatraemia and hyperkalaemia.

Precautions

Oral rehydration salts or effervescent tablets should be reconstituted only with water and at the volume stated. Fresh drinking water is generally appropriate, but freshly boiled and cooled water is preferred when the solution is for infants or when drinking water is not available. The solution should not be boiled after it is prepared. Other ingredients such as sugar should not be added. Unused solution should be stored in a refrigerator and discarded within 24 hours of preparation.

Oral rehydration solutions are not appropriate for patients with gastrointestinal obstruction, oliguric or anuric renal failure, or when parenteral rehydration therapy is indicated as in severe dehydration or intractable vomiting.

Uses and Administration

Oral rehydration solutions are used for oral replacement of electrolytes and fluids in patients with dehydration, particularly that associated with acute diarrhoea of various aetiologies (p.1694).

The dosage of oral rehydration solutions should be tailored to the individual based on body-weight and the stage and severity of the condition. The initial aim of treatment is to rehydrate the patient, and, subsequently, to maintain hydration by replacing any further losses due to continuing diarrhoea and vomiting and normal losses from respiration, sweating, and urination. Initial rehydration should be rapid, over 3 to 4 hours, unless the patient is hypernatraemic, in which case rehydration over 12 hours is appropriate.

For adults, a usual dose of 200 to 400 mL of oral rehydration solution for every loose motion has been suggested. The dosage for children is 200 mL for every loose motion, and for infants is 1 to 1.5 times their usual feed volume. Normal feeding can continue after the initial fluid deficit has been corrected. Breast feeding should continue between administrations of oral rehydration solution.

Sodium content and osmolarity. The original standard WHO oral rehydration solution contained 90 mmol/litre of sodium and 111 mmol/litre of glucose.[1-3] While it has been used safely and effectively,[4] it does not reduce the volume or duration of diarrhoea,[3] and solutions with reduced sodium content and osmolarity have been suggested to be more effective.[1,2] WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced osmolarity.[4] However, there have been concerns that the reduced sodium content of this formulation may increase the risk of hyponatraemia in patients with cholera,[3,5,6] and especially in adults.[4] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[4] Solutions containing less sodium have been recommended in more developed countries: 60 mmol/litre in Europe,[7] and 45 to 90 mmol/litre in the USA.[8]

For discussion of modified formulations of oral rehydration solutions in the treatment of diarrhoea, including the use of cereal-based and low osmolarity preparations, see oral rehydration therapy under Diarrhoea, p.1694.

1. Hahn S, *et al.* Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/06/05).
2. CHOICE Study Group. Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration salts solution in children with acute watery diarrhea. *Pediatrics* 2001; **107:** 613–18.
3. Fuchs GJ. A better oral rehydration solution? An important step, but not a leap forward. *BMJ* 2001; **323:** 59–60.
4. Anonymous. New oral rehydration solution adopted by WHO and UNICEF. *WHO Drug Inf* 2004; **18:** 138–40.
5. Hirschhorn N, *et al.* Formulation of oral rehydration solution. *Lancet* 2002; **360:** 340–1.
6. Cash R, *et al.* Oral rehydration and hyponatraemia. *Lancet* 1999; **354:** 1733–4.
7. Booth I, *et al.* Recommendations for composition of oral rehydration solutions for the children of Europe: report of an ESPGAN working group. *J Pediatr Gastroenterol Nutr* 1992; **14:** 113–15.
8. King CK, *et al.* Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR* 2003; **52** (RR-16): 1–16. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm (accessed 06/02/06)

Oral versus intravenous rehydration. Although intravenous rehydration is advised for patients with the most severe dehydration (see Diarrhoea, p.1694) it is also widely used in some countries in the management of less severe degrees of fluid loss.[1,2] However, a meta-analysis of 16 randomised controlled studies in children with gastroenteritis (5 of which included children with severe dehydration) found that oral or nasogastric rehydration with an appropriate rehydration solution was at least as effective as intravenous rehydration in terms of weight gain and intestinal losses, and was associated with a lower incidence of adverse effects and a reduced length of hospital stay.[3] The authors concluded that there was no evidence to support the ongoing use of intravenous rehydration in most cases of childhood gastroenteritis.

1. Elliott EJ, *et al.* Pre-admission management of acute gastroenteritis. *J Paediatr Child Health* 1996; **32:** 18–21.
2. Ford-Jones EL, *et al.* Hospitalization for community-acquired, rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. *Arch Pediatr Adolesc Med* 2000; **154:** 578–85.
3. Fonseca BK, *et al.* Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med* 2004; **158:** 483–90.

Preparations

BP 2008: Oral Rehydration Salts;
USP 31: Oral Rehydration Salts;
WHO/UNICEF: Oral Rehydration Salts.

Proprietary Preparations: some preparations are listed in Part 3.

Bicarbonate

Bicarbonato.

Description. Bicarbonate is an alkalinising agent given as bicarbonate-containing salts (sodium or potassium bicarbonate) or bicarbonate-producing salts (acetate, citrate, or lactate salts). Allowance should be made for the effect of the cation.

Incompatibility. Bicarbonate-producing or bicarbonate-containing solutions have been reported to be incompatible with a wide range of drugs. In many cases this incompatibility is a function of the alkaline nature of the bicarbonate solution. Precipitation of insoluble carbonates may occur, as may production of gaseous carbon dioxide when the bicarbonate ion is reduced by acidic solutions.

Potassium Bicarbonate

E501; Hydrogenuhličitan draselný; Kalii Hydrocarbonas; Kalii Hydrogenocarbobnas; Kalii hydrogenocarbonas; Kalio-vandenilio karbonatas; Kálium-hidrogén-karbonát; Kaliumvätekarbonat; Kaliumvetykarbonaatti; Monopotassium Carbonate; Potasio, bicarbonato de; Potassium, bicarbonate de; Potassium Hydrogen Carbonate; Potasu wodorowęglan; Potasyum Bikarbonat.

$KHCO_3$ = 100.1.
CAS — 298-14-6.
ATC — A12BA04.
ATC Vet — QA12BA04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Potassium Hydrogen Carbonate; Potassium Bicarbonate BP 2008). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. When heated in the dry state or in solution, it is gradually converted to potassium carbonate. A freshly prepared 5% solution in water has a pH of not more than 8.6.

USP 31 (Potassium Bicarbonate). Colourless, odourless, transparent monoclinic prisms or white granular powder. Freely soluble in water; practically insoluble in alcohol. Its solutions are neutral or alkaline to phenolphthalein.

Equivalence. Each g of potassium bicarbonate represents about 10 mmol of potassium and of bicarbonate. Potassium bicarbonate 2.56 g is equivalent to about 1 g of potassium.

Potassium Citrate

Citronan draselný monohydrát; E332; Kalii citras; Kalii Citras Monohydricus; Kalio citratas; Kaliumcitrat; Kaliumsitraatti; Potasio, citrato de; Potassium, citrate de; Potasu cytrynian; Potasyum Sitrat; Trikálium-citrát; Tripotassium Citrate. Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate monohydrate.

$C_6H_5K_3O_7,H_2O$ = 324.4.
CAS — 866-84-2 (anhydrous potassium citrate); 6100-05-6 (potassium citrate monohydrate).
ATC — A12BA02.
ATC Vet — QA12BA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Potassium Citrate). Transparent, hygroscopic crystals or a white or almost white granular powder. Very soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 31 (Potassium Citrate). Transparent crystals or a white granular powder. It is odourless and is deliquescent in moist air. Soluble 1 in 1 of water and 1 in 2.5 of glycerol; almost insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of potassium citrate (anhydrous) represents about 9.8 mmol of potassium and 3.26 mmol of citrate. Each g of potassium citrate (monohydrate) represents about 9.3 mmol of potassium and 3.08 mmol of citrate. Potassium citrate (monohydrate) 2.77 g is equivalent to about 1 g of potassium.

Sodium Acetate

E262; Natrii Acetas; Natrii acetas trihydricus; Natrio acetatas trihidratas; Natrium Aceticum; Nátrium-acetát; Natriumacetat trihydrat; Natriumasetaattitrihydraatti; Octan sodný trihydrát; Sodio, acetato de; Sodium (acétate de) trihydraté; Sodu octan.

$CH_3.CO_2Na,3H_2O$ = 136.1.
CAS — 127-09-3 (anhydrous sodium acetate); 6131-90-4 (sodium acetate trihydrate).
ATC — B05XA08.
ATC Vet — QB05XA08.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*
US also allows the anhydrous form.

Ph. Eur. 6.2 (Sodium Acetate Trihydrate). Colourless crystals. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Store in airtight containers.

USP 31 (Sodium Acetate). It contains three molecules of water of hydration or is anhydrous. Colourless, transparent crystals, or a white, granular crystalline powder, or white flakes. It is odourless or has a faint acetous odour. It is efflorescent in warm dry air. Soluble 1 in 0.8 of water, 1 in 0.6 of boiling water, and 1 in 19 of alcohol. pH of a solution in water containing the equivalent of 3% of anhydrous sodium acetate is between 7.5 and 9.2. Store in airtight containers.

Equivalence. Each g of sodium acetate (anhydrous) represents about 12.2 mmol of sodium and of acetate. Each g of sodium acetate (trihydrate) represents about 7.3 mmol of sodium and of acetate. Sodium acetate (anhydrous) 3.57 g is equivalent to about 1 g of sodium. Sodium acetate (trihydrate) 5.92 g is equivalent to about 1 g of sodium.

Sodium Acid Citrate

Disodium Hydrogen Citrate; Disodu wodorocytrynian; E331; Natrium Citricum Acidum; Sodio, citrato ácido de.

$C_6H_6Na_2O_7,1\frac{1}{2}H_2O$ = 263.1.
CAS — 144-33-2.

Pharmacopoeias. In *Br.*

BP 2008 (Sodium Acid Citrate). A white, odourless or almost odourless, powder. Freely soluble in water; practically insoluble in alcohol. A 3% solution in water has a pH of 4.9 to 5.2.
The BP gives Disodium Hydrogen Citrate as an approved synonym.

Equivalence. Each g of sodium acid citrate (sesquihydrate) represents about 7.6 mmol of sodium and 3.8 mmol of citrate. Sodium acid citrate (sesquihydrate) 5.72 g is equivalent to about 1 g of sodium.

Sodium Bicarbonate

Baking Soda; E500; Hydrogenuhličitan sodný; Monosodium Carbonate; Natrii Bicarbonas; Natrii hydrogenocarbonas; Natrio-vandenilio karbonatas; Nátrium-hidrogén-karbonát; Natriumvätekarbonat; Natriumvetykarbonaatti; Sal de Vichy; Sodio, hidrogenocarbonato de; Sodium Acid Carbonate; Sodium, bicarbonate de; Sodium Hydrogen Carbonate; Sodu wodorowęglan; Sodyum Bikarbonat.

$NaHCO_3$ = 84.01.
CAS — 144-55-8.
ATC — B05CB04; B05XA02.
ATC Vet — QB05CB04; QB05XA02; QG04BQ01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Sodium Hydrogen Carbonate; Sodium Bicarbonate BP 2008). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. The pH of a freshly prepared 5% solution in water is not more than 8.6. When heated in the dry state or in solution, it gradually changes into sodium carbonate.

USP 31 (Sodium Bicarbonate). A white crystalline powder that slowly decomposes in moist air. Soluble 1 in 12 of water; insoluble in alcohol. Its solutions, when freshly prepared with cold water, without shaking, are alkaline to litmus; alkalinity increases on standing, agitation, or heating.

Equivalence. Each g of sodium bicarbonate (anhydrous) represents about 11.9 mmol of sodium and of bicarbonate. Sodium bicarbonate 3.65 g is equivalent to about 1 g of sodium.

Sodium Citrate

Citronan sodný dihydrát; E331; Natrii citras; Natrii Citras Dihydricus; Natrio citratas; Natriumcitrat; Natriumsitraatti; Sodio, citrato de; Sodium, citrate de; Sodu cytrynian; Sodyum Sitrat; Trinátrium-citrát; Trisodium Citrate. Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

$C_6H_5Na_3O_7,2H_2O$ = 294.1.
CAS — 68-04-2 (anhydrous sodium citrate); 6132-04-3 (sodium citrate dihydrate).
ATC — B05CB02.
ATC Vet — QB05CB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *Viet.*
Int. and *US* specify anhydrous or dihydrate.

Ph. Eur. 6.2 (Sodium Citrate). A white or almost white, crystalline powder or white or almost white, granular crystals; slightly deliquescent in moist air. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 31 (Sodium Citrate). It is anhydrous or contains two molecules of water of hydration. Colourless crystals, or a white crystalline powder. The hydrous form is soluble 1 in 1.5 of water and 1 in 0.6 of boiling water; insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of sodium citrate (anhydrous) represents about 11.6 mmol of sodium and 3.9 mmol of citrate. Each g of sodium citrate (dihydrate) represents about 10.2 mmol of sodium and 3.4 mmol of citrate. Sodium citrate (anhydrous) 3.74 g is equivalent to about 1 g of sodium. Sodium citrate (dihydrate) 4.26 g is equivalent to about 1 g of sodium.

Storage. Sterilised solutions when stored may cause separation of particles from glass containers and solutions containing such particles must not be used.

Sodium Lactate

E325; Lactato de sodio; Natrii lactatis; Natriumlaktaatti; Natriumlaktat; Sodium, lactate de. Sodium 2-hydroxypropionate.

$C_3H_5NaO_3$ = 112.1.
CAS — 72-17-3.

Pharmacopoeias. *Chin., Eur.* (see p.vii), and *US* include preparations of sodium lactate.

Ph. Eur. 6.2 (Sodium Lactate Solution). It contains a minimum of 50% w/w of sodium lactate and is a mixture of the two enantiomers in about equal proportions. Sodium (*S*)-Lactate Solution contains a minimum of 50% w/w of sodium lactate, not less than 95% of which is the (*S*)-enantiomer. The solutions are clear, colourless, slightly syrupy liquids. Miscible with water and with alcohol. pH 6.5 to 9.0.

USP 31 (Sodium Lactate Solution). It is an aqueous solution containing at least 50% sodium lactate. A clear, colourless or practically colourless, slightly viscous liquid, odourless or having a slight, not unpleasant, odour. Miscible with water. pH between 5.0 and 9.0. Store in airtight containers.

Equivalence. Each g of sodium lactate (anhydrous) represents about 8.9 mmol of sodium and of lactate. Sodium lactate (anhydrous) 4.88 g is equivalent to about 1 g of sodium.

Adverse Effects and Treatment

Excessive use of bicarbonate or bicarbonate-forming compounds may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop, especially in hypocalcaemic patients. Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium ions may be of particular importance.

Excessive doses of *sodium salts* may also lead to sodium overloading and hyperosmolality (see Adverse Effects of Sodium, p.1686). Sodium bicarbonate given orally can cause stomach cramps, belching, and flatulence. Extravasation of irritant hypertonic sodium bicarbonate solutions resulting in local tissue necrosis has been reported after intravenous dosage.

Excessive doses of *potassium salts* may lead to hyperkalaemia (see Adverse Effects of Potassium, p.1684). Ingestion of potassium salts can cause gastrointestinal adverse effects, and tablet formulations may cause contact irritation due to high local concentrations of potassium.

Excessive oral doses of *citrate salts* may have a laxative effect.

Effects on the gastrointestinal tract. In addition to minor gastrointestinal effects (see above), spontaneous rupture of the stomach, although an exceedingly rare event, has been reported on several occasions after ingestion of sodium bicarbonate. The bicarbonate was believed to have resulted in the rapid production of enough carbon dioxide to rupture a stomach already distended with food, liquid, or air.[1,2]

1. Mastrangelo MR, Moore EW. Spontaneous rupture of the stomach in a healthy adult man after sodium bicarbonate ingestion. *Ann Intern Med* 1984; **101:** 649.
2. Lazebnik N, *et al.* Spontaneous rupture of the normal stomach after sodium bicarbonate ingestion. *J Clin Gastroenterol* 1986; **8:** 454–6.

Effects on mental state. Sodium lactate infusions have been reported to induce panic attacks, especially in patients with anxiety states, and have been used as a pharmacological model in the evaluation of mechanisms involved in panic disorder.[1] However, the mechanism that underlies panic attacks induced by lactate remains unknown,[1] and it has been suggested[2] that rapid administration of the large sodium load may be involved. There has also been a report[3] of a patient receiving oral lactate (as calcium lactate) who was suffering from panic disorder associated with agoraphobia; when lactate was discontinued, the patient reported a reduction in panic intensity without a decrease in the frequency of attacks.

1. Bourin M, *et al.* Provocative agents in panic disorder. *Therapie* 1995; **50:** 301–6.
2. Peskind ER, *et al.* Sodium lactate and hypertonic sodium chloride induce equivalent panic incidence, panic symptoms, and hypernatremia in panic disorder. *Biol Psychiatry* 1998; **44:** 1007–16.
3. Robinson D, *et al.* Possible oral lactate exacerbation of panic disorder. *Ann Pharmacother* 1995; **29:** 539–40.

Epileptogenic effect. Alkalosis may precipitate seizures; however, absence seizures have also been reported to be associated with sodium bicarbonate administration in a child in whom the serum pH was normal.[1]

1. Reif S, *et al*. Absence seizures associated with bicarbonate therapy and normal serum pH. *JAMA* 1989; **262:** 1328–9.

Precautions

Bicarbonate or bicarbonate-forming compounds should not generally be given to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid–base status is essential.

Sodium-containing salts should be given extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism (see Sodium, p.1686).

Potassium-containing salts should be given with considerable care to patients with renal or adrenocortical insufficiency, cardiac disease, or other conditions that may predispose to hyperkalaemia (see Potassium, p.1685).

Abuse. High doses of bicarbonate have been taken by athletes to enhance performance in endurance sports by buffering hydrogen ions produced in conjunction with lactic acid.[1] Bicarbonates have also been used to alkalinise the urine and prolong the half-life of basic drugs, notably sympathomimetics and stimulants, thereby avoiding detection; however, such a practice may enhance toxicity.

1. Kennedy M. Drugs and athletes—an update. *Adverse Drug React Bull* 1994; (Dec): 639–42.

Interactions

The effect of oral bicarbonate or bicarbonate-forming compounds in raising intra-gastric pH may reduce or increase the rate and/or extent of absorption of a number of drugs (see also Antacids, p.1692). Alkalinisation of the urine leads to increased renal clearance of acidic drugs such as salicylates, tetracyclines, and barbiturates. Conversely, it prolongs the half-life of basic drugs and may result in toxicity (see also under Abuse, above).

Sodium bicarbonate enhances lithium excretion. The use of *potassium-containing salts* with drugs that increase serum-potassium concentrations such as ACE inhibitors and potassium-sparing diuretics should generally be avoided (p.1685). *Citrate salts* taken orally can enhance the absorption of aluminium from the gastrointestinal tract (see Toxicity, p.1706 under Adverse Effects of Aluminium Hydroxide). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations, including many effervescent or dispersible tablets, are best avoided by patients with renal failure taking aluminium-containing compounds.

Pharmacokinetics

Oral bicarbonate, such as sodium bicarbonate, neutralises gastric acid with the production of carbon dioxide. Bicarbonate not involved in that reaction is absorbed and in the absence of a deficit of bicarbonate in the plasma, bicarbonate ions are excreted in the urine, which is rendered alkaline, and there is an accompanying diuresis.

Acetates such as potassium acetate and sodium acetate, citrates such as potassium citrate, sodium acid citrate, and sodium citrate, and lactates such as sodium lactate are metabolised, after absorption, to bicarbonate.

Uses and Administration

Bicarbonate-providing salts are alkalinising agents used for a variety of purposes including the correction of metabolic acidosis, alkalinisation of the urine, and as antacids.

When an alkalinising agent is indicated for treating acute or chronic **metabolic acidosis** (p.1667), sodium bicarbonate is usually used. In conditions when acute metabolic acidosis is associated with tissue hypoxia, such as *cardiac arrest* and *lactic acidosis*, the role of such alkalinising agents is controversial (see p.1667, and for guidelines on advanced cardiac life support, p.1156). Sodium lactate has been given as an alternative to sodium bicarbonate in acute metabolic acidosis, but is no longer recommended because of the risk of precipitating lactic acidosis. In *chronic hyperchloraemic acidosis* associated with potassium deficiency, potassium bicarbonate may be preferred to sodium bicarbonate. The citrate salts of potassium or sodium have also been used as alternatives to sodium bicarbonate in treating chronic metabolic acidosis resulting from *renal disorders*. Sodium bicarbonate, lactate and acetate, and potassium acetate are used as bicarbonate sources in *dialysis fluids* (p.1670).

The dose of bicarbonate required for the treatment of acidotic states must be calculated on an individual basis, and is dependent on the acid–base balance and electrolyte status of the patient. In the treatment of chronic acidosis bicarbonate has been given orally and doses providing 57 mmol (4.8 g sodium bicarbonate) or more daily may be required. In severe acidosis, sodium bicarbonate has been given intravenously by continuous infusion usually as a 1.26% (150 mmol/litre) solution or by slow intravenous injection of a stronger (hypertonic) solution of up to 8.4% (1000 mmol/litre) sodium bicarbonate (but see the discussion on metabolic acidosis, p.1667). For the correction of acidosis during advanced cardiac life support procedures, doses of 50 mmol of sodium bicarbonate (50 mL of an 8.4% solution) may be given intravenously to adults. Frequent monitoring of serum-electrolyte concentrations and acid–base status is essential during treatment of acidosis.

Sodium bicarbonate may be used in the management of **hyperkalaemia** (p.1669) to promote the intracellular uptake of potassium and correct associated acidosis, although there is some debate as to its value. Some sources suggest that 50 to 100 mL of an 8.4% solution may be given in severe hyperkalaemia accompanied by acidosis, although more dilute solutions have been used, and care is required, particularly if there is accompanying renal impairment.

Sodium bicarbonate, sodium citrate, and potassium citrate cause **alkalinisation of the urine**. They may therefore be given to relieve discomfort in mild *urinary-tract infections* (p.199) and to prevent the development of uric-acid renal calculi in the initial stages of *uricosuric* therapy for hyperuricaemia in chronic gout (for example, see Precautions for Probenecid, p.558). In both cases, they are given with a liberal fluid intake, usually by mouth, in divided doses of up to about 10 g daily. Sodium bicarbonate may also be used to alkalinise the urine in *acute poisoning* with weakly acidic drugs such as salicylates and phenoxyacetate pesticides; use with a diuretic for ‘forced alkaline diuresis’ is no longer recommended.

When given orally, sodium bicarbonate and potassium bicarbonate neutralise acid secretions in the gastrointestinal tract and sodium bicarbonate in particular is therefore frequently included in **antacid** preparations (p.1692). To relieve *dyspepsia* doses of about 1 to 5 g of sodium bicarbonate in water have been taken when required. Sodium citrate has been widely used as a ‘clear’ (non-particulate) antacid, usually with an H_2-antagonist, for the *prophylaxis of acid aspiration* associated with anaesthesia (p.1693). Sodium bicarbonate is also used in various preparations for *double-contrast radiography* where production of gas (carbon dioxide) in the gastrointestinal tract is necessary. Similarly, solutions containing sodium bicarbonate or citrate have been used to treat acute *oesophageal impaction*.

Sodium bicarbonate and sodium or potassium citrate are used as buffering or alkalinising agents in *pharmaceutical formulation*. Sodium or potassium bicarbonate and anhydrous sodium citrate are used in effervescent tablet formulations.

Individual salts also have **other specific uses**. A 5% solution of sodium bicarbonate can be administered as ear drops to soften and remove *ear wax* (see under Docusates, p.1725). Sodium bicarbonate injection has been used to treat *extravasation of anthracycline antineoplastics* (p.640) although as mentioned in Adverse Effects, above, hypertonic solutions may themselves cause necrosis.

Sodium citrate has anti-clotting properties and is used, as sodium acid citrate, with other agents in solutions for the anticoagulation and preservation of blood for *transfusion* purposes. Similarly, sodium citrate 3% irrigation may be useful for the dissolution of *blood clots in the bladder* as an alternative to sodium chloride 0.9%. Enemas containing sodium citrate are given rectally as *osmotic laxatives*. Sodium citrate is also a common ingredient in *cough* mixtures. Eye drops containing sodium citrate 10% have been used in the treatment of chemical *eye burns* (below); they may be used with potassium ascorbate eye drops (see Uses of Vitamin C Substances, p.1984).

Eye disorders. Sodium bicarbonate is used in the management of blepharitis, an inflammation of the margin of the eyelids with various causes. It may be allergic in nature or associated with seborrhoea of the scalp. Infection of the eyelids can produce ulcerative blepharitis, a condition characterised by the formation of yellow crusts which may glue the eyelashes together. Parasites occasionally cause blepharitis. The condition is first treated by cleaning the eyes and eyelids with sodium bicarbonate solution or a suitable bland eye lotion; simple eye ointment or diluted baby shampoo can also be used to soften crusts to aid removal. If an infection is present, antibacterials may be required (p.171). Long-term management consists of daily cleansing of the lid margins with a bland eye lotion.

EYE BURNS. Both heat and chemicals can burn the eye, causing damage to the conjunctiva, cornea, and underlying structures. Burn severity may be influenced by the amount of burning substance that enters the eye and the duration of contact, its temperature and impact force, whether it is a liquid or solid, its pH, and osmolarity.[1,2] Hydrofluoric acid, sulfurous acid, and alkalis readily penetrate the corneal stroma.[2] Immediate irrigation is essential, and a duration of at least 15 to 30 minutes is recommended; it may need to be repeated periodically.

Water or sodium chloride 0.9% solution may be used initially, but because they are hypotonic to the eye there can be an increased uptake of the fluid and diffusion of the burning substance into the deeper layers of the cornea, resulting in oedema. To reduce this risk solutions with higher osmolarities have been suggested, if available, and include balanced salt solution, buffered solutions such as lactated Ringer's solution, and commercial decontamination preparations with amphoteric and chelating properties.[1,2]

For acid and alkali burns ascorbate and citrate eye drops have been tried, and ascorbate given orally, based on suggestions that ascorbate may scavenge free radicals and citrate may reduce the release of free radicals and proteolytic enzymes in burn tissue.[1] However, a retrospective analysis of 121 patients with alkali burns to the eye suggested those with less severe burns (grades 1 and 2) did not benefit from an intensive topical therapy regimen including 10% ascorbate drops and 10% citrate drops;[3] a trend to more rapid healing and better visual outcome were seen in patients with grade 3 burns but in those with the most severe damage (grade 4) the regimen made no difference. In the management of hydrofluoric acid burns of the eye, calcium gluconate has also been used after initial irrigation (see p.2322). Other general treatments that may be required include topical application of anaesthesia, corticosteroids, and antibacterials, treatment for glaucoma, and surgery.[1,2]

1. Schrage NF, *et al.* Eye burns: an emergency and continuing problem. *Burns* 2000; **26:** 689–99.
2. Kuckelkorn R, *et al.* Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand* 2002; **80:** 4–10.
3. Brodovsky SC, *et al.* Management of alkali burns: an 11-year retrospective review. *Ophthalmology* 2000; **107:** 1829–35.

Osteoporosis. Potassium bicarbonate in an oral dose of 1 to 2 mmol/kg daily improved mineral balance and bone metabolism in a short-term study.[1] However, the authors cautioned against the use of bicarbonate to treat or prevent osteoporosis (p.1084) without further study.[2]

1. Sebastian A, *et al.* Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994, **330:** 1776–81.
2. Sebastian A, Morris RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; **331:** 279.

Renal calculi. Citrate forms soluble complexes with calcium, thereby reducing urinary saturation of stone-forming calcium salts. Potassium citrate has a hypocalciuric effect when given orally, probably due to enhanced renal calcium absorption. Urinary calcium excretion is unaffected by sodium citrate, since the alkali-mediated hypocalciuric effect is offset by a sodium-linked calciuresis.[1] Potassium citrate may be beneficial in reducing the rate of stone formation in patients with hypocitraturia[2,3] or hypercalciuria.[4] As mentioned in Uses above, sodium bicarbonate or sodium or potassium citrate may also be used for their alkalinising action, as an adjunct to a liberal fluid intake, to prevent development of uric-acid renal calculi during uricosuric therapy.

Other causes of renal calculi and their treatment are discussed on p.2181.

Urinary alkalinisation with sodium bicarbonate, sodium citrate, or potassium citrate may be useful in the management of cystine stone formation in patients with cystinuria (see under Penicillamine, p.1459).

1. Anonymous. Citrate for calcium nephrolithiasis. *Lancet* 1986; **i:** 955.
2. Pak CYC, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med* 1986; **104:** 33–7.
3. Tekin A, *et al.* Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol (Baltimore)* 2002; **168:** 2572–4.
4. Pak CYC, *et al.* Prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions. *J Urol (Baltimore)* 2003; **169:** 465–9.

Preparations

BP 2008: Alginate Raft-forming Oral Suspension; Alkaline Gentian Mixture; Aromatic Magnesium Carbonate Mixture; Compound Magnesium Trisilicate Oral Powder; Compound Sodium Bicarbonate Tablets; Compound Sodium Chloride Mouthwash; Kaolin and Morphine Mixture; Kaolin Mixture; Magnesium Trisilicate Mixture; Potassium Citrate Mixture; Sodium Bicarbonate Ear Drops; Sodium Bicarbonate Eye Lotion; Sodium Bicarbonate Intravenous Infusion; Sodium Bicarbonate Oral Solution; Sodium Citrate Eye Drops; Sodium Citrate Irrigation Solution; Sodium Lactate Intravenous Infusion;
BPC 1968: Effervescent Potassium Tablets;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 31: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant Sodium Citrate Solution; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Bicarbonate Effervescent Tablets for Oral Solution; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Potassium Citrate Extended-release Tablets; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Sodium Acetate Injection; Sodium Acetate Solution; Sodium Bicarbonate Injection; Sodium Bicarbonate Oral Powder; Sodium Bicarbonate Tablets; Sodium Citrate and Citric Acid Oral Solution; Sodium Lactate Injection; Sodium Lactate Solution; Tricitrates Oral Solution; Trikates Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: LTK250; Urokit; ***Austral.:*** Chlorvescent; Sodibic; Urocit-K; ***Austria:*** Oxalyt; Uralyt-U; ***Belg.:*** Uralyt-U; ***Braz.:*** Acalka†; Citrosodine†; Litocit; ***Canad.:*** Bromo Seltzer; Eno; K-Citra; K-Lyte; Polycitra-K; ***Chile:*** Acalka; Eucerin; Sal De Yasta†; ***Cz.:*** Alkaligen†; Uralyt-U; ***Fr.:*** Elgydium Bicarbonate†; Potensium gelule; ***Ger.:*** Alkala T; Apocit; bicaNorm; Blanel; Kalitrans; Kalium; Kohlensaurebad Bastian; Nephrotrans; Uralyt-U; ***Gr.:*** Citrolithin; ***Hong Kong:*** Urocit-K; ***Hung.:*** Alkaligen; ***India:*** Alkasol; Citralka; Oricitral; ***Irl.:*** Cystopurin; ***Israel:*** Babic; Uralyt-U; ***Ital.:*** Citrosodina; Uralyt-U; ***Jpn:*** Meylon; ***Malaysia:*** Urocit-K; ***Mex.:*** Betsol Z; Bicarnat; Debonal; ***Neth.:*** Citra-Lock; Hospasol; ***Norw.:*** Kajos; ***NZ:*** Citravescent; ***Philipp.:*** Acalka; ***Pol.:*** Citrolyt; Litocid; ***Port.:*** Acalka; Hospasol; Uralyt-U; ***S.Afr.:*** Crystacit; SB Gripe Water; Uralyt-U; ***Singapore:*** Gripe Water†; Urocit-K†; ***Spain:*** Acalka; Hospasol; Plurisalina; ***Swed.:*** Kajos; ***Switz.:*** Nephrotrans; Uralyt-U†; ***Thai.:*** Acalka; Uralyt-U; ***Turk.:*** Anti-Asidoz; Urocid-K; ***UK:*** Boots Gripe Mixture 1 Month Plus; Canesten Oasis; Cymalon Cranberry; Cystitis Relief; Cystocalm; Cystopurin; ***USA:*** Citra pH; K + Care†; K-Lyte; Neut; Urocit-K; ***Venez.:*** Policitra.

Multi-ingredient: numerous preparations are listed in Part 3.

Calcium

Calcio; Kalsiyum; Kalzium.
Ca = 40.078.

Description. Calcium is a cation given as various calcium-containing salts.

Incompatibility. Calcium salts have been reported to be incompatible with a wide range of drugs. Complexes may form resulting in the formation of a precipitate.

Calcium Acetate

Acetate of Lime; Calcii acetas; Calcio, acetato de; Calcium, acétate de; E263; Kalcio acetatas; Kalciumacetat; Kalcium-acetát; Kalsiumasetaatti; Kalsiyum Asetat; Lime Acetate.
$C_4H_6CaO_4$ = 158.2.
CAS — 62-54-4.
ATC — A12AA12.
ATC Vet — QA12AA12.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Calcium Acetate). A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 7.2 to 8.2. Store in airtight containers.
USP 31 (Calcium Acetate). A white, odourless or almost odourless, hygroscopic, crystalline powder. It decomposes to calcium carbonate and acetone when heated to above 160°. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in dehydrated alcohol, in acetone, and in benzene. A 5% solution in water has a pH of 6.3 to 9.6. Store in airtight containers.

Equivalence. Each g of calcium acetate (anhydrous) represents about 6.3 mmol of calcium. Calcium acetate (anhydrous) 3.95 g is equivalent to about 1 g of calcium.

Calcium Chloride

Calcii Chloridum; Calcii chloridum dihydricum; Calcio, cloruro de; Calcium Chloratum; Calcium, chlorure de; Chlorid vápenatý; Cloreto de Cálcio; Cloruro de Calcio; E509; Kalcio chloridas; Kalciumklorid; Kalcium-klorid; Kalsiumkloridi; Kalsiyum Klorür; Wapnia chlorek.
$CaCl_2,xH_2O$ = 110.0 (anhydrous); 147.0 (dihydrate).
CAS — 10043-52-4 (anhydrous calcium chloride); 7774-34-7 (calcium chloride hexahydrate); 10035-04-8 (calcium chloride dihydrate).
ATC — A12AA07; B05XA07; G04BA03.
ATC Vet — QA12AA07; QB05XA07; QG04BA03.

Pharmacopoeias. *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.* include the dihydrate.
Eur. also specifies the hexahydrate.
Ph. Eur. 6.2 (Calcium Chloride Dihydrate; Calcii Chloridum Dihydricum). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol. Store in airtight containers.
Ph. Eur. 6.2 (Calcium Chloride Hexahydrate; Calcii Chloridum Hexahydricum). A white or almost white, crystalline mass or colourless crystals. Very soluble in water; freely soluble in alcohol. F.p. about 29°.
USP 31 (Calcium Chloride). White, hard, odourless fragments or granules. Is deliquescent. Soluble 1 in 0.7 of water, 1 in 0.2 of boiling water, 1 in 4 of alcohol, and 1 in 2 of boiling alcohol. pH of a 5% solution in water is between 4.5 and 9.2. Store in airtight containers.

Equivalence. Each g of calcium chloride (dihydrate) represents about 6.8 mmol of calcium and 13.6 mmol of chloride. Calcium chloride (dihydrate) 3.67 g is equivalent to about 1 g of calcium.

Each g of calcium chloride (hexahydrate) represents about 4.56 mmol of calcium and 9.13 mmol of chloride. Calcium chloride (hexahydrate) 5.47 g is equivalent to about 1 g of calcium.

Calcium Citrate

Calcio, citrato de; Tricalcium Citrate. Tricalcium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.
$C_{12}H_{10}Ca_3O_{14},4H_2O$ = 570.5.
CAS — 5785-44-4.

Pharmacopoeias. In *US.*
USP 31 (Calcium Citrate). A white, odourless, crystalline powder. Slightly soluble in water; insoluble in alcohol; freely soluble in diluted 3N hydrochloric acid and in diluted 2N nitric acid.

Equivalence. Each g of calcium citrate (tetrahydrate) represents about 5.3 mmol of calcium and 3.5 mmol of citrate. Calcium citrate (tetrahydrate) 4.74 g is equivalent to about 1 g of calcium.

Calcium Glubionate *(USAN, rINN)*

Calcii Glubionas; Calcium Gluconate Lactobionate Monohydrate; Calcium Gluconogalactogluconate Monohydrate; Glubionate de Calcium; Glubionato de calcio. Calcium D-gluconate lactobionate monohydrate.
Кальция Глубионат
$(C_{12}H_{21}O_{12},C_6H_{11}O_7)Ca,H_2O$ = 610.5.
CAS — 31959-85-0 (anhydrous calcium glubionate); 12569-38-9 (calcium glubionate monohydrate).
ATC — A12AA02.
ATC Vet — QA12AA02.

Pharmacopoeias. *US* includes Calcium Glubionate Syrup.

Equivalence. Each g of calcium glubionate (monohydrate) represents about 1.6 mmol of calcium. Calcium glubionate (monohydrate) 15.2 g is equivalent to about 1 g of calcium.

Calcium Gluceptate

Calcium Glucoheptonate *(pINN)*; Calcii glucoheptonas; Calcium, glucoheptonate de; Glucoheptonate de Calcium; Glucoheptonato de calcio; Kalcio gliukoheptonatas; Kalciumglukoheptonat; Kalcium-glükoheptonát; Kalcium-glukoheptonát; Kalsiumglukoheptonaatti.
Кальция Глюкогептонат
$C_{14}H_{26}CaO_{16}$ = 490.4.
CAS — 17140-60-2 (anhydrous calcium gluceptate); 29039-00-7 (anhydrous calcium gluceptate).
ATC — A12AA10.
ATC Vet — QA12AA10.

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows anhydrous or with varying amounts of water of hydration.
Ph. Eur. 6.2 (Calcium Glucoheptonate). A mixture in variable proportions of calcium di(D-*glycero*-D-*gulo*-heptonate) and calcium di(D-*glycero*-D-*ido*-heptonate). A white or very slightly yellow, hygroscopic, amorphous powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 10% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.
USP 31 (Calcium Gluceptate). It is anhydrous or contains varying amounts of water of hydration. It consists of the calcium salt of the alpha-epimer of glucoheptonic acid or of a mixture of the alpha and beta epimers of glucoheptonic acid. A white to faintly yellow amorphous powder. It is stable in air, but the hydrous forms may lose part of their water of hydration on standing. Freely soluble in water; insoluble in alcohol and in many other organic solvents. pH of a 10% solution in water is between 6.0 and 8.0.

Equivalence. Each g of calcium gluceptate (anhydrous) represents about 2 mmol of calcium. Calcium gluceptate (anhydrous) 12.2 g is equivalent to about 1 g of calcium.

Calcium Gluconate

Calcii gluconas; Calcii Gluconas Monohydricus; Calcio, gluconato de; Calcium, gluconate de; Calcium Glyconate; E578; Glukonan vápenatý monohydrát; Kalcio gliukonatas; Kalciumglukonat; Kalcium-glükonát; Kalsiumglukonaatti; Wapnia glukonian. Calcium D-gluconate monohydrate.
$C_{12}H_{22}CaO_{14},H_2O$ = 448.4.
CAS — 299-28-5 (anhydrous calcium gluconate); 18016-24-5 (calcium gluconate monohydrate).
ATC — A12AA03; D11AX03.
ATC Vet — QA12AA03; QD11AX03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *Viet.* Also in *US* as the anhydrous or the monohydrate form.
Calcium borogluconate is included as an injection in *BP(Vet).*
Ph. Eur. 6.2 (Calcium Gluconate). A white or almost white, crystalline or granular, powder. Sparingly soluble in water; freely soluble in boiling water.
USP 31 (Calcium Gluconate). It is anhydrous or contains one molecule of water of hydration. White, odourless, crystalline granules or powder. Slowly soluble 1 in 30 of water; soluble 1 in 5 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of calcium gluconate (monohydrate) represents about 2.2 mmol of calcium. Calcium gluconate (monohydrate) 11.2 g is equivalent to about 1 g of calcium.

Calcium Glycerophosphate

Calcii glycerophosphas; Calcio, glicerofosfato de; Calcium Glycerinophosphate; Calcium, glycérophosphate de; Calcium Glycerylphosphate; Glycerofosforečnan vápenatý; Kalcio glicerofosfatas; Kalcium-glicerofoszfát; Kalciumglycerofosfat; Kalsiumglyserofosfaatti.

$C_3H_7CaO_6P(+xH_2O)$ = 210.1 (anhydrous).
CAS — 27214-00-2 (anhydrous calcium glycerophosphate).
ATC — A12AA08.
ATC Vet — QA12AA08.

Pharmacopoeias. In *Eur.* (see p.vii), *US.*, and *Viet.*
Ph. Eur. 6.2 (Calcium Glycerophosphate). A mixture in variable proportions of calcium (*RS*)-2,3-dihydroxypropyl phosphate and of calcium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. It loses not more than 12% of its weight on drying.
USP 31 (Calcium Glycerophosphate). A mixture, in variable proportions, of calcium *(RS)*-2,3-dihydroxypropyl phosphate and calcium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. Store at a temperature between 20° and 25°, excursions permitted between 15° and 30°.

Equivalence. Each g of calcium glycerophosphate (anhydrous) represents about 4.8 mmol of calcium. Calcium glycerophosphate (anhydrous) 5.24 g is equivalent to about 1 g of calcium.

Calcium Hydrogen Phosphate

Calcii et Hydrogenii Phosphas; Calcii hydrogenophosphas; Calcio, hidrogenofosfato de; Calcium, hydrogénophosphate de; Calcium Hydrophosphoricum; Calcium Monohydrogen Phosphate; Dicalcium Orthophosphate; Dicalcium Phosphate; E341; Hydrogenfosforečnan vápenatý; Kalcio-vandenilio fosfatas; Kalcium-hidrogén-foszfát; Kalciumvätefosfat; Kalsiumvetyfosfaatti; Wapna wodorofosforan. Calcium hydrogen orthophosphate.

$CaHPO_4$ = 136.1 (anhydrous); 172.1 (dihydrate).
CAS — 7757-93-9 (anhydrous calcium hydrogen phosphate); 7789-77-7 (calcium hydrogen phosphate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*, which includes monographs for the anhydrous substance and the dihydrate form.
Ph. Eur. 6.2 (Calcium Hydrogen Phosphate, Anhydrous; Calcii Hydrogenophosphas Anhydricus). A white or almost white, crystalline powder, or colourless crystals. Practically insoluble in water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.
Ph. Eur. 6.2 (Calcium Hydrogen Phosphate Dihydrate; Calcii Hydrogenophosphas Dihydricus; Calcium Hydrogen Phosphate BP 2008). A white or almost white, crystalline powder. Practically insoluble in cold water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.
The BP 2008 gives Dibasic Calcium Phosphate as an approved synonym.
USP 31 (Anhydrous Dibasic Calcium Phosphate).
USP 31 (Dibasic Calcium Phosphate Dihydrate).

Equivalence. Each g of calcium hydrogen phosphate (dihydrate) represents about 5.8 mmol of calcium and of phosphate. Calcium hydrogen phosphate (dihydrate) 4.29 g is equivalent to about 1 g of calcium.

Calcium Lactate

Calcii lactas; Calcio, lactato de; Calcium, lactate de; E327; Kalcio laktatas; Kalciumlaktat; Kalcium-laktát; Kalsiumlaktaatti; Kalsiyum Laktat; Mléčnan vápenatý; Wapnia mleczan. Calcium 2-hydroxypropionate.

$C_6H_{10}CaO_6,xH_2O$ = 218.2 (anhydrous); 308.3 (pentahydrate); 272.3 (trihydrate).
CAS — 814-80-2 (anhydrous calcium lactate); 41372-22-9 (hydrated calcium lactate); 5743-47-5 (calcium lactate pentahydrate); 63690-56-2 (calcium lactate pentahydrate).
ATC — A12AA05.
ATC Vet — QA12AA05.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Eur. has separate monographs for the anhydrous substance, the monohydrate, the pentahydrate, and the trihydrate. *US* allows anhydrous or hydrous forms. *Viet.* has monographs for the pentahydrate and the trihydrate.
Ph. Eur. 6.2 (Calcium Lactate, Anhydrous; Calcii Lactas Anhydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.
Ph. Eur. 6.2 (Calcium Lactate Monohydrate; Calcii Lactas Monohydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.
Ph. Eur. 6.2 (Calcium Lactate Pentahydrate; Calcii Lactas Pentahydricus). A white or almost white, slightly efflorescent, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.
The BP 2008 gives Calcium Lactate as an approved synonym.
Ph. Eur. 6.2 (Calcium Lactate Trihydrate; Calcii Lactas Trihydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.
USP 31 (Calcium Lactate). White, practically odourless, granules or powder. The pentahydrate is somewhat efflorescent and at 120° becomes anhydrous. The pentahydrate is soluble 1 in 20 of water and practically insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of calcium lactate (trihydrate) represents about 3.7 mmol of calcium. Each g of calcium lactate (pentahydrate) represents about 3.2 mmol of calcium. Calcium lactate (pentahydrate) 7.7 g and calcium lactate (trihydrate) 6.8 g are each equivalent to about 1 g of calcium.

Calcium Lactate Gluconate

Calcio, gluconato lactato de.

$Ca_5(C_3H_5O_3)_6,(C_6H_{11}O_7)_4,2H_2O$ = 1551.4.
ATC — A12AA06.
ATC Vet — QA12AA06.

Equivalence. Each g of calcium lactate gluconate (dihydrate) represents about 3.2 mmol of calcium. Calcium lactate gluconate (dihydrate) 7.74 g is equivalent to about 1 g of calcium.

Calcium Lactobionate

Calcii Lactobionas; Calcio, lactobionato de; Calcium Lactobionate Dihydrate; Kalciumlaktobionat; Kalsiumlaktobionaatti. Calcium 4-*O*-β-D-galactopyranosyl-D-gluconate dihydrate.

$C_{24}H_{42}CaO_{24},2H_2O$ = 790.7.
CAS — 110638-68-1.

Pharmacopoeias. In *US.*
USP 31 (Calcium Lactobionate). pH of a 5% solution in water is between 5.4 and 7.4.

Equivalence. Each g of calcium lactobionate (dihydrate) represents about 1.3 mmol of calcium. Calcium lactobionate (dihydrate) 19.7 g is equivalent to about 1 g of calcium.

Calcium Levulinate *(BAN)*

Calcii Laevulas; Calcii laevulinas; Calcii Laevulinas Dihydricus; Calcii Levulinas Dihydricum; Calcio, levulinato de; Calcium Laevulate; Calcium Laevulinate; Calcium, lévulinate de; Kalcio levulinatas; Kalciumlevulat; Kalcium-levulát dihydrát; Kalciumlevulinat; Kalcium-levulinát; Kalsiumlevulaatti; Kalsiumlevulinaatti; Lévulinate Calcique. Calcium 4-oxovalerate dihydrate.

$C_{10}H_{14}CaO_6,2H_2O$ = 306.3.
CAS — 591-64-0 (anhydrous calcium levulinate); 5743-49-7 (calcium levulinate dihydrate).
ATC — A12AA30.
ATC Vet — QA12AA30.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Calcium Levulinate Dihydrate). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 6.8 to 7.8. Protect from light.
USP 31 (Calcium Levulinate). A white crystalline or amorphous powder, having a faint odour suggestive of burnt sugar. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.5.

Equivalence. Each g of calcium levulinate (dihydrate) represents about 3.3 mmol of calcium. Calcium levulinate (dihydrate) 7.64 g is equivalent to about 1 g of calcium.

Calcium Phosphate

Calcii Phosphas; Calcio, fosfato de; Calcium Orthophosphate; E341; Fosfato Tricalcico; Fosforečnan vápenatý; Kalcio fosfatas; Kalcium-foszfát; Phosphate Tertiaire de Calcium; Phosphate tricalcique; Precipitated Calcium Phosphate; Tricalcii phosphas; Tricalcium Phosphate; Trikalciumfosfat; Trikalsiumfosfaatti; Wapnia fosforan.

CAS — 7758-87-4 (tricalcium diorthophosphate); 12167-74-7 (calcium hydroxide phosphate).
ATC — A12AA01.
ATC Vet — QA12AA01.

Description. Calcium phosphate is not a clearly defined chemical entity but is a mixture of calcium phosphates that has been most frequently described as either tricalcium diorthophosphate, $Ca_3(PO_4)_2$ = 310.2, or calcium hydroxide phosphate, $Ca_5OH(PO_4)_3$ = 502.3.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Viet.* Also in *USNF.*
Ph. Eur. 6.2 (Calcium Phosphate). It consists of a mixture of calcium phosphates and contains 35 to 40% of Ca. A white or almost white powder. Practically insoluble in water; dissolves in dilute hydrochloric acid and in dilute nitric acid.
The BP 2008 gives Tribasic Calcium Phosphate as an approved synonym.
USNF 26 (Tribasic Calcium Phosphate). It consists of a variable mixture of calcium phosphates having the approximate composition $10CaO.3P_2O_5.H_2O$. It contains not less than 34% and not more than 40% of calcium. A white, odourless, powder. Practically insoluble in water; insoluble in alcohol; readily soluble in 3N hydrochloric acid and in 2N nitric acid.

Calcium Pidolate *(pINNM)*

Calcii Pidolas; Calcium Pyroglutamate; Pidolate de Calcium; Pidolato de calcio. Calcium 5-oxopyrrolidine-2-carboxylate.

Кальций Пидолат

$Ca(C_5H_6NO_3)_2$ = 296.3.
CAS — 31377-05-6.

Equivalence. Each g of calcium pidolate (anhydrous) represents about 3.4 mmol of calcium. Calcium pidolate (anhydrous) 7.39 g is equivalent to about 1 g of calcium.

Calcium Silicate

Calcio, silicato de; E552.

CAS — 1344-95-2; 10101-39-0 (calcium metasilicate); 10034-77-2 (calcium diorthosilicate); 12168-85-3 (calcium trisilicate).
ATC — A02AC02.
ATC Vet — QA02AC02.

Description. A naturally occurring mineral, the most common forms being calcium metasilicate ($CaSiO_3$ = 116.2), calcium diorthosilicate (Ca_2SiO_4 = 172.2), and calcium trisilicate (Ca_3SiO_5 = 228.3). It is usually found in hydrated forms containing various amounts of water of crystallisation. Commercial calcium silicate is prepared synthetically.

Pharmacopoeias. In *USNF.*
USNF 26 (Calcium Silicate). Crystalline or amorphous calcium silicate is a compound of calcium oxide and silicon dioxide containing not less than 4% of CaO and not less than 35% of SiO_2. A white to off-white free-flowing powder. Insoluble in water; with mineral acids it forms a gel. A 5% aqueous suspension has a pH of 8.4 to 11.2.

Calcium Sodium Lactate

Calcio, lactato sódico de.

$2C_3H_5NaO_3,(C_3H_5O_3)_2Ca,4H_2O$ = 514.4.

Equivalence. Each g of calcium sodium lactate (tetrahydrate) represents about 1.9 mmol of calcium and 3.9 mmol of sodium and of lactate. Calcium sodium lactate (tetrahydrate) 12.8 g is equivalent to about 1 g of calcium.

Adverse Effects and Treatment

Oral calcium salts can cause gastrointestinal irritation; calcium chloride is generally considered to be the most irritant of the commonly used calcium salts.

Injection of calcium salts can also produce irritation, and intramuscular or subcutaneous injection in particular can cause local reactions including sloughing or necrosis of the skin; solutions of calcium chloride are extremely irritant and should not be injected intramuscularly or subcutaneously. Soft-tissue calcification has followed the use of calcium salts parenterally.

Excessive amounts of calcium salts may lead to hypercalcaemia. This complication is usually associated with parenteral use, but can occur after oral dosage, usually in patients with renal failure or who are also taking vitamin D. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac arrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to symptoms of hypercalcaemia, as well as a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcaemia will usually resolve if calcium and other contributory drugs such as vitamin D are stopped (see also Vitamin D-mediated Hypercalcaemia, p.1668). If hypercalcaemia is severe, urgent treatment is required as outlined on p.1668.

Precautions

Solutions of calcium salts, particularly calcium chloride, are irritant, and care should be taken to prevent extravasation during intravenous injection. Calcium salts should be given cautiously to patients with renal impairment, or diseases associated with hypercalcaemia such as sarcoidosis and some malignancies. In addition, they should generally be avoided in patients with calcium renal calculi, or a history of renal calculi. Calcium chloride, because of its acidifying nature, is unsuitable for the treatment of hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure.

Plasma-calcium concentrations should be monitored closely in patients with renal impairment and during parenteral dosage and if large doses of vitamin D are used concurrently.

Interactions

Hypercalcaemia has occurred when calcium salts are given with thiazide diuretics or vitamin D. Vitamin D increases the gastrointestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma-calcium concentrations should be monitored in patients receiving the drugs together.

Bran decreases the gastrointestinal absorption of calcium, and may therefore decrease the efficacy of calcium supplements. Corticosteroids also reduce calcium absorption.

Calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication; parenteral calcium therapy is best avoided in patients receiving cardiac glycosides. Citrate salts increase the absorption of aluminium from the gastrointestinal tract (see Toxicity, under Adverse Effects of Aluminium Hydroxide, p.1706), therefore patients with renal failure taking aluminium compounds should avoid taking calcium citrate. Calcium salts reduce the absorption of a number of other drugs such as bisphosphonates, fluoride, some fluoroquinolones, and tetracyclines; doses should be separated by at least 3 hours.

Pharmacokinetics

Calcium is absorbed mainly from the small intestine by active transport and passive diffusion. About one-third of ingested calcium is absorbed although this can vary depending upon dietary factors and the state of the small intestine; also absorption is increased in calcium deficiency and during periods of high physiological requirement such as during childhood or pregnancy and lactation. 1,25-Dihydroxycholecalciferol (calcitriol), a metabolite of vitamin D, enhances the active phase of absorption.

Excess calcium is mainly excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair, and nails. Calcium crosses the placenta and is distributed into breast milk.

Human Requirements

Calcium is the most abundant mineral in the body and is an essential body electrolyte. However, defining individual calcium requirements has proved difficult and guidelines vary widely by country and culture. Some authorities have adopted a factorial approach. For example, in the UK the dietary reference value (DRV) represents the apparent calcium requirements of healthy people under the prevailing dietary circumstances. The amount of calcium absorbed varies according to several factors including the requirements of the body, but is normally only about 30 to 40% of the dietary intake.

The richest dietary sources of calcium are milk and milk products. Significant amounts can also be consumed in green leafy vegetables, fortified flour, the soft bones of fish, and hard water.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p.1925) have been published for calcium.[1] In the USA recommended dietary allowances (RDA) had been set,[2] but have been replaced by dietary reference intakes (see p.1925).[3] In the UK the estimated average requirement (EAR) for adults is 525 mg (13.1 mmol) daily and the reference nutrient intake (RNI) for adults is 700 mg (17.5 mmol) daily; these figures are based on a mean absorption of calcium of 30% from mixed diets. In the USA the traditional RDA was 800 mg daily for adults aged over 25 years; this figure was based on an absorption rate of 40%. Under the new dietary reference intakes, adequate intakes (AI) for calcium have been set, which are higher in some age groups than the previous RDAs.[3] For adults aged up to 50 years the AI is 1 g daily, and for those 51 years or older, it is 1.2 g daily.[3] The tolerable upper intake is considered to be 2.5 g daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Table 1. Some calcium salts and their calcium content.

Calcium salt	Calcium content per g mg	mmol	mEq
Calcium acetate (anhydrous)	253	6.3	12.6
Calcium carbonate	400	10.0	20.0
Calcium chloride (dihydrate)	273	6.8	13.6
Calcium chloride (hexahydrate)	183	4.6	9.1
Calcium citrate (tetrahydrate)	211	5.3	10.5
Calcium glubionate (monohydrate)	66	1.6	3.3
Calcium glucoheptonate (anhydrous)	82	2.0	4.1
Calcium gluconate (monohydrate)	89	2.2	4.5
Calcium glycerophosphate (anhydrous)	191	4.8	9.5
Calcium hydrogen phosphate (dihydrate)	233	5.8	11.6
Calcium lactate (anhydrous)	184	4.6	9.2
Calcium lactate (trihydrate)	147	3.7	7.3
Calcium lactate (pentahydrate)	130	3.2	6.5
Calcium lactate gluconate (dihydrate)	129	3.2	6.4
Calcium lactobionate (dihydrate)	51	1.3	2.5
Calcium levulinate (dihydrate)	131	3.3	6.5
Calcium phosphate [$10CaO.3P_2O_5.H_2O$]	399	10.0	19.9
Calcium pidolate (anhydrous)	135	3.4	6.7
Calcium silicate [$CaSiO_3$]	345	8.6	17.2
Calcium sodium lactate (tetrahydrate)	78	1.9	3.9

Uses and Administration

Calcium salts are used in the management of **hypocalcaemia** (p.1668) and **calcium deficiency states** resulting from dietary deficiency or ageing (see also Osteoporosis, p.1084). Doses may be expressed in terms of mmol or mEq of calcium, mass (mg) of calcium, or mass of calcium salt (for comparative purposes, see Table 1, above).

In simple deficiency states calcium salts may be given orally, usually in doses of 10 to 50 mmol (400 mg to 2 g) of calcium daily adjusted to the individual patient's requirements.

In severe acute hypocalcaemia or hypocalcaemic tetany parenteral dosage is necessary, generally by slow intravenous injection or continuous infusion of calcium chloride or calcium gluconate (see also Administration, below). A typical dose is 2.25 to 4.5 mmol of calcium by slow intravenous injection, either repeated as required, or followed by continuous intravenous infusion of about 9 mmol daily. 2.25 mmol of calcium is provided by 10 mL of calcium gluconate 10%. Calcium gluceptate and calcium glycerophosphate with calcium lactate have been given by the intramuscular route; the chloride and gluconate are unsuitable for this route because of their irritancy. The intravenous route is used in children.

Intravenous calcium salts are also used to reverse the toxic cardiac effects of potassium in the emergency treatment of severe **hyperkalaemia** (p.1669), and as an antidote to magnesium in severe **hypermagnesaemia** (p.1668). For these indications, 2.25 to 4.5 mmol of calcium (10 to 20 mL of calcium gluconate 10%) is commonly used.

Individual calcium salts have specific uses. Calcium carbonate (p.1714) or acetate are effective phosphate binders and are given orally to reduce phosphate absorption from the gut in patients with **hyperphosphataemia**; this is particularly relevant to patients with chronic renal failure in order to prevent the development of renal osteodystrophy (p.1086). The initial dose of calcium carbonate is 2.5 g daily titrated to a maximum of 17 g daily. A typical initial dose of calcium acetate is 3 or 4 g daily; most patients require 6 to 12 g daily.

Calcium carbonate and calcium silicate, given orally, are used for their **antacid** properties (p.1692).

Some of the calcium salts discussed here also have *pharmaceutical uses* as diluents in capsules and tablets, buffers and dissolution aids in dispersible tablets, disintegrant and anticaking agents, and as a basis or abrasive in dental preparations. Calcium phosphate is also used as a bone graft substitute.

Homoeopathy. Various calcium salts have been used in homoeopathic medicines under the following names:

- Calcium acetate: Calcarea acetica; Calc. ace.
- Calcium arsenite: Calcium arsenicosum; Calcarea arsenicosa; Cal. ars.
- Calcium chloride: Calcarea muriatica; Cal. mur.
- Calcium hydrogen phosphate: Calcium phosphoricum
- Calcium hypophosphite: Calcarea hypophosphorosa; Calc. hyp.
- Calcium oxalate: Calcarea oxalica; Cal. oxal.
- Calcium phosphate: Calcarea phosphorica; Calc. phos.; Cal. phos.
- Calcium picrate: Calcarea picrata; Cal. pic.
- Calcium silicate: Calcarea silicata; Calc. sil.

Other calcium salts used in homoeopathy and described elsewhere include: calcium bromide (p.2269), calcium carbonate (p.1714), calcium fluoride (p.1932), calcium hydroxide (p.2272), calcium iodide (p.1553), and calcium sulfate (p.2273).

Administration. Some prefer calcium chloride to calcium gluconate for parenteral preparations,[1,2] because retention of the chloride is greater and more predictable than of the gluconate, and results in a more predictable increase in extracellular ionised calcium concentration. However, calcium chloride is considered to be the most irritant of the calcium salts in general use (see Adverse Effects, above).

Calcium gluconate has been given by the intraperitoneal route[3] for the treatment of chronic hypocalcaemia after parathyroidectomy in a patient undergoing continuous ambulatory peritoneal dialysis, resulting in improved systemic bioavailability compared with oral and intravenous use.

1. Worthley LIG, Phillips PJ. Intravenous calcium salts. *Lancet* 1980; **ii:** 149.
2. Broner CW, *et al.* A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990; **117:** 986–9.
3. Stamatakis MK, Seth SK. Treatment of chronic hypocalcemia with intraperitoneal calcium. *Am J Health-Syst Pharm* 1995; **52:** 201–3.

Bites and stings. Calcium gluconate 10% solution has been given intravenously as an alternative to the use of conventional muscle relaxants for the management of pain and muscle spasm associated with neurotoxic spider envenomation (p.2239) by species such as *Latrodectus mactans* (black widow spider).[1,2] Although the precise mechanism of action of calcium in the alleviation of neuromuscular symptoms is unknown it is believed to be due to the replenishment of calcium stores in the sarcoplasmic reticulum of muscle depleted by stimulation.

1. Binder LS. Acute arthropod envenomation: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 163–73.
2. Woestman R, *et al.* The black widow: is she deadly to children? *Pediatr Emerg Care* 1996; **12:** 360–4.

Bone disease. Calcium is essential for the development and maintenance of normal bone, and calcium salts may be indicated in the treatment of some bone disorders associated with calcium deficiency, such as certain types of osteomalacia and rickets (p.1084). Oral doses of 1 to 3 g of calcium daily are used in osteomalacia.

Oral calcium supplements can also be used as an adjunct in the management of osteoporosis (p.1084) and corticosteroid-induced osteoporosis (see Effects on Bones and Joints, under Corticosteroids, p.1491).

Cramps. Calcium salts are one of a number of interventions that have been tried in the management of cramps (see Muscle Spasm, p.1887). However, evidence for these interventions is mostly lacking and a small systematic review concluded that oral calcium was not of benefit for leg cramps during pregnancy.[1]

1. Young GL, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/06/05).

Diagnosis of insulinoma. Calcium stimulates the release of insulin from insulinomas. Intra-arterial calcium gluconate, followed by hepatic venous sampling, has been found to be accurate and sensitive in the diagnosis and localisation of insulinomas,[1-4] even when other investigations have been negative.[5,6]

1. Doppman JL, *et al.* Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med* 1995; **123:** 269–73.
2. Lo CY, *et al.* Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. *Surgery* 2000; **128:** 903–9.
3. Brändle M, *et al.* Assessment of selective arterial calcium stimulation and hepatic venous sampling to localize insulin-secreting tumours. *Clin Endocrinol (Oxf)* 2001; **55:** 357–62.
4. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005; **19:** 783–98.
5. O'Shea D, *et al.* Localization of insulinomas by selective intraarterial calcium injection. *J Clin Endocrinol Metab* 1996; **81:** 1623–7.
6. Pereira PL, *et al.* Insulinoma and islet cell hyperplasia: value of the calcium intraarterial stimulation test when findings of other preoperative studies are negative. *Radiology* 1998; **206:** 703–9.

Fluoride toxicity. Inorganic fluoride is corrosive to skin and mucous membranes and acute intoxication disrupts many physiological systems; severe burns and profound hypocalcaemia may ensue. Absorption of the fluoride can be prevented by conversion to an insoluble form such as calcium fluoride and thus irrigation of skin (or gastric lavage as appropriate) with lime water, milk, or a 1% solution of calcium gluconate is recommended. Immediate treatment should also consist of 10 mL of calcium gluconate 10% intravenously, repeated after one hour; 30 mL should be given if tetany is present. In the short term affected skin and tissue should be injected with a 10% solution of calcium gluconate at a dose of 0.5 mL/cm^2 and burnt skin treated with a calcium gluconate 2.5% gel.[1]

See also under Hydrofluoric Acid, p.2322.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.

Hypertension. Meta-analysis suggests that calcium supplementation results in a small reduction in systolic and diastolic blood pressure.[1] Although the effect was too small to support the use of calcium supplementation for preventing or treating hypertension (p.1171), it is possible that calcium supplementation might have beneficial effects on blood pressure in those with an inadequate intake. In a controlled trial, calcium with vitamin D supplementation reduced systolic blood pressure more effectively than calcium alone.[2]

1. Griffith LE, *et al.* The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999; **12:** 84–92.
2. Pfeifer M, *et al.* Effects of a short-term vitamin D and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86:** 1633–7.

PREGNANCY. Despite an earlier meta-analysis[1] which concluded that calcium supplementation during pregnancy reduced systolic and diastolic blood pressure and the incidence of pre-eclampsia and hypertension, results from a double-blind, placebo-controlled trial in a total of 4589 women indicated that calcium supplementation during normal pregnancy did not prevent pre-eclampsia, pregnancy-associated hypertension without pre-eclampsia, or a number of other related disorders.[2] A subsequent review[3] found that calcium supplementation was beneficial, but it was noted that there was a wide variation in results between different studies; most of the effect was in studies including women identified as being at high risk for pre-eclampsia, and results from studies including lower-risk women found that calcium had no effect. The high-risk studies were carried out in areas with a low dietary calcium intake, suggesting that benefit might be greatest in such populations. However, a further study[4] in 8325 women living in areas with a low calcium intake but not specifically at high risk found that calcium supplementation had no significant effect on the incidence of pre-eclampsia, although it did reduce the risk of severe pre-eclamptic complications. An updated meta-analysis,[5] which included this study, concluded that calcium supplementation during pregnancy was safe and that it did reduce the incidence of pre-eclampsia and serious complications, particularly in high-risk women.

For discussions of hypertension in pregnancy and eclampsia and pre-eclampsia, see p.1171 and p.470, respectively.

1. Bucher HC, *et al.* Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1113–17. Correction. *ibid.*; **276:** 1388.
2. Levine RJ, *et al.* Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; **337:** 69–76.
3. DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA* 1999; **282:** 664–70.
4. Villar J, *et al.* World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006; **194:** 639–49.
5. Hofmeyr GJ, *et al.* Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 17/01/08).

Malignant neoplasms. There is some evidence that calcium supplementation may modestly reduce the risk[1-3] of colorectal cancer and its recurrence.[4-6] This protective effect appears to be more pronounced for advanced colorectal lesions,[7] and when serum concentrations of vitamin D are in the higher range.[8]

1. Wu K, *et al.* Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002; **94:** 437–46.
2. McCullough ML, *et al.* Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* 2003; **14:** 1–12.
3. Cho E, *et al.* Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004; **96:** 1015–22. Correction. *ibid.*; 1724.
4. Baron JA, *et al.* Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999; **340:** 101–7.
5. Bonithon-Kopp C, *et al.* Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000; **356:** 1300–6.
6. Martínez ME, *et al.* Calcium, vitamin D, and risk of adenoma recurrence (United States). *Cancer Causes Control* 2002; **13:** 213–20.
7. Wallace K, *et al.* Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; **96:** 921–5.
8. Grau MV, *et al.* Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1765–71.

Premenstrual syndrome. Calcium supplementation was effective in relieving the luteal phase symptoms of premenstrual syndrome (p.2099) in 1 study.[1] A review of this and other studies suggested that calcium supplementation at a dose of 1.2 to 1.6 g daily should be considered in patients with premenstrual syndrome.[2]

1. Thys-Jacobs S, *et al.* Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998; **179:** 444–52.
2. Ward MW, Holimon TD. Calcium treatment for premenstrual syndrome. *Ann Pharmacother* 1999; **33:** 1356–8.

Preparations

BP 2008: Calcium and Ergocalciferol Tablets; Calcium Chloride Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Effervescent Calcium Gluconate Tablets;
BPC 1973: Calcium with Vitamin D Tablets;
USP 31: Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution; Calcium Acetate Tablets; Calcium Chloride Injection; Calcium Glubionate Syrup; Calcium Gluceptate Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Calcium Levulinate Injection; Calcium with Vitamin D Tablets; Dibasic Calcium Phosphate Tablets; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Calcimax; Calcio Cit Simple; Calcional Citrato; Calcium-Sandoz; Citramar; Findeclin Combi; Ostram; Procalcio; Raffo-Ca; Regucal; Royen; Sigmacal; ***Austral.:*** Celloids CP 57; Citracal†; Sandocal; ***Austria:*** Calcium Fresenius; Calcium-Sandoz; Mono Kalz; Ostram; Phos-Ex; ***Belg.:*** Sandoz Calcium; ***Braz.:*** Calcium-Sandoz; Calcium-Sandoz F; Miocalven; Osteocalcic†; ***Canad.:*** Calciject; Calcium-Rougier†; Calcium-Sandoz†; Osteocit; ***Chile:*** Calcimin; Elcal I†; Kaplus; Ostram; Phoslo; ***Cz.:*** Phosphosorb; ***Denm.:*** Calcium-Sandoz; Phos-Ex; ***Fin.:*** Calcium-Sandoz; Phos-Ex; ***Fr.:*** CAL Ocean; Calcium-Sandoz; Kalcikidz†; Ostram; ***Ger.:*** Calciretard; Calcitrat; Calcium Eifelfango†; Calcium Fresenius†; Calcium-Sandoz; Cerasorb; Eubiolac; Phos-Ex; ***Gr.:*** Neocalcit; Osteorel; Osteus; ***Hong Kong:*** Calcium Unison; Calcium Vida; Calcium-Sandoz†; Citracal; Gluco-Calcium†; Mega-Cal; ***Hung.:*** Bano; Calcimusc; Calcium-Sandoz; Citrokalcium; ***India:*** Calcium-Sandoz; Phosforid; ***Indon.:*** Dumocalcin; Licokalk; ***Irl.:*** Calcium-Sandoz†; Sandocal; ***Israel:*** Calcium-Sandoz; ***Ital.:*** Calcetat; Calcium-Sandoz; ***Malaysia:*** Ca Lac†; Citracal†; Trocium†; ***Mex.:*** Bionokaltran; Bon-Ker†; Calcidef; Calcifox; Calcigenol Doble; Calciofem; Calcium-Sandoz; Calcival; Ostram†; ***Neth.:*** Calcium-Sandoz; Phos-Ex; ***Norw.:*** Calcium-Sandoz; Phos-Ex; ***NZ:*** Calcium-Sandoz; ***Philipp.:*** Calcebone; United Home Calactate; ***Pol.:*** Calcium Calfit; Calcium Syrop; Ostical; Ostram; Sanosvit Calcium; Satural; ***Port.:*** Calcium-Sandoz; Phosphosorb; Sandocal; ***Rus.:*** Calcium-Sandoz Forte (Кальций-Сандоз Форте); ***S.Afr.:*** Calcium-Sandoz; Glucal; ***Singapore:*** Calcium-Sandoz; Citracal; Hydrofluoric Acid Antidote†; Os-Cal; Vitacal; ***Spain:*** Calcio 20 Emulsion; Calcium-Sandoz Forte; Calcium-Sandoz†; Ibercal; Oseofort; Ostram; Royen; Tepox Cal; ***Swed.:*** Calcium-Sandoz; Phos-Ex; ***Switz.:*** Calcium-Sandoz; ***Thai.:*** Calcibon†; Calcium Unison; Calcium-Sandoz; Calsorp; Calvin; Kal-Forte; Lo-P-Caps; ***Turk.:*** Anti-Fosfat Ca; Calcium-Sandoz; Phos-Ex; ***UK:*** BioCalth; Calcium-Sandoz; Ostram; Phos-Ex; Sandocal; ***USA:*** Cal-C; Cal-Citrate; Cal-G; Cal-Lac; Calphron; Citracal; Oyster Calcium; PhosLo; Posture; ***Venez.:*** Calcibon; Calcitrex; Calcium-Sandoz; Citracal; Maxical; Oscale.

Multi-ingredient: ***Arg.:*** Anartrit; Anusol-A; Beriplast P; Calcimax D3; Calcio Cit; Calcional D3; Calcium D†; Cavirox Cit; Citramar D; Flucalin; Isaflavon; Magnesio Incaico; Noacid Diates; Ostram D3; Regucal D; Sojar Plus-Calcio; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Bioglan Cirflo†; Bioglan Mens Super Soy/Clover; Bioglan Soy Power Plus; Cardioplegia A; Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Chelated Cal-Mag; Duo Celloids CPIP; Duo Celloids CPMP; Duo Celloids PCCP; Duo Celloids SPCP; Extralife Meno-Care; Extralife Sleep-Care; FAB Tri-Cal; Magnesium Plus†; PhytoLife; Prosteo†; Silicic Complex†; Soy Forte with Black Cohosh†; Tisseel Duo; Tyroseng†; ***Austria:*** Beriplast; Calcipot C; Calcipot D ; Calcisan; Calcisan B + C; Calcisan C; Calcisan D; Centramin; Coldargan; Coldistan; EST; Famel cum Codein; Famel cum Ephedrin; Lactolavol; Macalvit; Maxi-Kalz; Mega-Calcium; Orocholin; Ruticalzon; Tissucol; Tissucol Duo Quick; ***Belg.:*** Sandoz Calcium + Vitamine C†; Tissucol Duo; Topcal D3†; ***Braz.:*** Alergo Glucalbet†; Beriplast P; Calcifix B12; Calcifix Irradiado; Calcigenol; Calcinol Complexo; Calcium D3; Calcium-Sandoz + Vitamina C; Miocalven D; OsteoNutri; Regulador Xavier N-1†; Rhum Creosotado; Tissucol†; ***Canad.:*** Calcium Magnesium Plus†; Calcium Stanley†; Kid's Chewable Cal-Mag†; Mega Cal Calcium†; Tisseel; ***Chile:*** Beriplast P; C-1000-C†; Calcigran; Calcimax D3; Calcio 520; Calcio Cm; Calcio Nil Forte†; Calcio Nil†; Calciovit Puro; Calcium-Sandoz Forte D; Caprimida D Balance; Crevet Calcio + D3 + C; Elcal-D; Kaplus-D; Ostram D3; Trical-D; Tridin†; ***Cz.:*** Calcium C Neo; Calcium C†; Calcium-Sandoz FF; Calcium-Sandoz Forte; Methiaden Calcium†; OsvaRen; Tissucol; Tridin; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** D-Calsor; Mega-Calcium; Ostram-Vit D †; Tisseel Duo Quick; ***Fr.:*** Beriplast; Ca-C†; Calciforte; Carbophos; Cataridol†; Chloro-Magnesion†; Cristopal†; Curasten; Desintex Infantile; Dops; Estrofort; Frubiose Vitamine D†; Galactogil; Galirene†; Gastropax; Ostram Vitamine D ; Quixil; Tissucol; Vagostabyl; Verrulyse-Methionine; ***Ger.:*** Acidovert†; Beriplast; Calcipot; Calcium Braun; Calcium-dura Vit D ; Calcium-Rutinion†; calcivitase†; Ermsech†; Ferro-C-Calcium; Fluoril; Frubiase Calcium forte 500; Frubiase Calcium T; Hicoton†; Junisana†; Oscevitin-A†; Ossofortin†; Osspulvit S forte†; Osspulvit S†; Quixil; rohasal†; Tissucol Duo S; Tissucol-Kit; Tridin; ***Gr.:*** Beriplast P; Caldesil; Cidominet; Decal; Flavobion-C; Frubiose-N†; Gluta-calcium†; Iodocollyre; Mega-calcium; ***Hong Kong:*** Beriplast P; Ca-C†; Callimon; Caltrate + D; Caltrate Plus; Citracal + D; Liverall†; Magesto; Mega-Cal with Vit D; Osteocare; Scott's Emulsion Orange; Tisseel; Tridin; ***Hung.:*** Beriplast P; Burofix†; Calciphedrin†; Calcium-Sandoz + Vitamin C; Caldea†; Coldargan; Fagifor†; Tissucol-Kit; Tridin; Trypsin†; ***India:*** Alfacip Plus; Aristrol Forte†; Cadisper C; Cafe-Kit†; Calcinol; Catarest; Cato-Bell; CKP; Cotaryl; Gynae-CVP; Kalpastic; Kalzana; Macalvit; Milical; Milical-XP†; Omilcal; Ossivite; Ostebon; Ostocalcium; Ostocalcium B-12; Sigmacalvit; Siochrome; Styptocid; Styptocip†; ***Indon.:*** Beriplast; Cal-95; Calc-Os; Calcidin; Calcimega; Calcium Ad; Calcium-Sandoz; Calcium-Sandoz Forte; Calcium-Sandoz Vit C; Calosbon; Calsical; Cavit D3; CDR Fortos; Dumocalcin Plus; Hi-Bone; Jointfit; LaktaFit; Licokalk Plus; Menoxa; Osimax; Ossovit; Osteocare; Osteopor; Oxcal; Scott's E Vita; Scott's Emulsion; Steopor; Thymcal; Totilac; Vosteon; ***Irl.:*** Bio-Calcium + D ; Bio-Calcium + D + K; Caltrate Plus; Chocovite; Decal; Osteofos D3; ***Israel:*** Beriplast; Calcium Citrate; Calcium-Sandoz + Vit C; Quixil; Tisseel; ***Ital.:*** Beriplast; Biotassina; Calcio Dobetin; Calciozim†; Calciumcafe; Calisvit; CalplusD3; Caltrate; Famel†; Foscald3; Ginvapast; Jodo Calcio Vitaminico; Katoxyn; Lactocol; Osteofos D3; Osteosil Calcium; Ostram D ; Otofluor; Polijodurato; Quixil; Rex; Sedocalcio; Sedopuer F; Silvia Osteo; Tissucol; Tridin; ***Malaysia:*** Adult Citrex Cal-Mag-D3; Bio-Enhanced Calcium Plus; Calcium-Sandoz + Vitamin C; Calcium-Sandoz Forte†; Citracal + D†; Dumocalcin†; Junior Citrex Cal-Mag-D3; Milical; Supa Biocal Vitahealth†; ***Mex.:*** Bedoce-Cal; Beriplast P; C-1000-C; Calciyodina; Calpharma; Caltrec†; Domeboro; Emulsion de Scott; Fluoxytil; Osteocalcio; Posture D; Sandoz Calcium + D; Serracal; Tissucol†; ***Neth.:*** Beriplast P; Calisvit; Quixil; Tissucol; Tissucol Duo; ***Philipp.:*** Caltrate Plus; Glutaphos; Her Soy Plus; Osteo-4; Osteocare; Time-Cee; Ton-A; ***Pol.:*** Ascalcin; Ascalcin Plus; Ascorutical; Beriplast; Calcium C; Sirupus Pini Compositus; Sirupus Tussipini; Sirupus Tussipini D; Wamag; ***Port.:*** Bidiam; Ca-C; Calcigenol; Calcium 600†; Decalcit; Mucal†; Ostram D3†; Osvaren; Osvical; Quixil; Tissucol Duo; ***Rus.:*** Antigrippin-ANVI (Антигриппин-АНВИ); Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); ***S.Afr.:*** Phytopause BSF; Sandoz Calcium-C†; Vitaplus C Plus; ***Singapore:*** BoneCare; Ca-C; Cavit-D3; Citracal + D; Dumocalcin; Flexeze†; Lacto Calcium†; Os-Cal + D; Vita Calmag Zn†; Vitacal; Vitacal + D; ***Spain:*** Alka-Seltzer; Beriplast P Combi; Boldolaxin†; Calcio 20 Complex; Calcio 20 Fuerte; Calcium-Sandoz Forte D; Creacal†; Duplicalcio 150†; Duplicalcio B12; Duplicalcio Hidraz†; Ginejuvent; Ibercal D; Mencalisvit; Metafisol; Osteomerck; Osvical D; Tepox Cal D; Tissucol Duo; Trabex; ***Swed.:*** Macalvit; Relaxit; Tisseel Duo Quick; ***Switz.:*** Beriplast P; C-Calcium; Ca-C†; Calcium D Sauter; Calcivit; Callimon†; Calpred; Decalcit; Demostan N; Famel; Fungex; Ginvapast; Glucocalcium; Phytopharma Calcium; Pidocal†; Stilex; Tissucol; Tissucol Duo S; Vin Tonique de Vial†; ***Thai.:*** Bio-Calcium + D3 + K; Biocalron; Ca-C; Cal-D-Vita; Calcalcin; Calchew; Calcioday-D†; Calcium D; Caltrate Plus; Calvin Plus; Combi-Cal†; Gluco-Calcium; Ostone-B12; Phocium†; ***Turk.:*** Beriplast P; Calcidine; Calcimax D3; Calcium Picken; Calcium-Sandoz C; Caltrate; Folic Plus; Fosfokalsiyum; Fungecyl; Kalsifluor; Nature Made Oyster Shell Calcium; Osteocare; Tisseel VH; ***UK:*** Calcimax; Calcium and Ergocalciferol Tablets; Calcium Clear; Calfovit D3; Caltrate Plus; Crampex; Glykola; Haliborange Calcium Plus Vitamin D; Osteo-Life; Osteocare; Osteopro; Phytolife Plus; S.P.H.P.; Salivix; Tisseel; ***USA:*** Artiss; Bayer Womens Aspirin Plus Calcium; Bluboro†; Boropak†; Calcet; Calphosan; Caltrate Plus; Calvite P & D; Citracal + D; Citracal Creamy Bites†; Citracal Plus with Magnesium; Domeboro; Ester-C Plus; GEM 21S; Mag-Cal Mega; Magonate; Oyster Calcium with Vitamin D; Pedi-Boro Soak Paks; Posture-D; PremesisRx; ***Venez.:*** A-D-Vit; Calcibon D; Calcibon D Magnesio; Calcibon D Soya; Calcibon Natal; Calcinor D; Calciofar D; Calciogenol; Calcion D Plus; Calcitrex D3; Calpal D†; Citracal D; Dicalcico†; Gestocal†; Maltocalcine.

Used as an adjunct in: ***Swed.:*** Deltison.

Magnesium

Magnesio; Magnésium; Magnez.

Mg = 24.305.

Description. Magnesium is a cation given as various magnesium-containing salts.

Incompatibility. Magnesium salts have been reported to be incompatible with a wide range of drugs.

Magnesium Acetate

Magnesii acetas tetrahydricus; Magnesio, acetato de; Magnésium (acétate de) tétrahydraté; Magnesiumacetattetrahydrat; Magnesiumasetaattitetrahydraatti; Magnézium acetáttetrahidrát; Magnezu octan; Magnio acetatas tetrahidratas; Octan hořečnatý tetrahydrát.

$C_4H_6MgO_4,4H_2O$ = 214.5.

CAS — 142-72-3 (anhydrous magnesium acetate); 16674-78-5 (magnesium acetate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Magnesium Acetate Tetrahydrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 7.5 to 8.5.

Equivalence. Each g of magnesium acetate (tetrahydrate) represents about 4.7 mmol of magnesium and the equivalent of bicarbonate. Magnesium acetate (tetrahydrate) 8.83 g is equivalent to about 1 g of magnesium.

Magnesium Ascorbate

Magnesio, ascorbato de.

$(C_6H_7O_6)_2Mg$ = 374.5.
CAS — 15431-40-0.

Equivalence. Each g of magnesium ascorbate (anhydrous) represents about 2.7 mmol of magnesium. Magnesium ascorbate (anhydrous) 15.4 g is equivalent to about 1 g of magnesium.

Magnesium Aspartate

Bázisos magnézium-aszpartát-dihidrát; Magnesii aspartas dihydricus; Magnesii Hydrogenoaspartas Dihydricus; Magnesio, aspartato de; Magnésium (aspartate de) dihydraté; Magnesium Aspartate Dihydrate; Magnesiumaspartaattidihydraatti; Magnesiumaspartatdihydrat; Magnesium-hydrogen-aspartát dihydrát; Magnio aspartatas dihidratas. Magnesium aminosuccinate dihydrate; Magnesium di[(*S*)-2-aminohydrogenobutane-1,4-dioate].

$C_8H_{12}MgN_2O_8,2H_2O$ = 324.5.
CAS — 18962-61-3 (anhydrous magnesium aspartate); 2068-80-6 (anhydrous magnesium aspartate or magnesium aspartate dihydrate); 7018-07-7 (magnesium aspartate tetrahydrate);.
ATC — A12CC05.
ATC Vet — QA12CC05.

Pharmacopoeias. *Eur.* (see p.vii) includes the dihydrate form of the (*S*)-aspartate. *Ger.* includes the tetrahydrate form of the racemic aspartate.
Ph. Eur. 6.2 (Magnesium Aspartate Dihydrate; Magnesium Aspartate BP 2008). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water. A 2.5% solution in water has a pH of 6.0 to 8.0.

Equivalence. Each g of magnesium aspartate (dihydrate) represents about 3.1 mmol of magnesium. Magnesium aspartate (dihydrate) 13.4 g is equivalent to about 1 g of magnesium.

Each g of magnesium aspartate (tetrahydrate) represents about 2.8 mmol of magnesium. Magnesium aspartate (tetrahydrate) 14.8 g is equivalent to about 1 g of magnesium.

Magnesium Chloride

Chlorid hořečnatý; Chlorure de Magnésium Cristallisé; Cloreto de Magnésio; E511; Magnesii chloridum; Magnesio, cloruro de; Magnesium Chloratum; Magnésium, chlorure de; Magnesiumklorid; Magnesiumkloridi; Magnézium-klorid; Magnezu chlorek; Magnio chloridas.

$MgCl_2,xH_2O$ = 95.21 (anhydrous); 203.3 (hexahydrate).
CAS — 7786-30-3 (anhydrous magnesium chloride); 7791-18-6 (magnesium chloride hexahydrate).
ATC — A12CC01; B05XA11.
ATC Vet — QA12CC01; QB05XA11.

Pharmacopoeias. *Eur.* (see p.vii), *US*, and *Viet.* include the hexahydrate.
Eur. also includes magnesium chloride 4.5-hydrate.
Ph. Eur. 6.2 (Magnesium Chloride Hexahydrate; Magnesii Chloridum Hexahydricum). Colourless, hygroscopic crystals. Very soluble in water; freely soluble in alcohol. Store in airtight containers.
Ph. Eur. 6.2 (Magnesium Chloride 4.5-Hydrate; Magnesii Chloridum 4.5-Hydricum; Partially Hydrated Magnesium Chloride BP 2008). A white or almost white, hygroscopic, granular powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.
USP 31 (Magnesium Chloride). Colourless, odourless, deliquescent flakes or crystals, which lose water when heated to 100° and lose hydrochloric acid when heated to 110°. Very soluble in water; freely soluble in alcohol. pH of a 5% solution in water is between 4.5 and 7.0. Store in airtight containers.

Equivalence. Each g of magnesium chloride (hexahydrate) represents about 4.9 mmol of magnesium and 9.8 mmol of chloride. Magnesium chloride (hexahydrate) 8.36 g is equivalent to about 1 g of magnesium.

Magnesium Gluceptate

Magnesio, glucoheptonato de; Magnesium Glucoheptonate.

$C_{14}H_{26}MgO_{16}$ = 474.7.

Equivalence. Each g of magnesium gluceptate (anhydrous) represents about 2.1 mmol of magnesium. Magnesium gluceptate (anhydrous) 19.5 g is equivalent to about 1 g of magnesium.

Magnesium Gluconate

Magnesii gluconas; Magnesio, gluconato de; Magnésium, gluconate de. Magnesium D-gluconate hydrate.

$C_{12}H_{22}MgO_{14}(+xH_2O)$ = 414.6 (anhydrous).
CAS — 3632-91-5 (anhydrous magnesium gluconate); 59625-89-7 (magnesium gluconate dihydrate).
ATC — A12CC03.
ATC Vet — QA12CC03.

Pharmacopoeias. In *Eur.* (see p.vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.
Ph. Eur. 6.2 (Magnesium Gluconate). A white or almost white, amorphous, hygroscopic, crystalline or granular powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. Store in airtight containers.
USP 31 (Magnesium Gluconate). Colourless crystals or a white powder or granules. Is odourless. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 5% solution in water is between 6.0 and 7.8.

Equivalence. Each g of magnesium gluconate (anhydrous) represents about 2.4 mmol of magnesium. Magnesium gluconate (anhydrous) 17.1 g is equivalent to about 1 g of magnesium.

Magnesium Glycerophosphate

Glycerofosforečnan hořečnatý; Magnesii glycerophosphas; Magnesio, glicerofosfato de; Magnesium Glycerinophosphate; Magnésium, glycérophosphate de; Magnesiumglycerofosfat; Magnesiumglyserofosfaatti; Magnézium-glicerofoszfát; Magnio glicerofosfatas.

$C_3H_7MgO_6P(+xH_2O)$ = 194.4 (anhydrous).
CAS — 927-20-8 (anhydrous magnesium glycerophosphate).

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Magnesium Glycerophosphate). A mixture, in variable proportions, of magnesium (*R,S*)-2,3-dihydroxypropyl phosphate and magnesium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. It may be hydrated. A white or almost white, hygroscopic powder. Practically insoluble in alcohol; dissolves in dilute solutions of acids. Store in airtight containers.

Equivalence. Each g of magnesium glycerophosphate (anhydrous) represents about 5.1 mmol of magnesium. Magnesium glycerophosphate (anhydrous) 8 g is equivalent to about 1 g of magnesium.

Magnesium Lactate

Magnesii lactas; Magnesio, lactato de; Magnésium, lactate de; Magnesiumlaktaatti; Magnesiumlaktat; Magnesium-laktát; Magnezu mleczan. Magnesium 2-hydroxypropionate.

$C_6H_{10}MgO_6$ = 202.4.
CAS — 18917-93-6.
ATC — A12CC06.
ATC Vet — QA12CC06.

Pharmacopoeias. *Eur.* (see p.vii) includes the dihydrate.
Ph. Eur. 6.2 (Magnesium Lactate Dihydrate; Magnesii Lactas Dihydricus). A white or almost white, crystalline or granular powder. Slightly soluble in water; soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 6.5 to 8.5.

Equivalence. Each g of magnesium lactate (anhydrous) represents about 4.9 mmol of magnesium. Magnesium lactate (anhydrous) 8.33 g is equivalent to about 1 g of magnesium.

Magnesium Phosphate

Magnesio, fosfato de; Tribasic Magnesium Phosphate; Trimagnesium Phosphate.

$Mg_3(PO_4)_2,5H_2O$ = 352.9.
CAS — 7757-87-1 (anhydrous magnesium phosphate); 10233-87-1 (magnesium phosphate pentahydrate).
ATC — B05XA10.
ATC Vet — QB05XA10.

Pharmacopoeias. In *US*.
Ger. includes Magnesium Hydrogen Phosphate Trihydrate ($MgHPO_4,3H_2O$ = 174.3).
USP 31 (Magnesium Phosphate). A white, odourless, powder. Almost insoluble in water; readily soluble in dilute mineral acids.

Equivalence. Each g of magnesium phosphate (pentahydrate) represents about 8.5 mmol of magnesium and 5.7 mmol of phosphate. Magnesium phosphate (pentahydrate) 4.84 g is equivalent to about 1 g of magnesium.

Magnesium Pidolate *(pINNM)*

Magnesii pidolas; Magnésium, pidolate de; Magnesium Pyroglutamate; Magnesiumpidolaatti; Magnesiumpidolat; Magnesium-pidolát; Magnézium-pidolát; Magnio pidolatas; Pidolate de Magnesium; Pidolato de magnesio. Magnesium 5-oxopyrrolidine-2-carboxylate.

Магния Пидолат

$(C_5H_6NO_3)_2Mg$ = 280.5.
CAS — 62003-27-4.
ATC — A12CC08.
ATC Vet — QA12CC08.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Magnesium Pidolate). An amorphous, white or almost white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 10% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Equivalence. Each g of magnesium pidolate (anhydrous) represents about 3.6 mmol of magnesium. Magnesium pidolate (anhydrous) 11.5 g is equivalent to about 1 g of magnesium.

Magnesium Sulfate

518; Epsom Salts; Magnesii sulfas; Magnesio, sulfato de; Magnésium, sulfate de; Magnesium Sulphate; Magnesiumsulfaatti; Magnesiumsulfat; Magnézium-szulfát; Magnezu siarczan; Magnio sulfatas; Sal Amarum; Sel Anglais; Sel de Sedlitz; Síran hořečnatý.

$MgSO_4,xH_2O$ = 120.4 (anhydrous); 246.5 (heptahydrate).
CAS — 7487-88-9 (anhydrous magnesium sulfate); 10034-99-8 (magnesium sulfate heptahydrate).
ATC — A06AD04; A12CC02; B05XA05; D11AX05; V04CC02.
ATC Vet — QA06AD04; QA12CC02; QB05XA05; QD11AX05; QV04CC02.

Pharmacopoeias. *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.* include the heptahydrate.
US allows the dried form, the monohydrate, or the heptahydrate form.
The dried form is included in *Br.*
Ph. Eur. 6.2 (Magnesium Sulphate Heptahydrate; Magnesii Sulfas Heptahydricus). A white or almost white, crystalline powder or brilliant, colourless crystals. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.
The BP 2008 gives Epsom Salts as an approved synonym.
BP 2008 (Dried Magnesium Sulphate). A white odourless or almost odourless powder, prepared by drying magnesium sulfate (heptahydrate) at 100° until it has lost about 25% of its weight; it contains 62 to 70% of $MgSO_4$. Freely soluble in water; more rapidly soluble in hot water.
The BP gives Dried Epsom Salts as an approved synonym.
USP 31 (Magnesium Sulfate). It is the dried form, monohydrate, or the heptahydrate. Small, colourless crystals, usually needle-like. It effloresces in warm dry air. Soluble 1 in 0.8 of water and 1 in 0.5 of boiling water; freely but slowly soluble 1 in 1 of glycerol; sparingly soluble in alcohol. pH of a 5% solution in water is between 5.0 and 9.2.

Equivalence. Each g of magnesium sulfate (heptahydrate) represents about 4.1 mmol of magnesium. Magnesium sulfate (heptahydrate) 10.1 g is equivalent to about 1 g of magnesium.

Adverse Effects

Excessive parenteral doses of magnesium salts lead to the development of hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade. Other symptoms of hypermagnesaemia may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, bradycardia, coma, and cardiac arrest.

Hypermagnesaemia is uncommon after oral magnesium salts except in the presence of renal impairment. Ingestion of magnesium salts may cause gastrointestinal irritation and watery diarrhoea.

Effects on the gastrointestinal tract. There are isolated reports of paralytic ileus in patients receiving magnesium salts.[1,2] Delayed intestinal transit has also been reported in a neonate who received an intramuscular overdose of magnesium.[3] See also Pregnancy, under Precautions, below.

1. Hill WC, *et al.* Maternal paralytic ileus as a complication of magnesium sulfate tocolysis. *Am J Perinatol* 1985; **2:** 47–8.
2. Golzarian J, *et al.* Hypermagnesemia-induced paralytic ileus. *Dig Dis Sci* 1994; **39:** 1138–42.
3. Narchi H. Neonatal hypermagnesemia: more causes and more symptoms. *Arch Pediatr Adolesc Med* 2001; **155:** 1074.

Hypersensitivity. Hypersensitivity reactions characterised by urticaria were described in 2 women after receiving magnesium sulfate intravenously.[1]

1. Thorp JM, *et al.* Hypersensitivity to magnesium sulfate. *Am J Obstet Gynecol* 1989; **161:** 889–90.

Treatment of Adverse Effects

The management of hypermagnesaemia is reviewed on p.1668.

Hypermagnesaemia. A patient with hypermagnesaemia of a degree that is normally fatal was successfully treated using assisted ventilation, calcium chloride administered intravenously, and forced diuresis with mannitol infusions.[1] In another report, a 7-year-old boy given an Epsom salt (magnesium sulfate) enema for abdominal cramping, developed asystole and died, despite aggressive attempts at resuscitation. Such enemas should be avoided because of the risk of significant, unpredictable rectal absorption, leading to toxic hypermagnesaemia.[2]

1. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. *Obstet Gynecol* 1990; **76:** 984–6.
2. Tofil NM, *et al.* Fatal hypermagnesemia caused by an Epsom salt enema: a case illustration. *South Med J* 2005; **98:** 253–6.

Precautions

Parenteral magnesium salts should generally be avoided in patients with heart block or severe renal impairment. They should be used with caution in less severe degrees of renal impairment and in patients with myasthenia gravis. Patients should be monitored for clinical signs of excess magnesium (see Adverse Effects, above), particularly when being treated for conditions not associated with hypomagnesaemia such as eclampsia. An intravenous preparation of a calcium salt should be available in case of toxicity. When used for hypomagnesaemia, serum-magnesium concentrations should be monitored.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided (see also Pregnancy, below).

Oral magnesium salts should be used cautiously in patients with renal impairment. Taking with food may decrease the incidence of diarrhoea. Chronic diarrhoea from long-term use may result in electrolyte imbalance.

Breast feeding. In breast milk samples from 10 pre-eclamptic women given magnesium sulfate, mean magnesium concentrations 24 hours after delivery were about 6.4 mg per 100 mL, and significantly higher than those in control subjects. However, by 48 and 72 hours after delivery, values were not significantly different. In both treated and control subjects, milk-magnesium concentrations were about twice those of maternal plasma concentrations. Although total doses of magnesium given to mothers may differ, the authors considered any increased magnesium load to a breast-fed infant to be quite small, about 1.5 mg of additional magnesium daily, and unlikely to significantly alter magnesium clearance from the neonate.[1] Based on this, the American Academy of Pediatrics considers that use of magnesium sulfate is therefore usually compatible with breast feeding.[2]

1. Cruikshank DP, *et al.* Breast milk magnesium and calcium concentrations following magnesium sulfate treatment. *Am J Obstet Gynecol* 1982; **143:** 685–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/04)

Hepatic disorders. Severe hypermagnesaemia and hypercalcaemia developed in 2 patients with hepatic encephalopathy given magnesium sulfate enemas; both patients died, one during and one after asystole. It was recommended that patients with liver disease who might develop renal impairment, or in whom renal failure is established, should not be prescribed enemas containing magnesium for treatment of hepatic encephalopathy as serious magnesium toxicity can occur, which may contribute to death.[1]

1. Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *BMJ* 1986; **293:** 1013–14. Correction. *ibid.*; 1222.

Pregnancy. The meconium-plug syndrome (abdominal distention and failure to pass meconium) has been described in 2 neonates who were hypermagnesaemic after their mothers had received magnesium sulfate for eclampsia.[1] It was believed that the hypermagnesaemia may have depressed the function of intestinal smooth muscle. See also Effects on the Gastrointestinal Tract, above. In 36 hypermagnesaemic infants born to pre-eclamptic mothers treated with magnesium sulfate, significant neurobehavioural impairment persisted for over 24 hours after birth. Impairment was manifest by prolonged weakness in activities such as head lag, ventral suspension, suck reflex, and cry response; improvement corresponded to the decrease in plasma-magnesium concentrations.[2]

In studies in women with[3] and without[4] pre-eclampsia there were decreases in short-term fetal heart rate variability when women were given intravenous magnesium sulfate; however, although variability is considered a sign of fetal well-being the decrease was considered clinically insignificant.

1. Sokal MM, *et al.* Neonatal hypermagnesemia and the meconium-plug syndrome. *N Engl J Med* 1972; **286:** 823–5.
2. Rasch DK, *et al.* Neurobehavioral effects of neonatal hypermagnesemia. *J Pediatr* 1982; **100:** 272–6.
3. Atkinson MW, *et al.* The relation between magnesium sulfate therapy and fetal heart rate variability. *Obstet Gynecol* 1994; **83:** 967–70.
4. Hallak M, *et al.* The effect of magnesium sulfate on fetal heart rate parameters: a randomized, placebo-controlled trial. *Am J Obstet Gynecol* 1999; **181:** 1122–7.

Interactions

Parenteral magnesium sulfate potentiates the effects of competitive and depolarising neuromuscular blockers (p.1904). The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. Similarly, parenteral magnesium sulfate and nifedipine have been reported to have additive effects (p.1353).

Oral magnesium salts decrease the absorption of tetracyclines and bisphosphonates, and doses should be separated by a number of hours.

Pharmacokinetics

About one-third of magnesium is absorbed from the small intestine after oral doses and even soluble magnesium salts are generally very slowly absorbed. The fraction of magnesium absorbed increases if magnesium intake decreases. In plasma, about 25 to 30% of magnesium is protein bound. Parenteral magnesium salts are excreted mainly in the urine, and oral doses are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are distributed into breast milk. Magnesium crosses the placenta.

Human Requirements

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte which is a cofactor in numerous enzyme systems.

The body is very efficient at maintaining magnesium concentrations by regulating absorption and renal excretion, and symptoms of deficiency are rare. It is therefore difficult to establish a daily requirement.

Foods rich in magnesium include nuts, unmilled grains, and green vegetables.

UK and US recommended dietary intake. In the United Kingdom dietary reference values (DRV—see Human Requirements, p.1925)[1] and in the United States recommended daily allowances (RDA)[2] have been published for magnesium. In the UK the estimated average requirement (EAR) is 200 mg (or 8.2 mmol) daily for adult females and 250 mg (or 10.3 mmol) daily for adult males; the reference nutrient intake (RNI) is 270 mg (or 10.9 mmol) daily for adult females and 300 mg (or 12.3 mmol) daily for adult males; no increment is recommended during pregnancy but an increment of 50 mg (or 2.1 mmol) daily in the RNI is advised during lactation. In the USA under the new dietary reference intakes an EAR of 330 to 350 mg daily has been set in adult males and 255 to 265 mg daily in adult females; the corresponding RDAs are 400 to 420 mg and 310 to 320 mg daily.[2] An increase in RDA to 350 to 360 mg is recommended during pregnancy but the standard RDA is considered adequate during lactation. A tolerable upper intake level of 350 mg daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Uses and Administration

Some magnesium salts are given as a source of magnesium ions in the treatment of **magnesium deficiency and hypomagnesaemia** (p.1668). Doses may be expressed in terms of mmol or mEq of magnesium, mass (mg) of magnesium, or mass of magnesium salt (for comparative purposes, see Table 2, above). In acute or severe hypomagnesaemia, magnesium may be given parenterally, usually as the chloride or sulfate. One suggested regimen is 20 mmol of magnesium in 1 litre of infusion solution (glucose 5% or sodium chloride 0.9%) given *intravenously* over 3 hours. Alternatively, 35 to 50 mmol of magnesium in 1 litre of infusion solution may be given over a period of 12 to 24 hours. Up to a total of 160 mmol may be required over 5 days. In those receiving parenteral nutrition, doses of about 12 mmol magnesium daily may be given to prevent recurrence of the deficit. Magnesium sulfate can also be given *intramuscularly* for severe magnesium deficiency. A recommended dose is 1 mmol/kg of magnesium, given over a period of 4 hours; this route is stated to be painful. Careful monitoring of plasma-magnesium and other electrolyte concentrations is essential. Doses should be reduced in renal impairment. Other salts which are, or have been, used parenterally include magnesium ascorbate, magnesium aspartate hydrochloride, and magnesium pidolate.

Table 2. Some magnesium salts and their magnesium content.

Magnesium salt	Magnesium content per g		
	mg	mmol	mEq
Magnesium acetate (tetrahydrate)	113	4.7	9.3
Magnesium ascorbate (anhydrous)	65	2.7	5.3
Magnesium aspartate (dihydrate)	75	3.1	6.2
Magnesium aspartate (tetrahydrate)	67	2.8	5.5
Magnesium chloride (hexahydrate)	120	4.9	9.8
Magnesium gluceptate (anhydrous)	51	2.1	4.2
Magnesium gluconate (anhydrous)	59	2.4	4.8
Magnesium glycerophosphate (anhydrous)	125	5.1	10.3
Magnesium lactate (anhydrous)	120	4.9	9.9
Magnesium phosphate (pentahydrate)	207	8.5	17.0
Magnesium pidolate (anhydrous)	87	3.6	7.1
Magnesium sulfate (heptahydrate)	99	4.1	8.1

In simple deficiency states magnesium salts may be given *orally* in doses adjusted according to individual requirements. For preventing recurrence of hypomagnesaemia, doses of 24 mmol daily in divided doses have been recommended. Salts that are, or have been, used orally include magnesium aspartate, magnesium chloride, magnesium citrate, magnesium fluoride, magnesium gluceptate, magnesium gluconate, magnesium glycerophosphate, magnesium lactate, magnesium levulinate, magnesium orotate, and magnesium pidolate.

Magnesium salts such as the carbonate, hydroxide, oxide, and trisilicate are widely used for their **antacid** properties (p.1692). Magnesium salts also act as **osmotic laxatives** (see Constipation, p.1693); the salts generally used for this purpose are magnesium sulfate (an oral dose of 5 to 10 g in 250 mL of water being given for rapid bowel evacuation) and magnesium hydroxide (p.1743).

Parenteral magnesium sulfate has some specific uses. It is used for the emergency treatment of some **arrhythmias** such as torsade de pointes (see below) and those associated with hypokalaemia (p.1669). The usual dose is 2 g of magnesium sulfate (8 mmol of magnesium) given intravenously over 10 to 15 minutes and repeated once if necessary.

Parenteral magnesium sulfate is also used for the prevention of recurrent seizures in pregnant women with **eclampsia** (see below). Debate continues as to which dosage regimen is most appropriate. Typically an intravenous loading dose of 4 g of magnesium sulfate (16 mmol of magnesium) is given over 10 to 15 minutes. This is then followed by either an infusion of 1 g (4 mmol magnesium) per hour (for at least 24 hours after the last seizure) or by deep intramuscular injection of 5 g (20 mmol magnesium) into each buttock then

5 g intramuscularly every 4 hours (for at least 24 hours after the last seizure). Should seizures recur under either regimen, then an additional intravenous dose of 2 to 4 g can be given. It is essential to monitor for signs of hypermagnesaemia, and to stop magnesium dosage should this occur. Doses should be reduced in renal impairment.

The use of magnesium sulfate in **acute myocardial infarction** and **premature labour** is discussed below.

Dried magnesium sulfate has been used in the form of Magnesium Sulphate Paste (BP 2008) as an application to inflammatory skin conditions such as boils and carbuncles, but prolonged or repeated use may damage the surrounding skin.

◊ General references.

1. McLean RM. Magnesium and its therapeutic uses: a review. *Am J Med* 1994; **96:** 63–76.
2. Fawcett WJ, *et al.* Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83:** 302–20.
3. Fox C, *et al.* Magnesium: its proven and potential clinical significance. *South Med J* 2001; **94:** 1195–1201.
4. Gums JG. Magnesium in cardiovascular and other disorders. *Am J Health-Syst Pharm* 2004; **61:** 1569–76.

Anaesthesia. Magnesium sulfate has been used to prevent the undesirable haemodynamic response sometimes associated with intubation (p.1900). It has also been tried in the treatment of postanaesthetic shivering (p.1779).

Arrhythmias. Cardiac function is strongly influenced by electrolyte concentrations and some cardiac arrhythmias (p.1160) may be associated with magnesium deficiency. Parenteral magnesium has a role in the management of torsade de pointes and some other arrhythmias, and has also been used to prevent postoperative atrial fibrillation. However, for the suggestion that it did not have an antiarrhythmic effect in patients with myocardial infarction see Myocardial Infarction, below.

Further references.

1. Frick M, *et al.* The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. *Eur Heart J* 2000; **21:** 1177–85.
2. Stuhlinger HG, *et al.* Der Stellenwert von Magnesium bei Herzrhythmusstorungen. *Wien Med Wochenschr* 2000; **150:** 330–4.
3. Piotrowski AA, Kalus JS. Magnesium for the treatment and prevention of atrial tachyarrhythmias. *Pharmacotherapy* 2004; **24:** 879–95.
4. Shiga T, *et al.* Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *Am J Med* 2004; **117:** 325–33.
5. Alghamdi AA, *et al.* Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. *J Card Surg* 2005; **20:** 293–9.
6. Miller S, *et al.* Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart* 2005; **91:** 618–23.

Eclampsia and pre-eclampsia. Parenteral magnesium sulfate has become the preferred treatment for seizures associated with **eclampsia** (p.470). Studies and systematic reviews have shown it to be more effective than phenytoin,[1,2] diazepam,[1,3] or lytic cocktail,[4] as well as causing fewer adverse effects. Its advantages included a rapid effect and lack of sedation in the mother or the infant.[5] It was also considered to have a wide safety margin with the added security of calcium gluconate being an easily available antidote should overdose occur. Subsequent meta-analysis[6] and systematic review[2-4] reinforced this favourable view.

Magnesium sulfate may also be used to prevent eclampsia in **pre-eclamptic** patients; trials have shown it to be more effective than phenytoin,[7] or nimodipine.[8] A randomised placebo-controlled study[9] involving over 10 000 women in 33 countries found that treatment with magnesium sulfate approximately halved the risk of developing eclampsia; the number of maternal deaths was also less in the treatment group although the differences in risk between this group and the placebo group were not significant.

Despite some concerns about the effects on the fetus of magnesium sulfate use in premature labour, (see below), many,[10,11] including WHO, consider magnesium sulfate the drug of choice for both treatment and prevention of eclampsia. Moreover, follow-up studies of the international study mentioned above found that it was not associated with an increased risk of death or disability in the children at 18 months[12] and in the mothers at 2 years.[13]

1. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345:** 1455–63. Correction. *ibid.*; **346:** 258.
2. Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 21/06/05).
3. Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 21/06/05).
4. Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 21/06/05).
5. Saunders N, Hammersley B. Magnesium for eclampsia. *Lancet* 1995; **346:** 788–9.
6. Chien PFW, *et al.* Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. *Br J Obstet Gynaecol* 1996; **103:** 1085–91.
7. Lucas MJ, *et al.* A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; **333:** 201–5.
8. Belfort MA, *et al.* A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med* 2003; **348:** 304–11.
9. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; **359:** 1877–90.
10. Roberts JM, *et al.* Preventing and treating eclamptic seizures. *BMJ* 2002; **325:** 609–10.
11. WHO. Managing complications in pregnancy and childbirth: a guide for midwives and doctors: headache, blurred vision, convulsions or loss of consciousness, elevated blood pressure. Available at: http://www.who.int/reproductive-health/impac/Symptoms/Headache_blood_pressure_S35_S56.html (accessed 18/05/04)
12. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for children at 18 months. *BJOG* 2007; **114:** 289–99.
13. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for women at 2 years. *BJOG* 2007; **114:** 300–9.

Hypokalaemia. Potassium and magnesium homoeostasis are linked, and hypokalaemia with increased urine potassium excretion may occur in patients with hypomagnesaemia. In this situation, correction of potassium deficit usually requires magnesium to be given as well. Magnesium sulfate at doses greater than those required to correct hypomagnesaemia has been associated with greater improvements in potassium balance than doses just sufficient to correct hypomagnesaemia.[1]

1. Hamill-Ruth RJ, McGory R. Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomized, controlled trial. *Crit Care Med* 1996; **24:** 38–45.

Migraine. Low magnesium concentrations are thought to be important in the pathogenesis of migraine (p.616), but the precise role of magnesium supplementation in the disorder remains to be determined.[1] In a double-blind study,[2] 24 mmol magnesium daily (in the form of magnesium citrate) reduced the incidence of migraine headache by 42% compared with a reduction of 16% with placebo. However, in another similar study,[3] 20 mmol magnesium daily (in the form of magnesium aspartate hydrochloride) was no more effective than placebo in producing a 50% reduction in migraine frequency or intensity. Intravenous magnesium sulfate has shown benefit in the treatment of migraine attacks,[4] especially in those with aura,[5,6] or in patients with low serum-magnesium levels.[7]

1. Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. *Clin Neurosci* 1998; **5:** 24–7.
2. Peikert A, *et al.* Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; **16:** 257–63.
3. Pfaffenrath V, *et al.* Magnesium in the prophylaxis of migraine: a double-blind placebo-controlled study. *Cephalalgia* 1996; **16:** 436–40.
4. Demirkaya Ş, *et al.* Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* 2001; **41:** 171–7.
5. Bigal ME, *et al.* Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2002; **22:** 345–53.
6. Bigal ME, *et al.* Eficácia de três drogas sobre a aura migranosa: um estudo randomizado placebo controlado. *Arq Neuropsiquiatr* 2002; **60:** 406–9.
7. Mauskop A, *et al.* Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study. *Clin Sci* 1995; **89:** 633–6.

Myocardial infarction. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium. Magnesium might have an antiarrhythmic effect (see also Arrhythmias, above) and protect the myocardium against reperfusion injury including myocardial stunning (delayed recovery of myocardial contractility function). Intravenous magnesium salts have been used for cardiac arrhythmias and in an overview of studies in patients with suspected myocardial infarction their use, generally within 12 hours of the onset of chest pain, reduced mortality.[1] The beneficial effect on mortality appeared to be confirmed by the LIMIT-2 study[2] in which 8 mmol of magnesium was given by intravenous injection before thrombolysis and followed by a maintenance infusion of 65 mmol over the next 24 hours. Benefit was confirmed at follow-up an average of 2.7 years later;[3] however, there was no evidence of an antiarrhythmic effect. These beneficial effects were not borne out by the larger ISIS-4 study,[4] although there were slight differences in the magnesium regimen and its timing which might have played a part in these contradictory results. In an attempt to resolve the controversy, the MAGIC trial[5] was designed to test the hypothesis that early use of magnesium in a similar dose to that used in the LIMIT-2 study would reduce short-term mortality in patients with ST elevation myocardial infarction. No benefit or harm of magnesium was observed, and at present the routine use of magnesium in myocardial infarction (p.1175) cannot be recommended.

Patients with acute myocardial infarction may have magnesium deficiency and long-term treatment with oral magnesium has been tried, but in one study was associated with an increased risk of adverse cardiac events and could not be recommended for secondary prevention.[6]

1. Teo KK, *et al.* Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991; **303:** 1499–1503.
2. Woods KL, *et al.* Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992; **339:** 1553–8.
3. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1994; **343:** 816–19.
4. Fourth International Study of Infarct Survival Collaborative Group. ISIS–4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
5. The Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) trial: a randomised controlled trial. *Lancet* 2002; **360:** 1189–96.
6. Galløe AM, *et al.* Influence of oral magnesium supplementation on cardiac events among survivors of an acute myocardial infarction. *BMJ* 1993; **307:** 585–7.

Porphyria. Magnesium sulfate is one of the drugs that has been used for seizure prophylaxis in patients with porphyria (p.471) who continue to experience convulsions while in remission.

Premature labour. Magnesium sulfate has been given intravenously to suppress initial uterine contractions in the management of premature labour[1-3] (p.2003). Although it has been found to possess similar efficacy to beta$_2$ agonists,[4,5] and is widely used, in particular in the USA, a systematic review[6] concluded it was ineffective at delaying birth or preventing preterm birth. Other magnesium salts have also sometimes been given orally.[7,8] Retrospective observational studies found a lower incidence of cerebral palsy in children with birth-weights of less than 1500 g when mothers were treated with magnesium sulfate for pre-eclampsia, eclampsia or premature labour.[9,10] However, increased total paediatric mortality was noted in an interim analysis of a trial of antenatal magnesium sulfate in preterm labour,[11] and the trial was subsequently stopped. Although they considered the safety of magnesium sulfate well established in gestation at term, the authors cautioned against the use of magnesium sulfate in very preterm labour. Subsequent studies found that magnesium sulfate was associated with increased perinatal mortality in low birth-weight offspring, particularly when doses of more than 48 g were used,[12] and that neonates with intraventricular haemorrhage (p.1050) had mothers with higher serum-magnesium concentrations at delivery.[13] Some studies have commented[14,15] on other results, including trials of magnesium for treatment and prevention of eclampsia (see above), and have concluded, along with a systematic review[6] that its use as a tocolytic increases the risk of infant mortality.

Although magnesium sulfate is widely used, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[16] It is not recommended in Europe,[17] and some in the USA have called for such use to be stopped.[18,19]

1. Amon E, *et al.* Tocolysis with advanced cervical dilatation. *Obstet Gynecol* 2000; **95:** 358–62.
2. Terrone DA, *et al.* A prospective, randomized, controlled trial of high and low maintenance doses of magnesium sulfate for acute tocolysis. *Am J Obstet Gynecol* 2000; **182:** 1477–82.
3. Katz VL, Farmer RM. Controversies in tocolytic therapy. *Clin Obstet Gynecol* 1999; **42:** 802–19.
4. Wilkins IA, *et al.* Efficacy and side effects of magnesium sulfate and ritodrine as tocolytic agents. *Am J Obstet Gynecol* 1988; **159:** 685–9.
5. Chau AC, *et al.* A prospective comparison of terbutaline and magnesium for tocolysis. *Obstet Gynecol* 1992; **80:** 847–51.
6. Crowther CA, *et al.* Magnesium sulphate for preventing preterm birth in threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 21/06/05).
7. Martin RW, *et al.* Comparison of oral ritodrine and magnesium gluconate for ambulatory tocolysis. *Am J Obstet Gynecol* 1988; **158:** 1440–3.
8. Ridgway LE, *et al.* A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. *Am J Obstet Gynecol* 1990; **163:** 879–82.
9. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995; **95:** 263–9.
10. Schendel DE, *et al.* Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. *JAMA* 1996; **276:** 1805–10.
11. Mittendorf R, *et al.* Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997; **350:** 1517–18.
12. Scudiero R, *et al.* Perinatal death and tocolytic magnesium sulfate. *Obstet Gynecol* 2000; **96:** 178–82.
13. Mittendorf R, *et al.* Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage. *J Pediatr* 2002; **140:** 540–6.
14. Mittendorf R, *et al.* If tocolytic magnesium sulfate is associated with excess total pediatric mortality, what is its impact? *Obstet Gynecol* 1998; **92:** 308–11.
15. Mittendorf R, *et al.* The Magpie trial. *Lancet* 2002; **360:** 1330–1.

16. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Management of preterm labor (ACOG Practice Bulletin number 43, May 2003). *Obstet Gynecol* 2003; **101:** 1039–47.
17. Di Renzo GC, Roura LC. European Association of Perinatal Medicine-Study Group on Preterm Birth. Guidelines for the management of spontaneous preterm labor. *J Perinat Med* 2006; **34:** 359–66. Also available at: http://www.reference-global.com/doi/pdfplus/10.1515/JPM.2006.073 (accessed 02/07/08)
18. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol* 2006; **108:** 986–9.
19. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; **357:** 477–87.

Pulmonary hypertension of the newborn. Preliminary studies have suggested that intravenous magnesium sulfate may be effective in treating persistent pulmonary hypertension of the newborn, as mentioned on p.1179.

Respiratory disorders. Magnesium sulfate, given intravenously over 20 minutes in doses of 1.2 g to patients with acute exacerbations of chronic obstructive pulmonary disease (p.1112) who had received inhaled salbutamol, appeared to have moderate efficacy.[1]

Infusion of magnesium has been reported to be of benefit in some patients with acute asthma (p.1108), but results have been conflicting;[2-5] meta-analyses of these and other studies concluded that its routine use was not justified, but that it may benefit some patients with severe exacerbations.[6,7] A meta-analysis of 5 studies in children concluded that intravenous magnesium sulfate is likely to be an effective adjunct to standard therapy in the symptomatic treatment of moderate to severe acute childhood asthma.[8] Inhalation of magnesium has also been investigated, either alone or with salbutamol; another meta-analysis considered that it improved pulmonary function, particularly in combination with a $beta_2$ agonist, with the best results seen in more severe cases.[9]

1. Skorodin MS, *et al.* Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 1995; **155:** 496–500.
2. Skobeloff EM, *et al.* Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* 1989; **262:** 1210–13.
3. Green SM, Rothrack SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med* 1992; **21:** 260–5.
4. Ciarallo L, *et al.* Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996; **129:** 809–14.
5. Silverman RA, *et al.* IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002; **122:** 489–97.
6. Rowe BH, *et al.* Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 21/06/05).
7. Alter HJ, *et al.* Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. *Ann Emerg Med* 2000; **36:** 191–7.
8. Cheuk DKL, *et al.* A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005; **90:** 74–7.
9. Blitz M, *et al.* Inhaled magnesium sulfate in the treatment of acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/12/07).

Stroke. Intravenous magnesium sulfate has been investigated for a neuroprotective effect in stroke (p.1185), but results have been largely disappointing.[1]

1. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004; **363:** 439–45.

Tetanus. Magnesium sulfate has been found to minimise autonomic disturbance in ventilated patients and control spasms in non-ventilated patients when used in the treatment of tetanus (p.1901).

References.

1. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; **57:** 811–17.
2. William S. Use of magnesium to treat tetanus. *Br J Anaesth* 2002; **88:** 152–3.

Preparations

BP 2008: Magnesium Chloride Injection; Magnesium Sulphate Injection; Magnesium Sulphate Mixture; Magnesium Sulphate Paste;
USP 31: Magnesium Gluconate Tablets; Magnesium Sulfate in Dextrose Injection; Magnesium Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Biomag; Magnebe; Magnesoide†; ***Austral.:*** Celloids MP 65; Mag 50†; Magmin; ***Austria:*** Cormagnesin; Emgecard; FX Passage; Magium; Magnesium Diasporal; Magnesulf; Magvital; Mg 5-Longoral; Solumag; Ultra-Mag; ***Belg.:*** Magnespasmyl; Ultra-Mg; ***Braz.:*** Mag-Tab; Magnolat†; Magnoston; Pidomag; Sal Amargo Purificado; ***Canad.:*** Maglucate; Magnolex; Magnorol; Proflavanol C; Slow-Mag†; ***Chile:*** Mag-Tab; ***Cz.:*** Coradol†; Cormagnesin†; Magnerot; Magnesium Diasporal†; Mg 5-Granulat†; Mg 5-Longoral†; ***Fr.:*** Efimag†; Ionimag†; Mag 2; Magnespasmyl; Magnogene; Megamag; Solumag†; Spasmag; Top-Mag; Vivamag†; ***Ger.:*** Basti-Mag; Cormagnesin; FX Passage; Magium; Magnaspart; Magnerot; Magnerot A; magnerot Classic; Magnesiocard; Magnesium Diasporal; Magnesium Verla; Magnesium Verla N; Magnesorot; metamagnesol†; Mg 5-Granulat†; Mg 5-Longoral; Mg 5-Sulfat; Mgnor; Nourymag†; Power Orot; Retterspitz Darmreinigungspulver ST; ***Gr.:*** Mag 2; Solumag; Trofocard; ***Hung.:*** Astat†; Cormagnesin; Magnerot; Magnesiocard; ***India:*** Mag; ***Irl.:*** Magnesium Verla; ***Ital.:*** Actimag†; Mag 2; MG 50; Olimag†; Solumag; ***Mex.:*** Conducat†; Ifupeptol Magnesiado; Magnefusin†; ***Pol.:*** Asmag; Biomag; Laktomag; Laktomag B ; Magnefar; Slow-Mag; ***Port.:*** Cormagnesin; Magnesiocard; Magnesona; Magnespasmil; Magnoral; Metabol-Mg; ***Rus.:*** Cormagnesin (Кормагнезин); Magnerot (Магнерот); ***S.Afr.:*** Be-Lax; Magnesit; SB Laxative Mixture; Slow-Mag; ***Spain:*** Actimag; Magnesioboi; Sulmetin†; ***Switz.:*** Mag 2; Mag-Min; Magnegon; Magnesiocard; Magnesium Biomed; Magnesium Vital; Magnesium-Sandoz; Magnespasmyl†; Magnogene; Mg 5-Granoral; Mg 5-Longoral; Mg 5-Oraleff; Mg 5-Sulfat; Solmag†; ***UK:*** Kest; ***USA:*** Almora†; Chloromag; Mag-G; Mag-SR; Mag-Tab; Magtrate; Slow-Mag.

Multi-ingredient: ***Arg.:*** Anartrit; Antikatarata†; Drenocol†; Magnesia Phosphorica I Oligoplex; Magnesio Incaico; Mylanta Extra; Nervigenol Magnesio†; Noacid Diates; Sigmafem; Sigmaflex; Total Magnesiano con Ginseng; Veraldid; ***Austral.:*** Aspartatol; Bio Magnesium; Bioglan Bioage Peripheral; Caprilate; Cardioplegia A; Cardioplegia Concentrate; Celloid Compounds Magcal Plus; Chelated Cal-Mag; Citri Slim+Trim; Duo Celloids CPMP; Duo Celloids PCMP; Duo Celloids PPMP; Duo Celloids PSMP; Duo Celloids SPMP; Duo Celloids SSMP; Extralife Migrai-Care; Extralife Sleep-Care; K-Mag†; Kali Mag†; Machlor; Mag-Oro; Magnesium Plus†; Magnoplasm; ML 20†; Pro-Shape†; Salvital; Zinvit; Zinvit C; Zinvit G; ***Austria:*** Cascara-Salax; Centramin; Corozell; Elozell; Elozell spezial; Gladixol; Illings Bozner Maycur-Tee†; Mag Kottas May-Cur-Tee; Maycardin K; Trommcardin; Trommgallol; ***Braz.:*** Alcafelol†; Sal de Andrews; ***Canad.:*** Osmopak-Plus; ***Chile:*** Cholinogo; ***Cz.:*** Acne Lotio†; Cardilan; Magne-B ; Solutio Thomas cum Procaino; Tromcardin; ***Fin.:*** Wicnelact; ***Fr.:*** Biopause; Cataridol†; Cemaflavone; Chloro-Magnesion†; Cristopal†; Decramp; Delbiase†; Ionyl; Kaologeais; Karayal; Magne-B ; Osmogel; Phosphoneuros; Prefagyl†; Revitalose; Spasmag; Supro; Thalgo Tonic; Tryptonat; Uvimag B ; ***Ger.:*** Ardeycordal N†; Bascardial†; Biomagnesin; Cardio-Kreislauf-Longoral; Cardioplegin N†; Cordesin; Galacordin; Geo-magnit†; Kalium-Magnesium†; Lacoerdin Mg Plus†; Magium K; Magnerot N; Magnesium compositum†; Movicard; rohasal†; Scordal†; Septacord; Tromcardin; Trophicard; ***Gr.:*** Cardioplegia; Magnesium Sandoz; ***Hong Kong:*** Cardioplegia; Osteocare; ***Hung.:*** Aspacardin†; Magne-B ; Osteocare; Panangin; Tromcardin; Vition; ***India:*** Calcinol; Cotaryl; ***Indon.:*** Cardioplegia; Osteocare; ***Irl.:*** Andrews; Bio-Calcium + D ; ***Ital.:*** Briovitase; Calmason; Fertomcidina-U; Fisioreve; Hiperogyn; Polase; Reocol†; Sedofit; Vagostabil; ***Malaysia:*** Adult Citrex Cal-Mag-D3; Cardioplegia; Junior Citrex Cal-Mag-D3; ***Mex.:*** Chofabol; Cidetox; Dicentril; Gavicid†; Hepedren; Peptochol†; Ulgel; ***Philipp.:*** Osteocare; ***Pol.:*** Aspargin; Bemag; Filomag B ; Maglek B ; Magne-B ; Magne-Balans Plus; Magnefar B ; Magnezytki; Magnokal; Magsolvit B ; Magvit B ; Osteogel; Slow-Mag B ; Wamag; ***Port.:*** Actilam; Miostenil; Polase; ***Rus.:*** Magne B6 (Магне B6); Panangin (Панангин); ***S.Afr.:*** Phytopause BSF; Ultimag; ***Singapore:*** Cardioplegia; Vita Calmag Zn†; ***Spain:*** Darmen Salt; Depurativo Richelet; Eupeptina; Lebersal; Magnesium Pyre; Magnogene; Salmagne; Sugarbil; Sulmetin Papaver; Sulmetin Papaverina†; ***Switz.:*** Acne Lotion; Activital Forte; Kawaform†; Klyx Magnum; Magnesium Complexe; Siesta-1; Vigoran†; ***Thai.:*** Calcioday-D†; Cardioplegia; ***Turk.:*** Osteocare; ***UK:*** Andrews; Pegina; ***USA:*** Chlor-3; Mag-Cal Mega; Mag-SR plus Calcium; Magonate; ***Venez.:*** Calcinor D; Fugras; Kalsis.

Phosphate

Fosfato.

Description. Phosphate is an anion given as various potassium or sodium salts.

Incompatibility. Phosphates are incompatible with calcium salts; the mixing of calcium and phosphate salts can lead to the formation of insoluble calcium-phosphate precipitates. Incompatibility has also been reported with magnesium salts.

Monobasic Potassium Phosphate

Dihydrogenfosforečnan draselný; E340; Kalii dihydrogenophosphas; Kalio-divandenilio fosfatas; Kálium-dihidrogén-foszfát; Kaliumdivätefosfat; Kaliumdivetyfosfaatti; Monopotassium Phosphate; Phosphate monopotassique; Potasio, dihidrogenofosfato de; Potassium Acid Phosphate; Potassium Biphosphate; Potassium Dihydrogen Phosphate; Potasu diwodorofosforan. Potassium dihydrogen orthophosphate.

KH_2PO_4 = 136.1.
CAS — 7778-77-0.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Potassium Dihydrogen Phosphate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.
USNF 26 (Monobasic Potassium Phosphate). Colourless crystals or a white granular or crystalline powder. Is odourless. Freely soluble in water; practically insoluble in alcohol. pH of a 1% solution in water is about 4.5. Store in airtight containers.

Equivalence. Each g of monobasic potassium phosphate represents about 7.3 mmol of potassium and of phosphate.

Dibasic Potassium Phosphate

Dikalii phosphas; Dikalio fosfatas; Dikaliumfosfaatti; Dikaliumfosfat; Dikálium-hidrogén-foszfát; Dipotasio, hidrogenofosfato de; Dipotassium Hydrogen Phosphate; Dipotassium Phosphate; Dipotasu wodorofosforan; E340; Hydrogenfosforečnan draselný; Kalii Hydrogenophosphas; Phosphate dipotassique; Potassium Phosphate. Dipotassium hydrogen orthophosphate.

K_2HPO_4 = 174.2.
CAS — 7758-11-4.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Dipotassium Phosphate; Dipotassium Hydrogen Phosphate BP 2008). A very hygroscopic, white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. Store in airtight containers.
USP 31 (Dibasic Potassium Phosphate). Colourless or white, somewhat hygroscopic, granular powder. Freely soluble in water; very slightly soluble in alcohol. pH of a 5% solution in water is between 8.5 and 9.6.

Equivalence. Each g of dibasic potassium phosphate represents about 11.5 mmol of potassium and 5.7 mmol of phosphate.

Monobasic Sodium Phosphate

Dihydrogenfosforečnan sodný; E339; Monobazik Sodyum Fosfat; Natrii dihydrogenophosphas; Natrio-divandenilio fosfatas; Natrium Phosphoricum Monobasicum; Nátrium-dihidrogén-foszfát; Natriumdivätefosfat; Natriumdivetyfosfaatti; Phosphate monosodique; Sodio, dihidrogenofosfato de; Sodium Acid Phosphate; Sodium Biphosphate; Sodium Dihydrogen Phosphate; Sodu diwodorofosforan; Sodyum Dihidrojen Fosfat. Sodium dihydrogen orthophosphate.

NaH_2PO_4,xH_2O.
CAS — 7558-80-7 (anhydrous monobasic sodium phosphate); 10049-21-5 (monobasic sodium phosphate monohydrate); 13472-35-0 (monobasic sodium phosphate dihydrate).
ATC — A06AD17; A06AG01.
ATC Vet — QA06AD17; QA06AG01.

Pharmacopoeias. In *Eur.* (see p.vii) (with $2H_2O$); in *Chin.* (with $1H_2O$). *Br.* also includes monographs for the anhydrous and monohydrate forms. *US* permits the anhydrous, monohydrate, and dihydrate forms.
Ph. Eur. 6.2 (Sodium Dihydrogen Phosphate Dihydrate; Natrii Dihydrogenophosphas Dihydricus). A white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.
The BP 2008 gives Sodium Acid Phosphate as an approved synonym.
BP 2008 (Anhydrous Sodium Dihydrogen Phosphate). A white, slightly deliquescent, crystals or granules. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.
BP 2008 (Sodium Dihydrogen Phosphate Monohydrate). A white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.
USP 31 (Monobasic Sodium Phosphate). It contains one or two molecules of water of hydration, or is anhydrous. Colourless crystals or white crystalline powder. Is odourless and is slightly deliquescent. Freely soluble in water; practically insoluble in alcohol. Its solutions are acid to litmus and effervesce with sodium carbonate. pH of a 5% solution in water of the monohydrate form is between 4.1 and 4.5.

Equivalence. Each g of monobasic sodium phosphate (anhydrous) represents about 8.3 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (monohydrate) represents about 7.2 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (dihydrate) represents about 6.4 mmol of sodium and of phosphate.

Dibasic Sodium Phosphate

Dibazik Sodyum Hidrojen Fosfat; Dinatrii phosphas; Dinatrio fosfatas; Dinatriumfosfaatti; Dinatriumfosfat; Dinátrium-hidrogén-foszfát; Disodio, hidrogenofosfato de; Disodium Hydrogen Phosphate; Disodium Phosphate; Disodu fosforan; Disodu wodorofosforan; Disodyum Hidrojen Fosfat; E339; Hydrogenfosforečnan sodný; Natrii Hydrogenophosphas; Natrii Phosphas; Natrii Phosphatis; Natriumfosfaatti; Natriumfosfat; Phosphate disodique; Sodium Phosphate. Disodium hydrogen orthophosphate.

Na_2HPO_4,xH_2O.
CAS — 7558-79-4 (anhydrous dibasic sodium phosphate); 10028-24-7 (dibasic sodium phosphate dihydrate); 7782-85-6 (dibasic sodium phosphate heptahydrate); 10039-32-4 (dibasic sodium phosphate dodecahydrate).
ATC — A06AD17; A06AG01; B05XA09.
ATC Vet — QA06AD17; QA06AG01; QB05XA09.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.* The pharmacopoeias may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (Na_2HPO_4 = 142.0), the dihydrate ($Na_2HPO_4,2H_2O$ = 178.0), the heptahydrate ($Na_2HPO_4,7H_2O$ = 268.1), and the dodecahydrate ($Na_2HPO_4,12H_2O$ = 358.1), although not necessarily all will be found in any one pharmacopoeia.
Ph. Eur. 6.2 (Disodium Phosphate, Anhydrous; Dinatrii Phosphas Anhydricus; Anhydrous Disodium Hydrogen Phosphate BP 2008). A white or almost white, hygroscopic powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline. Store in airtight containers.
Ph. Eur. 6.2 (Disodium Phosphate Dihydrate; Dinatrii Phosphas Dihydricus; Disodium Hydrogen Phosphate Dihydrate BP 2008). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline.
The BP 2008 gives Sodium Phosphate Dihydrate as an approved synonym.
Ph. Eur. 6.2 (Disodium Phosphate Dodecahydrate; Dinatrii Phosphas Dodecahydricus; Disodium Hydrogen Phosphate Dodecahydrate BP 2008). Colourless, transparent, very efflorescent crystals. Very soluble in water; practically insoluble in alcohol. A 10% solution in water is slightly alkaline.

USP 31 (Dibasic Sodium Phosphate). It is dried, or contains one, two, seven, or twelve molecules of water of hydration.
The dried substance is a white powder that readily absorbs moisture. It is soluble 1 in 8 of water; insoluble in alcohol.
The heptahydrate is a colourless or white, granular or caked salt that effloresces in warm, dry air. It is freely soluble in water; very slightly soluble in alcohol. Its solutions are alkaline to phenolphthalein, a 0.1M solution having a pH of about 9.
Store all forms in airtight containers.

Equivalence. Each g of dibasic sodium phosphate (anhydrous) represents about 14.1 mmol of sodium and 7.0 mmol of phosphate. Each g of dibasic sodium phosphate (dihydrate) represents about 11.2 mmol of sodium and 5.6 mmol of phosphate. Each g of dibasic sodium phosphate (heptahydrate) represents about 7.5 mmol of sodium and 3.7 mmol of phosphate. Each g of dibasic sodium phosphate (dodecahydrate) represents about 5.6 mmol of sodium and 2.8 mmol of phosphate.

Tribasic Sodium Phosphate

E339; Sodio, fosfato de; Trisodium Orthophosphate; Trisodium Phosphate.

Na_3PO_4 = 163.9.
CAS — 7601-54-9.
ATC — A06AD17; A06AG01.
ATC Vet — QA06AD17; QA06AG01.

Pharmacopoeias. In *USNF.*

USNF 26 (Tribasic Sodium Phosphate). It is anhydrous or contains 1 to 12 molecules of water of hydration. White, odourless crystals or granules, or a crystalline powder. Freely soluble in water; insoluble in alcohol. pH of a 1% solution in water is between 11.5 and 12.0. Store in airtight containers.

Equivalence. Each g of tribasic sodium phosphate (anhydrous) represents about 18.3 mmol of sodium and 6.1 mmol of phosphate.

Adverse Effects and Treatment

Excessive doses of intravenous phosphate cause hyperphosphataemia, particularly in patients with renal failure. Hyperphosphataemia leads in turn to hypocalcaemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcaemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure. Hyperphosphataemia, hypocalcaemia, and tissue calcification are rare after oral or rectal doses (but see Effects on Electrolytes, and Effects on the Kidneys, below).

Adverse effects of oral phosphates may include nausea, vomiting, diarrhoea, and abdominal pain. When they are being used for indications other than their laxative effects, diarrhoea may necessitate a reduction in dosage. Sodium phosphates given rectally for bowel evacuation may cause local irritation.

Phosphates are given as the potassium or sodium salts or both, and may thus be associated with hyperkalaemia, and hypernatraemia and dehydration. Sodium phosphate may cause hypokalaemia.

Treatment of adverse effects involves withdrawal of phosphate, general supportive measures, and correction of serum-electrolyte concentrations, especially calcium. Measures to remove excess phosphate such as oral phosphate binders and haemodialysis may be required (see also Hyperphosphataemia, p.1669).

Effects on electrolytes. Although less common than after intravenous therapy, hyperphosphataemia, accompanied by hypocalcaemia or other severe electrolyte disturbances and resulting in tetany[1,2] and even death,[2] has been reported after the use of phosphate enemas. Similar effects have also been reported with the use of oral phosphate laxatives,[3-7] and in the USA, the FDA has issued warnings of the risk of electrolyte disturbances after the use of high oral doses of sodium phosphate, particularly in vulnerable patients.[8] Infants or children,[2,9,10] the elderly,[4,11] and those with renal impairment,[1,4,11] or congestive heart failure[4] have often had these adverse effects. Licensed product information for one oral sodium phosphate bowel cleanser (*Visicol; Salix, USA*) states that there have been reports of generalised tonic-clonic seizures and/or loss of consciousness in patients with no history of seizures; these cases were associated with electrolyte abnormalities, and low serum osmolality.

Hyperphosphataemia may precipitate nephrocalcinosis, causing an acute phosphate nephropathy, see Effects on the Kidneys, below.

1. Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema. *Lancet* 1985; **ii:** 1433.
2. Martin RR, *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; **257:** 2190–2.
3. Peixoto Filho AJ, Lassman MN. Severe hyperphosphatemia induced by a phosphate-containing oral laxative. *Ann Pharmacother* 1996; **30:** 141–3.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adverse Drug React Bull* 1997; **16:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 04/08/08)
5. Ullah N, *et al.* Fatal hyperphosphatemia from a phosphosoda bowel preparation. *J Clin Gastroenterol* 2002; **34:** 457–8.
6. Woo YM, *et al.* A life threatening complication after ingestion of sodium phosphate bowel preparation. *BMJ* 2006; **333:** 589–90.
7. Domico MB, *et al.* Severe hyperphosphatemia and hypocalcemic tetany after oral laxative administration in a 3-month-old infant. *Pediatrics* 2006; **118:** e1580–e1583. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/e1580 (accessed 13/12/06)
8. FDA. Safety of Sodium Phosphates Oral Solution (issued 17th September, 2001). Available at: http://www.fda.gov/cder/drug/safety/sodiumphospate.htm (accessed 18/05/04)
9. McCabe M, *et al.* Phosphate enemas in childhood: cause for concern. *BMJ* 1991; **302:** 1074.
10. Harrington L, Schuh S. Complications of Fleet enema administration and suggested guidelines for use in the pediatric emergency department. *Pediatr Emerg Care* 1997; **13:** 225–6.
11. Boivin MA, Kahn SR. Symptomatic hypocalcemia from oral sodium phosphate: a report of two cases. *Am J Gastroenterol* 1998; **93:** 2577–9.

Effects on the kidneys. Acute renal failure and nephrocalcinosis have been reported after the use of oral phosphate-based cathartics for bowel cleansing.[1,2] Although relatively rare with oral preparations, this acute phosphate nephropathy is a serious adverse effect; most patients were left with chronic renal insufficiency, and some developed end-stage renal disease. Potential contributing factors include inadequate hydration, increased age, a history of hypertension and arteriosclerosis, and concurrent use of ACE inhibitors, angiotensin receptor antagonists, diuretics, or NSAIDs.[2] The FDA has issued warnings[3] about the use of oral sodium phosphate products, especially in patients with impaired renal function, dehydration, or uncorrected electrolyte abnormalities, or in those taking drugs likely to contribute to the risk of nephropathy. The patient should be advised to take the correct dose of oral sodium phosphate, to drink sufficient liquid during bowel cleansing, and to avoid other phosphate-containing laxatives. Patients at increased risk should have their electrolytes and renal function monitored.

Nephrocalcinosis has also been reported in children with hypophosphataemic rickets treated with calcitriol and phosphate supplements; this was found to be associated with the phosphate dose.[4]

1. Desmeules S, *et al.* Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; **349:** 1006–7.
2. Markowitz GS, *et al.* Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; **16:** 3389–96.
3. FDA. Oral sodium phosphate products for bowel cleansing (issued May 2006). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/OSP_solutionHCP.pdf (accessed 11/12/06)
4. Verge CF, *et al.* Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; **325:** 1843–8.

Local toxicity. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotising effect of the phosphate on the rectum.[1]

1. Sweeney JL, *et al.* Rectal gangrene: a complication of phosphate enema. *Med J Aust* 1986; **144:** 374–5.

Precautions

Phosphates should not generally be given to patients with severe renal impairment. They should be avoided in patients who may have low serum-calcium concentrations, as these may decrease further, and in patients with infected phosphate renal calculi. Potassium phosphates should be avoided in patients with hyperkalaemia and sodium phosphates should generally be avoided in patients with congestive heart failure, hypertension, and oedema. Serum electrolytes and renal function should be monitored during therapy, particularly if phosphates are given parenterally.

Oral or rectal sodium phosphate preparations for bowel evacuation should not be used in patients with gastrointestinal obstruction, inflammatory bowel disease, and conditions where there is likely to be increased colonic absorption. They should be used cautiously in elderly and debilitated patients, and in those with pre-existing electrolyte disturbances (see Effects on Electrolytes, above).

Interactions

Oral phosphate supplements should not be used with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce its absorption. Vitamin D increases the gastrointestinal absorption of phosphates and therefore increases the potential for hyperphosphataemia.

Hyperphosphataemia, hypocalcaemia, and hypernatraemia are more likely to occur with phosphate enemas or oral laxatives if these are given to patients receiving diuretics or other drugs that may affect serum electrolytes. The risk of ectopic calcification may be increased by concurrent use of calcium supplements or calcium-containing antacids.

The risk of hyperkalaemia is increased if potassium phosphates are given with drugs that can increase serum-potassium concentrations.

Pharmacokinetics

About two-thirds of ingested phosphate is absorbed from the gastrointestinal tract. Excess phosphate is mainly excreted in the urine, the remainder being excreted in the faeces.

◊ References.

1. Larson JE, *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; **5:** 45–9.

Human Requirements

Phosphorus requirements are usually regarded as equal to those of calcium.

Most foods contain adequate amounts of phosphate, particularly meat and dairy products, hence deficiency is virtually unknown except in certain disease states, in patients receiving total parenteral nutrition, or in those who have received phosphate-binding drugs for prolonged periods; for further details see under Hypophosphataemia, p.1669.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p.1925)[1] and in the USA dietary reference intakes including recommended dietary allowances (RDA)[2] have been published for phosphorus. In the UK the reference nutrient intake (RNI) for adults is about 550 mg (17.5 mmol) daily; no additional amount is recommended for pregnancy although an additional amount of about 440 mg (14.3 mmol) daily is advised during lactation. In the USA the RDA is 1250 mg daily for those aged 9 to 18 years and 700 mg daily in adults; no increase in RDA is recommended during pregnancy and lactation. A tolerable upper intake level of 4 g daily has been set in adults aged up to 70 years; in those older than 70 a maximum of 3 g daily is recommended.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Uses and Administration

Phosphates are used in the management of **hypophosphataemia** caused by phosphate deficiency or hypophosphataemic states (p.1669). Doses of up to 100 mmol of phosphate daily may be given orally. The intravenous route is seldom necessary, but a dose of up to 9 mmol of phosphate as monobasic potassium phosphate may be given over 12 hours and repeated every 12 hours as necessary for severe hypophosphataemia. Alternatively, 0.2 to 0.5 mmol/kg phosphate, up to a maximum of 50 mmol, may be given over 6 to 12 hours (see also below). Plasma-electrolyte concentrations, especially phosphate and calcium, and renal function should be carefully monitored. Reduced doses may be necessary in patients with renal impairment. Phosphate supplements are used in total parenteral nutrition regimens; typical daily requirements are 20 to 30 mmol of phosphate.

Phosphates act as mild osmotic **laxatives** (p.1693) when given orally as dilute solutions or by the rectal route. Phosphate enemas or concentrated oral solutions are used for bowel cleansing before surgery or endoscopy procedures. Preparations typically combine monobasic and dibasic sodium phosphates but the composition and dosage do vary slightly. Phosphate enemas act within 2 to 5 minutes, whereas the oral solutions act within 30 minutes to 6 hours.

Phosphates also have **other uses**. They lower the pH of urine and have been given as adjuncts to urinary antibacterials that depend on an acid urine for their activity. Phosphates have also been used for the prophylaxis of calcium renal calculi; the phosphates reduce urinary excretion of calcium thus preventing calcium deposition. A suggested oral dose for both uses is 7.4 mmol of phosphate four times daily.

Butafosfan (1-butylamino-1-methylethylphosphinic acid) and the sodium salt of toldimfos (4-dimethylamino-*O*-tolylphosphinic acid) are used as phosphorus sources in veterinary medicine.

Bowel evacuation. A review concluded that the efficacy and tolerability of oral sodium phosphate solution was generally similar to, or significantly better than, that of polyethylene glycol-based or other colorectal cleansers in patients preparing for colorectal-related procedures.[1]

1. Curran MP, Plosker GL. Oral sodium phosphate solution: a review of its use as a colorectal cleanser. *Drugs* 2004; **64:** 1697–1714.

Hypercalcaemia. Intravenous phosphates have been used to lower plasma-calcium concentrations in hypercalcaemic emergencies (p.1668), but because of their potential to cause serious adverse effects other drugs are now preferred. Oral phosphates may be used to prevent gastrointestinal absorption of calcium in the treatment of hypercalcaemia. The dose in adults is up to 100 mmol phosphate daily adjusted according to response.

Hypophosphataemia. Phosphate salts are given in the management of hypophosphataemia when a phosphate deficiency is identified, as discussed in Uses and Administration, above. Intravenous phosphates are associated with serious adverse effects if hypophosphataemia is over-corrected, and the rise in serum-phosphorus concentration cannot be predicted from a given dose. Consequently, it has been recommended[1-4] that intravenous phosphate be used cautiously in the treatment of severe hypophosphataemia (for the standard rate and dose see Uses and Administration, above). However, some advocate a more aggressive fixed-dose regimen in critically ill patients.[5-7]

1. Vannatta JB, *et al.* Efficacy of intravenous phosphorus therapy in the severely hypophosphataemic patient. *Arch Intern Med* 1981; **141:** 885–7.
2. Anonymous. Treatment of severe hypophosphatemia. *Lancet* 1981; **ii:** 734.
3. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; **7:** 123–8.
4. Coyle S, *et al.* Treatment of hypophosphataemia. *Lancet* 1992; **340:** 977.
5. Perreault MM, *et al.* Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Ann Pharmacother* 1997; **31:** 683–8.
6. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. *Am J Emerg Med* 2000; **18:** 457–61.
7. Charron T, *et al.* Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Med* 2003; **29:** 1273–8.

Osteomalacia. Vitamin D deficiency, or its abnormal metabolism, is the most usual cause of osteomalacia and rickets (p.1084); however, phosphate depletion may also contribute, and phosphate supplementation may be given as appropriate. A suggested oral dose for vitamin-D-resistant hypophosphataemic osteomalacia in adults is 65 to 100 mmol phosphate daily, and for vitamin D-resistant rickets in children is 32 to 48 mmol phosphate daily.

RICKETS OF PREMATURITY. Dietary deficiency of phosphorus is unusual, but can occur in small premature infants fed exclusively on human breast milk. The phosphate intake in these infants appears to be inadequate to meet the needs of bone mineralisation, and hypophosphataemic rickets can develop. It has been proposed that this condition, variably called metabolic bone disease of prematurity, or rickets of prematurity, could be prevented by giving phosphorus supplements to very low-birth-weight babies (less than about 1000 g) fed on breast milk alone.[1] A suggested regimen is to add 10 to 15 mg of phosphorus per 100 mL of feed (as buffered sodium phosphate) until the infant reached 2000 g. Concomitant calcium and vitamin D supplementation are also recommended.[1] A placebo-controlled study[2] in infants weighing less than 1250 g at birth confirmed that phosphate supplements (50 mg daily) could prevent the development of the bone defects of rickets of prematurity.

1. Brooke OG, Lucas A. Metabolic bone disease in preterm infants. *Arch Dis Child* 1985; **60:** 682–5.
2. Holland PC, *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; **335:** 697–701. Correction. *ibid.*; 1408–9.

Preparations

BP 2008: Dipotassium Hydrogen Phosphate Injection; Phosphates Enema; Sterile Potassium Dihydrogen Phosphate Concentrate;
Ph. Eur.: Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 31: Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Potassium Phosphates Injection; Sodium Phosphates Injection; Sodium Phosphates Oral Solution; Sodium Phosphates Rectal Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Dicofan; Enemol; Fleet Enema†; Fosfacol; Fosfafarma; Fosfo-Dom; Fosfoadital; Fosfobarigraf; Gadolax; Kritel Enema; Prontonema; Silaxa; Tekfema; ***Austral.:*** Celloids PP 85; Celloids SP 96; Fleet Phospho-Soda; Fleet Ready-to-Use; Phosphate-Sandoz; Phosphoprep; ***Austria:*** Fleet Phospho-Soda; Relaxyl; ***Belg.:*** Colexklysma; Fleet Enema; Fleet Phospho-Soda; Practo-Clyss; ***Braz.:*** Fleet Enema; Phosfoenema; ***Canad.:*** Fleet Enema; Fleet Phospho-Soda; ***Chile:*** Fabulaxol; Fleet Enema; Fleet Fosfosoda; ***Denm.:*** Fleet; ***Fin.:*** K-Fosfosteril†; ***Fr.:*** Fleet Phospho-Soda; ***Ger.:*** Fleet Phospho-Soda; ***Gr.:*** Bioklysm; Enema Cooper; Fleet Enema; Fosfolax; Klysmol; ***Hong Kong:*** Fleet Enema; Fleet Phospho-Soda; Unima; ***Hung.:*** Fleet Phospho-Soda; Optacid; ***India:*** Exit; ***Indon.:*** Fleet Enema; Fleet Phosposoda; ***Irl.:*** Fleet; ***Israel:*** Fleet Enema; ***Ital.:*** Clisma Fleet; Fosfo-Soda Fleet; ***Malaysia:*** Fleet Enema; Fleet Phospho-Soda; ***Mex.:*** Deplecat†; Fleet Enema Fosf-Sodio; Fleet PS; ***Neth.:*** Fleet Gebruiksklaar Klysma; Phosphoral; ***NZ:*** Fleet Phosphate Enema; Fleet Phospho-Soda; ***Philipp.:*** Fleet Enema; Phospho-Soda; ***Pol.:*** Enema; Fleet Phospho-Soda; Phospho-Laxative; Rectanal; ***Port.:*** Fleet Enema; Fleet Phospho-Soda; ***Singapore:*** Fleet Enema†; Fleet Phospho-Soda†; ***Spain:*** Fosfoevac; Fosfosoda; ***Swed.:*** Phosphoral; ***Turk.:*** BT Enema; Fleet Enema; Fleet Fosfo Soda; ***UK:*** Fleet Phospho-Soda; Fleet Ready-to-Use; ***USA:*** Fleet Enema; Fleet Phospho-Soda; K-Phos Original; OsmoPrep; Visicol; ***Venez.:*** Fleet Enema; Fleet Fosfosoda.

Multi-ingredient: ***Arg.:*** Colonil; ***Austral.:*** Cal Alkyline; Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Duo Celloids PPIP; Duo Celloids PPMP; Duo Celloids SPCF; Duo Celloids SPCP; Duo Celloids SPIP; Duo Celloids SPMP; Duo Celloids SPPC; Duo Celloids SPPP; Duo Celloids SPPS; Duo Celloids SPS; Duo Celloids SPSS; Gingo A†; Ginkgo Plus Herbal Plus Formula 10†; Lifesystem Herbal Plus Formula 11 Ginkgo†; Lifesystem Herbal Plus Formula 2 Valerian†; Magnesium Plus†; ML 20†; Potasi; Travad†; Valerian Plus Herbal Plus Formula 12†; ***Austria:*** Clysmol; Prepacol; Reducto; ***Belg.:*** Lavement au Phosphate†; Prepacol; ***Braz.:*** Digestron†; ***Canad.:*** Enemol; Gent-L-Tip†; Normo Gastryl; Phosphate-Novartis; Phosphates; ***Cz.:*** Blend-a-Med†; Mopasol; Prepacol; ***Denm.:*** Phosphoral; ***Fin.:*** Phosphoral; ***Fr.:*** Bactident; Digedryl; Hepargitol; Normacol Lavement; Normogastryl†; Oxyboldine; Phosphoneuros; Phosphore Medifa; Prefagyl†; Prepacol; Tavag; ***Ger.:*** Isogutt†; Klistier; Klysma Salinisch†; Lecicarbon; Practo-Clyss; Prepacol; Reducto-spezial; ***Gr.:*** Enter-Out; Fleet Phospho-Soda; Kathargon; Mineralin; Phospho-Laxat; Phosphoclean; Trifalac; ***Hong Kong:*** PMS-Enemol†; ***Hung.:*** Nilacid; Vition; ***India:*** Cotaryl; ***Indon.:*** Fosen; Kalkurenal; ***Irl.:*** Fletchers Phosphate Enema; ***Israel:*** Calciless; Soffodex; ***Ital.:*** Clisflex; Clisma-Lax; Enemac; IperClean; Phospho-Lax; Pomag; ***Malaysia:*** Unima; ***Mex.:*** Travad†; ***Neth.:*** Colex; ***Norw.:*** Phosphoral; ***NZ:*** Phosphate-Sandoz; ***Pol.:*** Phosphor; Sal Ems Artificiale; Sal Ems Factitium; Sal Vichy Factitium; ***S.Afr.:*** Colo-Prep; Lenolax; Phosphate-Sandoz; Sabax Fosenema; ***Singapore:*** ENTsol; ***Spain:*** Alcalinos Gelos; Darmen Salt; Enema Casen; Eupeptina; Foslainco; Lebersal; ***Switz.:*** Colophos; Freka-Clyss; Lecicarbon; Practo-Clyss†; ***Thai.:*** Swiff; Uni-Ma; ***UK:*** Carbalax; Fletchers Phosphate Enema†; Phosphate-Sandoz; Salivix; ***USA:*** K-Phos MF; K-Phos Neutral; K-Phos No.2; MSP-Blu; Neutra-Phos; Neutra-Phos-K; Phos-NaK; Summers Eve Post-Menstrual; Urelle; Uretron; Urimar-T; Urimax; UriSym†; Uro Blue; Urogesic Blue; Utira; ***Venez.:*** Fisiolin; Polantac.

Potassium

Kalium; Potasio.
K = 39.0983.

Description. Potassium salts covered in this section are those principally given as a source of potassium ions, but consideration should also be given to the effect of the anion. Phosphate salts of potassium are covered under Phosphate, p.1682, and the bicarbonate and citrate salts under Bicarbonate, p.1673.

Potassium Acetate

E261; Kalii acetas; Kalio acetatas; Kaliumacetat; Kálium-acetát; Kaliumasetaatti; Octan draselný; Potasio, acetato de; Potassium, acétate de; Potasu octan.
$CH_3.CO_2K$ = 98.14.
CAS — 127-08-2.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Potassium Acetate). Deliquescent white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from moisture.
USP 31 (Potassium Acetate). Colourless, monoclinic crystals, or a white crystalline powder. It is odourless or has a faint acetous odour. Deliquesces on exposure to moist air. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 3 of alcohol. pH of a 5% solution in water is between 7.5 and 8.5. Store in airtight containers.

Equivalence. Each g of potassium acetate (anhydrous) represents about 10.2 mmol of potassium. Potassium acetate (anhydrous) 2.51 g is equivalent to about 1 g of potassium.

Potassium Aspartate

Aspartate monopotassique hémihydraté; Kalii hydrogenoaspartas hemihydricus; Kalio-divandenilio aspartatas hemihidratas; Kalium-hydrogen-aspartát hemihydrát; Kaliumväteaspartathemihydrat; Kaliumvetyaspartaattihemihydraatti; Potassium Hydrogen Aspartate Hemihydrate. Potassium aminosuccinate hemihydrate.
$C_4H_6KNO_4,\frac{1}{2}H_2O$ = 180.2.
CAS — 7259-25-8 (hemihydrate).

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Potassium Hydrogen Aspartate Hemihydrate). A white or almost white, powder or crystalline powder, or colourless crystals. Very soluble in water; practically insoluble in alcohol and in dichloromethane. pH of a 2.5% solution in water is between 6.0 and 7.5.

Equivalence. Each g of potassium aspartate represents about 5.5 mmol of potassium. Potassium aspartate 4.61 g is equivalent to about 1 g of potassium.

Potassium Chloride

Chlorid draselný; Cloreto de Potássio; E508; Kalii chloridum; Kalio chloridas; Kalium Chloratum; Kaliumklorid; Kálium-klorid; Kaliumkloridi; Potasio, cloruro de; Potassium, chlorure de; Potasu chlorek.
KCl = 74.55.
CAS — 7447-40-7.
ATC — A12BA01; B05XA01.
ATC Vet — QA12BA01; QB05XA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Potassium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in dehydrated alcohol.
USP 31 (Potassium Chloride). Colourless, elongated, prismatic, or cubical crystals, or a white, granular powder. Is odourless. Soluble 1 in 2.8 of water, and 1 in 2 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of potassium chloride represents about 13.4 mmol of potassium. Potassium chloride 1.91 g is equivalent to about 1 g of potassium.

Potassium Gluconate

E577; Potasio, gluconato de. Potassium D-gluconate.
$CH_2OH.[CH(OH)]_4.CO_2K$ = 234.2.
CAS — 299-27-4 (anhydrous potassium gluconate); 35398-15-3 (potassium gluconate monohydrate).
ATC — A12BA05.
ATC Vet — QA12BA05.

Pharmacopoeias. In *Fr.*
US permits anhydrous or the monohydrate.
USP 31 (Potassium Gluconate). It is anhydrous or contains one molecule of water of hydration. A white or yellowish-white, odourless, crystalline powder or granules. Soluble 1 in 3 of water; practically insoluble in dehydrated alcohol, in chloroform, in ether, and in benzene. Its solutions are slightly alkaline to litmus. Store in airtight containers.

Equivalence. Each g of potassium gluconate (anhydrous) represents about 4.3 mmol of potassium. Each g of potassium gluconate (monohydrate) represents about 4 mmol of potassium. Potassium gluconate (anhydrous) 5.99 g and potassium gluconate (monohydrate) 6.45 g are each equivalent to about 1 g of potassium.

Potassium Sulfate

E515; Kalii sulfas; Kalio sulfatas; Kalium Sulfuricum; Kaliumsulfaatti; Kaliumsulfat; Potasio, sulfato de; Potassii Sulphas; Potassium, sulfate de; Potassium Sulphate; Síran draselný; Tartarus Vitriolatus.
K_2SO_4 = 174.3.
CAS — 7778-80-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Potassium Sulphate). A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in dehydrated alcohol.

Equivalence. Each g of potassium sulfate represents about 11.5 mmol of potassium. Potassium sulfate 2.23 g is equivalent to about 1 g of potassium.

Potassium Tartrate

E336; Potasio, tartrato de; Potasu winian.
$C_4H_4K_2O_6,\frac{1}{2}H_2O$ = 235.3.
CAS — 921-53-9 (anhydrous potassium tartrate).

Equivalence. Each g of potassium tartrate (hemihydrate) represents about 8.5 mmol of potassium. Potassium tartrate (hemihydrate) 3.00 g is equivalent to about 1 g of potassium.

Adverse Effects

Excessive doses of potassium may lead to the development of hyperkalaemia (p.1669), especially in patients with renal impairment. Symptoms include paraesthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and confusion. Cardiac toxicity is of particular concern after intravenous dosage.

Pain or phlebitis may occur when given intravenously via peripheral veins, particularly at higher concentrations.

Nausea, vomiting, diarrhoea, and abdominal cramps may occur with oral potassium salts. There have been numerous reports of gastrointestinal ulceration, sometimes with haemorrhage and perforation or with the late formation of strictures, after the use of enteric-coated tablets of potassium chloride. Ulceration has also occurred after the use of sustained-release tablets.

Treatment of Adverse Effects

The treatment of hyperkalaemia discussed on p.1669 also applies when hyperkalaemia occurs during potassium therapy. However, in mild hyperkalaemia that has developed on long-term treatment, stopping the potassium supplement and other drugs that may increase plasma-potassium concentrations, and avoidance of foods with a high potassium content may be sufficient to correct the hyperkalaemia.

In cases of acute oral overdosage of potassium supplements, the stomach should be emptied by gastric lavage in addition to the measures described on p.1669.

Precautions

Potassium salts should be given with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Excessive use of potassium-containing salt substitutes or potassium supplements may lead to accumulation of potassium especially in patients with renal insufficiency. Regular monitoring of clinical status, serum electrolytes, and the ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Liquid or effervescent preparations are preferred to solid dosage forms for oral use; use of the former, with or after food, may reduce gastric irritation. Solid oral dosage forms of potassium salts should not be given to patients with gastrointestinal ulceration or obstruction. They should be given with care to patients in whom passage through the gastrointestinal tract may be delayed, as in pregnant patients. Treatment should be stopped if severe nausea, vomiting, or abdominal distress develops.

Potassium chloride should not be used in patients with hyperchloraemia.

Direct injection of potassium chloride concentrates without appropriate dilution may cause instant death. For the view that glucose-containing solutions should not be used for the initial intravenous administration of potassium in hypokalaemia see Administration, below.

Interactions

Potassium supplements should be used with caution, if at all, in patients receiving drugs that increase serum-potassium concentrations. These include potassium-sparing diuretics, ACE inhibitors, ciclosporin, and drugs that contain potassium such as the potassium salts of penicillin. Similarly, the concomitant use of potassium-containing salt substitutes for flavouring food should be avoided. Antimuscarinics delay gastric emptying and consequently may increase the risk of gastrointestinal adverse effects in patients receiving solid oral dosage forms of potassium.

Table 3. Some potassium salts and their potassium content.

Potassium salt	Potassium content per g		
	mg	mmol	mEq
Potassium acetate (anhydrous)	398	10.2	10.2
Potassium aspartate	217	5.5	5.5
Potassium bicarbonate	391	10.0	10.0
Potassium chloride	524	13.4	13.4
Potassium citrate (anhydrous)	383	9.8	9.8
Potassium citrate (monohydrate)	361	9.3	9.3
Potassium gluconate (anhydrous)	167	4.3	4.3
Potassium gluconate (monohydrate)	155	4.0	4.0
Potassium sulfate (anhydrous)	449	11.5	11.5
Potassium tartrate (hemihydrate)	332	8.5	8.5

Pharmacokinetics

Potassium salts other than the phosphate, sulfate, and tartrate are generally readily absorbed from the gastrointestinal tract. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

Human Requirements

Potassium is an essential body electrolyte. However, requirements are difficult to determine and have been estimated from the amount accumulated during growth and reported urinary and faecal excretion.

Over 90% of dietary potassium is absorbed from the gastrointestinal tract. Potassium is particularly abundant in vegetables, potatoes, and fruit.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p.1925)[1] have been estimated for potassium. The reference nutrient intake (RNI) for adults is 3.5 g (90 mmol) daily. In the USA, no recommended dietary allowance (RDA) has been established for potassium. However a daily intake of 1.6 to 2 g (40 to 50 mmol) is considered adequate for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.

Uses and Administration

Potassium salts in this section are used for the prevention and treatment of potassium depletion and/or **hypokalaemia** (p.1669) and have been used in the prevention of **diuretic-induced hypokalaemia** (see Hydrochlorothiazide, Effects on Electrolyte Balance, p.1308). Doses may be expressed in terms of mmol or mEq of potassium, mass (mg) of potassium, or mass of potassium salt (for comparative purposes see Table 3, below). Treatment should be monitored by plasma-potassium estimations because of the risk of inducing hyperkalaemia, especially where there is renal impairment.

Potassium chloride is probably the most commonly used potassium salt; this is because hypochloraemic alkalosis, which is often associated with hypokalaemia, can be corrected by the chloride ions. An alkalinising salt such as potassium acetate, potassium bicarbonate, or potassium citrate may be preferable if a metabolic acidosis, such as occurs in renal tubular acidosis, accompanies the hypokalaemia (see p.1667). Other salts that are or have been used in the management of potassium deficiency include potassium ascorbate, potassium aspartate, potassium benzoate, potassium gluceptate, potassium gluconate, potassium phosphate, and potassium tartrate. Typical doses for the prevention of hypokalaemia may be up to 50 mmol daily and similar doses may be adequate in mild potassium deficiency. However, higher doses may be needed in more severe deficiency. Patients with renal impairment should receive correspondingly lower doses. *Oral* treatment is used for prophylaxis and is also suitable for treating most cases of hypokalaemia. Oral potassium salts are more irritating than the corresponding sodium salts; they should be taken with or after meals with plenty of fluid; liquid preparations are preferable.

An *intravenous* potassium salt may be required in severe acute hypokalaemia. This normally entails infusing a solution containing 20 mmol of potassium in 500 mL over 2 to 3 hours under ECG control. A recommended maximum dose is 2 to 3 mmol/kg of potassium in 24 hours. Higher concentrations have been given when an infusion pump has been used (see Administration below). Adequate urine flow must be ensured and careful monitoring of plasma-potassium and other electrolyte concentrations is essential. Potassium chloride is the salt most commonly used and solutions intended for intravenous use that are in a concentrated form (such as 1.5 or 2 mmol/mL) *must* be diluted to the appropriate concentration before use. There should be careful and thorough mixing when adding concentrated potassium chloride solutions to infusion fluids. Potassium chloride is also available as premixed infusions with sodium chloride and/or glucose containing 10 to 40 mmol/litre of potassium (but see also Administration, below). Potassium acetate is also given intravenously.

Amongst **other uses**, the sulfate, and tartrate salts of potassium have been given orally as osmotic laxatives (p.1693).

Some potassium salts are used as sodium-free condiments when sodium intake must be restricted.

Potassium chloride is sometimes used as an excipient in pharmaceutical formulations.

Administration. The standard concentration and rate of administration of potassium chloride for infusion is discussed in Uses and Administration, above. However, higher concentrations (200 or 300 mmol/litre) and faster infusion rates have been used, via an infusion pump, for cases of severe symptomatic hypokalaemia, especially with fluid overload.[1,2]

There has been controversy regarding the preferred route of administration of these higher concentrations of potassium chloride.[1] The central route avoids the problems of pain and phlebitis when potassium is given peripherally. However, it has been suggested that high concentrations of potassium given centrally may carry a greater risk of cardiac toxicity if the infusion is carried directly to the heart. Use of lidocaine has improved tolerability of peripheral administration of potassium chloride.[2]

Intravenous potassium is usually given in sodium chloride and/or glucose infusion. However, it has been pointed out that glucose can reduce serum-potassium concentrations, and that glucose-free solutions should be used for the initial intravenous administration of potassium in hypokalaemia.[3]

1. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med* 1990; **150:** 613–17.
2. Pucino F, *et al.* Patient tolerance to intravenous potassium chloride with and without lidocaine. *Drug Intell Clin Pharm* 1988; **22:** 676–9.
3. Agarwal A, Wingo CS. Treatment of hypokalaemia. *N Engl J Med* 1999; **340:** 154–5.

Diabetic ketoacidosis. As discussed under Diabetic Emergencies on p.435, potassium replacement is given in diabetic ketoacidosis to restore total body stores of potassium and thereby prevent the hypokalaemia induced by insulin.

Hypertension. A meta-analysis[1] has reported that potassium supplementation results in reductions of both systolic and diastolic blood pressure. The size of the effect in hypertensive patients was sufficiently great to suggest a possible role in the treatment of hypertension (p.1171); effects in normotensive subjects were less marked but consistent with a role for potassium supplementation in preventing hypertension. Most studies have used potassium chloride, but an effect has also been demonstrated with the aspartate[2] and the citrate.[3]

1. Whelton PK, *et al.* Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277:** 1624–32.
2. Franzoni F, *et al.* Antihypertensive effect of oral potassium aspartate supplementation in mild to moderate arterial hypertension. *Biomed Pharmacother* 2005; **59:** 25–9.
3. He FJ, *et al.* Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension* 2005; **45:** 571–4.

Myocardial infarction. A glucose, insulin, and potassium infusion has been investigated in acute myocardial infarction (see p.452).

Termination of pregnancy. Solutions of potassium chloride are used to reduce fetal numbers in multifetal pregnancies[1-3] or for severe fetal malformation by abolishing the fetal cardiac activity. The solution is injected into the thorax of the fetus without affecting the others which are allowed to continue to term. Alternatively, potassium chloride may be injected into the umbilical vein when access to the fetal heart is difficult. A retrospective comparison[4] found both techniques to be effective. Significantly smaller doses were required for the umbilical route, possibly because a sustained dose is delivered directly to the fetal heart and myocardium, compared with intraventricular injection.

1. Wapner RJ, *et al.* Selective reduction of multifetal pregnancies. *Lancet* 1990; **335:** 90–3.
2. Berkowitz RL, *et al.* The current status of multifetal pregnancy reduction. *Am J Obstet Gynecol* 1996; **174:** 1265–72.
3. De Catte L, Foulon W. Obstetric outcome after fetal reduction to singleton pregnancies. *Prenat Diagn* 2002; **22:** 206–10.
4. Bhide A, *et al.* Comparison of feticide carried out by cordocentesis versus cardiac puncture. *Ultrasound Obstet Gynecol* 2002; **20:** 230–2.

Preparations

BP 2008: Bumetanide and Prolonged-release Potassium Tablets; Effervescent Potassium Chloride Tablets; Potassium Chloride and Glucose Intravenous Infusion; Potassium Chloride and Sodium Chloride Intravenous Infusion; Potassium Chloride Oral Solution; Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion; Prolonged-release Potassium Chloride Tablets; Sterile Potassium Chloride Concentrate;
USP 31: Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Potassium Ace-

tate Injection; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Chloride Extended-release Capsules; Potassium Chloride Extended-release Tablets; Potassium Chloride for Injection Concentrate; Potassium Chloride for Oral Solution; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Potassium Chloride Oral Solution; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Gluconate and Potassium Chloride for Oral Solution; Potassium Gluconate and Potassium Chloride Oral Solution; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate Elixir; Potassium Gluconate Tablets; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Trikates Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Co-Salt; Control K; Gluco-K; Kaon; Orakit; QBE Elixir†; ***Austral.:*** Celloids PC 73; Celloids PS 29; Chlorvescent; Duro-K; KSR†; Slow-K; Span-K; ***Austria:*** KCl-retard; Micro-Kalium; ***Belg.:*** Chloropotassuril; Kali-Sterop†; Kalium Durettes†; Steropotassium; Ultra-K; ***Braz.:*** Clotassio; Decorfen; ***Canad.:*** Apo-K; K-10; K-Dur; K-Lor†; K-Lyte/Cl; Kaon†; Micro-K; Potassium-Rougier†; Proflavanol C; Roychlor†; Slow-K; ***Chile:*** Kaion Retard; Sal Dietetica; Slow-K; Yonka; ***Cz.:*** Kaldyum; Kalnormin; Spofalyt-Kalium†; ***Denm.:*** Kaleorid; ***Fin.:*** Durekal; Kalinorm; Kalisol; Kalisteril†; ***Fr.:*** Diffu-K; Kaleorid; Nati-K; ***Ger.:*** Kalinor-retard P; Kalium-Duriles†; Kalium†; KCl-retard; Rekawan; ***Gr.:*** Sopa-K; ***Hong Kong:*** Addi-K†; Apo-K; Kalium†; KSR; Slow-K; Span-K; ***Hung.:*** Kaldyum; Kalium Durules; Kalium-R; ***India:*** Diucontin-K; Keylyte; Potklor; ***Irl.:*** Kay-Cee-L; Slow-K; ***Israel:*** Slow-K; ***Ital.:*** K-Flebo; Kadalex; Lento-Kalium; ***Malaysia:*** Apo-K; Beacon K; KSR†; Slow-K; ***Mex.:*** Ceposil; Clor-K-Zaf; Corpotasin GK; Corpotasin LP; K-Dur; Kaliolite; Kasele†; Kelefusin; Potasoral; ***Neth.:*** Kalium Durettes†; Slow-K; ***Norw.:*** Kaleorid; ***NZ:*** Chlorvescent; K-SR†; Slow-K; Span-K; ***Philipp.:*** Ion-O-Trate; Kalium; ***Pol.:*** Kaldyum; Kalimat; Kalipoz; ***S.Afr.:*** Micro-K; Plenish-K; Sandoz K; Slow-K; Swiss-Kal SR†; ***Singapore:*** Addi-K†; Apo-K; KSR†; ***Spain:*** AP Inyect Cloruro Potasico; Boi K; Boi K Aspartico; Boi K Gluconato; Potasion; Potasion Solucion; ***Swed.:*** Kaleorid†; Kalitabs; Kalium Duretter†; Kalium Retard; ***Switz.:*** Kaliglutol; Plus Kalium retard; ***Thai.:*** Addi-K; Enpott; Kaliject; Potassride; ***Turk.:*** Kadaleks; ***UK:*** Kay-Cee-L; Slow-K; ***USA:*** Cena-K; Gen-K; K + 10; K + 8†; K-Dur; K-G Elixir; K-Lease†; K-Lor; K-Lyte/Cl; K-Norm†; K-Tab; Kaon; Kaon-Cl; Kay Ciel; Klor-Con; Klorvess; Klotrix; Micro-K; Potasalan; Rum-K†; Slow-K†; Ten-K; ***Venez.:*** Kaon†; Konat†.

Multi-ingredient: ***Arg.:*** Dialitica II; Potasio C; Water Pill c Potasio†; ***Austral.:*** Aspartatol; Cardioplegia A; Cardioplegia Concentrate; Digestaid; Duo Celloids PCCP; Duo Celloids PCIP; Duo Celloids PCMP; Duo Celloids PSMP; Duo Celloids PSPC; Duo Celloids SPPC; Duo Celloids SPPS; Duo Celloids SSPC; Extralife Uri-Care; Iron Compound†; K-Mag†; Kali Mag†; Mag-Oro; Potasi; Silicic Complex†; ***Austria:*** Centramin; Corozell; Elozell; Elozell spezial; Gladixol; Maycardin K; Trommcardin; ***Braz.:*** Albicon; Furosemide Composto; Hidrion; ***Canad.:*** Uracyst Test Kit; ***Chile:*** Sal Lite; Sal Liviana En Sodio; ***Cz.:*** Acidigen†; Aviril H†; Cardilan; Solutio Thomas cum Procaino; Tromcardin; ***Denm.:*** Burinex med kaliumklorid; Centyl med Kaliumklorid; ***Fin.:*** Miral; ***Fr.:*** Decramp; Rhinodoron; ***Ger.:*** Ardeycordal N†; Bascardial†; Cardio-Kreislauf-Longoral; Chinosol; Cordesin; Galacordin; Kalium-Magnesium†; Magium K; Movicard; Rhinodoron; Septacord; Tromcardin; Trophicard; ***Gr.:*** Cardioplegia; ***Hong Kong:*** Cardioplegia; ***Hung.:*** Acidigen†; Aspacardin†; Panangin; Tromcardin; ***India:*** Cotaryl; ***Indon.:*** Cardioplegia; Totilac; ***Irl.:*** Burinex K†; Centyl K; Diumide-K Continus; Low Centyl K; ***Israel:*** Lyteers; ***Ital.:*** Briovitase; Polase; Pomag; Potassion; Potassium MG†; ***Malaysia:*** Burinex K†; Cardioplegia; Pot-Citra; ***Mex.:*** Corpotasin CL; Forcremol; Kaposalt; ***Norw.:*** Burinex K; Centyl med Kaliumklorid; ***Philipp.:*** Diumide-K; ***Pol.:*** Aspargin; Magne-Balans Plus; Magnokal; Sal Ems Artificiale; Sal Ems Factitium; ***Port.:*** Miostenil; Polase; Safrux; ***Rus.:*** Panangin (Панангин); Triresid K (Трирезид К); ***S.Afr.:*** Burinex K; Kloref; Lenurex-K; Urirex-K; ***Singapore:*** Burinex K; Cardioplegia; ***Spain:*** Acetuber; Glucopotasico; Leberetic; Potasico; Salcedol; Suero Potassico Bieffe ME†; ***Swed.:*** Centyl K; Salures-K; ***Thai.:*** Cardioplegia; ***Turk.:*** Kadeks; Sensodyne-F; ***UK:*** Burinex K†; Centyl K; Kloref; Lasikal; Neo-NaClex-K; Sando-K; Sensodyne-F; ***USA:*** Chlor-3; K-Lyte/Cl; Klorvess; Slo-Salt-K†; Temp Tab; Tri-K; Twin-K†.

Sodium

Natrium; Sód; Sodio.

Na = 22.98976928.

Description. Sodium chloride is the principal sodium salt used as a source of sodium ions. Sodium salts used chiefly as sources of bicarbonate ions, such as the acetate, bicarbonate, citrate, and lactate, are covered under Bicarbonate, p.1673. Phosphate salts of sodium are covered under Phosphate, p.1682.

Sodium Chloride

Chlorid sodný; Chlorure de Sodium; Cloreto de Sódio; Natrii chloridum; Natrio chloridas; Natriumklorid; Nátrium-klorid; Natriumkloridi; Salt; Sodio, cloruro de; Sodium, chlorure de; Sodu chlorek; Sodyum Klorür.

NaCl = 58.44.

CAS — 7647-14-5.

ATC — A12CA01; B05CB01; B05XA03.

ATC Vet — QA12CA01; QB05CB01; QB05XA03.

NOTE. An aqueous solution of sodium chloride 0.9% is often known as physiological saline.

SALINE is a code approved by the BP 2008 for use on single unit doses of eye drops containing sodium chloride 0.9% where the individual container may be too small to bear all the appropriate labelling information. HECL is a similar code approved for hyetellose and sodium chloride eye drops.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Sodium Chloride). A white or almost white, crystalline powder or colourless crystals or white or almost white pearls. Freely soluble in water; practically insoluble in dehydrated alcohol.

USP 31 (Sodium Chloride). Colourless cubic crystals or white crystalline powder. Soluble 1 in 2.8 of water, 1 in 2.7 of boiling water, and 1 in 10 of glycerol; slightly soluble in alcohol.

Equivalence. Each g of sodium chloride represents about 17.1 mmol of sodium and of chloride. Sodium chloride 2.54 g is equivalent to about 1 g of sodium.

Storage. Solutions of some sodium salts, including sodium chloride, when stored, may cause separation of solid particles from glass containers and solutions containing such particles must not be used.

Adverse Effects

Adverse effects of sodium salts are attributable to electrolyte imbalances from excess sodium; there may also be effects due to the specific anion.

Retention of excess sodium in the body usually occurs when there is defective renal sodium excretion. This leads to the accumulation of extracellular fluid to maintain normal plasma osmolality, which may result in pulmonary and peripheral oedema and their consequent effects.

Hypernatraemia (a rise in plasma osmolality) is usually associated with inadequate water intake, or excessive water losses (see p.1670). It rarely occurs after therapeutic doses of sodium chloride, but has occurred with the use of hypertonic saline for induction of emesis or for gastric lavage and after errors in the formulation of infant feeds. Hypernatraemia may also occur after inappropriate intravenous use of hypertonic saline.

The most serious effect of hypernatraemia is dehydration of the brain which causes somnolence and confusion progressing to convulsions, coma, respiratory failure, and death. Other symptoms include thirst, reduced salivation and lachrymation, fever, sweating, tachycardia, hypertension or hypotension, headache, dizziness, restlessness, irritability, weakness, and muscular twitching and rigidity.

Gastrointestinal effects associated with acute oral ingestion of hypertonic solutions or excessive amounts of sodium chloride include nausea, vomiting, diarrhoea, and abdominal cramps.

Excessive use of chloride salts may cause a loss of bicarbonate with an acidifying effect.

Intra-amniotic injection of hypertonic solutions of sodium chloride, which has been used for termination of pregnancy, has been associated with serious adverse effects including disseminated intravascular coagulation, renal necrosis, cervical and uterine lesions, haemorrhage, pulmonary embolism, pneumonia, and death.

◊ General references.

1. Moder KG, Hurley DL. Fatal hypernatremia from exogenous salt intake: report of a case and review of the literature. *Mayo Clin Proc* 1990; **65:** 1587–94. Correction. *ibid.* 1991; **66:** 439.
2. Martos Sánchez I, *et al.* Hipernatremia grave por administración accidental de sal común. *An Esp Pediatr* 2000; **53:** 495–8.
3. Adeleye O, *et al.* Hypernatremia in the elderly. *J Natl Med Assoc* 2002; **94:** 701–5.
4. Coulthard MG, Haycock GB. Distinguishing between salt poisoning and hypernatraemic dehydration in children. *BMJ* 2003; **326:** 157–60. Correction. *ibid.*; 497.

Treatment of Adverse Effects

In patients with mild sodium excess, drinking water and restricting sodium intake is sufficient. However, in the event of recent acute oral overdose of sodium chloride, gastric lavage should be carried out along with general symptomatic and supportive treatment. Serum-sodium concentrations should be measured, and if severe hypernatraemia is present this should be treated (see p.1670).

Precautions

Sodium salts should be used with caution in patients with hypertension, heart failure, peripheral or pulmonary oedema, renal impairment, pre-eclampsia, or other conditions associated with sodium retention.

When sodium supplements are given orally, adequate water intake should be maintained. Sustained-release tablets should not be given to patients with gastrointestinal disorders associated with strictures or diverticula because of the risk of obstruction.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Pharmacokinetics

Sodium chloride is well absorbed from the gastrointestinal tract. Excess sodium is mainly excreted by the kidney, and small amounts are lost in the faeces and sweat.

Human Requirements

The body contains about 4 mol (92 g) of sodium of which about one-third is found in the skeleton and about half is present in the extracellular fluid.

The body can adapt to a wide range of intakes by adjustment of renal excretion through physical and hormonal factors. Loss through the skin is significant only if excessive sweating occurs. Sodium requirements may be increased with exercise or exposure to high ambient temperatures in the short term, until the body adjusts.

Sodium is widely available in foods and is also added as salt during processing, cooking, and at the table. Dietary deficiency of sodium is therefore extremely rare and more concern has been expressed that current intakes are excessive. Restriction of sodium intake, by limiting the amount of culinary salt consumed, may be a useful aid in the management of some patients with hypertension (p.1171).

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p.1925)[1] have been published for sodium. The reference nutrient intake (RNI) for adults is 1.6 g of sodium (70 mmol) daily, which is about 4 g of sodium chloride. In the USA, it has been recommended that daily intakes of sodium be limited to 2.4 g (6 g of sodium chloride) or less.[2] Dietary intake is often in excess of these recommendations, and may be a factor in essential hypertension,[3] and osteoporosis.[4]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Midgley JP, *et al.* Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275:** 1590–7.
4. Devine A, *et al.* A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995; **62:** 740–5.

Uses and Administration

Sodium chloride is used in the management of deficiencies of sodium and chloride ions in salt-losing conditions (see Hyponatraemia, p.1670). Sodium chloride solutions are used as a source of sodium chloride and water for hydration.

A 0.9% solution in water is iso-osmotic, and thus in most cases isotonic with serum and lachrymal secretions. Doses may be expressed in terms of mEq or mmol of sodium, mass (mg) of sodium, or mass of sodium salt. For comparative purposes, see Table 4, below.

A typical oral replacement dose of sodium chloride in **chronic salt-losing conditions** is about 2.4 to 4.8 g (about 40 to 80 mmol of sodium) daily as a modified-release preparation, accompanied by a suitable fluid intake; doses of up to 12 g daily may be necessary in

Table 4. Some sodium salts and their sodium content.

	Sodium content per g		
Sodium salt	mg	mmol	mEq
Sodium acetate (anhydrous)	280	12.2	12.2
Sodium acetate (trihydrate)	169	7.3	7.3
Sodium acid citrate	175	7.6	7.6
Sodium bicarbonate	274	11.9	11.9
Sodium chloride	394	17.1	17.1
Sodium citrate (anhydrous)	267	11.6	11.6
Sodium citrate (dihydrate)	235	10.2	10.2
Sodium lactate	205	8.9	8.9

severe cases. Oral supplements are also used for the prevention of muscle cramps during routine haemodialysis (p.1671); a suggested dose is about 6 to 10 g of a modified-release preparation per dialysis session.

Glucose facilitates the absorption of sodium from the gastrointestinal tract, and solutions containing sodium chloride and glucose usually with additional electrolytes (see p.1672) are used for oral rehydration in acute diarrhoea (p.1694).

The concentration and dosage of sodium chloride solutions for intravenous use is determined by several factors including the age, weight, and clinical condition of the patient and in particular the patients' hydration state. Serum-electrolyte concentrations should be carefully monitored. In severe sodium depletion, 2 to 3 litres of sodium chloride 0.9% may be given over 2 to 3 hours and thereafter at a slower rate. If there is combined water and sodium depletion a 1 to 1 mixture of sodium chloride 0.9% and glucose 5% may be appropriate. Although hypertonic sodium chloride solutions may be used in certain patients with severe acute dilutional hyponatraemia, over-rapid correction may have severe neurological adverse effects (see Hyponatraemia, p.1670). Solutions containing 1.8 to 5% are available.

In **hypernatraemia** with volume depletion (p.1670), sodium chloride 0.9% may be used to maintain plasma-sodium concentrations with expanding fluid volume. Sodium chloride 0.9% (or rarely, in marked hypernatraemia, 0.45%) is used for fluid replacement in diabetic ketoacidosis (see Diabetic Emergencies, p.435).

Among its **other uses**, sodium chloride solution 0.9%, being isotonic, is a useful fluid for sterile irrigations, for example, of the eye or bladder, and general skin or wound cleansing. The 0.9% concentration is also widely used as a vehicle or diluent for the parenteral administration of other drugs. Nasal drops of sodium chloride 0.9% are used to relieve nasal congestion. A mouthwash containing sodium chloride is also available for oral hygiene.

Sodium chloride solutions should *not* be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Sodium chloride is sometimes used as an excipient in capsules and tablets.

Homoeopathy. Sodium chloride has been used in homoeopathic medicines under the following names: Natrium muriaticum; Nat. Mur.; Natrii chloridum; Natricum chloratum; Natrum muriaticum.

NOTE. Do not confuse Natricum chloratum with sodium chlorate (p.2389).

Catheters and cannulas. For reference to sodium chloride 0.9% being used to maintain the patency of catheters and cannulas, and to its equivalent efficacy to heparin, see Catheters and Cannulas under Uses and Administration of Heparin, p.1304.

Cystic fibrosis. Inhalation of 4 mL of a hypertonic solution of sodium chloride (7%) twice daily for 48 weeks in 82 patients with stable cystic fibrosis (p.166) was associated with a moderate but sustained improvement in lung function and a marked reduction in the number of exacerbations and need for antibiotics, when compared with 80 placebo-treated patients.[1] There was, however, no difference in the rate of change of lung function. Each inhalation was preceded by a bronchodilator to minimise airway narrowing; adverse reactions to the active treatment were nonetheless reported in 14 patients and included cough, chest tightness or pharyngitis, sinusitis, haemoptysis, sneezing, and vomiting. As a result, 6 patients withdrew from the study, but the effects resolved in the remainder without the need for dose reduction or interruption. Hypertonic saline was considered to be an inexpensive and safe adjunctive therapy in patients with cystic fibrosis.

1. Elkins MR, *et al.* A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006; **354:** 229–40.

Termination of pregnancy. Trans-abdominal intra-amniotic instillation of sodium chloride 20% (maximum volume 200 to 250 mL) has been used for the termination of second-trimester pregnancy. However, serious adverse effects have occurred (see above), and other methods are generally preferred (p.2004).

Preparations

BP 2008: Compound Sodium Chloride Mouthwash; Potassium Chloride and Sodium Chloride Intravenous Infusion; Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion; Sodium Chloride and Glucose Intravenous Infusion; Sodium Chloride Eye Drops; Sodium Chloride Eye Lotion; Sodium Chloride Intravenous Infusion; Sodium Chloride Irrigation Solution; Sodium Chloride Oral Solution; Sodium Chloride Solution; Sodium Chloride Tablets;
USP 31: Bacteriostatic Sodium Chloride Injection; Dextrose and Sodium Chloride Injection; Fructose and Sodium Chloride Injection; Half-strength Lactated Ringer's and Dextrose Injection; Inulin in Sodium Chloride Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Mannitol in Sodium Chloride Injection; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride in Sodium Chloride Injection; Sodium Chloride and Dextrose Tablets; Sodium Chloride Inhalation Solution; Sodium Chloride Injection; Sodium Chloride Irrigation; Sodium Chloride Ophthalmic Ointment; Sodium Chloride Ophthalmic Solution; Sodium Chloride Tablets; Sodium Chloride Tablets for Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Aqua Lent Limpia Cristales; Hypersol; Larmabak; Muro 128; Nasomicina Salina†; Oftalook; Relente; Salfis†; Xylisol; Yusin Tears I; ***Austral.:*** Bausch & Lomb Sensitive Eyes Saline; Fess; Hypergel; Lens Plus; Mucolyt†; Narium; Otrivin Saline Baby; Slow-Sodium; ***Austria:*** Ery-Set; SmartDose; Uro-Pract†; ***Belg.:*** Lyomer Plus; Naaprep†; Natriclo†; Physiologica; Physiorhine; ***Braz.:*** Afrin Natural; Alive; Fluimare; Fluimucil Solucao Nasal; Maxidrate; Multisoro; Narisoro; Nasolac†; Nazosoro†; Novo Rino-S; Rino-Ped†; Rinoben; Rinoflux; Rinosoro; Salsep; Sinustrat Solucao Natural; Snif; Sorine; Sorine Pediatrico; Soro Nasal†; Soroliv; Soroneo; Sterimar†; ***Canad.:*** Certified Nasal; Hypergel; Lens Plus Buffered Saline Solution†; Mesalt; Muro 128†; Nasal Physiologic Solution; Normigel; Rhinaris Saline; Safeway Nasal; Salinex; Softwear; ***Chile:*** Fisiolimp; Fludrop†; Larmabak; Pediasea; Printan; Respirex; Rinodan; Rinokid; Rinosteryl; Sinus; Sterimar; Suero Fisiologico†; ***Denm.:*** Viskose ojendraber; ***Fin.:*** Natrosteril; ***Fr.:*** Erjean; Hypergel; Irriclens; L'Oceane; Larmabak; Larmes Artificielles†; NormIgel; Physiologica; Physiomer; Physiosoin; Polyrinse; Selgine; Serophta; Sinomarin; Sterimar; Tonimer Baby; Versol†; Vesirig†; ***Ger.:*** Adsorbonac; Freka-Drainjet; Isogutt akut; Isotone Kochsalz; Isotonische Kochsalzlosung; Olynth salin; Otrisal†; Rhinomer; Rhinospray Atlantik; Rhinoton plus†; Sterimar†; Tetrisal; ***Gr.:*** Babynose†; Clinofar†; Larmabak†; Otrisalin†; Phy-O; Rhinodose†; Selva N†; ***Hong Kong:*** Atomic Enema; Larmabak; Nasal Physiological Solution; Sinomarin; Sterimar; Unison Enema; ***Hung.:*** Rins-Sal; Salsol A; Unilarm†; ***Indon.:*** Otsu-NS; Wida NSl; ***Irl.:*** Sterimar; ***Israel:*** Baby AF; Clean-AF; Drossanose; Normasol; Ocean Spray; Otrivini; Sterimar; Tinok AF; Tipotaf; Uro-Tainer†; ***Ital.:*** Adsorbonac; Hydrabak; Libenar; Narhinel; Naribel†; Otrivin Baby; Physiodose; Physiomer; Rinowash; Serophta†; Sterimar; ***Malaysia:*** Sterimar; ***Mex.:*** Alcacat†; Corni Limp; Hiperton; Muro 128; Sterimar; ***Mon.:*** Unilarm; ***NZ:*** Narium; ***Philipp.:*** Larmabak; Physiomer; Salinase; Snif; ***Pol.:*** Solnasin; ***Port.:*** Libenar†; Lyomer†; Rhinomer†; Sterimar†; Tonimer†; ***Rus.:*** Salin (Салин); ***S.Afr.:*** Polyrinse; Vicks Vapomist; ***Singapore:*** Adsorbonac†; Larmabak; Sterimar; ***Spain:*** Antiedema; Apir Clorurado; Fisiologica; Fisiologico; Fisiologico Bieffe M; Fisiologico Braun; Fisiologico Farmacelsia; Fisiologico Isoton†; Fisiologico Mein; Fisiologico Serra Pamies; Fisiologico Vitulia; Flebobag Fisio; Fleboflex Salina Fisio; Fleboplast Fisio; Freeflex Cloruro Sodico; Irrigacion CLNA†; Meinvenil Fisiologico; Plast Apyr Fisiologico; Solucion Fisio; Suero Fisiologico; Suero Fisiologico Isoton; Suero Fisiologico†; ***Swed.:*** SmartDose†; ***Switz.:*** Drossa-Nose; Fluimare; Naaprep; nasmer; Nose Fresh†; Physiologic; Physiosoin; Rhinomer; Serophy; Siccoral; Sterimar†; Tracheo Fresh†; Triomer; ***Thai.:*** U-Enema; ***Turk.:*** Berko-Fiz; Fizyolen; Fizyosol; Lyomer; Otrisalin; Physiodose; Physiologica Gifrer; Rhinomer; Ser Damla; Serum Fizyolojik; Sinomarin; Sterimar; Tonimer; ***UAE:*** Normaline; ***UK:*** Askina; Equaleze; Irriclens; Irripod; Miniversol; Normasol; Slow-Sodium; Stericlens; Sterimar; Steripod; Tubilux; Uriflex S; Uro-Tainer M; Versol; ***USA:*** Adsorbonac; Afrin Moisturizing Saline Mist; Ak-NaCl; Ayr Saline; Breathe Free; Broncho Saline; Dristan Saline Spray; HuMist Nasal Mist; Marlin Salt System; Muro 128; Muroptic; NaSal; Nasal Moist; Normaline; Ocean; Pretz; Salinex; SeaMist; Your Choice; ***Venez.:*** Larmabak; Nafavine.

Multi-ingredient: ***Arg.:*** Dialitica II; Phylarm; Yusin Tears II; ***Austral.:*** Cardioplegia A; Minims Artificial Tears†; ***Austria:*** Gluco-Salzlosung; Osmofundin 10%; ***Belg.:*** Alcasol; Ocal; Physiologica; ***Braz.:*** Glicofisiologica†; Malvona†; Nasolin; Novo Rino; Rinotil†; Sinustrat; Sinustrat Vasoconstritor; Sorine Adulto; ***Canad.:*** Sclerodex; ***Chile:*** Concentrado Basico; Nasivin; Sal Lite; Sal Liviana En Sodio; ***Cz.:*** Acidigen†; ***Fr.:*** Amukine; Biolau; Cataridol†;Ceruspray; Dacryoserum; Emoform Gencives; Kamillosan Ocean; Ophtaclair; Phylarm†; Potensium sel de table; Proceane Isotonique; Rhinodoron; Selso; Serozinc; ***Ger.:*** Kochsalz mit Glucose; Mar Plus†; Nisita†; Nubral 4†; Nubral Forte†; Rhinodoron; Tutofusin S†; Weleda-Rheumasalbe M; ***Gr.:*** Eyesalt†; ***Hong Kong:*** Eye Wash; ***Hung.:*** Acidigen†; Nisita†; ***India:*** Andre; Catarest; Cato-Bell; Cotaryl; Neotomic; ***Irl.:*** Minims Artificial Tears; ***Israel:*** Lyteers; Snore-No-More; ***Ital.:*** Aquasalina†; AZ 15; IperClean; Kamillosan Ocean; Sterimar Cu; Sterimar Mn; Troca Flu Spray Nasale; Vulnopur; ***Mex.:*** Amuchina†; Nasalub; ***Neth.:*** Symbial; ***Norw.:*** Salidex; ***Philipp.:*** Soothing Eye Wash; ***Pol.:*** Gargarin; Sal Ems Artificiale; Sal Ems Factitium; Sal Vichy Factitium; ***Port.:*** Glucanet†; Glucosalino; ***S.Afr.:*** Mrs Johnsons American Soothing Syrup; ***Singapore:*** ENTsol; ***Spain:*** Apir Glucosalino; Flebobag Glucosalina; Fleboplast Glucosalina; Freeflex Glucosalina; Glucosalina; Glucosalino; Humectante; Meinvenil Glucosalina; Plast Apyr Glucosalino; Potasico; Solurrinol; Suero Glucosalino; Suero Potassico Bieffe ME†; ***Switz.:*** Amuchina Med; Glucosalin; Glucosaline; Kemerhinose; Narifresh; Nose Fresh au D-panthenol; Perfusion mixte; Pommade Nasale Radix†; Prorhinel; Rhinocure; Rhinocure simplex; Siccalix; ***Thai.:*** Eye-Gene; Eye-Gene Soft; Mano; Opsil†; Visotone; ***Turk.:*** Isodeksol; Izodeks; Kadeks; ***UK:*** Asonor; Blink; Minims Artificial Tears; ***USA:*** Chlor-3; Clear Eyes CLR; Massengill; Nasal-Ease; Slo-Salt-K†; Summers Eve Post-Menstrual; Temp Tab; Trichotine; ***Venez.:*** Dextro-Sal†; Fisiolin; Glucofisiologica†.

Gases

This chapter includes monographs on gases with medical or pharmaceutical uses and applications (such as oxygen, carbon dioxide, helium, and nitrogen) as well as those where the medical interest lies primarily in management of their toxicity or adverse effects (such as carbon monoxide or hydrogen sulfide). Also included are some compressed and liquefied gases used as refrigerants and aerosol propellants. Nitric oxide gas is used in bronchopulmonary disorders and is discussed in Cardiovascular Drugs (p.1358). Other gases with medical uses can be found in Disinfectants and Preservatives (p.1622) and General Anaesthetics (p.1779).

Refrigerants and Aerosol Propellants

A number of compressed and liquefied gases are used as refrigerants and as aerosol propellants; these include nitrogen, nitrous oxide, carbon dioxide, propane, and the butanes. Chlorofluorocarbons (CFCs) were widely used but because of environmental hazards their general use has been severely restricted and they are being phased out in medicine and pharmacy. Hydrogenated chlorofluorocarbons (hydrochlorofluorocarbons) and nonchlorinated fluorocarbons (hydrofluorocarbons) are being developed as alternatives, although neither are devoid of environmental effects.

The evaporation of halogenated hydrocarbon propellants produces an intense cold that numbs the tissues, and they have been used as topical analgesics (see Rubefacients and Topical Analgesia, p.5).

Refrigerants and aerosol propellants have been subject to deliberate abuse. Inhalation of high concentrations of halogenated hydrocarbons for their euphoriant effect may result in CNS depression, cardiac arrhythmias, respiratory depression, and death. Propane and butane can act as simple asphyxiants. Heat can cause the decomposition of halogenated hydrocarbons into irritant and toxic gases such as hydrogen chloride and phosgene.

Toxicity. Reviews have covered the toxicity and adverse effects that may occur as a consequence of the deliberate abuse of aerosol propellants[1-4] as well as the hazards associated with occupational exposure.[5] Further references relevant to the toxicity of individual agents are given in the monographs.

1. Volatile substance abuse—an overview. *Hum Toxicol* 1989; **8:** 255–344.
2. Ashton CH. Solvent abuse. *BMJ* 1990; **300:** 1356–6.
3. Anderson HR. Increase in deaths from deliberate inhalation of fuel gases and pressurised aerosols. *BMJ* 1990; **301:** 41.
4. Kurtzman TL, *et al.* Inhalant abuse by adolescents. *J Adolesc Health* 2001; **28:** 170–80.
5. Matthews G. Toxic gases. *Postgrad Med J* 1989; **65:** 224–32.

Bromochlorodifluoromethane

Bromoclorodifluorometano.

$CBrClF_2$ = 165.4.

Profile

Bromochlorodifluoromethane has been used as a fire-extinguishing agent.

◊ Reports of toxicity after the misuse or abuse of fire extinguishers containing bromochlorodifluoromethane,[1-3] and in persons exposed in other ways.[4,5]

1. Steadman C, *et al.* Abuse of fire-extinguishing agent and sudden death in adolescents. *Med J Aust* 1984; **141:** 115–17.
2. Lerman Y, *et al.* Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). *Hum Exp Toxicol* 1991; **10:** 125–8.
3. Gerhardt RT. Acute Halon (bromochlorodifluoromethane) toxicity by accidental and recreational inhalation. *Am J Emerg Med* 1996; **14:** 675–7.
4. Matrat M, *et al.* Reactive airways dysfunction syndrome caused by bromochlorodifluoromethane from fire extinguishers. *Occup Environ Med* 2004; **61:** 712–14.
5. Lo SH, *et al.* Grand rounds: outbreak of hematologic abnormalities in a community of people exposed to leakage of fire extinguisher gas. *Environ Health Perspect* 2006; **114:** 1713–17.

Butane

n-Butane; Butano; E943a.

C_4H_{10} = 58.12.

CAS — 106-97-8.

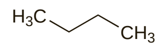

Pharmacopoeias. In *USNF.*

USNF 26 (Butane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40°.

Profile

Butane is used as an aerosol propellant (above). It is widely used as a fuel.

Abuse. Reports of toxicity associated with the abuse of butane.[1-9]

1. Gunn J, *et al.* Butane sniffing causing ventricular fibrillation. *Lancet* 1989; **i:** 617.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; **323:** 1638.
3. Roberts MJD, *et al.* Asystole following butane gas inhalation. *Br J Hosp Med* 1990; **44:** 294.
4. Williams DR, Cole SJ. Ventricular fibrillation following butane gas inhalation. *Resuscitation* 1998; **37:** 43–5.
5. Rieder-Scharinger J, *et al.* Multiorganversagen nach Butangasinhalation: ein Fallbericht. *Wien Klin Wochenschr* 2000; **112:** 1049–52.
6. Wehner F, *et al.* Tödliche Inhalation von Butan-Propan-Gas. *Arch Kriminol* 2002; **209:** 164–8.
7. El-Menyar AA, *et al.* A teenager with angiographically normal epicardial coronary arteries and acute myocardial infarction after butane inhalation. *Eur J Emerg Med* 2005; **12:** 137–41.
8. Harris D, Mirza Z. Butane encephalopathy. *Emerg Med J* 2005; **22:** 676–7.
9. Doogue M, Barclay M. Death due to butane abuse—the clinical pharmacology of inhalants. *N Z Med J* 2005; **118:** U1732.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Batistol†; Frionex; ***Fr.:*** Cliptol Sport†.

Carbon Dioxide

Anglies dioksidas; Carbone, dioxyde de; Carbonei dioxidum; Carbonei Dioxydum; Carbonic Acid Gas; Carbonic Anhydride; Dióxido de carbono; E290; Hiilidioksidi; Koldioxid; Oxid uhličitý; Szén-dioxid; Węgla dwutlenek.

CO_2 = 44.01.

CAS — 124-38-9.

ATC — V03AN02.

ATC Vet — QV03AN02.

NOTE. Carbon dioxide is about 1⁄ times as heavy as air.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Carbon Dioxide). A colourless gas. Soluble 1 in about 1 of water by volume at 20° and at a pressure of 101 kpA. Store liquefied under pressure in suitable containers.

The BP 2008 directs that carbon dioxide should be kept in approved metal cylinders which are painted grey and carry a label stating 'Carbon Dioxide'. In addition, 'Carbon Dioxide' or the symbol 'CO_2' should be stencilled in paint on the shoulder of the cylinder.

USP 31 (Carbon Dioxide). A colourless, odourless gas. Its solutions are acid to litmus. One volume dissolves in about 1 volume of water. Store in cylinders.

Adverse Effects

Above a concentration of 6%, carbon dioxide causes headache, dizziness, confusion, palpitations, hypertension, dyspnoea, increased depth and rate of respiration, and CNS depression. Concentrations of about 20% and higher produce convulsions and loss of consciousness; inhalation of 50% carbon dioxide is reported to produce central effects similar to anaesthetics. The inhalation of high concentrations may produce respiratory acidosis.

Abrupt withdrawal of carbon dioxide after prolonged inhalation commonly produces pallor, hypotension, dizziness, severe headache, and nausea or vomiting.

Skin contact with solid carbon dioxide may cause frostbite.

Uses and Administration

Carbon dioxide has been added to the oxygen in certain types of pump oxygenators to maintain the carbon dioxide content of the blood.

Although carbon dioxide stimulates respiration, it is seldom used for this purpose. Treatment of carbon monoxide poisoning with carbon dioxide/oxygen mixtures is discouraged due to the risk of respiratory acidosis.

Inhalation of carbon dioxide has been tried for relief of intractable hiccup (p.976). Carbonated vehicles are useful for masking the unpleasant taste of some medicinal preparations.

Solid carbon dioxide, or 'dry ice' has a temperature of –80° and has been used to treat warts (p.1584) and naevi by cryotherapy.

Carbon dioxide may be used as the insufflating gas for laparoscopy and as a contrast agent in radiography (p.1474).

Carbon Monoxide *(USAN)*

Anglies monoksidas; Carbone, monoxyde de; Carbonei monoxidum; Hiilimonoksidi; Karbon Monoksit; Kolmonoxid; Monóxido de carbono; Węgla tlenek.

CO = 28.01.

CAS — 630-08-0.

Description. Carbon monoxide is a colourless, odourless, tasteless, highly flammable gas.

Adverse Effects

Carbon monoxide is produced by incomplete combustion of organic materials and is highly toxic when inhaled; infants, small children, and elderly people are particularly susceptible. Although the number of cases of poisoning in countries such as the UK has fallen as the availability of coal gas has declined and as changes have been made to motor vehicles to improve their exhaust fumes, carbon monoxide is still a major cause of poisoning. Common sources of carbon monoxide include poorly maintained and ventilated heating systems and improperly burnt fuel in domestic fires.

When inhaled, carbon monoxide combines with haemoglobin in the blood to form carboxyhaemoglobin, which is unable to transport oxygen; the symptoms of carbon monoxide poisoning are largely due to anoxia. The skin and tissues may turn a classic cherry red in patients poisoned with carbon monoxide although this is seen most often after death.

The symptoms of carbon monoxide poisoning are varied and depend on the degree and duration of exposure. Unconsciousness may occur suddenly but is commonly preceded by headache, dizziness, weakness, nausea, and vomiting, which may be misdiagnosed as a viral illness or food poisoning. Other symptoms may include skin lesions, excessive sweating, pyrexia, increased respiration, mental dullness and confusion, visual disturbances, convulsions, hypotension, tachycardia or other cardiac arrhythmias, myocardial ischaemia, and possibly myocardial infarction. Death may result from respiratory failure, pulmonary oedema, cardiovascular failure, or cerebral damage. The lethal concentration of carboxyhaemoglobin in the blood is about 50% or more. Concentrations over 1000 ppm of carbon monoxide in inspired air may be fatal in 1 hour. Neurological and psychiatric sequelae may develop some weeks later in the survivors of severe poisoning and therefore a prolonged follow-up of such patients is advised; symptoms include memory impairment, apathy, mutism, irritability, personality change, gait disturbance, and urinary and faecal incontinence. Chronic carbon monoxide exposure may present as a non-specific illness with headache, nausea, and flu-like symptoms.

◊ General references.

1. Meredith T, Vale A. Carbon monoxide poisoning. *BMJ* 1988; **296:** 77–9.
2. Crawford R, *et al.* Carbon monoxide poisoning in the home: recognition and treatment. *BMJ* 1990; **301:** 977–9.
3. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med* 1998; **339:** 1603–8.
4. WHO. Carbon Monoxide. *Environmental Health Criteria 213.* Geneva: WHO, 1999. Available at: http://www.inchem.org/documents/ehc/ehc/ehc213.htm (accessed 05/07/04)
5. Satran D, *et al.* Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. *J Am Coll Cardiol* 2005; **45:** 1513–16.
6. Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. *J Neurol Sci* 2007; **262:** 122–30.

Treatment of Adverse Effects

The patient should be removed from the contaminated atmosphere and an effective airway established. Oxygen (100%) should be given until the blood carboxyhaemoglobin concentration has fallen below dangerous levels (usually 5%). Management is then usually symptomatic and supportive with attention being given to the possible need to treat or correct any cardiovascular disorders, metabolic acidosis, or cerebral oedema. Hyperbaric oxygen therapy may be considered in pregnant patients or in severe poisoning (if the patient is, or has been, unconscious; if the carboxyhaemoglobin concentration exceeds 20%; or if there are neurological symptoms or cardiac complications) but is of unproven benefit (see below) and its use is controversial.

◊ References.

1. Anonymous. Treatment of carbon monoxide poisoning. *Drug Ther Bull* 1988; **26:** 77–9.
2. Ely EW, *et al.* Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning. *Am J Med* 1995; **98:** 145–55.

Hyperbaric oxygen therapy. The use of hyperbaric oxygen therapy in the management of carbon monoxide poisoning is controversial.[1] It is of theoretical benefit since it increases the rate at which carboxyhaemoglobin dissociates, and beneficial results have been reported in patients with carbon monoxide poisoning.[2,3] Its use has therefore been widely recommended, particularly in patients with severe poisoning. However, the availability of hyperbaric oxygen is limited, and it remains unclear which patients should receive therapy; a systematic review considered its value unproven.[1] A controlled trial[4] comparing hyperbaric oxygen with normobaric oxygen (at higher levels than commonly used) in patients with severe poisoning found no benefit from hyperbaric oxygen, but a later study[5] using a different regimen did find a reduction in cognitive sequelae. Hyperbaric oxygen has been successfully used in pregnant patients with carbon monoxide poisoning[6] and its use should possibly be considered earlier in pregnant patients due to the risks to the fetus from hypoxia.

1. Juurlink DN, *et al.* Hyperbaric oxygen for carbon monoxide poisoning. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 20/06/08).
2. Gorman DF. Problems and pitfalls in the use of hyperbaric oxygen for the treatment of poisoned patients. *Med Toxicol Adverse Drug Exp* 1989; **4:** 393–9.
3. Hawkins M, *et al.* Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Br J Anaesth* 2000; **84:** 584–6.
4. Scheinkestel CD, *et al.* Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust* 1999; **170:** 203–10.
5. Weaver LK, *et al.* Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; **347:** 1057–67.
6. Van Hoesen KB, *et al.* Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning: a case report and literature review. *JAMA* 1989; **261:** 1039–43. Correction. *ibid.* 1990; **263:** 2750.

Uses

Carbon monoxide has been used in low concentrations as a tracer gas in measurements of lung function. Carbon monoxide labelled with carbon-11 may also be used to assess the blood volume.

Chlorofluorocarbons

CFCs; Clorofluorocarbonos.

Cryofluorane *(rINN)*

CFC-114; Criofluorano; Cryofluoranum; Dichlorotetrafluoroethane; Propellant 114; Refrigerant 114; Tetrafluorodichloroethane. 1,2-Dichloro-1,1,2,2-tetrafluoroethane.

Криофлуоран

$C_2Cl_2F_4$ = 170.9.

CAS — 76-14-2.

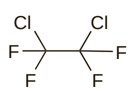

Pharmacopoeias. In *USNF.*

USNF 26 (Dichlorotetrafluoroethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40°.

Dichlorodifluoromethane

CFC-12; Diclorodifluorometano; Difluorodichloromethane; Propellant 12; Refrigerant 12.

CCl_2F_2 = 120.9.

CAS — 75-71-8.

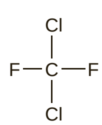

Pharmacopoeias. In *USNF.*

USNF 26 (Dichlorodifluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40°.

Trichlorofluoromethane

CFC-11; Fluorotrichloromethane; Propellant 11; Refrigerant 11; Trichloromonofluoromethane; Triclorofluorometano.

CCl_3F = 137.4.

CAS — 75-69-4.

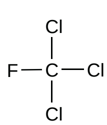

NOTE. Trichlorofluoromethane is a gas above 24°.

Pharmacopoeias. In *USNF.*

USNF 26 (Trichloromonofluoromethane). A clear, colourless gas having a faint ethereal odour. Store in airtight cylinders at a temperature not exceeding 40°.

Profile

Chlorofluorocarbons are used as refrigerants and as aerosol propellants (p.1688). They may also be used as a spray for topical anaesthesia, the intense cold produced by the rapid evaporation of the spray making the tissues insensitive.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Algispray.

Multi-ingredient: ***Austral.:*** Derm-Freeze; ***USA:*** Aerofreeze; Fluori-Methane†; Fluro-Ethyl.

Dimethyl Ether

Dimethyl Oxide; Éter dimetílico; Methoxymethane; Oxybismethane.

C_2H_6O = 46.07.

CAS — 115-10-6.

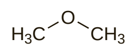

Profile

Dimethyl ether is used as a refrigerant, aerosol propellant (p.1688), and topical anaesthetic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Histofreezer†; ***Fr.:*** Freeze; Histofreezer†; ***Irl.:*** Wartner; ***Israel:*** Wartner; ***NZ:*** Wartner; ***UK:*** Histofreezer; PR Freeze Spray; Ralgex Freeze Spray; Wartner; ***USA:*** Compound W Freeze Off.

Helium

E939; Helio; Hélium.

He = 4.002602.

CAS — 7440-59-7.

ATC — V03AN03.

ATC Vet — QV03AN03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Helium). A colourless, inert gas. Store as a compressed gas or liquid at cryogenic temperatures, in appropriate containers.

USP 31 (Helium). A colourless, odourless, tasteless gas which is not combustible and does not support combustion. Very slightly soluble in water. Store in cylinders.

Profile

As helium is less dense than nitrogen, breathing a mixture of 80% helium and 20% oxygen requires less effort than breathing air. Thus mixtures containing various concentrations of oxygen ('Heliox') have been used in patients with respiratory disorders. Due to the low solubility of helium, mixtures of helium and oxygen are used by divers or others working under high pressure to prevent the development of decompression sickness (caisson disease); they are preferred to compressed air as they do not cause nitrogen narcosis. Helium has been used in pulmonary function testing.

Breathing helium increases vocal pitch and causes voice distortion. Cerebral artery gas embolism has been reported after inhalation of helium from a pressurised container.

◊ Reviews.

1. Rodrigo GJ, *et al.* Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. *Chest* 2003; **123:** 891–6.
2. Colebourn CL, *et al.* Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia* 2007; **62:** 34–42.
3. Harris PD, Barnes R. The uses of helium and xenon in current clinical practice. *Anaesthesia* 2008; **63:** 284–93.

Hydrochlorofluorocarbons

HCFCs; Hidroclorofluorocarbonos.

Chlorodifluoroethane

Clorodifluoroetano; Propellant 142b; Refrigerant 142b. 1-Chloro-1,1-difluoroethane.

$C_2H_3ClF_2$ = 100.5.

CAS — 75-68-3.

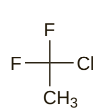

Chlorodifluoromethane

Clorodifluorometano; Propellant 22; Refrigerant 22.

$CHClF_2$ = 86.47.

CAS — 75-45-6.

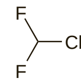

Profile

Hydrochlorofluorocarbons are used as refrigerants and as aerosol propellants (p.1688).

Hydrofluorocarbons

HFAs; HFCs; Hidrofluorocarbonos; Hydrofluroalkanes.

Apaflurane *(BAN, rINN)*

Apaflurano; Apafluranum; Heptafluoropropane; HFA-227; HFC-227. 1,1,1,2,3,3,3-Heptafluoropropane.

Апафлуран

C_3HF_7 = 170.0.

CAS — 431-89-0.

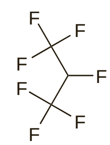

Difluoroethane

Difluoroetano; Ethylene Fluoride; HFC-152a; Propellant 152a; Refrigerant 152a. 1,1-Difluoroethane.

$C_2H_4F_2$ = 66.05.

CAS — 75-37-6.

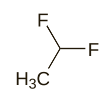

Norflurane *(BAN, USAN, rINN)*

Fluorocarbon 134a; GR-106642X; HFA-134a; HFC-134a; Norflurano; Norfluranum; Propellant 134a; Refrigerant 134a. 1,1,1,2-Tetrafluoroethane.

Норфлуран

$C_2H_2F_4$ = 102.0.

CAS — 811-97-2.

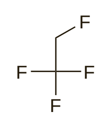

Profile

Hydrofluorocarbons are used as refrigerants and as aerosol propellants (p.1688). They are nonchlorinated and cause less ozone depletion than chlorinated fluorocarbons, which may lead to less detrimental effects on the environment. They are being used to replace chlorinated fluorocarbons as propellants in medicinal inhalers.

◊ References.

1. Denyer LH, *et al.* GR106642X, a non-chlorinated propellant for use in metered-dose inhalers: safety, tolerability and pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 1994; **38:** 509P.
2. Taggart SCO, *et al.* GR106642X: a new, non-ozone depleting propellant for inhalers. *BMJ* 1995; **310:** 1639–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Gebauers Spray & Stretch.

Hydrogen Sulfide

Hydrogen Sulphide; Siarkowodór; Sulfuro de hidrógeno; Sulphuretted Hydrogen.

H_2S = 34.08.

CAS — 7783-06-4.

Description. Hydrogen sulfide is a colourless flammable gas with a characteristic odour.

Adverse Effects

Hydrogen sulfide is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein. Concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. At concentrations of about 0.005% and above hydrogen sulfide causes anosmia and its unpleasant odour is no longer detectable. Pulmonary irritation, oedema, and respiratory failure usually occur after acute poisoning; prolonged exposure to low concentrations may cause severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, cough, nausea, vomiting and diarrhoea, pharyngitis, headache, dizziness, and lassitude. There are some similarities to poisoning with cyanides.

◊ General references.

1. WHO. Hydrogen Sulfide. *Environmental Health Criteria 19*. Geneva: WHO, 1981. Available at: http://www.inchem.org/documents/ehc/ehc/ehc019.htm (accessed 05/07/04)

Treatment of Adverse Effects

In poisoning with hydrogen sulfide the patient should be removed from the contaminated atmosphere and an effective airway established. Inhalation of amyl nitrite or parenteral therapy with sodium nitrite have been suggested; this produces methaemoglobin, which may bind sulfide. Oxygen should be given; hyperbaric oxygen therapy has also been suggested. The conjunctival sacs should be carefully washed out if eye irritation is severe. Management is then usually symptomatic and supportive.

◊ References.

1. Gorman DF. Problems and pitfalls in the use of hyperbaric oxygen for the treatment of poisoned patients. *Med Toxicol Adverse Drug Exp* 1989; **4:** 393–9.

Uses

Hydrogen sulfide is widely used in many industrial processes.

Isobutane

E943b; Isobutano; 2-Methylpropane.

C_4H_{10} = 58.12.

Pharmacopoeias. In *USNF.*

USNF 26 (Isobutane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40°.

Profile

Isobutane is used as an aerosol propellant (p.1688).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Histofreezer†; ***Fr.:*** Cliptol Sport†; Freeze; ***UK:*** Histofreezer; ***USA:*** Compound W Freeze Off.

Nitrogen

Azot; Azotas; Azote; Dusík; E941; Kvävgas; Nitrogén; Nitrogenium; Nitrógeno; Nitrogenum; Stickstoff; Typpi.

N_2 = 28.0134.

CAS — 7727-37-9.

ATC — V03AN04.

ATC Vet — QV03AN04.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Nitrogen). The monograph applies to nitrogen for medicinal use. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20° and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

The BP 2008 directs that nitrogen should be kept in approved metal cylinders, the shoulders of which are painted black and the remainder grey. The cylinder should carry a label stating 'Nitrogen'.

Ph. Eur. 6.2 (Nitrogen, Low-oxygen). The monograph applies to nitrogen used in the production of an inert atmosphere for finished medicinal products that are particularly sensitive to degradation by oxygen. A colourless, odourless gas. Soluble 1 in about 62 of water and 1 in about 10 of alcohol by volume at 20° and at a pressure of 101 kpA. Store as a compressed gas or a liquid in appropriate containers.

USNF 26 (Nitrogen). A colourless, odourless, tasteless gas. It is non-flammable and does not support combustion. Soluble 1 in about 65 of water v/v and 1 in about 9 of alcohol v/v at 20° and at a pressure of 760 mmHg. Store in cylinders.

USNF 26 (Nitrogen 97 Percent). It contains not less than 97% v/v of nitrogen. Store in cylinders or in a low-pressure collecting tank.

Adverse Effects

Nitrogen narcosis has been reported after use of nitrogen at high pressure as in deep-water diving. Under high pressure, nitrogen dissolves in blood and lipid. If decompression is too rapid, nitrogen effervesces from body stores producing gas emboli and leads to the syndrome of decompression sickness. Skin contact with liquid nitrogen causes frostbite or burns.

◊ References.

1. Roblin P, *et al.* Liquid nitrogen injury: a case report. *Burns* 1997; **23:** 638–40.
2. Kernbach-Wighton G, *et al.* Clinical and morphological aspects of death due to liquid nitrogen. *Int J Legal Med* 1998; **111:** 191–5.
3. Koplewitz BZ, *et al.* Gastric perforation attributable to liquid nitrogen ingestion. *Pediatrics* 2000; **105:** 121–3.
4. Kim DH, Lee HJ. Evaporated liquid nitrogen-induced asphyxia: a case report. *J Korean Med Sci* 2008; **23:** 163–5.

Uses and Administration

Nitrogen is used as a diluent for pure oxygen or other active gases and as an inert gas to replace air in containers holding oxidisable substances. Liquid nitrogen is used as a cryotherapeutic agent for the removal of warts (p.1584) and for preservation of tissues and organisms.

Oxygen

Deguonis; E948; Happi; Kyslík; Ossigeno; Oxigén; Oxígeno; Oxygène; Oxygenium; Oxygenum; Sauerstoff; Tlen.

O_2 = 31.9988.

CAS — 7782-44-7.

ATC — V03AN01.

ATC Vet — QV03AN01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Oxygen). A colourless, odourless gas. Soluble 1 in about 32 of water by volume at 20° and at a pressure of 101 kPa. Store as a compressed gas or liquid in appropriate containers.

The BP 2008 directs that oxygen should be kept in approved metal cylinders, the shoulders of which are painted white and the remainder black. The cylinder should carry a label stating 'Oxygen'. In addition, 'Oxygen' or the symbol 'O_2' should be stencilled in paint on the shoulder of the cylinder.

Ph. Eur. 6.2 (Air, Medicinal; Aer Medicinalis; Medical Air BP 2008). It is compressed ambient air containing not less than 20.4% and not more than 21.4% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20° and at a pressure of 101 kPa. Store as a gas in suitable containers.

Ph. Eur. 6.2 (Air, Synthetic Medicinal; Aer Medicinalis Artificiosus; Synthetic Air BP 2008). It is a mixture of nitrogen and oxygen containing between 21.0% and 22.5% of oxygen. A colourless, odourless gas. Soluble 1 in about 50 of water by volume at 20° and at a pressure of 101 kPa. Store as a compressed gas in suitable containers.

USP 31 (Oxygen). A colourless, odourless, tasteless gas that supports combustion more energetically than does air. Soluble 1 in about 32 of water v/v and 1 in about 7 of alcohol v/v at 20° and at a pressure of 760 mmHg. Store in cylinders or in a pressurised storage tank.

USP 31 (Medical Air). A natural or synthetic mixture of gases consisting largely of nitrogen and oxygen. It contains not less than 19.5% and not more than 23.5% of oxygen. Store in cylinders or in a low pressure collecting tank.

USP 31 (Oxygen 93 Percent). It contains not less than 90% v/v and not more than 96% v/v of oxygen, the remainder consisting mostly of argon and nitrogen. Store in cylinders or in a low-pressure collecting tank.

Adverse Effects

Oxygen toxicity depends upon both the inspired pressure (a function of concentration and barometric pressure) and the duration of exposure, the safe duration decreasing as the pressure increases. At lower pressures of up to 2 atmospheres absolute, pulmonary toxicity occurs before CNS toxicity; at higher pressures, the reverse applies. Symptoms of pulmonary toxicity include a decrease in vital capacity, cough, and substernal distress. Symptoms of CNS toxicity include nausea, mood changes, vertigo, twitching, convulsions, and loss of consciousness.

Hyperbaric oxygen therapy. In a review of hyperbaric oxygen therapy[1] the following were mentioned as potential complications: barotrauma (ear or sinus trauma, tympanic membrane rupture, or rarely pneumothorax or air embolism); oxygen toxicity (CNS toxicity or pulmonary toxicity); and reversible visual changes.

1. Grim PS, *et al.* Hyperbaric oxygen therapy. *JAMA* 1990; **263:** 2216–20.

Retinopathy of prematurity. In the 1940s and 1950s an epidemic of retinopathy of prematurity, affecting perhaps 10 000 babies, was attributed to excessive use of oxygen in neonates. This resulted in the use of oxygen being reduced or curtailed and the incidence of the condition fell dramatically. However, in the 1970s and later an unexpected resurgence of retinopathy of prematurity occurred (probably *not* due to excessive oxygen use). It was suggested[1,2] that oxygen plays only a minor part and that retinopathy of prematurity is a multifactorial condition that affects the most immature and sick children; the increased incidence may reflect the improved survival of these very premature neonates. A study[3] of supplemental oxygen in infants with prethreshold retinopathy of prematurity suggested that therapy was safe, but a beneficial effect could not be confirmed. However, a retrospective study[4] in premature neonates given supplemental oxygen found that retinopathy of prematurity was more common in those maintained at higher oxygen saturations.

1. Anonymous. Retinopathy of prematurity. *Lancet* 1991; **337:** 83–4.
2. Holmström G. Retinopathy of prematurity. *BMJ* 1993; **307:** 694–5.
3. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. *Pediatrics* 2000; **105:** 295–310.
4. Tin W, *et al.* Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F106–F110.

Precautions

Any fire or spark is highly dangerous in the presence of increased oxygen concentrations especially when oxygen is used under pressure.

Metal cylinders containing oxygen should be fitted with a reducing valve by which the rate of flow can be controlled. It is important that the reducing valve should be free from all traces of oil or grease, as otherwise a violent explosion may occur. Combustible material soaked in liquid oxygen is potentially explosive and the low temperature of liquid oxygen may cause unsuitable equipment to become brittle and crack. Liquid oxygen should not be allowed to come into contact with the skin as it produces severe 'cold burns'.

Oxygen intended for aviation or mountain rescue must have a sufficiently low moisture content to avoid blocking of valves by ice on freezing.

High concentrations of oxygen should be avoided in patients whose respiration is dependent upon hypoxic drive, otherwise carbon dioxide retention and respiratory depression may ensue.

Neonates. The use of supplemental oxygen in neonates is controversial.[1] Although the use of 100% oxygen for the resuscitation of asphyxiated term neonates has been standard, there is some evidence that the use of room air (21% oxygen) is equally effective and possibly safer than 100% oxygen although a systematic review[2] concluded that there was insufficient evidence for recommendations to be made. Guidelines[3,4] for neonatal resuscitation state that the use of less concentrated oxygen or room air in preference to 100% oxygen is reasonable, but that supplemental oxygen should be available if room air is used initially. Use of supplemental oxygen in preterm neonates has been associated with an increased risk of retinopathy of prematurity, although other factors are probably also involved (see under Adverse Effects, above). However, another study[5] has reported that supplemental oxygen has beneficial effects on sleep patterns in premature neonates. Although there is some evidence for a link between neonatal oxygen therapy and childhood cancer, this remains to be confirmed.[6]

1. Higgins RD, *et al.* Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. *Pediatrics* 2007; **119:** 790–6.
2. Tan A, *et al.* Air versus oxygen for resuscitation of infants at birth. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 07/06/06).
3. Resuscitation Council (UK). Resuscitation Guidelines 2005: newborn life support. Available at: http://www.resus.org.uk/pages/nls.pdf (accessed 07/06/06)
4. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 13: neonatal resuscitation guidelines. *Circulation* 2005; **112:** (suppl 1): IV188–IV195. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-188 (accessed 07/06/06)
5. Simakajornboon N, *et al.* Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. *Pediatrics* 2002; **110:** 884–8.
6. Spector LG, *et al.* Childhood cancer following neonatal oxygen supplementation. *J Pediatr* 2005; **147:** 27–31.

Uses and Administration

Oxygen is given by inhalation to correct hypoxaemia in conditions causing respiratory failure (below) and in conditions where the oxygen content of the air breathed is inadequate such as high-altitude disorders (p.1168). Oxygen is of value in the treatment of poisoning with a number of substances, including carbon monoxide (p.1688), cyanides (p.2045), and dichloromethane (p.2021). It provides enhanced oxygenation in inhalation injury. Oxygen is also given by inhalation to subjects working in pressurised spaces and to divers to reduce the concentration of nitrogen inhaled. It is used as a diluent of volatile and gaseous anaesthetics.

Oxygen is usually given by means of nasal prongs or via a face mask; these can usually deliver concentrations of up to 60%. Tight-fitting anaesthetic-type masks, or delivery via an endotracheal tube or oxygen tent, can provide higher concentrations of up to 100%. Face masks are often used for domiciliary oxygen therapy when flow rates are 2 or 4 litres/minute. Oxygen is usually supplied compressed in metal cylinders although oxygen concentrators, which produce oxygen-enriched air, are useful for domiciliary therapy, especially in patients using large quantities of oxygen. Oxygen may also be supplied at low temperature in insulated containers as liquid oxygen.

In respiratory failure in conditions not usually associated with retention of carbon dioxide, such as pneumonia, pulmonary oedema, or fibrosing alveolitis, oxygen should be given in high concentrations (usually 40 to 100%). Concentrations of 40 to 60% should be used in acute severe asthma even though carbon dioxide retention may have increased as the patient's condition deteriorated. High concentrations of oxygen should always be reduced as soon as possible to the lowest concentration needed to correct hypoxaemia in order to prevent development of any associated oxygen toxicity, including increased carbon dioxide retention. High concentrations of oxygen should be used in carbon monoxide poisoning and, in selected patients, treatment with hyperbaric oxygen considered.

In respiratory failure associated with chronic obstructive pulmonary disease (conditions such as chronic bronchitis and emphysema) oxygen is usually given initially at an inspired concentration of up to 28%. High concentrations are to be avoided as they may enhance carbon dioxide retention and narcosis.

Oxygen at a pressure greater than 1 atmosphere absolute, i.e. hyperbaric oxygen therapy (below), is given by enclosing the patient in a special high-pressure chamber. It may be used in carbon monoxide poisoning, as an adjunct in the treatment of severe anaerobic infections, especially gas gangrene, and for the treatment of decompression sickness and gas emboli.

◊ General references.

1. Naylor-Shepherd MF, *et al.* Oxygen homeostasis: theory, measurement, and therapeutic implications. *DICP Ann Pharmacother* 1990; **24:** 1195–1203.
2. Gribbin HR. Management of respiratory failure. *Br J Hosp Med* 1993; **49:** 461–77.
3. Tarpy SP, Celli BR. Long-term oxygen therapy. *N Engl J Med* 1995; **333:** 710–14.
4. Bateman NT, Leach RM. ABC of oxygen: acute oxygen therapy. *BMJ* 1998; **317:** 798–801.
5. Rees PJ, Dudley F. ABC of oxygen: oxygen therapy in chronic lung disease. *BMJ* 1998; **317:** 871–4.
6. Rees PJ, Dudley F. ABC of oxygen: provision of oxygen at home. *BMJ* 1998; **317:** 935–8.
7. Treacher DF, Leach RM. ABC of oxygen: oxygen transport: basic principles. *BMJ* 1998; **317:** 1302–6.
8. Leach RM, Treacher DF. ABC of oxygen: oxygen transport: tissue hypoxia. *BMJ* 1998; **317:** 1370–3.
9. Balfour-Lynn IM, *et al.* Home oxygen for children: who, how and when? *Thorax* 2005; **60:** 76–81.

Cluster headache. Inhalation of 100% oxygen can provide rapid and effective treatment of cluster headache attacks (p.616) but practical difficulties associated with its use result in other drugs being preferred. It has been noted that the evidence of value is limited.

References.

1. Fogan L. Treatment of cluster headache: a double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985; **42:** 362–3.
2. Rozen TD. High oxygen flow rates for cluster headache. *Neurology* 2004; **63:** 593.
3. Bennett MH, *et al.* Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).

Hyperbaric oxygen therapy. The use of hyperbaric oxygen therapy, which involves the intermittent inhalation of 100% oxygen under a pressure of greater than 1 atmosphere in a specialised chamber, has been reviewed.[1-3] In the 1960s hyperbaric therapy was used for disorders such as *myocardial infarction, stroke, senility,* and *cancer* but clinical studies and experience have shown little benefit and enthusiasm has since waned. Hyperbaric oxygen therapy has also been tried in *multiple sclerosis* but there is little evidence of benefit. There are, however, other disorders for which the evidence supporting the efficacy of hyperbaric oxygen is much stronger.

Hyperbaric oxygen is a safe and effective primary therapy for *decompression sickness* and *air or gas embolism.* The effect is achieved through the mechanical reduction in bubble size in the blood brought about by an increase in ambient pressure; the increased oxygenation of blood due to the additional pressure used for these conditions (often 6 rather than 2 or 3 atmospheres) is also beneficial.

The role of hyperbaric oxygen therapy in *carbon monoxide poisoning* is unclear but it should be considered in selected patients (see p.1688). Its mechanism of action is not fully understood; it increases the rate at which carboxyhaemoglobin concentrations decline, increases intracellular delivery of oxygen, and may also reduce lipid peroxidation and thus spare neuronal cell membranes.

Hyperbaric oxygen is used as adjunctive therapy in *clostridial infections (gas gangrene)* (p.171). Early treatment appears to reduce systemic toxic reactions (probably by inhibiting the production of alpha toxin by the anaerobic bacteria, *Clostridium*) thus enabling patients to tolerate surgery more readily; additionally there is a clearer demarcation of viable and nonviable tissue. *Necrotising fasciitis* (p.180) is another infection in which hyperbaric oxygen therapy may be useful.

There is some evidence that hyperbaric oxygen may be useful in other types of *wounds.* In an *acute crush injury* therapy may reduce oedema via vasoconstriction and reverse ischaemia by increased oxygen delivery. In *problem wounds,* including venous ulcers, therapy may increase the tissue oxygen tension and stimulate angioneogenesis but it is emphasised that it is adjunctive therapy and not a replacement for meticulous local care. Hyperbaric oxygen therapy might also reduce the risk of major amputation in patients with chronic *diabetic foot ulcer.*[4,5] Improved healing of leg ulcers has been reported[6] with use of hyperbaric oxygen therapy in patients with livedoid vasculopathy. Other wounds in which therapy may be beneficial include thermal burns and compromised skin grafts and flaps. The management of burns and wounds is described on p.1578 and p.1585, respectively.

Radiation therapy can damage normal adjacent tissue resulting in tissue hypoxia and eventual cell death. Hyperbaric oxygen therapy appears to aid in salvaging such tissue by stimulating angioneogenesis in marginally viable tissue and has been demonstrated to be beneficial in osteoradionecrosis, radiation-induced haemorrhagic cystitis (p.2178), and other radiation-damaged soft tissue.[7]

There has been interest in the use of hyperbaric oxygen in children with *cerebral palsy,* although a randomised study[8] found that it was no better than pressurised air. However, improved neurological outcomes have been reported with hyperbaric oxygen therapy in neonates with hypoxic-ischaemic encephalopathy.[9]

1. Grim PS, *et al.* Hyperbaric oxygen therapy. *JAMA* 1990; **263:** 2216–20.
2. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med* 1996; **334:** 1642–8.
3. Leach RM, *et al.* ABC of oxygen: hyperbaric oxygen therapy. *BMJ* 1998; **317:** 1140–3.
4. Wang C, *et al.* Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; **138:** 272–9.
5. Roeckl-Wiedmann I, *et al.* Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; **92:** 24–32.
6. Juan W-H, *et al.* Livedoid vasculopathy: long-term follow-up results following hyperbaric oxygen therapy. *Br J Dermatol* 2006; **154:** 251–5.
7. Pasquier D, *et al.* Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. *Radiother Oncol* 2004; **72:** 1–13.
8. Collet J-P, *et al.* Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. *Lancet* 2001; **357:** 582–6.
9. Liu Z, *et al.* Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic-ischaemic encephalopathy: systematic review of Chinese literature. *BMJ* 2006; **333:** 374–6.

Respiratory failure. Respiratory failure occurs when the arterial plasma partial pressure of oxygen (P_aO_2) and of carbon dioxide (P_aCO_2) cannot be maintained within normal physiological limits.[1] Respiratory failure can be classified into 2 types, both of which are characterised by a low P_aO_2 (hypoxaemia). However, in type I the P_aCO_2 is normal or low whereas in type II, referred to as ventilatory failure, P_aCO_2 is raised (hypercapnia). Some conditions, for example asthma, can produce either type of respiratory failure.

Management of respiratory failure mainly involves giving oxygen to reverse hypoxaemia, and specific therapy for any underlying condition. Respiratory stimulants may be considered in some situations.

In type I respiratory failure oxygen is used in high concentrations. Nasal prongs and certain face masks can provide concentrations of up to 60% but if concentrations higher than this are needed then tight-fitting anaesthetic-type masks or methods of delivery such as endotracheal intubation have to be used.

In type II respiratory failure both high and low concentrations are used according to need.

Patients with *acute severe asthma* (p.1108) should usually be given oxygen at high concentrations of 40 to 60%. In patients with exacerbations of chronic respiratory disorders such as *chronic obstructive pulmonary disease* (COPD, p.1112) the aim is to improve hypoxaemia without increasing hypercapnia and respiratory acidosis.[2] The initial concentration of oxygen to give in COPD exacerbations is controversial. During the transfer to hospital, UK guidelines[3] recommend starting at 40% and titrating upwards if the oxygen saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93 to 94%. Special care is needed for patients with known type II respiratory failure, especially if they require a long ambulance journey or receive oxygen at home for a prolonged period before an ambulance arrives, as uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis, and respiratory arrest. In hospital, arterial blood gases should be used to guide treatment. Other guidelines[4] consider that lower initial oxygen concentrations of 24 to 28% are usually sufficient. Patients with exacerbations of chronic ventilatory failure already have an increased central drive to the respiratory muscles and therefore respiratory stimulants such as doxapram have a limited role but may be indicated for short-term use if hypercapnia worsens as a result of oxygen. For most patients with chronic obstructive pulmonary disease, non-invasive ventilation is the initial treatment of choice for hypercapnic ventilatory failure during exacerbations.[3] Respiratory stimulants may be considered in the management of *postanaesthetic hypoventilation.* Although naloxone can reverse respiratory depression caused by opioid analgesics careful dosage adjustment is required as it can also abolish analgesia. Specific antagonists such as naloxone and flumazenil are also used to treat hypoventilation associated with opioid and benzodiazepine overdosage, respectively. If oxygen therapy fails to raise P_aO_2 in respiratory failure and there is worsening hypercapnia and respiratory acidosis the use of artificial ventilation should be considered.

Severe respiratory failure in *neonates* may result from various disorders. Use of surfactant or inhaled nitric oxide may be of benefit in some cases but extracorporeal membrane oxygenation (ECMO), where blood is removed from the neonate, oxygenated, and re-injected in a continuous circuit that also removes carbon dioxide, may be required.[5] ECMO has also been used in older children and in adults,[6] but is less well established.

1. Gribbin HR. Management of respiratory failure. *Br J Hosp Med* 1993; **49:** 461–77.
2. Plant PK, Elliott MW. Chronic obstructive pulmonary disease 9: management of ventilatory failure in COPD. *Thorax* 2003; **58:** 537–42.
3. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; **59** (suppl 1): 1–232. Also available at: http://thorax.bmj.com/content/vol59/suppl_1/ (accessed 18/12/07)
4. McKenzie DK, *et al.* The COPDX plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease 2007. Available at: http://www.copdx.org.au/guidelines/documents/COPDX_Sep28_2007.pdf (accessed 18/12/07)
5. Barrington KJ, Finer NN. Care of near term infants with respiratory failure. *BMJ* 1997; **315:** 1215–18.
6. Peek GJ, *et al.* Extracorporeal membrane oxygenation: potential for adults and children? *Hosp Med* 1998; **59:** 304–8.

Wounds. Hyperbaric oxygen therapy may have a role in the management of infected and problem wounds (see above). Supplemental normobaric oxygen has been tried in the prevention of postoperative wound infections, but results of controlled studies[1-3] have been contradictory and its role is not established.

1. Greif R, *et al.* Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000; **342:** 161–7.
2. Pryor KO, *et al.* Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *JAMA* 2004; **291:** 79–87.
3. Belda FJ, *et al.* Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA* 2005; **294:** 2035–42.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Kalinox; Medimix; ***S.Afr.:*** Entonox; ***UK:*** Entonox; Equanox.

Propane

Dimethylmethane; E944; Propano; Propyl Hydride.

C_3H_8 = 44.10.

CAS — 74-98-6.

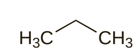

Pharmacopoeias. In *USNF.*

USNF 26 (Propane). A colourless gas. It is highly flammable and explosive. Store in airtight cylinders at a temperature not exceeding 40°.

Profile

Propane is used as a refrigerant and as an aerosol propellant (p.1688). It is also widely used as a fuel.

◊ Reports of toxicity associated with the abuse or misuse of propane.[1-6]

1. James NK, Moss ALH. Cold injury from liquid propane. *BMJ* 1989; **299:** 950–1.
2. Siegel E, Wason S. Sudden death caused by inhalation of butane and propane. *N Engl J Med* 1990; **323:** 1638.
3. Tsoukali H, *et al.* Death during deliberate propane inhalation. *Forensic Sci Int* 1998; **93:** 1–4.
4. McLennan JJ, *et al.* Propane-associated autoerotic fatalities. *Am J Forensic Med Pathol* 1998; **19:** 381–6.
5. Grosse K, Grosse J. Propanmissbrauch: extreme Dosissteigerung durch Toleranzentwicklung. *Nervenarzt* 2000; **71:** 50–3.
6. Jackowski C, *et al.* Autoerotic accident by inhalation of propane-butane gas mixture. *Am J Forensic Med Pathol* 2005; **26:** 355–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Histofreezer†; ***Fr.:*** Cliptol Sport†; Freeze; Histofreezer†; ***Ger.:*** Olbas; ***Irl.:*** Wartner; ***Israel:*** Wartner; ***NZ:*** Wartner; ***UK:*** Histofreezer; Wartner; ***USA:*** Compound W Freeze Off.

Gastrointestinal Drugs

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- Peptic ulcer disease, p.1702
- Zollinger-Ellison syndrome, p.1704

This chapter describes the principal drugs used in the treatment of gastrointestinal disorders, and the choice of treatment for some of the main disorders.

Gastrointestinal Drug Groups

Antacids

Antacids are basic compounds that neutralise hydrochloric acid in the gastric secretions. They are used in the symptomatic management of gastrointestinal disorders associated with gastric hyperacidity such as dyspepsia, gastro-oesophageal reflux disease, and peptic ulcer disease (see below).

Antacids do not reduce the volume of hydrochloric acid secreted and elevation of the gastric pH may actually promote an increase in acid secretion. However, this is usually minor and short-lived except after large doses of calcium carbonate. Antacids are normally given between meals and at bedtime when symptoms of gastric hyperacidity usually occur; the presence of food in the stomach can prolong the neutralising activity. Some calculate doses as mEq or mmol of acid-neutralising capacity, but the relationship between neutralising capacity and beneficial effect is not straightforward. Other factors, including formulation (liquid preparations are more effective than solids) and duration of action (relatively insoluble antacids are longer acting) are also important.

Aluminium salts tend to produce constipation and to delay gastric emptying, while magnesium salts have the reverse effect; a combination of the two may reduce adverse gastrointestinal effects. Another advantage of combined antacid formulations is that a slow-acting antacid such as aluminium hydroxide may be combined with a more rapidly acting drug such as magnesium hydroxide to improve the onset and duration of effect. Alternatively, complexes containing both aluminium and magnesium may be used, such as almasilate, hydrotalcite, and magaldrate. Other drugs that may be combined with antacid formulations include simeticone, which acts as a defoaming agent to reduce excess gas in the stomach, and alginates, which form a gel or foam on the surface of the stomach contents thereby impeding reflux and protecting the oesophageal mucosa from acid attack.

Calcium carbonate and sodium bicarbonate are both rapidly acting but have disadvantages: calcium carbonate is usually reserved for short-term treatment because of the risks of rebound acid secretion and metabolic alkalosis, while sodium bicarbonate is absorbed and is contra-indicated in patients who must control sodium intake (e.g. in heart failure, hypertension, renal failure, cirrhosis, or pregnancy).

Antacids may interact with numerous other drugs, affecting the rate and extent of their absorption, and in some cases their renal elimination. Changes in gastric pH affect the dissolution of other drugs, and together with altered gastric emptying can markedly influence absorption. Aluminium compounds in particular are noted for their propensity to adsorb other drugs and to form insoluble complexes that are not absorbed. Antacids that alter urinary pH will affect renal clearance of drugs that are weak acids or bases. Several mechanisms may play a part in any particular interaction. Interactions can be minimised by giving antacids and other medication 2 to 3 hours apart.

Antacids in this chapter include aluminium salts, magnesium salts, and calcium carbonate. For sodium bicarbonate, see p.1673.

Described in this chapter are

Aceglutamide Aluminium, p.1704	Basic Aluminium Carbonate, p.1706
Alexitol Sodium, p.1704	Bismuth Compounds, p.1710
Almagate, p.1705	Calcium Carbonate, p.1714
Almasilate, p.1705	Dihydroxyaluminum Sodium Carbonate, p.1723
Aloglutamol, p.1705	Hydrotalcite, p.1733
Aluminium Glycinate, p.1706	Magaldrate, p.1742
Aluminium Hydroxide, p.1706	Magnesium Carbonate, p.1743
Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel, p.1707	Magnesium Hydroxide, p.1743
Aluminium Phosphate, p.1707	Magnesium Oxide, p.1744
Aluminium Sodium Silicate, p.1707	Magnesium Trisilicate, p.1744

Antidiarrhoeals

Antidiarrhoeals are used as adjuncts in the symptomatic treatment of diarrhoea (see below), although the main aim in the management of *acute* diarrhoea is the correction of fluid and electrolyte depletion with rehydration therapy; this is especially important in infants and young children and antidiarrhoeals are not generally recommended for this age group. Their use is also limited in *chronic* diarrhoea since treatment aimed at the underlying disorder will often alleviate the diarrhoea.

Described in this chapter are drugs that reduce intestinal motility such as the opioid analogues diphenoxylate and loperamide, and adsorbents such as attapulgite and kaolin. Bulking agents (which include bran and ispaghula) have also been used for diarrhoea and for adjusting faecal consistency in patients with colostomies.

Described in this chapter are

Albumin Tannate, p.1704	Ispaghula, p.1737
Attapulgite, p.1709	Kaolin, p.1738
Bismuth Compounds, p.1710	Lidamidine, p.1740
Bran, p.1712	Loperamide, p.1741
Chalk, p.1716	Racecadotril, p.1765
Difenoxin, p.1723	Smectites, p.1771
Diphenoxylate, p.1724	Zaldaride, p.1778

Antiemetics

Antiemetics are a diverse group of drugs used to treat or prevent nausea and vomiting, including that associated with cancer therapy, anaesthesia, and motion sickness (see below).

The choice of drug depends partly on the cause of nausea and vomiting. For example, hyoscine or an antihistamine are used in motion sickness whereas dopamine antagonists (such as metoclopramide and domperidone) and serotonin 5-HT_3-receptor antagonists (5-HT_3 antagonists), such as ondansetron, are ineffective. Conversely, nausea and vomiting associated with cancer chemotherapy is often hard to control and special regimens have been devised including the use of the 5-HT_3 antagonists, dexamethasone, and, more recently, the neurokinin-1 receptor antagonist aprepitant.

Described in this chapter are

Alizapride, p.1704	Granisetron, p.1733
Aprepitant, p.1708	Indisetron, p.1736
Azasetron, p.1709	Itopride, p.1737
Bromopride, p.1713	Mecloxamine Citrate, p.1744
Cerium Oxalate, p.1715	Metoclopramide, p.1747
Clebopride, p.1722	Metopimazine, p.1750
Difenidol, p.1723	Nabilone, p.1750
Dolasetron, p.1725	Ondansetron, p.1756
Domperidone, p.1726	Palonosetron, p.1759
Dronabinol, p.1728	Ramosetron, p.1765
Fosaprepitant, p.1732	Tropisetron, p.1777
Ginger, p.1732	

Antisecretory drugs

Antisecretory drugs are used in the treatment and prophylaxis of peptic ulcer disease (below); some are also employed in other disorders associated with gastric hyperacidity such as gastro-oesophageal reflux disease and dyspepsia (below). They may be divided into:

- *Histamine H_2-receptor antagonists* (H_2-antagonists), which act by blocking histamine H_2-receptors on gastric parietal cells, thereby antagonising the normal stimulatory effect of endogenous histamine on gastric acid production. Those described in this chapter include cimetidine, famotidine, nizatidine, and ranitidine.
- *Proton pump inhibitors*, which act by blocking the enzyme system responsible for active transport of protons into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) of the gastric parietal cell, also known as the 'proton pump'. Those described in this chapter include lansoprazole, omeprazole, pantoprazole, and rabeprazole.
- *Selective antimuscarinics*, which block cholinergic stimulation of gastric acid production with fewer adverse effects than less selective antimuscarinics (see Atropine, p.1221), but have largely been superseded. Pirenzepine (p.1762) is an example.
- *Prostaglandin analogues*, which inhibit gastric acid secretion by a direct action on the parietal cell and may also inhibit gastrin release and possess cytoprotective properties. Misoprostol (p.2013) is an example.

Described in this chapter are

Cimetidine, p.1716	Omeprazole, p.1753
Ebrotidine, p.1728	Pantoprazole, p.1760
Eseridine Salicylate, p.1729	Rabeprazole, p.1765
Esomeprazole, p.1729	Ranitidine Bismuth Citrate, p.1768
Famotidine, p.1730	Ranitidine, p.1766
Lafutidine, p.1739	Revaprazan, p.1768
Lansoprazole, p.1739	Roxatidine, p.1769
Niperotidine, p.1751	Urogastrone, p.1778
Nizatidine, p.1751	

Antispasmodics

Antispasmodics are drugs used for their relaxant action on smooth muscle, either direct or through an antimuscarinic action on the parasympathetic innervation. They play a role in the management of gastrointestinal spasm and irritable bowel syndrome (below) as well as other disorders associated with smooth muscle spasm. Those described in this chapter are mainly antimuscarinics; drugs in other chapters that may be used for relaxation of smooth muscle include calcium-channel blockers (p.1154) and nitrates (p.1155), as well as drugs with less well defined mechanisms of action such as papaverine (p.2191).

Described in this chapter are

Alverine Citrate, p.1708	Methanthelinium Bromide, p.1747
Butropium Bromide, p.1713	Methylbenactyzium Bromide, p.1747
Buzepide Metiodide, p.1714	Octatropine Methylbromide, p.1752
Ciclonium Bromide, p.1716	Oxapium Iodide, p.1759
Cimetropium Bromide, p.1720	Oxyphencyclimine Hydrochloride, p.1759
Clidinium Bromide, p.1722	Oxyphenonium Bromide, p.1759
Dicycloverine Hydrochloride, p.1722	Parapenzolate Bromide, p.1761
Difemerine Hydrochloride, p.1723	Pargeverine Hydrochloride, p.1761
Dihexyverine Hydrochloride, p.1723	Peppermint Leaf, p.1761
Diisopromine Hydrochloride, p.1724	Peppermint Oil, p.1761
Drofenine Hydrochloride, p.1727	Phenamazide Hydrochloride, p.1761
Fentonium Bromide, p.1731	Pipenzolate Bromide, p.1762
Hyoscine, p.1733	Piperidolate Hydrochloride, p.1762
Hyoscine Butylbromide, p.1734	Pipethanate Ethobromide, p.1762
Hyoscine Hydrobromide, p.1734	Platyphylline Acid Tartrate, p.1763
Hyoscine Methobromide, p.1734	Poldine Metilsulfate, p.1763
Hyoscine Methonitrate, p.1734	Prifinium Bromide, p.1764
Hyoscyamine, p.1736	Propantheline Bromide, p.1764
Hyoscyamine Hydrobromide, p.1736	Tiemonium, p.1776
Hyoscyamine Sulfate, p.1736	Timepidium Bromide, p.1777
Isopropamide Iodide, p.1736	Valethamate Bromide, p.1778
Mebeverine Hydrochloride, p.1744	
Mepenzolate Bromide, p.1745	

Laxatives

Laxatives (purgatives or cathartics) promote defaecation and are used in the treatment of constipation (see below) and for bowel evacuation before investigational procedures, such as endoscopy or radiological examination, or before surgery.

Laxatives are frequently used for self-medication. Abuse of laxatives is a well-known phenomenon that may occasionally lead to toxicity.

Laxatives may be classified according to their mode of action. There is, however, a degree of overlap between the various groups and in some cases the precise mechanisms of action are not fully understood. Many traditionally used laxatives have fallen from use owing to the violence of their action or their adverse effect profile.

- *Bulk laxatives* (bulk-forming laxatives or bulking agents) cause retention of fluid and an increase in faecal mass resulting in stimulation of peristalsis. Owing to their hydrophilic nature, bulk laxatives may also be used to control diarrhoea and to regulate the consistency of effluent in colostomy patients. Those described in this chapter include bran, ispaghula, and sterculia.
- *Stimulant laxatives* (contact laxatives) act by directly stimulating nerve endings in the colonic mucosa, thereby increasing intestinal motility. It is this group of laxatives which is most commonly associated with abuse. Those described in this chapter include bisacodyl, cascara, phenolphthalein, senna, and sodium picosulfate.
- *Osmotic laxatives* act by increasing intestinal osmotic pressure thereby promoting retention of fluid within the bowel. Those described in this chapter include saline laxatives such as magnesium citrate, magnesium hydroxide, and sodium sulfate (for magnesium sulfate and sodium phosphate see p.1679 and p.1682 respectively). Lactulose may also be classified as an osmotic laxative because its breakdown products exert a similar effect. Also included in this group are the hyperosmotic laxatives such as glycerol (p.2314) and sorbitol (p.1965), and the macrogols (p.2336).
- *Faecal softeners* (emollient laxatives) are claimed to act by decreasing surface tension and increasing penetration of intestinal fluid into the faecal mass. Those described in this chapter include docusate (which is also believed to have a stimulant action).

For the lubricant laxative liquid paraffin see p.2030.

Described in this chapter are

Aloes, p.1705
Aloin, p.1705
Bisacodyl, p.1710
Bisoxatin, p.1712
Bran, p.1712
Buckthorn, p.1713
Casanthranol, p.1715
Cascara, p.1715
Cassia Pulp, p.1715
Colocynth, p.1722
Dantron, p.1722
Docusates, p.1724
Euonymus, p.1730
Fig, p.1731
Frangula, p.1732
Ipomoea, p.1736
Ispaghula, p.1737
Jalap, p.1737
Lactitol, p.1738
Lactulose, p.1738
Liquorice, p.1740
Magnesium Citrate, p.1743
Magnesium Hydroxide, p.1743
Magnesium Oxide, p.1744
Manna, p.1744
Pentaerythritol, p.1761
Phenolphthalein, p.1762
Polycarbophil, p.1763
Potassium Acid Tartrate, p.1764
Potassium Sodium Tartrate, p.1764
Prune, p.1765
Psyllium Seed, p.1737
Rhubarb, p.1768
Senna, p.1769
Sodium Picosulfate, p.1771
Sodium Sulfate, p.1771
Sodium Tartrate, p.1772
Sterculia, p.1772
Tamarind, p.1776

Mucosal protectants

Cytoprotective drugs (mucosal protectants) play a role in the management of peptic ulcer disease (below). They may be divided into:

- *Chelates or complexes*, which coat the gastric mucosa preferentially at sites of ulceration by forming an adherent complex with proteins. Those described in this chapter include sucralfate and tripotassium dicitratobismuthate (which also has an antibacterial role in regimens aimed at eradicating *Helicobacter pylori*)
- *Miscellaneous drugs* include liquorice and its derivatives, such as carbenoxolone, which may act by stimulating the synthesis of protective mucus

Described in this chapter are

Benexate, p.1710
Carbenoxolone, p.1714
Cetraxate, p.1716
Dosmalfate, p.1727
Ebrotidine, p.1728
Ecabet, p.1728
Enoxolone Aluminium, p.1729
Gefarnate, p.1732
Irsogladine, p.1736
Liquorice, p.1740
Nocloprost, p.1752
Ornoprostil, p.1759
Plaunotol, p.1763
Polaprezinc, p.1763
Rebamipide, p.1768
Sofalcone, p.1772
Sucralfate, p.1772
Sulglicotide, p.1775
Teprenone, p.1776
Tripotassium Dicitratobismuthate, p.1711
Troxipide, p.1778

Prokinetic drugs

Prokinetic drugs stimulate the motility of the gastrointestinal tract. Gastrointestinal smooth muscle exhibits intrinsic motor activity which is modified by autonomic innervation, local reflexes, and gastrointestinal hormones. This activity produces peristaltic waves, which move the gut contents from stomach to anus, and segmentations, which encourage digestion. Prokinetic drugs may act at various points within this complex system to enhance gastrointestinal movement. Those described in this chapter include metoclopramide, cisapride, and domperidone. Other drugs with prokinetic properties include parasympathomimetics such as bethanechol (p.2265) or neostigmine (p.631), and the macrolide antibacterial erythromycin (p.269).

Described in this chapter are

Aclatonium Napadisilate, p.1704
Bromopride, p.1713
Cinitapride, p.1720
Cisapride, p.1720
Clebopride, p.1722
Domperidone, p.1726
Itopride, p.1737
Linaclotide Acetate, p.1740
Lubiprostone, p.1742
Metoclopramide, p.1747
Mosapride, p.1750
Renzapride, p.1768
Tegaserod, p.1776

Management of Gastrointestinal Disorders

The management of some gastrointestinal disorders is discussed below.

Aspiration syndromes

Regurgitation and aspiration of gastric contents (Mendelson's syndrome) is a potential cause of morbidity and mortality associated with anaesthesia, especially in obstetrics and in emergency surgery. Chemical pneumonitis and respiratory distress result from the acid aspiration, the risk of which is increased by the drugs given as adjuncts to anaesthesia such as opioid analgesics and atropine.

Apart from good anaesthetic technique, including a prohibition on oral intake before elective procedures, efforts to **prevent** or reduce the problem have focussed mainly on increasing the pH of gastric contents to above 2.5, and in reducing gastric volume. However, there is little evidence to show that reduced gastric acidity or volume is associated with decreased morbidity or mortality in patients who have aspirated gastric contents,[1] and some do not recommend the routine pre-operative use of pharmacological prophylaxis in patients undergoing elective surgery with no apparent increased risk for pulmonary aspiration.[1] Similarly there is little evidence to support the routine use of prophylactic drugs in women undergoing normal labour (particularly with the increased use of regional anaesthetic techniques).[2]

The *H_2-antagonists* decrease gastric acid secretion and may decrease gastric fluid volume. However, they do not affect the pH of fluid already in the stomach; they must therefore be given some time before anaesthesia, which limits their value in emergency procedures. Cimetidine is considered effective in most patients, although where more prolonged reduction of acidity is required H_2-antagonists with a longer duration of action such as ranitidine or famotidine may be preferred. Nizatidine has the advantage of a relatively rapid onset of action.[3] The *proton pump inhibitors* have also been tried, but results have been variable. Combination with a prokinetic drug may produce better results.[4]

Because of the lack of effect of antisecretory drugs on the pH of existing gastric fluid H_2-antagonists may be combined with *antacids* to neutralise gastric acidity. Although magnesium trisilicate has been extensively used[5] without apparent problems particulate antacids are potentially toxic to the lung, which is why soluble antacids such as sodium citrate have been widely favoured. An effervescent formulation of sodium citrate with cimetidine has been reported to raise gastric pH above 2.5 in more than 98% of patients undergoing caesarean section.[6]

A third component of prophylactic regimens for acid aspiration may be use of a *prokinetic drug* such as metoclopramide. These increase gastric emptying and thereby decrease the volume of stomach contents, and also increase pressure at the lower oesophageal sphincter. The ability of metoclopramide to reverse the effects of opioids on gastric emptying appears to depend on the route: 10 mg given intravenously after opioid analgesia is reported to be effective in promoting gastric emptying, whereas the same dose intramuscularly is not.[7]

If aspiration occurs, pulmonary damage may result within seconds; **treatment** has included removal of any particulate matter, and measures to maintain the airway and ensure adequate oxygenation. Corticosteroids have been used but are no longer considered helpful.[8]

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Constipation

The pattern of normal defaecation is extremely variable, which makes constipation hard to define, and to some extent subjective. However, expert consensus considers that it occurs if 2 or more of the following features are present for at least 12 weeks in the previous year: less than 3 defaecations in a week, or hard or lumpy stool, straining, feeling of incomplete evacuation or anorectal blockage, or need for manual assistance, on at least a quarter of occasions.[1] New onset constipation, especially in patients over 50 years of age, or accompanying symptoms such as anaemia, abdominal pain, weight loss, or overt or occult blood in the stool should provoke urgent investigation because of the risk of malignancy or other serious bowel disorder.[2-5] Constipation can be a symptom of a range of disorders or of drug toxicity[2,5,6] and appropriate management of any underlying cause is required. It tends to be more common in the elderly, in women, and in late pregnancy.[1,2]

Certain subtypes of constipation have been identified: patients may be subdivided according to whether intestinal transit time is slow or normal, or whether there is pelvic floor dysfunction (dyssynergia; outlet obstruction; anismus).[2,3,5,7]

There is relatively little evidence to guide management. In general, stepped or graded management is favoured, beginning with advice on lifestyle (including exercise and adequate hydration), and dietary modification if appropriate.[2,4-6,8] An increase in fibre intake, preferably through a high-fibre diet, is useful in patients with normal transit times although it is less beneficial in slow-transit constipation.[5,7] In patients with pelvic floor dysfunction, biofeedback training may be instituted.[3,5,7]

Where lifestyle changes and dietary modification are insufficient, a laxative may be considered. Because of the lack of clear evidence to guide the choice of laxative, practice varies considerably. Many favour the use of either a bulk laxative or an osmotic laxative as a first choice option,[2-4,7] with stimulant laxatives tending to be reserved as a second-line option, and diphenylmethane derivatives being preferred to anthraquinones.[2,3,6] For the treatment of opioid-induced constipation unresponsive to usual laxative therapy opioid antagonists such as *methylnaltrexone* have been tried.

- *Bulk laxatives* include bran, ispaghula, methylcellulose and related compounds, psyllium, or sterculia. Bulk laxatives are of particular value in those with small hard stools. However, they have a delayed onset of action (up to 72 hours) and they may exacerbate symptoms of flatulence, bloating, and cramping;[6] use should be avoided where these are severe. A gradual increase in dose may help reduce such effects.[7] They may not be the first choice for elderly patients who are frail or immobile since the resulting soft faeces may result in faecal incontinence,[9] and should only be given where fluid intake is adequate, because of the risk of obstruction.[7]

- *Osmotic laxatives* include saline laxatives such as magnesium hydroxide and magnesium sulfate, poorly absorbed sugars such as lactulose or sorbitol, and macrogols (often formulated with electrolytes). Some favour the use of macrogol 3350 or 4000, for which there is reasonable evidence of benefit in chronic constipation,[5,6] although in practice lactulose, which is less effective in the elderly than a combination of bulking and stimulant laxatives (see below), is widely used.[6] In the USA, a saline laxative such as magnesium hydroxide has been recommended,[3,4,7] although saline laxatives may not be acceptable to some patients because they can cause watery stool and urgency.
- *Stimulant laxatives* in current use include diphenylmethane derivatives such as bisacodyl or sodium picosulfate, and anthraquinone-containing drugs such as senna. They have a more rapid onset of action than bulk laxatives or lactulose, and are usually given at night to help produce a bowel motion the following morning. Many traditional stimulant laxatives have fallen from use because of adverse effects, and it has been widely thought that their prolonged use or abuse may irreversibly damage colonic nerves and muscles; however, the evidence for this is poor, and appropriate stimulant laxatives used at licensed doses are unlikely to cause significant harm.[10,11] Tolerance can occur but seems to be uncommon in the majority of users.[10,11] Combined preparations are also available, and a combination of senna and fibre has been found to be more effective than the osmotic laxative lactulose in elderly patients with chronic constipation.[12]
- *Other laxatives* include the docusates, surfactants that are used as stool softeners,[7] but their efficacy used alone for constipation is not well established;[4] perhaps for this reason, they are often formulated with a stimulant or osmotic laxative. Stool softeners would have potential value for patients with haemorrhoids or anal fissures, or those in whom straining is potentially hazardous (such as the elderly or those with existing cardiovascular disease). Liquid paraffin has also been used as a lubricant for the passage of stool,[7] but should be used with caution because of its adverse effects, which include anal seepage and the risks of granulomatous disease of the gastrointestinal tract or of lipoid pneumonia on aspiration. Although it has been recommended in some countries for constipation in children,[13,14] the UK CSM considers it should not be used in those under 3 years of age. Prokinetic drugs have theoretical advantages in patients with slow-transit constipation, but few suitable drugs are available,[5] although selective 5-HT_4 agonists such as tegaserod have been used in constipation-predominant irritable bowel syndrome (p.1699) and in chronic constipation.

Rectal administration of laxatives using enemas or suppositories is appropriate in patients requiring rapid relief from constipation. Phosphate enemas should be used with caution because of the risks of absorption of significant amounts of phosphate.[4] Glycerol and bisacodyl may be given as suppositories to promote faecal evacuation; they should not be used regularly, as changes in the rectal epithelium have been seen with bisacodyl, and the effect of glycerol on rectal mucosa is unclear.[4]

During *pregnancy* the preferred options for management are increased fluid intake, exercise, and dietary fibre;[2] bulking agents may be given as fibre supplements, and stimulant laxatives such as senna reserved for cases where these are ineffective.[2,15]

Faecal impaction is the inability to pass a hard collection of stool, and may result in overflow diarrhoea. Faecal impaction should be treated with a laxative enema and/or a lubricant and manual disimpaction.[4,5,9] Oral laxatives should not be used because of the risk of colonic perforation.[9] When all stool has been cleared, it is important to institute measures, often including regular laxatives, to prevent constipation and recurrent impaction.[5,7,9]

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Decreased gastrointestinal motility

Decreased gastrointestinal motility may occur in any part of the gastrointestinal tract, with symptoms depending on the site. It is of varying aetiology and often secondary to some other disorder, such as infection, metabolic or electrolyte disturbance (for example in gastroparesis due to diabetic neuropathy—see also p.433), or insult to the gastrointestinal tract (for example, paralytic or adynamic ileus is frequently a consequence of abdominal surgery and is a serious adverse effect of some drugs).

Acute loss of gastrointestinal motility is often self-limiting once the underlying cause has been treated. Provided the ability of gastrointestinal smooth muscle to contract has not been lost, however, prokinetic drugs such as metoclopramide or domperidone, or erythromycin, or drugs capable of stimulating functional contraction including parasympathomimetics such as neostigmine or bethanechol, may be used. The opioid μ-receptor antagonist alvimopan has recently been introduced for the treatment of postoperative ileus. Injection of botulinum toxin into the pyloric sphincter may produce temporary symptomatic improvement in patients with refractory gastroparesis. Gastric electrical stimulation may also be an option.

Drugs are less successful in chronic conditions such as chronic intestinal pseudo-obstruction where neuromuscular function of the gastrointestinal tract has some intrinsic abnormality.

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Diarrhoea

Diarrhoea is characterised by liquid stools and increased stool weight and frequency of defaecation. Although diarrhoea is commonly associated with infection (see Gastroenteritis, p.171), it may also result from the accumulation of nonabsorbed osmotically active solutes in the gastrointestinal lumen, as in lactase deficiency, or from the gastrointestinal effects of secretory stimuli other than the enterotoxins from an infection. It may also occur when intestinal motility or morphology is altered.

Acute diarrhoea may lead to excessive water and electrolyte loss and dehydration, and is potentially life-threatening in infants; frail and elderly patients are also at risk. Severe dehydration associated with acute diarrhoea (greater than 10% loss of body-weight), requires *intravenous rehydration therapy* with Ringer's lactate solution or normal saline.[1-4] Intravenous therapy is also needed for patients who are unable to drink. Otherwise, *oral rehydration therapy* to correct fluid and electrolyte depletion should form the basis of treatment for acute diarrhoea[1-5] and an oral rehydration solution containing essential electrolytes (sodium, potassium, chloride, and bicarbonate or citrate) and glucose is indicated regardless of the age of the patient or the cause of the diarrhoea. A rehydration phase, which involves the replenishment of fluid and electrolytes lost through the diarrhoea, is followed by a maintenance phase to replace continuing losses. Oral rehydration therapy does not stop diarrhoea, which usually continues for a limited period, although it can reduce stool output and vomiting. Oral rehydration therapy may need to be modified if the diarrhoea is associated with malnutrition.[6] (Malnourished children may also benefit from zinc supplementation in acute diarrhoea—see p.2000; vitamin A supplementation may also be important in reducing mortality—see p.1973.) The rationale for the composition of oral rehydration solutions is that glucose absorption is coupled to the active transport of electrolytes,[7] the absorption of which theoretically increases in efficiency as the ratio of carbohydrate to sodium approaches 1:1.

WHO originally recommended a solution containing 90 mmol/litre of sodium and 111 mmol/litre of glucose; this type of preparation has been used effectively in developing countries where diarrhoeas are commonly bacterial in origin. There is now evidence from studies and meta-analyses to suggest that solutions of reduced sodium content and osmolarity are safe and effective and may be preferable to the original standard WHO solution, even in developing countries,[8-11] and WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced total osmolarity of 245 mmol/litre.[12] Despite concerns about the possible increased risk of hyponatraemia with the use of the reduced osmolarity solutions in patients with cholera,[13-15] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[12]

In developed countries viral diarrhoeas, which are associated with less electrolyte loss, are more common, and reduced osmolarity solutions are favoured.[2] Commercial preparations available in the UK, for example, usually provide 50 to 60 mmol/litre of sodium and 90 to 111 mmol/litre of glucose; the total osmolarity is slightly hypotonic (about 250 mmol/litre) to prevent possible induction of osmotic diarrhoea.[16] Similar preparations are available in other developed countries.[17]

Areas of debate have included the necessity for inclusion of citrate or bicarbonate,[16] and whether cereal-based rather than glucose-based rehydration solutions would be preferable. There is considerable evidence that cereal-based solutions tend to produce more rapid resolution of diarrhoea, although one study has suggested that the reduction in stool output is temporary,[18] and another found that a glucose-based solution was equally effective when combined with early re-introduction of feeding.[19] In 1994, a review of clinical studies concluded that a rice-based rehydration solution should be recommended for patients with cholera, but that there was no reason to change from WHO's glucose-based formulation for children with non-cholera diarrhoea.[20] A study in 48 patients with cholera compared the use of standard glucose-based oral rehydration therapy, standard therapy plus rice flour, and standard therapy plus amylase-resistant starch.[21] The addition of amylase-resistant starch to standard oral rehydration solution was shown to reduce stool output and to reduce the duration of diarrhoea,[21] although the methodology of this study was questioned[22] and further investigation of such solutions is required.

Home remedies[1] that have been used for oral rehydration include coconut water, rice water, soups, weak tea, and solutions of various salts and sugars; these may be of value when more conventional oral rehydration solutions are unavailable. The use of cordials and soft drinks with low pH and high osmolality, however, may exacerbate diarrhoea and dehydration.[17]

Oral rehydration therapy should be combined with *dietary measures*, particularly in children, to avoid malnutrition owing to low food intake during the illness, and as mentioned above, may need to be modified if the diarrhoea is associated with malnutrition. Breast feeding should be continued throughout rehydration therapy,[2,4,16] as such feeding may decrease stool output and shorten the duration of diarrhoea.[2] Dilution of formula feeds does not seem to be of clinical benefit and may even prolong symptoms.[4,7] Withholding food during diarrhoea in adults or children is not recommended.[1,10]

There is considerable interest in the potential use of probiotic bacteria, or prebiotic foods intended to stimulate the growth of beneficial species in the gastrointestinal tract, in the management of diarrhoea. Although meta-analyses have suggested that treatment with lactic-acid producing organisms may reduce stool frequency and disease duration in children with acute infectious diarrhoea,[23] and may reduce the risk of antibacterial-associated diarrhoea in children,[24] the role of probiotics and prebiotics remains to be established,[4,7] particularly since many commercial products are poorly characterised.

Oral rehydration therapy prevents dehydration, but does not necessarily shorten the duration of the diarrhoea, and patients therefore frequently desire the symptomatic relief provided by *drug therapy.* Use of such therapy should be balanced against the risk that it may distract from the need for oral rehydration therapy and may have undesirable adverse effects. WHO considers that antidiarrhoeal drug therapy is of limited value for acute infectious diarrhoea, does not reduce fluid and electrolyte loss, may delay the expulsion of causative micro-organisms, and should never be used in children.[25] However, it has been pointed out that extrapolating results in children to adult treatment is unwarranted; there is no good evidence that antidiarrhoeal drugs prolong illness or retard expulsion of pathogens, and no reason to withhold medication in otherwise healthy adults.[26] Short courses of antidiarrhoeals are often used in practice (frequently as self medication) if symptoms are causing discomfort.[3,26,27]

The main groups of antidiarrhoeal drugs are adsorbents such as attapulgite, kaolin, and pectin, and drugs that reduce intestinal motility such as diphenoxylate, loperamide, and codeine. Oral loperamide has been recommended as the treatment of choice, particularly for self-medication,[3,26] although bismuth salicylate, which has antisecretory properties, is probably equally effective,[3] and may be preferred in some countries such as the USA.[27] Other drugs with antisecretory properties are under investigation; they include the enkephalinase inhibitor racecadotril, which unlike other antidiarrhoeal drugs is of interest as a potential adjunct in children.[4] Bulk laxatives such as methylcellulose have also been used for symptomatic treatment because of their absorptive capacity.

Antibacterial and antiprotozoal drugs have been used for infective diarrhoeas, including the prophylaxis and treatment of travellers' diarrhoea (see Gastro-enteritis, p.171 and p.824), but their overuse encourages the development of resistance and prophylaxis is not recommended. Vaccines are being developed for the prevention of rotaviral diarrhoeas (p.2236).

Chronic diarrhoea may be associated with underlying disease and therefore symptomatic relief is less appropriate than treatment of the disease itself. For example, colestyramine will reduce the diarrhoea associated with bile acid malabsorption. Where the disease process responsible for chronic diarrhoea cannot be satisfactorily suppressed, however, symptomatic relief may be appropriate,[28] for example in diabetic diarrhoea (see under Diabetic Complications, p.433).

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Diverticular disease

Diverticula are small hernias or pouches of mucosa that develop through the muscular wall of the gut (especially the colon) or other hollow organs; they increase in prevalence with increasing age. Diverticular disease (the presence of colonic diverticula) is usually asymptomatic, but may be associated with symptoms of abdominal pain and altered bowel habit (diverticulosis). Occasionally there may be severe life-threatening complications such as inflammation and necrosis of diverticula (diverticulitis), perforation, fistula formation, obstruction, or haemorrhage. There is some evidence that the use of NSAIDs may be associated with an increase in diverticular complications such as perforation.

In uncomplicated diverticular disease, treatment is with a high-fibre diet, gradually supplemented if necessary with a bulk laxative such as bran or ispaghula, to ease constipation, although the evidence to support such management is limited. Supplements may not relieve the other symptoms of diverticular disease. The antibacterial rifaximin may be of benefit in improving symptoms; giving rifaximin and fibre supplementation has been shown to be more effective than fibre supplementation alone. Rifaximin has also been combined with 5-aminosalicylates, chiefly mesalazine; the latter may be of benefit in maintaining remission. Use of probiotics, in the form of lactic-acid-producing organisms, after a non-absorbed antibacterial such as rifaximin has also produced some evidence of additional benefit. Antispasmodics such as antimuscarinics or mebeverine may be useful in relieving pain due to muscle spasm.

Diverticulitis requires treatment with broad-spectrum antibacterials and fluid support; analgesia may be needed for severe pain. If peritonitis or abscess develops, surgical intervention may be necessary. Surgical resection is usually considered when fistula, perforation, or obstruction are present.

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Dumping syndrome

The word dumping in this context is used to describe the unnaturally rapid transport of gastric contents to the small intestine. The dumping syndrome is an important cause of morbidity after gastrointestinal surgery, and is thought to be due to the destruction of normal regulatory mechanisms in the upper gastrointestinal tract.[1,2] Early dumping begins within 10 to 30 minutes of the ingestion of a meal (typically, symptoms are triggered by hyperosmolar, carbohydrate-rich food) and has gastrointestinal symptoms (fullness, abdominal pain, nausea and vomiting, explosive diarrhoea) and vasomotor symptoms (sweating, weakness, dizziness, flushing, and palpitations). The effects are thought to be due to fluid shifts from the intravascular space to the bowel lumen. Some patients have late dumping, 1 to 4 hours after a meal, with only the vasomotor symptoms; it appears to be due to reactive hypoglycaemia caused by high carbohydrate concentrations in the small intestine.

The mainstays of therapy are dietary modifications, taking small frequent meals low in carbohydrate, followed by liquids 30 minutes later. Attempts to slow or reduce carbohydrate absorption have involved the use of dietary fibre (guar gum or pectin) or α-glucosidase inhibitors such as acarbose; acarbose and pectin have also been tried in combination.[3] However, such agents may themselves cause gastrointestinal disturbances and they do not seem to be helpful in most patients.[2] More recently, beneficial results with somatostatin have led to the use of its longer-acting analogue, octreotide.[2,4] Octreotide substantially reduces the symptoms of both early and late dumping, probably by slowing gastric emptying and by inhibiting the release of gastrointestinal mediators (peptide hormones such as neurotensin), and prevents hyperinsulinaemia and subsequent reactive hypoglycaemia. It may be given up to 2 hours before a meal.

In the minority of patients who do not respond to medical therapy surgery may be required.[1,2]

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Dyspepsia

Dyspepsia, also commonly known as indigestion or heartburn, is a frequent but ill-defined disorder primarily associated with epigastric discomfort or pain. It may be a symptom of specific diseases such as peptic ulcer disease, gastro-oesophageal reflux disease, gastric carcinoma, chronic pancreatitis, or gallstones. However, in many patients there is no identifiable systemic disease, in which case it is known as non-ulcer dyspepsia or functional dyspepsia.

A number of reviews and recommendations have addressed the subject of dyspepsia,[1-7] and, in the UK, various authoritative guidelines have been issued.[8,9] The initial management of non-ulcer dyspepsia usually includes advice to avoid alcohol, caffeine, smoking, and aggravating foods, and to eat small regular meals to aid digestion. Results of studies of drugs for non-ulcer dyspepsia have been variable and difficult to evaluate since the condition tends to be self-limiting, and there is often a large placebo response.[10]

Drugs that suppress gastric acid such as antacids or antisecretory drugs are often used. Antacids may give some symptomatic relief, and are widely used for self-medication.[9] However, long-term use is inappropriate. Similarly, H_2-antagonists are often tried, especially for symptoms of reflux, and a systematic review[10] has suggested benefit, at least in a proportion of patients. Proton pump inhibitors (PPIs) are also widely used; although a systematic review considered their relative efficacy in non-ulcer dyspepsia versus H_2-antagonists to be unclear,[11] others[5-7] consider them superior to H_2-antagonists. They may be useful for on-demand therapy to manage symptoms long-term.[9]

It is not clear what role *Helicobacter pylori* plays in the pathology of non-ulcer dyspepsia. One meta-analysis found eradication to be of no benefit in non-ulcer dyspepsia,[12] but another, incorporating more patients, found that a small benefit existed,[13] although it noted that most patients positive for *H. pylori* will continue to have symptoms after eradication. As a result there has been much debate about the appropriateness of so-called 'test and treat' strategies, but UK[9] and US[4,5] guidelines consider them a valid alternative to a trial of a PPI in the initial management of uninvestigated dyspepsia.

Initial management of dyspepsia in patients under 55 years of age who do not have so-called 'alarm symptoms' (such as chronic gastrointestinal bleeding, unintentional weight loss, difficulty swallowing, persistent vomiting, iron deficiency anaemia, or epigastric mass) should therefore consist of either:[4,9]

- an empirical one-month course of a PPI, *or*
- testing for *Helicobacter pylori* and appropriate eradication therapy. Those who are *H. pylori*-negative should be prescribed an empirical trial of acid suppression with a PPI for 1 to 2 months

Patients over 55 years of age, or those with alarm symptoms, should be referred for endoscopy. After endoscopy, treatment should be targeted at the underlying diagnosis.[4]

Prokinetic drugs may be given, particularly if an underlying gastrointestinal motility disorder is suspected. Meta-analysis has suggested that prokinetic therapy may be more effective than an H_2-antagonist in non-ulcer dyspepsia,[10,14] but this may be due to publication bias.[10] In addition, cisapride is no longer available in many countries and evidence for domperidone or metoclopramide is limited. Results with motilin agonists (derivatives of erythromycin) and 5-HT_3 antagonists have been disappointing to date.[3] Other approaches to drug therapy include the use of an insoluble bismuth salt, and the use of antispasmodics. Antidepressants may have a limited role in some patients,[5,7] and various herbal medications have been tried, though the quality of any studies is generally poor.[7]

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Gastrointestinal spasm

Pain or discomfort of the gastrointestinal tract may be due to spasm of the smooth muscle of the gut; such pain and spasm may be associated with the irritable bowel syndrome (see below), dyspepsia (see above), or diverticular disease (see above). Antispasmodic drugs have traditionally been used in patients thought to have gastrointestinal spasm, and have mainly been of two types: antimuscarinics such as dicycloverine, and direct smooth muscle relaxants such as mebeverine; use of antimuscarinics, in particular, has tended to be limited by concern about their adverse effects.

Colic is a general term used to describe spasmodic or griping pain, usually of the viscera, and when not otherwise qualified is often understood to refer to pain in the gastrointestinal tract. Infant colic is common in the first few months of childhood,[1] and tends to be managed by non-pharmacological measures and assessment of the feeding technique. Elimination of cows' milk protein appears to be of benefit, but use of a low-lactose formula is not.[1] Tilactase has been added to feeds to aid lactose digestion but the extent of any benefit is unclear. Traditional remedies such as gripe water, which contains essential oils of dill or fennel and is mildly carminative, are of dubious efficacy. Antimuscarinic antispasmodics, although effective[1] may be associated with adverse effects, and are no longer considered appropriate.[2] Simeticone suspension, given before feeds, is commonly used but has been found to be no better than placebo.[2,3] It has been reported that sucrose, given as a 12% solution, improves infant colic.[4]

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Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease results from the reflux of gastric or duodenal contents into the oesophagus. Symptoms include heartburn, acid regurgitation, and dysphagia (difficulty in swallowing); oesophageal inflammation and ulceration (reflux oesophagitis), and stricture formation may occur. Extra-oesophageal symptoms may include cough, horseness, and asthma. Some patients develop Barrett's oesophagus (below), which is a risk factor for oesophageal cancer (p.664).

Lifestyle advice on weight loss, raising the head of the bed, stopping smoking, and avoidance of alcohol and aggravating foods such as chocolate and coffee is often given as part of initial **management**,[1-5] although the evidence for most of these interventions other than weight loss and bed position is lacking.[3]

Patients often manage initial mild symptoms with over-the-counter therapies, including *antacids* and antisecretory drugs. Although the placebo response is often high, meta-analysis has shown some additional symptomatic benefit from antacids, *histamine H_2-antagonists*, and in particular for combinations of an antacid with an alginate;[6] such combinations are believed to form an alkaline 'raft' above the stomach contents that impedes reflux and protects the oesophageal mucosa.

The symptoms and management of gastro-oesophageal reflux disease may overlap with those of dyspepsia (see above), and initial symptomatic management is likely to be similar.[4] Patients who do not have alarm symptoms that would indicate a need for prompt endoscopy should be treated with an appropriate dose of a *proton pump inhibitor* (PPI) for 1 to 2 months.[4,5] Such treatment is more effective for empirical management than an H_2-antagonist,[7] and is appropriate therapy for endoscopy-negative disease[7] as well as for patients with reflux oesophagitis.[8] There is no evidence for the superiority of any particular PPI, nor for greater benefit from doubling doses in patients with reflux oesophagitis.[7]

A significant minority of patients do not, however, respond to PPIs; reasons may include poor compliance, nocturnal acid breakthrough, non-acid reflux, and hypersensitivity to acid.[4,5] Trying an alternative PPI or increasing the dose has been suggested[4] (despite the lack of evidence to support this[7]). However, in refractory cases, giving a proton pump inhibitor with an H_2-antagonist may be more effective than just increasing the dose of the former.[4,9]

Alternatively, a *prokinetic drug* such as metoclopramide may improve gastro-oesophageal sphincter function and accelerate gastric emptying. These appear to be as effective as H_2-antagonists,[1] although they are probably less effective than PPIs.[7] An H_2-antagonist used with cisapride may be more effective than either drug alone.[1] However, concern over the risk of cardiotoxicity and potential for serious interactions with cisapride has led to severe restrictions on its use.

In patients with mild disease, a trial of withdrawal of drug therapy is appropriate after successful initial treatment.[1] Short courses of therapy as and when symptoms demand (intermittent treatment) may be effective in uncomplicated disease.[10] However, most patients with oesophagitis relapse when treatment is withdrawn, and long-term **maintenance** therapy is likely to be required.[1,4,5] As in acute management, PPIs appear to be the most effective maintenance treatment, although the 'step-down' approach of reduced maintenance doses, which is widely favoured,[4,5] may produce less benefit than continuing to give full dose PPIs.[11] H_2 antagonists were found to be of marginal benefit for maintenance, although they did give some symptomatic relief, and although prokinetic drugs (cisapride) and sucralfate were also reported to be more effective than placebo their value was considered dubious.[11] Another approach is to use a combination for maintenance, and in one study omeprazole with cisapride provided more effective maintenance than ranitidine or cisapride alone or in combination.[12] Again, however, cisapride is now unlikely to be used in practice because of the risks.

Helicobacter pylori **eradication** does not heal or prevent relapse of gastro-oesophageal reflux disease,[1] and some epidemiological evidence has appeared to suggest that *H. pylori* infection protects against gastro-oesophageal reflux disease.[13] However, there is no clinical evidence that eradication of *H. pylori* exacerbates gastro-oesophageal reflux disease or significantly increases the risk of its development.[14,15]

In patients who have a poor response to drug therapy, or in those with complications such as oesophageal stricture or ulceration, **surgery** to re-establish gastro-oesophageal competence may be considered.[1,4,5] Submucosal implants and various other endoscopic techniques have also been investigated.[4] Although surgery is as effective as drug treatment, it carries greater associated risks, and many patients continue to require antisecretory drugs.[4]

Investigational approaches to drug therapy include the development of drugs with GABAergic actions similar to those of baclofen (but without its CNS effects), cholecystokinin antagonists such as loxiglumide, and cannabinoid CB_1 agonists; motilin receptor agonists such as alemcinal and mitemcinal do not appear to be of much benefit.[16]

A minority of patients with gastro-oesophageal reflux disease develop **Barrett's oesophagus** (columnar lined oesophagus, CLO), in which the normal oesophageal squamous lining is replaced with a metaplastic columnar epithelium. This is most common in patients with long-standing disease but may represent part of a spectrum of possible responses to acid reflux rather than a progression from less severe to more severe disease.[4] The abnormal epithelium in Barrett's oesophagus shows dysplastic changes that may progress to oesophageal adenocarcinoma. However, not all patients go on to develop cancer, and many aspects of management are controversial.

Management of acid reflux, as for other forms of gastro-oesophageal reflux disease, is the mainstay of management.[17-20] Long-term treatment with PPIs appears to be effective;[19] the use of maximal doses, perhaps in combination with an H_2-antagonist at night, is advocated by some[20] but evidence to support twice daily (double) dosing is lacking.[19] As the altered epithelium is relatively less sensitive to acid, symptom control does not necessarily equate to suppression of reflux.[20] There is a lack of good evidence that control of acid reflux produces anything other than limited regression of the abnormal epithelium, or alters the risk of progression to malignancy,[19,20] although there are some results that suggest benefit.[21,22] Some evidence suggests that additional chemoprevention with aspirin or another NSAID might offer benefits in reducing cancer risk,[19,23] but this remains investigational. The roles of screening, surveillance, and endoscopic ablation therapy or photodynamic therapy (5-aminolaevulinic acid or porfimer) remain matters of debate.[17,19,20]

In **infants**, gastro-oesophageal reflux is common but usually resolves spontaneously with increasing age and requires no treatment. Occasionally, it may be associated with complications such as failure to thrive, oesophagitis, and pulmonary symptoms of acid regurgitation, but can be managed by upright positioning and the use of thickened foods; drug therapy is controversial,[24] and the evidence base is poor.[25] It has been suggested that where drug therapy is needed, an alginate-antacid combination may be appropriate initially;[24] PPIs are probably safe but are not well studied in infants.[25] Cisapride has been given[24,25] but the risk of cardiotoxicity makes the use of cisapride in infants extremely problematic (see p.1720). Metoclopramide may have some benefit but again this must be weighed against the risk of adverse effects.[26] Evidence of benefit with domperidone is poor,[27] and it too has the potential for serious adverse effects, but restrictions on cisapride have led to its over-use.[25] Erythromycin has been investigated in infants with food intolerance, though not in gastro-oesophageal reflux itself; there is a risk of promoting bacterial resistance from such use.[25]

Gastro-oesophageal reflux is commonly encountered during normal **pregnancy**, and is generally managed by lifestyle and dietary modifications.[28] If drug therapy is required, nonsystemically absorbed antacids or sucralfate should be tried first. If these are ineffective, ranitidine may be tried. Proton pump inhibitors are reserved for women with severe or complicated reflux disease,[28] due to concerns about their safety in pregnancy, although the relative risk associated with exposure seems to be quite low (see under Precautions of Omeprazole, p.1755).

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Haemorrhoids

Haemorrhoids ('piles') are venous swellings of the tissues around the anus: those above the dentate line (the point where the modified skin of the outer anal canal becomes gut epithelium), which usually protrude into the anal canal, are termed internal haemorrhoids, while those below this point are called external haemorrhoids. Due to internal pressure, internal haemorrhoids tend to congest, bleed, and eventually prolapse; with external haemorrhoids painful thrombosis may develop.[1-3]

Initial treatment of internal haemorrhoids involves a high-fibre diet and avoidance of straining at stool, so bulk laxatives and faecal softeners may be indicated.[2] The prime objective of drug therapy is to control the acute bleeding phase so that definitive therapy can be scheduled.[1] Small bleeding haemorrhoids may be injected with a sclerosing agent such as oily phenol injection, but rubber band ligation, or perhaps a technique such as infra-red coagulation, is more effective and associated with fewer complications.[3-5] More severe and prolonged prolapse generally requires surgery.[2,3,6] Surgical excision to remove the clot is used for thrombosed external haemorrhoids.[7]

An enormous range of mainly topical drug treatments is available for symptomatic relief, but in many cases their value is at best unproven.

Topical preparations are usually made up in a lubricating or emollient base. Local anaesthetics may be included to relieve pain, and corticosteroids may be used where infection is not present: preparations containing either group of drugs are intended only for short-term use. Inclusion of antibacterials is thought to be of little value and may encourage the development of resistant organisms. Some preparations include heparinoids. Other agents frequently included for their soothing properties include various bismuth salts, zinc oxide, hamamelis, resorcinol, and peru balsam.[2,3] Topical nitrates have also been used.[1]

Bioflavonoids and various derivatives of aesculus may also be included in topical preparations; they have also been given systemically in some countries as have some other compounds such as calcium dobesilate and tribenoside, presumably for their supposed action on venous capillary walls. Oral micronised bioflavonoid preparations may reduce symptoms as an adjunct to surgery.[1,6,8]

Other agents that have been used in the treatment of haemorrhoids include pilewort (ficaria) and combinations of yeast extract with shark-liver oil.

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Hepatic encephalopathy

Hepatic encephalopathy (portal systemic encephalopathy) is a metabolically related dysfunction of the brain associated with abnormalities of liver function. It may be acute, as in patients with fulminant hepatic failure, or chronic, with acute episodes precipitated by some triggering factor, as in patients with cirrhosis or other chronic liver disease.

Treatment is aimed at identifying and correcting any precipitating factor, decreasing the production and absorption of ammonia in the gut, and increasing metabolism of ammonia in the tissues. Precipitating factors include infection, increased protein load due to gastrointestinal haemorrhage or high protein intake, alcohol abuse, electrolyte imbalance, and certain drugs (notably anxiolytics, hypnotics, and diuretics).

Restriction of dietary protein intake is a mainstay of short-term treatment, but in the long-term, care must be taken to provide adequate protein to avoid malnutrition. A daily protein intake of 0.5 to 1.5 g/kg has been recommended.[1-3] There is some evidence that vegetable protein is better tolerated than animal protein.[4,5] Giving branched-chain amino acids (valine, isoleucine, and leucine) by infusion or as dietary supplements may facilitate adequate protein intake in some patients.[1,3-5] Supplementation with ornithine aspartate has been used to increase metabolic conversion of ammonia to urea and glutamine.[2,4,5] Sodium benzoate has also been tried.[4,5]

Active drug treatment may begin with bowel cleansing by means of a magnesium sulfate enema, especially if the patient is constipated. Lactulose is then the treatment of choice in many cases, particularly in the elderly, the constipated, and those with renal impairment. It is usually given orally although it may be used rectally[2,5] or by nasogastric tube[2] when oral use is not feasible.[5] It reduces colonic pH and absorption of ammonia and aromatic amino acids. The lactulose analogue lactitol is also used.[6] However, a recent meta-analysis[7] was unable to find sufficient evidence to support or refute the use of nonabsorbable disaccharides, such as lactulose and lactitol, for hepatic encephalopathy. The disaccharidase inhibitor voglibose has been tried to reduce intestinal uptake of disaccharides and promote fermentation, with effects similar to lactulose.[5]

Alternatively, locally active antibacterials have been given to reduce the urease-producing bacteria.[2] Neomycin is the traditional drug but adverse effects such as ototoxicity and nephrotoxicity may be a problem, particularly if used long-term. Metronidazole is also used,[4] and rifaximin has been tried. A combination of lactulose and neomycin[4] or metronidazole has been tried in patients who fail to respond to single-drug therapy.

In low grade chronic recurrent encephalopathy *Lactobacillus acidophilus* or *Enterococcus faecium* SF68 have been tried orally in an attempt to produce a more favourable bowel flora. Results have been inconsistent.[5,8] *Helicobacter pylori* is a urease-producing organism, but the relevance of *H. pylori* infection to hepatic encephalopathy is unclear.[9]

Investigational therapy has also attempted to affect cerebral function directly. Flumazenil, a benzodiazepine antagonist, has been tried, on the basis of the suspected role of endogenous benzodiazepine-like agonists.[2,10] A systematic review[11] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended. Similarly, although dopaminergics such as levodopa or bromocriptine have been given, on the grounds that impaired dopaminergic neurotransmission may play a role in the syndrome,[2] evidence to support their use was not forthcoming from a systematic review.[12]

Liver transplantation (p.1815) is the ultimate therapy for end-stage cirrhosis, acute liver failure, or patients with severe refractory hepatic encephalopathy.[4]

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Inflammatory bowel disease

Inflammatory bowel disease (IBD) covers chronic non-specific inflammatory conditions of the gastrointestinal tract, of which the two major forms are *Crohn's disease* and *ulcerative colitis*.

Crohn's disease is characterised by thickened areas of the gastrointestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas; affected areas may occur in any part of the gastrointestinal tract, interspersed with areas of relatively normal tissue; the terminal ileum is frequently involved. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss, and rectal bleeding. Extra-intestinal manifestations may include joint inflammation, skin lesions, mouth ulcers, and liver disorders.

In **ulcerative colitis**, disease is confined to the colon and rectum, inflammation is superficial but continuous over the affected area, and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis); in severe disease, ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication. Symptoms include diarrhoea and rectal bleeding. The extra-intestinal manifestations are similar to those of Crohn's disease.

Drug treatments.

Although there are important differences between Crohn's disease and ulcerative colitis which affect their management, the broad principles of treatment, and the drugs used, are similar.[1-6] The aminosalicylate derivatives are generally the first choice in mild to moderate active disease, and are of particular value for maintenance treatment of ulcerative colitis; the role of maintenance treatment in Crohn's disease is less well established. Corticosteroids are also used in the initial treatment of active disease, dosage and route varying with disease site and severity. Immunosuppressant or biological therapy may be helpful in severe or chronic active disease. For Crohn's disease an elemental diet (see p.1923) may have some value in active disease, but diet plays a lesser role in ulcerative colitis.

- Oral sulfasalazine, a **5-aminosalicylate** derivative (5-aminosalicylic acid linked to sulfapyridine), is of value in producing remission of mild ulcerative colitis;[7] results in Crohn's disease have been more equivocal.[5,8]

  The discovery that 5-aminosalicylate was the active component of sulfasalazine led to the development of numerous derivatives, including mesalazine (5-aminosalicylic acid itself, either used rectally, or orally in slow-release or enteric-coated form), olsalazine (2 molecules of 5-aminosalicylic acid joined by an azo bond), and a variety of forms, such as balsalazide, in which the active moiety was joined to inert carriers. All the above have been shown to be effective in active ulcerative colitis, and may be better tolerated than sulfasalazine, since many of the latter's adverse effects are due to its sulfonamide portion. In patients who can tolerate sulfasalazine, the newer drugs have no clinical advantage for remission induction.[7] Nevertheless, the risk of adverse effects on starting sulfasalazine therapy has led to increasing use of the newer derivatives. The 5-aminosalicylates are also recommended for the maintenance of remission in ulcerative colitis;[3,4,9] in contrast, although they are often used in practice it is unclear that they are of value for maintenance in patients with Crohn's disease.[3,5,6,10]
- The other major group of drugs used in the treatment of IBD is the **corticosteroids**, particularly for more severe ulcerative colitis, and in Crohn's disease. Rectal use may be appropriate in some patients with distal ulcerative colitis or proctitis; oral prednisone or prednisolone is often used in more severe and extensive disease, and in the most severe cases intravenous corticosteroids (usually hydrocortisone or methylprednisolone) may be given. Unfortunately, treatment of IBD is often prolonged, and adverse effects remain a problem, hence the interest in poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol. Oral budesonide is more effective than mesalazine in inducing remission in Crohn's disease and although it may be slightly less effective than conventional corticosteroids, adverse effects are reduced.[11] Corticosteroids are not suitable for maintenance of remission in IBD,[3,12] and inability to withdraw corticosteroid treatment without precipitating relapse (corticosteroid dependence) is a therapeutic challenge.
- Other drugs used in active IBD include **immunosuppressants**. The majority of studies have been with azathioprine, or its metabolite mercaptopurine. Because they have a slow onset of action (months) their use in acute disease is limited, but they are of benefit in remission induction in patients with chronically active disease, particularly corticosteroid-resistant or corticosteroid-dependent disease; they may also be used for maintenance in both ulcerative colitis and Crohn's disease, often in combination with other drugs.[3-6,13] Low-dose intramuscular methotrexate also appears to be useful in active Crohn's disease (although evidence for the oral route is lacking),[14] but does not appear to be of value in ulcerative colitis.[4,6] Conversely, ciclosporin has not generally proved useful in chronically active inflammatory bowel disease but may have some value in the short-term treatment of acute severe ulcerative colitis.[6,15] Tacrolimus also appears to be of benefit in severe ulcerative colitis,[6] and possibly in Crohn's disease;[16] mycophenolate mofetil has been tried, although the limited evidence is equivocal.[16]
- Of increasing importance in the management of severe or refractory forms of IBD are the so-called '**biological therapies**', comprising in particular anti-tumour-necrosis factor antibodies such as infliximab, adalimumab, and certolizumab pegol. These have been shown to be effective for induction therapy and maintenance in both ulcerative colitis and Crohn's disease.[6,17] The anti-integrin antibody natalizumab is effective in inducing remission in Crohn's disease.[18] Thalidomide, a tumour necrosis factor inhibitor, has also been tried in Crohn's disease with some benefit,[16,19] but another such inhibitor, pentoxifylline, was ineffective.[20]
- **Metronidazole** is useful in fistulising perineal Crohn's disease and may be used in colonic Crohn's disease. It is usually given for 3 months. Ciprofloxacin is an alternative, and has also been given with metronidazole,[21,22] although the combination may not be very well tolerated. There has been interest in the possible causal role of *Mycobacterium paratuberculosis* in Crohn's disease,[23] but a study of 2 years of antituberculous therapy with clarithromycin, rifabutin, and clofazimine in patients with Crohn's disease found no evidence of sustained benefit, suggesting that the organism probably did not play a significant role.[24] Antibacterials do not have a role in ulcerative colitis, except for infection prophylaxis in severe attacks.
- Many **other drugs** are being or have been tried in IBD, including immunoglobulins, some interleukins, interferons, ICAM-antisense oligonucleotides such as alicaforsen, the anti-CD3 antibody visilizumab, short-chain fatty acids, heparin, factor XIII, rosiglitazone, and aminosalicylic acid (4-aminosalicylic acid as opposed to 5-aminosalicylic acid). There have been some short-term responses to the anti-integrin antibody, MLN-02,[25] and to the anti-interleukin-12 antibody, ABT-874.[26] There is limited evidence of improvement in disease severity from the use of the granulocyte-macrophage colony-stimulating factor sargramostim,[27] which is thought able to stimulate intestinal innate immune defence processes that may be impaired in Crohn's disease. Nicotine has been tried in ulcerative colitis, based on the observation that the disease is rare in smokers. Studies have suggested that nicotine, supplied via transdermal patch, may have benefit in active disease,[28] although it is ineffective for maintenance.[29] Rectal and oral formulations of nicotine are under investigation.

Nutritional and dietary therapies.

Correction of nutritional deficiencies may be necessary in severe IBD, but dietary modification may also have therapeutic effects. In Crohn's disease, enteral feeding, often with an elemental diet is effective in inducing remission (p.1923), although corticosteroids are more effective;[30] there is also some evidence of benefit in maintaining remission.[31] Elemental diets are useful in children and those unable to tolerate corticosteroids. The role of omega-3 fatty acids has been investigated: when given orally as enteric-coated formulations, they appear to be of benefit in maintaining remission in Crohn's disease.[32] In contrast, failure to find evidence of benefit in maintaining remission in ulcerative colitis[33] may have been due to the failure to use such formulations.

There has been some interest in manipulation of the bowel flora through use of lactobacilli and other probiotic bacteria. There have been some reports of benefit in ulcerative colitis,[34,35] and probiotics may be useful in the management of pouchitis,[3,4] but there is no good evidence to date of benefit in Crohn's disease.[36] The observation that inflammatory bowel disease is uncommon in developing countries where most people carry helminths has led to preliminary studies of bowel colonisation using *Trichuris suis* ova (porcine whipworm) in active Crohn's disease[37] and ulcerative colitis.[38]

Surgery.

In patients with ulcerative colitis surgical colectomy is curative, and may avoid the risks of long-term corticosteroid therapy and the increased risk of bowel cancer to which patients with inflammatory bowel disease are subject. Formation of an ileoanal pouch, which acts as a reservoir for the ileal contents, avoids the necessity for a standard ileostomy and maintains a degree of continence in suitable patients. Curative surgery is not possible in Crohn's disease, since recurrence elsewhere in the gut is almost inevitable, but resection of the affected area becomes necessary in many patients during the course of their illness.

CHOICE OF THERAPY

Ulcerative colitis.

- ACTIVE DISEASE:
  - ***mild to moderate***

    In mild to moderate *distal* disease topical mesalazine, preferably in combination with an oral aminosalicylate (mesalazine, balsalazide, or olsalazine), is the treatment of choice.[3,4] Selected patients may benefit from oral sulfasalazine. Patients intolerant of topical mesalazine may be given a topical corticosteroid instead, though they are less effective.[39] Suppositories are suitable for *proctitis* but foam or liquid enemas are required for more proximal disease (*proctocolitis*).[3] Patients who fail to improve on a combination of oral aminosalicylate with topical mesalazine or corticosteroid may require an oral corticosteroid (e.g. prednisone or prednisolone 40 mg daily).[3,4,6]

    In *left-sided* or more *extensive* ulcerative colitis the preferred therapy is an oral aminosalicylate;[3,4,6] olsalazine is best avoided in patients with *pancolitis* as it may be more likely to produce diarrhoea than mesalazine or balsalazide.[3] There is some evidence that the benefits of aminosalicylates are dose related,[4,6] and some controversy exists as to the optimum induction dose: use of higher doses initially may produce better responses,[4,6] but there is an increased risk of toxicity. Topical therapy is unlikely to be of benefit alone, but may be added for the relief of rectal symptoms.[3,6]

    Patients who fail to respond to oral aminosalicylates should be given an oral corticosteroid (as above). The corticosteroid should be reduced gradually (tapered) over several weeks once response is achieved.[3,4] Since long-term treatment with corticosteroids is undesirable, patients with *chronic active disease* who are at high risk of relapse when the corticosteroid is withdrawn (corticosteroid-dependent disease) should be treated with a thiopurine (azathioprine or mercaptopurine) as a corticosteroid sparing drug.[3,4] Thiopurines may also be effective in inducing remission in some patients who do not respond to oral corticosteroids, although their slow onset of action is problematic.[4] In patients with more extensive, moderate to severe disease, infliximab may be an option.[6]
  - ***severe***

    Patients who present with severe colitis or who fail to respond to maximal oral treatment should be admitted to hospital for treatment with intravenous corticosteroids.[3,4,6] Patients should be given appropriate supportive therapy (including nutritional support if the patient is malnourished, intravenous antibacterials for infection, and blood transfusion if markedly anaemic).[3,4] Those who fail to respond to intravenous corticosteroids within a few days should be considered for second-line treatment with ciclosporin,[3,4,6] or possibly infliximab or tacrolimus.[6] Patients who respond to intravenous ciclosporin may be given oral continuation treatment for 3 to 6 months.[3] Drug therapy is ineffective in up to 40% of patients with severe colitis,[4] and colectomy is an alternative.[3,4]
- MAINTENANCE:

  Lifelong maintenance therapy is generally recommended for patients with ulcerative colitis once remission is achieved, particularly in those with left-sided or more extensive disease, or those with distal disease who relapse more than once a year.[3,4] The treatment of choice is an oral aminosalicylate,[3,4,6] most often mesalazine,[6] although in those that can tolerate it sulfasalazine is possibly more effective.[9] Topical mesalazine has been used for maintenance in patients with distal disease,[3,6] but patients are less likely to be compliant.[3] Corticosteroids are ineffective in maintaining remission and associated with severe adverse effects on prolonged use. Azathioprine may be used for maintenance therapy, but is best reserved for patients who relapse frequently despite aminosalicylate maintenance, or who are unable to tolerate such therapy.[3] Patients with gastrointestinal intolerance of azathioprine may be tried cautiously with mercaptopurine; alternatively, surgery may be considered.[3] Infliximab is also effective for maintenance of remission, especially in patients who remain corticosteroid dependent despite alternative therapies.[6]

- POUCHITIS.

  Ileoanal pouch anastomosis allows for surgical removal of the colon without loss of continence or the need for an ostomy, but subsequent inflammation of the pouch (pouchitis) occurs in about half of all patients.[4] On the basis of limited evidence it is considered to be best treated by a short course of antibacterials (metronidazole or ciprofloxacin).[3,4] If these are ineffective, mesalazine or corticosteroids may be considered.[3] Use of a probiotic formulation, VSL-3, containing a mixture of bacteria, may also be of benefit.[3,4]

Crohn's disease.

- ACTIVE DISEASE:
  - ***mild to moderate***

    First-line therapy in mild to moderate Crohn's disease is a matter of some debate. Oral mesalazine is of limited benefit in *ileal* or *ileocaecal* disease,[5,6] and some consider that it should not be used at all,[6] although others recommend high doses as an appropriate initial therapy.[3] Aminosalicylates may be of more benefit in *colonic* disease, particularly sulfasalazine if it can be tolerated.[3,5,6] Others favour the use of oral budesonide as first-line therapy for mild to moderate ileocaecal disease;[5,6] although it is somewhat less effective than conventional oral corticosteroids, which are an option in more active disease,[3,5] it produces fewer adverse effects. Opinion also varies on the use of topical mesalazine in colonic disease,[3,5] although it is widely used.[5] Nutritional support (enteral feeding or the use of elemental diets) may be considered as an alternative to drug therapy or surgery in selected patients.[3]
  - ***moderate to severe***

    In outpatients with moderate to severe disease, and those who fail to respond to initial therapy with budesonide or aminosalicylates, conventional oral corticosteroids, typically in a dose corresponding to 40 mg of prednisolone daily (or up to 1 mg/kg daily), are recommended.[3,5,6] Once response has been achieved, dosage should be gradually tapered off.[3,5] In patients who have relapsed, azathioprine or mercaptopurine may be added,[5] but they are not best suited to induction of remission because of the delay in onset.[6] Methotrexate may be an alternative in selected patients.[5]

    In patients with severe extensive or *fulminant* disease intravenous corticosteroids should be given.[3,5,6] Adding intravenous metronidazole may be advisable, because of the difficulty of distinguishing active disease from a septic complication.[3] Infliximab should be considered in patients with disease *refractory* to corticosteroids;[3,5,6] adalimumab or certolizumab pegol may be alternatives.[6]
  - ***fistulising disease***

    Simple perianal fistulae can be treated with metronidazole or ciprofloxacin.[3,6] Azathioprine or mercaptopurine are also potentially effective,[3] while infliximab is recommended in patients who do not respond to other treatment.[3,6] An alternative to infliximab is adalimumab.[6] Surgery is appropriate for complex or persistent fistulae.[3,6]
  - ***chronic active and corticosteroid dependent disease***

    Azathioprine or mercaptopurine are the drugs of choice in corticosteroid dependent disease.[3] If they are ineffective or not tolerated, intramuscular methotrexate may be considered;[5] it is also considered appropriate for the management of chronic active disease.[3] Infliximab is generally reserved for patients who fail first-line therapy, as an alternative to surgical resection.[3]
- MAINTENANCE:

  The most important intervention in maintaining remission in patients with Crohn's disease is probably to persuade those who smoke to stop smoking.[3] Mesalazine appears to be of limited benefit at best for the maintenance of remission,[3,5,10,40] although it is widely used,[6] and the other aminosalicylates are considered inappropriate.[3,5] Corticosteroids are also not effective for maintenance,[3,5,12] although budesonide may delay relapse for a limited period.[5,6] In patients who required corticosteroids to achieve remission, the usual drug treatment for maintenance is a thiopurine (azathioprine or mercaptopurine).[3,5,6] In patients who achieved remission with intramuscular methotrexate, it may be continued for maintenance;[3] it is also an option in patients intolerant of thiopurines.[5] Thiopurine maintenance may need to be continued for several years,[5] or even indefinitely.[6] Infliximab is also an option for maintenance, particularly in patients brought to remission with the same drug,[3,5] or those who cannot maintain remission or who remain corticosteroid dependent despite the use of maintenance immunosuppression.[6] Alternatives may be adalimumab or certolizumab pegol.[6] The use of omega-3 fatty acids (fish oils) has been investigated for maintenance of remission in Crohn's disease, with some apparent benefit.[32]

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Irritable bowel syndrome

Irritable bowel syndrome is a functional gastrointestinal disorder of abdominal pain and altered bowel habit; pain is characteristically relieved by defaecation and may be associated with increase or decrease in stool frequency. There may be abdominal bloating. Women are more often affected than men. Most patients have symptoms intermittently, with flares lasting several days followed by periods of remission.[1] Patients may be classified as having different subtypes of the syndrome, depending on the nature of the main symptoms.

Given the heterogeneity of the condition, only a minority of patients will respond to any given treatment, and this together with a high placebo response rate limits the evidence base for treatment.[1-3] The mainstay of treatment is explanation and reassurance, coupled with sensible advice about lifestyle.[1,4] Dietary modification should involve increasing the amount of vegetable fibre in the diet initially (but see below); some patients respond to exclusion of particular foods but this is probably best reserved for more refractory cases, and should not be allowed to compromise proper nutrition.[1]

Formal psychological therapies may be appropriate in some patients, especially if they have other psychological problems such as marked anxiety or depression, or are unwilling to consider symptomatic drug therapy.[1] Hypnotherapy may have a role in refractory patients,[1] but a systematic review, although noting promising results, was unable to confirm benefit.[5]

Many drug treatments have been tried in irritable bowel syndrome. Short-term drug therapy may be useful in managing symptoms,[1-4,6-9] and should be directed according to which predominate:

- in patients in whom *diarrhoea* is predominant, loperamide may be considered; it is preferred to other opioid antidiarrhoeal drugs because it does not pass the blood-brain barrier. Alternatively, colestyramine may be of benefit. The 5-HT_3 antagonist alosetron is also available in some countries for use in women with severe symptoms unresponsive to conventional therapy; it was previously withdrawn due to gastrointestinal toxicity
- in *constipation-predominant* forms of the syndrome fibre supplementation is often advocated. However, insoluble fibre, such as bran, may exacerbate pain and bloating in some patients, and if fibre supplements are to be given, soluble fibre, such as ispaghula, is preferable.[1] The benefits of bulking agents in general have been questioned.[9] An osmotic laxative or stool softener may

be added in patients who fail to respond to fibre, but stimulant laxatives should be avoided or used only occasionally.[1] Tegaserod, a partial agonist at 5-HT_4 receptors, has also been effective in this group of patients

- in patients with *abdominal pain*, 'as-needed' antispasmodics may be tried. These should be taken before meals if abdominal pain occurs principally after eating. Examples include alverine, dicycloverine, hyoscine, mebeverine, peppermint oil, and pinaverium. A systematic review considered the evidence of benefit to be greatest for hyoscine derivatives and pinaverium;[9] it was unable to show benefit for tricyclic antidepressants against abdominal pain, although low-dose tricyclics have been suggested for second-line use in patients unresponsive to antispasmodics.[1] Analgesic use should be minimised
- patients whose symptoms are associated with mild or masked *depression* may obtain benefit from antidepressant therapy; a depressed patient with increased bowel frequency and abdominal pain may benefit from a tricyclic antidepressant, which slows intestinal transit. It has been suggested that patients with constipation may be better treated with an SSRI.

Many other drugs have been tried in irritable bowel syndrome, but results have mostly been variable.[2,3] Interest in new pharmacological approaches has included investigation of cholecystokinin antagonists (loxiglumide and dexloxiglumide); new 5-HT_3-antagonists such as cilansetron and 5-HT_4-agonists such as ATI-7505 as well as compounds with mixed actions such as renzapride; κ-opioid agonists such as asimadoline and possibly μ-opioid antagonists such as alvimopan; the 2,3-benzodiazepine receptor modulator dextofisopam; chloride channel activators such as lubiprostone; melatonin; non-absorbed antibacterials such as neomycin or rifaximin, or more promisingly the use of probiotic mixtures of lactic acid-producing organisms; guanylate cyclase-C agonists (linaclotide); and recombinant human nerve growth factors.[10,11] Many herbal medicines have also been tried: a systematic review found the studies mostly to be small and of poor quality, but suggested that there was evidence of benefit for some herbal combinations including Chinese traditional medicines such as tongxie yaofang.[12]

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Microscopic colitis

Microscopic colitis covers the diseases collagenous colitis and lymphocytic colitis, which are characterised by chronic, watery, non-bloody diarrhoea with intra-epithelial lymphocytic infiltration; in collagenous colitis this is accompanied by a thickened band of collagen immediately below the surface epithelium of the colonic mucosa.[1-4] Although originally considered to be rare, more recent studies have suggested an increased incidence;[2-4] differentiating from the diarrhoea-predominant form of irritable bowel syndrome (p.1699) may be difficult. It has been suggested that the disease is more common in middle-aged women,[2] but others dispute this.[3]

The evidence base for management is limited, and is complicated by the fact that the disease may remit spontaneously.[2-4] Initial measures may include dietary modification, with avoidance of caffeine[2,3] or lactose-containing foods.[2] A possible association with NSAIDs has been suggested; such drugs should be withdrawn, or their use minimised, if possible.[2,3] Drug treatment has been largely empirical, and relapse is quite common once treatment stops. Antidiarrhoeal treatment with loperamide or fibre supplements has been proposed initially.[1-3,5] Systematic review[6] has suggested that budesonide (see also p.1521), and probably bismuth salicylate, are of benefit in collagenous colitis, and they may be considered for second-line therapy.[3] Data from a small study suggested that bismuth salicylate might also be beneficial for lymphocytic colitis, although no firm conclusions could be drawn.[7] In unresponsive patients, sulfasalazine or another 5-aminosalicylate may be considered;[1-3] it has been suggested that mesalazine or olsalazine may be less effective (though better tolerated) than sulfasalazine.[1,2] Other drugs that may be tried in resistant cases include colestyramine, antibacterials such as metronidazole or erythromycin, oral prednisolone, or immunosuppressants such as azathioprine, mercaptopurine, or methotrexate.[1-3,5] Octreotide and verapamil have also been reported to relieve symptoms.[3]

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Mouth ulceration

Recurrent ulceration of the oral mucosa is usually idiopathic and self-limiting and is known as recurrent aphthous stomatitis or recurrent aphthous ulceration. However, oral ulcers (canker sores) may also be caused by mechanical trauma, nutritional deficiencies (particularly iron, folic acid, or vitamin B_{12}), drug reactions, or underlying disease such as Behçet's syndrome (p.1499).

Management includes identifying any underlying disease or nutritional deficiency and treating these as appropriate. Usually no underlying cause can be found, and treatment is purely symptomatic; it may include topical anti-inflammatories, local anaesthetics, antiseptics, astringents, or antihistamines. The value of many of these drugs in reducing symptoms remains anecdotal, and no treatments have yet been proven to reduce the incidence of recurrences.

Where ulceration is due to minor trauma frequent use of a warm saline or compound thymol glycerin mouthwash may be all that is required to relieve discomfort and swelling. Alternatively, pain relief may be obtained with local anaesthetics or analgesics, but their effectiveness in oral ulceration is limited by their relatively short duration of action when applied topically. Salicylates are widely used, mainly as choline salicylate gel, although they themselves have the potential for local irritation and ulceration. Benzydamine spray or mouthwash may also be helpful. Lidocaine, as a gel or lozenges, may be of value in pain that has not responded to other measures. Topical corticosteroids are probably the most effective symptomatic treatment for recurrent aphthous stomatitis. Pellets or lozenges of hydrocortisone are allowed to dissolve next to an ulcer, or triamcinolone in an oral paste formulation may be used, although the paste may sometimes be difficult to apply. Mouthwashes have been employed particularly when ulceration is widespread in the mouth and a dexamethasone mouthwash has been used effectively. The healing properties of carbenoxolone have also been employed as a gel or mouthwash, and the mast-cell stabilising agent amlexanox is also used as an oral paste.

Mechanical protection may be provided by a paste or powder of carmellose sodium, although application may be difficult.

Use of an antiseptic mouthwash such as chlorhexidine or povidone-iodine may be helpful, since secondary bacterial infection can delay healing. Chlorhexidine is also available as a gel. Tetracyclines, used as mouthwashes, reportedly reduce ulcer pain and duration, but their potential for adverse effects if swallowed must be borne in mind. Use of hydrogen peroxide 3% is inadvisable, as it can cause ulceration, but application of a 1.5% solution to individual ulcers, with a topical corticosteroid, may be helpful in producing resolution.

A wide variety of other drugs have been tried in aphthous ulceration. Sucralfate may be of benefit. Drugs such as levamisole and thalidomide, although possibly beneficial, are unlikely to be suitable in most cases because of their adverse effects, although thalidomide is used, for example, for aphthous stomatitis in patients with AIDS. Pentoxifylline, which, like thalidomide, inhibits tumour necrosis factor production, has been used in patients with minor recurrent aphthous ulceration. Systemic corticosteroids are generally reserved for cases with severe underlying disease.

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Nausea and vomiting

Vomiting follows stimulation of the vomiting centre in the medulla of the brain. This may be via the chemoreceptor trigger zone, which is sensitive to many drugs and to certain metabolic disturbances, or from actions on other areas such as the vestibular apparatus of the ear (in motion sickness), the cerebral cortex (in psychogenic vomiting), and multiple peripheral receptors. In adults vomiting is almost invariably preceded by a sensation of nausea.

In situations where it can be anticipated, such as motion sickness, surgery, and cancer therapy, antiemetic drugs are given prophylactically, but if this fails they may need to be given therapeutically. Vomiting of unknown origin should ideally not be treated until the underlying cause has been found. If vomiting is prolonged, dehydration, hypokalaemia, and alkalosis may occur and replacement of fluid and electrolytes may be necessary, especially in young children and the elderly.

Cancer chemotherapy. Nausea and vomiting are common adverse effects of cancer chemotherapy and for many patients represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff or a needle and this problem may be severe enough in some cases to hinder or prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. The cerebral cortex is probably responsible for anticipatory vomiting. Mechanisms involving 5-HT_3-receptors are important in the pathogenesis of *acute cisplatin-associated vomiting*, whereas different mechanisms are probably involved in *delayed emesis*.

The emetic potential of antineoplastics varies in terms of severity and incidence. A risk classification system, based on the proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis, has been developed. Although there are slight variations in published lists,[1-3] examples of risk for some common drugs include:

- *high (more than 90% frequency of emesis)* and can be very severe with chlormethine, cisplatin, high-dose cyclophosphamide, dacarbazine, dactinomycin, and streptozocin
- *moderate (30 to 90% frequency of emesis)* with carboplatin, more modest doses of cyclophosphamide, doxorubicin, epirubicin, irinotecan, high-dose methotrexate, and oxaliplatin

- *low (10 to 30% frequency of emesis)* with etoposide, fluorouracil, lower doses of methotrexate, and taxanes
- *minimal (less than 10% frequency of emesis)* with bleomycin, oral chlorambucil, fludarabine, oral methotrexate, rituximab, and vinca alkaloids

Emetogenicity may depend to some extent on the dose, route, and schedule of chemotherapy. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

The *onset and duration* of vomiting also varies from drug to drug. For cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. *Acute emesis* (that occurring within 24 hours of chemotherapy) has generally been easier to control than *delayed emesis* (that occurring more than 24 hours after chemotherapy) or *anticipatory emesis*. In patients whose regimens are given over several days delayed emesis from the initial doses may overlap with acute emesis from later doses.

MANAGEMENT. Guidelines for the management of nausea and vomiting associated with chemotherapy have been produced.[1-3] It is important that effective antiemetic prophylaxis is given from the first course of chemotherapy, to avoid subsequent problems with anticipatory vomiting. With the antiemetic drugs now available it should be possible to control acute emesis; delayed emesis has proved more resistant but new treatments are becoming available. Drugs used in antiemetic regimens have included:

- dopamine antagonists such as metoclopramide, domperidone, and some phenothiazines such as prochlorperazine
- corticosteroids such as dexamethasone
- 5-HT_3 antagonists such as ondansetron
- neurokinin-1 (NK-1) receptor antagonists such as aprepitant
- cannabinoids such as nabilone
- benzodiazepines such as lorazepam
- antihistamines such as diphenhydramine

The choice depends on the emetogenicity of the cancer chemotherapy regimen, as well as factors such as the age of the patient.

- For prophylaxis of *acute emesis* associated with *highly emetogenic chemotherapy*, a 5-HT_3 antagonist with dexamethasone and aprepitant (or fosaprepitant) is recommended.[1-3] At equipotent doses, dolasetron, granisetron, ondansetron, and tropisetron are effective and equally safe.[1,2] Palonosetron, which has a prolonged action, may also be used. High-dose metoclopramide was formerly used, but frequently caused extrapyramidal adverse effects, particularly in patients under 30 years of age; diphenhydramine was used to reduce these effects
- For prophylaxis of *acute emesis* associated with *moderately emetogenic chemotherapy*, dexamethasone with a 5-HT_3 antagonist is suggested.[1-3] Aprepitant (or fosaprepitant) may be added for patients given an anthracycline and cyclophosphamide or other chemotherapy drugs of moderate emetic risk
- Dexamethasone alone may be used for prophylaxis with chemotherapy of *low emetic risk*;[1-3] alternatives include prochlorperazine or metoclopramide.[2] No routine prophylactic antiemetic needs to be given for chemotherapy of *minimal emetic risk*;[1-3] however, as-needed or prophylactic use of dexamethasone, a phenothiazine, or metoclopramide is common, particularly for patients with poor emetic control during previous therapy[1]
- Lorazepam may be used for its amnestic, sedative, and anxiolytic effects as an adjunct to antiemetics when *anticipatory emesis* is a problem
- Good control of acute emesis is important in preventing *delayed emesis*. In addition, for prophylaxis of delayed emesis from highly emetogenic chemotherapy, a combination of dexamethasone with aprepitant may be used. After moderately emetogenic chemotherapy, prophylaxis with a single drug such as dexamethasone, a 5-HT_3 antagonist, or metoclopramide (with or without diphenhydramine) may be sufficient.[1-3] Aprepitant or dexamethasone alone has been suggested for patients given an anthracycline with cyclophosphamide[1,3]

Cannabinoids such as dronabinol and nabilone have been used for chemotherapy-induced nausea and vomiting, usually as second-line drugs. Although they have some advantages because of their effects on mood, their use is limited by adverse effects.[4]

If *breakthrough emesis* occurs, management is often difficult. The general principle of treatment is to add an additional antiemetic from a different class; multiple concurrent drugs, perhaps in alternating schedules or by alternating routes may need to be considered. Since oral dosage may not be feasible because of ongoing vomiting, treatment is often given by the rectal or intravenous routes.[2] More intensive prophylactic treatment should be considered in subsequent courses.

Motion sickness has been described as a normal reaction to stimuli that occur during passive transportation and to which the individual is not adapted. The term embraces all forms of travel sickness including sea sickness, car sickness, train sickness, and air sickness. It is a type of vertigo in which autonomic symptoms predominate, therefore signs and symptoms include pallor, sweating, increased salivation, yawning, malaise, and hyperventilation.

MANAGEMENT. The aim is to *prevent* motion sickness and antiemetics are more effective if given prophylactically before nausea and vomiting has developed. The principal drugs used are the antimuscarinic hyoscine and some of the centrally acting antihistamines.[5,6] In some countries dexamfetamine has been tried,[6] although its adverse effects and the risk of abuse make it an unlikely choice. Antiemetic drugs *not* effective against motion sickness include metoclopramide, domperidone, chlorpromazine, and 5-HT_3 antagonists. Ginger has been tried. Evidence for the value of wrist acupressure is equivocal.[6]

For short-term protection against motion sickness hyoscine hydrobromide has been shown to be effective.[7] It can be taken by mouth about 30 minutes before a journey followed by further doses every 6 hours if necessary. Transdermal hyoscine has a longer duration of action, but the patches need to be applied to the skin several hours before travelling.

There is little good evidence comparing the effectiveness of antihistamines with hyoscine against motion sickness,[7] but they are often better tolerated. They are usually given by mouth and include cinnarizine, cyclizine, dimenhydrinate, meclozine, and promethazine; all have similar efficacy, but differ in onset and duration of action and in the extent of adverse effects such as drowsiness. Their antimuscarinic properties may contribute to their effects. Non-sedating antihistamines (e.g. astemizole and terfenadine) penetrate poorly into the CNS and do not appear to be effective against motion sickness.

Once motion sickness has developed, gastric motility is inhibited and oral antiemetics are unlikely to be effective. Where intramuscular injection is feasible, promethazine appears to be the most effective treatment. If exposure is likely to be prolonged, transdermal hyoscine may be useful, but will not provide benefit for some hours.[6]

Palliative care. Nausea and vomiting are common in terminal illness, and may be prolonged. Causes may include gastric irritation or stasis, bowel obstruction, renal failure, hypercalcaemia, raised intracranial pressure, infection, or the effects of drugs or radiation; anxiety, cough, and pain may exacerbate the condition.[8-10]

MANAGEMENT. Management will depend on the cause of the nausea and vomiting.[9] The evidence base for many antiemetics in terminal care is poor; it is perhaps best for metoclopramide, but evidence for many common and apparently effective interventions, such as haloperidol, cyclizine, and levomepromazine, is conflicting.[11] However, guidelines have been developed, either empirically or based on considerations of the likely causes. Recommendations include:[9]

- any correctable causes should be managed appropriately, and treatment for exacerbating conditions (such as anxiety) given
- an appropriate antiemetic should be given immediately, and repeated as often as necessary. If nausea is continuous or vomiting frequent, subcutaneous injection or continuous subcutaneous infusion may be preferred to the oral route. The usual initial choice for palliative care in the UK is between metoclopramide (preferred if the cause is gastric stasis, gastritis, or functional bowel obstruction), haloperidol (favoured in drug-induced vomiting, hypercalcaemia, and renal failure), and cyclizine (raised intracranial pressure, motion sickness, organic bowel obstruction)
- if treatment fails an alternative drug may be considered, or combination therapy may be necessary (prokinetics such as metoclopramide should not be combined with antimuscarinic drugs as their actions are antagonistic). Dexamethasone (usually added to the regimen), or levomepromazine or olanzapine (broad-spectrum antiemetics; these are usually substituted for the previous regimen) are useful where first-line drugs fail. Olanzapine is usually used if levomepromazine is too sedative. Other phenothiazines, notably prochlorperazine, and the phenothiazine antihistamine promethazine, are sometimes still used, but chlorpromazine is less effective than levomepromazine where a broad-spectrum drug is required. The role of 5-HT_3 antagonists is limited but they may be useful in nausea and vomiting secondary to chemotherapy (above) or radiotherapy (below), or sometimes in bowel obstruction or renal failure
- if there is colic or a need to reduce secretions, hyoscine butylbromide should be given, alone or with cyclizine. If this is inadequate in patients with obstruction, octreotide may be helpful

Non-drug measures may include appropriate diet and avoidance of unpleasant odours, adequate hydration, and regular mouth care.[8] Acupressure and acupuncture may provide some benefit.[10]

Postoperative nausea and vomiting (PONV) is a common and distressing adverse effect of anaesthesia and surgery;[12-16] it is seen in some 20 to 30% of patients undergoing surgery under general anaesthesia,[13,14,17] and is perceived by patients as a problem comparable to postoperative pain.[18]

Risk factors for PONV include a history of motion sickness or previous PONV, female sex, not smoking, use of opioids during or after surgery, use of volatile inhaled anaesthetics or nitrous oxide, and prolonged surgery.[13-17,19,20] It is widely considered that certain types of surgery carry an increased risk, but this is now being questioned.[13,14] A study comparing various predictive models found that none was perfect, but that a simplified model based on history, sex, smoking status, and opioid use was as effective as more complex methods.[19]

MANAGEMENT. Prediction of risk is of value since much of the management of PONV focuses on prevention. It is generally agreed that prophylaxis should be reserved for patients at moderate to high risk. In these, various strategies may be adopted to *reduce risk* where possible, including the use of regional anaesthesia or total intravenous anaesthesia with propofol (but see also p.1793), avoidance of nitrous oxide, minimal use of opioids, adequate hydration (especially with colloids), and possibly the use of intraoperative supplemental oxygen (although not all studies found this of benefit).[13,14] Avoidance of high-dose neostigmine (limiting the dose to a maximum of 2.5 mg in adults) has also been suggested.[14] There is evidence that some nonpharmacological interventions, such as acupuncture of the P6 point, may also be effective, especially for nausea.[21]

Many types of drugs have been tried as *prophylactic antiemetics*. These include the 5-HT_3 antagonists, phenothiazines such as prochlorperazine, butyrophenones such as droperidol, antihistamines such as promethazine, cyclizine, or dimenhydrinate, and some other drugs such as dexamethasone and hyoscine.[16,20] A large and well-designed multicentre study (the IMPACT trial) has shown that ondansetron, droperidol, and dexamethasone are of similar efficacy;[22] it also confirmed that avoidance of volatile anaesthetics and nitrous oxide was of as much benefit in preventing PONV as use of a prophylactic antiemetic. The evidence suggests that other 5-HT_3 antagonists are of similar efficacy to ondansetron.[14] Evidence for some of the older drugs is less extensive, although benefit has often been shown in individual studies.[13,14] Systematic reviews have confirmed the benefit of prophylaxis with dimenhydrinate[23] and transdermal hyoscine[24] but have suggested that metoclopramide, which has been widely used, is in fact of little value in preventing PONV,[25,26] perhaps because the doses used are too low.[26] However, another systematic review[27] included metoclopramide in a list of drugs that reliably prevented PONV compared with placebo; other drugs listed were cyclizine, dexamethasone, dolasetron, droperidol, granisetron, ondansetron, and tropisetron. Ginger root has also been suggested, but again does not seem to be effective in this context,[28] although there is some evidence of benefit for intramuscular ephedrine.[29] Clonidine has also been reported to produce benefit,[30,31] possibly secondary to reduced sympathetic tone and lower use of inhalation anaesthetics and opioids. Neurokinin-1 antagonists such as aprepitant may also be effective.[20]

In patients at moderate risk of PONV, therefore, in addition to risk reduction, use of a single prophylactic antiemetic may be considered:[13,14] this might be a 5-HT_3 antagonist, droperidol (although concerns about effects on QT interval have restricted its availability), or dexamethasone; or perhaps transdermal hyoscine, dimenhydrinate, or another drug such as promethazine or a heterocyclic phenothiazine (prochlorperazine or perphenazine). In patients at higher risk, or in whom nausea and vomiting would be particularly problematic, a combination of antiemetics from different classes should be given,[13,14] since the IMPACT study has shown that the effects of such interventions are additive.[22]

If PONV develops, *treatment* will depend on whether prophylaxis was given. In patients who have received no prophylaxis, or only dexamethasone, a small dose of a 5-HT_3 antagonist has been recommended.[13,14] If PONV occurs within 6 hours of surgery despite antiemetic prophylaxis, additional doses of the same drug convey no further benefit, and treatment with drugs from another class is recommended.[14,16,20] Beyond this time any suitable drug may be used, but dexamethasone and transdermal hyoscine are not recommended for treatment because of their slow onset of action.[14]

Pregnancy. Nausea and vomiting or 'morning sickness' is common in the first trimester of pregnancy, but is generally mild and does not require drug therapy. Dietary modification such as eating small frequent carbohydrate meals is widely thought to be helpful.[32] A systematic review has suggested that pyridoxine, which has been shown to be of benefit, should be tried first if drug therapy is required.[32] Benefit has also been reported with ginger root,[32,33] but evidence of benefit from stimulation of the P6 acupuncture point is ambiguous.[32] A number of antihistamines such as buclizine, dimenhydrinate, hydroxyzine, meclozine, promethazine, and thiethylperazine have also been tried, and appear to be more effective than placebo,[32] but there are obvious concerns about potential effects on the fetus (see Pregnancy, under Precautions for Antihistamines, p.563). Although no real evidence of a teratogenic effect exists,[34] therapy has tended to be reserved for severe cases, and short-term use.

Persistent vomiting and severe nausea may progress to *hyperemesis gravidarum* if adequate hydration cannot be maintained; the condition occurs in up to 1% of pregnancies.[35] Management of hyperemesis includes hospitalisation for intravenous fluid and electrolyte replacement, and this is usually sufficient. Routine thiamine supplementation, by mouth if tolerated, otherwise parenterally, has been recommended to reduce the risk of Wernicke's encephalopathy[35,36] (p.1977), although there is some dissent from this view.[37] If hyperemesis fails to respond to rehydration, antiemetics should be used; options include domperidone, phenothiazines, and antihistamines.[35] It has been suggested that hyperemesis unresponsive to conventional therapy may respond to oral prednisolone or intravenous hydrocortisone.[35] There have also been anecdotal reports of ondansetron being used successfully in life-threatening hyperemesis gravidarum unresponsive to conventional treatment,[38] although a double-blind pilot study found it to be no more effective than promethazine.[39] A systematic review found no evidence of benefit for any intervention in hyperemesis gravidarum.[32]

Radiotherapy. The risk of emesis with radiotherapy varies with the treatment given, particularly the area of the body irradiated. However, emetic risk, and recommendations for use of antiemetics, are less clearly defined than in the situation of chemotherapy-induced nausea and vomiting.[1] Use of a prophylactic 5-HT_3 antagonist is usually recommended in patients receiving radiation to the upper abdomen. Dexamethasone may be added for those receiving total body irradiation.[1,2] For radiotherapy of minimal emetogenic potential, treatment on an as-needed only basis has been suggested.[1]

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Oesophageal motility disorders

Oesophageal disorders, many due to disturbances in oesophageal motility, may produce non-cardiac chest pain, similar to that of angina pectoris, from which they must be differentiated.

Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. It is accompanied by dilatation and abnormal peristalsis in the oesophagus, which becomes a reservoir for the unassimilated matter; symptoms include dysphagia and sometimes pain. The treatment of choice is mechanical dilatation of the sphincter or, if necessary, surgery. Laparoscopic techniques have reduced the risks associated with surgery, and this may become the preferred treatment. Taking isosorbide dinitrate or nifedipine before eating results in some improvement in achalasia, but these drugs have a role only as a temporary measure, or when other options are not suitable. Sildenafil is under investigation. More recently, injection of botulinum toxin into the lower oesophageal sphincter has been found to be effective, but remission in the long-term is better with mechanical dilatation than botulinum toxin. Therefore, it has been recommended that botulinum toxin be reserved for patients thought to be at risk from mechanical dilatation or surgery.

Oesophageal spasm, although frequently asymptomatic, can produce dysphagia and pain. Drug treatment of diffuse oesophageal spasm, or its variant 'nutcracker oesophagus' which is characterised by high amplitude peristalsis in the oesophagus, is often ineffective. Antimuscarinic antispasmodics, nitrates, and calcium-channel blockers have been tried in an attempt to relax the smooth muscle, but results are often disappointing; experience with nifedipine in patients with nutcracker oesophagus suggests that decrease in oesophageal pressure may not correlate with reduction in pain. As with achalasia, minimally invasive surgery is effective for these conditions. Sildenafil is also under investigation.

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Peptic ulcer disease

Peptic ulceration is a common condition consisting of a distinct break in the gastrointestinal mucosa, usually of the stomach or duodenum. Duodenal ulcers are rarely malignant but gastric ulcers are more commonly associated with malignancy.

The aetiology of peptic ulcer disease is probably multifactorial but the bacterium *Helicobacter pylori* plays an important role. Abnormalities of normal mucosal defence mechanisms, and, in the case of gastric ulcer, reflux of duodenal contents into the stomach or delayed gastric emptying may also be involved. Other factors include emotional stress, smoking, alcohol, and drugs such as NSAIDs or corticosteroids.

Peptic ulcer disease usually presents as dyspeptic pain, sometimes associated with nausea, vomiting, anorexia, heartburn, or bloating. Patients may develop complications such as bleeding, obstruction, or perforation.

Certain simple measures such as bed rest, dietary modification, and cessation of smoking, may accelerate ulcer healing, but these play an adjuvant role, and the basis of treatment is pharmacological. Treatment is aimed at eradicating *H. pylori* with antibacterials and neutralising or inhibiting acid activity with antisecretory drugs. Surgical treatment is used in patients with acute complications such as perforation, haemorrhage, obstruction, or pyloric stenosis, or in patients with recurrent or intractable ulcer disease, or where there is suspicion of malignancy.

Anti-Helicobacter therapy. The presence of *H. pylori* should usually be confirmed before therapy to eradicate the infection is started. The urea breath test is the most widely used method to test for *H. pylori*, but may produce false-negatives if used during or too soon after treatment with proton pump inhibitors (see under Omeprazole, p.1755) or antibacterials. There is good evidence that eradication therapy has benefits both in healing ulcers and preventing recurrence, especially for duodenal ulcer.[1] Many different regimens have been tried, using various combinations of oral antibacterials with antisecretory drugs. Expert consensus is that any treatment regimen should achieve at least 80% eradication of *H. pylori*,[2] and the most appropriate regimen may therefore depend to some extent on local patterns of resistance.

The following recommendations have been made by an international expert group:[2]

- ***where clarithromycin resistance is below 15 to 20%***
  - **triple therapy** with a proton pump inhibitor (PPI), clarithromycin, and metronidazole (provided the prevalence of metronidazole resistance is less than 40%), for 14 days

    or

    PPI, clarithromycin, and amoxicillin, for 14 days

    or
  - **quadruple therapy** with a bismuth compound, a PPI, and two antibacterials, for 14 days. Such a regimen used in the UK (usually for rescue therapy, see below) comprises a proton pump inhibitor with tripotassium dicitratobismuthate, tetracycline, and metronidazole
  - treatment for 7 days rather than 14 may be acceptable where local studies show it to be effective (in the UK, the *BNF* considers that adverse effects and poor compliance are likely to offset any therapeutic gain from 14-day regimens)
- ***in areas of high clarithromycin resistance*** it may be appropriate to consider antibacterial susceptibility testing before beginning treatment; regimens that may be considered include:

  bismuth-containing quadruple therapy as above

  or

  PPI, amoxicillin, and metronidazole (provided metronidazole resistance is low)

  or

  PPI, tetracycline, and metronidazole
- testing to confirm eradication, at least 4 weeks after treatment, is recommended; a urea breath test is the preferred method
- rescue treatments in patients with refractory disease should be based on antibacterial susceptibility testing. In the UK, the *BNF* considers that the bismuth-based quadruple therapy regimen referred to above may be effective.
- other antibacterials that have been investigated in eradication regimens (mainly as rescue treatments) include rifabutin and levofloxacin, although there might be concerns about selecting for mycobacterial resistance if the former were to be used widely, and increasing fluoroquinolone resistance may limit the value of the other

There is some evidence that a **sequential regimen** of a PPI (pantoprazole) with amoxicillin for 5 days, followed by the PPI with a nitroimidazole antibacterial (tinidazole) and clarithromycin for a further 5 days, is more effective than a standard 10-day triple therapy regimen, especially in patients with clarithromycin-resistant strains of *H. pylori*.[3] The potential value of such regimens remains to be more widely demonstrated.[2,4]

The use of **dual therapy** regimens comprising a PPI and an antibacterial is no longer recommended. Similarly, although acid suppressive therapy has sometimes been continued after completing eradication therapy, the *BNF* considers this unnecessary, unless the ulcer is large or complicated by bleeding or perforation.

Before the advent of *H. pylori* eradication therapy, drug treatment of gastric and duodenal ulcers relied mainly on antisecretory therapy. Four to 8 weeks of H_2-antagonist or proton pump inhibitor therapy was required for ulcer healing. Because of the high incidence of relapse, these drugs were then often given as maintenance therapy. Numerous other drugs were formerly used in peptic ulcer disease before the development of H_2-antagonists and proton pump inhibitors, including antacids, antimuscarinics such as pirenzepine, and mucosal protectants such as sucralfate.

NSAID-induced ulceration. The ulcerogenic effects of NSAIDs have been attributed to inhibition of prostaglandin synthesis and mucosal cell proliferation, and the ulcers they cause may differ from non-iatrogenic ulcers in their pathology and prognosis.[5,6] Although considered to be independent risk factors for peptic ulcer disease, *H. pylori* infection and NSAID use may act synergistically in peptic ulceration and ulcer bleeding.[7,8] If peptic ulceration develops during treatment with an NSAID the drug should be withdrawn if possible. If this can be done, the ulcer may be treated with an antisecretory drug such as an H_2-antagonist or PPI given for 4 to 8 weeks. If NSAIDS have to be continued, *treatment* is with antisecretory drugs or the prostaglandin analogue misoprostol.[5,6] Ulcers tend to heal more slowly with H_2-antagonists if NSAIDs are continued, whereas the rate of ulcer healing with PPIs appears not to be affected. There is also some evidence that omeprazole is more effective at healing NSAID-associated ulceration than misoprostol.[9] Patients at high risk of NSAID-associated gastrointestinal complications, including those with a history of these events, should receive *prophylactic therapy*.[5,6] A systematic review[10] concluded that misoprostol, PPIs, and double-dose H_2 antagonists are effective at preventing chronic NSAID-associated gastric and duodenal ulcers. Standard doses of H_2-antagonists prevent NSAID-associated duodenal ulceration, but appear to be less effective in preventing gastric ulceration. Another systematic review also found that misoprostol, and probably PPIs, were effective in reducing the risk of symptomatic NSAID-associated ulceration, as was the use of specific inhibitors of cyclo-oxygenase-2 such as celecoxib;[11] combination of a cyclo-oxygenase-2 inhibitor with a PPI may be appropriate in very high risk patients.[12] After healing of NSAID-associated ulceration, omeprazole prophylaxis was more effective than ranitidine,[13] and was more effective and better tolerated than misoprostol.[9] Whether *H. pylori* eradication is appropriate in patients receiving long-term NSAIDs remains debatable. There is some evidence that eradication reduces the risk of bleeding in patients who have not previously taken NSAIDs,[2,14] and testing and eradication in patients taking PPIs long-term for prevention of NSAID-induced ulceration has been advocated by an expert consensus, since there is evidence that combination of *H. pylori* infection and long-term acid suppression may accelerate the development of pre-malignant changes in the stomach.[2] However, PPI maintenance is more effective than *H. pylori* eradication in preventing ulcer recurrence or bleeding in patients taking NSAIDs,[2] and there is no convincing evidence that eradication speeds ulcer healing.[14]

Stress ulceration may occur in the stomach or the duodenum following major physical trauma such as burns or surgery, or after severe sepsis or illness. H_2-antagonists and sucralfate are widely used for the prevention of stress ulceration in high-risk patients in intensive care units,[15-17] and is increasingly used, though with little evidence, in less severely ill patients.[18] Pirenzepine is used in a few countries, and some[15] prefer it in neurosurgical patients and those with head trauma. H_2-antagonists may be given by mouth, nasogastric tube, or by the intravenous route (intermittent or continuous). It has been suggested that the rise in gastric pH which results from such use may predispose patients to nosocomial pneumonia due to bacterial overgrowth in the stomach and retrograde colonisation of the pharynx. Sucralfate does not increase gastric pH, and meta-analysis has indicated that it may be as effective as an H_2-antagonist in reducing bleeding, and is associated with lower rates of pneumonia and mortality.[19] The findings of a subsequent large randomised study[20] by the same authors were at odds with those of this meta-analysis, suggesting that intravenous ranitidine was more effective than sucralfate given orally or via nasogastric tube in reducing clinically significant gastrointestinal bleeding. Moreover, there was no difference in rate of ventilator-associated mortality between ranitidine and sucralfate recipients. A further meta-analysis[21] has in turn raised doubts about the efficacy of ranitidine; no significant benefit was found for ranitidine, compared with placebo, in the prevention of bleeding. One clinical guideline suggests that, given the conflicting evidence, the choice between antacids, H_2-antagonists, and sucralfate be made on an institutional basis.[16] PPIs are also used for stress ulcer prophylaxis, although the evidence base for such use is lacking.[17]

Bleeding ulcer. Peptic ulceration is responsible for about 50% of all cases of upper gastrointestinal bleeding: the condition is potentially life-threatening and in severe cases prompt resuscitation with intravenous fluids and blood may be required. About 80% of patients will stop bleeding spontaneously without recurrence, but the remaining 20% are at risk of severe morbidity or death,[22] and early stratification into low- and high-risk categories on the basis of clinical and endoscopic criteria is important for proper management.[22,23] No treatment may be needed for low-risk patients, but those with a clot in an ulcer bed should undergo irrigation and appropriate treatment of the underlying lesion, and high-risk patients should be given immediate endoscopic injection therapy for haemostasis.[22]

Many different solutions have been used for endoscopic injection, including adrenaline (alone or with sclerosants such as monoethanolamine or lauromacrogol), alcohol, fibrin glue, sodium tetradecyl sulfate, thrombin, or saline (normal or hypertonic); none has been clearly shown to be superior.[22] Adrenaline injection will achieve haemostasis in up to 95% of patients although bleeding will recur in up to 20% of these; there is little evidence that addition of sclerosants reduces the rate of rebleeding, and their use may lead to life-threatening necrosis of the injected area.[23] Thermal, laser, or multipolar (coaptive) or plasma electrocoagulative endoscopic techniques are also of benefit, and again there is no clear evidence to prefer one over another.[22] Combining injection with thermal coagulation may be of greater benefit than either alone; UK guidelines consider it may be better in a subset of patients with active arterial bleeding, although it is not considered to offer additional benefit in most patients,[23] while subsequent Canadian guidelines consider the combination superior.[22] The use of mechanical clips may also be effective,[22,23] especially for actively bleeding large vessels.[23] If endoscopic treatments fail to stop bleeding, or rebleeding occurs, further endoscopic therapy may be considered, but otherwise patients require surgery.[22,23]

There is good evidence from systematic review[24] that treatment with PPIs reduces rebleeding and surgery in patients with acute bleeding peptic ulcers; one such review did not show reduced mortality,[24] although others consider it to have been demonstrated.[22] An intravenous bolus of a PPI followed by continuous infusion is recommended in patients who have undergone successful endoscopic therapy.[22,23] There is no evidence that any PPI is superior to others.[22,25] Some suggest that high-dose PPI therapy (oral or intravenous, depending on the degree of risk) should also be considered in patients awaiting endoscopy.[22]

In contrast, there is no evidence that H_2-antagonists are of benefit in the treatment of acute nonvariceal bleeding, and somatostatin, octreotide, or tranexamic acid are not recommended.[22,23]

Eradication of *H. pylori* is recommended in those patients positive for the organism;[22,23] eradication therapy is superior to antisecretory drugs alone in preventing rebleeding.[26]

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Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is a rare disorder characterised by the presence of a gastrin-producing tumour (gastrinoma), which leads to hypersecretion of gastric acid and consequent peptic ulcer disease (often with complications such as perforation or bleeding), diarrhoea, or malabsorption. Gastrinomas usually occur in the non-beta islet cells of the pancreas or in the duodenal wall. Up to two-thirds are malignant. About 20 to 25% of cases are seen in patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome.

Initial treatment is aimed at controlling the hypersecretion of gastric acid with an antisecretory drug. Giving enough medication just to control symptoms is not considered adequate, and it is important that acid secretion is reduced below 10 mmol/hour. Intravenous H_2-antagonists or proton pump inhibitors may be required initially. Once the symptoms have been controlled the tumour can be investigated for surgical removal. When complete removal is not possible then antisecretory therapy is continued indefinitely. A proton pump inhibitor is the drug of choice; it profoundly reduces acid secretion with once- or twice-daily use, although relatively high doses are required compared with those used in other conditions. An H_2-antagonist such as cimetidine or ranitidine may be used as an alternative to omeprazole, and, as with omeprazole, daily doses are higher than those used for other conditions; they are given in 3 or 4 divided doses. The somatostatin analogue octreotide can be used to reduce serum gastrin, but has to be given subcutaneously, and is not well tolerated.

Parietal cell vagotomy may be performed to reduce acid secretion if the tumour is not found, to allow lower doses of antisecretory drugs to be used.

References.

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Aceglutamide Aluminium *(USAN, rINNM)*

Aceglutamida de aluminio; Acéglutamide d'Aluminium; Aluminii Aceglutamidum; KW-110. Pentakis (N^2-acetyl-L-glutaminato)tetrahydroxytrialuminium.

Алюминий Ацеглутамид

$C_{35}H_{59}Al_3N_{10}O_{24}$ = 1084.8.

CAS — 12607-92-0.

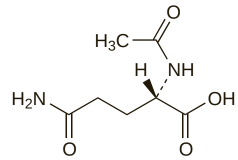

(aceglutamide)

Pharmacopoeias. In *Jpn.*

Profile

Aceglutamide aluminium, a complex of aceglutamide with aluminium hydroxide, is an antacid with general properties similar to those of aluminium hydroxide (p.1706). It is given orally in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Glumal.

Aclatonium Napadisilate *(BAN, rINN)*

Aclatonii Napadisilas; Aclatonium Napadisylate; Celatonium Napadisilate; Choline Naphthalene-1,5-Disulphonate (2:1) Dilactate Diacetate; Napadisilate d'Aclatonium; Napadisilato de aclatonio; SKF-100916-J; TM-723. 2-(2-Acetoxypropionyloxy)ethyltrimethylammonium naphthalene-1,5-disulphonate (2:1).

Аклатония Нападизилат

$2C_{10}H_{20}NO_4,C_{10}H_6O_6S_2$ = 722.8.

CAS — 55077-30-0.

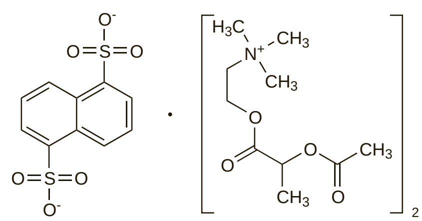

Profile

Aclatonium napadisilate is a cholinergic agonist given orally for its prokinetic properties in the management of decreased gastrointestinal motility (p.1694) after gastrointestinal surgery, and to relieve symptoms of biliary dyskinesia and chronic gastritis.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Abovis.

Albumin Tannate

Albumiinitannaatti; Albúmina, tanato de; Albumini Tannas; Albumintannat; Albutannin; Tannin Albuminate.

Альбумин Таннат

CAS — 9006-52-4.
ATC — A07XA01.
ATC Vet — QA07XA01.

Pharmacopoeias. In *Jpn.*

Profile

Albumin tannate, a compound of tannin with albumin, is given orally for its astringent properties in the treatment of diarrhoea (p.1694). It is stated to liberate tannic acid (p.2394) in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Tannalbin; ***Ger.:*** Tannalbin; ***Neth.:*** Entosorbine-N; Tannalbin†; ***Pol.:*** Taninal.

Multi-ingredient: ***Austria:*** Neoplex; ***Belg.:*** Tanalone; ***Cz.:*** Tannacomp†; ***Fin.:*** Tannopon; ***Ger.:*** Tannacomp; ***Hung.:*** Bolus Adstringens; ***Pol.:*** Salotannal; ***Spain:*** Demusin; Salitanol Estreptomicina.

Alexitol Sodium *(BAN, rINN)*

Alexitol sódico; Alexitol Sodique; Alexitolum Natricum. Sodium poly(hydroxyaluminium) carbonate-hexitol complex.

Алекситол Натрий

CAS — 66813-51-2.

Profile

Alexitol sodium is an antacid with general properties similar to those of aluminium hydroxide (p.1706). It is given orally in doses of 360 to 720 mg when required, up to a maximum of sixteen 360-mg tablets in 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Actal; ***Malaysia:*** Actal; ***Singapore:*** Actal; ***Thai.:*** Actal; ***UK:*** Actal.

Multi-ingredient: ***Malaysia:*** Actal Plus.

Alicaforsen *(rINN)*

Alicaforsén; Alicaforsenum. 2′-Deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioadenylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thioguanylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-(*R*)-*P*-thiocytidylyl-(3′→5′)-2′-deoxyadenosine.

Аликафорсен

$C_{192}H_{244}N_{75}O_{98}P_{19}S_{19}$ = 6368.2.

CAS — 185229-68-9.

Alicaforsen Sodium *(USAN, rINNM)*

Alicaforsen Nonadecasodium; Alicaforsén sódico; Alicaforsen Sodique; Alicaforsenum Natricum; Isis-2302.

Аликафорсен Натрий

$C_{192}H_{225}N_{75}Na_{19}O_{98}P_{19}S_{19}$ = 6785.8.

CAS — 331257-52-4.

Profile

Alicaforsen is an antisense oligonucleotide that inhibits the production of the cellular adhesion molecule ICAM-1, which plays a role in the inflammatory response involved in inflammatory bowel disease. It has been tried in ulcerative colitis and pouchitis, and with less success in Crohn's disease.

◊ References.

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Alizapride Hydrochloride *(rINNM)*

Alizapride, Chlorhydrate d'; Alizapridi Hydrochloridum; Hidrocloruro de alizaprida. *N*-(1-Allyl-2-pyrrolidinylmethyl)-6-methoxy-1*H*-benzotriazole-5-carboxamide hydrochloride.

Ализаприда Гидрохлорид

$C_{16}H_{21}N_5O_2,HCl$ = 351.8.

CAS — 59338-93-1 (alizapride); 59338-87-3 (alizapride hydrochloride).
ATC — A03FA05.
ATC Vet — QA03FA05.

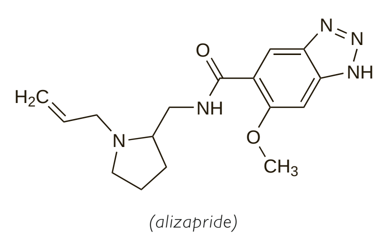

(alizapride)

Adverse Effects and Precautions

As for Metoclopramide, (see p.1748).

Pharmacokinetics

Alizapride is well absorbed from the gastrointestinal tract. It is mainly excreted unchanged in the urine and has an elimination half-life of about 3 hours.

Uses and Administration

Alizapride is a substituted benzamide similar to metoclopramide (p.1749), which is used to control nausea and vomiting (p.1700) associated with a variety of disorders. It is given as the hydrochloride but doses are expressed in terms of the base. Alizapride 50 mg is equivalent to about 55.8 mg of alizapride hydrochloride.

Alizapride hydrochloride is given in usual oral doses equivalent to 75 to 300 mg of alizapride daily in divided doses. For children's doses, see below. It is also given by intravenous or intramuscular injection in doses equivalent to 50 to 200 mg of alizapride daily.

For patients receiving cancer chemotherapy usual daily doses equivalent to alizapride 2 to 5 mg/kg have been given intravenously or intramuscularly in 2 divided doses, one 30 minutes before and one 4 to 8 hours after the cytotoxic regimen. For highly emetic regimens requiring doses above 5 mg/kg it may be given by intravenous infusion over 15 minutes every 2 hours for 5 doses, starting 30 minutes before the cytotoxic. It has been recommended that the total dose given with a course of chemotherapy does not exceed 4.5 g.

Administration in children. Alizapride hydrochloride has been given to children for the symptomatic treatment of nausea and vomiting in oral doses equivalent to 5 mg/kg of alizapride daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gastriveran; ***Belg.:*** Litican; ***Braz.:*** Superan; ***Fr.:*** Plitican; ***Ger.:*** Vergentan; ***Ital.:*** Limican; ***Neth.:*** Litican; ***Port.:*** Plitican†.

Almagate *(BAN, USAN, rINN)*

Almagaatti; Almagát; Almagat; Almagatas; Almagato; Almagatum; LAS-3876. Aluminium trimagnesium carbonate heptahydroxide dihydrate.

Альмагат

$AlMg_3(CO_3)(OH)_7,2H_2O = 315.0.$
CAS — 66827-12-1 (almagate); 72526-11-5 (anhydrous almagate).
ATC — A02AD03.
ATC Vet — QA02AD03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Almagate). A white or almost white, fine crystalline powder. It contains 15.0 to 17.0% aluminium calculated as aluminium oxide, 36.0 to 40.0% magnesium calculated as magnesium oxide, and 12.5 to 14.5% carbonic acid calculated as carbon dioxide. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves with effervescence and heating in dilute mineral acids. The filtrate of a 4% suspension in water has a pH of 9.1 to 9.7. Store in airtight containers.

Profile

Almagate is a hydrated aluminium-magnesium hydroxycarbonate. It is an antacid with general properties similar to those of aluminium hydroxide (p.1706) and magnesium carbonate (p.1743). It is given orally in doses of 1 to 1.5 g.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Almax; ***Spain:*** Almax; Deprece†; Obetine.

Almasilate *(BAN, rINN)*

Almasilato; Almasilatum; Aluminium Magnesium Silicate Hydrate; Magnesium Aluminosilicate Hydrate; Magnesium Aluminum Silicate Hydrate.

Алмазилат

$Al_2O_3.MgO.2SiO_2,xH_2O = 262.4$ (anhydrous).
CAS — 71205-22-6; 50958-44-6.
ATC — A02AD05.
ATC Vet — QA02AD05.

Profile

Almasilate is an artificial form of aluminium magnesium silicate hydrate. It is an antacid (p.1692) that is given orally in doses of up to about 1 g.

A hydrated native aluminium magnesium silicate (p.2141) is used as a suspending, thickening, and stabilising agent in pharmaceutical preparations. Attapulgite (p.1709) is another native form.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gelusil†; ***Ger.:*** Gelusil; Megalac; Simagel; ***Spain:*** Alubifar.

Multi-ingredient: ***Austria:*** Gastripan; ***Ger.:*** Gelusil-Lac; Neo-Pyodron N; Ultilac N; ***India:*** Entasid; ***Spain:*** Dolcopin; ***Switz.:*** Gelusil N.

Aloes

Acíbar; Alavijų sultys, koncentruotos ir išdžiovintos (Cape aloes); Áloe, acíbar; Aloe barbadensis (Barbados aloes); Aloe, Barbados (Barbados aloes); Aloe barbadoská (Barbados aloes); Aloe capensis (Cape aloes); Aloe, Kap (Cape aloes); Aloe kapská (Cape aloes); Aloès des Barbades (Barbados aloes); Aloès du Cap (Cape aloes); Alona barbadoska (Barbados aloes); Alona przylądkowa (Cape aloes); Barbadosi áloé (Barbados aloes); Barbadosin aloe (Barbados aloes); Kap-áloé (Cape aloes); Kapin aloe (Cape aloes); Tikrųjų alavijų sultys, koncentruotos ir išdžiovintos (Barbados aloes).

Алоэ Барбадосское (Barbados aloes); Алоэ Капское (Cape aloes)
CAS — 8001-97-6; 67479-27-0 (aloe gum).

NOTE. Do not confuse with Aloe vera (p.1588).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Aloes, Barbados; Aloe barbadensis). The concentrated and dried juice of the leaves of *Aloe barbadensis.* It contains not less than 28% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses, slightly shiny or opaque with a conchoidal fracture, or a brown powder. Partly soluble in boiling water; soluble in hot alcohol. Store in airtight containers. Protect from light.
The BP 2008 lists Curaçao Aloes as an approved synonym.
Ph. Eur. 6.2 (Aloes, Cape; Aloe capensis). The concentrated and dried juice of the leaves of various species of *Aloe*, mainly *Aloe ferox* and its hybrids. It contains not less than 18% of hydroxyanthracene derivatives expressed as barbaloin and calculated with reference to the dried drug. Dark brown masses tinged with green and having a shiny conchoidal fracture, or a greenish-brown powder. Partly soluble in boiling water; soluble in hot alcohol; practically insoluble in ether. Store in airtight containers. Protect from light.
USP 31 (Aloe). The dried latex of the leaves of *Aloe barbadensis* (*A. vera*) known in commerce as Curaçao Aloe, or of *A. ferox* and its hybrids, known in commerce as Cape Aloe (Liliaceae). It yields not less than 50% of water-soluble extractive. It has a characteristic, somewhat sour and disagreeable, odour. Curaçao Aloe is brownish-black, opaque masses with a fractured, uneven, waxy, and somewhat resinous surface. Cape Aloe is dusty to dark brown irregular masses, the surfaces of which are often covered with a yellowish powder. Its fracture is smooth and glassy.

Adverse Effects and Precautions

As for Senna, p.1769, although aloes has a more drastic and irritant action.

Uses and Administration

Aloes is an anthraquinone stimulant laxative (p.1693) but other less toxic drugs are generally preferred.

Homoeopathy. Aloes have been used in homoeopathic medicines under the following names: Aloe; Cape aloes; Aloe capensis; Aloe socotrina; Alo. soc.

Preparations

BP 2008: Compound Benzoin Tincture;
Ph. Eur.: Aloes Dry Extract, Standardised;
USP 31: Compound Benzoin Tincture.

Proprietary Preparations (details are given in Part 3)
Fr.: Contre-Coups de l'Abbe Perdrigeon; Vulcase; ***Ger.:*** Dr Janssens Teebohnen†; Krauterlax; Rheogen†; ***Pol.:*** Biostymina.

Multi-ingredient: ***Arg.:*** Genolaxante; ***Austral.:*** Herbal Cleanse†; Lexat†; Peritone; ***Austria:*** Artin; Dragees Neunzehn†; Waldheim Abfuhrdragees forte; Waldheim Abfuhrdragees mild; ***Belg.:*** Grains de Vals; ***Braz.:*** Camomila; Paratonico; ***Canad.:*** Extra Strong Formula 12†; Laxative†; ***Chile:*** Aloelax; Bulgarolax; ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; ***Fr.:*** Alco-Aloe; Ideolaxyl; Opobyl; Petites Pilules Carters; Tonilax; ***Ger.:*** Aristochol†; Chol-Kugeletten Neu; Cholhepan N; Pascoletten N†; ***Israel:*** Laxative Comp; ***Ital.:*** Frerichs Maldifassi†; Grani di Vals; Lassativi Vegetali; Puntualax†; ***Pol.:*** Alax; Apinorm; Bioaron C; Boldaloin; Boldovera; Tabulettae Laxantes; ***Rus.:*** Doktor Mom (Доктор Мом); ***S.Afr.:*** Helmontskruie; Lewensessens; Moultons Herbal Extract; Turulington Tincture; Wonderkroonessens; ***Spain:*** Alofedina; Crislaxo; Cynaro Bilina; Laxante Sanatorium; Nico Hepatocyn; Opobyl; Pildoras Zeninas; ***Switz.:*** Padma-Lax; Padmed Laxan; Phytolaxin; Schweden-Mixtur H nouvelle formulation; ***UK:*** Dual-Lax Normal Strength; Laxative Tablets; Natural Herb Tablets; Out-of-Sorts; Senokot Dual Relief; Sure-Lax (Herbal); ***USA:*** Diaparene Corn Starch; Vagisil.

Aloglutamol

Trometamol Glucaldrate. 2-Amino-2-hydroxymethylpropane-1,3-diol gluconate dihydroxyaluminate.

Алоглутамол

$C_{10}H_{24}AlNO_{12} = 377.3.$
CAS — 13755-41-4.
ATC — A02AB06.
ATC Vet — QA02AB06.

Profile

Aloglutamol has been used as an antacid (p.1692).

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Sabro.

Aloin *(BAN)*

Alloin; Aloína.

Алоин

CAS — 5133-19-7; 8015-61-0; 1415-73-2 (barbaloin).

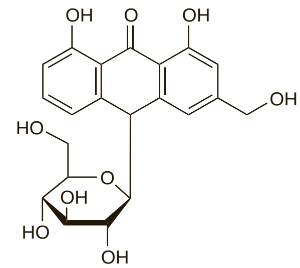

(barbaloin)

Profile

Aloin is a crystalline substance obtained from aloes (see above). It consists of *C*-glycosides such as barbaloin. Aloin is an anthraquinone stimulant laxative. Like aloes it is very irritant and other less toxic laxatives are generally preferred. Aloin is used as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Felaxen†; ***UK:*** Calsalettes.

Multi-ingredient: ***Austral.:*** Ford Pills; ***Braz.:*** Pilulas Ross; ***Canad.:*** Bicholate; ***Hung.:*** Artin†; ***Israel:*** Laxative; Laxative Comp; ***Ital.:*** Boldina He; Cuscutine; Grani di Vals; ***Mex.:*** Redotex; Redotex NF; ***S.Afr.:*** Brooklax Pills; Doans Backache Pills; SB 3 Triple Action Pills; ***Spain:*** Laxante Bescansa Aloico; ***UK:*** Dual-Lax Extra Strong; Modern Herbals Laxative.

Alosetron Hydrochloride *(BANM, USAN, rINNM)*

Alosétron, Chlorhydrate d'; Alosetroni Hydrochloridum; GR-68755C; Hidrocloruro de alosetrón. 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-imidazol-4-yl)methyl]-1*H*-pyrido[4,3-*b*]indol-1-one hydrochloride.

Алосетрона Гидрохлорид

$C_{17}H_{18}N_4O,HCl = 330.8.$
CAS — 122852-42-0 (alosetron); 122852-69-1 (alosetron hydrochloride).
ATC — A03AE01.
ATC Vet — QA03AE01.

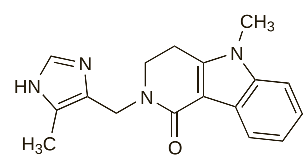

(alosetron)

Adverse Effects

Serious gastrointestinal adverse effects have occurred with alosetron, and as a result, it was withdrawn from the market in the USA and subsequently reintroduced with more restricted indications. These adverse effects include severe constipation leading to obstruction, ileus, perforation, impaction, toxic megacolon, and secondary ischaemia, as well as ischaemic colitis. Fatalities have been reported.

Other gastrointestinal effects reported include abdominal distension and pain, nausea, reflux, and haemorrhoids. Adverse effects reported rarely include cardiac arrhythmias, cholecystitis, altered bilirubin levels, tremor, headache, myalgia, malaise, fatigue, and CNS effects such as confusion, anxiety, depression, and sedation. Urticaria, skin reactions, nail disorders, and alopecia can occur. Hyperglycaemia, hypoglycaemia, and disorders of calcium and phosphate metabolism have been reported.

Incidence of adverse effects. The incidence of serious gastrointestinal adverse effects with alosetron has been reviewed.[1] Pooled data from clinical studies suggested that the rate of ischaemic colitis in patients taking alosetron was about 0.15%, or 6.4 cases per 1000 patient-years. Results from postmarketing surveillance (before and after its temporary withdrawal from the

US market) were estimated to represent a rate of 1 case per 1000 patient-years. Serious complications of constipation did not seem to be increased in the population of alosetron users.

1. Chang L, *et al.* Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol* 2006; **101:** 1069–79.

Precautions

Alosetron should be stopped immediately in patients who develop constipation or symptoms of ischaemic colitis such as new or worsening abdominal pain or blood in the stool. Treatment with alosetron should not be resumed in patients who develop ischaemic colitis.

Alosetron should not be used in patients with a history of severe or chronic constipation, intestinal obstruction or stricture, toxic megacolon, or gastrointestinal perforation or adhesions. It is also contra-indicated in patients with a history of ischaemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state, and those with current or previous inflammatory bowel disease or diverticulitis.

Alosetron should not be used in those with severe hepatic impairment or a history thereof; it should be used with caution in patients with mild to moderate hepatic impairment. Elderly patients may be at increased risk of severe complications if constipation develops.

Interactions

Plasma concentrations of alosetron are markedly increased, and its half-life prolonged roughly threefold, when given with fluvoxamine; such a combination should be avoided. Licensed product information recommends that use with other more moderate inhibitors of cytochrome P450 isoenzyme CYP1A2 (such as quinolone antibacterials and cimetidine) should be avoided unless clinically necessary, because of the risk of similar interactions. Ketoconazole also increases plasma alosetron concentrations; care should be taken if alosetron is used with this or other potent inhibitors of the CYP3A4 isoenzyme (including clarithromycin, telithromycin, HIV-protease inhibitors, voriconazole, and itraconazole).

Pharmacokinetics

Alosetron is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached about 1 hour after an oral dose. Plasma concentrations are 30 to 50% lower in men than in women given the same oral dose; clearance is lower in women. Bioavailability is about 60%; the extent and rate of absorption are slightly reduced by food. Plasma protein binding is about 82%. Alosetron is extensively metabolised via cytochrome P450 isoenzymes, particularly CYP1A2, although CYP2C9 and CYP3A4 also play a role. Numerous metabolites are excreted in the urine and faeces; only 6% of a dose is recovered unchanged from the urine. The terminal elimination half-life of alosetron is reported to be about 1.5 hours.

◊ References.

1. Koch KM, *et al.* Sex and age differences in the pharmacokinetics of alosetron. *Br J Clin Pharmacol* 2002; **53:** 238–42.

Uses and Administration

Alosetron is a 5-HT_3 antagonist used in the treatment of severe diarrhoea-predominant irritable bowel syndrome (p.1699) in women who have not responded to conventional therapy; effectiveness in men has not been established. It is given orally as the hydrochloride but doses are expressed in terms of the base; alosetron hydrochloride 1.12 mg is equivalent to about 1 mg of alosetron.

The initial dose is the equivalent of alosetron 500 micrograms twice daily for 4 weeks; if tolerated, the dose may then be increased if necessary to 1 mg twice daily. If symptoms are not adequately controlled after 4 weeks of treatment with the higher dose, alosetron should be stopped.

◊ References.

1. Lembo A, *et al.* Alosetron in irritable bowel syndrome: strategies for its use in a common gastrointestinal disorder. *Drugs* 2003; **63:** 1895–1905.
2. Mayer EA, Bradesi S. Alosetron and irritable bowel syndrome. *Expert Opin Pharmacother* 2003; **4:** 2089–98.
3. Cremonini F, *et al.* Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003; **15:** 79–86.
4. Andresen V, Hollerbach S. Reassessing the benefits and risks of alosetron: what is its place in the treatment of irritable bowel syndrome? *Drug Safety* 2004; **27:** 283–92.
5. Lembo AJ, *et al.* Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: analysis of two controlled trials. *Clin Gastroenterol Hepatol* 2004; **2:** 675–82.
6. Chey WD, *et al.* Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2004; **99:** 2195–2203.
7. Chang L, *et al.* A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol* 2005; **100:** 115–23.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lotronex†; ***Mex.:*** Liminos†; ***USA:*** Lotronex.

Basic Aluminium Carbonate

Aluminium Hydroxycarbonate; Aluminum Carbonate, Basic *(USAN)*; Carbonato básico de aluminio.

Основный Углекислый Алюминий

Profile

Basic aluminium carbonate is a combination of aluminium hydroxide and aluminium carbonate. It is an antacid with general properties similar to those of aluminium hydroxide (below).

Basic aluminium carbonate has also been given orally as a phosphate binder in the treatment of hyperphosphataemia. For a discussion of the choice of phosphate binders, see Renal Osteodystrophy, p.1086.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Port.:*** Gastropensan.

Aluminium Formate

Aluminium Triformate.

Муравьинокислый Алюминий; Формиат Алюминия

$Al(CHO_2)_3,3H_2O = 216.1.$

CAS — 7360-53-4 (anhydrous aluminium formate).

Profile

Aluminium formate has astringent properties and has been used in topical preparations for mouth disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Dynexan Zahnfleischtropfen.

Multi-ingredient: ***Austria:*** Cional; Dynexan; Methyment; ***S.Afr.:*** Dynexan.

Aluminium Glycinate

Aluminio, glicinato de; Basic Aluminium Aminoacetate; Dihydroxyaluminum Aminoacetate. (Glycinato-*N*,*O*)dihydroxyaluminium hydrate.

Алюминия Глицинат

$C_2H_6AlNO_4(+xH_2O) = 135.1$ (anhydrous).

CAS — 13682-92-3 (anhydrous aluminium glycinate); 41354-48-7 (aluminium glycinate hydrate).

ATC — A02AB07.

ATC Vet — QA02AB07.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Aluminium Glycinate). A white or almost white, odourless or almost odourless, powder. It contains 34.5 to 38.5% of Al_2O_3 calculated on the dried substance, and not more than 12% loss of weight on drying. Practically insoluble in water and in organic solvents; it dissolves in dilute mineral acids and in aqueous solutions of alkali hydroxides. A 4% suspension in water has a pH of 6.5 to 7.5.

USP 31 (Dihydroxyaluminum Aminoacetate). A white, odourless, powder. It may contain small amounts of aluminium oxide and aminoacetic acid. It loses not more than 14.5% of its weight on drying. Insoluble in water and in organic solvents; soluble in dilute mineral acids and in solutions of fixed alkalis. A 4% suspension in water has a pH of 6.5 to 7.5.

Profile

Aluminium glycinate is an antacid with general properties similar to those of aluminium hydroxide (below). It has been given in doses of up to 1 g by mouth.

Preparations

USP 31: Dihydroxyaluminum Aminoacetate Magma.

Proprietary Preparations (details are given in Part 3)
Denm.: Almin.

Multi-ingredient: ***Arg.:*** Dafne; ***Austria:*** Gastripan; ***Belg.:*** Alucid; ***Chile:*** Sinacid; ***Denm.:*** Alminox; ***Fr.:*** Acidrine; ***Ger.:*** Acidrine†; ***Gr.:*** Novalox; ***Indon.:*** Acidrine; ***Ital.:*** Acidrine; ***Pol.:*** Proacid; ***Spain:*** Gastroglutal†; Meteoril; Natrocitral; Secrepat.

Used as an adjunct in: ***Austria:*** Ambene N; Indobene; ***Braz.:*** Reumix†; Somalgin; ***Chile:*** Butartrol; Flexono; ***Ger.:*** Indomet-ratiopharm m†; ***Ital.:*** Aspirina 03; ***Switz.:*** Bonidon; ***USA:*** Buffex.

Aluminium Hydroxide

Aliuminio hidroksidas; Alumiinihydroksidi; Aluminii Hydroxidum; Aluminii oxidum hydricum; Aluminium Oxidum Hydricum; Aluminium (oxyde d') hydraté; Aluminiumhydroxid; Aluminum Hydroxide; Alüminyum Hidroksit; Glinu wodorotlenek; Hidróxido de aluminio; Hydroxid hlinitý; Wasserhaltiges Aluminiumoxid.

Алюминий Гидроксид

CAS — 21645-51-2 [$Al(OH)_3$].

ATC — A02AB01.

ATC Vet — QA02AB01.

NOTE. Algeldrate (*USAN*, *pINN*) is defined as a hydrated aluminium hydroxide with the general formula of $Al(OH)_3,xH_2O$.

Compounded preparations of aluminium hydroxide may be represented by the following names:

- Co-magaldrox *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Aluminium Oxide, Hydrated; Dried Aluminium Hydroxide BP 2008). It contains the equivalent of 47 to 60% Al_2O_3. It is a white or almost white, amorphous powder. Practically insoluble in water; it dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers at a temperature not exceeding 30°.

Ph. Eur. 6.2 (Aluminium Hydroxide, Hydrated, for Adsorption; Aluminii Hydroxidum Hydricum ad Adsorptionem). A white or almost white, translucent, viscous, colloidal gel. A supernatant may be formed upon standing. A clear or almost clear solution is obtained with alkali hydroxide solutions and with mineral acids. pH 5.5 to 8.5. Store at a temperature not exceeding 30°. Do not allow to freeze.

USP 31 (Aluminum Hydroxide Gel). A suspension of amorphous aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It is a white viscous suspension from which small amounts of clear liquid may separate on standing. It has a pH of between 5.5 and 8.0. Store in airtight containers. Avoid freezing.

USP 31 (Dried Aluminum Hydroxide Gel). An amorphous form of aluminium hydroxide in which there is a partial substitution of carbonate for hydroxide. It contains the equivalent of not less than 76.5% of $Al(OH)_3$ and may contain varying quantities of basic aluminium carbonate and bicarbonate. The labelling requirements states that 1 g of dried aluminium hydroxide gel is equivalent to 765 mg of $Al(OH)_3$. It is a white, odourless, tasteless, amorphous powder. Insoluble in water and in alcohol; soluble in dilute mineral acids and in solutions of fixed alkali hydroxides. A 4% aqueous dispersion has a pH of not more than 10.0. Store in airtight containers.

Adverse Effects and Precautions

Aluminium hydroxide, like other aluminium compounds, is astringent and may cause constipation; large doses can cause intestinal obstruction.

Excessive doses, or even normal doses in patients with low-phosphate diets, may lead to phosphate depletion accompanied by increased bone resorption and hypercalciuria with the risk of osteomalacia.

Aluminium salts are not, in general, well absorbed from the gastrointestinal tract, and systemic effects are therefore rare in patients with normal renal function. However, care is necessary in patients with chronic renal impairment: osteomalacia or adynamic bone disease, encephalopathy, dementia, and microcytic hypochromic anaemia have been associated with aluminium accumulation in such patients given large doses of aluminium hydroxide as a phosphate-binding agent. Similar adverse effects have also been associated with the aluminium content of dialysis fluids.

Aluminium hydroxide used as an adjuvant in adsorbed vaccines has been associated with the formation of granulomas.

Children. For the suggestion that aluminium-containing antacids should not be used in infants, see Toxicity, below.

Porphyria. Aluminium hydroxide is considered by some to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals.*

UK licensed product information states that aluminium hydroxide may be unsafe in patients with porphyria undergoing haemodialysis.

Toxicity. References to aluminium toxicity in dialysis patients and the possible association between aluminium ingestion and Alzheimer's disease are included under Aluminium (see p.2254).

Aluminium accumulation does not generally appear to be significant in patients with normal renal function taking therapeutic doses of aluminium-containing antacids, and there is little evidence that such antacids are a risk factor for Alzheimer's disease.[1] Elevated plasma-aluminium concentrations have been reported in infants with normal renal function given aluminium-containing antacids but there were no obvious signs of toxicity.[2] There have, however, been reports of phosphate depletion and rickets in a few infants caused by the use of antacids containing magnesium and aluminium hydroxides. In these cases the antacid had been started within a few months of birth and continued for up to 8 months. In reports that described a total of 3 infants,[3,4] the authors suggested that the use of soya-based infant feeding formulas, the phytates of which can interfere with mineral absorption, may have exacerbated the phosphate-binding effect of the antacid. In another case[5] a dosing error resulted in the infant receiving an excessive dose of antacid for 6 months. The *BNFC* advises against the use of any aluminium-containing antacid in neonates and infants.

Aluminium accumulation resulting in osteomalacia or encephalopathy with seizures and dementia has been reported in children with renal failure (but not on dialysis) treated with aluminium-containing phosphate binders.[6-10] In an adult male patient with severe chronic renal failure who was not on dialysis, self-medication with antacids for at least 3 years resulted in aluminium toxicity associated with encephalopathy, bone disease, and microcytic anaemia.[11] Aluminium-containing antacids should therefore be used with caution in patients with chronic renal failure, especially in children.

Oral citrate salts increase the absorption of aluminium from the gastrointestinal tract[12] and patients with renal failure taking aluminium compounds should avoid citrate-containing preparations, which include many effervescent or dispersible tablets.[13,14] Ascorbic acid has also been reported to enhance aluminium absorption.[15]

1. Flaten TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45:** 203–6.
2. Tsou VM, *et al.* Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991; **87:** 148–51.
3. Pivnick EK, *et al.* Rickets secondary to phosphate depletion: a sequela of antacid use in infancy. *Clin Pediatr (Phila)* 1995; **34:** 73–8.
4. Shetty AK, *et al.* Rickets and secondary craniosynostosis associated with long-term antacid use in an infant. *Arch Pediatr Adolesc Med* 1998; **152:** 1243–5.
5. Robinson RF, *et al.* Metabolic bone disease after chronic antacid administration in an infant. *Ann Pharmacother* 2004 **38:** 265–8.
6. Pedersen S, Nathan E. Water treatment and dialysis dementia. *Lancet* 1982; **ii:** 1107.
7. Griswold WR, *et al.* Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. *Pediatrics* 1983; **71:** 56–8.
8. Randall ME. Aluminium toxicity in an infant not on dialysis. *Lancet* 1983; **i:** 1327–8.
9. Sedman AB, *et al.* Encephalopathy in childhood secondary to aluminum toxicity. *J Pediatr* 1984; **105:** 836–8.
10. Andreoli SP, *et al.* Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. *N Engl J Med* 1984; **310:** 1079–84.
11. Zatta P, *et al.* A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis. *Nephrol Dial Transplant* 2004; **19:** 2929–31.
12. Walker JA, *et al.* The effect of oral bases on enteral aluminum absorption. *Arch Intern Med* 1990; **150:** 2037–9.
13. Mees EJD, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59:** 322.
14. Main J, Ward MK. Potentiation of aluminium absorption by effervescent analgesic tablets in a haemodialysis patient. *BMJ* 1992; **304:** 1686.
15. Domingo JL, *et al.* Effect of ascorbic acid on gastrointestinal aluminium absorption. *Lancet* 1992; **338:** 1467.

Interactions

As outlined on p.1692, aluminium compounds used as antacids interact with many other drugs, both by alterations in gastric pH and emptying, and by direct adsorption and formation of complexes that are not absorbed. Interactions can be minimised by giving the aluminium compound and any other medication 2 to 3 hours apart. The absorption of aluminium from the gastrointestinal tract may be enhanced if aluminium compounds are taken with citrates or ascorbic acid (see Toxicity, above).

Pharmacokinetics

Aluminium hydroxide, given orally, slowly reacts with the hydrochloric acid in the stomach to form soluble aluminium chloride, some of which is absorbed. The presence of food or other factors that decrease gastric emptying prolongs the availability of aluminium hydroxide to react and may increase the amount of aluminium chloride formed. About 100 to 500 micrograms of the cation is reported to be absorbed from standard daily doses of an aluminium-containing antacid, leading to about a doubling of usual aluminium concentrations in the plasma of patients with normal renal function.

Absorbed aluminium is eliminated in the urine, and patients with renal failure are therefore at particular risk of accumulation (especially in bone and the CNS), and aluminium toxicity (see above).

The aluminium compounds remaining in the gastrointestinal tract, which account for most of a dose, form insoluble, poorly absorbed aluminium salts in the intestines including hydroxides, carbonates, phosphates and fatty acid derivatives, which are excreted in the faeces.

Uses and Administration

Aluminium hydroxide is used as an antacid (p.1692). It is given orally in doses of up to about 1 g, between meals and at bedtime. In order to reduce the constipating effects, aluminium hydroxide is often given with a magnesium-containing antacid, such as magnesium oxide or magnesium hydroxide.

Aluminium hydroxide binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It may thus be used to treat hyperphosphataemia in patients with chronic renal failure (although aluminium accumulation may be a problem—see Renal Osteodystrophy, p.1086) or associated secondary hyperparathyroidism (p.1087). With this use the dose must be adjusted to the individual patient's requirement but up to about 10 g daily may be given orally in divided doses with meals.

Aluminium hydroxide is also used as an adjuvant in adsorbed vaccines.

Polymyositis and dermatomyositis. Corticosteroids form the basis of the management of polymyositis (p.1510) but the calcinosis that may occur in dermatomyositis does not always respond well. Aluminium hydroxide 1.68 to 2.24 g daily produced clinical improvement with complete clearing of most calcified nodules after 1 year in a patient with calcinosis cutis complicating juvenile dermatomyositis.[1] The calcified masses are made up of hydroxyapatite and amorphous calcium phosphate and reduction in phosphate absorption by aluminium hydroxide probably helped to reverse their formation. Subsequent cases[2,3] have also reported benefit from aluminium hydroxide treatment in the management of calcinosis.

1. Wang W-J, *et al.* Calcinosis cutis in juvenile dermatomyositis: remarkable response to aluminium hydroxide therapy. *Arch Dermatol* 1988; **124:** 1721–2.
2. Nakagawa T, Takaiwa T. Calcinosis cutis in juvenile dermatomyositis responsive to aluminium hydroxide treatment. *J Dermatol* 1993; **20:** 558–60.
3. Wananukul S, *et al.* Calcinosis cutis presenting years before other clinical manifestations of juvenile dermatomyositis: report of two cases. *Australas J Dermatol* 1997; **38:** 202–5.

Preparations

BP 2008: Aluminium Hydroxide Oral Suspension; Aluminium Hydroxide Tablets; Co-magaldrox Oral Suspension; Co-magaldrox Tablets; Compound Magnesium Trisilicate Tablets;
USP 31: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aluminum Hydroxide Gel; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Dried Aluminum Hydroxide Gel; Dried Aluminum Hydroxide Gel Capsules; Dried Aluminum Hydroxide Gel Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Pepsamar; ***Austral.:*** Alu-Tab; ***Austria:*** Anti-Phosphat; ***Braz.:*** Aludroxil; Aziram; Biodrox†; Ductogel; Fluagel†; Gastromax; Gastrox; Gelpan†; Hidroxialiv†; Kaogel†; Mylanta Plus; Natusgel†; Noacid†; Pepsamar; Peptgel; ***Canad.:*** Alu-Tab†; Alugel; Amphojel; Basaljel; ***Chile:*** Risthal†; ***Ger.:*** Aludrox; Anti-Phosphat; ***Gr.:*** Alu-Cap; Pepsamar; ***Hong Kong:*** Alu-Tab; ***India:*** Aludrox; Tricaine-MPS; ***Irl.:*** Aludrox; ***Israel:*** Alu-Cap; ***Ital.:*** Polisilon†; ***Malaysia:*** Alu-Tab; ***Mex.:*** Domigel; Magnalum†; ***NZ:*** Alu-Tab; Amphojel†; ***Philipp.:*** Alu-Tab; ***Pol.:*** Alusal; ***Port.:*** Gelumina†; Pepsamar; ***S.Afr.:*** Alukon; Amphojel; ***Singapore:*** Alu-Tab; ***Spain:*** Alugel; Pepsamar; ***Switz.:*** Anti-phosphate; Gastracol; ***UK:*** Alu-Cap; Aludrox†; ***USA:*** ALternaGEL; Alu-Cap†; Alu-Tab; Amphojel; Dialume; Nephrox; ***Venez.:*** Gelidral†.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Arg.:*** Dristan Analgesico†; Dristan Compuesto; Truxa R†; ***Braz.:*** Analtrix†; Butazolon†; Posdrink; Redentil†; Resprax; ***Canad.:*** C2 with Codeine†; ***Chile:*** Silartrin†; ***Fr.:*** Finidol†; ***Gr.:*** Ascriptin†; ***Indon.:*** Naspro; ***Israel:*** Ascriptin†; ***Ital.:*** Ascriptin; Via Mal; ***Mex.:*** Ascriptin; Meproso-na-F; ***Switz.:*** Alcacyl; Contre-Douleurs plus; Contre-Douleurs†; ***USA:*** Arthritis Pain Formula; Ascriptin; Asprimox; Cama Arthritis Pain Reliever; Cope; Magnaprin†; Vanquish; ***Venez.:*** Ascriptin.

Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel

F-MA 11; Hidróxido de aluminio y carbonato de magnesio desecado, gel de.

Profile

Aluminium hydroxide-magnesium carbonate co-dried gel is a co-precipitate of aluminium hydroxide and magnesium carbonate dried to contain a proportion of water for antacid activity. It is an antacid with general properties similar to those of aluminium hydroxide (above) and magnesium carbonate (p.1743). It has been given in oral doses of about 450 to 900 mg, usually 3 times daily after meals and before bedtime.

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Link; ***Fin.:*** Link; PeeHoo†; ***Gr.:*** Regla pH†; ***Indon.:*** Stomacain; Veragel; ***Mex.:*** Gelasim; ***Neth.:*** Regla pH; Remegel; ***Norw.:*** Link; ***Swed.:*** Link; ***UK:*** Dijex†.

Multi-ingredient: ***Belg.:*** Barexal; Nozid†; Regla pH Forte†; Syngel; ***Braz.:*** Andursil; ***Canad.:*** Diovol; Diovol Plus; Gastrocalm; Thunas Hyperacidity Tablets†; ***Chile:*** Algicote; Disfrutab; Ditopax; ***Fr.:*** Gastropulgite; ***Ger.:*** Colina Spezial; Duoventrinetten N; ***Hong Kong:*** Diovol Plus; Simeco†; Veragel; ***Indon.:*** Aludonna; Di-Gel; Farmacrol; Gastran; Oskamag; Polycrol; Simeco; ***Irl.:*** Algicon†; ***Israel:*** Silain; ***Mex.:*** Algicon†; Ditopax; Ditopax-F; ***Neth.:*** Algicon; Muthesa N; Rigoletten; ***Port.:*** Di-Gel; Di-Gel Forte†; ***Rus.:*** Gastal (Гастал); ***Singapore:*** Meclosil; Veragel DMS; ***Spain:*** Acilene†; Acylene†; ***Switz.:*** Anacidol†; Andursil; Gastropulgite†; Refluxine†; ***Thai.:*** Defomil; Diovol; Kremil; Kremil-S; Machto; Simeco; Veragel; ***UK:*** Algicon†; Simeco; ***Venez.:*** Ditosil.

Used as an adjunct in: ***Indon.:*** Rheumapill.

Aluminium Phosphate

Aliuminio fosfatas; Alumiinifosfaatti; Aluminii phosphas; Aluminio, fosfato de; Aluminium, phosphate d'; Aluminiumfosfát; Alumínium-foszfát; Aluminum Phosphate; Fosfato de aluminio; Fosforečnan hlinitý; Glinu fosforan; Glinu fosforanu.

Алюминия Фосфат

CAS — 7784-30-7 ($AlPO_4$).

ATC — A02AB03.

ATC Vet — QA02AB03.

Pharmacopoeias. In *Viet.*

Eur. (see p.vii) includes hydrated aluminium phosphate and also a gel. *US* includes as a gel.

Ph. Eur. 6.2 (Aluminium Phosphate, Hydrated; Aluminii Phosphas Hydricus; Dried Aluminium Phosphate BP 2008). A white or almost white powder. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. A 4% suspension in water has a pH of 5.5 to 7.2. Store in airtight containers.

Ph. Eur. 6.2 (Aluminium Phosphate Gel; Aluminii Phosphatis Liquamen). It is aluminium phosphate in gel form containing 19 to 21% of $AlPO_4$. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids. pH 6.0 to 8.0. Store in airtight containers.

USP 31 (Aluminum Phosphate Gel). A 4 to 5% suspension of aluminium phosphate ($AlPO_4$) in water and has a pH of 6.0 to 7.2. It is a white viscous suspension from which small amounts of water separate on standing. Store in airtight containers.

Profile

Aluminium phosphate is an antacid with general properties similar to those of aluminium hydroxide (p.1706), but it does not produce phosphate depletion.

Aluminium phosphate is also used as an adjuvant in adsorbed vaccines.

Preparations

USP 31: Aluminum Phosphate Gel.

Proprietary Preparations (details are given in Part 3)

Austria: Phosphalugel; ***Belg.:*** Phosphalugel†; ***Cz.:*** Gasterin†; ***Fr.:*** Phosphalugel; ***Ger.:*** Phosphalugel; ***Ital.:*** Fosfalugel; ***Port.:*** Phosphalugel; ***Rus.:*** Phosphalugel (Фосфалюгель); ***Switz.:*** Phosphalugel†.

Multi-ingredient: ***Austria:*** Phoscortil; ***Fr.:*** Moxydar; Seroxydar.

Aluminium Sodium Silicate

E554; Natrii aluminii silicas; Silicato de sodio y de aluminio; Sodium Aluminium Silicate; Sodium Aluminosilicate; Sodium et aluminium, silicate de; Sodium Silicoaluminate.

Алюмосиликат Натрия

CAS — 1344-00-9.

Profile

Aluminium sodium silicate is an antacid with general properties similar to those of aluminium hydroxide (p.1706). Aluminium silicate has been used similarly. They are also used as food additives.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Sulfuryl; ***Port.:*** Acnoil Free.

Multi-ingredient: ***Austria:*** Diphlogen; ***Fr.:*** Anti-H†; Cerat Inalterable; Sulfuryl; ***Ger.:*** Enelbin-Paste N; Sulfredox†; ***Hong Kong:*** Epilon; ***Port.:*** Mucal†; ***Thai.:*** Ulgastrin.

Alverine Citrate *(BANM, USAN, rINNM)*

Alvérine, citrate d'; Alverini citras; Citrato de alverina; Dipropyline Citrate; Phenpropamine Citrate. *N*-Ethyl-3,3′-diphenyldipropylamine citrate.

Альверина Цитрат

$C_{20}H_{27}N,C_6H_8O_7$ = 473.6.

CAS — 150-59-4 (alverine); 5560-59-8 (alverine citrate).

ATC — A03AX08.

ATC Vet — QA03AX08.

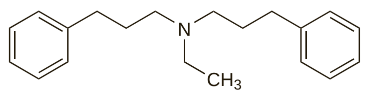

(alverine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Alverine Citrate). A white or almost white crystalline powder. Slightly soluble in water and in dichloromethane; sparingly soluble in alcohol. A 0.5% solution in water has a pH of 3.5 to 4.5. Protect from light.

Adverse Effects and Precautions

Nausea, headache, pruritus, rash, and dizziness have been reported. Allergic reactions, including anaphylaxis, have also occurred. Alverine is contra-indicated in patients with intestinal obstruction or paralytic ileus.

Effects on the liver. Acute hepatitis was attributed to alverine citrate in 2 separate cases.[1,2] Evidence of an immune reaction, including antinuclear antibodies, was found in 1 case.[1]

1. Malka D, *et al.* Acute hepatitis caused by alverine associated with anti-lamin A and C autoantibodies. *J Hepatol* 1997; **27:** 399–403.
2. Arhan M, *et al.* Alverine citrate induced acute hepatitis. *World J Gastroenterol* 2004; **10:** 2303–4.

Pharmacokinetics

Alverine is absorbed from the gastrointestinal tract after oral doses and is rapidly metabolised to an active metabolite, peak plasma concentrations of which occur 1 to 1.5 hours after an oral dose. Further metabolism to inactive metabolites occurs; metabolites are excreted in the urine by active renal secretion.

Uses and Administration

Alverine is an antispasmodic that acts directly on intestinal and uterine smooth muscle. It is used for the relief of smooth muscle spasm in the treatment of gastrointestinal disorders such as irritable bowel syndrome (p.1699). It is also used in the treatment of dysmenorrhoea (p.6).

Alverine citrate is given to adults and adolescents from the age of 12 years in oral doses of 60 to 120 mg one to three times daily. Alverine has also been given by suppository as the base. Alverine citrate 67.3 mg is equivalent to about 40 mg of alverine.

Irritable bowel syndrome. Alverine citrate is widely used as an antispasmodic in the management of irritable bowel syndrome. However, a 12-week study[1] in 107 patients found that alverine citrate was no better than placebo for the relief of symptoms and improvement in general well-being. A marked placebo effect occurred and symptomatic improvement was reported by at least half the placebo group.

1. Mitchell SA, *et al.* Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: results of a double-blind, randomized, placebo-controlled trial. *Aliment Pharmacol Ther* 2002; **16:** 1187–95.

Preparations

BP 2008: Alverine Capsules.

Proprietary Preparations (details are given in Part 3)

Belg.: Spasmine; ***Hong Kong:*** Profenil; Spasmonal; ***Irl.:*** Spasmonal; ***Malaysia:*** Spasmonal†; ***Pol.:*** Spasmolina; ***Singapore:*** Spasmonal; ***Thai.:*** Spasmonal; ***UK:*** Relaxyl†; Spasmonal.

Multi-ingredient: ***Arg.:*** Meteospasmyl; ***Austral.:*** Alvercol†; ***Belg.:*** Normacol Antispasmodique†; ***Cz.:*** Meteospasmyl; ***Fr.:*** Hepatoum; Meteospasmyl; Schoum; ***Hung.:*** Meteospasmyl; ***Indon.:*** Spasmium; ***Malaysia:*** Meteospasmyl; ***Mex.:*** Meteospasmyl; ***Pol.:*** Meteospasmyl; ***Rus.:*** Meteospasmyl (Метеоспазмил); ***S.Afr.:*** Alvercol†; ***Singapore:*** Meteospasmyl; ***Thai.:*** Meteospasmyl; ***Turk.:*** Meteospasmyl; ***UK:*** Spasmonal Fibre†.

Alvimopan *(BAN, USAN, rINN)*

ADL-8-2698; Alvimopán; Alvimopanum; LY-246736. [((2*S*)-2-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-3-phenylpropanoyl)amino]acetic acid.

Альвимопан

$C_{25}H_{32}N_2O_4$ = 424.5.

CAS — 156053-89-3 (anhydrous alvimopan); 170098-38-1 (alvimopan dihydrate).

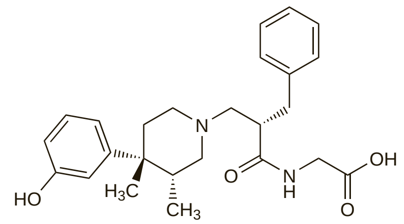

(anhydrous alvimopan)

Profile

Alvimopan is a peripherally acting selective antagonist of opioid μ-receptors that is used in the treatment of postoperative ileus. It is given in a 12-mg oral dose between 30 minutes and up to 5 hours before surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days. Alvimopan is also under investigation for opioid-induced constipation.

◊ References.

1. Taguchi A, *et al.* Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001; **345:** 935–40.
2. Leslie JB. Alvimopan for the management of postoperative ileus. *Ann Pharmacother* 2005; **39:** 1502–10.
3. Herzog TJ, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. *Am J Obstet Gynecol* 2006; **195:** 445–53.
4. Tan EK, *et al.* Meta-analysis: Alvimopan vs. placebo in the treatment of post-operative ileus. *Aliment Pharmacol Ther* 2007; **25:** 47–57.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Entereg.

Aprepitant *(USAN, rINN)*

Aprépitant; Aprepitantum; L-754030; MK-869; MK-0869. 3-[((2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-{[(α*R*)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy}morpholino)methyl]-Δ^2-1,2,4-triazolin-5-one.

Апрепитант

$C_{23}H_{21}F_7N_4O_3$ = 534.4.

CAS — 170729-80-3.

ATC — A04AD12.

ATC Vet — QA04AD12.

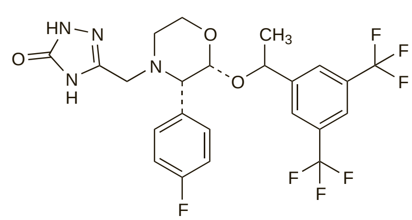

Adverse Effects and Precautions

The most common adverse effects associated with aprepitant are headache, constipation, diarrhoea, dyspepsia, anorexia, fatigue, hiccups, eructation, and dizziness. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are common. Other reported effects have included abdominal pain, oedema, tinnitus, and flushing. Epigastric discomfort, dysgeusia, dry mouth, and stomatitis have also occurred. Thirst, polyuria, dysuria, haematuria, urinary frequency, arthralgia, myalgia, bradycardia, hyperglycaemia, disorientation, euphoria, anxiety, photosensitivity, and skin disorders have been reported. Anaemia and febrile neutropenia may occur. Other adverse effects reported include hypertension or hypotension, hyponatraemia, hypokalaemia, insomnia, miosis, reduced visual acuity, weight changes, sensory disturbances, throat irritation, sneezing, abnormal bowel sounds, acid reflux, perforating duodenal ulcer, dyspnoea, cough, wheezing, and hyperhidrosis. Conjunctivitis, pharyngitis, respiratory-tract infections, urinary-tract infections, candidiasis, and herpes simplex can occur. Stevens-Johnson syndrome and angioedema with urticaria have been reported.

Licensed product information recommends caution in patients with severe hepatic impairment as clinical data are lacking in this patient group.

Interactions

During its use for 3 or 4 days in the prevention of nausea and vomiting associated with cancer chemotherapy, aprepitant produces moderate inhibition of the cytochrome P450 isoenzyme CYP3A4. Exposure to oral CYP3A4 substrates may increase substantially; the effect of aprepitant on intravenous CYP3A4 substrates is expected to be less. However, on cessation of aprepitant a transient mild induction of CYP3A4 may become apparent with a maximum effect reached 3 to 5 days later; this effect is maintained for a few days then slowly declines and is clinically insignificant about 2 weeks after stopping aprepitant. Caution is therefore required when using it with drugs that are primarily metabolised by this isoenzyme. Aprepitant should not be given with astemizole, cisapride, pimozide, or terfenadine as increased plasma concentrations of these drugs could cause serious life-threatening reactions. As aprepitant is also a substrate for CYP3A4, other drugs that inhibit or induce this isoenzyme may in turn increase or decrease plasma concentrations of aprepitant.

When aprepitant is used to prevent postoperative nausea and vomiting, in a single lower dose than that used with cancer chemotherapy, the effect of aprepitant on CYP3A4 is not expected to be clinically significant.

Aprepitant also causes a delayed induction of CYP2C9 and may lower plasma concentrations of drugs metabolised by this isoenzyme, such as warfarin, phenytoin, or tolbutamide.

Aprepitant may increase systemic exposure to corticosteroids; when given together it is recommended that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. It should be noted that the dose of dexamethasone in the regimens recommended for nausea and vomiting associated with cancer chemotherapy already accounts for this interaction (see Administration, below).

The efficacy of oral contraceptives might be reduced by aprepitant. Licensed product information suggests that alternative methods of contraception should be used during and for 1 to 2 months after stopping any dose of aprepitant.

Pharmacokinetics

Aprepitant is absorbed from the gastrointestinal tract with peak plasma concentrations achieved after about 4 hours. Bioavailability is about 60% at usual doses. It crosses the blood-brain barrier; plasma protein binding is reported to be more than 95%. Aprepitant undergoes extensive hepatic metabolism, mainly via oxidation by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP1A2 and CYP2C19 mediate minor metabolic pathways. The resultant metabolites have weak activity and are excreted in the urine and in the faeces. Aprepitant is not excreted unchanged in the urine. The terminal half-life is about 9 to 13 hours.

◊ References.

1. Majumdar AK, *et al.* Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *J Clin Pharmacol* 2006; **46:** 291–300.

Uses and Administration

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist used in the management of nausea and vomiting (p.1700). It is given orally in doses up to 125 mg, with a corticosteroid and a 5-HT_3 antagonist, in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy (for details, see Administration, below).

For the prevention of postoperative nausea and vomiting a single oral dose of aprepitant 40 mg may be given within the 3 hours before induction of anaesthesia.

Administration. Licensed product information for aprepitant suggests the following 4-day regimen for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy:

- day 1: aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg and intravenous ondansetron 32 mg (both 30 minutes before chemotherapy)
- days 2 and 3: aprepitant 80 mg with oral dexamethasone 8 mg in the morning
- day 4: oral dexamethasone 8 mg in the morning.

In patients receiving moderately emetogenic chemotherapy, a 3-day regimen has been suggested as follows:

- day 1: aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg (30 minutes before chemotherapy); ondansetron is given in 2 doses of 8 mg by mouth, one taken 30 to 60 minutes before chemotherapy, and one taken 8 hours after the first dose
- days 2 and 3: aprepitant 80 mg in the morning.

Administration in renal impairment. A study in 8 patients with severe renal impairment (24-hour creatinine clearance less than 30 mL/minute per 1.73 m^2) and 8 patients with end-stage renal disease requiring haemodialysis found that pharmacokinetic parameters of aprepitant were not sufficiently different from those in 16 matched controls to warrant dosage adjustment in renal impairment.[1] Licensed product information concurs with this.

1. Bergman AJ, *et al.* Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clin Pharmacokinet* 2005; **44:** 637–47.

Nausea and vomiting. Studies[1-8] and reviews.[9,10]

1. Campos D, *et al.* Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001; **19:** 1759–67.
2. Poli-Bigelli S, *et al.* Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97:** 3090–8.
3. de Wit R, *et al.* Addition of the oral NK antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol* 2003; **21:** 4105–11.
4. Hesketh PJ, *et al.* The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003; **21:** 4112–19.
5. Warr DG, *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005; **23:** 2822–30. Correction. *ibid.*; 5851. [dosage error in abstract]
6. Warr DG, *et al.* The oral NK antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. *Eur J Cancer* 2005; **41:** 1278–85.
7. Herrstedt J, *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005; **104:** 1548–55.
8. Diemunsch P, *et al.* Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. *Curr Med Res Opin* 2007; **23:** 2559–65.
9. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2004; **64:** 777–94.
10. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 2005; **39:** 77–85.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Emend; ***Austral.:*** Emend; ***Belg.:*** Emend; ***Braz.:*** Emend; ***Cz.:*** Emend; ***Denm.:*** Emend; ***Fin.:*** Emend; ***Fr.:*** Emend; ***Ger.:*** Emend; ***Gr.:*** Emend; ***Hong Kong:*** Emend; ***Hung.:*** Emend; ***Irl.:*** Emend; ***Ital.:*** Emend; ***Malaysia:*** Emend; ***Norw.:*** Emend; ***NZ:*** Emend; ***Port.:*** Emend; ***Rus.:*** Emend (Эменд); ***S.Afr.:*** Emend; ***Singapore:*** Emend; ***Spain:*** Emend; ***Swed.:*** Emend; ***Switz.:*** Emend; ***Thai.:*** Emend; ***UK:*** Emend; ***USA:*** Emend; ***Venez.:*** Emend.

Attapulgite

Atapulgit; Atapulgita.

Аттапульгит

CAS — 1337-76-4; 12174-11-7.

ATC — A07BC04.

ATC Vet — QA07BC04.

Pharmacopoeias. In *Br.*

Activated attapulgite is included in *Br., It.,* and *US.* Colloidal activated attapulgite is included in *US.*

BP 2008 (Attapulgite). A purified native hydrated aluminium magnesium silicate essentially consisting of the clay mineral palygorskite. A light, cream or buff, very fine powder, free or almost free from gritty particles. A 5% suspension in water has a pH of 7.0 to 9.5.

BP 2008 (Activated Attapulgite). Attapulgite that has been carefully heated to increase its adsorptive capacity.

USP 31 (Activated Attapulgite). Processed native aluminium magnesium silicate which has been carefully heated. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water.

USP 31 (Colloidal Activated Attapulgite). A native aluminium magnesium silicate that has been purified. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water. A 10% suspension in water has a pH of 7.0 to 9.5.

◊ NOTE. Another native aluminium magnesium silicate is described on p.2141.

Profile

Attapulgite is highly adsorbent and is used in a wide range of products including fertilisers, pesticides, and pharmaceuticals. Activated attapulgite is an adsorbent antidiarrhoeal used as an adjunct in the management of diarrhoea (p.1694) in a daily dose of up to 9 g orally in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Actapulgite; ***Canad.:*** Fowlers; Kaopectate; ***Fr.:*** Actapulgite; ***Hong Kong:*** Gastrosorb; ***Indon.:*** Biodiar; Enterogit; Kaotate; New Diatabs; Teradi; ***Malaysia:*** Entox-P†; ***Philipp.:*** Polymagma; ***Rus.:*** Neointestopan (Неоинтестопан); ***Switz.:*** Actapulgite; ***Thai.:*** Entox-P†; ***Turk.:*** Diyasorb; ***UAE:*** Kaptin II; ***USA:*** Diasorb; Kaopectate Advanced Formula†; Kaopectate Maximum Strength; Rheaban Maximum Strength†; ***Venez.:*** Streptomagma.

Multi-ingredient: ***Arg.:*** Enterobacticel; ***Austral.:*** Diareze; ***Braz.:*** Diazol; Dispeptrin; ***Chile:*** Diaren; Diarfin†; Entero Micinovo; Enterol; Liracol; Nifurat†; ***Fr.:*** Gastropulgite; Mucipulgite; ***Hong Kong:*** Enterocin Compound; ***Indon.:*** Andikap; Arcapec; Diagit; Entrogard; Fitodiar; Licopec; Molagit; Neo Diastop; Neo Entrostop; Neo Koniform; ***Ital.:*** Streptomagma; ***S.Afr.:*** Kantrexil; ***Switz.:*** Gastropulgite†; Mucipulgite†; ***Turk.:*** Streptomagma; ***UK:*** Diocalm Dual Action; ***Venez.:*** Micyn-2; Mycin-2†; Strediazin c Atapulguita†; Streptomagma.

Azasetron Hydrochloride *(rINNM)*

Azasétron, Chlorhydrate d'; Azasetroni Hydrochloridum; Hidrocloruro de azasetrón; Nazasetron Hydrochloride; Y-25130. (±)-6-Chloro-3,4-dihydro-4-methyl-3-oxo-*N*-3-quinuclidinyl-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride.

Азасетрона Гидрохлорид

$C_{17}H_{20}ClN_3O_3,HCl = 386.3.$

CAS — 123040-69-7 (azasetron); 141922-90-9 (azasetron hydrochloride).

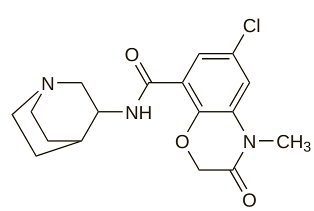

(azasetron)

Profile

Azasetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p.1756). It is used as an antiemetic in the management of nausea and vomiting induced by cytotoxic therapy. Azasetron hydrochloride is given in a usual dose of 10 mg once daily by mouth or intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Serotone†; ***Jpn:*** Serotone.

Balsalazide Sodium *(BANM, rINNM)*

Balsalazida sódica; Balsalazide Disodium *(USAN)*; Balsalazide Sodique; Balsalazine Disodium; BX-661A; Natrii Balsalazidum. 5-[4-(2-Carboxyethylcarbamoyl)phenylazo]salicylic acid, disodium salt, dihydrate.

Натрий Балсалазид

$C_{17}H_{13}N_3Na_2O_6,2H_2O = 437.3.$

CAS — 80573-04-2 (balsalazide); 150399-21-6 (balsalazide disodium dihydrate).

ATC — A07EC04.

ATC Vet — QA07EC04.

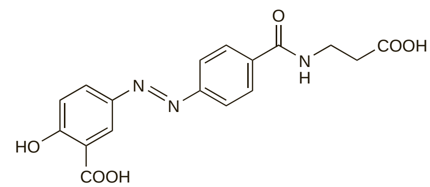

(balsalazide)

Adverse Effects and Precautions

As for Mesalazine, p.1745. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. Balsalazide should not be used in patients with severe hepatic impairment or moderate or severe renal impairment; care is required in those with lesser degrees of hepatic or renal impairment, and in asthma, bleeding disorders, or active peptic ulcer disease.

◊ Reviews.

1. Baker DE. Safety of balsalazide therapy in the treatment of inflammatory bowel disease. *Rev Gastroenterol Disord* 2005; **5:** 135–41.

Hypersensitivity. A case of acute pericarditis, cholestasis, and vasculitis resulting from hypersensitivity to balsalazide has been reported.[1] The authors noted similarities to mesalazine-associated pericarditis and lupus-like syndrome (see Effects on the Cardiovascular System, p.1745).

1. Adhiyaman V, *et al.* Hypersensitivity reaction to balsalazide. *BMJ* 2000; **320:** 613.

Pharmacokinetics

Very little of an oral dose of balsalazide is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 5-aminosalicylic acid (mesalazine), which is active, and 4-aminobenzoylalanine, which is considered to be an inert carrier. About 25% of the released mesalazine is absorbed and acetylated, as described under mesalazine (p.1746). A small proportion of 4-aminobenzoylalanine is absorbed and acetylated by first-pass metabolism through the liver. The acetylated metabolites are excreted in the urine.

Uses and Administration

Balsalazide consists of mesalazine linked to 4-aminobenzoylalanine via an azo bond. This bond is broken by colonic bacteria, releasing the active mesalazine (p.1746). Balsalazide sodium is given in the treatment of mild to moderate active ulcerative colitis (p.1697), in an oral dose of 2.25 g three times daily until remission or for up to 12 weeks. For maintenance of remission of ulcerative colitis a dose of 1.5 g twice daily is recommended, adjusted as necessary up to 6 g daily. For doses in children, see below.

◊ Reviews.

1. Muijsers RBR, Goa KL. Balsalazide: a review of its therapeutic use in mild-to-moderate ulcerative colitis. *Drugs* 2002; **62:** 1689–705.

Administration in children. Balsalazide sodium is not licensed in the UK for use in children under 18 years of age. However, the *BNFC* suggests that, in those aged 12 years and over, 2.25 g may be given orally three times daily for an acute attack of mild to moderate ulcerative colitis, until remission occurs, or for up to 12 weeks. For maintenance, 1.5 g twice daily is recommended, adjusted according to response up to a maximum of 6 g daily.

In the USA, licensed doses in children aged 5 to 17 years are 750 mg three times daily by mouth, or 2.25 g three times daily; treatment may be continued for up to 8 weeks.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Benoquin; ***Austral.:*** Colazide; ***Cz.:*** Colazide†; ***Denm.:*** Premid; ***Ital.:*** Balzide; ***Norw.:*** Colazid; ***UK:*** Colazide; ***USA:*** Colazal.

Multi-ingredient: ***Swed.:*** Colazid.

Benexate Hydrochloride *(rINNM)*

Bénexate, Chlorhydrate de; Benexati Hydrochloridum; Hidrocloruro de benexato. Benzyl salicylate *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride.

Бенексата Гидрохлорид

$C_{23}H_{27}N_3O_4,HCl = 445.9.$

CAS — 78718-52-2 (benexate); 78718-25-9 (benexate hydrochloride); 91574-91-3 (benexate hydrochloride betadex).

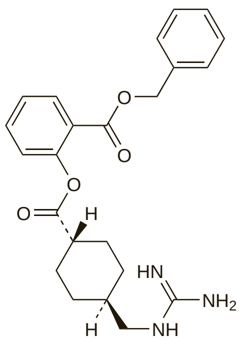

(benexate)

Profile

Benexate hydrochloride is a mucosal protectant that has been used in the management of peptic ulcer disease. The β-cyclodextrin clathrate, benexate hydrochloride betadex, has been given in an oral dose of 400 mg twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Ulgut.

Bisacodyl *(BAN, rINN)*

Bisacodilo; Bisacodylum; Bisakodil; Bisakodilis; Bisakodyl; Bisakodyyli; Biszakodil. 4,4′-(2-Pyridylmethylene)di(phenyl acetate).

Бисакодил

$C_{22}H_{19}NO_4 = 361.4.$

CAS — 603-50-9.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.

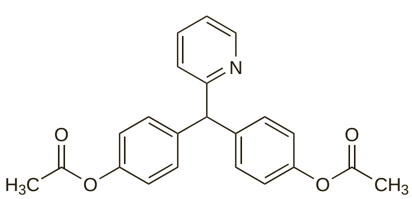

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Bisacodyl). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute mineral acids. Protect from light.

USP 31 (Bisacodyl). A white to off-white crystalline powder. Practically insoluble in water; soluble in benzene; soluble 1 in 210 of alcohol, 1 in 2.5 of chloroform, and 1 in 275 of ether; sparingly soluble in methyl alcohol.

Bisacodyl Tannex *(BANM, USAN, rINNM)*

CAS — 1336-29-4.
ATC — A06AB02; A06AG02.
ATC Vet — QA06AB02; QA06AG02.

Adverse Effects

Bisacodyl and other stimulant laxatives may cause abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Hypersensitivity reactions, including angioedema and anaphylactoid reactions, have been reported rarely. When given rectally, bisacodyl sometimes causes irritation and may cause proctitis or sloughing of the epithelium. To avoid gastric irritation bisacodyl tablets are enteric-coated.

Precautions

As with other laxatives, prolonged use should be avoided. Bisacodyl should not be given to patients with intestinal obstruction or acute abdominal conditions such as appendicitis; care should also be taken in patients with inflammatory bowel disease. It should not be used in patients with severe dehydration. The suppositories should preferably be avoided in patients with anal fissures, proctitis, or ulcerated haemorrhoids.

Handling. Inhalation of bisacodyl powder and contact with eyes, skin, and mucous membranes should be avoided.

Pharmacokinetics

On oral or rectal use bisacodyl is converted to the active desacetyl metabolite bis(*p*-hydroxyphenyl)-pyridyl-2-methane by intestinal and bacterial enzymes. Absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories; the small amount absorbed is excreted in the urine as the glucuronide. Bisacodyl is mainly excreted in the faeces.

Uses and Administration

Bisacodyl is a diphenylmethane stimulant laxative (p.1693) used for the treatment of constipation (p.1693) and for bowel evacuation before investigational procedures or surgery. Its action is mainly in the large intestine and it is usually effective within 6 to 12 hours after oral doses, within 15 to 60 minutes after rectal use by suppository, and within 5 to 20 minutes when given as an enema. Bisacodyl tablets should be swallowed whole and should not be taken within 1 hour of milk or antacids.

For constipation, bisacodyl is given in usual doses of 5 to 10 mg daily as enteric-coated tablets given at night or 10 mg as a suppository or enema given in the morning. Oral doses of 10 to 20 mg are given for complete bowel evacuation, followed by 10 mg as a suppository the next morning. For doses in children, see below.

A complex of bisacodyl with tannic acid (bisacodyl tannex) has been given with a barium sulfate enema before radiographic examination of the colon.

Administration in children. For **constipation**, the following oral doses of bisacodyl are recommended for children, to be taken at night:

- 4 to 10 years: 5 mg
- over 10 years: 5 to 10 mg

Alternatively, the following rectal doses are recommended, to be inserted in the morning:

- under 10 years: 5 mg
- over 10 years: 10 mg

The *BNFC* gives similar doses, but limits the use of suppositories in children to those aged over 2 years.

For **bowel clearance before surgery or radiological investigation**, the following doses are recommended:

- 4 to 10 years: 5 mg orally the night before, followed by 5 mg as a suppository the next morning
- over 10 years: 10 to 20 mg orally the night before, followed by 10 mg as a suppository the next morning

The *BNFC* gives similar doses but allows for the use of oral doses for 2 nights before the procedure, followed, if necessary, by the rectal dose 1 hour before the procedure.

Preparations

BP 2008: Bisacodyl Suppositories; Gastro-resistant Bisacodyl Tablets;
USP 31: Bisacodyl Delayed-release Tablets; Bisacodyl Rectal Suspension; Bisacodyl Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Dulcolax; Laxamin; Modaton; Tractoduo; ***Austral.:*** Bisalax; Dulcolax; ***Austria:*** Dulcolax; Laxbene; ***Belg.:*** Carters; Dulcolax; Henafurine; Mucinum; Nosik-Lax; Purgo-Pil; ***Braz.:*** Bisalax; Cronoplex; Dislax†; Dulcolax; Fideine; Isilax; Plesonax; ***Canad.:*** Alophen; Bisacolax; Carters Little Pills; Correctol; Dulcolax; Feen-A-Mint†; Gentlax; Laxcodyl†; Soflax EX; ***Chile:*** Alsylax; ***Cz.:*** Fenolax; Pyrilax†; Stadalax; ***Denm.:*** Dulcolax; Perilax; Toilax; ***Fin.:*** Metalax; Toilax; ***Fr.:*** Contalax; Dulcolax; ***Ger.:*** Agaroletten; Bekunis Bisacodyl; Bisco-Zitron; Drix Bisacodyl; Dulcolax; Florisan N; Laxagetten; Laxanin N†; Laxans-ratiopharm; Laxbene†; Laxoberal Bisa; Laxysat Burger; Marienbader Pillen N; Mediolax; Pyrilax; Stadalax†; Tempolax; Tirgon; Vinco-Abfuhr-Perlen†; ***Gr.:*** Dulcolax; Florisan N; ***Hong Kong:*** Dulcolax; Marcholax; ***Hung.:*** Dulcolax; Stadalax; ***India:*** Bo-Lax; Dulcolax; JuLax; JuLax-M†; ***Indon.:*** Bicolax; Dulcolax; Laxacod; Laxamex; Stolax; ***Irl.:*** Dulcolax; Toilax; ***Israel:*** Atzirut X; Contalax; Laxadin; ***Ital.:*** Alaxa; Confetto CM; Dulcolax; Normalene; Stixenil; Verecolene CM; ***Malaysia:*** Beacolux†; Dulcolax; ***Mex.:*** Dulcolan; ***Neth.:*** Bekunis Bisacodyl; Dulcolax; Kruidvat Laxeertabletten; Nourilax; Toilax; Trekpleister Laxeerdragees†; ***Norw.:*** Dulcolax; Toilax; ***NZ:*** Dulcolax; Fleet Laxative; ***Philipp.:*** Dulcolax; Vesilac; ***Port.:*** Dulcolax; Moderlax; ***Rus.:*** Dulcolax (Дульколакс); ***S.Afr.:*** Dulcolax; Megalax†; Perilax; ***Singapore:*** Dulcolax; ***Spain:*** Dulco Laxo; ***Swed.:*** Dulcolax; Toilax; ***Switz.:*** Bekunis Dragees; Demolaxin; Dulcolax; Muxol; Prontolax; Tavolax nouvelle formule; ***Thai.:*** Conlax; Dulcolax; Emulax; Gencolax; Kadolax; Laxcodyl; Laxitab; Vacolax; ***Turk.:*** Bisakol; Sekolaks; ***UAE:*** Laxocodyl; ***UK:*** Biolax; Dulcolax; Entrolax; ***USA:*** Alophen; Bisa-Lax; Correctol; Doxidan; Dulcolax; Evac-Q-Tabs; Ex-Lax Ultra; Feen-A-Mint; Fleet Bisacodyl; Fleet Laxative; Gentlax; Modane; ***Venez.:*** Dulcolan.

Multi-ingredient: ***Arg.:*** En-Ga-Lax; Laxicona; Nigalax; ***Austral.:*** Coloxyl; Durolax X-Pack†; Go Kit; Go Kit Plus†; ***Austria:*** Laxbene; Prepacol; Purgazen; Purigoa†; ***Belg.:*** Prepacol; Softene; ***Canad.:*** Bicholate; Extra Strong Formula 12†; Fruitatives†; Gentlax S; Royvac Kit; ***Chile:*** Laxogeno; ***Cz.:*** Prepacol; ***Fr.:*** Prepacol; ***Ger.:*** Potsilo N; Prepacol; ***Gr.:*** Florisan; ***Hung.:*** Laxbene; ***NZ:*** Coloxyl; ***Port.:*** Bekunis; ***Spain:*** Bekunis Complex; Boldolaxin†; ***Thai.:*** Bisolax; ***Turk.:*** Bekunis; ***USA:*** Dulcolax Bowel Prep Kit; Fleet Prep Kit No. 1; Fleet Prep Kit No. 2; Fleet Prep Kit No. 3; HalfLytely; X-Prep Bowel Evacuant Kit-1.

Bismuth Compounds

Bismuto, compuestos de.

Висмут Соединения

Bismuth compounds have been used for their astringent and antidiarrhoeal properties in a variety of gastrointestinal disorders, and have been applied topically in skin disorders and anorectal disorders such as haemorrhoids. Certain salts are active against *Helicobacter pylori* and are used in the treatment of peptic ulcer disease.

Bismuth Aluminate *(USAN)*

Aluminato de bismuto; Aluminum Bismuth Oxide.

Алюминат Висмута

$Bi_2(Al_2O_4)_3,10H_2O = 952.0.$

CAS — 12284-76-3 (anhydrous bismuth aluminate).

Pharmacopoeias. In *Chin.* and *Fr.*

Bismuth Citrate

Citrato de bismuto.

Цитрат Висмута

$BiC_6H_5O_7 = 398.1.$

CAS — 813-93-4.

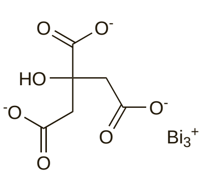

NOTE. Do not confuse with bismuth subcitrate potassium (p.1711) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p.1711).

Pharmacopoeias. In *US*.

USP 31 (Bismuth Citrate). A white, amorphous or crystalline powder. Insoluble in water and in alcohol; soluble in dilute ammonia solution and in solutions of alkali citrates. Store in airtight containers. Protect from light. Prevent exposure to temperatures above 40°.

Bismuth Oxide

Bismuth Trioxide; Óxido de bismuto.

Оксид Висмута

$Bi_2O_3 = 466.0.$

CAS — 1304-76-3.

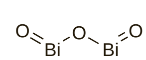

Bismuth Salicylate

Basic Bismuth Salicylate; Bázisos bizmut-szalicilát; Bismuth Oxysalicylate; Bismuth, sous-salicylate de; Bismuth Subsalicylate *(USAN)*; Bismuthi subsalicylas; Bismuto subsalicilatas; Salicilato de bismuto; Salicylan bismutitý zásaditý; Vismutsubsalicylat; Vismuttisubsalisylaatti.

Салицилат Висмута

$C_7H_5BiO_4$ = 362.1.

CAS — 14882-18-9.

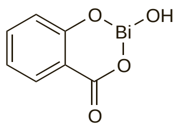

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Bismuth Subsalicylate). A complex of bismuth and salicylic acid. It contains not less than 56% and not more than 59.4% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition. Protect from light.

USP 31 (Bismuth Subsalicylate). A basic salt corresponding to $C_7H_5BiO_4$ and containing not less than 56.0% and not more than 59.4% of Bi and not less than 36.5% and not more than 39.3% of total salicylates. It is a fine, odourless, white to off-white microcrystalline powder. Practically insoluble in water, in alcohol, and in ether. It reacts with alkalis and mineral acids. Store in airtight containers. Protect from light.

Bismuth Subcarbonate *(USAN)*

Basic Bismuth Carbonate; Basisches Wismutkarbonat; Bázisos bizmutkarbonát; Bism. Carb.; Bismuth Carbonate; Bismuth Oxycarbonate; Bismuth, sous-carbonate de; Bismuthi subcarbonas; Bismuto subkarbonatas; Bismutylum Carbonicum; Carbonato de Bismutila; Subcarbonato de bismuto; Uhličitan bismutitý zásaditý; Vismutsubkarbonat; Vismuttisubkarbonaatti.

Основный Углекислый Висмут

CBi_2O_5 = 510.0.

CAS — 5892-10-4 (anhydrous bismuth subcarbonate); 5798-45-8 (bismuth subcarbonate hemihydrate).

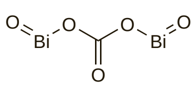

(anhydrous bismuth subcarbonate)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in mineral acids with effervescence. Protect from light.

USP 31 (Bismuth Subcarbonate). A white or almost white powder. Practically insoluble in water, in alcohol, and in ether; dissolves in dilute acids with effervescence. Protect from light.

Bismuth Subcitrate Potassium *(USAN)*

1001277; Biskalcitrate potassium; Bismuth Biscalcitrate; Bismuth biskalcitrate. Bismuth pentapotassium dihydroxide bis(2-hydroxypropane-1,2,3-tricarboxylate hydrate).

Основный Калиевый Цитрат Висмута

$C_{12}H_{14}BiK_5O_{17}$ = 834.7.

CAS — 880149-29-1.

NOTE. Do not confuse with bismuth citrate (p.1710) or tripotassium dicitratobismuthate (colloidal bismuth subcitrate, p.1711).

Bismuth Subgallate *(USAN)*

Basic Bismuth Gallate; Basisches Wismutgallat; Bázisos bizmutgallát; Bism. Subgall.; Bismuth Oxygallate; Bismuth, sous-gallate de; Bismuthi subgallas; Bismuto subgalatas; Bizmut Subgalat; Bizmutu galusan zasadowy; Gallan bismutitý zásaditý; Subgalato de bismuto; Vismutsubgallat; Vismuttisubgallaatti.

Основный Галловокислый Висмут

$C_7H_5BiO_6$ = 394.1.

CAS — 99-26-3.

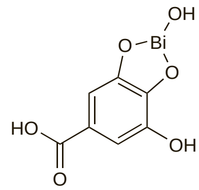

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Bismuth Subgallate). A complex of bismuth and gallic acid. It contains not less than 48% and not more than 51% of Bi, calculated with reference to the dried substance. A yellow powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition and in alkali hydroxides, producing a reddish-brown liquid. Protect from light.

USP 31 (Bismuth Subgallate). A basic salt containing 52 to 57% of Bi_2O_3 when dried at 105° for 3 hours. It is an odourless amorphous bright yellow powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; insoluble in very dilute mineral acids; dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulfuric acids; readily dissolves in solutions of alkali hydroxides to form a clear yellow liquid which rapidly becomes deep red. Store in airtight containers. Protect from light.

Bismuth Subnitrate

Basic Bismuth Nitrate; Basisches Wismutnitrat; Bázisos bizmut-nitrát; Bism. Subnit.; Bismuth Hydroxide Nitrate Oxide; Bismuth Nitrate, Heavy; Bismuth Oxynitrate; Bismuth, sous-nitrate de; Bismuth (Sous-Nitrate de) Lourd; Bismuthi subnitras; Bismuthyl Nitrate; Bismuto subnitratas; Bismuto subnitratas sunkusis; Bizmut Subnitrat; Bizmutu azotan zasadowy; Bizmutu(III) azotan zasadowy; Magistery of Bismuth; Nitrato de Bismutilo; Subazotato de Bismuto; Subnitrato de bismuto; Vismutsubnitrat; Vismuttisubnitraatti; White Bismuth.

Основный Азотнокислый Висмут

$Bi_5O(OH)_9(NO_3)_4$ = 1462.0.

CAS — 1304-85-4.

ATC — A02BX12.

ATC Vet — QA02BX12.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Fr. also includes Bismuth (Sous-Nitrate de) Léger (Bismuthi Subnitras Levis) which is described as a variable mixture of bismuth hydroxide, carbonate, and subnitrate.

Ph. Eur. 6.2 (Bismuth Subnitrate, Heavy). It contains not less than 71% and not more than 74% of Bi, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water and in alcohol; dissolves in mineral acids with decomposition.

USP 31 (Bismuth Subnitrate). A basic salt containing not less than 79% of Bi_2O_3 calculated on the dried basis. It is a white, slightly hygroscopic powder. Practically insoluble in water and in alcohol; readily dissolves in nitric and hydrochloric acids.

Tripotassium Dicitratobismuthate

Bizmut Subsitrat; Colloidal Bismuth Subcitrate; Dicitratobismutato tripotásico; Tripotasyum Disitratobizmutat.

Висмут Трикалия Дицитрат

CAS — 57644-54-9.

ATC — A02BX05.

ATC Vet — QA02BX05.

NOTE. Do not confuse with bismuth citrate (p.1710) or bismuth subcitrate potassium (p.1711).

Adverse Effects, Treatment, and Precautions

The bismuth compounds listed above are insoluble or very poorly soluble, and bismuth toxicity does not appear to be common if they are used for limited periods. However, excessive or prolonged dosage may produce symptoms of bismuth poisoning, and for this reason long-term systemic therapy is not recommended. Reversible encephalopathy (see below) was once a problem in some countries, notably France and Australia; bone and joint toxicity had also occurred, sometimes associated with the encephalopathy. This led to restrictions on the use of bismuth salts and a virtual disappearance of these toxic effects.

Nausea and vomiting have been reported. Darkening or blackening of the faeces and tongue may occur due to conversion to bismuth sulfide in the gastrointestinal tract.

The effects of *acute bismuth intoxication* include gastrointestinal disturbances, skin reactions, stomatitis, and discoloration of mucous membranes; a characteristic blue line may appear on the gums. There may be renal failure and liver damage.

Other adverse effects may not be related to the bismuth content. With bismuth subnitrate given orally there is a risk of the nitrate being reduced in the intestines to nitrite and the development of methaemoglobinaemia. Absorption of salicylate occurs from oral bismuth salicylate and therefore the adverse effects, treatment of adverse effects, and precautions of aspirin (p.20) should be considered.

Gastric lavage should be considered in overdosage; activated charcoal by mouth and the use of a chelating agent such as dimercaprol, succimer, or unithiol have been recommended (see also Overdosage, below). Renal function should be monitored for 10 days after acute overdosage.

Bismuth compounds should not be given to patients with moderate to severe renal impairment.

Encephalopathy. Reviews[1,2] and reports[3-11] of bismuth encephalopathy. Many of the original reports implicated bismuth subgallate or subnitrate, in most but not all cases at high doses or for prolonged periods; toxicity has also occurred with other salts.[6-9] Patients receiving the subcitrate (480 mg daily) or the subnitrate (1.8 g daily) for 8 weeks in the treatment of *Helicobacter pylori* infection, showed no evidence of neurological changes compared with a control group.[12]

1. Winship KA. Toxicity of bismuth salts. *Adverse Drug React Acute Poisoning Rev* 1983; **2:** 103–21.
2. Slikkerveer A, de Wolff FA. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; **4:** 303–23.
3. Morrow AW. Request for reports: adverse reactions with bismuth subgallate. *Med J Aust* 1973; **1:** 912.
4. Martin-Bouyer G. Intoxications par les sels de bismuth administrés par voie orale: enquête épidémiologique. *Therapie* 1976; **31:** 683–702.
5. Stahl JP, *et al.* Encéphalites au sel insoluble de bismuth: toujours d'actualité. *Nouv Presse Med* 1982; **11:** 3856.
6. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; **2:** 167.
7. Weller MPI. Neuropsychiatric symptoms following bismuth intoxication. *Postgrad Med J* 1988; **64:** 308–10.
8. Mendelowitz PC, *et al.* Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; **112:** 140–1.
9. Playford RJ, *et al.* Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; **31:** 359–60.
10. Von Bose MJ, Zaudig M. Encephalopathy resembling Creutzfeldt-Jakob disease following oral, prescribed doses of bismuth nitrate. *Br J Psychiatry* 1991; **158:** 278–80.
11. Teepker M, *et al.* Myoclonic encephalopathy caused by chronic bismuth abuse. *Epileptic Disord* 2002; **4:** 229–33.
12. Noach LA, *et al.* Bismuth salts and neurotoxicity: a randomised, single-blind and controlled study. *Hum Exp Toxicol* 1995; **14:** 349–55.

TOPICAL APPLICATION. Encephalopathy has been associated with the use of bismuth iodoform paraffin paste (BIPP) for the packing of wound cavities after surgery to the head and neck, although there is some debate as to whether the bismuth or the iodoform component is responsible—see p.1650.

Overdosage. Bismuth salicylate or tripotassium dicitratobismuthate in recommended doses are rarely associated with serious adverse effects but there are reports of renal failure,[1-6] encephalopathy,[7-9] and neurotoxicity[1] in acute[1-6,8] or chronic[7,9] overdose. Bismuth has been detected in the blood, urine, stools, and kidneys of these patients; a blood concentration of 1.6 micrograms/mL was found[2] 4 hours after an oral dose of 9.6 g.

The optimal treatment of bismuth overdosage is unknown. Gastric lavage, purgation, and hydration should be considered, even if the patient presents late, as bismuth may be absorbed from the colon.[1,2] Chelating agents may be effective; unithiol has been reported to increase the renal clearance of bismuth with a reduction in the blood concentration.[7] Haemodialysis may be necessary[1-3] but whether this hastens tissue clearance is uncertain. Haemodialysis plus unithiol treatment has been reported to successfully eliminate bismuth.[6] Peritoneal dialysis has also been effectively used in a paediatric patient.[5]

Prolonged ingestion of bismuth salicylate in excessive doses by an elderly diabetic was associated with hearing disturbances, vertigo, acid–base abnormalities and mild clotting disturbances.[10] The toxicity was thought to be due to the salicylate component.

1. Hudson M, Mowat NAG. Reversible toxicity in poisoning with colloidal bismuth subcitrate. *BMJ* 1989; **299:** 159.
2. Taylor EG, Klenerman P. Acute renal failure after colloidal bismuth subcitrate overdose. *Lancet* 1990; **335:** 670–1.
3. Huwez F, *et al.* Acute renal failure after overdose of colloidal bismuth subcitrate. *Lancet* 1992; **340:** 1298.

4. Akpolat I, *et al.* Acute renal failure due to overdose of colloidal bismuth. *Nephrol Dial Transplant* 1996; **11:** 1890–8.
5. İşlek İ, *et al.* Reversible nephrotoxicity after overdose of colloidal bismuth subcitrate. *Pediatr Nephrol* 2001; **16:** 510–14.
6. Hruz P, *et al.* Fanconi's syndrome, acute renal failure, and tonsil ulcerations after colloidal bismuth subcitrate intoxication. *Am J Kidney Dis* 2002; **39:** E18.
7. Playford RJ, *et al.* Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure. *Gut* 1990; **31:** 359–60.
8. Hasking GJ, Duggan JM. Encephalopathy from bismuth subsalicylate. *Med J Aust* 1982; **2:** 167.
9. Mendelowitz PC, *et al.* Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Ann Intern Med* 1990; **112:** 140–1.
10. Vernace MA, *et al.* Chronic salicylate toxicity due to consumption of over-the-counter bismuth subsalicylate. *Am J Med* 1994; **97:** 308–9.

Toxicity from non-conventional use. The FDA has warned against use of an injectable product called bismacine or chromacine, which contains large amounts of bismuth. There are reports of death or serious adverse effects associated with its use. Although unlicensed for any use, bismacine has apparently been used in alternative medicine to treat Lyme disease.[1]

1. FDA. FDA warns consumers and health care providers not to use bismacine, also known as chromacine (issued 21st July 2006). Available at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01415.html (accessed 28/01/08)

Interactions

Bismuth salts given orally reduce the absorption of tetracyclines, possibly by chelation or by reducing tetracycline solubility as a result of increasing the gastric pH. This interaction can be minimised by separating doses of the two drugs by a couple of hours. The clinical significance of this interaction to the use of bismuth salts for peptic ulcer disease is unclear; tripotassium dicitratobismuthate or bismuth salicylate have been given at the same time as tetracycline as part of triple therapy for the eradication of *Helicobacter pylori*.

Antisecretory drugs. Pretreatment with *omeprazole* resulted in about a threefold increase in absorption of bismuth from tripotassium dicitratobismuthate in 6 healthy subjects.[1] The mean peak plasma concentration of bismuth after a single dose of 240 mg of tripotassium dicitratobismuthate was increased from 36.7 to 86.7 nanograms/mL after omeprazole suggesting an increased risk of toxicity from combined therapy. The mechanism was thought to be the increase in gastric pH produced by the antisecretory drug as similar results had been reported with *ranitidine*.[2] However, the clinical significance of these interactions to the use of antisecretory drugs with bismuth compounds for eradication of *Helicobacter pylori* is unclear; bismuth compounds have been combined with proton pump inhibitors or H_2 antagonists in short-term regimens as part of triple or quadruple therapy.

1. Treiber G, *et al.* Omeprazole-induced increase in the absorption of bismuth from tripotassium dicitrato bismuthate. *Clin Pharmacol Ther* 1994; **55:** 486–91.
2. Nwokolo CU, *et al.* The effect of histamine H_2-receptor blockade on bismuth absorption from three ulcer-healing compounds. *Gastroenterology* 1991; **101:** 889–94.

Pharmacokinetics

Poorly soluble bismuth compounds are largely converted to insoluble bismuth oxide, hydroxide, and oxychloride in the acidic environment of the stomach. Most of the bismuth compounds included in this monograph are thus only slightly absorbed. Increased gastric pH may increase bismuth absorption—see Antisecretory Drugs, above. Unabsorbed bismuth is excreted in the faeces. Absorbed bismuth is distributed throughout body tissues, including bone, and is slowly excreted in the urine and bile. It has a plasma half-life of about 5 days and continues to be excreted for about 12 weeks after stopping therapy.

◊ References.

1. Nwokolo CU, *et al.* The absorption of bismuth from oral doses of tripotassium dicitrato bismuthate. *Aliment Pharmacol Ther* 1989; **3:** 29–39.
2. Froomes PRA, *et al.* Absorption and elimination of bismuth from oral doses of tripotassium dicitrato bismuthate. *Eur J Clin Pharmacol* 1989; **37:** 533–6.
3. Lacey LF, *et al.* Comparative pharmacokinetics of bismuth from ranitidine bismuth citrate (GR122311X), a novel anti-ulcerant and tripotassium dicitrato bismuthate (TDB). *Eur J Clin Pharmacol* 1994; **47:** 177–80.

Uses and Administration

Some insoluble salts of bismuth are given orally for their supposed antacid action and for their mildly astringent action in various gastrointestinal disorders, including diarrhoea (p.1694) and dyspepsia (p.1695). Such salts include the aluminate, salicylate, subcarbonate, and subnitrate. Bismuth salicylate, which is given as an antidiarrhoeal and weak antacid in doses up to about 4 g daily in divided doses, possesses in addition the properties of the salicylates.

Tripotassium dicitratobismuthate is active against *Helicobacter pylori* and has been used as triple therapy (with metronidazole and either tetracycline or amoxicillin) to eradicate this organism and thereby prevent relapse of duodenal ulcer. It is also used as a mucosal protectant for the treatment of peptic ulcer disease (p.1702). Bismuth subcitrate potassium and bismuth salicylate are also active against *H. pylori* and have been used similarly in eradication regimens.

The usual oral dose of tripotassium dicitratobismuthate in benign gastric and duodenal ulceration is 240 mg twice daily, or 120 mg four times daily before food. Treatment is for a period of 4 weeks, extended to 8 weeks if necessary. Maintenance therapy with tripotassium dicitratobismuthate is not recommended although treatment may be repeated after a drug-free interval of one month. When used as part of triple therapy the usual dose of tripotassium dicitratobismuthate has been 120 mg four times daily for 2 weeks. The usual dose of bismuth salicylate as part of triple therapy is 525 mg four times daily for 2 weeks. Appropriate antisecretory treatment with a histamine H_2-antagonist or a proton pump inhibitor is usually added to these regimens.

A complex of bismuth citrate with ranitidine, ranitidine bismuth citrate (p.1768), is also used in the treatment of peptic ulcer disease.

Some insoluble salts of bismuth have been used topically in the treatment of skin disorders, wounds, and burns. Some have been used as ingredients of ointments or suppositories (sometimes containing more than one bismuth salt) in the treatment of haemorrhoids and other anorectal disorders (p.1697). Bismuth compounds that have been used topically and/or rectally include the oxide, subgallate, and subnitrate; bismuth resorcinol compounds have also been used. For the use of bismuth subnitrate and iodoform paste as a wound dressing, see Iodoform, p.1650.

Numerous other salts and compounds of bismuth have been promoted for various therapeutic purposes. Glycobiarsol was formerly given orally as an amoebicide.

Homoeopathy. Bismuth has been used in homoeopathic medicines under the following names: Bismuthum; Bismutum metallicum.

Bismuth oxide has been used in homoeopathic medicines under the following names: Bismuthum oxydatum; Bis. ox.

Bismuth subnitrate has been used in homoeopathic medicines under the following names: Heavy bismuth subnitrate; Bismuthi subnitras ponderosus; Bismutum subnitricum; Bism. sub.

Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste;
USP 31: Bismuth Subsalicylate Magma; Bismuth Subsalicylate Oral Suspension; Bismuth Subsalicylate Tablets; Compound Resorcinol Ointment; Milk of Bismuth.

Proprietary Preparations (details are given in Part 3)
Arg.: Re-Dux; Sesamoil; ***Braz.:*** Pepto-Bismol; Peptosan†; Peptulan; Senophile†; ***Canad.:*** Bismed†; Maalox Multi-action; Neo-Laryngobis; Pepto-Bismol; Personnel; ***Cz.:*** De-Nol†; Jatrox†; ***Fr.:*** Amygdorectol†; ***Ger.:*** Angass S†; Dermatol†; Haemo-Exhirud Bufexamac; Katulcin-R†; Stryphnasal N; Telen†; Ulkowis†; ***Gr.:*** De-Nol; ***Hong Kong:*** De-Nol; ***Hung.:*** De-Nol†; ***India:*** Trymo; ***Indon.:*** Scantoma; ***Irl.:*** De-Noltab†; ***Israel:*** Kalbeten; Pink Bismuth; ***Ital.:*** De-Nol; ***Mex.:*** Biselic†; Bismed; Bismofarma; Bisval; Facidmol; Itamol; Pepto-Bismol; Siparox; Sucrato; ***Neth.:*** De-Nol; ***NZ:*** De-Nol; ***Port.:*** De-Nol†; ***Rus.:*** De-Nol (Де-Нол); ***S.Afr.:*** De-Nol; ***Singapore:*** De-Nol; ***Spain:*** Gastrodenol; Rectamigdol; ***Switz.:*** Amygdorectol; ***Thai.:*** Gastro-Bismol; ***Turk.:*** De-Nol; Dermatol; ***UK:*** De-Noltab; Pepto-Bismol; ***USA:*** Bismatrol; Children's Kaopectate; Devrom; K-Pek†; Kao-Tin; Kaopectate; Kapectolin; Maalox Total Stomach Relief; Peptic Relief; Pepto-Bismol; ***Venez.:*** Pepto-Bismol†.

Multi-ingredient: ***Arg.:*** Anusol; Anusol Duo S; Benitol; Bismuto con Pectina; Colistop; Colistoral†; Crema De Bismuto; Cutidermin†; Gastop; Gastranil†; Gastricur; Histidanol†; Lemil; Mabis; ***Belg.:*** Gastrofilm†; Procto-Synalar; Rectovasol; ***Braz.:*** Aftine; Anusol-HC; Bismu-Jet; Bisuisan†; Claudemor; Colutoide; Cutisanol; Magnesia Bisurada; Neoseptil†; Salicilato de Bismuto Composto†; Senophile†; ***Canad.:*** Bismutal; Onrectal; Pepto-Bismol; Thunas Pile†; ***Cz.:*** Carbocit; Mastu S; Sagittaproct†; Spofax; Suspensio Visnevski cum Pice Liquida Herbacos; ***Fin.:*** Tannopon; ***Fr.:*** Anoreine; Anusol; Cutiphile†; Paps; Pholcones Bismuth; ***Ger.:*** Angass; Anisan†; Bismolan H Corti; Bismolan N†; Bismolan†; Combustin Heilsalbe; Duoventrin; Eulatin N; Eulatin NN; Faktu akut; Friosmin N†; Hamo-ratiopharm N; Hamoagil plus; Mastu S; Nervogastrol N†; Pascomag†; Spasmo-Nervogastrol†; Tamposit N†; Ventricon N; Vit-u-pept†; Wismut comp†; ***Hong Kong:*** Anusol; Anusol-HC†; Haemoral; Mastu S; Rowatanal; ***Hung.:*** Bolus Adstringens; Dermaforine†; Mastu S; Nilacid; ***Indon.:*** Anusol; Anusol-HC; ***Irl.:*** Anugesic-HC; Anusol; Anusol-HC; Rowatanal; ***Israel:*** Anusol†; Hemo; Rectozorin; Rekiv; ***Ital.:*** Antiemorroidali; Anusol; ***Malaysia:*** Rowatanal; ***Mex.:*** Estomacurol; Heliton; ***Neth.:*** Anaesthetica; Roteroblong Maagtabletten; Theranal; ***Pol.:*** Gastro; Hemorectal; ***Port.:*** Claudemor†; Servetinal†; Synalar Rectal; ***Rus.:*** Anaesthesol (Анестезол); Anusol (Анузол); Neo-Anusol (Нео-анузол); Proctosan (Проктозан); Simetrid (Симетрид); ***S.Afr.:*** Anugesic; Anusol; Arola Rosebalm; Biskapect; Bisma Rex†; Chloropect; Enterodyne; Kantrexil; Sentinel Ulcer Mixture; ***Singapore:*** Rowatanal; ***Spain:*** Grietalgen; Grietalgen Hidrocort†; Hemodren Compuesto†; Nasopomada; Pomada Infantil Vera†; Sabanotropico; Synalar Rectal; ***Switz.:*** Bismorectal; Cicafissan; Euproctol N; Fissan†; Furodermal; Haemocortin; Haemolan; La pommade du Dr Brand; Leucen; Magenpulver Hafter†; Magentabletten Hafter†; Rectoseptal-Neo bismuthe; ***Thai.:*** Anusol; Biodan†; Mastu S; Ulgastrin; ***Turk.:*** Dermikolin; Hemoralgine; Kortos; Metamorfoz; ***UK:*** Anugesic-HC; Anusol; Anusol-HC, Plus HC; Bisma-Rex; Hemocane; Moorland; OxBipp; Stomach Mixture; ***USA:*** Anumed; Anumed HC; BFI; Calmol; Helidac; Hem-Prep; Hemril; K-C; Kao-Paverin; Kaodene Non-Narcotic; Mammol; Pylera; Rectagene Medicated Rectal Balm; ***Venez.:*** Claudemor†; Klincosal; Polantac.

Bisoxatin Acetate *(BANM, USAN, rINNM)*

Acetato de bisoxatina; Bisoxatin Diacetate; Bisoxatine, Acétate de; Bisoxatini Acetas; Wy-8138. 2,2-Bis(4-hydroxyphenyl)-1,4-benzoxazin-3(2*H*,4*H*)-one diacetate.

Бизоксатина Ацетат

$C_{24}H_{19}NO_6$ = 417.4.

CAS — 17692-24-9 (bisoxatin); 14008-48-1 (bisoxatin acetate).

ATC — A06AB09.

ATC Vet — QA06AB09.

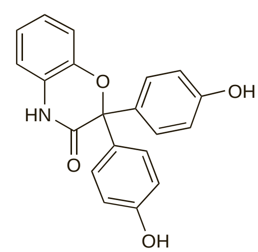

(bisoxatin)

Profile

Bisoxatin acetate is a stimulant laxative that has been used in the treatment of constipation (p.1693).

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Wylaxine; ***Venez.:*** Regoxal.

Bran

Crusca; Farelo; Kleie; Salvado; Son.

Отруби

Description. Bran consists of the fibrous outer layers of cereal grains. It contains celluloses, polysaccharides or hemicelluloses, protein, fat, minerals, and moisture and may contain part of the germ or embryo. Bran provides water-insoluble fibre and, depending on the source, may also provide water-soluble fibre (see also Dietary Role, below). It comprises about 12% of the weight of the grain and is a byproduct of flour milling. It is available in various grades.

Pharmacopoeias. *US* includes wheat bran.

USP 31 (Wheat Bran). The outer fraction of the cereal grain (comprising the pericarp, seed coat (testa), nucellar tissue, and aleurone layer) derived from *Triticum aestivum*, *T. compactum*, *T. durum*, or other common einkorn and emmer wheat cultivars. It is obtained by milling and processing the whole wheat grain, and is available in a variety of particle sizes depending on the degree of milling. It contains not less than 36% of dietary fibre. It is a light tan powder having a characteristic aroma. Practically insoluble in cold water and in alcohol.

Adverse Effects

Large quantities of bran may temporarily increase flatulence and abdominal distension, and intestinal obstruction may occur rarely.

Colonic atony. Colonic atony has been reported in patients who had increased their intake of dietary fibre to relieve constipation associated with systemic sclerosis.[1]

1. Gough A, *et al.* Dietary advice in systemic sclerosis: the dangers of a high fibre diet. *Ann Rheum Dis* 1998; **57:** 641–2.

Diarrhoea. A report of diarrhoea induced by a dramatic increase in fibre intake. Reduction of dietary fibre led to a return to normal bowel habit in 2 to 3 days.[1]

1. Saibil F. Diarrhea due to fiber overload. *N Engl J Med* 1989; **320:** 599.

Intestinal obstruction. Intestinal obstruction associated with excessive bran intake has been reported.[1-3]

1. Allen-Mersh T, De Jode LR. Is bran useful in diverticular disease? *BMJ* 1982; **284:** 740.
2. Cooper SG, Tracey EJ. Small-bowel obstruction caused by oat-bran bezoar. *N Engl J Med* 1989; **320:** 1148–9.
3. Miller DL, *et al.* Small-bowel obstruction from bran cereal. *JAMA* 1990; **263:** 813–14.

Precautions

Bran is contra-indicated in patients with intestinal obstruction or with undiagnosed abdominal symptoms. There is a particular risk of intestinal or oesophageal obstruction if bulk laxatives are swallowed dry; they should be taken with sufficient fluid and should not be taken immediately before going to bed. Wheat bran should be avoided in gluten enteropathies and coeliac disease.

Interactions

Bran may reduce the absorption of some drugs when given together by mouth. Interference with iron, zinc, and calcium absorption has been reported; calcium phosphate may be added to bran to neutralise fytic acid, which can contribute to such interference.

Uses and Administration

The main use of bran is as a bulk laxative and source of dietary fibre in the management of disorders of the gastrointestinal tract such as constipation (p.1693), especially in diverticular disease (p.1695); it is also widely used in irritable bowel syndrome, although its value has been questioned (see p.1699). It should always be taken with plenty of fluid.

Bran is used as the basis for some breakfast cereals.

Dietary role. There is no precise definition for the complex mixture of substances known as dietary fibre. It has been defined as *plant* polysaccharides and lignin resistant to hydrolysis by the digestive enzymes of humans but this covers many substances other than cell-wall and related polysaccharides. Non-starch polysaccharides are the major component of the plant cell wall and are used as an index of dietary fibre. They comprise water-soluble fibres such as pectins, gums, and mucilages and water-insoluble fibres such as cellulose. Wheat, maize, and rice contain mainly insoluble non-starch polysaccharides whereas oats, barley, and rye have a significant proportion of soluble fibres.[1] Because the USA originally included nondigestible *animal* carbohydrates in the definition of fibre, the Food and Nutrition Board in the USA proposed a new definition of fibre, whereby dietary fibre consists of nondigestible carbohydrates and lignin that are intrinsic and intact in plants, and functional fibre consists of isolated, nondigestible plant or animal carbohydrates that have beneficial physiological effects in humans. Total fibre is the sum of dietary and functional fibre.[2]

In the UK, dietary reference values (DRV) have been published for non-starch polysaccharides.[1] It has been proposed[1] that adult diets should contain an average for the population of 18 g daily (individual range 12 to 24 g daily) non-starch polysaccharide from a variety of foods whose constituents contain it as a naturally integrated component. Children should receive proportionately less non-starch polysaccharide according to body size. No evidence exists for benefit of intakes of non-starch polysaccharide in excess of 32 g daily, and therefore there is no advantage in exceeding this amount.

In the USA, an adult dietary fibre intake of 20 to 35 g daily has been suggested; children should consume an amount equivalent to their age plus 5 g daily.[3]

1. DOH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington DC: National Academy Press, 2002/2005. Also available at: http://www.nap.edu/openbook.php?record_id=10490 (accessed 04/04/08)
3. Marlett JA, *et al.* Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2002; **102:** 993–1000. Also available at: http://www.eatright.org/cps/rde/xchg/ada/hs.xsl/advocacy_10175_ENU_HTML.htm (accessed 28/03/07)

Disease prevention. Diseases such as colorectal cancer, ischaemic heart disease, diabetes mellitus, and obesity are common in affluent developed countries but occur rarely in rural Africa. This difference in disease patterns has been linked to the low fibre intake in developed countries compared with rural Africans. However, there are many other differences in diet and lifestyle, such as a lower intake of fat, protein, and sugar in rural Africans and less exposure to toxins and pollutants, any of which could contribute to the difference. The excessive consumption of energy-rich foods may be more to blame for diseases of affluence than is deficiency of dietary fibre.[1]

Results from large prospective cohort studies have been conflicting as to whether there is any *reduction in risk* of **colorectal cancer** associated with a high intake of dietary fibre, and have mostly failed to show a reduction in the *recurrence rate* of colorectal adenomas (although most adenomas do not develop into cancer, and so the relevance of these results is unclear[2]). A pooled analysis of 13 prospective cohort studies found a significant inverse association between dietary fibre intake and colorectal cancer. However, after adjusting for other risk factors, this association was attenuated and no longer statistically significant. There was some suggestion that intake of dietary fibre from cereals and from whole-grain foods were both associated with a weak reduction in the risk of rectal cancer.[3] Some have commented[4] that fibre is a broad term encompassing a wide range of organic material, which may have a large number of actions on digestive physiology. Furthermore, there is some concern that the use of fibre supplements is not entirely without harmful effects: it has been pointed out that fermentable fibre substrates can stimulate cell proliferation in the colon.[5] However, the role of cell proliferation as a marker for the development of colonic cancer is questioned by some authors.[6]

A small randomised crossover study[7] in patients with type 2 **diabetes mellitus** suggested that an increased intake of dietary fibre was associated with improved glycaemic control, decreased hyperinsulinaemia, and lower plasma lipid concentrations. In prospective cohort studies, inverse associations were found between whole-grain intake and the risk of type 2 diabetes mellitus;[8-11] in some studies, this inverse association persisted for cereal fibre intake,[9-11] but in one the protective effect of whole grain could not entirely be explained by fibre content.[8]

Fibre may act as an obstacle to energy intake by displacing available calories and nutrients from the diet, by increasing satiety, and by decreasing the absorption efficiency of the small intestine. Epidemiological studies support the hypothesis that a higher dietary fibre intake prevents **obesity**; populations that report higher fibre consumption also demonstrate lower obesity rates.[12] Weight gain was inversely associated with increases in the intake of whole grains but positively associated with increases in the intake of refined grains, emphasising the importance of distinguishing whole-grain from refined-grain products.[13]

A large prospective cohort study in men found an inverse association between whole-grain intake and the incidence of **coronary heart disease**; the finding was even stronger for bran intake. These associations were attenuated, but not eliminated, by adjustment for other risk factors for coronary heart disease.[14] There is some suggestion that diets high in fibre may have a moderate effect on blood pressure reduction.[15]

1. Anonymous. The bran wagon. *Lancet* 1987; **i:** 782–3.
2. Byers T. Diet, colorectal adenomas, and colorectal cancer. *N Engl J Med* 2000; **342:** 1206–7.
3. Park Y, *et al.* Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 2005; **294:** 2849–57.
4. Goodlad RA. Dietary fibre and the risk of colorectal cancer. *Gut* 2001; **48:** 587–9.
5. Wasan HS, Goodlad RA. Fibre-supplemented foods may damage your health. *Lancet* 1996; **348:** 319–20.
6. Hill MJ, Leeds AR. Fibre and colorectal cancer. *Lancet* 1996; **348:** 957.
7. Chandalia M, *et al.* Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 2000; **342:** 1392–8.
8. Liu S, *et al.* A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000; **90:** 1409–15.
9. Meyer KA, *et al.* Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000; **71:** 921–30.
10. Fung TT, *et al.* Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* 2002; **76:** 535–40.
11. Montonen J, *et al.* Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* 2003; **77:** 622–9.
12. Slavin JL. Dietary fiber and body weight. *Nutrition* 2005; **21:** 411–18.
13. Liu S, *et al.* Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr* 2003; **78:** 920–7.
14. Jensen MK, *et al.* Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* 2004; **80:** 1492–9.
15. He J, *et al.* Effect of dietary fiber intake on blood pressure: a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2004; **22:** 73–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Fibracap†; Trifibra Mix; ***Canad.:*** Novo-Fibre; ***Fr.:*** Doses-O-Son; ***Irl.:*** Trifyba†; ***Ital.:*** Crusken; ***Malaysia:*** Fibrosine†; ***Mex.:*** Fisiolax†; ***Neth.:*** Fiberform; ***Port.:*** Infibran; ***Singapore:*** Fibrosine; ***Swed.:*** Fiberform; Fiberform Mix; ***Switz.:*** Fibion†.

Multi-ingredient: ***Arg.:*** Centella Queen Reductora; Gelax; Gurfi Fibras†; Salutaris; ***Austral.:*** Neo-Trim Fibre†; Prochol†; Proslender†; ***Austria:*** Herbelax; ***Fr.:*** Maxi-Flore; Stimulance; ***Ital.:*** Bio Fibralax Bi-Attivo; Ecofibra; Levoplus; Plurilac; Resource Benefiber; Sedastip; Stimulance; ***Mex.:*** Psilumax; ***NZ:*** Stimulance; ***Pol.:*** Magnezytki; Otrebuski; ***Port.:*** Stimulance†; ***Venez.:*** Senokot con Fibra†.

Bromopride *(rINN)*

Bromoprida; Bromopridum; CM-8252; VAL-13081. 4-Amino-5-bromo-*N*-(2-diethylaminoethyl)-*o*-anisamide.

Бромоприд

$C_{14}H_{22}BrN_3O_2$ = 344.2.
CAS — 4093-35-0.
ATC — A03FA04.
ATC Vet — QA03FA04.

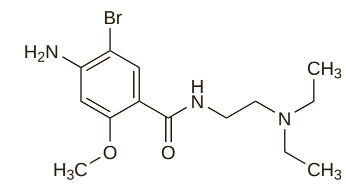

Profile

Bromopride is a substituted benzamide similar to metoclopramide (p.1747), used in a variety of gastrointestinal disorders including nausea and vomiting (p.1700) and motility disorders. It is given in a usual oral dose of 20 to 60 mg daily in divided doses, or 20 mg daily by intramuscular or intravenous injection. The hydrochloride is also used.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Bilenzima; Bromoprid†; Digerex; Digesan; Digesprid; Digestil; Digestina; Digeston†; Pangest; Plamet; Pridecil; ***Ital.:*** Procirex; Valopride.

Multi-ingredient: ***Braz.:*** Digecap-Zimatico; Enziprid†; Lansoprid; Primeral; ***Port.:*** Modulanzime.

Buckthorn

Bacca Spinae Cervinae; Espino cerval; Kreuzdorn; Nerprun.

Жостер Слабительный; Крушина Слабительная

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p.1732) and from Sea Buckthorn (p.2384).

Pharmacopoeias. In *Ger.*

Profile

Buckthorn is the dried ripe fruit of *Rhamnus cathartica* (Rhamnaceae); the bark is also occasionally used. Buckthorn is an anthraquinone stimulant laxative.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Neo-Cleanse; ***UK:*** Cleansing Herbs; Lion Cleansing Herbs.

Butropium Bromide *(rINN)*

Bromuro de butropio; Butropii Bromidum; Butropium, Bromure de. (−)-(1*R*,3*r*,5*S*)-8-(4-Butoxybenzyl)-3-[(*S*)-tropoyloxy]tropanium bromide.

Бутропия Бромид

$C_{28}H_{38}BrNO_4$ = 532.5.
CAS — 29025-14-7.

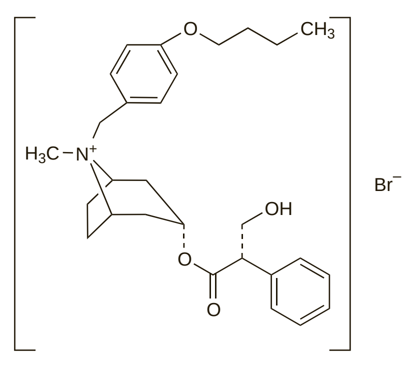

Pharmacopoeias. In *Jpn.*

Profile

Butropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used in the symptomatic treatment of visceral spasms in an oral dose of 30 mg daily in 3 divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Coliopan; ***Jpn:*** Coliopan; ***Malaysia:*** Coliopan; ***Singapore:*** Coliopan†.

Buzepide Metiodide *(rINN)*

Buzépide, Métiodure de; Buzepidi Metiodidum; Diphexamide Iodomethylate; FI-6146; Metazepium Iodide; Metioduro de buzepida; R-661. 1-(3-Carbamoyl-3,3-diphenylpropyl)-1-methylperhydroazepinium iodide.

Бузепида Метйодид

$C_{23}H_{31}IN_2O = 478.4.$

CAS — 15351-05-0.

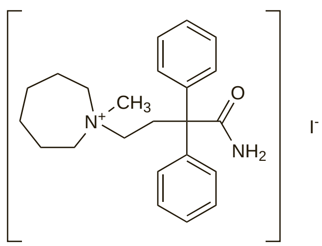

Profile

Buzepide metiodide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been given with other compounds for upper respiratory-tract disorders and in gastrointestinal disorders with smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Vesadol†; ***Ital.:*** Denoral†.

Calcium Carbonate

Calcii carbonas; Calcii Carbonas Praecipitatus (precipitated calcium carbonate); Calcium, carbonate de; Carbonato de calcio; Creta Preparada; E170; Kalcio karbonatas; Kalciumkarbonat; Kalcium-karbonát; Kalsiumkarbonaatti; Kalsiyum karbonat; Precipitated Calcium Carbonate; Precipitated Chalk; Uhličitan vápenatý; Wapnia węglan; Wapnia węglan strącony (precipitated calcium carbonate).

Кальция Карбонат

$CaCO_3 = 100.1.$

CAS — 471-34-1.

ATC — A02AC01; A12AA04.

ATC Vet — QA02AC01; QA12AA04.

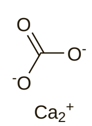

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Calcium Carbonate). A white or almost white powder. Practically insoluble in water.

USP 31 (Calcium Carbonate). A fine, white, odourless, microcrystalline powder. Practically insoluble in water; its solubility in water is increased by the presence of carbon dioxide or ammonium salts although the presence of any alkali hydroxide reduces its solubility; insoluble in alcohol; dissolves with effervescence in acetic acid, in hydrochloric acid, and in nitric acid.

Adverse Effects, Treatment, and Precautions

Calcium carbonate may occasionally cause constipation. Flatulence from released carbon dioxide may occur in some patients. High doses or prolonged use may lead to gastric hypersecretion and acid rebound. Like other calcium salts (see p.1676), calcium carbonate can cause hypercalcaemia, particularly in patients with renal impairment or after high doses. Alkalosis (p.1667) may also occur as a result of the carbonate anion. There have been rare reports of the milk-alkali syndrome, see below, and tissue calcification.

For precautions to be observed with the use of calcium carbonate, see Calcium, p.1676.

Milk-alkali syndrome. The milk-alkali syndrome of hypercalcaemia, alkalosis and renal impairment was first identified in the 1920s and may still occur in patients who ingest large amounts of calcium and absorbable alkali,[1,2] and in patients being treated for osteoporosis with calcium carbonate plus other drugs that may increase the absorption of calcium.[1] It is not uncommon as a cause of hypercalcaemia requiring hospitalisation.[1] The syndrome has also been reported in a patient taking recommended doses of antacids containing calcium carbonate for chronic epigastric discomfort,[3] and in a pregnant woman taking high, but not grossly excessive, doses of calcium (about 3 g of elemental calcium daily).[4] Metastatic calcification can develop.[5]

For reference to thiazide diuretics increasing the risk of the milk-alkali syndrome in patients taking moderately large doses of calcium carbonate, see p.1310.

1. Picolos MK, *et al.* Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol (Oxf)* 2005; **63:** 566–76.
2. Felsenfeld AJ, Levine BS. Milk alkali syndrome and the dynamics of calcium homeostasis. *Clin J Am Soc Nephrol* 2006; **1:** 641–54.
3. Camidge R, Peaston R. Recommended dose antacids and severe hypercalcaemia. *Br J Clin Pharmacol* 2001; **52:** 341–2.
4. Gordon MV, *et al.* Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy. *Med J Aust* 2005; **182:** 350–1.
5. Duthie JS, *et al.* Milk-alkali syndrome with metastatic calcification. *Am J Med* 1995; **99:** 102–3.

Interactions

As for other calcium salts, p.1677.

As outlined on p.1692, antacids, including calcium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving calcium carbonate and any other medication 2 to 3 hours apart.

Omeprazole. In a study[1] of 18 women over the age of 65, the use of omeprazole for a week significantly reduced the absorption of calcium from a calcium carbonate supplement given on an empty stomach. Fractional calcium absorption was reduced from 9.1% with placebo to 3.5% with omeprazole.

1. O'Connell MB, *et al.* Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med* 2005; **118:** 778–81.

Pharmacokinetics

Calcium carbonate is converted to calcium chloride by gastric acid. Some of the calcium is absorbed from the intestines and the unabsorbed portion is excreted in the faeces, as described for other calcium salts, p.1677.

Uses and Administration

Calcium carbonate is used as an antacid (p.1692), usually in oral doses of up to about 1.5 g. It is often given with other antacids, especially magnesium-containing antacids.

Calcium carbonate is also used as a calcium supplement in deficiency states and as an adjunct in the management of osteoporosis, as described under Calcium, p.1677.

Calcium carbonate binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It is used to treat hyperphosphataemia in patients with chronic renal failure (see Renal Osteodystrophy, p.1086) or associated secondary hyperparathyroidism (p.1087). For this purpose, initial doses of 2.5 g daily by mouth in divided doses have been given, increased to up to 17 g daily in divided doses as required. The *BNFC* suggests the following doses in infants and children, given 3 or 4 times daily with or before meals, and adjusted as necessary:

- 1 month to 1 year of age, 120 mg
- 1 to 6 years, 300 mg
- 6 to 12 years, 600 mg
- 12 to 18 years, 1.25 g

Calcium carbonate is also used as a food additive.

Homoeopathy. Native forms of calcium carbonate have been used in homoeopathic medicines under the following names: Calcarea Carbonica; Calc. Carb.; Calcium carbonicum Hahnemanni; Conchae; Calcium Carbonate of Hahnemann; Cal. carb.

Preparations

BP 2008: Alginate Raft-forming Oral Suspension; Calcium and Colecalciferol Tablets; Chewable Calcium Carbonate Tablets;
USP 31: Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aluminum Subacetate Topical Solution; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate Lozenges; Calcium Carbonate Oral Suspension; Calcium Carbonate Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bica†; Calcio Acido; Calcional; Calcium-Sandoz; Cavirox Junior†; Dexacid†; Mylanta Pocket†; Pluscal; Renacalcio; Ultracalcium; Uvasal Tums; ***Austral.:*** Andrews Tums Antacid; Cal-Sup; Caltrate; Sandocal; Titralac; ***Austria:*** Calcium-Sandoz; Dreisacarb; ***Belg.:*** Cacit; Calci-Chew; Sandoz Calcium; Steocar; ***Braz.:*** Calcium-Sandoz F; Calciumvit†; Calsan; Maxicalc; Natecal†; Nutricalcio†; Os-Cal; Osporin†; Osseopor; ***Canad.:*** Apo-Cal; Cal-500; Calcite; Calcium Oyster Shell; Calcium-Sandoz†; Calsan; Caltrate; Hi Potency Cal; Maalox Extra Strength; Maalox Quick Dissolve†; Maalox Regular Strength; Neo Cal; Nu Cal; Os-Cal; Tums; ***Chile:*** Aplical†; Calcefor; Calcefor Cap; Calcio; Calcium Factor; Calcium-Sandoz; Calcivorin; Caprimida; Elcal; Kaplus; Levucal; Natecal; Sanidecal; ***Cz.:*** Maxi-Kalz; Vitacalcin; ***Denm.:*** Calcium-Sandoz; ***Fin.:*** Calcichew; Calcium-Sandoz; Kalcidon; Kalcipos; ***Fr.:*** Cacit; Calcidia; Calcidose; Calciprat; Calcium-Sandoz; Calperos; Calprimum; Caltrate; Densical; Densical vitamine D ; Eucalcic; Fixical; Osteocal; Perical; ***Ger.:*** Basti-Cal†; Biolectra Calcium†; Calci-Gry; Calcigamma; Calcimagon; Calcimed†; Calcitridin†; Calcium AL; Calcium beta; Calcium Dago†; Calcium Heumann†; Calcium Hexal†; Calcium Stada; Calcium Verla; Calcium von CT; Calcium-dura; Calcium-Sandoz; CC-Nefro; Dreisacarb; Loscalcon; Ospur Ca; Vivural†; ***Gr.:*** Alcamex; Body-Calcin; Calcioral; Tums; ***Hong Kong:*** Apo-Cal; Calcichew†; Calcium-Sandoz†; Caltrate; Os-Cal; Scott's Hi-Calcium; Titralac; ***Hung.:*** Beres Calcium; Calcicarb; Calcichew; Calcium-Sandoz; ***India:*** Calcium-Sandoz; Sandocal†; ***Indon.:*** Calcium-Sandoz Junior Strength; Calnat; Calos; Calsan; Osteocal; Stomacain; ***Irl.:*** Cacit†; Calcichew; Rennie Chewable Tablets; Rowarolan; Sandocal; Tums†; ***Israel:*** Calci-Rav; Calcimore; Calcium-Sandoz; Caltrate; Fast; Tums; Tzarevet X; ***Ital.:*** Adiecal; Biocalcium; Cacit; Cal-Car; Calbisan†; Calciodie; Calciopiu; Calcium-Sandoz; Calma; Carbo; Carbosint; Carbotop†; Citracal†; Fervical†; Idracal; Lubical; Metocal; Recal; Salicalcium†; Savecal; Top Calcium; Unical†; ***Malaysia:*** Apo-Cal†; Cal-Sup; Caltrate; ***Mex.:*** Bexacal; Calcifar; Calcium-Sandoz; Calsan; Caltrate; Ciocar; Grisical†; Mubonet; Osteomin; Solibone; Tums; ***Neth.:*** Cacit; Calci-Chew; Calcium-Sandoz; ***Norw.:*** Calcium-Sandoz; Titralac; ***NZ:*** Calcium-Sandoz; Caltrate; Osteo; Titralac; ***Philipp.:*** Calci-Aid; Calcium-Sandoz; Calmate; Calsan; Tums; ***Pol.:*** Additiva Calcium; Calcium-Sandoz Forte; Calperos; FrutiCal; Ostical; Vicalvit; ***Port.:*** Calcior; Calcioral; Calcitab; Calcium-Sandoz; Natecal; Sandocal; Tums; ***Rus.:*** Calcium-Sandoz Forte (Кальций-Сандоз Форте); ***S.Afr.:*** Calcichew; Calcium-Sandoz; Calsuba; Caltrate; Titralac; Tums; ***Singapore:*** Cal-Sup†; Calcium-Sandoz; Caltrate; ***Spain:*** Calcio 20†; Calcium-Sandoz Forte; Caosina; Carbocal; Cimascal; Densical; Fortical†; Mastical; Natecal; ***Swed.:*** Calcitugg; Calcium-Sandoz; Kalcidon; Kalcipos; Kalcitena; ***Switz.:*** Calcium-Sandoz; Calperos; Fixateur phospho-calcique; Maxi-calc†; ***Thai.:*** Bo-Ne-Ca; Cal-Os; Calcanate; Calcar; Calcarbonate; Calcium Central Poly; Calcium-Sandoz; Calsum; Caltab; Caltrate; Carbocal; Carbocalc; Kal-Forte; Prima-Cal; Sorcal†; Weifa-Calcium; ***Turk.:*** Anti-Fosfat Cc; Calcium-Sandoz; ***UK:*** Adcal; Cacit; Calcichew; Rapeze; Remegel; Rennie Soft Chews; Sandocal; Sea-Cal; Setlers; Titralac†; Tums; ***USA:*** Alka-Mints; Alkets†; Amitone†; Antacid; Calci-Chew; Calci-Mix; Calcium-600; Caltrate; Chooz; Equilet†; Maalox Antacid/Calcium†; Maalox Childrens; Maalox Quick Dissolve†; Mallamint; Mylanta; Nephro-Calci; Os-Cal; Oysco; Oyst-Cal; Rolaids Extra Strength Softchews; Surpass; Titralac Extra Strength; Trial Antacid; Tums; ***Venez.:*** Calcion; Calcium-Sandoz; Caltrate†; Foscalvit; Frutacid; Oscal†; Sandocal; Titralac; Tums.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Arg.:*** Aspirina; Bufferin†; ***Braz.:*** Bufferin; ***Canad.:*** Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA; ***Hung.:*** Kalmopyrin; ***Ital.:*** Bufferin†; ***Pol.:*** Calcipiryna; Polopiryna S; ***USA:*** Adprin-B; Ascriptin; Asprimox; Bufferin; Extra Strength Bayer Plus; Magnaprin†.

Carbenoxolone Sodium *(BANM, USAN, rINNM)*

Carbenoxolona sódica; Carbénoxolone Sodique; Disodium Enoxolone Succinate; Karbenoksolon Sodyum; Natrii Carbenoxolonum. 3β-(3-Carboxypropionyloxy)-11-oxo-olean-12-en-30-oic acid, Disodium Salt.

Натрий Карбеноксолон

$C_{34}H_{48}Na_2O_7 = 614.7.$

CAS — 5697-56-3 (carbenoxolone); 7421-40-1 (carbenoxolone disodium).

ATC — A02BX01.

ATC Vet — QA02BX01.

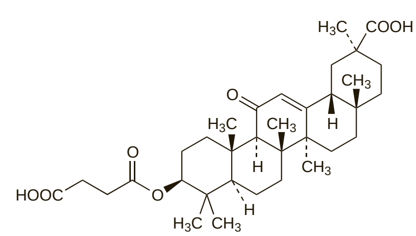

(carbenoxolone)

Pharmacopoeias. In *Br.*

BP 2008 (Carbenoxolone Sodium). A white or pale cream-coloured, hygroscopic powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 10% solution in water has a pH of 8.0 to 9.2.

Adverse Effects, Treatment, and Precautions

Carbenoxolone sodium has mineralocorticoid-like effects and ingestion may produce sodium and water retention and hypokalaemia. This may cause or exacerbate hypertension, heart failure, oedema, alkalosis, and muscle weakness and damage, and systemic carbenoxolone should therefore be used with caution, if at all, in patients with cardiovascular disease. If hypokalaemia is prolonged, renal impairment can occur. Care is needed in pre-existing hepatic or renal impairment. Regular monitoring of weight and blood pressure is advised; if hypokalaemia, oedema, or a significant rise in blood pressure occurs, carbenoxolone therapy should be stopped. Potassium depletion may be corrected with potassium supplements. Systemic use of carbenoxolone sodium is contra-indicated in patients with hypokalaemia, in pregnancy, in the elderly, and in children.

◊ Muscle weakness,[1-5] muscle necrosis,[4] myopathy,[1] hypertension,[2] headache,[2] cardiac failure,[2] mental confusion,[4] areflexia,[3] renal tubular dysfunction,[5] and acute tubular necrosis[4] have all been associated with carbenoxolone-induced hypokalaemia. Carbenoxolone-induced hypertension may have precipitated the onset of fatal polyarteritis in a patient predisposed to this condition.[6]

1. Fyfe T, *et al.* Myopathy and hypokalaemia in carbenoxolone therapy. *BMJ* 1969; **3:** 476.
2. Davies GJ, *et al.* Complications of carbenoxolone therapy. *BMJ* 1974; **3:** 400–2.
3. Royston A, Prout BJ. Carbenoxolone-induced hypokalaemia simulating Guillain-Barré syndrome. *BMJ* 1976; **2:** 150–1.
4. Descamps C, *et al.* Rhabdomyolysis and acute tubular necrosis associated with carbenoxolone and diuretic treatment. *BMJ* 1977; **1:** 272.
5. Dickinson RJ, Swaminathan R. Total body potassium depletion and renal tubular dysfunction following carbenoxolone therapy. *Postgrad Med J* 1978; **54:** 836–7.
6. Sloan J, Weaver JA. A case of polyarteritis developing after carbenoxolone therapy. *Ir Med J* 1968; **1:** 505–7.

Handling. Carbenoxolone sodium powder is irritant to nasal membranes.

Interactions

Because of the risk of toxicity, carbenoxolone should not be taken with digitalis glycosides unless serum-electrolyte concentrations are measured at weekly intervals and precautions are taken to avoid hypokalaemia.

Although amiloride or spironolactone relieve sodium and water retention, they antagonise the efficacy of systemic carbenoxolone and should not be used with it. The hypokalaemia associated with diuretics may be exacerbated by carbenoxolone.

Pharmacokinetics

Carbenoxolone sodium is absorbed from the gastrointestinal tract, mainly from the stomach. It is highly bound to plasma proteins. Carbenoxolone is chiefly excreted in the faeces via the bile. It appears to undergo enterohepatic circulation.

Uses and Administration

Carbenoxolone sodium is a synthetic derivative of glycyrrhizic acid (p.2316) that was formerly used as a mucosal protectant in peptic ulcer disease and has been given with antacids and alginic acid in gastro-oesophageal reflux disease.

Carbenoxolone sodium is one of many topical treatments for the symptomatic management of mouth ulceration (p.1700). It is usually used as a 2% gel; a 1% mouthwash has been used.

Mental function. High cortisol concentrations have been associated with poorer memory and neuronal loss in some patients. Carbenoxolone inhibits 11-β-hydroxysteroid dehydrogenase type 1, and thus may selectively lower intracellular cortisol. In a small crossover study in 10 healthy elderly men, carbenoxolone 100 mg three times daily by mouth for 4 weeks significantly improved verbal fluency compared with placebo, but did not influence visual or verbal memory, nonverbal reasoning, or processing speed. Twelve patients with stable type 2 diabetes were given carbenoxolone at the same dose for 6 weeks. Verbal memory was significantly improved compared with placebo, but verbal fluency and other scores were unaltered. All subjects were given amiloride 10 mg daily to prevent mineralocorticoid adverse effects (but see Interactions, above).[1]

1. Sandeep TC, *et al.* 11β-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci U S A* 2004; **101:** 6734–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Bioral; ***Austria:*** Rowadermat; ***Hong Kong:*** Herpesan; ***Hung.:*** Carbosan; ***Irl.:*** Carbosan; ***Malaysia:*** Herpesan; ***Philipp.:*** Rowagel; ***Singapore:*** Herpesan; ***Spain:*** Sanodin; ***UK:*** Bioplex†; Bioral†.

Multi-ingredient: ***Irl.:*** Pyrogastrone; ***UK:*** Pyrogastrone†.

Casanthranol *(USAN)*

Casantranol.

Казантранол

CAS — 8024-48-4.

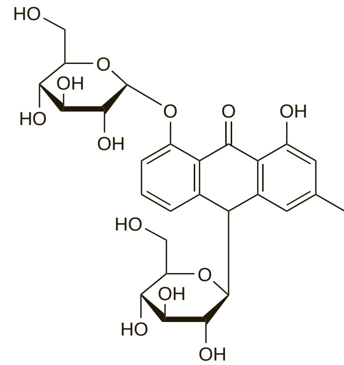

(cascaroside A)

Pharmacopoeias. In *US.*

USP 31 (Casanthranol). It is obtained from cascara. It contains not less than 20% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 80% consists of cascarosides, both calculated as cascaroside A ($C_{27}H_{32}O_{14}$ = 580.5).

It is a light tan to brown, amorphous, hygroscopic powder. Freely soluble in water with some residue; partially soluble in methyl alcohol and in hot isopropyl alcohol; practically insoluble in acetone. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Profile

Casanthranol is an anthraquinone stimulant laxative with general properties similar to those of senna (p.1769). It is given in usual oral doses of 30 to 60 mg daily with a faecal softener. In severe cases a dose of 90 mg daily, or 60 mg twice daily, may be given.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Cascalax†; ***Neth.:*** Cascalax.

Multi-ingredient: ***Arg.:*** Bil 13; En-Ga-Lax; ***Canad.:*** Peri-Colace†; ***Spain:*** Laxvital; ***USA:*** Black-Draught†; Docusoft Plus; Genasoft Plus Softgels†; Laxative & Stool Softener; Peri-Dos Softgels†; Silace-C†.

Cascara

Amerikinių šaltekšnių žievė; Cáscara sagrada; Cascararinde; Chittem Bark; Kaszkarabokor kéreg; Kůra řešetláku Purshova; Rhamni purshianae cortex; Rhamni Purshiani Cortex; Sacred Bark; Sagradabark; Sagradankuori.

Жостер Пурша; Крушина Пурша

CAS — 8047-27-6; 8015-89-2 (cascara sagrada extract).
ATC — A06AB07.
ATC Vet — QA06AB07.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cascara). The dried, whole or fragmented bark of *Rhamnus purshianus* (=*Frangula purshiana*). It contains not less than 8.0% of hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both expressed as cascaroside A ($C_{27}H_{32}O_{14}$ = 580.5). and calculated with reference to the dried drug. Protect from light.

USP 31 (Cascara Sagrada). The dried bark of *Rhamnus purshianus* (Rhamnaceae). It contains not less than 7% of total hydroxyanthracene derivatives calculated on the dried basis, of which not less than 60% consists of cascarosides, both calculated as cascaroside A. It has a distinct odour.

Profile

Cascara is an anthraquinone stimulant laxative with general properties similar to those of senna (p.1769). It has been used in the treatment of constipation in oral doses equivalent to about 20 mg of total hydroxyanthracene derivatives daily.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cascara, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/06)

Preparations

BP 2008: Cascara Dry Extract; Cascara Tablets;
USP 31: Aromatic Cascara Fluidextract; Cascara Sagrada Extract; Cascara Sagrada Fluidextract; Cascara Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Natulax; ***Braz.:*** Laxsotrin; ***Fr.:*** Peristaltine; ***Ger.:*** Legapas; ***Port.:*** Laxolen†.

Multi-ingredient: ***Arg.:*** Bilidren; Calculina†; Cascara Sagrada Bouzen†; Cascara Sagrada Oligoplex; Cascara Sagrada Puler†; Veracolate; Yuyo; ***Austral.:*** Colax; Peritone; ***Austria:*** Cascara-Salax; Dragees Neunzehn†; Silberne; ***Belg.:*** Grains de Vals; Vethoine; ***Braz.:*** Bilifel†; Boldopeptan†; Chofranina; Composto Emagrecedor†; Emagrevit†; Eparema; Jurubileno†; Pilulas De Witt's†; Prisoventril†; Solvobil; Ventre Livre†; ***Canad.:*** Bicholate; Cholasyn II; Cholasyn†; Control; Doulax; Extra Strong Formula 12†; Herbal Laxative; Herbal Laxative plus Yogurt; Herbal Laxative†; Herbalax†; Herbolax; Herborex; Laxaco; Laxative†; Mucinum†; Thunas Laxative†; ***Chile:*** Bulgarolax; ***Fr.:*** Dragees Fuca; Dragees Vegetales Rex; Grains de Vals; Imegul†; Mucinum a l'Extrait de Cascara; ***Hong Kong:*** Mucinum Cascara†; ***Ital.:*** Amaro Medicinale; Coladren; Combilax; Confetti Lassativi CM; Critichol; Digelax†; Dis-Cinil Complex; Draverex; Eparema; Eparema-Levul; Eupatol; Fave di Fuca; Grani di Vals; Hepatos; Hepatos B12; Lassatina†; Magisbile†; Mepalax; Schias-Amaro Medicinale†; Solvobil; Stimolfit; Vadolax†; ***Norw.:*** Cosylan; ***Port.:*** Caroid†; Mucinum; ***S.Afr.:*** Moultons Herbal Extract; Veracolate†; ***Spain:*** Crislaxo; Lipograsil; Menabil Complex†; Nico Hepatocyn; Pildoras Zeninas; ***Swed.:*** Emulax; ***Switz.:*** Padma-Lax; Padmed Laxan; ***Thai.:*** Flatulence; Hemolax; Veracolate; ***UK:*** Dual-Lax Extra Strong; Dual-Lax Normal Strength; Jacksons Herbal Laxative; Laxative Tablets; Modern Herbals Laxative; Modern Herbals Pile; Natural Herb Tablets; Out-of-Sorts; Pileabs; Piletabs; Rhuaka; Senokot Dual Relief; Skin Eruptions Mixture; ***USA:*** Concentrated Milk of Magnesia-Cascara; ***Venez.:*** Gameral.

Cassia Pulp

Fístula, pulpa de caña.

Мякоть Амалтас

Profile

Cassia pulp is the evaporated aqueous extract of crushed ripe cassia fruits (cassia pods), *Cassia fistula* (Leguminosae). It is a mild anthraquinone stimulant laxative with general properties similar to those of senna (p.1769).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Fitolax; Florlax; Fontolax; Forlax; Frutalax†; Laxarine†; Laxtam; Naturetti; Sene Composta†; Tamaril; Tamarine; Tamarix†; ***Fr.:*** Benetransit; ***Ital.:*** Miracolon; Tamarine; ***Mex.:*** Naturetti†; ***S.Afr.:*** Entressdruppels HM; ***Spain:*** Pruina.

Cerium Oxalate

Cerii Oxalas; Cerio, oxalato de; Ceriumoksalaatti; Ceriumoxalat.

Церия Оксалат

CAS — 139-42-4 (anhydrous cerous oxalate); 15053-73-3 (cerous oxalate decahydrate).
ATC — A04AD02.
ATC Vet — QA04AD02.

NOTE. Cerium oxalate has been defined as consisting of about 50% of cerous oxalate ($(C_2O_4)_3Ce_2,10H_2O$) with the oxalates of numerous other rare earths, especially lanthanum, praseodymium, and neodymium. Oxalates of the form $(C_2O_4)_3Ce_2,xH_2O$ are also referred to as cerium or cerous oxalate.

Profile

Cerium oxalate has been used as an antiemetic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Novonausin†.

Certolizumab Pegol *(BAN, USAN, rINN)*

CDP-870; Certolizumab Pégol; Certolizumabum Pegolum; PHA-738144.

Цертолизумаб Пегол

CAS — 428863-50-7.
ATC — L04AB05.
ATC Vet — QL04AB05.

Adverse Effects and Precautions

As for Infliximab, p.69.

Interactions

As for Infliximab, p.71

Uses and Administration

Certolizumab pegol is a pegylated tumour necrosis factor antibody fragment. It is used in the treatment of patients with moderate to severe, active Crohn's disease (p.1697) who have had an inadequate response to conventional treatment. The initial dose is 400 mg given as two subcutaneous injections of 200 mg, repeated after 2 and 4 weeks. Patients who have a clinical response may then receive a maintenance dose of 400 mg every 4 weeks. Certolizumab pegol is also under investigation in the treatment of rheumatoid arthritis and psoriasis.

◊ References.

1. Schreiber S, *et al.* A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005; **129:** 807–18. Correction. *ibid.*; 1808. [dose]
2. Sandborn WJ, *et al.* PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357:** 228–38.
3. Schreiber S, *et al.* PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357:** 239–50. Correction. *ibid.*: 1357.

Preparations

Proprietary Preparations (details are given in Part 3)
Switz.: Cimzia; ***USA:*** Cimzia.

Cetraxate Hydrochloride *(USAN, rINNM)*

Cétraxate, Chlorhydrate de; Cetraxati Hydrochloridum; DV-1006; Hidrocloruro de cetraxato. 4-(2-Carboxyethyl)phenyl tranexamate hydrochloride; 4-(2-Carboxyethyl)phenyl *trans*-4-aminomethylcyclohexanecarboxylate hydrochloride.

Цетраксата Гидрохлорид

$C_{17}H_{23}NO_4,HCl = 341.8.$

CAS — 34675-84-8 (cetraxate); 27724-96-5 (cetraxate hydrochloride).

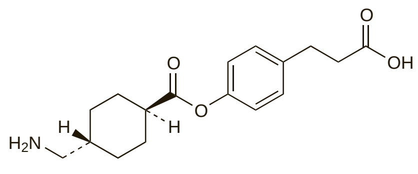

(cetraxate)

Pharmacopoeias. In *Jpn.*

Profile

Cetraxate hydrochloride is stated to be a mucosal protectant with actions on gastric microcirculation as well as prostaglandin synthesis and kallikrein. It is used in the treatment of gastritis and peptic ulcer disease (p.1702) in oral doses of 600 to 800 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Neuer.

Chalk

Creta; Prepared Chalk.

Мел

$CaCO_3 = 100.1.$

CAS — 13397-25-6.

Pharmacopoeias. In *Br.*

BP 2008 (Chalk). A native form of calcium carbonate freed from most of its impurities by elutriation and dried. It consists of the calcareous shells and detritus of various foraminifera and contains not less than 97.0% and not more than 100.5% of $CaCO_3$, calculated with reference to the dried substance.

White or greyish-white, odourless or almost odourless, amorphous, earthy, small friable masses, usually conical in form, or in powder. Practically insoluble in water; slightly soluble in water containing carbon dioxide; it absorbs water readily.

Profile

Chalk has been used as an adsorbent antidiarrhoeal. Calcium carbonate (precipitated chalk) is used as an antacid, calcium supplement, and phosphate binder, see p.1714.

Calabash chalk, also known as Calabar stone, la craie or argile, nzu, mabele, ebumba, or ulo, is ingested by some pregnant women to alleviate morning sickness. It is traditionally used by Nigerian or West African women in the form of blocks, pellets, or powders. Calabash chalk either occurs naturally or is produced from clay and mud which may be mixed with other ingredients including sand, wood ash, and sometimes, salt. However, it contains high levels of lead, as well as arsenic (see Contamination, below).

Contamination. Concern with regard to the safety of calabash chalk has arisen, particularly with regard to its lead and arsenic content.[1-3] Analysis of calabash chalk samples available in the UK found that the major component of calabash chalk was an aluminium silicate hydroxide from the kaolin clay group. Lead concentrations in the samples were found to be about 40 mg/kg, almost 40 times the EU recommended guidelines. Potentially toxic chromium concentrations (dependent on the oxidation state) were also found. Arsenic, cadmium, and mercury were not detectable in any of the analysed samples. Persistent organic pollutants were also identified in one sample.[1] Calabash chalk is traditionally used by pregnant women, often those from Nigerian and West African communities, as a remedy for morning sickness. Health authorities in various countries have issued warnings, and advised people, especially pregnant and breast-feeding women, not to consume calabash chalk.[2,3]

1. Dean JR, *et al.* Characterisation and analysis of persistent organic pollutants and major, minor and trace elements in calabash chalk. *Chemosphere* 2004; **57:** 21–5.
2. Health Canada. Calabash chalk may pose health risk for pregnant and breastfeeding women (issued 2nd October 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_136_e.html (accessed 03/10/07)
3. Food Standards Agency. Lead contamination of calabash chalk (issued 15th October 2002). Available at: http://www.food.gov.uk/enforcement/alerts/2002/oct/94151 (accessed 03/10/07)

Preparations

BP 2008: Compound Magnesium Trisilicate Oral Powder.
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *S.Afr.:* Behoedmiddel vir Kinders.

Ciclonium Bromide *(rINN)*

Asta-3746; Bromuro de ciclonio; Ciclonii Bromidum; Ciclonium, Bromure de. Diethylmethyl{2-[(α-methyl-α-5-norbornen-2-ylbenzyl)oxy]ethyl}ammonium bromide.

Циклония Бромид

$C_{22}H_{34}BrNO = 408.4.$

CAS — 29546-59-6.

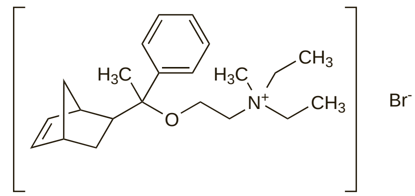

NOTE. The name cyclonium or ciclonium iodide has been used to describe an unrelated antispasmodic, oxapium iodide (p.1759).

Profile

Ciclonium bromide is an antimuscarinic that has been used in the treatment of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)
Thai.: Adamon†.
Multi-ingredient: *Arg.:* Espasmo Motrax†; ***Turk.:*** Doladamon-P.

Cilansetron *(USAN, rINN)*

Cilansétron; Cilansetrón; Cilansetronum; KC-9946. (−)-(*R*)-5,6,9,10-Tetrahydro-10-[(2-methylimidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one.

Цилансетрон

$C_{20}H_{21}N_3O = 319.4.$

CAS — 120635-74-7.
ATC — A03AE03.
ATC Vet — QA03AE03.

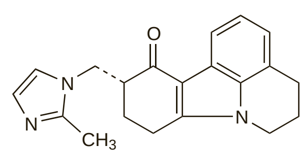

Profile

Cilansetron is a 5-HT_3 antagonist under investigation for the treatment of diarrhoea-predominant irritable bowel syndrome.

Cimetidine *(BAN, USAN, rINN)*

Cimetidin; Cimetidina; Cimetidinas; Cimétidine; Cimetidinum; Cymetydyna; Simetidiini; Simetidin; SKF-92334. 2-Cyano-1-methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]guanidine.

Циметидин

$C_{10}H_{16}N_6S = 252.3.$

CAS — 51481-61-9.
ATC — A02BA01.
ATC Vet — QA02BA01.

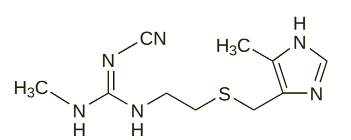

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Cimetidine). A white or almost white, polymorphic powder. Slightly soluble in water; soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute mineral acids. Store in airtight containers. Protect from light.

USP 31 (Cimetidine). A white to off-white crystalline powder, odourless or with a slight mercaptan odour. Slightly soluble in water and in chloroform; soluble in alcohol and in macrogol 400; practically insoluble in ether; sparingly soluble in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Cimetidine Hydrochloride *(BANM, USAN, rINNM)*

Cimétidine, chlorhydrate de; Cimetidin-hidroklorid; Cimetidin-hydrochlorid; Cimetidinhydroklorid; Cimetidini hydrochloridum; Cimetidino hidrochloridas; Hidrocloruro de cimetidina; Simetidiinihydrokloridi.

Циметидина Гидрохлорид

$C_{10}H_{16}N_6S,HCl = 288.8.$

CAS — 70059-30-2.
ATC — A02BA01.
ATC Vet — QA02BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Cimetidine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in dehydrated alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

USP 31 (Cimetidine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects

Adverse reactions to cimetidine and other histamine H_2-antagonists are generally infrequent. The commonest adverse effects reported have been diarrhoea and other gastrointestinal disturbances, dizziness, tiredness, headache, and rashes.

Altered liver function tests have occurred and there have been rare reports of hepatotoxicity. Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred. Other adverse effects that have been reported rarely are hypersensitivity reactions and fever, arthralgia and myalgia, blood disorders including agranulocytosis, leucopenia, and thrombocytopenia, acute pancreatitis, interstitial nephritis, hallucinations and depression, and cardiovascular disorders including bradycardia, tachycardia, and heart block. Rapid intravenous injection should be avoided as there have been rare associations with cardiac arrest and arrhythmias; transient hypotension has also been seen.

In patients such as the elderly, those with chronic lung disease, diabetes mellitus, or the immunocompromised, treatment with H_2-antagonists may be associated with an increased risk of developing community-acquired pneumonia.

Cimetidine has a weak anti-androgenic effect and gynaecomastia and impotence have also occasionally occurred in men; these are usually reversible.

Incidence of adverse effects. In a meta-analysis of 24 double-blind placebo-controlled studies,[1] the incidence of adverse effects with cimetidine was not significantly different from placebo. The most common adverse effects reported by patients taking cimetidine who were followed up for at least one year[2,3] were diarrhoea, headache, fatigue, skin rash or pruritus, and gynaecomastia. The incidence of adverse effects was dose-related and decreased with length of treatment.[3] No fatal adverse effect of cimetidine could be found in a mortality survey involving 9928 patients taking cimetidine and 9351 controls;[4] although the mortality rate was higher in the cimetidine patients, this was explained by the presence of underlying disease (known or unknown) before starting cimetidine treatment and the use of cimetidine to counter adverse gastric effects of other drugs. Follow-up of 9377 of these cimetidine-treated patients for a further 3 years[5] still revealed no fatal disorder attributable to cimetidine treatment and a steady fall in the excess death rate in cimetidine users was seen with increasing length of follow-up; by the fourth year there was little difference between the observed and expected death rate. Cimetidine still appeared to be safe after 10 years of follow-up.[6]

1. Richter JM, *et al.* Cimetidine and adverse reactions: a meta-analysis of randomized clinical trials of short-term therapy. *Am J Med* 1989; **87:** 278–84.
2. Colin Jones DG, *et al.* Post-marketing surveillance of the safety of cimetidine: twelve-month morbidity report. *Q J Med* 1985; **54:** 253–68.
3. Bardhan KD, *et al.* Safety of longterm cimetidine (CIM) treatment: the view from one centre. *Gut* 1990; **31:** A599.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
5. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
6. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 10 year mortality report. *Gut* 1992; **33:** 1280–4.

Carcinogenicity. An association between H_2-antagonists and gastric cancer was proposed after individual case reports, the finding of tumours in long-term high-dose *animal* studies, and the possibility that nitrites and nitroso compounds may be produced, but seemed of little clinical relevance.[1,2] The excess risk of gastric cancer reported in patients taking cimetidine[3-6] or ranitidine[6] decreases with time and there is no evidence for any long-term persistence of the effect.[6] The increased risk may be explained by misdiagnosis and inappropriate cimetidine treatment of existing malignancy.[3-5] An apparently protective effect has been seen for H_2-antagonist use starting 10 or more years before diagnosis of gastric cancer.[6]

The observed excess risk for cancers of the respiratory system is probably related to smoking, since this is causally related to both peptic ulcer and lung cancer and the excess risk does not decline with time.[3-5]

1. Penston J, Wormsley KG. H -receptor antagonists and gastric cancer. *Med Toxicol* 1986; **1:** 163–8.
2. Møller H, *et al.* Use of cimetidine and other peptic ulcer drugs in Denmark 1977–1990 with analysis of the risk of gastric cancer among cimetidine users. *Gut* 1992; **33:** 1166–9.
3. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
5. Møller H, *et al.* Cancer occurrence in a cohort of patients treated with cimetidine. *Gut* 1989; **30:** 1558–62.
6. La Vecchia C, *et al.* Histamine-2-receptor antagonists and gastric cancer risk. *Lancet* 1990; **336:** 355–7.

Effects on the blood. A review[1] in 1988 noted that leucopenia, thrombocytopenia, and pancytopenia have all been reported with cimetidine and ranitidine, with neutropenia and agranulocytosis occurring most often. There were also isolated reports of haemolytic anaemia and leucocytosis associated with cimetidine therapy. The overall incidence of cimetidine-associated blood cytopenia was estimated as 2.3 per 100 000 treated patients; the incidence for ranitidine was less and although there were reports with famotidine the incidence had not been determined. A subsequent case-control study,[2] concluded that the risk of hospitalisation due to neutropenia in patients receiving a 6-week course of cimetidine was no more than 1 in 116 000, while agranulocytosis did not occur in more than 1 in 573 000 patients.

A review[3] of the safety profile of famotidine noted that as of May 1992 there had been 60 reports of serious blood dyscrasias in patients receiving famotidine, of which 22 were considered possibly related to drug therapy (6 cases of pancytopenia or bone marrow depression, 5 of thrombocytopenia, 4 of leucopenia, 3 of combined leucopenia and thrombocytopenia, and 3 of agranulocytosis).

1. Aymard J-P, *et al.* Haematological adverse effects of histamine H -receptor antagonists. *Med Toxicol* 1988; **3:** 430–48.
2. Strom BL, *et al.* Is cimetidine associated with neutropenia? *Am J Med* 1995; **99:** 282–90.
3. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; **18:** 36–54.

Effects on the cardiovascular system. Bradycardia,[1-4] AV block,[5,6] tachycardia,[7] and hypotension[4,8] have been reported during cimetidine treatment given by mouth and by intravenous injection or infusion. Although there are studies in patients[9] and healthy subjects[10,11] that have found no significant cardiovascular effects associated with cimetidine treatment, it is likely that a small proportion of patients are more susceptible to the cardiovascular effects of cimetidine. Caution is recommended if the drug is given intravenously to patients with cardiovascular disease (see Precautions, below).

See also under Overdosage, below.

1. Jefferys DB, Vale JA. Cimetidine and bradycardia. *Lancet* 1978; **i:** 828.
2. Ligumsky M, *et al.* Cimetidine and arrhythmia suppression. *Ann Intern Med* 1978; **89:** 1008–9.
3. Tanner LA, Arrowsmith JB. Bradycardia and H antagonists. *Ann Intern Med* 1988; **109:** 434–5.
4. Drea EJ, *et al.* Cimetidine-associated adverse reaction. *DICP Ann Pharmacother* 1990; **24:** 581–3.
5. Tordjman T, *et al.* Complete atrioventricular block and long-term cimetidine therapy. *Arch Intern Med* 1984; **144:** 861.
6. Ishizaki M, *et al.* First-degree atrioventricular block induced by oral cimetidine. *Lancet* 1987; **i:** 225–6.
7. Dickey W, Symington M. Broad-complex tachycardia after intravenous cimetidine. *Lancet* 1987; **i:** 99–100.
8. Mahon WA, Kolton M. Hypotension after intravenous cimetidine. *Lancet* 1978; **i:** 828.
9. Jackson G, Upward JW. Cimetidine, ranitidine, and heart rate. *Lancet* 1982; **ii:** 265.
10. Hughes DG, *et al.* Cardiovascular effects of H -receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
11. Hilleman DE, *et al.* Impact of chronic oral H -antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.

Effects on the endocrine system. Cimetidine has dose-related mild anti-androgenic properties and reduced sperm counts and raised serum-prolactin concentrations have been reported in men during cimetidine treatment[1] as have gynaecomastia, breast tenderness, and impotence.[2] Those symptoms resolved after withdrawal of cimetidine,[1,2] reduction of the dose,[2] or transfer to ranitidine.[2]

A study by the Boston Collaborative Drug Surveillance Program, using data from 81 535 men in the UK, found that cimetidine was associated with an incidence of 3.29 cases of gynaecomastia per 1000 person years, representing a relative risk 7.2 times greater than that of non-users.[3] The period at highest risk seemed to be between the seventh and twelfth month after starting treatment, and the occurrence was related to dose, with most of the risk associated with doses over 1 g daily. This large study found no significant risk of gynaecomastia with ranitidine or omeprazole. However, there have been isolated reports of gynaecomastia or impotence with ranitidine (p.1766), nizatidine (p.1751), and famotidine (p.1730).

1. Wang C, *et al.* Effect of cimetidine on gonadal function in man. *Br J Clin Pharmacol* 1982; **13:** 791–4.
2. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.
3. García Rodríguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994; **308:** 503–6. Correction. *ibid.*; 819.

Effects on the eyes. Ocular pain, blurred vision, and a rise in intra-ocular pressure occurred in a patient with chronic glaucoma during treatment with cimetidine; ocular symptoms associated with raised intra-ocular pressure subsequently developed during ranitidine treatment.[1] However, a study suggested that cimetidine had no effect on intra-ocular pressure.[2] A cohort study involving 140 128 patients receiving anti-ulcer therapy, 68 504 of whom received cimetidine, found no evidence that any of the drugs were associated with a major increased risk of vascular or inflammatory disorders of the eye.[3]

1. Dobrilla G, *et al.* Exacerbation of glaucoma associated with both cimetidine and ranitidine. *Lancet* 1982; **i:** 1078.
2. Feldman F, Cohen MM. Intraocular pressure and H receptor antagonists. *Lancet* 1982; **i:** 1359.
3. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.

Effects on the kidneys. A review[1] of the nephrotoxicity and hepatotoxicity of H_2-antagonists noted that mild elevation of serum-creatinine was relatively common after use of cimetidine but appeared to have no clinical significance. However, the authors found 25 published reports of acute interstitial nephritis associated with this class of drug (20 with cimetidine, 4 with ranitidine, and 1 with famotidine) and 16 cases reported to the Australian Drug Reaction Advisory Committee (ADRAC) between 1972 and 1999 (11 with cimetidine, 4 with ranitidine, and 1 with famotidine). Symptoms were mostly non-specific, and did not seem to be associated with the rash, arthralgia, and flank pain that may be seen in nephritis induced by other drugs. Nephritis invariably resolved when the drug was withdrawn; in 6 cases, rechallenge resulted in prompt return of clinical features, although there was some evidence that patients who developed nephrotoxicity with one H_2-antagonist might be able to tolerate substitution with another. The effect was rare (an earlier analysis estimated an incidence of around 1 in 100 000 treated patients[2]) but with the increasing availability of over-the-counter H_2-antagonist formulations it was important to be aware of the risk.

1. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H receptor antagonists. *Drug Safety* 2001; **24:** 39–57.
2. Rowley-Jones D, Flind AC. Cimetidine-induced renal failure. *BMJ* 1982; **285:** 1422–3.

Effects on the liver. A cohort study[1] involving 108 891 patients given cimetidine, ranitidine, famotidine, or omeprazole between 1990 and 1993, found 33 cases meeting the authors' definition of clinically serious liver injury (cholestatic in 8 cases, hepatocellular in 15 and mixed in 10), most of whom presented with jaundice. Of these cases of liver injury, 12 were among current users of cimetidine, compared with 5 among users of ranitidine and 1 omeprazole user. It was estimated that the incidence of hepatotoxicity among patients using cimetidine was 2.3 cases per 10 000 users, and the adjusted relative risk was 5.5 times that of non-users. The relative risk for use of ranitidine or omeprazole was calculated at 1.7 and 2.1 respectively. The risk with cimetidine was greatest at high doses (800 mg daily or above) and at the beginning of therapy. For reports of liver damage with famotidine and cimetidine, see p.1730.

1. García Rodríguez LA, *et al.* The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 183–8.

Effects on the nervous system. Cimetidine has been associated with a number of adverse neurological effects including confusion,[1-8] bizarre behaviour,[9] reversible brain stem syndrome (with ataxia, dysarthria, visual impairment, deafness, and paraesthesia),[10] coma,[8,11] convulsions,[7] encephalopathy,[12] visual hallucinations,[9,13,14] paranoia,[5] chorea,[15,16] myopathy,[17] and neuropathy.[18,19] These reactions occur mainly in patients who are elderly, critically ill, or with impaired renal or hepatic function, in whom there may be increased penetration of the blood-brain barrier by cimetidine. Single-dose studies in young healthy subjects[20] have found no adverse changes in performance, central nervous function, or subjective assessment of mood after oral cimetidine 200 or 400 mg.

There is no clear evidence that cimetidine is a more frequent cause of CNS reactions than ranitidine, famotidine, or nizatidine.[21]

1. Robinson TJ, Mulligan TO. Cimetidine and mental confusion. *Lancet* 1977; **ii:** 719.
2. Spears JB. Cimetidine and mental confusion. *Am J Hosp Pharm* 1978; **35:** 1035.
3. Wood CA, *et al.* Cimetidine and mental confusion. *JAMA* 1978; **239:** 2550–1.
4. McMillen MA, *et al.* Cimetidine and mental confusion. *N Engl J Med* 1978; **298:** 284–5.
5. Kinnell HG, Webb A. Confusion associated with cimetidine. *BMJ* 1979; **ii:** 1438.
6. Mogelnicki SR, *et al.* Physostigmine reversal of cimetidine-induced mental confusion. *JAMA* 1979; **241:** 826–7.
7. Edmonds ME, *et al.* Cimetidine: does neurotoxicity occur? Report of three cases. *J R Soc Med* 1979; **72:** 172–5.
8. Sonnenblick M, *et al.* Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature. *Postgrad Med J* 1982; **58:** 415–18.
9. Papp KA, Curtis RM. Cimetidine-induced psychosis in a 14-year-old girl. *Can Med Assoc J* 1984; **131:** 1081–4.
10. Cumming WJK, Foster JB. Cimetidine-induced brainstem dysfunction. *Lancet* 1978; **i:** 1096.
11. Levine ML. Cimetidine-induced coma in cirrhosis of the liver. *JAMA* 1978; **240:** 1238.
12. Niv Y, *et al.* Cimetidine and encephalopathy. *Ann Intern Med* 1986; **105:** 977.
13. Agarwal SK. Cimetidine and visual hallucinations. *JAMA* 1978; **240:** 214.
14. Rushton AR. Pseudohypoparathyroidism, cimetidine, and neurologic toxicity. *Ann Intern Med* 1983; **98:** 677.
15. Kushner MJ. Chorea and cimetidine. *Ann Intern Med* 1982; **96:** 126.
16. Lehmann AB. Reversible chorea due to ranitidine and cimetidine. *Lancet* 1988; **ii:** 158.
17. Feest TG, Read DJ. Myopathy associated with cimetidine? *BMJ* 1980; **281:** 1284–5.
18. Walls TJ, *et al.* Motor neuropathy associated with cimetidine. *BMJ* 1980; **281:** 974–5.
19. Atkinson AB, *et al.* Neurological dysfunction in two patients receiving captopril and cimetidine. *Lancet* 1980; **ii:** 36–7.
20. Nicholson AN, Stone BM. The H -antagonists, cimetidine and ranitidine: studies on performance. *Eur J Clin Pharmacol* 1984; **26:** 579–82.
21. Cantú TG, Korek JS. Central nervous system reactions to histamine-2 receptor blockers. *Ann Intern Med* 1991; **114:** 1027–34.

Effects on the skin. Widespread erythrosis-like lesions in a 36-year-old man were probably induced by cimetidine.[1] There has been a report[2] of a skin eruption clinically consistent with erythema annulare centrifugum developing in a patient after 6 months of treatment with cimetidine; the eruption resolved after withdrawal of cimetidine and reappeared on rechallenge. The condition had not recurred during therapy with ranitidine. Erythema multiforme eruptions occurred after both cimetidine and famotidine in one patient (see p.1730). There have been reports of the Stevens-Johnson syndrome during cimetidine treatment in patients with a history of hypersensitivity to penicillin[3] or sulfonamides,[4] and a report of toxic epidermal necrolysis.[5]

Urticarial vasculitis[6] and alopecia[7] have also been associated with cimetidine treatment.

1. Angelini G, *et al.* Cimetidine and erythrosis-like lesions. *BMJ* 1979; **i:** 1147–8.
2. Merrett AC, *et al.* Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; **283:** 698.
3. Ahmed AH, *et al.* Stevens-Johnson syndrome during treatment with cimetidine. *Lancet* 1978; **ii:** 433.
4. Guan R, Yeo PPB. Stevens-Johnson syndrome: was it cimetidine? *Aust N Z J Med* 1983; **13:** 182.
5. Tidwell BH, *et al.* Cimetidine-induced toxic epidermal necrolysis. *Am J Health-Syst Pharm* 1998; **55:** 163–4.
6. Mitchell GG, *et al.* Cimetidine-induced cutaneous vasculitis. *Am J Med* 1983; **75:** 875–6.
7. Khalsa JH, *et al.* Cimetidine-associated alopecia. *Int J Dermatol* 1983; **22:** 202–4.

Fever. There are reports of febrile reactions associated with cimetidine.[1-4] Fever has also been reported with famotidine (p.1730) and ranitidine (p.1766).

1. Ramboer C. Drug fever with cimetidine. *Lancet* 1978; **i:** 330–1.
2. McLoughlin JC, *et al.* Cimetidine fever. *Lancet* 1978; **ii:** 499–500.
3. Corbett CL, Holdsworth CD. Fever, abdominal pain, and leucopenia during treatment with cimetidine. *BMJ* 1978; **i:** 753–4.
4. Landolfo K, *et al.* Cimetidine-induced fever. *Can Med Assoc J* 1984; **130:** 1580.

Hypersensitivity. Facial oedema,[1] laryngospasm,[1] pruritus,[2,3] rash,[2,3] angioedema[3] and anaphylaxis[4] have been reported in patients receiving cimetidine by mouth or intravenously.

See also under Effects on the Skin, above.

1. Delaunois L. Hypersensitivity to cimetidine. *N Engl J Med* 1979; **300:** 1216.
2. Hadfield WA. Cimetidine and giant urticaria. *Ann Intern Med* 1979; **91:** 128–9.
3. Sandhu BS, Requena R. Hypersensitivity to cimetidine. *Ann Intern Med* 1982; **97:** 138.
4. Knapp AB, *et al.* Cimetidine-induced anaphylaxis. *Ann Intern Med* 1982; **97:** 374–5.

Infection. Treatment with H_2-antagonists may predispose patients to salmonella infection, probably because the decrease in gastric acidity reduces the gastric killing of ingested organisms.[1] The greatest increase in risk was seen in patients over 65 years of age.

There are conflicting data on whether the use of H_2-antagonists for prophylaxis of stress ulcers in critically ill patients increases the risk for pneumonia (see under Peptic Ulcer Disease, p.1702). However, a case-control study in a large cohort of patients in primary care suggested that the risk of developing pneumonia in these less-severely ill patients was increased by antisecretory drugs: the relative risk was 1.63 in patients receiving H_2-antagonists, and 1.89 in those prescribed a proton pump inhibitor; there was also some evidence of a dose-response relationship in the latter group.[2]

Data from case-control studies[3] suggest that gastric acid suppression by H_2-antagonists may also be a risk factor for *Clostridium difficile*-associated disease. A case-control study in very low birth-weight infants found that use of H_2-antagonists was associated with an increased incidence of necrotising enterocolitis.[4] The authors postulate that this could be due to bacterial overgrowth in a less acidic gastric environment.

1. Neal KR, *et al.* Recent treatment with H antagonists and antibiotics and gastric surgery as risk factors for salmonella infection. *BMJ* 1994; **308**: 176.
2. Laheij RJF, *et al.* Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292:** 1955–60.
3. Dial S, *et al.* Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294:** 2989–95.
4. Guillet R, *et al.* National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; **117:** e137–42. Also available at: http://pediatrics.aappublications.org/cgi/reprint/117/2/e137 (accessed 09/04/08)

Malabsorption. Vitamin B_{12} deficiency has been reported in association with acid-suppressive therapy, including H_2-antagonists. The deficiency was thought to result from impaired release of vitamin B_{12} from food protein, which requires gastric acid and pepsin.[1]

1. Ruscin JM, *et al.* Vitamin B deficiency associated with histamine -receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother* 2002; **36:** 812–16.

Overdosage. No serious toxic effects were noted in reports[1-3] of overdosage in patients who took cimetidine 5.2 to 20 g (including one patient who took about 12 g daily for 5 days[1]). Resultant plasma concentrations had been up to 57 micrograms/mL compared with a usual peak plasma concentration of 1 microgram/mL after a 200-mg dose. However, an overdose of about 12 g produced high pulse rate, dilated pupils, speech disturbances, agitation and disorientation in one patient[4] and respiratory depression in another patient who had chronic schizophrenia and was also taking trifluoperazine and hydroxyzine.[5] Also, fatal bradycardia has been reported after overdosage with an unknown amount of cimetidine and diazepam.[6] In a review of 881 cases of cimetidine overdose, excluding cases where several drugs were taken, it was concluded that the toxicity of cimetidine after acute overdose was very low.[7] No symptoms were observed in 79% of cases, which included ingestions of up to 15 g of cimetidine, and only 3 patients had moderate clinical manifestations (dizziness and bradycardia; CNS depression; vomiting). No patients had major medical outcomes and there were no fatalities. Gastric emptying was performed in 34% of cases but supportive measures and symptomatic treatment alone may be adequate. Forced diuresis does not appear to enhance the excretion of cimetidine from the body, and is not recommended.[3]

1. Gill GV. Cimetidine overdose. *Lancet* 1978; **i:** 99.
2. Illingworth RN, Jarvie DR. Absence of toxicity in cimetidine overdosage. *BMJ* 1979; **i:** 453–4.
3. Meredith TJ, Volans GN. Management of cimetidine overdose. *Lancet* 1979; **ii:** 1367.
4. Nelson PG. Cimetidine and mental confusion. *Lancet* 1977; **ii:** 928.
5. Wilson JB. Cimetidine overdosage. *BMJ* 1979; **i:** 955.
6. Hiss J, *et al.* Fatal bradycardia after intentional overdose of cimetidine and diazepam. *Lancet* 1982; **ii:** 982.
7. Krenzelok EP, *et al.* Cimetidine toxicity: an assessment of 881 cases. *Ann Emerg Med* 1987; **1:** 1217–21.

Precautions

Before giving cimetidine or other histamine H_2-antagonists to patients with gastric ulcers the possibility of malignancy should be considered since these drugs may mask symptoms and delay diagnosis. They should be given in reduced dosage to patients with renal impairment.

Intravenous injections of cimetidine should be given slowly and intravenous infusion is preferred, particularly for high doses and in patients with cardiovascular impairment.

Breast feeding. In the UK, manufacturers advise that mothers receiving cimetidine avoid breast feeding. Cimetidine is reported to be actively transported into breast milk, resulting in a milk:serum ratio 5.5 times higher than that expected with passive diffusion.[1] In one case, where cimetidine was detected in the milk of a nursing mother in concentrations higher than in her plasma, it was calculated[2] that the maximum amount of cimetidine that an infant could ingest assuming an intake of about 1 litre of milk daily and fed at the time of peak concentrations would be about 6 mg. However, the Committee on Drugs of the American Academy of Pediatrics has pointed out that there was no evidence of signs or symptoms attributable to the drug in the infant in this case,[3] despite 6 months of breast feeding, and cimetidine has been classified by that body as usually compatible with breast feeding.[4]

1. Oo CY, *et al.* Active transport of cimetidine into human milk. *Clin Pharmacol Ther* 1995; **58:** 548–55.
2. Somogyi A, Gugler R. Cimetidine excretion into breast milk. *Br J Clin Pharmacol* 1979; **7:** 627–9.
3. Berlin CM. Cimetidine and breast-feeding. *Pediatrics* 1991; **88:** 1294.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Burns. The clearance of cimetidine has been reported to be increased in burn patients, with the increase correlating to the size of the burn.[1] Despite another study that reported a decreased renal clearance (but an increased non-renal clearance) early in the evolution of burn injury,[2] it has been recommended that the dosage of cimetidine be increased in patients with burns, depending on the extent of injury. A requirement for increased dosage has also been noted in paediatric burns patients.[3]

1. Martyn JAJ, *et al.* Increased cimetidine clearance in burn patients. *JAMA* 1985; **253:** 1288–91.
2. Ziemniak JA, *et al.* Cimetidine kinetics during resuscitation from burn shock. *Clin Pharmacol Ther* 1984; **36:** 228–33.
3. Martyn JAJ, *et al.* Alteration by burn injury of the pharmacokinetics and pharmacodynamics of cimetidine in children. *Eur J Clin Pharmacol* 1989; **36:** 361–7.

Helicobacter pylori testing. In one study,[1] 2 of 11 patients with *Helicobacter pylori* infection had false-negative urea breath tests while receiving high dose ranitidine (600 mg daily). The breath test became positive again within 5 days of stopping therapy. The manufacturers of the breath test recommend it should not be performed for at least 2 weeks after stopping antisecretory drug therapy.

1. Chey WD, *et al.* Lansoprazole and ranitidine affect the accuracy of the C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997; **92:** 446–50.

Hepatic impairment. An increased resistance to H_2-receptor antagonists has been reported in patients with cirrhosis, see Ranitidine, p.1766. For a suggestion that dosage reduction of cimetidine may be required in patients with portal systemic encephalopathy, see Administration in Hepatic Impairment, below.

Porphyria. Cimetidine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

For reference to clinical and biochemical improvement in porphyric patients receiving cimetidine, see below.

Renal impairment. The clearance of cimetidine is reduced in renal impairment and dosage reduction is recommended (see under Administration in Renal Impairment, below).

Interactions

Cimetidine and other H_2-antagonists can reduce the absorption of drugs such as dasatinib, ketoconazole, and possibly itraconazole, whose absorption is dependent on an acid gastric pH. For the effect of itraconazole on cimetidine see Antifungals, below.

Cimetidine may inhibit the hepatic metabolism of many drugs by binding to cytochrome P450 isoenzymes, notably CYP1A2, CYP2C9, CYP2D6, and CYP3A4. Although many such interactions may occur, only a few are considered clinically significant, notably those with phenytoin, theophylline, lidocaine, and oral anticoagulants. Avoidance of the combination, or a reduction in the dosage of these drugs may be required.

◊ Cimetidine can affect a wide range of drugs[1-4] but these interactions are of clinical significance for only a few, particularly those that have a narrow therapeutic index where the risk of toxicity may necessitate adjustment of dosage. The majority of interactions are due to binding of cimetidine to cytochrome P450 isoenzymes in the liver with subsequent inhibition of microsomal oxidative metabolism and increased bioavailability or plasma concentrations of drugs metabolised by these enzymes. A few interactions are due to competition for renal tubular secretion. Other mechanisms of interaction such as changes in hepatic blood flow play only a minor role.

Significant or potentially significant interactions have occurred with

- antiepileptics such as phenytoin (p.500) and carbamazepine (p.475)
- biguanide antidiabetics (p.438)
- lidocaine (p.1864)
- nifedipine (p.1353)
- opioid analgesics (p.103)
- procainamide (p.1378)
- theophylline (p.1145)
- tricyclic antidepressants such as amitriptyline (p.380)
- warfarin and other oral anticoagulants (p.1430)
- zalcitabine (p.913)
- zolmitriptan (p.628)

Combinations of these drugs and cimetidine should be avoided or used with caution, with monitoring of effects or plasma-drug concentrations and reductions in dosage as appropriate.

Famotidine, nizatidine, and ranitidine do not inhibit cytochrome P450, and the potential for drug interactions is therefore reduced.

1. Penston J, Wormsley KG. Adverse reactions and interactions with H -receptor antagonists. *Med Toxicol* 1986; **i:** 192–216.
2. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. *Clin Pharmacokinet* 1987; **12:** 321–66.
3. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
4. Shinn AF. Clinical relevance of cimetidine drug interactions. *Drug Safety* 1992; **7:** 245–67.

Alcohol. Any interaction between H_2-antagonists and alcohol is generally thought unlikely to be clinically significant (see p.1627).

Antacids. Single-dose studies of the interaction between cimetidine and antacids[1] have shown reduced bioavailability of cimetidine as well as no interaction. The neutralising capacity of the antacid appears to be a factor in determining whether an interaction occurs and a dose with less than 50 mmol neutralising capacity will have little, if any, effect on cimetidine absorption. There is no evidence that the therapeutic efficacy of cimetidine is reduced and with long-term use of the combination the bioavailability of cimetidine is unlikely to be reduced.

1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.

Antifungals. *Itraconazole* increased the area under the concentration-time curve of cimetidine, and reduced the total plasma clearance and renal tubular secretory clearance of cimetidine in a pharmacokinetic study in 8 healthy subjects.[1] The authors proposed that this was due to inhibition of P-glycoprotein-mediated renal tubular secretion.

1. Karyekar CS, *et al.* Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004; **44:** 919–27.

Antimuscarinics. The antimuscarinic *propantheline* delays gastric emptying and reduces intestinal motility and has been reported to reduce the bioavailability of cimetidine.[1]

1. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.

Prokinetic drugs. *Metoclopramide* may reduce the bioavailability of cimetidine possibly due to reduction of gastrointestinal transit time.[1-3] A similar interaction has been reported between cimetidine and the prokinetic drug *cisapride*.[4] The clinical significance of this interaction is questionable since such combinations may be clinically effective, although the use of cisapride is now restricted in many countries.

1. Gugler R, *et al.* Impaired cimetidine absorption due to antacids and metoclopramide. *Eur J Clin Pharmacol* 1981; **20:** 225–8.
2. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.
3. Barzaghi N, *et al.* Effects on cimetidine bioavailability of metoclopramide and antacids given two hours apart. *Eur J Clin Pharmacol* 1989; **37:** 409–10.
4. Kirch W, *et al.* Cisapride-cimetidine interactions; enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.

Sucralfate. Licensed product information for the mucosal protectant sucralfate states that it has been shown to reduce the bioavailability of cimetidine and other H_2 antagonists, presumably due to binding in the gastrointestinal tract. The effect can be avoided by separating doses of the two drugs by 2 hours, but it is not clear whether the interaction has a clinical significance.

Pharmacokinetics

Cimetidine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are obtained after about an hour when given on an empty stomach; a second peak may be seen after about 3 hours. Food delays the rate and may slightly decrease the extent of absorption, with the peak plasma concentration occurring after about 2 hours.

The bioavailability of cimetidine after oral doses is about 60 to 70%. Cimetidine is widely distributed and has a volume of distribution of about 1 litre/kg and is weakly bound, about 20%, to plasma proteins. The elimination half-life from plasma is about 2 hours and is increased in renal impairment. Cimetidine is partially metabolised in the liver to the sulfoxide and to hydroxymethylcimetidine. About 50% of an oral dose, and 75% of an intravenous dose, is excreted unchanged in the urine in 24 hours. Cimetidine crosses the placental barrier and is distributed into breast milk.

◊ Reviews.

1. Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. *Clin Pharmacokinet* 1983; **8:** 463–95.

2. Lin JH. Pharmacokinetic and pharmacodynamic properties of histamine H -receptor antagonists: relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet* 1991; **20:** 218–36.
3. Gladziwa U, Klotz U. Pharmacokinetics and pharmacodynamics of H -receptor antagonists in patients with renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 319–32.

Children. Renal function is limited in the first few months of life and half-lives of 1.1 to 3.7 hours have been reported for cimetidine in neonates.[1-3] A dosage regimen for neonates based on renal function has been suggested[1] with 15 to 20 mg/kg daily for full-term neonates, but with lower doses for premature neonates and those with renal dysfunction. However, single doses of 5 to 7 mg/kg may be sufficient to suppress gastric acid secretion in neonates.[3]

In older infants and children maturation of renal function is complete and the clearance of cimetidine is increased compared with that in adults while younger children show higher clearance values than older children. A typical dosage regimen for children is 30 mg/kg daily, in 3 or 4 divided doses.[4] However, even this dose might not produce optimal control of gastric acid.[5]

1. Ziemniak JA, *et al.* The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984; **7:** 30–8.
2. Lloyd CW, *et al.* The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985; **19:** 203–5.
3. Stile IL, *et al.* Pharmacokinetic evaluation of cimetidine in newborn infants. *Clin Ther* 1985; **7:** 361–4.
4. Somogyi A, *et al.* Cimetidine pharmacokinetics and dosage requirements in children. *Eur J Pediatr* 1985; **144:** 72–6.
5. Lambert J, *et al.* Efficacy of cimetidine for gastric acid suppression in pediatric patients. *J Pediatr* 1992; **120:** 474–8.

Uses and Administration

Cimetidine is a histamine H_2-antagonist and inhibits actions of histamine mediated by H_2-receptors such as gastric acid secretion and pepsin output. It is used where inhibition of gastric acid secretion may be beneficial, as in peptic ulcer disease, including stress ulceration (p.1702), gastro-oesophageal reflux disease (p.1696), selected cases of persistent dyspepsia (p.1695), pathological hypersecretory states such as the Zollinger-Ellison syndrome (p.1704), and in patients at risk of acid aspiration (p.1693) during general anaesthesia or child birth. Cimetidine may also be used to reduce malabsorption and fluid loss in patients with the short bowel syndrome and to reduce the degradation of enzyme supplements given to patients with pancreatic insufficiency.

Cimetidine may be given orally, by the nasogastric route, or parenterally by the intravenous or intramuscular routes; the total daily dose by any route should not normally exceed 2.4 g. Although some formulations are prepared as the hydrochloride, strengths and doses are expressed in terms of the base. Cimetidine 100 mg is equivalent to about 114.4 mg of cimetidine hydrochloride. Doses should be reduced in renal impairment and may also need to be reduced in hepatic impairment (see below).

SPECIFIC DISEASE DOSES.

In the management of benign **gastric** and **duodenal ulceration** a single daily oral dose of 800 mg at bedtime is recommended, which should be given for at least 4 weeks in the case of duodenal, and for at least 6 weeks in the case of gastric, ulcers. Where appropriate a maintenance dose of 400 mg may then be given once daily at bedtime, or twice daily in the morning and at bedtime. Other regimens have also been used for treatment and maintenance.

In **gastro-oesophageal reflux disease** the recommended oral dose is 400 mg four times daily (with meals and at bedtime), or 800 mg twice daily, for 4 to 8 weeks. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, an oral dose of 300 or 400 mg four times daily is normally used, although sometimes higher doses may be necessary.

Doses of 200 to 400 mg orally, by nasogastric tube, or parenterally (200 mg only for direct intravenous injection) every 4 to 6 hours are recommended for the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract. In patients at risk of developing the **acid aspiration syndrome**, an oral dose of 400 mg may be given 90 to 120 minutes before the induction of anaesthesia, or at the start of labour (in obstetric practice), and doses of up to 400 mg (by the parenteral route if appropriate, see below) may be repeated at intervals of 4 hours if required.

Doses of up to 200 mg four times daily have been taken for non-ulcer **dyspepsia**; 100 mg at night has been used in the prophylaxis of nocturnal heartburn.

To reduce the degradation of pancreatic enzyme supplements, patients with **pancreatic insufficiency**, as in cystic fibrosis (p.166), may be given oral cimetidine 800 to 1600 mg daily in 4 divided doses, 60 to 90 minutes before meals.

PARENTERAL ADMINISTRATION.

In the UK, the usual dose of cimetidine by intravenous injection is 200 mg, which should be given slowly over at least 5 minutes and may be repeated every 4 to 6 hours. If a larger dose is required, or if the patient has cardiovascular impairment, intravenous infusion is recommended. For an intermittent intravenous infusion the recommended dose is 200 to 400 mg every 4 to 6 hours if necessary. For a continuous intravenous infusion the recommended rate is 50 to 100 mg/hour. The usual intramuscular dose is 200 mg which may be repeated at intervals of 4 to 6 hours. In the USA, parenteral dosage recommendations are 300 mg every 6 to 8 hours by intramuscular injection or by slow intravenous injection over at least 5 minutes. The same dosage may be given by intermittent intravenous infusion over 15 to 20 minutes; for continuous intravenous infusion the recommended rate is 37.5 mg/hour, which may be preceded by 150 mg as an intravenous loading dose. However, a rate of 50 mg/hour is recommended for prevention of stress ulceration.

CHILDREN'S DOSES.

For **children** over one year of age 25 to 30 mg/kg daily may be given in divided doses, by mouth or parenterally. Under 1 year of age, 20 mg/kg daily in divided doses has been used (see also Children, under Pharmacokinetics, above).

Administration in hepatic impairment. The bioavailability of cimetidine may be increased in patients with cirrhosis[1,2] and a dosage reduction of up to 40% has been suggested in patients with portal systemic encephalopathy.[3] However, UK and US licensed drug information does not include recommendations for dosage adjustment in hepatic impairment.

1. Gugler R, *et al.* Altered disposition and availability of cimetidine in liver cirrhotic patients. *Br J Clin Pharmacol* 1982; **14:** 421–30.
2. Cello JP, Øie S. Cimetidine disposition in patients with Laennec's cirrhosis during multiple dosing therapy. *Eur J Clin Pharmacol* 1983; **25:** 223–9.
3. Ziemniak JA, *et al.* Hepatic encephalopathy and altered cimetidine kinetics. *Clin Pharmacol Ther* 1983; **34:** 375–82.

Administration in renal impairment. The dosage of cimetidine should be reduced in patients with renal impairment; suggested doses according to creatinine clearance (CC) are:

- CC over 50 mL/minute: normal dosage
- CC 30 to 50 mL/minute: 200 mg four times daily
- CC 15 to 30 mL/minute: 200 mg three times daily
- CC 0 to 15 mL/minute: 200 mg twice daily

Cimetidine is removed by haemodialysis, but not significantly removed by peritoneal dialysis.

Bladder disorders. Cimetidine effectively relieved symptoms in patients with painful bladder disease (encompassing conditions including cystitis, painful bladder syndrome, and urethral syndrome), especially suprapubic pain and nocturia, despite no apparent histological change in the bladder mucosa after treatment.[1]

1. Thilagarajah R, *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001; **87:** 207–12.

Dapsone toxicity. Cimetidine might reduce the haemolysis and methaemoglobinaemia associated with dapsone. For references supporting this suggestion, see Effects on the Blood, under Dapsone, p.261.

Diagnostic use. Cimetidine blocks renal tubular secretion of creatinine and has been used experimentally to improve the accuracy of estimations of glomerular filtration rate from creatinine clearance in patients with renal disease.[1] Best results were achieved with a bolus dose of 1.2 g and the use of such a high dose was questioned.[2]

1. van Acker BAC, *et al.* Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 1992; **340:** 1326–9.
2. Agarwal R. Creatinine clearance with cimetidine for measurement of GFR. *Lancet* 1993; **341:** 188.

Echinococcosis. Cimetidine has been given with albendazole to increase its effect (by inhibiting its metabolism) in the treatment of echinococcosis (p.136).

Immunomodulation. Studies in *mice* and humans have shown that H_2-antagonists have an immunoregulatory effect.[1] T-lymphocyte suppressor cells have histamine H_2 receptors and cimetidine has been reported to reduce activity of these cells, thus enhancing immune response.[1,2] There is also some evidence that it enhances cellular immunity, notably natural killer cell activity.[3] This discovery has led to the investigation of cimetidine in a number of disorders associated with alteration of the immune response including eosinophilic fasciitis, herpesvirus infections, mucocutaneous candidiasis,[4] hypogammaglobulinaemia,[5] and various malignancies.[1]

1. Kumar A. Cimetidine: an immunomodulator. *DICP Ann Pharmacother* 1990; **24:** 289–95.
2. Snyman JR, *et al.* Cimetidine as modulator of the cell-mediated immune response in vivo using the tuberculin skin test as parameter. *Br J Clin Pharmacol* 1990; **29:** 257–60.
3. Katoh J, *et al.* Cimetidine and immunoreactivity. *Lancet* 1996; **348:** 404–5.
4. Polizzi B, *et al.* Successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis. *Am J Med Sci* 1996; **311:** 189–90.
5. White WB, Ballow M. Modulation of suppressor-cell activity by cimetidine in patients with common variable hypogammaglobulinemia. *N Engl J Med* 1985; **312:** 198–202.

EOSINOPHILIC FASCIITIS. Eosinophilic fasciitis is a scleroderma-like syndrome of inflammation of the muscle fascia and associated eosinophilia and hypergammaglobulinaemia. Although it responds well to corticosteroid therapy in most cases, cimetidine has also been tried. The effect of cimetidine on eosinophilic fasciitis is unpredictable with both remission[1-4] and lack of response[5,6] having been reported in a few patients.

1. Solomon G, *et al.* Eosinophilic fasciitis responsive to cimetidine. *Ann Intern Med* 1982; **97:** 547–9.
2. Laso FJ, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 1026.
3. Garcia-Morteo O, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1984; **100:** 318–19.
4. Farrell AM, *et al.* Eosinophilic fasciitis associated with autoimmune thyroid disease and myelodysplasia treated with pulsed methylprednisolone and antihistamines. *Br J Dermatol* 1999; **140:** 1185–7.
5. Loftin EB. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 111–12.
6. Herson S, *et al.* Cimetidine in eosinophilic fasciitis. *Ann Intern Med* 1990; **113:** 412–13.

HERPESVIRUS AND PAPILLOMAVIRUS INFECTIONS. Although there have been numerous isolated and anecdotal reports of a beneficial response to cimetidine in patients with infections due to various *herpesviruses* (p.853), including genital herpes simplex,[1] infectious mononucleosis,[2,3] and herpes zoster[4-7] some of these reports have been criticised[8,9] mainly on the grounds that the majority of cases of herpes zoster will resolve within 2 to 3 weeks whether any treatment is given or not. Also, a double-blind placebo-controlled study involving 63 patients with herpes zoster[10] found no evidence that cimetidine relieved the pain or accelerated the rate of healing of lesions.

There are reports[11] of benefit from the use of cimetidine in patients with *viral warts* (p.1584), but controlled studies have failed to show significant benefit.[12,13]

1. Wakefield D. Cimetidine in recurrent genital herpes simplex infection. *Ann Intern Med* 1984; **101:** 882.
2. Goldstein JA. Cimetidine and mononucleosis. *Ann Intern Med* 1983; **99:** 410–11.
3. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med* 1986; **105:** 139.
4. Hayne ST, Mercer JB. Herpes zoster: treatment with cimetidine. *Can Med Assoc J* 1983; **129:** 1284–5.
5. Shandera R. Treatment of herpes zoster with cimetidine. *Can Med Assoc J* 1984; **131:** 279.
6. Mavligit GM, Talpaz M. Cimetidine for herpes zoster. *N Engl J Med* 1984; **310:** 318–19.
7. Arnot RS. Herpes zoster and cimetidine. *Med J Aust* 1984; **141:** 903.
8. Tyrrell DL. Course of herpes zoster. *Can Med Assoc J* 1984; **130:** 1109.
9. Giles KE. Herpes zoster and cimetidine. *Med J Aust* 1985; **142:** 283.
10. Levy DW, *et al.* Cimetidine in the treatment of herpes zoster. *J R Coll Physicians Lond* 1985; **19:** 96–8.
11. Glass AT, *et al.* Cimetidine therapy for recalcitrant warts in adults. *Arch Dermatol* 1996; **132:** 680–2.
12. Karabulut AA, *et al.* Is cimetidine effective for nongenital warts: a double-blind, placebo-controlled study. *Arch Dermatol* 1997; **133:** 533–4.
13. Rogers CJ, *et al.* Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; **41:** 123–7.

MALIGNANT NEOPLASMS. Because of its immunomodulatory effects cimetidine has been tried, with some reported benefit,[1-3] as an adjuvant in the management of a variety of malignant neoplasms such as those of the gastrointestinal tract (see p.664). However, a large randomised study[4] failed to show any benefit for cimetidine compared with placebo in gastric cancer. A similar study with ranitidine also failed to show any significant benefit.[5]

1. Tønnesen H, *et al.* Effect of cimetidine on survival after gastric cancer. *Lancet* 1988; **ii:** 990–2.
2. Adams WJ, Morris DL. Short-course cimetidine and survival with colorectal cancer. *Lancet* 1994; **344:** 1768–9.

3. Matsumoto S. Cimetidine and survival with colorectal cancer. *Lancet* 1995; **346:** 115.
4. Langman MJS, *et al.* Prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. *Br J Cancer* 1999; **81:** 1356–62.
5. Primrose JN, *et al.* A prospective randomised controlled study of the use of ranitidine in patients with gastric cancer. *Gut* 1998; **42:** 17–19.

Mastocytosis. Cimetidine, alone or with an antihistamine (histamine H_1-antagonist), has been reported to relieve gastrointestinal symptoms,[1,2] pruritus, and urticaria[3,4] in patients with mastocytosis (p.1138).

1. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. *Ann Intern Med* 1979; **90:** 769–71.
2. Linde R, *et al.* Combination H1 and H2 receptor antagonist therapy in mastocytosis. *Ann Intern Med* 1980; **92:** 716.
3. Simon RA. Treatment of systemic mastocytosis. *N Engl J Med* 1980; **302:** 231.
4. Frieri M, *et al.* Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. *Am J Med* 1985; **78:** 9–14.

Paracetamol toxicity. It has been suggested that cimetidine might be of use in the treatment of paracetamol poisoning (see p.108) because of its inhibition of the cytochrome P450 system. However, there appears to be no evidence to support the claims of benefit made in some anecdotal reports.[1]

1. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.

Porphyria. There are reports[1-3] of patients with acute intermittent porphyria (p.1448) showing clinical and biochemical improvement during treatment with cimetidine. Cimetidine is, however, considered to be unsafe in patients with porphyria (see under Precautions, above).

1. Baccino E, *et al.* Cimetidine in the treatment of acute intermittent porphyria. *JAMA* 1989; **262:** 3000.
2. Horie Y, *et al.* Clinical usefulness of cimetidine treatment for acute relapse in intermittent porphyria. *Clin Chim Acta* 1995; **234:** 171–5.
3. Cherem JH, *et al.* Cimetidine and acute intermittent porphyria. *Ann Intern Med* 2005; **143:** 694–5.

Skin disorders. Cimetidine has been used alone[1-8] or with an antihistamine (H_1-antagonist)[5,8,9] in various skin disorders. H_2-antagonists such as cimetidine and ranitidine have produced improvement in certain types of *urticaria* (p.1584), especially those associated with cold or angioedema. Their routine use in urticaria is controversial, but in practice their addition to conventional treatment can be tried in resistant cases.[10-12] Little additional benefit has been found with combination therapy in dermographic urticaria.[13] Although they may act by antagonism of H_2-receptors on cutaneous blood vessels, other mechanisms of action may be involved.[8] Patients with *pruritus* (p.1582) of various causes may also respond to H_2-antagonists,[1,2,6,7,9] but studies in larger groups of patients have demonstrated no benefit.[3-5,14]

1. Easton P, Galbraith PR. Cimetidine treatment of pruritus in polycythemia vera. *N Engl J Med* 1978; **299:** 1134.
2. Hess CE. Cimetidine for the treatment of pruritus. *N Engl J Med* 1979; **300:** 370.
3. Harrison AR, *et al.* Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 433–4.
4. Scott GL, Horton RJ. Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 434. Correction. *ibid.*; 936.
5. Zappacosta AR, Hauss D. Cimetidine doesn't help pruritus of uremia. *N Engl J Med* 1979; **300:** 1280.
6. Schapira DV, Bennett JM. Cimetidine for pruritus. *Lancet* 1979; **i:** 726–7.
7. Aymard JP, *et al.* Cimetidine for pruritus in Hodgkin's disease. *BMJ* 1980; **280:** 151–2.
8. Theoharides TC. Histamine (H)-receptor antagonists in the treatment of urticaria. *Drugs* 1989; **37:** 345–55.
9. Deutsch PH. Dermatographism treated with hydroxyzine and cimetidine and ranitidine. *Ann Intern Med* 1984; **101:** 569.
10. Advenier C, Queille-Roussel C. Rational use of antihistamines in allergic dermatological conditions. *Drugs* 1989; **38:** 634–44.
11. Ormerod AD. Urticaria: recognition, causes, and treatment. *Drugs* 1994; **48:** 717–30.
12. Greaves MW. Chronic urticaria. *N Engl J Med* 1995; **332:** 1767–72.
13. Sharpe GR, Shuster S. In dermographic urticaria H receptor antagonists have a small but therapeutically irrelevant additional effect compared with H antagonists alone. *Br J Dermatol* 1993; **129:** 575–9.
14. Raisch DW, *et al.* Evaluation of a non-food and drug administration-approved use of cimetidine: treatment of pruritus resulting from epidural morphine analgesia. *DICP Ann Pharmacother* 1991; **25:** 716–8.

Preparations

BP 2008: Cimetidine Injection; Cimetidine Oral Solution; Cimetidine Oral Suspension; Cimetidine Tablets;
USP 31: Cimetidine in Sodium Chloride Injection; Cimetidine Injection; Cimetidine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Tagamet†; Ulcerfen; ***Austral.:*** Cimehexal; Magicul; Sigmetadine†; Tagamet; ***Austria:*** Acidex; Cimetag; Neutromed; Neutronorm; Sodexx Cimetidine; Ulcometin; Ulcostad; ***Belg.:*** Doccimeti; Nuardin; Tagamet; ***Braz.:*** Cigamete; Cimetetax†; Cimetidan; Cimetil†; Cimetilab; Cimetin†; Cimetina†; Cimetinax; Cimetival; Cinetidina†; Cinton†; Climatidine†; Duomet†; Etidine; Gastidin†; Laveran†; Novacimet†; Pristonal; Prometidine; Stomakon†; Tagaliv; Tagamet; Tranimet†; Ulcedine; Ulcenon; Ulcerac; Ulceracid†; Ulcimet; Ulcinax; Ulcitag†; Ulcitrat; ***Canad.:*** Gaviscon Prevent†; Novo-Cimetine; Nu-Cimet; Tagamet†; ***Cz.:*** CimLich†; Lock-2†; Primamet; ***Denm.:*** Aciloc; Acinil; Cimecodan; Hocimin†; Novamet; ***Fr.:*** Stomedine; Tagamet; ***Ger.:*** Azucimet†; Cime; Cimebeta; Cimehexal; Cimet†; CimLich; duraH2†; Gastroprotect; H 2 Blocker; Sigacimet†; Tagamet; ***Gr.:*** Alkastom†; Besidin†; Cimeton†; Gastrolene†; Tagamet; Tamper; ***Hong Kong:*** Cementin; Cimedine; Cimeta; Cimulcer†; Citidine; Gastab; Gastidine; Maritidine; Simaglen; Syncomet; Tagadine†; Tagamet; Ulcomet; ***Hung.:*** Histodil; ***India:*** Cimet†; ***Indon.:*** Cimexol; Corsamet; Licomet; Nulcer; Sanmetidin; Tagamet; Ulcedine; Ulcumet; Ulcusan; Ulsikur; Xepamet; ***Irl.:*** Cedine; Cimagen; Cimeldine; Dyspamet; Galenamet; Geramet; Pinamet; Tagamet; ***Israel:*** Cemidin; Cimetag; Cimi†; Tagamet; ***Ital.:*** Biomag; Brumetidina; Dina†; Etideme; Notul†; Stomet; Tagamet; Temic; Ulcedin; Ulcodina†; Ulcomedina†; Ulis; ***Malaysia:*** Cimulcer; Shintamet; Tagamet; Ulcidine†; Xepamet†; ***Mex.:*** Alcatex†; Antil†; Cimebec; Cimedul; Cimeffer; Cimetase; Colimet; Columina†; Gastrodina; Metidisol†; Procimeti; Sercim; Sinegastrin; Tagamet; Ulcedine†; Ulmarin; Ulserral; ***Neth.:*** Tagamet; ***Norw.:*** Cimal; Tagamet; ***NZ:*** Cytine; ***Philipp.:*** Antag; Ciclem; Cimecid; Cimulcer; Duogastril; Montidin; Tagamet; Ulcenon; ***Pol.:*** Altramet; Cimegast; ***Port.:*** Cim; Evicer†; Tagamet; Ulceridine†; ***Rus.:*** Histodil (Гистодил); ***S.Afr.:*** Aci-Med; Cimlok; Cinadine; Cymi; Hexamet; Lenamet; Secadine; Tagamet; Ulcim; ***Singapore:*** Cementin; Cimulcer; Citidine; Erlmetin†; Gastromet†; Himetin; Shintamet; Tagamet; Xepamet; ***Spain:*** Ali Veg; Fremet; Mansal†; Tagamet; ***Swed.:*** Acinil; Tagamet; ***Switz.:*** Malimed†; Tagamet†; ***Thai.:*** Aidar†; Alserine†; Cencamet; Cidine; Cigamet; Cimet-P†; Cimetine; Cimidine†; Cimulcer†; Citidine; Climet; CMD†; Duotric; Gastrodin†; Iwamet; Manomet; Med-Gastramet†; Milamet; Peptica; Pondarmett; Promet; Rinadine; Sertidine; Siamidine; Simaglen; Simex; Tagamet†; Ulcedine; Ulcemet; Ulcimet; Umamett; ***UAE:*** Cimetag; ***UK:*** Acitak†; Dyspamet; Galenamet; Peptimax†; Tagamet; Ultec†; Zita; ***USA:*** Tagamet; ***Venez.:*** Cavimet†; Cimetix†; Gadol; Iscaten†; Mempotal†.

Multi-ingredient: ***Neth.:*** Aciflux.

Cimetropium Bromide *(rINN)*

Bromuro de cimetropio; Cimetropii Bromidum; Cimétropium, Bromure de; DA-3177; Hyoscine-*N*-(cyclopropylmethyl) Bromide. 8-(Cyclopropylmethyl)-6β,7β-epoxy-3α-hydroxy-1αH,5αH-tropanium bromide, (−)-(*S*)-tropate.

Циметропия Бромид

$C_{21}H_{28}BrNO_4$ = 438.4.
CAS — 51598-60-8.
ATC — A03BB05.
ATC Vet — QA03BB05.

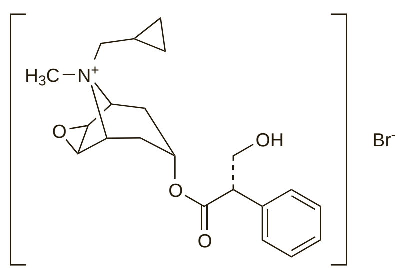

Profile

Cimetropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an antispasmodic in the treatment of gastrointestinal disorders, in usual doses of 50 mg two or three times daily orally or by rectal suppository. It has also been given intramuscularly or intravenously in usual doses of 5 mg.

◊ References.

1. Dobrilla G, *et al.* Longterm treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. *Gut* 1990; **31:** 355–8.
2. Marzio L, *et al.* Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. *Dig Dis Sci* 1994; **39:** 1389–94.
3. Savino F, *et al.* Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr* 2002; **34:** 417–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Alginor.

Cinitapride *(rINN)*

Cinitaprida; Cinitapridum. 4-Amino-*N*-[1-(3-cyclohexen-1-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide.

Цинитаприд

$C_{21}H_{30}N_4O_4$ = 402.5.
CAS — 66564-14-5.

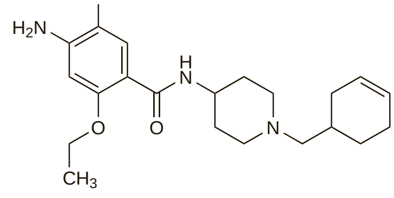

Profile

Cinitapride is a substituted benzamide used for its prokinetic properties. It is given as the acid tartrate in oral doses of 1 mg three times daily before meals in the management of gastroparesis and gastro-oesophageal reflux disease (p.1696).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cinigest; Paxapride; Rogastril; ***Mex.:*** Pemix; ***Spain:*** Blaston; Cidine.

Cisapride *(BAN, USAN, rINN)*

Cisaprid; Cisaprida; Cisapridas; Cisapride monohydraté; Cisapridum; Cisapridum monohydricum; Ciszaprid; Cyzapryd jednowodny; R-51619; Sisapridi. *cis*-4-Amino-5-chloro-*N*-{1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl}-2-methoxybenzamide monohydrate.

Цизаприд

$C_{23}H_{29}ClFN_3O_4,H_2O$ = 484.0.
CAS — 81098-60-4 (anhydrous cisapride).
ATC — A03FA02.
ATC Vet — QA03FA02.

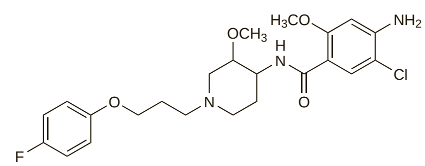

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cisapride Monohydrate; Cisapride BP 2008). A white or almost white powder; it exhibits polymorphism. Practically insoluble in water; soluble in dichloromethane; freely soluble in dimethylformamide; sparingly soluble in methyl alcohol. Protect from light.

Cisapride Tartrate *(BANM, rINNM)*

Cisapride, tartrate de; Cisapridi tartras; Cisaprido tartratas; Cisaprid-tartarát; Cisapridtartrat; Ciszaprid-tartarát; Sisapriditartraatti; Tartrato de cisaprida.

Цизаприда Тартрат

$C_{27}H_{35}ClFN_3O_{10}$ = 616.0.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cisapride Tartrate). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in dimethylformamide. Protect from light.

Adverse Effects

The most commonly reported adverse effects with cisapride are gastrointestinal disturbances including abdominal cramps, borborygmi, and diarrhoea. Headache and lightheadedness may also occur. Hypersensitivity (including rash, pruritus, and bronchospasm), convulsions, extrapyramidal effects, and increased urinary frequency, have occasionally been reported. Cases of arrhythmia, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT interval prolongation have occurred rarely; fatalities have resulted, and have led to severe restrictions on its use (see Effects on the Heart, below). There have been a few cases of disturbances in liver function among patients receiving cisapride.

Incidence of adverse effects. A comparison of data from prescription-event monitoring in over 13 000 recipients of cisapride and from a further 9726 recipients involved in a controlled study showed that diarrhoea, in about 2 to 4% of patients, was the commonest adverse effect reported.[1] Other relatively common adverse effects were headache, abdominal pain, nausea and vomiting, and constipation, all in around 1 to 1.5% of patients. There were 46 reports in the prescription-event monitoring data of increased urinary frequency (plus a further 20 among the controlled study patients), and 5 reports of arrhythmias.

1. Wager E, *et al.* A comparison of two cohort studies evaluating the safety of cisapride: prescription-event monitoring and a large phase IV study. *Eur J Clin Pharmacol* 1997; **52:** 87–94.

Effects on the heart. Seven reports[1] of cardiac effects associated with cisapride were submitted to the WHO Programme for International Drug Monitoring between 1989 and 1991. They included palpitations in 4, tachycardia and hypertension in 1, and extrasystole in 2. Subsequent reports implicated cisapride in the development of prolonged QT interval and torsade de pointes or ventricular fibrillation or both.[2,3] By December 1999 the FDA had received 341 reports of heart rhythm abnormalities associated with cisapride use, including 80 reports of deaths. Most patients were either receiving other drugs known to impair cisapride metabolism (see Interactions, below) or had other factors predisposing to arrhythmias. In the light of earlier reports of cardiac effects and of evidence for a direct effect of cisapride on the heart at therapeutic concentrations, in 1998 the UK CSM **contra-indicated**[2] the use of cisapride in patients receiving drugs that could inhibit cisapride metabolism or that prolong the QT interval, as well as in patients with a history of QT interval prolongation, ventricular arrhythmia, or torsade de pointes, or other risk factors for arrhythmia (see Precautions, below). Neonates[4] (especially of low gestational age[5]) are vulnerable to cisapride-induced QT interval prolongation, and the CSM also specifically contra-indicated use in premature neonates[2] and noted that there were insufficient data to support use in children up to the age of 12. Other studies have also noted a prolongation of QT interval in children.[6,7] However, some commentators have questioned the general contra-indication in prematurity,[8] and one retrospective analysis estimated the rate of serious adverse events such as arrhythmia in premature newborns to be less than 1 in 11 000, excluding those cases related to concurrent treatment with a contra-indicated drug or to overdose.[9] Conversely, others emphasise the lack of objective evidence of benefit for cisapride in most paediatric indications.[10] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition has published recommendations on the use of cisapride in paediatric gastro-oesophageal reflux disease,[11] including that the total daily dose of cisapride should rarely exceed 800 micrograms/kg, and that ECG monitoring should be performed before and after 3 days of treatment in certain groups such as premature infants.

The use of cisapride has also been the subject of warnings and restrictions in other countries. In the USA, prescribing information was amended in January 2000 to recommend that all patients should receive an ECG before beginning cisapride therapy and extending the contra-indications to use; the drug was subsequently **withdrawn** from general supply, remaining available only in severely restricted cases. In July 2000 cisapride was also withdrawn completely from the UK market.[12] In Europe, the European Commission decided that cisapride-containing products could be maintained with restricted indications; all patients given cisapride should be enrolled in either a study or registry of clinical safety, or a study of clinical effectiveness.[13] Despite a withdrawal of cisapride from general supply, a retrospective cohort study in South Korea found that it was still in use there up to 2 years later; in many instances cisapride had been given with contra-indicated drugs, which was associated with an increase in the risk of all-cause mortality.[14]

1. Olsson S, Edwards IR. Tachycardia during cisapride treatment. *BMJ* 1992; **305:** 748–9.
2. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
3. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996; **335:** 290–1.
4. Bernardini S, *et al.* Effect of cisapride on QTc interval in neonates. *Arch Dis Child Fetal Neonatal Ed* 1997; **77:** F241–3.
5. Dubin A, *et al.* Cisapride associated with QTc prolongation in very low birth weight preterm infants. *Pediatrics* 2001; **107:** 1313–16.
6. Hill SL, *et al.* Proarrhythmia associated with cisapride in children. *Pediatrics* 1998; **101:** 1053–6.
7. Khongphatthanayothin A, *et al.* Effects of cisapride on QT interval in children. *J Pediatr* 1998; **133:** 51–6.
8. Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants, and children. *Arch Dis Child* 1998; **79:** 469–71.
9. Ward RM, *et al.* Cisapride: a survey of the frequency of use and adverse events in premature newborns. *Pediatrics* 1999; **103:** 469–72.
10. Cairns P. The risks and benefits of cisapride. *Arch Dis Child* 1999; **80:** 493.
11. Vandenplas Y, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux: the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999; **28:** 518–28.
12. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid) withdrawn. *Current Problems* 2000; **26:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
13. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Cisapride: licences cancelled. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
14. Choi N-K, *et al.* Increase in mortality rate following coprescription of cisapride and contraindicated drugs. *Ann Pharmacother* 2007; **41:** 667–73.

Effects on the respiratory system. Chest tightness, wheezing, and a fall in peak flow rate occurred in a patient with severe brittle asthma after taking cisapride 10 mg.[1] Four other cases of bronchospasm associated with cisapride were discussed in a subsequent report;[2] in 2 of these cases symptoms resolved on withdrawal and recurred on rechallenge.

1. Nolan P, *et al.* Cisapride and brittle asthma. *Lancet* 1990; **336:** 1443.
2. Pillans P. Bronchospasm associated with cisapride. *BMJ* 1995; **311:** 1472.

Effects on the urinary tract. There had been 12 cases of urinary disturbances associated with use of cisapride[1] reported to the Australian Adverse Drug Reactions Advisory Committee between March 1991 and July 1993. Five reports were of urinary incontinence, 8 involved frequency, and individual reports involved cystitis, hesitancy, and urinary retention. The majority of the cases involved women, and most patients were elderly.

1. Boyd IW, Rohan AP. Urinary disorders associated with cisapride. *Med J Aust* 1994; **160:** 579–80.

Precautions

Cisapride should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions as in gastrointestinal haemorrhage, obstruction, perforation, or immediately after surgery.

Cisapride is **contra-indicated** in the following patients:

- those receiving potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as macrolide antibacterials, azole antifungals, HIV-protease inhibitors, or nefazodone (see also Interactions, below)
- those taking other drugs that predispose to electrolyte disturbances or that prolong the QT interval
- those with a personal or family history of QT interval prolongation
- those with a history of ventricular arrhythmia or torsade de pointes

Furthermore, it should not be given to those with other risk factors for arrhythmia including:

- clinically significant heart disease
- uncorrected electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia)
- renal failure
- respiratory failure

Use is also contra-indicated in premature infants for up to 3 months after birth.

Cisapride should be used with caution and in reduced doses in patients with hepatic or renal impairment. All patients should have their ECG, serum electrolytes, and renal function monitored before and during treatment.

Care should be taken not to exceed the recommended dose.

Breast feeding. No adverse effects have been observed in breast-fed infants whose mothers were receiving cisapride, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Interactions

Cisapride is metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with drugs that significantly inhibit this enzyme is contra-indicated as it may result in increased plasma concentrations of cisapride and hence a greater risk of QT interval prolongation and ventricular arrhythmias. Examples of such drugs include the azole antifungals ketoconazole, fluconazole, itraconazole, and miconazole; the macrolide antibacterials troleandomycin, azithromycin, erythromycin, and clarithromycin; the NNRTIs delavirdine and efavirenz; and the HIV-protease inhibitors. Nefazodone may interact similarly.

Cisapride should not be used in patients receiving other medication known to prolong the QT interval, including quinine or halofantrine, terfenadine, astemizole, certain antiarrhythmics such as amiodarone or quinidine, some antidepressants such as amitriptyline, phenothiazine antipsychotics, and sertindole. Cimetidine may enhance cisapride bioavailability. Grapefruit juice also increases the bioavailability of cisapride and they should not be taken together. In addition, drugs such as potassium-sparing diuretics, or insulin in acute settings, can result in altered electrolyte balance, and use with cisapride may also increase the risk of arrhythmias.

Antimuscarinics and possibly opioid analgesics may antagonise the gastrointestinal effects of cisapride. Because cisapride increases intestinal motility it may affect the absorption of other drugs, either diminishing absorption from the stomach or enhancing absorption from the small intestine. Prothrombin times may be increased in some patients receiving oral anticoagulants, and the effects of alcohol and some other CNS depressants may be enhanced.

◊ Reviews.

1. Bedford TA, Rowbotham DJ. Cisapride: drug interactions of clinical significance. *Drug Safety* 1996; **15:** 167–75.
2. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet* 2000; **39:** 49–75.

Cardiovascular drugs. Near syncope and a prolonged QT interval occurred in a patient taking cisapride and *diltiazem*.[1] Diltiazem may have inhibited the metabolism of cisapride. For mention of cisapride possibly reducing the absorption of *digoxin*, see p.1262.

1. Thomas AR, *et al.* Prolongation of the QT interval related to cisapride-diltiazem interaction. *Pharmacotherapy* 1998; **18:** 381–5.

H_2-antagonists. *Cimetidine*[1] but not *ranitidine*[2] has been reported to enhance the bioavailability of oral cisapride, possibly by inhibition of cisapride metabolism (cimetidine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4). Cisapride conversely increases the rate of absorption and decreases the oral bioavailability of both cimetidine[1] and ranitidine (see p.1766).

1. Kirch W, *et al.* Cisapride-cimetidine interaction: enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.
2. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.

Pharmacokinetics

Cisapride is readily absorbed from the gastrointestinal tract, with peak plasma concentrations achieved 1 to 2 hours after an oral dose. It undergoes extensive first-pass metabolism in the liver and gut wall, resulting in an absolute bioavailability of 35 to 40%. The main metabolic pathways are oxidative *N*-dealkylation by the cytochrome P450 isoenzyme CYP3A4, producing the major metabolite norcisapride, and aromatic hydroxylation. More than 90% of a dose is excreted as metabolites in the urine and faeces in about equal amounts. A small amount is distributed into breast milk. The elimination half-life is about 10 hours. Cisapride is about 98% bound to plasma proteins.

Uses and Administration

Cisapride is a substituted benzamide used for its prokinetic properties. It stimulates gastrointestinal motility, probably by increasing the release of acetylcholine in the gut wall at the level of the myenteric plexus, increases the resting tone of the lower oesophageal sphincter, and increases the amplitude of lower oesophageal contractions. Gastric emptying is accelerated and the mouth-to-caecum transit time is reduced. Colonic peristalsis is also increased which decreases colonic transit time. Cisapride apparently lacks antidopaminergic effects (unlike metoclopramide, p.1747, to which it is chemically related) or direct parasympathomimetic activity and it does not affect prolactin release or gastric secretion. It is reported to be an agonist at serotonin-4 ($5\text{-}HT_4$) receptors.

Cisapride has been used mainly in the treatment of gastro-oesophageal reflux disease (p.1696), in disorders associated with decreased gastric motility (p.1694), and in non-ulcer dyspepsia. However, as mentioned under Effects on the Heart, above, its use is severely restricted by its propensity to cause cardiac arrhythmias, and it has been withdrawn completely in many countries, including the UK.

Cisapride is given as the monohydrate, but doses are calculated in terms of the anhydrous substance. Cisapride monohydrate 10.39 mg is equivalent to about 10 mg of anhydrous cisapride. It is taken orally 15 to 30 minutes before a meal and at bedtime, if necessary. Where still licensed, a usual oral dose is 5 to 10 mg three to four times daily up to a maximum daily dose of 40 mg. For discussion of dosage and use in children, see below.

Doses of cisapride should be reduced in patients with hepatic or renal impairment (see below).

Administration in children. Where still licensed, neonates, infants, and children have been given cisapride 200 micrograms/kg orally three or four times daily up to a maximum daily dose of 800 micrograms/kg. However, there are particular safety concerns over the use of cisapride in children because of the risk of cardiac arrhythmias (see Effects on the Heart, above). Special care is needed in neonates and cisapride is contra-indicated in premature neonates for 3 months after birth due to the increased risk of QT interval prolongation in this patient group.

Its efficacy has also been questioned and a systematic review[1] of the use of cisapride in children found no clear evidence that cisapride had a statistically significant effect in reducing symptoms of gastro-oesophageal reflux disease compared with placebo.

1. Augood C, *et al.* Cisapride treatment for gastro-oesophageal reflux in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 10/01/07).

Administration in hepatic or renal impairment. In patients with hepatic impairment the dose of cisapride should be half the usual dose, followed by adjustment depending on clinical response. In cases where renal impairment is not considered to contra-indicate the use of cisapride, a similar reduction in dose has been recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cisap†; Cispride†; Digenormotil†; Etacril†; Fabrapride; Kinetizine†; Prepulsid†; Pulsar; Regalisa†; ***Austral.:*** Prepulsid†; ***Austria:*** Prepulsid†; ***Belg.:*** Prepulsid; ***Braz.:*** Prepulsid; ***Chile:*** Gastrokin†; Gastromet; Marovil†; Ondax; Prepulsid†; Tono-Cis†; ***Cz.:*** Prepulsid†; ***Denm.:*** Prepulsid†; ***Fin.:*** Prepulsid†; ***Fr.:*** Prepulsid; ***Gr.:*** Alimix†; Bozaktral; Cefanyl†; Cevilor†; Ciscaprid†; Dolyzinax†; Elpegon†; Epasan†; Gastridol†; Kinussen†; Lamafer†; Lasapride†; Lirebin†; Lycalin†; Minsk†; Nastilox†; Oferin†; Ruvetine†; Saprimix†; Spabucol†; Systilan†; ***Hong Kong:*** Prepulsid†; ***Hung.:*** Coordinax†; ***India:*** Alipride; Cisalone†; Gastro; ***Indon.:*** Acpulsif; Disflux; Ethiprid; Guarposid; Pridesia; Stimulit; ***Irl.:*** Prepulsid†; ***Israel:*** Prepulsid; ***Mex.:*** Aposada; Cepriser; Enteropride; Eriken; Expril; Kinestase; Maprilex; Mavisid; Nodrix; Prepulsid†; Presistin; Profercol; Sapriken; Unamol; ***Neth.:*** Prepulsid; ***Norw.:*** Prepulsid†; ***NZ:*** Prepulsid†; ***Pol.:*** Gasprid; Gastronax; ***Port.:*** Prepulsid; ***S.Afr.:*** Prepulsid; ***Spain:*** Arcasin†; Fisiogastrol†; Kelosal†; Prepulsid†; ***Swed.:*** Prepulsid†; ***Switz.:*** Prepulsid†; ***Thai.:*** Cipasid; Cipride†; Cisapin†; Cisaride; Esorid†; Metison†; Palcid†; Prepulsid†; Pri-De-Sid†; ***Venez.:*** Adamin†; Cisamod; Isaprid†; Motilar†.

Multi-ingredient: ***Arg.:*** Digenormotil Plus†; Gastrimet Enzimatico†; Gastrimet†; Pulsar Enzimatico†; Pulsar Plus†; ***India:*** Gastro MPS; ***Mex.:*** Ergex.

Clebopride *(BAN, USAN, rINN)*

Cleboprida; Clébopride; Clebopridum; LAS-9273. 4-Amino-*N*-(1-benzyl-4-piperidyl)-5-chloro-*o*-anisamide.

Клебоприд

$C_{20}H_{24}ClN_3O_2$ = 373.9.
CAS — 55905-53-8.
ATC — A03FA06.
ATC Vet — QA03FA06.

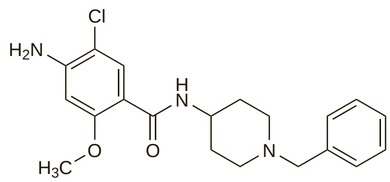

Clebopride Malate *(BANM, rINNM)*

Clébopride, malate de; Clebopridi malas; Klebeprid malát; Klebopridimalaatti; Klebopridmalat; Kleboprid-malát; Klebeprido malatas; Malato de cleboprida.

Клебоприда Малат

$C_{20}H_{24}ClN_3O_2,C_4H_6O_5$ = 508.0.
CAS — 57645-91-7.
ATC — A03FA06.
ATC Vet — QA03FA06.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Clebopride Malate). A white or almost white, crystalline powder. Sparingly soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. The pH of a 1% solution in water is 3.8 to 4.2. Protect from light.

Profile

Clebopride is a substituted benzamide similar to metoclopramide (p.1747), that is used for its antiemetic and prokinetic actions in nausea and vomiting (p.1700) and various other gastrointestinal disorders. It is given as the malate but doses are expressed in terms of the base. Clebopride malate 679 micrograms is equivalent to about 500 micrograms of clebopride.

Clebopride malate is given in a usual oral dose equivalent to clebopride 0.5 mg three times daily before meals or 0.5 to 1 mg by intramuscular or intravenous injection for acute symptoms. For dosage in children see below.

Administration in children. Adolescents aged 12 to 20 years may be given clebopride malate orally in a dose equivalent to clebopride 250 micrograms three times daily. An oral dose of 15 to 20 micrograms/kg daily in 3 divided doses may be used for children under 12; the following doses have been recommended:

- 1 to 4 years: 50 micrograms 3 times daily
- 4 to 8 years: 100 micrograms 3 times daily
- 8 to 10 years: 150 micrograms 3 times daily
- 10 to 12 years: 200 micrograms 3 times daily

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gastridin; ***Indon.:*** Clast; ***Ital.:*** Motilex; ***Port.:*** Clebofex; Clebutec; ***Spain:*** Cleboril.

Multi-ingredient: ***Arg.:*** Eudon; Gastridin-E; Somasedan; ***Spain:*** Clanzoflat; Flatoril.

Clidinium Bromide *(BAN, USAN, rINN)*

Bromuro de clidinio; Clidinii Bromidum; Clidinium, Bromure de; Klidiniumbromid; Klidiniumbromidi; Klidinyum Bromür; Ro-2-3773. 3-Benziloyloxy-1-methylquinuclidinium bromide.

Клидиния Бромид

$C_{22}H_{26}BrNO_3$ = 432.4.
CAS — 7020-55-5 (clidinium); 3485-62-9 (clidinium bromide).

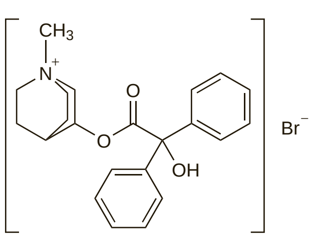

Pharmacopoeias. In *US.*

USP 31 (Clidinium Bromide). A white or nearly white, practically odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clidinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used alone or more often with chlordiazepoxide in the symptomatic treatment of peptic ulcer disease and other gastrointestinal disorders.

Preparations

USP 31: Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Libraxin; ***Canad.:*** Apo-Chlorax; Librax; ***Chile:*** Gastrolen; Lerogin; Libraxin; Lironex†; Sedogastrol†; Tensoliv; ***Fin.:*** Librax; ***Fr.:*** Librax; ***Gr.:*** Distedon; Librax; ***Hong Kong:*** Bralix; Librax; Medocalum†; ***India:*** Equirex; Normaxin; Spasrax; ***Indon.:*** Braxidin; Cliad; Klidibrax; Librax; Melidox; Renagas; ***Israel:*** Nirvaxal; ***Ital.:*** Librax; ***Malaysia:*** Apo-Chlorax†; Liblan; ***Port.:*** Librax; ***S.Afr.:*** Librax; ***Singapore:*** Apo-Chlorax; Chlobax; Librax; Medocalum; ***Switz.:*** Librax; Librocol; ***Thai.:*** Kenspa; Librax; Pobrax†; Tumax; Zepobrax†; ***Turk.:*** Klipaks; Librax; ***USA:*** Clindex; Librax; ***Venez.:*** Librax.

Colocynth

Bitter Apple; Bitter Cucumber; Colocinto; Colocynth Pulp; Colocynthis; Coloquinte; Coloquintidas; Koloquinthen.

Колоцинт

NOTE. The synonym Bitter Apple has also been applied to the fruits of *Solanum incanum.*

Profile

Colocynth is the dried pulp of the fruit of *Citrullus colocynthis* (Cucurbitaceae). It has a drastic purgative and irritant action and has been superseded by less toxic laxatives.

Homoeopathy. Colocynth has been used in homoeopathic medicines under the following names: Colocynthis; Coloc.

Dantron *(BAN, rINN)*

Antrapurol; Chrysazin; Danthron; Dantrón; Dantrone; Dantroni; Dantronum; Dianthon; Dioxyanthrachinonum. 1,8-Dihydroxyanthraquinone.

Дантрон

$C_{14}H_8O_4$ = 240.2.
CAS — 117-10-2.
ATC — A06AB03.
ATC Vet — QA06AB03.

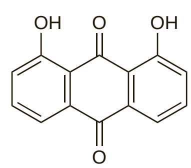

NOTE. Compounded preparations of dantron may be represented by the following names:

- Co-danthramer *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively
- Co-danthrusate (*BAN*)—dantron 5 parts and docusate sodium 6 parts (w/w).

Pharmacopoeias. In *Br.*

BP 2008 (Dantron). An orange, odourless or almost odourless, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether; dissolves in solutions of alkali hydroxides.

Adverse Effects and Precautions

As for Senna, p.1769. Dantron may colour the urine pink or red. Discoloration and superficial sloughing of perianal skin can occur after prolonged contact, therefore dantron should not be used in infants wearing nappies (diapers) and should be used with caution in incontinent patients. The mucosa of the large intestine may be discoloured with prolonged use or high dosage.

In *rodents*, dantron has been associated with the development of intestinal and liver tumours. Consequently, its use has been restricted, see Uses and Administration, below.

◊ References to adverse effects occurring with dantron-containing laxatives include individual cases of leucopenia with liver damage,[1] greyish-blue skin discoloration,[2] and orange vaginal discharge.[3] There has also been a report of intestinal sarcoma in an 18-year-old girl with a history of prolonged use of a dantron-containing laxative.[4] In May 2000 the UK CSM restricted the use of dantron to terminally ill patients on the grounds that preclinical evidence had increased and dantron was now established as a potential human carcinogen.[5]

1. Tolman KG, *et al.* Possible hepatotoxicity of Doxidan. *Ann Intern Med* 1976; **84:** 290–2.
2. Darke CS, Cooper RG. Unusual case of skin discoloration. *BMJ* 1978; **1:** 1188–9.
3. Greer IA. Orange periods. *BMJ* 1984; **289:** 323.
4. Patel PM, *et al.* Anthraquinone laxatives and human cancer: an association in one case. *Postgrad Med J* 1989; **65:** 216–17.
5. Committee on Safety of Medicines/Medicine Control Agency. Danthron restricted to constipation in the terminally ill. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 08/11/06)

Breast feeding. The American Academy of Pediatrics[1] state that, although usually compatible with breast feeding, use of dantron by breast-feeding mothers has been reported to cause increased bowel activity in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/06)

Pharmacokinetics

Dantron is metabolised by bacteria in the colon. Dantron or its metabolites are absorbed from the gastrointestinal tract, as indicated by discoloration of urine in some patients. Dantron or its metabolites are excreted in the faeces and the urine, and also in other secretions including breast milk.

Uses and Administration

Dantron is an anthraquinone stimulant laxative but, unlike senna (p.1769), it is not a glycoside. It is given orally to treat constipation (p.1693) and is effective within 6 to 12 hours. However, because of concern over *rodent* carcinogenicity it has been withdrawn in some countries, and its use restricted in others. In the UK, it may be used only in terminally ill patients.

Dantron is given in doses of 25 to 75 mg when given with poloxamer 188 (p.1918) as co-danthramer, and in doses of 50 to 150 mg when given with docusate sodium (p.1725) as co-danthrusate. Doses are usually given at bedtime. For doses in children, see below.

Administration in children. Children under 12 years have been given dantron 12.5 to 25 mg orally as co-danthramer or 50 mg as co-danthrusate. Doses are usually given at bedtime. Children aged 12 years and over may be treated with the adult dose (see Uses and Administration, above).

The *BNFC* recommends similar doses to these, but restricts the use of co-danthramer to children aged 2 years and over, and the use of co-danthrusate to those aged 6 years and over.

Dantron should not be used in infants wearing nappies (diapers) as it may cause discoloration and superficial sloughing of the skin.

Preparations

BP 2008: Co-danthrusate Capsules.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Fenogar†; ***Chile:*** Modane; ***Irl.:*** Ailax; Codalax; Cotron; ***Mex.:*** Modaton; ***NZ:*** Codalax†; Conthram†; ***UK:*** Ailax†; Capsuvac; Codalax; Danlax; Normax.

Dicycloverine Hydrochloride

(BANM, rINNM)

Cloridrato de Diciclovenina; Dicikloverin-hidroklorid; Dicikloverino hidrochloridas; Dicyclomine Hydrochloride; Dicyclovérine, chlorhydrate de; Dicycloverini hydrochloridum; Dicykloverin-hydrochlorid; Dicykloverinhydroklorid; Disykloveriinihydrokloridi; Hidrocloruro de diciclovenina. 2-Diethylaminoethyl bicyclohexyl-1-carboxylate hydrochloride.

Дицикловерина Гидрохлорид

$C_{19}H_{35}NO_2,HCl$ = 345.9.
CAS — 77-19-0 (dicycloverine); 67-92-5 (dicycloverine hydrochloride).
ATC — A03AA07.
ATC Vet — QA03AA07.

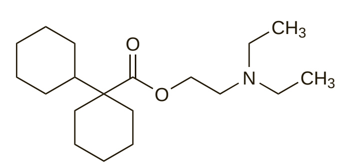

(dicycloverine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dicycloverine Hydrochloride). A white or almost white, crystalline powder. It shows polymorphism. Soluble in water; freely soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.0 to 5.5.

USP 31 (Dicyclomine Hydrochloride). A fine white, practically odourless, crystalline powder. Soluble 1 in 13 of water, 1 in 5 of alcohol, 1 in 2 of chloroform and of glacial acetic acid, and 1 in 770 of ether. pH of a 1% solution in water is between 5.0 and 5.5.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Dicycloverine hydrochloride should not be given to infants younger than 6 months of age.

Apnoea. Reports[1-3] of severe apnoea in infants aged 5 to 10 weeks associated with the use of dicycloverine.

1. Williams J, Watkin-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *BMJ* 1984; **288:** 901.
2. Edwards PDL. Dicyclomine in babies. *BMJ* 1984; **288:** 1230.
3. Spoudeas H, Shribman S. Dicyclomine in babies. *BMJ* 1984; **288:** 1230.

Pregnancy. For a review of the risks to the fetus of antiemetic therapy during pregnancy, with particular reference to *Debendox* (*Bendectin*: dicycloverine with doxylamine and pyridoxine), see under Antihistamines on p.563.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Dicycloverine hydrochloride is a tertiary amine antimuscarinic with effects similar to but weaker than those of atropine (p.1219); it also has a direct antispasmodic action.

Dicycloverine is used in gastrointestinal spasm, particularly that associated with the irritable bowel syndrome. For adults, 10 to 20 mg of dicycloverine hydrochloride is given orally 3 times daily; in the USA, up to 40 mg four times daily has been recommended where adverse effects permit. Children aged 6 months to 2 years may be given 5 to 10 mg up to 3 or 4 times daily; doses are usually given 15 minutes before meals. Children aged 2 to 12 years may be given 10 mg three times daily.

Dicycloverine hydrochloride may be given intramuscularly in doses of 20 mg given 4 times daily to patients in whom oral therapy is temporarily impractical, but should not be used for longer than 1 to 2 days.

Preparations

BP 2008: Dicycloverine Oral Solution; Dicycloverine Tablets;
USP 31: Dicyclomine Hydrochloride Capsules; Dicyclomine Hydrochloride Injection; Dicyclomine Hydrochloride Syrup; Dicyclomine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Babypasmil; ***Austral.:*** Merbentyl†; ***Braz.:*** Bentyl; ***Canad.:*** Bentylol; Formulex†; Lomine; ***Hong Kong:*** Dicymine; ***India:*** Cyclominol; Cyclopam; Dysmen; Spasmo-Proxyvon; Spasmonil; ***Irl.:*** Merbentyl†; ***Israel:*** Notensyl; ***Mex.:*** Bentyl; Clominal; Dicigon; Diclomin; Sediclon; ***NZ:*** Merbentyl†; ***Philipp.:*** Bentyl; Dilomin; Relestal; Spasdon; ***Port.:*** Optimal†; ***Rus.:*** Trigan (Триган); ***S.Afr.:*** Clomin†; Medicyclomine†; Merbentyl; ***Thai.:*** Dicomin; Dicymine; ***UK:*** Merbentyl; ***USA:*** Antispas; Bentyl; Byclomine; Dibent; Or-Tyl; ***Venez.:*** Ciclan†; Diciclor†; Mabex.

Multi-ingredient: ***Arg.:*** Dafne; ***Chile:*** Profisin; ***Hong Kong:*** Colimix; Dicymine Co; Epilon; Veragel; ***India:*** Colimex; Colirid; Cyclo-Meff; Cyclopam; Diclospa; Dysmen; Nicispas; Normaxin; Parvon-Spas; Spasmo-Proxyvon; Spasmo-Proxyvon Forte; Spasmocip Plus; Spasmoflexon†; Spasmonil; Spasmonil Plus; Trigan-D; Ze-Spas; ***Ital.:*** Merankol Pastiglie; ***Malaysia:*** Colimix; Uphacol†; ***Mex.:*** Alphalox-D; Exhidrol; Farcolan; ***Port.:*** Nausefe; ***Rus.:*** Trigan-D (Триган-Д); ***S.Afr.:*** Acugel; Alkalite D; Alumag D; Alumite D; Asic; Betaclomin; Co-Gel; Gelumen; Kolantyl; Medigel; Microgel; Neutragel-D; pH 550†; Propan Gel-S; Remotrox; Spasmogel; ***Singapore:*** Colimix; Meclosil; Veragel DMS; ***Spain:*** Colchimax; Neocolan; ***Thai.:*** Berclomine; Biodan†; Cymine; Difemic; Kremil-S; Mainnox; Med-Anspasmic†; Spasticone; Veragel; ***UK:*** Kolanticon; ***Venez.:*** Clopina†; Dicigel.

Difemerine Hydrochloride *(rINNM)*

Difémérine, Chlorhydrate de; Difemerini Hydrochloridum; Hidrocloruro de difemerina; UP-57. 2-Dimethylamino-1,1-dimethylethyl benzilate hydrochloride.

Дифемерина Гидрохлорид

$C_{20}H_{25}NO_3,HCl = 363.9.$

CAS — 80387-96-8 (difemerine); 70280-88-5 (difemerine hydrochloride).

ATC — A03AA09.

ATC Vet — QA03AA09.

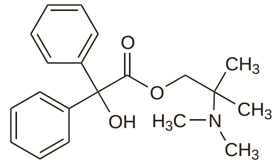

(difemerine)

Profile

Difemerine hydrochloride is an antimuscarinic with effects similar to those of atropine (p.1219) and was used in the symptomatic treatment of visceral spasms.

Difenidol Hydrochloride *(BANM, rINNM)*

Difénidol, Chlorhydrate de; Difenidoli Hydrochloridum; Diphenidol Hydrochloride *(USAN)*; Hidrocloruro de difenidol; SKF-478 (difenidol); SKF-478-A; SKF-478-J (difenidol embonate). 1,1-Diphenyl-4-piperidinobutan-1-ol hydrochloride.

Дифенидола Гидрохлорид

$C_{21}H_{27}NO,HCl = 345.9.$

CAS — 972-02-1 (difenidol); 3254-89-5 (difenidol hydrochloride); 26363-46-2 (difenidol embonate).

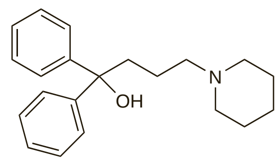

(difenidol)

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Difenidol hydrochloride is an antiemetic that probably acts through the chemoreceptor trigger zone. It is claimed to control vertigo by means of a specific effect on the vestibular apparatus. Difenidol also has a weak peripheral antimuscarinic action.

It has been used in the treatment of some forms of nausea and vomiting (p.1700) such as those associated with surgery, radiotherapy, and cancer chemotherapy. It has also been used for the symptomatic treatment of vertigo (p.565), nausea and vomiting due to Ménière's disease (p.564), and other labyrinthine disturbances.

It has been given in oral doses equivalent to 25 to 50 mg of difenidol every 4 hours as required. Difenidol hydrochloride has also been given parenterally.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Vontrol†; ***Chile:*** Vontrol; ***Hong Kong:*** Cephadol; ***Jpn:*** Cephadol; ***Malaysia:*** Cephadol; ***Mex.:*** Biomitin; Diphafen; Hemetiken; Lansenol; Nautrol; Normavom; Serratol; Sons; Vontrol; Voxamine; ***Philipp.:*** Cephadol; ***Singapore:*** Cephadol†; ***Thai.:*** Cephadol.

Difenoxin *(BAN, USAN, rINN)*

Difenoxilic Acid; Difenoxina; Difénoxine; Difenoxinum; Diphenoxylic Acid; McN-JR-15403-11. 1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.

Дифеноксин

$C_{28}H_{28}N_2O_2 = 424.5.$

CAS — 28782-42-5.

ATC — A07DA04.

ATC Vet — QA07DA04.

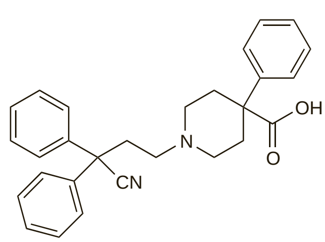

Difenoxin Hydrochloride *(BANM, rINNM)*

Difénoxine, Chlorhydrate de; Difenoxini Hydrochloridum; Difenoxylic Acid Hydrochloride; Diphenoxylic Acid Hydrochloride; Hidrocloruro de difenoxina; R-15403.

Дифеноксина Гидрохлорид

$C_{28}H_{28}N_2O_2,HCl = 461.0.$

CAS — 35607-36-4.

ATC — A07DA04.

ATC Vet — QA07DA04.

Profile

Difenoxin is the principal active metabolite of diphenoxylate (p.1724) and has similar actions and uses. It is given orally as the hydrochloride, but doses are in terms of the base; difenoxin hydrochloride 1.1 mg is equivalent to about 1 mg of difenoxin.

In the treatment of diarrhoea (p.1694), the usual dose in adults is the equivalent of difenoxin 2 mg initially, followed by 1 mg after each loose stool or every 3 to 4 hours as required, up to a maximum of 8 mg daily.

Preparations of difenoxin usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Motofen.

Dihexyverine Hydrochloride *(USAN, rINNM)*

Dihexiverine Hydrochloride; Dihexyvérine, Chlorhydrate de; Dihexyverini Hydrochloridum; Hidrocloruro de dihexiverina; JL-1078. 2-Piperidinoethyl bicyclohexyl-1-carboxylate hydrochloride.

Дигексиверина Гидрохлорид

$C_{20}H_{35}NO_2,HCl = 358.0.$

CAS — 561-77-3 (dihexyverine); 5588-25-0 (dihexyverine hydrochloride).

ATC — A03AA08.

ATC Vet — QA03AA08.

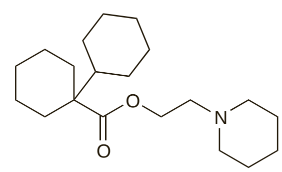

(dihexyverine)

Profile

Dihexyverine hydrochloride is an antimuscarinic with effects similar to those of atropine (p.1219). It has been given in the symptomatic treatment of gastrointestinal spasm.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Spasmodex†.

Dihydroxyaluminum Sodium Carbonate

Aluminium Sodium Carbonate Hydroxide; Carbonato sódico de dihidroxialuminio; Dihidroksialüminyum Sodyum Karbonat; Dihydroksialuminiumnatriumkarbonaatti; Dihydroxialuminiinatrii Carbonas; Dihydroxialuminiumnatriumkarbonat; Dihydroxyaluminium Sodium Carbonate. Sodium (carbonato)dihydroxyaluminate(1-).

Дигидрооксиалюминия Натрия Карбонат

$CH_2AlNaO_5 = 144.0.$

CAS — 41342-54-5 (carbaldrate); 12011-77-7 (dihydroxyaluminium sodium carbonate); 16482-55-6 (dihydroxyaluminium sodium carbonate).

ATC — A02AB04.

ATC Vet — QA02AB04.

NOTE. The name Carbaldrate (*rINN*) has been applied to (CH_2AlNaO_5,nH_2O), a form of sodium (carbonato)dihydroxyaluminate(1-) hydrate.

Pharmacopoeias. In *US.*

USP 31 (Dihydroxyaluminum Sodium Carbonate). A fine white odourless powder. It loses not more than 14.5% of its weight on drying. Practically insoluble in water and in organic solvents;

The symbol † denotes a preparation no longer actively marketed

soluble in dilute mineral acids with the evolution of carbon dioxide. A 4% suspension in water has a pH of 9.9 to 10.2. Store in airtight containers.

Profile

Dihydroxyaluminum sodium carbonate is an antacid with general properties similar to aluminium hydroxide (p.1706) that is given in doses of about 300 to 600 mg by mouth.

Preparations

USP 31: Dihydroxyaluminum Sodium Carbonate Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Antacidum; ***Denm.:*** Noacid; ***Ger.:*** Kompensan; ***Pol.:*** Alugastrin; Gastrinal; ***Port.:*** Kompensan; ***Switz.:*** Kompensan; ***Turk.:*** Dank; Kompensan.

Multi-ingredient: ***Ger.:*** Kompensan-S†; ***Port.:*** Kompensan-S.

Diisopromine Hydrochloride *(rINNM)*

Diisopromine, Chlorhydrate de; Di-isopromine Hydrochloride; Diisopromini Hydrochloridum; Hidrocloruro de diisopromina. *NN*-Di-isopropyl-3,3-diphenylpropylamine hydrochloride.

Диизопромина Гидрохлорид

$C_{21}H_{29}N,HCl$ = 331.9.

CAS — 5966-41-6 (diisopromine); 24358-65-4 (diisopromine hydrochloride).

ATC — A03AX02.

ATC Vet — QA03AX02.

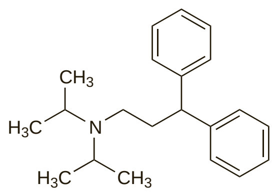

(diisopromine)

Profile

Diisopromine hydrochloride is an antispasmodic used with sorbitol in various gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Biliflux†; ***S.Afr.:*** Agofell.

Diphenoxylate Hydrochloride

(BANM, rINNM)

Difenoksilaattihydrokloridi; Difenoksilat Hidroklorür; Difenoksilato hidrochloridas; Difenoxilát-hidroklorid; Difenoxilathydroklorid; Difenoxylát-hydrochlorid; Diphénoxylate, chlorhydrate de; Diphenoxylati hydrochloridum; Hidrocloruro de difenoxilato; R-1132. Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.

Дифеноксилата Гидрохлорид

$C_{30}H_{32}N_2O_2,HCl$ = 489.0.

CAS — 915-30-0 (diphenoxylate); 3810-80-8 (diphenoxylate hydrochloride).

ATC — A07DA01.

ATC Vet — QA07DA01.

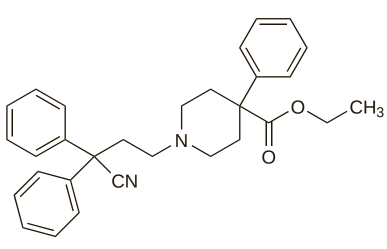

(diphenoxylate)

NOTE. Compounded preparations of diphenoxylate hydrochloride may be represented by the following names:

- Co-phenotrope (*BAN*)—diphenoxylate hydrochloride 100 parts and atropine sulfate 1 part (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Diphenoxylate Hydrochloride). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Diphenoxylate Hydrochloride). A white odourless crystalline powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol and in acetone; freely soluble in chloroform; practically insoluble in ether and in petroleum spirit; soluble in methyl alcohol. A saturated solution in water has a pH of about 3.3.

Dependence and Withdrawal

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse. Short-term use of diphenoxylate with atropine in the recommended dosage carries a negligible risk of dependence, although prolonged use or use of high doses may produce dependence of the morphine type (see p.101).

Adverse Effects and Treatment

Diphenoxylate is related to the opioid analgesics (p.102), and its adverse effects and their treatment are similar, particularly in overdosage. Reported adverse effects include: gastrointestinal effects such as anorexia, nausea and vomiting, abdominal distension or discomfort, paralytic ileus, toxic megacolon, and pancreatitis; nervous system effects such as headache, drowsiness, dizziness, restlessness, euphoria, depression, numbness of the extremities; and hypersensitivity reactions including angioedema, urticaria, pruritus, and swelling of the gums. Signs of overdosage may be delayed and patients should be observed for at least 48 hours. Young children are particularly susceptible to the effects of overdosage.

The presence of subclinical doses of atropine sulfate in preparations containing diphenoxylate may give rise to the adverse effects of atropine in susceptible individuals or in overdosage—see Atropine Sulfate, p.1219.

Precautions

Diphenoxylate hydrochloride should be avoided in patients with jaundice, intestinal obstruction, antibiotic-associated colitis, or diarrhoea associated with enterotoxin-producing bacteria, and should be used with caution in patients with hepatic impairment. It should also be used with caution in young children, in whom response is more variable, and is not generally recommended for use in infants. Patients with inflammatory bowel disease receiving diphenoxylate should be carefully observed for signs of toxic megacolon and diphenoxylate stopped promptly should abdominal distension occur.

Interactions

Because of the structural relationship of diphenoxylate to pethidine (p.113) there is a theoretical risk of hypertensive crisis if diphenoxylate is used with MAOIs. Diphenoxylate may potentiate the effects of other CNS depressants such as alcohol, barbiturates, and some anxiolytics.

Pharmacokinetics

Diphenoxylate hydrochloride is well absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver, mainly to diphenoxylic acid (difenoxin, p.1723), which has antidiarrhoeal activity; other metabolites include hydroxydiphenoxylic acid. It is excreted mainly as metabolites and their conjugates in the faeces; lesser amounts are excreted in urine. It may be distributed into breast milk.

Uses and Administration

Diphenoxylate hydrochloride is a synthetic derivative of pethidine (p.113) with little or no analgesic activity; it reduces intestinal motility and is used in the symptomatic treatment of acute and chronic diarrhoea (p.1694). It may also be used to reduce the frequency and fluidity of the stools in patients with colostomies or ileostomies.

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse; UK preparations are all in the form of co-phenotrope (see above).

In **acute diarrhoea** the usual initial dose for adults is 10 mg orally, followed by 5 mg every six hours, later reduced as the diarrhoea is controlled. In the UK, diphenoxylate hydrochloride is not licensed for children under 4 years of age. Suggested initial doses for children are: 4 to 8 years, 2.5 mg three times daily; 9 to 12 years, 2.5 mg four times daily; over 12 years, 5 mg three times daily. While emphasising that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age, the *BNFC* allows for a dose of 1.25 mg three times daily for children aged 2 to 4 years. In the USA, diphenoxylate is not recommended for children under the age of 2 years and an initial dose of 0.3 to 0.4 mg/kg (up to an effective maximum of 10 mg) daily in 4 divided doses is suggested for children aged 2 to 12 years. (For the view that antidiarrhoeal drugs should not be used at all in children, see p.1694.)

Similar initial doses are used for **chronic diarrhoea**, and subsequently reduced as necessary. If clinical improvement is not seen after 10 days of treatment with the maximum daily dose of 20 mg (in adults) further use is unlikely to result in any benefit.

Diarrhoea. Co-phenotrope (see above) may be considered as an alternative to loperamide in the management of faecal incontinence in adults, see Diarrhoea, under Loperamide, p.1742.

Substance dependence. Diphenoxylate may be useful[1] in the symptomatic management of diarrhoea associated with opioid withdrawal syndromes (p.101).

1. DOH. *Drug misuse and dependence: guidelines on clinical management*. London: HMSO, 1999. Also available at: http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf (accessed 18/01/06)

Preparations

USP 31: Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Lofenoxal; Lomotil; ***Braz.:*** Lomotil; ***Canad.:*** Lomotil; ***Cz.:*** Reasec; ***Fr.:*** Diarsed; ***Hong Kong:*** Dhamotil; Dimotil; Lomotil; ***Hung.:*** Reasec; ***India:*** Lomotil; ***Irl.:*** Lomotil; ***Malaysia:*** Atrotil†; Beamotil; Dhamotil; Lomotil†; Setmotil†; ***NZ:*** Diastop; Lomotil†; ***Pol.:*** Reasec; ***Port.:*** Lomotil†; ***S.Afr.:*** Lomotil; ***Singapore:*** Beamotil; Dhamotil; Lomotil; Remodil†; ***Thai.:*** Dilomil†; Lomotil; ***Turk.:*** Lomotil; ***UAE:*** Intard; ***UK:*** Dymotil; Lomotil; ***USA:*** Logen; Lomotil; Lonox; ***Venez.:*** Lomotil†.

Multi-ingredient: ***Braz.:*** Colestase; ***India:*** Lomofen.

Docusates

Docusatos.

Docusate Calcium *(USAN)*

Dioctyl Calcium Sulfosuccinate; Dioctyl Calcium Sulphosuccinate; Docusato cálcico. Calcium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Кальция

$C_{40}H_{74}CaO_{14}S_2$ = 883.2.

CAS — 128-49-4.

Pharmacopoeias. In *US.*

USP 31 (Docusate Calcium). A white amorphous solid with the characteristic odour of octil alcohol. Soluble 1 in 3300 of water; very soluble in alcohol, in macrogol 400, and in maize oil.

Docusate Potassium *(USAN)*

Dioctyl Potassium Sulfosuccinate; Dioctyl Potassium Sulphosuccinate; Docusato potásico. Potassium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Калия

$C_{20}H_{37}KO_7S$ = 460.7.

CAS — 7491-09-0.

Pharmacopoeias. In *US.*

USP 31 (Docusate Potassium). A white amorphous solid with a characteristic odour suggestive of octil alcohol. Sparingly soluble in water; soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Docusate Sodium *(BAN, USAN, rINN)*

Dioctyl Sodium Sulfosuccinate; Dioctyl Sodium Sulphosuccinate; Docusate sodique; Docusato de sodio; Docusato sódico; Docusatum Natricum; Dokusaattinatrium; Dokusát sodná sůl; Dokusatnatrium; Dokuzát-nátrium; Dokuzato natrio druska; DSS; Natrii docusas; Sodium Dioctyl Sulphosuccinate; Sodu dokuzynian. Sodium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Натрий

$C_{20}H_{37}NaO_7S = 444.6$.

CAS — 577-11-7.

ATC — A06AA02.

ATC Vet — QA06AA02.

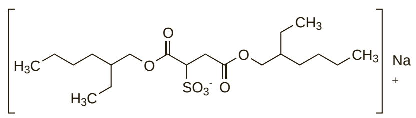

NOTE. Compounded preparations of docusate sodium may be represented by the following names:

- Co-danthrusate (*BAN*)—docusate sodium 6 parts and dantron 5 parts.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Docusate Sodium). White or almost white, hygroscopic, waxy masses or flakes. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 31 (Docusate Sodium). A white wax-like plastic solid with a characteristic odour suggestive of octil alcohol. Slowly soluble 1 in 70 of water; freely soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Adverse Effects and Precautions

Adverse effects occur rarely with docusates; diarrhoea, nausea, abdominal cramps, and skin rash have been reported. Anorectal pain or bleeding have occasionally occurred after rectal doses.

Like all laxatives, docusates should not be used when intestinal obstruction or undiagnosed abdominal symptoms are present; prolonged use should be avoided. Docusate sodium should not be given rectally to patients with haemorrhoids or anal fissures.

Docusate sodium should not be used to soften ear wax when the ear is inflamed or the ear drum perforated.

Hypersensitivity. Docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Allergic contact dermatitis has been reported from one such preparation; patch testing confirmed the reaction to docusate sodium.[1]

1. Lee A-Y, Lee K-H. Allergic contact dermatitis from dioctyl sodium sulfosuccinate in a topical corticosteroid. *Contact Dermatitis* 1998; **38:** 355–6.

Pregnancy. Hypomagnesaemia in a neonate, manifested by jitteriness, was considered to be secondary to maternal hypomagnesaemia caused by maternal use of docusate sodium during pregnancy.[1]

1. Schindler AM. Isolated neonatal hypomagnesaemia associated with maternal overuse of stool softener. *Lancet* 1984; **ii:** 822.

Interactions

Docusates may enhance the gastrointestinal uptake of other drugs, such as liquid paraffin (and the two should not be given together). Dosage of anthraquinone laxatives may need to be reduced if used with docusates. It has also been suggested that giving docusates with aspirin increases the incidence of adverse effects on the gastrointestinal mucosa.

Pharmacokinetics

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile. Docusate sodium is also distributed into breast milk.

Uses and Administration

Docusates are given as the calcium or sodium salt and are used as laxatives in the management of constipation (p.1693) or to reduce straining in patients with haemorrhoids (p.1697) or anal fissure. They are also used as adjuncts for bowel evacuation before abdominal radiological procedures. Docusate potassium has also been used.

Docusates are anionic surfactants which have been considered to act primarily by increasing the penetration of fluid into the faeces, but may also have other effects on intestinal fluid secretion, and probably act both as stimulants and as faecal softening agents.

The usual daily oral dose of docusate calcium is 240 mg. Docusate sodium is given in usual oral doses of 50 to 300 mg daily in divided doses, although doses of up to 500 mg daily may be used. (For administration in children, see below). The effect is usually seen within 12 to 72 hours. When used as an adjunct to abdominal radiological procedures, an oral dose of 400 mg is given with the barium meal. It is also given rectally as an enema in doses of 120 mg; the effect is usually seen in 5 to 20 minutes. Docusate sodium is also used with anthraquinone stimulant laxatives such as casanthranol (p.1715), dantron (p.1722), and senna (p.1769).

Docusate sodium is used for softening wax in the ear as ear drops containing 0.5 or 5%.

Docusate sodium and other docusate salts are widely used as anionic surfactants in pharmaceutical formulations.

Administration in children. Docusate sodium by mouth is licensed in the UK for the treatment of **chronic constipation** in children aged 6 months and over. More specific dose details are also provided in the *BNFC* as follows:

- 6 months to 2 years: 12.5 mg three times daily
- 2 to 12 years: 12.5 to 25 mg three times daily

Children aged 12 years and over may be given the adult doses for constipation, either orally or rectally (see Uses and Administration, above). Adult formulations are not licensed for use in children under 12 years.

In the USA, children aged 2 to 12 years may be given docusate sodium in doses of 50 to 150 mg daily, either as a single daily dose or in divided doses. Docusate *calcium* is generally only used in the USA for children aged 12 years and over.

Docusate sodium is also used as an **adjunct in abdominal radiological procedures**. UK licensed product information suggests that children may be given an oral dose of 75 mg (30 mL of docusate sodium paediatric solution 12.5 mg per 5 mL) with the barium meal. The *BNFC* recommends that those aged 12 years and over are given the usual adult dose (see above).

Ear wax removal. Cerumen or ear wax is a normal secretion of the ceruminous glands present in the lining of the external auditory canal. Excessive accumulation or impaction of ear wax may decrease hearing acuity, and may also produce dizziness, vertigo, reflex coughing, tinnitus, and otalgia.

Syringing of the external auditory canal with warm water may be used to remove wax from the ear. However, complications include pain, perforation of the ear drum, deafness, dizziness, vertigo, tinnitus, and infection.[1-6] Contra-indications to ear syringing include past perforation, ear infection, previous ear surgery; syringing may be difficult in children.[1,6]

A ceruminolytic agent may be given as ear drops to soften, loosen, or dissolve cerumen instead. They may also be used immediately before syringing, or for several days beforehand.[1-3,5,6] Traditionally, fixed oils such as arachis oil, olive oil, or almond oil have been used.[1] Some still advocate the use of olive oil to reduce the recurrence of impacted cerumen,[3] while others consider it to be ineffective.[5] Other ceruminolytics that have been reported as effective include docusates,[4,7,8] peroxides such as hydrogen peroxide or urea hydrogen peroxide,[4,9] and trolamine polypeptide oleate-condensate,[4,8] although some studies have found these to be no more effective in removing wax than a saline control.[10,11] Other agents that have been used include acetic acid,[4] choline salicylate,[12] methyltrypsin solution,[5] and an oily solution of paradichlorobenzene and chlorobutanol.[4,12] Glycerol and sodium bicarbonate solution have also been used. However, a comparative study *in vitro* of the efficacy of various wax dispersing agents found the most effective to be water, which had originally been included as a control,[13] and a systematic review[14] concluded that saline or water ear drops seemed to be as good as proprietary agents for the removal of ear wax, although there was a lack of good quality studies on which to base recommendations.

Ear candling is a traditional folk remedy that has been used to remove cerumen, but studies indicate it is ineffective, and may deposit wax in the ear canal or cause burn injuries.[3,4]

1. Sharp JF, *et al.* Ear wax removal: a survey of current practice. *BMJ* 1990; **301:** 1251–3.
2. Grossan M. Cerumen removal—current challenges. *Ear Nose Throat J* 1998; **77:** 541–6, 548.
3. Grossan M. Safe, effective techniques for cerumen removal. *Geriatrics* 2000; **55:** 80, 83–6.
4. Dimmitt P. Cerumen removal products. *J Pediatr Health Care* 2005; **19:** 332–6.
5. Midani A, *et al.* Safety and efficacy of Sofenz ceruminolytic solution. *Ear Nose Throat J* 2006; **85:** 87–8, 90–2.
6. Aung T, Mulley GP. Removal of ear wax. *BMJ* 2002; **325:** 27.
7. Chen DA, Caparosa RJ. A nonprescription cerumenolytic. *Am J Otol* 1991; **12:** 475–6.
8. Singer AJ, *et al.* Ceruminolytic effects of docusate sodium: a randomized, controlled trial. *Ann Emerg Med* 2000; **36:** 228–32.
9. Fahmey S, Whitefield M. Multicentre clinical trial of Exterol as a cerumenolytic. *Br J Clin Pract* 1982; **36:** 197–204.
10. Whatley VN, *et al.* Randomized clinical trial of docusate, triethanolamine polypeptide, and irrigation in cerumen removal in children. *Arch Pediatr Adolesc Med* 2003; **157:** 1177–80.
11. Roland PS, *et al.* Randomized, placebo-controlled evaluation of Cerumenex and Murine earwax removal products. *Arch Otolaryngol Head Neck Surg* 2004; **130:** 1175–7.
12. Dummer DS, *et al.* A single-blind, randomized study to compare the efficacy of two ear drop preparations ('Audax' and 'Cerumol') in the softening of ear wax. *Curr Med Res Opin* 1992; **13:** 26–30.
13. Andaz C, Whittet HB. An in vitro study to determine efficacy of different wax-dispersing agents. *ORL J Otorhinolaryngol Relat Spec* 1993; **55:** 97–9.
14. Burton MJ, Dorée CJ. Ear drops for the removal of ear wax. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 13/11/06).

Preparations

BP 2008: Co-danthrusate Capsules; Compound Docusate Enema; Docusate Capsules; Docusate Oral Solution; Paediatric Docusate Oral Solution; ***USP 31:*** Docusate Calcium Capsules; Docusate Potassium Capsules; Docusate Sodium Capsules; Docusate Sodium Solution; Docusate Sodium Syrup; Docusate Sodium Tablets; Ferrous Fumarate and Docusate Sodium Extended-release Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cerumex; Otoclean Solucion de Limpieza†; Phillips†; ***Austral.:*** Coloxyl; Rectalad; Waxsol; ***Belg.:*** Norgalax; ***Canad.:*** Calax; Colace; Correctol Stool Softener; Ex-Lax Stool Softener†; Regulex†; Selax; Silace; Soflax; Surfak†; ***Chile:*** Regal†; ***Fr.:*** Jamylene; Norgalax†; ***Ger.:*** Otitex; Otowaxol; ***Hong Kong:*** Norgalax†; Waxsol; ***India:*** Desol; Laxicon; ***Indon.:*** Forumen; Waxsol; ***Irl.:*** Norgalax†; Waxsol; ***Malaysia:*** Soluwax; Waxsol†; ***Mex.:*** Correctol†; ***Neth.:*** Norgalax; ***NZ:*** Coloxyl; Waxsol; ***Philipp.:*** Otosol; ***Pol.:*** Laxol; Laxopol; ***Port.:*** Norgalax; ***S.Afr.:*** Waxsol NF; ***Singapore:*** Norgalax†; Soluwax; Waxsol; ***Spain:*** Dama-Lax†; ***Switz.:*** Norgalax; ***Thai.:*** Cusate; Dewax; Waxsol; ***UK:*** Clear Ear; Dioctyl; Docusol; DulcoEase; Fletchers Enemette†; Molcer; Norgalax; Waxsol; ***USA:*** Colace; D-S-S; DC Softgels; Dioctyn; Docusoft; DOK; DOS Softgel; Dulcolax Stool Softener; Ex-Lax Stool Softener; Regulax SS; Silace; Sof-lax; Sulfolax; Surfak.

Multi-ingredient: ***Arg.:*** Candilax; Nigalax; ***Austral.:*** Chemists Own Natural Laxative with Softener; Coloxyl; Coloxyl with Senna; Combilax; Sennesoft; Soflax; ***Austria:*** Purigoa†; Yal; ***Belg.:*** Laxavit; Softene; ***Braz.:*** Ventre Livre†; ***Canad.:*** Fruitatives†; Gentlax S; Peri-Colace†; Senna-S; Senokot-S; ***Cz.:*** Yal; ***Denm.:*** Analka; Glyoktyl; Klyx; ***Fin.:*** Klyx; ***Fr.:*** Doculyse; ***Ger.:*** Norgalax Miniklistier; Yal; ***Gr.:*** Florisan; ***Hung.:*** Yal†; ***India:*** Hepasules; Pursennid-In†; ***Israel:*** Migraleve; ***Ital.:*** Macrolax; Sorbiclis; ***Mex.:*** Clyss-Go; ***Neth.:*** Klyx; ***Norw.:*** Klyx; ***NZ:*** Coloxyl; Coloxyl with Senna; Laxsol; ***Port.:*** Clyss-Go; ***Spain:*** Boldolaxin†; Laxvital; Migraleve; ***Swed.:*** Emulax; Klyx; ***Switz.:*** Klyx Magnum; Yal; ***Thai.:*** Bisolax; Hemorhin; ***UK:*** Capsuvac; Normax; ***USA:*** Docusoft Plus; Doxidan†; Dulcolax Bowel Prep Kit; Ex-Lax Gentle Strength; Genasoft Plus Softgels†; Laxative & Stool Softener; Nu-Natal Advanced; Peri-Colace; Peri-Dos Softgels†; Senna Plus; Senna-S; Senokot-S; Silace-C†; Therevac Plus; Therevac SB; X-Prep Bowel Evacuant Kit-1; ***Venez.:*** Clys-Go†; Senokot con Docusato.

Used as an adjunct in: ***India:*** Softeron; Softeron-Z; ***Indon.:*** Fercee; Viliron; ***Philipp.:*** TriHEMIC; ***USA:*** Anemagen OB†; Citracal Prenatal; Citracal Prenatal + DHA; Ferro-Dok; Hem Fe; Hemaspan†; Natal Extra†; Nephron FA; Obstetrix; Optinate Omega-3; Prenatal; TriHEMIC; Vinate GT.

Dolasetron Mesilate *(BANM, rINNM)*

Dolasétron, Mésilate de; Dolasetron Mesylate *(USAN)*; Dolasetroni Mesilas; MDL-73147EF (dolasetron or dolasetron mesilate); Mesilato de dolasetrón. (6*R*,8*r*,9a*S*)-3-Oxoperhydro-2*H*-2,6-methanoquinolizin-8-yl indole-3-carboxylate methanesulphonate.

Доласетрона Мезилат

$C_{19}H_{20}N_2O_3,CH_4O_3S = 420.5$.

CAS — 115956-12-2 (dolasetron); 115956-13-3 (dolasetron mesilate).

ATC — A04AA04.

ATC Vet — QA04AA04.

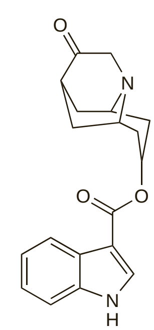

(dolasetron)

Pharmacopoeias. In *US*.

USP 31 (Dolasetron Mesylate). A white to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in sodium chloride 0.9%. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dolasetron mesilate 10 mg/mL prepared from

The symbol † denotes a preparation no longer actively marketed

commercially available tablets found them to be stable for at least 90 days when stored at 3 to 5° and at 23 to 25°.

1. Johnson CE, *et al.* Stability of dolasetron in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 2242–4.

Adverse Effects and Precautions

As for Ondansetron, p.1757. Diarrhoea, anorexia, and abdominal pain may also occur. Various ECG changes have been noted with dolasetron. Dolasetron should be used with caution in patients who have, or may develop, prolongation of the QT interval or other alterations in cardiac conduction intervals, and in those with electrolyte imbalances. Other adverse effects include dyspepsia, flatulence, taste disturbances, fever, chills or shivering, sleep disorders, fatigue, and drowsiness. There have been rare reports of intestinal obstruction, pancreatitis, jaundice, seizures, bronchospasm, cardiac arrhythmias, and oedema. Local reactions may occur on intravenous use. No dosage reduction is considered necessary in renal or hepatic impairment, despite possible reductions in clearance.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Phlebitis. Venous irritation has been reported after intravenous use of dolasetron; diluting subsequent doses with sodium chloride 0.9% and infusing it more slowly markedly reduced the frequency of phlebitis.[1]

1. Oshiro MM. Dolasetron-associated venous irritation. *Am J Health-Syst Pharm* 2000; **57:** 1533–4.

Interactions

Plasma concentrations of hydrodolasetron, the active metabolite of dolasetron, are increased by cimetidine and atenolol and decreased by rifampicin. Dolasetron should be used with caution in patients taking drugs that prolong the QT interval, including those likely to cause electrolyte disturbances (see also p.1757).

Pharmacokinetics

Dolasetron given orally or intravenously is rapidly converted to the active metabolite hydrodolasetron by carbonyl reductase, a ubiquitous enzyme. Peak plasma concentrations of hydrodolasetron occur 1 hour after oral, and 0.6 hours after intravenous, doses of dolasetron. The apparent oral bioavailability of dolasetron determined as hydrodolasetron is about 75%. It has a mean elimination half-life of about 7 to 8 hours.

Hydrodolasetron is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A and about 50 to 60% is eliminated unchanged in the urine. Two thirds of a dose of dolasetron is recovered in the urine and one third in the faeces.

Clearance of hydrodolasetron is increased in children, but is not altered in the elderly. Clearance is reduced in severe hepatic impairment (Child-Pugh category B or C) and in severe renal impairment (creatinine clearance less than 10 mL/min) after oral use. After intravenous use, clearance is reduced in severe renal impairment but apparently unchanged in severe hepatic impairment.

◊ References.

1. Lerman J, *et al.* Pharmacokinetics of the active metabolite (MDL 74,156) of dolasetron mesylate after oral or intravenous administration to anesthetized children. *Clin Pharmacol Ther* 1996; **60:** 485–92.
2. Dempsey E, *et al.* Pharmacokinetics of single intravenous and oral doses of dolasetron mesylate in healthy elderly volunteers. *J Clin Pharmacol* 1996; **36:** 903–10.
3. Stubbs K, *et al.* Pharmacokinetics of dolasetron after oral and intravenous administration of dolasetron mesylate in healthy volunteers and patients with hepatic dysfunction. *J Clin Pharmacol* 1997; **37:** 926–36.
4. Dimmitt DC, *et al.* Pharmacokinetics of oral and intravenous dolasetron mesylate in patients with renal impairment. *J Clin Pharmacol* 1998; **38:** 798–806.
5. Dimmitt DC, *et al.* Effect of infusion rate on the pharmacokinetics and tolerance of intravenous dolasetron mesylate. *Ann Pharmacother* 1998; **32:** 39–44.

Uses and Administration

Dolasetron is a 5-HT_3 antagonist with antiemetic actions similar to those of ondansetron (see p.1757). It is used as the mesilate in the prevention of nausea and vomiting (p.1700) associated with chemotherapy, and in the prevention and treatment of postoperative nausea and vomiting.

For *prevention* of acute **nausea and vomiting** associated with **chemotherapy** dolasetron mesilate may be given orally in a dose of 100 mg (in the USA) or 200 mg (in most other countries including the UK) within 1 hour before treatment. Alternatively, it may be given in a dose of 1.8 mg/kg, or 100 mg, by intravenous injection at a rate of up to 100 mg over 30 seconds about 30 minutes before chemotherapy; the same dose may be diluted to 50 mL with a suitable infusion solution and given intravenously over up to 15 minutes. To protect against delayed emesis, a further 200-mg dose may be given orally once daily; in Europe and the UK dolasetron may not normally be given for more than 4 consecutive days per chemotherapy cycle although some countries permit use for up to 7 days.

When given for the *prevention* of **postoperative** nausea and vomiting the recommended dose is usually 50 mg of dolasetron mesilate orally before induction of anaesthesia or 12.5 mg intravenously at the end of anaesthesia. In the USA, it is given as a 100-mg oral dose within 2 hours before surgery, or 12.5 mg intravenously about 15 minutes before the end of anaesthesia. The same intravenous dose may be given for the *treatment* of postoperative nausea and vomiting.

The use of dolasetron mesilate in **children** is licensed in some countries, including the USA. However, others have not licensed such use and in the UK it is contra-indicated in children and adolescents under 18 years of age because they may be at increased risk of acute changes in the QT interval, and there have been reports of cardiac conduction disorders, cardiac arrest, and myocardial infarction in children treated with dolasetron. In the USA, children over 2 years of age may be given dolasetron mesilate 1.8 mg/kg orally (within 1 hour before chemotherapy) or intravenously (about 30 minutes before chemotherapy), up to a maximum dose of 100 mg, to prevent acute chemotherapy-induced nausea and vomiting. For prevention of postoperative nausea and vomiting, 1.2 mg/kg by mouth, up to a maximum of 100 mg, may be given within 2 hours before surgery; or 350 micrograms/kg, up to a maximum of 12.5 mg, may be given intravenously 15 minutes before the end of anaesthesia. The same intravenous dose may be given to treat established postoperative nausea and vomiting.

◊ Reviews.

1. Balfour JA, Goa KL. Dolasetron: a review of its pharmacology and therapeutic potential in the management of nausea and vomiting induced by chemotherapy, radiotherapy or surgery. *Drugs* 1997; **54:** 273–98.
2. Anonymous. Dolasetron for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drug Ther* 1998; **40:** 53–4.

Pruritus. Dolasetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p.1758).

Preparations

USP 31: Dolasetron Mesylate Injection; Dolasetron Mesylate Oral Solution; Dolasetron Mesylate Oral Suspension; Dolasetron Mesylate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Anzemet†; ***Austral.:*** Anzemet; ***Austria:*** Anzemet; ***Braz.:*** Anzemet; ***Canad.:*** Anzemet; ***Cz.:*** Anzemet†; ***Fin.:*** Anzemet†; ***Fr.:*** Anzemet; ***Ger.:*** Anemet; ***Gr.:*** Anzemet; ***Hung.:*** Anemet†; ***Ital.:*** Anzemet; ***Mex.:*** Anzemet; ***Neth.:*** Anzemet; ***S.Afr.:*** Zamanon; ***Switz.:*** Anzemet; ***UK:*** Anzemet; ***USA:*** Anzemet; ***Venez.:*** Anzemet.

Domperidone *(BAN, USAN, rINN)*

Domperidon; Domperidona; Domperidonas; Dompéridone; Domperidoni; Domperidonum; R-33812. 5-Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one.

Домперидон

$C_{22}H_{24}ClN_5O_2$ = 425.9.

CAS — 57808-66-9.

ATC — A03FA03.

ATC Vet — QA03FA03.

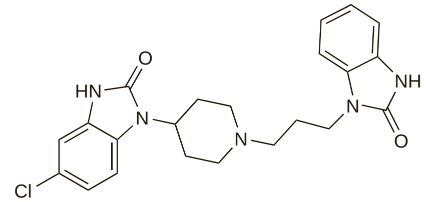

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Domperidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in dimethylformamide. Protect from light.

Domperidone Maleate *(BANM, rINNM)*

Dompéridone, maléate de; Domperidoni maleas; Domperidonimaleaatti; Domperidonmaleat; Domperidon-maleát; Domperidon-maleinát; Domperidono maleatas; Maleato de domperidona.

Домперидона Малеат

$C_{22}H_{24}ClN_5O_2,C_4H_4O_4$ = 542.0.

CAS — 99497-03-7.

ATC — A03FA03.

ATC Vet — QA03FA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Domperidone Maleate). A white or almost white powder; it exhibits polymorphism. Very slightly soluble in water and in alcohol; sparingly soluble in dimethylformamide; slightly soluble in methyl alcohol. Protect from light.

Adverse Effects

Plasma-prolactin concentrations may be increased, which may lead to galactorrhoea or gynaecomastia. There have been reports of reduced libido, and rashes and other allergic reactions. Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide (p.1748); however, there have been reports of dystonic reactions.

Domperidone by injection has been associated with convulsions, arrhythmias, and cardiac arrest. Fatalities have restricted use by this route.

Effects on the cardiovascular system. Sudden death has occurred in cancer patients given domperidone *intravenously* in high doses.[1-3] Four cancer patients experienced cardiac arrest after high intravenous doses[4] and 2 of 4 similar patients had ventricular arrhythmias.[5] After such reports the injection has been withdrawn from general use in many countries, including the UK.

Prolongation of the QT interval has been reported in an infant given *oral* domperidone, with normalisation after the drug was stopped.[6]

1. Joss RA, *et al.* Sudden death in cancer patient on high-dose domperidone. *Lancet* 1982; **i:** 1019.
2. Giaccone G, *et al.* Two sudden deaths during prophylactic antiemetic treatment with high doses of domperidone and methylprednisolone. *Lancet* 1984; **ii:** 1336–7.
3. Weaving A, *et al.* Seizures after antiemetic treatment with high dose domperidone: report of four cases. *BMJ* 1984; **288:** 1728.
4. Roussak JB, *et al.* Cardiac arrest after treatment with intravenous domperidone. *BMJ* 1984; **289:** 1579.
5. Osborne RJ, *et al.* Cardiotoxicity of intravenous domperidone. *Lancet* 1985; **ii:** 385.
6. Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. *Pediatr Cardiol* 2005; **26:** 720–3.

Effects on the endocrine system. There have been reports of galactorrhoea with gynaecomastia[1] or mastalgia[2,3] generally associated with raised serum-prolactin concentrations. Gynaecomastia without galactorrhoea has also been reported.[4]

1. Van der Steen M, *et al.* Gynaecomastia in a male infant given domperidone. *Lancet* 1982; **ii:** 884–5.
2. Cann PA, *et al.* Galactorrhoea as side effect of domperidone. *BMJ* 1983; **286:** 1395–6.
3. Cann PA, *et al.* Oral domperidone: double blind comparison with placebo in irritable bowel syndrome. *Gut* 1983; **24:** 1135–40.
4. Keating JP, Rees M. Gynaecomastia after long-term administration of domperidone. *Postgrad Med J* 1991; **67:** 401–2.

Extrapyramidal effects. There are reports of extrapyramidal symptoms,[1,2] including acute dystonic reactions[3] and neuroleptic malignant syndrome[4] in individual patients given domperidone.

1. Sol P, *et al.* Extrapyramidal reactions due to domperidone. *Lancet* 1980; **ii:** 802.

2. Debontridder O. Extrapyramidal reactions due to domperidone. *Lancet* 1980; **ii:** 802. Correction, *ibid.*; 1259.
3. Casteels-Van Daele M, *et al.* Refusal of further cancer chemotherapy due to antiemetic drug. *Lancet* 1984; **i:** 57.
4. Spirt MJ, *et al.* Neuroleptic malignant syndrome induced by domperidone. *Dig Dis Sci* 1992; **37:** 946–8.

Precautions

Domperidone is not recommended for chronic use or for the routine prophylaxis of postoperative nausea and vomiting. Domperidone should be used with great caution if given intravenously, because of the risk of arrhythmias, especially in patients predisposed to cardiac arrhythmias or hypokalaemia.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given domperidone, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, the FDA in the USA has issued a warning against the use of domperidone to increase milk production because of the possibility of serious adverse effects.[2] Others have commented that these warnings were based on data from patients with malignant disease receiving high doses of intravenous domperidone, and that if the mother were taking smaller oral doses, the total amount of drug ingested by an infant would be extremely small. They recommend that low-dose domperidone should still be considered for lactating women with decreased milk supply who are unresponsive to non-pharmacological measures to enhance lactation. However, patients should be warned of the risk of arrhythmias at high doses, and women with known cardiac disease should not take domperidone.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)
2. FDA. FDA warns against women using unapproved drug, domperidone, to increase milk production (June 7, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01292.html (accessed 30/06/04)
3. da Silva OP, Knoppert DC. Domperidone for lactating women. *Can Med Assoc J* 2004; **171:** 725–6.

Interactions

As with other dopamine antagonists (see Metoclopramide, p.1749), there is a theoretical potential that domperidone may antagonise the hypoprolactinaemic effect of drugs such as bromocriptine. In addition, the prokinetic effects of domperidone may alter the absorption of some drugs. Opioid analgesics and antimuscarinics may antagonise the prokinetic effects of domperidone.

Domperidone is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with ketoconazole has been reported to produce a threefold increase in plasma concentrations of domperidone, and an associated slight prolongation in QT interval. Similar increases in domperidone concentrations might theoretically be seen with other potent inhibitors of CYP3A4 such as erythromycin or ritonavir, and such combinations may be best avoided.

Pharmacokinetics

Although absorption is rapid, the systemic bioavailability of domperidone is only about 15% in fasting subjects given an oral dose; this is increased when domperidone is given after food. The low bioavailability is thought to be due to first-pass hepatic and intestinal metabolism. The bioavailability of rectal domperidone is similar to that after oral doses, although peak plasma concentrations are only about one-third that of an oral dose and are achieved after about an hour, compared with 30 minutes after an oral dose.

Domperidone is more than 90% bound to plasma proteins, and has a terminal elimination half-life of about 7.5 hours. It undergoes rapid and extensive hepatic metabolism. The main metabolic pathways are *N*-dealkylation by cytochrome P450 isoenzyme CYP3A4, and aromatic hydroxylation by CYP3A4, CYP1A2, and CYP2E1. About 30% of an oral dose is excreted in urine within 24 hours, almost entirely as metabolites; the remainder of a dose is excreted in faeces over several days, about 10% as unchanged drug. It does not readily cross the blood-brain barrier.

Small amounts of domperidone are distributed into breast milk; concentrations are 10 to 50% of those in maternal serum.

Uses and Administration

Domperidone is a dopamine antagonist with actions and uses similar to those of metoclopramide (p.1749). It is used as an antiemetic for the short-term treatment of nausea and vomiting of various aetiologies (p.1700). It is not considered suitable for chronic nausea and vomiting, nor for the routine prophylaxis of postoperative vomiting.

Domperidone is also used for its prokinetic actions in dyspepsia (p.1695) and has been tried in diabetic gastroparesis (see Diabetic Complications, p.433). It has been given with paracetamol in the symptomatic treatment of migraine (p.616).

Domperidone is used as the maleate in tablet preparations and as the base in suppositories and the oral suspension; doses are expressed in terms of the base. Domperidone maleate 12.73 mg is equivalent to about 10 mg of domperidone. Domperidone has been given parenterally, but this route has been associated with severe adverse effects (see above).

For the treatment of **nausea and vomiting** domperidone may be given in oral doses of 10 to 20 mg three or four times daily up to a maximum daily dose of 80 mg or it may be given rectally in a dose of 60 mg twice daily. For doses in children see below.

For the symptomatic management of non-ulcer **dyspepsia** similar oral doses of 10 mg taken up to four times daily (the last dose to be taken at night) have been recommended; if necessary, an increase in the dose to 20 mg may be prescribed. An initial course of treatment should not normally exceed 2 to 4 weeks. In **migraine**, a dose of 20 mg has been given orally up to every 4 hours, with paracetamol, as required, up to a maximum of 4 doses in 24 hours.

◊ Reviews.

1. Prakash A, Wagstaff AJ. Domperidone: a review of its use in diabetic gastropathy. *Drugs* 1998; **56:** 429–45.
2. Barone JA. Domperidone: a peripherally acting dopamine -receptor antagonist. *Ann Pharmacother* 1999; **33:** 429–40.
3. Ahmad N, *et al.* Making a case for domperidone in the treatment of gastrointestinal motility disorders. *Curr Opin Pharmacol* 2006; **6:** 571–6.
4. Reddymasu SC, *et al.* Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol* 2007; **102:** 2036–45.

Administration in children. UK licensed product information states that children may be given domperidone in oral doses equivalent to 250 to 500 micrograms/kg three or four times daily; a total daily dose of 2.4 mg/kg or 80 mg, whichever is less, should not be exceeded. Alternatively, children weighing more than 15 kg may be given a rectal dose of 30 mg twice daily. The *BNFC* gives similar doses, but specifies use in children over 2 years; in those children over 35 kg, it allows an oral dose of 10 to 20 mg three or four times daily (maximum 80 mg daily) or a rectal dose of 60 mg twice daily.

Gastro-oesophageal reflux disease. A systematic review of the use of domperidone in infants and young children with gastro-oesophageal reflux (p.1696), which identified 4 randomised controlled studies of such use, considered that there was very little evidence of its efficacy in reducing symptoms.[1] Some suggest that it has been overused because of the lack of a suitable alternative after withdrawal of cisapride in many countries.[2]

1. Pritchard DS, *et al.* Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol* 2005; **59:** 725–9.
2. Vandenplas Y, *et al.* The diagnosis and management of gastro-oesophageal reflux in infants. *Early Hum Dev* 2005; **81:** 1011–24.

Parkinsonism. Domperidone is used to control gastrointestinal effects of dopaminergic drugs given in the management of parkinsonism (p.791). It may be of use in those patients who experience peripheral effects with levodopa despite the use of peripheral dopa-decarboxylase inhibitors and for patients using dopamine agonists such as bromocriptine or apomorphine since peripheral dopa-decarboxylase inhibitors are ineffective for preventing the peripheral effects of these drugs. Although domperidone does not readily cross the blood-brain barrier there have been isolated reports of extrapyramidal effects associated with its use (see above). Consequently there has been concern over its potential to produce central effects and some consider that domperidone should only be used in patients with parkinsonism when safer antiemetic measures have failed.[1,2] However, this view has been contested both by the manufacturers and other authors.[3,4] In a subsequent review of the use of domperidone in Parkinson's disease it was considered[5] that domperidone might produce central blockade of the therapeutic effects of levodopa if given at a high oral dosage such as 120 mg daily for prolonged periods but also noted that such high doses were rarely required to control levodopa-induced vomiting.

Domperidone was found to significantly improve anorexia, nausea, vomiting, abdominal bloating, and regurgitation in patients taking levodopa.[6] Dysphagia and constipation were unaffected; these are thought to be more likely a reflection of the disease process. Doses ranged from 50 to 120 mg daily, with most patients responding to 80 mg daily. No central effects were noted.

1. Leeser J, Bateman DN. Domperidone. *BMJ* 1985; **290:** 241.
2. Bateman DN. Domperidone. *BMJ* 1985; **290:** 1079.
3. Lake-Bakaar G, Cameron HA. Domperidone. *BMJ* 1985; **290:** 241–2.
4. Critchley P, *et al.* Domperidone. *BMJ* 1985; **290:** 788.
5. Parkes JD. Domperidone and Parkinson's disease. *Clin Neuropharmacol* 1986; **9:** 517–32.
6. Soykan I, *et al.* Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. *Mov Disord* 1997; **12:** 952–7.

Preparations

BP 2008: Domperidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ecuamon; Euciton; Moperidona; Motilium; Peridon; ***Austral.:*** Motilium; ***Austria:*** Motilium; ***Belg.:*** Docdomperi; Domperitop; Motilium; Zilium; ***Braz.:*** Domperol†; Motilium; Peridal; ***Canad.:*** Motilium†; ***Chile:*** Donegal; Dosin; Gasdol; Idon; Restol; Siligaz; ***Cz.:*** Motilium; ***Denm.:*** Motilium; ***Fr.:*** Biperidys; Motilium; Motilyo; Peridys; ***Ger.:*** Domidon; Motilium; ***Gr.:*** Cilroton; ***Hong Kong:*** Costi; Dompeon; Doridone; Motilium; Qualidom; Rabugen; ***Hung.:*** Motilium; ***India:*** Domperi; Domperon; Domstal; Nautigo; Stopvom; Vomistop; ***Indon.:*** Costil; DOM; Domedon; Domet; Dometa; Dometic; Galflux; Gerdilium; Monell; Motilium; Novotil; Regit; Tilidon; Vometa; Vomidone; Vomistop; Vomitas; Vosedon; ***Irl.:*** Domerid; Motilium; ***Israel:*** Motilium; ***Ital.:*** Digestivo Giuliani; Fobidon†; Gastronorm; Motilium; Peridon; Permod; Permotil; Riges; Stalcare; ***Jpn:*** Nauzelin; ***Malaysia:*** Domper; Motilium; Rabugen; ***Mex.:*** Biolix; Emiken; Motilium; Seronex; ***Neth.:*** Gastrocure; Motilium; ***NZ:*** Motilium; ***Philipp.:*** Dompenyl; Gilax; Motilium; ***Port.:*** Cinet; Mogasinte; Motilium; Nausidone; Nefius; Nordonil†; Remotil; ***Rus.:*** Motilak (Мотилак); Motilium (Мотилиум); Motonium (Мотониум); Passagix (Пассажикс); ***S.Afr.:*** Motilium; Vomidon; ***Singapore:*** Dompel; Dompenyl†; Domper; Doridone; Mirax; Motilium; ***Spain:*** Motilium; ***Switz.:*** Motilium; ***Thai.:*** Dany; Dolium; Domerdon; Domidone; Domper-M; Domperdone; Donum; Mirax; Mocydone; Modomed; Molax; Moticon; Motidom; Motilium; Movelium; Ninlium; Peptomet†; Peridom-M; Pondperdone; Rabugen-M; ***Turk.:*** Motilium; ***UK:*** Motilium; Vivadone; ***Venez.:*** Agilam; Tilium; Tonun.

Multi-ingredient: ***Arg.:*** Alplax Net; Ansielix Digest; Bigetric; Bilagol; Dom-Polienzim; Euciton Complex; Euciton Reflux; Euciton Stress; Faradil Novo; Megalex; Moperidona AF; Moperidona Enzimatica; Praxis; Sidomal; Tensium Gastric; Tetralgin Novo; Vegestabil Digest; ***Belg.:*** Touristil; ***Braz.:*** Lansodom; ***India:*** Aciloc RD; Domcet; Esoz-D; Nogacid D; Okacid D; Okalan D; Pantosec D; Praize-D; Vertigil; ***UK:*** Domperamol†.

Dosmalfate *(rINN)*

Dosmalfato; Dosmalfatum; F-3616; F-3616. {μ_7-[(Diosmin heptasulfato)(7-)]}tetracontahydroxytetradecaaluminium.

Дозмальфат

$C_{28}H_{60}Al_{14}O_{71}S_7$ = 2134.9.

CAS — 122312-55-4.

Profile

Dosmalfate is a cytoprotective drug derived from diosmin (p.2304), that is used for the prevention and treatment of NSAID-associated peptic ulcer disease (p.1702) in an oral dose of 1.5 g twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Diotul.

Drofenine Hydrochloride *(pINNM)*

Drofénine, Chlorhydrate de; Drofenini Hydrochloridum; Hexahydroadiphenine Hydrochloride; Hidrocloruro de drofenina. 2-(Diethylamino)ethyl α-phenylcyclohexaneacetate hydrochloride.

Дрофенина Гидрохлорид

$C_{20}H_{31}NO_2,HCl$ = 353.9.

CAS — 1679-76-1 (drofenine); 548-66-3 (drofenine hydrochloride).

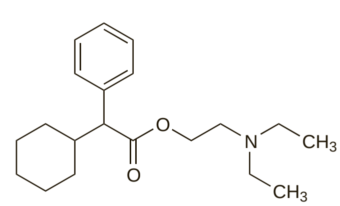

(drofenine)

The symbol † denotes a preparation no longer actively marketed

Pharmacopoeias. In *Swiss*.

Profile

Drofenine hydrochloride is an antimuscarinic available in preparations for the treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Espasmo Cibalena; ***Austria:*** Spasmoplus; ***Belg.:*** Spasmoplus†; ***Chile:*** Espasmo Cibalgina; Espasmo Cibalgina Compuesta; ***Ger.:*** Spasmo-Cibalgin S†; ***Ital.:*** Spasmo-Cibalgina†; ***Mex.:*** Espasmo Cibalgina; ***Switz.:*** Lunadon; Spasmo-Cibalgin comp†; Spasmo-Cibalgin†.

Dronabinol *(USAN, rINN)* ⊗

Dronabinolum; NSC-134454; Δ^9-Tetrahydrocannabinol; Δ^9-THC. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol.

Дронабинол

$C_{21}H_{30}O_2$ = 314.5.
CAS — 1972-08-3.
ATC — A04AD10.
ATC Vet — QA04AD10.

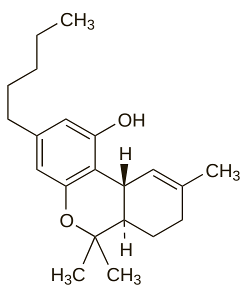

Pharmacopoeias. In *US*.

USP 31 (Dronabinol). Store at a temperature between 8° and 15° in airtight glass containers in an inert atmosphere. Protect from light.

Adverse Effects and Precautions

As for Nabilone, p.1750. The most frequent adverse effects of dronabinol include abdominal pain, nausea and vomiting, dizziness, euphoria, paranoid reactions, and somnolence. Seizures and seizure-like activity have been reported; dronabinol should be used with caution in those with a history of seizure disorders, and therapy should be stopped if seizures occur.

Abuse. The abuse liability of dronabinol was rated as being substantially lower than that of cannabis.[1]

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 03/07/08)

Breast feeding. US licensed product information states that dronabinol is concentrated in breast milk and recommends that it should not be used in breast-feeding mothers.

Pharmacokinetics

After oral doses dronabinol is slowly and erratically absorbed from the gastrointestinal tract; the bioavailability of an oral dose is about 10 to 20%, due to extensive first-pass metabolism. Peak plasma concentrations of dronabinol and its 11-hydroxy metabolite are achieved about 2 to 4 hours after a dose by mouth. It is widely distributed and is extensively protein bound, with a volume of distribution of about 10 litres/kg. Elimination is biphasic, with an initial half-life of about 4 hours, and a terminal half-life of about 25 to 36 hours.

Dronabinol is extensively metabolised, mainly in the liver by cytochrome P450 isoenzymes; the primary metabolite, 11-hydroxydronabinol is also active. The 11-hydroxy metabolite is converted to other, more polar and acidic compounds which are excreted in faeces via the bile, and in the urine. About 50% of an oral dose is recovered in faeces within 72 hours and 10 to 15% in urine. Many of the metabolites have relatively prolonged half-lives, and accumulation may occur with repeated dosage.

Dronabinol is distributed into breast milk and crosses the placenta.

◊ References.

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42:** 327–60.
2. McGilveray IJ. Pharmacokinetics of cannabinoids. *Pain Res Manag* 2005; **10:** 15A–22A.

Uses and Administration

Dronabinol, the major psychoactive constituent of cannabis (p.2274), has antiemetic properties and is used for the control of **nausea and vomiting** associated with cancer chemotherapy (p.1700) in patients who have failed to respond adequately to conventional antiemetics.

The usual initial oral dose of dronabinol is 5 mg/m² given 1 to 3 hours before the first dose of the antineoplastic drug with subsequent doses being given every 2 to 4 hours after chemotherapy to a maximum of 4 to 6 doses daily. If necessary, the dose may be increased by increments of 2.5 mg/m² to a maximum dose of 15 mg/m², if adverse effects permit.

Dronabinol also has appetite-stimulant effects and is used in the treatment of **anorexia** associated with weight loss in patients with AIDS. For this purpose 2.5 mg may be taken twice daily, before lunch and supper, reduced to a single 2.5-mg dose in the evening in patients who tolerate the drug poorly. If necessary, and if adverse effects permit, doses may also be increased up to 20 mg daily in divided doses.

Dronabinol is used with cannabidiol, another cannabinoid, in a buccal spray preparation as adjunctive treatment for the symptomatic relief of **neuropathic pain** in multiple sclerosis in adults; this combination is also used as adjunctive analgesic treatment in adult patients with advanced cancer and is under investigation for a number of other conditions (see under Cannabis, p.2275).

◊ General references.

1. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med* 1997; **126:** 791–8.
2. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs* 2000; **60:** 1303–14.
3. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
4. Berman JS, *et al.* Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; **112:** 299–306.
5. Costa B. On the pharmacological properties of Delta9-tetrahydrocannabinol (THC). *Chem Biodivers* 2007; **4:** 1664–77.
6. Beaulieu P, Ware M. Reassessment of the role of cannabinoids in the management of pain. *Curr Opin Anaesthesiol* 2007; **20:** 473–7.

Alzheimer's disease. There is some suggestion[1] that dronabinol may decrease agitation in patients with Alzheimer's disease.

1. Volicer L, *et al.* Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; **12:** 913–19.

Anorexia. Dronabinol is used for the management of anorexia in patients with HIV-associated wasting (p.858). However, although dronabinol may stimulate appetite and prevent weight loss,[1] it does not appear to produce significant weight gain, and may produce less benefit than megestrol acetate.[2] Benefits were also less than those of megestrol in patients with anorexia associated with malignant disease.[3]

1. Beal JE, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; **10:** 89–97.
2. Timpone JG, *et al.* The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; **13:** 305–15.
3. Jatoi A, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; **20:** 567–73.

Multiple sclerosis. Anecdotal evidence has suggested that cannabinoids might improve symptoms in patients with multiple sclerosis (p.892); a review[1] considered evidence of effectiveness to be lacking. In a large placebo-controlled study, treatment with dronabinol or oral cannabis extract had no benefit on objective assessment of spasticity;[2] however, there were improvements in walking time, and subjective improvements in both spasticity and pain. A subsequent small controlled study found dronabinol to have a modest but clinically relevant effect on central neuropathic pain in patients with multiple sclerosis.[3]

Dronabinol is used with cannabidiol, another cannabinoid, in a buccal spray preparation for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

1. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.
2. Zajicek J, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362:** 1517–26.
3. Svendsen KB, *et al.* Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; **329:** 253–7.

Tourette's syndrome. Preliminary studies[1,2] indicate that dronabinol may reduce tic severity in Tourette's syndrome (see Tics, p.954).

1. Müller-Vahl KR, *et al.* Treatment of Tourette's syndrome with Δ -tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; **35:** 57–61.
2. Müller-Vahl KR, *et al.* Δ -Tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; **64:** 459–65.

Preparations

USP 31: Dronabinol Capsules.

Proprietary Preparations (details are given in Part 3)
Canad.: Marinol; ***Israel:*** Ronabin†; ***S.Afr.:*** Elevat†; ***USA:*** Marinol.

Multi-ingredient: ***Canad.:*** Sativex.

Ebrotidine *(rINN)*

Ebrotidina; Ébrotidine; Ebrotidinum. *p*-Bromo-*N*-[(*E*)-({2-[({2-[(diaminomethylene)amino]-4-thiazolyl}methyl)thio]ethyl}amino)methylene]benzenesulfonamide.

Эбротидин

$C_{14}H_{17}BrN_6O_2S_3$ = 477.4.
CAS — 100981-43-9.

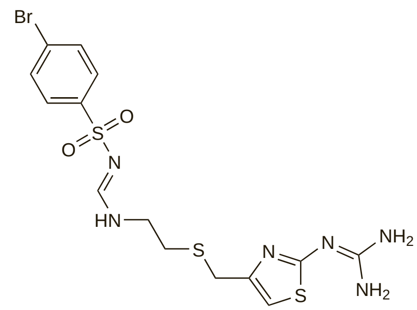

Profile

Ebrotidine is a histamine H_2-antagonist with general properties similar to those of cimetidine (p.1716), but which also has cytoprotective actions. It has been used in peptic ulcer disease. Serious liver damage has been reported.

◊ References.

1. Patel SS, Wilde MI. Ebrotidine. *Drugs* 1996; **51:** 974–80.
2. Various. Ebrotidine: a new generation H -receptor antagonist and gastroprotective agent. *Arzneimittelforschung* 1997; **47:** 427–590.
3. Andrade RJ, *et al.* Acute liver injury associated with the use of ebrotidine, a new H -receptor antagonist. *J Hepatol* 1999; **31:** 641–6.

Ecabet Sodium *(rINNM)*

Ecabet sódico; Écabet Sodique; Natrii Ecabetum; 12-Sulphodehydroabietic Acid, Monosodium Salt; TA-2711. 13-Isopropyl-12-sulphopodocarpa-8,11,13-trien-15-oic acid pentahydrate, sodium salt.

Экабет Натрий

$C_{20}H_{27}NaO_5S,5H_2O$ = 492.6.
CAS — 33159-27-2 (ecabet); 86408-72-2 (ecabet sodium).

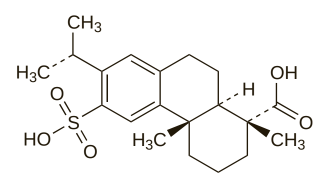

(ecabet)

Profile

Ecabet sodium is a cytoprotective drug used in the treatment of peptic ulcer disease (p.1702). The suggested oral dose is 1 g of ecabet sodium twice daily.

It is also under investigation as eye drops in the management of dry eye.

◊ References.

1. Murata H, *et al.* Combination therapy of ecabet sodium and cimetidine compared with cimetidine alone for gastric ulcer: prospective randomized multicenter study. *J Gastroenterol Hepatol* 2003; **18:** 1029–33.
2. Lee JH, *et al.* Efficacy and safety of ecabet sodium on functional dyspepsia: a prospective, double-blinded, randomized, multi-center controlled trial. *World J Gastroenterol* 2006; **12:** 2756–61.

Administration. The use of ecabet sodium as a rectal enema has been investigated in patients with ulcerative colitis.[1,2]

1. Kono T, *et al.* Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol* 2001; **96:** 793–7.
2. Iizuka M, *et al.* Efficacy of ecabet sodium enema on steroid resistant or steroid dependent ulcerative colitis. *Gut* 2006; **55:** 1523.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Gastrom.

Enoxolone Aluminium *(BANM, rINNM)*

Aluminii Enoxolonum; Aluminium Glycyrrhetate; Aluminium Glycyrrhetinate; Enoxolona de aluminio; Enoxolone Aluminum; Énoxolone d'Aluminium. 3β-Hydroxy-11-oxo-olean-12-en-30-oic acid, aluminium salt.

Алюминий Эноксолон

$(C_{30}H_{46}O_4)_3.Al = 1439.0.$

CAS — 4598-66-7.

ATC — D03AX10.

ATC Vet — QD03AX10.

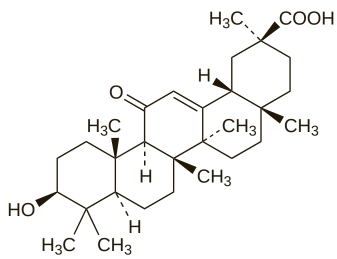

(enoxolone)

Profile

Enoxolone aluminium is an analogue of carbenoxolone (p.1714) that has been used in preparations for the treatment of peptic ulcer disease and other gastrointestinal disorders. It has also been used in preparations for skin disorders and mouth and throat disorders.

Primary pulmonary hypertension. *In-utero* exposure to enoxolone was implicated in a fatal case of neonatal primary pulmonary hypertension; the mother had used a lotion for prurigo that contained enoxolone and the authors supposed it had contributed at least in part to the pulmonary hypertension.[1]

1. Navarre-Belhassen C, *et al.* An unexpected case of primary pulmonary hypertension of the neonate (PPHN): potential role of topical administration of enoxolone. *J Perinat Med* 2002; **30:** 437–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Spain: Gastroalgine.

Eseridine Salicylate *(rINNM)*

Éséridine, Salicylate d'; Eseridini Salicylas; Eserine Aminoxide Salicylate; Eserine Oxide Salicylate; Physostigmine Aminoxide Salicylate; Physostigmine *N*-Oxide Salicylate; Salicilato de eseridina. (4aS,9aS)-2,3,4,4a,9,9a-Hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-ylmethylcarbamate salicylate.

Эзеридина Салицилат

$C_{15}H_{21}N_3O_3,C_7H_6O_3 = 429.5.$

CAS — 25573-43-7 (eseridine); 5995-96-0 (eseridine salicylate).

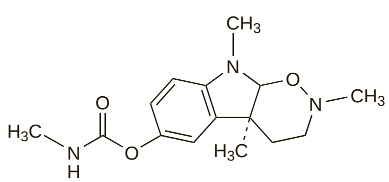

(eseridine)

Profile

Eseridine salicylate, a derivative of physostigmine, is an inhibitor of cholinesterase activity that has been given orally for dyspepsia in doses of up to 4.5 mg 3 times daily, taken 30 minutes before meals.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Geneserine.

Esomeprazole *(BAN, rINN)*

Esomepratsoli; Esomeprazol; Ésoméprazole; Esomeprazolum; H-199/18; Perprazole. 5-Methoxy-2-{(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazole.

Эзомепразол

$C_{17}H_{19}N_3O_3S = 345.4.$

CAS — 119141-88-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

Esomeprazole Magnesium *(BANM, USAN, rINNM)*

Esomeprazol; Esomeprazol magnésico; Ésoméprazole magnésique; Ésoméprazole Magnesique; Esomeprazolum magnesicum; H199/18 (esomeprazole); Magnesii Esomeprazolum; Perprazole (esomeprazole). 5-Methoxy-2-{(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazole magnesium (2:1) trihydrate.

Магния Эзомепразол

$C_{34}H_{36}MgN_6O_6S_2,3H_2O = 767.2.$

CAS — 217087-09-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

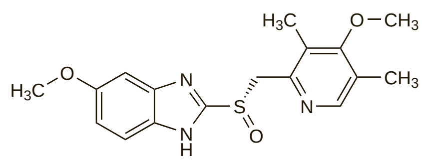

(esomeprazole)

Pharmacopoeias. In *US.*

USP 31 (Esomeprazole Magnesium). A white to slightly coloured powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

Esomeprazole Sodium *(BANM, USAN, rINNM)*

Esomeprazol sódico; Ésoméprazole Sodique; Natrii Esomeprazolum.

Натрий Эзомепразол

$C_{17}H_{19}N_3NaO_3S = 368.4.$

CAS — 161796-78-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

Adverse Effects and Precautions

As for Omeprazole, p.1753.

◊ General references.

1. Davies M, *et al.* Safety profile of esomeprazole: results of a prescription-event monitoring study of 11 595 patients in England. *Drug Safety* 2008; **31:** 313–23.

Effects on the cardiovascular system. For discussion of cardiac effects ostensibly seen with esomeprazole, see under Omeprazole, p.1753.

Effects on the kidneys. For reports of interstitial nephritis associated with esomeprazole see p.1753.

Effects on the skin. For mention of exacerbation of vitiligo with esomeprazole, see p.1754.

Fever. For a report of hyperpyrexia associated with esomeprazole, see under Omeprazole, p.1754.

Interactions

As for Omeprazole, p.1755.

◊ References.

1. Andersson T, *et al.* Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 523–37.

Pharmacokinetics

Esomeprazole is rapidly absorbed after oral doses, with peak plasma levels occurring after about 1 to 2 hours. It is acid labile and an enteric-coated formulation has been developed. Bioavailability of esomeprazole increases with both dose and repeated administration to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolised by the cytochrome P450 isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the faeces.

◊ References.

1. Andersson T, *et al.* Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 411–26.
2. Sostek MB, *et al.* Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole. *Br J Clin Pharmacol* 2007; **64:** 386–90.

Metabolism. As for omeprazole (p.1755), the cytochrome P450 isoenzyme CYP2C19 is involved in the metabolism of esomeprazole, and individuals who are deficient in this enzyme are poor metabolisers of esomeprazole. However, there is some suggestion that the metabolism of esomeprazole is less dependent on this genotype, as there may be a metabolic shift towards the CYP3A4-mediated pathway.[1]

1. Schwab M, *et al.* Esomeprazole-induced healing of gastro-esophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther* 2005; **78:** 627–34.

Uses and Administration

Esomeprazole is the *S*-isomer of the proton pump inhibitor omeprazole (p.1753) and is used similarly in the treatment of peptic ulcer disease and NSAID-associated ulceration (p.1702), in gastro-oesophageal reflux disease (p.1696), and the Zollinger-Ellison syndrome (p.1704). It is given as the magnesium or sodium salt but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg and esomeprazole sodium 21.3 mg are each equivalent to about 20 mg of esomeprazole.

Usual doses for **peptic ulcer disease**, as a component of a triple therapy regimen with amoxicillin and clarithromycin, are the equivalent of 20 mg esomeprazole orally twice daily for 7 days, or 40 mg once daily for 10 days.

Oral doses of 20 mg daily, for 4 to 8 weeks, are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients at risk of such lesions who require continued NSAID treatment.

In the UK, the dose for treatment of severe (erosive) **gastro-oesophageal reflux disease** is 40 mg once daily for 4 weeks, extended for a further 4 weeks if necessary; in the USA, where doses of 20 or 40 mg daily are permitted for initial treatment, a further 4 to 8 weeks of treatment may be considered for patients who do not heal after 4 to 8 weeks. For maintenance, or for symptomatic disease without erosive oesophagitis, doses equivalent to 20 mg of esomeprazole daily may be used in both countries.

For the treatment of **Zollinger-Ellison syndrome**, the recommended initial oral dose of esomeprazole is 40 mg twice daily, which is then adjusted as needed. The majority of patients can be controlled on doses between 80 and 160 mg daily, although doses of 240 mg have been given. Doses above 80 mg daily should be given in 2 divided doses.

PARENTERAL DOSAGE.

Similar doses to the above may be given intravenously for gastro-oesophageal reflux disease and NSAID-associated ulceration. Esomeprazole is given as the sodium salt by slow intravenous injection over at least 3 minutes or by intravenous infusion over 10 to 30 minutes.

Doses of esomeprazole may need to be reduced in patients with hepatic impairment (see below).

◊ References.

1. Maton PN, *et al.* Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis. *Drug Safety* 2001; **24:** 625–35.
2. Scott LJ, *et al.* Esomeprazole: a review of its use in the management of acid-related disorders. *Drugs* 2002; **62:** 1503–38.
3. Keating GM, Figgitt DP. Intravenous esomeprazole. *Drugs* 2004; **64:** 875–82.
4. Metz DC, *et al.* Comparison of the effects of intravenously and orally administered esomeprazole on acid output in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; **22:** 813–21.
5. Edwards SJ, *et al.* Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther* 2006; **24:** 743–50.

6. Morgner A, *et al.* Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. *Expert Opin Pharmacother* 2007; **8:** 975–88.
7. Blandizzi C, *et al.* Clinical efficacy of esomeprazole in the prevention and healing of gastrointestinal toxicity associated with NSAIDs in elderly patients. *Drugs Aging* 2008; **25:** 197–208.

Administration. *In-vitro* studies found that almost the entire contents of an esomeprazole capsule is deliverable through small calibre and standard sizes of nasogastric and gastrostomy tubes.[1,2]

1. White CM, *et al.* Delivery of esomeprazole magnesium enteric-coated pellets through small caliber and standard nasogastric tubes and gastrostomy tubes in vitro. *Am J Health-Syst Pharm* 2002; **59:** 2085–8.
2. Shah SA, *et al.* Delivery of esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. *Am J Health-Syst Pharm* 2006; **63:** 1882–7.

Administration in children. UK licensed product information allows for the use of adult doses of esomeprazole (see Uses and Administration, above) in children over 12 years.

In the USA licensed doses, which may be given once daily for up to 8 weeks for the treatment of gastro-oesophageal reflux in children, are:

- 1 to 11 years: 10 mg
- 12 to 17 years: 20 or 40 mg

For healing erosive oesophagitis in children, the following doses based on body-weight are licensed in the USA to be given once daily for up to 8 weeks:

- less than 20 kg: 10 mg
- 20 kg or over: 10 or 20 mg

Administration in hepatic impairment. No dosage adjustment of esomeprazole is considered necessary for patients with mild to moderate hepatic impairment (Child-Pugh Classes A and B, respectively). For patients with severe hepatic impairment (Child-Pugh Class C), a daily dose of 20 mg should not be exceeded.

Administration in renal impairment. Although no dosage adjustment is considered necessary in patients with renal impairment, UK licensed product information advises caution in those with severe renal impairment, as experience in these patients is limited.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Esomax; Nexium; ***Austral.:*** Nexium; ***Austria:*** Nexium; ***Belg.:*** Nexiam; ***Braz.:*** Nexium; ***Canad.:*** Nexium; ***Chile:*** Nexium; Ulcratex; ***Cz.:*** Nexium; ***Denm.:*** Nexium; ***Fin.:*** Nexium; ***Fr.:*** Inexium; ***Ger.:*** Nexium; ***Gr.:*** Nexium; ***Hong Kong:*** Nexium; ***Hung.:*** Nexium; ***India:*** Esomac; Esoz; Sompraz; ***Indon.:*** Nexium; ***Irl.:*** Nexium; ***Israel:*** Nexium; ***Ital.:*** Axagon; Esopral; Lucen; Nexium; ***Malaysia:*** Nexium; ***Mex.:*** Nexium; ***Neth.:*** Esopral; Nexium; ***Norw.:*** Nexium; ***Philipp.:*** Nexium; ***Pol.:*** Nexium; ***Port.:*** Nexium; ***Rus.:*** Nexium (Нексиум); ***S.Afr.:*** Nexiam; ***Singapore:*** Nexium; ***Spain:*** Axiago; Nexium; ***Swed.:*** Nexium; ***Switz.:*** Nexium; ***Thai.:*** Nexium; ***Turk.:*** Nexium; ***UK:*** Nexium; ***USA:*** Nexium; ***Venez.:*** Esoz; Nexium.

Multi-ingredient: ***Austral.:*** Nexium Hp; ***India:*** Esoz-D; ***Swed.:*** Nexium Hp.

Euonymus

Evónimo; Fusain Noir Pourpré; Spindle Tree Bark; Wahoo Bark.

Бересклетова Кора

Profile

Euonymus is the dried root-bark of *Euonymus atropurpureus* (=*Evonymus atropurpurea*) (Celastraceae). It is reported to have laxative, choleretic, and diuretic activity.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Jecopeptol; ***UK:*** Acidosis; GB Tablets; Indigestion Mixture.

Famotidine *(BAN, USAN, rINN)*

Famotidiini; Famotidin; Famotidina; Famotidinas; Famotidinum; L-643341; MK-208; YM-11170. 3-[2-(Diaminomethyleneamino)-thiazol-4-ylmethylthio]-*N*-sulphamoylpropionamidine.

Фамотидин

$C_8H_{15}N_7O_2S_3$ = 337.4.

CAS — 76824-35-6.

ATC — A02BA03.

ATC Vet — QA02BA03.

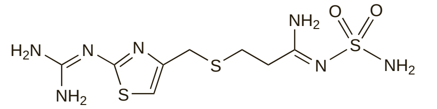

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Famotidine). A white or yellowish-white, crystalline powder or crystals. It exhibits polymorphism. Very slightly soluble in water and in dehydrated alcohol; freely soluble in glacial acetic acid; practically insoluble in ethyl acetate. It dissolves in dilute mineral acids. Protect from light.

USP 31 (Famotidine). A white to pale yellowish-white crystalline powder. Very slightly soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethylformamide and in glacial acetic acid; slightly soluble in methyl alcohol. Protect from light.

Stability. References.

1. Quercia RA, *et al.* Stability of famotidine in an extemporaneously prepared oral liquid. *Am J Hosp Pharm* 1993; **50:** 691–3.
2. Dentinger PJ, *et al.* Stability of famotidine in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2000; 1340–2.

Adverse Effects

As for Cimetidine, p.1716. Unlike cimetidine, famotidine is reported to have little or no anti-androgenic effect, although there are isolated reports of gynaecomastia and impotence.

◊ General references.

1. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; **18:** 36–54.

Effects on the blood. For reports of blood dyscrasias, some serious, occurring with famotidine, see under Cimetidine p.1717.

Effects on the cardiovascular system. Famotidine 40 mg daily by mouth reduced cardiac output and stroke volume, compared with placebo, cimetidine, or ranitidine in healthy subjects.[1] Similar effects seen in another study[2] were delayed by pretreatment with ranitidine. However, other workers have found that oral famotidine had no effect on exercise capacity or left ventricular systolic function in healthy subjects,[3] and that famotidine 20 mg intravenously had no effect on any of the haemodynamic parameters measured in 11 critically ill patients.[4] As with other H_2-antagonists (p.1717), bradycardia and AV block has been reported with famotidine,[5] as has a case of QT prolongation.[6]

1. Hinrichsen H, *et al.* Hemodynamic effects of different H -receptor antagonists. *Clin Pharmacol Ther* 1990; **48:** 302–8.
2. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
3. Hillermann DE, *et al.* Impact of chronic oral H -antagonist therapy of left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.
4. Heiselman DE, *et al.* Hemodynamic status during famotidine infusion. *DICP Ann Pharmacother* 1990; **24:** 1163–5.
5. Schoenwald PK, *et al.* Complete atrioventricular block and cardiac arrest following intravenous famotidine administration. *Anesthesiology* 1999; **90:** 623–6.
6. Endo T, *et al.* Famotidine and acquired long QT syndrome. *Am J Med* 2000; **108:** 438–9.

Effects on the endocrine system. Hyperprolactinaemia and breast engorgement occurred in a woman during the fourth month of treatment with famotidine 80 mg daily;[1] she had mistakenly been given twice the usual maximum dose. Recovery occurred when famotidine was withdrawn. Transient hyperprolactinaemia and galactorrhoea have also been reported in a woman after standard doses (40 mg daily) of famotidine.[2] There have been a few instances of impotence.[3]

1. Delpre G, *et al.* Hyperprolactinaemia during famotidine therapy. *Lancet* 1993; **342:** 868.
2. Güven K. Hyperprolactinemia and galactorrhea with standard-dose famotidine therapy. *Ann Pharmacother* 1995; **29:** 788.
3. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.

Effects on the kidneys. For mention of acute interstitial nephritis associated with H_2-antagonists, including famotidine, see under Cimetidine, p.1717.

Effects on the liver. Mixed hepatocellular jaundice[1] and acute hepatitis[2] have been associated with use of famotidine; in the latter case hepatitis later recurred when the patient was given cimetidine.

1. Ament PW, *et al.* Famotidine-induced mixed hepatocellular jaundice. *Ann Pharmacother* 1994; **28:** 40–2.
2. Hashimoto F, *et al.* Hepatitis following treatments with famotidine and then cimetidine. *Ann Pharmacother* 1994; **28:** 37–9.

Effects on the nervous system. Similarly to other H_2-antagonists (p.1717), CNS reactions have occurred with famotidine, particularly in the elderly and those with renal failure.[1-3] In one report,[1] convulsions and mental deterioration in 2 elderly patients with renal failure were associated with grossly elevated plasma and CSF concentrations of the drug; symptoms resolved within 3 days of withdrawing famotidine. In another elderly patient with renal impairment, delirium was associated with use of famotidine but did not occur with cimetidine.[4]

1. Yoshimoto K, *et al.* Famotidine-associated central nervous system reactions and plasma and cerebrospinal drug concentrations in neurosurgical patients with renal failure. *Clin Pharmacol Ther* 1994; **55:** 693–700.
2. Catalano G, *et al.* Famotidine-associated delirium: a series of six cases. *Psychosomatics* 1996; **37:** 349–55.
3. Odeh M, Oliven A. Central nervous system reactions associated with famotidine: report of five cases. *J Clin Gastroenterol* 1998; **27:** 253–4.
4. Yuan R-Y, *et al.* Delirium following a switch from cimetidine to famotidine. *Ann Pharmacother* 2001; **35:** 1045–8.

Effects on the skin. Toxic epidermal necrolysis or erythema multiforme have been reported after use of famotidine;[1,2] the second patient had a recurrence with cimetidine.

1. Brunner M, *et al.* Toxic epidermal necrolysis (Lyell syndrome) following famotidine administration. *Br J Dermatol* 1995; **133:** 814–15.
2. Horiuchi Y, Ikezawa K. Famotidine-induced erythema multiforme: cross-sensitivity with cimetidine. *Ann Intern Med* 1999; **131:** 795.

Fever. Famotidine 20 mg intravenously every 12 hours was associated with hyperpyrexia in a patient with facial and cranial trauma.[1] Rectal temperature in the 24 hours after starting famotidine was 40.5° and remained elevated for the 5 days of famotidine treatment, despite use of antipyretics. Withdrawal of famotidine resulted in a return to normal temperature within 24 hours.

1. Norwood J, *et al.* Famotidine and hyperpyrexia. *Ann Intern Med* 1990; **112:** 632.

Precautions

As for Cimetidine, p.1718.

Hepatic impairment. For a report of increased resistance to H_2-antagonists in patients with liver cirrhosis, see Ranitidine, p.1766.

Renal impairment. In patients with renal impairment, famotidine clearance is reduced and the elimination half-life increased, resulting in increased serum-drug concentrations and in some cases clinical sequelae (see Effects on the Nervous System, above). The half-life of famotidine in healthy subjects is about 3 hours, but in patients with a creatinine clearance less than 38 mL/minute[1] or those with end-stage renal disease[2] it has been reported to be 19.3 hours and 27.2 hours respectively. A 50% reduction in the dose of famotidine in patients with renal impairment has therefore been recommended. However, it may not be sufficient to adjust the dose only on the basis of creatinine clearance since famotidine is partly eliminated by tubular secretion, which may also be diminished.[1] A chart review[3] in patients with end-stage renal disease suggested that most patients would tolerate a dose of 20 mg daily, although a few might need further adjustment to prevent mental status changes.

Haemodialysis does not effectively remove famotidine from the systemic circulation. The proportion removed depends on the type of membrane used; with a high flux polysulfone membrane about 16% is reported to be removed, but only 6% with a cuprophan membrane.[2] Continuous ambulatory peritoneal dialysis is reported to remove about 5% of a dose.[2] Continuous haemofiltration may remove about 16% of a dose;[2] intermittent haemofiltration is reported to remove about 4%[4] or 8%.[2] Dosage supplements of famotidine are not required during or after dialysis or filtration procedures.

1. Inotsume N, *et al.* Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. *Eur J Clin Pharmacol* 1989; **36:** 517–20.
2. Gladziwa U, *et al.* Pharmacokinetics and dynamics of famotidine in patients with renal failure. *Br J Clin Pharmacol* 1988; **26:** 315–21.
3. Redmond AM, *et al.* Use of famotidine in adult patients with end-stage renal disease: assessment of dosing and mental status changes. *Am J Med Sci* 2005; **330:** 8–10.
4. Saima S, *et al.* Hemofiltrability of H -receptor antagonist, famotidine, in renal failure patients. *J Clin Pharmacol* 1990; **30:** 159–62.

Interactions

Unlike cimetidine (see p.1718) famotidine does not inhibit cytochrome P450, and therefore is considered to have little effect on the metabolism of other drugs. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of some other drugs.

Antacids. Giving famotidine 40 mg with a 10-mL dose of antacid containing 800 mg *aluminium hydroxide* with 800 mg *magnesium hydroxide*,[1] resulted in a decrease in the bioavailability of famotidine that was considered clinically insignificant. Giving famotidine with a 30-mL dose of the same antacid resulted in a greater reduction in the absorption of famotidine from the gastrointestinal tract, but the interaction could be minimised by separating ingestion by 2 hours.[2]

1. Lin JH, *et al.* Effects of antacids and food on absorption of famotidine. *Br J Clin Pharmacol* 1987; **24:** 551–3.
2. Barzaghi N, *et al.* Impaired bioavailability of famotidine given concurrently with a potent antacid. *J Clin Pharmacol* 1989; **29:** 670–2.

Probenecid. Probenecid in a total dose of 1500 mg had a significant effect on the pharmacokinetics of famotidine 20 mg in 8 healthy subjects.[1] The maximum serum concentration of famotidine and the area under the concentration/time curve were significantly increased and renal clearance significantly reduced.

These effects were explained by inhibition of the renal tubular secretion of famotidine by probenecid.

1. Inotsume N, *et al.* The inhibitory effect of probenecid on renal excretion of famotidine in young, healthy volunteers. *J Clin Pharmacol* 1990; **30:** 50–6.

Theophylline. Although famotidine is considered not to interfere with the metabolism of other drugs there is a report of a clinically significant interaction with theophylline—see p.1145.

Pharmacokinetics

Famotidine is readily but incompletely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring 1 to 3 hours after oral doses. The bioavailability of oral famotidine is about 40 to 45% and is not significantly affected by the presence of food.

The elimination half-life from plasma is reported to be about 3 hours and is prolonged in renal impairment. Famotidine is weakly bound, about 15 to 20%, to plasma proteins. A small proportion of famotidine is metabolised in the liver to famotidine *S*-oxide. About 25 to 30% of an oral dose, and 65 to 70% of an intravenous dose, is excreted unchanged in the urine in 24 hours, primarily by active tubular secretion. Famotidine is also found in breast milk.

◊ Reviews.

1. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. *Clin Pharmacokinet* 1991; **21:** 178–94.

Children. Famotidine 300 micrograms/kg intravenously was given to 10 children aged 2 to 7 years, after cardiac surgery and before extubation, to prevent aspiration.[1] This dose (equivalent to about 20 mg in adults) induced a rise in the intragastric pH within 1 hour of being given and the pH remained above 3.5 for about 9 hours. The mean elimination half-life was 3.3 hours, similar to the value in healthy adults and it was considered that doses in children need therefore only be adjusted according to body-weight and renal function. This conclusion was supported by a review of 8 studies in children over 1 year of age.[2] Conversely, in infants aged 5 to 19 days, the mean elimination half-life was prolonged (10.5 hours) secondary to reduced renal clearance.[3] This was confirmed by another study,[4] which indicated that reduced clearance was found in infants under 3 months of age, but that pharmacokinetics in older infants were similar to those previously reported for children and adults.

1. Kraus G, *et al.* Famotidine: pharmacokinetic properties and suppression of acid secretion in paediatric patients following cardiac surgery. *Clin Pharmacokinet* 1990; **18:** 77–81.
2. James LP, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in paediatric patients. *Clin Pharmacokinet* 1996; **31:** 103–10.
3. James LP, *et al.* Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998; **38:** 1089–95. Correction. *ibid.* 2000; **40:** 1298.
4. Wenning LA, *et al.* Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005; **44:** 395–406.

Distribution into breast milk. The peak concentration of famotidine in breast milk, which occurred in 8 women 6 hours after an oral dose of 40 mg, was similar to the peak plasma concentration which occurred 2 hours after the dose.[1]

1. Courtney TP, *et al.* Excretion of famotidine in breast milk. *Br J Clin Pharmacol* 1988; **26:** 639P.

Enterohepatic recirculation. Some individuals have a second peak in the plasma concentration of famotidine, which could be due to enterohepatic recirculation. However, a maximum of 0.43% of a dose of famotidine was excreted in the bile of 2 patients following single doses of 20 mg intravenously or 40 mg by mouth indicating that significant recirculation had not occurred.[1]

1. Klotz U, Walker S. Biliary excretion of H -receptor antagonists. *Eur J Clin Pharmacol* 1990; **39:** 91–2.

Uses and Administration

Famotidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p.1719).

Famotidine may be given orally or intravenously.

In the management of benign **gastric** and **duodenal ulceration** (p.1702) the dose is 40 mg daily orally at bedtime, for 4 to 8 weeks. A dose of 20 mg twice daily has also been given. A maintenance dose of 20 mg at bedtime may be given to prevent recurrence of duodenal ulceration. In **gastro-oesophageal reflux disease** (p.1696) the recommended oral dose is 20 mg twice daily for 6 to 12 weeks, or up to 40 mg twice daily if there is oesophageal ulceration. A maintenance dose of 20 mg twice daily may be given to prevent recurrence. For the short-term symptomatic relief of heartburn or non-ulcer **dyspepsia** (p.1695) a dose of 10 mg up to twice daily is suggested. In the **Zollinger-Ellison syndrome** (p.1704) the initial oral dose is 20 mg every 6 hours, increased as necessary; doses up to 800 mg daily have been used.

The usual dose of famotidine by the intravenous route is 20 mg and may be given by injection over at least 2 minutes or as an infusion over 15 to 30 minutes; the dose may be repeated every 12 hours.

Doses of famotidine should be reduced in patients with renal impairment (see below).

Administration. Although famotidine is most usually given as a film-coated tablet, an alternative wafer formulation, designed to dissolve on the tongue without the need for water, has also been developed.[1]

Parenteral formulations of famotidine are also available in some countries. Although licensed product information recommends that intravenous injections be given over at least 2 minutes, a study that compared rapid intravenous injection (over up to 1 minute) with slow intravenous infusion found both to be safe.[2] Continuous infusion has however been reported by others[3] to be more effective in the prevention of stress ulceration than bolus injection.

1. Schwartz JI, *et al.* Novel oral medication delivery system for famotidine. *J Clin Pharmacol* 1995; **35:** 362–7.
2. Fish DN. Safety and cost of rapid iv injection of famotidine in critically ill patients. *Am J Health-Syst Pharm* 1995; **52:** 1889–94.
3. Baghaie AA, *et al.* Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: results of a prospective, randomized, crossover study. *Crit Care Med* 1995; **23:** 687–91.

Administration in renal impairment. The dosage of famotidine should be reduced in patients with renal impairment. In the UK, a 50% reduction is suggested for patients whose creatinine clearance is less than 10 mL/minute; in the USA this reduction is recommended in all those with creatinine clearance less than 50 mL/minute. Alternatively, the dosage interval may be prolonged to 36 to 48 hours.

Immunomodulation. *MALIGNANT NEOPLASMS.* References[1-3] to the use of adjuvant famotidine in patients with malignant neoplasms, including use with interleukin-2 infusions.[2,3]

1. Parshad R, *et al.* Effect of preoperative short course famotidine on TILs and survival in breast cancer. *Indian J Cancer* 2005; **42:** 185–90.
2. Quan WD, *et al.* Continuous infusion interleukin-2 and famotidine in metastatic kidney cancer. *Cancer Biother Radiopharm* 2006; **21:** 515–19.
3. Quan WD, *et al.* Continuous infusion interleukin-2 and intravenous famotidine in metastatic melanoma. *Cancer Biother Radiopharm* 2006; **21:** 607–12.

Schizophrenia. There are reports of improvement in schizophrenic symptoms (p.955) in patients given famotidine.[1-4]

1. Kaminsky R, *et al.* Effect of famotidine on deficit symptoms of schizophrenia. *Lancet* 1990; **335:** 1351–2.
2. Rosse RB, *et al.* Famotidine adjunctive pharmacotherapy of schizophrenia: a case report. *Clin Neuropharmacol* 1995; **18:** 369–74.
3. Rosse RB, *et al.* An open-label study of the therapeutic efficacy of high-dose famotidine adjuvant pharmacotherapy in schizophrenia: preliminary evidence for treatment efficacy. *Clin Neuropharmacol* 1996; **19:** 341–8.
4. Martinez MC. Famotidine in the management of schizophrenia. *Ann Pharmacother* 1999; **33:** 742–7.

Preparations

BP 2008: Famotidine Tablets;
USP 31: Famotidine for Oral Suspension; Famotidine Injection; Famotidine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ulcelac; ***Austral.:*** Amfamox†; Ausfam; Famohexal; Pamacid; Pepcid†; Pepcidine; Pepzan; ***Austria:*** Eradix; Famohexal; Famosin; Pepcid; Sodexx Famotidine; Tetacid; Ulcusan; ***Belg.:*** Pepcidine†; ***Braz.:*** Famodine†; Famoset; Famotid; Famotil†; Famox; Famoxil†; ***Canad.:*** Acid Control; Acid Halt; Maalox H Acid Controller; Pepcid; Peptic Guard; Ulcidine†; ***Chile:*** Anulbet†; Fibonel†; Gastrium; ***Cz.:*** Famosan; Quamatel; Ulceran†; Ulfamid; ***Denm.:*** Pepcidin†; ***Fin.:*** Pepcid; Pepcidin; ***Fr.:*** Pepcidac; Pepdine; ***Ger.:*** Fadul; Famo; Famobeta; Famonerton; Pepcid†; Pepdul; ***Gr.:*** Ansilan; Banatin; Cepal†; Esseldon; Gasterogen; Imposergon; Mostrelan; Panalba; Peptan; Rosagenus; Sedanium-R; Vexurat; ***Hong Kong:*** Ausfam; Beilande; Fadine; Famine; Famocid; Famodine; Famolta; Famopsin; Famotin; Famox; Gastrodomina; LAfamo; Marmodine; Motidine; Pepcidine; Phyzidine; Quamatel; Servipep†; Ulceran†; Vida Famodine; ***Hung.:*** Motidin; Peptigal†; Quamatel; Servipep†; ***India:*** Blocacid†; Fadine; Famodin; Famonite; Famowal; Famtac; Fudone; Ulcimax; ***Indon.:*** Antidine; Corocyd; Denufam; Faberdin; Facid; Famocid; Fluktan; Gasfamin; Gaster; Gestofam; Ifamul; Interfam; Lexmodine; Nulcefam; Pompaton; Promocid; Purifam; Regastin; Renapepsa; Tismafam; Ulcerid; Ulfam; Ulmo; ***Irl.:*** Pepcid; ***Israel:*** Apogastine; Famo; Gastro; Rogasti; Zarex†; ***Ital.:*** Famodil; Gastridin; Motiax; ***Jpn:*** Gaster; ***Malaysia:*** Acidine†; Fadine†; Famopsin; Pepcidine; Pepzan; Ulceran; Voker; ***Mex.:*** Adiatin; Amofat†; Androtin; Durater; Eufatin†; Fabutin; Fagatrim†; Famoxal; Fatoril†; Fawodin†; Ludex; Pepcidine; Sertidine; Sigafam†; Ultidin; ***Neth.:*** Pepcid; Pepcidin; ***Norw.:*** Famotal; Pepcid; Pepcidin; ***NZ:*** Famox; Pepcid†; Pepcidine†; Pepzan; ***Philipp.:*** Famorila; Famtine; H2 Bloc; Hista-Bloc; Motid; Pepcidine; Ulcefam; ***Pol.:*** Famidyna; Famogast; Quamatel; Ulfamid; ***Port.:*** Digeslit†; Dinul; Dipsin; Fatidin; Gastopride†; Gastrifam†; Lasa; Mensoma; Nulceran†; Pepcidina; ***Rus.:*** Famocid (Фамоцид); Famonit (Фамонит); Famosan (Фамосан); Gastrosidin (Гастросидин); Quamatel (Квамател); Ulceran (Ульцеран); Ulfamid (Ульфамид); ***Singapore:*** Blocacid†; Famoc; Famopril; Famopsin†; Famotin; Famox†; Motidine; Pepcidine; Pepzan; Ulceran; ***Spain:*** Brolin†; Confobos; Cronol; Digervin; Dispromil†; Eviantrina; Fagastril; Famokey; Famulcer; Fanosin†; Fanox†; Gastenin; Gastrion; Gastrodomina; Gastropen†; Ingastri; Invigan; Nos†; Nulcerin; Pepcid; Rubacina; Tairal; Tamin; Tipodex; Ulcetrax†; Ulgarine; Vagostal; ***Swed.:*** Pepcid; Pepcidin; ***Switz.:*** Pepcid†; Pepcidine†; ***Thai.:*** Agufam; Fadine†; Famoc; Famocid†; Famonox; Famopsin; Famosia; Famotab; Famotin†; Fasidine; Motidine; Pepcidine; Pepcine; Pepdenal; Pepfamin; Peptoci; Pepzan†; Pharmotidine†; Ulceran; Ulcofam†; Ulfamet; ***Turk.:*** Duovel; Famec; Famo; Famodin; Famogast; Famoser; Famotep; Famotsan; Gasterol; Gastifam; Gastrofam; Gastrosidin; Neotab; Nevofam; Notidin; Pepdif; ***UAE:*** Famotec; ***UK:*** Pepcid; Ultra Heartburn Relief; ***USA:*** Mylanta AR Acid Reducer†; Pepcid; ***Venez.:*** Dinamot; Fadipina†; Famogel; Famulcer; Isomina; Klinotal; Medalin; Neutracid; Pepcidine†; Ulcenol.

Multi-ingredient: ***Arg.:*** Actual; Megalex Antiacido; Mylanta Extra; ***Canad.:*** Pepcid Complete; ***Fin.:*** Pepcid Duo; ***Fr.:*** Pepcidduo; ***Ger.:*** Pepciddual; ***Indon.:*** Neosanmag Fast; Promag Double Action; ***Ital.:*** Pepciddual; ***Mex.:*** Facidex Total; ***Norw.:*** Pepcidduo; ***Spain:*** Pepdual; ***Swed.:*** Pepcid Duo; ***UK:*** Pepcidtwo; ***USA:*** Pepcid Complete.

Fedotozine *(rINN)*

Fedotozina; Fédotozine; Fedotozinum; JO-1196 (tartrate). (+)-(*R*)-α-Ethyl-*N*,*N*-dimethyl-α-{[(3,4,5-trimethoxybenzyl)oxy]methyl}benzylamine.

Федотозин

$C_{22}H_{31}NO_4$ = 373.5.
CAS — 123618-00-8 (fedotozine); 133267-27-3 (fedotozine tartrate).

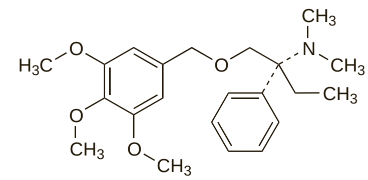

Profile

Fedotozine is a peripherally acting selective agonist of opioid κ-receptors that has been investigated in dyspepsia and the irritable bowel syndrome.

◊ References.

1. Delvaux M. Pharmacology and clinical experience with fedotozine. *Expert Opin Invest Drugs* 2001; **10:** 97–110.

Fentonium Bromide *(rINN)*

Bromuro de fentonio; Fa-402; Fentonii Bromidum; Fentonium, Bromure de; Ketoscilium; *N*-(4-Phenylphenacyl)-1-hyoscyaminium Bromide; Z-326. (−)-(1*R*,3*r*,5*S*)-8-(4-Phenylphenacyl)-3-[(*S*)-tropoyloxy]tropanium bromide.

Фентония Бромид

$C_{31}H_{34}BrNO_4$ = 564.5.
CAS — 5868-06-4.
ATC — A03BB04.
ATC Vet — QA03BB04.

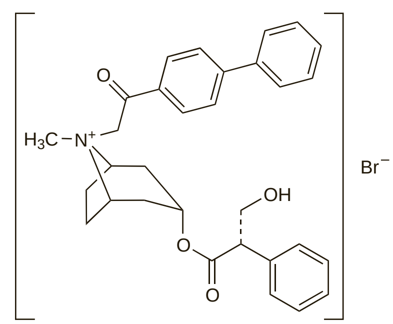

Profile

Fentonium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used to relieve visceral spasms.

Fig

Carica; Ficus; Higo.

Инжир; Фикус

Pharmacopoeias. In *Br.* and *Swiss.*

BP 2008 (Fig). The sun-dried succulent fruit of *Ficus carica* containing not less than 60.0% of water-soluble extractive. Store in a dry place.

Profile

Fig is a mild laxative and demulcent usually used with other laxatives.

Effects on the skin. Skin reactions and photodermatitis have followed application of home-made decoctions of fig leaves to the skin.[1,2]

1. Ozdamar E, *et al.* An unusual cause of burn injury: fig leaf decoction used as a remedy for a dermatitis of unknown etiology. *J Burn Care Rehabil* 2003; **24:** 229–33.
2. Bassioukas K, *et al.* Erythrodermic phytophotodermatitis after application of aqueous fig-leaf extract as an artificial suntan promoter and sunbathing. *Contact Dermatitis* 2004; **51:** 94–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Carilax; Frugelletten; Herbelax; Neda Fruchtewurfel; ***Braz.:*** Bilifel†; ***Denm.:*** Figen; ***Fr.:*** Carres Parapsyllium; Preservation; ***Ger.:*** florabio Mann-Feigen-Sirup mit Senna†; florabio Manna-Feigen; ***Switz.:*** Agarol Soft; Dragees aux figues avec du sene; Fruttasan; Pursana; Valverde Constipation dragees; Valverde Constipation sirop; ***UK:*** Califig.

Fosaprepitant *(rINN)*

Fosaprépitant; Fosaprepitantum. {3-[((2*R*,3*S*)-2-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl)methyl]-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl}phosphonic acid.

Фозапрепитант

$C_{23}H_{22}F_7N_4O_6P$ = 614.4.

CAS — 172673-20-0.

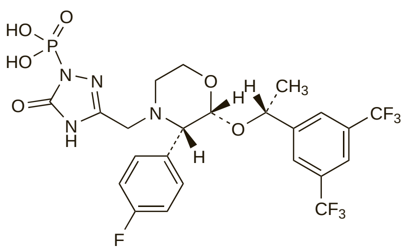

Fosaprepitant Meglumine *(rINNM)*

Fosaprepitant Dimeglumine; Fosaprepitant meglumina; Fosaprépitant Méglumine; Meglumini Fosaprepitantum; MK-0517. 1-Deoxy-1-(methylamino)-D-glucitol {3-[((2*R*,3*S*)-2-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-4-morpholinyl)methyl]- 2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl}phosphonate.

Меглумина Фозапрепитант

$C_{23}H_{22}F_7N_4O_6P, 2C_7H_{17}NO_5$ = 1004.8.

CAS — 265121-04-8.

Stability. US licensed product information states that, once reconstituted and diluted as directed in sodium chloride 0.9%, a solution of fosaprepitant meglumine is stable for 24 hours at room temperature (at or below 25°).

Adverse Effects and Precautions

As for Aprepitant, p.1708.

Interactions

As for Aprepitant, p.1708.

Pharmacokinetics

Fosaprepitant is rapidly converted to aprepitant; for the pharmacokinetics of aprepitant, see p.1708.

Uses and Administration

Fosaprepitant is a prodrug of the antiemetic aprepitant (p.1708), which is a neurokinin-1 receptor antagonist. Fosaprepitant meglumine is used for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy. Doses are expressed in terms of the base; 188 mg of fosaprepitant meglumine is equivalent to about 115 mg of fosaprepitant. A dose of fosaprepitant meglumine equivalent to 115 mg fosaprepitant may be given intravenously instead of oral aprepitant, with a corticosteroid and a 5-HT_3 antagonist (for details, see Administration, under Aprepitant, p.1709). The reconstituted dose of fosaprepitant is diluted in 110 mL of sodium chloride 0.9% to a final concentration of 1 mg/mL and infused over 15 minutes.

◊ References.

1. Navari RM. Fosaprepitant (MK-0517): a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Expert Opin Invest Drugs* 2007; **16:** 1977–85.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Ivemend; ***Port.:*** Ivemend; ***UK:*** Ivemend; ***USA:*** Emend.

Frangula Bark

Alder Buckthorn Bark; Amieiro Negro; Bourdaine; Faulbaumrinde; Frángula, corteza de; Frangulabark; Frangulae cortex; Kora kruszyny; Krušinová kůra; Kutyabengekéreg; Paatsamankuori; Rhamni Frangulae Cortex; Šaltekšnių žievė.

Кора Крушины

CAS — 8057-57-6 (frangula extract).

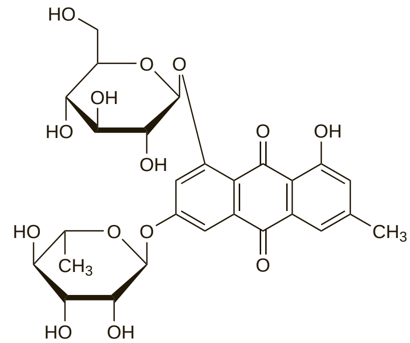

(glucofrangulin A)

NOTE. The name Buckthorn Bark has also been used; distinguish Frangula Bark from Buckthorn (p.1713) and from Sea Buckthorn (p.2384).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Frangula Bark). The dried, whole or fragmented bark of the stems and branches of *Rhamnus frangula* (=*Frangula alnus*). It contains not less than 7.0% of glucofrangulins, expressed as glucofrangulin A ($C_{27}H_{30}O_{14}$ = 578.5) and calculated with reference to the dried drug. Protect from light.

Profile

Frangula bark is an anthraquinone stimulant laxative with actions and uses similar to those of senna (p.1769).

Homoeopathy. Frangula bark has been used in homoeopathic medicines under the following names: Frangula; Rhamnus frangula; Rham. fr.

Preparations

Ph. Eur.: Frangula Bark Dry Extract, Standardised.

Proprietary Preparations (details are given in Part 3)

Fr.: Depuratif des Alpes; ***Switz.:*** Arkocaps†; Elixir frangulae compositum.

Multi-ingredient: ***Austral.:*** Granocol†; Normacol Plus; ***Austria:*** Abfuhrtee†; Artin; Dragees Neunzehn†; Gallesyn; Laxalpin; Laxolind; Mag Kottas Krauterexpress Abfuhrtee; Mag Kottas May-Cur-Tee; Planta Lax; Waldheim Abfuhrdragees mild; ***Belg.:*** Depuratif des Alpes; Grains de Vals; Normacol Plus†; ***Canad.:*** Extra Strong Formula 12†; Herbal Laxative; Herbalax†; ***Cz.:*** Abdomilon†; Abfuhr-Heilkrautertee†; Cholagol; Reduktan; The Salvat; ***Denm.:*** Ferroplex-frangula; ***Fr.:*** Dragees Fuca; Dragees Vegetales Rex; Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane Circulation du Sang No 12; Normacol a la Bourdaine†; Tonilax; ***Ger.:*** Heumann Abfuhrtee Solubilax N†; Hevertolax duo†; ***Hong Kong:*** Hepatofalk; Normacol Plus; ***Hung.:*** Cholagol; ***India:*** Kanormal; ***Irl.:*** Normacol Plus; ***Israel:*** Encypalmed; Rekiv; ***Ital.:*** Draverex; Fave di Fuca; Frangulina†; Lactolas; Neoform†; ***Mex.:*** Normacol†; ***Neth.:*** Roteroblong Maagtabletten; ***NZ:*** Granocol; Normacol Plus; ***Pol.:*** Alax; Cholavisol; Cholesol; Gastro; Laxantol; Rhelax; Senalax K; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; ***Port.:*** Normacol Plus; ***S.Afr.:*** Normacol Plus; ***Singapore:*** Normacol Plus; ***Spain:*** Normacol Forte; ***Switz.:*** Colosan plus; Lapidar 10; Linoforce; LinoMed; Normacol avec bourdaine nouvelle formule†; Padma-Lax; Padmed Laxan; Phyto-Laxia; Phytolaxin; ***UK:*** Herbulax; Lustys Herbalene; Natravene; Normacol Plus.

Gefarnate *(BAN, rINN)*

DA-688; Géfarnate; Gefarnato; Gefarnatum; Geranyl Farnesylacetate. A mixture of stereoisomers of 3,7-dimethylocta-2,6-dienyl 5,9,13-trimethyltetradeca-4,8,12-trienoate.

Гефарнат

$C_{27}H_{44}O_2$ = 400.6.

CAS — 51-77-4.

ATC — A02BX07.

ATC Vet — QA02BX07.

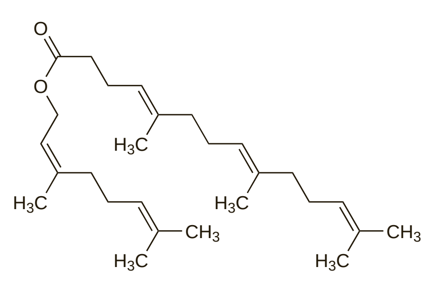

Profile

Gefarnate is a cytoprotective that has been used in the treatment of peptic ulcer disease and gastritis. An ophthalmic preparation is under investigation for the treatment of corneal and conjunctival epithelial disorders.

Ginger

Gengibre; Gingembre; Gyömbér gyökértörzs; Imbierų šakniastiebiai; Ingefära; Ingwer; Inkivääri; Jengibre; Zázvorový oddenek; Zingib.; Zingiber; Zingiberis rhizoma.

Имбирь

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US. US* also includes the powdered form.

Ph. Eur. 6.2 (Ginger). The dried, whole or cut rhizome of *Zingiber officinale*, with the cork removed, either completely or from the wide flat surfaces only. Whole or cut, it contains not less than 1.5% of essential oil, calculated with reference to the anhydrous drug. It has a characteristic aromatic odour. Protect from light.

The BP 2008 states that ginger may be known in commerce as unbleached ginger.

USP 31 (Ginger). The scraped, partially scraped, or unscraped rhizome of *Zingiber officinale* (Zingiberaceae), known in commerce as unbleached ginger. It contains not less than 4.5% of alcohol-soluble extractive and not less than 10% of water-soluble extractive. Store at 8° to 15°. Protect from light and moisture.

Profile

Ginger has carminative properties. It is used as a flavouring agent and has been tried for the prophylaxis of motion sickness and nausea and vomiting in pregnancy, although it does not seem to be effective for postoperative nausea and vomiting (p.1700).

Ginger oil is used in aromatherapy.

Homoeopathy. Ginger has been used in homoeopathic medicines under the following names: Zingiber; Zingiber officinale; Zing.

Nausea and vomiting. References.

1. Arfeen Z, *et al.* A double-blind randomized controlled trial of ginger for the prevention of postoperative nausea and vomiting. *Anaesth Intensive Care* 1995; **23:** 449–52.
2. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth* 2000; **84:** 367–71.
3. Grant KL, Lutz RB. Ginger. *Am J Health-Syst Pharm* 2000; **57:** 945–7.
4. Vutyavanich T, *et al.* Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. *Obstet Gynecol* 2001; **97:** 577–82.
5. Smith C, *et al.* A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. *Obstet Gynecol* 2004; **103:** 639–45.
6. Boone SA, Shields KM. Treating pregnancy-related nausea and vomiting with ginger. *Ann Pharmacother* 2005; **39:** 1710–13.
7. Chaiyakunapruk N, *et al.* The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obstet Gynecol* 2006; **194:** 95–9.

Preparations

BP 2008: Aromatic Cardamom Tincture; Strong Ginger Tincture; Weak Ginger Tincture;
USP 31: Ginger Capsules; Ginger Tincture.

Proprietary Preparations (details are given in Part 3)

Austral.: Travacalm Natural; ***Canad.:*** Gravol Natural Source; ***Ger.:*** Zintona; ***Switz.:*** Zintona; ***Thai.:*** Zinaxin†; ***UK:*** Travel Sickness; Zinaxin.

Multi-ingredient: ***Austral.:*** Bioglan Ginger-Vite Forte; Bioglan Psylli-Mucil Plus; Boswellia Complex; Boswellia Compound; Broncafect; Cal Alkyline; Diaco; Digestive Aid; Dyzco; Extralife Arthri-Care; Feminine Herbal Complex; Ginkgo Plus Herbal Plus Formula 10†; Herbal Cleanse†; Herbal Digestive Formula†; Lifesystem Herbal Plus Formula 11 Ginkgo†; PC Regulax†; Peritone; PMS Support†; PMT Complex†; Travelaide†; ***Austria:*** Mariazeller; ***Braz.:*** Broncol; Tussifen†; ***Canad.:*** Cayenne Plus†; Chase Kolik Gripe Water; ***Cz.:*** Klosterfrau Melisana; Naturland Grosser Swedenbitter†; ***Fr.:*** Arthrolib; Evacrine; ***Ger.:*** Fovysat†; Gallexier; Gastricard†; Gastrosecur†; Gastrysat; JuViton†; Majocarmin forte†; Presselin Dyspeptikum†; Unex Amarum†; ***Hong Kong:*** Magesto; ***India:*** Carmicide; Happy'tizer; Papytazyme; Tummy Ease; Well-Beeing†; ***Indon.:*** Avogin; Pectum; Pregnasea; ***Ital.:*** Donalg; Lozione Same Urto; Pik Gel; ***Malaysia:*** Dandelion Complex†; Strepsils Cough Lozenge; Strepsils Cough Syrup; Total Man†; Zinaxin Plus†; ***Philipp.:*** Bo-D-Fense; Ruflex; ***Pol.:*** Melisana Klosterfrau; ***Rus.:*** Dipana (Дипана); Doktor Mom (Доктор Мом); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Suprima-Broncho (Суприма-бронхо); ***S.Afr.:*** Helmontskruie; Lewensessens; Wonderkroonessens; ***Singapore:*** Artrex†; ***Switz.:*** Padma-Lax; Padmed Laxan; Tisane pour les problemes de prostate; ***Thai.:*** Carmicide†; Flatulence; Magesto; Mesto-Of; Papytazyme†; Zinaxin

Plus; ***UK:*** Arheumacare; Digestive; HRI Golden Seal Digestive; Indian Brandee; Indigestion Relief; Neo Baby Gripe Mixture; Neo Gripe Mixture; Traveleeze; Wind & Dyspepsia Relief; Zinopin; ***Venez.:*** Ervossil; Jengimiel; Jengimiel Sabila.

Granisetron Hydrochloride

(BANM, USAN, rINNM)

BRL-43694A; Granisétron, chlorhydrate de; Granisetron-hydrochlorid; Granisetronhydroklorid; Granisetroni hydrochloridum; Granisetronihydrokloridi; Granisetrono hidrochloridas; Hidrocloruro de granisetrón. 1-Methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide hydrochloride.

Гранисетрона Гидрохлорид

$C_{18}H_{24}N_4O,HCl = 348.9.$

CAS — 109889-09-0 (granisetron); 107007-99-8 (granisetron hydrochloride).

ATC — A04AA02.

ATC Vet — QA04AA02.

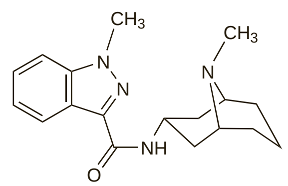

(granisetron)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; sparingly soluble in dichloromethane; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 6.5.

Adverse Effects and Precautions

As for Ondansetron, p.1757, although no dosage reduction is considered necessary in renal or hepatic impairment.

Carcinogenicity. The manufacturer (*Roche*) has reported an increased incidence of hepatic neoplasms in *rodents* given very high doses of granisetron for prolonged periods, but the clinical relevance of these results is unknown. Although mutagenicity and genotoxicity have not been seen in some tests, others have reported an increased incidence of polyploidy or unscheduled DNA synthesis in exposed cells.

Effects on the cardiovascular system. For a discussion of the effects of $5\text{-}HT_3$ antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Interactions

The metabolism of granisetron is induced by phenobarbital.

Pharmacokinetics

Granisetron is rapidly absorbed after oral doses, with peak plasma concentrations occurring after about 2 hours. Oral bioavailability is about 60% as a result of first-pass hepatic metabolism. Granisetron has a large volume of distribution of around 3 litres/kg; plasma protein binding is about 65%. The pharmacokinetics exhibit considerable interindividual variation, and the elimination half-life after an intravenous dose is reported to be around 4 to 5 hours in healthy subjects but about 9 to 12 hours in cancer patients. It is metabolised in the liver, primarily by *N*-demethylation, with less than 20% of a dose recovered unchanged in urine, the remainder being excreted in faeces and urine as metabolites. Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Uses and Administration

Granisetron is a $5\text{-}HT_3$ antagonist with an antiemetic action similar to that of ondansetron (p.1757). It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting (p.1700). Granisetron is given as the hydrochloride, but doses are expressed in terms of the base. Granisetron hydrochloride 1.1 mg is equivalent to about 1 mg of granisetron base.

For acute **nausea and vomiting** associated with **chemotherapy** granisetron is used in *prevention* and *treatment* in similar doses.

- In the UK, a dose equivalent to 3 mg of granisetron is diluted to a volume of 20 to 50 mL with a suitable infusion solution and given intravenously over 5 minutes before the start of chemotherapy; alternatively this dose may be given in 15 mL of infusion solution as a bolus over not less than 30 seconds. The dose may be repeated up to twice in 24 hours; doses should be given at least 10 minutes apart and a total daily dose of 9 mg should not be exceeded. The efficacy of granisetron may be enhanced by the use of dexamethasone. The recommended oral dose is 1 to 2 mg within one hour before therapy begins, then 2 mg daily as a single dose or in 2 divided doses.
- For use in children, an intravenous infusion of 40 micrograms/kg, up to a maximum total dose of 3 mg, has been recommended, diluted in 10 to 30 mL of infusion fluid and given over 5 minutes. This dose may be repeated once within 24 hours, but at least 10 minutes after the original infusion. Alternatively, children may be given 20 micrograms/kg (up to 1 mg) orally twice daily for up to 5 days during therapy; the first dose should be given within 1 hour before the start of chemotherapy.
- In the USA, lower intravenous doses of the equivalent of granisetron 10 micrograms/kg are recommended in both adults and children over 2 years of age, beginning within 30 minutes before chemotherapy. Oral doses are the same as those described for the UK above.

For the *prevention* of nausea and vomiting associated with **radiotherapy** the recommended adult oral dosage is 2 mg daily taken within 1 hour of irradiation. The drug has also been given intravenously for the *treatment and prevention* of nausea and vomiting associated with radiotherapy, in similar doses to those recommended above for emetogenic chemotherapy. In the UK, the *BNFC* has recommended similar oral and intravenous doses to those given above (for chemotherapy-induced nausea and vomiting) in both the treatment and prevention of radiotherapy-induced nausea and vomiting in children.

For the *prevention* of **postoperative** nausea and vomiting in adults 1 mg is diluted to 5 mL and given by intravenous injection over 30 seconds. Injection should be completed before induction of anaesthesia. The same dose may be given up to twice daily for the *treatment* of established postoperative nausea and vomiting.

Transdermal and intranasal formulations of granisetron are under investigation.

◊ References.

1. Adams VR, Valley AW. Granisetron: the second serotonin-receptor antagonist. *Ann Pharmacother* 1995; **29:** 1240–51. Correction. *ibid.* 1996; **30:** 1043.
2. Wilson AJ, *et al.* Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting. *Br J Anaesth* 1996; **76:** 515–18.
3. Taylor AM, *et al.* A double-blind, parallel-group, placebo-controlled, dose-ranging, multicenter study of intravenous granisetron in the treatment of postoperative nausea and vomiting in patients undergoing surgery with general anesthesia. *J Clin Anesth* 1997; **9:** 658–63.
4. Blower PR. Granisetron: relating pharmacology to clinical efficacy. *Support Care Cancer* 2003; **11:** 93–100.
5. Minami M. Granisetron: is there a dose-response effect on nausea and vomiting? *Cancer Chemother Pharmacol* 2003; **52:** 89–98.
6. Prentice HG. Granisetron in the control of nausea and vomiting associated with bone marrow transplantation: a review of its efficacy and tolerability. *Support Care Cancer* 2003; **11:** 501–8.
7. Corman SL, *et al.* Low-dose granisetron for postoperative nausea and vomiting prophylaxis. *Ann Pharmacother* 2004; **38:** 710–13.
8. Goldsmith B. First choice for radiation-induced nausea and vomiting—the efficacy and safety of granisetron. *Acta Oncol* 2004; **43** (suppl 15): 19–22.
9. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist* 2004; **9:** 673–86.

Pain. For reference to the use of granisetron in various painful syndromes see under Uses and Administration of Ondansetron, p.1758

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aludal; Eumetic†; Granitron; Kytril†; Rigmoz†; ***Austral.:*** Kytril; ***Austria:*** Kytril; ***Belg.:*** Kytril; ***Braz.:*** Kytril; ***Canad.:*** Kytril; ***Chile:*** Kytril; ***Cz.:*** Emegar; Kytril; ***Denm.:*** Kytril; ***Fin.:*** Kytril; ***Fr.:*** Kytril; ***Ger.:*** Kevatril; ***Gr.:*** Granitron; Kytril; ***Hong Kong:*** Kytril; ***Hung.:*** Granigen; Kytril; ***India:*** Granicip; ***Indon.:*** Kytril; ***Irl.:*** Kytril; ***Israel:*** Kytril; Setron; ***Ital.:*** Kytril; ***Jpn:*** Kytril; ***Malaysia:*** Kytril; ***Mex.:*** Kytril; ***Neth.:*** Kytril; ***Norw.:*** Kytril†; ***NZ:*** Kytril; ***Philipp.:*** Kytril; ***Port.:*** Kytril; ***Rus.:*** Kytril (Китрил); ***S.Afr.:*** Kytril; ***Singapore:*** Kytril; ***Spain:*** Kytril; ***Swed.:*** Kytril; ***Switz.:*** Kytril; ***Thai.:*** Kytril; ***Turk.:*** Kytril; Setron; ***UK:*** Kytril; ***USA:*** Kytril; ***Venez.:*** Granicip; Kytril; Rubrum.

Hydrotalcite *(BAN, rINN)*

Hidrotalcita; Hidrotalsit; Hydrotalcit; Hydrotalcitum; Hydrotalsiitti. Aluminium magnesium carbonate hydroxide hydrate.

Гидроталцит

$Mg_6Al_2(OH)_{16}CO_3,4H_2O = 604.0.$

CAS — 12304-65-3.

ATC — A02AD04.

ATC Vet — QA02AD04.

NOTE. Compounded preparations of hydrotalcite may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Br.*

BP 2008 (Hydrotalcite). A hydrated form of an aluminium magnesium basic carbonate corresponding to the formula $Al_2Mg_6(OH)_{16}CO_3,4H_2O$. It contains not less than 15.3% and not more than 18.7% of Al_2O_3 and not less than 36.0% and not more than 44.0% of MgO. The ratio of Al_2O_3 to MgO is not less than 0.40 and not more than 0.45. A white or almost white, free-flowing, granular powder. Practically insoluble in water; it dissolves in dilute mineral acids with slight effervescence. A 4% suspension in water has a pH of 8.0 to 10.0.

Profile

Hydrotalcite is an antacid (see p.1692) that is given in oral doses of up to about 1 g.

Preparations

BP 2008: Hydrotalcite Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Talcid; Talidat; ***Cz.:*** Rutacid; Talcid; Talidat; ***Ger.:*** Ancid; Megalac; Talcid; Talidat; ***Gr.:*** Talcid; ***Hung.:*** Talcid; Tisacid; ***Israel:*** Talcid†; ***Malaysia:*** Swecon; ***Mex.:*** Talcid; ***Neth.:*** Talcid; Talidat; Ultacit; ***Pol.:*** Malgacid; Rutacid; Talcid; Ulcetal; ***Port.:*** Talidat†; ***Rus.:*** Rutacid (Рутацид); Talcid (Тальцид); ***S.Afr.:*** Altacite; ***Spain:*** Talcid; ***Turk.:*** Talcid; ***Venez.:*** Baytalcid†.

Multi-ingredient: ***Indon.:*** Promag; ***Jpn:*** Eki Cabe; ***Philipp.:*** Simeco; ***UK:*** Altacite Plus.

Hyoscine *(BAN)*

Escopolamina; Hioscina; Hioscyna; Hyoscin; Hyoscinum; Hyoskiini; Scopolamine; Scopolaminum; Skopolamiini; Skopolamin; Skopolamina; Tropato de epoxitropina. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*s*)-6,7-Epoxy-3[(*S*)-tropoyloxy] tropane.

Гиосцин

$C_{17}H_{21}NO_4 = 303.4.$

CAS — 51-34-3.

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

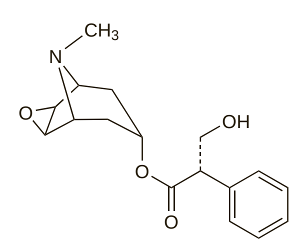

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hyoscine:
Burundanga.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hyoscine). A white or almost white, crystalline powder or colourless crystals. M.p. 66° to 70°. Soluble in water; freely soluble in alcohol.

Hyoscine Butylbromide *(BANM)*

Butilbromuro de hioscina; Butylscopolamine Bromide; Butylscopolaminii Bromidum; *N*-Butylscopolammonium Bromide; Butylscopolamonii Bromidum; Butylskopolaminium-bromid; Escopolamina, butilbromuro de; Hioscino butilbromidas; Hioszcin-butilbromid; Hiyosin Bütilbromür; Hyoscinbutylbromid; Hyoscine-*N*-butyl Bromide; Hyoscini butylbromidum; Hyoskiinibutyylibromidi; Scopolamine *N*-Butyl Bromide; Scopolamine Butylbromide; Scopolamine, butylbromure de; Scopolamini butylbromidum; Scopolomini Butylbromidum; Skopolamino butilbromidas; Szkopolamin-butilbromid. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*r*)-6,7-Epoxy-8-butyl-3-[(*S*)-tropoyloxy]tropanium bromide.

Гиосцина Бутилбромид

$C_{21}H_{30}BrNO_4$ = 440.4.

CAS — 149-64-4.

ATC — A03BB01.

ATC Vet — QA03BB01.

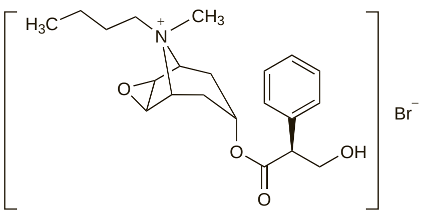

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Hyoscine Butylbromide). A white or almost white, crystalline powder. Freely soluble in water and in dichloromethane; sparingly soluble in dehydrated alcohol. A 5% solution in water has a pH of 5.5 to 6.5.

Hyoscine Hydrobromide *(BANM)*

Bromhidrato de Escopolamina; Escopolamina, hidrobromuro de; Hidrobromuro de hioscina; Hioscino hidrobromidas; Hioscyny bromowodorek; Hioszcin-hidrobromid; Hiyosin Hidrobromür; Hyoscinhydrobromid; Hyoscini hydrobromidum; Hyoskiinihydrobromidi; Ioscina Bromidrato; Scopolamine Bromhydrate; Scopolamine, bromhydrate de; Scopolamine Hydrobromide; Scopolamini hydrobromidum; Scopolamini Hydrobromidum Trihydricum; Skopolamiinihydrobromidi; Skopolamin-bromid trihydrát; Skopolaminhydrobromid; Skopolamino hidrobromidas; Szkopolamin-butilbromid. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxytropan-3-yl (*S*)-tropate hydrobromide trihydrate.

Гиосцина Гидробромид

$C_{17}H_{21}NO_4,HBr,3H_2O$ = 438.3.

CAS — 114-49-8 (anhydrous hyoscine hydrobromide); 6533-68-2 (hyoscine hydrobromide trihydrate).

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.

NOTE. HYO is a code approved by the BP 2008 for use on single unit doses of eye drops containing hyoscine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Hyoscine Hydrobromide). A white or almost white, efflorescent, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Store in well-filled airtight containers of small capacity. Protect from light.

USP 31 (Scopolamine Hydrobromide). Colourless or white crystals, or white granular powder. Is odourless and slightly efflorescent in dry air. Soluble 1 in 1.5 of water and 1 in 20 of alcohol; slightly soluble in chloroform; insoluble in ether. pH of a 5% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Hyoscine Methobromide *(BAN)*

Epoxymethamine Bromide; Escopolamina, metilbromuro de; Hyoscine Methylbromide; Methscopolamine Bromide; Metilbromuro de hioscina; Metobromuro de escopolamina; Metobromuro de hioscina; Scopolamine Methobromide; Scopolamine Methylbromide. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium bromide.

Гиосцина Метобромид

$C_{18}H_{24}BrNO_4$ = 398.3.

CAS — 155-41-9.

ATC — A03BB03; S01FA03.

ATC Vet — QA03BB03; QS01FA03.

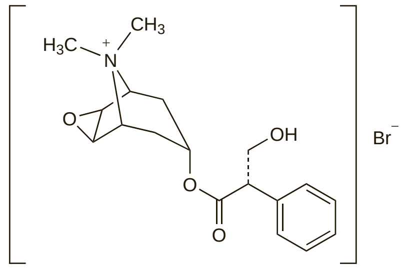

Pharmacopoeias. In *US.*

USP 31 (Methscopolamine Bromide). Store in airtight containers. Protect from light.

Hyoscine Methonitrate *(BANM)*

Escopolamina, metilnitrato de; Hyoscine Methylnitrate; Methscopolamine Nitrate; Methylhyoscini Nitras; Methylscopolamine Nitrate; Methylscopolamini Nitras; Metilnitrato de hioscina; Metonitrato de escopolamina; Metonitrato de hioscina; Metylskopolaminnitrat; Metyyliskopolamiininitraatti; Scopolamine Methonitrate; Scopolamine Methylnitrate. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*)-6,7-Epoxy-8-methyl-3-[(*S*)-tropoyloxy]tropanium nitrate.

Гиосцина Метонитрат

$C_{18}H_{24}N_2O_7$ = 380.4.

CAS — 6106-46-3.

ATC — A03BB03; S01FA03.

ATC Vet — QA03BB03; QS01FA03.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. In contrast to atropine, hyoscine produces central depression at therapeutic doses and symptoms include drowsiness and fatigue. Toxic doses of hyoscine produce stimulation of the CNS in a similar manner to atropine. However, hyoscine does not stimulate the medullary centres and therefore does not produce the increases in respiration rate or blood pressure seen with atropine. Hyoscine may produce CNS stimulation rather than depression at therapeutic doses if used in the presence of pain without opioid analgesics; symptoms include excitement, restlessness, hallucinations, or delirium.

Patients who experience drowsiness should not drive or operate machinery. Caution has been advised in elderly patients and in patients with impaired liver, or kidney function, as adverse CNS effects have been stated to be more likely in these patients. There have been rare reports of an increase in frequency of seizures in epileptic patients.

The quaternary derivatives, such as the butylbromide, methobromide, or methonitrate, do not readily cross the blood-brain barrier, so central effects are rare.

Abuse. Hyoscine has been used by criminals to incapacitate and produce anterograde amnesia in their victims in crimes such as drug-facilitated rape ('date rape'), robbery, and kidnapping. In some countries in South America there has been a particular problem with the use of powders or extracts of plants containing hyoscine for such crimes. A powder, known locally as burundanga, prepared from the borrachero or borracchio tree (also referred to as cacao sabanero) has been blown into the victim's face or given in drinks, chocolate, or chewing gum.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of hyoscine by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/01/06)

Effects on the eyes. *ANISOCORIA.* Although bilateral mydriasis has occurred with the use of transdermal hyoscine, development of a unilateral fixed dilated pupil (anisocoria) may be due to contamination of a finger with hyoscine in handling the device, and then rubbing the eye.[1-6] Similarly, anisocoria has been attributed[7] to ocular contamination after handling broken hyoscine methobromide tablets.

1. Chiaramonte JS. Cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; **306:** 174.
2. Lepore FE. More on cycloplegia from transdermal scopolamine. *N Engl J Med* 1982; **307:** 824.
3. McCrary JA, Webb NR. Anisocoria from scopolamine patches. *JAMA* 1982; **248:** 353–4.
4. Bienia RA, *et al.* Scopolamine skin-disks and anisocoria. *Ann Intern Med* 1983; **99:** 572–3.
5. Riddick FA, Jordan JD. Cruise ship anisocoria. *Ann Intern Med* 1992; **117:** 95.
6. Lin Y-C. Anisocoria from transdermal scopolamine. *Paediatr Anaesth* 2001; **11:** 626–7.
7. Nussdorf JD, Berman EL. Anisocoria associated with the medical treatment of irritable bowel syndrome. *J Neuroophthalmol* 2000; **20:** 100–101.

GLAUCOMA. A few cases of angle-closure glaucoma, both unilateral[1] and bilateral,[2] have been associated with transdermal hyoscine devices.

1. Hamill MB. *et al.* Transdermal scopolamine delivery system (TRANSDERM-V) and acute angle-closure glaucoma. *Ann Ophthalmol* 1983; **15:** 1011–12.
2. Fraunfelder FT. Transdermal scopolamine precipitating narrow-angle glaucoma. *N Engl J Med* 1982; **307:** 1079.

STRABISMUS. Strabismus developed in a 4-year-old boy during treatment with transdermal hyoscine patches for drooling.[1] The strabismus resolved shortly after stopping hyoscine.

1. Good WV, Crain LS. Esotropia in a child treated with a scopolamine patch for drooling. *Pediatrics* 1996; **97:** 126–7.

Effects on mental function. There have been reports of psychotic reactions associated with the transdermal use of hyoscine.[1-6] Psychotic reactions have also occurred after instillation of hyoscine eye drops.[7]

1. Osterholm RK, Camoriano JK. Transdermal scopolamine psychosis. *JAMA* 1982; **247:** 3081.
2. Rodysill KJ, Warren JB. Transdermal scopolamine and toxic psychosis. *Ann Intern Med* 1983; **98:** 561.
3. MacEwan GW, *et al.* Psychosis due to transdermally administered scopolamine. *Can Med Assoc J* 1985; **133:** 431–2.
4. Ziskind AA. Transdermal scopolamine-induced psychosis. *Postgrad Med* 1988; **84:** 73–6.
5. Rubner O, *et al.* Ungewöhnlicher Fall einer Psychose infolge einer Langzeiteinwirkung mit einem Skopolaminmembranpflaster: Paranoid-halluzinatorische und delirante Symptomatik. *Nervenarzt* 1997; **68:** 77–9.
6. Minagar A, *et al.* Transderm-induced psychosis in Parkinson's disease. *Neurology* 1999; **53:** 433–4.
7. Barker DB, Solomon DA. The potential for mental status changes associated with systemic absorption of anticholinergic ophthalmic medications: concerns for the elderly. *DICP Ann Pharmacother* 1990; **24:** 847–50.

Effects on the oesophagus. A patient developed pain on swallowing after 4 days of treatment with hyoscine. Endoscopy showed oesophageal ulceration, which healed completely after 8 weeks of esomeprazole treatment.[1]

1. Philcox S, Keegan A. A case of hyoscine-related oesophagitis. *Med J Aust* 2007; **186:** 650–1.

Effects on the skin. Contact dermatitis occurred in 16 men being treated for seasickness with transdermal hyoscine for 6 weeks to 15 months.[1]

1. Gordon CR, *et al.* Allergic contact dermatitis caused by transdermal hyoscine. *BMJ* 1989; **298:** 1220–1.

Porphyria. Hyoscine butylbromide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. A report[1] of hyoscine toxicity in a neonate born to a mother who had received a total of 1.8 mg of hyoscine in divided doses with pethidine and levorphanol before delivery. The neonate was lethargic, barrel chested, and had a heart rate of 200 beats/minute. Symptoms subsided when physostigmine 100 micrograms was given intramuscularly.

1. Evens RP, Leopold JC. Scopolamine toxicity in a newborn. *Pediatrics* 1980; **66:** 329–30.

Withdrawal. A withdrawal syndrome of dizziness and nausea[1,2] can occur in patients who have used transdermal hyoscine patches for several days; hypersalivation and diarrhoea has also been described.[3] In reported cases, transdermal hyoscine had been used continuously for 7 or 10 days to prevent motion sickness. Symptoms usually begin 2 or 3 days after the last patch has been removed, and may last for a few days.

1. Meyboom RHB. More on Transderm Scop patches. *N Engl J Med* 1984; **311:** 1377.
2. Saxena K, Saxena S. Scopolamine withdrawal syndrome. *Postgrad Med* 1990; **87:** 63–6.
3. Feder RE. Transdermal scopolamine withdrawal syndrome. *Clin Neuropharmacol* 1999; **22:** 120.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

The sedative effect of hyoscine may be enhanced by alcohol or other CNS depressants.

Pharmacokinetics

Hyoscine is readily absorbed from the gastrointestinal tract after oral doses of the hydrobromide. It is almost entirely metabolised, probably in the liver; only a small proportion of an oral dose is excreted unchanged in the urine. It crosses the blood-brain barrier and has been stated to cross the placenta. Hyoscine is also well absorbed after application to the skin.

The quaternary derivatives, such as the butylbromide or methobromide, are poorly absorbed from the gastrointestinal tract and do not readily pass the blood-brain barrier.

◊ References.

1. Ebert U, *et al.* Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *J Clin Pharmacol* 1998; **38:** 720–6.
2. Nachum Z, *et al.* Scopolamine bioavailability in combined oral and transdermal delivery. *J Pharmacol Exp Ther* 2001; **296:** 121–3.

Uses and Administration

Hyoscine is a tertiary amine antimuscarinic with central and peripheral actions (see Action of Antimuscarinics, p.1221). It is a more powerful suppressant of salivation than atropine, and usually slows rather than increases heart rate, especially in low doses. Its central action differs from that of atropine in that it depresses the cerebral cortex and produces drowsiness and amnesia. Hyoscine hydrobromide is also a tertiary amine, whereas hyoscine butylbromide, hyoscine methobromide, and hyoscine methonitrate are quaternary ammonium derivatives.

Hyoscine and hyoscine hydrobromide are used in the management of motion sickness and other forms of nausea and vomiting; hyoscine hydrobromide is also given as a premedicant in anaesthesia, and to produce mydriasis and cycloplegia. Hyoscine butylbromide and other quaternary ammonium derivatives are used in conditions associated with visceral spasms. Hyoscine methobromide has also been employed as an adjunct in the treatment of peptic ulcer disease.

Other hyoscine salts or derivatives that have been used include hyoscine borate, hyoscine hydrochloride, and hyoscine oxide hydrobromide.

See under headings below for details of dosage and administration of hyoscine and its salts in specific indications.

Anaesthesia. The role of antimuscarinics, including hyoscine, in anaesthesia is discussed under Atropine on p.1221. For the use of hyoscine in the prevention of postoperative nausea and vomiting, see below.

For premedication hyoscine hydrobromide is injected subcutaneously or intramuscularly in doses of 200 to 600 micrograms, usually with papaveretum about half to one hour before induction of general anaesthesia. In the UK, a dose of 15 micrograms/kg is licensed in children (the *BNFC* suggests that this dose is appropriate from 1 to 12 years of age; older children may be given the adult dose). If necessary for acute use, the same doses may be given by intravenous injection.

Anoxic seizures. For mention of the use of transdermal hyoscine as an alternative to atropine in the management of reflex anoxic seizures in children, see p.1221.

Biliary and renal colic. Hyoscine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p.5) although the evidence for such use is weak. Hyoscine butylbromide 20 mg is given by intramuscular or slow intravenous injection; this may be repeated after 30 minutes if necessary to a maximum daily dose of 100 mg. See also Palliative Care, below.

References.

1. Holdgate A, Oh CM. Is there a role for antimuscarinics in renal colic? A randomized controlled trial. *J Urol (Baltimore)* 2005; **174:** 572–5.

Cardiac disorders. Although hyoscine is not one of the conventional therapies for heart failure (p.1165) or myocardial infarction (p.1175), low-dose transdermal hyoscine can increase cardiac vagal activity and thereby reduce the autonomic imbalance seen in patients with these conditions.[1-3] Improved exercise tolerance has been reported after 1 week of treatment with transdermal hyoscine in a small open study in 14 patients with mild to moderate heart failure.[4]

1. Casadei B, *et al.* Low doses of scopolamine increase cardiac vagal tone in the acute phase of myocardial infarction. *Circulation* 1993; **88:** 353–7.
2. La Rovere MT, *et al.* Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation* 1994; **90:** 838–43.
3. Venkatesh G, *et al.* Double blind placebo controlled trial of short term transdermal scopolamine on heart rate variability in patients with chronic heart failure. *Heart* 1996; **76:** 137–43.
4. De Vecchis R, *et al.* Different impact of carvedilol and transdermal scopolamine on cardiovascular performance of mild-moderate chronic heart failure patients: evidence of useful effects of scopolamine on tolerance to work load. *Minerva Cardioangiol* 2000; **48:** 393–401.

Depression. Rapid reductions in severity of depression were seen after intravenous hyoscine hydrobromide 4 micrograms/kg was given to patients with major depressive disorders or bipolar disorders (see Depression, p.373). Repeat doses showed more benefit than single doses. Clinical effects persisted beyond the treatment period, which led the authors to conclude the effects were not due to anticholinergic euphoria. While noting that the optimal schedule and potential long-term use of hyoscine as an antidepressant needed further study, they also concluded that hyoscine could be a relatively safe and well-tolerated intervention for achieving a rapid initial antidepressant response.[1]

1. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 2006; **63:** 1121–9.

Dysmenorrhoea. Hyoscine as the butylbromide or hydrobromide has been used for its antispasmodic action in the treatment of dysmenorrhoea. (p.6), but the *BNF* considers that antispasmodics do not generally provide significant relief.

Eye disorders. Hyoscine hydrobromide is used in the eye for its mydriatic and cycloplegic actions (p.1874) usually in a concentration of 0.25%. It has a faster onset and shorter duration of action than atropine although the effects may still persist for up to 3 to 7 days. It may be useful for patients who are hypersensitive to atropine.

Gastrointestinal disorders. Hyoscine has been used as an antispasmodic (p.1692) to relieve the pain of smooth muscle spasm associated with the gastrointestinal tract.[1]

In such conditions the licensed UK dose is 20 mg of hyoscine butylbromide intramuscularly or by slow intravenous injection, repeated after 30 minutes if necessary, up to a maximum of 100 mg daily; alternatively, 20 mg may be given orally four times daily. In irritable bowel syndrome (p.1699) the recommended oral starting dose is 10 mg three times daily which may be increased to 20 mg four times daily, if necessary. Children aged 6 to 12 years may be given 10 mg three times daily by mouth for gastrointestinal spasms. As an adjunct in the treatment of peptic ulcer disease; hyoscine methobromide has been licensed in the USA in a dose of 2.5 mg half an hour before meals and 2.5 to 5 mg at bedtime. Hyoscine may also be useful as an antispasmodic in diagnostic procedures of the gastrointestinal tract.

The antiemetic effect of hyoscine is discussed under Nausea and Vomiting, below.

1. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs* 2007; **67:** 1343–57.

Hyperhidrosis. Adverse effects of antimuscarinics given orally generally preclude their use by this route for the management of hyperhidrosis (p.1580), but some, such as hyoscine, have been applied topically as alternatives to aluminium salts. Hyoscine hydrobromide applied as a 3% cream was successful in reducing gustatory sweating, consisting of flushing and sweating over the right mandible during eating, in a patient who had previously undergone surgical excision of the right submandibular salivary gland.[1] The use of transdermal or injectable hyoscine was reported[2] to be effective for the control of opioid-associated sweating in 2 patients receiving palliative care (see also below for other uses of hyoscine in palliative care).

1. Bailey BMW, Pearce DE. Gustatory sweating following submandibular salivary gland removal. *Br Dent J* 1985; **158:** 17–18.
2. Mercadante S. Hyoscine in opioid-induced sweating. *J Pain Symptom Manage* 1998; **15:** 214–15.

Nausea and vomiting. Hyoscine is an effective agent in the prevention of **motion sickness** and is one of the principal drugs used. It may be given orally for short-term protection or by transdermal patch for a prolonged duration of action.

In the UK, a usual oral dose of hyoscine hydrobromide is 300 micrograms taken 30 minutes before a journey, followed by 300 micrograms every 6 hours if required up to a maximum of 3 doses in 24 hours. Children aged 4 to 10 years may be given 75 to 150 micrograms and those over 10 years, 150 to 300 micrograms. Children aged 3 to 4 years may be given 75 micrograms 20 minutes before a journey, repeated if necessary to a maximum total dose of 150 micrograms in 24 hours. Hyoscine is also given via a transdermal patch which is placed behind the ear and supplies 1 mg over 3 days. The patch is licensed in the UK for adults and children aged 10 years and over and should be applied 5 to 6 hours before travelling or on the preceding evening and removed at the end of the journey.

An intranasal formulation of hyoscine hydrobromide has been investigated for the treatment and prevention of motion sickness.

Transdermal hyoscine has been used in adults and children for the prevention of **postoperative nausea and vomiting**.

Hyoscine hydrobromide has also been given by intravenous, subcutaneous, or intramuscular injection for its antiemetic effect in a usual dose of 300 to 600 micrograms.

The other drugs used in the management of motion sickness and postoperative nausea and vomiting are discussed on p.1700.

References.

1. Kranke P, *et al.* The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2002; **95:** 133–43.
2. Nachum Z, *et al.* Transdermal scopolamine for prevention of motion sickness: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet* 2006; **45:** 543–66.
3. Spinks AB, *et al.* Scopolamine (hyoscine) for preventing and treating motion sickness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 03/04/08).

Palliative care. The *BNF* includes doses for hyoscine in palliative care. *Hyoscine hydrobromide* is used in palliative care to reduce excessive respiratory secretions. A dose of 400 to 600 micrograms may be given by subcutaneous injection every 4 to 8 hours. Alternatively 0.6 to 2.4 mg may be given over 24 hours by continuous subcutaneous infusion. In younger patients the *BNFC* suggests a dose of 10 micrograms/kg (up to a maximum of 600 micrograms) by subcutaneous or intravenous injection every 4 to 8 hours. Alternatively, 1.5 to 2.5 micrograms/kg per hour may be given by continuous subcutaneous or intravenous infusion. Care should be taken to avoid the discomfort of a dry mouth. Hyoscine may also be given as a transdermal patch in some countries.

Hyoscine hydrobromide may be given sublingually for the pain of bowel colic in a dose of 300 micrograms 3 times daily.

Hyoscine butylbromide is also used in palliative care in the treatment of bowel colic; however, it may not be adequate for the control of respiratory secretion. It is given as a subcutaneous infusion in a dose of 20 to 60 mg every 24 hours. A single subcutaneous dose of 20 mg reviewed after 30 minutes, has been suggested if it is tried for excessive respiratory secretion.[1]

The use of hyoscine in palliative care has been reviewed.[2,3] Hyoscine hydrobromide may be more effective than glycopyrronium bromide in drying secretions, and has a rapid onset of action, but it can produce both sedation and agitation; there is no clear evidence favouring one antimuscarinic over another.[1]

1. Bennett M, *et al.* Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. *Palliat Med* 2002; **16:** 369–74.
2. Muir JC, von Gunten CF. Antisecretory agents in gastrointestinal obstruction. *Clin Geriatr Med* 2000; **16:** 327–34.
3. Spiller JA, Fallon M. The use of Scopoderm in palliative care. *Hosp Med* 2000; **61:** 782–4.

Urinary incontinence. Antimuscarinics have been used in the management of urge incontinence (p.2180) but the incidence of adverse effects can be high. Results of a small study[1] suggested that transdermal hyoscine might be of benefit in females with detrusor instability.

1. Muskat Y, *et al.* The use of scopolamine in the treatment of detrusor instability. *J Urol (Baltimore)* 1996; **156:** 1989–90.

Vertigo. Hyoscine has a long history of use in the management of vertigo, although other drugs are now preferred (p.565).

Preparations

BP 2008: Hyoscine Butylbromide Injection; Hyoscine Butylbromide Tablets; Hyoscine Eye Drops; Hyoscine Injection; Hyoscine Tablets;
USP 31: Methscopolamine Bromide Tablets; Scopolamine Hydrobromide Injection; Scopolamine Hydrobromide Ophthalmic Ointment; Scopolamine Hydrobromide Ophthalmic Solution; Scopolamine Hydrobromide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Buscapina; Cifespasmo; Colobolina; Luar-G; Pasmodina; Rupe-N†; ***Austral.:*** Buscopan; Kwells; Setacol; Travacalm HO; ***Austria:*** Buscopan; Scopoderm; ***Belg.:*** Aspasmine†; Buscopan; ***Braz.:*** Buscopan; Hiospan; Uni Hioscin; ***Canad.:*** Buscopan; Transderm-V; ***Chile:*** Buscapina; ***Cz.:*** Buscolysin†; Buscopan; ***Denm.:*** Buscopan; Scopoderm; ***Fin.:*** Buscopan; Scopoderm; ***Fr.:*** Scoburen; Scopoderm TTS; ***Ger.:*** Boro-Scopol; BS Carino; BS-ratiopharm; Buscolysin†; Buscopan; Scopoderm TTS; Spasman scop; Spasmowern; ***Gr.:*** Buscopan; ***Hong Kong:*** Buscopalamin; Buscopan; Busopin; Copan; Dhacopan; Hysopan; Scopoderm TTS†; Vidaspan; ***Hung.:*** Buscopan; ***India:*** Buscopan; Hyospan; ***Indon.:*** Buscopan; Gitas; Hyscopan; Scobutrin; Scopamin; Spashi; Spasmolit; ***Irl.:*** Buscopan; Kwells; ***Ital.:*** Buscopan; Transcop; ***Jpn:*** Buscopan; ***Malaysia:*** Buscopan; Colospan†; Dhacopan; Fucon; Hyomide; Spasmoliv†; Vacopan; Vascopan†; ***Mex.:*** Alpin; Biomesina; Bipasmin; Bipasmin N; Brolamina; Buscapina; Busina; Busprina-S†; Butiral; Cryopina; Espacil; Excosine-S; Grafin; Hiosinotil†; Hiosultrina; Lemophar; Liliam†; Selpiran-S; Serralpina; ***Neth.:*** Buscopan; Scopoderm TTS; ***Norw.:*** Buscopan; Scopoderm; ***NZ:*** Buscopan; Gastro-Soothe; Scopoderm TTS; ***Philipp.:*** Ascopen; Buscomed; Buscopan; Busopin; Gastride; Rotomide; Scolmin; Spasmosan; ***Pol.:*** Buscolysin; Buscopan; Scopolan; ***Port.:*** Buscopan; ***Rus.:*** Buscopan (Бускопан); ***S.Afr.:*** Buscopan; Hyospasmol; Scopaject; Scopex; ***Singapore:*** Buscopan; Colospan†; Dhacopan; Fucon; Hyomide; Spasmoliv; Vacopan; ***Spain:*** Buscapina; Vorigeno†; ***Swed.:*** Buscopan; Scopoderm; ***Switz.:*** Buscopan; ***Thai.:*** Amcopan; Antispa; Bacotan; Buscono; Buscopan; Butyl; Cencopan; Eralga; Higan; Hy-Spa; Hybutyl; Hyosmed; Hyospan; Hyostan; Hyozin†; Hytic†; Kanin; Myspa; Scopas; Spalox; Spascopan; Spasgone-H; Spatab†; U-Oscine; Uricine; Vacopan; Vescopolamine; ***Turk.:*** Buscopan; Butopan; Molit; Spazmol; ***UAE:*** Scopinal; ***UK:*** Buscopan; Joy-Rides; Kwells; Scopoderm TTS; ***USA:*** Pamine; Scopace; Transderm Scop; ***Venez.:*** Buscapina; Hiocin.

Multi-ingredient: ***Arg.:*** 6 Copin; Buscapina Compositum; Buscapina Compositum N; Buscapina Fem; Cavodan†; Cifespasmo Compuesto; Colobolina D; Dislembral†; Espasmo Biotenk; Gastrolina Compuesta; Ibu-Buscapina†; Lisalgil Compuesto; Luar-G Compositum; Novopasmil Compuesto; Pasmodina Compuesta; Rupe-N Compuesto; ***Austral.:*** Donnagel; Donnalix; Donnatab; Travacalm; ***Austria:*** Buscopamol; Buscopan Compositum; Modiscop; ***Belg.:*** Buscopan Compositum; Spasma†; ***Braz.:*** Algexin; Analverin Composto†; Analverin Plus†; Binospan; Bioscina Composta†; Buscopan Composto; Buscopan Plus; Buscoveran Composto; Butilamin; Disbuspan; Dorspan; Ductopan†; Espasmodid Composto; Hioariston; Hiospan Composto; Inib-Dor†; Kindpasm; Neocopan; Sedabel†; Tropinal; Uzara†; Vagoplex†; Veratropan Composto; ***Chile:*** Algion; Buscapina Compositum; Dolcopin; Kordinol Compuesto†; Novalona; ***Ger.:*** Buscopan Plus; ***Gr.:*** Buscopan Plus; Spasmo-Apotel; ***Hong Kong:*** Epilon; Unigan; Virulex Forte; ***Indon.:*** Aludonna; Buscopan Plus; Gitas Plus; Procolic; Scopamin Plus; Spashi Plus; Spaslic; Unthecol; ***Irl.:*** Feminax; ***Ital.:*** Buscopan Compositum; Spasmeridan; ***Mex.:*** Algosfar; Anadil; Benfol; Biomesina Compuesta; Bipasmin Compuesto; Bipasmin Compuesto N; Bipasmin Compuesto NF†; Buscapina Compositum; Buscapina Compositum N; Busconet; Busepan; Busprina; Colepren; Donodol Compuesto; Escapin-N; Espacil Compuesto;

Espasmogress; Hiosinotil Compuesto†; Hiosultrina-F; Infafren Compuesto; Neo-Pasmonal; Ortran†; Pasmodil; Pirobutil; Precicol; Prestodol Compuesto; Retodol Compositum; Selpiran; Selpiran Compuesto; Serralpina Compuesta; Viladol Plus; ***Philipp.:*** Buscopan Plus; ***Pol.:*** Scopolan Compositum; Vegantalgin H; ***Port.:*** Buscopan Compositum N; ***S.Afr.:*** Buscopan Compositum; Donnatal; Millerspas; Respinol; Respinol Compound; Scopex Co; Virobis†; ***Spain:*** Buscapina Compositum; Midriati; Nolotil Compositum†; Oragalin Espasmolitico; Psico Blocan; ***Swed.:*** Spasmofen; ***Switz.:*** Nardyl; ***Thai.:*** Amcopan Plus; Buscopan Plus; Donnatal†; Pacopan; Spasgone; Unigan; ***Turk.:*** Buscopan Compositum; Molit Plus; Skopolin; Spazmol Plus; Tanko-Buskas; Tranko-Buskas; ***UK:*** Feminax; ***USA:*** Accuhist LA†; AeroHist Plus; AeroKid; AH-chew; Alkabel; AllePak; AlleRx; Antispasmodic Elixir; Barbidonna†; Bellahist-D; Bellatal; Chlor-Mes; Chlor-Mes D; CPM PSE MSC; CPM/PE/MSC; DA Chewable; DA II; Dallergy; Dehistine; Dexphen M; Donnatal; DriHist; Dura-Vent/DA; Durahist; Durahist D; Ex-Histine; Extendryl; Extendryl DM; Extendryl PEM; Hista-Vent DA; Histatab D; Histor-D Timecelles; Hyosophen; Mescolor†; Murocoll-2; Nacon; NoHist Plus; Norel DM; Omnihist LA; Pamine FQ Kit; Pannaz; PCM; Prehist D; PSE MSC; Ralix; Redur-PCM; Relcof PSE; Rescon-MX; Ryneze; Stahist; Susano; Xiral†; ***Venez.:*** Brugesina; Buscapina Compositum; Buscapina Plus; Butilamina Compuesta; Diezol Compuesto†; Fenopol†; Hioscinol Compuesto†; Sarifan Compuesto†; Vuscobras.

Hyoscyamine *(BAN)*

Hiosciamina; Hyoscyamin; (−)-Hyoscyamine; *l*-Hyoscyamine; Hyoscyaminum; Hyoskyamiini. (−)-(1*R*,3*r*,5*S*)-Tropan-3-yl (*S*)-tropate.

Гиосциамин

$C_{17}H_{23}NO_3$ = 289.4.

CAS — 101-31-5.

ATC — A03BA03.

ATC Vet — QA03BA03.

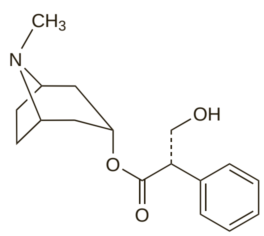

Description. Hyoscyamine is an alkaloid obtained from various solanaceous plants. It is the laevo-isomer of atropine into which it can be converted by heating or by the action of alkali.

Pharmacopoeias. In *US.*

USP 31 (Hyoscyamine). A white crystalline powder. M.p. 106° to 109°. Slightly soluble in water and in benzene; freely soluble in alcohol, in chloroform, and in dilute acids; sparingly soluble in ether. Its solutions are alkaline to litmus. Store in airtight containers. Protect from light.

Hyoscyamine Hydrobromide *(BANM)*

Bromidrato de Hiosciamina; Hiosciamina, hidrobromuro de; Hyoscyamine Bromhydrate.

Гиосциамина Гидробромид

$C_{17}H_{23}NO_3,HBr$ = 370.3.

CAS — 306-03-6.

ATC — A03BA03.

ATC Vet — QA03BA03.

Pharmacopoeias. In *US.*

USP 31 (Hyoscyamine Hydrobromide). White, odourless, crystals or crystalline powder. M.p. not less than 149°. Freely soluble in water; soluble 1 in 2.5 of alcohol, 1 in 1.7 of chloroform, and 1 in 2300 of ether. pH of a 5% solution in water is about 5.4. Store in airtight containers. Protect from light.

Hyoscyamine Sulfate

Hiosciamina, sulfato de; Hiosciamino sulfatas; Hioscyjaminy siarczan; Hioszciamin-szulfát; Hyoscyamin sulfát dihydrát; Hyoscyamine, sulfate d'; Hyoscyamine Sulphate *(BANM)*; Hyoscyamini sulfas; Hyoscyamini Sulfas Dihydricus; Hyoscyaminsulfat; Hyoscyaminum Sulfuricum; Hyoskyamiinisulfaatti; Iosciamina Solfato.

Гиосциамина Сульфат

$(C_{17}H_{23}NO_3)_2,H_2SO_4,2H_2O$ = 712.8.

CAS — 620-61-1 (anhydrous hyoscyamine sulfate); 6835-16-1 (hyoscyamine sulfate dihydrate).

ATC — A03BA03.

ATC Vet — QA03BA03.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Hyoscyamine Sulphate). A white or almost white, crystalline powder or colourless needles. Very soluble in water; sparingly soluble or soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Store in airtight containers. Protect from light.

USP 31 (Hyoscyamine Sulfate). A white or almost white, crystalline powder or colourless needles. It is deliquescent and affected by light. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; practically insoluble in ether. pH of a 1% solution in water is about 5.3.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Hyoscyamine is a tertiary amine antimuscarinic with the actions of atropine (which is racemic hyoscyamine, see p.1219); hyoscyamine, the laevo-isomer, has about twice the potency of atropine since the dextro-isomer has only very weak antimuscarinic activity. Hyoscyamine is used mainly in the relief of conditions associated with visceral spasm. It has also been given for rhinitis and was formerly used in the treatment of parkinsonism.

Hyoscyamine is given in usual doses of 150 to 300 micrograms up to four times daily by mouth, but it is more usually employed as the sulfate; the hydrobromide is also used. Suggested doses of hyoscyamine sulfate are 125 to 250 micrograms orally or sublingually every four hours as needed, up to a maximum of 1.5 mg in 24 hours. Modified-release oral preparations of hyoscyamine sulfate are available in some countries; dosage is specific to a particular formulation. Hyoscyamine sulfate has also been given by injection.

Preparations

USP 31: Hyoscyamine Sulfate Elixir; Hyoscyamine Sulfate Injection; Hyoscyamine Sulfate Oral Solution; Hyoscyamine Sulfate Tablets; Hyoscyamine Tablets.

Proprietary Preparations (details are given in Part 3)

Canad.: Levsin†; ***Denm.:*** Egazil; ***Fin.:*** Egazil†; ***Fr.:*** Duboisine†; ***Hong Kong:*** Levsin; ***Norw.:*** Egazil; ***Swed.:*** Egazil; ***USA:*** A-Spas†; Anaspaz; Cystospaz; Donnamar; ED-SPAZ; Gastrosed; IB-Stat; Levbid; Levsin; Levsinex; Mar-Spas; Neosol; NuLev; Symax.

Multi-ingredient: ***Austral.:*** Donnagel; Donnalix; Donnatab; ***Braz.:*** Anal-verin†; Neogrein; Ormigrein; Tropinal; ***Cz.:*** Solutan†; ***Indon.:*** Aludonna; Feminax; ***Ital.:*** Antispasmina Colica; ***S.Afr.:*** Donnatal; Millerspas; ***Switz.:*** Nardyl; ***Thai.:*** Donnatal†; ***USA:*** Accuhist LA†; Alkabel; Antispasmodic Elixir; Atrosept; Barbidonna†; Bellacane; Bellahist-D; Bellatal; Dolsed†; Donnatal; Hyosophen; MHP-A; MSP-Blu; Phenazopyridine Plus; Prosed/DS; Pyridium Plus; Stahist; Susano; Trac Tabs 2X†; Trellium Plus; UAA; Urelief Plus; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira.

Indisetron Hydrochloride *(rINNM)*

Hidrocloruro de indisetrón; Indisétron, Chlorhydrate d'; Indisetron Dihydrochloride; Indisetroni Hydrochloridum; N-3389. *N*-(3,9-Dimethyl-*endo*-3,9-diazabicyclo[3.3.1]non-7-yl)-1*H*-indazole-3-carboxamide dihydrochloride.

Индисетрона Гидрохлорид

$C_{17}H_{23}N_5O,2HCl$ = 386.3.

CAS — 141549-75-9 (indisetron); 160472-97-9 (indisetron dihydrochloride).

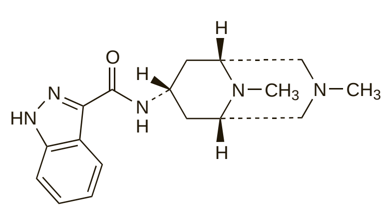

(indisetron)

Profile

Indisetron is a 5-HT_3-receptor antagonist with general properties similar to those of ondansetron (p.1756); it is also stated to be an antagonist at 5-HT_4 receptors. Indisetron hydrochloride is used as an antiemetic in the management of nausea and vomiting associated with chemotherapy.

Ipomoea

Ipomoea Root; Mexican Scammony Root; Orizaba Jalap Root; Scammony Root.

Ипомея

Ipomoea Resin

Ipomoea, resina de; Mexican Scammony Resin; Scammony Resin.

CAS — 9000-34-4.

Profile

Ipomoea is the dried root of *Ipomoea orizabensis* (Convolvulaceae). Ipomoea resin is a mixture of glycosidal resins obtained from ipomoea and it has a drastic purgative and irritant action. It has been superseded by less toxic laxatives.

Irsogladine Maleate *(rINNM)*

Irsogladine, Maléate d'; Irsogladini Maleas; Maleato de irsogladina; MN-1695. 2,4-Diamino-6-(2,5-dichlorophenyl)-*S*-triazine maleate.

Ирсогладина Малеат

$C_9H_7Cl_2N_5.C_4H_4O_4$ = 372.2.

CAS — 57381-26-7 (irsogladine); 84504-69-8 (irsogladine maleate).

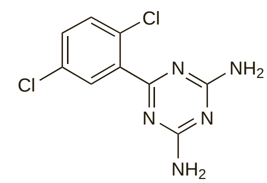

(irsogladine)

Profile

Irsogladine maleate is a cytoprotective drug that is used in the treatment of peptic ulcer disease (p.1702) in a usual oral dose of 4 mg daily. It has also been investigated for mucositis and mouth ulceration.

Mucositis. Irsogladine maleate 2 mg twice daily by mouth has been reported[1] to reduce the incidence of aphthous stomatitis in a small study in patients being treated with methotrexate for rheumatoid arthritis.

1. Yoshida T, Hirakata M. Therapeutic benefits of irsogladine maleate on aphthous stomatitis induced by methotrexate in rheumatoid arthritis. *J Rheumatol* 2003; **30:** 2082–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Gaslon N.

Isopropamide Iodide *(BAN, rINN)*

Ioduro de isopropamida; Isopropamide, Iodure d'; Isopropamidi Iodidum. (3-Carbamoyl-3,3-diphenylpropyl)di-isopropylmethylammonium iodide.

Изопропамида Йодид

$C_{23}H_{33}IN_2O$ = 480.4.

CAS — 7492-32-2 (isopropamide); 71-81-8 (isopropamide iodide).

ATC — A03AB09.

ATC Vet — QA03AB09.

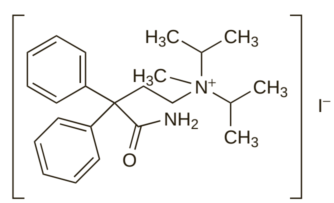

Pharmacopoeias. In *US.*

USP 31 (Isopropamide Iodide). A white to pale yellow crystalline powder. Soluble 1 in 50 of water, 1 in 10 of alcohol, and 1 in 5 of chloroform; very slightly soluble in ether and in benzene. Protect from light.

Profile

Isopropamide iodide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease, in the relief of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm, in rhinitis, and for the relief of symptoms of colds.

Isopropamide bromide has been used similarly.

Preparations

USP 31: Isopropamide Iodide Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Plidex†; ***Braz.:*** Ornatrol†; ***Canad.:*** Stelabid†; ***Ital.:*** Raffreddoremed; Valtrax; ***Mex.:*** Stelabid.

Ispaghula

Egyiptomi útifűmag (ispaghula seed); Egyiptomi útifűmaghéj (ispaghula husk); Ispaghul, graine d' (ispaghula seed); Ispaghul (graine d'), tégument de la (ispaghula husk); Ispagula; Ispagula Kabuğu; Ispagulafrö (ispaghula seed); Ispagulafröskal (ispaghula husk); Ispagulansiemen (ispaghula seed); Ispagulansiemenkuori (ispaghula husk); Kepek; Kiaušininių gysločių sėklos (ispaghula seed); Kiaušininių gysločių sėklų luobelės (ispaghula husk); Łupina nasienna babki jajowatej (ispaghula husk); Nasienie babki jajowatej (ispaghula seed); Osemení jitrocele vejčitého (ispaghula husk); Plantaginis ovatae semen (ispaghula seed); Plantaginis ovatae seminis tegumentum (ispaghula husk); Psilio; Semeno jitrocele vejčitého (ispaghula seed); Zaragatona.

Шелуха Исфагулы (ispaghula husk)

Pharmacopoeias. Monographs for the husk and seed are included in *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ispaghula Husk; Plantaginis Ovatae Seminis Tegumentum). The episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 12.0% of its weight on drying. Protect from light.

Ph. Eur. 6.2 (Ispaghula Seed; Plantaginis Ovatae Semen). The dried ripe seeds of *Plantago ovata* (*P. ispaghula*). The powdered drug loses not more than 10.0% of its weight on drying. Protect from light.

USP 31 (Psyllium Husk). The cleaned, dried seed coat (epidermis), in whole or in powdered form, separated by winnowing and threshing from the seeds of *Plantago ovata* (known in commerce as Blond Psyllium, Indian Psyllium, or Ispaghula), or from *Plantago arenaria* (*Plantago psyllium*), known in commerce as Spanish or French Psyllium.

USP 31 (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*).

Psyllium Hemicellulose *(USAN)*

CAS — 9034-32-6.

Pharmacopoeias. In *US.*

USP 31 (Psyllium Hemicellulose). The alkali soluble fraction of the husk from *Plantago ovata* consisting of highly substituted arabinoxylan polysaccharides. These polysaccharides are linear chains of xylose units to which are attached single units of arabinose and additional xylose. Rhamnose, galactose, glucose, and rhamnosyluronic acid residues are also present as minor constituents. It contains not less than 75.0% of dietary soluble fibre, calculated on the dried basis. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Psyllium Seed

Blešníkové semeno; Bolhafűmag; Flea Seed; Loppfrö; Nasienie płesznika; Psilio, semilla de; Psyllii semen; Psyllium, graine de; Psylliuminsiemen; Smiltyninių gysločių sėklos.

ATC — A06AC01.

ATC Vet — QA06AC01.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *US* under the title of Plantago Seed.

Ph. Eur. 6.2 (Psyllium Seed). The ripe, whole, dry seeds of *Plantago afra* (*P. psyllium*) or *Plantago indica* (*P. arenaria*). It loses not more than 14.0% of its weight on drying. Protect from light and moisture.

USP 31 (Plantago Seed). The cleaned, dried, ripe seed of *Plantago ovata*, or of *Plantago psyllium*, or of *Plantago indica* (*P. arenaria*) (see also Ispaghula, above).

Adverse Effects and Precautions

Large quantities of ispaghula and other bulk laxatives may temporarily increase flatulence and abdominal distension; hypersensitivity reactions have been reported. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are taken with insufficient fluid. Therefore, they should always be taken with at least 150 mL of water or other liquid. Ispaghula and bulk laxatives should not be taken immediately before going to bed because reduced gastric motility may impair intestinal passage and cause obstruction. They should be avoided by patients who have difficulty swallowing.

Bulk laxatives should not be given to patients with pre-existing faecal impaction, intestinal obstruction, or colonic atony.

Hypersensitivity. Hypersensitivity reactions associated with the ingestion or inhalation of ispaghula or psyllium have been reported.[1-9] Symptoms have included rash, rhinitis, urticaria, bronchospasm, and anaphylactic shock; in one case, anaphylaxis was fatal.[9] In most patients, sensitisation was thought to have occurred during occupational exposure.

1. Busse WW, Schoenwetter WF. Asthma from psyllium in laxative manufacture. *Ann Intern Med* 1975; **83:** 361–2.
2. Gross R. Acute bronchospasm associated with inhalation of psyllium hydrophilic mucilloid. *JAMA* 1979; **241:** 1573–4.
3. Suhonen R, *et al.* Anaphylactic shock due to ingestion of psyllium laxative. *Allergy* 1983; **38:** 363–5.
4. Zaloga GP, *et al.* Anaphylaxis following psyllium ingestion. *J Allergy Clin Immunol* 1984; **74:** 79–80.
5. Kaplan MJ. Anaphylactic reaction to "Heartwise". *N Engl J Med* 1990; **323:** 1072–3.
6. Lantner RR, *et al.* Anaphylaxis following ingestion of a psyllium-containing cereal. *JAMA* 1990; **264:** 2534–6.
7. Freeman GL. Psyllium hypersensitivity. *Ann Allergy* 1994; **73:** 490–2.
8. Vaswani SK, *et al.* Psyllium laxative-induced anaphylaxis, asthma, and rhinitis. *Allergy* 1996; **51:** 266–8.
9. Khalili B, *et al.* Psyllium-associated anaphylaxis and death: a case report and review of the literature. *Ann Allergy Asthma Immunol* 2003; **91:** 579–84.

Interactions

Ispaghula and other bulk-forming laxatives may delay or reduce the gastrointestinal absorption of other drugs such as cardiac glycosides, coumarin derivatives, lithium, or vitamins (such as vitamin B_{12}) and minerals (such as calcium, iron, or zinc). Intervals of 30 minutes to 1 hour are recommended between ispaghula and other drugs or food, although some recommend as much as 3 hours between bulk-forming laxatives and other drugs. The dose of insulin may need to be reduced in diabetic patients taking ispaghula.

Lithium. For reference to ispaghula possibly reducing the absorption of lithium, see Gastrointestinal Drugs, p.405.

Uses and Administration

Ispaghula seed, ispaghula husk, and psyllium seed are bulk laxatives (p.1693). They absorb water in the gastrointestinal tract to form a mucilaginous mass which increases the volume of faeces and hence promotes peristalsis. They are used in the treatment of constipation (p.1693), especially in diverticular disease (p.1695) and irritable bowel syndrome (p.1699), and when excessive straining at stool must be avoided, for example after anorectal surgery or in the management of haemorrhoids. The ability to absorb water and increase faecal mass means that they may also be used in the management of diarrhoea (p.1694) and for adjusting faecal consistency in patients with colostomies.

The usual oral dose is about 3.5 g one to three times daily, although higher doses have been given. It should be taken immediately after mixing in at least 150 mL water or fruit juice. The full effect may not be achieved for up to 3 days.

Ispaghula is also given for mild to moderate hypercholesterolaemia as an adjunct to a lipid-lowering diet. The recommended dose is about 7 g daily.

Hyperlipidaemias. Preparations of ispaghula have been reported[1-4] to lower serum-cholesterol concentrations in patients with mild to moderate hypercholesterolaemia. They have also been given with reduced doses of a bile-acid binding resin in the treatment of hyperlipidaemia,[5] which is reported to be effective and better tolerated than full doses of the resin alone. Similarly, psyllium supplementation with 10 mg of simvastatin was found to be as effective in lowering cholesterol as 20 mg of simvastatin alone.[6] However, ispaghula or psyllium should be regarded as adjuncts to dietary modification rather than substitutes for it. For a discussion of the hyperlipidaemias and their management, see p.1169.

1. Anderson JW, *et al.* Cholesterol-lowering effect of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* 1988; **148:** 292–6.
2. Bell LP, *et al.* Cholesterol-lowering effects of psyllium hydrophilic mucilloid: adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. *JAMA* 1989; **261:** 3419–23.
3. Anderson JW, *et al.* Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000; **71:** 472–9.
4. Anderson JW, *et al.* Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am J Clin Nutr* 2000; **71:** 1433–8.
5. Spence JD, *et al.* Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* 1995; **123:** 493–9.
6. Moreyra AE, *et al.* Effect of combining psyllium fiber with simvastatin in lowering cholesterol. *Arch Intern Med* 2005; **165:** 1161–6.

Preparations

BP 2008: Ispaghula Husk Effervescent Granules; Ispaghula Husk Granules; Ispaghula Husk Oral Powder;
USP 31: Psyllium Hydrophilic Mucilloid for Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Agarol Fibras Naturales†; Agiofibras; Herbaccion Laxante†; Konsyl; Lostamucil; Metamucil; Motional; Mucofalk; Plantaben; ***Austral.:*** Agiofibe; Ford Fibre; Fybogel; Metamucil; Mucilax†; Natural Fibre†; ***Austria:*** Agiocur; Laxans; Metamucil; ***Belg.:*** Colofiber; Fybogel†; Spagulax; ***Braz.:*** Agiofibra; Fibracare; Loraga†; Metamucil; Plantaben; ***Canad.:*** Laxucil; Metamucil; Mucillium; Natural Source Laxative†; Novo-Mucilax; Prodiem Plain†; ***Chile:*** Euromucil; Fibrasol; Metamucil†; Plantaben; ***Denm.:*** Vi-Siblin; ***Fin.:*** Agiocur; Laxamucil; Vi-Siblin; ***Fr.:*** Mucivital; Spagulax; Spagulax Mucilage; Transilane; ***Ger.:*** Agiocur; Flosa; Flosine; Laxiplant Soft†; Metamucil; Mucofalk; Pascomucil; ***Hong Kong:*** Agiocur; Fibermate; Fybogel†; Metamucil; Mucofalk; Naturlax; Transilane; ***India:*** Isogel; ***Indon.:*** Mucofalk; Mulax; ***Irl.:*** Fybogel; Regulan; ***Israel:*** Agiocur; Konsyl; Mucivital†; Planten†; ***Ital.:*** Agiofibre; Fibrolax; Planten; Psyllogel; ***Malaysia:*** Fybogel; Mucofalk; ***Mex.:*** Agiofibra; Fibromucil; Finalax; Fybogel; Hormolax; Konsyl†; Metamucil; Mucilag; Mugasin; Novagon; Plantaben; Siludane†; ***Neth.:*** Metamucil; Mucofalk; Regucol; Volcolon; ***Norw.:*** Lunelax; Vi-Siblin; ***NZ:*** Isogel; Metamucil; Mucilax; ***Philipp.:*** Fibermate; Mucofalk; ***Pol.:*** Mucofalk; ***Port.:*** Agiocur; Laxat; Mucofalk; Prontolax; Vetilax; ***S.Afr.:*** Agiobulk; Agiogel†; Fybogel; Metamucil†; ***Singapore:*** Fybogel; Mucilin; Mucofalk; ***Spain:*** Biolid; Cenat; Duphafibra; Laxabene; Laxisoft†; Metamucil; Plantaben; ***Swed.:*** Lunelax; Vi-Siblin; ***Switz.:*** Agiolax mite; Colosoft†; Laxiplant Soft; Metamucil; Mucilar; Valverde regulateur du transit intestinal granules†; ***Thai.:*** Agiocur†; Fybogel; Metamucil; Mucilin; Mucofalk†; ***Turk.:*** Otaci Musillium; ***UK:*** Fibrelief; Fybogel; Isogel; Ispagel; Konsyl†; Regulan; ***USA:*** Fiberall; Hydrocil Instant; Konsyl; Konsyl-D; Metamucil; Mylanta Natural Fiber†; Reguloid; Serutan; Syllact; ***Venez.:*** Agiofibe; Siliumbran.

Multi-ingredient: ***Arg.:*** Agiolax; Cholesterol Reducing Plan†; Gelax; Isalax Fibras; Kronolax†; Medilaxan; Mermelax; Prompt†; Rapilax Fibras; Salutaris; ***Austral.:*** Agiolax; Bioglan Psylli-Mucil Plus; Herbal Cleanse†; Nucolox; PC Regulax†; ***Austria:*** Agiolax; ***Belg.:*** Agiolax; Spagulax K; Spagulax Sorbitol; ***Braz.:*** Agiolax; Parapsyl; Plantax†; ***Canad.:*** Prodiem Plus†; ***Chile:*** Bilaxil; ***Cz.:*** Agiolax; ***Fin.:*** Agiolax; ***Fr.:*** Agiolax; Carres Parapsyllium; Filigel; Imegul†; Parapsyllium; Spagulax au Citrate de Potassium; Spagulax au Sorbitol; ***Ger.:*** Agiolax; ***Hong Kong:*** Agiolax; Fybogel Mebeverine†; ***Irl.:*** Fybogel Mebeverine; ***Israel:*** Agiolax; ***Ital.:*** Agiolax; Agioslim; Duolaxan†; Fibrolax Complex; Psyllogel Fermenti; ***Mex.:*** Agiolax; Psilumax; ***Neth.:*** Agiolax; ***Norw.:*** Agiolax; ***NZ:*** Nucolox†; ***Pol.:*** Agiolax; Laxamix; Otrebuski; ***Port.:*** Agiolax; Excess†; ***S.Afr.:*** Agiolax; ***Spain:*** Agiolax; ***Swed.:*** Agiolax; Vi-Siblin S; ***Switz.:*** Agiolax; Mucilar Avena; ***Thai.:*** Agiolax; ***Turk.:*** Otaci Diyet Life Psyllium Plus; ***UK:*** Cleansing Herbs; Fibre Dophilus; Fibre Plus; Fybogel Mebeverine; Lion Cleansing Herbs; Manevac; ***USA:*** Perdiem; Senna Prompt; ***Venez.:*** Agiolax; Avensyl; Fiberfull; Fibralax†; Senokot con Fibra†.

Itopride Hydrochloride *(rINNM)*

HC-803; Hidrocloruro de itoprida; HSR-803; Itopride, Chlorhydrate d'; Itopridi Hydrochloridum. *N*-{*p*-[2-(Dimethylamino)ethoxy]benzyl}veratramide hydrochloride.

Итоприда Гидрохлорид

$C_{20}H_{26}N_2O_4,HCl = 394.9.$

CAS — 122898-67-3 (itopride).

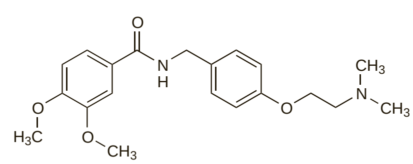

(itopride)

Profile

Itopride hydrochloride is a substituted benzamide with general properties similar to those of metoclopramide (p.1747) that has been used for its prokinetic and antiemetic actions in oral doses of 50 mg three times daily before meals.

◊ References.

1. Holtmann G, *et al.* A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; **354:** 832–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Ganaton; ***India:*** Itoprid; ***Jpn:*** Ganaton; ***Malaysia:*** Ganaton.

Jalap

Jalap Root; Jalap Tuber; Jalapa; Jalapenwurzel; Vera Cruz Jalap.

Ялапа

Jalap Resin

Jalapa, resina de; Jalapenharz.

CAS — 9000-35-5.

Profile

Jalap is the dried tubercles of *Ipomoea purga* (=*Exogonium purga*) (Convolvulaceae). Jalap resin is a mixture of glycosidal resins obtained by extraction of jalap with alcohol and it has a drastic purgative and irritant action. It has been superseded by less toxic laxatives.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Jalapa Composta†; ***Canad.:*** Herbal Laxative; ***S.Afr.:*** SB 3 Triple Action Pills.

Kaolin

Bolus Alba; Caolín; E559; Kaoliini; Kaolinas; Kaolinum; Weisser Ton.

Каолин

CAS — 1332-58-7.
ATC — A07BC02.
ATC Vet — QA07BC02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some pharmacopoeias do not differentiate between the heavy and light varieties.

Ph. Eur. 6.2 (Kaolin, Heavy). A purified, natural, hydrated aluminium silicate of variable composition. It is a fine, white or greyish-white, unctuous powder. Practically insoluble in water and in organic solvents.

BP 2008 (Light Kaolin). A native hydrated aluminium silicate, freed from most of its impurities by elutriation, and dried. It contains a suitable dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2008 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

BP 2008 (Light Kaolin (Natural)). It is Light Kaolin which does not contain a dispersing agent. It is a light, white, odourless or almost odourless, unctuous powder free from gritty particles. Practically insoluble in water and in mineral acids.

The BP 2008 directs that when Kaolin or Light Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied, unless it is ascertained that Light Kaolin (Natural) is required.

USP 31 (Kaolin). A native hydrated aluminium silicate, powdered and freed from gritty particles by elutriation. It is a soft, white or yellowish-white powder or lumps with an earthy or clay-like taste and when moistened with water assumes a darker colour and develops a marked clay-like odour. Insoluble in water, in cold dilute acids, and in solutions of alkali hydroxides.

Profile

Light kaolin and light kaolin (natural) are adsorbent antidiarrhoeal agents that have been used as adjuncts to rehydration therapy in the management of diarrhoea (p.1694). Up to about 24 g daily may be taken orally in divided doses. Kaolin is often combined with other antidiarrhoeals, especially pectin.

Kaolin can form insoluble complexes with some drugs in the gastrointestinal tract and reduce their absorption; oral doses should not be taken at the same time.

Externally, light kaolin is used as a dusting powder. Kaolin is liable to be heavily contaminated with bacteria, and when used in dusting powders, it should be sterilised.

Heavy kaolin is used in the preparation of kaolin poultice, which is applied topically with the intention of reducing inflammation and alleviating pain (see Rubefacients and Topical Analgesia, p.5).

Light kaolin is also used as a food additive.

Preparations

BP 2008: Kaolin and Morphine Mixture; Kaolin Mixture; Kaolin Poultice.

Proprietary Preparations (details are given in Part 3)

Braz.: Kaogel†; ***UK:*** Childrens Diarrhoea Mixture; Entrocalm.

Multi-ingredient: ***Arg.:*** Anusol-A; Argeal; Endomicina†; Gastranil†; Opocarbon; Opocler†; ***Austral.:*** Bis-Pectin†; Chemists Own Diarrhoea Mixture†; Diarcalm; Donnagel; Kaomagma with Pectin†; Kaomagma†; ***Belg.:*** Alopate; Neutroses; ***Braz.:*** Atalin†; Digastril†; Eviprostat†; Gastrobene; Kaomagma; Kaopectin†; ***Chile:*** Furazolidona; ***Fr.:*** Anti-H†; Antiphlogistine†; Argeal; Gastropax; Kaobrol†; Kaologeais; Kaomuth; Karayal; Keracnyl; Neutroses; ***Ger.:*** Kaoprompt-H; rohasal†; ***Gr.:*** Fissan-Pate†; Kaopectate†; ***Hong Kong:*** Calamine-D†; Uni-Kaotin; ***Hung.:*** Bolus Adstringens; Bolus Laxans; ***Indon.:*** Kaopectate; Neo Diaform; Neo Kaocitin; Neo Kaolana; Neo Kaominal; ***Irl.:*** Kaopectate†; ***Israel:*** Digestif-Ara†; Kaopectin; Kapectin Forte†; Zincod; ***Ital.:*** Katoxyn; Neutrose S Pellegrino; Streptomagma; ***Malaysia:*** Beakopectin†; Kaopectate†; ***Mex.:*** Ameban; Caopecfar; Colfur; Contefur†; Coralzul; Depofin; Dia-Par Compuesto; Dibapec Compuesto; Estibal; Exofur; Facetin-D; Farpectol; Furoxona CP; Fuzotyl†; Hidromagma†; Isocar; K-Omistron; Kaomycin; Kaopectate; Kapecfuran; Kediar; Lactopectin; Neokap; Neoxil; Olam; Optazol; Quimefuran; Suyodil; Tapzol con Neomicina†; Treda; Trilor†; Yodozona; ***S.Afr.:*** Betapect; Bipectinol; Biskapect; Bolus Eucalypti Comp; Chloropect; Collodene; Enterolyte; Gastropect; Kao†; Kaopectin†; Kaostatex; Pectin-K; Pectrolyte; SB Diarrhoea Mixture; ***Singapore:*** Beakopectin; Kaomix; Kaopectate†; ***Switz.:*** Argent†; Cicafissan; Fissan†; Gyrosan†; Neo-Decongestine; Neutroses; Padma-Lax; Padmed Laxan; Phlogantin; ***Thai.:*** Alkamine; Alumag; Alupep; Antacil†; Cenopec; Coccila†; Conmag; Di-Su-Frone†; Difuran; Disento; Disento PF; Droximag†; Furasian; Furopectin†; Kaopectal; Med-Kafuzone†; ***UAE:*** Kaptin; ***UK:*** Collis Browne's; De Witt's Antacid; Junior Kao-C; Kaodene†; KLN; Moorland; Opazimes; ***USA:*** K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Mexsana; ***Venez.:*** Kaopecon†; Kaopectate†; Klincosal; Niosilin; Parepectolin†; Pec-Kao†; Sendafur†.

Lactitol *(BAN, rINN)*

E966; β-Galactosido-sorbitol; Lactit; Lactitolum; Lactobiosit; Lactositol; Laktitol; Laktitoli; Laktitolis. 4-*O*-(β-D-Galactopyranosyl)-D-glucitol.

Лактитол

$C_{12}H_{24}O_{11}$ = 344.3.
CAS — 585-86-4.
ATC — A06AD12.
ATC Vet — QA06AD12.

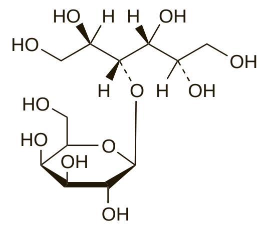

Pharmacopoeias. In *USNF. Eur.* (see p.vii) includes the monohydrate.

Ph. Eur. 6.2 (Lactitol Monohydrate). A white or almost white crystalline powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane.

USNF 26 (Lactitol). It may be the anhydrous form, the monohydrate, or the dihydrate. White or light brown, odourless, crystals. It has a mild, sweet taste, and no aftertaste.

Profile

Lactitol is a disaccharide analogue of lactulose (below) and has similar actions and uses.

Lactitol monohydrate is used as an oral powder or solution in the management of hepatic encephalopathy (p.1697) and in constipation (p.1693). Lactitol monohydrate 1.05 g is equivalent to about 1 g of anhydrous lactitol.

In the treatment of hepatic encephalopathy, lactitol monohydrate is given in usual oral doses of 500 to 700 mg/kg daily in 3 divided doses at meal times. The dose is subsequently adjusted to produce 2 soft stools daily.

In the treatment of constipation, lactitol monohydrate is given in an initial dose of 20 g daily as a single dose with the morning or evening meal, subsequently adjusted to produce one stool daily. A dose of 10 g daily may be sufficient for many patients.

Doses should be mixed with food or liquid, and 1 to 2 glasses of liquid should be drunk with the meal.

Lactitol is a permitted sweetener in foods.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Importal; Neda-Lactitol; Portolac†; ***Belg.:*** Importal; Normolaxil; Portolac; ***Braz.:*** Sigmalac; ***Cz.:*** Importal†; ***Denm.:*** Importal; ***Fin.:*** Lalax; ***Fr.:*** Importal; ***Ger.:*** Importal; ***Gr.:*** Importal; ***Israel:*** Importal†; Novolax; ***Ital.:*** Portolac; ***Jpn:*** Portolac; ***Neth.:*** Importal; ***Norw.:*** Importal†; ***NZ:*** Importal; ***Port.:*** Importal; ***Spain:*** Emportal; Oponaf; ***Swed.:*** Importal; ***Switz.:*** Importal; ***Thai.:*** Importal; ***Turk.:*** Importal.

Multi-ingredient: ***Ital.:*** Levoplus.

Lactulose *(BAN, USAN, rINN)*

Lactulosa; Lactulosum; Laktuliozė; Laktuloosi; Laktulos; Laktulosa; Laktüloz; Laktulóz. 4-*O*-β-D-Galactopyranosyl-D-fructose.

Лактулоза

$C_{12}H_{22}O_{11}$ = 342.3.
CAS — 4618-18-2.
ATC — A06AD11.
ATC Vet — QA06AD11.

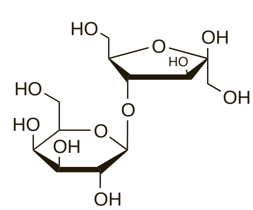

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. Chin.* only contains specifications for a solution. *US* only contains specifications for a solution and a concentrated liquid.

Ph. Eur. 6.2 (Lactulose). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in toluene.

Ph. Eur. 6.2 (Lactulose, Liquid; Lactulose Solution BP 2008). An aqueous solution of lactulose. It contains not less than 62.0% w/v of lactulose; it may contain lesser amounts of other sugars including lactose, epilactose, galactose, tagatose, and fructose. It may contain a suitable antimicrobial preservative. It is a clear, colourless or pale brownish-yellow, viscous liquid. Miscible with water. It may be a supersaturated solution or may contain crystals that disappear on heating.

USP 31 (Lactulose Concentrate). A colourless to amber syrupy liquid that may exhibit some precipitation and darkening on standing. Miscible with water. Store in airtight containers preferably at a temperature between 2° and 30°.

Adverse Effects

Lactulose may cause abdominal discomfort associated with flatulence or cramps. Nausea and vomiting have occasionally been reported after high doses. Some consider the taste to be unpleasant; this can be minimised by dilution in water, fruit juice, or milk, or by mixing the dose with food. Prolonged use or excessive dosage may result in diarrhoea with excessive loss of water and electrolytes, particularly potassium. Hypernatraemia has been reported.

Lactic acidosis. Severe lactic acidosis developed in a patient with adynamic ileus who was being given lactulose for hepatic encephalopathy.[1]

1. Mann NS, *et al.* Lactulose and severe lactic acidosis. *Ann Intern Med* 1985; **103:** 637.

Precautions

Lactulose should not be given to patients with galactosaemia or intestinal obstruction. It should not be used in patients on a low galactose diet and care should be taken in patients with lactose intolerance or in diabetic patients because of the presence of some free galactose and lactose.

Pharmacokinetics

Taken orally, lactulose passes essentially unchanged into the large intestine where it is metabolised by saccharolytic bacteria with the formation of simple organic acids, mainly lactic acid and small amounts of acetic and formic acids. The small amount of absorbed lactulose is subsequently excreted unchanged in the urine.

Uses and Administration

Lactulose is a synthetic disaccharide osmotic laxative (p.1693) used in the treatment of constipation (p.1693) and in hepatic encephalopathy (p.1697). Lactulose is broken down by colonic bacteria mainly into lactic acid. This exerts a local osmotic effect in the colon resulting in increased faecal bulk and stimulation of peristalsis. It may take up to 48 hours before an effect is obtained. When larger doses are given for hepatic encephalopathy the pH in the colon is reduced significantly and the absorption of ammonium ions and other toxic nitrogenous compounds is decreased, leading to a fall in blood-ammonia concentration and an improvement in mental function.

Lactulose is usually given orally as a solution containing about 3.35 g of lactulose per 5 mL, with other sugars such as galactose and lactose; an oral powder formulation is also available in some countries. In the treatment of **constipation**, the usual initial dose is 10 to 20 g (15 to 30 mL) given daily in a single dose or in 2 divided doses; doses up to 45 mL daily of the solution (or up to 40 g of the reconstituted oral powder formulation) have been given. The dose is gradually adjusted according to the patient's needs. For doses in children, see below.

In **hepatic encephalopathy**, an oral dose of 60 to 100 g (90 to 150 mL) is given daily in 3 divided doses. The dose is subsequently adjusted to produce 2 or 3 soft stools each day. Lactulose solution 200 g (300 mL) mixed with 700 mL of water or sodium chloride 0.9% has been used as a retention enema; the enema is retained for 30 to 60 minutes, repeated every 4 to 6 hours until the patient is able to take oral medication.

◊ References.

1. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora: clinical consequences. *Drugs* 1997; **53:** 930–42.
2. Schumann C. Medical, nutritional and technological properties of lactulose: an update. *Eur J Nutr* 2002; **41** (suppl): I17–I25.

Administration in children. In the UK, children may be given the following oral doses of lactulose 3.35 g per 5 mL solution for constipation; doses may be adjusted according to response:

- 1 month to 1 year: 2.5 mL twice daily
- 1 to 5 years: 5 mL twice daily
- 5 to 10 years: 10 mL twice daily
- 10 to 18 years: 15 mL twice daily

Diagnosis and testing. *THE SUGAR ABSORPTION TEST.* In healthy individuals lactulose is largely unabsorbed from the gastrointestinal tract, but in, for example, coeliac disease there is increased permeability to disaccharides such as lactulose and a paradoxical decrease in the absorption of monosaccharides. This led to the development of the differential sugar absorption test in which 2 sugars are given simultaneously by mouth and the urinary recovery of each is determined; mannitol is commonly used as the monosaccharide component and lactulose as the disaccharide. Alternatives include mannitol plus cellobiose and rhamnose plus lactulose. This absorption test is useful in the investigation of intestinal disease.[1]

The lack of a standardised test solution has hampered comparison of test results. Although hyperosmolar solutions are better at determining intestinal damage,[2] some have preferred to use low osmolar solutions because of the risk of inducing osmotic diarrhoea, especially in children.

A study found the sugar absorption test to be strongly predictive of an organic cause of chronic diarrhoea; it may be useful in improving the selection of patients who need further evaluation.[3]

THE LACTOSE BREATH TEST (hydrogen breath test). Lactulose is converted by bacteria in the large bowel to short chain fatty acids with the production of small quantities of hydrogen gas. The hydrogen is rapidly absorbed and is exhaled in the breath and measurement of its production is used to measure orocaecal transit time and carbohydrate malabsorption. However, even small doses of lactulose shortens transit time, which may limit the value of this test.[4]

The test is also diagnostic for bacterial overgrowth in the small intestine, which is increased in irritable bowel syndrome. Although hydrogen is produced in most subjects, methane is also produced in up to 50% of healthy subjects, and data suggest there may be clinical implications to different gas profiles. A study found that the presence of methane was associated with constipation, and with constipation-predominant irritable bowel syndrome. Methane production was infrequent in diarrhoea-predominant irritable bowel syndrome and virtually absent in inflammatory bowel disease. Diarrhoea and inflammatory bowel disease were associated with hydrogen production. Whether the type of bacterial flora causally determines symptoms is as yet unknown.[5]

1. Uil JJ, *et al.* Clinical implications of the sugar absorption test: intestinal permeability test to assess mucosal barrier function. *Scand J Gastroenterol* 1997; **223** (suppl): 70–8.
2. Uil JJ, *et al.* Sensitivity of a hyperosmolar or "low"-osmolar test solution for sugar absorption in recognizing small intestinal mucosal damage in coeliac disease. *Dig Liver Dis* 2000; **32:** 195–200.
3. Di Leo V, *et al.* Lactulose/mannitol test has high efficacy for excluding organic causes of chronic diarrhea. *Am J Gastroenterol* 2003; **98:** 2245–52.
4. Miller MA, *et al.* Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. *Dig Dis Sci* 1997; **42:** 10–18.
5. Pimentel M, *et al.* Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003; **48:** 86–92.

Preparations

BP 2008: Lactulose Oral Powder;
Ph. Eur.: Liquid Lactulose;
USP 31: Lactulose Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Genocolan; Lactulon; Lafelax; Medixin; Tenualax; ***Austral.:*** Actilax; Duphalac; Genlac; Lac-Dol; Lactocur; ***Austria:*** Bifiteral; Duphalac; Laevolac; ***Belg.:*** Bifiteral; Certalac†; Duphalac; ***Braz.:*** Colonac; Farlac; Lactulona; Pentalac†; ***Canad.:*** Acilac†; Gen-Lac; Laxilose†; ***Chile:*** Axant; Dismam; Duphalac; Rencef†; ***Cz.:*** Duphalac; Lactecon; Laevolac†; ***Denm.:*** Danilax†; Medilax; ***Fin.:*** Duphalac; Levolac; Loraga†; ***Fr.:*** Duphalac; Laxaron; ***Ger.:*** Bifinorma; Bifiteral; Eugalac; Hepa-Merz Lact†; Hepaticum-Lac-Medice†; Kattwilact†; Lactocur; Lactuflor; Lactuverlan; Laevilac S; Medilet†; Tulotract; ***Gr.:*** Duphalac; Purgolac†; ***Hong Kong:*** Danilax; Duphalac; Laevolac; Martulose; ***Hung.:*** Duphalac; Laevolac; ***India:*** Duphalac; Livoluk; ***Indon.:*** Constipen; Dulcolactol; Duphalac; Lactulax; Lantulos; Laxadilac; Opilax; Pralax; Solac; ***Irl.:*** Dulax; Duphalac; Gerelax; Laxose; ***Israel:*** Avilac; Gerelax; Lactulax; Laevolac; ***Ital.:*** Biolac†; Dia-Colon; Duphalac; Epalat EPS; Epalfen; Lactoger†; Laevolac; Lassifar†; Lattubio†; Lattulac; Lis†; Normase; Osmolac†; Sintolatt; Verelait; ***Jpn:*** Monilac; ***Malaysia:*** Dhactulose; Duphalac; Lactul; Lactumed†; ***Mex.:*** Lactulax; Regulact; ***Neth.:*** Duphalac; Epalfen; Laxeersiroop; Legendal; ***Norw.:*** Duphalac; Levolac; ***NZ:*** Laevolac; ***Philipp.:*** Duphalac; Lilac; ***Pol.:*** Duphalac; Lactulol; Normalac; Normase; ***Port.:*** Colsanac; Duphalac; Lactecon†; Laevolac; Obstipar; ***Rus.:*** Duphalac (Дюфалак); Normase (Нормазе); Portalac (Порталак); ***S.Afr.:*** Adco-Liquilax; Duphalac; Lacson; Laxette; ***Singapore:*** Dhactulose; Duphalac; Lactus; ***Spain:*** Belmalax; Duphalac; ***Swed.:*** Duphalac; Laktipex; Loraga; ***Switz.:*** Duphalac; Gatinar; Legendal; Rudolac; ***Thai.:*** Duphalac; Hepalac; Laevolac†; ***Turk.:*** Duphalac; Lactulac; Laevolac; Laktol; Osmolak; ***UAE:*** Soflax; ***UK:*** Duphalac; Lactugal; Lemlax; Regulose; ***USA:*** Cephulac; Cholac†; Chronulac; Constilac; Constulose; Duphalac; Enulose; Kristalose; ***Venez.:*** Lactulona; Moderan.

Multi-ingredient: ***Arg.:*** Bifidosa; ***Fr.:*** Melaxose; Transulose; ***Ger.:*** Eugalan Topfer; ***Indon.:*** Laktobion; ***Ital.:*** Combilax; Lactolas; Lactomannan; Levoplus; Naturalass; ***Neth.:*** Transulose; ***Port.:*** Melaxose.

Lafutidine *(rINN)*

FRG-8813; Lafutidina; Lafutidinum. (±)-2-(Furfurylsulfinyl)-*N*-[(*Z*)-4-{[4-(piperidinomethyl)-2-pyridyl]oxy}-2-butenyl]acetamide.
Лафутидин
$C_{22}H_{29}N_3O_4S$ = 431.5.
CAS — 118288-08-7.
ATC — A02BA08.
ATC Vet — QA02BA08.

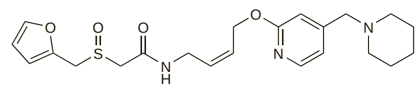

Profile

Lafutidine, like cimetidine (p.1716), is a histamine H_2-antagonist. It is used in the management of peptic ulcer disease.

◊ References.

1. Uesugi T, *et al.* The efficacy of lafutidine in improving preoperative gastric fluid property: a comparison with ranitidine and rabeprazole. *Anesth Analg* 2002; **95:** 144–7.
2. Mikawa K, *et al.* Lafutidine vs cimetidine to decrease gastric fluid acidity and volume in children. *Can J Anaesth* 2003; **50:** 425–6.
3. Isomoto H, *et al.* Lafutidine, a novel histamine H2-receptor antagonist, vs lansoprazole in combination with amoxicillin and clarithromycin for eradication of Helicobacter pylori. *Helicobacter* 2003; **8:** 111–19.
4. Inamori M, *et al.* Early effects of lafutidine or rabeprazole on intragastric acidity: which drug is more suitable for on-demand use? *J Gastroenterol* 2005; **40:** 453–8.
5. Higuchi K, *et al.* Lafutidine can improve the quality of gastric ulcer healing in humans: a randomized, controlled, multicenter trial. *Inflammopharmacology* 2006; **14:** 226–30.
6. Yamagishi H, *et al.* Stronger inhibition of gastric acid secretion by lafutidine, a novel H(2) receptor antagonist, than by the proton pump inhibitor lansoprazole. *World J Gastroenterol* 2008; **14:** 2406–10.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Protecadin; Stogar.

Lansoprazole *(BAN, USAN, rINN)*

A-65006; AG-1749; Lansopratsoli; Lansoprazol; Lansoprazolum. 2-({3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl} sulphinylbenzimidazole.
Лансопразол
$C_{16}H_{14}F_3N_3O_2S$ = 369.4.
CAS — 103577-45-3.
ATC — A02BC03.
ATC Vet — QA02BC03.

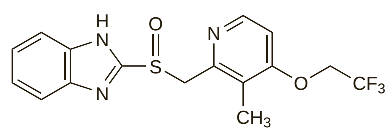

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Lansoprazole). A white or brownish powder. Practically insoluble in water; soluble in anhydrous alcohol; very slightly soluble in acetonitrile. It exhibits polymorphism. Store in airtight containers. Protect from light.

USP 31 (Lansoprazole). A white to brownish-white powder. Practically insoluble in water; freely soluble in dimethylformamide. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects and Precautions

As for Omeprazole, p.1753.

◊ Reviews.

1. Freston JW, *et al.* Safety profile of lansoprazole: the US clinical trial experience. *Drug Safety* 1999; **20:** 195–205.

Effects on the blood. For a report of thrombocytopenia with lansoprazole, see under Omeprazole, p.1753.

Effects on the endocrine system. For cases of gynaecomastia associated with lansoprazole, see p.1753.

Effects on the gastrointestinal tract. Glossitis (associated in some cases with black tongue or stomatitis) has been reported in a few patients taking lansoprazole as part of a triple therapy regimen for *Helicobacter pylori* elimination in peptic ulcer disease.[1] Discoloured tongue has been reported in a patient taking lansoprazole alone.[2]

An increase in gastritis occurred in patients infected with *Helicobacter pylori* when given long-term lansoprazole therapy.[3] For further discussion of the link between *H. pylori*, gastritis, and proton pump inhibitor use, see Gastrointestinal Tumours, p.1754.

For a suggestion that the incidence of diarrhoea may be greater with lansoprazole than omeprazole see Incidence of Adverse Effects, p.1753. Cases of microscopic colitis have been reported with use of lansoprazole.[4] UK licensed product information states that stopping therapy should be considered in the case of severe and/or persistent diarrhoea.

1. Greco S, *et al.* Glossitis, stomatitis, and black tongue with lansoprazole plus clarithromycin and other antibiotics. *Ann Pharmacother* 1997; **31:** 1548.
2. Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; **144:** 1293–4.
3. Berstad AE, *et al.* Helicobacter pylori gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. *Gut* 1997; **41:** 740–7.
4. Hilmer SN, *et al.* Microscopic colitis associated with exposure to lansoprazole. *Med J Aust* 2006; **184:** 185–6.

Effects on the musculoskeletal system. For reference to a case of eosinophilia and myalgia related to lansoprazole therapy, see p.1753.

Effects on the skin. For mention of skin reactions to lansoprazole, see p.1754.

Interactions

As for Omeprazole, p.1755. Antacids and sucralfate may reduce the bioavailability of lansoprazole, and should not be taken within 1 hour of a dose of lansoprazole.

◊ For reference to a lack of effect of lansoprazole on diazepam, see Gastrointestinal Drugs, p.991, and for a clinically insignificant effect on theophylline clearance, see p.1145. For reference to glossitis occurring when lansoprazole was used with some antibacterials, see Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

Lansoprazole is rapidly absorbed after oral doses, with peak plasma concentrations achieved after about 1.5 to 2 hours. Bioavailability is reported to be 80% or more even with the first dose, although the drug must be given in an enteric-coated form since lansoprazole is unstable at acid pH. Food slows the absorption of lansoprazole and reduces the bioavailability by about 50%. It is extensively metabolised in the liver, primarily by cytochrome P450 isoenzyme CYP2C19 to form 5-hydroxyl-lansoprazole and by CYP3A4 to form lansoprazole sulfone. Metabolites are excreted mainly in faeces via the bile; only about 15 to 30% of a dose is excreted in urine. The plasma elimination half-life is around 1 to 2 hours but the duration of action is much longer. Lansoprazole is about 97% bound to plasma protein. Clearance is decreased in elderly patients, and in hepatic impairment.

◊ References.

1. Hussein Z, *et al.* Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 1993; **36:** 391–8.
2. Flouvat B, *et al.* Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects. *Br J Clin Pharmacol* 1993; **36:** 467–9.
3. Delhotal-Landes B, *et al.* Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol* 1993; **45:** 367–71.
4. Delhotal Landes B, *et al.* Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995; **28:** 458–70.
5. Karol MD, *et al.* Lansoprazole pharmacokinetics in subjects with various degrees of kidney function. *Clin Pharmacol Ther* 1997; **61:** 450–8.
6. Tran A, *et al.* Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther* 2002; **71:** 359–67.

Metabolism. As for omeprazole (p.1755), the cytochrome P450 isoenzyme CYP2C19 (*S*-mephenytoin hydroxylase) is involved in the hydroxylation of lansoprazole, and individuals who are deficient in this enzyme are poor metabolisers of lansoprazole.[1,2] There is some suggestion that the effect of this genetic polymorphism on lansoprazole may be less than the effect on omeprazole.[3]

1. Pearce RE, *et al.* Identification of the human P450 enzymes involved in lansoprazole metabolism. *J Pharmacol Exp Ther* 1996; **277:** 805–16.
2. Sohn DR, *et al.* Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4′-hydroxylation phenotype status. *Clin Pharmacol Ther* 1997; **61:** 574–82.
3. Kim K-A, *et al.* Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther* 2002; **72:** 90–9.

Uses and Administration

Lansoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p.1755). It is used in the treatment of peptic ulcer disease and in oth-

The symbol † denotes a preparation no longer actively marketed

er conditions where inhibition of gastric acid secretion may be beneficial.

Lansoprazole is usually given orally as capsules, dispersible tablets, or suspension containing enteric-coated granules. Once daily regimens are taken before food in the morning. An intravenous formulation is also available.

For the relief of acid-related **dyspepsia** (p.1695) intermittent courses of lansoprazole may be given in doses of 15 or 30 mg once daily, for 2 to 4 weeks.

In the treatment of **gastro-oesophageal reflux disease** (p.1696) the dose is 15 to 30 mg once daily for 4 to 8 weeks; thereafter maintenance therapy can be continued with 15 or 30 mg once daily according to response. In patients unable to take oral therapy, lansoprazole may be given by intravenous infusion for the treatment of erosive oesophagitis for up to 7 days; a dose of 30 mg over 30 minutes daily is recommended.

Lansoprazole is given for the treatment of **peptic ulcer disease** (p.1702) in the UK in doses of 30 mg once daily. Treatment is continued for 2 to 4 weeks for duodenal and 4 to 8 weeks for gastric ulcer. In the USA, a dose of 15 mg daily for 4 weeks is recommended for duodenal ulcer, and 30 mg once daily is given for up to 8 weeks for gastric ulceration. When appropriate, 15 mg daily may be used as maintenance therapy for the prevention of relapse of duodenal ulcer. Lansoprazole may be combined with antibacterials in one-week **triple therapy** regimens for the eradication of *Helicobacter pylori*. Effective regimens include lansoprazole 30 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily; lansoprazole with amoxicillin and metronidazole has also been used. In patients with **NSAID-associated ulceration** a dose of 30 mg daily for 4 to 8 weeks is recommended; 15 to 30 mg daily may be used as prophylaxis for patients who require continued NSAID treatment.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p.1704) the initial dose is 60 mg once daily, adjusted as required. Doses of up to 90 mg twice daily have been used. Daily doses greater than 120 mg should be given in divided doses.

In the USA, **children** aged from 1 to 11 years may be given lansoprazole for the short-term treatment of erosive oesophagitis and symptomatic gastro-oesophageal reflux disease. Children weighing 30 kg or less should be given 15 mg once daily, and those weighing more than 30 kg are given 30 mg once daily, for up to 12 weeks. Doses of up to 30 mg twice daily have been used. In children aged from 12 to 17 years, lansoprazole 30 mg once daily for up to 8 weeks may be used for erosive oesophagitis, and 15 mg once daily for up to 8 weeks may be used for symptomatic gastro-oesophageal reflux disease. Although not licensed for children in the UK, the *BNFC* recommends comparable oral daily doses of 0.5 to 1 mg/kg in children up to 30 kg in weight, and 15 or 30 mg once daily in those over 30 kg.

Doses of lansoprazole may need to be reduced in patients with hepatic impairment (see below).

◊ General references. For general reviews of proton pump inhibitors, see Omeprazole, p.1756.

1. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; **54:** 473–500.
2. Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. *Drugs* 2001; **61:** 1801–33.
3. Freston JW, *et al.* Lansoprazole for maintenance of remission of erosive oesophagitis. *Drugs* 2002; **62:** 1173–84.
4. Dando TM, Plosker GL. Intravenous lansoprazole: in erosive oesophagitis. *Drugs* 2004; **64:** 2085–9.
5. Croom KF, Scott LJ. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs* 2005; **65:** 2129–35.

Administration. Lansoprazole *capsules* should be swallowed whole and not crushed or chewed. Lansoprazole *dispersible tablets* should be placed on the tongue and allowed to disintegrate and the resultant granules swallowed; alternatively, the tablets may be swallowed whole with a glass of water. The tablets should not be crushed or chewed. The tablets may also be dispersed in a small amount of water and given via an oral syringe, or via a nasogastric tube. Lansoprazole *granules for oral suspension* should be reconstituted in a little water and swallowed immediately. Where the suspension formulation is not available, the contents of the capsules (enteric-coated granules) can be sprinkled on a small amount of soft food (such as yogurt or apple sauce) or mixed with a little fruit juice and swallowed. For administration via a nasogastric tube, the contents of a capsule may be mixed with 40 mL of apple juice; additional apple juice may be used to flush the tube.

Administration in hepatic impairment. Exposure to lansoprazole is increased in patients with hepatic impairment. Licensed product information recommends that patients with moderate to severe liver disease should be kept under supervision, and that the daily dose should be reduced by 50%.

Preparations

USP 31: Lansoprazole Delayed-Release Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Ilsatec†; Lanzopral; Mesactol; Ogasto†; ***Austral.:*** Zoton; ***Austria:*** Agopton; Lansobene; ***Belg.:*** Dakar; ***Braz.:*** Anzoprol†; Lanogastro; Lanz; Lanzol; Lanzopept; Neozol; Ogastro; Prazol; ***Canad.:*** Prevacid; ***Chile:*** Fudermex; Gastride; Lanzopral; Ogasto†; Unival; ***Cz.:*** Lansone†; Lansoprol; Lanzul; ***Denm.:*** Lanzo; ***Fin.:*** Lanzo; Zolt; ***Fr.:*** Lanzor; Ogast; Ogastoro; ***Ger.:*** Agopton; Lanzor; ***Gr.:*** Elcodil; Lanciprol; Lanso; Laprazol; ***Hong Kong:*** Takepron; ***Hung.:*** Lansacid; Lansogen; Lansone; Lansoptol; Levant; Protonexa; Refluxon; ***India:*** Chexid; Lancus; Lanzol; ***Indon.:*** Compraz; Digest; Gastrolan; Inhipraz; Lancid; Lapraz; Laproton; Lasgan; Laz; Loprezol; Nufaprazol; Prazotec; Prolanz; Prosogan; Protica; Pysolan; Solans; Sopralan; Ulceran; ***Irl.:*** Lanziop; Lanzol; Razolager; Zomel; Zoton; Zotrole; ***Israel:*** Lanton; Zoton; ***Ital.:*** Lansox; Limpidex; Zoton; ***Jpn:*** Prevacid; Takepron; ***Malaysia:*** Prevacid; ***Mex.:*** Bonzol; Ilsatec; Imidex; Keval; Lafin; Lanodizol; Mavilan; Mediprim; Ogastro; Olan; Palatrin; Pranix; Safemar; Uldapril; Ulpax; ***Neth.:*** Prezal; ***Norw.:*** Lanzo; ***NZ:*** Solox; Zoton†; ***Philipp.:*** Lanzohex; Prevacid; Pylison; ***Pol.:*** LansoLek; Lanzostad; Lanzul; ***Port.:*** Alexin; Dispepci; Gastrex; Gastrolanzo; Gastroliber; Lansox; Lanzogastro; Lapol; Lizul†; Monolitum†; Ogasto; Pampe; Pepzol†; Ulcertec; ***Rus.:*** Acrilans (Акриланз); Epicur (Эпикур); Helicol (Геликол); Lanzap (Ланзап); ***S.Afr.:*** Adco-Roznal; Lancap; Lansoloc; Lanzor; ***Singapore:*** Prevacid; ***Spain:*** Bamalite; Estomil; Eudiges; Lanzol; Monolitum; Opiren; Pro Ulco; Protoner; ***Swed.:*** Lanzo; ***Switz.:*** Agopton; ***Thai.:*** Prevacid; ***Turk.:*** Aprazol; Degastrol; Helicol; Lansazol; Lansoprol; Lansor; Lanzedin; Ogastro; Opagis; Vogast; Zoprol; ***UAE:*** Lanfast; ***UK:*** Zoton; ***USA:*** Prevacid; ***Venez.:*** Biolanz; Gastrazol; Ilsatec†; Lansovax; Lanzap†; Lanzol; Lanzopral; Ogastro.

Multi-ingredient: ***Arg.:*** Heliklar†; ***Braz.:*** Anzopac†; H-Bacter; Helicopac; Heliklar; Lansodom; Lansoprid; Pylorikit; Pyloripac; Pyloritrat; ***Canad.:*** Hp-Pac; ***Fin.:*** Helipak A; Helipak K; Helipak T; ***India:*** Okalan D; Pylokit; ***Mex.:*** Pylopac; ***Turk.:*** Helipak; ***UK:*** Heliclear†; HeliMet†; ***USA:*** Prevpac.

Used as an adjunct in: ***USA:*** Prevacid NapraPAC.

Lidamidine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lidamidina; Lidamidine, Chlorhydrate de; Lidamidini Hydrochloridum; WHR-1142A. *N*-(2,6-Dimethylphenyl)-*N'*-[imino(methylamino)methyl]urea hydrochloride.

Лидамидина Гидрохлорид

$C_{11}H_{16}N_4O,HCl = 256.7.$

CAS — 66871-56-5 (lidamidine); 65009-35-0 (lidamidine hydrochloride).

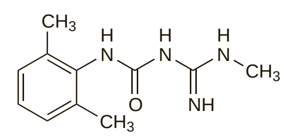

(lidamidine)

Profile

Lidamidine is an alpha$_2$-adrenergic receptor stimulant used as the hydrochloride for the management of diarrhoea and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Idealid†; Supra.

Linaclotide Acetate *(USAN, rINNM)*

Acetato de linaclotida; Linaclotide, Acétate de; Linaclotidi Acetas; MD-1100; MM-416775. [9-L-Tyrosine]heat-stable enterotoxin (Escherichia coli)-(6-19)-peptide monoacetate salt.

Линаклотида Ацетат

$C_{59}H_{79}N_{15}O_{21}S_6,C_2H_4O_2 = 1586.8.$

CAS — 851199-59-2 (linaclotide); 851199-60-5 (linaclotide acetate).

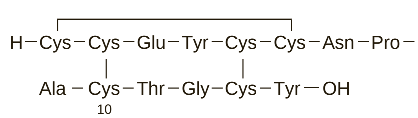

Profile

Linaclotide is a guanylate cyclase-C agonist being studied in the treatment of constipation-predominant irritable bowel syndrome and chronic constipation.

◊ References.

1. Harris LA, Crowell MD. Linaclotide, a new direction in the treatment of irritable bowel syndrome and chronic constipation. *Curr Opin Mol Ther* 2007; **9:** 403–10.
2. Andresen V, *et al.* Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007; **133:** 761–8.

Liquorice

Alcaçuz; Édesgyökér; Gancao; Glycyrrhiza; Korzeń lukrecji; Lakritsijuuri; Lakritsrot; Lékořicový kořen; Licorice; Liquiritiae radix; Liquorice Root; Orozuz; Raiz de Regaliz; Regaliz; Réglisse, racine de; Saldymedžių šaknys; Süssholzwurzel.

Лакрица

Description. Liquorice is the dried rhizome and roots of *Glycyrrhiza glabra*. Those of *G. glabra* var. *typica* are known in commerce as Spanish Liquorice, those of *G. glabra* var. *glandulifera* as Russian Liquorice, and those of *G. glabra* var. *β-violacea* as Persian Liquorice.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US. Eur.* (see p.vii) also includes Liquorice Dry Extract for Flavouring Purposes. *US* also includes Powdered Licorice and Powdered Licorice Extract. *Br.* also includes Liquorice Root for use in Traditional Herbal Medicine and Processed Liquorice Root for use in Traditional Herbal Medicinal Product.

Ph. Eur. 6.2 (Liquorice Root; Liquorice BP 2008). The dried unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* and/or *G. inflata* and/or *G. uralensis*. It contains not less than 4% of glycyrrhizic acid. Protect from light.

USP 31 (Licorice). The roots, rhizomes, and stolons of *Glycyrrhiza glabra* or *G. uralensis*. It contains not less than 2.5% of glycyrrhizic acid, calculated on the dried basis. Store in a cool, dry place.

BP 2008 (Liquorice Root for use in THM). It is the dried unpeeled root and rhizome of *Glycyrrhiza uralensis*, *G. inflata*, or *G. glabra*. For use in traditional Chinese medicines. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

BP 2008 (Processed Liquorice Root for use in THMP). Liquorice Root for use in THM which has been cleaned, softened, sliced transversely or longitudinally to form uniform pieces, and dried. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

Adverse Effects and Precautions

Liquorice has mineralocorticoid-like actions manifesting as sodium and water retention and hypokalaemia (see below).

Deglycyrrhizinised liquorice is not usually associated with such adverse effects.

Mineralocorticoid effects. Mineralocorticoid effects have been reported after excessive or prolonged ingestion of liquorice. The liquorice may be ingested in confectionery (including liquorice-flavoured chewing gum), tea, soft drinks, herbal medicines, cough mixtures, or by chewing tobacco. The enzyme 11-β-hydroxysteroid dehydrogenase (cortisol oxidase) converts cortisol to cortisone, preventing cortisol gaining access to non-specific mineralocorticoid receptors. This enzyme is inhibited by glycyrrhetinic acid (produced by the hydrolysis of glycyrrhizic acid, a natural constituent of liquorice), resulting in increased concentrations of cortisol in the body, enhancing its physiological effects.[1-3]

Clinical manifestations include consequences of sodium retention such as hypertension,[4-10] and hypokalaemia, which can result in neuromuscular disturbances ranging from muscle weakness,[11] myoclonus,[12] and myopathy[10] to paralysis[13-15] and rhabdomyolysis.[15-17] Arrhythmias[16,18] and fatal cardiac arrest[19] have also been reported.

Increased amounts of cortisol in vascular smooth muscle may cause vasoconstriction. Vasospasm of vessels supplying the optic nerve may have caused transient visual disturbances reported after liquorice ingestion.[2]

Other reported effects of liquorice include growth retardation in a boy with Addison's disease;[20] liquorice was thought to have potentiated the effect of hydrocortisone.

Endocrine effects of liquorice have been reviewed.[21] Conflicting effects on testosterone and prolactin have been reported. Components of liquorice root (which has been tried for menopausal symptoms) have both oestrogenic and anti-oestrogenic activity, and it has reportedly caused gynaecomastia.

Individuals vary markedly in their susceptibility to liquorice-induced adverse effects.[1] Those consuming 400 mg glycyrrhetinic acid daily generally experience adverse effects, but a regular daily intake of no more than 100 mg of glycyrrhetinic acid (about 50 g of liquorice sweets) has produced adverse effects in some who appear more sensitive to its effects. Some consider a daily intake of 10 mg glycyrrhetinic acid to be a safe daily dose for adults; the amount of salt consumed needs to be considered as even a low dose of liquorice may induce sodium overload in those consuming high amounts of sodium chloride.[3]

1. Walker BR, Edwards CR. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994; **23:** 359–77.
2. Dobbins KRB, Saul RF. Transient visual loss after licorice ingestion. *J Neuroophthalmol* 2000; **20:** 38–41.
3. Frey FJ, Ferrari P. Pastis and hypertension—what is the molecular basis? *Nephrol Dial Transplant* 2000; **15:** 1512–14.
4. van Uum SH. Liquorice and hypertension. *Neth J Med* 2005; **63:** 119–20.
5. Dellow EL, *et al.* Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. *Nephrol Dial Transplant* 1999; **14:** 218–20.
6. Woywodt A, *et al.* Turkish pepper (extra hot). *Postgrad Med J* 2000; **76:** 426–8.
7. Janse A, *et al.* The old lady who liked liquorice: hypertension due to chronic intoxication in a memory-impaired patient. *Neth J Med* 2005; **63:** 149–50.
8. Russo S, *et al.* Low doses of liquorice can induce hypertension encephalopathy. *Am J Nephrol* 2000; **20:** 145–8.
9. Hall RC, Clemett RS. Central retinal vein occlusion associated with liquorice ingestion. *Clin Experiment Ophthalmol* 2004; **32:** 341.
10. Hussain RM. The sweet cake that reaches parts other cakes can't! *Postgrad Med J* 2003; **79:** 115–16.
11. Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. *Clin Neurol Neurosurg* 2003; **105:** 286–7.
12. Ishiguchi T, *et al.* Myoclonus and metabolic alkalosis from licorice in antacid. *Intern Med* 2004; **43:** 59–62.
13. Elinav E, Chajek-Shaul T. Licorice consumption causing severe hypokalemic paralysis. *Mayo Clin Proc* 2003; **78:** 767–8.
14. Lin S-H, *et al.* An unusual cause of hypokalemic paralysis: chronic licorice ingestion. *Am J Med Sci* 2003; **325:** 153–6.
15. van den Bosch AE, *et al.* Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. *Neth J Med* 2005; **63:** 146–8.
16. Bauchart J-J, *et al.* Alcohol-free pastis and hypokalaemia. *Lancet* 1995; **346:** 1701.
17. Firenzuoli F, Gori L. Rabdomiolisi da liquirizia. *Recenti Prog Med* 2002; **93:** 482–3.
18. Eriksson JW, *et al.* Life-threatening ventricular tachycardia due to liquorice-induced hypokalaemia. *J Intern Med* 1999; **245:** 307–10.
19. Haberer JP, *et al.* Severe hypokalaemia secondary to overindulgence in alcohol-free "pastis". *Lancet* 1984; **i:** 575–6.
20. Doeker BM, Andler W. Liquorice, growth retardation and Addison's disease. *Horm Res* 1999; **52:** 253–5.
21. Armanini D, *et al.* History of the endocrine effects of licorice. *Exp Clin Endocrinol Diabetes* 2002; **110:** 257–61.

Pregnancy. Studies in Finnish women indicated that heavy consumption of liquorice (equivalent to ≥ 500 mg/week of glycyrrhizic acid) during pregnancy was associated with an increased risk of preterm delivery.[1,2] Consumption of large amounts of liquorice was a social habit noted to occur in some northern European countries.

1. Strandberg TE, *et al.* Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol* 2001; **153:** 1085–8.
2. Strandberg TE, *et al.* Preterm birth and licorice consumption during pregnancy. *Am J Epidemiol* 2002; **156:** 803–5.

Uses and Administration

Liquorice is used as a flavouring and sweetening agent. It has demulcent and expectorant properties and has been used in cough preparations. It has ulcer-healing properties that may result from stimulation of mucus synthesis. It contains constituents that produce mineralocorticoid effects (see above). Liquorice may also possess some antispasmodic and laxative properties.

Deglycyrrhizinised liquorice has a reduced mineralocorticoid activity and has been used, usually with antacids, for the treatment of peptic ulcer disease (p.1702).

◊ Reviews.

1. Fiore C, *et al.* A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol* 2005; **99:** 317–24.

Preparations

Ph. Eur.: Liquorice Ethanolic Liquid Extract, Standardised;
USP 31: Licorice Fluidextract.

Proprietary Preparations (details are given in Part 3)
Braz.: Alcalergin; Brefus†; ***Cz.:*** Gallentee†; ***Fr.:*** Depiderm; Trio D†; ***Ger.:*** Fichtensirup N†; Lakriment Neu†; Suczulen mono†.

Multi-ingredient: numerous preparations are listed in Part 3.

Loperamide Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de loperamida; Loperamid Hidroklorür; Loperamid hydrochlorid; Lopéramide, chlorhydrate de; Loperamid-hidroklorid; Loperamidhydroklorid; Loperamidi hydrochloridum; Loperamidihydrokloridi; Loperamido hidrochloridas; R-18553.
4-(4-*p*-Chlorophenyl-4-hydroxypiperidino)-*NN*-dimethyl-2,2-diphenylbutyramide hydrochloride.

Лоперамида Гидрохлорид

$C_{29}H_{33}ClN_2O_2$,HCl = 513.5.

CAS — 53179-11-6 (loperamide); 34552-83-5 (loperamide hydrochloride).

ATC — A07DA03.

ATC Vet — QA07DA03.

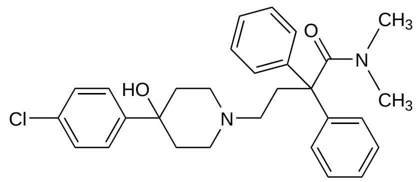

(loperamide)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Loperamide Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Loperamide Hydrochloride). A white to slightly yellow powder. Slightly soluble in water and in dilute acids; freely soluble in chloroform and in methyl alcohol; very slightly soluble in isopropyl alcohol.

Loperamide Oxide *(BAN, rINN)*

Loperamid oxid; Lopéramide Oxyde; Lopéramide, oxyde de; Loperamidi oxidum; Loperamidioksidi; Loperamido oksidas; Loperamidoxid; Loperamidum Oxidum; Óxido de loperamida; R-58425.

Лоперамида Оксид

$C_{29}H_{33}ClN_2O_3$ = 493.0.

CAS — 106900-12-3.

ATC — A07DA05.

ATC Vet — QA07DA05.

Pharmacopoeias. *Eur.* (see p.vii) includes the monohydrate.

Ph. Eur. 6.2 (Loperamide Oxide Monohydrate; Loperamidi Oxidum Monohydricum). A white or almost white, slightly hygroscopic, powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Abdominal pain or bloating, nausea, constipation, dry mouth, dizziness, fatigue, and hypersensitivity reactions including skin rashes have been reported. Loperamide has been associated with paralytic ileus, particularly in infants and young children, and deaths have been reported. Depression of the CNS, to which children or those with hepatic impairment may be more sensitive, may be seen in overdosage; constipation and urinary retention also occur. Naloxone hydrochloride (see p.1454) has been recommended for treatment of severe overdosage.

Toxicity. Toxic megacolon has been reported[1,2] after use of loperamide. Severe effects reported in young children have included loss of consciousness[3,4] and delirium.[5] Several cases of paralytic ileus have also occurred in children,[6,7] some of which were fatal.[6]

1. Brown JW. Toxic megacolon associated with loperamide therapy. *JAMA* 1979; **241:** 501–2.
2. Walley T, Milson D. Loperamide related toxic megacolon in Clostridium difficile colitis. *Postgrad Med J* 1990; **66:** 582.
3. Minton NA, Smith PGD. Loperamide toxicity in a child after a single dose. *BMJ* 1987; **294:** 1383.
4. Chanzy S, *et al.* Perte de connaissance chez une jeune enfant secondaire à la prise de lopéramide. *Arch Pediatr* 2004; **11:** 826–7.
5. Schwartz RH, Rodriguez WJ. Toxic delirium possibly caused by loperamide. *J Pediatr* 1991; **118:** 656–7.
6. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
7. Dudink J, *et al.* Ileus na gebruik van loperamide bij een kind met acute diarree. *Ned Tijdschr Geneeskd* 2003; **147:** 670–2.

Precautions

Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular where ileus or constipation occur, and should be avoided in patients with abdominal distension, acute inflammatory bowel disease, or antibiotic-associated colitis. Loperamide should not be used alone in patients with dysentery.

Loperamide should be used with caution in patients with hepatic impairment because of its considerable first-pass metabolism in the liver. It should also be used with caution in young children because of a greater variability of response in this age group; it is not recommended for use in infants (see Uses and Administration, below).

Breast feeding. Loperamide is distributed into breast milk in small amounts.[1] The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of loperamide by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Nikodem VC, Hofmeyr GJ. Secretion of the antidiarrhoeal agent loperamide oxide in breast milk. *Eur J Clin Pharmacol* 1992; **42:** 695–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/01/06)

Interactions

Loperamide may increase the gastrointestinal absorption of desmopressin (p.2186).

Antifungals. A pharmacokinetic study in 12 healthy subjects found that *itraconazole* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Itraconazole also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of itraconazole with gemfibrozil (see Cardiovascular Drugs, below) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Antivirals. In a single-dose study,[1] oral *ritonavir* significantly increased the bioavailability of loperamide, possibly through inhibition of the cytochrome P450 isoenzyme CYP3A4, and not necessarily as originally supposed through P-glycoprotein inhibition. No serious adverse effects occurred. Licensed information for one UK preparation of loperamide (*Imodium; Janssen-Cilag, UK*) states that the clinical relevance of the pharmacokinetic interaction with P-glycoprotein inhibitors such as ritonavir is unknown.

For the effect of loperamide on *saquinavir*, and the corresponding effect of the antiviral on loperamide concentrations, see Gastrointestinal Drugs, under Interactions of Indinavir, p.884.

1. Tayrouz Y, *et al.* Ritonavir increases loperamide plasma concentrations without evidence for P-glycoprotein involvement. *Clin Pharmacol Ther* 2001; **70:** 405–14.

Cardiovascular drugs. A pharmacokinetic study in 12 healthy subjects found that *gemfibrozil* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Gemfibrozil also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of gemfibrozil with itraconazole (see Antifungals, above) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Co-trimoxazole. Use with co-trimoxazole increases the bioavailability of loperamide,[1] apparently by inhibiting its first-pass metabolism.

1. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; **41:** 125–8.

Quinidine. A small study[1] found that giving quinidine with loperamide caused respiratory depression in 8 healthy subjects; when given with placebo, loperamide produced no respiratory depression. The authors supposed that inhibition of P-glycoprotein by quinidine had increased entry of loperamide into the CNS.

1. Sadeque AJM, *et al.* Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin Pharmacol Ther* 2000; **68:** 231–7.

Pharmacokinetics

About 40% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract to undergo first-pass metabolism in the liver and excretion in the faeces via the bile as inactive conjugate; there is slight urinary excretion. Little intact drug reaches the systemic circulation. The elimination half-life is reported to be about 10 hours.

Metabolism. Loperamide is metabolised to desmethylloperamide through *N*-demethylation. An *in-vitro* study established that this occurs mainly via cytochrome P450 isoenzymes CYP2C8 and CYP3A4; CYP2B6 and CYP2D6 also play a role. Loperamide is also a substrate of P-glycoprotein.[1]

1. Kim K-A, *et al.* Identification of cytochrome P450 isoforms involved in the metabolism of loperamide in human liver microsomes. *Eur J Clin Pharmacol* 2004; **60:** 575–81.

Uses and Administration

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** the usual initial dose for adults is loperamide hydrochloride 4 mg followed by 2 mg after each loose stool to a maximum of 16 mg daily; the usual daily dose is 6 to 8 mg. In the UK, it is not licensed for children under 4 years of age. Suggested doses for older children are: 4 to 8 years, 1 mg three or four times daily for up to 3 days; 9 to 12 years, 2 mg four times daily for up to 5 days. In the USA, loperamide is not recommended for children under the age of 2 years and an initial dose of 1 mg three times daily is suggested for children aged 2 to 5 years. (For restrictions on the use of loperamide in children and the view that antidiarrhoeal drugs should not be used at all in children, see Diarrhoea, below.)

In **chronic diarrhoea** the usual initial dose for adults is 4 to 8 mg daily in divided doses subsequently adjusted as necessary; doses of 16 mg daily should not be exceeded. If no improvement has been seen after treatment with 16 mg daily for at least 10 days, further use is unlikely to be of benefit. Although not licensed for use in children for chronic diarrhoea, in the UK the *BNFC* allows for the following oral doses of loperamide hydrochloride:

- 1 month to 1 year: 100 to 200 micrograms/kg twice daily, given 30 minutes before feeds; up to a maximum of 2 mg/kg daily in divided doses may be required
- 1 to 12 years: 100 to 200 micrograms/kg (maximum dose 2 mg) three to four times daily; up to 1.25 mg/kg daily in divided doses may be required, to a maximum of 16 mg daily
- 12 to 18 years: 2 to 4 mg two to four times daily, to a maximum of 16 mg daily

Loperamide is also given as the prodrug, **loperamide oxide**, which is converted to loperamide in the gastrointestinal tract. It has been given for acute diarrhoea in doses of 2 to 4 mg initially followed by 1 mg after each loose stool, to a maximum of 8 mg daily.

Diarrhoea. The mainstay of treatment for acute diarrhoea (p.1694) is rehydration therapy. Antidiarrhoeals may have a role for symptomatic relief in adults with acute diarrhoea, and loperamide is often chosen in such circumstances,[1] but WHO does not recommend the use of *any* antidiarrhoeal drug in children with diarrhoea. Similarly, in the UK the *BNFC* considers that antimotility drugs are not to be recommended for acute diarrhoea in children under 12 years of age. There have been problems regarding the use of antidiarrhoeals such as loperamide in young children in developing countries. Manufacturers have considered that a lower age limit is acceptable in those countries than is recommended in the UK or USA; even that lower limit is not always observed in practice and there have been reports of serious toxicity in very young children.[2] In response to such reports the manufacturers withdrew concentrated drops of loperamide worldwide and the syrup from countries where the WHO had a programme for control of diarrhoeal diseases,[3] but tablets and capsules remain available. In some countries the use of antidiarrhoeals is now restricted by law.

In the UK, NICE states that loperamide is the antidiarrhoeal of first choice in adults with faecal incontinence;[4] it can be used long-term in doses from 500 micrograms to 16 mg daily as needed. Loperamide should be started at a very low dose which can be increased as needed, and then adjusted in response to stool consistency. It should not be given to those with hard or infrequent stools, those with acute diarrhoea of unknown cause, or with acute ulcerative colitis. Patients who are unable to tolerate loperamide may be offered codeine phosphate (p.37) or co-phenotrope (see Diphenoxylate Hydrochloride, p.1724).

For mention of the use of loperamide in the management of diarrhoea caused by chemotherapy, see p.640.

1. Wingate D, *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhoea. *Aliment Pharmacol Ther* 2001; **15:** 773–82.
2. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
3. Gussin RZ. Withdrawal of loperamide drops. *Lancet* 1990; **335:** 1603–4.
4. NICE. Faecal incontinence: the management of faecal incontinence in adults (issued June 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG49NICEGuidance.pdf (accessed 31/03/08)

PRODRUG THERAPY. References to the use of *loperamide oxide* in diarrhoea.

1. Van Den Eynden B, *et al.* New approaches to the treatment of patients with acute, nonspecific diarrhea: a comparison of the effects of loperamide and loperamide oxide. *Curr Ther Res* 1995; **56:** 1132–41.
2. Hughes IW, *et al.* First-line treatment in acute non-dysenteric diarrhoea: clinical comparison of loperamide oxide, loperamide and placebo. *Br J Clin Pract* 1995; **49:** 181–5.
3. van Outryve M, Toussaint J. Loperamide oxide for the treatment of chronic diarrhoea in Crohn's disease. *J Int Med Res* 1995; **23:** 335–41.
4. Sun WM, *et al.* Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol* 1997; **32:** 34–8.

Preparations

BP 2008: Loperamide Capsules;
USP 31: Loperamide Hydrochloride Capsules; Loperamide Hydrochloride Oral Solution; Loperamide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Colifilm; Contem; Custey; Dotalsec; Elcoman; Ionet; Lansek A; Lefa Enteril L; Minicam; Plexol; Plorinoc; Regulane; Salvaxil†; Suprasec; Viltar; ***Austral.:*** Chemists Own Diarrhoea Relief; Gastro-Stop; Harmonise; Imodium; Neogastro†; ***Austria:*** Enterobene; Imodium; Lopedium; Normakut; ***Belg.:*** Imodium; ***Braz.:*** Diafuran; Diarresec†; Diasec†; Imosec; Loperin; Magnostase; ***Canad.:*** Anti-Diarrheal; Diahalt†; Diarr-Eze; Diarrhoea Relief; Imodium; Loperacap; ***Chile:*** Capent; Coliper; Lopediar; ***Cz.:*** Dissenten; Imodium; Loperon; ***Denm.:*** Dialope; Imodium; Propiden; Travello†; ***Fin.:*** Imocur; Imodium; Lopex†; ***Fr.:*** Altocel†; Arestal; Diaretyl; Dyspagon; Ercestop; Imodium; Imodiumlingual; Imossel; Indiaral; Nabutil†; ***Ger.:*** Azuperamid†; Boxolip; duralopid; Endialop; Endiaron†; Imodium; Lop-Dia; Lopalind; Lopedium; Lopepham†; Lopera akut†; Loperhoe; ***Gr.:*** Imodium; Neo-Enteroseptol; ***Hong Kong:*** Colodium†; Diatabs Reformulated; Imodium; Imodonl; Loper; Loperamil; Loperax; Loperium; Lopermide†; Mar-Loper; Reximide; Synodium; Vacontil†; Vidaperamide; ***Hung.:*** Enterobene; Imodium; Lopedium; Loperacap; ***India:*** Diarlop; Lopamide; Roko; ***Indon.:*** Alphamid; Amerol; Antidia; Colidium; Diadium; Diasec; Imodium; Imomed; Imore; Imosa; Inamid; Lexadium; Lodia; Loremid; Motilex; Normotil; Normudal; Opox; Oramide; Primodium; Renamid; Xepare; Zeroform; ***Irl.:*** Arret; Diarrest RF; Imodium; ***Israel:*** Imodium; Loperid; Loperium; Rekamide; Shilshul X; Stopit; ***Ital.:*** Diarstop; Diarzero; Dissenten; Imodium; Lopemid; Ramidox†; Tebloc†; ***Malaysia:*** Beamodium; Diatrol†; Imocap†; Imodium; Imotab†; Loperax†; Loperium; Lopermide; Loramide; Miraton†; Vacontil; ***Mex.:*** Acanol; Acqta; Apo-Pera; Biolid†; Cryoperacid; Deroser; Dialacid†; Diaperol; Dilostop†; Exclefin; F9†; Hurplex; Imodium; Lomotil; Lop; Nodiamex; Permidal; Pramidal; Raxamida†; Rediarin; Top-Dal; Valfam; ***Neth.:*** Arestal; Diacure; Diarem; Imodium; Kruidvat Diarreeremmer; Trekpleister Diarreeremmer†; ***Norw.:*** Imodium; Travello; ***NZ:*** Diamide; Dicap; Imodium; Nodia; ***Philipp.:*** Diamide; Diaperyl; Diatabs (Reformulated); Imodium; Lormide; Tymedon; ***Pol.:*** Imodium; Laremid; Stoperan; ***Port.:*** Dyspagon; Fulcalrex; Imodium; Loprex; Loride; ***Rus.:*** Imodium (Имодиум); Lopedium (Лопедиум); ***S.Afr.:*** Betaperamide; Gastron; Imodium; Lenide-T; Lopedium; Loperastat; Norimode; Prodium; ***Singapore:*** Colodium†; IMD†; Imodium; Loperamil; Lopermide; Loramide†; Lorpa; Vacontil; ***Spain:*** Elissan; Fortasec; Imodium; Imosec†; Loperan; Loperkey; Protector; Salvacolina; Taguinol; ***Swed.:*** Dimor; Imodium; Primodium; Travello; ***Switz.:*** Binaldan; Imodium; Lopimed; Zorotop; ***Thai.:*** Diarent; Diarodil; Entermid; Imodium; Impelium; Lomide; Lomy†; Lopamine†; Lopela; Lopercin; Loperdium; Loperia; Lopermide; Operium†; Perasian; SBOB†; ***Turk.:*** Diadef; Lopermid; ***UK:*** Arret; Diah-Limit; Diaquitte; Diareze; Diocalm Ultra; Diocaps; Entrocalm; Imodium; Norimode; Normaloe; ***USA:*** Imodium; K-Pek II; Kao-Paverin; Kaopectate II†; Neo-Diaral; Pepto Diarrhea Control; ***Venez.:*** Glucitol; Imodium; Loperam; Mentaden†; Oldan†; Polonit†.

Multi-ingredient: ***Arg.:*** Neo Kef; Neomas L; Regulane AF; ***Austral.:*** Imodium Advanced; ***Austria:*** Imodium Plus; ***Belg.:*** Imodium Plus; ***Braz.:*** Imodium Plus†; ***Canad.:*** Imodium Advanced; ***Cz.:*** Imodium Plus; ***Denm.:*** Imodium med Simethicon; ***Fr.:*** Imodiumduo; ***Ger.:*** Imodium Plus; ***Hong Kong:*** Imodium Plus; ***Hung.:*** Imodium Komplett†; ***Mex.:*** Imodium Plus; ***NZ:*** Imodium Advanced; ***Pol.:*** Imodium Plus; ***Port.:*** Imodium Plus; ***S.Afr.:*** Imodium Plus; ***Spain:*** Imodium Plus; ***Switz.:*** Imodium Plus; ***Thai.:*** Imodium Plus; ***UK:*** Imodium Plus; ***USA:*** Imodium Advanced.

Loxiglumide *(rINN)*

CR-1505; CR-2017 (dexloxiglumide); Loxiglumida; Loxiglumidum. (±)-4-(3,4-Dichlorobenzamido)-*N*-(3-methoxypropyl)-*N*-pentylglutaramic acid.

Локсиглумид

$C_{21}H_{30}Cl_2N_2O_5$ = 461.4.

CAS — 107097-80-3 (loxiglumide); 119817-90-2 (dexloxiglumide).

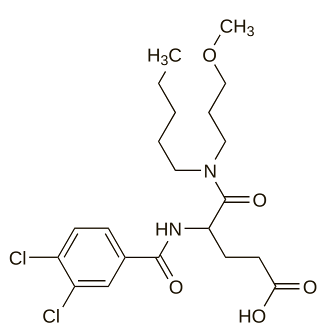

Profile

Loxiglumide is a specific cholecystokinin antagonist related to proglumide (see p.1764), and has been investigated in biliary and gastrointestinal dyskinesias, constipation and irritable bowel syndrome, and pancreatitis.

The *R*-isomer of loxiglumide, dexloxiglumide is also under investigation for constipation-predominant irritable bowel syndrome.

◊ References.

1. Shiratori K, *et al.* Clinical evaluation of oral administration of a cholecystokinin-A receptor antagonist (loxiglumide) to patients with acute, painful attacks of chronic pancreatitis: a multicenter dose-response study in Japan. *Pancreas* 2002; **25:** e1–e5.
2. Cremonini F, *et al.* Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005; **100:** 652–63.
3. Persiani S, *et al.* Pharmacokinetic profile of dexloxiglumide. *Clin Pharmacokinet* 2006; **45:** 1177–88.

Lubiprostone *(USAN, rINN)*

Lubiprostona; Lubiprostonum; RU-0211; SPI-0211. (−)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-Difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid.

Лубипростон

$C_{20}H_{32}F_2O_5$ = 390.5.

CAS — 136790-76-6; 333963-40-9.

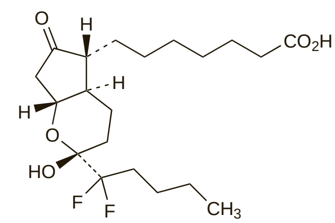

Adverse Effects and Precautions

The most common adverse effect of lubiprostone is nausea, which is dose-dependent and may be severe in some patients. Symptoms can be reduced by taking lubiprostone with food. Diarrhoea also occurs commonly, and other gastrointestinal effects include abdominal distension and pain, flatulence, and vomiting. Other reported adverse effects include headache, dizziness, fatigue, dyspnoea, and peripheral oedema. Chest discomfort, back pain, and arthralgia can occur.

Lubiprostone is contra-indicated in patients with a history of mechanical gastrointestinal obstruction.

Pharmacokinetics

A negligible amount of lubiprostone is absorbed systemically after an oral dose. It is rapidly and extensively metabolised by carbonyl reductase, probably in the stomach and jejunum.

Uses and Administration

Lubiprostone is a chloride-channel activator that acts locally in the gut to increase intestinal fluid secretion, which increases motility. It is used in the treatment of chronic idiopathic constipation (p.1693) in a dose of 24 micrograms twice daily, taken orally with food. It is also under investigation in the treatment of constipation-predominant irritable bowel syndrome.

◊ References.

1. McKeage K, *et al.* Lubiprostone. *Drugs* 2006; **66:** 873–9.
2. Anonymous. Lubiprostone (Amitiza) for chronic constipation. *Med Lett Drugs Ther* 2006; **48:** 47–8.
3. Ambizas EM, Ginzburg R. Lubiprostone: a chloride channel activator for treatment of chronic constipation. *Ann Pharmacother* 2007; **41:** 957–64.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Amitiza.

Magaldrate *(BAN, USAN, rINN)*

Aluminum Magnesium Hydroxide Sulfate; AY-5710; Magaldraatti; Magaldrát; Magaldrat; Magaldratas; Magaldrato; Magaldratum.

Магальдрат

$Al_5Mg_{10}(OH)_{31}(SO_4)_2,xH_2O$ = 1097.3 (anhydrous).

CAS — 74978-16-8.
ATC — A02AD02.
ATC Vet — QA02AD02.

NOTE. Magaldrate was formerly described as Aluminium Magnesium Hydroxide ($AlMg_2(OH)_7$ monohydrate, *CAS—1317-26-6*).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Magaldrate). A combination of aluminium and magnesium hydroxides (see p.1706 and p.1743 respectively) and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated with reference to the dried substance. A white or almost white crystalline powder. Practically insoluble in water and in alcohol; soluble in dilute mineral acids. It loses between 10 and 20% of its weight on drying at 200° for 4 hours.

USP 31 (Magaldrate). A combination of aluminium and magnesium hydroxides and sulfates. It contains the equivalent of 90 to

105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated on the dried basis. A white odourless crystalline powder. Insoluble in water and in alcohol; soluble in dilute solutions of mineral acids. It loses between 10 and 20% of its weight on drying at 200° for 4 hours.

Profile

Magaldrate is an antacid (see p.1692) that is given in oral doses of up to about 2 g.

Preparations

BP 2008: Magaldrate Oral Suspension;
USP 31: Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Magaldrate Oral Suspension; Magaldrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Riopan; ***Austria:*** Riopan; ***Belg.:*** Gastricalm; Riopan; ***Braz.:*** Riopan; ***Cz.:*** Marax†; ***Fr.:*** Riopan; ***Ger.:*** Gastripan; Gastrostad†; Glysan; Hevert-Mag; Magastron; Marax; Riopan; Simaphil; ***Gr.:*** Felfar; Riopan; ***Ital.:*** Gadral; Magaltop; Magralibi; Riopan; ***Pol.:*** Malugastrin; ***Port.:*** Riopan; ***Rus.:*** Magalphil (Магалфил); ***S.Afr.:*** Riopone; ***Spain:*** Bemolan; Gastromol; Magion; Minoton; ***Switz.:*** Riopan; ***USA:*** Iosopan; Riopan; ***Venez.:*** Cremag.

Multi-ingredient: ***Arg.:*** Aci-Tip; Carbogasol Antiacido†; ***Austral.:*** Mylanta Heartburn Relief†; ***Braz.:*** Riopan Plus; ***Chile:*** Aci-Tip†; Antiax; ***Hong Kong:*** Nilcid-MPS†; ***India:*** Maglid; pH4; Rolac Plus; Ulgel†; ***Indon.:*** Asidrat; Magalat; Nudramag; ***Mex.:*** Nilcid†; Riopan; ***Spain:*** Compagel†; ***Turk.:*** Asidopan Plus; Simelgat Plus; ***UK:*** Bisodol Extra; Bisodol Heartburn Relief; ***USA:*** Iosopan Plus; Lowsium Plus; Riopan Plus; ***Venez.:*** Cremalon.

Magnesium Carbonate

Bázisos magnézium-karbonát; E504; Magnesii Carbonas; Magnesii subcarbonas; Magnesio, carbonato de; Magnésium, carbonate de; Magnesiumsubkarbonaatti; Magnesiumsubkarbonat; Magnezu węglan; Magnezyum Karbonate; Magnio subkarbonatas; Uhličitan hořečnatý zásaditý.

Магния Карбонат

CAS — 546-93-0 (anhydrous magnesium carbonate); 23389-33-5 (hydrated normal magnesium carbonate); 39409-82-0 (hydrated basic magnesium carbonate).
ATC — A02AA01; A06AD01.
ATC Vet — QA02AA01; QA06AD01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US*, and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.
Ph. Eur. 6.2 (Magnesium Carbonate, Heavy; Magnesii Subcarbonas Ponderosus). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. 15 g has an apparent volume before settling of not more than 60 mL. Practically insoluble in water; dissolves in dilute acids with strong effervescence.
Ph. Eur. 6.2 (Magnesium Carbonate, Light; Magnesii Subcarbonas Levis). A hydrated basic magnesium carbonate containing the equivalent of 40 to 45% of MgO. A white or almost white powder. 15 g has an apparent volume before settling of at least 100 mL. Practically insoluble in water; dissolves in dilute acids with strong effervescence.
USP 31 (Magnesium Carbonate). A basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate containing the equivalent of 40.0 to 43.5% of MgO. It is an odourless, bulky white powder or light, white, friable masses. Practically insoluble in water; insoluble in alcohol; dissolves in dilute acids with effervescence.

Profile

Magnesium carbonate is an antacid with general properties similar to those of magnesium hydroxide (below) that is given in oral doses of up to about 500 mg. When given orally, it reacts with gastric acid to form soluble magnesium chloride and carbon dioxide in the stomach; the carbon dioxide may cause flatulence and eructation. Magnesium carbonate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium carbonate may be used as a magnesium supplement. It is also used as a food additive.

Preparations

BP 2008: Aromatic Magnesium Carbonate Mixture; Compound Magnesium Trisilicate Oral Powder; Kaolin Mixture; Magnesium Sulphate Mixture; Magnesium Trisilicate Mixture;
USP 31: Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Calcium and Magnesium Carbonates Oral Suspension; Calcium and Magnesium Carbonates Tablets; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Polvo Roge; ***Austria:*** Magnofit; ***Fr.:*** Mag 2; Mag 2 Junior; Sargemag; ***Ger.:*** Biolectra Magnesium 365; Palmicol; ***Gr.:*** Limonata Citromagnes; ***Hung.:*** Magnosolv; ***Ital.:*** Magnofit; ***Pol.:*** Additiva Magnesium; Magnezin; ***S.Afr.:*** Be-Lax; ***Switz.:*** Magnesium Nutrimed; ***USA:*** Mag-Carb.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Arg.:*** Bufferin†; Dristan Analgesico†; Dristan Compuesto; ***Braz.:*** Bufferin; Somalgin; ***Canad.:*** Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA; ***Ital.:*** Bufferin†; ***USA:*** Adprin-B; Bufferin; Buffex; Extra Strength Bayer Plus.

Magnesium Citrate

Magnesii citras; Magnesio, citrato de; Magnésium, citrate de.

Магний Цитрат

$C_{12}H_{10}Mg_3O_{14}$ = 451.1.
CAS — 3344-18-1.
ATC — A06AD19; A12CC04; B05CB03.
ATC Vet — QA06AD19; QA12CC04; QB05CB03.

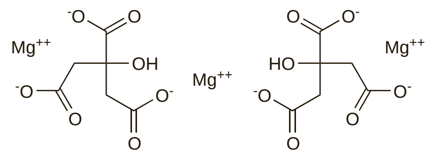

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Magnesium Citrate, Anhydrous). A white or almost white, fine, slightly hygroscopic powder. Soluble in water; practically insoluble in alcohol. It dissolves in dilute hydrochloric acid. Store in non-metallic, airtight containers.
USP 31 (Magnesium Citrate). A 5% suspension in water has a pH of 5.0 to 9.0. Store in airtight containers.

Profile

Magnesium citrate is an osmotic laxative (p.1693) used as a bowel evacuant before investigational procedures or surgery of the colon. Dosages have ranged from about 11 to 25 g of magnesium citrate. In the UK, an aqueous solution containing magnesium citrate is prepared from a sachet (*Citramag*) containing about 11.6 g of magnesium carbonate and about 17.8 g of anhydrous citric acid by mixing with 200 mL of hot water. After the solution has cooled, one dose (the contents of one sachet) is taken by mouth at 8 a.m. the day before the procedure, and a second dose between 2 and 4 p.m. For doses in children, see below. A high fluid intake and low residue diet are needed with such bowel preparations. Magnesium citrate is also used with sodium picosulfate, p.1771.

Magnesium citrate is given as a magnesium supplement in doses of up to about 1.9 g daily by mouth.

For the general properties of magnesium salts, see p.1678.

Administration in children. The *BNFC* recommends the following oral doses of magnesium citrate (*Citramag*) for use as a bowel cleanser in children, to be taken on the day before the procedure:

- 5 to 10 years: ⁄ of a sachet at 8 a.m. and ⁄ of a sachet between 2 and 4 p.m.
- 10 to 18 years: ⁄ to 1 sachet at 8 a.m. and ⁄ to 1 sachet between 2 and 4 p.m.

For reconstitution directions, see above.

Migraine. For mention of the use of magnesium supplementation, including magnesium citrate, for the prophylaxis of migraine, see p.1681.

Preparations

USP 31: Magnesium Citrate for Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Holomagnesio; Limonada Roge; ***Austral.:*** Mag Cit Prep†; ***Austria:*** Magnesium Diasporal; Magnofit; ***Belg.:*** Magnetop†; ***Canad.:*** Citro-Mag; Mag-Citrate; ***Cz.:*** Magnesium Diasporal†; Magnesol†; ***Ger.:*** Magnesium Diasporal; Magnesium Verla N; Presselin Heilozon P†; ***Hong Kong:*** Citro-Mag†; ***Hung.:*** Magnesium Diasporal†; ***Pol.:*** Magnesol; ***Switz.:*** Magnegon; Magnesium Biomed; Magnesium Diasporal; Magnesium-Sandoz; ***UK:*** Citramag; ***USA:*** Evac-Q-Mag.

Multi-ingredient: ***Arg.:*** Holomagnesio B6; Magnebe; Total Magnesiano B6; ***Austral.:*** Go Kit; Go Kit Plus†; ***Austria:*** Magnosolv; ***Belg.:*** Carbobel; ***Canad.:*** Royvac Kit; ***Chile:*** Laxogeno; ***Fr.:*** Citrocholine; Magne-B ; ***Ger.:*** Acidovert†; Lithurex S†; Magnerot N; ***Gr.:*** Magnesium Sandoz; ***Hung.:*** Beres Magnezium + B ; Magurlit†; Pregmag; ***Irl.:*** Picolax; ***Ital.:*** Pomag; ***Spain:*** Salmagne; ***UK:*** CitraFleet; Picolax.

Magnesium Hydroxide

E528; Hydroxid hořečnatý; Magnesii hydroxidum; Magnesio, hidróxido de; Magnesium Hydrate; Magnésium, hydroxyde de; Magnesiumhydroksidi; Magnesiumhydroxid; Magnézium-hidroxid; Magnezyum Hidroksit; Magnio hidroksidas.

Магния Гидроксид

$Mg(OH)_2$ = 58.32.
CAS — 1309-42-8.
ATC — A02AA04; G04BX01.
ATC Vet — QA02AA04; QG04BX01.

NOTE. Compounded preparations of magnesium hydroxide may be represented by the following names:

- Co-magaldrox *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of magnesium hydroxide and aluminium hydroxide respectively.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Magnesium Hydroxide). A fine white or almost white amorphous powder. Practically insoluble in water; dissolves in dilute acids. A solution in water is alkaline to phenolphthalein.
USP 31 (Magnesium Hydroxide). A bulky white powder. Practically insoluble in water, in alcohol, in chloroform, and in ether; soluble in dilute acids. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for magnesium salts in general, see p.1679. Magnesium hydroxide may cause diarrhoea, an effect that is dose-dependent. Hypermagnesaemia may occur, usually in patients with renal impairment.

Hypermagnesaemia. There have been reports of hypermagnesaemia in infants given magnesium-containing antacids,[1-3] and in an adult patient with normal renal function but bowel obstruction.[4]

1. Brand JM, Greer FR. Hypermagnesemia and intestinal perforation following antacid administration in a premature infant. *Pediatrics* 1990; **85:** 121–4.
2. Alison LH, Bulugahapitiya D. Laxative induced magnesium poisoning in a 6 week old infant. *BMJ* 1990; **300:** 125.
3. Sullivan JE, Berman BW. Hypermagnesemia with lethargy and hypotonia due to administration of magnesium hydroxide to a 4-week-old infant. *Arch Pediatr Adolesc Med* 2000; **154:** 1272–4.
4. Laughlin SA, McKinney PE. Antacid-induced hypermagnesemia in a patient with normal renal function and bowel obstruction. *Ann Pharmacother* 1998; **32:** 312–15.

Interactions

As outlined on p.1692, antacids, including magnesium salts, interact with many other drugs both by alterations in gastric pH and emptying, and by formation of complexes that are not absorbed. Interactions can be minimised by giving the antacid and any other medications 2 to 3 hours apart.

Pharmacokinetics

Magnesium hydroxide, given orally, reacts relatively rapidly with hydrochloric acid in the stomach to form magnesium chloride and water. About 30% of the magnesium ions are absorbed from the small intestine, as described for Magnesium Salts, p.1680.

Uses and Administration

Magnesium hydroxide is an antacid (see p.1692) that is given in oral doses of up to about 1 g. It is often given with aluminium-containing antacids such as aluminium hydroxide which counteract its laxative effect.

Magnesium hydroxide is also given as an osmotic laxative (p.1693) in oral doses of about 2 to 5 g.

Magnesium hydroxide has also been used as a food additive and as a magnesium supplement in deficiency states.

Preparations

BP 2008: Co-magaldrox Oral Suspension; Co-magaldrox Tablets; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Magnesium Hydroxide Mixture;
USP 31: Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Aspirin, Alumina, and Magnesia Tablets; Calcium Carbonate and Magnesia Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magnesia Tablets; Magnesium Hydroxide Paste; Milk of Magnesia.

Proprietary Preparations (details are given in Part 3)
Arg.: Leche de Magnesia Phillips; Magnesia San Pellegrino; ***Braz.:*** Leite de Magnesia de Phillips; Leite de Magnesia†; Magnesiol†; Mylanta Plus; ***Canad.:*** Milk of Magnesia; Phillips' Magnesia Tablets; Phillips' Milk of Magnesia; ***Chile:*** Leche de Magnesia Phillips; Magnesia Pasteur; Tabletas Antiacidas; ***Denm.:*** Magnesia; ***Fin.:*** Emgesan; Magnesiamaito; ***Fr.:*** Carbonex; Magnesie S Pellegrino†; ***Gr.:*** Milk of Magnesia; ***Hung.:*** Antagel M; ***India:*** Tricaine-MPS; ***Indon.:*** Laxasium; ***Irl.:*** Milk of Magnesia; ***Israel:*** Magnesia S Pellegrino; Milk of Magnesia; ***Ital.:*** Citrato Espresso S. Pellegrino; Magnesia S Pellegrino; Magnesia Volta†; ***Mex.:*** Leche de Magnesia Normex; ***Port.:*** Leite Magnesia Phillips; Magnesia San Pellegrino; ***S.Afr.:*** Babys own Tummy Tablets; Deopens†; ***Spain:*** Magnesia; Magnesia San Pellegrino; ***Swed.:*** Emgesan; ***Switz.:*** Magnesia S Pellegrino; ***Thai.:*** Milk of Magnesia; ***Turk.:*** Magcine; Magnesie Calcinee; Magnesium Naneli Lafar; Magnokal; ***UK:*** Milk of Magnesia; ***USA:*** Dulcolax; Milk of Magnesia; Pedia-Lax; Phillips' Chewable; Phillips' Milk of Magnesia; ***Venez.:*** Magnesia San Pellegrino.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Canad.:*** C2 with Codeine†; ***Denm.:*** Kodamid; Kodimagnyl; Magnyl; ***Gr.:*** Ascriptin†; ***Indon.:*** Naspro; Rheumapill; ***Israel:*** Ascriptin†; ***Ital.:*** Ascriptin; Aspirina 03; ***Mex.:*** Ascriptin; ***USA:*** Arthritis Pain Formula; Ascriptin; Asprimox; Cope; Magnaprin†; Vanquish; ***Venez.:*** Ascriptin.

Magnesium Oxide

E530; Magnesii oxidum; Magnesio, óxido de; Magnésium, oxyde de; Magnesiumoksidi; Magnesiumoxid; Magnezu tlenek; Magnezyum Oksit; Magnio oksidas; Nehéz magnézium; Oxid hořečnatý.

Магния Оксид

MgO = 40.30.

CAS — 1309-48-4.

ATC — A02AA02; A06AD02; A12CC10.

ATC Vet — QA02AA02; QA06AD02; QA12CC10.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some pharmacopoeias include a single monograph that permits both the light and heavy varieties while some have 2 separate monographs for the 2 varieties.

Ph. Eur. 6.2 (Magnesium Oxide, Heavy; Magnesii Oxidum Ponderosum). A fine, white or almost white powder. 15 g has an apparent volume before settling of not more than 60 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

Ph. Eur. 6.2 (Magnesium Oxide, Light; Magnesii Oxidum Leve). A fine, white or almost white, amorphous powder. 15 g has an apparent volume before settling of at least 100 mL. Practically insoluble in water; dissolves in dilute acids with at most slight effervescence.

USP 31 (Magnesium Oxide). A very bulky, white powder, or a relatively dense, white powder, or a granulated powder. Practically insoluble in water; insoluble in alcohol; soluble in dilute acids. Store in airtight containers.

Profile

Magnesium oxide is an antacid with general properties similar to those of magnesium hydroxide (above). It is given in usual oral doses of about 400 mg. It is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium oxide has been used for its osmotic laxative properties in bowel preparation; oral doses of 3.5 g are given for this purpose, combined with bisacodyl or sodium picosulfate.

Magnesium oxide is also used as a magnesium supplement in deficiency states in oral doses of up to 800 mg (20 mmol) daily. It is also used as a food additive.

Preparations

USP 31: Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aromatic Cascara Fluidextract; Aspirin, Alumina, and Magnesium Oxide Tablets; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Oxide Capsules; Magnesium Oxide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Magneforte†; Polvo Roge; SG 33; ***Austria:*** Magnonorm; Magnotab; ***Denm.:*** Salilax; ***Fr.:*** Mag 2 Junior; Magocean; Sargemag; Thalamag; ***Ger.:*** Biolectra Magnesium 240; Biolectra Magnesium 365; Magium; Magnesium Diasporal; Magnesium Tonil; Magnetrans extra; Magnetrans forte; Magno Sanol; ***Hung.:*** Magnosolv; ***NZ:*** Mylanta Effervescent†; ***S.Afr.:*** Solumag; ***Swed.:*** Salilax; ***Thai.:*** Magoral; ***Turk.:*** Magnezi Kalsine; ***USA:*** Mag-200; Mag-Caps; Mag-Ox; Maox; Uro-Mag.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Arg.:*** Aspirina; Bufferin†; ***Braz.:*** Bufferin; ***Canad.:*** Aspirin with Stomach Guard; Bufferin; Tri-Buffered ASA; ***Ital.:*** Bufferin†; ***Pol.:*** Aspimag; Cardiofil; ***USA:*** Adprin-B; Bufferin; Cama Arthritis Pain Reliever; Extra Strength Bayer Plus.

Magnesium Trisilicate

E553(a); Magnesii trisilicas; Magnesio, trisilicato de; Magnésium, trisilicate de; Magnesiumtrisilikaatti; Magnesiumtrisilikat; Magnézium-triszilikát; Magnezyum Trisilikat; Magnio trisilikatas; Trikřemičitan hořečnatý.

Магния Трисиликат

CAS — 14987-04-3 (anhydrous magnesium trisilicate); 39365-87-2 (magnesium trisilicate hydrate).

Description. Magnesium trisilicate is a hydrated magnesium silicate. The code E553(a) has been applied to both magnesium silicate and to magnesium trisilicate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *US,* and *Viet.*

Ph. Eur. 6.2 (Magnesium Trisilicate). It has a variable composition corresponding approximately to the formula $Mg_2Si_3O_8,xH_2O$ containing not less than 29% of magnesium oxide and not less than the equivalent of 65% of silicon dioxide, both calculated with reference to the ignited substance. A white or almost white powder. Practically insoluble in water and in alcohol.

USP 31 (Magnesium Trisilicate). A compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% of magnesium oxide and not less than 45% of silicon dioxide. A fine, white, odourless, powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids.

Profile

Magnesium trisilicate is a hydrated magnesium silicate. It is an antacid with general properties similar to those of magnesium hydroxide (p.1743). It may be given in typical oral doses of up to about 500 mg as required, although higher doses have been given.. When given orally it reacts more slowly with hydrochloric acid in the stomach than magnesium hydroxide. Magnesium trisilicate is often given with aluminium-containing antacids such as aluminium hydroxide, which counteract its laxative effect.

Magnesium trisilicate is also used as a food additive and as a pharmaceutical excipient.

Effects on the kidneys. The formation of renal calculi containing silica is unusual, but has been reported in a small number of patients. In most of these cases, stone formation was attributed to the prolonged, and sometimes excessive, intake of antacids that contained magnesium trisilicate.[1,2]

1. Haddad FS, Kouyoumdjian A. Silica stones in humans. *Urol Int* 1986; **41:** 70–6.
2. Lee M-H, *et al.* Silica stone—development due to long time oral trisilicate intake. *Scand J Urol Nephrol* 1993; **27:** 267–9.

Preparations

BP 2008: Compound Magnesium Trisilicate Oral Powder; Compound Magnesium Trisilicate Tablets; Magnesium Trisilicate Mixture;
USP 31: Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Magnesium Trisilicate Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Swed.:*** Deltison.

Manna

Maná; Manne en Larmes.

Манна

Profile

Manna is the dried exudation from the bark of the European flowering ash, *Fraxinus ornus* (Oleaceae), containing about 40 to 60% of mannitol (p.1330). It has been used as an osmotic laxative.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Naturland Grosser Swedenbitter†; ***Ger.:*** florabio Mann-Feigen-Sirup mit Senna†; florabio Manna-Feigen; Infi-tract†.

Mebeverine Hydrochloride *(BANM, USAN, rINNM)*

CSAG-144; Hidrocloruro de mebeverina; Mébévérine, chlorhydrate de; Mebeverini hydrochloridum. 4-[Ethyl(4-methoxy-α-methylphenethyl)amino]butyl veratrate hydrochloride.

Мебеверина Гидрохлорид

$C_{25}H_{35}NO_5,HCl$ = 466.0.

CAS — 3625-06-7 (mebeverine); 2753-45-9 (mebeverine hydrochloride).

ATC — A03AA04.

ATC Vet — QA03AA04.

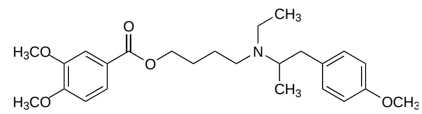

(mebeverine)

Pharmacopoeias. In *Br.*

BP 2008 (Mebeverine Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Adverse Effects and Precautions

Although adverse effects appear rare, gastrointestinal disturbances, dizziness, headache, insomnia, anorexia, and decreased heart rate have been reported in patients receiving mebeverine. Cases of hypersensitivity, including erythematous rash, urticaria, and angioedema, have also been reported. Mebeverine should be avoided in patients with paralytic ileus. Based on theoretical concerns, it should be used with care in patients with marked hepatic or renal impairment, and those with cardiac disorders such as heart block.

Cystic fibrosis. A 24-year-old man with cystic fibrosis, given mebeverine hydrochloride for lower abdominal pain and constipation, was found to have a perforated stercoral ulcer with generalised peritonitis.[1] It was suggested that mebeverine produced colonic stasis, which predisposed the patient to ulceration,[1] but the manufacturers[2] considered that the development of constipation and distal intestinal syndrome (meconium ileus equivalent) in this patient precipitated the development of stercoral ulceration. It was recommended[1] that antispasmodics such as mebeverine should not be used for the symptomatic treatment of distal intestinal syndrome in cystic fibrosis.

1. Hassan W, Keaney N. Mebeverine-induced perforated colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **335:** 1225.
2. Whitehead AM. Perforation of colon in distal intestinal syndrome of cystic fibrosis. *Lancet* 1990; **336:** 446.

Porphyria. Mebeverine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pharmacokinetics

Mebeverine is rapidly absorbed after oral doses with peak plasma concentrations occurring in 1 to 3 hours. It is 75% bound to albumin in plasma. Mebeverine is completely metabolised by hydrolysis to veratric acid and mebeverine alcohol, the latter of which may then be conjugated. The metabolites are excreted in the urine.

Uses and Administration

Mebeverine hydrochloride is an antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract. It is used in conditions such as irritable bowel syndrome (p.1699) in a usual oral dose of 135 mg three times daily before meals; 100 mg three times daily has also been used. A modified-release preparation is also available, taken as 200 mg twice daily. The embonate is also used for oral liquid preparations in a dose equivalent to 150 mg of the hydrochloride three times daily. The *BNFC* suggests that the following hydrochloride-equivalent doses may be given three times daily, based on age:

- 25 mg for those aged 3 to 4 years
- 50 mg for those 4 to 8 years
- 100 mg for those 8 to 10 years
- 135 to 150 mg for those over 10 years

Preparations

BP 2008: Mebeverine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Duspatalin; ***Austral.:*** Colese; Colofac; ***Austria:*** Colofac; ***Belg.:*** Duspatalin; Spasmonal†; ***Braz.:*** Duspatalin; ***Chile:*** Doloverina; Duspatal; Evadol; Meditoina; ***Cz.:*** Duspatalin; ***Denm.:*** Duspatalin; ***Fr.:*** Colopriv; Duspatalin; Spasmopriv; ***Ger.:*** Duspatal; Mebemerck; ***Gr.:*** Duspatalin; Gastromins†; ***Hong Kong:*** Duspatalin; ***Hung.:*** Duspatalin; ***India:*** Colospa; ***Indon.:*** Duspatalin; Irbosyd; ***Irl.:*** Colofac; ***Israel:*** Colotal; ***Ital.:*** Duspatal; ***Malaysia:*** Duspatalin; Lezpain; Mebetin; ***Mex.:*** Arluy; ***Neth.:*** Duspatal; ***NZ:*** Colofac; ***Philipp.:*** Duspatalin; ***Pol.:*** Duspatalin; ***Port.:*** Duspatal; ***Rus.:*** Duspatalin (Дюспаталин); ***S.Afr.:*** Bevispas; Colofac; ***Singapore:*** Duspatalin; Mebetin; ***Spain:*** Duspatalin; ***Switz.:*** Duspatalin; ***Thai.:*** Colofac; Duspatin; Menosor; ***Turk.:*** Duspatalin; Duspaverin; ***UK:*** Colofac; Equilon†; IBS Relief†.

Multi-ingredient: ***Hong Kong:*** Fybogel Mebeverine†; ***Irl.:*** Fybogel Mebeverine; ***UK:*** Fybogel Mebeverine.

Mecloxamine Citrate *(rINNM)*

Citrato de mecloxamina; Mécloxamine, Citrate de; Mecloxamini Citras. 2-[1-(4-Chlorophenyl)-1-phenylethoxy]-*N,N*-dimethyl-1-propanamine citrate.

Меклоксамина Цитрат

$C_{19}H_{24}ClNO,C_6H_8O_7$ = 510.0.

CAS — 5668-06-4 (mecloxamine); 56050-03-4 (mecloxamine citrate).

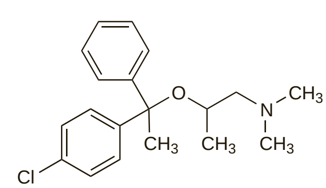

(mecloxamine)

Profile

Mecloxamine citrate is reported to have antimuscarinic properties and has been used for its antiemetic action in antimigraine preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Avamigran; ***Turk.:*** Avmigran.

Mepenzolate Bromide *(BAN, rINN)*

Bromuro de mepenzolato; Mepentsolaattibromidi; Mepenzolatbromid; Mépenzolate, Bromure de; Mepenzolate Methylbromide; Mepenzolati Bromidum; Mepenzolone Bromide. 3-Benziloyloxy-1,1-dimethylpiperidinium bromide.

Мепензолата Бромид

$C_{21}H_{26}BrNO_3$ = 420.3.

CAS — 25990-43-6 (mepenzolate); 76-90-4 (mepenzolate bromide).

ATC — A03AB12.

ATC Vet — QA03AB12.

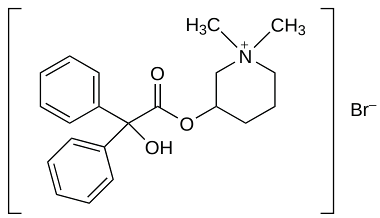

Pharmacopoeias. In *Jpn.*

Profile

Mepenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been used in the relief of gastrointestinal disorders associated with smooth muscle spasm and as an adjunct in the treatment of peptic ulcer disease. Up to 200 mg daily may be given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Trancolon†; ***Swed.:*** Cantil†; ***USA:*** Cantil.

Multi-ingredient: ***Jpn:*** Trancolon P†.

Mesalazine *(BAN, rINN)*

5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalamine *(USAN)*; Mesalatsiini; Mesalazin; Mesalazina; Mesalazinas; Mésalazine; Mesalazinum. 5-Amino-2-salicylic acid.

Месалазин

$C_7H_7NO_3$ = 153.1.

CAS — 89-57-6.

ATC — A07EC02.

ATC Vet — QA07EC02.

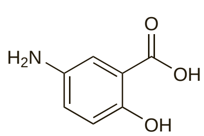

NOTE. Distinguish from 4-aminosalicylic acid (Aminosalicylic Acid, p.201) which is used in the treatment of tuberculosis.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mesalazine). An almost white or light grey or light pink powder or crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. Store in airtight containers. Protect from light.

USP 31 (Mesalamine). Light tan to pink needle-shaped crystals, odourless or with a slight characteristic odour. The colour may darken on exposure to air. Slightly soluble in water; very slightly soluble in dehydrated alcohol, in acetone, and in methyl alcohol; practically insoluble in butyl alcohol, in chloroform, in dichloromethane, in ether, in ethyl acetate, in *n*-hexane, and in propyl alcohol; soluble in dilute hydrochloric acid and in dilute alkali hydroxides. A 2.5% suspension in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Mesalazine may cause headache and gastrointestinal disturbances, such as nausea, diarrhoea, and abdominal pain. Hypersensitivity reactions may occasionally occur. Some patients may experience exacerbation of symptoms of colitis. There are some reports of myocarditis, pericarditis, pancreatitis, interstitial nephritis, nephrotic syndrome, allergic lung reaction, increased liver enzyme values, hepatitis, lupus-like syndrome, skin reactions, alopecia, peripheral neuropathy, myalgia, and arthralgia. There have been rare reports of blood disorders including aplastic anaemia, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, and methaemoglobinaemia.

Mesalazine should not be given to patients with severe renal or hepatic impairment, or salicylate hypersensitivity. It should be used with caution in the elderly, and in mild to moderate renal or hepatic impairment, active peptic ulceration, or sulfasalazine allergy.

If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. It is recommended that renal function is monitored before and during therapy (see Effects on the Kidneys, below).

◊ Many of the adverse effects associated with sulfasalazine (sulfapyridine linked to mesalazine) therapy have been attributed to the sulfapyridine moiety and most patients unable to tolerate sulfasalazine because of hypersensitivity or adverse reactions can be transferred to mesalazine without adverse effects occurring.[1-4] However, a small number of patients also have adverse effects while taking mesalazine and these are often very similar to those seen with sulfasalazine.[1-4] They may include nausea, abdominal discomfort or pain, exacerbation of diarrhoea, headache, fever, and rashes. Mesalazine is not generally associated with sulfasalazine's adverse effects on sperm (although there has been a case of reversible male infertility attributed to mesalazine—see under Sulfasalazine, p.1774). An analysis of adverse reactions reported to the UK CSM between 1991 and 1998 found no evidence of a significant difference in the frequency of serious adverse effects for mesalazine and sulfasalazine in the treatment of inflammatory bowel disease.[5] Reports of pancreatitis and interstitial nephritis (see Effects on the Kidneys, below), were more common with mesalazine. However, it has been pointed out that 80% of patients intolerant to sulfasalazine will tolerate mesalazine without problems.[6]

Mesalazine therapy should be started cautiously in patients with a history of sulfasalazine **hypersensitivity** and it should be withdrawn if signs of sensitivity develop or if there is diarrhoea or rectal bleeding. It has been suggested[2] that patients with a history of sulfasalazine hypersensitivity should be given test doses of mesalazine before starting a full course.

1. Dew MJ, *et al.* Treatment of ulcerative colitis with oral 5-aminosalicylic acid in patients unable to take sulphasalazine. *Lancet* 1983; **ii:** 801.
2. Campieri M, *et al.* 5-Aminosalicylic acid as rectal enema in ulcerative colitis patients unable to take sulphasalazine. *Lancet* 1984; **i:** 403.
3. Donald IP, Wilkinson SP. The value of 5-aminosalicylic acid in inflammatory bowel disease for patients intolerant or allergic to sulphasalazine. *Postgrad Med J* 1985; **61:** 1047–8.
4. Rao SS, *et al.* Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. *Scand J Gastroenterol* 1987; **22:** 332–6.
5. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; **51:** 536–9.
6. D'Haens G, van Bodegraven AA. Mesalazine is safe for the treatment of IBD. *Gut* 2004; **53:** 155.

Breast feeding. The concentrations of mesalazine in maternal plasma and breast milk in a woman taking 500 mg three times daily, were 410 and 110 nanograms/mL respectively.[1] Although it was considered that the amount of mesalazine distributed into breast milk was small and that it was safe during breast feeding,[2,3] maternal use of mesalazine 500 mg suppositories twice daily has been associated with watery diarrhoea in a breast-fed infant[2] and for this reason the American Academy of Pediatrics considers that mesalazine should be given with caution to breast-feeding mothers.[4]

1. Jenss H, *et al.* 5-Aminosalicylic acid and its metabolite in breast milk during lactation. *Am J Gastroenterol* 1990; **85:** 331.
2. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989; **i:** 383.
3. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. *Lancet* 1993; **342:** 618–19.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/02/06)

Effects on the blood. Although uncommon, mesalazine-associated adverse effects on the blood have been reported, including thrombocytopenia,[1,2] neutropenia,[3] severe aplastic anaemia,[4,5] and pancytopenia.[6] In July 1995 the UK CSM stated that it had been notified of 49 haematological reactions suspected of being associated with mesalazine,[7] including 5 reports of aplastic anaemia, 1 of agranulocytosis, 11 of leucopenia, and 17 of thrombocytopenia. There had been 3 fatalities. They recommended a blood count and immediate withdrawal of the drug if a dyscrasia was suspected. Intensive immunosuppressive treatment has been used in the management of mesalazine-associated aplastic anaemia.[5,8]

1. Daneshmend TK. Mesalazine-associated thrombocytopenia. *Lancet* 1991; **337:** 1297–8.
2. Farrell RJ, *et al.* Mesalamine-associated thrombocytopenia. *Am J Gastroenterol* 1999; **94:** 2304–6.
3. Wyatt S, *et al.* Filgrastim for mesalazine-associated neutropenia. *Lancet* 1993; **341:** 1476.
4. Abboudi ZH, *et al.* Fatal aplastic anaemia after mesalazine. *Lancet* 1994; **343:** 542.
5. Otsubo H, *et al.* Mesalazine-associated severe aplastic anemia successfully treated with antithymocyte globulin, cyclosporine and granulocyte colony-stimulating factor. *Int J Hematol* 1998; **68:** 445–8.
6. Kotanagi H, *et al.* Pancytopenia associated with 5-aminosalicylic acid use in a patient with Crohn's disease. *J Gastroenterol* 1998; **33:** 571–4.
7. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)
8. Laidlaw ST, Reilly JT. Antilymphocyte globulin for mesalazine-associated aplastic anaemia. *Lancet* 1994; **343:** 981–2.

Effects on the cardiovascular system. Myocarditis associated with chest pain and ECG abnormalities has been reported[1,2] in 2 patients taking mesalazine; 1 patient died in cardiogenic shock.[2] It has been suggested that mesalazine or sulfasalazine should be replaced by glucocorticoids if cardiac symptoms arise during treatment.[2] Pericarditis[3,4] with fever, rash, dyspnoea, pleural and pericardial effusions, and arthritis, has been described, and is considered to constitute a drug-induced lupus-like syndrome. Constrictive pericarditis with an absence of other lupus-like symptoms developed in a patient taking mesalazine for inflammatory bowel disease.[5] Based on reported cases of mesalazine-induced pericarditis, symptoms of this potentially life-threatening adverse effect have tended to arise 2 to 4 weeks after starting mesalazine, although symptom onset may be delayed by concurrent corticosteroid treatment.[6] Mesalazine cardiotoxicity presenting as an acute coronary syndrome, without myocarditis or pericarditis, has also been reported.[7]

1. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
2. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.
3. Dent MT, *et al.* Mesalazine induced lupus-like syndrome. *BMJ* 1992; **305:** 159.
4. Lim AG, Hine KR. Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994; **308:** 113.
5. Oxentenko AS, *et al.* Constrictive pericarditis in chronic ulcerative colitis. *J Clin Gastroenterol* 2002; **34:** 247–51.
6. Waite RA, Malinowski JM. Possible mesalamine-induced pericarditis: case report and literature review. *Pharmacotherapy* 2002; **22:** 391–4.
7. Amin HE, *et al.* Mesalamine-induced chest pain: a case report. *Can J Cardiol* 2000; **16:** 667–9.

Effects on fertility. For a report of reversible male infertility occurring with mesalazine, see under Sulfasalazine, p.1774.

Effects on the hair. For a report of accelerated loss of scalp hair in 2 patients receiving mesalazine enemas, see under Sulfasalazine, p.1774.

Effects on the kidneys. Between February 1988 and December 1990 the UK CSM[1] received 9 reports of serious nephrotoxic reactions associated with the use of *Asacol*, a modified-release mesalazine preparation. The reactions included 4 cases of interstitial nephritis, 3 of severe renal failure, and 2 cases of nephrotic syndrome. A subsequent case report[2] indicated that by September 1998 the number of such reports for mesalazine totalled 104, including 35 cases of interstitial nephritis. The authors considered that monitoring of renal function was required in patients receiving mesalazine. A protocol for such monitoring was subsequently suggested,[3] and a similar protocol has been adopted in UK licensing information for mesalazine, with serum creatinine being estimated:

- before treatment
- every 3 months for the first year
- every 6 months for the next 4 years
- annually thereafter

The nephrotic syndrome[4] and interstitial nephritis[5] have also been reported with sulfasalazine, and interstitial nephritis with olsalazine (see p.1752). A large UK epidemiologic study found no difference in risk of renal disease between mesalazine and sulfasalazine. The study also concluded that the risk of renal disease associated with mesalazine and related compounds is low and may be partly attributable to the underlying disease.[6] Overall nephrotoxicity has been estimated to occur in about 1 in 4000 UK patients per year taking aminosalicylate-based therapy.[7]

1. Committee on Safety of Medicines. Nephrotoxicity associated with mesalazine (Asacol). *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Popoola J, *et al.* Late onset interstitial nephritis associated with mesalazine treatment. *BMJ* 1998; **317:** 795–7.
3. Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14:** 1–6.
4. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. *BMJ* 1990; **301:** 818.
5. Dwarakanath AD, *et al.* Sulphasalazine induced renal failure. *Gut* 1992; **33:** 1006–1007.

6. Van Staa TP, *et al.* 5-Aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004; **126:** 1733–9.
7. Muller AF, *et al.* Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005; **21:** 1217–24.

Effects on the liver. A case of chronic hepatitis and liver fibrosis has been reported after prolonged use of mesalazine.[1] The authors considered that mesalazine should be stopped when liver dysfunction occurred.

1. Deltenre P, *et al.* Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. *Gut* 1999; **44:** 886–8.

Effects on the nervous system. Peripheral neuropathy,[1] mainly affecting the legs, has occurred during mesalazine treatment. The symptoms resolved on stopping the drug. Mononeuritis multiplex was part of the presentation of an eosinophilic reaction attributed to mesalazine in an asthmatic patient;[2] Churg-Strauss syndrome developed after withdrawal of mesalazine, but the patient subsequently recovered without sequelae.

1. Woodward DK. Peripheral neuropathy and mesalazine. *BMJ* 1989; **299:** 1224.
2. Morice AH, *et al.* Mesalazine activation of eosinophil. *Lancet* 1997; **350:** 1105.

Effects on the pancreas. Pancreatitis has been reported as an adverse effect of mesalazine.[1-4] In 2 patients,[1,2] with abdominal pain and raised amylase activity, this reaction to mesalazine was confirmed by rechallenge and symptoms resolved on mesalazine withdrawal. By February 1994 the UK CSM had received 15 reports[3] of pancreatitis associated with mesalazine therapy. However, a case control study suggested that inflammatory bowel disease, rather than the use of mesalazine, may be associated with an increased risk of acute pancreatitis (see under Sulfasalazine, p.1774)

1. Sachedina B, *et al.* Acute pancreatitis due to 5-aminosalicylate. *Ann Intern Med* 1989; **110:** 490–2.
2. Deprez P, *et al.* Pancreatitis induced by 5-aminosalicylic acid. *Lancet* 1989; **ii:** 445–6.
3. Committee on Safety of Medicines. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
4. Adachi E, *et al.* Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. *Int J Pancreatol* 1999; **25:** 217–21.

Effects on the respiratory system. Pulmonary complications have been rarely reported with mesalazine. There have though been cases of interstitial lung disease, with features of hypersensitivity pneumonia.[1] Symptoms have included dyspnoea, cough, fever, and pleuritic chest pain, with the onset of symptoms varying from a few days to several years after starting mesalazine therapy. Although pulmonary complications can also be associated with inflammatory bowel disease itself, there has been a report[2] of eosinophilic pleural effusion in a patient who was given mesalazine in the absence of an established diagnosis of inflammatory bowel disease.

Pulmonary complications have also been reported with sulfasalazine (p.1774), and pulmonary symptoms may also manifest as part of a broader lupus-like syndrome (see Effects on the Cardiovascular System, above).

1. Foster RA, *et al.* Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. *Inflamm Bowel Dis* 2003; **9:** 308–15.
2. Trisolini R, *et al.* Eosinophilic pleural effusion due to mesalamine: report of a rare occurrence. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; **17:** 288–91.

Lupus. A lupus-like syndrome has been reported in 4 patients receiving mesalazine who developed antinuclear antibody (ANA)-positivity with at least one clinical feature of lupus, such as arthropathy, skin rashes, or acute inflammation unrelated to the underlying condition.[1] In all 4 cases symptoms resolved upon stopping mesalazine. For similar reports, see Effects on the Cardiovascular System, above.

1. Kirkpatrick AW, *et al.* Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. *Can J Gastroenterol* 1999; **13:** 159–62.

Pregnancy. Renal insufficiency in a neonate whose mother received mesalazine 2 to 4 g daily by mouth during the second trimester of pregnancy was suggested to be due to the drug,[1] although the proposed mechanism, inhibition of prostaglandin synthesis in the neonatal kidney, has been questioned.[2] A subsequent case-control study[3] found that use of oral mesalazine in 165 pregnant women with inflammatory bowel disease was not associated with a greater incidence of malformations. However, women treated with mesalazine were more likely to have preterm deliveries and newborns with decreased birth-weights, although the disease may have been a factor in this finding. A commentator on this study,[4] considered that active inflammatory bowel disease was a greater risk to pregnancy than drug treatment. In a further cohort of 123 pregnancies,[5] oral mesalazine at doses of 3 g daily or less did not increase the risk of fetal malformations or affect pregnancy outcome. The researchers concluded that further information was required on doses higher than 3 g daily. In another study,[6] all of 19 pregnancies in women receiving rectal mesalazine were full-term with no fetal abnormalities. A Danish cohort study[7] found an increased risk of still-birth and preterm birth in women who had been prescribed mesalazine or olsalazine during pregnancy, but no significant increased risk of malformations. The risk of still-birth was greatest in women with ulcerative colitis who were prescribed corticosteroids and either mesalazine or olsalazine, and the risk of preterm birth was greatest in women with ulcerative colitis who were prescribed either mesalazine or olsalazine alone. The authors acknowledged that it was difficult to distinguish between the increase in risk due to disease state, and the increase in risk due to medication.[7] For a discussion of sulfasalazine in pregnancy, see p.1774.

1. Colombel J-F, *et al.* Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? *Lancet* 1994; **344:** 620–1.
2. Marteau P, Devaux CB. Mesalazine during pregnancy. *Lancet* 1994; **344:** 1708–9.
3. Diav-Citrin O, *et al.* The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; **114:** 23–8.
4. Sachar D. Exposure to mesalamine during pregnancy increased preterm deliveries (but not birth defects) and decreased birth weight. *Gut* 1998; **43:** 316.
5. Marteau P, *et al.* Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; **12:** 1101–8.
6. Bell CM, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* 1997; **92:** 2201–2.
7. Nørgård B, *et al.* Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; **52:** 243–7.

Interactions

Preparations formulated to release mesalazine in the colon should not be given with drugs, such as lactulose, that lower colonic pH as they may prevent the release of mesalazine (but see Gastrointestinal Drugs below).

Anticoagulants. For reference to a case of mesalazine reducing the effect of *warfarin*, see Gastrointestinal Drugs, p.1430.

Antineoplastics. For mention of 5-aminosalicylates such as mesalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Mercaptopurine, p.744.

Gastrointestinal drugs. Although it has been suggested that *lactulose* could delay the intestinal release of mesalazine from modified-release preparations, a study found no evidence that lactulose influenced the release or disposition of mesalazine.[1] Similarly, *omeprazole* did not appear to increase the likelihood of premature mesalazine release.

1. Hussain FN, *et al.* Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* 1998; **46:** 173–5.

Pharmacokinetics

If given orally as conventional formulations, mesalazine would be extensively absorbed from the upper gastrointestinal tract, with little of the drug reaching the colon. Oral preparations are therefore generally formulated to release the drug in the terminal ileum and colon, where it is thought to exert a mainly local action. The specific release characteristics differ somewhat between formulations and this, together with interindividual variation, makes comparison of pharmacokinetic data between studies difficult. Even with modified-release preparations some 30 to 50% of an oral dose is thought to be lost to absorption in healthy subjects. Absorption from rectal dosage forms has also varied widely, with factors such as the dose, the formulation, and the pH also playing a role, but mean absorption of around 10 to 30% of a rectal dose has been reported.

The absorbed portion of mesalazine is almost completely acetylated in the gut wall and in the liver to acetyl-5-aminosalicylic acid. The rate of acetylation, and hence the concentration of parent drug and metabolite in the systemic circulation, may be dose dependent and subject to saturation. The acetylated metabolite is excreted mainly in urine by tubular secretion, with traces of the parent compound.

The plasma half-life of mesalazine is reported to be about 40 minutes and it is 40 to 50% bound to plasma proteins; the acetylated metabolite has a plasma half-life of 70 minutes and is about 80% bound to plasma proteins.

Only negligible quantities of mesalazine cross the placenta. Amounts distributed into breast milk are very small.

◊ Reviews.

1. De Vos M. Clinical pharmacokinetics of slow release mesalazine. *Clin Pharmacokinet* 2000; **39:** 85–97.
2. Sandborn WJ, *et al.* Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003; **17:** 29–42.

Uses and Administration

Mesalazine is an anti-inflammatory drug structurally related to the salicylates and active in inflammatory bowel disease (p.1697); it is considered to be the active moiety of sulfasalazine (p.1773). Mesalazine is thought to act locally on the inflamed intestinal tissue, rather than systemically. Although its precise mechanism of action is uncertain, it may be due to inhibition of prostaglandin and leukotriene synthesis in the gastrointestinal mucosa.

Mesalazine is given orally or rectally in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis. Some products are also used for the *maintenance of remission* of Crohn's ileo-colitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. Recommended doses for some UK preparations are as follows:

- *Asacol 400 mg* tablets (*Procter and Gamble, UK*), *Ipocol* tablets (*Sandoz, UK*), *Mesren* tablets (*IVAX, UK*): acute attack, initially 2.4 g daily in divided doses; maintenance of remission, 1.2 to 2.4 g daily in divided doses. The *BNFC* includes similar doses for children aged 12 to 18 years
- *Asacol 800 mg* tablets (*Procter and Gamble, UK*): mild acute exacerbations, 2.4 g daily in divided doses; moderate acute exacerbations, 4.8 g daily in divided doses; maintenance of remission, up to 2.4 g daily in divided doses
- *Mezavant* tablets (*Shire, UK*): acute attack, initially 2.4 to 4.8 g once daily; maintenance of remission, 2.4 g once daily
- *Pentasa* tablets (*Ferring, UK*): acute attack, initially up to 4 g daily in 2 or 3 divided doses; maintenance of remission, adjusted individually from an initial dose of 1.5 g daily in 2 or 3 divided doses. The *BNFC* includes the same doses for children aged 15 to 18 years. For children aged 5 to 15 years: acute attack, 15 to 20 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 10 mg/kg (maximum 500 mg) 2 or 3 times daily
- *Pentasa* granules (*Ferring, UK*): acute attack, initially, up to 4 g daily in 2 to 4 divided doses; maintenance of remission, 2 g daily in 2 divided doses. The *BNFC* includes the same dose for acute attack in children aged 12 to 18 years, and 0.5 to 1 g twice daily for maintenance of remission. For children aged 5 to 12 years: acute attack, 15 to 20 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 10 mg/kg (maximum 500 mg) 2 or 3 times daily
- *Salofalk* tablets (*Falk, UK*): acute attack, initially 1.5 g daily in 3 divided doses; maintenance of remission, 0.75 to 1.5 g daily in divided doses. The *BNFC* includes the same dose for acute attack in children aged 12 to 18 years, and 250 to 500 mg given 2 or 3 times daily for maintenance of remission
- *Salofalk* granules (*Falk, UK*): acute attack, initially 1.5 to 3 g daily, either once daily, or in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses. The *BNFC* includes similar doses for children aged 12 to 18 years. For children aged 6 to 12 years: acute attack, 10 to 15 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 7.5 to 15 mg/kg (maximum 500 mg) twice daily (or 250 mg given 3 times daily for those weighing less than 40 kg)

Mesalazine may be given rectally, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. Recommended doses for some UK preparations are as follows (the *BNFC* also suggests that these doses are suitable for children aged 12 to 18 years):

- *Asacol* suppositories (*Procter and Gamble, UK*): 0.75 to 1.5 g daily in divided doses
- *Asacol* foam enema (*Procter and Gamble, UK*): 1 g daily for disease affecting the rectosigmoid region; 2 g daily for disease involving the descending colon
- *Pentasa* suppositories and suspension enema (*Ferring, UK*): 1 g daily
- *Salofalk* suppositories (*Falk, UK*): 0.5 to 1 g given 2 or 3 times daily
- *Salofalk* foam enema and suspension enema (*Falk, UK*): 2 g daily

Similar preparations are available in other countries, and in the USA a suspension enema containing 4 g of mesalazine has been used.

◊ References.

1. Clemett D, Markham A. Prolonged-release mesalazine: a review of its therapeutic potential in ulcerative colitis and Crohn's disease. *Drugs* 2000; **59:** 929–56.
2. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2:** 379–88.
3. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 01/06/07).
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
6. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **23:** 841–55.
7. van Bodegraven AA, Mulder CJ. Indications for 5-aminosalicylate in inflammatory bowel disease: is the body of evidence complete? *World J Gastroenterol* 2006; **12:** 6115–23.
8. Anonymous. Once-daily mesalamine (Lialda) for ulcerative colitis. *Med Lett Drugs Ther* 2007; **49:** 25–6.
9. McCormack PL, *et al.* Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs* 2007; **67:** 2635–42.
10. Kale-Pradhan PB, *et al.* Multi-Matrix System Mesalamine: to use or not to use. *Ann Pharmacother* 2008; **42:** 265–9.

Administration. Because the release characteristics of different formulations of mesalazine vary, they should not be regarded as interchangeable.[1] This applies even to those formulations where the dosage is apparently similar.[2] However, a study established that an oral once-daily regimen was bioequivalent to a twice-daily regimen of the same product (*Pentasa (Ferring, France)*).[3]

1. Forbes A, Chadwick C. Mesalazine preparations. *Lancet* 1997; **350:** 1329.
2. Benbow AG, Gould I. Mesalazine preparations. *Lancet* 1998; **351:** 68.
3. Gandia P, *et al.* Is once-daily mesalazine equivalent to the currently used twice-daily regimen? A study performed in 30 healthy volunteers. *J Clin Pharmacol* 2007; **47:** 334–42.

Diverticular disease. In a study involving 218 patients with a history of recurrent attacks of acute diverticulitis (p.1695), half were assigned to treatment with oral rifaximin 400 mg twice daily for 7 days, and half received rifaximin plus a modified-release formulation of mesalazine 800 mg three times daily, again for 7 days. Courses were then repeated, with rifaximin at the same dose and mesalazine at 800 mg twice daily, for 7 days in each month, and patients followed for 12 months. The combination of rifaximin and mesalazine was significantly more effective in reducing symptomatic episodes and normalisation of bowel habit than rifaximin alone: 89 of 107 patients given the combination were symptom-free at 12 months, compared with 44 of 105 given just the antibacterial.[1] Similarly, the same group found that in patients with uncomplicated diverticular disease given 10 days of treatment with rifaximin and mesalazine (*Pentacol; Sofar, Ital.*) in the doses above, followed by mesalazine 1.6 g daily for 8 weeks, 70 of 86 completing the study were completely asymptomatic, suggesting that daily mesalazine alone was an effective maintenance therapy, although longer-term studies were needed.[2] Mesalazine has also been investigated in combination with a probiotic preparation of lactic-acid-producing organisms.[3]

1. Tursi A, *et al.* Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 2002; **34:** 510–15.
2. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit* 2004; **10:** PI70–PI73.
3. Tursi A, *et al.* Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol* 2006; **40:** 312–16.

Preparations

USP 31: Mesalamine Delayed-Release Tablets; Mesalamine Extended-Release Capsules; Mesalamine Rectal Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Bufexan; Pentasa; Salofalk; Suprimal; Xalazina; Yolecol; ***Austral.:*** Mesasal; Pentasa; Salofalk; ***Austria:*** Claversal; Pentasa; Salofalk; ***Belg.:*** Asacol†; Claversal; Colitofalk; Pentasa; ***Braz.:*** Asalit; Chron-ASA; Mesacol; Pentasa†; ***Canad.:*** Asacol; Mesasal; Pentasa; Salofalk; ***Chile:*** Pentasa; Salofalk; ***Cz.:*** Asacol; Pentasa; Salofalk; Samezil; ***Denm.:*** Asacol; Mesasal; Pentasa; ***Fin.:*** Asacol; Pentasa; Salofalk; ***Fr.:*** Fivasa; Pentasa; Rowasa; ***Ger.:*** Asacolitin; Claversal; Pentasa; Salofalk; ***Gr.:*** Asacol; Asalazin†; Crohnezine; Ectospasmol; Empenox; Enterin; Favorat; Laboxantryl; Mesagin†; Pentasa; Prozylex†; Salofalk; ***Hong Kong:*** Asacol; Pentasa; Salofalk; ***Hung.:*** Asacol; Huma-Col-Asa; Pentasa; Salofalk; Xalazin; ***India:*** Asacol; Mesacol; ***Indon.:*** Salofalk; ***Irl.:*** Asacolon; Pentasa; Salofalk; ***Israel:*** Asacol; Pentasa; Rafassal; ***Ital.:*** Asacol; Asalex; Asamax; Asavixin; Claversal; Enteraproct; Enterasin; Lextrasa; Mesaflor; Pentacol; Pentasa; Plimage; Quota; Salofalk†; Xalazin†; ***Jpn:*** Pentasa; ***Malaysia:*** Pentasa; Salofalk; ***Mex.:*** Asacol; Kenzomyl†; Pentasa; Salofalk; Seramine; ***Neth.:*** Asacol; Asamax; Claversal; Pentasa; Salofalk; ***Norw.:*** Asacol; Mesasal; Pentasa; ***NZ:*** Asacol; Pentasa; ***Philipp.:*** Pentasa; Salofalk; ***Pol.:*** Asamax; Colitan; Jucolon; Pentasa; Salofalk; ***Port.:*** Asacol; Claversal; Pentasa; Salofalk; ***Rus.:*** Mesacol (Месакол); Pentasa (Пентаса); Samezil (Самезил); ***S.Afr.:*** Asacol; Mesasal; Pentasa; ***Singapore:*** Asacol; Pentasa; Salofalk; ***Spain:*** Claversal; Lixacol; Pentasa; Salofalk; ***Swed.:*** Asacol; Mesasal; Pentasa; Salofalk; ***Switz.:*** Asacol; Asazine; Mesazine; Pentasa; Salofalk; ***Thai.:*** Asacol†; Mesacol; Salofalk; ***Turk.:*** Asacol; Salofalk; ***UK:*** Asacol; Ipocol; Mesren; Mezavant; Pentasa; Salofalk; ***USA:*** Asacol; Canasa; Lialda; Pentasa; Rowasa.

Methanthelinium Bromide *(BAN, pINN)*

Bromuro de metantelinio; Dixamonum Bromidum; Methantheline Bromide; Methanthelinii Bromidum; Méthanthélinium, Bromure de; MTB-51; SC-2910. Diethylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl]ammonium bromide.

Метантелиния Бромид

$C_{21}H_{26}BrNO_3$ = 420.3.
CAS — 5818-17-7 (methanthelinium); 53-46-3 (methanthelinium bromide).
ATC — A03AB07.
ATC Vet — QA03AB07.

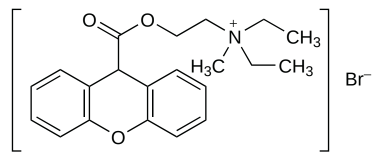

Profile

Methanthelinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease, in gastrointestinal disorders associated with smooth muscle spasm, and in the management of urinary incontinence. A usual oral dose in gastrointestinal disorders is 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Vagantin.

Methylbenactyzium Bromide *(rINN)*

Benactyzine Methobromide; Bromuro de metilbenacticio; Methylbenactyzii Bromidum; Méthylbénactyzium, Bromure de. Diethyl(2-hydroxyethyl)methylammonium bromide benzilate.

Метилбенактизия Бромид

$C_{21}H_{28}BrNO_3$ = 422.4.
CAS — 3166-62-9.

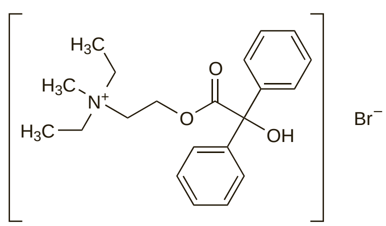

Pharmacopoeias. In *Jpn.*

Profile

Methylbenactyzium bromide, a derivative of benactyzine (p.383), is an antimuscarinic with effects similar to those of atropine (p.1219). It has been given orally for the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Anxiolit plus.

Methylnaltrexone Bromide *(USAN, rINN)*

Bromure de Méthylnaltrexone; Bromuro de Metilnaltrexona; Methylnaltrexonii Bromidum; MRZ-2663BR; Naltrexone Methobromide. (17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

Метилнальтрексон Бромид

$C_{21}H_{26}BrNO_4$ = 436.3.
CAS — 83387-25-1 (methylnaltrexone); 73232-52-7 (methylnaltrexone bromide).

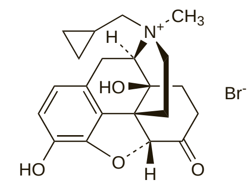

and epimer at N+

Profile

Methylnaltrexone bromide is a selective peripherally acting antagonist of opioid μ-receptors that is used for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness, when response to usual laxative therapy is insufficient. It is also being studied for treatment of opioid-induced urinary retention and postoperative ileus.

For the treatment of opioid-induced constipation methylnaltrexone bromide may be given once every 48 hours by subcutaneous injection in the following doses according to body-weight: patients less than 38 kg in weight, 150 micrograms/kg; 38 to 62 kg, 8 mg; 62 to 114 kg, 12 mg; more than 114 kg, 150 micrograms/kg.

◊ References.

1. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Ann Pharmacother* 2007; **41:** 984–93.
2. Reichle FM, Conzen PF. Methylnaltrexone, a new peripheral μ-receptor antagonist for the prevention and treatment of opioid-induced extracerebral side effects. *Curr Opin Investig Drugs* 2008; **9:** 90–100.
3. Thomas J, *et al.* Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008; **358:** 2332–43.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Relistor; ***USA:*** Relistor.

Metoclopramide *(BAN, rINN)*

Metoclopramida; Métoclopramide; Metoclopramidum; Metoklopramid; Metoklopramidas; Metoklopramidi. 4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide.

Метоклопрамид

$C_{14}H_{22}ClN_3O_2$ = 299.8.
CAS — 364-62-5.
ATC — A03FA01.
ATC Vet — QA03FA01.

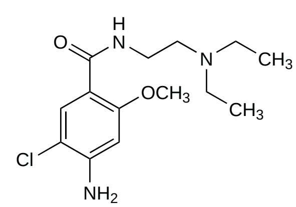

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Metoclopramide). A white or almost white, fine powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble to slightly soluble in alcohol; slightly soluble in dichloromethane.

Metoclopramide Hydrochloride *(BANM, USAN, rINNM)*

AHR-3070-C; DEL-1267; Hidrocloruro de metoclopramida; Métoclopramide, chlorhydrate de; Metoclopramidi hydrochloridum; Metoclopramidi Hydrochloridum Monohydricum; Metoklopramid Hidroklorür; Metoklopramid-hidroklorid; Metoklopramid-hydrochlorid monohydrát; Metoklopramidhydroklorid; Metoklopramidihydrokloridi; Metoklopramido hidrochloridas; Metoklopramidu chlorowodorek; MK-745.

Метоклопрамида Гидрохлорид

$C_{14}H_{22}ClN_3O_2,HCl,H_2O$ = 354.3.
CAS — 7232-21-5 (anhydrous metoclopramide hydrochloride); 54143-57-6 (metoclopramide hydrochloride monohydrate); 2576-84-3 (anhydrous metoclopramide dihydrochloride).
ATC — A03FA01.
ATC Vet — QA03FA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Metoclopramide Hydrochloride). A white or almost white, crystalline powder or crystals. Very soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Metoclopramide Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder.

Very soluble in water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether. Store in airtight containers. Protect from light.

Incompatibility. Proprietary preparations of metoclopramide hydrochloride are stated to be incompatible with cephalothin sodium, chloramphenicol sodium, and sodium bicarbonate.

Cisplatin, cyclophosphamide, doxorubicin hydrochloride, morphine hydrochloride, or diamorphine hydrochloride are stated to be compatible with metoclopramide hydrochloride but compatibility is dependent upon factors such as the particular formulation, drug concentration, and temperature.

Adverse Effects

Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms (usually acute dystonic reactions); these are more common in children and young adults, and at daily doses above 500 micrograms/kg. Parkinsonism and tardive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patients, and especially in elderly women.

Other adverse effects include restlessness, drowsiness, anxiety, and diarrhoea. Hypotension, hypertension, dizziness, headache, and depression may occur and there are isolated reports of blood disorders, hypersensitivity reactions (rash, bronchospasm), and neuroleptic malignant syndrome. Disorders of cardiac conduction have been reported with intravenous metoclopramide.

Metoclopramide stimulates prolactin secretion and may cause galactorrhoea or related disorders. Transient increases in plasma-aldosterone concentrations have been reported.

Effects on the blood. Agranulocytosis was associated with use of metoclopramide on 2 separate occasions.[1] Both episodes resolved within 2 to 3 weeks of withdrawing metoclopramide. Methaemoglobinaemia[2-4] and sulfhaemoglobinaemia[5,6] have also been reported. Methaemoglobinaemia (p.1451) may be treated with methylthioninium chloride. In one case,[3] the patient died despite treatment with this drug; blood samples taken before death were found to be haemolysed, and assays showed deficiency in G6PD activity (for the view that methylthioninium chloride should not be used in G6PD-deficient patients, see Uses of Methylthioninium Chloride, p.1451).

1. Harvey RL, Luzar MJ. Metoclopramide-induced agranulocytosis. *Ann Intern Med* 1988; **108:** 214–15.
2. Grant SCD, *et al.* Methaemoglobinaemia produced by metoclopramide in an adult. *Eur J Clin Pharmacol* 1994; **47:** 89.
3. Karadsheh NS, *et al.* Metoclopramide-induced methemoglobinemia in a patient with co-existing deficiency of glucose-6-phosphate dehydrogenase and NADH-cytochrome b5 reductase: failure of methylene blue treatment. *Haematologica* 2001; **86:** 659–60.
4. Mérieau E, *et al.* Métoclopramide et méthémoglobinémie néonatale. *Arch Pediatr* 2005; **12:** 438–41.
5. Van Veldhuizen PJ, Wyatt A. Metoclopramide-induced sulfhemoglobinemia. *Am J Gastroenterol* 1995; **90:** 1010–11.
6. Aravindhan N, Chisholm DG. Sulfhemoglobinemia presenting as pulse oximetry desaturation. *Anesthesiology* 2000; **93:** 883–4.

Effects on the cardiovascular system. Reports of hypotension,[1] hypertension,[2,3] and supraventricular tachycardia[4] associated with metoclopramide. Bradycardia followed by total heart block,[5] and sinus arrest,[6] have also been reported.

1. Park GR. Hypotension following metoclopramide administration during hypotensive anaesthesia for intracranial aneurysm. *Br J Anaesth* 1978; **50:** 1268–9.
2. Sheridan C, *et al.* Transient hypertension after high doses of metoclopramide. *N Engl J Med* 1982; **307:** 1346.
3. Filibeck DJ, *et al.* Metoclopramide-induced hypertensive crisis. *Clin Pharm* 1984; **3:** 548–9.
4. Bevacqua BK. Supraventricular tachycardia associated with postpartum metoclopramide administration. *Anesthesiology* 1988; **68:** 124–5.
5. Midttun M, Øberg B. Total heart block after intravenous metoclopramide. *Lancet* 1994; **343:** 182–3.
6. Malkoff MD, *et al.* Sinus arrest after administration of intravenous metoclopramide. *Ann Pharmacother* 1995; **29:** 381–3.

Effects on the endocrine system. *ALDOSTERONISM.* Metoclopramide has been reported to increase plasma-aldosterone concentrations in healthy individuals[1] and in patients with liver cirrhosis and ascites associated with secondary hyperaldosteronism.[2] Increased plasma aldosterone after metoclopramide use has also been associated with the development of oedema in a patient with congestive heart failure.[3] The metoclopramide-induced aldosterone response was blunted by giving neostigmine beforehand.[1]

1. Sommers DK, *et al.* Effect of neostigmine on metoclopramide-induced aldosterone secretion in man. *Eur J Clin Pharmacol* 1989; **36:** 411–13.
2. Mazzacca G, *et al.* Metoclopramide and secondary hyperaldosteronism. *Ann Intern Med* 1983; **98:** 1024–5.
3. Zumoff B. Metoclopramide and edema. *Ann Intern Med* 1983; **98:** 557.

HYPERPROLACTINAEMIA. Hyperprolactinaemia, galactorrhoea, and pituitary adenoma occurred in a 49-year-old woman with reflux oesophagitis who had received metoclopramide for 3 months.[1] Her plasma-prolactin concentrations fell to normal and her symptoms resolved over 4 months after withdrawal of metoclopramide. The pituitary tumour was considered to be incidental to, and not caused by, metoclopramide therapy. A 21-year-old female developed mastodynia, galactorrhoea, and hyperprolactinaemia after 2 days of treatment with metoclopramide;[2] she had previously taken domperidone intermittently without any problems. Her symptoms resolved rapidly on stopping therapy.

1. Cooper BT, *et al.* Galactorrhoea, hyperprolactinaemia, and pituitary adenoma presenting during metoclopramide therapy. *Postgrad Med J* 1982; **58:** 314–15.
2. Bozzolo M, *et al.* Medikamentös induzierte Hyperprolaktinämie und Galaktorrhöe. *Schweiz Rundsch Med Prax* 1992; **81:** 1511–13.

Effects on mental state. There are isolated reports of dose-related delirium, depression, and uncontrollable crying in patients treated with metoclopramide in doses of 40 to 80 mg daily.[1-3] Symptoms resolved on reducing the dose or withdrawing metoclopramide, and tolerance could be achieved by gradually increasing the dose. In another report,[4] a patient developed acute akathisia (see Extrapyramidal Effects below) shortly after starting metoclopramide 10 mg four times daily; this was accompanied by restlessness, anxiety, and irritability. Despite stopping the drug after 2 days, and treatment with paroxetine and lorazepam, the patient started to experience panic attacks, which increased in frequency and severity; he also developed agoraphobia. Two months after taking metoclopramide he was diagnosed with major depressive disorder, which included intermittent suicidal ideation. Following aggressive therapy and hospitalisation, his symptoms gradually resolved.

Insomnia, with or without daytime drowsiness, has also been reported in patients taking metoclopramide 40 mg daily.[5]

Hypersensitivity psychosis has also been reported, shortly after stopping metoclopramide.[6] Symptoms included hallucinations, delusional experiences, anxiety, restlessness, and sleep disturbances; improvement and gradual resolution were noted after treatment with risperidone.

1. Bottner RK, Tullio CJ. Metoclopramide and depression. *Ann Intern Med* 1985; **103:** 482.
2. Adams CD. Metoclopramide and depression. *Ann Intern Med* 1985; **103:** 960.
3. Fishbain DA, Rogers A. Delirium secondary to metoclopramide hydrochloride. *J Clin Psychopharmacol* 1987; **7:** 281–2.
4. Anfinson TJ. Akathisia, panic, agoraphobia, and major depression following brief exposure to metoclopramide. *Psychopharmacol Bull* 2002; **36:** 82–93.
5. Saxe TG. Metoclopramide side effects. *Ann Intern Med* 1983; **98:** 674.
6. Lu M-L, *et al.* Metoclopramide-induced supersensitivity psychosis. *Ann Pharmacother* 2002; **36:** 1387–90.

Extrapyramidal effects. The Adverse Reactions Register of the UK CSM for the years 1967 to 82 contained 479 reports of extrapyramidal reactions in which metoclopramide was the suspected drug: 455 were for dystonic-dyskinetic reactions, 20 for parkinsonism, and 4 for tardive dyskinesia.[1]

Acute **dystonic-dyskinetic** reactions occur most commonly in children and young adults[1-3] and about 70% of reactions are in females;[1,3] many are associated with doses above those recommended by the manufacturers.[1,3,4] Symptoms reported include oculogyric crisis,[4,5] opisthotonus,[6] torticollis,[5,7] trismus,[5,7] a tetanus-like reaction,[8] and blue coloration of the tongue;[6] akathisia after the use of metoclopramide alone,[9] or with droperidol[10] or haloperidol[9] has been reported (see also Effects on Mental State, above). The effects usually occur within 72 hours of starting treatment[1] but have been reported within 30 minutes of receiving metoclopramide.[4] They can occur in patients who have previously taken metoclopramide without complications[5,8,10] and may be precipitated by other drugs. Although generally self-limiting, deaths have occurred.[1,5] The reactions are readily reversed by an antihistamine such as diphenhydramine,[7] or an antimuscarinic such as benzatropine;[4,6] prophylactic use of diphenhydramine has been suggested for patients with a history of extrapyramidal reactions and in those less than 30 years of age.[7,8]

Metoclopramide-associated **parkinsonism** is thought to occur less commonly than the acute dystonias and is seen mainly in older patients. Symptoms usually appear several months after starting metoclopramide, but may occur within days or not for several years. Withdrawal of metoclopramide usually results in resolution of symptoms, although it may take several months.[1] A study has suggested that metoclopramide-induced parkinsonism (misdiagnosed as idiopathic Parkinson's disease) may be more common in the elderly than generally realised.[11]

Tardive dyskinesia may rarely be associated with use of metoclopramide. The reaction is usually confined to elderly patients after prolonged oral use,[12,13] but it has been reported with short-term high-dose parenteral use as an antiemetic in cancer chemotherapy,[14] and a case has been reported in an 8-year-old child treated with metoclopramide for gastro-oesophageal reflux disease in usual doses.[15] The average duration of treatment before the onset of symptoms was 14 months (range 4 to 44 months) in a report of 11 cases[13] and 26 months (range 8 to 60 months) in a report of 12 cases;[16] some patients did not experience symptoms until after withdrawal of metoclopramide. Tardive dyskinesia is potentially irreversible and its management is difficult.[16] Some patients improve after withdrawal of metoclopramide but symptoms persisting during follow-up periods of up to 3 years have been reported.[12,13] The emphasis must be on prevention, hence the recommendation that metoclopramide should not be prescribed for the long-term treatment of minor symptoms, especially in elderly patients.[16]

1. Bateman DN, *et al.* Extrapyramidal reactions with metoclopramide. *BMJ* 1985; **291:** 930–2.
2. Anonymous. Measuring therapeutic risk. *Lancet* 1989; **ii:** 139–40.
3. Adverse Drug Reactions Advisory Committee. Metoclopramide—choose the dose carefully. *Aust Adverse Drug React Bull* 1990; Feb.
4. Tait P, *et al.* Metoclopramide side effects in children. *Med J Aust* 1990; **152:** 387.
5. Pollera CF, *et al.* Sudden death after acute dystonic reaction to high-dose metoclopramide. *Lancet* 1984; **ii:** 460–1.
6. Alroe C, Bowen P. Metoclopramide and prochlorperazine: "the blue-tongue sign". *Med J Aust* 1989; **150:** 724–5.
7. Kris MG, *et al.* Extrapyramidal reactions with high-dose metoclopramide. *N Engl J Med* 1983; **309:** 433–4.
8. Della Valle R, *et al.* Metoclopramide-induced tetanus-like dystonic reaction. *Clin Pharm* 1985; **4:** 102–3.
9. Akagi H, Kumar TM. Akathisia: overlooked at a cost. *BMJ* 2002; **324:** 1506–7.
10. Barnes TRE, *et al.* Acute akathisia after oral droperidol and metoclopramide preoperative medication. *Lancet* 1982; **ii:** 48–9.
11. Avorn J, *et al.* Increased incidence of levodopa therapy following metoclopramide use. *JAMA* 1995; **274:** 1780–2.
12. Grimes JD, *et al.* Long-term follow-up of tardive dyskinesia due to metoclopramide. *Lancet* 1982; **ii:** 563.
13. Wiholm B-E, *et al.* Tardive dyskinesia associated with metoclopramide. *BMJ* 1984; **288:** 545–7.
14. Breitbart W. Tardive dyskinesia associated with high-dose intravenous metoclopramide. *N Engl J Med* 1986; **315:** 518.
15. Putnam PE, *et al.* Tardive dyskinesia associated with use of metoclopramide in a child. *J Pediatr* 1992; **121:** 983–5.
16. Orme ML'E, Tallis RC. Metoclopramide and tardive dyskinesia in the elderly. *BMJ* 1984; **289:** 397–8.

Hypersensitivity. A patient given intravenous metoclopramide and butylhyoscine for gastrointestinal disturbances developed pruritus, generalised urticaria, hypotension, and loss of consciousness. She was treated with intravenous fluid, antihistamines, and corticosteroids. Skin prick tests revealed a response to metoclopramide, suggesting an IgE-mediated allergic reaction.[1]

1. Kerstan A, *et al.* Anaphylaxis during treatment of nausea and vomiting: IgE-mediated metoclopramide allergy. *Ann Pharmacother* 2006; **40:** 1889–90.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS, p.972) has occurred very rarely with metoclopramide. In a report of a case with a fatal outcome, it was noted that 17 additional cases had been published in the years 1978 to 1998, three of which resulted in death.[1] A case report in a 6-month-old female with Freeman-Sheldon syndrome[2] given metoclopramide suggested that pre-existing fever and myopathy may be predisposing factors. In another case,[3] a burns patient, there was some suggestion that the patient may have been susceptible to neuroleptic hyperthermic syndromes such as NMS and malignant hyperthermia. Metoclopramide should be stopped immediately if NMS occurs, and the patient treated urgently with bromocriptine.

1. Nonino F, Campomori A. Neuroleptic malignant syndrome associated with metoclopramide. *Ann Pharmacother* 1999; **33:** 644–5.
2. Stein MH, *et al.* Neuroleptic malignant syndrome induced by metoclopramide in an infant with Freeman-Sheldon syndrome. *Anesth Analg* 2006; **103:** 786–7.
3. Nachreiner R, *et al.* Neuroleptic malignant syndrome associated with metoclopramide in a burn patient. *J Burn Care Res* 2006; **27:** 237–41.

Precautions

Metoclopramide should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions, as in gastrointestinal haemorrhage, obstruction, perforation, or for a few days after surgery. There have been reports of hypertensive crises in patients with phaeochromocytoma given metoclopramide, thus its use is not recommended in such patients; caution is advised in patients with hypertension.

Children, young adults, and the elderly should be treated with care as they are at increased risk of extrapyramidal reactions; in the UK, use of metoclopramide is restricted in patients under 20 years (see Administration in Children, below). Patients on prolonged therapy should be reviewed regularly. Care should also be taken when metoclopramide is given to patients with renal or hepatic impairment, epilepsy, Parkinson's disease, or a history of depression, atopy (including asthma), or porphyria.

Metoclopramide may cause drowsiness or impaired reactions; patients so affected should not drive or operate machinery.

Breast feeding. Metoclopramide is excreted into breast milk. The American Academy of Pediatrics[1] considers that the use of metoclopramide by mothers during breast feeding may be of concern, owing to its dopamine-receptor blocking activity. UK licensed product information states that problems in humans have not been reported.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)

Porphyria. Metoclopramide has been associated with acute attacks of porphyria and is considered to be unsafe in porphyric patients, although there is conflicting evidence of porphyrinogenicity, and indeed some have used it successfully in the management of acute attacks.[1]

1. Elder GH, *et al.* Metoclopramide and acute porphyria. *Lancet* 1997; **350:** 1104.

Interactions

Metoclopramide should be used with caution in patients taking other drugs that can also cause extrapyramidal reactions, such as the phenothiazines. Increased toxicity may occur if metoclopramide is given to patients receiving lithium, and caution is advisable with other centrally active drugs such as antiepileptics. Metoclopramide should be used with care with other drugs acting at central dopamine receptors, such as pergolide. Combining metoclopramide with CNS depressant drugs can lead to increased sedative effects. Antimuscarinics and opioid analgesics antagonise the gastrointestinal effects of metoclopramide.

The absorption of other drugs may be affected by metoclopramide; it may either diminish absorption from the stomach (as with digoxin) or enhance absorption from the small intestine (for example, with alcohol, ciclosporin, levodopa, aspirin, or paracetamol). It inhibits serum cholinesterase and may prolong neuromuscular blockade produced by suxamethonium (see p.1912) and mivacurium (p.1907). Metoclopramide may also increase prolactin blood concentrations and therefore interfere with drugs which have a hypoprolactinaemic effect such as bromocriptine (but see p.800). It has been suggested that it should not be given to patients receiving MAOIs.

Antidepressants. For reference to extrapyramidal effects and other adverse effects suggestive of serotonin syndrome in patients taking metoclopramide with SSRIs or venlafaxine, see Gastrointestinal Drugs under Interactions for Fluoxetine (p.397) and Venlafaxine (p.429) respectively.

Carbamazepine. For a report of neurotoxicity associated with the use of metoclopramide with carbamazepine, see p.475.

Hydroxyzine. Acute anxiety, rigidity, generalised tremor, opisthotonus, and hypertension developed in a 20-year-old man given metoclopramide 10 mg intravenously and hydroxyzine 100 mg intramuscularly.[1] The adverse effects occurred 30 minutes after giving hydroxyzine and it was suggested that hydroxyzine potentiated the onset of the reaction.

1. Fouilladieu JL, *et al.* Possible potentiation by hydroxyzine of metoclopramide's undesirable side effects. *Anesth Analg* 1985; **64:** 1227–8.

Pharmacokinetics

Metoclopramide is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption. However, it undergoes hepatic first-pass metabolism, which varies considerably between subjects, and hence absolute bioavailability and plasma concentrations are subject to wide interindividual variation. On average, the bioavailability of oral metoclopramide is about 80%, but it varies between about 30 and 100%. Peak plasma concentrations of metoclopramide occur about 1 to 2 hours after an oral dose. Bioavailability is equally variable after rectal or intranasal doses, although it may be somewhat better if the drug is given intramuscularly. Metoclopramide is weakly bound to plasma proteins (13 to 30%).

Metoclopramide is widely distributed in the body, and readily crosses the blood-brain barrier into the CNS. It also freely crosses the placenta, and has been reported to attain concentrations in fetal plasma about 60 to 70% of those in maternal plasma. Concentrations in breast milk may be higher than those in maternal plasma, particularly in the early puerperium, although concentrations decrease somewhat in the late puerperium.

Elimination of metoclopramide is biphasic, with a terminal elimination half-life of about 4 to 6 hours, although this may be prolonged in renal impairment, with consequent elevation of plasma concentrations. It is excreted in the urine, about 85% of a dose being eliminated in 72 hours, 20% as unchanged metoclopramide and the remainder as sulfate or glucuronide conjugates, or as metabolites. About 5% of a dose is excreted in faeces via the bile.

Uses and Administration

Metoclopramide hydrochloride is a substituted benzamide used for its prokinetic and antiemetic properties. It stimulates the motility of the upper gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion and increases gastric peristalsis, leading to accelerated gastric emptying. Duodenal peristalsis is also increased which decreases intestinal transit time. The resting tone of the gastro-oesophageal sphincter is increased and the pyloric sphincter is relaxed. Metoclopramide possesses parasympathomimetic activity as well as being a dopamine-receptor antagonist with a direct effect on the chemoreceptor trigger zone. It may have serotonin-receptor (5-HT_3) antagonist properties.

Metoclopramide is used in disorders of decreased gastrointestinal motility (p.1694) such as gastroparesis or ileus; in gastro-oesophageal reflux disease (p.1696) and dyspepsia (p.1695); and in nausea and vomiting (p.1700) associated with various gastrointestinal disorders, with migraine, after surgery, and with cancer therapy. Metoclopramide is of no value in the prevention or treatment of motion sickness. It may be used to stimulate gastric emptying during radiographic examinations, to facilitate intubation of the small bowel, and in the management of aspiration syndromes (p.1693).

It is usually given as the hydrochloride monohydrate with doses expressed as the anhydrous hydrochloride. In the USA, the strength of preparations of the hydrochloride monohydrate is usually expressed in terms of the base. Metoclopramide hydrochloride 10.5 mg is equivalent to about 10.0 mg of the anhydrous substance, which is equivalent to about 8.9 mg of the anhydrous base.

For most purposes the total daily dose should not exceed 500 micrograms/kg; dosage reduction is recommended in renal and perhaps hepatic impairment (see Administration in Hepatic or Renal Impairment, below).

- In the UK, the recommended dose orally, intramuscularly, or by slow intravenous injection, is 10 mg (expressed as anhydrous metoclopramide hydrochloride) three times daily.
- In the USA, the recommended dose is 10 to 15 mg (expressed as the base) up to four times daily.
- Single doses of 10 to 20 mg (expressed as anhydrous base or anhydrous hydrochloride) should be considered where appropriate.

Modified-release preparations of metoclopramide are available; 15 mg (expressed as anhydrous metoclopramide hydrochloride) is given twice daily.

In the UK, the use of metoclopramide is restricted in patients under 20 years of age (see Administration in Children, below).

An intranasal formulation of metoclopramide is available in some countries.

The base, the dihydrochloride, and the glycyrrhizate have also been used.

High-dose therapy. High doses of metoclopramide have been used, often with other drugs such as dexamethasone, in the treatment of the nausea and vomiting associated with cancer chemotherapy. The loading dose of metoclopramide before cancer therapy is 2 to 4 mg/kg given as a continuous intravenous infusion over 15 to 20 minutes; it is followed by a maintenance dose of 3 to 5 mg/kg, again as a continuous intravenous infusion, given over 8 to 12 hours. Alternatively, initial doses of up to 2 mg/kg by intravenous infusion over at least 15 minutes may be given before cancer therapy and repeated every 2 or 3 hours. The total dosage by either continuous or intermittent infusion should not normally exceed 10 mg/kg in 24 hours.

Administration. ***INTRANASAL.*** References.

1. Ormrod D, Goa KL. Intranasal metoclopramide. *Drugs* 1999; **58:** 315–22. Commentaries. *ibid.*; 323–4.

Administration in children. In the UK, the use of metoclopramide is restricted in patients under 20 years of age to severe intractable vomiting of known cause, chemotherapy- or radiotherapy-induced vomiting, as an aid to gastrointestinal intubation, and in premedication. Licensed oral and parenteral (intramuscular or intravenous) doses for all indications, except premedication, are:

- for those aged 15 to 19 years and weighing 60 kg and over: 10 mg three times daily
- 15 to 19 years (30 to 59 kg): 5 mg three times daily
- 9 to 14 years (30 kg and over): 5 mg three times daily
- 5 to 9 years (20 to 29 kg): 2.5 mg three times daily
- 3 to 5 years (15 to 19 kg): 2 mg two or three times daily
- 1 to 3 years (10 to 14 kg): 1 mg two or three times daily
- under 1 year (up to 10 kg): 1 mg twice daily

Where body-weight is below that specified for a given age group, the dose should reflect the weight rather than the age, so that a lower dose is chosen.

The *BNFC* gives similar doses, but specifies:

- 1 month to 1 year (up to 10 kg): 100 micrograms/kg (maximum 1 mg) twice daily
- neonate: 100 micrograms/kg every 6 to 8 hours (by mouth or intravenous injection only)

For **premedication** in diagnostic procedures, licensed doses (for use as a single dose by mouth or parenterally 5 to 10 minutes before the examination and subject to the same body-weight considerations as above) are:

- for those aged 15 to 19 years: 10 mg
- 9 to 14 years: 5 mg
- 5 to 9 years: 2.5 mg
- 3 to 5 years: 2 mg
- under 3 years: 1 mg

The *BNFC* gives similar oral doses, but specifies:

- 1 month to 3 years (up to 14 kg): 100 micrograms/kg (maximum 1 mg) by mouth

In the USA metoclopramide is licensed for use in children only to facilitate small bowel intubation in those resistant to conventional methods. A single intravenous dose, based on age, is recommended as follows:

- over 14 years: 10 mg
- 6 to 14 years: 2.5 to 5 mg
- under 6 years: 100 micrograms/kg

Administration in hepatic or renal impairment. Total clearance of metoclopramide is significantly reduced in patients with **renal impairment**[1-3] and the elimination half-life is prolonged to up to 19 hours.[2] This may be due to impaired metabolism[1,2] or to an alteration in enterohepatic circulation of metoclopramide.[1] Accumulation of metoclopramide could therefore occur in renal impairment with a possible increased risk of adverse effects. Dosage reductions of at least 50% have therefore been recommended in patients with moderate to severe renal impairment.[1,2] US licensed product information recommends this dose reduction in those patients whose creatinine clearance is below 40 mL/minute; UK information advises caution in severe or chronic renal impairment, but gives no guidance on dosage reduction.

Patients undergoing haemodialysis do not require dosage supplements since relatively little metoclopramide is cleared by this process.[2,3]

UK licensed product information recommends that the dose of metoclopramide should be reduced in patients with clinically significant **hepatic impairment**, although no recommendations on the size of the reduction are given; caution is advised in liver disease, due to loss of conjugation. The US product information notes that metoclopramide undergoes minimal hepatic metabolism and has been used safely in some patients with advanced liver disease (whose renal function was normal), and it makes no such recommendation for reduction of dose. Decreases in clearance and increases in half-life and area under the plasma concentration-time curve have been reported in patients with cirrhosis given metoclopramide.[4,5]

1. Bateman DN, *et al.* The pharmacokinetics of single doses of metoclopramide in renal failure. *Eur J Clin Pharmacol* 1981; **19:** 437–41.
2. Lehmann CR, *et al.* Metoclopramide kinetics in patients with impaired renal function and clearance by haemodialysis. *Clin Pharmacol Ther* 1985; **37:** 284–9.
3. Wright MR, *et al.* Effect of haemodialysis on metoclopramide kinetics in patients with severe renal failure. *Br J Clin Pharmacol* 1988; **26:** 474–7.

4. Hellstern A, *et al.* Absolute bioavailability of metoclopramide given orally or by enema in patients with normal liver function or with cirrhosis of the liver. *Arzneimittelforschung* 1987; **37:** 733–6.
5. Magueur E, *et al.* Pharmacokinetics of metoclopramide in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; **31:** 185–7.

Blood disorders. Responses to treatment with metoclopramide have been reported in patients with Diamond-Blackfan anaemia, probably through induction of prolactin release, although the mechanism by which prolactin affects erythropoiesis is unclear.[1,2] In a pilot study, 3 out of 9 evaluable patients responded after 12 to 15 weeks of therapy; high serum ferritin, pituitary dysfunction, male sex, and younger age may have contributed to the poor response to metoclopramide in other patients.[1] In another case, response was seen by the fourth week of treatment; at the time of the report, the patient had remained asymptomatic and transfusion independent for 8 months.[2]

1. Abkowitz JL, *et al.* Response of Diamond-Blackfan anemia to metoclopramide: evidence for a role for prolactin in erythropoiesis. *Blood* 2002; **100:** 2687–91.
2. Akiyama M, *et al.* Successful treatment of Diamond-Blackfan anemia with metoclopramide. *Am J Hematol* 2005; **78:** 295–8.

Hiccup. Metoclopramide has been used in the management of intractable hiccup. For a discussion of hiccup and its management see p.976.

Lactation induction. Metoclopramide has been used[1,2] in doses of 10 mg three times daily for its dopamine antagonist properties to stimulate lactation in women who wish to breast feed and in whom mechanical stimulation of the nipple alone is inadequate, including mothers of adopted babies or babies born to surrogates.[3,4] However, pharmacological lactation induction should be viewed as adjunctive to mechanical methods and the duration of therapy should probably be limited to 7 to 14 days.[1,2] In addition, the efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[5] Young women are at increased risk of extrapyramidal effects from metoclopramide—see under Adverse Effects, above. There has also been concern about the presence of the drug in breast milk. For a discussion of lactation inhibition and induction, see p.2003.

1. Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993; **12:** 479–80.
2. Gabay MP. Galactogogues: medications that induce lactation. *J Hum Lact* 2002; **18:** 274–9.
3. Cheales-Siebenaler NJ. Induced lactation in an adoptive mother. *J Hum Lact* 1999; **15:** 41–3.
4. Biervliet FP, *et al.* Induction of lactation in the intended mother of a surrogate pregnancy: case report. *Hum Reprod* 2001; **16:** 581–3.
5. Hansen WF, *et al.* Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005; **105:** 383–9.

Migraine. Metoclopramide is used in the treatment of migraine (p.616) to alleviate nausea and vomiting and gastric stasis, which commonly develop as a migraine attack progresses and can lead to poor absorption of oral antimigraine preparations. It may also be given to counteract nausea and vomiting from the use of ergotamine. Metoclopramide is included in some combination analgesic preparations for the treatment of acute attacks of migraine. In a study, oral lysine aspirin with metoclopramide was as effective as oral sumatriptan in the treatment of migraine.[1] Metoclopramide with sumatriptan may be effective in patients unresponsive to a triptan alone.[2]

Parenteral metoclopramide has also been shown to be an effective treatment for acute migraine; it reduces pain, and to some extent nausea (although other antiemetics may be more effective), and a systematic review concluded that it should be considered a first-line treatment for migraine in the emergency department.[3] A later study found intravenous metoclopramide (with intermittent doses of diphenhydramine) to be comparable to subcutaneous sumatriptan in terms of pain relief at both 2 and 24 hours after treatment.[4]

1. Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–6.
2. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; **43:** 729–33.
3. Colman I, *et al.* Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; **329:** 1369–72.
4. Friedman BW, *et al.* A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; **64:** 463–8.

Orthostatic hypotension. Metoclopramide has been tried in the management of some patients with orthostatic hypotension, as mentioned on p.1530.

Tourette's syndrome. A small, short-term study in children and adolescents with Tourette's syndrome (see Tics, p.954) or chronic tic disorders found that treatment with oral metoclopramide (up to 40 mg daily) significantly reduced tic score and severity compared with placebo.[1]

1. Nicolson R, *et al.* A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2005; **44:** 640–6.

Variceal haemorrhage. Metoclopramide 20 mg intravenously controlled bleeding from oesophageal varices within 15 minutes in 10 of 11 patients compared with 4 of 11 patients given placebo; all patients were treated by sclerotherapy.[1] Lower oesophageal sphincter pressure is increased by metoclopramide, thus reducing blood flow to varices and achieving haemostasis; another study[2] found use of metoclopramide with intravenous glyceryl trinitrate to be more effective than glyceryl trinitrate alone in reducing intravariceal pressure.

For a discussion of variceal haemorrhage and its management, see p.2346.

1. Hosking SW, *et al.* Pharmacological constriction of the lower oesophageal sphincter: a simple method of arresting variceal haemorrhage. *Gut* 1988; **29:** 1098–1102.
2. Sarin SK, Saraya A. Effects of intravenous nitroglycerin and nitroglycerin and metoclopramide on intravariceal pressure: a double blind, randomized study. *Am J Gastroenterol* 1995; **90:** 48–53.

Preparations

BP 2008: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets;
USP 31: Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Celit†; Fonderyl; Lizarona; Metoc; Midatenk; Novomit; Praux; Primavera-N; Primperil; Reliveran; Rilaquin; Rupemet; Saften; Sintegran; ***Austral.:*** Maxolon; Pramin; ***Austria:*** Gastro-Timelets; Gastronerton; Gastrosil; Metogastron; Paspertin; Pramidin; ***Belg.:*** Dibertil; Docmetoclo; Movistal†; Primperan; ***Braz.:*** Aristopramida; Citroplus†; Clopra†; Emetic; Eucil; Fluccil; Metoclosan; Metoplamin; Metovit†; Nausil†; Neolasil; No-Vomit; Plagex; Plamida; Plamidasil; Plamivon; Plasil; Pramil; Vopax†; ***Canad.:*** Apo-Metoclop; ***Chile:*** Hemibe; Itan; ***Cz.:*** Cerucal; Degan; MCP; Pramidin†; ***Denm.:*** Emperal; Gastro-Timelets; Primperan; ***Fin.:*** Metopram; Primperan; ***Fr.:*** Anausin; Primperan; ***Ger.:*** Cerucal; Gastronerton; Gastrosil†; Gastrotranquil†; Hyrin†; MCP; MCPham†; Paspertin; ***Gr.:*** Primeran†; Primperan; ***Hong Kong:*** Maril; Martomide; Maxolon; Metocyl†; Metram; Primperan; ***Hung.:*** Cerucal; Paspertin†; ***India:*** Maxeron; Metocontin; Perinorm; Reglan; Tomid†; Vominorm; ***Indon.:*** Clopramel; Damaben; Emeran; Ethiferan; Gavistal; Lexapram; Mepramide; Metolon; Nilatika; Nofoklam; Normastin; Obteran; Opram; Piralen; Plasil; Praminal; Primperan; Raclonid; Reguloop; Sotatic; Tivomit; Tomit; Vertivom; Vilapon; Vomidex; Vomipram; Vomitrol; Zumatrol; ***Irl.:*** Antimet; Gastrobid Continus; Maxolon; Metocyl; ***Israel:*** Pramin; ***Ital.:*** Citroplus†; Clopan†; Delipramil; Isaprandil; Plasil; Pramidin; Randum; ***Jpn:*** Primperan; ***Malaysia:*** Maril; Maxolon; Metocyl†; Primperan; Pulin; ***Mex.:*** Biopram; Carnotprim; Cirulan; Clorimet-Z; Dolmisin; Eudiges; Gigemet; Hopram; Meclomid; Midetol; Mipramid; Plasil; Polcotec; Pradex; Pramilem; Pramotil†; Primperan; Propace; Synespramid; ***Neth.:*** Primperan; ***Norw.:*** Afipran; Primperan; ***NZ:*** Maxolon; Metamide; ***Philipp.:*** Biclomet; Novom; Plasil; ***Pol.:*** Pramidin; ***Port.:*** Metoclan†; Primperan; Reglan†; ***Rus.:*** Apo-Metoclop (Апо-метоклоп); Cerucal (Церукал); Perinorm (Перинорм); ***S.Afr.:*** Acumet; Ametic†; Betaclopramide; Clopamon; Contromet; Maxolon; Metalon; Perinorm; Pramalon; Setin; ***Singapore:*** Maril; Maxolon†; Metocyl†; Metolon†; Primperan; Pulin; ***Spain:*** Metagliz†; Primperan; ***Swed.:*** Primperan; ***Switz.:*** Gastrosil; Paspertin; Primperan; ***Thai.:*** Emetal; Gensil; H-Peran; Hawkperan†; Maril; Meramide†; Met-Sil; Metoclor; Nausil; Plasil; ***Turk.:*** Metoklamide; Metpamid; Primperan; ***UAE:*** Premosan; ***UK:*** Gastrobid Continus†; Gastroflux†; Maxolon; Primperan; ***USA:*** Clopra†; Maxolon†; Octamide; Reclomide; Reglan; ***Venez.:*** Clodoxin; Clop†; Irtopan; Mepramida; Peremid†; Pradamin†; Pramide; Primperan; Vibralen†.

Multi-ingredient: *Arg.:* Bil 13 Enzimatico; Bitecain AA; Digesplen; Facilgest†; Factorine; Faradil; Faradil Enzimatico; Migral Compositum; Pakinase; Pankreon Total; Tetralgin; Vacuobil Plus; ***Austral.:*** Anagraine; Metomax; ***Austria:*** Ceolat Compositum; Paspertase; ***Belg.:*** Migpriv; ***Braz.:*** Cefalium; Diagrin†; Digeplus; Emetrol†; Enjool†; Essen; Estac†; Plagon; Plasil Enzimatico; Sintozima; Vominil†; ***Chile:*** Aero Itan; Aeroflat†; Aerogastrol; Digespar; Garceptol; Gaseofin†; No-Ref; Pangastren; ***Cz.:*** Cephalgan†; Migpriv†; Migranerton; ***Denm.:*** Migpriv†; ***Fin.:*** Migpriv; ***Fr.:*** Cephalgan†; Migpriv; ***Ger.:*** Migraeflux MCP; Migralave + MCP; Migrane-Neuridal; Migranerton; Paspertase†; ***Gr.:*** Premig; ***Hung.:*** Migpriv; ***India:*** Okanorm Plus; Pacimol-M; Paramet; ***Indon.:*** Primadol; Primperan Compositum; ***Irl.:*** Paramax; ***Ital.:*** Geffer; Migpriv; Migraprim; ***Mex.:*** Antigram; Digenor; Digenor Plus; Espaven MD; Espraden; Plasil Enzimatico; Pramigel; Primpesasy; ***Neth.:*** Migrafin; ***Norw.:*** Migpriv†; ***NZ:*** Paramax; ***Pol.:*** Migpriv; ***Spain:*** Aero Plus†; Aeroflat; Anti Anorex Triple; Novo Aerofil Sedante†; Paidozim; Salcemetic†; Suxidina; ***Swed.:*** Migpriv; ***Switz.:*** Migpriv; ***UK:*** Migramax; Paramax.

Metopimazine *(BAN, USAN, rINN)*

EXP-999; Metopimazina; Métopimazine; Metopimazinum; RP-9965. 1-[3-(2-Methylsulphonylphenothiazin-10-yl)propyl]piperidine-4-carboxamide.

Метопимазин

$C_{22}H_{27}N_3O_3S_2$ = 445.6.
CAS — 14008-44-7.
ATC — A04AD05.
ATC Vet — QA04AD05.

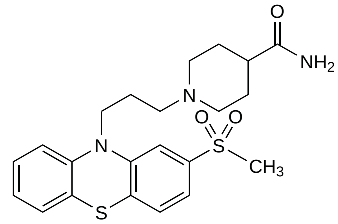

Pharmacopoeias. In *Fr.*

Profile

Metopimazine, a phenothiazine dopamine antagonist, is an antiemetic with general properties similar to those of chlorpromazine (p.969). It is used in the management of nausea and vomiting, including that associated with cancer chemotherapy (p.1700). It is given in usual oral doses of 15 to 30 mg daily, in 2 to 4 divided doses; similar daily doses have been given by rectum in 3 divided doses. It has also been given by injection in a dose of 10 to 20 mg daily, usually intramuscularly but occasionally by the intravenous route. Higher doses of 30 to 50 mg daily by intramuscular injection or intravenous infusion have been given for chemotherapy-induced nausea and vomiting.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Vogalene; ***Fr.:*** Vogalene; Vogalib.

Mosapride Citrate *(rINNM)*

AS-4370; Citrato de mosaprida; Mosapride, Citrate de; Mosapridi Citras; Rimopride Citrate. (±)-4-Amino-5-chloro-2-ethoxy-*N*-{[4-(*p*-fluorobenzyl)-2-morpholinyl]methyl}benzamide citrate dihydrate.

Мозаприда Цитрат

$C_{21}H_{25}ClFN_3O_3,C_6H_8O_7,2H_2O$ = 650.0.
CAS — 112885-41-3 (mosapride); 112885-42-4 (mosapride citrate).

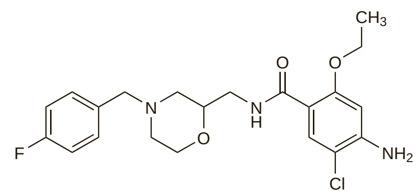

(mosapride)

Profile

Mosapride is a substituted benzamide used for its prokinetic properties. It is reported to be an agonist at 5-HT_4 receptors, increasing acetylcholine release and stimulating gastrointestinal motility (see also Cisapride, p.1721), as well as having 5-HT_3 antagonist properties. It is given orally as the citrate dihydrate, but doses are expressed as the anhydrous citrate, and are 5 mg three times daily before or after meals.

◊ References.

1. Sakashita M, *et al.* Pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. *Arzneimittelforschung* 1993; **43:** 867–72.
2. Ruth M, *et al.* The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; **12:** 35–40.
3. Ruth M, *et al.* The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; **15:** 1115–21.
4. Asakawa H, *et al.* Effect of mosapride on glycemic control and gastric emptying in type 2 diabetes mellitus patients with gastropathy. *Diabetes Res Clin Pract* 2003; **61:** 175–82.
5. Liu Z, *et al.* Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. *Mov Disord* 2005; **20:** 680–6.
6. He M, *et al.* Mosapride citrate prolongs survival in stroke patients with gastrostomy. *J Am Geriatr Soc* 2007; **55:** 142–4.
7. Curran MP, Robinson DM. Mosapride: in gastrointestinal disorders. *Drugs* 2008; **68:** 981–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Galopran; Intesul; Levusid; Lostapride; Mosar; Vagantyl; ***India:*** Mosafe; Mosapid; Mosart; Peripride; ***Jpn:*** Gasmotin.

Multi-ingredient: *Arg.:* Gastrimet†; Mosar Enzimatico; Mosar Plus.

Nabilone *(BAN, USAN, rINN)* ⊗

Compound 109514; Lilly-109514; Nabilon; Nabilona; Nabiloni; Nabilonum. (±)-(6a*R*,10a*R*)-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromen-9-one.

Набилон

$C_{24}H_{36}O_3$ = 372.5.
CAS — 51022-71-0.
ATC — A04AD11.
ATC Vet — QA04AD11.

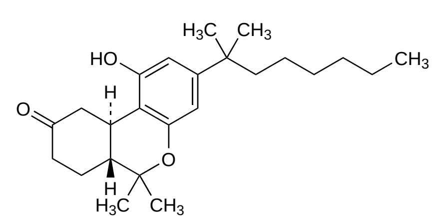

Adverse Effects

Nabilone may produce adverse effects similar to those of cannabis (see p.2275). The most common adverse effects are drowsiness, vertigo, and dry mouth. Neurological effects have included ataxia, confusion, disorientation, dizziness, euphoria, dysphoria, hallucinations, psychosis, depression, headache, decreased concentration, blurred vision, sleep disturbances, decreased coordination, and tremors. Adverse cardiovascular reactions including hypotension, orthostatic hypotension, and tachycardia have occurred. Gastrointestinal disturbances, decreased appetite, and abdominal pain have also been reported.

Precautions

Nabilone is extensively metabolised and largely excreted in bile, and therefore is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with a history of psychiatric disorders or depression, or those with hypertension or heart disease.

Because of the possibility of CNS depression, patients should be warned not to drive or operate machinery.

The possibility of dependence similar to that of cannabis should be borne in mind.

Interactions

Nabilone has been shown to have an additive CNS depressant effect when given with alcohol, codeine, diazepam, or other CNS depressants.

Pharmacokinetics

Nabilone is well absorbed from the gastrointestinal tract and is rapidly and extensively metabolised; one or more of the metabolites may be active. The major excretory pathway is the biliary system; about 65% of a dose is excreted in the faeces and about 20% in the urine. The elimination half-life of nabilone is about 2 hours, but the half-life of its combined metabolites is about 35 hours after an oral dose.

◊ References.

1. Rubin A, *et al.* Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther* 1977; **22:** 85–91.

Uses and Administration

Nabilone, a synthetic cannabinoid with antiemetic properties, is used for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics (p.1700).

The usual initial oral dose for adults is 1 mg twice daily, increased to 2 mg twice daily if necessary. The first dose should be given the evening before starting chemotherapy, and the second dose 1 to 3 hours before the first dose of antineoplastic. Nabilone may be given throughout each cycle of chemotherapy and for 48 hours after the last dose of chemotherapy, if required. The dose of nabilone should not exceed 6 mg daily, given in 3 divided doses.

◊ Reviews.

1. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
2. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Invest Drugs* 2008; **17:** 85–95.

Multiple sclerosis. There is a report of reduction in spasticity and nocturia, and improvement in mood and well-being, in a patient with multiple sclerosis (p.892) who received nabilone 1 mg every second day.[1] A subsequent small crossover study[2] in patients with chronic upper motor neurone syndrome found that oral nabilone 1 mg daily reduced spasticity-related pain in this group. There are also anecdotal reports of improvement in symptoms in patients with multiple sclerosis who took cannabis, however, a review[3] considered evidence of effectiveness to be lacking.

1. Martyn CN, *et al.* Nabilone in the treatment of multiple sclerosis. *Lancet* 1995; **345:** 579.
2. Wissel J, *et al.* Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol* 2006; **253:** 1337–41.
3. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cesamet; ***Canad.:*** Cesamet; ***Irl.:*** Cesamet†; ***USA:*** Cesamet.

Niperotidine Hydrochloride *(rINNM)*

Hidrocloruro de niperotidina; Nipérotidine, Chlorhydrate de; Niperotidini Hydrochloridum; Piperonyl Ranitidine Hydrochloride. *N*-[2-({5-[(Dimethylamino)methyl]furfuryl}thio)ethyl]-2-nitro-*N'*-piperonyl-1,1-ethenediamine hydrochloride.

Нипepoтидина Гидрохлорид

$C_{20}H_{26}N_4O_5S,HCl = 471.0.$

CAS — 84845-75-0 (niperotidine).

ATC — A02BA05.

ATC Vet — QA02BA05.

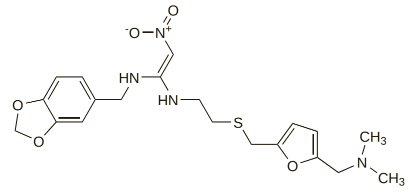

(niperotidine)

Profile

Niperotidine hydrochloride is a histamine H_2-receptor antagonist with general properties similar to those of cimetidine (p.1716). Severe hepatic disorders have occurred in patients receiving niperotidine.

◊ References.

1. Gasbarrini G, *et al.* Acute liver injury related to the use of niperotidine. *J Hepatol* 1997; **27:** 583–6.

Nizatidine *(BAN, USAN, rINN)*

LY-139037; Nitsatidiini; Nizatidin; Nizatidina; Nizatidinas; Nizatidinum; ZL-101. 4-[2-(1-Methylamino-2-nitrovinylamino)ethylthiomethyl]thiazol-2-ylmethyl(dimethyl)amine; *N*-[2-(2-Dimethylaminomethylthiazol-4-ylmethylthio)ethyl]-*N'*-methyl-2-nitrovinylidenediamine.

Низатидин

$C_{12}H_{21}N_5O_2S_2 = 331.5.$

CAS — 76963-41-2.

ATC — A02BA04.

ATC Vet — QA02BA04.

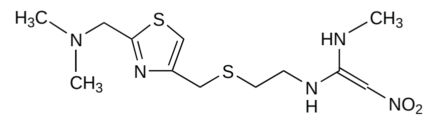

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Nizatidine). An almost white or slightly brownish, crystalline powder. Sparingly soluble in water; soluble in methyl alcohol. A 1% solution in water has a pH of 8.5 to 10.0.

USP 31 (Nizatidine). An off-white to buff crystalline solid. Sparingly soluble in water; freely soluble in chloroform; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects

As for Cimetidine, p.1716. Some patients taking nizatidine may experience excessive sweating and urticaria; anaemia may also occur.

Nizatidine is considered to have little or no anti-androgenic activity although there are isolated reports of gynaecomastia and impotence.

Effects on the cardiovascular system. Nizatidine has been reported to reduce heart rate in healthy subjects,[1,2] an effect that was not seen when they were pretreated with ranitidine[1] or also given the antimuscarinic pirenzepine.[2] As with other H_2-antagonists (see Cimetidine, p.1717), tachycardia, bradycardia, orthostatic hypotension and syncope have been reported rarely with rapid intravenous injection of nizatidine.

1. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
2. Hinrichsen H, *et al.* Dose-dependent heart rate reducing effect of nizatidine, a histamine H -receptor antagonist. *Br J Clin Pharmacol* 1993; **35:** 461–6.

Effects on the endocrine system. A report of reversible impotence in a patient taking nizatidine 300 mg at night.[1]

1. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.

Effects on the skin. Similarly to cimetidine (p.1717), vasculitis has been reported with nizatidine.[1] Exfoliative dermatitis has also occurred.

1. Suh J-G, *et al.* Leukocytoclastic vasculitis associated with nizatidine therapy. *Am J Med* 1997; **102:** 216–17.

Precautions

As for Cimetidine, p.1718.

Interactions

Unlike cimetidine (p.1718) nizatidine does not inhibit cytochrome P450, and therefore is considered to have little effect on the metabolism of other drugs. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of some other drugs.

Pharmacokinetics

Nizatidine is readily and almost completely absorbed from the gastrointestinal tract. The bioavailability of nizatidine after oral doses exceeds 70% and may be slightly increased by the presence of food. It is widely distributed and is about 35% bound to plasma proteins.

The elimination half-life of nizatidine is 1 to 2 hours and is prolonged in renal impairment. Nizatidine is partly metabolised in the liver: nizatidine *N*-2-oxide, nizatidine *S*-oxide, and *N*-2-monodesmethylnizatidine have been identified, the latter having about 60% of the activity of nizatidine.

More than 90% of a dose of nizatidine is excreted in the urine, in part by active tubular secretion, within 12 hours, about 60% as unchanged drug. Less than 6% is excreted in the faeces. Nizatidine is distributed into breast milk.

◊ References.

1. Callaghan JT, *et al.* A pharmacokinetic profile of nizatidine in man. *Scand J Gastroenterol* 1987; **22** (suppl 136): 9–17.
2. Abdel-Rahman SM, *et al.* Single-dose pharmacokinetics of nizatidine (Axid) in children. *J Clin Pharmacol* 2002; **42:** 1089–96.
3. Blum RA, *et al.* Pharmacokinetics and pharmacodynamics of a novel nizatidine controlled-release formulation in healthy subjects. *J Clin Pharmacol* 2003; **43:** 74–83.

Bioavailability. The bioequivalence of 3 oral liquid formulations of nizatidine was investigated relative to a commercially available nizatidine capsule. Of the 3 liquid formulations, one was a commercially available oral syrup (15 mg/mL), and 2 others were extemporaneously prepared, one as a solution in apple juice (1.2 mg/mL) and another as a suspension in an infant formula (*Enfamil; Ross, USA*; 15 mg/mL). Nizatidine in apple juice showed markedly less bioavailability, whereas the other 2 formulations were considered to be bioequivalent to the reference capsule.[1]

1. Abdel-Rahman SM, *et al.* The bioequivalence of nizatidine (Axid) in two extemporaneously and one commercially prepared oral liquid formulations compared with capsule. *J Clin Pharmacol* 2003; **43:** 148–53.

Distribution into breast milk. About 0.1% of an oral dose of nizatidine was secreted in breast milk in a study in lactating women.[1] The milk to serum ratio varied (from 1:1 to 4.9:1) with the time of samples.

1. Obermeyer BD, *et al.* Secretion of nizatidine into human breast milk after single and multiple doses. *Clin Pharmacol Ther* 1990; **47:** 724–30.

Uses and Administration

Nizatidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p.1719). It is given orally and by intravenous infusion.

In the management of benign **gastric** and **duodenal ulceration** (p.1702) a single daily oral dose of nizatidine 300 mg at night is recommended, which should be given initially for 4 weeks and may be extended to 8 weeks if necessary; alternatively 150 mg may be given twice daily in the morning and evening. Where appropriate a maintenance dose of 150 mg daily may be given at night. In patients who are unsuited to receive oral therapy nizatidine may be given on a short-term basis by continuous intravenous infusion of 10 mg/hour; alternatively 100 mg may be diluted in 50 mL of infusion fluid and be given over 15 minutes, three times daily. The total intravenous dose should not exceed 480 mg daily.

In **gastro-oesophageal reflux disease** (p.1696) an oral dose of 150 to 300 mg twice daily is recommended for up to 12 weeks. In children aged 12 years and older, a dose of 150 mg twice daily may be given for up to 8 weeks.

For the short-term symptomatic relief of **dyspepsia** a dose of 75 mg, repeated if necessary, up to a maximum of 150 mg daily may be taken by mouth for up to 14 days.

Doses of nizatidine should be reduced in patients with renal impairment (see below).

Administration in renal impairment. The dosage of nizatidine should be reduced in patients with renal impairment according to creatinine clearance (CC). Licensed product information recommends the following oral doses in renal impairment:

- CC 20 to 50 mL/minute: doses should be reduced by 50%, *or* where the standard dose would be 150 mg daily, 150 mg may be given on alternate days
- CC less than 20 mL/minute: doses should be reduced by 75%, *or* where the standard dose would be 300 mg daily, 150 mg may be given on alternate days, and where the standard dose would be 150 mg daily, 150 mg may be given every third day

Preparations

BP 2008: Nizatidine Intravenous Infusion;
USP 31: Nizatidine Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Nizac; Tacidine; Tazac; ***Austria:*** Ulxit; ***Belg.:*** Panaxid†; ***Braz.:*** Axid; ***Canad.:*** Axid; ***Chile:*** Nizaxid; ***Denm.:*** Izatax; Nizax; ***Fin.:*** Nizax; ***Fr.:*** Nizaxid; ***Ger.:*** Gastrax†; Nizax; ***Gr.:*** Axid†; Flectar†; Flexidon†; Ozeltan†; Ulcogastrin†; ***Hong Kong:*** Axid; ***Hung.:*** Naxidin; ***Indon.:*** Axid; ***Irl.:*** Axid; ***Ital.:*** Cronizat; Nizax; Zanizal†; ***Malaysia:*** Axid†; ***Mex.:*** Axid; Uldadin†; ***Neth.:*** Axid; ***Philipp.:*** Axid; ***Port.:*** Nizaxid; Prospaxid; ***S.Afr.:*** Antizid; ***Spain:*** Distaxid; ***Swed.:*** Nizax†; ***Switz.:*** Calmaxid†; ***Thai.:*** Axid†; ***Turk.:*** Axid; ***UK:*** Axid; ***USA:*** Axid; ***Venez.:*** Axid†.

Nocloprost *(rINN)*

Nocloprostum. (*Z*)-7-[(1*R*,2*R*,3*R*,5*R*)-5-Chloro-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyl-1-octenyl]cyclopentyl]-5-heptenoic acid.

Ноклопрост

$C_{22}H_{37}ClO_4$ = 401.0.

CAS — 79360-43-3.

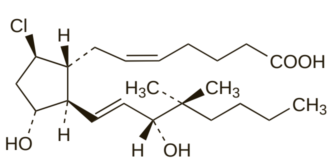

Profile

Nocloprost is a synthetic analogue of dinoprostone (prostaglandin E_2) that has been investigated in the treatment of peptic ulcer disease.

◊ References.

1. Täuber U, *et al.* Pharmacokinetics of nocloprost in human volunteers and its relation to dose. *Eur J Clin Pharmacol* 1993; **44:** 497–500.
2. Konturek JW, *et al.* Epidermal growth factor in gastric ulcer healing by nocloprost, a stable prostaglandin E2 derivative. *Scand J Gastroenterol* 1997; **32:** 980–4.

Octatropine Methylbromide *(BAN, rINN)*

Anisotropine Methobromide; Anisotropine Methylbromide *(USAN)*; Metilbromuro de octatropina; Octatropine, Méthylbromure d'; Octatropini Methylbromidum. (1*R*,3*r*,5*S*)-8-Methyl-3-(2-propylvaleryloxy)tropanium bromide.

Октатропина Метилбромид

$C_{17}H_{32}BrNO_2$ = 362.3.

CAS — 80-50-2.

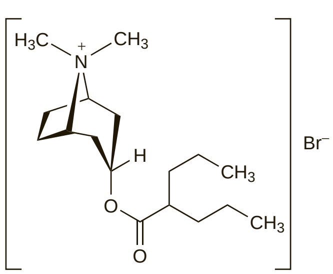

Pharmacopoeias. In *It.*

Profile

Octatropine methylbromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease and to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Espasmo Dioxadol; ***Chile:*** Bufacyl; Valpin; ***Ital.:*** Valpinax.

Olsalazine Sodium *(BANM, USAN, rINNM)*

Azodisal Sodium; CI Mordant Yellow 5; CJ-91B; Colour Index No. 14130; Natrii Olsalazinum; Olsalatsiininatrium; Olsalazin disodná sůl; Olsalazin Sodyum; Olsalazina sódica; Olsalazine sodique; Olsalazinnatrium; Olsalazino natrio druska; Olsalazinum Dinatricum; Olsalazinum natricum; Olszalazin-nátrium; Sodium Azodisalicylate. Disodium 5,5′-azodisalicylate.

Натрий Ольсалазин

$C_{14}H_8N_2Na_2O_6$ = 346.2.

CAS — 6054-98-4.

ATC — A07EC03.

ATC Vet — QA07EC03.

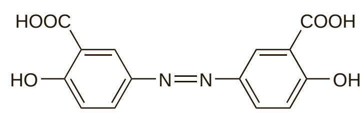

(olsalazine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Olsalazine Sodium). A yellow, fine, crystalline powder; it exhibits polymorphism. Sparingly soluble in water; soluble in dimethyl sulfoxide; very slightly soluble in methyl alcohol.

Adverse Effects and Precautions

As for Mesalazine, p.1745. The most common adverse effects associated with olsalazine sodium are diarrhoea, arthralgia, and skin rashes. Diarrhoea may be watery in some patients; it may resolve with dosage reduction but can be severe enough to require withdrawal of treatment. Diarrhoea is less likely if the drug is taken after meals. There have been a few reports of blood dyscrasias. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Incidence of adverse effects. In an open study[1] of olsalazine 1 g daily by mouth involving 160 patients with active ulcerative colitis and a history of sulfasalazine intolerance, 103 (64.4%) patients had no adverse effects; 29 patients reported only minor adverse effects: gastrointestinal disturbances in 22 patients, transient skin rash in 3, and headache, increased salivation, cough, and irritability each in one patient. The most common adverse effect was frequent loose stools which affected 25 patients, 20 of whom had to stop treatment. This adverse effect occurred early in treatment, within 10 hours of the first dose in 13 patients. Severe diarrhoea was more frequent in patients with widespread disease, but the incidence of diarrhoea did not correlate with disease severity.

A subsequent study[2] in healthy subjects has shown that olsalazine has a significant inhibitory effect on water and electrolyte absorption in the small intestine, which may account, at least in part, for the induction of diarrhoea. Patients with extensive colitis have reduced colonic absorptive function and may be less able to assimilate the increased colonic inflow volumes.

1. Sandberg-Gertzén H, *et al.* Azodisal sodium in the treatment of ulcerative colitis: a study of tolerance and relapse-prevention properties. *Gastroenterology* 1986; **90:** 1024–30.
2. Raimundo AH, *et al.* Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. *Gut* 1991; **32:** 270–4.

Breast feeding. A study[1] involving a 39-year-old woman with Crohn's disease found that olsalazine did not appear to present a clinically significant risk to the breast-fed infant. Olsalazine was undetectable in the breast milk for 48 hours after a single oral 500-mg dose, and although small amounts of the metabolite acetylated 5-aminosalicylic acid were detected in breast milk the infant showed no adverse effects during the 3 weeks afterwards in which the mother continued taking olsalazine.

1. Miller LG, *et al.* Disposition of olsalazine and metabolites in breast milk. *J Clin Pharmacol* 1993; **33:** 703–6.

Effects on the blood. As of July 1995, the UK CSM had received 4 reports of blood dyscrasias associated with olsalazine, none of them fatal.[1] It was recommended that a blood count be performed and the drug stopped immediately if there was suspicion of a dyscrasia. See also under Mesalazine, p.1745.

1. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)

Effects on the kidneys. A report of nephrotoxicity, characterised by interstitial nephritis, was associated with the use of olsalazine.[1] Symptoms resolved on stopping of the drug. See also under Mesalazine, p.1745.

1. Wilcox GM, *et al.* Nephrotoxicity associated with olsalazine. *Am J Med* 1996; **100:** 238–40.

Interactions

Antineoplastics. For mention of 5-aminosalicylates such as olsalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Mercaptopurine, p.744.

Pharmacokinetics

Very little of an oral dose of olsalazine is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 2 molecules of 5-aminosalicylic acid (mesalazine). Some mesalazine is absorbed and acetylated (see p.1746) but systemic concentrations of mesalazine and its metabolite are lower than after comparable oral doses of mesalazine, perhaps because there is less release of mesalazine in the small intestine, where absorption is better. Mesalazine concentrations in the colon after a dose of olsalazine are stated to be about 1000 times greater than systemic concentrations.

The small amounts (1 to 2% of the dose or less) of intact olsalazine that are absorbed are excreted mainly in urine; the elimination half-life after an intravenous dose has been calculated at about 1 hour. Some olsalazine is metabolised by sulfate conjugation in the liver: the elimination half-life of the metabolite is reported to be about 7 days.

◊ References.

1. Ryde EM. Pharmacokinetic aspects of drugs targeted for the colon, with special reference to olsalazine. *Acta Pharm Suec* 1988; **25:** 327–8.
2. Laursen LS, *et al.* Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; **31:** 1271–6.

Uses and Administration

Olsalazine consists of two molecules of mesalazine (p.1745) linked with an azo bond. It is activated in the colon where the active mesalazine is released. It is used as the sodium salt in the management of acute mild ulcerative colitis and for the maintenance of remission (see Inflammatory Bowel Disease, p.1697). The usual initial dose of olsalazine sodium is 1 g by mouth daily in divided doses and this is gradually increased, if necessary, over one week, to a maximum dose of 3 g daily. The usual dose for the maintenance of remission is 500 mg twice daily. Doses should be taken after meals and a single dose should not exceed 1 g. Although not licensed for use in children, the *BNFC* includes a dose for children aged 2 years and over; the adult dose may be given for management of an acute attack of mild ulcerative colitis, and a dose of 250 to 500 mg twice daily may be used for maintenance.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dipentum†; ***Austral.:*** Dipentum; ***Austria:*** Dipentum; ***Canad.:*** Dipentum; ***Chile:*** Dipentum; ***Denm.:*** Dipentum; ***Fin.:*** Dipentum; ***Fr.:*** Dipentum; ***Ger.:*** Dipentum; ***Gr.:*** Dipentum†; ***Hong Kong:*** Dipentum; ***Hung.:*** Dipentum†; ***Irl.:*** Dipentum; ***Israel:*** Dipentum†; ***Ital.:*** Dipentum†; ***Neth.:*** Dipentum; ***Norw.:*** Dipentum; ***NZ:*** Dipentum; ***S.Afr.:*** Dipentum; ***Spain:*** Rasal†; ***Swed.:*** Dipentum; ***Switz.:*** Dipentum; ***Turk.:*** Dipentum; ***UK:*** Dipentum; ***USA:*** Dipentum.

Omeprazole *(BAN, USAN, rINN)*

H-168/68; Omepratsoli; Omeprazol; Omeprazolas; Oméprazole; Omeprazolum. (*RS*)-5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridylmethylsulphinyl)benzimidazole.

Омепразол

$C_{17}H_{19}N_3O_3S = 345.4$.

CAS — 73590-58-6.

ATC — A02BC01.

ATC Vet — QA02BC01.

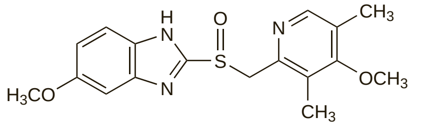

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Omeprazole). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature between 2° and 8°. Protect from light.

USP 31 (Omeprazole). A white to off-white powder. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 8°. Protect from moisture.

Omeprazole Magnesium *(BANM, USAN, rINNM)*

Magnesii Omeprazolum; Omeprazol magnésico; Oméprazole magnésique; Oméprazole Magnesique; Omeprazolum magnesicum.

Магния Омепразол

$C_{34}H_{36}MgN_6O_6S_2 = 713.1$.

CAS — 95382-33-5.

ATC — A02BC01.

ATC Vet — QA02BC01.

Pharmacopoeias. In *US.*

USP 31 (Omeprazole Magnesium). A white to off-white powder. Very soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Omeprazole Sodium *(BANM, USAN, rINNM)*

Natrii Omeprazolum; Omepratsolinatrium; Omeprazol sódico; Omeprazol sodná sůl monohydrát; Oméprazole sodique; Omeprazolnatrium; Omeprazol-nátrium; Omeprazolo natrio druska; Omeprazolum natricum; Omeprazolum Natricum Monohydricum.

Натрий Омепразол

$C_{17}H_{18}N_3NaO_3S = 367.4$.

CAS — 95510-70-6.

ATC — A02BC01.

ATC Vet — QA02BC01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Omeprazole Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane; soluble in propylene glycol. The pH of a 2% solution in water is 10.3 to 11.3. Store in airtight containers. Protect from light.

Adverse Effects

Proton pump inhibitors are generally well tolerated, and adverse effects are relatively infrequent. The adverse effects reported most often with omeprazole and other proton pump inhibitors have been headache, diarrhoea, and skin rashes; they have sometimes been severe enough to require stopping treatment. Other effects include pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Hypersensitivity reactions, including fever, bronchospasm, angioedema, and anaphylaxis have been reported. Effects on the CNS include occasional insomnia, somnolence, and vertigo; reversible confusional states, agitation, depression, and hallucinations have occurred in severely ill patients. Raised liver enzymes, and isolated cases of hepatitis, jaundice, hepatic failure, and hepatic encephalopathy, have been reported. Other adverse effects reported rarely include paraesthesia, blurred vision, alopecia, stomatitis, increased sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, blood disorders (including agranulocytosis, leucopenia, and thrombocytopenia), gynaecomastia, impotence, and interstitial nephritis.

Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects.

Early toxicological studies identified carcinoid-like tumours of the gastric mucosa in *rats* given very high doses of omeprazole over long periods; this is reviewed in more detail under Gastrointestinal Tumours, below.

Incidence of adverse effects. Prescription-event monitoring for 16 205 patients prescribed omeprazole, 17 329 prescribed lansoprazole, and 11 541 prescribed pantoprazole indicated that adverse events were reported infrequently, with the most common being gastrointestinal disturbances and headache. The incidences of diarrhoea, the most commonly reported event, per 1000 days of exposure, were 0.18 for omeprazole, 0.39 for lansoprazole, and 0.23 for pantoprazole. Despite the inherent biases of such a cohort study, there did seem to be some evidence that lansoprazole might be associated with a somewhat greater risk of diarrhoea, particularly in the elderly.[1]

1. Martin RM, *et al.* The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. *Br J Clin Pharmacol* 2000; **50:** 366–72.

Effects on the blood. There have been rare cases of leucopenia, agranulocytosis, thrombocytopenia, and pancytopenia, with omeprazole and other proton pump inhibitors such as lansoprazole and pantoprazole.[1-3] Auto-immune haemolytic anaemia has also been reported with omeprazole.[4]

1. Holt TL, *et al.* Neutropenia associated with omeprazole. *Med J Aust* 1999; **170:** 141–2.
2. Zlabek JA, Anderson CG. Lansoprazole-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 809–11.
3. Watson TD, *et al.* Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 758–61.
4. Butt MI, *et al.* Autoimmune haemolytic anaemia associated with use of omeprazole. *Br J Hosp Med* 2007; **68:** 108.

Effects on the cardiovascular system. Results and preliminary analyses from 2 studies raised concerns about a possible increased risk of myocardial infarction, cardiac failure, and cardiac-related sudden death in patients taking *omeprazole* or *esomeprazole* compared with patients who received surgery for gastro-oesophageal reflux disease.[1,2] However, an FDA safety review found that patients who underwent surgery tended to be younger and less likely to have a history of cardiac problems or cardiac risk factors than those treated with one of the drugs.[2] The FDA concluded that long-term use of these drugs is not likely to be associated with an increased risk of cardiac problems.[3] However, while Health Canada[4] considered that there was no evidence to support such an increased risk with long-term use of esomeprazole they were unable to make such a definitive conclusion for omeprazole.

1. FDA. Early communication about an ongoing safety review: omeprazole (Prilosec) esomeprazole (Nexium) (issued 9th August 2007). Available at: http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm (accessed 28/01/08)
2. FDA. Follow-up to the August 9, 2007, communication about the ongoing safety review of omeprazole and esomeprazole (issued 10th December 2007). Available at: http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole_update.htm (accessed 28/01/08)
3. FDA. FDA's safety reviews of Prilosec and Nexium find no evidence of increased rates of cardiac events (issued 10th December 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01754.html (accessed 28/01/08)
4. Health Canada. Health Canada completes safety review of Losec (omeprazole) and Nexium (esomeprazole) (issued 27 February 2008). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34-eng.php (accessed 09/07/08)

Effects on the endocrine system. Up to December 1991, WHO had received 30 reports of impotence or gynaecomastia which might have been due to omeprazole;[1] of these reports 15 were of impotence, 13 of gynaecomastia in men, and 2 of breast enlargement in women. The Spanish Pharmacovigilance System reported 24 cases of gynaecomastia in association with use of proton pump inhibitors, including lansoprazole and rabeprazole, between January 1982 and July 2006. In most of the cases, gynaecomastia improved after stopping the drug.[2] For reference to a case-control study showing no statistical link between gynaecomastia and omeprazole, see under Cimetidine, p.1717.

1. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. *BMJ* 1992; **305:** 451–2.
2. Carvajal A, *et al.* Gynaecomastia associated with proton pump inhibitors: a case series from the Spanish Pharmacovigilance System. *Drug Safety* 2007; **30:** 527–31.

Effects on the eyes. Visual disturbances associated with the use of omeprazole have included 6 cases of irreversible blindness or visual impairment in severely ill patients given the drug intravenously, and 13 cases of visual disturbances associated with oral use.[1] As a result of concern about these effects the availability of intravenous omeprazole was restricted in Germany; however, the consensus appears to be that a causal link has not been established between omeprazole and these ocular effects. Suggestions that visual (and also auditory[2]) impairment could follow drug-induced vasculitis[2-4] appear to be contentious.[1,5-7] A cohort study involving 140 128 patients receiving antisecretory therapy, 33 988 of whom received omeprazole, found no evidence that any of the drugs used was associated with a major increase in risk of vascular or inflammatory disorders of the eye;[8] however, the statistical power of this study was not high.[9]

1. Creutzfeldt WC, Blum AL. Safety of omeprazole. *Lancet* 1994; **343:** 1098.
2. Schönhöfer PS. Intravenous omeprazole and blindness. *Lancet* 1994; **343:** 665.
3. Schönhöfer PS. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369–70.
4. Schönhöfer PS, *et al.* Ocular damage associated with proton pump inhibitors. *BMJ* 1997; **314:** 1805.
5. Colin-Jones D. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369.
6. Lessell S. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67.
7. Sachs G. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67–8.
8. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.
9. Merlo J, Ranstam J. Ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 449.

Effects on the kidneys. Acute interstitial nephritis developed in 2 elderly patients given *omeprazole* for the treatment of gastro-oesophageal reflux disease.[1,2] When the drug was stopped, renal function improved rapidly in 1 patient, but recurred upon rechallenge,[1] while in the other renal function remained severely affected for several months.[2] It was postulated that this adverse effect might have an allergic mechanism.[2] In these cases interstitial nephritis was associated with rash and eosinophilia; however, a further 2 cases of acute interstitial nephritis associated with omeprazole therapy in elderly patients[3,4] did not exhibit these symptoms. In another report, associated rash without eosinophiluria was seen.[5]

The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[6] stated in April 2003 that it had received 18 biopsy-confirmed reports of interstitial nephritis associated with the use of omeprazole. These patients had presented with symptoms including weight loss, malaise, fever, and nausea; polyuria and polydipsia occurred in one case. Most patients had raised plasma-urea and/or plasma-creatinine concentrations. ADRAC had also received 2 reports of interstitial nephritis associated with *rabeprazole*.[6] A case report (in March 2005) of 2 cases of interstitial nephritis associated with the omeprazole isomer *esomeprazole* noted that, by October 2004, the manufacturer had reported being aware of some 15 cases worldwide possibly associated with the drug, and at least 200 associated with omeprazole.[7] Acute interstitial nephritis has also been associated with the use of *pantoprazole* in an elderly woman for the treatment of gastro-oesophageal reflux disease.[8]

1. Ruffenach SJ, *et al.* Acute interstitial nephritis due to omeprazole. *Am J Med* 1992; **93:** 472–3.
2. Christensen PB, *et al.* Renal failure after omeprazole. *Lancet* 1993; **341:** 55.
3. Assouad M, *et al.* Recurrent acute interstitial nephritis on rechallenge with omeprazole. *Lancet* 1994; **344:** 549.
4. Jones B, *et al.* Acute interstitial nephritis due to omeprazole. *Lancet* 1994; **344:** 1017–18.
5. Kuiper JJ. Omeprazole-induced acute interstitial nephritis. *Am J Med* 1993; **95:** 248.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Interstitial nephritis with the proton pump inhibitors. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0304.htm (accessed 07/05/04)
7. Geevasinga N, *et al.* Acute interstitial nephritis secondary to esomeprazole. *Med J Aust* 2005; **182:** 235–6.
8. Ra A, Tobe SW. Acute interstitial nephritis due to pantoprazole. *Ann Pharmacother* 2004; **38:** 41–5.

Effects on the liver. Raised liver enzymes have occurred with omeprazole and other proton pump inhibitors, and there have been isolated cases of hepatotoxicity. For a study suggesting a relatively low incidence of acute liver injury in patients receiving omeprazole see Cimetidine, p.1717.

References.

1. Jochem V, *et al.* Fulminant hepatic failure related to omeprazole. *Am J Gastroenterol* 1992; **87:** 523–5.
2. Kourg SI, *et al.* Omeprazole and the development of acute hepatitis. *Eur J Emerg Med* 1998; **5:** 467–9.

Effects on the musculoskeletal system. Progressive muscular weakness suggestive of *myopathy* developed in a 78-year-old patient given oral omeprazole.[1] After 4 weeks of treatment the patient required assistance in walking and rising from squatting. Weakness resolved on withdrawal of the drug, but returned on rechallenge. Acute myopathy has also been reported after a single infusion of omeprazole.[2] Analysis of the WHO adverse drug reaction database in March 2005 revealed 868 reports associating proton pump inhibitors with *myalgia*, of which 292 cases had symptoms indicative of muscle disorders including *polymyositis* and *rhabdomyolysis*.[3] Reports implicated omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole, and it was suggested that myopathy was probably a class effect. The mechanism might involve induction of auto-immune antibodies.

A report of 5 cases of *arthralgia*, sometimes associated with swelling of the affected joints, in patients receiving omeprazole,[4] also noted that some reported cases of omeprazole-associated headache were accompanied by arthralgia or myalgia. In another case[5] arthralgia in a patient with a hereditary myopathy receiving omeprazole appeared to represent one aspect of a drug-induced *lupus* syndrome, being accompanied by malaise, fever, Raynaud's phenomenon, raised antinuclear antibody titres, and anticardiolipin and antihistone antibodies. Symptoms resolved on withdrawal of the drug.

A case of *eosinophilia* and myalgia related to lansoprazole treatment has been reported.[6]

There has also been a report of 2 cases of acute *gout* associated with omeprazole;[7] in one patient symptoms, which resolved on withdrawal, recurred on rechallenge. However, case control studies have failed to show an increased risk of polyarthralgia[8] or gout[9] associated with omeprazole use.

A large case-control study found an increased risk of *hip fracture* with more than 1 year of proton pump inhibitor therapy, especially with those patients on high doses.[10] The authors theorised that calcium malabsorption secondary to acid suppression may explain this association. While further studies were deemed necessary to confirm these findings, they suggested that calcium intake be emphasised in elderly patients taking proton pump inhibitors.

1. Garrote FJ, *et al.* Subacute myopathy during omeprazole therapy. *Lancet* 1992; **340:** 672.
2. Tuccori M, *et al.* Acute severe myopathy following a single infusion of omeprazole. *Ann Pharmacother* 2006; **40:** 352–3.
3. Clark DWJ, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol* 2006; **62:** 473–9.
4. Beutler M, *et al.* Arthralgias and omeprazole. *BMJ* 1994; **309:** 1620.
5. Sivakumar K, Dalakas MC. Autoimmune syndrome induced by omeprazole. *Lancet* 1994; **344:** 619–20.
6. Smith JD, *et al.* Possible lansoprazole-induced eosinophilic syndrome. *Ann Pharmacother* 1998; **32:** 196–200.
7. Kraus A, Flores-Suárez LF. Acute gout associated with omeprazole. *Lancet* 1995; **345:** 461–2.
8. Meier CR, Jick H. Omeprazole, H blockers, and polyarthralgia: case-control study. *BMJ* 1997; **315:** 1283.
9. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997; **44:** 175–8.
10. Yang Y-X, *et al.* Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296:** 2947–53. Correction. *ibid.* 2007; **297:** 470.

Effects on the nervous system. Ataxia has been reported in a patient given omeprazole;[1] symptoms resolved on stopping the drug. A patient given rabeprazole developed marked anxiety with panic attacks, episodic night terrors, confusion, and attention deficit.[2] Her symptoms resolved 2 days after stopping therapy. A month later, she was given esomeprazole, with no adverse neuropsychiatric symptoms. The authors hypothesised that rabeprazole use had resulted in significantly greater plasma gastrin concentrations than esomeprazole, which may have affected gastrin receptors in the brain.

1. Varona L, *et al.* Gait ataxia during omeprazole therapy. *Ann Pharmacother* 1996; **30:** 192.
2. Polimeni G, *et al.* Rabeprazole and psychiatric symptoms. *Ann Pharmacother* 2007; **41:** 1315–17.

Effects on the respiratory system. An intractable, dry, non-productive cough started abruptly in a 42-year-old non-smoker given omeprazole for gastro-oesophageal reflux disease (GORD). The cough was initially thought to be related to the GORD and treatment was continued for 4 months, without any cessation in the cough. Omeprazole was stopped, and the cough ceased abruptly, with no recurrence during a 2-year follow-up.[1]

1. Howaizi M, Delafosse C. Omeprazole-induced intractable cough. *Ann Pharmacother* 2003; **37:** 1607–9.

Effects on the skin. An extensive blistering erythematous skin rash in an elderly woman given omeprazole[1] was characteristic of acute disseminated epidermal necrosis. The UK CSM had received 223 reports of cutaneous reactions to omeprazole up to August 1992, including 6 of erythema multiforme, but none of this severity. Other severe reactions that have subsequently been reported include a toxic bullous skin reaction,[2] exfoliative dermatitis,[3,4] erythema multiforme,[4] toxic erythema,[4] and dermatomyositis.[5] One patient developed exfoliative dermatitis with both omeprazole and lansoprazole.[4] The authors of this report noted that by January 1998 a total of 1296 skin reactions to omeprazole, 500 to lansoprazole, and 44 to pantoprazole, had been reported to the CSM. Most were non-specific rashes, pruritus, urticaria, erythematous rashes, and photosensitive eruptions. A lichenoid reaction that occurred in a patient taking omeprazole cleared after ceasing the drug, but recurred during treatment with both lansoprazole and pantoprazole.[6] Proton pump inhibitors, including esomeprazole, have been reported to worsen vitiligo.[7]

For a report of urticaria and angioedema possibly associated with the formulation of omeprazole see Hypersensitivity, below. For the association of rash with interstitial nephritis, see Effects on the Kidneys, above.

1. Cox NH. Acute disseminated epidermal necrosis due to omeprazole. *Lancet* 1992; **340:** 857.
2. Stenier C, *et al.* Bullous skin reaction induced by omeprazole. *Br J Dermatol* 1995; **133:** 343–4.
3. Epelde Gonzalo FD, *et al.* Exfoliative dermatitis related to omeprazole. *Ann Pharmacother* 1995; **29:** 82–3.
4. Cockayne SE, *et al.* Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole. *Br J Dermatol* 1999; **141:** 173–5.
5. Pan Y, *et al.* Omeprazole-induced dermatomyositis. *Br J Dermatol* 2006; **154:** 557–8.
6. Bong JL, *et al.* Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; **320:** 283.
7. Schallreuter KU, Rokos H. From the bench to the bedside: proton pump inhibitors can worsen vitiligo. *Br J Dermatol* 2007; **156:** 1371–3.

Fever. Fever, associated with severe myalgia and headache, was seen in a 64-year-old man on 2 occasions, several hours after taking a dose of esomeprazole.[1] Although it was suggested[2] that the patient's hyperpyrexia was due to a hypersensitivity reaction, the authors argued[3] that esomeprazole may have interfered with the hypothalamic regulatory centres of body temperature.[1,3]

1. Grattagliano I, *et al.* Esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 757–60.
2. Su SS, *et al.* Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1764.
3. Grattagliano I. Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1765.

Gastrointestinal tumours. Early toxicological studies in *rats* given high doses of omeprazole over 2 years identified carcinoid tumours of the gastric mucosa associated with complete block of gastric acid secretion leading to *hypergastrinaemia and hyperplasia of enterochromaffin-like cells*.[1] This has been the main issue concerning the safety of omeprazole and other proton pump inhibitors and initially led to restrictions in use and duration of treatment. A drug manufacturer, *Glaxo*, developed a new test to detect genotoxicity of antisecretory drugs which indicated that a genotoxic effect of omeprazole could not be discounted.[2] This study was heavily criticised; more established genotoxicity tests have been reported to be negative for omeprazole,[3-5] and other groups have not been able to replicate the findings with the new test.[6] The lowest doses at which *Glaxo* found[2] a genotoxic effect of omeprazole were 10 to 20 mg/kg and the clinical significance of their results was questioned.[3] Long-term studies of omeprazole in patients with Zollinger-Ellison syndrome have found no increase in fasting serum-gastrin concentrations and no evidence of gastric carcinoid tumours.[7,8] For mention of the risk of proton pump inhibitors delaying the diagnosis of gastric carcinoma, see under Precautions, below. Hypergastrinaemia can occur with both short- and long-term omeprazole therapy,[9] and may be higher in patients with *Helicobacter pylori* infection.[10,11] Patients who had *H. pylori* eradicated before long-term omeprazole treatment had lower gastrin concentrations than those who did not, since *H. pylori* eradication reduced the pretreatment gastrin concentrations.[12]

H. pylori is also a cause of *atrophic gastritis*, another risk factor for stomach cancer, and one study found that omeprazole increased the risk of atrophic gastritis in *H. pylori*-positive patients with gastro-oesophageal reflux disease.[13] However, the results of this study require confirmation since it was nonrandomised and retrospective. Nevertheless, some have suggested that it may be appropriate to eradicate *H. pylori* before long-term treatment with a proton pump inhibitor.[12,13] Conversely, there is some evidence that *H. pylori* may be protective in gastro-oesophageal reflux disease.[14]

There has been a report of *gastric polyps* developing in 3 of 8 patients after receiving omeprazole 20 or 40 mg daily for one year.[15] In a subsequent report it was noted that these omeprazole-induced fundic gland polyps had remained asymptomatic and non-malignant for up to five years after their onset.[16]

Further long-term studies of omeprazole may be needed before a realistic risk assessment can be made.

1. Ekman L, *et al.* Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985; **20** (suppl 108): 53–69.
2. Burlinson B, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419.
3. Ekman L, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419–20.
4. Wright NA, Goodlad RA. Omeprazole and genotoxicity. *Lancet* 1990; **335:** 909–10.
5. Helander HF, *et al.* Omeprazole and genotoxicity. *Lancet* 1990; **335:** 910–11.
6. Goodlad RA. Acid suppression and claims of genotoxicity: what have we learned? *Drug Safety* 1994; **10:** 413–19.
7. Lloyd-Davies KA, *et al.* Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. *Aliment Pharmacol Ther* 1988; **2:** 13–32.
8. Maton PN, *et al.* Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 1989; **97:** 827–36.
9. Koop H, *et al.* Serum gastrin levels during long-term omeprazole treatment. *Aliment Pharmacol Ther* 1990; **4:** 131–8.
10. Sanduleanu S, *et al.* Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol Ther* 1999; **13:** 145–53.
11. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. *Gut* 2006; **55:** 1217–21.
12. El-Nujumi A, *et al.* Eradicating Helicobacter pylori reduces hypergastrinaemia during long term omeprazole treatment. *Gut* 1998; **42:** 159–65.
13. Kuipers EJ, *et al.* Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; **334:** 1018–22.
14. Labenz J, Malfertheiner P. Helicobacter pylori in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997; **41:** 277–80.
15. Graham JR. Gastric polyposis: onset during long-term therapy with omeprazole. *Med J Aust* 1992; **157:** 287–8.
16. Graham JR. Gastric acne: omeprazole-induced fundic gland polyposis. *Med J Aust* 1998; **168:** 93.

Hypersensitivity. Cases of anaphylactic reactions after treatment with omeprazole, lansoprazole, and pantoprazole, have been reported in the literature and to WHO.[1]

Urticaria, facial angioedema, and bronchospasm in a patient given omeprazole capsules did not recur when the patient was given omeprazole granules and the reaction might have been precipitated by the ingredients of the capsule shell.[2]

See also under Effects on the Kidney, and Effects on the Musculoskeletal System, above.

1. Natsch S, *et al.* Anaphylactic reactions to proton-pump inhibitors. *Ann Pharmacother* 2000; **34:** 474–6.
2. Haeney MR. Angio-oedema and urticaria associated with omeprazole. *BMJ* 1992; **305:** 870.

Infection. Oesophageal candidiasis occurred in 2 elderly patients given omeprazole but was successfully treated with antifungal therapy. It was postulated that gastric acid secretion and a degree of physiological reflux of acid into the oesophagus might normally play a protective role in preventing candidal infection.[1] A case-control study found that yeast was recovered more often from peritoneal cultures in those patients with community-acquired peritonitis who had previously used proton pump inhibitors, although the trend was non-significant.[2] The profound reduction in acid secretion produced by omeprazole may also predispose to gastrointestinal infection;[3] there is some evidence for an increased risk of community-acquired pneumonia,[3] and campylobacter infection,[4] as well as a report of recurrent salmonellal infection.[5] Data from cohort and case-control studies[6-8] suggest that gastric acid suppression by proton pump inhibitors may also be a risk factor for *Clostridium difficile*-associated diarrhoea. For evidence of an increased risk of pneumonia in primary-care patients prescribed proton pump inhibitors see p.1717.

1. Larner AJ, Lendrum R. Oesophageal candidiasis after omeprazole therapy. *Gut* 1992; **33:** 860–1.
2. Cat TB, *et al.* Potential influence of antisecretory therapy on the development of Candida-associated intraabdominal infection. *Ann Pharmacother* 2008; **42:** 185–91.
3. Canani RB, *et al.* Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; **117:** e817–e820.
4. Neal KR, *et al.* Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. *BMJ* 1996; **312:** 414–15.
5. Wingate DL. Acid reduction and recurrent enteritis. *Lancet* 1990; **335:** 222.
6. Cunningham R, *et al.* Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. *J Hosp Infect* 2003; **54:** 243–5.
7. Dial S, *et al.* Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *Can Med Assoc J* 2004; **171:** 33–8.
8. Dial S, *et al.* Use of gastric acid–suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294:** 2989–95.

Lupus syndrome. For a report of drug-induced lupus syndrome associated with omeprazole therapy, see Effects on the Musculoskeletal System, above.

Malabsorption. Omeprazole has been reported to result in a substantial reduction in *cyanocobalamin* (vitamin B_{12}) absorption,[1] probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy.[2] UK licensed product information recommends that severely ill children, who may have borderline body stores of cyanocobalamin, should have serum vitamin B_{12} concentrations monitored if they require long-term therapy. Omeprazole has also been reported to impair the bioavailability of dietary *vitamin C*.[3] *Fat* malabsorption, secondary to increased deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with omeprazole treatment.[4] For the suggestion that proton pump inhibitors can cause *calcium* malabsorption, see Effects on the Musculoskeletal System, above.

1. Marcuard SP, *et al.* Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B). *Ann Intern Med* 1994; **120:** 211–15.
2. Termanini B, *et al.* Effect of long-term gastric acid suppressive therapy on serum vitamin B levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998; **104:** 422–30.
3. Henry EB, *et al.* Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther* 2005; **22:** 539–45.
4. Shindo K, *et al.* Omeprazole induces altered bile acid metabolism. *Gut* 1998; **42:** 266–71.

Overdosage. A report of 2 cases of overdosage with omeprazole.[1] The major clinical features were drowsiness, headache (possibly due to a metabolite), and tachycardia. Both patients recovered uneventfully without specific treatment.

1. Ferner RE, Allison TR. Omeprazole overdose. *Hum Exp Toxicol* 1993; **12:** 541–2.

Precautions

Before giving omeprazole or other proton pump inhibitors to patients with gastric ulcers the possibility of malignancy should be excluded since these drugs may mask symptoms and delay diagnosis. Omeprazole and other proton pump inhibitors should be used with caution in hepatic impairment and dose adjustment may be required.

Gastric carcinoma. Proton pump inhibitors relieve dyspeptic symptoms associated with gastric carcinoma and can therefore delay its diagnosis. In addition, there is some evidence that they may also endoscopically 'heal' early gastric carcinoma so that the diagnosis is missed.[1] Consequently, some commentators recommend that proton pump inhibitors should not be prescribed for symptom control before endoscopy in patients at risk for gastric carcinoma.[2]

1. Wayman J, *et al.* The response of early gastric cancer to proton-pump inhibitors. *N Engl J Med* 1998; **338:** 1924–5.
2. Griffin SM, Raimes SA. Proton pump inhibitors may mask early gastric cancer: dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998; **317:** 1606–7.

Helicobacter infection. Treatment with proton pump inhibitors may cause false-negative results in the urea breath test for *Helicobacter pylori* infection. In one study in patients with *H. pylori* infection, 4 weeks of treatment with lansoprazole 30 mg daily caused 33% of patients to have negative urea breath tests.[1] The breath test became positive again in all patients within 2 weeks of stopping lansoprazole therapy. In a similar study, 52% of patients had negative urea breath tests for *H. pylori* while receiving omeprazole 20 mg daily, and the breath test became positive again in all patients within 2 to 6 days of stopping treatment.[2] The manufacturers of the urea breath test for *H. pylori* recommend that it should not be performed for at least 2 weeks after stopping treatment with an antisecretory drug.

For a discussion of the link between proton pump inhibitors, *H. pylori*, and gastritis, see under Gastrointestinal Tumours above.

1. Laine L, *et al.* Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. *Ann Intern Med* 1998; **129:** 547–50.
2. Connor SJ, *et al.* The effect of dosing with omeprazole on the accuracy of the C-urea breath test in Helicobacter pylori-infected subjects. *Aliment Pharmacol Ther* 1999; **13:** 1287–93.

Hepatic impairment. In patients with cirrhosis an increase in omeprazole bioavailability, and elimination half-life has been reported.[1] For dosage adjustment in hepatic impairment see Administration in Hepatic Impairment, below.

1. Andersson T, *et al.* Pharmacokinetics of [C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.

Pregnancy. Proton pump inhibitors are not generally licensed for use during pregnancy (although the UK has licensed omeprazole for such use), but a meta-analysis[1] of 5 studies of exposure to proton pump inhibitors during the first trimester, involving 593 exposed infants, found the relative risk of major abnormalities associated with such exposure to be only 1.18, with a 95% confidence interval ranging from 0.72 to 1.94. Meta-analysis of exposures to omeprazole (from 4 studies only) gave a relative risk of 1.05 (95% confidence interval 0.59 to 1.85). It was concluded that exposure to proton pump inhibitors, and omeprazole in particular, did not pose an important teratogenic risk. A retrospective epidemiological study of data from the Swedish Medical Birth Registry, which identified 955 exposed infants, also found no evidence of significant risk after exposure to omeprazole during pregnancy.[2]

1. Nikfar S, *et al.* Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002; **47:** 1526–9.
2. Källén BAJ. Use of omeprazole during pregnancy–no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001; **96:** 63–8.

Interactions

Omeprazole and other proton pump inhibitors are metabolised by the cytochrome P450 system, primarily by isoenzyme CYP2C19, and to a smaller extent by CYP3A4. Inhibitors or inducers of these isoenzymes may affect exposure to omeprazole and other proton pump inhibitors. In turn, proton pump inhibitors may alter the metabolism of some drugs metabolised by these enzymes. Omeprazole may prolong the elimination of diazepam, phenytoin, and warfarin (but see below). Omeprazole and other proton pump inhibitors can reduce the absorption of drugs such as dasatinib, ketoconazole, and itraconazole, whose absorption is dependent on an acid gastric pH. With voriconazole, the plasma concentration of both drugs may be increased (for further information, see below). Other proton pump inhibitors may be similarly affected by voriconazole. Omeprazole and other proton pump inhibitors should not be used with atazanavir, as it substantially reduces exposure to atazanavir.For further information on interactions between proton pump inhibitors and HIV-protease inhibitors, see Table 1, under Antivirals, p.917.

◊ Omeprazole is metabolised primarily by the cytochrome P450 isoenzyme CYP2C19 (see Metabolism, below) and therefore may interact with diazepam (see under Gastrointestinal Drugs, p.991). Some metabolism of phenytoin (see p.500), tolbutamide, and the *R*-enantiomer of warfarin (see p.1430) also takes place by CYP2C19, but the effects seen have been minor.[1] Although some induction of CYP1A2, which metabolises caffeine and theophylline (p.1145), has been reported this does not appear to be clinically significant.[2] While some consider the effect of omeprazole on CYP3A4 activity to be insignificant,[3] others have noted an increasing body of evidence that competitive inhibition of intestinal CYP3A4 by omeprazole may affect the first-pass metabolism of a number of drugs.[4] A review concluded that, while omeprazole and possibly esomeprazole have a considerable potential for drug interactions, lansoprazole, pantoprazole and rabeprazole are associated with a lower incidence of drug interactions.[4]

For a study *in vitro* suggesting that omeprazole affected CYP3A4 metabolism of tacrolimus, see under Interactions of Tacrolimus, p.1845. For more on the effect of proton pump inhibitors on tacrolimus, see Gastrointestinal Drugs, p.1845.

For reference to the possibility of enhanced digoxin absorption with omeprazole, see p.1262. For a study suggesting that omeprazole reduces the absorption of cyanocobalamin and vitamin C, see Malabsorption, above, and for its effect on calcium absorption see p.1714. For reference to possible interactions between methotrexate and omeprazole, see p.748.

1. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; **31:** 9–28.
2. Rizzo N, *et al.* Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. *Eur J Clin Pharmacol* 1996; **49:** 491–5.
3. Tateishi T, *et al.* Omeprazole does not affect measured CYP3A4 activity using the erythromycin breath test. *Br J Clin Pharmacol* 1995; **40:** 411–12.
4. Blume H, *et al.* Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Safety* 2006; **29:** 769–84.

Clarithromycin. Studies in healthy subjects have indicated that use of omeprazole with clarithromycin results in an approximate 30% increase in peak plasma concentrations of omeprazole, and an increase in its mean half-life from 1.2 to 1.6 hours.[1] At the same time, plasma concentrations of clarithromycin were also modestly increased, as were local concentrations in gastric tissue and mucus.[1] Clarithromycin inhibits[2] the metabolism of omeprazole mediated by the cytochrome P450 isoenzyme CYP3A4. The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; **39:** 2078–83.
2. Furuta T, *et al.* Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999; **66:** 265–74.

Fluvoxamine. Omeprazole and other proton pump inhibitors are metabolised mainly by cytochrome P450 isoenzyme CYP2C19, which shows genetically determined polymorphism, yielding extensive metabolisers and poor metabolisers. Fluvoxamine increased exposure to omeprazole, lansoprazole, and rabeprazole in patients who were extensive metabolisers, but had no effect on pharmacokinetic parameters in poor metabolisers.[1-3] Dose reductions may need to be considered in patients treated with fluvoxamine and proton pump inhibitors.

1. Yasui-Furukori N, *et al.* Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol* 2004; **57:** 487–94.
2. Yasui-Furukori N, *et al.* Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *J Clin Pharmacol* 2004; **44:** 1223–9.
3. Uno T, *et al.* Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status. *Br J Clin Pharmacol* 2006; **61:** 309–14.

Voriconazole. When omeprazole is given with voriconazole, exposure to both drugs is increased. UK licensed product information for omeprazole states that a dose adjustment of omeprazole is not routinely indicated, unless patients have severe hepatic impairment and long-term therapy is indicated. However, UK licensed product information for voriconazole states that, while no dosage adjustment is considered necessary for voriconazole, when patients already receiving omeprazole are started on voriconazole, the dose of omeprazole should be halved. Other proton pump inhibitors may be similarly affected by voriconazole.

Pharmacokinetics

Omeprazole is rapidly but variably absorbed after oral doses. Absorption is not significantly affected by food. Omeprazole is acid-labile and the pharmacokinetics of the various formulations developed to improve oral bioavailability may vary. The absorption of omeprazole also appears to be dose-dependent; increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first-pass hepatic metabolism. In addition, bioavailability is higher after long-term use.

Bioavailability of omeprazole may be increased in elderly patients, in some ethnic groups such as Chinese, and in patients with hepatic impairment, but is not markedly affected in patients with renal impairment.

On absorption, omeprazole is almost completely metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19 to form hydroxy-omeprazole, and to a small extent by CYP3A4 to form omeprazole sulfone. The metabolites are inactive, and are excreted mostly in the urine and to a lesser extent in bile. The elimination half-life from plasma is reported to be about 0.5 to 3 hours. Omeprazole is about 95% bound to plasma proteins.

◊ References.

1. Andersson T, *et al.* Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol* 1990; **39:** 195–7.
2. Andersson T, Regårdh C-G. Pharmacokinetics of omeprazole and metabolites following single intravenous and oral doses of 40 and 80 mg. *Drug Invest* 1990; **2:** 255–63.
3. Ching MS, *et al.* Oral bioavailability of omeprazole before and after chronic therapy in patients with duodenal ulcer. *Br J Clin Pharmacol* 1991; **31:** 166–70.
4. Landahl S, *et al.* Pharmacokinetic study of omeprazole in elderly healthy volunteers. *Clin Pharmacokinet* 1992; **23:** 469–76.
5. Andersson T, *et al.* Pharmacokinetics of [C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.
6. Jacqz-Aigrain E, *et al.* Pharmacokinetics of intravenous omeprazole in children. *Eur J Clin Pharmacol* 1994; **47:** 181–5.
7. Litalien C, *et al.* Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005; **44:** 441–66.
8. Fock KM, *et al.* Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin Pharmacokinet* 2008; **47:** 1–6.

Metabolism. The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are poor metabolisers of omeprazole. This occurs in about 3% of Caucasians and 15% of Chinese, Japanese, and Koreans. These individuals have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A4, and some by CYP2D6 to form desmethylomeprazole.

References.

1. Andersson T, *et al.* Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; **36:** 521–30.
2. Caraco Y, *et al.* Ethnic and genetic determinants of omeprazole disposition and effect. *Clin Pharmacol Ther* 1996; **60:** 157–67.
3. Karam WG, *et al.* Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; **24:** 1081–7.

Uses and Administration

Omeprazole is a proton pump inhibitor. It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase), the 'proton pump' of the gastric parietal cell. It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes (p.1693), dyspepsia (below), gastro-oesophageal reflux disease (p.1696), peptic ulcer disease (p.1702), and the Zollinger-Ellison syndrome (p.1704).

Esomeprazole (p.1729), an isomer of omeprazole, is also used.

Omeprazole may be given orally as the base or magnesium salt, or intravenously as the sodium salt. Doses are expressed in terms of the base. Omeprazole magnesium 10.32 mg and omeprazole sodium 10.64 mg are each equivalent to about 10 mg of omeprazole.

For the relief of acid-related **dyspepsia** omeprazole is given in usual doses of 10 or 20 mg daily orally for 2 to 4 weeks.

The usual dose for the treatment of **gastro-oesophageal reflux disease** is 20 mg orally once daily for 4 weeks, followed by a further 4 to 8 weeks if not fully healed. In refractory oesophagitis, a dose of 40 mg daily may be used. Maintenance therapy after healing of oesophagitis is 20 mg once daily, and for acid reflux is 10 mg daily. For dosage in children see below.

In the management of **peptic ulcer disease** a single daily dose of 20 mg orally, or 40 mg in severe cases, is given. Treatment is continued for 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer. Where appropriate, a dose of 10 to 20 mg once daily may be given for maintenance.

For the eradication of *Helicobacter pylori* in peptic ulceration omeprazole may be combined with antibacterials in dual or triple therapy. Effective **triple therapy** regimens include omeprazole 20 mg twice daily or 40 mg once daily combined with: amoxicillin 500 mg and metronidazole 400 mg, both three times daily; clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice daily; or with amoxicillin 1 g and clarithromycin 500 mg, both twice daily. These regimens are given for 1 week. **Dual therapy** regimens such as omeprazole 20 mg twice daily or 40 mg daily with either amoxicillin 750 mg to 1 g twice daily or clarithromycin 500 mg three times daily, are less effective and must be given for 2 weeks. Omeprazole alone may be continued for a further 4 to 8 weeks.

Doses of 20 mg daily orally are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients with a history of gastroduodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with the **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20 to 120 mg daily, but doses up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses (usually 2).

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

The dose of omeprazole may need to be reduced in patients with hepatic impairment (see below).

PARENTERAL DOSAGE.

In patients who are unsuited to receive oral therapy omeprazole sodium may be given on a short-term basis by intravenous infusion, in a usual dose equivalent to 40 mg of the base over a period of 20 to 30 minutes in 100 mL of sodium chloride 0.9% or glucose 5%. It may also be given by slow intravenous injection. Higher intravenous doses have been given to patients with Zollinger-Ellison syndrome.

◊ General reviews.

1. Richardson P, *et al.* Proton pump inhibitors: pharmacology and rationale for use in gastrointestinal disorders. *Drugs* 1998; **56:** 307–35.
2. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. *Drugs* 1998; **56:** 447–86.
3. Berardi RR, Welage LS. Proton-pump inhibitors in acid-related diseases. *Am J Health-Syst Pharm* 1998; **55:** 2289–98.
4. Brown GJE, Yeomans ND. Prevention of the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: the role of proton pump inhibitors. *Drug Safety* 1999; **21:** 503–12.
5. Erstad BL. Proton-pump inhibitors for acute peptic ulcer bleeding. *Ann Pharmacother* 2001; **35:** 730–40.
6. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003; **63:** 2739–54.
7. Dekel R, *et al.* The role of proton pump inhibitors in gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 277–95.
8. Anonymous. Proton pump inhibitors for GERD in children. *Med Lett Drugs Ther* 2007; **49:** 17–18.

Administration. Omeprazole is given orally as tablets or capsules containing enteric-coated pellets or granules, which should be swallowed whole and not crushed or chewed. In children or patients with swallowing difficulties, UK licensed product information (*Losec; AstraZeneca*) states that the tablet be dispersed in water and then mixed with fruit juice (with a pH less than 5) or yogurt before swallowing without chewing. Similarly the contents of the capsules can be mixed with water, fruit juice (with a pH less than 5) or yogurt and swallowed without chewing. A mixture of omeprazole and sodium bicarbonate as a powder for oral suspension is available in some countries.

Administration in children. Licensed UK *oral* doses of omeprazole for the treatment of gastro-oesophageal reflux disease in children 1 year of age and over are determined by body-weight as follows:

- 10 to 20 kg: 10 mg once daily
- over 20 kg: 20 mg once daily

These doses may be doubled if necessary. Treatment may be given for 4 to 12 weeks.

For gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including NSAID-associated ulceration, prophylaxis of acid aspiration, and Zollinger-Ellison syndrome, the *BNFC* recommends an oral dose of 700 micrograms/kg once daily in neonates and children 1 month to 2 years of age. If needed, doses may be increased in neonates after 7 to 14 days, to 1.4 mg/kg once daily; some neonates may require up to 2.8 mg/kg once daily. Children's doses may be increased up to 3 mg/kg (to a maximum of 20 mg) once daily.

For *parenteral* dosage in children the *BNFC* recommends an intravenous dose of 500 micrograms/kg (to a maximum of 20 mg) once daily in children aged 1 month to 12 years; this may be increased to 2 mg/kg (to a maximum of 40 mg) once daily if needed.

For the eradication of *Helicobacter pylori* in children, the *BNFC* recommends an oral dose of omeprazole 1 to 2 mg/kg (to a maximum dose of 40 mg) once daily. This is given with antibacterial therapy under specialist supervision.

For administration of the tablets or capsules to children, see Administration, above.

Administration in hepatic impairment. Bioavailability and half-life of omeprazole can increase in patients with hepatic impairment. UK licensed product information recommends that a maximum daily oral dose of 20 mg be used in these patients; a daily intravenous dose of 10 to 20 mg is considered sufficient.

Asthma. Gastro-oesophageal reflux has been suggested as a potential exacerbating factor for asthma (p.1108), and acid suppressive therapy with omeprazole has been reported to reduce asthma symptoms in some[1] but not other[2] studies. A meta-analysis of acid suppressive therapy concluded it was not effective in improving asthma symptoms in most patients with gastro-oesophageal reflux,[3] and the link between reflux and asthma symptoms has been disputed.[4]

1. Harding SM, *et al.* Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; **100:** 395–405.
2. Ford GA, *et al.* Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-oesophageal reflux: a placebo-controlled cross-over study. *Postgrad Med J* 1994; **70:** 350–4.
3. Gibson PG, *et al.* Gastro-oesophageal reflux treatment for asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 11/12/07).
4. Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. *Chest* 1999; **115:** 848–56.

Dyspepsia. Although earlier UK guidelines on the use of proton pump inhibitors in dyspepsia (p.1695) suggested that they should not be used routinely in non-ulcer dyspepsia,[1] subsequent guidelines on its general management in both the UK[2] and the US[3] consider that a 1-month empirical trial in patients aged under 55 without symptoms suggestive of more serious disease is a valid first-line treatment.

1. NICE. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia (issued July 2000). Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf (accessed 11/02/08)
2. NICE. Dyspepsia: management of dyspepsia in adults in primary care (Clinical Guideline 17: issued August 2004, updated June 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf (accessed 11/02/08)
3. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; **129:** 1753–5. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508505018172.pdf (accessed 11/02/08)

Inflammatory bowel disease. There are a few reports[1-3] of responses to omeprazole in patients with inflammatory bowel disease (p.1697). Combination of omeprazole with mesalazine has also been tried.[2]

1. Heinzow U, Schlegelberger T. Omeprazole in ulcerative colitis. *Lancet* 1994; **343:** 477.
2. Dickinson JB. Is omeprazole helpful in inflammatory bowel disease? *J Clin Gastroenterol* 1994; **18:** 317–19.
3. Guslandi M, Tittobello A. Symptomatic response to omeprazole in inflammatory bowel disease. *J Clin Gastroenterol* 1996; **22:** 159–60.

Scleroderma. Gastro-oesophageal reflux is one of the gastrointestinal manifestations of systemic sclerosis, and proton pump inhibitors such as omeprazole play a major role in the management of such gastrointestinal disease.[1] For a discussion of the broader management of the condition see p.1817.

1. Williamson DJ. Update on scleroderma. *Med J Aust* 1995; **162:** 599–601.

Preparations

BP 2008: Gastro-resistant Omeprazole Capsules; Gastro-resistant Omeprazole Tablets;
USP 31: Omeprazole Delayed-Release Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Acimed; Aziatop; Brux; Danlox; Fabrazol; Fendiprazol; Gastec; Gastroprazol; Gastrotem; Klomeprax; Losec; Mucoxol; Omeprasec; Pepticus†; Pravil; Procelac; Prysma; Regulacid; Timezol; Ulcozol; Zoltenk; ***Austral.:*** Acimax; Losec; Maxor†; Meprazol; Omepral; Probitor; ***Austria:*** Helicostad; Losec; Lostad; Medoprazol; Omec; Omegastron; Omepralan; Probitor†; Semiglen†; ***Belg.:*** Docomepra; Logastric; Losec; Omepratop; Sedacid; ***Braz.:*** Belprazol†; Bioprazol†; Elprazol†; Estomepe; Eupept; Fegran†; Gasec; Gaspiren; Gastrib†; Gastrium; Gastrozol; Klispel; Lomepral†; Loprazol; Losaprol†; Losar†; Losec; Lozap†; Lozeprel; Lozix†; Meprazan; Mesopran†; Neoprazol; Novoprazol†; Omegastrol; Omenax; Omep†; Omepramed; Omeprazin; Omeprotec†; Oprazon; Peprazol; Pepsicaps; Prazolex; Prazonil; Prazotom†; Ulcecaps†; Ulcefor; Ulcozol†; Uniprazol; Victrix; Zolpramex†; ***Canad.:*** Losec; ***Chile:*** Lomex; Losec; Micromex; Omeprax; Pepticum†; Prazolo†; Ulc-Out; Ulcelac; Ulcrux†; Zatrol; Zomepral; ***Cz.:*** Apo-Ome; Gasec; Helicid; Lomac; Losec; Loseprazol; Omepirex; Omeprol; Omolin; Onprelen; Oprazole†; Ortanol; Pepticum†; Problok†; Tulzol; Ultop; ***Denm.:*** Losec; ***Fin.:*** Losec; ***Fr.:*** Mopral; Zoltum; ***Ger.:*** Antra; Gastracid; Ome TAD; Ome-nerton; Ome-Puren; Ome-Q; Omebeta; Omedoc; Omegamma; OmeLich; Omelind; Omep; ***Gr.:*** Assoprol; Belifax; Elibactin; Elkostop; Elkotheran; Eselan; Esopraz; Ezipol; Gertalgin; Glaveral; Inhiplex; Kerlofin; Lanex; Lenar; Lomezec; Loproc; Lordin; Losec; Lozaprin; Malortil; Meprolen; Novek; Odamesol; Odasol; Ofnimarex; Omeprol; Penrazol; Pipacid; Prazolin; Probitor; Rythmogastryl; Sedacid; Sieral; Silato; Ufonitren; Veralox; Zolldenol; ***Hong Kong:*** Losec; ***Hung.:*** Losec; Omegen; Omep; Omeprawin; Ulzol; ***India:*** Biocid; Lomac; Nogacid; Ocid; Olit; Omezol; Promisec; Ulzol†; ***Indon.:*** Contral; Dudencer; Loklor; Losec; Meisec; Norsec; Omevell; OMZ; Onic; Opm; Oprezol; Ozid; Prohibit; Promezol; Protop; Pumpitor; Redusec; Regasec; Rocer; Socid; Stomacer; Ulzol; Zepral; Zollocid; ***Irl.:*** BySec; Lopraz; Losamel; Losec; Losepine; Ulcid; ***Israel:*** Losec; Omepradex; ***Ital.:*** Antra; Losec; Mepral; Omeprazen; ***Jpn:*** Omepral; ***Malaysia:*** Gasec; Losec; Medoprazole; Omelon; Omesec; Omez; Omezole; Probitor†; Romesec; Zenpro†; Zimor; ***Mex.:*** Alboz; Aleprozil; Apopraza; Argaryn†; Azoran; Danovag; Domer; Gerdex; Grizol; Hopram†; Ibax; Inhibitron; Logazil; Lopram; Losec; Medral; Mopral; Mornin; Olexin; Omecaps; Ometec; Opramid; Osiren; Ozoken; Panzer; Pastrizol; Pentren; Prazidec; Prazolit; Sarox; Solcer; Suifac; Tarzol; Ucetal; Ulsen; Ultizol; Ultromep; Usaltron; Vulcasid; Zoral; Zulmedx; ***Neth.:*** Losec; Omeprazostad†; Omepstad†; Omezol†; Omolin; Romisan; ***Norw.:*** Losec; ***NZ:*** Losec; Omezol; ***Philipp.:*** Gastriloc; Hovizol; Losec; Mepracid; Omenole; Omepron; Omizac; OMZ; Opehex; Peptisolv; Premio; Promesec; Puroxel; Risek; Tansinel; Ulsek; Zyom; ***Pol.:*** Bioprazol; Gasec; Helicid; Losec; Notis; Omar; Ortanol; Polprazol; Prazol; Ulzol; ***Port.:*** Belmazol; Bloprazol; Eugastrim; Gasec; Losec; Mepraz; Novek; Nuclosina†; Omepra; Omeratio; Omerol†; Ometon; Omezolan; Prazentol; Prazex; Prazolene; Proclor; Proton; ***Rus.:*** Gastrozol (Гастрозол); Helicid (Хелицид); Helol (Хелол); Losec (Лосек); Ocid (Оцид); Omez (Омез); Omipix (Омипикс); Omitox (Омитокс); Omizac (Омизак); Romesec (Ромесек); Sopral (Сопрал)†; Ultop (Ультоп); Ulzol (Улзол); Zerocid (Зероцид); ***S.Afr.:*** Altosec; Losec; Omez; Omiloc; Ulzec; ***Singapore:*** Losec; Ocid; Olit; Omesec; Omezole; Penrazole; Proceptin; Romesec; Zenpro; Zimor; ***Spain:*** Audazol; Aulcer; Belmazol; Ceprandal; Dolintol; Elgam; Emeproton; Gastrimut; Indurgan; Ipirasa; Losec; Miol; Mopral†; Norpramin; Novek; Nuclosina; Omapren; Ompranyt; Parizac; Pepticum; Prysma; Sanamidol; Ulceral; Ulcesep; Ulcometion; Zimor; ***Swed.:*** Losec; ***Switz.:*** Amanol; Antra; Antramups; Gastroprazol; Omed; omepra-basan†; Omezol; Oprazol; ***Thai.:*** Airomet; Desec; Dosate; Duogas; Eselan; Eucid; Gaster; Gomec; Lomac; Losec; Madiprazole; Meiceral; Metsec; Miracid; Nocid; O-Sid; Olit; Omez; Omicap; Oprazole; Probitor; Severon†; Stomec; Ulprazole; Zefxon; Zimor†; ***Turk.:*** Demeprazol; Erbolin; Losec; Omegast; Omeprazid; Omeprol; Prosek; ***UAE:*** Risek; ***UK:*** Heartburn Relief; Losec; Zanprol; ***USA:*** Prilosec; ***Venez.:*** Fordex; Gastronol; Losec; Meprox†; Omebloc; Omevax; Omez†; Omezul; Parsolen; Prazol†; Probitor; Promezol; Tecol†.

Multi-ingredient: ***Austral.:*** Klacid HP 7; Losec Hp 7; ***Braz.:*** Erradic; Helicocid Triplice†; Omepramix; ***Canad.:*** Losec 1-2-3 A; Losec 1-2-3 M; ***Fin.:*** Losec Helira†; ***India:*** Helipac; Nogacid D; Okacid D; OTC HP Kit; ***Malaysia:*** Pylobact Combi; ***NZ:*** Klacid HP 7†; Losec Hp 7; ***Philipp.:*** OAC Hp7; ***Rus.:*** Pylobact (Пилобакт); ***S.Afr.:*** Losec 20 Triple†; ***USA:*** Zegerid.

Ondansetron *(BAN, rINN)*

GR-38032; Ondansétron; Ondansetrón; Ondansetroni; Ondansetronum. (±)-1,2,3,9-Tetrahydro-9-methyl-3-(2-methylimidazol-1-ylmethyl)-carbazol-4(9*H*)-one.

Ондансетрон

$C_{18}H_{19}N_3O$ = 293.4.
CAS — 99614-02-5; 116002-70-1.
ATC — A04AA01.
ATC Vet — QA04AA01.

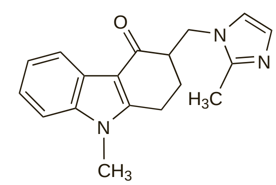

Pharmacopoeias. In *US.*

USP 31 (Ondansetron). A white to off-white powder. Sparingly soluble in water; very soluble in acid solutions. Store in airtight containers. Protect from light.

Ondansetron Hydrochloride *(BANM, USAN, rINNM)*

GR-38032F; Hidrocloruro de ondansetrón; Ondansétron, chlorhydrate d'; Ondansetron hydrochlorid; Ondansetronhydroklorid; Ondansetroni hydrochloridum; Ondansetronihydrokloridi; Ondansetrono hidrochloridas; Ondanstroni Hydrochloridum; Ondánszetronhidroklorid; SN-307.

Ондансетрона Гидрохлорид

$C_{18}H_{19}N_3O,HCl,2H_2O$ = 365.9.
CAS — 99614-01-4; 103639-04-9.
ATC — A04AA01.
ATC Vet — QA04AA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Ondansetron Hydrochloride Dihydrate). A white or almost white powder. Sparingly soluble in water and in alcohol; slightly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 31 (Ondansetron Hydrochloride). A white to off-white powder. Sparingly soluble in water and in alcohol; very slightly soluble in acetone, in chloroform, and in ethyl acetate; slightly soluble in dichloromethane and in isopropyl alcohol; soluble in methyl alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Ondansetron hydrochloride and dexamethasone sodium phosphate were not compatible when high concentrations were combined in polypropylene syringes.[1] Lower concentrations (up to 640 micrograms/mL of ondansetron and 400 micrograms/mL of dexamethasone phosphate) were stable in 50 mL containers of infusion fluid for 30 days under refrigeration. Compatibility has been reported for 24 hours in plastic syringes at 4° or 23° with a variety of other drugs,[2] and with several antineoplastics (cytarabine, dacarbazine, doxorubicin, etoposide, or methotrexate) in PVC infusion bags for 48 hours at room temperature.[3]

1. Hagan RL, *et al.* Stability of ondansetron hydrochloride and dexamethasone sodium phosphate in infusion bags and syringes for 32 days. *Am J Health-Syst Pharm* 1996; **53:** 1431–5.
2. Stewart JT, *et al.* Stability of ondansetron hydrochloride and 12 medications in plastic syringes. *Am J Health-Syst Pharm* 1998; **55:** 2630–4.
3. Stewart JT, *et al.* Stability of ondansetron hydrochloride and five antineoplastic medications. *Am J Health-Syst Pharm* 1996; **53:** 1297–1300.

Adverse Effects and Precautions

Ondansetron and other 5-HT_3 antagonists may cause headache, a sensation of flushing or warmth, hiccups, and constipation. A transient rise in liver enzymes has occasionally occurred. There have been rare reports of immediate hypersensitivity reactions, including anaphylaxis. Chest pain, arrhythmias, hypotension, tachycardia, and bradycardia have been reported rarely. Dizziness and transient visual disturbances such as blurred vision (or very rarely, transient blindness) have been reported during rapid intravenous injection. Transient ECG changes including QT interval prolongation have occurred very rarely, mainly with intravenous ondansetron. Seizures and movement disorders, including extrapyramidal reactions such as dystonia, dyskinesia, and oculogyric crisis have been reported. Rashes and urticaria have also occurred. Injection site reactions may develop, and local burning sensations are common after insertion of suppositories.

5-HT_3 antagonists should generally not be used in patients who have had a hypersensitivity reaction to a member of this drug class. They should be used with care in patients with signs of subacute intestinal obstruction or ileus. Ondansetron should be given in reduced doses to patients with moderate to severe hepatic impairment.

Effects on the cardiovascular system. Chest pain and/or cardiac arrhythmias that might have been associated with ondansetron were reported[1] in 4 patients, 2 of whom died. In 3 subsequent patients who developed severe chest or anginal pain, treatment with ondansetron was stopped.

The manufacturers (*Glaxo*) had at that time no evidence of a causal relationship between ondansetron and episodes of chest pain and cardiac abnormalities.[2] Giving ondansetron or granisetron intravenously produced no clinically important cardiovascular changes in a study in 12 healthy subjects.[3] Since then, however, myocardial ischaemia has been reported with both ondansetron[4] and dolasetron;[5] in the latter case this led to an acute myocardial infarction. Supraventricular tachycardia reported with dolasetron was attributed to an interaction with sevoflurane.[6] Another study in healthy subjects found that dolasetron mainly altered ECG parameters indicative of ventricular depolarisation, whereas ondansetron affected mainly ventricular repolarisation.[7] However, ECG changes were transient and asymptomatic. Studies of high-dose intravenous granisetron[8-10] found no significant adverse effects on pulse, blood pressure, or ECG measurements. A review[11] of the electrocardiographic and cardiovascular effects of the 5-HT_3 antagonists concluded that although this class of drugs may cause small, transient ECG changes, the clinical benefits of the drugs outweighed the small theoretical risk of any clinically significant cardiovascular events. Nonetheless, the use of dolasetron in children has been contra-indicated in the UK (see Uses and Administration, p.1726).

1. Ballard HS, *et al.* Ondansetron and chest pain. *Lancet* 1992; **340:** 1107.
2. Palmer JBD, Greenstreet YL. Ondansetron and chest pain. *Lancet* 1992; **340:** 1410.
3. Boike SC, *et al.* Cardiovascular effects of i.v. granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health-Syst Pharm* 1997; **54:** 1172–6.
4. Bosek V, *et al.* Acute myocardial ischemia after administration of ondansetron hydrochloride. *Anesthesiology* 2000; **92:** 885–7.
5. Arole A, *et al.* Coronary vasospasm leading to an acute myocardial infarction after the administration of dolasetron. *J Clin Anesth* 2005; **17:** 72–4.
6. Higgins DJ, Bunker NJ. Dolasetron and peri-operative cardiac arrhythmia. *Anaesthesia* 2005; **60:** 936–7.
7. Benedict CR, *et al.* Single-blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. *J Cardiovasc Pharmacol* 1996; **28:** 53–9.
8. Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability. *Anticancer Drugs* 2003; **14:** 739–44.
9. Carmichael J, Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. *Cancer Chemother Pharmacol* 2004; **53:** 123–8.
10. Aapro M, Bourke JP. Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic [sic]: results of a pilot study. *Eur J Cancer* 2003; **39:** 927–31.
11. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine receptor antagonists. *Ann Pharmacother* 2003; **37:** 1276–86.

Effects on the eyes. Blurring followed by transient loss of vision has been reported after rapid intravenous injection of ondansetron.[1] Oculogyric crisis may occur as part of extrapyramidal reactions seen with ondansetron, see Effects on the Nervous System, below.

1. Cherian A, Maguire M. Transient blindness following intravenous ondansetron. *Anaesthesia* 2005; **60:** 938–9.

Effects on the liver. Although disturbances in liver enzyme values have been reported in patients given ondansetron, more severe symptoms of liver disorder appear to be very rare; however, there is a report of severe jaundice associated with ondansetron as an antiemetic for chemotherapy.[1] Symptoms did not recur when the patient received granisetron.

1. Verrill M, Judson I. Jaundice with ondansetron. *Lancet* 1994; **344:** 190–1.

Effects on the nervous system. Tonic-clonic movements and frothing at the mouth occurred in a patient 90 minutes after an infusion of ondansetron;[1] the patient responded to diazepam intravenously. The manufacturers had seen 10 patients who developed *seizures* during initial clinical studies, but considered that, unlike this case, all these patients had predisposing factors. Hypotension and generalised tonic-clonic seizures were reported in a patient with metastatic breast cancer given ondansetron as an intravenous bolus.[2] Although seizures might have been due to brain metastases, the authors concluded that ondansetron had been the likely cause, since the patient experienced no further problems when antiemetic therapy was changed to metoclopramide. *Extrapyramidal reactions* in patients given ondansetron as part of a chemotherapy regimen[3,4] and for postoperative nausea and vomiting[5-7] have also been reported. In one case,[7] transient multifocal encephalopathy developed. Clinical manifestations such as clonus, oculogyric crisis, and oromandibular and limb dystonia resembled those of structural brain injury, and response to diphenhydramine was poor; despite this, the patient made a full neurological recovery over the course of 12 hours.

1. Sargent AI, *et al.* Seizure associated with ondansetron. *Clin Pharm* 1993; **12:** 613–15.
2. Sharma A, Raina V. Generalised seizures following ondansetron. *Ann Oncol* 2001; **12:** 131–2.
3. Krstenansky PM, *et al.* Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1994; **28:** 280.
4. Mathews HG, Tancil CG. Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1996; **30:** 196.
5. Stonell C. An extrapyramidal reaction to ondansetron. *Br J Anaesth* 1998; **81:** 658.
6. Tolan MM, *et al.* Perioperative extrapyramidal reactions associated with ondansetron. *Anesthesiology* 1999; **90:** 340–1.
7. Ritter MJ, *et al.* Ondansetron-induced multifocal encephalopathy. *Mayo Clin Proc* 2003; **78:** 1150–2.

Hypersensitivity. Anaphylactoid reactions have been reported in patients given ondansetron injections. The FDA stated in October 1993 that it had received 24 reports of such reactions,[1] mostly occurring after the first ondansetron dose of the second or third chemotherapy cycle, and characterised by urticaria, angioedema, hypotension, bronchospasm, and dyspnoea. Similar effects have been reported in a patient with no prior exposure to ondansetron.[2]

Cross-sensitivity between 5-HT_3 antagonists has been reported;[3] 2 patients who had had a mild hypersensitivity reaction to one 5-HT_3 antagonist developed a more severe reaction after exposure to another. In the first case severe acute asthma, cyanosis, and loss of consciousness developed after ondansetron in a patient who had previously experienced an asthmatic reaction after tropisetron. The second patient had developed pruritus after a tropisetron injection and urticaria after ondansetron, and subsequently developed anaphylactic shock 5 minutes after a further dose of tropisetron. It was recommended that another 5-HT_3 antagonist should not be given as a replacement to patients who developed a hypersensitivity reaction to a drug of this class.

1. Chen M, *et al.* Anaphylactoid-anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993; **119:** 862.
2. Weiss KS. Anaphylactic reaction to ondansetron. *Arch Intern Med* 2001; **161:** 2263.
3. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine -receptor antagonists: a class effect? *Lancet* 1996; **347:** 584–5.

Interactions

Ondansetron does not appear to induce or inhibit the cytochrome P450 isoenzyme system, but it is itself metabolised by multiple hepatic isoenzymes, including CYP3A4, CYP2D6, and CYP1A2. US licensed product information states that inducers or inhibitors of these isoenzymes may change the clearance and half-life of ondansetron, but that on the basis of available data, no dose adjustments are recommended. UK licensed product information states that enzyme inhibition of one isoenzyme is usually compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement. Potent inducers of CYP3A4, such as phenytoin, carbamazepine, and rifampicin, have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Because of the reports of transient ECG changes in some patients taking 5-HT_3 antagonists (see above), there is a theoretical need for caution if given with other drugs that prolong QT-interval; however, clinical evidence of a significant interaction seems to be mostly lacking.

Analgesics. For evidence of reduced analgesic efficacy of *tramadol* in patients also given 5-HT_3-receptor antagonists, such as ondansetron, see p.131.

Antibacterials. *Rifampicin* pretreatment reduced the area under the plasma concentration-time curve of oral ondansetron by 65% and of intravenous ondansetron by 48% in healthy subjects.[1] Use of rifampicin, or other potent inducers of cytochrome P450 isoenzyme CYP3A4, with ondansetron may reduce antiemetic efficacy.

1. Villikka K, *et al.* The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999; **65:** 377–81.

Antineoplastics. For mention of retrospective studies suggesting a change of pharmacokinetic parameters of high-dose cyclophosphamide and cisplatin when given with an ondansetron-containing antiemetic regimen, see Gastrointestinal Drugs, p.703.

Pharmacokinetics

Peak plasma concentrations of ondansetron occur about 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose. The absolute bioavailability is about 60%, mainly because of hepatic first-pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first-pass metabolism.

Ondansetron is extensively distributed in the body; about 70 to 75% of the drug in plasma is protein bound. It is metabolised in the liver through multiple enzymatic pathways; ondansetron is a substrate for cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6. Less than 5% of a dose is excreted unchanged in the urine.

The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use. The terminal elimination half-life is prolonged to about 5 hours in the elderly and in those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patients with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced, with elimination half-lives of 15 to 32 hours; dosage restriction is advisable (see Administration in Hepatic Impairment, below). In general, children have a higher clearance than adults, although age-related reductions in clearance have also been reported, with younger children having lower clearances. Use of weight-based doses compensates for these changes and normalises exposure in paediatric patients.

◊ References.

1. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **29:** 95–109.
2. Figg WD, *et al.* Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol* 1996; **36:** 206–15.
3. Van Den Berg CM, *et al.* Pharmacokinetics of three formulations of ondansetron hydrochloride in healthy volunteers: 24-mg oral tablet, rectal suppository, and iv infusion. *Am J Health-Syst Pharm* 2000; **57:** 1046–50.

Uses and Administration

Ondansetron is a 5-HT_3 antagonist (5-HT_3-receptor antagonist) with antiemetic activity. It is used in the management of **nausea and vomiting** induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. For the management of nausea and vomiting, and the important role of 5-HT_3 antagonists, see p.1700.

Ondansetron is given by intramuscular or slow intravenous injection or infusion as the hydrochloride, by mouth as the hydrochloride or base, or rectally as the base. Doses are expressed in terms of the base. Ondansetron hydrochloride 4.99 mg is equivalent to about 4 mg of ondansetron base.

Numerous dosing schedules of ondansetron have been used; some typical examples are cited below.

For *highly emetogenic* **chemotherapy** the following dose schedules appear to be equally effective in *preventing* acute emesis:

- a single dose of 8 mg by slow intravenous or intramuscular injection immediately before treatment

or

- 8 mg by slow intravenous or intramuscular injection immediately before treatment, either followed by a continuous intravenous infusion of 1 mg/hour for up to 24 hours, or by a further two doses of 8 mg two to four hours apart

or

- a single dose of 32 mg given by intravenous infusion over at least 15 minutes immediately before treatment

or

- 150 micrograms/kg by intravenous infusion over 15 minutes, beginning 30 minutes before chemotherapy, and repeated 4 and 8 hours after the first dose

or

- a 16-mg suppository rectally, given 1 to 2 hours before treatment

or

- a single oral dose of 24 mg taken 30 minutes before the start of single-day chemotherapy

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by giving intravenous dexamethasone sodium phosphate 20 mg before chemotherapy.

Similar regimens to those given above are used for preventing acute emesis with *less emetogenic chemotherapy* and/or **radiotherapy** and also include:

- 8 mg can be given orally up to 2 hours before treatment followed by 8 mg 8 to 12 hours later

To protect against delayed emesis these regimens are followed by oral ondansetron 8 mg twice daily, or 16 mg rectally once daily, for up to 5 days after the end of a course of chemotherapy.

For children the licensed dose in the UK is 5 mg/m^2 intravenously immediately before chemotherapy, followed by 4 mg orally 12 hours later. A dose of 4 mg orally twice daily may be continued for up to 5 days after the end of chemotherapy. The *BNFC* allows (in children aged 1 to 12 years) for 5 mg/m^2 intravenously before chemotherapy (up to a maximum single dose of 8 mg), which can be repeated every 8 to 12 hours during chemotherapy and for at least 24 hours afterwards; alternatively oral doses of 4 mg can be given every 8 to 12 hours for up to 5 days after intravenous use. In the USA a licensed regimen in children over 6 months of age is 150 micrograms/kg by intravenous infusion 30 minutes before chemotherapy, repeated 4 and 8 hours after the first dose. Alternatively, for children aged 4 to 11 years, an oral dose of 4 mg may be given 30 minutes before the start of chemotherapy, with subsequent 4-mg doses given 4 and 8 hours thereafter. An oral dose of 4 mg three times daily may be given for 1 to 2 days after the end of chemotherapy.

To *prevent* **postoperative nausea and vomiting** adults may be given:

- 16 mg orally an hour before anaesthesia

or

- 8 mg orally an hour before anaesthesia followed by 2 further doses of 8 mg at 8-hour intervals

or

- a single dose of 4 mg by intramuscular or slow intravenous injection at induction of anaesthesia

For the *treatment* of postoperative nausea and vomiting a single 4-mg dose by intramuscular or slow intravenous injection is recommended.

In the UK, children aged 2 years and over may be given 100 micrograms/kg by slow intravenous injection, up to a maximum dose of 4 mg, both for the prevention and treatment of postoperative nausea and vomiting; in the USA this dose is licensed from 1 month of age.

In patients with moderate or severe *hepatic impairment* it is recommended that the total daily dose of ondansetron should not exceed 8 mg (see below).

◊ Reviews.

1. Perez EA. A risk-benefit assessment of serotonin 5-HT receptor antagonists in antineoplastic therapy-induced emesis. *Drug Safety* 1998; **18:** 43–56.
2. Gregory RE, Ettinger DS. 5-HT receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. *Drugs* 1998; **55:** 173–89.
3. Lindley C, Blower P. Oral serotonin type 3-receptor antagonists for prevention of chemotherapy-induced emesis. *Am J Health-Syst Pharm* 2000; **57:** 1685–97.
4. Culy CR, *et al.* Ondansetron: a review of its use as an antiemetic in children. *Paediatr Drugs* 2001; **3:** 441–79.
5. Gridelli C. 5-HT -receptor antagonists in the control of delayed-onset emesis. *Anticancer Res* 2003; 23: 2773–82.
6. Constenla M. 5-HT receptor antagonists for prevention of late acute-onset emesis. *Ann Pharmacother* 2004; **38:** 1683–91.
7. Aapro M. 5-HT -receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. *Oncology* 2005; **69:** 97–109.
8. Anonymous. 5HT -receptor antagonists as antiemetics in cancer. *Drug Ther Bull* 2005; **43:** 57–62.

Administration. Ondansetron has been successfully used by continuous *subcutaneous* infusion to control intractable nausea and vomiting.[1] Despite concern about the low pH of ondansetron injection there was no problem with the skin at the infusion site. An *oral* protocol for chemotherapy-induced emesis in children has been described;[2] efficacy was similar to intravenous use.

1. Mulvenna PM, Regnard CFB. Subcutaneous ondansetron. *Lancet* 1992; **339:** 1059.
2. Walker PC, *et al.* Promoting the use of oral ondansetron in children receiving cancer chemotherapy. *Am J Health-Syst Pharm* 2001; **58:** 598–602.

Administration in hepatic impairment. Licensed drug information recommends that the dose of ondansetron should not exceed 8 mg daily in patients with moderate or severe hepatic impairment. When this dose was given intravenously to patients with hepatic impairment, those with severe impairment showed an increase in the area under the plasma concentration/time curve and in the terminal plasma half-life, and a decrease in plasma clearance.[1] The authors of this study, some of whom worked for the manufacturers (*Glaxo*), considered that ondansetron should be restricted to once daily dosage in severe hepatic impairment.

1. Blake JC, *et al.* The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment. *Br J Clin Pharmacol* 1993; **35:** 441–3.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment of bulimia nervosa. Preliminary reports have indicated that ondansetron may be of benefit in the treatment of this disorder.[1,2]

1. Faris PL, *et al.* Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. *Lancet* 2000; **355:** 792–7.
2. Fung SM, Ferrill MJ. Treatment of bulimia nervosa with ondansetron. *Ann Pharmacother* 2001; **35:** 1270–3.

Fatigue. Preliminary results indicated that treatment with 5-HT_3 antagonists such as ondansetron and tropisetron may be of benefit in patients with chronic fatigue.[1] Ondansetron 4 mg twice daily by mouth was reported[2] to resolve fatigue in a woman with chronic hepatitis C. In a randomised study in 36 patients with chronic hepatitis C, this dose of ondansetron given for 1 month significantly improved fatigue scores at day 15 and day 60 (beyond the treatment period) when compared with placebo.[3] The authors noted that patient awareness that constipation was a possible effect of active treatment may have potentially unblinded the study. Further confirmation by larger studies is needed.

1. Späth M, *et al.* Treatment of chronic fatigue syndrome with 5-HT receptor antagonists—preliminary results. *Scand J Rheumatol* 2000; **113** (suppl): 72–7.
2. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999; **354:** 397.
3. Piche T, *et al.* Effect of ondansetron, a 5-HT receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 1169–73.

Pain. Preliminary results from a small crossover study[1] indicated that oral ondansetron was more effective than paracetamol in relieving the pain of fibromyalgia, a chronic disorder that responds poorly to conventional analgesics. A single bolus of ondansetron given to patients with chronic neuropathic pain significantly reduced pain scores 2 hours after injection in a placebo-controlled study;[2] this effect may be due to an action on 5-HT_3 receptors in the spinal cord.

Other 5-HT_3 antagonists such as granisetron[3-5] and tropisetron[6-8] have also been investigated in various painful syndromes.

1. Hrycaj P, *et al.* Pathogenetic aspects of responsiveness to ondansetron (5-hydroxytryptamine type 3 receptor antagonist) in patients with primary fibromyalgia syndrome—a preliminary study. *J Rheumatol* 1996; **23:** 1418–23.
2. McCleane GJ, *et al.* Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. *Anesth Analg* 2003; **97:** 1474–8.
3. Voog O, *et al.* Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders. *Life Sci* 2000; **68:** 591–602.
4. Dubey PK, Prasad SS. Pain on injection of propofol: the effect of granisetron pretreatment. *Clin J Pain* 2003; **19:** 121–4.
5. Ernberg M, *et al.* Effects on muscle pain by intramuscular injection of granisetron in patients with fibromyalgia. *Pain* 2003; **101:** 275–82.
6. Farber L, *et al.* Short-term treatment of primary fibromyalgia with the 5-HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. *Int J Clin Pharmacol Res* 2001; **21:** 1–13.
7. Stratz T, *et al.* Local treatment of tendinopathies: a comparison between tropisetron and depot corticosteroids combined with local anesthetics. *Scand J Rheumatol* 2002; **31:** 366–70.
8. Spath M, *et al.* Efficacy and tolerability of intravenous tropisetron in the treatment of fibromyalgia. *Scand J Rheumatol* 2004; **33:** 267–70.

Pruritus. There are several case reports[1,2] of cholestatic pruritus (p.1582) responding to intravenous or oral ondansetron, including one in pregnancy.[3] However, results from controlled studies[4-6] have been mixed. It is similarly unclear if ondansetron is of benefit in pruritus due to renal failure,[7-9] and results have been conflicting from controlled studies evaluating its use in opioid-induced pruritus.[10-15] There are reports of ondansetron ameliorating the pruritus associated with some skin disorders.[16] Other 5-HT_3 antagonists such as tropisetron[9] and dolasetron[14] have also been investigated.

1. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. *Lancet* 1993; **341:** 1277.
2. Raderer M, *et al.* Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994; **330:** 1540.
3. Schumann R, Hudcova J. Cholestasis of pregnancy, pruritus and 5-hydroxytryptamine 3 receptor antagonists. *Acta Obstet Gynecol Scand* 2004; **83:** 861–2.
4. Müller C, *et al.* Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur J Gastroenterol Hepatol* 1998; **10:** 865–70.
5. O'Donohue JW, *et al.* A controlled trial of ondansetron in the pruritus of cholestasis. *Aliment Pharmacol Ther* 2005; **21:** 1041–5.
6. Jones EA, *et al.* Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology* 2007; **54:** 1196–9.
7. Balaskas EV, *et al.* Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. *Nephron* 1998; **78:** 395–402.
8. Murphy M, *et al.* A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. *Br J Dermatol* 2003; **148:** 314–7.
9. Weisshaar E, *et al.* Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; **13:** 298–304.
10. Borgeat A, Stirnemann H-R. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. *Anesthesiology* 1999; **90:** 432–6.
11. Korhonen AM, *et al.* Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. *Acta Anaesthesiol Scand* 2003; **47:** 1292–7.
12. Wells J, *et al.* Intrathecal fentanyl-induced pruritus during labour: the effect of prophylactic ondansetron. *Int J Obstet Anesth* 2004; **13:** 35–9.
13. Waxler B, *et al.* Prophylactic ondansetron does not reduce the incidence of itching induced by intrathecal sufentanil. *Can J Anesth* 2004; **51:** 685–9.
14. Iatrou CA, *et al.* Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2005; **101:** 1516–20.
15. Siddik-Sayyid SM, *et al.* Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? *Anesth Analg* 2007; **104:** 421–4.
16. Zenker S, *et al.* Behandlung von Pruritus als Symptom von Hauterkrankungen mit dem Serotonin-Rezeptorantagonisten Ondansetron. *J Dtsch Dermatol Ges* 2003; **1:** 705–10.

Psychiatric disorders. Ondansetron has been tried experimentally in a number of psychiatric disorders including schizophrenia,[1-3] and psychosis in patients with parkinsonism,[4] and may be of value in moderating tardive dyskinesia.[5] A reduction in tic severity in Tourette's syndrome (p.954) has been reported,[6] and preliminary results have suggested benefit in obsessive-compulsive disorder,[7] and bulimia nervosa (see above). It is also reported to be under investigation in the management of panic attacks (p.952). For the more conventional management of schizophrenia, parkinsonism, and obsessive-compulsive disorder see p.955, p.791, and p.952, respectively.

1. White A, *et al.* Ondansetron in the treatment of schizophrenia. *Lancet* 1991; **337:** 1173.
2. Adler LE, *et al.* Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. *Am J Psychiatry* 2005; **162:** 386–8.
3. Levkovitz Y, *et al.* The effect of ondansetron on memory in schizophrenic patients. *Brain Res Bull* 2005; **65:** 291–5.
4. Zoldan J, *et al.* Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT receptor antagonist. *Neurology* 1995; **45:** 1305–8.
5. Sirota P, *et al.* Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am J Psychiatry* 2000; **157:** 287–9.

6. Toren P, *et al.* Ondansetron treatment in Tourette's disorder: a 3-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 499–503.
7. Hewlett WA, *et al.* Pilot trial of ondansetron in the treatment of 8 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 1025–30.

Substance dependence. Ondansetron is being studied in the management of alcohol dependence (p.1626). However, in one study[1] a significant reduction in alcohol consumption was found only in lighter drinkers after subgroup analysis. Another study[2] found a reduction in alcohol consumption by patients with early-onset alcoholism (onset before age 25) who took ondansetron compared with placebo. No such effect was seen, however, in patients with late-onset alcoholism. Further study found that ondansetron also effectively ameliorated mood disturbances including symptoms of depression, anxiety, and hostility, in early-onset alcoholics.[3] Self-reported alcohol consumption also reduced in adolescents (between ages 14 and 20) with alcohol dependence who were given ondansetron in an open study.[4]

1. Sellers EM, *et al.* Clinical efficacy of the 5-HT antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res* 1994; **18:** 879–85.
2. Johnson BA, *et al.* Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. *JAMA* 2000; **284:** 963–71.
3. Johnson BA, *et al.* Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. *Alcohol Clin Exp Res* 2003; **27:** 1773–9.
4. Dawes MA, *et al.* A prospective, open-label trial of ondansetron in adolescents with alcohol dependence. *Addict Behav* 2005; **30:** 1077–85.

Preparations

USP 31: Ondansetron Hydrochloride Oral Suspension; Ondansetron Injection; Ondansetron Oral Solution; Ondansetron Orally Disintegrating Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cetron; Dantenk; Dismolan; Emivox†; Espasevit; Finaber; Finoxi; Tiosalis; Zofran; ***Austral.:*** Ondaz; Onsetron; Zofran; ***Austria:*** Glaxosetron; Ondanoglax; Ondensan; Zofran; ***Belg.:*** Zofran; ***Braz.:*** Ansentron; Injectrax; Modifical; Nausedron; Ontrax; Vonau; Zofran; ***Canad.:*** Zofran; ***Chile:*** Amilene; Gardoton; Izofran; Odanex; Oncoemet; Trorix; ***Cz.:*** Danemet; Emeset; Emetron†; Novetron; Ondemet; Setron†; Setronon; Zofran; ***Denm.:*** Hexatron; Zofran; ***Fin.:*** Zofran; ***Fr.:*** Zophren; ***Ger.:*** Zofran; ***Gr.:*** Biosetron; Cruzafen; Dentron; Fedral; Odnatron; Onda; Ondameton; Ondaren; Ondaseprol; Setrodan; Vefron; Zetron; Zodatron; Zofron; Zophralen; ***Hong Kong:*** Zofran; ***Hung.:*** Antivom; Emetron; Ondagen; Zofran; ***India:*** Emeset; Periset; Vomiof; ***Indon.:*** Cedantron; Dantroxal; Entron; Frazon; Invomit; Narfoz; Ondavell; Onetic 4; Vomceran; Zantron; Zofran; ***Irl.:*** Emital; Zofran; ***Israel:*** Zofran; ***Ital.:*** Zofran; ***Malaysia:*** Osetron; Zofran; ***Mex.:*** Danac; Modifical; Precirux; Zofran; ***Neth.:*** Zofran; ***Norw.:*** Zofran; ***NZ:*** Onsetron; Zofran; ***Philipp.:*** Emodan; Zofran; ***Pol.:*** Atossa; Emetron; Setronon; Zofran; ***Port.:*** Nausiend; Otobrol; Zofran; ***Rus.:*** Emetron (Эметрон); Setronon (Сетронон); Zofran (Зофран); ***S.Afr.:*** Dantron; Nausetron; Zofran; ***Singapore:*** Zofran; ***Spain:*** Fixca†; Yatrox; Zofran; ***Swed.:*** Zofran; ***Switz.:*** Zofran; ***Thai.:*** Dantron; Emeset; Onsia; Vomitron†; Zetron; Zofran; ***Turk.:*** Zofer; Zofran; Zoltem; ***UK:*** Ondemet; Zofran; ***USA:*** Zofran; ***Venez.:*** Dismolan; Emeset; Tructum; Zofran.

Ornoprostil *(rINN)*

Ornoprostilo; Ornoprostilum; OU-1308. Methyl (−)-(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-ε,5-dioxocyclopentaneheptanoate.

Орнопростил

$C_{23}H_{38}O_6$ = 410.5.

CAS — 70667-26-4.

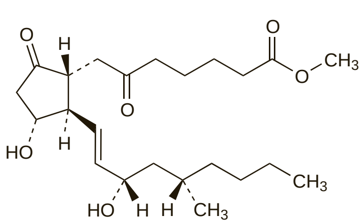

Profile

Ornoprostil is a synthetic prostaglandin analogue that has been used in the treatment of peptic ulcer disease.

Oxapium Iodide *(rINN)*

Ciclonium Iodide; Cyclonium Iodide; Ioduro de oxapio; Oxapii Iodidum; Oxapium, Iodure d'; SH-100. 1-(2-Cyclohexyl-2-phenyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium iodide.

Оксапия Йодид

$C_{22}H_{34}INO_2$ = 471.4.

CAS — 6577-41-9.

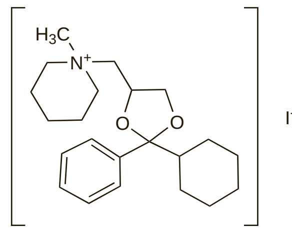

NOTE. Distinguish from ciclonium bromide, p.1716, an unrelated antispasmodic.

Pharmacopoeias. In *Jpn.*

Profile

Oxapium iodide is an antimuscarinic that has been used as an antispasmodic in the treatment of gastrointestinal disorders and renal calculi.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Esperan.

Oxyphencyclimine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de oxifenciclimina; Oksifensiklimin Hidroklorür; Oxyphencyclimine, Chlorhydrate d'; Oxyphencyclimini Hydrochloridum. 1,4,5,6-Tetrahydro-1-methylpyrimidin-2-ylmethyl α-cyclohexylmandelate hydrochloride.

Оксифенциклимина Гидрохлорид

$C_{20}H_{28}N_2O_3$,HCl = 380.9.

CAS — 125-53-1 (oxyphencyclimine); 125-52-0 (oxyphencyclimine hydrochloride).

ATC — A03AA01.

ATC Vet — QA03AA01.

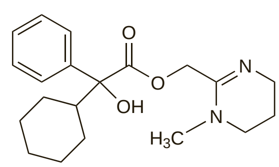

(oxyphencyclimine)

Profile

Oxyphencyclimine hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease and for the relief of smooth muscle spasms in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Daricon; ***Thai.:*** Daricon†; Med-Spastic†; Oxyno; Proclimine.

Multi-ingredient: ***Hong Kong:*** Rudd-U†; ***Turk.:*** Spazmo-Valibrin.

Oxyphenonium Bromide *(BAN, rINN)*

Bromuro de oxifenonio; Oksyfenoniowy bromek; Oxphenonii Bromidum; Oxyphenonii Bromidum; Oxyphenonium Bromatum; Oxyphénonium, Bromure d'. 2-(α-Cyclohexylmandeloyloxy)ethyldiethylmethylammonium bromide.

Оксифенония Бромид

$C_{21}H_{34}BrNO_3$ = 428.4.

CAS — 14214-84-7 (oxyphenonium); 50-10-2 (oxyphenonium bromide).

ATC — A03AB03.

ATC Vet — QA03AB03.

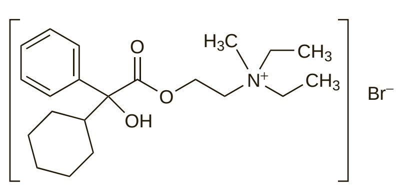

Pharmacopoeias. In *Pol.*

Profile

Oxyphenonium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been given orally to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Antrenyl; ***Pol.:*** Spasmophen; ***S.Afr.:*** Spastrex†.

Multi-ingredient: ***Cz.:*** Endiform†.

Palonosetron Hydrochloride

(USAN, rINNM)

Hidrocloruro de palonosetrón; Palonosétron, Chlorhydrate de; Palonosetroni Hydrochloridum; RS-25259-197. (3a*S*)-2,3,3a,4,5,6-Hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.

Палоносетрона Гидрохлорид

$C_{19}H_{24}N_2O$,HCl = 332.9.

CAS — 135729-56-5 (palonosetron); 135729-55-4 (palonosetron hydrochloride); 135729-62-3 (palonosetron hydrochloride).

ATC — A04AA05.

ATC Vet — QA04AA05.

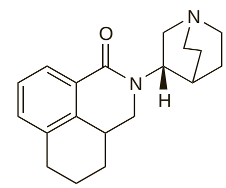

(palonosetron)

Stability. The stability of palonosetron hydrochloride at concentrations of 5 and 30 micrograms/mL was assessed in polyvinyl chloride bags of the following 4 infusion solutions: glucose 5%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, and glucose 5% in lactated Ringer's solution. All solutions were considered to be physically and chemically stable for at least 48 hours at room temperature exposed to light, and for 14 days under refrigeration.[1]

Palonosetron 50 micrograms/mL was found to be physically and chemically stable during simulated Y-site administration with the following drugs: fentanyl citrate 50 micrograms/mL, hydromorphone hydrochloride 500 micrograms/mL, morphine sulfate 15 mg/mL, pethidine hydrochloride 10 mg/mL, and sufentanil citrate (12.5 micrograms/mL of sufentanil).[2]

1. Trissel LA, Xu QA. Physical and chemical stability of palonosetron HCl in 4 infusion solutions. *Ann Pharmacother* 2004; **38:** 1608–11.
2. Trissel LA, *et al.* Physical and chemical stability of palonosetron hydrochloride with five opiate agonists during simulated Y-site administration. *Am J Health-Syst Pharm* 2007; **64:** 1209–13.

Adverse Effects and Precautions

As for Ondansetron, p.1757, although no dosage reduction is considered necessary in hepatic impairment. Diarrhoea, fatigue, and abdominal pain may also occur. Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored if given palonosetron.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Interactions

As for Ondansetron, p.1757.

Pharmacokinetics

Palonosetron has a volume of distribution of around 7 to 8 litres/kg; plasma protein binding is about 62%. About 50% of a dose is metabolised in the liver by cytochrome P450 isoenzymes (notably CYP2D6, but also CYP3A4 and CYP1A2). About 80% of a dose is recovered in the urine within 144 hours, as palonosetron and its metabolites. The mean elimination half-life is reported to be about 40 hours.

◊ References.

1. Hunt TL, *et al.* Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol* 2005; **45:** 589–96.
2. Shah A, *et al.* Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects. *J Clin Pharmacol* 2006; **46:** 1139–45.

Uses and Administration

Palonosetron is a 5-HT_3 antagonist used in the prevention of nausea and vomiting induced by cytotoxic chemotherapy and for the prevention of postoperative nausea and vomiting. Palonosetron is given as the hydrochloride but doses are expressed in terms of the base; 280.8 micrograms of palonosetron hydrochloride is equivalent to about 250 micrograms of palonosetron.

For the prevention of acute and delayed **nausea and vomiting** associated with initial and repeat courses of moderately or highly emetogenic cancer **chemotherapy**, a dose of 250 micrograms is given intravenously over 30 seconds about 30 minutes before chemotherapy. Repeated dosing within 7 days is not recommended.

For the prevention of **postoperative** nausea and vomiting, for up to 24 hours after surgery, a single dose of 75 micrograms is given intravenously over 10 seconds immediately before the induction of anaesthesia. Efficacy beyond 24 hours has not been demonstrated.

◊ References.

1. Eisenberg P, *et al.* Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer* 2003; **98:** 2473–82.
2. Gralla R, *et al.* Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003; **14:** 1570–7.
3. Anonymous. Palonosetron (Aloxi) for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drugs Ther* 2004; **46:** 27–8.
4. Siddiqui MAA, Scott LJ. Palonosetron. *Drugs* 2004; **64:** 1125–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Onicit; ***Chile:*** Onicit; ***Cz.:*** Aloxi; ***Gr.:*** Aloxi; ***Hung.:*** Aloxi; ***Indon.:*** Paloxi; ***Irl.:*** Aloxi; ***Ital.:*** Aloxi; ***Mex.:*** Onicit; ***Neth.:*** Aloxi; ***Pol.:*** Aloxi; ***UK:*** Aloxi; ***USA:*** Aloxi; ***Venez.:*** Onicit.

Pantoprazole *(BAN, USAN, rINN)*

BY-1023; Pantopratsoli; Pantoprazol; Pantoprazolum; SKF-96022.
5-Difluoromethoxybenzimidazol-2-yl 3,4-dimethoxy-2-pyridylmethyl sulphoxide.

Пантопразол

$C_{16}H_{15}F_2N_3O_4S$ = 383.4.
CAS — 102625-70-7.
ATC — A02BC02.
ATC Vet — QA02BC02.

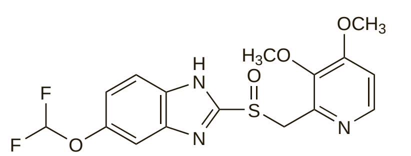

Pantoprazole Sodium *(BANM, USAN, rINNM)*

Natrii Pantoprazolum; Pantoprazol sódico; Pantoprazole sodique; Pantoprazolum natricum. Pantoprazole sodium sesquihydrate.

Натрий Пантопразол

$C_{16}H_{14}F_2N_3NaO_4S, 1 \frac{1}{2} H_2O$ = 432.4.
CAS — 138786-67-1 (anhydrous pantoprazole sodium); 164579-32-2 (pantoprazole sodium sesquihydrate).
ATC — A02BC02.
ATC Vet — QA02BC02.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Pantoprazole Sodium Sesquihydrate). A white or almost white powder. Freely soluble in water and in alcohol; practically insoluble in hexane. Protect from light.

Stability. A suspension of pantoprazole 2 mg/mL in sterile water and sodium bicarbonate was deemed to be physically and chemically stable[1] in amber polyethylene terephthalate bottles for 62 days at 2° to 8°.

1. Dentinger PJ, *et al.* Stability of pantoprazole in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59:** 953–6.

Adverse Effects and Precautions

As for Omeprazole, p.1753. Dosage may need to be reduced in severe hepatic impairment; liver function should be monitored regularly, and therapy stopped if liver enzymes are elevated.

Incidence of adverse effects. In a postmarketing surveillance study of the 6-month period after the launch of pantoprazole in England (UK), the adverse effects reported most frequently were diarrhoea, nausea, and headache. Other effects included malaise or lassitude, rash, other gastrointestinal disturbances, myalgia, and oedema.[1]

1. Wilton LV, *et al.* The pharmacovigilance of pantoprazole: the results of postmarketing surveillance on 11 541 patients in England. *Drug Safety* 2003; **26:** 121–32.

Effects on the blood. For a report of thrombocytopenia with pantoprazole, see under Omeprazole, p.1753.

Effects on the kidneys. For reports of interstitial nephritis associated with pantoprazole see p.1753.

Effects on the skin. For mention of skin reactions to pantoprazole, see p.1754.

Interactions

As for Omeprazole, p.1755.

◊ For reference to a lack of effect of pantoprazole on diazepam, see Gastrointestinal Drugs, p.991, and for a lack of effect on theophylline, see p.1145. Licensed product information states that there are reports of increased prothrombin time in patients taking pantoprazole and warfarin, but for reports suggesting a lack of effect on warfarin, see p.1430. For a report of severe generalised myalgia and bone pain attributed to the use of methotrexate with pantoprazole, see Gastrointestinal Drugs, p.748.

Pharmacokinetics

Pantoprazole is rapidly absorbed and peak plasma-pantoprazole concentrations are achieved about 2 to 2.5 hours after an oral dose. The oral bioavailability is about 77% with the enteric-coated tablet formulation, and does not vary after single or multiple doses. Pantoprazole is about 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19, to desmethylpantoprazole; small amounts are also metabolised by CYP3A4, CYP2D6, and CYP2C9. Metabolites are excreted mainly (about 80%) in the urine, with the remainder being excreted in faeces via the bile. The terminal elimination half-life is about 1 hour, and is prolonged in hepatic impairment; the half-life in patients with cirrhosis was 3 to 6 hours. Although the elimination half-life has been reported to be 3.5 to 10 hours in slow metabolisers (see also Metabolism under Omeprazole, p.1755), minimal accumulation occurs with once-daily dosing.

◊ References.

1. Pue MA, *et al.* Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 1993; **44:** 575–8.

Bioavailability. A suspension of pantoprazole in sodium bicarbonate solution was rapidly absorbed, and peak plasma concentrations were comparable to that of the tablet. However, bioavailability of the suspension was about 25% lower than that of the tablet; the amount of sodium bicarbonate used may affect the bioavailability.[1]

1. Ferron GM, *et al.* Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. *Am J Health-Syst Pharm* 2003; **60:** 1324–9.

Uses and Administration

Pantoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p.1755). It is given as the sodium salt but doses are expressed in terms of the base. Pantoprazole sodium 11.28 mg is equivalent to about 10 mg of pantoprazole. Once-daily doses should be given in the morning.

In the treatment of **gastro-oesophageal reflux disease** (p.1696), the usual oral dose is 20 to 40 mg once daily for 4 weeks, increased to 8 weeks if necessary; in the USA, up to 16 weeks of therapy is permitted for healing of erosive oesophagitis. For maintenance therapy, treatment can be continued with 20 to 40 mg daily. Alternatively, for recurring symptoms, an on-demand regimen of 20 mg daily may be given.

The usual dose for the treatment of **peptic ulcer disease** (p.1702) is 40 mg once daily. Treatment is usually given for 2 to 4 weeks for duodenal ulceration, or 4 to 8 weeks for benign gastric ulceration. For the eradication of *Helicobacter pylori* pantoprazole may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include pantoprazole 40 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

Patients who require prophylaxis for **NSAID-associated ulceration** may take 20 mg daily.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p.1704), the initial dose is 80 mg daily, adjusted as required. Doses of up to 240 mg daily have been used. Daily doses greater than 80 mg should be given in 2 divided doses.

PARENTERAL DOSAGE.

Pantoprazole may also be given intravenously, as the sodium salt, over 2 to 15 minutes, either as a slow injection or a short-term infusion. For peptic ulceration or gastro-oesophageal reflux disease, the recommended dose is 40 mg daily. A dose of 80 mg once or twice daily may be used for Zollinger-Ellison syndrome; up to 240 mg daily may be given in divided doses. Patients should be switched to oral therapy as soon as possible.

Doses of pantoprazole may need to be reduced in patients with hepatic impairment (see below).

◊ Reviews.

1. Anonymous. Pantoprazole—a third proton pump inhibitor. *Drug Ther Bull* 1997; **35:** 93–4.
2. Poole P. Pantoprazole. *Am J Health-Syst Pharm* 2001; **58:** 999–1008.
3. Cheer SM, *et al.* Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; **63:** 101–32.
4. Gisbert JP, *et al.* Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2004; **16:** 89–99.
5. Lehmann FS, Beglinger C. Role of pantoprazole in the treatment of gastro-oesophageal reflux disease. *Expert Opin Pharmacother* 2005; **6:** 93–104.

Administration. The safety and tolerability profiles of intravenous pantoprazole given in 10 mL of sodium chloride 0.9% over 2 minutes were similar to those given over 15 minutes in 100 mL.[1]

1. Micalizzi M, *et al.* Comparative tolerability of 2- and 15-minute intravenous infusions of pantoprazole. *Am J Health-Syst Pharm* 2007; **64:** 1822–6.

Administration in hepatic impairment. Dosage of pantoprazole may need to be reduced in severe hepatic impairment, or doses given only on alternate days. A maximum dose of 20 mg daily orally or intravenously, or 40 mg orally on alternate days, has been suggested. Doses above 40 mg daily have not been studied in patients with hepatic impairment. Liver enzymes should be monitored during therapy, and pantoprazole should be stopped if elevations occur.

Administration in renal impairment. Most studies have not found the pharmacokinetics of pantoprazole to be altered in patients with renal impairment[1] and licensed drug information in the UK and US generally does not recommend dosage adjustment in this group; however some UK sources, including the *BNF*, suggest that a maximum dose of 40 mg daily should be observed.

1. Cheer SM, *et al.* Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. *Drugs* 2003; **63:** 101–132.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gastromax; Pangest; Pantocas; Pantop; Pantus; Peptazol; Sipar; Supracam; Ulserch†; Zurcal†; ***Austral.:*** Somac; ***Austria:*** Pantoloc; Zurcal; ***Belg.:*** Pantozol; Zurcale; ***Braz.:*** Gastropan; Noprop†; Pantocal; Pantopaz†; Pantozol; Pantrat; Peptovit†; Ziprol; Zurcal; ***Canad.:*** Panto; Pantoloc; ***Chile:*** Singastril†; Ulcemex; Zurcal; ***Cz.:*** Apo-Panto; Controloc; Nolpaza; Panogastin; ***Denm.:*** Pantoloc; ***Fin.:*** Somac; ***Fr.:*** Eupantol; Inipomp; ***Ger.:*** Pantozol; Pantozol-Rifun†; Rifun; ***Gr.:*** Controloc; Pantosec; Zurcazol; ***Hong Kong:*** Pantoloc; ***Hung.:*** Controloc; Nolpaza; Pantacid; Zimpax; ***India:*** Eracid†; Pantodac; Pantop; Pantosec; Pentaloc; Praize; ***Indon.:*** Pantozol; ***Irl.:*** Protium; ***Israel:*** Controloc; ***Ital.:*** Pantecta; Pantopan; Pantorc; Peptazol; ***Malaysia:*** Controloc; ***Mex.:*** Pantozol; Prazolan; Tecta; Zolpra; Zurcal; ***Neth.:*** Pantorc; Pantozol; ***Norw.:*** Somac; ***NZ:*** Somac; ***Philipp.:*** Pantoloc; Ulcepraz; ***Pol.:*** Controloc; ***Port.:*** Apton; Pantoc; Praoz; Zurcal; ***Rus.:*** Sunpraz (Санпраз); ***S.Afr.:*** Controloc; Pantocid; Pantoloc; Topzole; ***Singapore:*** Controloc; ***Spain:*** Anagastra; Pantecta; Pantocarm; Ulcotenal; ***Swed.:*** Pantoloc; ***Switz.:*** Pantozol; Zurcal; ***Thai.:*** Controloc; ***Turk.:*** Panthec; Panto; Pantpas; Pulcet; ***UK:*** Protium; ***USA:*** Protonix; ***Venez.:*** Pantop.

Multi-ingredient: ***Austral.:*** Somac-MA; ***Austria:*** Helipac; ***Ger.:*** ZacPac; ***India:*** Pantosec D; Praize-D; ***Malaysia:*** Klacid HP 7; ***Neth.:*** PantoPAC.

Parapenzolate Bromide *(USAN, rINN)*

Bromuro de parapenzolato; Parapenzolate, Bromure de; Parapenzolati Bromidum; Sch-3444. 4-Benziloyloxy-1,1-dimethylpiperidinium bromide.

Парапензолата Бромид

$C_{21}H_{26}BrNO_3$ = 420.3.

CAS — 5634-41-3.

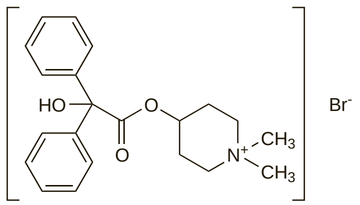

Profile

Parapenzolate bromide is a quaternary ammonium antimuscarinic that has been used for the relief of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Tranvagal†.

Pargeverine Hydrochloride *(rINNM)*

Pargeverina, hidrocloruro de; Pargévérine, Chlorhydrate de; Pargeverini Hydrochloridum; Propinox Hydrochloride. 2-(Dimethylamino)ethyldiphenyl(2-propynyloxy)acetate hydrochloride.

Паргеверина Гидрохлорид

$C_{21}H_{23}NO_3,HCl$ = 373.9.

CAS — 13479-13-5 (pargeverine); 2765-97-1 (pargeverine hydrochloride).

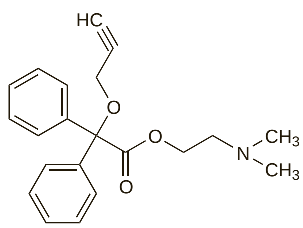

(pargeverine)

Profile

Pargeverine is reported to possess antimuscarinic and smooth-muscle relaxant properties and has been used in the treatment of gastrointestinal and smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nova Paratopina; Pasmosedan†; Sertal; ***Chile:*** Bevitex; Bramedil; Pasmocalm†; Viadil; Viplan; Viproxil; ***Mex.:*** Bipasmin; Plidan; ***Port.:*** Vagopax; ***Venez.:*** Plidan.

Multi-ingredient: ***Arg.:*** Apasmo Compuesto; Binvex; Espasmo Dolex; Nova Paratropina Compositum; Pasmosedan Compuesto†; Propalgin; Sertal Compuesto; ***Chile:*** Bramedil Compuesto; Scopanil; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; ***Mex.:*** Firac Plus; Plidan Compuesto; ***Venez.:*** Dologinex; Plidan Compuesto.

Pentaerythritol

Pentaeritritol; Tetramethylolmethane. 2,2-Bis(hydroxymethyl)propane-1,3-diol.

Пентаэритритол

$C_5H_{12}O_4$ = 136.1.

CAS — 115-77-5.

ATC Vet — QA06AD14.

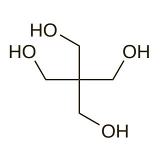

Profile

Pentaerythritol is an osmotic laxative used in the treatment of constipation (p.1693) in oral doses of 5 to 15 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Auxitrans; Hydrafuca†.

Peppermint Leaf

Black Mint; Borsosmentalevél; Hoja de Menta; Hortelã-Pimenta; Liść mięty pieprzowej; List máty peprné; Menta piperita, hoja de; Menth. Pip.; Mentha Piperita; Menthae piperitae folium; Menthe Poivrée; Menthe poivrée, feuille de; Pepparmyntblad; Peppermint; Pfefferminzblätter; Piparmintunlehti; Pipirmėčių lapai; White Mint.

Листья Мяты Перечной

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Peppermint Leaf). The whole or cut dried leaves of *Mentha × piperita*, containing not less than 1.2% v/w of essential oil if whole, or not less than 0.9% v/w if cut. It has a characteristic and penetrating odour and a characteristic aromatic taste. Protect from light.

USNF 26 (Peppermint). The dried leaf and flowering top of *Mentha piperita* (Labiatae). It has an aromatic, characteristic odour and a pungent taste, and produces a cooling sensation in the mouth.

Peppermint Oil

Borsosmentaolaj; Essence de Menthe Poivrée; Essência de Hortelã-Pimenta; Menta piperita, aceite esencial de; Menthae piperitae aetheroleum; Menthae Piperitae Etheroleum; Menthe poivrée, huile essentielle de; Nane Yağı; Ol. Menth. Pip.; Olejek miętowy; Oleum Menthae Piperitae; Pepparmyntolja; Pfefferminzöl; Piparminttuöljy; Pipirmėčių eterinis aliejus; Silice máty peprné.

Масло Мяты Перечной

CAS — 8006-90-4.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Peppermint Oil). It is obtained by steam distillation from the fresh overground parts of the flowering plant of *Mentha × piperita*. It contains 30.0 to 55.0% menthol, 14.0 to 32.0% menthone, and 2.8 to 10.0% menthyl acetate, 3.5 to 14.0% cineole, 1.5 to 10.0% isomenthone, 1.0 to 9.0% menthofuran, 1.0 to 5.0% limonene, not more than 4.0% pulegone, and not more than 1.0% carvone; the ratio of eucalyptol content to limonene content is greater than two.

It is a colourless, pale yellow, or pale greenish-yellow liquid with a characteristic odour and taste followed by a sensation of cold. Miscible with alcohol and with dichloromethane. Store in well-filled, airtight containers. Protect from light and heat.

USNF 26 (Peppermint Oil). The volatile oil distilled with steam from the fresh overground parts of the flowering plant *Mentha piperita* (Labiatae), rectified by distillation, and neither partially nor wholly dementholised. It yields not less than 5% of esters calculated as menthyl acetate and not less than 50% of total menthol, free and as esters.

It is a colourless or pale yellow liquid with a strong, penetrating, characteristic odour and a pungent taste, followed by a sensation of cold when air is drawn into the mouth. Soluble 1 in 3 of alcohol (70%) with not more than slight opalescence. Store in airtight containers at a temperature not exceeding 40°.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that PVC bottles softened and distorted fairly rapidly in the presence of peppermint oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastic medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Adverse Effects and Precautions

Peppermint oil can be irritant and may rarely cause hypersensitivity reactions. Reported reactions include erythematous skin rash, headache, bradycardia, muscle tremor, and ataxia. Heartburn has also been reported.

Effects on the cardiovascular system. Idiopathic atrial fibrillation occurred in 2 patients addicted to 'peppermints'. Normal rhythm was restored when peppermint-sucking ceased.[1]

1. Thomas JG. Peppermint fibrillation. *Lancet* 1962; **i:** 222.

Hypersensitivity. Exacerbation of asthma, with wheezing and dyspnoea, was associated with the use of paste-based toothpastes containing peppermint or wintergreen as a flavouring.[1]

1. Spurlock BW, Dailey TM. Shortness of (fresh) breath—toothpaste-induced bronchospasm. *N Engl J Med* 1990; **323:** 1845–6.

Interactions

Adverse effects may be more likely if peppermint oil is taken with alcohol. Enteric-coated capsules containing peppermint oil should not be taken immediately after food or with antacids. There is some evidence that peppermint oil can inhibit the cytochrome P450 isoenzyme CYP3A4, and may affect the clearance of drugs whose metabolism is mediated by this enzyme.

◊ References.

1. Dresser GK, *et al.* Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. *Clin Pharmacol Ther* 2002; **72:** 247–55.

Uses and Administration

Peppermint oil is an aromatic carminative that relaxes gastrointestinal smooth muscle and relieves flatulence and colic. Enteric-coated capsules containing peppermint oil are used for the relief of symptoms of the irritable bowel syndrome or gastrointestinal spasm secondary to other disorders. Usual oral doses in adults and adolescents from the age of 15 years are 0.2 mL three times daily, (increased to 0.4 mL three times daily if necessary) for up to 2 to 3 months. The capsules should be taken half to one hour before food and swallowed whole, not chewed.

Peppermint oil is used as a flavour and with other volatile agents in preparations for respiratory-tract disorders. It is also used in aromatherapy.

Peppermint leaf, the source of the oil, has also been used for its carminative and flavouring properties.

Gastrointestinal disorders. Menthol (p.2340), the major constituent of peppermint oil, has properties similar to those of calcium-channel blockers on smooth muscle such as that in the human gut.[1] Reviews[2,3] of the use of peppermint oil in irritable bowel syndrome (p.1699) concluded that there was some evidence of its benefit.

The relaxant effect of peppermint oil on the gastrointestinal tract has been used to reduce spasm during endoscopy by giving solubilised peppermint oil directly into the lumen, through the accessory channel of the endoscope. It has been described as effective during colonoscopy[4] and may be more effective than intramuscular hyoscine butylbromide during upper gastrointestinal endoscopy.[5] Addition of peppermint oil to barium enema has also been tried and appears to reduce spasm[6,7] and the need for intravenous antispasmodics.[6]

1. Grigoleit H-G, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. *Phytomedicine* 2005; **12:** 612–16.
2. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol* 1998; **93:** 1131–5.
3. Grigoleit H-G, Grigoleit P. Peppermint oil in irritable bowel syndrome. *Phytomedicine* 2005; **12:** 601–6.
4. Asao T, *et al.* An easy method for the intraluminal administration of peppermint oil before colonoscopy and its effectiveness in reducing colonic spasm. *Gastrointest Endosc* 2001; **53:** 172–7.
5. Hiki N, *et al.* Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* 2003; **57:** 475–82.
6. Sparks MJW, *et al.* Does peppermint oil relieve spasm during barium enema? *Br J Radiol* 1995; **68:** 841–3.
7. Asao T, *et al.* Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with Buscopan. *Clin Radiol* 2003; **58:** 301–5.

Preparations

BP 2008: Concentrated Peppermint Emulsion; Gastro-resistant Peppermint Oil Capsules; Peppermint Spirit;
USNF 26: Peppermint Water;
USP 31: Peppermint Spirit.

Proprietary Preparations (details are given in Part 3)

Austral.: Mintec; ***Austria:*** Colpermin; ***Cz.:*** China-Oel†; Colpermin; Gallentee†; Ki-Min-To†; Mata Pieporna†; Matovy; Nat Maty Peprne; ***Fr.:*** Localbiotal; ***Ger.:*** Chiana†; China-Oel†; Euminz; Inspirol Heilpflanzenol; Medacalm; Mentacur†; spasmo gallo sanol N; Wildkrauterol special K; ***Gr.:*** Colpermin; ***Hong Kong:*** Colpermin; ***Irl.:*** Colpermin; ***Israel:*** China Oel; Colpermin; Po Sum On Medicated Oil; ***Ital.:*** Carmint; Mintoil; ***Mex.:*** Colpermin†; ***NZ:*** Mintec; ***Port.:*** Colominte; ***S.Afr.:*** Pepermentdruppels; ***Singapore:*** Colpermin; ***Switz.:*** Chiana-Oel; Colpermin; ***Thai.:*** Colpermin; ***Turk.:*** China Oel; Colpermin; ***UK:*** Colpermin; Equilon Herbal; Mintec; Obbekjaers.

Multi-ingredient: numerous preparations are listed in Part 3.

Phenamazide Hydrochloride

Fenamazida, hidrocloruro de; Phenamacide Hydrochloride. (±)-α-Aminobenzeneacetic acid 3-methylbutyl ester hydrochloride.

$C_{13}H_{19}NO_2,HCl$ = 257.8.

CAS — 84580-27-8 (phenamazide); 31031-74-0 (phenamazide hydrochloride).

Profile

Phenamazide is an antimuscarinic with actions similar to those of atropine (p.1219). It has been used as the hydrochloride in the treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Aklonin†.

Phenolphthalein (BAN, rINN)

Dihydroxyphthalophenone; Fenolftalein; Fenolftaleína; Fenolftaleinas; Fenoliftaleiini; Fenoloftaleina; Phénolphtaléine; Phenolphtaleinum; Phenolphthaleinum. 3,3-Bis(4-hydroxyphenyl)-phthalide.

Фенолфталеин

$C_{20}H_{14}O_4$ = 318.3.

CAS — 77-09-8.

ATC — A06AB04.

ATC Vet — QA06AB04.

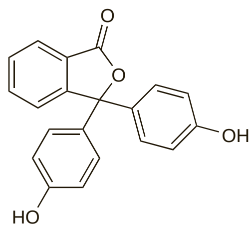

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Phenolphthalein). A white or almost white powder. Practically insoluble in water; soluble in alcohol. Protect from light.

Adverse Effects and Precautions

As for Bisacodyl, p.1710. Hypersensitivity reactions, usually as skin rashes or eruptions, have occurred with phenolphthalein. Phenolphthalein may cause pink discoloration of alkaline urine.

Tumours have occurred in *rats* and *mice* given very high doses of phenolphthalein; there does not appear to be evidence of carcinogenicity in humans, but phenolphthalein-containing products have been withdrawn in many countries because of concerns about long-term safety.

Effects on the skin. Reports of skin reactions associated with phenolphthalein include fixed drug eruptions,[1,2] erythema multiforme reactions,[1,3] and toxic epidermal necrolysis.[4,5]

1. Baer RL, Harris H. Types of cutaneous reactions to drugs. *JAMA* 1967; **202:** 710–13.
2. Savin JA. Current causes of fixed drug eruptions. *Br J Dermatol* 1970; **83:** 546–9.
3. Shelley WB, *et al.* Demonstration of intercellular immunofluorescence and epidermal hysteresis in bullous fixed drug eruption due to phenolphthalein. *Br J Dermatol* 1972; **86:** 118–25.
4. Kar PK, *et al.* Toxic epidermal necrolysis in a patient induced by phenolphthalein. *J Indian Med Assoc* 1986; **84:** 189–93.
5. Artymowicz RJ, *et al.* Phenolphthalein-induced toxic epidermal necrolysis. *Ann Pharmacother* 1997; **31:** 1157–9.

Overdosage. The most likely consequence of phenolphthalein overdosage is excessive purgation, which may require fluid and electrolyte replacement. However, a possible association with acute pancreatitis occurred in a 34-year-old man who inadvertently ingested phenolphthalein 2 g. There was complete recovery with no sequelae from the pancreatitis.[1] Widespread organ failure with disseminated intravascular coagulation, massive liver damage, pulmonary oedema, renal failure, and myocardial damage in a second patient[2] were attributed to self-poisoning with an unknown quantity of phenolphthalein-containing laxative, although the diagnosis was problematic. The patient died despite intensive support.

1. Lambrianides AL, Rosin RD. Acute pancreatitis complicating excessive intake of phenolphthalein. *Postgrad Med J* 1984; **60:** 491–2.
2. Sidhu PS, *et al.* Fatal phenolphthalein poisoning with fulminant hepatic failure and disseminated intravascular coagulation. *Hum Toxicol* 1989; **8:** 381–4.

Pharmacokinetics

Up to 15% of phenolphthalein given orally is subsequently excreted in the urine. Enterohepatic circulation occurs and the glucuronide is excreted in the bile. Elimination may take several days.

Uses and Administration

Phenolphthalein is a diphenylmethane stimulant laxative that has been used for the treatment of constipation (p.1693) and for bowel evacuation before investigational procedures or surgery. It has been withdrawn in many countries because of concern over its carcinogenic potential after reports of tumours in *rodents.*

It has been given in pills or tablets, and as an emulsion with liquid paraffin. Yellow phenolphthalein, an impure form, has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Fructines; ***Chile:*** Felaxen†; ***Cz.:*** Confetto Falqui†; ***Israel:*** Easylax; ***S.Afr.:*** Brooklax; Dr Mackenzies Veinoids; Laxador; Laxene; Laxicaps P†; SB Strong-Lax; Super-Tabs; Surge; ***Singapore:*** Regulim†; ***Switz.:*** Reguletts; ***Thai.:*** Purmolax†; Regulim; ***Turk.:*** Alin; Laksafenol; ***Venez.:*** Agarolax†.

Multi-ingredient: ***Arg.:*** Cascara Sagrada Bouzen†; Cascara Sagrada Pulier†; Genolaxante; Veracolate; ***Austral.:*** Ford Pills; ***Austria:*** Waldheim Abfuhrdragees forte; ***Belg.:*** Grains de Vals; ***Braz.:*** Emagrex†; Fenogar†; Manolio†; Obesidex†; Obesifran†; Prisoventril†; ***Chile:*** Agarol; Bulgarolax; Fenokomp 39; Fenolftaleina Compuesta†; Oblax A-1-1; ***Ger.:*** Vencipon N†; ***Hung.:*** Artin†; Bilagit†; ***India:*** Agarol†; Jetomisol-P; ***Indon.:*** Laxadine; ***Israel:*** Laxative; Laxative Comp; ***Port.:*** Byl†; Caroid†; ***S.Afr.:*** Brooklax Pills; Redupon†; SB 3 Triple Action Pills; Veracolate†; ***Spain:*** Laxante Bescansa Aloico; Mahiou†; ***Switz.:*** Paragar; ***Thai.:*** Emulax; Veracolate; Zenda†; ***Turk.:*** Karboseptin; Musilaks; ***UK:*** Fam-Lax; ***USA:*** Agoral; Doxidan†; ***Venez.:*** Agarol†.

Pipenzolate Bromide (BAN, rINN)

Bromuro de pipenzolato; Pipenzolat Bromür; Pipenzolate, Bromure de; Pipenzolate Methylbromide; Pipenzolati Bromidum. 3-Benziloyloxy-1-ethyl-1-methylpiperidinium bromide.

Пипензолата Бромид

$C_{22}H_{28}BrNO_3$ = 434.4.

CAS — 13473-38-6 (pipenzolate); 125-51-9 (pipenzolate bromide).

ATC — A03AB14.

ATC Vet — QA03AB14.

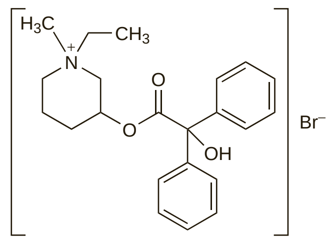

Profile

Pipenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of gastrointestinal disorders characterised by smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Ila-med m; ***Mex.:*** Expal; Pipzen; ***Turk.:*** Piptalin.

Multi-ingredient: ***Chile:*** Baldmin; Gasorbol; Sinpasmon; ***Indon.:*** Piptal; ***Mex.:*** Espasal; Espasin†; Expal Compuesto; Finprob; ***Turk.:*** Asilon; Libkol; ***UAE:*** Alinal†.

Piperidolate Hydrochloride (BANM, rINNM)

Hidrocloruro de piperidolato; Pipéridolate, Chlorhydrate de; Piperidolati Hydrochloridum. 1-Ethyl-3-piperidyl diphenylacetate hydrochloride.

Пиперидолата Гидрохлорид

$C_{21}H_{25}NO_2,HCl$ = 359.9.

CAS — 82-98-4 (piperidolate); 129-77-1 (piperidolate hydrochloride).

ATC — A03AA30.

ATC Vet — QA03AA30.

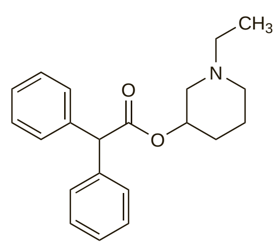

(piperidolate)

Profile

Piperidolate hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p.1219). It has been given in the symptomatic treatment of smooth muscle spasm associated with gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Dactil OB.

Multi-ingredient: ***Braz.:*** Dactil OB.

Pipethanate Ethobromide (rINNM)

Ethylpipethanate Bromide; Etobromuro de pipetanato; Piperilate Ethobromide; Pipéthanate, Ethobromure de; Pipethanati Ethobromidum. 1-(2-Benziloyloxyethyl)-1-ethylpiperidinium bromide.

Пипетаната Этобромид

$C_{23}H_{30}BrNO_3$ = 448.4.

CAS — 4546-39-8 (pipethanate); 23182-46-9 (pipethanate ethobromide).

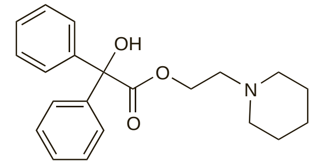

(pipethanate)

Profile

Pipethanate ethobromide is an antimuscarinic with actions similar to those of atropine (p.1219). It has been used in the symptomatic treatment of visceral spasms in oral doses of up to 160 mg daily in divided doses. Pipethanate ethobromide has also been given intramuscularly or intravenously in doses of 10 to 20 mg daily and rectally in doses of 60 or 120 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Nospasmin; ***Ital.:*** Spasmodil; ***Jpn:*** Panpurol†.

Multi-ingredient: ***Chile:*** Nospasmin Compuesto.

Pirenzepine Hydrochloride (BANM, USAN, rINNM)

Hidrocloruro de pirenzepina; LS-519 (pirenzepine); LS-519-Cl2; Pirentsepiinidihydrokloridimonohydraatti; Pirenzepin-dihidrokloridmonohidrát; Pirenzepin-dihydrochlorid monohydrát; Pirenzepindihydrokloridmonohydrat; Pirenzépine, Chlorhydrate de; Pirenzépine (dichlorhydrate de) monohydraté; Pirenzepini dihydrochloridum monohydricum; Pirenzepini Hydrochloridum; Pirenzepino dihidrochloridas monohidratas. 5,11-Dihydro-11-(4-methylpiperazin-1-ylacetyl)pyrido[2,3-*b*][1,4]benzodiazepin-6-one dihydrochloride monohydrate.

Пирензепина Гидрохлорид

$C_{19}H_{21}N_5O_2,2HCl,H_2O$ = 442.3.

CAS — 28797-61-7 (pirenzepine); 29868-97-1 (pirenzepine hydrochloride).

ATC — A02BX03.

ATC Vet — QA02BX03.

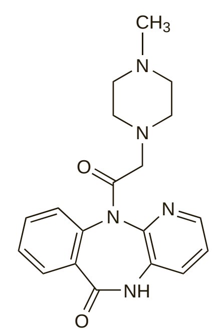

(pirenzepine)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Pirenzepine Dihydrochloride Monohydrate; Pirenzepine Hydrochloride BP 2008). A white or yellowish crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane; slightly soluble in methyl alcohol. A 10% solution in water has a pH of 1.0 to 2.0. Protect from light.

Adverse Effects and Precautions

Dry mouth and blurred vision have been reported but the risk of antimuscarinic effects (see Atropine Sulfate, p.1219) may be reduced. Pirenzepine should be used with caution in patients with renal impairment, particularly those with end-stage renal failure.

Effects on the blood. Thrombocytopenia in one patient and agranulocytosis in another was probably associated with the use of pirenzepine.[1]

1. Stricker BHC, *et al.* Blood disorders associated with pirenzepine. *BMJ* 1986; **293:** 1074.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics

Pirenzepine is absorbed from the gastrointestinal tract but the bioavailability is reported to be only about 20 to 30%, and is decreased to about 10 to 20% when taken with food. Very little pirenzepine is metabolised. About 10% of an oral dose is excreted unchanged in the urine, the remainder being excreted in the faeces.

Pirenzepine has an elimination half-life of about 12 hours and is about 12% bound to plasma proteins. Diffusion across the blood-brain barrier is poor and only minimal amounts are present in breast milk.

Renal impairment. The renal clearance and total plasma clearance of pirenzepine may be significantly reduced in patients with renal impairment,[1,2] with clearance decreasing proportionately with the degree of renal impairment. The half-life of pirenzepine is increased with reported values ranging from 14 to 20 hours.[1-3] Plasma concentrations of pirenzepine may be reduced by up to about 50% during haemodialysis.[2,3]

1. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with hepatic insufficiency and combined renal- and hepatic insufficiency. *Eur J Clin Pharmacol* 1989; **36:** 71–3.
2. Krakamp B, *et al.* Steady-state intravenous pharmacokinetics of pirenzepine in patients with differing degrees of renal dysfunction. *Eur J Clin Pharmacol* 1989; **36:** 75–8.
3. MacGregor T, *et al.* Oral pharmacokinetics of pirenzepine in patients with chronic renal insufficiency, failure, and maintenance haemodialysis. *Eur J Clin Pharmacol* 1990; **38:** 405–6.

Uses and Administration

Pirenzepine is a selective M_1 tertiary amine antimuscarinic that displays a preferential action on the gastric mucosa thus causing a reduction in the secretion of gastric acid; it also reduces the secretion of pepsin. At therapeutic doses it has few other antimuscarinic actions.

Pirenzepine hydrochloride has been used in the management of peptic ulcer disease (p.1702) in a usual oral dose of 50 mg two or three times daily for 4 to 6 weeks. It has also been given by slow intravenous injection in doses of up to 60 mg daily.

Myopia. Pirenzepine ophthalmic gel has been investigated[1-3] in children for its potential in slowing the progression of myopia. In a study[3] involving 353 children with myopia, pirenzepine 2% gel given once or twice daily into the lower eyelid for 1 year was associated with reduced progression: at 12 months myopia had progressed by a mean of 0.7 and 0.47 dioptres in children assigned to once and twice daily dosage respectively, compared with 0.84 dioptres in those given placebo. The gel was generally well tolerated, the most frequent adverse effects being development of papillae or follicles, or abnormalities of accommodation such as mydriasis or cycloplegia. Of 55 patients who failed to complete the study, 31 did so as a result of adverse effects.

1. Bartlett JD, *et al.* A tolerability study of pirenzepine ophthalmic gel in myopic children. *J Ocul Pharmacol Ther* 2003; **19:** 271–9.
2. Siatkowski RM, *et al.* US Pirenzepine Study Group. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol* 2004; **122:** 1667–74.
3. Tan DTH, *et al.* Asian Pirenzepine Study Group. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology* 2005; **112:** 84–91.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Droxol†; ***Austria:*** Gastrozepin; ***Cz.:*** Gastrozepin†; ***Ger.:*** Gastricur†; Gastrozepin; Ulcoprotect†; ***Gr.:*** Gastrozepin†; ***Ital.:*** Frazim†; Gastropiren; ***Jpn:*** Gastrozepin; ***Neth.:*** Gastrozepin†; ***Port.:*** Gastrozepina†; ***Rus.:*** Gastrozepin (Гастроцепин); ***Switz.:*** piren-basan†; ***Thai.:*** Cevanil†; ***Venez.:*** Ligeral†.

Multi-ingredient: ***Arg.:*** Duo Vizerul†.

Platyphylline Acid Tartrate

Platyphylline Bitartrate; Platyphyllini Hydrotartras. 1,2-Dihydro-12-hydroxysenecionan-11,16-dione hydrogen tartrate.

Платифиллина Битартрат

$C_{18}H_{27}NO_5,C_4H_6O_6$ = 487.5.

CAS — 480-78-4 (platyphylline); 1257-59-6 (platyphylline acid tartrate).

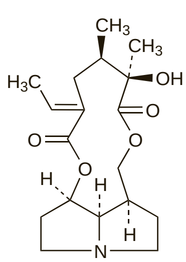

(platyphylline)

Profile

Platyphylline acid tartrate is a pyrrolizidine alkaloid occurring in *Senecio platyphyllus* and other *Senecio* spp. It has antimuscarinic actions and has been given with papaverine in antispasmodic preparations.

Plaunotol (rINN)

CS-684; Plaunotolum. (2*Z*,6*E*)-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-6-methyl-2,6-octadiene-1,8-diol.

Плаунотол

$C_{20}H_{34}O_2$ = 306.5.

CAS — 64218-02-6.

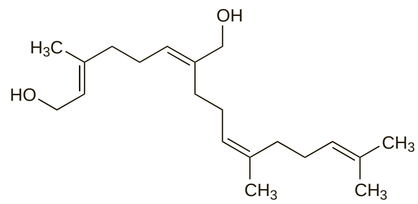

Profile

Plaunotol is a complex aliphatic alcohol extracted from the Thai medicinal plant plau-noi (*Croton sublyratus* (Euphorbiaceae)). It is reported to possess cytoprotective properties and has been used in the treatment of gastritis and peptic ulcer disease in an oral dose of 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Kelnac; ***Thai.:*** Kelnac.

Polaprezinc (rINN)

Polaprézinc; Polaprezincum; Z-103; Zinc-L-carnosine. *catena*-Poly{zinc-μ-[β-alanyl-L-histidinato(2-)-*N*,*N*[N],*O*:*N*[τ]]}.

Полапрезинк

$(C_9H_{12}N_4O_3Zn)_n$.

CAS — 107667-60-7.

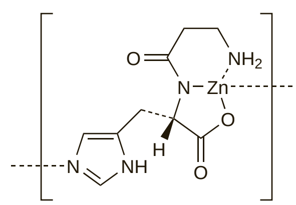

Profile

Polaprezinc is a cytoprotective agent used in the treatment of peptic ulcer disease.

Poldine Metilsulfate (BAN, pINN)

IS-499; McN-R-726-47; Metilsulfato de poldina; Poldine Methosulphate; Poldine Methylsulfate *(USAN)*; Poldine Methylsulphate; Poldine, Métilsulfate de; Poldini Metilsulfas. (*RS*)-2-Benziloyloxymethyl-1,1-dimethylpyrrolidinium methylsulphate.

Польдина Метилсульфат

$C_{21}H_{26}NO_3,CH_3O_4S$ = 451.5.

CAS — 596-50-9 (poldine); 545-80-2 (poldine metilsulfate).

ATC — A03AB11.

ATC Vet — QA03AB11.

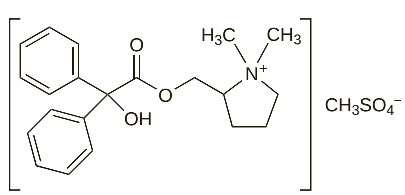

Pharmacopoeias. In *Br.*

BP 2008 (Poldine Metilsulfate). A white odourless or almost odourless crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. A 1% solution in water has a pH of 5.0 to 7.0.

Profile

Poldine metilsulfate is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219) and has been used in the management of gastrointestinal disorders, including peptic ulcer disease.

Preparations

BP 2008: Poldine Tablets.

Polycarbophil (BAN, rINN)

Policarbofilo; Polycarbophile; Polycarbophilum.

Поликарбофил

CAS — 9003-97-8.

Pharmacopoeias. In *US.*

USP 31 (Polycarbophil). It is polyacrylic acid cross-linked with divinyl glycol. White to creamy-white granules, with a characteristic, ester-like odour. Swells in water to a range of volumes, depending primarily on the pH. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. A 1% mixture in water has a pH of not more than 4.0. Store in airtight containers.

Polycarbophil Calcium (BANM, rINNM)

AHR-3260B; Calcii Polycarbophilum; Calcium Polycarbophil *(USAN)*; Policarbofilo cálcico; Polycarbophile Calcique; Polycarbophilum Calcii; Polykarbofiilikalsium; Polykarbofilkalcium; Polykarbophilum Calcicum; WI-140.

Кальций Поликарбофил

CAS — 126040-58-2.

ATC — A06AC08.

ATC Vet — QA06AC08.

Pharmacopoeias. In *US.*

USP 31 (Calcium Polycarbophil). A white to creamy-white powder. Insoluble in water, in common organic solvents, and in dilute acids and alkalis. It loses not more than 10% of its weight on drying and contains not less than 18% and not more than 22% of calcium, calculated on the dried basis. Store in airtight containers.

Adverse Effects and Precautions

As for Ispaghula, p.1737. Polycarbophil calcium releases calcium ions in the gastrointestinal tract and should be avoided by patients who must restrict their calcium intake.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such bulk laxatives are swallowed dry. Therefore, they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Interactions

The calcium component of polycarbophil calcium may produce interactions typical of calcium salts (p.1677), such as reducing the absorption of tetracyclines from the gastrointestinal tract; it should not be taken within 2 hours of the antibacterial. Polycarbophil calcium has also been reported to decrease the absorption of ciprofloxacin and mycophenolate mofetil.

Uses and Administration

Polycarbophil calcium has similar properties to ispaghula (p.1737) and is used as a bulk laxative and for adjusting faecal consistency. After ingestion calcium ions are replaced by hydrogen ions from gastric acid and the resultant polycarbophil exerts a hydrophilic effect in the intestines.

It is given orally in a usual dose equivalent to 1 g of polycarbophil up to four times daily, as necessary. Doses should be taken with at least 250 mL of water.

Polycarbophil is used topically as a vaginal moisturiser and as an ocular lubricant.

◊ References.

1. Danhof IE. Pharmacology, toxicology, clinical efficacy, and adverse effects of calcium polycarbophil, an enteral hydrosorptive agent. *Pharmacotherapy* 1982; **2:** 18–28.
2. Toskes PP, *et al.* Calcium polycarbophil compared with placebo in irritable bowel syndrome. *Aliment Pharmacol Ther* 1993; **7:** 87–92.
3. Chiba T, *et al.* Colonic transit, bowel movements, stool form, and abdominal pain in irritable bowel syndrome by treatments with calcium polycarbophil. *Hepatogastroenterology* 2005; **52:** 1416–20.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Fibercon†; ***Austral.:*** Replens; ***Austria:*** Fibercon†; ***Belg.:*** Replens†; ***Braz.:*** Muvinor; ***Canad.:*** Replens; ***Gr.:*** Fibercon†; ***Israel:*** Fibercon†; ***Ital.:*** Modula; Replens; ***Jpn:*** Colonel; ***Mex.:*** Fibercon†; ***Neth.:*** Fibercon†; ***Spain:*** Replens†; ***Swed.:*** Replens; ***Thai.:*** Fibercon†; ***USA:*** Equalactin; Fiber-Lax; Fibercon; FiberNorm; Replens.

Multi-ingredient: ***Ital.:*** Ormobyl CM†; ***USA:*** Aquasite†.

Potassium Acid Tartrate

E336; Hydrogenvinan draselný; Kalii hydrogenotartras; Kaliovandenilio tartratas; Kalium Hydrotartaricum; Kálium-hidrogéntartarát; Kaliumvätetartrat; Kaliumvetytartraatti; Potassium Bitartrate (USAN); Potassium Hydrogen Tartrate; Potassium, hydrogénotartrate de; Potasu wodorowinian; Purified Cream of Tartar; Tartarus Depuratus; Tartrato ácido de potasio; Weinstein.

Кислый Виннокислый Калий

$C_4H_5KO_6$ = 188.2.

CAS — 868-14-4.

ATC — A12BA03.

ATC Vet — QA12BA03.

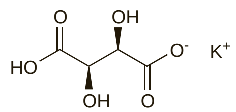

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Potassium Hydrogen Tartrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

USP 31 (Potassium Bitartrate). Colourless or slightly opaque crystals or a white, crystalline powder. Slightly soluble in water; soluble in boiling water; very slightly soluble in alcohol. A saturated solution is acid to litmus. Store in airtight containers.

Profile

Potassium acid tartrate is given with sodium bicarbonate as a suppository for the treatment of constipation (p.1693) and for bowel evacuation before investigational procedures or surgery. Carbon dioxide gas is produced in the rectum, which stimulates defaecation within 5 to 30 minutes.

Potassium acid tartrate is used as a food additive and pharmaceutical aid.

Potassium acid tartrate has been used as an ingredient of preparations for potassium supplementation, although other potassium salts are usually preferred. For the general properties of potassium salts, see p.1684.

Preparations

BPC 1968: Effervescent Potassium Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Austria:* Lecicarbon; ***Braz.:*** Circanetten†; Varicell†; ***Ital.:*** Potassion; ***Swed.:*** Relaxit; ***Thai.:*** Circanetten; ***USA:*** Ceo-Two.

Potassium Sodium Tartrate

E337; Kalii natrii tartras; Kalio-natrio tartratas; Kalium Natrium Tartaricum; Kálium-nátrium-tartarát; Kaliumnatriumtartraatti; Kaliumnatriumtartrat; Potassium et de sodium, tartrate de; Rochelle Salt; Seignette Salt; Sodii et Potassii Tartras; Sodium Potassium Tartrate; Sodu potasu winian; Tartarus Natronatus; Tartrato de potasio y de sodio; Vinan draselno-sodný.

Виннокислый Калий-натрий

$C_4H_4KNaO_6,4H_2O$ = 282.2.

CAS — 304-59-6 (anhydrous sodium potassium tartrate); 6381-59-5 (sodium potassium tartrate tetrahydrate); 6100-16-9 (sodium potassium tartrate tetrahydrate).

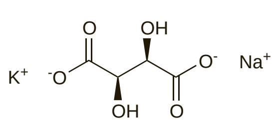

(anhydrous sodium potassium tartrate)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Potassium Sodium Tartrate Tetrahydrate). A white or almost white, crystalline powder or colourless transparent crystals. Very soluble in water; practically insoluble in alcohol.

USP 31 (Potassium Sodium Tartrate). Colourless crystals or a white, crystalline powder, with a cooling, saline taste. It effloresces slightly in warm dry air, the crystals often being coated with a white powder. Soluble 1 in 1 of water; practically insoluble in alcohol. Store in airtight containers.

Profile

Potassium sodium tartrate has been used as an osmotic laxative (p.1693). It is also used as a food additive.

For the general properties of potassium salts, see p.1684, and of sodium salts, see p.1686.

Preparations

BPC 1973: Compound Effervescent Powder.

Proprietary Preparations (details are given in Part 3)
Gr.: Trigolax.

Multi-ingredient: *Austria:* Laxalpin; ***Fr.:*** Romarene; ***Philipp.:*** Castoria; ***UK:*** Jaaps Health Salt.

Prifinium Bromide (rINN)

Bromuro de prifinio; PDB; Prifinii Bromidum; Prifinium, Bromure de; Pyrodifenium Bromide. 3-Diphenylmethylene-1,1-diethyl-2-methylpyrrolidinium bromide.

Прифиния Бромид

$C_{22}H_{28}BrN$ = 386.4.

CAS — 10236-81-4 (prifinium); 4630-95-9 (prifinium bromide).

ATC — A03AB18.

ATC Vet — QA03AB18.

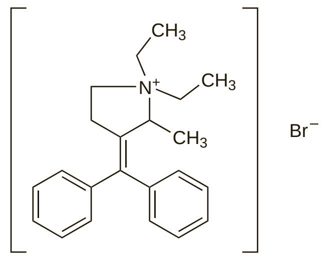

Profile

Prifinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It is structurally related to diphemanil metilsulfate (p.2295).

Prifinium bromide is used to relieve smooth muscle spasms. Oral doses usually range from 90 to 180 mg daily in 3 divided doses. It has also been given rectally in a dose of 60 mg three or four times daily, or by subcutaneous, intramuscular, or intravenous injection in a dose of 15 mg given 2 to 4 times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Riabal†; ***Ital.:*** Riabal; ***Jpn:*** Padrin†; ***Mex.:*** Anespas; ***Rus.:*** Riabal (Риабал); ***Thai.:*** Riabal†.

Proglumide (BAN, USAN, rINN)

CR-242; Proglumida; Proglumidum; W-5219; Xylamide. (±)-4-Benzamido-*N*,*N*-dipropylglutaramic acid.

Проглумид

$C_{18}H_{26}N_2O_4$ = 334.4.

CAS — 6620-60-6.

ATC — A02BX06.

ATC Vet — QA02BX06.

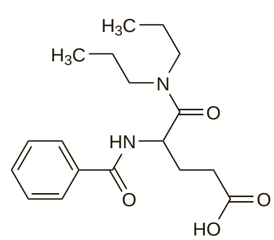

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Proglumide is a cholecystokinin antagonist with an inhibitory effect on gastric secretion. It has been used in the treatment of peptic ulcer disease (p.1702) and other gastrointestinal disorders in usual doses of 400 mg two to four times daily by mouth before meals; up to 800 mg three times daily may be given. It has also been given by intramuscular or intravenous injection in a dose of 400 to 800 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Milid; ***Ital.:*** Milid†; ***Port.:*** Milid†.

Propantheline Bromide (BAN, rINN)

Bromuro de propantelina; Propanteliinibromidi; Propantelin Bromür; Propantelinbromid; Propantelin-bromid; Propantelino bromidas; Propanthéline, bromure de; Propanthelini bromidum; Propanthelinii Bromidum; Propanthelinium-bromid. Di-isopropylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl]ammonium bromide.

Пропантелина Бромид

$C_{23}H_{30}BrNO_3$ = 448.4.

CAS — 298-50-0 (propantheline); 50-34-0 (propantheline bromide).

ATC — A03AB05.

ATC Vet — QA03AB05.

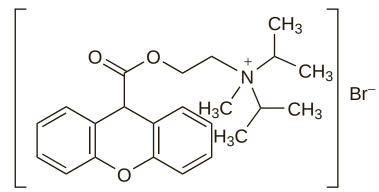

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Propantheline Bromide). A white or yellowish-white, slightly hygroscopic powder. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 31 (Propantheline Bromide). White or practically white, odourless, crystals. Very soluble in water, in alcohol, and in chloroform; practically insoluble in ether and in benzene.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Contact dermatitis has been reported after topical application of propantheline bromide.

Buccal and oesophageal ulceration. Severe buccal mucosal ulceration has been reported[1] in a 95-year-old woman as a result of retaining emepronium bromide tablets in her mouth, and recurred on giving propantheline bromide tablets.

1. Huston GJ, *et al.* Anticholinergic drugs, buccal ulceration and mucosal potential difference. *Postgrad Med J* 1978; **54:** 331–2.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics

Propantheline bromide is incompletely absorbed from the gastrointestinal tract and bioavailability is reported to be reduced by food; it is extensively metabolised in the small intestine before absorption. The plasma elimination half-life after a single oral dose has been reported to be about 2 to 3 hours. Propantheline is eliminated mainly in the urine as metabolites and less than 10% as unchanged drug. The duration of action is about 6 hours.

Uses and Administration

Propantheline bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an antispasmodic (p.1692) for conditions associated with gastrointestinal spasm, and as an adjunct in the treatment of peptic ulcer disease (p.1702). The usual initial oral dose is 15 mg three times daily, 30 to 60 minutes before meals, and 30 mg at bedtime; doses of up to 120 mg daily may be needed in some patients. In elderly patients, doses of 7.5 mg three times daily may be sufficient. Doses of 300 micrograms/kg (to a maximum of 15 mg) given 3 or 4 times daily have been used for the relief of gastrointestinal spasm in children aged 1 month to 12 years; older children may be given the adult dose.

Propantheline bromide has been used in the treatment of adult enuresis or urinary incontinence, and in hyperhidrosis (see below), in doses similar to those given above.

Hyperhidrosis. Some antimuscarinics, including propantheline, have been applied topically in the treatment of hyperhidrosis (p.1580). Adverse effects of antimuscarinics given by mouth generally preclude their use by this route, although oral propantheline was used successfully to control excessive sweating in 2 patients with spinal cord injuries,[1] and it is sometimes used in palliative care to control night sweats. The *BNF* notes that propantheline may be used for gustatory sweating in patients with diabetic neuropathy.

1. Canaday BR, Stanford RH. Propantheline bromide in the management of hyperhidrosis associated with spinal cord injury. *Ann Pharmacother* 1995; **29:** 489–92.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that propantheline should not be recommended for the treatment of urinary incontinence (p.2180) or overactive bladder in women; other antimuscarinics are preferred.[1]

1. National Institute for Health and Clinical Excellence. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf (accessed 03/07/08)

Preparations

BP 2008: Propantheline Tablets;
USP 31: Propantheline Bromide Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pro-Banthine; ***Canad.:*** Propanthel†; ***Denm.:*** Ercoril; ***India:*** Pro-Banthine; ***Indon.:*** Pro-Banthine; ***Mex.:*** Propanthel†; ***NZ:*** Pro-Banthine; ***S.Afr.:*** Pro-Banthine; ***UK:*** Pro-Banthine; ***USA:*** Pro-Banthine.

Multi-ingredient: ***Indon.:*** Methaphyllin; ***Ital.:*** Lexil.

Prune

Ameixa; Ciruela; Prunus.

Слива Домашняя (*Prunus domestica*)

Profile

Prune is the dried ripe fruits of the plum *Prunus domestica* and some other species of *Prunus* (Rosaceae). It has laxative and demulcent properties.

◊ References.

1. Stacewicz-Sapuntzakis M, *et al.* Chemical composition and potential health effects of prunes: a functional food? *Crit Rev Food Sci Nutr* 2001; **41:** 251–86.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Viviolax†.

Multi-ingredient: ***Arg.:*** Cirulaxia; Mermelax; ***Austral.:*** Neo-Cleanse; Prolax†; ***Canad.:*** Fruitatives†; ***Chile:*** Tamarine; ***Fr.:*** Carres Parapsyllium; Laxarine; ***Mex.:*** Ciruelax Jalea; Laxacaps.

Rabeprazole Sodium *(BANM, USAN, rINNM)*

E-3810; LY-307640; Natrii Rabeprazolum; Rabeprazol sódico; Rabeprazol Sodyum; Rabéprazole sodique; Rabeprazolum natricum; Sodium Pariprazole. 2-({[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)-1*H*-benzimidazole sodium.

Натрий Рабепразол

$C_{18}H_{20}N_3NaO_3S$ = 381.4.

CAS — 117976-89-3 (rabeprazole); 117976-90-6 (rabeprazole sodium).

ATC — A02BC04.

ATC Vet — QA02BC04.

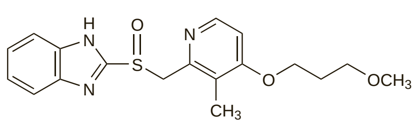

(rabeprazole)

Adverse Effects and Precautions

As for Omeprazole, p.1753.

Effects on the endocrine system. For cases of gynaecomastia associated with rabeprazole see p.1753.

Effects on the kidneys. For reports of interstitial nephritis associated with rabeprazole see p.1753.

Effects on the nervous system. For a report of neuropsychiatric symptoms associated with rabeprazole, see under Omeprazole, p.1754.

Interactions

As for Omeprazole (p.1755) but clinically significant interactions with diazepam, phenytoin, theophylline, or warfarin have not been found in healthy subjects.

Pharmacokinetics

Rabeprazole is rapidly absorbed and peak plasma concentrations are reached about 3.5 hours after an oral dose. The oral bioavailability is about 52% with the enteric-coated tablet formulation, because of first-pass metabolism, and does not appear to vary after single or repeated doses. Rabeprazole is about 97% bound to plasma proteins. It is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP2C19 and CYP3A4 to the thioether, thioether carboxylic acid, sulfone, and desmethylthioether. Metabolites are excreted principally in the urine (about 90%) with the remainder in the faeces. The plasma half-life is about 1 hour, increased two to threefold in hepatic impairment, 1.6 times in CYP2C19 slow metabolisers (see also Metabolism under Omeprazole, p.1755), and by 30% in the elderly.

◊ References.

1. Yasuda S, *et al.* Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4-hydroxylation status. *Clin Pharmacol Ther* 1995; **58:** 143–54.
2. Keane WF, *et al.* Rabeprazole: pharmacokinetics and tolerability in patients with stable, end-stage renal failure. *J Clin Pharmacol* 1999; **39:** 927–33.

Uses and Administration

Rabeprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p.1755). It is given orally as rabeprazole sodium in the form of enteric-coated tablets. It is normally taken in the morning.

In the treatment of severe (erosive or ulcerative) **gastro-oesophageal reflux disease** (p.1696), the usual dose of rabeprazole sodium is 20 mg once daily for 4 to 8 weeks; in the USA, a further 8-week course is permitted for healing of erosive oesophagitis. Thereafter, maintenance therapy can be continued with 10 or 20 mg daily depending on the response. For symptomatic disease without erosive or ulcerative oesophagitis a dose of 10 or 20 mg may be given once daily for 4 weeks; in the USA, a further 4-week course is permitted. Once symptoms have resolved, a dose of 10 mg once daily may be given as necessary.

For the treatment of active **peptic ulcer disease** (p.1702), 20 mg daily is given for 4 to 8 weeks for duodenal ulcer and 6 to 12 weeks for gastric ulcer. For the eradication of *Helicobacter pylori* rabeprazole sodium may be combined with two antibacterials in a 1-week **triple therapy** regimen. Effective regimens include 20 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily.

For **Zollinger-Ellison syndrome** (p.1704), the starting dose is 60 mg once daily, adjusted according to response. Doses up to 120 mg daily have been given; when the daily dose is more than 100 mg it should be given in 2 divided doses.

◊ Reviews.

1. Prakash A, Faulds D. Rabeprazole. *Drugs* 1998; **55:** 261–7.
2. Anonymous. Rabeprazole. *Med Lett Drug Ther* 1999; **41:** 110–12.
3. Carswell CI, Goa KL. Rabeprazole: an update of its use in acid-related disorders. *Drugs* 2001; **61:** 2327–2356.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pariet; Rabec; ***Austral.:*** Pariet; ***Austria:*** Pariet; ***Belg.:*** Pariet; ***Braz.:*** Pariet; ***Canad.:*** Pariet; ***Chile:*** Gastrodine; ***Denm.:*** Pariet; ***Fin.:*** Pariet; ***Fr.:*** Pariet; ***Ger.:*** Pariet; ***Gr.:*** Pariet; ***Hong Kong:*** Pariet; ***Hung.:*** Pariet; ***India:*** Odirab; Rabeloc; Rabicip; ***Indon.:*** Pariet; ***Irl.:*** Pariet; ***Ital.:*** Pariet; ***Jpn:*** Pariet; ***Malaysia:*** Pariet; ***Mex.:*** Pariet; ***Neth.:*** Pariet; ***Philipp.:*** Pariet; ***Pol.:*** Pariet; ***Port.:*** Pariet; ***Rus.:*** Pariet (Париет); ***S.Afr.:*** Pariet; ***Singapore:*** Pariet; ***Spain:*** Aciphex; Pariet; ***Swed.:*** Pariet; ***Switz.:*** Pariet; ***Thai.:*** Pariet; ***Turk.:*** Pariet; ***UK:*** Pariet; ***USA:*** Aciphex; ***Venez.:*** Pariet.

Racecadotril *(rINN)*

Acetorphan; Racécadotril; Racecadotrilo; Racecadotrilum. (±)-*N*-{2-[(Acetylthio)methyl]-1-oxo-3-phenylpropyl}glycine phenylmethyl ester; *N*-[(*R,S*)-3-acetylthio-2-benzylpropanoyl]glycine benzyl ester; (±)-*N*-[α-(Mercaptomethyl)hydrocinnamoyl]glycine benzyl ester acetate.

Рацекадотрил

$C_{21}H_{23}NO_4S$ = 385.5.

CAS — 81110-73-8.

ATC — A07XA04.

ATC Vet — QA07XA04.

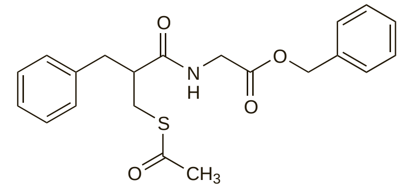

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Racecadotril). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane.

Profile

Racecadotril is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thus reducing intestinal secretions. It is given orally in doses of 100 mg three times daily before meals for up to 7 days for the symptomatic management of acute diarrhoea (p.1694).

The *S*-form of racecadotril (sinorphan, ecadotril—see Natriuretic Peptides, p.1347) has been investigated for hypertension and heart failure.

◊ References.

1. Baumer P, *et al.* Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea. *Gut* 1992; **33:** 753–8.
2. Roge J, *et al.* The enkephalinase inhibitor, acetorphan, in acute diarrhoea: a double-blind, controlled clinical trial versus Loperamide. *Scand J Gastroenterol* 1993; **28:** 352–4.
3. Beaugerie L, *et al.* Treatment of refractory diarrhoea in AIDS with acetorphan and octreotide: a randomized crossover study. *Eur J Gastroenterol Hepatol* 1996; **8:** 485–9.
4. Salazar-Lindo E, *et al.* Racecadotril in the treatment of acute watery diarrhea in children. *N Engl J Med* 2000; **343:** 463–7.
5. Matheson AJ, Noble S. Racecadotril. *Drugs* 2000; **59:** 829–35.
6. Alam NH, *et al.* Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut* 2003; **52:** 1419–23.
7. Wang H-H, *et al.* A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol* 2005; **11:** 1540–3.
8. Szajewska H, *et al.* Systematic review: racecadotril in the treatment of acute diarrhoea in children. *Aliment Pharmacol Ther* 2007; **26:** 807–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Tiorfan; ***Fr.:*** Tiorfan; ***Ger.:*** Tiorfan; ***Gr.:*** Hidrasec; ***Indon.:*** Hidrasec; ***Mex.:*** Hidrasec; ***Port.:*** Tiorfan; ***Spain:*** Tiorfan; ***Thai.:*** Hidrasec†; ***Venez.:*** Hidrasec.

Ramosetron Hydrochloride *(rINNM)*

Hidrocloruro de ramosetrón; Ramosétron, Chlorhydrate de; Ramosetroni Hydrochloridum; YM-060. (−)-(*R*)-1-Methylindol-3-yl 4,5,6,7-tetrahydro-5-benzimidazolyl ketone hydrochloride.

Рамосетрона Гидрохлорид

$C_{17}H_{17}N_3O,HCl$ = 315.8.

CAS — 132036-88-5 (ramosetron); 132907-72-3 (ramosetron hydrochloride).

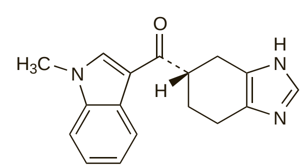

(ramosetron)

Profile

Ramosetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p.1756). Ramosetron hydrochloride is given for its antiemetic properties in the management of nausea and vomiting induced by cancer chemotherapy in usual doses of 300 micrograms once daily intravenously, or 100 micrograms once daily by mouth. Ramosetron is also under investigation in the management of diarrhoea-predominant irritable bowel syndrome.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Nasea; ***Jpn:*** Nasea; ***Philipp.:*** Nasea; ***Thai.:*** Nasea.

Ranitidine *(BAN, USAN, rINN)*

AH-19065; Ranitidiini; Ranitidin; Ranitidina; Ranitidinum. *NN*-Dimethyl-5-[2-(1-methylamino-2-nitrovinylamino)ethylthiomethyl]furfurylamine.

Ранитидин

$C_{13}H_{22}N_4O_3S$ = 314.4.
CAS — 66357-35-5.
ATC — A02BA02.
ATC Vet — QA02BA02.

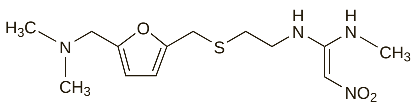

Ranitidine Hydrochloride *(BANM, rINNM)*

AH-19065; Hidrocloruro de ranitidina; Ranitidiinihydrokloridi; Ranitidin Hidroklorür; Ranitidine, chlorhydrate de; Ranitidin-hidroklorid; Ranitidin-hydrochlorid; Ranitidinhydroklorid; Ranitidini hydrochloridum; Ranitidino hidrochloridas; Ranitydyny chlorowodorek.

Ранитидина Гидрохлорид

$C_{13}H_{22}N_4O_3S,HCl$ = 350.9.
CAS — 66357-59-3.
ATC — A02BA02.
ATC Vet — QA02BA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Ranitidine Hydrochloride). A white or pale yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water; sparingly soluble or slightly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Ranitidine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. It is sensitive to light and to moisture. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Stability and incompatibility. References.

1. Chilvers MR, Lysne JM. Visual compatibility of ranitidine hydrochloride with commonly used critical-care medications. *Am J Hosp Pharm* 1989; **46:** 2057–8.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.
3. Williams MF, *et al.* In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrition mixtures. *Am J Hosp Pharm* 1990; **47:** 1574–9.
4. Galante LJ, *et al.* Stability of ranitidine hydrochloride at dilute concentration in intravenous infusion fluids at room temperature. *Am J Hosp Pharm* 1990; **47:** 1580–4.
5. Galante LJ, *et al.* Stability of ranitidine hydrochloride with eight medications in intravenous admixtures. *Am J Hosp Pharm* 1990; **47:** 1606–10.
6. Stewart JT, *et al.* Stability of ranitidine in intravenous admixtures stored frozen, refrigerated, and at room temperature. *Am J Hosp Pharm* 1990; **47:** 2043–6.
7. Montoro JB, Pou L. Comment on stability of ranitidine hydrochloride in total nutrient admixtures. *Am J Hosp Pharm* 1991; **48:** 2384.
8. Stewart JT, *et al.* Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm* 1994; **51:** 1802–7.
9. Crowther RS, *et al.* In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother* 1995; **29:** 859–62.

Adverse Effects

As for Cimetidine, p.1716. Unlike cimetidine, ranitidine has little or no anti-androgenic effect, despite isolated reports of gynaecomastia and impotence.

◊ General references.

1. Wormsley KG. Safety profile of ranitidine: a review. *Drugs* 1993; **46:** 976–85.

Carcinogenicity. For a discussion of the possible association between histamine H_2-antagonists and cancer, including mention of a study with ranitidine, see Cimetidine, p.1717.

Effects on the blood. For a discussion of the adverse haematological effects of H_2-antagonists, see Cimetidine, p.1717.

Effects on the cardiovascular system. Similarly to cimetidine (p.1717), bradycardia,[1,2] AV block,[2] and cardiac arrest[3] have been reported rarely during ranitidine therapy. A positive inotropic effect, without significant changes in heart rate or blood pressure, has also been reported in healthy subjects[4] and pretreatment with ranitidine has blocked the cardiac depressant effects seen in some subjects given famotidine or nizatidine.[5] Although studies in critically ill patients[6] and healthy subjects[7,8] have found no adverse haemodynamic effects associated with ranitidine, it is likely that a small proportion of patients are more susceptible to the cardiovascular effects of ranitidine. Caution is recommended when ranitidine is given intravenously, particularly in patients with cardiovascular disease.

1. Johnson WS, Miller DR. Ranitidine and bradycardia. *Ann Intern Med* 1988; **108:** 493.
2. Tanner LA, Arrowsmith JB. Bradycardia and H antagonists. *Ann Intern Med* 1988; **109:** 434–5.
3. Hart AM. Cardiac arrest associated with ranitidine. *BMJ* 1989; **299:** 519.
4. Meyer EC, *et al.* Inotropic effects of ranitidine. *Eur J Clin Pharmacol* 1990; **39:** 301–3.
5. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
6. Vohra SB, *et al.* The haemodynamic effects of ranitidine injected centrally in optimally resuscitated patients. *Br J Hosp Med* 1989; **42:** 149.
7. Hughes DG, *et al.* Cardiovascular effects of H -receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
8. Hilleman DE, *et al.* Impact of chronic oral H -antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.

Effects on the endocrine system. Unlike cimetidine (p.1717), ranitidine does not bind to androgen receptors and has little, if any, anti-androgenic effect. Studies in men taking ranitidine for the management of duodenal ulcer[1,2] reported no significant changes in the plasma concentrations of testosterone, luteinising hormone, follicle-stimulating hormone, or prolactin after up to 2 years of treatment; no significant changes in sperm concentration, motility, or morphology were noted.[1] There have been isolated reports of gynaecomastia,[3] loss of libido,[4] and impotence[5] associated with ranitidine, but in 9 patients with cimetidine-induced breast changes and impotence, transfer to ranitidine resulted in resolution of these symptoms.[6]

1. Wang C, *et al.* Ranitidine does not affect gonadal function in man. *Br J Clin Pharmacol* 1983; **16:** 430–2.
2. Knigge U, *et al.* Plasma concentrations of pituitary and peripheral hormones during ranitidine treatment for two years in men with duodenal ulcer. *Eur J Clin Pharmacol* 1989; **37:** 305–7.
3. Tosi S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; **i:** 160.
4. Smith RN, Elsdon-Dew RW. Alleged impotence with ranitidine. *Lancet* 1983; **ii:** 798.
5. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.
6. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.

Effects on the eyes. For a report of an increase in intra-ocular pressure associated with ranitidine, see under Cimetidine, p.1717. A cohort study involving 140 128 patients receiving anti-ulcer therapy, 70 389 of whom received ranitidine, found no evidence that any of the drugs studied were associated with a major increased risk of vascular or inflammatory disorders of the eye.[1]

For reference to loss of colour vision in a child receiving ranitidine see under Effects on the Nervous System, below.

1. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.

Effects on the kidneys. For reference to interstitial nephritis associated with H_2-antagonists including ranitidine, see under Cimetidine, p.1717.

Effects on the liver. There have been some case reports of ranitidine hepatotoxicity.[1-3] The increase in relative risk seen in a large cohort study involving 108 891 patients receiving antisecretory therapy was less for ranitidine (1.7:1) than for cimetidine (see p.1717).

1. Souza Lima MA. Ranitidine and hepatic injury. *Ann Intern Med* 1986; **105:** 140.
2. Ramrakhiani S, *et al.* Possible cholestatic injury from ranitidine with a review of the literature. *Am J Gastroenterol* 1998; **93:** 822–6.
3. Liberopoulos EN, *et al.* Possible ranitidine-induced cholestatic jaundice. *Ann Pharmacother* 2002; **36:** 172.

Effects on the nervous system. Ranitidine has been associated with adverse neurological effects including confusion,[1-8] loss of colour vision,[4] aggressiveness,[2,4,6] lethargy,[8] somnolence,[8] disorientation,[8] depression,[8] hallucinations,[1,7-9] and severe headache.[10] As with cimetidine (p.1717) these reactions occur mainly in the elderly, the severely ill, or patients with renal or hepatic impairment. Single-dose studies in young healthy subjects have found no adverse changes in performance, CNS function, or subjective assessment of mood after oral doses of ranitidine 150 or 300 mg.[11]

1. Hughes JD, *et al.* Mental confusion associated with ranitidine. *Med J Aust* 1983; **2:** 12–13.
2. Silverstone PH. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
3. Epstein CM. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
4. De Giacomo C, *et al.* Ranitidine and loss of colour vision in a child. *Lancet* 1984; **ii:** 47.
5. Mani RB, *et al.* H -receptor blockers and mental confusion. *Lancet* 1984; **ii:** 98.
6. Mandal SK. Psychiatric side effects of ranitidine. *Br J Clin Pract* 1986; **40:** 260.
7. MacDermott AJ, *et al.* Acute confusional episodes during treatment with ranitidine. *BMJ* 1987; **294:** 1616.
8. Slugg PH, *et al.* Ranitidine pharmacokinetics and adverse central nervous system reactions. *Arch Intern Med* 1992; **152:** 2325–9.
9. Price W, *et al.* Ranitidine-associated hallucinations. *Eur J Clin Pharmacol* 1985; **29:** 375–6.
10. Epstein CM. Ranitidine. *N Engl J Med* 1984; **310:** 1602.
11. Nicholson AN, Stone BM. The H -antagonists, cimetidine and ranitidine: studies on performance. *Eur J Clin Pharmacol* 1984; **26:** 579–82.

Effects on the skin. A report of vasculitic rash occurring in 3 patients undergoing ranitidine therapy.[1] In each case the rash cleared after withdrawal of the drug.

See also under Hypersensitivity, below, and also Cimetidine, p.1717.

1. Haboubi N, Asquith P. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; **296:** 897.

Fever. A report[1] of pyrexia associated with ranitidine. Apart from raised temperature the patient was otherwise well; fever resolved on stopping ranitidine and recurred on rechallenge.

1. Kavanagh GM, *et al.* Ranitidine fever. *Lancet* 1993; **341:** 1422.

Hypersensitivity. Respiratory stridor and an urticarial rash occurred in a patient shortly after taking the first dose of ranitidine;[1] the symptoms responded to adrenaline subcutaneously.

1. Brayko CM. Ranitidine. *N Engl J Med* 1984; **310:** 1601–2.

Meningitis. A 30-year-old man developed aseptic meningitis on 3 occasions after use of ranitidine.[1] In each case symptoms resolved rapidly on withdrawal of the drug.

1. Durand JM, *et al.* Ranitidine and aseptic meningitis. *BMJ* 1996; **312:** 886. Correction. *ibid.*; 1392.

Precautions

As for Cimetidine, p.1718.

Helicobacter pylori testing. For reference to the effect of ranitidine on the urea breath test for *Helicobacter pylori*, see p.1718.

Hepatic impairment. Sixteen of 27 patients with cirrhosis of the liver and indications for treatment with an H_2-antagonist (peptic ulcer, gastritis, or reflux oesophagitis) failed to respond to ranitidine 300 mg compared with 6 failures from 32 patients without cirrhosis. Famotidine 40 mg was given to 10 of the cirrhotic nonresponders and 8 still had no response; 7 of these patients were given cimetidine 800 mg and only 1 responded. In the control group, all 3 patients given famotidine did not respond and only 1 responded when given cimetidine. It was concluded that the incidence of non-response to H_2-antagonists is increased in patients with liver cirrhosis but no explanation could be given for this effect.[1] Interestingly there is an earlier report of patients with cirrhosis demonstrating increased bioavailability and decreased clearance of ranitidine.[2]

1. Walker S, *et al.* Frequent non-response to histamine H -receptor antagonists in cirrhotics. *Gut* 1989; **30:** 1105–9.
2. Young CJ, *et al.* Effects of cirrhosis and ageing on the elimination and bioavailability of ranitidine. *Gut* 1982; **23:** 819–23.

Porphyria. Ranitidine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Renal impairment. For evidence of reduced clearance of ranitidine in patients with renal impairment see Administration in Renal Impairment, below.

Interactions

Unlike cimetidine (p.1718), ranitidine does not seem to affect cytochrome P450 to any great extent, and therefore is considered to have little effect on the metabolism of other drugs. However, as with other H_2-antagonists, its effects on gastric pH may alter the absorption of some other drugs.

◊ A review comparing the drug interactions of ranitidine with those of cimetidine.[1]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.

Cisapride. Peak plasma concentrations of ranitidine were achieved more rapidly in 12 healthy subjects who also took cisapride.[1] The clinical significance is questionable and such combinations have been used clinically, although the use of cisapride is now restricted in most countries.

1. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.

Pharmacokinetics

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 2 to 3 hours after oral doses. Food does not significantly impair absorption. The bioavailability of ranitidine after oral doses is about 50%. Ranitidine is rapidly absorbed on intramuscular injection, with peak plasma concentrations occurring in about 15 minutes. It is weakly bound, about 15%, to plasma proteins.

The elimination half-life is about 2 to 3 hours and is increased in renal impairment. A small proportion of ranitidine is metabolised in the liver to the *N*-oxide, the *S*-oxide, and desmethylranitidine; the *N*-oxide is the major metabolite but accounts for only about 4 to 6% of a dose. About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in

24 hours, primarily by active tubular secretion; there is some excretion in the faeces. Ranitidine crosses the placental barrier and is distributed into breast milk.

Distribution into breast milk. A study in a mother given multiple doses of ranitidine showed higher concentrations in breast milk than in serum; the minimum milk concentration occurred between 1 and 2 hours after a dose and the highest concentration was towards the end of the 12-hour dosing interval.[1] The amount that would be ingested by the infant could not be reliably estimated because of the variable milk to serum ratio.

1. Kearns GL, *et al*. Appearance of ranitidine in breast milk following multiple dosing. *Clin Pharm* 1985; **4:** 322–4.

Enterohepatic recycling. Some individuals have a second peak in the plasma concentration of ranitidine, which could be due to enterohepatic recirculation. However, only 0.7 to 2.6% and 0.3 to 1.0% of a dose of ranitidine was excreted into the bile of 3 patients in 24 hours after 50 mg given intravenously or 300 mg by mouth respectively, indicating that significant recirculation did not occur.[1]

1. Klotz U, Walker S. Biliary excretion of H -receptor antagonists. *Eur J Clin Pharmacol* 1990; **39:** 91–2.

Neonates. Renal function is limited in the first month of life, and reduced clearance of ranitidine would be expected. Blood samples taken from 27 full-term neonates given a single intravenous dose of ranitidine 2.4 mg/kg revealed the following pharmacokinetic data: elimination half-life, 3.45 hours; total volume of distribution, 1.52 litres/kg; total plasma clearance, 5.02 mL/kg per minute.[1] None of the infants had renal or hepatic impairment. In another study,[2] an elimination half-life of 6.61 hours was found in 13 full-term neonates given ranitidine 2 mg/kg. See also Administration in Children, below.

1. Fontana M, *et al.* Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993; **68:** 602–3.
2. Wells TG, *et al.* Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998; **38:** 402–7.

Uses and Administration

Ranitidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (p.1719).

Ranitidine may be given orally or parenterally by the intravenous or intramuscular routes. Although most preparations contain ranitidine hydrochloride, strengths and doses are expressed in terms of the base. Ranitidine hydrochloride 111.6 mg is equivalent to about 100 mg of ranitidine.

In the management of benign **gastric** and **duodenal ulceration** (p.1702) a single daily oral dose of 300 mg at bedtime or 150 mg twice daily (in the morning and at bedtime) is given initially for at least 4 weeks. A dose of 300 mg twice daily may also be used in duodenal ulcer. Where appropriate a maintenance dose of 150 mg daily may be given at bedtime. Ranitidine 150 mg twice daily may be given during therapy with NSAIDs for prophylaxis against duodenal ulceration. A suggested dose for the treatment of peptic ulcer in children is 2 to 4 mg/kg twice daily to a maximum of 300 mg in 24 hours; a maintenance dose of 2 to 4 mg/kg once daily may be used, to a maximum of 150 mg daily.

For duodenal ulcer associated with *Helicobacter pylori* infection, ranitidine in a usual oral dose of 300 mg once daily or 150 mg twice daily may be given as part of triple therapy with amoxicillin 750 mg and metronidazole 500 mg, both three times daily, for 2 weeks. Therapy with ranitidine should then be continued for a further 2 weeks.

In **gastro-oesophageal reflux disease** (p.1696) the oral dose is 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or, if required, 12 weeks. This may be increased to 150 mg four times daily for up to 12 weeks in severe cases. In the maintenance of healing erosive oesophagitis, a dose of 150 mg twice daily may be used. Although there is limited data on the use of ranitidine for gastro-oesophageal reflux disease and erosive oesophagitis in children, a dose of 5 to 10 mg/kg daily, usually given in 2 divided doses, has been used. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, (p.1704) the initial oral dose is usually 150 mg twice or three times daily and may be increased if necessary; doses of up to 6 g daily have been used. Alternatively, an intravenous infusion may be given, initially at a rate of 1 mg/kg per hour; the rate may be increased by increments of 500 micrograms/kg per hour, beginning after 4 hours, if required.

For the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract, parenteral therapy may be given as a slow intravenous injection of a 50-mg priming dose followed by a continuous intravenous infusion of 125 to 250 micrograms/kg per hour. Oral doses of 150 mg twice daily may be given once oral feeding is resumed.

In patients at risk of developing the **acid aspiration syndrome** (p.1693) during general anaesthesia, an oral dose of 150 mg may be given 2 hours before the induction of anaesthesia and preferably also 150 mg the previous evening. Alternatively, a dose of 50 mg may be given by intramuscular or slow intravenous injection 45 to 60 minutes before the induction of anaesthesia. In obstetric patients, at the start of labour an oral dose of 150 mg may be given and may be repeated at intervals of 6 hours if required.

In patients with chronic episodic **dyspepsia** (p.1695), a dose of 150 mg twice daily orally for up to 6 weeks may be given. For the short-term symptomatic relief of dyspepsia a dose of 75 mg, repeated if necessary up to a maximum of 4 doses daily, may be taken. Treatment should be restricted to a maximum of 2 weeks of continuous use at one time.

PARENTERAL DOSAGE.

The usual dose of ranitidine by intramuscular or intravenous injection is 50 mg, which may be repeated every 6 to 8 hours; the intravenous injection should be given slowly over not less than 2 minutes and should be diluted to contain 50 mg in 20 mL. For an intermittent intravenous infusion the recommended dose in the UK is 25 mg/hour given for 2 hours which may be repeated every 6 to 8 hours. A rate of 6.25 mg/hour has been suggested for continuous intravenous infusion although higher rates may be used for conditions such as Zollinger-Ellison syndrome or in patients at risk from stress ulceration (see above).

DOSAGE IN RENAL IMPAIRMENT.

For dosage in renal impairment, see below.

Administration in children. The disposition of ranitidine in children is not significantly different from that in young adults and an oral dose of 2 mg/kg (about equal to an adult dose of 150 mg) has been used for the prevention of acid aspiration in children undergoing surgery.[1] A study in premature infants being treated with dexamethasone for bronchopulmonary dysplasia found that infusion of ranitidine 62.5 micrograms/kg per hour was sufficient to raise and maintain gastric pH above 4 to help protect against gastrointestinal bleeding and perforation.[2] Another study found 500 micrograms/kg twice daily to be sufficient for preterm infants, but that 1.5 mg/kg three times daily was needed for full-term infants.[3] A minimum dosage of 3 mg/kg daily was suggested for stress ulcer prophylaxis in older infants and children.[4]

1. Christensen S, *et al.* Effects of ranitidine and metoclopramide on gastric fluid pH and volume in children. *Br J Anaesth* 1990; **65:** 456–60.
2. Kelly EJ, *et al.* The effect of intravenous ranitidine on the intragastric pH of preterm infants receiving dexamethasone. *Arch Dis Child* 1993; **69:** 37–9.
3. Kuusela A-L. Long term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F151–F153.
4. Harrison AM, *et al.* Gastric pH control in critically ill children receiving intravenous ranitidine. *Crit Care Med* 1998; **26:** 1433–6.

Administration in renal impairment. A study in patients with varying degrees of renal impairment[1] found that the mean terminal half-life of ranitidine was increased from 2.09 hours in subjects with normal renal function to between 4.23 and 8.45 hours in patients with renal impairment, the degree of prolongation being proportional to the degree of impairment as measured by glomerular filtration rate. As a result of these findings it was recommended that the dose of ranitidine should be halved in patients with a glomerular filtration rate of 20 mL/minute or less. Licensed drug information therefore recommends that dosage of ranitidine be reduced in patients with severe renal impairment.

For patients with a creatinine clearance of less than 50 mL/minute, an *oral* dose of 150 mg daily is recommended, which may be cautiously increased to 150 mg every 12 hours if needed.

For *intravenous* use, licensed recommendations vary between countries. In the UK, individual doses may be reduced to 25 mg, while the frequency is adjusted in the USA to give a recommended usual dose of 50 mg every 18 to 24 hours, which may be cautiously increased to every 12 hours or more often if necessary.

Ranitidine 150 mg daily provided adequate serum concentrations without excessive accumulation in 20 patients undergoing regular haemodialysis.[2] The serum-ranitidine concentrations fell by about 50% during a 4-hour haemodialysis session but less than 3% of the dose was removed and supplemental doses after dialysis were considered unnecessary.

1. Dixon JS, *et al.* The effect of renal function on the pharmacokinetics of ranitidine. *Eur J Clin Pharmacol* 1994; **46:** 167–71.
2. Comstock TJ, *et al.* Ranitidine accumulation in patients undergoing chronic hemodialysis. *J Clin Pharmacol* 1988; **28:** 1081–5.

Cystic fibrosis. A comparative study involving 29 patients with cystic fibrosis (p.166) found that ranitidine was more effective than cisapride in improving dyspeptic symptoms and gastric emptying and distension.[1] Antisecretory drugs are also used in this condition to decrease the inactivation of oral pancreatic enzyme therapy.

1. Cucchiara S, *et al.* Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 1996; **128:** 485–8.

Immunomodulation. Like cimetidine (see p.1719), ranitidine has been proposed to have immunoregulatory effects. However, ranitidine 300 mg twice daily had no effect on absolute CD4 cell counts or plasma HIV RNA in patients with HIV infection in a placebo-controlled study.[1] Similarly, ranitidine had no significant benefit in patients with gastric cancer (see Malignant Neoplasms, p.1719).

1. Bartlett JA, *et al.* A placebo-controlled trial of ranitidine in patients with early human immunodeficiency virus infection. *J Infect Dis* 1998; **177:** 231–4.

Skin disorders. As with cimetidine (p.1720), ranitidine has been tried in various skin disorders. Ranitidine 300 mg twice daily by mouth has been reported to be of benefit as an adjuvant to local treatment with corticosteroids and a moisturising ointment in patients with *atopic dermatitis*.[1] There are reports of improvements in *psoriasis* after use of ranitidine,[2-4] although this is a field that is notoriously difficult to evaluate because of the chronic relapsing and remitting nature of the disease, and others have failed to show benefit.[5]

1. Veien NK, *et al.* Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind placebo-controlled trial. *J Am Acad Dermatol* 1995; **32:** 1056–7.
2. Witkamp L, *et al.* An open prospective clinical trial with systemic ranitidine in the treatment of psoriasis. *J Am Acad Dermatol* 1993; **28:** 778–81.
3. Smith KC. Ranitidine useful in the management of psoriasis in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 1994; **33:** 220–1.
4. Kristensen JK, *et al.* Systemic high-dose ranitidine in the treatment of psoriasis: an open prospective clinical trial. *Br J Dermatol* 1995; **133:** 905–8.
5. Çetin L, *et al.* High-dose ranitidine is ineffective in the treatment of psoriasis. *Br J Dermatol* 1997; **137:** 1021–2.

Preparations

BP 2008: Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets; ***USP 31:*** Ranitidine in Sodium Chloride Injection; Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acidex; Alivian; Aludrox AC†; Aprical†; Ciscomax†; Dualid; Espaven; Faboacid-R; Fendibina; Gastrial; Gastrolets; Gastrosedol; Gastrozac; Insuflen†; Lorbitidina; Luvier; Notrab; Prednocris; Ranimed; Ranitic; Ranitidi GNO†; Ranitral; Ranitul; Raticina; Reco; Reflux; Sustac; Taural; Telus†; Tegrand; Tomag†; Ulcotenk; Urgis; Vingional; Vizerul; Zantac; ***Austral.:*** Ausran; Heartburn Relief†; Rani 2; Ranihexal; Ranitic; Ranoxyl; Ulcaid; Zantac; ***Austria:*** Ranic; Raninorm; Ranityrol†; Ulsal; Zantac; Zantarac; ***Belg.:*** Docraniti; Gastran; Zantac; ***Braz.:*** Antagon; Antak; Antidin; Aziliv; Gastrat†; Label; Logat; Neosac; Nititom†; Prevulcer†; Rabiodina†; Radan†; Raniclor; Ranidin; Ranidina; Ranidine; Raniflex†; Ranitak†; Ranitil; Ranitin; Ranitinol; Ranition; Ranitrat; Ranitzen†; Ranizol†; Ranytisan†; Rhanitak†; Tazepin†; Ulceridina; Ulcerit†; Ulcerocin; Ulcoren; Ultidin; Zadine†; Zylium; ***Canad.:*** Acid Reducer; Novo-Ranidine; Nu-Ranit; Zantac; ***Chile:*** Aciflux†; Ranicel; Ranitax; Tipac; Zantac; ***Cz.:*** Arnetin†; Histac; Raniberl†; Ranisan; Ranital; Ranitin†; Ulcosan; Ulran†; Zantac; ***Denm.:*** Aducin†; Kuracid; Ranicodan; Ranikur†; Zantac; ***Fin.:*** Esofex†; Inside Brus; Ranicur; Ranil; Ranimex; Ranixal; Zantac; ***Fr.:*** Azantac; Raniplex; ***Ger.:*** Azuranit†; Junizac; Phamoranit†; Ran Lich; Rani; Rani-nerton; Raniberl; Ranibeta; Ranibloc; Ranicux; Ranidura T; Ranimerck; Raniprotect; Ranitab; Ranitic; Ranitidoc; Sostril; Zantic; ***Gr.:*** Alphadine; Aova; B-Alcerin†; Baroxal; Bindazac; Blumol; Brixoral; Ceftrinal; Epadoren; Ezopta; Galebiron; Gaproxen; Gertocalm; Lomadryl; Lumaren; Narigen; Nipodur; Nitised; Odanet†; Ptinolin; Raniclon; Ranizac; Restopon; Ribolin; Rothonal; Semuele; Smaril; Soredine†; Specinor; Sveltanet; Synthomanet; Tupast; Verlost; Yara; Zantac; Zoliden; Zurfix; ***Hong Kong:*** Gastril†; Hyzan; LAtac; Lumeran; Novo-Ranidine; Radin; Ranolta; Simetac; Synitidine; Ulticer; Zantac; Zendhin; ***Hung.:*** Histac; Huma-Ranidine†; Ranitic; Ulceran; Ulcosin; Umaren; Xanomel†; Zantac; ***India:*** Aciloc; Consec; Histac; R-Loc; Rantac†; Ultac; Zinetac; ***Indon.:*** Acran; Aldin; Anitid; Chopintac; Conranin; Fordin; Gastridin; Hexer; Radin; Rancus; Ranilex; Ranin; Ranticid; Rantin; Ratinal; Renatac; Scanarin; Tricker; Ulceranin; Wiacid; Xeradin; Zantac; Zantadin; Zumaran; ***Irl.:*** Gertac; Ranitic; Ranopine; Xanomel; Zandine†; Zantac; ***Israel:*** Zanidex; Zantac; ***Ital.:*** Dolilux; Duoran†; Raniben; Ranibloc; Ranidex; Ranidil; Sensigard; Ulcex; Zantac; ***Jpn:*** Zantac; ***Malaysia:*** Arnetin; Histac; Hyzan†; Rintac†; Vesyca; X'tac; Zantac; Zendhin; ***Mex.:*** Acloral; Agrisen; Aldivina; Alter-H †; Alvidina†; Anistal; Anticina; Apoprin†; Avintac; Azantac; Cauteridol; Credaxol; Dinaxin; Driges; Flatmed; Galidrin; Gastrec; Gastridin; Gasyran†; Iqfadina; Katalem; Microdit†; Microtid; Midaven; Neugal; Offentina; Radyn; Ranepal; Ranifarm; Ranifur; Raniger; Ranisen; Ranulin†; Ranzil†; Raudil; Redacid; Serranit; Serviradine; Sinhcloran; Syngasy; Terodul; Tianak; Ulcedin†; Ulcevit; Ulgastrin; Ulkodin; Ulmodhyl; Ulsaven; Ultran; Unitin; ***Neth.:*** Azantac; Zantac; ***Norw.:*** Inside Brus; Zantac; ***NZ:*** Zantac; ***Philipp.:*** Aceptin; Aciloc; Ameket; Ceranid; Dalycrid; Danitin; Eu-Ran; Incid; Mordek; Pep-Bloc; Ramadine; Ranitab; Rapidin; Raxide; Renfort; Ulcemed; Ulceragon; Ulceral; Ulcergo; Ulcerix; Ulcin; Ulran; Zantac; Zeptag; ***Pol.:*** Gastranin Zdrovit; Novo-Ranidine; Raniberl; Ranic; Ranigast; Ranimax; Ranisan; Ranitin; Riflux; Solvertyl; Zantac; ***Port.:*** Bloculcer; Gastridina; Gastrolav; Gastrulcer; Pep-Rani; Peptab; Peptifar; Quardin†; Ran†; Ranitine; Stacer; Ulcecur†; Ulcerol†; Zantac; ***Rus.:*** Aciloc (Ацилок); Histac (Гистак); Ranigast (Ранигаст); Ranisan (Ранисан); Rantac (Рантак); Ulran (Ульран)†; Zantac (Зантак); Zoran (Зоран); ***S.Afr.:*** Gl-Tak†; Histak; Ranihexal; Ranteen†; Ulcaid; Ultak; Zantac; ***Singapore:*** Gastran†; Histac; Hyzan; Lumaren; Neoceptin-R; Rani†; Ranidine; Ratic; Xanidine; Zantac; Zendhin; Zoran†; ***Spain:*** Alquen; Arcid; Ardoral; Coralen; Denulcer; Fagus; Lake; Meticel†; Quantor; Ran H2; Ranidin; Ranix; Ranuber; Rubiulcer; Tanidina; Terposen; Toriol; Underacid; Zantac; ***Swed.:*** Artonil; Inside; Rani-Q; Zantac; ***Switz.:*** Ranimed; Ranisifar; Ulcidine; Zantic; ***Thai.:*** Aciloc; Histac; Radine†; Ranicid; Ranidine; Rantac; Ratic; Ratica; Utac; Xanidine; Zanamet; Zantac; Zantidon; Zardil; ***Turk.:*** Ranitab; Ranitine; Ranobel; Rozon; Santanol; Ulcuran; Zandid; Zantac; ***UAE:*** Rantag; ***UK:*** Gavilast; Ranitic; Ranitil; Rantec; Ranzac; Vivatak†; Zaedoc†; Zantac; ***USA:*** Zantac; ***Venez.:*** Aplom; Enteral; Gastac; Ranibloc; Ranifesa†; Ranix†; Ranizan†; Retamin; Vizerul; Zantac; Zoran†.

Multi-ingredient: ***Arg.:*** Duo Vizerul†; Euciton Reflux; Megalex; ***India:*** Aciloc RD; ***Mex.:*** Ergex.

Ranitidine Bismuth Citrate *(BAN, USAN)*

A complex of ranitidine and bismuth citrate; GR-122311X; Ranitidin Bizmut Sitrat; Ranitidin Bizmutreks; Ranitidina y bismuto, citrato de; Ranitidine Bismutrex. *N*-[2-({5-[(Dimethylamino)methyl]furfuryl}thio)-ethyl]-*N*′-methyl-2-nitro-1,1-ethenediamine, compound with bismuth(3+) citrate (1:1).

Ранитидин Висмут Цитрат

$C_{13}H_{22}N_4O_3S,C_6H_5BiO_7$ = 712.5.
CAS — 128345-62-0.
ATC — A02BA07.
ATC Vet — QA02BA07.

Adverse Effects and Precautions

Ranitidine bismuth citrate would be expected to combine the adverse effects of both bismuth compounds (p.1711) and ranitidine (p.1766). Blackening of the tongue and faeces is common, and gastrointestinal disturbances, headache, mild anaemia, and altered liver enzyme values have been reported. Rarely, hypersensitivity reactions (including anaphylaxis), have occurred.

Ranitidine bismuth citrate should not be given to patients with moderate to severe renal impairment. It is not suitable for long-term or maintenance therapy because of the risk of bismuth accumulation. As with other antisecretory drugs, the possibility of malignancy should be considered when giving ranitidine bismuth citrate to patients with gastric ulcers since the drug may mask symptoms and delay diagnosis.

Interactions

Ranitidine bismuth citrate would be expected to have the interactions of bismuth compounds (p.1712), and ranitidine (p.1766).

Pharmacokinetics

After oral doses, ranitidine bismuth citrate dissociates into its ranitidine and bismuth components in the stomach. For the pharmacokinetics of ranitidine, see p.1766, and for those of bismuth, see p.1712.

◊ References.

1. Lacey LF, *et al.* Comparative pharmacokinetics of bismuth from ranitidine bismuth citrate (GR122311X), a novel anti-ulcerant and tripotassium dicitrato bismuthate (TDB). *Eur J Clin Pharmacol* 1994; **47:** 177–80.
2. Koch KM, *et al.* Pharmacokinetics of bismuth and ranitidine following single doses of ranitidine bismuth citrate. *Br J Clin Pharmacol* 1996; **42:** 201–5.
3. Koch KM, *et al.* Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. *Br J Clin Pharmacol* 1996; **42:** 207–11.

Uses and Administration

Ranitidine bismuth citrate is a complex of ranitidine with bismuth and citrate, which releases ranitidine and bismuth in the gastrointestinal tract and therefore possesses both the actions of the bismuth compounds (p.1712) and of ranitidine (p.1767). It has been used in the management of peptic ulcer disease (p.1702), and may be given with antibacterials for the eradication of *Helicobacter pylori* infection and the prevention of relapse of peptic ulcer disease.

Doses are 400 mg twice daily orally; treatment has usually been given for 4 to 8 weeks for duodenal ulceration and for 8 weeks for benign gastric ulceration. Ranitidine bismuth citrate should not be used for treatment, and a maximum of 16 weeks of treatment (two 8-week courses or four 4-week courses) may be given in a 12-month period. For duodenal ulceration where *H. pylori* infection is present, ranitidine bismuth citrate has been given as part of a 7-day triple therapy regimen, typically combined with any two of clarithromycin 500 mg twice daily, amoxicillin 1 g twice daily, or metronidazole 400 mg twice daily. Alternatively, a 14-day dual therapy regimen of ranitidine bismuth citrate combined with clarithromycin 500 mg two or three times daily has been used. In both regimens ranitidine bismuth citrate alone may be continued to a total of 28 days.

◊ References.

1. Bardhan KD, *et al.* GR122311X (ranitidine bismuth citrate), a new drug for the treatment of duodenal ulcer. *Aliment Pharmacol Ther* 1995; **9:** 497–506.
2. Peterson WL, *et al.* Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H.pylori and reducing ulcer recurrence. *Aliment Pharmacol Ther* 1996; **10:** 251–61.
3. Anonymous. Pylorid, H. pylori and peptic ulcer. *Drug Ther Bull* 1996; **34:** 69–70.
4. van der Wouden EJ, *et al.* One-week triple therapy with ranitidine bismuth citrate, clarithromycin and metronidazole versus two-week dual therapy with ranitidine bismuth citrate and clarithromycin for Helicobacter pylori infection: a randomized, clinical trial. *Am J Gastroenterol* 1998; **93:** 1228–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pylorid†; ***Austria:*** Helirad; Pylorisin; ***Belg.:*** Pylorid†; ***Braz.:*** Pylorid; ***Cz.:*** Eradipak†; ***Denm.:*** Pylorid†; ***Fin.:*** Pylorid; ***Gr.:*** Pylorid; ***Hong Kong:*** Pylorid†; ***Hung.:*** Pylorid†; ***Irl.:*** Pylorid†; ***Ital.:*** Elicodil†; Pylorid; ***Mex.:*** Azanplus; ***Neth.:*** Pylorid†; ***Norw.:*** Pylorid; ***Port.:*** Pylorid†; ***Spain:*** Pylorid; ***Switz.:*** Pylorid†; ***Thai.:*** Pylorid†; ***Turk.:*** Pylorid; ***UK:*** Pylorid†; ***Venez.:*** Pylorid.

Multi-ingredient: ***Austral.:*** Pylorid-KA.

Rebamipide *(rINN)*

Rebamipida; Rébamipide; Rebamipidum. (±)-α-(*p*-Chlorobenzamido)-1,2-dihydro-2-oxo-4-quinolinepropionic acid.

Ребамипид

$C_{19}H_{15}ClN_2O_4$ = 370.8.
CAS — 90098-04-7; 111911-87-6.

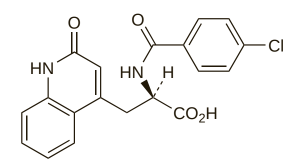

and enantiomer

Profile

Rebamipide is stated to possess cytoprotective properties and is used in the treatment of peptic ulcer disease (p.1702) and gastritis in usual oral doses of 100 mg three times daily. It has also been used rectally for the treatment of intestinal inflammation. Rebamipide eye drops are under investigation in the treatment of dry eye.

◊ References.

1. Makiyama K, *et al.* Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005; **50:** 2323–9.
2. Miyata M, *et al.* Successful treatment of severe pouchitis with rebamipide refractory to antibiotics and corticosteroids: a case report. *World J Gastroenterol* 2006; **12:** 656–8.
3. Miwa H, *et al.* Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. *J Gastroenterol Hepatol* 2006; **21:** 1826–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Mucosta; ***Jpn:*** Mucosta; ***Philipp.:*** Mucosta; ***Thai.:*** Mucosta.

Renzapride *(BAN, rINN)*

ATL-1251; BRL-24924A; Renzaprida; Renzapridum. (±)-*endo*-4-Amino-*N*-(1-azabicyclo[3.3.1]non-4-yl)-5-chloro-*o*-anisamide.

Рензаприд

$C_{16}H_{22}ClN_3O_2$ = 323.8.
CAS — 88721-77-1; 112727-80-7.

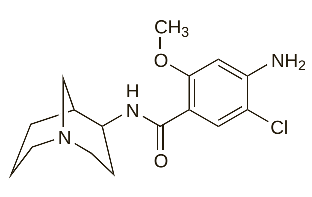

Profile

Renzapride is a substituted benzamide with prokinetic actions on gastrointestinal motility. It also has $5-HT_4$ agonist and $5-HT_3$ antagonist activity. It is under investigation for the management of gastrointestinal disorders including irritable bowel syndrome.

◊ References.

1. Tack J, *et al.* Pilot study of the efficacy of renzapride on gastrointestinal motility and symptoms in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; **23:** 1655–65.
2. George AM, *et al.* Clinical trial: renzapride therapy for constipation-predominant irritable bowel syndrome—multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting. *Aliment Pharmacol Ther* 2008; **27:** 830–7.

Revaprazan *(rINN)*

Révaprazan; Revaprazán; Revaprazanum. *N*-(4-Fluorophenyl)-4,5-dimethyl-6-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine.

Ревапразан

$C_{22}H_{23}FN_4$ = 362.4.
CAS — 199463-33-7.

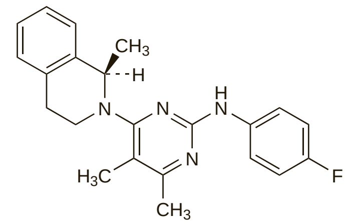

Revaprazan Hydrochloride *(USAN, rINNM)*

Hidrocloruro de revaprazán; Révaprazan, Chlorhydrate de; Revaprazani Hydrochloridum; YH-1238; YH-1885. *N*-(4-Fluorophenyl)-5,6-dimethyl-4-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine hydrochloride.

Ревапразана Гидрохлорид

$C_{22}H_{23}FN_4,HCl$ = 398.9.
CAS — 178307-42-1.

Profile

Revaprazan is a proton pump inhibitor that is under investigation for the management of gastric and duodenal ulceration, functional dyspepsia, and gastro-oesophageal reflux disease.

◊ References.

1. Sorbera LA, *et al.* Revaprazan hydrochloride. *Drugs Of The Future* 2004; **29:** 455.
2. Yu K-S, *et al.* Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 73–82.

Rhubarb

Chinese Rhubarb; Korzeń rzewienia; Rabarbaro; Rabarbarų šaknys; Rabarberrot; Raparperinjuuri; Ravent; Rebarbara-gyökértörzs; Reveňový kořen; Rhabarber; Rhei radix; Rhei Rhizoma; Rheum; Rhubarb Rhizome; Rhubarbe; Ruibarbo.

Ревень Аптечный

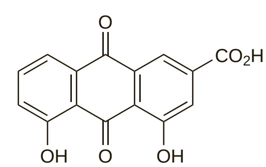

(rhein)

Description. Indian rhubarb (Himalayan rhubarb) consists of the dried rhizome and roots of *Rheum emodi*, *R. webbianum*, or some other related species of *Rheum*.
Rhapontic rhubarb (Chinese rhapontica) consists of the dried rhizomes of *R. rhaponticum*. It may occur as an adulterant of rhubarb, and pharmacopoeias specify a test to confirm its absence. Garden rhubarb, of which the leaf-stalks are used as food, is derived from *R. rhaponticum*.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn. Chin.* and *Jpn* also permit *Rheum tanguticum*, and *Jpn* also permits *R. coreanum*.
Ph. Eur. 6.2 (Rhubarb). The whole or cut, dried underground parts of *Rheum palmatum* or of *R. officinale* or of hybrids of these two species or of a mixture. The underground parts are often divided; the stem and most of the bark with the rootlets are removed. It contains not less than 2.2% of hydroxyanthracene derivatives, expressed as rhein ($C_{15}H_8O_6$ = 284.2), calculated with reference to the dried drug. Protect from light.

Adverse Effects and Precautions

As for Senna, p.1769.

Uses and Administration

Rhubarb is an anthraquinone stimulant laxative used similarly to senna (p.1770). It also exerts an astringent action due to the presence of gallic acid derivatives and tannins.

Homoeopathy. Rhubarb has been used in homoeopathic medicines under the following names: Rheum; Rhei radix; Rheum palmatum.

Preparations

BP 2008: Compound Rhubarb Tincture.

Proprietary Preparations (details are given in Part 3)
Cz.: Bukosan†; ***Ger.:*** Phytoestrol N; ***Pol.:*** Laxitab; Radirex; Rzewex.

Multi-ingredient: ***Arg.:*** Calculina†; LX-30; Oralsone Topic; Parodium; Pyralvex; ***Austral.:*** Betaine Digestive Aid; Neo-Cleanse; Pyralvex†; ***Austria:*** Abfuhrtee†; Eucarbon; Eucarbon Herbal; Novocholin; Pyralvex; Sabatif; Silberne; ***Belg.:*** Pyralvex; ***Braz.:*** Bilifel†; Bisuisan†; Boldopeptan†; Camomila; Eparema; Regulador Xavier N-2†; ***Canad.:*** Extra Strong Formula 12†; Herbal Laxative; Herbalax†; Herbolax; ***Cz.:*** Abdomilon†; Cynarosan†; Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; Pyralvex; Species Cholagogae Planta; Zlucnikova Cajova Smes; ***Fr.:*** Carres Parapsyllium; Depuratum; Parodium; Pyralvex; Resource Rhubagil; ***Ger.:*** Pyralvex; ***Gr.:*** Pyralvex; ***Hong Kong:*** Hepatofalk; Pyralvex; ***Hung.:*** Bolus Laxans; ***Indon.:*** Pyralvex; ***Irl.:*** Pyralvex; ***Israel:*** Davilla; Encypalmed; Eucarbon; Novicarbon; ***Ital.:*** Amaro Medicinale; Caramelle alle Erbe Digestive; Colax; Critichol; Digelax†; Dis-Cinil Complex; Eparema; Eparema-Levul; Eucarbon; Eupatol; Frerichs Maldifassi†; Lactolas; Lassatina†; Lassativi Vegetali; Magisbile†; Mepalax; Neoform†; Puntualax†; Pyralvex; Schias-Amaro Medicinale†; Stimolfit; ***Malaysia:*** Eucarbon†; ***Neth.:*** Pyralvex; ***Philipp.:*** Boie Carminative (Carminasen); Pyralvex; ***Pol.:*** Betasol; Diges-Tonic; Laxantol; Rhelax; ***Port.:*** Pyralvex; ***Rus.:*** Parodium (Пародиум); ***S.Afr.:*** Helmontskruie; Lewensessens; Moultons Herbal Extract; Pyralvex; Rubilax†; Wonderkroonessens; ***Singapore:*** Pyralvex; ***Spain:*** Crislaxo; Laxante Bescansa Aloico; Menabil Complex†; Pyralvex; Solucion Schoum; ***Switz.:*** Padma-Lax; Padmed Laxan; Pyralvex; Schweden-Mixtur H nouvelle formulation; ***Thai.:*** Pyralvex; ***Turk.:*** Eucarbon; Karboseptin; Piraldyne; Pyralvex; ***UK:*** Acidosis; Digestive; Fam-Lax; Fam-Lax Senna; HRI Golden Seal Digestive; Indian Brandee; Jacksons Herbal Laxative; Pegina; Pyralvex; Rhuaka; Stomach Mixture; Wind & Dyspepsia Relief; ***USA:*** Black-Draught†; ***Venez.:*** Cynascool; Natrossil; Orafilm†; Pinvex; Pyralvex†; Rheu-Tarx 1.

Roxatidine Acetate Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de acetato de roxatidina; Hoe-760; Hoe-062 (roxatidine); Pifatidine Hydrochloride; Roxatidine, Acétate Chlorhydrique de; Roxatidini Acetati Hydrochloridum; TZU-0460. *N*-{3-[(α-Piperidino-*m*-tolyl)oxy]propyl}glycolamide acetate monohydrochloride.

Роксатидина Ацетат Гидрохлорид

$C_{17}H_{26}N_2O_3,C_2H_2O,HCl = 384.9.$

CAS — 78273-80-0 (roxatidine); 97900-88-4 (roxatidine hydrochloride); 78628-28-1 (roxatidine acetate); 93793-83-0 (roxatidine acetate hydrochloride).
ATC — A02BA06.
ATC Vet — QA02BA06.

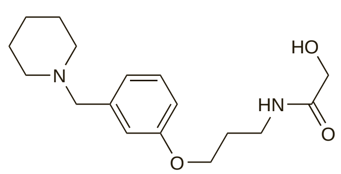

(roxatidine)

Pharmacopoeias. In *Jpn.*

Stability. The stability of roxatidine acetate hydrochloride in parenteral nutrition solutions was influenced by storage temperature and amino acid content and composition.[1]

1. Oh J, *et al.* Stability of roxatidine acetate in parenteral nutrient solutions containing different amino acid formulations. *Am J Health-Syst Pharm* 2005; **62:** 289–91.

Adverse Effects and Precautions

As for Cimetidine, p.1716.

Interactions

Unlike cimetidine (p.1718) roxatidine does not appear to affect cytochrome P450, and therefore is considered to have little effect on the metabolism of other drugs. However, like other H_2-antagonists its effects on gastric pH may alter the absorption of some other drugs.

Pharmacokinetics

Roxatidine acetate hydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 1 to 3 hours after doses by mouth. It is rapidly hydrolysed to the active desacetyl metabolite, roxatidine, by esterases in the liver, small intestine, and serum.

Over 90% of a dose is excreted in the urine as roxatidine and other metabolites. The elimination half-life of roxatidine is about 6 hours and is prolonged in renal impairment.

Small amounts of roxatidine have been reported to be distributed into breast milk.

Uses and Administration

Roxatidine acetate hydrochloride is an H_2-antagonist with actions and uses similar to those of cimetidine (p.1719).

In the management of peptic ulcer disease the oral dose is 150 mg at bedtime or 75 mg twice daily for 4 to 6 weeks. Where appropriate a maintenance dose of 75 mg at bedtime may be given to prevent the recurrence of ulcers. In gastro-oesophageal reflux disease the recommended dose is 150 mg at bedtime or 75 mg twice daily for 6 to 8 weeks. Gastritis has been managed with 75 mg once daily in the evening, and a dose of 75 mg twice daily has been used for Zollinger-Ellison syndrome.

When used as a pre-anaesthetic medication, an oral dose of roxatidine acetate hydrochloride 75 mg is given in the evening on the day before surgery and repeated 2 hours before the induction of anaesthesia; alternatively a single dose of 150 mg may be given the night before surgery.

Roxatidine acetate hydrochloride may also be given intravenously for the treatment of upper gastrointestinal tract haemorrhage in a dose of 75 mg twice daily by slow intravenous injection or by intravenous infusion.

For dosage in renal impairment, see below.

◊ Reviews.

1. Murdoch D. Roxatidine acetate: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic potential in peptic ulcer disease and related disorders. *Drugs* 1991; **42:** 240–60.

Administration in renal impairment. The dosage of roxatidine acetate hydrochloride should be reduced in patients with renal impairment. Suggested oral doses, based on creatinine clearance (CC), for patients on acute therapy are:

- CC 20 to 50 mL/minute: 75 mg at bedtime
- CC less than 20 mL/minute: 75 mg every 2 days

However, results in 6 patients with chronic renal failure and CC less than 20 mL/minute indicated that giving the recommended dose of roxatidine acetate hydrochloride, 75 mg every other day, was inadequate to maintain gastric pH above 4 for more than 6 hours. Subsequent study in 8 patients showed that a dose of 75 mg daily was well tolerated and effective.[1]

1. Gladziwa U, *et al.* Pharmacokinetics and pharmacodynamics of roxatidine in patients with renal insufficiency. *Br J Clin Pharmacol* 1995; **39:** 161–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Roxit†; ***Gr.:*** Roxane†; ***India:*** Rotane; ***Ital.:*** Gastralgin; Neo H2; Roxit; ***Jpn:*** Altat; ***Neth.:*** Roxit†; ***S.Afr.:*** Roxit†; ***Spain:*** Roxiwas†; Zarocs.

Senna

Alexandriai szenna termés (senna pods, Alexandrian); Listek senesu (senna leaf); Plod kasie ostrolisté (senna pods, Alexandrian); Plod kasie úzkolisté (senna pods, Tinnevelly); Sen; Séné de Khartoum ou d'Alexandrie, fruit de (senna pods, Alexandrian); Séné de l'Inde ou de Tinnevelly, fruit de (senna pods, Tinnevelly); Séné, feuille de (senna leaf); Sennabalja, alexandrinsk (senna pods, Alexandrian); Sennabalja, Tinnevelley- (senna pods, Tinnevelley); Sennae folium (senna leaf); Sennae fructus acutifoliae (senna pods, Alexandrian); Sennae fructus angustifoliae (senna pods, Tinnevelly); Sennanpalko, Aleksandrian (senna pods, Alexandrian); Sennanpalko, Tinnevelleyn (senna pods, Tinnevelley); Sennový list (senna leaf); Senų lapai (senna leaf); Senų vaisiai (senna pods, Alexandrian); Siauralapių senų vaisiai (senna pods, Tinnevelly); Sinameki; Szennalevél (senna leaf); Tinevelly szenna termés (senna pods, Tinnevelly).

Кассия Остролистная (Alexandrian senna); Сенна Остролистная (Alexandrian senna); Александрийский Лист (Alexandrian senna leaf)

CAS — 8013-11-4.
ATC — A06AB06.
ATC Vet — QA06AB06.

Description. Senna obtained commercially from *Cassia senna* (*C. acutifolia*) (Leguminosae) is known as Alexandrian senna or Khartoum senna and that from *Cassia angustifolia* (Leguminosae) as Tinnevelly senna.

Pharmacopoeias. Senna fruit, from Alexandrian and Tinnevelly senna is included in *Eur.* (see p.vii), *Int.*, and *US.* Senna leaf, from Alexandrian or Tinnevelly senna or both, is included in *Chin.*, *Eur.*, *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Senna Pods, Alexandrian; Sennae Fructus Acutifoliae; Alexandrian Senna Fruit BP 2008). The dried fruit of *Cassia senna* (*Cassia acutifolia*) containing not less than 3.4% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

Ph. Eur. 6.2 (Senna Pods, Tinnevelly; Sennae Fructus Angustifoliae; Tinnevelly Senna Fruit BP 2008). The dried fruit of *Cassia angustifolia* containing not less than 2.2% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

Ph. Eur. 6.2 (Senna Leaf; Sennae Folium). The dried leaflets of *Cassia senna* (=*Cassia acutifolia*), known as Alexandrian or Khartoum senna, or *Cassia angustifolia*, known as Tinnevelly senna, or a mixture of the two species. It contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B ($C_{42}H_{38}O_{20}$ = 862.7) with reference to the dried drug. Protect from light and moisture.

USP 31 (Senna Leaf). The dried leaflet of *Cassia acutifolia*, known in commerce as Alexandria senna, or *Cassia angustifolia*, known in commerce as Tinnevelly senna (Leguminosae). Protect from moisture and from light.

USP 31 (Senna Pods). The dried ripe fruit of *Cassia acutifolia* (Alexandrian senna) or *Cassia angustifolia* (Tinnevelly senna) containing not less than 3.4% or 2.2% respectively of anthraquinone glucosides, calculated as sennosides, on the dried basis. Protect from moisture and from light.

Sennosides

Senósidos.

Сеннозиды

CAS — 81-27-6 (sennoside A); 128-57-4 (sennoside B); 52730-36-6 (sennoside A, calcium salt); 52730-37-7 (sennoside B, calcium salt).

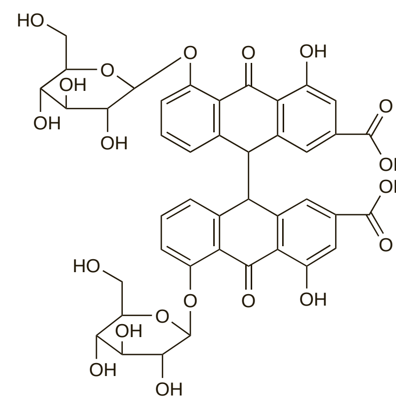

(sennoside A)

Pharmacopoeias. In *US.*

USP 31 (Sennosides). A partially purified natural complex of anthraquinone glucosides found in senna, isolated from *Cassia acutifolia* or *Cassia angustifolia* as calcium salts. It is a brownish powder. Soluble 1 in 35 of water, 1 in 2100 of alcohol, 1 in 3700 of chloroform, and 1 in 6100 of ether. A 10% solution in water has a pH of 6.3 to 7.3. Store at a temperature of 20° to 25°. Protect from moisture and from light.

Adverse Effects

Senna may cause mild abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Anthraquinone derivatives may colour the urine yellowish-brown at acid pH, and red at alkaline pH. Reversible melanosis coli has been reported following chronic use.

Abuse. Prolonged use or abuse of senna laxatives has been associated with finger clubbing,[1-5] hypokalaemia[3] and tetany,[1] hypertrophic osteoarthropathy,[4,5] intermittent urinary excretion of aspartylglucosamine,[2] hypogammaglobulinaemia,[3] reversible cachexia,[3] and hepatitis[6] or hepatic failure.[7] In one case, nephrocalcinosis was attributed to hypercalcaemia caused by excessive ingestion of calcium sennosides.[5]

1. Prior J, White I. Tetany and clubbing in patient who ingested large quantities of senna. *Lancet* 1978; **ii:** 947.
2. Malmquist J, *et al.* Finger clubbing and aspartylglucosamine excretion in a laxative-abusing patient. *Postgrad Med J* 1980; **56:** 862–4.
3. Levine D, *et al.* Purgative abuse associated with reversible cachexia, hypogammaglobulinaemia, and finger clubbing. *Lancet* 1981; **i:** 919–20.
4. Armstrong RD, *et al.* Hypertrophic osteoarthropathy and purgative abuse. *BMJ* 1981; **282:** 1836.
5. Lim AKH, *et al.* Anorexia nervosa and senna misuse: nephrocalcinosis, digital clubbing and hypertrophic osteoarthropathy. *Med J Aust* 2008; **188:** 121–2.
6. Beuers U, *et al.* Hepatitis after chronic abuse of senna. *Lancet* 1991; **337:** 372–3.
7. Vanderperren B, *et al.* Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacother* 2005; **39:** 1353–7.

Effects on the liver. Hepatitis has been reported in a patient drinking herbal tea containing senna. The patient was found to be a poor metaboliser for hepatic detoxification reactions; the authors cautioned against even small doses of herbal preparations in such patients.[1]

Hepatitis and hepatic failure have also been reported after abuse of senna laxatives, see Abuse, above.

1. Seybold U, *et al.* Senna-induced hepatitis in a poor metabolizer. *Ann Intern Med* 2004; **141:** 651.

Hypersensitivity. Hypersensitivity reactions manifesting as asthma and rhinoconjunctivitis have been reported in those manufacturing[1] or dispensing[2] senna products. However, a study of 125 workers involved in the manufacture of laxatives found only 4 cases of occupational asthma, although sensitisation to senna or ispaghula dust was present in 18 and 9 of the workers respectively, and other airway, eye, and skin symptoms were relatively frequent.[3]

A 2-year history of pruritic scaly erythematous plaques on the palmoplantar surfaces was reported[4] by a patient who had taken a sennoside laxative for 20 years. The lesions subsided over about 6 weeks on stopping the drug, and reappeared over the course of 8 weeks on restarting sennoside. However, patch testing and lymphocyte stimulation tests for sennoside were negative.

1. Helin T, Mäkinen-Kiljunen S. Occupational asthma and rhinoconjunctivitis caused by senna. *Allergy* 1996; **51:** 181–4.
2. Baggaley P. A shared allergy. *Pharm J* 1997; **259:** 724.
3. Marks GB, *et al.* Asthma and allergy associated with occupational exposure to ispaghula and senna products in a pharmaceutical work force. *Am Rev Respir Dis* 1991; **144:** 1065–9.
4. Fujita Y, *et al.* A case of interstitial granulomatous drug reaction due to sennoside. *Br J Dermatol* 2004; **150:** 1035–7.

Precautions

Senna should not be given to patients with nausea or vomiting, undiagnosed abdominal pain, or intestinal obstruction; care should also be taken in patients with inflammatory bowel disease. Prolonged use should generally be avoided.

Although anthraquinone derivatives may be distributed into breast milk the concentration achieved after usual maternal dosage is thought to be insufficient to affect the nursing infant (see also below).

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving senna, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/11/06)

Colonic perforation. There were early reports of colonic perforation with faecal peritonitis,[1,2] in one case fatal,[1] after use of a senna preparation containing total sennosides 142 mg for bowel preparation before barium enema. In 1985, the strength of the UK preparation was halved to contain 72 mg of total sennosides; it was subsequently withdrawn, although a similar preparation, at the higher strength, remains available in some countries. To reduce the risk of colonic perforation, patients with suspected stricture, inflammatory bowel disease, or impending obstruction should not receive a bowel stimulant.[2]

1. Galloway D, *et al*. Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; **284:** 472.
2. Cave-Bigley D. Faecal peritonitis after laxative preparation for barium enema. *BMJ* 1982; **284:** 740.

Pharmacokinetics

There is some absorption of anthraquinone laxatives after oral doses. Absorbed anthraquinones are metabolised in the liver. Unabsorbed senna is hydrolysed in the colon by bacteria to release the active free anthraquinones. Anthraquinones are excreted in urine and faeces and distributed into breast milk.

Uses and Administration

Senna is an anthraquinone stimulant laxative (p.1693) that is used to treat constipation (p.1693) and for bowel evacuation before investigational procedures or surgery. The active anthraquinones are liberated into the colon from the sennoside glycosides by colonic bacteria and an effect usually occurs within 6 to 12 hours of an oral dose.

For constipation, senna is usually given as tablets, granules, or syrup. In some countries it is available as suppositories. In the UK, doses of senna preparations are usually expressed in terms of total sennosides calculated as sennoside B. The usual adult oral dose is 15 to 30 mg as a single dose at bedtime. (For doses in children see Administration in Children, below.) In the USA, the usual adult dose is 15 to 30 mg once or twice daily, expressed in terms of total sennosides.

For bowel evacuation before investigational procedures, a dose of 105 to 157.5 mg of sennosides may be given orally as a liquid preparation on the day before the procedure (but see Colonic Perforation under Precautions, above).

The purified sennosides (sennosides A and B), and their calcium salts (calcium sennoside A and calcium sennoside B) are used similarly to senna.

Homoeopathy. Senna leaf has been used in homoeopathic medicines under the following names: Senna; Senna folium.

Administration in children. In the UK, the following oral doses of sennosides are licensed for use for constipation in children:

- aged 2 to 6 years: 3.75 to 7.5 mg once daily in the morning
- aged 6 to 12 years: 7.5 to 15 mg once daily at night or in the morning
- 12 years and over: 15 to 30 mg once daily, usually at bedtime

In addition, although not licensed for use in children under 2 years, the *BNFC* allows for an oral dose of syrup (containing sennosides 7.5 mg per 5 mL) of 0.5 mL/kg (to a maximum of 2.5 mL) once daily in those aged 1 month to 2 years.

Preparations

BP 2008: Senna Liquid Extract; Senna Tablets; Standardised Senna Granules;
Ph. Eur.: Senna Leaf Dry Extract, Standardised;
USP 31: Senna Fluidextract; Senna Syrup; Sennosides Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ciruela Fibra; Laxiruela; Laxiruela Ciruela Fibra; Laxuave Sen; ***Austral.:*** Bekunis Herbal Tea; Bekunis Instant; Laxettes; SennaPlus†; Sennetabs; Senokot; ***Austria:*** Bekunis; Colonorm; Darmol; Dragees Neunzehn Senna†; X-Prep; ***Belg.:*** Darlin; Fuca; Midro†; Prunasine; Senokot; Transix; ***Braz.:*** Senan; Sene; ***Canad.:*** Agarol Extra; Agarol with Sennosides; Ex-Lax; Experience; Glysennid†; GNC Herbal Laxative†; Herbal Laxative; Laxative Pills; Sennaprep; Sennatab; Senokot; X-Prep; ***Chile:*** Cholax; Naturlax; ***Cz.:*** Caj z Listu Senny; List Senny; Regulax†; Sennove Lusky; Sennovy List; Tisasen†; X-Prep†; ***Denm.:*** Pursennid; ***Fin.:*** Exprep; Pursennid; Sennapur; ***Fr.:*** Senokot; X-Prep; ***Ger.:*** Abfuhrtee N; Bekunis Instant; Bekunis-Krautertee N; Depuran; Heverto†; Liquidepur†; Midro Abfuhr; Midro Tee; Neda Fruchtewurfel; Ramend; Regulax N†; X-Prep†; ***Gr.:*** Bekunis†; Pursennid†; X-Prep; ***Hong Kong:*** Senokot; ***Hung.:*** Tisasen; X-Prep; ***India:*** Senade; Senalax; ***Irl.:*** Senokot; ***Israel:*** Bekunis; Ex-Lax; Florilax; Jungborn; Laxikal Forte; ***Ital.:*** Falquilax; Tisana Kelemata; X-Prep; ***Malaysia:*** Senokot; ***Mex.:*** Arsen; Bekunis; Ciruelax Comp; Ciruelax TE; Lagenbach; Sekalax†; Senokot; X-Prep; ***Neth.:*** Bekunis Plantaardig; Bekunis Senna; Sennocol; X-Praep; ***Norw.:*** Senokot; X-Prep; ***NZ:*** Senokot; ***Philipp.:*** Senokot; ***Pol.:*** Bekunis; Regulax; Senalax; Senefol; X-Prep; Xenna†; ***Port.:*** Bekunis; Pursennide; Senolax; X-Prep; ***Rus.:*** Glaxenna (Глаксенна); ***S.Afr.:*** Black Forest; Depuran; Gal; Hamburg Tea; Sennalax; Senokot; Soflax; X-Prep; ***Singapore:*** Senokot; ***Spain:*** Diolaxil†; Justelax; Laxante Bescansa Normal; Laxante Olan; Laxante Salud; Takata; X-Prep; ***Swed.:*** Pursennid; ***Switz.:*** Bekunis; Darmol; Demodon Neo; Fuca N; Grains de Vals Nouvelle formule; Irolax†; Kneipp Woerisetten S†; Midro; Tisane laxative H nouvelle formulation; X-Prep; ***Thai.:*** Senokot; ***Turk.:*** Pursennid; Roha-Lax; Senokot; X-M; ***UAE:*** Laxal; ***UK:*** Ex-Lax; Nylax with Senna; Senokot; Sure-Lax; ***USA:*** Black-Draught; Dosaflex; Dr Edwards Olive; Evac-U-Gen; Ex-Lax; Fletchers Castoria; Lax Pills; Little Tummys Laxative; Maximum Relief Ex-Lax; Senexon; Senna Smooth; Senna-Gen; Senokot; Senokotxtra; X-Prep; ***Venez.:*** Laxovar; Senlax; Senokot.

Multi-ingredient: ***Arg.:*** Agiolax; Calculina†; Candilax; Cirulaxia; Gelax; Kronolax†; LX-30; Medilaxan; Prompt†; Rapilax Fibras; ***Austral.:*** Agiolax; Chemists Own Natural Laxative with Softener; Coloxyl with Senna; Combilax; Neo-Cleanse; Peritone; Prolax†; Sennesoft; Soflax; ***Austria:*** Abfuhrtee St Severin; Abfuhrtee†; Agiolax; Carilax; Entschlackender Abfuhrtee EF-EM-ES; Eucarbon; Eucarbon Herbal; Frugelletten; Herbelax; Illings Bozner Maycur-Tee†; Laxalpin; Laxolind; Mag Kottas Krauterexpress Abfuhrtee; Mag Kottas May-Cur-Tee; Midro Tee; Neda Fruchtewurfel; Planta Lax; Pursennid; Sabatif; The Chambard-Tee; ***Belg.:*** Agiolax; Depuratif des Alpes; Tux†; ***Braz.:*** Agiolax; Circanetten†; Estomafitino†; Fitolax; Florlax; Fontolax; Frutalax†; Laxarine†; Laxtam; Naturetti; Plantax†; Sene Composta†; Tamaril; Tamarine; Tamarix†; Varicell†; ***Canad.:*** Cholasyn II; Cholasyn†; Control; Doulax; Extra Strong Formula 12†; Herbal Laxative; Herbal Laxative plus Yogurt; Herbalax†; Herbolax; Laxaco; Mucinum†; Prodiem Plus†; Senna-S; Senokot-S; Thunas Laxative†; ***Chile:*** Bilaxil; Instalax; Mielax; Naturlax; Tamarine; Te Laxante; ***Cz.:*** Abfuhr-Heilkrautertee†; Agiolax; Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; Projimava; Reduktan; Senalax; ***Denm.:*** Figen; ***Fin.:*** Agiolax; ***Fr.:*** Agiolax; Grains de Vals; Herbesan; Herbesan Instantane†; Ideolaxyl; Mediflor Tisane Contre la Constipation Passagere No 7; Mediflor Tisane Hepatique No 5; Modane; Mucinum a l'Extrait de Cascara; Pursennide; Tamarine; Vegelax†; ***Ger.:*** Agiolax; Alasenn; Heumann Abfuhrtee Solubilax N†; Hevertolax duo†; Presselin Stoffwechsel-Tee Hapeka 225 N†; Ramend Krauter†; ***Hong Kong:*** Agiolax; Mucinum Cascara†; ***Hung.:*** Bolus Laxans; ***India:*** Pursennid-In†; ***Irl.:*** Pripsen†; ***Israel:*** Agiolax; Eucarbon; Jungborn; Lido Tea; Midro-Tea; Novicarbon; ***Ital.:*** Agiolax; Colax; Combilax; Confetti Lassativi CM; Cuscutine; Eucarbon; Fibrolax Complex; Lactolas; Lassatina†; Midro; Ormobyl CM†; Ortisan; Pursennid; Senna-Specie Composta†; Stimolfit; Tamarine; Tisana Kelemata; ***Malaysia:*** Eucarbon†; ***Mex.:*** Agiolax; Ciruelax Jalea; Jarabe de Manzanas; Laxacaps; Naturetti†; ***Neth.:*** Agiolax; Prunacolon; Prunasine; ***Norw.:*** Agiolax; Pursennid; ***NZ:*** Coloxyl with Senna; Laxsol; ***Philipp.:*** Boie Carminative (Carminasen); Castoria; ***Pol.:*** Agiolax; Laxamix; Melisana Klosterfrau; Senalax K; ***Port.:*** Agiolax; Bekunis; Midro†; Mucinum; Xarope de Macas Reinetas; ***S.Afr.:*** Agiolax; Clairo; Rubilax†; ***Spain:*** Agiolax; Bekunis Complex; Crislaxo; Jarabe Manceau; Laxante Sanatorium; Laxomax†; Modane; Natusor Malvasen†; Pruina; Puntual; Puntualex; Pursenid; Senalsor†; ***Swed.:*** Agiolax; ***Switz.:*** Agiolax; Dragees aux figues avec du sene; Fruttasan; Lapidar 10; Linoforce; LinoMed; Phyto-Laxia; Phytolaxin; Pursennide; Schweden-Mixtur H nouvelle formulation; Tisane laxative; Tisane Provencale No 1; Valverde Constipation dragees; Valverde Constipation sirop; ***Thai.:*** Agiolax; Circanetten; ***Turk.:*** Bekunis; Eucarbon; Karboseptin; ***UK:*** Athera; Califig; Cleansing Herbs; Dual-Lax Extra Strong; Dual-Lax Normal Strength; Fam-Lax Senna; Fibre Plus; Jacksons Herbal Laxative; Kas-Bah; Laxative Tablets; Lion Cleansing Herbs; Lustys Herbalene; Manevac; Modern Herbals Laxative; Modern Herbals Menopause; Natural Herb Tablets; Out-of-Sorts; Pripsen; Rhuaka; Senokot Dual Relief; Skin Cleansing; Tabritis; ***USA:*** Black-Draught†; Ex-Lax Gentle Strength; Perdiem; Peri-Colace; Senna Plus; Senna Prompt; Senna-S; Senokot-S; X-Prep Bowel Evacuant Kit-1; ***Venez.:*** Agiolax; Fibralax†; Rheu-Tarx 1; Senokot con Docusato; Senokot con Fibra†.

Simeticone *(BAN, rINN)*

Activated Dimethicone; Activated Dimethylpolysiloxane; Activated Dimeticone; Antifoam A; Antifoam AF; Simethicone *(USAN)*; Simeticona; Siméticone; Simeticonum; Simetikon; Simetikonas; Simetikoni; Szimetikon.

Симетикон

CAS — 8050-81-5.

NOTE. Do not confuse with Dimeticone (p.2032).

Compounded preparations of simeticone may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Simeticone). It is prepared by incorporation of 4 to 7% silica into poly(dimethylsiloxane) with a degree of polymerisation between 20 and 400. It contains 90.5 to 99.0% of poly(dimethylsiloxane). It is a greyish-white, opalescent, viscous liquid. Practically insoluble in water and in methyl alcohol; very slightly soluble to practically insoluble in dehydrated alcohol; partly miscible with dichloromethane, with ethyl acetate, with methyl ethyl ketone, and with toluene.

USP 31 (Simeticone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, and silicon dioxide. It contains not less than 90.5% and not more than 99% of polydimethylsiloxane and not less than 4% and not more than 7% of silicon dioxide. A translucent, grey, viscous fluid. Insoluble in water, in alcohol, and in dehydrated alcohol; the liquid phase is soluble 1 in 10 of chloroform, of ether, and of benzene, leaving a residue of silicon dioxide. Store in airtight containers.

Profile

Simeticone is a mixture of liquid dimeticones containing finely divided silicon dioxide to enhance the defoaming properties of the silicone. It lowers surface tension and when given by mouth causes bubbles of gas in the gastrointestinal tract to coalesce, thus aiding their dispersion.

Simeticone is used for the relief of flatulence and abdominal discomfort due to excess gastrointestinal gas in disorders such as dyspepsia (p.1695) and gastro-oesophageal reflux disease (p.1696). Doses of 100 to 250 mg three or four times daily have been given. For many gastrointestinal disorders, it is given with an antacid.

Doses of about 20 to 40 mg of simeticone have been given with feeds to relieve colic in infants (see Gastrointestinal Spasm, p.1696).

Simeticone is also used as a defoaming agent in radiography or endoscopy of the gastrointestinal tract.

◊ A brief review of the use of simeticone for gastrointestinal symptoms concluded that although it was commonly prescribed with an antacid, there was no good evidence that this provided additional benefit. When used alone simeticone probably helped to relieve minor postoperative and postprandial symptoms and was a useful aid in upper gastrointestinal endoscopy.[1] However, some considered there was no convincing evidence that simeticone, alone or with antacids, was effective for the treatment of eructation, flatulence, or other signs or symptoms of excess gastrointestinal gas.[2]

1. Anonymous. Dimethicone for gastrointestinal symptoms? *Drug Ther Bull* 1986; **24:** 21–2.
2. Anonymous. Simethicone for gastrointestinal gas. *Med Lett Drugs Ther* 1996; **38:** 57–8.

Preparations

BP 2008: Simeticone for Oral Use; Simeticone Suspension for Infants;
USP 31: Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Calcium Carbonate, Magnesia, and Simethicone Tablets; Magaldrate and Simethicone Oral Suspension; Magaldrate and Simethicone Tablets; Simethicone Capsules; Simethicone Emulsion; Simethicone Oral Suspension; Simethicone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aesim; Aflat; Carbogasol; Carbogasol Forte; Espaven Antigas; Factor AG; Metiorisan; Mylanta Gas; Simecon; ***Austral.:*** Degas; Degas Infant Drops†; Infacol; Medefoam†; ***Austria:*** Antiflat; Disflatyl; Lefaxin; SAB Simplex; ***Braz.:*** Anflat†; Dimezin; Espasmo Flatol; Finigas; Flagass; Flatex; Flatol; For Gas; Freegas†; Gastroflat; Gazyme; Luftal; Luftrin†; Meticone; Mylanta Plus; Mylicon; Nogas†; Sanagas; Silidron; ***Canad.:*** Gas-X; Ovol; Phazyme; Siligaz; ***Chile:*** Flapex; Gasoff; Gasorbol†; Pepsidol†; ***Cz.:*** Ceolat†; Disflatyl†; Espumisan; Lefax; SAB Simplex; ***Denm.:*** Aeropax; Mylicon; ***Fin.:*** Cuplaton; Disflatyl; Minifom; ***Fr.:*** Siligaz; ***Ger.:*** Absorber HFV†; Aegrosan†; Ceolat; Elugan; Endo-Paractol; Espumisan; Ilio-Funkton; Imogas; Kompensan Dimeticon; Lefax; Meteosan†; SAB Simplex; ***Gr.:*** Ceolat†; Infacolic; ***Hong Kong:*** Air-X; Dentinox Colic Drops; Disflatyl; Gascon; Gasteel; Infacol; Ovol; ***Hung.:*** Espumisan; Infacol; SAB Simplex; ***India:*** Dimol; Tricaine-MPS; ***Indon.:*** Aeroson; Disflatyl; Flatunic; ***Irl.:*** Infacol; ***Israel:*** Gazim X; Simicol; ***Ital.:*** Meteosim; Mylicon; Polisilon†; Simecrin; Simetic; ***Malaysia:*** Cuplaton; Dentinox Colic Drops; Disflatyl; Gascoal; Gastyl; ***Mex.:*** Diflax†; Espaven Pediatrico; Liberan; ***Neth.:*** Aeropax; Ceolat†; Setlers Windfree; ***Norw.:*** Ceolat†; Minifom; Siloxan; ***NZ:*** De-Gas; Infacol; Medefoam†; ***Philipp.:*** Disflatyl; ***Pol.:*** Bobotic; Espumisan; Esputicon; Gastrosil; Infacol; Manti Gastop; Simet; ***Port.:*** Aero-Om; Imogas; ***Rus.:*** Disflatyl (Дисфлатил); Espumisan (Эспумизан); SAB Simplex (САБ Симплекс); Simicol (Симикол)†; ***S.Afr.:*** Telament; ***Singapore:*** Cuplaton; Gascoal; Infacol†; RidWind; ***Spain:*** Aero Red; Enterosilicona; ***Swed.:*** Minifom; ***Switz.:*** Disflatyl; Flatulex; Lefax; Polysilane; Simet-AF†; ***Thai.:*** Air-X; Airrox; Babcon†; Blow-X; Disflatyl; Gas-MM; Gas-X; Gassi; Gastyl; Logastin; Mylom; Ovol; Semeth; Sigas†; Simcone;

Simecon; Simetyl; Siticon; ***Turk.:*** Antiflat; Metsil; ***UAE:*** Salinal; ***UK:*** Asilone Windcheaters†; Dentinox Colic Drops; Infacol; Wind-Eze; ***USA:*** Baby Gas-X; Colicon; Degas; Extra Strength Mintox Plus; Flatulex; Gas Relief; Gas-X; Maalox Anti-Gas†; Major-Con; Mylanta Gas; Mylicon; Phazyme; SonoRx; ***Venez.:*** Antifom; Flatoril; Sicon†; Silicon†.

Multi-ingredient: numerous preparations are listed in Part 3.

Used as an adjunct in: ***Austria:*** Prontobario; ***Cz.:*** Prontobario†; ***Spain:*** Bario Dif.

Smectites

Смектиты

ATC — A07BC05 (diosmectite).

ATC Vet — QA07BC05 (diosmectite).

Profile

Smectites are natural mineral clays composed mainly of aluminium silicates and include aluminium magnesium silicate (p.2141), bentonite (p.2141), and Fuller's earth (p.1447). They have adsorbent properties and some, such as dioctahedral smectite (diosmectite), have been used in the management of diarrhoea. They are also used as pharmaceutical excipients and in industry.

◊ References.

1. Szajewska H, *et al.* Meta-analysis: smectite in the treatment of acute infectious diarrhoea in children. *Aliment Pharmacol Ther* 2006; **23:** 217–27.
2. Yen ZS, Lai MS. Smectite for acute diarrhoea in children. *Emerg Med J* 2006; **23:** 65–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Smecta; ***Fr.:*** Smecta; ***Ger.:*** Colina; ***Gr.:*** Smecta; ***Hong Kong:*** Smecta; ***Hung.:*** Smecta; ***Ital.:*** Diosmectal; Nodia; ***Malaysia:*** Smecta; ***Pol.:*** Smecta; ***Rus.:*** Smecta (Смекта); ***Singapore:*** Smecta; ***Thai.:*** Smecta.

Multi-ingredient: ***Belg.:*** Barexal; ***Ger.:*** Colina Spezial.

Sodium Picosulfate *(BAN, rINN)*

DA-1773; LA-391; Natrii picosulfas; Natrii Picosulfas Monohydricus; Natrio pikosulfatas; Natriumpikosulfaatti; Natriumpikosulfat; Nátrium-pikoszulfát; Picosulfate de Sodium; Picosulfato de sodio; Picosulphol; Pikosíran sodný monohydrát; Sodium, picosulfate de; Sodium Picosulphate. Disodium 4,4′-(2-pyridylmethylene)-di(phenyl sulphate).

Натрия Пикосульфат

$C_{18}H_{13}NNa_2O_8S_2,H_2O$ = 499.4.

CAS — 10040-45-6.

ATC — A06AB08.

ATC Vet — QA06AB08.

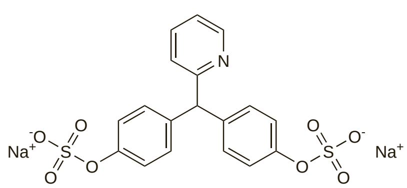

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Sodium Picosulfate). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol.

Adverse Effects and Precautions

As for Bisacodyl, p.1710 and p.1710.

Bowel evacuation. Sodium picosulfate with magnesium citrate was considered a safe and effective bowel cleansing agent in adults[1] and children[2] with inflammatory bowel disease. They tolerated the preparation as well as patients with other colonic disorders with no adverse effect on their disease symptoms. Patients should be kept well hydrated (it may be appropriate to carry out bowel preparation in hospital in frail or elderly patients to avoid the risks of over- or underhydration[3,4]), and this procedure should not be used in suspected toxic dilatation of the colon.

In Australia, the Adverse Drug Reactions Advisory Committee has warned that low volume sodium picosulfate solutions may cause marked dehydration, hyponatraemia, other electrolyte abnormalities, and associated complications. Patients at particular risk include infants, the elderly, the frail, and those with congestive heart failure or with renal impairment.[5]

A grand mal seizure in a 64-year-old female given sodium picosulfate with magnesium citrate was assumed to have been caused by hyponatraemia; the patient had normal electrolyte concentrations in the period before taking the bowel preparation. Care is needed when sodium picosulfate solutions are used in those with a low seizure threshold or potential sodium depletion.[6]

1. McDonagh AJG, *et al.* Safety of Picolax (sodium picosulphate-magnesium citrate) in inflammatory bowel disease. *BMJ* 1989; **299:** 776–7.
2. Evans M, *et al.* Safety of Picolax in inflammatory bowel disease. *BMJ* 1989; **299:** 1101–2.
3. Lewis M, *et al.* Bowel preparation at home in elderly people. *BMJ* 1997; **314:** 74.
4. Hanning CD. Bowel preparation at home in elderly people. *BMJ* 1997; **314:** 74.
5. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with sodium picosulphate bowel cleansing products. *Aust Adverse Drug React Bull* 2002; **21:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0202.pdf (accessed 03/07/08)
6. Frizelle FA, *et al.* Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum* 2005; **48:** 393–6.

Pharmacokinetics

Like bisacodyl (p.1710), sodium picosulfate is metabolised by colonic bacteria to the active compound bis(*p*-hydroxyphenyl)pyridyl-2-methane. Only a small amount of sodium picosulfate is absorbed after an oral dose; this is subsequently excreted in the urine.

Uses and Administration

Sodium picosulfate is a stimulant laxative related to bisacodyl (p.1710) used for the treatment of constipation (p.1693) and for evacuation of the colon before investigational procedures or surgery. When taken orally it is metabolised by colonic bacteria to an active form that stimulates bowel movements. It is usually effective within 6 to 12 hours although when used with magnesium citrate for bowel evacuation an effect may be seen within 3 hours.

For constipation it is given as a single oral dose of 5 to 10 mg, usually at bedtime. (For doses in children see below.)

For bowel evacuation, a dose of sodium picosulfate 10 mg with magnesium citrate (p.1743) is given in the morning and again in the afternoon of the day before examination.

Administration in children. In the UK, the following oral doses of sodium picosulfate have been recommended for children in the treatment of **constipation**; the dose is usually given at night:

- 1 month to 4 years: 250 micrograms/kg (maximum 5 mg)
- 4 to 10 years: 2.5 to 5 mg
- over 10 years: 5 to 10 mg

Most UK licensed product information gives similar doses to those above for **bowel cleansing**. Alternatively, some recommend that children may be given the following doses of a sachet containing sodium picosulfate 10 mg (with magnesium citrate):

- 1 to 2 years: ⁄ sachet in the morning and ⁄ sachet in the afternoon
- 2 to 4 years: ⁄ sachet in the morning and ⁄ sachet in the afternoon
- 4 to 9 years: 1 sachet in the morning and ⁄ sachet in the afternoon
- over 9 years: 1 sachet in the morning and 1 sachet in the afternoon

Preparations

BP 2008: Compound Sodium Picosulfate Powder for Oral Solution; Sodium Picosulfate Oral Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Agarol; Cirulaxia; Dagol; Dulcolax; Factor Laxante; Feen-A-Mint; Gotalax; Granulax†; Kritel; Laxamin; Modaton; Modernel†; Opalino; Rapilax; Rogelina†; Trali; Verilax; Yodolin; ***Austral.:*** Durolax SP; ***Austria:*** Agaffin; Agiopic; Guttalax; Laxasan; ***Belg.:*** Dulcolax Picosulphate; Fructines; Guttalax†; Laxoberon; Picolaxine; ***Braz.:*** Cronoplex; Diltin; Guttalax; Picolax†; Rapilax; ***Chile:*** Aguala; Cronolax; Guttalax; Laxantil; Laxoberal; ***Cz.:*** Agiolax Pico; Darmol†; Guttalax; Laxygal; Progut; Regulax Pikosulfat; ***Denm.:*** Actilax; Laxoberal; Picolon; ***Fin.:*** Laxoberon; ***Fr.:*** Fructines; ***Ger.:*** Agiolax Pico; Darmol Pico; Darmol†; Dulcolax NP; Laxans-ratiopharm Pico; Laxoberal; Liquidepur mit Natriumpicosulfat; Midro Pico†; Regulax Picosulfat; ***Gr.:*** Guttalax; Laxatol; ***Hong Kong:*** Sur-Lax; ***Hung.:*** Darmol; Guttalax; Laxygal; ***India:*** Cremalax; ***Indon.:*** Laxoberon; ***Irl.:*** Dulcolax Perles; Laxoberal; ***Ital.:*** Euchessina CM; Falquigut; Gocce Lassative Aicardi; Guttalax; ***Jpn:*** Laxoberon; ***Mex.:*** Anara; Laxoberon; ***Neth.:*** Dulcodruppels; Dulcopearls; ***Norw.:*** Laxoberal; ***Philipp.:*** Laxoberal; ***Port.:*** Fructines; Guttalax; Laxodal; Picolax; ***Rus.:*** Guttalax (Гутталакс); Laxygal (Лаксигал); ***Spain:*** Contumax; Evacuol; Ezor; Gutalax; Lubrilax; Skilax; ***Swed.:*** Cilaxoral; Laxoberal; ***Switz.:*** Fructines; Laxoberon; ***UK:*** Dulcolax; Laxoberal; ***Venez.:*** Lasoberon.

Multi-ingredient: ***Arg.:*** Agarol; Cascara Sagrada Oligoplex; ***Austral.:*** Colonprep†; Picolax†; Picoprep; Prep Kit-C; ***Belg.:*** Pilules de Vichy; ***Braz.:*** Agarol; Forlax; ***Canad.:*** Pico-Salax; ***Irl.:*** Picolax; ***Malaysia:*** Picoprep; ***NZ:*** Picoprep; ***Spain:*** Emuliquen Laxante; ***Switz.:*** Laxasan; ***UK:*** CitraFleet; Picolax.

Anhydrous Sodium Sulfate

Anhydrous Sodium Sulphate; Dried Sodium Sulphate; Exsiccated Sodium Sulphate; Natrii Sulfas; Natrii sulfas anhydricus; Natrio sulfatas, bevandenis; Natrium Sulfuricum Siccatum; Natriumsulfaatti, vedetön; Natriumsulfat, vattenfritt; Síran sodný; Sodium (sulfate de) anhydre; Sodu siarczan bezwodny; Sulfato de sodio anhidro; Vízmentes nátrium-szulfát.

Безводный Сульфат Натрия

Na_2SO_4 = 142.0.

CAS — 7757-82-6.

ATC — A06AD13; A12CA02.

ATC Vet — QA06AD13; QA12CA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Viet.*

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 6.2 (Sodium Sulphate, Anhydrous). A white or almost white, hygroscopic powder. Freely soluble in water. Store in airtight containers.

USP 31 (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33°, and loses all of its water of hydration at about 100°. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30°.

Sodium Sulfate

E514; Glauber's Salt; Natrii sulfas decahydricus; Natrii Sulphas; Natrio sulfatas dekahidratas; Natrium Sulfuricum Crystallisatum; Natriumsulfaattidekahydraatti; Natriumsulfatdekahydrat; Nátrium-szulfát-dekahidrát; Síran sodný dekahydrát; Sodium (sulfate de) décahydraté; Sodium Sulphate; Sodium Sulphate Decahydrate; Sodu siarczan dziesięciowodny; Sulfato de sodio.

Глауберова соль; Сульфат Натрия

$Na_2SO_4,10H_2O$ = 322.2.

CAS — 7727-73-3 (sodium sulfate decahydrate).

ATC — A06AD13; A12CA02.

ATC Vet — QA06AD13; QA12CA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Viet.*

US includes a single monograph for both the anhydrous form and the decahydrate.

Ph. Eur. 6.2 (Sodium Sulphate Decahydrate; Sodium Sulphate BP 2008). A white or almost white, crystalline powder or colourless, transparent crystals. Freely soluble in water; practically insoluble in alcohol. It partly dissolves in its own water of crystallisation at about 33°. It loses between 52.0 and 57.0% of its weight on drying.

USP 31 (Sodium Sulfate). It contains 10 molecules of water of hydration or is anhydrous. The decahydrate loses between 51 and 57% of its weight on drying and the anhydrous form loses not more than 0.5% of its weight. Large, colourless, odourless, transparent crystals or a granular powder. It effloresces rapidly in air, liquefies in its water of hydration at about 33°, and loses all of its water of hydration at about 100°. Freely soluble in water; insoluble in alcohol; soluble in glycerol. Store in airtight containers, preferably at a temperature not exceeding 30°.

Profile

Sodium sulfate has been used as an osmotic laxative (p.1693). It is also given in dilute solution (about 0.5%) with a high molecular weight macrogol for prompt bowel evacuation before investigational procedures or surgery (see Macrogols, p.2336).

Sodium sulfate is also used as an additive in foods.

For the general properties of sodium salts, see p.1686.

Preparations

USP 31: Sodium Sulfate Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Celloids SS 69.

Multi-ingredient: ***Arg.:*** Magnesia Phosphorica I Oligoplex; ***Austral.:*** Duo Celloids SPSS; Duo Celloids SSMP; Duo Celloids SSPC; Duo Celloids SSS; Iron Compound†; Liv-Detox†; Silybum Complex†; ***Canad.:*** Normo Gastryl; ***Fr.:*** Actisoufre; Digedryl; Hepargitol; Normogastryl†; Oxyboldine; Prefagyl†; ***Ital.:*** Argirofedrina†; ***Pol.:*** Sal Ems Artificiale; Sal Ems Factitium; Sal Vichy Factitium; ***Spain:*** Darmen Salt; Digestovital†; Leberetic; Lebersal; Salcedol; ***Switz.:*** Padma-Lax; Padmed Laxan; ***Thai.:*** Ulgastrin; ***USA:*** Triv; ***Venez.:*** Topdent†.

Sodium Tartrate

Disodium L-Tartrate; E335 (sodium tartrate or monosodium tartrate); Sodu winian; Tartrato de sodio.

Виннокислый Натрий

$C_2H_4O_2(CO_2Na)_2,2H_2O = 230.1.$

CAS — 868-18-8 (anhydrous sodium tartrate); 6106-24-7 (sodium tartrate dihydrate).

ATC — A06AD21.

ATC Vet — QA06AD21.

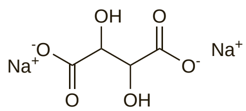

(anhydrous sodium tartrate)

Pharmacopoeias. In *USNF.*

USNF 26 (Sodium Tartrate). Transparent, colourless, odourless crystals. Freely soluble in water; insoluble in alcohol. pH of a 10% solution in water is between 7 and 9. Store in airtight containers.

Profile

Sodium tartrate has been used as an osmotic laxative. It is used as a food additive.

For the general properties of sodium salts, see p.1686.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Limonade Asepta.

Multi-ingredient: ***Arg.:*** Oral-B Enjuague Bucal Amosan†.

Sofalcone *(pINN)*

Sofalcona; Sofalconum; SU-88. {5-[(3-Methyl-2-butenyl)oxy]-2-{*p*-[(3-methyl-2-butenyl)oxy]cinnamoyl}phenoxy}acetic acid.

Софалькон

$C_{27}H_{30}O_6 = 450.5.$

CAS — 64506-49-6.

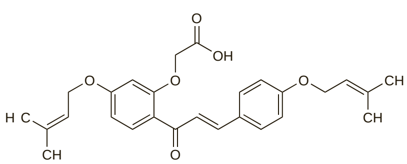

Profile

Sofalcone is reported to possess cytoprotective properties and is used in the treatment of gastritis and peptic ulcer disease (p.1702). An oral dose of 100 mg is given 3 times daily.

◊ References.

1. Isomoto H, *et al.* Sofalcone, a mucoprotective agent, increases the cure rate of Helicobacter pylori infection when combined with rabeprazole, amoxicillin and clarithromycin. *World J Gastroenterol* 2005; **11:** 1629–33.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Solon.

Sterculia

E416; Goma esterculia; Indian Tragacanth; Karaya; Karaya Gum; Sterculia Gum; Sterkülia.

Камедь Карайи; Стеркулия Жгучая (*Sterculia urens*)

CAS — 9000-36-6.

ATC — A06AC03.

ATC Vet — QA06AC03.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Sterculia). The gum obtained from *Sterculia urens* and other species of *Sterculia*. Irregular or vermiform pieces, greyish-white with a brown or pink tinge, with an odour resembling that of acetic acid. It contains not less than 14.0% of volatile acid (or not less than 10.0% if supplied in powdered form), calculated as acetic acid. Sparingly soluble in water, but swells into a homogeneous, adhesive, gelatinous mass; practically insoluble in alcohol. Store at a temperature not exceeding 25°.

Adverse Effects and Precautions

As for Ispaghula, p.1737. There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if such compounds are swallowed dry. Therefore they should always be taken with sufficient fluid and should not be taken immediately before going to bed. They should be avoided by patients who have difficulty swallowing.

Uses and Administration

Sterculia is used similarly to ispaghula (p.1737) as a bulk laxative and for adjusting faecal consistency. It has also been used as an aid to appetite control in the management of obesity (p.2149) but there is little evidence of efficacy. It is usually taken in the form of granules containing sterculia 62%; the dose is 1 to 2 sachets or 1 to 2 heaped 5 mL spoonfuls orally once or twice daily after meals. (For a dose in children see below.) The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Sterculia is used topically, as a paste or powder, for skin protection and sealing in the fitting of ileostomy and colostomy appliances. It has also been used in dental fixative powders, and as an emulsifier and stabiliser in foods.

Administration in children. In the UK, the recommended oral dose of granules, containing sterculia 62%, for constipation in children aged 6 to 12 years is ⁄ to 1 sachet, or ⁄ to one 5 mL spoonful, once or twice daily after meals. Children over 12 years may be dosed as for adults, see Uses and Administration, above. The granules are washed down without chewing with plenty of water. They may also be taken sprinkled onto soft foods such as yogurt.

Preparations

BP 2008: Sterculia Granules.

Proprietary Preparations (details are given in Part 3)

Austral.: Normafibe; ***Belg.:*** Normacol†; ***Braz.:*** Corega; ***Canad.:*** Normacol; ***Fr.:*** Inolaxine†; Normacol; ***Ger.:*** Decorpa†; Granamon†; ***Hong Kong:*** Normacol; ***Irl.:*** Normacol; ***Ital.:*** Normacol; ***Malaysia:*** Normacol†; ***Neth.:*** Normacol; ***NZ:*** Normacol; ***S.Afr.:*** Normacol; ***Singapore:*** Normacol; ***Swed.:*** Inolaxol; ***Switz.:*** Colosan mite; Inolaxine; Normacol; ***Thai.:*** Normacol†; ***UK:*** Normacol.

Multi-ingredient: ***Austral.:*** Alvercol†; Granocol†; Normacol Plus; ***Belg.:*** Normacol Antispasmodique†; Normacol Plus†; ***Fr.:*** Kaologeais; Karayal; Normacol a la Bourdaine†; Poly-Karaya; ***Hong Kong:*** Normacol Plus; ***India:*** Kanormal; ***Irl.:*** Normacol Plus; ***NZ:*** Granocol; Normacol Plus; ***Port.:*** Normacol Plus; ***S.Afr.:*** Alvercol†; Normacol Plus; ***Singapore:*** Normacol Plus; ***Spain:*** Normacol Forte; ***Switz.:*** Colosan plus; Normacol avec bourdaine nouvelle formule†; ***UK:*** Normacol Plus; Spasmonal Fibre†; ***Venez.:*** Polifix†.

Sucralfate *(BAN, USAN, rINN)*

Sucralfato; Sucralfatum; Sukralfaatti; Sükralfat; Sukralfat. Sucrose hydrogen sulphate basic aluminium salt; Sucrose octakis(hydrogen sulphate) aluminium complex; β-D-Fructofuranosyl-α-D-glucopyranoside octakis (hydrogen sulphate) aluminium complex.

Сукральфат

$C_{12}H_mAl_{16}O_nS_8.$

CAS — 54182-58-0.

ATC — A02BX02.

ATC Vet — QA02BX02.

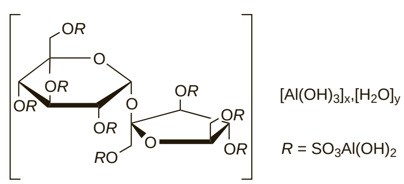

Pharmacopoeias. In *Chin., Jpn,* and *US.*

USP 31 (Sucralfate). The hydrous basic aluminium salt of sucrose octasulfate. Store in airtight containers.

Adverse Effects and Precautions

Constipation is the most frequently reported adverse effect of sucralfate although diarrhoea, nausea, vomiting, flatulence, or gastric discomfort may also occur. Other adverse effects include dry mouth, dizziness, drowsiness, headache, vertigo, back pain, and skin rashes. Hypersensitivity reactions such as pruritus, oedema, urticaria, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported.

Great caution is needed in patients with renal impairment (below) as absorption and accumulation of aluminium may cause adverse effects.

Bezoar formation. As of March 1999, the UK CSM was aware of 7 reports worldwide of bezoar formation associated with sucralfate use in intensive care patients.[1] It advised caution in the use of sucralfate in seriously ill patients because of the risks of bezoar formation and intestinal obstruction.[1] Patients with delayed gastric emptying or receiving concomitant enteral feeds may be at increased risk. A report by the French Pharmacovigilance System at about the same time made similar recommendations but also contra-indicated the use of sucralfate in premature and immature neonates.[2]

1. Committee on Safety of Medicines/Medicines Control Agency. Bezoar formation with sulcralfate [sic] (Antepsin). *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 07/11/06)
2. Guy C, Ollagnier M. Sucralfate et bézoard: bilan de l'enquête officielle de pharmacovigilance et revue de la littérature. *Therapie* 1999; **54:** 55–8.

Renal impairment. Sucralfate under acid conditions can release aluminium ions that may be absorbed systemically. Significant increases in the urinary excretion of aluminium have been seen in healthy subjects given sucralfate 4 g daily,[1,2] reflecting gastrointestinal absorption of aluminium; aluminium concentrations in serum and urine were significantly higher in patients with chronic renal impairment than in subjects with normal renal function,[3] and similar serum increases have been seen in children with acute renal failure.[4] Aluminium toxicity in patients with normal renal function receiving sucralfate would not be expected, but seizures, muscle weakness, bone pain,[1] and severe aluminium encephalopathy[5] have been reported in patients with end-stage renal disease requiring dialysis. Sucralfate should be used with caution in patients with renal impairment, especially if other aluminium-containing agents are also taken, and such patients should be monitored for signs of aluminium toxicity.[4,6]

1. Robertson JA, *et al.* Sucralfate, intestinal aluminium absorption, and aluminium toxicity in a patient on dialysis. *Ann Intern Med* 1989; **111:** 179–81.
2. Allain P, *et al.* Plasma and urine aluminium concentrations in healthy subjects after administration of sucralfate. *Br J Clin Pharmacol* 1990; **29:** 391–5.
3. Burgess E, *et al.* Aluminum absorption and excretion following sucralfate therapy in chronic renal insufficiency. *Am J Med* 1992; **92:** 471–5.
4. Thorburn K, *et al.* Aluminum accumulation in critically ill children on sucralfate therapy. *Pediatr Crit Care Med* 2001; **2:** 247–9.
5. Withers DJ, *et al.* Encephalopathy in patient taking aluminium-containing agents, including sucralfate. *Lancet* 1989; **ii:** 674.
6. Hemstreet BA. Use of sucralfate in renal failure. *Ann Pharmacother* 2001; **35:** 360–4.

Interactions

Sucralfate may interfere with the absorption of other drugs and it has been suggested that there should be an interval of 2 hours between giving sucralfate and other non-antacid medication. Some of the drugs reported to be affected by sucralfate include cimetidine, ranitidine, digoxin, fluoroquinolone antibacterials, ketoconazole, levothyroxine, phenytoin, tetracycline, quinidine, theophylline, and possibly warfarin. The recommended interval between sucralfate and antacids is 30 minutes. An interval of 1 hour should elapse between giving sucralfate and enteral feeding.

Pharmacokinetics

Sucralfate is only slightly absorbed from the gastrointestinal tract after oral doses. However, there can be some release of aluminium ions and of sucrose sulfate; small quantities of sucrose sulfate may then be absorbed and excreted, primarily in the urine; some absorption of aluminium may also occur (see Renal Impairment, above).

Uses and Administration

Sucralfate is a cytoprotective drug that, under acid gastrointestinal conditions, forms an adherent complex with proteins which coats the gastric mucosa and is reported to have a special affinity for ulcer sites. It also inhibits the action of pepsin and adsorbs bile salts.

Sucralfate has been used in the treatment of peptic ulcer disease (p.1702) and chronic gastritis. It is given orally and should be taken on an empty stomach before meals and at bedtime. The usual dose is 1 g four times daily or 2 g twice daily for 4 to 8 weeks; if necessary the dose may be increased to a maximum of 8 g daily. If longer-term therapy is required sucralfate may be given for up to 12 weeks. Where appropriate a maintenance dose of 1 g twice daily may be given to prevent the recurrence of duodenal ulcers.

For prophylaxis of gastrointestinal haemorrhage from stress ulceration the usual dose of sucralfate is 1 g six times daily; a dose of 8 g daily should not be exceeded. For children's doses see below.

Administration in children. Although sucralfate is not licensed in the UK for use in children under 15 years, the *BNFC* recommends the following oral doses for the treatment of peptic ulcer disease, or the prophylaxis of stress ulceration in children in intensive care (but see also under Bezoar Formation, above):

- 1 month to 2 years: 250 mg four to six times daily
- 2 to 12 years: 500 mg four to six times daily
- 12 to 18 years: 1 g four to six times daily

The oral suspension blocks fine-bore feeding tubes and tablets should be crushed and dispersed in water instead.

Gastrointestinal bleeding. Sucralfate is an effective drug for the prophylaxis and management of stress-induced gastrointestinal bleeding in severely ill patients but whether it should be chosen over an H_2-antagonist has been subject to debate. One study suggested it might reduce the risk of late-onset pneumonia compared with ranitidine.[1] Another study[2] found ranitidine to be more effective than sucralfate in reducing the risk of gastrointestinal bleeding; while there was a trend towards a lower rate of pneumonia among patients receiving sucralfate, the difference was not significant. However, meta-analyses[3] found an increased risk of pneumonia with ranitidine compared with sucralfate, but no difference in the rate of pneumonia with sucralfate and placebo; insufficient data were available to conduct a meta-analysis of sucralfate's efficacy in terms of rates of bleeding, and a re-assessment of recommendations for the prophylaxis of stress ulcers was called for. Later guidelines[4] concluded that the use of sucralfate did not influence the incidence of ventilator-associated pneumonia compared with placebo. For further discussion of stress ulceration and bleeding, including the use of sucralfate, see under Peptic Ulcer Disease, p.1702. There is also some evidence from a study[5] that sucralfate reduces gastrointestinal bleeding associated with NSAID use, although it does not prevent drug-induced gastric erosion.

In a study to assess whether oral prophylactic sucralfate could ameliorate the symptoms of acute radiation proctitis, sucralfate was found to increase the incidence of rectal bleeding compared with placebo; the cause of this increased bleeding was unclear.[6]

1. Prod'hom G, *et al.* Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Ann Intern Med* 1994; **120:** 653–62.
2. Cook D, *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; **338:** 791–7.
3. Messori A, *et al.* Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; **321:** 1103–6.
4. Dodek P, *et al.* Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; **141:** 305–13.
5. Hudson N, *et al.* Effect of sucralfate on aspirin induced mucosal injury and impaired haemostasis in humans. *Gut* 1997; **41:** 19–23.
6. Kneebone A, *et al.* The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial. *Int J Radiat Oncol Biol Phys* 2001; **51:** 628–35.

Gastro-oesophageal reflux disease. Although sucralfate has been tried for gastro-oesophageal reflux disease (p.1696) the results of studies have been inconsistent.[1-3] However, if lifestyle or dietary measures prove insufficient for the management of heartburn in pregnancy, sucralfate may be considered for first-line therapy.

1. Orlando RC. Sucralfate therapy and reflux esophagitis: an overview. *Am J Med* 1991; **91** (suppl 2A); 123S–124S.
2. Klinkenberg-Knol EC, *et al.* Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995; **49:** 695–710.
3. Simon B, *et al.* Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996; **10:** 441–6.

Mouth ulceration. Sucralfate has been investigated as a mouth rinse in the treatment and prophylaxis of stomatitis induced by cancer chemotherapy[1-3] although evidence of benefit for any drug is ambiguous (see Mucositis, p.640). One study[2] in 40 patients found a significant reduction in symptoms among 23 evaluable patients given sucralfate prophylactically. Seven patients withdrew due to aggravation of chemotherapy-induced nausea. It was suggested that to overcome this problem, the suspension should have a neutral taste, should not be swallowed after rinsing, and that rinsing should not be started until nausea had stopped. However, another study[4] involving 80 patients treated with fluorouracil for colorectal cancer found no significant difference in self-reported mucositis symptoms between patients given sucralfate suspension and those given placebo.

Sucralfate has also been reported to be of benefit in patients with recurrent aphthous stomatitis (mouth ulceration—p.1700). A study involving 21 such patients over 2 years found that topical application of sucralfate suspension 4 times daily was superior to treatment with an antacid (aluminium hydroxide with magnesium hydroxide) or placebo.[5]

In patients with Behçet's syndrome (p.1499), topical sucralfate suspension significantly decreased the frequency, healing time, and pain of oral ulceration, as well as the healing time and pain of genital ulceration,[6] when compared with placebo.

1. Pfeiffer P, *et al.* A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity. *Acta Oncol* 1990; **29:** 471–3.
2. Pfeiffer P, *et al.* Effect of prophylactic sucralfate suspension on stomatitis induced by cancer chemotherapy: a randomized, double-blind cross-over study. *Acta Oncol* 1990; **29:** 171–3.
3. Allison RR, *et al.* Symptomatic acute mucositis can be minimized or prophylaxed [sic] by the combination of sucralfate and fluconazole. *Cancer Invest* 1995; **13:** 16–22.
4. Nottage M, *et al.* Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer* 2003; **11:** 41–7.
5. Rattan J, *et al.* Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med* 1994; **236:** 341–3.
6. Alpsoy E, *et al.* The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999; **135:** 529–32.

Skin ulceration. Sucralfate has reportedly been applied topically with some success to treat bleeding skin ulcers (p.1585) associated with malignancy,[1] and to promote the healing of venous stasis ulcers.[2] It has been suggested that sucralfate promotes angiogenesis by binding to, and preventing degradation of, basic fibroblast growth factor (bFGF).[2] Topical sucralfate 7% cream was also reported to decrease pain and speed healing of the wound after open surgical removal of haemorrhoids.[3]

1. Regnard CFB. Control of bleeding in advanced cancer. *Lancet* 1991; **337:** 974.
2. Tsakayannis D, *et al.* Sucralfate and chronic venous stasis ulcers. *Lancet* 1994; **343:** 424–5.
3. Gupta PJ, *et al.* Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: a randomized, blinded, controlled study. *Dis Colon Rectum* 2008; **51:** 231–4.

Preparations

USP 31: Sucralfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antepsin; Netunal; Sucralmax; ***Austral.:*** Carafate; Ulcyte; ***Austria:*** Citogel; Sucralan; Sucralbene; Sucralstad†; Sucramed; Ulceral; Ulcogant; ***Belg.:*** Ulcogant; ***Braz.:*** Sucrafilm; ***Canad.:*** Novo-Sucralate; Sulcrate; ***Chile:*** Gastrocol†; Mulcatel; Sulcran; ***Cz.:*** Sucralan; Ulcogant; Venter; ***Denm.:*** Antepsin; Hexagastron; ***Fin.:*** Alsucral; Antepsin; ***Fr.:*** Keal; Ulcar; ***Ger.:*** Sucrabest; Sucraphil†; Ulcogant; ***Gr.:*** Peptonorm; Sucrate†; ***Hong Kong:*** Sucari; Ulsanic; ***Hung.:*** Alusulin; Ulcogant; Venter; ***India:*** Alfate; Sucrase; Ulcekon†; ***Indon.:*** Inpepsa; Musin; Neciblok; Ulcumaag; Ulsafate; Ulsicral; Ulsidex; ***Irl.:*** Antepsin; ***Israel:*** Ulsanic; ***Ital.:*** Antepsin; Citogel; Crafilm; Escudo; Gastrogel; Ipagastril†; Sucrager†; Sucral†; Sucralfin; Sucramal; Sucrate; Sucroril; Sugar; Sugast; Suril; Ulcrast; Zenodian†; ***Jpn:*** Ulcerlmin; ***Malaysia:*** Alsucral; Ulcertec; ***Mex.:*** Apo-Lato; Unival; ***Neth.:*** Ulcogant; ***Norw.:*** Antepsin; ***NZ:*** Carafate; ***Philipp.:*** Iselpin; ***Pol.:*** Ulgastran; Venter; ***Port.:*** Calfate; Cinebil; Sucralum†; Ulcermate; Ulcermin; Ulcimer; ***Rus.:*** Venter (Вентер); ***S.Afr.:*** Ulcetab; Ulsanic; ***Singapore:*** Alsucral; Ulcertec; ***Spain:*** Gastral; Urbal; ***Swed.:*** Andapsin; ***Switz.:*** Ulcogant; ***Thai.:*** Sucrafen†; Sucral; Sucrate†; Ulcefate; Ulcrafate; Ulsanic; ***Turk.:*** Antepsin; ***UAE:*** Sucralose; ***UK:*** Antepsin; ***USA:*** Carafate; ***Venez.:*** Dip; Exinol; Ulciram; Ulcon.

Multi-ingredient: ***Chile:*** Cicalfate; ***Fr.:*** Cicalfate; ***Gr.:*** Profenil†.

Used as an adjunct in: ***Ital.:*** Ketodol.

Sulfasalazine *(BAN, USAN, rINN)*

Salatsosulfapyridiini; Salazosulfapyridin; Salazosulfapyridine; Salazosulfapyridinum; Salicylazosulfapyridine; SI-88; Sulfasalatsiini; Sülfasalazin; Sulfasalazin; Sulfasalazina; Sulfasalazinas; Sulfasalazinum; Sulfasalazyna; Sulphasalazine; Szulfaszalazin. 4-Hydroxy-4′-(2-pyridylsulphamoyl)azobenzene-3-carboxylic acid.

Сульфасалазин

$C_{18}H_{14}N_4O_5S$ = 398.4.

CAS — 599-79-1.

ATC — A07EC01.

ATC Vet — QA07EC01.

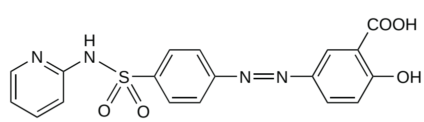

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Sulfasalazine). A bright yellow or brownish-yellow, fine powder. Practically insoluble in water and in dichloromethane; very slightly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Sulfasalazine). A fine odourless bright yellow or brownish-yellow powder. Practically insoluble in water, in chloroform, in ether, and in benzene; soluble 1 in 2900 of alcohol, and 1 in 1500 of methyl alcohol; soluble in aqueous solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Since sulfasalazine is metabolised to sulfapyridine and 5-aminosalicylic acid (mesalazine), its adverse effects and precautions are similar to those of sulfonamides (see Sulfamethoxazole, p.340) and of mesalazine (p.1745). Many adverse effects have been attributed to the sulfapyridine moiety and appear to be more common if serum-sulfapyridine concentrations are greater than 50 micrograms/mL, if the daily dose of sulfasalazine is 4 g or more, or in slow acetylators of sulfapyridine.

The most commonly reported adverse effects include nausea and vomiting, abdominal discomfort, headache, fever, and skin rash.

Adverse effects can be broadly divided into 2 groups:

- dose-related effects are dependent on acetylator phenotype, and largely predictable; this group includes nausea and vomiting, headache, haemolytic anaemia, and methaemoglobinaemia
- hypersensitivity reactions are essentially unpredictable and usually occur at the start of treatment; this group includes skin rash, aplastic anaemia, hepatic and pulmonary dysfunction, and auto-immune haemolysis

Oligospermia, reversible on withdrawal of sulfasalazine, has also been reported. Sulfasalazine treatment may result in yellow-orange discoloration of skin, urine, and other body fluids. Some soft contact lenses may be stained.

Sulfasalazine should not be given to patients with a history of sensitivity to sulfonamides or salicylates. Use in children under 2 years of age is contra-indicated because of the risk of kernicterus.

Blood counts should be performed at the start of therapy and at least once a month for a minimum of the first 3 months of treatment. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding develop. Care is advisable in patients with G6PD deficiency because of the risk of haemolytic anaemia.

Sulfasalazine should be used with caution in hepatic or renal impairment. Liver function tests should be carried out at monthly intervals for the first 3 months of treatment. Periodic monitoring of kidney function has also been recommended.

◊ The adverse effects associated with the use of sulfasalazine in patients with inflammatory bowel disease[1] or rheumatoid arthritis have been reviewed.[2,3] The type and incidence of adverse effects appear to be similar in both groups of patients.[2] Although most reactions are minor and patients may continue therapy at the same or reduced dosage, some patients stop treatment because of adverse effects and in these cases a hyposensitisation regimen may be considered.[1,4,5] **Hyposensitisation** should not be attempted in patients with a history of a serious adverse effect such as agranulocytosis, toxic epidermal necrolysis, erythema multiforme, frank haemolysis, or a severe hypersensitivity reaction.[1,4,5] An alternative to hyposensitisation in patients with inflammatory bowel disease who cannot tolerate sulfasalazine is to try a drug that supplies the active 5-aminosalicylic acid component without sulfapyridine, as the latter is thought to be responsible for many of the adverse effects. Examples include balsalazide, mesalazine, and olsalazine; however, some patients still experience hypersensitivity, see under Mesalazine, p.1745.

1. Taffet SL, Das KM. Sulfasalazine: adverse effects and desensitization. *Dig Dis Sci* 1983; **28:** 833–42.
2. Amos RS, *et al.* Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. *BMJ* 1986; **293:** 420–3.
3. Farr M, *et al.* Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. *Drugs* 1986; **32** (suppl 1): 49–53.
4. Purdy BH, *et al.* Desensitization for sulfasalazine skin rash. *Ann Intern Med* 1984; **100:** 512–14.
5. Bax DE, Amos RS. Sulphasalazine in rheumatoid arthritis: desensitising the patient with a skin rash. *Ann Rheum Dis* 1986; **45:** 139–40.

Breast feeding. Small amounts of sulfasalazine and its sulfapyridine metabolites are excreted in breast milk; the concentrations of sulfasalazine and total sulfapyridine may be up to 30% and 50% of maternal serum concentrations respectively.[1] Bloody diarrhoea in a breast-fed infant whose mother was taking sulfasalazine 3 g daily has been reported.[2] The mother was a slow acetylator with a relatively high blood concentration of sulfapyridine, which contributed to the appearance of the drug in the infant's blood. Based on this report, the American Academy of Pediatrics[3] considers that sulfasalazine should be given with caution to breast-feeding mothers. However, others consider that continued treatment with sulfasalazine can generally be recommended to breast-feeding mothers of healthy infants.[4] A small study initially involving 17 mother-child pairs concluded sulfasalazine treatment could continue throughout pregnancy and lactation. The study found negligible amounts of sulfasalazine, and its main metabolite sulfapyridine, were transferred to the child via breast feeding. The authors did however warn that this conclusion could not be applied to a prematurely born child or a child with haemolytic disease.[5]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Branski D, *et al.* Bloody diarrhea—a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* 1986; **5:** 316–17.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/02/06)
4. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
5. Esbjörner E, *et al.* Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatr Scand* 1987; **76:** 137–42.

Effects on the blood. Blood disorders constitute 19% of all reactions reported with sulfasalazine.[1] As of June 1993 the UK CSM was aware of 191 reports of neutropenia, leucopenia, or agranulocytosis (22 fatal), 44 reports of bone marrow depression or aplastic anaemia (13 fatal) and 30 reports of thrombocytopenia (1 fatal).[1]

Although blood dyscrasias were initially thought to be caused by the sulfapyridine moiety, subsequent experience has shown that the aminosalicylates can also cause haematological reactions (see Mesalazine, p.1745). The risk of blood dyscrasias with sulfasalazine has been estimated at 0.6 per 1000 in those given the drug for inflammatory bowel disease, but about 10 times greater in patients receiving sulfasalazine for rheumatoid arthritis.[2]

Sulfasalazine inhibits folic acid absorption, interferes with its metabolism, and can increase folic acid requirements through haemolysis of red blood cells.[3,4] These effects are not usually significant in patients with inflammatory bowel disease unless there are additional factors causing folate deficiency, such as intercurrent illness or an exacerbation of bowel disease.[3,4] However, clinical folate deficiency with macrocytosis, megaloblastic anaemia, or pancytopenia has been reported rarely.[3,4] Macrocytic anaemia associated with sulfasalazine may occur more commonly in patients with rheumatoid arthritis; it was found in 7 of 50 patients within 3 to 4 months of starting treatment with sulfasalazine.[5] The effects of sulfasalazine on folic acid metabolism appear to be dose-related and respond to withdrawal or dosage reduction, and folic acid supplements;[3-5] intravenous folinic acid may sometimes be needed.[4] Although the effects may be potentially serious, they are not a contra-indication to continuing sulfasalazine treatment.[4,5]

Patients with a history of leucopenia associated with gold therapy for rheumatoid arthritis should not be given sulfasalazine since a similar reaction may occur.[6]

1. Committee on Safety of Medicines/Medicines Control Agency. Sulphasalazine and fatal blood dyscrasias. *Current Problems* 1993; **19:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
3. Swinson CM, *et al.* Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut* 1981; **22:** 456–61.
4. Logan ECM, *et al.* Sulphasalazine associated pancytopenia may be caused by acute folate deficiency. *Gut* 1986; **27:** 868–72.
5. Prouse PJ, *et al.* Macrocytic anaemia in patients treated with sulphasalazine for rheumatoid arthritis. *BMJ* 1986; **293:** 1407.
6. Bliddal H, *et al.* Gold-induced leucopenia may predict a similar adverse reaction to sulphasalazine. *Lancet* 1987; **i:** 390.

Effects on the cardiovascular system. Reports include Raynaud's syndrome with sulfasalazine[1] and myocarditis with sulfasalazine and with mesalazine.[2] Myocarditis leading to fatal cardiogenic shock has been reported in a patient receiving mesalazine and it has been recommended that sulfasalazine or mesalazine should be replaced by glucocorticoids if cardiac symptoms arise.[3]

1. Reid J, *et al.* Raynaud's phenomenon induced by sulphasalazine. *Postgrad Med J* 1980; **56:** 106–7.
2. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
3. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.

Effects on fertility. Although successful pregnancies have been reported in the partners of men taking sulfasalazine,[1,2] male infertility is a well recognised complication of sulfasalazine treatment. Untreated inflammatory bowel disease is not associated with abnormal seminal quality or infertility, but oligospermia, reduced sperm motility, and an increase in morphological abnormalities are seen after treatment with sulfasalazine which may lead to infertility.[1-4] Oligospermia has been reported in 86% of men with inflammatory bowel disease treated with sulfasalazine.[1] Seminal characteristics and fertility return to normal within 2 to 3 months of withdrawing sulfasalazine and successful pregnancies have been reported after withdrawal.[1-3] The mechanism involved is thought to be a direct toxic effect on immature and developing spermatozoa, possibly due to the sulfapyridine moiety.[2-4] Improvement in seminal characteristics and successful pregnancies have been reported following substitution of mesalazine[4,5] or balsalazide[6] for sulfasalazine in patients with ulcerative colitis. However, reversible infertility, similar to that caused by sulfasalazine, has also been reported with mesalazine.[7]

1. Birnie GG, *et al.* Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22:** 452–5.
2. Riley SA, *et al.* Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28:** 1008–12.
3. Toovey S, *et al.* Sulphasalazine and male infertility: reversibility and possible mechanism. *Gut* 1981; **22:** 445–51.
4. Ó'Moráin C, *et al.* Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984; **25:** 1078–84.
5. Cann PA, Holdsworth CD. Reversal of male infertility on changing treatment from sulphasalazine to 5-aminosalicylic acid. *Lancet* 1984; **i:** 1119.
6. McIntyre PB, Lennard-Jones JE. Reversal with balsalazide of infertility caused by sulphasalazine. *BMJ* 1984; **288:** 1652–3.
7. Chermesh I, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36:** 551–2.

Effects on the gastrointestinal tract. Sulfasalazine-induced exacerbations of ulcerative colitis have been reported[1,2] and are probably caused by the salicylate moiety rather than sulfapyridine.[3] Other reported effects include intestinal villous atrophy.[4]

1. Schwartz AG, *et al.* Sulfasalazine-induced exacerbation of ulcerative colitis. *N Engl J Med* 1982; **306:** 409–12.
2. Ring FA, *et al.* Sulfasalazine-induced colitis complicating idiopathic ulcerative colitis. *Can Med Assoc J* 1984; **131:** 43–5.
3. Shanahan F, Targan S. Sulfasalazine and salicylate-induced exacerbation of ulcerative colitis. *N Engl J Med* 1987; **317:** 455.
4. Smith MA, *et al.* Angioimmunoblastic lymphadenopathy, sulphasalazine exposure and villous atrophy. *Postgrad Med J* 1985; **61:** 337–8.

Effects on the hair. Alopecia occurred on 2 occasions[1] after starting sulfasalazine 2 or 3 g daily in a patient with ulcerative colitis. On both occasions normal hair growth returned after treatment was stopped, and the patient was later successfully desensitised. However, alopecia that developed in another patient during sulfasalazine treatment did not recur on rechallenge.[2] In this case postpartum alopecia was considered to be the cause and these authors doubted whether sulfasalazine causes alopecia at all. Hair loss has been reported in 2 patients receiving mesalazine enemas.[3] However, remission of alopecia universalis has been reported during sulfasalazine treatment of rheumatoid arthritis.[4]

1. Breen EG, Donnelly S. Alopecia associated with sulphasalazine (Salazopyrin). *BMJ* 1986; **292:** 802.
2. Fich A, Eliakim R. Does sulfasalazine induce alopecia? *J Clin Gastroenterol* 1988; **10:** 466.
3. Kutty PK, *et al.* Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97:** 785–6.
4. Jawad ASM, Scott DGI. Remission of alopecia universalis during sulphasalazine treatment for rheumatoid arthritis. *BMJ* 1989; **298:** 675.

Effects on the kidneys. UK licensed product information advises that adequate fluid intake and avoidance of urinary acidifiers may reduce the incidence of crystalluria and stone formation. For reports of nephrotic syndrome and of interstitial nephritis associated with sulfasalazine treatment, see under Mesalazine, p.1745.

Effects on the pancreas. The UK CSM had received 6 reports of pancreatitis associated with sulfasalazine as of February 1994.[1] There had been further reports associated with mesalazine (see p.1746). However, a large Danish population-based case-control study concluded neither sulfasalazine nor mesalazine was associated with an increased risk of pancreatitis, and that any increased risk might be associated with inflammatory bowel disease itself.[2]

1. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Munk EM, *et al.* Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. *Am J Gastroenterol* 2004; **99:** 884–8.

Effects on the respiratory system. Although one study reviewed 50 cases of sulfasalazine-induced pulmonary complications, pulmonary toxicity remains a rare adverse effect.[1] Most reports include dyspnoea, cough, pulmonary infiltrates, fever, and eosinophilia, usually developing in the first few months of treatment although they may occur after several years.[1-3] Symptoms are generally readily reversible on withdrawal of sulfasalazine, although death due to fibrosing alveolitis has been reported,[2] and the need for corticosteroid therapy remains debatable.[1] These effects have also occurred with mesalazine, p.1746; they have been reported in patients with a history of sensitivity to salicylates, sulfonamides, or with no known sensitivity to these drugs.[2,3] Bronchiolitis obliterans organising pneumonia has been reported in a patient with rheumatoid arthritis receiving sulfasalazine;[4] clinical improvement occurred after sulfasalazine was stopped and corticosteroid therapy started.

1. Parry SD, *et al.* Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19:** 756–64.
2. Wang KK, *et al.* Pulmonary infiltrates and eosinophilia associated with sulfasalazine. *Mayo Clin Proc* 1984; **59:** 343–6.
3. Jordan A, Cowan RE. Reversible pulmonary disease and eosinophilia associated with sulphasalazine. *J R Soc Med* 1988; **81:** 233–5.
4. Ulubaş B, *et al.* Bronchiolitis obliterans organizing pneumonia associated with sulfasalazine in a patient with rheumatoid arthritis. *Clin Rheumatol* 2004; **23:** 249–51.

Effects on taste. Metallic taste has occurred in patients taking sulfasalazine for ulcerative colitis,[1] although diseases causing changes in gastrointestinal absorption may lead to zinc deficiency, which has itself been associated with a metallic taste. There has also been a report of two patients developing a reversible taste dysfunction, while taking sulfasalazine for rheumatoid arthritis.[2]

1. Ogburn RM. Sulfamethazine-related dysgeusia. *JAMA* 1979; **241:** 837.
2. Marcus RW. Sulfasalazine induced taste disturbances. *J Rheumatol* 1991; **18:** 634–5.

Lupus. A study in 11 patients with sulfasalazine-induced lupus found that induction of disease was more likely in patients who were slow acetylators of sulfapyridine, and who had HLA haplotypes associated with idiopathic SLE.[1] Furthermore, the risk of developing persistent SLE and lupus nephritis increased with duration of treatment and cumulative dose of sulfasalazine. Lupus-like syndrome has also occurred with mesalazine, see Lupus, p.1746.

1. Gunnarsson I, *et al.* Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1997; **36:** 1089–94.

Porphyria. Sulfasalazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Sulfasalazine and its sulfapyridine metabolites readily cross the placenta resulting in similar concentrations in the cord serum and maternal serum at delivery.[1,2] The concentration of the 5-aminosalicylic acid component of sulfasalazine in both cord serum and maternal serum is negligible.[1] There have been isolated reports of congenital abnormalities associated with use of sulfasalazine during pregnancy including coarctation of the aorta with a ventricular septal defect,[3,4] and genito-urinary disorders.[4] There is also a theoretical risk of kernicterus in the neonate if sulfasalazine is given close to delivery (see p.341). However, given the concentrations of sulfasalazine and its metabolites found in cord blood, the risk of kernicterus from maternal use is considered minimal.[2] There have been many successful and uncomplicated pregnancies during sulfasalazine therapy and the general consensus favours continuing sulfasalazine throughout pregnancy when indicated.[1,3-6] (See also Mesalazine, p.1746.) The minimum effective dose should be used and since sulfasalazine may precipitate folate deficiency (see Effects on the Blood, above), folic acid supplements are recommended.[7]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Järnerot G, *et al.* Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; **16:** 693–7.
3. Hoo JJ, *et al.* Possible teratogenicity of sulfasalazine. *N Engl J Med* 1988; **318:** 1128.
4. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. *Med J Aust* 1983; **1:** 528–9.
5. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
6. Korelitz BI. Commentary: observations on sulfasalazine in Crohn's disease and ulcerative colitis. *J Clin Pharmacol* 1987; **27:** 265–6.
7. Byron MA. Treatment of rheumatic diseases. *BMJ* 1987; **294:** 236–8.

Interactions

Giving sulfasalazine with antibacterial therapy may reduce conversion of sulfasalazine to its active metabolite (see below).

Sulfasalazine has been reported to interfere with the absorption of digoxin (p.1262) or folic acid (see Effects on the Blood, above) from the gastrointestinal tract.

Antibacterials. Since the effects of sulfasalazine depend on release of 5-aminosalicylic acid by bacterial metabolism in the gut, any drug that reduces the intestinal microflora may reduce the production of active metabolite. Evidence for this has been seen in patients also given *rifampicin* and *ethambutol*,[1] or in subjects also given *ampicillin*.[2] However, a decrease in clinical effect does not seem to have been seen.

1. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol* 1985; **19:** 526–8.
2. Houston JB, *et al.* Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* 1982; **14:** 395–8.

Antineoplastics. For mention of 5-aminosalicylates such as sulfasalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Mercaptopurine, p.744.

Pharmacokinetics

About 15% of an oral dose of sulfasalazine is absorbed from the small intestine, although some of this is subsequently returned to the intestine in bile via enterohepatic circulation. The great majority of the dose reaches the colon where the azo bond is cleaved by the action of the intestinal flora, producing sulfapyridine and 5-aminosalicylic acid (mesalazine). Results in patients who have undergone colectomy suggest that between 60 and 90% of the total dose is metabolised in this way, but the degree of metabolism depends both on the activity of the intestinal flora and the speed of intestinal transit; colonic metabolism is reduced in patients with diarrhoea (for example, in active inflammatory bowel disease).

The small amount of intact sulfasalazine that is absorbed is extensively protein bound and subsequently excreted unchanged in urine. It crosses the placenta and is found in breast milk.

After cleavage of the sulfasalazine molecule about 60 to 80% of available sulfapyridine is absorbed, and undergoes extensive metabolism by acetylation, hydroxylation, and glucuronidation. Peak steady-state concentrations of sulfapyridine are higher in slow acetylators than fast acetylators after similar doses and the former are 2 to 3 times more likely to have adverse effects. Some 60% of the original dose of sulfasalazine is excreted in urine as sulfapyridine and its metabolites. As with sulfasalazine, absorbed sulfapyridine crosses the placenta and is found in breast milk.

The 5-aminosalicylic acid (5-ASA) moiety is much less well absorbed. About one-third of liberated 5-ASA is absorbed and almost all of this is acetylated and excreted in urine. For further details of the pharmacokinetics of 5-aminosalicylic acid see under Mesalazine, p.1746.

◊ Reviews.

1. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clin Pharmacokinet* 1985; **10:** 285–302.

Uses and Administration

Sulfasalazine is a compound of a sulfonamide, sulfapyridine, with 5-aminosalicylic acid (mesalazine). Its activity is generally considered to lie in the 5-aminosalicylic acid moiety, which is released in the colon by bacterial metabolism, although intact sulfasalazine has some anti-inflammatory properties in its own right.

In inflammatory bowel disease (p.1697) it is used alone or as an adjunct to corticosteroids in the treatment of active ulcerative colitis and is effective in maintaining remission. Sulfasalazine may also be effective in the treatment of active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of severe or progressive rheumatoid arthritis (below).

In **inflammatory bowel disease** the usual initial adult dose of sulfasalazine is 1 to 2 g orally 4 times daily in the UK. However, doses over 4 g daily are associated with an increased risk of toxicity, and in the USA, therefore, the usual dose is 1 g given 3 or 4 times daily, and an initial dose of 500 mg every 6 to 12 hours may be recommended to lessen gastrointestinal adverse effects. Enteric-coated tablets are also claimed to reduce the incidence of adverse gastrointestinal effects. The overnight interval between doses should not exceed 8 hours. On remission the dose in patients with ulcerative colitis is gradually reduced to 2 g daily and then generally continued indefinitely. For children 2 years of age or older doses should be proportional to body-weight; initially 40 to 60 mg/kg may be given daily in divided doses reduced to 20 to 30 mg/kg daily for the maintenance of remission.

Sulfasalazine is also given rectally, as suppositories, initially at a dose of 1 g at night and in the morning. After three weeks the dosage is gradually reduced according to response. Rectal sulfasalazine can be given as 0.5 to 1 g night and morning as an adjunct to treatment by mouth. Sulfasalazine may also be given by enema in a dose of 3 g at bedtime. The *BNFC* suggests the following daily dosage may be given in divided doses to children as suppositories according to age: 5 to 8 years old: 1 g; 8 to 12 years old: 1.5 g; 12 to 18 years old: 2 g. Enemas, to be retained for at least 1 hour, may be given at night in doses of 1 to 1.5 g for children aged 2 to 7 years, 1.5 to 2.25 g for children aged 7 to 12 years, and 3 g for children 12 to 18 years.

In adult **rheumatoid arthritis** treatment is usually started with an oral dose of 500 mg daily, as enteric-coated tablets, for the first week; dosage is then increased by 500 mg daily each week to a maximum of 3 g daily given in 2 to 4 divided doses according to tolerance and response. In the USA, sulfasalazine can also be used for polyarticular juvenile rheumatoid arthritis in children aged 6 years and older who have not responded adequately to salicylates or other NSAIDs. A dose of 30 to 50 mg/kg daily is given in two divided doses, to a maximum dose of 2 g daily. To reduce adverse gastrointestinal effects, an enteric-coated tablet is used and the initial dose should be a quarter to a third of the planned maintenance; it is then increased weekly to reach the maintenance dose after one month.

Although sulfasalazine is not licensed for juvenile rheumatoid arthritis in the UK, the *BNFC* suggests that children aged 2 to 18 years are given an initial oral dose of 5 mg/kg twice daily for 1 week. The dose is then increased to 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, and maintained on a dose of 20 to 25 mg/kg twice daily. For children aged 2 to 12 years the maximum dose suggested is 2 g daily, and for children aged 12 to 18 years 3 g daily.

Psoriasis. In a double-blind placebo-controlled study involving 50 patients with moderate to severe plaque-type psoriasis (p.1583), sulfasalazine 3 to 4 g daily produced a significantly greater clinical improvement than placebo after 4 weeks of treatment with a further improvement at 8 weeks.[1]

See also Psoriatic Arthritis, below.

1. Gupta AK, *et al.* Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol* 1990; **126:** 487–93.

Pyoderma gangrenosum. Sulfasalazine is licensed in some countries for the treatment of pyoderma gangrenosum (p.1583), a condition that may be associated with inflammatory bowel disease, although published evidence of benefit is scanty.

References.

1. Shenefelt PD. Pyoderma gangrenosum associated with cystic acne and hidradenitis suppurativa controlled by adding minocycline and sulfasalazine to the treatment regimen. *Cutis* 1996; **57:** 315–9.

Rheumatoid arthritis. Sulfasalazine is considered to be a useful disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (p.11). Studies have found a beneficial clinical effect of sulfasalazine, compared with placebo, on tender and swollen joints, pain, and erythrocyte sedimentation rate.[1,2] Meta-analyses[3,4] of generally short-term comparative studies suggest that sulfasalazine is roughly comparable in efficacy to methotrexate, intramuscular gold (sodium aurothiomalate), and penicillamine. Other reviews[2,5] have also suggested that it may have similar efficacy to hydroxychloroquine and leflunomide. Although there are regional differences in the prescription of DMARDs, sulfasalazine has been widely used for initial therapy, especially of less severe disease.[5] In an open study[6] of 200 patients with rheumatoid arthritis who were randomly allocated to treatment with sulfasalazine or auranofin, 31% of the sulfasalazine recipients were still taking the drug after 5 years compared with 15% of auranofin recipients. Improvement over baseline was still significant at 5 years for those patients receiving sulfasalazine but not in those treated with auranofin. Although one study[7] failed to find convincing evidence that using sulfasalazine with methotrexate was more effective than either drug alone, other studies have shown that combination treatment with sulfasalazine plus methotrexate and hydroxychloroquine was more effective than methotrexate alone or with sulfasalazine or hydroxychloroquine or the combination of sulfasalazine with hydroxychloroquine.[8,9] A review of sulfasalazine use in the management of rheumatoid arthritis concluded that combination therapy may be of benefit in patients with early or advanced rheumatoid arthritis but that there is still a need for studies to determine the efficacy and tolerability of various combinations.[5]

1. Suarez-Almazor ME, *et al.* Sulfasalazine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 28/02/06).
2. Weinblatt ME, *et al.* Sulfasalazine treatment for rheumatoid arthritis: a metaanalysis of 15 randomized trials. *J Rheumatol* 1999; **26:** 2123–30.
3. Felson DT, *et al.* The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** 1449–61.
4. Capell HA, *et al.* Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient? *Ann Rheum Dis* 1993; **52:** 423–8.
5. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. *Drugs* 2005; **65:** 1825–49.
6. McEntegart A, *et al.* Sulfasalazine has a better efficacy/toxicity profile than auranofin—evidence from a 5 year prospective, randomized trial. *J Rheumatol* 1996; **23:** 1887–90.
7. Dougados M, *et al.* Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; **58:** 220–5.
8. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334:** 1287–91.
9. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.

JUVENILE IDIOPATHIC ARTHRITIS. Juvenile idiopathic arthritis (p.10) is generally managed similarly to rheumatoid arthritis, but there is limited experience with the use of some antirheumatic drugs in children. Sulfasalazine has produced significant improvement in studies of patients with juvenile chronic arthritis; a literature review found that it was consistently reported to be of benefit.[1] Adverse effects were reported to be similar to those in adults, with the exception of a serum-sickness-like reaction which was mostly seen in systemic onset patients and may be unique to juvenile rheumatoid arthritis.[1]

1. Brooks CD. Sulfasalazine for the management of juvenile rheumatoid arthritis. *J Rheumatol* 2001; **28:** 845–53.

Spondyloarthropathies. ***ANKYLOSING SPONDYLITIS.*** Sulfasalazine has been found to be effective[1] in the treatment of active ankylosing spondylitis (p.13), but there is evidence that it is more useful in the treatment of active disease and peripheral articular manifestations than in the management of chronic long-standing disease.[2-4] The active moiety appears to be sulfapyridine rather than mesalazine.[5] Sulfasalazine was no better than placebo for the treatment of inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis, but it was more effective than placebo in a subgroup of patients with no peripheral arthritis.[6]

1. Ferraz MB, *et al.* Meta-analysis of sulfasalazine in ankylosing spondylitis. *J Rheumatol* 1990; **17:** 1482–6.
2. Clegg DO, *et al.* Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis: a Department of Veterans Affairs Cooperative study. *Arthritis Rheum* 1996; **39:** 2004–12.
3. Clegg DO, *et al.* Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; **42:** 2325–9.
4. Chen J, Liu C. Sulfasalazine for ankylosing spondylitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 28/02/06).
5. Taggart A, *et al.* Which is the active moiety of sulfasalazine in ankylosing spondylitis? A randomized, controlled study. *Arthritis Rheum* 1996; **39:** 1400–5.
6. Braun J, *et al.* Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006; **65:** 1147–53.

PSORIATIC ARTHRITIS. A systematic review[1] of interventions for psoriatic arthritis (see p.13) concluded that sulfasalazine was one of only two drugs with published evidence of well proven efficacy in psoriatic arthritis (the other being high-dose parenteral methotrexate).

See also under Psoriasis, above.

1. Jones G, *et al.* Interventions for treating psoriatic arthritis. Available in The Cochrane Database of Systematic Reviews, Issue 3. Chichester: John Wiley; 2000 (accessed 29/04/05).

Preparations

BP 2008: Sulfasalazine Tablets;
USP 31: Sulfasalazine Delayed-release Tablets; Sulfasalazine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Azulfidine; Flogostop; ***Austral.:*** Pyralin; Salazopyrin; ***Austria:*** Colo-Pleon; Salazopyrin; ***Belg.:*** Salazopyrine; ***Braz.:*** Azulfin; Salazoprin; ***Canad.:*** Salazopyrin; SAS†; ***Chile:*** Azulfidine; ***Cz.:*** Salazopyrin; ***Denm.:*** Salazopyrin; ***Fin.:*** Salazopyrin; ***Fr.:*** Salazopyrine; ***Ger.:*** Azulfidine; Colo-Pleon; Pleon RA; ***Gr.:*** Salopyrine; ***Hong Kong:*** Salazopyrin; ***Hung.:*** Salazopyrin; ***India:*** Saaz; Salazar; Sazo; ***Indon.:*** Lazafin; Sulcolon; ***Irl.:*** Salazopyrin; ***Israel:*** Salazopyrin; ***Ital.:*** Salazopyrin; ***Jpn:*** Azulfidine; ***Malaysia:*** Salazopyrin; ***Mex.:*** Azulfidina; ***Neth.:*** Salazopyrine; ***Norw.:*** Salazopyrin; ***NZ:*** Salazopyrin; ***Pol.:*** Salazopyrin; ***Port.:*** Salazopirina; ***S.Afr.:*** Salazopyrin; ***Singapore:*** Salazopyrin; ***Spain:*** Salazopyrina; ***Swed.:*** Salazopyrin; ***Switz.:*** Salazopyrin; ***Thai.:*** Salazopyrin; Saridine; ***Turk.:*** Salazopryn; ***UK:*** Salazopyrin; Sulazine; ***USA:*** Azulfidine; ***Venez.:*** Azulfidine.

Sulglicotide *(BAN, rINN)*

Sulglicotida; Sulglicotidum; Sulglycotide.

Сульгликотид

CAS — 54182-59-1.
ATC — A02BX08.
ATC Vet — QA02BX08.

Profile

Sulglicotide is a sulfated glycopeptide with cytoprotective properties extracted from pig duodenum. It is used in the treatment of peptic ulcer disease (p.1702) and other gastrointestinal disorders in a usual oral dose of 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Gliptide; ***Venez.:*** Demucine†.

Tamarind

Tamarindo; West Indian Tamarind.

Индийский Финик; Плоды Тамаринда; Тамаринд

Pharmacopoeias. In *Fr.*

Profile

Tamarind is the fruits of *Tamarindus indica* (Leguminosae) freed from the brittle outer part of the pericarp and preserved with sugar or syrup. It contains tartaric, citric, and malic acid and their salts. Tamarind is used as a laxative with senna.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Delabarre.

Multi-ingredient: ***Arg.:*** Tamarine†; ***Austria:*** Frugelletten; Neda Fruchtewurfel; ***Braz.:*** Fitolax; Florlax; Fontolax; Frutalax†; Laxarine†; Laxtam; Naturetti; Tamaril; Tamarine; Tamarix†; ***Chile:*** Tamarine; ***Fr.:*** Carres Parapsyllium; Laxarine; Tamarine; ***Ital.:*** Ortisan; Tamarine; ***Mex.:*** Naturetti†; ***Spain:*** Dentomicin; Pruina.

Tegaserod Maleate *(BANM, USAN, rINNM)*

HTF-919; Maleato de tegaserod; SDZ-HTF-919; Tégasérod, Maléate de; Tegaserodi Maleas. 1-{[(5-Methoxyindol-3-yl)methylene]amino}-3-pentylguanidine maleate.

Тегасерода Малеат

$C_{16}H_{23}N_5O,C_4H_4O_4$ = 417.5.

CAS — 145158-71-0 (tegaserod); 189188-57-6 (tegaserod maleate).

ATC — A03AE02.

ATC Vet — QA03AE02.

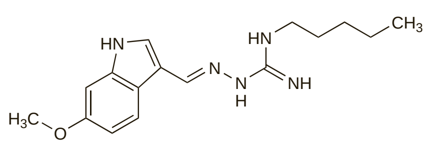

(tegaserod)

Stability and compatibility. Crushed tablets of tegaserod were found to be stable in water, and apple juice; the latter may mask the taste of the drug. Orange juice, milk, or yogurt were not recommended as vehicles because of incomplete dissolution or uncertainty about stability.[1]

1. Carrier M-N, *et al.* Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. *Am J Health-Syst Pharm* 2004; **61:** 1135–42.

Adverse Effects

The most common adverse effects of tegaserod are gastrointestinal disturbances including abdominal pain, diarrhoea, nausea, vomiting, and flatulence. Diarrhoea generally occurs within the first week of treatment and is usually transient but may be severe. Ischaemic colitis has been reported. Headache, dizziness, migraine, insomnia, fatigue, leg or back pain, and arthropathy have also been commonly reported. Cardiovascular adverse effects include hypotension and arrhythmias. Serious cardiovascular ischaemic events such as myocardial infarction, unstable angina pectoris, and stroke have occurred; fatalities have been reported. Other adverse effects include effects on the nervous system such as depression, and other gastrointestinal effects including cholelithiasis and dyspepsia.

◊ References.

1. Hasler WL, Schoenfeld P. Safety profile of tegaserod, a 5-HT receptor agonist, for the treatment of irritable bowel syndrome. *Drug Safety* 2004; **27:** 619–31.
2. Quigley EM, *et al.* Safety and tolerability of tegaserod in patients with chronic constipation: pooled data from two phase III studies. *Clin Gastroenterol Hepatol* 2006; **4:** 605–13.

Effects on the gastrointestinal tract. Severe diarrhoea, leading to hypovolaemia, hypotension, and syncope has been seen occasionally in patients receiving tegaserod. Some patients required hospitalisation for rehydration, and patients should be advised to stop taking the drug and seek medical attention if severe diarrhoea or associated dizziness or lightheadedness develop. In addition, ischaemic colitis has been reported rarely, and the drug should be stopped immediately in patients who develop symptoms such as rectal bleeding, bloody diarrhoea, or new and worsening abdominal pain.[1] The FDA noted that it had received 20 reports of ischaemic colitis in patients taking tegaserod between August 2002 and March 2004; in 3 cases, the effect only developed after several months (7 to 13) of therapy.[2] However, in reply the manufacturer (*Novartis*) suggested that there was no evidence from postmarketing surveillance to support an increased rate of ischaemic colitis over that normally seen in patients with irritable bowel syndrome, who are at increased risk of this diagnosis, nor any obvious pharmacological mechanism for such an adverse effect.[3]

1. Novartis, Canada. Important safety update: diarrhea and ischemic colitis in patients using Zelnorm (tegaserod hydrogen maleate) (issued 28/04/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_e.pdf (accessed 07/07/06)
2. Brinker AD, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1361–3.
3. Joelsson BE, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1363–4.

Effects on the heart. In an analysis of pooled data from 29 studies, 13 out of 11 614 patients taking tegaserod had serious cardiovascular ischaemic events, compared with 1 out of 7031 patients taking placebo. Events included unstable angina pectoris, stroke, and myocardial infarction, one of which was fatal.[1-3] Most of these patients had at least one cardiovascular risk factor, but for some, no cardiovascular disease or risk had been diagnosed at the onset of treatment with tegaserod.[2] Patients taking tegaserod should seek medical attention if they have severe chest pain, dyspnoea, dizziness, sudden onset of weakness, difficulty walking or talking, or any other symptoms suggestive of myocardial infarction or stroke.[1]

1. FDA Public Health Advisory. Tegaserod maleate (marketed as Zelnorm) (issued 30th March 2007). Available at: http://www.fda.gov/cder/drug/advisory/tegaserod.htm (accessed 31/05/07)
2. Novartis, Canada. Health Canada endorsed important safety information on Zelnorm (tegaserod hydrogen maleate) (issued 30th March 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_2_e.pdf (accessed 31/05/07)
3. Novartis, USA. Urgent: marketing and sales suspension notice for Zelnorm® tablets, 2-mg and 6-mg all lots within expiry (issued 30th March 2007). Available at: http://www.zelnorm.com/Dr_Doctor_Letter.pdf (accessed 31/05/07)

Precautions

Tegaserod is contra-indicated in patients with a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. Tegaserod should also not be given to patients who have diarrhoea or who frequently experience diarrhoea. It should be stopped in patients with new or sudden worsening of abdominal symptoms, hypotension, or syncope. Tegaserod should not be used in patients with severe renal impairment or moderate to severe hepatic impairment. For the possible cardiovascular risks of tegaserod therapy, see above; in the USA use is restricted, and it is contra-indicated in patients with a history of heart disease or symptoms suggestive of cardiac disorders.

Pharmacokinetics

Tegaserod is rapidly absorbed from the gastrointestinal tract with peak plasma levels occurring after about 1 hour. The absolute bioavailability of an oral dose is 10%; this is reduced by the presence of food. Tegaserod is widely distributed into the tissues and is about 98% bound to plasma proteins. Presystemic acid-catalysed hydrolysis in the stomach, and then oxidation and glucuronidation, produces the main metabolite, which is inactive; direct systemic glucuronidation also occurs. Two-thirds of an oral dose is excreted unchanged in the faeces and one-third excreted in the urine primarily as the main metabolite. The terminal half-life of tegaserod is about 11 hours.

◊ Reviews.

1. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT receptor partial agonist with promotile activity. *Clin Pharmacokinet* 2002; **41:** 1021–42.

Uses and Administration

Tegaserod is a partial agonist at $5\text{-}HT_4$ receptors and has prokinetic properties. It is used in women for the short-term treatment of irritable bowel syndrome (p.1699), particularly the constipation-predominant form. It has also been used for the treatment of chronic idiopathic constipation (p.1693) in men and women less than 65 years of age.

Tegaserod is given orally as the maleate but doses are expressed in terms of the base; 8.31 mg of tegaserod maleate is equivalent to about 6 mg of tegaserod. It is given in a dose of 6 mg twice daily before food. For irritable bowel syndrome, it is given for 4 to 6 weeks; a further 4 to 6 weeks of treatment may be given if a beneficial response is seen.

In March 2007, marketing of tegaserod was suspended in some countries because of a high incidence of cardiovascular ischaemic events (see Effects on the Heart, above). In the USA, the use of tegaserod was subsequently restricted to women younger than 55 years of age who have either constipation-predominant irritable bowel syndrome or chronic idiopathic constipation, and who meet specific guidelines; patients should have no known or pre-existing cardiac problems.

◊ References.

1. Wagstaff AJ, *et al.* Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. *Drugs* 2003; **63:** 1101–20.
2. Lea R, Whorwell PJ. Benefit-risk assessment of tegaserod in irritable bowel syndrome. *Drug Safety* 2004; **27:** 229–42.
3. Johanson JF, *et al.* Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. *Clin Gastroenterol Hepatol* 2004; **2:** 796–805.
4. Müller-Lissner S, *et al.* Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2005; **21:** 11–20.
5. Kamm MA, *et al.* Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol* 2005; **100:** 362–72.
6. Tack J, *et al.* A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* 2005; **54:** 1707–13.
7. Muller-Lissner S, *et al.* Safety, tolerability, and efficacy of tegaserod over 13 months in patients with chronic constipation. *Am J Gastroenterol* 2006; **101:** 2558–69.
8. Baun RF, Levy HB. Tegaserod for treating chronic constipation in elderly patients. *Ann Pharmacother* 2007; **41:** 309–13.
9. Evans BW, *et al.* Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 17/03/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Altezerod; Coloserod; Procinet; Tegarod; Zelmac; ***Austral.:*** Zelmac†; ***Braz.:*** Zelmac; ***Canad.:*** Zelnorm; ***Chile:*** Colonaid; Distimax; Tegasir; Ther; Zelmac; ***Cz.:*** Zelmac†; ***Hong Kong:*** Zelmac; ***India:*** Tegibs; Tegod; ***Indon.:*** Zelmac; ***Israel:*** Zelmac; ***Malaysia:*** Zelmac†; ***Mex.:*** Zelmac; ***NZ:*** Zelmac; ***Philipp.:*** Zelnorm; ***Rus.:*** Zelmac (Зелмак)†; ***S.Afr.:*** Zelnorm; ***Singapore:*** Zelmac; ***Switz.:*** Zelmac; ***Thai.:*** Zelmac; ***Turk.:*** Zelmac; ***USA:*** Zelnorm†; ***Venez.:*** Zelmac.

Teprenone *(rINN)*

E-671; Geranylgeranylacetone (5*E*, 9*E*,13*E* isomer); Teprenona; Téprénone; Teprenonum. 6,10,14,18-Tetramethyl-5,9,13,17-nonadecatetraen-2-one, mixture of (5*E*,9*E*,13*E*) and (5*Z*,9*E*,13*E*) isomers.

Тепренон

$C_{23}H_{38}O$ = 330.5.

CAS — 6809-52-5 (teprenone); 3796-63-2 (5E,9E,13E isomer); 3796-64-3 (5Z,9E,13E isomer).

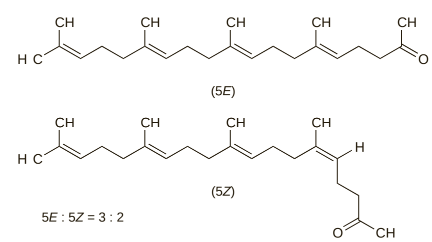

Profile

Teprenone is a cytoprotective drug that is used in the treatment of gastritis and peptic ulcer disease (p.1702) in a usual oral dose of 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Purubex; ***Jpn:*** Selbex; ***Philipp.:*** Selbex; ***Thai.:*** Selbex.

Tiemonium Iodide *(BAN, rINN)*

Ioduro de tiemonio; TE-114; Tiemonii Iodidum; Tiémonium, Iodure de. 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide.

Тиемония Йодид

$C_{18}H_{24}INO_2S$ = 445.4.

CAS — 6252-92-2 (tiemonium); 144-12-7 (tiemonium iodide).

ATC — A03AB17.

ATC Vet — QA03AB17.

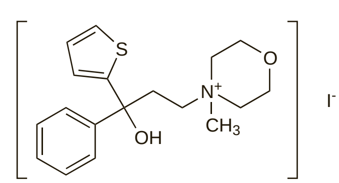

Tiemonium Metilsulfate

Tiemonio, metilsulfato de; Tiemonium Methylsulphate. 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methyl-morpholinium methylsulphate.

$C_{19}H_{27}NO_6S_2$ = 429.6.

CAS — 6504-57-0.

Profile

Tiemonium iodide and tiemonium metilsulfate are quaternary ammonium antimuscarinics with peripheral effects similar to those of atropine (p.1219) and are used in the relief of visceral spasms.

Tiemonium metilsulfate is given in an oral dose of 100 to 300 mg daily in divided doses. A dose of 5 mg has been given three times daily by intramuscular or slow intravenous injection. Tiemonium metilsulfate has also been given as a rectal suppository in daily doses of 20 to 40 mg.

Tiemonium iodide has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Visceralgine†; ***Fr.:*** Visceralgine; ***Indon.:*** Visceralgine.

Multi-ingredient: ***Belg.:*** Asodal; ***Fr.:*** Colchimax; Visceralgine Forte†; ***Venez.:*** Bort†.

Timepidium Bromide *(rINN)*

Bromuro de timepidio; SA-504; Timepidii Bromidum; Timépidium, Bromure de. 3-[Di-(2-thienyl)methylene]-5-methoxy-1,1-dimethylpiperidinium bromide monohydrate.

Тимепидия Бромид

$C_{17}H_{22}BrNOS_2,H_2O = 418.4.$

CAS — 35035-05-3.

ATC — A03AB19.

ATC Vet — QA03AB19.

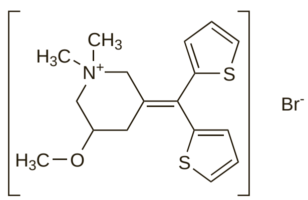

Pharmacopoeias. In *Jpn.*

Profile

Timepidium bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been given for the symptomatic treatment of visceral spasms in usual oral doses of 30 mg three times daily. It has also been given by subcutaneous, intramuscular, and intravenous injection in a dose of 7.5 mg.

Urinary metabolites of timepidium may cause a reddish coloration of the urine.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Sesden; ***Jpn:*** Sesden; ***Singapore:*** Sesden†.

Tridihexethyl Chloride *(BAN, rINNM)*

Cloruro de tridihexetilo; Tridihexéthyl, Chlorure de; Tridihexethyli Chloridum. (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)triethylammonium chloride.

Тридигексетила Хлорид

$C_{21}H_{36}ClNO = 354.0.$

CAS — 60-49-1 (tridihexethyl); 4310-35-4 (tridihexethyl chloride); 125-99-5 (tridihexethyl iodide).

ATC — A03AB08.

ATC Vet — QA03AB08.

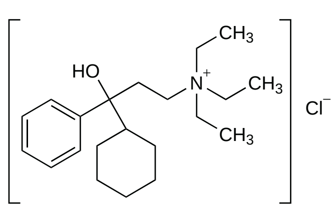

NOTE. Tridihexethyl Iodide is *rINN*.

Profile

Tridihexethyl chloride is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease.

Tropisetron *(BAN, rINN)*

Tropisétron; Tropisetrón; Tropisetroni; Tropisetronum. 1αH,5αH-Tropan-3α-yl indole-3-carboxylate.

Трописетрон

$C_{17}H_{20}N_2O_2 = 284.4.$

CAS — 89565-68-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

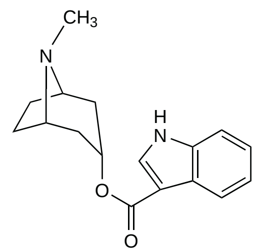

Tropisetron Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tropisetrón; ICS-205-930; Tropisétron, chlorhydrate de; Tropisetroni hydrochloridum.

Трописетрона Гидрохлорид

$C_{17}H_{20}N_2O_2,HCl = 320.8.$

CAS — 105826-92-4.

ATC — A04AA03.

ATC Vet — QA04AA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tropisetron Hydrochloride). A white or almost white powder. Freely soluble or soluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane.

Adverse Effects and Precautions

As for Ondansetron, p.1757. Fatigue, abdominal pain, and diarrhoea may also occur. Visual hallucinations, and an increase in blood pressure in patients with pre-existing hypertension, have been noted at high repeated doses. ECG changes such as prolongation of QT interval have been noted with high-dose intravenous tropisetron. The drug should therefore be used with caution in patients with cardiac rhythm or conduction disturbances. Care should be taken when driving or operating machinery. No dosage reduction is considered necessary in renal or hepatic impairment despite possible reductions in clearance.

Carcinogenicity. The manufacturer (*Novartis, UK*) has reported an increased incidence of hepatic neoplasms in male *mice* given high doses of tropisetron but it is suggested that these effects are both species and sex specific.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Interactions

Drugs that induce or inhibit hepatic enzymes may affect plasma concentrations of tropisetron. Licensed product information considers that any changes are usually unlikely to be clinically relevant with the recommended doses.

Tropisetron should be used with caution with antiarrhythmics, beta blockers, or drugs likely to prolong the QT interval, including those likely to cause electrolyte disturbances (see also p.1757).

Pharmacokinetics

Tropisetron is well absorbed after oral doses. Peak plasma concentrations are achieved within 3 hours. Absolute bioavailability depends on the dose since first-pass metabolism is saturable. It is 71% bound to plasma proteins. Tropisetron is metabolised by hydroxylation and conjugation, and metabolites are excreted mainly in the urine with a small amount in the faeces. The cytochrome P450 isoenzyme CYP2D6 is involved in tropisetron metabolism, and shows genetic polymorphism. The elimination half-life is about 8 hours in extensive metabolisers and up to 45 hours in poor metabolisers. Clearance is also reduced in patients with renal impairment.

Uses and Administration

Tropisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p.1757). It is used in the prevention of nausea and vomiting induced by cytotoxic therapy and in the treatment and prevention of postoperative nausea and vomiting (p.1700).

Tropisetron is given as the hydrochloride by slow intravenous injection or infusion, or orally. Doses are expressed in terms of tropisetron base; 5.64 mg of tropisetron hydrochloride is equivalent to about 5 mg of tropisetron base.

For the *prophylaxis* of acute **nausea and vomiting** associated with cytotoxic **chemotherapy** a single dose of 5 mg may be given by slow intravenous injection or infusion on the day of treatment, shortly before chemotherapy. The injection is given over not less than 1 minute; it may be given into a running infusion. For infusion, it is diluted into 100 mL of a suitable infusion fluid (such as sodium chloride 0.9% or glucose 5%), and given over 15 minutes. Subsequent doses of 5 mg daily are given orally, in the morning at least one hour before food, for a further 5 days.

Children over 2 years of age may be given 200 micrograms/kg (maximum dose 5 mg) before chemotherapy, by intravenous injection over at least 1 minute, or by infusion (at a concentration of 50 micrograms/mL in a suitable infusion fluid). In children weighing less than 25 kg the same dose may be given intravenously once daily for up to a further 4 days as required. In those weighing more than 25 kg, a dose of 5 mg may be given orally once daily for up to a further 5 days; if oral dosage is not possible the same dose may be given intravenously.

For the *treatment* of **postoperative** nausea and vomiting in adults 2 mg may be given by slow intravenous injection (over not less than 30 seconds), or by infusion (over 15 minutes), within 2 hours of the end of anaesthesia. For *prophylaxis*, the same dose may be given shortly before induction of anaesthesia.

◊ References.

1. Lee CR, *et al.* Tropisetron: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs* 1993; **46:** 925–43.
2. Simpson K, *et al.* Tropisetron: an update of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2000; **59:** 1297–1315.

Anxiety disorders. A dose-dependent anxiolytic effect was reported for tropisetron when studied in patients with generalised anxiety,[1] but clinical evidence for the benefit of 5-HT_3 antagonists in anxiety disorders is lacking.[2]

1. Lecrubier Y, *et al.* A randomized double-blind placebo-controlled study of tropisetron in the treatment of outpatients with generalized anxiety disorder. *Psychopharmacology (Berl)* 1993; **112:** 129–33.
2. Greenshaw AJ, Silverstone PH. The non-antiemetic uses of serotonin 5-HT receptor antagonists: clinical pharmacology and therapeutic applications. *Drugs* 1997; **53:** 20–39.

Fatigue. Tropisetron has been reported to be of benefit in patients with chronic fatigue, see under Uses and Administration of Ondansetron, p.1758.

Pain. For reference to the use of tropisetron in various painful syndromes, see under Uses and Administration of Ondansetron, p.1758.

Pruritus. Tropisetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p.1758).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Navoban; ***Austral.:*** Navoban; ***Austria:*** Navoban; ***Belg.:*** Novaban; ***Braz.:*** Navoban†; ***Chile:*** Navoban; ***Cz.:*** Navoban†; ***Denm.:*** Navoban; ***Fin.:*** Navoban; ***Fr.:*** Navoban; ***Ger.:*** Navoban; ***Gr.:*** Navoban; ***Hong Kong:*** Navoban; ***Hung.:*** Navoban; ***Indon.:*** Navoban; Setrovel; ***Israel:*** Navoban†; ***Ital.:*** Navoban; ***Jpn:*** Navoban; ***Malaysia:*** Navoban; ***Mex.:*** Navoban; ***Neth.:*** Novaban; ***Norw.:*** Navoban; ***NZ:*** Navoban; ***Philipp.:*** Navoban; ***Pol.:*** Navoban; ***Port.:*** Navoban; ***Rus.:*** Navoban (Навобан); Tropindol (Тропиндол)†; ***S.Afr.:*** Navoban; ***Spain:*** Navoban; Saronil; ***Swed.:*** Navoban; ***Switz.:*** Navoban; ***Thai.:*** Navoban; ***Turk.:*** Navoban; ***UK:*** Navoban; ***Venez.:*** Navoban.

Troxipide *(rINN)*

Troxipida; Troxipidum. (±)-3,4,5-Trimethoxy-*N*-3-piperidylbenzamide.

Троксипид

$C_{15}H_{22}N_2O_4$ = 294.3.
CAS — 30751-05-4.
ATC — A02BX11.
ATC Vet — QA02BX11.

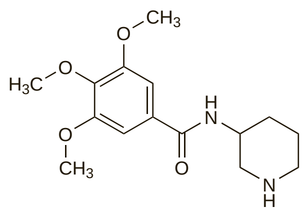

Profile

Troxipide is used for its cytoprotective properties in the treatment of gastritis and peptic ulcer disease (p.1702) in a usual oral dose of 100 mg three times daily, after food.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Aplace.

Urogastrone

Anthelone; EGF-URO; Epidermal Growth Factor; Murodermina; Uroanthelone; Uroenterone; Urogastrona.

Урогастрон

CAS — 9010-53-1.

Pharmacopoeias. *Chin.* includes monographs for recombinant human epidermal growth factor suitable for external use.

Uses

Urogastrone is a polypeptide first isolated from human urine. Two forms have been identified, β and γ urogastrone. The β form consists of 53 amino acids and is distinguishable from the γ form by an additional terminal arginine residue. The β form is reported to be identical to human epidermal growth factor and this term is widely used in the literature.

Urogastrone inhibits gastric acid secretion and has been tried in the treatment of peptic ulcer disease and other gastrointestinal disorders but its rapid destruction in the stomach has limited its clinical use.

It is a potent stimulator of cellular proliferation and has also been used as an aid to wound healing.

◊ Reviews.

1. Burgess AW. Epidermal growth factor and transforming growth factor α. *Br Med Bull* 1989; **45:** 401–24.
2. Miyazawa K. Role of epidermal growth factor in obstetrics and gynecology. *Obstet Gynecol* 1992; **79:** 1032–40.
3. Grazul-Bilska AT, *et al.* Wound healing: the role of growth factors. *Drugs Today* 2003; **39:** 787–800.
4. Klenkler B, Sheardown H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology. *Exp Eye Res* 2004; **79:** 677–88.

Gastrointestinal disorders. Intravenous infusion of urogastrone 250 nanograms/kg over 1 hour has been reported[1,2] to reduce the secretion of gastric acid in patients with duodenal ulcer (p.1702) or the Zollinger-Ellison syndrome (p.1704). Ulcer pain was relieved 30 to 60 minutes after the start of the infusion.[2] A dose of 100 nanograms/kg per hour by intravenous infusion has been used with partial success in an infant with microvillous atrophy[3] and was apparently beneficial in an infant with necrotising enteritis.[4]

Human epidermal growth factor has also shown some promise in the treatment of active ulcerative colitis. In a small study,[5] patients received daily enemas containing either recombinant human epidermal growth factor (5 micrograms in 100 mL) or placebo; all patients also received oral mesalazine. Ten of the 12 patients in the urogastrone group were in remission after 2 weeks treatment compared with 1 of the 12 patients in the placebo group, and this benefit was maintained for up to 12 weeks.

1. Koffman CG, *et al.* Effect of urogastrone on gastric secretion and serum gastrin concentration in patients with duodenal ulceration. *Gut* 1982; **23:** 951–6.
2. Elder JB, *et al.* Effect of urogastrone in the Zollinger-Ellison syndrome. *Lancet* 1975; **ii:** 424–7.
3. Walker-Smith JA, *et al.* Intravenous epidermal growth factor/urogastrone increases small-intestinal cell proliferation in congenital microvillous atrophy. *Lancet* 1985; **ii:** 1239–40.
4. Sullivan PB, *et al.* Epidermal growth factor in necrotising enteritis. *Lancet* 1991; **338:** 53–4.
5. Sinha A, *et al.* Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003; **349:** 350–7.

Wound healing. For a general discussion of the management of wounds and ulcers, see p.1585.

In a randomised double-blind study in 61 patients with diabetic foot ulcers, adding human epidermal growth factor 0.04% to an ulcer cream containing protein-free bovine blood extract was shown to significantly enhance wound healing and reduce healing time compared with either the cream alone or the cream plus human epidermal growth factor 0.02%.[1] Topical application of recombinant human epidermal growth factor 0.02% has also been reported to reduce pain and promote healing of exfoliated skin lesions in a patient with drug-induced Stevens-Johnson syndrome.[2]

The effect on the rate of wound healing of a cream containing sulfadiazine silver plus recombinant human epidermal growth factor (10 micrograms/mL) was compared with sulfadiazine silver alone in 12 patients each requiring skin grafts at 2 donor sites.[3] The cream containing epidermal growth factor accelerated the rate of epidermal regeneration in all patients and reduced the average time to 100% healing by about 1.5 days. Patients were followed up for a maximum of 1 year after cessation of therapy and no complications or clinical evidence of neoplasia at the healed donor sites occurred.

In contrast, recombinant human epidermal growth factor as an ophthalmic solution containing 30 or 100 micrograms/mL was investigated in patients who had undergone keratoplasty, but the weaker solution had no effect on the rate of re-epithelialisation, and the more concentrated one was actually associated with slower healing.[4]

1. Tsang MW, *et al.* Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; **26:** 1856–61.
2. Tsang MW, *et al.* The use of recombinant human epidermal growth factor (rhEGF) in a gentleman with drug-induced Steven Johnson syndrome. *Dermatol Online J* 2004; **10:** 25.
3. Brown GL, *et al.* Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; **321:** 76–9.
4. Dellaert MMMJ, *et al.* Influence of topical human epidermal growth factor on postkeratoplasty re-epithelialisation. *Br J Ophthalmol* 1997; **81:** 391–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** FCE; Hebermin†.

Valethamate Bromide

Valetamat Bromür; Valetamato, bromuro de. Diethylmethyl[2-(3-methyl-2-phenylvaleryloxy)ethyl]ammonium bromide.

$C_{19}H_{32}BrNO_2$ = 386.4.
CAS — 16376-74-2 (valethamate); 90-22-2 (valethamate bromide).

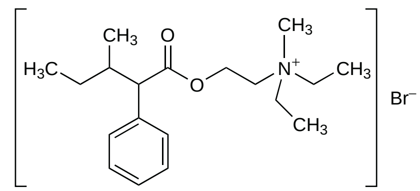

Profile

Valethamate bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been given orally, by injection or rectally in the symptomatic treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Epidosin; Valosin; ***Indon.:*** Epidosin; ***Turk.:*** Epidosin.
Multi-ingredient: ***Turk.:*** Epidosin Compozitum.

Zaldaride *(rINN)*

CGS-9343B (zaldaride maleate); Zaldarida; Zaldaridum. (±)-1-{1-[(4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidyl}-2-benzimidazolinone.

Зальдарид

$C_{26}H_{28}N_4O_2$ = 428.5.
CAS — 109826-26-8 (zaldaride); 109826-27-9 (zaldaride maleate).

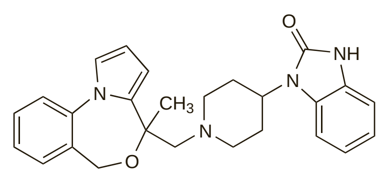

Profile

Zaldaride is a calmodulin antagonist that has been investigated as the maleate for the treatment of diarrhoea.

Diarrhoea. Studies in patients with travellers' diarrhoea (p.1694) have indicated that zaldaride in oral doses of 20 mg as the maleate four times daily is an effective antidiarrhoeal.[1,2] It was somewhat less effective than loperamide when given without a loading dose,[2] but a regimen of 40 mg initially, followed by 20 mg, about every 6 hours was as effective as loperamide 4 mg initially followed by 2 mg after each unformed stool.[3]

1. DuPont HL, *et al.* Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea. *Gastroenterology* 1993; **104:** 709–15.
2. Okhuysen PC, *et al.* Zaldaride maleate (a new calmodulin antagonist) versus loperamide in the treatment of traveler's diarrhea: randomized, placebo-controlled trial. *Clin Infect Dis* 1995; **21:** 341–4.
3. Silberschmidt G, *et al.* Treatment of travellers' diarrhoea: zaldaride compared with loperamide and placebo. *Eur J Gastroenterol Hepatol* 1995; **7:** 871–5.

General Anaesthetics

This chapter includes drugs used for the induction and maintenance of general anaesthesia. General anaesthetics are given either by inhalation or by intravenous or occasionally intramuscular injection (see Table, below).

Injectable	Inhalational
Barbiturate	*Halogenated*
Methohexital	Chloroform
Thiamylal	Desflurane
Thiopental	Enflurane
	Halothane
Miscellaneous	Isoflurane
Alfadolone	Methoxyflurane
Alfaxolone	Sevoflurane
Etomidate	Trichloroethylene
Ketamine	*Miscellaneous*
Propanidid	Cyclopropane
Propofol	Anaesthetic Ether
Sodium Oxybate	Nitrous Oxide
Tiletamine	Xenon

Adverse Effects of General Anaesthetics and their Treatment

The complex regimens used in general anaesthesia may produce complications both during and after the procedure. Adverse effects that may occur with general anaesthesia include involuntary muscle movements, hiccup, coughing, bronchospasm, laryngospasm, respiratory depression, hypotension, cardiac arrhythmias, and mild hypothermia.

After general anaesthesia many patients will experience drowsiness and impaired mental performance for at least 24 hours. Postoperative nausea with or without vomiting is common in the absence of antiemetic prophylaxis; nausea may last for 2 days but vomiting seldom persists beyond the first day. Other relatively common postanaesthetic effects include anorexia, malaise, fatigue, dizziness, and headache. Delirium has been noted in at least 10% of elderly general surgical patients and in up to 50% of elderly patients undergoing hip fracture repair.

Sore throat is frequent in patients who have been intubated or have had a throat pack inserted. Dry mouth as a result of premedication can add to the patient's discomfort. Manipulations for the maintenance of a clear airway may result in postoperative jaw pain.

Muscle pain, typically involving the neck, shoulders, and upper abdomen, may occur if the neuromuscular blocker suxamethonium has been given. It is usually worse on the second postoperative day and may last up to 6 days. Shoulder ache after laparoscopy resolves after 24 hours; it is due to accumulation of carbon dioxide under the diaphragm. Backache may occur after epidural or spinal anaesthesia. Urinary retention may follow regional block, cystoscopic or gynaecological surgery, or when there is prostatism.

Malignant hyperthermia (malignant hyperpyrexia—see under Dantrolene, p.1896) is a rare but potentially fatal complication of general anaesthesia that may be induced by inhalational anaesthetics (mainly halogenated hydrocarbons).

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics.

There has been concern over the possible danger to anaesthetists, dentists, and other personnel from exposure to volatile anaesthetics.

◊ References.

1. Anonymous. Following up day case anaesthesia in general practice. *Drug Ther Bull* 1990; **28:** 81–2.
2. Rowbotham DJ, Smith G, eds. Postoperative nausea and vomiting. *Br J Anaesth* 1992; **69** (suppl 1): 1S–68S.
3. O'Keeffe ST, NíChonchubhair Á. Postoperative delirium in the elderly. *Br J Anaesth* 1994; **73:** 673–87.
4. Marcantonio ER, *et al.* A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994; **271:** 134–9.
5. Davies CJ, *et al.* Delayed adverse reactions to drugs used in anaesthesia. *Adverse Drug React Bull* 1995; **171:** 647–50.
6. Klafta JM, *et al.* Neurological and psychiatric adverse effects of anaesthetics: epidemiology and treatment. *Drug Safety* 1995; **13:** 281–95.
7. Fee JPH, Thompson GH. Comparative tolerability profiles of the inhaled anaesthetics. *Drug Safety* 1997; **16:** 157–70.

Hypersensitivity. Type I hypersensitivity reactions have occurred with general anaesthetics.[1,2] In most patients the release of histamine and other mediators such as prostaglandins and leukotrienes is of no clinical importance but in a few susceptible individuals anaphylaxis may result. Numerous factors to identify those at risk have been proposed over the years along with suggested modifications for anaesthetic management. Of the drugs used in anaesthesia, neuromuscular blockers are associated with the highest incidence of anaphylaxis; the most commonly implicated is reported to be suxamethonium, followed by alcuronium[3] (see under the Adverse Effects of Suxamethonium, p.1910). It has been suggested[4] that routine prophylaxis with histamine H_1- and histamine H_2-antagonists should be considered as part of anaesthetic management but others[3] thought it better to avoid the use of combinations such as thiopental, suxamethonium, and alcuronium that are well known to cause histamine release.

1. McKinnon RP, Wildsmith JAW. Histaminoid reactions in anaesthesia. *Br J Anaesth* 1995; **74:** 217–28.
2. Sánchez Palacios A, *et al.* Reacciones alérgicas y pseudoalérgicas en las intervenciones quirúrgicas con anestesia general. *Allergol Immunopathol (Madr)* 2000; **28:** 24–36.
3. O'Connor B, Edwards ND. Reactions to gelatin plasma expanders. *Lancet* 1994; **344:** 328.
4. Lorenz W, *et al.* Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. *Lancet* 1994; **343:** 933–40.

Nausea and vomiting. For a discussion on postoperative nausea and vomiting and its management, see p.1700.

Shivering and its treatment. Postoperative shivering, also referred to as spontaneous postanaesthetic tremor, can occur in up to 65% of patients recovering from general anaesthesia;[1,2] its aetiology and relationship to thermoregulation is unclear.[1,3,4] Postoperative shivering may be part of a more generalised neurological disturbance associated with anaesthesia.[1] It also occurs after regional anaesthesia, especially when given epidurally, but this is probably produced by different mechanisms.[3] Muscular activity during shivering greatly increases metabolic rate, oxygen consumption, and cardiac output and may cause complications in patients with cardiac or respiratory disorders. It can also strain surgical sutures, raise intra-ocular pressure, and impede haemodynamic monitoring.

Although the relationship between postoperative shivering, body temperature, and heat loss is unclear, patients may respond to warming their environment and the use of blankets.[1,3] Postoperative shivering may sometimes be an appropriate thermoregulatory response to a low body temperature,[3] and it is important before starting therapy to check the patient's temperature and take suitable steps to avoid hypothermia.[1]

Numerous drugs have been tried for the management of postoperative shivering including the central and respiratory stimulant doxapram, the α_2-agonist clonidine, and the opioid analgesic pethidine.[2,4,5] Reviews have discussed[1-4] a number of other opioids that have been tried including morphine, alfentanil, butorphanol, fentanyl, and sufentanil but studies suggest that not all opioids are effective or that some may only be effective when given epidurally. However, this may be due to the use of insufficient doses rather than a true difference between opioids.[6] Tramadol and nefopam have also been tried.[2,5] Neuromuscular blockers have been used after cardiac surgery in order to reduce cardiovascular stress.[7] Vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.[8] However, as profound neuromuscular block is required to inhibit shivering, repeated or higher doses of vecuronium might be required to prevent recurrence. Other drugs that have been investigated include ketanserin,[2] ketamine,[9] and magnesium sulfate.[2]

1. Crossley AWA. Postoperative shivering. *Br J Hosp Med* 1993; **49:** 204–8.
2. Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology, and approaches to prevention and management. *Drugs* 2001; **61:** 2193–2205.
3. Anonymous. Perioperative shivering. *Lancet* 1991; **338:** 547–8.
4. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; **94:** 453–60.
5. Kranke P, *et al.* Single-dose parenteral pharmacological interventions for the prevention of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2004; **99:** 718–27.
6. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; **70** (suppl 1): 38.
7. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; **39:** 563–8.
8. Dupuis J-Y, *et al.* Pancuronium or vecuronium for treatment of shivering after cardiac surgery. *Anesth Analg* 1994; **79:** 472–81.
9. Sharma DR, Thakur JR. Ketamine and shivering. *Anaesthesia* 1990; **45:** 252–3.

Precautions for General Anaesthetics

Patients with impaired function of the adrenal cortex, for example, those who are being treated, or have recently been treated, with corticosteroids, may experience hypotension with the stress of anaesthesia. Treatment with corticosteroids, pre-operatively and postoperatively, may be necessary. Patients taking other long-term medication such as aspirin, oral anticoagulants, oestrogens, MAOIs, or lithium, may need to change their dosage or stop therapy before major elective surgery.

Patients with chronic diseases such as diabetes or hypertension may need adjustment to their therapy before anaesthesia. Anaesthetics should be used with caution in patients with cardiac, respiratory, renal, or hepatic impairment and care may be needed in elderly or obese patients.

Patients should not undertake hazardous tasks such as driving for at least 24 hours after a general anaesthetic; alcohol should also be avoided.

Intraoperative awareness. The use of neuromuscular blockers has enabled anaesthetic doses to be reduced. However, lack of a reliable method for detecting conscious awareness in patients with complete neuromuscular block has resulted in paralysed patients who have received inadequate anaesthesia being aware during surgery.[1,2] Recommendations to control this problem include premedication with sedative or amnesic drugs, induction with sufficient doses of intravenous anaesthetic, the use of effective analgesic techniques during surgery, and, in particular, adequate concentrations of inspired anaesthetic gas. However, even patients given lorazepam or opioids may have some recall and there is no certain way to avoid awareness in paralysed patients. One commentator[3] considered that the routine use of neuromuscular blockers during surgery should be re-assessed since modern anaesthetics and analgesics could provide good operating conditions without paralysis for most major surgical procedures.

1. Brighouse DI, Norman J. To wake in fright. *BMJ* 1992; **304:** 1327–8.
2. Jones JG. Memory of intraoperative events. *BMJ* 1994; **309:** 967–8.
3. Ponte J. Neuromuscular blockers during general anaesthesia. *BMJ* 1995; **310:** 1218–19.

Interactions of General Anaesthetics

Sensitisation of the myocardium to beta-adrenergic stimulation occurs with some anaesthetics and ventricular fibrillation may occur if *sympathomimetics* such as adrenaline and isoprenaline are also used. Enhanced hypotensive effects may result when anaesthetics are given with *ACE inhibitors*, *tricyclic antidepressants* (which may also increase the risk of arrhythmias), *MAOIs* (see also Anaesthesia, under Precautions for Phenelzine, p.417), *antihypertensives*, *antipsychotics*, or *beta blockers*. The effects of *competitive neuromuscular blockers* may be increased by inhalational anaesthetics. The use of anaesthetics with other *CNS depressant drugs* such as those used for premedication may produce synergistic effects on the CNS and, in some cases, a smaller dose of general anaesthetic should be given.

◊ Reviews.

1. Wood M. Pharmacokinetic drug interactions in anaesthetic practice. *Clin Pharmacokinet* 1991; **21:** 285–307.
2. Ransom ES, Mueller RA. Safety considerations in the use of drug combinations during general anaesthesia. *Drug Safety* 1997; **16:** 88–103.

Uses of General Anaesthetics

General anaesthetics depress the CNS and cause loss of consciousness associated with an inability to perceive pain. An ideal anaesthetic would produce unconsciousness, analgesia, and muscle relaxation suitable for all surgical procedures and would be metabolically inert and rapidly eliminated. No anaesthetic fulfils all these requirements in safe concentrations and it is customary to use a number of drugs to achieve the required conditions while minimising the risk of toxicity.

The activity of any anaesthetic is dependent on its ability to reach the brain. With inhalational anaesthetics there has to be a transfer from the alveolar space to the blood, then to the brain; recovery is a function of the removal of the anaesthetic from the brain. With injectable anaesthetics their activity is similarly dependent on their ability to penetrate the blood/brain barrier and recovery in turn is governed by their redistribution and excretion. The potency of inhalational anaesthetics is often expressed in terms of *minimum alveolar concentrations*, known as MAC values. The MAC of an anaesthetic is the concentration at 1 atmosphere that will produce immobility in 50% of subjects exposed to a noxious stimulus. Values given under the individual monographs are based on use without nitrous oxide as the latter can reduce the MAC. Other factors including age, body temperature, and concurrent medication such as opioid analgesics can also affect MAC values.

◊ General references.

1. Royston D, Cox F. Anaesthesia: the patient's point of view. *Lancet* 2003; **362:** 1648–58.
2. García-Miguel FJ, *et al.* Preoperative assessment. *Lancet* 2003; **362:** 1749–57.
3. Buhre W, Rossaint R. Perioperative management and monitoring in anaesthesia. *Lancet* 2003; **362:** 1839–46.
4. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; **362:** 1921–8.
5. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.
6. Stachnik J. Inhaled anesthetic agents. *Am J Health-Syst Pharm* 2006; **63:** 623–34. Correction. *ibid.* 2436.
7. Nathan N, Odin I. Induction of anaesthesia: a guide to drug choice. *Drugs* 2007; **67:** 701–23.

Anaesthesia. Many drugs are involved in achieving and maintaining conditions suitable for surgery. Conventional general anaesthesia may be divided into a number of stages including:

- premedication
- induction
- muscle relaxation and intubation
- maintenance
- analgesia
- reversal

A brief outline of the drugs typically used in each stage follows.

For **premedication**, benzodiazepines and some phenothiazines such as promethazine or alimemazine may be given to sedate and relieve *anxiety* in apprehensive patients. Butyrophenones such as droperidol have also been used. The benzodiazepines have useful amnesic and muscle-relaxant properties and short-acting oral forms are common in current regimens. The phenothiazines and butyrophenones are rarely used now although their antiemetic actions may be useful to control *postoperative nausea and vomiting* (see p.1700). Cloral hydrate is still used in some countries for pre-operative sedation. The use of barbiturates has largely ceased. For sedation of children the oral route is often preferred to injections, or the rectal route may be used in exceptional circumstances.

Antimuscarinics such as atropine, glycopyrronium, and hyoscine may be given to inhibit excessive *bronchial* and *salivary secretions* induced by intubation and some anaesthetics, although such use is less common nowadays. Antimuscarinics are also given as premedicants to reduce the intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol or by vagal stimulation. Hyoscine also provides some degree of amnesia.

Opioids, including morphine and its derivatives, papaveretum and pethidine, have been widely used before surgery to reduce anxiety, smooth induction of anaesthesia, reduce overall anaesthetic requirements, and provide pain relief during and after surgery. The routine use of opioids as premedicants is now rare and generally restricted to patients already in pain. However, they continue to find a role at induction (below).

Patients may also be given drugs that reduce the danger from regurgitation and *aspiration* of gastric contents (see under Aspiration Syndromes, p.1693), such as the histamine H_2-antagonists, cimetidine and ranitidine, and the proton pump inhibitor, omeprazole. Cardiovascular drugs may be needed during surgery to control *blood pressure* and counteract *arrhythmias*.

The aim of **induction** is to produce anaesthesia rapidly and smoothly. Induction may be achieved with intravenous or inhalational anaesthetics but intravenous induction may be more pleasant for the patient. Intravenous drugs used include the barbiturate thiopental, the benzodiazepine midazolam, and other anaesthetics such as etomidate, propofol, or ketamine. Small doses of short-acting opioids, for example alfentanil, fentanyl, or remifentanil, given before or at induction allow the use of smaller induction doses of some drugs used for anaesthesia, and this technique is particularly suitable for poor-risk patients.

After induction, **muscle relaxation** with a rapidly acting depolarising neuromuscular blocker such as suxamethonium aids **intubation** of the patient. Longer acting, competitive neuromuscular blockers may then be given to allow procedures such as abdominal surgery to be carried out under lighter anaesthesia. For more detail, see Anaesthesia, p.1900.

Maintenance of anaesthesia may be achieved with an inhalational anaesthetic, an intravenous anaesthetic, or an intravenous opioid, either alone or in combination.

Opioid analgesics may also be given for **analgesia** as supplements during general anaesthesia (see also Balanced Anaesthesia, under Anaesthetic Techniques, below). Long-acting opioids such as morphine or papaveretum may cause postoperative respiratory depression. The short-acting opioid fentanyl, and its congeners alfentanil and sufentanil, appear to produce fewer circulatory changes and may be preferred to other opioids, especially in cardiovascular surgery; remifentanil may be valuable for its very short duration of action. Various combinations of analgesic techniques, including the use of pre-emptive analgesia, are used or are being investigated for the management of surgical pain (see Postoperative Analgesia, p.4).

At the end of surgery drugs are sometimes given to accelerate recovery by **reversal** of the effects of the various agents used during anaesthesia. The *neuromuscular block* produced by competitive neuromuscular blockers may be reversed with anticholinesterases such as neostigmine and edrophonium but atropine or glycopyrronium are also needed to prevent bradycardia and other muscarinic actions developing. The opioid antagonist naloxone has been given to reverse opioid-induced *respiratory depression*. However, it may antagonise the analgesic effects of the opioids in the control of postoperative pain and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use. Flumazenil is a benzodiazepine antagonist that is used to reverse the *central sedative effects* of benzodiazepines in anaesthetic procedures.

ANAESTHETIC TECHNIQUES. A balanced combination of drugs with different actions is often used to provide the various components of general anaesthesia including unconsciousness, muscle relaxation, and analgesia. This technique, termed **balanced anaesthesia**, has been reported to minimise intra-operative cardiovascular depression, to facilitate a rapid return of consciousness, and to have a low incidence of postoperative adverse effects such as nausea and vomiting, and excitation. Typically an opioid is given before or with induction and anaesthesia is induced using nitrous oxide and an intravenous barbiturate such as thiopental. The opioid is then given in small incremental doses to achieve and maintain adequate analgesia during surgery. Opioid analgesics commonly used in this technique include morphine, fentanyl, sufentanil, and alfentanil; buprenorphine and nalbuphine have also been used.

In **total intravenous anaesthesia** (TIVA), induction and maintenance of anaesthesia is achieved with one or more anaesthetics given intravenously. This allows high inspired oxygen concentrations in situations where hypoxaemia may otherwise occur, and is advantageous in surgery where delivery of inhaled anaesthetic may be difficult (for example in bronchoscopy). Combinations used in TIVA include propofol with alfentanil or fentanyl, and midazolam with alfentanil. Neuromuscular blockers are given to produce muscle relaxation but there can be difficulty in assessing the depth of anaesthesia in patients who are paralysed for mechanical ventilation, and there have been reports of awareness during procedures under total intravenous anaesthesia (see also Intraoperative Awareness under Precautions, above).

Although now largely obsolete, use of a neuroleptic with an opioid analgesic produces an altered state of consciousness known as **neuroleptanalgesia** in which the patient is calm and indifferent to the surroundings yet is responsive to commands. The technique was used for diagnostic or therapeutic procedures such as minor surgery, endoscopy, and changing dressings. Neuroleptanalgesia can be converted to **neuroleptanaesthesia** by the concurrent administration of nitrous oxide in oxygen; a muscle relaxant may also be included. Neuroleptanaesthesia is particularly useful if the patient's cooperation is required, as consciousness soon returns once the nitrous oxide is stopped. The neuroleptic most commonly employed was droperidol and it was usually used with fentanyl although other opioids have also been used. These procedures have since evolved into **conscious sedation** and **monitored anaesthetic care** techniques employing newer drugs.

Ketamine used alone can produce a state of **dissociative anaesthesia** similar to that of neuroleptanalgesia in which the patient may appear to be awake but is unconscious. Marked analgesia and amnesia are produced, but there may be an increase in muscle tone and emergence reactions. Dissociative anaesthesia is considered suitable for use in various diagnostic procedures, dressing changes, and in minor surgery not requiring muscle relaxation.

Techniques using **local anaesthetics** are discussed on p.1853.

Alfadolone Acetate *(BANM, rINNM)*

Acetato de alfadolona; Alfadolone, Acétate d'; Alfadoloni Acetas; Alphadolone Acetate; GR-2/1574. 3α,21-Dihydroxy-5α-pregnane-11,20-dione 21-acetate.

Альфадолона Ацетат

$C_{23}H_{34}O_5$ = 390.5.

CAS — 14107-37-0 (alfadolone); 23930-37-2 (alfadolone acetate).

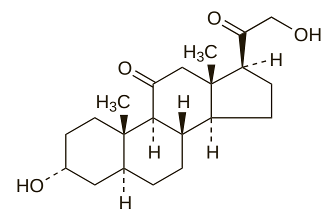

(alfadolone)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Alfadolone Acetate). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfadolone acetate has been used to enhance the solubility of alfaxalone (below). It possesses some anaesthetic properties and is considered to be about half as potent as alfaxalone.

Alfaxalone *(BAN, rINN)*

Alfaksaloni; Alfaxalon; Alfaxalona; Alfaxalonum; Alphaxalone; GR-2/234. 3α-Hydroxy-5α-pregnane-11,20-dione.

Альфаксалон

$C_{21}H_{32}O_3$ = 332.5.

CAS — 23930-19-0.

ATC — N01AX05.

ATC Vet — QN01AX05.

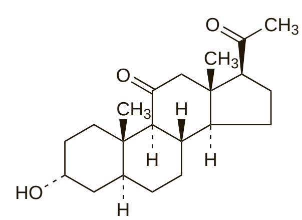

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Alfaxalone). A white to creamy white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol; freely soluble in chloroform.

Profile

Alfaxalone was formerly used with alfadolone acetate (above) ['Althesin'], as an intravenous anaesthetic for induction and maintenance of general anaesthesia.

Adverse reactions associated with polyethoxylated castor oil (present as a vehicle) led to the general withdrawal of alfaxalone with alfadolone acetate from human use. It is still used in veterinary medicine.

Porphyria. Alfaxalone:alfadolone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Chloroform

Chloroformium Anesthesicum; Chloroformum; Chloroformum pro Narcosi; Cloroformo. Trichloromethane.

$CHCl_3$ = 119.4.
CAS — 67-66-3.
ATC — N01AB02.
ATC Vet — QN01AB02.

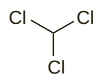

Pharmacopoeias. In *Br.*, *Chin.*, and *Viet.*
BP 2008 (Chloroform). A colourless volatile liquid with a characteristic odour. Not more than 5.0% v/v distils below 60° and the remainder distils at 60° to 62°. It contains 1.0 to 2.0% v/v of ethyl alcohol; amylene 50 micrograms/mL is permitted as an alternative to ethyl alcohol.
Slightly soluble in water; miscible with dehydrated alcohol, with ether, with fixed and volatile oils, and with most other organic solvents. Store in containers with glass stoppers or other suitable closures. Protect from light. The label should state whether it contains ethyl alcohol or amylene.

Stability. The addition of a small percentage of alcohol greatly retards the gradual oxidation that occurs when chloroform is exposed to air and light, and which results in its becoming contaminated with the very poisonous carbonyl chloride (phosgene) and with chlorine; the alcohol also serves to decompose any carbonyl chloride that may have been formed.

From a study[1] of chloroform losses from chloroform water and from 6 typical BPC mixtures under various conditions of storage the following shelf-lives were recommended: chloroform solutions and non-sedimented mixtures could be stored in well-closed well-filled containers for 2 months at ambient temperatures; when stored in partially-filled containers and periodically opened the shelf-life should not exceed 2 weeks; sedimented mixtures could be stored for 2 months in well-closed well-filled containers, but because loss of chloroform could be expected in containers periodically opened such mixtures should be prepared as required or packed in their final containers; for chloroform-containing mixtures in the home a shelf-life of 2 weeks was suggested.

1. Lynch M, *et al*. Chloroform as a preservative in aqueous systems: losses under "in-use" conditions and antimicrobial effectiveness. *Pharm J* 1977; **219:** 507–10.

Storage. It has been recommended[1] that if the period of use would exceed 6 weeks, PVC bottles should not be used for storing or dispensing: Chloroform and Morphine Tincture, or aqueous mixtures containing more than 5% thereof; mixtures or dispersions in which chloroform is present in excess of its aqueous solubility; aqueous mixtures containing chloroform and high concentrations of electrolytes; or of mixtures containing chloroform water.

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Adverse Effects and Precautions

Chloroform depresses respiration and produces hypotension. Cardiac output is reduced and arrhythmias may develop. Poisoning can lead to respiratory depression and cardiac arrest. Delayed hepatotoxic and nephrotoxic reactions have occurred 6 to 24 hours after a dose; symptoms may include abdominal pain, vomiting, and, at a later stage, jaundice.

Liquid chloroform is irritant to the skin and mucous membranes and may cause burns if spilt on them. Suitable precautions should be taken to avoid skin contact with chloroform as it can penetrate skin and produce systemic toxicity. Chloroform is not flammable. Care should be taken not to vaporise chloroform in the presence of a flame because of the production of toxic gases.

In the UK medicinal products are limited to a chloroform content of not more than 0.5% (w/w or v/v as appropriate) of chloroform. Exceptions include supply by a doctor or dentist, or in accordance with his prescription, to a particular patient, and supply for anaesthetic purposes.

In the USA the FDA has banned the use of chloroform in medicines and cosmetics, because of reported carcinogenicity in *animals*. It has also been withdrawn from systemic use in other countries.

The sale within or import into England and Wales and Scotland of food containing any added chloroform is prohibited.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving chloroform, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. Chloroform has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Uses and Administration

Chloroform is a volatile halogenated anaesthetic that was used by inhalation, but safer drugs are now preferred in general anaesthesia.

Chloroform is used as a carminative and as a flavouring agent and preservative. For these purposes it is usually employed as Chloroform Spirit (BP 2008) or Double-strength Chloroform Water (BP 2008) but doubts have been cast on the safety of the long-term use of chloroform in mixtures.

Externally, chloroform has a rubefacient action.

Chloroform is also used as a solvent.

Anaesthesia. An historical review of the use of chloroform in clinical anaesthesia.[1]

1. Payne JP. Chloroform in clinical anaesthesia. *Br J Anaesth* 1981; **53:** 11S–15S.

Preparations

BP 2008: Chloroform and Morphine Tincture; Chloroform Spirit; Double-strength Chloroform Water.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Dentophar; ***Rus.:*** Eludril (Элюдрил); Espol (Эспол); ***S.Afr.:*** Diphenhydramine Expectorant Syrup; Mrs Johnsons American Soothing Syrup; SB Toothache Drops; Tandpyndruppels; Vicks Acta Plus; ***Venez.:*** Fiometil†; Gamasol†; Iodex†; Rubefric†.

Cyclopropane *(rINN)*

Ciclopropano; Cyclopropanum; Trimethylene.

Циклопропан

C_3H_6 = 42.08.
CAS — 75-19-4.

Pharmacopoeias. In *US.*
USP 31 (Cyclopropane). A colourless highly flammable gas with a characteristic odour and pungent taste. Freely soluble in alcohol; soluble in fixed oils. One volume dissolves in about 2.7 volumes of water at 15°.

Stability. CAUTION. Mixtures of cyclopropane with oxygen or air at certain concentrations are explosive. Cyclopropane should not be used in the presence of an open flame or of any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage and supply. Cyclopropane is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Adverse Effects and Precautions

Cyclopropane depresses respiration to a greater extent than many other anaesthetics. Laryngospasm, cardiac arrhythmias, or hepatic injury may occur. Cyclopropane increases the sensitivity of the heart to sympathomimetic amines. Malignant hyperthermia has also been reported. Postoperative nausea, vomiting, and headache are frequent.

Cyclopropane should be used with caution in patients with bronchial asthma and cardiovascular disorders. Premedication with atropine may be advisable to reduce vagal tone.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Abuse. Two of 4 deaths from abuse of volatile anaesthetics in operating rooms were attributed to cyclopropane.[1]

1. Bass M. Abuse of inhalation anesthetics. *JAMA* 1984; **251:** 604.

Malignant hyperthermia. Malignant hyperthermia was associated with cyclopropane.[1]

1. Lips FJ, *et al*. Malignant hyperthermia triggered by cyclopropane during cesarean section. *Anesthesiology* 1982; **56:** 144–6.

Interactions

Care is advised if adrenaline or other sympathomimetics are given during cyclopropane anaesthesia. Potentiation of competitive neuromuscular blockers occurs after use of cyclopropane.

See also Interactions for General Anaesthetics, p.1779.

Uses and Administration

Cyclopropane is an anaesthetic that has been given by inhalation for analgesia and induction and maintenance of general anaesthesia. It produces skeletal muscle relaxation, is non-irritant, and induction and recovery are rapid, but it is difficult to use and handle and other anaesthetics are generally preferred. Because of the risk of explosion, it has usually been given by means of a closed circuit. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 9.2%.

Desflurane *(USAN, rINN)*

Desfluraani; Desfluran; Desflurano; Desfluranum; I-653. (±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether.

Десфлуран

$C_3H_2F_6O$ = 168.0.
CAS — 57041-67-5.
ATC — N01AB07.
ATC Vet — QN01AB07.

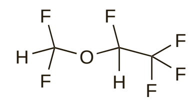

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Desflurane). A clear, colourless, mobile, heavy liquid. B.p. about 22°. Practically insoluble in water; miscible with anhydrous alcohol. Store in a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10°.
USP 31 (Desflurane). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Replace cap securely after each use. Protect from light.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias may occur. Desflurane may rarely precipitate malignant hyperthermia in susceptible individuals. It appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Nausea and vomiting have been reported in the postoperative period.

Desflurane is irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation, and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with desflurane. Desflurane may increase CSF pressure and should therefore be used with caution in patients with, or at risk from, raised intracranial pressure.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as desflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p.1779.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. A review[1] of *animal* and human studies concluded that the cardiorespiratory effects of desflurane were similar to those of isoflurane but that there might be better control of arterial pressure with desflurane during stressful stimuli. A study[2] in patients undergoing coronary artery bypass surgery showed that a state of haemodynamic stability suitable for patients at risk of myocardial ischaemia could be maintained when desflurane was used with the opioid analgesic fentanyl.

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesth Analg* 1992; **75:** S17–S31.
2. Parsons RS, *et al*. Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; **72:** 430–8.

Effects on the liver. Although considered to be less hepatotoxic than some other halogenated anaesthetics (see under Adverse Effects of Halothane, p.1784), delayed hepatotoxicity has occurred in a 65-year-old woman after maintenance anaesthesia involving desflurane.[1] She had received halothane on two previous occasions which may have caused sensitisation. Investigation of hepatocellular integrity (by measuring glutathione transferase alpha) in 30 women given desflurane indicated a mild subclinical disturbance.[2]

1. Martin JL, *et al.* Hepatotoxicity after desflurane anesthesia. *Anesthesiology* 1995; **83:** 1125–9.
2. Tiainen P, *et al.* Changes in hepatocellular integrity during and after desflurane or isoflurane anaesthesia in patients undergoing breast surgery. *Br J Anaesth* 1998; **80:** 87–9.

Effects on the respiratory tract. The irritant effect of desflurane on the lungs limits its role in the induction of anaesthesia, especially in children. Pre-operative use of nebulised lidocaine 4% failed to alleviate the response[1] although pretreatment with intravenous opioids may reduce the irritation.[2]

1. Bunting HE, *et al.* Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; **75:** 631–3.
2. Kong CF, *et al.* Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85:** 364–7.

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by desflurane (see p.1904). Lower doses of desflurane are required in those receiving opioids, benzodiazepines or other sedatives. Care is advised if adrenaline or other sympathomimetics are given to patients during desflurane anaesthesia.

See also Interactions of General Anaesthetics, p.1779.

◊ References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Desflurane has a low blood/gas partition coefficient and on inhalation its absorption, distribution, and elimination are reported to be more rapid than for other halogenated anaesthetics such as isoflurane or halothane. It is excreted mainly unchanged through the lungs. A small amount diffuses through the skin. About 0.02% of inhaled desflurane is metabolised in the liver and trichloroacetic acid has been detected in the serum and urine of patients given desflurane.

◊ References.

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Eger EI. Physicochemical properties and pharmacodynamics of desflurane. *Anaesthesia* 1995; **50** (suppl): 3–8.
3. Wissing H, *et al.* Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; **84:** 443–9.
4. Lu CC, *et al.* Pharmacokinetics of desflurane uptake into the brain and body. *Anaesthesia* 2004; **59:** 216–21.

Uses and Administration

Desflurane is a volatile halogenated anaesthetic administered by inhalation. It is structurally similar to isoflurane and has anaesthetic actions similar to those of halothane (p.1785). The minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranges from about 6% in the elderly to about 11% in infants. It is non-flammable and non-explosive in clinical concentrations but, because of its low boiling-point, it must be delivered by a special vaporiser, preferably within a closed circuit system.

Desflurane is used for induction and maintenance of general anaesthesia (p.1780), but because of its pungency is not recommended for induction in children. Concentrations of 4 to 11% v/v have been used for induction and usually produce surgical anaesthesia in 2 to 4 minutes. Concentrations of 2 to 6% v/v with nitrous oxide or 2.5 to 8.5% v/v in oxygen or oxygen-enriched air may be used to maintain anaesthesia. Higher concentrations of desflurane have been used but it is important to ensure adequate oxygenation; concentrations in excess of 17% v/v are not recommended. For concentrations used in patients with hepatic or renal impairment, see below.

As with other volatile halogenated anaesthetics supplemental neuromuscular blockers may be required. Recovery from anaesthesia is reported to be more rapid than with other halogenated anaesthetics.

Administration in hepatic or renal impairment. Desflurane concentrations of 1 to 4% v/v in oxygen and nitrous oxide have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery.

Anaesthesia. The characteristics of desflurane have been discussed in a number of reviews.[1-6] Its advantages are considered to include rapid induction and emergence from anaesthesia, and minimal metabolism makes end-organ toxicity unlikely. Emergence from anaesthesia and recovery of psychomotor and cognitive skills with desflurane is more rapid than after anaesthesia with other halogenated volatile anaesthetics such as isoflurane and possibly than after the intravenous anaesthetic propofol. This is considered to be of particular advantage for outpatient treatment, but studies so far have found no difference in time to discharge with desflurane or other general anaesthetics. Furthermore, the incidence of nausea and vomiting with desflurane is significantly greater than after the use of propofol. Desflurane's pungency may also limit its use for induction especially in children, although it is suitable for maintenance in this group and may be particularly suitable for neonates.[4]

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Patel SS, Goa KL. Desflurane: a review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia. *Drugs* 1995; **50:** 742–67.
3. Young CJ, Apfelbaum JL. Inhalational anesthetics: desflurane and sevoflurane. *J Clin Anesth* 1995; **7:** 564–77.
4. Hatch DJ. New inhalation agents in paediatric anaesthesia. *Br J Anaesth* 1999; **83:** 42–9.
5. Umbrain V, *et al.* Desflurane: a reappraisal. *Acta Anaesthesiol Belg* 2002; **53:** 187–91.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

Status epilepticus. For mention of the use of desflurane in the management of refractory status epilepticus, see p.469.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Suprane; ***Austral.:*** Suprane; ***Austria:*** Suprane; ***Canad.:*** Suprane; ***Cz.:*** Suprane; ***Denm.:*** Suprane; ***Fin.:*** Suprane; ***Ger.:*** Suprane; ***Gr.:*** Suprane; ***Hong Kong:*** Suprane; ***Hung.:*** Suprane; ***Indon.:*** Suprane; ***Israel:*** Sulorane; ***Ital.:*** Suprane; ***Malaysia:*** Suprane; ***Mex.:*** Suprane†; ***Neth.:*** Suprane; ***NZ:*** Suprane; ***Philipp.:*** Suprane; ***Pol.:*** Suprane; ***Port.:*** Suprane; ***S.Afr.:*** Suprane; ***Spain:*** Suprane; ***Swed.:*** Suprane; ***Switz.:*** Suprane; ***Thai.:*** Suprane; ***UK:*** Suprane; ***USA:*** Suprane; ***Venez.:*** Suprane†.

Enflurane *(BAN, USAN, rINN)*

Anaesthetic Compound No. 347; Compound 347; Enfluraani; Enfluran; Enflurano; Enfluranum; Methylflurether; NSC-115944. 2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane.

Энфлуран

$C_3H_2ClF_5O$ = 184.5.

CAS — 13838-16-9.

ATC — N01AB04.

ATC Vet — QN01AB04.

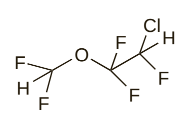

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Enflurane). A clear colourless volatile liquid having a mild sweet odour. Non-flammable. Distilling range 55.5° to 57.5°. Slightly soluble in water; miscible with organic solvents, with fats, and with oils. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias have been reported although the incidence of arrhythmias is lower with enflurane than with halothane. It sensitises the myocardium to sympathomimetics to a lesser extent than halothane. Compared with halothane, enflurane has a stimulant effect on the CNS and convulsions may occur when concentrations of enflurane are high or hypocapnia is present. Malignant hyperthermia has also been reported. Asthma and bronchospasm may occur. There have been reports of elevated serum-fluoride concentrations although resulting renal damage appears to be rare. There have been changes in measurements of hepatic enzymes and a number of reports of liver damage. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on the blood. The development of carboxyhaemoglobinaemia in patients anaesthetised with volatile anaesthetics is discussed under Precautions, below.

Effects on the kidneys. The nephrotoxicity of volatile anaesthetics has been reviewed.[1] Although enflurane released inorganic fluoride it appeared to be safe in patients with normal renal function. It had also been given to patients with mild to moderate renal impairment without any further deterioration. There was an increase in serum-fluoride concentrations when enflurane was given to a group of patients who had been receiving isoniazid, but there was no change in kidney function. Pretreatment of patients with a single dose of disulfiram before anaesthesia was found to produce a consistent and almost complete inhibition of enflurane metabolism as shown by substantial reductions in plasma-fluoride concentrations and urinary excretion of fluoride.[2]

1. Mazze RI. Nephrotoxicity of fluorinated anaesthetic agents. *Clin Anaesthesiol* 1983; **1:** 469–83.
2. Kharasch ED, *et al.* Clinical enflurane metabolism by cytochrome P450 2E1. *Clin Pharmacol Ther* 1994; **55:** 434–40.

Effects on the liver. A review[1] of 58 cases of suspected enflurane hepatitis considered enflurane to be the likely cause of the liver damage in 24. There was biochemical evidence of liver damage in 23 of these cases. Histology reports were available for 15 patients and all showed some degree of hepatocellular necrosis and degeneration.

While the incidence of liver damage from enflurane seemed to be lower than from halothane, the character of the injury was similar.

Another review[2] of the same cases plus an additional 30 (88 in all) came to different conclusions; the main author was a consultant to the manufacturer of enflurane. Of the 88 patients with suspected enflurane hepatitis, 30 were rejected because of insufficient evidence and 43 were considered to have other factors known to produce liver injury. This left 15 possible cases of enflurane hepatitis compared with the 24 identified by the first review. While agreeing that in the rare patient unexplained liver damage follows enflurane anaesthesia, it was considered that the incidence was too small to suggest an association. No consistent histological pattern was identified in this study.

See also under Adverse Effects in Halothane, p.1784.

1. Lewis JH, *et al.* Enflurane hepatotoxicity: a clinicopathologic study of 24 cases. *Ann Intern Med* 1983; **98:** 984–92.
2. Eger EI, *et al.* Is enflurane hepatotoxic? *Anesth Analg* 1986; **65:** 21–30.

Effects on respiration. Overall, enflurane is considered to produce more respiratory depression than halothane or isoflurane.[1,2]

1. Quail AW. Modern inhalation anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Merrett KL, Jones RM. Inhalational anaesthetic agents. *Br J Hosp Med* 1994; **52:** 260–3.

Precautions

Enflurane should be used with caution in patients with convulsive disorders. High concentrations of enflurane may cause uterine relaxation. In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as enflurane.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with enflurane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. Report[1] of a fatality in a 29-year-old student nurse anaesthetist who had applied enflurane to the herpes simplex lesions of her lower lip. She was found with an empty 250 mL bottle of enflurane.

1. Lingenfelter RW. Fatal misuse of enflurane. *Anesthesiology* 1981; **55:** 603.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Porphyria. Enflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during enflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by enflurane (see p.1904).

See also Interactions of General Anaesthetics, p.1779.

Antibacterials. For the effects of *isoniazid* on enflurane defluorination, see Effects on the Kidneys under Adverse Effects, above.

Antidepressants. It appeared likely that the enflurane-induced seizure activity seen in 2 patients could have been enhanced by *amitriptyline*.[1] It may be advisable to avoid the use of enflurane in patients requiring tricyclic antidepressants, especially when the patient has a history of seizures or when hyperventilation or high enflurane concentrations are a desired part of the anaesthetic technique.

1. Sprague DH, Wolf S. Enflurane seizures in patients taking amitriptyline. *Anesth Analg* 1982; **61:** 67–8.

Disulfiram. For the effect of disulfiram on the metabolism of enflurane, see Effects on the Kidneys under Adverse Effects, above.

Pharmacokinetics

Enflurane is absorbed on inhalation. The blood/gas partition coefficient is low. It is mostly excreted unchanged through the lungs. Up to 10% of inhaled administered enflurane is metabolised in the liver, mainly to inorganic fluoride.

◊ References.

1. Bengtson JP, *et al.* Uptake of enflurane and isoflurane during spontaneous and controlled ventilation. *Anaesth Intensive Care* 1992; **20:** 191–5.
2. Devchand D, *et al.* The uptake of enflurane during anaesthesia. *Anaesthesia* 1995; **50:** 491–5.

Uses and Administration

Enflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of isoflurane. It has anaesthetic actions similar to those of halothane (p.1785). Enflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.7% in middle age to 2.5% in children. Enflurane is given using a calibrated vaporiser for induction and maintenance of general anaesthesia (p.1780); it is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures (below).

To avoid CNS excitement a short-acting barbiturate or other intravenous induction agent is recommended before the inhalation of enflurane. Anaesthesia may be induced using enflurane alone with oxygen or in nitrous oxide-oxygen mixtures. In general, enflurane concentrations of 2 to 4.5% v/v produce surgical anaesthesia in 7 to 10 minutes. Anaesthesia may be maintained with a concentration of 0.5 to 3% v/v of enflurane; a concentration of 3% v/v should not be exceeded during spontaneous respiration. Although enflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Postoperative analgesia may be necessary.

Concentrations of 0.25 to 1% v/v of enflurane are used to provide analgesia for vaginal delivery during childbirth and of 0.5 to 1% v/v to supplement other general anaesthetics during caesarean section.

Pain. Enflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures although a study[1] was unable to confirm that it had an analgesic effect at subanaesthetic concentrations.

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Enforan; Inhelthran†; ***Austral.:*** Ethrane†; ***Austria:*** Ethrane; ***Braz.:*** Enfluthane; Etrane; ***Denm.:*** Efrane†; ***Fin.:*** Efrane†; ***Ger.:*** Ethrane†; ***Indon.:*** Ethrane; ***Irl.:*** Ethrane; ***Israel:*** Alyrane; Ethrane; ***Ital.:*** Ethrane†; ***Mex.:*** Enfran; Ethrane; ***Neth.:*** Ethrane†; ***NZ:*** Ethrane†; ***Philipp.:*** Alyrane; Ethrane; ***Rus.:*** Ethrane (Этран)†; ***S.Afr.:*** Ethrane; ***Swed.:*** Efrane†; ***Switz.:*** Ethrane†; ***Turk.:*** Ethrane; ***UK:*** Alyrane†; ***USA:*** Ethrane; ***Venez.:*** Ethrane.

Anaesthetic Ether

Aether ad Narcosin; Aether anaesthetícus; Aether pro Narcosi; Aether Purissimus; Altatáshoz való éter; Anestesiaeetteri, narkoosieetteri; Anestetinis eteris; Diethyl Ether; Éter anestésico; Eter do nakozy; Eter etylowy; Éter Puríssimo; Ether; Ether Anesthesicus; Éther anesthésique; Ether Anestheticus; Ether Ethylicus; Ether Ethylicus pro Narcosi; Ether k narkóze; Ethyl Ether; Narkoseter.

$(C_2H_5)_2O$ = 74.12.
CAS — 60-29-7.
ATC — N01AA01.
ATC Vet — QN01AA01.

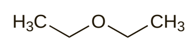

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of anaesthetic ether:
Sweet Vitriol.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Ether, Anaesthetic). Diethyl ether to which an appropriate quantity of a non-volatile antoxidant may have been added. It contains not more than 2 g/litre of water. A clear, colourless, volatile, highly flammable, and very mobile liquid. Distillation range 34° to 35°.

Soluble 1 in 15 of water; miscible with alcohol and with fatty oils. Store at a temperature of 8° to 15° in airtight containers. Protect from light. Ether remaining in a partly used container may deteriorate rapidly. The label should state the name and concentration of any added non-volatile antoxidant.

USP 31 (Ether). It consists of 96 to 98% of $C_4H_{10}O$, the remainder consisting of alcohol and water. Ether for anaesthetic use contains not more than 0.2% of water. It is a colourless, mobile, highly flammable, highly volatile liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. Its vapour, when mixed with air and ignited, may explode. B.p. about 35°.

Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly-filled, airtight containers, remote from fire and at a temperature not exceeding 40°. Protect from light. Ether to be used for anaesthesia must be preserved in airtight containers of not more than 3 kg capacity and is not to be used for anaesthesia if it has been removed from the original container longer than 24 hours.

Labelling. The label should state that it is suitable for use as an anaesthetic.

Stability. Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage. The Pharmaceutical Society of Great Britain's Department of Pharmaceutical Sciences found that free ether, even in low concentrations, caused softening of PVC bottles and was associated with loss by permeation.[1]

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Adverse Effects

Ether has an irritant action on the mucous membrane of the respiratory tract; it stimulates salivation and increases bronchial secretion. Laryngeal spasm may occur. Ether causes vasodilatation which may lead to a severe fall in blood pressure and it reduces blood flow to the kidneys; it also increases capillary bleeding. The bleeding time is unchanged but the prothrombin time may be prolonged. Ether may cause malignant hyperthermia in certain individuals. Alterations in kidney and liver function have been reported. Convulsions occasionally occur. Hyperglycaemia due to gluconeogenesis has been noted.

Recovery is slow from prolonged ether anaesthesia and postoperative vomiting is common. Acute overdosage of ether is characterised by respiratory failure and cardiac arrest.

Dependence on ether or ether vapour has been reported. Prolonged contact with ether spilt on any tissue produces necrosis.

See also Adverse Effects of General Anaesthetics, p.1779.

Precautions

Ether anaesthesia is contra-indicated in patients with diabetes mellitus, impaired kidney function, raised CSF pressure, and severe liver disease. Its use is not advisable in hot and humid conditions in patients with fever, as convulsions are liable to occur, particularly in children and in patients who have been given atropine.

See also Precautions for General Anaesthetics, p.1779.

Interactions

Ether enhances the action of competitive neuromuscular blockers to a greater degree than most other anaesthetics. However, it does not potentiate the arrhythmogenic effect of sympathomimetics, including adrenaline, as much as other inhalational anaesthetics.

See also Interactions of General Anaesthetics, p.1779.

Uses and Administration

Ether is an anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 1.92%. Ether is still used in some countries for the induction and maintenance of general anaesthesia although it has been replaced in many other countries by the halogenated anaesthetics. It possesses a respiratory stimulant effect in all but the deepest planes of anaesthesia. Ether also possesses analgesic and muscle relaxant properties. Premedication with an antimuscarinic such as atropine is necessary to reduce salivary and bronchial secretions.

Solvent ether is described on p.2023.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Hoffmans Druppels.

Etomidate *(BAN, USAN, rINN)*

Etomidaatti; Etomidát; Etomidat; Etomidatas; Étomidate; Etomidato; Etomidatum; R-16659; R-26490 (etomidate sulfate). *R*-(+)-Ethyl 1-(α-methylbenzyl)imidazole-5-carboxylate.

Этомидат

$C_{14}H_{16}N_2O_2$ = 244.3.
CAS — 33125-97-2.
ATC — N01AX07.
ATC Vet — QN01AX07.

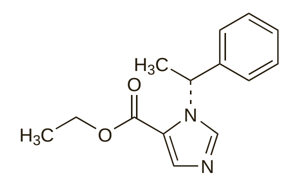

NOTE. Do not confuse with edetate; see Inappropriate Administration under Sodium Edetate, p.1464.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Etomidate). A white or almost white powder. M.p. about 68°. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Adverse Effects and Precautions

Excitatory phenomena (especially involuntary myoclonic muscle movements, which are sometimes severe) are common after injection of etomidate, but may be reduced by giving an opioid analgesic or a short-acting benzodiazepine beforehand. Pain on injection may be reduced by giving etomidate into a large vein in the arm rather than into the hand, or, again, by premedication with an opioid analgesic. Convulsions may occur rarely, as may laryngospasm and cardiac arrhythmias. Hypersensitivity reactions including anaphylaxis have been reported. Etomidate is associated with less hypotension than other drugs commonly used for induction.

Because etomidate inhibits adrenocortical function during maintenance anaesthesia (see below) its use is limited to induction of anaesthesia. In addition it should not be used in patients whose adrenocortical function is already reduced or at risk of being reduced.

Etomidate should be used with care in the elderly, who may be more prone to cardiac depression; lower doses may be required. The dose of etomidate should also be reduced in patients with hepatic cirrhosis. Caution may be appropriate in patients with pre-existing epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Effects on the endocrine system. Etomidate used for sedation in an intensive care unit was implicated in an increase in mortality.[1] The UK CSM agreed that etomidate could cause a significant fall in circulating plasma-cortisol concentrations, unresponsive to corticotropin stimulation.[2] As a result of this effect, use of etomidate is restricted to induction of anaesthesia. Licensed product information advises that the postoperative rise in serum-cortisol concentration, which has been observed after thiopental induction, is delayed for about 3 to 6 hours when etomidate is used for induction.

A study comparing the effects of etomidate with those of methohexital on the adrenocortical function of neonates borne by mothers who received these agents for induction of anaesthesia before caesarean section indicated that there was no evidence to preclude the use of etomidate in such patients. However, regardless of which anaesthetic agent was used, early feeding was recommended to avoid neonatal hypoglycaemia.[3]

1. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **i:** 1270.
2. Goldberg A. Etomidate. *Lancet* 1983; **ii:** 60.
3. Crozier TA, *et al.* Effects of etomidate on the adrenocortical and metabolic adaptation of the neonate. *Br J Anaesth* 1993; **70:** 47–53.

Hypersensitivity. Reactions involving immediate widespread cutaneous flushing or urticaria attributed to etomidate have been described.[1] There have also been reports[2,3] of anaphylactic reactions after injection of etomidate.

1. Watkins J. Etomidate: an 'immunologically safe' anaesthetic agent. *Anaesthesia* 1983; **38** (suppl): 34–8.
2. Sold M, Rothhammer A. Lebensbedrohliche anaphylaktoide reaktion nach etomidat. *Anaesthesist* 1985; **34:** 208–10.
3. Krumholz W, *et al.* Ein fall von anaphylaktoider reaktion nach gabe von etomidat. *Anaesthesist* 1984; **33:** 161–2.

Porphyria. Etomidate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

A reduced dose of etomidate may be necessary in patients who have received antipsychotics, sedatives, or opioids. The hypnotic effect of etomidate has been potentiated by other sedative drugs.

See also Interactions of General Anaesthetics, p.1779.

Calcium-channel blockers. Prolonged anaesthesia and Cheyne-Stokes respiration following etomidate injection has been reported in 2 patients also given *verapamil*.[1]

1. Moore CA, *et al.* Potentiation of etomidate anesthesia by verapamil: a report of two cases. *Hosp Pharm* 1989; **24:** 24–5.

General anaesthetics. For a report of synergy between *propofol* and etomidate, see p.1792.

Pharmacokinetics

After injection, etomidate is rapidly redistributed from the CNS to other body tissues, and undergoes rapid metabolism in the liver and plasma. Pharmacokinetics are complex and have been described by both 2- and 3-compartment models. Etomidate is about 76% bound to plasma proteins. It is mainly excreted in the urine, but some is excreted in the bile. It may cross the placenta and is distributed into breast milk.

◊ References.

1. Levron JC, Assoune P. Pharmacocinétique de l'étomidate. *Ann Fr Anesth Reanim* 1990; **9:** 123–6.
2. Sfez M, *et al.* Comparaison de la pharmacocinétique de l'étomidate chez l'enfant et chez l'adulte. *Ann Fr Anesth Reanim* 1990; **9:** 127–31.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.

Uses and Administration

Etomidate is an intravenous anaesthetic used for the induction of general anaesthesia (p.1780). Anaesthesia is rapidly induced and may last for 6 to 10 minutes with a single usual dose. Recovery is usually rapid without hangover effect. Etomidate has no analgesic activity.

For the induction of anaesthesia, etomidate is available as a conventional or an emulsion injection formulation. The usual dose is 300 micrograms/kg of etomidate given slowly, preferably into a large vein in the arm, although a lower dose of 150 micrograms/kg of the emulsion formulation may be sufficient. An initial dose of 150 to 200 micrograms/kg is recommended in the elderly, subsequently adjusted according to effects. Dosage should also be reduced in hepatic cirrhosis. Children may require up to 30% more than the usual adult dose of the emulsion formulation. Opioid analgesics or benzodiazepines as premedication reduce myoclonic muscle movements; opioids also reduce injection site pain. A neuromuscular blocker is necessary if intubation is required.

Administration in the elderly. A study[1] in elderly patients has demonstrated that although reducing the rate of intravenous injection of etomidate reduces the speed of induction, the dosage required is also reduced. Giving etomidate 0.2% solution at a rate of 10 mg/minute induced anaesthesia in a mean of 89.6 seconds and required a mean dose of 0.11 mg/kg. Corresponding values for a rate of 40 mg/minute were 47.7 seconds and 0.26 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Anaesthesia. Etomidate might be useful for induction if rapid tracheal intubation is required with a competitive neuromuscular blocker as it has been shown to reduce the time to onset of block with vecuronium.[1,2]

1. Gill RS, Scott RPF. Etomidate shortens the onset time of neuromuscular block. *Br J Anaesth* 1992; **69:** 444–6.
2. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 1997; **15:** 221–30.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used, but other anaesthetics including etomidate have also been tried[1] for intractable convulsive status epilepticus. However, like a number of other anaesthetics there have been reports of seizures associated with its use in anaesthesia,[2] especially in patients with epilepsy.

1. Yeoman P, *et al.* Etomidate infusions for the control of refractory status epilepticus. *Intensive Care Med* 1989; **15:** 255–9.
2. Nicoll K, Callender J. Etomidate-induced convulsion prior to electroconvulsive therapy. *Br J Psychiatry* 2000; **177:** 373.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Hypnomidate; ***Belg.:*** Hypnomidate; ***Braz.:*** Hypnomidate; ***Chile:*** Hypnomidate†; ***Cz.:*** Hypnomidate; ***Fr.:*** Hypnomidate; ***Ger.:*** Hypnomidate; ***Gr.:*** Hypnomidate; ***Mex.:*** Hypnomidate; ***Neth.:*** Hypnomidate; ***Pol.:*** Hypnomidate; ***Port.:*** Hypnomidato; ***S.Afr.:*** Hypnomidate; ***Spain:*** Hypnomidate; ***Turk.:*** Hypnomidate; ***UK:*** Hypnomidate; ***USA:*** Amidate.

Halothane *(BAN, rINN)*

Alotano; Halotaani; Halotán; Halotan; Halotanas; Halotano; Halothan; Halothanum; Phthorothanum. (*RS*)-2-Bromo-2-chloro-1,1,1-trifluoroethane.

Галотан

$CHBrCl.CF_3$ = 197.4.

CAS — 151-67-7.

ATC — N01AB01.

ATC Vet — QN01AB01.

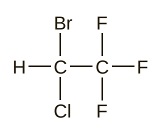

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Halothane). A clear, colourless, mobile, dense, non-flammable liquid. Distillation range 49° to 51°. Slightly soluble in water; miscible with dehydrated alcohol and with trichloroethylene. Halothane contains 0.01% w/w of thymol. Store at a temperature not greater than 25° in airtight containers. Protect from light.

USP 31 (Halothane). A colourless, mobile, non-flammable, heavy liquid having a characteristic odour resembling that of chloroform. It contains not less than 0.008% and not more than 0.012% of thymol, by weight, as a stabiliser. It should contain not more than 0.03% of water. Distillation range 49° to 51°.

Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not greater than 40°. Protect from light. Dispense only in the original container.

Incompatibility. In the presence of moisture, halothane reacts with many metals. Rubber and some plastics deteriorate when in contact with halothane vapour or liquid.

Stability. Halothane contains 0.01% w/w of thymol as a stabiliser; some commercial preparations may also contain up to 0.00025% w/w of ammonia. Thymol does not volatilise with halothane and therefore accumulates in the vaporiser. It may give a yellow colour to any remaining liquid; halothane that has discoloured should be discarded.

Adverse Effects

As with other halogenated anaesthetics, halothane has a depressant action on the cardiovascular system and reduces blood pressure; signs of overdosage are bradycardia and profound hypotension. It is also a respiratory depressant and can cause cardiac arrhythmias; there have been instances of cardiac arrest. The sensitivity of the heart to sympathomimetic amines is increased.

Adverse effects on the liver have limited its use in recent years (see below); these effects range from liver dysfunction to fatal hepatitis and necrosis and are more frequent following repeated use.

Halothane can produce nausea, vomiting, and shivering. Malignant hyperthermia has been reported.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on the cardiovascular system. The incidence of cardiac arrhythmias is higher with halothane than with enflurane or isoflurane; also the arrhythmogenic threshold with injected adrenaline is lower with halothane than isoflurane or enflurane.

Arrhythmias are considered to be very common in children anaesthetised with halothane and in the UK it is recommended that it should not be used for dental procedures outside hospital in those under 18 years old.

Effects on the kidneys. Renal failure has been reported after halothane anaesthesia,[1,2] sometimes with concurrent liver failure.[2]

1. Cotton JR, *et al.* Acute renal failure following halothane anesthesia. *Arch Pathol Lab Med* 1976; **100:** 628–9.
2. Gelman ML, Lichtenstein NS. Halothane-induced nephrotoxicity. *Urology* 1981; **17:** 323–7.

Effects on the liver. Liver damage has been recognised as an adverse effect of halothane for many years.[1-3] It may be severe, and associated with a high mortality.

Two types of hepatotoxicity are recognised; in **type I** there is a minor disturbance in liver function shown by increases in liver enzyme values; this may occur in up to 30% of patients given halothane,[4] or more if activity is measured by glutathione S-transferase rather than serum aminotransferase.[5] Subsequent re-exposure to halothane is not necessarily associated with liver damage.[2,6]

Type II hepatotoxicity, which is rarer, involves massive liver cell necrosis; reported incidences[2] range from 1 in 2500 to 1 in 36 000. Type II liver toxicity is characterised by several clinical features: non-specific gastrointestinal upset, delayed pyrexia, jaundice, eosinophilia, serum autoantibodies, rash, and arthralgia.[1,3] Biochemical tests of liver function show changes typical of hepatocellular damage; histological features are typified by centrilobular necrosis.[1] Several **risk factors** for development of serious toxicity have become apparent;[1-3] they include repeated exposure, previous adverse reactions to halothane (jaundice, pyrexia), female gender, obesity, middle age, genetic predisposition, enzyme induction, and a history of drug allergy.

The **causes** of halothane hepatotoxicity have been debated. Type I reactions may result from toxic products of halothane metabolism, possibly influenced by genetic factors or from an imbalance between hepatic oxygen supply and demand. Changes in cellular calcium homoeostasis may also be involved. Type II reactions are most likely immune-mediated.[1,2] It has been suggested[4] that metabolism of halothane produces a reactive metabolite which binds covalently to proteins in the endoplasmic reticulum of hepatocytes. In susceptible patients it is believed that these metabolite-modified proteins provoke an immune response which is responsible for the liver damage. Findings[7,8] have implicated the cytochrome P450 isoenzyme CYP2E1 as having a major role in the metabolism of halothane and patients with high levels of this isoenzyme may be predisposed to developing immune-medicated liver damage after halothane exposure.

The UK CSM,[9] after receiving 84 further reports of hepatotoxicity between 1978 and 1985, issued the following **guidelines** on **precautions** to be taken before using halothane:

- a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane
- repeated exposure to halothane within a period of at least 3 months should be avoided unless there are overriding clinical circumstances. An opinion has been expressed that the 3-month interval between exposures would be unlikely to prevent hepatotoxicity[2]
- a history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contra-indication to its future use in that patient

These guidelines were reiterated in 1997 after the CSM were notified of a further 15 cases of acute liver failure all requiring transplantation.[10]

The problem of patients sensitised to halothane who require **subsequent anaesthesia** with a volatile anaesthetic has been discussed.[4] Although the incidence of hepatotoxicity produced by *enflurane* appears to be less than with halothane it is of a similar nature and there have been reports of several patients who apparently had cross-sensitivity to both. Hepatotoxicity with *isoflurane* appears to be rare and it was suggested that for the majority of patients sensitised to halothane, isoflurane would be likely to be free from hepatotoxic effects. However, there has been a report[11] of a patient who had had two previous exposures to isoflurane and subsequently developed liver function abnormalities after receiving halothane. Hepatotoxicity with *desflurane* (see p.1781) might also be associated with sensitisation to halothane.

1. Ray DC, Drummond GB. Halothane hepatitis. *Br J Anaesth* 1991; **67:** 84–99.
2. Neuberger JM. Halothane and hepatitis: incidence, predisposing factors and exposure guidelines. *Drug Safety* 1990; **5:** 28–38.
3. Rosenak D, *et al.* Halothane and liver damage. *Postgrad Med J* 1989; **65:** 129–35.
4. Kenna JG, Neuberger JM. Immunopathogenesis and treatment of halothane hepatitis. *Clin Immunother* 1995; **3:** 108–24.

5. Allan LG, *et al.* Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; **i:** 771–4.
6. Neuberger J, Williams R. Halothane anaesthesia and liver damage. *BMJ* 1984; **289:** 1136–9.
7. Kharasch ED, *et al.* Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; **347:** 1367–71.
8. Kenna JC, *et al.* Formation of the C[F] CO-protein antigens implicated in the pathogenesis of halothane hepatitis is catalyzed in human liver microsomes in vitro by CYP 2E1. *Br J Clin Pharmacol* 1997; **43:** 209.
9. CSM. Halothane hepatotoxicity. *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
10. CSM/MCA. Safety issues in anaesthesia: reminder: hepatotoxicity with halothane. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)
11. Slayter KL, *et al.* Halothane hepatitis in a renal transplant patient previously exposed to isoflurane. *Ann Pharmacother* 1993; **27:** 101.

Precautions

The risk of halothane hepatitis led the UK CSM to issue guidelines on its use (see Effects on the Liver, under Adverse Effects, above). It is also recommended that patients be informed of any reactions and that this be done in addition to the updating of the patients' medical records.

It is recommended in the UK that halothane should not be used for dental procedures outside hospital in patients under 18 years old.

Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

Premedication with atropine has been recommended to reduce vagal tone and to prevent bradycardia and severe hypotension.

Allowance may need to be made for any increase in CSF pressure or in cerebral blood flow. Halothane should be used with caution in patients with phaeochromocytoma.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with halothane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. A brief review[1] of abuse of volatile anaesthetics found that of 14 patients who had ingested or sniffed halothane 10 had died. Another patient who had injected halothane intravenously also died. There has also been another report[2] of fatalities resulting from acute pulmonary oedema after intravenous injection of halothane.

1. Yamashita M, *et al.* Illicit use of modern volatile anaesthetics. *Can Anaesth Soc J* 1984; **31:** 76–9.
2. Berman P, Tattersal M. Self-poisoning with intravenous halothane. *Lancet* 1982; **i:** 340.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving halothane, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

Trace amounts of halothane have been detected in the breast milk of an anaesthetist exposed to environmental halothane in the operating theatre.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)
2. Coté CJ, *et al.* Trace concentrations of halothane in human breast milk. *Br J Anaesth* 1976; **48:** 541–3.

Porphyria. Halothane has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Adrenaline and most other sympathomimetics, and theophylline should be avoided during halothane anaesthesia since they can produce cardiac arrhythmias; the risk of arrhythmias is also increased if halothane is used in patients receiving dopaminergics. The effects of competitive neuromuscular blockers such as atracurium, and of ganglion blockers such as trimetaphan are enhanced by halothane and if required they should be given in reduced dosage. Morphine increases the depressant effects of halothane on respiration. Chlorpromazine also enhances the respiratory depressant effect of halothane. The effects of both ergometrine and oxytocin on the parturient uterus are diminished by halothane.

See also Interactions of General Anaesthetics, p.1779.

Antiepileptics. For a case of *phenytoin* intoxication associated with halothane anaesthesia, see p.497.

Benzodiazepines. *Midazolam* has been reported to potentiate the anaesthetic action of halothane.[1]

1. Inagaki Y, *et al.* Anesthetic interaction between midazolam and halothane in humans. *Anesth Analg* 1993; **76:** 613–17.

General anaesthetics. For a report that halothane increases serum concentrations of *propofol*, see p.1792.

Neuromuscular blockers. For the potentiation of the neuromuscular blockade of neuromuscular blockers such as *atracurium* by halothane, see p.1904. For increased toxicity during halothane anaesthesia, see *suxamethonium* p.1911.

Trichloroethane. A report[1] of 2 patients showing evidence of chronic cardiac toxicity after repeated exposure to trichloroethane. In both cases there was circumstantial evidence of a deterioration after routine anaesthetic use of halothane.

1. McLeod AA, *et al.* Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *BMJ* 1987; **294:** 727–9.

Xanthines. For references to increased cardiotoxicity when patients taking *theophylline* were anaesthetised with halothane, see p.1145.

Pharmacokinetics

Halothane is absorbed on inhalation. It has a relatively low solubility in blood and is more soluble in the neutral fats of adipose tissue than in the phospholipids of brain cells. Up to 80% of inhaled halothane is excreted unchanged through the lungs. Up to 20% is metabolised by the liver by oxidative and, under hypoxic conditions, reductive pathways. Urinary metabolites include trifluoroacetic acid and bromide and chloride salts (oxidative pathway) and fluoride salts (reductive pathway). Halothane diffuses across the placenta and has been detected in breast milk.

Uses and Administration

Halothane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 0.64% in the elderly to 1.08% in infants. It is non-flammable and is not explosive when mixed with oxygen at normal atmospheric pressure. It is not irritant to the skin and mucous membranes and does not produce necrosis when spilt on tissues. It suppresses salivary, bronchial, and gastric secretions and dilates the bronchioles. However, its use has diminished due to the risk of hepatotoxicity; in the UK, it is only available on a named-patient basis and in other countries, such as the USA, it has been withdrawn from the market.

Halothane is used for the induction and maintenance of general anaesthesia (p.1780) and is given using a calibrated vaporiser to provide close control over the concentration of inhaled vapour.

Anaesthesia may be induced with 2 to 4% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen; induction may also be started at a concentration of 0.5% v/v and increased gradually to the required level. For induction in children a concentration of 1.5 to 2% v/v has been used. It takes up to about 5 minutes to attain surgical anaesthesia and halothane produces little or no excitement in the induction period. The more usual practice is to induce anaesthesia with an intravenous agent. Anaesthesia is maintained with concentrations of 0.5 to 2% v/v depending on the flow rate used; the lower concentration is usually suitable for the elderly.

Adequate muscle relaxation is only achieved with deep anaesthesia so a neuromuscular blocker is given to increase muscular relaxation if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ineltano; ***Austral.:*** Fluothane; ***Austria:*** Fluothane†; ***Braz.:*** Fluothane; ***Chile:*** Fluothane†; ***Cz.:*** Narcotan; ***Fr.:*** Fluothane†; ***Ger.:*** Fluothane†; ***Gr.:*** Fluothane†; ***Hung.:*** Narcotan; ***India:*** Fluothane; ***Indon.:*** Fluothane; ***Israel:*** Fluothane†; ***Malaysia:*** Fluothane†; ***NZ:*** Fluothane; ***Pol.:*** Narcotan; ***S.Afr.:*** Fluothane†; ***Spain:*** Fluothane; ***Swed.:*** Fluothane†; ***Turk.:*** Fluothane; ***USA:*** Fluothane†.

Isoflurane *(BAN, USAN, rINN)*

Compound 469; Isofluraani; Isofluran; Isoflurano; Isofluranum; Izoflurán; Izofluran; Izofluranas. 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane.

Изофлуран

$C_3H_2ClF_5O$ = 184.5.

CAS — 26675-46-7.

ATC — N01AB06.

ATC Vet — QN01AB06.

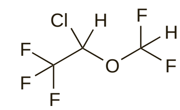

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Isoflurane). A clear, colourless, mobile, heavy liquid. B.p. about 48°. It is non-flammable. Practically insoluble in water; miscible with dehydrated alcohol and with trichloroethylene. Store in airtight containers. Protect from light.

USP 31 (Isoflurane). A clear, colourless, volatile liquid having a slight odour. B.p. about 49°. Insoluble in water; miscible with common organic solvents and with fats and oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, arrhythmias, and malignant hyperthermia have been reported; patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with isoflurane. Isoflurane differs from halothane and enflurane in that it produces less cardiac depression than either drug and heart rate may be increased. Also isoflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane and enflurane. The incidence of cardiac arrhythmias is lower with isoflurane than with halothane. Shivering, nausea, and vomiting have been reported in the postoperative period.

Induction with isoflurane is not as smooth as with halothane and this may be connected with its pungency; breath holding, coughing, and laryngospasm may occur. It has been reported to increase the cerebrospinal pressure and should be used with caution in patients with raised intracranial pressure. Isoflurane relaxes the uterine muscle; increased blood loss may occur after curettage or termination of pregnancy.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as isoflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p.1779.

◊ A comparison[1] of isoflurane and halothane for outpatient dental anaesthesia in children considered that isoflurane would produce fewer arrhythmias than halothane, but that the ease of induction and the quality of anaesthesia was inferior to that with halothane. Others[2] also found a higher incidence of coughing, salivation, and laryngospasm with isoflurane than halothane, but felt that it could be used as an alternative.

Further information on the adverse effects profile of isoflurane can be obtained from the report of and commentaries on an extensive multicentre study of patients undergoing anaesthesia with this agent.[3,4]

1. Cattermole RW, *et al.* Isoflurane and halothane for outpatient dental anaesthesia in children. *Br J Anaesth* 1986; **58:** 385–9.
2. McAteer PM, *et al.* Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *Br J Anaesth* 1986; **58:** 390–3.
3. Forrest JB, *et al.* A multi-centre clinical evaluation of isoflurane. *Can Anaesth Soc J* 1982; **29** (suppl): S1–S69.
4. Levy WJ. Clinical anaesthesia with isoflurane: a review of the multicentre study. *Br J Anaesth* 1984; **56:** 101S–112S.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. Committee on Safety of Medicines/Medicines Control Agency. Safety issues in anaesthesia: volatile anesthetic agents and carboxy-haemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. Isoflurane is considered to produce less cardiovascular depression than halothane. However, the results of a study[1] suggest that while this may be true for young patients, in elderly patients isoflurane appears to have a cardiac depressant effect similar to that of halothane.

1. McKinney MS, *et al.* Cardiovascular effects of isoflurane and halothane in young and elderly adult patients. *Br J Anaesth* 1993; **71:** 696–701.

CEREBRAL BLOOD FLOW. Autoregulation of cerebral blood flow appears to be impaired at higher concentrations of isoflurane. A study[1] in healthy subjects found that increasing isoflurane anaesthesia from a concentration of 1 to 2 MAC increased cerebral blood flow and reduced cerebral oxygen metabolism.

1. Olsen KS, *et al.* Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man. *Br J Anaesth* 1994; **72:** 66–71.

CORONARY CIRCULATION. Halothane, enflurane, and isoflurane decrease coronary perfusion pressure, coronary blood flow, ventricular function, and myocardial oxygen demand. Halothane and enflurane have a variable effect on coronary vascular resistance, but isoflurane dilates coronary vessels.[1] There has been concern over the potential of isoflurane to produce coronary steal and whether this effect is detrimental in patients with ischaemic heart disease.[2] However, despite conflicting results of individual studies[3-6] an early review[7] concluded that isoflurane could be used safely even in high-risk patients with coronary artery disease provided that blood pressure and heart rate were maintained close to baseline concentrations. A subsequent review[8] considered that more recent evidence supported the use of isoflurane as the anaesthetic agent of choice in patients with coronary heart disease.

1. Quail AW. Modern inhalational anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Stoelting RK. Anesthesiology. *JAMA* 1991; **265:** 3103–5.
3. Buffington CW, *et al.* The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the coronary artery surgery study registry. *Anesthesiology* 1988; **69:** 721–7.
4. Inoue K, *et al.* Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. *Anesth Analg* 1990; **71:** 469–74.
5. Slogoff S, *et al.* Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. *Anesth Analg* 1991; **72:** 22–7.
6. Stühmeier KD, *et al.* Isoflurane does not increase the incidence of intraoperative myocardial ischaemia compared with halothane during vascular surgery. *Br J Anaesth* 1992; **69:** 602–6.
7. Hogue CW, *et al.* Anesthetic-induced myocardial ischemia: the isoflurane-coronary steal controversy. *Coron Artery Dis* 1993; **4:** 413–19.
8. Agnew NM, *et al.* Isoflurane and coronary heart disease. *Anaesthesia* 2002; **57:** 338–47.

Effects on the kidneys. See under Metabolism in Pharmacokinetics, below.

Effects on the liver. Of 45 cases of isoflurane-associated hepatotoxicity reported to the FDA between 1981 and 1984 there was some other cause for the liver damage in 29. While isoflurane might have been one of the causes of the damage in the other 16 cases, there was not a reasonable likelihood of an association between isoflurane and postoperative liver impairment.[1] Subsequent rare cases of hepatotoxicity,[2-7] sometimes fatal,[2,5,7] have suggested that isoflurane may induce hepatitis, though much less frequently than halothane, and that there may be cross-sensitisation with other halogenated anaesthetics.

See also under the Adverse Effects of Halothane, p.1784.

1. Stoelting RK, *et al.* Hepatic dysfunction after isoflurane anesthesia. *Anesth Analg* 1987; **66:** 147–53.
2. Carrigan TW, Straughen WJ. A report of hepatic necrosis and death following isoflurane anesthesia. *Anesthesiology* 1987; **67:** 581–3.
3. Sinha A, *et al.* Isoflurane hepatotoxicity: a case report and review of the literature. *Am J Gastroenterol* 1996; **91:** 2406–9.
4. Hasan F. Isoflurane hepatotoxicity in a patient with a previous history of halothane-induced hepatitis. *Hepatogastroenterology* 1998; **45:** 518–22.
5. Turner GB, *et al.* Fatal hepatotoxicity after re-exposure to isoflurane: a case report and review of the literature. *Eur J Gastroenterol Hepatol* 2000; **12:** 955–9.
6. Malnick SDH, *et al.* Acute cholestatic hepatitis after exposure to isoflurane. *Ann Pharmacother* 2002; **36:** 261–3.
7. Ihtiyar E, *et al.* Fatal isoflurane hepatotoxicity without re-exposure. *Indian J Gastroenterol* 2006; **25:** 41–2.

Effects on the nervous system. Seizures associated with induction of anaesthesia with isoflurane have been reported in patients without known neurological abnormalities and not undergoing neurosurgery.[1,2] However, data from a retrospective analysis of patients undergoing intracranial surgery indicated that when convulsions occurred postoperatively in these conditions, it was the neurosurgical procedures rather than the anaesthetics that were responsible.[3]

See also under Status Epilepticus in Uses, below.

1. Poulton TJ, Ellingson RJ. Seizure associated with induction of anesthesia with isoflurane. *Anesthesiology* 1984; **61:** 471–6.
2. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg* 1985; **64:** 367–8.
3. Christys AR, *et al.* Retrospective study of early postoperative convulsions after intracranial surgery with isoflurane or enflurane anaesthesia. *Br J Anaesth* 1989; **62:** 624–7.

Effects on the respiratory tract. A study[1] conducted mainly in adults found that humidification of anaesthetic mixtures containing isoflurane could reduce respiratory complications such as coughing, laryngospasm, and breath-holding that were usually associated with the use of isoflurane for induction. However, a similar study[2] in children failed to confirm these findings.

1. van Heerden PV, *et al.* Effect of humidification on inhalation induction with isoflurane. *Br J Anaesth* 1990; **64:** 235–7.
2. McAuliffe GL, *et al.* Effect of humidification on inhalation induction with isoflurane in children. *Br J Anaesth* 1994; **73:** 587–9.

Effects on the skin. There have been rare reports of contact dermatitis to isoflurane in anaesthetists.[1,2]

1. Caraffini S, *et al.* Isoflurane: an uncommon cause of occupational airborne contact dermatitis. *Contact Dermatitis* 1998; **38:** 286.
2. Muncaster A, *et al.* Allergic contact dermatitis to isoflurane. *Br J Dermatol* 1999; **141:** (suppl 55): 96–7.

Porphyria. Isoflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by isoflurane (see p.1904). Care is advised if adrenaline and other sympathomimetics are given during isoflurane anaesthesia.

See also Interactions of General Anaesthetics, p.1779.

General anaesthetics. For a report that isoflurane increases serum concentrations of *propofol*, see p.1792.

Pharmacokinetics

Isoflurane is absorbed on inhalation. The blood/gas partition coefficient is lower than that of enflurane or halothane. It is mostly excreted unchanged through the lungs. About 0.2% of inhaled isoflurane is metabolised, mainly to inorganic fluoride.

Metabolism. In 26 patients sedated with isoflurane for 24 hours, plasma fluoride ion concentration increased from a mean of 4.03 nanomol/mL to 13.57 nanomol/mL in 12 hours after stopping sedation.[1] These fluoride concentrations were considered to be too low to cause clinical renal dysfunction. In 30 patients sedated with isoflurane for up to 127 hours (mean duration was 36 hours), mean plasma fluoride ion concentration increased[2] to 20.01 nanomol/mL during sedation and continued rising for 16 hours after stopping isoflurane to a maximum mean concentration of 25.34 nanomol/mL; thereafter, levels gradually declined to normal values by the fifth day. Despite the increased plasma fluoride ion concentrations, no biochemical or clinical evidence of deterioration in renal function was found. Giving isoflurane for 34 days to a patient with tetanus who required sedation to facilitate mechanical ventilation resulted[3] in sustained fluoride ion concentrations of 50 nanomol/mL and a peak concentration of 87 nanomol/mL. Although such concentrations are considered to be potentially nephrotoxic no clinical effect on renal function was found.

1. Kong KL, *et al.* Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects. *Br J Anaesth* 1990; **64:** 159–62.
2. Spencer EM, *et al.* Plasma inorganic fluoride concentrations during and after prolonged (>24h) isoflurane sedation: effect on renal function. *Anesth Analg* 1991; **73:** 731–7.
3. Stevens JJWM, *et al.* Prolonged use of isoflurane in a patient with tetanus. *Br J Anaesth* 1993; **70:** 107–109.

Uses and Administration

Isoflurane is a volatile halogenated anaesthetic given by inhalation. It is an isomer of enflurane and has anaesthetic actions similar to those of halothane (p.1785). Isoflurane has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.05% in the elderly to 1.87% in infants. It is used in the induction and maintenance of general anaesthesia (p.1780) although induction is more often carried out using an intravenous anaesthetic. Isoflurane is also used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures.

Isoflurane is given using a calibrated vaporiser. If it is used for induction then it is given with oxygen or oxygen and nitrous oxide mixtures and induction should start with an isoflurane concentration of 0.5% v/v increased to 1.5 to 3% v/v which generally produces surgical anaesthesia within 10 minutes. Its pungency may limit the rate of induction. Anaesthesia may be maintained with a concentration of 1 to 2.5% v/v with oxygen and nitrous oxide mixtures; 1.5 to 3.5% v/v may be required if used only with oxygen. Isoflurane 0.5 to 0.75% v/v with oxygen and nitrous oxide mixtures is suitable to maintain anaesthesia for caesarean section. Although isoflurane is reported to possess muscle relaxant properties, neuromuscular blockers may nevertheless be required. Recovery is rapid.

Anaesthesia. *CAESAREAN SECTION.* Isoflurane 0.8% v/v has been found to be a suitable supplement to nitrous oxide-oxygen anaesthesia for patients undergoing caesarean section.[1] It has been suggested[2] that an overpressure technique might be of use to further reduce awareness in such patients. Giving isoflurane at a concentration of 2% v/v for 5 minutes followed by concentrations of 1.5% v/v for the next 5 minutes and 0.8% v/v thereafter produced higher arterial concentrations of isoflurane in patients undergoing caesarean section than when it was given at a concentration of 1% v/v throughout.[2]

1. Dwyer R, *et al.* Uptake of halothane and isoflurane by mother and baby during Caesarean section. *Br J Anaesth* 1995; **74:** 379–83.
2. McCrirrick A, *et al.* Overpressure isoflurane at Caesarean section: a study of arterial isoflurane concentrations. *Br J Anaesth* 1994; **72:** 122–4.

Pain. Isoflurane is used in subanaesthetic doses to provide analgesia in obstetrics and other painful procedures but studies[1,2] have been unable to confirm that it had an analgesic effect at subanaesthetic concentrations. The use of isoflurane 0.2 or 0.25% v/v in a mixture of nitrous oxide 50% v/v and oxygen 50% v/v has been studied.[3,4]

1. Tomi K, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70:** 684–6.
2. Roth D, *et al.* Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials. *Br J Anaesth* 1996; **76:** 38–42.
3. Wee MYK, *et al.* Isoflurane in labour. *Anaesthesia* 1993; **48:** 369–72.
4. Bryden FM, *et al.* Isoflurane for removal of chest drains after cardiac surgery. *Br J Anaesth* 1994; **73:** 712P–713P.

Sedation. *INTENSIVE CARE.* The various drugs used to provide sedation in intensive care are discussed on p.957. Isoflurane is not usually considered for such a purpose but in a comparative 24-hour study[1] in 60 patients requiring mechanical ventilation, isoflurane 0.1 to 0.6% v/v in an air-oxygen mixture produced satisfactory sedation for a greater proportion of time than did the continuous infusion of midazolam 10 to 200 micrograms/kg per hour. Patients given isoflurane also recovered more rapidly. Isoflurane has also been used successfully for sedation over 5 days in a 3-year-old infant who required ventilation for pneumonia, a complication of the child's myasthenia gravis.[2] However, there has been some concern over high plasma fluoride concentrations after prolonged use of isoflurane (see under Metabolism in Pharmacokinetics, above).

1. Kong KL, *et al.* Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989; **298:** 1277–80.
2. McBeth C, Watkins TGL. Isoflurane for sedation in a case of congenital myasthenia gravis. *Br J Anaesth* 1996; **77:** 672–4.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used. Despite rare reports of seizures associated with the use of isoflurane in anaesthetic procedures (see Effects on the Nervous System, above) it has been used successfully,[1-3] typically in concentrations of 0.5 to 1% v/v, to control refractory convulsive status epilepticus. Although some[4] consider that isoflurane-induced coma may be more easy to control than barbiturate-induced coma, the use of isoflurane may be limited by the need for special anaesthetic equipment and continuous EEG monitoring.

1. Meeke RI, *et al.* Isoflurane for the management of status epilepticus. *DICP Ann Pharmacother* 1989; **23:** 579–81.
2. Hilz MJ, *et al.* Isoflurane anaesthesia in the treatment of convulsive status epilepticus. *J Neurol* 1992; **239:** 135–7.
3. Mirsattari SM, *et al.* Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 2004; **61:** 1254–9.
4. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Forane; Zuflax; ***Austral.:*** AErrane; Forthane; ***Austria:*** Forane; ***Belg.:*** Forene†; ***Braz.:*** Forane; Isoforine; Isothane†; ***Canad.:*** Forane; ***Chile:*** Forene; ***Cz.:*** AErrane; Forane; ***Denm.:*** Forene; ***Fin.:*** Forene; ***Ger.:*** Forene; ***Gr.:*** Forenium; ***Hong Kong:*** Forane; ***Hung.:*** AErrane; Forane; ***Indon.:*** AErrane; Forane; ***Irl.:*** Forane; ***Israel:*** AErrane; Forane; ***Ital.:*** AErrane; Forane; ***Malaysia:*** Forane; ***Mex.:*** Forane; Lisorane†; Sofloran; ***Neth.:*** AErrane; Forene; ***Norw.:*** Forene; ***NZ:*** AErrane; Forane; ***Philipp.:*** AErrane; Forane; ***Pol.:*** AErrane; Forane; ***Port.:*** Forene; ***Rus.:*** Forane (Форан)†; ***S.Afr.:*** AErrane; Forane; ***Singapore:*** Forane; ***Spain:*** AErrane; Forane; ***Swed.:*** Forene; ***Switz.:*** Forene; ***Thai.:*** AErrane; Forane; ***Turk.:*** AErrane; Forane; ***UK:*** AErrane; ***USA:*** Forane; Terrell; ***Venez.:*** Forene.

Ketamine Hydrochloride

(BANM, USAN, rINNM)

CI-581; CL-369; CN-52372-2; Hidrocloruro de ketamina; Ketamiinihydrokloridi; Ketamin Hidroklorür; Kétamine, chlorhydrate de; Ketamin-hidroklorid; Ketamin-hydrochlorid; Ketaminhydroklorid; Ketamini hydrochloridum; Ketamino hidrochloridas; Ketaminy chlorowodorek. (±)-2-(2-Chlorophenyl)-2-methylaminocyclohexanone hydrochloride.

Кетамина Гидрохлорид

$C_{13}H_{16}ClNO,HCl = 274.2.$

CAS — 6740-88-1 (ketamine); 1867-66-9 (ketamine hydrochloride).

ATC — N01AX03.

ATC Vet — QN01AX03.

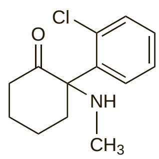

(ketamine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of ketamine:

Animal trank; Animal tranquilizer; Bump; Cat tranquilizer; Cat valium; Elephant tranquilizer; Green; Honey oil; Horse tranquilizer; Jet; Jet fuel; K; "K"; K wire; Kay Jay; K-blast; Keets; Keezy; Keller; Kellys day; Kenny; Ket; Keta; Ketaset; KFC; Kit kat; Kit-Kat; Kitty; KKK; Klarko K Kat; Klarky Kat; Kustard; Lady K; Naughty horsey; Old Man; Property of Sir John; Purple; Regretamine; Special K; Special "K"; Special la coke; Super acid; Super C; Super K; Tranquilizer; Triple K; Vetamine; Vitamin K; Wonky.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ketamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.1. Protect from light.

USP 31 (Ketamine Hydrochloride). A white crystalline powder having a slight characteristic odour. Soluble 1 in 4 of water, 1 in 14 of alcohol, 1 in 60 of dehydrated alcohol and of chloroform, and 1 in 6 of methyl alcohol; practically insoluble in ether. pH of a 10% solution in water is between 3.5 and 4.1. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Ketamine hydrochloride is incompatible with soluble barbiturates. The US licensed product information recommends that when use of diazepam and ketamine is required they should be given separately and not mixed in the same giving equipment.

Esketamine Hydrochloride *(BANM, rINNM)*

Esketamiinihydrokloridi; Eskétamine, Chlorhydrate d'; Eskétamine, chlorhydrate de; Esketamin-hydrochlorid; Esketaminhydroklorid; Esketamini hydrochloridum; Esketamino hidrochloridas; Hidrocloruro de esketamina; *S*-Ketamine Hydrochloride.

Эскетамина Гидрохлорид

CAS — 33643-46-8 (esketamine).

ATC — N01AX14.

ATC Vet — QN01AX14.

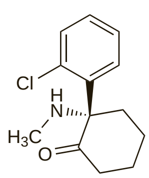

(esketamine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Esketamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 3.5 to 4.5. Protect from light.

Adverse Effects

Emergence reactions are common during recovery from ketamine anaesthesia and include vivid often unpleasant dreams, confusion, hallucinations, and irrational behaviour. Children and elderly patients appear to be less sensitive. Patients may also experience increased muscle tone, sometimes resembling seizures. Blood pressure and heart rate may be temporarily increased by ketamine; hypotension, arrhythmias, and bradycardia have occurred rarely.

Respiration may be depressed after rapid intravenous injection or with high doses. Apnoea and laryngospasm have occurred. Diplopia and nystagmus may occur. Nausea and vomiting, lachrymation, hypersalivation, and raised intra-ocular and CSF pressure have also been reported. Transient skin rashes and pain at the site of injection may occur.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on the cardiovascular system. Ketamine has been advocated by some for maintaining or increasing cardiovascular performance in selected patients during induction of anaesthesia as it may increase blood pressure and heart rate.[1] However, there have been reports of reduced cardiac and pulmonary performance in severely ill patients[1] and of arrhythmias.[2]

Some of the cardiovascular effects of ketamine may be attenuated by premedication with diazepam[2] or clonidine.[3]

1. Waxman K, *et al*. Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980; **59:** 355–8.
2. Cabbabe EB, Behbahani PM. Cardiovascular reactions associated with the use of ketamine and epinephrine in plastic surgery. *Ann Plast Surg* 1985; **15:** 50–2.
3. Tanaka M, Nishikawa T. Oral clonidine premedication attenuates the hypertensive response to ketamine. *Br J Anaesth* 1994; **73:** 758–62.

Effects on the liver. Changes in liver enzyme values have occurred after ketamine in an initial dose of 1 mg/kg followed by continuous infusion as a 0.1% solution.[1]

1. Dundee JW, *et al*. Changes in serum enzyme levels following ketamine infusions. *Anaesthesia* 1980; **35:** 12–16.

Effects on mental state. Mental disturbances following ketamine anaesthesia may vary in incidence from less than 5% to greater than 30%.[1] See also Abuse, below.

1. White PF, *et al.* Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* 1982; **56:** 119–36.

Effects on the skin. Harlequin-like colour skin changes were reported[1] in a 9-month-old boy during anaesthesia with ketamine 15 mg.

1. Wagner DL, Sewell AD. Harlequin color change in an infant during anesthesia. *Anesthesiology* 1985; **62:** 695.

Malignant hyperthermia. Malignant hyperthermia has been reported in a patient given ketamine.[1]

1. Rasore-Quartino A, *et al.* Forma atipica di ipertermia maligna: osservazione di un caso da ketamina. *Pathologica* 1985; **77:** 609–17.

Precautions

Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension or a history of cerebrovascular accident. Cardiac function should be monitored in patients found to have hypertension or cardiac decompensation. Ketamine should be used with caution in patients with elevated CSF pressure. It can raise intra-ocular pressure and should not be used in the presence of eye injury or increased intra-ocular pressure.

Ketamine does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant is used.

The use of ketamine should be avoided in patients prone to hallucinations or psychotic disorders. Verbal, tactile, and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.

See also Precautions for General Anaesthetics, p.1779.

Abuse. Health care workers in the USA were alerted to the dangers associated with the abuse of ketamine as long ago as 1979.[1] Similar concern had also been voiced in the UK[2] over the abuse of ketamine at social gatherings where it has been taken intranasally or orally. A WHO expert committee[3] considered in 2006 that the available information on ketamine was not sufficient to warrant international control. Studies in *animals* have shown that ketamine can produce dependence, however, reports of dependence in humans are limited (see below). Although tolerance may occur there is no evidence of a withdrawal syndrome (but see below). Ketamine abuse has been reported in a number of countries.

Ketamine produces a state of psychological dissociation resulting in hallucinations and out of body or near death experiences. It can induce a state of helplessness in which the user loses awareness of the environment and this together with severe loss of coordination and pronounced analgesia can put the user at great risk. Furthermore, some users experience a state in which they are unconcerned about whether they live or die. Ketamine has the potential for compulsive repeated use and there have been reports of users self-injecting ketamine several times a day for prolonged periods. Dependency may develop[4,5] and withdrawal symptoms requiring detoxification can occur.[4] Frequent use may produce long-lasting memory impairment.[6] Other adverse effects include a report[7] of an acute dystonic reaction in a 20-year old man following self-administration of ketamine intravenously.

In one case series[8] of 20 patients presenting to hospital after ketamine abuse the most common symptoms included anxiety, chest pain, and palpitations. Frequent complications included agitation and rhabdomyolysis. Symptoms were generally short lived with most patients discharged within 5 hours.

Some[2] suggest that patients seeking medical attention are best placed in a quiet darkened room to recover with diazepam being given for unresponsive panic attacks while others advocate that such patients should be admitted to an intensive care unit for close monitoring.[9] The use of intravenous fluids to prevent rhabdomyolysis has also been recommended.[8]

Long-term and frequent abuse of ketamine has been associated with adverse effects on the urinary tract.[10-12] Patients may present with symptoms of dysuria, frequency, urgency, urinary incontinence, suprapubic pain, and haematuria. Examination has shown in some cases a contracted shrunken bladder and ulcerative cystitis. Complications have included hydronephrosis and renal impairment.

Ketamine is tasteless, odourless, and colourless and has been misused to incapacitate the victim and produce amnesia in sexual assaults and drug-facilitated rape ('date rape').[4]

1. Anonymous. Ketamine abuse. *FDA Drug Bull* 1979; **9:** 24.
2. Jansen KLR. Non-medical use of ketamine. *BMJ* 1993; **306:** 601–2.
3. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)
4. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
5. Jansen KLR, Darracot-Cankovic R. The nonmedical use of ketamine, part two: A review of problem use and dependence. *J Psychoactive Drugs* 2001; **33:** 151–8.
6. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001; **96:** 749–60.
7. Felser JM, Orban DJ. Dystonic reaction after ketamine abuse. *Ann Emerg Med* 1982; **11:** 673–5.
8. Weiner AL, *et al.* Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* 2000; **18:** 447–51.
9. Gill PA. Non-medical use of ketamine. *BMJ* 1993; **306:** 1340.
10. Chu PSK, *et al.* 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007; **13:** 311–13.
11. Shahani R, *et al.* Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007; **69:** 810–12.
12. Cottrell AM, *et al.* Urinary tract disease associated with chronic ketamine use. *BMJ* 2008; **336:** 973.

Neurosurgery. Although the idea that ketamine should not be used in patients at risk from rises in intracranial pressure has limited its use in neurosurgical patients, a review[1] considered that if used with controlled ventilation and a GABA receptor agonist, and without nitrous oxide, it did not appear to have adverse effects in this group, and there was some evidence from *animal* studies that it might have neuroprotective properties.

1. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005; **101:** 524–34.

Interactions

Inhalational anaesthetics, such as ether and halothane, and other cerebral depressants may prolong the effect of ketamine and delay recovery. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with ketamine. It has been recommended that ketamine should not be used with ergometrine.

See also Interactions of General Anaesthetics, p.1779.

Neuromuscular blockers. For the enhancement of the effect of *tubocurarine* or *atracurium* by ketamine, see p.1904.

Thyroid drugs. For a reference to increased cardiovascular adverse effects with *levothyroxine*, see p.2173.

Xanthines. For a reference to seizures and tachycardia attributed to an interaction between ketamine and *theophylline*, see p.1145.

Pharmacokinetics

After intravenous boluses, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents ketamine's anaesthetic action, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite norketamine. Other metabolic pathways include hydroxylation of the cyclohexone ring and conjugation with glucuronic acid. The beta phase half-life is about 2.5 hours. Ketamine is excreted mainly in the urine as metabolites. It crosses the placenta.

◊ References.

1. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; **53:** 27–30.
2. Grant IS, *et al.* Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* 1981; **53:** 805–9.
3. Grant IS, *et al.* Ketamine disposition in children and adults. *Br J Anaesth* 1983; **55:** 1107–11. **14:** 144P.
4. Geisslinger G, *et al.* Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993; **70:** 666–71.
5. Malinovsky J-M, *et al.* Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; **77:** 203–7.

Uses and Administration

Ketamine is an anaesthetic given by intravenous injection, intravenous infusion, or intramuscular injection. It produces dissociative anaesthesia characterised by a trance-like state, amnesia, and marked analgesia which may persist into the recovery period. There is often an increase in muscle tone and the patient's eyes may remain open for all or part of the period of anaesthesia. Ketamine is used in general anaesthesia for diagnostic or short surgical operations that do not require skeletal muscle relaxation, for the induction of anaesthesia to be maintained with other drugs, and as a supplementary anaesthetic (see p.1780). It also has good analgesic properties in subanaesthetic doses. It is considered to be of particular value in children requiring frequent repeated anaesthesia. Recovery is relatively slow.

Ketamine is given as the hydrochloride but doses are expressed in terms of the equivalent amount of base; ketamine hydrochloride 1.15 mg is equivalent to about 1 mg of ketamine.

- For induction in adults and children the dose given by *intravenous injection* may range from the equivalent of 1 to 4.5 mg/kg of ketamine; a dose of 2 mg/kg given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds of the end of the injection and lasting for 5 to 10 minutes.
- The initial *intramuscular* dose may range from 6.5 to 13 mg/kg; an intramuscular dose of 10 mg/kg usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes. For diagnostic or other procedures not involving intense pain an initial intramuscular dose of 4 mg/kg has been used. Additional doses may be given for maintenance.
- For induction by *intravenous infusion* a total dose of 0.5 to 2 mg/kg is usually given at an appropriate infusion rate. Maintenance is achieved with 10 to 45 micrograms/kg per minute, the infusion rate being adjusted according to response.

Use should be preceded by atropine or another suitable antimuscarinic. Diazepam or another benzodiazepine may be given before surgery or as an adjunct to ketamine to reduce the incidence of emergence reactions.

The *S*-isomer, esketamine, is also given for similar uses in anaesthesia.

◊ Reviews.

1. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; **77:** 441–4.

Administration. Although ketamine hydrochloride is usually given intravenously or intramuscularly, oral[1,2] and rectal[3] dosage has been used successfully in children. Intranasal use of ketamine with midazolam in a neonate requiring anaesthesia has also been reported.[4] Unfortunately the onset of sedation with these three routes is too slow for emergency procedures and therefore a jet-injector of ketamine was developed[5] to provide non-traumatic, painless, and rapid anaesthesia in children. Intranasal and transdermal use may be useful in the management of pain (below); oral, rectal, and subcutaneous routes have also been tried.[6]

1. Tobias JD, *et al.* Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* 1992; **90:** 537–41.
2. Gutstein HB, *et al.* Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; **76:** 28–33.
3. Lökken P, *et al.* Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res* 1994; **102:** 274–80.
4. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
5. Zsigmond EK, *et al.* A new route, jet-injection for anesthetic induction in children—ketamine dose-range finding studies. *Int J Clin Pharmacol Ther* 1996; **34:** 84–8.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.

Nonketotic hyperglycinaemia. Ketamine was tried with strychnine in a newborn infant with severe nonketotic hyperglycinaemia (p.2393) and resulted in neurological improvement, although motor development remained unsatisfactory.[1] It was thought that ketamine might act by blocking N-methyl-D-aspartate (NMDA) receptors, which are activated in the CNS by glycine.

1. Tegtmeyer-Metadorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.

Pain. For a discussion of pain and its management, see p.2. Ketamine is used for its analgesic action in neuropathic or other pain unresponsive to conventional analgesics. (For mention of its use for outpatient procedures in children, see p.3.) Systematic reviews have found the evidence for such use to be limited,[1,2] and have also differed on its value for postoperative pain,[3-5] but it has been suggested[1] that ketamine is a reasonable third-line option for pain where standard analgesics have failed. Subcutaneous, intramuscular, intravenous, epidural, intrathecal, intranasal, transdermal, rectal, and oral routes have all been tried.[1,6]

1. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003; **97:** 1730–9.
2. Bell RF, *et al.* Ketamine as an adjuvant to opioids for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/06/05).
3. Elia N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* 2005; **113:** 61–70.
4. Bell RF, *et al.* Perioperative ketamine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
5. Subramaniam K, *et al.* Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; **99:** 482–95.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.

Status epilepticus. For the suggestion that ketamine may be tried in refractory status epilepticus, see p.469.

Preparations

BP 2008: Ketamine Injection;
USP 31: Ketamine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Cost; Inducmina; Ketalar; Ketanest; ***Austral.:*** Ketalar; ***Austria:*** Ketanest; ***Belg.:*** Ketalar; ***Braz.:*** Ketalar; ***Canad.:*** Ketalar; ***Chile:*** Ketalar†; ***Cz.:*** Calypsol; Narkamon; ***Denm.:*** Ketalar†; ***Fin.:*** Ketalar; Ketanest; ***Ger.:*** Keta†; Ketanest; ***Gr.:*** Ketalar†; ***Hong Kong:*** Ketalar; ***Hung.:*** Calypsol; ***India:*** Ketalar; Ketmin; ***Indon.:*** Anesject; Ivanes; Ketalar; KTM; ***Irl.:*** Ketalar; ***Israel:*** Ketalar; ***Malaysia:*** Calypsol†; Ketava; ***Mex.:*** Ketalin; ***Neth.:*** Ketanest; ***Norw.:*** Ketalar; ***NZ:*** Ketalar; ***Philipp.:*** Ketaject; Ketamax; Ketazol; Quetanex; ***Pol.:*** Calypsol; Ketanest; ***Port.:*** Ketalar; ***Rus.:*** Calypsol (Калипсол); ***S.Afr.:*** Brevinaze; ***Spain:*** Ketolar; ***Swed.:*** Ketalar; ***Switz.:*** Ketalar; ***Thai.:*** Calypsol; Keta-Hameln†; Ketalar; ***Turk.:*** Ketalar; ***UK:*** Ketalar; ***USA:*** Ketalar; ***Venez.:*** Keiran.

Methohexital *(BAN, rINN)*

Méthohexital; Methohexitalum; Methohexitone; Metoheksitaali; Metohexital. (±)-5-Allyl-1-methyl-5-(1-methylpent-2-ynyl)barbituric acid; 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.

Метогекситал

$C_{14}H_{18}N_2O_3$ = 262.3.
CAS — 151-83-7; 18652-93-2.
ATC — N01AF01; N05CA15.
ATC Vet — QN01AF01; QN05CA15.

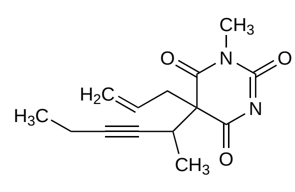

Pharmacopoeias. In *US.*

USP 31 (Methohexital). A white to faintly yellowish-white crystalline odourless powder. M.p. 92° to 96° but the range between beginning and end of melting does not exceed 3°. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, and in dilute alkalis.

Methohexital Sodium *(BANM, rINNM)*

Compound 25398; Enallynymalnatrium; Méthohexital Sodique; Methohexitone Sodium; Metohexital sódico; Natrii Methohexitalum.

Натрий Метогекситал

$C_{14}H_{17}N_2NaO_3$ = 284.3.
CAS — 309-36-4; 22151-68-4; 60634-69-7.
ATC — N01AF01; N05CA15.
ATC Vet — QN01AF01; QN05CA15.

Pharmacopoeias. *US* includes Methohexital Sodium for Injection.

USP 31 (Methohexital Sodium for Injection). A freeze-dried sterile mixture of methohexital sodium and anhydrous sodium carbonate as a buffer, prepared from an aqueous solution of methohexital, sodium hydroxide, and sodium carbonate. It is a white to off-white, essentially odourless, hygroscopic powder. pH of a 5% solution in water is between 10.6 to 11.6.

Incompatibility. Solutions of methohexital sodium are incompatible with acidic substances including a number of antibacterials, antipsychotics, neuromuscular blockers, antimuscarinics, and analgesics. Compounds commonly listed as incompatible include atropine sulfate, pethidine hydrochloride, metocurine iodide, fentanyl citrate, morphine sulfate, pentazocine lactate, silicones, suxamethonium chloride, tubocurarine chloride, and compound sodium lactate injection. Only preservative-free diluents should be used to reconstitute methohexital sodium; precipitation may occur if a diluent containing a bacteriostatic agent is used.

Stability. Solutions of methohexital sodium in Water for Injections are stable for at least 6 weeks at room temperature; however reconstituted solutions should be stored no longer than 24 hours as they contain no bacteriostatic agent. Solutions in glucose or sodium chloride injections are stable only for about 24 hours.

Adverse Effects and Precautions

As for Thiopental Sodium, p.1795.

Excitatory phenomena are more common and induction less smooth with methohexital than with thiopental. Methohexital should be used with caution, if at all, in patients with a history of epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Incidence of adverse effects. In a study of 4379 uses of methohexital in 2722 dental patients the total dose ranged from 20 mg to 560 mg (with a mean of 151 mg), and the duration of treatment was 8 to 32 minutes.[1] Complications included: restlessness not controlled by diazepam (292 cases), respiratory complications (214), uncontrollable crying during recovery (73), pain along vein (45) with thrombophlebitis (5), jactitations (22), and allergic reactions (10).

1. McDonald D. Methohexitone in dentistry. *Aust Dent J* 1980; **25:** 335–42.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving methohexital, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In a study[2] of 9 breast-feeding women undergoing general anaesthesia, it was estimated that the exposure of a breast-fed infant to methohexital would be less than 1% of the maternal dose after induction with methohexital. Breast feeding was not interrupted during the study and none of the infants appeared drowsy or sedated.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Borgatta L, *et al.* Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J Clin Pharmacol* 1997; **37:** 186–92.

Effects on the nervous system. Two case reports of seizures induced by methohexital in children with seizure disorders.[1] Seizures are considered a rare adverse effect of methohexital. In 48 000 patients given methohexital, only 3 developed clonic-type seizures.[2]

A case of a tonic-clonic seizure possibly due to an interaction between paroxetine and methohexital is discussed below.

1. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. *Anesthesiology* 1981; **54:** 333–5.
2. Metriyakool K. Seizures induced by methohexital. *Anesthesiology* 1981; **55:** 718.

Pain on injection. Methohexital is associated with severe pain particularly if veins on the back of the hands are used. The incidence of pain on injection may be reduced by using a forearm vein or by pre-injection with lidocaine.

Porphyria. Methohexital is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Rebound anaesthesia. Rebound of anaesthesia with abolition of reflexes and depression of respiration occurred in a 6-year-old boy[1] 100 minutes after anorectal induction with 27.6 mg/kg methohexital.

1. Kaiser H, Al-Rafai S. Wie sicher ist die rektale Narkoseeinleitung mit Methohexital in der Kinderanaesthesie? *Anaesthesist* 1985; **34:** 359–60.

Interactions

As for Thiopental Sodium, p.1795.

Antidepressants. A 42-year-old woman[1] had a generalised tonic-clonic seizure immediately after being anaesthetised with methohexital for the last in a series of 6 electroconvulsive therapies. She had been receiving *paroxetine* throughout the series. A previous course, without concurrent paroxetine, had been uneventful.

1. Folkerts H. Spontaneous seizure after concurrent use of methohexital anesthesia for electroconvulsive therapy and paroxetine: a case report. *J Nerv Ment Dis* 1995; **183:** 115–16.

Pharmacokinetics

Methohexital is less lipid soluble than thiopental but concentrations sufficient to produce anaesthesia are attained in the brain within 30 seconds of an intravenous dose. Methohexital is also absorbed when given rectally, producing an effect within about 5 to 11 minutes. Recovery from anaesthesia occurs quickly as a result of rapid metabolism and redistribution into other body tissues. Methohexital does not appear to concentrate in fatty tissues to the same extent as other barbiturate anaesthetics. Protein binding has been reported to be about 73%. Methohexital is rapidly metabolised in the liver through demethylation and oxidation. The terminal half-life ranges from 1.5 to 6 hours. Methohexital diffuses across the placenta and has been detected in breast milk.

◊ References.

1. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
2. Le Normand Y, *et al.* Pharmacokinetics and haemodynamic effects of prolonged methohexitone infusion. *Br J Clin Pharmacol* 1988; **26:** 589–94.
3. Redke F, *et al.* Pharmacokinetics and clinical experience of 20-h infusions of methohexitone in intensive care patients with postoperative pyrexia. *Br J Anaesth* 1991; **66:** 53–9.
4. van Hoogdalem EJ, *et al.* Pharmacokinetics of rectal drug administration, part I: general considerations and clinical applications of centrally acting drugs. *Clin Pharmacokinet* 1991; **21:** 11–26.

Uses and Administration

Methohexital is a short-acting barbiturate anaesthetic that has actions similar to those of thiopental (p.1796) but it is about 2 to 3 times more potent. It is given as the sodium salt and has similar uses to thiopental in anaesthesia. Induction of anaesthesia is less smooth than with thiopental and there may be excitatory phenomena. It has a shorter duration of action than thiopental and recovery after an induction dose occurs within 5 to 7 minutes although drowsiness may persist for some time.

As with other barbiturate anaesthetics the dose of methohexital required varies greatly according to the state of the patient and the nature of other drugs also being used (see under Precautions of Thiopental, p.1795, and Interactions of Thiopental, p.1795, for further details). Methohexital sodium is usually given intravenously as a 1% solution. Higher concentrations may markedly increase the incidence of adverse effects. A typical dose for induction of anaesthesia is 50 to 120 mg given at a rate of about 10 mg (1 mL of a 1% solution) every 5 seconds. For the maintenance of general anaesthesia methohexital sodium may be given by intravenous injection in doses of 20 to 40 mg every 4 to 7 minutes as required or it may be given as a 0.2% solution by continuous intravenous infusion at a rate of 3 mL/minute.

For dosage in children, see below.

Administration in children. Although intravenous use is considered preferable in adults, in the USA methohexital sodium has been licensed for use in children only by the intramuscular and rectal routes: usual doses for the induction of anaesthesia are 6.6 to 10 mg/kg intramuscularly, as a 5% solution, or 25 mg/kg rectally, as a 1% solution. In some countries methohexital sodium has also been given intravenously to children: doses in the range of 1 to 2 mg/kg have been used.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients has shown that although reducing the rate of intravenous dosage reduces the speed of induction, the dosage required is also reduced. Giving methohexital sodium 0.5% at a rate of 25 mg/minute induced anaesthesia in a mean of 83.8 seconds and required a mean dose of 0.56 mg/kg. Corresponding values for a rate of 100 mg/minute were 43.6 seconds and 1 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Dental sedation. Some anaesthetics are used as sedatives in dental procedures (see p.956). Methohexital has been tried for patient-controlled sedation in oral surgery under local anaesthesia.[1] In a group of 42 patients, results with 2.5 mg of methohexital compared favourably with those obtained in patients receiving 5 mg of propofol on demand, although patients in the methohexital group experienced a greater degree of postoperative drowsiness.

1. Hamid SK, *et al.* Comparison of patient-controlled sedation with either methohexitone or propofol. *Br J Anaesth* 1996; **77:** 727–30.

Preparations

USP 31: Methohexital Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Brietal; ***Austria:*** Brietal; ***Ger.:*** Brevimytal; ***Israel:*** Brietal†; ***Neth.:*** Brietal; ***Pol.:*** Brietal; ***Rus.:*** Brietal (Бриетал); ***USA:*** Brevital.

Methoxyflurane *(BAN, USAN, rINN)*

Méthoxyflurane; Methoxyfluranum; Metoksifluraani; Metoxifluran; Metoxiflurano; NSC-110432. 2,2-Dichloro-1,1-difluoro-1-methoxyethane; 2,2-Dichloro-1,1-difluoroethyl methyl ether.

Метоксифлуран

$C_3H_4Cl_2F_2O$ = 165.0.
CAS — 76-38-0.
ATC — N01AB03.
ATC Vet — QN01AB03.

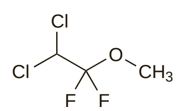

Pharmacopoeias. In *US.*

USP 31 (Methoxyflurane). A clear, practically colourless, mobile liquid having a characteristic odour. It may contain a suitable stabiliser. B.p. about 105°. Soluble 1 in 500 of water; miscible with alcohol, with acetone, with chloroform, with ether, and with fixed oils. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics respiratory depression, hypotension, and malignant hyperthermia have been reported. Methoxyflurane sensitises the myocardium to sympathomimetics to a lesser extent than halothane; arrhythmias appear to be rare.

Methoxyflurane impairs renal function in a dose-related manner due to the effect of the released fluoride on the distal tubule and may cause polyuric or oliguric renal failure, oxaluria being a prominent feature. Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of slower metabolism over several days resulting in prolonged production of fluoride ions, and metabolism to other potentially nephrotoxic substances.

There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis. Headache has been reported by some patients. Cardiac arrest, gastrointestinal adverse effects, delirium, and prolonged postoperative somnolence have been observed.

See also Adverse Effects of General Anaesthetics, p.1779.

Precautions

The use of methoxyflurane is limited because of its potential to cause renal toxicity. It should not be used to achieve deep anaesthesia or for surgical procedures expected to last longer than 4 hours. Methoxyflurane is contra-indicated in the presence of renal impairment. Renal function and urine output should be monitored during anaesthesia. As with other halogenated anaesthetics it is advisable not to give methoxyflurane to patients who have shown signs of liver damage or fever after previous anaesthesia involving halogenated anaesthetics. Patients with known, or suspected, susceptibility to malignant hyperthermia should not be anaesthetised with methoxyflurane. Allowance may need to be made for any increase in CSF pressure or in cerebral blood flow.

There is significant absorption of methoxyflurane by the rubber and soda lime in anaesthetic circuits. PVC plastics are partially soluble in methoxyflurane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. A 27-year-old nurse suffered from progressive renal disease and painful diffuse and multifocal periostitis, which had developed as a probable consequence of intermittent self-exposure to methoxyflurane possibly over a 9-year period.[1] There has also been a report[2] of hepatitis in a 39-year-old physician who repeatedly self-administered subanaesthetic concentrations of methoxyflurane for insomnia. Inhalation of about 2 mL of methoxyflurane had occurred once or twice almost every day for 6 weeks. A 125-mL bottle of methoxyflurane had been consumed in about 1 month.

1. Klemmer PJ, Hadler NM. Subacute fluorosis: a consequence of abuse of an organofluoride anesthetic. *Ann Intern Med* 1978; **89:** 607–11.
2. Okuno T, *et al.* Hepatitis due to repeated inhalation of methoxyflurane in subanaesthetic concentrations. *Can Anaesth Soc J* 1985; **32:** 53–5.

Porphyria. Methoxyflurane is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

Care is advised if adrenaline or other sympathomimetics are given to patients during methoxyflurane anaesthesia. The effects of competitive neuromuscular blockers are enhanced by methoxyflurane. The chronic use of hepatic enzyme-inducing drugs may enhance the metabolism of methoxyflurane thereby increasing the risk of nephrotoxicity. Use of nephrotoxic drugs with methoxyflurane should be avoided.

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

Methoxyflurane is absorbed on inhalation. The blood/gas partition coefficient is high. Methoxyflurane is metabolised to a greater extent than other inhalational anaesthetics. About 50 to 70% of absorbed methoxyflurane undergoes metabolism in the liver to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Methoxyflurane is very soluble in adipose tissue and excretion may be slow. Peak plasma concentrations of fluoride occur 2 to 4 days after a dose. Methoxyflurane crosses the placenta.

Uses and Administration

Methoxyflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 0.16%, but because of its low vapour pressure, induction of general anaesthesia with methoxyflurane is slow. In recommended concentrations it is non-flammable and not explosive when mixed with oxygen. Methoxyflurane possesses good analgesic properties. It does not produce appreciable skeletal muscle relaxation at the concentrations used. Methoxyflurane does not relax the uterus and has little effect on uterine contractions during labour. It is used in subanaesthetic doses to provide analgesia for painful procedures and trauma. In anaesthetic doses, it has been used mainly for maintenance of general anaesthesia (p.1780), but safer anaesthetics are preferred because of its nephrotoxicity.

Concentrations of about 0.2 to 0.7% v/v are used to provide analgesia to conscious patients. The recommended maximum total dose for intermittent self-administration is 6 mL of liquid per day or 15 mL/week.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Penthrane†; Penthrox; ***NZ:*** Penthrox.

Nitrous Oxide

Azote, protoxyde d'; Azoto Protossido; Azotu(I) tlenek; Diazoto oksidas; Dikväveoxid; Dinitrogen Oxide; Dinitrogenii oxidum; Dinitrogén-oxid; Distickstoffmonoxid; Dityppioksidi; E942; Laughing Gas; Nitrogen Monoxide; Nitrogen Oxide; Nitrogenii Monoxidum; Nitrogenii Oxidum; Nitrogenium Oxydulatum; Oxid dusný; Óxido nitroso; Oxyde Nitreux; Oxydum Nitrosum; Protoxyde d'Azote; Stickoxydul.

N_2O = 44.01.
CAS — 10024-97-2.
ATC — N01AX13.
ATC Vet — QN01AX13.

$$N\equiv N^{+}-O^{-}$$

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nitrous oxide:
Bulb; Buzz bomb; Cartridges; Fall down; Gas; Going to the dentist; Grocery store high; Hippy crack; Hysteria; Laughing gas; Nang; Nie; Nigh; Nitro; Nitrogen; Nitrous; Noss; Pan; Shoot the breeze; Tanks; Whippets; Wippets.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Nitrous Oxide). A colourless gas. One vol. measured at a pressure of 101 kPa dissolves, at 20°, in about 1.5 vol. of water. Store liquefied under pressure in suitable containers complying with the legal regulations.

The BP 2008 directs that Nitrous Oxide should be kept in approved metal cylinders which are painted blue and carry a label stating 'Nitrous Oxide'. In addition, 'Nitrous Oxide' or the symbol 'N_2O' should be stencilled in paint on the shoulder of the cylinder.

USP 31 (Nitrous Oxide). A colourless gas, without appreciable odour or taste. One litre at 0° and at a pressure of 760 mmHg weighs about 1.97 g. One volume dissolves in about 1.4 volumes of water at 20° and at a pressure of 760 mmHg; freely soluble in alcohol; soluble in ether and in oils.

Flammability. Nitrous oxide supports combustion.

Storage and supply. Nitrous oxide is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Cylinders containing 50% nitrous oxide and 50% oxygen should be protected from the cold to prevent separation of the gases. Cylinders exposed to temperatures lower than −7° should be rolled at room temperature to ensure mixing or alternatively stored horizontally for 24 hours at a temperature of not less than 10°.

Adverse Effects

The main complications after use of nitrous oxide are those due to varying degrees of hypoxia. Prolonged use has been followed by megaloblastic anaemia and peripheral neuropathy. Depression of white cell formation may also occur. There is a risk of increased pressure and volume from the diffusion of nitrous oxide into air-containing cavities. Malignant hyperthermia has been reported rarely.

See also Adverse Effects of General Anaesthetics, p.1779.

◊ Reviews.

1. Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous oxide. *Adverse Drug React Toxicol Rev* 1994; **13:** 193–206.
2. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: an update. *Br Dent J* 1995; **178:** 95–100.
3. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* 2003; **17:** 47–61.

Effects on the blood. Nitrous oxide interacts with vitamin B_{12}. This blocks the transmethylation reaction for which vitamin B_{12} is a coenzyme and results in depletion of methionine and tetrahydrofolate. Metabolic consequences have been attributed to depletion of either or both. Interference by nitrous oxide with DNA synthesis prevents production of both leucocytes and red blood cells by the bone marrow. Megaloblastic changes in bone marrow and impaired granulocyte production are found in patients exposed to anaesthetic concentrations of nitrous oxide for 24 hours. In patients with normal bone marrow, stores of mature granulocytes will normally be adequate to prevent leucopenia during exposure for up to 3 days; in patients exposed to nitrous oxide for longer periods of time, leucopenia will develop and exposure for 4 days or longer can result in agranulocytosis. In general, healthy surgical patients can be given nitrous oxide for up to 24 hours without harm. In situations where nitrous oxide is used for more than 24 hours, folinic acid 30 mg twice daily has been given to protect the haematopoietic system. Repeat exposure to nitrous oxide at intervals of less than 3 days will have a cumulative effect on DNA synthesis and megaloblastic marrow changes have been reported following multiple short-term exposure.[1] Depletion of methionine has been implicated in the neurological deficit (see below) seen mainly after chronic use of nitrous oxide. It may also account for the fetotoxicity observed in *rats*, see Pregnancy, under Precautions, below.

1. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B . *Br J Anaesth* 1987; **59:** 3–13.

Effects on the nervous system. Neurological disorders (mainly myeloneuropathies and neuropathies) have occurred in chronic abusers of nitrous oxide.[1,2] Similar effects have been noted after repeated use of nitrous oxide in hospitalised patients. These neurological effects are considered to be due to nitrous oxide-induced methionine deficiency (see Effects on the Blood, above). Psychosis, responsive to treatment with vitamin B_{12}, has also been reported in a patient abusing nitrous oxide.[3]

In patients with undiagnosed subclinical deficiency of vitamin B_{12} (a coenzyme involved in methionine synthesis) neurological manifestations, including those consistent with subacute combined degeneration of the spinal cord, have occurred after a single exposure to nitrous oxide for anaesthesia.[4,5] Acute paralysis, due to degeneration of the spinal cord, has also been reported in a malnourished patient who had been abusing nitrous oxide for 10 days for the self-treatment of a painful sprained ankle.[6]

1. Miller MA, *et al.* Nitrous oxide "whippit" abuse presenting as clinical B12 deficiency and ataxia. *Am J Emerg Med* 2004; **22:** 124.
2. Doran M, *et al.* Toxicity after intermittent inhalation of nitrous oxide for analgesia. *BMJ* 2004; **328:** 1364–5.
3. Sethi NK, *et al.* Nitrous oxide "whippit" abuse presenting with cobalamin responsive psychosis. *J Med Toxicol* 2006; **2:** 71–4.
4. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B -deficient subjects? *JAMA* 1986: **255:** 1605–6.
5. Nestor PJ, Stark RJ. Vitamin B myeloneuropathy precipitated by nitrous oxide anaesthesia. *Med J Aust* 1996; **165:** 174.
6. Cartner M, *et al.* Paralysis caused by "nagging". *Med J Aust* 2007; **187:** 366–7.

Malignant hyperthermia. An 11-year-old girl whose father had died from malignant hyperthermia after anaesthesia developed hyperthermia after anaesthesia with nitrous oxide and oxygen.[1]

1. Ellis FR, *et al.* Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *BMJ* 1974; **4:** 270–1.

Precautions

Hypoxic anaesthesia is dangerous and nitrous oxide should always be given with at least 20 to 30% oxygen. Nitrous oxide diffuses into gas-filled body cavities and care is essential when using it in patients at risk from such diffusion such as those with abdominal distension, occlusion of the middle ear, pneumothorax, or similar cavities in the pericardium or peritoneum. Care is also required in patients during or after air encephalography. Oxygen should be given during emergence from prolonged anaesthesia with nitrous oxide to prevent diffusion hypoxia where the alveolar oxygen concentration is diminished. See also Precautions for General Anaesthetics, p.1779. In addition to the above precautions, mixtures of equal parts of nitrous oxide and oxygen should not be used for analgesia in patients with head injuries with impairment of consciousness, maxillofacial injuries, decompression sickness, or those heavily sedated.

Nitrous oxide has been subject to abuse.

Abuse. 'Recreational' use or abuse of nitrous oxide has been referred to as "nagging" or "nanging". For some of the resulting adverse effects of nitrous oxide abuse, see Effects on the Nervous System, above.

Driving. A slight but quantified impairment in driving ability was found up to 30 minutes after 15 minutes' inhalation of nitrous oxide/oxygen mixtures.[1]

1. Moyes DG, *et al.* Driving after anaesthetics. *BMJ* 1979; **1:** 1425.

Epidural anaesthesia. Nitrous oxide diffuses into gas-filled body cavities and can increase the size of any air bubbles injected into the epidural space to determine placement of the needle in epidural anaesthesia.[1] This could result in uneven spread of the local anaesthetic and produce inadequate analgesia. The volume of air injected should be limited or another technique used to determine placement of the needle if nitrous oxide is to be given subsequently.

1. Stevens R, *et al.* Fate of extradural air bubbles during inhalation of nitrous oxide. *Br J Anaesth* 1994; **72:** 482P–483P.

Hazard to user. A scavenging system and effective ventilation may be necessary to control the nitrous oxide pollution that can occur when this gas is used for analgesia or anaesthesia. Risk areas include, in addition to operating theatres, delivery rooms and dental surgeries.[1-3] Occupational exposure can lead to serious toxicity with bone-marrow and neurological impairment.[2,3] Reduced fertility has been reported in female dental workers exposed to high concentrations of nitrous oxide;[4] such women also appear to have a higher rate of spontaneous abortion.[5] It has been suggested that nitrous oxide can also affect male fertility;[6] in one study a dose-related increase in the incidence of spontaneous abortion was found in the wives of men with occupational exposure to nitrous oxide.[7]

1. Munley AJ, *et al.* Exposure of midwives to nitrous oxide in four hospitals. *BMJ* 1986; **293:** 1063–4. Correction. *ibid.*; 1280.
2. Sweeney B, *et al.* Toxicity of bone marrow in dentists exposed to nitrous oxide. *BMJ* 1985; **291:** 567–9.
3. Brodsky JB, *et al.* Exposure to nitrous oxide and neurologic disease among dental professionals. *Anesth Analg* 1981; **60:** 297–301.
4. Rowland AS, *et al.* Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; **327:** 993–7.
5. Rowland AS, *et al.* Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284.
6. Brodsky JB. Nitrous oxide and fertility. *N Engl J Med* 1993; **328:** 284–5.
7. Cohen EN, *et al.* Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc* 1980; **101:** 21–31.

Pregnancy. Nitrous oxide is fetotoxic in *rats*.[1] However, retrospective reviews,[2] and individual case reports[3] have not shown nitrous oxide anaesthesia to be fetotoxic in humans. See also under Hazard to User, above.

1. Lane GA, *et al.* Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. *Science* 1980; **210:** 899–901.
2. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus: a review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth* 1986; **58:** 1348–56.
3. Park GR, *et al.* Normal pregnancy following nitrous oxide exposure in the first trimester. *Br J Anaesth* 1986; **58:** 576–7.

Vitamin B_{12} deficiency. For reports of neurological dysfunction associated with the use of nitrous oxide in patients with undiagnosed subclinical vitamin B_{12} deficiency, see Effects on the Nervous System, above.

Interactions

Use of nitrous oxide with an inhalational anaesthetic accelerates the uptake of the latter from the lungs. This phenomenon is known as the *second gas effect*. It is due to the disproportionate absorption of nitrous oxide into the blood resulting in an increased alveolar concentration of the second gas.

The use of high doses of opioids such as fentanyl with nitrous oxide may result in a drop in heart rate and cardiac output.

See also Interactions for General Anaesthetics, p.1779.

Methotrexate. Combined use of nitrous oxide and methotrexate may increase some of the adverse effects of methotrexate therapy, see p.748.

Pharmacokinetics

Nitrous oxide is rapidly absorbed on inhalation. The blood/gas partition coefficient is low and most of the inhaled nitrous oxide is rapidly eliminated unchanged through the lungs though small amounts diffuse through the skin.

Uses and Administration

Nitrous oxide is an anaesthetic given by inhalation. It is a weak anaesthetic with a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 110%. It has strong analgesic properties, but produces little muscle relaxation. Nitrous oxide must be given with oxygen, otherwise hypoxia will occur.

Nitrous oxide with oxygen has been used in the induction and maintenance of general anaesthesia (p.1780). However, it is now mainly used as an adjuvant to other inhalational or intravenous anaesthetics, permitting them to be used at significantly lower concentrations. It is also used, with oxygen, in subanaesthetic concentrations for analgesia and sedation in emergency care and obstetric and other painful procedures, including dental procedures (see p.956).

For maintenance of anaesthesia a mixture containing 50 to 66% nitrous oxide with oxygen is commonly used. Recovery is usually rapid from nitrous oxide anaesthesia.

Nitrous oxide 25 to 50% v/v with oxygen is used for analgesia; cylinders containing premixed nitrous oxide 50% v/v and oxygen 50% v/v are available in some countries.

Alcohol withdrawal syndrome. The symptoms of acute alcohol withdrawal (p.1626) are usually managed with benzodiazepines but nitrous oxide has been reported[1] to reduce symptoms when tried in alcohol withdrawal. In mild to moderate cases a single inhalation of up to 20 minutes' duration of a nitrous oxide-oxygen mixture in analgesic doses has been used. However, a more recent controlled trial[2] did not find that treatment with nitrous oxide relieved the symptoms of alcohol withdrawal or reduce cravings.

1. Gillman MA, Lichtigfeld FJ. Analgesic nitrous oxide for alcohol withdrawal: a critical appraisal after 10 years' use. *Postgrad Med J* 1990; **66:** 543–6.
2. Alho H, *et al.* Long-term effects of and physiological responses to nitrous oxide gas treatment during alcohol withdrawal: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2002; **26:** 1816–22.

Pain. A mixture of nitrous oxide 50% v/v and oxygen 50% v/v can provide good relief of pain (see Choice of Analgesic, p.2) without loss of consciousness and is suitable for self-administration. It has been widely used for analgesia and sedation during dental procedures. It is also used for short procedures such as dressing changes,[1,2] venepuncture and biopsy,[3] for pain relief during childbirth,[4] in the management of postoperative pain,[1] as an aid to postoperative physiotherapy, and for acute pain in emergency situations such as in ambulances and in the hospital setting.[3,5,6] Continuous inhalation of nitrous oxide-oxygen has been tried for periods longer than 24 hours in the management of pain in terminal cancer.[7] However, such a practice is not usually otherwise recommended[1] as it may result in megaloblastic bone-marrow changes.

1. Hull CJ. Control of pain in the perioperative period. *Br Med Bull* 1988; **44:** 341–56.
2. Gaukroger PB. Pediatric analgesia: which drug, which dose? *Drugs* 1991; **41:** 52–9.

3. Boulland P, *et al.* Mélange équimolaire oxygène-protoxyde d'azote (MEOPA): rappels théoriques et modalités pratiques d'utilisation. *Ann Fr Anesth Reanim* 2005; **24:** 1305–12.
4. Brownridge P. Treatment options for the relief of pain during childbirth. *Drugs* 1991; **41:** 69–80.
5. O'Sullivan Í, Benger J. Nitrous oxide in emergency medicine. *Emerg Med J* 2003; **20:** 214–17.
6. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* 2005; **22:** 901–8.
7. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. *JAMA* 1983; **250:** 511–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Pulmomix Forte†.

Multi-ingredient: ***Fr.:*** Kalinox; Medimix; ***S.Afr.:*** Entonox; ***UK:*** Entonox; Equanox.

Propanidid *(BAN, USAN, rINN)*

Bayer-1420; FBA-1420; Propanidide; Propanididum; TH-2180; WH-5668. Propyl 4-diethylcarbamoylmethoxy-3-methoxyphenylacetate.

Пропанидид

$C_{18}H_{27}NO_5$ = 337.4.
CAS — 1421-14-3.
ATC — N01AX04.
ATC Vet — QN01AX04.

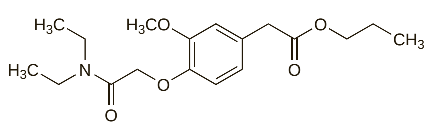

Profile

Propanidid has been used as an intravenous anaesthetic for rapid induction and for maintenance of general anaesthesia of short duration.

Commercial preparations of propanidid were provided as a liquid in polyethoxylated castor oil. Anaphylactoid reactions associated with the vehicle led to the general withdrawal of propanidid from use.

Porphyria. Propanidid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Progray; ***Mex.:*** Panitol.

Propofol *(BAN, USAN, rINN)*

Disoprofol; ICI-35868; Propofoli; Propofolis; Propofolum. 2,6-Diisopropylphenol; 2,6-Bis(1-methylethyl)phenol.

Пропофол

$C_{12}H_{18}O$ = 178.3.
CAS — 2078-54-8.
ATC — N01AX10.
ATC Vet — QN01AX10.

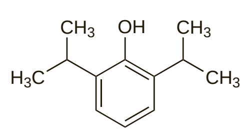

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Propofol). A colourless or very light yellow, clear liquid. Very slightly soluble in water; miscible with hexane and with methyl alcohol. Store under an inert gas. Protect from light.

USP 31 (Propofol). A clear, colourless to slightly yellowish liquid. Very slightly soluble in water; very soluble in dehydrated alcohol and in methyl alcohol; slightly soluble in cyclohexane and in isopropyl alcohol. Store under an inert gas in airtight containers. Protect from light.

Adverse Effects

Early studies with propofol used a preparation formulated with polyethoxylated castor oil. Because of anaphylactoid reactions the preparation was reformulated with a vehicle of soya oil and purified egg phosphatide. Adverse effects with this preparation include pain on injection especially if the injection is into a small vein. Local pain may be reduced by injection into a large vein or by injection of intravenous lidocaine. Apnoea may be frequent; apnoea lasting longer than 60 seconds has been reported to occur in 12% of patients. There are isolated reports of pulmonary oedema. Cardiovascular effects include a reduction in blood pressure and bradycardia. There have been reports of convulsions (sometimes delayed in onset) and involuntary movements. Fever and pancreatitis have occurred very rarely. Discoloration of urine has been reported following prolonged use. Anaphylactoid reactions have been reported. Nausea, vomiting, and headache may occur during recovery.

Children given propofol for prolonged sedation have suffered severe reactions and there have been fatalities, see below.

See also Adverse Effects of General Anaesthetics, p.1779.

Incidence of adverse effects. In May 1989 the UK CSM commented on the 268 reports of adverse reactions to propofol that it had received since propofol was introduced to the UK market, during which period about 2 million patients had been anaesthetised with the drug.[1] These included reports of:

- seizures (37 cases, 13 in known epileptics)
- involuntary movements (16 cases)
- opisthotonus (10 cases)
- anaphylactic reactions (32 cases)
- cardiac arrest (13 cases)
- delayed recovery (8 cases)

In 1992 the CSM pointed to the risk of **delayed convulsions** with propofol and its particular importance for day-case surgery.[2] While the incidence of convulsions was low (170 reports), 31% of the reports described the convulsions as delayed.

In June 1992 the CSM commented on the dangers of propofol for the **sedation of children** in intensive care,[3] a use for which it is contra-indicated in the UK. (This prohibition does not apply to its use for the sedation of ventilated adults—but see below—or to propofol's use as an *anaesthetic* in children. Sedation in children undergoing surgical and diagnostic procedures is not contra-indicated but is an unlicensed use, and is not recommended.[4])

The CSM reported that there had been 66 reports worldwide of serious adverse effects in children sedated with propofol, and some fatalities had ensued. The children had suffered neurological, cardiac, and renal effects, hyperlipidaemia, hepatomegaly, and metabolic acidosis. Five deaths had been reported to the CSM. These 5 children[5] were aged 4 weeks to 6 years and doses of propofol ranged from 4 to 10.7 mg/kg per hour. They developed metabolic acidosis, bradyarrhythmia, and progressive myocardial failure resistant to treatment. The latter has been reported by others to be significantly associated with the use of long-term, **high-dose** propofol infusions.[6]

Similar adverse effects resulting in fatalities have also been reported in **adult** patients with head injuries who received high doses of propofol infusion (greater than 5 mg/kg per hour) for long-term sedation.[7] The CSM subsequently reminded prescribers that the recommended dose range for sedation (up to 4 mg/kg per hour) should not be exceeded.[8] There has also been a report of death in a patient with a closed head injury who received propofol infusion at an average dose of 4.1 mg/kg per hour.[9]

The Australian Adverse Drug Reactions Advisory Committee[10] stated in December 2004 that it had received a report of lactic acidosis and another of torsade de pointes in adult patients receiving lower doses of propofol infusion, 30 and 100 mg/hour, respectively, for about 24 hours.

1. CSM. Propofol—convulsions, anaphylaxis and delayed recovery from anaesthesia. *Current Problems 26* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024442&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
2. CSM. Propofol and delayed convulsions. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
3. CSM. Serious adverse effects and fatalities in children associated with the use of propofol (Diprivan) for sedation. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)
4. CSM/MCA. Clarification: propofol (Diprivan) infusion contraindication. *Current Problems* 2002; **28:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
5. Parke TJ, *et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992; **305:** 613–16.
6. Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; **8:** 491–9.
7. Cremer OL, *et al.* Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; **357:** 117–18.
8. CSM/MCA. Long term, high dose propofol (Diprivan) infusion. *Current Problems* 2001; **27:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
9. Ernest D, French C. Propofol infusion syndrome: report of an adult fatality. *Anaesth Intensive Care* 2003; **31:** 316–19.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Propofol: danger of prolonged and high infusion rates in ICU. *Aust Adverse Drug React Bull* 2004; **23:** 23–4. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0412.htm (accessed 14/12/04)

Effects on the cardiovascular system. The main effect of propofol on the cardiovascular system is a fall in both systolic and diastolic blood pressure of 20 to 30%. The compensatory tachycardia seen after a fall in arterial pressure with other intravenous anaesthetics is not usually seen with propofol. Propofol can also decrease systemic vascular resistance, cardiac output, myocardial blood flow, and myocardial oxygen consumption. Bradycardia can occur even in those premedicated with antimuscarinics, and can occasionally be profound and lead to asystole.[1] Despite these cardiodepressant effects propofol in doses of 1.5 to 2.5 mg/kg does not generally cause unacceptable haemodynamic changes in patients with a healthy cardiovascular system although concern has been expressed about its safety in cardiac surgical patients.[2]

Patients (especially children) given propofol for continuous sedation in intensive care units have suffered adverse cardiac reactions with bradyarrhythmia, progressive myocardial failure, and death—see above.

1. Tramèr MR, *et al.* Propofol and bradycardia: causation, frequency and severity. *Br J Anaesth* 1997; **78:** 642–51.
2. Ginsberg R, Lippmann M. Haemodynamic effects of propofol. *Br J Anaesth* 1994; **72:** 370–1.

Effects on lipids. Prolonged infusion of propofol may be associated with increases in serum triglycerides. In one patient this was believed to have been the cause of necrotising pancreatitis.[1]

1. Metkus AP, *et al.* A firefighter with pancreatitis. *Lancet* 1996; **348:** 1702.

Effects on mental function. There have been anecdotal reports[1] of disinhibited behaviour or sexually orientated hallucinations associated with the use of propofol, but a study using subanaesthetic doses found no evidence that propofol produced euphoria or other mood changes.[2]

1. Canaday BR. Amorous, disinhibited behaviour associated with propofol. *Clin Pharm* 1993; **12:** 449–51.
2. Whitehead C, *et al.* The subjective effects of low-dose propofol. *Br J Anaesth* 1994; **72** (suppl 1): 89.

Effects on the nervous system. See under Precautions, below.

Effects on respiration. See under Precautions, below.

Hypersensitivity. Anaphylactic reactions associated with polyethoxylated castor oil used in propofol preparations had prompted a change to the use of soya oil and egg phosphatide in the formulation. A group of workers have reported a patient who experienced anaphylactic shock when given the reformulated emulsion.[1] A possible case of anaphylaxis to this formulation has also been reported in a child with allergies to egg and peanut oil.[2]

1. Laxenaire MC, *et al.* Anaphylactic shock due to propofol. *Lancet* 1988; **ii:** 739–40.
2. Hofer KN, *et al.* Possible anaphylaxis after propofol in a child with food allergy. *Ann Pharmacother* 2003; **37:** 398–401.

Infection. Between June 1990 and February 1993 62 cases of postsurgical infections identified in 7 hospitals in the USA were attributed to improper handling of propofol.[1] The infusion was not prepared aseptically and the syringes used in the infusion pumps were reused for several patients. Propofol is formulated as a soybean fat emulsion and the injection contains no antimicrobial preservative although, in the USA, the formulation now contains the microbial-retarding agent, disodium edetate (see under Administration, below). However, either formulation still has the potential to support microbial growth. UK and US licensed product information now warns of the importance of aseptic technique in the preparation and use of propofol. Microbial multiplication did not appear to be clinically significant when propofol infusions were prepared and given using conventional aseptic techniques.[2]

1. Bennett SN, *et al.* Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; **333:** 147–54.
2. Farrington M, *et al.* Do infusions of midazolam and propofol pose an infection risk to critically ill patients? *Br J Anaesth* 1994; **72:** 415–17.

Malignant hyperthermia. From an *in-vitro* study it was concluded that propofol does not trigger malignant hyperthermia.[1] There is a report of the safe use of propofol in 19 patients considered susceptible to malignant hyperthermia.[2]

1. Denborough M, Hopkinson KC. Propofol and malignant hyperpyrexia. *Lancet* 1988; **i:** 191.
2. Harrison GG. Propofol in malignant hyperthermia. *Lancet* 1991; **337:** 503.

Pain on injection. Product information suggests the use of lidocaine or alfentanil to reduce the pain associated with injection of conventional formulations of propofol (see Administration, below); alternatively, the larger veins in the forearm and antecubital fossa can be used. Studies indicate that metoclopramide[1] might also be effective. The pain is thought to be caused by the proportion of the propofol dose that is present in the aqueous rather than the oily phase of the emulsion. It has been suggested[2] that the analgesic effect of lidocaine, and possibly metoclopramide, is due to a pH-lowering effect, causing more propofol to be present in the oily phase, but a study showing that lidocaine given by iontophoresis also reduces pain[3] suggests this is not the only mechanism. In another attempt to reduce pain by decreasing the amount of aqueous propofol, a formulation containing a mixture of medium-chain and long-chain triglycerides (*Propofol-Lipuro*), assumed to improve distribution into the lipid phase, has been introduced in a number of countries. However, studies in adults[4] and children[5] suggest that the reduction in pain with the newer formulation is not as great as that achieved by mixing lidocaine with the conventional long-chain formulation.

1. Ganta R, Fee JPH. Pain on injection of propofol: comparison of lignocaine with metoclopramide. *Br J Anaesth* 1992; **69:** 316–17.
2. Eriksson M, *et al.* Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth* 1997; **78:** 502–6.
3. Sadler PJ, *et al.* Iontophoretically applied lidocaine reduces pain on propofol injection. *Br J Anaesth* 1999; **82:** 432–4.
4. Adam S, *et al.* Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg* 2004; **99:** 1076–9.
5. Nyman Y, *et al.* Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. *Br J Anaesth* 2005; **95:** 222–5.

Urine discoloration. A case report of dark green urine in a 16-year-old during a prolonged infusion of propofol.[1]

1. Bodenham A, *et al.* Propofol infusion and green urine. *Lancet* 1987; **ii:** 740.

Precautions

Propofol should not be given to patients known to be allergic to it. Propofol should be used with caution in patients with hypovolaemia, epilepsy, or lipid metabolism disorders, and in the elderly. Since there have been reports of delayed convulsions associated with the use of propofol it is recommended that special care should be taken when propofol is used for day-case surgery. When used in patients with increased intracranial pressure it should be given slowly to avoid a substantial decrease in mean arterial pressure and a resultant decrease in cerebral perfusion pressure. It is also recommended that propofol should not be used with ECT. Premedication with an antimuscarinic may be advisable since propofol does not cause vagal inhibition.

Propofol is used to provide continuous sedation for ventilated adult patients under intensive care. Account should be taken of increasing the patient's lipid load. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored. Children aged 16 years or less should not be sedated in this manner with propofol (see Incidence of Adverse Effects, above). Propofol is not recommended for use in obstetrics including caesarean section. See also Precautions for General Anaesthetics, p.1779.

For the need for aseptic handling of propofol see Administration, below.

Abuse. References to the abuse of propofol.

1. Kranioti EF, *et al.* Lethal self administration of propofol (Diprivan): a case report and review of the literature. *Forensic Sci Int* 2007; **167:** 56–8.
2. Wischmeyer PE, *et al.* A survey of propofol abuse in academic anesthesia programs. *Anesth Analg* 2007; **105:** 1066–71.

CNS effects. Epileptic activity was seen[1] on the EEGs of 3 patients given propofol and it was suggested that it might be useful in ECT, but others[2,3] found that the duration of seizures was less with propofol anaesthesia than with methohexital anaesthesia. It has been suggested that propofol should not be used with ECT[4] and this is the advice in UK licensed product information.

Some consider that abnormal movements induced by propofol are not associated with cortical seizure activity.[5,6] These appear to be more frequent with low doses of propofol[6] and can be abolished in children by increasing the induction dose of propofol from 3 to 5 mg/kg.

1. Hodkinson BP, *et al.* Propofol and the electroencephalogram. *Lancet* 1987; **ii:** 1518.
2. Simpson KH, *et al.* Seizure duration after methohexitone or propofol for induction of anaesthesia for electroconvulsive therapy (ECT). *Br J Anaesth* 1987; **59:** 1323P–1324P.
3. Rampton AJ, *et al.* Propofol and electroconvulsive therapy. *Lancet* 1988; **i:** 296–7.
4. Anonymous. Addendum: propofol better avoided with ECT at present. *Drug Ther Bull* 1990; **28:** 72.
5. Borgeat A, *et al.* Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. *Br J Anaesth* 1993; **70:** 459–61.
6. Borgeat A, *et al.* Propofol and epilepsy: time to clarify. *Anesth Analg* 1994; **78:** 198–9.

Impaired respiration. The manufacturer has stated[1] that some patients who have received propofol for sedation in regional anaesthesia have experienced bradypnoea or hypoxaemia, or both. A reduction in oxygen saturation has also been noted in other patients sedated for endoscopy.[2] UK product information therefore recommends that oxygen saturation should be monitored and that oxygen supplementation should be readily available.

1. Arnold BDC. Sedation with propofol during regional anaesthesia. *Br J Anaesth* 1993; **70:** 112.
2. Patterson KW, *et al.* Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth* 1991; **67:** 108–11.

Interactions

The use of propofol with other CNS depressants, including those used in premedication, may increase the sedative, anaesthetic, and cardiorespiratory depressant effects of propofol. It is recommended that propofol is given after opioids so that the dose of propofol can be carefully titrated against the response. The dosage of propofol should be reduced if used with nitrous oxide or halogenated anaesthetics. Although propofol does not potentiate the effects of neuromuscular blockers, bradycardia and asystole have occurred after use of propofol with atracurium or suxamethonium (but see under Adverse Effects, above for the effects of propofol itself on the cardiovascular system).

See also Interactions of General Anaesthetics, p.1779.

Benzodiazepines. Propofol and *midazolam* have been reported to act synergistically.[1-3]

1. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; **67:** 539–45.
2. McClune S, *et al.* Synergistic interaction between midazolam and propofol. *Br J Anaesth* 1992; **69:** 240–5.
3. Teh J, *et al.* Pharmacokinetic interactions between midazolam and propofol: an infusion study. *Br J Anaesth* 1994; **72:** 62–5.

Clonidine. Premedication with clonidine has been reported[1] to reduce intraoperative requirements of propofol.

1. Guglielminotti J, *et al.* Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine. *Br J Anaesth* 1998; **80:** 733–6.

Gastrointestinal drugs. The dose of propofol required for induction is reduced in patients given *metoclopramide*.[1]

1. Page VJ, Chhipa JH. Metoclopramide reduces the induction dose of propofol. *Acta Anaesthesiol Scand* 1997; **41:** 256–9.

General anaesthetics. Use with *halothane* or *isoflurane* has been reported to increase serum concentrations of propofol.[1] Synergy has been reported between propofol and *etomidate*.[2]

1. Grundmann U, *et al.* Propofol and volatile anaesthetics. *Br J Anaesth* 1994; **72** (suppl 1): 88.
2. Drummond GB, Cairns DT. Do propofol and etomidate interact kinetically during induction of anaesthesia? *Br J Anaesth* 1994; **73:** 272P.

Local anaesthetics. A reduction in the amount of propofol required to provide adequate hypnosis[1] or sedation[2] has been reported after *bupivacaine*[1] or *lidocaine*.[1,2] However, lidocaine is often added to propofol emulsions to reduce the pain of injection, see under Administration, below.

1. Ben-Shlomo I, *et al.* Hypnotic effect of iv propofol is enhanced by im administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; **78:** 375–7.
2. Mallick A, *et al.* Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. *Br J Anaesth* 1996; **77:** 731–4.

Opioids. In a study mean blood concentrations of propofol were higher in patients pretreated with *fentanyl* compared with patients maintained only on nitrous oxide.[1] However, others[2] were unable to confirm this interaction.

1. Cockshott ID, *et al.* Pharmacokinetics of propofol in female patients. *Br J Anaesth* 1987; **59:** 1103–10.
2. Dixon J, *et al.* Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. *Br J Anaesth* 1990; **64:** 142–7.

Pharmacokinetics

The pharmacokinetics of propofol are best described by a 3-compartment model. After a single bolus dose, two distribution phases are seen. The first phase has a half-life of 2 to 4 minutes. This is followed by a slow distribution phase with a half-life of 30 to 60 minutes. Significant metabolism of propofol occurs during the second phase. The termination of anaesthetic effect after a single intravenous bolus or maintenance infusion is due to extensive redistribution from the brain to other tissues and to metabolic clearance. Propofol is over 95% bound to plasma proteins. It undergoes extensive hepatic metabolism to conjugates which are eliminated in the urine. The terminal half-life ranges from 3 to 12 hours; with prolonged use, the terminal half-life may be longer. The pharmacokinetics of propofol do not appear to be altered by gender, chronic hepatic cirrhosis, or chronic renal impairment. Propofol crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Saint-Maurice C, *et al.* Pharmacokinetics of propofol in young children after a single dose. *Br J Anaesth* 1989; **63:** 667–70.
2. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet* 1989; **17:** 308–26.
3. Gin T, *et al.* Pharmacokinetics of propofol in women undergoing elective caesarean section. *Br J Anaesth* 1990; **64:** 148–53.
4. Servin F, *et al.* Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth* 1990; **65:** 177–83.
5. Jones RDM, *et al.* Pharmacokinetics of propofol in children. *Br J Anaesth* 1990; **65:** 661–7.
6. Morgan DJ, *et al.* Pharmacokinetics of propofol when given by intravenous infusion. *Br J Clin Pharmacol* 1990; **30:** 144–8.
7. Gin T, *et al.* Disposition of propofol at caesarean section and in the postpartum period. *Br J Anaesth* 1991; **67:** 49–53.
8. Bailie GR, *et al.* Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth* 1992; **68:** 486–91.
9. Altmayer P, *et al.* Propofol binding in human blood. *Br J Anaesth* 1994; **72** (suppl 1): 86.
10. Oei-Lim VLB, *et al.* Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment. *Br J Anaesth* 1998; **80:** 324–31.
11. Dawidowicz AL, *et al.* Free and bound propofol concentrations in human cerebrospinal fluid. *Br J Clin Pharmacol* 2003; **56:** 545–50.
12. Hiraoka H, *et al.* Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. *Br J Clin Pharmacol* 2005; **60:** 176–82.
13. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Uses and Administration

Propofol is a short-acting anaesthetic given intravenously for the induction and maintenance of general anaesthesia (p.1780). It is also used for sedation (p.956) in adult patients undergoing diagnostic procedures, in those undergoing surgery with local or regional anaesthesia, and in ventilated adult patients under intensive care. When used for anaesthesia, induction is rapid, as is recovery. Propofol has no analgesic activity and supplementary analgesia may be required.

Propofol is available as a 1 or 2% emulsion. The 1% emulsion may be given by intravenous injection or infusion, but the 2% emulsion is for infusion only. Infusions and injections should be prepared using aseptic techniques, see Administration, below.

Induction of **anaesthesia** is generally carried out by giving propofol by injection or infusion at a rate of 40 mg every 10 seconds; a rate of 20 mg every 10 seconds may be used in high-risk patients including elderly, neurosurgical, and debilitated patients. Most *adults* under 55 years of age can be anaesthetised by a dose of 1.5 to 2.5 mg/kg; high-risk patients usually require a dose of 1 to 1.5 mg/kg.

When used for maintenance propofol is infused at a rate of between 4 to 12 mg/kg per hour (or 3 to 6 mg/kg per hour for elderly and debilitated patients); alternatively intermittent bolus injections of 20 to 50 mg may be given; rapid bolus doses should be avoided in high-risk patients.

A novel delivery system is also available for the induction and maintenance of anaesthesia in adults. The Diprifusor target-controlled infusion system allows the speed of induction and depth of anaesthesia to be controlled by specifying target blood concentrations of propofol. Initial target concentrations for induction range from 4 to 8 micrograms/mL for patients under 55 years of age; lower initial target concentrations should be used in older and debilitated patients and should be increased gradually thereafter in steps of 0.5 to 1 microgram/mL at intervals of 1 minute to achieve a gradual induction of anaesthesia. Target concentrations for maintenance are 3 to 6 micrograms/mL.

In the UK, *children* aged 1 month and over may be given propofol for the induction and maintenance of anaesthesia. The dose should be adjusted for weight and age and administered slowly until the onset of anaesthesia. Most children aged over 8 years require an induction dose of 2.5 mg/kg; younger children may require a higher dose within the range of 2.5 to 4 mg/kg. Doses of 9 to 15 mg/kg per hour by intravenous infusion or intermittent bolus injections are suitable for maintenance. The 2% emulsion formulation of propofol should only be used in children aged over 3 years. In the USA, children aged 3 years and over may be given propofol for the induction of anaesthesia; those aged 2 months and over may receive propofol for maintenance of anaesthesia. Doses are similar to those used in the UK.

For **sedation** in diagnostic and surgical procedures in *adults* an initial infusion of 6 to 9 mg/kg per hour may be given for 3 to 5 minutes; alternatively 0.5 to 1 mg/kg may be injected slowly over 1 to 5 minutes. An infusion of 1.5 to 4.5 mg/kg per hour may be used for maintenance of sedation. High-risk patients usually require a 20% reduction in the maintenance dose.

For the sedation of ventilated adults propofol can be given by intravenous infusion in a dose of 0.3 to 4 mg/kg per hour. If the duration of sedation is in excess of 3 days, lipid concentrations should be monitored.

Propofol is contra-indicated for sedation in *children* aged 16 years or less.

◊ Reviews.

1. Langley MS, Heel RC. Propofol: a review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; **35:** 334–72.
2. Larijani GE, *et al.* Clinical pharmacology of propofol: an intravenous anesthetic agent. *DICP Ann Pharmacother* 1989; **23:** 743–9.
3. Bryson HM, *et al.* Propofol: an update of its use in anaesthesia and conscious sedation. *Drugs* 1995; **50:** 513–59.
4. Fulton B, Sorkin EM. Propofol: an overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. *Drugs* 1995; **50:** 636–57.

Administration. Propofol is formulated as an oil-in-water emulsion for injection. Strict aseptic techniques must be maintained when handling propofol as, in some countries (including the UK), the parenteral product contains no antimicrobial preservatives and the vehicle can support rapid growth of microorganisms. Aseptic techniques must also be applied to formulations, such as those available in the USA, that contain the microbial-retarding agent disodium edetate, as microbial growth is still possible. An emulsion containing 1% of propofol may be diluted with glucose 5% immediately before use but it should not be diluted to a concentration of less than 2 mg/mL. An emulsion containing 2 % of propofol should not be diluted. The use of a 5-micron filter needle to withdraw propofol emulsion from an ampoule does not cause significant loss of drug.[1] A reduction in concentration of propofol can occur when the diluted emulsion is run through polyvinyl chloride intravenous tubing.[1] Propofol 1 or 2% may be given into a running intravenous infusion through a Y-site close to the injection site and under these circumstances it is compatible with glucose 5%, sodium chloride 0.9%, and glucose with sodium chloride intravenous solutions.

Because injection of propofol can be painful, it may be mixed with alfentanil or lidocaine before use. UK licensed product information advises mixing lidocaine 0.5 or 1% injection (without preservatives) in a ratio of 1:20 with propofol injection 1% immediately before use; similarly, alfentanil injection 500 micrograms/mL may be mixed in a ratio of 1:20 to 1:50 with propofol 1%. It advises against mixing the 2% emulsion of propofol with other drugs.

1. Bailey LC, *et al.* Effect of syringe filter and I.V. administration set on delivery of propofol emulsion. *Am J Hosp Pharm* 1991; **48:** 2627–30.

Nausea and vomiting. It is commonly believed that propofol is associated with less postoperative nausea and vomiting than some other anaesthetics.[1,2] However, a review[3] concluded that any reduction in nausea and vomiting when using propofol anaesthesia may be short term and clinically relevant only for maintenance anaesthesia in procedures with an inherent risk of nausea and vomiting.

There are also reports[4-8] indicating that propofol may have some intrinsic antiemetic action when used in sub-hypnotic doses although a study[9] of the effect of sedative and non-sedative (subhypnotic) doses against apomorphine-induced vomiting has suggested that any antiemetic effect is probably due to sedation.

1. McCollum JSC, *et al.* The antiemetic action of propofol. *Anaesthesia* 1988; **43:** 239–40.
2. Woodward WM, *et al.* Comparison of post-operative nausea and vomiting after thiopentone/isoflurane or propofol infusion for 'bat-ear' correction in children. *Br J Anaesth* 1994; **72** (suppl 1): 92.
3. Tramèr M, *et al.* Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997: **78:** 247–55.
4. Borgeat A, *et al.* Adjuvant propofol for refractory cisplatin-associated nausea and vomiting. *Lancet* 1992; **340:** 679–80.
5. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
6. Borgeat A, *et al.* Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. *Can J Anaesth* 1994; **41:** 1117–19.
7. Ewalenko P, *et al.* Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth* 1996; **77:** 463–7.
8. Gan TJ, *et al.* Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. *Anesthesiology* 1997; **87:**779–84.
9. Thörn S-E, *et al.* Propofol effects upon apomorphine induced vomiting. *Br J Anaesth* 1994; **72** (suppl 1): 90.

Pruritus. Propofol is one of many drugs that have been tried in the management of pruritus (p.1582). Sub-hypnotic doses of propofol appear to have an antipruritic action. It has produced conflicting results in the treatment and prophylaxis of pruritus associated with epidural and intrathecal morphine[1-4] although it appears to be able to relieve cholestasis-associated pruritus.[5] It has been suggested that propofol might act by suppression of the spinal transmission of pruritic signals.

1. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76:** 510–12.
2. Törn K, *et al.* Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73:** 411–12.
3. Warwick JP, *et al.* The effect of subhypnotic doses of propofol on the incidence of pruritus after intrathecal morphine for caesarean section. *Anaesthesia* 1997; **52:** 270–5.
4. Beilin Y, *et al.* Subhypnotic doses of propofol do not relieve pruritus induced by intrathecal morphine after cesarean section. *Anesth Analg* 1998; **86:** 310–3.
5. Borgeat A, *et al.* Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; **104:** 244–7.

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used. Propofol is also used[1-4] although good controlled studies of its effectiveness are lacking; in addition, it has caused seizures when used in anaesthesia (see CNS Effects, under Precautions, above) and should be given with caution to patients with epilepsy. The risks of respiratory and cerebral depression, as well as of lipid overload with prolonged therapy, should also be borne in mind. It may induce involuntary movements and care is required to distinguish these from seizures. Nonetheless, it has a rapid onset of action and its effects are maintained while the infusion is maintained; recovery is rapid on stopping. A suggested regimen for management[2] is an initial intravenous bolus of 1 to 2 mg/kg followed by an infusion of 2 to 10 mg/kg per hour guided by EEG monitoring. The dose should be gradually reduced and the infusion tapered 12 hours after seizure activity is halted. Lower doses should be used in the elderly. A study[5] comparing propofol with high-dose barbiturates in patients with refractory status epilepticus concluded that recurrent seizures were common when propofol infusions were suddenly stopped but not when the infusions were gradually tapered.

1. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother* 1998; **32:** 1053–9.
2. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998; **338:** 970–6.
3. Marik PE, Varon J. The management of status epilepticus. *Chest* 2004; **126:** 582–91.
4. van Gestel JPJ, *et al.*Propofol and thiopental for refractory status epilepticus in children. *Neurology* 2005; **65:** 591–2.
5. Stecker MM, *et al.* Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998; **39:** 18–26.

Tetanus. Sedation with propofol has been used in the treatment of tetanus (p.1901) to control spasms and rigidity.

Preparations

BP 2008: Propofol Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Diprivan; Fresofol; Gobbifol; Oleo-Lax; Recofol†; ***Austral.:*** Diprivan; Recofol; ***Austria:*** Diprivan; ***Belg.:*** Diprivan; ***Braz.:*** Bioprofol†; Diprivan; Porpovan; Profolen; Pronest†; Propoabbott; Propovan; Provive†; ***Canad.:*** Diprivan; ***Chile:*** Diprivan; ***Cz.:*** Diprivan; Recofol; ***Denm.:*** Diprivan; ***Fin.:*** Diprivan†; Recofol; ***Fr.:*** Diprivan; ***Ger.:*** Disoprivan; Recofol†; ***Gr.:*** Diprivan; Recofol; ***Hong Kong:*** Diprivan; ***Hung.:*** Diprivan; Recofol†; ***India:*** Diprivan; ***Indon.:*** Diprivan; Fresofol; Recofol; Safol; ***Irl.:*** Diprivan; ***Israel:*** Diprivan; Diprofol; Recofol; ***Ital.:*** Diprivan; ***Malaysia:*** Diprivan; Fresofol; ***Mex.:*** Cryotol; Diprivan; Fresofol; Indufol; Propocam†; Provive; Recofol; ***Neth.:*** Diprivan; Recofol; ***Norw.:*** Diprivan; Recofol†; ***NZ:*** Diprivan; Fresofol; Recofol†; ***Philipp.:*** Diprivan; Fresofol; ***Pol.:*** Abbofol; Diprivan; Plofed; ***Port.:*** Diprivan; Recofol†; ***Rus.:*** Diprivan (Диприван); Recofol (Рекофол); ***S.Afr.:*** Diprivan; Recofol; ***Singapore:*** Diprivan; Pofol†; Recofol; ***Spain:*** Diprivan; Ivofol; Recofol; ***Swed.:*** Diprivan; Propolipid; Recofol; ***Switz.:*** Ansiven†; Disoprivan; Recofol; ***Thai.:*** Diprivan†; Fresofol; Pofol; Recofol; ***Turk.:*** Diprivan; Pofol; Recofol; ***UK:*** Diprivan; Propoven; ***USA:*** Diprivan; ***Venez.:*** Anespro; Diprivan; Profol.

Sevoflurane *(BAN, USAN, rINN)*

BAX-3084; MR-654; Sevofluraani; Sevofluran; Sévoflurane; Sevoflurano; Sevofluranum. Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether; 1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)-propane.

Севофлуран

$C_4H_3F_7O$ = 200.1.

CAS — 28523-86-6.

ATC — N01AB08.

ATC Vet — QN01AB08.

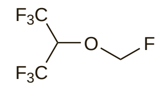

Pharmacopoeias. In *US.*

USP 31 (Sevoflurane). A clear, colourless, volatile, non-flammable liquid. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics sevoflurane may cause cardiorespiratory depression, hypotension, and malignant hyperthermia. However, the effects of sevoflurane on heart rate have only been seen at higher concentrations and it appears to have little effect on heart rhythm in comparison to other halogenated anaesthetics. Sevoflurane appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Other effects seen with sevoflurane include agitation, especially in children, laryngospasm, and increased cough and salivation. Acute renal failure has also been noted. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on the cardiovascular system. The cardiovascular effects of sevoflurane are similar to those of isoflurane (see p.1786) but it does not produce coronary steal. Also sevoflurane produces less tachycardia than isoflurane suggesting that it may be preferable in those predisposed to myocardial ischaemia.

Effects on the kidneys. Investigations[1] of the nephrotoxic potential of sevoflurane have found no evidence of renal function impairment despite peak plasma-fluoride ion concentrations greater than 50 nanomol/mL (a level considered to be nephrotoxic) being recorded in some patients at the end of sevoflurane anaesthesia,[2] and clinical experience would tend to support this.[3] The lack of renal toxicity with sevoflurane may be due to low concentrations of intrarenally generated fluoride ions;[4] in comparison, methoxyflurane defluorination in the kidney is much greater and may contribute to its known nephrotoxicity.

Compound A, formed by the breakdown of sevoflurane by carbon dioxide absorbents (see under Precautions, below), is nephrotoxic in *rats.*[1] However, studies in humans undergoing sevoflurane anaesthesia have detected no renal impairment postoperatively even when compound A was detected in the anaesthetic circuits.

1. Malan TP. Sevoflurane and renal function. *Anesth Analg* 1995; **81:** S39–S45.
2. Kobayashi Y, *et al.* Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. *Anesth Analg* 1992; **74:** 753–7.
3. Gentz BA, Malan TP. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs* 2001; **61:** 2155–62.
4. Kharasch ED, *et al.* Human kidney methoxyflurane and sevoflurane metabolism: intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. *Anesthesiology* 1995; **82:** 689–99.

Effects on the liver. There have been signs of hepatotoxicity in *animal* studies but in studies in humans, markers for hepatocellular dysfunction were no greater after sevoflurane anaesthesia than those after isoflurane.[1] UK licensed product information also states that there have only been rare postmarketing reports of hepatic failure and necrosis for which causality has not been established. The metabolism of sevoflurane differs from other halogenated anaesthetics in such a way that metabolites implicated in liver toxicity are not formed (see Pharmacokinetics, below).

1. Darling JR, *et al.* Comparison of the effects of sevoflurane with those of isoflurane on hepatic glutathione-S-transferase concentrations after body surface surgery. *Br J Anaesth* 1994; **73:** 268P.

Effects on the nervous system. Clonic and tonic seizure-like movements of the extremities have been reported[1] in a child during induction of anaesthesia using sevoflurane. It was considered that this might have been a result of seizure activity in the CNS or due to myoclonus of the extremities.

1. Adachi M, *et al.* Seizure-like movements during induction of anaesthesia with sevoflurane. *Br J Anaesth* 1992; **68:** 214–15.

Precautions

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with sevoflurane. Although the effects of sevoflurane on cerebral pressure are minimal in normal patients, safety in those with raised intracranial pressure has not been established and therefore sevoflurane should be used with caution. As emergence and recovery are particularly rapid with sevoflurane patients may require early postoperative pain relief.

See also Precautions for General Anaesthetics, p.1779.

Carbon dioxide absorbents. The breakdown of sevoflurane by carbon dioxide absorbents (such as soda lime) results in the formation of pentafluoroisopropenyl fluoromethyl ether (PIFE; compound A), and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE; Compound B). Compound A has been shown to be nephrotoxic in *rats* (see under Effects on the Kidneys, above). Even during short exposure times, as required for induction of anaesthesia, use of moist soda lime is important to minimise sevoflurane degradation, which is aggravated by a high potassium hydroxide content of the soda lime.[1]

Licensed product information states that increased amounts of compound A may be formed if barium hydroxide lime is used as a carbon dioxide absorbent rather than soda lime.

The use of desiccated carbon dioxide absorbents with sevoflurane has also been associated with rare cases of extreme heat and smoke or fire developing in the anaesthetic apparatus.[2]

1. Funk W, *et al.* Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. *Br J Anaesth* 1999; **82:** 193–8.
2. Abbott Laboratories, Canada. Important safety information regarding the use of Sevorane AF (sevoflurane) in conjunction with anesthesia machines. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/sevorane_hpc-cps-eng.pdf (accessed 08/08/08)

Interactions

Care is advised if adrenaline or other sympathomimetics are given during sevoflurane anaesthesia. The effects of competitive neuromuscular blockers such as atracurium are enhanced by sevoflurane (see p.1904). The metabolism, and hence toxicity, of sevoflurane may be increased by drugs or compounds that induce cytochrome P450 isoenzyme CYP2E1 including isoniazid and alcohol.

See also Interactions of General Anaesthetics, p.1779.

◊ References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Sevoflurane is absorbed on inhalation. The blood/gas partition coefficient is low. Up to 5% of the absorbed dose of sevoflurane is metabolised in the liver by the cytochrome P450 isoenzyme CYP2E1 and defluorinated to its major metabolites hexafluoroisopropanol (HFIP), inorganic fluoride, and carbon dioxide. HFIP is rapidly conjugated with glucuronic acid and eliminated in the urine. Sevoflurane crosses the placenta.

◊ References.

1. Behne M, *et al.* Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet* 1999; **36:** 13–26.

Uses and Administration

Sevoflurane is a volatile halogenated anaesthetic given by inhalation. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranging from 1.4% in the elderly to 3.3% in neonates. It is used for the induction and maintenance of general anaesthesia (p.1780). It is non-flammable. Sevoflurane has a nonpungent odour and does not cause respiratory irritation. It also has muscle relaxant properties which may be sufficient for some surgical procedures to be performed without a neuromuscular blocker. However, it possesses no analgesic properties.

Sevoflurane is given using a calibrated vaporiser. For induction, sevoflurane is given in concentrations of up to 5% v/v in adults, with oxygen or a mixture of oxygen and nitrous oxide. Concentrations of up to 7% v/v may be used in children. A short-acting barbiturate or other intravenous induction agent may be given before inhaling sevoflurane. Induction with sevoflurane is rapid (surgical anaesthesia in less than 2 minutes) and smooth because of its nonpungent odour. Maintenance of anaesthesia is achieved with a concentration of 0.5 to 3% v/v with or without nitrous oxide.

◊ Reviews.

1. Patel SS, Goa KL. Sevoflurane: a review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs* 1996; **51:** 658–700.
2. Smith I, *et al.* Sevoflurane—a long-awaited volatile anaesthetic. *Br J Anaesth* 1996; **76:** 435–45.
3. Grounds RM, Newman PJ. Sevoflurane. *Br J Hosp Med* 1997; **57:** 43–6.
4. Goa KL, *et al.* Sevoflurane in paediatric anaesthesia: a review. *Paediatr Drugs* 1999; **1:** 127–53.
5. Ghatge S, *et al.* Sevoflurane: an ideal agent for adult day-case anesthesia? *Acta Anaesthesiol Scand* 2003; **47:** 917–31.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Eraldin; Sevorane; ***Austral.:*** Sevorane; ***Austria:*** Sevorane; ***Belg.:*** Sevorane†; ***Braz.:*** Sevocris; Sevorane; ***Canad.:*** Sevorane; ***Chile:*** Sevorane; ***Cz.:*** Sevorane; ***Denm.:*** Sevorane; ***Fin.:*** Sevorane; ***Fr.:*** Sevorane; ***Ger.:*** Sevorane; ***Gr.:*** Sevorane; ***Hong Kong:*** Sevorane; ***Hung.:*** Sevorane; ***Indon.:*** Sevorane; ***Irl.:*** Sevorane; ***Israel:*** Sevorane; ***Ital.:*** Sevorane; ***Malaysia:*** Sevorane; ***Mex.:*** Sevorane; ***Neth.:*** Sevorane; ***Norw.:*** Sevorane; ***NZ:*** Sevorane; ***Philipp.:*** Sevorane; ***Pol.:*** Sevorane; ***Port.:*** Sevorane; ***Rus.:*** Sevoran (Севоран); ***S.Afr.:*** Ultane; ***Singapore:*** Sevorane; ***Spain:*** Sevorane; ***Swed.:*** Sevorane; ***Switz.:*** Sevorane; ***Thai.:*** Sevorane; ***Turk.:*** Sevorane; ***USA:*** Sojourn; Ultane; ***Venez.:*** Sevorane.

Sodium Oxybate *(USAN)*

NSC-84223; Oxibato sódico; Sodium Gamma-hydroxybutyrate; Wy-3478. Sodium 4-hydroxybutyrate.

$C_4H_7NaO_3$ = 126.1.

CAS — 502-85-2.

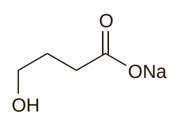

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of sodium oxybate or gamma-hydroxybutyrate:

Blue nitro; Blue verve; Caps; Cherry Meth; Date rape drug; Drogue Du Cambriolage Sexuel Parfait; Easy lay; Everclear; EZLay; Fantasy; G; Gamma Oh; Gamma-OH; GBH; Georgia home boy; GHB; Goop; Great hormones at bedtime; Grievous bodily harm; G-riffic; Jib; Liquid E; Liquid ecstacy; Liquid ecstasy; Liquid G; Liquid X; Organic quaalude; Salty water; Scoop; Sleep; Sleep-500; Soap; Somatomax; Somatomax PM; Vita-G; Water.

Pharmacopoeias. In *Chin.*

Adverse Effects

When used in general anaesthesia adverse effects with sodium oxybate include abnormal muscle movements during the induction period and nausea and vomiting. Occasional emergence delirium has been reported. Bradycardia frequently occurs. Respiration may be slowed and hypokalaemia has been reported.

The most common adverse reactions seen in patients taking sodium oxybate orally for the management of narcolepsy are dizziness, headache, and, particularly in women, nausea. Other common reactions include anorexia, vomiting, diarrhoea, peripheral oedema, abnormal dreams and nightmares, sleepwalking, confusion, depression, anxiety, insomnia, paraesthesia, somnolence, tremor, amnesia, blurred vision, sweating, muscle cramps, nocturnal enuresis, urinary incontinence, asthenia, and fatigue. Blood pressure may also be increased. Psychosis, convulsions, hallucinations, agitation, hypersensitivity, and faecal incontinence are less common; rarely, respiratory depression has been reported.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on electrolyte balance. A report of severe metabolic disorders occurring during therapy with sodium oxybate and tetracosactide in 4 patients with severe head injuries.[1] The disorders consisted of hypernatraemia, hypokalaemia, and metabolic acidosis.

1. Béal JL, *et al.* Troubles métaboliques induits par l'association gamma-hydroxy butyrate de sodium et tétracosactide chez le traumatisé crânien. *Therapie* 1983; **38:** 569–71.

Precautions

In general anaesthesia, sodium oxybate should not be given to patients with severe hypertension, bradycardia, conditions associated with defects of cardiac conduction, epilepsy, eclampsia, renal impairment, or alcohol abuse.

Treatment with oral sodium oxybate is contra-indicated in patients with succinic semialdehyde dehydrogenase deficiency, an enzyme involved in its metabolism to succinic acid. Its use is also contra-indicated in patients with epilepsy as safety and efficacy have not been established; convulsions have been reported with sodium oxybate use.

Patients with a history of depression or suicide attempt should be carefully monitored for depressive symptoms while taking sodium oxybate. The high sodium content of sodium oxybate (0.75 g of sodium in a 4.5 g daily dose) should be considered in patients with heart failure, hypertension, or impaired renal function.

Rebound symptoms with an increased frequency of cataplexy may be seen when sodium oxybate is stopped. There has also been rare reports of withdrawal symptoms such as insomnia, headache, dizziness, anxiety, hallucinations, and psychotic disorders following the illicit use of sodium oxybate (see Abuse, below).

See also Precautions for General Anaesthetics, p.1779.

Abuse. Reports[1] of acute poisoning with sodium oxybate following illicit use led the FDA to issue warnings[2] about its potential for abuse. It is usually supplied illicitly as the sodium salt under a variety of names (see above) and has been promoted for body building, weight loss, as a psychedelic substance, and as a sleep aid. Adverse effects include vomiting, drowsiness, amnesia, hypotonia, vertigo, respiratory depression, and involuntary movements. Seizure-like activity, bradycardia, hypotension, and respiratory arrest have also been reported. Resolution of symptoms occurs spontaneously over 2 to 96 hours. However, some patients have required hospitalisation and respiratory support and deaths have been reported in several countries.[3-5] Severity of symptoms depends on the dose of sodium oxybate and the presence of other drugs such as alcohol, benzodiazepines, cannabis, or amfetamines. Prolonged use of large doses may lead to a withdrawal syndrome on discontinuation.[6-8]

There is also a report of CNS depression after ingestion of a chemical derivative, gamma-butyrolactone (GBL).[9] Another derivative, 1,4-butanediol is abused similarly.[7] Withdrawal symptoms have also been associated with discontinuation of these 2 substances in abusers.[8]

1. CDC. Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *JAMA* 1991; **265:** 447–8.
2. FDA. Warning about GHB. *JAMA* 1991; **265:** 1802.
3. Anonymous. GBH death indicates increasing problem. *Pharm J* 1996; **256:** 441.
4. CDC. Gamma hydroxy butyrate use—New York and Texas, 1995–1996. *JAMA* 1997; **277:** 1511.
5. Caldicott DGE, *et al.* Fatalities associated with the use of γ-hydroxybutyrate and its analogues in Australasia. *Med J Aust* 2004; **181:** 310–13.
6. Galloway GP, *et al.* Physical dependence on sodium oxybate. *Lancet* 1994; **343:** 57.
7. Rodgers J, *et al.* Liquid ecstasy: a new kid on the dance floor. *Br J Psychiatry* 2004; **184:** 104–6.
8. Wojtowicz JM, *et al.* Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM* 2008; **10:** 69–74.
9. LoVecchio F, *et al.* Butyrolactone-induced central nervous system depression after ingestion of RenewTrient, a "dietary supplement". *N Engl J Med* 1998; **339:** 847–8.

Porphyria. Sodium oxybate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

In anaesthesia, sodium oxybate enhances the effects of opioid analgesics, barbiturates, and competitive neuromuscular blockers. The CNS depressant effects of sodium oxybate may be potentiated by alcohol, sedative-hypnotics, and other CNS depressants. The risk of respiratory depression may also be increased by benzodiazepines.

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

After oral doses sodium oxybate is rapidly but incompletely absorbed from the gastrointestinal tract; absolute bioavailability is about 25%. Peak concentrations are reached within 0.5 to 2 hours. Absorption may be delayed and decreased following a high fat meal. Protein binding is less than 1%. Sodium oxybate is metabolised in the liver via GHB dehydrogenase to succinic semialdehyde, which is then converted to succinic acid via another enzyme, succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle and is metabolised to carbon dioxide, which is expired, and water. Less than 5% of unchanged drug appears in the urine; faecal excretion is also negligible.

◊ References.

1. Palatini P, *et al.* Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol* 1993; **45:** 353–6.
2. Scharf MB, *et al.* Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. *Sleep* 1998; **21:** 507–14.

Uses and Administration

Sodium oxybate has hypnotic properties and, in its endogenous form, gamma-hydroxybutyrate (a catabolite of gamma-aminobutyric acid), increases dopamine concentrations in the brain. It is given intravenously usually with an opioid analgesic and a neuroleptic to produce general anaesthesia (p.1780). Skeletal muscle relaxants may also be necessary. Sodium oxybate given orally is used in the treatment of cataplexy in patients with narcolepsy; in the USA it is also indicated for the excessive daytime sleepiness associated with narcolepsy.

In general anaesthesia a solution of sodium oxybate equivalent to 20% of the acid is given slowly by intravenous injection, usually in a dose of 60 mg/kg; further smaller doses may be required in long procedures. In children 100 mg/kg may be used.

For the management of narcolepsy in adults, sodium oxybate is given in initial oral doses of 4.5 g daily, as two equally-divided doses. The first dose should be taken at bedtime while in bed and at least 2 to 3 hours after food; the second dose should be taken 2.5 to 4 hours later also while sitting in bed. Both doses should be prepared before going to bed: each dose should be diluted with 60 mL of water. The initial dose may be increased in steps of 1.5 g (0.75 g per dose) every 1 to 2 weeks to a maximum dose of 9 g daily. If therapy has been stopped for more than 14 consecutive days, titration should be restarted at the lowest dose. Reduced doses are recommended in patients with hepatic impairment (see below).

Administration in hepatic impairment. The recommended initial oral dose of sodium oxybate (see above) should be halved in patients with hepatic impairment. Subsequent increases should be monitored against effect.

Alcohol withdrawal syndrome. Gamma-hydroxybutyric acid has been reported[1] to be effective in reducing symptoms of alcohol withdrawal (p.1626) and to be of use as an aid in the maintenance of abstinence.[2,3] However, following reports of CNS toxicity associated with abuse of gamma-hydroxybutyric acid its role in the treatment of substance abuse disorders appears questionable.[4]

1. Gallimberti L, *et al.* Gamma-hydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet* 1989; **ii:** 787–9.
2. Gallimberti L, *et al.* Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double blind study. *Alcohol Clin Exp Res* 1992; **16:** 673–6.
3. Addolorato G, *et al.* Maintaining abstinence from alcohol with γ-hydroxybutyric acid. *Lancet* 1998; **351:** 38.
4. Quinn DI, *et al.* Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. *Clin Pharmacokinet* 1997; **33:** 344–400.

Narcoleptic syndrome. Sodium oxybate[1-7] given at night is used to improve cataplexy and excessive daytime sleepiness in patients with narcoleptic syndrome (p.2148).

For a reference to the pharmacokinetics of sodium oxybate in narcoleptic patients, see above.

1. Scharf MB, *et al.* The effects and effectiveness of γ-hydroxybutyrate in patients with narcolepsy. *J Clin Psychiatry* 1985; **46:** 222–5.
2. Mamelak M, *et al.* Treatment of narcolepsy with γ-hydroxybutyrate: a review of clinical and sleep laboratory findings. *Sleep* 1986; **9:** 285–9.
3. Scrima L, *et al.* Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. *Biol Psychiatry* 1989; **26:** 331–43.
4. US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002; **25:** 42–9.
5. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; **26:** 31–5.
6. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005; **6:** 415–21.
7. Lemon MD, *et al.* Sodium oxybate for cataplexy. *Ann Pharmacother* 2006; **40:** 433–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Alcover; ***Cz.:*** Xyrem; ***Fr.:*** Gamma-OH; ***Ger.:*** Somsanit; ***Hung.:*** Alcover†; ***Ital.:*** Alcover; ***Neth.:*** Xyrem; ***Port.:*** Xyrem; ***UK:*** Xyrem; ***USA:*** Xyrem.

Thiamylal Sodium

Tiamilal sódico. Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.

$C_{12}H_{17}N_2NaO_2S = 276.3.$

CAS — 77-27-0 (thiamylal); 337-47-3 (thiamylal sodium).

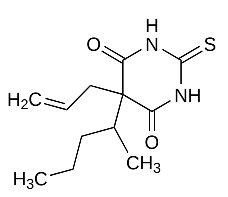

(thiamylal)

Pharmacopoeias. In *Jpn.*

Profile

Thiamylal sodium is a short-acting intravenous barbiturate anaesthetic. It is possibly slightly more potent than thiopental sodium (p.1796) and has similar actions and uses. It has been used for the production of complete anaesthesia of short duration, for the induction of general anaesthesia, or for inducing a hypnotic state.

Thiopental Sodium *(BANM, rINN)*

Natrium Isopentylaethylthiobarbituricum (cum Natrio Carbonico); Penthiobarbital Sodique; Sodyum Tiopental; Sodyum Tiopenton; Soluble Thiopentone; Thiomebumalnatrium cum Natrii Carbonate; Thiopental et carbonate sodiques; Thiopental Sodique; Thiopental Sodium and Sodium Carbonate; Thiopental sodná sůl a uhličitan sodný; Thiopentalum Natricum; Thiopentalum natricum et natrii carbonas; Thiopentobarbitalum Solubile; Thiopentone Sodium; Tiopentaalinatrium; Tiopentaalinatrium ja natriumkarbonaatti; Tiopental sódico; Tiopentalio natrio druska ir natrio karbonatas; Tiopentalnatrium; Tiopentál-nátrium és nátrium-karbonát; Tiopentalnatrium och natriumkarbonat. Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.

Тиопентал Натрий

$C_{11}H_{17}N_2NaO_2S = 264.3.$

CAS — 76-75-5 (thiopental); 71-73-8 (thiopental sodium).

ATC — N01AF03; N05CA19.

ATC Vet — QN01AF03; QN05CA19.

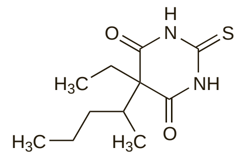

(thiopental)

NOTE. The name thiobarbital has been applied to thiopental and has also been used to describe a barbiturate of different composition.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some include thiopental sodium with, some without, anhydrous sodium carbonate; some only include a sterile mixture for injection.

Ph. Eur. 6.2 (Thiopental Sodium and Sodium Carbonate; Thiopental Sodium BP 2008). A yellowish-white hygroscopic powder. It contains 84 to 87% thiopental and 10.2 to 11.2% sodium. Freely soluble in water; partly soluble in dehydrated alcohol. Store in airtight containers. Protect from light.

USP 31 (Thiopental Sodium). A white to off-white crystalline powder, or yellowish-white to pale greenish-yellow hygroscopic powder. May have a disagreeable odour. Its solutions are alkaline to litmus, decompose on standing, and on boiling, precipitation occurs. Soluble in water and in alcohol; insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers.

Incompatibility. Solutions of thiopental sodium are incompatible with acidic and oxidising substances including some antibacterials, neuromuscular blockers and analgesics. Compounds commonly listed as incompatible include amikacin sulfate, benzylpenicillin salts, cefapirin sodium, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrronium bromide, morphine sulfate, pentazocine lactate, prochlorperazine edisilate, suxamethonium salts, and tubocurarine chloride. Solutions decompose on standing and precipitation occurs on boiling.

Stability. Loss of thiopental in PVC and cellulose propionate delivery systems has been reported,[1,2] but in another study,[3] no loss of potency was noted. Adsorption has been reported[4] not to occur in polyolefin infusion bags.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.
3. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.

Adverse Effects and Treatment

As for Phenobarbital, p.492.

Excitatory phenomena such as coughing, hiccuping, sneezing, and muscle twitching or jerking may occur with any of the barbiturate anaesthetics, particularly during induction, but they occur more frequently with methohexital than with thiopental. Cough, sneezing, and laryngeal spasm or bronchospasm may also occur during induction. The intravenous injection of concentrated solutions of thiopental sodium such as 5% may result in thrombophlebitis. Extravasation of barbiturate anaesthetics may cause tissue necrosis. Intra-arterial injection causes severe arterial spasm with burning pain and may cause prolonged blanching of the forearm and hand and gangrene of digits. Hypersensitivity reactions have been reported. Barbiturate anaesthetics can cause respiratory depression. They depress cardiac output and often cause an initial fall in blood pressure, and overdosage may result in circulatory failure. Arrhythmias may occur. Postoperative vomiting is infrequent but shivering may occur and there may be persistent drowsiness, confusion, and amnesia. Headache has also been reported.

See also under Adverse Effects of General Anaesthetics, p.1779.

Hypersensitivity. Anaphylactic reactions to thiopental have been reported[1,2] although such reactions are rare. There has also been a report of haemolytic anaemia and renal failure in association with the development of an anti-thiopental antibody in a patient who had undergone general anaesthesia induced by thiopental.[3]

1. Westacott P, *et al.* Anaphylactic reaction to thiopentone: a case report. *Can Anaesth Soc J* 1984; **31:** 434–8.
2. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
3. Habibi B, *et al.* Thiopental-related immune hemolytic anemia and renal failure: specific involvement of red-cell antigen I. *N Engl J Med* 1985; **312:** 353–5. Correction. *ibid.*; 1136.

Intra-arterial injection. Accidental intra-arterial injection of thiopental sodium produces severe arterial spasm with intense burning pain. Anaesthesia, paresis, paralysis, and gangrene may occur. Therapy has concentrated on dilution of injected thiopental, prevention and treatment of arterial spasm, prophylaxis of thrombosis, thrombectomy and other measures to sustain good blood flow. There has been a report[1] of the successful use of urokinase intra-arterially in the management of one patient accidentally given thiopental intra-arterially.

1. Vangerven M, *et al.* A new therapeutic approach to accidental intra-arterial injection of thiopentone. *Br J Anaesth* 1989; **62:** 98–100.

Precautions

Barbiturate anaesthetics are contra-indicated when there is dyspnoea or respiratory obstruction such as in acute severe asthma or when maintenance of an airway cannot be guaranteed.

Barbiturate anaesthetics should be used with caution in shock and dehydration, hypovolaemia, severe anaemia, hyperkalaemia, toxaemia, myasthenia gravis, myxoedema and other metabolic disorders, or in severe renal disease. Caution is also required in patients with cardiovascular disease, muscular dystrophies, adrenocortical insufficiency, or with increased intracranial pressure. Reduced doses are required in the elderly and in severe hepatic disease.

See also Precautions for General Anaesthetics, p.1779.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers received thiopental, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

In two groups of 8 women undergoing induction with thiopental, the milk-to-plasma ratio was less than 1 in both groups and it was considered that the effects of thiopental on breast-fed infants would be negligible.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Andersen LW, *et al.* Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol Scand* 1987; **31:** 30–2.

Porphyria. Barbiturates including thiopental sodium have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.

Interactions

Difficulty may be experienced in producing anaesthesia with the usual dose of barbiturate anaesthetics in patients accustomed to taking alcohol or other CNS depressants; additional anaesthetics may be necessary. Patients being treated with phenothiazine antipsychotics may experience increased hypotension. Some phenothiazines, especially promethazine, may also increase the incidence of excitatory phenomena produced by barbiturate anaesthetics; cyclizine may possibly have a similar effect. Opioid analgesics can potentiate the respiratory depressant effect of barbiturate anaesthetics and the dose of the anaesthetic may need to be reduced. Use with nitrous oxide greatly reduces the dose of barbiturate anaesthetics required for anaesthesia. Reduced doses of thiopental may be required in patients receiving sulfafurazole.

See also Interactions of General Anaesthetics, p.1779.

Antidepressants. Potentiation of barbiturate anaesthesia may be expected in patients receiving *tricyclic antidepressants* or *MAOIs* (see Anaesthesia under Precautions of Amitriptyline, p.378 and for Phenelzine, p.417, respectively).

Antipsychotics. For mention of the effect of *droperidol* on thiopental see Gastrointestinal Drugs, below.

Aspirin. Pretreatment with aspirin, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Gastrointestinal drugs. *Metoclopramide* profoundly reduced the dose of thiopental required to produce hypnosis in female patients; *droperidol* had a similar effect.[1]

1. Mehta D, *et al.* Metoclopramide decreases thiopental hypnotic requirement. *Anesth Analg* 1993; **77:** 784–7.

Probenecid. Pretreatment with probenecid, a highly protein-bound drug, has been shown to potentiate thiopental anaesthesia.[1]

1. Dundee JW, *et al.* Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* 1986; **3:** 247–51.

Pharmacokinetics

Thiopental is highly lipid soluble and when it is given intravenously as the sodium salt, concentrations sufficient to produce unconsciousness are achieved in the brain within 30 seconds. Onset of action occurs within 8 to 10 minutes when thiopental sodium is given rectally but absorption may be unpredictable if a suspension rather than a solution is used. Recovery from anaesthesia is also rapid due to redistribution to other tissues, particularly fat. About 80% of thiopental may be bound to plasma proteins, although reports show a wide range of figures. Thiopental is metabolised almost entirely in the liver, but as it is only released slowly from lipid stores this occurs at a very slow rate.

It is mostly metabolised to inactive metabolites but a small amount is desulfurated to pentobarbital. Repeated or continuous use can lead to accumulation of thiopental in fatty tissue and this can result in prolonged anaesthesia and respiratory and cardiovascular depression. Elimination of thiopental after bolus injection can be described by a triexponential curve. The terminal elimination half-life has been reported to be 10 to 12 hours in adults and about 6 hours in children. However, values of 26 to 28 hours have been reported in obese patients and pregnant patients at term. Thiopental readily diffuses across the placenta and is distributed into breast milk.

◊ References.

1. Gaspari F, *et al.* Elimination kinetics of thiopentone in mothers and their newborn infants. *Eur J Clin Pharmacol* 1985; **28:** 321–5.
2. Swerdlow BN, Holley FO. Intravenous anaesthetic agents: pharmacokinetic-pharmacodynamic relationships. *Clin Pharmacokinet* 1987; **12:** 79–110.
3. Esener Z, *et al.* Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69:** 586–8.
4. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.

Uses and Administration

Thiopental is a short-acting barbiturate anaesthetic. It is given intravenously, usually for the induction of general anaesthesia (p.1780), but may be used as the sole anaesthetic to maintain anaesthesia for short procedures with minimal painful stimuli. It is also used in anaesthesia as a supplement to other anaesthetics and as a hypnotic in balanced anaesthesia. Thiopental sodium may also be used intravenously in the control of refractory tonic-clonic status epilepticus and in neurosurgical patients to reduce increased intracranial pressure. It has also been given rectally for basal anaesthesia or basal narcosis.

Thiopental does not usually produce excitation and induction of anaesthesia is usually smooth. It has poor muscle relaxant properties and a muscle relaxant must be given before intubation is attempted. Thiopental also has poor analgesic properties and small doses may even lower the pain threshold. Recovery from moderate doses usually occurs within 10 to 30 minutes, but the patient may remain sleepy or confused for several hours. Large doses, repeated smaller doses, or continuous use may markedly delay recovery.

In **anaesthesia**, the dosage of thiopental varies greatly according to the state of the patient and the nature of other drugs being used concurrently (see under Precautions above and Interactions above for further details). Thiopental is usually given intravenously as the sodium salt as a 2.5% solution but a 5% solution is occasionally used. UK licensed product information states that a typical dose for inducing anaesthesia is 100 to 150 mg injected over 10 to 15 seconds, repeated after 30 to 60 seconds according to response. It also recommends that the total dosage used should not exceed 500 mg; in pregnant patients the total maximum dose is 250 mg. In some other countries, it is recommended that induction begin with a test dose of 25 to 75 mg; thereafter, a dose of 50 to 75 mg may be given at intervals of 20 to 40 seconds according to response. Once anaesthesia has been established, additional doses of 25 to 50 mg may be given as necessary. When thiopental is used as the sole anaesthetic, anaesthesia can be maintained by repeat doses as needed or by continuous intravenous infusion of a 0.2 or 0.4% solution.

To **reduce elevations of intracranial pressure** in neurological patients, thiopental sodium is licensed for use as intermittent bolus injections of 1.5 to 3 mg/kg if adequate ventilation is provided (but see also Cerebrovascular Disorders, below). Higher doses have been tried.

For suggested doses in refractory tonic-clonic **status epilepticus** see Status Epilepticus, below.

For dosage in *children* and the *elderly*, also see below.

◊ References.

1. Russo H, Bressolle F. Pharmacodynamics and pharmacokinetics of thiopental. *Clin Pharmacokinet* 1998; **35:** 95–134.

Administration in children. For the *induction of anaesthesia* in children, UK licensed product information recommends that thiopental sodium is given by slow intravenous injection (over 10 to 15 seconds) in a dose of 2 to 7 mg/kg; the dose may be repeated after 1 minute.

In the treatment of prolonged *status epilepticus* (see below), the *BNFC* recommends an initial dose of up to 2 mg/kg in neonates or up to 4 mg/kg in children aged 1 month and over, given as a slow intravenous injection; for all patients, this should then be followed by a continuous intravenous infusion of up to 8 mg/kg per hour, adjusted according to response.

Intravenous injections are normally given as a 2.5% solution; the *BNFC* recommends that intravenous infusions are given as a 0.25% solution.

Administration in the elderly. It is usually recommended that the dosage of barbiturate anaesthetics is reduced in the elderly. A study[1] in elderly patients demonstrated that although reducing the rate of intravenous injection reduced the speed of induction, the dosage required was also reduced. Giving thiopental sodium 2.5% solution at a rate of 125 mg/minute induced anaesthesia in a mean of 90.8 seconds and required a mean dose of 2.8 mg/kg. Corresponding values for a rate of 500 mg/minute were 40.8 seconds and 5 mg/kg, respectively.

1. Berthoud MC, *et al.* Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. *Br J Anaesth* 1993; **70:** 423–7.

Anaesthesia. Some of the adverse effects of the neuromuscular blocker suxamethonium may be reduced when thiopental is used as part of the anaesthetic regimen. For a suggestion that thiopental may help to counteract the rise in intra-ocular pressure associated with the use of suxamethonium for intubation, see under Anaesthesia, p.1900.

Cerebrovascular disorders. Barbiturates are considered to be suitable anaesthetics for use in patients with or at risk of raised intracranial pressure. Barbiturate-induced coma (commonly with pentobarbital or thiopental) has been used, both therapeutically and prophylactically, to protect the brain from ischaemia resulting from neurological insults including head injury, stroke, Reye's syndrome, and hepatic encephalopathy.[1-3] Rationale includes the ability of barbiturates to reduce intracranial pressure and to reduce metabolic demands of cerebral tissues. Although thiopental protected patients against the neuropsychiatric complications of cardiopulmonary bypass,[4] the Brain Resuscitation Clinical Trial I Study Group[5] found no cerebral benefit from thiopental in comatose survivors of cardiac arrest. Nor did others[6] observe any benefit from thiopental-induced coma in infants with severe birth asphyxia. A review in 1989 considered that there was no convincing evidence of improvement in neurological outcome to justify the risks of the procedure in conditions causing global ischaemia, although use of barbiturates without necessarily inducing coma might have a limited role in reduction of raised intracranial pressure refractory to other therapy. Use of barbiturates in the setting of regional cerebral ischaemia, including use during cardiopulmonary bypass to prevent focal neurological complications, remained controversial.[1] A systematic review[7] came to similar conclusions, pointing out that although the barbiturates may reduce intracranial pressure their hypotensive effects are likely to offset any beneficial action on cerebral perfusion, perhaps accounting for the lack of evidence for any clinical benefit.

For a discussion of the treatment of raised intracranial pressure, including a mention of the use of barbiturates, see p.1181.

1. Rogers MC, Kirsch JR. Current concepts in brain resuscitation. *JAMA* 1989; **261:** 3143–7.
2. Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. *Mayo Clin Proc* 1990; **65:** 684–707.
3. Woster PS, LeBlanc KL. Management of elevated intracranial pressure. *Clin Pharm* 1990; **9:** 762–72.
4. Nussmeier NA, *et al.* Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64:** 165–70.
5. Abramson NS, *et al.* Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; **314:** 397–403.
6. Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986; **61:** 1084–9.
7. Roberts I. Barbiturates for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 16/06/05).

Status epilepticus. General anaesthesia may be used to control refractory tonic-clonic status epilepticus (p.469). A short-acting barbiturate such as thiopental is usually used.

Doses of thiopental sodium in the treatment of status epilepticus appear to vary widely and may be defined by local clinical protocols. Licensed product information and the *BNF* recommend a dose of 75 to 125 mg intravenously as a 2.5% solution. Other regimens advocate an initial loading dose followed by further intermittent doses or a continuous infusion. One high dose regimen suggests an intravenous loading dose of 5 mg/kg followed after 30 minutes by an infusion given at a rate of 1 to 3 mg/kg per hour and adjusted to maintain a maximum blood concentration of 60 to 100 micrograms/mL.[1] It has been recommended that dosage should be continued for at least 12 hours after seizure activity has ceased and then slowly stopped.[2] Recovery may be prolonged.[3]

For the dose of thiopental in children see Administration in Children, above.

1. O'Brien MD. Management of major status epilepticus in adults. *BMJ* 1990; **301:** 918.
2. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
3. Parviainen I, *et al.* High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. *Neurology* 2002; **59:** 1249–51.

Preparations

BP 2008: Thiopental Injection;
USP 31: Thiopental Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Bensulf; Hipnopento; Pentothal†; ***Austral.:*** Pentothal; ***Belg.:*** Pentothal; ***Braz.:*** Thionembutal; Thiopentax; ***Canad.:*** Pentothal; ***Chile:*** Pentothal†; ***Denm.:*** Pentothal; ***Fin.:*** Pentothal; ***Ger.:*** Trapanal; ***Gr.:*** Pentothal; ***Hong Kong:*** Pentothal; ***Hung.:*** Trapanal†; ***India:*** Anesthal; ***Indon.:*** Pentothal; ***Irl.:*** Intraval Sodium†; ***Israel:*** Pentothal; ***Ital.:*** Farmotal; Pentothal; ***Malaysia:*** Pentotex; ***Mex.:*** Pentarim; Pentothal; Sodipental; ***Neth.:*** Pentothal; ***Norw.:*** Pentothal; ***NZ:*** Intraval; ***Philipp.:*** Pentobrim; Pentothal; ***Singapore:*** Pentothal†; ***Spain:*** Pentothal; Tiobarbital; ***Swed.:*** Pentothal; ***Switz.:*** Pentothal; ***Thai.:*** Pentothal; ***Turk.:*** Pental; Pentothal; ***USA:*** Pentothal; ***Venez.:*** Pentothal†.

Tiletamine Hydrochloride *(BANM, USAN, rINNM)*

CI-634; CL-399; CN-54521-2; Hidrocloruro de tiletamina; Tilétamine, Chlorhydrate de; Tiletamini Hydrochloridum. 2-Ethylamino-2-(2-thienyl)cyclohexanone hydrochloride.

Тилетамина Гидрохлорид

$C_{12}H_{17}NOS,HCl = 259.8.$

CAS — 14176-49-9 (tiletamine); 14176-50-2 (tiletamine hydrochloride).

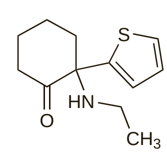

(tiletamine)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Tiletamine Hydrochloride). A white to off-white crystalline powder. Freely soluble in water; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol;

freely soluble in 0.1N hydrochloric acid. pH of a 10% solution in water is between 3.0 and 5.0. Store in airtight containers.

Profile

Tiletamine has similar properties to ketamine (p.1787). It is used as the hydrochloride with zolazepam (p.1037) for general anaesthesia in veterinary medicine.

Trichloroethylene *(rINN)*

Trichlorethylene; Trichlorethylenum; Trichloroethene; Trichloroéthylène; Trichloroethylenum; Trichloroetylen; Tricloroetileno.

Трихлороэтилен

$CHCl{:}CCl_2$ = 131.4.

CAS — 79-01-6.

ATC — N01AB05.

ATC Vet — QN01AB05.

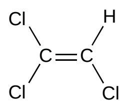

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trichloroethylene: Trichlo.

Stability. NOTE. Trichloroethylene used for anaesthetic purposes contains thymol 0.01% w/v as a stabiliser and is coloured blue for identification. It is non-flammable.

Adverse Effects and Precautions

Trichloroethylene increases the rate and decreases the depth of respiration and may be followed by apnoea. The sensitivity of the heart to beta-adrenergic activity may increase, possibly with ventricular arrhythmias.

Acute exposure to trichloroethylene may be followed by dizziness, lightheadedness, lethargy, nausea, and vomiting; hepatic and renal dysfunction may follow. Fatalities have occurred, although temporary unconsciousness is a more common manifestation.

Chronic poisoning may result in visual disturbances, intolerance to alcohol as manifested by transient redness of the face and neck (degreasers' or trichloroethylene flush), impairment of performance, hearing defects, neuralgia, and mild liver dysfunction. Prolonged contact with trichloroethylene can cause dermatitis, eczema, burns, and conjunctivitis.

Dependence has been reported in medical personnel and factory workers who regularly inhale trichloroethylene vapour.

If trichloroethylene is used as an anaesthetic it should not be used in closed-circuit apparatus since there is a reaction with soda lime to produce a toxic end product that may cause cranial nerve paralysis and possibly death.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

◊ Reviews of the toxicity of trichloroethylene.

1. Health and Safety Executive. Trichloroethylene. *Toxicity Review 6*. London: HMSO, 1982.
2. WHO. Trichloroethylene. *Environmental Health Criteria 50*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc50.htm (accessed 26/05/04)
3. Davidson IWF, Beliles RP. Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. *Drug Metab Rev* 1991; **23:** 493–599.

Abuse. Toxicity associated with inhalation of volatile substances including trichloroethylene has been reviewed.[1,2] Trichloroethylene can damage the kidney, liver, heart, and lung. However, in young healthy subjects, organ toxicity becomes apparent only with intensive and protracted abuse of volatile substances.

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Anonymous. Solvent abuse: little progress after 20 years. *BMJ* 1990; **300:** 135–6.

Carcinogenicity. The use of trichloroethylene in foods, drugs, and cosmetics was banned by the FDA after studies demonstrating that hepatocellular carcinomas could be induced in *mice* by chronic exposure to very high doses. However, similar effects have not been found in *rats* and larger species and several epidemiologic studies have failed to demonstrate an increased incidence of liver tumours, total mortality or mortality due to cancer in workers exposed to trichloroethylene. Suggestions that the carcinogenicity of trichloroethylene is due to one of its intermediate metabolites, cloral hydrate, have raised concern over the continuing use of cloral hydrate as a medicine. For further details, see p.979.

Effects on the liver. References[1,2] to hepatotoxicity after occupational exposure to trichloroethylene. See also Carcinogenicity, above.

1. McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; **45:** 122–6.
2. Schattner A, Malnick SDH. Anicteric hepatitis and uveitis in a worker exposed to trichloroethylene. *Postgrad Med J* 1990; **66:** 730–1.

Effects on the skin. A report[1] of scleroderma in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Interactions

The arrhythmogenic effects of trichloroethylene may be potentiated by sympathomimetics such as adrenaline. Alcohol consumption after chronic exposure to trichloroethylene may result in a reddening of the skin (see Adverse Effects and Precautions, above).

See also Interactions of General Anaesthetics, p.1779.

Pharmacokinetics

Trichloroethylene is rapidly absorbed by inhalation and ingestion. Percutaneous absorption can occur. Some of the inhaled trichloroethylene is slowly eliminated through the lungs; trichloroethylene is metabolised primarily in the liver, cloral hydrate (see p.979) being the first stable major metabolite formed; most is then metabolised to trichloroethanol and trichloroacetic acid which are excreted in the urine. The latter may be used as an indicator of industrial exposure. Trichloroethylene diffuses across the placenta.

Uses and Administration

Trichloroethylene is a volatile halogenated anaesthetic given by inhalation. It has been used in some countries for the maintenance of light anaesthesia (p.1780) but it has weak anaesthetic properties compared to other halogenated anaesthetics and poor muscle relaxant activity, and safer anaesthetics are generally preferred. It has also been used to supplement anaesthesia with nitrous oxide-oxygen or halothane. Trichloroethylene is a potent analgesic and has been used in subanaesthetic concentrations to provide analgesia for obstetrics, emergency management of trauma, and other acutely painful procedures.

Trichloroethylene is used in industry as a solvent for oils and fats, for degreasing metals, and for dry cleaning. It has also been used in type correction fluids but is no longer included in most brands.

Xenon

Ksenon; Xénon; Xenón; Xenonum.

Xe = 131.293.

ATC — N01AX15.

ATC Vet — QN01AX15.

Profile

Xenon is a non-explosive gas. Mixtures of 60 or 70% v/v xenon with oxygen have been tried as a general anaesthetic.

◊ References.

1. Lachmann B, *et al.* Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet* 1990; **335:** 1413–15.
2. Yagi M, *et al.* Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. *Br J Anaesth* 1995; **74:** 670–3.
3. Goto T, *et al.* Emergence times from xenon anaesthesia are independent of the duration of anaesthesia. *Br J Anaesth* 1997; **79:** 595–9.
4. Rossaint R, *et al.* Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; **98:** 6–13.
5. Sanders RD, *et al.* Xenon: no stranger to anaesthesia. *Br J Anaesth* 2003; **91:** 709–17.
6. Bedi A, *et al.* Use of xenon as a sedative for patients receiving critical care. *Crit Care Med* 2003; **31:** 2470–7.
7. Preckel B, Schlack W. Xenon—cardiovascularly inert? *Br J Anaesth* 2004; **92:** 786–9.
8. Sanders RD, *et al.* Xenon: elemental anaesthesia in clinical practice. *Br Med Bull* 2005; **71:** 115–35.
9. Baskar N, Hunter JD. Xenon as an anaesthetic gas. *Br J Hosp Med* 2006; **67:** 658–61.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Lenoxe.

Growth Hormone and its Modulators

Human growth is under a complex system of hormonal controls. Growth hormone is produced by specialised cells (somatotropes) in the anterior pituitary; production and secretion are under a system of double regulation by a release-inhibiting hormone, somatostatin, and a growth hormone-releasing hormone, somatorelin, both produced in the hypothalamus. These in turn are modulated by various stimuli: dopamine, serotonin, hypoglycaemia, stress or emotional excitement, and ingestion of protein-rich meals all stimulate growth hormone release, whereas glucose, free fatty acids, insulin-like growth factor and growth hormone itself all suppress it.

The effects of growth hormone in the body rely on its interaction with a distinct growth hormone receptor; some effects, such as stimulation of lipolysis and gluconeogenesis, are direct but others, including its anabolic and growth-promoting effects, are mediated by induction of insulin-like growth factors (somatomedins).

Included in this chapter are growth hormone itself, now generally given as recombinant somatropin (p.1799) or its synthetic methionyl analogue somatrem (p.1799), and somatomedins such as mecasermin (p.1807). Also included are the hypothalamic releasing hormone, somatorelin (p.1808), and its analogue sermorelin (p.1808); the hypothalamic inhibiting hormone, somatostatin (p.1809), and its analogues such as lanreotide (p.1803) and octreotide (p.1803); the growth hormone release stimulant pralmorelin (p.1807); and the growth hormone-receptor antagonist pegvisomant (p.1807). Their use in acromegaly and growth retardation is discussed in more detail below.

Acromegaly and gigantism

Acromegaly and gigantism are syndromes of excess growth hormone secretion, usually associated with a secretory pituitary adenoma (somatropinoma).

Excessive growth hormone secretion in childhood, while the epiphyses of the long bones are open, results in **gigantism**,[1] with a proportional growth spurt and skeletal enlargement. Other common features include obesity, coarse facial features, and disproportionately large hands and feet with thick fingers and toes. Puberty, with the increase in sex hormone secretion that leads to epiphyseal fusion, may be delayed by concomitant hypogonadism, leading to attainment of an even greater ultimate height. If growth hormone excess persists into adulthood, features of acromegaly may be superimposed on gigantism.

When excess growth hormone secretion develops first in adulthood the condition is known as **acromegaly**. Signs and symptoms tend to develop slowly and may be missed, sometimes for years. Growth hormone concentrations, and hence those of insulin-like growth factor I (IGF-I), which is produced in the liver in response to growth hormone, are elevated, sometimes markedly. The facial features become coarser, the jaw enlarges (prognathism), and hands and feet become enlarged. Peripheral neuropathy and carpal tunnel syndrome due to nerve entrapment, arthropathy, osteoarthritis, and muscle weakness, abnormal glucose tolerance, hypertension and left ventricular hypertrophy are all common, as is nodular goitre. Daytime somnolence may occur due to sleep apnoea. Acromegalics have an increased mortality if left untreated, largely due to cardiovascular disease.

Treatment. The biochemical goal of treatment is to normalise growth hormone and IGF-I concentrations in order to reduce some of the signs and symptoms of acromegaly and to reverse the increased risk of mortality.[2] Growth hormone is usually measured after an oral glucose tolerance test (OGTT); this suppresses growth hormone concentrations in healthy subjects, but not in patients with acromegaly. A growth hormone concentration below 1 microgram/litre after an OGTT may be used to exclude acromegaly at the initial diagnosis, and as a target in the assessment of treatment efficacy in acromegaly. Growth hormone concentrations taken as random samples or as mean 24-hour measures may also be used during the long-term monitoring of patients treated for acromegaly; in such circumstances a target concentration below 2.5 micrograms/litre is often used.[3] However, the target concentrations that have been suggested have changed over time with the development of more sensitive assays, and results must be interpreted in the context of the method used.[4] Random IGF-I concentrations should be reduced to normal for age and sex.[3,5]

As for most pituitary tumours, **surgery** is the mainstay of treatment.[2,5] The success rate depends on surgical expertise and the size and extension of the mass, with success rates higher for microadenomas (about 80%) than macroadenomas (less than 50%) depending on criteria.[3,6]

Drug therapy for acromegaly is indicated for patients who refuse surgery, are at increased risk from surgery, have active disease after surgery, or are awaiting the effects of radiotherapy (see below).[2] The somatostatin analogues, octreotide and lanreotide, reduce growth hormone secretion in most patients, but not all will have persistent suppression and normalisation of growth hormone levels.[7,8] Reported response rates vary, but effective growth hormone suppression occurs in about 50 to 55% of patients, and IGF-I is normalised in about 50 to 65%. Somatostatin analogues also produce tumour shrinkage, reducing tumour size by 20 to 50% in about 30% of patients, and improve signs and symptoms of acromegaly, including improvements in cardiac structure and function. Octreotide and lanreotide are given as sustained-release intramuscular injections.[7] Octreotide may be more effective than lanreotide, but not all formulations have been compared.[8] Octreotide can also be given by subcutaneous injection, but must be given three times daily, making it less attractive for long-term therapy. There have been some promising reports of the use of somatostatin analogues for primary therapy, but when there is visual or neurological compromise then surgery is preferred because drug therapy may not provide enough tumour shrinkage to relieve pressure on the optic chiasm.[7,9] There is some data to suggest that pre-operative use of somatostatin analogues could improve cardiovascular, respiratory, and metabolic functions and hence reduce morbidity associated with surgery, and improve remission rates, but further study is needed.[7,8,10] Dopaminergics can produce a paradoxical reduction in growth hormone secretion in some patients with acromegaly, providing symptomatic relief. Bromocriptine produces acceptable suppression of growth hormone secretion in less than 20% of patients.[9] A small study of quinagolide reported the normalisation of hormonal values in about 44% of patients, which was better than the poor responses to a depot preparation of bromocriptine, or cabergoline.[11] A later, open study, however, found that cabergoline produced a good response in about 40% of patients.[12] Dopaminergics are generally added to somatostatin analogue therapy[5] and may be most useful in patients with associated hyperprolactinaemia.[2,5,8] Pegvisomant is a growth hormone-receptor antagonist that may be used when other therapies have failed or are inappropriate.[2,8,13] It is reported[14,15] to lower IGF-I concentrations, improve signs and symptoms of acromegaly, and be well tolerated. Pegvisomant does not reduce growth hormone concentrations so these patients must be monitored by IGF-I measurement.[4] The addition of pegvisomant has also been reported to normalise IGF-I concentrations in patients with persistently elevated levels during somatostatin analogue therapy.[16]

Tumour regression induced by **radiotherapy** is a possible alternative when surgery cannot be performed, there is residual pituitary disease after surgery, or medical therapy has failed.[2,5,6] Although it reduces growth hormone concentrations in about 90% of patients[3] and tumour recurrence is rare[5] its effects are slow and it often produces hypopituitarism. Some consider these to be disadvantages and prefer to use drug treatment for management of tumours that persist after surgery.[5] Since it may take several years for growth hormone concentrations to fall, drug therapy is also given until the effects of radiation therapy are satisfactory.[2,5]

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Growth retardation

Stature follows a normal (bell-shaped) distribution within the population. Short stature has been defined as a height more than 2 standard deviations below the population mean, but there may be some difficulty in deciding at what point short stature becomes abnormal and to some extent this is determined by cultural as well as physiological norms. However, certain disorders are associated with well-defined deficiencies of growth which may be severe enough to warrant the description dwarfism. Some forms are associated with disorders of bone or cartilage growth (skeletal dysplasias), and many of these result additionally in disproportionate growth, as in the short-limbs and large head characteristic of achondroplasia. Other important causes of dwarfism include inadequate production of growth hormone (idiopathic growth hormone deficiency), either alone (isolated growth hormone deficiency) or combined with other pituitary hormone deficiencies as part of hypopituitarism; resistance to circulating growth hormone, as in Laron-type dwarfism, where there is a mutation of the growth hormone receptor; or defects in somatomedin synthesis. Some other endocrine causes of short stature include hypothyroidism, Cushing's syndrome, and Turner's syndrome. Severe chronic disease in childhood such as asthma, chronic renal failure, or liver disorders can result in some growth retardation as can inadequate nutrition due to malabsorption syndromes such as coeliac disease.

Endocrine causes of growth retardation are significant because they may be treatable by appropriate replacement therapy. Isolated growth hormone deficiency, or growth hormone and gonadotrophin deficiencies, are the commonest congenital forms of hypopituitarism. The deficiency is rarely complete, and since most children with short stature will not have growth hormone deficiency care is required in its diagnosis. Although provocative growth hormone tests, which use non-physiological means to stimulate growth hormone secretion, have long been considered the gold standard for diagnosis of growth hormone deficiency they have a number of limitations and some consider measurement of circulating somatomedins (insulin-like growth factors; IGFs) or their binding proteins to be more useful.[1] Different assays may give different results, and it has been advised that therapeutic decisions should be based on a combination of comprehensive clinical and height assessments, biochemical tests, and radiological evaluation.[2,3]

In children with confirmed growth hormone deficiency replacement therapy is appropriate, and is given by subcutaneous injections of synthetic human growth hormone (somatropin) or its methionyl analogue (somatrem). Treatment improves bone density[4,5] and growth velocity;[6,7] final adult height is also increased but the extent of the benefit is unclear. A cohort study of French children registered to receive growth hormone between 1973 and 1993 suggested that the eventual outcome was not as good as expected, and treated individuals remained short.[8] However, a large American cohort that included more than 11 000 growth-hormone deficient patients found that although treated patients remained below target heights, many did achieve heights within the normal range for chronological age.[9] Maximum growth rates occurred in the first year of treatment and fell progressively thereafter, with no significant difference between growth rates after 4 years compared with pretreatment rates. A further cohort study[10] from the same French register for 1987 to 1996 found that adult heights were similar whether patients completed treatment or stopped before reaching adult height, and that patients with severe growth hormone deficiency may respond better than those with less severe deficiency. Growth hormone treatment regimens have changed over the years, and it appears that with optimal treatment it may be possible for some growth-hormone deficient children to achieve their genetic height potential.[7] An important prognostic factor is age, and for optimum results treatment should be started as early as possible in an attempt to maximise height before the onset of puberty.[2,7]

In patients with multiple pituitary hormone deficiencies, genetic defects in growth hormone synthesis, or severe organic growth hormone deficiency, growth hormone therapy should be continued into adulthood. In other patients, growth hormone deficiency may or may not persist into adult life, and retesting should be done after the patient reaches adult height and after 1 to 3 months without therapy.[2,11] In those patients who need continued treatment, the dose of growth hormone should be gradually reduced in order to maintain IGF-I concentrations within the normal range.[11]

Somatorelin (growth hormone-releasing hormone) or its analogue sermorelin have also been tried to boost growth hormone secretion in patients with growth hormone deficiency. Although there have been reports of improved growth rates, there are limited data directly comparing these with growth hormone. One large study[12] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer. Pralmorelin is a small synthetic growth hormone-releasing peptide that is also under investigation.[13,14]

In patients with Laron dwarfism (growth hormone resistance or insensitivity), conventional growth hormone therapy is ineffective because of defects in the growth hormone receptors. However, replacement therapy with mecasermin, the recombinant form of insulin-like growth factor-I, may be of substantial benefit in the treatment of this disorder.[15]

The use of growth hormone in short stature other than that due to indisputable growth hormone deficiency is controversial. Benefit has been reported from growth hormone therapy in children with chronic renal failure,[16,17] in girls with Turner's syndrome (but see p.2081), in young children (6 months to 3 years of age) with Down's syndrome,[18,19] and in Prader-Willi syndrome[20] (p.2149), all of which are associated with marked growth retardation. However, many commentators see such interventions as essentially cosmetic. The treatment of idiopathic short stature in particular, for which no underlying disorder can be identified, in particular, poses problems as the risks and also the benefits in terms of final height are uncertain.[21] Children who are born small for gestational age usually experience catch-up growth by 2 years of age. In those who do not achieve this, growth hormone therapy can induce catch-up growth and improve childhood height scores; data on adult height are limited, however.[22] Guidelines suggest that therapy is justifiable in chronic renal insufficiency,[3,6,23] Turner's syndrome,[3,6,23] Prader-Willi syndrome,[3,23] and for children born small for gestational age.[3] However, sufficient evidence of benefit is lacking for other disorders including non-growth hormone deficient short stature and growth retardation associated with Down's syndrome, and some[6] consider that growth hormone should not be given to children with constitutional delay of growth. More recently, growth hormone therapy has improved growth rate and height in children with SHOX (short stature homeobox-containing gene) deficiency.[24] Mutations and deletions of the SHOX gene, a gene involved in bone and cartilage formation, are associated with various short stature conditions such as Léri-Weill dyschondrosteosis, and are now understood to play a role in the short stature of Turner's syndrome and in some cases of idiopathic short stature.

Although sex hormones have effects on growth they may also cause premature closure of the epiphyses when given to prepubertal or pubertal children, and this has limited their use. Nonetheless, anabolic drugs such as testosterone and oxandrolone have been used in boys, and oestrogen in girls, who have constitutional delay of growth associated with delayed puberty (see p.2079). Oestrogens are not generally used for growth promotion in girls with Turner's syndrome, but as replacement therapy to promote puberty when a satisfactory height has been reached (see p.2081).

A number of other drugs have been investigated in growth retardation. Clonidine, which can promote growth hormone-releasing hormone release, has been given to children with growth hormone deficiency as well as to short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[25-27] Gonadorelin analogues have also been given with growth hormone to short girls without growth hormone deficiency, in an attempt to slow bone maturation and delay puberty, thereby improving adult height.[28] However, a decrease in bone mineral density may outweigh any modest increase in height.[29] Where growth retardation is associated with zinc deficiency, zinc supplementation may be useful (see p.2000).

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Growth Hormone *(BAN)* ⊗

GH; Phyone; Somatotrophin; Somatotropin; Somatotropina; STH.

Гормон Роста; Соматотропин

CAS — 9002-72-6.

Somatrem *(BAN, USAN, pINN)* ⊗

Met-HGH; Methionyl Human Growth Hormone; Somatremum.

Соматрем

$C_{995}H_{1537}N_{263}O_{301}S_8$ = 22 256.

CAS — 82030-87-3.

ATC — H01AC02.

ATC Vet — QH01AC02.

Description. Somatrem is an analogue of somatropin containing an additional (methionyl) amino-acid residue. It may be produced in bacteria from recombinant DNA.

Sometribove (*BAN*) is methionyl bovine growth hormone.

Sometripor (*BAN*) is methionyl porcine growth hormone.

Somatropin *(BAN, USAN, rINN)* ⊗

CB-311; HGH; Human Growth Hormone; LY-137998; Somatropiini; Somatropina; Somatropinas; Somatropine; Somatropinum; Szomatropin.

Соматропин

$C_{990}H_{1528}N_{262}O_{300}S_7$ = 22 125.

CAS — 12629-01-5.

ATC — H01AC01.

ATC Vet — QH01AC01.

Description. Somatropin is synthetic human growth hormone having the normal structure of the major (22K) component of natural human pituitary growth hormone. It consists of a single polypeptide chain of 191 amino acids with disulfide linkages between positions 53 and 165 and between 182 and 189. For labelling purposes, the name may carry in parentheses an approved code in lower case letters indicative of the method of production: (epr) indicates production by enzymatic conversion of a precursor produced by a bacterium genetically modified by recombinant DNA technology; (rbe) indicates production from bacteria genetically modified by recombinant DNA technology; (rmc) indicates production from genetically engineered and transformed mammalian (mouse) cells.

Somidobove (*BAN*) is synthetic bovine growth hormone.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Somatropin). A protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary. A white or almost white powder, containing not less than 2.5 units/mg. Store at 2° to 8° in airtight containers.

Ph. Eur. 6.2 (Somatropin Concentrated Solution). A clear or slightly turbid, colourless solution. It may contain buffer salts and other auxiliary substances. Store at −20° in airtight containers. Avoid repeated freezing and thawing.

USP 31 (Somatropin). A protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilised powder or bulk solution by methods based on recombinant DNA technology. The lyophilised powder contains not less than 910 micrograms of somatropin per mg, calculated on the anhydrous basis. The bulk solution contains not less than 910 micrograms of somatropin per mg of total protein.

Store at −25° to −10° in airtight containers.

Units

4.4 units of human growth hormone (somatropin) are contained in 1.75 mg of freeze-dried purified human growth hormone, with 20 mg of glycine, 2 mg of mannitol, 2 mg of lactose, and 2 mg of sodium bicarbonate, in one ampoule of the first International Standard (1987).

The second International Standard for Somatropin (2000), rDNA-derived human growth hormone, has a defined content of 1.95 mg of protein per ampoule, with a specific activity of 3.0 units/mg. One mg of anhydrous Somatropin USP is equivalent to 3.0 USP Somatropin Units. Commercial preparations vary somewhat in the number of units/mg.

Adverse Effects and Precautions

Antibodies to growth hormone have been formed in some patients but these rarely seem to affect growth. There may be redness, itching, lumps, or lipoatrophy at the site of injection. Transient dose-related fluid retention with peripheral oedema and carpal tunnel syndrome has occurred; headache, muscle and joint pain, paraesthesia, and cases of benign intracranial hypertension have been reported. Although growth hormone has diabetogenic effects, high acute dosage has been associated with hypoglycaemia followed by hyperglycaemia. Growth hormone therapy may further increase the risk of ear disorders and otitis media in patients with Turner's syndrome, who are already at increased risk of ear and hearing disorders.

Growth hormone therapy is contra-indicated in patients with active neoplasms or intracranial lesions and should be stopped if evidence of tumour growth develops. Growth hormones should not be used for growth promotion in patients with closed epiphyses. Patients with scoliosis should be monitored during growth hormone therapy because of the risk of progression of scoliosis that can occur with rapid growth. Because of the diabetogenic effect of growth hormone it should be given with care to patients with diabetes mellitus; adjustment of antidiabetic therapy may be necessary. Somatropin is contra-indicated in patients with proliferative or preproliferative diabetic retinopathy. Hypothyroidism may develop during treatment, and may result in suboptimal response. Secondary hypoadrenalism may be unmasked by somatropin treatment, requiring glucocorticoid replacement therapy (see also Interactions, below). Growth hormone should not be used in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see also below). For the suggestion that growth hormone should not be used to treat acute catabolic states, as in patients with severe burns or who are otherwise critically ill, see Burns, under Uses and Administration, below.

◊ Reviews.

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Abuse. Growth hormone has been subject to abuse in sport for its anabolic effects. However, limited study data suggest that although it may increase lean body-mass, it has minimal effect on strength and athletic performance, and may worsen exercise capacity.[1]

1. Liu H, *et al.* Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008; **148:** 747–58.

Benign intracranial hypertension. Benign intracranial hypertension (pseudotumor cerebri) has been described[1,2] in patients given growth hormone treatment. In an analysis[3] of a post-marketing surveillance database (1985 to 2000) of almost 40 000 children and adolescents who had been treated with growth hormone for various conditions, benign intracranial hypertension was more common than in the general paediatric population. The incidence in new patients starting growth hormone therapy was estimated to be about 30 in 100 000, and it had occurred more frequently in patients with renal failure or Turner's syndrome. Headache and papilloedema were the most common symptom and sign, but these did not occur in all patients, and most cases had an onset of a few months. The condition was effectively managed by stopping growth hormone. A small number of patients were rechallenged after the benign intracranial hypertension had resolved, and most could be treated with doses that were 25 to 50% of the original dose. In a report of another case[4] it was pointed out that diagnosis may be complicated by the not infrequent occurrence of headache in patients receiving growth hormone; these normally resolved spontaneously.

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Carcinogenicity. Despite fears to the contrary, studies in children given growth hormone after cranial irradiation for brain tumours or CNS leukaemia have found no evidence that therapy with growth hormone increased the relapse rate.[1-3]

Cases of acute leukaemia have been reported among patients treated with growth hormones. An international workshop convened in 1988 to review known leukaemia cases in patients treated with growth hormones in Europe, North America, Japan, and Australia since 1959 found the observed incidence of leukaemia in growth hormone-treated patients to represent a twofold increase over the expected rate.[4] It was concluded that there may be a small increase in leukaemia incidence associated with growth hormone treatment of growth hormone-deficient patients, but that it was not clear that this was actually attributable to growth hormone. A later study involving 6284 patients treated with growth hormone between 1963 and 1985 in the USA confirmed an increase of about 2.5-fold in the incidence of leukaemia in this population, but noted that many of the patients had other risk factors for leukaemia.[5] It has been suggested that growth hormone deficiency is itself a risk factor for leukaemia and that perhaps this, rather than growth hormone treatment, is related to the increased incidence of leukaemia in these patients.[6] If there is any risk it is relatively small, and in view of the essential nature of growth hormone therapy in growth hormone-deficient children it was considered inappropriate and unwise to withhold it.[4] Further large cohort studies of survivors of childhood cancers[3] or patients treated for idiopathic growth hormone deficiency[7] have found that the use of growth hormone was not associated with an increased risk of leukaemia.

There is some evidence to suggest that growth hormone may increase the risk of solid tumours. The risk of secondary solid tumours was increased in a cohort of childhood cancer survivors, but the authors considered that the risk was probably quite small compared with the benefits of growth hormone therapy in these patients.[3] Another cohort of patients who had been treated for idiopathic growth hormone deficiency showed increased risks in the incidence and mortality of colorectal cancer.[7]

Further reports of malignancies associated with growth hormone therapy include two children with Bloom's syndrome (a rare chromosomal disorder affecting DNA replication), one of whom developed B-cell non-Hodgkin's lymphoma and the other stem-cell leukaemia.[8]

Continued surveillance of patients who have received growth hormone therapy has been encouraged.[9]

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4. Fisher DA, *et al.* Leukaemia in patients treated with growth hormone. *Lancet* 1988; **i:** 1159–60.
5. Fradkin JE, *et al.* Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993; **270:** 2829–32.
6. Rapaport R, *et al.* Relationship of growth hormone deficiency and leukemia. *J Pediatr* 1995; **126:** 759–61.
7. Swerdlow AJ, *et al.* Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet* 2002; **360:** 273–7.
8. Brock PR, *et al.* Malignant disease in Bloom's syndrome children treated with growth hormone. *Lancet* 1991; **337:** 1345–6.
9. Ogilvy-Stuart AL, Gleeson H. Cancer risk following growth hormone use in childhood: implications for current practice. *Drug Safety* 2004; **27:** 369–82.

Creutzfeldt-Jakob disease. Reports in 1985 of a small number of deaths from Creutzfeldt-Jakob disease in patients under 40 years of age who had received growth hormone extracted from human pituitary glands resulted in the suspension of the distribution of pituitary-derived growth hormone by the licensing authorities in a number of countries, including Australia, Canada, the Netherlands, the UK, and the USA. Preparations of non-pituitary-derived growth hormone are now available that are free from contamination with Creutzfeldt-Jakob agent. However, because of the long incubation period of the disease, cases are still being reported in patients who had received pituitary-derived growth hormone years previously.[1-4]

1. Brown P, *et al.* Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; **55:** 1075–81.
2. Croes EA, *et al.* Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. *J Neurol Neurosurg Psychiatry* 2002; **72:** 792–3.
3. Swerdlow AJ, *et al.* Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003; **61:** 783–91.
4. Hirst C. Iatrogenic Creutzfeldt-Jakob disease presenting 24 years after human growth hormone administration. *Br J Hosp Med* 2005; **66:** 592–3.

Effects on carbohydrate metabolism. A retrospective analysis[1] of data from a pharmacoepidemiological survey of children treated with growth hormone found a higher incidence of type 2 diabetes, compared with that found in untreated children. The researchers speculated that growth hormone treatment might precipitate the onset of type 2 diabetes in predisposed patients, and proposed that patients with risk factors for diabetes, including Turner's syndrome, Prader-Willi syndrome, or intrauterine growth retardation, be monitored. Studies of growth hormone have reported rises in serum concentrations of insulin, fasting and postprandial blood-glucose, and glycosylated haemoglobin, although these changes were generally small.[2] It has been noted that these effects appear to regress during treatment, but not always, and in some patients glucose intolerance or diabetes mellitus are not reversible after withdrawal of growth hormone.

Nonketotic hyperglycaemia developed within weeks of beginning growth hormone therapy in a 22-month-old child, leading to convulsions and metabolic acidosis; the patient died despite correction of the hyperglycaemia.[3]

1. Cutfield WS, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 2000; **355:** 610–13.
2. Jeffcoate W. Growth hormone therapy and its relationship to insulin resistance, glucose intolerance and diabetes mellitus: a review of recent evidence. *Drug Safety* 2002; **25:** 199–212.
3. Garg AK, Hyperglycemia during replacement growth hormone therapy. *J Pediatr* 1994; **125:** 329.

Effects on immune function. Growth hormone is generally considered to interact with the immune system although there is a lack of evidence that this is clinically significant.[1-4] There has been a report of acute renal transplant rejection in 2 children receiving treatment for growth retardation with somatropin.[5] In both children renal function of the transplant was stable for several years before somatropin was started, and growth hormone therapy had continued for some months before rejection occurred. It was suggested that during the first months of growth hormone therapy in transplant recipients, immunosuppressive therapy should be increased and transplant function carefully monitored. However, in subsequent studies[6,7] the use of growth hormone did not affect the incidence of rejection.

1. Church JA, *et al.* Immune functions in children treated with biosynthetic growth hormone. *J Pediatr* 1989; **115:** 420–3.
2. Rapaport R, Oleske J. Immune function during growth hormone therapy. *J Pediatr* 1990; **116:** 669–70.
3. Rekers-Mombarg LTM, *et al.* Immunologic studies in children with idiopathic short stature before and during growth hormone therapy. *Horm Res* 1995; **44:** 203–7.
4. Lebl J, *et al.* Immune system in adults with childhood-onset growth hormone deficiency: effect of growth hormone therapy. *Endocr Regul* 2000; **34:** 169–73.
5. Tydén G, *et al.* Acute renal graft rejection after treatment with human growth hormone. *Lancet* 1990; **336:** 1455–6.
6. Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *Arch Dis Child* 1998; **79:** 481–7.
7. Maxwell H, *et al.* Growth hormone and markers of immune function in children with renal transplants. *Pediatr Nephrol* 2000; **14:** 473–5.

Effects on the pancreas. A report of acute pancreatitis on starting growth hormone treatment in a patient with pseudohypoparathyroidism and growth hormone deficiency.[1] Ten further cases of acute pancreatitis associated with growth hormone treatment had been reported to the FDA at the time of writing.

1. Malozowski S, *et al.* Acute pancreatitis associated with growth hormone therapy for short stature. *N Engl J Med* 1995; **332:** 401–2.

Effects on skeletal muscle. A report of mild inflammatory myositis, with myalgia and muscle weakness, in 2 patients receiving growth hormone therapy.[1] It was suggested that the effect might be due to *m*-cresol used as a preservative in the preparation.

1. Yordam N. Myositis associated with growth hormone therapy. *J Pediatr* 1994; **125:** 671.

Gynaecomastia. A report of 22 cases of prepubertal gynaecomastia diagnosed during growth hormone treatment.[1]

1. Malozowski S, Stadel BV. Prepubertal gynecomastia during growth hormone therapy. *J Pediatr* 1995; **126:** 659–61.

Hypersensitivity. Generalised urticaria in a patient given somatropin was overcome by a desensitisation regimen.[1] The patient was subsequently maintained uneventfully on daily injections of somatropin.

1. Walker SB, *et al.* Systemic reaction to human growth hormone treated with acute desensitization. *Pediatrics* 1992; **90:** 108–9.

Iron deficiency. The view has been expressed[1] that given the increased production of haemoglobin and the prevalence of iron deficiency in patients treated with growth hormone, supplementation with iron should be considered in patients receiving growth hormone treatment.

1. Vihervuori E, *et al.* Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. *J Pediatr* 1994; **125:** 242–5.

Prader-Willi syndrome. One US manufacturer of somatropin has stated that as of April 2003 it was aware of 7 reports of death in children with Prader-Willi syndrome treated with growth hormone.[1] The patients shared one or more of the following risk factors: severe obesity, a history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. It was recommended that patients with Prader-Willi syndrome should be evaluated for upper airway obstruction, before beginning treatment, and if signs of such obstruction, such as snoring, developed during treatment therapy should be suspended. Somatropin was considered contra-indicated in these patients if they were severely obese or had severe respiratory impairment; licensed drug information in the USA had been amended accordingly. Early diagnosis and aggressive treatment of respiratory infections was also recommended. A few cases have been described in the literature.[2-4]

Children with Prader-Willi syndrome appear to have a higher incidence of respiratory problems such as sleep apnoea, hypoventilation, and infections than healthy children.[5] A prospective study[6] of 25 patients reported that sleep-disordered breathing had actually improved in most of them after 6 weeks of growth hormone therapy. However, there was a subgroup of 6 patients in which obstructive sleep apnoea and hypopnoea worsened; 4 of them had developed upper respiratory-tract infections and enlarged tonsils, and 2 had high serum concentrations of insulin-like growth factor I (IGF-I) and enlarged tonsils.

1. Pharmacia, USA. 2003 Safety alert: Genotropin (somatropin [rDNA origin] for injection). Available at: http://www.fda.gov/medwatch/SAFETY/2003/genotropin.htm (accessed 14/06/07)
2. Eiholzer U, *et al.* Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment: a case report. *Horm Res* 2002; **58** (suppl 3): 24–6.
3. Van Vliet G, *et al.* Sudden death in growth hormone-treated children with Prader-Willi syndrome. *J Pediatr* 2004; **144:** 129–31.
4. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
5. Eiholzer U. Deaths in children with Prader-Willi syndrome: a contribution to the debate about the safety of growth hormone treatment in children with PWS. *Horm Res* 2005; **63:** 33–9.
6. Miller J, *et al.* Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006; **91:** 413–17.

Interactions

High doses of corticosteroids may inhibit the growth promoting effects of growth hormone. Doses of growth hormone may need to be increased in women receiving oral oestrogen replacement therapy, and may require adjustment if the route of oestrogen administration is changed.

Pharmacokinetics

Somatropin is well absorbed after subcutaneous or intramuscular injection with a bioavailability varying from about 60 to 80%; peak serum concentrations may not be achieved for several hours. After intravenous injection it has a half-life of about 20 to 30 minutes but after subcutaneous or intramuscular doses serum concentrations decline with a half-life of 3 to 5 hours, due to more prolonged release from the injection site. It is metabolised in the liver and kidneys and excreted in bile.

Absorption. Studies of the pharmacokinetics of somatropin after transdermal jet injection from 2 devices in healthy subjects suggested that absorption was more rapid and peak serum concentration higher than after conventional subcutaneous injection of the same dose.[1,2] However this did not seem to result in any difference in the total amount absorbed, nor in the biological effect. A third device[3] provided a similar concentration-time profile for somatropin compared with conventional injection in healthy subjects. When studied in children with growth hormone deficiency, however, this device was considered to cause more bleeding, pain, soreness, and bruising at the injection site than a needle-injection pen device.

1. Verhagen A, *et al.* Pharmacokinetics and pharmacodynamics of a single dose of recombinant human growth hormone after subcutaneous administration by jet-injection: comparison with conventional needle-injection. *Eur J Clin Pharmacol* 1995; **49:** 69–72.
2. Agersø H, *et al.* Pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone administered by ZomaJet 2 Vision, a new needle-free device, compared to subcutaneous administration using a conventional syringe. *J Clin Pharmacol* 2002; **42:** 1262–8.
3. Dörr HG, *et al.* Are needle-free injections a useful alternative for growth hormone therapy in children? Safety and pharmacokinetics of growth hormone delivered by a new needle-free injection device compared to a fine gauge needle. *J Pediatr Endocrinol Metab* 2003; **16:** 383–92.

Uses and Administration

Somatropin is synthetic human growth hormone and somatrem its methionyl analogue.

Growth hormone is an anabolic hormone secreted by the anterior lobe of the pituitary, varying in size and amino-acid sequence between animal species. It promotes growth of skeletal, muscular, and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. The hormone has a diabetogenic action on carbohydrate metabolism. Secretion is pulsatile and dependent on neural and hormonal influences including a hypothalamic release-inhibiting hormone (see Somatostatin, p.1809), and a hypothalamic releasing hormone (see Somatorelin, p.1808). Sleep, hypoglycaemia, and physical or emotional stress result in increased secretion of growth hormone. The effects of growth hormone on skeletal growth are mediated by the somatomedins (see p.1807).

Somatropin or somatrem is given to children with open epiphyses for the treatment of short stature due to growth hormone deficiency (pituitary dwarfism) following assessment of pituitary function. Somatropin is also used in children with some other forms of growth retardation, such as that associated with Turner's syndrome, Noonan syndrome, SHOX (short stature homeobox-containing gene) deficiency, or chronic renal insufficiency, in short children born small for gestational age, and in idiopathic short stature. In Prader-Willi syndrome, somatropin is given to improve growth and body composition (but see also under Adverse Effects and Precautions, above). In adults, somatropin is given for confirmed growth hormone deficiency. It is also used in the management of wasting or cachexia associated with AIDS. In short bowel syndrome, somatropin is used to increase intestinal absorption of water, electrolytes, and nutrients from specialised nutritional support.

Doses should be individualised for each patient. Manufacturers vary somewhat in their estimates of the number of units/mg for somatropin and although some countries specify labelling in mg, others require labelling in units or both. Somatrem has been given in doses similar to those of somatropin, but is no longer generally available.

In *children with growth hormone deficiency,* the usual daily dose in the UK is 25 to 35 micrograms/kg by subcutaneous injection (0.07 to 0.1 units/kg), or 0.7 to 1 mg/m^2 (2 to 3 units/m^2). Similar doses are used in other countries, by subcutaneous or intramuscular injection, and the total weekly dose may be divided into 3, 6, or 7 doses. A suspension of somatropin for subcutaneous depot injection has also been used, given in a dose of 1.5 mg/kg on the same day of each month. Alternatively, the dose could be given as 750 micrograms/kg twice monthly (for example, on days 1 and 15 of each month).

In *Turner's syndrome* (gonadal dysgenesis), a subcutaneous daily dose of 45 to 50 micrograms/kg (0.14 units/kg), or 1.4 mg/m^2 (4.3 units/m^2), may be used, although higher doses of up to 67 micrograms/kg daily have been licensed for use in the USA. Doses of up to 66 micrograms/kg daily have been used for growth retardation related to *Noonan syndrome*. Daily doses of 45 to 50 micrograms/kg may be used in children with growth retardation due to *chronic renal insufficiency* or *SHOX deficiency.*

In children with growth retardation who were *born small for gestational age*, the licensed daily dose in the UK is 35 micrograms/kg by subcutaneous injection (0.1 units/kg), or 1 mg/m^2 (3 units/m^2). In the USA, the licensed dose is somewhat higher, at 480 micrograms/kg weekly, divided into 6 or 7 doses.

In children with *idiopathic short stature* somatropin is given subcutaneously in a weekly dose of up to 300 to 470 micrograms/kg divided into 6 or 7 doses.

In children with *Prader-Willi syndrome*, a daily dose of about 35 micrograms/kg, or 1 mg/m^2, is given subcutaneously; daily doses should not exceed 2.7 mg.

In *adults with growth hormone deficiency* lower doses are recommended. The initial dose is not more than 6 micrograms/kg (0.018 units/kg) subcutaneously daily. The dose can then be gradually increased according to patient response, to a usual maximum of 12.5 micrograms/kg daily. Alternatively, an initial dose in the range of 150 to 300 micrograms daily (0.45 to 0.9 units) is increased gradually at monthly intervals, based on clinical response, to a maintenance dose of no more than 1 mg daily. Dosage requirements may decline with increasing age. In the UK, it has been recommended that treatment should be re-assessed 9 months after starting therapy.

In the treatment of *HIV-associated wasting or cachexia* somatropin is given in doses of 100 micrograms/kg daily by subcutaneous injection at bedtime, to a maximum of 6 mg daily. A starting dose of 100 micrograms/kg on alternate days may be considered for patients who are at increased risk of adverse effects.

In *short bowel syndrome* somatropin is given subcutaneously in a dose of about 100 micrograms/kg daily (to a maximum of 8 mg daily) for 4 weeks.

Administration in adults. Growth hormone continues to be secreted in adult life, although secretion and activity gradually decline with increasing age, and it appears to play a role in maintaining skeletal and lean body-mass amongst other things. In adults with growth hormone deficiency (usually secondary to pituitary adenoma or its treatment) replacement therapy with growth hormone is reported to decrease body fat and abdominal adiposity, increase lean body-mass, and improve lipid profiles.[1-4] It may also increase bone density,[1,3] but many studies have been uncontrolled and of short duration, and any beneficial effect on bone density appears to be small.[5] Strength and exercise capacity can also be improved, although prolonged growth hormone therapy and physical training may be required to increase muscle performance.[3] Cardiac structure and function can be adversely affected by growth hormone deficiency, and replacement therapy in adults can have a positive effect on some cardiac parameters.[6] There are also some reports of improvements in quality of life;[3] although a study[7] using general standardised psychometric tests found no benefit, another[8] using a questionnaire developed for adults with hypopituitarism reported long-term benefits. Long-term data are not yet available to determine whether growth hormone therapy reduces the mortality rate in this group of patients, but it may provide some protection against myocardial infarction.[9] Guidelines on the use of growth hormone in adults with growth hormone deficiency have been issued.[10-13]

Less well established is the use of growth hormone in otherwise healthy elderly patients. Considerable controversy has attended suggestions that growth hormone therapy may retard or reverse some of the metabolic effects of ageing, and there is some concern that these patients may be at increased risk of adverse effects.[14] Studies[15] have shown that growth hormone can increase lean body-mass and decrease body fat, but functional ability does not necessarily improve and common adverse effects include peripheral oedema, carpal tunnel syndrome, arthralgias, and gynaecomastia.

Other uses for growth hormone in adult patients are discussed below.

1. Götherström G, *et al.* A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001; **86:** 4657–65.
2. Attanasio AF, *et al.* Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3-year results from the HypoCCS Database. *J Clin Endocrinol Metab* 2002; **87:** 1600–6.
3. Verhelst J, Abs R. Long-term growth hormone replacement therapy in hypopituitary adults. *Drugs* 2002; **62:** 2399–2412.
4. Maison P, *et al.* Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2004; **89:** 2192–9.
5. Davidson P, *et al.* Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2004; **60:** 92–8.
6. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003; **108:** 2648–52.
7. Baum HBA, *et al.* Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab* 1998; **83:** 3184–9.
8. Rosilio M, *et al.* Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab* 2004; **89:** 1684–93.

9. Svensson J, *et al.* Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab* 2004; **89:** 3306–12.
10. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab* 1998; **83:** 379–81. Also available at: http://www.ghresearchsociety.org/files/PortStevens.pdf (accessed 04/10/05)
11. AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. *Endocr Pract* 2003; **9:** 64–76. Also available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf (accessed 05/07/06)
12. NICE. Human growth hormone (somatropin) in adults with growth hormone deficiency: Technology Appraisal 64 (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA64_HGHadults_fullguidance.pdf (accessed 20/08/08)
13. Molitch ME, *et al.* Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 1621–34. Also available at: http://www.endo-society.org/guidelines/final/upload/042506_CG_HormoneBook.pdf (accessed 20/08/08)
14. Vance ML. Can growth hormone prevent aging? *N Engl J Med* 2003; **348:** 779–80.
15. Liu H, *et al.* Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146:** 104–15.

Burns. In children with severe burns requiring skin grafts, somatropin 200 micrograms/kg daily by intramuscular injection reduced donor-site healing times and hospitalisation times; subcutaneous somatropin 100 micrograms/kg daily was ineffective.[1] There has been some concern that growth hormone therapy might increase hypertrophic scar formation, but a study[2] of somatropin 50 micrograms/kg daily for 1 year after hospital discharge did not find this. Somatropin treatment given during hospitalisation has also been reported to ameliorate burn-induced growth delays in such children; those injured during non-growth-spurt years may benefit most.[3,4] Long-term therapy given for 1 year after wound healing may also improve weight, linear growth, lean body-mass, and bone mineral content.[5] However, the manufacturers have recommended that somatropin should not be used to treat acute catabolic states in critically ill and burn patients, as there is some evidence in adults that mortality may be increased.[6] The management of burns is described on p.1578.

1. Herndon DN, *et al.* Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; **212:** 424–9.
2. de Oliveira GV, *et al.* Growth hormone effects on hypertrophic scar formation: a randomized controlled trial of 62 burned children. *Wound Repair Regen* 2004; **12:** 404–11.
3. Low JFA, *et al.* Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet* 1999; **354:** 1789.
4. Low JFA, *et al.* The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns* 2001; **27:** 447–52.
5. Hart DW, *et al.* Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg* 2001; **233:** 827–34.
6. Takala J, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341:** 785–92.

Cachexia and lipodystrophy. Treatment with subcutaneous growth hormone has been reported[1,2] to reverse weight loss and improve body wasting in subjects with HIV disease (p.858). It can have beneficial effects on physical function, body-weight, lean body-mass, and measures of health-related quality of life.[3]

Some benefit has been reported[4-8] with growth hormone therapy in HIV-associated lipodystrophy.

Growth hormone therapy has also been reported to improve metabolic indicators of malnutrition in some[9] but not other[10] studies of patients undergoing haemodialysis.

1. Schambelan M, *et al.* Recombinant human growth hormone in patients with HIV-associated wasting: a randomized, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 873–82.
2. Moyle GJ, *et al.* Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2004; **35:** 367–75.
3. Goldsmith DR, Wagstaff AJ. Mammalian cell-derived somatropin: a review of its use in the management of HIV-associated wasting. *Drugs* 2006; **66:** 387–401.
4. Lo JC, *et al.* The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab* 2001; **86:** 3480–7.
5. Tai VW, *et al.* Effects of recombinant human growth hormone on fat distribution in patients with human immunodeficiency virus–associated wasting. *Clin Infect Dis* 2002; **35:** 1258–62.
6. Kotler DP, *et al.* Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; **35:** 239–52. Correction. *ibid.* 2006; **43:** 378–81.
7. Lo JC, *et al.* The effects of low-dose growth hormone in HIV-infected men with fat accumulation: a pilot study. *Clin Infect Dis* 2004; **39:** 732–5.
8. Grunfeld C, *et al.* Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12 week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr* 2007; **45:** 286–97.
9. Johannsson G, *et al.* Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. *Am J Kidney Dis* 1999; **33:** 709–17.
10. Kotzmann H, *et al.* One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract* 2003; **93:** c75–82.

Cardiovascular disorders. A few small uncontrolled studies have reported improvements in heart failure (p.1165) with the use of growth hormone.[1] A meta-analysis[2] of 12 studies using growth hormone in adults with chronic heart failure, including 8 placebo-controlled studies, also found evidence for improvement in several cardiovascular measures; however, individual results have been mixed and further study of long-term high-dose therapy is needed. A small underpowered study[3] of 6 months of treatment in children with dilated cardiomyopathy found only a trend towards improved cardiac function. Retrospective analysis[4] of a group of childhood cancer survivors found that growth hormone used to treat deficiency had some beneficial effects on anthracycline-induced left ventricular dysfunction, but that these diminished when growth hormone therapy was stopped.

1. Volterrani M, *et al.* Role of growth hormone in chronic heart failure: therapeutic implications. *Drugs* 2000; **60:** 711–19.
2. Le Corvoisier P, *et al.* Cardiac effects of growth hormone treatment in chronic heart failure: a meta-analysis. *J Clin Endocrinol Metab* 2007; **92:** 180–5.
3. McElhinney DB, *et al.* Recombinant human growth hormone treatment for dilated cardiomyopathy in children. Abstract: *Pediatrics* 2004; **114:** 1074–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/114/4/e452 (accessed 16/09/05)
4. Lipshultz SE, *et al.* Cardiac changes associated with growth hormone therapy among children treated with anthracyclines. *Pediatrics* 2005; **115:** 1613–22.

Fibromyalgia. Symptomatic improvement was reported after several months in a study of daily subcutaneous growth hormone injection in women with fibromyalgia,[1] a painful form of soft-tissue rheumatism (p.13), and low levels of insulin-like growth factor I (IGF-I).

1. Bennett RM, *et al.* A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med* 1998; **104:** 227–31.

Growth retardation. Growth hormone is a mainstay of the management of growth retardation[1] (p.1798) and guidelines[2-6] have been issued concerning its appropriate use.

1. Harris M, *et al.* Growth hormone treatment in children: review of safety and efficacy. *Pediatr Drugs* 2004; **6:** 93–106.
2. Drug and Therapeutics Committee, Lawson Wilkins Pediatric Endocrine Society. Guidelines for the use of growth hormone in children with short stature. *J Pediatr* 1995; **127:** 857–67.
3. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
4. NICE. Guidance on the use of human growth hormone (somatropin) in children with growth failure: Technology Appraisal 42 (May 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/HGHinChild-42-ALS.pdf (accessed 20/08/08)
5. Wilson TA, *et al.* Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003; **143:** 415–21.
6. AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. *Endocr Pract* 2003; **9:** 64–76. Also available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf (accessed 05/07/06)

Infertility. Growth hormone appears to sensitise the ovary to stimulation by gonadotrophins and it has been suggested that somatropin may have a role in the management of female infertility. However, studies of somatropin added to gonadotrophin regimens have generally been small, used different treatment protocols and outcome measures, and studied mixed groups of women in terms of the cause of infertility. Studies of women with poor response to ovarian stimulation have shown mixed results, and response may depend on the cause of infertility. Mixed results have also been reported in women with polycystic ovary syndrome. Benefits may be most likely in women with hypogonadotrophic hypogonadism,[1] but there is no additional benefit for women who have a normal ovarian response to gonadotrophins.[1,2] UK guidelines[3] for the treatment of infertility do not recommend its use. Growth hormone has also been tried similarly to enhance spermatogenesis in infertile men unresponsive to conventional therapy, but studies have been small, and despite some encouraging reports[4] others have found no benefit.[5,6]

For a discussion of infertility and the more usual drugs used in its management, see p.2080.

1. Artini PG, *et al.* Growth hormone cotreatment with gonadotropins in ovulation induction. *J Endocrinol Invest* 1996; **19:** 763–79.
2. Harper K, *et al.* Growth hormone for in vitro fertilization. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (issued February 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/Fertility_full.pdf (accessed 24/07/08) or http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 24/07/08)
4. Shoham Z, *et al.* Cotreatment with growth hormone for induction of spermatogenesis in patients with hypogonadotropic hypogonadism. *Fertil Steril* 1992; **57:** 1044–51.
5. Ovesen PG, *et al.* Vaeksthormonbehandling af maend med nedsat saedkvalitet. *Ugeskr Laeger* 1998; **160:** 176–80.
6. Giagulli VA. Absence of effect of recombinant growth hormone to classic gonadotropin treatment on spermatogenesis of patients with severe hypogonadotropic hypogonadism. *Arch Androl* 1999; **43:** 47–53.

Osteogenesis imperfecta. For reference to possible benefit from growth hormone therapy in patients with osteogenesis imperfecta, see p.1083.

Osteomalacia. As mentioned on p.1084, there has been some interest in the use of growth hormone in children with hypophosphataemic rickets.

Prader-Willi syndrome. Growth hormone treatment may be of benefit in the management of Prader-Willi syndrome (p.2149). It increases growth velocity and improves body composition, by reducing fat mass and increasing muscle mass. However, there is limited information about long-term efficacy, and the effect on growth velocity is reported to wane after 1 to 3 years of therapy. There are also specific contra-indications and precautions relating to the use of growth hormone in these patients (see under Adverse Effects and Precautions, above).

References.

1. Carrel AL, *et al.* Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr* 1999; **134:** 215–21.
2. Myers SE, *et al.* Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr* 2000; **137:** 42–9.
3. Burman P, *et al.* Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; **22:** 787–99.
4. Carrel AL, *et al.* Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab* 2002; **87:** 1581–5.
5. Whitman BY, *et al.* The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. Abstract: *Pediatrics* 2002; **109:** 308–9. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e35 (accessed 16/09/05)
6. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; **88:** 283–5.
7. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; **145:** 744–9.
8. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
9. Myers SE, *et al.* Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A* 2007; **143:** 443–8.

Short bowel syndrome. A combination of growth hormone, glutamine, and dietary modification may improve intestinal absorption of fluid, electrolytes, and other nutrients, and thus reduce parenteral nutrition requirements in patients with short bowel syndrome.[1] However, studies have produced conflicting results, and benefit may depend on a number of factors including the type and length of remaining bowel, the presence or absence of mucosal disease, and the doses of somatropin and glutamine.[2]

1. Keating GM, Wellington K. Somatropin (Zorbtive) in short bowel syndrome. *Drugs* 2004; **64:** 1375–81.
2. Matarese LE, *et al.* Growth hormone, glutamine, and modified diet for intestinal adaptation. *J Am Diet Assoc* 2004; **104:** 1265–72.

Veterinary and agricultural use. Bovine growth hormone or bovine somatotropin (bovine somatotropin; BST) can increase milk yield in dairy cows. There has been considerable debate about both animal welfare and human food safety, and although it is approved in the USA[1] its use is banned in the EU.[2]

1. FDA. CVM Update. Update on human safety of BST (February 5th, 1999). Available at: http://www.fda.gov/cvm/CVM_updates/BSTSAFUP.html (accessed 16/09/05)
2. Anonymous. Public health and consumer protection: animal welfare 1.2.220. Bulletin EU 12-1999. Available at: http://europa.eu/bulletin/en/9912/p102220.htm (accessed 05/07/06)

Preparations

BP 2008: Somatropin Injection;
Ph. Eur.: Somatropin for Injection;
USP 31: Somatropin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Biotropin; Genotropin; HHT; Hutrope; Norditropin; Saizen; Serostim†; ***Austral.:*** Genotropin; Humatro-Pen†; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Scitropin; ***Austria:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Belg.:*** Genotonorm; Humatrope; Norditropin; NutropinAq; Zomacton; ***Braz.:*** Biotropin†; Eutropin; Genotropin; Hormotrop; Humatrope; Norditropin; Saizen; Somatrop; ***Canad.:*** Humatrope; Nutropin; Protropin†; Saizen; Serostim; ***Chile:*** Genotonorm; HHT; Humatrope; Hutrope; Norditropin; Saizen†; ***Cz.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin; Zomacton; ***Denm.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Zomacton; ***Fin.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Fr.:*** Genotonorm; Maxomat; Norditropine; NutropinAq;

Saizen; Umatrope; Zomacton; **Ger.:** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; **Gr.:** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; **Hong Kong:** Genotropin; Humatrope; Norditropin; Saizen; Scitropin; Serostim; **Hung.:** Genotropin; Humatrope; Norditropin; Nutropin; Saizen†; Zomacton†; **India:** Saizen; **Indon.:** Eutropin; Genotropin; Norditropin; Saizen; **Irl.:** Genotropin; Norditropin; Saizen; Zomacton; **Israel:** Bio-Tropin; Genotropin; Norditropin; **Ital.:** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; **Jpn:** Growject; Norditropin; **Malaysia:** Genotropin; Norditropin; Saizen; **Mex.:** Cryo-Tropin; Genotropin; HHT; Humatrope; Norditropin; Saizen; Serostim; **Neth.:** Genotropin; Humatrope; Norditropin; Nutropin; Zomacton; **Norw.:** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; **NZ:** Genotropin; Norditropin; Saizen; **Philipp.:** GenHeal; Humatrope; Norditropin; Saizen; SciTropin; **Pol.:** Genotropin; **Port.:** Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin; Zomacton; **Rus.:** Genotropin (Генотропин); Humatrope (Хуматрон); Norditropin (Нордитропин); Saizen (Сайзен); **S.Afr.:** Genotropin; Humatrope; Norditropin; Saizen†; **Singapore:** Genotropin; Humatrope†; Norditropin; Saizen; Scitropin†; **Spain:** Genotonorm; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; **Swed.:** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; **Switz.:** Genotropin; Humatrope; Norditropine; Saizen; **Thai.:** Saizen; **Turk.:** Genotropin; Humatrope; Norditropin; Saizen; Zomacton; **UK:** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; **USA:** Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Protropin†; Saizen; Serostim; Tev-Tropin; Zorbtive; **Venez.:** Genotropin; Humatrope; Norditropin†; Saizen.

Lanreotide *(BAN, rINN)*

Angiopeptin; BIM-23014; BN-52030; DC-13-116; Lanreotid; Lanreotida; Lanréotide; Lanreotidi; Lanreotidum. 3-(2-Naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide cyclic (2→7)-disulfide.

Ланреотид

$C_{54}H_{69}N_{11}O_{10}S_2$ = 1096.3.

CAS — 108736-35-2.

ATC — H01CB03.

ATC Vet — QH01CB03.

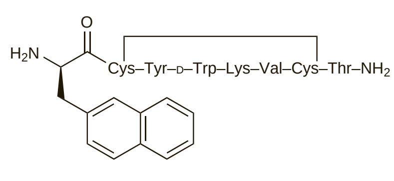

Lanreotide Acetate *(BANM, USAN, rINNM)*

Acetato de lanreotida; BIM-23014C; Lanréotide, Acétate de; Lanreotidi Acetas.

Ланреотида Ацетат

$C_{54}H_{69}N_{11}O_{10}S_2,x(C_2H_4O_2)$.

CAS — 127984-74-1.

ATC — H01CB03.

ATC Vet — QH01CB03.

Adverse Effects and Precautions

As for Octreotide Acetate, p.1803.

Interactions

As for Octreotide Acetate, p.1804.

Pharmacokinetics

After intravenous injection lanreotide has a terminal half-life of about 2.5 hours. Lanreotide is available as injectable depot preparations, and after subcutaneous or intramuscular use of these an initial rapid liberation of the drug is followed by more prolonged release with an apparent half-life of about 5 to 30 days. The absolute bioavailability is stated to range from about 50 to 80%, depending on the product.

Uses and Administration

Lanreotide is a somatostatin analogue with similar properties to those of octreotide (p.1804). It is given, as a long-acting depot injection, in the treatment of acromegaly (p.1798) and thyrotrophic adenoma, as well as in the symptomatic management of carcinoid syndrome (p.643).

Lanreotide is given as the acetate, but doses are usually expressed in terms of the base. The usual starting dose is equivalent to lanreotide 30 mg by intramuscular depot injection every 14 days. In acromegaly and carcinoid syndrome, this may be increased if necessary to 30 mg every 7 to 10 days; in thyrotrophic adenoma it may be increased to 30 mg every 10 days. An alternative preparation for acromegaly and carcinoid syndrome, given by deep subcutaneous injection every 28 days, delivers doses equivalent to 60, 90, or 120 mg of lanreotide. In patients with acromegaly who respond to treatment, lanreotide may be gradually reduced to maintenance doses of 120 mg given at intervals of up to 56 days. In those who are not adequately controlled, a maximum dose of 120 mg once every 28 days may be used.

Lanreotide has been tried for the prevention of restenosis in coronary blood vessels following angioplasty (see Reperfusion and Revascularisation Procedures, p.1181).

◊ References.

1. Wymenga ANM, *et al.* Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 1999; **17:** 1111–17.
2. Kuhn JM, *et al.* Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow release formulation of the somatostatin analog lanreotide. *J Clin Endocrinol Metab* 2000; **85:** 1487–91.
3. Ayuk J, *et al.* Long-term safety and efficacy of depot long-acting somatostatin analogs for the treatment of acromegaly. *J Clin Endocrinol Metab* 2002; **87:** 4142–6.
4. Caron P, *et al.* One-year follow-up of patients with acromegaly treated with fixed or titrated doses of lanreotide Autogel. *Clin Endocrinol (Oxf)* 2004; **60:** 734–40.
5. Ruszniewski P, *et al.* Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; **80:** 244–51.
6. Freda PU, *et al.* Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 4465–73.
7. Croxtall JD, Scott LJ. Lanreotide Autogel : a review of its use in the management of acromegaly. *Drugs* 2008; **68:** 711–23.

Administration in hepatic and renal impairment. The clearance of lanreotide, given by intravenous bolus, was significantly reduced in patients with severe chronic renal impairment requiring haemodialysis.[1] However, the authors of this study suggested that considering the wide therapeutic window of lanreotide, depot formulations may be given at the usual initial dose, with further doses adjusted according to response. Clearance of lanreotide was only slightly reduced in patients with moderate to severe hepatic impairment (Child-Pugh category B and C).[2] The UK licensed product information for one depot formulation (*Somatuline Autogel; Ipsen, UK*) given every 28 days recommends that dose adjustment is not necessary in renal or hepatic impairment. Another preparation (*Somatuline LA; Ipsen, UK*) usually given every 14 days suggests that renal and hepatic function should be monitored and the dosage interval adjusted as needed.

1. Barbanoj M, *et al.* Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. *Clin Pharmacol Ther* 1999; **66:** 485–91.
2. Tomlinson B, *et al.* Pharmacokinetic profile of the somatostatin analogue lanreotide in individuals with chronic hepatic insufficiency. *Clin Pharmacokinet* 2006; **45:** 1003–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Somatuline; **Austral.:** Somatuline; **Austria:** Somatuline; **Belg.:** Somatuline; **Braz.:** Somatuline†; **Cz.:** Somatuline; **Denm.:** Ipstyl; **Fin.:** Somatuline; **Fr.:** Somatuline; **Ger.:** Somatuline; **Gr.:** Somatuline; **Hong Kong:** Somatuline; **Hung.:** Somatuline; **Irl.:** Somatuline; **Israel:** Somatuline; **Ital.:** Ipstyl; **Neth.:** Somatuline; **Norw.:** Ipstyl; **Pol.:** Somatuline; **Port.:** Somatulina; **Rus.:** Somatuline (Соматулин); **Singapore:** Somatuline; **Spain:** Somatulina; **Swed.:** Somatuline; **Switz.:** Somatuline; **UK:** Somatuline; **USA:** Somatuline.

Octreotide Acetate *(BANM, USAN, rINNM)*

Acetato de octreotida; Octréotide, Acétate d'; Octreotidi Acetas; SMS-201-995 (octreotide). 2-(D-Phenylalanyl-L-cystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cystyl)-(2*R*,3*R*)-butane-1,3-diol acetate; D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7) disulphide acetate.

Октреотида Ацетат

$C_{49}H_{66}N_{10}O_{10}S_2,xC_2H_4O_2$ = 1019.2 (octreotide).

CAS — 83150-76-9 (octreotide); 79517-01-4 (octreotide acetate).

ATC — H01CB02.

ATC Vet — QH01CB02.

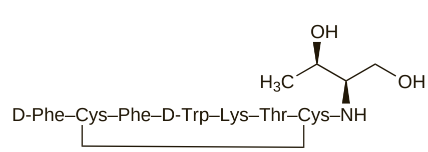

(octreotide)

Incompatibility. Apparent loss of insulin has been reported from a total parenteral nutrient solution containing octreotide; there may be an incompatibility.[1] Also the manufacturers had suggested that octreotide might be adsorbed onto plastics. However, a solution containing octreotide 200 micrograms/mL as the acetate was reported to be stable at 5° or −20° for up to 60 days when stored in polypropylene syringes.[2]

1. Rosen GH. Potential incompatibility of insulin and octreotide in total parenteral nutrient solutions. *Am J Hosp Pharm* 1989; **46:** 1128.
2. Ripley RG, *et al.* Stability of octreotide acetate in polypropylene syringes at 5 and −20°C. *Am J Health-Syst Pharm* 1995; **52:** 1910–11.

Adverse Effects and Precautions

There may be a transient local reaction at the site of injection of octreotide. Systemic adverse effects are mainly gastrointestinal and may include anorexia, nausea, vomiting, diarrhoea and steatorrhoea, abdominal discomfort, and flatulence. Use between meals or at bedtime may reduce these gastrointestinal effects. Hypersensitivity reactions and hair loss have been reported rarely.

Gallstones may develop on long-term therapy; there have been isolated reports of hepatic dysfunction and of biliary colic associated with drug withdrawal. Checks should be made for gallstones before prolonged therapy and at 6- to 12-month intervals during treatment. There have also been isolated reports of pancreatitis and of hepatic dysfunction without cholestasis. Hypoglycaemia may occur, especially in patients with insulinomas, but there is also a risk of hyperglycaemia or impaired glucose tolerance. Thyroid function should be monitored during octreotide therapy because of the possibility of hypothyroidism. Pituitary tumours that secrete growth hormone can expand during treatment, causing serious complications; patients should be monitored for signs of tumour expansion, such as visual field defects. Cardiac rhythm should be monitored during intravenous use of octreotide. Doses may need to be adjusted in patients with end-stage renal failure, in whom the clearance of octreotide is reduced.

Effects on the biliary tract. Octreotide has an inhibitory effect on gallbladder motility and bile secretion, accounting for the development of gallstones and biliary colic.[1-5]

1. Redfern JS, Fortuner WJ. Octreotide-associated biliary tract dysfunction and gallstone formation: pathophysiology and management. *Am J Gastroenterol* 1995; **90:** 1042–52.
2. Tauber JP, *et al.* The impact of continuous subcutaneous infusion of octreotide on gallstone formation in acromegalic patients. *J Clin Endocrinol Metab* 1995; **80:** 3262–6.
3. Hussaini SH, *et al.* Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996; **38:** 775–83.
4. Trendle MC, *et al.* Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; **79:** 830–4.
5. Moschetta A, *et al.* Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; **15:** 181–5.

Effects on carbohydrate metabolism. Changes in glucose tolerance may occur in patients with acromegaly who are treated with somatostatin analogues. In a study[1] of 90 patients treated with octreotide for 6 months, impaired glucose tolerance or frank diabetes developed in half of the 55 who initially had normal glucose tolerance. There was initial impaired glucose tolerance in 24 patients, which deteriorated in 4, remained stable in 10, and normalised in 10. Of the 11 patients who were diabetic before octreotide treatment, 8 remained diabetic but 1 improved to having impaired glucose tolerance and 2 to being normal. A later study[2] of 24 patients treated with either octreotide or lanreotide also found that glucose tolerance could remain stable, deteriorate, or improve. Overall, however, there was an improvement in insulin resistance but an impairment of insulin secretion, and a deterioration in glucose homoeostasis in nondiabetic patients.

There has been a report of deterioration in glucose tolerance leading to death from diabetic ketoacidosis when octreotide treatment was stopped in a patient with acromegaly and insulin-resistant diabetes mellitus.[3]

See also Diabetes Mellitus and Hyperinsulinism under Uses and Administration, below.

1. Koop BL, *et al.* Effect of octreotide on glucose tolerance in acromegaly. *Eur J Endocrinol* 1994; **130:** 581–6.
2. Baldelli R, *et al.* Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. *Clin Endocrinol (Oxf)* 2003; **59:** 492–9.
3. Abrahamson MJ. Death from diabetic ketoacidosis after cessation of octreotide in acromegaly. *Lancet* 1990; **336:** 318–19.

The symbol † denotes a preparation no longer actively marketed

Effects on the hair. Diffuse loss of scalp hair has been reported in 4 of 7 women who received octreotide; after withdrawal of octreotide in 3 of the women there was a complete recovery of scalp hair.[1] Other similar cases have also been reported. In one case, diffuse alopecia in a male patient was completely reversed when octreotide was replaced with lanreotide.[2]

1. Jönsson A, Manhem P. Octreotide and loss of scalp hair. *Ann Intern Med* 1991; **115:** 913.
2. Lami M-C, *et al.* Hair loss in three patients with acromegaly treated with octreotide. *Br J Dermatol* 2003; **149:** 655–6.

Effects on the liver. Hepatitis occurred in 2 acromegalic patients treated with octreotide 300 micrograms daily subcutaneously.[1,2] In both cases liver enzyme values returned to normal within 1 to 2 months of withdrawing octreotide, and recurred on rechallenge.

1. Arosio M, *et al.* Acute hepatitis after treatment of acromegaly with octreotide. *Lancet* 1988; **ii:** 1498.
2. González-Martín JA, *et al.* Acute liver injury and octreotide. *Am J Gastroenterol* 1996; **91:** 2434–5.

Effects on mental function. A woman with acromegaly developed manic symptoms on 2 separate occasions 2 months after starting treatment with octreotide.[1]

1. Fernández-Real J-M, *et al.* Octreotide-induced manic episodes in a patient with acromegaly. *Ann Intern Med* 2006; **144:** 704.

Effects on the pancreas. There have been reports of pancreatitis associated with octreotide[1-4] and lanreotide.[4] It has been suggested that octreotide-induced pancreatitis may result from spasm of the sphincter of Oddi, resulting in retention of activated pancreatic enzymes due to outflow obstruction.[3]

1. Fredenrich A, *et al.* Acute pancreatitis after short-term octreotide. *Lancet* 1991; **338:** 52–3.
2. Sadoul J-L, *et al.* Acute pancreatitis following octreotide withdrawal. *Am J Med* 1991; **90:** 763–4.
3. Bodemar G, Hjortswang H. Octreotide-induced pancreatitis: an effect of increased contractility of Oddi sphincter. *Lancet* 1996; **348:** 1668–9.
4. Cannavò S, *et al.* Octreotide and lanreotide treatment in active acromegaly. *J Clin Endocrinol Metab* 1997; **82:** 2376–7.

Pregnancy. There have been reports of women who have received lanreotide[1] or octreotide[2-5] during pregnancy. Most were receiving the drug for the treatment of acromegaly, although there is also a report[5] of octreotide use during pregnancy in a woman treated for nesidioblastosis. In most cases, the somatostatin analogue was stopped early in the pregnancy, but in some cases octreotide was continued to term. No maternal complications or congenital anomalies were described.

1. de Menis E, *et al.* Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report. *J Clin Endocrinol Metab* 1999; **84:** 1489.
2. Neal JM. Successful pregnancy in a woman with acromegaly treated with octreotide. *Endocr Pract* 2000; **6:** 148–50.
3. Fassnacht M, *et al.* Octreotide LAR treatment throughout pregnancy in an acromegalic woman. *Clin Endocrinol (Oxf)* 2001; **55:** 411–15.
4. Mikhail N. Octreotide treatment of acromegaly during pregnancy. *Mayo Clin Proc* 2002; **77:** 297–8.
5. Boulanger C, *et al.* Normal pregnancy in a woman with nesidioblastosis treated with somatostatin analog octreotide. *J Endocrinol Invest* 2004; **27:** 465–70.

Interactions

Octreotide has been associated with alterations in nutrient absorption and there is a theoretical possibility that it may affect the oral absorption of other drugs. Patients receiving insulin or oral hypoglycaemics may require dose adjustments of these drugs if octreotide is also used. The bioavailability of bromocriptine is increased by octreotide. It has been suggested that dosage of beta blockers, calcium-channel blockers, or drugs to control fluid and electrolyte balance may also need to be adjusted.

Ciclosporin. For a reference to octreotide reducing serum concentrations of ciclosporin, see p.1828.

Pharmacokinetics

Octreotide is rapidly absorbed after subcutaneous injection, with peak plasma concentrations reached about 25 to 40 minutes after a dose, and is distributed to body tissues. About 40 to 65% of the octreotide in the circulation is bound to plasma proteins. It is said to exhibit non-linear pharmacokinetics, with reduced clearance at high doses. Octreotide is removed from the body with a plasma elimination half-life of about 1.5 hours; half-life is prolonged in elderly patients, renal impairment, and liver cirrhosis. About a third of a dose is excreted unchanged in the urine. Octreotide diffuses across the placenta.

Uses and Administration

Octreotide is an octapeptide analogue of somatostatin (p.1809) with similar properties but a longer duration of action.

It is used as the acetate in the symptomatic management of carcinoid tumours and other secretory neoplasms such as VIPomas and glucagonomas. Octreotide acetate is also used in the treatment of acromegaly and the prevention of complications after pancreatic surgery, and may be used in the treatment of other disorders including variceal haemorrhage and HIV-associated diarrhoea. It has also been investigated in a variety of other disorders including the dumping syndrome.

In the management of **secretory neoplasms** octreotide acetate is given subcutaneously in an initial dose equivalent to 50 micrograms of octreotide once or twice daily gradually increased, according to response, to up to 600 micrograms daily in 2 to 4 divided doses. Higher doses have been used. If there is no benefit within a week of starting treatment for carcinoid tumour, continued therapy is not recommended.

Where a rapid response is required, the initial dose may be given by the intravenous route. In the UK licensed product information states that it should be diluted not less than 1 in 1 or not more than 1 in 9 in sodium chloride 0.9%, but in the USA product information permits the use of the undiluted solution as an intravenous bolus in emergencies; alternatively the dose may be given by intermittent infusion over 15 to 30 minutes, diluted in 50 to 200 mL of sodium chloride 0.9% or glucose 5%.

Once control has been established maintenance therapy with a depot preparation may be possible; initially 20 mg by intramuscular injection every 4 weeks is suggested. Subcutaneous injection with a rapid-acting preparation should be continued for 2 weeks after the first depot injection to provide symptomatic cover, and may be added to therapy when necessary thereafter. Maintenance doses of the depot preparation may be adjusted after 2 or 3 months to between 10 and 30 mg every 4 weeks, as necessary.

In **acromegaly**, the usual dose is the equivalent of 100 to 200 micrograms of octreotide three times daily by subcutaneous injection. In the USA it is suggested that dosage begin with 50 micrograms three times daily in order to minimise gastrointestinal disturbance. If there is no relevant reduction in growth hormone concentrations and no improvement in clinical symptoms within 3 months of starting treatment, octreotide should be stopped. Once control has been established maintenance therapy with a depot preparation is possible; an initial dose equivalent to 20 mg of octreotide given intramuscularly once every 4 weeks has been recommended for patients with acromegaly, adjusted after 3 months to between 10 and 30 mg every 4 weeks. For patients who are not adequately controlled on 30 mg, the dose may be further increased to 40 mg every 4 weeks. The depot preparation may also be used for short-term treatment before pituitary surgery, but the last dose should be given at least 3 to 4 weeks before surgery to ensure successful endocrine testing for tumour removal 5 to 6 weeks after surgery.

For the prevention of complications after **pancreatic surgery** the equivalent of 100 micrograms of octreotide may be given three times daily by subcutaneous injection of a rapid-acting preparation; treatment is given for 7 consecutive days, beginning at least 1 hour before laparotomy on the day of operation.

In the management of **variceal haemorrhage** in patients with cirrhosis, octreotide is given as a continuous intravenous infusion at a dose equivalent to octreotide 25 micrograms/hour for 48 hours. Doses up to 50 micrograms/hour have been used. Patients at high risk of re-bleeding may continue treatment for up to 5 days. Although not licensed for use in children in the UK, the *BNFC* includes a dose of 1 microgram/kg per hour by continuous intravenous infusion for children from 1 month to 18 years of age; higher doses may be needed initially, to a maximum dose of 50 micrograms/hour, and the dose should be reduced gradually over 24 hours once there is no active bleeding.

HIV-associated diarrhoea may be treated with an initial dose of octreotide 100 micrograms three times daily, given subcutaneously. If the diarrhoea is not controlled after a week, the dose may be increased to 250 micrograms three times daily, but if this is not effective after one week then octreotide therapy should be stopped.

◊ General reviews of octreotide.

1. Bloom SR, O'Shea D. Octreotide. *Prescribers' J* 1996; **36:** 120–4.
2. Lamberts SWJ, *et al.* Octreotide. *N Engl J Med* 1996; **334:** 246–54.

Acromegaly. Although surgery remains the most important method of treatment, octreotide has a useful role in the management of acromegaly (p.1798). It can reduce growth hormone concentrations, normalise IGF-I concentrations, reduce tumour size, and improve signs and symptoms.[1-4] There is also some evidence that it may improve cardiac function, which is usually compromised in these patients.[5-7] Octreotide can be given subcutaneously and this route is generally used initially to determine patient response and tolerance, but it must be given three times daily making it unattractive for long-term use. Intramuscular sustained-release octreotide is effective for maintenance therapy.[4,7,8] There is also increasing interest in the role of octreotide for primary therapy of acromegaly, instead of surgery[8,9] and a recent meta-analysis[10] concluded that tumour shrinkage was greatest when somatostatin analogues were given as primary rather than secondary therapy.

1. Vance ML, Harris AG. Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide: results of the International Multicenter Acromegaly Study Group. *Arch Intern Med* 1991; **151:** 1573–8.
2. Ezzat S, *et al.* Octreotide treatment of acromegaly: a randomized, multicenter study. *Ann Intern Med* 1992; **117:** 711–18.
3. van der Lely AJ, *et al.* A risk-benefit assessment of octreotide in the treatment of acromegaly. *Drug Safety* 1997; **17:** 317–24.
4. Freda PU. Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 2002; **87:** 3013–18.
5. Colao A, *et al.* Cardiovascular effects of depot long-acting somatostatin analog Sandostatin LAR in acromegaly. *J Clin Endocrinol Metab* 2000; **85:** 3132–40.
6. Colao A, *et al.* Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalization of growth hormone and insulin-like growth factor I levels on cardiac performance. *J Clin Endocrinol Metab* 2001; **86:** 1551–7.
7. McKeage K, *et al.* Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. *Drugs* 2003; **63:** 2473–99.
8. Ayuk J, *et al.* Long-term safety and efficacy of depot long-acting somatostatin analogs for the treatment of acromegaly. *J Clin Endocrinol Metab* 2002; **87:** 4142–6.
9. Bevan JS, *et al.* Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab* 2002; **87:** 4554–63.
10. Freda PU, *et al.* Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 4465–73.

Carcinoid syndrome and other secretory neoplasms. For a discussion of carcinoid tumours and other secretory neoplasms, including reference to the important role of octreotide, see p.643.

Reviews.

1. Öberg K, *et al.* Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; **15:** 966–73.
2. Delaunoit T, *et al.* Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. *Mayo Clin Proc* 2005; **80:** 502–6.

Cardiovascular disorders. There have been reports of benefit from octreotide in patients with postprandial hypotension and orthostatic hypotension (p.1530) associated with autonomic neuropathy.[1-5] Octreotide has also produced cardiac improvement in patients with acromegaly (see above). Promising results have been reported in patients with primary hypertrophic cardiomyopathy.[6,7]

1. Hoeldtke RD, *et al.* Treatment of autonomic neuropathy with a somatostatin analogue SMS-201-995. *Lancet* 1986; **ii:** 602–5.
2. Hoeldtke RD, Israel BC. Treatment of orthostatic hypotension with octreotide. *J Clin Endocrinol Metab* 1989; **68:** 1051–9.
3. Woo J, *et al.* Treatment of severe orthostatic hypotension with the somatostatin analogue octreotide. *Aust N Z J Med* 1990; **20:** 822–3.
4. Bordet R, *et al.* Octreotide in the management of orthostatic hypotension in multiple system atrophy: pilot trial of chronic administration. *Clin Neuropharmacol* 1994; **17:** 380–3.
5. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with midodrine and octreotide. *J Clin Endocrinol Metab* 1998; **83:** 339–43.
6. Günal AI, *et al.* Short term reduction of left ventricular mass in primary hypertrophic cardiomyopathy by octreotide injections. *Heart* 1996; **76:** 418–21.
7. Demirtaş E, *et al.* Effects of octreotide in patients with hypertrophic obstructive cardiomyopathy. *Jpn Heart J* 1998; **39:** 173–81.

Chylous effusion. Chylous effusion results in accumulation of a milky lymphatic fluid containing raised concentrations of white blood cells, triglycerides, and cholesterol. Chylothorax, when the effusion affects the pleural cavity, is generally a complication of malignancy or chest surgery, or may be idiopathic. Treatment usually involves catheter drainage and dietary modification; surgery is used when these measures fail. Octreotide has been used successfully in a number of cases, given subcutaneously or by continuous infusion, to treat chylothorax;[1-7] there are also reports of octreotide being ineffective.[8] Octreotide has also been used in chyloperitoneum[9-11] and for cervical chylous fistula.[12]

1. Demos NJ, *et al.* Somatostatin in the treatment of chylothorax. *Chest* 2001; **119:** 964–6.
2. Cheung Y, *et al.* Octreotide for treatment of postoperative chylothorax. *J Pediatr* 2001; **139:** 157–9.
3. Ottinger JG. Octreotide for persistent chylothorax in a pediatric patient. *Ann Pharmacother* 2002; **36:** 1106–7.
4. Demos NJ. Octreotide in the treatment of chylothorax. *Chest* 2002; **121:** 2080–1.
5. Al-Zubairy SA, Al-Jazairi AS. Octreotide as a therapeutic option for management of chylothorax. *Ann Pharmacother* 2003; **37:** 679–82.
6. Evans J, *et al.* Chylous effusions complicating lymphoma: a serious event with octreotide as a treatment option. *Hematol Oncol* 2003; **21:** 77–81.
7. Makrilakis K, *et al.* Successful octreotide treatment of chylous pleural effusion and lymphedema in the yellow nail syndrome. *Ann Intern Med* 2004; **141:** 246–7.
8. Mikroulis D, *et al.* Octreotide in the treatment of chylothorax. *Chest* 2002; **121:** 2079–80.
9. Bhatia C, *et al.* Octreotide therapy: a new horizon in treatment of iatrogenic chyloperitoneum. *Arch Dis Child* 2001; **85:** 234–5.
10. Leong RWL, *et al.* Chylous ascites caused by portal vein thrombosis treated with octreotide. *J Gastroenterol Hepatol* 2003; **18:** 1211–13.
11. Hwang J-B, *et al.* Resolution of refractory chylous ascites after Kasai portoenterostomy using octreotide. *J Pediatr Surg* 2004; **39:** 1806–7.
12. Suver DW, *et al.* Somatostatin treatment of massive lymphorrhea following excision of a lymphatic malformation. *Int J Pediatr Otorhinolaryngol* 2004; **68:** 845–50.

Cushing's syndrome. Cushing's syndrome (p.2344) can be caused by excessive secretion from an ectopic ACTH-secreting tumour. Many of these ectopic tumours express somatostatin receptors and it has been suggested that octreotide may be useful in the diagnosis, and possibly the treatment, of selected patients.[1] However, there are 5 types of somatostatin receptor,[2,3] and responses to octreotide have been variable,[4] even in the same patient.[3,5]

1. de Herder WW, Lamberts SWJ. Is there a role for somatostatin and its analogs in Cushing's syndrome? *Metabolism* 1996; **45** (suppl): 83–5.
2. de Herder WW, Lamberts SWJ. Octapeptide somatostatin-analogue therapy of Cushing's syndrome. *Postgrad Med J* 1999; **75:** 65–6.
3. Uwaifo GI, *et al.* Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome? *J Endocrinol Invest* 2003; **26:** 710–17.
4. Woodhouse NJY, *et al.* Acute and long-term effects of octreotide in patients with ACTH-dependent Cushing's syndrome. *Am J Med* 1993; **95:** 305–8.
5. Gill GV, *et al.* Carcinoid-associated ectopic ACTH syndrome with variable response to octreotide. *Postgrad Med J* 1999; **75:** 98–101.

Diabetes mellitus. Although octreotide has been reported to impair glucose tolerance, and even precipitate frank diabetes (see Effects on Carbohydrate Metabolism, under Adverse Effects, above), its variable effects on blood glucose and insulin have led to investigations[1,2] of its ability to induce beta cell rest in patients with diabetes mellitus (p.431) who still have residual insulin secretion. There is also some suggestion that it may be of benefit in the treatment or prevention of diabetic nephropathy[3,4] and retinopathy.[5-7] Benefit has been reported from the use of octreotide in patients with diabetic diarrhoea—see under Gastrointestinal Disorders, below.

1. Björk E, *et al.* Induction of β-cell rest in type 1 diabetes. *Diabetes Care* 1998; **21:** 427–30.
2. Vondra K, *et al.* Somatostatin: beneficial effects on remission in young adult patients with newly diagnosed diabetes mellitus type 1. *Physiol Res* 2004; **53:** 115–17.
3. Serri O, *et al.* Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *JAMA* 1991; **265:** 888–92.
4. Clemens A, *et al.* Octreotide (somatostatin analog) treatment reduces endothelial cell dysfunction in patients with diabetes mellitus. *Metabolism* 1999; **48:** 1236–40.
5. Grant MB, *et al.* The efficacy of octreotide in the therapy of severe nonproliferative and early proliferative diabetic retinopathy: a randomized controlled trial. *Diabetes Care* 2000; **23:** 504–9.
6. Boehm BO, *et al.* Octreotide reduces vitreous hemorrhage and loss of visual acuity risk in patients with high-risk proliferative diabetic retinopathy. *Horm Metab Res* 2001; **33:** 300–306.
7. Grant MB, Caballero S. Somatostatin analogues as drug therapies for retinopathies. *Drugs Today* 2002; **38:** 783–91.

Diagnosis and testing. Radiolabelled octreotide or other somatostatin analogues such as pentetreotide and depreotide may be used to visualise various malignant neoplasms which express somatostatin receptors.[1,2] Somatostatin receptor scintigraphy is the most sensitive method for imaging lesions in patients with Zollinger-Ellison syndrome.[3]

Octreotide may also have a role in the diagnosis of Cushing's syndrome, see above.

1. Breeman WAP, *et al.* Somatostatin receptor-mediated imaging and therapy: basic science, current knowledge, limitations and future perspectives. *Eur J Nucl Med* 2001; **28:** 1421–9.
2. van der Lely AJ, *et al.* Octreoscan radioreceptor imaging. *Endocrine* 2003; **20:** 307–11.
3. Gibril F, *et al.* Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas: a prospective study. *Ann Intern Med* 1996; **125:** 26–34.

Eye disorders. There are reports of response to octreotide in 2 patients with bilateral cystoid macular oedema, a refractory form of retinal oedema.[1,2] In 1 case the problem recurred when octreotide was twice withdrawn and each time responded to resumption of octreotide injections.[1]

1. Kuijpers RWAM, *et al.* Treatment of cystoid macular edema with octreotide. *N Engl J Med* 1998; **338:** 624–6.
2. Hernaez-Ortega MC, *et al.* Sandostatin LAR for cystoid diabetic macular edema: a 1-year experience. *Diabetes Res Clin Pract* 2004; **64:** 71–2.

Gastrointestinal disorders. Somatostatin inhibits gastric and intestinal secretion and the production of various active substances in the gastrointestinal tract. It also reduces splanchnic arterial blood flow and portal and gastric mucosal blood flow. These properties are made use of, usually in the form of octreotide, in the management of a number of gastrointestinal disorders including bleeding, refractory diarrhoea, fistulae, dumping syndrome, and nausea and vomiting secondary to bowel obstruction (see Other Gastrointestinal Disorders, below).

Octreotide is used particularly in the treatment of carcinoid syndrome arising from endocrine tumours (see Carcinoid Tumours, p.643).

BLEEDING. There have been mixed results with octreotide in the treatment of nonvariceal upper gastrointestinal bleeding. Although a large multicentre study[1] showed that octreotide had no benefit compared with placebo in the management of bleeding upper gastrointestinal ulcers, a meta-analysis that included somatostatin and octreotide suggested there might be some benefit.[2] Nevertheless, a later study[3] found that octreotide, given as an adjunct to endoscopic haemostasis using noradrenaline, did not seem to provide any additional benefit, and it is not recommended in the management of nonvariceal bleeding associated with peptic ulcer (p.1702).

Octreotide may be used in the management of variceal haemorrhage (see under Monoethanolamine, p.2346). A systematic review[4] of studies comparing somatostatin or its analogues with either placebo or no drug treatment found that although there was a small benefit in controlling bleeding, it was doubtful whether this benefit was worthwhile, and that deaths were not reduced. There is some evidence that octreotide is as effective as sclerotherapy in the control of acute bleeding.[5] A meta-analysis[6] of studies comparing octreotide with other therapies (including vasopressin, terlipressin, sclerotherapy, or balloon tamponade) for the control of acute variceal bleeding found that octreotide had a similar effect to sclerotherapy in the prevention of rebleeding and was more effective and associated with fewer major complications than vasopressin or terlipressin. However, there was no evidence of mortality benefit associated with octreotide use. Another systematic review[7] also found that sclerotherapy was no better than drug therapy, including octreotide, but associated with more frequent and severe adverse effects. Controlled studies have suggested that combination of octreotide infusion for 5 days with endoscopic ligation[8] or sclerotherapy[9,10] reduces the risk of rebleeding. In another study,[11] sclerotherapy with 48 hours of octreotide infusion was more effective at controlling bleeding than sclerotherapy alone, and octreotide was as effective as sclerotherapy in those with evidence of recent bleeding. However, another study[12] found that octreotide given subcutaneously for up to 29 days after sclerotherapy did not affect the rate of early rebleeding. Octreotide has also produced some benefit (combined with regular sclerotherapy), in the long-term management of patients with cirrhotic portal hypertension.[13]

1. Christiansen J, *et al.* Placebo-controlled trial with the somatostatin analogue SMS 201-995 in peptic ulcer bleeding. *Gastroenterology* 1989; **97:** 568–74.
2. Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H antagonists and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Ann Intern Med* 1997; **127:** 1062–71. Correction. *ibid.* 1998; **128:** 245.
3. Nikolopoulou VN, *et al.* The effect of octreotide as an adjunct treatment in active nonvariceal upper gastrointestinal bleeding. *J Clin Gastroenterol* 2004; **38:** 243–7.
4. Gøtzsche PC, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 21/08/08).
5. Jenkins SA, *et al.* A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997; **41:** 526–33.
6. Corley DA, *et al.* Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology* 2001; **120:** 946–54.
7. D'Amico G, *et al.* Emergency sclerotherapy versus medical interventions for bleeding oesophageal varices in cirrhotic patients. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/09/05).
8. Sung JJY, *et al.* Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995; **346:** 1666–9.
9. Besson I, *et al.* Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995; **333:** 555–60.
10. Zuberi BF, Baloch Q. Comparison of endoscopic variceal sclerotherapy alone and in combination with octreotide in controlling acute variceal hemorrhage and early rebleeding in patients with low-risk cirrhosis. *Am J Gastroenterol* 2000; **95:** 768–71.
11. Freitas DS, *et al.* Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepatogastroenterology* 2000; **47:** 1310–14.
12. Primignani M, *et al.* Sclerotherapy plus octreotide versus sclerotherapy alone in the prevention of early rebleeding from esophageal varices: a randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 1995; **21:** 1322–7.
13. Jenkins SA, *et al.* Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage. *BMJ* 1997; **315:** 1338–41.

DIARRHOEA. Octreotide has been tried for its effects on gastrointestinal secretion and intestinal transit time in the management of severe refractory diarrhoea associated with a variety of conditions. A review[1] found that studies were generally small, and that although there appeared to be an overall benefit associated with the use of octreotide, response was influenced by the cause of diarrhoea. There are reports of octreotide controlling diarrhoea associated with amyloidosis,[2-4] diabetes mellitus,[5-11] and bone marrow transplantation.[12,13] Although octreotide was reported to be useful in a case of microvillous atrophy,[14] others have not found it to be effective.[15] There have been reports of benefit in refractory AIDS-associated diarrhoea,[16] and it has been licensed for this use in some countries, but a double-blind, controlled study found octreotide to be no more beneficial than placebo.[17] In patients with the short bowel syndrome and jejunostomies or ileostomies, octreotide may be useful in decreasing faecal mass[18] or jejunal efflux,[19] and increasing small bowel transit time.[20] Octreotide has also been used with some benefit in refractory diarrhoea associated with chemotherapy, particularly with regimens that include fluorouracil[21,22] and irinotecan.[23] In a small series of patients[24] the use of depot octreotide controlled most episodes of diarrhoea, and allowed the continuation of chemotherapy in some cases.

1. Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. *Aliment Pharmacol Ther* 2001; **15:** 1889–97.
2. O'Connor CR, O'Dorisio TM. Amyloidosis, diarrhea, and a somatostatin analogue. *Ann Intern Med* 1989; **110:** 665–6.
3. Gilanders IA, *et al.* Octreotide therapy for diarrhoea. *Postgrad Med J* 1997; **73:** 62.
4. Jeong Y-S, *et al.* Successful treatment of protein-losing enteropathy due to AA amyloidosis with somatostatin analogue and high dose steroid in ankylosing spondylitis. *Clin Exp Rheumatol* 2000; **18:** 619–21.
5. Tsai S-T, *et al.* Diabetic diarrhea and somatostatin. *Ann Intern Med* 1986; **104:** 894.
6. Michaels PE, Cameron RB. Octreotide is cost-effective therapy in diabetic diarrhea. *Arch Intern Med* 1991; **151:** 2469.
7. Mourad FH, *et al.* Effective treatment of diabetic diarrhea with somatostatin analogue, octreotide. *Gut* 1992; **33:** 1578–80.
8. Nakabayashi H, *et al.* Marked improvement of diabetic diarrhea with the somatostatin analogue octreotide. *Arch Intern Med* 1994; **154:** 1863–7.
9. Virally-Monod ML, *et al.* Variable efficacy of octreotide in diabetic diarrhea. *Diabetes Metab* 1996; **22:** 356–8.
10. Murao S, *et al.* Severe diabetic diarrhea successfully treated with octreotide, a somatostatin analogue. *Endocr J* 1999; **46:** 477–8.
11. Meyer C, *et al.* Octreotide treatment of severe diabetic diarrhoea. *Intern Med J* 2003; **33:** 617–8.
12. Crouch MA, *et al.* Octreotide acetate in refractory bone marrow transplant-associated diarrhea. *Ann Pharmacother* 1996; **30:** 331–6.
13. Ippoliti C, *et al.* Use of octreotide in the symptomatic management of diarrhea induced by graft-versus-host disease in patients with hematological malignancies. *J Clin Oncol* 1997; **15:** 3350–4.
14. Couper RTL, *et al.* Clinical response to the long acting somatostatin analogue SMS 201-995 in a child with congenital microvillus atrophy. *Gut* 1989; **30:** 1020–4.
15. Beck NS, *et al.* Microvillus inclusion disease in two Korean infants. *J Korean Med Sci* 1997; **12:** 452–6.
16. Montaner JSG, *et al.* Octreotide therapy in AIDS-related, refractory diarrhea: results of a multicentre Canadian-European study. *AIDS* 1995: **9:** 209–10.
17. Simon DM, *et al.* Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome–associated diarrhea. *Gastroenterology* 1995; **108:** 1753–60. Correction. *ibid.*; **109:** 1024.
18. Ladefoged K, *et al.* Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut* 1989; **30:** 943–9.
19. Nightingale JMD, *et al.* Jejunal efflux in short bowel syndrome. *Lancet* 1990; **336:** 765–8.
20. Nehra V, *et al.* An open trial of octreotide long-acting release in the management of short bowel syndrome. *Am J Gastroenterol* 2001; **96:** 1494–8.
21. Goumas P, *et al.* Octreotide acetate in the treatment of fluorouracil-induced diarrhea. *Oncologist* 1998; **3:** 50–3.
22. Zidan J, *et al.* Octreotide in the treatment of severe chemotherapy-induced diarrhea. *Ann Oncol* 2001; **12:** 227–9.
23. Barbounis V, *et al.* Control of irinotecan-induced diarrhea by octreotide after loperamide failure. *Support Care Cancer* 2001; **9:** 258–60.
24. Rosenoff S. Resolution of refractory chemotherapy-induced diarrhea (CID) with octreotide long-acting formulation in cancer patients: 11 case studies. *Support Care Cancer* 2004; **12:** 561–70.

FISTULAE. Octreotide has been used in the management of postoperative small-bowel fistulae. There have been mixed reports, but some have found reduced fistula output,[1,2] with the time to spontaneous fistula closure either reduced[1] or unchanged.[2] Octreotide has also been reported to accelerate healing of pancreatic cutaneous fistulae of various causes,[3] but others[4] have found no benefit from octreotide in preventing pancreatic fistula formation after pancreaticoduodenectomy. A systematic review[5] of controlled trials commented on the variation in trial methods and conflicting results, but concluded that there is probably benefit in giving octreotide preoperatively to prevent complications of pancreatic surgery, and that in established postoperative fistulae it may have a limited role in reducing fistula output and reducing the time to fistula closure. In a series of 5 patients[6] with Crohn's disease who were treated for 8 weeks with high-dose octreotide, enterocutaneous fistulae closed in 4 cases.

1. Nubiola-Calonge P, *et al.* Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. *Lancet* 1987; **ii:** 672–4.
2. Alivizatos V, *et al.* Evaluation of the effectiveness of octreotide in the conservative treatment of postoperative enterocutaneous fistulas. *Hepatogastroenterology* 2002; **49:** 1010–12.
3. Prinz RA, *et al.* Treatment of pancreatic cutaneous fistulas with a somatostatin analog. *Am J Surg* 1988; **155:** 36–42.
4. Barnett SP, *et al.* Octreotide does not prevent postoperative pancreatic fistula or mortality following pancreaticoduodenectomy. *Am Surg* 2004; **70:** 222–7.
5. Li-Ling J, Irving M. Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials. *Br J Surg* 2001; **88:** 190–9.
6. Lavy A, Yasin K. Octreotide for enterocutaneous fistulas of Crohn's disease. *Can J Gastroenterol* 2003; **17:** 555–8.

OTHER GASTROINTESTINAL DISORDERS. Other gastrointestinal disorders in which octreotide might be useful include dumping syndrome[1,2] (p.1695), reactive (or postprandial) hypoglycaemia,[3] and protein-losing enteropathy associated with intestinal lymphangiectasia.[4,5] Nausea and vomiting secondary to bowel obstruction in patients terminally ill with cancer may also be relieved by octreotide.[6,7] The *BNF* states that in palliative care a dose of 300 to 600 micrograms may be given by subcutaneous infusion over 24 hours to reduce intestinal secretions and vomiting.

1. Vecht J, *et al.* Long-term results of octreotide-therapy in severe dumping syndrome. *Clin Endocrinol (Oxf)* 1999; **51:** 619–24.
2. Li-Ling J, Irving M. Therapeutic value of octreotide for patients with severe dumping syndrome—a review of randomised controlled trials. *Postgrad Med J* 2001; **77:** 441–2.
3. Lehnert H, *et al.* Treatment of severe reactive hypoglycemia with a somatostatin analogue (SMS 201-995). *Arch Intern Med* 1990; **150:** 2401–2.
4. Klingenberg RD, *et al.* Type I intestinal lymphangiectasia treated successfully with slow-release octreotide. *Dig Dis Sci* 2003; **48:** 1506–9.
5. Lee HL, *et al.* Successful treatment of protein-losing enteropathy induced by intestinal lymphangiectasia in a liver cirrhosis patient with octreotide: a case report. *J Korean Med Sci* 2004; **19:** 466–9.
6. Ripamonti C, *et al.* The role of somatostatin and octreotide in bowel obstruction: pre-clinical and clinical results. *Tumori* 2001; **87:** 1–9.
7. Mystakidou K, *et al.* Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Res* 2002; **22:** 1187–92.

Hypercalcaemia. There have been individual reports of hypercalcaemia associated with raised plasma concentrations of parathyroid hormone-related protein (hypercalcaemia of malignancy—p.1083) being successfully controlled with octreotide in patients with malignant pancreatic endocrine tumours[1,2] and adrenal phaeochromocytoma.[3] Octreotide also resolved hypercalcaemia occurring in a patient with VIPoma and vasoactive intestinal peptide concentrations declined.[4] In two patients with a parathyroid hormone-related protein secreting carcinoid tumour, octreotide reduced protein concentrations in both patients[5,6] but controlled hypercalcaemia in only one.[6] Octreotide also normalised calcium concentrations in a patient with hypercalcaemia related to B cell lymphoma.[7] In many of these cases, hypercalcaemia had previously been resistant to treatment with bisphosphonates.

1. Wynick D, *et al.* Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone related protein. *BMJ* 1990; **300:** 1314–15.
2. Dodwell D, *et al.* Treatment of a pancreatic tumour secreting parathyroid hormone related protein. *BMJ* 1990; **300:** 1653.
3. Harrison M, *et al.* Somatostatin analogue treatment for malignant hypercalcaemia. *BMJ* 1990; **300:** 1313–14. Correction. *ibid.*; **301:** 97 [dosage error].
4. Venkatesh S, *et al.* Somatostatin analogue: use in the treatment of vipoma with hypercalcaemia. *Am J Med* 1989; **87:** 356–7.
5. Mantzoros CS, *et al.* Intractable hypercalcaemia due to parathyroid hormone-related peptide secretion by a carcinoid tumour. *Clin Endocrinol (Oxf)* 1997; **46:** 373–5.
6. Barhoum M, *et al.* Intractable hypercalcemia due to a metastatic carcinoid secreting parathyroid hormone-related peptide and interleukin-6: response to octreotide. *Am J Med Sci* 1999; **318:** 203–5.
7. Pezzilli R, *et al.* Octreotide for the treatment of hypercalcemia related to B cell lymphoma. *Oncology* 1997; **54:** 517–18.

Hyperinsulinism. As well as reactive hypoglycaemia (see under Other Gastrointestinal Disorders, above), octreotide has been used to control inappropriate insulin secretion, both in the short-term and long-term, in children with hypoglycaemia of infancy,[1-4] or nesidioblastosis.[5-7] Although not licensed in the UK for children, the *BNFC* includes a dose of octreotide for persistent hyperinsulinaemic hypoglycaemia unresponsive to diazoxide and glucose. For neonates an initial dose of 2 to 5 micrograms/kg may be given every 6 to 8 hours subcutaneously and adjusted according to response. For children aged from 1 month to 18 years, an initial dose of 1 to 2 micrograms/kg every 4 to 6 hours may be used. Doses up to 7 micrograms/kg every 4 hours may be required in rare cases.

Octreotide has also been used to treat a patient with hyperinsulinaemia induced by quinine.[8,9] For mention of investigations of octreotide for the reverse effect, see Diabetes Mellitus, above.

1. Kirk JMW, *et al.* Somatostatin analogue in short term management of hyperinsulinism. *Arch Dis Child* 1988; **63:** 1493–4.
2. DeClue TJ, *et al.* Linear growth during long-term treatment with somatostatin analog (SMS 201-995) for persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr* 1990; **116:** 747–50.
3. Thornton PS, *et al.* Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993; **123:** 637–43.
4. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; **82:** F98–F107.
5. Hindmarsh P, Brook CGD. Short-term management of nesidioblastosis using the somatostatin analogue SMS 201-995. *N Engl J Med* 1987; **316:** 221–2.
6. Delemarre-van de Waal HA, *et al.* Long-term treatment of an infant with nesidioblastosis using a somatostatin analogue. *N Engl J Med* 1987; **316:** 222–3.
7. Behrens R, *et al.* Unusual course of neonatal hyperinsulinaemic hypoglycaemia (nesidioblastosis). *Arch Dis Child* 1998; **78:** F156.
8. Phillips RE, *et al.* Effectiveness of SMS 201-995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia. *Lancet* 1986; **i:** 713–16.
9. Phillips RE, *et al.* Hypoglycaemia and counterregulatory hormone responses in severe falciparum malaria: treatment with Sandostatin. *Q J Med* 1993; **86:** 233–40.

Malignant neoplasms. See also Carcinoid Syndrome, above. For mention of the use of octreotide to treat nausea and vomiting associated with malignant gastrointestinal obstruction see under Other Gastrointestinal Disorders, above. Octreotide has also proved of benefit in some patients with cancer pain (see Pain, below). An unconventional regimen using octreotide or somatostatin with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was investigated in patients with a variety of advanced malignancies and found to be ineffective.[1,2]

1. Italian Study Group for the Di Bella Multitherapy Trials. Evaluation of an unconventional cancer treatment (the Di Bella multitherapy): results of phase II trials in Italy. *BMJ* 1999; **318:** 224–8.
2. Buiatti E, *et al.* Results from a historical survey of the survival of cancer patients given Di Bella multitherapy. *Cancer* 1999; **86:** 2143–9.

HEPATOCELLULAR CARCINOMA. In a study in 58 patients with advanced hepatocellular carcinoma (p.667) treatment with octreotide was associated with prolongation of survival compared with no treatment.[1] In a further case report[2] cancer regression occurred in a patient given octreotide, and a study[3] found better survival in patients treated with octreotide and tamoxifen compared with fluorouracil and mitomycin. However, other studies of octreotide in patients with advanced hepatocellular carcinoma failed to demonstrate any benefit.[4,5]

1. Kouroumalis E, *et al.* Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998; **42:** 442–7.
2. Siveke JT, *et al.* Complete regression of advanced HCC with long acting octreotide. *Gut* 2003; **52:** 1531. Correction. *ibid.*; 1800.
3. Pan D-Y, *et al.* Tamoxifen combined with octreotide or regular chemotherapeutic agents in treatment of primary liver cancer: a randomized controlled trial. *Hepatobiliary Pancreat Dis Int* 2003; **2:** 211–15.
4. Yuen M-F, *et al.* A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002; **36:** 687–91.
5. Lersch C, *et al.* Treatment of HCC with pravastatin, octreotide, or gemcitabine - a critical evaluation. *Hepatogastroenterology* 2004; **51:** 1099–1103.

MENINGIOMA. Octreotide has been reported to suppress headaches and visual disturbances associated with meningioma in a small number of patients.[1-3] Doses were generally started at 100 micrograms three times daily subcutaneously, but were increased to 500 micrograms three times daily in some cases because of tolerance. Although it was thought that octreotide may have had a beneficial effect on the meningioma size in one case,[1] others found no evidence of tumour shrinkage.[2,3]

1. Rünzi MW, *et al.* Successful treatment of meningioma with octreotide. *Lancet* 1989; **i:** 1074.
2. García-Luna PP, *et al.* Clinical use of octreotide in unresectable meningiomas: a report of three cases. *J Neurosurg Sci* 1993; **37:** 237–41.
3. Jaffrain-Rea M-L, *et al.* Visual improvement during octreotide therapy in a case of episellar meningioma. *Clin Neurol Neurosurg* 1998; **100:** 40–3.

THYMOMA. A patient with thymoma and pure red cell aplasia, in whom corticosteroids alone failed to control anaemia, had complete remission after treatment with octreotide and prednisone, and subsequently remained well on long-term maintenance therapy with octreotide 500 micrograms twice daily subcutaneously and prednisone 200 micrograms/kg daily.[1] In a study[2] that included 32 patients with thymoma and a positive octreotide scan, octreotide therapy alone (500 micrograms subcutaneously three times daily for up to 1 year) or with prednisone (600 micrograms/kg daily) had modest activity; there were 2 complete and 10 partial responses overall.

1. Palmieri G, *et al.* Successful treatment of a patient with a thymoma and pure red-cell aplasia with octreotide and prednisone. *N Engl J Med* 1997; **336:** 263–5. Correction. *ibid.*; 1039.
2. Loehrer PJ, *et al.* Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group phase II trial. *J Clin Oncol* 2004; **22:** 293–9. Correction. *ibid.*; 2261.

Nesidioblastosis. For reference to the use of octreotide in nesidioblastosis, see Hyperinsulinism, above.

Obesity. Hypothalamic obesity can be a complication of hypothalamic damage caused by insults such as head trauma, brain tumours, and cranial surgery or irradiation. Octreotide has improved body-weight, body-mass index, and regulation of insulin secretion in small studies of children with hypothalamic obesity.[1,2] Octreotide is also under investigation in the treatment of Prader-Willi syndrome (p.2149).[3]

1. Lustig RH, *et al.* Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr* 1999; **135:** 162–8.
2. Lustig RH, *et al.* Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003; **88:** 2586–92.
3. Haqq AM, *et al.* Circulating ghrelin levels are suppressed by meals and octreotide therapy in children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2003; **88:** 3573–6.

Pain. Octreotide 120 to 480 micrograms daily was given by continuous intrathecal infusion to 6 patients with cancer pain that had been poorly controlled by opioid analgesics.[1] All patients obtained good pain relief, 3 reporting pain to be totally absent. Sustained decrease in incapacitating bone pain has also been reported in a patient with skeletal metastasis of a gastrinoma who was given subcutaneous octreotide 100 micrograms three times daily.[2] The pain of hypertrophic pulmonary osteoarthropathy (a paraneoplastic syndrome of periostitis, arthropathy, and gynaecomastia seen particularly with squamous cell lung cancer) has also been reported to respond to octreotide.[3] However, a controlled study of octreotide in cancer pain found that it was no better than placebo in most patients.[4] (General guidelines for the management of cancer pain are discussed on p.5.) Octreotide has also been reported to ease headache associated with meningioma (above), and pituitary adenoma (see Acromegaly, above, and Pituitary Adenoma, below).

The use of intrathecal octreotide has also been described[5] in 2 patients with severe intractable non-malignant pain. During 5 years of treatment, octreotide provided a beneficial degree of pain relief and allowed a reduction in opioid dosage. However, the dose of octreotide had to be gradually increased, suggesting tolerance to the analgesic effect; one patient was receiving a daily dose of 648 micrograms.

1. Penn RD, *et al.* Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992; **49:** 13–19.
2. Burgess JR, *et al.* Effective control of bone pain by octreotide in a patient with metastatic gastrinoma. *Med J Aust* 1996; **164:** 725–7.
3. Johnson SA, *et al.* Treatment of resistant pain in hypertrophic pulmonary osteoarthropathy with subcutaneous octreotide. *Thorax* 1997; **52:** 298–9.
4. De Conno F, *et al.* Subcutaneous octreotide in the treatment of pain in advanced cancer patients. *J Pain Symptom Manage* 1994; **9:** 34–8.
5. Paice JA, *et al.* Intrathecal octreotide for relief of intractable nonmalignant pain: 5-year experience with two cases. *Neurosurgery* 1996; **38:** 203–7.

Pancreatic disorders. Octreotide has been tried in the treatment of acute pancreatitis, but was found to be ineffective.[1] For reference to the use of octreotide in the management of pancreatic endocrine tumours, see under Carcinoid Tumours (p.643); for its use in pancreatic fistulae, see under Gastrointestinal Disorders, above.

1. Uhl W, *et al.* A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; **45:** 97–104.

Pituitary adenoma. Octreotide has a role in the management of pituitary adenomas that cause acromegaly (see above). It has also been used in the management of rare tumours such as thyrotropin-secreting pituitary adenomas, usually when surgery or radiotherapy have failed. Octreotide may reduce concentrations of thyrotropin and normalise thyroid hormones in most patients; tumour shrinkage also occurs in at least a third of cases.[1-4] Octreotide has also been tried in the management of other rare adenomas such as clinically nonfunctioning adenomas, but results have been mixed; in a few cases there has been relief of symptoms such as headache without any change in tumour volume.[5]

1. Chanson P, *et al.* Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas: a follow-up of 52 patients. *Ann Intern Med* 1993; **119:** 236–40.
2. Caron P, *et al.* Efficacy of the long-acting octreotide formulation (octreotide-Lar) in patients with thyrotropin-secreting pituitary adenomas. *J Clin Endocrinol Metab* 2001; **86:** 2849–53.
3. Beck-Peccoz P, Persani L. Medical management of thyrotropin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 83–8.
4. Socin HV, *et al.* The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol* 2003; **148:** 433–42.
5. Colao A, *et al.* Somatostatin analogs in treatment of non-growth hormone–secreting pituitary adenomas. *Endocrine* 2003; **20:** 279–83.

Pretibial myxoedema. Pretibial myxoedema (deposition of glycosaminoglycans in the subcutaneous tissue of the shins) is associated with Graves' disease (see Hyperthyroidism, p.2165). There are reports of apparent benefit from the use of octreotide for this condition. In one case,[1,2] octreotide given for 6 months after surgical removal of the myxoedematous tissue may have prevented its recurrence. In another,[3] octreotide injected intralesionally was reported to improve and control the condition. However, in other cases[4] subcutaneous octreotide has been ineffective.

1. Derrick EK, *et al.* Successful surgical treatment of severe pretibial myxoedema. *Br J Dermatol* 1995; **133:** 317–18.
2. Felton J, *et al.* Successful combined surgical and octreotide treatment of severe pretibial myxoedema reviewed after 9 years. *Br J Dermatol* 2003; **148:** 825–6.
3. Shinohara M, *et al.* Refractory pretibial myxoedema with response to intralesional insulin-like growth factor 1 antagonist (octreotide): downregulation of hyaluronic acid production by the lesional fibroblasts. *Br J Dermatol* 2000; **143:** 1083–6.
4. Rotman-Pikielny P, *et al.* Lack of effect of long-term octreotide therapy in severe thyroid-associated dermopathy. *Thyroid* 2003; **13:** 465–70.

Raised intracranial pressure. For a reference to octreotide being tried in idiopathic intracranial hypertension, see p.1181.

Sulfonylurea overdose. Octreotide has been used in the treatment of severe refractory cases of sulfonylurea-induced hypoglycaemia (see p.461).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Sandostatin; ***Austral.:*** Sandostatin; ***Austria:*** Sandostatin; ***Belg.:*** Sandostatine; ***Braz.:*** Sandostatin; ***Canad.:*** Sandostatin; ***Chile:*** Sandostatin; ***Cz.:*** Sandostatin; ***Denm.:*** Sandostatin; ***Fin.:*** Sandostatin; ***Fr.:*** Sandostatine; ***Ger.:*** Sandostatin; ***Gr.:*** Sandostatin; ***Hong Kong:*** Sandostatin; ***Hung.:*** Sandostatin; ***India:*** Sandostatin; ***Indon.:*** Sandostatin; ***Irl.:*** Sandostatin; ***Israel:*** Sandostatin; ***Ital.:*** Longastatina; Samilstin; Sandostatina; ***Malaysia:*** Sandostatin; ***Mex.:*** Proclose; Sandostatina; ***Neth.:*** Sandostatine; ***Norw.:*** Sandostatin; ***NZ:*** Sandostatin; ***Philipp.:*** Sandostatin; ***Port.:*** Sandostatina; ***Rus.:*** Sandostatin (Сандостатин); ***S.Afr.:*** Sandostatin; ***Singapore:*** Sandostatin; ***Spain:*** Sandostatin; ***Swed.:*** Sandostatin; ***Switz.:*** Sandostatine; ***Thai.:*** Sandostatin; ***Turk.:*** Sandostatin; ***UK:*** Sandostatin; ***USA:*** Sandostatin; ***Venez.:*** Sandostatin.

Multi-ingredient: ***Pol.:*** Sandostatin.

Pegvisomant *(USAN, rINN)*

B2036-PEG; Pegvisomantti; Pegvisomantum. 18-L-Aspartic acid-21-L-asparagine-120-L-lysine-167-L-asparagine-168-L-alanine-171-L-serine-172-L-arginine-174-L-serine-179-L-threonine growth hormone (human), reaction product with polyethylene glycol.

Пэгвизомант

CAS — 218620-50-9.

ATC — H01AX01.

ATC Vet — QH01AX01.

Adverse Effects and Precautions

Adverse effects commonly reported with the use of pegvisomant include gastrointestinal disturbances, elevated liver function tests, flu-like symptoms, fatigue, injection site reactions, arthralgia, myalgia, peripheral oedema, headache, dizziness, somnolence, tremor, sweating, pruritus, rash, sleep disorders, hypercholesterolaemia, weight gain, hyperglycaemia, hunger, and hypertension.

Liver function tests should be measured before starting pegvisomant, then every 4 to 6 weeks for the first 6 months of therapy. In the USA, it is also recommended that further testing take place twice in the next 6 months and then twice in the following year.

Pegvisomant is structurally similar to growth hormone and may cause assays to overestimate growth hormone concentrations.

Effects on the skin. Lipohypertrophy has been described in patients who have consistently injected pegvisomant into the same subcutaneous area.[1,2] The efficacy of pegvisomant was also reduced in one case, but lipohypertrophy resolved and pegvisomant efficacy improved when the patient used the recommended technique of injection site rotation.[2]

1. Maffei P, *et al.* Lipohypertrophy in acromegaly induced by the new growth hormone receptor antagonist pegvisomant. *Ann Intern Med* 2006; **145:** 310–12.
2. Marazuela M, *et al.* Pegvisomant-induced lipohypertrophy: report of a case with histopathology. *Ann Intern Med* 2007; **147:** 741–3.

Interactions

Pegvisomant may increase insulin sensitivity. In patients with diabetes, doses of insulin or oral hypoglycaemics may need to be decreased because of the increased risk of hypoglycaemia. Patients taking opioid analgesics may require higher serum concentrations of pegvisomant to achieve appropriate IGF-I suppression.

Pharmacokinetics

Pegvisomant is absorbed slowly after subcutaneous injection, and peak serum concentrations occur after about 33 to 77 hours. It is slowly eliminated from serum, with a half-life estimated to range from 74 to 172 hours. Renal clearance of pegvisomant is negligible.

Uses and Administration

Pegvisomant is a protein of recombinant DNA origin to which several polyethylene glycol polymers are covalently bound. It is an analogue of human growth hormone that acts as an antagonist at growth hormone receptors, and is used in the treatment of acromegaly (below). A loading dose of 40 or 80 mg is given subcutaneously, followed by 10 mg daily. Further dose adjustments, in increments of 5 mg, are made according to serum concentrations of IGF-I, which should be measured every 4 to 6 weeks. The maintenance dose should not exceed 30 mg daily.

Acromegaly. Pegvisomant may be used in patients with acromegaly (p.1798) who have not responded adequately to surgery, radiotherapy, or somatostatin analogues, or when these therapies are unsuitable or not tolerated. The combination of pegvisomant with a somatostatin analogue is also under investigation in patients whose response to a somatostatin analogue alone is inadequate.

References.

1. Trainer PJ, *et al.* Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 2000; **342:** 1171–7.
2. Herman-Bonert VS, *et al.* Growth hormone receptor antagonist therapy in acromegalic patients resistant to somatostatin analogs. *J Clin Endocrinol Metab* 2000; **85:** 2958–61.
3. van der Lely AJ, *et al.* Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001; **358:** 1754–9.
4. Clemmons DR, *et al.* Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. *J Clin Endocrinol Metab* 2003; **88:** 4759–67.
5. Muller AF, *et al.* Growth hormone receptor antagonists. *J Clin Endocrinol Metab* 2004; **89:** 1503–11.
6. Feenstra J, *et al.* Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 2005; **365:** 1644–6. Correction. *ibid.*; 1620.
7. Jehle S, *et al.* Alternate-day administration of pegvisomant maintains normal serum insulin-like growth factor-I levels in patients with acromegaly. *J Clin Endocrinol Metab* 2005; **90:** 1588–93.
8. Colao A, *et al.* Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. *Eur J Endocrinol* 2006; **154:** 467–77.
9. Pivonello R, *et al.* Treatment with growth hormone receptor antagonist in acromegaly: effect on cardiac structure and performance. *J Clin Endocrinol Metab* 2007; **92:** 476–82. Correction. *ibid.*; 1605.
10. Neggers SJCMM, *et al.* Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *J Clin Endocrinol Metab* 2007; **92:** 4598–4601.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Somavert; ***Belg.:*** Somavert; ***Braz.:*** Somavert; ***Cz.:*** Somavert; ***Denm.:*** Somavert; ***Fin.:*** Somavert; ***Fr.:*** Somavert; ***Ger.:*** Somavert; ***Gr.:*** Somavert; ***Irl.:*** Somavert; ***Ital.:*** Somavert; ***Neth.:*** Somavert; ***Norw.:*** Somavert; ***Port.:*** Somavert; ***Spain:*** Somavert; ***Swed.:*** Somavert; ***UK:*** Somavert; ***USA:*** Somavert.

Pralmorelin Dihydrochloride *(USAN, rINNM)* ⊗

Dihidrocloruro de pralmorelina; GHRP-2 (pralmorelin); Growth Hormone-releasing Peptide-2 (pralmorelin); KP-102 (pralmorelin); Pralmoréline, Dichlorhydrate de; Pralmorelini Dihydrochloridum; WAY-GPA-748. D-Alanyl-3-(2-naphthyl)-D-alanyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide dihydrochloride.

Пральморелина Дигидрохлорид

$C_{45}H_{55}N_9O_6,2HCl = 890.9.$

CAS — 158861-67-7 (pralmorelin); 158827-34-0 (pralmorelin dihydrochloride).

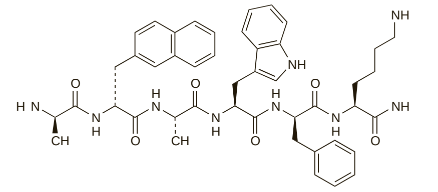

(pralmorelin)

Profile

Pralmorelin is a small synthetic peptide that stimulates the release of growth hormone. It is under investigation in the diagnosis of growth hormone deficiency and for the treatment of growth retardation (p.1798).

◊ References.

1. Mericq V, *et al.* Effects of eight months treatment with graded doses of a growth hormone (GH)-releasing peptide in GH-deficient children. *J Clin Endocrinol Metab* 1998; **83:** 2355–60.
2. Mahajan T, Lightman SL. A simple test for growth hormone deficiency in adults. *J Clin Endocrinol Metab* 2000; **85:** 1473–6.
3. Gondo RG, *et al.* Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor. *J Clin Endocrinol Metab* 2001; **86:** 3279–83.

Somatomedins ⊗

IGFs; Insulin-like Growth Factors; Somatomedinas; Sulphation Factors.

Description. Somatomedins are a group of polypeptide hormones related to insulin and usually known individually as insulin-like growth factors (IGFs), with molecular weights of about 7000 to 8000. They are synthesised in the liver, kidney, muscle, and other tissues.

Mecasermin *(BAN, USAN, rINN)* ⊗

CEP-151; FK-780; IGF-1; IGF-I; Insulin-like growth factor I (human); Mecasermina; Mécasermine; Mecaserminum; rhIGF-1; Somatomedin C.

Мекасермин

$C_{331}H_{512}N_{94}O_{101}S_7 = 7648.6.$

CAS — 68562-41-4; 67763-96-6.

ATC — H01AC03.

ATC Vet — QH01AC03.

Mecasermin Rinfabate *(USAN, rINN)* ⊗

Mecasermina rinfabato; Mécasermine Rinfabate; Mecaserminum Rinfabas; rhIGF-I/rhIGFBP-3. A complex of insulin-like growth factor I (human) with insulin-like growth factor-binding protein IGFBP-3 (human).

Мекасермин Ринфабат

CAS — 478166-15-3.

ATC — H01AC05.

ATC Vet — QH01AC05.

Adverse Effects and Precautions

Since the somatomedins are considered to be responsible for many of the actions of growth hormone similar adverse effects (see p.1800) might be expected, and have been seen with mecasermin. Hypoglycaemia is common but symptoms can generally be avoided if mecasermin is given within 20 minutes of food. Tonsillar hypertrophy can develop; patients should be monitored for complications such as snoring, sleep apnoea, and chronic middle ear effusions. Thickening of the soft tissues of the face can also occur. Cardiomegaly and valvulopathy have been reported in a few patients. Although a relationship between cardiac changes and mecasermin therapy has not been confirmed, echocardiogram monitoring has been recommended. Injection site hypertrophy may occur, but can be avoided or resolved by proper rotation of injection sites.

Effects on the eyes. For concerns about an increased risk of retinopathy in diabetic patients receiving mecasermin, see under Diabetes Mellitus, below.

Intravenous administration. Syncope in the absence of hypoglycaemia has been reported in patients given mecasermin by intravenous bolus, accompanied in some cases by convulsions, asystole, bradycardia, hypotension, or dizziness.[1] Reports appear to have ceased since recommendations that mecasermin should not be given intravenously at rates greater than 24 micrograms/kg per hour. Arthralgia, nerve palsies, and hypophosphataemia and dyspnoea have been associated with high-dose intravenous bolus therapy.[2] Mecasermin is now given by subcutaneous injection (see Uses and Administration, below).

1. Malozowski S, Stadel B. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 549.
2. Usala A-L. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121:** 550.

Pharmacokinetics

After subcutaneous injection, mecasermin has a bioavailability of almost 100% in healthy subjects. In the circulation it is bound to 6 binding proteins, with more than 80% bound to binding protein 3 (IGFBP-3). However, IGFBP-3 is greatly reduced in patients with severe primary IGF-I deficiency, such that there is an increase in the clearance of mecasermin. Mecasermin is metabolised in the liver and the kidney, and has a terminal half-life of about 6 hours in children with severe primary IGF-I deficiency.

After subcutaneous injection of mecasermin rinfabate in children with severe primary IGF-I deficiency, the half-life of free IGF-I is prolonged to about 13 hours and IGFBP-3 has a half-life of about 54 hours.

Uses and Administration

The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body. Insulin-like growth factor I (IGF-I) is believed to be responsible for many of the anabolic effects of growth hormone. It is secreted primarily by the liver, regulated principally by growth hormone and insulin secretion; IGF-I may also be secreted in other tissues, where it may exert local hormonal (paracrine) effects. In the circulation, IGF-I is almost completely protein bound; 6 binding proteins have been identified and production of some of these is also under the control of growth hormone. In addition to its anabolic effects IGF-I, which is structurally related to insulin, also has potent hypoglycaemic properties.

IGF-I is available as mecasermin, a product of recombinant DNA technology. It is used in the treatment of growth failure in children with severe primary IGF-I deficiency (such as Laron-type dwarfism, in which an abnormality of the growth hormone receptor results in an inability to secrete endogenous IGF-I—see Growth Retardation, below). It may also be used in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone. However, it is not recommended for children less than 2 years of age because of a lack of data. The starting dose of mecasermin is 40 to 80 micrograms/kg twice daily by subcutaneous injection. After 1 week, if this dose is tolerated, it may be increased by 40 micrograms/kg per dose to a maximum of 120 micrograms/kg twice daily. Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia. The dose should be reduced if hypoglycaemia occurs with recommended doses despite adequate food intake. If the patient is unable to eat for any reason, the dose of mecasermin should be withheld.

Mecasermin rinfabate is a recombinant protein complex of IGF-I and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). It is under investigation in the management of amyotrophic lateral sclerosis and myotonic muscular dystrophy.

IGF-II (IGF-2) is thought to play an important role in fetal growth, although its function in adults is uncertain. It is closely related in structure to IGF-I, but is not under the control of growth hormone.

◊ General reviews.

1. Laron Z. Somatomedin-1 (insulin-like growth factor-I) in clinical use: facts and potential. *Drugs* 1993; **45:** 1–8.
2. Bondy CA, *et al.* Clinical uses of insulin-like growth factor I. *Ann Intern Med* 1994; **124:** 593–601.
3. Le Roith D. Insulin-like growth factors. *N Engl J Med* 1997; **336:** 633–40.
4. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol* 2001; **54:** 311–16.
5. Kemp SF, *et al.* Efficacy and safety of mecasermin rinfabate. *Expert Opin Biol Ther* 2006; **6:** 533–8.

Diabetes mellitus. Patients with type 1 diabetes mellitus (p.431) have low circulating levels of insulin-like growth factor I (IGF-I), and there has been considerable interest in the therapeutic potential of mecasermin in these patients.[1] Randomised studies[2,3] have found that mecasermin 40 micrograms/kg once or twice daily by subcutaneous injection improves metabolic control in the short term when added to insulin therapy. Insulin doses can also be reduced in some patients.[3] However, the role of IGF-I in the development of diabetic complications is unclear and there has been some concern about its proliferative effect in diabetic retinopathy.[1] Optic disc swelling and worsening of retinopathy have been reported with higher doses of mecasermin.[3] Mecasermin rinfabate is being studied in an attempt to limit adverse effects such as oedema, jaw pain, headache, Bells' palsy, and retinal oedema.[4]

Mecasermin has also been reported to improve insulin sensitivity and to lower concentrations of insulin, glucose, and C-peptide in patients with syndromes of severe insulin resistance or type 2 diabetes mellitus.[1]

1. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. *Diabetes Technol Ther* 2000; **2:** 69–80.
2. Acerini CL, *et al.* Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350:** 1199–1204.
3. Thrailkill KM, *et al.* Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. *Diabetes Care* 1999; **22:** 585–92.
4. Clemmons DR, *et al.* The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab* 2000; **85:** 1518–24.

Growth retardation. Mecasermin is used in the treatment of Laron-type dwarfism (growth hormone resistance), a form of growth retardation (p.1798). Doses of 150 to 240 micrograms/kg daily, given subcutaneously, have stimulated linear growth and normalised biochemical abnormalities in these patients.[1] During long-term use, growth hormone and insulin are persistently suppressed, preventing hypoglycaemia and stabilising blood-glucose concentrations. There is also an increase in the production of the insulin-like growth factor binding protein-3, which prolongs the half-life of mecasermin so that a progressive dose reduction is needed to avoid overdosage and adverse effects.[2]

1. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; **84:** 4397–4404.
2. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89:** 1031–44.

Motor neurone disease. Mecasermin is under investigation for the management of amyotrophic lateral sclerosis, a form of motor neurone disease (p.2380). Mecasermin may have modest benefits but there is not enough available evidence to assess conclusively.[1]

1. Mitchell JD, *et al.* Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/08/08).

Osteoporosis. Mecasermin[1] and mecasermin rinfabate[2] have been investigated as stimulants of bone formation in osteoporosis (p.1084). Some beneficial effects on bone density have been reported.

1. Grinspoon S, *et al.* Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002; **87:** 2883–91.
2. Boonen S, *et al.* Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002; **87:** 1593–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Increlex; ***Fr.:*** Increlex; ***UK:*** Increlex; ***USA:*** Increlex; Iplex†.

Somatorelin *(rINN)* ⊗

GHRF; GHRH; GRF; GRF-44; Growth Hormone-releasing Factor (Human); Growth Hormone-releasing Hormone; Somatoliberin; Somatoreliini; Somatorelina; Somatoréline; Somatorelinum.

Соматорелин

$C_{215}H_{358}N_{72}O_{66}S$ = 5039.7.

CAS — 83930-13-6.

ATC — V04CD05.

ATC Vet — QV04CD05.

Sermorelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de sermorelina; GRF(1-29)NH_2 (sermorelin); Growth Hormone-releasing Factor (Human)-(1-29)-peptide Amide (sermorelin); Sermoréline, Acétate de; Sermorelini Acetas. Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate hydrate.

Серморелина Ацетат

$C_{149}H_{246}N_{44}O_{42}S.xC_2H_4O_2.yH_2O$ = 3357.9 (sermorelin).

CAS — 86168-78-7 (sermorelin); 114466-38-5 (sermorelin acetate).

ATC — H01AC04; V04CD03.

ATC Vet — QH01AC04; QV04CD03.

Adverse Effects and Precautions

Facial flushing and pain at the injection site may occur after injection of sermorelin acetate. Headache, nausea and vomiting, dysgeusia, and tightness in the chest have also been reported. Antibodies to somatorelin may develop on repeated use.

Sermorelin should be used with care in patients with epilepsy. Uncontrolled hypothyroidism, obesity, hyperglycaemia, or elevated plasma fatty acids may impair response to sermorelin. Sermorelin should not be used to treat growth retardation in children whose growth hormone response to stimulation tests is inadequate. Treatment should cease once the epiphyses have closed.

Interactions

Drugs that affect the secretion of growth hormone may interfere with the diagnostic efficacy of somatorelin or sermorelin; these include growth hormone itself, somatostatin, insulin, corticosteroids, and cyclo-oxygenase inhibitors such as aspirin and indometacin. Growth hormone concentrations may be raised by clonidine and levodopa. The response to somatorelin or sermorelin may also be reduced by antimuscarinic drugs such as atropine, and by antithyroid drugs such as propylthiouracil.

Uses and Administration

Somatorelin is a peptide, secreted by the hypothalamus, that promotes the release of growth hormone from the anterior pituitary. It exists as 44-, 40-, and 37-amino acid peptides; the 44-amino acid form may possibly be converted to the smaller forms but all are reported to be active, the activity residing in the first 29 amino acid residues. Sermorelin is a synthetic peptide corresponding to the 1–29 amino acid sequence of somatorelin.

Sermorelin acetate is used for the diagnosis of growth hormone deficiency. The usual dose is the equivalent of sermorelin 1 microgram/kg by intravenous injection in the morning after an overnight fast. A normal response to sermorelin indicates that the somatotrophs are functional, but does not exclude growth hormone deficiency due to hypothalamic dysfunction; to establish a diagnosis it must be used with other tests. Somatorelin acetate is used similarly.

Sermorelin has also been used for the treatment of growth hormone deficiency in children; doses equivalent to 30 micrograms/kg, as the acetate, may be given once daily at bedtime by subcutaneous injection.

Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation and has been investigated in the treatment of HIV-associated wasting.

Diagnostic use. Somatorelin (in its 40- or 44-amino acid forms) has been used in the assessment of growth hormone deficiency.[1-3] It has usually been given as a single intravenous injection in doses of 1 microgram/kg or total doses of up to 200 micrograms. Subsequent normal or exaggerated increases in serum-growth hormone concentrations have occurred in healthy subjects,[1,2] and in patients with hypothalamic tumours[3] or acromegaly,[2] but not in patients with hypopituitarism.[2] A synthetic 29-amino-acid sequence of somatorelin, sermorelin acetate is now available for the diagnosis of growth hormone deficiency. However, it has been suggested that the test is not useful for screening as it does not test the hypothalamic-pituitary axis, and that it should not be used in routine clinical practice.[4] The use of sermorelin with the synthetic hexapeptide growth-hormone-releasing peptide-6 has also been reported.[5,6]

1. Thorner MO, *et al.* Human pancreatic growth-hormone-releasing factor selectively stimulates growth-hormone secretion in man. *Lancet* 1983; **i:** 24–8. Correction. *ibid.*; 256.
2. Wood SM, *et al.* Abnormalities of growth hormone release in response to human pancreatic growth hormone releasing factor (GRF (1-44)) in acromegaly and hypopituitarism. *BMJ* 1983; **286:** 1687–91.
3. Grossman A, *et al.* Growth-hormone-releasing factor in growth hormone deficiency: demonstration of a hypothalamic defect in growth hormone release. *Lancet* 1983; **ii:** 137–8.
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.
5. Popovic V, *et al.* GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults. *Lancet* 2000; **356:** 1137–42.
6. Leal A, *et al.* A single growth hormone (GH) determination is sufficient for the diagnosis of GH-deficiency in adult patients using the growth hormone releasing hormone plus growth hormone releasing peptide-6 test. *Clin Endocrinol (Oxf)* 2002; **57:** 377–84.

Growth retardation. Sermorelin has been studied in children with growth hormone deficiency (p.1798), usually given in doses of 30 micrograms/kg subcutaneously daily. Although there have been reports of improved growth rates,[1-3] there are limited data directly comparing these with growth hormone. One large study[4] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer.

1. Neyzi O, *et al.* Growth response to growth hormone-releasing hormone(1—29)-NH compared with growth hormone. *Acta Paediatr Suppl* 1993; **388:** 16–21.
2. Lanes R, *et al.* Long term therapy with a single daily subcutaneous dose of growth hormone releasing hormone (1-29) in prepubertal growth hormone deficient children. *J Pediatr Endocrinol* 1994; **7:** 303–8.
3. Ogilvy-Stuart AL, *et al.* Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. *Clin Endocrinol (Oxf)* 1997; **46:** 571–8.
4. Thorner M, *et al.* Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. *J Clin Endocrinol Metab* 1996; **81:** 1189–96.

Lipodystrophy. In a placebo-controlled study[1] of 31 men with HIV-related lipodystrophy, insulin-like growth factor I (IGF-I) concentrations and body composition measures were improved in those given sermorelin 1 mg twice daily subcutaneously for 12 weeks.

1. Koutkia P, *et al.* Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 2004; **292:** 210–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Geref; ***Belg.:*** GHRH; ***Denm.:*** Somatrel†; ***Fin.:*** Geref; ***Fr.:*** Stimu-GH; ***Ger.:*** GHRH; ***Gr.:*** Geref; ***Hong Kong:*** Geref†; ***Irl.:*** Geref; ***Ital.:*** Geref; GHRH; ***Neth.:*** GHRH; ***Norw.:*** Geref; ***Port.:*** Geref†; ***Spain:*** Geref; ***Swed.:*** Geref†; ***Switz.:*** Geref†; GHRH; ***UK:*** Geref†; GHRH; ***USA:*** Geref.

Somatostatin *(BAN, rINN)*

GH-RIF; GHRIH; Growth-hormone-release-inhibiting Hormone; Somatostatiini; Somatostatina; Somatostatinas; Somatostatine; Somatostatinum; Somatotrophin-release-inhibiting Factor; Szomatosztatin. Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys cyclic (3→14) disulphide.

Соматостатин

$C_{76}H_{104}N_{18}O_{19}S_2$ = 1637.9.
CAS — 38916-34-6.
ATC — H01CB01.
ATC Vet — QH01CB01.

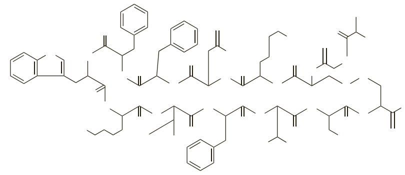

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Somatostatin). A cyclic tetradecapeptide having the structure of the hypothalamic hormone that inhibits the release of human growth hormone. It is produced by chemical synthesis and contains not more than 15% w/w of acetic acid. A white amorphous powder. Freely soluble in water and in acetic acid; practically insoluble in dichloromethane. Store in airtight containers at a temperature of 2° to 8°. Protect from light and moisture.

Somatostatin Acetate *(BANM, rINNM)*

Acetato de somatostatina; Somatostatiiniasetaatti; Somatostatin Asetat; Somatostatinacetat; Somatostatine, Acétate de; Somatostatini Acetas.

Соматостатина Ацетат
ATC — H01CB01.
ATC Vet — QH01CB01.

Adverse Effects and Precautions

Abdominal discomfort, flushing, nausea, and bradycardia have been associated with too rapid infusion. Because of the short half-life of somatostatin adverse effects are generally transitory on stopping or reducing the infusion. Giving with parenteral nutrition has been suggested because of the inhibitory effects of somatostatin on intestinal absorption; blood glucose should be monitored since somatostatin may interfere with the secretion of insulin and glucagon.

Effects on the kidneys. Somatostatin has been reported to have an inhibitory effect on renal function[1,2] and severe water retention and hyponatraemia have been reported.[3]

1. Walker BJ, *et al.* Somatostatin and water excretion. *Lancet* 1983; **i:** 1101–2.
2. Vora JP, *et al.* Effect of somatostatin on renal function. *BMJ* 1986; **292:** 1701–2.
3. Halma C, *et al.* Life-threatening water intoxication during somatostatin therapy. *Ann Intern Med* 1987; **107:** 518–20.

Uses and Administration

Somatostatin is a polypeptide obtained from the hypothalamus or by synthesis. The naturally occurring form has a cyclic structure. Although somatostatin derived from the hypothalamus is a 14-amino-acid peptide, a longer, 28-amino-acid form also exists in some tissues. Somatostatin inhibits the release of growth hormone (p.1799) from the anterior pituitary. It also inhibits the release of thyrotrophin (p.2177) and corticotropin (p.1523) from the pituitary, glucagon and insulin from the pancreas, and appears to have a role in the regulation of duodenal and gastric secretions. In the CNS it appears to play a role in the perception of pain.

It has been tried in a variety of disorders such as upper gastrointestinal haemorrhage including variceal haemorrhage (see under Monoethanolamine, p.2346), insulin resistance, and the management of hormone-secreting tumours and other hypersecretory disorders. However, it has a very short duration of action and several analogues of somatostatin have been produced in an attempt to prolong its activity as well as making its inhibitory effects more specific. Octreotide (p.1803) and lanreotide (p.1803) are such analogues.

Somatostatin is usually given as the acetate. In the treatment of gastrointestinal haemorrhage, such as acute bleeding from oesophageal varices, somatostatin acetate equivalent to somatostatin 250 micrograms has been given by intravenous bolus over 3 to 5 minutes, followed by a continuous infusion of 250 micrograms/hour (about 3.5 micrograms/kg per hour) until the bleeding has stopped, which is usually within 12 to 24 hours. The infusion may then be continued for a further 48 to 72 hours to prevent recurrent bleeding. In some cases, the infusion may be continued to a maximum of 120 hours.

Malignant neoplasms. Somatostatin given with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was ineffective in the treatment of advanced malignancies (see Malignant Neoplasms, under Uses and Administration of Octreotide, p.1806).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Stilamin†; ***Austria:*** Somatin; Somatolan; ***Belg.:*** Modustatine†; ***Braz.:*** Stilamin; ***Canad.:*** Stilamin; ***Cz.:*** Stilamin†; ***Fr.:*** Modustatine; ***Ger.:*** Aminopan†; ***Gr.:*** Atostan; Eklivan; Sadolin; Somabion; Somargen; Somaritin; Somastin; Stilamin; ***Hong Kong:*** Stilamin; ***Hung.:*** Somatin†; Stilamin†; ***India:*** Somastin; Stilamin†; ***Indon.:*** Stilamin; ***Ital.:*** Etaxene; Ikestatina; Modustatina; Nastoren; Resurmide; Stilamin; Zecnil†; ***Malaysia:*** Stilamin; ***Mex.:*** Stilamin†; ***Neth.:*** Stilamin†; ***Port.:*** Stilamin†; ***S.Afr.:*** Stilamin; ***Singapore:*** Stilamin; ***Spain:*** Somiaton†; Somonal; ***Switz.:*** Stilamin; ***Thai.:*** Etaxene; Stilamin; ***Turk.:*** Somatosan; Stilamin; ***Venez.:*** Ikestatina; Stilamin.

Vapreotide *(BAN, USAN, rINN)*

BMY-41606; RC-160; Vapreotida; Vapréotide; Vapreotidum. D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide.

Вапреотид

$C_{57}H_{70}N_{12}O_9S_2$ = 1131.4.
CAS — 103222-11-3.
ATC — H01CB04.
ATC Vet — QH01CB04.

D-Phe – Cys – Tyr – D-Trp – Lys – Val – Cys – Trp – NH_2

Profile

Vapreotide is a somatostatin analogue similar to octreotide (p.1803). It is under investigation in the management of various disorders, including bleeding oesophageal varices, gastrointestinal and pancreatic fistulas, acromegaly, carcinoid tumours, and for the prevention of postoperative complications following pancreatic surgery.

◊ References.

1. Eriksson B, *et al.* The use of new somatostatin analogues, lanreotide and octastatin, in neuroendocrine gastro-intestinal tumours. *Digestion* 1996; **57** (suppl 1): 77–80.
2. Calès P, *et al.* Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med* 2001; **344:** 23–8.
3. Anonymous. Vapreotide: BMY 41606, RC 160, Sanvar. *Drugs R D* 2003; **4:** 326–30.

Immunosuppressants

Asthma, p.1810
Blood disorders, p.1810
Diabetes mellitus, p.1810
Gastrointestinal disorders, p.1810
  Inflammatory bowel disease, p.1810
Liver disorders, p.1810
Lung disorders, p.1810
  Diffuse parenchymal lung disease, p.1810
Neurological disorders, p.1810
  Multiple sclerosis, p.1810
  Myasthenia gravis, p.1810
Ocular disorders, p.1810
Organ and tissue transplantation, p.1810
  Corneal transplantation, p.1811
  Haematopoietic stem cell transplantation, p.1811
  Heart transplantation, p.1812
  Intestinal transplantation, p.1813
  Kidney transplantation, p.1813
  Liver transplantation, p.1815
  Lung transplantation, p.1815
  Pancreatic transplantation, p.1816
Renal disorders, p.1816
Rheumatoid arthritis, p.1816
Sarcoidosis, p.1816
Scleroderma, p.1817
Skin and connective tissue disorders, p.1817

The compounds described in this chapter are used in diseases considered to have an auto-immune component, and in organ and tissue transplantation. The choice of an immunosuppressant is discussed below.

Choice of Immunosuppressant

Asthma

Immunosuppressant drugs do not play a role in the regular management of asthma (p.1108). In individual patients requiring oral corticosteroids for chronic severe asthma immunosuppressants have however been investigated for their anti-inflammatory and corticosteroid-sparing properties.

Blood disorders

For the use of immunosuppressants in aplastic anaemia, see p.1042.

Diabetes mellitus

For a discussion of diabetes mellitus and its treatment, including the experimental use of immunosuppressants, see p.431. See also Pancreatic Transplantation, below.

Gastrointestinal disorders

Inflammatory bowel disease. A number of immunosuppressants have been tried in inflammatory bowel disease (p.1697), with some success, but the mainstays of drug therapy remain the aminosalicylates and the corticosteroids. Immunosuppressants may be valuable in some circumstances for their corticosteroid-sparing effect and for chronic active disease refractory to other treatments.

Liver disorders

For a discussion of the role of immunosuppressants, and particularly azathioprine, in the management of chronic active hepatitis, see p.1501. For the use of immunosuppressants in primary biliary cirrhosis see under Ursodeoxycholic Acid, p.2408.

Lung disorders

Diffuse parenchymal lung disease. Corticosteroids, usually with azathioprine (or occasionally cyclophosphamide), are the mainstay of treatment for diffuse parenchymal lung disease (p.1502) such as cryptogenic fibrosing alveolitis.

Neurological disorders

Multiple sclerosis. Immunosuppressants have been tried in the treatment of multiple sclerosis (p.892), although in some studies the benefit obtained may have been outweighed by toxicity.

Myasthenia gravis. Patients with myasthenia gravis (p.629) who require immunosuppression are usually treated with corticosteroids. Azathioprine is used mainly in myasthenia gravis for its corticosteroid-sparing effect but may also be of use when corticosteroids are contra-indicated or when response to their use alone is insufficient. Ciclosporin, mycophenolate mofetil, and tacrolimus have been tried similarly.

Ocular disorders

Immunosuppressants have been used with some success in ocular disorders with inflammatory or immunological components. In *scleritis* and *uveitis* (see p.1512 and p.1515) corticosteroids, given topically, intra-ocularly, or systemically are widely used when treatment is needed, but in unresponsive disease, or in patients with unacceptable adverse effects, immunosuppressants such as azathioprine, ciclosporin, or mycophenolate mofetil, may be given. Daclizumab, leflunomide, sirolimus, and tacrolimus have also been tried in uveitis. Immunosuppressants may be valuable in the management of *Behçet's disease*, *rheumatoid arthritis*, or *Wegener's granulomatosis*, (see p.1499, p.11, and p.1515, respectively), including their associated ocular lesions. Ciclosporin or azathioprine have been used with corticosteroids in the management of both ocular and vascular symptoms of *Cogan's syndrome* (p.1502). Ciclosporin has also been used topically in corneal ulceration, see p.1831.

In *Graves' ophthalmopathy* (see under Hyperthyroidism, p.2165), ciclosporin with oral glucocorticoids has been used as an effective alternative treatment.

Reviews.

1. McCluskey PJ, *et al.* Management of chronic uveitis. *BMJ* 2000; **320:** 555–8.
2. Jabs DA, *et al.* Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000; **130:** 492–513.
3. Kulkarni P. Review: uveitis and immunosuppressive drugs. *J Ocul Pharmacol Ther* 2001; **17:** 181–7.
4. Dunn JP. Review of immunosuppressive drug therapy in uveitis. *Curr Opin Ophthalmol* 2004; **15:** 293–8.
5. Hemady RK, *et al.* Immunosuppressive agents and nonsteroidal anti-inflammatory drugs for ocular immune and inflammatory disorders. *Ophthalmol Clin North Am* 2005; **18:** 511–28.

Organ and tissue transplantation

Although surgical techniques suitable for the removal of organs and tissues from a donor, and their engraftment into a host, have existed for many years, such grafts would not normally survive for long. The host's CD4 T-cells recognise foreign antigens from donor cells. A CD4 cell is then activated by antigen-presenting cells to secrete interleukin-2 and induce T-cell proliferation. Activated T-cells mediate a rejection response, by increasing the activity and function of B-cells, cytotoxic CD8 T-cells, and macrophages, either directly, or by cytokine release. Only from the 1960s with the development of drugs capable of attenuating or suppressing this response, did transplantation start to become a feasible mode of treatment.

The drugs available vary in their mechanisms of action, and are often combined for optimum effect. **Corticosteroids** (glucocorticoids) act at several points in the immune cascade, including antigen recognition and production of lymphokines. The **calcineurin inhibitors** ciclosporin and tacrolimus prevent formation of cytotoxic T-cells by inhibiting calcineurin activation, an important step in the release of interleukin-2 from helper T-cells, while polyclonal or monoclonal **antibodies** such as antilymphocyte immunoglobulins and muromonab-CD3 bind to and deplete T-cell populations. Basiliximab and daclizumab function as **interleukin-2 receptor antagonists**. **Anti-proliferative drugs** such as azathioprine and mycophenolate mofetil act by preventing cell division of lymphocytes. Sirolimus and everolimus are **proliferation signal inhibitors** that inhibit the T-cell response to cytokines.

Immunosuppressant regimens may be divided into those aimed at:

- prevention of rejection in the early period after transplantation
- long-term maintenance prophylaxis
- treatment of acute episodes of rejection.

In haematopoietic stem cell transplantation, where an immunologically competent tissue is transplanted, it is the donor cells which attack host tissues (graft-versus-host disease), and immunosuppression is required for prophylaxis of this condition.

Because of the critical nature of the early stage, when the organ or tissue must recover normal function, and perhaps to permit better long-term tolerance, initial immunosuppressant regimens tend to use higher doses than maintenance therapy. Standard protocols are usually based around ciclosporin or tacrolimus, combined with corticosteroids and an anti-proliferative agent (triple therapy). Where appropriate, a course of monoclonal or polyclonal antibodies is added to the standard regimen for induction (quadruple therapy). This is usually only required in individuals at increased risk of acute rejection, such as children or patients with a previous transplant or pregnancy, multiple blood transfusions, or a poor HLA-matching. However, it also enables delayed introduction of ciclosporin or tacrolimus in patients at risk of nephrotoxicity, and the use of low-dose regimens, allowing for withdrawal of corticosteroids.

No one immunosuppressive regimen has been identified as being superior to others in pregnancy, and although there are known theoretical risks to mother and fetus, successful pregnancies are now common in transplant recipients. The incidence of structural malformation has not been noted to be increased compared with the general population, but newer regimens have yet to be evaluated.

Since immunosuppressant therapy must in most cases be given for the lifetime of the graft, in long-term maintenance the toxicity of the drugs used, and the risks of infection, neoplasia, post-transplant diabetes mellitus, gout, hyperlipidaemia, and osteoporosis, must be considered. Doses and numbers of drugs used tend to be reduced, and in particular there is a tendency to taper or even eliminate the doses of corticosteroids used in maintenance regimens because of the potential sequelae of prolonged corticosteroid use. Post-transplant cardiovascular disease is a leading cause of death and graft loss. The risk varies between types of transplant, and specific recommendations for prophylaxis may differ.

The use of less intensive maintenance regimens must be balanced against the risk of an acute rejection episode, and the likelihood of its responding to therapy. High-dose corticosteroids and polyclonal or monoclonal antibodies often play a role in the rescue therapy of patients with acute rejection episodes, although much depends upon the severity of the reaction, and whether such episodes have occurred previously.

The management of immunosuppression for the transplantation of particular organs is discussed in more detail below. With the use of suitable immunosuppressant regimens long-term graft survival can be obtained after transplantation. Ultimately, however, the complications of chronic rejection are likely to lead to loss of the graft: the induction of specific tolerance to the donor organ remains the goal of much research. In allogeneic haematopoietic stem cell transplantation, where the aim of immunosuppression is prevention of graft-versus-host disease rather than rejection, immunosuppressant therapy can often be tapered off and eventually withdrawn.

Much interest has been aroused by the possibility of organ transplants from *animals*, genetically modified to reduce complement-mediated hyperacute rejection. It is not clear whether such xenotransplantation will require modified immunosuppressive regimens.

◊ General reviews on immunosuppression and transplantation.

1. Hong JC, Kahan BD. Immunosuppressive agents in organ transplantation: past, present, and future. *Semin Nephrol* 2000; **20:** 108–25.
2. Chapman LE, Bloom ET. Clinical xenotransplantation. *JAMA* 2001; **285:** 2304–6.
3. del Mar Fernández de Gatta M, *et al.* Immunosuppressive therapy for paediatric transplant patients: pharmacokinetic considerations. *Clin Pharmacokinet* 2002; **41:** 115–35.
4. Lee MA. Transplantation: drug aspects of immunosuppression. *Hosp Pharm* 2003; **10:** 201–3, 205, 207.
5. Monaco AP. The beginning of clinical tolerance in solid organ allografts. *Exp Clin Transplant* 2004; **2:** 153–61.
6. Tan HP, *et al.* Immunosuppressive preconditioning or induction regimens: evidence to date. *Drugs* 2006; **66:** 1535–45.

◊ Some reviews of the adverse effects and precautions associated with transplantation, and their management.

1. Chan SE, *et al.* Treatment of hepatitis C in solid organ transplantation. *Drugs* 2004; **64:** 489–98.
2. Slifkin M, *et al.* Viral prophylaxis in organ transplant patients. *Drugs* 2004; **64:** 2763–92.
3. Buell JF, *et al.* Malignancy after transplantation. *Transplantation* 2005; **80** (suppl 2): S254–S264.
4. Stamp L, *et al.* Gout in solid organ transplantation: a challenging clinical problem. *Drugs* 2005; **65:** 2593–2611.

5. Smith JM, McDonald RA. Emerging viral infections in transplantation. *Pediatr Transplant* 2006; **10:** 838–43.
6. McKay DB, Josephson MA. Pregnancy in recipients of solid organs—effects on mother and child. *N Engl J Med* 2006; **354:** 1281–93.
7. Dharnidharka VR. Post-transplant lymphoproliferative disease: association with induction therapy? *Drugs* 2006; **66:** 429–38.
8. Wheeler DC, Krentz AJ. New-onset diabetes after transplantation. *Br J Hosp Med* 2007; **68:** 190–4.
9. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs* 2007; **67:** 1167–98.
10. Morrissey PE, *et al.* Medication noncompliance and its implications in transplant recipients. *Drugs* 2007; **67:** 1463–81.

◊ References to some experimental procedures.

1. Devauchelle B, *et al.* First human face allograft: early report. *Lancet* 2006; **368:** 203–9.
2. Ruan D, *et al.* Intervertebral disc transplantation in the treatment of degenerative spine disease: a preliminary study. *Lancet* 2007; **369:** 993–9.

Corneal transplantation. For reference to the use of immunosuppressants to treat graft rejection after corneal transplant see Corneal Graft Rejection, p.1502.

Haematopoietic stem cell transplantation. Haematopoietic stem cell transplantation (HSCT) is used in the treatment of a variety of malignancies, notably leukaemias and lymphomas; to permit the use of very high-dose chemotherapy in the management of some solid tumours (bone marrow rescue); and to treat some other serious disorders affecting the bone marrow, such as aplastic anaemia and the haemoglobinopathies.[1,2]

HSCT may be **autologous**, in which case the patient's own stem cells are harvested or **allogeneic**, where stem cells are harvested from a healthy donor matched as closely as possible for HLA type.[3,4] The haematopoietic stem cells themselves may be derived from:

- bone marrow (classical bone marrow transplantation, BMT)
- peripheral blood (peripheral blood stem cell transplantation, PBSCT)
- umbilical cord blood

PBSCT is convenient as collection does not require hospitalisation or general anaesthesia for the donor, and clinical studies have shown more rapid engraftment of neutrophils and platelets compared with BMT.[2,5-7] However, allogeneic PBSCT appears to increase the risk of graft-versus-host disease[1,2,6-10] (see below). Allogeneic PBSCT was associated with decreased relapse rates and improved disease-free survival but similar overall survival in adults, when compared with BMT.[6] However, in children, allogeneic PBSCT was associated with higher mortality and treatment failure than BMT although relapse rates were similar; advanced disease status and use of colony-stimulating factor were also associated with poorer outcome.[7] Use of umbilical cord blood is associated with slightly delayed engraftment,[2,11-13] and hence, perhaps, an increased risk of fatal infection,[2,11] but a lower risk[2,12,14] of graft-versus-host disease (see below). A meta-analysis[15] confirmed these findings, but found a similar relapse rate, and equivalent survival for cord blood transplantation compared with unrelated BMT. It has mainly been used for transplants in children, since the total number of stem cells in a donation often falls short of the levels deemed necessary for engraftment in an adult.[1,2,5,13] However, cord blood is increasingly used for transplants in adults.[16] Since cell dose correlated with outcome in most studies, strategies have been developed to increase progenitor cell numbers in the cord blood units; techniques include pooled or sequential cord blood transplantation, or expansion of the cord blood cells with cytokines. Combination cord blood and bone marrow transplants, and reduced intensity regimens are under investigation.[16-18]

With autologous HSCT problems of **compatibility** do not arise, but if abnormal cell clones are present in the marrow (as in leukaemia) or stem cells they may be transferred back into the patient and cause disease relapse.[1] Allogeneic HSCT requires immunosuppression for about 6 months[19] to prevent graft-versus-host disease (see below) until a new immunological balance is achieved.

The patient is normally prepared by **conditioning** with total body irradiation, or myeloablative chemotherapy with drugs such as cyclophosphamide or busulfan, or more often both, in order to destroy host bone marrow cells.[5,20] In autologous procedures, harvesting of bone marrow or peripheral blood must be carried out before conditioning. Bone marrow is aspirated from the donor, and infused into the recipient via an indwelling catheter or directly into a peripheral vein. Peripheral blood stem cells are collected by cell separation after mobilisation, which is best achieved by a combination of chemotherapy and granulocyte or granulocyte-macrophage colony-stimulating factor.[1,2,5] Infection is a major cause of morbidity and mortality after transplantation, so prophylactic cover with antimicrobials[2,21,22] and normal immunoglobulins is recommended,[21] although the value of the latter has been questioned.[23] Granulocyte colony-stimulating factors are sometimes used after allogeneic transplants to hasten haematopoietic recovery. While a meta-analysis found no evidence for an increase in risk for acute or chronic graft-versus-host disease,[24] a large study found delayed platelet engraftment, increased graft-versus-host disease, and increased mortality in those given growth factors after allogeneic bone marrow transplants; these effects were not seen in patients given allogeneic PBSCT.[25]

In addition to such supportive care, patients who have received allogeneic transplants require immunosuppressive therapy aimed at the prevention of **graft-versus-host disease** (GVHD). GVHD is usually characterised as *acute* or *chronic* depending on the manifestations, and the time of presentation[1,4,5,10,26-28] (by convention acute disease occurs within a hundred days of transplantation, and chronic disease after this time, although in practice there is considerable overlap).

The organ systems primarily affected are skin, liver, lung, and gastrointestinal tract. Both forms are marked by maculopapular rashes, which in severe disease may progress to bullous lesions and epidermal necrolysis. Liver disease may include cholestatic jaundice (usually in the acute form) and hepatitis; symptoms may need to be distinguished from the veno-occlusive disease (VOD) which sometimes complicates bone marrow transplantation and is due to the pre-transplant conditioning regimen (VOD may respond to treatment with antithrombin III[29] or defibrotide[30,31]). Ursodeoxycholic acid has been found to be of benefit for the prophylaxis of hepatic complications.[32] The main symptom of gastrointestinal GVHD is diarrhoea, often severe and painful. In patients with chronic GVHD other manifestations may include arthritis, mucositis, lung disease, and scleroderma.

Most modern regimens for the prophylaxis of GVHD after allogeneic HSCT are based on ciclosporin. Although GVHD still occurs in many ciclosporin-treated patients, morbidity is much reduced and survival improved. Combination regimens have been tried for prophylaxis, particularly ciclosporin or tacrolimus with methotrexate, but also combinations with other drugs including antilymphocyte immunoglobulins, corticosteroids, mycophenolate mofetil, and sirolimus.[9,19,33] Monoclonal antibodies have been used to produce T-cell depletion or reduce the effects of circulating cytokines.[9,27]

Acute GVHD is usually treated primarily by the addition of corticosteroids (usually methylprednisolone) to the prophylactic regimen until symptoms are controlled, followed by gradual tapering of the dose. Mycophenolate mofetil, antilymphocyte immunoglobulins, interleukin-2 receptor antibodies, etanercept, and infliximab have also been tried.[2,9,19,34-36] PUVA therapy and extracorporeal photopheresis have been used[2,9] and infusion of mesenchymal stem cells is also under investigation.[9,37]

Chronic GVHD has no specific standard therapy; most centres use a combination of corticosteroids and a calcineurin inhibitor (ciclosporin or tacrolimus).[2,10,19,38,39] Drugs that have been tried for salvage therapy include mycophenolate mofetil, sirolimus, daclizumab, thalidomide, pentostatin, etanercept, infliximab, and rituximab.[10,19,35,38] PUVA therapy with extracorporeal photopheresis has also been used, with good response rates,[10,38] and recommendations for use have been published in the UK.[40] Mesenchymal stem cell infusion may be a potential therapy.[10] Octreotide is recommended for the symptomatic treatment of diarrhoea.[41]

Donor T-cells reactive to recipient minor histocompatibility antigens can inhibit the growth of abnormal cells, and may also target aberrantly expressed proteins, provoking a 'graft-versus-tumour' effect, which reduces relapse, both after allogeneic transplantation and among patients in whom GVHD develops.[1] Indeed, many leukaemia patients who relapse after allogeneic transplant can be reinduced into remission by an additional infusion of donor lymphocytes.[2] Consequently, too effective an immunosuppressant regimen may not always be desirable, and leukaemic patients given bone marrow transplants purged of T-cells, which virtually abolishes GVHD, do not have a better survival rate than those given conventional prophylaxis (engraftment too is reduced in the absence of all T-cells). Specific donor marrow T-cell depletion has been investigated as the sole form of GVHD prophylaxis.[42] In a multicentre randomised study, marrow T-cell depletion was found to reduce but not abolish the incidence of acute GVHD, accelerate neutrophil recovery and reduce toxicity compared to transplantation with T-cell replete marrow; however, disease-free survival at 3 years did not differ due to higher rates of relapse in some patients, and a higher incidence of serious infection in T-cell depleted marrow recipients.[43] The observation of graft-versus-malignancy effects has led to the development of low-dose non-myeloablative conditioning regimens (with or without donor lymphocyte infusions) for elderly or more sensitive patients who might have been unable to receive the standard aggressive therapy.[1-3,15,44-48] Safety and efficacy of these reduced-intensity regimens has led to wider application;[1] however, the lower mortality rate may be offset by a higher relapse rate,[1] and poor engraftment.[2]

The combination of irradiation, chemotherapy, and immunosuppression can cause the development of **secondary malignancies** in long-term survivors of HSCT.[1,49-52]

Intracoronary injection of haematopoietic stem cells into the heart is under investigation for cardiac disease,[53] **intramuscular** injection has also been investigated in peripheral vascular disease.[54] There is also interest in HSCT in some auto-immune disorders.[54]

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Heart transplantation. Marked improvements have been seen in the outcome of heart transplantation since the introduction of ciclosporin, which has resulted in a reduced incidence and severity of rejection episodes.[1] The 1-year survival rate is about 80%.[1,2]

A common **immunosuppressive regimen** consists of triple therapy with ciclosporin or tacrolimus, azathioprine or mycophenolate, and corticosteroids.[3-6] Some centres also use induction therapy with antilymphocyte immunoglobulins (polyclonal antibodies) or muromonab-CD3.[4,7]

Induction therapy increases the risk of infection and lymphoproliferative disorders, but does delay the first rejection episode and allows transplantation in higher risk groups. It also enables calcineurin inhibitor use to be delayed in patients with initial poor renal function[7] and corticosteroids to be stopped as maintenance therapy in some groups of patients.[8] Muromonab-CD3 may be associated with a higher incidence of adverse reactions than polyclonal antibodies. Sensitisation to muromonab-CD3 is strongly associated with vascular rejection, and this and the dose-related propensity for lymphoproliferative disease with muromonab-CD3 have led to a decline in its use; some consider it should be abandoned in favour of polyclonal preparations.[7,9] The interleukin-2 receptor antibodies basiliximab and daclizumab have also been used for induction therapy.[2,7,10,11] However, daclizumab use has been associated with an increased risk of death due to infection, mostly in patients given additional immunosuppressive treatment with antilymphocyte drugs for early postoperative complications.[11] The interleukin-2 receptor antibodies have not as yet been associated with an additional risk of malignancies.[7] Alemtuzumab is under investigation for induction therapy in heart transplantation.[7,9]

There does not seem to be any great clinical benefit of tacrolimus over ciclosporin in heart transplant patients,[9,12,13] although some have reported reduced rates of histological rejection,[14,15] and there is evidence that patients of Afro-Caribbean origin in particular may be more prone to acute rejection with ciclosporin than with tacrolimus.[16] It has been suggested that tacrolimus be substituted for ciclosporin in those patients suffering persistent rejection, or adverse effects associated with ciclosporin,[17] or with hyperlipidaemia or hypertension.[18] Microemulsifying ciclosporin may be associated with less rejection than the oil-based formulation.[19]

The use of mycophenolate mofetil instead of azathioprine in triple therapy has been shown to reduce mortality and rejection in the first year after heart transplantation,[20] and a retrospective review[21] concluded that the advent of mycophenolate mofetil has contributed to improved survival in cardiac transplant recipients. Although lower mycophenolic acid (MPA) concentrations may be associated with an increased allograft rejection,[22] there appears to be no benefit in monitoring MPA concentrations beyond the first year in heart transplant recipients,[23] and MPA levels may be affected by concomitant immunosuppression, see Immunosuppressants under Interactions of Mycophenolate, p.1837.

Many variations of regimens exist, and different drugs have been substituted or used adjunctively in order to decrease the doses, and thus alleviate the adverse effects associated with calcineurin inhibitors and/or corticosteroids. Substituting cyclophosphamide for azathioprine for 6 weeks after transplantation is reported to reduce the development of anti-muromonab-CD3 antibodies from induction therapy.[24] Substitution of mycophenolate mofetil with intravenous pulse cyclophosphamide for 4 months post-transplantation appeared to decrease the risk of rejection in a small, non-randomised study in sensitised allograft recipients.[25]

Alternative adjunctive therapies are the proliferation signal inhibitors, sirolimus and everolimus,[2,9] which allow for use of lower doses of calcineurin inhibitors, thus preserving renal function; however, long-term data are limited, and there is little experience with these drugs in paediatric patients. Use of sirolimus with ciclosporin and corticosteroids markedly reduced the incidence of acute rejection in a small open-label study.[26] However, the use of sirolimus with mycophenolate mofetil was associated with a higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors to this combination.[27]

It has been suggested that the high doses of corticosteroids used increase the risk of cardiac adverse events in the longer term, and protocols that wean patients from corticosteroids after 6 months postoperatively have been used,[28,29] without apparent increases in infection or rejection. Corticosteroid avoidance or early withdrawal regimens are feasible in many, if not most, paediatric heart transplant recipients.[9]

In the early post-transplant period, the most significant **causes of morbidity** are infection and rejection episodes.[8,9] Other complications post-transplant include right ventricular failure and cardiac arrhythmias.[30] Co-trimoxazole is used to protect against *Pneumocystis jirovecii* infection, and ganciclovir as prophylaxis against CMV.[3] Rejection is usually treated with corticosteroids, but other drugs have been used for corticosteroid-resistant cases,[8] including antilymphocyte immunoglobulins and muromonab-CD3.[4,29] In repetitive rejection, tacrolimus may be substituted for ciclosporin, and mycophenolate mofetil for azathioprine.[4,5] Adjunctive methotrexate, total lymphoid irradiation and photopheresis have all been tried.[8]

In the late post-transplant period, malignancy and coronary artery disease are the most significant problems.[3,7,8] About 5% of paediatric heart transplant recipients have been reported to develop post-transplant lymphoproliferative disease (PTLD).[2,31] The strongest risk factor for PTLD is the development of primary Epstein-Barr virus infection after transplantation although children who are seropositive for the virus are not necessarily protected from this complication.[2,9] Despite treatment with chemotherapy or a reduction in immunosuppression, PTLD is associated with significant morbidity and mortality; acute rejection may occur in those whose immunosuppression is reduced.[2] Rituximab and cellular immunotherapy are novel therapeutic approaches for PTLD.[9] Cardiac allograft vasculopathy (also termed coronary artery vasculopathy, or chronic rejection) is a major cause of death and prevention of its progression is a major therapeutic goal.[2,3,9,32,33] It is thought to be mainly an immunological response, but can be accelerated by the classical risk factors of dyslipidaemia, obesity, glucose intolerance, and smoking, as well as by postoperative CMV infection, and immunosuppression itself.[3,6,8,34] Long-term use of calcineurin inhibitors is associated with renal dysfunction and also contributes to hypertension and hyperlipidaemia, all of which may exacerbate cardiac allograft vasculopathy.[33] Calcium-channel blockers have been used to decrease the incidence of coronary artery disease, but it has remained a difficult complication to treat.[34] HMG-CoA reductase inhibitors such as pravastatin and simvastatin are recommended[35,36] for the treatment of hyperlipidaemia; pravastatin or atorvastatin have been used in paediatric heart transplant patients.[2] There is evidence that statin therapy substantially improves survival.[37] Fibric acid derivatives may be considered in those patients with hypertriglyceridaemia not controlled by diet alone.[36] Supplementation with antioxidant vitamins such as C or E may reduce the progression of arteriosclerosis after transplantation,[38] and a small study[39] found that omega-3 fatty acids improved blood pressure control in hypertensive transplant recipients. There is some suggestion that sirolimus[26,40] and everolimus[41] may be of benefit in preventing cardiac allograft vasculopathy in adults; data are lacking in paediatric patients.[2,9] Retransplantation for graft failure due to cardiac allograft vasculopathy may be necessary.[33]

Improved surgical techniques and the use of ciclosporin have also made possible successful combined *heart-lung* transplants, although these may require enhanced or modified immunosuppression to prevent obliterative bronchiolitis, a possible manifestation of chronic rejection.[42] Early rejection after transplantation is the most important risk factor for the development of bronchiolitis obliterans syndrome although pathogenesis is unclear.[43] Lung infection,[42] or oxidative stress and lack of glutathione[43] may be factors in the aggravation or onset of bronchiolitis obliterans syndrome.

Donor-specific tolerance, whereby the patient permanently accepts their graft without the need for long-term immunosuppression, while remaining immunocompetent, remains the ultimate goal in cardiac transplantation.[6,9]

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Intestinal transplantation. Transplantation of the *small bowel* is becoming more common, especially in children.[1] There are 3 types of intestinal allograft: the isolated intestine, combined liver and intestine, and the multivisceral graft, which can also include the pancreas, stomach, liver, and kidneys.[2-5] Combined liver and small intestine transplants are used for patients dependent on parenteral nutrition and with irreversible intestinal and hepatic failure, while intestine-only transplants tend to be used for intestinal failure in patients with severe progressive complications of parenteral nutrition, such as recurring sepsis and impending loss of central venous access.[1,5-8] Multivisceral transplants are most common in patients with diffuse gastrointestinal motility disorders.[3,4] Transplantation of the *colon* is avoided because of poorer outcomes and increased risk of sepsis.[9] Overall patient and graft survival varies according to the type of intestinal allograft, and between transplant centres, but is increasing, and reported to be about 50% at 5 years post-transplant.[1]

Tacrolimus and tapered corticosteroid doses[1,2,9-13] are the basis of the standard immunosuppressive regimen. In some centres, corticosteroid-free protocols are used, with induction therapy, and tacrolimus alone as maintenance.[5,13] Prostaglandins[8,9] such as alprostadil may also be given to augment mucosal immunosuppression, and improve splanchnic and renal blood flow. Induction therapy with antilymphocyte immunoglobulins or the interleukin-2 receptor antibodies basiliximab and daclizumab is used to prevent rejection.[1,9,11,13-15] Alemtuzumab has also been used.[12,13,15]

Adjunctive immunosuppressants have been added to the maintenance regimen. Azathioprine has been used.[5,11] Sirolimus has also been tried,[1,4,8,9,14] but combining tacrolimus with sirolimus does not have additional benefit over tacrolimus alone.[15] Sirolimus maintenance monotherapy, after induction, is increasingly favoured.[15] Any role for mycophenolate mofetil in intestinal transplantation is questionable,[12,14,16] owing to its gastrointestinal toxicity and poor absorption in intestinal transplant recipients, particularly during rejection.

Substantial morbidity occurs with intestinal transplants and acute rejection, manifested by diarrhoea, fever, and ileus, is common.[1,2,5,9] Initial treatment is with corticosteroids, and most centres increase the dose of tacrolimus as well. Antilymphocyte immunoglobulins or muromonab-CD3 may be used for severe or corticosteroid-unresponsive episodes.[1,2,7,9,13,15] Azathioprine, sirolimus, or mycophenolate mofetil have also been used adjunctively for treatment of rejection,[1,7] although concerns persist about the use of mycophenolate in intestinal transplantation (see above). Chronic rejection, a common cause of late graft dysfunction, is more difficult to treat.[1,9,16] Infliximab has been tried.[17]

Bacterial, viral, and fungal infections are also common post-transplant,[1,2,9,16] and may be confused with rejection.[4,16] Protocols for antimicrobial prophylaxis and treatment are similar to those used for other solid organ transplants. Selective gastrointestinal decontamination with non-absorbable oral antibacterials is usually performed during the first fortnight after transplantation, and during moderate to severe rejection episodes.[10,11] The high level of immunosuppression necessary in intestinal transplantation makes recipients particularly susceptible to post-transplant lymphoproliferative disease associated with Epstein-Barr virus infection.[1,2,4,6,16] Controlling rejection by more potent immunosuppression is difficult because of these complications, so the induction of immune tolerance through adjunctive bone marrow infusion is being investigated.[1,2,12,14] Graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p.1811) may occur and there may be a recurrence of the original disease.[2]

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Kidney transplantation. The transplantation of kidneys is now established as the ultimate therapy for end-stage renal disease. There is no single generally accepted immunosuppressant regimen, and different centres have achieved good results with a variety of strategies.[1] Therapy should be tailored to the individual patient. A number of factors affect the intensity of immunotherapy required, including the donor source (living or cadaveric) and degree of HLA histocompatibility, and the age, race and panel reactive antibody titre of the recipient.[1]

A widely used approach consists of **triple therapy** with a *calcineurin inhibitor* (ciclosporin or tacrolimus), an *anti-proliferative* (azathioprine or mycophenolate mofetil), and a *corticosteroid* (prednisolone).[2,3] Triple therapy is popular because it allows the use of lower doses of nephrotoxic calcineurin inhibitors, and the eventual tapering or even elimination of corticosteroids in some patients.[1]

Many variations of triple therapy regimens have been used.

- Azathioprine has largely been replaced by mycophenolate mofetil, which lowers the incidence of acute rejection and reduces the risk of chronic allograft failure.[4,5] This has been challenged, however, by a study[6] in which mycophenolate mofetil was found to be no better than azathioprine in prevention of acute rejection. The drugs were given with microemulsifying ciclosporin and corticosteroids, and ciclosporin dosage was targeted to plasma trough concentrations. The authors noted that previous studies attesting greater efficacy with mycophenolate mofetil had been carried out using the older standard ciclosporin formulation, and that the possibility of better activity with mycophenolate mofetil could not be excluded in patients in whom target ciclosporin concentrations are not achieved.
- Tacrolimus has been substituted for ciclosporin because it appeared to be more effective in preventing acute rejection than either the older oil-based formulation,[4] or the newer microemulsifying formulation.[7,8] Although it has been suggested that this does not lead to improved survival of either patients or grafts,[9] a systematic review[10] concluded that use of tacrolimus did improve graft survival, with a 44% reduction in graft loss within the first 6 months of transplantation; acute rejection was reduced by almost a third and severe rejection by half. The benefit in graft survival diminished with higher concentrations of tacrolimus. However, although tacrolimus may have a better cardiovascular risk profile than ciclosporin,[7,11,12] patients are two to three times more likely to develop diabetes and to have neurological adverse effects.[10] Choice of calcineurin inhibitor is therefore strongly influenced by adverse effect profiles.[9,13,14]
- There is some evidence of synergism between sirolimus and ciclosporin[15] and *addition* of sirolimus to ciclosporin-based regimens may reduce the incidence of acute rejection.[4,16] Combining sirolimus with tacrolimus instead of ciclosporin may be even more effective.[4] However, sirolimus may augment the nephrotoxicity of both ciclosporin[2] and tacrolimus,[5] and its use with full-dose calcineurin inhibitors has been associated with significantly reduced rates of allograft survival.[17] In an attempt to reduce the chronic allograft nephropathy (see below) associated particularly with calcineurin inhibitors, sirolimus has been given with azathioprine or mycophenolate mofetil, as an *alternative* to ciclosporin-based protocols. Comparable rejection rates and better renal function have been reported, although the use of sirolimus may increase the risk of cardiovascular-related morbidity and mortality, and safety has not been established.

Sequential quadruple therapy, in which antibody-based induction therapy is given postoperatively, in addition to triple therapy,[2,13] is also used. The antibodies are usually stopped once good graft function is achieved.[1] The regimen may improve long-term graft survival in patients with delayed graft function.[18]

Polyclonal lymphocyte-depleting antibodies are associated with a low incidence of rejection but evidence of their benefit in terms of graft survival is lacking; rabbit antilymphocyte immunoglobulin appears to be better than that of equine origin. Use of muromonab-CD3 has declined because of poor tolerability and an increased risk of lymphoproliferative disease.[19] The more specific interleukin-2 receptor antibodies basiliximab and daclizumab are widely used and appear to reduce the incidence of rejection episodes without increased toxicity.[4,5,18-21] Alemtuzumab has also been used, but data for this drug are comparatively limited.[19,22,23]

Some consider the interleukin-2 receptor antibodies to be the first-line choice for induction therapy because of their superior safety profile. While there appears to be no difference between rabbit antilymphocyte immunoglobulins and interleukin-2 receptor antibodies in terms of efficacy, acute rejection in high-risk patients appears to occur less often with rabbit antilymphocyte immunoglobulins, which may be the preferred choice in patients who are highly sensitised or receiving a second transplant.[19] Basiliximab or daclizumab, used as part of a ciclosporin-based regimen, are recommended in the UK as options for induction therapy in children and adolescents undergoing renal transplantation, irrespective of immunological risk.[14]

As immunosuppressant regimens have developed the role of corticosteroids has come to be questioned, mainly because of the adverse effects associated with their prolonged use.[4,9,24,25] Studies indicate that corticosteroid **withdrawal** is feasible in many patients initially given triple therapy,[1,26] although there is debate about the long-term consequences of this for graft survival.[4,25,27,28] Corticosteroid-sparing regimens may increase the risk of acute or chronic rejection, and the benefit associated with them may be limited by the high proportion of patients who need to resume corticosteroid therapy. Nevertheless, such regimens are considered to be feasible, even in the early period after transplantation. Even complete avoidance of corticosteroids may be possible with induction therapy using interleukin-2 receptor antibodies. However, it is crucial to individualise therapy, and caution is advised for high-risk patients, such as African Americans, sensitised, previously transplanted patients, or those with previous acute rejection episodes. Some consider the best approach to rapid corticosteroid withdrawal to be induction therapy (with antilymphocyte immunoglobulins in high-risk patients), calcineurin inhibitors, and mycophenolate mofetil.[25] Protocols that withdraw, minimise, or avoid calcineurin inhibitors have also been investigated.[28-33] Ciclosporin withdrawal is considered by some[30] to be more feasible for patients treated with mycophenolate mofetil than those given azathioprine. However, the most effective regimen in terms of patient and graft survival benefit, and minimisation of rejection and adverse effects, remains to be determined.[28] Data on long-term outcomes are lacking.[28,29,31]

Where an **acute rejection** episode occurs treatment is likely to be with high-dose corticosteroids, or with drugs such as antilymphocyte immunoglobulins, or muromonab-CD3, which are potent and effective reversers of rejection.[1,2,13] European guidelines recommend that the antibody preparations be reserved for corticosteroid-resistant rejection or more severe episodes,[18] but approaches remain varied.[1] Tacrolimus,[4] mycophenolate mofetil,[4] sirolimus,[34] and gusperimus[3,22] have been effective in reversing acute rejection episodes. Ciclosporin and azathioprine are ineffective in treating established rejection. Interleukin-2 receptor antibodies have not been shown to reverse established rejection episodes.[3] There has also been evidence that asymptomatic CMV infection may be associated with episodes of late acute rejection;[35] ganciclovir is reported to improve graft function in such circumstances. However, augmented or rescue immunosuppressive therapy predisposes the patient to infections such as CMV, which may itself mimic late acute rejection, and contribute to chronic rejection.[36]

Severe, recurrent, late episodes of acute rejection are considered to be a major risk factor for the development of **chronic rejection**. Manifested clinically by declining renal function, hypertension, and low-grade proteinuria, the term chronic allograft nephropathy is used.[4] Long-term calcineurin inhibitor treatment and inadequate immunosuppression may contribute to this, but there is some suggestion that the addition of mycophenolate mofetil can delay this process.[4] Protocols using sirolimus, and allowing for the early withdrawal of calcineurin inhibitors have been investigated; improved renal function has been reported, but use of sirolimus may increase the risk of coronary artery disease, and long-term results are lacking.[17,37,38]

Although newer drugs have decreased the incidence of acute rejection, there is only limited evidence that this has improved longer-term **graft survival**.[39-41] The one-year cadaveric graft survival is about 88% and about 60% at 10 years.[42] Recurrence of the original disease or *de novo* renal disease may also cause graft failure.[43] Pentoxifylline[44] and gusperimus[45] may improve graft survival.

Cardiovascular disease is a major cause of **death** in renal transplant patients.[46] Corticosteroids and ciclosporin can impair endothelial function, cause hypertension, and hyperlipidaemia. Sirolimus has also been implicated in hyperlipidaemia.[46] Dyslipidaemia occurs in about 60% of patients after renal transplantation;[12,46] HMG-CoA reductase inhibitors (statins) and dietary modification have been recommended as first-line treatment by some,[12] whereas others[47] recommend drug treatment with various lipid-lowering drugs only if lifestyle changes are insufficient. Modification of the immunosuppressive protocols, as discussed above, may also be effective.[12]

Hyperuricaemia is a common problem among renal transplant recipients;[48] the use of ciclosporin is an independent risk factor for new-onset gout after transplantation.[49] Use of sirolimus is also associated with an increased risk, whereas use of tacrolimus and mycophenolate mofetil carries a lower risk. Hyperuricaemia, besides having direct deleterious effects on the graft, may potentiate chronic renal dysfunction induced by calcineurin inhibitors, and contribute to chronic allograft nephropathy.[48] New-onset gout after transplantation may also be associated with hypertension, cardiovascular disease, and death.[49]

Morbidity and mortality have improved with reductions in cardiac, vascular and infectious complications, but there has been no decrease in death from **malignancy**, and the risk of developing cancer has been estimated to be about 100% by 30 years post-transplant.[50] Compared with the general population, renal transplant recipients have a three- to fivefold higher risk of malignancy; cancers tend to be more aggressive in transplant recipients, and solid organ tumours have a poorer prognosis. The most common malignancies include non-melanoma skin cancers and post-transplant lymphoproliferative disease (PTLD).[51,52] While not all malignancies are a consequence of transplantation or immunosuppressive therapy,[51] both the duration and intensity of immunosuppression have been linked to this increased incidence.[52] Other risk factors include increasing age, male gender,[53] sun exposure, and cigarette smoking.[51]

It is difficult to assess the impact of individual drugs on cancer risk;[51] some studies have found an increased incidence in patients given ciclosporin (compared with azathioprine) or muromonab-CD3.[53] Data are conflicting on the carcinogenic effects of mycophenolate.[51] Proliferation signal inhibitors such as sirolimus and everolimus have been reported to carry less of a risk, possibly as a result of their mode of action.[51-54] Although long-term data are needed, some have suggested that conversion from calcineurin inhibitors to proliferation signal inhibitors should be considered in high-risk patients.[52-54]

Nonmyeloablative conditioning regimens allowing for the development of immunological **tolerance** specific to the donor remain the ultimate goal of renal transplantation.[4,55] There are reports of the development of chimerism and tolerance allowing withdrawal of all immunosuppression in a few patients in whom kidney transplants were combined with haematopoietic stem cell transplantation.[56,57]

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Liver transplantation. Marked improvements have occurred in the outcome and reliability of liver transplantation and it is now seen as standard therapy for acute and chronic hepatic failure, regardless of aetiology,[1-3] and some metabolic disorders.[4] The 1-year patient and graft survival rates[2,4,5] are about 90%.

The liver induces some tolerance and liver transplant recipients usually require less immunosuppression than other solid organ transplant patients.[6] **Immunosuppressive regimens** generally combine a calcineurin inhibitor (ciclosporin or tacrolimus) with a corticosteroid and azathioprine or mycophenolate mofetil; such triple therapy prevents acute rejection episodes in the majority of cases.[7-9] Double therapy with ciclosporin or tacrolimus and corticosteroids is also used,[8,10] and monotherapy with a calcineurin inhibitor alone has also been used, allowing for complete corticosteroid withdrawal or avoidance.[10]

A review of corticosteroid-free strategies in liver transplantation concluded that up to 50% of patients can avoid corticosteroids with little modification of their maintenance immunosuppressive regimen; adding mycophenolate mofetil and/or induction therapy with antibodies can increase this percentage, although over-immunosuppression may be a problem. Although data are weak and limited, corticosteroid avoidance is not advised with calcineurin inhibitor monotherapy, nor with calcineurin inhibitors and azathioprine; it may be feasible with tacrolimus and mycophenolate mofetil, or with calcineurin inhibitors and antibodies. Benefits of corticosteroid avoidance are seen in growth rates in children, diabetes mellitus, dyslipidaemia, CMV infection, and possibly other infections.[11] Patients with underlying auto-immune hepatitis or inflammatory bowel disease may be relatively refractory to corticosteroid withdrawal.[12]

Tacrolimus is better than ciclosporin at preventing acute rejection in liver transplantation. It is also marginally better at preventing patient death and graft loss, but it increases the risk of post-transplant diabetes.[13] Studies of different formulations of ciclosporin found a reduced incidence of rejection with the microemulsifying formulation compared with the older oil-based product.[5]

The use of azathioprine in liver transplant patients has been limited due to its possible hepatotoxicity.[10] Mycophenolate mofetil has been used in place of azathioprine, to reduce the dose of the calcineurin inhibitor or corticosteroid used, and possibly prevent rejection.[2,8] Calcineurin inhibitors have been replaced with mycophenolate mofetil in an attempt to improve renal function,[10] although a small study has suggested that this monotherapy carries a high risk of rejection.[14] The long-term efficacy of calcineurin inhibitor minimisation or avoidance has yet to be determined.[15] The role of sirolimus in liver transplantation has yet to be evaluated.[3] There have been reports of efficacy when used with a calcineurin inhibitor,[1,9] which might allow dose reduction[9] or withdrawal of therapy[5] in patients with toxicity from tacrolimus or ciclosporin, but excess mortality, graft loss, and hepatic artery thrombosis has been associated with such use.

Induction therapy with antilymphocyte immunoglobulins or muromonab-CD3 has declined due to the high incidence of infection and lymphoproliferative disease associated with their use, and they are generally reserved for the treatment of corticosteroid-resistant acute rejection.[2,4,8,9] The use of interleukin-2 receptor antibodies, basiliximab, and daclizumab, is increasing;[10] initial studies suggest they decrease the number of rejection episodes.[8,9] It has been suggested that they may be of benefit in those with pre-transplant renal impairment by allowing for delayed introduction or lower doses of calcineurin inhibitors.[16] The use of alemtuzumab has also been investigated.[10,15]

The induction of complete immune **tolerance** remains the ultimate goal in liver transplantation.[10,17,18] It may be feasible to reduce or stop all immunosuppression in long-term stable liver transplant patients.[6,19] The term 'operational tolerance' is used to define stable graft function without features of rejection and without immunosuppressive treatment; 'prope tolerance' refers to stable graft function in patients with minimal immunosuppression.[10,19] Although it is not uncommon for rejection to eventually occur in those withdrawn from immunosuppression, this may be reversed by resumption of therapy, with a small rate of graft loss. Favourable markers for successful withdrawal appear to be at least 2 years of post-transplant follow-up, low incidence of previous rejection episodes, non-auto-immune primary liver disease, and possibly minimal post-transplant immunosuppression.[19]

Most **acute rejection** episodes occur during the first 3 to 6 months of therapy.[12] Early acute rejection does not affect patient or graft survival[6,20,21] and, if mild, may be associated with increased survival.[1] Late acute rejection, occurring after 30 days post-transplant may be related to reduction or withdrawal of immunosuppressive therapy.[22] It has a worse prognosis, with reports of up to half of patients developing graft loss.[21] Corticosteroids are used in the first-line treatment of acute rejection.[11,23] For corticosteroid-resistant rejection, muromonab-CD3 or antilymphocyte immunoglobulins are used, and increasing the dose of tacrolimus, or conversion from ciclosporin to tacrolimus, may also be effective.[2,4,9] Interleukin-2 receptor antibodies may also be used. Mycophenolate mofetil or sirolimus have been added to treat recurrent acute rejection.[23] **Chronic rejection** is almost always preceded by one or more episodes of corticosteroid-resistant acute rejection,[21,22] and although its incidence has decreased[5,21-23] to less than 5%, it remains difficult to treat. Corticosteroids are generally ineffective; conversion from ciclosporin to tacrolimus has been reported to be effective,[21] as has addition of mycophenolate mofetil to tacrolimus, followed by interleukin-2 receptor antibodies, and then sirolimus in non-responsive patients.[23]

The main **complications** encountered with liver transplants are infection in the early post-transplant period, vascular and biliary complications, recurrent disease (particularly viral recurrence), and adverse effects due to immunosuppressants.[4,6,22,23]

Sepsis is an important cause of death in the early post-transplant period.[6,24,25] Patients at increased risk, including those with malnutrition, fulminant liver failure, or renal insufficiency, require particularly cautious immunosuppression and more aggressive antibacterial and antifungal prophylaxis regimens.

Recurrence of hepatitis B infection is common.[26] Although the introduction of hepatitis B immunoglobulins and lamivudine have improved the prospects for these patients, combination antiviral therapy and a modified immunosuppression protocol are usually needed.[3,6,7,20,21] Hepatitis C recurrence is almost universal in infected patients,[11,21,27] with a probable reduction in long-term graft survival.[7,20,21] The use of corticosteroids and muromonab-CD3 appears to be associated with more severe recurrence of hepatitis C. Treatment with interferon alfa plus ribavirin appears promising.[26-28]

Nephrotoxicity from ciclosporin or tacrolimus can be a significant problem after long-term therapy.[29] Long-term renal function is affected by the function in the early post-transplant period, so serum creatinine concentrations at 1 and 3 months are often used to predict toxicity.[7] Cardiovascular complications may follow metabolic abnormalities such as diabetes mellitus, hypertension, hyperlipidaemia, and obesity. Dose reduction or change of the calcineurin inhibitor used, corticosteroid withdrawal, or use of statins could minimise the cardiovascular risk post-transplantation.[30-32] Malignancy may occur after prolonged immunosuppression.[4,20,23]

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Lung transplantation. Lung transplantation has become accepted therapy[1-4] for end-stage pulmonary disease such as pulmonary hypertension, cystic fibrosis, emphysema, and pulmonary fibrosis, with a 1-year survival of 70% or more.[2] The rate of death is highest in the first year after transplantation, with infection and primary graft failure the leading causes of early death.[1,5]

Immunosuppressant therapy is usually with a triple therapy regimen of ciclosporin or tacrolimus, azathioprine or mycophenolate mofetil, and a corticosteroid.[1-9] Some centres also use induction therapy with polyclonal or monoclonal antibodies, although its use is controversial. While induction therapy may reduce the incidence and severity of acute rejection, and allow for a delay in calcineurin inhibitor therapy, there is an increased risk of infection and of post-transplant lymphoproliferative disease.[2,3,5,10] Antilymphocyte immunoglobulins and muromonab-CD3 have been used; the interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly used,[1,2,10] although experience with these drugs in lung transplantation is limited.[11] Alemtuzumab is under investigation for induction;[1,2,10,11] preliminary results are promising. Corticosteroids remain a mainstay in lung transplantation,[5,10-12] although corticosteroid-free regimens have been investigated, with promising results, and further study is warranted.[11,12] Sirolimus has been investigated in lung transplantation, but its early use as a primary immunosuppressant is not recommended due to its potent antifibrotic effects;[1,2] sirolimus may also induce pulmonary toxicity.[10] Cases of fatal anastomotic dehiscence have been reported, and concerns about wound healing complications have led to recommendations to only use sirolimus after initial airway bronchial wound healing is completed, or not until at least 3 months after transplant.[10] Everolimus is also under investigation for adjunctive use in lung transplantation.[10,11]

Acute rejection occurs more frequently with lung transplants than with other solid organ transplants;[1,13] from early reports in 60 to 100% of cases, incidence has apparently decreased to about 35% in those receiving induction therapy and about 45% in those without induction therapy,[10] although some centres have reported figures as high as 85%.[13] High doses of intravenous corticosteroids are generally used to control acute episodes of rejection.[3,7,10,13] Corticosteroid-refractory rejection demands further intervention, although no consensus exists. Evidence supports the conversion of ciclosporin to tacrolimus for patients with persistent acute rejection.[10] Other therapies include the use of monoclonal or polyclonal antibodies, plasmapheresis, and total lymphoid irradiation.[10,13] Inhaled ciclosporin has also been used to treat refractory acute rejection.[1,10]

Lung transplant recipients are at high risk of **infection** as a result of impaired pulmonary defence mechanisms, and post-transplant antibacterial prophylaxis is routine.[2]

Patients at risk for CMV should be given ganciclovir.[2,7,12] There is no consensus on standard antifungal prophylaxis after lung transplant, but some centres use oral azole therapy or inhaled amphotericin.[2] Respiratory viruses pose a substantial risk to the lung allograft,[2,4,12] and may contribute to chronic rejection. The main complication encountered in the long term and major cause of late mortality is **chronic rejection** manifesting as bronchiolitis obliterans syndrome (obliterative bronchiolitis).[1,2,7,13] This is characterised by progressive airway obstruction and may be present in up to 40% of patients at 2 years, and in 60 to 70% who survive for 5 years.[7] Young children and living donor lung transplant recipients may have a lower risk for the development of this syndrome.[5] The frequency and severity of acute rejection episodes are the main risk factors for the development of bronchiolitis obliterans, but CMV infection, airway ischaemia and HLA mismatching may also play a part.[1,4,6,7,12-15] There are no proven effective therapies,[4] and the prognosis is poor, with 40% mortality within 3 years of diagnosis.[7] Augmentation of immunosuppression is often tried, but may exacerbate the risk of infection.[4] Some centres change the maintenance regimen, converting ciclosporin to tacrolimus, and azathioprine to mycophenolate mofetil, along with a short course of high-dose corticosteroids.[10,13] Inhaled ciclosporin has also been used, with reports of a trend towards survival benefit.[10] Improvement in pulmonary function has been seen with maintenance azithromycin.[10,13,15] Statins may decrease the risk of developing bronchiolitis obliterans syndrome, and promising results have been reported with the use of total lymphoid irradiation.[13] Re-transplantation may be necessary.[4,13]

Post-transplant lymphoproliferative disorders (PTLD) occur in lung transplant recipients, often in association with a primary Epstein-Barr virus infection.[3,4,12] The incidence is high in paediatric patients, ranging from 13 to 20%. Initial treatment involves a reduction in immunosuppression, or chemotherapy with rituximab.[3,12]

The induction of immune tolerance remains the ultimate goal in lung transplantation.[1,11]

Combined *heart-lung* transplants have also been performed, see under Heart Transplantation, above.

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Pancreatic transplantation. Transplantation of the pancreas may be considered in some diabetic patients. In the vast majority of cases, pancreatic grafts have been transplanted together with a kidney (simultaneous pancreas-as-kidney or SPK) in patients with end-stage diabetic nephropathy, which has produced better graft survival than transplanting the pancreas alone.[1-3] However, pancreas transplants after renal allografting (PAK), or solitary pancreatic transplantation (PTA), are becoming more common,[3] and approaching comparable survival rates.[2,4] Advances in surgical and preservation techniques, together with new immunosuppressants, have helped to improve survival.[1] Overall patient survival has been estimated to be about 98% at 1 year, with graft survival of about 78%.[5]

The pancreas is a highly immunogenic organ, so extensive **immunosuppression** is required. Standard treatment often consists of quadruple therapy.[2,6,7] Induction therapy is followed by maintenance therapy with a calcineurin inhibitor (ciclosporin or tacrolimus), corticosteroids, and azathioprine or mycophenolate mofetil.[2,7] Induction therapy reduces rejection rates, and may allow for corticosteroid withdrawal, but patient or graft survival is not altered.[6,7] The use of induction therapy varies between centres,[8] and may be dependent on the type of pancreatic transplant.[9] The interleukin-2 receptor antibodies basiliximab and daclizumab are increasingly favoured. Rabbit antilymphocyte immunoglobulins are also used, but the use of muromonab-CD3 has declined.[7] Alemtuzumab is under investigation.[5]

Tacrolimus is usually preferred to ciclosporin[2-4,6,7,9] as it appears to allow for rapid tapering or even complete withdrawal of corticosteroids, causes less rejection, and may increase graft survival and reduce the risk of pancreatic thrombosis. Mycophenolate mofetil is now preferred to azathioprine,[2,6-9] as it decreases rejection rates, although patient and graft survival rates are comparable.[6,7,9] Early withdrawal of corticosteroids appears to be safe and feasible in pancreatic transplantation,[6,7] without an increase in rejection rates; patients may, however, require slightly higher doses of calcineurin inhibitors, which increases the risk of nephrotoxicity.[7] Although the precise role of sirolimus in pancreatic transplantation has yet to be defined, it may be used with a low-dose calcineurin inhibitor, thus mitigating renal dysfunction,[2] or as a substitute for an antimetabolite,[7,9] or as the chief drug in a calcineurin inhibitor-free maintenance protocol, or for episodes of rejection.[7] Sirolimus used with tacrolimus may allow for rapid withdrawal of corticosteroids.[9]

Episodes of rejection are treated with corticosteroids or antilymphocyte immunoglobulins.[2,7] Conversion to tacrolimus from ciclosporin is used, and for those patients on tacrolimus, sirolimus has been tried.[2]

Pancreatic transplantation facilitates normal carbohydrate metabolism and has the potential to improve patient survival and reduce the incidence of diabetic nephropathy. However, there has been concern over the long-term **complications** of immunosuppression,[10] and whether islet-cell autoantibodies might produce diabetes in the transplanted graft (although this is certainly not inevitable with adequate immunosuppression).[11] The incidence of hyperglycaemia induced by immunosuppressive regimens after transplantation appears to be less in pancreatic transplants than in recipients of other organs.[5] Explanations for the absence of a higher diabetogenic effect of tacrolimus after pancreatic transplantation compared with other solid organ transplants may include a more cautious dose of tacrolimus in diabetic patients, the use of tacrolimus with corticosteroid-free protocols, and the use of pancreatic grafts from young donors who may be more resistant to a diabetogenic effect.[9]

One possible alternative to complete pancreatic transplantation is an **islet-cell** graft. These have rarely been successful,[1] with insulin independence at 1 year[3] only in about 10% of cases. However, the use of carefully prepared islet cells from more than one donor and a modified immunosuppressant protocol[12] has produced greatly improved results. In this 'Edmonton Protocol', corticosteroids were completely avoided because of diabetogenic effects. Induction therapy with daclizumab was used, followed by maintenance with sirolimus and low-dose tacrolimus.[12] Short-term follow-up data indicated that patients with unstable type I diabetes benefited in terms of glucose control from islet transplantation.[13] Reported insulin independence was 80% at 1 year after use of the 'Edmonton protocol'[14] and 10% at 5 years post-transplant.[15] Thus, engrafting an adequate beta-cell mass appears to be the critical factor for transplant success.[8] Insulin independence has been reported with single organs from cadaveric donors.[16] Further study of the 'Edmonton protocol' confirmed that islet-cell transplantation may successfully restore endogenous insulin production and glycaemic stability in patients with type I diabetes mellitus. Insulin independence is gradually lost again in most cases, but persistent islet function without insulin independence confers benefit in terms of glycaemic control, provided the patient can tolerate the immunosuppressive regimen. Islet transplantation may be best for highly selected patients with severe hypoglycaemia or labile type I diabetes mellitus, provided all other attempts to stabilise glycaemic control have been tried. For patients seeking long-term insulin independence, whole pancreas transplantation is a better option at present.[17] See also under Diabetes Mellitus, p.431.

The induction of tolerance,[3,5,10,18] the possibility of neogenesis of beta cells from pancreatic stem or precursor cells,[10,18,19] less toxic immunosuppressive therapy, and enhanced islet engraftment[17] remain focuses of investigation in islet transplantation.

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Renal disorders

Corticosteroids and immunosuppressants are commonly used in the treatment of glomerular kidney disease (p.1504).

Rheumatoid arthritis

Disease-modifying antirheumatic drugs (DMARDs) including immunosuppressants may be given to patients with rheumatoid arthritis (p.11) in an attempt to modify the course of the disease. Ciclosporin appears to be effective, but adverse effects have been a problem. The use of low-dose regimens may help to minimise nephrotoxicity. Use of ciclosporin with methotrexate has produced clinical improvement in patients who had only partial responses to methotrexate alone, but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy. Tacrolimus is licensed in some countries for use in refractory rheumatoid arthritis.

Azathioprine has been used, with beneficial short-term effects, but is reported to be no more effective than other DMARDs and significantly more toxic; it may however be useful with prednisone in rheumatoid vasculitis. Mycophenolate mofetil may be effective in rheumatoid arthritis, but further studies are needed.

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Sarcoidosis

Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. In patients in whom these are ineffective or poorly tolerated, immunosuppressants have been given, with variable results.

Scleroderma

The term scleroderma has been used for both systemic sclerosis, an uncommon multisystem disease characterised by collagen proliferation and fibrosis throughout the body, and for localised fibrotic changes of the skin (morphea) which rarely progresses to involve other organs. In systemic sclerosis, Raynaud's syndrome secondary to vascular involvement usually precedes skin changes; oedema is followed by thickening and tightening of the skin of hands and face, and sometimes limbs and trunk, before progressing to atrophy and contractures. Cutaneous changes may be limited or take a more aggressive diffuse form. Decreased gastrointestinal motility, dysphagia and gastro-oesophageal reflux, arthritis, muscle weakness, and cardiac involvement may occur. Among the most serious potential symptoms, which may result in death, are pulmonary disease and renal failure with malignant hypertension.[1-7]

Many treatments have been tried for localised scleroderma.[4,5] Symptomatic therapies include emollients and topical and systemic antipruritics. Topical, intralesional, and systemic corticosteroids may be useful, especially in early inflammatory stages. Other treatments include topical and systemic vitamin D analogues, topical tacrolimus, and imiquimod cream. Oral therapies used include ciclosporin, colchicine, hydroxychloroquine, interferon gamma, penicillamine, phenytoin, and methotrexate. Phototherapy with UV light, with or without psoralens, has also been reported to be of benefit.

There is a paucity of adequately controlled studies for systemic scleroderma; no treatment has been clearly shown to affect the progression of the disease, and much management is essentially symptomatic. Immunosuppressants are probably appropriate in the early oedematous stages of diffuse scleroderma.[1,6,8] Antilymphocyte immunoglobulins have been tried as an induction therapy in early stages of the disease.[8] Ciclosporin has been found to be beneficial, both for skin and visceral manifestations, but its use has been limited by nephrotoxicity and hypertension.[1,3,8-10] Tacrolimus has also been tried, though again adverse effects limit its benefit.[8-10] Mycophenolate mofetil has been tried after antilymphocyte immunoglobulins with reports of significant skin improvement.[10] Cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilise pulmonary function, and increase survival, especially in early disease, in a number of studies.[7] Other novel immunosuppressive strategies include bone marrow ablation followed by peripheral blood stem cell transplantation (see Haematopoietic Stem Cell Transplantation, p.1811),[1,3,5,8] photopheresis with a psoralen, and the induction of oral tolerance with native bovine type I collagen.[8] Rituximab is under investigation.[10]

Penicillamine has been widely used as an antifibrotic drug, but with variable effects; usual doses proved to be no more effective than lower doses,[1,8,11] and it is considered by some to be no more effective than placebo.[5] Interferons alfa and gamma have produced variable results;[5,8] the latter is under investigation for pulmonary fibrosis.[3] Some other drugs have been investigated for their antifibrotic properties, including halofuginone, minocycline and relaxin.[8,11] There is some evidence that oxidative stress is involved in the pathogenesis of scleroderma, so antoxidants like probucol may also be useful.[8] Other drugs that have been investigated include potassium aminobenzoate, and thymopentin.

Many patients will require therapy for organ-specific symptoms.

- *Skin* flexibility may be maintained by emollients,[12] and systemic antihistamines can relieve itching, an early feature of diffuse cutaneous scleroderma.[8] Methotrexate has been used with some benefit.[1,3,5,7,8,11]
- Most progress has been made in the management of *vascular* symptoms. ACE inhibitors are considered to be the standard treatment for patients with renal ischaemia,[3,5,6,13] although some 30% of patients will still eventually require renal replacement therapy.[8] For patients who develop pulmonary arterial hypertension the prostaglandins epoprostenol, iloprost, or treprostinil may be given intravenously;[1,3,5,6,8] some have also been investigated subcutaneously[6] or by inhalation.[3,5,6] Sildenafil or bosentan are also used.[3,5-7] There is some evidence that epoprostenol and bosentan may be associated with improved survival as well as symptomatic improvement.[3] Novel therapies for pulmonary arterial hypertension include ambrisentan[7] and sitaxentan.[6,7]

  Treatment of Raynaud's syndrome (see under Vasospastic Arterial Disorders, p.1188) unresponsive to nonpharmacological therapy involves the use of calcium-channel blockers such as nifedipine or diltiazem.[1,3,12] Topical nitrates have been used, and intravenous epoprostenol or iloprost are used in acute attacks.[1,3,6,8] Oral iloprost has been tried with variable results.[6] Bosentan can prevent the development of new digital ulcers but may not speed the healing of existing ones.[3] Calcitonin gene-related peptide is being investigated as an alternative to iloprost.[1] Because elevated levels of serotonin have been found in patients with Raynaud's phenomenon, SSRIs and ketanserin have been used.[1] Atorvastatin[6] and sildenafil[13] have been reported to be helpful. Dietary supplementation with antoxidant vitamins, fish oils, and evening primrose oil has been of anecdotal benefit.[1,8,14] Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome.[6,14]

  Cardiac involvement may be underdiagnosed;[8] ACE inhibitors or digoxin may be used.[1]
- *Lung* fibrosis is usually treated with cyclophosphamide,[1,3,5,8,15] with or without a corticosteroid such as prednisolone. There is no evidence for corticosteroids alone in lung scleroderma, and high dose may precipitate scleroderma renal crisis, leading to irreversible renal failure.[7] As mentioned above, interferon gamma is under investigation.
- In patients with *gastrointestinal* disease, proton pump inhibitors such as omeprazole, sometimes with prokinetic drugs, are extremely effective for oesophageal involvement, and broad spectrum antibacterials are helpful for small bowel bacterial overgrowth.[1,8]

NSAIDs and corticosteroids must be used with care in scleroderma because of the risk of exacerbating renal and other problems.[1,8]

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2. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004; **140:** 37–50.
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4. Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18:** 606–13.
5. Chung L, *et al.* Systemic and localized scleroderma. *Clin Dermatol* 2006; **24:** 374–92.
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9. Morton SJ, Powell RJ. Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma. *Rheumatology (Oxford)* 2000; **39:** 865–9.
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11. Matucci-Cerinic M, *et al.* Clinical trials in systemic sclerosis: lessons learned and outcomes. *Arthritis Res Ther* 2007; **9** (suppl 2): S7. Also available at: http://arthritis-research.com/content/pdf/ar2191.pdf (accessed 15/04/08)
12. Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004; **18:** 429–62.
13. Moore SC, Hermes DeSantis ER. Treatment of complications associated with systemic sclerosis. *Am J Health-Syst Pharm* 2008; **65:** 315–21.
14. Gaby AR. Natural remedies for scleroderma. *Altern Med Rev* 2006; **11:** 188–95.
15. Tashkin DP, *et al.* Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354:** 2655–66.

Skin and connective tissue disorders

Immunosuppressants are used in various skin and connective tissue disorders, including Behçet's syndrome (p.1499), eczema (p.1579), pemphigus and pemphigoid (p.1582), polymyositis (p.1510), psoriasis (p.1583), SLE (p.1513), and the various vasculitic syndromes (p.1515). See also Scleroderma, above.

Abetimus Sodium *(USAN, rINNM)*

Abetimus sódico; Abétimus Sodique; LJP-394; Natrii Abetimusum.

Натрий Абетимус

CAS — 169147-32-4.

ATC — L04AA22.

ATC Vet — QL04AA22.

Profile

Abetimus sodium is an immunomodulator that arrests the production of antibodies to double-stranded DNA. It is under investigation for the treatment of lupus nephritis in patients with SLE.

◊ References.

1. Alarcón-Segovia D, *et al.* LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2003; **48:** 442–54.
2. Wallace DJ, Tumlin JA. LJP 394 (abetimus sodium, Riquent) in the management of systemic lupus erythematosus. *Lupus* 2004; **13:** 323–7.
3. Cardiel MH. Abetimus sodium: a new therapy for delaying the time to, and reducing the incidence of, renal flare and/or major systemic lupus erythematosus flares in patients with systemic lupus erythematosus who have a history of renal disease. *Expert Opin Invest Drugs* 2005; **14:** 77–88.
4. Furie R. Abetimus sodium (Riquent) for the prevention of nephritic flares in patients with systemic lupus erythematosus. *Rheum Dis Clin North Am* 2006; **32:** 149–56.
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Antilymphocyte Immunoglobulins

Inmunoglobulinas antilinfocitarias.

Иммуноглобулины Антилимфоцитарные

ATC — L04AA03 (antilymphocyte immunoglobulin, horse); L04AA04 (antilymphocyte immunoglobulin, rabbit).

ATC Vet — QL04AA03 (antilymphocyte immunoglobulin, horse); QL04AA04 (antithymocyte immunoglobulin, rabbit).

Description. Antilymphocyte immunoglobulins are polyclonal antibodies to human lymphocytes produced by the purification of sera from appropriately immunised animals. The term antilymphocyte immunoglobulin (ALG; lymphocyte immune globulin) implies a product raised against all lymphocyte subsets. The term antithymocyte immunoglobulin (antithymocyte gammaglobulin; antithymocyte globulin; ATG) implies specificity for T-cells (thymus lymphocytes or thymocytes). However, in practice the nomenclature does not seem to be used consistently, and both terms tend to be used for antibodies raised against T-cells. Nomenclature normally includes an indication of the animal source of the immunoglobulin e.g. antithymocyte immunoglobulin (horse), or antithymocyte immunoglobulin (rabbit).

In addition to the purified immunoglobulins the native sera (antilymphocyte serum and antithymocyte serum, sometimes referred to as lymphocytic antiserum and thymitic antiserum) have also been used as immunosuppressants.

Pharmacopoeias. *Eur.* (see p.vii) includes an anti-T lymphocyte immunoglobulin.

Ph. Eur. 6.2 (Anti-T Lymphocyte Immunoglobulin for Human Use, Animal; Immunoglobulinum Anti-T Lymphocytorum ex Animale ad Usum Humanum). A liquid or freeze-dried preparation containing immunoglobulins, obtained from serum or plasma of animals, mainly rabbits or horses, immunised with human lymphocytic antigens. It has the property of diminishing the number and function of immunocompetent cells, in particular T-lymphocytes. It contains principally immunoglobulin G, and may contain antibodies against other lymphocyte subpopulations and against other cells. It is intended for intravenous administration, after dilution with a suitable diluent where applicable. Protect from light.

Adverse Effects and Precautions

Common adverse reactions to antilymphocyte immunoglobulins include fever, chills, and skin reactions including rash, pruritus, and urticaria, which may be manifestations of hypersensitivity. Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. To minimise fever and chills, the first dose can be infused over at least 6 hours. Dyspnoea, hypotension, chest, back or flank pain may indicate anaphylaxis, which can occur in up to 1% of patients. Fever, pruritus, rashes, myalgia, and arthralgia may represent serum sickness, especially in patients with aplastic anaemia. Use with other immunosuppressants may reduce the incidence or severity of hypersensitivity but increase the risk of acquired systemic infections, such as CMV or herpes simplex. Enhanced immunosuppression may also increase the incidence of post-transplant lymphoproliferative disease or other malignancies.

Leucopenia and thrombocytopenia are also common. Although usually transient, dosage adjustment may be necessary if they become severe or prolonged, and if unremitting, they may warrant stopping therapy. Other adverse effects include dizziness, malaise, headache, abdominal pain, gastrointestinal disturbances, hypertension, peripheral oedema, asthenia, hyperkalaemia, and tachycardia. Nephrotoxicity has been reported.

Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should generally be avoided for the same reason. Thrombophlebitis may be avoided by infusion into a vein with a rapid blood flow. To identify those at risk of anaphylaxis, patients should be tested for skin sensitivity before infusion. If there is a locally positive skin reaction, alternative therapy should be considered although hypersensitivity reactions may still occur in patients whose skin test is negative. If there is a systemic reaction, further doses of antilymphocyte immunoglobulins should not be given. Facilities for management of anaphylaxis (see p.1205) should be available during treatment, and the patient should be observed continuously.

Effects on the kidneys. Acute renal failure has been reported after the use of antilymphocyte immunoglobulins.[1,2] Prolonged anuria requiring haemodialysis has occurred.[2]

1. Levine JM, *et al.* Antithymocyte globulin-induced acute renal failure. *Am J Kidney Dis* 1999; **34:** 1155.
2. Barakat RK, *et al.* Prolonged renal failure secondary to antithymocyte globulin treatment in severe aplastic anemia. *Ann Pharmacother* 2007; **41:** 895–8.

Uses and Administration

Antilymphocyte immunoglobulins are antibodies, raised in *animals*, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity.

They may be added to existing immunosuppressant regimens to treat acute rejection episodes in patients who have undergone organ or tissue transplantation. Alternatively, they may be given prophylactically as part of a combination immunosuppressant regimen with several other agents. For discussion of the role of antilymphocyte immunoglobulins in transplantation, see p.1810 *et seq*.

Antilymphocyte immunoglobulins are also used in the treatment of aplastic anaemia (p.1042) in patients unsuitable for bone marrow transplantation, and have been tried in other immunological disorders. They are under investigation for the treatment of myelodysplastic syndromes (p.654).

Different antilymphocyte preparations may vary in their activity, as may different lots of the same preparation. However, daily doses in **transplantation** have usually ranged from 10 to 30 mg/kg of *equine* immunoglobulin, or 1 to 2.5 mg/kg of *rabbit* immunoglobulin. For **aplastic anaemia**, doses of *equine* immunoglobulin range from 10 to 20 mg/kg daily; regimens vary in different countries.

For children's doses, see Administration in Children, below.

Doses of antilymphocyte immunoglobulin are given as a slow intravenous infusion diluted in sodium chloride 0.9%, or other suitable diluent. It has been recommended that the final dilution should contain no more than 1 mg/mL of immunoglobulin and be given over 4 hours or more, via an in-line filter.

Administration in children. Although data in children are limited, licensed product information in the USA states that doses of *equine* immunoglobulin for transplantation in children have ranged from 5 to 25 mg/kg daily. The dose for *rabbit* immunoglobulin is not thought to differ from that for adults, namely 1.5 mg/kg daily, based on limited European studies and US compassionate use.

Organ and tissue transplantation. Antilymphocyte immunoglobulin derived from *rabbits* was found to be more effective than the *equine* product in treating acute rejection and preventing recurrent rejection in adult kidney transplantation (p.1813); patient and graft survival rates and the incidence of infection did not differ significantly.[1] Although unlicensed for induction therapy in the USA, some consider rabbit antilymphocyte immunoglobulin to be safe and effective for such use in adult renal transplantation.[2,3] Rabbit immunoglobulin induction is also considered safe and effective[4,5] in paediatric renal transplant recipients. The incidence of acute rejection was lower in rabbit immunoglobulin recipients than in those given the equine product;[6] however, rates of Epstein-Barr virus (EBV) infection were higher with the rabbit product. Patient and graft survival rates, incidence of chronic rejection, EBV lymphoma, or other infection did not differ significantly between the 2 groups.

In adult renal transplant recipients considered to be at high risk for acute rejection or delayed graft function, induction with rabbit antilymphocyte immunoglobulin reduced the incidence and severity of acute rejection (but not the incidence of delayed graft function) compared with basiliximab induction. Patients receiving antilymphocyte immunoglobulin had a greater incidence of infection but a lower incidence of CMV disease; patient and graft survival were similar in the 2 groups.[7]

Induction therapy with antilymphocyte immunoglobulins has also been shown to be beneficial in other solid organ transplants, with lower rates of rejection reported in liver (p.1815), pancreas (p.1816), kidney-pancreas, heart (p.1812), and heart-lung transplantation. Use in lung transplantation remains controversial due to a higher incidence of CMV infection.[8] Induction protocols differ between institutions.

In haematopoietic stem cell transplant recipients (p.1811), those given rabbit antilymphocyte immunoglobulin prior to a matched unrelated donor (MUD) transplant had comparable outcomes to those given matched related donor (MRD) transplants but no antilymphocyte immunoglobulin; the authors supposed that the use of antilymphocyte immunoglobulin caused MUD recipients to behave clinically like MRD recipients.[9] A review of the use of antilymphocyte immunoglobulins in haematopoietic stem cell transplantation concluded that it significantly reduces the severity and incidence of acute graft-versus-host disease (GVHD) and chronic GVHD. This protective effect is dependent on the dose, the timing of infusion, and the brand used. However, antilymphocyte immunoglobulin induction therapy delays immune reconstitution and there is an increased risk of infection; the use of an antilymphocyte immunoglobulin is a risk factor for EBV reactivation.[10]

1. Gaber AO, *et al.* Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation* 1998; **66:** 29–37.
2. Hardinger KL. Rabbit antithymocyte globulin induction therapy in adult renal transplantation. *Pharmacotherapy* 2006; **26:** 1771–83.
3. Wong W, *et al.* Comparison of two dosages of thymoglobulin used as a short-course for induction in kidney transplantation. *Transpl Int* 2006; **19:** 629–35.
4. Ault BH, *et al.* Short-term outcomes of Thymoglobulin induction in pediatric renal transplant recipients. *Pediatr Nephrol* 2002; **17:** 815–18.
5. Hastings MC, *et al.* Five years' experience with thymoglobulin induction in a pediatric renal transplant population. *Pediatr Transplant* 2006; **10:** 805–10.
6. Khositseth S, *et al.* Thymoglobulin versus ATGAM induction therapy in pediatric kidney transplant recipients: a single-center report. *Transplantation* 2005; **79:** 958–63.
7. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
8. Beiras-Fernandez A, *et al.* Induction of immunosuppression with polyclonal antithymocyte globulins: an overview. *Exp Clin Transplant* 2003; **1:** 79–84.
9. Duggan P, *et al.* Unrelated donor BMT recipients given pretransplant low-dose antithymocyte globulin have outcomes equivalent to matched sibling BMT: a matched pair analysis. *Bone Marrow Transplant* 2002; **30:** 681–6.
10. Bacigalupo A. Antithymocyte globulin for prevention of graft-versus-host disease. *Curr Opin Hematol* 2005; **12:** 457–62.

Preparations

Ph. Eur.: Anti-T Lymphocyte Immunoglobulin for Human Use, Animal.

Proprietary Preparations (details are given in Part 3)

Arg.: Apasmil†; Linfoglobulina; Timoglobulina; ***Austral.:*** Atgam; ***Austria:*** Thymoglobuline; ***Belg.:*** ATG; Thymoglobuline; ***Braz.:*** Lymphoglobuline†; Thymoglobuline†; ***Canad.:*** Atgam; Thymoglobulin; ***Chile:*** Linfoglobulina; Timoglobulina; ***Cz.:*** ATG; Lymphoglobuline†; Thymoglobuline; ***Denm.:*** Thymoglobuline; ***Fin.:*** Thymoglobuline; ***Fr.:*** Lymphoglobuline; Thymoglobuline; ***Ger.:*** Lymphoglobulin; Tecelac†; Thymoglobulin; ***Gr.:*** Lymphoglobuline; Thymoglobuline; ***Hong Kong:*** ATG; Atgam; Lymphoglobuline†; Thymoglobuline; ***India:*** Thymoglobulin; ***Israel:*** ATG; Lymphoglobuline; Thymoglobuline; ***Ital.:*** Lymphoglobuline; Thymoglobuline; ***Malaysia:*** Atgam; Lymphoglobuline†; Thymoglobuline; ***Mex.:*** Atgam; Tecelac; ***Neth.:*** ATG; Lymphoglobuline; Thymoglobuline; ***NZ:*** Atgam; ***Pol.:*** ATG; Lymphoglobuline; Tecelac; Thymoglobuline; ***Port.:*** Timoglobulina; ***Rus.:*** Atgam (Атгам); ***S.Afr.:*** Atgam; Lymphoglobuline; Thymoglobuline; ***Singapore:*** ATG†; Atgam; Lymphoglobuline†; Thymoglobuline; ***Spain:*** Atege; Atgam†; Linfoglobulina; Timoglobulina; ***Swed.:*** ATG; Thymoglobuline; ***Switz.:*** ATG; Atgam†; Lymphoglobuline; Thymoglobuline; ***Thai.:*** ATG; Lymphoglobuline†; Thymoglobuline†; ***Turk.:*** Lymphoglobuline; Thymoglobuline; ***UK:*** Thymoglobuline; ***USA:*** Atgam; ***Venez.:*** Atgam; Linfoglobulina†.

Azathioprine *(BAN, USAN, rINN)*

Atsatiopriini; Azathioprin; Azathioprinum; Azatioprin; Azatioprina; Azatioprinas; Azatiopryna; BW-57322; NSC-39084. 6-(1-Methyl-4-nitroimidazol-5-ylthio)purine.

Азатиоприн

$C_9H_7N_7O_2S$ = 277.3.

CAS — 446-86-6.

ATC — L04AX01.

ATC Vet — QL04AX01.

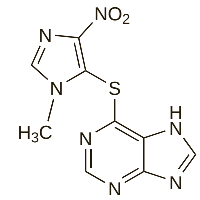

NOTE. The abbreviation AZT, which has sometimes been used for azathioprine, has also been used to denote the antiviral zidovudine.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Azathioprine). A pale yellow powder. Practically insoluble in water and in alcohol; soluble in dilute solutions of alkali hydroxides; sparingly soluble in dilute mineral acids. Protect from light.

USP 31 (Azathioprine). A pale yellow, odourless powder. Insoluble in water; very slightly soluble in alcohol and in chloroform; sparingly soluble in dilute mineral acids; soluble in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Adverse Effects

Dose-related bone-marrow depression is common with use of azathioprine; this may be manifested as leucopenia or, less often, thrombocytopenia or anaemia, and rarely, as agranulocytosis, pancytopenia, or aplastic anaemia. Myelosuppression is generally reversible, and may occasionally be delayed. Macrocytic, including megaloblastic, anaemia has occurred. Patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) may be at increased risk of myelotoxicity. Azathioprine has also been associated with the development of liver damage; it has been suggested that cholestatic symptoms may be due to the mercaptopurine moiety. Rarely, delayed and potentially fatal veno-occlusive liver disease has occurred.

Other adverse effects associated with azathioprine include gastrointestinal disturbances, reversible alopecia, and symptoms including rashes, muscle and joint pains, fever, rigors, pneumonitis, pancreatitis, tachycardia, renal dysfunction, and hypotension, some or all of which may represent hypersensitivity reactions. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely.

Solutions for injection are irritant.

◊ References.

1. Lawson DH, *et al.* Adverse effects of azathioprine. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 161–71.

Carcinogenicity. Immunosuppression, including that with azathioprine, may be associated with an increased risk of certain neoplasms such as lymphomas and skin cancers in transplant recipients,[1] in patients with inflammatory bowel disease,[2,3] and in patients with rheumatoid arthritis.[4-6] Partly because of lower doses of immunosuppressants used in inflammatory bowel disease, the risk of lymphoma in these patients appears to be less than that associated with transplant recipients;[7] this risk appears to be far outweighed by the benefits of immunosuppressant therapy in inflammatory bowel disease. Rheumatic diseases may themselves be associated with an increased risk of malignancy that is independent of treatment, but one study[5] concluded that there is a further risk related to the duration of exposure to immunosuppressive drugs, including azathioprine. A recent systematic review[8] of the use of azathioprine for multiple sclerosis concluded that, when the balance between the benefits and harms were considered, azathioprine was a reasonable alternative to interferon beta in patients who frequently relapse and require corticosteroids. Other evidence in the literature suggested that the long-term risk of malignancy may be related to use for longer than 10 years and a cumulative dose above 600 g and the reviewers recommended that this dose should not be exceeded.

Skin cancer may be a particular risk in immunosuppressed patients with a history of high sun exposure.[7] A synergistic clastogenic effect has been noted with azathioprine and long-wave ultraviolet light.

1. Kinlen LJ, *et al.* Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979; **2:** 1461–6.
2. Kandiel A, *et al.* Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54:** 1121–5.
3. Kwon JH, Farrell RJ. The risk of lymphoma in the treatment of inflammatory bowel disease with immunosuppressive agents. *Crit Rev Oncol Hematol* 2005; **56:** 169–78.

4. Silman AJ, *et al.* Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis* 1988; **47:** 988–92.
5. Asten P, *et al.* Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; **26:** 1705–14.
6. Patel P, *et al.* Azathioprine induced Hodgkin lymphoma: a case report and review of literature. *Am J Clin Oncol* 2005; **28:** 427–8.
7. Boyle J, *et al.* Cancer, warts, and sunshine in renal transplant patients: a case-control study. *Lancet* 1984; **i:** 702–5.
8. Casetta I, *et al.* Azathioprine for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).

Effects on the blood. Neutropenia in patients receiving mercaptopurine has been reported to correlate negatively with the concentration of the metabolite tioguanine nucleotide in erythrocytes,[1] and it has been suggested that measurement of metabolite concentrations in erythrocytes,[2] or activity of the enzyme thiopurine methyltransferase (TPMT),[3-6] permits prediction of those individuals likely to experience severe bone-marrow toxicity with mercaptopurine and the related drugs tioguanine and azathioprine. However, not all studies have found such correlations,[7] and effects on the bone marrow with this class of drugs are probably multifactorial;[8,9] low activity of other enzymes such as lymphocyte 5-nucleotidase,[10] and other factors, may contribute to toxicity. A review[9] of studies investigating TPMT activity in patients with Crohn's disease concluded that measurement of TPMT activity on starting azathioprine has a role in identifying those at risk of severe myelosuppression. Lower TPMT activities correlate with low neutrophil counts in the initial 4 months of thiopurine therapy; identification of the heterozygote might allow for safer management (see Therapeutic Drug Monitoring, below). However, in those patients established on therapy, TPMT did not predict clinical response or toxicity. Pure red cell aplasia occurs rarely with use of azathioprine; reported cases have all been in renal transplant recipients. In one such case,[11] reduction of the dose and use of erythropoietin was ineffective; however, the patient recovered within weeks of stopping azathioprine.

1. Lennard L, *et al.* Childhood leukaemia: a relationship between intracellular 6-mercaptopurine metabolites and neutropenia. *Br J Clin Pharmacol* 1983; **16:** 359–63.
2. Maddocks JL, *et al.* Azathioprine and severe bone marrow depression. *Lancet* 1986; **i:** 156.
3. Schütz E, *et al.* Azathioprine-induced myelosuppression in thiopurine methyltransferase deficient heart transplant recipient. *Lancet* 1993; **341:** 436.
4. Lennard L, *et al.* Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993; **69:** 577–9.
5. Jackson AP, *et al.* Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997; **136:** 133–4.
6. Black AJ, *et al.* Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. *Ann Intern Med* 1998; **129:** 716–18.
7. Boulieu R, *et al.* Intracellular thiopurine nucleotides and azathioprine myelotoxicity in organ transplant patients. *Br J Clin Pharmacol* 1997; **43:** 116–18.
8. Soria-Royer C, *et al.* Thiopurine-methyl-transferase activity to assess azathioprine myelotoxicity in renal transplant recipients. *Lancet* 1993; **341:** 1593–4.
9. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002; **51:** 143–6.
10. Kerstens PJSM, *et al.* 5-Nucleotidase and azathioprine-related bone-marrow toxicity. *Lancet* 1993; **342:** 1245–6.
11. Agrawal A, *et al.* Azathioprine-induced pure red cell aplasia: case report and review. *Transplant Proc* 2004; **36:** 2689–91.

Effects on the liver. A review[1] of drug-related hepatotoxicity noted that azathioprine has been associated with hepatocanalicular cholestasis, in which the interference with bile flow is combined with hepatocyte damage, and with several hepatic vascular disorders, including focal sinusoidal dilatation, peliosis, and veno-occlusive disease. A later review[2] grouped reported cases into three syndromes: hypersensitivity, idiosyncratic cholestatic reaction, and presumed endothelial cell injury, with the imidazole and 6-mercaptopurine components of azathioprine playing different roles in pathogenesis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Romagnuolo J, *et al.* Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 1998; **12:** 479–83.

Hypersensitivity. In 2 of 5 renal transplant recipients with acute allergic reactions associated with azathioprine, the symptoms (interstitial nephritis) were initially mistaken for acute rejection episodes.[1] In another report,[2] shock, fever, and acute renal insufficiency in a patient led to an initial mistaken diagnosis of sepsis, and it was recommended that a hypersensitivity reaction be considered as a cause if any of these symptoms occurred within 4 weeks of azathioprine ingestion. Other reported features of hypersensitivity include malaise, gastrointestinal disturbances, myalgia, arthralgia, fever, headache and raised liver enzymes.[3,4] Skin lesions have been reported, with maculopapular erythema occurring most frequently; purpura, urticaria, and erythema nodosum-like lesions have also been described.[4,5] Skin biopsies often showed features of leucocytoclastic vasculitis.[4] Stevens-Johnson syndrome has also been reported.[5] In some cases, skin patch testing for azathioprine was negative;[3,5] a drug-induced lymphocyte stimulation test (which evaluates the antigen specific reactivity of lymphocytes by measuring the proliferation of peripheral blood lymphocytes exposed to the suspected drug) has been proposed as a sensitive and reliable test for azathioprine hypersensitivity.[5]

1. Parnham AP, *et al.* Acute allergic reactions associated with azathioprine. *Lancet* 1996; **348:** 542–3.
2. Fields CL, *et al.* Hypersensitivity reaction to azathioprine. *South Med J* 1998; **91:** 471–4.
3. Hinrichs R, *et al.* Azathioprine hypersensitivity in a patient with peripheral demyelinating polyneuropathy. *Br J Dermatol* 2003; **148:** 1076–7.
4. Sinico RA, *et al.* Azathioprine hypersensitivity: report of two cases and review of the literature. *J Nephrol* 2003; **16:** 272–6.
5. Mori H, *et al.* Drug eruption caused by azathioprine: value of using the drug-induced lymphocytes stimulation test for diagnosis. *J Dermatol* 2004; **31:** 731–6.

Precautions

Regular monitoring of blood counts is required. Patients with renal or hepatic impairment require more frequent monitoring of blood counts and may need reduced doses; liver function tests should be performed in hepatic impairment. Consideration should be given to testing patients for thiopurine methyltransferase (TPMT) activity. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Azathioprine should generally be avoided in pregnancy (see below).

For a recommendation that the cumulative dose of azathioprine should not exceed 600 g in patients with multiple sclerosis, see under Carcinogenicity, above.

Breast feeding. Low concentrations of mercaptopurine have been found in human colostrum and breast milk of patients taking azathioprine.[1] Breast feeding by these patients has not been recommended because of the potential risk of immunosuppression in the infant.[1-3] However, there are reports[1,2] of 3 breast-fed infants, whose mothers had been taking doses of 75 or 100 mg of azathioprine daily, in whom no evidence of immunosuppression was found. All 3 had normal blood counts, no increase in infections, and above average growth rate. In one case, the levels of mercaptopurine were determined at 2 days and after 2 weeks of breast feeding,[1] and in the other 2 cases, no levels were determined.[2] In a third report, 31 breast-milk samples were collected from 10 breast-feeding women (taking from 75 to 150 mg azathioprine daily);[3] low concentrations of mercaptopurine were only detected in one case. The neonates were followed for up to 28 days, and showed no signs of immunosuppression, nor were mercaptopurine and tioguanine nucleotides detectable in their red blood cells. The authors concluded that breast feeding should not be withheld in infants of mothers receiving azathioprine. However, they cautioned that there were no data on the effect of thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, below) on metabolite concentrations in breast milk, and expressed concern as to whether a TPMT-deficient infant, unable to inactivate mercaptopurine absorbed into the breast milk, will be exposed to significant blood levels of the drug. In a study of 4 mothers and their infants,[4] all of whom had the wild-type TPMT genotype (with normal TPMT activity), infant exposure to azathioprine through breast milk was undetectable. The authors also cautioned that mothers taking higher doses or those with decreased TPMT activity might transfer more drug to the infant. It has been noted[5] that many breast-fed infants would have already been exposed to potentially much higher concentrations of mercaptopurine *in utero*.

1. Coulam CB, *et al.* Breast-feeding after renal transplantation. *Transplant Proc* 1982; **14:** 605–9.
2. Grekas DM, *et al.* Immunosuppressive therapy and breast-feeding after renal transplantation. *Nephron* 1984; **37:** 68.
3. Sau A, *et al.* Azathioprine and breastfeeding—is it safe? *Br J Obstet Gynaecol* 2007; **114:** 498–501.
4. Gardiner SJ, *et al.* Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; **62:** 453–6.
5. Moretti ME, *et al.* Breast-feeding during maternal use of azathioprine. *Ann Pharmacother* 2006; **40:** 2269–72.

Pregnancy. Azathioprine and/or its metabolites have been found in low concentrations in fetal blood after maternal use of azathioprine.[1] Azathioprine is teratogenic in *animals*, and congenital abnormalities, chromosomal aberrations,[2] fetal growth retardation,[3,4] low birth-weight, and spontaneous abortion have been reported in the offspring of pregnant women taking azathioprine. Neonatal leucopenia and thrombocytopenia have also been reported after maternal exposure.[5] Cohort studies have found an increased risk of congenital abnormalities, perinatal mortality, and preterm births after maternal or paternal exposure to azathioprine.[6,7] However, adverse birth outcomes may be related to the underlying disease rather than use of azathioprine or mercaptopurine,[8] and some consider its use in inactive inflammatory bowel disease to be safe;[9] however, there is suggestion that those with active disease, especially Crohn's disease, may have a higher incidence of spontaneous abortion, premature births, or still-births.[9] Given the nature of the severe chronic conditions for which azathioprine is generally used, stopping therapy in patients who become pregnant may not be necessary or desirable, but it seems prudent to avoid its use where possible during pregnancy.

1. de Boer NKH, *et al.* Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. *Am J Gastroenterol* 2006; **101:** 1390–2.
2. The Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; **87:** 839–45.
3. Pirson Y, *et al.* Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
4. Hou S. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med* 1985; **313:** 328.
5. Davison JM, *et al.* Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; **92:** 233–9.
6. Nørgård B, *et al.* Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol Ther* 2003; **17:** 827–34.
7. Nørgård B, *et al.* The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; **19:** 679–85.
8. Langagergaard V, *et al.* Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; **25:** 73–81.
9. Alstead EM, *et al.* Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* 1990; **99:** 443–6.

Interactions

The effects of azathioprine are enhanced by allopurinol and the dose of azathioprine should be reduced to one-third to one-quarter of the usual dose when allopurinol is given. A further dose reduction or alternative therapy should be considered in those patients with low or absent thiopurine methyltransferase (TPMT) activity.

◊ In addition to being affected by allopurinol, azathioprine may itself affect other drugs including the following:

- competitive neuromuscular blockers (antagonism, see under Immunosuppressants on p.1904)
- vaccines (reduced response or generalised infection, see p.2202)
- warfarin (inhibition, see Immunosuppressants p.1431).

Gastrointestinal drugs. For mention of *5-aminosalicylates* inhibiting the metabolism of thiopurines such as azathioprine, and increasing their toxicity, see Mercaptopurine, p.744.

Mercaptopurine. The Institute for Safe Medication Practices in the USA reported a case in which a patient with a history of Crohn's disease was prescribed azathioprine and mercaptopurine by separate practitioners. The patient developed profound myelosuppression, severe sepsis, and died. Many drug information software programs were found to not warn of this possible therapeutic duplication.[1]

1. Institute for Safe Medication Practices. Duplication with azathioprine and mercaptopurine (issued 29 June, 2006). Available at: http://www.ismp.org/Newsletters/acutecare/articles/20060629_3.asp?ptr=y (accessed 15/01/08)

Pharmacokinetics

Azathioprine is well absorbed from the gastrointestinal tract when given orally. After oral or intravenous doses it disappears rapidly from the circulation and is extensively metabolised to mercaptopurine (which is then further metabolised—see p.744). Both azathioprine and mercaptopurine are about 30% bound to plasma proteins. About 10% of a dose of azathioprine is reported to be split between the sulfur and the purine ring to give 1-methyl-4-nitro-5-thioimidazole. The proportion of different metabolites is reported to vary between patients. Metabolites and small amounts of unchanged azathioprine and mercaptopurine are eliminated in the urine. Azathioprine is distributed into breast milk in low concentrations.

Therapeutic drug monitoring. Although plasma concentrations of 6-thiouric acid (the inactive product of mercaptopurine, and hence of azathioprine) can be readily measured in patients who have been receiving azathioprine, they are of little value in therapeutic drug monitoring.[1] The active moieties are the tioguanine nucleotides (6-TGN) formed intracellularly, which appear to have extremely long half-lives,[2] and mean erythrocyte concentrations of which appear to vary considerably between individuals.[2] The formation of other inactive metabolites is catalysed by thiopurine methyltransferase (TPMT) and its activity is genetically determined, with a trimodal distribution in the general population; 0.3% have low activity of TPMT, 11% have intermediate activity, and 89% have normal or high activity. Patients with low or intermediate activity appear to shift metabolism toward production of 6-TGN.

Because excess concentrations of 6-TGN have been associated with leucopenia, it has been suggested[3] that:

- patients with normal or high TPMT activity receive standard doses of azathioprine or mercaptopurine
- those with intermediate TPMT activity have reduced doses
- those with low activity not be treated with either drug

However, these recommendations remain controversial.[4] Haematological toxicity is not always explained by TPMT status, and other factors may be involved[5] (see also Effects on the Blood, above). Some consider that TPMT deficiency is not a contra-indication to thiopurine therapy; an initial dose reduction to 10 to 15% of the standard azathioprine dose has been used in TPMT-deficient patients with inflammatory bowel disease.[5] There are a proportion of patients in whom TPMT activity is very high; these patients appear to respond less well to standard doses, and higher-than-standard doses have been recommended.[6] While recommendations for pre-treatment measurement of TPMT status remain controversial,[4,5] some consider the avoidance of potentially fatal toxicity a compelling argument for TPMT assessment before thiopurine therapy is started.[6] However, TPMT units and normal ranges vary between laboratories depending on the methodology used,[6] and TPMT genotype or phenotype testing is not a surrogate for monitoring of complete blood counts.[4]

Because low concentrations of erythrocyte 6-TGN have been associated with disease relapse in lymphomas and leukaemias, a small study[7] of patients with inflammatory bowel disease attempted to define a therapeutic window of drug efficacy. Without monitoring TPMT genotype, treatment efficacy was found to correlate with erythrocyte 6-TGN levels. It was concluded that patients who remain symptomatic despite apparently therapeutic 6-TGN concentrations should be treated with adjunctive or alternative immunosuppression or surgery. However, a large study[8] did not confirm disease correlation with 6-TGN concentrations, and concluded that therapeutic drug monitoring of 6-TGN may be premature. It was noted that methodological differences, such as assay technique, existed between their study and others. As the role of routine monitoring of 6-TGN remains controversial,[4,9,10] it has been suggested that selective monitoring, such as in those with low or intermediate TPMT activity, be considered.[3] Some consider the measurement of 6-TGN useful to assess treatment compliance, or in cases of malabsorption.[4]

1. Chan GLC, *et al.* Pharmacokinetics of 6-thiouric acid and 6-mercaptopurine in renal allograft recipients after oral administration of azathioprine. *Eur J Clin Pharmacol* 1989; **36:** 265–71.
2. Chan GLC, *et al.* Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. *J Clin Pharmacol* 1990; **30:** 358–63.
3. Sandborn WJ. Rational dosing of azathioprine and 6-mercaptopurine. *Gut* 2001; **48:** 591–2.
4. Lichtenstein GR. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. *Gastroenterology* 2004; **127:** 1558–64.
5. Teml A, *et al.* Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clin Pharmacokinet* 2007; **46:** 187–208.
6. Sanderson J, *et al.* Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? *Ann Clin Biochem* 2004; **41:** 294–302.
7. Cuffari C, *et al.* Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001; **48:** 642–6.
8. Lowry PW, *et al.* Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. *Gut* 2001; **49:** 665–70.
9. Dubinsky MC. Monitoring of AZA/6-MP treatment in children with IBD is necessary. *Inflamm Bowel Dis* 2003; **9:** 386–8.
10. Griffiths AM. Monitoring of azathioprine/6-mercaptopurine treatment in children with IBD is not necessary. *Inflamm Bowel Dis* 2003; **9:** 389–91.

Uses and Administration

Azathioprine is an immunosuppressive antimetabolite with similar actions to those of mercaptopurine (p.744), to which it is converted in the body. Its effects may not be seen for several weeks after a dose. It is given orally, but where this is not feasible it may be given by slow intravenous injection or by infusion as azathioprine sodium. If given by infusion, the required dose should be diluted to a concentration of 0.25 to 2.5 mg/mL in sodium chloride 0.9% or glucose 5%, and infused over 30 to 60 minutes.

Azathioprine is mainly used as an immunosuppressant for the prevention of rejection in **organ and tissue transplantation** (p.1810). The dose for this purpose, given orally or intravenously, varies from 1 to 5 mg/kg daily and depends partly on the regimen used; the higher doses are used initially, adjusted according to clinical response and haematological tolerance.

Azathioprine is also used in **auto-immune diseases** or conditions that are considered to have an auto-immune component, see below. The usual dose of azathioprine, given orally or intravenously, in these conditions is in the range of 1 to 3 mg/kg daily. If no improvement is seen after 12 weeks, therapy may be stopped.

For doses in children, see Administration in Children, below.

Use of azathioprine with a corticosteroid (p.1495) may have a corticosteroid-sparing effect.

Blood counts should be carried out regularly during treatment and azathioprine withdrawn or the dosage reduced at the first indication of bone-marrow depression. Measurement of thiopurine methyltransferase (TPMT) activity may be used to identify patients at risk of haematological toxicity, although this cannot substitute for blood count monitoring.

Administration in children. UK licensed product information for azathioprine allows for the same doses in children as those used in adults (see Uses and Administration, above), both in organ and tissue transplantation and for diseases with an auto-immune component. The *BNFC* recommends that children aged 1 month to 18 years be given a maintenance dose of 1 to 3 mg/kg once daily for suppression of **transplant rejection**; alternatively, the total daily dose may be given in 2 divided doses. Although unlicensed for **severe ulcerative colitis and Crohn's disease**, the *BNFC* states that azathioprine may be given to children aged 2 to 18 years in an oral dose of 2 mg/kg (if necessary up to 3 mg/kg) once daily, reduced according to response to the lowest effective dose; alternatively, the total daily dose may be given in 2 divided doses.

Administration in hepatic or renal impairment. UK licensed product information states that controlled studies have not supported the suggestion that toxicity of azathioprine might be enhanced in the presence of renal impairment. Nevertheless, doses used should be at the lower end of the normal range, and haematological response should be carefully monitored. US licensed product information also recommends low doses, while stating that relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine and/or its metabolites.

UK licensed product information states that the metabolism of azathioprine may be impaired in patients with hepatic dysfunction; regular blood counts and liver function tests should be performed and the dosage of azathioprine reduced if hepatic or haematological toxicity occurs.

Blood disorders. Immunosuppressants such as azathioprine are occasionally tried in auto-immune haemolytic anaemia (p.1043) refractory to other treatment and may permit reduction of corticosteroid dosage. Similarly in patients with idiopathic thrombocytopenic purpura (p.1505), immunosuppressants may be tried as a last resort. Azathioprine with a corticosteroid has been tried in the rare condition of acquired haemophilia (p.1048).

Cogan's syndrome. Azathioprine has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p.1502).

Connective tissue and muscular disorders. Azathioprine is one of many drugs tried for disease control in Behçet's syndrome[1] (p.1499) and SLE[2] (p.1513). In polymyositis (p.1510), combined therapy with azathioprine and a corticosteroid has been found to be better than a corticosteroid alone for maintenance long-term.[3] However, there is also some evidence that methotrexate may be more effective in refractory polymyositis than azathioprine.[4]

1. Yazici H, *et al.* A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; **322:** 281–5.
2. Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. *Lupus* 2001; **10:** 152–3.
3. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. *Arthritis Rheum* 1981; **24:** 45–8.
4. Joffe MM, *et al.* Drug therapy of the idiopathic inflammatory myopathies; predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med* 1993; **94:** 379–87.

Inflammatory bowel disease. Azathioprine, or its metabolite mercaptopurine, is used to induce remission in chronically active inflammatory bowel disease (p.1697), and to maintain remission, particularly in Crohn's disease.[1-3] They have a useful corticosteroid-sparing effect. Azathioprine may also be useful as a postoperative maintenance treatment in Crohn's disease.[4] In patients with ulcerative colitis, azathioprine may be an effective maintenance therapy for those who are refractory to or intolerant of mesalazine or sulfasalazine; it may also be useful for patients who require repeated courses of corticosteroids.[5]

Continuation of azathioprine therapy beyond 4 years has had conflicting results in terms of relapse rates and flare incidence. A randomised study in patients with Crohn's disease and in clinical remission, having been treated with azathioprine for at least 42 months, found that relapse rates were higher in those patients continued on placebo compared with those continued on azathioprine.[6] In another study of patients with corticosteroid-dependent Crohn's disease, a breakthrough of symptoms during continuous therapy was common, particularly after 48 months on azathioprine.[7] In an analysis of 1176 patients with inflammatory bowel disease, the authors concluded that stopping azathioprine therapy may be considered after 3 to 4 years in Crohn's disease patients in complete remission and without corticosteroid requirements but that continuation appears beneficial in all other Crohn's disease patients and for patients with ulcerative colitis.[8]

The onset of benefit from oral azathioprine may be delayed for several months. One study[9] reported that a more rapid response could be achieved with an intravenous loading dose but a later study failed to confirm this.[10]

1. Sandborn W, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 15/01/08).
2. Pearson DC, *et al.* Azathioprine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 15/01/08).
3. Fraser AG, *et al.* The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50:** 485–9.
4. Myrelid P, *et al.* Azathioprine as a postoperative prophylaxis reduces symptoms in aggressive Crohn's disease. *Scand J Gastroenterol* 2006; **41:** 1190–5.
5. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
6. Lémann M, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128:** 1812–18.
7. Chebli JM, *et al.* Long-term results with azathioprine therapy in patients with corticosteroid-dependent Crohn's disease: open-label prospective study. *J Gastroenterol Hepatol* 2007; **22:** 268–74.
8. Holtmann MH, *et al.* Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51:** 1516–24.
9. Sandborn WJ, *et al.* An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* 1995; **109:** 1808–17.
10. Sandborn WJ, *et al.* Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease: North American Azathioprine Study Group. *Gastroenterology* 1999; **117:** 527–35.

Leprosy. For mention of the use of azathioprine as a corticosteroid-sparing agent in the management of type 1 lepra reactions, see p.176.

Liver disorders. Azathioprine has been widely used with corticosteroids to produce and maintain remission of chronic active hepatitis (p.1501); such combination therapy, which also permits a reduction in corticosteroid dosage, is generally thought to be more effective than azathioprine alone. Patients successfully maintained in remission for at least a year on azathioprine with a corticosteroid can subsequently be maintained on azathioprine (at a dose of 2 mg/kg daily) alone.[1] Results in patients with primary biliary cirrhosis (p.2408) have been more equivocal, and initial studies did not indicate much benefit from azathioprine, although a later study did seem to indicate improved survival and disease retardation.[2]

1. Johnson PJ, *et al.* Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; **333:** 958–63.
2. Christensen E, *et al.* Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: final results of an international trial. *Gastroenterology* 1985; **89:** 1084–91.

Lung disorders. Although corticosteroids remain the mainstay of treatment for the various forms of diffuse parenchymal lung disease (p.1502) including cryptogenic fibrosing alveolitis (CFA), there is some evidence that combined therapy with azathioprine improves survival in the latter condition,[1] and the British Thoracic Society now recommends that initial treatment of CFA should be with oral prednisolone plus azathioprine 2 to 3 mg/kg daily.[2]

1. Raghu G, *et al.* Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; **144:** 291–6.
2. British Thoracic Society. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999; **54** (suppl 1): S1–S30. Also available at: http://www.brit-thoracic.org.uk/portals/0/Clinical%20Information/DPLD/Guidelines/Parenchymaltext.pdf (accessed 17/07/08)

Neuromuscular disorders. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for myasthenia gravis (p.629). It may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient. Azathioprine is not usually used alone because it may be several months before any beneficial effect is seen. Some studies have also indicated modest benefit from azathioprine in patients with multiple sclerosis (p.892). It has been suggested that the benefits are too slight to justify the toxicity of the required doses, but it has also been pointed out that in terms of relapse reduction azathioprine appears as effective as newer treatments such as interferon beta. For a recommendation that the cumulative dose of azathioprine should not exceed 600 g, see under Carcinogenicity, above.

Ocular disorders. For mention of the use of azathioprine in various disorders characterised by ocular lesions such as scleritis or uveitis, see p.1810.

Polymyalgia rheumatica. Azathioprine may be used for its corticosteroid-sparing properties in patients who require corticosteroid treatment for polymyalgia rheumatica (p.1510) and in whom withdrawal is difficult.

Psoriatic arthritis. Azathioprine may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p.13) when the arthritis is not controlled by physical therapy and NSAIDs.

Rheumatoid arthritis. Although azathioprine may be beneficial in rheumatoid arthritis (p.11) in the short-term, its toxicity is significantly more severe than other disease-modifying antirheumatic drugs (DMARDs).[1] It may, however, be useful in patients with severe disease unresponsive to other DMARDs especially in those with extra-articular manifestations such as vasculitis.[2]

1. Suarez-Almazor ME, *et al.* Azathioprine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).
2. Heurkens AHM, *et al.* Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151:** 2249–54.

Sarcoidosis. Cytotoxic immunosuppressants such as azathioprine have been tried in patients with sarcoidosis (p.1512) who do not respond to or cannot tolerate corticosteroids.

Skin disorders. Like other immunosuppressants, azathioprine has been tried in various refractory skin disorders, notably in pemphigus and pemphigoid[1,2] (see below). Other conditions in which it has been tried include atopic eczema,[3-8] nodular prurigo,[9] chronic actinic dermatitis,[3,6] pyoderma gangrenosum,[4] erythema multiforme,[4,10] pompholyx, and plaque psoriasis,[6] as well as in the skin manifestations of systemic disorders such as dermatomyositis and lupus erythematosus.[2] Guidelines for the use of azathioprine in dermatology have been developed.[1] The recommended dose for azathioprine in dermatological disorders is 1 to 3 mg/kg daily, adjusted according to response. Treatment should be withdrawn if no response is seen within 3 months. Azathioprine should not be used in dermatology patients with very low or absent thiopurine methyltransferase (TPMT) activity (see Therapeutic Drug Monitoring, above), due to the danger of prolonged and severe myelosuppression (see Effects on the Blood, above). If azathioprine is given to patients with low TPMT activity, doses of 0.5 to 1 mg/kg daily should be used, with monitoring for myelosuppression. Patients with normal to high TPMT activity should be started on doses at the higher end of the range of 1 to 3 mg/kg daily; in those who do not respond, and have not experienced adverse effects, doses above this range may be considered for a trial period.

1. Anstey AV, *et al.* British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151:** 1123–32. Also available at: http://www.bad.org.uk/healthcare/guidelines/Azathioprine.pdf (accessed 15/01/08)
2. Patel AA, *et al.* Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol* 2006; **55:** 369–89.
3. Younger IR, *et al.* Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25:** 281–6.
4. Tan BB, *et al.* Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1997; **136:** 351–5.
5. Lear JT, *et al.* A retrospective review of the use of azathioprine in severe atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 47): 38.
6. Scerri L. Azathioprine in dermatological practice: an overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999; **455:** 343–8.
7. Murphy L-A, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147:** 308–15.
8. Meggitt SJ, *et al.* Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367:** 839–46.
9. Lear JT, *et al.* Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134:** 1151.
10. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128:** 542–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Other immunosuppressants may be added to maintain disease control and allow a reduction in corticosteroid dosage, and azathioprine is commonly used in this way in pemphigus vulgaris.[1] There is limited evidence to suggest that azathioprine may also be effective as monotherapy to induce remission in mild pemphigus.[1] Azathioprine has been used similarly in bullous pemphigoid, but there is some disagreement about its efficacy,[2] and guidelines suggest that it should only be considered if the corticosteroid cannot be reduced to an acceptable dose.[3]

1. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37. Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 15/01/08)
2. Walsh SRA, *et al.* Bullous pemphigoid: from bench to bedside. *Drugs* 2005; **65:** 905–26.
3. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21. Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 15/01/08)

Vasculitic syndromes. Azathioprine has been tried in vasculitic syndromes, including giant cell arteritis (p.1503), microscopic polyangiitis (p.1510), Churg-Strauss syndrome (p.1501), Takayasu's arteritis (p.1514), and Wegener's granulomatosis (p.1515). In general it is most useful in maintenance for its corticosteroid-sparing effect. Cyclophosphamide tends to be preferred where a more aggressive regimen is required, as in some combinations for induction of remission.

Preparations

BP 2008: Azathioprine Tablets;
USP 31: Azathioprine Oral Suspension; Azathioprine Sodium for Injection; Azathioprine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Imuran; ***Austral.:*** Azahexal; Azamun; Azapin; Imuran; Thioprine; ***Austria:*** Azaallen; Azaglax; Azarek†; Glaxoprin; Imurek; ***Belg.:*** Imuran; ***Braz.:*** Aseroprin†; Imunen; Imuran; ***Canad.:*** Imuran; ***Chile:*** Azafalk†; Imuran; ***Cz.:*** Azaprine; Immunoprin; Imuran; ***Denm.:*** Imurel; ***Fin.:*** Azamun; Imuprin†; Imurel; ***Fr.:*** Imurel; ***Ger.:*** Aza-Q; Azafalk; Azathiodura; Colinsan; Imurek; Zytrim; ***Gr.:*** Imuran†; ***Hong Kong:*** Azamun†; Imuran; ***Hung.:*** Imuran; ***India:*** Azoran; Imuran; Transimune; ***Indon.:*** Imuran; ***Irl.:*** Imuger; Imuran; ***Israel:*** Azopi; Imuran; ***Malaysia:*** Imuran; ***Mex.:*** Azatrilem; Imuran; Satedon†; ***Neth.:*** Imuran; ***Norw.:*** Imurel; ***NZ:*** Azamun; Imuran; Thioprine; ***Philipp.:*** Imuran; ***Pol.:*** Imuran; ***Port.:*** Imuran; ***Rus.:*** Imuran (Имуран)†; ***S.Afr.:*** Azamun; Azapress; Imuran; Zaprine; ***Singapore:*** Imuran; ***Spain:*** Imurel; ***Swed.:*** Imurel; ***Switz.:*** Azarek; Imurek; ***Thai.:*** Imuran; ***Turk.:*** Imuran; ***UK:*** Immunoprin†; Imuran; ***USA:*** Azasan; Imuran; ***Venez.:*** Azaprin.

Multi-ingredient: *Ger.:* Azamedac.

Basiliximab *(BAN, USAN, rINN)*

Basiliksimab; Basiliksimabi; Basiliximabum; chRFT5; SDZ-CHI-621. Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer.

Базиликсимаб

CAS — 179045-86-4.
ATC — L04AC02.
ATC Vet — QL04AC02.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with basiliximab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, sneezing, hypotension, tachycardia, cardiac failure, wheezing, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. Capillary leak syndrome and cytokine release syndrome have been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Patients in whom other immunosuppression was prematurely stopped, after initial therapy with basiliximab, appear to be at increased risk of hypersensitivity reactions. Therapy should be permanently stopped if a severe reaction occurs.

Giving basiliximab as a bolus may cause nausea, vomiting, and local reactions, including pain.

Pharmacokinetics

Basiliximab has a terminal half-life of about 7 days in adults and about 9 days in children.

Uses and Administration

Basiliximab is a chimeric murine/human monoclonal antibody similar to daclizumab (p.1833) that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection episodes in patients undergoing renal transplantation, and is given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids; azathioprine or mycophenolate mofetil may also be added to the regimen. Doses are given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes. The recommended dose for adults is 20 mg, given within 2 hours before transplant surgery and repeated once after 4 days. (For children's doses, see Administration in Children, below). The second dose should be withheld if graft loss or a severe hypersensitivity reaction occurs.

Administration in children. Licensed product information recommends the following intravenous doses of basiliximab in children over 1 year of age, for prophylaxis of acute rejection in allogeneic renal transplantation, as part of an immunosuppressive regimen containing ciclosporin and corticosteroids:

- body-weight under 35 kg: 10 mg within 2 hours before transplantation surgery; 10 mg 4 days after surgery
- body-weight 35 kg or more: 20 mg within 2 hours before transplantation surgery; 20 mg 4 days after surgery (same as adults, see Uses and Administration, above)

Doses may be given either as an intravenous bolus, or diluted to a usual concentration of 400 micrograms/mL in sodium chloride 0.9% or glucose 5%, for infusion over 20 to 30 minutes.

Organ and tissue transplantation. Basiliximab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813), including paediatric renal transplant recipients;[1-6] it is usually given as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. A small study found that basiliximab significantly reduced the occurrence of rejection episodes in those treated with dual therapy (calcineurin inhibitor and corticosteroids) but not in those given triple therapy (including mycophenolate).[7] In a study of paediatric renal transplant recipients, addition of basiliximab to a tacrolimus-based regimen was safe, but did not result in a lower incidence of rejection episodes.[8] There is some suggestion that antilymphocyte immunoglobulins may be more effective than basiliximab in reduction of acute rejection in adult renal transplant patients,[9,10] although some consider basiliximab to offer improved clinical efficacy over antilymphocyte immunoglobulin induction in paediatric patients,[11] and others have commented[12] that graft survival at 12 months has been similar with each drug. Two reviews[13,14] concluded that the use of basiliximab in renal transplantation was safe and effective, with reduced rates of acute rejection, but no long-term benefit in terms of graft survival; basiliximab appears to allow the safe withdrawal of corticosteroids or the use of corticosteroid-free immunosuppressive regimens.

There is a short report suggesting that the use of a single dose is as effective as the standard 2-dose regimen in renal transplantation in terms of the incidence of acute rejection.[15]

Basiliximab has also been investigated in liver transplantation (p.1815). Given with dual therapy to adult patients, it was found to reduce the incidence of acute rejection episodes in the first year when compared with placebo, including patients positive for hepatitis C.[16] Basiliximab with dual therapy also reduced the incidence of acute graft rejection in small paediatric studies.[17,18] In paediatric liver transplantation, corticosteroid-free immunosuppressive regimens using basiliximab and tacrolimus have been associated with significantly lower rejection rates at 1 year than corticosteroid-based regimens.[19,20]

Basiliximab has been investigated for the prevention of rejection in heart,[21,22] lung,[23,24] and pancreatic transplantation (see p.1812). It has been reported to be effective[25] in the treatment of corticosteroid-refractory acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811).

1. Nashan B, *et al.* Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997; **350:** 1193–8. Correction. *ibid.*; 1484.
2. Kahan BD, *et al.* Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999; **67:** 276–84.
3. Thistlethwaite JR, *et al.* Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. *Transplantation* 2000; **70:** 784–90.
4. Ponticelli C, *et al.* A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; **72:** 1261–7.
5. Swiatecka-Urban A, *et al.* Basiliximab induction improves the outcome of renal transplants in children and adolescents. *Pediatr Nephrol* 2001; **16:** 693–6.
6. Pape L, *et al.* Single centre experience with basiliximab in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 276–80.
7. Lee BM, *et al.* Effect of basiliximab on renal allograft rejection within 1 year after transplantation. *Transplant Proc* 2006; **38:** 2025–8.
8. Grenda R, *et al.* A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006; **6:** 1666–72.
9. Heilman RL, *et al.* Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. *Transplant Proc* 2006; **38:** 1307–13.
10. Brennan DC, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355:** 1967–77.
11. Clark G, *et al.* Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; **17:** 1304–9.
12. Josephson MA. Rabbit antithymocyte globulin or basiliximab for induction therapy? *N Engl J Med* 2006; **355:** 2033–5.
13. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; **63:** 2803–35.
14. Boggi U, *et al.* A benefit-risk assessment of basiliximab in renal transplantation. *Drug Safety* 2004; **27:** 91–106.
15. Baquero A, *et al.* Basiliximab: a comparative study between the use of the recommended two doses versus a single dose in living donor kidney transplantation. *Transplant Proc* 2006; **38:** 909–10.
16. Neuhaus P, *et al.* Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. *Liver Transpl* 2002; **8:** 132–42.
17. Ganschow R, *et al.* First experience with basiliximab in pediatric liver graft recipients. *Pediatr Transplant* 2001; **5:** 353–8.
18. Ganschow R, *et al.* Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant* 2005; **9:** 741–5.
19. Reding R, *et al.* Steroid-free liver transplantation in children. *Lancet* 2003; **362:** 2068–70.

20. Spada M, *et al.* Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant* 2006; **6:** 1913–21.
21. Segovia J, *et al.* A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. *Transplantation* 2006; **81:** 1542–8.
22. Mattei MF, *et al.* Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *J Heart Lung Transplant* 2007; **26:** 693–9.
23. Hachem RR, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; **24:** 1320–6.
24. Borro JM, *et al.* Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc* 2005; **37:** 3996–8.
25. Funke VAM, *et al.* Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. *Bone Marrow Transplant* 2006; **37:** 961–5.

Skin disorders. There are a few case reports of successful treatment with basiliximab in psoriasis[1-4] (p.1583), chronic atopic dermatitis[5] (see Eczema, p.1579), lichen planus,[6] and epidermolysis bullosa acquisita[7] (p.1579).

1. Salim A, *et al.* Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). *Br J Dermatol* 2000; **143:** 1121–2.
2. Mrowietz U, *et al.* Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. *Arch Dermatol* 2000; **136:** 675–6.
3. Owen CM, Harrison PV. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. *Clin Exp Dermatol* 2000; **25:** 195–7.
4. Bell HK, Parslew RAG. Use of basiliximab as a cyclosporin-sparing agent in palmoplantar pustular psoriasis with myalgia as an adverse effect. *Br J Dermatol* 2002; **147:** 606–7.
5. Kägi MK, Heyer G. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. *Br J Dermatol* 2001; **145:** 350–1.
6. Rebora A, *et al.* Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 2002; **138:** 1100–1.
7. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. *Acta Derm Venereol (Stockh)* 2001; **81:** 72.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Simulect; ***Austral.:*** Simulect; ***Belg.:*** Simulect; ***Braz.:*** Simulect; ***Canad.:*** Simulect; ***Chile:*** Simulect; ***Cz.:*** Simulect; ***Denm.:*** Simulect; ***Fin.:*** Simulect; ***Fr.:*** Simulect; ***Ger.:*** Simulect; ***Gr.:*** Simulect; ***Hong Kong:*** Simulect; ***Hung.:*** Simulect; ***Irl.:*** Simulect; ***Israel:*** Simulect; ***Ital.:*** Simulect; ***Malaysia:*** Simulect; ***Mex.:*** Simulect; ***Neth.:*** Simulect; ***Norw.:*** Simulect; ***NZ:*** Simulect; ***Philipp.:*** Simulect; ***Pol.:*** Simulect; ***Port.:*** Simulect; ***Rus.:*** Simulect (Симулект); ***S.Afr.:*** Simulect; ***Spain:*** Simulect; ***Swed.:*** Simulect; ***Switz.:*** Simulect; ***Thai.:*** Simulect; ***Turk.:*** Simulect; ***UK:*** Simulect; ***USA:*** Simulect; ***Venez.:*** Simultec.

Belatacept *(USAN, rINN)*

Bélatacept; Belataceptum; BMS-224818; LEA-29Y.

Белатацепт

CAS — 706808-37-9.

Profile

Belatacept is a derivative of abatacept (p.14). It is a fusion protein and co-stimulation blocker that prevents T-cell activation. Belatacept is under investigation for the management of solid organ transplant rejection.

◊ References.

1. Vincenti F, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353:** 770–81.

Biolimus A9

42-*O*-(2-Ethoxyethyl) rapamycin.

$C_{55}H_{87}NO_{14}$ = 986.3.

CAS — 851536-75-9.

Profile

Biolimus A9 is an analogue of sirolimus (p.1841). A biolimus A9-releasing stent has been developed to reduce restenosis after coronary artery stent placement.

Brequinar Sodium *(USAN, rINNM)*

Brequinar sódico; Bréquinar Sodique; DuP-785; Natrii Brequinarum; NSC-368390. Sodium 6-fluoro-2-(2′-fluoro-4-biphenylyl)-3-methyl-4-quinolinecarboxylate.

Натрий Брехинар

$C_{23}H_{14}F_2NO_2Na$ = 397.3.

CAS — 96187-53-0 (brequinar); 96201-88-6 (brequinar sodium).

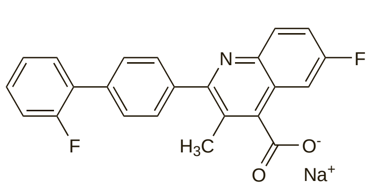

Profile

Brequinar sodium is an inhibitor of pyrimidine metabolism with potent immunosuppressant properties that has been investigated for the prevention and treatment of rejection episodes after organ and tissue transplantation and for treating various cancers.

Ciclosporin *(BAN, rINN)*

27-400; Ciclosporina; Ciclosporina A; Ciclosporine; Ciclosporinum; Ciklosporin; Ciklosporinas; Cyclosporin; Cyclosporin A; Cyclosporine *(USAN)*; Cyklosporin; OL-27-400; Siklosporiini; Siklosporin. Cyclo{-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-L-threonyl]-L-homoalanyl-(*N*-methylglycyl)-(*N*-methyl-L-leucyl)-L-valyl-(*N*-methyl-L-leucyl)-L-alanyl-D-alanyl-(*N*-methyl-L-leucyl)-(*N*-methyl-L-leucyl)-(*N*-methyl-L-valyl)-}.

Циклоспорин

$C_{62}H_{111}N_{11}O_{12}$ = 1202.6.

CAS — 59865-13-3.

ATC — L04AD01.

ATC Vet — QL04AD01; QS01XA90.

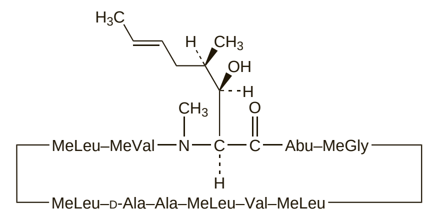

Cyclosporin A

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ciclosporin). A substance produced by *Beauveria nivea* (=*Tolypocladium inflatum* Gams) or obtained by any other means. A white or almost white powder; practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cyclosporine). A white to almost white powder. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol; slightly soluble in saturated hydrocarbons. Store in airtight containers. Protect from light.

Incompatibility. The plasticiser diethylhexyl phthalate, which is a possible carcinogen, was leached from PVC containers by ciclosporin preparations containing polyoxyl castor oil.[1] Such preparations should not be given through PVC tubing nor stored in PVC containers. Polysorbate 80, which is an excipient in other ciclosporin preparations, also leached plasticiser from PVC,[1] and similar precautions would apply to preparations so formulated. UK licensed product information further recommends that containers and stoppers be free of silicone oil and fatty substances.

For reported incompatibility between ciclosporin and mycophenolate, see Incompatibility, under Mycophenolate, p.1836.

1. Pearson SD, Trissel LA. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am J Hosp Pharm* 1993; **50:** 1405–9.

Stability. Ciclosporin was stable over 72 hours after dilution in glucose 5% or glucose/amino-acid solutions and storage at room temperature in the dark; similar stability was seen after dilution in lipid emulsion, but dilutions in sodium chloride 0.9% were considered to be stable only for 8 hours.[1] In all cases miscibility in the diluent was poor and vigorous shaking was required after addition to produce even distribution of ciclosporin. An extemporaneously compounded paste produced from ciclosporin oral solution (*Sandimmun*) in an oral gel base was found to be stable[2] for at least 31 days in aluminium-lined ointment tubes stored at 2° to 37°.

1. McLeod HL, *et al.* Stability of cyclosporin in dextrose 5%, NaCl 0.9%, dextrose/amino acid solution, and lipid emulsion. *Ann Pharmacother* 1992; **26:** 172–5.
2. Ghnassia LT, *et al.* Stability of cyclosporine in an extemporaneously compounded paste. *Am J Health-Syst Pharm* 1995; **52:** 2204–7.

Adverse Effects and Treatment

Nephrotoxicity, manifesting as raised serum creatinine and urea, is the major adverse effect of ciclosporin. It is related to drug-plasma concentrations and is usually reversible on reduction of the dose. In renal graft recipients episodes of nephrotoxicity may be difficult to distinguish from graft rejection. Interstitial fibrosis may develop during long-term therapy.

Other frequent adverse effects include hypertension, gastrointestinal disturbances, fatigue, hepatotoxicity, hypertrichosis, gum hyperplasia, tremor, headaches, hyperlipidaemias, hyperkalaemia, hypomagnesaemia, hyperuricaemia, paraesthesia, and muscle cramps and myalgia. Less commonly, anaemia, thrombocytopenia, rashes, weight increase, oedema, pancreatitis, myopathy, neuropathy, and hyperglycaemia have been reported. Glomerular capillary thrombosis has occurred, and may progress to graft failure. Encephalopathy, manifest as convulsions, confusion, visual disturbances including blindness, movement disorders, or psychiatric disturbances, has been reported. Optic disc oedema, including papilloedema with possible visual impairment secondary to benign intracranial hypertension, has occurred rarely.

Anaphylactoid reactions have occurred after intravenous use; it has been suggested that these represent a reaction to the polyoxyl castor oil vehicle of the intravenous preparation.

There is an increased incidence of certain malignancies and a predisposition to infection in patients receiving ciclosporin therapy.

Alopecia. Although ciclosporin is more often associated with reports of hypertrichosis, there have been cases of alopecia areata developing in patients given ciclosporin,[1] sometimes with complete hair loss (alopecia universalis).[2,3]

1. Davies MG, Bowers PW. Alopecia areata arising in patients receiving cyclosporin immunosuppression. *Br J Dermatol* 1995; **132:** 835–6.
2. Monti M, *et al.* Alopecia universalis in liver transplant patients treated with cyclosporin. *Br J Dermatol* 1995; **133:** 663–4.
3. Parodi A, *et al.* Alopecia universalis and cyclosporin A. *Br J Dermatol* 1996; **135:** 657.

Carcinogenicity. The use of ciclosporin in **organ transplant** recipients is associated with an increased incidence of malignancy, notably lymphoma,[1] and also skin cancer and Kaposi's sarcoma. The manufacturers have stated that of an estimated 5550 transplant patients who had been treated with ciclosporin by February 1984, lymphoproliferative disorders had been reported in 40; this represented an overall incidence of 0.7%, varying from 0.2 to 8% in different series.[2] In 1991, a report of 12 cases of lymphoproliferative disorders among 132 paediatric liver graft recipients estimated the incidence at about 2.8% per year for the first 6 years after transplantation, giving a cumulative risk of nearly 20% after 7 years.[3] There is evidence that the incidence of malignancy is related to dose,[2,4] and is greater when ciclosporin is used with other potent immunosuppressants.[2] In addition, the incidence of malignancy varies geographically, possibly reflecting environmental triggers and genetic susceptibility.[5]

It has been suggested that these lymphomas represent proliferation of B-cells under the influence of Epstein-Barr virus, a process normally prevented by the T-cells which are specifically inhibited by ciclosporin.[3] The resultant, usually polyclonal, lymphoproliferative tumours appear to regress on prompt excision of the affected tissue and reduction or withdrawal of the immunosuppressant regimen, in most cases without graft loss.[6] However, the need for vigilance and rapid response to these conditions has been stressed, since the responsive polyclonal disorder may evolve into a monoclonal, frankly malignant form; where the presentation is indistinguishable from a classic non-Hodgkins lymphoma the prognosis is much less good.[3] Interestingly, use of lower dose ciclosporin regimens appears to maintain normal elimination of Epstein-Barr virus-infected B-cells by specific T-cells,[7] and may lead to a reduced incidence of malignancy compared with earlier results.[4,7]

The risk of skin cancers in ciclosporin recipients is further increased by the exposure to sunlight.[8] Prophylactic retinoid therapy may prevent skin cancer in patients with renal transplants.[9]

There is no clear evidence that ciclosporin is associated with an increased incidence of malignancy compared with other immunosuppressants, although in one study dysplastic skin lesions were found in 14 of 64 transplant patients receiving ciclosporin compared with 3 of 33 previous similar patients who had received azathioprine.[10] However, such comparisons are difficult, not least because many transplant patients tend to have received multiple immunosuppressant agents. The safety of ciclosporin in **dermatology** patients has been reviewed.[11] Despite reports of lymphomas and other malignancies in dermatology patients treated with ciclosporin, a 5-year cohort study showed no increased risk of lymphoma or internal malignancies. While there was an increased risk of non-melanoma skin cancers, especially squamous cell carcinoma, many patients had been previously exposed to PUVA, methotrexate, or other immunosuppressants. Adjusting for these variables, more than 2 years of cumulative treatment with ciclosporin was estimated to increase the risk of non-melanoma skin cancer by a factor of 3.3 when compared with less than 2 years of cumulative treatment.

1. Penn I. Cancers following cyclosporine therapy. *Transplantation* 1987; **43:** 32–5.
2. Beveridge T, *et al.* Lymphomas and lymphoproliferative lesions developing under cyclosporin therapy. *Lancet* 1984; **i:** 788.
3. Malatack JJ, *et al.* Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. *J Pediatr* 1991; **118:** 667–75.

4. Dantal J, *et al.* Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351:** 623–8.
5. Newstead CG. Assessment of risk of cancer after renal transplantation. *Lancet* 1998; **351:** 610–11.
6. Starzl TE, *et al.* Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; **i:** 583–7.
7. Crawford DH, Edwards JMB. Immunity to Epstein-Barr virus in cyclosporin A-treated renal allograft recipients. *Lancet* 1982; **i:** 1469–70.
8. Stockfleth E, *et al.* Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res* 2002; **160:** 251–8.
9. Bavinck JN, *et al.* Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995; **13:** 1933–8.
10. Shuttleworth D, *et al.* Epidermal dysplasia and cyclosporine therapy in renal transplant patients: a comparison with azathioprine. *Br J Dermatol* 1989; **120:** 551–4.
11. Behnam SM, *et al.* Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. *J Drugs Dermatol* 2005; **4:** 189–94.

Dysmorphic changes. There was pronounced coarsening of facial features in 11 children who were treated with prednisone and ciclosporin for renal transplantation and followed up for more than 6 months.[1] The changes resembled those seen with phenytoin therapy. In a 13-year-old patient given ciclosporin as part of an immunosuppressive regimen after lung transplantation, facial dysmorphism, which developed along with follicular disturbances, later improved upon conversion to tacrolimus.[2] Similarly, lip hypertrophy associated with ciclosporin use in 2 paediatric patients resolved after therapy was changed to tacrolimus.[3] A 58-year-old renal transplant recipient on long-term ciclosporin therapy developed progressive facial changes, including swelling and distortion of the nose (rhinophyma);[4] surgery or physical ablation of excess tissue may provide cosmetic improvement.

1. Reznik VM, *et al.* Changes in facial appearance during cyclosporin treatment. *Lancet* 1987; **i:** 1405–7.
2. Chastain MA, Millikan LE. Pilomatrix dysplasia in an immunosuppressed patient. *J Am Acad Dermatol* 2000; **43:** 118–22.
3. Cansick JC, Hulton S-A. Lip hypertrophy secondary to cyclosporin treatment. *Pediatr Nephrol* 2003; **18:** 710–11.
4. Brown S, *et al.* [Minerva picture]. *BMJ* 2005; **330:** 1218.

Effects on the blood. Erythraemia[1,2] and thrombocytosis[3] have both been reported with ciclosporin treatment, both of which may contribute to **thromboembolic complications.** One retrospective study reported 17 thromboembolic events (pulmonary embolism, renal-vein or deep-vein thrombosis, or haemorrhoidal thrombosis) in 13 of 90 renal allograft recipients treated with ciclosporin and corticosteroids, compared with only 1 episode of superficial thrombophlebitis in 90 similar patients treated with an azathioprine-based regimen.[4] However, other authors dispute that the incidence of thromboembolic events is any greater after ciclosporin than azathioprine,[5-7] and one group found the reverse.[8]

Other effects that have been associated with ciclosporin therapy include cases of the haemolytic-uraemic syndrome,[9] and thrombocytopenia,[10] or leucopenia.[11] Post-transplant thrombotic microangiopathy has also been reported.[12,13] This syndrome can include haemolytic anaemia and thrombocytopenia, and must be distinguished from rejection in renal transplant recipients. In those patients with a history of thrombotic microangiopathy, the risk of recurrence is high, irrespective of ciclosporin treatment.

1. Tatman AJ, *et al.* Erythraemia in renal transplant recipients treated with cyclosporin. *Lancet* 1988; **i:** 1279.
2. Innes A, *et al.* Cyclosporin and erythraemia. *Lancet* 1988; **ii:** 285.
3. Itami N, *et al.* Thrombocytosis after cyclosporin therapy in child with nephrotic syndrome. *Lancet* 1988; **ii:** 1018.
4. Vanrenterghem Y, *et al.* Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. *Lancet* 1985; **i:** 999–1002.
5. Bergentz S-E, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 101–2.
6. Zazgornik J, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 102.
7. Choudhury N, *et al.* Thromboembolic complications in cyclosporin-treated kidney allograft recipients. *Lancet* 1985; **ii:** 606.
8. Allen RD, *et al.* Venous thrombosis and cyclosporin. *Lancet* 1985; **ii:** 1004.
9. Bonser RS, *et al.* Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. *Lancet* 1984; **ii:** 1337.
10. Dejong DJ, Sayler DJ. Possible cyclosporine-associated thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 1007.
11. Michel F, *et al.* Bone marrow toxicity of cyclosporin in a kidney transplant patient. *Lancet* 1986; **ii:** 394.
12. Pisoni R, *et al.* Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Safety* 2001; **24:** 491–501.
13. Bren A, *et al.* Follow-up of kidney graft recipients with cyclosporine-associated hemolytic-uremic syndrome and thrombotic microangiopathy. *Transplant Proc* 2005; **37:** 1889–91.

Effects on the cardiovascular system. The principal cardiovascular adverse effect of ciclosporin is **hypertension.** This may be severe,[1] appears to be dose-related,[1,2] and is particularly common in recipients of cardiac or heart-lung grafts.[3,4] There may be an association with low serum-magnesium concentrations.[5] Mechanisms that may contribute to ciclosporin-induced hypertension include impaired sodium excretion,[6] enhanced sympathetic nervous activity,[3,7] effects on renal prostaglandin metabolism,[2] and direct damage to endothelial cells[8] with release of the potent vasoconstrictor endothelin,[9] all of which may be due to calcineurin inhibition.[10] Thus hypertension may occur independently of nephrotoxicity,[2,7] and may be difficult to treat with conventional antihypertensive regimens.[6] Calcium-channel blockers are the preferred class of antihypertensives for hypertension that develops after transplantation.[1,11] It is important to choose one that does not interact with ciclosporin (see Cardiovascular Drugs under Interactions, below).[1] Beta blockers may also be used. Diuretics are usually avoided.[11] For mention of the ability of calcium-channel blockers to ameliorate the nephrotoxic effects of ciclosporin, see Transplantation, under Diltiazem, p.1267, Nifedipine, p.1356, and Verapamil, p.1424 Occasionally, hypertension may be irreversible.[2,12]

Raynaud's syndrome has been reported with ciclosporin.[13] Conversely, use of ciclosporin has also reportedly caused erythromelalgia, with painful inflammatory vasodilatation of the extremities.[14] For a discussion of possible thromboembolic complications, see Effects on the Blood, above.

1. Textor SC, *et al.* Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc* 1994; **69:** 1182–93.
2. Porter GA, *et al.* Cyclosporine-associated hypertension. *Arch Intern Med* 1990; **150:** 280–3.
3. Scherrer U, *et al.* Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990; **323:** 693–9.
4. Weidle PJ, Vlasses PH. Systemic hypertension associated with cyclosporine: a review. *Drug Intell Clin Pharm* 1988; **22:** 443–51.
5. June CH, *et al.* Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. *Transplantation* 1986; **41:** 47–51.
6. Weinman EJ. Cyclosporine-associated hypertension. *Am J Med* 1989; **86:** 256–7.
7. Mark AL. Cyclosporine, sympathetic activity, and hypertension. *N Engl J Med* 1990; **323:** 748–50.
8. Zaal MJW, *et al.* Is cyclosporin toxic to endothelial cells? *Lancet* 1988; **ii:** 956–7.
9. Deray G, *et al.* Increased endothelin level after cyclosporine therapy. *Ann Intern Med* 1991; **114:** 809.
10. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72:** S9–12.
11. Taler SJ, *et al.* Cyclosporin-induced hypertension: incidence, pathogenesis and management. *Drug Safety* 1999; **20:** 437–49.
12. Sennesael JJ, *et al.* Hypertension and cyclosporine. *Ann Intern Med* 1986; **104:** 729.
13. Deray G, *et al.* Cyclosporin and Raynaud phenomenon. *Lancet* 1986; **ii:** 1092–3.
14. Thami GP, Bhalla M. Erythromelalgia induced by possible calcium channel blockade by ciclosporin. *BMJ* 2003; **326:** 910.

Effects on the gastrointestinal tract. There have been reports[1,2] of severe non-specific colitis associated with both elevated[1] and therapeutic[2] blood or serum concentrations of ciclosporin.

1. Innes A, *et al.* Cyclosporin toxicity and colitis. *Lancet* 1988; **ii:** 957. Correction. *ibid.*; 1094.
2. Bowen JRC, Sahi S. Cyclosporin induced colitis. *BMJ* 1993; **307:** 484.

Effects on glucose tolerance. Ciclosporin, particularly in high doses, may be associated with reduced insulin production,[1] impaired glucose tolerance,[2] and occasional overt diabetes mellitus,[3,4] although ciclosporin has also been tried, with some apparent benefit, in the treatment of recent-onset diabetes mellitus (for mention of the use of immunosuppressants in diabetes mellitus, see p.431). The incidence of fasting hyperglycaemia has been estimated at about 8% in ciclosporin-treated renal transplant recipients, compared with about 5% in those given an azathioprine-based regimen.[4]

1. Scott JP, Higenbottam TW. Adverse reactions and interactions of cyclosporin. *Med Toxicol* 1983; **3:** 107–27.
2. Gunnarsson R, *et al.* Deterioration in glucose metabolism in pancreatic transplant recipients given cyclosporin. *Lancet* 1983; **ii:** 571–2.
3. Bending JJ, *et al.* Diabetogenic effect of cyclosporin. *BMJ* 1987; **294:** 401–2.
4. Yagisawa T, *et al.* Deterioration in glucose metabolism in cyclosporine-treated kidney transplant recipients and rats. *Transplant Proc* 1986; **18:** 1548–51.

Effects on the kidneys. Ciclosporin nephrotoxicity comprises 2 distinct forms of renal injury.[1,2]

Acute nephrotoxicity is dose-related, and reversible.[1-4] It occurs shortly after starting ciclosporin and often presents as an asymptomatic increase in serum creatinine, which improves quickly on dosage adjustment or drug withdrawal.[2,5] It may be difficult to distinguish ciclosporin nephrotoxicity from acute graft rejection after kidney transplantation.[5] Extremely high intravenous doses of ciclosporin (21 mg/kg per 24 hours for 60 hours) have been associated with fatal acute tubular necrosis;[6] in another patient given an overdose of 30 mg/kg per 24 hours, the error was detected after 18 hours, and the necrosis deemed to be partially reversible.[7]

Acute ciclosporin nephrotoxicity appears to be related to a renal imbalance of vasoconstrictor and vasodilator mediators, leading to intense vasoconstriction within the kidney.[1,2] Stimulation of the renin-angiotensin system,[5] free radical damage,[1,2] and activation of the sympathetic nervous system[1,5] have been suggested to play a role; numerous vasoactive mediators, including prostaglandins, thromboxanes, nitric oxide, and endothelin-1, may be implicated.[2,3] However, studies with therapies affecting vasoactive factors have produced equivocal results.[1-3]

Chronic nephrotoxicity is related to long-term exposure to ciclosporin.[2] It may be difficult to distinguish between chronic ciclosporin nephrotoxicity and chronic allograft rejection or nephropathy.[4,5] There is a decline in glomerular filtration rate, which may be irreversible or only partially reversible in transplant patients;[3] Some cardiac transplant patients given higher doses than those used in renal transplantation have developed end-stage renal failure.[3] One study[8] in paediatric heart transplant patients found that the decline in renal function correlated with early exposure to ciclosporin. However, in non-transplant patients, renal function impairment has been reported to be reversible after stopping ciclosporin.[3,9] Long-term follow-up has not shown progressive loss of renal function in these patients.[3] Chronic nephrotoxicity is also associated with typical irreversible histological changes, such as interstitial fibrosis.[1-3] which may occur as a result of ischaemic damage secondary to the prolonged alterations in intrarenal haemodynamics.[3] The mechanism is not completely understood, and chronic nephrotoxicity can occur independently of acute renal dysfunction, dosage, or ciclosporin blood concentrations.[4]

Drugs tried to *ameliorate* the nephrotoxic effects of ciclosporin in patients who have undergone transplantation include calcium-channel blockers (see Transplantation, under Diltiazem, p.1267, Nifedipine, p.1356, and Verapamil, p.1424), clonidine, codergocrine,[10-12] omega-3 triglycerides,[13] misoprostol and other prostaglandin analogues,[14,15] and cilastatin.[16] Although benefits have been reported with some of these, hydration, careful monitoring of ciclosporin concentrations, and the use where possible of low-dose or intermittent regimens of ciclosporin appear to remain the major means of minimising nephrotoxicity. Calcium-channel blockers are used if hypertension occurs (see Effects on the Cardiovascular System, above).

1. Burdmann EA, *et al.* Cyclosporine nephrotoxicity. *Semin Nephrol* 2003; **23:** 465–76.
2. Cattaneo D, *et al.* Nephrotoxic aspects of cyclosporine. *Transplant Proc* 2004; **36** (suppl): 234S–239S.
3. Leaker B, Cairns HS. Clinical aspects of cyclosporin nephrotoxicity. *Br J Hosp Med* 1994; **52:** 529–34.
4. Vítko Š, Viklický O. Cyclosporine renal dysfunction. *Transplant Proc* 2004; **36** (suppl): 243S–247S.
5. Busauschina A, *et al.* Cyclosporine nephrotoxicity. *Transplant Proc* 2004; **36** (suppl): 229S–233S.
6. Shechter P. Acute tubular necrosis following high-dose cyclosporine A therapy. *Eur J Clin Pharmacol* 1996; **49:** 521–3.
7. Dussol B, *et al.* Acute tubular necrosis induced by high level of cyclosporine A in a lung transplant. *Transplantation* 2000; **70:** 1234–6.
8. Hornung TS, *et al.* Renal function after pediatric cardiac transplantation: the effect of early cyclosporin dosage. *Pediatrics* 2001; **107:** 1346–50.
9. Powles AV, *et al.* Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol* 1998; **138:** 443–9.
10. Heinrichs DA, *et al.* The effects of co-dergocrine on cyclosporin A pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1987; **24:** 117–18.
11. Nussenblatt RB, *et al.* Hydergine and cyclosporin nephrotoxicity. *Lancet* 1986; **i:** 1220–1.
12. Kho TL, *et al.* Hydergine and reversibility of cyclosporin nephrotoxicity. *Lancet* 1986; **ii:** 394–5.
13. Stoof TJ, *et al.* Does fish oil protect renal function in cyclosporin-treated psoriasis patients? *Br J Dermatol* 1990; **123:** 535.
14. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
15. Di Palo FQ, *et al.* Role of a prostaglandin E analogue in the prevention of acute graft rejection by cyclosporine. *N Engl J Med* 1990; **323:** 832.
16. Tejedor A, *et al.* Cilastatin protection against cyclosporin A-induced nephrotoxicity: clinical evidence. *Curr Med Res Opin* 2007; **23:** 505–13.

Effects on lipids. Marked hyperlipidaemia has been associated with ciclosporin therapy, with notable increases reported in low-density lipoprotein cholesterol,[1,2] and triglycerides. An increase in lipoprotein(a) has been reported,[3] but this was disputed.[4-6] Ciclosporin has been reported to have greater effects on lipids than azathioprine[7] or tacrolimus[8] post-transplantation. The use of corticosteroids with ciclosporin appears to have an additive adverse effect on lipids.[9] Lipid regulating drugs are used to decrease hypercholesterolaemia in transplant patients.

1. Luke DR, *et al.* Longitudinal study of cyclosporine and lipids in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1990; **30:** 163–9.
2. Ballantyne CM, *et al.* Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 1989; **262:** 53–6.
3. Webb AT, *et al.* Does cyclosporin increase lipoprotein(a) concentrations in renal transplant recipients? *Lancet* 1993; **341:** 268–70.
4. Kronenberg F, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 765.
5. Segarra A, *et al.* Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993; **341:** 766.
6. Hunt BJ, *et al.* Does cyclosporin affect lipoprotein(a) concentrations? *Lancet* 1994; **343:** 119–20.
7. Van den Dorpel MA, *et al.* Conversion from cyclosporine A to azathioprine treatment improves LDL oxidation in kidney transplant recipients. *Kidney Int* 1997; **51:** 1608–12.
8. Taylor DO, *et al.* A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. *J Heart Lung Transplant* 1999; **18:** 336–45.
9. Moore R, *et al.* Calcineurin inhibitors and post-transplant hyperlipidaemias. *Drug Safety* 2001; **24:** 755–66.

Effects on the nervous system. Adverse effects of ciclosporin on the CNS include tremor,[1-4] ataxia,[1-3] confusion[1,2,5] or agitation,[2] mental depression,[3] headache,[2,5] sleep disturbances,[2] lethargy,[1,2,6,7] or coma[2,5-7] (in one case coma persisted for 44 days),[8] convulsions,[2,3,5,9-13] leukoencephalopathy,[2,8,9,13] cortical blindness,[2,9] diplopia,[14] and spasticity or paralysis of the limbs.[1,2] Opsoclonus (an involuntary eye movement disorder) has also been reported.[13] In one reported case of posterior leukoencephalopathy, the patient developed irreversible abulia (impairment of ability to perform voluntary actions or make decisions; reduction in speech, movement, thought, and emotional reaction);[15] the patient initially presented with subtle symptoms of decreased appetite and reduced activity. Convulsions have sometimes been associated with hypertension and fluid retention,[11] but this is by no means always the case.[9,10]

Although neurotoxicity usually manifests within a month of beginning treatment, it may be delayed, and in one case occurred only after 3 years of ciclosporin therapy.[16] Severe CNS toxicity has been stated to vary in incidence from 0.1% in renal transplant patients to about 1.6% in bone marrow transplant recipients.[12] There is some evidence for an association of serious neurological effects with low total serum-cholesterol concentrations,[2] and the use of the intravenous formulation.[2] Neurotoxicity may also be associated with the use of lipid solutions.[17] An association with hypomagnesaemia has also been proposed[3] but may just represent concomitant nephrotoxicity.[18] Convulsions may be more likely or more severe in patients with a familial history of epilepsy,[19] subclinical aluminium overload,[20] or in those also given high-dose corticosteroids.[5,21,22]

The mechanism of toxicity is unknown but may be associated with disturbance of the blood-brain barrier;[10,12,23] it has been suggested that the metabolite M-17, or possibly other metabolites, are responsible for neurotoxicity.[6] Ciclosporin may be selectively toxic for glial cells, and alteration of sympathetic outflow by calcineurin inhibition may also mediate neurotoxicity.[24]

1. Atkinson K, *et al.* Cyclosporine-associated central-nervous-system toxicity after allogeneic bone-marrow transplantation. *N Engl J Med* 1984; **310:** 527.
2. de Groen PC, *et al.* Central nervous system toxicity after liver transplantation: the role of cyclosporine and cholesterol. *N Engl J Med* 1987; **317:** 861–6.
3. Thompson CB, *et al.* Association between cyclosporin neurotoxicity and hypomagnesaemia. *Lancet* 1984; **ii:** 1116–20.
4. Munhoz RP, *et al.* Movement disorders secondary to long-term treatment with cyclosporine A. *Arq Neuropsiquiatr* 2005; **63:** 592–6.
5. Taque S, *et al.* Central neurotoxicity of cyclosporine in two children with nephrotic syndrome. *Pediatr Nephrol* 2004; **19:** 276–80.
6. Kunzendorf U, *et al.* Cyclosporin metabolites and central-nervous-system toxicity. *Lancet* 1988; **i:** 1223.
7. Lischke R, *et al.* Cyclosporine-related neurotoxicity in a patient after bilateral lung transplantation for cystic fibrosis. *Transplant Proc* 2004; **36:** 2837–9.
8. Berden JHM, *et al.* Severe central-nervous-system toxicity associated with cyclosporin. *Lancet* 1985; **i:** 219–20.
9. Hughes RL. Cyclosporine-related central nervous system toxicity in cardiac transplantation. *N Engl J Med* 1990; **323:** 420–1.
10. Gottrand F, *et al.* Cyclosporine neurotoxicity. *N Engl J Med* 1991; **324:** 1744–5.
11. Joss DV, *et al.* Hypertension and convulsions in children receiving cyclosporin A. *Lancet* 1982; **i:** 906.
12. Krupp P, *et al.* Encephalopathy associated with fat embolism induced by solvent for cyclosporin. *Lancet* 1989; **i:** 168–9.
13. Marchiori PE, *et al.* Cyclosporine A-induced ocular opsoclonus and reversible leukoencephalopathy after orthotopic liver transplantation: brief report. *Clin Neuropharmacol* 2004; **27:** 195–7.
14. Openshaw H. Eye movement abnormality associated with cyclosporin. *J Neurol Neurosurg Psychiatry* 2001; **70:** 809.
15. Nishie M, *et al.* Posterior encephalopathy subsequent to cyclosporin A presenting as irreversible abulia. *Intern Med* 2003; **42:** 750–5.
16. Welge-Lüssen UC, Gerhartz HH. Late onset of neurotoxicity with cyclosporin. *Lancet* 1994; **343:** 293.
17. De Klippel N. Cyclosporin leukoencephalopathy induced by intravenous lipid solution. *Lancet* 1992; **339:** 1114.
18. Allen RD, *et al.* Cyclosporin and magnesium. *Lancet* 1985; **i:** 1283–4.
19. Velu T, *et al.* Cyclosporin-associated fatal convulsions. *Lancet* 1985; **i:** 219.
20. Nordal KP, *et al.* Aluminium overload, a predisposing condition for epileptic seizures in renal-transplant patients treated with cyclosporin. *Lancet* 1985; **ii:** 153–4.
21. Durrant S, *et al.* Cyclosporin A, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 829–30.
22. Boogaerts MA, *et al.* Cyclosporin, methylprednisolone, and convulsions. *Lancet* 1982; **ii:** 1216–17.
23. Sloane JP, *et al.* Disturbance of blood-brain barrier after bone-marrow transplantation. *Lancet* 1985; **ii:** 280–1.
24. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.

Effects on skeletal muscle. Ciclosporin has occasionally been associated with myopathy.[1-6] The manufacturer noted that 29 cases had been reported by December 1990, which appeared to be divided into cases of toxic or non-specific myopathy or mild sensory motor neuropathy, which were generally dose-related; and rhabdomyolysis, often, but not always, when used with lovastatin or colchicine.[7] Rhabdomyolysis has also been reported when other statins were used with ciclosporin, see Lipid Regulating Drugs, under Interactions, below.

1. Noppen M, *et al.* Cyclosporine and myopathy. *Ann Intern Med* 1987; **107:** 945–6.
2. Goy J-J. Myopathy as possible side-effect of cyclosporin. *Lancet* 1989; **i:** 1446–7.
3. Grezard O, *et al.* Cyclosporin-induced muscular toxicity. *Lancet* 1990; **335:** 177.
4. Fernandez-Sola J, *et al.* Reversible cyclosporin myopathy. *Lancet* 1990; **335:** 362–3.
5. Wahie S, Meggitt SJ. Myotoxicity occurring with ciclosporin in a patient with atopic dermatitis. *Br J Dermatol* 2005; **153:** 1238.
6. Khan S, *et al.* Musculoskeletal and myotoxic side-effects in a patient treated for psoriasis. *Br J Dermatol* 2006; **155:** 481.
7. Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337:** 915.

Hyperplasia. Ciclosporin is well known to be associated with the development of gingival hyperplasia or gingival overgrowth: one review[1] has estimated the incidence at about 30% in transplant patients, while noting that reported values in the literature range from about 7 to 70%. A large study[2] found dosage and serum concentration of ciclosporin to be the most significant risk factors in the development of gingival hyperplasia. The presence of dental plaque may exacerbate the response, and good oral hygiene is important in preventing or minimising of gingival overgrowth.[1] Use with nifedipine (which can itself produce hyperplasia) may exacerbate overgrowth;[3] a cohort study[4] of renal transplant recipients found that amlodipine was associated with a greater prevalence of overgrowth than nifedipine. Overgrowth is generally reversible after dosage reduction or withdrawal of ciclosporin; where this is not feasible, surgical excision is recommended.[1] However, improvement or resolution of the overgrowth may also be produced by a course of azithromycin.[5-7] Similar benefit has been reported for metronidazole in some[8,9] but not all patients.[10] There are reports[11,12] of marked improvement in hyperplasia after changing treatment from ciclosporin to tacrolimus, including a case apparently resistant to azithromycin.[13]

Enlargement of the papillae of the tongue[14] and sebaceous gland hyperplasia[15] have also occurred in association with ciclosporin.

1. Brunet L, *et al.* Gingival enlargement induced by drugs. *Drug Safety* 1996; **15:** 219–31.
2. Thomas DW, *et al.* Risk factors in the development of cyclosporine-induced gingival overgrowth. *Transplantation* 2000; **69:** 522–6.
3. Slavin J, Taylor J. Cyclosporin, nifedipine, and gingival hyperplasia. *Lancet* 1987; **ii:** 739.
4. James JA, *et al.* The calcium channel blocker used with cyclosporin has an effect on gingival overgrowth. *J Clin Periodontol* 2000; **27:** 109–15.
5. Jucglà A, *et al.* The use of azithromycin for cyclosporin-induced gingival overgrowth. *Br J Dermatol* 1998; **138:** 198–9.
6. Nash MM, Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; **65:** 1611–15.
7. Citterio F, *et al.* Azithromycin treatment of gingival hyperplasia in kidney transplant recipients is effective and safe. *Transplant Proc* 2001; **33:** 2134–5.
8. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.
9. Cecchin E, *et al.* Treatment of cyclosporine-induced gingival hypertrophy. *Ann Intern Med* 1997; **126:** 409–10.
10. Aufricht C, *et al.* Oral metronidazole does not improve cyclosporine A-induced gingival hyperplasia. *Pediatr Nephrol* 1997; **11:** 552–5.
11. Thorp M, *et al.* The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. *Transplantation* 2000; **69:** 1218–20.
12. James JA, *et al.* Reduction in gingival overgrowth associated with conversion from cyclosporin A to tacrolimus. *J Clin Periodontol* 2000; **27:** 144–8.
13. Vallejo C, *et al.* Resolution of cyclosporine-induced gingival hyperplasia resistant to azithromycin by switching to tacrolimus. *Haematologica* 2001; **86:** 110.
14. Silverberg NB, *et al.* Lingual fungiform papillae hypertrophy with cyclosporin A. *Lancet* 1996; **348:** 967.
15. Boschnakow A, *et al.* Ciclosporin A-induced sebaceous gland hyperplasia. *Br J Dermatol* 2003; **149:** 198–200.

Hypersensitivity. Anaphylactoid reactions in 5 of 21 patients given intravenous ciclosporin infusions were found to be associated with improper mixing of the ciclosporin concentrate, which had a polyoxyl castor oil vehicle, with the infusion solution.[1] It was concluded that this had led to an initial bolus of polyoxyl castor oil that had triggered the anaphylactic reactions. Subsequent study indicated that peak concentrations of up to 9 times the intended concentration of ciclosporin and polyoxyl castor oil were present in the first 10 minutes of a poorly mixed infusion.[2] Anaphylactic shock after ingestion of ciclosporin capsules has been reported. The microemulsifying base containing corn oil and polyoxyl 40 hydrogenated castor oil, which is related to the polyoxyl castor oil vehicle used in the intravenous formulation, was considered to be the likely cause.[3]

1. Liau M, *et al.* High incidence of anaphylactoid reactions to iv cyclosporin A caused by improper dissolution of Cremophor EL. *Clin Pharmacol Ther* 1995; **57:** 209.
2. Liau-Chu M, *et al.* Mechanism of anaphylactoid reactions: improper preparation of high-dose intravenous cyclosporine leads to bolus infusion of Cremophor EL and cyclosporine. *Ann Pharmacother* 1997; **31:** 1287–91.
3. Kuiper RAJ, *et al.* Cyclosporine-induced anaphylaxis. *Ann Pharmacother* 2000; **34:** 858–61.

Hyperuricaemia. Ciclosporin therapy may be associated with marked hyperuricaemia,[1-3] which may lead (mainly in male patients[1]) to episodes of severe gouty arthritis.[1-3] It has been suggested that ciclosporin specifically reduces urate clearance by the kidney independently of its effects on glomerular filtration,[4,5] but this has been disputed.[6] Treatment of ciclosporin-induced gout can be difficult since interactions with NSAIDs may lead to enhanced renal toxicity[5] and patients who are also receiving azathioprine may experience increased bone-marrow toxicity if given allopurinol.[7] Benzbromarone appears to be an alternative[8] for treating hyperuricaemia in renal transplant recipients with a creatinine clearance greater than 25 mL/minute.

1. Lin H-Y, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1989; **321:** 287–92.
2. Kahl LE, *et al.* Gout in the heart transplant recipient: physiologic puzzle and therapeutic challenge. *Am J Med* 1989; **87:** 289–94.
3. Burack DA, *et al.* Hyperuricemia and gout among heart transplant recipients receiving cyclosporine. *Am J Med* 1992; **92:** 141–6.
4. Noordzij TC, *et al.* Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **322:** 335.
5. Farge D, *et al.* Hyperuricemia and gouty arthritis in heart transplant recipients. *Am J Med* 1990; **88:** 553.
6. Zürcher RM, *et al.* Hyperuricaemia in cyclosporin-treated patients: a GFR-related effect. *Nephrol Dial Transplant* 1996; **11:** 153–8.
7. Figg WD. Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 1990; **332:** 334–5.
8. Zürcher RM, *et al.* Excellent uricosuric efficacy of benzbromarone in cyclosporin-A-treated renal transplant patients: a prospective study. *Nephrol Dial Transplant* 1994; **9:** 548–51.

Overdosage. Anxiety, diarrhoea, vomiting, and perspiration, with weak and irregular pulse, occurred in a patient accidentally injected with 250 mg (estimated 6.25 mg/kg) of ciclosporin.[1] The patient subsequently developed atrial fibrillation, which was treated with digoxin, and in the next 36 hours showed signs of slight renal insufficiency. Two days later no adverse effects were apparent. Atrial fibrillation also developed in another patient accidentally given 1 g of microemulsifying oral ciclosporin.[2] No adverse renal, hepatic, or neurological effects were seen in a third patient[3] who took 25 g of ciclosporin over 8 days. There was a mild increase in blood pressure and other symptoms included burning sensations in the mouth and the extremities, dysgeusia, facial flushing, and gastrointestinal disturbances. Symptoms resolved within 2 weeks of stopping ciclosporin.

A patient accidentally given intravenous ciclosporin at 30 mg/hour for 13 hours, developed massive intracerebral oedema and brainstem compression and died despite stopping the infusion.[4]

Although ciclosporin is only minimally dialysable, whole blood exchange (therapeutic erythrocytapheresis followed by plasma exchange) has been used in the management of a patient inadvertently given 3.5 g of ciclosporin orally; the overdose was discovered too late for the use of activated charcoal or gastric lavage, and plasma exchange alone was considered unsuitable because of the partitioning of ciclosporin between plasma and erythrocytes. The patient, who had signs of nephrotoxicity and hepatotoxicity, recovered without long-term sequelae.[5]

For reference to tubular necrosis after extremely high intravenous doses of ciclosporin, see under Effects on the Kidneys, above.

1. Wallemacq PE, Lesne ML. Accidental massive IV administration of cyclosporine in man. *Drug Intell Clin Pharm* 1985; **19:** 29–30.
2. LoVecchio FA, Goltz HR. Atrial fibrillation following acute overdose with oral cyclosporine. *Ann Pharmacother* 2000; **34:** 405.
3. Baumhefner RW, *et al.* Huge cyclosporin overdose with favourable outcome. *Lancet* 1987; **ii:** 332.
4. de Perrot M, *et al.* Massive cerebral edema after i.v. cyclosporin overdose. *Transplantation* 2000; **70:** 1259–60.
5. Kwon SU, *et al.* Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. *J Heart Lung Transplant* 2006; **25:** 483–5.

Precautions

Regular monitoring of renal and hepatic function, blood pressure, and serum electrolytes (chiefly potassium and magnesium) is required in patients receiving ciclosporin. Serum lipids should also be monitored. Monitoring of plasma ciclosporin concentrations is mandatory in transplant patients. Dosage adjustment is often necessary in patients with renal impairment or other factors affecting plasma ciclosporin concentrations. Care is required in patients with hyperuricaemia, and intravenous formulations should be given cautiously to those who have previously received parenteral drugs formulated in polyoxyl castor oil, or to those with a history of allergic reactions.

Ciclosporin should not be used to treat atopic dermatitis, psoriasis, or rheumatoid arthritis in patients with persistently raised creatinine, uncontrolled hypertension, uncontrolled infections, or malignancy. An exception is patients with treated malignant or pre-malignant lesions of the skin who may receive ciclosporin as a last resort for psoriasis. Psoriatic patients should not be given concomitant ultraviolet irradiation and should avoid excessive sun exposure. Ciclosporin may increase the risk of benign intracranial hypertension.

The commercially available oral formulations of ciclosporin differ in their bioavailability, and patients should not be transferred from one to another without appropriate monitoring. Intra-uterine contraceptive devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Immunosuppressants may reduce the response to vaccines and use with live vaccines should generally be avoided as there is a possibility of generalised infection, see below.

Oral formulation. After development of the oral microemulsifying formulation of ciclosporin patients were switched from the old formulation on a 1:1 basis by weight initially, with monitoring of resultant ciclosporin concentrations and subsequent dosage adjustment. Results were generally good, despite some reports of nephrotoxicity or rejection in previously stable grafts,[1-4] and a meta-analysis[5] concluded that of *de novo* transplant recipients, those receiving the microemulsifying formulation had significantly fewer instances of rejection, and, in liver transplant recipients, significantly fewer adverse events.

1. Bennett WM, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 205.
2. Olyaei AJ, *et al.* Switching between cyclosporin formulations: what are the risks? *Drug Safety* 1997; **16:** 366–73.
3. Filler G, Ehrich J. Which cyclosporin formulation? *Lancet* 1996; **348:** 1176–7.
4. Gennery A, *et al.* Which cyclosporin formulation? *Lancet* 1996; **348:** 1177.
5. Shah MB, *et al.* A meta-analysis to assess the safety and tolerability of two formulations of cyclosporine: Sandimmune and Neoral. *Transplant Proc* 1998; **30:** 4048–53.

Breast feeding. The American Academy of Pediatrics considers that ciclosporin may possibly suppress the immune system in a nursing infant.[1] However, a study[2] in the breast-fed infants of 7 women given ciclosporin found that the amounts ingested by the infant produced undetectable blood concentrations. In another case it was estimated that a breast-fed infant received less than 100 micrograms/kg of ciclosporin daily.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/01/08)
2. Nyberg G, *et al.* Breast feeding during treatment with cyclosporine. *Transplantation* 1998; **65:** 253–5.
3. Thiru Y, *et al.* Successful breast feeding while mother was taking cyclosporin. *BMJ* 1997; **315:** 463.

Porphyria. Ciclosporin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*. However, there are reports of patients with acute intermittent porphyria given ciclosporin pre- and post-transplant with no exacerbation of symptoms.[1,2]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–15.
2. Warholm C, Wilczek H. Renal transplantation in a case of acute intermittent porphyria. *J Clin Pharmacol* 2003; **43:** 1158–60.

Pregnancy. Ciclosporin has been used successfully in pregnant women. However, in common with other immunosuppressants, fetal growth retardation may be a significant problem.[1-4] Patients with hypertension or graft dysfunction are more likely to have adverse outcomes, so patients should have stable graft function and be on maintenance therapy before considering pregnancy.[1,2] Serum ciclosporin concentrations may fall during pregnancy,[2,3,5] but although frequent monitoring is necessary, the altered immune state of pregnancy may protect against rejection episodes.[5] Ciclosporin should be used at the lowest possible dose to maintain efficacy, and one review[3] has recommended that the daily dose should be kept below 5 mg/kg.

One case of osseous malformation, resulting in hypoplasia of the right leg has been reported in an infant born to a ciclosporin-treated mother.[6]

1. Armenti VT, *et al.* Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1995; **59:** 476–9.
2. Armenti VT, *et al.* National Transplantation Pregnancy Registry (NTPR): cyclosporine dosing and pregnancy outcome in female renal transplant recipients. *Transplant Proc* 1996; **28:** 2111–12.
3. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimize fetal risks in organ transplant patients. *Ann Pharmacother* 1994; **28:** 1355–6.
4. Lamarque V, *et al.* Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. *Transplant Proc* 1997; **29:** 2480.
5. Thomas AG, *et al.* The effect of pregnancy on cyclosporine levels in renal allograft patients. *Obstet Gynecol* 1997; **90:** 916–19.
6. Pujals JM, *et al.* Osseous malformation in baby born to woman on cyclosporin. *Lancet* 1989; **i:** 667.

Interactions

Ciclosporin is extensively metabolised in the liver and plasma-ciclosporin concentrations may be affected by inducers or competitive inhibitors of hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. For example, use of carbamazepine, nevirapine, phenytoin, phenobarbital, rifampicin, St John's wort, and other inducers of hepatic enzymes may lead to lower plasma concentrations of ciclosporin, and increased plasma concentrations have been reported with some antifungals, macrolide antibacterials, HIV-protease inhibitors, the NNRTI delavirdine, some calcium-channel blockers, sex hormones, corticosteroids and grapefruit juice. In transplant patients frequent measurement of plasma ciclosporin and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of other drugs.

Concurrent use of statins may increase the risk of myopathy and rhabdomyolysis. Potassium-sparing diuretics should be avoided because of the risk of hyperkalaemia, and patients taking ciclosporin should avoid a high dietary intake of potassium. The risk of gingival hyperplasia may be increased by amlodipine or nifedipine.

During treatment with ciclosporin, vaccination may be less effective, and the use of live vaccines should generally be avoided.

Care should be taken when ciclosporin is given with other nephrotoxic drugs.

◊ Reviews of the interactions of ciclosporin.

1. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin. *Clin Pharmacokinet* 1990; **19:** 319–32 and 400–15.
2. Lake KD, Canafax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother* 1995; **36** (suppl B): 11–22.
3. Campana C, *et al.* Clinically significant drug interactions with cyclosporin: an update. *Clin Pharmacokinet* 1996; **30:** 141–79.
4. Chan L-N. Drug-nutrient interactions in transplant recipients. *J Parenter Enteral Nutr* 2001; **25:** 132–41.

Antibacterials. ***AMINOGLYCOSIDES.*** Increased nephrotoxicity has been reported after the use of aminoglycosides with ciclosporin.[1,2] However, a retrospective analysis in 21 patients given ciclosporin for allogeneic bone marrow transplant, in whom aminoglycosides were used if fever and neutropenia developed, showed no greater incidence of nephrotoxicity than in 20 autologous bone marrow recipients who did not receive ciclosporin, suggesting that these drugs can be given together provided careful monitoring is maintained.[3]

1. Termeer A, *et al.* Severe nephrotoxicity cause by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation* 1986; **42:** 220–1.
2. Morales JM, *et al.* Reversible acute renal toxicity by toxic sinergic effect between gentamicin and cyclosporine. *Clin Nephrol* 1988; **29:** 272.
3. Chandrasekar PH, Cronin SM. Nephrotoxicity in bone marrow transplant recipients receiving aminoglycoside plus cyclosporine or aminoglycoside alone. *J Antimicrob Chemother* 1991; **27:** 845–9.

CHLORAMPHENICOL. Marked rises in plasma-ciclosporin concentrations have been reported when chloramphenicol was given.[1-3] Ciclosporin trough concentrations should be monitored if these drugs are used together.[3]

1. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant recipient. *Med J Aust* 1994; **161:** 455.
2. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. *Ann Pharmacother* 1999; **33:** 252–3.
3. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.

MACROLIDES. Markedly raised blood concentrations of ciclosporin have been reported in patients also given *erythromycin*.[1-4] The mechanism involved appears to be a combination of decreased hepatic metabolism of ciclosporin and increased gastrointestinal absorption.[5] Similar elevations of ciclosporin concentrations have been noted after use with other macrolide antibacterials, including *clarithromycin*,[6-8] *josamycin*,[9,10] *midecamycin*,[11] *midecamycin acetate*,[12] and the structurally-related streptogramins, *pristinamycin*[13] and *quinupristin/dalfopristin*.[14] Small increases in ciclosporin concentrations have been seen with *roxithromycin*.[15] Increases in ciclosporin concentrations were attributed to *azithromycin* in 2 patients,[16,17] but a study in 6 patients found no effect.[18] *Spiramycin* does not appear to affect the pharmacokinetics of ciclosporin.[19,20]

1. Ptachcinski RJ, *et al.* Effect of erythromycin on cyclosporine levels. *N Engl J Med* 1985; **313:** 1416–17.
2. Martell R, *et al.* The effects of erythromycin in patients treated with cyclosporine. *Ann Intern Med* 1986; **104:** 660–1.
3. Wadhwa NK, *et al.* Interaction between erythromycin and cyclosporine in a kidney and pancreas allograft recipient. *Ther Drug Monit* 1987; **9:** 123–5.
4. Gupta SK, *et al.* Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; **27:** 475–81.
5. Ignoffo RJ, Kim LE. Erythromycin and cyclosporine drug interaction. *DICP Ann Pharmacother* 1991; **25:** 30–1.
6. Ferrari SL, *et al.* The interaction between clarithromycin and cyclosporine in kidney transplant recipients. *Transplantation* 1994; **58:** 725–7.
7. Treille S, *et al.* Kidney graft dysfunction after drug interaction between clarithromycin and cyclosporin. *Nephrol Dial Transplant* 1996; **11:** 1192–3.
8. Sádaba B, *et al.* Concurrent clarithromycin and cyclosporin A treatment. *J Antimicrob Chemother* 1998; **42:** 393–5.
9. Kreft-Jais C, *et al.* Effect of josamycin on plasma cyclosporine levels. *Eur J Clin Pharmacol* 1987; **32:** 327–8.
10. Azanza JR, *et al.* Possible interaction between cyclosporine and josamycin: a description of three cases. *Clin Pharmacol Ther* 1992; **51:** 572–5.
11. Alfonso I, *et al.* Interaction between cyclosporine A and midecamycin. *Eur J Clin Pharmacol* 1997; **52:** 79–80.
12. Couet W, *et al.* Effect of ponsinomycin on cyclosporin pharmacokinetics. *Eur J Clin Pharmacol* 1990; **39:** 165–7.
13. Garraffo R, *et al.* Pristinamycin increases cyclosporin blood levels. *Med Sci Res* 1987; **15:** 461.
14. Stamatakis MK, Richards JG. Interaction between quinupristin/dalfopristin and cyclosporine. *Ann Pharmacother* 1997; **31:** 576–8.
15. Billaud EM, *et al.* Interaction between roxithromycin and cyclosporin in heart transplant patients. *Clin Pharmacokinet* 1990; **19:** 499–502.
16. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron* 1995; **70:** 130.
17. Page RL, *et al.* Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 2001; **21:** 1436–43.
18. Gomez E, *et al.* Interaction between azithromycin and cyclosporin? *Nephron* 1996; **73:** 724.
19. Vernillet L, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1989; **27:** 789–94.
20. Kessler M, *et al.* Lack of effect of spiramycin on cyclosporin pharmacokinetics. *Br J Clin Pharmacol* 1990; **29:** 370–1.

PENICILLINS. Decreased plasma-ciclosporin concentrations and effect were seen in a patient given *nafcillin*.[1] Conversely, another study reported increased nephrotoxicity from the use of ciclosporin with nafcillin but no apparent increase in ciclosporin concentrations.[2]

1. Veremis SA, *et al.* Subtherapeutic cyclosporine concentrations during nafcillin therapy. *Transplantation* 1987; **43:** 913–15.
2. Jahansouz F, *et al.* Potentiation of cyclosporine nephrotoxicity by nafcillin in lung transplant recipients. *Transplantation* 1993; **55:** 1045–8.

QUINOLONES. A number of reports have indicated that the quinolone *ciprofloxacin* has no effect on the pharmacokinetics of ciclosporin.[1-3] However, there is a report of enhanced nephrotoxicity without a change in ciclosporin concentrations in a patient given ciprofloxacin,[4] and another report showing both enhanced nephrotoxicity and increased ciclosporin concentrations.[5] Furthermore, a small case-control study suggested an increase in transplant rejection with ciprofloxacin.[6] *Norfloxacin* has been reported to decrease clearance and increase blood concentrations of ciclosporin in paediatric patients,[7] probably by inhibition of ciclosporin metabolism. *Levofloxacin* did not alter ciclosporin pharmacokinetics in healthy subjects,[8] but a study in renal transplant patients found that levofloxacin partially inhibited the metabolism of ciclosporin;[9] no adverse effects and no supratherapeutic concentrations of ciclosporin were seen.

1. Hooper TL, *et al.* Ciprofloxacin: a preferred treatment for legionella infections in patients receiving cyclosporin A. *J Antimicrob Chemother* 1988; **22:** 952–3.
2. Tan KKC, *et al.* Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; **28:** 185–7.
3. Krüger HU, *et al.* Investigation of potential interaction of ciprofloxacin with cyclosporine in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1990; **34:** 1048–52.
4. Elston RA, Taylor J. Possible interaction of ciprofloxacin with cyclosporin A. *J Antimicrob Chemother* 1988; **21:** 679–80.
5. Nasir M, *et al.* Interaction between ciclosporin and ciprofloxacin. *Nephron* 1991; **57:** 245–6.
6. Wrishko RE, *et al.* Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; **64:** 996–9.
7. McLellan RA, *et al.* Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation. *Clin Pharmacol Ther* 1995; **58:** 322–7.
8. Doose DR, *et al.* Levofloxacin does not alter cyclosporine disposition. *J Clin Pharmacol* 1998; **38:** 90–93.
9. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45:** 169–75.

RIFAMYCINS. Use with *rifampicin* has been associated with marked decreases in blood-ciclosporin concentrations,[1-5] and has resulted in graft rejection.[1,3] Although it has been assumed that this effect represents induction of the hepatic metabolism of ciclosporin by rifampicin, there is some suggestion that rifampicin may decrease the absorption of ciclosporin or induce intestinal metabolism, resulting in reduced bioavailability.[6] Topical application of *rifamycin* has also been associated with a decrease in blood-ciclosporin concentrations in another patient;[7] ciclosporin concentrations rose immediately after withdrawal of rifamycin, suggesting that the effect was not due to enzyme induction.

1. Langhoff E, Madsen S. Rapid metabolism of cyclosporin and prednisone in kidney transplant patient receiving tuberculostatic treatment. *Lancet* 1983; **ii:** 1031.
2. Daniels NJ, *et al.* Interaction between cyclosporin and rifampicin. *Lancet* 1984; **ii:** 639.
3. Allen RDM, *et al.* Cyclosporin and rifampicin in renal transplantation. *Lancet* 1985; **i:** 980.
4. Freitag VL, *et al.* Effect of short-term rifampin on stable cyclosporine concentrations. *Ann Pharmacother* 1999; **33:** 871–2.
5. Zelunka EJ. Intravenous cyclosporine-rifampin interaction in a pediatric bone marrow transplant recipient. *Pharmacotherapy* 2002; **22:** 387–90.

6. Hebert MF, *et al.* Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. *Clin Pharmacol Ther* 1992; **52:** 453–7.
7. Renoult E, *et al.* Effect of topical rifamycin SV treatment on cyclosporin A blood levels in a renal transplant recipient. *Eur J Clin Pharmacol* 1991; **40:** 433–4.

STREPTOGRAMINS. Increased plasma concentrations of ciclosporin have occurred after therapy with *pristinamycin* and *quinupristin/dalfopristin* (see Macrolides, above).

SULFONAMIDES. Intravenous, but not oral, therapy with *sulfadimidine* and *trimethoprim* has been associated with falls in ciclosporin concentrations to subtherapeutic values.[1,2] Oral *sulfadiazine* has had a similar effect.[3] Conversely, *trimethoprim* and *co-trimoxazole* can cause rises in serum creatinine, and therefore may contribute to ciclosporin-induced nephrotoxicity.[4,5]

1. Wallwork J, *et al.* Cyclosporin and intravenous sulphadimidine and trimethoprim therapy. *Lancet* 1983; **i:** 366–7.
2. Jones DK, *et al.* Serious interaction between cyclosporin A and sulphadimidine. *BMJ* 1986; **292:** 728–9.
3. Spes CH, *et al.* Sulfadiazine therapy for toxoplasmosis in heart transplant recipients decreases cyclosporine concentration. *Clin Investig* 1992; **70:** 752–4.
4. Thompson JF, *et al.* Nephrotoxicity of trimethoprim and cotrimoxazole in renal allograft recipients treated with cyclosporine. *Transplantation* 1983; **36:** 204–6.
5. Ringden O, *et al.* Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. *Lancet* 1984; **i:** 1016.

Antidepressants. Giving *fluoxetine* to a patient receiving ciclosporin as part of an immunosuppressant regimen after cardiac transplantation was associated with a subsequent marked increase in ciclosporin trough blood concentrations to about twice their original value, necessitating a reduction in ciclosporin dosage.[1] After withdrawal of fluoxetine, ciclosporin concentrations fell, and dosage had to be increased. However, a study in 13 other patients given ciclosporin with fluoxetine failed to find any evidence of altered ciclosporin concentrations.[2] A nearly tenfold increase in ciclosporin concentration was seen in a cardiac transplant patient after use of *nefazodone*,[3] and there are 2 case reports[4] of ciclosporin toxicity due to interactions with nefazodone and *fluvoxamine* in renal transplant recipients. Ciclosporin concentrations decreased in a 10-year-old African American heart transplant recipient 22 days after starting *bupropion*. Despite an increase in ciclosporin dosage, ciclosporin concentrations decreased even further, necessitating another increase in ciclosporin dose, and withdrawal of bupropion.[5]

1. Horton RC, Bonser RS. Interaction between cyclosporin and fluoxetine. *BMJ* 1995; **311:** 422.
2. Strouse TB, *et al.* Fluoxetine and cyclosporine in organ transplantation: failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* 1996; **37:** 23–30.
3. Wright DH, *et al.* Nefazodone and cyclosporine drug-drug interaction. *J Heart Lung Transplant* 1999; **18:** 913–15.
4. Vella JP, Sayegh MH. Interactions between cyclosporine and newer antidepressant medications. *Am J Kidney Dis* 1998; **31:** 320–3.
5. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

ST JOHN'S WORT. Ciclosporin plasma levels are reduced by St John's wort.[1] This has lead to acute rejection episodes in transplant patients,[2] and the two drugs should not be used together.[3]

1. Bauer S, *et al.* Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003; **55:** 203–11.
2. Ernst E. St John's wort supplements endanger the success of organ transplantation. *Arch Surg* 2002; **137:** 316–19.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)

Antiepileptics. Use with the antiepileptics *carbamazepine*,[1-3] *phenobarbital*,[4] and *phenytoin*,[5] which are all inducers of hepatic cytochrome P450, has been associated with a reduction in blood-ciclosporin concentrations. *Oxcarbazepine* also decreased ciclosporin trough concentrations in a kidney transplant recipient with epilepsy; concentrations were corrected by an increase in ciclosporin dose. The dose of oxcarbazepine also had to be reduced due to hyponatraemia, and ciclosporin concentrations remained stable thereafter.[6] *Valproate* has been successfully used in ciclosporin-treated patients without apparent interaction.[1,2]

1. Hillebrand G, *et al.* Valproate for epilepsy in renal transplant recipients receiving cyclosporine. *Transplantation* 1987; **43:** 915–16.
2. Schofield OMV, *et al.* Cyclosporin A in psoriasis: interaction with carbamazepine. *Br J Dermatol* 1990; **122:** 425–6.
3. Cooney GF, *et al.* Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients. *Pharmacotherapy* 1995; **15:** 353–6.
4. Carstensen H, *et al.* Interaction between cyclosporin A and phenobarbitone. *Br J Clin Pharmacol* 1986; **21:** 550–1.
5. Freeman DJ, *et al.* Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites. *Br J Clin Pharmacol* 1984; **18:** 887–93.
6. Rösche J, *et al.* Possible oxcarbazepine interaction with cyclosporine serum levels: a single case study. *Clin Neuropharmacol* 2001; **24:** 113–16.

Antifungals. The imidazole *ketoconazole* is a potent inhibitor of hepatic cytochrome P450 and markedly increased blood-ciclosporin concentrations have resulted when conventional formulations of the latter were given with the antifungal.[1-4] The interaction has been used, similarly to the calcium-channel blockers (see below), to permit therapeutic blood concentrations of ciclosporin to be achieved at lower doses;[5-8] however, this method may result in considerable variations in ciclosporin pharmacokinetics, and has been criticised on several grounds.[9] It was noted[10] that this improved bioavailability of ciclosporin was not seen when the microemulsifying formulation (see Absorption under Pharmacokinetics, below) was given with ketoconazole, suggesting that bioavailability was already maximal. Increased ciclosporin concentrations have also been reported with *itraconazole*,[11,12] and it has also been suggested[13] that use be made of this interaction, similarly to ketoconazole, to allow for decreased ciclosporin doses. *Voriconazole* also increases exposure to ciclosporin, and ciclosporin concentrations should be closely monitored.[14,15] There is a single report of increased ciclosporin plasma concentrations with use of *miconazole*.[16] However, although such an interaction has also been reported with *fluconazole*,[17,18] a small study has failed to note any significant interaction;[19,20] it has been suggested that an interaction may take place only at high doses of fluconazole,[21] or that sex and ethnicity may play a role.[18]

Increased nephrotoxicity may occur if ciclosporin is used with *amphotericin B*,[22,23] while liposomal amphotericin B has been reported possibly to exacerbate ciclosporin neurotoxicity.[24] There is a report of decreased ciclosporin concentrations in a patient after addition of *griseofulvin* to therapy.[25] Modest decreases have also been seen in ciclosporin concentrations when *terbinafine* was given.[26] *Micafungin* modestly inhibits ciclosporin metabolism; however, in a minority of patients it may cause a significant increase in ciclosporin concentrations.[27]

1. Ferguson RM, *et al.* Ketoconazole, cyclosporin metabolism, and renal transplantation. *Lancet* 1982; **ii:** 882–3.
2. Dieperink H, Møller J. Ketoconazole and cyclosporin. *Lancet* 1982; **ii:** 1217.
3. Shepard JH, *et al.* Cyclosporine-ketoconazole: a potentially dangerous drug-drug interaction. *Clin Pharm* 1986; **5:** 468.
4. Gomez DY, *et al.* The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 15–19.
5. First MR, *et al.* Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989; **ii:** 1198–1201.
6. Keogh A, *et al.* Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995; **333:** 628–33.
7. El-Husseini A, *et al.* Concomitant administration of cyclosporine and ketoconazole in idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2004; **19:** 2266–71.
8. El-Husseini A, *et al.* Co-administration of cyclosporine and ketoconazole in idiopathic childhood nephrosis. *Pediatr Nephrol* 2004; **19:** 976–81.
9. Frey FJ. Concomitant cyclosporin and ketoconazole. *Lancet* 1990; **335:** 109–10.
10. Akhlaghi F, *et al.* Pharmacokinetics of cyclosporine in heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2001; **20:** 431–8.
11. Kramer MR, *et al.* Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med* 1990; **113:** 327–9.
12. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12:** 325–34.
13. Florea NR, *et al.* Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. *Transplant Proc* 2003; **35:** 2873–7.
14. Romero AJ, *et al.* Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. *Clin Pharmacol Ther* 2002; **71:** 226–34.
15. Groll AH, *et al.* Pharmacokinetic interaction between voriconazole and ciclosporin A following allogeneic bone marrow transplantation. *J Antimicrob Chemother* 2004; **53:** 113–14.
16. Horton CM, *et al.* Cyclosporine interactions with miconazole and other azole-antimycotics: a case report and review of the literature. *J Heart Lung Transplant* 1992; **11:** 1127–32.
17. Collignon P, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **i:** 1262.
18. Mathis AS, *et al.* Sex and ethnicity may chiefly influence the interaction of fluconazole with calcineurin inhibitors. *Transplantation* 2001; **71:** 1069–75.
19. Krüger HU, *et al.* Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; **24:** 781–6.
20. Ehninger G, *et al.* Interaction of fluconazole with cyclosporin. *Lancet* 1989; **ii:** 104–5.
21. López-Gil JA. Fluconazole-cyclosporine interaction: a dose-dependent effect? *Ann Pharmacother* 1993; **27:** 427–30.
22. Kennedy MS, *et al.* Acute renal toxicity with combined use of amphotericin B and cyclosporine after marrow transplantation. *Transplantation* 1983; **35:** 211–15.
23. Furrer K, *et al.* Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogenic stem cell transplantation. *Swiss Med Wkly* 2002; **132:** 316–20.
24. Ellis ME, *et al.* Is cyclosporin neurotoxicity enhanced in the presence of liposomal amphotericin B? *J Infect* 1994; **29:** 106–7.
25. Abu-Romeh SH, *et al.* Ciclosporin A and griseofulvin: another drug interaction. *Nephron* 1991; **58:** 237.
26. Lo ACY, *et al.* The interaction of terbinafine and cyclosporine A in renal transplant patients. *Br J Clin Pharmacol* 1997; **43:** 340–1.
27. Hebert MF, *et al.* Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 954–60.

Antigout drugs. A patient who had been receiving maintenance doses of ciclosporin for some years, with consistent whole-blood trough concentrations of around 130 nanograms/mL at doses of 175 mg twice daily had a rise in ciclosporin concentrations to 410 nanograms/mL after 2 months of treatment with *allopurinol* 200 mg daily.[1] Ciclosporin concentrations returned to their previous levels over several weeks after stopping allopurinol, and rose again on rechallenge. Dosage of ciclosporin was then reduced. For a report of a low dose of allopurinol being added to a ciclosporin-containing immunosuppressive regimen, see Organ and Tissue Transplantation, p.554.

UK licensed product information states that *colchicine* may increase ciclosporin concentrations.

In a report of 120 heart transplant recipients with hyperuricaemia, *sulfinpyrazone* reduced ciclosporin concentrations, and 2 patients needed treatment for acute rejection.[2]

1. Gorrie M, *et al.* Allopurinol interaction with cyclosporin. *BMJ* 1994; **308:** 113.
2. Caforio ALP, *et al.* Sulfinpyrazone reduces cyclosporine levels: a new drug interaction in heart transplant recipients. *J Heart Lung Transplant* 2000; **19:** 1205–8.

Antimalarials. A large rise in serum-ciclosporin concentration was seen on 2 occasions in a renal graft recipient when *chloroquine* was added to his medication for malaria prophylaxis.[1] *Quinine* has been reported to reduce ciclosporin concentrations.[2]

1. Finielz P, *et al.* Interaction between cyclosporin and chloroquine. *Nephron* 1993; **65:** 333.
2. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J* 1991; **32:** 189–90.

Antineoplastics. Elevated plasma-ciclosporin concentrations and an increased incidence of nephrotoxic effects and hypertension have been reported in patients receiving ciclosporin for psoriasis who had been previously,[1] or concurrently,[2] treated with *methotrexate*. Conversely, methotrexate has been used effectively with reduced-dose ciclosporin in graft-versus-host disease.[3] Severe renal failure has been reported when standard oral doses of ciclosporin were given after high-dose intravenous *melphalan* (used as a bone marrow conditioning agent before allogeneic bone marrow transplantation).[4] A retrospective analysis of allogeneic haematopoietic stem cell transplant patients taking ciclosporin found that, in those given a conditioning regimen containing *cyclophosphamide*, mean serum-ciclosporin concentrations were reduced; no effect on the incidence of graft-versus-host disease could be established.[5]

UK licensed product information states that *imatinib* may increase ciclosporin concentrations.

Ciclosporin increases plasma-*doxorubicin* concentrations and toxicity (see p.714), and has been used to increase oral absorption of *paclitaxel* (see p.760). For the effects of ciclosporin on the pharmacokinetics of *teniposide* and *etoposide*, see p.778 and p.719, respectively.

Ciclosporin and its analogues have been given with antineoplastics for their ability to inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, thus resulting in raised intracellular concentrations of the other drug.

1. Powles AV, *et al.* Cyclosporin toxicity. *Lancet* 1990; **i:** 610.
2. Korstanje MJ, *et al.* Cyclosporine and methotrexate: a dangerous combination. *J Am Acad Dermatol* 1990; **23:** 320–1.
3. Stockschlaeder M, *et al.* A pilot study of low-dose cyclosporin for graft-versus-host prophylaxis in marrow transplantation. *Br J Haematol* 1992; **80:** 49–54.
4. Morgenstern GR, *et al.* Cyclosporin interaction with ketoconazole and melphalan. *Lancet* 1982; **ii:** 1342.
5. Nagamura F, *et al.* Effect of cyclophosphamide on serum cyclosporine levels at the conditioning of hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **32:** 1051–8.

Antiobesity drugs. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported[1-3] in transplant recipients given *orlistat*. It was postulated[2] that the interaction was a result of reduced absorption of ciclosporin in the presence of orlistat and that at least 2 hours should elapse between doses of these two drugs. However, despite this dosing interval, there has been a further report[3] of subtherapeutic plasma levels of ciclosporin. The patient had had severe diarrhoea, and the subsequent decreased absorption of fats was thought to have decreased the absorption of ciclosporin.

An increase in ciclosporin trough concentrations occurred when a renal transplant patient was given *sibutramine*;[4] both drugs are metabolised by cytochrome P450 isoenzyme 3A4.

1. Nägele H, *et al.* Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. *Eur J Clin Pharmacol* 1999; **55:** 667–9.
2. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med* 2000; **342:** 1141–2.
3. Barbaro D, *et al.* Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. *Endocr Pract* 2002; **8:** 124–6.
4. Clerbaux G, *et al.* Interaction between sibutramine and cyclosporine. *Am J Transplant* 2003; **3:** 906.

Antivirals. For a report of mutual elevations in the area under the plasma concentration-time curves for ciclosporin and the HIV-protease inhibitor *saquinavir*, see Indinavir, p.883.

Bifendate. In 2 patients given maintenance doses of ciclosporin, trough whole-blood concentrations decreased from 97.7 nanograms/mL to 49.0 nanograms/mL and from 127.5 nanograms/mL to 45.0 nanograms/mL respectively when bifendate was given. Ciclosporin concentrations returned to pretreatment levels over several weeks once bifendate was stopped.[1]

1. Kim YS, *et al.* The effect of diphenyl-dimethyl-dicarboxylate on cyclosporine-A blood level in kidney transplants with chronic hepatitis. *Korean J Intern Med* 1997; **12:** 67–9.

Cardiovascular drugs. *ACE INHIBITORS.* There may be an increased risk of hyperkalaemia when ACE inhibitors are used with ciclosporin. Acute renal failure, associated with use of *enalapril*, has been reported in 2 patients given ciclosporin after renal transplantation.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

ANTIARRHYTHMICS. Marked rises in serum-ciclosporin concentrations despite reductions in dose have been noted in recipients of organ transplants after treatment with *amiodarone*.[1-3] A rise in serum ciclosporin has similarly been seen in a patient given both ciclosporin and *propafenone*.[4]

1. Mamprin F, *et al.* Amiodarone-cyclosporine interaction in cardiac transplantation. *Am Heart J* 1992; **123:** 1725–6.
2. Egami J, *et al.* Increase in cyclosporine levels due to amiodarone therapy after heart and heart-lung transplantation. *J Am Coll Cardiol* 1993; **21:** 141A.
3. Chitwood KK, *et al.* Cyclosporine-amiodarone interaction. *Ann Pharmacother* 1993; **27:** 569–71.
4. Spes CH, *et al.* Ciclosporin-propafenone interaction. *Klin Wochenschr* 1990; **68:** 872.

ANTICOAGULANTS. Treatment with *warfarin* for deep-vein thrombosis in a patient maintained on ciclosporin for pure red cell aplasia resulted in a relapse of the latter and a significant fall in ciclosporin blood concentrations.[1] Increase in the ciclosporin dose restored control of the aplasia but resulted in a marked increase in prothrombin activity requiring an increase in warfarin dosage. The results suggest that each drug interferes with the activity of the other. The influence of the patient's other medications (including phenobarbital and folic acid), if any, is unknown, although it has been suggested[2,3] that the phenobarbital had enhanced the metabolism of both drugs. In another report,[2] a patient on long-term warfarin for deep-vein thrombosis was started on ciclosporin for lymphoma relapse, and subsequently required larger doses of warfarin. During use of *acenocoumarol* with ciclosporin, the dose of ciclosporin had to be increased[3] in one patient and both drugs decreased[4] in another. It appears that the interaction between ciclosporin and anticoagulants is unpredictable[3] and dependent on the anticoagulant used.[2]

1. Snyder DS. Interaction between cyclosporine and warfarin. *Ann Intern Med* 1988; **108:** 311.
2. Turri D, *et al.* Oral anticoagulants and cyclosporin A. *Haematologica* 2000; **85:** 893–4.
3. Borrás-Blasco J, *et al.* Interaction between cyclosporine and acenocoumarol in a patient with nephrotic syndrome. *Clin Nephrol* 2001; **55:** 338–40.
4. Campistol JM, *et al.* Interaction between ciclosporin A and Sintrom. *Nephron* 1989; **53:** 291–2.

ANTIPLATELET DRUGS. *Ticlopidine* decreased serum-ciclosporin concentrations in isolated cases,[1-3] but a study in 20 heart transplant patients failed to show any interaction between ciclosporin and low-dose ticlopidine.[4] For reports of rhabdomyolysis occurring in patients stabilised on ciclosporin and a statin when *clopidogrel* was added to their treatment, see p.1250.

1. Birmelé B, *et al.* Interaction of cyclosporin and ticlopidine. *Nephrol Dial Transplant* 1991; **6:** 150–1.
2. Verdejo A, *et al.* Probable interaction between cyclosporin A and low dose ticlopidine. *BMJ* 2000; **320:** 1037.
3. Feriozzi S, *et al.* Treatment with ticlopidine is associated with reduction of cyclosporin A blood levels. *Nephron* 2002; **92:** 249–50.
4. Boissonnat P, *et al.* A drug interaction study between ticlopidine and cyclosporin in heart transplant recipients. *Eur J Clin Pharmacol* 1997; **53:** 39–45.

BETA BLOCKERS. Ciclosporin plasma concentrations increased when *carvedilol* was added to treatment regimens of renal[1] and cardiac[2] transplant patients. Considerable interindividual variation was seen in one study,[1] so it is recommended that ciclosporin concentrations should be monitored carefully if the drugs are used together.

1. Kaijser M, *et al.* Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients. *Clin Transplant* 1997; **11:** 577–81.
2. Bader FM, *et al.* The effect of β-blocker use on cyclosporine level in cardiac transplant recipients. *J Heart Lung Transplant* 2005; **24:** 2144–7.

BOSENTAN. There is a complex interaction between ciclosporin and bosentan. If the drugs are given together reduced ciclosporin concentrations and increased bosentan concentrations may occur; further details are given on p.1235.

CALCIUM-CHANNEL BLOCKERS. The calcium-channel blockers *diltiazem*,[1-3] *lercanidipine*, *nicardipine*,[4,5] and *verapamil*[6,7] have all been associated with increases in ciclosporin blood concentrations. It has been suggested that such an interaction can be used to obtain effective ciclosporin concentrations with lower doses.[8] In addition, there is some evidence of mitigation of ciclosporin-induced nephrotoxicity when calcium-channel blockers are given (see Effects on the Kidneys, above), and they are useful for ciclosporin-induced hypertension (see Effects on the Cardiovascular System, above). However, some caution is required: one report has pointed out that diltiazem does not increase ciclosporin concentrations in all cases,[9] while others have found that use together alters the pattern of ciclosporin metabolites, and that pharmacokinetic changes are greater in female than in male patients.[10] Therefore, some prefer a calcium-channel blocker that does not alter ciclosporin pharmacokinetics for hypertension and renal protection. *Nifedipine* has not been shown to increase blood-ciclosporin concentrations.[6] For a report of increased nifedipine toxicity with ciclosporin see Immunosuppressants, p.1353. Other calcium-channel blockers that do not appear to affect ciclosporin pharmacokinetics include *felodipine*[7,11] and *isradipine*.[7,12] Ciclosporin concentrations have been reported to increase or to remain unchanged with *amlodipine*.[13] Use of amlodipine or nifedipine with ciclosporin may exacerbate the problem of gingival hyperplasia—see Hyperplasia under Adverse Effects, above.

1. Brockmöller J, *et al.* Pharmacokinetic interaction between cyclosporin and diltiazem. *Eur J Clin Pharmacol* 1990; **38:** 237–42.
2. Bourge RC, *et al.* Diltiazem-cyclosporine interaction in cardiac transplant recipients: impact on cyclosporine dose and medication costs. *Am J Med* 1991; **90:** 402–4.
3. Åsberg A, *et al.* Pharmacokinetic interactions between microemulsion formulated cyclosporine A and diltiazem in renal transplant recipients. *Eur J Clin Pharmacol* 1999; **55:** 383–7.
4. Todd P, *et al.* Nicardipine interacts with cyclosporin. *Br J Dermatol* 1989; **121:** 820.
5. Kessler M, *et al.* Influence of nicardipine on renal function and plasma cyclosporin in renal transplant patients. *Eur J Clin Pharmacol* 1989; **36:** 637–8.
6. Tortorice KL, *et al.* The effects of calcium channel blockers on cyclosporine and its metabolites in renal transplant patients. *Ther Drug Monit* 1990; **12:** 321–8.
7. Yildiz A, *et al.* Interaction between cyclosporine A and verapamil, felodipine, and isradipine. *Nephron* 1999; **81:** 117–18.
8. Sketris IS, *et al.* Effect of calcium-channel blockers on cyclosporine clearance and use in renal transplant patients. *Ann Pharmacother* 1994; **28:** 1227–31.
9. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996; **42:** 642–4.
10. Bleck JS, *et al.* Diltiazem increases blood concentrations of cyclized cyclosporine metabolites resulting in different cyclosporine metabolite patterns in stable male and female renal allograft recipients. *Br J Clin Pharmacol* 1996; **41:** 551–6.
11. Cohen DJ, *et al.* Influence of oral felodipine on serum cyclosporine concentrations. *Clin Transplant* 1994; **8:** 541–5.
12. Endresen L, *et al.* Lack of effect of the calcium antagonist isradipine on cyclosporine pharmacokinetics in renal transplant patients. *Ther Drug Monit* 1991; **13:** 490–5.
13. Schrama YC, Koomans HA. Interactions of cyclosporin A and amlodipine: blood cyclosporin A levels, hypertension and kidney function. *J Hypertens* 1998; **16** (suppl): S33–S38.

CARDIAC GLYCOSIDES. For reference to the effect of ciclosporin on serum-digoxin concentrations, see under Digoxin, p.1262.

CLONIDINE. Addition of clonidine to the regimen of a 3-year-old child who had developed hypertension after a renal transplant resulted in a marked increase in whole blood ciclosporin concentrations, despite a reduction in ciclosporin dose.[1] Ciclosporin concentrations fell rapidly on withdrawal of clonidine.

1. Gilbert RD, *et al.* Interaction between clonidine and cyclosporine A. *Nephron* 1995; **71:** 105.

DIURETICS. Enhanced nephrotoxicity, without apparent change in ciclosporin blood concentrations, has been seen in individual patients after addition of *metolazone*[1] or *amiloride* with *chlorothiazide*[2] to their regimen. Severe nephrotoxicity, resulting in loss of graft function, has been seen in a renal transplant patient given *mannitol* with ciclosporin;[3] graft function recovered on withdrawal of the diuretic.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.
2. Deray G, *et al.* Enhancement of cyclosporin nephrotoxicity by diuretic therapy. *Clin Nephrol* 1989; **32:** 47.
3. Brunner FP, *et al.* Mannitol potentiates cyclosporine nephrotoxicity. *Clin Nephrol* 1986; **25** (suppl 1): S130–6.

LIPID REGULATING DRUGS. A study in 10 renal transplant recipients indicated that use of ciclosporin with *probucol* markedly reduced the whole blood and plasma concentrations of the former in 9 of them, compared with use of ciclosporin alone.[1] *Bezafibrate* has been reported to increase blood concentrations of ciclosporin, with resultant nephrotoxicity.[2] However, other studies with bezafibrate have found a small decrease in ciclosporin concentrations,[3] or no effect,[4,5] despite an increase in serum creatinine in each study. Conflicting effects have also been reported with other fibrates: decreased[6] and unchanged[7] ciclosporin concentrations have occurred with *fenofibrate*, and both a decrease[8] and lack of effect[9] have also occurred with *gemfibrozil*.

In 1 study, *simvastatin* increased the unbound fraction of ciclosporin in the blood, resulting in a modest increase in apparent ciclosporin clearance.[10] In renal transplant recipients, *atorvastatin* increased ciclosporin blood concentrations in 4 out of 10 patients in one study[11] but was deemed to have minimal clinical effect in others.[12,13] Ciclosporin concentrations were unaffected by *cerivastatin*,[11,14] *fluvastatin*,[15] *lovastatin*,[16] and *pravastatin*.[16,17] A literature review concluded that the statins do not interact with ciclosporin to a clinically relevant degree. However, given the narrow therapeutic range of ciclosporin, the increase in systemic exposure to statins, and reports of rhabdomyolysis when used together, the authors advise that ciclosporin levels be monitored when starting statin therapy, and that lower doses of statins be used.[18] For the effects of ciclosporin on plasma levels of statins and reports of rhabdomyolysis, see Immunosuppressants, under Interactions of Simvastatin, p.1393.

1. Gallego C, *et al.* Interaction between probucol and cyclosporine in renal transplant patients. *Ann Pharmacother* 1994; **28:** 940–3.
2. Hirai M, *et al.* Elevated blood concentrations of cyclosporine and kidney failure after bezafibrate in renal graft recipient. *Ann Pharmacother* 1996; **30:** 883–4.
3. Barbir M, *et al.* Maxepa versus bezafibrate in hyperlipidemic cardiac transplant recipients. *Am J Cardiol* 1992; **70:** 1596–1601.
4. Lipkin GW, Tomson CRV. Severe reversible renal failure with bezafibrate. *Lancet* 1993; **341:** 371.
5. Jespersen B, Tvedegaard E. Bezafibrate induced reduction of renal function in a renal transplant recipient. *Nephrol Dial Transplant* 1995; **10:** 702–3.
6. Boissonnat P, *et al.* The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. *Transplantation* 1994; **58:** 245–7.
7. de Lorgeril M, *et al.* Pharmacokinetics of cyclosporine in hyperlipidaemic long-term survivors of heart transplantation: lack of interaction with the lipid-lowering agent, fenofibrate. *Eur J Clin Pharmacol* 1992; **43:** 161–5.
8. Fehrman-Ekholm I, *et al.* Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. *Nephron* 1996; **72:** 483.
9. Pisanti N, *et al.* Lack of effect of gemfibrozil on cyclosporine blood concentrations in kidney-transplanted patients. *Am J Nephrol* 1998; **18:** 199–203.
10. Akhlaghi F, *et al.* Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipients. *Br J Clin Pharmacol* 1997; **44:** 537–42.
11. Renders L, *et al.* Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant* 2001; **16:** 141–6.
12. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
13. Taylor PJ, *et al.* Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother* 2004; **38:** 205–8.
14. Mück W, *et al.* Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther* 1999; **65:** 251–61.
15. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; **62:** 1559–64.
16. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; **62:** 311–21.
17. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; **25:** 2732–4.
18. Åsberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; **63:** 367–78.

Colchicine. Use of ciclosporin with colchicine may result in myopathy or rhabdomyolysis—see Effects on Skeletal Muscle, under Adverse Effects, above. For reports of adverse effects and increased serum-ciclosporin concentrations when given with colchicine, see also p.556.

Corticosteroids. It has been suggested that use of ciclosporin with corticosteroids increases plasma concentrations of both drugs, but not all studies support this—see Immunosuppressants, p.1495.

Gastrointestinal drugs. Giving *cisapride*[1] or *metoclopramide*[2] to renal transplant recipients receiving ciclosporin has been reported to increase peak ciclosporin concentrations and increase the speed of absorption. *Cimetidine*,[3,4] *ranitidine*,[3] or *famotidine*,[4] do not appear to affect ciclosporin pharmacokinetics. A literature review[5] noted that although there are reports of cimetidine influencing peak concentrations of ciclosporin, there is no support for a pharmacokinetic interaction. A pharmacodynamic interaction between ciclosporin and histamine H_2-receptor antagonists, resulting in a potentiation of nephrotoxicity, is also unlikely.

1. Finet L, *et al.* Effects of cisapride on the intestinal absorption of cyclosporine in renal transplant recipients. *Gastroenterology* 1991; **100:** A209.
2. Wadhwa NK, *et al.* The effect of oral metoclopramide on the absorption of cyclosporine. *Transplant Proc* 1987; **19:** 1730–3.
3. Barri YM, *et al.* Cimetidine or ranitidine in renal transplant patients receiving cyclosporine. *Clin Transplant* 1996; **10:** 34–8.
4. Shaefer MS, *et al.* Evaluation of the pharmacokinetic interaction between cimetidine or famotidine and cyclosporine in healthy men. *Ann Pharmacother* 1995; **29:** 1088–91.
5. Lewis SM, McCloskey WW. Potentiation of nephrotoxicity by H -antagonists in patients receiving cyclosporine. *Ann Pharmacother* 1997; **31:** 363–5.

Grapefruit juice. Grapefruit juice increases the bioavailability of oral ciclosporin,[1-4] including the microemulsion formulation,[5] leading to marked increases in blood-ciclosporin concentrations; intravenous ciclosporin is unaffected. The effect appears to be due to inhibition of cytochrome P450 enzymes in the gut wall by substances present in grapefruit juice,[3] resulting in transiently reduced ciclosporin metabolism. Although it has been suggested that the effect might be used similarly to that of calcium-channel blockers or ketoconazole in reducing the required dose of ciclosporin,[2] others have pointed out that grapefruit juice is not standardised and its effects are variable.[6]

Pomelo juice has also reportedly increased ciclosporin bioavailability; pomelo is a citrus fruit closely related to grapefruit.[7]

1. Proppe DG, *et al.* Influence of chronic ingestion of grapefruit juice on steady-state blood concentrations of cyclosporine A in renal transplant patients with stable graft function. *Br J Clin Pharmacol* 1995; **39:** 337–8.
2. Yee GC, *et al.* Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **345:** 955–6.
3. Hollander AAMJ, *et al.* The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clin Pharmacol Ther* 1995; **57:** 318–24.
4. Ducharme MP, *et al.* Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. *Clin Pharmacol Ther* 1995; **57:** 485–91.
5. Ku Y-M, *et al.* Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *J Clin Pharmacol* 1998; **38:** 959–65.
6. Johnston A, Holt DW. Effect of grapefruit juice on blood cyclosporin concentration. *Lancet* 1995; **346:** 122–3.
7. Grenier J, *et al.* Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. *Clin Pharmacol Ther* 2006; **79:** 255–62.

Hypoglycaemic drugs. Use of *glibenclamide* with ciclosporin in 6 patients was associated with a mean 57% increase in the steady-state plasma concentration of ciclosporin, suggesting that dosage adjustment may be necessary when both drugs are given.[1]

Troglitazone decreased ciclosporin-blood concentrations by 32%, necessitating an increase in ciclosporin dosage.[2]

For the effect of ciclosporin on *repaglinide*, see under Interactions of Repaglinide, p.458.

1. Islam SI, *et al.* Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. *Ther Drug Monit* 1996; **18:** 624–6.
2. Burgess SJ, *et al.* Effect of troglitazone on cyclosporine whole blood levels. *Transplantation* 1998; **66:** 272–3.

Immunosuppressants. There has been a report of altered ciclosporin requirements in paediatric renal graft patients treated with *basiliximab*,[1] but others have failed to note such an effect,[2] and whether an interaction exists is unclear.

Treatment of acute rejection of kidney grafts in 10 patients using *muromonab-CD3* resulted in increases in mean trough ciclosporin concentrations, despite a reduction in ciclosporin dosage.[3] Once muromonab-CD3 was withdrawn the dosage of ciclosporin had to be increased again to provide adequate concentrations. In a retrospective study[4] of renal transplant recipients given ciclosporin and either muromonab-CD3 or antilymphocyte immunoglobulin, ciclosporin trough concentrations were found to be raised on day 5 postoperatively in the patients receiving muromonab-CD3. Although no differences were found in trough concentrations on days 7 and 10, the doses of ciclosporin had by then been adjusted based on the levels obtained on day 5.

For the effects of ciclosporin on the pharmacokinetics of *everolimus*, *mycophenolate mofetil*, and *sirolimus*, see p.1834, p.1837, and p.1841 respectively.

Tacrolimus inhibits ciclosporin metabolism *in vitro*[5] but did not alter the pharmacokinetics of intravenous ciclosporin in 7 liver transplant patients.[6] However, there is a possibility of increased nephrotoxicity when the drugs are used together, so licensed product information contraindicates such use.

1. Strehlau J, *et al.* Interleukin-2 receptor antibody-induced alterations of ciclosporin dose requirements in paediatric transplant recipients. *Lancet* 2000; **356:** 1327–8.
2. Vester U, *et al.* Basiliximab in paediatric liver-transplant recipients. *Lancet* 2001; **357:** 388–9.
3. Vrahnos D, *et al.* Cyclosporin levels during OKT3 treatment of acute renal allograft rejection. *Pharmacotherapy* 1991; **11:** 278.
4. Vasquez EM, Pollak R. OKT3 therapy increases cyclosporine blood levels. *Clin Transplant* 1997; **11:** 38–41.
5. Venkataramanan R, *et al.* Pharmacokinetics of FK 506 in transplant patients. *Transplant Proc* 1991; **23:** 2736–40.
6. Jain AB, *et al.* Pharmacokinetics of cyclosporine and nephrotoxicity in orthotopic liver transplant patients rescued with FK 506. *Transplant Proc* 1991; **23:** 2777–9.

Methoxsalen. In a pharmacokinetic study, a single oral dose of methoxsalen significantly increased the oral bioavailability of ciclosporin.[1]

1. Rheeders M, *et al.* Drug-drug interaction after single oral doses of the furanocoumarin methoxsalen and cyclosporine. *J Clin Pharmacol* 2006; **46:** 768–75.

Methylphenidate. Methylphenidate led to an increase in ciclosporin concentrations in a 10-year-old African American boy, necessitating reduction of the ciclosporin dose.[1] The patient had previously had to stop bupropion because of decreased ciclosporin concentrations.

1. Lewis BR, *et al.* Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol* 2001; **11:** 193–8.

NSAIDs. Raised serum-ciclosporin trough concentrations, together with small increases in serum creatinine and BUN concentrations, followed the use of *sulindac* in a previously-stabilised renal graft recipient taking an immunosuppressive regimen including ciclosporin.[1] Increased renal impairment was seen when sulindac or *naproxen* were added to ciclosporin therapy in patients with rheumatoid arthritis.[2] Nephrotoxicity, in the absence of significantly raised blood-ciclosporin concentrations, has been reported in other patients given *diclofenac* with ciclosporin.[3] Ciclosporin may also increase plasma-diclofenac concentrations, see p.45. In general, because of the known potential of NSAIDs to adversely affect renal function, careful monitoring of renal function is advised if these drugs are added to ciclosporin therapy or their dosages altered.

1. Sesin GP, *et al.* Sulindac-induced elevation of serum cyclosporine concentration. *Clin Pharm* 1989; **8:** 445–6.
2. Altman RD, *et al.* Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. *Am J Med* 1992; **93:** 396–402.
3. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.

Octreotide. A marked reduction in ciclosporin serum concentrations was seen in 10 diabetic patients with pancreatic transplants when octreotide was also given;[1] it was suggested that if these 2 drugs are used together the oral dosage of ciclosporin needs to be increased on average by 50%.

1. Landgraf R, *et al.* Effect of somatostatin analogue (SMS 201-995) on cyclosporine levels. *Transplantation* 1987; **44:** 724–5.

Quercetin. In a small study in healthy males, pre-treatment with the flavonoid quercetin significantly increased the peak concentration and bioavailability of ciclosporin.[1]

1. Choi JS, *et al.* Effect of quercetin on the pharmacokinetics of oral cyclosporine. *Am J Health-Syst Pharm* 2004; **61:** 2406–9.

Retinoids. After a report of increased whole-blood ciclosporin concentrations and nephrotoxicity in a patient given *etretinate* with ciclosporin, *in-vitro* results indicated that etretinate inhibited hepatic microsomal metabolism of ciclosporin, as did *acitretin* and *isotretinoin*.[1] However, a study failed to find evidence of such an interaction *in vitro*.[2]

1. Shah IA, *et al.* The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. *Br J Dermatol* 1993; **129:** 395–8.
2. Webber IR, Back DJ. Effect of etretinate on cyclosporin metabolism in vitro. *Br J Dermatol* 1993; **128:** 42–4.

Sex hormones. Raised ciclosporin concentrations in blood have been seen when therapy with *danazol*,[1] *methyltestosterone*,[2] or *norethisterone*[1] was given with ciclosporin, and clinical evidence of both nephrotoxicity[1,2] and hepatotoxicity[2] has been seen. Severe hepatotoxicity and raised plasma-ciclosporin trough values also resulted when an oral contraceptive containing *levonorgestrel* and *ethinylestradiol* was taken by a woman receiving ciclosporin;[3] she had taken the same contraceptive before beginning ciclosporin without ill-effects.

1. Ross WB, *et al.* Cyclosporin interaction with danazol and norethisterone. *Lancet* 1986; **i:** 330.
2. Møller BB, Ekelund B. Toxicity of cyclosporine during treatment with androgens. *N Engl J Med* 1985; **313:** 1416.
3. Deray G, *et al.* Oral contraceptive interaction with cyclosporin. *Lancet* 1987; **i:** 158.

Ursodeoxycholic acid. In a heart transplant patient with short bowel syndrome, ursodeoxycholic acid increased the trough concentrations of ciclosporin by enhancing its absorption.[1] In an attempt to determine whether this interaction would aid the attainment of therapeutic ciclosporin concentrations after heart transplantation, a patient with a jejunoileal bypass was given ciclosporin both with and without ursodeoxycholic acid; no difference was noted in the bioavailability of ciclosporin.[2] Small studies in liver transplant recipients found no alteration in ciclosporin pharmacokinetics when given single doses of ursodeoxycholic acid,[3] nor any difference in ciclosporin requirements between patients given ursodeoxycholic acid and those given placebo.[4] Another study in 12 liver transplant patients, 6 of whom had cholestatic liver dysfunction, found that ursodeoxycholic acid increased the rate of absorption of ciclosporin, but that peak concentrations and bioavailability did not change significantly.[5] In a study using microemulsifying ciclosporin in liver transplant recipients, ursodeoxycholic acid reduced the absorption rate and bioavailability of ciclosporin in 9 patients without cholestasis, but increased absorption rate and bioavailability in 3 cholestatic patients.[6] UK licensed product information for the microemulsifying formulation states that ursodeoxycholic acid increases ciclosporin concentrations.

1. Gutzler F, *et al.* Ursodeoxycholic acid enhances the absorption of cyclosporine in a heart transplant patient with short bowel syndrome. *Transplant Proc* 1992; **24:** 2620–1.
2. Kino KJ, Wittkowsky AK. Influence of bile acid replacement on cyclosporine absorption in a patient with jejunoileal bypass. *Pharmacotherapy* 1995; **15:** 350–2.
3. Maboundou CW, *et al.* A single dose of ursodiol does not affect cyclosporine absorption in liver transplant patients. *Eur J Clin Pharmacol* 1996; **50:** 335–7.
4. Söderdahl G, *et al.* Ursodeoxycholic acid increased bile flow and affects bile composition in the early postoperative phase following liver transplantation. *Transpl Int* 1998; **11** (suppl): S231–S238.
5. Al-Quaiz MN, *et al.* Variable effect of ursodeoxycholic acid on cyclosporin absorption after orthotopic liver transplantation. *Transpl Int* 1994; **7:** 190–4.
6. Caroli-Bosc F-X, *et al.* Ursodeoxycholic acid modulates cyclosporin A oral absorption in liver transplant recipients. *Fundam Clin Pharmacol* 2000; **14:** 601–9.

Vaccines. Efficacy of immunoprophylaxis may be expected to be reduced during ciclosporin therapy, and use of live virus vaccines, in particular, is contra-indicated in immunocompromised patients;[1] there has also been concern that vaccine antigens given during ciclosporin therapy might induce tolerance and result in increased rather than decreased susceptibility to diseases.

1. Grabenstein JD, Baker JR. Comment: cyclosporine and vaccination. *Drug Intell Clin Pharm* 1985; **19:** 679–80.

Vitamins. For reference to increased absorption of ciclosporin when given with a water-soluble macrogol derivative of *vitamin E*, see Absorption, under Pharmacokinetics, below.

Pharmacokinetics

The pharmacokinetics of ciclosporin are variable and difficult to determine. Results vary depending on the assay used, and values obtained by different methods are not strictly comparable.

Absorption of conventional formulations of ciclosporin from the gastrointestinal tract is variable and incomplete. An oral microemulsifying formulation with improved absorption characteristics is available and is more rapidly and completely absorbed, with peak concentrations achieved about 1.5 to 2 hours after a dose.

Ciclosporin is widely distributed throughout the body. Distribution in the blood is concentration-dependent, with between 41 and 58% in erythrocytes and 10 to 20% in leucocytes; the remainder is found in plasma, about 90% protein-bound, mostly to lipoprotein. Because of distribution into blood cells whole blood concentrations are higher than, and not comparable with, plasma concentrations; where peak plasma concentrations are reported to be about 1 nanogram/mL (by specific HPLC assay) for each mg of oral ciclosporin, whole blood concentrations for each mg range from about 1.4 to 2.7 nanograms/mL. Ciclosporin is reported to cross the placenta, and to be distributed into breast milk.

Clearance from the blood is biphasic. The terminal elimination half-life of an oral dose is reported to range from about 5 to 20 hours; clearance in children is more rapid.

Ciclosporin is extensively metabolised in the liver and primarily excreted in faeces via the bile. About 6% of a dose is reported to be excreted in urine, less than 0.1% unchanged.

Absorption. Ingestion of conventional *oral* formulations of ciclosporin with food may increase its bioavailability, although the effect only appears to be significant when the meal is high in fat;[1] ingestion with food and added bile acids may also increase absorption moderately.[2] A micelle-forming macrogol derivative of vitamin E (tocofersolan) has also been reported to markedly increase ciclosporin absorption.[3,4]

Because of the problems of variable oral absorption, an oral microemulsifying formulation has been developed that offers greatly improved and more predictable bioavailability,[5-8] particularly in liver transplant patients with impaired bile flow.[5] It should be noted that the formulation of this product in fact includes a vitamin E compound.

However, a study[9] has suggested that contrary to previous assumptions, conventional formulations of ciclosporin are quite well absorbed, and that the low bioavailability is due to extensive cytochrome-mediated metabolism in the gut wall (see also Metabolism, below). If this were the case, the improved bioavailability seen with the microemulsifying formulation is presumably less to do with improved absorption than with protection from such metabolism.

Very little drug is absorbed after application to the *eye*; ciclosporin accumulates on the ocular surface and cornea, achieving concentrations considered suitable for local immunomodulation. Corneal concentrations are affected by the choice of vehicle, but intra-ocular penetration is low. Little or no ocular metabolism is considered to occur in humans.[10]

1. Gupta SK, *et al.* Effect of food on the pharmacokinetics of cyclosporine in healthy subjects following oral and intravenous administration. *J Clin Pharmacol* 1990; **30:** 643–53.
2. Lindholm A, *et al.* The effect of food and bile acid administration on the relative bioavailability of cyclosporin. *Br J Clin Pharmacol* 1990; **29:** 541–8.
3. Sokol RJ, *et al.* Improvement of cyclosporin absorption in children after liver transplantation by means of water-soluble vitamin E. *Lancet* 1991; **338:** 212–15.
4. Chang T, *et al.* The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 297–303.
5. Trull AK, *et al.* Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. *Br J Clin Pharmacol* 1995; **39:** 627–31.
6. van den Borne BEEM, *et al.* Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1995; **39:** 172–5.
7. Friman S, Bäckman L. A new microemulsion formulation of cyclosporin: pharmacokinetic and clinical features. *Clin Pharmacokinet* 1996; **30:** 181–93.

8. Schädeli F, *et al.* Population pharmacokinetic model to predict steady-state exposure to once-daily cyclosporin microemulsion in renal transplant recipients. *Clin Pharmacokinet* 2002; **41:** 59–69.
9. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.
10. Tang-Liu DD-S, Acheampong A. Ocular pharmacokinetics and safety of ciclosporin, a novel topical treatment for dry eye. *Clin Pharmacokinet* 2005; **44:** 247–61.

Distribution. The distribution characteristics of ciclosporin are clinically important; binding in blood and plasma is of importance in determining immunosuppressive activity after organ transplantation.[1] The unbound concentration of ciclosporin may have a closer association with both renal and cardiac allograft rejection than the total (bound plus unbound) concentration.

1. Akhlaghi F, Trull AK. Distribution of cyclosporin in organ transplant recipients. *Clin Pharmacokinet* 2002; **41:** 615–37.

Ethnicity and sex. Gender-dependent racial differences in the pharmacokinetics of ciclosporin have been suggested.[1] African American women showed larger clearances of intravenous and oral ciclosporin (microemulsifying formulation) than African American men, and white women. There were no significant differences in clearance between men of different ethnic origin, or between white men and women. Overall bioavailability was also lower in African Americans compared with white subjects. However, other studies[2,3] found no differences in relative bioavailability between races.

Differences in hepatic cytochrome P450 isoenzyme CYP3A and intestinal P-glycoprotein activity may account for interindividual variability in ciclosporin disposition, and it has been speculated that polymorphic CYP3A5 expression might contribute to interracial differences.[4] However, most studies[5,6] have found little or no association between CYP3A4 or CYP3A5 genotype and ciclosporin pharmacokinetics, although one study found that patients with a CYP3A4 variant allele had a small but significantly higher oral clearance of ciclosporin.[7] However, black and Asian transplant recipients were found to have a reduced oral clearance in this study, independent of their CYP3A genotype, and in apparent contradiction to the literature. The authors commented that most of the studies had been conducted with the older oil-based products, and use of the microemulsifying formulation had not been associated with significant differences in ciclosporin pharmacokinetics between ethnic groups.[7] Genotyping of transplant recipients was considered unlikely to be of use in optimising ciclosporin dosage in clinical practice.[6,7]

1. Min DI, *et al.* Gender-dependent racial difference in disposition of cyclosporine among healthy African American and white volunteers. *Clin Pharmacol Ther* 2000; **68:** 478–86.
2. Stein CM, *et al.* Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. *Clin Pharmacol Ther* 2001; **69:** 317–23.
3. Pollak R, *et al.* Cyclosporine bioavailability of Neoral and Sandimmune in white and black de novo renal transplant recipients. *Ther Drug Monit* 1999; **21:** 661–3.
4. Yates CR, *et al.* The effect of CYP3A5 and MDR1 polymorphic expression on cyclosporine oral disposition in renal transplant patients. *J Clin Pharmacol* 2003; **43:** 555–64.
5. Hesselink DA, *et al.* Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74:** 245–54.
6. Anglicheau D, *et al.* CYP3A5 and MDR1 genetic polymorphisms and cyclosporine pharmacokinetics after renal transplantation. *Clin Pharmacol Ther* 2004; **75:** 422–33.
7. Hesselink DA, *et al.* Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther* 2004; **76:** 545–56.

Metabolism. *In vitro*[1] and *in vivo*[2-4] evidence indicates that the low oral bioavailability of ciclosporin is due to first-pass metabolism in the gastrointestinal tract rather than the liver.

1. Tjia JF, *et al.* Cyclosporin metabolism by the gastrointestinal mucosa. *Br J Clin Pharmacol* 1991; **31:** 344–6.
2. Kolars JC, *et al.* First-pass metabolism of cyclosporin by the gut. *Lancet* 1991; **338:** 1488–90.
3. Hoppu K, *et al.* Evidence for pre-hepatic metabolism of oral cyclosporine in children. *Br J Clin Pharmacol* 1991; **32:** 477–81.
4. Wu C-Y, *et al.* Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin Pharmacol Ther* 1995; **58:** 492–7.

Therapeutic drug monitoring. Considerable debate has attended the necessity for therapeutic monitoring of ciclosporin concentrations and also on the questions of which assay methods to use and whether to measure drug concentrations in whole blood or plasma.

Before the introduction of specific monoclonal radio-immunoassay the high performance liquid chromatography (HPLC) assay for ciclosporin had the advantage of being specific for the parent compound, and some suggested it to be the method of choice.[1,2] However, it is a more complex procedure, is not universally available, and is slower to perform than radio-immunoassay.[1,3-5] Specific monoclonal radio-immunoassays are now widely available; a comparative study of specific and non-specific radio-immunoassays, HPLC, and polyclonal fluorescence polarisation immunoassay (FPIA) found that the specific assays, used on whole blood samples, gave the best correlation with clinical events.[6]

Because the distribution of ciclosporin between blood cells and plasma is temperature-dependent,[7] plasma concentrations may be twice as high at 37° as at 21°. The temperature at which samples are stored and processed may therefore considerably influence results. In consequence, measurement of drug concentrations in whole blood is to be preferred.[1,3,4,8] However, many, particularly early, clinical studies have given plasma or serum concentrations, which makes comparison of literature data difficult. This problem is compounded by a considerable degree of variation between laboratories,[9,10] even when the same technique is used,[10] and by circadian variations in ciclosporin metabolism which mean that samples should be taken at the same time of day.[11] Since ciclosporin concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[12]

Because of the variability in results caused by difficulties in monitoring it has proved difficult to determine precisely the ciclosporin concentrations associated with therapeutic benefit and toxicity,[1,3-5] and it has been suggested that measurement of the therapeutic concentrations is unnecessary (provided the patient's clinical condition and renal function are monitored) when low-dose ciclosporin is being given (for example, in psoriasis).[13] However, others consider that it is always critical that ciclosporin blood trough concentrations are regularly measured,[14] in addition to other monitoring. A study in paediatric haematopoietic stem cell transplant recipients found a significant relationship between ciclosporin blood trough concentrations and the severity of acute graft-versus-host disease (GVHD); with lower trough concentrations, GVHD was more severe during the early post-transplantation period.[15] It has been suggested[16] that trough ciclosporin concentrations (C_0), measured by a specific method in whole blood, should not be less than 150 nanograms/mL during the first month after renal transplantation, although lower concentrations are subsequently acceptable; trough concentrations of 250 to 300 nanograms/mL are recommended in the 3 months after liver transplantation.

Other methods of monitoring ciclosporin therapy include monitoring the area under the concentration-time curve (AUC), limited sampling strategies, and Bayesian forecasting.[14,17-21] However, these methods also have limitations, often requiring several samples at inconvenient times for the patient, and can involve complex calculations.

Maximum calcineurin inhibition occurs in the first 1 to 2 hours after ciclosporin dosing, and it was hypothesised that AUC in the first 4 hours after a dose, or the blood concentration at 2 hours after a dose (C_2) might better predict immunosuppressive efficacy than trough concentrations (C_0) or AUC over 12 hours.[22] A large study[23] in liver transplant recipients found that measuring C_2 was superior to C_0 monitoring, resulting in a reduction of the incidence and severity of rejection. It was pointed out that these results could not necessarily be extrapolated to different transplant groups and that analysis when sampling high ciclosporin concentrations needed to be extremely accurate.[24] Data from lung transplant recipients found measurements of C_0 but not C_2 or C_6 to be associated with the risk of acute lung allograft rejection.[25] However, there was some suggestion that C_2 predicted rejection better than C_0 in renal[26] and heart[27] transplant recipients also. In paediatric renal transplant recipients,[22] C_2 monitoring was found to be a better predictor of ciclosporin exposure during the absorption phase than C_0.

An international consensus group considered C_2 to be the best time-point predictor of exposure to ciclosporin during the first 4 hours postdose.[28] This was based on data from studies in adult renal, liver, heart, and lung transplant recipients, as well as in paediatric renal and liver transplant patients; patients had received microemulsifying ciclosporin. C_2 monitoring was also able to identify high, intermediate, or low absorbers of ciclosporin. Additional monitoring beyond the C_2 time point was considered necessary in low absorbers to identify true low absorbers from slow absorbers. Target C_2 concentrations at various times post-transplantation were recommended for adult renal and liver transplant patients receiving ciclosporin microemulsion.

For adult renal transplant recipients:

- 1 month post-transplant: C_2 1.5 to 2 micrograms/mL (this should be achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 2 months post-transplant: C_2 1.5 micrograms/mL;
- 3 months post-transplant: C_2 1.3 micrograms/mL;
- 4 to 6 months post-transplant: C_2 1.1 micrograms/mL;
- 7 to 12 months post-transplant: C_2 0.9 micrograms/mL;
- 12 months post-transplant or more: C_2 0.8 micrograms/mL

For adult liver transplant recipients:

- 0 to 6 months post-transplant: C_2 1 micrograms/mL (initially achieved by days 3 to 5 after transplantation to maximise clinical benefit);
- 6 to 12 months post-transplant: C_2 0.8 micrograms/mL;
- more than 12 months post-transplant: C_2 0.6 micrograms/mL

Data on long-term clinical benefit of monitoring in terms of rejection prophylaxis and overall safety profile were lacking, and target levels were not established for other transplant groups. A 15-minute 'window of opportunity' before and after the 2-hour time point was considered to provide an acceptable (10%) margin of error, during which time the C_2 sample could be taken.[28] Findings from a 3-year prospective study of C_2 monitoring in stable renal transplant recipients suggested that this method offered clinical benefits in terms of control of hypertension and dyslipidaemia, and protection against chronic renal allograft dysfunction.[29] Australasian guidelines[30] stated that definitive target ciclosporin C_2 concentrations in various organ types or times post-transplant remained to be finalised, and that further evidence supporting C_2 monitoring was needed before C_0 monitoring could be definitively replaced. They recommended that samples clearly indicate which sampling time had been used, that concentrations be preferably reported in units of micrograms/litre, and that each report state the assay method used for analysis. Monitoring practices based on one formulation should not be applied to another formulation unless there was clear evidence of bioequivalence in patients. A subsequent study of C_2 monitoring in heart transplant patients[31] found that higher C_2 concentrations were associated with less episodes of acute cellular rejection. However, in renal transplant patients,[32,33] C_2 concentrations did not predict rejection. A multicentred, retrospective French study[34] determined that, in renal transplant patients monitored on C_0, most patients had C_2 concentrations below the target ranges recommended by the international consensus group; the authors suggested that lower C_2 ranges might be targeted in the early- and long-term post-transplantation periods for those given interleukin-2 receptor antibodies, and that optimal therapeutic windows for ciclosporin monitoring based on C_2 needed more definition. A review of limited sampling strategies in liver transplant patients[35] concluded that, while C_2 monitoring might be better than C_0 monitoring to improve acute rejection rate in the early post-transplantation period, the evidence was not strong, and that further well-designed studies were needed. A review of ciclosporin monitoring after allogeneic stem cell transplantation[36] acknowledged that C_2 monitoring might be preferable to trough concentration monitoring in these patients, but also stated that optimal strategies remained to be defined and that randomised studies were needed.

There has been concern that differences in blood ciclosporin results from various assay systems would necessitate assay-specific target ranges for monitoring. Most transplant centres have developed target ciclosporin ranges that reflect the methodology in use. A study[37] of 5 different assay methods, including radio-immunoassay, HPLC, and FPIA, found that when measuring C_0, this would indeed be the case, but that with C_2 monitoring, differences in the results from the various assay methods were not statistically significant, and were unlikely to be of clinical significance. Different proportions of parent ciclosporin and metabolites were thought to be the reason for this disparity at the two time points. The authors considered that a single target therapeutic range could be adopted when monitoring C_2 concentrations, regardless of the assay method used.

1. Ptachcinski RJ, *et al.* Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. *J Clin Pharmacol* 1986; **26:** 358–66.
2. Varghese Z, *et al.* How to measure cyclosporin. *Lancet* 1984; **i:** 1407–8.
3. Faynor SM, *et al.* Therapeutic drug monitoring of cyclosporine. *Mayo Clin Proc* 1984; **59:** 571–2.
4. Burkle WS. Cyclosporine pharmacokinetics and blood level monitoring. *Drug Intell Clin Pharm* 1985; **19:** 101–5.
5. Rodighiero V. Therapeutic drug monitoring of cyclosporin: practical applications and limitations. *Clin Pharmacokinet* 1989; **16:** 27–37.
6. Lindholm A, *et al.* A prospective study of cyclosporine concentration in relation to its therapeutic effect and toxicity after renal transplantation. *Br J Clin Pharmacol* 1990; **30:** 443–52.
7. Dieperink H. Temperature dependency of cyclosporin plasma levels. *Lancet* 1983; **i:** 416.
8. Bandini G, *et al.* Measuring cyclosporin in plasma. *Lancet* 1983; **i:** 762.
9. Moyer TP. Measurement of cyclosporine: a challenge to the professional laboratory organizations. *Ther Drug Monit* 1985; **7:** 123–4.
10. Johnston A, *et al.* The United Kingdom Cyclosporin Quality Assessment Scheme. *Ther Drug Monit* 1986; **8:** 200–204.
11. Venkataramanan R, *et al.* Diurnal variation in cyclosporine kinetics. *Ther Drug Monit* 1986; **8:** 380–1.
12. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
13. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.
14. Dumont RJ, Ensom MHH. Methods for clinical monitoring of cyclosporin in transplant patients. *Clin Pharmacokinet* 2000; **38:** 427–47.
15. Martin P, *et al.* Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. *Bone Marrow Transplant* 2003; **32:** 777–84.
16. Lindholm A. Therapeutic monitoring of cyclosporin—an update. *Eur J Clin Pharmacol* 1991; **41:** 273–83.
17. David O, Johnston A. Limited sampling strategies. *Clin Pharmacokinet* 2000; **39:** 311–13.
18. Leger F, *et al.* Maximum A Posteriori Bayesian estimation of oral cyclosporin pharmacokinetics in patients with stable renal transplants. *Clin Pharmacokinet* 2002; **41:** 71–80.
19. Bourgoin H, *et al.* Bayesian estimation of cyclosporin exposure for routine therapeutic drug monitoring in kidney transplant patients. *Br J Clin Pharmacol* 2005; **59:** 18–27.
20. Tokui K, *et al.* Dose adjustment strategy for oral microemulsion formulation of cyclosporine: population pharmacokinetics-based analysis in kidney transplant patients. *Ther Drug Monit* 2004; **26:** 287–94.

21. Saint-Marcoux F, *et al.* Patient characteristics influencing ciclosporin pharmacokinetics and accurate Bayesian estimation of ciclosporin exposure in heart, lung and kidney transplant patients. *Clin Pharmacokinet* 2006; **45:** 905–22.
22. Weber LT, *et al.* Cyclosporin A absorption profiles in pediatric renal transplant recipients predict the risk of acute rejection. *Ther Drug Monit* 2004; **26:** 415–24.
23. Levy G, *et al.* Improved clinical outcomes for liver transplant recipients using cyclosporine monitoring based on 2-hr post-dose levels (C). *Transplantation* 2002; **73:** 953–9.
24. Holt DW. Cyclosporine monitoring based on C sampling. *Transplantation* 2002; **73:** 840–1.
25. Trull A, *et al.* Randomized, trough blood cyclosporine concentration-controlled trial to compare the pharmacodynamics of Sandimmune and Neoral in de novo lung transplant recipients. *Ther Drug Monit* 1999; **21:** 17–26.
26. Pescovitz MD, *et al.* Two-hour post-dose cyclosporine level is a better predictor than trough level of acute rejection of renal allografts. *Clin Transplant* 2002; **16:** 378–82.
27. Solari SG, *et al.* Cyclosporine monitoring with 2-hour postdose levels in heart transplant recipients. *Ther Drug Monit* 2005; **27:** 417–21.
28. Levy G, *et al.* Patient management by Neoral C monitoring: an international consensus statement. *Transplantation* 2002; **73** (suppl): S12–S18.
29. Citterio F, *et al.* Results of a three-year prospective study of C monitoring in long-term renal transplant recipients receiving cyclosporine microemulsion. *Transplantation* 2005; **79:** 802–6.
30. Morris RG, *et al.* Cyclosporin monitoring in Australasia: 2002 update of consensus guidelines. *Ther Drug Monit* 2002; **24:** 677–88.
31. Delgado DH, *et al.* Monitoring of cyclosporine 2-hour post-dose levels in heart transplantation: improvement in clinical outcomes. *J Heart Lung Transplant* 2005; **24:** 1343–6.
32. Gotti E, *et al.* Blood cyclosporine level soon after kidney transplantation is a major determinant of rejection: insights from the Mycophenolate Steroid-Sparing Trial. *Transplant Proc* 2005; **37:** 2037–40.
33. Einecke G, *et al.* Limitations of C monitoring in renal transplant recipients. *Nephrol Dial Transplant* 2005; **20:** 1463–70.
34. Loichot C, *et al.* Cyclosporine monitoring in renal transplant recipients with induction therapy: C levels in patients monitored on C . *Fundam Clin Pharmacol* 2006; **20:** 91–6.
35. Marin JG, *et al.* Is C2 monitoring or another limited sampling strategy superior to C0 monitoring in improving clinical outcomes in adult liver transplant recipients? *Ther Drug Monit* 2006; **28:** 637–42.
36. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.
37. Johnston A, *et al.* Monitoring cyclosporin in blood: between-assay differences at trough and 2 hours post-dose (C2). *Ther Drug Monit* 2003; **25:** 167–73.

Uses and Administration

Ciclosporin is a powerful immunosuppressant that appears to act specifically on lymphocytes, mainly helper T-cells. It forms a complex with the receptor protein cyclophilin; this complex binds to and inhibits the activation of calcineurin, an important step in the production of lymphokines, including interleukin-2, and results in a depression of cell-mediated immune response. Unlike cytotoxic immunosuppressants such as cyclophosphamide it has little effect on bone marrow.

Ciclosporin is used, usually with corticosteroids (and often with other immunosuppressants), in organ and tissue transplantation for the prophylaxis of graft rejection, or in the management of graft rejection in patients previously treated with other immunosuppressants. It is also used in severe forms of atopic dermatitis, psoriasis, or rheumatoid arthritis, usually when conventional therapy is ineffective or inappropriate, and is used in nephrotic syndrome.

Ciclosporin has been tried in other diseases considered to have an auto-immune component, as indicated by the cross-references given below; they include aplastic anaemia, asthma, Behçet's syndrome, chronic active hepatitis, multiple sclerosis, myasthenia gravis, sarcoidosis, scleritis or uveitis, scleroderma, and various skin disorders.

Ciclosporin is given orally as liquid-filled capsules or as an oily solution, which may be diluted with milk or fruit juice (not grapefruit) immediately before use to improve palatability. Microemulsifying formulations with improved bioavailability are available in a number of countries. When changing between preparations, the initial dose of the new formulation should be the same (mg for mg), and should subsequently be adjusted as necessary based on blood-ciclosporin concentrations, serum creatinine, and blood pressure monitoring. The daily dose of ciclosporin is taken in 2 divided doses, although the conventional formulation is sometimes given as a single daily dose.

In **organ transplantation** the usual initial oral dose of ciclosporin is 10 to 15 mg/kg daily, beginning 4 to 12 hours before transplantation, and continued for 1 to 2 weeks; lower initial doses may be given with other immunosuppressants (e.g. with corticosteroids or as part of 'triple' or 'quadruple' therapy). Dosage may subsequently be reduced gradually to a daily maintenance dose of 2 to 6 mg/kg.

Kidney function and blood pressure should be monitored regularly, as well as blood concentrations of ciclosporin (see Therapeutic Drug Monitoring, above), and dosage should be adjusted as necessary. Hepatic function should also be monitored.

Ciclosporin may also be given intravenously, at one-third of the oral dose, in patients in whom oral dosage is not feasible. It is given by slow intravenous infusion over 2 to 6 hours, the 5% concentrate being diluted 1:20 to 1:100 in sodium chloride 0.9% or glucose 5%, to give a 0.05 to 0.25% solution of ciclosporin. Because of the risk of anaphylactoid reactions, which have been attributed to the polyoxyl castor oil vehicle, patients should be transferred to oral therapy as soon as possible.

For the prevention of graft rejection in **bone marrow transplantation**, and prevention and treatment of graft-versus-host disease, an initial dose of 3 to 5 mg/kg daily by the intravenous route is recommended, starting the day before transplantation and continuing for up to 2 weeks until maintenance by mouth, in doses of 12.5 mg/kg daily can be instituted. If oral treatment is used to begin therapy the recommended dose is 12.5 to 15 mg/kg daily followed by 12.5 mg/kg daily for maintenance. The maintenance dose is continued for at least 3 to 6 months, then gradually reduced until ciclosporin is withdrawn altogether; this may take up to a year after transplantation.

Ciclosporin given by inhalation is under investigation for the prevention and treatment of graft rejection after lung transplantation in some countries.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

In the treatment of **psoriasis**, ciclosporin may be given in usual initial oral doses of 2.5 mg/kg daily (a maximum of 5 mg/kg daily is recommended in the UK and 4 mg/kg daily in the USA), in 2 divided doses, reduced once remission is achieved to the lowest effective maintenance dose. Treatment should be stopped if there is insufficient response to the maximum dose within 6 weeks. A similar dosage range may be given for a maximum of 8 weeks in the treatment of severe **atopic dermatitis**.

In **rheumatoid arthritis** oral ciclosporin may be given in initial daily doses of 2.5 mg/kg, divided into two doses, for a period of 6 or 8 weeks. If the clinical effect is insufficient dosage may then be gradually increased to a maximum of 4 mg/kg daily; if there is no response after 3 to 4 months, treatment should be stopped.

For **nephrotic syndrome** secondary to glomerular kidney disease (minimal change nephropathy, focal glomerulosclerosis, or membranous nephropathy) dosage of ciclosporin depends on age and renal function. To induce remission in patients with normal renal function 5 mg/kg daily may be given to adults, in 2 divided doses orally. In patients with renal impairment the initial dose should not exceed 2.5 mg/kg daily. Treatment may be stopped if there is no response after 3 months (or 6 months in patients with membranous nephropathy). In patients who do respond, maintenance doses should be gradually reduced to the minimum effective value.

For doses in children, see Administration in Children, below.

Eye drops containing ciclosporin 0.05% are used in the management of **dry eye** associated with ocular inflammation. A topical emulsion of ciclosporin is under investigation for the treatment of vernal keratoconjunctivitis, a severe form of chronic allergic conjunctivitis.

Ciclosporin can inhibit the P-glycoprotein cellular pump responsible for multidrug resistance, and has been given with antineoplastics to raise their intracellular concentrations. Nonimmunosuppressive ciclosporin analogues such as valspodar (p.2410) are also being investigated for their ability to reverse multidrug resistance.

Administration. It has been suggested that calculating doses in mg/kg may not be the best way to achieve the desired blood concentrations of ciclosporin.[1] (See also Therapeutic Drug Monitoring, above) Retrospective study of 1071 renal transplant recipients indicated that blood ciclosporin concentrations were not significantly correlated with patient weight, the best prediction of trough blood concentration being given by the formula:

$$\text{Blood concentration (nanograms/mL)} = \text{dose in mg/day} \times (1.34 + 0.00011 \times \text{days after transplant} - 0.0049 \times \text{height in cm})$$

This formula appeared useful in predicting blood concentrations in prospective studies; from the seventh day after transplantation target trough concentrations could be expected to be about 0.3 times the daily ciclosporin dose in mg.

1. Bock HA, *et al.* Weight-independent dosing of cyclosporine—an alternative to the mg/kg doctrine. *Transplantation* 1994; **57:** 1484–9.

INHALATION. Aerosolised ciclosporin given by inhalation has proved effective[1,2] in the management of acute graft rejection in lung transplantation (p.1815). Doses were up to 300 mg daily via a nebuliser, in either propylene glycol or ethanol solvents.[3] Pulmonary delivery of ciclosporin has been reviewed.[3,4] A positive association between deposited aerosolised ciclosporin dose and improvement in lung function was found in 15 subjects treated over 2 years postoperatively.[5] In a case-control study,[6] aerosolised ciclosporin improved survival among lung transplant recipients with bronchiolitis obliterans. In a randomised controlled study, inhaled ciclosporin given prophylactically did not improve the rate of acute rejection, but it did improve chronic rejection-free survival and overall survival.[7]

A dry powder formulation of ciclosporin for inhalation use has been developed in order to overcome problems of local irritation with propylene glycol; feasibility and efficacy studies with this new formulation are needed.[8]

1. Keenan RJ, *et al.* Efficacy of inhaled cyclosporine in lung transplant recipients with refractory rejection: correlation of intragraft cytokine gene expression with pulmonary function and histologic characteristics. *Surgery* 1995; **118:** 385–91.
2. Iacono AT, *et al.* Dose-related reversal of acute lung rejection by aerosolized cyclosporine. *Am J Respir Crit Care Med* 1997; **155:** 1690–8.
3. Klyashchitsky BA, Owen AJ. Nebulizer-compatible liquid formulations for aerosol pulmonary delivery of hydrophobic drugs: glucocorticoids and cyclosporine. *J Drug Target* 1999; **7:** 79–99.
4. Corcoran TE. Inhaled delivery of aerosolized cyclosporine. *Adv Drug Deliv Rev* 2006; **58:** 1119–27.
5. Corcoran TE, *et al.* Preservation of post-transplant lung function with aerosol cyclosporin. *Eur Respir J* 2004; **23:** 378–83.
6. Iacono AT, *et al.* Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J* 2004; **23:** 384–90.
7. Iacono AT, *et al.* A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; **354:** 141–50.
8. Zijlstra GS, *et al.* Characterization of a cyclosporine solid dispersion for inhalation. *AAPS J* 2007; **9:** E190–E199.

OCULAR. Topical ciclosporin, in strengths ranging from 0.05 to 2% has been shown to be effective[1,2] in the treatment of various ocular surface disorders, particularly dry eye (see below) and atopic keratoconjunctivitis. It has also been used for corneal ulcers, glaucoma (see below), as adjunctive therapy in corneal allograft rejection, and for the ocular manifestations of graft-versus-host disease.

A silicone matrix ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation.

1. Tatlipinar S, Akpek EK. Topical ciclosporin in the treatment of ocular surface disorders. *Br J Ophthalmol* 2005; **89:** 1363–7.
2. Foulks GN. Topical cyclosporine for treatment of ocular surface disease. *Int Ophthalmol Clin* 2006; **46:** 105–22.

ORAL. The microemulsifying formulation of ciclosporin has been reviewed.[1,2] For discussion of the potential problems involved in converting from conventional to microemulsion oral formulations see under Precautions, above.

1. Noble S, Markham A. Cyclosporin: a review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral). *Drugs* 1995; **50:** 924–41.
2. Dunn CJ, *et al.* Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) in organ transplantation. *Drugs* 2001; **61:** 1957–2016.

Administration in children. UK licensed product information states that, while experience with ciclosporin in children is limited, **transplant** patients from 3 months of age have received the drug at the same doses recommended for adults (see Uses and Administration, above). However, at doses above the recommended range, children seem to be more susceptible to fluid retention, convulsions, and hypertension. These effects respond to dose reduction.

In contrast, US licensed product information states that, while data in children are lacking, transplant recipients as young as 6 months and 1 year have received the standard formulation and microemulsifying formulation, respectively, with no unusual adverse effects, and that children have generally required and tolerated higher doses of the standard formulation than those used in adults.

The *BNFC* advises to consult local treatment protocols for details of use in organ transplantation.

For the treatment of **psoriasis** and **atopic dermatitis** doses recommended by the *BNFC* for children from 1 month of age are the same as for adults (see Uses and Administration, above).

In the treatment of **nephrotic syndrome** UK licensed product information states that children may be given 6 mg/kg daily by mouth, in 2 divided doses, if renal function is normal. The dose should not exceed 2.5 mg/kg daily in patients with impaired renal function. The *BNFC* specifies use from 1 month of age.

Although ciclosporin is not licensed in the UK for use in **ulcerative colitis**, the *BNFC* recommends the following initial doses in refractory disease in children, which are then adjusted according to ciclosporin blood concentrations and response:

- orally in those aged 2 to 18 years: 2 mg/kg twice daily (maximum 5 mg/kg twice daily)
- by intravenous infusion in those aged 3 to 18 years: 0.5 to 1 mg/kg twice daily

Aplastic anaemia. Ciclosporin, usually combined with antilymphocyte immunoglobulin, is used in patients with aplastic anaemia when bone marrow transplantation is unsuitable (see p.1042).

Asthma. Ciclosporin is being considered as a potential treatment for some cases of refractory asthma (p.1108). A controlled study[1] in patients with chronic severe asthma requiring long-standing oral corticosteroid treatment found that addition of ciclosporin in an initial dose of 5 mg/kg daily to their regimen resulted in significant improvement in lung function and a reduced frequency of disease exacerbation, compared with placebo. The results were interesting because of the improvement in what had been considered 'irreversible' airflow obstruction. A subsequent study[2] from the same centre involving 39 patients with severe corticosteroid-dependent asthma found that low-dose ciclosporin by mouth (an initial dose of 5 mg/kg daily) permitted a reduction in the daily dosage of prednisolone, from a median of 10 to 3.5 mg daily. However, a systematic review[3] considered that, given the adverse effects of ciclosporin, any clinical benefit was debatable.

1. Alexander AG, *et al.* Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992; **339:** 324–8.
2. Lock SH, *et al.* Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996; **153:** 509–14.
3. Evans DJ, *et al.* Cyclosporin as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 15/01/08).

Behçet's syndrome. Ciclosporin has been tried in Behçet's syndrome, see p.1499.

Cogan's syndrome. Ciclosporin has been used with corticosteroids for severe Cogan's syndrome with large-vessel vasculitis (see p.1502).

Corneal ulcer. Ciclosporin 1% eye drops, with lamellar keratoplasty, proved effective in treating Mooren's ulcer, a possibly auto-immune corneal disease that is difficult to manage and can lead to blindness.[1] Treatment with topical ciclosporin alone may also be useful[2] in patients with sterile corneal ulcers associated with rheumatoid disease.

1. Chen J, *et al.* Mooren's ulcer in China: a study of clinical characteristics and treatment. *Br J Ophthalmol* 2000; **84:** 1244–9.
2. Gottsch JD, Akpek EK. Topical cyclosporin stimulates neovascularization in resolving sterile rheumatoid central corneal ulcers. *Trans Am Ophthalmol Soc* 2000; **98:** 81–90.

Dermatomyositis. Ciclosporin may be of benefit in refractory dermatomyositis, see Polymyositis and Dermatomyositis, below.

Diabetes mellitus. Immunosuppressants have been used in attempts to prolong the so called 'honeymoon period' in recently diagnosed diabetics (p.431). Ciclosporin has apparently produced modest benefits in such a context,[1-3] but its overall value remains to be determined.

1. Bougneres PF, *et al.* Factors associated with early remission of type 1 diabetes in children treated with cyclosporine. *N Engl J Med* 1988; **318:** 663–70.
2. The Canadian-European Randomized Control Trial Group. Cyclosporin-induced remission of IDDM after early intervention: association of 1 yr of cyclosporin treatment with enhanced insulin secretion. *Diabetes* 1988; **37:** 1574–82.
3. Carel JC, *et al.* Cyclosporine delays but does not prevent clinical onset in glucose intolerant pre-type 1 diabetic children. *J Autoimmun* 1996; **9:** 739–45.

Diffuse parenchymal lung disease. There are reports of benefit from the use of ciclosporin in diffuse parenchymal lung disease (p.1502), although data are too limited to support its use.

Dry eye. Topical ciclosporin has been found to be beneficial[1,2] for keratoconjunctivitis sicca (dry eye—see p.2140). Further studies[3,4] found ciclosporin 0.05% and 0.1% to be the most appropriate formulations since no additional benefit was found with higher concentrations[3] and both were significantly better than placebo.[4]

Topical ciclosporin has also been reported to be beneficial for patients with dry eyes secondary to graft-versus-host disease.[5]

1. Laibovitz RA, *et al.* Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993; **12:** 315–23.
2. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology* 2007; **114:** 76–9.
3. Stevenson D, *et al.* Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. *Ophthalmology* 2000; **107:** 967–74.
4. Sall K, *et al.* Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology* 2000; **107:** 631–9.
5. Lelli GJ, *et al.* Ophthalmic cyclosporine use in ocular GVHD. *Cornea* 2006; **25:** 635–8.

Eczema. Ciclosporin is effective in atopic eczema (atopic dermatitis),[1-3] where it is used as adjunctive therapy (see p.1579). It is generally reserved for short-term treatment (up to 8 weeks) in patients with severe disease unresponsive to all conventional therapies, although reports have described long-term use in adult patients.[4] It has also been suggested[5] that long-term remission is possible, even in those treated with short courses. Ciclosporin has been used for both short courses[6,7] and continuous therapy in children.[8] A systematic review and meta-analysis[9] that incorporated most of these studies concluded that the mean clinical improvement in disease severity after 6 to 8 weeks of ciclosporin treatment is about 55%; however, the true benefit may be somewhat lower due to publication bias. Higher initial doses of 4 to 5 mg/kg led to a more rapid response, and the mean benefit after 2 weeks at this dose was about 40%. In a small, open, crossover study,[10] the microemulsifying form was considered equivalent or superior in tolerability and efficacy when compared with the conventional formulation. Responses have also been reported in severe eczematisation associated with Darier's disease[11] (p.1578).

1. van Joost T, *et al.* Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994; **130:** 634–40.
2. Munro CS, *et al.* Maintenance treatment with cyclosporin in atopic eczema. *Br J Dermatol* 1994; **130:** 376–80.
3. Granlund H, *et al.* Cyclosporin in atopic dermatitis: time to relapse and effect of intermittent therapy. *Br J Dermatol* 1995; **132:** 106–12.
4. Berth-Jones J, *et al.* Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; **136:** 76–81.
5. Granlund H, *et al.* Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol (Stockh)* 1998; **78:** 40–3.
6. Zaki I, *et al.* Treatment of severe atopic dermatitis in childhood with cyclosporin. *Br J Dermatol* 1996; **135** (suppl 48): 21–4.
7. Berth-Jones J, *et al.* Cyclosporine in severe childhood atopic dermatitis: a multicenter study. *J Am Acad Dermatol* 1996; **34:** 1016–21.
8. Harper JI, *et al.* Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142:** 52–8.
9. Schmitt J, *et al.* Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21:** 606–19.
10. Chawla M, *et al.* Comparison of the steady state pharmacokinetics of two formulations of cyclosporin in patients with atopic dermatitis. *Br J Dermatol* 1996; **135** (suppl 48): 9–14.
11. Shahidullah H, *et al.* Darier's disease: severe eczematization successfully treated with cyclosporin. *Br J Dermatol* 1994; **131:** 713–16.

Glaucoma. Topical ciclosporin has produced some encouraging results[1] when used as an adjunct to reduce formation of scar tissue and improve outcome of glaucoma filtering surgery. It has been suggested[2] that topical ciclosporin 0.5% may be substituted for topical corticosteroids in the treatment of postkeratoplasty glaucoma.

1. Turaçli E, *et al.* A comparative clinical trial of mitomycin C and cyclosporin A in trabeculectomy. *Eur J Ophthalmol* 1996; **6:** 398–401.
2. Perry HD, *et al.* Topical cyclosporin A in the management of postkeratoplasty glaucoma. *Cornea* 1997; **16:** 284–8.

Glomerular kidney disease. Ciclosporin has been tried in a number of forms of glomerular kidney disease (p.1504) but use has been cautious because of fears about nephrotoxicity. Nonetheless, responses have been seen in patients with corticosteroid-resistant minimal change nephropathy,[1,2] focal glomerulosclerosis,[1-3] and membranous nephropathy.[4-6]

1. Nyrop M, Olgaard K. Cyclosporin A treatment of severe steroid resistant nephrotic syndrome in adults. *J Intern Med* 1990; **227:** 65–8.
2. Niaudet P, *et al.* Steroid-resistant idiopathic nephrotic syndrome and ciclosporin. *Nephron* 1991; **57:** 481.
3. Chishti AS, *et al.* Long-term treatment of focal segmental glomerulosclerosis in children with cyclosporine given as a single daily dose. *Am J Kidney Dis* 2001; **38:** 754–60.
4. Cattran DC, *et al.* A controlled trial of cyclosporine in patients with progressive membranous nephropathy. *Kidney Int* 1995; **47:** 1130–5.
5. Cattran DC, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; **59:** 1484–90.
6. Goumenos DS. What have we learned from the use of ciclosporin A in the treatment of nephrotic patients with idiopathic membranous nephropathy? *Expert Opin Pharmacother* 2008; **9:** 1695–1704.

Hepatitis. In chronic active hepatitis (p.1501), some evidence suggests that ciclosporin may offer an alternative therapy in patients with severe auto-immune (non-viral) disease where corticosteroids alone or with azathioprine do not suffice.

Histiocytic syndromes. As mentioned in the discussion on p.650 ciclosporin has been tried in patients with advanced Langerhans-cell histiocytosis.

Inflammatory bowel disease. Ciclosporin has been tried with variable success as a second-line drug in inflammatory bowel disease (p.1697). Intravenous high-dose ciclosporin has shown some efficacy in refractory ulcerative colitis,[1] and a review[2] concluded that intravenous ciclosporin should be offered to selected patients as an alternative to surgery. Treatment should be started at 2 mg/kg daily, as it appears to be as effective as 4 mg/kg daily. A systematic review,[3] which included only 2 studies, concluded that short-term ciclosporin may be used where surgery is the only option, but that this is not based on strong evidence.

Benefit from ciclosporin in Crohn's disease is less clear. A systematic review[4] concluded that low dose (5 mg/kg daily) oral ciclosporin is not effective for induction of remission in Crohn's disease. While some studies suggest that higher oral doses or intravenous ciclosporin might be beneficial, these are not considered to be useful alternatives for long-term management due to the risk of nephrotoxicity and the availability of other proven therapy.

1. Loftus CG, *et al.* Cyclosporin for refractory ulcerative colitis. *Gut* 2003; **52:** 172–3.
2. Pham CQD, *et al.* Cyclosporine for severe ulcerative colitis. *Ann Pharmacother* 2006; **40:** 96–101.
3. Shibolet O, *et al.* Cyclosporine A for induction of remission in severe ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 15/01/08).
4. McDonald JWD, *et al.* Cyclosporine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/01/08).

Leprosy. For mention of the use of ciclosporin in the management of type 1 lepra reactions in patients with leprosy, see p.176.

Lichen planus. Lichen planus is a skin disorder generally controlled with corticosteroids (see p.1580), although ciclosporin has also been used. Ciclosporin has been given successfully in relatively low doses (3 to 5 mg/kg by mouth) to produce remission of severe lichen planus,[1] but such therapy may be associated with the development of hypertension and impairment of renal function. Use of topical ciclosporin for oral lichen planus has been tried, but results have been variable.[2-8] One such study failed to note any benefit long-term from either ciclosporin mouthwash or corticosteroid oral paste.[7]

1. Pigatto PD, *et al.* Cyclosporin A for treatment of severe lichen planus. *Br J Dermatol* 1990; **121:** 121–3.
2. Eisen D, *et al.* Cyclosporin wash for oral lichen planus. *Lancet* 1990; **335:** 535–6.
3. Eisen D, *et al.* Effect of topical cyclosporine rinse on oral lichen planus: a double-blind analysis. *N Engl J Med* 1990; **323:** 290–4.
4. Levell NJ, *et al.* Lack of effect of cyclosporin mouthwash in oral lichen planus. *Lancet* 1991; **337:** 796–7.
5. Ho VC, Conklin RJ. Effect of topical cyclosporine rinse on oral lichen planus. *N Engl J Med* 1991; **325:** 435.
6. Porter SR, *et al.* The efficacy of topical cyclosporin in the management of desquamative gingivitis due to lichen planus. *Br J Dermatol* 1993; **129:** 753–5.
7. Sieg P, *et al.* Topical cyclosporin in oral lichen planus: a controlled, randomized prospective trial. *Br J Dermatol* 1995; **132:** 790–4.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154:** 139–45.

Lupus nephritis. Ciclosporin has been investigated for SLE (p.1513), particularly lupus nephritis. Significant reductions in proteinuria have been reported,[1-6] although controlled studies are needed.

1. Fu LW, *et al.* Clinical efficacy of cyclosporin A Neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 1998; **37:** 217–21.
2. Tam LS, *et al.* Long-term treatment of lupus nephritis with cyclosporin A. *Q J Med* 1998; **91:** 573–80.
3. Hallegua D, *et al.* Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. *Lupus* 2000; **9:** 241–51.
4. Fujinaga S, *et al.* Treatment of steroid-resistant membranous lupus nephritis with plasmapheresis and low-dose cyclosporine. *Pediatr Nephrol* 2007; **22:** 616–17.
5. Rihova Z, *et al.* Treatment of lupus nephritis with cyclosporine—an outcome analysis. *Kidney Blood Press Res* 2007; **30:** 124–8.
6. Ogawa H, *et al.* Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. *Mod Rheumatol* 2007; **17:** 92–7.

Multiple sclerosis. As noted on p.892, immunosuppressants, including ciclosporin, have produced modest benefit in patients with multiple sclerosis. However, it has been concluded that the scanty benefits of therapy are outweighed by the toxicity of the doses required.

Muscular dystrophies. A study in 15 boys with Duchenne muscular dystrophy (p.1507) given ciclosporin 5 mg/kg daily by mouth in divided doses, adjusted according to trough serum concentrations of ciclosporin, found that muscular force generation was improved during treatment, but declined again once treatment ceased.[1] The clinical significance, if any, of this effect remains to be established.

1. Sharma KR, *et al.* Cyclosporine increases muscular force generation in Duchenne muscular dystrophy. *Neurology* 1993; **43:** 527–32.

Myasthenia gravis. Ciclosporin may be of use as an alternative to azathioprine in the management of myasthenia gravis (p.629) for its corticosteroid-sparing effect[1] or when patients are intolerant of or unresponsive to corticosteroids and azathioprine.[2-4] It appears to be of similar efficacy to azathioprine[5] with a more rapid effect but serious adverse effects such as nephrotoxicity may limit its use.

1. Tindall RSA, *et al.* A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Y Acad Sci* 1993; **681:** 539–51.
2. Bonifati DM, Angelini C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. *J Neurol* 1997; **244:** 542–7.
3. Ciafaloni E, *et al.* Retrospective analysis of the use of cyclosporine in myasthenia gravis. *Neurology* 2000; **55:** 448–50.
4. Lavrnic D, *et al.* Cyclosporine in the treatment of myasthenia gravis. *Acta Neurol Scand* 2005; **111:** 247–52.
5. Schalke BCG, *et al.* Ciclosporin A vs azathioprine in the treatment of myasthenia gravis: final results of a randomized, controlled double-blind clinical trial. *Neurology* 1988; **38** (suppl 1): 135.

Organ and tissue transplantation. Ciclosporin has greatly improved the prospects for successful organ and tissue transplantation, and is a mainstay of regimens used to prevent rejection of solid organ grafts as well as being used for the prevention of graft-versus-host disease in bone marrow transplantation. For more detailed discussion of organ and tissue transplantation and the role of ciclosporin, see p.1810. Ciclosporin has also occasionally been used for corneal graft rejection (p.1502) in high-risk patients, where corticosteroids alone are insufficient. An ocular implant that provides sustained release of ciclosporin (LX-201) is under investigation for the prevention of rejection in corneal transplantation. Inhaled ciclosporin is under investigation in lung transplantation, see p.1815 and under Administration, above.

A few selected references to the use of ciclosporin in transplantation are given below.

1. Frei UA, *et al.* Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. *Transplantation* 1998; **65:** 1455–60.
2. Eisen HJ, *et al.* Safety, tolerability, and efficacy of cyclosporine microemulsion in heart transplant recipients: a randomized, multicenter, double-blind comparison with the oil-based formulation of cyclosporine—results at 24 months after transplantation. *Transplantation* 2001; **71:** 70–78.
3. Thervet E, *et al.* Benefit-risk assessment of ciclosporin withdrawal in renal transplant recipients. *Drug Safety* 2004; **27:** 457–76.
4. Hesselink DA, *et al.* The use of cyclosporine in renal transplantation. *Transplant Proc* 2004; **36** (suppl): 99S–106S.
5. Pape L, *et al.* Cyclosporine in pediatric kidney transplantation. *Transplant Proc* 2004; **36** (suppl): 203S–207S.
6. Banner NR, Yacoub MH. Cyclosporine in thoracic organ transplantation. *Transplant Proc* 2004; **36** (suppl): 302S–308S.
7. Patel JK, Kobashigawa JA. Cardiac transplant experience with cyclosporine. *Transplant Proc* 2004; **36** (suppl): 323S–330S.
8. Johnston A, *et al.* Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *Eur J Clin Pharmacol* 2004; **60:** 389–95.
9. Schrem H, *et al.* Update on liver transplantation using cyclosporine. *Transplant Proc* 2004; **36:** 2525–31.
10. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006; **38:** 169–74.

Pemphigus. Although pemphigus is usually treated with corticosteroids (see p.1582), ciclosporin has also been tried in a few patients with pemphigus vulgaris, with variable results.[1-3] A small, randomised study[4] found that use of corticosteroids with ciclosporin had no advantage over corticosteroids alone.

1. Luisi AF, Stoukides CA. Cyclosporine for the treatment of pemphigus vulgaris. *Ann Pharmacother* 1994; **28:** 1183–5.
2. Vardy DA, Cohen AD. Cyclosporine therapy should be considered for maintenance of remission in patients with pemphigus. *Arch Dermatol* 2001; **137:** 505.
3. Gooptu C, Staughton RCD. Use of topical cyclosporin in oral pemphigus. *J Am Acad Dermatol* 1998; **38:** 860–1.
4. Ioannides D, *et al.* Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. *Arch Dermatol* 2000; **136:** 868–72.

Polymyositis and dermatomyositis. Ciclosporin may be of benefit[1] in refractory polymyositis and dermatomyositis (see p.1510).

1. Qushmaq KA, *et al.* Cyclosporin A in the treatment of refractory adult polymyositis/dermatomyositis: population based experience in 6 patients and literature review. *J Rheumatol* 2000; **27:** 2855–9.

Primary biliary cirrhosis. In primary biliary cirrhosis (p.2408) some benefit has been reported with ciclosporin, but there are problems with toxicity. A systematic review[1] concluded that, despite improvements in pruritus and liver biochemical variables, ciclosporin did not delay the progression of the disease, and that its use outside of clinical studies could not be recommended.

1. Gong Y, *et al.* Cyclosporin A for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 15/01/08).

Psoriasis. Ciclosporin is used to induce remission or prevent relapse in severe refractory psoriasis (p.1583). Response to ciclosporin has been reported for virtually all the clinical manifestations of the disease,[1] including pustular psoriasis of pregnancy.[2-4] Benefit has also been reported in children with severe refractory psoriasis,[1,5] although exposure should be limited in view of the potential for cumulative toxicity.

Doses of 2.5 to 5 mg/kg daily given for up to 12 weeks produced marked improvement in the majority of patients with severe plaque psoriasis.[6] This intermittent therapy allows for a lower cumulative dose of ciclosporin and in turn decreases the risk of nephrotoxicity or hypertension.[7] Recommendations have been made in the UK for the use of ciclosporin in the management of psoriasis;[8] for those with severe stable disease, an initial starting dose of 2.5 mg/kg daily is suggested, with dose increases of 0.5 to 1 mg/kg daily made at intervals of 2 to 4 weeks, according to clinical response, and up to a maximum of 5 mg/kg daily. Treatment is given for about 12 weeks, and use of adjunctive topical therapy is recommended. Ciclosporin should be stopped once remission is achieved, and restarted at the previous effective dose if the patient relapses. In acute flares of the disease, ciclosporin may be started at higher doses (maximum 5 mg/kg daily) and titrated down as symptoms improve. The patient's renal function and blood pressure should be monitored before and during treatment. In a minority of patients requiring long-term continuous therapy, the duration of treatment should be limited to a maximum of 2 years, and an annual assessment of the patient's glomerular filtration rate is recommended. In most studies, maintenance doses were less than 3.5 mg/kg daily.

Reviews[1,9] have concluded that patients on short-term ciclosporin therapy for psoriasis do not require routine therapeutic drug monitoring (see above). However, some consider that monitoring of trough concentrations is necessary in those treated with greater than 3 mg/kg daily, or in those at risk of renal impairment.[9] Monitoring may also be useful when compliance is questionable, or drug interactions are suspected.[1]

1. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatol Treat* 2005; **16:** 258–77.
2. Edmonds EVJ, *et al.* Pustular psoriasis of pregnancy treated with ciclosporin and high-dose prednisolone. *Clin Exp Dermatol* 2005; **30:** 709–10.
3. Kura MM, Surjushe AU. Generalized pustular psoriasis of pregnancy treated with oral cyclosporin. *Indian J Dermatol Venereol Leprol* 2006; **72:** 458–9.
4. Kapoor R, Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. *Arch Dermatol* 2006; **142:** 1373–5.
5. Pereira TM, *et al.* Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20:** 651–6.
6. Faerber L, *et al.* Cyclosporine in severe psoriasis: results of a meta-analysis in 579 patients. *Am J Clin Dermatol* 2001; **2:** 41–7.
7. Ho VC. The use of ciclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004; **150** (suppl. 67): 1–10.
8. Griffiths CEM, *et al.* Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004; **150** (suppl. 67): 11–23.
9. Heydendael VMR, *et al.* Cyclosporin trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147:** 122–9.

Psoriatic arthritis. One study[1] has shown that low-dose ciclosporin effectively improves joint complaints in psoriatic arthritis (see under Spondyloarthropathies, p.13), and another[2] found ciclosporin to be more effective than sulfasalazine.

1. Mahrle G, *et al.* Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis: a prospective multicentre study. *Br J Dermatol* 1996; **135:** 752–7.
2. Salvarani C, *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; **28:** 2274–82.

Pyoderma gangrenosum. There have been reports[1-5] of responses to ciclosporin in patients with pyoderma gangrenosum (p.1583).

1. Sassolas B, *et al.* Pyoderma gangrenosum with pathergic phenomenon in pregnancy. *Br J Dermatol* 2000; **142:** 827–8.
2. Vena GA, Cassano N. Can we still suggest the topical cyclosporin treatment in cutaneous disorders? *J Eur Acad Dermatol Venereol* 2001; **15:** 18–19.
3. Schöfer H, Baur S. Successful treatment of postoperative pyoderma gangrenosum with cyclosporin. *J Eur Acad Dermatol Venereol* 2002; **16:** 148–51.
4. Patrone P, *et al.* Pyoderma gangrenosum of the scalp treated with cyclosporine A. *Int J Dermatol* 2002; **41:** 916–18.
5. Park H-J, *et al.* Recalcitrant oral pyoderma gangrenosum in a child responsive to cyclosporine. *J Dermatol* 2003; **30:** 612–16.

Rheumatoid arthritis. Various disease-modifying antirheumatic drugs (DMARDs) are used in rheumatoid arthritis (p.11) in an attempt to modify the disease process. Ciclosporin has produced responses in active disease,[1-4] and there is some evidence that it can slow radiological progression of disease[4] as well as providing symptomatic relief; a systematic review[5] has concluded it has an important clinical benefit in the short-term (up to one year) treatment of progressive disease. There has been some concern about associated nephrotoxicity,[1] but the use of low-dose regimens may help to minimise this.

Ciclosporin has also been combined with other DMARDs. Use with methotrexate has reportedly produced responses in patients unresponsive to methotrexate alone,[6] but some investigators found that a combination of methotrexate, ciclosporin and intra-articular corticosteroids was no more effective than standard DMARD therapy.[7] Others consider that ciclosporin monotherapy is of limited benefit, but that combination therapy with methotrexate is one of the best options to control aggressive disease.[8]

International consensus recommendations for the use of ciclosporin in rheumatoid arthritis[9] suggest that it may be considered in patients who are candidates for DMARDs and who do not have risk factors such as malignancy, uncontrolled hypertension, renal dysfunction, cytopenias, or marked disorder of liver function. They recommend a starting dose of between 2.5 and 3 mg/kg daily, increased if necessary after 4 to 8 weeks, in increments of 0.5 or 1 mg/kg at 1 to 2 month intervals, up to a maximum of 5 mg/kg daily, particular care being taken at doses over 4 mg/kg daily. Once the patient's disease has been stable for at least 3 months the daily dose should be decreased monthly or bimonthly in decrements of 0.5 mg/kg to the lowest effective dose. If it is only partially effective after 3 months at the maximum tolerable dose another medication should be considered instead or in addition; if there is no response to the maximum tolerable dose after 3 months, ciclosporin should be stopped. Patients should be carefully monitored before and during therapy.

Ciclosporin has been shown to have a corticosteroid-sparing effect and control the fever of juvenile idiopathic arthritis.[10] In patients with refractory juvenile idiopathic arthritis, adding ciclosporin to methotrexate therapy has been reported to elicit significant clinical improvement.[11]

1. Yocum DE, *et al.* Cyclosporin A in severe, treatment-refractory rheumatoid arthritis: a randomized study. *Ann Intern Med* 1988; **109:** 863–9.
2. Tugwell P, *et al.* Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. *Lancet* 1990; **335:** 1051–5.
3. Landewé RBM, *et al.* A randomized, double-blind, 24-week controlled study of low-dose cyclosporine versus chloroquine for early rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 637–43.
4. Førre Ø, *et al.* Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine: results of a 48-week multicenter study comparing low-dose cyclosporine with placebo. *Arthritis Rheum* 1994; **37:** 1506–12.
5. Wells G, *et al.* Cyclosporine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 15/01/08).
6. Tugwell P, *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; **333:** 137–41.
7. Proudman SM, *et al.* Treatment of poor-prognosis early rheumatoid arthritis. *Arthritis Rheum* 2000; **43:** 1809–19.
8. Gremese E, Ferraccioli GF. Benefit/risk of cyclosporine in rheumatoid arthritis. *Clin Exp Rheumatol* 2004; **22** (suppl 35): S101–S107.
9. Panayi GS, Tugwell P. The use of cyclosporin A microemulsion in rheumatoid arthritis: conclusions of an international review. *Br J Rheumatol* 1997; **36:** 808–11.
10. Gerloni V, *et al.* Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis: results of a 10-year prospective study. *Rheumatology (Oxford)* 2001; **40:** 907–13.
11. Ravelli A, *et al.* Combination therapy with methotrexate and cyclosporine A in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; **20:** 569–72.

Sarcoidosis. Corticosteroids are the usual therapy for symptomatic sarcoidosis (p.1512), and other agents are very much second-line; ciclosporin is one of a number of immunosuppressants that have been tried with variable results.

Scleritis. Ciclosporin is used alone or with corticosteroids in the treatment of scleritis (see p.1512).

Scleroderma. There are a few reports of responses to ciclosporin in patients with scleroderma (p.1817).

Toxic epidermal necrolysis. Ciclosporin, given either enterally[1] or intravenously,[2] has been reported to be of benefit in toxic epidermal necrolysis.

1. Arévalo JM, *et al.* Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; **48:** 473–8.
2. Hashim N, *et al.* Early cyclosporine treatment of incipient toxic epidermal necrolysis induced by concomitant use of lamotrigine and sodium valproate. *Acta Derm Venereol* 2004; **84:** 90–1.

Uveitis. Ciclosporin is used in uveitis, see p.1515.

Vasculitic syndromes. For the use of ciclosporin in Takayasu's arteritis and Wegener's granulomatosis, see p.1514 and p.1515, respectively.

Preparations

USP 31: Cyclosporine Capsules; Cyclosporine Injection; Cyclosporine Oral Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cermox; Gengraf†; Restasis; Sandimmun; ***Austral.:*** Cicloral; Cysporin; Neoral; Sandimmun; ***Austria:*** Cicloralhexal; Neoimmun; Sandimmun; ***Belg.:*** Neoral-Sandimmun; Sandimmun; ***Braz.:*** Gengraf; Restasis; Sandimmun; Sigmasporin; Zinograf†; ***Canad.:*** Neoral; Sandimmune; ***Chile:*** Gengraf; Modusik-A; Restasis; Sandimmun; ***Cz.:*** Consupren†; Equoral; Sandimmun; Sigmasporon; ***Denm.:*** Sandimmun; ***Fin.:*** Sandimmun; ***Fr.:*** Neoral; Sandimmun; ***Ger.:*** Cicloral; Immunosporin; Sandimmun; ***Gr.:*** Restasis; Sandimmun; ***Hong Kong:*** Gengraf; Sandimmun; ***Hung.:*** Sandimmun; ***India:*** Imusporin; Panimun Bioral; Sandimmun; ***Indon.:*** Sandimmun; ***Irl.:*** Neoral; Sandimmun; ***Israel:*** Deximune; Sandimmun; Sangcya; ***Ital.:*** Sandimmun; ***Jpn:*** Papilock; ***Malaysia:*** Gengraf; Sandimmun; ***Mex.:*** Immulem; Modusik-A; Restasis; Sandimmun; Supremunn; ***Neth.:*** Neoral; Sandimmune; ***Norw.:*** Sandimmun; ***NZ:*** Gengraf; Neoral; Sandimmun; ***Philipp.:*** Restasis; Sandimmun; ***Pol.:*** Equoral; Sandimmun; ***Port.:*** Ciclostar; Sandimmun; ***Rus.:*** Consupren (Консупрен); Sandimmun (Сандиммун); ***S.Afr.:*** Ciclohexal; Sandimmun; ***Singapore:*** Gengraf; ***Spain:*** Sandimmun; ***Swed.:*** Sandimmun; ***Switz.:*** Ciclosol; Sandimmun; ***Thai.:*** Consupren; Equoral; Gengraf; Restasis; Sanda; Sandimmun; ***Turk.:*** Gengraf; Sandimmun; ***UAE:*** Sigmasporin; ***UK:*** Neoral; Sandimmun; ***USA:*** Gengraf; Neoral; Restasis; Sandimmune; ***Venez.:*** Imusporin; Restasis; Sandimmun.

Daclizumab *(BAN, USAN, rINN)*

Dacliximab; Daclizumabum; Daklitsumabi; Daklizumab; Humanised Anti-Tac Antibody; Ro-24-7375. Immunoglobulin G 1, (human-mouse monoclonal 1H4 γ-chain, anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer.

Даклизумаб

CAS — 152923-56-3.

ATC — L04AC01.

ATC Vet — QL04AC01.

Adverse Effects and Precautions

Severe acute hypersensitivity reactions have occurred rarely with daclizumab. These have included anaphylactoid-type reactions such as rash, urticaria, pruritus, hypotension, hypoxia, tachycardia, cardiac arrest, wheezing, dyspnoea, bronchospasm, pulmonary oedema, peripheral oedema, laryngeal oedema, and respiratory failure. Injection site reactions have also been reported. Reactions have been seen both on initial exposure and with subsequent therapy. Therapy should be permanently stopped if a severe reaction occurs.

Effects on mortality. Increased mortality was reported in cardiac transplant recipients given an immunosuppressive regimen of daclizumab with ciclosporin, mycophenolate mofetil, and corticosteroids. Some deaths were associated with severe infection and use with antilymphocyte immunoglobulins.[1,2]

1. Roche, USA. 2003 safety alert: Zenapax (daclizumab). Available at: http://www.fda.gov/medwatch/SAFETY/2003/zenapax.htm (accessed 15/01/08)
2. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.

Pharmacokinetics

The recommended regimen of daclizumab (see below) should result in serum concentrations sufficient to saturate interleukin-2 receptors for about 90 days post-transplantation in adult patients, and 120 days in paediatric patients. The terminal elimination half-life of daclizumab has ranged from 11 to 38 days.

Uses and Administration

Daclizumab is a humanised monoclonal murine antibody that functions as an interleukin-2 receptor antagonist by binding to the alpha chain (CD25 antigen, Tac subunit) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is used in the prevention of acute graft rejection after kidney transplantation as part of an immunosuppressive regimen that includes ciclosporin and corticosteroids. It is given in a dose of 1 mg/kg intravenously over 15 minutes within 24 hours before surgery and repeated at intervals of 2 weeks for a total of 5 doses. The required dose is diluted in 50 mL of sodium chloride 0.9%, and may be infused either centrally or peripherally. Daclizumab is also under investigation for its immunosuppressant properties in other forms of transplantation (see below) and in various diseases with an auto-immune component.

Administration in children. The dose for daclizumab in children aged 1 year and over is the same as in adults (see Uses and Administration, above).

Multiple sclerosis. Daclizumab has been tried[1-4] in patients with relapsing-remitting or secondary progressive multiple sclerosis; benefit has been reported.

1. Bielekova B, *et al.* Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon β. *Proc Natl Acad Sci U S A* 2004; **101:** 8705–8.
2. Rose JW, *et al.* Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56:** 864–7.
3. Rose JW, *et al.* Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007; **69:** 785–9.
4. Martin R. Humanized anti-CD25 antibody treatment with daclizumab in multiple sclerosis. *Neurodegener Dis* 2008; **5:** 23–6.

Ocular disorders. There have been reports of benefit with daclizumab in ocular inflammatory disorders[1] including scleritis, ocular cicatricial pemphigoid, and uveitis, all of which had been resistant to conventional therapy.

1. Papaliodis GN, *et al.* Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003; **110:** 786–9.

Organ and tissue transplantation. Daclizumab is used as induction therapy to reduce the incidence of acute rejection episodes after kidney transplantation (p.1813);[1-4] it is usually given as part of an immunosuppressive regimen that includes a calcineurin inhibitor and corticosteroids.

There are reports of successful corticosteroid withdrawal and corticosteroid-free regimens using daclizumab.[5] An attempt at using daclizumab to avoid use of ciclosporin after renal transplantation was unsuccessful, with a high rate of overall acute rejection in the daclizumab group.[6]

Daclizumab has also been investigated for the prevention of acute rejection after heart,[7] liver,[8,9] and lung[10] transplantation (see p.1812) but increased mortality has followed its use in patients receiving heart grafts[11] (see also under Adverse Effects and Precautions, above).

Daclizumab has also been tried in the management of acute graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p.1811). While some consider it a viable alternative for corticosteroid-refractory acute GVHD,[12] others found that when daclizumab was used with corticosteroids to treat acute GVHD, this combination had a significantly deleterious effect on patient survival.[13]

Controlled studies that directly compare 2 doses of daclizumab with the standard 5-dose regimen in kidney transplantation are lacking; despite this, many centres use a 2-dose regimen.[14] In a small, retrospective analysis[15] of simultaneous kidney-pancreas transplant recipients (p.1816), patients receiving 1 to 3 doses of daclizumab in addition to triple therapy had a significantly higher incidence of rejection than those receiving 4 to 5 doses. There was no difference in patient or graft survival. A larger multicentre study[16,17] found that simultaneous kidney-pancreas recipients given daclizumab 2 mg/kg every 14 days for 2 doses had a similar incidence of rejection to those given the standard 5-dose regimen; mean time to onset of rejection was delayed in the 2-dose regimen but there was no beneficial effect of daclizumab on graft survival at 3 years. A small comparative study[18] in heart transplant recipients found 2 doses of daclizumab to be at least as effective as the 5-dose regimen; no significant differences were observed for mortality. A novel 3-dose regimen has been investigated in liver transplantation.[19]

1. Vincenti F, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 1998; **338:** 161–5.
2. Nashan B, *et al.* Reduction of acute renal allograft rejection by daclizumab. *Transplantation* 1999; **67:** 110–15.
3. Bumgardner GL, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; **72:** 839–45.
4. Ciancio G, *et al.* Daclizumab induction, tacrolimus, mycophenolate mofetil and steroids as an immunosuppression regimen for primary kidney transplant recipients. *Transplantation* 2002; **73:** 1100–6.
5. ter Meulen CG, *et al.* Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. *Am J Transplant* 2004; **4:** 803–10.
6. Åsberg A, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006; **82:** 62–8.
7. Beniaminovitz A, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med* 2000; **342:** 613–19.
8. Niemeyer G, *et al.* Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; **2:** 454–60.
9. Figueras J, *et al.* Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. *Transpl Int* 2006; **19:** 641–8.
10. Garrity ER, *et al.* Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; **71:** 773–7.
11. Hershberger RE, *et al.* Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; **352:** 2705–13.
12. Bordigoni P, *et al.* Daclizumab, an efficient treatment for steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2006; **135:** 382–5.
13. Lee SJ, *et al.* Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood* 2004; **104:** 1559–64.
14. van Gelder T, *et al.* Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; **64:** 1737–41.
15. Bruce DS, *et al.* Multicenter survey of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplantation* 2001; **72:** 1637–43.
16. Stratta RJ, *et al.* One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc* 2004; **36:** 1080–1.
17. Stratta RJ, *et al.* A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc* 2005; **37:** 3531–4.
18. Ortiz V, *et al.* Induction therapy with daclizumab in heart transplantation—how many doses? *Transplant Proc* 2006; **38:** 2541–3.
19. Washburn WK, *et al.* A novel three-dose regimen of daclizumab in liver transplant recipients with hepatitis C: a pharmacokinetic and pharmacodynamic study. *Liver Transpl* 2006; **12:** 585–91.

Skin disorders. There are reports of successful treatment with daclizumab in psoriasis (p.1583),[1,2] pemphigus vulgaris,[3] bullous pemphigoid[4] (see Pemphigus and Pemphigoid, p.1582), and epidermolysis bullosa acquisita[5] (p.1579). Cutaneous manifestations of adult T-cell leukaemia/lymphoma have also been reported to respond to daclizumab.[6]

1. Wohlrab J, *et al.* Treatment of recalcitrant psoriasis with daclizumab. *Br J Dermatol* 2001; **144:** 209–10.
2. Dichmann S, *et al.* Humanized monoclonal anti-CD25 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; **47:** 635–6.
3. Renkl A, *et al.* A novel therapeutic option in pemphigus vulgaris: humanized monoclonal anti-CD25 antibody. *Br J Dermatol* 2004; **150:** 1220–2.
4. Mockenhaupt M, *et al.* Daclizumab: a novel therapeutic option in severe bullous pemphigoid. *Acta Derm Venereol* 2005; **85:** 65–6.
5. Egan CA, *et al.* Treatment of epidermolysis bullosa acquisita with the humanised anti-Tac mAb daclizumab. *Clin Immunol* 2001; **101:** 146–51.
6. Osborne GEN, *et al.* Novel treatment of Sézary-like syndrome due to adult T-cell leukaemia/lymphoma with daclizumab (humanized anti-interleukin-2 receptor α antibody). *Br J Dermatol* 2006; **155:** 617–20.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Zenapax; ***Austral.:*** Zenapax; ***Austria:*** Zenapax; ***Belg.:*** Zenapax†; ***Braz.:*** Zenapax; ***Canad.:*** Zenapax; ***Chile:*** Zenapax; ***Cz.:*** Zenapax; ***Denm.:*** Zenapax; ***Fin.:*** Zenapax; ***Fr.:*** Zenapax; ***Ger.:*** Zenapax; ***Gr.:*** Zenapax; ***Hong Kong:*** Zenapax; ***Hung.:*** Zenapax; ***Irl.:*** Zenapax; ***Israel:*** Zenapax; ***Ital.:*** Zenapax; ***Mex.:*** Zenapax; ***Neth.:*** Zenapax; ***NZ:*** Zenapax; ***Philipp.:*** Zenapax; ***Pol.:*** Zenapax; ***Port.:*** Zenapax; ***S.Afr.:*** Zenapax; ***Singapore:*** Zenapax†; ***Spain:*** Zenapax; ***Swed.:*** Zenapax; ***Switz.:*** Zenapax; ***Thai.:*** Zenapax; ***Turk.:*** Zenapax; ***UK:*** Zenapax; ***USA:*** Zenapax; ***Venez.:*** Zenapax.

Everolimus *(USAN, rINN)*

Évérolimus; Everolimús; Everolimusum; NVP-RAD-001; RAD-001; SDZ-RAD; SDZ-RAD-666. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone.

Эверолимус

$C_{53}H_{83}NO_{14}$ = 958.2.

CAS — 159351-69-6.

ATC — L04AA18.

ATC Vet — QL04AA18.

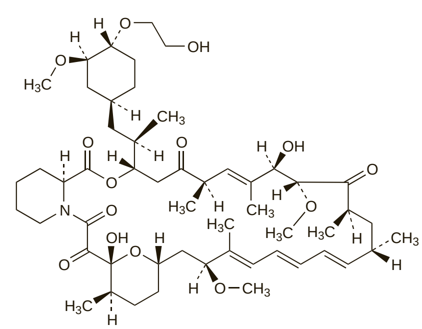

Adverse Effects

Leucopenia, thrombocytopenia, and anaemia occur commonly with everolimus. Haemolysis has been reported rarely. Other common adverse effects include hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypertension, lymphocele, venous thromboembolism, and gastrointestinal upsets. Pneumonia, pneumonitis, hepatitis, jaundice, renal tubular necrosis, and pyelonephritis may occur. Acne and oedema occur frequently; rashes and myalgia occur rarely.

Effects on the lungs. Pulmonary toxicity is a well-known adverse effect in patients given sirolimus (p.1841) and similar toxicity has occurred[1] in patients given everolimus.

1. Expósito V, *et al.* Everolimus-related pulmonary toxicity in heart transplant recipients. *J Heart Lung Transplant* 2008; **27:** 797–800.

Interactions

Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall; plasma concentrations may be affected by inducers or competitive inhibitors of P-glycoprotein, or hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4. Use with live vaccines should be avoided.

◊ References.

1. Kovarik JM, *et al.* Everolimus drug interactions: application of a classification system for clinical decision making. *Biopharm Drug Dispos* 2006; **27:** 421–6.

Immunosuppressants. The bioavailability of everolimus was significantly increased when given with *ciclosporin*,[1] and dose adjustment of everolimus may be necessary if the ciclosporin dose is altered (see Administration, below).

In contrast, results from a small study implied that *tacrolimus* appeared to have a minimal effect on everolimus blood concentrations, and the dose of everolimus, when used with tacrolimus, may need to be higher than that given with ciclosporin in order to achieve therapeutic everolimus blood concentrations.[2]

1. Kovarik JM, *et al.* Differential influence of two cyclosporine formulations on everolimus pharmacokinetics: a clinically relevant pharmacokinetic interaction. *J Clin Pharmacol* 2002; **42:** 95–9.
2. Kovarik JM, *et al.* Differential pharmacokinetic interaction of tacrolimus and cyclosporine on everolimus. *Transplant Proc* 2006; **38:** 3456–8.

Ketoconazole. In a pharmacokinetic study in 12 healthy subjects,[1] ketoconazole increased the maximum concentration of everolimus by an average of 3.9-fold; area under the concentration-time curve was also increased by about 15-fold. The half-life of everolimus was significantly prolonged, and its clearance reduced. Since ketoconazole inhibits both cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, the authors supposed that both pathways might have contributed to this interaction. The interaction was deemed to be clinically relevant and they advised against use of these 2 drugs together.

1. Kovarik JM, *et al.* Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* 2005; **45:** 514–18.

Rifampicin. In a pharmacokinetic study,[1] rifampicin increased the clearance of everolimus, decreasing exposure to everolimus by about 63%. Licensed product information recommends against the combined use of these drugs.

1. Kovarik JM, *et al.* Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother* 2002; **36:** 981–5.

Verapamil. Verapamil increased the bioavailability of everolimus; the half-life of everolimus was essentially unchanged. The dose of everolimus should be reduced when these two drugs are given together, but the amount should be determined by blood concentrations and clinical monitoring. Verapamil concentrations may also be affected by everolimus, but the mechanism is unclear; any dose adjustment of verapamil should be guided by blood pressure monitoring.[1]

1. Kovarik JM, *et al.* Pharmacokinetic interaction between verapamil and everolimus in healthy subjects. *Br J Clin Pharmacol* 2005; **60:** 434–7.

Pharmacokinetics

Peak plasma concentrations of everolimus occur about 1 to 2 hours after an oral dose. Plasma protein binding is about 74%. Everolimus is metabolised in the liver and to some extent in the gastrointestinal wall; most metabolites are excreted in the faeces with small amounts found in urine.

◊ References.

1. Kovarik JM, *et al.* Clinical development of an everolimus pediatric formulation: relative bioavailability, food effect, and steady-state pharmacokinetics. *J Clin Pharmacol* 2003; **43:** 141–7.
2. Kirchner GI, *et al.* Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004; **43:** 83–95.

Therapeutic drug monitoring. Licensed product information recommends routine monitoring of whole blood everolimus concentrations. Patients with trough levels of 3 nanograms/mL or greater have been found to have a lower incidence of acute rejection in both renal and cardiac transplantation; an upper limit of 8 nanograms/mL is recommended. Monitoring is considered especially important in those with hepatic impairment (see under Uses, below) and if ciclosporin formulation or dosage is changed (see Administration, below).

Further references.

1. Kovarik JM, *et al.* Exposure-response relationships for everolimus in de novo kidney transplantation: defining a therapeutic range. *Transplantation* 2002; **73:** 920–5.
2. Kovarik JM, *et al.* Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. *Ther Drug Monit* 2004; **26:** 499–505.
3. Starling RC, *et al.* Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. *Am J Transplant* 2004; **4:** 2126–31.
4. Lorber MI, *et al.* Therapeutic drug monitoring for everolimus in kidney transplantation using 12-month exposure, efficacy, and safety data. *Clin Transplant* 2005; **19:** 145–52.
5. Mabasa VH, Ensom MH. The role of therapeutic monitoring of everolimus in solid organ transplantation. *Ther Drug Monit* 2005; **27:** 666–76.
6. Kovarik JM, *et al.* Everolimus in pulmonary transplantation: pharmacokinetics and exposure-response relationships. *J Heart Lung Transplant* 2006; **25:** 440–6.

Uses and Administration

Everolimus is a derivative of sirolimus (p.1841). It is used as a proliferation signal inhibitor in the prevention of graft rejection episodes in patients undergoing renal or cardiac transplantation as part of an immunosuppressive regimen that includes ciclosporin (microemulsifying) and corticosteroids. The recommended adult oral dose is 750 micrograms twice daily, begun as soon as possible after transplantation, and given at the same time as ciclosporin (see Administration, below). Doses of everolimus should be reduced in patients with hepatic impairment, see below.

Everolimus is also under investigation for the treatment of renal cell carcinoma.

Everolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

Administration. Everolimus is given with ciclosporin and corticosteroids. Ciclosporin exposure reduction is recommended 1 month after transplantation. Because ciclosporin interacts with everolimus, and the dose adjustments of ciclosporin will affect exposure to everolimus, licensed product information for everolimus recommends that levels of both drugs be monitored to minimise the risk of graft rejection. Before dose reduction of ciclosporin, everolimus whole blood concentrations should be at least 3 nanograms/mL (see Therapeutic Drug Monitoring, above, and under Ciclosporin, p.1829).

In renal transplantation, ciclosporin doses should be adjusted to the following target ciclosporin concentration ranges, as measured 2 hours after the dose of ciclosporin:

- weeks 0-4: 1000 to 1400 nanograms/mL
- weeks 5-8: 700 to 900 nanograms/mL
- weeks 9-12: 550 to 650 nanograms/mL
- weeks 13-52: 350 to 450 nanograms/mL

In cardiac transplantation, ciclosporin levels are adjusted according to ciclosporin blood trough levels.

Administration in hepatic impairment. The clearance of everolimus was significantly reduced in patients with moderate hepatic impairment.[1] Product information states that the dose should be reduced by 50% in mild to moderate hepatic impairment (Child-Pugh class A or B) with further titration of the dose based on therapeutic drug monitoring (see under Pharmacokinetics, above). Everolimus has not been studied in severe hepatic impairment.

1. Kovarik JM, *et al.* Influence of hepatic impairment on everolimus pharmacokinetics: implications for dose adjustment. *Clin Pharmacol Ther* 2001; **70:** 425–30.

Organ and tissue transplantation. References.

1. Eisen HJ, *et al.* Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; **349:** 847–58.
2. Vitko S, *et al.* Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant* 2004; **4:** 626–35.
3. Nashan B, *et al.* Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. *Transplantation* 2004; **78:** 1332–40.
4. Lorber MI, *et al.* Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; **80:** 244–52.
5. Vitko S, *et al.* Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2005; **5:** 2521–30. Correction. *ibid.* 2006; **6:** 243.
6. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; **6:** 169–77.
7. Pascual J. Everolimus in clinical practice—renal transplantation. *Nephrol Dial Transplant* 2006; **21** (suppl 3): iii18–iii23.
8. Webster AC, *et al.* Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 18/02/08).
9. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs* 2006; **66:** 547–70.
10. Snell GI, *et al.* Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. *Am J Transplant* 2006; **6:** 169–77.
11. Levy G, *et al.* Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; **12:** 1640–8.
12. Chapman JR, *et al.* Proliferation signal inhibitors in transplantation: questions at the cutting edge of everolimus therapy. *Transplant Proc* 2007; **39:** 2937–50.

Psoriasis. A patient with psoriasis and a poor response to conventional therapy was treated with everolimus and ciclosporin. All manifestations improved after 4 weeks of therapy, but treatment had to be stopped after the patient developed leucopenia.[1]

1. Frigerio E, *et al.* Severe psoriasis treated with a new macrolide: everolimus. *Br J Dermatol* 2007; **156:** 372–4.

Reperfusion and revascularisation procedures. References to the use of everolimus-eluting stents.

1. Grube E, *et al.* Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* 2004; **109:** 2168–71.
2. Grube E, Buellesfeld L. Everolimus for stent-based intracoronary applications. *Rev Cardiovasc Med* 2004; **5** (suppl): S3–S8.
3. Tsuchiya Y, *et al.* Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials). *Am J Cardiol* 2006; **98:** 464–9.
4. Ormiston JA, *et al.* First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. *Catheter Cardiovasc Interv* 2007; **69:** 128–31.
5. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: a novel second generation drug-eluting stent. *Expert Rev Med Devices* 2007; **4:** 11–21.
6. Stone GW, *et al.* SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 2008; **299:** 1903–13.
7. Biondi-Zoccai G, *et al.* Percutaneous coronary intervention with everolimus-eluting stents (Xience V): systematic review and direct-indirect comparison meta-analyses with paclitaxel-eluting stents (Taxus) and sirolimus-eluting stents (Cypher). *Minerva Cardioangiol* 2008; **56:** 55–65.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Certican; ***Austral.:*** Certican; ***Austria:*** Certican; ***Belg.:*** Certican; ***Braz.:*** Certican; ***Chile:*** Certican; ***Cz.:*** Certican; ***Denm.:*** Certican; ***Fin.:*** Certican; ***Fr.:*** Certican; ***Ger.:*** Certican; ***Gr.:*** Certican; ***Hung.:*** Certican; ***Israel:*** Certican; ***Ital.:*** Certican; ***Mex.:*** Certican; ***Neth.:*** Certican; ***Norw.:*** Certican; ***Pol.:*** Certican; ***Port.:*** Certican; ***S.Afr.:*** Certican; ***Spain:*** Certican; ***Swed.:*** Certican; ***Switz.:*** Certican; ***Thai.:*** Certican; ***Venez.:*** Certican.

Gavilimomab *(rINN)*

Gavilimomabum. Immunoglobulin M, anti-(human antigen CD147)(mouse monoclonal ABX-CBL μ-chain), disulfide with mouse monoclonal ABX-CBL light chain, pentamer.

Гавилимомаб

CAS — 244096-20-6.

Profile

Gavilimomab is an anti-CD147 monoclonal antibody of murine origin that has been investigated for the treatment of acute graft-versus-host disease.

◊ References.

1. Deeg HJ, *et al.* Treatment of steroid-refractory acute graft-versus-host disease with anti-CD147 monoclonal antibody ABX-CBL. *Blood* 2001; **98:** 2052–8.
2. Macmillan ML, *et al.* A phase 2/3 multicenter randomized clinical trial of ABX-CBL versus ATG as secondary therapy for steroid-resistant acute graft-versus-host disease. *Blood* 2007; **109:** 2657–62.

Gusperimus Hydrochloride *(rINNM)*

BMS-181173; BMY-42215-1; Deoxyspergualin Hydrochloride; 15-Deoxyspergualin Hydrochloride; Guspérimus, Chlorhydrate de; Gusperimus Trihydrochloride *(USAN)*; Gusperimusi Hydrochloridum; Hidrocloruro de gusperimús; NKT-01; NSC-356894.

(±)-*N*-[({4-[(3-Aminopropyl)amino]butyl}carbamoyl)hydroxymethyl]-7-guanidinoheptanamide trihydrochloride.

Гусперимуса Гидрохлорид

$C_{17}H_{37}N_7O_3,3HCl = 496.9.$

CAS — 104317-84-2 (gusperimus); 89149-10-0 (gusperimus); 85468-01-5 (gusperimus hydrochloride).

ATC — L04AA19.

ATC Vet — QL04AA19.

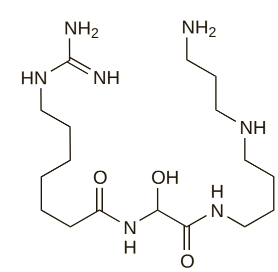

(gusperimus)

Profile

Gusperimus is a guanidine derivative that inhibits both cell-mediated and antibody-mediated immunity. It is used in the treatment of renal graft rejection, and has been investigated in the management of graft-versus-host disease and Wegener's granulomatosis. For mention of its role in reversing acute graft rejection in kidney transplantation, see p.1813.

Gusperimus is used as the hydrochloride. A dose of 3 to 5 mg/kg of gusperimus hydrochloride given daily for 7 days, by intravenous infusion over 3 hours, has been suggested in the treatment of acute renal graft rejection. Treatment may be continued for a further 3 days if required.

Adverse effects reported with gusperimus include bone-marrow depression, numbness of face and extremities, headache, gastrointestinal disturbances, alterations in liver enzyme values, and facial flushing. Rapid injection should be avoided as an acute increase in plasma concentration may produce respiratory depression.

◊ References.

1. Ramos EL, *et al.* Deoxyspergualin: mechanism of action and pharmacokinetics. *Transplant Proc* 1996; **28:** 873–5.
2. Tanabe K, *et al.* Effect of deoxyspergualin on the long-term outcome of renal transplantation. *Transplant Proc* 2000; **32:** 1745–6.
3. Amada N, *et al.* Prophylactic use of deoxyspergualin improves long-term graft survival in living related renal transplant recipients transfused with donor-specific blood. *Transplant Proc* 2001; **33:** 2256–7.
4. Birck R, *et al.* 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003; **14:** 440–7.
5. Schmitt WH, *et al.* Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol Dial Transplant* 2005; **20:** 1083–92.
6. Amada N, *et al.* Deoxyspergualin prophylaxis with tacrolimus further improves long-term graft survival in living-related renal-transplant recipients transfused with donor-specific blood. *Transplant Proc* 2005; **37:** 927–9.
7. Nojima M, *et al.* Combined therapy of deoxyspergualin and plasmapheresis: a useful treatment for antibody-mediated acute rejection after kidney transplantation. *Transplant Proc* 2005; **37:** 930–3.
8. Kawagishi N, *et al.* Usage of deoxyspergualin on steroid-resistant acute rejection in living donor liver transplantation. *Tohoku J Exp Med* 2006; **208:** 225–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Spanidin; ***Jpn:*** Spanidin.

Inolimomab *(rINN)*

BT-563; Inolimomabum. Immunoglobulin G1, anti-(human interleukin 2 receptor α-chain) (mouse monoclonal B-B10 γ1-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer.

Инолимомаб

CAS — 152981-31-2.

Profile

Inolimomab is a murine/human monoclonal antibody similar to daclizumab (p.1833) that acts as an interleukin-2 receptor antagonist at the alpha chain (CD25) of the interleukin-2 receptor on the surface of activated T-lymphocytes. It is under investigation for the treatment of graft-versus-host disease after organ transplantation (p.1810).

◊ References.

1. Winkler M. Inolimomab (OPi). *Curr Opin Investig Drugs* 2002; **3:** 1464–7.
2. Wabbijn M, *et al.* Ten-year follow-up of recipients of a kidney or heart transplant who received induction therapy with a monoclonal antibody against the interleukin-2 receptor. *Exp Clin Transplant* 2004; **2:** 201–7.
3. Bay JO, *et al.* Inolimomab in steroid-refractory acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation: retrospective analysis and comparison with other interleukin-2 receptor antibodies. *Transplantation* 2005; **80:** 782–8.

Mizoribine *(rINN)*

HE-69; Mizoribina; Mizoribinum. 5-Hydroxy-1-β-D-ribofuranosylimidazole-4-carboxamide.

Мизорибин

$C_9H_{13}N_3O_6$ = 259.2.

CAS — 50924-49-7.

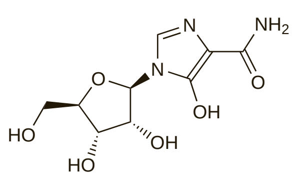

Profile

Mizoribine is an oral immunosuppressant that is used for the management of rejection in kidney transplantation, for nephrotic syndrome associated with primary glomerular disease, for lupus nephritis, and for rheumatoid arthritis.

Adverse effects include myelosuppression, hyperuricaemia, gastrointestinal disturbances, and hypersensitivity reactions. Stevens-Johnson syndrome has also been reported.

◊ Although oral doses of mizoribine of 1 to 3 mg/kg daily have been recommended in renal transplantation, higher doses (above 5 mg/kg daily) have been widely used. Similarly, an oral dose of 50 mg three times daily has been recommended for patients with nephrotic syndrome associated with primary glomerular disease or lupus nephritis, and in rheumatoid arthritis, but high-dose regimens have been investigated.

Further references.

1. Tanabe K, *et al.* Long-term results in mizoribine-treated renal transplant recipients: a prospective, randomized trial of mizoribine and azathioprine under cyclosporine-based immunosuppression. *Transplant Proc* 1999; **31:** 2877–9.
2. Yoshioka K, *et al.* A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. *Kidney Int* 2000; **58:** 317–24.
3. Yokota S. Mizoribine: mode of action and effects in clinical use. *Pediatr Int* 2002; **44:** 196–8.
4. Takei S. Mizoribine in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. *Pediatr Int* 2002; **44:** 205–9.
5. Honda M. Nephrotic syndrome and mizoribine in children. *Pediatr Int* 2002; **44:** 210–6.
6. Nagaoka R, *et al.* Mizoribine treatment for childhood IgA nephropathy. *Pediatr Int* 2002; **44:** 217–23.
7. Tsuzuki K. Role of mizoribine in renal transplantation. *Pediatr Int* 2002; **44:** 224–31.
8. Shibasaki T, *et al.* A randomized open-label comparative study of conventional therapy versus mizoribine onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clin Exp Nephrol* 2004; **8:** 117–26.
9. Akiyama T, *et al.* Mizoribine in combination therapy with tacrolimus for living donor renal transplantation: analysis of a nationwide study in Japan. *Transplant Proc* 2005; **37:** 843–5.
10. Tanaka H, *et al.* Long-term mizoribine intermittent pulse therapy for young patients with flare of lupus nephritis. *Pediatr Nephrol* 2006; **21:** 962–6.
11. Tanaka E, *et al.* Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. *Mod Rheumatol* 2006; **16:** 214–19.
12. Sugitani A, *et al.* Revival of effective and safe high-dose mizoribine for the kidney transplantation. *Clin Transplant* 2006; **20:** 590–5.
13. Kawasaki Y, *et al.* Efficacy of single dose of oral mizoribine pulse therapy two times per week for frequently relapsing nephrotic syndrome. *J Nephrol* 2007; **20:** 52–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Bredinin.

Muromonab-CD3 *(USAN, rINN)*

Muromonabum-CD3; OKT3.

Муромонаб-CD3

ATC — L04AA02.

ATC Vet — QL04AA02.

Description. A murine monoclonal antibody comprising a purified IgG_{2a} immunoglobulin with a heavy chain having a molecular weight of about 50 000 daltons and a light chain with a molecular weight of about 25 000 daltons.

Pharmacopoeias. In *Chin.*

Adverse Effects, Treatment, and Precautions

An acute cytokine release syndrome occurs in most patients, typically 30 to 60 minutes after the first few doses of muromonab-CD3 (although it may occur later). Frequency and severity tend to decrease with successive doses, while prophylactic corticosteroids may reduce initial adverse reactions (see Uses and Administration, below). The syndrome ranges from a more frequently reported, mild, self-limiting, flu-like illness to a less common, severe, and life-threatening, shock-like reaction, which may include serious cardiovascular and CNS manifestations. Typical clinical manifestations of the cytokine release syndrome include high fever, chills or rigors, headache, tremor, gastrointestinal disturbances, myalgia, and generalised weakness. Rash and pruritus may also occur. Cardiorespiratory findings may include apnoea, dyspnoea, bronchospasm or wheezing, tachypnoea, respiratory arrest or failure, acute respiratory distress syndrome, angina, myocardial infarction, chest pain or tightness, tachycardia, hypertension, hypotension, cardiac failure, pulmonary oedema, hypoxaemia, and arrhythmias. Reversible impairment of renal function may also be associated with the syndrome.

Other reported effects of muromonab-CD3 include encephalopathy, cerebral oedema, and a syndrome resembling aseptic meningitis, with headache, fever, stiff neck, and photophobia; seizures have also occurred. Hypersensitivity reactions, including fatal anaphylaxis, have been reported and may be difficult to distinguish from the cytokine release syndrome.

As with other potent immunosuppressants, treatment with muromonab-CD3 may increase the risk of serious infections and the development of certain malignancies. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason.

Muromonab-CD3 should not be given to patients with uncontrolled hypertension, or in patients hypersensitive to products of murine origin. It should be avoided in patients with a history of seizures. Because fluid overload is associated with an increased risk of pulmonary oedema due to the cytokine release syndrome, muromonab-CD3 is contra-indicated in patients who have undergone a more than 3% weight gain in the week preceding therapy, or who have radiographic evidence of fluid overloading. Repeated courses of muromonab-CD3 may be less effective because of the development of antibodies to the drug. Paediatric patients may be at increased risk of serious adverse effects following muromonab-CD3 therapy.

Effects on the blood. *THROMBOEMBOLISM.* Intragraft thromboses developed in 9 of 93 consecutive kidney transplant recipients given high-dose muromonab-CD3 (10 mg daily) as part of their immunosuppressive regimen.[1] In one patient the thrombosis was in the renal artery, and in 3 in the renal vein; the remainder had thromboses in the glomerular capillaries and thrombotic microangiopathy similar to that of haemolytic-uraemic syndrome. The authors suggested that muromonab-CD3 has procoagulant effects, perhaps mediated by released tumour necrosis factor; these effects had also been seen in 3 patients receiving muromonab-CD3 at conventional doses (5 mg daily). Another group[2] has also reported an apparently increased incidence of acute vascular thrombosis in patients given muromonab-CD3 at conventional doses, but in the experience of others,[3] despite evidence of activation of coagulation by the drug, treatment of acute rejection with 5 mg daily was not associated with thromboembolic complications. US licensed product information states that the relationship to dose remains unclear, but that the relative risk appears to be greater with doses above the recommended dose.

1. Abramowicz D, *et al.* Induction of thromboses within renal grafts by high-dose prophylactic OKT3. *Lancet* 1992; **339:** 777–8.
2. Gomez E, *et al.* Main graft vessels thromboses due to conventional-dose OKT3 in renal transplantation. *Lancet* 1992; **339:** 1612–13.
3. Raasveld MHM, *et al.* Thromboembolic complications and dose of monoclonal OKT3 antibody. *Lancet* 1992; **339:** 1363–4.

Effects on the ears. Bilateral sensorineural hearing loss has occurred after muromonab-CD3 therapy. In one case series, 5 out of 7 patients were affected, showing a mean hearing loss of 18 decibels.[1] Tinnitus may also occur.[1,2] Although symptoms are generally reversible,[1,2] one patient still showed a deficit in hearing after 6 months.[3]

1. Hartnick CJ, *et al.* Reversible sensorineural hearing loss following administration of muromonab-CD3 (OKT3) for cadaveric renal transplant immunosuppression. *Ann Otol Rhinol Laryngol* 2000; **109:** 45–7.
2. Hartnick CJ, *et al.* Reversible sensorineural hearing loss after renal transplant immunosuppression with OKT3 (muromonab-CD3). *Ann Otol Rhinol Laryngol* 1997; **106:** 640–2.
3. Michals M, *et al.* Hearing loss associated with muromonab-CD3 therapy. *Clin Pharm* 1988; **7:** 867–8.

Effects on the nervous system. Generalised seizures were reported in 2 uraemic kidney-graft recipients given muromonab-CD3.[1] Delayed graft function may result in the accumulation of uraemic toxins which combine with cytokines released by the immunosuppressant to produce the effects on the CNS. Seizures and encephalopathy were reported in siblings given muromonab-CD3 after renal transplantation, and appeared to predispose one of them to develop ciclosporin neurotoxicity.[2] A neurological syndrome characterised by akinetic mutism, blepharospasm, anomic aphasia, and delirium, occurred in a heart transplant patient given muromonab-CD3; symptoms resolved after stopping therapy.[3]

The manufacturers have warned that children treated with muromonab-CD3 may be at increased risk of nervous system complications, notably cerebral oedema that may result in fatal cerebral herniation. Since 1986, and as of May 2004, 9 cases of cerebral oedema had been reported worldwide in children, resulting in 6 deaths. Cerebral herniation had occurred within a few hours to 1 day after injection. Signs include the sudden appearance of severe headache, seizures, impaired mental function, drowsiness and lethargy, and coma.[4]

1. Seifeldin RA, *et al.* Generalized seizures associated with the use of muromonab-CD3 in two patients after kidney transplantation. *Ann Pharmacother* 1997; **31:** 586–9.

2. Thaisetthawatkul P, *et al.* Muromonab-CD3-induced neurotoxicity: report of two siblings, one of whom had subsequent cyclosporin-induced neurotoxicity. *J Child Neurol* 2001; **16:** 825–31.
3. Pittock SJ, *et al.* OKT3 neurotoxicity presenting as akinetic mutism. *Transplantation* 2003; **75:** 1058–60.
4. Janssen-Ortho, Canada. Important new safety information on Orthoclone OKT*3 (muromonab-CD3) (issued 17 May 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/orthoclone_okt3_pa-ap-eng.pdf (accessed 18/02/08)

Pharmacokinetics

Therapeutic drug monitoring. US licensed product information states that serum concentrations of muromonab-CD3 are measurable using an enzyme-linked immunosorbent assay (ELISA). Studies in organ transplant recipients found that patients less than 10 years of age had higher concentrations than patients aged 10 to 50 years. Subsequent clinical experience has shown that serum concentrations of muromonab-CD3 greater than or equal to 800 nanograms/mL block the function of T-cells. Reduced T-cell clearance or low plasma concentrations of muromonab-CD3 provide a basis for adjusting muromonab dosage or stopping therapy.

In adults, periodic monitoring to ensure plasma muromonab-CD3 concentrations of 800 nanograms/mL or greater, or CD3-positive cells less than 25 cells/mm^3 is recommended. Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require increased doses of muromonab-CD3 to achieve similar depletion of CD3-positive cells and therapeutic serum concentrations; both T-cell clearance and plasma muromonab-CD3 should be monitored daily in children.

Uses and Administration

Muromonab-CD3 is a murine monoclonal antibody to the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response; the antibody thus specifically blocks T-cell generation and function, to exert an immunosuppressant effect without affecting the bone marrow.

It is used in the treatment of acute allograft rejection in organ transplant recipients, in doses of 5 mg daily by intravenous injection for 10 to 14 days. For children's doses, see Administration in Children, below. The dose of any other immunosuppressant therapy may need to be reduced. Patients should be monitored closely after the first few doses of muromonab-CD3 because of the risk of cytokine release syndrome and hypersensitivity reactions. The first dose may be preceded by intravenous methylprednisolone sodium succinate, in a dose of 8 mg/kg, 1 to 4 hours before muromonab-CD3. Paracetamol and antihistamines may also be given with muromonab-CD3 to reduce early reactions.

Muromonab-CD3 has also been given experimentally as part of regimens for the prophylaxis of graft rejection. For further details of the use of muromonab-CD3 in the treatment and prophylaxis of graft rejection see Organ and Tissue Transplantation, p.1810, *et seq.*

◊ References.

1. ten Berge IJM, *et al.* Guidelines for optimal use of muromonab CD3 in transplantation. *BioDrugs* 1999; **11:** 277–84.
2. Flechner SM. A randomized prospective trial of low-dose OKT3 induction therapy to prevent rejection and minimize side effects in recipients of kidney transplants. *Transplantation* 2000; **69:** 2374–81.
3. Henry ML, *et al.* A randomized prospective trial of OKT3 induction in the current immunosuppression era. *Clin Transplant* 2001; **15:** 410–14.
4. Benfield MR, *et al.* A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. *Pediatr Transplant* 2005; **9:** 282–92.
5. Knop S, *et al.* OKT3 muromonab as second-line and subsequent treatment in recipients of stem cell allografts with steroid-resistant acute graft-versus-host disease. *Bone Marrow Transplant* 2005; **36:** 831–7.
6. Sevmis S, *et al.* OKT3 treatment for steroid-resistant acute rejection in kidney transplantation. *Transplant Proc* 2005; **37:** 3016–18.
7. Wilmot I, *et al.* OKT3 treatment in refractory pediatric heart transplant rejection. *J Heart Lung Transplant* 2005; **24:** 1793–7.

Administration in children. The initial recommended doses in children given muromonab-CD3 for acute allograft rejection are as follows:

- those weighing 30 kg or less: 2.5 mg daily
- those weighing more than 30 kg: 5 mg daily

Doses are given by intravenous injection for 10 to 14 days.

Paediatric patients are known to have higher CD3 lymphocyte counts than adults, and often require doses to be titrated upwards. The initial dose may be subsequently adjusted in 2.5 mg increments to achieve T-cell clearance (CD3-positive cells less than 25 cells/mm^3) and ensure therapeutic serum concentrations of muromonab-CD3 (of 800 nanograms/mL or greater, see Therapeutic Drug Monitoring, above).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Orthoclone OKT3; ***Belg.:*** Orthoclone OKT3; ***Braz.:*** Orthoclone OKT3; ***Canad.:*** Orthoclone OKT3; ***Chile:*** Ior T3†; ***Cz.:*** Cedetrin-T†; Orthoclone OKT3†; ***Fin.:*** Orthoclone OKT3; ***Fr.:*** Orthoclone OKT3; ***Ger.:*** Orthoclone OKT3; ***Gr.:*** Orthoclone; ***Hong Kong:*** Orthoclone OKT3†; ***Israel:*** Orthoclone OKT3; ***Ital.:*** Orthoclone OKT3; ***Malaysia:*** Orthoclone OKT3†; ***Mex.:*** Ior-T3; Orthoclone OKT3; ***Neth.:*** Orthoclone OKT3; ***Norw.:*** Orthoclone OKT3; ***NZ:*** Orthoclone OKT3; ***S.Afr.:*** Orthoclone; ***Swed.:*** Orthoclone OKT3; ***Switz.:*** Orthoclone OKT3; ***Thai.:*** Orthoclone OKT3†; ***Turk.:*** Orthoclone OKT3; ***USA:*** Orthoclone OKT3.

Mycophenolate

ATC — L04AA06.
ATC Vet — QL04AA06.

Mycophenolic Acid *(BAN, USAN, rINN)*

Acide Mycophénolique; Ácido micofenólico; Acidum Mycophenolicum; Lilly-68618; MPA; NSC-129185. (*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid.

Микофеноловая Кислота

$C_{17}H_{20}O_6$ = 320.3.
CAS — 24280-93-1.
ATC — L04AA06.
ATC Vet — QL04AA06.

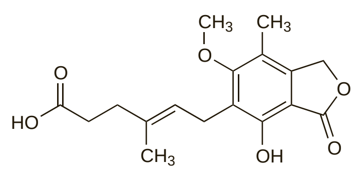

Mycophenolate Mofetil *(BANM, USAN, rINNM)*

Micofenolato de mofetilo; Mikofenolat Mofetil; Mikofenolato mofetilis; Mofetilis Mycophenolas; Mofetil-mykofenolát; Mycophenolas Mofetil; Mycophenolas Mofetilum; Mycophenolas-mofetil; Mycophénolate mofétil; Mycophénolate, Mofétil de; Mycophenolate Morpholinoethyl; Mykofenolaattimofetiili; Mykofenolatmofetil; RS-61443. 2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate.

Микофеноловаяа Мофетил

$C_{23}H_{31}NO_7$ = 433.5.
CAS — 115007-34-6.
ATC — L04AA06.
ATC Vet — QL04AA06.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Mycophenolate Mofetil). A white or almost white, crystalline powder. M.p. about 96°. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. Protect from light.

USP 31 (Mycophenolate Mofetil). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; soluble in methyl alcohol; freely soluble in acetone. Store in airtight containers.

Mycophenolate Mofetil Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro del micofenolato de mofetilo; Mycophénolate, Mofétil Chlorhydrate de; Mycophenolati Mofetili Hydrochloridum; RS-61443-190. 2-Morpholinoethyl (*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate hydrochloride.

Микофеноловой Мофетила Гидрохлорид

$C_{23}H_{31}NO_7,HCl$ = 470.0.
CAS — 116680-01-4.
ATC — L04AA06.
ATC Vet — QL04AA06.

Incompatibility. Solutions of mycophenolate mofetil hydrochloride were found to be physically compatible and chemically stable with solutions containing clinically relevant concentrations of cefepime, dopamine, noradrenaline, tacrolimus, and vancomycin, for up to 4 hours of simulated Y-site administration. However, combining ciclosporin and mycophenolate resulted in effervescence and chemical instability.[1]

1. Cochran BG, *et al.* Physical compatibility and chemical stability of mycophenolate mofetil during simulated Y-site administration with commonly coadministered drugs. *Am J Health-Syst Pharm* 2007; **64:** 1410–14.

Stability. UK and US licensed product information states that, after reconstitution of *mycophenolate mofetil oral suspension,* it may be stored at room temperature (15° to 30°) or in a refrigerator (2° to 8°) for up to 60 days; it should not be frozen.

UK licensed product information for *mycophenolate mofetil hydrochloride solution for infusion* states that the infusion should be started within 3 hours of reconstitution and dilution; solutions may be kept at room temperature (15° to 30°). A study found that solutions of mycophenolate mofetil hydrochloride in concentrations equivalent to mycophenolate mofetil 1, 5, or 10 mg/mL were stable for 7 days when stored at 4° or 25° in PVC infusion bags.[1] However, it was noted that a progressive discoloration occurred in bags unprotected from light and stored at 25°; further study was required to determine the source of the discoloration.

1. Certain E, *et al.* Stability of i.v. mycophenolate mofetil in 5% dextrose injection in polyvinyl chloride infusion bags. *Am J Health-Syst Pharm* 2002; **59:** 2434–9.

Mycophenolate Sodium *(BANM, USAN, rINNM)*

ERL-080; Micofenolato sódico; Mycophénolate de Sodium; Natrii Mycophenolas. Sodium 4(*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

Натрий Микофеноловая

$C_{17}H_{19}NaO_6$ = 342.3.
CAS — 37415-62-6.
ATC — L04AA06.
ATC Vet — QL04AA06.

Adverse Effects, Treatment, and Precautions

Mycophenolate is associated with gastrointestinal disturbances, particularly diarrhoea and vomiting; gastrointestinal haemorrhage and perforation have occurred. Leucopenia may develop; as with other immunosuppressants there is an increased risk of infection and certain malignancies in patients receiving mycophenolate mofetil (see below). To minimise any risk of skin cancer, exposure to sunlight or ultraviolet light should be limited. Thrombocytopenia and anaemia are also common; there have been reports of aplastic anaemia and bone-marrow depression, sometimes fatal. Regular full blood counts are recommended during therapy, and treatment may need to be stopped if severe neutropenia develops. Other reported adverse effects include asthenia, fever, pain, headache, renal impairment, hypertension or hypotension, hyperglycaemia, disturbances of electrolytes and blood lipids, peripheral oedema, pleural effusion, dyspnoea, cough, acne, rash, alopecia, dizziness, insomnia or somnolence, paraesthesia, and tremor. Agitation, depression, anxiety, tachycardia, and arthralgia are also common. Abnormal hepatic function tests have also been reported. Hypersensitivity reactions, including angioedema and anaphylaxis, have occurred. Pancreatitis and hepatitis have been reported. There are rare reports of interstitial lung disorders, including fatal pulmonary fibrosis. Other less common adverse effects include renal tubular necrosis, haematuria, conjunctivitis, blurred vision, and impotence. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have also been reported. Mycophenolate is teratogenic in *animals*; malformations, especially of the external ear, and other facial abnormalities, have been reported in infants after maternal exposure to mycophenolate (see below).

Mycophenolate should be given with care to patients with severe renal impairment or active disorders of the gastrointestinal tract. Intra-uterine devices should be used with caution in those given immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided in these patients for the same reason.

Mycophenolate mofetil and mycophenolate sodium should not be indiscriminately interchanged or substituted because of their differing pharmacokinetic profiles.

Effects on the gastrointestinal tract. The adverse effects of mycophenolate mofetil on the gastrointestinal tract appeared to be mostly of an irritative nature and included diarrhoea, abdominal pain, nausea and vomiting, anorexia, dyspepsia, and occasionally gastrointestinal haemorrhage or perforation.[1] Paediatric patients tended to have a higher incidence of adverse gastrointestinal events than adults. There was some evidence that adverse effects were related to peak plasma concentrations of the drug.

A review comparing the adverse effect profile of enteric-coated mycophenolate sodium with that of mycophenolate mofetil found a similar incidence of gastrointestinal adverse effects with the two formulations. It was noted that the pathophysiology of the gastrointestinal disturbances seen with mycophenolate is complex and not fully understood. An increased incidence of diarrhoea has been seen with higher mycophenolic acid (MPA) concentrations, possibly due to a direct effect of MPA on intestinal enterocytes, caused by its inhibitory effect on inosine monophosphate dehydrogenase. While exposure to MPA may be higher with the enteric-coated formulation, studies have not shown an appreciable increase in gastrointestinal adverse effects with mycophenolate sodium; the enteric coating might have diminished the direct effect of MPA on enterocytes in the upper gastrointestinal tract.[2] Two studies found that gastrointestinal adverse effects decreased after patients were switched from mycophenolate mofetil to enteric-coated mycophenolate sodium.[3,4]

1. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. *Drug Safety* 2001; **24:** 645–63.
2. Behrend M, Braun F. Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. *Drugs* 2005; **65:** 1037–50.
3. Calvo N, *et al.* Renal transplant patients with gastrointestinal intolerability to mycophenolate mofetil: conversion to enteric-coated mycophenolate sodium. *Transplant Proc* 2006; **38:** 2396–7.
4. Boswell A, *et al.* Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in patients with gastrointestinal side effects: case studies. *Prog Transplant* 2006; **16:** 138–40.

Handling. The UK licensed product information for film-coated gastro-resistant tablets of mycophenolate sodium (*Myfortic, Novartis*) warns that if it is necessary to crush the tablets, inhalation of the powder or direct contact of the powder with the skin or mucous membranes should be avoided.

Infection. The use of mycophenolate mofetil was not found to increase the risk of CMV infection in 2 small studies.[1,2] However, it did appear to be associated with an increased frequency[1] and severity[2] of CMV disease (defined as CMV infection plus evidence of viral syndrome). The number of organs affected in patients with CMV disease was also higher in those treated with mycophenolate mofetil.[2]

A retrospective study[3] found that the use of a protocol containing mycophenolate mofetil and tacrolimus was an independent risk factor for the development of CMV disease, but that the dose of mycophenolate mofetil was not. The authors interpreted this to mean that either the combination of mycophenolate mofetil and tacrolimus had an overall stronger immunosuppressive effect than other regimens, or that this protocol bore a specific risk for the development of CMV disease. The pharmacokinetics of mycophenolic acid (MPA), a metabolite of mycophenolate mofetil, and its interaction with tacrolimus, must be considered, with further studies taking MPA levels into account (see Immunosuppressants, under Interactions, below).

In contrast to these findings, another retrospective study[4] found that, although no patient developed CMV disease, the use of mycophenolate mofetil was an independent risk factor for the development of CMV infection in those patients initially seropositive for the CMV antigen.

In a study comparing the adverse effects of mycophenolate mofetil and enteric-coated mycophenolate sodium in renal transplant patients, the overall incidence of infections was similar. However, patients receiving mycophenolate sodium had significantly fewer serious infections. The incidence of CMV infection was very low and similar in both groups.[5]

In February 2008 the manufacturer in agreement with the EMEA warned[6] that isolated cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, had been reported in patients receiving mycophenolate mofetil (*CellCept, Roche*) for transplant rejection or SLE; a diagnosis of PML should be considered in patients who develop neurological symptoms while receiving mycophenolate mofetil. It was also recommended that consideration should be given to reducing the total immunosuppression in patients who develop PML but with a reminder that such a reduction may place the graft at risk in transplant patients.

1. ter Meulen CG, *et al.* The influence of mycophenolate mofetil on the incidence and severity of primary cytomegalovirus infections and disease after renal transplantation. *Nephrol Dial Transplant* 2000; **15:** 711–14.
2. Sarmiento JM, *et al.* Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. *Clin Transplant* 2000; **14:** 136–8.
3. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; **34:** 1164–70.
4. Hambach L, *et al.* Increased risk of complicated CMV infection with the use of mycophenolate mofetil in allogeneic stem cell transplantation. *Bone Marrow Transplant* 2002; **29:** 903–6.
5. Budde K, *et al.* Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *Am J Transplant* 2003; **4:** 237–43.
6. Roche, UK. Reports of progressive multifocal leukoencephalopathy (PML) in CellCept (mycophenolate mofetil) treated patients (issued 18th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014106&RevisionSelectionMethod=Latest (accessed 19/05/08)

Pregnancy. There have been reports of spontaneous abortions and structural malformations in infants born to women taking mycophenolate. The manufacturers of mycophenolate mofetil (*Roche, USA*) have warned that use of the drug during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, oesophagus, and kidney.[1] Women of child-bearing potential should have a negative pregnancy test within 1 week of starting mycophenolate therapy. Women taking mycophenolate should use effective contraception, from at least 4 weeks before starting therapy, and until 6 weeks after stopping mycophenolate.

1. Roche, USA. Important changes in the CellCept (mycophenolate mofetil) prescribing information—use of CellCept is associated with increased pregnancy loss and congenital malformations/change from pregnancy category C to pregnancy category D (issued October 2007). Available at: http://www.fda.gov/Medwatch/SAFETY/2007/CellCept_dearhcpoct07.pdf (accessed 18/02/08)

Interactions

Mycophenolate may compete with other drugs that undergo active renal tubular secretion, resulting in increased concentrations of either drug. Antacids, polycarbophil calcium, sevelamer, or colestyramine may reduce absorption of mycophenolate. Rifampicin decreases exposure to mycophenolate (in patients not also taking ciclosporin); mycophenolic acid (MPA) concentrations should be monitored when rifampicin and mycophenolate are used together. See above for precautions about use with live vaccines.

Antacids. Although giving mycophenolate mofetil with an antacid mixture (aluminium and magnesium hydroxides) or food both resulted in reductions in peak plasma concentrations of mycophenolic acid (MPA), the differences were small compared with interindividual variation, and were considered unlikely to be clinically significant.[1]

UK licensed product information for mycophenolate sodium states that, although magnesium- or aluminium-containing antacids decrease MPA exposure and peak plasma concentrations, they may be used intermittently for the treatment of occasional dyspepsia; chronic use of antacids is not recommended.

1. Bullingham R, *et al.* Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. *Br J Clin Pharmacol* 1996; **41:** 513–16.

Antibacterials. A selective bowel decontamination regimen of *tobramycin*, *cefuroxime*, and the antifungal *nystatin*, apparently inhibited the enterohepatic recycling of mycophenolic acid (MPA), thereby reducing the bioavailability of mycophenolate in liver transplant recipients.[1] *Norfloxacin*, *metronidazole*, or a combination of the two, reduced exposure to MPA and mycophenolic acid glucuronide (see Metabolism, below) when given to healthy subjects receiving mycophenolate mofetil. The effect of the antibacterials appeared to be additive.[2] Rapid reductions in MPA concentrations were seen after renal transplant patients stabilised on mycophenolate were given either *ciprofloxacin* or *amoxicillin with clavulanic acid*; MPA concentrations recovered to baseline within 3 days of stopping antibacterial therapy, and the effect was seen to wane with continued dosage of antibacterials for 14 days.[3] *Rifampicin* markedly reduced exposure to MPA in a heart-lung transplant recipient, possibly through induction of mycophenolate glucuronidation.[4] A study in renal transplant recipients given rifampicin confirmed this reduction in MPA exposure, concluding that the mechanism was induction of glucuronidation and inhibition of enterohepatic circulation.[5]

1. Schmidt LE, *et al.* The effect of selective bowel decontamination on the pharmacokinetics of mycophenolate mofetil in liver transplant recipients. *Liver Transpl* 2001; **7:** 739–42.
2. Naderer OJ, *et al.* The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol* 2005; **45:** 219–26.
3. Borrows R, *et al.* The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. *Ther Drug Monit* 2007; **29:** 122–6.
4. Kuypers DRJ, *et al.* Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. *Clin Pharmacol Ther* 2005; **78:** 81–8.
5. Naesens M, *et al.* Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther* 2006; **80:** 509–21.

Immunosuppressants. Stopping *ciclosporin* therapy in renal transplant recipients was found to increase serum concentrations of mycophenolic acid (MPA),[1,2] leading to the hypothesis that ciclosporin inhibits the enterohepatic circulation of MPA. In contrast,[3,4] *tacrolimus* therapy increased serum concentrations of MPA, apparently by inhibiting conversion to mycophenolic acid glucuronide (MPAG). While the studies have been criticised,[5] it has been pointed out that an interaction cannot be excluded.[6] An increased incidence of CMV disease has been reported in renal transplant recipients given a triple therapy regimen containing tacrolimus and mycophenolate mofetil.[7] Based on a study[8] in children it has been recommended that mycophenolate mofetil be given in initial doses of 600 mg/m² twice daily with ciclosporin but 300 mg/m² twice daily with tacrolimus; 500 mg/m² twice daily was suggested if no calcineurin inhibitor was given. It is also recommended that dose adjustments are made using therapeutic drug monitoring. However, a pharmacokinetic study[9] showed that changes in MPA exposure with tacrolimus varied with the dose of mycophenolate mofetil used and that this effect was not adequately reflected by MPA trough concentrations (see Therapeutic Drug Monitoring, below). Another study found marked interindividual variability in MPA and MPAG pharmacokinetics when patients were given ciclosporin microemulsion or tacrolimus in the early stages after renal transplantation. This variability was greater in those given ciclosporin than in those given tacrolimus, and mean total MPA concentrations were about half that of patients in the tacrolimus group.[10] A randomised crossover study compared the effect of ciclosporin microemulsion or tacrolimus on the pharmacokinetics of MPA when each of these were given with enteric-coated mycophenolate sodium to stable renal transplant recipients.[11] In comparison with use with ciclosporin, giving mycophenolate sodium with tacrolimus resulted in a moderate increase in the total exposure of MPA and decreased maximum concentrations and total exposure to the metabolites MPAG and the acyl glucuronide. The results were not statistically significant, and the authors suggested that on this basis, doses of mycophenolate sodium need not be adjusted when converting stable renal transplant patients from one calcineurin inhibitor to the other. However, they recommended that mycophenolate sodium dose adjustments should be based on both the pharmacokinetic data and the clinical situation.

UK licensed product information has stated that ciclosporin reduces MPA exposure, and may decrease MPA concentrations when these two drugs are given together. The exact extent of the decrease is not known for mycophenolate sodium, but may be about 20%, extrapolated from data for mycophenolate mofetil. However, since efficacy studies used this combination, no dose adjustment of mycophenolate is considered necessary. If concomitant ciclosporin therapy is interrupted or stopped, an increase in MPA of about 30% is to be expected, and dosage should be re-evaluated depending on the immunosuppressive regimen. While not commenting on dose adjustment when used with tacrolimus, UK licensed product information for mycophenolate sodium stated that stable renal transplant patients showed increased MPA exposure and decreased MPAG when tacrolimus was substituted for ciclosporin.

Pharmacokinetic analyses found that use of *sirolimus* with mycophenolate led to greater MPA exposure,[12,13] but lower MPAG exposure,[14] when compared with ciclosporin plus mycophenolate. Therapeutic drug monitoring of MPA is recommended in transplant recipients given both mycophenolate and sirolimus;[12,13] guidelines are needed when switching patients from ciclosporin to sirolimus, since the same dose of mycophenolate mofetil would lead on average to a 50% increase in MPA exposure in patients receiving sirolimus compared with ciclosporin.[13]

1. Smak Gregoor PJH, *et al.* Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999; **68:** 1603–6.
2. Shipkova M, *et al.* Effect of cyclosporine withdrawal on mycophenolic acid pharmacokinetics in kidney transplant recipients with deteriorating renal function: preliminary report. *Ther Drug Monit* 2001; **23:** 717–21.
3. Zucker K, *et al.* Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol* 1997; **5:** 225–32.
4. Hübner GI, *et al.* Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 1999; **21:** 536–9.
5. van Gelder T, *et al.* [Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients]. *Ther Drug Monit* 2000; **22:** 639.
6. Hübner GI, Sziegoleit W. [Drug interaction between mycophenolate mofetil and tacrolimus detectable within therapeutic mycophenolic acid monitoring in renal transplant patients.] *Ther Drug Monit* 2000; **22:** 498–9.
7. Kuypers DRJ, *et al.* Role of immunosuppressive drugs in the development of tissue-invasive cytomegalovirus infection in renal transplant recipients. *Transplant Proc* 2002; **34:** 1164–70.
8. Filler G, *et al.* Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. *Pediatr Nephrol* 2000; **14:** 100–104.
9. Kuypers DRJ, *et al.* Long-term changes in mycophenolic acid exposure in combination with tacrolimus and corticosteroids are dose dependent and not reflected by trough plasma concentration: a prospective study in 100 de novo renal allograft recipients. *J Clin Pharmacol* 2003; **43:** 866–80.

10. Atcheson BA, *et al.* Mycophenolic acid pharmacokinetics and related outcomes early after renal transplant. *Br J Clin Pharmacol* 2005; **59:** 271–80.
11. Kaplan B, *et al.* Randomized calcineurin inhibitor cross over study to measure the pharmacokinetics of co-administered enteric-coated mycophenolate sodium. *Clin Transplant* 2005; **19:** 551–8.
12. Büchler M, *et al.* Higher exposure to mycophenolic acid with sirolimus than with cyclosporine cotreatment. *Clin Pharmacol Ther* 2005; **78:** 34–42.
13. Picard N, *et al.* A comparison of the effect of ciclosporin and sirolimus on the pharmokinetics [sic] of mycophenolate in renal transplant patients. *Br J Clin Pharmacol* 2006; **62:** 477–84.
14. Pescovitz MD, *et al.* Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *Br J Clin Pharmacol* 2007; **64:** 758–71.

Iron. Absorption of mycophenolate mofetil after oral doses was markedly reduced by iron preparations in a study in 7 healthy subjects:[1] mean peak serum concentrations of mycophenolic acid were reduced from 20.1 to 1.3 micrograms/mL. However, in contrast, a study in 16 healthy subjects found no interaction between iron supplements and mycophenolate mofetil,[2] and 2 studies in renal transplant patients found no significant effect of oral iron supplements on the absorption of mycophenolate mofetil.[3,4]

1. Morii M, *et al.* Impairment of mycophenolate mofetil absorption by iron ion. *Clin Pharmacol Ther* 2000; **68:** 613–6.
2. Ducray PS, *et al.* Absence of an interaction between iron and mycophenolate mofetil absorption. *Br J Clin Pharmacol* 2005; **62:** 492–5.
3. Mudge DW, *et al.* The effect of oral iron admiinistration [sic] on mycophenolate mofetil absorption in renal transplant recipients: a randomized, controlled trial. *Transplantation* 2004; **77:** 206–9.
4. Lorenz M, *et al.* Ferrous sulfate does not affect mycophenolic acid pharmacokinetics in kidney transplant patients. *Am J Kidney Dis* 2004; **43:** 1098–1103.

Pharmacokinetics

Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract; enteric-coated mycophenolate sodium is also extensively absorbed. Mycophenolate undergoes presystemic metabolism to active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen; these have been reported at between 6 to 12 hours after a dose of mycophenolate mofetil, and at between 6 to 8 hours after a dose of mycophenolate sodium. MPA is metabolised by glucuronidation to the inactive mycophenolic acid glucuronide. The majority of a dose of mycophenolate is excreted in the urine as this glucuronide, with negligible amounts of MPA; about 6% of a dose is recovered in faeces. MPA is 97% bound to plasma albumin. The mean half-life of MPA after oral and intravenous doses of mycophenolate mofetil has been reported to be 17.9 hours and 16.6 hours, respectively; an MPA half-life of about 12 hours has been reported for mycophenolate sodium.

◊ References.

1. Bullingham RES, *et al.* Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 1998; **34:** 429–55.
2. Gabardi S, *et al.* Enteric-coated mycophenolate sodium. *Ann Pharmacother* 2003; **37:** 1685–93.
3. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet* 2007; **46:** 13–58.
4. Filler G, *et al.* Pharmacokinetics of mycophenolate mofetil and sirolimus in children. *Ther Drug Monit* 2008; **30:** 138–42.
5. Lévesque E, *et al.* Pharmacokinetics of mycophenolate mofetil and its glucuronide metabolites in healthy volunteers. *Pharmacogenomics* 2008; **9:** 869–79.

Bioavailability. A study in renal transplant patients found single doses of mycophenolate sodium 640 mg and 720 mg to be bioequivalent to mycophenolate mofetil 1 g. The 720-mg dose most closely approximated the mycophenolic acid (MPA) exposure of the mycophenolate mofetil dose.[1] The authors noted that since the study was conducted in patients given ciclosporin, bioequivalence of MPA exposure between these two formulations could not be assumed for patients receiving other immunosuppressants. A meta-analysis of 3 studies in stable renal transplant recipients concluded that mycophenolate mofetil and enteric-coated mycophenolate sodium give equivalent mycophenolate exposure in these patients.[2]

1. Arns W, *et al.* Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant* 2005; **19:** 199–206.
2. Johnston A, *et al.* Bioequivalence of enteric-coated mycophenolate sodium and mycophenolate mofetil: a meta-analysis of three studies in stable renal transplant recipients. *Transplantation* 2006; **82:** 1413–18.

Metabolism. Mycophenolate mofetil is rapidly de-esterified in the body to active mycophenolic acid (MPA), which is subsequently converted to inactive mycophenolic acid glucuronide (MPAG) in the gastrointestinal tract, liver and possibly kidney. This conversion to MPAG is considered to be the most important and rate limiting step.[1] MPA undergoes enterohepatic circulation, with MPAG formed in the liver being excreted into bile and converted back to MPA in the gastrointestinal tract. A further metabolite, the acyl glucuronide, has been shown to be active *in vitro*, inhibiting human inosine monophosphate dehydrogenase,[1,2] and may have implications in therapeutic drug monitoring (see below). MPA is extensively bound to albumin in patients with normal renal and hepatic function, but this binding may be affected in transplant patients by several factors such as hypoalbuminaemia, hyperbilirubinaemia, and uraemia. Accumulation of MPAG leads to an increase in unbound MPA, and a subsequent increase in MPA clearance.[2]

A crossover study to compare the metabolism of mycophenolate mofetil with mycophenolate sodium[3] found that the onset of MPA absorption was delayed with mycophenolate sodium, consistent with its enteric-coated formulation. However, MPA exposure was considered to be bioequivalent, and MPA metabolism did not differ significantly between the two formulations. MPAG was confirmed as being the principal metabolite of MPA, and the authors considered that acyl glucuronide exposure was of a sufficient magnitude to potentially contribute to immunosuppression and toxicity.

1. Shaw LM, *et al.* Pharmacokinetic, pharmacodynamic, and outcome investigations as the basis for mycophenolic acid therapeutic drug monitoring in renal and heart transplant patients. *Clin Biochem* 2001; **34:** 17–22.
2. Shaw LM, *et al.* Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001; **23:** 305–15.
3. Tedesco-Silva H, *et al.* Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. *Transplant Proc* 2005; **37:** 852–5.

Therapeutic drug monitoring. Mycophenolic acid (MPA) concentration appears to correlate with efficacy and toxicity.[1] Patients with low MPA concentrations may be at increased risk of transplant rejection,[2-5] or graft-versus-host disease,[5] and there is some evidence that a high MPA concentration correlates with increased adverse effects.[4,6] Fixed doses of mycophenolate mofetil have been reported to lead to variable MPA exposure,[7,8] and other immunosuppressants can affect MPA concentrations, see under Interactions, above. Therapeutic drug monitoring of mycophenolate mofetil is therefore considered necessary.[1]

Assay procedures to measure MPA concentrations include high performance liquid chromatography (HPLC) and an enzyme-multiplied immunoassay technique (EMIT). However, the acyl glucuronide metabolite of MPA (see Metabolism, above) may cross-react with the latter method, leading to higher measured concentrations than with HPLC.[8,9] This overestimation of MPA exposure using EMIT was reported to be about 24 to 35%, with the greatest bias seen in kidney recipients early after transplantation. However, in paediatric renal transplant patients, EMIT showed comparable diagnostic efficacy to HPLC, and is an acceptable assay for MPA in this population.[8] Another suggested approach is to measure inosine monophosphate dehydrogenase activity directly, (see Metabolism, above) but this has produced variable results.[10]

A review[9] concluded that while some studies show a correlation between MPA trough concentration (C_o) and acute allograft rejection, MPA area under the concentration-time curve (AUC) is predictive of the risk for rejection, and that both have limitations. An abbreviated AUC involving more practical blood sampling regimens may be more appropriate, and a trough concentration between 1 and 3.5 mg/litre has been proposed. For paediatric transplant recipients, a predose trough concentration, as measured by EMIT assay, of between 1.6 and 3.5 mg/litre has been recommended.[11] However, it has been pointed out[12] that the therapeutic range may be different at different time points after transplantation, and among different patient populations; concomitant drugs may also influence this range. The following target concentrations have been recommended for transplant patients taking mycophenolate mofetil:[13]

- MPA AUC 30 to 60 mg × hours/litre as determined by HPLC in the first 30 days post-transplantation
- for renal transplant recipients on a ciclosporin-based regimen, MPA C_0 greater than or equal to 1.3 mg/litre, as measured by HPLC
- for renal transplant recipients on a tacrolimus-based regimen, MPA C_0 greater than or equal to 1.9 mg/litre, as measured by HPLC
- for cardiac transplant recipients, MPA C_0 greater than or equal to 2 mg/litre, as measured by EMIT, or 1.2 to 3.5 mg/litre as measured by HPLC
- for liver transplant recipients, target concentrations could not be definitively recommended; similar targets to renal transplantation were suggested until more data are available

Some have stated that the contribution of MPA trough level monitoring during mycophenolate mofetil therapy is unproven, given the lack of data in paediatric renal transplant patients, and in cardiac and liver transplantation, and that adherence to recommended target ranges for MPA cannot ensure an improved clinical outcome.[14]

It has also been pointed out that, because of differing pharmacokinetic profiles, algorithms developed for mycophenolate mofetil cannot be used for patients treated with mycophenolate sodium.[15]

Measurements of unbound MPA concentrations may be of benefit in patients with renal or hepatic impairment, as factors such as hypoalbuminaemia and renal dysfunction affect the binding of MPA.[9] In liver transplant patients, plasma protein binding of MPA increased as albumin concentration increased and as bilirubin concentration decreased, leading to decreased unbound fraction of MPA, and contributing to large intra- and interindividual pharmacokinetic variability.[16] A population pharmacokinetic study considered the complexity in determining MPA pharmacokinetics to be underestimated.[17] Bayesian forecasting using only 3 samples has been reported to accurately predict MPA exposure.[18,19]

A study in 6 patients with psoriasis concluded that MPA trough concentrations (measured by EMIT) did not predict efficacy or toxicity, but instead were useful to evaluate compliance.[20]

For the view that MPA trough concentrations may not adequately reflect exposure in patients also receiving tacrolimus, see Interactions, Immunosuppressants, above.

1. Mourad M, *et al.* Therapeutic monitoring of mycophenolate mofetil in organ transplant recipients: is it necessary? *Clin Pharmacokinet* 2002; **41:** 319–27.
2. van Gelder T, *et al.* A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; **68:** 261–6.
3. DeNofrio D, *et al.* Mycophenolic acid concentrations are associated with cardiac allograft rejection. *J Heart Lung Transplant* 2000; **19:** 1071–6.
4. Tredger JM, *et al.* Monitoring mycophenolate in liver transplant recipients: toward a therapeutic range. *Liver Transpl* 2004; **10:** 492–502.
5. Jacobson P, *et al.* Relationship of mycophenolic acid exposure to clinical outcome after hematopoietic cell transplantation. *Clin Pharmacol Ther* 2005; **78:** 486–500.
6. Mourad M, *et al.* Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant patients treated with mycophenolate mofetil. *Clin Chem* 2001; **47:** 88–94.
7. David-Neto E, *et al.* The need of mycophenolic acid monitoring in long-term renal transplants. *Clin Transplant* 2005; **19:** 19–25.
8. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. *Clin J Am Soc Nephrol* 2007; **2:** 184–91.
9. Shaw LM, *et al.* Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* 2001: **23:** 305–15.
10. Shaw LM, *et al.* Monitoring of mycophenolic acid in clinical transplantation. *Ther Drug Monit* 2002; **24:** 68–73.
11. Filler G. Value of therapeutic drug monitoring of MMF therapy in pediatric transplantation. *Pediatr Transplant* 2006; **10:** 707–11.
12. Venkataramanan R, Shaw LM. Therapeutic monitoring of mycophenolic acid in liver transplant patients. *Liver Transpl* 2004; **10:** 503–5.
13. van Gelder T, *et al.* Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* 2006; **28:** 145–54.
14. Kaplan B. Mycophenolic acid trough level monitoring in solid organ transplant recipients treated with mycophenolate mofetil: association with clinical outcome. *Curr Med Res Opin* 2006; **22:** 2355–64.
15. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
16. Pisupati J, *et al.* Intraindividual and interindividual variations in the pharmacokinetics of mycophenolic acid in liver transplant patients. *J Clin Pharmacol* 2005; **45:** 34–41.
17. Shum B, *et al.* Population pharmacokinetic analysis of mycophenolic acid in renal transplant recipients following oral administration of mycophenolate mofetil. *Br J Clin Pharmacol* 2003; **56:** 188–97.
18. Le Guellec C, *et al.* Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in stable renal transplant patients. *Clin Pharmacokinet* 2004; **43:** 253–66.
19. Zahr N, *et al.* Pharmacokinetic study of mycophenolate mofetil in patients with systemic lupus erythematosus and design of Bayesian estimator using limited sampling strategies. *Clin Pharmacokinet* 2008; **47:** 277–84.
20. Daudén E, *et al.* Plasma trough levels of mycophenolic acid do not correlate with efficacy and safety of mycophenolate mofetil in psoriasis. *Br J Dermatol* 2004; **150:** 132–5.

Uses and Administration

Mycophenolic acid is an immunosuppressant derived from *Penicillium stoloniferum*. It is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. It is given with other immunosuppressants, for the prevention of graft rejection, and has also been tried in diseases with an autoimmune or immune-mediated inflammatory component.

It has been used mainly as the morpholinoethyl derivative, mycophenolate mofetil, or its hydrochloride salt; doses of both are expressed as mycophenolate mofetil. 1.08 g of mycophenolate mofetil hydrochloride is equivalent to about 1 g of mycophenolate mofetil. An enteric-coated formulation of mycophenolate sodium (the sodium salt of mycophenolic acid) is also available in some countries. Doses are expressed in terms of the acid; mycophenolate sodium 769 mg is equivalent to about 720 mg of mycophenolic acid.

In patients to whom oral therapy cannot initially be given, mycophenolate mofetil may be given for up to 14 days by intravenous infusion. Infusions are given as the hydrochloride salt. It is dissolved in glucose 5% to a final concentration equivalent to mycophenolate mofetil 6 mg/mL, and given over 2 hours through either a central or peripheral vein.

In the prophylaxis of acute **renal** graft rejection in adults, the conventional formulation of mycophenolate mofetil is given orally in doses of 1 g twice daily, usually within 72 hours of transplantation; the equivalent dose may be given by intravenous infusion, but is usually started within 24 hours after transplantation.

The enteric-coated formulation of mycophenolate sodium is also given for the prophylaxis of acute renal graft rejection to adults in a dose equivalent to mycophenolic acid 720 mg twice daily; the two formulations cannot be indiscriminately interchanged or substituted.

In the prophylaxis of **cardiac** graft rejection in adults, mycophenolate mofetil 1.5 g twice daily is given by mouth, within 5 days after transplantation, or by intravenous infusion at an equivalent dose.

For use in the prophylaxis of rejection in **hepatic** transplantation in adults, the equivalent of mycophenolate mofetil 1 g twice daily is given by intravenous infusion for the first 4 days after transplantation, with subsequent conversion to 1.5 g twice daily by mouth as soon as it can be tolerated.

For doses of mycophenolate used for organ transplantation in children see Administration in Children, below.

Patients should undergo regular blood counts; if neutropenia develops consideration should be given to interrupting mycophenolate treatment, reducing the dose, or stopping therapy.

Administration in children. Oral mycophenolate mofetil is licensed from the age of 2 years in the UK, and from 3 months of age in the USA. For prevention of **renal** graft rejection in patients up to 18 years of age, the recommended oral dose of mycophenolate mofetil is 600 mg/m^2 twice daily, up to a maximum of 1 g twice daily. Patients with a body-surface of 1.25 to 1.5 m^2 may be given 750 mg twice daily, whereas those with a body-surface of greater than 1.5 m^2 may be given the same dose as adults (see Uses and Administration, above). In the UK, the *BNFC* allows for use from 1 month to 18 years at 600 mg/m^2 twice daily orally or by infusion when used with ciclosporin and corticosteroids, but recommends 300 mg/m^2 twice daily when used with tacrolimus and corticosteroids; the maximum in both cases is 2 g daily.

UK licensed product information states that no data are available for paediatric cardiac and hepatic transplant patients. However, for prophylaxis of rejection in **hepatic** transplantation, the *BNFC* recommends mycophenolate mofetil 10 mg/kg twice daily, orally or by intravenous infusion, for children aged from 1 month to 18 years. This may be increased to 20 mg/kg twice daily, to a maximum of 2 g daily. The dose is the same whether used with either ciclosporin and corticosteroids, or tacrolimus and corticosteroids.

Administration in hepatic or renal impairment. Licensed product information in the UK and USA states that no dose adjustments of mycophenolate mofetil are needed for renal transplant recipients with severe *hepatic* parenchymal disease. However, it is not known whether dose adjustments are necessary for those with hepatic disease of differing aetiology. No data are available for cardiac transplant patients with severe hepatic parenchymal disease. UK licensed product information states that no dose adjustments are needed for mycophenolate sodium in renal transplant patients with hepatic impairment.

US licensed product information states that exposure to mycophenolic acid (MPA) is increased in patients with chronic *renal* impairment. Although mean MPA concentrations in patients with delayed renal graft function were comparable to those transplant patients without delayed renal graft function, there is a potential for a transient increase in MPA concentrations if renal graft function is delayed. However, dose adjustment does not appear to be necessary in these patients. UK licensed product information states that in renal transplant patients with severe chronic renal impairment (GFR less than 25 mL/minute per 1.73 m^2), oral or intravenous doses of mycophenolate mofetil above 1 g twice daily should be avoided outside the immediate post-transplantation period; the daily dose of mycophenolate sodium in these patients should not exceed 1.44 g. No dose adjustments of mycophenolate are needed in those with delayed renal graft function. No data are available for cardiac or hepatic transplant recipients with severe chronic renal impairment.

Chronic active hepatitis. Mycophenolate mofetil may be of benefit in patients with auto-immune hepatitis (p.1501) who are intolerant of or unresponsive to azathioprine or other standard therapy.[1-3]

1. Richardson PD, *et al.* Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J Hepatol* 2000; **33:** 371–5.
2. Devlin SM, *et al.* Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. *Can J Gastroenterol* 2004; **18:** 321–6.
3. Inductivo-Yu I, *et al.* Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2007; **5:** 799–802.

Eczema. Mycophenolate mofetil (typically 1 to 3 g daily by mouth) has been reported[1-3] to be safe and effective in the treatment of moderate-to-severe, refractory eczema (p.1579).

1. Neuber K, *et al.* Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* 2000; **143:** 385–91.
2. Grundmann-Kollmann M, *et al.* Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 2001; **137:** 870–3.
3. Heller M, *et al.* Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; **157:** 127–32.

Eye disorders. Retrospective evaluations of treatment outcomes in patients with chronic inflammatory eye disease treated with mycophenolate mofetil found that it was effective in controlling inflammation and had a useful corticosteroid-sparing effect.[1,2] Mycophenolate mofetil, used either alone or adjunctively, has been reported[3-7] to be of benefit in refractory uveitis (p.1515). Oral doses of 600 mg/m^2 twice daily or 1 g twice daily have been used in children; the latter dose has also been used in adults with uveitis. There was some suggestion mycophenolate might be less effective in those patients initially unresponsive to azathioprine.[5]

1. Baltatzis S, *et al.* Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. *Ophthalmology* 2003; **110:** 1061–5.
2. Thorne JE, *et al.* Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology* 2005; **112:** 1472–7.
3. Zierhut M, *et al.* Immunsuppressive Therapie mit Mycophenolat Mofetil (CellCept) in der Behandlung der Uveitis. *Ophthalmologe* 2001; **98:** 647–51.
4. Greiner K, *et al.* Effizienz von Mycophenolat-Mofetil bei der Therapie der intermediären und posterioren Uveitis. *Ophthalmologe* 2002; **99:** 691–4.
5. Lau CH, *et al.* Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation. *Clin Experiment Ophthalmol* 2003; **31:** 487–91.
6. Siepmann K, *et al.* Mycophenolate mofetil is a highly effective and safe immunosuppressive agent for the treatment of uveitis: a retrospective analysis of 106 patients. *Graefes Arch Clin Exp Ophthalmol* 2006; **244:** 788–94.
7. Doycheva D, *et al.* Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 2007; **91:** 180–4.

Glomerular kidney disease. Mycophenolate mofetil, in usual oral doses of 1 to 2 g daily, has been reported[1-3] to be of benefit in various forms of glomerular kidney disease (p.1504); in childhood nephrotic syndrome, it was reported to have a significant corticosteroid-sparing effect, reduce relapse rates,[4] and benefit renal function.[5]

1. Choi MJ, *et al.* Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int* 2002; **61:** 1098–1114.
2. Karim MY, Abbs IC. Mycophenolate mofetil in nonlupus glomerulonephropathy. *Lupus* 2005; **14** (suppl): s39–s41.
3. Segarra A, *et al.* Efficacy and safety of 'rescue therapy' with mycophenolate mofetil in resistant primary glomerulonephritis—a multicenter study. *Nephrol Dial Transplant* 2007; **22:** 1351–60.
4. Bagga A, *et al.* Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 2003; **42:** 1114–20.
5. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil. *Pediatr Nephrol* 2004; **19:** 101–4.

Idiopathic thrombocytopenic purpura. Mycophenolate mofetil has been reported[1-4] to be of benefit in small numbers of patients with refractory idiopathic thrombocytopenic purpura (p.1505).

1. Howard J, *et al.* Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. *Br J Haematol* 2002; **117:** 712–15.
2. Hou M, *et al.* Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. *Eur J Haematol* 2003; **70:** 353–7.
3. Kotb R, *et al.* Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: a single center preliminary study. *Eur J Haematol* 2005; **75:** 60–64.
4. Provan D, *et al.* Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. *Am J Hematol* 2006; **81:** 19–25.

Inflammatory bowel disease. Mycophenolate mofetil has been investigated as an alternative to azathioprine in Crohn's disease (see Inflammatory Bowel Disease, p.1697). A randomised study in 70 patients compared therapy with corticosteroids plus mycophenolate mofetil or azathioprine in patients with moderate or severe Crohn's disease. The authors concluded that the mycophenolate regimen produced a clinical response earlier than the azathioprine regimen, and that mycophenolate should be considered in patients allergic or unresponsive to azathioprine or mercaptopurine.[1] However, it has been suggested[2] that the study may have been too short to draw definite conclusions, given the known delayed therapeutic effect of azathioprine. A beneficial effect for 5 out of 6 patients with severe Crohn's disease was reported[3] after 3 months of therapy with oral mycophenolate mofetil 1 g twice daily, but this effect was not sustained beyond 6 months.[4] Others have also noted relapse or lack of response to be relatively common;[5,6] while mycophenolate may have a role in those who cannot tolerate, or are refractory to, azathioprine, the latter remains the immunosuppressant of choice due to its greater ability to prevent flare-ups.[2]

1. Neurath MF, *et al.* Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; **44:** 625–8.
2. Miehsler W, *et al.* Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol* 2001; **96:** 782–7.
3. Florin THJ, *et al.* Treatment of steroid refractory inflammatory bowel disease (IBD) with mycophenolate mofetil (MMF). *Aust N Z J Med* 1998; **28:** 344–5.
4. Radford-Smith GL, *et al.* Mycophenolate mofetil in IBD patients. *Lancet* 1999; **354:** 1386–7.
5. Ford AC, *et al.* Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **17:** 1365–9.
6. Wenzl HH, *et al.* Mycophenolate mofetil for Crohn's disease: short-term efficacy and long-term outcome. *Aliment Pharmacol Ther* 2004; **19:** 427–34.

Multiple sclerosis. In a small open-label study, 5 out of 7 patients with multiple sclerosis (p.892) benefited from mycophenolate mofetil; 3 of these patients reported improved movement.[1] A retrospective review[2] of mycophenolate mofetil treatment (given either adjunctively or as monotherapy) in 79 patients, reported subjective improvements in 12 patients given adjunctive therapy.

1. Ahrens N, *et al.* Mycophenolate-mofetil in the treatment of refractory multiple sclerosis. *J Neurol* 2001; **248:** 713–14.
2. Frohman EM, *et al.* Mycophenolate mofetil in multiple sclerosis. *Clin Neuropharmacol* 2004; **27:** 80–83.

Myasthenia gravis. Mycophenolate mofetil has been investigated[1-4] in the treatment of myasthenia gravis (p.629). However negative results have been reported from controlled studies.

1. Meriggioli MN, *et al.* Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. *Ann N Y Acad Sci* 2003; **998:** 494–9.
2. Meriggioli MN, *et al.* Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. *Neurology* 2003; **61:** 1438–40.
3. Ciafaloni E. Mycophenolate mofetil and myasthenia gravis. *Lupus* 2005; **14** (suppl): s46–s49.
4. Cahoon WD, Kockler DR. Mycophenolate mofetil treatment of myasthenia gravis. *Ann Pharmacother* 2006; **40:** 295–8.

Organ and tissue transplantation. Mycophenolate mofetil is used for the prophylaxis of graft rejection in kidney (p.1813), heart (p.1812), and liver transplantation (p.1815), and has also been used after transplantation of the lung (p.1815), pancreas (p.1816), and intestines (p.1813). It has been used as an alternative to, or replacement for, azathioprine, and may result in fewer rejections. However, in a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression. It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811).

A few selected references to the use of mycophenolate mofetil in transplantation are given below.

1. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345:** 1321–5.
2. Halloran P, *et al.* Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 1997; **63:** 39–47. Correction. *ibid.*; 618.
3. Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. *Transplantation* 1998; **65:** 1450–4. Correction. *ibid.*; **66:** 817.
4. Oh JM, *et al.* Comparison of azathioprine and mycophenolate mofetil for the prevention of acute rejection in recipients of pancreas transplantation. *J Clin Pharmacol* 2001; **41:** 861–9.
5. Salvadori M, *et al.* Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2003; **4:** 231–6.
6. Sollinger HW. Mycophenolates in transplantation. *Clin Transplant* 2004; **18:** 485–92.
7. Remuzzi G, *et al.* Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. *Lancet* 2004; **364:** 503–12.
8. Budde K, *et al.* Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. *Transplant Proc* 2005; **37:** 912–15.

9. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. *Drugs* 2005; **65:** 799–805.
10. Manzia TM, *et al.* Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; **37:** 2616–17.
11. Ciancio G, *et al.* Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; **80** (suppl 2): S191–S200.
12. Srinivas TR, *et al.* The impact of mycophenolate mofetil on long-term outcomes in kidney transplantation. *Transplantation* 2005; **80** (suppl 2): S211–S220.
13. Kobashigawa JA, Meiser BM. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation* 2005; **80** (suppl 2): S235–S243.
14. Kaplan B. Enteric-coated mycophenolate sodium (Myfortic): an overview of current and future use in transplantation. *Drugs* 2006; **66** (suppl 2): 1–8.
15. Kobashigawa JA, *et al.* Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, Myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. *J Heart Lung Transplant* 2006; **25:** 935–41.
16. Zimmerhackl LB, *et al.* Mycophenolate mofetil (Cellcept) in pediatric renal transplantation. *Transplant Proc* 2006; **38:** 2038–40.
17. Schmeding M, *et al.* Mycophenolate mofetil in liver transplantation—is monotherapy safe? *Clin Transplant* 2006; **20** (suppl 17): 75–9.

Pemphigus and pemphigoid. Mycophenolate mofetil has been used successfully in the treatment of pemphigus and pemphigoid (p.1582), both with prednisolone[1-3] and alone.[4] In a randomised, non-blinded study,[5] adjuvant mycophenolate mofetil was found to be as effective as adjuvant azathioprine; corticosteroid-sparing effects were similar and there was a trend towards fewer adverse effects with mycophenolate.

1. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; **135:** 54–6.
2. Williams JV, *et al.* Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 2000; **142:** 506–8.
3. Powell AM, *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; **149:** 138–45.
4. Bredlich R-O, *et al.* Mycophenolate mofetil monotherapy for pemphigus vulgaris. *Br J Dermatol* 1999; **141:** 934.
5. Beissert S, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142:** 1447–54.

Polymyositis and dermatomyositis. Mycophenolate mofetil has been reported to be of benefit in refractory cases of polymyositis and dermatomyositis (p.1510), allowing for tapering of corticosteroid doses.[1-3] Despite benefit in 6 out of 10 patients in another study,[4] 3 patients developed opportunistic infection, which was fatal in 1 case. While acknowledging that other factors may have had a role in this, the authors advised caution in the use of mycophenolate in dermatomyositis.

1. Gelber AC, *et al.* Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. *J Rheumatol* 2000; **27:** 1542–5.
2. Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. *Rheumatology (Oxford)* 2005; **44:** 386–9.
3. Edge JC, *et al.* Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol* 2006; **142:** 65–9.
4. Rowin J, *et al.* Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology* 2006; **66:** 1245–7.

Primary biliary cirrhosis. Despite initial reports[1] of benefit with mycophenolate mofetil in the treatment of primary biliary cirrhosis (p.2408), a small study found no clinical benefit when it was given to patients with incomplete responses to ursodeoxycholic acid.[2]

1. Jones EA. Rationale for trials of long-term mycophenolate mofetil therapy for primary biliary cirrhosis. *Hepatology* 2002; **35:** 258–62.
2. Talwalkar JA, *et al.* Mycophenolate mofetil for the treatment of primary biliary cirrhosis in patients with an incomplete response to ursodeoxycholic acid. *J Clin Gastroenterol* 2005; **39:** 168–71.

Psoriasis. Mycophenolate mofetil has proved successful in some cases of psoriasis (p.1583) refractory to conventional therapies,[1-3] and topical application (as a 2% cream) has been investigated.[4]

1. Grundmann-Kollmann M, *et al.* Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000; **42:** 835–7.
2. Geilen CC, *et al.* Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; **144:** 583–6.
3. Zhou Y, *et al.* Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003; **7:** 193–7.
4. Wohlrab J, *et al.* Topical application of mycophenolate mofetil in plaque-type psoriasis. *Br J Dermatol* 2001; **144:** 1263–4.

Rheumatoid arthritis. Mycophenolate mofetil has been tried in rheumatoid arthritis (p.11); reports suggest it may effectively suppress synovial inflammation.[1]

1. McMurray RW, Harisdangkul V. Mycophenolate mofetil: selective T cell inhibition. *Am J Med Sci* 2002; **323:** 194–6.

Sarcoidosis. Mycophenolate mofetil has been used as an adjunct in the successful treatment of patients with mucocutaneous sarcoidosis (p.1512)[1] and neurosarcoidosis.[2] It was reported to have a significant corticosteroid-sparing effect in an adolescent with renal involvement,[3] and was effective in a case of severe, relapsing, corticosteroid-dependent gastrointestinal sarcoidosis.[4]

1. Kouba DJ, *et al.* Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatol* 2003; **148:** 147–8.
2. Chaussenot A, *et al.* Neurosarcoïdose et mycophénolate mofétil. *Rev Neurol (Paris)* 2007; **163:** 471–5.
3. Moudgil A, *et al.* Successful steroid-sparing treatment of renal limited sarcoidosis with mycophenolate mofetil. *Pediatr Nephrol* 2006; **21:** 281–5.
4. O'Connor AS, *et al.* Pancreatitis and duodenitis from sarcoidosis: successful therapy with mycophenolate mofetil. *Dig Dis Sci* 2003; **48:** 2191–5.

Scleroderma. There are reports of response to mycophenolate in patients with scleroderma (p.1817).

References.

1. Nihtyanova SI, *et al.* Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. *Rheumatology (Oxford)* 2007; **46:** 442–5.
2. Vanthuyne M, *et al.* A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheumatol* 2007; **25:** 287–92.
3. Shenin M, *et al.* The use of mycophenolate mofetil for the treatment of systemic sclerosis. *Endocr Metab Immune Disord Drug Targets* 2008; **8:** 11–14.

Systemic lupus erythematosus. Mycophenolate mofetil by mouth plus prednisolone, given for 12 months, was found to be as effective as oral cyclophosphamide plus prednisolone, for 6 months, followed by azathioprine plus prednisolone for 6 months,[1] in the treatment of Chinese patients with diffuse proliferative *lupus nephritis* (see Systemic Lupus Erythematosus, p.1513). However, some[2,3] have cautioned about generalising these findings to other patients since mycophenolate was compared with oral and not intravenous pulsed cyclophosphamide, which is considered the standard of care in those with diffuse proliferative disease. Patients with poorer prognoses were also considered to have been excluded or underrepresented in the study, and follow-up was short. However, in a 24-week unblinded study[4] oral mycophenolate mofetil was more effective in inducing complete remission than intermittent intravenous cyclophosphamide when used as induction therapy for active lupus nephritis and appeared to be better tolerated. Also, there have been reports of benefit with mycophenolate mofetil in patients with various forms of refractory lupus nephritis, including proliferative disease and membranous nephropathy,[5-7] and some consider it a good therapeutic alternative.[8,9] A review[10] concluded that limited data support induction with cyclophosphamide followed by maintenance with azathioprine or mycophenolate; in selected patients induction with mycophenolate is a reasonable alternative. Meta-analyses concluded that daily oral mycophenolate mofetil, in average or median doses of 1 to 2 g, was more effective than pulsed intravenous or oral cyclophosphamide,[11] and that mycophenolate reduced the risk of failure to induce remission during induction therapy when compared with cyclophosphamide.[12] However, the role of racial and ethnic differences in lupus remain poorly understood, and enrolment of varying ethnic populations in studies can significantly affect results of therapy.[13] Furthermore, it has been pointed out that subjects in studies included in one meta-analysis had relatively preserved renal function, and results cannot be generalised to patients with moderate to severe renal impairment and rapidly progressive glomerulonephritis.[14] While acknowledging data of mycophenolate use in children are limited, another review[15] concluded that from data in adults, mycophenolate is an acceptable alternative to intravenous cyclophosphamide in the induction phase for newly diagnosed patients with mild to moderate nephritis and intact renal function; it may also be suitable if there is concern about a patient's future fertility. However, the optimal dose and length of induction treatment with mycophenolate are still unknown.

Mycophenolate mofetil has been used to control extra-renal manifestations of SLE,[16,17] although it was ineffective in a small number of patients with severe refractory cutaneous disease.[18] Oral mycophenolate sodium 1.44 g daily has been reported to be effective in the treatment of patients with subacute cutaneous lupus erythematosus resistant to standard therapy.[19]

1. Chan TM, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; **343:** 1156–62.
2. Falk RJ. Treatment of lupus nephritis—a work in progress. *N Engl J Med* 2000; **343:** 1182–3.
3. Karassa FB, Isenberg DA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2001; **344:** 382–3. Correction. *ibid.*; 1176.
4. Ginzler EM, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; **353:** 2219–28.
5. Kingdon EJ, *et al.* The safety and efficacy of MMF in lupus nephritis: a pilot study. *Lupus* 2001; **10:** 606–11.
6. Kapitsinou PP, *et al.* Lupus nephritis: treatment with mycophenolate mofetil. *Rheumatology (Oxford)* 2004; **43:** 377–80.
7. Spetie DN, *et al.* Mycophenolate therapy of SLE membranous nephropathy. *Kidney Int* 2004; **66:** 2411–15.
8. Ginzler EM, Aranow C. Mycophenolate mofetil in lupus nephritis. *Lupus* 2005; **14:** 59–64.
9. Pisoni CN, *et al.* Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. *J Rheumatol* 2005; **32:** 1047–52.
10. Lenz O, *et al.* Defining the role of mycophenolate mofetil in the treatment of proliferative lupus nephritis. *Drugs* 2005; **65:** 2429–36.
11. Moore RA, Derry S. Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. *Arthritis Res Ther* 2006; **8:** R182.
12. Walsh M, *et al.* Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2007; **2:** 968–75.
13. Dooley MA. Mycophenylate [sic] mofetil: what role in the treatment of lupus? *Lupus* 2006; **15:** 179–82.
14. Contreras G, Sosnov J. Role of mycophenolate mofetil in the treatment of lupus nephritis. *Clin J Am Soc Nephrol* 2007; **2:** 879–82.
15. Paredes A. Can mycophenolate mofetil substitute cyclophosphamide treatment of pediatric lupus nephritis? *Pediatr Nephrol* 2007; **22:** 1077–82.
16. Karim MY, *et al.* Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. *Rheumatology (Oxford)* 2002; **41:** 876–82.
17. Pisoni CN, *et al.* Mycophenolate mofetil and systemic lupus erythematosus: an overview. *Lupus* 2005; **14** (suppl): s9–s11.
18. Pisoni CN, *et al.* Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. *Clin Exp Rheumatol* 2005; **23:** 393–6.
19. Kreuter A, *et al.* Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007; **156:** 1321–7.

Vasculitic syndromes. Mycophenolate mofetil has been tried in a number of the vasculitic syndromes, including Churg-Strauss syndrome (p.1501), polyarteritis nodosa and microscopic polyangiitis (p.1510), Takayasu's arteritis (p.1514), and Wegener's granulomatosis (p.1515).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: CellCept; Imuxgen; Munotras; Myfortic; ***Austral.:*** CellCept; Myfortic; ***Austria:*** CellCept; Myfortic; ***Belg.:*** CellCept; Myfortic; ***Braz.:*** CellCept; Myfortic; Refrat†; ***Canad.:*** CellCept; Myfortic; ***Chile:*** CellCept; Myfortic; ***Cz.:*** CellCept; Myfenax; Myfortic; ***Denm.:*** CellCept; Myfortic; ***Fin.:*** CellCept; Myfortic; ***Fr.:*** CellCept; Myfortic; ***Ger.:*** CellCept; Myfortic; ***Gr.:*** CellCept; Myfortic; ***Hong Kong:*** CellCept; Myfortic; ***Hung.:*** CellCept; Myfortic; ***India:*** Cellmune; Mycept; ***Indon.:*** CellCept; Myfortic; ***Irl.:*** CellCept; Myfortic; ***Israel:*** CellCept; Myfortic; ***Ital.:*** CellCept; Myfortic; ***Jpn:*** CellCept; ***Malaysia:*** CellCept; Myfortic; ***Mex.:*** CellCept; Myfortic; ***Neth.:*** CellCept; Myfortic; ***Norw.:*** CellCept; Myfortic; ***NZ:*** CellCept; ***Philipp.:*** CellCept; Myfortic; ***Pol.:*** CellCept; Myfortic; ***Port.:*** CellCept; Myfortic; ***Rus.:*** Myfortic (Майфортик); ***S.Afr.:*** CellCept; Myfortic; ***Singapore:*** CellCept; ***Spain:*** CellCept; Myfortic; ***Swed.:*** CellCept; Myfortic; ***Switz.:*** CellCept; Myfortic; ***Thai.:*** CellCept; Myfortic; ***Turk.:*** CellCept; ***UK:*** CellCept; Myfortic; ***USA:*** CellCept; Myfortic; ***Venez.:*** CellCept; Myfortic.

Reparixin *(USAN, rINN)*

DF-1681Y; Reparixina; Réparixine; Reparixinum; Repertaxin. (2*R*)-2-[4-(2-Methylpropyl)phenyl]-*N*-methylsulfonylpropanamide.

Репариксин

$C_{14}H_{21}NO_3S$ = 283.4.

CAS — 266359-83-5.

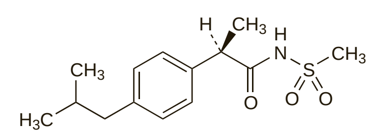

Reparixin Lysine *(rINNM)*

Reparixin L-Lysine; Reparixina lisina; Réparixine Lysine; Reparixinum Lysinum; Repertaxin L-Lysine. Reparixin compound with L-lysine (1:1); .

Репариксин Лизин

$C_{14}H_{21}NO_3S,C_6H_{14}N_2O_2$; = 429.6.

CAS — 266359-93-7.

Profile

Reparixin is an inhibitor of interleukin-8. Reparixin and reparixin lysine are under investigation for the prevention of delayed graft function in organ transplantation.

Sirolimus (BAN, USAN, rINN)

AY-22989; AY-022989; NSC-226080; Rapamycin; Sirolimús; Sirolimusum; Sirolimuusi; Wy-090217. (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-{(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29-(4H,6H,31H)-pentone.

Сиролимус

$C_{51}H_{79}NO_{13}$ = 914.2.

CAS — 53123-88-9.

ATC — L04AA10.

ATC Vet — QL04AA10.

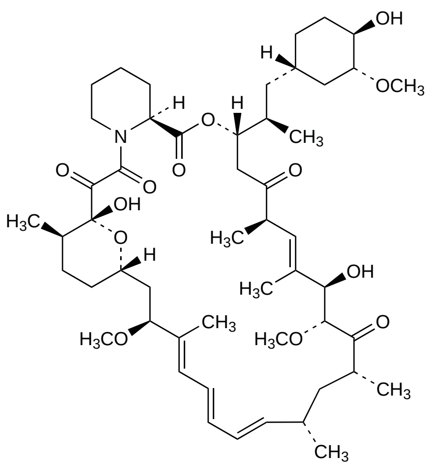

Adverse Effects and Precautions

The most frequent adverse effects of sirolimus include peripheral oedema, lymphocele, hypokalaemia, hypophosphataemia, hyperlipidaemia, hypercholesterolaemia, hyperglycaemia, tachycardia, venous thromboembolism, gastrointestinal disturbances, stomatitis, arthralgia, epistaxis, acne, rash, and bone necrosis. Anaemia, thrombocytopenia, neutropenia or leucopenia are common, especially at higher doses. Infections, including urinary-tract infections, pyelonephritis, CMV, Epstein-Barr virus, herpes zoster, and pneumocystis pneumonia, are also common, and antimicrobial prophylaxis for pneumonia is recommended for the first year after transplantation.

Thrombotic thrombocytopenic purpura and the haemolytic-uraemic syndrome may occur, as may hypersensitivity, including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis. There are reports of fluid accumulation, including lymphoedema, pleural effusions, and pericardial effusions. Pulmonary embolism, pulmonary haemorrhage, and pancreatitis may occur rarely. Renal impairment, proteinuria, or nephrotic syndrome may develop; renal function should be monitored, especially when given with ciclosporin. In patients with delayed graft function, sirolimus may delay recovery of renal function. There are reports of hepatotoxicity, and rarely, fatal hepatic necrosis. Excess mortality, graft loss, and hepatic artery thrombosis has been associated with the use of sirolimus in immunosuppressive regimens in liver transplant recipients and therefore use in such patients is not recommended. Interstitial lung disease has been reported, including some fatalities, although other cases resolved on stopping or reducing the dose of sirolimus. Abnormal wound healing after transplant surgery has been reported with the use of sirolimus, especially in those with a BMI greater than 30 kg/m^2; bronchial anastomotic dehiscence, including some fatal cases, has occurred in lung transplant recipients and use in the latter is not recommended. There is an increased risk of lymphoma and other malignancies with immunosuppression, and to minimise any risk of skin cancer, exposure to sunlight or ultraviolet light should be limited.

Sirolimus may have adverse effects on sperm parameters; azoospermia and infertility have been reported. These effects are usually reversible on stopping sirolimus.

Immunosuppressants may reduce the response to vaccines, and the use of live vaccines should be avoided. Intra-uterine devices should be used with caution during immunosuppressive therapy, as there is an increased risk of infection.

Hypersensitivity reactions and subacute thrombosis have occurred with use of the sirolimus-eluting stent; fatalities have been reported.

Effects on the kidneys. There are a number of reports of proteinuria and renal dysfunction associated with sirolimus. A review[1] concluded that the vast majority of evidence suggested that proteinuria was mediated by glomerular haemodynamic mechanisms due to withdrawal of other immunosuppressants in kidneys with chronic glomerular injury, as in those transplant patients with chronic allograft dysfunction. Whether sirolimus directly causes proteinuria and/or mediates direct glomerular toxicity remains to be resolved and further studies are needed.

1. Rangan GK. Sirolimus-associated proteinuria and renal dysfunction. *Drug Safety* 2006; **29:** 1153–61.

Effects on the lungs. Pulmonary toxicity, including interstitial pneumonitis,[1-7] and alveolar haemorrhage,[5,8,9] has been reported in association with sirolimus. There was some suggestion in one series that the incidence of interstitial pneumonitis might be higher in patients who switched from calcineurin inhibitors to sirolimus than in those who were started on sirolimus after transplantation.[6] Possible risk factors include giving a loading dose, late use of sirolimus compared with initial therapy, and higher sirolimus dose and trough concentrations; additional risk factors include allograft dysfunction, hypervolaemia, and male gender.[7] Acute respiratory distress has been reported in a 1-year-old heart transplant recipient 3 days after starting sirolimus.[10] Pulmonary alveolar proteinosis has also been reported in a renal transplant patient 2 years after starting sirolimus; symptoms resolved markedly upon stopping sirolimus.[11]

Similar toxicity has occurred with everolimus (p.1833).

1. Morelon E, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 225–6.
2. Singer SJ, *et al.* Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000; **343:** 1815–16.
3. Morelon E, *et al.* Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001; **72:** 787–90.
4. Lennon A, *et al.* Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation* 2001; **72:** 1166–7.
5. Pham P-T T, *et al.* Sirolimus-associated pulmonary toxicity. *Transplantation* 2004; **77:** 1215–20.
6. Champion L, *et al.* Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med* 2006; **144:** 505–9.
7. Morath C, *et al.* Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc* 2007; **39:** 99–102.
8. Vlahakis NE, *et al.* Sirolimus-associated diffuse alveolar hemorrhage. *Mayo Clin Proc* 2004; **79:** 541–5.
9. Khalife WI, *et al.* Sirolimus-induced alveolar hemorrhage. *J Heart Lung Transplant* 2007; **26:** 652–7.
10. Das BB, *et al.* Acute sirolimus pulmonary toxicity in an infant heart transplant recipient: case report and literature review. *J Heart Lung Transplant* 2007; **26:** 296–8.
11. Pedroso SL, *et al.* Pulmonary alveolar proteinosis: a rare pulmonary toxicity of sirolimus. *Transpl Int* 2007; **20:** 291–6.

Effects on the nervous system. Posterior reversible encephalopathy syndrome (a neurotoxic condition involving oedema of the white matter in the posterior parts of the brain and characterised by headache, confusion, and visual disturbances) has been reported after use of sirolimus.[1,2]

1. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. *Neurology* 2007; **68:** 2039–40.
2. Moskowitz A, *et al.* Posterior reversible encephalopathy syndrome due to sirolimus. *Bone Marrow Transplant* 2007; **39:** 653–4.

Thrombosis. There was an apparent clustering of reports of subacute thrombosis associated with the use of the sirolimus-eluting stent soon after its marketing approval in 2003.[1] However, subsequent studies[2] and additional data from 2063 patients[3] suggest that use of the sirolimus-eluting stent is not associated with an excess risk of subacute thrombosis compared with bare-metal stents.

1. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; **351:** 1593–5.
2. Jeremias A, *et al.* Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation* 2004; **109:** 1930–2.
3. US Food and Drug Administration. FDA public health web notification: final update of information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER sirolimus-eluting coronary stent (issued 18/10/04). Available at: http://www.fda.gov/cdrh/safety/cypher3.pdf (accessed 18/03/08)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, HIV-protease inhibitors, the NNRTI delavirdine, and diltiazem may increase plasma concentrations of sirolimus. Conversely, inducers of this isoenzyme, such as nevirapine and rifampicin, may reduce plasma concentrations of sirolimus. Use of sirolimus with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein is not recommended. Grapefruit juice should not be taken with sirolimus. Ciclosporin can affect the rate and extent of sirolimus absorption and it is recommended that these drugs be given 4 hours apart. Use of sirolimus with a calcineurin inhibitor may also increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, or thrombotic microangiopathy. Use of sirolimus with an ACE inhibitor may increase the risk of developing angioedema. See above for precautions about use with live vaccines.

Immunosuppressants. Concentrations of sirolimus, and area under the concentration-time curve were significantly higher when sirolimus and *ciclosporin* were given together than when the 2 drugs were given 4 hours apart,[1,2] and a synergistic effect has been suggested.[3] This effect may allow for lower doses[4] or early withdrawal[5] of ciclosporin, resulting in improved renal function and less nephrotoxicity. However, for the risk of increased thrombotic reactions see above.

Sirolimus may decrease blood concentrations of *tacrolimus*.

1. Kaplan B, *et al.* The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* 1998; **63:** 48–53.
2. Zimmerman JJ, *et al.* Pharmacokinetic interactions between sirolimus and microemulsion cyclosporine when orally administered jointly and 4 hours apart in healthy volunteers. *J Clin Pharmacol* 2003; **43:** 1168–76.
3. Kahan BD, Kramer WG. Median effect analysis of efficacy versus adverse effects of immunosuppressants. *Clin Pharmacol Ther* 2001; **70:** 74–81.
4. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
5. Johnson RWG, *et al.* Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; **72:** 777–86.

Pharmacokinetics

Sirolimus is rapidly absorbed after doses of the oral solution, with a time to peak concentration of about 2 hours. Absorption is variably affected by food, especially high-fat meals. Sirolimus is extensively bound to plasma proteins. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Metabolism occurs by demethylation or hydroxylation, and the majority of a dose is excreted via the faeces, with only about 2% excreted in the urine. In healthy subjects, the bioavailability of a single dose of the tablet formulation is about 27% higher than the oral solution, bioavailability of which is only about 14%. However, this difference is less marked in renal transplant recipients, and when switching between formulations, licensed product information recommends giving the same dose, with trough concentrations verified 1 to 2 weeks later. The terminal half-life in stable renal transplant patients after multiple oral doses has been reported to be about 62 hours; the half-life in men was reported to be significantly longer than in women (about 72 hours compared with about 61 hours).

◊ References.

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.

Genetic factors. Renal transplant recipients with at least one CYP3A5*1 allele had lower exposure to sirolimus than those patients homozygous for CYP3A5*3, and patients with CYP3A5*1/*1 and *1/*3 genotypes required significantly higher sirolimus daily dosage to achieve the same blood concentrations at steady state as the *3/*3 genotypes.[1] Determination of this cytochrome P450 isoenzyme polymorphism could be useful for individualising doses of sirolimus.

1. Le Meur Y, *et al.* CYP3A5*3 influences sirolimus oral clearance in de novo and stable renal transplant recipients. *Clin Pharmacol Ther* 2006; **80:** 51–60.

Therapeutic drug monitoring. The immunosuppressive efficacy and the occurrence and severity of adverse effects of sirolimus correlate with blood concentrations.[1] There is also a good correlation between sirolimus trough concentrations and the area under the concentration-time curve (AUC); the trough concentration is therefore a useful surrogate marker for sirolimus exposure.[2] When sirolimus is used with ciclosporin, whole blood trough concentrations of sirolimus between 4 and 12 nanograms/mL are associated with protection from acute rejection episodes and adverse events. Black patients may require higher doses of sirolimus to achieve a similar exposure to non-black patients; trough concentrations in the higher end of the range are recommended to reduce the risk of rejection.[3] When ciclosporin therapy is stopped, a target trough concentration of sirolimus of about 12 to 20 nanograms/mL is recommended (see also Uses and Administration, below).

Daily monitoring of sirolimus is not necessary due to the relatively long half-life of the drug (about 60 hours). Furthermore, sirolimus concentrations are variable early after transplantation due to physiological changes from surgery and concurrent dose adjustments in other immunosuppressants. The first sample should be taken about 4 days or more after the initial loading dose, and then weekly for the first month and every 2 weeks for the second month.[3] Monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing.[2,3]

After the first 2 months of dose titration, routine therapeutic drug monitoring is not considered necessary in all patients, although it is considered warranted in patients receiving concurrent CYP3A4 and/or P-glycoprotein inducers or inhibitors. Monitoring may also be needed in those at high risk of rejection, those displaying signs of toxicity, or those in whom compliance is a problem.[3] Patients with liver disease, hyperlipidaemia, or leucopenia should also have their sirolimus blood concentrations determined,[2] and concentrations in children should be monitored.[3] Licensed product information states that the recommended 24-hour trough concentrations for sirolimus are based on chromatographic assay methods, and that these values are not interchangeable with immunoassay methods.

Bayesian forecasting has also been proposed as an accurate predictor of sirolimus pharmacokinetics.[4,5]

1. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin Pharmacokinet* 2001; **40:** 573–85.
2. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
3. Stenton SB, *et al.* Sirolimus: the evidence for clinical pharmacokinetic monitoring. *Clin Pharmacokinet* 2005; **44:** 769–86.
4. Dansirikul C, *et al.* A Bayesian approach for population pharmacokinetic modelling of sirolimus. *Br J Clin Pharmacol* 2006; **62:** 420–34.
5. Djebli N, *et al.* Sirolimus population pharmacokinetic/pharmacogenetic analysis and Bayesian modelling in kidney transplant recipients. *Clin Pharmacokinet* 2006; **45:** 1135–48.

Uses and Administration

Sirolimus is a macrolide compound obtained from *Streptomyces hygroscopicus* and has potent immunosuppressant properties. Sirolimus binds to a protein (FK binding protein-12; FKBP-12; FKPB-12) and this complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase for cell cycle progression thus suppressing cytokine-driven T-cell proliferation.

Sirolimus is used for the prevention of graft rejection in kidney transplantation (p.1813), and is being investigated for induction of remission in some auto-immune diseases. Sirolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement. They are also used in the treatment of severe claudication and critical limb ischaemia of infrapopliteal lesions (which is the most severe form of arterial disease in the leg).

For prevention of graft rejection, sirolimus is given with ciclosporin and corticosteroids as soon as possible after transplantation. A loading dose of 6 mg is given orally, followed by a maintenance dose of 2 mg daily, 4 hours after ciclosporin. In patients 13 years of age or more who weigh less than 40 kg a loading dose of 3 mg/m^2, followed by initial maintenance doses of 1 mg/m^2 daily, is recommended. It is recommended that the dose of sirolimus should be adjusted to obtain whole blood trough concentrations of 4 to 12 nanograms/mL (by chromatographic assay), and the doses of ciclosporin and corticosteroids gradually reduced. After 2 to 3 months, ciclosporin should be gradually stopped over 4 to 8 weeks, and the dose of sirolimus adjusted to obtain trough concentrations of about 12 to 20 nanograms/mL. In the USA, ciclosporin may be continued for up to 4 months; sirolimus trough concentrations of 16 to 24 nanograms/mL have been recommended for the first year after transplantation; thereafter, the concentrations should be 12 to 20 nanograms/mL. In patients at high immunological risk (defined as black [Afro-Caribbean] patients and/or repeat renal transplant patients), sirolimus may be used with ciclosporin and corticosteroids for the first year after transplantation. The recommended loading dose is 15 mg, followed by an initial maintenance dose of 5 mg daily; adjustments thereafter are made on the basis of whole blood trough concentrations. In patients in whom ciclosporin withdrawal is unsuccessful or cannot be attempted, sirolimus should not be used for more than 3 months after transplantation.

Sirolimus has been shown to possess antifungal and antineoplastic properties. It is under investigation for gene regulation in gene therapy.

Administration. A study in renal transplant recipients judged the tablet and oral solution formulations of sirolimus to be therapeutically equivalent.[1] Licensed product information states that while 2 mg of oral solution has been shown to be clinically equivalent to 2 mg of the oral tablet formulation, and the two are hence interchangeable, it is not known whether higher doses of the oral solution are clinically equivalent to the same doses as tablets. When switching patients between formulations, it is recommended to give the same dose and verify the sirolimus trough concentrations 1 to 2 weeks later; verification of trough concentrations is also recommended when switching between different tablet strengths.

1. Mathew TH, *et al.* A comparative study of sirolimus tablet versus oral solution for prophylaxis of acute renal allograft rejection. *J Clin Pharmacol* 2006; **46:** 76–87.

Administration in children. Sirolimus is not licensed for use in children under 13 years of age. For doses in children aged 13 years or older, and weighing under 40 kg, see Uses and Administration, above. In the UK, the *BNFC* recommends local treatment protocols be consulted for details of doses to be used in children; official guidance from NICE recommends that sirolimus be used as a component of immunosuppressive regimens in children and adolescents only if intolerance necessitates the withdrawal of a calcineurin inhibitor.[1]

1. NICE. Immunosuppressive therapy for renal transplantation in children and adolescents (Technology Appraisal 99, issued April 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA099guidance.pdf (accessed 07/02/08)

Administration in hepatic impairment. Exposure to sirolimus and half-life are both increased in patients with mild to moderate hepatic impairment (Child-Pugh category A or B). UK licensed product information states that in patients with hepatic impairment, it is not necessary to modify the loading dose of sirolimus, but whole blood trough concentrations should be closely monitored in these patients. US licensed product information states that the maintenance dose should be reduced by about one-third in patients with mild to moderate hepatic impairment.

A study[1] involving 9 patients with severe hepatic impairment (Child-Pugh category C) indicated that an initial dosage reduction of about 60% followed by therapeutic drug monitoring might be suitable in these patients. For patients with severe hepatic impairment UK and US licensed product information state that the maintenance dose should be reduced by about one half.

1. Zimmerman JJ, *et al.* Pharmacokinetics of sirolimus (rapamycin) in subjects with severe hepatic impairment. *J Clin Pharmacol* 2008; **48:** 285–92.

Kaposi's sarcoma. Transplant recipients are susceptible to the development of Kaposi's sarcoma (p.675) as a result of long-term immunosuppressive therapy. In 15 renal transplant recipients with biopsy-proven Kaposi's sarcoma, therapy with ciclosporin and mycophenolate was stopped, and sirolimus started. After 1 month, cutaneous lesions had regressed in 12 patients and after 6 months biopsy specimens were negative for Kaposi's sarcoma.[1] While stopping ciclosporin or mycophenolate has led to remission of Kaposi's sarcoma,[2] sirolimus may have an antineoplastic action independent of its immunosuppressive effect.[1] In renal transplant recipients, those who received sirolimus-based therapy after ciclosporin withdrawal at month 3 had a reduced incidence of both skin and non-skin (including Kaposi's sarcoma) malignancies at 5 years after transplantation, compared with those who continued with sirolimus and ciclosporin therapy.[3]

1. Stallone G, *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352:** 1317–23.
2. Dantal J, Soulillou J-P. Immunosuppressive drugs and the risk of cancer after organ transplantation. *N Engl J Med* 2005; **352:** 1371–3.
3. Campistol JM, *et al.* Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17:** 581–9.

Lymphangioleiomyomatosis. Improvements in left lung function have been noted in a patient with lymphangioleiomyomatosis treated with sirolimus after transplantation of the right lung.[1] For mention of the use of medroxyprogesterone in this rare disease, see Respiratory Disorders, p.2114.

1. Egan JJ, *et al.* Sirolimus for lymphangioleiomyomatosis lesions. *N Engl J Med* 2008; **358:** 1963–4.

Organ and tissue transplantation. Sirolimus is used for the prophylaxis of graft rejection in kidney transplantation (p.1813), initially as an adjunct to calcineurin inhibitor-based regimens. It is increasingly used for corticosteroid or calcineurin inhibitor withdrawal, although long-term data are lacking, and the safety of ciclosporin withdrawal in high-risk patients has not been adequately studied and is not recommended. Sirolimus has been investigated for liver (p.1815), heart (p.1812), pancreas (p.1816), and lung (p.1815) transplantation, although safety has not been established. In *de novo* renal transplant patients, there was an increased risk of rejection in those given sirolimus and mycophenolate and corticosteroids with an interleukin-2 receptor antibody, compared with those not given an interleukin-2 receptor antibody. In a small study of heart transplant recipients switched from standard immunosuppressive therapy with a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, to sirolimus with mycophenolate mofetil, there was an increased incidence of acute rejection; target sirolimus and mycophenolate concentrations may have been insufficient to maintain adequate immunosuppression.

A few selected references to the use of sirolimus in transplantation are given below.

1. Vasquez EM. Sirolimus: a new agent for prevention of renal allograft rejection. *Am J Health-Syst Pharm* 2000; **57:** 437–51.
2. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; **356:** 194–202.
3. Ingle GR, *et al.* Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000; **34:** 1044–55.
4. Johnson RW. Sirolimus (Rapamune) in renal transplantation. *Curr Opin Nephrol Hypertens* 2002; **11:** 603–7.
5. Radovancevic B, Vrtovec B. Sirolimus therapy in cardiac transplantation. *Transplant Proc* 2003; **35** (suppl): 171S–176S.
6. Trotter JF. Sirolimus in liver transplantation. *Transplant Proc* 2003; **35** (suppl): 193S–200S.
7. MacDonald AS. Rapamycin in combination with cyclosporine or tacrolimus in liver, pancreas, and kidney transplantation. *Transplant Proc* 2003; **35** (suppl): 201S–208S.
8. Neff GW, *et al.* Ten years of sirolimus therapy in orthotopic liver transplant recipients. *Transplant Proc* 2003; **35** (suppl): 209S–216S.
9. Dupont P, Warrens AN. The evolving role of sirolimus in renal transplantation. *QJM* 2003; **96:** 401–9.
10. Kahan BD. Sirolimus: a ten-year perspective. *Transplant Proc* 2004; **36:** 71–5.
11. Lo A, *et al.* Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004; **77:** 1228–35.
12. Kuypers DRJ. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Safety* 2005; **28:** 153–81.
13. Mehrabi A, *et al.* The role and value of sirolimus administration in kidney and liver transplantation. *Clin Transplant* 2006; **20** (Suppl 17): 30–43.
14. Mulay AV, *et al.* Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. *Transplantation* 2006; **82:** 1153–62.
15. Augustine JJ, *et al.* Use of sirolimus in solid organ transplantation. *Drugs* 2007; **67:** 369–91.
16. House AA, *et al.* Sirolimus use in recipients of expanded criteria donor kidneys. *Drugs* 2008; **68** (suppl 1): 41–9.

Psoriasis. Sirolimus has been investigated both systemically[1,2] and topically[3,4] in the treatment of psoriasis (p.1583).

1. Reitamo S, *et al.* A double-blind study in patients with severe psoriasis to assess the clinical activity and safety of rapamycin (sirolimus) alone or in association with a reduced dose of cyclosporine. *Br J Dermatol* 1999; **141:** 978–9.
2. Reitamo S, *et al.* Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2001; **145:** 438–45.
3. Ormerod AD, *et al.* Penetration, safety and efficacy of the topical immunosuppressive sirolimus in psoriasis. *Br J Dermatol* 1999; **141:** 975.
4. Ormerod AD, *et al.* Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005; **152:** 758–64.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Coronary stents that elute sirolimus effectively reduce restenosis[1-8] and have been widely used. There is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis,[9-12] although not all studies have noted differences.[13] The risk of late stent thrombosis may be increased with drug eluting stents,[14] although the evidence is controversial,[15] and their role in complex interventions is not yet established.[16,17] Oral sirolimus may also be effective in preventing restenosis.[18-21]

1. Morice M-C, *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346:** 1773–80.
2. Moses JW, *et al.* Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349:** 1315–23.

3. Lemos PA, *et al.* Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003; **41:** 2093–9.
4. Holmes DR, *et al.* Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004; **109:** 634–40.
5. Vishnevetsky D, *et al.* Sirolimus-eluting coronary stent. *Am J Health-Syst Pharm* 2004; **61:** 449–56.
6. Cheng-Lai A, Frishman WH. Sirolimus-eluting coronary stents: novel devices for the management of coronary artery disease. *Am J Ther* 2004; **11:** 218–28.
7. Spaulding C, *et al.* A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 989–97.
8. Kastrati A, *et al.* Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356:** 1030–9.
9. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
10. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
11. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
12. Stettler C, *et al.* Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370:** 937–48.
13. Galløe AM, *et al.* SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 2008; **299:** 409–16.
14. Stone GW, *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356:** 998–1008.
15. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; **356:** 1020–9.
16. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297:** 1992–2000.
17. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297:** 2001–9.
18. Hausleiter J, *et al.* Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* 2004; **110:** 790–5.
19. Waksman R, *et al.* Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the Oral Rapamune to Inhibit Restenosis (ORBIT) study. *J Am Coll Cardiol* 2004; **44:** 1386–92.
20. Rodriguez AE, *et al.* ORAR II Investigators. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) Study. *J Am Coll Cardiol* 2006; **47:** 1522–9.
21. Rodriguez AE, *et al.* Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* 2005; **91:** 1433–7.

Uveitis. Sirolimus has been reported to be effective in the treatment of patients with refractory uveitis.[1]

1. Shanmuganathan VA, *et al.* The efficacy of sirolimus in the treatment of patients with refractory uveitis. *Br J Ophthalmol* 2005; **89:** 666–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rapamune; ***Austral.:*** Rapamune; ***Austria:*** Rapamune; ***Belg.:*** Rapamune; ***Braz.:*** Rapamune; ***Canad.:*** Rapamune; ***Chile:*** Rapamune; ***Cz.:*** Rapamune; ***Denm.:*** Rapamune; ***Fin.:*** Rapamune; ***Fr.:*** Rapamune; ***Ger.:*** Rapamune; ***Gr.:*** Rapamune; ***Hong Kong:*** Rapamune; ***Hung.:*** Rapamune; ***India:*** Rapamune; ***Irl.:*** Rapamune; ***Israel:*** Rapamune; ***Ital.:*** Rapamune; ***Malaysia:*** Rapamune; ***Mex.:*** Rapamune; ***Neth.:*** Rapamune; ***Norw.:*** Rapamune; ***NZ:*** Rapamune; ***Philipp.:*** Rapamune; ***Pol.:*** Rapamune; ***Port.:*** Rapamune; ***S.Afr.:*** Rapamune; ***Singapore:*** Rapamune; ***Spain:*** Rapamune; ***Swed.:*** Rapamune; ***Switz.:*** Rapamune; ***Thai.:*** Rapamune; ***Turk.:*** Rapamune; ***UK:*** Rapamune; ***USA:*** Rapamune; ***Venez.:*** Rapamune.

Tacrolimus *(BAN, USAN, rINN)*

FK-506; FR-900506; Tacrolimús; Tacrolimusum; Takrolimus; Takrolimuusi; Tsukubaenolide. (−)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-{(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl}-14,16,-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone monohydrate.

Такролимус

$C_{44}H_{69}NO_{12},H_2O$ = 822.0.

CAS — 104987-11-3 (anhydrous tacrolimus); 109581-93-3 (tacrolimus monohydrate).

ATC — D11AX14; L04AD02.

ATC Vet — QD11AX14; QL04AD02.

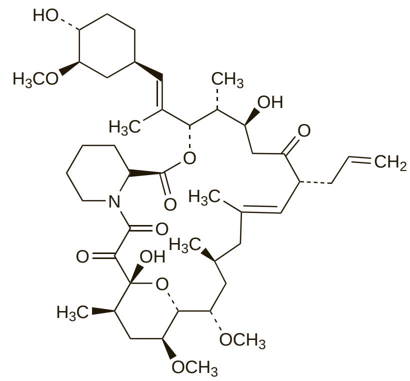

Adverse Effects, Treatment, and Precautions

The most common adverse effects after **systemic** use of tacrolimus include tremor, headache, paraesthesias, nausea and diarrhoea, hypertension, insomnia, and impaired renal function. Disturbances of serum electrolytes, notably hyperkalaemia, and hyperglycaemic conditions, including diabetes mellitus, occur frequently. Hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia are common. Anaemia, leucopenia, and thrombocytopenia also occur commonly. Other common adverse effects include mood changes, anxiety, confusion, dizziness, tinnitus, visual disturbances, peripheral neuropathies, and convulsions; constipation, dyspepsia, gastrointestinal perforation and ulceration, and gastrointestinal haemorrhage; dyspnoea, parenchymal lung disorders, pleural effusions, pharyngitis, cough, nasal congestion and inflammation; alopecia, acne, skin rashes, and pruritus; and arthralgia, muscle cramps, asthenia, febrile disorders, oedema, and liver dysfunction. Tachycardia is common; ventricular arrhythmias, cardiac arrest, heart failure, palpitations, and ECG changes are less frequent. Cardiomyopathies, including ventricular hypertrophy have also been reported; most cases have been reversible, and occurring primarily in children with tacrolimus blood concentrations much higher than the recommended maximum levels. Coagulation disorders, neutropenia, and pancytopenia have occurred, as have asthma, acute respiratory distress syndrome, hypoproteinaemia, deep limb venous thrombosis, paralytic ileus, acute and chronic pancreatitis, and haemolytic uraemic syndrome. Coma, CNS haemorrhage, encephalopathy, amnesia, and speech and language abnormalities have also been reported. There are rare reports of thrombotic thrombocytopenic purpura, hypoprothrombinaemia, and hirsutism. Toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic artery thrombosis, and veno-occlusive liver disease have occurred rarely.

Tacrolimus injection is formulated with polyoxyl castor oil: anaphylactoid reactions have occurred, and appropriate means for their management should be available in patients given the injection. Use of tacrolimus should be avoided in patients hypersensitive to macrolides.

Dosage reduction may be necessary in patients with hepatic impairment. Care is also required in patients with pre-existing renal impairment, and dosage reduction may prove advisable in such patients. Monitoring of blood concentrations of tacrolimus is recommended in all patients, especially during episodes of diarrhoea as concentrations may be significantly affected. Renal and hepatic function, blood pressure, serum glucose electrolytes, haematological and cardiac function, as well as neurological and visual status, coagulation values, and plasma protein should be monitored regularly. As with other immunosuppressants, patients receiving tacrolimus are at increased risk of infection and malignancy. Intra-uterine devices should be used with caution during immunosuppressive therapy as there is an increased risk of infection. Use of live vaccines should be avoided for the same reason. Tacrolimus may affect visual or neurological function, and patients so affected should not drive or operate dangerous machinery.

Topical tacrolimus has been associated with local irritation and skin disorders including an increased incidence of herpes simplex and zoster infections; headache and 'flu-like' symptoms have also been reported. Facial flushing and skin irritation has been reported after consumption of alcohol. Exposure of the skin to sunlight should be minimised and the use of artificial sources of ultraviolet light avoided. Carcinogenicity studies in *animals* have reported an increase in the incidence of lymphoma and skin cancers associated with topical tacrolimus and rare cases of skin malignancy and lymphoma have been reported in patients (see also below).

Skin infections should be treated before starting therapy with topical tacrolimus. It should not be used in immunocompromised patients or those with conditions that might increase systemic absorption of tacrolimus. It must also not be applied to pre-malignant or malignant skin conditions; some malignant skin conditions may mimic eczema.

Breast feeding. Tacrolimus is distributed into breast milk. Tacrolimus concentrations were measured in milk from a liver transplant recipient on a dose of 100 micrograms/kg daily. The authors estimated that the infant would ingest only 0.06% (0.06 micrograms/kg daily) of the mother's weight-adjusted dose. No adverse effects were noted in the infant at 2.5 months of age.[1]

Licensed product information recommends that women should avoid breast feeding while taking tacrolimus.

1. French AE, *et al.* Milk transfer and neonatal safety of tacrolimus. *Ann Pharmacother* 2003; **37:** 815–18.

Carcinogenicity. The systemic use of tacrolimus increases the risk of malignancy.

Carcinogenicity studies in *animals* have also reported an increase in the incidence of malignancies associated with the topical calcineurin inhibitors, tacrolimus and pimecrolimus. As of December 2004 the FDA had received reports of 19 cases of lymphoma or cutaneous tumours associated with topical tacrolimus, of which 4 cases were a recurrence or aggravation of a pre-existing malignancy, and 3 other cases were confounded by other possible risk factors. At this same date, the FDA had also received reports of 10 cases of malignancy in patients treated with topical pimecrolimus, including 6 cutaneous tumours. Although the potential for systemic immunosuppression from topical use was unknown and the role of the drug in these cases was uncertain, the FDA recommended that topical calcineurin inhibitors should only be used as a second-line drug for short-term and intermittent treatment of eczema, and that they should not be used in immunocompromised patients or in children younger than 2 years of age.[1,2] Similar warnings have been issued in the European Union.[3] However, there has been some debate about the risk of malignancy associated with the topical use of these drugs, and a number of groups[4-6] have examined the evidence used by the FDA. They found that after topical application in humans the serum concentrations of these drugs were usually low or undetectable, that there was no evidence of systemic immunosuppression as measured by response to childhood immunisation and delayed hypersensitivity, no evidence of an increase in malignancy in clinical studies or compared with the general population, and that none of the reported lymphoma cases resembled the usual presentation and histology seen with systemic immunosuppression-associated lymphoma. They concluded that based on available data the risk of cancer from topical calcineurin inhibitors was theoretical and unknown. A review[7] of skin cancer risk found that there was no conclusive evidence from *rodent* studies to suggest that topical calcineurin inhibitors were associated with an increase in skin cancers, or a potentiation of UV-associated immunosuppression and carcinogenicity. There was also no evidence of an increased risk of skin cancer in human studies. In general, there seems to be agreement that long-term data are still needed to determine the carcinogenic risk, if there is any, from topical tacrolimus and pimecrolimus. Until long-term safety data are available some[8] consider that it would be prudent if topical calcineurin inhibitors were:

- not used in children under 2 years of age
- not used continuously for more than 6 weeks, with an application-free period of up to 2 weeks
- avoided in immunocompromised patients
- avoided in patients with neoplasia
- avoided in those with skin disorders liable to lead to increased systemic absorption

Patients should also be encouraged to use a broad-spectrum sunscreen daily on all sunlight-exposed skin.

1. FDA. Alert for healthcare professionals: tacrolimus (marketed as Protopic) 03/05. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/ProtopicHCP.pdf (accessed 18/03/08)
2. FDA. Alert for healthcare professionals: pimecrolimus (marketed as Elidel) 03/05. Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/ElidelHCP.pdf (accessed 18/03/08)
3. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): reports of malignancies. *Current Problems* 2006; **31:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Fonacier L, *et al.* Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005; **115:** 1249–53.
5. Bieber T, *et al.* Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology* 2005; **211:** 77–8.
6. Berger TG, *et al.* The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006; **54:** 818–23.
7. Ring J, *et al.* Review of the potential photo-cocarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. *J Eur Acad Dermatol Venereol* 2005; **19:** 663–71.
8. Ring J, *et al.* The US FDA 'black box' warning for topical calcineurin inhibitors: an ongoing controversy. *Drug Safety* 2008; **31:** 185–98.

Effects on the blood. Severe anaemia due to selective depression of erythropoiesis in a patient given tacrolimus resolved when tacrolimus was replaced with ciclosporin.[1] More generalised bone marrow suppression,[2] post-transplant thrombotic microangiopathy,[3] and red cell aplasia[4] have also been reported. Hypoplasia occurring in a liver transplant recipient,[5] was characterised by a slow but complete recovery after substituting tacrolimus with ciclosporin.

1. Winkler M, *et al.* Anaemia associated with FK 506 immunosuppression. *Lancet* 1993; **341:** 1035–6.
2. de-la-Serna-Higuera C, *et al.* Tacrolimus-induced bone marrow suppression. *Lancet* 1997; **350:** 714–15.
3. Trimarchi HM, *et al.* FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation* 1999; **67:** 539–44.
4. Misra S, *et al.* Red cell aplasia in children on tacrolimus after liver transplantation. *Transplantation* 1998; **65:** 575–7.
5. Nosari A, *et al.* Bone marrow hypoplasia complicating tacrolimus (FK506) therapy. *Int J Hematol* 2004; **79:** 130–2.

Effects on carbohydrate metabolism. The development of diabetes mellitus after solid organ transplantation is common,[1,2] which may be attributed to the diabetogenic effects of immunosuppressive drugs. Incidence has appeared to be increased in both adult[3] and paediatric[4] renal transplant recipients given tacrolimus. However, a retrospective review[2] found no significant difference in incidence between patients receiving tacrolimus or ciclosporin but found instead a correlation between the absence of an antiproliferative agent and the development of diabetes. A retrospective study of liver transplant recipients found that, although those given tacrolimus had a greater incidence of diabetes mellitus, hepatitis C infection was the only factor predictive of its development.[1] In contrast, a meta-analysis[5] found the incidence of new-onset diabetes mellitus (NODM) to be significantly higher among patients receiving tacrolimus compared with those receiving ciclosporin after solid organ transplantation. An observational study[6] confirmed this finding, and found it to be unrelated to corticosteroid dosage, although relatively high doses of corticosteroids were used across the study. A retrospective study[7] found tacrolimus to be significantly more diabetogenic than ciclosporin, even when corticosteroid dosing was lower with tacrolimus. An analysis of data for 8839 patients[8] found the risk of NODM to be greatest with high tacrolimus doses, but the increased risk versus ciclosporin was sustained even with lower tacrolimus doses. Higher corticosteroid doses potentiated the diabetogenic effect of tacrolimus, but even the lowest dosage group for tacrolimus and corticosteroids had higher rates of NODM than all ciclosporin groups; there was no association between corticosteroid dose and NODM for any dosage of ciclosporin. In a small, retrospective study,[9] conversion from tacrolimus to ciclosporin resulted in marked improvement of glucose metabolism, and even reversal of diabetes mellitus in a significant proportion of patients.

1. AlDosary AA, *et al.* Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver Transpl* 2002; **8:** 356–61.
2. First MR, *et al.* Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. *Transplantation* 2002; **73:** 379–86.
3. Pirsch JD, *et al.* A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; **63:** 977–83.
4. Al-Uzri A, *et al.* Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; **72:** 1020–4.
5. Heisel O, *et al.* New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004; **4:** 583–95.
6. Kamar N, *et al.* Diapason Study Group. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; **22:** 1986–93.
7. Hoitsma AJ, Hilbrands LB. Relative risk of new-onset diabetes during the first year after renal transplantation in patients receiving tacrolimus or cyclosporine immunosuppression. *Clin Transplant* 2006; **20:** 659–64.
8. Burroughs TE, *et al.* Influence of early posttransplantation prednisone and calcineurin inhibitor dosages on the incidence of new-onset diabetes. *Clin J Am Soc Nephrol* 2007; **2:** 517–23.
9. Bouchta NB, *et al.* Conversion from tacrolimus to cyclosporin is associated with a significant improvement of glucose metabolism in patients with new-onset diabetes mellitus after renal transplantation. *Transplant Proc* 2005; **37:** 1857–60.

Effects on the cardiovascular system. Hypertrophic cardiomyopathy, and in some cases heart failure, has been described in paediatric patients receiving tacrolimus after organ grafting (small bowel or liver).[1] Symptoms largely resolved on stopping or reducing dosage. A similar case had been found *post mortem* in an adult,[2] and the UK CSM[3] was aware of 29 reported cases worldwide as of July 1995. Echocardiographic monitoring of patients receiving tacrolimus has been recommended, with dose reduction or withdrawal in those who developed hypertrophic changes.[3] However, echocardiographic abnormalities may be quite common after orthotopic liver transplantation in adults, with no obvious relationship to the use of tacrolimus,[4] and a retrospective analysis concluded that tacrolimus is not a risk factor for hypertrophic cardiomyopathy in adult transplant recipients.[5]

Severe hypertension was documented in 5 out of 10 paediatric patients who received intravenous tacrolimus after renal transplant surgery. All patients responded to intravenous labetalol. By contrast none of 11 children who received ciclosporin at the same institution developed hypertension.[6] However, a review[7] concluded that tacrolimus causes less hypertension than ciclosporin, resulting in a better cardiovascular risk profile in renal transplant recipients, and possibly ultimately prolonging graft survival.

1. Atkison P, *et al.* Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet* 1995; **345:** 894–6.
2. Natazuka T, *et al.* Immunosuppressive drugs and hypertrophic cardiomyopathy. *Lancet* 1995; **345:** 1644.
3. Committee on Safety of Medicines/Medicines Control Agency. Tacrolimus (Prograf) and hypertrophic cardiomyopathy in transplant patients. *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 18/03/08)
4. Dollinger MM, *et al.* Tacrolimus and cardiotoxicity in adult liver transplant recipients. *Lancet* 1995; **346:** 507.
5. Coley KC, *et al.* Lack of tacrolimus-induced cardiomyopathy. *Ann Pharmacother* 2001; **35:** 985–9.
6. Booth CJ, *et al.* Intravenous tacrolimus may induce severe hypertension in renal transplant recipients. *Arch Dis Child* 1999; **80** (suppl 1): A27.
7. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. *Transplantation* 2001; **72** (suppl): S9–12.

Effects on the kidneys. A comparison in patients who had undergone liver transplantation suggested that nephrotoxicity was more of a problem in those receiving tacrolimus than in those given a ciclosporin-based regimen.[1] In particular intravenous tacrolimus during the first week after transplantation was associated with acute renal failure in 4 of 20 patients. Furthermore, on follow-up for 1 year, GFR was somewhat lower in the tacrolimus-treated group. A small study compared GFR and effective renal plasma flow (ERPF), at various stages after transplantation, in renal and liver transplant recipients given tacrolimus.[2] In renal transplant patients, the GFR, although lower than normal, was increased after transplant, and remained stable over 3 months. ERPF, however, was significantly lower at 3 months. In liver transplant recipients, despite being lower than normal, GFR and ERPF were unchanged at 1 year post-transplant.

1. Porayko MK, *et al.* Nephrotoxic effects of primary immunosuppression with FK-506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc* 1994; **69:** 105–11.
2. Agarwala S, *et al.* Evaluation of renal function in transplant patients on tacrolimus therapy. *J Clin Pharmacol* 2002; **42:** 798–805.

Effects on the nervous system. Although many of the symptoms of neurotoxicity induced by tacrolimus are similar to those of ciclosporin (p.1824), some symptoms such as headaches, tremor, and sleep disturbances, appear to be more prevalent with tacrolimus, and the incidence of tacrolimus-induced neurotoxicity appears to be higher in liver transplant recipients.[1]

Severe peripheral neuropathy together with signs of cerebral dysfunction has been reported in 2 patients receiving tacrolimus.[2] Among other central effects, tacrolimus has also been associated with speech disorders, including severe dysarthria and mutism in 1 patient;[3] some degree of speech dysfunction, in the form of an apparent Norwegian accent, appeared to be permanent in this case.

Encephalopathy, sometimes occurring within the reversible posterior leukoencephalopathy syndrome (RPLS), has been reported with use of tacrolimus.[4-8] Presenting symptoms included acute severe headache, seizures, cortical blindness, disorientation, and hypertension.

Miller Fisher syndrome, a variant of Guillain-Barré syndrome, has been attributed to tacrolimus use in a liver transplant recipient.[9] Clinical manifestations included ataxia, ophthalmoplegia, and areflexia.

1. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13:** 313–26.
2. Ayres RCS, *et al.* Peripheral neurotoxicity with tacrolimus. *Lancet* 1994; **343:** 862–3.
3. Boeve BF, *et al.* Dysarthria and apraxia of speech associated with FK-506 (tacrolimus). *Mayo Clin Proc* 1996; **71:** 969–72.
4. Kiemeneij IM, *et al.* Acute headache as a presenting symptom of tacrolimus encephalopathy. *J Neurol Neurosurg Psychiatry* 2003; **74:** 1126–7.
5. Nakazato T, *et al.* Reversible posterior leukoencephalopathy syndrome associated with tacrolimus therapy. *Intern Med* 2003; **42:** 624–5.
6. Frühauf NR, *et al.* Late onset of tacrolimus-related posterior leukoencephalopathy after living donor liver transplantation. *Liver Transpl* 2003; **9:** 983–5.
7. Schuuring J, *et al.* Severe tacrolimus leukoencephalopathy after liver transplantation. *Am J Neuroradiol* 2003; **24:** 2085–8.
8. Lavigne CM, *et al.* Tacrolimus leukoencephalopathy: a neuropathologic confirmation. *Neurology* 2004; **63:** 1132–3.
9. Kaushik P, *et al.* Miller Fisher variant of Guillain-Barré syndrome requiring a cardiac pacemaker in a patient on tacrolimus after liver transplantation. *Ann Pharmacother* 2005; **39:** 1124–7.

Effects on skeletal muscle. Severe acute rhabdomyolysis, leading to fatal acute renal failure, developed in an 18-month-old child given tacrolimus after bone marrow transplantation.[1] Seizures, severe rhabdomyolysis, and acute renal failure were reported in a renal transplant patient taking tacrolimus and a monoclonal antibody.[2]

1. Hibi S, *et al.* Severe rhabdomyolysis associated with tacrolimus. *Lancet* 1995; **346:** 702.
2. Fontana I, *et al.* Severe rhabdomyolysis and acute renal failure in a kidney transplant patient treated with tacrolimus and chimaeric CD25 monoclonal antibody. *Transplant Proc* 2004; **36:** 711–2.

Effects on the skin. Three children developed lentigines (small pigmented macules) while receiving long-term (9 months to 4 years) treatment with topical tacrolimus 0.1% for eczema. The lesions developed primarily in the areas where tacrolimus had been applied. Despite withdrawal of tacrolimus, the lentigines still persisted at review 6 to 18 months later. The authors noted that use of tacrolimus was outside the product's licensed indications, and that the clinical implications of their findings remained uncertain.[1]

1. Hickey JR, *et al.* Does topical tacrolimus induce lentigines in children with atopic dermatitis? A report of three cases. *Br J Dermatol* 2005; **152:** 152–4.

Hepatitis. For the suggestion that dosage requirements of tacrolimus may be reduced in children with hepatitis C see Administration, below.

Infection. For a report of an increased incidence of CMV disease in renal transplant recipients given a regimen combining tacrolimus and mycophenolate mofetil see under Interactions, p.1837.

Overdosage. A report[1] of 12 cases of acute overdose with tacrolimus described overdoses of up to 30 times the prescribed dose. Three patients were asymptomatic, while 7 showed mild transient renal and hepatic impairment, nausea, and mild hand tremors. One patient suffered renal failure, histoplasmosis, and sepsis 48 hours after admission for the overdose. The outcome was unknown in one patient. All 8 symptomatic patients recovered when tacrolimus concentrations returned to normal. No specific treatment regimen has been recommended, but patients have been treated with gastric lavage, oral activated charcoal, and phenytoin. The latter is used both to prevent seizures and to enhance tacrolimus metabolism by stimulation of cytochrome P450. Patients should be closely monitored for known signs and symptoms of tacrolimus toxicity. In a further series of 5 cases,[2] acute ingestion of tacrolimus was reported to be well tolerated, and adequately managed with conservative treatment.

1. Curran CF, *et al.* Acute overdoses of tacrolimus. *Transplantation* 1996; **62:** 1376.
2. Mrvos R, *et al.* Tacrolimus (FK 506) overdose: a report of five cases. *J Toxicol Clin Toxicol* 1997; **35:** 395–9.

Porphyria. Data are limited on the use of tacrolimus in patients with porphyria. There has been a report of a patient with acute intermittent porphyria given tacrolimus for 5 days before renal transplantation, and maintenance tacrolimus post-transplantation, without exacerbation of symptoms.[1]

1. Barone GW, *et al.* The tolerability of newer immunosuppressive medications in a patient with acute intermittent porphyria. *J Clin Pharmacol* 2001; **41:** 113–5.

Pregnancy. Tacrolimus crosses the placenta. Licensed product information states that, although *systemic* tacrolimus has shown abortifacient and teratogenic properties in *animal* studies, limited data in humans show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy compared with other immunosuppressants. However, use of tacrolimus has been associated with neonatal hyperkalaemia, which appears to normalise spontaneously, and neonatal renal dysfunction; the neonate should be monitored for potential adverse effects.

There are no adequate data from the use of *topical* tacrolimus in pregnancy.

Further references.

1. Kainz A, *et al.* Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000; **70:** 1718–21.
2. Jain AB, *et al.* Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; **76:** 827–32.
3. Baumgart DC, *et al.* Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005; **54:** 1822–3.

Interactions

Increased nephrotoxicity may result if tacrolimus is given with other potentially nephrotoxic drugs: use with ciclosporin should be avoided for this reason. Similarly, concurrent use with neurotoxic drugs should be avoided. High potassium intake or potassium-sparing diuretics should also be avoided in patients receiving tacrolimus.

Tacrolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme system, such as azole antifungals, bromocriptine, calcium-channel blockers, cimetidine, some corticosteroids, ciclosporin, danazol, HIV-protease inhibitors, the NNRTI delavirdine, macrolide antibacterials, and metoclopramide, may produce increased blood concentrations of tacrolimus. The metabolism of tacrolimus may also be inhibited by grapefruit juice and they should not be taken together. Equally, inducers of this enzyme system (such as carbamazepine, nevirapine, phenobarbital, phenytoin, rifampicin, and St John's wort) may reduce blood concentrations of tacrolimus. Sirolimus can also decrease blood concentrations of tacrolimus. For a warning concerning the use of live vaccines in patients receiving immunosuppressants see Adverse Effects and Precautions, above.

Facial flushing or skin irritation may occur if alcohol is consumed by patients using topical tacrolimus.

◊ The cytochrome P450 isoenzyme subfamily CYP3A, and P-glycoprotein, are involved in the pharmacokinetic pathways of tacrolimus.[1] Drugs known to interact with these systems will probably affect tacrolimus concentrations, primarily by influencing oral bioavailability rather than clearance.[2] A study[3] *in vitro* found that metabolism of tacrolimus by CYP3A in human liver microsomes was inhibited by bromocriptine, corticosterone, dexamethasone, ergotamine, erythromycin, ethinylestradiol, josamycin, ketoconazole, miconazole, midazolam, nifedipine, omeprazole, tamoxifen, troleandomycin, and verapamil. No effect on tacrolimus metabolism was seen with aspirin, amphotericin B, captopril, cefotaxime, ciprofloxacin, diclofenac, diltiazem, doxycycline, furosemide, glibenclamide, imipramine, lidocaine, paracetamol, prednisolone, progesterone, ranitidine, sulfamethoxazole, trimethoprim, or vancomycin.

1. van Gelder T. Drug interactions with tacrolimus. *Drug Safety* 2002; **25:** 707–12.
2. Christians U, *et al.* Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet* 2002; **41:** 813–51.
3. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.

Antibacterials. Increased concentrations of tacrolimus in plasma have been reported with *erythromycin*;[1] the interaction was accompanied by some evidence of nephrotoxicity. A similar interaction has been reported between tacrolimus and *clarithromycin*.[2,3] For reference to the effects of macrolides on tacrolimus metabolism *in vitro* see above.

Treatment with *rifampicin* has been found to substantially decrease tacrolimus concentrations.[4,5] A pharmacokinetic study found that rifampicin induces metabolism of tacrolimus in both the liver and intestine, probably by induction of the cytochrome P450 isoenzyme subfamily CYP3A and P-glycoprotein.[6] Both *metronidazole*[7,8] and *chloramphenicol*[9,10] increased the blood concentrations of tacrolimus. This is probably due to inhibition of metabolism, and dosage reduction of the immunosuppressant may be necessary when either drug is given with tacrolimus. A pharmacokinetic study[11] found that *levofloxacin* partially inhibited the metabolism of tacrolimus, and recommended that drug concentrations be monitored when these 2 drugs are used together.

Plasma concentrations of tacrolimus are also increased by *quinupristin/dalfopristin*.

1. Jensen C, *et al.* Interaction between tacrolimus and erythromycin. *Lancet* 1994; **344:** 825.
2. Wolter K, *et al.* Interaction between FK 506 and clarithromycin in a renal transplant patient. *Eur J Clin Pharmacol* 1994; **47:** 207–8.
3. Ibrahim RB, *et al.* Tacrolimus-clarithromycin interaction in a patient receiving bone marrow transplantation. *Ann Pharmacother* 2002; **36:** 1971–2.
4. Furlan V, *et al.* Interactions between FK506 and rifampicin or erythromycin in pediatric liver recipients. *Transplantation* 1995; **59:** 1217–18.
5. Chenhsu R-Y, *et al.* Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother* 2000; **34:** 27–31.
6. Hebert MF, *et al.* Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 1999; **39:** 91–6.
7. Herzig K, Johnson DW. Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy. *Nephrol Dial Transplant* 1999; **14:** 521–3.
8. Page RL, *et al.* Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother* 2005; **39:** 1109–13.
9. Schulman SL, *et al.* Interaction between tacrolimus and chloramphenicol in a renal transplant recipient. *Transplantation* 1998; **65:** 1397–8.
10. Mathis AS, *et al.* Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* 2002; **4:** 169–74.
11. Federico S, *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45:** 169–75.

Antidepressants. Tacrolimus trough concentrations reduced sharply in a patient who took *St John's wort*, and returned to previous levels on stopping the St John's wort.[1] St John's wort induces cytochrome P450 isoenzyme CYP3A4, enhancing the metabolism of tacrolimus. A pharmacokinetic study[2] confirmed this, finding an increase in tacrolimus clearance; the authors concluded that potential consequences of this interaction in transplant recipients are rejection and graft loss.

1. Bolley R, *et al.* Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 2002; **73:** 1009.
2. Hebert MF, *et al.* Effects of St. John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 89–94.

Antiepileptics. For the effect of tacrolimus on *phenytoin*, see Immunosuppressants in Phenytoin, p.500.

Antifungals. Elevated plasma-tacrolimus concentrations have been reported in patients given *clotrimazole*,[1] *fluconazole*,[2] or *voriconazole*[3]; a reduction in the dose of tacrolimus was likely to be necessary if it were given with an azole antifungal. A study involving tacrolimus and *ketoconazole* suggested that an increase in the oral bioavailability of tacrolimus from a mean of 14 to 30% when given with the azole was probably due to decreased cytochrome P450 isoenzyme CYP3A4 metabolism in the gut wall, or improved absorption due to inhibition of P-glycoprotein mediated efflux, rather than an effect on hepatic metabolism.[4] Similarly, a 50% reduction in tacrolimus dosage was found to be necessary when the drug was given with *itraconazole*.[5] It has been suggested that the interaction could be exploited to reduce the cost of immunosuppressant regimens.[6] In another study of itraconazole with tacrolimus,[7] 1 patient required a 20% increase in the dose of tacrolimus, 3 patients required no dose adjustment, and 5 patients required tacrolimus dose reductions, ranging from 20 to 76.5%. The authors concluded that the magnitude of the dose reduction is dependent on the initial tacrolimus serum concentration and the final target concentration.

1. Mieles L, *et al.* Interaction between FK506 and clotrimazole in a liver transplant recipient. *Transplantation* 1991; **52:** 1086–7.
2. Mañez R, *et al.* Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; **57:** 1521–3.
3. Venkataramanan R, *et al.* Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob Agents Chemother* 2002; **46:** 3091–3.
4. Floren LC, *et al.* Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. *Clin Pharmacol Ther* 1997; **62:** 41–9.
5. Capone D, *et al.* Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. *Ann Pharmacother* 1999; **33:** 1124–5.
6. Kramer MR, *et al.* Dose adjustment and cost of itraconazole prophylaxis in lung transplant recipients receiving cyclosporine and tacrolimus (FK506). *Transplant Proc* 1997; **29:** 2657–9.
7. Leather H, *et al.* Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12:** 325–34.

Antivirals. Ten- to fiftyfold reductions in tacrolimus dosage were necessary to maintain therapeutic tacrolimus trough concentrations, in 6 HIV-positive liver transplant recipients receiving tacrolimus-based immunosuppressive therapy, when antiretroviral therapy including an HIV-protease inhibitor was started postoperatively.[1] This effect was more pronounced with *nelfinavir* than *indinavir.* In contrast, 4 HIV-positive kidney transplant recipients received antiretroviral therapy without protease inhibitors, and required only conventional doses of tacrolimus. The authors caution that some protease inhibitors can act as both inducers and inhibitors of the cytochrome P450 isoenzyme CYP3A4. While the inhibitory effect appears to predominate when given with tacrolimus, if the protease inhibitor is withdrawn suddenly the CYP3A4 system may remain induced, and a sudden decrease in tacrolimus concentration may occur; this had occurred in one case. For this reason, they concluded that great caution and frequent tacrolimus monitoring are necessary when protease inhibitors are introduced or withdrawn in transplant recipients receiving tacrolimus.

Dramatic increases in tacrolimus blood concentrations have been reported after addition of *lopinavir/ritonavir* in HIV-positive liver transplant recipients.[2-4] Some patients did not need further tacrolimus for up to 3 weeks, even with normal hepatic function; with hepatic dysfunction, 1 mg of tacrolimus provided a therapeutic concentration for up to 5 weeks, and in one patient the tacrolimus concentration increased for the next few days with the introduction of lopinavir/ritonavir without any additional dose of tacrolimus. The authors recommended a pre-emptive decrease in tacrolimus dose by at least 50% one day before starting therapy with lopinavir/ritonavir, and withholding tacrolimus for the next few days; therapy should then be guided by therapeutic drug monitoring of tacrolimus blood concentrations.[3] The usual dose of tacrolimus while a patient is on lopinavir/ritonavir is expected to be about 0.5 to 1 mg weekly.[2,3] In contrast, *efavirenz* did not appreciably affect tacrolimus pharmacokinetics.[4]

1. Jain AKB, *et al.* The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* 2002; **8:** 841–5.
2. Schonder KS, *et al.* Tacrolimus and lopinavir/ritonavir interaction in liver transplantation. *Ann Pharmacother* 2003; **37:** 1793–6.
3. Jain AB, *et al.* Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003; **9:** 954–60.
4. Teicher E, *et al.* Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV co-infected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet* 2007; **46:** 941–52.

Calcium-channel blockers. Dosage requirements for tacrolimus were substantially reduced in 22 liver graft recipients who also received *nifedipine*, compared with 28 patients given tacrolimus alone, in a 1-year retrospective study.[1]

Tacrolimus toxicity has been reported in a liver transplant patient shortly after starting *diltiazem*.[2]

1. Seifeldin RA, *et al.* Nifedipine interaction with tacrolimus in liver transplant recipients. *Ann Pharmacother* 1997; **31:** 571–5.
2. Hebert MF, Lam AY. Diltiazem increases tacrolimus concentrations. *Ann Pharmacother* 1999; **33:** 680–2.

Danazol. Nephrotoxicity and tremors associated with elevated concentrations of tacrolimus developed in a patient given danazol with the immunosuppressant.[1] The effect might have been due to inhibition of the metabolism of tacrolimus.

1. Shapiro R, *et al.* FK 506 interaction with danazol. *Lancet* 1993; **341:** 1344–5.

Deoxyschizandrin. Mean blood concentrations of tacrolimus in 12 healthy subjects rose from 22.2 to 66.4 nanograms/mL after they had received 13 days of treatment with SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin.[1] During the study the area under the concentration-time curve (AUC) of tacrolimus also rose by 164.2% while oral clearance fell by 49%. It was suggested that constituents of *Schisandra sphenanthera* may act as inhibitors of the cytochrome P450 isoenzyme CYP3A4 and/or P-glycoprotein.

1. Xin H-W, *et al.* Effects of *Schisandra sphenanthera* extract on the pharmacokinetics of tacrolimus in healthy volunteers. *Br J Clin Pharmacol* 2007; **64:** 469–75.

Gastrointestinal drugs. In 2 renal transplant recipients, tacrolimus trough concentrations increased markedly after introduction of *lansoprazole* and returned to normal after it was stopped.[1,2] One of the patients was later given *rabeprazole* with no effect on tacrolimus concentration.[2] The same effects were apparent in a study of healthy subjects,[3] with lansoprazole increasing the concentration and decreasing the clearance of tacrolimus, but the degree of interaction was found to depend, at least partly, upon the genetic status of the patients. The authors supposed that certain ethnic groups might be at higher risk for this interaction. In contrast, rabeprazole appears less affected by genotypic status, and had minimal effect on tacrolimus pharmacokinetics; the authors considered it a safer proton pump inhibitor than lansoprazole for those with cytochrome P450 isoenzyme CYP2C19 gene mutation who were receiving tacrolimus. An *in-vitro* study suggested that omeprazole inhibited the metabolism of tacrolimus.[4] Despite a study reporting no clinically relevant interaction between omeprazole and tacrolimus in renal transplant recipients,[5] increased tacrolimus concentrations were reported when a paediatric liver transplant patient was started on omeprazole.[6]

1. Takahashi K, *et al.* Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* 2004; **38:** 791–4.
2. Homma M, *et al.* Effects of lansoprazole and rabeprazole on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. *Transplantation* 2002; **73:** 303–4.
3. Itagaki F, *et al.* Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. *J Pharm Pharmacol* 2004; **56:** 1055–9.
4. Christians U, *et al.* Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. *Br J Clin Pharmacol* 1996; **41:** 187–90.
5. Pascual J, *et al.* Interaction between omeprazole and tacrolimus in renal allograft recipients: a clinical-analytical study. *Transplant Proc* 2005; **37:** 3752–3.
6. Moreau C, *et al.* Interaction between tacrolimus and omeprazole in a pediatric liver transplant recipient. *Transplantation* 2006; **81:** 487–8.

Immunosuppressants. *Sirolimus* may decrease blood concentrations of tacrolimus; in stable renal transplant recipients given both drugs, mean exposure and trough concentrations of tacrolimus decreased by about 30% relative to tacrolimus alone. Tacrolimus may inhibit *ciclosporin* metabolism *in vitro*, with the possibility of increased nephrotoxicity (see under Ciclosporin, p.1828). Tacrolimus may also increase concentrations of mycophenolic acid, a metabolite of *mycophenolate mofetil* (see under Mycophenolate Mofetil, p.1837), and the risk of infection may be increased if used together.

Pharmacokinetics

Absorption of tacrolimus after oral doses is reported to be erratic. Oral bioavailability varies very widely; the mean value is in the range of 20 to 25%. The rate and extent of absorption of tacrolimus is decreased by the presence of food, with the effect most pronounced after a high-fat meal. There is little or no systemic exposure to tacrolimus after topical use (but see Absorption, below). After intravenous doses it is widely distributed to the tissues; it is extensively bound to erythrocytes in the blood, and variations in red cell binding account for much of the variability in pharmacokinetics. The portion in plasma is about 99% bound to plasma proteins. Tacrolimus is extensively metabolised in the liver, principally by cytochrome P450 isoenzyme CYP3A4, and excreted, primarily in bile, almost entirely as metabolites. Considerable metabolism also occurs in the intestinal wall. Whole-blood elimination half-life has been reported to average 43 hours in healthy subjects, and to range from about 12 to 16 hours in transplant patients.

◊ References.

1. Gruber SA, *et al.* Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. *J Clin Pharmacol* 1994; **34:** 859–64.
2. Jusko WJ, *et al.* Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther* 1995; **57:** 281–90.
3. Venkataramanan R, *et al.* Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995; **29:** 404–30.
4. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. *Clin Pharmacokinet* 2001; **40:** 283–95.
5. Bekersky I, *et al.* Comparative tacrolimus pharmacokinetics: normal versus mildly hepatically impaired subjects. *J Clin Pharmacol* 2001; **41:** 628–35.
6. Reding R, *et al.* Efficacy and pharmacokinetics of tacrolimus oral suspension in pediatric liver transplant recipients. *Pediatr Transplant* 2002; **6:** 124–6.
7. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; **43:** 623–53.
8. Kuypers DRJ, *et al.* Time-related clinical determinants of long-term tacrolimus pharmacokinetics in combination therapy with mycophenolic acid and corticosteroids: a prospective study in one hundred de novo renal transplant recipients. *Clin Pharmacokinet* 2004; **43:** 741–62.
9. Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. *Drug Metab Pharmacokinet* 2007; **22:** 328–35.
10. Antignac M, *et al.* Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients. *Br J Clin Pharmacol* 2007; **64:** 750–7.

Absorption. A single topical application of a 0.1% tacrolimus ointment to an infant for the treatment of chronic dermatitis, resulted in high serum-tacrolimus concentrations (24 nanograms/mL). Tacrolimus levels decreased over 7 days, after which another smaller, single application of 0.03% tacrolimus ointment again resulted in high serum concentrations. The authors cautioned against its use in young children and diseases with decreased skin barrier function.[1] In another report,[2] elevated blood tacrolimus concentrations were seen after application of 0.1% tacrolimus ointment to a large area of the body of a patient with erythroderma; again, caution in conditions where the skin barrier is disrupted was advised.

1. Kameda G, *et al.* Unexpected high serum levels of tacrolimus after a single topical application in an infant. *J Pediatr* 2003; **143:** 280. Correction. *ibid.*; 462.
2. Teshima D, *et al.* Increased topical tacrolimus absorption in generalized leukemic erythroderma. *Ann Pharmacother* 2003; **37:** 1444–7.

Bioavailability. Bioavailability of tacrolimus appears to be influenced by the type and timing of meals. Food, particularly high-fat meals, significantly reduced bioavailability, compared with the fasting state.[1] Ingestion of tacrolimus up to 1.5 hours after a meal also considerably reduced absorption.[2] UK licensed product information states that tacrolimus should be taken on an empty stomach, or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. Gastrointestinal metabolism of tacrolimus is thought to be extensive, significantly affecting its bioavailability,[3] and differences in this metabolism may account for apparent differences in availability according to ethnic origin.[4]

1. Bekersky I, *et al.* Effect of low- and high-fat meals on tacrolimus absorption following 5 mg single oral doses to healthy human subjects. *J Clin Pharmacol* 2001; **41:** 176–82.
2. Bekersky I, *et al.* Effect of time of meal consumption on bioavailability of a single oral 5 mg tacrolimus dose. *J Clin Pharmacol* 2001; **41:** 289–97.
3. Tuteja S, *et al.* The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients. *Transplantation* 2001; **71:** 1301–7.
4. Mancinelli LM, *et al.* The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. *Clin Pharmacol Ther* 2001; **69:** 24–31.

Genetic factors. Renal transplant recipients homozygous for CYP3A5*3 required lower doses to reach target trough concentrations of tacrolimus compared with CYP3A5*1 allele carriers;[1] the latter group can be expected to have a tacrolimus clearance 25 to 45% greater than that of homozygotes.[2] Determination of the cytochrome P450 isoenzyme genotype before transplantation may identify patients at risk for underimmunosuppression or toxicity.

1. Hesselink DA, *et al.* Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74:** 245–54.
2. Utecht KN, *et al.* Effects of genetic polymorphisms on the pharmacokinetics of calcineurin inhibitors. *Am J Health-Syst Pharm* 2006; **63:** 2340–8.

Therapeutic drug monitoring. There is a good correlation between tacrolimus trough concentrations and systemic exposure, and analysis at other time points is not considered to offer any advantage.[1] However, since tacrolimus concentrations appear to be generally higher in the morning than the evening, some have suggested that the morning might be the best time for therapeutic drug monitoring.[2]

Microparticle enzyme immunoassay (MEIA) and enzyme-linked immunosorbent assay (ELISA) have both been used to measure tacrolimus whole blood concentrations. A study[3] of liver transplant recipients found that increasing trough tacrolimus concentrations, as measured by the ELISA, correlated with decreasing risk of acute rejection, but increasing risk of nephrotoxicity. The authors suggested a trough blood concentration of less than 15 nanograms/mL to minimise nephrotoxicity. While several studies have shown that adverse effects are more closely correlated with tacrolimus concentrations than with dose, the correlation between concentrations and allograft rejection has not been established. There is some suggestion that measuring the unbound concentration of tacrolimus may be a better correlate for rejection than whole blood concentrations.[4]

Licensed product information states that blood trough concentrations of tacrolimus should be monitored during the post-transplantation period; blood should be drawn about 12 hours after dosing, just before the next dose. Samples which are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they may be frozen at –20° for up to 12 months. The frequency of monitoring is based on clinical need; about twice-weekly during the early post-transplant period is recommended, followed by periodic monitoring during maintenance therapy. Trough concentrations should also be monitored after dose adjustment, although it may take several days before changes become apparent. Monitoring is also recommended after changes in the immunosuppressive regimen, or when other drugs are given which may alter tacrolimus blood concentrations. The majority of patients can be successfully managed if blood concentrations are maintained below 20 nanograms/mL. In practice, in the early post-transplant period, whole blood trough concentrations have generally been in the range of 5 to 20 nanograms/mL in liver transplant recipients, and 10 to 20 nanograms/mL in kidney and heart transplant recipients. During maintenance therapy, blood concentrations have generally been between 5 to 15 nanograms/mL in liver, kidney, and heart transplant patients.

Bayesian forecasting has also been used.[5]

UK licensed product information states that the relationship between tacrolimus trough concentrations and systemic exposure is similar for the standard formulation (*Prograf, Astellas*) and the prolonged-release formulation (*Advagraf, Astellas*).

1. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. *Ther Drug Monit* 2006; **28:** 720–5.
2. Baraldo M, Furlanut M. Chronopharmacokinetics of ciclosporin and tacrolimus. *Clin Pharmacokinet* 2006; **45:** 775–88.
3. Venkataramanan R, *et al.* Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. *J Clin Pharmacol* 2001; **41:** 542–51.
4. Zahir H, *et al.* Factors affecting variability in distribution of tacrolimus in liver transplant recipients. *Br J Clin Pharmacol* 2004; **57:** 298–309.
5. Fukudo M, *et al.* Forecasting of blood tacrolimus concentrations based on the Bayesian method in adult patients receiving living-donor liver transplantation. *Clin Pharmacokinet* 2003; **42:** 1161–78.

Uses and Administration

Tacrolimus is a potent macrolide (macrolactam) immunosuppressant derived from *Streptomyces tsukubaensis*, and has actions similar to those of ciclosporin (see p.1830). Tacrolimus binds to an intracellular protein, FKBP-12, and then forms a complex with calcium, calmodulin, and calcineurin, which inhibits the activity of calcineurin. This interferes with the production of lymphokines such as interleukin-2 and inhibits T-lymphocyte activation, resulting in immunosuppression.

Tacrolimus is used to prevent or manage rejection in patients receiving organ transplants, as indicated by the cross-references given in Organ and Tissue Transplantation, below. Tacrolimus has been tried in a few patients with refractory auto-immune or immune-mediated disorders; in some countries it is licensed for use in myasthenia gravis, in rheumatoid arthritis that is unresponsive to conventional therapy, and in lupus nephritis where corticosteroids are ineffective or contra-indicated. Tacrolimus is also applied topically in the management of moderate to severe atopic eczema. Tacrolimus-releasing stents have been developed to reduce restenosis after coronary artery stent placement.

UK licensed product information recommends that oral tacrolimus should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximum absorption.

For **transplantation**, in adult patients in the UK, the initial ***oral*** daily doses, to be given in 2 divided doses, are:

- *liver* transplantation: 100 to 200 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 200 to 300 micrograms/kg, starting within 24 hours of completion of surgery
- *heart* transplantation: 75 micrograms/kg, after antibody induction, and within 5 days of completion of surgery, and when the patient is stable

  Alternatively, tacrolimus has been given orally within 12 hours of transplantation, in patients without other organ dysfunction, at an initial oral dose of 2 to 4 mg daily, with mycophenolate mofetil and corticosteroids, or with sirolimus and corticosteroids

If the patient's condition does not permit oral use, therapy may be started ***intravenously***, by continuous 24-hour infusion; suggested initial adult daily doses are:

- *liver* transplantation: 10 to 50 micrograms/kg
- *kidney* transplantation: 50 to 100 micrograms/kg
- *heart* transplantation: 10 to 20 micrograms/kg

For rejection therapy, increased tacrolimus doses, supplemental corticosteroid therapy, and short courses of monoclonal or polyclonal antibodies have been used. For conversion to tacrolimus from another immunosuppressant, in liver and kidney transplant recipients treatment should begin with the initial oral dose recommended for primary immunosuppression. For heart transplant patients converted to tacrolimus, an initial oral dose of 150 micrograms/kg daily, in 2 divided doses, is recommended. UK dose recommendations for rejection therapy in other allografts are based on limited data. The following initial ***oral*** daily doses of tacrolimus have been used:

- *lung* transplantation: 100 to 150 micrograms/kg
- *pancreatic* transplantation: 200 micrograms/kg
- *intestinal* transplantation: 300 micrograms/kg

In the USA, the following initial ***oral*** daily doses, given in 2 divided doses, are recommended for adult patients:

- *liver* transplantation: 100 to 150 micrograms/kg, starting about 6 hours after transplantation
- *kidney* transplantation: 200 micrograms/kg, starting within 24 hours of transplantation, but delayed if necessary until renal function has recovered
- *heart* transplantation: 75 micrograms/kg, starting no sooner than 6 hours after transplantation

For most transplant patients, initial oral therapy is recommended. If ***intravenous*** tacrolimus therapy is needed, the recommended starting daily doses, to be given as a continuous infusion, are:

- *liver* transplantation: 30 to 50 micrograms/kg
- *kidney* transplantation: 30 to 50 micrograms/kg
- *heart* transplantation: 10 micrograms/kg

Tacrolimus doses are usually reduced in the post-transplant period; in some cases other immunosuppressant therapy can be stopped, leading to tacrolimus monotherapy or tacrolimus-based dual therapy. Maintenance dosage should be adjusted according to whole-blood trough concentrations in individual patients: it is suggested that most patients can be satisfactorily maintained at whole-blood concentrations below 20 nanograms/mL. (see Therapeutic Drug Monitoring, above)

Prolonged-release capsules of tacrolimus are also available in some countries for the prevention of rejection in adult liver or kidney transplantation, and the treatment of allograft rejection. Patients maintained on the twice-daily standard formulation are converted to once daily prolonged-release capsules at the same total daily dose; the prolonged-release formulation should be given in the morning, and tacrolimus trough concentrations should be monitored to maintain similar systemic exposure.

For doses used in paediatric transplant recipients, see Administration in Children, below.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, tacrolimus may be applied twice daily as a 0.03 or 0.1% ointment; an attempt should be made to use the lower strength or reduce the frequency of application when possible. Either strength may be used in adults; for treatment in children, see Administration in Children, below. Treatment should be continued only until resolution of signs and symptoms. UK licensed product information recommends that if no signs of improvement are seen after 2 weeks of treatment, further treatment options should be considered; in the USA, if clinical manifestations do not improve within 6 weeks, diagnosis of atopic eczema should be confirmed through re-examination.

◊ Reviews.

1. Winkler M, Christians U. A risk-benefit assessment of tacrolimus in transplantation. *Drug Safety* 1995; **12:** 348–57.
2. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. *Drugs* 2000; **59:** 323–89.
3. Skaehill PA. Tacrolimus in dermatologic disorders. *Ann Pharmacother* 2001; **35:** 582–8.
4. Woo DK, James WD. Topical tacrolimus: a review of its uses in dermatology. *Dermatitis* 2005; **16:** 6–21.
5. Simpson D, Noble S. Tacrolimus ointment: a review of its use in atopic dermatitis and its clinical potential in other inflammatory skin conditions. *Drugs* 2005; **65:** 827–58.
6. First MR, Fitzsimmons WE. Modified release tacrolimus. *Yonsei Med J* 2004; **45:** 1127–31.
7. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
8. Chisholm MA, Middleton MD. Modified-release tacrolimus. *Ann Pharmacother* 2006; **40:** 270–5.
9. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. *Drugs* 2007; **67:** 1931–43.
10. First MR. First clinical experience with the new once-daily formulation of tacrolimus. *Ther Drug Monit* 2008; **30:** 159–66.

Administration. The mean dose of tacrolimus required to produce a standard trough concentration of 10 to 15 nanograms/mL was reported to be 96% higher in 7 black renal graft recipients than in 20 such patients of white or Asian descent.[1] (For mention of the effect of ethnicity on the bioavailability of tacrolimus see under Pharmacokinetics, above.)

Children generally require relatively higher doses than adults to achieve the same blood concentrations (see Administration in Children, below). There is limited evidence that children with hepatitis C required on average one-third of the dose of tacrolimus needed by children without the virus.[2]

1. Andrews PA, *et al.* Racial variation in dosage requirements of tacrolimus. *Lancet* 1996; **348:** 1446.
2. Moreno M, *et al.* Monitoring of tacrolimus as rescue therapy in pediatric liver transplantation. *Ther Drug Monit* 1998; **20:** 376–9.

Administration in children. For **transplantation** in paediatric patients in the UK, tacrolimus is given in the following initial **oral** daily doses, in 2 divided doses:

- *liver* transplantation: 300 micrograms/kg, starting about 12 hours after completion of surgery
- *kidney* transplantation: 300 micrograms/kg, starting within 24 hours of completion of surgery; a lower dose of 200 micrograms/kg has been used in adolescents to prevent very high trough concentrations
- *heart* transplantation, *after antibody induction*: 100 to 300 micrograms/kg

If the patient's condition does not allow for oral use, therapy may be started ***intravenously***, by continuous 24-hour infusion; intravenous therapy may be given for up to 7 days, but should be converted to oral therapy as soon as clinically possible. Suggested daily doses are:

- *liver* transplantation: 50 micrograms/kg
- *kidney* transplantation: 75 to 100 micrograms/kg

For *heart* transplantation *without antibody induction*, patients may be started on intravenous doses of 30 to 50 micrograms/kg daily, as a continuous 24-hour infusion. The first oral dose should be started 8 to 12 hours after stopping intravenous infusion, at a dose of 300 micrograms/kg daily, given in 2 divided doses.

For rejection therapy after *liver* and *kidney* transplantation, treatment is as for adults (see Uses and Administration, above). For paediatric *heart* transplant patients converted to tacrolimus, an initial oral dose of 200 to 300 micrograms/kg daily, in 2 divided doses, is recommended.

In the USA, the following ***oral*** daily doses, given in 2 divided doses, are recommended for children:

- *liver* transplantation: 150 to 200 micrograms/kg, starting about 6 hours after transplantation

Intravenous doses are as for adults (see Uses and Administration, above).

Doses are adjusted according to whole-blood trough concentrations (see Therapeutic Drug Monitoring, above); children generally require doses per kg 1⁄ to 2 times higher than adults to achieve the same concentrations.

For the treatment of **atopic eczema**, where conventional therapies are ineffective or unsuitable, the following treatment schedules have been recommended in children:

- 2 to 16 years: apply 0.03% ointment thinly twice daily, for up to 3 weeks, then reduce to once daily until lesion clears. The 0.1% ointment is not licensed for use in children under 16, although it has been used (see Eczema, below).

  For reference to the development of lentigines in children given long-term treatment with the higher strength preparation see Effects on the Skin under Adverse Effects, above
- 16 years and older: as for adults (see Uses and Administration, above)

Treatment duration is as for adults (see Uses and Administration, above).

Eczema. Topical tacrolimus has been found to be safe and effective[1-3] for short-term use in the treatment of moderate to severe atopic eczema (p.1579). In adult patients, the efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment in one study[4] and more effective than a combination of 0.1% hydrocortisone butyrate ointment (applied to the trunk and extremities) and 1% hydrocortisone acetate ointment (applied to the head and neck) in another study.[5] In paediatric patients 2 to 15 years of age,[6,7] both 0.03 and 0.1% tacrolimus were significantly more effective than 1% hydrocortisone acetate ointment. In 18 of 19 patients with facial atopic eczema resistant to 0.03% tacrolimus ointment,[8] there was significant improvement upon application of a 0.03% lotion formulation, and 6 patients were positive to a patch test for white petrolatum, an ingredient of the commercial ointment. A meta-analysis concluded that topical tacrolimus 0.1% was as effective as potent topical corticosteroids and more effective than mild topical corticosteroids for the treatment of eczema; however, tacrolimus was significantly more likely to cause skin burning than corticosteroids.[9]

Results from a small, open-label study suggest that long-term intermittent use of tacrolimus ointment may reverse the skin atrophy induced by topical corticosteroids.[10] In another study,[11] adult and paediatric patients (2 to 15 years of age) with atopic eczema were treated continuously or intermittently with tacrolimus 0.1% ointment for up to 4 years; almost 60% of patients were evaluated for at least 2 years and about 38% for at least 3 years. The majority of patients received tacrolimus monotherapy, although some used topical corticosteroids at some point. There was no indication of an increased risk of adverse effects with the long-term use of tacrolimus, nor was there an indication of an increased risk for any cutaneous infection with increased duration of exposure to tacrolimus. In general, however, long-term use of topical tacrolimus should be avoided because of concerns about potential carcinogenicity (see under Adverse Effects, above).

1. Gianni LM, Sulli MM. Topical tacrolimus in the treatment of atopic dermatitis. *Ann Pharmacother* 2001; **35:** 943–6.
2. Allen BR. Tacrolimus ointment: its place in the therapy of atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 401–3.
3. Anonymous. Topical tacrolimus—a role in atopic dermatitis? *Drug Ther Bull* 2002; **40:** 73–5.
4. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 547–55.
5. Reitamo S, *et al.* A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2005; **152:** 1282–9.
6. Reitamo S, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109:** 539–46.
7. Reitamo S, *et al.* 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. *Br J Dermatol* 2004; **150:** 554–62.
8. Sugiura H, *et al.* An open study of a lotion formulation to improve tolerance of tacrolimus in facial atopic dermatitis. *Br J Dermatol* 2001; **145:** 795–8.
9. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330:** 516–22.
10. Kyllönen H, *et al.* Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol* 2004; **150:** 1174–81.
11. Hanifin JM, *et al.* US Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005; **53** (suppl 2): S186–S194.

Encephalitis. Compared with historical untreated controls, 7 patients with Rasmussen encephalitis (a progressive neurological disorder thought to have an auto-immune origin) had a superior outcome in terms of neurological function and progression rate of cerebral hemiatrophy after treatment with tacrolimus, but no better seizure outcome.[1] The control patients had more severe disease, but since only 1 patient on tacrolimus showed a cognitive decline, and none became eligible for hemispherectomy, the authors concluded prospective studies would be useful.

1. Bien CG, *et al.* An open study of tacrolimus therapy in Rasmussen encephalitis. *Neurology* 2004; **62:** 2106–9.

Glomerular kidney disease. Tacrolimus has been reported[1-5] to be effective in inducing remission in patients with glomerular kidney disease (p.1504); it has been used as monotherapy from first presentation, as well as in patients refractory to standard therapy, and in those with corticosteroid-dependent disease. However, a small, longitudinal study[6] in children with severe corticosteroid-dependent nephrotic syndrome given tacrolimus after inadequate response to ciclosporin, reported no better management of disease with tacrolimus, although it was beneficial for some children.

1. Segarra A, *et al.* Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; **17:** 655–62.
2. Duncan N, *et al.* Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. *Nephrol Dial Transplant* 2004; **19:** 3062–7.
3. Westhoff TH, *et al.* Tacrolimus in steroid-resistant and steroid-dependent nephrotic syndrome. *Clin Nephrol* 2006; **65:** 393–400.
4. Bhimma R, *et al.* Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. *Am J Nephrol* 2006; **26:** 544–51.
5. Praga M, *et al.* Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney Int* 2007; **71:** 924–30.
6. Sinha MD, *et al.* Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. *Nephrol Dial Transplant* 2006; **21:** 1848–54.

Hepatitis. In auto-immune chronic active hepatitis (p.1501), some evidence suggests that tacrolimus may offer an alternative therapy when corticosteroids alone or with azathioprine do not suffice.

Ichthyosis. For mention of the use of tacrolimus in ichthyosis see p.1580.

Inflammatory bowel disease. There are reports of response to tacrolimus in patients with inflammatory bowel disease (IBD; p.1697). Tacrolimus has been given orally,[1-4] intravenously,[1] or topically,[5,6] in the treatment of ulcerative colitis[1,3,4] and Crohn's disease,[1-3,5,6] refractory to standard therapy. A systematic review[7] of 23 reports of tacrolimus use in 286 patients concluded that oral tacrolimus was a reasonable and effective alternative for fistulising Crohn's disease, although the evidence base was poor and comparative studies with infliximab were needed. Tacrolimus was also a possible alternative in IBD cases unresponsive to corticosteroids. Intravenous use was not deemed to confer any advantage over oral dosage; topical tacrolimus might be an option in certain cases.

1. Fellermann K, *et al.* Tacrolimus: a new immunosuppressant for steroid refractory inflammatory bowel disease. *Transplant Proc* 2001; **33:** 2247–8.
2. Ierardi E, *et al.* Oral tacrolimus long-term therapy in patients with Crohn's disease and steroid resistance. *Aliment Pharmacol Ther* 2001; **15:** 371–7.
3. Bousvaros A, *et al.* Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000; **137:** 794–9.

4. Ogata H, *et al.* A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55:** 1255–62. Correction. *ibid.*; 1684. [dosage error in abstract]
5. Casson DH, *et al.* Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47:** 436–40.
6. Hart AL, *et al.* Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007; **13:** 245–53.
7. Gonzalez-Lama Y, *et al.* The role of tacrolimus in inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2006; **51:** 1833–40.

Myasthenia gravis. Tacrolimus has been reported to be effective in the management of myasthenia gravis (p.629) in patients resistant to conventional therapy, or for whom standard therapy is contra-indicated.[1,2] In an open-label study, 79 patients with myasthenia gravis, who had undergone thymectomy and were on high doses of prednisone and ciclosporin, were switched from ciclosporin to tacrolimus. Initial doses of tacrolimus were 0.1 mg/kg daily, given in 2 divided doses. Dosage was subsequently adjusted to achieve plasma concentrations between 7 and 8 nanograms/mL; tacrolimus doses of 6 to 10 mg daily were needed. After 1 year doses were reduced to achieve concentrations of about 6 nanograms/mL. Doses of prednisone were reduced, and finally withdrawn in all but 2 patients; 73 patients received tacrolimus for more than 3 years. All patients were able to resume normal daily activities.[3] Tacrolimus is licensed for use for myasthenia gravis in some countries, in a usual dose of 3 mg once daily by mouth. Tacrolimus (initial daily dose 3 mg orally) was also reported to reduce corticosteroid dosage in another small study; treatment was continued long-term and efficacy was maintained for up to 3 years.[4] There is some suggestion that tacrolimus may be more effective in thymomatous myasthenia gravis than in non-thymomatous disease.[5]

Tacrolimus has also been used as first-line adjunctive therapy with prednisolone; it was reported to decrease the daily prednisolone dose, and the need for plasmapheresis and high-dose intravenous methylprednisolone.[6]

1. Evoli A, *et al.* Successful treatment of myasthenia gravis with tacrolimus. *Muscle Nerve* 2002; **25:** 111–14.
2. Shimojima Y, *et al.* Tacrolimus in refractory patients with myasthenia gravis: coadministration and tapering of oral prednisolone. *J Clin Neurosci* 2006; **13:** 39–44.
3. Ponseti JM, *et al.* Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. *Neurology* 2005; **64:** 1641–3.
4. Tada M, *et al.* Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. *J Neurol Sci* 2006; **247:** 17–20.
5. Mitsui T, *et al.* Beneficial effect of tacrolimus on myasthenia gravis with thymoma. *Neurologist* 2007; **13:** 83–6.
6. Nagane Y, *et al.* Efficacy of low-dose FK506 in the treatment of Myasthenia gravis—a randomized pilot study. *Eur Neurol* 2005; **53:** 146–50.

Ocular disorders. For mention of the use of tacrolimus in various disorders characterised by ocular lesions such as uveitis, see p.1810.

Organ and tissue transplantation. Tacrolimus has been used both for primary immunosuppression and for the control of graft rejection. Much of the initial experience with the drug was for liver grafts, (p.1815), but it is also used in the transplantation of heart (p.1812), kidney (p.1813), lung (p.1815), pancreas (p.1816), and intestines (p.1813). It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811).

A few selected references to the use of tacrolimus in transplantation are given below.

1. European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; **344:** 423–8.
2. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; **331:** 1110–15.
3. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. *Clin Transplant* 1997; **11:** 299–312.
4. Gruessner RWG, *et al.* Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. *Clin Transplant* 1998; **12:** 260–2.
5. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002; **359:** 741–6.
6. O'Grady JG, *et al.* Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. *Lancet* 2002; **360:** 1119–25.
7. Scott LJ, *et al.* Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003; **63:** 1247–97.
8. Kelly D, *et al.* Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. *Lancet* 2004; **364:** 1054–61.
9. Webster AC, *et al.* Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; **331:** 810–14.
10. McCormack PL, *et al.* Tacrolimus: in heart transplant recipients. *Drugs* 2006; **66:** 2269–79.
11. Haddad EM, *et al.* Cyclosporin versus tacrolimus for liver transplanted patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/03/08).
12. Wente MN, *et al.* Review of the clinical experience with a modified release form of tacrolimus [FK506E (MR4)] in transplantation. *Clin Transplant* 2006; **20** (suppl 17): 80–4.
13. Patel JK, Kobashigawa JA. Tacrolimus in heart transplant recipients: an overview. *BioDrugs* 2007; **21:** 139–43.
14. Joseph A, *et al.* Tacrolimus immunosuppression in high-risk corneal grafts. *Br J Ophthalmol* 2007; **91:** 51–5.

Psoriasis. Tacrolimus has been shown to be effective in the treatment of psoriasis (p.1583) when used orally[1] or topically.[2-4]

1. The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; **132:** 419–23.
2. Remitz A, *et al.* Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; **141:** 103–7.
3. Clayton TH, *et al.* Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; **149:** 419–20.
4. Brune A, *et al.* Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; **24:** 76–80.

Pyoderma gangrenosum. There are reports of response to tacrolimus, given orally,[1-3] or topically,[4-9] or both,[10,11] in patients with pyoderma gangrenosum (p.1583). A small study[12] found topical tacrolimus 0.3% in carmellose sodium paste to be more effective than clobetasol propionate 0.05% for peristomal pyoderma gangrenosum.

Systemic absorption, resulting in tacrolimus blood concentrations equivalent to oral dosing, has been reported in patients with pyoderma gangrenosum in whom tacrolimus was applied directly onto ulcerated areas;[13,14] therapeutic drug monitoring has been suggested for patients treated with topical tacrolimus over large skin areas or with impaired skin barriers.

1. Abu-Elmagd K, *et al.* Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). *Ann Intern Med* 1993; **119:** 595–8.
2. D'Incà R, *et al.* Tacrolimus to treat pyoderma gangrenosum resistant to cyclosporine. *Ann Intern Med* 1998; **128:** 783–4.
3. Lyon CC, *et al.* Recalcitrant pyoderma gangrenosum treated with systemic tacrolimus. *Br J Dermatol* 1999; **140:** 562–4.
4. Schuppe H-C, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Lancet* 1998; **351:** 832.
5. Reich K, *et al.* Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; **139:** 755–7.
6. Vidal D, Alomar A. Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus. *Br J Dermatol* 2004; **150:** 387–8.
7. Lally A, *et al.* Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141:** 1175–6.
8. Chiba T, *et al.* Topical tacrolimus therapy for pyoderma gangrenosum. *J Dermatol* 2005; **32:** 199–203.
9. Kontos AP, *et al.* An open-label study of topical tacrolimus ointment 0.1% under occlusion for the treatment of pyoderma gangrenosum. *Int J Dermatol* 2006; **45:** 1383–5.
10. Jolles S, *et al.* Combination oral and topical tacrolimus in therapy-resistant pyoderma gangrenosum. *Br J Dermatol* 1999; **140:** 564–5.
11. Deckers-Kocken JM, Pasmans SG. Successful tacrolimus (FK506) therapy in a child with pyoderma gangrenosum. *Arch Dis Child* 2005; **90:** 531.
12. Lyon CC, *et al.* Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 13–17.
13. Ghislain P-D, *et al.* Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol* 2004; **150:** 1052–3.
14. Pitarch G, *et al.* Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol* 2006; **86:** 64–5.

Reperfusion and revascularisation procedures. References to the use of tacrolimus-eluting stents.

1. García-Tejada J, *et al.* Carbo-stent liberador de tacrolimus Janus : resultados inmediatos y seguimiento clínico a medio plazo. *Rev Esp Cardiol* 2007; **60:** 197–200.
2. Han Y-L, *et al.* Midterm outcomes of prospective, randomized, single-center study of the Janus tacrolimus-eluting stent for treatment of native coronary artery lesions. *Chin Med J (Engl)* 2007; **120:** 552–6.

Rheumatoid arthritis. In a small, open-label study[1] of 12 patients with rheumatoid arthritis (p.11) refractory to other disease-modifying antirheumatic drugs including ciclosporin, 7 had significant response to tacrolimus after treatment for 6 months, with 4 of these patients maintaining this response after 2 years of therapy. In a larger controlled study,[2] tacrolimus improved disease activity in patients with rheumatoid arthritis resistant to methotrexate. Similarly, an open-label multicentre study involving 80 patients with active disease inadequately responsive to methotrexate alone, addition of tacrolimus 3 mg daily by mouth to methotrexate therapy produced a clinical improvement in about half. The regimen was considered to be generally well tolerated.[3] Tacrolimus in an oral dose of 3 mg once daily has been licensed for use in refractory rheumatoid arthritis in some countries; elderly patients may be given 1.5 mg once daily.[4,5]

1. Gremillion RB, *et al.* Tacrolimus (FK506) in the treatment of severe, refractory rheumatoid arthritis: initial experience in 12 patients. *J Rheumatol* 1999; **26:** 2332–6.
2. Furst DE, *et al.* Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* 2002; **46:** 2020–8.
3. Kremer JM, *et al.* Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a six-month, open-label study. *Arthritis Rheum* 2003; **48:** 2763–8.
4. Curran MP, Perry CM. Tacrolimus: in patients with rheumatoid arthritis. *Drugs* 2005; **65:** 993–1001.
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Scleroderma. There are reports of response to tacrolimus in patients with scleroderma (p.1817).

Skin disorders. Topical tacrolimus has been used to treat various skin disorders. Aside from its licensed use in eczema (above), and use in psoriasis and pyoderma gangrenosum (see above), there are reports of benefit in granuloma annulare,[1,2] lichen sclerosus,[3] lichen striatus,[4] pityriasis alba,[5] pityriasis lichenoides,[6] seborrhoeic dermatitis,[7] as well as the skin manifestations of angiolymphoid hyperplasia,[8] pruritus due to primary biliary cirrhosis,[9] and facial cutaneous lupus erythematosus.[10]

1. Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
2. Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1042–3.
3. Hengge UR, *et al.* Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155:** 1021–8.
4. Sorgentini C, *et al.* Lichen striatus in an adult: successful treatment with tacrolimus. *Br J Dermatol* 2004; **150:** 776–7.
5. Rigopoulos D, *et al.* Tacrolimus ointment 0.1% in pityriasis alba: an open-label, randomized, placebo-controlled study. *Br J Dermatol* 2006; **155:** 152–5.
6. Simon D, *et al.* Successful treatment of pityriasis lichenoides with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1033–5.
7. Braza TJ, *et al.* Tacrolimus 0.1% ointment for seborrhoeic dermatitis: an open-label pilot study. *Br J Dermatol* 2003; **148:** 1242–4.
8. Mashiko M, *et al.* A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol* 2006; **154:** 803–4.
9. Aguilar-Bernier M, *et al.* Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152:** 808–9.
10. Tzung T-Y, *et al.* Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol* 2007; **156:** 191–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prograf; Protopic; Tacraf; Tacro-Tic; Tacroinmun; ***Austral.:*** Prograf; ***Austria:*** Prograf; Protopic; ***Belg.:*** Prograft; Protopic; ***Braz.:*** Prograf; Protopic; ***Canad.:*** Prograf; Protopic; ***Chile:*** Cromidin; Prograf; Protopic; T-Inmun; ***Cz.:*** Advagraf; Prograf; Protopic; Protopy; ***Denm.:*** Prograf; Protopic; ***Fin.:*** Prograf; Protopic; ***Fr.:*** Advagraf; Prograf; Protopic; ***Ger.:*** Prograf; Protopic; ***Gr.:*** Prograf; Protopic; ***Hong Kong:*** Prograf; Protopic; ***Hung.:*** Prograf; Protopic; ***India:*** Mustopic; PanGraf; Tacroz†; ***Indon.:*** Protopic; ***Irl.:*** Prograf; Protopic; ***Israel:*** Prograf; Protopic; ***Ital.:*** Prograf; Protopic; ***Jpn:*** Prograf; Protopic; ***Malaysia:*** Prograf; Protopic; ***Mex.:*** Limustin; Proalid; Prograf; ***Neth.:*** Prograf; Prograft; Protopic; Protopy; ***Norw.:*** Prograf; Protopic; ***NZ:*** Prograf; ***Philipp.:*** Prograf; Protopic; ***Pol.:*** Prograf; Protopic; ***Port.:*** Prograf; Protopic; Protopy; ***Rus.:*** Prograf (Програф); ***S.Afr.:*** Prograf; ***Singapore:*** Prograf; Protopic; ***Spain:*** Prograf; Protopic; ***Swed.:*** Prograf; Protopic; ***Switz.:*** Prograf; Protopic; ***Thai.:*** Prograf; Protopic; ***Turk.:*** Prograf; ***UK:*** Advagraf; Prograf; Protopic; ***USA:*** Prograf; Protopic; ***Venez.:*** Prograf.

Voclosporin *(USAN, rINN)*

ISA-247; ISATX-247; LX-211; R-1524; Voclosporina; Voclosporine; Voclosporinum. Cyclo{L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)nona-6,8-dienoyl]-(2S)-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl}.

Воклоспорин

$C_{63}H_{111}N_{11}O_{12}$ = 1214.6.

CAS — 515814-01-4.

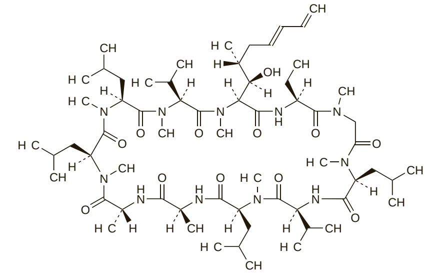

Profile

Voclosporin is an analogue of ciclosporin (p.1822) that is under investigation for the treatment of uveitis, psoriasis, and for the prevention of rejection in organ transplantation.

◊ References.

1. Dumont FJ. ISAtx-247 (Isotechnika/Roche). *Curr Opin Investig Drugs* 2004; **5:** 542–50.
2. Anonymous. ISA 247: trans-ISA 247, trans-R 1524, ISA(TX)247, ISAtx 247, ISATx247, LX 211, LX211, R 1524, R-1524. *Drugs R D* 2007; **8:** 103–12.
3. Papp K, *et al.* Efficacy of ISA247 in plaque psoriasis: a randomised, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371:** 1337–42.

Zotarolimus *(USAN, rINN)*

ABT-578; Zotarolimusum. (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-Dihydroxy-10,21-dimethoxy-3-{(2*R*)-1-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]propan-2-yl}-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-octadecahydro-5*H*-23,27-epoxypyrido-[2,1-*c*][1,4]oxaazahentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone.

Зотаролимус

$C_{52}H_{79}N_5O_{12}$ = 966.2.

CAS — 221877-54-9.

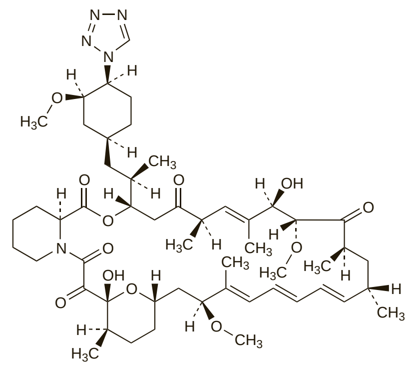

Profile

Zotarolimus is an analogue of sirolimus (p.1841) that is used in the form of a drug-eluting stent to reduce the risk of restenosis after percutaneous coronary stenting.

Reperfusion and revascularisation procedures. References to the use of zotarolimus-eluting stents.

1. Burke SE, *et al.* Zotarolimus (ABT-578) eluting stents. *Adv Drug Deliv Rev* 2006; **58:** 437–46.
2. Fajadet J, *et al.* ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; **114:** 798–806.
3. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting endeavor stent. *J Interv Cardiol* 2006; **19:** 405–13.
4. Korovesis S, *et al.* Subacute thrombosis following implantation of zotarolimus-eluting stent. *Hellenic J Cardiol* 2006; **47:** 310–2.
5. Kandzari DE, *et al.* ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2006; **48:** 2440–7.
6. Chen Y-W, *et al.* Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *J Cardiovasc Pharmacol* 2007; **49:** 228–35.
7. Gershlick A, *et al.* ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol* 2007; **100** (suppl 2): S45–S55.
8. Meredith IT, *et al.* Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. *Am J Cardiol* 2007; **100** (suppl 2): S56–S61.
9. Jain AK, *et al.* Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. *Am J Cardiol* 2007; **100** (suppl 2): S77–S83.

Local Anaesthetics

Local anaesthetics produce reversible loss of function or sensation by preventing or diminishing the conduction of nerve impulses near to the site of their application or injection. Because their mode of action is to decrease permeability of the nerve cell membrane to sodium ions, they also have a membrane stabilising effect.

Most clinically useful local anaesthetics have the same general chemical configuration of an amine portion joined to an aromatic residue by an ester or amide link. The type of linkage is important in determining the properties of the drug.

For a classification of local anaesthetics, see Table 1, below.

Table 1. Classification of local anaesthetics.

Amide type	Ester type
Articaine	*Esters of benzoic acid*
Bupivacaine	Amylocaine
Cinchocaine	Cocaine
Ethyl parapiperidinoacetylaminobenzoate	Propanocaine
Etidocaine	*Esters of meta-aminobenzoic acid*
Levobupivacaine	Proxymetacaine
Lidocaine	
Mepivacaine	*Esters of para-aminobenzoic acid*
Oxetacaine	Benzocaine
Prilocaine	Butacaine
Ropivacaine	Butoxycaine
Tolycaine	Butyl aminobenzoate
Trimecaine	Chloroprocaine
Miscellaneous	Oxybuprocaine
Diperodon	Parethoxycaine
Dyclonine	Procaine
Ethyl chloride	Propoxycaine
Ketocaine	Tetracaine
Myrtecaine	Tricaine
Octacaine	
Pramocaine	
Propipocaine	
Quinisocaine	

Adverse Effects

Adverse effects apparent after local anaesthesia may be caused by the anaesthetic or errors in technique, or may be the result of blockade of the sympathetic nervous system. Local anaesthetics may produce systemic adverse effects as a result of raised plasma concentrations that occur when the rate of uptake into the circulation exceeds the rate of breakdown, for example, after

- accidental intravascular injection
- excessive or too rapid doses
- absorption of large amounts through mucous membranes or damaged skin
- absorption of large amounts from inflamed or highly vascular areas

The systemic toxicity of local anaesthetics mainly involves the CNS and the cardiovascular system. Excitation of the CNS may be manifested by restlessness, excitement, nervousness, paraesthesias, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors, and convulsions. Numbness of the tongue and perioral region, and lightheadedness followed by sedation may appear as early signs of systemic toxicity. Excitation when it occurs may be transient and followed by depression with drowsiness, respiratory failure, and coma. There may be effects on the cardiovascular system with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmias and cardiac arrest may occur. Hypotension often accompanies spinal and epidural anaesthesia; inappropriate positioning of the patient may be a contributory factor for women in labour.

Hypersensitivity reactions are rare and generally limited to local anaesthetics of the ester type. There appears to be no cross-sensitivity between ester- and amide-type local anaesthetics. Idiosyncrasy to local anaesthetics has been reported. Hypersensitivity reactions to preservatives in local anaesthetic preparations have also occurred.

Some local anaesthetics cause methaemoglobinaemia.

Fetal intoxication has occurred after the use of local anaesthetics in labour, either as a result of transplacental diffusion or after accidental injection of the fetus.

Prolonged use of topical anaesthetics in the eye causes corneal damage.

Adverse effects may also be caused by vasoconstrictors given with the anaesthetic.

◊ Reviews.

1. McCaughey W. Adverse effects of local anaesthetics. *Drug Safety* 1992; **7:** 178–189.
2. Berde CB. Toxicity of local anesthetics in infants and children. *J Pediatr* 1993; **122** (suppl): S14–S20.
3. Naguib M, *et al.* Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety* 1998; **18:** 221–50.
4. Dalens BJ, Mazoit J-X. Adverse effects of regional anaesthesia in children. *Drug Safety* 1998; **19:** 251–68.
5. Cox B, *et al.* Toxicity of local anaesthetics. *Best Pract Res Clin Anaesthesiol* 2003; **17:** 111–36.

Adverse effects of central block. Central nerve block (see under Local Anaesthetic Techniques, below), comprising spinal or epidural block, is very widely used and certain adverse effects are particularly associated with the technique. Systemic effects (see Adverse Effects, above) are more likely with epidural than with spinal block, because of the larger doses used.

Total spinal anaesthesia from extreme spread of a block or accidental penetration of the dura during an epidural block produces unconsciousness, hypotension, and respiratory arrest. Less extensive spread to the cervical region is usually associated with nausea, agitation, and hypotension.

Hypotension (associated with venodilatation and decreased cardiac output secondary to sympathetic block) is the **cardiovascular** effect most often associated with the technique, and may be especially problematic in pregnancy. Other cardiovascular complications may include bradycardia or heart block; cardiac arrest has also been reported unexpectedly after spinal anaesthesia.

Post-dural puncture headache (see under Treatment of Adverse Effects, below) is probably the most common **neurological complication** related to these procedures and may be accompanied by tinnitus or photophobia. Headache after spinal block may rarely be caused by meningitis. Backache is a frequent postoperative complication of epidural, spinal, or general anaesthesia. Cranial nerve lesions and reversible loss of hearing in the low frequency range, usually affecting both ears, have been reported rarely following spinal block. Neurological complications associated with these blocks may also rarely include paraplegia caused by arachnoiditis, or trauma or compression of the spinal cord after development of a haematoma or abscess. Transient radicular irritation involving the lower back, buttocks, and thighs may develop within 24 hours of spinal block; recovery is usually within 1 week. Cauda equina syndrome, the symptoms of which include urinary retention, loss of perineal sensation, loss of sexual function, and faecal incontinence, is also a rare complication which can present many months after spinal block. There is some evidence that, although still rare, the incidence of neurotoxic complications after spinal anaesthesia is greater with lidocaine than with other commonly used local anaesthetics such as bupivacaine and tetracaine. The incidence of persistent lumbosacral neuropathy may be as high as 1 in 200 after continuous spinal anaesthesia with lidocaine.

Perioperative shivering has been associated with epidural block.

References.

1. Kalmanovitch DVA, Simmons P. Post-anaesthetic complications in the home. *Prescribers' J* 1988; **28:** 124–31.
2. Wildsmith JAW, Lee JA. Neurological sequelae of spinal anaesthesia. *Br J Anaesth* 1989; **63:** 505–7.
3. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anaesthesia. *Drug Safety* 1990; **5:** 179–94.
4. Anonymous. Perioperative shivering. *Lancet* 1991; **338:** 547–8.
5. Broome IJ. Hearing loss and dural puncture. *Lancet* 1993: **341:** 667–8.
6. Russell R, *et al.* Assessing long term backache after childbirth. *BMJ* 1993; **306:** 1299–1303.
7. Harding SA, *et al.* Meningitis after combined spinal-extradural anaesthesia in obstetrics. *Br J Anaesth* 1994; **73:** 545–7.
8. Gielen M. Spinal anaesthesia: hearing loss, failure, transient radicular irritation. *Anaesthesia* 1998; **53** (suppl 2): 23–5.
9. Horlocker TT, Wedel DJ. Neurologic complications of spinal and epidural anesthesia. *Reg Anesth Pain Med* 2000; **25:** 88–98.
10. Johnson ME. Potential neurotoxicity of spinal anesthesia with lidocaine. *Mayo Clin Proc* 2000; **75:** 921–32.
11. Zaric D, *et al.* Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 17/05/06).

Effects on the ears. Symptoms such as vertigo, nausea, and nystagmus, which have been reported after the use of local anaesthetics in the external[1] or middle ear,[2] may result from penetration of the local anaesthetic into the inner ear. For reference to hearing disturbances associated with spinal block, see under Adverse Effects of Central Block, above.

1. Raine NMN, Whittet HB. Emla cream and induced vertigo. *Br J Hosp Med* 1994; **51:** 614–15.
2. Blair Simmons F, *et al.* Lidocaine in the middle ear: a unique cause of vertigo. *Arch Otolaryngol* 1973; **98:** 42–3.

Effects on wound healing. A review of the literature[1] found evidence that local infiltration of local anaesthetics can have detrimental effects on the first two stages of wound healing. The size of the effect on mature wound strength remains to be determined.

1. Brower MC, Johnson ME. Adverse effects of local anesthetic infiltration on wound healing. *Reg Anesth Pain Med* 2003; **28:** 233–40.

Hypersensitivity. Local anaesthetics may provoke types I and IV hypersensitivity reactions. Type I reactions (e.g. anaphylaxis) to local anaesthetics are generally rare. They occur more often with the ester-type than with the amide-type drugs, probably because of the metabolism of the former to para-aminobenzoic acid (PABA). Nevertheless, severe or fatal reactions have been associated not only with ester-type local anaesthetics such as tetracaine[1] and procaine[2] but also with the amide-type local anaesthetics lidocaine[3-7] and prilocaine.[3] Intolerance may also have been the cause of death in a patient who received mepivacaine for paracervical anaesthesia.[8] Hypotension during dental anaesthesia is usually a vasovagal response unrelated to the type of local anaesthetic used and may be prevented by the use of diazepam. Patients sensitised by topical application may then develop anaphylactic reactions when treated systemically.[9] The use of drugs such as benzocaine or tetracaine in lozenges or throat sprays may also sensitise patients.[10]

Some patients diagnosed as being hypersensitive to local anaesthetics may have reacted to preservatives in the preparations.[11] Cross-hypersensitivity reactions may also occur between some ester-type local anaesthetics and topical preparations, such as sunscreens, that contain PABA or related compounds.[12]

Skin testing may be of benefit in patients who will require future local anaesthesia and when a patient's history does not rule out a possible allergic reaction. However, testing itself can cause severe or anaphylactic reactions.[9,13]

Type IV reactions (i.e. delayed reactions) to local anaesthetics have also been reported, albeit rarely.[14-17]

For reports of the incidence of allergy to local anaesthetics determined by patch testing, see under individual monographs.

1. Moriwaki K, *et al.* A case report of anaphylactic shock induced by tetracaine used for spinal anesthesia. *Masui* 1986; **35:** 1279–84.
2. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; **i:** 355.
3. Fisher MM, Pennington JC. Allergy to local anaesthesia. *Br J Anaesth* 1982; **54:** 893–4.
4. Howard JJ, *et al.* Adult respiratory distress syndrome following administration of lidocaine. *Chest* 1982; **81:** 644–5.
5. Promisloff RA, DuPont DC. Death from ARDS and cardiovascular collapse following lidocaine administration. *Chest* 1983; **83:** 585.
6. Ruffles SP, Ayres JG. Fatal bronchospasm after topical lignocaine before bronchoscopy. *BMJ* 1987; **294:** 1658–9.
7. Ball IA. Allergic reactions to lignocaine. *Br Dent J* 1999; **186:** 224–6.
8. Grimes DA, Cates W. Deaths from paracervical anesthesia used for first-trimester abortion, 1972–1975. *N Engl J Med* 1976; **295:** 1397–9.
9. Mulvey PM. Allergy to local anaesthetics. *Med J Aust* 1980; **1:** 386.
10. Verbov J. Drug eruptions. *Practitioner* 1979; **222:** 400–9.
11. Wildsmith JAW, *et al.* Alleged allergy to local anaesthetic drugs. *Br Dent J* 1998; **184:** 507–10.
12. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anesthesia. *Drug Safety* 1990; **5:** 179–94.
13. Brown DT, *et al.* Allergic reaction to an amide local anaesthetic. *Br J Anaesth* 1981; **53:** 435–7.
14. Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; **25:** 45–8.
15. Craft DV, Good RP. Delayed hypersensitivity reaction of the knee after injection of arthroscopy portals with bupivacaine (Marcaine). *Arthroscopy* 1994; **10:** 305–8.
16. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.
17. Ban M, Hattori M. Delayed hypersensitivity due to epidural block with ropivacaine. *BMJ* 2005; **330:** 229.

Methaemoglobinaemia. Methaemoglobinaemia has been reported with several local anaesthetics including tetracaine,[1] benzocaine,[1-5] and lidocaine[1,6] but is more commonly associated with the use of prilocaine.[7-10] It may occur after local injection or topical use. It has been suggested that the effect is due to the presence of an aniline group in the structure or, in the case of lidocaine and prilocaine, metabolism to an aniline-like structure. Methaemoglobinaemia may result from the use of usual doses as well as exposure to toxic concentrations of local anaesthetic;[1,9] with prilocaine doses of 8 mg/kg or more [above recommended maxima] usually produce symptoms.[11]

Methaemoglobinaemia has occurred after the topical application of a eutectic preparation of prilocaine and lidocaine.[8,10] Although increases in methaemoglobin concentrations are generally small after the use of this mixture in infants[12,13] and children,[14] some infants may be particularly susceptible to induced methaemoglobinaemia during the first 3 months of life probably due to their limited enzyme capacity.[12] The *BNF* states that eutectic prilocaine/lidocaine cream may be used under specialist supervision in infants over 1 month of age, and in some other countries the cream is also licensed for limited use in neonates (see also Surface Anaesthesia under Lidocaine, p.1866). However, UK licensed product information does not recommend its use in children under 1 year old.

Use with drugs such as sulfonamides[8] or antimalarials[11] may predispose to methaemoglobinaemia. Patients with haemoglobinopathies or G6PD deficiency may also be at greater risk.[1]

1. Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981; **38:** 89–93.
2. Rodriguez LF, *et al.* Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. *Ann Pharmacother* 1994; **28:** 643–9.
3. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 1996; **30:** 1251–4.
4. LeClaire AC, *et al.* Methemoglobinemia secondary to topical benzocaine use in a lung transplant patient. *Ann Pharmacother* 2005; **39:** 373–6.
5. FDA. FDA Public Health Advisory: benzocaine sprays marketed under different names, including Hurricaine, Topex, and Cetacaine (issued 10th February, 2006). Available at: http://www.fda.gov/cder/drug/advisory/benzocaine.htm (accessed 16/03/06)
6. Karim A, *et al.* Methemoglobinemia complicating topical lidocaine used during endoscopic procedures. *Am J Med* 2001; **111:** 150–3.
7. Mandel S. Methemoglobinemia following neonatal circumcision. *JAMA* 1989; **261:** 702.
8. Jakobson B, Nilsson A. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: a case report. *Acta Anaesthesiol Scand* 1985; **29:** 453–5.
9. Knobeloch L, *et al.* CDC. Prilocaine-induced methemoglobinemia—Wisconsin, 1993. *MMWR* 1994; **43:** 655–7.
10. Parker JF, *et al.* EMLA toxicity after application for allergy skin testing. *Pediatrics* 2004; **113:** 410–11.
11. Reynolds F. Adverse effects of local anaesthetics. *Br J Anaesth* 1987; **59:** 78–95.
12. Nilsson A, *et al.* Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990; **64:** 72–6.
13. Brisman M, *et al.* Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr* 1998; **87:** 1191–4.
14. Frayling IM, *et al.* Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. *BMJ* 1990; **301:** 153–4.

Pregnancy. As mentioned under Adverse Effects of Central Block, above, hypotension may be particularly problematic for patients receiving epidural or spinal block for analgesia during labour. In addition it has been suggested that patients receiving epidural analgesia during labour may have an increased risk of pyrexia, which can lead to fetal compromise.[1]

The use of paracervical block has fallen out of favour because of serious adverse effects on the fetus.

1. Fusi L, *et al.* Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; **i:** 1250–2.

Treatment of Adverse Effects

At the first signs of local anaesthetic toxicity from parenteral dosage, the injection should be stopped; in some cases it may also be possible to apply a tourniquet to limit further systemic absorption. Subsequent management, regardless of the route, is supportive. If systemic reactions develop, steps should be taken to maintain the circulation and respiration and to control convulsions. A patent airway must be established and oxygen given, together with assisted ventilation if necessary. The circulation should be maintained with infusions of intravenous fluids. Vasopressors have been suggested in the treatment of marked hypotension although their use is accompanied by a risk of CNS excitation. Ephedrine is preferred for the management of hypotension associated with spinal or epidural block, particularly in pregnancy. Vasopressors should not be given to patients receiving oxytocic drugs. Convulsions may be controlled with intravenous benzodiazepines such as diazepam although these drugs may also depress respiration and the circulation. Intravenous phenobarbital is used for persistent convulsions.

Methaemoglobinaemia may be treated with intravenous methylthioninium chloride.

Post-dural puncture headache. Headache after puncture of the dura mater during procedures such as lumbar puncture or central nerve blocks is thought to be caused by subsequent leakage of CSF. The incidence of such post-dural puncture headache is significantly reduced by the use of small, blunt needles which produce a smaller hole in the dura and separate its fibres rather than cutting them.

When treatment is necessary conservative therapy such as analgesics and hydration will relieve symptoms in the majority of patients with mild post-dural puncture headache within 1 to 2 days. Bed rest does not reduce the incidence but once headache develops the patient may feel some relief when recumbent. If the headache persists for a further 24 hours measures such as epidural saline or dextran 40 or the use of intravenous caffeine and sodium benzoate may be effective; oral caffeine has also been shown to be of benefit. However, perhaps the most widely favoured measure, despite a lack of good evidence, is the epidural injection of autologous blood to form a blood patch over the dural puncture. There have been anecdotal reports of success using corticotropin or tetracosactide but such reports of relief with sumatriptan were not confirmed by a controlled study.

References.

1. Choi A, *et al.* Pharmacologic management of postdural puncture headache. *Ann Pharmacother* 1996; **30:** 831–9.
2. Broadley SA, Fuller GN. Lumbar puncture needn't be a headache. *BMJ* 1997; **315:** 1324–5.
3. Serpell MG, *et al.* Prevention of headache after lumbar puncture: questionnaire survey of neurologists and neurosurgeons in United Kingdom. *BMJ* 1998; **316:** 1709–10.
4. Evans RW, *et al.* Assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2000; **55:** 909–14. Also available at: http://www.neurology.org/cgi/reprint/55/7/909.pdf (accessed 11/08/08)
5. Sudlow C, Warlow C. Epidural blood patching for preventing and treating post-dural puncture headache. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 17/05/06).
6. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* 2003; **91:** 718–29.
7. Armon C, Evans RW. Addendum to assessment: prevention of post-lumbar puncture headaches: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005; **65:** 510–12. Also available at: http:// www.neurology.org/cgi/reprint/65/4/510.pdf (accessed 11/08/08)

Precautions

As with any drug local anaesthetics are contra-indicated in patients with known hypersensitivity. However, it might be possible to avoid reactions by using a local anaesthetic of the alternative chemical type. Facilities for resuscitation should be available when local anaesthetics are given parenterally.

Local anaesthetics should not be used in patients with complete heart block. They should be given cautiously to the elderly, to the debilitated, to children, and to patients with epilepsy, impaired cardiac conduction or respiratory function, shock, or hepatic impairment; patients with myasthenia gravis are particularly susceptible to the effects of local anaesthetics. Ester-type local anaesthetics are contra-indicated in patients with low plasma-cholinesterase concentrations. Techniques such as epidural or spinal block should not be used in patients with cerebrospinal diseases, cardiogenic or hypovolaemic shock, or altered coagulation status. Because of the risk of transmitting infection into the CNS these techniques should not be employed where there is pyogenic infection of the skin at or adjacent to the injection site.

Because of the risk of systemic adverse effects when local anaesthetics are absorbed too rapidly, they should not be injected into or applied to inflamed or infected tissues or to damaged skin or mucosa. For similar reasons, the rate of injection should not be too rapid and great care must be taken to avoid inadvertent intravascular injection. The risk of adverse effects from the uptake of local anaesthetics into the circulation may be reduced by the inclusion of adrenaline to produce vasoconstriction, but the lowest effective concentration of adrenaline should be used. Solutions containing adrenaline should not, however, be used for producing anaesthesia in appendages such as digits, because the profound ischaemia that follows may lead to gangrene. Mepivacaine and prilocaine tend to produce less vasodilatation at low concentrations than other local anaesthetics and may be useful where the addition of vasoconstrictors is contra-indicated (but see also under Action, below).

When used in the mouth or throat, local anaesthetics may impair swallowing and increase the risk of aspiration. Patients who have received local anaesthetics for procedures such as laryngoscopy or tracheoscopy should be cautioned not to eat or drink for at least 3 to 4 hours after the anaesthetic.

The cornea may be damaged by prolonged topical application of local anaesthetics, particularly cocaine. Patients should be warned not to rub or touch the eye while anaesthesia persists and the anaesthetised eye should be protected from dust and bacterial contamination.

Local anaesthetics may be ototoxic and should not be instilled into the middle ear.

The application of local anaesthetics to the skin for prolonged periods or to extensive areas should be avoided.

Precautions for central block. Epidural or spinal block may rarely result in paraplegia caused by an induced haematoma or abscess, and have thus been considered unsuitable in patients with pre-existing neurological disease, infection at the puncture site, or blood disorders, or in those receiving aspirin or full-dose anticoagulant therapy. Such therapy may be stopped at an appropriate time before surgery if central block is planned. It is necessary to balance the risk of withholding anticoagulation against the risk of bleeding in the individual patient. Epidural or spinal block in patients given low-dose anticoagulant therapy to prevent postoperative deep-vein thrombosis is still controversial. For further discussion and recommendations see Spinal Anaesthesia, p.1303.

A study in the USA[1] involving 891 patients found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia compared with placebo; it was considered that the recommendation to stop aspirin 7 to 10 days before delivery was unjustified.

1. Sibai BM, *et al.* Low-dose aspirin in correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; **172:** 1553–7.

Tachyphylaxis. The effect of successive epidural injections of 2% solutions of lidocaine, mepivacaine, or prilocaine was reduced by 25 to 30% with each injection when the interval between the disappearance of analgesia and re-injection was more than 10 minutes but anaesthesia was augmented if this interval was less than 10 minutes.[1] Such tachyphylaxis, associated with the prolonged epidural use of all local anaesthetics, has also been reviewed.[2]

1. Bromage PR, *et al.* Tachyphylaxis in epidural analgesia 1: augmentation and decay of local anesthesia. *J Clin Pharmacol* 1969; **9:** 30–8.
2. Mogensen T. Tachyphylaxis to epidural local anaesthetics. *Dan Med Bull* 1995; **42:** 141–6.

Test dose. A test dose is recommended in epidural block to check for accidental intravenous or intrathecal injection but negative results should be treated with caution.[1] Accidental intravenous placement of the needle is notoriously more difficult to detect than inadvertent subarachnoid placement. Adrenaline has been added to the test solution to aid detection of intravenous injection but is considered by some to be of little value.[2,3]

1. Scott DB. Test doses in extradural block. *Br J Anaesth* 1988; **61:** 129–30.
2. Thornburn J. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia. *Br J Anaesth* 1989; **62:** 578–81.
3. Narchi P, *et al.* Heart rate response to an iv test dose of adrenaline and lignocaine with and without atropine pretreatment. *Br J Anaesth* 1991; **66:** 583–6.

Interactions

The metabolism of ester-type local anaesthetics may be inhibited by anticholinesterases, increasing the risk of systemic toxicity.

Ester derivatives such as tetracaine, benzocaine, or procaine that are hydrolysed to para-aminobenzoic acid may antagonise the activity of aminosalicylic acid or sulfonamides. Ester-type local anaesthetics such as procaine and cocaine that are hydrolysed by plasma cholinesterase may competitively enhance the neuromuscular blocking activity of suxamethonium; the amide local anaesthetic, lidocaine may have a similar effect.

There is an increased risk of myocardial depression when amide-type local anaesthetics such as bupivacaine, levobupivacaine, lidocaine, or ropivacaine are given with antiarrhythmics.

If local anaesthetics containing adrenaline are given for epidural or paracervical block during labour the use of an oxytocic drug post partum may lead to severe hypertension. Although there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and MAOIs or tricyclic antidepressants, great care should nevertheless be taken to avoid inadvertent intravenous doses of the local anaesthetic preparation.

For further details of interactions between local anaesthetics and other drugs, see under individual monographs.

Pharmacokinetics

Most local anaesthetics are readily absorbed through mucous membranes, and through damaged skin. Local anaesthetics are weak bases and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibre where ionisation can occur.

Anaesthetics of the ester type are hydrolysed by esterases in the plasma and, to a lesser extent, in the liver. The effect of spinal anaesthetics lasts until the drug is taken up into the blood circulation since there is little esterase in the spinal fluid.

Amide-type anaesthetics are metabolised in the liver and, in some cases, the kidneys. While there is little protein binding with most ester-type anaesthetics, the amide types are considerably bound.

◊ References.

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Smith C. Pharmacology of local anaesthetic agents. *Br J Hosp Med* 1994; **52:** 455–60.
4. Mazoit J-X, Dalens BJ. Pharmacokinetics of local anaesthetics in infants and children. *Clin Pharmacokinet* 2004; **43:** 17–32.

Uses and Administration

Local anaesthetics act by preventing the generation and transmission of impulses along nerve fibres and at nerve endings; depolarisation and ion-exchange are inhibited. The effects are reversible. They are used for the local relief of painful conditions, and to prevent pain and discomfort of various medical and surgical procedure (see below). In general, loss of pain (analgesia) occurs before loss of sensory and autonomic function (anaesthesia) and loss of motor function (paralysis), but this may depend on the drug used and the site into which it is given.

Local anaesthetics vary in their potency and speed of onset and duration of action. The anaesthetic must penetrate the lipoprotein nerve sheath in its unionised form before it can act and therefore drugs with high lipid-solubility tend to have a greater potency and duration of action and a faster onset than drugs with low lipid-solubility. The most protein-bound drugs tend to have the longest duration of action.

The potency of local anaesthetics is traditionally compared against that of procaine, which is low; chloroprocaine, lidocaine, mepivacaine, and prilocaine are similar or somewhat more potent; etidocaine is of intermediate potency, bupivacaine and ropivacaine highly potent, and tetracaine extremely potent.

Speed of onset and duration of action also depend on the technique used (see Local Anaesthetic Techniques, below), the type of block, and the site of administration.

The speed of onset and duration of action of local anaesthetics may be increased by the addition of a vasoconstrictor, which has the effect of reducing the uptake of the local anaesthetic into the circulation from the injection site. Solutions containing adrenaline 1 in 200 000 are generally advocated, although higher concentrations such as 1 in 80 000 may be used in dentistry where the total dose is small. The total amount of adrenaline injected should not exceed 500 micrograms although the amount of adrenaline absorbed varies considerably with the site of injection; some consider that the maximum dose should be 200 micrograms. Other vasoconstrictors including noradrenaline are also used, but the 2002 *Dental Practitioners' Formulary* in the UK considered that noradrenaline should not be used since it presented no advantages and when given at relatively high concentrations had occasionally been associated with severe hypertensive episodes. Vasoconstrictors should not be used when producing a nerve block in an appendage such as a digit, as gangrene may occur. Vasoconstrictors have been added to injections for spinal block, but their use is not recommended because of the danger of reducing the blood supply to the spinal cord.

Local anaesthetics are generally given as acidic solutions of the water-soluble hydrochloride salts; alkalinisation of these solutions or formulation as a carbonated base may increase the speed of onset (see pH of solutions, below).

The dosage of individual local anaesthetics depends on the injection site and the procedure used. The smallest effective dose and the lowest effective concentration should be used. Smaller doses are usually needed in the elderly, in children, in debilitated patients, and in cardiac disease. Doses should also be reduced in the presence of hepatic disease. Meticulous attention to technique is essential particularly in nerve block and spinal procedures. Injections for central nerve blocks, such as epidural (including caudal block) and spinal block should not contain preservatives.

Action. The intrinsic vasoactivity of a local anaesthetic can influence its rate of removal from the site of action and therefore its duration of action. Ester-type local anaesthetics such as tetracaine and procaine are more likely to produce vasodilatation than amide-type local anaesthetics such as cinchocaine, lidocaine, mepivacaine, and prilocaine after intradermal doses.[1] However, cocaine differs from other ester-type local anaesthetics in that it produces vasoconstriction. The amide-type local anaesthetics can produce vasoconstriction but, apart from prilocaine, their vasoconstrictor activity has generally been found to decline with increasing concentration,[1,2] and, in a study, lidocaine and bupivacaine produced more vasodilatation than vasoconstriction at the higher concentrations tested.[2] Mepivacaine has produced greater and more consistent vasoconstriction than lidocaine, cinchocaine, or prilocaine after intradermal injection[1] but this greater vasoactivity is not always evident.[3]

1. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics: an intradermal study. *Br J Anaesth* 1985; **57:** 1006–11.
2. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. *Br J Anaesth* 1976; **48:** 1171–4.
3. Goebel WM, *et al.* Comparative circulatory levels of 2 per cent mepivacaine and 2 per cent lignocaine. *Br Dent J* 1980; **148:** 261–4.

Administration. Systemic toxic effects of local anaesthetics are related to blood concentrations and, as absorption varies considerably according to the site of injection, it has been suggested[1,2] that recommendation of a single maximum dose without regard to the site of the procedure is meaningless. If a plasma-lidocaine concentration of 5 micrograms/mL were required for toxicity then this would be achieved by injection of 300 mg in the intercostal area, 500 mg epidurally, 600 mg in the region of the brachial plexus, or 1000 mg subcutaneously. The reduction of peak concentrations obtained by the addition of adrenaline was also dependent on the site of injection. Furthermore, most cases of severe toxicity did not result from overdosage but from inadvertent intravascular injection or too rapid injection.

1. Scott DB. "Maximum recommended doses" of local anaesthetic drugs. *Br J Anaesth* 1989; **63:** 373–4.
2. Scott DB. Safe use of lignocaine. *BMJ* 1989; **299:** 56.

CARBONATED SOLUTIONS. The use of carbonated solutions of local anaesthetics instead of the usual hydrochloride salts has been discussed in several reviews.[1-3] Although some early studies indicated that carbonated solutions of bupivacaine, lidocaine, or prilocaine produced earlier onset of anaesthesia and improved the quality of epidural or brachial plexus blocks not all subsequent studies have confirmed these results. A method for preparing carbonated solutions has been published[4] but proprietary preparations of such solutions of bupivacaine or lidocaine may be available in some countries.

1. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; **58:** 701–16.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.
4. Bromage PR. Improved conduction blockade in surgery and obstetrics: carbonated local anesthetics. *Can Med Assoc J* 1967; **97:** 1377–84.

PH OF SOLUTIONS. The pain associated with infiltration of local anaesthetics can be reduced by buffering the solution to physiological pH with sodium bicarbonate.[1,2] Although buffering itself does not appear to compromise the efficacy of anaesthesia,[2] alkalinisation of the solution may reduce the solubility of the local anaesthetic and cause precipitation.[2-4] To enhance stability local anaesthetic solutions are usually prepared at an acidic pH and it is therefore recommended that if solutions are buffered they should be used immediately.[2] (Solutions containing adrenaline require an acidic pH.)

Similar pH adjustments of solutions for intravenous regional anaesthesia have been reported to reduce the amount of local venous irritation and thrombophlebitis[5] and to increase the speed of onset and the duration of the block.[6] However, it has been noted that at alkaline pH lidocaine can lower surface tension, thereby altering drop size and potentially resulting in a decreased dose if such solutions are infused via a drop counting device rather than a volume pump.[7] Alkalinisation of a solution used for epidural block for caesarean section has been reported to result in a more rapid onset of action and denser block.[8]

Alkalinisation has also been used to hasten the onset of peripheral nerve block[9] by increasing the proportion of the lipid-soluble nonionised free base but the effect in epidural block has been inconsistent.[10,11]

1. McKay W, *et al.* Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesth Analg* 1987; **66:** 572–4.
2. Cristoph RA, *et al.* Pain reduction in local anesthetic administration through pH buffering. *Ann Emerg Med* 1988; **17:** 117–20.
3. Bourget P, *et al.* Factors influencing precipitation of pH-adjusted bupivacaine solutions. *J Clin Pharm Ther* 1990; **15:** 197–204.
4. Nakano NI. Temperature-dependent aqueous solubilities of lidocaine, mepivacaine, and bupivacaine. *J Pharm Sci* 1979; **68:** 667–8.
5. Yudenfreund SM, *et al.* pH-Buffered 2-chloroprocaine for intravenous regional anesthesia. *DICP Ann Pharmacother* 1989; **23:** 614–15.
6. Armstrong P, *et al.* Effect of alkalinization of prilocaine on IV regional anaesthesia. *Br J Anaesth* 1989; **63:** 625P–626P.
7. Leor R, *et al.* The influence of pH on the intravenous delivery of lidocaine solutions. *Eur J Clin Pharmacol* 1990; **39:** 521–3.
8. Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural caesarean section. *Br J Anaesth* 1991; **67:** 699–703.
9. Coventry DM, Todd JG. Alkalinization of bupivacaine for sciatic nerve blockade. *Br J Anaesth* 1989; **62:** 227P.
10. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
11. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.

Anorectal disorders. See under Surface Anaesthesia, below.

Cough. Drugs such as lidocaine or bupivacaine have been given by inhalation in severe intractable cough (p.1547), including cough caused by malignant neoplasms.[1-4] Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, nebulised local anaesthetics should be used in controlled circumstances only; there may also be temporary loss of the swallowing reflex.

Intravenous lidocaine has also been tried for the prevention of fentanyl-induced cough.[5-7]

1. Howard P, *et al.* Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977; **71:** 19–24.
2. Stewart CJ, Coady TJ. Suppression of intractable cough. *BMJ* 1977; **i:** 1660–1.
3. Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. *JAMA* 1984; **252:** 2456–7.
4. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1741.
5. Lin C-S, *et al.* Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. *Can J Anesth* 2004; **51:** 654–9.
6. Pandey CK, *et al.* Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. *Anesth Analg* 2004; **99:** 1696–8.
7. Pandey CK, *et al.* Intravenous lidocaine 0.5 mg.kg effectively suppresses fentanyl-induced cough. *Can J Anesth* 2005; **52:** 172–5.

Endoscopy. Local anaesthetics such as lidocaine are sometimes used before endoscopy to improve patient comfort and facilitate passage of the endoscope. As mentioned in the discussion on drugs used in endoscopy (see p.956) some consider that the use of local anaesthetics for procedures such as gastrointestinal endoscopy should probably be reserved for those patients who prefer not to be sedated as their use in addition to premedication with opioids or benzodiazepines appears to serve little purpose.

References.

1. Chuah SY, *et al.* Topical anaesthesia in upper gastrointestinal endoscopy. *BMJ* 1991; **303:** 695.
2. Jameson JS, *et al.* Topical anaesthesia improves toleration for upper gastrointestinal endoscopy. *Gut* 1992; **33** (suppl): S51.
3. Randell T, *et al.* Topical anaesthesia of the nasal mucosa for fibreoptic airway endoscopy. *Br J Anaesth* 1992; **68:** 164–7.

Mouth ulceration. For the role of local anaesthetics in the management of mouth ulceration, see p.1700.

Pain. Pain and its general management are discussed on p.2. Local anaesthetics are used in a variety of situations for the management of pain. They are usually given by local injection or applied topically but are sometimes used intravenously in techniques such as intravenous regional anaesthesia, which involves the continuous infusion of local anaesthetics such as lidocaine to produce general analgesia. However, the technique is potentially dangerous and seldom employed.

NERVE BLOCKS. Nerve blocks produce analgesia by interrupting the nervous transmission of pain signals either by temporary inhibition of conduction or by destruction of the nerve. Nerve blocks may be used alone or with analgesics in the management of acute or chronic pain associated with a well-defined anatomical site, especially when the pain is unresponsive to or not adequately controlled by conventional therapy. The route of administration and method used depend on the site to be blocked but may include peripheral nerve block, autonomic nerve blocks such as sympathetic nerve blocks and coeliac plexus block, and central nerve blocks such as epidural (including caudal) and spinal block. **Local anaesthetics** are used when a temporary effect is required. **Neurolytics** such as phenol or alcohol or freezing of the nerve (cryoanalgesia) produce more prolonged block, but even so the effects may last no more than a few months, and the variable and non-selective neural damage produced correlates poorly with pain relief; some consider the risk of complications to outweigh the benefits obtained.[1]

The use of nerve blocks in the *management of cancer* (p.5) has declined following the refinement of the use of conventional analgesics. Some consider that their value may be limited to patients with a life expectancy of 3 months or less[2] and that the main benefit of nerve blocks in cancer is to produce maximum pain relief rapidly. However, others consider that chemical and thermal neurolysis can provide long-term control of severe cancer pain without a substantial incidence of adverse effects.[3] Neurolytic blocks may be of particular value in cancer pain syndromes involving the viscera or the torso, but are rarely applicable in the management of extremity pain.[4] Neuropathic pain is rarely helped by somatic neural block and may even be aggravated,[1] but block of the splanchnic nerves or coeliac plexus with alcohol or phenol is reputed to be effective in relieving severe intractable pain caused by cancer of the pancreas, stomach, small intestine, gallbladder, or other abdominal viscera, especially when the cancer has not spread to the parietal peritoneum.[5]

Similar neurolytic blocks preceded by a local anaesthetic have also been used in patients with *severe intractable pain* of chronic pancreatitis, postcholecystectomy syndrome, or other chronic abdominal visceral diseases unrelieved by medical or surgical therapy.

Central nerve blocks using local anaesthetics with or without **opioids** are used for the *management of acute pain* such as labour pain (p.7) and postoperative pain (p.4) including that in children (p.3); they are also sometimes used for cancer pain.[1,6]

Sympathetic nerve blocks using repeated injections of local anaesthetics or neurolytics have been used for sympathetically maintained pain. Intravenous regional sympathetic block is an alternative when a single limb is involved;[1] guanethidine is one of the drugs that has been used.[7]

Injections of local anaesthetics with or without **corticosteroids** are often used for blocks of localised painful joints. Nerve blocks are also used to block localised painful trigger areas[8] such as postoperative or post-traumatic neuroma formation and for focal muscle pain.

For the role of nerve blocks in the management of low back pain, see p.7.

1. Hanks GW, Justins DM. Cancer pain: management. *Lancet* 1992; **339:** 1031–6.
2. WHO. Cancer pain relief and palliative care: report of a WHO expert committee. *WHO Tech Rep Ser 804*, 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_804.pdf (accessed 11/08/08)
3. American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Practice guidelines for cancer pain management. *Anesthesiology* 1996; **84:** 1243–7. Also available at: http://www.asahq.org/publicationsAndServices/cancer.html (accessed 11/08/08)
4. Marshall KA. Managing cancer pain: basic principles and invasive treatments. *Mayo Clin Proc* 1996; **71:** 472–7.
5. Bonica JJ. Management of pain with regional analgesia. *Postgrad Med J* 1984; **60:** 897–904.
6. Hunt R, Massolino J. Spinal bupivacaine for the pain of cancer. *Med J Aust* 1989; **150:** 350.
7. Hannington-Kiff JG. Relief of causalgia in limbs by regional intravenous guanethidine. *BMJ* 1979; **2:** 367–8.
8. Foley KM. The treatment of cancer pain. *N Engl J Med* 1985; **313:** 84–95.

Postherpetic neuralgia. For the role of local anaesthetics in the management of postherpetic neuralgia, see p.9.

Premature ejaculation. A cream containing lidocaine 2.5% and prilocaine 2.5% has been applied topically to the penis for a desensitising effect in the management of premature ejaculation (p.2181). The cream is usually applied to the penis and covered with a condom for a period of time, then washed off before sexual intercourse. It has been reported to increase intravaginal ejaculatory latency time compared with a placebo cream,[1] and a study[2] of different application times found 20 minutes to be the optimum. Longer application times were associated with erection loss because of numbness of the penis, and delayed ejaculation. Decreased vaginal sensitivity in female partners, from residual anaesthetic, has also been reported.[1]

1. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int* 2004; **93:** 1018–21.
2. Atikeler MK, *et al.* Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* 2002; **34:** 356–9.

Soft-tissue rheumatism. For the adjunctive use of local anaesthetics in the management of soft-tissue rheumatism, see p.13.

Spasticity. The management of spasticity (p.1887) involves physiotherapy and the use of antispastic drugs. Other approaches to treatment include nerve blocks with local anaesthetics; these can improve spasticity but should generally only be used when further muscle relaxation would not increase disability.

Stuttering. Local anaesthetics have been tried in the treatment of stuttering (p.1001).

Local Anaesthetic Techniques

Local anaesthetics are used in several techniques. In order of increasing level of anaesthesia they are: surface or topical anaesthesia; infiltration anaesthesia; and regional nerve block, including peripheral nerve block, sympathetic nerve block, and central nerve block which includes epidural and spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be given intravenously for regional anaesthesia in the extremities.

Infiltration anaesthesia

Infiltration anaesthesia is produced by injection of a local anaesthetic such as lidocaine or bupivacaine directly into and around the field of operation without attempting to identify individual nerves. The drug used should not be absorbed too rapidly otherwise the anaesthesia will wear off too quickly for practical use; some local anaesthetics require the addition of a vasoconstrictor in low concentrations, which can increase the duration of infiltration anaesthesia and reduce peak plasma concentrations of the local anaesthetic. Infiltration anaesthesia is extensively used in dentistry.

Anaesthesia of small areas by infiltration techniques requires a relatively large amount of local anaesthetic, which is not a problem for minor surgery but would be for more extensive areas that required anaesthesia. The amount of local anaesthetic used can be reduced and the duration of anaesthesia increased by blocking specific nerves that innervate the area. This may be carried out at several levels. In *field block* anaesthesia subcutaneous injection of a local anaesthetic close to the nerves around the area to be anaesthetised blocks sensory nerve paths. This is a form of infiltration anaesthesia, but the technique requires less drug for a given area to be anaesthetised.

Intravenous regional anaesthesia

Intravenous regional anaesthesia (Bier's block) involves injection of a dilute solution of local anaesthetic into a suitable limb vein after exsanguination and application of a tourniquet, in order to produce anaesthesia distal to it. Arterial flow must remain occluded for at least 20 minutes after injection and adrenaline should not be used. Intravenous regional anaesthesia may be used for short procedures where postoperative pain is not marked, such as manipulation of fractures and minor surgical procedures to the limbs. Although a safe procedure when performed correctly, complications have arisen; there have been fatalities associated with the use of bupivacaine, and prilocaine is the drug of choice. Facilities for resuscitation should be available.

Regional nerve block

Regional nerve block anaesthesia involves specific blocks at the levels of major nerves or spinal roots, and may include peripheral nerve block, sympathetic nerve block, and central nerve block including epidural and spinal block. For a discussion of the use of nerve blocks in the management of pain, see Nerve Blocks, above.

Central nerve block. Central nerve block includes epidural and spinal block.

Epidural block (also referred to as *extradural* or *peridural block*) is widely used to provide analgesia or anaesthesia in surgical and obstetric procedures. It involves injecting a local anaesthetic such as lidocaine, bupivacaine, or ropivacaine, alone or with a small dose of an opioid analgesic into the epidural space in the lumbar, sacral (*caudal block*), thoracic, or cervical regions. Introduction of a cannula into the epidural space enables prolonged analgesia or anaesthesia (epidural anaesthesia) to be provided through the use of 'top-up' doses or continuous infusion of the drugs. A vasoconstrictor is sometimes added to reduce systemic exposure to the local anaesthetic. A test dose at the intended injection site is recommended before starting epidural anaesthesia to ensure that the main dose is not accidentally injected intravascularly or into the subarachnoid space.

Spinal block (also referred to as *subarachnoid* or *intrathecal block*) is produced by injecting a solution of a suitable drug such as bupivacaine within the spinal subarachnoid space, causing temporary paralysis of the nerves with which it comes into contact. It may be used, for example, to produce spinal anaesthesia in surgical procedures on the lower body. Vasoconstrictors have been added to prolong the duration of the block but the effect is not always clinically useful and there is a danger of restricting the blood supply to the spinal cord; therefore this practice is not recommended. The somatic level at which anaesthesia occurs depends on many factors including the specific gravity or baricity of the anaesthetic solution used and the positioning of the patient.

For the adverse effects of and precautions for central block, see above.

Peripheral nerve block. Peripheral nerve block anaesthesia involves injection into or around a peripheral nerve or plexus supplying the part to be anaesthetised; motor fibres may be blocked as well as sensory fibres. *Brachial plexus block* is widely used for procedures involving the arm; lower limb blocks are less simple although *sciatic* and *femoral blocks* may be combined to permit surgery below the knee. Other peripheral nerve blocks such as those for the head and neck, or *intercostal* or *paravertebral blocks* for local anaesthesia of the trunk, are mostly highly specialised techniques. Lidocaine, prilocaine, bupivacaine, or ropivacaine have all been widely used for peripheral nerve blocks. Adrenaline is often added as a vasoconstrictor.

Pudendal block (usually with prilocaine) may be useful in obstetrics before forceps delivery, but as mentioned under Labour Pain on p.7, the technique of *paracervical local anaesthetic block* has largely fallen out of favour because of the high incidence of serious adverse effects on the fetus.

Sympathetic nerve block. Sympathetic nerve block such as *stellate ganglion blockade* and *lumbar sympathectomy* is used in the management of a range of painful conditions and vascular diseases (see under Complex Regional Pain Syndrome on p.6). Temporary block is obtained using local anaesthetics such as lidocaine or bupivacaine but permanent block may be produced with use of neurolytic agents such as phenol (see Pain, p.1657) or alcohol (see Pain, p.1627).

Surface anaesthesia

Surface or topical anaesthesia blocks the sensory nerve endings in the skin or mucous membranes. Many local anaesthetics are effective surface anaesthetics, a notable exception being procaine. Penetration of intact skin by most local anaesthetics is poor whereas absorption through mucous membranes may be rapid. However, reliable percutaneous anaesthesia can be achieved by application of a eutectic mixture of lidocaine and prilocaine to intact skin (see under Surface Anaesthesia in Lidocaine, p.1866). Eutectic mixtures may be of value in providing surface anaesthesia for a number of minor medical or surgical procedures. Tetracaine also provides reliable percutaneous anaesthesia. Other methods of dermal delivery of local anaesthetics include a transdermal patch of lidocaine (either alone or with tetracaine), an iontophoretic drug delivery system incorporating lidocaine and adrenaline. Anaesthesia of the skin and subcutaneous tissues is also discussed under Infiltration Anaesthesia, above.

There are a number of special uses of topical anaesthesia including anaesthetising the cornea during ophthalmological procedures and the throat and larynx before intubation and bronchoscopy. Absorption from the respiratory tract is rapid and care is essential to avoid giving a toxic dose. Great care is also necessary when using local anaesthetics to anaesthetise the urethra; if trauma has occurred, rapid absorption of the drug may occur and give rise to serious adverse effects.

Local anaesthetics have been included in topical preparations to relieve the pain of haemorrhoids (p.1697) but good evidence of their efficacy is lacking. Similar uses include pain relief in pruritus ani and anal fissure. Excessive application of local anaesthetics to the rectal mucosa should be avoided as absorption can occur; use for periods of no longer than a few days is recommended to prevent sensitisation of the anal skin. Local anaesthetics are sometimes included in topical preparations for the relief of pruritus (p.1582). However, they are only marginally effective and can very occasionally cause sensitisation. The use of local anaesthetics in rubefacient and topical analgesic preparations is mentioned on p.5.

Amylocaine Hydrochloride *(BANM)*

Amilocaína, hidrocloruro de; Amyleinii Chloridum; Amylocain. Hydrochlor.; Chlorhydrate d'Amyléine. 1-(Dimethylaminomethyl)-1-methylpropyl benzoate hydrochloride.

$C_{14}H_{21}NO_2,HCl = 271.8.$

CAS — 532-59-2 (amylocaine hydrochloride); 644-26-8 (amylocaine hydrochloride).

Profile

Amylocaine, a benzoic acid ester, is a local anaesthetic (p.1850) used mainly as the hydrochloride in a range of preparations for application to the skin or mucous membranes. It has also been used in preparations for the relief of painful anorectal conditions and has been included in oral mixtures for the relief of coughs.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Dolodent.

Multi-ingredient: ***Belg.:*** Dentophar; Odonto-Baby; Rectovasol; ***Braz.:*** Fonergin; Hemodotti; ***Cz.:*** Avenoc; ***Fr.:*** Collustan†; Elenol; Parkipan†; Pulmoll; ***Hong Kong:*** Frazoline; ***Ital.:*** Dentinale; Proctosedyl; ***Spain:*** Hemodren Compuesto†; ***Thai.:*** Bacal; Basina; Biochin†; Izac†; Medcin; Mybacin.

Articaine Hydrochloride *(BANM, USAN, rINNM)*

40045; Articaïne, chlorhydrate d'; Articaini hydrochloridum; Artikaiinihydrokloridi; Artikain Hidroklorür; Artikain-hidroklorid; Artikain-hydrochlorid; Artikainhydroklorid; Artikaino hidrochloridas; Carticaine Hydrochloride; Carticaini Hydrochloridum; Hidrocloruro de articaína; Hoe-045; Karticainhydroklorid; Kartikaiinihydrokloridi; Kartikain Hidroklorür. Methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate hydrochloride.

Артикаина Гидрохлорид

$C_{13}H_{20}N_2O_3S,HCl = 320.8.$

CAS — 23964-58-1 (articaine); 23964-57-0 (articaine hydrochloride).

ATC — N01BB08.

ATC Vet — QN01BB08.

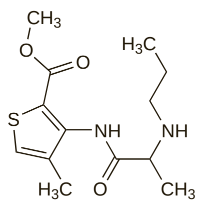

(articaine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Articaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

Profile

Articaine hydrochloride is an amide local anaesthetic (p.1850). It has been used as a 1 or 2% solution with or without adrenaline for infiltration and regional anaesthesia. A 4% solution of articaine hydrochloride with adrenaline is used similarly in dentistry. A hyperbaric solution of articaine hydrochloride with glucose has been used for spinal block.

Porphyria. Articaine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Septanest; Ubistesin; Ultracain Dental; ***Belg.:*** Ubistesin†; ***Canad.:*** Astracaine†; ***Cz.:*** Septanest S; Supracain; Ubistesin; Ultracain D-S†; Ultracain†; ***Denm.:*** Septanest; Septocaine; Ubistesin; ***Fin.:*** Septocaine; Ubistesin; Ultracain D-Suprarenin; ***Fr.:*** Alphacaine; Predesic†; Ubistesin Adrenalinee; ***Ger.:*** Ubistesin; Ultracain; Ultracain D-S; Ultracain hyperbar†; Ultracain Suprarenin; ***Hong Kong:*** Ubistesin; ***Hung.:*** Ubistesin; Ultracain D-S; ***Ital.:*** Alfacaina; Cartidont; Citocartin; Primacaine†; Sarticain; Septanest; Ubistesin; ***Neth.:*** Septanest; Ubistesin; Ultracain D-S; ***Norw.:*** Septocaine; ***NZ:*** Septanest; ***Port.:*** Alphacaine; Artinibsa; Artinostrum; Meganest; Septanest; Ubistesin; ***Rus.:*** Ultracain (Ультракаин); ***Spain:*** Articaina C/E; Meganest; Ultracain; ***Switz.:*** Alphacaine; Rudocaine; Septanest; Ubistesin; Ultracaine D-S; ***Turk.:*** Ultracain; ***UK:*** Septanest; ***USA:*** Septocaine.

Benzocaine *(BAN, rINN)*

Anaesthesinum; Anestezin; Anesthamine; Bensokain; Bentsokaiini; Benzocaína; Benzocaïne; Benzocainum; Benzokain; Benzokaina; Benzokainas; Ethoform; Éthoforme; Ethyl Aminobenzoate; Ethylis Aminobenzoas. Ethyl 4-aminobenzoate.

Бензокаин

$C_9H_{11}NO_2 = 165.2.$

CAS — 94-09-7.

ATC — C05AD03; D04AB04; N01BA05; R02AD01.

ATC Vet — QC05AD03; QD04AB04; QN01AX92; QN01BA05; QR02AD01.

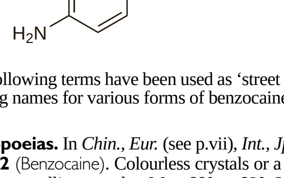

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of benzocaine:

Coco snow.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Benzocaine). Colourless crystals or a white or almost white, crystalline powder. M.p. 89° to 92°. Very slightly soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Benzocaine). Small, white crystals or a white odourless crystalline powder. M.p. 88° to 92°. Soluble 1 in 2500 of water, 1 in 5 of alcohol, 1 in 2 of chloroform, 1 in 4 of ether, and 1 in 30 to 50 of almond oil or olive oil; dissolves in dilute acids.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Abuse. Benzocaine has been used as an adulterant or 'cutting' agent in the preparation of cocaine for illicit use and adverse effects such as methaemoglobinaemia have been seen after cocaine overdosage as a result of the benzocaine content.[1]

1. McKinney CD, *et al.* Benzocaine-adultered street cocaine in association with methemoglobinemia. *Clin Chem* 1992; **38:** 596–7.

Hypersensitivity. The incidence of positive reactions in patients patch tested with benzocaine has ranged from 3.3 to 5.9%.[1,2] Patch testing with benzocaine has been recommended by The International Contact Dermatitis Research Group as an indicator of contact hypersensitivity to local anaesthetics. However, it was found that of 40 patients who had had positive reactions to benzocaine with tetracaine and cinchocaine, 21 were not allergic to benzocaine alone.[3]

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.
2. Bandmann H-J, *et al.* Dermatitis from applied medicaments. *Arch Dermatol* 1972; **106:** 335–7.
3. Beck MH, Holden A. Benzocaine—an unsatisfactory indicator of topical local anaesthetic sensitization for the UK. *Br J Dermatol* 1988; **118:** 91–4.

Precautions

As for Local Anaesthetics in general, p.1851.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

See under Local Anaesthetics, p.1852.

Uses and Administration

Benzocaine, a para-aminobenzoic acid ester, is a local anaesthetic used for surface anaesthesia (p.1853); it has low potency and low systemic toxicity. It is used, often with other drugs such as analgesics, antiseptics, antibacterials, antifungals, and antipruritics, for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, haemorrhoids, anal pruritus, and ear pain.

Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat. Gels, pastes, solutions, and sprays containing benzocaine in concentrations of up to 20% have been used for surface anaesthesia of the mouth and throat.

Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations up to 20% for topical analgesia and anaesthesia.

Benzocaine has also been used as the hydrochloride.

Obesity. It has been reported[1] that despite the inclusion of benzocaine in some over-the-counter appetite suppressants there is no good evidence of its value in obesity (p.2149).

1. Anonymous. A nasal decongestant and a local anesthetic for weight control? *Med Lett Drugs Ther* 1979; **21:** 65–6.

Preparations

USP 31: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Benzocaine and Menthol Topical Aerosol; Benzocaine Cream; Benzocaine Gel; Benzocaine Lozenges; Benzocaine Ointment; Benzocaine Otic Solution; Benzocaine Topical Aerosol; Benzocaine Topical Solution; Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cerax; Lanacaina†; Lodoc; ***Austral.:*** Applicaine; ***Austria:*** Anaestherit; ***Braz.:*** Solarcaine; ***Canad.:*** Anbesol; Anbesol Baby; Anbesol Extra Strength; Baby Orajel; Detane†; Maintain; ManDelay; Orajel; Outgro; Zilactin Baby; Zilactin Tooth & Gum Pain Reliever; Zilactin Toothache Swab; Zilactin-B; ***Chile:*** Anbesol; Baby Orajel†; BBdent Gel Topico; Dentispray; Foille; Kalmafta; Orajel†; ***Cz.:*** Babydent; ***Ger.:*** Anaesthesin; Anaesthesin N; Flavamed Halstabletten†; Kontakto Derm†; Labocane; Subcutin N; Zahnerol N†; ***Hung.:*** Babydent; ***Israel:*** Anadent; Baby Gel; Lanacane; Maintain; ***Mex.:*** Auralyt; Gomas Garde B; Graneodin B; ***NZ:*** Solarcaine; ***Pol.:*** Baby Orajel; Orajel; ***Port.:*** Dentispray; Topigel; ***Rus.:*** Relief Advance (Релиф Адванс); ***S.Afr.:*** Kiddigum; ***Spain:*** Dentispray; Gartricin†; Hurricaine; Lanacane; Nani Pre Dental; ***UK:*** AAA; Burneze; Lanacane; Orajel; Ultra Chloraseptic; Ultracare; ***USA:*** Americaine Anesthetic†; Americaine Otic†; Americaine†; Baby Anbesol; Baby Orajel; Benz-O-Sthetic; Benzodent; Chigger-Tox; Dent's Extra Strength Toothache Gum; Dent's Maximum Strength Toothache Drops; Dent-O-Kain; Dermoplast; Detane; Hurricaine; Lanacane; Medicone; Mycinettes; Numzident†; Orabase Baby; Orabase Gel; Orabase-B; Orajel; OraMagic Plus; Otocain; SensoGARD; Trocaine; Zilactin-B Medicated.

Multi-ingredient: ***Arg.:*** Adermicina; Adermicina A; Algiodent; Anginotrat; Apracur Bucofaringeo†; Arnecrem†; Aseptobron Caramelos; Aseptobron N; Bagociletas; Balsamina; Bucoangin N; Bucotricin; Caext; Callicida; Caramelos Antibioticos; Caramelos Antibioticos Lefmar; Caramelos Oriental; Carnot Colutorio; Cartiflex; Collubiazol; Coltix†; Cristalomicina; Dermo Vagisil Crema; Dermosan; Detebencil; Dotrin; Esculeol P; Esmedent con Fluor; Fanaletas; Filotricin A; Flebotropin†; Fonergine; Gargaletas; Graneodin; Graneodin N; Hexa-Defital; Iodotiazol†; Leroid†; Lyndan; Muco-Anestyl†; Mucobase; Muelita; Nene Dent; Neo Coltirot; No-Tos Pocket; Oralsone C; Otocalmia; Otoseptil; Parencias†; Pastillas Lorbi; Pastillas Medex; Pruripelen†; Pulmosan Caramelos; Razagleda Plus†; Salicrem; Sapucai†; Suavisan N; Suavisan†; Sulfanoral T; Tavinex; ***Austral.:*** Animine; Auralgan; Ayrton's Chilblain; Cepacaine; Cepacol Anaesthetic; Cepacol Cough & Sore Throat; Cornkil†; Le Trim-BM†; Nyal Toothache Drops; Rectinol; ***Austria:*** Dequalinetten; Dorithricin; Herposicc; Sulgan 99; Tyrothricin comp; Tyrothricin compositum; ***Belg.:*** Transvane; ***Braz.:*** Albicon; Amidalin†; Amigdagen; Amigdamicin†; Andolba; Anginotricin; Bromil; Cepacaina; Cetildrops†; Claudemor; Dentalivio†; Dequadin; Fenotricin†; Gargotan†; Gingilone; Larintil†; Malvatricin Pastilhas; Malvona†; Mentozil†; Mirorroidin†; Neopiridin; Otovix†; Passilin†; Predmicin; Sanilin; Senol†; Silencium; Traumac; ***Canad.:*** Anbesol Maximum Strength; Antibiotic Cold Sore Ointment; Appedrine†; Auralgan; Bionet; Boil Ease†; Cepacol Extra Strength; Chloraseptic Lozenges; Dexatrim†; Endospray†; Kank-A; Lanacane Medicated Cream; Onrectal; Orajel Mouth Sore Medicine; Orajel Ultra Mouth Sore; Osmopak-Plus; Oxipor; Rectogel; Rectogel HC; Solarcaine; Sore Throat Lozenges; Tanac; Thermo-Gel; Throat Lozenges; Thunas Pile†; Vagisil; ***Chile:*** Aucusik; Cariamyl; Kank-Eze; Konirub; Lerfimin; Medikem†; Orajel Compuesto†; Otandrol; Solarcaine Spray Aerosol; ***Cz.:*** Dr Rentschler Halstabletten†; Herbadent; Hexoral; Hexoraletten N; ***Denm.:*** Dolodent; Hexokain; ***Fin.:*** Bafucin; Toncils; ***Fr.:*** Nestosyl; Sedorrhoide; ***Ger.:*** Anaesthesin-Rivanol; Combustin Heilsalbe; Dolo-Dobendan; Dorithricin Original; Eulatin NN; Frubizin Forte†; Gelum†; Hexoraletten N; Inspirol Halsschmerztabletten†; Nordapanin N†; Nordathricin N†; Salistoperm†; Stipo†; Trachiform†; Tyrosolvetten†; ***Gr.:*** Myalgesic†; ***Hong Kong:*** Borraginol-N; Pharynx; Setronges†; Tyricine; Tyrocaine; Tyrothricin Co; ***Hung.:*** Almagel A; Dorithricin; ***India:*** Chloromycetin Ear Drops; Clearwax; Healex; Nit-N-Mite†; Paraxin Ear†; Perfocyn; Proctosedyl; Scaboma; Tytin; Waxolve; ***Indon.:*** Benzomid; Borraginol-N; Borraginol-S; FG Ointment; Otolin; ***Irl.:*** Dequacaine; Merocaine; Tyrozets; ***Israel:*** Anadent†; Dentin; Gingisan; Hemo; Kalgaron; Kank-A; Noxacorn; Otomycin; Proctozorin-N; Pronestin; Rafathricin with Benzocaine; Rectozorin; ***Ital.:*** Antiscabbia Candioli al DDT Terapeutico; Antiscabbia CM; Boma; Dentosedina; Fialetta Odontalgica Dr Knapp; Foille Scottature; Foille Sole; Golamixin; Labocaina; Pinselina Knapp; Prepacort H; Preparazione Antiemorroidaria†; Proctidol; Proctosedyl; Proctosoll; Sedalen Cort†; Sedilene Procto†; ***Malaysia:*** Cetylpyridinium B; Horf; Pharynx; Setronges†; ***Mex.:*** Cepacaina; Cloran Otico; Graneodin D Mentol; Ofodex; Otifar; Otolone†; Soldrin; Sufrexal P; Trociletas B; ***NZ:*** Auralgan; Cepacaine; Cepacol Anaesthetic; Cepacol Cough Discs; Lanacane; Solarcaine; Toothache Drops†; ***Philipp.:*** Auralgan; United Home Burn Ointment; ***Pol.:*** Dentosept A; Dermopur; Hemorol; Icy Rub; Puder Plynny; Puder Plynny z Anestezyna; Pudroderm; Pudrospan; Rectosec; Sanofil; Sapoven AT; Savarix; Septolete Plus; Variderm; ***Port.:*** Afonina; Anginova; Claudemor†; Dek; Dropcina; Halitol†; Hibitane Menta†; Hibitane†; Medifon; Mentocaina R; Otoceril; Solpic†; Tantum Verde; ***Rus.:*** Almagel A (Алмагель А); Anaesthesol (Анестезол); Heparin Ointment (Гепариновая Мазь); Nigepan (Нигепан); Septolete Plus (Септолете Плюс); ***S.Afr.:*** AAA†; Auralyt; Aurasept; Aurone Forte; Benzet†; Calasthetic; Cepacaine; Cepacol Cough Discs; Cetoxol; Covancaine; Covotop; Endcol Lozenges; Histamed; Medi-Kain†; Medi-Keel A; Orochlor; Otised; Oto-Phen Forte; Oxipor VHC; Prodol; Trochain; Viodor; ***Singapore:*** Dorithricin; Pharynx; ***Spain:*** Angileptol; Antihemorroidal; Bucodrin; Bucometasana; Bucospray; Callicida Rojo; Callivoro Marthand; Callix; Caltoson Balsamico; Cicatral; Cremsol; Dentikrisos; Diformiltricina; Drill; Edifaringen; Faringenilo; Faringesic; Gargaril; Garydol; Gradin Del D Andreu†; Grietalgen; Grietalgen Hidrocort†; Hemoal; Hemodren Compuesto†; Hibitane; Mastiol; Miozets; Nasopomada; Neo Analsona; Oto Difusor†; Oto Vitna†; Otocerum; Otonina†; Otosedol Biotico; Pastillas Koki Ment Tiro; Phonal; Sedofarin; Topicaina†; Tos Mai; Vicks Formula 44†; ***Swed.:*** Bafucin; ***Switz.:*** Benzocaine PD; Neocones; ***Thai.:*** Auralgan†; Doproct; Iwazin; Sigatricin; Trocacin; Troneo†; ***Turk.:*** Emedur; Kataljin; Kortos; Ma-Ka-Ta; ***UK:*** Anthisan Plus; Dequacaine; Intralgin†; Merocaine; Rinstead; Solarcaine; Tyrozets; Wasp-Eze; ***USA:*** Aerocaine†; Allergen; Americaine First Aid†; Anbesol; Anbesol Cold Sore Therapy; Auralgan; Auroguard Otic; Auroto†; Babee; Bicozene; Boil Ease; Boyol Salve; Calamycin; Cepacol Anesthetic; Cepacol Maximum Strength Sore Throat; Cepacol Ultra Sore Throat Plus Cough; Cetacaine; Chiggerex; Chloraseptic Sore Throat; Cough-X; Cy-Gesic; Cylex; Dendracin Neurodendtraxcin; Dentapaine; Dermacoat; Dermasept Antifungal; Dermoplast Antibacterial; Double-Action Toothache Kit; Foille; Fungi-Nail; Hem-Prep; Kank-A; Legatrin Rub; Lipmagik; Maximum Strength Anbesol; Medicone Derma†; Numzit†; Orabase Lip; Orajel Mouth Aid; Orajel PM; Orasept; Orasol; Otocalm†; Pazo; Rectagene Medicated Rectal Balm; Rid-a-Pain; Solarcaine; Soothaderm; Sting-Eze; Sting-Kill; Tanac; Tanac Dual Core; Therevac Plus; Tigan†; Toothache Gel; Triban†; Tympagesic†; Unguentine Maximum Strength; Vagi-Gard Medicated Cream; Vagisil; Z-Xtra; ***Venez.:*** Claudemor†; Otan; Otofrin†.

Bupivacaine Hydrochloride

(BANM, USAN, rINNM)

AH-2250; Bupivacaïne, chlorhydrate de; Bupivacaini hydrochloridum; Bupivacaini Hydrochloridum Monohydricum; Bupivakaiinihydrokloridi; Bupivakain Hidroklorür; Bupivakain-hidroklorid; Bupivakain-hydrochlorid monohydrát; Bupivakainhydroklorid; Bupivakaino hidrochloridas; Bupiwakainy chlorowodorek; Hidrocloruro de bupivacaína; LAC-43; Win-11318. (±)-(1-Butyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride monohydrate.

Бупивакаина Гидрохлорид

$C_{18}H_{28}N_2O,HCl,H_2O = 342.9.$

CAS — 2180-92-9 (bupivacaine); 18010-40-7 (anhydrous bupivacaine hydrochloride); 14252-80-3 (bupivacaine hydrochloride monohydrate).

ATC — N01BB01.

ATC Vet — QN01BB01.

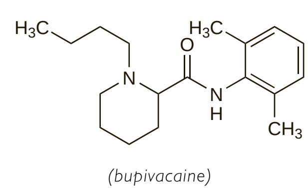

(bupivacaine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Bupivacaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Bupivacaine Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in acetone and in chloroform. A 1% solution in water has a pH of 4.5 to 6.0.

Stability of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

For reference to the stability of admixtures of bupivacaine and fentanyl in solution, with or without adrenaline, see under Fentanyl, p.56.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Bupivacaine appears to be more cardiotoxic than other local anaesthetics. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts.

◊ For reference to the toxic threshold for bupivacaine plasma concentrations, see Absorption under Pharmacokinetics, below.

Effects on the cardiovascular system. Bupivacaine[1,2] and etidocaine[2] appear to be more cardiotoxic than most other commonly used local anaesthetics and marked cardiovascular depression may occur at plasma concentrations only slightly above those for CNS toxicity.[2] Fatalities have occurred. Simultaneous seizures and cardiovascular collapse may develop rapidly on inadvertent intravascular injection and even prompt oxygenation and blood pressure support might not prevent cardiac arrest.[2] Ventricular fibrillation which is very resistant to normal methods of defibrillation may develop. Since lidocaine and the other local anaesthetics have additive effects on the CNS bretylium may be preferable to lidocaine for the treatment of induced arrhythmias.[1] Seizures and life-threatening ventricular fibrillation have also been reported after systemic absorption of bupivacaine solutions in an adolescent patient undergoing wound debridement.[3] Fatal cardiotoxicity has occurred after the use of bupivacaine in intravenous regional anaesthesia, possibly due to leakage past the tourniquet, and the use of bupivacaine in this technique should be avoided.[1] Fatalities have also been associated with the use of 0.75% solutions for epidural anaesthesia in obstetric patients and this strength is no longer recommended for obstetric anaesthesia. See also Labour Pain under Uses and Administration, below.

1. Anonymous. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; **ii:** 1192–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51:** 285–7.
3. Yan AC, Newman RD. Bupivacaine-induced seizures and ventricular fibrillation in a 13-year-old girl undergoing wound debridement. *Pediatr Emerg Care* 1998; **14:** 354–5.

Effects on the eyes. Bilateral retinal haemorrhages developed in a 47-year-old woman[1] after receiving a caudal block with bupivacaine 0.5%. The haemorrhages cleared and her usual vision returned by 3 months.

1. Ling C, *et al.* Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993; **77:** 316–17.

Prolonged block. Use of bupivacaine in regional anaesthesia may result in prolonged block.[1,2]

1. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. *Br J Anaesth* 1975; **47:** 520–2.
2. Brockway MS, *et al.* Prolonged brachial plexus block with 0.42% bupivacaine. *Br J Anaesth* 1989; **63:** 604–5.

Precautions

As for Local Anaesthetics in general, p.1851.

Bupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Renal impairment. Spinal block was more rapid in onset and of shorter duration in patients with chronic renal failure given 3 mL of bupivacaine 0.75% than in control patients.[1]

1. Orko R, *et al*. Subarachnoid anaesthesia with 0.75% bupivacaine in patients with chronic renal failure. *Br J Anaesth* 1986; **58:** 605–9.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Antiarrhythmics. There is an increased risk of myocardial depression when bupivacaine and antiarrhythmics are given together.

Beta blockers. *Propranolol* reduced the clearance of bupivacaine by 35% in 6 healthy subjects.[1] There is a risk of increased bupivacaine toxicity if these drugs are used together.

1. Bowdle TA, *et al.* Propranolol reduces bupivacaine clearance. *Anesthesiology* 1987; **66:** 36–8.

Calcium-channel blockers. There is a theoretical risk that the adverse effects of bupivacaine on the heart might be enhanced in patients taking calcium-channel blockers, but evidence of a clinical problem is lacking.

Histamine H_2-antagonists. Studies of the effect of H_2-antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While a group of workers[1] found that pretreatment with *cimetidine* decreased the clearance of bupivacaine, others have failed to find any significant pharmacokinetic effects.[2,3] Similarly, pretreatment with *ranitidine* has either increased plasma concentrations of bupivacaine[4] or had no significant effect.[3]

1. Noble DW, *et al.* Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* 1987; **59:** 735–7.
2. Pihlajamäki KK. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* 1988; **26:** 403–6.
3. Flynn RJ, *et al.* Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* 1989; **62:** 87–91.
4. Wilson CM. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* 1986; **58:** 1330P–1331P.

Local anaesthetics. For reference to the effect of bupivacaine on the protein binding of *lidocaine* and *mepivacaine*, see p.1864 and p.1866, respectively.

Pharmacokinetics

Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine mainly as metabolites with only 5 to 6% as unchanged drug.

Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

See also under Local Anaesthetics, p.1852.

Absorption. The toxic threshold for bupivacaine plasma concentrations is considered by some[1] to lie in the range of 2 to 4 micrograms/mL and in the UK the maximum single recommended dose for anhydrous bupivacaine hydrochloride is 150 mg (equivalent to about 2 mg/kg). Giving bupivacaine for *regional anaesthesia* of the head and neck in a mean total dose of 3.4 mg/kg has produced mean peak plasma concentrations of 3.56 micrograms/mL (with adrenaline) and 4.95 micrograms/mL (without adrenaline), without producing toxicity.[2] Similarly, *intrapleural* bupivacaine 0.5% in a dose of 2.5 mg/kg has produced mean peak plasma concentrations of 2.57 and 3.22 micrograms/mL (with or without adrenaline, respectively) without producing toxicity.[3] A further study[4] in which a 72-hour interpleural infusion of bupivacaine hydrochloride with adrenaline was given to cholecystectomy patients showed appreciable interpatient variability in steady-state plasma drug concentrations (range 1.3 to 3.2 micrograms/mL; mean 2.1 micrograms/mL); no patient suffered any adverse effects. Bilateral *intercostal* nerve blocks using bupivacaine 2 mg/kg have also produced concentrations within the presumed toxic range without adverse effects but the use of adrenaline with this block did not reliably reduce peak plasma-bupivacaine concentrations.[5]

Stellate ganglion block with bupivacaine 0.25% has produced a mean peak plasma concentration of 0.34 and 0.47 micrograms/mL after doses of 10 or 20 mL, respectively.[6] Giving bupivacaine 0.5% in a dose of 3 mg/kg with or without adrenaline for *sciatic* and *femoral nerve block* produced mean peak plasma concentrations below 0.8 micrograms/mL.[7]

Intra-articular bupivacaine is rapidly absorbed from the synovial membrane of the knee during arthroscopy but plasma concentrations did not exceed 0.35 micrograms/mL after controlled pressure-irrigation with isotonic solutions containing up to 200 mg.[8] Although a group of workers found that the maximum plasma concentrations of bupivacaine after intra-articular injection of 30 mL of a 0.5% solution for arthroscopy was 0.875 micrograms/mL they suggested that adrenaline should probably be added to minimise absorption.[9]

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; **56:** 485–92.
3. Gin T, *et al.* Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. *Br J Anaesth* 1990; **64:** 662–6.
4. Kastrissios H, *et al.* The disposition of bupivacaine following a 72h interpleural infusion in cholecystectomy patients. *Br J Clin Pharmacol* 1991; **32:** 251–4.
5. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* 1990; **64:** 436–41.
6. Hardy PAJ, Williams NE. Plasma concentrations of bupivacaine after stellate ganglion block using two volumes of 0.25% bupivacaine plain solution. *Br J Anaesth* 1990; **65:** 243–4.
7. Misra U, *et al.* Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; **66:** 310–13.
8. Debruyne D, *et al.* Monitoring serum bupivacaïne levels during arthroscopy. *Eur J Clin Pharmacol* 1985; **27:** 733–5.
9. Butterworth JF, *et al.* Effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection of bupivacaine for knee arthroscopy. *Br J Anaesth* 1990; **65:** 537–9.

Surface anaesthesia. Studies of the absorption of bupivacaine after surface application.

1. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.

Pregnancy. Bupivacaine crosses the placenta to a lesser degree than lidocaine or mepivacaine following maternal injection. Values of 0.2 to 0.4 have been reported[1,2] for the ratio of fetal to maternal concentrations for bupivacaine compared with values of 0.5 to 0.7 quoted[2,3] for lidocaine and mepivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the fetal circulation[2] (see also under Protein Binding, below). Addition of adrenaline to the injection does not appear to affect the placental transfer rate of bupivacaine.[4] Measurement of a beta-phase half-life of 25 hours in the neonate compared with 1.25 hours in mothers suggests that the neonate is less able to metabolise bupivacaine.[5]

1. Denson DD, *et al.* Serum bupivacaine concentrations in term parturients following continuous epidural analgesia for labor and delivery. *Ther Drug Monit* 1984; **6:** 393–8.
2. Blogg CE, Simpson BR. Obstetric analgesia and the newborn baby. *Lancet* 1974; **i:** 1283.
3. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
4. Reynolds F, *et al.* Effect of time and adrenaline on the feto-maternal distribution of bupivacaine. *Br J Anaesth* 1989; **62:** 509–14.
5. Caldwell J, *et al.* Pharmacokinetics of bupivacaine administered epidurally during childbirth. *Br J Clin Pharmacol* 1976; **3:** 956P–957P.

Protein binding. The two major binding proteins for bupivacaine in the blood are α_1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α_1-acid glycoprotein for bupivacaine but has no effect on albumin affinity.[1] Binding of bupivacaine is reduced during pregnancy but it is considered that the increase in free bupivacaine concentrations is unlikely to cause a clinically significant increase in the risk of CNS or cardiovascular toxicity.[2]

As fetal plasma contains little α_1-acid glycoprotein the binding capacity for bupivacaine is reduced and this may contribute to the difference between maternal and fetal plasma concentration at delivery[3] (see also under Pregnancy, above).

Ageing, uncomplicated by disease, does not affect the protein binding of bupivacaine.[4]

1. Denson D, *et al*. Alpha -acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 1984; **35:** 409–15.
2. Denson DD, *et al.* Bupivacaine protein binding in the term parturient: effects of lactic acidosis. *Clin Pharmacol Ther* 1984; **35:** 702–9.
3. Petersen MC, *et al.* Relationship between the transplacental gradients of bupivacaine and α -acid glycoprotein. *Br J Clin Pharmacol* 1981; **12:** 859–62.
4. Veering BT, *et al.* Age does not influence the serum protein binding of bupivacaine. *Br J Clin Pharmacol* 1991; **32:** 501–3.

Uses and Administration

Bupivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It has a slow onset and a long duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor, and absorption into the circulation from the site of injection is reduced. Slow accumulation occurs with repeated doses. It is used mainly for infiltration anaesthesia and regional nerve blocks, particularly epidural block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural block in obstetrics. (Local anaesthetic techniques are discussed on p.1853.)

Bupivacaine is a racemic mixture but the *S*(−)-isomer levobupivacaine (see p.1862) is also used. The carbonated solution of bupivacaine is also available for injection in some countries (see p.1852).

In recommended doses bupivacaine produces complete sensory blockade but the concentration of bupivacaine solution used affects the extent of motor blockade achieved. A 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce motor block and some muscle relaxation, and complete motor block and muscle relaxation can be achieved with a 0.75% solution.

The dosage of bupivacaine used depends on the site of injection and the procedure used, as well as the status of the patient. Bupivacaine is given as the hydrochloride monohydrate salt although doses are expressed in terms of the anhydrous hydrochloride; bupivacaine hydrochloride monohydrate 10.55 mg is equivalent to about 10 mg anhydrous bupivacaine hydrochloride. In the UK the suggested general **maximum single dose** of bupivacaine hydrochloride is 150 mg with or without adrenaline followed if necessary by doses of up to 50 mg every 2 hours. In the USA the recommended maximum single dose is 175 mg of the plain preparation or 225 mg when given with adrenaline; doses may be repeated at intervals of not less than 3 hours but the total daily dose should not exceed 400 mg. The dose should be reduced in the elderly, in children, in debilitated patients, and in cardiac or hepatic disease.

A test dose of bupivacaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Subsequent doses should be given in small increments.

Solutions with or without adrenaline may be used for most **local anaesthetic techniques** and procedures apart from dental infiltration, when adrenaline is added to the solution (see below).

- For *infiltration anaesthesia* bupivacaine hydrochloride is typically used as a 0.25% solution in doses up to the recommended maximum (see above). When a longer duration of anaesthesia is required, as in dental or surgical procedures of the maxillary and mandibular area, a 0.5% solution with adrenaline 1 in 200 000 has been used but a total dose of 90 mg (18 mL) should not be exceeded over a single dental sitting.
- For *peripheral nerve block* the usual dose is 12.5 mg (5 mL) as a 0.25% solution or 25 mg (5 mL) as a 0.5% solution, although doses up to the recommended maximum single dose (see above) may also be given. A 0.75% solution has been used for *retrobulbar block* in ophthalmic surgery in a dose of 15 to 30 mg (2 to 4 mL).
- For *sympathetic nerve block* 50 to 125 mg (20 to 50 mL) as a 0.25% solution is recommended.
- For *lumbar epidural block* in surgery a 0.25% solution of bupivacaine hydrochloride may be used in a dose of 25 to 50 mg (10 to 20 mL) or as a 0.5% solution in a dose of 50 to 100 mg (10 to 20 mL). A 0.75% solution is also used for induction of lumbar epidural block in non-obstetric surgery in a single dose of 75 to 150 mg (10 to 20 mL). For *caudal block* in surgery 37.5 to 75 mg (15 to 30 mL) as a 0.25% solution or 75 to 150 mg (15 to 30 mL) as a 0.5% solution may be used. In the management of **acute pain** bupivacaine may be given as an epidural bolus or by continuous infusion. For analgesia during *labour*, doses of 15 to 30 mg (6 to 12 mL) as a 0.25% solution or 30 to 60 mg (6 to 12 mL) as a 0.5% solution have been recommended as a bolus for lumbar block. Alternatively, when given as an infusion, a dose of 10 to 15 mg (10 to 15 mL) per hour as a 0.1% solution or 10 to 15 mg (8 to 12 mL) per hour as a 0.125% solution has been recommended for lumbar block. Bupivacaine may also be given as a bolus caudal injection for labour pain; doses of 25 to 50 mg (10 to 20 mL) as a 0.25% solution or 50 to 100 mg (10 to 20 mL) as a 0.5% solution are recommended. For *postoperative pain* bupivacaine may be given as an epidural infusion in doses of 4 to 15 mg (4 to 15 mL) per hour as a 0.1% solution or 5 to 15 mg (4 to 12 mL) per hour as a 0.125% solution.
- Hyperbaric solutions of bupivacaine hydrochloride without adrenaline may be used for *spinal block*. Preparations containing 0.5% are available and are given in doses of 10 to 20 mg (2 to 4 mL).

Action. Addition of potassium chloride 0.2 mmol to 40 mL of bupivacaine 0.25% solution resulted in a more rapid onset of sensory loss than the same dose of plain bupivacaine in patients undergoing brachial plexus block for forearm or hand surgery.[1]

Hyaluronidase did not increase the speed of onset of brachial plexus block produced by bupivacaine 0.5%, with or without adrenaline, but did reduce the duration of anaesthesia.[2]

Bupivacaine encapsulated in liposomes can prolong postsurgical analgesic action without motor block.[3,4]

For a comparison of the vasoactivity of bupivacaine and some other local anaesthetics, see p.1852.

1. Parris MR, Chambers WA. Effects of the addition of potassium to prilocaine or bupivacaine: studies on brachial plexus blockade. *Br J Anaesth* 1986; **58:** 297–300.
2. Keeler JF, *et al.* Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992; **68:** 68–71.
3. Boogaerts S, *et al.* Epidural administration of liposomal bupivacaine for the management of postsurgical pain. *Br J Anaesth* 1993; **70:** (suppl 1): 104.
4. Boogaerts JG, *et al.* Pharmacokinetic-pharmacodynamic specific behaviour of liposome-associated bupivacaine in humans. *Br J Anaesth* 1995; **74** (suppl 1): 74.

Administration in children. Bupivacaine 0.25% injected intra-operatively up to a maximum dose of 1.5 mg/kg with adrenaline has been used in infants for the control of postoperative pain due to pyloromyotomy and appears to attenuate some of the cardiac and respiratory effects associated with the use of general anaesthesia alone.[1] Doses of 2.5 mg of bupivacaine for each year of age, as a 0.5% solution, have been used for ilio-inguinal nerve block in children undergoing herniotomy.[2] A study[3] in infants undergoing abdominal surgery found that an epidural infusion of bupivacaine produced comparable analgesia to an intravenous infusion of morphine. It was considered that bupivacaine might be preferable to morphine in neonates and young infants who are particularly prone to respiratory depression, but older children might require additional sedation or analgesia to prevent postoperative restlessness.

1. McNicol LR, *et al.* Peroperative bupivacaine for pyloromyotomy pain. *Lancet* 1990; **335:** 54–5.
2. Smith BAC, Jones SEF. Analgesia after herniotomy in a paediatric day unit. *BMJ* 1982; **285:** 1466.
3. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70:** 10–16.

Labour pain. For a discussion of the management of labour pain, including mention of the use of local anaesthetics, see p.7.

Early experience in nearly 1000 patients suggested that 8 mL of a 0.5% solution of bupivacaine with adrenaline was the optimum dose for epidural block during labour;[1] pain relief lasted for about 2 hours. Decreasing the concentration of the final dose to 0.25% reduced the persistence of sensory and motor nerve block after delivery. Others[2] found that bupivacaine 0.375% was the most suitable concentration for epidural analgesia when using a regimen of regular 'top-up' doses of 0.5 mg/kg about every 90 minutes. However, the use of low doses of bupivacaine 0.25% for epidural analgesia in primiparous women was associated with a lower incidence of forceps delivery and oxytocin augmentation.[3] Although an even lower concentration of bupivacaine (0.0625%) used with sufentanil[4] produced analgesia similar to that with 0.125% bupivacaine used alone, the duration of the second stage of labour and the incidence of instrumental and surgical delivery were not reduced. Similar results were obtained using bupivacaine 0.0625% with diamorphine 0.005%; in addition pruritus and drowsiness produced by diamorphine were considered to be troublesome in many patients.[5] However, a large UK study[6,7] compared a traditional epidural regimen using 10 mL boluses of bupivacaine 0.25% given up to every hour, with two lower-dose regimens using bupivacaine 0.1% with fentanyl 2 micrograms/mL, and found the lower dose techniques were at least as effective and were associated with a lower incidence of instrumental delivery.

Combined spinal-epidural blocks, in which an initial intrathecal injection of bupivacaine or bupivacaine with an opioid is given before starting the epidural, are also used,[6-9] and have been found to give excellent results,[7] although they may have no advantages over a low-dose epidural technique.[10]

Intrathecal injections containing bupivacaine have also been given alone[11,12] for the management of labour pain but the use of this route alone is usually associated with anaesthesia and management of postoperative pain in caesarean section. Bupivacaine has also been tried with lidocaine for epidural anaesthesia in caesarean section in order to reduce the dose of bupivacaine and minimise cardiotoxicity.[13]

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *Br J Anaesth* 1972; **44:** 66–74.
2. Purdy G, *et al.* Continuous extradural analgesia in labour: comparison between "on demand" and regular "top-up" injections. *Br J Anaesth* 1987; **59:** 319–24.
3. Turner MJ, *et al.* Primiparous women using epidural analgesia. *BMJ* 1990; **300:** 123.
4. Auroy Y, Benhamou D. Extradural analgesia for labour: 0.125% bupivacaine vs 0.0625% bupivacaine with 0.2 micrograms mL sufentanil. *Br J Anaesth* 1995; **74** (suppl 1): 105–6.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; **358:** 19–23.
7. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Randomized controlled trial comparing traditional with two "mobile" epidural techniques: anesthetic and analgesic efficacy. *Anesthesiology* 2002; **97:** 1567–75.
8. Stacey RGW, *et al.* Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71:** 499–502.
9. Collis RE, *et al.* Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345:** 1413–16.
10. Simmons SW, *et al.* Combined spinal-epidural versus epidural analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/02/08).
11. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
12. McHale S, *et al.* Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *Br J Anaesth* 1992; **69:** 634–6.
13. Howell P, *et al.* Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *Br J Anaesth* 1990; **65:** 648–53.

Preparations

BP 2008: Bupivacaine and Adrenaline Injection; Bupivacaine Injection; ***USP 31:*** Bupivacaine Hydrochloride in Dextrose Injection; Bupivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Bupicaina; Bupigobbi; Bupinex; Caina G; Duracaine; ***Austral.:*** Marcain; ***Austria:*** Bucain; Carbostesin; Dolanaest; ***Belg.:*** Marcaine; ***Braz.:*** Bupiabbott; Bupiabbott Plus; Marcaina; Neocaina; ***Canad.:*** Marcaine; Sensorcaine; ***Chile:*** Duracaine†; ***Cz.:*** Marcaine; ***Denm.:*** Marcain; ***Fin.:*** Bicain; Marcain; ***Fr.:*** Marcaine†; ***Ger.:*** Bucain; Carbostesin; Dolanaest; ***Gr.:*** Marcaine; ***Hong Kong:*** Marcain; ***Hung.:*** Bucaine; Marcain; ***India:*** Marcain; Sensorcaine; ***Indon.:*** Bucain; Decain; Marcain; ***Irl.:*** Marcain; ***Israel:*** Kamacaine; Marcaine; ***Ital.:*** Bupibil; Bupicain; Bupiforan; Bupisen; Bupisolver; Bupixamol; Marcaina; ***Malaysia:*** Marcain; ***Mex.:*** Buvacaina; ***Neth.:*** Bupiforan; Marcaine; ***Norw.:*** Marcain; ***NZ:*** Marcain; ***Philipp.:*** Senpivac; Sensorcaine; ***Pol.:*** Marcaine; ***Port.:*** Bupinostrum; Marcaina; ***Rus.:*** Anekain (Анекаин); Bupicaine (Бупикаин)†; Marcain (Маркаин); ***S.Afr.:*** Macaine; Regibloc; ***Singapore:*** Marcain; ***Spain:*** Svedocain; ***Swed.:*** Marcain; ***Switz.:*** Carbostesin; Duracain; ***Thai.:*** Marcain; ***Turk.:*** Marcaine; ***UK:*** Marcain; ***USA:*** Marcaine; Sensorcaine; ***Venez.:*** Duracaina.

Multi-ingredient: ***Austral.:*** Marcain with Fentanyl; Marcain with Pethidine†; ***Fin.:*** Solomet c bupivacain hydrochlorid; ***NZ:*** Bupafen; Marcain with Fentanyl; ***USA:*** Duocaine.

Butacaine Sulfate *(rINNM)*

Butacain. Sulph.; Butacaïne, Sulfate de; Butacaine Sulphate *(BANM)*; Butacaini Sulfas; Sulfato de butacaína. 3-Dibutylaminopropyl 4-aminobenzoate sulphate.

Бутакаина Сульфат

$(C_{18}H_{30}N_2O_2)_2,H_2SO_4 = 711.0.$

CAS — 149-16-6 (butacaine); 149-15-5 (butacaine sulfate).

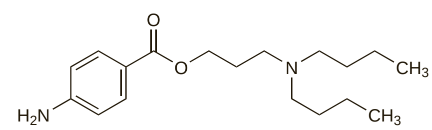

(butacaine)

Profile

Butacaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) used for surface anaesthesia. It has been used topically, as the sulfate, in solutions for dental pain and in ear and nasal drops.

Butoxycaine Hydrochloride

Butoxicaína, hidrocloruro de; Butoxycaini Hydrochloridum. 2-Diethylaminoethyl-(*p*-butoxybenzoate) hydrochloride.

$C_{17}H_{27}NO_3,HCl = 329.9.$

CAS — 3772-43-8 (butoxycaine); 2350-32-5 (butoxycaine hydrochloride).

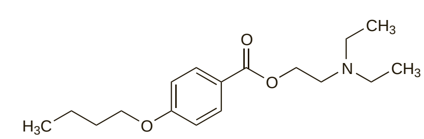

(butoxycaine)

Profile

Butoxycaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) that has been used as the base or hydrochloride for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Bismolan†.

Butyl Aminobenzoate

Butamben (*USAN*); Butilaminobenzoato; Butoforme. Butyl 4-aminobenzoate.
$C_{11}H_{15}NO_2$ = 193.2.
CAS — 94-25-7.

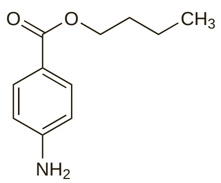

Pharmacopoeias. In *Fr.* and *US.*
USP 31 (Butamben). A white, odourless, crystalline powder. M.p. 57° to 59°. Soluble 1 in 7000 of water; soluble in alcohol, in ether, in chloroform, in fixed oils, and in dilute acids. It slowly hydrolyses when boiled with water.

Butyl Aminobenzoate Picrate

Abbott-34842; Butamben Picrate (*USAN*); Butilaminobenzoato, picrato de.
$(C_{11}H_{15}NO_2)_2,C_6H_3N_3O_7$ = 615.6.
CAS — 577-48-0.

Profile

Butyl aminobenzoate, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) that has been used for surface anaesthesia of the skin and mucous membranes. It has also been used for relief of pain and pruritus associated with anorectal disorders. A suspension of butyl aminobenzoate 5 or 10% has been given epidurally.

Butyl aminobenzoate picrate has been applied to the skin as an ointment.

◊ References.

1. Korsten HH, *et al.* Long-lasting epidural sensory blockade by n-butyl-p-aminobenzoate in the terminally ill intractable cancer pain patient. *Anesthesiology* 1991; **75:** 950–60.
2. Armstrong DG, Kanat IO. Analgesic efficacy of topical butamben picrate. *J Am Podiatr Med Assoc* 1995; **85:** 738–40.
3. Shulman M, *et al.* Nerve blocks with 5% butamben suspension for the treatment of chronic pain syndromes. *Reg Anesth Pain Med* 1998; **23:** 395–401.

Preparations

USP 31: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Erythromycin Ethylsuccinate Injection.

Proprietary Preparations (details are given in Part 3)
Braz.: Unguento Picrato de Butesin.

Multi-ingredient: ***Austral.:*** Butesin Picrate†; ***Chile:*** Butesin; ***Fr.:*** Nestosyl; Preparation H; ***India:*** Proctosedyl; ***Ital.:*** Prurex; ***Spain:*** Alvogil; Topicaina†; ***Switz.:*** Alvogyl; ***USA:*** Cetacaine.

Chloroprocaine Hydrochloride (*rINNM*)

Chloroprocaïne, Chlorhydrate de; Chloroprocaini Hydrochloridum; Hidrocloruro de cloroprocaína. 2-Diethylaminoethyl 4-amino-2-chlorobenzoate hydrochloride.
Хлоропрокаина Гидрохлорид
$C_{13}H_{19}ClN_2O_2,HCl$ = 307.2.
CAS — 133-16-4 (chloroprocaine); 3858-89-7 (chloroprocaine hydrochloride).
ATC — N01BA04.
ATC Vet — QN01BA04.

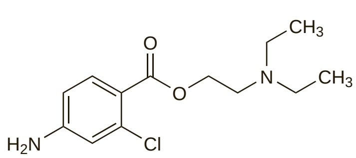

(chloroprocaine)

Pharmacopoeias. In *US.*
USP 31 (Chloroprocaine Hydrochloride). A white odourless crystalline powder. Soluble 1 in 20 of water and 1 in 100 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Solutions are acid to litmus.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850. Chloroprocaine is said to be unsuitable for intravenous regional anaesthesia (Bier's block) because of a high incidence of thrombophlebitis associated with such use. It is also contra-indicated in spinal anaesthesia due to potential neurotoxicity.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

Chloroprocaine is hydrolysed rapidly in the circulation by plasma cholinesterase. It has a half-life of 19 to 26 seconds in adults. It is excreted in the urine mainly as metabolites.

See also under Local Anaesthetics, p.1852.

Uses and Administration

Chloroprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1852. It has properties similar to those of procaine (p.1869). It has a rapid onset (6 to 12 minutes) and short duration (one hour) of action.

Chloroprocaine is used as the hydrochloride for infiltration, peripheral nerve block, and central nerve block including lumbar and caudal epidural blocks. It may be given, if necessary, with adrenaline 1 in 200 000 to delay absorption and reduce toxicity. Chloroprocaine is not an effective surface anaesthetic. It should not be used for spinal anaesthesia. (Local anaesthetic techniques are discussed on p.1853.)

The dosage of chloroprocaine used depends on the site of injection and the procedure used. In adults the **maximum single dose** of chloroprocaine hydrochloride without adrenaline should not exceed 800 mg; when given with adrenaline 1 in 200 000 the maximum single dose should not exceed 1 g. A test dose of chloroprocaine, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular injection. Doses for various procedures include:

- *mandibular nerve block*: 40 to 60 mg (2 to 3 mL) as a 2% solution
- *infra-orbital nerve block*: 10 to 20 mg (0.5 to 1 mL) as a 2% solution
- *brachial plexus block*: 600 to 800 mg (30 to 40 mL) as a 2% solution
- *digital nerve block*: 30 to 40 mg (3 to 4 mL) as a 1% solution without adrenaline
- in obstetrics a dose of 200 mg (10 mL) per side as a 2% solution is suggested for *pudendal block* and for a *paracervical block* a 1% solution in a dose of 30 mg (3 mL) at each of 4 sites
- *lumbar epidural block*: 40 to 50 mg (2 to 2.5 mL) as a 2% solution or 60 to 75 mg (2 to 2.5 mL) as a 3% solution for each segment to be anaesthetised, the usual total dose being 300 to 750 mg with smaller repeat doses being given at intervals of 40 to 50 minutes
- *caudal block*: 300 to 500 mg (15 to 25 mL) as a 2% solution or 450 to 750 mg (15 to 25 mL) as a 3% solution may be given and repeated at intervals of 40 to 60 minutes

Dosages should be reduced in children, elderly or debilitated patients, and those with cardiac or liver disease. For children concentrations of 0.5 to 1% are suggested for infiltration and 1 to 1.5% for nerve block procedures.

Preparations

USP 31: Chloroprocaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Canad.: Nesacaine; ***Switz.:*** Ivracain; Nesacain; ***USA:*** Nesacaine.

Cinchocaine (*BAN, rINN*)

Cincainum; Cinchocaïne; Cinchocainum; Cincocaína; Cinkokain; Dibucaine; Sinkokaiini. 2-Butoxy-*N*-(2-diethylaminoethyl)cinchoninamide; 2-Butoxy-*N*-(2-diethylaminoethyl)quinoline-4-carboxamide.
Цинхокаин
$C_{20}H_{29}N_3O_2$ = 343.5.
CAS — 85-79-0.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.

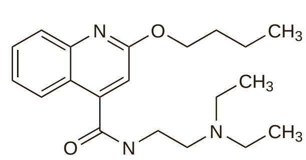

Pharmacopoeias. In *US.*
USP 31 (Dibucaine). A white to off-white powder, with a slight characteristic odour. M.p. 62.5° to 66°. Soluble 1 in 4600 of water, 1 in 0.7 of alcohol, 1 in 0.5 of chloroform, and 1 in 1.4 of ether; soluble in 1N hydrochloric acid. It darkens on exposure to light. Store in airtight containers. Protect from light.

Cinchocaine Hydrochloride (*BANM, rINNM*)

Cincaini Chloridum; Cinchocaïne, chlorhydrate de; Cinchocaini hydrochloridum; Cinchokain-hidroklorid; Cinchokain-hydrochlorid; Cinchokaino hidrochloridas; Cinkokainhydroklorid; Dibucaine Hydrochloride; Dibucainium Chloride; Hidrocloruro de cincocaína; Percainum; Sinkokaiinihydrokloridi; Sinkokain Hidroklorür; Sovcainum.
Цинхокаина Гидрохлорид
$C_{20}H_{29}N_3O_2,HCl$ = 379.9.
CAS — 61-12-1.
ATC — C05AD04; D04AB02; N01BB06; S01HA06.
ATC Vet — QC05AD04; QD04AB02; QN01BB06; QS01HA06.

NOTE. This compound was originally marketed under the name Percaine, but accidents occurred owing to the confusion of this name with procaine.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Cinchocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals; it is hygroscopic. It agglomerates very easily. Very soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. A 2% solution in water has a pH of 5.0 to 6.0. Store in airtight containers. Protect from light.
USP 31 (Dibucaine Hydrochloride). Colourless or white to off-white crystals or white to off-white, crystalline powder. It is odourless, somewhat hygroscopic, and darkens on exposure to light. Freely soluble in water, in alcohol, in acetone, and in chloroform. Its solutions have a pH of about 5.5. Store in airtight containers. Protect from light.

Profile

Cinchocaine is an amide local anaesthetic (p.1850) that is now generally only used for surface anaesthesia. It is one of the most potent and toxic of the long-acting local anaesthetics and its parenteral use was restricted to spinal anaesthesia.

For surface anaesthesia cinchocaine has been used, as the base or hydrochloride, in creams and ointments containing up to 1% and in suppositories for the temporary relief of pain and itching associated with skin and anorectal conditions. Cinchocaine benzoate has also been used topically.

Action. For a comparison of the vasoactivity of cinchocaine and some other local anaesthetics, see p.1852.

Plasma cholinesterase deficiency. For mention of the use of cinchocaine in the determination of plasma cholinesterase activity, see under Precautions of Suxamethonium Chloride, p.1911.

Preparations

USP 31: Dibucaine Cream; Dibucaine Hydrochloride Injection; Dibucaine Ointment.

Proprietary Preparations (details are given in Part 3)
Braz.: Nupercainal; ***Canad.:*** Nupercainal; ***Denm.:*** Cincain; ***Ger.:*** Dolo-Posterine N; ***India:*** Nupercainal; ***Port.:*** Nupercainal; ***Swed.:*** Cincain; ***UK:*** Nupercainal; ***USA:*** Nupercainal.

Multi-ingredient: ***Arg.:*** Procto Venart; Proctyl; Scheriproct; Ultraproct; ***Austral.:*** Proctosedyl; Rectinol HC; Scheriproct; Ultraproct; ***Austria:*** Ciloprin cum Anaesthetico†; Scheriproct; Ultraproct; ***Belg.:*** Scheriproct; Tri-histalex; Ultraproct; ***Braz.:*** Proctyl; Senol†; Ultraproct; ***Canad.:*** Nupercainal; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; ***Chile:*** Scheriproct; Ultraproct; ***Cz.:*** Aviril H†; Faktu; Otobacid N; Proctosedyl†; Proctospre†; Spofax; ***Denm.:*** Proctosedyl; ***Fin.:*** Ciloprin cum Anaesthetico†; Faktu†; Proctosedyl; Scheriproct; ***Fr.:*** Deliproct; Ultraproct; ***Ger.:*** Anumedin†; Faktu; Otobacid N; Procto-Kaban†; Proctospre†; Scheriproct†; Ultraproct†; ***Gr.:*** Scheriproct Neo; ***Hong Kong:*** Borraginol-N; Decatylen; Faktu; Proctosedyl†; Proctosone†; Ultraproct†; ***India:*** Otogesic; ***Indon.:*** Borraginol-N; Faktu; Ultraproct; ***Irl.:*** Proctosedyl; Scheriproct; Ultraproct; ***Ital.:*** Ultraproct; ***Jpn:*** Una A Gel; ***Malaysia:*** Decatylen; Proctosedyl; Proctosone†; ***Mex.:*** Proctoacid; Scheriproct; Ultraproct; ***Neth.:*** Proctosedyl; ***Norw.:*** Proctosedyl; Scheriproct; ***NZ:*** Proctosedyl; Ultraproct; ***Philipp.:*** Faktu; Proctosedyl; Ultraproct; ***Pol.:*** Proctosone; ***Port.:*** Decatyleno; Faktu; Scheriproct; ***Rus.:*** Ultraproct (Ультрапрокт); ***S.Afr.:*** Cepacaine†; Medi-Keel A; Proctosedyl; Scheriproct; ***Singapore:*** Decatylen; Faktu†; Proctosedyl; ***Spain:*** Anestesia Loc Braun S/A; Ruscus; Scheriproct; ***Swed.:*** Proctosedyl†; Scheriproct N; ***Switz.:*** Ciloprin ca†; Decatylene Neo; Faktu; Locaseptil-Neo; Scheriproct; ***Thai.:*** Proctosedyl; Scheriproct†; ***Turk.:*** Ultraproct; ***UAE:*** Supraproct-S; ***UK:*** Proctosedyl; Scheriproct; Ultraproct; Uniroid-HC; ***USA:*** Corticaine; ***Venez.:*** Scheriproct.

Coca ⊗

Coca Leaves; Hoja de Coca.

Profile

Coca is the dried leaves of *Erythroxylum coca* (Bolivian or Huanuco leaf) or of *E. truxillense* (Peruvian or Truxillo leaf) (Erythroxylaceae), indigenous to Bolivia and Peru and cultivated in Colombia and Indonesia.

Coca leaves contain about 0.7 to 1.5% of total alkaloids, of which cocaine, cinnamyl-cocaine, and α-truxilline are the most important.

Coca was formerly used for its stimulant action and for the relief of gastric pain, nausea, and vomiting, but it has no place in modern medicine. The practice of coca leaf chewing still continues in South America.

Cocaine *(BAN)* ⊗

Cocaína; Cocainum; Kokaiini; Kokain; Methyl Benzoylecgonine. (1*R*,2*R*,3*S*,5*S*)-2-(Methoxycarbonyl)tropan-3-yl benzoate.

$C_{17}H_{21}NO_4$ = 303.4.

CAS — 50-36-2.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

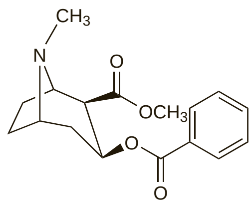

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cocaine:

24-7; 151; 256; A1-Yola; All-American drug; Angie; Apple jacks; Aspirin; Aunt; Aunt Nora; Baby T; Bad; Badrock; Bahsay; Baise; Ball; Balls Mahoney; Bane; Barbs; Basa; Base; Baseball; Basing; Basuco; Batman; Bazooka; Bazulco; Beak; Beam; Beamers; Beans; Beat; Beautiful boulders; Bebe; Beemers; Berni; Bernice; Bernie; Bernie's flakes; Bernie's gold dust; Big bloke; Big C; Big flake; Big rush; Bill blass; Billie hoke; Bing; Bing Crosby; Bings; Birdie powder; Biscuits; Bjs; BJ's; B.J.'s; Black rock; Blanca; Blanco; Blast; Blizzard; Blotter; Blow; Blowcaine; Blowout; Blue; Bobo; Bogota Bullion; Bolivian; Bolivian marching powder; Bollo; Bolo; Bomb; Bonecrusher; Bones; Booger; Booger Sugar; Boost; Booth; Bopper; Botray; Boubou; Boulder; Boulya; Bouncing powder; Boutros; Boy; Branco; Breakfast of champions; Brick; Brooke Shields; Bubble gum; Bugar sugar; Buger sugar; Bullia capital; Bullion; Bump; Bumper; Bunk; Burese; Burnese; Bush; Butler; Butter; Butter Sandwich; Butter Sandwiches; Butu; C; Cabello; Cadillac; Caine; Cakes; California cornflakes; Came; Candy; Candy C; Candy cane; Candy sugar; Candycaine; Cane; Cap; Caps; Capsula; Carnie; Carrie; Carrie Nation; Casper; Casper the ghost; Cat's pee; Caviar; CDs; C-dust; Cecil; C-game; Cha; Chabbie; Chach; Chalk; Champagne; Champagne of drugs; Chan; Chandi; Chang; Charlie; Charlie girl; Chaz; Cheap basing; Cheddar; Cheese; Chemical; Chewies; Chez; Chinese Sky Candy; Ching; Chippy; Choe; Cholly; Climax; Cloud; Cloud nine; Coc; Co-caee-na; Coca; Coca-Cola; Coco; Coconut; Cokane; Coke; Cola; Colombian Dancing Dust; Colombian Foot Soldiers; Colombian Marching Powder; Colombo; Colorado; Combol; Cookie; Cookies; Coover; Coovers; Corine; Cornbread; Corrine; Corrinne; Crack; Crackers; Crank; Crib; Crill; Cristaux; Crow; Crumbs; Crunch & Munch; Crusty treats; Crystal; Cubes; Cuch; Dama blanca; Demo; Demolish; Devil drug; Devil's dandruff; Devilsmoke; Dice; Dime; Dime special; Dip; Dirty basing; Divits; DOA; Double bubble; Double yoke; Dream; Duct; Dust; Dutch Bliss; Eastside player; Egg; Eggs; El Perico; Electric koolaid; Esnortiar; Eve; Everclear; Eye opener; Eye openers; Famous dimes; Farlopa; Fast white lady; Fat bags; Fifty-one; Fish scales; Flake; Flave; Florida snow; Foo Foo; Foo foo stuff; Foo-foo dust; Foolish powder; Freebase; Freeze; French fries; Fries; Friskie powder; Fry; Gak; Garbage rock; Gas; Gear; Geek; Get your own; Gift-of-the-sun; Gift-of-the-sun-god; Gin; Girl; Girlfriend; Glad stuff; Glo; Gold; Gold dust; Gold star; Golf ball; Golf balls; Gooka; Gravel; Green gold; Grit; Grits; Groceries; Gulosa; Gutter glitter; Hail; Half track; Hamburger; Hamburger helper; Hamburgers; Handball; Happy dust; Happy powder; Happy trails; Hard; Hard ball; Hard line; Hard rock; Hardball; Have a dust; Haven dust; Heaven; Heaven dust; Heavy stuff; Hell; Henry VIII; Her; Hit; Hocus-Pocus; Hollywood; Homer; Hooter; Hoove; Hotcakes; How do you like me now?; Hubba; Hubba, I am back; Hubbas; Hunter; I am back; Ice; Ice cube; Icing; Inca message; Incentive; Issues; Ivory flakes; Jam; Jejo; Jelly; Jelly beans; Jessica Simpson; "Jiffy"; Johnny; Johnson; Joy powder; Junk; Kangaroo; Kangoroo; Kate; Kibbles & Bits; King; King's habit; Kitty; Kokomo; Kryptonite; Kubba; Kubs; Kuff; Lady; Lady C; Lady caine; Lady snow; Late night; Leaf; Lido; Line; Lines; Liquid lady; Llello; Love; Love affair; Lucifer Left-Nostril; Ma'a; Mama coca; Marching dust; Marching powder; Mayo; Merca; Merck; Merk; Mighty white; Mix; Mixed jive; Mobbeles; Mojo; Monster; Mosquitos; Movie star drug; Mr. B.; Mujer; Munch; Neige; Neve; New addition; Nieve; Nighttrain; Nose; Nose candy; Nose powder; Nose stuff; Nuggets; Number 3; One-fifty-one; One-to-one; Oyster stew; Pala; Paradise; Paradise white; Pariba; Parlay; Partying; Pasta; Paste; Patico; Pearl; Pebbles; Pee Wee; Pepsi; Percia; Percio; Perico; Peruvian; Peruvian flake; Peruvian lady; Peruvian Marching Powder; P.F.; Picnic in Stevenage; Piece; Piedra; Piedras; Pile; Piles; Pimp; Polvo blanco; Pony; Pop; Powder; Powder diamonds; Press; Prime time; Primo; Product; Purple caps; Purple haze; Quick; Quik; Quill; Race horse Charlie; Racehorse Charlie; Railers; Rane; Raw; Ready rock; Real tops; Red caps; Regular "P"; Rest in peace; Ringer; Ringers; Roca; Rock; Rock attack; Rocks; Rocks of hell; Rocky III; Rooster; Rox; Roxanne; Royalty; Roz; Rush; Schmeck; Schoolboy; Schoolcraft; Scorpion; Scottie; Scotty; Scrabble; Scramble; Scruples; Serpico 21; Seven-Up; Sevenup; Shabu; Shake; She; Sherms; Shit; Shnazzle; Shneg; Shootin' Caine; Showbiz Sherbert; Shrile; Sightball; Skeeter; Skeezell; Slab; Sleet; Sleigh ride; Smack; Smoke; Snai; Sniff; Snort; Snow; Snow bird; Snow coke; Snow cone; Snow soke; Snow toke; Snow Train; Snow white; Snowcones; Soap; Society high; Soda; Soft; Soup; Space; Space dust; Speed; Speed boat; Square time Bob; Squares; Squib; Squirrel; Star; Star dust; Star-spangled powder; Stardust; Stone; Stones; Strawberry; Street Caviar; Studio fuel; Suga buga; Sugar; Sugar block; Sugar boogers; Super cloud; Sutta; Sweet stuff; Swell up; T; Talco; Tardust; Teenager; Teeth; Tension; The champagne of stimulants; The devil; The great white hope; Thing; Tissue; Tony; Toot; Tootie; Top gun; Topo; Tornado; Toss up; Toss-ups; Trails; Trey; Troop; Turkey; Turtle stuff; Tutti-frutti; Tweaks; Twenty rock; Twinkie; Ultimate; Uptown; Uzi; Wacky dust; Wash; Washed rock; Wave; Weasel dust; Whack; White; White ball; White boy; White cloud; White Devil; White dragon; White dust; White ghost; White girl; White horse; White lade; White lady; White Lion; White mosquito; White Pony; White powder; White stuff; White sugar; White tornado; Whites; Whiz bang; Window pane; Wings; Witch; Woolies; Wrecking crew; Yada; Yadidi; Yahoo; Yak; Yale; Yam; Yams; Ya Yo; Yao; Yay; Yayo; Yayoo; Yay-yo; Yeah-O; Yeaho; Yee Yoo; Yeo; Yeyo; Yimyom; Yiz; Yola; Zing; Zip; Zulu.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Cocaine). It may be obtained from the leaves of *Erythroxylum coca* and other spp. of *Erythroxylum*, or by synthesis. Colourless crystals or a white, crystalline powder. It is slightly volatile. M.p. 96° to 98°. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform; soluble in arachis oil; slightly soluble in liquid paraffin.

USP 31 (Cocaine). Colourless to white crystals or white, crystalline powder. M.p. 96° to 98°. Soluble 1 in 600 of water, 1 in 7 of alcohol, 1 in 1 of chloroform, 1 in 3.5 of ether, 1 in 12 of olive oil, and 1 in 80 to 100 of liquid paraffin. A saturated solution in water is alkaline to litmus. Protect from light.

Cocaine Hydrochloride *(BANM)* ⊗

Chloridrato de Cocaína; Cocaína, hidrocloruro de; Cocaïne, chlorhydrate de; Cocaine Hydrochlor.; Cocaini hydrochloridum; Cocainium Chloratum; Kokaiinihydrokloridi; Kokain-hidroklorid; Kokain-hydrochlorid; Kokainhydroklorid; Kokaino hidrochloridas; Kokainy chlorowodorek.

$C_{17}H_{21}NO_4$,HCl = 339.8.

CAS — 53-21-4.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

ATC Vet — QN01BC01; QR02AD03; QS01HA01; QS02DA02.

NOTE. CCN is a code approved by the BP 2008 for use on single unit doses of eye drops containing cocaine hydrochloride where the individual containers may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Cocaine Hydrochloride). Colourless crystals or a white or almost white crystalline powder. M.p. about 197° with decomposition. Very soluble in water; freely soluble in alcohol. Protect from moisture and light.

USP 31 (Cocaine Hydrochloride). Colourless crystals or white, crystalline powder. Soluble 1 in 0.5 of water, 1 in 3.5 of alcohol, and 1 in 15 of chloroform; soluble in glycerol; insoluble in ether. Protect from light.

Stability in solutions. ***ALKALIS.*** Solutions of cocaine hydrochloride are adversely affected by alkalis.

PHENOL. A stability study[1] was conducted in response to queries over conflicting data on the incompatibility of cocaine hydrochloride solutions and phenol. Some pharmacists had reported that cocaine hydrochloride eye drops preserved with phenol had shown no sign of physical incompatibility. The BPC 1973 states that cocaine hydrochloride is incompatible with phenol but suggests that cocaine hydrochloride solutions may be preserved with chlorocresol. The study found that there was no sign of physical incompatibility in aqueous solutions containing cocaine hydrochloride 5% and phenol 0.5% stored for a year at temperatures of 0° to 37° but there was a fall in pH, greatest at the higher temperatures, which was suggestive of chemical change. It was recommended that such solutions should be stored in a cool place.

1. *PSGB Lab Report P/75/14* 1975.

Adverse Effects

Because the therapeutic use of cocaine is now very restricted many reports of adverse effects occur in the context of abuse. However, both systemic and local effects have followed its use as a surface anaesthetic. Although some effects are similar to those of other local anaesthetics (p.1850), cocaine differs in that it acts as a potent indirect-acting sympathomimetic. It stimulates the CNS causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hypertonia, and hyperreflexia. Convulsions, coma, and metabolic acidosis may develop. Symptoms of CNS stimulation and sympathetic overactivity are very marked in overdosage with cocaine. A single oral dose of 1 g may be fatal, but some persons have a cocaine idiosyncrasy and severe toxicity may occur after doses of only 10 mg intravenously. Systemic absorption of small doses may slow the heart, but with increasing doses tachycardia, hypertension, and ventricular fibrillation occur.

High concentrations of cocaine should not be used topically as, in addition to risks of systemic toxicity after absorption, lasting local damage may occur.

Topical application of cocaine to the cornea can cause corneal damage with clouding, pitting, sloughing, and occasionally ulceration. Topical application to the nose or mouth has been reported to cause loss of smell and taste respectively.

Prolonged use of cocaine by nasal inhalation may cause mucosal damage or perforation of the nasal septum.

Abuse. Cocaine abuse and its effects have been discussed in a number of reviews.[1-6]

Cocaine abuse was once only in the form of chewing of coca leaves containing small amounts of cocaine, but processing of the leaves has led to abuse with a variety of more dangerous preparations containing higher concentrations of cocaine.[7] Coca paste, produced by maceration of the leaves with petrol and sulfuric acid, contains about 40 to 90% of cocaine sulfate and is smoked with tobacco or cannabis. Treatment of coca paste with hydrochloric acid produces cocaine hydrochloride, which is abused by intravenous injection, either alone or with diamorphine, or by sniffing to achieve nasal absorption. Alkaloidal cocaine (cocaine base; 'freebase'), which is abused by smoking, is produced by treating cocaine hydrochloride with alkali, followed either by heating (to form 'crack' cocaine) or by extracting the base from ether or another organic solvent. The route by which cocaine is taken determines the rate and extent of its absorption, and hence the abuse potential, although once absorbed, the pharmacokinetics are independent of route. Intravenous cocaine hydrochloride and smoked cocaine base have a greater potential for abuse than intranasal cocaine hydrochloride because of their greater rapidity and intensity of effects.

The psychological effects of cocaine abuse may be described by a cycle of initial euphoria followed by dysphoria and finally schizophreniform psychosis.[7,8] Euphoria may be accompanied by other symptoms of stimulation such as sexual arousal, anorexia, insomnia, hyperexcitability, loquacity, and grandiosity, and users may appear manic. After a short time these feelings are replaced by symptoms of dysphoria including considerable anxiety, fear, depression, apathy, irritability, and suspiciousness. Dysphoria may be ameliorated by repeated use, so the user develops the need to take the drug continuously to feel relatively well, but repeated use appears to diminish the intensity of the effects.[7] During euphoria and dysphoria users may experience a wide range of physical symptoms including palpitations, headache, dizziness, gastrointestinal effects, hyperhidrosis, tremors, tachycardia, hypertension, fever, and myoclonic jerks. Seizures can also occur after repeated use. In chronic abusers psychological deterioration may eventually occur, resulting in loss of mental function, compulsive disorders, suicidal ideation, psychopathic disorders, and ultimately a psychosis resembling acute paranoid schizophrenia similar to that seen with amfetamines.[7,8] Symptoms may include paranoia, stereotyped behaviour, delusions, loss of impulse control, violence, and visual, olfactory, auditory, gustatory, and tactile hallucinations. Overdosage can result in death due to status epilepticus, hyperthermia, ventricular tachycardia, and cardiac or respiratory arrest.[7]

For further details of the adverse effects of cocaine abuse, including effects due to use during pregnancy, see below.

1. Johanson C-E, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; **41:** 3–52.
2. Warner EA. Cocaine abuse. *Ann Intern Med* 1993: **119:** 226–35.
3. Strang J, *et al.* Cocaine in the UK—1991. *Br J Psychiatry* 1993; **162:** 1–13.
4. Das G. Cocaine abuse in North America: a milestone in history. *J Clin Pharmacol* 1993; **33:** 296–310.
5. Hatsukami DK, Fischman MW. Crack cocaine and cocaine hydrochloride: are the differences myth or reality? *JAMA* 1996; **276:** 1580–8.
6. Brownlow HA, Pappachan J. Pathophysiology of cocaine abuse. *Eur J Anaesthesiol* 2002; **19:** 395–414.
7. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
8. Leikin JB, *et al.* Clinical features and management of intoxication due to hallucinogenic drugs. *Med Toxicol Adverse Drug Exp* 1989; **4:** 324–50.

ADULTERATION. For a report of methaemoglobinaemia as a result of the ingestion of cocaine adulterated with benzocaine, see Abuse under Adverse Effects of Benzocaine, p.1854.

BREAST FEEDING. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by breast-feeding mothers, cocaine has caused signs of intoxication in the infant, notably diarrhoea, vomiting, irritability, seizures, and tremulousness.

Acute intoxication has been reported in a breast-fed child whose mother was using cocaine intranasally.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)
2. Chasnoff IJ, *et al.* Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; **80:** 836–8.

Effects on the blood. References.

1. Leissinger CA. Severe thrombocytopenia associated with cocaine use. *Ann Intern Med* 1990; **112:** 708–10.

Effects on the cardiovascular system. There appears to be no relationship between underlying heart disease and the risk of cocaine-induced cardiac effects and cardiac events can occur regardless of the route of abuse.[1] Cardiovascular toxicity due to cocaine may be related to individual sensitivity and therefore may not be predictable or dose dependent.[2] Patients with plasma cholinesterase deficiency are particularly at risk for sudden death.[3] Other risk factors for cardiovascular disease, such as cigarette smoking or pre-existing atherosclerosis, may exacerbate the cardiac toxicity of cocaine.[4-6] Cocaine blocks reuptake of catecholamines at adrenergic nerve endings and thus produces sympathetic stimulation of the cardiovascular system. Accumulation of catecholamines predisposes the myocardium to arrhythmias,[7] and sinus tachycardia, supraventricular or ventricular tachyarrhythmias, myocarditis, and sudden arrhythmic death may occur.[7-9] Severe hypertension can lead to cerebrovascular accidents and stroke has occurred even in young adults without other predisposing conditions.[10,11] However, the exact mechanism of cocaine-induced stroke remains unclear and other implicated effects include vasospasm, cerebral vasculitis, enhanced platelet aggregation, and cardioembolism.[12] Aortic dissection and rupture of the aorta have also occurred.[6] Up to 25% of emergency admissions to US urban hospitals with nontraumatic chest pain have detectable amounts of cocaine or its metabolites in their urine, but only a minority of these have myocardial infarction,[6] as chest pain without signs of myocardial infarction also commonly occurs.[8] Asymptomatic myocardial ischaemia manifesting as episodes of ST segment elevation has also been reported during withdrawal of cocaine.[13] The mechanism for these changes is probably multifactional, including increased myocardial oxygen demand, coronary vasoconstriction, and enhanced platelet aggregation and thrombus formation.[6,14] The immediate vasoconstrictor effect of cocaine may be followed by delayed or recurrent vasoconstriction due to its active metabolites, benzoylecgonine and ethyl methyl ecgonine.[6]

Vasoconstriction may also produce ischaemia in the fingers, toes, spinal cord,[8] spleen,[15] and intestines.[16] Renal ischaemia and infarction may also occur.[17,18] Other reported cardiovascular effects include dilated cardiomyopathy and premature atherosclerosis.[6]

1. VanDette JM, Cornish LA. Medical complications of illicit cocaine use. *Clin Pharm* 1989; **8:** 401–11.
2. Thadani PV. Cardiovascular toxicity of cocaine: underlying mechanisms. *J Appl Cardiol* 1990; **5:** 317–20.
3. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
4. Moliterno DJ, *et al.* Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med* 1994; **330:** 454–9.
5. Higgins ST, *et al.* Influence of cocaine use on cigarette smoking. *JAMA* 1994; **272:** 1724.
6. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001; **345:** 351–8. Correction. *ibid.*; 1432.
7. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
8. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1990; **32:** 92–4.
9. Bauman JL, *et al.* Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; **34:** 902–11.
10. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med* 1990; **113:** 821–7.
11. Levine SR, *et al.* Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med* 1990; **323:** 699–704.
12. Treadwell SD, Robinson TG. Cocaine use and stroke. *Postgrad Med J* 2007; **83:** 389–94.
13. Nademanee K, *et al.* Myocardial ischemia during cocaine withdrawal. *Ann Intern Med* 1989; **111:** 876–80.
14. Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. *Clin Med Res* 2007; **5:** 172–6.
15. Novielli KD, Chambers CV. Splenic infarction after cocaine use. *Ann Intern Med* 1991; **114:** 251–2.
16. Freudenberger RS, *et al.* Intestinal infarction after intravenous cocaine administration. *Ann Intern Med* 1990; **113:** 715–16.
17. Sharff JA. Renal infarction associated with intravenous cocaine use. *Ann Emerg Med* 1984; **13:** 1145–7.
18. Bemanian S, *et al.* Cocaine-induced renal infarction: report of a case and review of the literature. *BMC Nephrol* 2005; **6:** 10. Available at: http://www.biomedcentral.com/1471-2369/6/10 (accessed 22/06/06)

Effects on the CNS. Severe CNS depression with deep coma has been seen in a few cocaine abusers after prolonged binges.[1]

1. Roberts JR, Greenberg MI. Cocaine washout syndrome. *Ann Intern Med* 2000; **132:** 679–80.

Effects on the kidneys. For reference to renal failure following rhabdomyolysis associated with cocaine abuse, see under Effects on the Muscles, below. There has been a report[1] of acute renal failure occurring in a 16-year-old girl secondary to cocaine abuse but without evidence of rhabdomyolysis.

For reference to renal ischaemia and infarction due to cocaine abuse, see under Effects on the Cardiovascular System, above.

1. Leblanc M, *et al.* Cocaine-induced acute renal failure without rhabdomyolysis. *Ann Intern Med* 1994; **121:** 721–2.

Effects on the lungs. Smoking the free base has resulted in pulmonary complications not encountered with other methods of abuse for cocaine. Associated adverse effects have included pulmonary oedema, hypersensitivity pneumonitis, pulmonary haemorrhage, obliterative bronchiolitis, abnormalities of pulmonary function, pneumomediastinum, and pneumothorax.[1] Severe or life-threatening exacerbations of asthma have also been reported.[2]

1. Ettinger NA, *et al.* A review of the respiratory effects of smoking cocaine. *Am J Med* 1989; **87:** 664–8.
2. Rubin RB, Neugarten J. Cocaine-associated asthma. *Am J Med* 1990; **88:** 438–9.

Effects on the mouth. Abuse of cocaine can produce several adverse effects in the oral cavity including perforation of the palate (usually after perforation of the nasal septum), gingival lesions, and erosions of the teeth.[1]

1. Brand HS, *et al.* Cocaine and oral health. *Br Dent J* 2008; **204:** 365–9.

Effects on the muscles. Rhabdomyolysis, sometimes progressing to renal failure, has been associated with free-base smoking or injection of cocaine hydrochloride.[1-3]

1. Roth D, *et al.* Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; **319:** 673–7.
2. Herzlich BC, *et al.* Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988; **109:** 335–6.
3. Pogue VA, Nurse HM. Cocaine-associated acute myoglobinuric renal failure. *Am J Med* 1989; **86:** 183–6.

Effects on sexual function. While the initial euphoria of cocaine abuse may be accompanied by sexual arousal, sexual dysfunction can occur[1] and male infertility has been reported.[2] Priapism associated with cocaine abuse has also occurred.[3]

1. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
2. Bracken MB, *et al.* Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril* 1990; **53:** 315–22.
3. Altman AL, *et al.* Cocaine associated priapism. *J Urol* 1999; **161:** 1817–18.

Effects on the skin. Urticarial vasculitis occurred in a young man after intranasal abuse of cocaine.[1]

1. Hofbauer GFL, *et al.* Urticarial vasculitis following cocaine use. *Br J Dermatol* 1999; **141:** 600–601.

Overdosage. References to fatal overdosage from cocaine abuse.

1. Greenland VC, *et al.* Vaginally administered cocaine overdose in a pregnant woman. *Obstet Gynecol* 1989; **74:** 476–7.
2. Peretti FJ, *et al.* Cocaine fatality: an unexplained blood concentration in a fatal overdose. *Forensic Sci Int* 1990; **48:** 135–8.
3. Karch SB, *et al.* Relating cocaine blood concentrations to toxicity–an autopsy study of 99 cases. *J Forensic Sci* 1998; **43:** 41–5.

Pregnancy. The effects of cocaine abuse during pregnancy have been reviewed.[1-4] Women who abuse cocaine during pregnancy appear to have an increased risk of spontaneous abortion,[5] abruptio placentae[6,7] and associated still-births,[8] premature labour,[9-11] and other birth complications.[9-11] These effects may be due to vasoconstriction by cocaine increasing maternal blood pressure and reducing placental blood flow.[12] Uterine rupture[13] during pregnancy and rupture of ectopic pregnancies[14] have also been associated with cocaine. Neonates born to mothers abusing cocaine have an increased risk of intra-uterine growth retardation and may have lower birth-weight, smaller head size, and shorter length.[6,8-10,15-17] Cocaine is possibly teratogenic and congenital abnormalities associated with abuse include cardiovascular abnormalities,[9,18,19] limb reduction defects,[20] intestinal atresia or infarction,[20] skull defects,[8] and genito-urinary tract anomalies.[21] Neurobehavioural impairment[22] and signs of transient CNS irritability[23] may also occur. Some workers[24,25] have found effects on cognition and motor delays while others have found effects on arousal and attention regulation rather than cognitive processes.[26] Cocaine can increase neonatal cerebral blood flow[27] and cerebral infarction and associated seizures have occurred in neonates whose mothers took cocaine near to the onset of labour.[28] Evidence on the risk of intraventricular haemorrhage is conflicting.[7,24]

1. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol* 1992; **79:** 778–89.
2. Volpe JJ. Effects of cocaine use on the fetus. *N Engl J Med* 1992; **327:** 399–407. Correction. *ibid.*; 1039.
3. Wiggins RC. Pharmacokinetics of cocaine in pregnancy and effects on fetal maturation. *Clin Pharmacokinet* 1992; **22:** 85–93.
4. Fajemirokun-Odudeyi O, Lindow SW. Obstetric implications of cocaine use in pregnancy: a literature review. *Eur J Obstet Gynecol Reprod Biol* 2004; **112:** 2–8.
5. Chasnoff IJ, *et al.* Cocaine use in pregnancy. *N Engl J Med* 1985; **313:** 666–9.
6. Dombrowski MP, *et al.* Cocaine abuse is associated with abruptio placentae and decreased birth weight, but not shorter labor. *Obstet Gynecol* 1991; **77:** 139–41.
7. Dusick AM, *et al.* Risk of intracranial hemorrhage and other adverse outcomes after cocaine exposure in a cohort of 323 very low birth weight infants. *J Pediatr* 1993; **122:** 438–45.
8. Bingol N, *et al.* Teratogenicity of cocaine in humans. *J Pediatr* 1987; **110:** 93–6.
9. Little BB, *et al.* Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol* 1989; **73:** 157–60.
10. Mastrogiannis DS, *et al.* Perinatal outcome after recent cocaine usage. *Obstet Gynecol* 1990; **76:** 8–11.
11. Spence MR, *et al.* The relationship between recent cocaine use and pregnancy outcome. *Obstet Gynecol* 1991; **78:** 326–9.
12. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
13. Gonsoulin W, *et al.* Rupture of unscarred uterus in primigravid woman in association with cocaine abuse. *Am J Obstet Gynecol* 1990; **163:** 526–7.
14. Thatcher SS, *et al.* Cocaine use and acute rupture of ectopic pregnancies. *Obstet Gynecol* 1989; **74:** 478–9.
15. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; **320:** 762–8.
16. Chasnoff IJ, *et al.* Temporal patterns of cocaine use in pregnancy: perinatal outcome. *JAMA* 1989; **261:** 1741–4.
17. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol* 1991; **77:** 361–4.
18. Lipshultz SE, *et al.* Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr* 1991; **118:** 44–51.
19. Shaw GM, *et al.* Maternal use of cocaine during pregnancy and congenital cardiac anomalies. *J Pediatr* 1991; **118:** 167–8.
20. Hoyme HE, *et al.* Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 1990; **85:** 743–7.
21. Chávez GF, *et al.* Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 1989; **262:** 795–8.
22. Singer LT, *et al.* Neurobehavioural sequelae of fetal cocaine exposure. *J Pediatr* 1991; **119:** 667–72.
23. Doberczak TM, *et al.* Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 1988; **113:** 354–8.
24. Singer LT, *et al.* Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; **124:** 765–71.
25. Azuma SD, Chasnoff IJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics* 1993; **92:** 396–402.
26. Mayes LC, *et al.* Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. *Pediatrics* 1995; **95:** 539–45.
27. van der Bor M, *et al.* Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. *Pediatrics* 1990; **85:** 733–6.
28. Chasnoff IJ, *et al.* Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; **108:** 456–9.

Treatment of Adverse Effects

As for Local Anaesthetics in general, p.1851.

Cocaine overdosage. In the emergency management of overdosage with cocaine the general aims are to establish adequate ventilation and support the circulation. If oral ingestion of a large amount is suspected the stomach should be emptied and activated charcoal given.[1] A tourniquet may be applied to limit absorption if the drug was injected. Patients who have swallowed packages containing cocaine for the purpose of smuggling, may be given laxatives but surgical intervention may be required if signs of toxicity appear.[2]

Sedation with intravenous diazepam may be sufficient to manage the symptoms of cocaine overdose. Sedation with benzodiazepines may also be appropriate initial therapy for hypertension or tachyarrhythmias since the excessive sympathetic tone is largely centrally mediated.[3] Severe life-threatening arrhythmias may require treatment with intravenous propranolol although, following a report of paradoxical hypertension presumably due to unopposed α-adrenergic stimulation, a beta blocker with both α- and β-adrenergic effects such as labetalol is preferred by some if hypertension is also present;[2,4] sodium nitroprusside[3,4] or phentolamine[3,5] may also be used. Although labetalol can reduce the hypertension it does not alleviate cocaine-induced coronary vasoconstriction;[6] it has therefore been suggested that glyceryl trinitrate would be preferable for patients with cocaine-induced chest pain.[5,6] Chest pain may also be treated with aspirin. Calcium-channel blockers such as verapamil may also be of use as an antagonist for coronary artery vasoconstriction induced by cocaine.[5] There is concern about the use of lidocaine for the treatment of cocaine-induced arrhythmias as lidocaine may enhance toxicity.[5] Diazepam should be used to manage seizures[1,4] but if they cannot be controlled phenytoin can be used as an adjunct.[1] Hyperthermia should be treated with physical cooling but the use of dantrolene may also be necessary.[1] Control of anxiety and agitation with benzodiazepines when combined with rapid cooling may also have the effect of decreasing heat production in hyperthermic patients.[3] Metabolic acidosis should be monitored and treated where necessary.[1,4] Short-acting barbiturates or benzodiazepines may be used for dysphoric agitation but drugs that lower the seizure threshold or aggravate hyperthermia such as phenothiazines or haloperidol should be avoided.[1]

1. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
2. Ramrakha P, Barton I. Drug smuggler's delirium. *BMJ* 1993; **306:** 470–1.
3. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1996; **38:** 43–6.
4. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
5. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.
6. Boehrer JD, *et al.* Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med* 1993; **94:** 608–10.

Cocaine withdrawal syndrome. Cocaine can produce psychological dependence but does not produce a major physical withdrawal syndrome. The management of cocaine abuse and dependence has been reviewed.[1-3] There is no advantage to gradual withdrawal and it is best for the patient to stop the drug abruptly.[1,4] The three major psychiatric complications associated with cocaine withdrawal are dysphoric agitation, severe depression, and psychotic symptoms.[1] Such complications are initially managed with psychosocial treatments. However patients with more severe dependence or those who fail to respond to psychosocial treatments should be considered for drug therapies. Dysphoric agitation is best treated with diazepam; propranolol may also be used in more persistent cases. Depressive symptoms during the acute post-cocaine phase are usually transient and require no treatment other than close observation. Desipramine has been used with equivocal results; it appears to be of most benefit in patients who have antecedent or consequent symptoms of severe depression.[3] Trazodone and imipramine have also been tried but had more adverse effects than desipramine.[3] Furthermore, a systematic review has concluded that there was no evidence to support the use of antidepressants[5] in the treatment of cocaine dependence. Antipsychotics such as chlorpromazine, haloperidol, and promazine have been used to manage patients with psychotic symptoms associated with cocaine dependence.[1]

Several drugs have been tried in the maintenance of abstinence from cocaine.[1] Lithium may be useful in patients with bipolar disorder or cyclothymic personality. Methylphenidate may be helpful in patients with attention deficit disorders but has potential for abuse itself. Phenothiazine derivatives have been tried in the control of impulsive behaviour and to decrease cocaine craving, although adverse effects may limit their acceptability. Carbamazepine has been reported to suppress the craving for cocaine although this has not been supported by subsequent studies.[3] Buprenorphine has been investigated to suppress cocaine and opioid use in patients dependent on both drugs.[3] Anxiolytics or antidepressants are considered unlikely to be of benefit in maintaining abstinence.[3] MAOIs such as phenelzine have been used in a manner analogous to the use of disulfiram in alcohol abuse to provoke unpleasant reactions if patients relapse.[6] Disulfiram itself has also been tried with some success (see below).

There is evidence to suggest that cocaine use affects the dopaminergic modulation of CNS function, and several drugs that interact with the dopamine system have been tried in the treatment of cocaine abuse and dependence.[3,7] For most drugs the results have been disappointing or equivocal although disulfiram and selegiline may warrant further investigation.[7]

1. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
2. Kleber HD. Pharmacotherapy, current and potential, for the treatment of cocaine dependence. *Clin Neuropharmacol* 1995; **18** (suppl 1): S96–S109.
3. Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996; **334:** 965–72.
4. DoH. *Drug misuse and dependence: guidelines on clinical management*. London: HMSO, 1999. Also available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/04.00dh/04.00en/documents/digitalasset/dh_4078198.pdf (accessed 11/08/08)
5. Lima MS, *et al.* Antidepressants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 21/04/08).
6. Brewer C. Cocaine and crack. *BMJ* 1989; **299:** 792.
7. Gorelick DA, *et al.* Agents in development for the management of cocaine abuse. *Drugs* 2004; **64:** 1547–73.

Precautions

As for Local Anaesthetics in general, p.1851.

Since some patients have a marked sensitivity to cocaine, giving a test dose before use on mucous membranes has been suggested. Cocaine should not be applied to damaged mucosa because of the risk of systemic toxicity from enhanced absorption. Ophthalmic preparations of cocaine should not be applied to the eyes for prolonged periods as damage to the cornea may occur not only from the local action of cocaine, but also from loss of the protective eyelid reflexes. As with other mydriatics, there is also a risk of cocaine precipitating angle-closure glaucoma in patients predisposed to the condition. Patients receiving cocaine for surface anaesthesia should be monitored for possible cardiovascular effects. Cocaine should be used with great caution in patients with hypertension, cardiovascular disease, or thyrotoxicosis. It is not recommended for use during pregnancy or breast feeding.

Abuse. Cocaine is subject to abuse. See under Adverse Effects, above.

Gilles de la Tourette's syndrome. Gilles de la Tourette's syndrome, which had been well controlled for 10 years by haloperidol, was precipitated in a 27-year-old man after intranasal use of cocaine on one occasion.[1]

1. Mesulam M-M. Cocaine and Tourette's syndrome. *N Engl J Med* 1986; **315:** 398.

Myasthenia gravis. Report of a patient in whom cocaine abuse first unmasked and then exacerbated myasthenia gravis.[1]

1. Berciano J, *et al.* Myasthenia gravis unmasked by cocaine abuse. *N Engl J Med* 1991; **325:** 892.

Porphyria. Cocaine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Cocaine and adrenaline enhance each other's sympathomimetic effects and should preferably not be used together. Caution is needed if cocaine is used with other drugs that may also potentiate the action of catecholamines such as guanethidine or MAOIs.

Adrenaline. In a report[1] of 3 cases of arrhythmias associated with the use of a paste containing cocaine 25% and adrenaline 0.18% for local anaesthesia of the nasal mucosa, the amount of cocaine applied to the nasal mucosa ranged from about 2.5 to 4.5 mg/kg. The maximum recommended dose of cocaine alone in healthy adults is 1.5 mg/kg.

1. Nicholson KEA, Rogers JEG. Cocaine and adrenaline paste: a fatal combination? *BMJ* 1995; **311:** 250–1.

Alcohol. In the presence of alcohol, cocaine is metabolised to its ethyl homologue cocaethylene.[1] Cocaethylene appears to have the same stimulant effects as cocaine but it has a longer half-life and *animal* studies suggest that it is more toxic than the parent drug. However, a review of the literature concluded that the use of cocaine with alcohol did not cause more cardiovascular problems than expected from the additive effects of each drug.[2]

1. Randall T. Cocaine, alcohol mix in body to form even longer lasting, more lethal drug. *JAMA* 1992; **267:** 1043–4.
2. Pennings EJM, *et al.* Effects of concurrent use of alcohol and cocaine. *Addiction* 2002; **97:** 773–83.

Beta blockers. *Propranolol* potentiated cocaine-induced coronary vasoconstriction after intranasal dosage of cocaine in a placebo-controlled study.[1] Because of a possible risk of paradoxical hypertension associated with the use of propranolol to manage arrhythmias associated with cocaine overdosage some prefer the use of labetalol for this indication (see under Treatment of Adverse Effects, above).

1. Lange RA, *et al.* Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990; **112:** 897–903.

Haloperidol. For the effect of haloperidol in cocaine abusers, see under Chlorpromazine, p.974.

Pharmacokinetics

Cocaine may be slowly absorbed from some sites because of the vasoconstriction it produces, but absorption occurs from all sites of application, including mucous membranes and the gastrointestinal tract, and may be enhanced when there is inflammation. Cocaine is rapidly absorbed when smoked.

Cocaine is rapidly metabolised by plasma esterases and hepatic esterases to ecgonine methyl ester. Benzoylecgonine, another major metabolite of cocaine, may be produced by spontaneous hydrolysis. Cocaine is also demethylated to the active metabolite norcocaine which is not excreted but undergoes further metabolism. There is considerable interindividual variation in the plasma half-life of cocaine possibly due to differences in esterase activity.

Cocaine and its metabolites are excreted in the urine, about 10% appearing as unchanged drug; they may be detectable in urine for several days or even weeks after use. Cocaine crosses the blood-brain barrier and accumulates within the CNS. It does not appear to undergo rapid metabolism within the brain and concentrations in the CNS after acute intoxication may greatly exceed those in plasma.

Cocaine crosses the placenta and the presence of its metabolites in neonatal hair has been used to indicate intra-uterine exposure. Cocaine is distributed into breast milk.

See also under Local Anaesthetics, p.1852.

◊ References.

1. Busto U, *et al.* Clinical pharmacokinetics of non-opiate abused drugs. *Clin Pharmacokinet* 1989; **16:** 1–26.
2. Graham K, *et al.* Determination of gestational cocaine exposure by hair analysis. *JAMA* 1989; **262:** 3328–30.
3. Burke WM, Ravi NV. Urinary excretion of cocaine. *Ann Intern Med* 1990; **112:** 548–9.
4. Ravi NV, Burke WM. Cocaine and traffic accident fatalities in New York City. *JAMA* 1990; **263:** 2887.
5. Schenker S, *et al.* The transfer of cocaine and its metabolites across the term human placenta. *Clin Pharmacol Ther* 1993; **53:** 329–39.

Absorption. Cocaine is rapidly absorbed from the pulmonary vasculature when smoked and the speed of onset of its effects is similar to that obtained after intravenous injection.[1] Absorption from mucous membranes is delayed by vasoconstriction and peak plasma concentrations of up to 474 nanograms/mL have been obtained 15 to 120 minutes after application of doses of 1.5 to 2 mg/kg to the nasal mucosa as a 10% cocaine hydrochloride solution;[2,3] cocaine may still be detectable in the nose several hours later and this may result in prolonged systemic absorption.[2] In a study it was estimated that only 5% of the total dose of cocaine hydrochloride used prior to nasal surgery was absorbed from the nasal mucosa following application of 500 mg of cocaine hydrochloride as a 25% paste with adrenaline or 200 mg as a 10% solution with adrenaline (Moffett's solution) and blood concentrations were well below those associated with toxicity[4] (but see also Adrenaline, under Interactions, above). Peak serum concentrations of cocaine have been obtained after 50 to 90 minutes after oral use and are similar to those obtained after nasal application.[3]

1. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
2. Van Dyke C, *et al.* Cocaine: plasma concentrations after intranasal application in man. *Science* 1976; **191:** 859–61.
3. Van Dyke C, *et al.* Oral cocaine: plasma concentrations and central effects. *Science* 1978; **200:** 211–13.
4. Quiney RE. Intranasal topical cocaine: Moffett's method or topical cocaine paste? *J Laryngol Otol* 1986; **100:** 279–83.

Uses and Administration

Cocaine, a benzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1852. It is used as a surface anaesthetic but, because of systemic adverse effects and its abuse potential, its use is now almost entirely restricted to surgery of the ear, nose, and throat. It has been largely replaced by other drugs in ophthalmology because of its corneal toxicity, although it may still be useful in removal or debridement of the corneal epithelium. Cocaine also blocks the uptake of catecholamines at adrenergic nerve endings and potentiates the action of catecholamines. Its sympathomimetic actions cause tachycardia, peripheral vasoconstriction, a rise in blood pressure, and mydriasis. The use of cocaine with sympathomimetics such as adrenaline increases the risk of cardiac arrhythmias. Despite this hazard some use this combination in otolaryngology to improve the operative field and reduce absorption.

When applied to mucous membranes, surface anaesthesia develops rapidly and persists for 30 minutes or longer depending on the concentration of cocaine used, the dose, and on the vascularity of the tissue.

Cocaine hydrochloride is used in aqueous solutions; cocaine hydrochloride 1.12 g is equivalent to about 1 g of cocaine. Solutions containing up to 4% have been used in ophthalmology (but precautions for ophthalmic use should be considered, see above).

Solutions containing up to 10% of cocaine are applied to the nasal mucosa in otolaryngological procedures. Pastes containing up to 25% of cocaine have also been applied.

In order to avoid systemic effects, the usual maximum total dose recommended for application to the nasal mucosa in healthy adults is 1.5 mg/kg. It should be used only by those skilled in the precautions needed to minimise absorption and the consequent risk of arrhythmias.

Cocaine was used with diamorphine or morphine for the relief of severe pain, especially in terminal illness, but this use is now obsolete.

Cocaine solutions should *never* be given by injection; other local anaesthetics are equally effective and much safer.

◊ References.

1. Middleton RM, Kirkpatrick MB. Clinical use of cocaine: a review of the risks and benefits. *Drug Safety* 1993; **9:** 212–17.
2. Latorre F, Klimek L. Does cocaine still have a role in nasal surgery? *Drug Safety* 1999; **20:** 9–13.

Preparations

BP 2008: Cocaine Eye Drops;
USP 31: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Cocaine Hydrochloride Tablets for Topical Solution.

Diperodon Hydrochloride *(BANM, rINNM)*

Diperocaine Hydrochloride; Dipérodon, Chlorhydrate de; Diperodoni Hydrochloridum; Hidrocloruro de diperodón. 3-Piperidinopropylene bis(phenylcarbamate) hydrochloride.

Диперодона Гидрохлорид

$C_{22}H_{27}N_3O_4,HCl = 433.9.$
CAS — 101-08-6 (anhydrous diperodon); 51552-99-9 (diperodon monohydrate); 537-12-2 (diperodon hydrochloride).

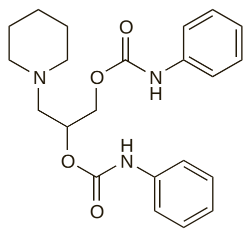

(diperodon)

Profile

Diperodon is a local anaesthetic (p.1850) that has been used as the base or the hydrochloride for surface anaesthesia.

Dyclonine Hydrochloride *(BANM, rINNM)*

Dyclocaine Hydrochloride; Dyclocaini Chloridum; Dyclonine, Chlorhydrate de; Dyclonini Hydrochloridum; Hidrocloruro de diclonina. 4′-Butoxy-3-piperidinopropiophenone hydrochloride.

Диклонина Гидрохлорид

$C_{18}H_{27}NO_2,HCl = 325.9.$
CAS — 586-60-7 (dyclonine); 536-43-6 (dyclonine hydrochloride).
ATC — N01BX02; R02AD04.
ATC Vet — QN01BX02; QR02AD04.

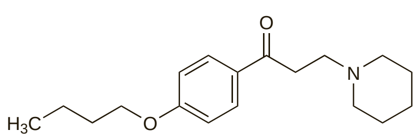

(dyclonine)

Pharmacopoeias. In *US.*

USP 31 (Dyclonine Hydrochloride). White crystals or white crystalline powder, with a slight odour. Soluble 1 in 60 of water, 1 in 24 of alcohol, and 1 in 2.3 of chloroform; soluble in acetone; practically insoluble in ether and in hexane. A 1% solution in water has a pH of 4.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Dyclonine hydrochloride is a local anaesthetic (p.1850) used topically for surface anaesthesia of the skin and mucous membranes. Lozenges containing up to 3 mg and throat sprays containing 0.1% of dyclonine hydrochloride have been used for the temporary relief of pain associated with sore throats or mouth irritation; a 1% gel has also been used. A concentration of 0.75% has been used on the skin. It may cause irritation at the site of application.

Preparations

USP 31: Dyclonine Hydrochloride Gel; Dyclonine Hydrochloride Topical Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Cepacol Spray; Sucrets; Sucrets for Kids; ***Israel:*** Childrens Cherry Sucrets†; Sucrets Children's Formula†; Sucrets Maximum Strength†; ***USA:*** Dyclone†; Sucrets Childrens Formula; Sucrets Original Formula Sore Throat Wild Cherry; Sucrets Throat Spray.

Multi-ingredient: *Canad.:* Tanac†; ***USA:*** Cepacol Maximum Strength Sore Throat; Skin Shield; Sucrets Complete; Sucrets Maximum Strength Sore Throat; Tanac.

Ethyl Chloride

Aethylium Chloratum; Chlorethyl; Cloruro de etilo; Ethyli Chloridum; Ethylis Chloridum; Etylklorid; Etylu chlorek; Etyylikloridi; Hydrochloric Ether; Monochlorethane. Chloroethane.

$C_2H_5Cl = 64.51.$
CAS — 75-00-3.
ATC — N01BX01.
ATC Vet — QN01BX01.

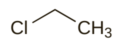

Pharmacopoeias. In *Pol.* and *US.*

USP 31 (Ethyl Chloride). A colourless, mobile, very volatile liquid at low temperatures or under pressure, with a characteristic ethereal odour. B.p. 12° to 13°. Slightly soluble in water; freely soluble in alcohol and in ether. Store in airtight containers, preferably hermetically sealed.

Stability. Ethyl chloride is highly flammable and mixtures of the gas with 5 to 15% of air are explosive.

Adverse Effects and Precautions

As for Chloroform, p.1781.

Cutaneous sensitisation can occur rarely. Thawing of frozen tissue following surgery may be painful and prolonged spraying onto the skin can cause chemical frostbite. Freezing may also distort the histological structure of biopsy specimens. Ethyl chloride should not be applied to broken skin or mucous membranes.

Uses and Administration

Owing to its low boiling-point and the intense cold produced by evaporation, ethyl chloride has been used as a local anaesthetic in minor surgery but such use is not generally recommended. It has also been used topically for the relief of pain and to test the effectiveness of regional anaesthesia. Ethyl chloride was formerly used as an inhalational anaesthetic but has no place in modern anaesthetic practice.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Chloraethyl Dr Henning; WariActiv; ***Hong Kong:*** WariActiv; ***Hung.:*** Chloraethyl†; ***Israel:*** Chloraethyl Dr Henning; ***Mex.:*** Traumazol; ***Spain:*** Cloretilo Chemirosa; ***Switz.:*** Chlorethyl; ***UK:*** Cryogesic.

Multi-ingredient: *USA:* Fluro-Ethyl.

Ethyl *p*-Piperidinoacetylaminobenzoate

EPAB; *p*-Piperidinoacetilaminobenzoato de etilo; SA-7. 4-[(1-Piperidinylacetyl)amino]benzoic acid ethyl ester.

$C_{16}H_{22}N_2O_3 = 290.4.$
CAS — 41653-21-8.

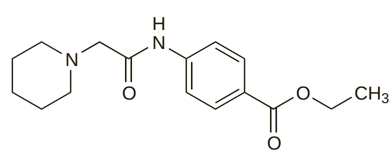

Profile

Ethyl *p*-piperidinoacetylaminobenzoate is an amide local anaesthetic (p.1850) that has been given orally for the symptomatic relief of gastritis.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Sulcain.

Multi-ingredient: *Hong Kong:* Sulcain†; ***Singapore:*** Sulcain†; ***Thai.:*** Sulcain†.

Etidocaine *(BAN, USAN, rINN)*

Etidocaína; Étidocaïne; Etidocainum; Etidokaiini; Etidokain. (±)-2-(*N*-Ethylpropylamino)-butyro-2′,6′-xylidide.

Этидокаин

$C_{17}H_{28}N_2O = 276.4.$
CAS — 36637-18-0.
ATC — N01BB07.
ATC Vet — QN01BB07.

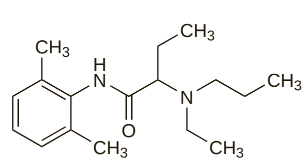

Etidocaine Hydrochloride *(BANM, rINNM)*

Étidocaïne, Chlorhydrate d'; Etidocaini Hydrochloridum; Hidrocloruro de etidocaína; W-19053.

Этидокаина Гидрохлорид

$C_{17}H_{28}N_2O,HCl = 312.9.$
CAS — 36637-19-1.
ATC — N01BB07.
ATC Vet — QN01BB07.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Effects on the cardiovascular system. For a discussion of the cardiotoxicity of etidocaine, see under the Adverse Effects of Bupivacaine Hydrochloride, p.1855.

Porphyria. Etidocaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

Etidocaine is rapidly absorbed into the circulation after parenteral injection and is about 95% bound to plasma proteins. It crosses the placenta but the ratio of fetal to maternal concentrations is relatively low. It also diffuses across the blood-brain barrier. Etidocaine is metabolised in the liver and its numerous metabolites are excreted in the urine; less than 10% of the drug is excreted unchanged. The plasma elimination half-life of etidocaine is 2 to 3 hours in adults.

See also under Local Anaesthetics, p.1852.

Pregnancy. After maternal injection etidocaine rapidly crosses the placenta[1] but the degree of transfer is less than for other local anaesthetics including bupivacaine.[2] The ratio of fetal to maternal concentrations of etidocaine varies but values up to about 0.35 are usual.[1,2] Some metabolites appear to be transferred to a greater degree than the parent compound[1]. Etidocaine is highly protein bound but the fraction of unbound drug in plasma increases in pregnant women during delivery.[1] Protein binding of etidocaine is also reduced in fetal plasma.[3] Although neonates are able to metabolise etidocaine it appears that they are less able to do so than adults; a mean elimination half-life of 6.42 hours has been reported in neonates.[3]

1. Morgan DJ, *et al.* Disposition and placental transfer of etidocaine in pregnancy. *Eur J Clin Pharmacol* 1977; **12:** 359–65.
2. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
3. Morgan D, *et al.* Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates: 11: etidocaine. *Eur J Clin Pharmacol* 1978; **13:** 365–71.

Uses and Administration

Etidocaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It has a rapid onset and a long duration of action. Etidocaine has been used for infiltration anaesthesia, peripheral nerve block, and epidural block, usually with adrenaline 1 in 200 000. (Local anaesthetic techniques are discussed on p.1853.)

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Duranest†.

Fomocaine Hydrochloride *(BANM, rINNM)*

Fomocaïne, Chlorhydrate de; Fomocaini Hydrochloridum; Hidrocloruro de fomocaína. 4-[3-(α-Phenoxy-*p*-tolyl)propyl]morpholine hydrochloride.

Фомокаина Гидрохлорид

$C_{20}H_{25}NO_2,HCl = 347.9.$
CAS — 17692-39-6 (fomocaine); 56583-43-8 (fomocaine hydrochloride).

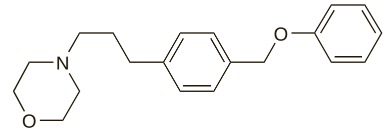

(fomocaine)

Profile

Fomocaine is a local anaesthetic that has been included, as the hydrochloride, in mixed products intended for use in infected skin conditions.

Ketocaine Hydrochloride *(rINNM)*

Chetocaina Cloridrata; Hidrocloruro de ketocaína; Kétocaïne, Chlorhydrate de; Ketocaini Hydrochloridum. 2′-(2-Di-isopropylaminoethoxy)butyrophenone hydrochloride.

Кетокаина Гидрохлорид

$C_{18}H_{29}NO_2,HCl = 327.9.$

CAS — 1092-46-2 (ketocaine); 1092-47-3 (ketocaine hydrochloride).

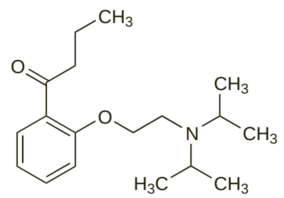

(ketocaine)

Profile

Ketocaine hydrochloride is a local anaesthetic (p.1850) that has been used as a surface anaesthetic in suppositories or ointments for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Proctolyn.

Levobupivacaine *(BAN, rINN)*

S(−)-Bupivacaine; Levobupivacaína; Lévobupivacaïne; Levobupivacainum; Levobupivakaiini; Levobupivakain. (S)-1-Butyl-2-piperidylformo-2′,6′-xylidide.

Левобупивакаин

$C_{18}H_{28}N_2O = 288.4.$

CAS — 27262-47-1.

ATC — N01BB10.

ATC Vet — QN01BB10.

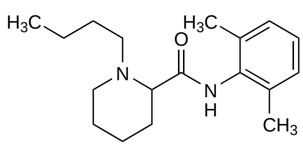

Levobupivacaine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levobupivacaína; Lévobupivacaïne, Chlorhydrate de; Levobupivacaini Hydrochloridum; Levobupivakain Hidroklorür.

Левобупивакаина Гидрохлорид

$C_{18}H_{28}N_2O,HCl = 324.9.$

CAS — 27262-48-2.

ATC — N01BB10.

ATC Vet — QN01BB10.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Levobupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is also contra-indicated for epidural block in obstetrics.

Effects on the cardiovascular system. It has been suggested[1] that levobupivacaine may have a lower risk of causing cardiotoxicity than bupivacaine (for the effects of bupivacaine on the cardiovascular system see p.1855).

1. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* 2001; **61:** 333–42.

Interactions

For interactions associated with local anaesthetics, see p.1851. Plasma concentrations of levobupivacaine may be reduced by enzyme-inducing drugs such as rifampicin. Levobupivacaine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP1A2 and there is a theoretical possibility that substrates for or inhibitors of these isoenzymes may adversely alter plasma concentrations of levobupivacaine.

Pharmacokinetics

The pharmacokinetics of levobupivacaine are similar to those of the racemic form, bupivacaine (p.1855). Levobupivacaine is at least 97% bound to plasma proteins. After intravenous doses the mean half-life is about 80 minutes. Levobupivacaine is extensively metabolised and excreted as its metabolites mainly in the urine, with smaller amounts appearing in the faeces. 3-Hydroxylevobupivacaine is a major metabolite and its formation is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 is also involved in the metabolism of levobupivacaine.

Uses and Administration

Levobupivacaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It is the S-enantiomer of bupivacaine (p.1854). Levobupivacaine is given as the hydrochloride for infiltration anaesthesia and regional nerve blocks including epidural block; however it is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is also contra-indicated for epidural blocks in obstetrics. (Local anaesthetic techniques are discussed on p.1853.)

Levobupivacaine hydrochloride is available in solutions containing the equivalent of 0.25 to 0.75% of levobupivacaine. The dosage depends on the site of injection and the procedure used as well as the status of the patient. The recommended **maximum single dose** is 150 mg. The total daily dose should not exceed 400 mg. A test dose of a suitable local anaesthetic, preferably with adrenaline, should be given before commencing epidural block with levobupivacaine to detect inadvertent intravascular injection. Subsequent doses of levobupivacaine should be given in small increments. Levobupivacaine should be given in reduced doses to elderly, debilitated, or acutely ill patients.

- For **surgical anaesthesia** doses of levobupivacaine for *epidural block* are 50 to 100 mg (10 to 20 mL) as a 0.5% solution, or 75 to 150 mg (10 to 20 mL) as a 0.75% solution; for caesarean section, doses are 75 to 150 mg (15 to 30 mL) as a 0.5% solution. The dose for *spinal block* is 15 mg (3 mL) as a 0.5% solution.
- For *peripheral nerve blocks*, doses are 2.5 to 150 mg as a 0.25 or 0.5% solution; a volume of 40 mL should not be exceeded. Alternatively doses for peripheral block have been expressed on the basis of body-weight: 1 to 2 mg/kg (0.4 mL/kg) as a 0.25 or 0.5% solution.
- For *infiltration anaesthesia* up to 150 mg (60 mL) as a 0.25% solution may be used. For peribulbar block in *ophthalmic* procedures 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution may be given. For ilioinguinal or iliohypogastric blocks in **children** under 12 years, doses of levobupivacaine are 0.625 to 2.5 mg/kg (0.25 to 0.5 mL/kg) as a 0.25 or 0.5% solution.
- In the management of **acute pain** levobupivacaine may be given as an epidural bolus or by continuous infusion. For pain relief during *labour* 15 to 50 mg (6 to 20 mL) as a 0.25% solution is given as a bolus. Alternatively, a 0.125% solution may be given as an infusion in a dose of 5 to 12.5 mg (4 to 10 mL) per hour, or a 0.0625% solution may be given in a dose of 5 to 12.5 mg (8 to 20 mL) per hour. For *postoperative pain* 10 to 25 mg (4 to 10 mL) per hour as a 0.25% solution, 12.5 to 18.75 mg (10 to 15 mL) per hour as a 0.125% solution, or 12.5 to 18.75 mg (20 to 30 mL) per hour as a 0.0625% solution may be given as an epidural infusion.

In some countries such as the UK, licensed product information recommends that a lower concentration such as the 0.125% solution should be used if other analgesics are also given for pain relief; in other countries product information has specifically stated that the 0.125% solution should only be used for adjunctive therapy with fentanyl or clonidine. When necessary, dilutions should be made with sodium chloride 0.9%.

◊ Reviews

1. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs* 2000; **59:** 551–79.

Action. A comparison[1] of epidural bupivacaine with levobupivacaine in women in labour found that levobupivacaine had 98% of the potency of the racemate, a clinically insignificant difference. However it was pointed out that whereas the concentration of bupivacaine solutions was expressed in terms of the hydrochloride, solutions of levobupivacaine had their strength expressed in terms of the free base. When calculations were made in terms of molar equivalents levobupivacaine appeared to be 13% less potent than racemic bupivacaine. The difference in expression should be borne in mind when evaluating comparative studies.

1. Lyons G, *et al*. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; **81:** 899–901.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Chirocaine; ***Austria:*** Chirocaine; ***Belg.:*** Chirocaine; ***Braz.:*** Novabupi; ***Chile:*** Chirocaina; ***Cz.:*** Chirocaine; ***Fin.:*** Chirocaine; ***Fr.:*** Chirocaine; ***Gr.:*** Chirocaine; ***Hong Kong:*** Chirocaine; ***Hung.:*** Chirocaine; ***Irl.:*** Chirocaine; ***Ital.:*** Chirocaine; ***Mex.:*** Quirocaine; ***Neth.:*** Chirocaine; ***Norw.:*** Chirocaine; ***NZ:*** Chirocaine†; ***Philipp.:*** SensiBloq; ***Port.:*** Chirocaine; ***S.Afr.:*** Chirocaine; ***Singapore:*** Chirocaine; ***Spain:*** Chirocane; ***Swed.:*** Chirocaine; ***Switz.:*** Chirocaine; ***Turk.:*** Chirocaine; ***UK:*** Chirocaine; ***USA:*** Chirocaine†; ***Venez.:*** Chirocaina.

Lidocaine *(BAN, rINN)*

Lidocaína; Lidocaïne; Lidocainum; Lidokaiini; Lidokain; Lidokaina; Lidokainas; Lignocaine. 2-Diethylaminoaceto-2′,6′-xylidide.

Лидокаин

$C_{14}H_{22}N_2O = 234.3.$

CAS — 137-58-6.

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

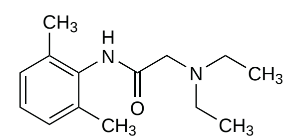

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Lidocaine). A white or almost white, crystalline powder. M.p. 66° to 70°. Practically insoluble in water; very soluble in alcohol and in dichloromethane.

USP 31 (Lidocaine). A white to slightly yellow crystalline powder with a characteristic odour. M.p. 66° to 69°. Practically insoluble in water; very soluble in alcohol and in chloroform; freely soluble in ether and in benzene; dissolves in oils.

Eutectic mixture. Lidocaine forms a mixture with prilocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Lidocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lidocaína; Lidocaïne, chlorhydrate de; Lidocaini hydrochloridum; Lidocaini Hydrochloridum Monohydricum; Lidokaiinihydrokloridi; Lidokain Hidroklorür; Lidokain-hidroklorid; Lidokain-hydrochlorid monohydrát; Lidokainhydroklorid; Lidokaino hidrochloridas; Lidokainy chlorowodorek; Lignoc. Hydrochlor.; Lignocaine Hydrochloride; Lignokain Hidroklorür.

Лидокаина Гидрохлорид

$C_{14}H_{22}N_2O,HCl,H_2O = 288.8.$

CAS — 73-78-9 (anhydrous lidocaine hydrochloride); 6108-05-0 (lidocaine hydrochloride monohydrate).

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

NOTE. LIDFLN is a code approved by the BP 2008 for use on single unit doses of eye drops containing lidocaine hydrochloride and fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Lidocaine Hydrochloride). A white, or almost white, crystalline powder. M.p. 74° to 79°. Very soluble in water; freely soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 31 (Lidocaine Hydrochloride). A white, odourless, crystalline powder. M.p. 74° to 79°. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Incompatibility. Lidocaine hydrochloride has been reported to be incompatible in solution with amphotericin B,[1] sulfadiazine sodium,[2] methohexital sodium,[2] cefazolin sodium,[3] or phenytoin sodium.[4]

Acid stable drugs such as adrenaline hydrochloride, noradrenaline acid tartrate, or isoprenaline may begin to deteriorate within several hours of admixture with lidocaine hydrochloride as lidocaine solutions may raise the pH of the final solution above the maximum pH for their stability. Such extemporaneous mixtures should be used promptly after preparation.[5]

1. Whiting DA. Treatment of chromoblastomycosis with high local concentrations of amphotericin B. *Br J Dermatol* 1967; **79:** 345–51.
2. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.
3. Kleinberg ML, *et al.* Stability of antibiotics frozen and stored in disposable hypodermic syringes. *Am J Hosp Pharm* 1980; **37:** 1087–8.
4. Kirschenbaum HL, *et al.* Stability and compatibility of lidocaine hydrochloride with selected large-volume parenterals and drug additives. *Am J Hosp Pharm* 1982; **39:** 1013–15.
5. Parker EA. Xylocaine hydrochloride 2% injection. *Am J Hosp Pharm* 1971; **28:** 805.

pH of solutions. For the effect pH has on the surface tension and administration of lidocaine solutions by infusion, see under Administration in Uses and Administration, p.1852. For its effect on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

Stability. Although there was no decrease in the lidocaine content of lidocaine hydrochloride and adrenaline injection during transport and storage under tropical conditions, the content of adrenaline fell to almost zero in some samples after several months; supply of the injection as a dry powder and separate solvent should be considered for the tropics.[1]

The lidocaine content of buffered cardioplegic solutions has been reported[2] to decrease when stored in PVC containers at ambient temperature, but not when stored at 4°. This loss appeared to result from pH-dependent sorption of lidocaine onto the plastic and did not occur when lidocaine solutions were stored in glass bottles.

1. Abu-Reid IO, *et al.* Stability of drugs in the tropics: a study in Sudan. *Int Pharm J* 1990; **4:** 6–10.
2. Lackner TE, *et al.* Lidocaine stability in cardioplegic solution stored in glass bottles and polyvinyl chloride bags. *Am J Hosp Pharm* 1983; **40:** 97–101.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Effects on the CNS. Suspected psychotic reactions have been reported in 6 patients given intravenous lidocaine for the treatment of cardiac disorders.[1] In another case,[2] 2 patients developed signs of cerebral ataxia after topical use of lidocaine for endoscopy.

When compared with other local anaesthetics, lidocaine may be associated with an increased risk of neurotoxic complications when used for spinal anaesthesia, (see under Adverse Effects of Central Block, p.1850).

1. Turner WM. Lidocaine and psychotic reactions. *Ann Intern Med* 1982; **97:** 149–50.
2. Perney P, *et al.* Transitory ataxia related to topically administered lidocaine. *Ann Pharmacother* 2004; **38:** 828–30.

Effects on the skin. Erythema and pigmentation of the upper lip in a child after local dental infiltration of lidocaine was attributed to a type of fixed drug eruption.[1] Erythema may also occur after topical use of some lidocaine formulations, such as transdermal patches, while transient blanching of the skin is frequent after application of eutectic lidocaine/prilocaine mixtures to the skin.[2]

True hypersensitivity reactions, including dermatitis, are rare (see also p.1850) but can occur.[3]

1. Curley RK, *et al.* An unusual cutaneous reaction to lignocaine. *Br Dent J* 1987; **162:** 113–14.
2. Villada G, *et al.* Local blanching after epicutaneous application of EMLA cream: a double-blind randomized study among 50 healthy volunteers. *Dermatologica* 1990; **181:** 38–40.
3. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.

Overdosage. The most serious effects of lidocaine intoxication are on the CNS and cardiovascular system and overdosage can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Intoxication with lidocaine is relatively common and can occur as a result of acute overdosage after poor control of intravenous maintenance infusions or accidental injection of concentrated solutions. However, it more commonly results from inadvertent intravascular dosage during regional anaesthesia, or from too rapid injection of antiarrhythmic doses, particularly in patients with circulatory insufficiency, or when clearance is reduced due to heart failure, liver disease, old age, or through interaction with other drugs.[1] Seizures have also been reported after excessive doses given subcutaneously.[2] Although the bioavailability of lidocaine is low it may be sufficient to result in significant toxicity when swallowed[1] and there have been reports of CNS effects, seizures, and death in children[3-7] and adults[8-10] after the ingestion of topical solutions and after the use of viscous preparations in the mouth. Death has also ensued after gargling with a 4% lidocaine solution.[11] Lidocaine is absorbed from mucous membranes and serious toxicity has been reported after urethral[12] or rectal[13] instillation of lidocaine preparations.

1. Denaro CP, Benowitz NL. Poisoning due to class 1B antiarrhythmic drugs: lignocaine, mexiletine and tocainide. *Med Toxicol Adverse Drug Exp* 1989; **4:** 412–28.
2. Pelter MA, *et al.* Seizure-like reaction associated with subcutaneous lidocaine injection. *Clin Pharm* 1989; **8:** 767–8.
3. Sakai RI, Lattin JE. Lidocaine ingestion. *Am J Dis Child* 1980; **134:** 323.
4. Rothstein P, *et al.* Prolonged seizures associated with the use of viscous lidocaine. *J Pediatr* 1982; **101:** 461–3.
5. Mofenson HC, *et al.* Lidocaine toxicity from topical mucosal application. *Clin Pediatr (Phila)* 1983; **22:** 190–2.
6. Giard MJ, *et al.* Seizures induced by oral viscous lidocaine. *Clin Pharm* 1983; **2:** 110.
7. Amitai Y, *et al.* Death following accidental lidocaine overdose in a child. *N Engl J Med* 1986; **314:** 182–3.
8. Parish RC, *et al.* Seizures following oral lidocaine for esophageal anesthesia. *Drug Intell Clin Pharm* 1985; **19:** 199–201.
9. Fruncillo RJ, *et al.* CNS toxicity after ingestion of topical lidocaine. *N Engl J Med* 1982; **306:** 426–7.
10. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
11. Zuberi BF, *et al.* Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. *Gut* 2000; **46:** 435.
12. Dix VW, Tresidder GC. Collapse after use of lignocaine jelly for urethral anaesthesia. *Lancet* 1963; **i:** 890.
13. Pottage A, Scott DB. Safety of "topical" lignocaine. *Lancet* 1988; **i:** 1003.

Pregnancy. Serious adverse effects of epidural anaesthesia are rare but lidocaine may have transient effects on the neonatal auditory system.[1]

1. Bozynski MEA, *et al.* Effect of prenatal lignocaine on auditory brain stem evoked response. *Arch Dis Child* 1989; **64:** 934–8.

Precautions

As for Local Anaesthetics in general, p.1851.

In general lidocaine should not be given to patients with hypovolaemia, heart block or other conduction disturbances, and should be used with caution in patients with congestive heart failure, bradycardia, or respiratory depression. Lidocaine is metabolised in the liver and must be given with caution to patients with hepatic impairment. The plasma half-life of lidocaine may be prolonged in conditions that reduce hepatic blood flow such as cardiac and circulatory failure. Metabolites of lidocaine may accumulate in patients with renal impairment.

The intramuscular injection of lidocaine may increase creatine phosphokinase concentrations that can interfere with the diagnosis of acute myocardial infarction.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving lidocaine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Cerebrovascular disorders. Lidocaine 5 mg/kg by intravenous infusion over 30 minutes was associated with a 12% reduction in cerebral blood flow in healthy subjects although this returned to normal within 60 minutes.[1] Cerebral blood flow in patients with diabetes was lower than in healthy subjects, but was unaffected by lidocaine infusion, indicating reduced cerebrovascular reactivity.

1. Kastrup J, *et al.* Intravenous lidocaine and cerebral blood flow: impaired microvascular reactivity in diabetic patients. *J Clin Pharmacol* 1990; **30:** 318–23.

Porphyria. Lidocaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Renal impairment. The pharmacokinetics of lidocaine and its metabolite monoethylglycinexylidide appear to be unaffected in patients with renal failure except that accumulation of the metabolite glycinexylidide may occur during infusions of 12 hours or more.[1] Data to predict the amount of lidocaine and glycinexylidide removed during haemodialysis have been provided.[2,3] Lidocaine does not appear to be removed during haemofiltration.[4]

1. Collinsworth KA, *et al.* Pharmacokinetics and metabolism of lidocaine in patients with renal failure. *Clin Pharmacol Ther* 1975; **18:** 59–64.
2. Gibson TP, Nelson HA. Drug kinetics and artificial kidneys. *Clin Pharmacokinet* 1977; **2:** 403–26.
3. Lee CC, Marbury TC. Drug therapy in patients undergoing haemodialysis: clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1984; **9:** 42–66.
4. Saima S, *et al.* Negligible removal of lidocaine during arteriovenous hemofiltration. *Ther Drug Monit* 1990; **12:** 154–6.

Smoking. The effects of smoking on lidocaine therapy are unclear. Studies in a limited number of patients have found reduced systemic bioavailability suggestive of induction of drug-metabolising activity[1] and an inconsistent effect on protein binding.[2,3]

1. Huet P-M, Lelorier J. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin Pharmacol Ther* 1980; **28:** 208–15.
2. McNamara PJ, *et al.* Effect of smoking on binding of lidocaine to human serum proteins. *J Pharm Sci* 1980; **69:** 749–51.
3. Davis D, *et al.* The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1985; **19:** 261–5.

Interactions

For interactions associated with local anaesthetics, see p.1851.

The clearance of lidocaine may be reduced by propranolol and cimetidine (see below). The cardiac depressant effects of lidocaine are additive with those of beta blockers and of other antiarrhythmics. Additive cardiac effects may also occur when lidocaine is given with intravenous phenytoin; however, the long-term use of phenytoin and other enzyme-inducers may increase dosage requirements of lidocaine (see Antiepileptics, below). Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonises the effect of lidocaine.

Antiarrhythmics. Lidocaine toxicity, arising from the use of an oral preparation containing lidocaine, has been reported[1] in a patient who was receiving *mexiletine*. There are individual reports of seizures or heart failure and cardiac arrest in patients who received intravenous lidocaine with *ajmaline*,[2] *amiodarone*,[3,4] or *tocainide*.[5] Delirium has been reported in a patient who received lidocaine with *procainamide*.[6]

1. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
2. Bleifeld W. Side effects of antiarrhythmic drugs. *Naunyn Schmiedebergs Arch Pharmacol* 1971; **269:** 282–97.
3. Siegmund JB, *et al.* Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* 1993; **21:** 513–15.
4. Keidar S, *et al.* Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* 1982; **104:** 1384–5.
5. Forrence E, *et al.* A seizure induced by concurrent lidocaine-tocainide therapy—is it just a case of additive toxicity? *Drug Intell Clin Pharm* 1986; 20: 56–9.
6. Ilyas M, *et al.* Delirium induced by a combination of anti-arrhythmic drugs. *Lancet* 1969; **ii:** 1368–9.

Antiepileptics. Studies in healthy subjects and patients with epilepsy[1,2] suggest that long-term use of drugs such as *phenytoin* or *barbiturates* may increase dosage requirements for lidocaine due to induction of drug-metabolising microsomal enzymes. Phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma.[3]

The cardiac depressant effects of lidocaine may be dangerously enhanced by intravenous phenytoin.[4]

1. Heinonen J, *et al.* Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* 1970; **14:** 89–95.
2. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* 1979; **8:** 21–31.
3. Routledge PA, *et al.* Lignocaine disposition in blood in epilepsy. *Br J Clin Pharmacol* 1981; **12:** 663–6.
4. Wood RA. Sinoatrial arrest: an interaction between phenytoin and lignocaine. *BMJ* 1971; **1:** 645.

Beta blockers. Significant increases in plasma-lidocaine concentrations have occurred with *propranolol*,[1-4] owing to a reduction in the clearance of lidocaine from plasma. A similar interaction has occurred with *nadolol*[3] and *metoprolol*,[2] although in another study[5] metoprolol did not alter the pharmacokinetics of lidocaine. The hepatic metabolism of lidocaine may be reduced as a result of a fall in hepatic blood flow associated with reduced cardiac output or it may be caused by direct inhibition of hepatic microsomal enzymes.[6] Significant impairment of lidocaine clearance would therefore be most likely to occur with those drugs that lack intrinsic sympathomimetic activity and have a greater effect on cardiac output or with the more lipid-soluble drugs that have greater effects on microsomal oxygenases. The reduction in clearance produced by propranolol seems to be mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow.[4]

1. Ochs HR, *et al.* Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 1980; **303:** 373–7.
2. Conrad KA, *et al.* Lidocaine elimination: effects of metoprolol and of propranolol. *Clin Pharmacol Ther* 1983; **33:** 133–8.
3. Schneck DW, *et al.* Effects of nadolol and propranolol on plasma lidocaine clearance. *Clin Pharmacol Ther* 1984; **36:** 584–7.
4. Bax NDS, *et al.* The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. *Br J Clin Pharmacol* 1985; **19:** 597–603.
5. Miners JO, *et al.* Failure of 'therapeutic' doses of β-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine. *Br J Clin Pharmacol* 1984; **18:** 853–60.
6. Tucker GT, *et al.* Effects of β-adrenoceptor antagonists on the pharmacokinetics of lignocaine. *Br J Clin Pharmacol* 1984; **17** (suppl 1): 21S–28S.

H_2-antagonists. There have been numerous studies[1-4] of the interaction between *cimetidine* and lidocaine but differences between the studies make interpretation of the overall clinical significance of the results difficult. Cimetidine appears to reduce the hepatic metabolism of lidocaine; it may also reduce its clearance by decreasing hepatic blood flow. Significant increases in plasma-lidocaine concentrations have been reported. Changes in protein binding are not generally important but patients with myocardial infarction who have increased levels of α_1-acid glycoprotein may be partially protected from increases in concentrations of free lidocaine.[5] Since it is not possible to identify those patients at risk all patients receiving both drugs should be closely monitored for signs of toxicity. The use of other H_2-antagonists may be preferable. In studies in healthy subjects *ranitidine* either had no effect on lidocaine kinetics[6] or produced changes consistent with small reductions in hepatic blood flow.[7]

1. Feely J, *et al.* Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 1982; **96:** 592–4.
2. Knapp AB, *et al.* The cimetidine-lidocaine interaction. *Ann Intern Med* 1983; **98:** 174–7.
3. Patterson JH, *et al.* Influence of a continuous cimetidine infusion on lidocaine plasma concentrations in patients. *J Clin Pharmacol* 1985; **25:** 607–9.
4. Bauer LA, *et al.* Cimetidine-induced decrease in lidocaine metabolism. *Am Heart J* 1984; **108:** 413–15.
5. Berk SI, *et al.* The effect of oral cimetidine on total and unbound serum lidocaine concentrations in patients with suspected myocardial infarction. *Int J Cardiol* 1987; **14:** 91–4.
6. Feely J, Guy E. Lack of effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1983; **15:** 378–9.
7. Robson RA, *et al.* The effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1985; **20:** 170–3.

Local anaesthetics. Although a number of drugs were shown to reduce the amount of lidocaine bound to α_1-acid glycoprotein only the displacement produced by *bupivacaine* was considered to be of possible clinical significance.[1]

There is concern about the use of lidocaine to treat *cocaine*-induced arrhythmias as lidocaine may enhance toxicity.[2]

1. Goolkasian DL, *et al.* Displacement of lidocaine from serum α-acid glycoprotein binding sites by basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 413–17.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.

Neuromuscular blockers. The possible interaction between neuromuscular blockers and antiarrhythmics including lidocaine is discussed under Atracurium, p.1903.

Oral contraceptives. For mention of the effect of oral contraceptives on the protein binding of lidocaine, see under Protein Binding in Pharmacokinetics, below.

Pharmacokinetics

Lidocaine is readily absorbed from the gastrointestinal tract, from mucous membranes, and through damaged skin. Absorption through intact skin is poor. It is rapidly absorbed from injection sites including muscle.

After an intravenous dose lidocaine is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lidocaine is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of binding is variable but is about 66%. Plasma protein binding of lidocaine depends in part on the concentrations of both lidocaine and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of lidocaine (see under Protein Binding, below).

Plasma concentrations decline rapidly after an intravenous dose with an initial half-life of less than 30 minutes; the elimination half-life is 1 to 2 hours but may be prolonged if infusions are given for longer than 24 hours or if hepatic blood flow is reduced.

Lidocaine is largely metabolised in the liver and any alteration in liver function or hepatic blood flow can have a significant effect on its pharmacokinetics and dosage requirements. First-pass metabolism is extensive and bioavailability is about 35% after oral doses. Metabolism in the liver is rapid and about 90% of a given dose is dealkylated to form monoethylglycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lidocaine and since their half-lives are longer than that of lidocaine, accumulation, particularly of glycinexylidide, may occur during prolonged infusions. Further metabolism occurs and metabolites are excreted in the urine with less than 10% of unchanged lidocaine. Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Drugs that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also affect the clearance of lidocaine (see Interactions, above). Renal impairment does not affect the clearance of lidocaine but accumulation of its active metabolites can occur.

Lidocaine crosses the placenta and blood-brain barrier; it is distributed into breast milk.

See also under Local Anaesthetics, p.1852.

◊ References.

1. Nattel S, *et al.* The pharmacokinetics of lignocaine and β-adrenoceptor antagonists in patients with acute myocardial infarction. *Clin Pharmacokinet* 1987; **13:** 293–316.

Absorption. SURFACE APPLICATION. Serum-lidocaine concentrations were usually so low as to be unmeasurable in patients who gargled and expectorated 15 mL (300 mg) of a 2% viscous solution before endoscopy[1] and mean peak serum concentrations of lidocaine were below those associated with toxicity following endotracheal application of 100 mg of lidocaine by spray.[2] The relative bioavailability of lidocaine has been found to be higher when applied to the upper respiratory tract than after administration to the lower respiratory tract.[3] Acceptably low plasma-lidocaine concentrations were noted with the following regimen used before bronchoscopy: a 4% lidocaine solution gargled for 30 seconds, a 2% solution sprayed onto the oropharynx, a 2% jelly applied to the oropharynx and nasal passages, and a 1% solution injected through a bronchoscope.[4] However, a fatality has been reported following the use of lidocaine as a gargle (see Overdosage, above); the absorption of intranasal lidocaine can also be highly variable.[5] For bronchoscopy, inhalation of lidocaine from a nebuliser rather than a direct spray may result in lower peak serum concentrations.[6]

Absorption of lidocaine is generally poor through intact skin. However, there is some evidence that absorption may be greater after application to the skin of preterm infants.[7]

1. Fazio A, *et al.* Lidocaine serum concentrations following endoscopy. *Drug Intell Clin Pharm* 1987; **21:** 752–3.
2. Scott DB, *et al.* Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br J Anaesth* 1976; **48:** 899–902.
3. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.
4. Ameer B, *et al.* Systemic absorption of topical lidocaine in elderly and young adults undergoing bronchoscopy. *Pharmacotherapy* 1989; **9:** 74–81.
5. Scavone JM, *et al.* The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol* 1989; **28:** 722–4.
6. Labedzki L, *et al.* Reduced systemic absorption of intrabronchial lidocaine by high-frequency nebulization. *J Clin Pharmacol* 1990; **30:** 795–7.
7. Barrett DA, Rutter N. Percutaneous lignocaine absorption in newborn infants. *Arch Dis Child* 1994; **71:** F122–F124.

Protein binding. Lidocaine is markedly bound to α_1-acid glycoprotein (AAG), a plasma protein which is increased after trauma, surgery, burns, myocardial infarction, in chronic inflammatory disorders such as Crohn's disease, and in cancer. Protein binding may therefore be greatly increased in these conditions and reduced in neonates, the nephrotic syndrome, and in liver disease when AAG concentrations are lower than normal. This can result in an eightfold variation in the free fraction of lidocaine between these conditions.[1] Measurement of free drug concentrations may be a better guide to dosage requirements than measurement of total plasma concentrations.[2] AAG concentrations may also be reduced by oestrogens[3] leading to a higher free fraction of lidocaine in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives.[3,4] Protein binding may also be affected by other concomitant drug therapy or smoking (for further details, see Antiepileptics under Interactions, above and Precautions, Smoking, above).

1. Routledge PA. Pharmacological terms: protein binding. *Prescribers' J* 1988; **28:** 34–5.
2. Shand DG. α-Acid glycoprotein and plasma lidocaine binding. *Clin Pharmacokinet* 1984; **9** (suppl 1): 27–31.
3. Routledge PA, *et al.* Sex-related differences in the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1981; **11:** 245–50.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29:** 522–6.

Uses and Administration

Lidocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It is used for infiltration anaesthesia and regional nerve blocks. It has a rapid onset of action and anaesthesia is obtained within a few minutes; it has an intermediate duration of action. The speed of onset and duration of action of lidocaine are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced. It is generally given as the hydrochloride. Lidocaine hydrochloride monohydrate 1.23 g or anhydrous lidocaine hydrochloride 1.16 g are both equivalent to about 1 g of lidocaine. A carbonated solution of lidocaine is also available in some countries for injection (see p.1852). Lidocaine is also a useful surface anaesthetic but it may be rapidly and extensively absorbed following topical application to mucous membranes, and systemic effects may occur. Hyaluronidase (p.2321) has been added to preparations of lidocaine used for surface and infiltration anaesthesia but may enhance systemic absorption. (Local anaesthetic techniques are discussed on p.1853.)

Lidocaine is included in some injections, such as depot corticosteroids, to prevent pain, itching, and other local irritation. Lidocaine sodium has also been included in intramuscular injections of some antibacterials to reduce the pain on injection.

Lidocaine is also a class Ib antiarrhythmic used in the treatment of ventricular arrhythmias, especially after myocardial infarction. It has been given by intravenous infusion in the treatment of refractory status epilepticus.

USE IN LOCAL ANAESTHESIA.

The dose of lidocaine hydrochloride used for local anaesthesia depends on the site of injection and the procedure used. Specific licensed doses for individual procedures are not always available in the UK, although US product information often includes them (see below). When given with adrenaline, the suggested general **maximum single dose** of lidocaine hydrochloride is 500 mg; without adrenaline, the recommended maximum single dose in the UK is 200 mg and in the USA, 300 mg, except for spinal anaesthesia (see below). Lidocaine hydrochloride solutions containing adrenaline 1 in 200 000 are used for infiltration anaesthesia and nerve blocks including epidural block; higher concentrations of adrenaline are seldom necessary, except in dentistry, where solutions of lidocaine hydrochloride with adrenaline 1 in 80 000 are widely used. Doses should be reduced in children, the elderly, and in debilitated patients. A test dose, preferably with adrenaline, should be given before starting epidural block to detect inadvertent intravascular or subarachnoid dosage.

The following doses have been recommended for individual **local anaesthetic procedures** in the USA:

- For percutaneous *infiltration anaesthesia*, 5 to 300 mg (1 to 60 mL of a 0.5% solution, or 0.5 to 30 mL of a 1% solution).
- The dosage in *peripheral nerve block* depends on the route. For brachial plexus block 225 to 300 mg (15 to 20 mL) as a 1.5% solution is used; for intercostal nerve block 30 mg (3 mL) is given as a 1% solution; for paracervical block a 1% solution is used in a dose of 100 mg (10 mL) on each side, repeated not more frequently than every 90 minutes; for paravertebral block a 1% solution may be used in doses of 30 to 50 mg (3 to 5 mL); a 1% solution is recommended for pudendal block in doses of 100 mg (10 mL) on each side; for retrobulbar block a 4% solution may be used in doses of 120 to 200 mg (3 to 5 mL).
- For *sympathetic nerve block* a 1% solution is recommended; doses are 50 mg (5 mL) for cervical block and 50 to 100 mg (5 to 10 mL) for lumbar block.
- For *epidural anaesthesia* 2 to 3 mL of solution is needed for each dermatome to be anaesthetised but usual total doses and recommended concentrations are: lumbar epidural 250 to 300 mg (25 to 30 mL) as a 1% solution for analgesia and 225 to 300 mg (15 to 20 mL) as a 1.5% solution or 200 to 300 mg (10 to 15 mL) as a 2% solution for anaesthesia, and for thoracic epidural a 1% solution may be used at doses of 200 to 300 mg (20 to 30 mL). In obstetric caudal analgesia up to 300 mg (30 mL) is used as a 0.5% or 1% solution and in surgical caudal analgesia a 1.5% solution may be used in doses of 225 to 300 mg (15 to 20 mL). For continuous epidural anaesthesia, the maximum doses should not be repeated more frequently than every 90 minutes.

- A hyperbaric solution of 1.5% or 5% lidocaine hydrochloride in glucose 7.5% solution is available for *spinal anaesthesia*; adrenaline should not be used. Doses of up to 50 mg (1 mL) as a 5% solution and 9 to 15 mg (0.6 to 1 mL) as a 1.5% solution have been used during labour for a normal vaginal delivery. Up to 75 mg (1.5 mL) as the 5% solution has been used for caesarean section and 75 to 100 mg (1.5 to 2 mL) for other surgical procedures.
- For *intravenous regional anaesthesia* a 0.5% solution without adrenaline has been used in doses of 50 to 300 mg (10 to 60 mL); a maximum dose of 4 mg/kg has been recommended for adults.

Lidocaine may be used in a variety of formulations for **surface anaesthesia**.

- Lidocaine ointment is used for *anaesthesia of skin and mucous membranes* with a maximum recommended total dose of 20 g of 5% ointment (equivalent to 1 g of lidocaine base) in 24 hours.
- Gels are used for *anaesthesia of the urinary tract* and the dose used varies in different countries. The manufacturers in the UK have suggested the following doses given as a 2% gel: in females 60 to 100 mg of lidocaine hydrochloride inserted into the urethra several minutes before examination; in males 200 mg instilled initially followed by 60 to 100 mg. A 1% gel may also be used. The doses used in the USA are similar: in females 60 to 100 mg of lidocaine hydrochloride as a 2% gel is inserted into the urethra several minutes before examination; in males 100 to 200 mg is used before catheterisation and 600 mg before sounding or cystoscopy.

  A gel may also be applied for the treatment of *major aphthae* in immunocompromised patients; a dose of 20 to 30 mg (2 to 3 mL) as a 1% gel or 40 to 60 mg (2 to 3 mL) as a 2% gel is used. A maximum volume of up to 15 mL is recommended within 24 hours.
- Topical solutions are used for *surface anaesthesia of mucous membranes of the mouth, throat, and upper gastrointestinal tract*. For painful conditions of the mouth and throat a 2% solution may be used: 300 mg (15 mL) may be rinsed and ejected or, for pharyngeal pain, the solution is gargled and swallowed if necessary; it should not be used more frequently than every 3 hours. The recommended maximum daily dose in the USA for topical oral solutions is 2.4 g. Doses of 40 to 300 mg as a 4% solution (1 to 7.5 mL) are used before bronchoscopy, bronchography, laryngoscopy, oesophagoscopy, endotracheal intubation, and biopsy in the mouth and throat. Lidocaine in a strength of 10% has also been used as a spray for application to mucous membranes for the prevention of pain during various procedures including use in otorhinolaryngology, dentistry, introduction of instruments into the respiratory and gastrointestinal tracts, and in obstetrics. The dose depends on the extent of the site to be anaesthetised; 10 to 50 mg is generally sufficient for dentistry and otorhinolaryngology; for other procedures, the maximum dose in a 24-hour period is 200 mg. For laryngotracheal anaesthesia 160 mg of lidocaine hydrochloride as a 4% solution is sprayed or instilled as a single dose into the lumen of the larynx and trachea.
- Lidocaine is used *rectally* as suppositories, sprays, ointments, and creams in the treatment of haemorrhoids and other painful perianal conditions.
- *Eye drops* containing lidocaine hydrochloride 4% with fluorescein are used in tonometry.
- A *eutectic mixture* containing lidocaine base 2.5% and prilocaine base 2.5% is applied as a cream under an occlusive dressing to produce *surface anaesthesia of the skin* before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts (see also under Surface Anaesthesia, below).
- Other methods of dermal delivery include a *transdermal patch* of lidocaine 5% for the treatment of pain associated with postherpetic neuralgia, and an *iontophoretic drug delivery system* incorporating lidocaine and adrenaline. A transdermal patch containing lidocaine 70 mg with tetracaine 70 mg is also available for surface anaesthesia, as is an *intradermal injection system* delivering lidocaine hydrochloride 500 micrograms.

USE IN ARRHYTHMIAS.

For the treatment of **ventricular arrhythmias** lidocaine is given *intravenously* as the hydrochloride. It may be used in advanced cardiac life support for cardiac arrest due to ventricular fibrillation and pulseless ventricular tachycardia when direct current shocks (together with adrenaline) have failed to restore a normal rhythm. For adults, a usual dose of 1 to 1.5 mg/kg can be given and repeated as necessary to a maximum total dose of 3 mg/kg. The *endotracheal* route has been employed when intravenous access cannot be obtained, although doses should probably be larger than those employed intravenously; the precise endotracheal dose has not yet been established, however.

Lidocaine is also used in other ventricular arrhythmias in which the patient is in a more stable condition. In these circumstances lidocaine hydrochloride is usually given as a loading dose followed by an infusion. Usual doses are 50 to 100 mg or 1 to 1.5 mg/kg as a direct *intravenous injection* at a rate of 25 to 50 mg/minute. If no effect is seen within 5 to 10 minutes of this loading dose, it may be repeated once or twice to a maximum dose of 200 to 300 mg in 1 hour. A *continuous intravenous infusion* is usually commenced after loading, at a dose of 1 to 4 mg/minute. It is rarely necessary to continue this infusion for longer than 24 hours, but in the event that a longer infusion is required, the dose may need to be reduced to avoid potential toxicity resulting from an increase in the half-life. Dosage may need to be reduced in the elderly and in patients with heart failure or liver disorders.

In emergency situations, lidocaine hydrochloride has also been given for arrhythmias by *intramuscular* injection into the deltoid muscle in a dose of 300 mg, repeated if necessary after 60 to 90 minutes.

Action. For a comparison of the vasoactivity of lidocaine and some other local anaesthetics, see p.1852.

Burns. Lidocaine given intravenously has been reported to have produced pain relief in a few patients with second-degree burns.[1]

1. Jönsson A, *et al.* Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; **338:** 151–2.

Cardiac arrhythmias. Lidocaine is classified as a class Ib antiarrhythmic drug (p.1153) and may be used in the treatment of ventricular arrhythmias, including those associated with cardiac arrest and myocardial infarction, although other drugs are usually preferred (see Cardiac Arrhythmias, p.1160). It is usually given intravenously (see above). Lidocaine may also be used during advanced cardiac life support (p.1156).

Lidocaine has been considered for the *prophylaxis* of ventricular fibrillation in patients with proven or suspected myocardial infarction. However, while some studies have identified a protective effect of lidocaine,[1,2] in others it was not shown to reduce mortality and might even have increased it,[3,4] and thus is no longer generally recommended.

It has been suggested that the increased mortality sometimes seen with lidocaine might be associated with the duration of treatment; a study[5] found that patients who received a bolus dose of lidocaine followed by a 40-hour continuous infusion for prophylaxis of ventricular arrhythmias experienced more episodes of heart failure than patients who received the bolus dose followed by an 8-hour infusion.

1. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy: suggestive evidence that lidocaine prophylaxis prevents death in acute myocardial infarction. *JAMA* 1981; **246:** 2455–9.
2. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; **313:** 1105–10.
3. MacMahon S, *et al.* Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA* 1988; **260:** 1910–16.
4. Hine LK, *et al.* Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Ann Intern Med* 1989; **149:** 2694–8.
5. Pharand C, *et al.* Lidocaine prophylaxis for fatal ventricular arrhythmias after acute myocardial infarction. *Clin Pharmacol Ther* 1995; **57:** 471–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. Lidocaine is one of a large number of drugs that has been tried in the treatment of hiccups without strong evidence of their efficacy. It has been given intravenously, or in the form of a 2% viscous solution taken by mouth. Nebulised lidocaine has also been tried.[1]

1. Neeno TA, Rosenow EC. Intractable hiccups: consider nebulized lidocaine. *Chest* 1996; **110:** 1129–30.

Intubation. Lidocaine has produced conflicting results when used to attenuate the pressor response and rise in intra-ocular pressure induced by procedures such as tracheal intubation.[1-5] For an overall discussion of this problem, see under Anaesthesia, p.1900.

1. Tam S, *et al.* Attenuation of circulatory responses to endotracheal intubation using intravenous lidocaine: a determination of the optimal time of injection. *Can Anaesth Soc J* 1985; **32:** S65.
2. Murphy DF, *et al.* Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation. *Br J Ophthalmol* 1986; **70:** 596–8.
3. Drenger B, Pe'er J. Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *Br J Ophthalmol* 1987; **71:** 546–8.
4. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. *Br J Anaesth* 1990; **65:** 216–19.
5. Mostafa SM, *et al.* Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation. *Br J Anaesth* 1990; **64:** 515–17.

Migraine and cluster headache. Despite periodic interest, lidocaine has so far failed to find an accepted role in the management of migraine (p.616) or cluster headache (p.616). Lidocaine has been tried for the emergency parenteral treatment of migraine, but in a comparative study with dihydroergotamine or chlorpromazine it was found to be less effective than either.[1] While some workers have found that intranasal instillation of lidocaine has produced rapid relief of headache in some patients with acute migraine (though early relapse was common)[2] others have found it to be ineffective.[3] It has also been reported to be effective in aborting individual attacks of headache during cluster periods in patients with cluster headache.[4,5] However, most patients do not appear to obtain complete pain relief.

1. Bell R, *et al.* A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* 1990; **19:** 1070–82.
2. Maizels M, *et al.* Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* 1996; **276:** 319–21.
3. Blanda M, *et al.* Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* 2001; **8:** 337–42.
4. Kittrelle JP, *et al.* Cluster headache: local anesthetic abortive agents. *Arch Neurol* 1985; **42:** 496–8.
5. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995; **35:** 83–4.

Neuropathic pain syndromes. Lidocaine may be useful in the management of some types of neuropathic pain syndromes (p.8). The pain of *postherpetic neuralgia* has been significantly reduced by the application of lidocaine 5% transdermal patches[1-3] although a systematic review[4] found insufficient evidence to recommend its use as first-line therapy; intravenous lidocaine[5] and a eutectic mixture of lidocaine and prilocaine (see Surface Anaesthesia below) have also been of benefit. Other syndromes where intravenous lidocaine therapy has been tried include *diabetic neuropathy*[6] and *central neuropathic pain* associated with stroke or spinal cord injury.[7]

1. Rowbotham MC, *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65:** 39–44.
2. Comer AM, Lamb HM. Lidocaine patch 5%. *Drugs* 2000, **59:** 245–9.
3. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs* 2004; **64:** 937–47.
4. Khaliq W, *et al.* Topical lidocaine for the treatment of postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 22/04/08).
5. Attal N, *et al.* Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; **62:** 218–25.
6. Kastrup J, *et al.* Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *BMJ* 1986; **292:** 173.
7. Attal N, *et al.* Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; **54:** 564–74.

Pleurodesis. Lidocaine has been instilled intrapleurally as a 1% solution in doses of up to 300 mg to relieve the severe chest pain associated with the use of tetracycline for pleurodesis.[1-3] While the larger doses were significantly more effective[2] toxic plasma concentrations were less likely to occur if a dose of 3 mg/kg or less was used.[3]

1. Harbecke RG. Intrapleurally given tetracycline with lidocaine. *JAMA* 1980; **244:** 1899–1900.
2. Sherman S, *et al.* Optimum anesthesia with intrapleural lidocaine during chemical pleurodesis with tetracycline. *Chest* 1988; **93:** 533–6.
3. Wooten SA, *et al.* Systemic absorption of tetracycline and lidocaine following intrapleural instillation. *Chest* 1988; **94:** 960–3.

Status epilepticus. Lidocaine hydrochloride may be used to control status epilepticus (p.469) resistant to more conventional treatment, particularly in those with respiratory disease. It has a rapid onset of action but its effect is short-lived and continuous infusion may be necessary.[1] It should also be noted that doses producing high plasma concentrations of lidocaine can result in CNS toxicity including seizures.[1] Recurrence of seizures associated with the withdrawal of prolonged lidocaine therapy may be due to its accumulated metabolites exerting an excitatory effect on the nervous system when the inhibitory effect of lidocaine is being reduced.[2]

Lidocaine was used instead of diazepam for 42 episodes of status epilepticus in 36 patients who either had limited pulmonary reserve or who had not responded to intravenous diazepam.[3] Lidocaine 1.5 to 2 mg/kg (usually a dose of 100 mg) was given as a single intravenous dose over 2 minutes. This dose was repeated once if there was no positive response to the first dose (11 episodes) or if the seizures recurred (19 episodes). Subsequently a continuous infusion of lidocaine at a rate of 3 to 4 mg/kg per hour was given in the 7 episodes that recurred after the second dose; 5 of these showed a positive response. The 11 episodes not responding to the first dose did not respond to the second dose or to a continuous infusion. In a retrospective analysis[4] of 37 children with status epilepticus, lidocaine was effective in only 19 of 53 episodes; however, in a few cases it was effective where other drugs had failed, and those patients who responded did so rapidly (within 5 minutes of being given the drug).

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; **1:** 26–44.
2. Wallin A, *et al.* Lidocaine treatment of neonatal convulsions, a therapeutic dilemma. *Eur J Clin Pharmacol* 1989; **36:** 583–6.
3. Pascual J, *et al.* Role of lidocaine (lignocaine) in managing status epilepticus. *J Neurol Neurosurg Psychiatry* 1992; **55:** 49–51.
4. Hamano S-I, *et al.* Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; **48:** 220–2.

Surface anaesthesia. ***EUTECTIC MIXTURES.*** A cream containing lidocaine 2.5% and prilocaine 2.5% as a eutectic mixture can produce local anaesthesia when applied topically to intact skin. It appears to be of value in minor medical or surgical procedures in *adults* and *children*,[1-3] such as venepuncture, intravenous or arterial cannulation, retrobulbar injections, lumbar puncture, curettage of molluscum contagiosum lesions, genital wart removal, split skin grafting, laser treatment, extracorporeal shock wave therapy, separation of preputial adhesions, and circumcision. It has also been tried as an anaesthetic for the ear drum in preparation for otological procedures such as myringotomy and grommet insertion but is potentially ototoxic and should not be used in the presence of a perforation. Postherpetic neuralgia (p.9) has also been treated with some success.[4,5]

The eutectic cream is usually applied to skin under an occlusive dressing for at least 60 minutes although it has been suggested that for children aged 1 to 5 years 30 minutes may be sufficient.[6] The manufacturers suggest a maximum application time of 5 hours. The onset and duration of the effect may be affected by the site of application.[2] When used for the removal of genital warts an occlusive dressing is not necessary and the application time recommended by the manufacturer is 5 to 10 minutes. The level of anaesthesia begins to decline after 10 to 15 minutes when applied to the genital mucosa and any procedure should be started immediately.

Eutectic mixtures of lidocaine and prilocaine have also been used in *neonates* to reduce the pain of puncture procedures[7] and for circumcision,[8,9] and appear to be safe and efficacious. There has been concern that excessive absorption (particularly of prilocaine) might lead to methaemoglobinaemia (see p.1850), and UK licensing information recommends that the eutectic cream not be used in children less than 1 year old. However, there seems to be little evidence of this, and the *BNF* considers that it may be used under specialist supervision in infants over 1 month of age. Similarly, in other countries, including the USA, the cream is licensed for use in neonates provided that their gestational age is at least 37 weeks, and that methaemoglobin values are monitored in those aged 3 months or less; it should not be used in infants under 1 year who are receiving methaemoglobin-inducing drugs.

Systemic absorption of both drugs from the eutectic cream appears to be minimal across intact skin[6] even after prolonged or extensive use.[10] However, it should not be used on wounds or mucous membranes (except for genital warts in adults) and should not be used for atopic dermatitis. It should not be applied to or near the eyes because it causes corneal irritation, and it should not be instilled in the middle ear. It should be used with caution in patients with anaemia or congenital or acquired methaemoglobinaemia. Transient paleness, redness, and oedema may occur following application.

Some studies suggest that a topical gel formulation of tetracaine 4% can produce longer and more rapid anaesthesia than the above lidocaine with prilocaine cream (see Surface Anaesthesia, under Uses and Administration of Tetracaine, p.1872). It has also been suggested[11] that topical tetracaine may have practical advantages over the eutectic mixture of lidocaine and prilocaine, which has to be applied for at least one hour, and causes vasoconstriction at the site of application which can make venepuncture difficult.

1. Lee JJ, Rubin AP. Emla cream and its current uses. *Br J Hosp Med* 1993; **50:** 463–6.
2. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). *Drugs* 1993; **46:** 126–51.
3. Koren G. Use of the eutectic mixture of local anesthetics in young children for procedure-related pain. *J Pediatr* 1993; **122** (suppl): S30–S35.
4. Litman SJ, *et al.* Use of EMLA cream in the treatment of postherpetic neuralgia. *J Clin Anesth* 1996; **8:** 54–7.
5. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996; **335:** 32–42.
6. Hanks GW, White I. Local anaesthetic creams. *BMJ* 1988; **297:** 1215–16.
7. Gourrier E, *et al.* Use of EMLA cream in a department of neonatology. *Pain* 1996; **68:** 431–4.
8. Taddio A, *et al.* Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med* 1997; **336:** 1197–1201.
9. Brady-Fryer B, *et al.* Pain relief for neonatal circumcision. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 16/06/05).
10. Scott DB. Topical anaesthesia of intact skin. *Br J Parenter Ther* 1986; **7:** 134–5.
11. Russell SCS, Doyle E. Paediatric anaesthesia. *BMJ* 1997; **314:** 201–3.

Tinnitus. Tinnitus is the perception of a noise that arises or appears to arise within the head.

Objective tinnitus may be audible to others and arises from lesions outside the auditory system. Subjective tinnitus (tinnitus aurium) originates from sites within the auditory system and is perceived only by the patient. A simple and remediable cause of tinnitus can be impacted ear wax. Tinnitus is often associated with head injury, vertigo, and hearing loss, including age-related and noise-induced hearing loss. It may also be a symptom of an underlying disorder such as Ménière's disease, may be associated with anxiety or depressive disorders, or may be a manifestation of drug toxicity (for example with aspirin or quinine). In such cases, treatment of the underlying disorder or removal of the offending drug can resolve the tinnitus.

Treatment of tinnitus is difficult although reassurance and counselling are often effective in helping patients to tolerate their condition. Maskers or, if the tinnitus is associated with hearing loss, hearing aids are also used; surgery is rarely indicated. Intravenous lidocaine has proven to be effective in reducing or eliminating tinnitus but the effect only lasts for a few hours and is, therefore, impractical for most patients. Efforts to find an effective oral analogue of lidocaine have not, so far, been successful. Other drugs that have been tried include benzodiazepines such as alprazolam and clonazepam, the antiepileptics carbamazepine and phenytoin, tricyclic antidepressants, and the loop diuretic furosemide, but adverse effects limit their use. Ginkgo biloba has been tried but there are doubts about its value.

References.

1. Luxon LM. Tinnitus: its causes, diagnosis, and treatment. *BMJ* 1993; **306:** 1490–1.
2. Robson AK, Birchall JP. Management of tinnitus. *Prescribers' J* 1994; **34:** 1–7.
3. Coles RRA. Drug treatment of tinnitus in Britain. In: Reich GE, Vernon JA, eds. *Proceedings of the fifth international tinnitus seminar.* Portland: American Tinnitus Association, 1995.
4. Vesterager V. Tinnitus—investigation and management. *BMJ* 1997; **314:** 728–31.
5. Simpson JJ, Davies WE. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999; **20:** 12–18.
6. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999; **109:** 1202–11.
7. Lockwood AH, *et al.* Tinnitus. *N Engl J Med* 2002; **347:** 904–10.

Preparations

BP 2008: Lidocaine and Adrenaline Injection; Lidocaine and Chlorhexidine Gel; Lidocaine Gel; Lidocaine Injection; Lidocaine Ointment; Sterile Lidocaine Solution;
USP 31: Lidocaine and Prilocaine Cream; Lidocaine Hydrochloride and Dextrose Injection; Lidocaine Hydrochloride and Epinephrine Injection; Lidocaine Hydrochloride Injection; Lidocaine Hydrochloride Jelly; Lidocaine Hydrochloride Oral Topical Solution; Lidocaine Hydrochloride Topical Solution; Lidocaine Ointment; Lidocaine Oral Topical Solution; Lidocaine Topical Aerosol; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Fidecaina; Gobbicaina; Indican; Larjancaina; Regiocaina; Solvente Indoloro; Xylocaina; ***Austral.:*** Lignospan†; Nurocain; Stud 100; Xylocaine; Xylocaine Special Adhesive; Xylocard; ***Austria:*** Lidocorit; Neo-Xylestesin; Neo-Xylestesin forte; Xylanaest; Xylocain; Xylocard; Xyloneural; ***Belg.:*** Linisol†; Xylocaine; Xylocaine Visqueuse; Xylocard; ***Braz.:*** Dermomax; Gel-Lido; Lidial; Lidocabbott; Lidocalm†; Lidogel; Lidogeyer†; Lidojet†; Lidospray; Lidoston; Xylestesin; Xylocaina; ***Canad.:*** Afterburn; Betacaine; Lidodan; Solarcaine Lidocaine; Xylocaine; Xylocard; Zilactin-L; ***Chile:*** Calmante de Denticion†; Dentaliv; Dimecaina; Exido; Gelcain; Odongel; Prolong; Solin; Xylocaina; ***Cz.:*** Trachisan; Xylestesin-A†; Xylestesin†; Xylocaine; ***Denm.:*** Xylocain; Xyloplyin; ***Fin.:*** Lidocard; Xylocain; ***Fr.:*** Dynexan; Mesocaine; Versatis; Xylocaine; Xylocard; ***Ger.:*** Gelicain; Haemo-Exhirud Bufexamac; Heweneural; Licain; Lidesthesin; Lidocard; Lidoject; LidoPosterine; Rowo-629†; Trachisan Halsschmerztabletten; Xylestesin-A, Xylestesin centro†; Xylestesin-S†; Xylestesin, Xylestesin-F†; Xylocain; Xylocain f.d. Kardiologie; Xylocitin; Xylocitin cor; Xyloneural; ***Gr.:*** Ecocain†; Lidoderm; Osagel; Sensolid; Utiblack; Xylocaine; Xylol; Xylozan; ***Hong Kong:*** Xylestesin-A; Xylocaine; Xylocard†; ***India:*** Gesicain; Tivision; Xylocaine; Xylocard; ***Indon.:*** Extracaine; Garianes; Lidodex; Lidonest; Pehacain; Xylocaine; ***Irl.:*** Xylocaine; ***Israel:*** After Burn; Esracain; Lidocadren†; LidoPen; Stud 100; Xylocaine; ***Ital.:*** Basicaina; Ecocain; Lident Adrenalina†; Lident Andrenor†; Lidofast; Lidomol†; Lidosen; Lidrian; Luan; Odontalg; Ortodermina; Xilo-Mynol; Xylocaina; Xylonor; Xyloplyina; ***Jpn:*** Penles; ***Malaysia:*** Denkan; Xylocaine; Xylocard†; ***Mex.:*** Betacaine; Hipoden; Pharmacaine; Pisacaina; Sensipharma; Sunicaine; Unicaine; Uvega; Xylocaina; ***Neth.:*** Dentinox; Lepan; Lignospan; Nolaid; Otalgan; Unguentum contra haemorrhoides PCH; Xylocaine; ***Norw.:*** Xylocain; ***NZ:*** Virasolve; Xylestesin-A; Xylocaine; Xylocard; ***Philipp.:*** Dentocaine; Lygnonex; Xylocaine; Xylocard; ***Pol.:*** Lidoposterin; Xylocaine; ***Port.:*** Lidonostrum; Lincaina; Octocaine; Xilonibsa; Xylocaina; Xylocard†; ***Rus.:*** Lidochlor (Лидохлор); Versatis (Версатис); ***S.Afr.:*** Lignospan Special†; Peterkaien; Remicaine; Remicard; Xylocaine; Xylotox; ***Singapore:*** Dube†; Xylocaine; ***Spain:*** Aeroderm†; Dermovagisil; Octocaine; Xilonibsa; Xylocaina; Xylonor 2% Sin Vasoconst; Xylonor Especial; ***Swed.:*** Xylocain; Xylocard; ***Switz.:*** Dynexan nouvelle formule; Kenergon; Lignospan†; Neo-Sinedol; Neurodol Tissugel; Rapidocaine; Sedagul; Solarcaine; Xylesine; Xylestesin-F†; Xylestesin-S "special"†; Xylocain; Xylocard; Xyloneural; Xyloplyin†; ***Thai.:*** Docaine; LD-Caine; Lido Spray†; Lidocation; Lidocaton†; Neo-Lidocaton†; Udocaine; Xylocaine; Xylocard†; ***Turk.:*** Anestol; Aritmal; Jetokain; Jetosel; Ksilidin; Lidobag; Lidosel; Lokalen; Xylocain; ***UAE:*** Ecocain; ***UK:*** Dequaspray; Laryng-O-Jet; Lignostab-A†; Premjact; Stud; Vagisil; Versatis; Xylocaine; Xylotox†; ***USA:*** Anestacon; Anestafoam; Dentipatch; Dilocaine; Dr Scholl's Cracked Heel Relief; Duo-Trach Kit; L-M-X4; LidaMantle; Lidoderm; LidoPen; Lidosense†; Lidosite; LTA; Nervocaine; Octocaine; Xylocaine; Zilactin-L; Zingo; ***Venez.:*** Cifarcaina; Farmacaina; Nenedent; Xylocaina†.

Multi-ingredient: numerous preparations are listed in Part 3.

Mepivacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de mepivacaína; Mépivacaïne, chlorhydrate de; Mepivacaini Chloridum; Mepivacaini hydrochloridum; Mepivakainihydrokloridi; Mepivakain-hidroklori d; Mepivakain-hydrochlorid; Mepivakainhydroklorid; Mepivakaino hidrochloridas. (1-Methyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride.

Мепивакаина Гидрохлорид

$C_{15}H_{22}N_2O,HCl = 282.8.$

CAS — 96-88-8 (mepivacaine); 22801-44-1 ((±)-mepivacaine); 1722-62-9 (mepivacaine hydrochloride).

ATC — N01BB03.

ATC Vet — QN01BB03.

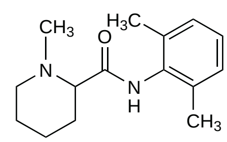

(mepivacaine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Mepivacaine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.0.

USP 31 (Mepivacaine Hydrochloride). A white, odourless, crystalline solid. Freely soluble in water and in methyl alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of about 4.5.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Porphyria. Mepivacaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Local anaesthetics. Studies *in vitro* showed that *bupivacaine* dramatically reduced the binding of mepivacaine to α-1-acid glycoprotein.[1]

1. Hartrick CT, *et al.* Influence of bupivacaine on mepivacaine protein binding. *Clin Pharmacol Ther* 1984; **36:** 546–50.

Pharmacokinetics

Mepivacaine is about 78% bound to plasma proteins. The plasma half-life has been reported to be about 2 to 3 hours in adults and about 9 hours in neonates. It is rapidly metabolised in the liver and less than 10% of a dose is reported to be excreted unchanged in the urine. Over 50% of a dose is excreted as metabolites into the bile but these probably undergo enterohepatic circulation as only small amounts appear in the faeces. Several metabolites are also excreted via the kidneys and include glucuronide conjugates of hydroxy compounds and an *N*-demethylated compound, 2′,6′-pipecoloxylidide. Mepivacaine crosses the placenta.

See also under Local Anaesthetics, p.1852.

Pregnancy. There is considerable transfer of mepivacaine across the placenta after maternal doses and the ratio of fetal to maternal concentrations[1] is about 0.7. Although neonates have a very limited capacity to metabolise mepivacaine it appears they are able to eliminate the drug.[2]

1. Lurie AO, Weiss JB. Blood concentration of mepivacaine and lidocaine in mother and baby after epidural anesthesia. *Am J Obstet Gynecol* 1970; **106:** 850–6.
2. Meffin P, *et al*. Clearance and metabolism of mepivacaine in the human neonate. *Clin Pharmacol Ther* 1973; **14:** 218–25.

Uses and Administration

Mepivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It is mainly used for infiltration anaesthesia, peripheral nerve block, and epidural block. (Local anaesthetic techniques are discussed on p.1853.) Mepivacaine has a rapid onset and an intermediate duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced.

The dosage of mepivacaine hydrochloride varies with the site of injection and the type of **local anaesthetic procedure**. In adults, the **maximum single dose** of mepivacaine hydrochloride should not generally exceed 400 mg and the total dose in 24 hours should not exceed 1 g. Doses should be reduced in the elderly, in debilitated patients, and in those with cardiac or hepatic impairment. Concentrations of less than 2% should be used in children under 3 years or weighing less than about 14 kg (30 pounds); the dose in children should not exceed 5 to 6 mg/kg.

- For *infiltration anaesthesia* up to 400 mg as a 1% (40 mL) or 0.5% (80 mL) solution is used. For *dental infiltration and nerve block* a 2% solution with a vasoconstrictor or a 3% plain solution is used. For anaesthesia at a single site in the jaw a dose of 36 mg (1.8 mL) as a 2% solution or 54 mg (1.8 mL) as a 3% solution is used. For anaesthesia of the entire oral cavity 180 mg (9 mL) as a 2% solution or 270 mg (9 mL) as a 3% solution is used. Some recommend that no more than 400 mg should be given at a single dental sitting.
- For *peripheral nerve blocks*, namely *cervical, brachial plexus, intercostal,* and *pudendal blocks*, 1 or 2% solutions may be used in doses of 50 to 400 mg (5 to 40 mL) as a 1% solution, or 100 to 400 mg (5 to 20 mL) as a 2% solution. For pudendal block half of the dose is injected on each side. For *paracervical block* a dose of up to 100 mg (10 mL) as a 1% solution on each side has been suggested allowing an interval of 5 minutes between sides. This may be repeated at an interval of not less than 90 minutes, and for a combined paracervical and pudendal block up to 150 mg (15 mL) as a 1% solution is injected on each side. For therapeutic nerve block in the management of pain 10 to 50 mg (1 to 5 mL) as a 1% solution or 20 to 100 mg (1 to 5 mL) as a 2% solution may be given.
- For *epidural block* usual doses are: 150 to 300 mg (15 to 30 mL) as a 1% solution, 150 to 375 mg (10 to 25 mL) as a 1.5% solution, or 200 to 400 mg (10 to 20 mL) as a 2% solution. Hyperbaric solutions of mepivacaine hydrochloride without adrenaline have also been used for *spinal block*.

Mepivacaine has been included in the intramuscular injections of other drugs to minimise the pain produced at the injection site.

Mepivacaine has also been used as a surface anaesthetic but other local anaesthetics such as lidocaine are more effective.

Action. For a comparison of the vasoactivity of mepivacaine and some other local anaesthetics, see p.1852.

Preparations

USP 31: Mepivacaine Hydrochloride and Levonordefrin Injection; Mepivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Mepigobbi; ***Austral.:*** Carbocaine; Scandonest†; ***Austria:*** Mepinaest; Scandicain; Scandonest; ***Belg.:*** Scandicaine; ***Canad.:*** Carbocaine; Polocaine†; ***Cz.:*** Mepivastesin; Scandonest; ***Denm.:*** Carbocain; Carboplyin; Scandonest; ***Fr.:*** Carbocaine; ***Ger.:*** Meaverin; Mecain; Mepihexal; Mepivastesin; Scandicain; ***Hong Kong:*** Mepivastesin; ***Ital.:*** Carbocaina; Carbosen; Mepi-Mynol; Mepibil; Mepicain; Mepident; Mepiforan; Mepisolver; Mepivamol; Mepivirgi; Molcain†; Optocain; Pericaina; Scandonest; ***Neth.:*** Scandicaine; Scandonest; ***Norw.:*** Carbocain; Scandonest; ***Port.:*** Isogaine; Mepivastesin; Scandinibsa; Scandonest; ***S.Afr.:*** Carbocaine; Scandonest†; ***Spain:*** Isogaine; Scandinibsa; ***Swed.:*** Carbocain; ***Switz.:*** Scandicain; Scandonest; ***Thai.:*** Mepicaton; ***USA:*** Carbocaine; Carbocaine with Neo-Cobefrin; Isocaine; Polocaine.

Multi-ingredient: ***Ger.:*** Meaverin†; Thesit†.

Used as an adjunct in: ***Austria:*** Estradurin; ***Belg.:*** Estradurine; ***Denm.:*** Estradurin; ***Fin.:*** Estradurin; ***Ger.:*** Estradurin†; ***Jpn:*** Amasulin; Bestcall; Lilacillin†; Pansporin; Takesulin; ***Malaysia:*** Nevramin†; ***Neth.:*** Estradurin; ***Norw.:*** Estradurin; ***Port.:*** Linamin Plus†; ***Singapore:*** Nevramin; ***Swed.:*** Estradurin; ***Switz.:*** Estradurin; ***Thai.:*** Nevramin.

Myrtecaine *(rINN)*

Mirtecaína; Myrtécaïne; Myrtecainum; Nopoksamin; Nopoxamine. 2-[2-(10-Norpin-2-en-2-yl)ethoxy]triethylamine.

Миртекаин

$C_{17}H_{31}NO$ = 265.4.

CAS — 7712-50-7.

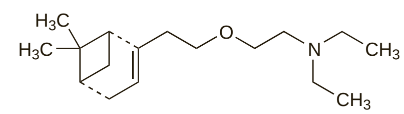

Profile

Myrtecaine is a local anaesthetic (p.1850) used topically as the base or laurilsulfate in rubefacient preparations for the treatment of muscle and joint pain. Myrtecaine laurilsulfate is also used in preparations with antacids for the symptomatic relief of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Algesal; Flexicamin Crema†; ***Austria:*** Algesal; Latesyl; Rheugesal; ***Chile:*** Sinacid; ***Cz.:*** Algesal; ***Fr.:*** Acidrine; Algesal Suractive; ***Ger.:*** Acidrine†; Algesal; Algesalona†; ***Gr.:*** Algesal Suractive; ***Hung.:*** Algesal; ***Indon.:*** Acidrine; Algesal Superactive; ***Ital.:*** Acidrine; ***Mex.:*** Algesal†; ***Neth.:*** Algesal Forte; ***Port.:*** Algesal; Latesil; ***Spain:*** Algesal; ***Switz.:*** Algesal†; Algesalona†; ***Turk.:*** Algesal Suractive; ***Venez.:*** Lemazol.

Octacaine Hydrochloride *(pINNM)*

Hidrocloruro de octacaína; Octacaïne, Chlorhydrate d'; Octacaini Hydrochloridum. 3-Diethylaminobutyranilide hydrochloride.

Октакаина Гидрохлорид

$C_{14}H_{22}N_2O,HCl$ = 270.8.

CAS — 13912-77-1 (octacaine); 59727-70-7 (octacaine hydrochloride).

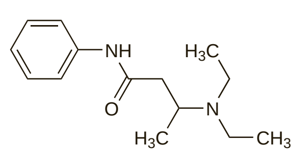

(octacaine)

Profile

Octacaine hydrochloride is a local anaesthetic (p.1850) that has been used for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Switz.:*** Batramycine†.

Oxetacaine *(BAN, rINN)*

Oksetakaiini; Oksetakain; Oxetacaína; Oxétacaïne; Oxetacainum; Oxetakain; Oxethazaine *(USAN)*; Wy-806. 2,2′-(2-Hydroxyethylimino)bis[*N*-(αα-dimethylphenethyl)-*N*-methylacetamide].

Оксетакаин

$C_{28}H_{41}N_3O_3$ = 467.6.

CAS — 126-27-2 (oxetacaine); 13930-31-9 (oxetacaine hydrochloride).

ATC — C05AD06.

ATC Vet — QC05AD06.

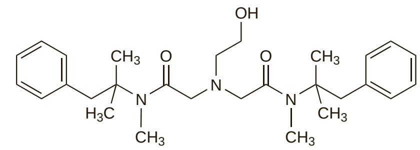

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2008 (Oxetacaine). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol; very soluble in chloroform; soluble in ethyl acetate.

Profile

Oxetacaine is an amide anaesthetic (p.1850) that is stated to have a prolonged action. It is administered orally with antacids for the symptomatic relief of gastro-oesophageal reflux disease (p.1696). It has also been used as the hydrochloride in ointments and suppositories for the relief of pain associated with haemorrhoids.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Tricaine-MPS; ***Ital.:*** Emoren; ***Jpn:*** Strocain.

Multi-ingredient: ***Arg.:*** Mucaine; ***Austral.:*** Mucaine; ***Austria:*** Tepilta; ***Belg.:*** Muthesa; ***Braz.:*** Droxaine; ***Canad.:*** Mucaine; ***Chile:*** Mucaine†; ***Cz.:*** Muthesa Compositum†; ***Fr.:*** Mutesa; ***Ger.:*** Tepilta; ***Gr.:*** Oxaine-M; ***Hong Kong:*** Antacaine; Gastrocaine; Milzine†; Mucaine; Oxema Improved; Strocain; ***India:*** Mucaine; Pepticaine; ***Ital.:*** Gastrodue†; ***NZ:*** Mucaine†; ***Philipp.:*** Geltazine; ***S.Afr.:*** Mucaine; ***Singapore:*** Mucaine; Strocain; ***Spain:*** Natrocitral; Roberfarin; ***Switz.:*** Muthesa; ***Thai.:*** Mucaine; Strocain; ***Turk.:*** Mucaine.

Oxybuprocaine Hydrochloride

(BANM, rINNM)

Benoxinate Hydrochloride; Hidrocloruro de oxibuprocaína; Oksibuprokaiinihydrokloridi; Oksibuprokain Hidroklorür; Oksibuprokaino hidrochloridas; Oxibuprokain-hidroklorid; Oxibuprokainhydroklorid; Oxybuprocaïne, chlorhydrate d'; Oxybuprocaini hydrochloridum; Oxybuprokain hydrochlorid. 2-Diethylaminoethyl 4-amino-3-butoxybenzoate hydrochloride.

Оксибупрокаина Гидрохлорид

$C_{17}H_{28}N_2O_3,HCl$ = 344.9.

CAS — 99-43-4 (oxybuprocaine); 5987-82-6 (oxybuprocaine hydrochloride).

ATC — D04AB03; S01HA02.

ATC Vet — QD04AB03; QS01HA02.

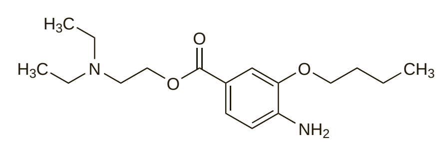

(oxybuprocaine)

NOTE. OXB, formerly BNX, is a code approved by the BP 2008 for use on single unit doses of eye drops containing oxybuprocaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Oxybuprocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Benoxinate Hydrochloride). White or slightly off-white, crystals or crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 0.8 of water, 1 in 2.6 of alcohol, and 1 in 2.5 of chloroform; insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.0.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Effects on the eyes. Fibrinous iritis and moderate corneal swelling occurred in 2 patients after the use of a 0.4% or 1% solution of oxybuprocaine hydrochloride for topical anaesthesia of the eye for minor surgery.[1] The effects may have been due to inadvertent entry of the drug into the anterior chamber of the eye.

1. Haddad R. Fibrinous iritis due to oxybuprocaine. *Br J Ophthalmol* 1989; **73:** 76–7.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Uses and Administration

Oxybuprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1852. It is used for surface anaesthesia (p.1853) and is reported to be less irritant than tetracaine when applied to the conjunctiva in therapeutic concentrations.

Oxybuprocaine is used as the hydrochloride in a 0.4% solution in short ophthalmological procedures. One drop instilled into the conjunctival sac anaesthetises the surface of the eye sufficiently to allow tonometry after 60 seconds and a further drop after 90 seconds provides adequate anaesthesia for the fitting of contact lenses. Three drops at 90-second intervals produces sufficient anaesthesia after 5 minutes for removal of a foreign body from the corneal epithelium, or for incision of a Meibomian cyst through the conjunctiva. The sensitivity of the cornea is normal again after about 1 hour.

A 1% solution of oxybuprocaine hydrochloride is used for surface anaesthesia of the ear, nose, and throat.

Preparations

BP 2008: Oxybuprocaine Eye Drops;
USP 31: Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Oftalmocaina†; ***Austria:*** Benoxinat; Novain; ***Belg.:*** Unicaine; ***Braz.:*** Oxinest; ***Cz.:*** Benoxi; Novesin; ***Fin.:*** Oftan Obucain; ***Fr.:*** Cebesine; Novesine†; ***Ger.:*** Benoxinat SE†; Conjuncain-EDO; Novesine; Oxbarukain†; ***Hong Kong:*** Benoxinate†; Novesin†; ***Hung.:*** Humacain; ***India:*** Bendzon; ***Israel:*** Localin; ***Ital.:*** Novesina; ***Malaysia:*** Novesin†; ***Philipp.:*** Oxyben; ***Port.:*** Anestocil; ***Rus.:*** Inokain (Инокаин); ***S.Afr.:*** Novesin; ***Singapore:*** Novesin†; ***Spain:*** Prescaina; ***Switz.:*** Cebesin; Novesin; ***Thai.:*** Novesin; ***Turk.:*** Benoxinate; Novesin.

Multi-ingredient: ***Austral.:*** Fluress; ***Austria:*** Flurekain; ***Cz.:*** Thilorbin†; ***Fin.:*** Oftan Flurekain; ***Fr.:*** Collu-Blache†; ***Ger.:*** Thilorbin; ***Mex.:*** Mentalgina; ***NZ:*** Fluress†; ***Port.:*** Fluotest; Mebocaina; ***Spain:*** Anestesi Doble; Fluotest; ***Swed.:*** Fluress; ***Switz.:*** Collu-Blache; Mebucaine; ***UAE:*** B-Cool; ***USA:*** Flu-Oxinate†; Fluorox; Flurate; Fluress; Flurox.

Parethoxycaine Hydrochloride *(rINNM)*

Hidrocloruro de paretoxicaína; Paréthoxycaïne, Chlorhydrate de; Parethoxycaini Hydrochloridum. 2-Diethylaminoethyl 4-ethoxybenzoate hydrochloride.

Парэтоксикаина Гидрохлорид

$C_{15}H_{23}NO_3,HCl = 301.8.$

CAS — 94-23-5 (parethoxycaine); 136-46-9 (parethoxycaine hydrochloride).

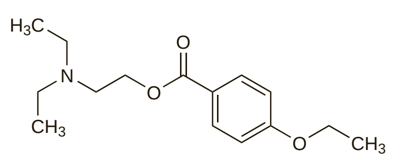

(parethoxycaine)

Profile

Parethoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850) that has been used in pastilles for painful conditions of the mouth and throat.

Pramocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pramocaína; Pramocaïne, Chlorhydrate de; Pramocaini Hydrochloridum; Pramoksiinihydrokloridi; Pramoxine Hydrochloride; Pramoxinhydroklorid; Pramoxini Hydrochloridum; Pramoxinium Chloride. 4-[3-(4-Butoxyphenoxy)propyl]morpholine hydrochloride.

Прамокаина Гидрохлорид

$C_{17}H_{27}NO_3,HCl = 329.9.$

CAS — 140-65-8 (pramocaine); 637-58-1 (pramocaine hydrochloride).
ATC — C05AD07; D04AB07.
ATC Vet — QC05AD07; QD04AB07.

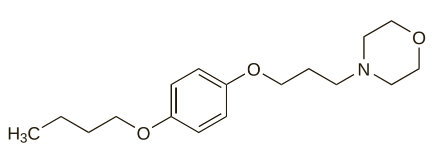

(pramocaine)

Pharmacopoeias. In *US.*

USP 31 (Pramoxine Hydrochloride). A white or almost white crystalline powder; it may have a faint aromatic odour. Freely soluble in water and in alcohol; soluble 1 in 35 of chloroform; very slightly soluble in ether. A 1% solution in water has a pH of about 4.5. Store in airtight containers.

Profile

Pramocaine hydrochloride is a local anaesthetic (p.1850) used for surface anaesthesia. It is used alone or with corticosteroids and other drugs, usually in a concentration of 1%, in a wide range of formulations for the relief of pain and itching associated with minor skin conditions and anorectal disorders. Initial burning or stinging may occur following topical application. It should not be used for the nose or eyes. The base has been used similarly.

Preparations

USP 31: Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Jelly.

Proprietary Preparations (details are given in Part 3)
Fr.: Tronothane; ***Israel:*** Anti Itch; ***Ital.:*** Tronotene; ***S.Afr.:*** Anugesic; ***Spain:*** Balsabit; Pramox; ***USA:*** Campho-Phenique Cold Sore Treatment & Scab Relief; Fleet Pain Relief; Pramox; Prax; Proctofoam; Sarna Sensitive Anti-Itch; Tronothane.

Multi-ingredient: ***Arg.:*** Anusol Duo; Anusol Duo S; Anusol-A; Tocorectal; ***Belg.:*** Nestosyl; ***Canad.:*** Anugesic-HC; Anusol Plus; Anuzinc HC Plus; Anuzinc Plus; Aveeno Anti-Itch; Caladryl; Hemorrhoid Ointment; Onguent Hemorrhoidal; Polysporin Itch Relief; PrameGel; Pramox HC; Proctodan-HC; Proctofoam-HC; Sarna-P; ***Chile:*** Caladryl Clear; ***Irl.:*** Anugesic-HC; Proctofoam-HC; ***Israel:*** Epifoam; Hemorid; Procto-Glyvenol; Proctofoam-HC; ***Ital.:*** Proctofoam-HC; ***Mex.:*** Caladryl Clear; Soyaloid Apruri; ***Neth.:*** Nestosyl; ***S.Afr.:*** Anugesic; Proctofoam†; ***UK:*** Anugesic-HC; Proctofoam-HC; ***USA:*** 1 + 1-F; AmLactin AP; Analpram-HC; Anusol; Bactine Pain Relieving Cleansing; Betadine Plus First Aid Antibiotics & Pain Reliever; Bite & Itch Lotion; Caladryl; Caladryl Clear; Cortane-B; Cortic ND; Cyotic; Enzone; Epifoam; HC Pramoxine; Hemorid For Women; Itch-X; Mediotic-HC; Neosporin + Pain Relief; Novacort; Oti-Med†; Otomar-HC; Phicon; Phicon-F; PrameGel; Pramosone; PramOtic; Preparation H; Proctofoam-HC; Sarna Ultra; Summers Eve Anti-Itch; Tri-Biozene; Tri-Otic†; Tronolane; Tucks; Zone-A; Zoto-HC.

Prilocaine *(BAN, USAN, rINN)*

Prilocaína; Prilocaïne; Prilocainum; Prilokaiini; Prilokain; Prilokainas. 2-Propylaminopropiono-*o*-toluidide.

Прилокаин

$C_{13}H_{20}N_2O = 220.3.$

CAS — 721-50-6.
ATC — N01BB04.
ATC Vet — QN01BB04.

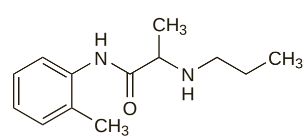

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Prilocaine). A white or almost white, crystalline powder. M.p. 36° to 39°. Slightly soluble in water; very soluble in alcohol and in acetone.

USP 31 (Prilocaine). A white or almost white powder or crystal aggregates. M.p. 36° to 39°. Slightly soluble in water; very soluble in alcohol and in acetone. Store at a temperature below 25°.

Eutectic mixture. Prilocaine forms a mixture with lidocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Prilocaine Hydrochloride *(BANM, USAN, rINNM)*

Astra-1512; Hidrocloruro de prilocaína; L-67; Prilocaïne, chlorhydrate de; Prilocaini hydrochloridum; Prilokaiinihydrokloridi; Prilokain Hidroklorür; Prilokain hydrochlorid; Prilokain-hidroklorid; Prilokainhydroklorid; Prilokaino hidrochloridas; Propitocaine Hydrochloride.

Прилокаина Гидрохлорид

$C_{13}H_{20}N_2O,HCl = 256.8.$

CAS — 721-50-6 (prilocaine); 1786-81-8 (prilocaine hydrochloride).
ATC — N01BB04.
ATC Vet — QN01BB04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Prilocaine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. M.p. 168° to 171°. Freely soluble in water and in alcohol; very slightly soluble in acetone.

USP 31 (Prilocaine Hydrochloride). A white odourless crystalline powder. M.p. 166° to 169°. Soluble 1 in 3.5 of water, 1 in 4.2 of alcohol, and 1 in 175 of chloroform; very slightly soluble in acetone; practically insoluble in ether.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Prilocaine has relatively modest toxicity compared with most amide-type local anaesthetics. However, dose-related methaemoglobinaemia and cyanosis, attributed to the metabolite *o*-toluidine, appear to occur more frequently with prilocaine than with other local anaesthetics (see Methaemoglobinaemia, p.1850). Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 mg/kg but the very young may be more susceptible. Methaemoglobinaemia has been observed in neonates whose mothers received prilocaine shortly before delivery and it has also been reported after prolonged topical application of a prilocaine/lidocaine eutectic mixture in children. (See under Surface Anaesthesia in Lidocaine, p.1866 for precautions to be observed with such a eutectic mixture.) Methaemoglobinaemia may be treated by giving oxygen followed, if necessary, by an injection of methylthioninium chloride.

Prilocaine is contra-indicated for paracervical block in obstetrics.

Prilocaine should be avoided in patients with anaemia, congenital or acquired methaemoglobinaemia, cardiac or ventilatory failure, or hypoxia.

Effects on the CNS. For reference to the prilocaine serum concentrations associated with CNS toxicity, see Absorption under Pharmacokinetics, below.

Porphyria. Prilocaine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Methaemoglobinaemia may occur at lower doses of prilocaine in patients receiving therapy with other drugs known to cause such conditions (e.g. sulfonamides such as sulfamethoxazole in co-trimoxazole).

Neuromuscular blockers. For a possible interaction between *mivacurium* and prilocaine, see under Atracurium, p.1904.

Pharmacokinetics

Prilocaine is reported to be 55% bound to plasma proteins. It is rapidly metabolised mainly in the liver and also in the kidneys and is excreted in the urine mainly as metabolites. One of the principal metabolites excreted in the urine is *o*-toluidine, which is believed to cause the methaemoglobinaemia observed after large doses. Prilocaine crosses the placenta and during prolonged epidural anaesthesia may produce methaemoglobinaemia in the fetus. It is distributed into breast milk.

See also under Local Anaesthetics, p.1852.

Absorption. Peak serum concentrations of prilocaine hydrochloride attained after the use of 8.5 mL of a 1% solution for retrobulbar and facial nerve block were well below the concentration of 20 micrograms/mL associated with CNS toxicity due to prilocaine.[1]

1. Goggin M, *et al.* Serum concentrations of prilocaine following retrobulbar block. *Br J Anaesth* 1990; **64:** 107–9.

Uses and Administration

Prilocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It has a similar anaesthetic potency to lidocaine. However, it has a slower onset of action, less vasodilator activity, and a slightly longer duration of action; it is also less toxic. Prilocaine hydrochloride is used for infiltration anaesthesia and nerve blocks in solutions of 0.5%, 1%, and 2%. A 1% solution is also used for epidural analgesia and a 2% solution is used for epidural anaesthesia; for intravenous regional anaesthesia 0.5% solutions are used. A 3% solution with the vasoconstrictor felypressin (p.2302) or a 4% solution without are used for dental procedures. A 4% solution with adrenaline 1 in 200 000 is also used for dentistry in some countries. Carbonated solutions of prilocaine have also been tried in some countries in epidural and brachial plexus nerve blocks (see under Administration, p.1852). Prilocaine is used for surface anaesthesia in a eutectic mixture with lidocaine. (Local anaesthetic techniques are discussed on p.1853.)

The dosage used in various **local anaesthetic procedures** varies with the site of injection and the procedure used. The recommended **maximum single dose** in adults for prilocaine hydrochloride is 400 mg if used alone, or 300 mg if used with felypressin. Doses should be reduced in elderly or debilitated patients. The dose for children over 6 months of age is up to 5 mg/kg. For *dental infiltration* or *dental nerve blocks*, the usual adult dose of prilocaine hydrochloride without felypressin is 40 to 80 mg (1 to 2 mL) as a 4% solution; children under 10 years generally require about 40 mg (1 mL). Similar doses of the 4% solution with adrenaline (1:200 000) may be used for most routine dental procedures. The usual adult dose of prilocaine hydrochloride with felypressin 0.03 international units/mL is 30 to 150 mg (1 to 5 mL) as a 3% solution; children under 10 years generally require 30 to 60 mg (1 to 2 mL).

A eutectic mixture of prilocaine base 2.5% and lidocaine base 2.5% (see Surface Anaesthesia, under Lidocaine, p.1866) is applied as a cream under an occlusive dressing to produce *surface anaesthesia* of the skin before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts.

Action. For a comparison of the vasoactivity of prilocaine and some other local anaesthetics, see p.1852.

Infiltration anaesthesia. Addition of felypressin at a concentration of 0.03 international units/mL to prilocaine 3% injection did not reduce plasma concentrations of prilocaine after infiltration of a 60-mg dose into the upper premolar region.[1]

1. Cannell H, Whelpton R. Systemic uptake of prilocaine after injection of various formulations of the drug. *Br Dent J* 1986; **160:** 47–9.

Preparations

BP 2008: Prilocaine Injection;
USP 31: Lidocaine and Prilocaine Cream; Prilocaine and Epinephrine Injection; Prilocaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Citanest; Citanest Dental; ***Belg.:*** Citanest; ***Braz.:*** Citanest; Citocaina; ***Canad.:*** Citanest†; ***Denm.:*** Citanest Octapressin; ***Fin.:*** Citanest Octapressin; ***Ger.:*** Xylonest; ***Ital.:*** Citanest con Octapressin; ***Mex.:*** Citanest Octapresin†; Pristesin F; ***Neth.:*** Citanest; Citanest Octapressine; ***Norw.:*** Citanest Octapressin; ***NZ:*** Citanest; Citanest with Octapressin†; ***Spain:*** Citanest; Citanest Octapressin; ***Swed.:*** Citanest; Citanest Octapressin; ***Switz.:*** Citanest Octapressin; Xylonest; ***Turk.:*** Citanest; Citanest Octapressin; ***UK:*** Citanest; Citanest with Octapressin; ***USA:*** Citanest.

Multi-ingredient: ***Arg.:*** Emla; ***Austral.:*** Emla; ***Austria:*** Emla; ***Belg.:*** Emla; ***Braz.:*** Emla; ***Canad.:*** Emla; ***Chile:*** Eutecaina; ***Cz.:*** Emla; ***Denm.:*** Emla; Oraqix; ***Fin.:*** Emla; Oraqix; ***Fr.:*** Emla; Emlapatch; Oraqix; ***Ger.:*** Emla; ***Gr.:*** Emla; Prinex; ***Hong Kong:*** Emla; ***Indon.:*** Emla; Estesia; Topsy; ***Irl.:*** Emla; ***Israel:*** Emla; ***Ital.:*** Emla; ***Malaysia:*** Emla; ***Mex.:*** Emla; ***Neth.:*** Emla; Oraqix; ***Norw.:*** Emla; Oraqix; ***NZ:*** Emla; ***Philipp.:*** Emla; ***Pol.:*** Emla; ***Port.:*** Emla; Oraqix; ***Rus.:*** Emla (Эмла); ***S.Afr.:*** Emla; Topla; ***Singapore:*** Emla; ***Spain:*** Emla; ***Swed.:*** Emla; Oraqix; ***Switz.:*** Emla; ***Thai.:*** Emla; ***Turk.:*** Emla; ***UK:*** Emla; Oraqix; ***USA:*** Emla.

Procaine Hydrochloride *(BANM, rINNM)*

Allocaine; Ethocaine Hydrochloride; Hidrocloruro de procaína; Novocainum; Procaïne, chlorhydrate de; Procaini hydrochloridum; Procainii Chloridum; Procainium Chloride; Prokaiinihydrokloridi; Prokain Hidroklorür; Prokain-hidroklorid; Prokain-hydrochlorid; Prokainhydroklorid; Prokaino hidrochloridas; Prokainy chlorowodorek; Syncaine. 2-Diethylaminoethyl 4-aminobenzoate hydrochloride.

Прокаина Гидрохлорид

$C_{13}H_{20}N_2O_2,HCl = 272.8.$

CAS — 59-46-1 (procaine); 51-05-8 (procaine hydrochloride).

ATC — C05AD05; N01BA02; S01HA05.

ATC Vet — QC05AD05; QN01BA02; QS01HA05.

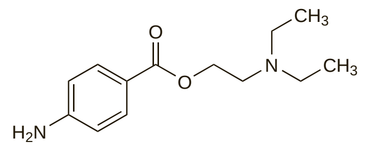

(procaine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Procaine Hydrochloride). A white or almost white crystalline powder or colourless crystals. Very soluble in water; soluble in alcohol. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Procaine Hydrochloride). Odourless, small, white crystals or white, crystalline powder. Soluble 1 in 1 of water and 1 in 15 of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Incompatibility. Procaine hydrochloride has been reported to be incompatible with aminophylline, barbiturates, magnesium sulfate, phenytoin sodium, sodium bicarbonate, and amphotericin B.

Stability of solutions. Degradation of procaine in a cardioplegic solution containing magnesium, sodium, potassium, and calcium salts was found to be temperature dependent.[1] At a storage temperature of 6° the shelf-life of the solution was 5 weeks and this was increased to 9 weeks when the storage temperature was −10°. Using carbon dioxide instead of nitrogen in the head space did not affect stability of procaine.

1. Synave R, *et al*. Stability of procaine hydrochloride in a cardioplegic solution containing bicarbonate. *J Clin Hosp Pharm* 1985; **10:** 385–8.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Effects on the cardiovascular system. Severe hypotension leading to cardiac arrest and death developed in a patient following the infusion of 600 mg of procaine for malignant hyperthermia.[1]

1. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; **i:** 355.

Hypersensitivity. Of 600 persons with dermatitis or eczema submitted to patch testing with 2% aqueous solution of procaine hydrochloride, 4.8% gave a positive reaction.[1]

For reports of hypersensitivity including anaphylactic reactions associated with procaine and other local anaesthetics, see under Adverse Effects of Local Anaesthetics, p.1850.

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.

Systemic lupus erythematosus. The limited theoretical risk from using procaine for local anaesthesia in patients who have had procainamide-induced SLE was aired some years ago.[1-3]

1. Dubois EL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.
2. Alarcón-Segovia D. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.
3. Lee SL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; **238:** 2201.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Diuretics. Use with *acetazolamide* extends the plasma half-life of procaine.[1]

1. Calvo R, *et al*. Effects of disease and acetazolamide on procaine hydrolysis by red blood cell enzymes. *Clin Pharmacol Ther* 1980; **27:** 179–83.

Pharmacokinetics

Procaine is poorly absorbed from mucous membranes and is usually given parenterally. It is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver. Only about 6% is bound to plasma proteins. About 80% of the para-aminobenzoic acid is excreted unchanged or conjugated in the urine. About 30% of the diethylaminoethanol is excreted in the urine, the remainder being metabolised in the liver.

See also under Local Anaesthetics, p.1852.

Uses and Administration

Procaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1852. Because of its poor penetration of intact mucous membranes, procaine is ineffective for surface application and has been chiefly used by injection, although in general it has been replaced by lidocaine and other local anaesthetics. It has a slow onset of action and a short duration of action. It has vasodilator activity and therefore a vasoconstrictor may be added to delay absorption and increase the duration of action. Procaine has mainly been used for infiltration anaesthesia, peripheral nerve blocks, and spinal block. (Local anaesthetic techniques are discussed on p.1853.) It has also been used in cardioplegic solutions to protect the myocardium during cardiac surgery.

For *infiltration anaesthesia* 0.25 or 0.5% solutions of procaine hydrochloride have been used in doses of 350 to 600 mg.

For *peripheral nerve block* a usual dose of 500 mg of procaine hydrochloride has been given as a 0.5% (100 mL), 1% (50 mL), or 2% (25 mL) solution. Doses up to 1 g have been used. For infiltration and peripheral nerve block adrenaline has been added to solutions, in general to give a final concentration of 1 in 200 000 to 1 in 100 000.

Procaine hydrochloride has been used with propoxycaine in dentistry.

Procaine forms poorly soluble salts or conjugates with some drugs, for example penicillin, and is used to prolong their action after injection. It may also reduce the pain of injection.

Procaine-*N*-glucoside hydrochloride has been included in a preparation for gastrointestinal disorders, and procaine ascorbate has been included in a multivitamin preparation.

Action. For a comparison of the vasoactivity of procaine and some other local anaesthetics, see p.1852.

Preparations

USP 31: Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Procaine Hydrochloride and Epinephrine Injection; Procaine Hydrochloride Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Endocaina†; Fadacaina; Procanest; ***Austria:*** Geroaslan H3; Gerovital H3; Novanaest; ***Canad.:*** Novocain†; ***Ger.:*** Hewedolor Procain; Lophakomp-Procain; Novocain†; Pasconeural-Injektopas; ***Hong Kong:*** Gerovital H3; ***Ital.:*** Lenident; ***USA:*** Novocain; ***Venez.:*** Artrocel; Bioquel; Genaplex.

Multi-ingredient: ***Arg.:*** 6 Copin; Dastonil; Gero H3 Aslan†; Gingeron; Muco-Anestyl†; Otalex G; Otonorthia; Sicadentol Plus†; ***Austral.:*** Cardioplegia Concentrate; ***Austria:*** Aslavital; Causat; Gerontin; KH3; Regenerin†; ***Braz.:*** Aftine; Algidente†; Bismu-Jet; Claudemor; Colutoide; Dentisan; Fonergin; Otobel†; Otoloide; Oturga; Passaja†; Pradente†; Timpanol†; Usedent†; ***Chile:*** Betonvit†; Diltotal; KH3-Vit†; KH3†; Megavit†; Pantiban; ***Cz.:*** Solutan†; Solutio Thomas cum Procaino; ***Denm.:*** Kardioplex; ***Ger.:*** Bismolan N†; Cardioplegin N†; Gero H3 Aslan; Hewedolor plus Coffein; KH3†; NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; Otalgan; Polytamin†; Procaneural†; Revicain comp plus†; Revicain comp†; Revicain†; Veno-Kattwiga N†; ***Gr.:*** Cardioplegia; ***Hong Kong:*** Cardioplegia; KH3; ***Hung.:*** Hemorid; Noditran†; Trypsin†; ***Indon.:*** Cardioplegia; ***Israel:*** Bedodeka Antineuralgica†; ***Ital.:*** Dentosedina; Ginvapast; Mios; Neo-Ustiol; Otalgan; Otomidone; Otopax; Rinantipiol†; Ustiosan; ***Malaysia:*** Cardioplegia; ***NZ:*** KH3; ***Port.:*** Claudemor†; Otocalma†; ***Rus.:*** Solutan (Солутан); ***S.Afr.:*** Salusa†; Universal Earache Drops; ***Singapore:*** Cardioplegia; ***Spain:*** Anestesia Loc Braun S/A; Co Bucal; Coliriocilina Adren Astr; Dentol Topico; Eupnol; Kanafosal; Kanafosal Predni; Neocolan; Nulacin Fermentos; Oftalmol Ocular; Otalgan†; Otosedol; Tangenol†; ***Switz.:*** Anaestalgin; Ginvapast; Otalgan; Otosan; ***Thai.:*** Cardioplegia; KH3.

Used as an adjunct in: ***Arg.:*** Betametasona B12; ***Braz.:*** Cianotrat-Dexa; Dexa-Neuriberi†; Dexacobal; Dexador; Dexagil; Dexaneurin; ***Ger.:*** Eukalisan N; ***Ital.:*** Neuroftal†; ***Malaysia:*** Alinamin B12†; ***Singapore:*** Alinamin B12†; ***Spain:*** Sulmetin Papaverina†; Sulmetin†; ***USA:*** Hytinic†.

Propanocaine Hydrochloride *(rINNM)*

467D$_3$; Hidrocloruro de propanocaína; Propanocaïne, Chlorhydrate de; Propanocaini Hydrochloridum. 3-Diethylamino-1-phenylpropyl benzoate hydrochloride.

Пропанокаина Гидрохлорид

$C_{20}H_{25}NO_2,HCl = 347.9.$

CAS — 493-76-5 (propanocaine); 1679-79-4 (propanocaine hydrochloride).

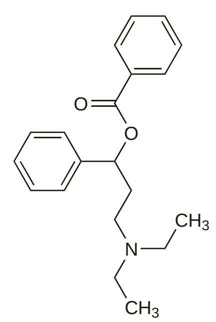

(propanocaine)

Profile

Propanocaine hydrochloride, a benzoic acid ester, is a local anaesthetic (p.1850) that has been used topically for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Detraine.

Propipocaine *(rINN)*

Propipocaína; Propipocaïne; Propipocainum; Propoxypiperocaine. 3-Piperidino-4′-propoxypropiophenone.

Пропипокаин

$C_{17}H_{25}NO_2$ = 275.4.

CAS — 3670-68-6.

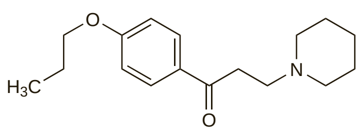

Profile

Propipocaine is a local anaesthetic (p.1850) that has been used for surface anaesthesia.

Propoxycaine Hydrochloride *(rINNM)*

Hidrocloruro de propoxicaína; Propoxycaïne, Chlorhydrate de; Propoxycaini Hydrochloridum; Propoxycainium Chloride. 2-Diethylaminoethyl 4-amino-2-propoxybenzoate hydrochloride.

Пропоксикаина Гидрохлорид

$C_{16}H_{26}N_2O_3$,HCl = 330.9.

CAS — 86-43-1 (propoxycaine); 550-83-4 (propoxycaine hydrochloride).

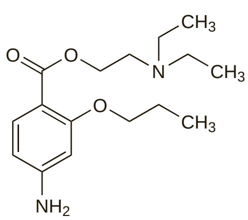

(propoxycaine)

Pharmacopoeias. In *US.*

USP 31 (Propoxycaine Hydrochloride). A white odourless crystalline solid. It discolours on prolonged exposure to light and air. Soluble 1 in 2 of water, 1 in 10 of alcohol, and 1 in 80 of ether; practically insoluble in acetone and in chloroform. A 2% solution in water has a pH of about 5.4. Protect from light.

Profile

Propoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p.1850). It has been used with procaine hydrochloride and a vasoconstrictor for infiltration anaesthesia and nerve block in dental procedures. Propoxycaine has a more rapid onset and a longer duration of action than that of procaine.

Preparations

USP 31: Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proxymetacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de proximetacaína; Proksimetakain Hidroklorür; Proparacaine Hydrochloride; Proparakain Hidroklorür; Proxymétacaïne, Chlorhydrate de; Proxymetacaini Hydrochloridum. 2-Diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride.

Проксиметакаина Гидрохлорид

$C_{16}H_{26}N_2O_3$,HCl = 330.9.

CAS — 499-67-2 (proxymetacaine); 5875-06-9 (proxymetacaine hydrochloride).

ATC — S01HA04.

ATC Vet — QS01HA04.

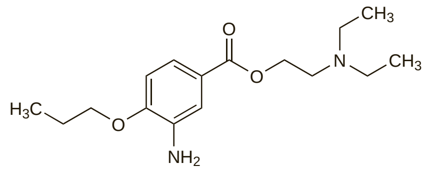

(proxymetacaine)

NOTE. PROX is a code approved by the BP 2008 for use on single unit doses of eye drops containing proxymetacaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PROXFLN is a similar code approved for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Proxymetacaine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Soluble in water and in chloroform; very soluble in dehydrated alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5.7 to 6.4. Protect from light.

USP 31 (Proparacaine Hydrochloride). A white to off-white, or faintly buff-coloured, odourless, crystalline powder. Soluble in water, in warm alcohol, and in methyl alcohol; insoluble in ether and in benzene.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

A severe immediate-type corneal reaction to proxymetacaine may rarely occur. Allergic contact dermatitis has also been reported.

Effects on the skin. Exacerbation of Stevens-Johnson syndrome has been reported[1] in a woman after ophthalmic anaesthesia with proxymetacaine hydrochloride.

1. Ward B, *et al.* Dermatologic reaction in Stevens-Johnson syndrome after ophthalmic anesthesia with proparacaine hydrochloride. *Am J Ophthalmol* 1978; **86:** 133–5.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

See under Local Anaesthetics, p.1852.

Uses and Administration

Proxymetacaine hydrochloride, a meta-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1852. It is used for surface anaesthesia (p.1853) in ophthalmology in a concentration of 0.5%. Proxymetacaine is of similar potency to tetracaine in equal concentrations and induces anaesthesia within about 20 seconds. The duration of action may be 15 minutes or longer. Instillation of 1 or 2 drops permits tonometry after 30 seconds. For removal of foreign bodies or sutures from the cornea 1 or 2 drops are instilled every 5 to 10 minutes for up to 3 applications, or 1 or 2 drops are instilled 2 to 3 minutes before the procedure. For deeper anaesthesia such as needed for cataract extraction 1 drop is instilled every 5 to 10 minutes to a total of 5 to 7 applications.

Trigeminal neuralgia. There have been anecdotal reports that proxymetacaine eye drops relieved trigeminal neuralgia (p.9) refractory to carbamazepine.[1,2] However, a controlled study failed to demonstrate any benefit.[3]

1. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by ophthalmic anesthetic. *JAMA* 1991; **265:** 2807.
2. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by optical anesthesia. *JAMA* 1991; **266:** 1649.
3. Kondziolka D, *et al.* The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia: a randomized double-blind placebo-controlled trial. *J Neurosurg* 1994; **80:** 993–7.

Preparations

BP 2008: Proxymetacaine Eye Drops;
USP 31: Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Proparacaine Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Anestalcon; Poencaina; ***Austral.:*** Alcaine; Ophthetic†; ***Belg.:*** Alcaine; ***Braz.:*** Anestalcon; Visonest; ***Canad.:*** Ak-Taine; Alcaine; Diocaine†; Ophthetic†; ***Chile:*** Anestalcon; ***Ger.:*** Proparakain-POS; ***Gr.:*** Alcaine; ***Hong Kong:*** Alcaine; ***Malaysia:*** Alcaine; ***Mex.:*** Alcaine; ***Norw.:*** Alcaine; ***NZ:*** Ophthetic; ***Philipp.:*** Alcaine; ***Pol.:*** Alcaine; ***Rus.:*** Alcaine (Алкаин); ***Singapore:*** Alcaine; ***Switz.:*** Alcaine; ***Turk.:*** Alcaine; Opticaine; ***USA:*** Ak-Taine; Alcaine; Ocu-Caine; Ophthetic; Parcaine; ***Venez.:*** Alcaine; Oftaine†; Poencaina.

Multi-ingredient: ***Canad.:*** Fluoracaine†; ***USA:*** Fluoracaine; Fluorocaine.

Quinisocaine Hydrochloride *(BANM, rINNM)*

Chinisocainum Hydrochloride; Dimethisoquin Hydrochloride *(USAN)*; Dimethisoquinium Chloride; Hidrocloruro de quinisocaína; Quinisocaïne, Chlorhydrate de; Quinisocaini Hydrochloridum. 2-(3-Butyl-1-isoquinolyloxy)-*NN*-dimethylethylamine hydrochloride.

Хинизокаина Гидрохлорид

$C_{17}H_{24}N_2O$,HCl = 308.8.

CAS — 86-80-6 (quinisocaine); 2773-92-4 (quinisocaine hydrochloride).

ATC — D04AB05.

ATC Vet — QD04AB05.

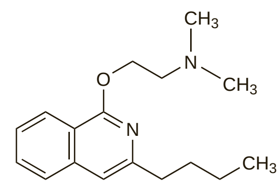

(quinisocaine)

Profile

Quinisocaine hydrochloride is a local anaesthetic (p.1850) that has been used as a surface anaesthetic in the form of an ointment or cream in a concentration of 0.5% for the relief of pruritus, anogenital or anorectal irritation, and minor skin conditions. It has also been used as suppositories.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Quotane; ***Ger.:*** Haenal; Isochinol†; ***Switz.:*** Isochinol.

Multi-ingredient: ***Fr.:*** Rectoquotane.

Ropivacaine Hydrochloride

(BANM, rINNM)

AL-281; Hidrocloruro de ropivacaína; Ropivacaïne, chlorhydrate de; Ropivacaini hydrochloridum; Ropivakaiinihydrokloridi; Ropivakain Hidroklorür; Ropivakainhydroklorid. (*S*)-2′,6′-Dimethyl-1-propylpiperidine-2-carboxanilide hydrochloride monohydrate.

Ропивакаина Гидрохлорид

$C_{17}H_{26}N_2O$,HCl,H_2O = 328.9.

CAS — 84057-95-4 (ropivacaine); 98717-15-8 (anhydrous ropivacaine hydrochloride); 132112-35-7 (ropivacaine hydrochloride monohydrate).

ATC — N01BB09.

ATC Vet — QN01BB09.

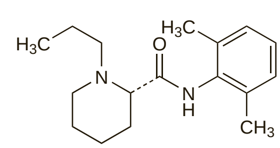

(ropivacaine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Ropivacaine Hydrochloride Monohydrate). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. pH of a 2% solution in water is 4.5 to 6.0.

USP 31 (Ropivacaine Hydrochloride). A white crystalline powder. Soluble in water. A 1% solution in water has a pH of 4.5 to 6.0.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Ropivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics.

Effects on the cardiovascular system. Ropivacaine is structurally related to bupivacaine, but data from extensive *animal* studies suggest that ropivacaine may be less cardiotoxic than bupivacaine.[1] Results from a study[2] in 12 healthy male volunteers support these data; at doses producing CNS symptoms cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine than with bupivacaine.

1. Cederholm I. Preliminary risk-benefit analysis of ropivacaine in labour and following surgery. *Drug Safety* 1997; **16:** 391–402.
2. Knudsen K, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78:** 507–14.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Giving ropivacaine with general anaesthetics, opioid analgesics, or drugs structurally related to amide-type local anaesthetics (e.g. certain antiarrhythmics) may result in potentiation of adverse effects.

The metabolism of ropivacaine is mediated by the cytochrome P450 isoenzyme CYP1A2 and the potential exists for interactions between ropivacaine and other drugs that inhibit or act as a substrate for this isoenzyme. Prolonged use of ropivacaine should be avoided in patients treated with potent CYP1A2 inhibitors, such as fluvoxamine. Plasma concentrations of ropivacaine may be reduced by enzyme-inducing drugs such as rifampicin.

Pharmacokinetics

Ropivacaine is about 94% bound to plasma proteins. The terminal elimination half-life has been reported to be 1.8 hours. It is extensively metabolised in the liver, predominantly by aromatic hydroxylation which is mediated by the cytochrome P450 isoenzyme CYP1A2; the isoenzyme CYP3A4 plays a minor role in the metabolism of ropivacaine. The metabolites are excreted mainly in the urine; about 1% of a dose is excreted as unchanged drug. Some metabolites also have a local anaesthetic effect but less than that of ropivacaine. Ropivacaine crosses the placenta.

See also under Local Anaesthetics, p.1852.

Uses and Administration

Ropivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. It is a long-acting local anaesthetic, although onset and duration of action are dependent upon the site of injection; the presence of a vasoconstrictor such as adrenaline has no effect. Ropivacaine is used for epidural block, peripheral nerve block, and infiltration anaesthesia and field block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). (Local anaesthetic techniques are discussed on p.1853.) At high doses ropivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (p.7) and in postoperative analgesia (p.4).

Like bupivacaine (p.1854), ropivacaine has a differential blocking effect on nerve fibres and, at the lowest concentration used, there is good differentiation between sensory and motor block. The onset and duration of sensory block produced by ropivacaine is generally similar to that obtained with bupivacaine but the motor block is often slower in onset, shorter in duration, and less intense.

Ropivacaine hydrochloride is given in concentrations of 0.2 to 1%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient. The dose of ropivacaine should be reduced in the elderly, and in acutely ill or debilitated patients. A test dose of lidocaine with adrenaline should be given before starting epidural block with ropivacaine to detect inadvertent intravascular administration.

- For **surgical anaesthesia**, doses of ropivacaine hydrochloride for *lumbar epidural block* are 75 to 150 mg (15 to 30 mL) as a 0.5% solution, or 112.5 to 187.5 mg (15 to 25 mL) as a 0.75% solution, or 150 to 200 mg (15 to 20 mL) as a 1% solution; for caesarean section, doses are 100 to 150 mg (20 to 30 mL) as a 0.5% solution or 112.5 to 150 mg (15 to 20 mL) as a 0.75% solution. Doses for *thoracic epidural block* to establish a block for postoperative pain relief are 25 to 75 mg (5 to 15 mL) as a 0.5% solution or 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution; the actual dose used depends on the level of the injection.
- For *peripheral nerve block* of major nerves such as the brachial plexus, typical doses are 175 to 250 mg (35 to 50 mL) as a 0.5% solution; 225 to 300 mg (30 to 40 mL) as a 0.75% solution has also been recommended for brachial plexus block.
- For *infiltration anaesthesia* and *field block* up to 200 mg (40 mL) as a 0.5% solution or up to 225 mg (30 mL) as a 0.75% solution may be used.
- In the management of **acute pain** ropivacaine hydrochloride is used as a 0.2% solution for epidural block (0.5% solutions may be used for infiltration). Doses for *lumbar epidural block* are 20 to 40 mg (10 to 20 mL) as an initial bolus followed by 20 to 30 mg (10 to 15 mL) at intervals of not less than 30 minutes. Alternatively, 12 to 20 mg (6 to 10 mL) per hour may be given as a continuous epidural infusion; if additional pain relief is required, doses of up to 28 mg (14 mL) per hour may be given. Doses for *thoracic epidural block* are 12 to 28 mg (6 to 14 mL) per hour as a continuous infusion.
- For *infiltration anaesthesia* doses are 2 to 200 mg (1 to 100 mL) as a 0.2% solution or 5 to 200 mg (1 to 40 mL) as a 0.5% solution.
- In neonates, infants, and children aged up to 12 years, ropivacaine hydrochloride may be used for the management of peri- and postoperative pain. A 0.2% solution is given in a dose of 2 mg/kg (1 mL/kg) to achieve a *caudal epidural block.*

◊ References.

1. Markham A, Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52:** 429–49.
2. McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76:** 300–307.
3. Morton C. Ropivacaine. *Br J Hosp Med* 1997; **58:** 97–100.
4. Stienstra R. The place of ropivacaine in anesthesia. *Acta Anaesthesiol Belg* 2003; **54:** 141–8.
5. Zink W, Graf BM. Benefit-risk assessment of ropivacaine in the management of postoperative pain. *Drug Safety* 2004; **27:** 1093–1114.
6. Simpson D, *et al.* Ropivacaine: a review of its use in regional anaesthesia and acute pain management. *Drugs* 2005; **65:** 2675–2717.

Preparations

USP 31: Ropivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Naropin; ***Austral.:*** Naropin; ***Austria:*** Naropin; ***Belg.:*** Naropin; ***Braz.:*** Naropin; Ropi; ***Canad.:*** Naropin; ***Chile:*** Naropin; ***Cz.:*** Naropin; ***Denm.:*** Naropin; ***Fin.:*** Naropin; ***Fr.:*** Naropeine; ***Ger.:*** Naropin; ***Gr.:*** Naropeine; ***Hong Kong:*** Naropin; ***Hung.:*** Naropin; ***Indon.:*** Naropin; ***Irl.:*** Naropin; ***Israel:*** Narop; ***Ital.:*** Naropina; ***Malaysia:*** Naropin; ***Mex.:*** Naropin; ***Neth.:*** Naropin; ***Norw.:*** Naropin; ***NZ:*** Naropin; ***Philipp.:*** Naropin; ***Pol.:*** Naropin; ***Port.:*** Naropeine; ***Rus.:*** Naropin (Наропин); ***S.Afr.:*** Naropin; ***Singapore:*** Naropin; ***Spain:*** Naropin; ***Swed.:*** Narop; ***Switz.:*** Naropin; ***Thai.:*** Naropin†; ***Turk.:*** Naropin; ***UK:*** Naropin; ***USA:*** Naropin; ***Venez.:*** Naropin†.

Multi-ingredient: ***Austral.:*** Naropin with Fentanyl; ***NZ:*** Naropin with Fentanyl.

Tetracaine *(BAN, rINN)*

Amethocaine; Tetracaína; Tétracaïne; Tetracainum; Tetrakaiini; Tetrakain. 2-Dimethylaminoethyl 4-butylaminobenzoate.

Тетракаин

$C_{15}H_{24}N_2O_2$ = 264.4.

CAS — 94-24-6.

ATC — C05AD02; D04AB06; N01BA03; S01HA03.

ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.

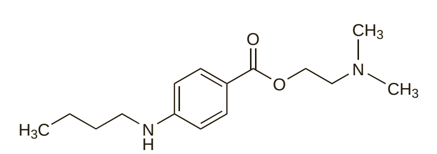

Pharmacopoeias. In *US.*

USP 31 (Tetracaine). A white or light yellow waxy solid. M.p. 41° to 46°. Very slightly soluble in water; soluble 1 in 5 of alcohol and 1 in 2 of chloroform or of ether; soluble in benzene. Store in airtight containers. Protect from light.

Tetracaine Hydrochloride *(BANM, rINNM)*

Amethocaine Hydrochloride; Dicainum; Hidrocloruro de tetracaína; Tétracaïne, chlorhydrate de; Tetracaini hydrochloridum; Tetracainii Chloridum; Tetrakaiinihydrokloridi; Tetrakain Hidroklorür; Tetrakain hydrochlorid; Tetrakainhidroklorid; Tetrakainhydroklorid; Tetrakaino hidrochloridas; Tetrakainy chlorowodorek.

Тетракаина Гидрохлорид

$C_{15}H_{24}N_2O_2$,HCl = 300.8.

CAS — 136-47-0.

ATC — C05AD02; D04AB06; N01BA03; S01HA03.

ATC Vet — QC05AD02; QD04AB06; QN01BA03; QS01HA03.

NOTE. TET is a code approved by the BP 2008 for use on single unit doses of eye drops containing tetracaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Tetracaine Hydrochloride). A white or almost white, slightly hygroscopic, polymorphic, crystalline powder. Freely soluble in water; soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Tetracaine Hydrochloride). A fine, white, odourless, hygroscopic, polymorphic, crystalline powder. Very soluble in water; soluble in alcohol; insoluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1850.

Tetracaine has high systemic toxicity. Absorption of tetracaine from mucous membranes is rapid and adverse reactions can occur abruptly without the appearance of prodromal signs or convulsions; fatalities have occurred.

A stinging sensation may occur when tetracaine is used in the eye. Mild erythema at the site of application is frequently seen with topical use; slight oedema or pruritus occur less commonly. Blistering of the skin may occur.

Urethral stricture. There has been a report[1] of a sudden increase in the incidence of urethral stricture after transurethral surgery, which may have been due to an increase in the concentration of tetracaine hydrochloride in the lubricant gel from 0.1 to 3%.

1. Pansadoro V. Role of local anaesthetics in urethral strictures after transurethral surgery. *Lancet* 1990; **336:** 64.

Precautions

As for Local Anaesthetics in general, p.1851.

Tetracaine should not be applied to inflamed, traumatised, or highly vascular surfaces. It should not be used to provide anaesthesia for bronchoscopy or cystoscopy, as lidocaine is a safer alternative.

Interactions

For interactions associated with local anaesthetics, see p.1851.

Pharmacokinetics

See under Local Anaesthetics, p.1852. Tetracaine is reported to be about 15% bioavailable after application of a 4% gel to intact skin, with a mean absorption and elimination half-life of about 75 minutes.

Uses and Administration

Tetracaine, a para-aminobenzoic acid ester, is a potent local anaesthetic with actions and uses similar to those described on p.1852. It is used for surface anaesthesia and spinal block; its use in other local anaesthetic techniques is restricted by its systemic toxicity.

Tetracaine is generally used as the hydrochloride in solutions and creams, and as the base in gels or ointments.

For *anaesthesia of the eye*, solutions containing 0.5 to 1% tetracaine hydrochloride have been used; ointments have also been used. Instillation of a 0.5% solution produces anaesthesia within 25 seconds that lasts for 15 minutes or longer and is suitable for use before minor surgical procedures.

For *topical anaesthesia*, a 4% gel is used as a *percutaneous local anaesthetic* before *venepuncture or venous cannulation*. The gel is applied to the centre of the area to be anaesthetised and covered with an occlusive dressing. Gel and dressing are removed after 30 minutes for venepuncture and after 45 minutes for venous cannulation. A single application generally provides anaesthesia for 4 to 6 hours. This method is not suitable for premature infants or those less than 1 month of age. A transdermal patch containing tetracaine 70 mg with lidocaine 70 mg is available for surface anaesthesia of intact skin in connection with *needle puncture* and in cases of *superficial surgical procedures*. A cream or an ointment has been used for painful conditions of the *anus or rectum*.

Tetracaine hydrochloride has also been used in the *mouth* in sprays and lozenges.

Tetracaine hydrochloride has also been used for *spinal block* usually as a 0.5% solution.

Action. For a comparison of the vasoactivity of tetracaine with some other local anaesthetics, see p.1852.

Spinal block. A study[1] in 40 patients indicated that for patients undergoing caesarean section with spinal anaesthesia (see Central Nerve Block, p.1853) doses of 12 or 14 mg of tetracaine provided better intraoperative analgesia than doses of 8 or 10 mg without leading to excessive spread of the block.

1. Hirabayashi Y, *et al.* Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *Br J Anaesth* 1995; **75:** 266–8.

Surface anaesthesia. A topical gel formulation of tetracaine 4% appears to provide more rapid and prolonged surface anaesthesia (see p.1853) than a eutectic mixture of lidocaine and prilocaine.[1,2] In a double-blind placebo-controlled study[3] the tetracaine gel formulation was significantly better than the eutectic mixture in reducing pain caused by laser treatment of portwine stains. Similar findings were also seen in a comparative study[4] and a systematic review[5] in children requiring venous cannulation, although others have questioned the efficacy of tetracaine gel in peripheral insertion of a central catheter.[6] The same formulation appears to be effective when incorporated into a transdermal patch.[7] Patches containing a mixture of lidocaine and tetracaine have also been tried[8,9] and are licensed in some countries for surface anaesthesia of intact skin in connection with needle puncture and in cases of superficial surgical procedures.

There have been reports of seizures and death in children after the use of a mixture of tetracaine, adrenaline, and cocaine on mucosal surfaces;[10] application of preparations of tetracaine to highly vascular surfaces is contra-indicated. A gel containing a mixture of lidocaine, adrenaline, and tetracaine has been found to be an effective alternative to the cocaine-containing preparation.[11]

Tetracaine has also been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy.[12] Liposome-encapsulated tetracaine has also been shown to provide adequate surface anaesthesia.[13]

1. McCafferty DF, *et al.* In vivo assessment of percutaneous local anaesthetic preparations. *Br J Anaesth* 1989; **62:** 17–21.
2. Rømsing J, *et al.* Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth* 1999; **82:** 637–8.
3. McCafferty DF, *et al.* Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; **78:** 286–9.
4. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000; **82:** 309–10.
5. Lander JA, *et al.* EMLA and amethocaine for reduction of children's pain associated with needle insertion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/04/08).
6. Lemyre B, *et al.* How effective is tetracaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial. *BMC Med* 2006; **4:** 11. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-11.pdf (accessed 21/06/06)
7. McCafferty DF, Woolfson AD. New patch delivery system for percutaneous local anaesthesia. *Br J Anaesth* 1993; **71:** 370–4.
8. Berman B, *et al.* Self-warming lidocaine/tetracaine patch effectively and safely induces local anesthesia during minor dermatologic procedures. *Dermatol Surg* 2005; **31:** 135–8.
9. Schecter AK, *et al.* Randomized, double-blind, placebo-controlled study evaluating the lidocaine/tetracaine patch for induction of local anesthesia prior to minor dermatologic procedures in geriatric patients. *Dermatol Surg* 2005; **31:** 287–91.
10. Wong S, Hart LL. Tetracaine/adrenaline/cocaine for local anesthesia. *DICP Ann Pharmacother* 1990; **24:** 1181–3.
11. Ernst AA, *et al.* Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. *Pediatrics* 1995; **95:** 255–8.
12. Yotsuyanagi T, *et al.* Mucosa-adhesive film containing local analgesic. *Lancet* 1985; **ii:** 613.
13. Fisher R, *et al.* Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA. *Br J Anaesth* 1998; **81:** 972–3.

Preparations

BP 2008: Tetracaine Eye Drops;
USP 31: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Tetracaine and Menthol Ointment; Tetracaine Hydrochloride Cream; Tetracaine Hydrochloride for Injection; Tetracaine Hydrochloride in Dextrose Injection; Tetracaine Hydrochloride Injection; Tetracaine Hydrochloride Ophthalmic Solution; Tetracaine Hydrochloride Topical Solution; Tetracaine Ointment; Tetracaine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Tray-Te; ***Braz.:*** Anestesico; ***Canad.:*** Ametop; Cepacol Viractin†; Pontocaine; Viractin; ***Fr.:*** Solutricine Maux de Gorge; ***Ger.:*** Ophtocain N; ***Hong Kong:*** Ametop; ***Irl.:*** Ametop†; ***Israel:*** Pontocaine†; ***Mex.:*** Ponti; ***NZ:*** Ametop†; ***S.Afr.:*** Covostet; ***Spain:*** Anestesia Topi Braun C/A; Anestesia Topi Braun S/A; Anestesico; Hemonet; Lubricante Urol; ***Swed.:*** Tetrakain; ***UK:*** Ametop; Anethaine; ***USA:*** Cepacol Viractin Cold Sore Treatment; Pontocaine.

Multi-ingredient: ***Arg.:*** Bagociletas con Anestesia; Clevosan; Drill; ***Austria:*** Dynexan; Herviros; Neocones; ***Braz.:*** Anesdente do Bebe†; Anestesiol†; Hexomedine; Oto Betnovate; Oto-Biotic†; Um Instante†; ***Canad.:*** Endospray†; ***Cz.:*** Drill; ***Fr.:*** Aphtoral; Broncorinol maux de gorge†; Cantalene; Codetricine vitamine C†; Drill; Eludril; Hexomedine†; Oromedine; Solutricine Maux de Gorge; ***Ger.:*** Acoin; Gingicain D; Herviros†; ***Hung.:*** Drill; ***Israel:*** Anaesthetic Ear Drops; Otidin; ***Ital.:*** Corizzina†; Donalg; Odongi; Recto-Reparil; Ruscoroid; ***NZ:*** Topicaine; ***Pol.:*** Ruskorex; ***Port.:*** Anucet; Colircusi Anestesico; Drill; Hemofissural; Lubrificante Anestesico; Rapydan; Xilonibsa†; ***Rus.:*** Drill (Дрилл); ***S.Afr.:*** Dynexan; ***Spain:*** Anestesi Doble; Blastoestimulina; Carbocaina†; Dentikrisos; Neocones; Otogen Calmante; Resorborina; Topicaina†; Vinciseptil Otico; ***Switz.:*** Angidine; Eludril; Tyrothricine + Gramicidine; ***Turk.:*** Hemoralgine; Otimisin; ***UK:*** Eludril; Rapydan; ***USA:*** Cetacaine; Pliaglis; Stypto-Caine; Synera.

Tolycaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tolicaína; Tolycaïne, Chlorhydrate de; Tolycaini Hydrochloridum. Methyl 2-(2-diethylaminoacetamido)-*m*-toluate hydrochloride.

Толикаина Гидрохлорид

$C_{15}H_{22}N_2O_3$,HCl = 314.8.
CAS — 3686-58-6 (tolycaine); 7210-92-6 (tolycaine hydrochloride).

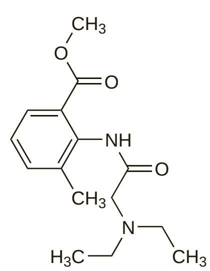

(tolycaine)

Profile

Tolycaine hydrochloride is an amide local anaesthetic (p.1850) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Ger.:*** Tardocillin.

Tricaine Mesilate

Metacaine Mesylate; Tricaína, mesilato de; Tricaine Mesylate; TS-222. Ethyl 3-aminobenzoate methanesulphonate.

$C_{10}H_{15}NO_5S$ = 261.3.
CAS — 886-86-2.
ATC Vet — QN01AX93.

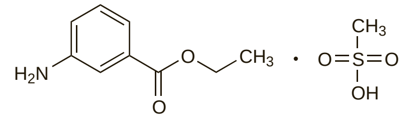

Profile

Tricaine mesilate is a derivative of an isomer of benzocaine (see p.1854) and although it has been used as a local anaesthetic in human medicine it is now mainly used as an anaesthetic and tranquilliser for fish and other cold-blooded animals.

Trimecaine Hydrochloride *(rINNM)*

Hidrocloruro de trimecaína; Trimécaïne, Chlorhydrate de; Trimecaini Hydrochloridum; Trimecainium Chloratum; Trimekainhydrochlorid. 2-Diethylamino-2′,4′,6′-trimethylacetanilide hydrochloride.

Тримекаина Гидрохлорид

$C_{15}H_{24}N_2O$,HCl = 284.8.
CAS — 616-68-2 (trimecaine); 1027-14-1 (trimecaine hydrochloride).

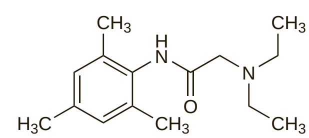

(trimecaine)

Profile

Trimecaine hydrochloride is an amide local anaesthetic (p.1850) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Mesocain.

Multi-ingredient: ***Cz.:*** Mesocain; Septonex Plus; ***Rus.:*** Levosin (Левосин); Simetrid (Симетрид).

Used as an adjunct in: ***Austria:*** Ketazon†.

Miotics Mydriatics and Antiglaucoma Drugs

Glaucoma and ocular hypertension, p.1873
Mydriasis and cycloplegia, p.1874
Reversal of mydriasis, p.1874
Strabismus, p.1874

Included in this chapter are a variety of drugs used in the eye to alter accommodation and produce mydriasis or cycloplegia, or in the treatment of glaucoma. Some drugs used for these purposes, or in other ocular disorders, but with other primary uses, may be found elsewhere in *Martindale*.

Glaucoma and ocular hypertension

Intra-ocular pressure rises when there is an imbalance between production and drainage of aqueous humour in the eye. Aqueous humour is secreted by the ciliary body and flows into the posterior chamber of the eye. It then passes through the pupil into the anterior chamber from where about 75% drains from the eye through the trabecular meshwork into Schlemm's canal and then into the episcleral veins. The remainder is removed by the uveoscleral route, passing through the ciliary muscle and finally into the episcleral tissues.

The term **ocular hypertension** is used to describe intra-ocular pressure above an upper normal value of 21 mmHg when there are no signs of optic nerve damage. The term **glaucoma** is used to describe a group of conditions characterised by cupping (excavation) of the optic disc and damage of the optic nerve leading to gradual but irreversible visual loss; glaucoma is one of the most common causes of blindness.

Raised intra-ocular pressure is an important risk factor for glaucoma, and as it is the only one that can be altered, current therapy for glaucoma is directed at lowering it. The aim is not just to reduce intra-ocular pressure to a normal value but to a level at which damage to the optic nerve ceases.[1-5] Some patients may have raised intra-ocular pressure for many years without evidence of glaucoma. Whether these patients would receive long-term benefit from a reduction in intra-ocular pressure has been a matter of debate. However, recent randomised trials[6,7] have shown that topical ocular hypotensive treatment was effective in preventing or delaying the onset of open-angle glaucoma in patients with raised intra-ocular pressure. In addition, another study[8,9] has found that lowering intra-ocular pressure slows the progression of glaucoma. A meta-analysis[10] has also confirmed that lowering intra-ocular pressure reduces the risk of visual field loss in the long term in patients with ocular hypertension or newly diagnosed glaucoma. Similarly, a systematic review[11] concluded that topically lowering intra-ocular pressure had a protective effect on the visual field. Some[12] consider that only high-risk patients with raised intra-ocular pressure should be treated; such risk factors include thin central corneal thickness measurement, large cup-to-disc ratio, older age, intra-ocular pressure fluctuation, and a family history of blindness. In practice, many ophthalmologists consider that therapy is indicated if the intra-ocular pressure is higher than 30 mmHg. Glaucoma can also occur and progress in patients with an intra-ocular pressure within the normal range (normal tension glaucoma).

Raised intra-ocular pressure associated with glaucoma is usually due to reduced outflow of aqueous humour from the eye. Glaucoma is described as open-angle or angle-closure depending on the mechanism of the obstruction of drainage and may be acute or chronic. Glaucoma may also be referred to as primary or secondary. **Primary glaucoma** is usually associated with a direct disturbance of outflow whereas **secondary glaucoma** develops as a consequence of a number of diseases or of trauma.

The most common form of glaucoma is **chronic open-angle glaucoma** (simple glaucoma; wide-angle glaucoma), which is due to blockage in drainage through the trabecular meshwork. Intra-ocular pressure increases gradually, and the condition is usually asymptomatic until well advanced and severe damage has occurred. Usually, both eyes are affected. Risk factors include old age, diabetes, Afro-Caribbean race, a family history of glaucoma, and myopia. A '**steroid glaucoma**' may be produced, after a few weeks of treatment with eye drops containing corticosteroids, in patients predisposed to open-angle glaucoma; the risk with systemic corticosteroids appears to be less.

In contrast, **angle-closure glaucoma** (closed-angle glaucoma; narrow-angle glaucoma) usually occurs as an acute emergency. Patients present with a painful red eye, sweating, and nausea and vomiting as a result of a rapid rise in intra-ocular pressure. This can result from blockage of the flow of aqueous humour into the anterior chamber. The resulting rise in intra-ocular pressure bows the iris against the trabecular meshwork, restricting outflow and thereby further raising intra-ocular pressure. It usually occurs in patients with hypermetropia who have a shallow anterior chamber and a narrow filtration angle. The use of mydriatics in such patients is generally considered to be contra-indicated on the grounds that dilatation of the pupil could precipitate an acute attack of angle-closure glaucoma, but see Glaucoma, under Tropicamide, p.1886.

ANTIGLAUCOMA DRUGS.

Drugs used in the treatment of glaucoma[1,3-5,13-15] lower intra-ocular pressure by a variety of mechanisms and their effects are often additive. Most are used topically although a few are given by systemic routes.

- ***Beta blockers*** inhibit beta receptors in the ciliary epithelium and thereby reduce the secretion of aqueous humour. They have traditionally been the drugs of first choice for initial and maintenance treatment of open-angle and other chronic glaucomas and of ocular hypertension; other drugs are used with them when further reductions in intra-ocular pressure are required. Advantages over miotics (below) include a lack of effect on pupil size and accommodation; in addition they can be given once or twice daily which may improve compliance. They are also better tolerated than miotics but can produce systemic effects, and their safety, particularly in the elderly, has been questioned.[16,17] Cardioselective beta blockers may cause fewer pulmonary adverse effects, such as bronchoconstriction, than non-selective beta blockers. Studies suggest that individual topical beta blockers are probably equally effective in reducing intra-ocular pressure but if a non-selective beta blocker is used an additional reduction in pressure may not be obtained with adrenaline (see below). However, a meta-analysis has suggested that timolol may be more effective than betaxolol.[18]
- Topical ***prostaglandin analogues*** or ***prostamides***, such as latanoprost, bimatoprost, and travoprost, lower intra-ocular pressure by increasing uveoscleral outflow. They are increasingly a first choice, alone or as adjuncts, in the treatment of ocular hypertension or open-angle glaucoma. A meta-analysis of the effectiveness of common antiglaucoma drugs found bimatoprost, travoprost, and latanoprost to be the most effective in lowering intra-ocular pressure.[18] They are given once daily and appear to be well-tolerated. They do not affect pupil size or accommodation, but may cause a potentially irreversible increase in brown pigmentation of the iris; the long-term significance of this effect is unknown. Unoprostone, which needs to be used twice daily, appears to be less effective than the other prostaglandin analogues.[19]
- ***Parasympathomimetic miotics*** help trabecular drainage by constricting the pupil and pulling open the trabecular meshwork. However, this can cause blurred vision and browache, especially in younger patients, and the small pupil may cause problems if central vision is already limited. Parasympathomimetic miotics also reduce uveoscleral outflow and this can cause a paradoxical increase in intra-ocular pressure in patients with a recessed anterior angle. They should not be used in the presence of inflammation as adhesions may form between the pupil and the lens (posterior synechiae). Topical miotics were once the mainstay of glaucoma treatment but their ocular adverse effects and multiple dosing regimens have limited their use. Pilocarpine is the most frequently used and is indicated in the treatment of open-angle glaucoma and other chronic glaucomas. It is often added to treatment with other drugs when further reductions in intra-ocular pressure are required. Carbachol is sometimes used when resistance or intolerance to pilocarpine develops. Physostigmine is more potent than pilocarpine but is poorly tolerated and is rarely used now; it was used with pilocarpine but rarely alone. Stronger or longer-acting anticholinesterase miotics such as ecothiopate can cause pupillary block and induce angle-closure glaucoma. They are usually only used in patients refractory to other antiglaucoma treatment or in those in whom the lens of the eye has been removed (aphakic patients). Pilocarpine is also used in the emergency treatment of angle-closure glaucoma before surgery or laser therapy.
- ***Carbonic anhydrase inhibitors*** such as acetazolamide reduce production of aqueous humour by a mechanism independent of their diuretic action. They are used as part of the emergency treatment of angle-closure glaucoma to produce a rapid reduction in intra-ocular pressure before surgery or laser therapy. Systemic doses may also be added to treatment in open-angle glaucoma and other chronic glaucomas in patients refractory to standard treatment but many patients are unable to tolerate prolonged therapy. Topical carbonic anhydrase inhibitors, such as dorzolamide or brinzolamide, have a lower potential to produce adverse effects. They are used similarly to other topical drugs either alone or as an adjunct in patients resistant to or intolerant of first-line drugs.
- Topical ***alpha$_2$-adrenoceptor agonists*** such as apraclonidine and brimonidine lower intra-ocular pressure by reducing production of aqueous humour. Apraclonidine is used alone or as an adjunct to other drugs in the control of intra-ocular pressure associated with ocular surgery or in the short-term to delay laser treatment or surgery for patients with glaucoma not adequately controlled with other drugs; tachyphylaxis and ocular irritation limit its long-term use. Brimonidine is used similarly. Clonidine has also been used in some countries.
- Other topical ***sympathomimetics*** such as dipivefrine increase outflow of aqueous humour through the trabecular meshwork and the uveoscleral route and may also reduce its rate of production. They are used in open-angle glaucoma and other chronic glaucomas usually when further reductions in intra-ocular pressure are required in patients receiving beta blockers (but may not produce an additive effect if used with a non-selective beta blocker).[20] As they produce pupillary dilatation they can induce an acute attack if used in angle-closure glaucoma. Adrenaline can cause eye irritation and produce systemic effects; it is now rarely used. Dipivefrine is converted into adrenaline by corneal esterases and ocular adverse effects are usually less than with adrenaline itself although, again, it is rarely used. Guanethidine, an adrenergic neurone blocker, reduces aqueous humour secretion and is used either alone or in combination to enhance and prolong the effect of adrenaline; prolonged use can cause fibrosis and corneal changes.
- ***Osmotic diuretics*** reduce vitreous volume and can produce a marked reduction in intra-ocular pressure. They are used in the short-term management of glaucoma when a rapid reduction in intra-ocular pressure is required before surgery. Mannitol and urea are both given intravenously and have a faster onset than glycerol or isosorbide given orally.
- Several ***other drugs*** are used topically in glaucoma and ocular hypertension. The alpha-adrenergic antagonist dapiprazole is used in some countries.

DIAGNOSIS OF GLAUCOMA.

Open-angle glaucoma is asymptomatic in its early stages and the use of screening methods for detecting early disease is of great importance.[21] Measurement of intra-ocular pressure alone is a poor diagnostic tool and direct examination of the optic nerve together with visual field examination and intra-ocular pressure tonometry is considered to be more reliable.[1,3-5] Provocative tests such as placing the patient prone in a dark room are sometimes used to identify eyes suffering from or at risk of *angle-closure glaucoma*. Short-acting mydriatics have also been used but are not without risk. Long-term follow-up of patients whose treatment had been determined by the use of a provocative test using phenylephrine with pilocarpine has suggested that this test is neither sensitive nor specific.[22]

TREATMENT OF GLAUCOMA.

Open-angle glaucoma is frequently treated first with a topical beta blocker or, increasingly, a prostaglandin analogue. It may be necessary to combine these drugs or add others such as a topical alpha$_2$-adrenoceptor agonist or a

The symbol † denotes a preparation no longer actively marketed

topical carbonic anhydrase inhibitor to control intra-ocular pressure. Miotics are usually reserved for third-line use. It has been suggested that each type of drug should be tried alone first before resorting to combination therapy.

If further reduction of intra-ocular pressure is required a systemic carbonic anhydrase inhibitor may be used but long-term treatment is poorly tolerated. If this is unsuccessful, surgery (trabeculectomy) or laser treatment (trabeculoplasty) is usually indicated. Laser treatment appears to be as effective as topical drug therapy[23] although its effects may be short-lived.[24] It has been suggested that it might be of use in the initial treatment of older patients who cannot use eye drops or when surgery needs to be postponed or is contra-indicated.[1] Some also recommend that laser treatment is tried before a miotic or an oral carbonic anhydrase inhibitor, because of the potential adverse effects associated with these drugs.[5] Early studies in the UK suggested that surgery was superior to drug or laser treatment in reducing intra-ocular pressure and preserving vision;[24] however, a later study[25] showed no difference in the progression of visual field loss in patients with newly diagnosed glaucoma after the initial use of surgery or drug treatment. A recent systematic review has also found that in early mild open-angle glaucoma progression of the disease over 5 years was no different if first treatment was with medication or trabeculectomy but trabeculectomy was associated with more eye discomfort, an increased risk of cataract, and reduction in visual acuity.[26] The early use of surgery was often advocated in Europe, especially in younger patients, although it is now rarely used as the primary form of treatment, even in the UK.[4]

It is essential to start treatment for an *acute attack of angle-closure glaucoma* within 24 to 48 hours. If treatment is delayed adhesions may form between the iris and the cornea (peripheral anterior synechiae) and the trabecular meshwork may be damaged. *Chronic angle-closure glaucoma* may then develop with permanently raised intra-ocular pressure which ultimately leads to total loss of vision (absolute glaucoma). The initial treatment aims to produce a rapid reduction in intra-ocular pressure. A miotic such as pilocarpine is used topically to constrict the pupil while a carbonic anhydrase inhibitor such as acetazolamide is given orally or by intravenous injection. Osmotic diuretics such as mannitol or urea given intravenously or glycerol or isosorbide given orally may also be used. When intra-ocular pressure has been reduced sufficiently, laser therapy or surgery is performed on both eyes to increase drainage of aqueous humour. If further topical treatment is required after surgery, treatment is usually as for open-angle glaucoma. Beta blockers, with or without adrenaline, are preferred to pilocarpine as there is a risk of posterior synechiae forming when pilocarpine is used.

Glaucoma filtering surgery such as trabeculectomy can be highly effective in reducing intra-ocular pressure, but in some groups of patients, such as children, Afro-Caribbeans, or those who have had previous ocular surgery, there is a high failure rate, usually due to formation of scar tissue.[27] The scar formation is associated with proliferation of fibroblasts; subconjunctival injection of antiproliferative drugs such as fluorouracil has been shown to reduce the failure rate of surgery but at a cost of increased epithelial toxicity and conjunctival wound leaks.[27] A study group[28] reporting on the long-term follow-up of patients treated with fluorouracil recommended that fluorouracil should still be used in the surgical management of glaucoma in patients with a history of ocular surgery, but in view of the increased incidence of late-onset conjunctival wound leaks at the dosage they employed, suggested caution in its use in eyes with good prognoses. Single intraoperative doses of mitomycin have been applied topically as an alternative to the regimen of multiple injections required with fluorouracil. Rates of success comparable with those for fluorouracil have been achieved but there is a risk of adverse effects that could affect vision;[29] long-term safety of antiproliferative drugs remains to be determined.

Postoperative ocular hypertension may occur after surgery on the anterior chamber of the eye or procedures such as trabeculoplasty. Acetylcholine or carbachol instilled directly into the anterior chamber of the eye (intracameral instillation) are used intra-operatively to reduce early postoperative rises in intra-ocular pressure in procedures such as cataract extraction. The short action of acetylcholine can be an advantage as prolonged miosis is associated with severe postoperative pain. However, some consider carbachol to be the more effective drug;[30,31] standard antiglaucoma drugs including beta blockers, pilocarpine, apraclonidine, and carbonic anhydrase inhibitors have also been used for prophylaxis of postoperative ocular hypertension.

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7. Higginbotham EJ, *et al.* The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals. *Arch Ophthalmol* 2004; **122:** 813–20.
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31. Hollands RH, *et al.* Control of intraocular pressure after cataract extraction. *Can J Ophthalmol* 1990; **25:** 128–32.

Mydriasis and cycloplegia

Drugs that dilate the pupil (mydriatics) and paralyse accommodation (cycloplegics) are used topically in the examination of the eye and other ophthalmic procedures. They are also used in the management of inflammatory conditions of the eye to treat or prevent the formation of adhesions between the lens and the iris (see Uveitis, p.1515) and in strabismus (below).

Mydriasis requires either paralysis of the pupillary constrictor muscles, which can be achieved with antimuscarinics, or stimulation of the dilator muscles, as produced by sympathomimetics. Cycloplegia results from paralysis of the ciliary muscles (antimuscarinics, but not sympathomimetics, have this effect).

Antimuscarinics used in ophthalmology vary in onset and duration of action. *Atropine* can take up to 40 minutes or more to produce mydriasis, which persists for at least 7 days; it takes 1 to 3 hours to produce cycloplegia and 6 to 12 days for recovery of accommodation. *Hyoscine* has a shorter duration of action than atropine, although the effects may still persist for 3 to 7 days. For ophthalmic procedures, antimuscarinics such as *homatropine*, *cyclopentolate*, or *tropicamide*, with a more rapid onset and shorter duration of action than atropine, may be preferable. Recovery occurs up to 6 hours after tropicamide, and up to 24 hours after cyclopentolate; after homatropine it may take up to 3 days. Cycloplegia with homatropine may be incomplete, and particularly for young children (who are often resistant to the action of homatropine) cyclopentolate or atropine may be preferred.

The most common topical sympathomimetic is *phenylephrine*, but *hydroxyamfetamine* is also used in some countries. They are often used with an antimuscarinic to enhance mydriasis, especially in patients who might respond poorly to antimuscarinics alone, such as those with dark irides or diabetes, or those who are receiving prolonged miotic therapy. *Adrenaline* has been used for maintenance of mydriasis during ophthalmic surgery.

The local anaesthetic *cocaine* also has an independent mydriatic effect but because of concern over corneal toxicity it is now little used in ophthalmology.

Miosis (pupil constriction) resistant to conventional mydriatics often develops during ocular surgery, possibly due to the release of prostaglandins and other substances associated with trauma. *NSAIDs* are prostaglandin synthetase inhibitors and have been tried before ocular surgery to prevent or reduce intra-operative miosis. They do not possess intrinsic mydriatic properties.

Reversal of mydriasis

Topical miotics (mydriolytics) are sometimes used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but do not appear to be in routine clinical use. *Pilocarpine* can counteract the mydriatic effect of topical sympathomimetics, such as phenylephrine and hydroxyamfetamine, but is ineffective against mydriasis produced by antimuscarinics, such as homatropine, and may impair vision further when used with tropicamide. Furthermore, there is also the risk that pilocarpine might precipitate angle-closure glaucoma in susceptible patents. *Dapiprazole* appears to be safer than pilocarpine when used to reverse sympathomimetic-induced mydriasis and is effective to some degree against tropicamide-induced mydriasis. It also appears to enhance recovery of accommodation after the use of cycloplegics.

The rate of reversal of mydriasis is generally slower in patients with dark irides than in those with lighter irides.

Strabismus

Strabismus, sometimes referred to as a squint or cast, is a lack of coordination of the visual axes of the eyes so that the eyes are usually either turned towards (convergent strabismus; esotropia) or away (divergent strabismus; exotropia) from each other. It can arise from a physical defect of the attachment of the extra-ocular muscles to the eye or from paralysis, spasms, or overactivity affecting the extra-ocular muscles of one of the eyes. In young children strabismus or other conditions that prevent a clear image being formed on the retina can result in visual impairment (amblyopia) in the affected eye if not treated.

Treatment for strabismus often consists of eye exercises, and methods to force preferential use of the affected eye by restricting vision through the healthy eye. This is accomplished either by using an eye patch or by penalisation with glasses or the cycloplegic drug *atropine*. However, as prolonged use of atropine eye drops may be required there is a risk of systemic toxicity. Surgery may sometimes be necessary. Extra-ocular injection of *botulinum A toxin* has been used to weaken an overactive extra-ocular eye muscle as an aid to eye realignment; repeated injections may be required. Long-acting parasympathomimetic miotics such as *demecarium*, *dyflos*, and *ecothiopate* have been used in the diagnosis and management of convergent strabismus due to excessive accommodation. Centrally-acting drugs such as *levodopa* and *citicoline* have also been investigated. With any form of treatment care has to be taken not to induce amblyopia in the healthy eye.

References.

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2. Donahue SP. Pediatric strabismus. *N Engl J Med* 2007; **356:** 1040–7.

Aceclidine *(USAN, rINN)*

Aceclidina; Acéclidine; Aceclidinum. 1-Azabicyclo[2.2.2]octan-3-ol acetate; 3-Quinuclidinol acetate; 3-Acetoxyquinuclidine.

Ацеклидин

$C_9H_{15}NO_2$ = 169.2.
CAS — 827-61-2.
ATC — S01EB08.
ATC Vet — QS01EB08.

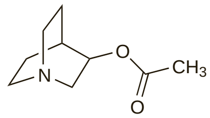

Aceclidine Hydrochloride *(rINNM)*

Acéclidine, Chlorhydrate d'; Aceclidini Hydrochloridum; Hidrocloruro de aceclidina.

Ацеклидина Гидрохлорид

$C_9H_{15}NO_2$,HCl = 205.7.
CAS — 6109-70-2.
ATC — S01EB08.
ATC Vet — QS01EB08.

Profile

Aceclidine hydrochloride is a parasympathomimetic miotic (see Pilocarpine, p.1884) that is a cholinergic agonist. It has been used in eye drops to lower intra-ocular pressure in patients with glaucoma.

Use. Aceclidine has been tried for the management of disturbances of night vision after laser refractive surgery.[1]

1. Randazzo A, *et al.* Pharmacological management of night vision disturbances after refractive surgery: results of a randomized clinical trial. *J Cataract Refract Surg* 2005; **31:** 1764–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Glaucostat†; Glaunorm; ***Ital.:*** Glaunorm; ***Neth.:*** Glaucocare†; ***Port.:*** Glaucostat†.

Multi-ingredient: ***Ital.:*** Glautimol.

Acetazolamide *(BAN, rINN)* ⊗

Acetazolam; Acetazolamid; Acetazolamida; Acetazolamidas; Acétazolamide; Acetazolamidum; Asetatsoliamidi; Asetazolamid. 5-Acetamido-1,3,4-thiadiazole-2-sulphonamide; *N*-(5-Sulphamoyl-1,3,4-thiadiazol-2-yl)acetamide.

Ацетазоламид

$C_4H_6N_4O_3S_2$ = 222.2.
CAS — 59-66-5.
ATC — S01EC01.
ATC Vet — QS01EC01.

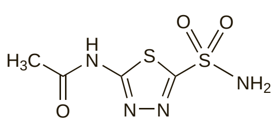

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Acetazolamide). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Acetazolamide). A white to faintly yellowish-white, odourless, crystalline powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol. Store in airtight containers.

Acetazolamide Sodium *(BANM, rINNM)* ⊗

Acetazolamida sódica; Acétazolamide Sodique; Natrii Acetazolamidum; Sodium Acetazolamide.

Натрий Ацетазоламид

$C_4H_5N_4NaO_3S_2$ = 244.2.
CAS — 1424-27-7.
ATC — S01EC01.
ATC Vet — QS01EC01.

Stability. Solutions of acetazolamide sodium in glucose 5% and sodium chloride 0.9% were stable for 5 days at 25° with a loss of potency of less than 7.2%.[1] At 5° the loss of potency in both solutions was less than 6% after 44 days of storage. Small reductions in pH were recorded, possibly due to the formation of acetic acid during the decomposition of acetazolamide. At –10° the loss in potency after 44 days of storage was less than 3% in both solutions. Results were similar in samples thawed in tap water and in a microwave oven.

An oral suspension of acetazolamide 25 mg/mL prepared from tablets with the aid of sorbitol solution 70% was stable for at least 79 days at 5°, 22°, and 30°. It was recommended that the formulation be maintained at pH 4 to 5 and stored in amber glass bottles.[2]

1. Parasrampuria J, *et al.* Stability of acetazolamide sodium in 5% dextrose or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1987; **44:** 358–60.
2. Alexander KS, *et al.* Stability of acetazolamide in suspension compounded from tablets. *Am J Hosp Pharm* 1991; **48:** 1241–4.

Adverse Effects

Common adverse effects of acetazolamide are malaise, fatigue, depression, excitement, headache, weight loss, and gastrointestinal disturbances. Drowsiness and paraesthesia involving numbness and tingling of the face and extremities are also common with high doses in particular. Diuresis can be troublesome, but generally abates after a few days of continuous therapy. Acidosis may develop during treatment and is generally mild but severe metabolic acidosis has occasionally been reported, especially in elderly or diabetic patients or those with renal impairment. Electrolyte imbalances including hyponatraemia and hypokalaemia may occasionally occur; hypokalaemia is generally transient and rarely clinically significant.

Blood dyscrasias occur rarely and may include aplastic anaemia, agranulocytosis, leucopenia, thrombocytopenia, and thrombocytopenic purpura. Acetazolamide can give rise to crystalluria, renal calculi, and renal colic; renal lesions, possibly due to a hypersensitivity reaction, have also been reported.

Other adverse reactions include allergic skin reactions, fever, thirst, dizziness, ataxia, irritability, confusion, reduced libido, haematuria, glycosuria, renal failure, abnormal liver function tests, loss of appetite, alterations in taste, transient myopia, and tinnitus and hearing disturbances. Rare reactions include photosensitivity, hepatitis or cholestatic jaundice, flaccid paralysis, and convulsions.

Intramuscular injections are painful owing to the alkalinity of the solution.

Effects on the blood. Severe, often fatal, blood dyscrasias have been reported in patients taking acetazolamide. By 1989, the National Registry of Drug-Induced Ocular Side Effects in the USA[1] had received reports of haematological reactions possibly due to carbonic anhydrase inhibitors in 139 patients, of which 50 cases (36%) were fatal. Most deaths were due to aplastic anaemia. Over half the reactions occurred during the first 6 months of therapy. The value of periodic blood analysis in patients taking carbonic anhydrase inhibitors for prolonged periods has been debated[2-7] but is advised by licensed product information. The US National Registry has recommended[8] that initial and 6-monthly blood analysis should be undertaken.

1. Fraunfelder FT, Bagby GC. Possible hematologic reactions associated with carbonic anhydrase inhibitors. *JAMA* 1989; **261:** 2257.
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5. Lichter PR. Carbonic anhydrase inhibitors, blood dyscrasias, and standard-of-care. *Ophthalmology* 1988; **95:** 711–12.
6. Mogk LG, Cyrlin MN. Blood dyscrasias and carbonic anhydrase inhibitors. *Ophthalmology* 1988; **95:** 768–71.
7. Miller RD. Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 745–6.
8. Fraunfelder FT, *et al.* Hematologic reactions to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1985; **100:** 79–81.

Effects on electrolyte balance. Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly, in diabetic patients, and in those with renal impairment.[1-6] Raised plasma-acetazolamide concentrations have been reported in elderly patients, probably attributable to reduced renal function, and in 6 of 9 glaucoma patients this was associated with hyperchloraemic metabolic acidosis.[7] A single-dose study[8] in 4 elderly patients found that reduced acetazolamide clearance correlated with renal function. Urea and electrolyte concentrations should be measured before and during treatment with acetazolamide, particularly in the elderly and in other patients, such as diabetics, who may have renal impairment.

1. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *BMJ* 1981; **283:** 1527–8.
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7. Chapron DJ, *et al.* Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.
8. Chapron DJ, *et al.* Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.

Effects on endocrine function. Hirsutism occurred in a 2½-year-old girl after treatment for 16 months with acetazolamide for congenital glaucoma.[1] There was no evidence of virilisation.

1. Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; **78:** 327–8.

Effects on the kidneys. Large reductions in glomerular filtration rate occurred during treatment with carbonic anhydrase inhibitors in 3 type 1 diabetics with nephropathy and glaucoma.[1] Kidney function improved when the drug was withdrawn.

1. Skøtt P, *et al.* Effect of carbonic anhydrase inhibitors on glomerular filtration rate in diabetic nephropathy. *BMJ* 1987; **294:** 549.

Effects on the liver. For a report of liver damage associated with use of acetazolamide, see Hypersensitivity, below.

Effects on the skin. Rashes, including severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported during acetazolamide therapy; the fact that acetazolamide is a sulfonamide-derivative has been suggested as a cause for these reactions. Photosensitivity has also been noted rarely.

Severe exacerbation of rosacea occurred in a patient taking acetazolamide for glaucoma; the rosacea improved on withdrawal of acetazolamide and relapsed again on its reintroduction.[1]

1. Shah P, *et al.* Severe exacerbation of rosacea by oral acetazolamide. *Br J Dermatol* 1993; **129:** 647–8.

Extravasation. Extravasation was reported in a patient after intravenous acetazolamide and led to severe ulceration requiring surgery to repair the skin defect.[1] It was recommended that 1 to 2 mL of sodium citrate 3.8% should be injected subcutaneously near the site of extravasation in order to neutralise the alkaline effects of the acetazolamide injection.

1. Callear A, Kirkby G. Extravasation of acetazolamide. *Br J Ophthalmol* 1994; **78:** 731.

Hypersensitivity. A 54-year-old man with glaucoma who was treated with acetazolamide 500 mg daily for 26 days developed a generalised erythematous rash and became delirious, dehydrated, markedly jaundiced, with peripheral circulatory failure, and died from cholestatic jaundice with hepatic coma and anuria.[1] Drug-induced hypersensitivity and hepatitis due to acetazolamide was suspected.

Anaphylaxis has also been reported[2] after a single oral dose in a patient who had not previously received acetazolamide. However, the patient was hypersensitive to sulfonamides and the reaction may have been caused by cross-sensitivity.

1. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol* 1967; **51:** 348–9.
2. Tzanakis N, *et al.* Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol* 1998; **82:** 588.

Precautions

Acetazolamide is contra-indicated in the presence of sodium or potassium depletion, in hyperchloraemic acidosis, in conditions such as Addison's disease and adrenocortical insufficiency, and in marked hepatic or renal impairment. Encephalopathy may be precipitated in patients with hepatic dysfunction. It should not be used in chronic angle-closure glaucoma since it may mask deterioration of the condition. Since acetazolamide is a sulfonamide derivative, it should not be used in patients with a history of sulfonamide hypersensitivity.

Acetazolamide should be given with care to patients likely to develop acidosis or with diabetes mellitus; severe metabolic acidosis may occur in the elderly, and in patients with renal impairment, pulmonary obstruction, or emphysema. Acetazolamide may increase the risk of hyperglycaemia in diabetic patients.

Periodic monitoring of plasma electrolytes and blood count is recommended during long-term therapy and patients should be cautioned to report any unusual skin rashes. Acetazolamide is teratogenic in *animals*.

Some adverse effects such as drowsiness and myopia may affect a patient's ability to perform skilled tasks including driving.

Breast feeding. Acetazolamide has been detected in breast milk.[1] However, there have been no reports of adverse effects in breast-fed infants whose mothers were receiving acetazolamide and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Söderman P, *et al*. Acetazolamide excretion into human breast milk. *Br J Clin Pharmacol* 1984; **17:** 599–600.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 17/03/06)

Diabetes mellitus. For a brief discussion of metabolic acidosis in patients with diabetes, see Effects on Electrolyte Balance, above.

For a report of deterioration in renal function in patients with diabetic nephropathy who were given carbonic anhydrase inhibitors, see Effects on the Kidneys, above.

The elderly. A retrospective review[1] of 222 patients with glaucoma indicated that those aged 40 years or less tolerated treatment with carbonic anhydrase inhibitors much better than older patients. A single-dose study[2] of acetazolamide in 4 elderly subjects indicated that the capacity to clear acetazolamide from plasma correlated with creatinine clearance and was thus reduced in the elderly. They also had reduced plasma protein binding and the combination of these factors predisposed the elderly to enhanced accumulation of acetazolamide in erythrocytes.

Plasma-acetazolamide concentrations exceeded the **therapeutic range** (5 to 10 micrograms/mL) in 9 of 12 elderly patients receiving acetazolamide for glaucoma or metabolic alkalosis.[3] Hyperchloraemic metabolic acidosis was detected in 6 of 9 glaucoma patients. The excessive plasma concentrations were attributed to age-related reductions in renal function. It was suggested that elderly patients may require reduced doses of acetazolamide.

For reports of symptomatic metabolic acidosis associated with use of acetazolamide in the elderly, see Effects on Electrolyte Balance, above.

1. Shrader CE, *et al*. Relationship of patient age and tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol* 1983; **96:** 730–3.
2. Chapron DJ, *et al*. Influence of advanced age on the disposition of acetazolamide. *Br J Clin Pharmacol* 1985; **19:** 363–71.
3. Chapron DJ, *et al*. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989; **29:** 348–53.

Interference with laboratory estimations. Acetazolamide interfered with an HPLC method of assay for theophylline[1] resulting in an unnecessary dose reduction and worsening apnoea in an infant. Other workers[2] pointed out that the interference depended on the solvent used in the extraction, and presented evidence to suggest that acetazolamide may not interfere with other assay methods for theophylline.

1. Mecrow IK, Goldie BP. Acetazolamide interferes with theophylline assay. *Lancet* 1987; **i:** 558.
2. Kelsey HC, *et al*. Interference by acetazolamide in theophylline assay depends on the method. *Lancet* 1987; **ii:** 403.

Renal impairment. For a brief discussion of metabolic acidosis in patients with renal impairment, see Effects on Electrolyte Balance, above.

Interactions

By rendering the urine alkaline acetazolamide reduces the urinary excretion, and so may enhance the effects, of drugs such as amfetamines, ephedrine, and quinidine; conversely, urinary alkalinisation can reduce the effects of methenamine and its compounds. Acetazolamide may enhance antiepileptic-induced osteomalacia. Use of acetazolamide with aspirin may result in severe acidosis and increase CNS toxicity. Acetazolamide may affect fluid and electrolyte balance leading to interactions similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Unlike thiazides, however, acetazolamide may increase the excretion of lithium.

Antacids. *Sodium bicarbonate* therapy enhances the risk of renal calculus formation in patients taking acetazolamide.[1]

1. Rubenstein MA, Bucy JG. Acetazolamide-induced renal calculi. *J Urol (Baltimore)* 1975; **114:** 610–12.

Antiepileptics. For severe osteomalacia in patients taking acetazolamide with *phenytoin* and other antiepileptics, see Diuretics, p.499. Acetazolamide may increase serum concentrations of *carbamazepine*, see Diuretics, p.475.

Antineoplastics. Alkalinisation of the urine by acetazolamide increases the solubility of *methotrexate* in the urine and also increases its excretion. This effect has been exploited therapeutically to reduce the nephrotoxicity of methotrexate (see Effects on the Kidneys, p.746).

Benzodiazepines. Ventilatory depression in a mountain climber with acute mountain sickness was considered to be due to the potentiation of *triazolam* by acetazolamide.[1]

1. Masuyama S, *et al*. 'Ondine's Curse': side effect of acetazolamide? *Am J Med* 1989; **86:** 637.

Local anaesthetics. For the effect of acetazolamide on *procaine*, see p.1869.

Salicylates. Salicylates displace acetazolamide from plasma protein binding sites and reduce its renal clearance,[1] leading to elevated plasma-acetazolamide concentrations. In addition acidosis produced by acetazolamide may increase salicylate toxicity by enhancing salicylate tissue penetration.[2] Severe metabolic acidosis has been reported[3] in patients with normal renal function given acetazolamide with salicylates.

Use of salicylates with acetazolamide should be avoided if possible, particularly if renal dysfunction is present. If the combination is used, patients should be carefully monitored for symptoms of CNS toxicity such as lethargy, confusion, somnolence, tinnitus, and anorexia.

1. Sweeney KR, *et al*. Toxic interaction between acetazolamide and salicylate: case report and a pharmacokinetic explanation. *Clin Pharmacol Ther* 1986; **40:** 518–24.
2. Anderson CJ, *et al*. Toxicity of combined therapy with carbonic anhydrase inhibitors and aspirin. *Am J Ophthalmol* 1978; **86:** 516–19.
3. Cowan RA, *et al*. Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. *BMJ* 1984; **289:** 347–8.

Pharmacokinetics

Acetazolamide is fairly rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 2 hours after oral doses. It has been estimated to have a plasma half-life of about 3 to 6 hours. It is tightly bound to carbonic anhydrase and high concentrations are present in tissues containing this enzyme, particularly red blood cells and the renal cortex; it is highly bound to plasma proteins. It is excreted unchanged in the urine and has been detected in breast milk.

◊ References.

1. Lehmann B, *et al*. The pharmacokinetics of acetazolamide in relation to its use in the treatment of glaucoma and to its effects as an inhibitor of carbonic anhydrases. *Adv Biosci* 1969; **5:** 197–217.

Uses and Administration

Acetazolamide is an inhibitor of carbonic anhydrase with weak diuretic activity and is used mainly in the management of glaucoma. Other indications include epilepsy and high-altitude disorders.

By inhibiting carbonic anhydrase in the eye acetazolamide decreases the formation of aqueous humour and so decreases intra-ocular pressure. It is used in the preoperative management of angle-closure **glaucoma**, or as an adjunct in the treatment of open-angle glaucoma. In the treatment of glaucoma the usual oral dose is 250 to 1000 mg daily; divided doses should be used for amounts greater than 250 mg daily. Modified-release preparations are also available. Although not licensed for children in the UK, the *BNFC* suggests that those aged 1 month to 12 years may be given acetazolamide in oral doses of 10 to 20 mg/kg daily, to a maximum of 750 mg daily, in 2 to 4 divided doses.

Acetazolamide is also used, either alone or with other antiepileptics, for the treatment of various forms of **epilepsy** in oral doses of 250 to 1000 mg daily in divided doses. Licensed product information in the UK suggests an oral dose for children of 8 to 30 mg/kg daily. The *BNFC* recommends an initial oral dose of 2.5 mg/kg 2 or 3 times daily in neonates and children up to 12 years of age; this may then be increased to a maintenance dose of 5 to 7 mg/kg 2 or 3 times daily. The total daily dose for children should not exceed 750 mg.

When oral dosing is impracticable, acetazolamide may be given parenterally as the sodium salt; acetazolamide sodium 275 mg is equivalent to about 250 mg of acetazolamide. It may be given by intramuscular injection but the intravenous route is preferred due to the alkalinity of the solution. Doses are similar to those given orally.

Acetazolamide is also used to prevent or ameliorate the symptoms of **high-altitude disorders**. Prompt descent will still be necessary if severe symptoms such as cerebral oedema or pulmonary oedema occur. The usual oral dose is 500 to 1000 mg daily in divided doses. It may also be given as a modified-release preparation.

Acetazolamide also increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, by inhibiting the reaction catalysed by carbonic anhydrase in the renal tubules, and so promotes an alkaline diuresis. When given orally as an immediate-release preparation, its effect begins within 60 to 90 minutes and lasts for 8 to 12 hours. However, continuous use is associated with metabolic acidosis and an accompanying loss of diuretic activity. Therefore, although acetazolamide has been used as a diuretic, it has largely been superseded by drugs such as the thiazides or furosemide. For **diuresis** the usual oral dose is 250 to 375 mg and is given either once daily or on alternate days; intermittent therapy is required for a continued effect.

Administration in the elderly. For the suggestion that reduced doses may be required in elderly patients see under Precautions, above.

Epilepsy. Acetazolamide may be used in the treatment of epilepsy (p.465) as an alternative or adjunct to first-line drugs for refractory partial seizures with or without secondary generalisation. It is also effective in a number of other refractory forms of epilepsy including atypical absence, tonic, atonic, myoclonic, and menstruation-related seizures (catamenial epilepsy).[1-5] It is believed to act by inhibition of carbonic anhydrase in glial cells in the CNS.[6] The major drawback to the chronic use of acetazolamide is the rapid development of tolerance,[6] but this may be delayed or prevented by using it as an adjunct to other antiepileptics. Acetazolamide has been successfully used in management of seizures in children from 1 year of age.[5]

1. Resor SR, Resor LD. Chronic acetazolamide monotherapy in the treatment of juvenile myoclonic epilepsy. *Neurology* 1990; **40:** 1677–81.
2. Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. *Ann Pharmacother* 1996; **30:** 514–19.
3. Hoddevik GH. Acetazolamid—verdt en renessanse i epilepsibehandlingen? *Tidsskr Nor Laegeforen* 2000; **120:** 1042–5.
4. Lim LL, *et al*. Acetazolamide in women with catamenial epilepsy. *Epilepsia* 2001; **42:** 746–9.
5. Katayama F, *et al*. Long-term effectiveness and side effects of acetazolamide as an adjunct to other anticonvulsants in the treatment of refractory epilepsies. *Brain Dev* 2002; **24:** 150–4.
6. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. *Pharmacol Rev* 1990; **42:** 223–86.

Glaucoma. Acetazolamide may be given orally or parenterally in the acute management of angle-closure glaucoma (p.1873) and to minimise rises in intra-ocular pressure associated with ocular surgery.[1,2] It may also be given orally in the long-term management of primary and secondary open-angle glaucoma but is usually used as a second-line drug and added to topical beta blockers. However, up to 50% of patients are unable to tolerate oral therapy because of adverse effects[3] although topical carbonic anhydrase inhibitors such as dorzolamide may be better tolerated. Attempts have been made to reduce the adverse effects of acetazolamide by modifying the dosage schedule. A single-dose study[4] showed that doses of acetazolamide greater than 63 mg produced no greater reductions in intra-ocular pressure in patients with ocular hypertension. Another study[5] reported that acetazolamide 250-mg tablets twice daily controlled intra-ocular pressure adequately while producing fewer adverse effects than 250 mg four times daily and it was suggested that there was no advantage in using the modified-release capsule formulation (500 mg twice daily). A study in patients with open-angle glaucoma[6] found that most patients were adequately controlled by a single night-time dose of acetazolamide 500 mg either as tablets or modified-release capsules. The night-time dose also reduced the severity of adverse effects compared with the same dose given in the morning, and could aid compliance.

1. Ladas ID, *et al*. Prophylactic use of acetazolamide to prevent intraocular pressure elevation following Nd-YAG laser posterior capsulotomy. *Br J Ophthalmol* 1993; **77:** 136–8.
2. Edmunds B, Canning CR. The effect of prophylactic acetazolamide in patients undergoing extensive retinal detachment repair. *Eye* 1996; **10:** 328–30.
3. Hurvitz LM, *et al*. New developments in the drug treatment of glaucoma. *Drugs* 1991; **41:** 514–32.
4. Friedland BR, *et al*. Short-term dose response characteristics of acetazolamide in man. *Arch Ophthalmol* 1977; **95:** 1809–12.
5. Ledger-Scott M, Hurst J. Comparison of the bioavailability of two acetazolamide formulations. *Pharm J* 1985; **235:** 451.
6. Joyce PW, Mills KB. Comparison of the effect of acetazolamide tablets and sustets on diurnal intraocular pressure in patients with chronic simple glaucoma. *Br J Ophthalmol* 1990; **74:** 413–16.

High-altitude disorders. Acetazolamide is the most frequently used drug for the prophylaxis of high-altitude disorders (p.1168). It accelerates the process of acclimatisation, thus reducing the incidence of acute mountain sickness and associated symptoms such as headache, nausea, vomiting, and lethargy. The optimum dose is not clear. A systematic review[1] concluded that 750 mg daily effectively prevented acute mountain sickness, but that a dose of 500 mg daily was not effective. However, these conclusions have been criticised, and a subsequent controlled study[2] found that a dose of 125 mg twice daily reduced the incidence of acute mountain sickness by about 50%. Acetazolamide may also have some benefit in relieving symptoms once they have developed although experience is limited. It does not prevent or protect against pulmonary or cerebral oedema.

1. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321:** 267–72.
2. Basnyat B, *et al.* Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 2003; **4:** 45–52.

Macular oedema. For mention of the use of acetazolamide to treat macular oedema associated with uveitis, see Uveitis, p.1515.

Ménière's disease. In Ménière's disease (p.564) high concentrations of carbonic anhydrase are found in the labyrinth, and acetazolamide, a carbonic anhydrase inhibitor, has been tried for both diagnosis and treatment.[1] A dose of 500 mg by intravenous injection has been suggested for diagnosis of fluctuating Ménière's disease.[1] Oral treatment with the drug, however, has not been particularly effective and has been associated with a high incidence of adverse effects.[2]

1. Brookes GB. Ménière's disease: a practical approach to management. *Drugs* 1983; **25:** 77–89.
2. Brookes GB, Booth JB. Oral acetazolamide in Ménière's disease. *J Laryngol Otol* 1984; **98:** 1087–95.

Neuromuscular disorders. Acetazolamide may be of benefit in some neuromuscular disorders, including hypokalaemic periodic paralysis (p.1670). Doses of 375 to 500 mg daily were effective in 2 patients with severe paralysis and were well tolerated.[1] Preliminary observations in 5 other patients showed a striking improvement in 3. In a further 12 patients,[2] doses of 125 mg were given three times daily to children and 250 mg two to six times daily to adults. There was dramatic improvement in 10 of the 12 and this lasted for up to 43 months. Chronic weakness between attacks in 10 patients was improved in 8.

Acetazolamide may reduce the frequency of attacks in patients with hyperkalaemic periodic paralysis (p.1669). It has also been used in episodic ataxia.[3]

1. Resnick JS, *et al.* Acetazolamide prophylaxis in hypokalemic periodic paralysis. *N Engl J Med* 1968; **278:** 582–6.
2. Griggs RC, *et al.* Acetazolamide treatment of hypokalemic periodic paralysis: prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970; **73:** 39–48.
3. Melberg A, *et al.* Loss of control after a cup of coffee. *Lancet* 1997; **350:** 1220.

Raised intracranial pressure. Acetazolamide has been used to reduce raised intracranial pressure (p.1181). It has a role in the management of idiopathic intracranial hypertension. It has also been tried in the treatment of immunocompromised patients with chronically raised intracranial pressure due to cryptococcal meningitis,[1] although a controlled trial[2] was terminated early due to serious adverse events possibly due to additive toxicity with amphotericin. However, acetazolamide was used successfully for long-term treatment in 2 immunocompetent patients[3] with raised intracranial pressure following fungal meningitis.

The *BNFC* suggests an initial dose of 8 mg/kg of acetazolamide 3 times daily for the treatment of raised intracranial pressure in children aged 1 month to 12 years; the dose may be increased to a maximum of 100 mg/kg daily as necessary. Acetazolamide may be given orally or by slow intravenous injection.

1. Johnston SRD, *et al.* Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect* 1992; **24:** 185–9.
2. Newton PN, *et al.* A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis* 2002; **35:** 769–72.
3. Patel S, *et al.* Acetazolamide therapy and intracranial pressure. *Clin Infect Dis* 2002; **36:** 538.

Preparations

BP 2008: Acetazolamide Tablets;
USP 31: Acetazolamide for Injection; Acetazolamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diamox; ***Austral.:*** Diamox; ***Austria:*** Diamox; ***Belg.:*** Diamox; ***Braz.:*** Diamox; Zolamox; ***Canad.:*** Diamox; ***Cz.:*** Diluran; ***Denm.:*** Diamox†; ***Fin.:*** Diamox; Odemin; ***Fr.:*** Defiltran; Diamox; ***Ger.:*** Diamox; Diuramid; Glaupax; ***Gr.:*** Diamox; ***Hong Kong:*** Diamox; ***Hung.:*** Huma-Zolamide; ***India:*** Diamox; ***Indon.:*** Diamox; ***Irl.:*** Diamox; ***Israel:*** Diamox†; Uramox; ***Ital.:*** Diamox; ***Mex.:*** Aceta-Diazol; Akezol; Diamox†; ***Neth.:*** Diamox; Glaupax†; ***Norw.:*** Diamox; ***NZ:*** Diamox; ***Philipp.:*** Cetamid; Diamox; ***Pol.:*** Diuramid; ***Port.:*** Carbinib; ***Rus.:*** Diacarb (Диакарб); ***S.Afr.:*** Azomid; Diamox; ***Spain:*** Edemox; ***Swed.:*** Diamox†; ***Switz.:*** Diamox; Glaupax; ***Thai.:*** Diamox; ***Turk.:*** Diazomid; ***UK:*** Diamox; ***USA:*** Dazamide†; Diamox; ***Venez.:*** Diamox†.

Acetylcholine Chloride *(BAN, rINN)*

Aceticholino chloridas; Acetilkolin-klorid; Acetylcholin chlorid; Acétylcholine, chlorure d'; Acetylcholini chloridum; Acetylkolinklorid; Acetylocholiny chlorek; Asetilkolin Klorür; Asetyylikoliinikloridi; Cloruro de acetilcolina. (2-Acetoxyethyl)trimethylammonium chloride.

Ацетилхолина Хлорид

$C_7H_{16}ClNO_2$ = 181.7.

CAS — 51-84-3 (acetylcholine); 60-31-1 (acetylcholine chloride).

ATC — S01EB09.

ATC Vet — QS01EB09.

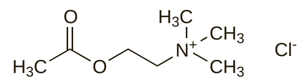

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Jpn includes Acetylcholine Chloride for Injection.

Ph. Eur. 6.2 (Acetylcholine Chloride). A very hygroscopic, white or almost white crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 31 (Acetylcholine Chloride). White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. It is decomposed by hot water and by alkalis. Store in airtight containers.

Adverse Effects

Because it is rapidly hydrolysed in the body by cholinesterases the toxicity of acetylcholine is normally relatively low.

Systemic adverse effects of the choline esters include nausea and vomiting, abdominal pain, flushing, sweating, salivation, lachrymation, rhinorrhoea, eructation, diarrhoea, urinary frequency, headache, bradycardia, peripheral vasodilatation leading to hypotension, and bronchoconstriction.

Ocular adverse effects after local application of choline esters to the eye include corneal oedema, clouding, and decompensation, persistent bullous keratopathy, retinal detachment, and postoperative iritis.

Treatment of Adverse Effects

Atropine sulfate may be given intravenously, intramuscularly, or subcutaneously to control the muscarinic and most nicotinic effects of the choline esters. Supportive treatment may be required.

Precautions

Choline esters are generally contra-indicated for *systemic use* in intestinal or urinary obstruction or where increased muscular activity of the urinary or gastrointestinal tract is liable to be harmful. They are also contra-indicated in asthma and obstructive airways disease, in cardiovascular disorders including bradycardia or heart block and recent myocardial infarction, and in hypotension, vagotonia, epilepsy, parkinsonism, hyperthyroidism, peptic ulceration, and pregnancy. Choline esters should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse effects are liable to occur, calling for emergency treatment with atropine.

Although acetylcholine is normally rapidly hydrolysed in the body, systemic effects have followed *topical application* of choline esters to the eye, albeit rarely, and caution is advisable in the above conditions.

Interactions

As for Neostigmine, p.632. Acetylcholine is hydrolysed in the body by cholinesterase and its effects are markedly prolonged and enhanced if given after anticholinesterases.

Beta blockers. Severe bronchospasm with subsequent pulmonary oedema was reported[1] after intra-ocular injection of acetylcholine chloride in a patient also receiving *metoprolol* by mouth.

1. Rasch D, *et al.* Bronchospasm following intraocular injection of acetylcholine in a patient taking metoprolol. *Anesthesiology* 1983; **59:** 583–5.

NSAIDs. According to licensed product information for acetylcholine chloride ophthalmic preparations, there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Uses and Administration

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body (see below). It is used as a miotic to reduce postoperative rises in intra-ocular pressure associated with cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery (see p.1873) but is ineffective when applied topically as it is hydrolysed more rapidly than it can penetrate the cornea. Doses of 0.5 to 2 mL of a freshly prepared 1% solution of acetylcholine chloride are therefore instilled directly into the anterior chamber of the eye (intracameral instillation). Miosis occurs within seconds and lasts for about 20 minutes. A second application may be made if prolonged miosis is required.

Action. Acetylcholine is a powerful quaternary ammonium parasympathomimetic but its action is transient as it is rapidly destroyed by cholinesterase. It is released from postganglionic parasympathetic nerves and also from some postganglionic sympathetic nerves to produce peripheral actions which correspond to those of muscarine. It is accordingly a vasodilator and cardiac depressant, a stimulant of the vagus and the parasympathetic nervous system, and it has a tonic action on smooth muscle. It also increases lachrymal, salivary, and other secretions. All the muscarinic actions of acetylcholine are abolished by atropine.

Acetylcholine also has actions that correspond to those of nicotine and is accordingly a stimulant of skeletal muscle, the autonomic ganglia, and the adrenal medulla. The nicotinic actions of acetylcholine on skeletal muscle are blocked by competitive neuromuscular blockers; they are also inhibited by massive doses or discharge of acetylcholine itself, which has clinical application in relation to the mode of action of suxamethonium (p.1912).

Drugs that mimic or enhance the actions of acetylcholine in the body are known as **parasympathomimetics** and may be classified into 2 distinct pharmacological groups:

- **cholinergic agonists**, such as bethanechol, carbachol, methacholine, and pilocarpine which act directly on effector cells to mimic the effects of acetylcholine. They are sometimes referred to as cholinomimetics or true parasympathomimetics; some such as bethanechol, carbachol, and methacholine are choline esters
- **anticholinesterases** (cholinesterase inhibitors) which inhibit the enzymic hydrolysis of acetylcholine by acetylcholinesterase and other cholinesterases, thereby prolonging and enhancing its actions in the body. They may be classified by the length of time taken to restore active enzyme following binding of enzyme to drug. The 'reversible' anticholinesterases such as ambenonium, neostigmine, physostigmine, and pyridostigmine generally produce enzyme inhibition for a few hours, whereas 'irreversible' anticholinesterases such as dyflos and ecothiopate produce extremely prolonged inhibition, and return of cholinesterase activity depends on synthesis of new enzyme. Centrally acting reversible anticholinesterases include donepezil, galantamine, rivastigmine, and tacrine

Drugs such as fampridine and guanidine, which enhance the release of acetylcholine from nerve terminals, also have similar effects.

Diagnosis and testing. *AUTONOMIC FAILURE.* Acetylcholine has been used in a sweat-spot test for autonomic neuropathy in diabetic patients.[1] An area on the dorsum of the foot is painted with iodine and starch, followed by intradermal injection of acetylcholine into the centre of the area. Sweat produced in response to acetylcholine reacts with the iodine and starch to produce fine black dots corresponding to the pores of the sweat glands; a normal response is indicated by a uniform distribution of dark spots whereas in diabetic autonomic neuropathy this pattern is lost to a varying degree. A similar test has been carried out[2] to assess sympathetic nerve function and therefore predict the success of lumbar sympathectomy in patients with critical limb ischaemia.

1. Ryder REJ, *et al.* Acetylcholine sweatspot test for autonomic denervation. *Lancet* 1988; **i:** 1303–5.
2. Altomare DF. Acetylcholine sweat test: an effective way to select patients for lumbar sympathectomy. *Lancet* 1994; **344:** 976–8.

Preparations

USP 31: Acetylcholine Chloride for Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Miochol; ***Belg.:*** Miochole; ***Canad.:*** Miochol-E; Miochol†; ***Chile:*** Miochol-E†; ***Fin.:*** Miochol-E; ***Fr.:*** Miochole; ***Ger.:*** Miochol-E; ***Gr.:*** Miochol-E; ***Hong Kong:*** Miochol-E; ***Indon.:*** Miochol-E; ***Irl.:*** Miochol; ***Israel:*** Miochol; Miochol-E; ***Ital.:*** Miochol-E; Miovisin; ***Mex.:*** Iloc; ***Neth.:*** Miochol; ***NZ:*** Miochol; ***Port.:*** Miochol; ***S.Afr.:*** Covochol; Miochol; ***Singapore:*** Miochol-E†; ***Swed.:*** Miochol-E; ***Switz.:*** Miochol; ***Thai.:*** Miochol†; ***Turk.:*** Miochol-E; ***UK:*** Miochol; ***USA:*** Miochol.

Apraclonidine Hydrochloride

(BANM, USAN, rINNM)

AL-02145 (apraclonidine); *p*-Aminoclonidine Hydrochloride; Aplonidine Hydrochloride; Apraclonidine, chlorhydrate d'; Apraclonidini hydrochloridum; Hidrocloruro de apraclonidina; NC-14. 2-[(4-Amino-2,6-dichlorophenyl)imino]imidazolidine hydrochloride; 2,6-Dichloro-N^1-imidazolidin-2-ylidene-*p*-phenylenediamine hydrochloride.

Апраклонидина Гидрохлорид

$C_9H_{10}Cl_2N_4,HCl$ = 281.6.

CAS — 66711-21-5 (apraclonidine); 73218-79-8 (apraclonidine hydrochloride).

ATC — S01EA03.

ATC Vet — QS01EA03.

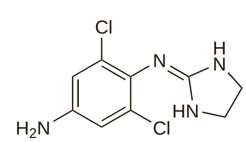

(apraclonidine)

NOTE. APR is a code approved by the BP 2008 for use on single unit doses of eye drops containing apraclonidine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *US.*

USP 31 (Apraclonidine Hydrochloride). A white to off-white, odourless to practically odourless powder. Soluble 1 in 34 of water, 1 in 74 of alcohol, and 1 in 13 of methyl alcohol; insoluble in chloroform, in ethyl acetate, and in hexanes. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse effects after perioperative instillation of apraclonidine into the eye include hyperaemia, lid retraction, and mydriasis. Some patients may develop an exaggerated reduction in intra-ocular pressure. On regular instillation an ocular intolerance reaction may occur, characterised by hyperaemia, ocular pruritus, increased lachrymation, ocular discomfort, and oedema of the lids and conjunctiva; treatment should be stopped if these symptoms occur. Other adverse effects reported include dry mouth and nose, conjunctivitis, conjunctival blanching, blurred vision, asthenia, headache, and taste disturbances.

Systemic absorption can occur after application to the eye and may result in adverse effects similar to those of clonidine (p.1247). Cardiovascular effects have been reported; therefore apraclonidine should be used with caution in patients with severe cardiovascular disease, including hypertension, and in patients with a history of vasovagal attacks. Drowsiness may also occur. Depression has rarely been associated with use of apraclonidine and it should be used with caution in depressed patients.

Interactions

Systemic absorption may occur after topical application of apraclonidine to the eye and there is a theoretical possibility of interactions similar to those reported with clonidine (p.1248). Since the effects of apraclonidine on circulating catecholamines are unknown, licensed product information recommends that MAOIs should not be given with apraclonidine; tricyclic and related antidepressants and systemic sympathomimetics should also be avoided or used with caution.

Uses and Administration

Apraclonidine is an alpha$_2$-adrenoceptor agonist derived from clonidine (p.1247). It reduces intra-ocular pressure when instilled into the eye and is used in patients undergoing eye surgery, and as an adjunct in the management of glaucoma (p.1873). The reduction in intra-ocular pressure begins within an hour of instillation and is maximal after about 3 to 5 hours.

Apraclonidine is used as the hydrochloride, but the strength of an ophthalmic solution is usually expressed in terms of the base. Apraclonidine hydrochloride 11.5 mg is equivalent to about 10 mg of apraclonidine.

To control or prevent a postoperative increase in intra-ocular pressure in patients undergoing anterior segment laser surgery, a 1% solution is instilled into the eye one hour before surgery and again immediately upon completion of surgery.

For short-term adjunctive therapy in patients with raised intra-ocular pressure not controlled by conventional therapy, a 0.5% solution may be instilled three times daily.

There is a loss of effect over time (tachyphylaxis) with apraclonidine and the benefit in most patients lasts for less than a month.

Preparations

USP 31: Apraclonidine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Iopidine†; ***Austral.:*** Iopidine; ***Austria:*** Iopidine; ***Belg.:*** Iopidine; ***Braz.:*** Iopidine†; ***Canad.:*** Iopidine; ***Chile:*** Iopidine†; ***Cz.:*** Iopidine†; ***Denm.:*** Iopidine; ***Fin.:*** Iopidine; ***Fr.:*** Iopidine; ***Ger.:*** Iopidine; ***Gr.:*** Iopidine; ***Hong Kong:*** Iopidine; ***India:*** Alfadrops; ***Irl.:*** Iopidine; ***Israel:*** Iopidine; ***Ital.:*** Iopidine; ***Jpn:*** Iopidine†; ***Malaysia:*** Iopidine†; ***Mex.:*** Iopidine; ***Neth.:*** Iopidine; ***Norw.:*** Iopidine; ***NZ:*** Iopidine†; ***Port.:*** Iopidine; ***S.Afr.:*** Iopidine; ***Singapore:*** Iopidine; ***Spain:*** Iopimax; ***Swed.:*** Iopidine; ***Switz.:*** Iopidine; ***Turk.:*** Iopidine; ***UK:*** Iopidine; ***USA:*** Iopidine; ***Venez.:*** Iopidine†.

Befunolol Hydrochloride *(rINNM)* ⊗

Béfunolol, Chlorhydrate de; Befunololi Hydrochloridum; BFE-60; Hidrocloruro de befunolol. 7-[2-Hydroxy-3-(isopropylamino)propoxy]-2-benzofuranyl methyl ketone hydrochloride.

Бефунолола Гидрохлорид

$C_{16}H_{21}NO_4,HCl = 327.8.$

CAS — 39552-01-7 (befunolol); 39543-79-8 (befunolol hydrochloride).

ATC — S01ED06.

ATC Vet — QS01ED06.

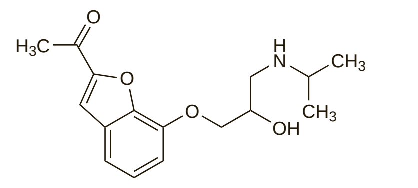

(befunolol)

Profile

Befunolol is a beta blocker (p.1225). It is used as the hydrochloride in the management of ocular hypertension and open-angle glaucoma (p.1873). Eye drops containing befunolol hydrochloride 0.25%, 0.5%, or 1% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Glauconex†; ***Gr.:*** Thilonium†; ***Ital.:*** Betaclar; ***Jpn:*** Bentos; ***Mon.:*** Bentos.

Bimatoprost *(BAN, USAN, rINN)*

AGN-192024; Bimatoprostum. (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl}-*N*-ethyl-5-heptenamide.

Биматопрост

$C_{25}H_{37}NO_4 = 415.6.$

CAS — 155206-00-1.

ATC — S01EE03.

ATC Vet — QS01EE03.

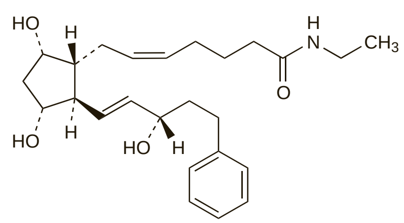

Adverse Effects and Precautions

As for Latanoprost, p.1882. Ocular pruritus is common. Hypertension and headache also commonly occur.

Pharmacokinetics

Small amounts of bimatoprost are absorbed from eye drops, with peak blood concentrations seen within 10 minutes of dosing. Bimatoprost is metabolised by oxidation, de-ethylation and glucuronidation and is excreted mainly in the urine with about 25% appearing in the faeces. The elimination half-life is 45 minutes.

Uses and Administration

Bimatoprost is a synthetic prostamide, a fatty-acid amide that is structurally related to dinoprost (prostaglandin F_2). It is used to reduce intra-ocular pressure in the treatment of open-angle glaucoma and ocular hypertension (p.1873). Reduction in pressure starts about 4 hours after instillation and is maximal within 8 to 12 hours; the effect lasts for at least 24 hours. It is given once daily in the evening as a 0.03% ophthalmic solution.

◊ References.

1. Sherwood M, *et al.* Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. *Surv Ophthalmol* 2001; **45** (suppl 4): S361–S368.
2. Brandt JD, *et al.* Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: a 3-month clinical trial. *Ophthalmology* 2001; **108:** 1023–31.
3. Whitcup SM, *et al.* A randomised, double masked, multicentre clinical trial comparing bimatoprost and timolol for the treatment of glaucoma and ocular hypertension. *Br J Ophthalmol* 2003; **87:** 57–62.
4. Cantor LB, *et al.* Intraocular pressure-lowering efficacy of bimatoprost 0.03% and travoprost 0.004% in patients with glaucoma or ocular hypertension. *Br J Ophthalmol* 2006; **90:** 1370–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lumigan; ***Austral.:*** Lumigan; ***Austria:*** Lumigan; ***Belg.:*** Lumigan; ***Braz.:*** Lumigan; ***Canad.:*** Lumigan; ***Chile:*** Lumigan; ***Cz.:*** Lumigan; ***Denm.:*** Lumigan; ***Fin.:*** Lumigan; ***Fr.:*** Lumigan; ***Ger.:*** Lumigan; ***Gr.:*** Lumigan; ***Hong Kong:*** Lumigan; ***Hung.:*** Lumigan; ***India:*** Lumigan; ***Irl.:*** Lumigan; ***Israel:*** Lumigan; ***Ital.:*** Lumigan; ***Malaysia:*** Lumigan†; ***Mex.:*** Lumigan; ***Neth.:*** Lumigan; ***Norw.:*** Lumigan; ***NZ:*** Lumigan; ***Philipp.:*** Lumigan; ***Pol.:*** Lumigan; ***Port.:*** Lumigan; ***S.Afr.:*** Lumigan; ***Singapore:*** Lumigan; ***Spain:*** Lumigan; ***Swed.:*** Lumigan; ***Switz.:*** Lumigan; ***Thai.:*** Lumigan; ***Turk.:*** Lumigan; ***UK:*** Lumigan; ***USA:*** Lumigan; ***Venez.:*** Lumigan.

Multi-ingredient: ***Cz.:*** Ganfort; ***Gr.:*** Ganfort; ***Port.:*** Ganfort; ***UK:*** Ganfort.

Brimonidine Tartrate *(BANM, USAN, rINNM)*

AGN-190342-LF; Brimonidin Tartrat; Brimonidine, Tartrate de; Brimonidini Tartras; Tartrato de brimonidina; UK-14304-18. 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline D-tartrate.

Бримонидина Тартрат

$C_{11}H_{10}BrN_5,C_4H_6O_6 = 442.2.$

CAS — 59803-98-4 (brimonidine); 79570-19-7 (brimonidine tartrate).

ATC — S01EA05.

ATC Vet — QS01EA05.

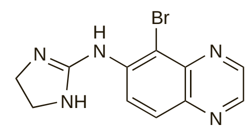

(brimonidine)

Adverse Effects and Precautions

As for Apraclonidine Hydrochloride, p.1878.

In children. Systemic adverse effects, occasionally severe,[1] have been reported in children treated with brimonidine eye drops. In one study[2] adverse effects were reported in 70 of 83 children given adjunctive brimonidine, the most common effects being lethargy and excessive sleepiness; other effects included ocular irritation and blurred vision. Hypothermia occurred in a few cases, mainly in older children. Effects suggesting CNS depression, such as cyanosis and breathing difficulty, were rare, and were most likely in children less than 6 years of age or weighing less than 20 kg. Alternative medication should be considered in this group. In the UK, licensed product information contra-indicates use in neonates and infants under 2 years of age; use in children under 12 years of age is not recommended.

1. Sztajnbok J. Failure of naloxone to reverse brimonidine-induced coma in an infant. *J Pediatr* 2002; **140:** 485–6.
2. Al-Shahwan S, *et al.* Side-effect profile of brimonidine tartrate in children. *Ophthalmology* 2005; **112:** 2143–8.

Interactions

As for Apraclonidine Hydrochloride, p.1878.

Uses and Administration

Brimonidine is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of apraclonidine (p.1878). It is used to lower intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (p.1873), as an alternative or adjunct to topical beta blocker therapy. It may also be used as adjunctive therapy in patients with raised intra-ocular pressure not controlled by topical monotherapy with other drugs such as latanoprost and travoprost. The reduction in intra-ocular pressure is maximal about 2 hours after topical use.

In the management of glaucoma or ocular hypertension, eye drops containing brimonidine tartrate 0.1, 0.15, or 0.2% are instilled two or three times daily.

Glaucoma. References to the use of brimonidine in glaucoma and raised intra-ocular pressure.

1. Adkins JC, Balfour JA. Brimonidine: a review of its pharmacological properties and clinical potential in the management of open-angle glaucoma and ocular hypertension. *Drugs Aging* 1998; **12:** 225–41.
2. Cantor LB. The evolving pharmacotherapeutic profile of brimonidine, an alpha 2-adrenergic agonist, after four years of continuous use. *Expert Opin Pharmacother* 2000; **1:** 815–34.
3. David R. Brimonidine (Alphagan): a clinical profile four years after launch. *Eur J Ophthalmol* 2001; **11** (suppl 2): S72–S77.
4. Lee DA, Gornbein JA. Effectiveness and safety of brimonidine as adjunctive therapy for patients with elevated intraocular pressure in a large, open-label community trial. *J Glaucoma* 2001; **10:** 220–6.

5. Katz LJ. Twelve-month evaluation of brimonidine-purite versus brimonidine in patients with glaucoma or ocular hypertension. *J Glaucoma* 2002; **11:** 119–26.
6. Sherwood MB, *et al.* Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol* 2006; **124:** 1230–8.
7. Fung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91:** 62–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alphagan; Brimo-Klonal; Brimopress; Oftalmotonil; ***Austral.:*** Alphagan; Enidin; ***Austria:*** Alphagan; ***Belg.:*** Alphagan; ***Braz.:*** Alphagan; ***Canad.:*** Alphagan; ***Chile:*** Agglad Ofteno; Alphagan; Brimopress; ***Cz.:*** Alphagan; ***Denm.:*** Alphagan; ***Fin.:*** Alphagan; ***Fr.:*** Alphagan; ***Ger.:*** Alphagan; ***Gr.:*** Alphagan; Benil; Brimodine; Brinal; Brinidin; ***Hong Kong:*** Alphagan; ***Hung.:*** Alphagan†; ***India:*** Brimodin; Iobrim; ***Irl.:*** Alphagan; ***Israel:*** Alphagan; ***Ital.:*** Alphagan; ***Malaysia:*** Alphagan; ***Mex.:*** Agglad; Alphagan; Nor-Tenz; ***Neth.:*** Alphagan; ***Norw.:*** Alphagan; ***NZ:*** Alphagan; ***Philipp.:*** Alphagan; ***Pol.:*** Alphagan; ***Port.:*** Alphagan; ***S.Afr.:*** Alphagan; ***Singapore:*** Alphagan; ***Spain:*** Alphagan; ***Swed.:*** Alphagan; ***Switz.:*** Alphagan; ***Thai.:*** Alphagan; ***Turk.:*** Alphagan; ***UK:*** Alphagan; ***USA:*** Alphagan; ***Venez.:*** Agglad Ofteno; Alphagan.

Multi-ingredient: ***Arg.:*** Combigan; ***Austral.:*** Combigan; ***Braz.:*** Combigan; ***Canad.:*** Combigan; ***Chile:*** Combigan; ***Cz.:*** Combigan; ***Gr.:*** Combigan; ***Hung.:*** Combigan; ***India:*** Brimodin P; ***Irl.:*** Combigan; ***Mex.:*** Combigan-D; ***NZ:*** Combigan; ***Port.:*** Combigan; ***Switz.:*** Combigan; ***UK:*** Combigan; ***USA:*** Combigan.

Brinzolamide *(BAN, USAN, rINN)* ⊗

AL-4862; Brintsolamidi; Brinzolamid; Brinzolamida; Brinzolamidum. (*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide.

Бринзоламид

$C_{12}H_{21}N_3O_5S_3$ = 383.5.
CAS — 138890-62-7.
ATC — S01EC04.
ATC Vet — QS01EC04.

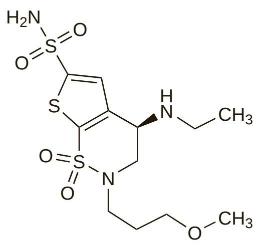

Pharmacopoeias. In *US.*

USP 31 (Brinzolamide). A white or almost white powder. Insoluble in water; slightly soluble in alcohol and in methyl alcohol.

Adverse Effects and Precautions

As for Dorzolamide, p.1880.

Effects on the eyes. Corneal oedema has been noted in the eyes of 2 patients after the long-term use of brinzolamide 1% eye drops;[1] both patients recovered after brinzolamide was stopped.

1. Zhao JC, Chen T. Brinzolamide induced reversible corneal decompensation. *Br J Ophthalmol* 2005; **89:** 389–90.

Uses and Administration

Brinzolamide is a carbonic anhydrase inhibitor with actions and uses similar to those of dorzolamide (p.1880). It is used to reduce intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p.1873), either alone or as adjunctive therapy with a topical beta blocker. A 1% suspension is instilled into the eye two or three times daily.

Glaucoma. References.

1. Cvetkovic RS, Perry CM. Brinzolamide : a review of its use in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 2003; **20:** 919–47.

Preparations

USP 31: Brinzolamide Ophthalmic Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Azopt; ***Austral.:*** Azopt; ***Austria:*** Azopt; ***Belg.:*** Azopt; ***Braz.:*** Azopt; ***Canad.:*** Azopt; ***Chile:*** Azopt; ***Cz.:*** Azopt; ***Denm.:*** Azopt; ***Fin.:*** Azopt; ***Fr.:*** Azopt; ***Ger.:*** Azopt; ***Gr.:*** Azopt; ***Hong Kong:*** Azopt; ***Hung.:*** Azopt; ***Indon.:*** Azopt; ***Irl.:*** Azopt; ***Israel:*** Azopt; ***Ital.:*** Azopt; ***Malaysia:*** Azopt; ***Mex.:*** Azopt; ***Neth.:*** Azopt; ***Norw.:*** Azopt; ***NZ:*** Azopt; ***Philipp.:*** Azopt; ***Pol.:*** Azopt; ***Port.:*** Azopt; ***Rus.:*** Azopt (Азопт); ***S.Afr.:*** Azoptic; ***Singapore:*** Azopt; ***Spain:*** Azopt; ***Swed.:*** Azopt; ***Switz.:*** Azopt; ***Thai.:*** Azopt; ***Turk.:*** Azopt; ***UK:*** Azopt; ***USA:*** Azopt; ***Venez.:*** Azopt.

Carbachol *(BAN, rINN)*

Carbach.; Carbacholi Cloridum; Carbacholine; Carbacholum; Carbacholum Chloratum; Carbacol; Choline Chloride Carbamate; Karbachol; Karbacholis; Karbakol; Karbakoli; Karbaminocholiny chlorek. *O*-Carbamoylcholine chloride; (2-Carbamoyloxyethyl)trimethylammonium chloride.

Карбахол

$C_6H_{15}ClN_2O_2$ = 182.6.
CAS — 51-83-2.
ATC — N07AB01; S01EB02.
ATC Vet — QA03AB92; QN07AB01; QS01EB02.

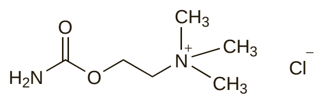

NOTE. CAR is a code approved by the BP 2008 for use on single unit doses of eye drops containing carbachol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Carbachol). A white or almost white, crystalline, hygroscopic powder. Very slightly soluble in water; sparingly soluble in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

USP 31 (Carbachol). A white powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers.

Incompatibility. Chlorocresol (0.025 to 0.1%) and chlorobutanol (0.5%) were both found to be incompatible with a solution of carbachol (0.8%) and sodium chloride (0.69%), very slight precipitates forming on heating and increasing on standing.[1]

1. *PSGB Lab Report No.911* 1962.

Adverse Effects, Treatment, and Precautions

As described for choline esters under Acetylcholine Chloride, p.1877. Carbachol has substantial nicotinic activity which may be unmasked by the use of atropine to counteract muscarinic effects.

Carbachol also produces adverse effects and requires precautions similar to those of other miotics such as pilocarpine (p.1885) when used in the eye, but may produce more ciliary spasm than pilocarpine.

Effects on the gastrointestinal tract. Fatal oesophageal rupture has been reported[1] after subcutaneous injection of carbachol to relieve urinary retention.

1. Cochrane P. Spontaneous oesophageal rupture after carbachol therapy. *BMJ* 1973; **1:** 463–4.

Overdosage. Life-threatening attacks of profuse sweating, intestinal cramps, explosive defaecation, hypothermia, hypotension, and bradycardia occurred in a 36-year-old man after deliberate poisoning with 30 to 40 mg of carbachol.[1] The patient's 10-year-old son had died after poisoning with a similar dose of carbachol.

1. Sangster B, *et al.* Two cases of carbachol intoxication. *Neth J Med* 1979; **22:** 27–8.

Interactions

NSAIDs. Licensed UK product information for acetylcholine chloride ophthalmic preparations states that there have been reports that acetylcholine and carbachol were ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Uses and Administration

Carbachol, a choline ester, is a quaternary ammonium parasympathomimetic with the muscarinic and nicotinic actions of acetylcholine (p.1877). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine.

Carbachol has a miotic action and is usually given intra-ocularly to produce miosis in ocular surgery and to reduce postoperative rises in intra-ocular pressure; up to 0.5 mL of a 0.01% solution is instilled into the anterior chamber of the eye (intracameral instillation). The maximum degree of miosis is usually obtained within 2 to 5 minutes of intra-ocular instillation and miosis lasts for 24 hours.

Eye drops containing up to 3% of carbachol have also been used to lower intra-ocular pressure in glaucoma, usually three times daily with other miotics (see below). Miosis occurs within 10 to 20 minutes of instillation and lasts for 4 to 8 hours; reduction in intra-ocular pressure lasts for 8 hours.

Carbachol has been used for the treatment of urinary retention including postoperative urinary retention. It has also been used in some countries for the treatment of decreased gastrointestinal motility.

Dry mouth. Carbachol has been used as an alternative to pilocarpine in the treatment of radiation-induced xerostomia.[1] The overall treatment of dry mouth is discussed on p.2140.

1. Joensuu H. Treatment for post-irradiation xerostomia. *N Engl J Med* 1994; **330:** 141–2.

Glaucoma and ocular hypertension. Carbachol is sometimes used as an alternative to pilocarpine in the management of glaucoma (p.1873) when resistance or intolerance to pilocarpine develops. It is also instilled into the anterior chamber of the eye (intracameral instillation) to minimise postoperative rises in intra-ocular pressure associated with ocular surgery, and some[1,2] have found it to be more effective than acetylcholine.

1. Ruiz RS, *et al.* Effects of carbachol and acetylcholine on intramuscular pressure after cataract extraction. *Am J Ophthalmol* 1989; **107:** 7–10.
2. Hollands RH, *et al.* Control of intraocular pressure after cataract extraction. *Can J Ophthalmol* 1990; **25:** 128–32.

Preparations

USP 31: Carbachol Intraocular Solution; Carbachol Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Miostat; ***Austral.:*** Miostat; ***Belg.:*** Miostat; ***Braz.:*** Miostat†; ***Canad.:*** Carbastat†; Miostat; ***Cz.:*** Jestryl†; Miostat; ***Fin.:*** Doryl†; ***Ger.:*** Carbamann; Doryl†; Jestryl†; ***Hong Kong:*** Miostat†; ***Hung.:*** Miostat; ***Israel:*** Miostat; ***Ital.:*** Mioticol; ***Malaysia:*** Miostat; ***Neth.:*** Miostat; ***Philipp.:*** Miostat; ***Pol.:*** Miostat; ***S.Afr.:*** Miosys†; ***Singapore:*** Miostat; ***Swed.:*** Isopto Karbakolin; Miostat; ***Switz.:*** Doryl†; Miostat; ***Thai.:*** Miostat; ***Turk.:*** Miostat; ***USA:*** Carbastat; Miostat; ***Venez.:*** Miostat†.

Multi-ingredient: ***Ital.:*** Mios.

Cyclopentolate Hydrochloride

(BANM, rINNM)

Ciklopentolát-hidroklorid; Ciklopentolato hidrochloridas; Cloridrato de Ciclopentolato; Cyclopentolate, chlorhydrate de; Cyclopentolati hydrochloridum; Cyklopentolát hydrochlorid; Cyklopentolathydroklorid; Hidrocloruro de ciclopentolato; Siklopentolat Hidroklorür; Syklopentolaattihydrokloridi. 2-Dimethylaminoethyl 2-(1-hydroxycyclopentyl)-2-phenylacetate hydrochloride.

Циклопентолата Гидрохлорид

$C_{17}H_{25}NO_3,HCl$ = 327.8.
CAS — 512-15-2 (cyclopentolate); 5870-29-1 (cyclopentolate hydrochloride).
ATC — S01FA04.
ATC Vet — QS01FA04.

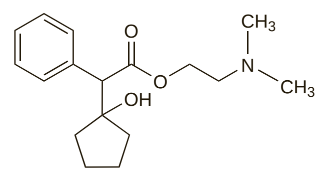

(cyclopentolate)

NOTE. CYC is a code approved by the BP 2008 for use on single unit doses of eye drops containing cyclopentolate hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Cyclopentolate Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 31 (Cyclopentolate Hydrochloride). A white crystalline powder, which develops a characteristic odour on standing. Very soluble in water; freely soluble in alcohol; insoluble in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store at a temperature not exceeding 8° in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Eye drops of cyclopentolate hydrochloride may cause temporary irritation.

Abuse. Cyclopentolate eye drops have been abused.[1] One of 2 patients who did so had been instilling 200 to 400 drops of cyclopentolate into both eyes daily for about 4 months, presumably for its CNS effects, and experienced intense nausea, vomiting, weakness, and tremors on withdrawal.

1. Sato EH, *et al.* Abuse of cyclopentolate hydrochloride (Cyclogyl) drops. *N Engl J Med* 1992; **326:** 1363–4.

Hypersensitivity. Two children developed hypersensitivity reactions shortly after the instillation of 1% cyclopentolate hydrochloride eye drops into each eye.[1] Both children initially had a facial rash but in one of them the rash later spread to include the arms and legs and was accompanied by mild breathlessness.

1. Jones LWJ, Hodes DT. Possible allergic reactions to cyclopentolate hydrochloride: case reports with literature review of uses and adverse reactions. *Ophthalmic Physiol Opt* 1991; **11:** 16–21.

Systemic toxicity. Ten of 66 patients (29 males and 37 females) who received one drop of 2% cyclopentolate in each eye developed mild to moderate systemic toxicity; 9 of the 10 were female.[1] Toxic signs included physical weakness, nausea, lightheadedness, changes in emotional attitude, unprovoked weeping, and loss of equilibrium; tachycardia was always present but changes in blood pressure were insignificant. Spontaneous recovery occurred within 1 hour to several days.

As with atropine, it has been recommended that cyclopentolate eye drops should not be used during the first 3 months of life because of the possible association with development of amblyopia. Systemic toxicity has also been reported in neonates given ocular cyclopentolate.[2]

A 4-year-old boy with cerebral palsy and paraplegia suffered tonic-clonic seizures, facial flushing, and tachycardia 70 minutes after one drop of a 1% cyclopentolate solution was instilled into each eye to dilate his pupils.[3] The child had no history of convulsions and had received 1% cyclopentolate eye drops on 2 previous occasions without incident. In a more recent case,[4] a 23-month-old boy experienced a tonic-clonic seizure lasting 30 minutes after the use of cyclopentolate 1% and phenylephrine 10% eye drops. One drop of each was instilled into both eyes every 5 minutes for 3 doses; the seizure occurred 45 minutes after the last dose. The child was found to have low pseudocholinesterase activity, an enzyme likely to be involved in the metabolism of cyclopentolate.

1. Awan KJ. Adverse systemic reactions of topical cyclopentolate hydrochloride. *Ann Ophthalmol* 1976; **8:** 695–8.
2. Bauer CR, *et al.* Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant. *J Pediatr* 1973; **92:** 501–5.
3. Fitzgerald DA, *et al.* Seizures associated with 1% cyclopentolate eyedrops. *J Paediatr Child Health* 1990; **26:** 106–7.
4. Demayo AP, Reidenberg MM. Grand mal seizure in a child 30 minutes after Cyclogyl (cyclopentolate hydrochloride) and 10% Neo-Synephrine (phenylephrine hydrochloride) eye drops were instilled. Abstract: *Pediatrics* 2004; **113:** 1390–1. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/5/e499 (accessed 24/11/05)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Cyclopentolate hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1219). It is used to produce mydriasis and cycloplegia (p.1874) for ophthalmic diagnostic procedures and also in the treatment of uveitis and iritis (p.1515). It acts more quickly than atropine and has a shorter duration of action; the maximum mydriatic effect is produced 30 to 60 minutes after instillation, and may persist for up to 24 hours or longer in some patients; the maximum cycloplegic effect is produced within 25 to 75 minutes and accommodation recovers within 6 to 24 hours.

For diagnostic procedures, instillation of a 0.5% ophthalmic solution of cyclopentolate hydrochloride, repeated after about 5 to 15 minutes, is usually sufficient for adults. Higher strengths have been used. For children a 1% solution is instilled similarly, although some recommend that strengths greater than 0.5% should not be used in infants and that cyclopentolate should not be used at all during the first 3 months of life.

In the treatment of uveitis and iritis, a 0.5% ophthalmic solution of cyclopentolate hydrochloride is instilled into the eye up to four times daily.

Deeply pigmented eyes are more resistant to pupillary dilatation and may require the use of a 1% solution.

Preparations

BP 2008: Cyclopentolate Eye Drops;
USP 31: Cyclopentolate Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciclopenal; ***Austral.:*** Cyclogyl; ***Belg.:*** Cyclogyl; Cyclopentol†; ***Braz.:*** Ciclolato; Cicloplegico; ***Canad.:*** Cyclogyl; Diopentolate†; ***Chile:*** Cyclogyl; ***Cz.:*** Cyclogyl†; ***Denm.:*** Cyclogyl; ***Fin.:*** Oftan Syklo†; ***Fr.:*** Skiacol; ***Ger.:*** Zykolat-EDO; ***Gr.:*** Cyclogyl; ***Hong Kong:*** Cyclogyl; ***Hung.:*** Humapent; ***India:*** Bell Pentolate; Cyclate; Cyclogyl; ***Irl.:*** Mydrilate; ***Ital.:*** Ciclolux; ***Malaysia:*** Colircusi Cicloplejico; Cyclogyl; ***Mex.:*** Refractyl; ***Neth.:*** Cyclogyl; Cyclomydril†; ***NZ:*** Cyclogyl; ***Port.:*** Cicloplegicedol; Midriodavi; ***S.Afr.:*** Cyclogyl; ***Singapore:*** Cyclogyl; ***Spain:*** Cicloplejico; ***Swed.:*** Cyclogyl; ***Switz.:*** Cyclogyl; ***Thai.:*** Cyclogyl; ***Turk.:*** Siklomid; Sikloplejin; ***UK:*** Mydrilate; ***USA:*** Ak-Pentolate; Cyclogyl; Ocu-Pentolate; Pentolair; ***Venez.:*** Cicloftal†; Cyclogyl.

Multi-ingredient: ***Israel:*** Cyclopentolate†; ***Malaysia:*** Cyclomydril; ***Rus.:*** Cyclomed (Цикломед); ***S.Afr.:*** Cyclomydril; ***Singapore:*** Cyclomydril; ***USA:*** Cyclomydril.

Demecarium Bromide *(BAN, rINN)*

BC-48; Bromuro de demecario; Demecarii Bromidum; Démécarium, Bromure de; Demekariumbromid; Demekariumbromidi. *N,N'*-Decamethylenebis(*N,N,N*-trimethyl-3-methylcarbamoyloxyanilinium) dibromide.

Демекария Бромид

$C_{32}H_{52}Br_2N_4O_4$ = 716.6.
CAS — 16505-84-3 (demecarium); 56-94-0 (demecarium bromide).
ATC — S01EB04.
ATC Vet — QS01EB04.

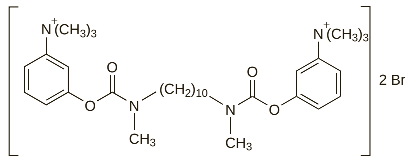

Pharmacopoeias. In *US.*

USP 31 (Demecarium Bromide). A white or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in acetone; soluble in ether. pH of a 1% solution in water is between 5.0 and 7.0. Store in airtight containers. Protect from light.

Profile

Demecarium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase with a long duration of action similar to that of ecothiopate iodide (p.1881). It has been used as a 0.125 or 0.25% ophthalmic solution in the treatment of open-angle glaucoma and in the diagnosis and management of accommodative convergent strabismus.

Preparations

USP 31: Demecarium Bromide Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
USA: Humorsol†.

Diclofenamide *(BAN, rINN)* ⊗

Dichlorphenamide; Diclofenamida; Diclofénamide; Diclofenamidum; Diklofenamid; Diklofenamidi. 4,5-Dichlorobenzene-1,3-disulphonamide.

Диклофенамид

$C_6H_6Cl_2N_2O_4S_2$ = 305.2.
CAS — 120-97-8.
ATC — S01EC02.
ATC Vet — QS01EC02.

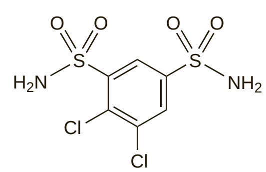

Pharmacopoeias. In *Chin., Jpn,* and *US.*

Profile

Diclofenamide is an inhibitor of carbonic anhydrase with properties similar to those of acetazolamide (p.1875). When given orally its effect begins within 1 hour and lasts for 6 to 12 hours.

Diclofenamide is used to reduce intra-ocular pressure in glaucoma (p.1873). The usual initial oral dose is 100 to 200 mg, then 100 mg every 12 hours until the desired response is obtained, followed by a maintenance dose of 25 to 50 mg one to three times daily. Diclofenamide sodium has been given by injection.

Preparations

USP 31: Dichlorphenamide Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Oratrol†; ***Cz.:*** Oratrol†; ***Gr.:*** Oratrol†; ***Ital.:*** Antidrasi; Fenamide; Glaumid†; ***Spain:*** Glauconide; ***USA:*** Daranide†.

Dorzolamide Hydrochloride

(BANM, USAN, rINNM) ⊗

Dorzolamid Hidroklorür; Dorzolamide, chlorhydrate de; Dorzolamidi hydrochloridum; Hidrocloruro de dorzolamida; L-671152 (dorzolamide); MK-507; MK-0507. (4*S*,6*S*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulphonamide 7,7-dioxide hydrochloride.

Дорзоламида Гидрохлорид

$C_{10}H_{16}N_2O_4S_3$,HCl = 360.9.
CAS — 120279-96-1 (dorzolamide); 130693-82-2 (dorzolamide hydrochloride).
ATC — S01EC03.
ATC Vet — QS01EC03.

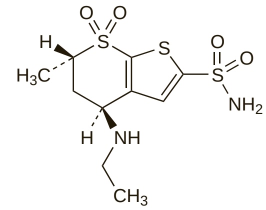

(dorzolamide)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dorzolamide Hydrochloride). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in anhydrous alcohol; slightly soluble in methyl alcohol. It exhibits polymorphism.

USP 31 (Dorzolamide Hydrochloride). A white to off-white crystalline powder. Soluble in water. Store at 15° to 30°. Protect from light.

Adverse Effects and Precautions

Local ocular adverse effects may occur with dorzolamide eye drops and include conjunctivitis, keratitis, burning or stinging, eyelid inflammation or irritation, and blurred vision. Dorzolamide may be absorbed systemically, resulting in adverse effects and precautions similar to those of acetazolamide (see p.1875). Other adverse effects reported are headache, bitter taste, epistaxis, fatigue, and nausea.

Interactions

Systemic absorption may occur after topical application of dorzolamide to the eye and there is a theoretical possibility of interactions similar to those reported with acetazolamide (see p.1876).

Uses and Administration

Dorzolamide is a carbonic anhydrase inhibitor with actions similar to those of acetazolamide (p.1876). It is used in the management of open-angle glaucoma, pseudo-exfoliative glaucoma, and ocular hypertension (p.1873), either alone or as an adjunct to a topical beta blocker.

Dorzolamide is given as eye drops containing dorzolamide hydrochloride equivalent to 2% of the base. For monotherapy it is usually given three times daily; a twice-daily regimen is recommended when used with a beta blocker.

◊ References.

1. Martens-Lobenhoffer J, Banditt P. Clinical pharmacokinetics of dorzolamide. *Clin Pharmacokinet* 2002; **41:** 197–205.
2. Lesk MR, *et al.* Effectiveness and safety of dorzolamide-timolol alone or combined with latanoprost in open-angle glaucoma or ocular hypertension. *Ann Pharmacother* 2008; **42:** 498–504.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Biodrop†; Dorlamida; Poenglausil†; Trusopt; ***Austral.:*** Trusopt; ***Austria:*** Trusopt; ***Belg.:*** Trusopt; ***Braz.:*** Ocupress; Trusopt; ***Canad.:*** Trusopt; ***Chile:*** Glaucotensil; Trusopt; ***Cz.:*** Trusopt; ***Denm.:*** Trusopt; ***Fin.:*** Trusopt; ***Fr.:*** Trusopt; ***Ger.:*** Trusopt; ***Gr.:*** Trusopt; ***Hong Kong:*** Trusopt; ***Hung.:*** Trusopt; ***India:*** Dorzox; ***Irl.:*** Trusopt; ***Israel:*** Trusopt; ***Ital.:*** Trusopt; ***Malaysia:*** Trusopt; ***Mex.:*** Trusopt; ***Neth.:*** Trusopt; ***Norw.:*** Trusopt; ***NZ:*** Trusopt; ***Philipp.:*** Trusopt; ***Pol.:*** Trusopt; ***Port.:*** Trusopt; ***Rus.:*** Trusopt (Трусопт); ***S.Afr.:*** Trusopt; ***Singapore:*** Trusopt; ***Spain:*** Trusopt; ***Swed.:*** Trusopt; ***Switz.:*** Trusopt; ***Thai.:*** Trusopt; ***Turk.:*** Trusopt; ***UK:*** Trusopt; ***USA:*** Trusopt; ***Venez.:*** Dorzol; Glaucotensil D; Trusopt.

Multi-ingredient: ***Arg.:*** Cosopt; Dorlamida T; Dorzoflax†; Glaucotensil TD; Timed D; ***Austral.:*** Cosopt; ***Austria:*** Cosopt; Timsopt; ***Belg.:*** Cosopt; ***Braz.:*** Cosopt; ***Canad.:*** Cosopt; ***Chile:*** Cosopt; Dorsof T; Glaucotensil T; Glausolets Plus; Tiof Plus; ***Cz.:*** Cosopt; ***Denm.:*** Cosopt; ***Fin.:*** Cosopt; ***Fr.:*** Cosopt; ***Ger.:*** Cosopt; ***Gr.:*** Cosopt; Tesol†; ***Hong Kong:*** Cosopt; ***Hung.:*** Cosopt; ***Irl.:*** Cosopt; ***Israel:*** Cosopt; ***Ital.:*** Cosopt; ***Malaysia:*** Cosopt; ***Mex.:*** Cosopt; ***Neth.:*** Cosopt; ***Norw.:*** Cosopt; ***NZ:*** Cosopt; ***Philipp.:*** Cosopt; ***Pol.:*** Cosopt; ***Port.:*** Cosopt; Timosopt; ***S.Afr.:*** Cosopt; ***Singapore:*** Cosopt; ***Swed.:*** Cosopt; ***Switz.:*** Cosopt; ***Thai.:*** Cosopt; ***Turk.:*** Cosopt; ***UK:*** Cosopt; ***USA:*** Cosopt; ***Venez.:*** Cosopt; Dobet; Glaucotensil T.

Dyflos *(BAN)*

DFP; Difluorophate; Di-isopropyl Fluorophosphate; Di-isopropylfluorophosphonate; Fluostigmine; Isoflurofato; Isoflurophate. Di-isopropyl phosphorofluoridate.

$C_6H_{14}FO_3P$ = 184.1.

CAS — 55-91-4.

ATC — S01EB07.

ATC Vet — QS01EB07.

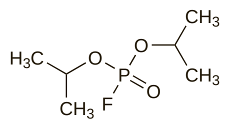

Pharmacopoeias. In *US*.

USP 31 (Isoflurophate). A clear, colourless, or faintly yellow liquid. Specific gravity about 1.05. Sparingly soluble in water; soluble in alcohol and in vegetable oils. It is decomposed by moisture with the evolution of hydrogen fluoride. Store at 8° to 15° in sealed containers.

Profile

Dyflos is an irreversible inhibitor of cholinesterases with actions similar to those of ecothiopate iodide (below). It has been used mainly in the treatment of open-angle glaucoma, particularly in aphakic patients and when other drugs have proved inadequate; it has usually been given as a 0.025% ophthalmic ointment. It was also used in the diagnosis and management of accommodative convergent strabismus.

Handling. The vapour of dyflos is very toxic. The eyes, nose, and mouth should be protected when handling dyflos, and contact with the skin should be avoided. Dyflos can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Preparations

USP 31: Isoflurophate Ophthalmic Ointment.

Ecothiopate Iodide *(BAN, rINN)*

Echothiophate Iodide; Ecostigmine Iodide; Écothiopate, Iodure d'; Ecothiopati Iodidum; Ekotiopaattijodidi; Ekotiopatjodid; Ioduro de ecotiopato; MI-217. (2-Diethoxyphosphinylthioethyl)trimethylammonium iodide.

Экотиопата Йодид

$C_9H_{23}INO_3PS$ = 383.2.

CAS — 6736-03-4 (ecothiopate); 513-10-0 (ecothiopate iodide).

ATC — S01EB03.

ATC Vet — QS01EB03.

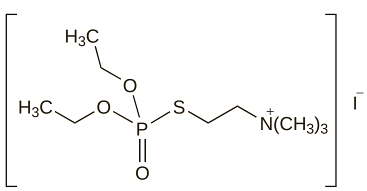

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Echothiophate Iodide). A white, crystalline, hygroscopic solid having a slight mercaptan-like odour. Soluble 1 in 1 of water, 1 in 25 of dehydrated alcohol, and 1 in 3 of methyl alcohol; practically insoluble in other organic solvents. Its solutions in water have a pH of about 4. Store in airtight containers preferably at a temperature below 0°. Protect from light.

Adverse Effects

As for Neostigmine, p.631. For adverse effects of miotics, see also Pilocarpine, p.1885.

Ecothiopate is an irreversible cholinesterase inhibitor; its action, and hence its adverse effects, may be prolonged.

Plasma and erythrocyte cholinesterases may be reduced by treatment with eye drops of ecothiopate or other long-acting anticholinesterases, and systemic toxicity occurs more frequently than with shorter-acting miotics. Acute iritis, retinal detachment, or precipitation of acute glaucoma may occasionally occur, and iris cysts (especially in children) or lens opacities may develop on prolonged treatment.

Treatment of Adverse Effects

To treat the systemic effects of poisoning, atropine sulfate may be given parenterally with pralidoxime chloride as for intoxication with organophosphorus insecticides (see p.1460); subconjunctival injection of pralidoxime has been used to reverse severe ocular adverse effects. Supportive treatment, including assisted ventilation, should be given as necessary.

To prevent or reduce development of iris cysts in patients receiving ecothiopate eye drops, phenylephrine eye drops may be given simultaneously.

Precautions

As for Neostigmine, p.632. For precautions of miotics, see also under Pilocarpine, p.1885. In general, as with other long-acting anticholinesterases, ecothiopate should be used only where therapy with other drugs has proved ineffective. Ecothiopate iodide should not be used in patients with iodine hypersensitivity.

Interactions

As for Neostigmine, p.632. The possibility of an interaction remains for a considerable time after stopping long-acting anticholinesterases such as ecothiopate.

Uses and Administration

Ecothiopate is an irreversible inhibitor of cholinesterase; its actions are similar to those of neostigmine (p.632) but much more prolonged. Its miotic action begins within 1 hour of its application and may persist for 1 to 4 weeks; it causes a reduction in intra-ocular pressure, which is maximal after 24 hours and may persist for days or weeks.

Ecothiopate iodide is used mainly in the treatment of open-angle glaucoma (p.1873), particularly in aphakic patients and when other drugs have proved inadequate. It is given as drops of a 0.03 to 0.25% ophthalmic solution. Licensed product information states that 2 daily doses are preferred to allow for diurnal variations in intra-ocular pressure, although it has also been given once daily or on alternate days. It is advisable to give the single dose or one of the 2 daily doses at bedtime.

Ecothiopate iodide eye drops are also used in the diagnosis and management of accommodative convergent strabismus (p.1874).

Preparations

USP 31: Echothiophate Iodide for Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Austral.: Phospholine Iodide†; ***Austria:*** Phospholinjodid†; ***USA:*** Phospholine Iodide†.

Eucatropine Hydrochloride *(BANM, rINNM)*

Clorhidrato de Euftalmina; Eucatropine, Chlorhydrate d'; Eucatropini Hydrochloridum; Eucatropinium Chloride; Hidrocloruro de eucatropina. 1,2,2,6-Tetramethyl-4-piperidyl mandelate hydrochloride.

Эукатропина Гидрохлорид

$C_{17}H_{25}NO_3$,HCl = 327.8.

CAS — 100-91-4 (eucatropine); 536-93-6 (eucatropine hydrochloride).

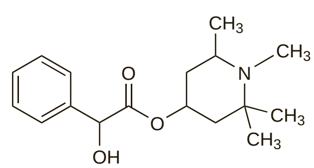

(eucatropine)

Pharmacopoeias. In *US*.

USP 31 (Eucatropine Hydrochloride). A white, odourless, granular powder. Very soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Profile

Eucatropine hydrochloride is a tertiary amine antimuscarinic that has been used as a mydriatic. It has little or no effect on accommodation.

Preparations

USP 31: Eucatropine Hydrochloride Ophthalmic Solution.

Homatropine *(BAN)*

Homatropiini; Homatropin; Homatropina; Homatropinum. (1*R*,3*r*,5*S*)-Tropan-3-yl (*RS*)-mandelate.

$C_{16}H_{21}NO_3$ = 275.3.

CAS — 87-00-3.

ATC — S01FA05.

ATC Vet — QS01FA05.

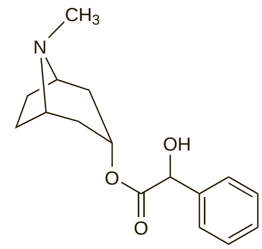

Homatropine Hydrobromide *(BANM)*

Homatr. Hydrobrom.; Homatropiinihydrobromidi; Homatropina, hidrobromuro de; Homatropine, bromhydrate d'; Homatropin-hidrobromid; Homatropinhydrobromid; Homatropin-hydrobromid; Homatropini hydrobromidum; Homatropinium Bromide; Homatropino hidrobromidas; Homatropinum Bromatum; Homatropiny bromowodorek; Omatropina Bromidrato; Oxytolyltropine Hydrobromide; Tropyl Mandelate Hydrobromide.

$C_{16}H_{21}NO_3$,HBr = 356.3.

CAS — 51-56-9.

ATC — S01FA05.

ATC Vet — QS01FA05.

NOTE. HOM is a code approved by the BP 2008 for use on single unit doses of eye drops containing homatropine hydrobromide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Homatropine Hydrobromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Homatropine Hydrobromide). White crystals or a white crystalline powder. Soluble 1 in 6 of water, 1 in 40 of alcohol, and 1 in 420 of chloroform; insoluble in ether. pH of a 2% solution in water is between 5.7 and 7.0. Store in airtight containers. Protect from light.

Homatropine Methylbromide *(BANM, rINN)*

Homatropiinimetyylibromidi; Homatropine Methobromide; Homatropine, méthylbromure d'; Homatropini methylbromidum; Homatropin-methylbromid; Homatropin-metilbromid; Homatropinmetylbromid; Homatropino metilbromidas; Methylhomatropinium Bromatum; Methylhomatropinium Bromide; Metilbromuro de homatropina. (1*R*,3*r*,5*S*)-3-[(±)-Mandeloyloxy]-8-methyltropanium bromide.

Гоматропина Метилбромид

$C_{16}H_{21}NO_3$,CH_3Br = 370.3.

CAS — 80-49-9.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*.

Ph. Eur. 6.2 (Homatropine Methylbromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Protect from light.

USP 31 (Homatropine Methylbromide). A white, odourless, powder that slowly darkens on exposure to light. Very soluble in water; freely soluble in alcohol and in acetone containing about 20% of water; practically insoluble in acetone and in ether. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Ophthalmic use. Antimuscarinic toxicity (including ataxia, restlessness, excitement, hallucinations) has been reported in children[1] and the elderly[2,3] given homatropine eye drops.

1. Hoefnagel D. Toxic effects of atropine and homatropine eyedrops in children. *N Engl J Med* 1961; **264:** 168–71.
2. Reid D, Fulton JD. Tachycardia precipitated by topical homatropine. *BMJ* 1989; **299:** 795–6.
3. Tune LE, *et al.* Anticholinergic delirium caused by topical homatropine ophthalmologic solution: confirmation by anticholinergic radioreceptor assay in two cases. *J Neuropsychiatr Clin Neurosci* 1992; **4:** 195–7.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Homatropine is a tertiary amine antimuscarinic with effects similar to those of atropine (p.1219). It is used as the hydrobromide, also a tertiary amine, to produce mydriasis and cycloplegia (p.1874); its actions are more rapid and of shorter duration than those of atropine, but it is less potent and has a relatively weak cycloplegic effect. In general, onset of action is between 30 and 60 minutes, and recovery within 1 to 3 days. Homatropine hydrobromide is generally used as a 1, 2, or 5% ophthalmic solution. For the determination of refraction, instillation may be repeated if necessary 5 to 10 minutes later. In the treatment of uveitis (p.1515), the eye drops should be instilled two or three times daily, or up to every 3 to 4 hours if required.

The *BNFC* recommends that eye drops containing 0.5% homatropine hydrobromide are used once daily or on alternate days for uveitis in children aged 3 months to 2 years; older children may be given 1 or 2% eye drops twice daily.

Homatropine has also been used as the quaternary ammonium methobromide derivative in the treatment of gastrointestinal spasm and as an adjunct in peptic ulcer disease; homatropine methobromide has also been included in preparations used for the treatment of coughs.

Preparations

BP 2008: Homatropine Eye Drops;
USP 31: Homatropine Hydrobromide Ophthalmic Solution; Homatropine Methylbromide Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiespasmodico; Dallapasmo; Espasmotropin; Paratropina; ***Braz.:*** Espasmo Flatol; Novatropina; ***Gr.:*** Nopar; ***Malaysia:*** Homa†; ***Mex.:*** Homasedin†; Homogrin; Infafren Simple; Pasmolit; ***Spain:*** Homatrop; ***Venez.:*** Litropina.

Multi-ingredient: ***Arg.:*** Antispasmina; Asestor; Bellatotal; Bibol Leloup; Biliosan Compuesto†; Carbon Tabs; Colistop; Dimaval; Espasmo Ibupirac†; Espasmofin; Factor AG Antiespasmodico; Hepatodirectol; Ibupirac Fem; Opoenterol†; Paratropina Antigas; Paratropina Compuesta; Sumal; Zimerol; ***Braz.:*** Analgosedan†; Asmatiron†; Atapec†; Belacodid†; Bromalgina†; Calmazin†; Codeverin†; Dipirol†; Enterobion†; Espasmalgon†; Espasmo Colic†; Espasmo Luftal; Etaverol†; Flagass Baby; Marsonil†; Migrane; Naquinto†; Pasmalgin†; Plenocedan†; Sedalene; Sedalin; Spasmotropin; Tropinal; Vagoplex†; ***Chile:*** Codelasa; ***Hung.:*** Bilagit†; Neo-Bilagit; Ridol†; Troparinum; ***India:*** Dysfur-M†; ***Mex.:*** Bontal; Contefur†; Coralzul; Dialgin; Facetin-D; Fuzotyl†; Neopecsul; Neoxil; Sultroquin†; Tasakal†; Threchop; Trilor†; Yodozona; ***Philipp.:*** Creamalin HM; ***Spain:*** Cortenema; ***Thai.:*** Polyenzyme-I; ***USA:*** Hycodan; Hydromet; Hydropane; Tussigon; ***Venez.:*** Frevag†; Metilfedrin†.

Latanoprost *(BAN, USAN, rINN)*

Latanoprosti; Latanoprostum; PhXA-41; XA-41. Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl}-5-heptenoate.

Латанопрост

$C_{26}H_{40}O_5$ = 432.6.

CAS — 130209-82-4.

ATC — S01EE01.

ATC Vet — QS01EE01.

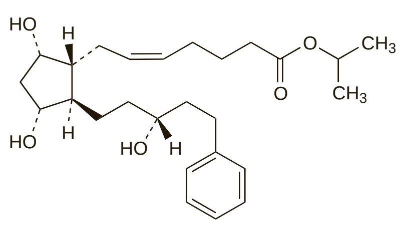

Adverse Effects and Precautions

Latanoprost eye drops may produce a gradual increase in the amount of brown pigment in the iris, due to increased melanin content of melanocytes. This change in eye colour is most evident in patients with mixed colour irises, and may be permanent in some patients. The onset of iris pigmentation is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. Darkening, thickening, and lengthening of eye lashes may occur and are reversible upon stopping treatment. Darkening of the palpebral skin has been reported rarely. Ocular irritation, conjunctival hyperaemia, transient punctate epithelial erosions and eyelid oedema may occur; there have also been rare reports of iritis and/or uveitis, and macular oedema. Systemic effects may also occur, see below for further details. Dizziness, headache, arthralgia, and myalgia have also been reported.

Effects on the eyes. Latanoprost has been associated with various adverse effects on the eyes, including case reports of cystoid macular oedema[1] and bilateral optic disc oedema.[2] Licensed product information states that reports of macular oedema have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with risk factors for cystoid macular oedema such as those with diabetic retinopathy or retinal vein occlusion.

Herpes simplex dendritic keratitis developed in 2 patients during latanoprost therapy.[3] The author suggested that the biochemical changes in the cornea caused by latanoprost may predispose to herpes keratitis.

1. Wardrop DRA, Wishart PK. Latanoprost and cystoid macular oedema in a pseudophake. *Br J Ophthalmol* 1998; **82:** 843–4.
2. Stewart O, *et al.* Bilateral optic disc oedema associated with latanoprost. *Br J Ophthalmol* 1999; **83:** 1092–3.
3. Ekatomatis P. Herpes simplex dendritic keratitis after treatment with latanoprost for primary open angle glaucoma. *Br J Ophthalmol* 2001; **85:** 1008–9.

Systemic effects. The use of latanoprost eye drops has been associated with systemic adverse reactions. In a case report[1] of 2 patients with latanoprost-associated hypertension the authors mentioned that other events including peripheral and facial oedema, dyspnoea, exacerbation of asthma, tachycardia, and chest pain or angina pectoris had been reported. Another case report[2] also referred to exacerbation of angina. Although a study[3] involving 24 stable asthmatics found that latanoprost eye drops had no effect on pulmonary function or asthma symptoms, UK licensed product information recommends caution in patients with asthma.

1. Peak AS, Sutton BM. Systemic adverse effects associated with topically applied latanoprost. *Ann Pharmacother* 1998; **32:** 504–5.
2. Mitra M, *et al.* Exacerbation of angina associated with latanoprost. *BMJ* 2001; **323:** 783.
3. Hedner J, *et al.* Latanoprost and respiratory function in asthmatic patients: randomized, double-masked, placebo-controlled crossover evaluation. *Arch Ophthalmol* 1999; **117:** 1305–9.

Interactions

Paradoxical increases in intra-ocular pressure have been reported after the concomitant ophthalmic use of 2 prostaglandin analogues. UK licensed product information states that the use of 2 or more prostaglandin analogues or derivatives is not recommended.

Uses and Administration

Latanoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) that is used to reduce intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension (p.1873). Reduction of intra-ocular pressure starts about 3 to 4 hours after instillation and is maximal after 8 to 12 hours; pressure reduction lasts for at least 24 hours. A 0.005% ophthalmic solution is instilled once daily, preferably in the evening.

◊ References.

1. Patel SS, Spencer CM. Latanoprost: a review of its pharmacological properties, clinical efficacy and tolerability in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging* 1996; **9:** 363–78.
2. Einarson TR, *et al.* Meta-analysis of the effect of latanoprost and brimonidine on intraocular pressure in the treatment of glaucoma. *Clin Ther* 2000; **22:** 1502–15.
3. Zhang WY, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001; **85:** 983–90.
4. Feldman RM. An evaluation of the fixed-combination of latanoprost and timolol for use in open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother* 2004; **5:** 909–21.
5. Bayer A, *et al.* Clinical predictors of latanoprost treatment effect. *J Glaucoma* 2005; **14:** 260–3.
6. Diestelhorst M, Larsson LI. European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology* 2006; **113:** 70–6.
7. Fung AT, *et al.* Meta-analysis of randomised controlled trials comparing latanoprost with brimonidine in the treatment of open-angle glaucoma, ocular hypertension or normal-tension glaucoma. *Br J Ophthalmol* 2007; **91:** 62–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Glaucostat; Klonaprost; Latanoflax; Louten; Ocuprost†; Paraiop; Tanamof; Xalatan; ***Austral.:*** Xalatan; ***Austria:*** Xalatan; ***Belg.:*** Xalatan; ***Braz.:*** Xalatan; ***Canad.:*** Xalatan; ***Chile:*** Gaax; Latof; Louten; Xalatan; ***Cz.:*** Xalatan; ***Denm.:*** Xalatan; ***Fin.:*** Xalatan; ***Fr.:*** Xalatan; ***Ger.:*** Xalatan; ***Gr.:*** Xalatan; ***Hong Kong:*** Xalatan; ***Hung.:*** Xalatan; ***India:*** 9PM; ***Indon.:*** Xalatan; ***Irl.:*** Xalatan; ***Israel:*** Xalatan; ***Ital.:*** Xalatan; ***Malaysia:*** Xalatan; ***Mex.:*** Gaap Ofteno; Latsol; Xalatan; ***Neth.:*** Xalatan; ***Norw.:*** Xalatan; ***NZ:*** Xalatan; ***Philipp.:*** Xalatan; ***Pol.:*** Xalatan; ***Port.:*** Xalatan; ***Rus.:*** Xalatan (Ксалатан); ***S.Afr.:*** Xalatan; ***Singapore:*** Xalatan; ***Spain:*** Xalatan; ***Swed.:*** Xalatan; ***Switz.:*** Xalatan; ***Thai.:*** Xalatan; ***Turk.:*** Xalatan; ***UK:*** Xalatan; ***USA:*** Xalatan; ***Venez.:*** Gaap Ofteno; Laprost; Latanopress; Xalatan.

Multi-ingredient: ***Arg.:*** Louten T; Ocuprostim; Xalacom; ***Austral.:*** Xalacom; ***Austria:*** Xalacom; ***Belg.:*** Xalacom; ***Braz.:*** Xalacom; ***Canad.:*** Xalacom; ***Chile:*** Gaax T; Latof-T; Xalacom; ***Cz.:*** Xalacom; ***Denm.:*** Xalcom; ***Fin.:*** Xalcom; ***Fr.:*** Xalacom; ***Ger.:*** Xalacom; ***Gr.:*** Xalacom; ***Hong Kong:*** Xalacom; ***Hung.:*** Xalacom; ***Indon.:*** Xalacom; ***Irl.:*** Xalacom; ***Israel:*** Xalacom; ***Ital.:*** Xalacom; ***Malaysia:*** Xalacom; ***Mex.:*** Xalacom; ***Neth.:*** Xalacom; ***Norw.:*** Xalcom; ***NZ:*** Xalacom; ***Philipp.:*** Xalacom; ***Pol.:*** Xalacom; ***Port.:*** Tavu; Xalacom; ***Rus.:*** Xalacom (Ксалаком); ***S.Afr.:*** Xalacom; ***Singapore:*** Xalacom; ***Spain:*** Xalacom; ***Swed.:*** Xalcom; ***Switz.:*** Xalacom; ***Thai.:*** Xalacom; ***UK:*** Xalacom; ***Venez.:*** Xalacom.

Levobetaxolol Hydrochloride *(USAN, rINNM)* ⊗

AL-1577A (levobetaxolol or levobetaxolol hydrochloride); Hidrocloruro de levobetaxolol; Lévobétaxolol, Chlorhydrate de; Levobetaxololi Hydrochloridum. (−)-(*S*)-1-{*p*-[2-(Cyclopropylmethoxy)ethyl]phenoxy}-3-isopropylaminopropan-2-ol hydrochloride.

Левобетаксолола Гидрохлорид

$C_{18}H_{29}NO_3,HCl$ = 343.9.

CAS — 93221-48-8 (levobetaxolol); 116209-55-3 (levobetaxolol hydrochloride).

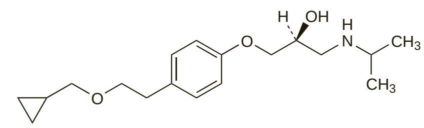

(levobetaxolol)

Profile

Levobetaxolol, the *S*-isomer of betaxolol (p.1231) is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have no significant membrane-stabilising properties.

Levobetaxolol has been used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Betaxon†.

Levobunolol Hydrochloride

(BANM, USAN, rINNM) ⊗

(−)-Bunolol Hydrochloride; *l*-Bunolol Hydrochloride; Hidrocloruro de levobunolol; Lévobunolol, Chlorhydrate de; Levobunolol Hidroklorür; Levobunololhydroklorid; Levobunololi Hydrochloridum; Levobunololihydrokloridi; W-7000A. (−)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride.

Левобунолола Гидрохлорид

$C_{17}H_{25}NO_3,HCl$ = 327.8.

CAS — 47141-42-4 (levobunolol); 27912-14-7 (levobunolol hydrochloride).

ATC — S01ED03.

ATC Vet — QS01ED03.

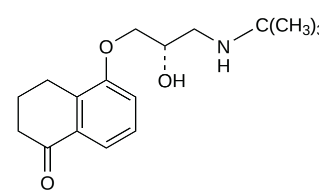

(levobunolol)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Levobunolol Hydrochloride). A white or pinkish-white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of between 4.5 and 6.5. Protect from light.

USP 31 (Levobunolol Hydrochloride). A white odourless crystalline powder. Soluble in water and in methyl alcohol; slightly soluble in alcohol and in chloroform. A 5% solution in water has a pH between 4.5 and 6.5.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Some systemic absorption is reported to occur after topical application to the eye. After oral doses levobunolol is rapidly and almost completely absorbed from the gastrointestinal tract. It is extensively metabolised in the liver; the principal metabolite, dihydrolevobunolol, is reported to possess beta-blocking activity. The metabolites and some unchanged drug are excreted in the urine.

Uses and Administration

Levobunolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties.

Levobunolol is used as the hydrochloride to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension (p.1873). It begins to act 1 hour after instillation with maximal effect seen between 2 and 6 hours; the effect may be maintained for up to 24 hours. Levobunolol hydrochloride is usually used as a 0.5% ophthalmic solution instilled once or twice daily; alternatively a 0.25% solution may be instilled twice daily.

Preparations

BP 2008: Levobunolol Eye Drops;
USP 31: Levobunolol Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Betagan; Levunolol; ***Austral.:*** Betagan; ***Austria:*** Vistagan; ***Belg.:*** Betagan; ***Braz.:*** B-Tablock; Betagan; ***Canad.:*** Betagan; Ophtho-Bunolol†; ***Chile:*** Betagen; ***Cz.:*** Vistagan; ***Denm.:*** Betagan; ***Fr.:*** Betagan; ***Ger.:*** Vistagan; ***Gr.:*** Pentila†; Vistagan; ***Hong Kong:*** Betagan; ***Hung.:*** Vistagan; ***Irl.:*** Betagan; ***Israel:*** Betagan; ***Ital.:*** Vistagan; ***Malaysia:*** Betagan†; ***Mex.:*** Betagan; ***Neth.:*** Betagan; ***NZ:*** Betagan; ***Port.:*** Betagan; ***S.Afr.:*** Betagan; ***Singapore:*** Betagan; ***Spain:*** Betagan; ***Switz.:*** Vistagan; ***Thai.:*** Betagan; ***Turk.:*** Betagan; ***UK:*** Betagan; ***USA:*** Ak-Beta; Betagan; ***Venez.:*** Vistagan.

Multi-ingredient: *Canad.:* Probeta†.

Methazolamide *(BAN, rINN)* ⊗

Metazolamida; Méthazolamide; Methazolamidum. *N*-(4-Methyl-2-sulphamoyl-Δ^2-1,3,4-thiadiazolin-5-ylidene)acetamide.

Метазоламид

$C_5H_8N_4O_3S_2$ = 236.3.
CAS — 554-57-4.
ATC — S01EC05.
ATC Vet — QS01EC05.

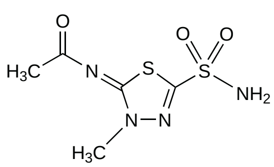

Pharmacopoeias. In *US*.
USP 31 (Methazolamide). A white or faintly yellow crystalline powder with a slight odour. Very slightly soluble in water and in alcohol; slightly soluble in acetone; soluble in dimethylformamide. Protect from light.

Adverse Effects and Precautions

As for Acetazolamide, p.1875.

Hypersensitivity. Cholestatic hepatitis with jaundice, rash, and subsequent pure red cell aplasia was associated with methazolamide in a patient.[1] Drug-induced hypersensitivity was suspected as the cause of the reaction.

1. Krivoy N, *et al*. Methazolamide-induced hepatitis and pure RBC aplasia. *Arch Intern Med* 1981; **141:** 1229–30.

Pharmacokinetics

Methazolamide is absorbed from the gastrointestinal tract more slowly than acetazolamide. It has been reported not to be extensively bound to plasma protein, and to have a half-life of about 14 hours. About 15 to 30% of the dose is excreted in the urine; the fate of the remainder is unknown.

Uses and Administration

Methazolamide is an inhibitor of carbonic anhydrase with actions similar to those of acetazolamide (p.1876). It is used in the treatment of glaucoma (p.1873) in oral doses of 50 to 100 mg two or three times daily. Its action is less prompt but of longer duration than that of acetazolamide, lasting for 10 to 18 hours.

The diuretic activity of methazolamide is less pronounced than that of acetazolamide.

Preparations

USP 31: Methazolamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Glaumetax†; ***Canad.:*** Neptazane†; ***Israel:*** Neptazane†; ***Thai.:*** Neptazane†; ***USA:*** GlaucTabs†; MZM†.

Metipranolol *(BAN, USAN, rINN)* ⊗

BMOI-004; Methypranolol; Métipranolol; Metipranololum; VUAB-6453 (SPOFA); VUFB-6453. 1-(4-Acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol; 4-(2-Hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethylphenyl acetate.

Метипранолол

$C_{17}H_{27}NO_4$ = 309.4.
CAS — 22664-55-7.
ATC — S01ED04.
ATC Vet — QS01ED04.

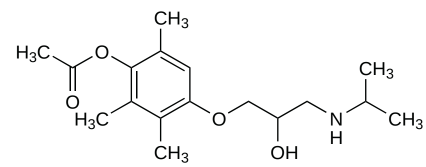

NOTE. MPR is a code approved by the BP 2008 for use on single unit doses of eye drops containing metipranolol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Br.*
BP 2008 (Metipranolol). A white crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; dissolves in dilute mineral acids. The filtrate of a 2.5% suspension in water has a pH of 9.0 to 10.0. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Conjunctivitis, conjunctival leucoplakia, transient stinging, as well as other ocular adverse effects have been reported with metipranolol eye drops. Granulomatous anterior uveitis has been reported rarely; a high incidence reported in the UK may have been associated with changes induced by radiation sterilisation of metipranolol eye drops in their final container, but this preparation is no longer available.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Uses and Administration

Metipranolol is a non-cardioselective beta blocker (p.1225). It is reported to be largely lacking in intrinsic sympathomimetic activity and membrane-stabilising properties.

Metipranolol is used to reduce raised intra-ocular pressure in the management of open-angle glaucoma and ocular hypertension (p.1873). Eye drops usually containing metipranolol 0.1 or 0.3% are used twice daily.

Metipranolol has also been used by mouth in the management of cardiovascular disorders.

Preparations

BP 2008: Metipranolol Eye Drops.

Proprietary Preparations (details are given in Part 3)
Austria: Beta-Ophtiole; ***Belg.:*** Beta-Ophtiole; ***Cz.:*** Trimepranol; ***Ger.:*** Betamann; ***Ital.:*** Turoptin; ***Malaysia:*** Beta-Ophtiole†; ***Neth.:*** Beta-Ophtiole; ***Philipp.:*** Beta-Ophtiole; ***Pol.:*** Betamann; ***Port.:*** Beta-Ophtiole; ***S.Afr.:*** Beta-Ophtiole; ***Singapore:*** Beta-Ophtiole†; ***Switz.:*** Turoptin†; ***Thai.:*** Beta-Ophtiole†; ***Turk.:*** Turoptin; ***USA:*** OptiPranolol.

Multi-ingredient: *Austria:* Betacarpin; ***Belg.:*** Normoglaucon; ***Cz.:*** Trimecryton†; ***Ger.:*** Normoglaucon; Torrat†; Tri-Torrat†; ***Gr.:*** Beta Opthiole; Ripix†; ***Hong Kong:*** Torrat†; ***Ital.:*** Ripix; ***Malaysia:*** Normoglaucon†; ***Neth.:*** Normoglaucon; ***Pol.:*** Normoglaucon; ***Port.:*** Normoglaucon; ***Singapore:*** Normoglaucon†; ***Switz.:*** Ripix; ***Thai.:*** Normoglaucon†.

Nipradilol *(rINN)* ⊗

K-351; Nipradilolum; Nipradolol. 8-[2-Hydroxy-3-(isopropylamino)propoxy]-3-chromanol 3-nitrate.

Нипрадилол

$C_{15}H_{22}N_2O_6$ = 326.3.
CAS — 81486-22-8.

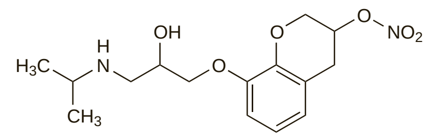

Profile

Nipradilol is a non-cardioselective beta blocker (p.1225). It is also reported to have direct vasodilating activity. It is used in the management of glaucoma and ocular hypertension (p.1873); eye drops containing nipradilol 0.05% are instilled twice daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Hypadil.

Paraoxon

E-600. Diethyl *p*-nitrophenyl phosphate.
$C_{10}H_{14}NO_6P$ = 275.2.
CAS — 311-45-5.
ATC — S01EB10.
ATC Vet — QS01EB10.

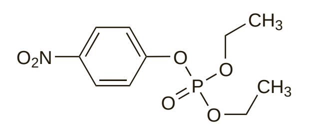

Profile

Paraoxon is a potent inhibitor of cholinesterase activity that has been used with other miotics in the treatment of glaucoma. It is the active metabolite of the organophosphorus insecticide parathion (p.2048) and therefore produces similar toxicity but with a faster onset.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ital.:* Mios.

Physostigmine *(BAN)*

Eserine; Fisostigmina; Fysostigmiini; Fysostigmin; Physostigminum. (3a*S*,8a*R*)-1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl methylcarbamate.
$C_{15}H_{21}N_3O_2$ = 275.3.
CAS — 57-47-6.
ATC — S01EB05; V03AB19.
ATC Vet — QA03AX90; QA03FA90; QS01EB05; QV03AB19.

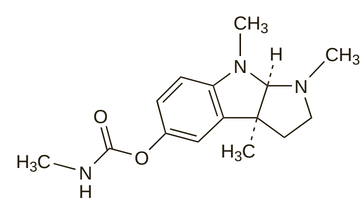

Description. An alkaloid obtained from the calabar bean (ordeal bean; chopnut), the seed of *Physostigma venenosum* (Leguminosae).

Pharmacopoeias. In *US*.
USP 31 (Physostigmine). An alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum* (Leguminosae). It is a white, odourless, microcrystalline powder which acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals. M.p. not lower than 103°. Slightly soluble in water; freely soluble in alcohol; very soluble in chloroform and in dichloromethane; soluble in fixed oils and in benzene. Store in airtight containers. Protect from light.

Physostigmine Salicylate *(BANM)*

Eserine Salicylate; Ésérine, salicylate d'; Eserini salicylas; Ezerino salicilatas; Fisostigmina, salicilato de; Fizostigmino salicilatas; Fizostygminy salicylan; Fizosztigmin-szalicilát; Fysostigmiinisalisylaatti; Fysostigminsalicylat; Fysostigmin-salicylát; Physostig. Sal.; Physostigmine Monosalicylate; Physostigmini salicylas.
$C_{15}H_{21}N_3O_2,C_7H_6O_3$ = 413.5.
CAS — 57-64-7.
ATC — S01EB05; V03AB19.
ATC Vet — QS01EB05; QV03AB19.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Physostigmine Salicylate). Colourless or almost colourless crystals. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Sparingly soluble in water; soluble in alcohol. A 0.9% solution in water has a pH of 5.1 to 5.9. Store in airtight containers. Protect from light. Aqueous solutions are unstable.

USP 31 (Physostigmine Salicylate). White, shining, odourless, crystals or white powder. It acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 75 of water, 1 in 16 of alcohol, 1 in 6 of chloroform, and 1 in 250 of ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. See below.

Physostigmine Sulfate

Ésérine, sulfate d'; Eserine Sulphate; Eserini Sulfas; Ezerino sulfatas; Fisostigmina, sulfato de; Fizostigmino sulfatas; Fizosztigmin-szulfát; Fysostigmiinisulfaatti; Fysostigminsulfat; Fysostigmin-sulfát; Physostig. Sulph.; Physostigmine Sulphate *(BANM)*; Physostigmini sulfas.

$(C_{15}H_{21}N_3O_2)_2,H_2SO_4$ = 648.8.
CAS — 64-47-1.
ATC — S01EB05; V03AB19.
ATC Vet — QS01EB05; QV03AB19.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Physostigmine Sulphate). A white or almost white, hygroscopic crystalline powder. It becomes red on exposure to air and light; the colour develops more quickly in the presence of moisture. Very soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 3.5 to 5.5. Store in well-filled airtight glass containers. Protect from light. Aqueous solutions are unstable.

USP 31 (Physostigmine Sulfate). A white, odourless, microcrystalline powder. It is deliquescent in moist air, and acquires a red tint on exposure to heat, light, or air, or on contact with traces of metals for long periods. Soluble 1 in 4 of water, 1 in 0.4 of alcohol, and 1 in 1200 of ether. Store in airtight containers. Protect from light.

Stability. In aqueous solutions physostigmine is hydrolysed to eseroline and subsequently oxidised to the red compound rubreserine and other coloured products. Solutions for injection or ophthalmic use should not be used if more than slightly discoloured.

Adverse Effects, Treatment, and Precautions

Systemic effects as for Neostigmine, p.631, although usually more severe. Physostigmine crosses the blood-brain barrier and may therefore produce CNS effects.

For adverse effects and precautions for topical miotics see also under Pilocarpine, p.1885. Physostigmine is not well tolerated when used in the eyes for long periods and may produce follicles in the conjunctiva; hypersensitivity reactions are also common. Prolonged use of ophthalmic ointments containing physostigmine may cause depigmentation of the lid margins in dark-skinned patients.

Overdosage. Symptomatic and supportive treatment, including the use of diazepam and atropine where necessary, is generally recommended for systemic toxicity due to physostigmine. However, in an early report, the use of atropine in a patient who had taken 1 g of physostigmine had to be abandoned after it produced tachycardia and multifocal ventricular ectopic beats.[1] In a similar case of severe poisoning a slow intravenous injection of propranolol 5 mg reduced the high pulse rate and controlled pulse irregularities despite frequent intravenous doses of atropine.[2]

1. Cumming G, *et al.* Treatment and recovery after massive overdosage of physostigmine. *Lancet* 1968; **ii:** 147–9.
2. Valero A. Treatment of severe physostigmine poisoning. *Lancet* 1968; **ii:** 459–60.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Physostigmine is readily absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes. It is largely destroyed in the body by hydrolysis of the ester linkage by cholinesterases; a parenteral dose is claimed to be destroyed within 2 hours. It crosses the blood-brain barrier. Little is excreted in the urine.

◊ Small studies suggest marked interindividual differences in the absorption and metabolism of physostigmine salicylate after doses of up to 4 mg by mouth, perhaps because of saturable presystemic metabolism.[1-3] Oral bioavailability ranged from 5.2 to 11.7% in 3 of 5 subjects.[3]

In a study[4] of a single application of a physostigmine (base) transdermal system in 6 subjects, the mean absolute bioavailability was 36% (range 12.6 to 53.2%); the interindividual variability in absolute bioavailability was decreased by about 30% in comparison with an oral solution of physostigmine salicylate. There was continued absorption of physostigmine after removal of the transdermal system, indicating a drug reservoir in the skin.

In a study[5] of 9 patients with Alzheimer's disease, a mean elimination half-life for physostigmine of 16.4 minutes was reported with intravenous physostigmine salicylate. Cholinesterase inhibition was more prolonged than suggested by its elimination half-life.

1. Gibson M, *et al.* Physostigmine concentrations after oral doses. *Lancet* 1985; **i:** 695–6.
2. Sharpless NS, Thal LJ. Plasma physostigmine concentrations after oral administration. *Lancet* 1985; **i:** 1397–8.
3. Whelpton R, Hurst P. Bioavailability of oral physostigmine. *N Engl J Med* 1985; **313:** 1293–4.
4. Walker K, *et al.* Pharmacokinetics of physostigmine in man following a single application of a transdermal system. *Br J Clin Pharmacol* 1995; **39:** 59–63.
5. Asthana S, *et al.* Clinical pharmacokinetics of physostigmine in patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **58:** 299–309.

Uses and Administration

Physostigmine is a reversible tertiary amine inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632). Physostigmine has been used, alone or more usually with other miotics such as pilocarpine, to decrease intraocular pressure in glaucoma (p.1873). It is a more potent miotic than pilocarpine but is rarely tolerated for prolonged periods. When it is used in glaucoma physostigmine has usually been given as eye drops containing 0.25 or 0.5% of the salicylate or as an ophthalmic ointment containing 0.25% of the sulfate.

Physostigmine crosses the blood-brain barrier and has been used to reverse the central as well as the peripheral effects of agents with antimuscarinic actions after overdosage but such treatment is not usually recommended. Physostigmine is also under investigation in the management of Alzheimer's disease (see Dementia, below).

Antimuscarinic poisoning. As physostigmine penetrates the blood-brain barrier it has been used to reverse the central effects of poisoning with agents that have antimuscarinic actions including tricyclic antidepressants, antihistamines, some antiemetics, some antiparkinsonian drugs, and phenothiazines. However, reviewers agree that in general such use is inappropriate and hazardous. Physostigmine does not appear to affect the mortality rate in tricyclic antidepressant poisoning[1] and its use can lead to severe cardiac[2,3] and respiratory effects[2,3] and to convulsions.[3,4]

1. Aquilonius S-M, Hedstrand U. The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiol Scand* 1978; **22:** 40–5.
2. Caine ED. Anticholinergic toxicity. *N Engl J Med* 1979; **300:** 1278.
3. Newton RW. Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; **231:** 941–3.
4. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.

Baclofen overdosage. For references to the use of physostigmine in the treatment of baclofen overdosage, see p.1888.

Cerebellar ataxias. Double-blind controlled studies indicate that physostigmine[1,2] can produce symptomatic improvement in some patients with cerebellar ataxia including those with hereditary forms of spinocerebellar degeneration such as Friedreich's ataxia. However, another study did not show any significant improvement in patients given physostigmine for cerebellar ataxia.[3]

1. Rodriguez-Budelli MM, *et al.* Action of physostigmine on inherited ataxias. *Adv Neurol* 1978; **21:** 195–202.
2. Aschoff JC, *et al.* Physostigmin in der Behandlung von Kleinhirnataxien. *Nervenarzt* 1996; **67:** 311–18.
3. Wessel K, *et al.* Double-blind crossover study with physostigmine in patients with degenerative cerebellar diseases. *Arch Neurol* 1997; **54:** 397–400.

Dementia. Physostigmine has been studied in the symptomatic management of Alzheimer's disease (see Dementia, p.362). However, a systematic review concluded that the evidence of its effectiveness was limited and the benefits shown were not convincing.[1] Small early studies with oral physostigmine in Alzheimer's disease were inconclusive; a larger multicentre study[2] using controlled-release physostigmine found that it produced some improvement in cognitive and global function, but gastrointestinal adverse effects were common and led to a high drop-out rate.

1. Coelho Filho JM, Birks J. Physostigmine for dementia due to Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 17/03/06).
2. Thal LJ, *et al.* A 24-week randomized trial of controlled-release physostigmine in patients with Alzheimer's disease. *Neurology* 1999; **52:** 1146–52.

Preparations

USP 31: Physostigmine Salicylate Injection; Physostigmine Salicylate Ophthalmic Solution; Physostigmine Sulfate Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Austria: Anticholium; ***Cz.:*** Anticholium; ***Ger.:*** Anticholium; ***Gr.:*** Anticholium; ***USA:*** Antilirium.

Multi-ingredient: ***India:*** Bi-Miotic.

Pilocarpine *(BAN)*

Pilocarpina; Pilocarpinum; Pilokarpiini; Pilokarpin. (3*S*,4*R*)-3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]furan-2(3*H*)-one.

$C_{11}H_{16}N_2O_2$ = 208.3.
CAS — 92-13-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

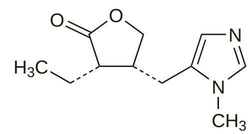

Description. An alkaloid obtained from the leaves of jaborandi, *Pilocarpus microphyllus* (Rutaceae) and other species of *Pilocarpus*.

Pharmacopoeias. In *US.*

USP 31 (Pilocarpine). A viscous, exceedingly hygroscopic, oily liquid or crystals. M.p. about 34°. Soluble in water, in alcohol, and in chloroform; sparingly soluble in ether and in benzene; practically insoluble in petroleum spirit. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Pilocarpine Borate

Pilocarpina, borato de.

$C_{11}H_{16}N_2O_2,xBH_3O_3$.
CAS — 16509-56-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

Pilocarpine Hydrochloride *(BANM)*

Pilocarp. Hydrochlor.; Pilocarpina, hidrocloruro de; Pilocarpine, chlorhydrate de; Pilocarpine Monohydrochloride; Pilocarpini Chloridum; Pilocarpini hydrochloridum; Pilocarpinium Chloratum; Pilokarpiinihydrokloridi; Pilokarpin Hidroklorür; Pilokarpin-hidroklorid; Pilokarpin-hydrochlorid; Pilokarpinhydroklorid; Pilokarpino hidrochloridas; Pilokarpiny chlorowodorek.

$C_{11}H_{16}N_2O_2,HCl$ = 244.7.
CAS — 54-71-7.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

NOTE. PIL is a code approved by the BP 2008 for use on single unit doses of eye drops containing pilocarpine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Pilocarpine Hydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. Very soluble in water and in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Pilocarpine Hydrochloride). Colourless, translucent, odourless, hygroscopic crystals. Soluble 1 in 0.3 of water, 1 in 3 of alcohol, and 1 in 360 of chloroform; insoluble in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. Pilocarpine hydrochloride oral solution, prepared from powder or eye drops and buffered at pH 5.5, was found[1] to be stable for 60 days at 25° and for 90 days at 4°.

1. Fawcett JP, *et al.* Formulation and stability of pilocarpine oral solution. *Int J Pharm Pract* 1994; **3:** 14–18.

Pilocarpine Nitrate *(BANM)*

Pilocarp. Nit.; Pilocarpina, nitrato de; Pilocarpine Mononitrate; Pilocarpine, nitrate de; Pilocarpini nitras; Pilocarpinii Nitras; Pilocarpinium Nitricum; Pilokarpiininitraatti; Pilokarpinnitrat; Pilokarpin-nitrát; Pilokarpino nitratas.

$C_{11}H_{16}N_2O_2,HNO_3$ = 271.3.
CAS — 148-72-1.
ATC — N07AX01; S01EB01.
ATC Vet — QN07AX01; QS01EB01.

NOTE. PIL is a code approved by the BP 2008 for use on single unit doses of eye drops containing pilocarpine nitrate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Pilocarpine Nitrate). Colourless crystals, or white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 31 (Pilocarpine Nitrate). Shining white crystals. Soluble 1 in 4 of water and 1 in 75 of alcohol; insoluble in chloroform and in ether. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Systemic effects and cautions are as for Neostigmine, p.631.

With the *oral* use of pilocarpine, sweating is a common problem; caution is needed to avoid dehydration in patients who may sweat excessively and who cannot maintain an adequate fluid intake. Paradoxical hypertension and constipation, confusion, and increased urinary frequency have also been reported. Licensed product information states that it should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision or dizziness may affect the performance of skilled tasks including driving. In addition pilocarpine should be given with care to those with cognitive or psychiatric disturbances, with renal calculi or renal impairment, or with biliary-tract disorders. Dosage should be reduced in patients with hepatic impairment (see Administration in Hepatic Impairment, below).

After *ocular* use pilocarpine is usually better tolerated than the anticholinesterases, but in common with other miotics may produce ciliary spasm, ocular pain and irritation, blurred vision, lachrymation, myopia, and browache. Conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block have been reported. Lens opacities have occurred after prolonged use. Treatment with miotics should be stopped if symptoms of systemic toxicity develop.

Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, acute uveitis, anterior uveitis, and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment of the eye. If possible, treatment with long-acting miotics should be stopped before surgery on the eye as there is an increased risk of hyphaema. Miotics should be used with extreme caution in patients with a history of retinal detachment and in young patients with myopia. Care is also needed in patients with corneal or conjunctival damage. Miosis may cause blurred vision and difficulty with dark adaptation and caution is necessary with night driving or when hazardous tasks are undertaken in poor illumination. Miotics should not be used by patients wearing soft contact lenses.

Asthma. A reminder that topical miotics can precipitate bronchospasm in susceptible patients.[1] However, the severity of the reaction induced by carbachol has been reported to be less than that produced by timolol. Bronchospastic complications are much less likely to occur with pilocarpine but have nevertheless been reported. As inhalations of methacholine are used to induce bronchospasm in the diagnosis of latent asthma, the risk of exacerbating asthma should be considered before methacholine is used in the eye.

1. Prakash UBS, *et al.* Pulmonary complications from ophthalmic preparations. *Mayo Clin Proc* 1990; **65:** 521–9.

Dementia. In patients with dementia of Alzheimer type, CNS symptoms may be induced or exacerbated by the use of pilocarpine eye drops.[1,2]

1. Reyes PF, *et al.* Mental status changes induced by eye drops in dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1987; **50:** 113–15.
2. Fraunfelder FT, Morgan R. The aggravation of dementia by pilocarpine. *JAMA* 1994; **271:** 1742–3.

Glaucoma. Miotics usually lower intra-ocular pressure by decreasing the resistance to outflow of aqueous humour from the anterior chamber through the trabecular network. However, they appear to reduce uveoscleral outflow and this may cause a paradoxical rise in intra-ocular pressure in patients with severely compromised trabecular outflow as was reported in a patient with post-traumatic angle-recession glaucoma.[1] It has been recommended that pilocarpine should be avoided after drainage operations for glaucoma because its miotic effect can increase the occurrence of posterior pupillary synechiae; a topical beta blocker is usually adequate if control of intra-ocular pressure is required.[2] Pilocarpine-induced miosis was shown to cause a significant deterioration in visual field in patients with chronic open-angle glaucoma.[3] It was suggested that this should be an important consideration when choosing therapy for glaucoma, particularly in cases where field loss approaches the permitted legal minimum for driving. Of 53 patients receiving long-term therapy with pilocarpine gel, 15 developed a corneal haze, which persisted for at least 2 years in 13; although the patients remained asymptomatic the long-term effects were unknown.[4] Many patients using the gel also developed superficial punctate keratitis which usually cleared spontaneously during treatment.

1. Bleiman BS, Schwartz AL. Paradoxical intraocular pressure response to pilocarpine: a proposed mechanism and treatment. *Arch Ophthalmol* 1979; **97:** 1305–6.
2. Phillips CI, *et al.* Posterior synechiae after glaucoma operations: aggravation by shallow anterior chamber and pilocarpine. *Br J Ophthalmol* 1987; **71:** 428–32.
3. Webster AR, *et al.* The effect of pilocarpine on the glaucomatous visual field. *Br J Ophthalmol* 1993; **77:** 721–5.
4. Johnson DH, *et al.* Corneal changes during pilocarpine gel therapy. *Am J Ophthalmol* 1986; **101:** 13–15.

Hypersensitivity. Contact urticaria involving the eyelids has been reported[1] in a patient after treatment with pilocarpine eye drops for glaucoma.

1. O'Donnell BF, Foulds IS. Contact allergic dermatitis and contact urticaria due to topical ophthalmic preparations. *Br J Ophthalmol* 1993; **77:** 740–1.

Retinal detachment. The use of miotics has been implicated in numerous reports as a cause of retinal detachment but reviews of the subject have concluded that there is little factual evidence to support the association.[1,2] However, there is circumstantial evidence that retinal detachment is more likely to occur with strong miotics. Furthermore, patients with myopia or pre-existing retinal damage appear to be at greater risk and there is the possibility that even low concentrations of relatively mild miotics such as 1% pilocarpine might precipitate retinal detachment.

1. Alpar JJ. Miotics and retinal detachment: a survey and case report. *Ann Ophthalmol* 1979; **11:** 395–401.
2. Beasley H, Fraunfelder FT. Retinal detachments and topical ocular miotics. *Ophthalmology* 1979; **86:** 95–8.

Systemic absorption. Systemic adverse effects after the ophthalmic use of pilocarpine are thought to be rare and reports of toxicity mainly involve elderly patients treated for acute angle-closure glaucoma prior to surgery and given relatively high doses.[1,2] It may not be feasible to stop the miotic in these circumstances. In a report of psychotic reaction in such a patient,[2] pilocarpine was continued but the patient was instructed on how to minimise absorption by closing the lachrymal canal; an atypical antipsychotic with minimal antimuscarinic effects (risperidone) was also given.

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Sirois FJ. Pilocarpine psychosis. *Psychosomatics* 2005; **46:** 88.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Mean elimination half-lives for pilocarpine have been reported to be 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of the hydrochloride, respectively. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. About 30% of an oral dose is excreted in the urine as pilocarpine and its inactive metabolites, including pilocarpic acid; the fate of the remaining 70% is unknown. Data from *animal* studies indicate that pilocarpine is distributed into breast milk at concentrations similar to those in the plasma.

Uses and Administration

Pilocarpine is a direct-acting tertiary amine parasympathomimetic that has the muscarinic effects of acetylcholine (p.1877). It is used mainly in the treatment of glaucoma (p.1873) and in the treatment of dry eye (p.2140) or dry mouth (below); it has also been used as a diaphoretic in diagnostic tests for cystic fibrosis and leprosy (below). Topical application of pilocarpine to the eye produces miosis (pupil constriction) by contraction of the iris sphincter muscle; contraction of the ciliary muscle results in increased accommodation. Constriction of the pupil also pulls open the trabecular meshwork in the eye and this in turn facilitates drainage of aqueous humour and reduction of intra-ocular pressure. After the use of eye drops, miosis occurs in about 10 to 30 minutes and lasts 4 to 8 hours while peak reduction in intra-ocular pressure occurs within 75 minutes and the reduction usually persists for 4 to 14 hours.

Pilocarpine is used in the treatment of open-angle **glaucoma** (but see also Glaucoma, under Adverse Effects, above) and is commonly given with topical beta blockers or sympathomimetics. It is used as the hydrochloride or the nitrate, usually as 0.5 to 4% eye drops given up to 4 times daily, adjusted according to response. Solutions containing 0.25 to 10% of the hydrochloride may also be available and the higher strengths may sometimes be required in patients with heavily pigmented irides. A modified-release system inserted into the conjunctival sac and releasing 20 or 40 micrograms of pilocarpine per hour for 7 days, and a 4% ophthalmic gel have also been used. Pilocarpine may be used before surgery as part of the emergency treatment of acute attacks of angle-closure glaucoma.

The miotic action of pilocarpine has been used to antagonise the effects of sympathomimetic mydriatics on the eye and in surgical procedures on the eye. Pilocarpine borate has been used similarly in ophthalmology to the hydrochloride and nitrate.

Pilocarpine hydrochloride is used in the treatment of **dry mouth** following radiotherapy for malignant neoplasms of the head and neck. It increases salivary flow only in patients with residual salivary gland function. The initial oral dose is 5 mg three times daily with or immediately after meals, increased gradually if necessary after 4 weeks until an adequate response is obtained, up to a maximum of 10 mg three times daily. Oral doses of 5 mg four times daily are used to treat **dry eye** or mouth in patients with Sjögren's syndrome; this dose may be increased to a maximum of 30 mg daily. Treatment should be stopped if no improvement occurs after 3 months of use. For doses in patients with hepatic impairment, see below.

Administration in hepatic impairment. UK licensed product information recommends that daily doses of *oral* pilocarpine should be reduced in patients with moderate to severe cirrhosis. The dose may gradually be increased to 5 mg three times daily if tolerated.

In the USA, licensed information suggests that the starting oral dose of pilocarpine should be 5 mg twice daily in patients with moderate hepatic impairment (Child-Pugh category B); it is not recommended in those with severe impairment (Child-Pugh category C) because of a lack of pharmacokinetic studies in these patients.

Diagnosis and testing. *CYSTIC FIBROSIS.* The fact that individuals with cystic fibrosis have abnormally high concentrations of sodium and chloride in their sweat has been used in the diagnosis of this condition and pilocarpine iontophoresis has been used to promote sweating as part of that test.[1] Despite the fact that neonatal genetic screening for cystic fibrosis-causing mutations is now possible, sweat testing using pilocarpine iontophoresis remains the gold standard for diagnosis, and can help avoid the small likelihood of diagnostic error.[2,3] US guidelines[3] note that sweat electrolytes may be transiently elevated during the first 24 hours of life, but sweat testing may be performed from 48 hours onward if an adequate sample can be obtained.

1. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics* 1959; **23:** 545–9.
2. Parad RB, *et al.* Sweat testing infants detected by cystic fibrosis newborn screening. *J Pediatr* 2005; **147** (suppl): S69–S72.
3. LeGrys VA, *et al.* Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. *J Pediatr* 2007; **151:** 85–9.

LEPROSY. The induction of sweat secretion by intradermal injection of pilocarpine nitrate has been used to assess the functional status of dermal nerves in patients with leprotic skin lesions.[1]

1. Joshi PB. Pilocarpine test in assesment of therapeutic efficacy in maculoanaesthetic leprosy. *Lepr India* 1976; **48:** 55–60.

Dry mouth. Pilocarpine is used as a sialogogue in the treatment of dry mouth (p.2140) after radiotherapy of the head and neck,[1,2] although benefit may not be entirely related to preservation of salivation.[3,4] A systematic review[5] based on 3 studies found limited evidence to support such use; although about half of the patients responded to pilocarpine, response did not occur in some for up to 12 weeks and adverse effects were common. Pilocarpine may also be of use in the management of drug-induced oral dryness,[6] and is used as a treatment for dry mouth and dry eye in the auto-immune disease, Sjögren's syndrome.[1,7-10]

1. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs* 1995; **49:** 143–55.
2. Taylor SE. Efficacy and economic evaluation of pilocarpine in treating radiation-induced xerostomia. *Expert Opin Pharmacother* 2003; **4:** 1489–97.
3. Gorsky M, *et al.* The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97:** 190–5.
4. Gornitsky M, *et al.* Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98:** 45–52.
5. Davies AN, Shorthose K. Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 10/06/08).

6. Götrick B, *et al.* Oral pilocarpine for treatment of opioid-induced oral dryness in healthy adults. *J Dent Res* 2004; **83:** 393–7.
7. Nelson JD, *et al.* Oral pilocarpine for symptomatic relief of keratoconjunctivitis sicca in patients with Sjögren's syndrome. *Adv Exp Med Biol* 1998; **438:** 979–83.
8. Vivino FB, *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. *Arch Intern Med* 1999; **159:** 174–81.
9. Tsifetaki N, *et al.* Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; **62:** 1204–7.
10. Baudouin C, *et al.* Traitements actuels de la xérophtalmie dans le syndrome de Gougerot-Sjögren. *Rev Med Interne* 2004; **25:** 376–82.

Reversal of mydriasis. Pilocarpine has been used to reverse the effects of mydriatics after surgery or ophthalmoscopic examination but other miotics may be preferred (see p.1874). It counteracts the mydriatic effects of sympathomimetics, such as phenylephrine and hydroxyamfetamine,[1] but is ineffective against mydriasis produced by antimuscarinics, such as homatropine,[1] and may impair vision further when used with tropicamide.[2] Furthermore, there is also the risk of pilocarpine precipitating angle-closure glaucoma in susceptible patients (see Glaucoma, under Precautions, above and also Glaucoma, in Tropicamide, p.1886).

1. Anastasi LM, *et al.* Effect of pilocarpine in counteracting mydriasis. *Arch Ophthalmol* 1968; **79:** 710–15.
2. Nelson ME, Orton HP. Counteracting the effects of mydriatics: does it benefit the patient? *Arch Ophthalmol* 1987; **105:** 486–9.

Preparations

BP 2008: Pilocarpine Hydrochloride Eye Drops; Pilocarpine Nitrate Eye Drops;
USP 31: Pilocarpine Hydrochloride Ophthalmic Solution; Pilocarpine Nitrate Ophthalmic Solution; Pilocarpine Ocular System.

Proprietary Preparations (details are given in Part 3)
Arg.: Alvis†; Gel Carpina†; Isopto Carpina; Klonocarpina†; Omaclopil; Pilocarpol; Pilomed; Sonadryl; Tensiocap; Wetol; Xao Pil; ***Austral.:*** Isopto Carpine; Pilopt; PV Carpine; ***Austria:*** Pilorcarpin Puroptal; Salagen; ***Belg.:*** Isopto Carpine; Pilo; Salagen; ***Braz.:*** Isopto Carpine; Pilocan; ***Canad.:*** Diocarpine†; Isopto Carpine; Miocarpine†; Pilopine HS; Salagen; ***Chile:*** Pilogel; ***Cz.:*** Pilogel; Pilopos; Pilotonina†; Salagen†; ***Fin.:*** Isopto Carpine; Salagen; ***Fr.:*** Pilo; Salagen; ***Ger.:*** Borocarpin-S; Pilo-Stulln†; Pilocarpol†; Pilomann; Pilomann-Ol; Pilopos; Salagen; Spersacarpin; ***Gr.:*** Cidren; Dispercarpine; Isopto Carpine; Pilocollyre; Pilofar; Pilotina†; Prothenol; Saglion; Salagen; Salivoral; Sumario; Xerocap; ***Hong Kong:*** Isopto Carpine†; Pilogel†; Salagen; Spersacarpine†; ***Hung.:*** Humacarpin; Pilogel†; Salagen; ***India:*** Carpo-Miotic; Locarp; Pilocar; ***Irl.:*** Isopto Carpine†; Pilogel; Salagen; ***Israel:*** Glaucocarpine; Mi-Pilo; Salagen; ***Ital.:*** Dropilton; Pilogel†; Pilotonina; Salagen; ***Malaysia:*** Isopto Carpine; Pilo†; Spersacarpine†; ***Mex.:*** Caliprene; Pil; Pilo; ***Neth.:*** Isopto Carpine†; Pilogel; Salagen; ***Norw.:*** Isopto Carpine; Pilo†; ***NZ:*** Isopto Carpine†; Ocusert; Pilopt; ***Philipp.:*** Isopto Carpine; ***Port.:*** Pilocarcil; Piloplex†; Salagen; ***Rus.:*** Oftan Pilocarpin (Офтан Пилокарпин); ***S.Afr.:*** Isopto Carpine; Pilogel; ***Singapore:*** Isopto Carpine; Pilogel; ***Spain:*** Isopto Carpina; Salagen; ***Swed.:*** Salagen; ***Switz.:*** Salagen; Spersacarpine; ***Thai.:*** Isopto Carpine; Salagen; ***Turk.:*** Pilogel; Pilokarsol; Pilosed; ***UK:*** Pilogel; Salagen; ***USA:*** Adsorbocarpine; Akarpine; Isopto Carpine; Ocu-Carpine; Ocusert†; Pilocar; Pilopine HS; Piloptic; Pilopto-Carpine; Pilostat; Salagen; ***Venez.:*** Isopto Carpina†; Pilocar.

Multi-ingredient: ***Arg.:*** Amplus; Glaucocin†; Glaucotensil; Ofal P†; Pilotim; Timpilo†; ***Austral.:*** Timpilo; ***Austria:*** Betacarpin; Fotil; Normastigmin mit Pilocarpin; Pilostigmin Puroptal; Thiloadren; Timpilo; ***Belg.:*** Carteopil; Normoglaucon; ***Canad.:*** Timpilo†; ***Cz.:*** Fotil; Glauko Biciron†; Ipecarin†; Timpilo†; ***Denm.:*** Fotil; Timpilo†; ***Fin.:*** Fotil; Timpilo†; ***Fr.:*** Carpilo; Pilobloq; Timpilo†; ***Ger.:*** Fotil; Glauko Biciron; Normoglaucon; Syncarpin-N†; Thiloadren N; Timpilo†; TP-Ophtal; ***Gr.:*** Dropiltim; Fotil†; Ripix†; Ryvina†; T+P; Thilocombin†; Timpilo; Yvano; ***Hong Kong:*** Timpilo; ***Hung.:*** Fotil; ***India:*** Bi-Miotic; ***Israel:*** Timpilo; ***Ital.:*** Equiton; Mios; Pilobloc; Pilodren†; Ripix; Timicon; ***Malaysia:*** Normoglaucon†; Timpilo†; ***Neth.:*** Fotil; Normoglaucon; ***Norw.:*** Fotil; Timpilo†; ***NZ:*** Timpilo; ***Philipp.:*** Fotil; ***Pol.:*** Fotil; Normoglaucon; ***Port.:*** Fotil; Normoglaucon; Timoglau Plus; ***Rus.:*** Fotil (Фотил); ***Singapore:*** Normoglaucon†; Timpilo†; ***Swed.:*** Fotil; Timpilo†; ***Switz.:*** Arteopilo; Fotil†; Ripix; Timpilo†; ***Thai.:*** Fotil†; Normoglaucon†; ***USA:*** E-Pilo†; PE†.

Travoprost *(BAN, USAN, rINN)*

AL-6221; Travoprosti; Travoprostum. Isopropyl (*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-{(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl}cyclopentyl)-5-heptenoate.

Травопрост

$C_{26}H_{35}F_3O_6$ = 500.5.
CAS — 157283-68-6.
ATC — S01EE04.
ATC Vet — QS01EE04.

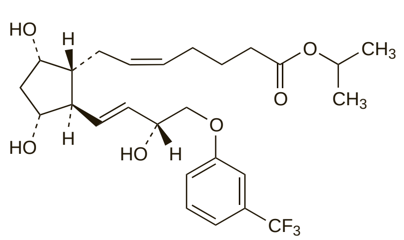

Adverse Effects and Precautions

As for Latanoprost, p.1882.

Effects on the eyes. Severe iritis and corneal oedema developed in an elderly woman 3 weeks after restarting travoprost after eye surgery;[1] rechallenge was positive. The authors commented that the UK MHRA was aware of one other case of uveitis associated with travoprost.

1. Kumarasamy M, Desai SP. Anterior uveitis is associated with travoprost. *BMJ* 2004; **329:** 205.

Uses and Administration

Travoprost is a synthetic analogue of dinoprost (prostaglandin F_2). It is used in the treatment of open-angle glaucoma and ocular hypertension (p.1873), as a 0.004% ophthalmic solution once daily, preferably in the evening. The reduction in pressure starts about 2 hours after instillation and is maximal after 12 hours; the effect is maintained for at least 24 hours.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Arvo; Glaucoprost; Travatan; ***Austral.:*** Travatan; ***Austria:*** Travatan; ***Belg.:*** Travatan; ***Braz.:*** Travatan; ***Canad.:*** Travatan; ***Chile:*** Travatan; ***Cz.:*** Travatan; ***Denm.:*** Travatan; ***Fin.:*** Travatan; ***Fr.:*** Travatan; ***Ger.:*** Travatan; ***Gr.:*** Travatan; ***Hong Kong:*** Travatan; ***Hung.:*** Travatan; ***Indon.:*** Travatan; ***Irl.:*** Travatan; ***Israel:*** Travatan; ***Ital.:*** Travatan; ***Malaysia:*** Travatan; ***Mex.:*** Travatan; ***Neth.:*** Travatan; ***Norw.:*** Travatan; ***NZ:*** Travatan; ***Philipp.:*** Travatan; ***Pol.:*** Travatan; ***Port.:*** Travatan; ***Rus.:*** Travatan (Траватан); ***S.Afr.:*** Travatan; ***Singapore:*** Travatan; ***Spain:*** Travatan; ***Swed.:*** Travatan; ***Switz.:*** Travatan; ***Thai.:*** Travatan; ***Turk.:*** Travatan; ***UK:*** Travatan; ***USA:*** Travatan; ***Venez.:*** Travatan.

Multi-ingredient: ***Cz.:*** DuoTrav; ***Gr.:*** DuoTrav; ***Hung.:*** DuoTrav; ***NZ:*** DuoTrav; ***Pol.:*** DuoTrav; ***Port.:*** DuoTrav; ***UK:*** DuoTrav.

Tropicamide *(BAN, USAN, rINN)*

Bistropamide; Ro-1-7683; Tropicamida; Tropicamidum; Tropikamid; Tropikamidas; Tropikamidi. *N*-Ethyl-*N*-(4-pyridylmethyl)tropamide; (2*RS*)-*N*-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide.

Тропикамид

$C_{17}H_{20}N_2O_2$ = 284.4.
CAS — 1508-75-4.
ATC — S01FA06.
ATC Vet — QS01FA06.

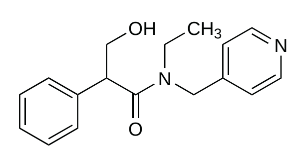

NOTE. TRO is a code approved by the BP 2008 for use on single unit doses of eye drops containing tropicamide where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Tropicamide). A white or almost white, crystalline powder. M.p. 95° to 98°. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Tropicamide). A white or practically white crystalline powder, odourless or having not more than a slight odour. M.p. 96° to 100°. Slightly soluble in water; freely soluble in chloroform and in solutions of strong acids. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

◊ References.

1. Vuori M-L, *et al.* Systemic absorption and anticholinergic activity of topically applied tropicamide. *J Ocul Pharmacol* 1994; **10:** 431–7.

Glaucoma. The use of mydriatics is considered liable to provoke an acute attack in patients with glaucoma or a tendency to glaucoma; licensed product information generally contra-indicates their use in such patients. However, a systematic review concluded that in fact a history of open-angle glaucoma did not predispose to acute angle closure under mydriasis, and that mydriasis with tropicamide in particular appeared to be safe and should be recommended in all patients when thorough retinal examination was indicated.[1] In contrast, the use of pilocarpine to reverse mydriatics was potentially harmful.

1. Pandit RJ, Taylor R. Mydriasis and glaucoma: exploding the myth. A systematic review. *Diabet Med* 2000; **17:** 693–9.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Tropicamide is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1219). It is used as eye drops to produce mydriasis and cycloplegia (p.1874). It has a more rapid onset and a shorter duration of effect than atropine: mydriasis is produced within 20 to 40 minutes of use and usually lasts for about 6 hours; cycloplegia is maximal within about 30 minutes and is short-lasting, with complete recovery of accommodation normally within 6 hours. Tropicamide has been reported to be inadequate for cycloplegia in children.

To produce **mydriasis**, a 0.5% solution is instilled 15 to 20 minutes before examination of the eye. To produce **cycloplegia** a 1% solution is used and repeated after 5 minutes; a further instillation may be necessary to prolong the effect after 20 to 30 minutes.

Dementia. Tropicamide has been studied for use in the differential diagnosis of Alzheimer's disease (see Dementia, p.362). Excessive pupil dilatation in response to tropicamide eye drops occurred in patients with signs and symptoms of Alzheimer's disease.[1] However, a double-blind placebo-controlled study[2] in similar patients and healthy subjects indicated that this was not a reliable diagnostic test for Alzheimer's disease.

1. Gómez-Tortosa E, *et al.* Pupil response to tropicamide in Alzheimer's disease and other neurodegenerative disorders. *Acta Neurol Scand* 1996; **94:** 104–9.
2. Graff-Radford NR, *et al.* Tropicamide eyedrops cannot be used for reliable diagnosis of Alzheimer's disease. *Mayo Clin Proc* 1997; **72:** 495–504.

Preparations

BP 2008: Tropicamide Eye Drops;
USP 31: Tropicamide Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Midriaticum†; Mydril; ***Austral.:*** Mydriacyl; ***Austria:*** Mydral; Mydriaticum; ***Belg.:*** Mydriacyl; Tropicol; ***Braz.:*** Ciclomidrin; Mydriacyl; Tropinom; ***Canad.:*** Diotrope†; Mydriacyl; ***Chile:*** Mydriacyl; ***Cz.:*** Mydriacyl†; Mydrum; ***Denm.:*** Mydriacyl; ***Fr.:*** Mydriaticum; ***Ger.:*** Mydriaticum; Mydrum; ***Gr.:*** Tropixal; ***Hong Kong:*** Mydriacyl; Mydriaticum†; ***Hung.:*** Mydrum; ***India:*** Tmide; Tropico; ***Indon.:*** Midric; ***Irl.:*** Mydriacil; ***Israel:*** Mydramide; ***Ital.:*** Tropimil; Visumidriatic; ***Malaysia:*** Mydriacyl; ***Mex.:*** Myriacyl; ***Norw.:*** Mydrian†; ***NZ:*** Mydriacyl; ***Philipp.:*** Mydriacyl; ***Port.:*** Tropicil Top; ***Rus.:*** Mydriacyl (Мидриацил); Mydrum (Мидрум); ***S.Afr.:*** Mydriacyl; Mydriaticum; ***Singapore:*** Mydriacyl; ***Swed.:*** Mydriacyl; ***Switz.:*** Mydriaticum; ***Thai.:*** Mydriacyl; ***Turk.:*** Tropamid; ***UK:*** Mydriacyl; ***USA:*** Mydral; Mydriacyl; Ocu-Tropic; Opticyl; Tropicacyl; ***Venez.:*** Mydriacyl; Mydrox†.

Multi-ingredient: ***Arg.:*** Fotorretin; Sensu; Tropioftal F; ***Canad.:*** Diophenyl-T†; ***Fr.:*** Mydriasert; ***Hong Kong:*** Mydrin-P; ***India:*** Itrop Plus; Tropico Plus; ***Ital.:*** Visumidriatic Fenilefrina; ***Philipp.:*** Sanmyd-P; ***Port.:*** Mydriasert; ***USA:*** Paremyd; ***Venez.:*** Dyfrin†; Fotorretin.

Unoprostone Isopropyl *(rINNM)*

Isopropyl Lunoprostone; Isopropyl Unoprostone; UF-021; Unoprostona de isopropilo; Unoprostone, Isopropyle d'; Unoprostoni Isopropylas. Isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate.

Унопростона Изопропил

$C_{25}H_{44}O_5$ = 424.6.
CAS — 120373-36-6 (unoprostone); 120373-24-2 (unoprostone isopropyl).
ATC — S01EE02.
ATC Vet — QS01EE02.

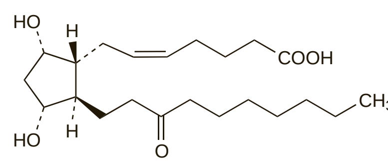

(unoprostone)

Profile

Unoprostone, like latanoprost (p.1882), is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as the isopropyl ester for the treatment of glaucoma and ocular hypertension (p.1873). An ophthalmic solution containing unoprostone isopropyl 0.12 or 0.15% is instilled twice daily.

◊ References.

1. Yamamoto T, *et al.* Clinical evaluation of UF-021 (Rescula; isopropyl unoprostone). *Surv Ophthalmol* 1997; **41** (suppl 2): S99–S103.
2. Eisenberg DL, Camras CB. A preliminary risk-benefit assessment of latanoprost and unoprostone in open-angle glaucoma and ocular hypertension. *Drug Safety* 1999; **20:** 505–14.
3. de Arruda Mello PA, *et al.* Safety of unoprostone isopropyl as mono- or adjunctive therapy in patients with primary open-angle glaucoma or ocular hypertension. *Drug Safety* 2002; **25:** 583–97.
4. Chiba T, *et al.* Comparison of iridial pigmentation between latanoprost and isopropyl unoprostone: a long term prospective comparative study. *Br J Ophthalmol* 2003; **87:** 956–9.
5. Stewart WC, *et al.* The safety and efficacy of unoprostone 0.15% versus brimonidine 0.2%. *Acta Ophthalmol Scand* 2004; **82:** 161–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rescula; ***Austria:*** Rescula; ***Braz.:*** Rescula; ***Chile:*** Rescula; ***Cz.:*** Rescula; ***Hung.:*** Rescula; ***Jpn:*** Rescula; ***Mex.:*** Rescula; ***Neth.:*** Rescula; ***Philipp.:*** Rescula; ***Singapore:*** Rescula†; ***Switz.:*** Rescula†; ***Thai.:*** Rescula; ***USA:*** Rescula†; ***Venez.:*** Rescula.

Muscle Relaxants

The muscle relaxants included in this chapter are used in the management of musculoskeletal and neuromuscular disorders. There are 2 main types:

- **centrally acting relaxants**—these generally have a selective action on the CNS and are principally used for relieving painful muscle spasms or spasticity occurring in musculoskeletal and neuromuscular disorders. Their mechanism of action may be due to their CNS-depressant activity. Baclofen and tizanidine are two examples.
- **directly acting relaxants**—dantrolene is a drug that has a direct action on skeletal muscle and is used for the relief of spasticity associated with a variety of conditions.

Also included in this chapter are **botulinum toxins A and B**, which inhibit the release of acetylcholine at the motor nerve terminals.

Some benzodiazepines are also used in the treatment of muscle spasms; further details may be found under Diazepam, p.986.

Other drugs that block transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia are discussed in the chapter on Neuromuscular Blockers, p.1900.

Drugs used to relax *smooth muscle* include the various antispasmodics (p.1692) used for their antimuscarinic or direct smooth-muscle relaxant effects in the management of gastrointestinal disorders, as well as some other drugs such as papaverine (p.2191).

Muscle spasm

Spasm is a painful involuntary contraction of muscle that can cause involuntary movement, interfere with function, and cause distortion. It is a symptom of many muscular and other types of disorders and treatment should primarily be aimed at the underlying cause. Centrally acting muscle relaxants and benzodiazepines are used to treat muscle spasms such as *splinting* that occur in response to local trauma or musculoskeletal and joint disorders. Splinting is a reflex muscular spasm that produces muscular rigidity and acts as a protective mechanism to prevent movement and further damage of the affected part. Short courses of muscle relaxants may be considered in the management of acute low back pain (p.7).

Cramps are muscle spasms of abrupt onset that occur at rest and usually last for a few seconds or minutes. They are often precipitated by dehydration and hyponatraemia produced by vigorous exercise, excessive sweating, diarrhoea, and vomiting, or may be associated with drug therapy or haemodialysis (see Haemodialysis-induced Cramp, p.1671). Pregnant women, the elderly, and those with peripheral vascular disease, appear to be particularly susceptible to night cramps of the feet or legs, the cause of which is not well understood.

The management of muscle cramps has been reviewed.[1,2] Quinine has traditionally been used for *nocturnal cramps* but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. Meta-analyses[3,4] have indicated that although quinine was modestly effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind; patients should be closely monitored over a period of at least 4 weeks while the efficacy of quinine was assessed. In the UK, it is recommended that treatment should be stopped every 3 months to see whether it is still needed.[5] In the USA, the FDA has ruled that quinine products should no longer be used for the management of nocturnal cramps.[6,7] There is little convincing evidence to support the use of other drugs.[1,2,6]

A systematic review[8] concluded that magnesium (as the lactate and citrate) is modestly effective in the treatment of *leg cramps in pregnancy*; calcium salts were ineffective, and although early evidence suggested benefit with sodium chloride, high doses were required with their attendant cardiovascular risks.

1. McGee SR. Muscle cramps. *Arch Intern Med* 1990; **150:** 511–18.
2. Butler JV, *et al.* Nocturnal leg cramps in older people. *Postgrad Med J* 2002; **78:** 596–8.
3. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
4. Man-Son-Hing M, *et al.* Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
5. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
6. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
7. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
8. Young GL, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/06/05).

Spasticity

The term spasticity has been loosely applied to various disorders of motor control resulting from CNS disease and marked by effects such as increased muscle tone, exaggerated stretch reflexes, impaired voluntary movement, weakness, loss of dexterity, abnormal posture, and often disturbed gait. In some patients muscle spasm and pain may be more distressing than impaired movement. Other complications may include contractures, pressure sores, and infection. Spasticity is a feature of neurological conditions such as multiple sclerosis, cerebral palsy, head injury, and stroke, particularly if there are spinal lesions.

Spasticity is disabling and difficult to treat when severe, but mild or moderate forms may be effectively managed by conservative treatment. Some patients may even use spasticity to provide a means of posture control and care should be taken that treatment does not lead to increased disability.

Various discussions on the management of spasticity have been published.[1-10] The mainstay of management is physiotherapy with antispastic drugs, although the evidence for the latter is rather scanty.[9,11,12] Baclofen, dantrolene, diazepam, and tizanidine are the drugs most often used. These 4 drugs act via different mechanisms, which are not fully understood.

Baclofen is thought to act at the spinal cord level but may also have supraspinal sites of action. It is a powerful neuronal depressant and may exert its inhibitory effects by acting as an agonist at GABA (gamma aminobutyric acid) receptors. *Diazepam* is also thought to act centrally by enhancing the response to GABA. In contrast, *dantrolene* acts directly on muscles, possibly by interfering with the release of calcium from muscular sarcoplasmic reticulum needed for contraction. *Tizanidine* is a centrally acting relaxant and α-adrenergic agonist; it is thought to act at spinal and supraspinal levels by inhibiting the presynaptic activity of excitatory interneurones.[7] It can produce additive effects with baclofen, allowing a reduction in the dosage of both drugs; use with benzodiazepines is not recommended because of the potential for interactions. All these are usually given by mouth but baclofen may also be given intrathecally in severe chronic spasticity.[10,13,14] Injection directly into the spinal subarachnoid space allows immediate delivery to the site of action in the spinal cord and the use of considerably lower doses than those given orally. It has been reported[15] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing, and that others have been able to reduce the dosage required.

Other drugs that may produce some benefit or are being studied in spasticity include *other benzodiazepines, clonidine, gabapentin,* and *memantine*.

Alternative approaches to treatment include nerve blocks using *local anaesthetics*; they should generally only be used when further muscle relaxation would not increase disability. *Chemical neurolysis* using alcohol or phenol is only considered when there is intractable continuous pain. Local injections of *botulinum A toxin* have produced some encouraging results in the management of limb spasticity in post-stroke or spinal injury patients and in children with cerebral palsy;[16-18] its temporary effect may be an advantage over chemical neurolysis but the need for regular injections may limit acceptability in children.[16] Systematic reviews[19,20] have found insufficient evidence to support or refute such use in children with cerebral palsy.

Nondrug treatments have included electrical stimulation techniques such as transcutaneous nerve stimulation and dorsal column stimulation; vibration applied to agonist spastic muscles to improve voluntary movement; cooling to decrease afferent inputs from peripheral receptors; and orthopaedic surgery or neurosurgery.

1. Young RR. Spasticity: a review. *Neurology* 1994; **44** (suppl 9): S12–S20.
2. Ko CK, Ward AB. Management of spasticity. *Br J Hosp Med* 1997; **58:** 400–5.
3. Kita M, Goodkin DE. Drugs used to treat spasticity. *Drugs* 2000; **59:** 487–95.
4. Anonymous. The management of spasticity. *Drug Ther Bull* 2000; **38:** 44–6.
5. Bhakta BB. Management of spasticity in stroke. *Br Med Bull* 2000; **56:** 476–85.
6. Burchiel KJ, Hsu FPK. Pain and spasticity after spinal cord injury: mechanisms and treatment. *Spine* 2001; **26** (suppl): S146–S160.
7. Ward AB. A summary of spasticity management – a treatment algorithm. *Eur J Neurol* 2002; **9** (suppl 1): 48–52.
8. Abbruzzese G. The medical management of spasticity. *Eur J Neurol* 2002; **9** (suppl 1): 30–4.
9. Montané E, *et al.* Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. *Neurology* 2004; **63:** 1357–63.
10. Verrotti A, *et al.* Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol* 2006; **34:** 1–6.
11. Taricco M, *et al.* Pharmacological interventions for spasticity following spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/06/05).
12. Shakespeare DT, *et al.* Anti-spasticity agents for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 16/06/05).
13. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
14. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
15. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.
16. Neville B. Botulinum toxin in the cerebral palsies. *BMJ* 1994; **309:** 1526–7.
17. Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. *Phys Med Rehabil Clin N Am* 2003; **14:** 901–10.
18. Preiss RA, *et al.* The effects of botulinum toxin (BTX-A) on spasticity of the lower limb and on gait in cerebral palsy. *J Bone Joint Surg Br* 2003; **85:** 943–8.
19. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
20. Wasiak J, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 07/05/08).

Afloqualone *(rINN)*

Aflocualona; Afloqualonum; HQ-495. 6-Amino-2-fluoromethyl-3-*o*-tolylquinazolin-4(3*H*)-one.

Афлоквалон

$C_{16}H_{14}FN_3O = 283.3.$

CAS — 56287-74-2.

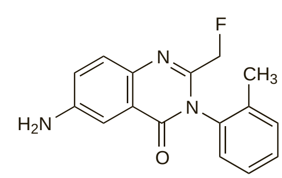

Pharmacopoeias. In *Jpn.*

Profile

Afloqualone is a centrally acting skeletal muscle relaxant that has been given orally for the treatment of muscle spasm associated with musculoskeletal conditions. Photosensitivity reactions have been reported.

◊ References.

1. Ishikawa T, *et al.* Photoleukomelanodermatitis (Kobori) induced by afloqualone. *J Dermatol* 1994; **21:** 430–3.

Baclofen *(BAN, USAN, rINN)*

Aminomethyl Chlorohydrocinnamic Acid; Ba-34647; Baclofène; Baclofeno; Baclofenum; Baklofeeni; Baklofén; Baklofen; Baklofenas. β-Aminomethyl-*p*-chlorohydrocinnamic acid; (*RS*)-Amino-3-(4-chlorophenyl)butyric acid.

Баклофен

$C_{10}H_{12}ClNO_2$ = 213.7.

CAS — 1134-47-0.

ATC — M03BX01.

ATC Vet — QM03BX01.

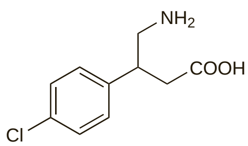

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Baclofen). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 31 (Baclofen). A white to off-white, odourless or practically odourless, crystalline powder. Slightly soluble in water; very slightly soluble in methyl alcohol; insoluble in chloroform. Store in airtight containers.

Adverse Effects

Adverse effects associated with baclofen are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

The most common adverse effects include drowsiness, nausea, dizziness, lassitude, lightheadedness, confusion, fatigue, muscular pain and weakness, and hypotension. Other adverse effects include euphoria, hallucinations, depression, headache, tinnitus, convulsions, paraesthesias, slurred speech, dry mouth, taste alterations, vomiting, diarrhoea or constipation, ataxia, nystagmus, tremors, insomnia, visual disturbances, skin rashes, pruritus, increased sweating, urinary disturbances, respiratory or cardiovascular depression, blood sugar changes, alterations in liver function values, and a paradoxical increase in spasticity. Problems with erection and ejaculation have also been reported with intrathecal baclofen; these are usually reversible on withdrawal of therapy.

Overdosage may lead to muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma, and convulsions (see also below).

Stopping baclofen abruptly may result in a withdrawal syndrome (see under Precautions, below).

Effects on the nervous system. Epilepsy, progressing to status epilepticus, has been associated with the use of baclofen in a patient who had had no history of seizures.[1] Baclofen had been given in a dose of 80 mg daily and symptoms had resolved after gradual withdrawal and the use of antiepileptics.

1. Rush JM, Gibberd FB. Baclofen-induced epilepsy. *J R Soc Med* 1990; **83:** 115–16.

Treatment of Adverse Effects

Treatment of baclofen overdosage is symptomatic. Consideration should be given to the use of activated charcoal in adults who have ingested more than 100 mg, and children who have taken more than 5 mg/kg, within an hour of presentation. Alternatively, gastric lavage may be considered in adults within an hour of ingesting a life-threatening overdose. Haemodialysis should be considered in severe cases. Observation should continue for at least 6 hours after ingestion. For the use of physostigmine salicylate in the treatment of intrathecal baclofen overdosage, see below.

Overdosage. Atropine sulfate 600 micrograms intravenously[1] was used to treat a patient who had ingested 420 mg of baclofen and had failed to improve after gastric lavage and induced diuresis. Bradycardia, hypotension, hypothermia, and respiratory depression all improved and no further treatment was needed. The clinical course and management of acute intoxication in 8 adolescents, who ingested estimated amounts of baclofen ranging from 60 to more than 600 mg, has also been described.[2]

Accidental *intrathecal* overdosage has caused respiratory depression, decreased alertness, coma, muscle weakness, and vomiting.[3] Mild intrathecal bolus overdoses of baclofen in patients without cardiac compromise have been treated using physostigmine although the use of physostigmine in poisoning is now generally considered hazardous (see Antimuscarinic Poisoning, p.1884). Physostigmine salicylate was given intravenously in a dose of 1 to 2 mg over 5 minutes and repeated if necessary at intervals of 30 to 60 minutes.[3,4] Physostigmine was ineffective in a patient who accidentally received 10 mg of baclofen intrathecally;[5] in such severe overdosage, respiratory support and time to recover is needed.[4] A lumbar tap to remove about 30 to 50 mL of CSF may help to reduce the intrathecal concentration of baclofen if implemented soon after the overdose.

1. Ferner RE. Atropine treatment for baclofen overdose. *Postgrad Med J* 1981; **57:** 580–1.
2. Perry HE, *et al.* Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* 1998; **101:** 1045–8.
3. Müller-Schwefe G, Penn RD. Physostigmine in the treatment of intrathecal baclofen overdose. *J Neurosurg* 1989; **71:** 273–5.
4. Penn RD, Kroin JS. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533–4.
5. Saltuari L, *et al.* Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533.

Precautions

Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulcer and avoided in those with active peptic ulcer disease. It should also be used with caution in patients with severe psychiatric disorders or epilepsy or convulsive disorders since these disorders may be exacerbated by baclofen. Liver function should be monitored in patients with liver disease; patients with renal impairment need a reduced dose. Baclofen should be used with caution in patients with respiratory impairment. Observations of increased blood sugar concentrations suggest caution in patients with diabetes mellitus. Care is also required in the elderly, in whom adverse effects may be more common, and in patients with cerebrovascular disease (who tolerate baclofen poorly). It should be used with caution in patients who use their spasticity to maintain posture or to increase function. Urine retention may be exacerbated in patients with hypertonic bladder sphincters. Baclofen may cause drowsiness; patients affected should not drive or operate machinery.

Abrupt withdrawal of baclofen may result in a withdrawal syndrome and exacerbation of spasticity; dosage should be reduced gradually over at least 1 to 2 weeks, or longer if symptoms occur.

Anaesthesia. Acute bradycardia and hypotension occurred after rib retraction in 3 patients given baclofen 30 mg orally 90 minutes before thoracic surgery under general anaesthesia, but not in a further 3 patients given placebo.[1] Giving atropine and ephedrine relieved bradycardia and hypotension in 2 patients, but a brief cardiac arrest occurred in 1. Baclofen may disturb autonomic control of the circulation during general anaesthesia and surgery.

1. Sill JC, *et al*. Bradycardia and hypotension associated with baclofen used during general anaesthesia. *Anesthesiology* 1986; **64:** 255–8.

Breast feeding. The concentrations of baclofen found in breast milk are small[1] and UK licensed product information states that no undesirable effects are to be expected in breast-fed infants. The American Academy of Pediatrics also considers that baclofen is usually compatible with breast feeding; no adverse effects have been seen in breast-feeding infants whose mothers were receiving baclofen.[2]

1. Eriksson G, Swahn C-G. Concentrations of baclofen in serum and breast milk from a lactating woman. *Scand J Clin Lab Invest* 1981; **41:** 185–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/06/04)

Peptic ulcer. Results of a study of baclofen-stimulated gastric acid secretion in 10 healthy subjects given 600 micrograms/kg intravenously suggested that patients on baclofen might be at risk from baclofen-induced hyperacidity.[1]

1. Pugh S, *et al*. Clinical and experimental significance of the newly discovered activity of baclofen (PCP-GABA) as a stimulant of gastric acid secretion. *Gut* 1985; **26:** A545.

Porphyria. Baclofen is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy and the neonate. Two successful pregnancies have been reported[1] in a woman receiving intrathecal baclofen; there was no evidence of teratogenicity, and neurodevelopmental outcome in the children seemed normal. However, convulsions were seen in a week-old infant whose mother had taken oral baclofen during pregnancy.[2] The convulsions, which were refractory to antiepileptics, lidocaine, and pyridoxine, ceased within 30 minutes of giving baclofen to the infant.

1. Calderón Muñoz F, *et al.* Pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. *Ann Pharmacother* 2000; **34:** 956.
2. Ratnayaka BDM, *et al.* Neonatal convulsions after withdrawal of baclofen. *BMJ* 2001; **323:** 85.

Renal impairment. Reports of baclofen toxicity in patients with severe renal impairment.[1] Most patients had received 15 mg or more of baclofen daily although one patient who had received the manufacturer's suggested dose of 5 mg daily still developed toxic symptoms after only 4 days of treatment.

1. Chen K-S, *et al*. Baclofen toxicity in patients with severely impaired renal function. *Ann Pharmacother* 1997; **31:** 1315–20.

Respiratory disorders. Baclofen might precipitate bronchoconstriction in susceptible individuals. A patient with asthma developed symptomatic bronchoconstriction after taking baclofen on two separate occasions.[1] Another patient who had a history of exercise-induced dyspnoea and wheezing was found to have bronchial hyperresponsiveness to methacholine only after taking baclofen.

1. Dicpinigaitis PV, *et al.* Baclofen-induced bronchoconstriction. *Ann Pharmacother* 1993; **27:** 883–4.

Withdrawal. Psychiatric reactions including hallucinations, paranoia, delusions, psychosis, anxiety, confusion, and agitation have been reported[1-4] on abrupt withdrawal of oral baclofen; symptoms generally resolved on restarting. Convulsions have also been reported.[5] The abrupt withdrawal of intrathecal baclofen may also result in high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity which in rare cases has advanced to rhabdomyolysis, multiple organ failure, and death.[6-8]

Except for serious adverse reactions, the dose of oral baclofen should be gradually reduced: the UK CSM recommends reduction over at least 1 to 2 weeks or longer if symptoms occur. Similarly, the FDA has advised against the abrupt withdrawal of intrathecal baclofen.[8]

1. Lees AJ, *et al*. Hallucinations after withdrawal of baclofen. *Lancet* 1977; **i:** 858.
2. Stein R. Hallucinations after sudden withdrawal of baclofen. *Lancet* 1977; **ii:** 44–5.
3. Harrison SA, Wood CA. Hallucinations after preoperative baclofen discontinuation in spinal cord injury patients. *Drug Intell Clin Pharm* 1985; **19:** 747–9.
4. Committee on Safety of Medicines/Medicines Control Agency. Severe withdrawal reactions with baclofen. *Current Problems* 1997; **23:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Barker I, Grant IS. Convulsions after abrupt withdrawal of baclofen. *Lancet* 1982; **ii:** 556–7.
6. Grenier B, *et al.* Hyperthermie grave liée à un sevrage brutal de baclofène administré de façon continue par voie intrathécale. *Ann Fr Anesth Reanim* 1996; **15:** 659–62.
7. Green LB, Nelson VS. Death after acute withdrawal of intrathecal baclofen: case report and literature review. *Arch Phys Med Rehabil* 1999; **80:** 1600–4.
8. Coffey RJ [Medtronic]. Important drug warning (issued April 2002). Available at: http://www.fda.gov/medwatch/SAFETY/2002/baclofen.pdf (accessed 23/06/04)

Interactions

Alcohol and other CNS depressants may exacerbate the CNS effects of baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium. There may be increased weakness if baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy. Ibuprofen (see below) and other drugs that produce renal insufficiency may reduce baclofen excretion leading to toxicity.

Dopaminergics. For reports of patients with Parkinson's disease taking *levodopa* who have had adverse effects when given baclofen, see under Levodopa, on p.808.

NSAIDs. There has been a report of an elderly patient who developed baclofen toxicity after *ibuprofen* therapy was also started.[1] It appeared that acute renal insufficiency caused by ibuprofen had impaired baclofen excretion.

1. Dahlin PA, George J. Baclofen toxicity associated with declining renal clearance after ibuprofen. *Drug Intell Clin Pharm* 1984; **18:** 805–8.

Pharmacokinetics

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract after an oral dose. Peak plasma concentrations occur about 0.5 to 3 hours after ingestion, but the rate and extent of absorption vary between patients, and may vary inversely with the dose. After oral doses some baclofen crosses the blood-brain barrier, with concentrations in CSF about 12% of those in the plasma. About 30% of baclofen is bound to plasma proteins. About 70 to 80% of a dose is excreted in the urine mainly as unchanged drug; about 15% is metabolised in the liver. The elimination half-life of baclofen is about 3 to 4 hours in plasma and about 1 to 5 hours in the CSF. Baclofen crosses the placenta and is distributed into breast milk.

Absorption. A crossover study in 5 healthy subjects given baclofen 20 mg orally after an overnight fast or a standardised breakfast showed that baclofen was rapidly absorbed in both cases, and the rate and extent of absorption were not significantly altered by the presence of food.[1] There is no need to modify the current practice of giving baclofen with food to minimise gastrointestinal adverse effects.

1. Peterson GM, *et al*. Food does not affect the bioavailability of baclofen. *Med J Aust* 1985; **142:** 689–90.

Uses and Administration

Baclofen, an analogue of gamma-aminobutyric acid (p.2308), is a centrally acting skeletal muscle relaxant. It interferes with the release of excitatory neurotransmitters and inhibits monosynaptic and polysynaptic transmission at the spinal cord level. It may also act at supraspinal sites producing CNS depression. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions.

Baclofen is given *orally* in divided doses, preferably with or after food or milk. The initial dose of baclofen is 5 mg three times daily for 3 days, increased to 10 mg three times daily for 3 days, then in similar increments and intervals until either a dose of 20 mg three times daily is reached or until the desired therapeutic effect is obtained. Higher doses have been used. Doses of more than 80 to 100 mg daily are not generally recommended although doses of up to 150 mg daily have been given to carefully supervised patients.

In the UK a dosage range of 0.75 to 2 mg/kg daily has been used for children; in children over 10 years a maximum daily dosage of 2.5 mg/kg may be given. It is usual to start with a low dose of 2.5 mg given four times daily, increased cautiously about every 3 days until the desired therapeutic effect is obtained. The recommended daily maintenance doses are: 12 months to 2 years, 10 to 20 mg; 2 to 6 years, 20 to 30 mg; 6 to 10 years, 30 to 60 mg.

Elderly patients should receive lower initial doses, although final maintenance doses may be in the same range as younger adults. For dosage in renal impairment, see below.

If no benefit is apparent within 6 weeks of achieving the maximum dosage, therapy should probably be gradually withdrawn.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of spasticity in patients intolerant of, or unresponsive to, oral baclofen. Before beginning the intrathecal regimen any existing antispastic therapy should be gradually withdrawn to avoid overdosage or drug interactions. Intrathecal test doses are given initially to determine if there is going to be any benefit before implanting a controlled infusion pump. It is important that patients are monitored closely in experienced centres during screening and immediately after implantation of the infusion pump and that resuscitation equipment is available for immediate use.

Test doses start at 25 or 50 micrograms given over at least 1 minute and are increased by 25 micrograms every 24 hours until a dose of 100 micrograms is reached or a positive response of about 4 to 8 hours is obtained. Patients who fail to respond to a test dose of up to 100 micrograms are considered to be unsuitable for intrathecal treatment. For children aged 4 to 18 years with spasticity of cerebral origin an initial test dose of 25 micrograms is recommended. However, the manufacturers do not recommend the use of intrathecal baclofen in patients in this age group with spasticity of spinal origin.

For patients showing a positive response lasting for longer than 8 to 12 hours, the test dose that was required to produce the response can then be given as a 24-hour infusion; if the response to the test dose lasted 8 to 12 hours or less, then a dose equivalent to twice the test dose is given. Daily dosage can then be adjusted as required. Maintenance doses range from about 10 micrograms to 2 mg daily, depending on the cause of spasticity, with most patients being adequately maintained with 300 to 800 micrograms daily.

Administration in renal impairment. Doses of baclofen should be reduced in renal impairment or in patients undergoing chronic haemodialysis; 5 mg daily by mouth has been suggested (but see also under Precautions, above).

Dystonias. There have been reports of improvement in patients with various forms of dystonia (p.809) treated with baclofen[1-5] although there has also been a report[6] of a patient whose condition deteriorated during baclofen therapy.

1. Narayan RK, *et al*. Intrathecal baclofen for intractable axial dystonia. *Neurology* 1991; **41:** 1141–2.
2. Greene PE, Fahn S. Baclofen in the treatment of idiopathic dystonia in children. *Mov Disord* 1992; **7:** 48–52.
3. van Hilten BJ, *et al*. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; **343:** 625–30.
4. Albright AL, *et al*. Intrathecal baclofen for generalized dystonia. *Dev Med Child Neurol* 2001; **43:** 652–7.
5. Jaffe MS, Nienstedt LJ. Intrathecal baclofen for generalized dystonia: a case report. *Arch Phys Med Rehabil* 2001; **82:** 853–5.
6. Silbert PL, Stewart-Wynne EG. Increased dystonia after intrathecal baclofen. *Neurology* 1992; **42:** 1639–40.

Gastro-oesophageal reflux disease. Baclofen has been tried[1,2] in the treatment of gastro-oesophageal reflux disease (p.1696). It may control gastro-oesophageal reflux by inhibiting transient sphincter relaxation. Although both studies reported a reduction in the number of reflux episodes there was no effect on acid reflux symptoms. However, a subsequent study[3] has shown a positive effect on the symptoms of acid reflux. It has been suggested that although baclofen may be of benefit, its adverse CNS effects mean that new oral selective GABA-B agonists should be developed for this indication.[4]

1. Van Herwaarden MA, *et al*. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. *Aliment Pharmacol Ther* 2002; **16:** 1655–62.
2. Zhang Q, *et al*. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50:** 19–24.
3. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003; **52:** 464–70.
4. Tonini M, *et al*. Progress with novel pharmacological strategies for gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 347–61.

Hiccup. Baclofen has been given orally in daily divided doses ranging from 10 to 80 mg for the management of intractable hiccup (p.976) poorly controlled by other drugs. It has also been combined with gabapentin.

References.

1. Burke AM, *et al*. Baclofen for intractable hiccups. *N Engl J Med* 1988; **319:** 1354.
2. Lance JW, Bassil GT. Familial intractable hiccup relieved by baclofen. *Lancet* 1989; **ii:** 276–7.
3. Yaqoob M, *et al*. Baclofen for intractable hiccups. *Lancet* 1989; **ii:** 562–3.
4. Ramirez FC, Graham DY. Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, cross-over study. *Am J Gastroenterol* 1992; **87:** 1789–91.
5. Ramirez FC, Graham DY. Hiccups, compulsive water drinking, and hyponatremia. *Ann Intern Med* 1993; **118:** 649.
6. Walker P, *et al*. Baclofen, a treatment for chronic hiccup. *J Pain Symptom Manage* 1998; **16:** 125–32.
7. Hernández JL, *et al*. Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.

Migraine and cluster headache. The efficacy of baclofen in conditions such as trigeminal neuralgia or various types of neuropathic pain suggested that it may be useful in migraine or cluster headache. Pilot studies confirmed these hypotheses with baclofen proving useful for prophylaxis[1] in migraine (p.616) and for treatment[2] in cluster headache (p.616).

1. Hering-Hanit R. Baclofen for prevention of migraine. *Cephalalgia* 1999; **19:** 589–91.
2. Hering-Hanit R, Gadoth N. The use of baclofen in cluster headache. *Curr Pain Headache Rep* 2001; **5:** 79–82.

Pain. Like some other muscle relaxants baclofen is used in the management of painful conditions associated with muscle spasm or spasticity (see below). The use of muscle relaxants for conditions such as acute low back pain is referred to on p.7. Baclofen does not appear to possess conventional analgesic activity[1] but may potentiate the analgesia produced by opioid analgesics,[2] and has been used as an adjuvant in neuropathic pain,[3,4] notably trigeminal neuralgia[5] (p.9).

1. Terrence CF, *et al*. Is baclofen an analgesic? *Clin Neuropharmacol* 1983; **6:** 241–5.
2. Panerai AE, *et al*. Baclofen prolongs the analgesic effect of fentanyl in man. *Br J Anaesth* 1985; **57:** 954–5.
3. Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994; **9:** 500–9.
4. Slonimski M, *et al*. Intrathecal baclofen in pain management. *Reg Anesth Pain Med* 2004; **29:** 269–76.
5. Fromm GH, *et al*. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol* 1984; **15:** 240–4.

Spasticity. Baclofen is one of the main drugs used in the management of spasticity (see p.1887). It is used to reduce muscle spasm and pain especially in spinal cord lesions in conditions such as multiple sclerosis or paraplegia. Baclofen is also used for spasticity of cerebral origin.

Oral doses of 30 to 80 mg daily are usually quite well tolerated,[1] but patients with severe spasticity often require high doses of baclofen before a response occurs and, consequently, some may fail to respond because adverse effects limit increases in dosage. Intrathecal baclofen is therefore sometimes tried as this produces much higher concentrations in the CNS than oral doses.[1-3] It may be given intrathecally by bolus injection or by continuous infusion; infusion is probably preferred[4] to minimise the risk of overdosage. Because patients are screened for response before beginning continuous infusion, results have generally been good.[1]

There is a large interindividual variation in the dose required to produce improvement in spasticity:

- in patients with spasticity of spinal origin, maintenance doses have ranged from 12 micrograms to about 2 mg daily, with most adequately managed on 300 to 800 micrograms daily
- in patients with spasticity of cerebral origin, maintenance doses have ranged from 22 micrograms to 1.4 mg daily, with an average daily dose of 276 micrograms after 12 months and 307 micrograms after 24 months
- for children under the age of 12 years with spasticity of cerebral origin, maintenance doses have ranged from 24 micrograms to about 1.2 mg daily, with an average daily dose of 274 micrograms

An increased dose of baclofen may be given at night to prevent spasms that interfere with sleep.

Although reports of tolerance to the effect of intrathecal baclofen have raised doubt[5] over whether long-term benefit can be maintained, a number of workers have achieved long-term efficacy.[6-9] It has been reported[10] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing and others have been able to reduce the dosage required.

1. Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety* 2004; **27:** 799–818.
2. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
3. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
4. Penn RD, Kroin JS. Intrathecal baclofen. *N Engl J Med* 1989; **321:** 1414–15.
5. Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Ann Pharmacother* 1993; **27:** 767–74.
6. Penn RD, *et al*. Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989; **320:** 1517–21.
7. Azouvi P, *et al*. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Arch Phys Med Rehabil* 1996; **77:** 35–9.
8. Dario A, *et al*. Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. *Acta Neurol Scand* 2002; **105:** 83–7.
9. Campbell WM, *et al*. Long-term safety and efficacy of continuous intrathecal baclofen. *Dev Med Child Neurol* 2002; **44:** 660–5.
10. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.

Stiff-man syndrome. There have been anecdotal case reports[1] of benefit with intrathecal baclofen in a patient with stiff-man syndrome (see under Muscle Spasm, p.993) inadequately controlled with other drugs or oral baclofen. However, in a double-blind placebo-controlled study[2] clinical improvement was evident in only 1 of 3 patients given intrathecal baclofen.

1. Stayer C, *et al*. Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. *Neurology* 1997; **49:** 1591–7.
2. Silbert PL, *et al*. Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. *Neurology* 1995; **45:** 1893–7.

Tardive dyskinesia. Baclofen is one of many drugs that have been tried in antipsychotic-induced tardive dyskinesia (see Extrapyramidal Disorders, p.971) but its efficacy is unclear. A systematic review[1] found the effects of baclofen, and other gamma-aminobutyric acid agonists to be inconclusive and unconvincing in the management of antipsychotic-induced tardive dyskinesia. The review also pointed out that the adverse effects caused by use of these drugs might outweigh any benefits.

1. Soares KVS, *et al*. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 20/10/05).

Tetanus. The management of tetanus is described on p.1901 and p.196. Beneficial responses have been seen with baclofen by continuous intrathecal infusion,[1-5] usually in doses of 1 to 2 mg daily.[1,5] However, the therapeutic range of intrathecal baclofen in severe tetanus may be very narrow and deep coma with loss of spontaneous respiration and reflexes has been reported[6] after an increase in dosage from 1.2 mg to 2 mg daily. This adverse effect could be fatal in the absence of ventilatory support. To avoid the risk of secondary infection from an indwelling intraspinal catheter intermittent intrathecal baclofen has also been used.[7,8]

1. Müller H, *et al.* Intrathecal baclofen in tetanus. *Lancet* 1986; **i:** 317–18.
2. Dressnandt J, *et al.* Intrathecal baclofen in tetanus: four cases and a review of reported cases. *Intensive Care Med* 1997; **23:** 896–902.
3. Engrand N, *et al.* The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology* 1999; **90:** 1773–6.
4. Boots RJ, *et al.* The treatment of tetanus with intrathecal baclofen. *Anaesth Intensive Care* 2000; **28:** 438–42.
5. Santos ML, *et al.* Intrathecal baclofen for the treatment of tetanus. *Clin Infect Dis* 2004; **38:** 321–8.
6. Romijn JA, *et al.* Reversible coma due to intrathecal baclofen. *Lancet* 1986; **ii:** 696.
7. Demaziere J, *et al.* Intermittent intrathecal baclofen for severe tetanus. *Lancet* 1991; **337:** 427.
8. Saissy JM, *et al.* Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; **18:** 241–4.

Tourette's syndrome. Improvement was noted in children with Tourette's syndrome (see Tics, p.954) treated with baclofen compared with placebo in a small study.[1]

1. Singer HS, *et al.* Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. *Neurology* 2001; **56:** 599–604.

Urinary incontinence. Baclofen has been used with some benefit in the management of urinary incontinence and retention (p.2180) secondary to lesions of the spinal cord.

References.

1. Hachen HJ, Krucker V. Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. *Eur Urol* 1977; **3:** 237–40.
2. Leyson JFJ, *et al.* Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol (Baltimore)* 1980; **124:** 82–4.
3. Kums JJM, Delhaas EM. Intrathecal baclofen infusion in patients with spasticity and neurogenic bladder disease. *World J Urol* 1991; **9:** 153–6.

Preparations

BP 2008: Baclofen Oral Solution; Baclofen Tablets;
USP 31: Baclofen Oral Suspension; Baclofen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baclodox; Lioresal; ***Austral.:*** Baclo; Baclohexal†; Clofen; Lioresal; Stelax; ***Austria:*** Lioresal; ***Belg.:*** Lioresal; ***Braz.:*** Baclon; Lioresal; ***Canad.:*** Lioresal; Liotec†; Nu-Baclo; ***Chile:*** Cetril; Lioresyl; ***Denm.:*** Lioresal; ***Fin.:*** Baclon; Baclopar; Lioresal; ***Fr.:*** Lioresal; ***Ger.:*** Lebic; Lioresal; ***Gr.:*** Jofen†; Lioresal; Miorel; Vioridon; ***Hong Kong:*** Lioresal; Stelax; ***Hung.:*** Lioresal; ***India:*** Lioresal; ***Indon.:*** Lioresal; ***Irl.:*** Baclopar; Lioresal; ***Israel:*** Baclosal; Lioresal; ***Ital.:*** Lioresal; ***Malaysia:*** Clofen; Lioresal; ***Neth.:*** Lioresal; ***Norw.:*** Lioresal; ***NZ:*** Pacifen; ***Philipp.:*** Lioresal; Onelaxant-R; ***Port.:*** Lioresal; ***Rus.:*** Baclosan (Баклосан); ***S.Afr.:*** Lioresal; ***Singapore:*** Lioresal†; ***Spain:*** Lioresal; ***Swed.:*** Lioresal; ***Switz.:*** Lioresal; ***Thai.:*** Baclosal; Fenisal; Liobac; Lioresal; ***Turk.:*** Lioresal; ***UK:*** Baclospas†; Lioresal; Lyflex; ***USA:*** Kemstro; Lioresal; ***Venez.:*** Lioresal.

Botulinum Toxins

Toxinas botulínicas.
ATC — M03AX01.
ATC Vet — QM03AX01.

Description. Botulinum toxins A and B are neurotoxins produced by *Clostridium botulinum*. They are proteins comprising a heavy chain thought to be responsible for binding to the target cells and translocation of the toxin across the cell membrane, linked by a disulfide bond to a light chain responsible for the toxic activity.

Botulinum A Toxin

Botuliinitoksiini tyyppi A; Botulinum A Toksini; Toxin typ A mot botulism; Toxina botulínica A; Toxine botulinique type A; Toxinum botulinicum typum A.

Pharmacopoeias. *Eur.* (see p.vii) includes the injection.
Ph. Eur. 6.2 (Botulinum Toxin Type A for Injection; Toxinum Botulinicum Typum A ad Iniectabile). A dried preparation containing purified botulinum neurotoxin type A, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type A.

Botulinum B Toxin

Botulinum B Toksini; Toxina botulínica B.

Units

The dose of preparations containing botulinum toxins A or B is expressed in terms of units, but the available preparations are used at different doses for the same indications, and the units of one preparation cannot be considered to apply to another.

Adverse Effects

Injections of botulinum toxins have been associated with a transient burning sensation, bruising at the injection site, and local weakness. Adverse reactions related to the spread of botulinum toxins distant to the site of injection have been reported and sometimes this was associated with significant debility or a fatal outcome in very rare cases. Exaggerated muscle weakness may occur with therapeutic doses. Deep or misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles. Overdosage can produce a widespread paralysis.

There have been occasional reports of hypersensitivity reactions such as skin rashes and flu-like symptoms. There have also been rare reports of cardiovascular adverse effects, including arrhythmia and myocardial infarction, and of seizures or convulsions, particularly in predisposed patients.

- The most common adverse effects **after injection into muscles around the eye**, such as in the management of blepharospasm, hemifacial spasm, or strabismus, are ptosis, lachrymation, photophobia, ocular irritation, and facial swelling. Some patients may be unable to close the eyelid completely. Other adverse effects that have been reported include ectropion and entropion, and diplopia. Patients experience a reduction in blinking and this can lead to dry eye, keratitis, and corneal damage. Angle-closure glaucoma has been reported. Vertical deviation has also occurred in patients treated for horizontal strabismus. Needle penetrations of the eye during treatment of strabismus have resulted in vitreous and retrobulbar haemorrhages.
- Dysphagia is the most common adverse effect **after injection into neck muscles** in the treatment of spasmodic torticollis and there may be pooling of saliva with risk of aspiration in severely affected patients (*important*, see also Precautions, below). Dry mouth, paralysis of the vocal cords, and weakness of the neck muscles may also occur. Generalised weakness, malaise, nausea, and visual disturbances have occasionally been reported. Other effects which have occurred rarely include drowsiness, numbness, stiffness, ptosis, and headache. Respiratory difficulties, associated with the use of large doses, have occurred on rare occasions.
- Adverse effects most frequently associated with **injection into the lower limbs** in the treatment of cerebral palsy include falling, leg pain, and local and general weakness; lethargy and leg cramps have also been reported.
- Common adverse effects **after injection into the upper limb** in the treatment of spasticity associated with stroke are arm pain, dysphagia, muscle weakness, and hypertonia. A perceived increase in non-axillary sweating, within one month of the injection, has been reported after treatment for hyperhidrosis of the axillae; rarely, mild transient weakness of the arms has also occurred.
- Headache is the most frequent adverse effect **after injection into the muscles around the forehead** in the treatment of glabellar (frown) lines. Other adverse effects frequently reported include ptosis, facial pain, muscle weakness, and nausea.

◊ Reviews.

1. Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Dis Mon* 2002; **48:** 336–56.

Incidence of adverse effects. It has been suggested that the difference between botulinum A toxin preparations may not be confined to just a numerical dosage adjustment.[1] Reviews of the literature have suggested that there may also be a difference in the incidence of adverse effects. The reported frequency of dysphagia for *Dysport* (28% and 44%) in patients with spasmodic torticollis was greater than that for *Botox* (9.5 to 17%). This variation might relate to differences in bioactivity not recognised by the mouse lethality bioassay which is used to determine the potency of preparations.

1. Borodic G. Therapeutic botulinum toxin. *Lancet* 1994; **344:** 1370.

Angiosarcoma. It has been suggested[1] that botulinum A toxin injection might have acted as a triggering factor for angiosarcoma in a 66-year-old patient being treated for blepharospasm.

1. Kárpáti S, *et al.* Human herpesvirus type 8-positive facial angiosarcoma developing at the site of botulinum toxin injection for blepharospasm. *Br J Dermatol* 2000; **143:** 660–2.

Antibody formation. Neutralising antibodies that reduce or abolish the beneficial effects of treatment have been found after prolonged treatment with botulinum A toxin.[1] A review[2] in 1994 considered that there was growing concern over the development of antibodies after repeated injections, as many of the conditions for which botulinum toxin is indicated require indefinite treatment. Antibody formation was reported to be more common with high doses (as in spasmodic torticollis) than after low doses (as for blepharospasm). The occurrence of antibodies appeared to correlate with the dose per injection, the quantity of botulinum protein given per injection, the number of injections given, and the frequency of injections.

Antibodies have also developed after the use of botulinum B toxin. However, botulinum toxin B is antigenically distinct from botulinum A toxin, and may be of value in patients who develop resistance to treatment associated with antibody formation to type A toxin.[3] Botulinum F toxin is also antigenically distinct and is being studied in a similar way.

1. Hambleton P, *et al.* Antitoxins and botulinum toxin treatment. *BMJ* 1992; **304:** 959–60.
2. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
3. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.

Biliary colic. A 43-year-old woman with no history of gallbladder disease had single episodes of biliary colic after each of 3 sessions of treatment with botulinum A toxin for blepharospasm.[1] Botulinum A toxin might have exerted a systemic effect to block acetylcholine release leading to gallbladder hypomotility with delayed emptying and stasis.

1. Schnider P, *et al.* Gallbladder dysfunction induced by botulinum A toxin. *Lancet* 1993; **342:** 811–12.

Dysphagia. By November 1993, the UK CSM had received 4 reports of severe dysphagia with choking in patients given injections of botulinum A toxin into the neck muscles as a treatment for torticollis.[1] The dysphagia developed 5 to 7 days after the injection and in one patient it was persisting 6 weeks after the injection. The dysphagia led to aspiration of the stomach contents into the lungs and one patient with a history of poor lung function died from bronchopneumonia. Dysphagia is also reported to be a common adverse effect in patients with spasmodic torticollis being treated with Botulinum B toxin.[2]

See also Incidence of Adverse Effects, above for further reference to dysphagia as an adverse effect.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: botulinum type A toxin (Dysport)—severe dysphagia with unlicensed route of administration. *Current Problems* 1993; **19:** 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Lew MF, *et al.* The safety and efficacy of botulinum toxin type B in the treatment of patients with cervical dystonia: summary of three controlled clinical trials. *Neurology* 2000; **55** (suppl 5): S29–S35.

Effects on the eyes. Acute angle-closure glaucoma has been reported[1] in an 83-year-old woman after a series of injections of botulinum A toxin for the treatment of blepharospasm. Permanent extra-ocular muscle damage after botulinum A toxin injection into the left inferior rectus muscle has been reported[2] in a 70-year-old man.

1. Corridan P, *et al.* Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; **74:** 309–10.
2. Mohan M, *et al.* Permanent extraocular muscle damage following botulinum toxin injection. *Br J Ophthalmol* 1999; **83:** 1309–10.

Treatment of Adverse Effects

The use of artificial tears may relieve keratitis and dry eye. In the event of overdosage general supportive care is required. The patient should be monitored for several days for signs of paralysis and artificial respiration may be necessary. Since the effects of botulinum toxins are irreversible once bound to nerve terminals, it is doubtful that specific botulinum antitoxin (p.2207) will be of value unless given very rapidly after overdosage.

Precautions

Botulinum toxin is contra-indicated in generalised disorders of muscle activity such as myasthenia gravis. As with other biological products, the potential for botulinum toxin to cause anaphylaxis should be considered. Botulinum toxins should be given with extreme caution to patients with neurological disorders or a history of dysphagia or aspiration. Patients or their carers should be advised to seek immediate medical attention if problems with swallowing or speech, or respiratory disorders develop.

Botulinum toxins should only be used by appropriately qualified and trained specialists. Injections must be made with great care, especially those into the neck, to avoid unintended paralysis; the relevant anatomy, and any alterations due to previous surgery, must be understood before injection. Botulinum toxins should not be given if there is any infection at the proposed injection site.

The effects of botulinum toxins in pregnancy are unknown; fetal malformations and abortion have been reported in *rabbits*, and licensed product information recommends that botulinum toxins should not be given to pregnant women. Breast feeding is also considered a contra-indication: it is not clear whether the toxin is distributed into breast milk.

When **injected into the muscles around the eyes**, as for the treatment of blepharospasm, hemifacial spasm, or strabismus, reduced blinking can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with seventh cranial nerve disorders. Corneal sensation should be carefully tested in previously treated eyes, injection into the lower eyelid area avoided, and any resulting epithelial defect vigorously treated.

Handling. Residual botulinum A toxin or spillages should be inactivated by autoclaving or use of a dilute hypochlorite solution (0.5%). Botulinum B toxin may be decontaminated in a similar manner; a strong caustic solution may also be used.

Interactions

The effect of botulinum toxins may theoretically be potentiated by aminoglycosides or spectinomycin. Interactions may also occur with other drugs that have neuromuscular blocking activity, including lincosamides, polymyxins, tetracyclines, and muscle relaxants.

Uses and Administration

Botulinum toxins cause neuromuscular blockade by inhibiting the calcium-ion mediated release of acetylcholine at the motor nerve terminals, resulting in a diminished endplate potential and subsequent flaccid paralysis of the affected muscles. The paralysis persists until new nerve terminals form, usually within 2 to 4 months.

Botulinum A toxin is given as a complex usually with haemagglutinin by local injection in the treatment of hemifacial spasm, blepharospasm, spasmodic torticollis, lower limb spasticity in children with cerebral palsy, and upper limb spasticity associated with stroke in adults. Botulinum A toxin is also used for the management of strabismus and hyperhidrosis, and has also been approved for the treatment of glabellar (frown) lines in adults up to 65 years of age. It is being investigated for use in the management of several other disorders. Botulinum B toxin is also used in the management of spasmodic torticollis and, being antigenically distinct, it has the potential for use in patients who develop resistance to treatment due to the development of antibodies to type A toxin.

Doses of botulinum toxins A and B are expressed in terms of units, which have not been standardised between preparations (see under Units, above). Doses are therefore specific to each individual preparation; details are given below.

Botulinum F toxin is under investigation for the treatment of similar neuromuscular disorders.

◊ Reviews.

1. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
2. Hughes AJ. Botulinum toxin in clinical practice. *Drugs* 1994; **48:** 888–93.
3. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 1. *Am J Health-Syst Pharm* 2006; **63:** 145–52.
4. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 2. *Am J Health-Syst Pharm* 2006; **63:** 225–32.

Achalasia. The treatment of choice for achalasia (see Oesophageal Motility Disorders, p.1702) is mechanical dilatation of the lower oesophageal sphincter, or if necessary surgery, but more recently injection of botulinum A toxin[1-3] has been found to be effective. However, one year after treatment only 7 of 22 (32%) patients who received botulinum A toxin were in symptomatic remission compared with 14 of 20 (70%) patients treated with mechanical dilatation.[4] It was recommended that its use would be better reserved for patients thought to be at risk from mechanical dilatation or surgery.[3-5] Another study[6] showed that intrasphincteric injection of botulinum toxin A was safe and effective for the treatment of achalasia in the short and medium term, although only a weak correlation with dose emerged.

1. Pasricha PJ, *et al.* Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **332:** 774–8. Correction. *ibid.*; **333:** 75.
2. Cuillière C, *et al.* Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut* 1997; **41:** 87–92.
3. da Silveira EBV, Rogers AI. Treatment of achalasia with botulinum A toxin. *Am J Ther* 2002; **9:** 157–61.
4. Vaezi MF, *et al.* Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999; **44:** 231–9.
5. Spiess AE, Kahrilas PJ. Treating achalasia: from whalebone to laparoscope. *JAMA* 1998; **280:** 638–42.
6. Annesse V, *et al.* A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000; **46:** 597–600.

Anal fissure. Anal fissure is a superficial tear in the mucosa of the distal anal canal characterised by pain on defaecation, rectal bleeding, and spasm of the anal sphincter. Healing, which is usually uneventful, may be helped by conservative management with bran and bulk laxatives and topical local anaesthetics for pain relief. Surgical treatment has been used for patients who develop a chronic condition but has been associated with high rates of long-term incontinence and recurrence. Although systematic reviews considered that surgery was more effective than alternative medical therapies,[1,2] a number of these have been investigated.[3] As hypertonicity of the internal anal sphincter may be involved in the pathophysiology of chronic anal fissure, local injections of botulinum A toxin have been used to produce paresis of this sphincter.[4-6] The duration of the effect appears to be long enough to allow complete healing of the fissure in most patients although some may relapse; a long-term, follow-up trial[7] involving 57 completely healed patients, noted a high recurrence rate (41.5%) once the effects of botulinum toxin disappeared. Temporary incontinence had been the only adverse effect reported during treatment.

Topical application of nitrates can relax the anal sphincter; numerous studies[8-10] have reported benefit from topical application of glyceryl trinitrate, although a high rate of spontaneous resolution with placebo has cast doubt over the degree of advantage in some studies.[1,9] Follow-up[11] of patients treated with glyceryl trinitrate indicated that after 24 to 38 months most had not experienced further problems or had had occasional recurrences which in the majority of cases had responded to further topical treatment. Isosorbide dinitrate ointment has also been tried, and may be of benefit with botulinum A toxin.[12]

Topical calcium antagonists also seem to be effective. Both diltiazem[13-15] and nifedipine[16,17] seem to be of benefit and there is evidence that they may be a better choice than topical glyceryl trinitrate.[16,17] Nifedipine has been combined with botulinum toxin;[17] it has also been given orally.[18]

1. Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 2004; **47:** 422–31.
2. Nelson R. Non surgical therapy for anal fissure. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/05/08).
3. Cook TA, *et al.* The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. *Aliment Pharmacol Ther* 2001; **15:** 887–98.
4. Jost WH, Schimrigk K. Botulinum toxin in therapy of anal fissure. *Lancet* 1995; **345:** 188–9.
5. Maria G, *et al.* A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med* 1998; **338:** 217–20.
6. Jost WH. Ten years' experience with botulin toxin in anal fissure. *Int J Colorectal Dis* 2002; **17:** 298–302.
7. Minguez M, *et al.* Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterology* 2002; **123:** 112–17.
8. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*: 656.
9. Bailey HR, *et al.* Fissure Study Group. A study to determine the nitroglycerin ointment dose and dosing interval that best promote the healing of chronic anal fissures. *Dis Colon Rectum* 2002; **45:** 1192–9.
10. Scholefield JH, *et al.* A dose finding study with 0.1%, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut* 2003; **52:** 264–9.
11. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
12. Lysy J, *et al.* Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut* 2001; **48:** 221–4.
13. Jonas M, *et al.* A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
14. Jonas M, *et al.* Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
15. Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Dis* 2003; **5:** 256–7.
16. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
17. Tranqui P, *et al.* Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; **49:** 41–5.
18. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.

Anismus. Anismus is a condition in which inappropriate contraction of the anal sphincters occurs when bowel evacuation is attempted; it seems to be a form of dystonia.

Treatment with botulinum A toxin was investigated in 7 patients with intractable constipation due mainly to anismus.[1] The toxin was injected bilaterally into the puborectalis muscle using an electromyographically guided needle; patients were allowed to continue with their laxatives throughout the study if required. Symptoms improved in all but one of the patients, although two patients could not be regarded as treatment successes because they developed faecal incontinence; four patients had an excellent clinical outcome. However, another study involving 24 patients found the clinical effectiveness of botulinum A toxin to be limited, and further studies are needed to determine its role in the treatment of anismus.[2]

1. Hallan RI, *et al.* Treatment of anismus in intractable constipation with botulinum A toxin. *Lancet* 1988; **ii:** 714–17.
2. Ron Y, *et al.* Botulinum toxin type-A in therapy of patients with anismus. *Dis Colon Rectum* 2001; **44:** 1821–6.

Blepharospasm. Blepharospasm is a focal dystonia characterised by repeated involuntary blinking caused by spasms of the orbicularis oculi muscle of the eye, and can result in functional blindness. Blepharospasm is often associated with other dystonias of the head and neck, such as Meige syndrome, in which patients also suffer from involuntary contractures of the muscles around the mouth. Oral drug treatment as used for dystonias in general (see p.809) is usually ineffective, and surgery (facial nerve avulsion) is often followed by recurrent spasm.[1] Local injections of botulinum A toxin into the orbicularis oculi muscle mimic the effect of surgical denervation of the muscle and are reported[2-6] to have been effective in over 70% of patients. Symptomatic improvement has been reported to last from about 9 to 15 weeks; no increase in duration of effect is apparent following multiple injections. In one retrospective study in patients with blepharospasm and Meige syndrome, treatment with botulinum A toxin was still effective in most patients 11 years after the start of therapy.[4]

For blepharospasm botulinum A toxin is injected into the orbicularis oculi of the upper and lower lids; injection into additional sites in the brow area and upper facial area may be indicated if the spasms interfere with vision. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox* (*Allergan, UK*) is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 3 days and reaches a peak after 1 to 2 weeks; each treatment lasts for about 3 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Botox* (*Allergan*) is also available in the USA and given in similar doses, although higher cumulative doses of up to 200 units are allowed in a 30-day period
- The preparation *Xeomin (Merz, UK)* is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 4 days; each treatment lasts for about 3 to 4 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit.
- For the preparation *Dysport* (*Ipsen, UK*) the initial dose is a total of 120 units per eye given as subcutaneous injections of 20 and 40 units per site. Subsequently the total dose may need to be reduced to 60 to 80 units per eye. With this preparation the relief of symptoms may begin within 2 to 4 days with a maximum effect being obtained within 2 weeks. Injections of *Dysport* should be repeated every 12 weeks or as required.

1. Kennedy RH, *et al.* Treatment of blepharospasm with botulinum toxin. *Mayo Clin Proc* 1989; **64:** 1085–90.
2. Grandas F. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg Psychiatry* 1988; **51:** 767–72.
3. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
4. Mauriello JA, *et al.* Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. *Br J Ophthalmol* 1996; **80:** 1073–6.
5. Defazio G, Livrea P. Primary blepharospasm: diagnosis and management. *Drugs* 2004; **64:** 237–44.
6. Costa J, *et al.* Botulinum toxin type A therapy for blepharospasm. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 28/03/06).

Cosmetic use. Botulinum A toxin has been used for the cosmetic treatment of facial lines and wrinkles and age-related neck degeneration.[1-5]

For the temporary improvement in appearance of moderate to severe glabellar (frown) lines two doses of botulinum A toxin are injected into each of the corrugator muscles and one dose into the procerus muscle. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*: the preparation *Botox Cosmetic* (*Allergan, USA*) is injected intramuscularly, not closer than 1 cm above the central eyebrow. A dose of 4 units is given into each of 5 sites to a total dose of

20 units. An effect is obtained in 1 to 2 days which increases in intensity in the first week; each treatment lasts for about 3 to 4 months. More frequent dosing is not recommended as safety and effectiveness have not been evaluated.

A preparation with a similar dosage regimen (*Vistabel; Allergan, UK*) is available in the UK.

1. Olver JM. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. *Br J Ophthalmol* 1998; **82:** 528–33.
2. Song KH. Botulinum toxin type A injection for the treatment of frown lines. *Ann Pharmacother* 1998 **32:** 1365–7.
3. Anonymous. Cosmetic use of botulinum toxin. *Med Lett Drugs Ther* 1999; **41:** 63–4.
4. Anonymous. Botulinum toxin (Botox Cosmetic) for frown lines. *Med Lett Drugs Ther* 2002; **44:** 47–8.
5. Carruthers A. Botulinum toxin type A: history and current cosmetic use in the upper face. *Dis Mon* 2002; **48:** 299–322.

Gastric motility disorders. Some benefit has been reported from the use of botulinum A toxin injection in gastric motility disorders (p.1694). In an open-label study[1] 6 diabetic patients with gastroparesis experienced an improvement in gastric emptying after treatment with botulinum A toxin.

1. Ezzeddine D, *et al.* Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002; **55:** 920–3.

Hand dystonia. Hand dystonia, or hand cramp, is a type of focal dystonia (p.809). It is more commonly reported in people who perform repetitive movements with their hands, such as writers, keyboard operators, and musicians. Treatment was traditionally with antimuscarinics, although with limited success, but botulinum toxin has increasingly become the first-line option.[1] A double-blind study reported that 8 out of 10 patients had greater subjective improvement in focal hand dystonia, compared with placebo, after treatment with botulinum A toxin given by the intramuscular route; objective improvement in muscle strength was seen in 6 patients.[2] However, pain and severe weakness in the shoulder region resembling neuralgic amyotrophy has been reported[3] in 2 patients injected with botulinum A toxin for writer's cramp. It was considered that if unexplained pain occurred in the shoulder or upper arm after a first injection of botulinum A toxin further injections were contra-indicated.

1. Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. *Mov Disord* 2004; **19** (suppl 8): S116–S119.
2. Cole R, *et al.* Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 1995; **10:** 466–71.
3. Sheean GL, *et al.* Pain and remote weakness in limbs injected with botulinum toxin A for writer's cramp. *Lancet* 1995; **346:** 154–6.

Headache. The therapeutic effect of botulinum A toxin in headache was first seen as a coincidental adverse effect in patients receiving the drug for hyperfunctional facial lines. A review[1] of subsequent studies concluded that efficacy could be demonstrated for the prophylaxis of migraine (p.616); a small number of patients who received treatment during the acute phase of a migraine attack also experienced pain relief. Contradictory results had been reported in the studies evaluating tension-type headache (p.617) and continue to be reported.[2-4] However, in the original review[1] it was emphasised that an important finding had been the need to inject botulinum A toxin at the site of the pain or trigger points and not on a standardised basis, and that this should be considered in future studies. Improvement had been noted in individual cases of cluster headache (p.616) and in some patients with headache attributed to disorders of the neck.

Some benefit has also been seen with botulinum B toxin in the treatment of migraine and tension-type headaches.[5]

1. Göbel H, *et al.* Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol* 2001; **248** (suppl 1): 34–8.
2. Ondo WG, *et al.* Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 2004; **24:** 60–5.
3. Schulte-Mattler WJ, *et al.* Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain* 2004; **109:** 110–14.
4. Rozen D, Sharma J. Treatment of tension-type headache with Botox: a review of the literature. *Mt Sinai J Med* 2006; **73:** 493–8.
5. Fadeyi MO, Adams QM. Use of botulinum toxin type B for migraine and tension headaches. *Am J Health-Syst Pharm* 2002; **59:** 1860–2.

Hemifacial spasm. Hemifacial spasm is characterised by involuntary unilateral synchronous contractions of muscles innervated by the facial nerve. The spasms usually begin with twitching of muscles around the eye or mouth but as the disease progresses their frequency increases and they spread to involve the rest of the facial muscles. Hemifacial spasm may be improved by surgery but there is a risk of irreversible paralysis. Few drugs are effective for hemifacial spasm but carbamazepine has been reported to have been of help on occasions. Reports suggest that injections of botulinum A toxin may be effective in relieving symptoms in at least 75% of patients but there do not appear to be any studies comparing it against other treatments. Repeat injections are required by most patients every 3 to 4 months but long-term efficacy appears to be maintained. Dosage regimens of botulinum A toxin used in hemifacial spasm are similar to those used for blepharospasm (see above) although an electromyographically guided needle may be required to identify small muscles around the mouth.

References.

1. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
2. Chen R-S, *et al.* Botulinum toxin A injection in the treatment of hemifacial spasm. *Acta Neurol Scand* 1996; **94:** 207–11.
3. Boghen DR, Lesser RL. Blepharospasm and hemifacial spasm. *Curr Treat Options Neurol* 2000; **2:** 393–400.
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5. Defazio G, *et al.* Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol* 2002; **59:** 418–20.
6. Costa J, *et al.* Botulinum toxin type A therapy for hemifacial spasm. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).

Hyperhidrosis. A number of drugs and surgical techniques have been used in the treatment of hyperhidrosis (p.1580). Botulinum A toxin is used in the management of focal hyperhidrosis because of its ability to block cholinergic transmission at nerve terminals innervating the sweat glands. Encouraging results have been obtained in patients with severe resistant focal hyperhidrosis using intradermal[1,2] or subcutaneous[3,4] injections and results from two larger multicentre studies[5,6] confirm that intradermal injection of botulinum A is effective and well-tolerated for the treatment of axillary hyperhidrosis. In the UK, it is given for this purpose as the preparation *Botox* (*Allergan, UK*), by intradermal injection in doses of 50 units to each axilla, evenly distributed in multiple sites approximately 1 to 2 cm apart. Clinical improvement generally occurs within a week of injection, and may last for 4 to 7 months; repeat injections may be given once the effects of the previous injection have subsided. *Botox* (*Allergan*) is also available in the USA for the treatment of axillary hyperhidrosis; it is given in similar doses.

Some workers[7] prefer to use intradermal injections for palmar hyperhidrosis in order to minimise the risk of reversible weakness of the small muscles of the hand reported with subcutaneous injection.

1. Naumann M, *et al.* Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998; **134:** 301–4.
2. Schnider P, *et al.* Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145:** 289–93.
3. Schnider P, *et al.* Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997; **136:** 548–52.
4. Schnider P, *et al.* Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
5. Heckmann M, *et al.* Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; **344:** 488–93.
6. Naumann M, *et al.* Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *BMJ* 2001; **323:** 596–9.
7. Heckmann M, *et al.* Optimizing botulinum toxin therapy for hyperhidrosis. *Br J Dermatol* 1998; **138:** 553–4.

Hyperlachrymation. Botulinum A toxin may be of benefit[1,2] in the management of hyperlachrymation ('crocodile tears').

1. Riemann R, *et al.* Successful treatment of crocodile tears by injection of botulinum toxin into the lacrimal gland: a case report. *Ophthalmology* 1999; **106:** 2322–4.
2. Keegan DJ, *et al.* Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol* 2002; **86:** 43–6.

Laryngeal dystonias. Botulinum A toxin has been tried in the treatment of spasmodic dysphonia,[1-3] focal laryngeal dystonia,[4] and dysfunctional spasm after total laryngectomy.[5] Botulinum B toxin has also been used.[6]

1. Whurr R, *et al.* Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. *Int J Lang Commun Disord* 1998; **33** (suppl): 327–9.
2. Gibbs SR, Blitzer A. Botulinum toxin for the treatment of spasmodic dysphonia. *Otolaryngol Clin North Am* 2000; **33:** 879–94.
3. Watts CCW, *et al.* Botulinum toxin injections for the treatment of spasmodic dysphonia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 07/05/08).
4. Marion M-H, *et al.* Stridor and focal laryngeal dystonia. *Lancet* 1992; **339:** 457–8.
5. Crary MA, *et al.* Using botulinum toxin A to improve speech and swallowing function following total laryngectomy. *Arch Otolaryngol Head Neck Surg* 1996; **122:** 760–3.
6. Sataloff RT, *et al.* Botulinum toxin type B for treatment of spasmodic dysphonia: a case report. *J Voice* 2002; **16:** 422–4.

Micturition disorders. Preliminary results[1] suggest that injection of botulinum A toxin into the detrusor muscle can increase functional bladder capacity and restore continence in patients with urinary incontinence (p.2180) after spinal cord injury who are resistant to antimuscarinics. Similar results[2] have been found in children with detrusor hyperreflexia caused by myelomeningocele.

Botulinum A toxin has also been tried in other bladder dysfunctions.[3,4] Reviews[5,6] have concluded that although there is some evidence that injection of botulinum toxins into the detrusor wall can improve symptoms of overactive bladder syndrome, further studies are warranted.

In a few small studies[7,8] the injection of botulinum A toxin into the prostate gland has been reported to relieve the symptoms of urinary retention associated with benign prostatic hyperplasia (p.2178).

1. Schurch B, *et al.* Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol (Baltimore)* 2000; **164:** 692–7.
2. Schulte-Baukloh H, *et al.* Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002; **59:** 325–7.
3. Phelan MW, *et al.* Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol (Baltimore)* 2001; **165:** 1107–10.
4. Smith CP, *et al.* Botulinum toxin in urology: evaluation using an evidence-based medicine approach. *Nat Clin Pract Urol* 2004; **1:** 31–7.
5. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006; **66:** 1301–18.
6. Duthie J, *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).
7. Maria G, *et al.* Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003; **62:** 259–65.
8. Kuo H-C. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005; **65:** 670–4.

Nystagmus. Surgery, corrective spectacles, and drug therapy have all been tried for the treatment of nystagmus (rapid involuntary movement of the eyeball). Retrobulbar injection of botulinum A toxin has produced improvement in patients with acquired or congenital nystagmus.[1-4] In 6 patients with acquired nystagmus visual acuity was improved, and the amplitude of the nystagmus was reduced, but the frequency was generally unchanged and the need for repeated injections and adverse effects such as diplopia limited patient acceptability.[1]

1. Repka MX, *et al.* Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; **112:** 1320–4.
2. Carruthers J. The treatment of congenital nystagmus with Botox. *J Pediatr Ophthalmol Strabismus* 1995; **32:** 306–8.
3. Lennerstrand G, *et al.* Treatment of strabismus and nystagmus with botulinum toxin type A: an evaluation of effects and complications. *Acta Ophthalmol Scand* 1998; **76:** 27–37.
4. Stahl JS, *et al.* Medical treatment of nystagmus and its visual consequences. *J R Soc Med* 2002; **95:** 235–7.

Ocular surgery. Ptosis is a common adverse effect of botulinum A toxin but therapeutic ptosis induced with botulinum toxin has been described as a useful adjunct in the management of patients undergoing epikeratoplasty since it promoted stabilisation of the epithelium on the graft.[1]

1. Freegard T, *et al.* Therapeutic ptosis with botulinum toxin in epikeratoplasty. *Br J Ophthalmol* 1993; **77:** 820–2.

Pain. There have been anecdotal reports of the use of botulinum A toxin in the treatment of painful disorders such as postcholecystectomy pain associated with sphincter of Oddi dysfunction,[1] and relief of orofacial pain associated with temporomandibular joint dysfunction[2] and facial arthromyalgia.[3] Promising results have been obtained from an open study[4] investigating botulinum toxin as a treatment for chronic refractory tennis elbow in 14 patients. Its efficacy in relieving pain in other chronic conditions such as low back pain, and myofascial pain, in addition to improving function, has also been shown in individual studies.[5] The general management of pain is discussed on p.2 with separate sections on biliary and renal colic (p.5), low back pain (p.7), orofacial pain (p.8), and soft-tissue rheumatism (p.13).

1. Pasricha PJ, *et al.* Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. *Gut* 1994; **35:** 1319–21.
2. Girdler NM. Use of botulinum toxin to alleviate facial pain. *Br J Hosp Med* 1994; **52:** 363.
3. Girdler NM. Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
4. Morré HHE, *et al.* Treatment of chronic tennis elbow with botulinum toxin. *Lancet* 1997; **349:** 1746.
5. Lang AM. Botulinum toxin therapy for myofascial pain disorders. *Curr Pain Headache Rep* 2002; **6:** 355–60.

Sialorrhoea. Botulinum toxins may be effective in the treatment of sialorrhoea and drooling associated with conditions such as cerebral palsy[1] and Parkinson's disease.[2] A review[3] found botulinum toxin A to be safe and effective in the treatment of sialorrhoea; however, further studies are warranted.

1. Jongerius PH, *et al.* Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics* 2004; **114:** 620–7.
2. Ondo WG, *et al.* A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. *Neurology* 2004; **62:** 37–40.
3. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. *Ann Pharmacother* 2007; **41:** 79–85.

Spasmodic torticollis. Spasmodic torticollis (cervical dystonia) is a focal dystonia (p.809) characterised by spasmodic rotation of the head as a result of dystonic spasm of the neck muscles. The head may turn to one side (torticollis), extend (retrocollis), or flex (antecollis). Spasms may be repetitive or sustained. Response of spasmodic torticollis to drug therapy is usually poor and surgery has been associated with potentially serious complications. Intramuscular injections of botulinum toxins can be effective but dysphagia, which can have severe consequences (see under Adverse Effects, above) occurs in a significant number of patients. Other adverse effects have included lethargy, local weakness, vertigo, and dysphonia.

When injecting botulinum toxins localisation of the involved muscles with electromyographic guidance may be useful. Multiple injection sites allow more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. Bilateral injection of the sternocleidomastoid muscle is not recommended as there is an increased risk of adverse effects, especially dysphagia. Reduced doses may be required for patients with reduced muscle mass.

Doses of botulinum toxins, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation.*

In the UK the usual initial dose of botulinum A toxin as the preparation *Dysport* (*Ipsen*, *UK*) is 500 units injected in divided doses into the two or three most active neck muscles:

- for *rotational torticollis*, 350 units is given initially into the splenius capitis muscle (ipsilateral to the direction of the chin/head rotation) and 150 units into the sternocleidomastoid muscle (contralateral to rotation)
- for *laterocollis*, 350 units is given initially into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternocleidomastoid muscle; if associated with *shoulder elevation*, ipsilateral trapezoid or levator scapulae muscles may also require treatment; if 3 muscles need treatment, 300 units are injected into the splenius capitis muscle, 100 units into the sternocleidomastoid muscle, and 100 units into the third muscle
- for *retrocollis*, 250 units is given into each of the splenius capitis muscles which may be followed after 6 weeks by bilateral trapezius injections in a dose of up to 250 units per muscle; bilateral splenii injections may increase the risk of neck muscle weakness

Subsequent doses may range from 250 to 1000 units, although the higher doses may be accompanied by an increase in adverse effects such as dysphagia; doses above 1000 units are not recommended. An initial effect is usually observed within 1 week; injections usually need to be repeated every 12 weeks or as required.

In the UK, botulinum A toxin as the preparation *Xeomin (Merz, UK)* is indicated for spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements. In practice, the maximum total dose is usually not more than 200 units but up to 300 units may be given. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia. An initial effect is usually observed within 1 week; each treatment lasts for about 3 to 4 months and injections may be repeated if necessary after at least 10 weeks.

Recommended doses in the UK for botulinum A toxin as the preparation *Botox* (*Allergan*, *UK*) are listed below but licensed product information states that in practice the maximum total dose is not usually more than 200 units. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia.

- *Type I* (head rotated toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 50 to 100 units divided amongst at least 2 sites; levator scapulae: total of 50 units amongst 1 or 2 sites; scalene: total of 25 to 50 units amongst 1 or 2 sites; splenius capitis: total of 25 to 75 units amongst 1 to 3 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type II* (head rotation only)—sternocleidomastoid muscle: total dosage of 25 to 100 units divided amongst at least 2 sites if more than 25 units is given
- *Type III* (head tilted toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 25 to 100 units at posterior border divided amongst at least 2 sites if more than 25 units is given; levator scapulae: total of 25 to 100 units amongst at least 2 sites; scalene: total of 25 to 75 units amongst at least 2 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type IV* (bilateral posterior cervical muscle spasm with elevation of the face)—splenius capitis and splenius cervicis: a total dosage of 50 to 200 units divided amongst 2 to 8 sites and which include both sides of the neck

Botulinum A toxin as the preparation *Botox* (*Allergan*, *USA*) is also available in the USA for the treatment of spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements.

In the UK the usual initial dose of botulinum B toxin as the preparation *NeuroBloc* (*Zeneus Pharma*, *UK*) is 5000 to 10 000 units given by intramuscular injection in divided doses into the two to four most affected muscles.

Botulinum B toxin as the preparation *Myobloc* (*Solstice*, *USA*) is also available in the USA. The initial dose is 2500 to 5000 units given by intramuscular injection divided between the affected muscles. Licensed product information recommends that patients with no history of tolerating botulinum injections should be started on a lower initial dose.

References.

1. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990; **53:** 640–3.
2. Greene P, *et al.* Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990; **40:** 1213–18.
3. Anderson TJ, *et al.* Botulinum toxin treatment of spasmodic torticollis. *J R Soc Med* 1992; **85:** 524–9.
4. Brans JWM, *et al.* Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 1996; **46:** 1066–72.
5. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.
6. Brashear A, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1439–46.
7. Velickovic M, *et al.* Cervical dystonia: pathophysiology and treatment options. *Drugs* 2001; **61:** 1921–43.
8. Figgitt DP, Noble S. Botulinum toxin B: a review of its therapeutic potential in the management of cervical dystonia. *Drugs* 2002; **62:** 705–22.
9. Dressler D, *et al.* Botulinum toxin type B in antibody-induced botulinum toxin type A therapy failure. *J Neurol* 2003; **250:** 967–9. Correction. *ibid.*; 1263–5.
10. Walker FO. Botulinum toxin therapy for cervical dystonia. *Phys Med Rehabil Clin N Am* 2003; **14:** 749–66.
11. Lew MF. Duration of effectiveness of botulinum toxin type B in the treatment of cervical dystonia. *Adv Neurol* 2004; **94:** 211–15.
12. Jankovic J. Treatment of cervical dystonia with botulinum toxin. *Mov Disord* 2004; **19** (suppl 8): S109–S115.
13. Costa J, *et al.* Botulinum toxin type B for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/03/06).
14. Costa J, *et al.* Botulinum toxin type A therapy for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).
15. Comella CL, *et al.* Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology* 2005; **65:** 1423–9.
16. Costa J, *et al.* Botulinum toxin type A versus anticholinergics for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 07/05/08).

Spasticity. The mainstay of management of spasticity, as discussed on p.1887, is physiotherapy together with antispastic drugs. Chemical neurolysis should only be considered when there is intractable continuous pain. Local injections of botulinum A toxin, as an alternative to chemical neurolysis, have been used in the management of limb spasticity in multiple sclerosis,[1] and in post-stroke patients,[1-5] and children with cerebral palsy.[6-12] However, systematic reviews[13,14] have found insufficient evidence to support or refute such use in children with cerebral palsy. Botulinum B toxin has also been tried.[11,15]

Doses of botulinum A toxin, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation:* Botulinum A toxin is used in the management of dynamic equinus foot deformity associated with spasticity in children with cerebral palsy.

- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Botox* (*Allergan*, *UK*) is 4 units/kg injected into each of 2 sites in the medial and lateral heads of the gastrocnemius muscle. When both lower limbs are to be injected on the same occasion this total dose should be divided between the 2 limbs. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 2 months.
- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen*, *UK*) is 10 to 30 units/kg divided between both calf muscles, primarily targeted to the gastrocnemius muscle. The maximum dose administered should not exceed 1000 units per patient. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 12 weeks.

Botulinum A toxin is also used in the treatment of upper limb spasticity in adults.

- In the treatment of upper limb spasticity associated with stroke, the exact dosage and number of injection sites of botulinum A toxin as the preparation *Botox* (*Allergan*, *UK*) should be tailored to the individual based on the muscles involved, the severity of the spasticity, and the presence of local weakness. The manufacturer recommends a total dose of 50 units into the flexor digitorum profundus, the flexor digitorum sublimis, the flexor carpi radialis, or the flexor carpi ulnaris, and a total dose of 20 units into the adductor pollicis or flexor pollicis longus. In clinical studies, cumulative doses did not exceed 360 units at any treatment session.
- In the treatment of focal spasticity of the arm, the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen*, *UK*) is 1000 units divided into: a dose of 150 units into the flexor digitorum profundus, the flexor carpi ulnaris, and the flexor carpi radialis; 150 to 250 units into the flexor digitorum superficialis; and 300 to 400 units into the biceps brachii. All muscles should be injected at one site except the biceps brachii which should be injected at 2 sites. Lower doses are recommended in patients whose target muscles are small, where the biceps brachii is not to be injected, or in patients receiving multi-level injections. Clinical improvement generally occurs within the first 2 weeks.

1. Sheean G. Botulinum toxin treatment of adult spasticity : a benefit-risk assessment. *Drug Safety* 2006; **29:** 31–48.
2. Simpson DM, *et al.* Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996; **46:** 1306–10.
3. Bhakta BB, *et al.* Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatry* 1996; **61:** 30–5.
4. Burbaud P, *et al.* A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 1996; **61:** 265–9.
5. Brashear A, *et al.* Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; **347:** 395–400.
6. Zelnik N, *et al.* The role of botulinum toxin in the treatment of lower limb spasticity in children with cerebral palsy—a pilot study. *Isr J Med Sci* 1997; **33:** 129–33.
7. Carr LJ, *et al.* Position paper on the use of botulinum toxin in cerebral palsy. *Arch Dis Child* 1998; **79:** 271–3.
8. Fehlings D, *et al.* An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr* 2000; **137:** 331–7.
9. Ubhi T, *et al.* Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000; **83:** 481–7.
10. Koman LA, *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics* 2001; **108:** 1062–71.
11. Berweck S, Heinen F. Use of botulinum toxin in pediatric spasticity (cerebral palsy). *Mov Disord* 2004; **19** (suppl 8): S162–S167.
12. Bjornson K, *et al.* Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; **120:** 49–58.
13. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
14. Wasiak J, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 07/05/08).
15. Brashear A, *et al.* Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. *Arch Phys Med Rehabil* 2004; **85:** 705–9.

Stiff-man syndrome. A patient with stiff-man syndrome (see Muscle Spasm, p.993) had marked improvement of ambulation and cessation of pain after injection of botulinum A toxin into affected paraspinal muscles.[1] In another case report, improvement in rigidity and muscle spasm was reported[2] in 2 patients after botulinum treatment; muscle spasms reduced within 3 days of treatment. It was also found that there was an increase in the duration of effect of botulinum A toxin after each subsequent injection and only a gradual return of painful spasm.

1. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. *Mov Disord* 1993; **8:** 371–3.
2. Liguori R, *et al.* Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. *Mov Disord* 1997; **12:** 1060–3.

Strabismus. Botulinum A toxin has been used to weaken overactive extra-ocular muscles as an alternative or adjunct to surgery in the correction of strabismus (p.1874). Not all patients respond to botulinum A toxin and many patients who do respond require more than one injection to maintain improvement. Botulinum A toxin does not appear to offer a better degree of correction than traditional surgery, and it has been suggested that it should be reserved for use in patients unresponsive to, or unsuitable for, surgery. In the USA botulinum A toxin as the preparation *Botox* (*Allergan*, *USA*) is indicated for the treatment of strabismus in patients 12 years of age or older. Depending on the direction and degree of deviation to be corrected the recommended initial dose of Botox to be injected into any one extra-ocular muscle ranges from 1.25 to 5 units. Paralysis is usually seen within the first 2 days and increases in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a further 2 to 6 weeks. It is recommended that patients are re-examined 7 to 14 days after injection to assess the effect of the dose given. If treatment is required for residual or recurrent strabismus, patients are either given treatment at the previous dosage if response was judged to have been adequate or up to twice the previous dose if paralysis had been incomplete; no more than 25 units should be injected into any one muscle. Repeat injections should not be given until the effects of the previous dose have dissipated. Injections should be diluted with unpreserved 0.9% sodium chloride solution so that the volume given per muscle is between 0.05 mL and 0.15 mL. Injections should also be made using an electromyographically guided needle to aid location of the target muscle.

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1. Biglan AW, *et al.* Management of strabismus with botulinum A toxin. *Ophthalmology* 1989; **96:** 935–43.
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6. Petitto VB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. *Ophthalmology* 1991; **98:** 509–13.
7. Elston J. Is botulinum toxin helpful in squint management? *Br J Ophthalmol* 1998; **82:** 105.

8. Tejedor J, Rodríguez JM. Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin. *Br J Ophthalmol* 1999; **83:** 783–7.
9. Dawson EL, Lee JP. Does botulinum toxin have a role in the treatment of small-angle esotropia? *Strabismus* 2004; **12:** 257–60.
10. Dawson EL, *et al.* Does botulinum toxin have a role in the treatment of secondary strabismus? *Strabismus* 2005; **13:** 71–3.

Stuttering. Botulinum toxin may be of benefit in the treatment of stuttering (p.1001).[1,2]

1. Brin MF, *et al.* Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology* 1994; **44:** 2262–6.
2. Cordivari C, *et al.* New therapeutic indications for botulinum toxins. *Mov Disord* 2004; **19** (suppl 8): S157–S161.

Tourette's syndrome. Improvement in tics was noted in patients with Tourette's syndrome (see Tics, p.954) treated with botulinum A toxin.[1,2]

1. Kwak CH, *et al.* Botulinum toxin in the treatment of tics. *Arch Neurol* 2000; **57:** 1190–3.
2. Marras C, *et al.* Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; **56:** 605–10.

Tremor. Local injection of botulinum A toxin[1-4] has been tried in patients with essential tremor (p.1231) that fails to respond to conventional treatment. Botulinum A toxin injection has also been successfully used to treat essential palatal tremor[5-7] and associated symptoms such as uncomfortable ear clicking.

1. Henderson JM, *et al.* Botulinum toxin A in non-dystonic tremors. *Eur Neurol* 1996; **36:** 29–35.
2. Jankovic J, *et al.* A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996; **11:** 250–6.
3. Pacchetti C, *et al.* Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000; **21:** 349–53.
4. Brin MF, *et al.* A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001; **56:** 1523–8.
5. Deuschl G, *et al.* Ear click in palatal tremor: its origin and treatment with botulinum toxin. *Neurology* 1991; **41:** 1677–9.
6. Jamieson DRS, *et al.* Ear clicks in palatal tremor caused by activity of the levator veli palatini. *Neurology* 1996; **46:** 1168–9.
7. Cho JW, *et al.* Case of essential palatal tremor: atypical features and remarkable benefit from botulinum toxin injection. *Mov Disord* 2001; **16:** 779–82.

Vaginismus. Report[1] of one patient who had relief of vaginismus (painful involuntary spasm of the vaginal or perianal muscles severe enough to prevent intercourse) for more than 24 months after injection of botulinum toxin into the vaginal wall muscles.

1. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. *Lancet* 1997; **349:** 252–3.

Preparations

Ph. Eur.: Botulinum Toxin Type A for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Botox; Dysport; ***Austral.:*** Botox; Dysport; ***Austria:*** Botox; Dysport; NeuroBloc; ***Belg.:*** Botox; Dysport; ***Braz.:*** Botox; Dysport; Prosigne; ***Canad.:*** Botox; ***Chile:*** Dyslor; ***Cz.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Denm.:*** Botox; Dysport; Vistabel; ***Fin.:*** Botox; Dysport; Vistabel; ***Fr.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Ger.:*** Botox; Dysport; NeuroBloc†; Xeomin; ***Gr.:*** Botox; Dysport; Vistabel; ***Hong Kong:*** Botox; BTXA; Dysport; ***Hung.:*** Botox; Dysport; Vistabel; ***Indon.:*** Lanzox; ***Irl.:*** Botox; Dysport; NeuroBloc; ***Israel:*** Botox; Dysport; ***Ital.:*** Botox; Dysport; NeuroBloc; Vistabex; ***Jpn:*** Botox; ***Malaysia:*** Botox; Dysport; ***Mex.:*** Botox; ***Neth.:*** Botox; Dysport; NeuroBloc; ***Norw.:*** Botox; Dysport; Vistabel; ***NZ:*** Botox; Dysport; ***Philipp.:*** Botox; Dysport; ***Pol.:*** Botox; Dysport; ***Port.:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Rus.:*** Botox (Ботокс); Dysport (Диспорт); ***S.Afr.:*** Botox; ***Singapore:*** Botox; Dysport; ***Spain:*** Botox; Dysport; NeuroBloc; Vistabel; ***Swed.:*** Botox; Dysport; Vistabel; ***Switz.:*** Botox; Dysport; Vistabel; ***Thai.:*** Botox; Dysport; ***Turk.:*** Botox; Dysport; ***UK:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***USA:*** Botox; Myobloc; ***Venez.:*** Botox; Dysport.

Carisoprodol *(BAN, rINN)*

Carisoprodolum; Isopropylmeprobamate; Karisoprodol; Karisoprodoli; Karizoprodol; Karizoprodolis. 2-Methyl-2-propyltrimethylene carbamate isopropylcarbamate.

Каризопродол

$C_{12}H_{24}N_2O_4$ = 260.3.
CAS — 78-44-4.
ATC — M03BA02.
ATC Vet — QM03BA02.

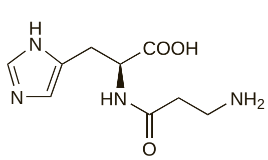

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Carisoprodol). A white or almost white fine powder. M.p. 92° to 95°. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.

USP 31 (Carisoprodol). A white crystalline powder having a mild characteristic odour. M.p. 91° to 94°. Soluble 1 in 2083 of water, 1 in 2.5 of alcohol and of acetone, and 1 in 2.3 of chloroform. Store in airtight containers.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Meprobamate, p.1006.

The most common adverse effects reported with carisoprodol are drowsiness, dizziness, and headache. Sedation may affect the performance of skilled tasks and affected patients should not drive or operate machinery. Poor metabolisers, deficient in the cytochrome P450 isoenzyme CYP2C19, may be at greater risk of drowsiness.

Idiosyncratic reactions may occur within minutes of a dose in patients who have not previously received carisoprodol. Such reactions have been reported rarely and include anaphylactic shock, syncope, tachycardia, confusion, transient quadriplegia, and bronchospasm. Cross-reactivity can occur with its metabolite meprobamate.

Overdosage may result in seizures, stupor, coma, shock, respiratory depression, and rarely death.

Carisoprodol should be used with caution in patients with impaired hepatic or renal function.

Cases of dependence and abuse have been reported with the prolonged use of carisoprodol, particularly in patients with a history of addiction; withdrawal reactions have also occurred when treatment is suddenly stopped after prolonged use or the use of high doses. The increased risk of abuse and addiction with carisoprodol, as well as the risk of altered mental state and psychomotor impairment, has led the EMEA and some other authorities to recommend that it is suspended from the market; in the USA, however, it is recommended that use is limited to 2 to 3 weeks.

Abuse. Analysis[1] of data from the Norwegian Prescription Database found that carisoprodol was used in higher doses than recommended indicating its potential as a drug of abuse. Subsequently, the Norwegian Medicines Agency and the EMEA have recommended for suspension (see above).

1. Bramness JG, *et al.* Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; **64:** 210–18.

Breast feeding. Carisoprodol is distributed into breast milk, achieving concentrations 2 to 4 times those in maternal plasma; UK licensed product information and the *BNF* recommend that it is best avoided in women who are breast feeding although US licensed product information states to use with caution.

Dependence. There are reports of carisoprodol dependence, probably due to its metabolism to meprobamate.[1,2] In one case the patient had symptoms of meprobamate withdrawal that resolved with a dose-reducing schedule of meprobamate.

Dependence may occur more often when carisoprodol is given in high doses and for prolonged periods, especially in patients with a history of alcohol or drug dependence or in those with marked personality disorders. One group[2] found that patients with a history of substance abuse were twice as likely to use carisoprodol in larger doses to those prescribed than those with no such history.

The risk of dependence with carisoprodol has led the EMEA and some other authorities to recommend its suspension from the market (see above).

1. Luehr JG, *et al.* Mail-order (veterinary) drug dependence. *JAMA* 1990; **263:** 657.
2. Reeves RR, *et al.* Carisoprodol (Soma): abuse potential and physician unawareness. *J Addict Dis* 1999; **18:** 51–6.

Porphyria. Carisoprodol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The CNS effects of carisoprodol may be potentiated by alcohol or other CNS depressants. Carisoprodol may cause hepatic enzyme induction and it may therefore affect the metabolism of a number of drugs. The metabolism of carisoprodol is mediated by the cytochrome P450 isoenzyme CYP2C19; use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of carisoprodol, however, there is a lack of data.

Pharmacokinetics

Carisoprodol is absorbed from the gastrointestinal tract and peak plasma concentrations are reached after 1.5 to 2 hours. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C19, which shows genetic polymorphism, and excreted in urine as metabolites, including meprobamate. The terminal elimination half-life of carisoprodol is about 2 hours. It is distributed in substantial amounts into breast milk.

◊ References.

1. Olsen H, *et al.* Carisoprodol elimination in humans. *Ther Drug Monit* 1994; **16:** 337–40.

Uses and Administration

Carisoprodol is a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. After oral doses its effects begin within about 30 minutes and last for 4 to 6 hours. It is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. A usual oral dose is 250 to 350 mg given three or four times daily for up to 2 to 3 weeks. Half the usual dose or less is recommended in elderly patients. It is also given with analgesics in compound preparations.

The EMEA and some other authorities have recommended for carisoprodol to be suspended from the market due to the increased risk of abuse and addiction, as well as the risk of altered mental state and psychomotor impairment.

Preparations

USP 31: Carisoprodol and Aspirin Tablets; Carisoprodol Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Listaflex; ***Canad.:*** Soma†; ***Denm.:*** Somadril†; ***India:*** Carisoma; ***Mex.:*** Somacid; ***Norw.:*** Somadril†; ***Spain:*** Mio Relax†; ***Swed.:*** Somadril†; ***Thai.:*** Myolax†; ***UK:*** Carisoma†; ***USA:*** Soma.

Multi-ingredient: ***Arg.:*** Algiseda; Flexicamin; Flexicamin A; Flexicamin B12; Flogiatrin; Flogiatrin B12; Ketazon Flex†; Mefenix Relax†; Naprontag Flex; Rumisedan Fuerte†; Solocalm Plus; Solocalm-Flex; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Diclofetamol; Dorilax; Flexalgin; Mio-Citalgan; Mioflex; Mioflex A; Mionevrix; Paceflex†; Sanilax; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Scutamil C†; ***Fin.:*** Somadril Comp†; ***Gr.:*** Relacton-C†; ***Hung.:*** Scutamil C†; ***India:*** Carisoma Compound; Somaflam; ***Indon.:*** New Skelan; Somadril Compound; ***Ital.:*** Soma Complex†; ***Mex.:*** Blocacid; Contraxen; Dolaren; Dorsal; Duoflex; Empatil; Naxodol; Profenlax; Somalgesic; ***Spain:*** Flexagil†; Relaxibys†; ***Swed.:*** Somadril Comp†; ***Thai.:*** Alaxan; Asialax; Cariso-Co†; Carisoma Compound†; Caritasone; Cenpadol; Muscelax; Myophen; Polixan; ***USA:*** Sodol Compound; Soma Compound with Codeine†; Soma Compound†; ***Venez.:*** Cotar†; Flexidone†; Praxona.

Chlorphenesin Carbamate *(BANM, USAN, pINNM)*

Carbamato de clorfenesina; Chlorphénésine, Carbamate de; Chlorphenesini Carbamatum; U-19646. 3-(4-Chlorophenoxy)propane-1,2-diol 1-carbamate.

Хлорфенезина Карбамат

$C_{10}H_{12}ClNO_4$ = 245.7.
CAS — 104-29-0 (chlorphenesin); 886-74-8 (chlorphenesin carbamate).

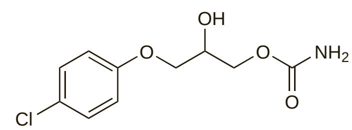

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Chlorphenesin carbamate produces drowsiness and dizziness. There may also be nausea, headache, weakness, confusion, agitation, and insomnia. Hypersensitivity reactions have been reported. There are rare reports of blood disorders.

It should be used with caution in patients with hepatic impairment. Patients affected by drowsiness should not drive or operate machinery.

Interactions

The CNS effects of chlorphenesin carbamate may be potentiated by alcohol or other CNS depressants.

Pharmacokinetics

Chlorphenesin carbamate is readily and completely absorbed from the gastrointestinal tract and partly metabolised in the liver. It is excreted in the urine, mainly as the glucuronide metabolite.

Uses and Administration

Chlorphenesin carbamate is a centrally acting skeletal muscle relaxant related to mephenesin (p.1897). Its mode of action may be related to general depressant effects on the CNS. It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 250 mg three times daily, adjusted according to response. It has been recommended that chlorphenesin carbamate should not be given for longer than 8 weeks.

Chlorphenesin base (p.529) is used as an antifungal.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rinlaxer; ***USA:*** Maolate†.

Chlorzoxazone *(BAN, rINN)*

Chlorobenzoxazolinone; Chlorzoxazonum; Clorzoxazona; Klooritsoksatsoni; Klorzoksazon; Klorzoxazon. 5-Chlorobenzoxazol-2(3*H*)-one.

Хлорзоксазон

$C_7H_4ClNO_2$ = 169.6.
CAS — 95-25-0.
ATC — M03BB03.
ATC Vet — QM03BB03.

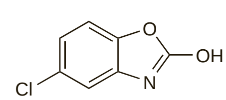

Pharmacopoeias. In *US.*

USP 31 (Chlorzoxazone). A white or practically white, practically odourless, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in methyl alcohol; soluble in solutions of alkali hydroxides and ammonia. Store in airtight containers.

Adverse Effects and Treatment

The most common adverse effects of chlorzoxazone are drowsiness and dizziness. There may occasionally also be gastrointestinal irritation and gastrointestinal bleeding has been reported rarely. Other effects that have occurred are headache, overstimulation, and rarely sensitivity reactions including skin rashes, petechiae, ecchymoses, urticaria and pruritus; very rarely, angioedema or anaphylactoid reactions may occur. Some patients taking chlorzoxazone have developed jaundice and liver damage suspected to be caused by the drug.

After overdosage there may be gastrointestinal disturbances, drowsiness, dizziness, headache, malaise, and sluggishness followed by marked loss of muscle tone, hypotension, and respiratory depression. Emptying the stomach by lavage should be considered, followed by activated charcoal and supportive therapy.

Effects on the liver. Hepatotoxicity, sometimes fatal, has been associated with chlorzoxazone treatment.[1]

1. Powers BJ, *et al.* Chlorzoxazone hepatotoxic reactions: an analysis of 21 identified or presumed cases. *Arch Intern Med* 1986; **146:** 1183–6.

Overdosage. Overdosage and coma occurred on 2 occasions in a patient taking chlorzoxazone; on the second occasion, the patient responded to intravenous flumazenil.[1]

1. Roberge RJ, *et al.* Two chlorzoxazone (Parafon forte) overdoses and coma in one patient: reversal with flumazenil. *Am J Emerg Med* 1998; **16:** 393–5.

Torticollis. There has been a report of a patient with a spasmodic torticollis-like syndrome, consisting of tonic deviation of the head to the right, clenching of the teeth, and dysarthria, which developed repeatedly within 2 hours of ingesting chlorzoxazone for low back pain.[1] Intravenous injection of benzatropine mesilate 1 mg gave rapid relief of symptoms.

1. Rosin MA. Chlorzoxazone-induced spasmodic torticollis. *JAMA* 1981; **246:** 2575.

Precautions

Chlorzoxazone should not be given to patients with impaired liver function and should be stopped if signs of liver toxicity appear. Patients should be advised to report to their doctor any signs or symptoms of possible liver toxicity such as fever, rash, jaundice, dark urine, anorexia, nausea, vomiting, or right upper quadrant pain. Chlorzoxazone may cause drowsiness; patients affected should not drive or operate machinery.

The urine of patients taking chlorzoxazone may be coloured orange or reddish-purple by a phenolic metabolite.

Porphyria. Chlorzoxazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The CNS effects of chlorzoxazone may be enhanced by alcohol and other CNS depressants.

Disulfiram. A study[1] of the efficacy of disulfiram as an inhibitor of the cytochrome P450 isoenzyme CYP2E1 (an enzyme involved in the metabolism of chlorzoxazone) found that a single 500-mg dose of disulfiram reduced plasma clearance of chlorzoxazone by 85%, resulting in a doubling of the latter's peak plasma concentrations and prolongation of its elimination half-life from a mean of 0.92 to 5.1 hours.

1. Kharasch ED, *et al.* Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* 1993; **53:** 643–50.

Isoniazid. Isoniazid inhibited the clearance of chlorzoxazone by 56% when given to 10 slow acetylator subjects resulting in an increase in sedation, headache, and nausea.[1] Two days after stopping isoniazid there had been a rebound increase in the clearance of chlorzoxazone by 56% over the pre-isoniazid clearance value. Similar but less pronounced effects have also been reported[2] in rapid acetylators with chlorzoxazone's pharmacokinetic parameters returning to baseline values in 2 days.

1. Zand R, *et al.* Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* 1993; **54:** 142–9.
2. O'Shea D, *et al.* Modulation of CYP2E1 activity by isoniazid in rapid and slow N-acetylators. *Br J Clin Pharmacol* 1997; **43:** 99–103.

Pharmacokinetics

Chlorzoxazone is reported to be completely absorbed after oral doses and peak plasma concentrations are achieved after 1 to 2 hours. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6-hydroxychlorzoxazone, and excreted in the urine primarily as the glucuronide metabolite. The elimination half-life of chlorzoxazone is about 1 hour.

Uses and Administration

Chlorzoxazone is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain. Its effects begin within an hour of an oral dose and last for 3 to 4 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 500 mg three or four times daily; the dose can often be reduced subsequently to 250 mg three or four times daily, although doses of up to 750 mg three or four times daily may be given if necessary. Chlorzoxazone is also given with analgesics in compound preparations.

Preparations

USP 31: Chlorzoxazone Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Fenarol-S†; ***Denm.:*** Paraflex; ***Hong Kong:*** Solaxin; ***Hung.:*** Myoflexin; ***India:*** Parafon DSC; ***Indon.:*** Solaxin; ***S.Afr.:*** Paraflex; ***Swed.:*** Paraflex; ***Thai.:*** Chlorzox†; ***Turk.:*** Paraflex; ***USA:*** Paraflex; Parafon Forte DSC; Remular-S.

Multi-ingredient: ***Arg.:*** Ibupirac Flex; Paraflex AN; Paraflex Plus; Rucaten Forte; ***Austria:*** Parafon; ***Braz.:*** Paralon; ***Canad.:*** Acetazone Forte; Acetazone Forte C8; Back-Aid; Parafon Forte; Tylenol Aches & Strains; ***Chile:*** Beserol-S; Brevex; Desdol; Flectadol; Tonoflex; Winasorb Flex; ***Fin.:*** Paraflex comp†; ***Hong Kong:*** Relaxin-P†; ***India:*** Cip-Zox; Dolocide MR; Duodil; Fenaplus-MR; Flamar-MX; Flexon-MR; Myospaz; Myospaz Forte; New Panazox; Nicip MR; Osteoflam-MR; Pacizox; Parafon; Systaflam; ***Malaysia:*** Paras; ***Mex.:*** Parafon Forte; Reumophan; Tafirol Flex; ***Philipp.:*** Parafon; ***S.Afr.:*** Parafon; ***Swed.:*** Paraflex comp†; ***Thai.:*** Cezox; Myora; Myoserv†; Parafon; ***Turk.:*** Mepadol; Muskazon; Parafon; ***USA:*** Flexaphen.

Cyclobenzaprine Hydrochloride *(USAN, rINNM)*

Cyclobenzaprine, Chlorhydrate de; Cyclobenzaprini Hydrochloridum; Hidrocloruro de ciclobenzaprina; MK-130 (cyclobenzaprine); Proheptatriene Hydrochloride; Ro-4-1557 (cyclobenzaprine); RP-9715 (cyclobenzaprine). 3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*NN*-dimethylpropylamine hydrochloride.

Циклобензаприна Гидрохлорид

$C_{20}H_{21}N,HCl = 311.8.$

CAS — 303-53-7 (cyclobenzaprine); 6202-23-9 (cyclobenzaprine hydrochloride).

ATC — M03BX08.

ATC Vet — QM03BX08.

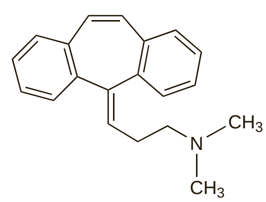

(cyclobenzaprine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cyclobenzaprine hydrochloride:

Cyclo; Cyclone.

Pharmacopoeias. In *US.*

USP 31 (Cyclobenzaprine Hydrochloride). A white to off-white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and in dichloromethane; insoluble in hydrocarbons.

Adverse Effects, Treatment, and Precautions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and shares their adverse effects and precautions (see Amitriptyline, p.376). Cyclobenzaprine should be used with caution in the elderly and patients with hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

It may cause drowsiness; patients affected should not drive or operate machinery.

The elderly. Symptoms of toxicity[1] (hallucinations, insomnia, and restlessness) were seen in a 76-year-old patient taking cyclobenzaprine at therapeutic doses. US licensed product information states that the elderly may be more likely to experience adverse effects such as hallucinations and confusion..

In another study[2] the mean elimination half-life of cyclobenzaprine in the elderly was longer than in younger subjects and clearance was reduced. It was suggested that it should be used in a reduced dose or frequency in the elderly.

1. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. *Arch Intern Med* 2000; **160:** 1373.
2. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Neuroleptic malignant syndrome. Report of a neuroleptic malignant-like syndrome associated with cyclobenzaprine in a 36-year-old man.[1] It was not clear whether the syndrome was due to an idiosyncratic reaction or to an overdose.

1. Theoharides TC, *et al.* Neuroleptic malignant-like syndrome due to cyclobenzaprine. *J Clin Psychopharmacol* 1995; **15:** 79–81.

Overdosage. Treatment of cyclobenzaprine overdose is mainly symptomatic and supportive. A large retrospective study[1] found that cyclobenzaprine hydrochloride overdoses of up to 1 g rarely present with the serious cardiovascular and neurological effects seen with tricyclic antidepressant overdoses. There were no reports of seizures, life-threatening arrhythmias, or fatalities. However, 150 patients required treatment in the intensive care unit, 13 patients needed assisted ventilation, and 8 were unresponsive to stimuli. It was noted that observation may be sufficient for overdoses of under 50 mg in children.

1. Spiller HA, *et al.* Five-year multicentre retrospective review of cyclobenzaprine toxicity. *J Emerg Med* 1995; **13:** 781–5.

Interactions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and may be subject to similar interactions (see Amitriptyline, p.379). The CNS effects of cyclobenzaprine may be enhanced by alcohol or other CNS depressants.

Antidepressants. A patient who already had QT prolongation associated with use of cyclobenzaprine and *fluoxetine*. developed torsade de pointes, progressing into ventricular fibrillation, when given *droperidol* as premedication prior to surgery.[1] QT abnormalities resolved on stopping cyclobenzaprine.

1. Michalets EL, *et al.* Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 1998; **32:** 761–5.

Antipsychotics. For a report of an interaction between cyclobenzaprine and *droperidol*, see Antidepressants above.

Pharmacokinetics

Cyclobenzaprine hydrochloride is readily and almost completely absorbed from the gastrointestinal tract, although plasma concentrations vary considerably among individuals given the same dose. About 93% is bound to plasma proteins and has a reported effective half-life of 8 to 37 hours. It is extensively metabolised, principally to glucuronide conjugates, and excreted in the urine. Cytochrome P450 isoenzymes CYP3A4, CYP1A2, and to a lesser extent CYP2D6 mediate its demethylation. Some unchanged drug appears in the bile and is excreted in the faeces.

◊ References.

1. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Uses and Administration

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant, related to the tricyclic antidepressants. It acts mainly at the brain stem to decrease tonic somatic motor activity influencing both alpha and gamma motor systems. Additional activity at spinal cord sites may be involved. Effects begin within 1 hour of a dose by mouth; the effects of a single dose have been reported to last as long as 12 to 24 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual dose is 5 mg three times daily given by mouth, increased if necessary to 10 mg three times daily. Treatment for more than 2 or 3 weeks is not recommended. A starting dose of 5 mg with less frequent dosing is recommended for elderly patients. For doses in patients with hepatic impairment, see below. A modified-release preparation of cyclobenzaprine hydrochloride is also available for once-daily dosing.

Administration in hepatic impairment. A starting dose of 5 mg of cyclobenzaprine hydrochloride by mouth, and perhaps less frequent dosing than usual (see above), is recommended for those with mild hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

Back pain. A meta-analysis[1] of 14 studies concluded that cyclobenzaprine hydrochloride, in the short term, improves low back pain (p.7). Doses given to patients were titrated and ranged from 10 to 60 mg daily with a median dose of 30 mg daily. Patients improved moderately in the first 4 days of treatment, with the effects of cyclobenzaprine hydrochloride gradually declining with time although there was some evidence of continued improvement at 2 weeks. Further studies are needed to determine the optimal length of use in the management of acute back pain. Adverse effects were common, occurring in at least 53% of patients.

1. Browning R, *et al.* Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med* 2001; **161:** 1613–20.

Fibromyalgia. Studies of the efficacy of cyclobenzaprine in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p.13), have produced conflicting results but a meta-analysis[1] of 5 such studies suggested that cyclobenzaprine had some modest benefit in the condition. Patients were more likely to report overall improvement and moderate reductions in individual symptoms, particularly sleep, while taking the drug.

1. Tofferi JK, *et al.* Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 2004; **51:** 9–13.

Preparations

USP 31: Cyclobenzaprine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Miosan; Mirtax; Musculare; ***Canad.:*** Flexeril†; Flexitec†; Novo-Cycloprine; ***Chile:*** Ciclamil; Masterelax†; Medarex; Nostaden; Reflexan; Relexil; Tensamon; Tensiomax; Tensodox; Tonalgen; Ziclob; ***Ital.:*** Flexiban; ***Port.:*** Flexiban; ***Spain:*** Yurelax; ***USA:*** Amrix; Fexmid; Flexeril.

Multi-ingredient: ***Arg.:*** Dorixina Relax; ***Braz.:*** Dolamin Flex; ***Mex.:*** Yuredol; ***Venez.:*** Dorixina Flex.

Dantrolene Sodium *(BANM, USAN, rINNM)*

Dantrolène Sodique; Dantroleno sódico; F-440; F-368 (dantrolene); Natrii Dantrolenum; Sodyum Dantrolen. The hemiheptahydrate of the sodium salt of 1-[5-(4-nitrophenyl)furfurylideneamino]imidazolidine-2,4-dione.

Натрий Дантролен

$C_{14}H_9N_4NaO_5,3\frac{1}{2}H_2O$ = 399.3.

CAS — 7261-97-4 (dantrolene); 14663-23-1 (anhydrous dantrolene sodium); 24868-20-0 (dantrolene sodium, hemiheptahydrate).

ATC — M03CA01.

ATC Vet — QM03CA01.

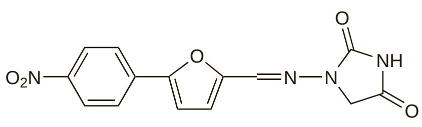

(dantrolene)

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Dantrolene Sodium). A yellowish-orange to orange crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in acetone; sparingly soluble in methyl alcohol.

USP 31 (Dantrolene Sodium). A fine orange to orange-brown powder. Sparingly soluble in acetone, in dimethyformamide, and in glycerol. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects associated with dantrolene sodium tend to occur at the start of treatment, but are often short lived and can be controlled by adjusting the dose. The most common adverse effects are drowsiness, dizziness, fatigue, weakness, and general malaise. Diarrhoea may be severe enough to require withdrawal. If diarrhoea recurs on restarting dantrolene, then treatment should probably be stopped permanently. Other adverse effects reported include nausea and vomiting, anorexia, constipation, abdominal cramps, gastrointestinal bleeding, tachycardia, unstable blood pressure, dyspnoea, rashes (often acneform), pruritus, chills and fever, headache, myalgia, nervousness, insomnia, confusion, visual disturbances, mental depression, dysphagia and speech disturbances, and seizures. Haematuria, crystalluria, urinary frequency and retention, and incontinence may occur. Rare but serious adverse effects include hepatotoxicity which may be fatal (see below) and pleural effusion with pericarditis.

Serious adverse effects do not appear to be a problem with the short-term use of intravenous dantrolene sodium in the treatment of malignant hyperthermia.

Effects on the liver. Dantrolene has caused hepatotoxicity with raised liver enzyme values, jaundice, and hepatitis;[1-3] fatalities have been reported.[1,3] Not all patients experienced symptoms such as anorexia, nausea, or abdominal discomfort before the onset of disease and the severity of hepatic injury was unrelated to clinical presentation. In the first report[1] the 14 fatalities occurred with doses in excess of 200 mg daily; a later review[3] found the mean dose associated with 27 fatalities to be 582 mg daily, while reports of non-fatal liver toxicity (95 cases) were associated with a mean dose of 263 mg daily. The onset of hepatic injury was usually between 1 and 6 months after starting treatment and fatalities were not reported in the first 2 months. Only rarely did injury develop before 45 days of treatment. Females appeared to be at greater risk of serious liver injury and the severity of reaction appeared to be age-related with most fatalities occurring in patients over 30 years of age. The liver injury was usually hepatocellular and might include ascending cholangitis; there was little evidence of hypersensitivity.

1. Utili R, *et al.* Dantrolene-associated hepatic injury: incidence and character. *Gastroenterology* 1977; **72:** 610–16.
2. Wilkinson SP, *et al.* Hepatitis from dantrolene sodium. *Gut* 1979; **20:** 33–6.
3. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 1990; **40:** 1427–32.

Effects on the lungs. Pulmonary oedema associated with heart failure,[1] and pleural effusions with eosinophilia[2-4] have been reported rarely in patients receiving dantrolene. These reactions generally resolve on withdrawal of the drug but resolution may take several months; corticosteroid therapy may be of benefit in dantrolene-related eosinophilic pleural effusion.[3]

1. Robillart A, *et al.* Insuffisance cardiaque par surdosage en dantrolène. *Ann Fr Anesth Reanim* 1986; **5:** 617–19.
2. Mahoney JM, Bachtel MD. Pleural effusion associated with chronic dantrolene administration. *Ann Pharmacother* 1994; **28:** 587–9.
3. Felz MW, Haviland-Foley DJ. Eosinophilic pleural effusion due to dantrolene: resolution with steroid therapy. *South Med J* 2001; **94:** 502–4.
4. Le-Quang B, *et al.* Dantrolene and pleural effusion: case report and review of literature. *Spinal Cord* 2004; **42:** 317–20.

Lymphomas. A case of fatal lymphocytic lymphoma was associated with prolonged dantrolene therapy (600 mg daily) for progressive spastic paraplegia.[1]

1. Wan HH, Tucker JS. Dantrolene and lymphocytic lymphoma. *Postgrad Med J* 1980; **56:** 261–2.

Precautions

It is recommended that dantrolene sodium should not be given to patients with active liver disease. Liver-function tests should be performed in all patients before and during treatment; if abnormal values are found, treatment should generally be stopped. The risk of liver injury may be increased in patients over 30 years of age, in females (especially those taking oestrogens), in those with a history of liver disease, and with doses above 400 mg daily (see under Effects on the Liver, above). Dantrolene sodium should be used with caution in patients with cardiac or pulmonary disorders. It should not be given to patients who use their spasticity to maintain posture or function or to patients with acute muscle spasm.

Dantrolene sodium may cause drowsiness; patients affected should not drive or operate machinery.

Interactions

The CNS effects of dantrolene sodium may be enhanced by alcohol or other CNS depressants. Use with other potentially hepatotoxic drugs such as oestrogens may possibly increase the risk of liver damage and should be avoided.

Calcium-channel blockers. Severe hyperkalaemia and myocardial depression occurred with intravenous dantrolene for prophylaxis of malignant hyperthermia in a patient also taking *verapamil* for angina.[1] The peak serum-potassium concentration was 7.1 mmol/litre 2.5 hours after the dantrolene infusion. *Nifedipine* was substituted for verapamil in a subsequent operation and only a small increase in serum potassium occurred after dantrolene. Ventricular fibrillation and cardiovascular collapse associated with hyperkalaemia have been seen with this combination in *animal* studies, and the manufacturers recommend that calcium-channel blockers and intravenous dantrolene should not be used together.

1. Rubin AS, Zablocki AD. Hyperkalaemia, verapamil, and dantrolene. *Anesthesiology* 1987; **66:** 246–9.

Pharmacokinetics

Dantrolene sodium is slowly and almost completely absorbed from the gastrointestinal tract after oral doses. It is metabolised in the liver mainly to the hydroxylated metabolite, which is nearly as potent as dantrolene sodium, and the acetamide metabolite which has weak muscle relaxant activity. It is excreted in the urine, mainly as metabolites with a small amount of unchanged dantrolene; some is excreted in the bile. Dantrolene is bound extensively to plasma proteins. The elimination half-life of oral dantrolene is about 9 hours, although half-lives of up to 12 hours have been reported after intravenous use.

Uses and Administration

Dantrolene sodium is a muscle relaxant with a direct action on skeletal muscle. It uncouples muscular contraction from excitation, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

It has an important role when given orally, for the symptomatic relief of chronic, severe spasticity (p.1887). It is also given, usually by intravenous injection, for the treatment of malignant hyperthermia.

For **spasticity**, the initial oral dose is 25 mg daily increased gradually as necessary, at 7-day intervals, over about 7 weeks to a maximum dose of 100 mg four times daily. If no response is achieved within 45 days treatment should be stopped. In children, US licensed product information suggests a dose of 500 micrograms/kg once daily, increased gradually if necessary to 2 mg/kg three times daily; dosage four times daily may be necessary for some children but a dose of 100 mg four times daily should not be exceeded.

In the treatment of **malignant hyperthermia**, dantrolene sodium is given, with supportive measures, in an initial dose of 1 mg/kg by rapid intravenous injection, repeated, if necessary, to a total dose of 10 mg/kg. An average dose of 2.5 mg/kg is usually effective. If a relapse or recurrence occurs, dantrolene should be given again at the last effective dose. In the USA, doses of 1 to 2 mg/kg orally four times daily have been recommended for up to 3 days after the crisis to prevent recurrence, and similar doses have been given for 1 to 2 days before surgery in individuals thought to be at risk of developing the syndrome. Prophylactic doses may also be given intravenously; 2.5 mg/kg has been recommended, infused over about 60 minutes, starting about 75 minutes before anticipated anaesthesia, with further doses during anaesthesia and surgery if signs of malignant hyperthermia develop.

Hyperthermia. Dantrolene is used in the treatment of hyperthermia associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, which occurs in the neuroleptic malignant syndrome (see below and p.972) and in malignant hyperthermia (see below). There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents such as carbon monoxide,[1] MAOIs,[2] and ethyltenamfetamine.[3] However, after suggestions that it might also be of use in cocaine intoxication, the manufacturers[4] warned physicians that they should not regard dantrolene as an effective treatment for all types of hyperthermia and rigidity accompanying poisoning.

Dantrolene has been tried as part of treatment for heat stroke (see under Fever and Hyperthermia, p.10) but does not appear to affect outcome.[5]

1. Ten Holter JBM, Schellens RLLAM. Dantrolene sodium for treatment of carbon monoxide poisoning. *BMJ* 1988; **296:** 1772–3.
2. Kaplan RF, *et al.* Phenelzine overdose treatment with dantrolene sodium. *JAMA* 1986; **255:** 642–4.
3. Tehan B. Ecstasy and dantrolene. *BMJ* 1993; **306:** 146.
4. Fox AW. More on rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1989; **321:** 1271.
5. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002; **346:** 1978–88.

MALIGNANT HYPERTHERMIA. Malignant hyperthermia (malignant hyperpyrexia) is a rare but potentially fatal syndrome associated with general anaesthesia, in which a sudden increase in the concentration of calcium in muscle cytoplasm initiates a series of metabolic disturbances. The disorder appears to be genetically determined and is more common in males. In susceptible individuals a reaction may be induced by inhalation anaesthetics (mainly halogenated hydrocarbons), suxamethonium, prolonged anaesthesia, pre-operative exercise, muscle trauma, fever, or anxiety. However, many reactions occur in individuals who have had uneventful general anaesthesia previously. Early signs and symptoms of the syndrome include tachycardia, unstable blood pressure, hypercapnia, rising temperature, and hyperventilation followed by metabolic acidosis and hyperkalaemia. Muscle rigidity develops in many patients and later there may be evidence of muscle damage including raised serum concentrations of creatine phosphokinase and other enzymes, myoglobinaemia, and myoglobinuria. Hyperthermia develops relatively late. Other late complications may include renal failure, intravascular coagulopathy, and pulmonary oedema.

Treatment should be started as soon as possible after symptoms appear with dantrolene being given by rapid intravenous injection until symptoms disappear.[1-3] Supportive treatment must also be given including immediate withdrawal of anaesthesia, giving oxygen, correction of acidosis with sodium bicarbonate, control of hyperkalaemia with insulin, and cooling procedures (see p.10).

The incidence of reactions in susceptible individuals can be reduced by avoiding triggering agents. Dantrolene has also been given prophylactically, but a high incidence of adverse effects has been reported,[4] and such use is not generally recommended.[3]

Susceptibility to malignant hyperthermia can be detected by histological examination of muscle fibres obtained by biopsy and study of their response to caffeine and/or halothane *in vitro*. Although such testing remains the gold standard for determining susceptibility, genetic testing is also being developed as an alternative.[5]

Dantrolene has been suggested[6] for use as a secondary drug in the treatment of a related and potentially fatal syndrome that has developed in some children after induction of anaesthesia with halothane and suxamethonium (see also Children, under Precautions of Suxamethonium, p.1911).

1. Britt BA. Dantrolene. *Can Anaesth Soc J* 1984; **31:** 61–75.
2. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.

3. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
4. Wedel DJ, *et al.* Clinical effects of intravenously administered dantrolene. *Mayo Clin Proc* 1995; **70:** 241–6.
5. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA* 2005; **293:** 2918–24.
6. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.

Neuroleptic malignant syndrome. Dantrolene has been used, usually alone or with bromocriptine, in the treatment of neuroleptic malignant syndrome (p.972), although some workers have not found it to be of use,[1] and evidence from controlled trials is lacking.[2] Doses reported for dantrolene have varied greatly.[3,4] For those patients unable to swallow and when rapid control of symptoms is required, doses of 1 mg/kg or more have been given initially by intravenous injection. Up to 600 mg has been given daily by mouth in divided doses.

1. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.
2. Krause T, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; **59:** 364–73.
3. Ward A, *et al.* Dantrolene: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32:** 130–68.
4. Harpe C, Stoudemire A. Aetiology and treatment of neuroleptic malignant syndrome. *Med Toxicol* 1987; **2:** 166–76.

Tetanus. Dantrolene has effectively controlled muscle spasms in the treatment of tetanus (see p.1901). It has also been used as an adjunct[1] to neuromuscular blockade; there are conflicting reports[2,3] of its value in avoiding mechanical ventilation.

1. Tidyman M, *et al.* Adjunctive use of dantrolene in severe tetanus. *Anesth Analg* 1985; **64:** 538–40.
2. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia* 1993; **48:** 969–71.
3. Possamai C, *et al.* Dantrolene infusion in severe tetanus. *Anaesthesia* 1997; **52:** 610.

Preparations

BP 2008: Dantrolene Oral Suspension;
USP 31: Dantrolene Sodium Capsules; Dantrolene Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Dantrium; ***Belg.:*** Dantrium; ***Braz.:*** Dantrolen; ***Canad.:*** Dantrium; ***Chile:*** Dantrium; ***Denm.:*** Dantrium; ***Fr.:*** Dantrium; ***Ger.:*** Dantamacrin; ***Gr.:*** Dantrium; Dantrolen; ***Hong Kong:*** Dantrium†; ***Irl.:*** Dantrium; ***Israel:*** Dantrium; ***Ital.:*** Dantrium; ***Neth.:*** Dantrium; ***NZ:*** Dantrium; ***Port.:*** Dantrium†; ***S.Afr.:*** Dantrium; ***Switz.:*** Dantamacrin; ***UK:*** Dantrium; ***USA:*** Dantrium.

Eperisone Hydrochloride *(rINNM)*

Épérisone, Chlorhydrate d'; Eperisoni Hydrochloridum; Hidrocloruro de eperisona. 4′-Ethyl-2-methyl-3-piperidinopropiophenone hydrochloride.

Эперизона Гидрохлорид

$C_{17}H_{25}NO,HCl = 295.8$.

CAS — 64840-90-0 (eperisone); 56839-43-1 (eperisone hydrochloride).

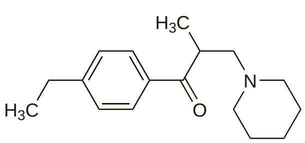

(eperisone)

Pharmacopoeias. In *Jpn.*

Profile

Eperisone is a centrally acting skeletal muscle relaxant that has been used in the symptomatic treatment of painful muscle spasm (p.1887) and spasticity (p.1887). It may also have a vasodilator action. Eperisone hydrochloride has been given by mouth in usual doses of 50 mg three times daily after food.

Effects on the skin. A non-pigmenting fixed drug eruption developed in a 42-year-old woman after taking oral diclofenac sodium and eperisone hydrochloride.[1] There was no residual hyperpigmentation and the rash and accompanying itching and burning sensation resolved within 7 days after stopping both drugs. On rechallenge with eperisone, an erythematous plaque developed at the same site within a couple of hours. The lesion disappeared within 5 days with no sequelae.

1. Choonhakarn C. Non-pigmenting fixed drug eruption: a new case due to eperisone hydrochloride. *Br J Dermatol* 2001; **144:** 1288–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Eprinoc; Epsonal; Forelax; Forres; Myonal; Myonep; Myori; Permyo; Rizonax; Zonal; ***Jpn:*** Myonal; ***Malaysia:*** Myonal; ***Philipp.:*** Myonal; ***Singapore:*** Myonal; ***Thai.:*** Myonal.

Idrocilamide *(rINN)*

Idrocilamida; Idrocilamidum; LCB-29. *N*-(2-Hydroxyethyl)cinnamamide.

Идроциламид

$C_{11}H_{13}NO_2 = 191.2$.

CAS — 6961-46-2.

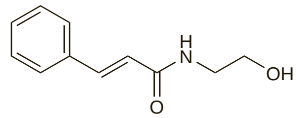

Adverse Effects

When given by mouth idrocilamide was reported to produce abdominal pain, nausea, and drowsiness. Excitement, euphoria and hallucinations, and depression may occur.

Uses and Administration

Idrocilamide is a centrally acting muscle relaxant. It is reported to have local muscle relaxant and anti-inflammatory effects and is now mainly used topically.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Srilane; ***Fr.:*** Srilane; ***Hong Kong:*** Srilane†; ***Switz.:*** Talval.

Mephenesin *(BAN, rINN)*

Cresoxydiol; Glykresin; Mefenesiini; Mefenesin; Mefenesina; Méphénésine; Mephenesinum. 3-(*o*-Tolyloxy)propane-1,2-diol.

Мефенезин

$C_{10}H_{14}O_3 = 182.2$.

CAS — 59-47-2.
ATC — M03BX06.
ATC Vet — QM03BX06.

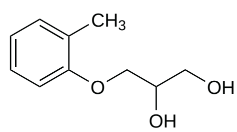

NOTE. The name tolynol has been applied to both mephenesin and *p*,α-dimethylbenzyl alcohol (p.2294).

Pharmacopoeias. In *It.*

Profile

Mephenesin is a centrally acting skeletal muscle relaxant used for the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. Its clinical usefulness is considered to be limited by its brief duration of action. It is given orally in doses of 1.5 to 3 g daily in divided doses. It is also applied topically, usually with rubefacients.

Porphyria. Mephenesin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Decontractyl; ***Ger.:*** DoloVisano M.

Multi-ingredient: ***Belg.:*** Algipan; ***Fr.:*** Algipan; Decontractyl; Traumalgyl; ***India:*** Acks; Flamar; Inflazone; Medicreme; Relaxyl; ***Ital.:*** Relaxar; ***S.Afr.:*** Spasmend.

Mephenoxalone *(rINN)*

AHR-233; Mefenoksalon; Mefenoxalona; Méphénoxalone; Mephenoxalonum; Methoxadone; OM-518. 5-(2-Methoxyphenoxymethyl)oxazolidin-2-one.

Мефеноксалон

$C_{11}H_{13}NO_4 = 223.2$.

CAS — 70-07-5.
ATC — N05BX01.
ATC Vet — QN05BX01.

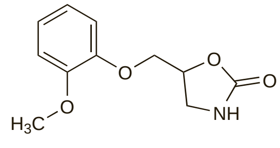

Profile

Mephenoxalone has actions similar to those of meprobamate (p.1006). It has been given orally in a dose of 200 to 400 mg three times daily as a muscle relaxant in the treatment of muscle spasm (p.1887). It has also been given for the treatment of anxiety.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dimexol; Dorsiflex; ***Neth.:*** Dorsiflex; ***Turk.:*** Dorsiflex.

Multi-ingredient: ***Turk.:*** Dorsilon.

Metaxalone *(BAN, USAN, rINN)*

AHR-438; Metaxalona; Métaxalone; Metaxalonum. 5-(3,5-Xylyloxymethyl)oxazolidin-2-one.

Метаксалон

$C_{12}H_{15}NO_3 = 221.3$.

CAS — 1665-48-1.

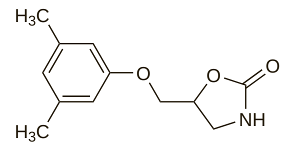

Adverse Effects, Treatment, and Precautions

As for Chlorzoxazone, p.1895.

Metaxalone may cause drowsiness; patients affected should not drive or operate machinery.

Patients taking metaxalone excrete in the urine a metabolite which gives a false positive reaction to copper sulfate-based tests for glycosuria.

Interactions

The CNS effects of metaxalone may be enhanced by alcohol and other CNS depressants.

Pharmacokinetics

Metaxalone is absorbed from the gastrointestinal tract, metabolised in the liver, and excreted in urine as metabolites. The plasma elimination half-life is about 2 to 3 hours.

Uses and Administration

Metaxalone is a centrally acting skeletal muscle relaxant. Its mode of action may be related to its sedative properties.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual oral dose is 800 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Skelaxin.

Methocarbamol *(BAN, rINN)*

Guaiphenesin Carbamate; Méthocarbamol; Methocarbamolum; Metocarbamol; Metokarbamol; Metokarbamoli. 2-Hydroxy-3-(2-methoxyphenoxy)propyl carbamate.

Метокарбамол

$C_{11}H_{15}NO_5 = 241.2$.

CAS — 532-03-6.
ATC — M03BA03.
ATC Vet — QM03BA03.

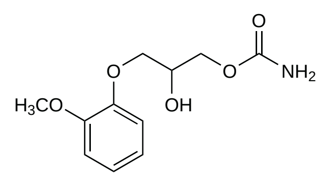

Pharmacopoeias. In *US.*

USP 31 (Methocarbamol). A white powder, odourless or having a slight characteristic odour. M.p. about 94° or, if previously ground to a fine powder, about 90°. Soluble 1 in 40 of water at 20°; sparingly soluble in chloroform; soluble in alcohol only with heating; insoluble in *n*-hexane and in benzene. Store in airtight containers.

Adverse Effects

Adverse effects reported with methocarbamol include nausea, vomiting, anorexia, lightheadedness, dizziness, lassitude, drowsiness, restlessness, anxiety, confusion, tremor, vertigo, blurred vision, fever, headache, convulsions, and hypersensitivity reactions including rashes, pruritus, urticaria, angioedema, and conjunctivitis with nasal congestion.

After injection patients may experience flushing and a metallic taste; incoordination, diplopia, nystagmus, vertigo, syncope, hypotension, bradycardia, and anaphylaxis have been reported. There may be sloughing and thrombophlebitis at the site of injection.

Precautions

Methocarbamol is contra-indicated in coma or pre-coma states, brain damage, myasthenia gravis, or in patients with a history of epilepsy. Caution is advisable in renal or hepatic impairment.

Methocarbamol may cause drowsiness; patients affected should not drive or operate machinery.

Preparations for injection may contain, as a solvent, a macrogol which could increase existing acidosis and urea retention in patients with renal impairment; such preparations should not be used in patients with known or suspected renal disease.

Abnormal coloration. Methocarbamol has been reported to cause brown to black or green discoloration of the urine on standing.[1]

1. Baran RB, Rowles B. Factors affecting coloration of urine and feces. *J Am Pharm Assoc* 1973; **NS13:** 139–42.

Interactions

The CNS effects of methocarbamol may be potentiated by alcohol or other CNS depressants. Methocarbamol has also been reported to potentiate the effects of anorectics and antimuscarinics, and to inhibit the effect of pyridostigmine.

Pharmacokinetics

Methocarbamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Its plasma half-life is reported to be about 1 to 2 hours. It is metabolised by dealkylation and hydroxylation and is excreted in urine primarily as the glucuronide and sulfate conjugates of its metabolites. A small amount is excreted in faeces.

Uses and Administration

Methocarbamol is a centrally acting skeletal muscle relaxant whose action may be due to general depressant effects on the CNS.

Methocarbamol is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. It is sometimes given with analgesics in compound preparations for the treatment of musculoskeletal pain.

The usual initial oral dose for muscle spasm is 1.5 g four times daily, reduced to a maintenance dose of about 4 g daily after 2 to 3 days. A dose of 750 mg three times daily may be sufficient for a therapeutic effect. Half the maximum daily dose or less may be sufficient for elderly patients.

Methocarbamol has also been given intravenously at a rate of not more than 300 mg/minute, by slow injection or by infusion in sodium chloride 0.9% or glucose 5% injection. The parenteral route should not be used for more than 3 consecutive days and the dose should not exceed 3 g daily. The patient should remain lying down during, and for 10 to 15 minutes after, intravenous doses. The US manufacturers state that the injection is hypertonic and extravasation should be avoided. However, it may also be given by intramuscular injection in a dose of up to 500 mg into each gluteal region at intervals of 8 hours.

Preparations

USP 31: Methocarbamol Injection; Methocarbamol Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Robaxin; ***Fr.:*** Lumirelax; ***Ger.:*** Ortoton; ***Hong Kong:*** Robaxin†; ***India:*** Robinax; ***Mex.:*** Remisol; Rexivin; ***S.Afr.:*** Robaxin; ***Spain:*** Robaxin; ***Thai.:*** Laxan; Manobaxine; Musxan; Myocin†; Myomethol; Robaxin†; ***UK:*** Robaxin; ***USA:*** Robaxin.

Multi-ingredient: *Canad.:* Aspirin Backache; Dodds Back Ease; Methoxacet; Methoxacet-C; Methoxisal; Methoxisal-C; Muscle & Back Pain Relief; Muscle & Back Pain Relief Extra Strength; Muscle & Back Pain Relief-8; Muscle Relaxant and Analgesic†; Obusforme†; Relaxophen; Robax Platinum; Robaxacet; Robaxacet-8; Robaxisal; Robaxisal-C; Spasmhalt; Spasmhalt-ASA; ***Ger.:*** Ortoton Plus; ***India:*** Flexinol; Ibugesic-M; Robiflam; Robinaxol; ***Mex.:*** Artridol; Carbafen; Carbager-Plus; Carbamox; Dolocam Plus; Flexamol; Malival Compuesto; Morlan; Remisol-Plus; Retoflam F; Reupat; Robaxifen; Robaxisal; Vengesic†; ***S.Afr.:*** Robaxisal; ***Spain:*** Robaxisal Compuesto; Robaxisal†; ***Turk.:*** Miyorel; ***Venez.:*** Beseroldos; Robaxifen; Robaxisal.

Pridinol Mesilate *(rINNM)*

C-238 (pridinol); Mesilato de pridinol; Pridinol, Mésilate de; Pridinol Mesylate; Pridinoli Mesilas. 1,1-Diphenyl-3-piperidinopropan-1-ol methanesulphonate.

Придинола Мезилат

$C_{20}H_{25}NO,CH_3SO_3H = 391.5.$
CAS — 511-45-5 (pridinol); 968-58-1 (pridinol hydrochloride); 6856-31-1 (pridinol mesilate).
ATC — M03BX03.
ATC Vet — QM03BX03.

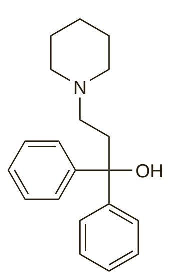

(pridinol)

Profile

Pridinol mesilate is a centrally acting muscle relaxant used in the symptomatic treatment of muscle spasm (p.1887). The usual initial oral dose is 2 to 8 mg three times daily, reduced to 4 to 8 mg daily for maintenance treatment. It is also given by intramuscular injection or rectally, and has been applied in compound topical preparations.

Pridinol has been used as the hydrochloride for its antimuscarinic properties in the management of parkinsonism (p.791).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Myoson; Parks†; ***Hong Kong:*** Konlax†; ***Ital.:*** Lyseen; ***Pol.:*** Polmesilat.

Multi-ingredient: *Arg.:* Blokium Flex; Curinflam Plus; Diclogesic Relax; Diclomar Flex; Diclonex Relax; Dioxaflex Plus; Dolvan Flex; Doxtran Flex; Flexidol Relax; Iglodine Flex; Metaflex Plus NF; Mextran Flex; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa Sport; Oxadisten; Pancloflex; Rodinac Flex; Silfox Flex; Tomanil Flex; Vesalion Flex; Viartril Flex; Voltaren Flex; Xedenol Flex; ***Ital.:*** Algolisina†.

Thiocolchicoside *(rINN)*

Thiocolchicosidum; Tiocolchicósido; Tiyokolşikozid. 3,10-Di(demethoxy)-3-glucopyranosyloxy-10-methylthiocolchicine.

Тиокольхикозид

$C_{27}H_{33}NO_{10}S = 563.6.$
CAS — 602-41-5.
ATC — M03BX05.
ATC Vet — QM03BX05.

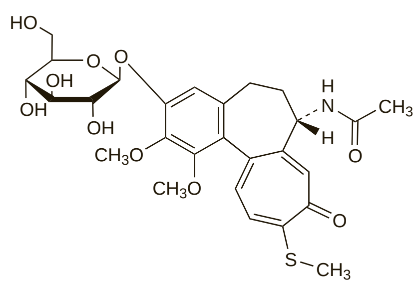

Pharmacopoeias. In *Fr.*

Profile

Thiocolchicoside is a muscle relaxant that has been claimed to possess GABA-mimetic and glycinergic actions. It is used in the symptomatic treatment of painful muscle spasm (p.1887). The usual initial oral dose is 16 mg daily given in 2 divided doses. It has also been given intramuscularly, in doses up to 8 mg daily, or applied as cream or ointment. Photosensitivity reactions may occur.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Coltrax; Muscoril; ***Cz.:*** Muscoril; ***Fr.:*** Coltramyl; Miorel; Myoplege; ***Gr.:*** Disintryl; Haliver; Klesidren; Musco-ril; Thiacomin†; ***India:*** Myoril; ***Ital.:*** Decontril; Miotens; Muscoflex; Muscoril; Sciomir; Strialisin; Teraside; Ticathion; Tiorilene; Tioside; ***Pol.:*** Muscoril; ***Port.:*** Coltramyl; Relmus; ***Turk.:*** Muscoflex; Muscoril; ***Venez.:*** Biocolchid; Coltrax; Colval; Cosiden†; Eusilen; Lampral; Tiochax; Tractil†.

Multi-ingredient: *Ital.:* Muscoril Trauma; ***Mex.:*** Neuroflax; ***Port.:*** Adalgur N; Relmus Compositum†; ***Spain:*** Adalgur; ***Venez.:*** Colfene.

Tizanidine Hydrochloride *(BANM, USAN, rINNM)*

AN-021; DS-103-282; DS-103-282-ch; Hidrocloruro de tizanidina; Tizanidine, Chlorhydrate de; Tizanidini Hydrochloridum. 5-Chloro-*N*-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine hydrochloride.

Тизанидина Гидрохлорид

$C_9H_8ClN_5S,HCl = 290.2.$
CAS — 51322-75-9 (tizanidine); 64461-82-1 (tizanidine hydrochloride).
ATC — M03BX02.
ATC Vet — QM03BX02.

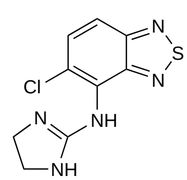

(tizanidine)

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Tizanidine Hydrochloride). Store in airtight containers.

Adverse Effects and Precautions

Tizanidine hydrochloride may cause drowsiness; patients affected should not drive or operate machinery. Other adverse effects include dry mouth, fatigue, dizziness or vertigo, muscle pain and weakness, insomnia, anxiety, headache, bradycardia, nausea, and gastrointestinal disturbances. Hallucinations have occurred on rare occasions. Many adverse effects have been found to be dose related and slow titration of doses appears to reduce the frequency of occurrence. Hypotension may occur.

Increases in liver enzymes and rarely acute hepatitis have been associated with tizanidine and it is contra-indicated in patients with severe hepatic dysfunction. In the UK it is recommended that liver function should be monitored monthly in all patients for the first 4 months and in those who develop symptoms suggestive of hepatic dysfunction; similarly, in the USA baseline assessment and monitoring at 1, 3, and 6 months is advised. Treatment should be stopped if liver enzymes are persistently raised.

Caution is required in the elderly and in patients with renal insufficiency.

Interactions

Tizanidine is metabolised by the cytochrome P450 isoenzyme CYP1A2 and use with ciprofloxacin or fluvoxamine, both potent inhibitors of this isoenzyme, is contra-indicated. Use with other more moderate inhibitors of CYP1A2 (such as other quinolone antibacterials, cimetidine, and antiarrhythmics such as amiodarone, mexiletine, propafenone, and verapamil) should be avoided unless clinically necessary. The CNS effects of tizanidine may be enhanced by alcohol or other CNS depressants. There may be an additive hypotensive effect when tizanidine is used in patients receiving antihypertensive therapy; bradycardia may also be enhanced if given with beta blockers or digoxin. Caution should be exercised when tizanidine is given with drugs known to increase the QT interval. The clearance of tizanidine has been reported to be lower in women receiving hormonal contraceptives.

Antibacterials. In a study of healthy subjects,[1] *ciprofloxacin*, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to elevate the plasma concentrations of tizanidine thereby potentiating its hypotensive and sedative effects.

1. Granfors MT, *et al.* Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; **76:** 598–606.

Antidepressants. In a study[1] in 10 healthy subjects, *fluvoxamine*, a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to increase tizanidine's peak plasma concentrations and elimination half-life 12-fold and 3-fold, respectively. An increased incidence of adverse effects associated with tizanidine such as hypotension, bradycardia, drowsiness, and dizziness was noted in these subjects.

A 70-year-old woman receiving fluvoxamine 150 mg daily and other medications developed bradycardia, dry mouth, urinary retention, and a low body temperature when given tizanidine 3 mg daily;[2] the patient improved when tizanidine was stopped. In a retrospective survey of medical records, the authors reported adverse effects associated with tizanidine in 6 of 23 patients also receiving fluvoxamine.

1. Granfors MT, *et al.* Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. *Clin Pharmacol Ther* 2004; **75:** 331–41.
2. Momo K, *et al.* Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther* 2004; **76:** 509–10.

Antiepileptics. For reference to an interaction between tizanidine and *phenytoin*, see p.500.

Cardiovascular drugs. Severe hypotension, occurring 2 hours after treatment with tizanidine, has been reported in a patient receiving antihypertensives, including *lisinopril*, and other medications.[1] The patient improved after tizanidine and antihypertensives were stopped; they were later resumed without lisinopril, and caused no problems.

1. Kao C-D, *et al.* Hypotension due to interaction between lisinopril and tizanidine. *Ann Pharmacother* 2004; **38:** 1840–3.

Oral contraceptives. Mean peak plasma concentrations after a single 4-mg dose of tizanidine were 3 times greater in 15 women using an oral contraceptive containing *ethinylestradiol* and *gestodene* than in controls;[1] the elimination half-life was not, however, significantly different. The effect appeared to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2 by the contraceptive, resulting in reduced presystemic metabolism of tizanidine. Because the therapeutic range of tizanidine is narrow, care should be exercised if it is given to patients taking oral contraceptives.

1. Granfors MT, *et al.* Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* 2005; **78:** 400–11.

Pharmacokinetics

Tizanidine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after oral doses. It is about 30% bound to plasma proteins. Tizanidine undergoes extensive first-pass metabolism in the liver mainly via the cytochrome P450 isoenzyme CYP1A2 and is excreted mainly in the urine as inactive metabolites. Elimination half-lives of 2 to 4 hours have been reported.

Uses and Administration

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α_2-adrenergic agonist structurally related to clonidine (p.1247) and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions.

Tizanidine hydrochloride is given orally, usually in divided doses; doses are expressed in terms of the base. Tizanidine hydrochloride 1.14 mg is equivalent to about 1 mg of tizanidine. The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily. Maintenance doses have been given in some countries in the form of modified-release preparations. For dosage in renal impairment, see below.

In the treatment of painful muscle spasm tizanidine hydrochloride is given in doses equivalent to 2 to 4 mg of the base three times daily.

Administration in renal impairment. In the UK, licensed product information recommends that in patients with renal insufficiency, treatment with tizanidine hydrochloride should be started with the equivalent of 2 mg of the base once daily; thereafter it advises a slow increase in the once-daily dose before increasing the frequency of administration. Similar recommendations are made in the USA.

Headache. Results from an open-label study[1] and a later controlled study[2] suggested that tizanidine might be of value in the prophylaxis of chronic daily headache. However, an earlier controlled study[3] failed to show any significant advantage over placebo in the treatment of chronic tension-type headache. In another study[4] tizanidine was also effective when given with a long-acting NSAID as part of a detoxification regimen for patients with chronic daily headaches induced by analgesic overuse.

1. Saper JR, *et al.* An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. *Headache* 2001; **41:** 357–68.
2. Saper JR, *et al.* Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; **42:** 470–82.
3. Murros K, *et al.* Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000; **40:** 633–7.
4. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002; **42:** 175–7.

Premedication. The value of tizanidine as a premedicant is being studied.[1] A dose of tizanidine 12 mg appears to have sedative and sympatholytic effects comparable with clonidine 150 micrograms.

1. Meittinen TJ, *et al.* The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996; **82:** 817–20.

Spasticity. The efficacy of tizanidine for spasticity (p.1887) associated with cerebral and spinal disorders[1,2] has been shown in several placebo-controlled studies and in comparative studies it has produced similar improvements in muscle tone to baclofen or diazepam. Carefully titrated doses of tizanidine and baclofen used together may have additive beneficial effects[1,2] but use with benzodiazepines is not recommended because of potential interactions.[1] It was considered that tizanidine might have the advantage of being better tolerated than baclofen.

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; **53:** 435–52.
2. Kamen L, *et al.* A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin* 2008; **24:** 425–39.

Preparations

USP 31: Tizanidine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sirdalud; ***Austria:*** Sirdalud; ***Belg.:*** Sirdalud; ***Braz.:*** Sirdalud; ***Canad.:*** Zanaflex; ***Chile:*** Sirdalud; ***Cz.:*** Sirdalud; ***Denm.:*** Sirdalud; ***Fin.:*** Sirdalud; ***Ger.:*** Sirdalud; ***Gr.:*** Sirdalud; ***Hung.:*** Sirdalud; ***India:*** Sirdalud; ***Indon.:*** Myores; Sirdalud; Zitanid; ***Irl.:*** Zanaflex; ***Ital.:*** Sirdalud; ***Mex.:*** Sirdalud; ***Neth.:*** Sirdalud; ***Philipp.:*** Sirdalud; Ternelax; ***Pol.:*** Sirdalud; ***Port.:*** Sirdalud; ***Rus.:*** Sirdalud (Сирдалуд); ***Spain:*** Sirdalud; ***Switz.:*** Sirdalud; ***Thai.:*** Sirdalud; Tizan; ***Turk.:*** Sirdalud; ***UK:*** Zanaflex; ***USA:*** Zanaflex; ***Venez.:*** Sirdalud.

Multi-ingredient: ***India:*** Kinectine-MR; Movon-MR; Niciflex-T; Nicip T; Nimulid MR; Valus-XT†; Vorth-XT†; Zerodol-MR.

Tolperisone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tolperisona; N-553; Tolpérisone, Chlorhydrate de; Tolperisoni Hydrochloridum. 2,4′-Dimethyl-3-piperidinopropiophenone hydrochloride.

Тольперизона Гидрохлорид

$C_{16}H_{23}NO,HCl = 281.8.$

CAS — 728-88-1 (tolperisone); 3644-61-9 (tolperisone hydrochloride).

ATC — M03BX04.

ATC Vet — QM03BX04.

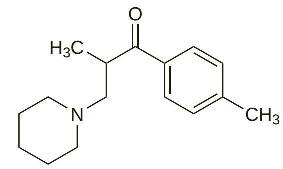

(tolperisone)

Pharmacopoeias. In *Jpn.*

Profile

Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity (p.1887) and muscle spasm (p.1887), in usual doses of 50 to 150 mg three times daily by mouth. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Miodom; ***Austria:*** Mydocalm; ***Cz.:*** Mydocalm; ***Ger.:*** Mydocalm; ***Hong Kong:*** Mydocalm; ***Hung.:*** Myderison; Mydeton; ***Jpn:*** Muscalm; ***Pol.:*** Mydocalm; Tolperis; ***Rus.:*** Mydocalm (Мидокалм); ***Switz.:*** Mydocalm; ***Thai.:*** Biocalm; Musocalm; Mydocalm; Mydono; Mydosone; Myoxan; Risocalm; Shiwalax†; Soneriper; Spamus†; Tanderon.

Multi-ingredient: ***Mex.:*** Mydocalm-A.

Neuromuscular Blockers

Anaesthesia, p.1900
Intensive care, p.1901
Tetanus, p.1901

Neuromuscular blockers (myoneuronal blockers) affect transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia, particularly to enable adequate muscle relaxation to be achieved with light anaesthesia. There are 2 main types of neuromuscular blockers: competitive (non-depolarising neuromuscular blockers) and depolarising neuromuscular blockers (see Table 1, below).

Table 1. Classification of neuromuscular blockers.

Competitive		Depolarising
Aminosteroidal	*Benzylisoquinolinium*	Suxamethonium
Pancuronium	Alcuronium	
Pipecuronium	Atracurium	
Rapacuronium	Cisatracurium	
Rocuronium	Doxacurium	
Vecuronium	Gallamine	
	Metocurine	
	Mivacurium	
	Tubocurarine	

- **Competitive neuromuscular blockers** act by competing with acetylcholine for receptors on the motor end-plate. Their action can be opposed by increasing the local concentration of acetylcholine, for example by giving an anticholinesterase such as neostigmine (p.631). Tubocurarine (p.1912) was formerly the standard reference drug of this type but its use has declined, therefore details of the actions and uses of competitive neuromuscular blockers are discussed under Atracurium, p.1902.
- **Depolarising neuromuscular blockers** act by depolarising the motor end-plate to prevent the normal response to acetylcholine; their action is not reversed by anticholinesterases. Suxamethonium (p.1909) is the standard reference drug of this type.

Other drugs that have muscle relaxant properties and which are used in the management of musculoskeletal and neuromuscular disorders are discussed in the chapter on Muscle Relaxants, p.1887.

◊ General references.

1. Agoston S, *et al.* Clinical pharmacokinetics of neuromuscular blocking drugs. *Clin Pharmacokinet* 1992; **22**: 94–115.
2. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 331–49.
3. Abel M, *et al.* Adverse effects of nondepolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 420–38.
4. Hunter JM. New neuromuscular blocking drugs. *N Engl J Med* 1995; **332:** 1691–9.
5. Naguib M, Magboul MMA. Adverse effects of neuromuscular blockers and their antagonists. *Drug Safety* 1998; **18:** 99–116.
6. Guay J, *et al.* Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; **34:** 483–96.
7. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
8. Sparr HJ, *et al.* Newer neuromuscular blocking agents: how do they compare with established agents? *Drugs* 2001; **61:** 919–42.
9. McManus MC. Neuromuscular blockers in surgery and intensive care, part 2. *Am J Health-Syst Pharm* 2001; **58:** 2381–95.
10. Brandom BW, Fine GF. Neuromuscular blocking drugs in pediatric anesthesia. *Anesthesiol Clin North America* 2002; **20:** 45–58.

Anaesthesia

Neuromuscular blockers are used in general anaesthesia for their muscle relaxant effects to facilitate intubation at induction and to provide continued relaxation during maintenance. Their use is determined partly by their onset and duration of action (see Table 2, below), but both onset and duration are dose-dependent and can therefore vary. Generally, *competitive neuromuscular blockers*, due to their slower onset and longer duration of action, are used in major operations, while the *depolarising neuromuscular blockers* (usually suxamethonium), with a much faster onset and shorter duration, are used for minor operations or manipulations and particularly for intubation. After use of suxamethonium to aid intubation, a longer-acting competitive drug may then be given to maintain muscle relaxation throughout the operation. Competitive neuromuscular blockers with a short to intermediate duration of action, such as atracurium and vecuronium, are more widely used than those with a longer duration of action such as pancuronium.

Suxamethonium has been widely used after induction of anaesthesia to aid **intubation**; however, because of the adverse effects such as myalgia associated with suxamethonium (see also below), alternative neuromuscular blockers have been investigated for intubation and some questioned the use of suxamethonium for *elective* procedures,[1] especially in day-case patients.[2] Some competitive blockers such as vecuronium have a relatively rapid onset of action and have been used for intubation during routine, planned surgery. However, they act too slowly to enable rapid intubation in an *emergency*, when suxamethonium remains the drug of choice. Although rocuronium, a competitive blocker, is only slightly slower in onset, and may be suitable in emergencies if suxamethonium is contra-indicated,[3-5] it has a much longer duration of action, and needs to be given with an opioid such as alfentanil,[6] or with propofol,[4] to obtain equivalent intubating conditions.

In attempting to create more favourable conditions for rapid intubation with competitive neuromuscular blockers and thus provide an alternative to suxamethonium, anaesthetists have tried using large doses[3] or combinations[7] of competitive blockers. Other methods tried include giving competitive neuromuscular blockers in divided doses in an attempt to shorten the onset to paralysis.[3,8] This so-called *priming principle* involves giving a small initial dose, termed the priming dose, followed by a large paralysing dose. Priming may be with 2 doses of the same competitive relaxant or a combination of 2 different relaxants which may then exhibit synergism. However, some consider[8] that priming techniques are associated with unacceptable adverse effects such as muscle weakness and aspiration, and that they are not safe, especially in the elderly.[3] In another technique, a single large dose of a neuromuscular blocker is given, followed by the induction anaesthetic as soon as the patient complains of weakness.[3] This is called the *timing principle* and although it has been successfully used with some neuromuscular blockers, problems such as perceived muscle weakness or shortness of breath may occur if the anaesthetic is not injected at the right moment.

The use of anaesthetic regimens that avoid or reduce the need for a neuromuscular blocker during intubation has also been investigated. The anaesthetic propofol with a short-acting opioid such as alfentanil has often been tried. In addition to its use alone, such a regimen has been combined successfully with low doses of suxamethonium[9] or rocuronium,[10] or standard doses of vecuronium,[11] to produce suitable conditions for intubation.

Procedures such as intubation can cause **complications**: an undesirable pressor response may occur, resulting in increased heart rate and arterial blood pressure. There may also be an increase in intracranial pressure and intra-ocular pressure. Furthermore, the use of suxamethonium to aid intubation is itself associated with a transient increase in intra-ocular pressure. Small doses of a competitive neuromuscular blocker have been given before suxamethonium[12] to prevent this rise in intra-ocular pressure, although some consider such a measure ineffective.[13] Opioids such as alfentanil and fentanyl appear to be effective in attenuating both the pressor response[14-16] and the rise in intra-ocular pressure[17,18] associated with intubation, but the use of lidocaine has produced conflicting results.[19-23] Many anaesthetics, with the exception of ketamine, reduce intra-ocular pressure to some extent and giving thiopental beforehand may help to counteract the effect of suxamethonium.[24]

Table 2. Relative speed of onset and duration of action of neuromuscular blockers.

Neuromuscular blocker	Onset*	Duration†
Alcuronium	Intermediate	Intermediate
Atracurium	Intermediate	Short/Intermediate
Cisatracurium	Intermediate	Short/Intermediate
Doxacurium	Slow	Long
Gallamine	Rapid	Intermediate
Mivacurium	Intermediate	Short
Pancuronium	Rapid	Long
Pipecuronium	Intermediate	Intermediate/Long
Rocuronium	Rapid	Intermediate
Suxamethonium	Ultra-rapid	Ultra-short
Tubocurarine	Intermediate/Slow	Intermediate
Vecuronium	Rapid	Intermediate

**Onset:*	*†Duration:*
Ultra-rapid, less than 1 minute	Ultra-short, less than 8 minutes
Rapid, 1 to 2 minutes	Short, 8 to 20 minutes
Intermediate, 2 to 4 minutes	Intermediate, 20 to 50 minutes
Slow, more than 4 minutes	Long, more than 50 minutes

Onset and duration of action are dose-dependent

Other drugs that have been used or tried in the prevention of the haemodynamic response to intubation include magnesium sulfate[25] and propofol.[26,27]

Competitive neuromuscular blockers are usually used to provide muscle relaxation during **maintenance** anaesthesia. Patients given a neuromuscular blocker generally require less anaesthetic permitting a state of 'lighter anaesthesia' and hence reducing the adverse effects of the anaesthetic. At the end of the procedure any residual block should be reversed with an anticholinesterase and the patient should be monitored until spontaneous respiration has resumed. For further details see Anaesthesia under Uses of General Anaesthetics, p.1780.

1. Steyn M, Morton NS. Tracheal intubation without neuromuscular block. *Br J Anaesth* 1994; **73:** 862.
2. Cartwright DP. Suxamethonium in day-case anaesthesia. *Br J Anaesth* 1993; **71:** 918–19.
3. Sparr HJ. Choice of the muscle relaxant for rapid-sequence induction. *Eur J Anaesthesiol* 2001; **18** (suppl 23): 71–6.
4. Perry JJ, *et al.* Are intubation conditions using rocuronium equivalent to those using succinylcholine. *Acad Emerg Med* 2002; **9:** 813–23.
5. Perry JJ, *et al.* Rocuronium versus succinylcholine for rapid sequence induction intubation. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 12/05/08).
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Intensive care

The use of neuromuscular blockers in patients requiring mechanical ventilation as part of intensive care has been discussed in a number of reviews[1-3] and guidelines.[4] Neuromuscular blockers are used to provide additional relaxation and facilitate ventilatory support in patients who fail to respond to sedation alone. It is important to ensure that such patients are adequately sedated and relatively pain free before these drugs are used. Patients who are considered most likely to benefit are those with spontaneous respiration that is counterproductive to mechanical ventilation. Patients with little inherent respiratory muscle activity are less likely to obtain an improvement in oxygenation. Neuromuscular blockers may also improve control of intracranial pressure in patients with intracranial hypertension, including prevention of rises in intracranial pressure associated with routine tracheobronchial suction.

Pancuronium has been widely used as a neuromuscular blocker in intensive care because of its tendency to increase arterial pressure and the majority of patients requiring a neuromuscular blocker can be adequately managed with pancuronium; however, its long duration of action may be a problem in some circumstances, and its vagolytic activity can also produce tachycardia. Vecuronium, atracurium, and cisatracurium have relatively few cardiovascular effects, but there has been some concern over the ability of the atracurium metabolite laudanosine to accumulate in the CNS (see Biotransformation, under Pharmacokinetics, p.1905). Atracurium and cisatracurium may also be more suitable in patients with hepatic or renal impairment as their metabolism does not lead to the accumulation of active metabolites. Other neuromuscular blockers that have been used in intensive care include doxacurium, pipecuronium, and rocuronium.

Close monitoring of neuromuscular blockade is recommended since the pharmacodynamics and pharmacokinetics of neuromuscular blockers may be altered in patients in intensive care;[1-4] this should also allow the lowest effective neuromuscular blocking dose to be used, and reduce adverse events. Prolonged neuromuscular blockade has been related to dosage.

Other factors that may potentiate neuromuscular blockade include drug interactions, electrolyte imbalance, hypothermia, or changes in acid–base balance.[1,3] Conversely, dosage requirements may be increased in patients with burns or in those receiving prolonged therapy. Tachyphylaxis has occurred with some neuromuscular blockers, but may resolve on switching to another blocker.

Prolonged neuromuscular blockade has been associated with adverse effects and should be avoided when possible. Recovery after withdrawal of prolonged treatment may be longer than pharmacologically predicted due to the accumulation of active metabolites; this is a particular problem for neuromuscular blockers with a long duration of action and for patients with hepatic or renal impairment. An acute myopathy has also followed prolonged use, most commonly with aminosteroid neuromuscular blockers (see Table 1, p.1900); there are case reports suggesting that use of corticosteroids might increase the risk.[4,5]

When rapid reversal of paralysis is necessary an anticholinesterase such as neostigmine may be used, but relatively little is known about the efficacy of anticholinesterases in reversing prolonged paralysis.[6]

Neonatal intensive care. Neuromuscular blockers such as pancuronium bromide are used in neonatal intensive care to obtain muscle relaxation during mechanical ventilation in infants with severe pulmonary disease, especially in those whose respiratory efforts are out of phase with the ventilator.[7] They are only used in infants at high risk of complications such as *pneumothorax* or *intraventricular haemorrhage*; their routine use in all ventilated neonates is not recommended.[8]

Abolition of spontaneous respiration during mechanical ventilation has had variable effects on the incidence of *pneumothorax* in infants with respiratory distress syndrome. Although a reduced incidence was found in one study[9] involving infants of less than 33 weeks' gestation, in another study[10] the incidence was reduced only in infants with a gestational age of 27 to 32 weeks; no reduction was obtained in those below 26 weeks' gestation. Paralysis also failed to reduce the incidence of pneumothorax or interstitial emphysema in a study[11] of infants with hyaline membrane disease but did appear to speed recovery of lung function.

The aetiology of *intraventricular haemorrhage* remains obscure but there is a well recognised association with gestational age;[12] less mature neonates are more susceptible and the incidence decreases sharply after 30 weeks' gestation. There appears to be an association between fluctuating cerebral blood-flow velocity in the first day of life and subsequent development of intraventricular haemorrhage.[13] Respiratory paralysis from the first day of life until 72 hours of age has been reported[14] to stabilise both cerebral and arterial blood-flow velocity and to produce a decrease in the incidence and severity of intraventricular haemorrhage in infants with respiratory distress syndrome. However, respiratory paralysis has also been reported to have no effect on the development of intraventricular haemorrhage.[9,10]

The use of neuromuscular blockers in the newborn is not without complications. Multiple joint contractures, possibly potentiated by use of aminoglycosides or phenobarbital, have been reported[15,16] in infants given pancuronium, and regular passive limb movements should be performed during paralysis. Marked oedema, severe disturbances of fluid balance, renal failure and death have been reported in 2 neonates.[17] Hypoxaemia may develop after induction of paralysis unless a significant increase in ventilator support is made;[9,13,18] hypotension may also occur.[19] Drugs such as pancuronium which are metabolised in the liver and excreted in the urine have a prolonged action in premature infants.[7] As with adults (see above), continuous use of neuromuscular blockers in neonates has been associated with prolonged neuromuscular block on withdrawal.[20]

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11. Pollitzer MJ, *et al.* Pancuronium during mechanical ventilation speeds recovery of lungs of infants with hyaline membrane disease. *Lancet* 1981; **i:** 346–8.
12. Miall-Allen VM, *et al.* Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. *Pediatrics* 1989; **83:** 657–61.
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14. Perlman JM, *et al.* Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med* 1985; **312:** 1353–7.
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18. Philips JB, *et al.* Hypoxaemia in ventilated neonates after pancuronium paralysis. *Lancet* 1979, **i:** 877.
19. McIntosh N. Hypotension associated with pancuronium use in the newborn. *Lancet* 1985; **ii:** 279.
20. Björklund LJ. Use of sedatives and muscle relaxants in newborn babies receiving mechanical ventilation. *Arch Dis Child* 1993; **69:** 544.

Tetanus

The clinical manifestations of tetanus after infection with *Clostridium tetani* are caused by the highly potent neurotoxin tetanospasmin produced by its germinating spores.

The muscular symptoms of generalised tetanus include trismus (lockjaw), glottal spasm, generalised muscle spasm, opisthotonus (spasm of the back muscles resulting in backward arching of the body), respiratory spasm, and paralysis. Other complications include electrolyte disturbances and autonomic dysfunction leading to cardiovascular effects such as hypertension, tachycardia, and peripheral vasoconstriction. Patients may have a milder form in which the twitching and muscle spasms are limited to the area near the site of the injury, but such localised tetanus is rare and can progress to the generalised form.

Treatment aims to destroy the causative organism and/or neutralise any unbound toxin in the body, to control rigidity and muscle spasms, and to control autonomic dysfunction. For the **antibacterial treatment and prevention** of tetanus and neutralisation of tetanospasmin, see p.196. After antibacterial therapy the mainstay of treatment of **rigidity and spasms** is sedation with *benzodiazepines* such as diazepam or midazolam; they may also reduce patient anxiety. *Opioid analgesics* can be added to treatment to provide analgesia and additional sedation; in addition, *fentanyl*, *morphine*, and *sufentanil* may control autonomic overactivity. *Antiepileptics*, particularly phenobarbital, may also provide additional sedation. *Chlorpromazine* is sometimes used with benzodiazepines to minimise rigidity and muscle spasms. Sedation with *propofol* may also control spasms and rigidity without the need for an additional relaxant; however, mechanical ventilation is required. Centrally acting muscle relaxants have also been tried to control muscle spasms. *Baclofen* has been given by the intrathecal route, but its therapeutic range in severe tetanus may be very narrow and deep coma and loss of spontaneous respiration has been reported. *Dantrolene* has also been reported to be effective. When muscle spasms are severe or interfere with respiration, *competitive neuromuscular blockers* have been used in addition to benzodiazepine sedation, to control spasms and to induce therapeutic paralysis so mechanical ventilation can be initiated.

Control of **autonomic overactivity** may be achieved with sedation; benzodiazepines, antiepileptics, and opioid analgesics have all been used (see above). *Beta blockers* such as propranolol have also been used; however, they are no longer recommended because of the potential for severe cardiovascular effects. Labetalol has both alpha- and beta-blocking activity but offers no advantage over propranolol. More recently, *esmolol*, a short-acting beta blocker, has been used. *Magnesium sulfate* has been found to minimise autonomic disturbance in ventilated patients and controls spasms in non-ventilated patients, but there is need for further investigation. **Electrolyte disturbance** is corrected with calcium and magnesium salts.

References.

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Alcuronium Chloride *(BAN, USAN, rINN)*

Alcuronii chloridum; Alcuronium, chlorure d'; Alkuronio chloridas; Alkuronium-chlorid; Alkuroniumklorid; Alkurónium-klorid; Alkuroniumkloridi; Allnortoxiferin Chloride; Cloruro de alcuronio; Diallylnortoxiferine Dichloride; Diallyltoxiferine Chloride; Ro-4-3816. *NN'*-Diallylbisnortoxiferinium dichloride.

Алкурония Хлорид

$C_{44}H_{50}Cl_2N_4O_2$ = 737.8.

CAS — 23214-96-2 (alcuronium); 15180-03-7 (alcuronium chloride).

ATC — M03AA01.

ATC Vet — QM03AA01.

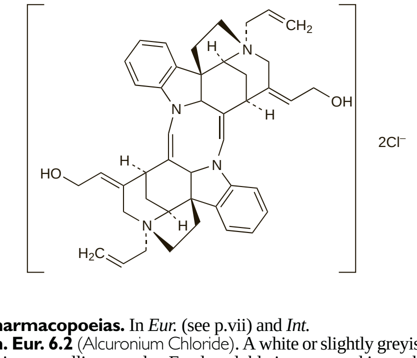

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Ph. Eur. 6.2 (Alcuronium Chloride). A white or slightly greyish-white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; practically insoluble in cyclohexane. Store under nitrogen in an airtight container. Protect from light.

Profile

Alcuronium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905) that is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900). It can induce histamine release to some degree. Anaphylactoid reactions have been associated with the use of alcuronium. It has some vagolytic action and may produce tachycardia; hypotension may also occur.

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 150 to 250 micrograms/kg has been given intravenously. Muscle relaxation occurs after about 2 minutes and the effect lasts for about 20 to 30 minutes. Supplementary doses of 30 micrograms/kg have been given to provide additional periods of muscle relaxation.

Porphyria. Alcuronium is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. Alcuronium crosses the placenta. No evidence of neuromuscular block was seen in any of the neonates born to 12 women who received alcuronium 15 to 30 mg by intravenous injection, 5 to 10.5 minutes before delivery[1] but caution was advised if alcuronium was given in obstetrics in high doses or for a prolonged period.

1. Ho PC, *et al.* Caesarean section and placental transfer of alcuronium. *Anaesth Intensive Care* 1981; **9:** 113–18.

Renal impairment. Alcuronium is excreted mainly by the kidneys and accumulation, with prolonged paralysis, may therefore be expected in patients with renal impairment given large or repeated doses. A prolonged elimination half-life has been reported in anuria.[1] However, doses of 160 micrograms/kg have been used without any problems in patients with chronic renal failure undergoing renal transplantation.[2] The average duration of action of this dose was 37 minutes and any residual neuromuscular blockade at the end of surgery was successfully reversed using atropine and neostigmine.

1. Raaflaub J, Frey P. Zur Pharmakokinetik von Diallyl-nor-toxiferin beim Menschen. *Arzneimittelforschung* 1972; **22:** 73–8.
2. Kaushik S, *et al.* Use of alcuronium in patients undergoing renal transplantation. *Br J Anaesth* 1984; **56:** 1229–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Alloferin†; ***Braz.:*** Alloferine†; ***Ger.:*** Alloferin; ***Hong Kong:*** Alloferin†; ***Malaysia:*** Alloferin†; ***S.Afr.:*** Alloferin; ***Singapore:*** Alloferin†.

Atracurium Besilate *(BAN, rINN)*

33A74; Atracurii besilas; Atracurium, bésilate d'; Atracurium Besylate *(USAN)*; Atrakurio besilatas; Atrakuriumbesilaatti; Atrakuriumbesilat; Atrakurium-besylát; Atrakuryum Besilat; Besilato de atracurio; BW-33A. 2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) di(benzenesulphonate).

Атракурия Безилат

$C_{53}H_{72}N_2O_{12},2C_6H_5O_3S = 1243.5.$

CAS — 64228-81-5.
ATC — M03AC04.
ATC Vet — QM03AC04.

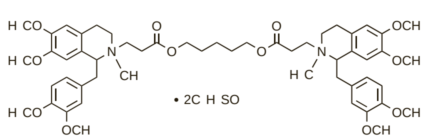

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Atracurium Besilate). A white to yellowish-white, slightly hygroscopic powder. It contains 55.0 to 60.0% of the *cis-cis* isomer, 34.5 to 38.5% of the *cis-trans* isomer, and 5.0 to 6.5% of the *trans-trans* isomer. Soluble in water; very soluble in alcohol, in acetonitrile, and in dichloromethane. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Atracurium Besylate). A white to off-white solid. It contains not less than 5.0% and not more than 6.5% of the *trans-trans* isomer, not less than 34.5% and not more than 38.5% of the *cis-trans* isomer, and not less than 55.0% and not more than 60.0% of the *cis-cis* isomer. It is unstable at room temperature. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Cisatracurium Besilate *(BAN, rINN)*

Bésilate de Cisatracurium; Besilato de cisatracurio; BW-51W (cisatracurium); BW-51W89 (cisatracurium); Cisatracurii Besilas; Cisatracurium, Bésilate de; Cisatracurium Besylate; Sisatrakuryum Bezilat; 51W89 (cisatracurium). (1*R*,1′*R*,2*R*,2′*R*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.

Цисатракурия Безилат

CAS — 96946-42-8.
ATC — M03AC11.
ATC Vet — QM03AC11.

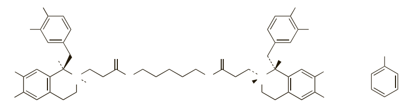

Incompatibility. Neuromuscular blockers are generally incompatible with alkaline solutions, for example barbiturates such as thiopental sodium. It is good practice not to give neuromuscular blockers in the same syringe, or simultaneously through the same needle, as other drugs.

The manufacturers state that cisatracurium is incompatible with ketorolac trometamol or propofol emulsion; in addition, lactated Ringer's injection with glucose 5% or lactated Ringer's solution should not be used as a diluent when preparing solutions of cisatracurium for infusion.

Stability. In a stability study,[1] solutions of cisatracurium (as the besilate) in concentrations of 2 or 10 mg/mL were stable for at least 90 days when stored in the original vials at 4° either exposed to or protected from light; similar solutions stored at 23° were stable for at least 45 days. Solutions of 2 mg/mL stored in plastic syringes at 4° or 23° were stable for at least 30 days. Solutions of 0.1, 2, or 5 mg/mL in 5% glucose injection or 0.9% sodium chloride injection in PVC minibags were stable for at least 30 days stored at 4°; the 5 mg/mL solution was also stable for at least 30 days stored at 23°.

1. Xu QA, *et al.* Stability of cisatracurium besylate in vials, syringes, and infusion admixtures. *Am J Health-Syst Pharm* 1998; **55:** 1037–41.

Adverse Effects

The adverse effects of competitive neuromuscular blockers are generally similar although they differ in their propensity to cause histamine release and associated cardiovascular effects. The latter appear to be rare with the aminosteroidal blockers and the benzylisoquinolinium blocker cisatracurium (see below). Competitive neuromuscular blockers with vagolytic activity may produce tachycardia and a rise in blood pressure. The use of blockers that lack an effect on the vagus will not counteract the bradycardia produced during anaesthesia by the other drugs employed or by vagal stimulation. Reduction in blood pressure with compensatory tachycardia may occur with some competitive neuromuscular blockers, in part because of sympathetic ganglion blockade or the release of histamine. Reduction in gastrointestinal motility and tone may occur as a result of ganglionic blockade.

Histamine release may also lead to wheal-and-flare effects at the site of injection, flushing, occasionally bronchospasm, and rarely anaphylactoid reactions.

Malignant hyperthermia has been associated rarely with competitive neuromuscular blockers.

Some competitive neuromuscular blockers such as pancuronium, tubocurarine, and vecuronium can cause a decrease in the partial thromboplastin time and prothrombin time.

In overdosage there is prolonged apnoea due to paralysis of the intercostal muscles and diaphragm, with cardiovascular collapse and the effects of histamine release.

Atracurium and its isomer cisatracurium have no significant vagal or ganglionic blocking activity at recommended doses. Unlike atracurium, cisatracurium does not induce histamine release and is therefore associated with greater cardiovascular stability.

For possible risks from their major metabolite laudanosine, see Biotransformation, under Pharmacokinetics, below.

Effects on body temperature. Competitive neuromuscular blockers are not considered to be a trigger factor for malignant hyperthermia; however, there have been rare case reports of apparent association. Two cases of mild malignant hyperthermia have been reported[1] where tubocurarine was probably the triggering drug. Each episode developed in a member of a family known to be susceptible to malignant hyperthermia, despite preventive measures such as prophylactic cooling, and avoidance of potent inhalation anaesthetics and depolarising neuromuscular blockers. Another case[2] was associated with the use of pancuronium.

1. Britt BA, *et al.* Malignant hyperthermia induced by curare. *Can Anaesth Soc J* 1974; **21:** 371–5.
2. Waterman PM, *et al.* Malignant hyperthermia: a case report. *Anesth Analg* 1980; **59:** 220–1.

Effects on the muscles. For reference to acute myopathy and prolonged muscle weakness after withdrawal of long-term continuous infusions of competitive neuromuscular blockers, see Intensive Care, p.1901.

Hypersensitivity. There have been reports of severe anaphylactoid reactions after use of atracurium[1,2] or cisatracurium.[3-5] For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Suxamethonium Chloride, p.1910.

1. Stirton-Hopkins C. Life-threatening reaction to atracurium. *Br J Anaesth* 1988; **60:** 597–8.
2. Oh TE, Horton JM. Adverse reactions to atracurium. *Br J Anaesth* 1989; **62:** 467–8.
3. Briassoulis G, *et al.* Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. *Paediatr Anaesth* 2000; **10:** 429–34.
4. Legros CB, *et al.* Severe anaphylactic reaction to cisatracurium in a child. *Anesth Analg* 2001; **92:** 648–9.
5. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; **33:** 816–19.

Treatment of Adverse Effects

It is essential to maintain assisted respiration in patients who have received a competitive neuromuscular blocker until spontaneous breathing is fully restored; in addition a cholinesterase inhibitor such as neostigmine is usually given intravenously, with atropine or glycopyrronium, to hasten reversal of the neuromuscular block. Patients need to be closely monitored after reversal of block to ensure that muscle relaxation does not return.

Severe hypotension may require intravenous fluid replacement and cautious use of a pressor agent; the patient should be positioned to facilitate venous return from the muscles.

Giving an antihistamine before induction of neuromuscular blockade may help to prevent histamine-induced adverse effects in patients with asthma or those susceptible to bronchospasm.

Reversal of neuromuscular blockade. For a discussion of the use of anticholinesterases for reversal of residual neuromuscular block produced by intermediate- or short-acting blockers after surgical or similar procedures, see under Neostigmine, p.633.

Precautions

Patients who have received a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Atracurium and other competitive neuromuscular blockers should be used with great care, if at all, in respiratory insufficiency or pulmonary disease and in the dehydrated or severely ill patient. The response to neuromuscular blockers is often unpredictable in patients with neuromuscular disorders and they should be used with great care in these patients (see below). Caution is also needed in patients with a history of conditions such as asthma where release of histamine would be a hazard. Care is also required in patients with a history of hypersensitivity to any neuromuscular blocker because high rates of cross-sensitivity have been reported. For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium Chloride, p.1910.

Resistance to the effects of competitive neuromuscular blockers may occur in patients with burns (see below). The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment: resistance appears to occur to some, such as doxacurium, metocurine, pancuronium, and tubocurarine, while dosage of others, including mivacurium and rocuronium, may need to be reduced because of a prolonged action.

Competitive neuromuscular blockers excreted mainly in the urine should be used with caution in renal impairment; a reduction in dosage may be necessary. Doses may need to be reduced in infants and neonates because of increased sensitivity to competitive muscle relaxants. Doses in obese patients should usually be based upon the patient's ideal body-weight rather than actual body-weight.

The effects of competitive neuromuscular blockers are increased by metabolic or respiratory acidosis and hypokalaemia, hypermagnesaemia, hypocalcaemia, and hypophosphataemia and dehydration. Competitive neuromuscular blockade may also be enhanced by raised body temperature and reduced in hypothermia.

In contrast to other competitive neuromuscular blockers, reduction in body temperature may necessitate a dosage reduction for *atracurium and its isomer cisatracurium* since cooling reduces the rate of inactivation of atracurium and cisatracurium, but physiological variations in body temperature and pH will not significantly affect their action.

Burns. The dose requirements of competitive neuromuscular blockers are increased in patients with burns,[1-3] the dose correlating with both the extent of the burn and time after injury. This resistance is usually not seen in patients with less than 10% body-surface burns but if more than 40% of the body-surface is affected the dose of competitive blocker may need to be up to five times higher than in patients without burns. Resistance peaks about 2 weeks after injury, persists for many months in patients with major burns, and decreases gradually with healing of the burn. The mechanism of resistance is multifactorial but may be partly explained by increased protein binding, increased volume of distribution, and increased numbers of acetylcholine receptors at the motor end-plate requiring more muscle relaxant to produce a given effect. Despite the high doses of competitive relaxants that are required, recovery from neuromuscular blockade is not seriously impaired and their effects can be reversed with usual doses of an anticholinesterase.

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; **26:** 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; **ii:** 1003–4.
3. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Cardiopulmonary bypass. The effect of cardiopulmonary bypass on the pharmacokinetics and pharmacodynamics of competitive neuromuscular blockers can be complex but generally their dosage may need to be reduced. Although the intensity of neuromuscular blockade of most competitive neuromuscular blockers is reduced by hypothermia[1] used during cardiopulmonary bypass, their use during this procedure is associated with rises in plasma concentrations, reduced clearance, and prolongation of the elimination half-life.[2-6] Various mechanisms, including reduced distribution to highly perfused tissues such as the lungs, have been proposed to explain this effect.[2] For atracurium, it appears that it is a reduction in the temperature-dependent inactivation by Hofmann elimination during hypothermia that enables lower doses to be used.[7]

1. Buzello W, *et al.* Unequal effects of cardiopulmonary bypass-induced hypothermia on neuromuscular blockade from constant infusion of alcuronium, d-tubocurarine, pancuronium, and vecuronium. *Anesthesiology* 1987; **66:** 842–6.
2. Walker JS, *et al.* Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *Br J Clin Pharmacol* 1983; **15:** 237–44.
3. Walker JS, *et al.* Altered d-tubocurarine disposition during cardiopulmonary bypass surgery. *Clin Pharmacol Ther* 1984; **35:** 686–94.
4. Wierda JMKH, Agoston S. Pharmacokinetics of vecuronium during hypothermic bypass. *Br J Anaesth* 1989; **63:** 627P–628P.
5. Smeulers NJ, *et al.* Hypothermic cardiopulmonary bypass influences the concentration-response relationship and the biodisposition of rocuronium. *Eur J Anaesthesiol* 1995; **12** (suppl 11): 91–4.
6. Asokumar B, *et al.* Pharmacokinetics of doxacurium during normothermic and hypothermic cardiopulmonary bypass surgery. *Can J Anaesth* 1998; **45:** 515–20.
7. Flynn PJ, *et al.* Use of atracurium in cardiac surgery involving cardiopulmonary bypass with induced hypothermia. *Br J Anaesth* 1984; **56:** 967–72.

Hepatic impairment. The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment (see Precautions, above) but alterations in the pharmacokinetics of atracurium and cisatracurium in patients with hepatic impairment (see Biotransformation, under Pharmacokinetics, below) do not appear to be clinically significant and a reduction in dosage is not generally recommended.

Neuromuscular disorders. Caution is needed if competitive neuromuscular blockers are given to patients with neuromuscular disease since severe complications have been reported.[1] Increased response may be seen in patients with paraplegia or quadriplegia, but resistance has been reported in patients with hemiplegia. Increased response also may occur in patients with amyotrophic lateral sclerosis, neurofibromatosis, and poliomyelitis; this is of little concern unless the respiratory muscles are involved when prolonged apnoea may occur. Patients with myasthenia gravis usually show increased sensitivity to competitive neuromuscular blockers although small doses have been given without complications. During remission of myasthenia gravis a normal response is usual but since remission is often incomplete, small intermittent doses are advised. A significantly greater exaggeration of response is seen in patients with the myasthenic syndrome. Both normal and increased responses have been reported in patients with myotonias or muscular dystrophies but exquisite sensitivity occurs in patients with ocular muscular dystrophy. A normal response to competitive relaxants may be expected in patients with multiple sclerosis, muscular denervation, Parkinson's disease, and tetanus.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61:** 173–87.

Pregnancy. A review[1] of the pharmacokinetics of neuromuscular blockers in pregnancy concluded that atracurium and mivacurium are the best choice in pregnancy since their actions are predictable; their duration of action is either unchanged or only slightly prolonged. Atracurium also has a low umbilical to maternal vein concentration (uv/mv) ratio. In general, it is advisable[1] to choose a neuromuscular blocker with a low uv/mv ratio and a short duration of action, and to inject the lowest dose required to produce adequate surgical conditions.

Atracurium 300 micrograms/kg given to 26 women undergoing caesarean section, with subsequent incremental doses of 100 or 200 micrograms/kg if necessary, produced good surgical relaxation in all patients without any complications.[2] Of the 26 neonates delivered, respiration was established within 90 seconds in 21, with an Apgar score of 10 at 5 minutes. The remaining 5 neonates were delivered by caesarean section because of fetal distress and were slower to start breathing.

A study[3] of 22 women in the immediate postpartum period found the onset and duration of cisatracurium to be significantly shorter when compared with nonpregnant patients.

1. Guay J, *et al.* Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; **34:** 483–96.
2. Frank M, *et al.* Atracurium in obstetric anaesthesia: a preliminary report. *Br J Anaesth* 1983; **55:** 113S-114S.
3. Pan PH, Moore C. Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients. *J Clin Anesth* 2001; **13:** 112–17.

Renal impairment. Although some differences in the pharmacokinetics of atracurium and cisatracurium have been reported in patients with renal impairment (see Biotransformation, under Pharmacokinetics, below), duration of their neuromuscular blocking action is not significantly dependent on renal function and usual doses may be given to such patients.[1,2] Atracurium has been given by infusion to patients with end-stage renal failure[3] when the initial dose required for induction of neuromuscular block was 37% higher than that required by patients without renal impairment. The increase could be explained by the larger extracellular fluid volume in patients with chronic renal failure.

Although the pharmacokinetics of atracurium and cisatracurium are not appreciably different in renal impairment, those of their metabolites may be (see Biotransformation, under Pharmacokinetics, below) and therefore it has been suggested that neuromuscular function should be monitored during use of atracurium.[4]

1. Hunter JM, *et al*. Use of the muscle relaxant atracurium in anephric patients: preliminary communication. *J R Soc Med* 1982; **75:** 336–340.
2. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1′R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
4. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.

Resistance. The aetiology of resistance to competitive blockers is not clear but might be due to pharmacodynamic or pharmacokinetic alterations associated with disease states such as burn injuries (see above) or hepatic impairment (see above) or therapy with other drugs (see Interactions, below). One review[1] noted that there had been numerous case reports of resistance to competitive neuromuscular blockers; most had been associated with use of single doses or short-term intermittent therapy, but more recent reports had documented resistance during continuous infusions in 9 patients of whom 7 had received atracurium and 2 rocuronium. Resistance to atracurium had followed 2 different patterns. Patients had required either usual or raised doses for initial control but both groups had subsequently required progressive increases. Most patients with resistance to atracurium were successfully managed by transfer to pancuronium or doxacurium.

1. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Tourniquets. Atracurium might be unsuitable for neuromuscular blockade of a limb that has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] Atracurium undergoes non-enzymatic degradation in plasma and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; **73:** 726.

Interactions

A number of drugs may influence neuromuscular transmission and thus interfere with the action of both competitive and depolarising neuromuscular blockers, resulting in potentiation or antagonism of neuromuscular block. Some interactions may be advantageous, such as the reversal of competitive neuromuscular block by anticholinesterases. In general, adverse interactions are potentially more serious in patients with impaired neuromuscular function (see Neuromuscular Disorders, above, and under Suxamethonium Chloride, p.1911).

Drug interactions affecting neuromuscular blockers of either type (competitive and depolarising) as well as those specific for competitive neuromuscular blockers are discussed below. For drug interactions specific to depolarising neuromuscular blockers see under Interactions of Suxamethonium Chloride, p.1911.

◊ Reviews.

1. Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Safety* 1996; **15:** 261–73.
2. Cammu G. Interactions of neuromuscular blocking drugs. *Acta Anaesthesiol Belg* 2001; **52:** 357–63.

Antiarrhythmics. *Lidocaine*, *procainamide*, *quinidine*, and *verapamil* all have some neuromuscular blocking activity and may enhance the block produced by neuromuscular blockers. Large doses of lidocaine may reduce the release of acetylcholine and act directly on the muscle membrane. Quinidine has a curare-like action at the neuromuscular junction and depresses the muscle action potential. If given during recovery from neuromuscular block it can result in muscle weakness and apnoea and it should be avoided, if possible, in the immediate postoperative period. For details regarding interactions with calcium-channel blockers, see below.

Antibacterials. Some antibacterials in very high concentration can produce a muscle paralysis that may be additive to or synergistic with that produced by neuromuscular blockers. The neuromuscular block produced by antibacterials may be enhanced in patients with intracellular potassium deficiency, low plasma-calcium concentration, neuromuscular disease, or a tendency to a high plasma-antibacterial concentration, for example after large doses or in renal impairment. The interaction appears to be more important for competitive neuromuscular blockers. The antibacterials most commonly implicated are aminoglycosides, lincosamides, polymyxins, and, more rarely, tetracyclines.

The *aminoglycosides* reduce release of, and sensitivity to, acetylcholine and their effect can be reversed, at least in part, by calcium, fampridine, or an anticholinesterase. The interaction can occur with aminoglycosides given by most routes. There are reports of potentiation of neuromuscular blockade occurring with many different aminoglycoside-neuromuscular blocker combinations[1-6] and all aminoglycosides should be used with extreme caution during surgery and in the postoperative period.

The *lincosamides* (*clindamycin* and *lincomycin*) can prolong the action of muscle relaxants producing a neuromuscular block that may be difficult to reverse with calcium or anticholinesterases.[7-9] Patients should be monitored for prolonged paralysis.

There have been reports of prolonged apnoea[2,5,8] after use of *polymyxins* (*colistin*, *polymyxin B*) with a neuromuscular blocker. The block is difficult to reverse; calcium may be partially successful, but neostigmine may increase the block.

Tetracyclines have weak neuromuscular blocking properties; potentiation of neuromuscular block has been reported in patients with myasthenia gravis.[2] Reversal of the block may be partly achieved with calcium, but the value of anticholinesterases is questionable.

The *ureidopenicillins* (*azlocillin* and *mezlocillin*), and the closely related *piperacillin*, are reported to prolong the block produced by vecuronium.[10,11]

Vancomycin has been reported to increase neuromuscular blockade by vecuronium.[12] Prolonged paralysis and apnoea has occurred in a patient recovering from suxamethonium-induced blockade after being given vancomycin.[13]

1. Hall DR, *et al.* Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. *Br J Anaesth* 1972; **44:** 1329–32.
2. Pittinger CB, *et al.* Antibiotic-induced paralysis. *Anesth Analg Curr Res* 1970; **49:** 487–501.
3. Waterman PM, Smith RB. Tobramycin-curare interaction. *Anesth Analg Curr Res* 1977; **56:** 587–8.
4. Regan AG, Perumbetti PPV. Pancuronium and gentamicin interaction in patients with renal failure. *Anesth Analg* 1980; **59:** 393.
5. Giala MM, Paradelis AG. Two cases of prolonged respiratory depression due to interaction of pancuronium with colistin and streptomycin. *J Antimicrob Chemother* 1979; **5:** 234–5.
6. Jedeikin R, *et al.* Prolongation of neuromuscular blocking effect of vecuronium by antibiotics. *Anaesthesia* 1987; **42:** 858–60.
7. Booij LHD, *et al.* Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man. *Anesth Analg* 1978; **57:** 316–21.
8. de Gouw NE, *et al.* Interaction of antibiotics on pipecuronium-induced neuromuscular blockade. *J Clin Anesth* 1993; **5:** 212–15.
9. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. *Anesth Analg* 2002; **94:** 123–4.
10. Tryba M. Wirkungsverstäkung nicht-depolarisierender Muskelrelaxantien durch Acylaminopenicilline: Untersuchungen am Beispiel von Vecuronium. *Anaesthesist* 1985; **34:** 651–5.
11. Tryba M, Klemm D. Wechselwirkungen zwischen Acylaminopenicillinen und nicht depolarisierenden Muskelrelaxantien. *Fortschr Antimikrob Antineoplast Chemother* 1985; **4–7:** 1827–33.
12. Huang KC, *et al.* Vancomycin enhances the neuromuscular blockade of vecuronium. *Anesth Analg* 1990; **70:** 194–6.
13. Albrecht RF, Lanier WL. Potentiation of succinylcholine-induced phase II block by vancomycin. *Anesth Analg* 1993; **77:** 1300–2.

Anticholinesterases. Anticholinesterases, including *ecothiopate*, *edrophonium*, *galantamine*, *neostigmine*, *pyridostigmine*, *rivastigmine*, and possibly *donepezil*, antagonise the effect of competitive neuromuscular blockers. Some anticholinesterases such as neostigmine inhibit both acetylcholinesterase and plasma cholinesterase, and are used clinically to antagonise competitive neuromuscular blockade. Conversely, anticholinesterases enhance the action of depolarising muscle relaxants such as suxamethonium thus prolonging neuromuscular block, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. See also Interactions in Suxamethonium Chloride, p.1911.

Antiepileptics. Resistance to competitive neuromuscular blockers has been reported in patients receiving chronic treatment with *carbamazepine*[1,2] or *phenytoin*[3,4] and rapid recovery from neuromuscular block may occur. In addition, children on chronic antiepileptic drugs (carbamazepine and/or phenytoin) were found to recover quicker from rocuronium-induced paralysis than those not on antiepileptics[5]. In a study[6] with cisatracurium, faster recovery rates were also recorded in patients receiving acute or chronic treatment with unspecified antiepileptics. However, atracurium[1] and mivacurium[7] appear to be unaffected by chronic carbamazepine therapy and the effect of chronic phenytoin treatment on atracurium has usually been minimal.[3] Although one study[8] did report that epileptic patients receiving one or more antiepileptics had significantly shorter times to recovery from atracurium, the authors pointed out that the patient populations were different from those in the previous studies.[1,3]

A report of sensitivity to vecuronium[9] has suggested that acute dosage of phenytoin may increase rather than decrease the effect of competitive neuromuscular blockers.

1. Ebrahim Z, *et al.* Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg* 1988; **67:** S55.
2. Whalley DG, Ebrahim Z. Influence of carbamazepine on the dose-response relationship of vecuronium. *Br J Anaesth* 1994; **72:** 125–6.
3. Ornstein E, *et al.* The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; **67:** 191–6.
4. Hernández-Palazón J, *et al.* Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol* 2001; **13:** 79–81.
5. Soriano SG, *et al.* Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth* 2000; **10:** 133–6.
6. Koenig HM, Edwards TL. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol* 2000; **12:** 314–18.
7. Spacek A, *et al.* Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block. *Br J Anaesth* 1996; **77:** 500–502.
8. Tempelhoff R, *et al.* Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg* 1990; **71:** 665–9.
9. Baumgardner JE, Bagshaw R. Acute versus chronic phenytoin therapy and neuromuscular blockade. *Anaesthesia* 1990; **45:** 493–4.

Antineoplastics. It has been recommended that atracurium should be used with care in patients receiving anti-oestrogenic drugs,[1] after a case of prolonged neuromuscular blockade with atracurium in a patient receiving *tamoxifen*. See also under Interactions of Suxamethonium Chloride, p.1911.

1. Naguib M, Gyasi HK. Antiestrogenic drugs and atracurium—a possible interaction? *Can Anaesth Soc J* 1986; **33:** 682–3.

Aprotinin. After reports of apnoea, caution has been advised when aprotinin is used with neuromuscular blockers.[1,2]

1. Chasapakis G, Dimas C. Possible interaction between muscle relaxants and the kallikrein-trypsin inactivator "Trasylol". *Br J Anaesth* 1966; **38:** 838–9.
2. Marcello B, Porati U. Trasylol e blocco neuromuscolare: nota preventiva. *Minerva Anestesiol* 1967; **33:** 814–15.

Benzodiazepines. There are conflicting reports of the effect of *diazepam* on neuromuscular blockers; potentiation,[1,2] or antagonism[1] of neuromuscular block, and a lack of interaction[3-5] have all been reported.

1. Feldman SA, Crawley BE. Interaction of diazepam with the muscle-relaxant drugs. *BMJ* 1970; **2:** 336–8.
2. Yuan H-B, *et al.* The interaction of diazepam with vecuronium: a clinical study. *Chin Med J* 1994; **54:** 259–64.
3. Bradshaw EG, Maddison S. Effect of diazepam at the neuromuscular junction. *Br J Anaesth* 1979; **51:** 955–60.
4. Asbury AJ, *et al.* Effect of diazepam on pancuronium-induced neuromuscular blockade maintained by a feedback system. *Br J Anaesth* 1981; **53:** 859–63.
5. Driessen JJ, *et al.* Benzodiazepines and neuromuscular blocking drugs in patients. *Acta Anaesthesiol Scand* 1986; **30:** 642–6.

Beta blockers. There is conflicting evidence for the effect of beta blockers on the activity of neuromuscular blockers. Lack of effect on depolarising neuromuscular block[1] and antagonism[2,3] or enhancement[4,5] of both competitive and depolarising block have been reported. The exact mechanism of interaction is not clear. There have also been reports of some neuromuscular blockers such as atracurium[6,7] and alcuronium[8] increasing the hypotension and bradycardia associated with the use of anaesthesia in patients receiving beta blockers; these include reports in patients using beta blockers in eye drops for glaucoma.

1. McCammon RL, *et al.* The effect of esmolol on the onset and duration of succinylcholine-induced neuromuscular blockade. *Anesthesiology* 1985; **63:** A317.
2. Varma YS, *et al.* Effect of propranolol hydrochloride on the neuromuscular blocking action of d-tubocurarine and succinylcholine in man. *Indian J Med Res* 1972; **60:** 266–72.
3. Varma YS, *et al.* Comparative effect of propranolol, oxprenolol and pindolol on neuromuscular blocking action of d-tubocurarine in man. *Indian J Med Res* 1973; **61:** 1382–6.
4. Rozen MS, Whan FM. Prolonged curarization associated with propranolol. *Med J Aust* 1972; **1:** 467–8.
5. Murthy VS, *et al.* Cardiovascular and neuromuscular effects of esmolol during induction of anesthesia. *J Clin Pharmacol* 1986; **26:** 351–7.
6. Glynne GL. Drug Interaction? *Anaesthesia* 1984; **39:** 293.
7. Rowlands DE. Drug Interaction? *Anaesthesia* 1984; **39:** 1252.
8. Yate B, Mostafa SM. Drug Interaction? *Anaesthesia* 1984; **39:** 728.

Botulinum A toxin. The neuromuscular block induced by botulinum toxins is enhanced by competitive neuromuscular blockers.

Calcium-channel blockers. Calcium-channel blockers such as diltiazem, nicardipine, nifedipine, and verapamil enhance the effect of competitive neuromuscular blockers.[1-6] *Verapamil* may interfere with the release of acetylcholine and prolonged use may lead to a reduction in intracellular calcium concentration. Potentiation of neuromuscular blockade has been reported[1,6] and the block may be resistant to reversal with neostigmine; edrophonium may be required. The dose requirement for vecuronium was reduced by as much as 50% in surgical patients receiving *diltiazem*.[2,3] A similar effect was seen with *nicardipine*,[4] which reduced the requirement for vecuronium in a dose-dependent fashion. The interaction of vecuronium with diltiazem appeared to be due to a pharmacodynamic mechanism[2] but nicardipine also reduced the plasma clearance of vecuronium, indicating a partial pharmacokinetic mechanism as well.[4] *Nifedipine* also caused an increase in the intensity and duration of action of atracurium and vecuronium when given during anaesthesia.[5]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Sumikawa K, *et al.* Reduction in vecuronium infusion dose requirements by diltiazem in humans. *Anesthesiology* 1992; **77:** A939.
3. Takasaki Y, *et al.* Diltiazem potentiates the neuromuscular blockade by vecuronium in humans. *Jpn J Anesthesiol* 1995; **44:** 503–7.
4. Kawabata K, *et al.* Decrease in vecuronium infusion dose requirements by nicardipine in humans. *Anesth Analg* 1994; **79:** 1159–64.
5. Jelen-Esselborn S, Blobner M. Wirkungsverstärkung von nichtdepolarisierenden Muskelrelaxanzien durch Nifedipin i.v. in Inhalationsanaesthesie. *Anaesthesist* 1990; **39:** 173–8.
6. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.

Cardiac inotropes. Pancuronium or suxamethonium may interact with *cardiac glycosides*[1] resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

Corticosteroids. Antagonism of the neuromuscular blocking effects of pancuronium[1] and vecuronium[2] has been reported in patients taking corticosteroids. This interaction may occur only with long-term corticosteroid treatment and may be expected with all competitive neuromuscular blockers.

For reference to a suggestion that use of corticosteroids might increase the risk of acute myopathy associated with prolonged use of neuromuscular blockers, see Intensive Care, p.1901.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Parr SM, *et al.* Betamethasone-induced resistance to vecuronium: a potential problem in neurosurgery? *Anaesth Intensive Care* 1991; **19:** 103–5.

Diuretics. *Furosemide*, and possibly *mannitol*, have been reported to enhance tubocurarine neuromuscular block in patients with renal failure,[1] but antagonism of tubocurarine by furosemide has also occurred.[2] Small doses of furosemide (less than 100 micrograms/kg) may inhibit protein kinase, which inhibits muscle contraction and potentiates neuromuscular blockade, whereas high doses inhibit phosphodiesterase, increasing cAMP activity and resulting in antagonism of neuromuscular blockade. The potassium-depleting effect of diuretics may enhance the effect of competitive neuromuscular blockers.

1. Miller RD, *et al.* Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology* 1976; **45:** 442–5.
2. Azar I, *et al.* Furosemide facilitates recovery of evoked twitch response after pancuronium. *Anesth Analg* 1980; **59:** 55–7.

Ganglion blockers. Prolonged neuromuscular blockade has been reported[1,2] in patients given neuromuscular blockers and *trimetaphan*. Trimetaphan may have direct neuromuscular blocking activity and some activity against plasma cholinesterase.

1. Wilson SL, *et al.* Prolonged neuromuscular blockade associated with trimethaphan: a case report. *Anesth Analg Curr Res* 1976; **55:** 353–6.
2. Poulton TH, *et al.* Prolonged apnea following trimethaphan and succinylcholine. *Anesthesiology* 1979; **50:** 54–6.

General anaesthetics. Neuromuscular blockers are potentiated in a dose-dependent manner by inhalation anaesthetics.[1-5] The dose of neuromuscular blocker may need to be reduced by up to 70%[1] depending on the anaesthetic used and its concentration, and on the choice of blocker; the interaction is of greater clinical importance with competitive blockers. *Isoflurane, enflurane, desflurane*, and *sevoflurane* produce the greater potentiation, followed by *halothane* and *cyclopropane.* Reversal of competitive block with an anticholinesterase has been reported to be reduced.[6,7] See also under Interactions of Suxamethonium Chloride, p.1911.

Potentiation of the neuromuscular blocking effects of tubocurarine[8] and atracurium[9] has been reported after the intravenous use of *ketamine*. Results from studies *in vitro* suggest that ketamine decreases sensitivity to acetylcholine and it would therefore be expected to potentiate all neuromuscular blockers, but no interaction was reported for pancuronium.[8] Early data[10] suggesting that ketamine potentiates suxamethonium-induced blockade have not been confirmed by later studies.[8,11]

For incompatibility between neuromuscular blockers and alkaline solutions such as thiopental sodium, see under Incompatibility, above.

1. Cannon JE, *et al.* Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67:** 503–6.
2. Swen J, *et al.* Interaction between nondepolarizing neuromuscular blocking agents and inhalation anesthetics. *Anesth Analg* 1989; **69:** 752–5.
3. Ghourin AF, White PF. Comparative effects of desflurane and isoflurane on vecuronium-induced neuromuscular blockade. *J Clin Anesth* 1992; **4:** 34–8.
4. Vanlinthout LEM, *et al.* Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; **76:** 389–95.
5. Wulf H, *et al.* Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. *Br J Anaesth* 1998; **80:** 308–12.
6. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesth* 1982; **54:** 441–5.
7. Gill SS, *et al.* Edrophonium antagonism of atracurium during enflurane anaesthesia. *Br J Anaesth* 1990; **64:** 300–5.
8. Johnston RR, *et al.* The interaction of ketamine with d-tubocurarine, pancuronium, and succinylcholine in man. *Anesth Analg Curr Res* 1974; **53:** 496–501.
9. Toft P, Helbo-Hansen S. Interaction of ketamine with atracurium. *Br J Anaesth* 1989; **62:** 319–20.
10. Bovill JG, *et al.* Current status of ketamine anaesthesia. *Lancet* 1971; **i:** 1285–8.
11. Helbo-Hansen HS, *et al.* Ketamine does not affect suxamethonium-induced neuromuscular blockade in man. *Eur J Anaesthesiol* 1989; **6:** 419–23.

Histamine H_2-antagonists. There are conflicting reports of the effects of histamine H_2-antagonists on neuromuscular blockade. *Cimetidine* has been variously reported to prolong suxamethonium-induced paralysis[1] or to have no effect.[2] *Famotidine* and *ranitidine* have been reported[2] not to interact with suxamethonium. Cimetidine, but not ranitidine, has been reported[3] to delay recovery from vecuronium-induced neuromuscular block. Neither drug appeared to affect recovery after the use of atracurium.

1. Kambam JR, *et al.* Effect of cimetidine on duration of action of succinylcholine. *Anesth Analg* 1987; **66:** 191–2.
2. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; **63:** 348–50.
3. McCarthy G, *et al.* Effect of H2-receptor antagonist pretreatment on vecuronium- and atracurium-induced neuromuscular blockade. *Br J Anaesth* 1991; **66:** 713–15.

Immunosuppressants. Antagonism of the neuromuscular blocking effects of competitive neuromuscular blockers has been reported with *azathioprine*,[1] although the effect may not be clinically important. Azathioprine probably inhibits phosphodiesterase activity at the motor nerve terminal resulting in increased release of acetylcholine. There have been reports of prolonged neuromuscular blockade with atracurium, pancuronium, and vecuronium in some patients receiving *ciclosporin* intravenously.[2,3] This effect has been attributed to an interaction with polyethoxylated castor oil used as the solvent for intravenous ciclosporin but a similar reaction has been reported in a patient receiving ciclosporin orally.[4]

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interaction with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
2. Crosby E, Robblee JA. Cyclosporine-pancuronium interaction in a patient with a renal allograft. *Can J Anaesth* 1988; **35:** 300–302.
3. Sidi A, *et al.* Prolonged neuromuscular blockade and ventilatory failure after renal transplantation and cyclosporine. *Can J Anaesth* 1990; **37:** 543–8.
4. Ganjoo P, Tewari P. Oral cyclosporine-vecuronium interaction. *Can J Anaesth* 1994; **41:** 1017.

Lithium. There have been isolated reports of prolonged neuromuscular blockade after the use of neuromuscular blockers in patients receiving lithium.[1,2]

1. Borden H, *et al.* The use of pancuronium bromide in patients receiving lithium carbonate. *Can Anaesth Soc J* 1974; **21:** 79–82.
2. Hill GE, *et al.* Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* 1976; **44:** 439–42.

Local anaesthetics. Healthy subjects who had undergone regional anaesthesia of the forearm experienced symptoms suggestive of local anaesthetic toxicity on deflation of the tourniquet cuff when mivacurium and *prilocaine* had been used together for anaesthesia;[1] giving prilocaine or mivacurium alone did not produce such an effect. The suggestion that mivacurium may alter vascular permeability, allowing a more rapid diffusion of prilocaine back into the blood from the tissues, should be investigated.[2]

The interaction between neuromuscular blockers and *lidocaine* is discussed in Antiarrhythmics above.

1. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; **78:** 222–3.
2. Torrance JM, *et al.* Interactions between mivacurium and prilocaine. *Br J Anaesth* 1997; **78:** 262.

Magnesium salts. Parenteral magnesium salts may potentiate the effects of competitive and depolarising neuromuscular blockers;[1] the neuromuscular block is deepened and prolonged and a reduction in the dose of the blocker may be needed. Magnesium salts should be used with caution in the postoperative period, as use shortly after recovery from neuromuscular block can lead to recurarisation.[2] Magnesium salts reduce release of and sensitivity to acetylcholine, thus contributing to neuromuscular blockade.

1. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; **32:** 23–7.
2. Fuchs-Buder T, Tassonyi E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. *Br J Anaesth* 1996; **76:** 565–6.

MAOIs. There appears to be a theoretical hazard with pancuronium in patients receiving MAOIs since it releases stored adrenaline;[1] alcuronium, atracurium, or vecuronium would appear to be suitable alternatives.

1. Stack CG, *et al.* Monoamine oxidase inhibitors and anaesthesia: a review. *Br J Anaesth* 1988; **60:** 222–7.

Neuromuscular blockers. A competitive neuromuscular blocker given shortly before a depolarising blocker such as suxamethonium antagonises the depolarising neuromuscular block. This interaction has been used clinically to reduce muscle fasciculations caused by suxamethonium (see Effects on the Muscles, p.1910) and tried for other adverse effects associated with suxamethonium (see Effects on Plasma-potassium Concentration, p.1910). To achieve this antagonism a small non-paralysing dose of a competitive blocker is given before suxamethonium. If a paralysing dose of a competitive blocker is followed some time later with a dose of suxamethonium, for example to facilitate abdominal closure, the resulting neuromuscular block is influenced by the competitive blocker used, the depth of residual block, the dose of suxamethonium, and whether an anticholinesterase is given; antagonism, enhancement, and a combination of the two have been seen.[1,2]

A competitive blocker is often given after the short-acting suxamethonium to maintain neuromuscular blockade during long procedures. The action of the competitive blocker has been reported to be considerably potentiated and prolonged in these circumstances,[3,4] and reduction in the dose of the competitive blocker may be appropriate.

Combination of competitive blockers may have additive or synergistic effects and the interaction may differ depending on which blocker is given first. Caution is needed if a small dose of a shorter-acting blocker is given near the end of an operation in which a long-acting blocker has been given previously, since the resulting block may be greater than expected and much longer than desired.[5-8]

1. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1988; **61:** 292–6.
2. Black AMS. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1989; **62:** 348–9.
3. d'Hollander AA, *et al.* Clinical and pharmacological actions of a bolus injection of suxamethonium: two phenomena of distinct duration. *Br J Anaesth* 1983; **55:** 131–4.
4. Ono K, *et al.* Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium. *Br J Anaesth* 1989; **62:** 324–6.
5. Rashkovsky OM, *et al.* Interaction between pancuronium bromide and vecuronium bromide. *Br J Anaesth* 1985; **57:** 1063–6.
6. Middleton CM, *et al.* Use of atracurium or vecuronium to prolong the action of tubocurarine. *Br J Anaesth* 1989; **62:** 659–63.
7. Kim KS, *et al.*Interactions between mivacurium and pancuronium. *Br J Anaesth* 1997; **79:** 19–23.
8. Motamed C, *et al.* Interaction between mivacurium and pancuronium: impact of the order of administration. *Eur J Clin Pharmacol* 2005; **61:** 175–7.

Sex hormones. Resistance to the neuromuscular blocking effects of suxamethonium and vecuronium in a patient was attributed to previous long-term therapy with *testosterone*,[1] although the exact mechanism could not be explained. See also under Interactions of Suxamethonium Chloride, p.1912.

1. Reddy P, *et al.* Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989; **70:** 871–3.

Smoking. Smoking may affect the dose requirements for neuromuscular blockers. One study[1] found that smokers needed more vecuronium than non-smokers; it was considered that the effect might be explained at the receptor level, although increased metabolism of vecuronium could not be excluded. In contrast, an earlier study[2] found the amount of atracurium required was reduced in smokers.

1. Teiriä H, *et al.* Effect of smoking on dose requirements for vecuronium. *Br J Anaesth* 1996; **76:** 154–5.
2. Kroeker KA, *et al.* Neuromuscular blockade in the setting of chronic nicotine exposure. *Anesthesiology* 1994; **81:** A1120.

Sympathomimetics. Intravenous *salbutamol* has been reported to enhance the blockade obtained with pancuronium and vecuronium.[1] See also under Interactions of Suxamethonium Chloride, p.1912.

1. Salib Y, Donati F. Potentiation of pancuronium and vecuronium neuromuscular blockade by intravenous salbutamol. *Can J Anaesth* 1993; **40:** 50–3.

Xanthines. Resistance to neuromuscular block with pancuronium, requiring an increase in dosage or transfer to vecuronium, has been reported in patients receiving *aminophylline* with[1] or without[2] corticosteroid therapy. It was suggested that this effect might be due to inhibition of phosphodiesterase by aminophylline resulting in increased release of acetylcholine at the nerve terminal.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Daller JA, *et al.* Aminophylline antagonizes the neuromuscular blockade of pancuronium but not vecuronium. *Crit Care Med* 1991; **19:** 983–5.

Pharmacokinetics

On intravenous injection both atracurium besilate and cisatracurium besilate undergo spontaneous degradation via Hofmann elimination (a non-enzymatic breakdown process occurring at physiological pH and temperature) to produce laudanosine and other metabolites. There is also ester hydrolysis by non-specific plasma esterases. The metabolites have no neuromuscular blocking activity.

About 80% of atracurium besilate is bound to plasma proteins. Atracurium besilate and its metabolites cross the placenta in clinically insignificant amounts. Excretion of atracurium and cisatracurium is in urine and bile, mostly as metabolites. The elimination half-life has been reported to be about 20 minutes for atracurium and 22 to 29 minutes for cisatracurium but laudanosine has an elimination half-life of about 3 to 6 hours.

◊ Reviews.

1. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. *Clin Pharmacokinet* 1999; **36:** 27–40.
2. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
3. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; **54:** 526–34.

Biotransformation. Atracurium and cisatracurium are degraded by Hofmann elimination and metabolised by non-specific plasma esterases. Hofmann elimination is generally believed to be the main route of degradation but *in-vitro* work suggests ester hydrolysis is more important.[1] Both routes are independent of renal and hepatic function and no dosage reduction is recommended for elderly patients or those with impaired renal or hepatic function. However, the elimination half-life of atracurium has been found to be slightly longer in elderly patients[2] and in those with hepatic cirrhosis[3] compared with young and healthy patients, although others[4] have found no change in the pharmacokinetics of atracurium in the elderly. Renal and hepatic involvement in the metabolism of atracurium[2] may help to explain any tendency to reduced elimination but this does not appear to be clinically significant. Although clearance of cisatracurium has been reported to be reduced in patients with renal failure[5] this appears to have little significant effect on its pharmacodynamics.[6] Differences in the pharmacokinetics of cisatracurium in patients with hepatic impairment have been reported to be minor.[7]

The major biotransformation product of atracurium and cisatracurium is *laudanosine*; it has no clinical neuromuscular blocking activity but has been associated with CNS stimulation in *animal* studies. It is more lipid soluble than atracurium and cisatracurium and has a half-life of around 3 hours compared with one of approximately 20 minutes for atracurium. Higher plasma-laudanosine concentrations have been reported in patients with renal failure[5,8,9] than in patients with normal renal function. The elimination half-life of laudanosine was found to be significantly greater in patients with hepatic cirrhosis[3] and in elderly patients[2] compared with healthy and young patients respectively. High plasma-laudanosine concentrations were also seen in 10 critically ill patients with acute respiratory distress syndrome;[10] no adverse effects were noted.

Laudanosine crosses the blood-brain barrier in man. The concentration of laudanosine in the CSF increases during an infusion of atracurium and the CSF-to-plasma ratio gradually increases. A ratio of 0.14 was found at 125 to 140 minutes[11] during an infusion of atracurium at a mean rate of 510 micrograms/kg per hour. No evidence of CNS stimulation has been reported in man although patients given atracurium[12] had a 20% higher mean arterial-thiopental concentration at awakening compared with patients given vecuronium, suggesting that laudanosine may have had a minor stimulatory effect on the CNS. The blood-brain barrier appears to be effective in preventing a very high concentration of laudanosine from reaching the CNS and it is considered unlikely[13] that concentrations great enough to provoke seizures will be reached. Cisatracurium may be associated with the production of less laudanosine than atracurium.[14]

1. Stiller RL, *et al.* In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1985; **57:** 1085–8.
2. Kent AP, *et al.* Pharmacokinetics of atracurium and laudanosine in the elderly. *Br J Anaesth* 1989; **63:** 661–6.
3. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *Br J Anaesth* 1989; **62:** 177–83.
4. d'Hollander AA, *et al.* Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology* 1983; **59:** 237–40.
5. Eastwood NB, *et al.* Pharmacokinetics of 1R-cis 1′R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. *Br J Anaesth* 1995; **75:** 431–5.
6. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1′R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
7. De Wolf AM, *et al.* Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anaesth* 1996; **76:** 624–8.
8. Fahey MR, *et al.* Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985; **57:** 1049–51.
9. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.
10. Farenc C, *et al.* Pharmacokinetic-pharmacodynamic modeling of atracurium in intensive care patients. *J Clin Pharmacol* 2001; **41:** 44–50.
11. Eddleston JM, *et al.* Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery. *Br J Anaesth* 1989; **63:** 525–30.
12. Beemer GH, *et al.* Production of laudanosine following infusion of atracurium in man and its effects on awakening. *Br J Anaesth* 1989; **63:** 76–80.
13. Yate PM, *et al.* Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *Br J Anaesth* 1987; **59:** 211–17.
14. Boyd AH, *et al.* Comparison of the pharmacokinetics and pharmacodynamics of an infusion of cis-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit. *Br J Anaesth* 1996; **76:** 382–8.

Uses and Administration

Competitive neuromuscular blockers act by competing with acetylcholine for receptors on the motor end-plate of the neuromuscular junction to produce blockade. The muscles that produce fine rapid movements such as those of the face are the first to be affected, followed by those of the limbs and torso; the last to be affected are those of the diaphragm. The paralysis is reversible with recovery occurring in reverse order. Restoration of normal neuromuscular function can be hastened by increasing the concentration of acetylcholine at the motor end-plate by giving an anticholinesterase such as neostigmine.

Atracurium and cisatracurium are competitive benzylisoquinolinium neuromuscular blockers. The commercial preparation of atracurium is a mixture of 10 stereoisomers of which cisatracurium constitutes about 15%. Cisatracurium, the *R-cis,1′R-cis*-isomer of atracurium, is about 3 times more potent than the mixture of isomers of atracurium. After an intravenous dose of atracurium, muscle relaxation begins in about 2 minutes and lasts for 15 to 35 minutes; onset may be slightly slower for cisatracurium.

Atracurium besilate and cisatracurium besilate are used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage.

For **atracurium besilate**, the usual initial dose for adults and children over 1 month of age is 300 to 600 micrograms/kg by intravenous injection. Subsequent doses of 100 to 200 micrograms/kg may be given as necessary, typically every 15 to 25 minutes for maintenance in prolonged procedures. It is recommended that in patients with cardiovascular disease the initial dose should be given over a period of 60 seconds.

Atracurium besilate may also be given by continuous intravenous infusion at a rate of 5 to 10 micrograms/kg per minute to maintain neuromuscular block during prolonged procedures. Somewhat higher infusion rates may be used in patients undergoing controlled ventilation in intensive care.

Cisatracurium is given as the besilate but doses are expressed as the base. Cisatracurium 1 mg is equivalent to about 1.34 mg of cisatracurium besilate. The usual initial dose for adults is 150 micrograms/kg by intravenous injection. The neuromuscular block may be extended with a maintenance dose of 30 micrograms/kg about every 20 minutes. The usual initial dose for children aged 1 month and over is 150 micrograms/kg. The neuromuscular block may be extended in children aged 2 years and over with a maintenance dose of 20 micrograms/kg about every 9 minutes. The *BNFC* suggests that a maintenance dose of 30 micrograms/kg, repeated about every 20 minutes, may be given to younger children aged 1 month and over; however, such use is unlicensed in the UK.

Cisatracurium besilate may also be given by continuous intravenous infusion to adults and children over 2 years of age at an initial rate equivalent to cisatracurium 3 micrograms/kg per minute followed by a rate of 1 to 2 micrograms/kg per minute after stabilisation.

◊ Reviews.

1. Bryson HM, Faulds D. Cisatracurium besilate: a review of its pharmacology and clinical potential in anaesthetic practice. *Drugs* 1997; **53:** 848–66.

Administration in infants and children. Children generally require larger doses of competitive neuromuscular blockers on a weight basis than adolescents or adults to achieve similar degrees of neuromuscular blockade and may recover more quickly. In contrast, neonates and infants under 1 year of age are more sensitive and usual doses may produce prolonged neuromuscular blockade (see also above for some suggested doses).

References.

1. Brandom BW, Fine GF. Neuromuscular blocking drugs in pediatric anesthesia. *Anesthesiol Clin North America* 2002; **20:** 45–58.

ECT. Competitive neuromuscular blockers have been used to reduce the intensity of muscle contractions and minimise trauma in patients receiving ECT, but suxamethonium (p.1912) is generally preferred because of its short duration of action.

Intravenous regional anaesthesia. Competitive neuromuscular blockers and/or opioid analgesics have been added to the local anaesthetic used in intravenous regional anaesthesia (p.1853) to improve the quality of anaesthesia. However atracurium (see Tourniquets under Precautions, above) and mivacurium (see Tourniquets, p.1907) might be unsuitable for such use.

Shivering. Various drugs have been tried in the treatment of postoperative shivering (p.1779). There are reports of neuromuscular blockers being used to treat shivering after cardiac surgery in order to reduce cardiovascular stress;[1] one study[2] has suggested that vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.

1. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; **39:** 563–8.
2. Dupuis J-Y, *et al.* Pancuronium or vecuronium for the treatment of shivering after cardiac surgery. *Anesth Analg* 1994; **79:** 472–81.

Tetanus. For a comment on the role of competitive neuromuscular blockers in the management of muscle spasms caused by tetanus, see p.1901.

Preparations

USP 31: Atracurium Besylate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Gelolagar; Nimbex†; Nimbium; Tracrium; Tracurix; Tracuron; ***Austral.:*** Nimbex; Tracrium; ***Austria:*** Nimbex; Tracrium; ***Belg.:*** Nimbex; Tracrium; ***Braz.:*** Abbottracurium; Nimbium; Sitrac†; Tracrium; Tracur; ***Canad.:*** Nimbex; ***Chile:*** Nimbex; Tracrium; ***Cz.:*** Nimbex; Tracrium; ***Denm.:*** Nimbex; Tracrium†; ***Fin.:*** Nimbex; ***Fr.:*** Nimbex; Tracrium; ***Ger.:*** Nimbex; Tracrium; ***Gr.:*** Nimbex; Tracrium; ***Hong Kong:*** Nimbex; Tracrium; ***Hung.:*** Nimbex; Tracrium; ***India:*** Tracrium; ***Indon.:*** Notrixum; Tracrium; Tramus; ***Irl.:*** Nimbex; Tracrium; ***Israel:*** Mycurium; Tracrium; ***Ital.:*** Acurmil; Nimbex; Tracrium; ***Malaysia:*** Nimbex; Tracrium; ***Mex.:*** Ifacur†; Nimbex; Relatrac; Trablok; Tracrium; ***Neth.:*** Nimbex; Tracrium; ***Norw.:*** Nimbex; ***NZ:*** Tracrium; ***Philipp.:*** Tracrium; ***Pol.:*** Abbocurium; Nimbex; Tracrium; ***Port.:*** Faulcurium; Nimbex; Tracrium; ***Rus.:*** Nimbex (Нимбекс); Tracrium (Тракриум); ***S.Afr.:*** Nimbex; Tracrium; ***Singapore:*** Nimbex†; Tracrium; ***Spain:*** Laurak; Nimbex; Tracrium; ***Swed.:*** Nimbex; Tracrium; ***Switz.:*** Nimbex; Tracrium; ***Thai.:*** Nimbex; Tracrium; ***Turk.:*** Dematrac; Nimbex; Tracrium; ***UK:*** Nimbex; Tracrium; ***USA:*** Nimbex; Tracrium.

Doxacurium Chloride *(BAN, USAN, rINN)*

BW-A938U; Cloruro de doxacurio; Doksakuriumkloridi; Doxacurii Chloridum; Doxacurium, Chlorure de; Doxakuriumklorid. A mixture of the (1*R*,1′*S*,2*S*,2′*R*), (1*R*,1′*R*,2*S*,2′*S*), and (1*S*,1′*S*,2*R*,2′*R*) stereoisomers (a *meso* isomer and two enantiomers respectively) of 1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′,8,8′-hexamethoxy-2,2′-dimethyl-1,1′-bis(3,4,5-trimethoxybenzyl)-2,2′-[butanedioylbis(oxytrimethylene)]di-isoquinolinium dichloride, all of which are in a *trans* configuration at the 1 and 2 positions of the isoquinolinium rings.

Доксакурия Хлорид

$C_{56}H_{78}Cl_2N_2O_{16}$ = 1106.1.

CAS — 133814-18-3 (doxacurium); 106819-53-8 (doxacurium chloride, meso isomer); 83348-52-1 (doxacurium chloride, total racemate).

ATC — M03AC07.

ATC Vet — QM03AC07.

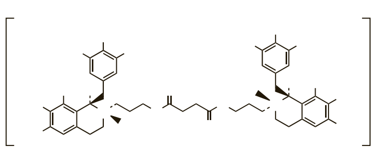

Profile

Doxacurium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1902). It has been used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures and to aid controlled ventilation. Doxacurium has little histamine-releasing activity and causes negligible vagal or sympathetic blockade so that significant cardiovascular adverse effects are not a problem.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Nuromax†; ***USA:*** Nuromax†.

Gallamine Triethiodide *(BANM, rINN)*

Benzcurine Iodide; Galamin Trietiyodür; Galamino trietjodidas; Gallamiinitrietjodidi; Gallamine, triéthiodure de; Gallamini triethiodidum; Gallamin-triethojodid; Gallamintrietjodid; Gallamin-trietjodid; Gallamone Triethiodide; Trietioduro de galamina. 2,2′,2″-(Benzene-1,2,3-triyltrioxy)tris(tetraethylammonium) tri-iodide.

Галламина Триэтйодид

$C_{30}H_{60}I_3N_3O_3$ = 891.5.

CAS — 153-76-4 (gallamine); 65-29-2 (gallamine triethiodide).

ATC — M03AC02.

ATC Vet — QM03AC02.

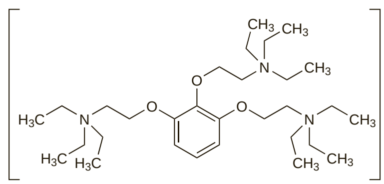

3 I

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Gallamine Triethiodide). A white, or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Gallamine Triethiodide). A white, hygroscopic, odourless, amorphous powder. Very soluble in water; sparingly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 5.3 and 7.0. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). Tachycardia often develops due to the vagolytic action of gallamine triethiodide and blood pressure may be raised. It has a small histamine-releasing effect; occasional anaphylactoid reactions have been reported. It should be avoided in patients hypersensitive to iodine and in severe renal impairment. Although competitive muscle relaxants have been given with great care to patients with myasthenia gravis (see Neuromuscular Disorders, p.1903), UK licensed product information for gallamine triethiodide recommended that it should not be used in such patients.

Cardiopulmonary bypass. Alterations in the pharmacokinetics of competitive neuromuscular blockers in patients undergoing surgery involving cardiopulmonary bypass usually necessitate the use of reduced doses (see p.1903). However, the pharmacokinetics of gallamine in patients undergoing cardiopulmonary bypass appear not to differ significantly from those in control patients.[1]

1. Shanks CA, *et al.* Gallamine disposition in open-heart surgery involving cardiopulmonary bypass. *Clin Pharmacol Ther* 1983; **33:** 792–9.

Renal impairment. Gallamine triethiodide is excreted unchanged in the urine and UK licensed product information considered that it should be avoided in severe renal impairment since prolonged paralysis may occur. Significantly prolonged elimination half-life and reduced clearance have been reported[1] in patients with chronic renal failure given gallamine triethiodide in initial doses of 2 mg/kg intravenously.

1. Ramzan MI, *et al.* Gallamine disposition in surgical patients with chronic renal failure. *Br J Clin Pharmacol* 1981; **12:** 141–7.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

After intravenous use gallamine triethiodide is distributed throughout body tissues. It is not metabolised, and is excreted in the urine as unchanged drug.

Uses and Administration

Gallamine triethiodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905). Muscle relaxation occurs within about 1 to 2 minutes after intravenous injection and lasts for about 20 to 30 minutes. It has been used to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial test dose of 20 mg may be given intravenously to the patient before anaesthesia to determine undue sensitivity. In the UK, initial doses of 80 to 120 mg by intravenous injection have been recommended, with further doses of 20 to 40 mg as required. In children, a dose of 1.5 mg/kg has been recommended, reduced to 600 micrograms/kg for neonates.

In some other countries lower doses have generally been used; an initial dose of 1 mg/kg intravenously, up to a maximum of 80 mg, with additional doses of 0.5 to 1 mg/kg after about 50 to 60 minutes if required.

Gallamine triethiodide has also been given intramuscularly, with or without hyaluronidase.

Preparations

BP 2008: Gallamine Injection;
USP 31: Gallamine Triethiodide Injection.

Proprietary Preparations (details are given in Part 3)
UK: Flaxedil†.

Metocurine Iodide *(USAN)*

Dimethyl Tubocurarine Iodide; (+)-*O*,*O*′-Dimethylchondrocurarine Di-iodide; Dimethyltubocurarine Iodide; Dimetiltubocurarinio, ioduro de; Metocurini Iodidum; Metokuriinijodidi; Metokurinjodid; Trimethyltubocurarine Iodide. (+)-6,6′,7′,12′-Tetramethoxy-2,2,2′,2′-tetramethyltubocuraranium di-iodide.

$C_{40}H_{48}I_2N_2O_6$ = 906.6.

CAS — 5152-30-7 (metocurine); 7601-55-0 (metocurine iodide).

ATC — M03AA04.

ATC Vet — QM03AA04.

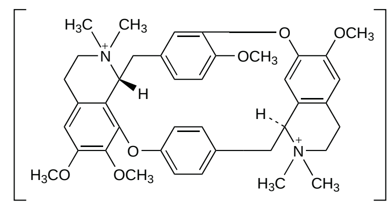

$2I^-$

Profile

Metocurine iodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905) that has been used to provide muscle relaxation in surgical and other procedures.

Metocurine iodide has a moderate risk of inducing histamine release; it also has some ganglion blocking activity.

Mivacurium Chloride *(BAN, USAN, rINN)*

BW-B1090U; Cloruro de mivacurio; Mivacurii Chloridum; Mivacurium, Chlorure de; Mivakuriumklorid; Mivakuriumkloridi; Mivakuryum Klorür. A mixture of the stereoisomers of (*E*)-1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′-tetramethoxy-2,2′-dimethyl-1,1′-bis(3,4,5-trimethoxybenzyl)-2,2′-[oct-4-enedioylbis(oxytrimethylene)]di-isoquinolinium dichloride.

Мивакурия Хлорид

$C_{58}H_{80}Cl_2N_2O_{14}$ = 1100.2.

CAS — 106861-44-3 (mivacurium chloride, total racemate).

ATC — M03AC10.

ATC Vet — QM03AC10.

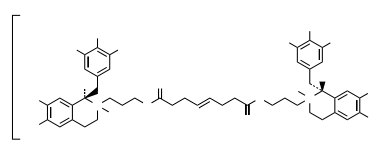

Incompatibility. See under Atracurium, p.1902 for details regarding the incompatibility of neuromuscular blockers.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). Mivacurium chloride has no significant vagal or ganglion blocking activity at recommended doses. It may induce histamine release especially when given in large doses rapidly.

Mivacurium should be used with caution, if at all, in patients with plasma cholinesterase deficiency, since its duration of action will be prolonged in such patients.

Burns. In common with other competitive muscle relaxants patients with burns may develop resistance to mivacurium and require increased doses (see under Atracurium, p.1903). However, as these patients may also have reduced plasma cholinesterase activity dosage requirements could also be reduced. Licensed product information recommends that such patients should be given a test dose of 15 to 20 micrograms/kg with subsequent dosage adjustments being guided by monitoring of the block.

Neuromuscular disorders. Neuromuscular blockade was successfully achieved with mivacurium in an obese elderly patient with myasthenia gravis requiring surgery.[1] Only about half the usual dose was required and even then recovery was delayed. See Atracurium, p.1903 for a discussion of the use of competitive neuromuscular blockers in patients with neuromuscular disorders.

1. Seigne RD, Scott RPF. Mivacurium chloride and myasthenia gravis. *Br J Anaesth* 1994; **72:** 468–9.

Plasma cholinesterase deficiency. There have been reports of prolonged neuromuscular block produced by mivacurium in patients with plasma cholinesterase deficiency.[1-4] Time to full recovery varied; one patient required up to 8 hours.

1. Goudsouzian NG, *et al.* Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. *Anesth Analg* 1993; **77:** 183–5.
2. Sockalingam I, Green DW. Mivacurium-induced prolonged neuromuscular block. *Br J Anaesth* 1995; **74:** 234–6.
3. Fox MH, Hunt PCW. Prolonged neuromuscular block associated with mivacurium. *Br J Anaesth* 1995; **74:** 237–8.
4. Zimmer S. Mivacurium and prolonged neuromuscular block. *Br J Anaesth* 1995; **75:** 823.

Tourniquets. Mivacurium might be unsuitable for neuromuscular blockade of a limb which has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] It is largely inactivated by the enzymatic action of plasma cholinesterase and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated. However, as for other competitive neuromuscular blockers, the use of mivacurium to supplement regional anaesthesia has produced prolonged muscle weakness well beyond cuff deflation.[2] This suggests that mivacurium is not broken down in the ischaemic limb and that recovery is not dependent on plasma concentrations of mivacurium.

See also Local Anaesthetics, under Interactions of Atracurium, p.1904, for a report of symptoms suggestive of local anaesthetic toxicity when prilocaine and mivacurium were used together.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; **73:** 726.
2. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; **78:** 222–3.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Metoclopramide. Metoclopramide, an inhibitor of plasma cholinesterase, was found to significantly prolong the duration of action of mivacurium in patients undergoing surgery, although in this study only marginal inhibition of plasma cholinesterase by metoclopramide occurred.[1]

1. Skinner HJ, *et al.* Influence of metoclopramide on plasma cholinesterase and duration of action of mivacurium. *Br J Anaesth* 1999; **82:** 542–5.

Pharmacokinetics

Mivacurium is a mixture of 3 stereoisomers, 2 of which (*cis-trans* and *trans-trans*) are considered to account for most of the neuromuscular blocking effect. All 3 isomers are inactivated by plasma cholinesterase. Renal and hepatic mechanisms are involved in their elimination with excretion in urine and bile.

◊ Reviews.

1. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.

Uses and Administration

Mivacurium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905).

On intravenous injection muscle relaxation occurs within 1.5 to 2.5 minutes, depending on the dose with a duration of action of about 10 to 20 minutes. It is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. Mivacurium is given as the chloride although doses are expressed in terms of mivacurium base. The initial dose by intravenous injection is 70 to 250 micrograms/kg. Doses up to 150 micrograms/kg may be given over 5 to 15 seconds but higher doses should be given over 30 seconds. In patients with asthma or cardiovascular disease, or those who are sensitive to falls in arterial blood pressure, it should be given over 60 seconds. To give a dose of 250 micrograms/kg for tracheal intubation, an injection of 150 micrograms/kg may be followed 30 seconds later by an injection of 100 micrograms/kg. Maintenance doses of 100 micrograms/kg may be given at intervals of 15 minutes. In children aged 2 to 6 months an initial dose of 150 micrograms/kg has been given; in children aged 7 months to 12 years, an initial dose of 200 micrograms/kg has been given. A maintenance dose of 100 micrograms/kg may be given every 6 to 9 minutes for children aged 2 months to 12 years.

Mivacurium chloride may also be given by continuous intravenous infusion for maintenance of block. For adults the initial rate is 8 to 10 micrograms/kg per minute adjusted every 3 minutes if necessary by increments of 1 microgram/kg per minute to a usual rate of 6 to 7 micrograms/kg per minute; in children aged 2 months to 12 years the usual dose is 11 to 14 micrograms/kg per minute.

Reduced doses may be required in the elderly and in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–99.
2. Frampton JE, McTavish D. Mivacurium: a review of its pharmacology and therapeutic potential in general anaesthesia. *Drugs* 1993; **45:** 1066–89.
3. Feldman S. Mivacurium. *Br J Hosp Med* 1997; **57:** 199–201.

Action. Mivacurium has a shorter duration of action than most other competitive neuromuscular blockers. Studies[1-3] suggest that it is a useful alternative to suxamethonium for the production of neuromuscular block of short duration and has the advantage that its block can be reversed with an anticholinesterase. For a discussion of the choice of anticholinesterase for reversal of neuromuscular block produced by short-acting blockers such as mivacurium, see under Neostigmine, p.633. Although its onset of action may be accelerated by giving a priming dose,[4] mivacurium has a slower onset than suxamethonium and so may not be a suitable alternative[5] when rapid intubation is required. For a general review of neuromuscular blockers, see Anaesthesia, p.1900.

1. Brandom BW, *et al.* Comparison of mivacurium and suxamethonium administered by bolus and infusion. *Br J Anaesth* 1989; **62:** 488–93.
2. Caldwell JE, *et al.* Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth* 1989; **63:** 393–9.
3. Goldberg ME, *et al.* Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesth Analg* 1989; **69:** 93–9.
4. Haxby EJ, *et al.* Mivacurium priming intervals. *Br J Anaesth* 1994; **72:** 485P.
5. Anonymous. Mivacurium—a new neuromuscular blocker. *Med Lett Drugs Ther* 1992; **34:** 82.

Administration in the elderly. In a study[1] comparing the effects of mivacurium in elderly and young adults, the duration of neuromuscular effects was prolonged in elderly patients by about 30%. The mean infusion requirement in elderly patients was 3.67 micrograms/kg per minute compared with 5.5 micrograms/kg per minute in young adults.

Licensed product information states that elderly patients may require decreased infusion rates or smaller or less frequent maintenance bolus doses.

1. Maddineni VR, *et al.* Neuromuscular and haemodynamic effects of mivacurium in elderly and young adult patients. *Br J Anaesth* 1994; **73:** 608–12.

Administration in hepatic or renal impairment. The pharmacokinetics of mivacurium have been studied in patients with renal[1-3] or hepatic impairment.[1,4,5] The duration of relaxation produced by mivacurium was about 1.5 times greater than normal in patients with end-stage renal disease and up to about 3 times greater than normal in patients with end-stage liver disease. Reduced plasma-cholinesterase activity in the patients with hepatic impairment may have played an important part in this effect. Although an anticholinesterase such as neostigmine hastens recovery by only a few minutes in healthy subjects, its use may be indicated in patients in whom recovery is delayed.[2]

Licensed product information recommends that in patients with end-stage renal or liver disease, the dose should be adjusted according to individual clinical response.

1. Cook DR, *et al.* Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. *Br J Anaesth* 1992; **69:** 580–5.
2. Phillips BJ, Hunter JM. Use of mivacurium chloride by constant infusion in the anephric patient. *Br J Anaesth* 1992: **68:** 492–8.
3. Head-Rapson AG, *et al.* Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. *Br J Anaesth* 1995; **75:** 31–6.
4. Devlin JC, *et al.* Pharmacodynamics of mivacurium chloride in patients with hepatic cirrhosis. *Br J Anaesth* 1993; **71:** 227–31.
5. Head-Rapson AG, *et al.* Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. *Br J Anaesth* 1994; **73:** 613–18.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Mivacron; ***Austral.:*** Mivacron; ***Austria:*** Mivacron; Novacrium; ***Belg.:*** Mivacron; ***Braz.:*** Mivacron†; ***Canad.:*** Mivacron†; ***Chile:*** Mivacron; ***Cz.:*** Mivacron; ***Denm.:*** Mivacron; ***Fin.:*** Mivacron; ***Fr.:*** Mivacron; ***Ger.:*** Mivacron; ***Gr.:*** Mivacron; ***Hong Kong:*** Mivacron; ***Hung.:*** Mivacron; ***Irl.:*** Mivacron; ***Israel:*** Mivacron†; ***Ital.:*** Mivacron; ***Malaysia:*** Mivacron; ***Neth.:*** Mivacron; ***Norw.:*** Mivacron; ***NZ:*** Mivacron; ***Pol.:*** Mivacron; ***Port.:*** Mivacron; ***Rus.:*** Mivacron (Мивакрон); ***S.Afr.:*** Mivacron; ***Singapore:*** Mivacron; ***Spain:*** Mivacron; ***Swed.:*** Mivacron; ***Switz.:*** Mivacron; ***Turk.:*** Mivacron; ***UK:*** Mivacron; ***USA:*** Mivacron†.

Pancuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pancuronio; NA-97; Org-NA-97; Pancuronii bromidum; Pancuronium, bromure de; Pankuronio bromidas; Pankuroniowy bromek; Pankuroniumbromid; Pankuronium-bromid; Pankuroniumbromidi; Pankuronyum Bromür. 1,1′-(3α,17β-Diacetoxy-5α-androstan-2β,16β-ylene)bis(1-methylpiperidinium) dibromide.

Панкурония Бромид

$C_{35}H_{60}Br_2N_2O_4$ = 732.7.

CAS — 15500-66-0.

ATC — M03AC01.

ATC Vet — QM03AC01.

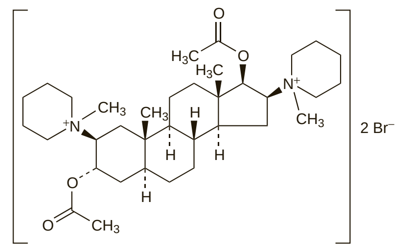

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Pancuronium Bromide). White, yellowish-white, or slightly pink, hygroscopic crystalline powder. Very soluble to freely soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Pancuronium Bromide). A white, yellowish-white, or slightly pink, crystalline hygroscopic powder. Freely soluble in water, in alcohol, and in dichloromethane. Store in airtight containers at a temperature of 15° to 25°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902).

Pancuronium has vagolytic and sympathomimetic action, which may cause tachycardia and hypertension, but does not produce ganglionic blockade. It has little histamine-releasing effect. Hypersensitivity reactions are relatively rare but bradycardia, bronchospasm, hypotension, and cardiovascular collapse have been reported. Pancuronium has been associated with excessive salivation in some patients.

Pancuronium should be used with caution in patients with raised catecholamine concentrations, or in those who are receiving drugs with sympathomimetic effects, as cardiovascular adverse effects are more likely in these patients.

Effects on the ears. A study[1] found that neonates who survived congenital diaphragmatic hernia were more likely to suffer from sensorineural hearing loss after prolonged use of pancuronium bromide during the neonatal period. However, the authors commented that the association is not necessarily causal and that further investigation is required.

1. Cheung P-Y, *et al.* Prolonged use of pancuronium bromide and sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia. *J Pediatr* 1999; **135:** 233–9.

Hypersensitivity. Reports of anaphylactoid or anaphylactic reactions associated with pancuronium bromide.

See also under Suxamethonium Chloride, p.1910.

1. Brauer FS, Ananthanarayan CR. Histamine release by pancuronium. *Anesthesiology* 1978; **49:** 434–5.
2. Patriarca G, *et al.* Pancuronium allergy: a case report. *Br J Anaesth* 1989; **62:** 210–12.
3. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
4. Sanchez-Guerrero IM, *et al.* Anaphylactoid reaction induced by pancuronium during general anaesthesia. *Eur J Anaesthesiol* 1998; **15:** 613–14.

Postoperative complications. Because of its prolonged duration of action, pancuronium may be more likely than other neuromuscular blockers to produce residual neuromuscular block; such residual block is associated with an increased incidence of postoperative respiratory complications.[1,2]

1. Berg H, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications: a prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41:** 1095–1103.
2. Bissinger U, *et al.* Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. *Physiol Res* 2000; **49:** 455–62.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

On intravenous injection pancuronium bromide is rapidly distributed into body tissues; about 80% may be bound to plasma proteins. A small proportion is metabolised in the liver to metabolites with weak neuromuscular blocking activity. It is largely excreted in urine as unchanged drug and metabolites; a small amount is excreted in bile. The plasma elimination half-life is about 2 hours. It crosses the placenta in small amounts.

Pregnancy. In 15 patients undergoing caesarean section[1] given pancuronium bromide 100 micrograms/kg intravenously with other agents, mean maternal arterial and umbilical venous serum concentrations of pancuronium bromide and metabolites were 520 and 120 nanograms/mL, respectively at delivery (mean of 13 minutes after injection), giving a fetal to maternal ratio of 0.23.

1. Wingard LB, *et al.* Modified fluorometric quantitation of pancuronium bromide and metabolites in human maternal and umbilical serums. *J Pharm Sci* 1979; **68:** 914–15.

Uses and Administration

Pancuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1905). Muscle relaxation occurs within about 1.5 to 2 minutes of intravenous injection and lasts for about 45 to 60 minutes.

Pancuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The initial dose for intubation is usually 50 to 100 micrograms/kg by intravenous injection, with maintenance doses of 10 to 20 micrograms/kg. Children may be given similar doses. Some manufacturers recommend a reduction in the initial dose to 20 to 60 micrograms/kg when pancuronium is given following suxamethonium. Doses of 30 to 40 micrograms/kg initially have been suggested in neonates, with maintenance doses of 10 to 20 micrograms/kg as necessary; in the UK, the *BNFC* suggests that higher doses may be used for neonates in some cases. In the USA, dosage based on an initial test dose of 20 micrograms/kg has been advocated for the neonate.

Adult patients under intensive care who require assisted ventilation for conditions such as intractable status asthmaticus or tetanus may be given 60 micrograms/kg intravenously every 1 to 1½ hours or less frequently.

Care should be taken when giving pancuronium to patients with hepatic or renal impairment, see below.

Administration in hepatic impairment. Prolonged neuromuscular blockade may occur in patients with liver disease given pancuronium bromide since increased elimination half-life with increased volume of distribution and reduced clearance has been reported.[1] However, the expanded distribution volume may necessitate an increase in the dose of pancuronium in these patients[1,2] and may be interpreted as resistance to the neuromuscular blocking effects of pancuronium.

1. Duvaldestin P, *et al.* Pancuronium pharmacokinetics in patients with liver cirrhosis. *Br J Anaesth* 1978; **50:** 1131–6.
2. Ward ME, *et al.* Althesin and pancuronium in chronic liver disease. *Br J Anaesth* 1975; **47:** 1199–1204.

Administration in renal impairment. Prolonged neuromuscular blockade may occur when pancuronium is given to patients with severe renal impairment. Pancuronium distributes rapidly into extracellular fluid after intravenous injection and the initial neuromuscular blockade produced will depend upon the peak drug concentration in this fluid. Since extracellular fluid volume is increased in chronic renal failure such patients may require a larger initial dose of pancuronium and a 45% increase in dose requirement has been reported[1] in patients with end-stage renal failure. Renal excretion is the main route of elimination and prolonged elimination half-life with reduced clearance may be expected in renal failure; total dose requirements may be reduced. The main infusion rate of pancuronium to maintain 90% blockade in patients with end-stage renal failure was reported to be 61.5% less than for patients with normal renal function.

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure. *Br J Anaesth* 1987; **59:** 995–1003.

Fetal paralysis. Pancuronium bromide 100 micrograms/kg of the estimated fetal-weight, given into the umbilical vein, produced fetal paralysis for about 40 minutes during intravascular exchange transfusion.[1] A dose of 200 to 300 micrograms/kg produced fetal paralysis for about 1 to 8 hours for more complicated transfusion procedures.[2] No adverse effects were reported.

1. Copel JA, *et al.* The use of intravenous pancuronium bromide to produce fetal paralysis during intravascular transfusion. *Am J Obstet Gynecol* 1988; **158:** 170–1.
2. Moise KJ, *et al.* Intravenous pancuronium bromide for fetal neuromuscular blockade during intrauterine transfusion for red-cell alloimmunization. *Obstet Gynecol* 1989; **74:** 905–8.

Neuroleptic malignant syndrome. Pancuronium is one of several drugs for which there have been isolated reports[1] of success in the management of neuroleptic malignant syndrome (p.972).

1. Sangal R, Dimitrijevic R. Neuroleptic malignant syndrome: successful treatment with pancuronium. *JAMA* 1985; **254:** 2795–6.

Preparations

BP 2008: Pancuronium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Bemicin; Pancuron; Pavulon; Plumger; ***Austral.:*** Pavulon; ***Braz.:*** Pancuron; Pavulon; ***Chile:*** Pavulon; ***Cz.:*** Pavulon; ***Denm.:*** Pavulon; ***Fin.:*** Pavulon; ***Fr.:*** Pavulon; ***Gr.:*** Pavulon; ***Hong Kong:*** Pavulon; ***Hung.:*** Pavulon†; ***India:*** Panconium; ***Indon.:*** Pavulon; ***Irl.:*** Pavulon†; ***Israel:*** Pavulon; ***Ital.:*** Pavulon; ***Jpn:*** Mioblock; ***Malaysia:*** Pavulon; ***Mex.:*** Bromurex; Panlem; ***Neth.:*** Pavulon; ***Norw.:*** Pavulon; ***Philipp.:*** Pavulon; ***Port.:*** Pancurox; Pavulon†; ***S.Afr.:*** Curon-B; Pavulon; ***Singapore:*** Pavulon; ***Spain:*** Pavulon†; ***Swed.:*** Pavulon; ***Switz.:*** Pavulon; ***Thai.:*** Pavulon; ***Turk.:*** Pavulon; ***USA:*** Pavulon†; ***Venez.:*** Panuron; Pavulon; Pesium.

Pipecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de pipecuronio; Pipecurium Bromide; Pipecuronii Bromidum; Pipécuronium, Bromure de; Pipekuroniumbromid; Pipekuroniumbromidi; RGH-1106. 1,1,1′,1′-Tetramethyl-4,4′-(3α,17β-diacetoxy-5α-androstan-2β,16β-diyl)dipiperazinium dibromide.

Пипекурония Бромид

$C_{35}H_{62}Br_2N_4O_4$ = 762.7.

CAS — 52212-02-9 (anhydrous pipecuronium bromide); 68399-57-5 (pipecuronium bromide dihydrate).

ATC — M03AC06.

ATC Vet — QM03AC06.

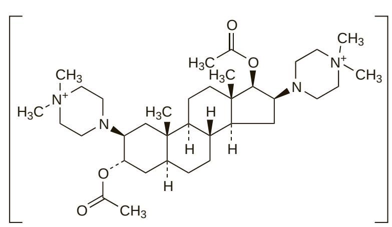

Profile

Pipecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1902). Pipecuronium is reported to have no significant cardiovascular adverse effects or histamine-related effects. On intravenous injection muscle relaxation occurs within 2.5 to 3 minutes with a duration of action of about 30 minutes to 2 hours, depending on the dose.

Pipecuronium bromide has been used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid mechanical ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. Initial doses of 80 to 100 micrograms/kg intravenously have been recommended, with subsequent doses of 10 to 20 micrograms/kg. Lower initial doses are given following suxamethonium or in patients at high risk: 50 to 60 micrograms/kg has been recommended, or 35 micrograms/kg for caesarean section.

◊ Reviews and studies.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–99.
2. Tassonyi E, *et al.* Pharmacokinetics of pipecuronium in infants, children and adults. *Eur J Drug Metab Pharmacokinet* 1995; **20:** 203–8.
3. Melloni C. Farmacologia clinica del pipecuronium; studio comparativo della sua durata clinica in anestesia bilanciata (propofol/fentanyl) vs isoflurano. *Minerva Anestesiol* 1995; **61:** 491–500.
4. Meretoja OA, Erkola O. Pipecuronium revisited: dose-response and maintenance requirement in infants, children, and adults. *J Clin Anesth* 1997; **9:** 125–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Arpilon†; ***Cz.:*** Arduan; ***Hung.:*** Arduan; ***Pol.:*** Arduan; ***Rus.:*** Aperomid (Аперомид)†; Arduan (Ардуан).

Rapacuronium Bromide *(BAN, USAN, rINN)*

Bromuro de rapacuronio; Org-9487; Rapacuronii Bromidum; Rapacuronium, Bromure de. 1-(3α-Acetoxy-2β-piperidino-17β-propionyloxy-5α-androstan-16β-yl)-1-allylpiperidinium bromide; 1-Allyl-1-(3α,17β-dihydroxy-2β-piperidino-5α-androstan-16β-yl)piperidinium bromide, 3-acetate 17-propionate.

Рапакурония Бромид

$C_{37}H_{61}BrN_2O_4$ = 677.8.

CAS — 156137-99-4.

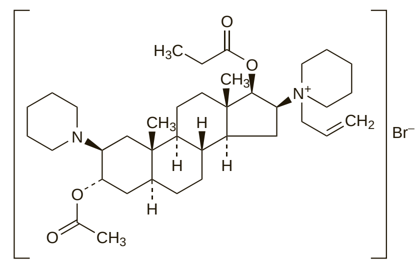

Profile

Rapacuronium bromide, an analogue of vecuronium (p.1913), is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1905). It was used to provide muscle relaxation in general anaesthesia for surgical procedures and for endotracheal intubation, but was withdrawn from the market after reports of severe bronchospasm, including fatalities.

◊ Reviews.

1. Wight WJ, Wright PMC. Pharmacokinetics and pharmacodynamics of rapacuronium bromide. *Clin Pharmacokinet* 2002; **41:** 1059–76.

Rocuronium Bromide *(BAN, USAN, rINN)*

Bromuro de rocuronio; Org-9426; Rocuronii bromidum; Rocuronium, bromure de; Rokuroniowy bromek; Rokuroniumbromid; Rokuronium-bromid; Rokuroniumbromidi; Rokuronyum Bromür. 1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide 17-acetate; 1-(17β-Acetoxy-3α-hydroxy-2β-morpholino-5α-androstan-16β-yl)-1-allylpyrrolidinium bromide.

Рокурония Бромид

$C_{32}H_{53}BrN_2O_4$ = 609.7.

CAS — 119302-91-9.

ATC — M03AC09.

ATC Vet — QM03AC09.

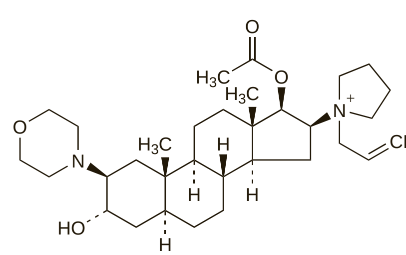

(rocuronium)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Rocuronium Bromide). An almost white or pale yellow, slightly hygroscopic, powder. Freely soluble in water and in dehydrated alcohol. A 1.0% solution in water has a pH of 8.9 to 9.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). Rocuronium is reported to have minimal cardiovascular and histamine-releasing effects. High doses (greater than 900 micrograms/kg of rocuronium bromide) have mild vagolytic activity. It should be used with caution in patients with biliary disease or hepatic or renal impairment.

Hepatic impairment. There have been conflicting reports of the pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic impairment. In contrast to earlier studies[1,2] one group of workers[3] found a significant reduction in the plasma clearance of rocuronium in patients with cirrhosis. The elimination half-life has been variously reported to be unchanged[1] or prolonged[2,3] with delayed recovery.[3] Some studies[2,3] found that the onset of action was not affected while one group of workers[1] reported a delay.

Licensed product information recommends that care should be taken when giving rocuronium to patients with clinically significant hepatic impairment (see also under Uses and Administration, below).

1. Khalil M, *et al.* Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. *Anesthesiology* 1994; **80:** 1241–7.
2. Magorian T, *et al.* The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg* 1995; **80:** 754–9.
3. van Miert MM, *et al.* The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *Br J Clin Pharmacol* 1997; **44:** 139–44.

Hypersensitivity. Although rocuronium is considered to have minimal histamine-releasing effects, histaminoid reactions have been reported[1] on induction of anaesthesia in 3 patients who had been given rocuronium. An increased incidence of severe hypersensitivity reactions (particularly anaphylactic shock) has been reported with rocuronium compared with other neuromuscular blockers available in France.[2] Fatalities have occurred.[3]

See also the discussion of the relative risks of hypersensitivity associated with neuromuscular blockers, under Suxamethonium Chloride, p.1910.

1. Neal SM, *et al.* Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84:** 108–11.
2. Mayer M. Information importante de pharmacovigilance: Esméron et manifestations allergiques. Available at: http://agmed.sante.gouv.fr/htm/10/filltrpsc/letesmer.pdf (accessed 28/05/04)
3. Baillard C, *et al.* Anaphylaxis to rocuronium. *Br J Anaesth* 2002; **88:** 600–602.

Pain on administration. Severe transient burning pain associated with injection of rocuronium was considered[1] to be responsible for the spontaneous movement sometimes seen in the arm or wrist into which rocuronium is given. It is recommended that rocuronium should be given only when a deep stage of unconsciousness has been achieved.

1. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? *Br J Anaesth* 1997; **79:** 382–3.

Renal impairment. In a study[1] of the pharmacokinetics and neuromuscular effects of rocuronium, the clearance of rocuronium was reduced in patients with renal failure when compared with healthy patients, but the accompanying increase in duration of clinical relaxation did not reach statistical significance. However, it was recommended that rocuronium should be used with caution in the presence of renal failure as there were large interpatient variations in both clinical response and pharmacokinetic parameters. It has been suggested[2] that chronic renal failure may have played a role in the prolongation of neuromuscular blockade in a 47-year-old woman given rocuronium 1 mg/kg. Although this dose is within the recommended adult dose range, it was criticised[3] as being excessive for a patient with renal impairment.

For recommendation that care should be taken when giving rocuronium to patients with renal failure, see under Uses and Administration, below.

1. Cooper RA, *et al.* Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (ORG 9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993; **71:** 222–6.
2. Lewis KS, *et al.* Prolonged neuromuscular blockade associated with rocuronium. *Am J Health-Syst Pharm* 1999; **56:** 1114–18.
3. Cozanitis DA, Booij HD. Muscle relaxants and renal failure. *Am J Health-Syst Pharm* 2000; **57:** 1713–14.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

On intravenous use plasma concentrations of rocuronium follow a three-compartment open model. There is an initial distribution phase with a half-life of 1 to 2 minutes followed by a slower distribution phase with a half-life of 14 to 18 minutes. It is reported to be about 30% bound to plasma proteins. The elimination half-life is about 1.2 to 1.4 hours. Up to 40% of a dose may be excreted in the urine within 24 hours; rocuronium is also excreted in the bile. The main metabolite of rocuronium, 17-desacetylrocuronium, is reported to have a weak neuromuscular blocking effect.

◊ References.

1. Khuenl-Brady KS, Sparr H. Clinical pharmacokinetics of rocuronium bromide. *Clin Pharmacokinet* 1996; **31:** 174–83.
2. McCoy EP, *et al.* Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth* 1996; **76:** 29–33.
3. Wierda JMKH, *et al.* Pharmacokinetics and pharmacokinetic-dynamic modelling of rocuronium in infants and children. *Br J Anaesth* 1997; **78:** 690–5.
4. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
5. Proost JH, *et al.* Urinary, biliary and faecal excretion of rocuronium in humans. *Br J Anaesth* 2000; **85:** 717–23.

Intensive care. The pharmacokinetics of rocuronium appear to differ between intensive care patients given prolonged dosage and surgical patients.[1] The volume of distribution at steady state may be increased, the plasma clearance decreased, and the terminal half-life prolonged. Recovery time on stopping may also be longer.

1. Sparr HJ, *et al.* Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. *Br J Anaesth* 1997; **78:** 267–73.

Pregnancy. The mean concentration of rocuronium in venous plasma of 32 patients given a dose of 600 micrograms/kg before undergoing caesarean section was 2412 nanograms/mL at delivery;[1] the ratio of mean concentrations of rocuronium in umbilical venous plasma to maternal venous plasma at this time was 0.16. In 12 of these patients the mean concentration of rocuronium in umbilical arterial plasma was 271 nanograms/mL giving a ratio of 0.62 for the mean concentration of rocuronium in arterial to venous umbilical plasma. The concentration of 17-desacetylrocuronium in maternal venous plasma was 178 nanograms/mL and was less than 25 nanograms/mL in umbilical plasma.

1. Abouleish E, *et al.* Rocuronium (Org 9426) for Caesarean section. *Br J Anaesth* 1994; **73:** 336–41.

Uses and Administration

Rocuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1905). After intravenous injection it produces muscle relaxation within 1 to 2 minutes with a duration of about 30 to 50 minutes. Rocuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. A usual initial dose is 600 micrograms/kg by intravenous injection; however, higher doses of 1 mg/kg are recommended for intubation during rapid sequence induction of anaesthesia. Usual maintenance doses are 150 micrograms/kg by injection, although these should be reduced to 75 to 100 micrograms/kg if prolonged inhalational anaesthesia is planned. Maintenance may also be by infusion at a rate of 300 to 600 micrograms/kg per hour although higher rates have been used in the USA. Similar doses to those used in adults have been used in the UK in infants and children older than one month but maintenance doses may be required more frequently. In the USA, rocuronium is licensed for use in children aged 3 months and over; again doses are similar to those used in adults.

For obese patients weighing more than 30% over their ideal body-weight UK licensed product information recommends that doses should be calculated according to lean body-mass; in the USA it is recommended that dosage should be based on actual body-weight. UK product information also recommends reduced maintenance doses of 75 to 100 micrograms/kg by injection in the elderly. For doses in hepatic or renal impairment, see below.

◊ Reviews and discussions.

1. Mirakhur RK. Newer neuromuscular blocking drugs: an overview of their clinical pharmacology and therapeutic use. *Drugs* 1992; **44:** 182–9.
2. Hunter JM. Rocuronium: the newest aminosteroid neuromuscular blocking drug. *Br J Anaesth* 1996; **76:** 481–3.

Administration in children. In a study involving 70 children, conditions for intubation were judged to be good to excellent within one minute of intravenous doses of rocuronium 600 or 900 micrograms/kg, with a trend to better conditions with the higher dose.[1]

1. Fuchs-Buder T, Tassonyi E. Intubating conditions and time course of rocuronium-induced neuromuscular block in children. *Br J Anaesth* 1996; **77:** 335–8.

INTRAMUSCULAR ROUTE. Intramuscular injection of rocuronium 1 mg/kg into the deltoid muscle permitted tracheal intubation to be carried out in lightly anaesthetised infants after 2.5 minutes.[1] In children a dose of 1.8 mg/kg enabled tracheal intubation after 3 minutes. However, the mean time to initial recovery after these large doses was 57 minutes in infants and 70 minutes in children. This prolonged duration of action may limit intramuscular use for brief procedures, particularly in children.

1. Reynolds LM, *et al.* Intramuscular rocuronium in infants and children: dose-ranging and tracheal intubating conditions. *Anesthesiology* 1996; **85:** 231–9.

Administration in hepatic or renal impairment. UK licensed product information recommends a reduced maintenance dose of 75 to 100 micrograms/kg in patients with hepatic or biliary-tract disease, or renal failure. Initial doses remain unaltered.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zemuron†; ***Austral.:*** Esmeron; ***Austria:*** Esmeron; ***Belg.:*** Esmeron; ***Braz.:*** Esmeron; Rocuron; ***Canad.:*** Zemuron; ***Chile:*** Esmeron; ***Cz.:*** Esmeron; ***Denm.:*** Esmeron; ***Fin.:*** Esmeron; ***Fr.:*** Esmeron; ***Ger.:*** Esmeron; ***Gr.:*** Esmeron; ***Hong Kong:*** Esmeron; ***Hung.:*** Esmeron; ***Indon.:*** Esmeron; Roculax; ***Irl.:*** Esmeron; ***Israel:*** Esmeron; ***Ital.:*** Esmeron; ***Jpn:*** Eslax; ***Malaysia:*** Esmeron; ***Mex.:*** Esmeron; ***Neth.:*** Esmeron; ***Norw.:*** Esmeron; ***NZ:*** Esmeron; ***Philipp.:*** Esmeron; ***Pol.:*** Esmeron; ***Port.:*** Esmeron; ***Rus.:*** Esmeron (Эсмерон); ***S.Afr.:*** Esmeron; ***Singapore:*** Esmeron; ***Spain:*** Esmeron; ***Swed.:*** Esmeron; ***Switz.:*** Esmeron; ***Thai.:*** Esmeron; ***Turk.:*** Esmeron; ***UK:*** Esmeron; ***USA:*** Zemuron; ***Venez.:*** Esmeron.

Suxamethonium Chloride *(BAN, pINN)*

Choline Chloride Succinate; Cloruro de suxametonio; Succicurarium Chloride; Succinylcholine Chloride; Suksametonio chloridas; Suksametoniowy chlorek; Suksametoniumkloridi; Süksinilkolin Klorür; Suxamethonii chloridum; Suxamethonii Chloridum Dihydricum; Suxamethonium chlorid dihydrát; Suxaméthonium, chlorure de; Suxametoniumklorid; Suxametonklorid; Szuxametónium-klorid. 2,2′-Succinyldioxybis(ethyltrimethylammonium) dichloride dihydrate.

Суксаметония Хлорид

$C_{14}H_{30}Cl_2N_2O_4,2H_2O$ = 397.3.

CAS — 306-40-1 (suxamethonium); 55-94-7 (suxamethonium bromide); 71-27-2 (anhydrous suxamethonium chloride); 6101-15-1 (suxamethonium chloride dihydrate); 541-19-5 (suxamethonium iodide).

ATC — M03AB01.

ATC Vet — QM03AB01.

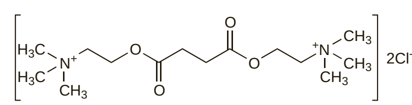

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Suxamethonium Chloride). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Succinylcholine Chloride). A white, odourless, crystalline powder. The anhydrous form is hygroscopic. Soluble 1 in 1 of water and 1 in 350 of alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water have a pH of about 4. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. Incompatibilities of neuromuscular blockers are discussed under Atracurium, p.1902.

Stability. A study of the loss of potency of suxamethonium chloride 20 mg/mL in water indicated that decomposition occurred at a considerably higher rate at 40° than at 25° and that the pH range of maximum stability was 3.75 to 4.50 for unbuffered solutions.[1] Assuming the usual conditions of manufacturing, transit, and storage the total loss of potency was estimated to be 7% and 9% respectively for injections kept at room temperature for 4 and 6 weeks. If unbuffered, suxamethonium chloride injection complying with USP 31 pH limits (3.0 to 4.5) must be stored at room temperature; it should not be kept for longer than 4 weeks.

1. Boehm JJ, *et al.* Shelf life of unrefrigerated succinylcholine chloride injection. *Am J Hosp Pharm* 1984; **41:** 300–2.

Adverse Effects

The neuromuscular blocking action of suxamethonium chloride is terminated by the enzyme plasma cholinesterase and prolonged apnoea may occur in patients with an atypical enzyme or with low enzyme activity. Apnoea may also occur following development of phase II block (see Uses and Administration, below) after high or repeated doses of suxamethonium chloride, although tachyphylaxis may also occur with repeated doses.

Transient fasciculations occur during the onset of depolarising block. Rhabdomyolysis, myoglobinaemia, and myoglobinuria have been reported and may be associated with muscle damage following fasciculations. Postoperative muscle pain occurs in some patients but is not directly related to the degree of fasciculation. A transient rise in intra-gastric pressure may occur secondary to fasciculation of abdominal muscles. A transient increase in intra-ocular pressure often occurs. Depolarisation of skeletal muscle produces an immediate increase in plasma-potassium concentration and this can have serious consequences in some patients (see below).

Stimulation of the vagus nerve and parasympathetic ganglia by suxamethonium chloride may be followed by bradycardia, other arrhythmias, and hypotension, and may be exacerbated by the raised plasma-potassium concentration; cardiac arrest has been reported. Tachycardia and an increase in blood pressure due to stimulation of sympathetic ganglia have also been reported.

Suxamethonium chloride may cause an increase in salivary, bronchial, and gastric secretion and other muscarinic effects. Salivary gland enlargement has occurred.

Direct release of histamine from mast cells occurs but this is not the main mechanism of hypersensitivity reactions (see Hypersensitivity, below). Flushing, skin rash, bronchospasm, and shock have been reported.

Other reported effects include prolonged respiratory depression and apnoea.

Suxamethonium chloride is implicated in the development of malignant hyperthermia (p.1896) in those patients with a genetic predisposition to the syndrome.

◊ Reviews.

1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 331–49.
2. Orebaugh SL. Succinylcholine: adverse effects and alternatives in emergency medicine. *Am J Emerg Med* 1999; **17:** 715–21.

Effects on intra-ocular pressure. Doses of suxamethonium are often followed 20 to 30 seconds later by a transient increase in intra-ocular pressure, which may be due in part to contracture of extra-ocular muscles. If suxamethonium is used during eye surgery after incision of the eyeball or in patients with a penetrating eye injury, there is a theoretical risk that any increase in intra-ocular pressure may result in extrusion of ocular contents and loss of sight. However, there appear to be few reports of vitreous extrusion associated with suxamethonium,[1] and a large retrospective study[2] has failed to find any evidence that suxamethonium caused additional eye damage in patients with penetrating eye injuries. Furthermore, the procedure of intubation itself is associated with a greater increase in intra-ocular pressure than that seen with suxamethonium. Nonetheless, some suggest that a rapid competitive neuromuscular blocker would be preferable to aid intubation in patients with penetrating eye injuries, after incision of the eyeball, and in glaucoma, although others consider that the risk of a transient rise of intra-ocular pressure in these situations should be weighed against the need for rapid intubation.[1,3] For a discussion on the use of various drugs to counteract the rise in intra-ocular pressure associated with suxamethonium and intubation in general, see under Anaesthesia, p.1900.

1. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **5:** 331–49.
2. Libonati MM, *et al.* The use of succinylcholine in open eye surgery. *Anesthesiology* 1985; **62:** 637–40.
3. Edmondson L. Intraocular pressure and suxamethonium. *Br J Anaesth* 1997; **79:** 146.

Effects on the muscles. Muscle fasciculations and postoperative muscle pain commonly follow use of suxamethonium. **Fasciculations** (generalised and desynchronised contractions of skeletal muscle fibres) occur during the onset of depolarising block in almost all patients given suxamethonium and may cause muscle damage. They are seen especially in the 'fine' muscles of the hands and face, and can be useful as an indication that suxamethonium is working. Attempts have been made to prevent their development with the aim of reducing postoperative muscle pain. However, there appears to be no direct correlation between the extent of visible fasciculations and muscle pain.[1,2] Slow infusion of suxamethonium[3] or giving divided doses[4] reduces fasciculations but not muscle pain.

Postoperative **muscle pain** is one of the most common adverse effects of suxamethonium and has been noted in about 50% of patients, although the reported incidence varies widely from around 1.5 to about 90%.[2] It usually occurs on the first postoperative day and lasts for 2 or 3 days, and most often affects muscles of the neck, shoulders, and upper abdomen.[2] The incidence and severity of muscle pain is increased in patients who are mobile soon after surgery and in females, but it occurs less often in children, pregnant women, and the elderly.[2]

The mechanism of suxamethonium-induced muscle pain is not fully understood; there have been many attempts to prevent it. Pretreatment with a small dose of a competitive neuromuscular blocker reduces both visible fasciculations and the incidence and severity of muscle pain,[1,2,5-8] but may delay the onset and alter the intensity of subsequent suxamethonium block[9] and impair conditions for intubation[1,9] (see Neuromuscular Blockers, under Interactions in Atracurium, p.1905). In addition, larger doses of suxamethonium are required;[10] consequently the practice is considered controversial by some authors.[10,11] Pretreatment with a small dose (10 mg) of suxamethonium in a 'self-taming' technique appears to offer no protection against muscle pain.[1,2] The choice of anaesthetic induction agent has been suggested to be significant, as has the timing of doses, but despite claims for benefit with, for example, propofol, this remains questionable.[2] Pretreatment with benzodiazepines or NSAIDs has produced conflicting results.[2] Other drugs that have been tried include lidocaine, calcium gluconate, and vitamin C; there is some evidence that lidocaine may be the most effective pretreatment.[2] Not all methods have concentrated on drug treatment. A simple regimen of stretching exercises before premedication has reduced the incidence of both fasciculations and postoperative muscle pain.[12]

Suxamethonium may also produce an increase in **jaw tension** (masseter spasm or trismus)[13] in both adults[14] and children[15,16] during the onset of neuromuscular blockade. Tracheal intubation is greatly hindered in affected patients. It is not possible to predict which patients will show this response and the mechanism is unknown, although in about 50% of patients it may indicate the onset of malignant hyperthermia. Pretreatment with a paralysing dose of a competitive neuromuscular blocker prevents the response[16] but it is not known whether this is clinically useful.

1. O'Sullivan EP, *et al.* Differential effects of neuromuscular blocking agents on suxamethonium-induced fasciculations and myalgia. *Br J Anaesth* 1988; **60:** 367–71.
2. Wong SF, Chung F. Succinylcholine-associated postoperative myalgia. *Anaesthesia* 2000; **55:** 144–52.
3. Feingold A, Velazquez JL. Suxamethonium infusion rate and observed fasciculations: a dose-response study. *Br J Anaesth* 1979; **51:** 241–5.
4. Wilson DB, Dundee JW. Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. *Anesthesiology* 1980; **52:** 273–5.
5. Bennetts FE, Khalil KI. Reduction of post-suxamethonium pains by pretreatment with four non-depolarising agents. *Br J Anaesth* 1981; **53:** 531–6.
6. Erkola O, *et al.* Five non-depolarizing muscle relaxants in precurarization. *Acta Anaesthesiol Scand* 1983; **27:** 427–32.
7. Sosis M, *et al.* Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. *Anesth Analg* 1987; **66:** 657–9.
8. Findlay GP, Spittal MJ. Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium. *Br J Anaesth* 1996; **76:** 526–9.
9. Pauca AL, *et al.* Inhibition of suxamethonium relaxation by tubocurarine and gallamine pretreatment during induction of anaesthesia in man. *Br J Anaesth* 1975; **47:** 1067–73.
10. McManus CM. Neuromuscular blockers in surgery and intensive care, part 2. *Am J Health-Syst Pharm* 2001; **58:** 2381–99.
11. Mencke T, *et al.* Pretreatment before succinylcholine for outpatient anesthesia? *Anesth Analg* 2002; **94:** 573–6.
12. Magee DA, Robinson RJS. Effect of stretch exercises on suxamethonium induced fasciculations and myalgia. *Br J Anaesth* 1987; **59:** 596–601.
13. Saddler JM. Jaw stiffness—an ill understood condition. *Br J Anaesth* 1991; **67**: 515–16.
14. Leary NP, Ellis FR. Masseteric muscle spasm as a normal response to suxamethonium. *Br J Anaesth* 1990; **64:** 488–92.
15. Van Der Spek AFL, *et al.* Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants. *Br J Anaesth* 1990; **64:** 21–7.
16. Smith CE, *et al.* Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children. *Br J Anaesth* 1990; **64:** 577–81.

Effects on plasma-potassium concentration. Suxamethonium causes depolarisation of motor end-plates in skeletal muscle, resulting in an immediate increase in plasma-potassium concentration. The rise is usually small, being about 0.5 mmol or less per litre, but suxamethonium is best avoided in patients whose plasma-potassium concentration is already high, such as those with renal impairment. An exaggerated response, with severe hyperkalaemia resulting in ventricular fibrillation and cardiac arrest, has been reported in patients with burns,[1,2] massive trauma, closed head injury, neuromuscular disease (see Neuromuscular Disorders, under Precautions, below), and severe long-lasting sepsis.[3] See also Children, under Precautions, below for reference to fatal cardiac arrest associated with hyperkalaemia in children. With burns or trauma the period of greatest risk is from about 10 to 90 days after the injury, but may be further prolonged if there is delayed healing or persistent infection. These patients may still react abnormally to suxamethonium 2 years after the injury. In neuromuscular disease the greatest risk period is usually from 3 weeks to 6 months after onset, but severe hyperkalaemia may occur after 24 to 48 hours or later than 6 months. Patients with severe sepsis for more than a week should be considered at risk of hyperkalaemia and suxamethonium should not be given until the infection has cleared. The mechanism of this hyperkalaemic response appears to be a supersensitivity of acetylcholine receptors in which the entire muscle fibre membrane, rather than discrete motor end-plate sites, becomes directly excitable by depolarising drugs. Depolarisation by suxamethonium thus results in release of potassium over the entire muscle fibre membrane and hyperkalaemia results.

Various methods have been tried to attenuate the hyperkalaemia, including pretreatment with a small dose of a competitive neuromuscular blocker[3,4] or with suxamethonium itself.[5,6] No method is reliable enough to be used clinically.

Anaesthetics such as thiopental and halothane can increase the hyperkalaemic response.[4]

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; **26:** 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; **ii:** 1003–4.
3. Kohlschütter B, *et al.* Suxamethonium-induced hyperkalaemia in patients with severe intra-abdominal infections. *Br J Anaesth* 1976; **48:** 557–62.
4. Dhanaraj VJ, *et al.* A study of the changes in serum potassium concentration with suxamethonium using different anaesthetic agents. *Br J Anaesth* 1975; **47:** 516–19.
5. Magee DA, Gallagher EG. "Self-taming" of suxamethonium and serum potassium concentration. *Br J Anaesth* 1984; **56:** 977–9.
6. Plötz J, Schreiber W. Side effects induced by suxamethonium on the skeletal muscle and their prevention. *Br J Anaesth* 1985; **57:** 1044–5.

Hypersensitivity. Hypersensitivity reactions to neuromuscular blockers are more common in women than in men,[1,2] in atopic patients and those who have a history of asthma or allergy,[2] and in patients who have had a previous reaction to anaesthetic drugs.[2] Circulatory collapse, flushing, skin rash, urticaria, and bronchospasm have occurred in hypersensitivity reactions associated with suxamethonium;[1,3,4] deaths have been reported.[3,5]

Data from intradermal testing has been used to qualify the **risk** of allergic reactions associated with the neuromuscular blockers:[6]

- benzylisoquinolinium blockers *alcuronium* and *tubocurarine* and the depolarising blocker *suxamethonium* were considered to be associated with the highest risk
- benzylisoquinolinium blockers *atracurium*, *cisatracurium*, *gallamine*, and *mivacurium* and the aminosteroid *rocuronium* presented an intermediate risk
- the aminosteroids *pancuronium* and *vecuronium* were considered to have the lowest risk

A type I immediate hypersensitivity reaction involving IgE antibodies is considered to be the **mechanism** of most hypersensitivity reactions associated with neuromuscular blockers.[2,5,7,8] Antibodies reacting with neuromuscular blockers, including suxamethonium, have been demonstrated.[5,8] The antibodies appear to be directed against quaternary or tertiary ammonium-ion groups which are present in neuromuscular blockers; such groups are also found in other drugs, cosmetics, disinfectants, and foods. This may help explain the cross-reactivity reported between different neuromuscular blockers[1,2,5,8,9] and how sensitisation occurs without prior exposure to any neuromuscular blocker.[2,5] At least 50% of patients sensitive to one neuromuscular blocker will react to one or more others[10] with some patients sensitive to most.[1] Intradermal skin tests are used to investigate and predict sensitivity to neuromuscular blockers, but their interpretation is controversial and it cannot be concluded that all patients with positive skin tests will have clinical sensitivity.[1,10] Although radioallergosorbent tests can detect antibodies to suxamethonium, alcuronium, and thiopental[3,11] some consider that their routine use is not justified as reactions could be avoided by taking an adequate patient history.[12]

However, neuromuscular blockers also have a direct effect on mast cells, releasing histamine without immunological involvement, and could cause anaphylactoid reactions. Histamine release associated with use of aminosteroidal blockers is rare compared with the benzylisoquinolinium blockers.[13] Tubocurarine is considered to be the most potent releaser of histamine, with pancuronium and vecuronium having only very weak activity. Suxamethonium is considered to have only 1% of the histamine-releasing activity of tubocurarine but is more likely to produce serious hypersensitivity reactions.

1. Youngmen PR, *et al.* Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; **ii:** 597–9.
2. Fisher MM, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; **62:** 559–64.
3. Brahams D. Fatal reaction to suxamethonium: case for screening by radioallergosorbent test? *Lancet* 1989; **i:** 1400–1.
4. Moneret-Vautrin DA, *et al.* Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. *Br J Anaesth* 1990; **64:** 743–5.
5. Fisher M, Baldo B. Adverse reactions to alcuronium: an Australian disease? *Med J Aust* 1983; **1:** 630–2.
6. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? *Br J Anaesth* 2001; **86:** 678–82.
7. Vervloet D. Anaphylactoid reactions to suxamethonium. *Lancet* 1983; **ii:** 1197.
8. Harle DG, *et al.* Detection of IgE antibodies to suxamethonium after anaphylactoid reactions during anaesthesia. *Lancet* 1984; **I:** 930–2.
9. Harle DG, *et al.* Cross-reactivity of metocurine, atracurium, vecuronium and fazadinium with IgE antibodies from patients unexposed to these drugs but allergic to other myoneural blocking drugs. *Br J Anaesth* 1985; **57:** 1073–6.
10. Withington DE. Relevance of histamine to the anaesthetist. *Br J Hosp Med* 1988; **40:** 264–70.
11. Assem ESK. Anaphylactic anaesthetic reactions: the value of paper radioallergosorbent tests for IgE antibodies to muscle relaxants and thiopentone. *Anaesthesia* 1990; **45:** 1032–8.
12. Noble DW, Yap PL. Screening for antibodies to anaesthetics. *BMJ* 1989; **299:** 2.
13. Naguib M, *et al.* Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; **75:** 588–92.

Treatment of Adverse Effects

Once suxamethonium chloride has been given assisted respiration should be maintained until spontaneous respiration has been fully restored. Transfusion of fresh frozen plasma or other source of plasma cholinesterase will help the destruction of the suxamethonium when prolonged paralysis is a result of atypical or low serum concentrations of plasma cholinesterase. Anticholinesterases should not normally be used since they potentiate the usual phase I block (see Uses and Administration, below). If the neuromuscular block ceases to be depolarising in type and acquires some features of a competitive block (phase II block) the cautious use of an anticholinesterase may be considered. A short-acting anticholinesterase such as edrophonium may be given intravenously and if an obvious improvement is maintained for several minutes, neostigmine may be given with atropine.

Severe hypersensitivity reactions should be treated promptly with supportive and symptomatic measures.

If malignant hyperthermia develops, it may be treated as described on p.1896.

The muscarinic effects of suxamethonium chloride, such as bradycardia and excessive salivary secretion, may be reduced by giving an antimuscarinic such as atropine before suxamethonium. A small dose of a competitive neuromuscular blocker given before suxamethonium has been used to reduce some of the adverse effects of suxamethonium on the muscles (see Effects on the Muscles, above).

Precautions

Patients given a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Suxamethonium chloride is contra-indicated in patients with atypical plasma cholinesterase and should be used with caution in patients with reduced plasma cholinesterase activity (see below), which may occur in certain disease states and following exposure to certain drugs. Plasma cholinesterase concentrations fall during pregnancy and the puerperium and therefore maternal paralysis may be mildly prolonged. Suxamethonium is contra-indicated in patients with burns, massive trauma, renal impairment with a raised plasma-potassium concentration, severe long-lasting sepsis, and severe hyperkalaemia, since suxamethonium-induced rises in plasma-potassium concentration can have serious consequences in such patients; patients who have been immobilised for prolonged periods may be at similar risk. It is contra-indicated in patients with a history of hypersensitivity to the drug and, because high rates of cross-sensitivity have been reported (see above), should be used with caution when hypersensitivity to any neuromuscular blocker has previously occurred. Suxamethonium should be avoided in patients with a penetrating eye injury, raised intra-ocular pressure or glaucoma, or those about to undergo incision of the eyeball in eye surgery, because of the risks from increased intra-ocular pressure (although see under Adverse Effects, above). Suxamethonium chloride produces muscle contractions before relaxation and should therefore be used with caution in patients with bone fractures. It is contra-indicated in patients with a personal or family history of malignant hyperthermia.

The response to suxamethonium chloride is often unpredictable in patients with neuromuscular disorders and it should be used with great caution in these patients (see below). Caution is also needed if it is given to a patient with cardiac or respiratory disease. Children may be at special risk from cardiac arrest associated with hyperkalaemia (see below).

Hypothermia may enhance the neuromuscular blocking effects of suxamethonium chloride and an increase in body temperature may reduce them.

Children. Reports of fatal cardiac arrests[1,2] in apparently healthy children and adolescents, who were subsequently found to have had undiagnosed myopathies, led to restrictions in the USA on the use of suxamethonium in this age group. Suxamethonium was contra-indicated except for emergency tracheal intubation or where an immediate securing of an airway was essential. Many anaesthetists disagreed[2] with this contra-indication and an FDA Committee advised[3] that it should be replaced by a warning about the possibility of cardiac arrest associated with hyperkalaemia with special attention being paid to male children who are considered to be at the highest risk. One British anaesthetist who questioned the rationale behind restricting the elective use of suxamethonium pointed out that alternatives to suxamethonium had not been shown to be as safe or effective for airway management.[4] The rare occurrence of cardiac arrest in children might be further reduced by taking a careful family history to exclude undiagnosed myopathies and by using an intravenous as opposed to inhalation induction when suxamethonium is to be used.[4] A survey had found that most cases of cardiac arrest in children in the UK associated with the use of suxamethonium had been caused by vagal overactivity in non-atropinised patients.

1. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine. *Anesthesiology* 1992; **77:** 1054.
2. Book WJ, *et al.* Adverse effects of depolarising neuromuscular blocking agents: incidence, prevention and management. *Drug Safety* 1994; **10:** 331–49.
3. *FDC Reports Pink Sheet* 1994; June 13: 16.
4. Hopkins PM. Use of suxamethonium in children. *Br J Anaesth* 1995; **75:** 675–7.

Neuromuscular disorders. Caution is needed if suxamethonium is to be given to patients with neuromuscular disease, since severe complications have been reported.[1] Hyperkalaemia and cardiac arrhythmias or cardiac arrest have been reported after use of suxamethonium in patients with hemiplegia, diffuse intracranial lesions (head injury, encephalitis, ruptured cerebral aneurysm), tetanus, paraplegia, acute anterior horn cell disease, and muscular dystrophies. An exaggerated response to suxamethonium has been reported in the myasthenic syndrome but resistance may occur in patients with neurofibromatosis. Resistance may also occur in patients with myasthenia gravis, but uneventful use has also been reported, although early onset of phase II block is possible in these patients. Muscle contractures and hyperkalaemia may be expected in amyotrophic lateral sclerosis and muscular denervation. Suxamethonium should be avoided in patients with myotonias, as response is unpredictable. It is recommended that suxamethonium is also avoided in hemiplegia, paraplegia, muscular denervation, and muscular dystrophies.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61:** 173–87.

Plasma cholinesterase deficiency. Suxamethonium is normally rapidly hydrolysed by plasma cholinesterase and the clinical effects usually last for only several minutes. Activity of the enzyme varies between individuals and prolonged paralysis following suxamethonium is commonly due to a hereditary or acquired reduction in plasma cholinesterase activity. The genes involved in the control of plasma cholinesterase production are termed usual, atypical (dibucaine-resistant), fluoride-resistant, and silent. About 96% of the population are homozygous for the usual gene. The commonest variant in western populations is the atypical form with about 3 to 4% of the population being heterozygous for this variant. They exhibit a slightly prolonged response to suxamethonium. Homozygotes for the atypical variant have a frequency of about 0.04%. They exhibit markedly prolonged apnoea following a standard dose of suxamethonium but can be readily identified by biochemical tests. The fluoride-resistant and silent variants occur very rarely. A measure of plasma cholinesterase activity can be obtained from the percentage inhibition of the enzyme by the local anaesthetic cinchocaine (commonly known in this context by its American name, dibucaine) to give the **dibucaine number**. Most normal people have a dibucaine number of about 80.

Acquired plasma cholinesterase deficiency is clinically less important than genetically determined deficiency. The enzyme is synthesised in the liver and **severe liver impairment** or malnutrition may cause abnormally low enzyme levels with some prolongation of suxamethonium activity. Reduced enzyme activity may also be found in severe anaemia, burns, cancer, collagen diseases, severe dehydration, severe infections, malnutrition, myocardial infarction, myxoedema, and renal impairment; plasmapheresis or plasma exchange removes significant amounts of plasma cholinesterase.

During **pregnancy** there is a rapid fall in plasma cholinesterase concentration that persists throughout pregnancy and for up to several weeks into the puerperium. The concentration of atypical plasma cholinesterase is also reduced in pregnancy and the puerperium. A number of **drugs** reduce plasma cholinesterase synthesis or activity and may prolong suxamethonium paralysis as discussed under Interactions, below.

References.

1. Wood GJ, Hall GM. Plasmapheresis and plasma cholinesterase. *Br J Anaesth* 1978; **50:** 945–9.
2. Evans RT, Wroe JM. Plasma cholinesterase changes during pregnancy: their interpretation as a cause of suxamethonium-induced apnoea. *Anaesthesia* 1980; **35:** 651–4.
3. Lumley J. Prolongation of suxamethonium following plasma exchange. *Br J Anaesth* 1980; **52:** 1149–50.
4. Williams FM. Clinical significance of esterases in man. *Clin Pharmacokinet* 1985; **10:** 392–403.
5. Robson N, *et al.* Plasma cholinesterase changes during the puerperium. *Anaesthesia* 1986; **41:** 243–9.
6. Cherala SR, *et al.* Placental transfer of succinylcholine causing transient respiratory depression in the newborn. *Anaesth Intensive Care* 1989; **17:** 202–4.

Renal impairment. Suxamethonium chloride may be given in usual doses to patients with renal failure[1,2] although it is usually recommended that it should be avoided if hyperkalaemia is also present (see Effects on Plasma-potassium Concentration above). However, in a retrospective review[3] of 38 patients with serum potassium levels greater than 5.5 mmol/litre given a standard intubation dose of suxamethonium, there were no reports of dysrhythmias or unexpected admissions to the intensive care unit.

Patients with renal failure given repeated doses of suxamethonium did not show an excessive increase in serum potassium; however sinus bradycardia commonly occurred and it was recommended that repeated injections should be avoided in such patients.[2] If necessary, pretreatment with glycopyrrolate or atropine to protect against bradycardia should be considered.

1. Ryan DW. Preoperative serum cholinesterase concentration in chronic renal failure. *Br J Anaesth* 1977; **49:** 945–9.
2. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. *Anesth Analg* 2000; **91:** 237–41.
3. Schow AJ, *et al.* Can succinylcholine be used safely in hyperkalemic patients? *Anesth Analg* 2002; **95:** 119–22.

Interactions

A number of drugs may interact with depolarising neuromuscular blockers such as suxamethonium. The mechanisms of interaction can include a direct effect on neuromuscular transmission or an alteration of enzyme activity and may result in potentiation or antagonism of neuromuscular block. In general, such interactions are potentially more serious in patients with impaired neuromuscular function or reduced activity of plasma cholinesterase, who are more sensitive to suxamethonium's effects.

Interactions common to competitive and depolarising neuromuscular blockers are covered under Atracurium, p.1903 whereas those specific for depolarising blockers are discussed below.

Antiarrhythmics. See under Atracurium, p.1903.

Antibacterials. See under Atracurium, p.1903.

Anticholinesterases. The action of suxamethonium may be markedly prolonged in patients using eye drops containing *ecothiopate*, a long-acting anticholinesterase that inhibits both acetylcholinesterase and plasma cholinesterase. After systemic absorption of ecothiopate, plasma cholinesterase activity may rapidly be reduced to 5% or less of normal and prolonged apnoea after use of suxamethonium has occurred. On stopping ecothiopate, enzyme activity remains depressed for 1 to 2 months. If a patient has used ecothiopate eye drops in the previous 2 months, suxamethonium should not be given unless normal plasma cholinesterase activity can be demonstrated; a competitive neuromuscular blocker is preferable. Exposure to *organophosphorus insecticides* may also reduce plasma cholinesterase activity resulting in prolonged paralysis after use of suxamethonium; enzyme activity may be totally abolished. Anticholinesterases including *edrophonium, neostigmine, pyridostigmine, rivastigmine, tacrine,* and possibly *donepezil* enhance the action of suxamethonium, although suxamethonium-induced phase II block can be reversed with an anticholinesterase. Care should be taken if there is a need to use suxamethonium for urgent short procedures after a competitive-neuromuscular-induced block has been antagonised with an anticholinesterase, as the resulting block may be greatly prolonged.[1]

1. Fleming NW, *et al.* Neuromuscular blocking action of suxamethonium after antagonism of vecuronium by edrophonium, pyridostigmine or neostigmine. *Br J Anaesth* 1996; **77:** 492–5.

Antiepileptics. The mean time to recovery from suxamethonium-induced neuromuscular block was 14.3 minutes in 9 patients receiving chronic treatment with *phenytoin* and/or *carbamazepine* compared with 10.0 minutes in 9 patients not receiving antiepileptics.[1]

1. Melton AT, *et al.* Prolonged duration of succinylcholine in patients receiving anticonvulsants: evidence for mild upregulation of acetylcholine receptors? *Can J Anaesth* 1993; **40:** 939–42.

Antineoplastics. *Cyclophosphamide* has been reported to prolong the neuromuscular block produced by suxamethonium through reduction of plasma cholinesterase activity, possibly by alkylation of the enzyme.[1] Since enzyme activity may be reduced by up to 70% for several days to several weeks, it was suggested[2] that suxamethonium should be avoided if possible in patients receiving cyclophosphamide. A more recent case report[3] would also support this suggestion. Other alkylating agents also reported to reduce plasma cholinesterase activity include *chlormethine, thiotepa,* and *tretamine*.[2]

1. Walker IR, *et al.* Cyclophosphamide, cholinesterase and anaesthesia. *Aust N Z J Med* 1972; **3:** 247–51.
2. Zsigmond EK, Robins G. The effect of a series of anti-cancer drugs on plasma cholinesterase activity. *Can Anaesth Soc J* 1972; **19:** 75–82.
3. Koseoglu V, *et al.* Acquired pseudocholinesterase deficiency after high-dose cyclophosphamide. *Bone Marrow Transplant* 1999; **24:** 1367–8.

Aprotinin. See under Atracurium, p.1904.

Benzodiazepines. See under Atracurium, p.1904.

Beta blockers. See under Atracurium, p.1904.

Cardiac inotropes. See under Atracurium, p.1904.

Ganglion blockers. See under Atracurium, p.1904.

General anaesthetics. Tachyphylaxis and phase II block (see Uses and Administration, below) develop earlier, and after smaller total doses of suxamethonium, when inhalation anaesthetics are used. *Halothane* may increase the incidence of arrhythmias associated with suxamethonium and can potentiate suxamethonium-induced muscle damage.[1] Suxamethonium should be used with caution with other drugs that might produce additive cardiovascular effects. Severe bradycardia and asystole have occurred when used in anaesthetic regimens with *propofol* and opioids such as *fentanyl*.

See also under Interactions of Atracurium, p.1904.

1. Laurence AS, Henderson P. Serum myoglobin after suxamethonium administration to children: effect of pretreatment before iv and inhalation induction. *Br J Anaesth* 1986; **58:** 126P.

Histamine H_2 antagonists. See under Atracurium, p.1904.

Lithium. See under Atracurium, p.1904.

Local anaesthetics. *Procaine*, *cocaine*, and *chloroprocaine* are ester-type local anaesthetics which are hydrolysed by plasma cholinesterase and may competitively enhance the neuromuscular blocking activity of suxamethonium. See also Antiarrhythmics under Atracurium, p.1903.

Magnesium salts. See under Atracurium, p.1904.

MAOIs. Reduction of plasma cholinesterase activity by *phenelzine* has been reported[1] to cause significant prolongation of suxamethonium paralysis. Enzyme activity may be reduced to 10% of normal and recovery can take up to a month. The dosage of suxamethonium may need to be substantially reduced or a competitive neuromuscular blocker used.

1. Bodley PO, *et al.* Low serum pseudocholinesterase levels complicating treatment with phenelzine. *BMJ* 1969; **3:** 510–12.

Metoclopramide. Dose-dependent prolongation of suxamethonium-induced neuromuscular blockade has been reported in patients given metoclopramide.[1,2] The potent inhibitory effect of metoclopramide on plasma cholinesterase may account for this interaction.

1. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; **63:** 348–50.
2. Kao YJ, *et al.* Dose-dependent effect of metoclopramide on cholinesterases and suxamethonium metabolism. *Br J Anaesth* 1990; **65:** 220–4.

Neuromuscular blockers. See under Atracurium, p.1905.

Sex hormones. *Oestrogens* and oestrogen-containing *oral contraceptives* reduce plasma cholinesterase activity[1] possibly due to suppression of hepatic synthesis of the enzyme, but little prolongation of suxamethonium paralysis may be expected since activity is reduced by only about 20%. See also under Atracurium, p.1905.

1. Robertson GS, Aberd MB. Serum protein and cholinesterase changes in association with contraceptive pills. *Lancet* 1967; **i:** 232–5.

Sympathomimetics. *Bambuterol* can inhibit plasma cholinesterase activity and so prolong the activity of suxamethonium.[1] Phase II block has been reported in some patients with abnormal plasma cholinesterase.[2]

1. Staun P, *et al.* The influence of 10 mg and 20 mg bambuterol on the duration of succinylcholine-induced neuromuscular blockade. *Acta Anaesthesiol Scand* 1990; **34:** 498–500.
2. Bang U, *et al.* The effect of bambuterol on plasma cholinesterase activity and suxamethonium-induced neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. *Acta Anaesthesiol Scand* 1990; **34:** 600–604.

Pharmacokinetics

After injection, suxamethonium is rapidly hydrolysed by plasma cholinesterase. One molecule of choline is split off rapidly to form succinylmonocholine which is then slowly hydrolysed to succinic acid and choline. About 10% of suxamethonium is excreted unchanged in the urine. Succinylmonocholine has weak muscle-relaxant properties mainly of a competitive nature.

The gene responsible for the expression of plasma cholinesterase exhibits polymorphism and enzyme activity varies between individuals (see under Precautions, above).

Small amounts of suxamethonium cross the placenta.

◊ Reviews.

1. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; **54:** 526–34.

Uses and Administration

Suxamethonium is a depolarising neuromuscular blocker used to produce muscle relaxation. It combines with cholinergic receptors of the motor end-plate to produce depolarisation but is resistant to breakdown by acetylcholinesterase. This prevents repolarisation and subsequent depolarisation, and a flaccid muscle paralysis occurs. This initial depolarisation block is commonly known as a **phase I block.** The muscles that produce fine rapid movements such as those of the face are the first to be affected followed by those of the limbs, abdomen, and chest; the diaphragm is affected last. Recovery occurs in reverse order. When excessive amounts of suxamethonium accumulate at the neuromuscular junction, for example after high or prolonged dosage, the nature of the block may change to one with characteristics similar to competitive block. This is commonly termed **phase II block** or **dual block** and may be associated with prolonged neuromuscular blockade and apnoea.

After intravenous injection suxamethonium chloride acts in about 30 to 60 seconds and has a duration of action of about 2 to 6 minutes. After intramuscular injection it acts in 2 to 3 minutes and has a duration of action of about 10 to 30 minutes.

Suxamethonium is used in surgical and other procedures in which a rapid onset and brief duration of muscle relaxation is needed (see Anaesthesia, p.1900), including intubation, endoscopies, and ECT. It is used as suxamethonium chloride, and is normally given by intravenous injection. The content of preparations of suxamethonium chloride may be described in terms of either the dihydrate or the anhydrous form, depending on the country of origin, and this should be borne in mind when evaluating the literature although the differences are small (anhydrous suxamethonium chloride 1 mg is equivalent to about 1.1 mg of the dihydrate).

Suxamethonium should be given after induction of general anaesthesia because paralysis is usually preceded by painful muscle fasciculations. A competitive neuromuscular blocker may sometimes be given before suxamethonium to try to reduce some of the adverse effects on the muscles (see Effects on the Muscles, above). Premedication with an antimuscarinic may be of value in reducing bradycardia and excessive salivation. Assisted ventilation is necessary.

An initial test dose of 100 micrograms/kg, or 5 to 10 mg, of suxamethonium chloride may be given intravenously if increased sensitivity is suspected. Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The response to suxamethonium varies considerably and the usual single dose of suxamethonium chloride for an adult is 0.3 to 1.1 mg/kg by intravenous injection. Supplementary doses of 50 to 100% of the initial dose may be given at 5 to 10 minute intervals if required but the total dose given by repeated intravenous injection or continuous infusion (see below) should not exceed 500 mg/hour. Infants and children are more resistant to suxamethonium than adults. A recommended intravenous dose for infants under one year of age is 2 mg/kg; a dose of 1 mg/kg is recommended for children 1 to 12 years old.

When a suitable vein is inaccessible suxamethonium chloride has been given by intramuscular injection in a dose of 3 to 4 mg/kg to a maximum total dose of 150 mg. The intramuscular dose for infants is up to 4 to 5 mg/kg and for older children up to 4 mg/kg to a maximum total dose of 150 mg.

For prolonged procedures in adults sustained relaxation may be obtained by continuous intravenous infusion of a 0.1 to 0.2% solution. A rate of 2.5 to 4 mg/minute is usually adequate but may be adjusted as necessary. The total dose given by repeated intravenous injection (see above) or continuous infusion should not exceed 500 mg/hour.

Suxamethonium bromide and suxamethonium iodide have also been used.

ECT. Suxamethonium chloride is used to decrease the muscular contractions associated with electrically induced convulsions. It temporarily paralyses muscles during ECT, preventing violent muscle contractions which can potentially result in broken bones and fractures.

Suxamethonium chloride remains the most commonly used neuromuscular blocker in ECT. However, patients with a history of malignant hyperthermia, neuroleptic malignant syndrome, catatonic schizophrenia, and organophosphate poisoning are more susceptible to adverse effects.[1] Mivacurium has been used, with satisfactory results, in at-risk-patients, although histamine release and hypotension may be a problem. Other competitive neuromuscular blockers tried include atracurium and vecuronium.

1. Ding Z, White PF. Anesthesia for electroconvulsive therapy. *Anesth Analg* 2002; **94:** 1351–64.

Preparations

BP 2008: Suxamethonium Chloride Injection;
USP 31: Succinylcholine Chloride for Injection; Succinylcholine Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Actirelax; Fosfitone; Succi†; ***Austral.:*** Scoline; ***Austria:*** Lysthenon; ***Belg.:*** Myoplegine†; ***Braz.:*** Quelicin; Succitrat; Succnil Colin; ***Canad.:*** Quelicin; ***Fin.:*** Sukolin; ***Fr.:*** Celocurine†; ***Ger.:*** Lysthenon; Pantolax; ***Gr.:*** Lycitrope; ***India:*** Midarine; ***Indon.:*** Quelicin; ***Irl.:*** Anectine; ***Israel:*** Succinyl; ***Ital.:*** Midarine; Myotenlis†; ***Malaysia:*** Ethicoline; Succinyl†; ***Mex.:*** Anectine; Uxicolin; ***Neth.:*** Curalest; ***Norw.:*** Curacit; ***NZ:*** Ethicholine†; ***Pol.:*** Chlorsuccillin; ***Port.:*** Mioflex; ***Rus.:*** Lysthenon (Листенон); ***S.Afr.:*** Scoline; ***Singapore:*** Ethicholine; ***Spain:*** Anectine; Mioflex; ***Swed.:*** Celocurin; ***Switz.:*** Lysthenon; Midarine; Succinolin; ***Thai.:*** Succinyl; ***Turk.:*** Lysthenon; ***UK:*** Anectine; ***USA:*** Anectine; Quelicin.

Tubocurarine Chloride *(BAN, rINN)*

Cloruro de tubocurarina; *d*-Tubocurarine Chloride; (+)-Tubocurarine Chloride Hydrochloride Pentahydrate; Tubocurarine, chlorure de; Tubocurarini chloridum; Tubocurarinii Chloridum Pentahydricum; Tubokurariinikloridi; Tubokurarinium-chlorid pentahydrát; Tubokurarinklorid; Tubokurarin-klorid; Tubokurarino chloridas. (+)-7′,12′-Dihydroxy-6,6′-dimethoxy-2,2′,2′-trimethyltubocuraranium dichloride pentahydrate.

Тубокурарина Хлорид

$C_{37}H_{42}Cl_2N_2O_6,5H_2O = 771.7.$

CAS — 57-95-4 (tubocurarine); 57-94-3 (anhydrous tubocurarine chloride); 6989-98-6 (tubocurarine chloride, pentahydrate).

ATC — M03AA02.

ATC Vet — QM03AA02.

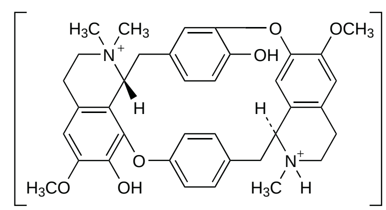

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Tubocurarine Chloride). A white or slightly yellowish crystalline powder. Soluble in water and in alcohol; practically insoluble in acetone; dissolves in solutions of alkali hydroxides. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers.

USP 31 (Tubocurarine Chloride). A white or yellowish-white to greyish-white, crystalline powder. Soluble 1 in 20 of water and 1 in 45 of alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). A transient fall in blood pressure commonly occurs, due in part to ganglionic blockade and the release of histamine; there may be an increase in heart rate. Tubocurarine has a greater propensity to cause histamine release than other competitive neuromuscular blockers in clinical use. Tubocurarine should be used with caution in patients with renal impairment. Resistance to the effect of tubocurarine may occur in patients with hepatic impairment.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

Tubocurarine chloride is a quaternary ammonium compound and absorption from the gastrointestinal tract is extremely poor. Absorption is slow and irregular when given intramuscularly. After intravenous injection tubocurarine is widely distributed throughout body tissues; less than 50% is bound to plasma proteins. After a single dose extensive redistribution to tissues is responsible for the termination of activity, but after a large single dose or repeated small doses tissue saturation occurs and renal excretion becomes the main determinant of duration. When given in usual doses it does not pass the blood-brain barrier, and does not appear to cross the placenta in significant amounts. Up to 75% of a dose is excreted unchanged in the urine in 24 hours, and up to 12% in bile. Biliary excretion is increased in renal impairment. A small proportion of a dose is metabolised in the liver.

Uses and Administration

Tubocurarine is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905). It may be obtained from extracts of the stems of *Chondodendron tomentosum* (Menispermaceae) and is one of the active principles of curare, by which name it is sometimes referred to in anaesthetic literature. Tubocurarine chloride is the chloride of (+)-tubocurarine. After intravenous injection of tubocurarine chloride neuromuscular block appears within 1 minute and lasts for about 30 minutes; the maximum effect is attained within 2 to 5 minutes.

Tubocurarine chloride has been used similarly to other competitive neuromuscular blockers to produce muscle relaxation in various procedures but has largely been replaced by other drugs with fewer cardiovascular effects and a lower potential for histamine release.

Doses used have varied according to the degree of muscle relaxation required. Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 6 to 9 mg intravenously has been suggested followed by 3 to 4.5 mg after 3 to 5 minutes if necessary; additional doses of 3 mg may be given as required for prolonged procedures. Higher doses have been given in some countries. It has also been given intramuscularly but absorption is slow and erratic. Tubocurarine should be given with caution in reduced doses to patients with renal impairment; if large or repeated doses are given neuromuscular block may be prolonged.

Tubocurarine chloride has also been used to control the muscle spasms of tetanus (p.1901).

Preparations

USP 31: Tubocurarine Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Decurin; ***Israel:*** Curarine†; Tubarine†.

Vecuronium Bromide *(BAN, USAN, rINN)*

Bromuro de vecuronio; Org-NC-45; Vecuronii bromidum; Vécuronium, bromure de; Vekuroniumbromid; Vekuronium-bromid; Vekuroniumbromidi; Vekuronyum Bromür; Wekuroniowy bromek. 1-(3α,17β-Diacetoxy-2β-piperidino-5α-androstan-16β-yl)-1-methylpiperidinium bromide.

Векурония Бромид

$C_{34}H_{57}BrN_2O_4$ = 637.7.

CAS — 50700-72-6.

ATC — M03AC03.

ATC Vet — QM03AC03.

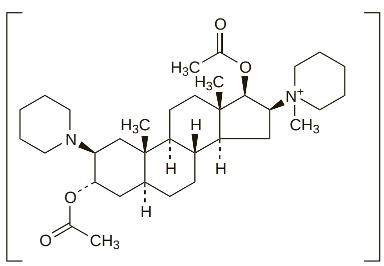

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Vecuronium Bromide). White or almost white crystals or crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol and in acetonitrile; freely soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

USP 31 (Vecuronium Bromide). White or creamy white crystals, or a crystalline powder. Slightly soluble in water and in acetone; sparingly soluble in alcohol. Store in airtight containers.

Incompatibility. A solution containing vecuronium bromide 1 mg/mL was found to be visually incompatible with furosemide.[1] For incompatibilities of competitive neuromuscular blockers in general, see under Atracurium on p.1902.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902).

Vecuronium bromide has little histamine-releasing activity although a local reaction at the site of injection has been reported; bronchospasm and anaphylactoid reactions have been rarely reported. It also has little vagolytic or ganglion-blocking activity and produces no significant adverse cardiovascular effects at usual doses.

Caution may be needed in patients with hepatic or renal impairment (see under Uses and Administration, below); dosage adjustments may be required in renal failure.

The elderly. It has been recommended that neuromuscular function should be monitored in elderly patients receiving vecuronium since there may be a risk of prolonged block.[1]

1. Slavov V, *et al.* Comparison of duration of neuromuscular blocking effect of atracurium and vecuronium in young and elderly patients. *Br J Anaesth* 1995; **74:** 709–11.

Pregnancy. The proportion of vecuronium crossing the placenta after doses of 60 to 80 micrograms/kg was considered clinically insignificant and its use during obstetric anaesthesia was considered safe for the newborn.[1]

1. Demetriou M, *et al.* Placental transfer of Org NC 45 in women undergoing caesarean section. *Br J Anaesth* 1982; **54:** 643–5.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

On intravenous injection vecuronium is rapidly distributed. It is taken up by the liver and partly metabolised; the metabolites have some neuromuscular blocking activity. It is excreted mainly in bile as unchanged drug and metabolites; some is also excreted in urine. The plasma elimination half-life is reported to range from about 30 to 80 minutes.

Uses and Administration

Vecuronium bromide is an aminosteroidal competitive neuromuscular blocker (see Atracurium, p.1905).

After intravenous injection muscle relaxation occurs within about 1.5 to 2 minutes and lasts for about 20 to 30 minutes.

Vecuronium bromide is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. The usual initial dose for intubation is 80 to 100 micrograms/kg by intravenous injection, although reduced initial doses of 30 to 50 micrograms/kg are suggested following the use of suxamethonium. Higher initial doses ranging from 150 to 300 micrograms/kg have sometimes been used for other procedures. However, it is recommended that the dose should not exceed 100 micrograms/kg in caesarean section or neonatal surgery. Maintenance doses of 20 to 30 micrograms/kg may be given as required during prolonged procedures; in the USA a lower maintenance dose of 10 to 15 micrograms/kg is recommended. Neuromuscular blockade may also be maintained with an intravenous infusion given at a rate of 0.8 to 1.4 micrograms/kg per minute but should be preceded by an initial bolus injection of 40 to 100 micrograms/kg. UK licensed product information recommends that in obese patients the dosage of vecuronium should be reduced taking into account lean body-mass.

Children older than 5 months can be given adult doses but children up to 1 year may have a more rapid response and the high initial dose for intubation may not be necessary. Neonates and infants below 5 months of age may be more sensitive to vecuronium and it is recommended that they should be given an initial test dose of 10 to 20 micrograms/kg, followed by increments according to response. The duration of action and recovery is longer in neonates and infants than in children and adults and they may require smaller maintenance doses given less frequently.

Administration in hepatic impairment. Although the manufacturers make no specific recommendations for dosage reduction in hepatic impairment, the duration of action of vecuronium was reported to be significantly prolonged in patients with cholestasis[1] or cirrhosis with oesophageal varices[2] given a dose of 200 micrograms/kg intravenously. Plasma clearance was significantly reduced and the elimination half-life significantly increased from a mean of 58 to 98 minutes.[1] A dose of 150 micrograms/kg was found to have a similar onset and duration of action in patients with hepatic impairment and healthy controls,[2] but a dose of 100 micrograms/kg had a slower onset and slightly shorter duration of action in those with liver disturbance.[3] After a dose of vecuronium, rapid and extensive hepatic uptake occurs, which largely determines its short duration of action. However, as the dose increases this mechanism becomes saturated, and hepatic elimination becomes more important in terminating activity. This would help to explain the variation in results seen with the different doses. Caution is needed if large single doses or repeated doses are given to patients with hepatic impairment.

1. Lebrault C, *et al.* Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. *Br J Anaesth* 1986; **58:** 983–7.
2. Hunter JM, *et al.* The use of different doses of vecuronium in patients with liver dysfunction. *Br J Anaesth* 1985; **57:** 758–64.
3. Bell CF, *et al.* Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985; **57:** 160–8.

Administration in renal impairment. A small proportion of vecuronium bromide is excreted in urine and it may be given in usual doses to patients with renal failure.[1,2] No clinically significant difference in elimination half-life, clearance, or duration of action were reported[1] between patients with renal failure and those with normal renal function. The onset of neuromuscular block may be slightly slower in renal failure[2] and these patients may require an increase of around 20% in the initial dose of vecuronium.[3] However, the dosage requirement for maintenance of neuromuscular block may be reduced by about 20%[3] and slight prolongation of block may occur if dosage is not adjusted, but reversal of residual block with neostigmine is prompt and effective.[2]

Resistance to vecuronium has been reported[2] in 2 anephric patients. Total doses of 620 and 660 micrograms/kg produced maximum neuromuscular block of 77% and 36%, respectively but, despite the high doses used, there were no adverse effects or residual curarisation.

1. Fahey MR, *et al.* Pharmacokinetics of Org NC 45 (Norcuron) in patients with and without renal failure. *Br J Anaesth* 1981; **53:** 1049–53.
2. Hunter JM, *et al.* Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *Br J Anaesth* 1984; **56:** 941–51.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Galaren; Gobbicuronio; Norcuron†; Rivecrum; Vecural; Vecuron; ***Austral.:*** Norcuron; ***Austria:*** Norcuron; ***Belg.:*** Norcuron; ***Braz.:*** Norcuron; Vecuron; ***Canad.:*** Norcuron†; ***Chile:*** Norcuron; ***Cz.:*** Norcuron; ***Fin.:*** Norcuron; ***Fr.:*** Norcuron; ***Ger.:*** Norcuron; ***Gr.:*** Norcuron; ***Hong Kong:*** Norcuron; ***Hung.:*** Norcuron; ***India:*** Norcuron; ***Indon.:*** Norcuron; ***Irl.:*** Norcuron†; ***Israel:*** Norcuron; ***Ital.:*** Norcuron; ***Jpn:*** Musculax; ***Malaysia:*** Norcuron; ***Mex.:*** Bromivec; Curlem; Norcuron; ***Neth.:*** Norcuron; ***Norw.:*** Norcuron; ***NZ:*** Norcuron; ***Philipp.:*** Norcuron; ***Pol.:*** Norcuron; ***Port.:*** Norcuron; ***Rus.:*** Norcuron (Норкурон); ***S.Afr.:*** Norcuron; ***Singapore:*** Norcuron; ***Spain:*** Norcuron; ***Swed.:*** Norcuron; ***Switz.:*** Norcuron; ***Thai.:*** Norcuron; ***Turk.:*** Norcuron; ***UK:*** Norcuron; ***USA:*** Norcuron; ***Venez.:*** Norcuron†; Prorelax; Vecuron.

Nonionic Surfactants

A surfactant is a compound that can reduce the interfacial tension between 2 immiscible phases. This is because the molecule contains 2 localised regions, one hydrophilic in nature and the other hydrophobic. Nonionic surfactants differ from anionic surfactants (p.2138) by the absence of charge on, or ionisation of, the molecule; they are generally less irritant than anionic or cationic surfactants.

Hydrophilic groups include the oxyethylene group (–O.CH_2.CH_2–) and the hydroxyl group (–OH). By varying the number of these groups in a hydrophobic molecule, such as a fatty acid, substances are obtained that range from strongly hydrophobic and water-insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. These 2 extreme types are not satisfactory as emulsifying agents, though they are useful stabilisers in the presence of efficient emulsifying agents. Between these extremes are the nonionic emulsifying agents in which the proportions of hydrophilic and hydrophobic groups are more evenly balanced; these include some of the macrogol esters and ethers, and sorbitan derivatives. Nonionic surfactants may be classified according to their *hydrophilic-lipophilic balance* (HLB). This is an arbitrary scale of values denoting the relative affinity of the surfactant for oil and water. Lipophilic surfactants have low HLB values (less than 10) and are generally used as antifoaming agents, water-in-oil emulsifying agents, and as wetting agents; hydrophilic surfactants have higher HLB values (greater than 10) and are generally used as oil-in-water emulsifying agents and solubilising agents.

Nonionic surfactants also have applications in the food, cosmetic, paint, pesticide, and textile industries as well as being used as oil slick dispersants. Some macrogol ethers such as nonoxinol 9 are used as spermicides.

By virtue of the processes used in their manufacture, nonionic surfactants are usually mixtures of related compounds; the properties of a particular material may vary from one manufacturer to another and there may be variation in batches from an individual source. Since nonionic surfactants do not ionise to any great extent in solution, they are generally compatible with both anionic and cationic substances, but they reduce the antimicrobial action of many preservatives.

The range of nonionic surfactants used in pharmaceutical practice is large and their classification can be varied and complex. The principal groups of nonionic surfactants are outlined below.

Glycol and glycerol esters are a group of nonionic surfactants consisting of fatty acid esters of glycols and glycerol. Hydrophobic properties predominate and these compounds are poor emulsifying agents if used alone, though they are useful stabilisers for both oil-in-water and water-in-oil emulsions. If a small amount of soap, sulfated fatty alcohol, or other surfactant is added to the esters, a 'self-emulsifying' product is formed, which is capable of producing satisfactory oil-in-water emulsions. **Acetoglycerides** are mixed glyceryl esters in which the glycerol is esterified partly with a fatty acid and partly with acetic acid.

Macrogol esters are polyoxyethylene esters of fatty acids, mainly stearates. The hydrophilic properties of the oxyethylene group are weaker than those of the hydroxyl group but by introducing a sufficient number into a fatty acid molecule, substances are produced in which the hydrophilic and hydrophobic properties are sufficiently well balanced for the esters to act as efficient oil-in-water emulsifying agents. They may also be used as wetting and solubilising agents. Since the ester linkage is prone to hydrolysis, these compounds are less resistant to acids and alkalis than the macrogol ethers.

Macrogol ethers are condensation products prepared by reaction between fatty alcohols or alkylphenols and ethylene oxide. The ether linkage confers good stability to acids and alkalis. Macrogol ethers are widely used in the preparation of oil-in-water emulsions and as wetting and solubilising agents.

Sorbitan derivatives are derivatives of the cyclic mono- or di-anhydrides of sorbitol. They consist of *sorbitan esters*, which are prepared by esterification of one or more of the hydroxyl groups in the anhydrides with a fatty acid such as stearic, palmitic, oleic, or lauric acid, and *polysorbates*, which are polyoxyethylene derivatives of the sorbitan esters. Sorbitan esters are oil-soluble, water-dispersible, nonionic surfactants and are effective water-in-oil emulsifiers. Polysorbates are more hydrophilic, water-soluble compounds and are used as oil-in-water emulsifying agents. By varying the number of oxyethylene groups in the molecule, and the type of fatty acid in the sorbitan ester, surfactants with a wide range of properties may be obtained.

Poloxamers are copolymers of polyoxyethylene and polyoxypropylene. They are used as oil-in-water emulsifiers and as solubilising and wetting agents in pharmaceutical preparations intended for internal use.

Other nonionic compounds with surface activity such as the higher fatty alcohols are covered in the chapter on Paraffins and Similar Bases (p.2028).

Diacetylated Monoglycerides

Monoglicéridos diacetilados.

Моноглицериды Диацетилированные

Pharmacopoeias. In *USNF.*

USNF 26 (Diacetylated Monoglycerides). Consists of glycerol esterified with edible fat-forming fatty acids and acetic acid. A clear liquid. Very soluble in alcohol 80%, in vegetable oils, and in mineral oils; sparingly soluble in alcohol 70%. Store in airtight containers. Protect from light.

Profile

Diacetylated monoglycerides have been used as plasticisers, pharmaceutical excipients, and food additives.

Diethylene Glycol Monopalmitostearate

Diethylene Glycol Monostearate; Diéthylène Glycol (Stéarate de); Diéthylèneglycol, palmitostéarate de; Diethylenglycoli Monopalmitostearas; Diethylenglycoli palmitostearas; Diethylenglykol monopalmitostearát; Diethylenglykol palmito stearát; Diethyleni Glycoli Stearas; Dietilenglicol, monopalmitoestearato de; Dietilenglikolio palmitostearatas; Dietilénglikol-monopalmitát és monosztearát; Dietyleenliglykolipalmitostearaatti; Dietylenglykolpalmitostearat; Diglycol Stearate.

Диэтиленгликоля Монопальмитостеарат

CAS — 106-11-6 (diethylene glycol monostearate); 36381-62-1 (diethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Diethylene Glycol Stearates.

Ph. Eur. 6.2 (Diethylene Glycol Palmitostearate). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids produced by esterification of diethylene glycol and stearic acid of vegetable or animal origin. It contains 45.0 to 60.0% of monoesters and 35.0 to 55.0% of diesters, and a maximum of 2.5% of free diethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Protect from light.

USNF 26 (Diethylene Glycol Stearates). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Store in airtight containers.

Profile

Diethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Diethylene glycol monolaurate and mono-oleate have also been used.

Ethylene Glycol Monopalmitostearate

Ethylene Glycol Monostearate; Ethylene Glycol Stearate; Éthylène Glycol (Stéarate d'); Éthylèneglycol, monopalmitostéarate d'; Ethyleneglycoli Monopalmitostearas; Ethylenglycoli monopalmitostearas; Ethylenglycoli Monostearas; Ethylenglykol-monopalmitostearát; Ethyleni Glycoli Stearas; Etilenglicol, monopalmitoestearato de; Etilenglikolio monopalmitostearatas; Etilénglikol-monopalmitát és monosztearát; Etyleeniglykolimonopalmitostearaatti; Etylenglykolmonopalmitostearat.

Этиленгликоля Монопальмитостеарат

CAS — 111-60-4 (ethylene glycol monostearate); 4219-49-2 (ethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Ethylene Glycol Stearates.

Ph. Eur. 6.2 (Ethylene Glycol Monopalmitostearate). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid and not more than 5% of free ethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Protect from light.

USNF 26 (Ethylene Glycol Stearates). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Store in airtight containers.

Profile

Ethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Ethylene glycol monolaurate and mono-oleate have also been used.

Glyceryl Behenate

Glicerol, behenato de.

Глицерил Бегенат

Pharmacopoeias. In *USNF. Eur.* (see p.vii) includes Glycerol Dibehenate.

Ph. Eur. 6.2 (Glycerol Dibehenate; Glyceroli Dibehenas). A mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 15 to 23% of monoacylglycerols, 40 to 60% of diacylglycerols, and 21 to 35% of triacylglycerols, obtained by esterification of glycerol and behenic acid. A hard, waxy mass or powder or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 65° to 77°.

USNF 26 (Glyceryl Behenate). A mixture of glycerides of fatty acids, mainly behenic acid. A fine powder with a faint odour. M.p. about 70°. Practically insoluble in water and in alcohol; soluble in chloroform. Store in airtight containers at a temperature not exceeding 35°.

Profile

Glyceryl behenate is used as a lubricant and binder in tablet-making.

Glyceryl Distearate

Glicerin-disztearát; Glicerol, diestearato de; Glicerolio distearatas; Glycerol Distearate; Glycérol, distéarate de; Glyceroldistearat; Glycerol-distearát; Glyceroli distearas; Glyserolidistearaatti.

Глицерилдистеарат

CAS — 1323-83-7.

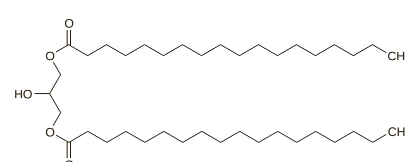

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Glycerol Distearate). A mixture of diacylglycerols, mainly distearoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 8 to 22% of monoacylglycerols, 40 to 60% of diacylglycerols, and 25 to 35% of triacylglycerols, obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A hard, waxy mass or powder, or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 50° to 60° (types I and II) or 50° to 70° (type III).
USNF 26 (Glyceryl Distearate). A mixture of diglycerides, mainly glyceryl distearate, together with variable quantities of monoglycerides and triglycerides. It contains 8 to 22% of monoglycerides, 40 to 60% of diglycerides, and 25 to 35% of triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.
Hard, waxy mass or powder, or white or almost white flakes. Insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane and in tetrahydrofuran. Store in airtight containers.

Profile
Glyceryl distearate is used as an emulsifying and/or solubilising agent.

Glyceryl Monolinoleate
Glicerin-monolinoleát; Glicerol, monolinoleato de; Glicerolio monolinoleatas; Glycerol Monolinoleate; Glycérol, monolinoléate de; Glyceroli monolinoleas; Glycerol-monolinolát; Glycerolmonolinoleat; Glyserolimonolinoleaatti; Monolinolein.

Глицерилмонолинолеат

CAS — 26545-74-4.

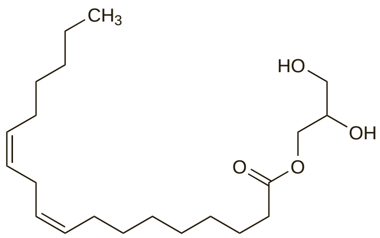

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Glycerol Monolinoleate). A mixture of monoacylglycerols, mainly mono-oleoylglycerol and monolinoleoylglycerol, together with variable quantities of di- and triacylglycerols. It contains 32 to 52% of monoacylglycerols, 40 to 55% of diacylglycerols, and 5 to 20% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of linoleic acid. A suitable antoxidant may be added.
Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.
USNF 26 (Glyceryl Monolinoleate). A mixture of monoglycerides, mainly glyceryl mono-oleate and glyceryl monolinoleate, together with variable quantities of diglycerides and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of linoleic acid. It contains 32 to 52% of monoglycerides, 40 to 55% of diglycerides, and 5 to 20% of triglycerides. A suitable antoxidant may be added.
Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile
Glyceryl monolinoleate is used as an emulsifying and/or solubilising agent.

Glyceryl Mono-oleate
Glicerol, monooleato de; Glycérol, mono-oléate de; Glyceroli mono-oleas; Monolein.

Глицерилмоноолеат

CAS — 25496-72-4.

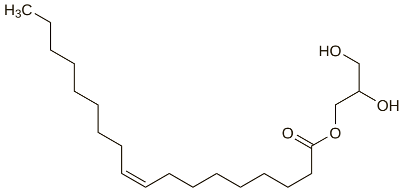

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Glycerol Mono-oleates). Mixtures of monoacylglycerols, mainly mono-oleoylglycerol, together with variable quantities of di- and triacylglycerols. They are defined by the nominal content of monoacylglycerols and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic acid, or by esterification of glycerol by oleic acid. A suitable antoxidant may be added.
Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.
USNF 26 (Glyceryl Monooleate). A mixture of monoglycerides, mainly glyceryl mono-oleate, together with variable quantities of di- and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of oleic acid, or by esterification of glycerol with oleic acid of vegetable or animal origin. It is defined by the nominal content of monoglycerides. A suitable antoxidant may be added.
Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile
Glyceryl mono-oleate has similar properties to glyceryl monostearate or self-emulsifying glyceryl monostearate (below).

Glyceryl Monostearate
Gliceril, monoestearato de; Glicerin-monosztearát; Glicerolio monostearatas; Glicerolu monostearynian; Glycérol, monostéarate de; Glyceroli monostearas; Glycerolmonostearat; Glycerol-monostearát; Glyserolimonostearaatti; GMS; Monostearin.

Глицерилмоностеарат

CAS — 31566-31-1 (glyceryl monostearate); 26657-96-5 (glyceryl monopalmitate).

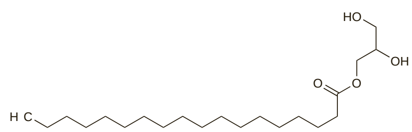

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Glycerol Monostearate 40-55). A mixture of monoacylglycerols, mainly monostearoylglycerol, together with variable quantities of di- and triacylglycerols. It contains 40 to 55% of monoacylglycerols, 30 to 45% of diacylglycerols, and 5 to 15% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of palmitic or stearic acid, or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.
A white or almost white, hard, waxy mass or unctuous powder or flakes. Practically insoluble in water; soluble in alcohol at 60°. M.p. 54° to 66°.
USNF 26 (Glyceryl Monostearate). It contains not less than 90% of monoglycerides of saturated fatty acids, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$ = 358.6) and glyceryl monopalmitate ($C_{19}H_{38}O_4$ = 330.5). It may contain a suitable antoxidant.
A white to yellowish wax-like solid, beads, flakes, or powder with a slight, agreeable, fatty odour. M.p. not below 55°. Insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble 1 in 10 of chloroform, 1 in 100 of ether and of methyl alcohol, 1 in 33 of isopropyl alcohol; dissolves in hot organic solvents such as alcohol, acetone, mineral or fixed oils, and benzene. Store in airtight containers. Protect from light.

Self-emulsifying Glyceryl Monostearate
Glicerol autoemulsionable, monoestearato de; Monostearato de glicerilo autoemulsionable; Monostearin Emulsificans; Self-emulsifying Mono- and Diglycerides of Food Fatty Acids; Self-emulsifying Monostearin.

Глицерилмоностеарат Самоэмульгирующийся

Pharmacopoeias. In *Br.*
BP 2008 (Self-emulsifying Glyceryl Monostearate). A mixture consisting principally of mono-, di-, and triglycerides of stearic and palmitic acids, and of minor proportions of other fatty acids; it may also contain free fatty acids, free glycerol, and soap. It contains not less than 30% of monoglycerides, not more than 7% of free glycerol, and not more than 6% of soap, calculated as sodium oleate, all calculated with reference to the anhydrous substance.
A white to cream-coloured, hard, waxy solid with a faint fatty odour. Dispersible in hot water; soluble in hot dehydrated alcohol and in hot liquid paraffin; soluble in hot vegetable oils, but may give turbid solutions at concentrations below 20%.

Incompatibility. Because of the presence of soap, self-emulsifying glyceryl monostearate is incompatible with acids and high concentrations of ionisable salts, hard water, calcium compounds, zinc oxide, and oxides of heavy metals.

Profile
Glyceryl monostearate is a poor water-in-oil emulsifying agent but it is a useful stabiliser of water-in-oil and oil-in-water emulsions in preparations for internal and external use. It has emollient properties. Glyceryl monostearate is also used in the food and cosmetic industries.
It is usual to add a small amount of soap, sulfated fatty alcohol, or other surfactant, to glyceryl monostearate, which has the effect of making the product self-emulsifying and capable of producing satisfactory oil-in-water emulsions. Self-emulsifying glyceryl monostearate is used as an emulsifying agent for oils, fats, solvents, and waxes in the preparation of bases of the non-emulsified, emulsified, and vanishing-cream types. It is not intended for inclusion in preparations for internal use.
Aqueous preparations containing self-emulsifying glyceryl monostearate should contain a preservative to prevent fungal or bacterial growth.

Macrogol Cetostearyl Ethers
Ceteareth Compounds; Macrogol, éteres cetoestearílicos de; Macrogol, ether cétostéarylique de; Macrogoli aether cetostearylicus; Makrogol-cetil-sztearil-éter; Makrogolcetostearyleter; Makrogolio cetostearilo eteris; Makrogolisetostearyylieetteri.

Полиэтиленгликоля и Цетостеарилового Спирта Эфиры

CAS — 68439-49-6.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Macrogol Cetostearyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly cetostearyl alcohol. It may contain some free macrogols and it contains various amounts of free cetostearyl alcohol. The amount of ethylene oxide reacted with cetostearyl alcohol is from 2 to 33 units per molecule (nominal value). White or yellowish-white waxy, unctuous mass, pellets, microbeads, or flakes. Macrogol cetostearyl ether with low numbers of ethylene oxide units per molecule is practically insoluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether with higher numbers of ethylene oxide units per molecule is dispersible or soluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether solidifies at 32° to 52°. Store in airtight containers. The labelling states the amount of ethylene oxide reacted with cetostearyl alcohol (nominal value).

Cetomacrogol 1000 *(BAN, rINN)*
Cétomacrogol 1000; Cetomacrogolum 1000; Éter monocetílico de polietilenglicol 1000; Polyethylene Glycol 1000 Monocetyl Ether; Polyoxyethylene Glycol 1000 Monocetyl Ether.

Кетомакрогол 1000; Цетомакрогол 1000

CAS — 9004-95-9 (macrogol cetyl ethers); 68439-49-6 (macrogol cetostearyl ethers).

Description. Cetomacrogol 1000 is a macrogol ether containing 20 to 24 oxyethylene groups in the polyoxyethylene chain. It may be prepared from either cetyl alcohol or from cetostearyl alcohol. It is represented by the formula $CH_3.[CH_2]_m.[O.CH_2.CH_2]_n.OH$, where m may be 15 or 17 and n may be 20 to 24. The more specific term macrogol cetostearyl ether (22), representing such an ether in which n = 22, has replaced cetomacrogol 1000 in BP formulations.
Macrogol cetyl ethers are also sometimes termed ceteth compounds.

Pharmacopoeias. In *Int.*

Incompatibility. Cetomacrogol has been reported to be incompatible with phenols and to reduce the antibacterial activity of quaternary ammonium compounds. Cetomacrogol may separate from solutions in the presence of a high concentration of electrolytes.

Polyoxyl 20 Cetostearyl Ether
Polioxil 20, éter cetoestearílico de.

Полиоксиэтилендиола 20 и Цетостеариловой Кислоты Эфир

CAS — 68439-49-6.

Pharmacopoeias. In *USNF.*
USNF 26 (Polyoxyl 20 Cetostearyl Ether). A mixture of the monocetostearyl (mixed hexadecyl and octadecyl) ethers of mixed macrogols, the average polymer length being equivalent to 17.2 to 25.0 oxyethylene units. A cream-coloured waxy unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in petroleum spirit. A 10% solution in water has a pH of 4.5 to 7.5. Store at a temperature of 8° to 15° in airtight containers.

Profile
Macrogol cetostearyl ethers are used as surfactants and emulsifiers. Macrogol cetostearyl ether (22) is used with cetostearyl alcohol (for example, in the form of Cetomacrogol Emulsifying Wax BP 2008) as an emulsifying agent for making oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and that are stable over a wide pH range. It is also used to disperse volatile oils in water to form transparent sols.

Preparations

BP 2008: Cetomacrogol Emulsifying Wax.

Macrogol 15 Hydroxystearate

Macrogol 15, hydroxystéarate de; Macrogoli 15 hydroxystearas; Makrogol hydroxystearát; Makrogol-15-hydroxistearat; Makrogoli-15-hydroksistearaatti; Makrogolio 15 hidroksistearatas.

Полиэтиленгликоля 15 Гидроксистеарат

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Macrogol 15 Hydroxystearate). A mixture of mainly mono- and di-esters of 12-hydroxystearic acid and macrogols obtained by ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains free macrogols. A yellowish, waxy mass. It solidifies at about 25°. Very soluble in water; soluble in alcohol; insoluble in liquid paraffin. Store in airtight containers.

Profile

Macrogol 15 hydroxystearate is a nonionic surfactant used as a solubilising agent.

Macrogol Lauril Ethers

α-Dodecyl-ω-hydroxypoly(oxyethylene); Éteres laurílicos de macrogol; Laureth Compounds; Lauromacrogols; Macrogol, éteres láuricos de; Macrogol, éther laurique de; Macrogol Lauryl Ethers; Macrogoli aether laurilicum; Makrogolilauryylieetteri; Makrogolio laurilo eteris; Makrogollauryleter; Oxypolyethoxydodecanes; Polyoxyl Lauryl Ethers.

Полиэтиленгликоля и Лаурилового Спирта Эфиры

CAS — 9002-92-0.

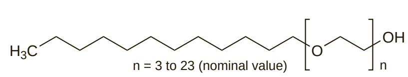

Description. Macrogol lauril ethers have the general formula $C_{12}H_{25}(OCH_2CH_2)_nOH$.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*. Also in *USNF.*

Ph. Eur. 6.2 (Macrogol Lauryl Ether). A mixture of ethers of mixed macrogols with fatty alcohols, mainly $C_{12}H_{26}O$. It contains a variable amount of free $C_{12}H_{26}O$ and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of $C_{12}H_{26}O$ is 3 to 23 (nominal value). Macrogol lauril ether with 3 to 5 units of ethylene oxide per molecule is a colourless liquid. Practically insoluble in water and in petroleum spirit; soluble or dispersible in alcohol. Macrogol lauril ether with 9 to 23 units of ethylene oxide per molecule is a white or almost white, waxy mass. Soluble or dispersible in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol lauril ether should be stored in airtight containers.

USNF 26 (Polyoxyl Lauryl Ether). A mixture of the monolauril ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 3 and not more than 23 oxyethylene units (nominal value). It contains various amounts of free lauril alcohol, and it may contain some free polyethylene glycols. Store in airtight containers in a dry place at a temperature of 8° to 15°.

Laureth 4 *(USAN)*

Лаурет 4

CAS — 9002-92-0.

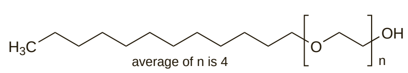

Description. A mixture of monolauril ethers of macrogols where the average value of *n* in the formula given above is 4.

Lauromacrogol 400 *(rINN)*

Laureth 9 *(USAN)*; Lauromacrogolum 400; Polidocanol; Polidocanolum; Polidokanol; Polidokanoli.

Лауромакрогол 400

CAS — 9002-92-0; 3055-99-0.
ATC — C05BB02.
ATC Vet — QC05BB02.

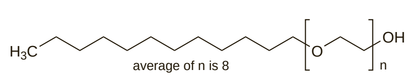

Description. Lauromacrogol 400 is a mixture of monolauril ethers of macrogols where the average value of *n* in the formula given above is 9 and the number 400 corresponds approximately to the average molecular mass of the macrogol portion. It has sometimes, however, been erroneously described as containing 8, rather than 9, oxyethylene groups. However, note that Lauromacrogol *(BAN)* is described as containing an average of 8 ethylene oxide groups per molecule.

Adverse Effects

There have been occasional reports of allergic skin reactions after topical application of preparations containing macrogol lauril ethers.

◊ A 63-year-old man developed pulmonary oedema, a dramatic fall in heart rate, transient left pyramidal syndrome and died after sclerotherapy with lauromacrogol 400 to control gastric variceal bleeding;[1] the fatality was attributed to the action of the drug that had passed into the systemic circulation. Another patient[2] suffered a reversible ischaemic neurological deficit after sclerotherapy with lauromacrogol 400 for varicose veins of the leg, and ischaemic stroke[3] and other neurological symptoms,[4] probably due to embolism after passage of foam through a patent foramen ovale, have been reported after foam injection sclerotherapy using the compound.

1. Paterlini A, *et al*. Heart failure and endoscopic sclerotherapy of variceal bleeding. *Lancet* 1984; **i:** 1241.
2. Van der Plas JPL, *et al*. Reversible ischaemic neurological deficit after sclerotherapy of varicose veins. *Lancet* 1994; **343:** 428.
3. Forlee MV, *et al*. Stroke after varicose vein foam injection sclerotherapy. *J Vasc Surg* 2006; **43:** 162–4.
4. Ceulen RPM, *et al*. Microembolism during foam sclerotherapy of varicose veins. *N Engl J Med* 2008; **358:** 1525–6.

Uses and Administration

Macrogol lauril ethers (laureth compounds) have been used as surfactants and spermicides. Lauromacrogol 400 is used as a sclerosant in the treatment of oesophageal and gastric varices (p.2346) and varicose veins (p.2347), and has been tried in endoscopic injection therapy for bleeding peptic ulcer (p.1702); it has also been used as a local anaesthetic and antipruritic (see p.1582) in combination topical preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aet; Aetoxy Sklerol; ***Austral.:*** Aethoxysclerol†; ***Austria:*** Aethoxysklerol; ***Belg.:*** Aethoxysklerol; ***Braz.:*** Aethoxysclerol†; ***Cz.:*** Aethoxysklerol; ***Denm.:*** Aethoxysklerol; ***Fin.:*** Aethoxysklerol; ***Fr.:*** Aetoxisclerol; ***Ger.:*** Aethoxysklerol; Anaesthesulf; Recessan; ***Gr.:*** Aethoxysklerol; Etoxisklerol; ***Hung.:*** Aethoxysklerol; ***Ital.:*** Atossisclerol Kreussler; ***Mex.:*** Farmaflebon; ***Neth.:*** Aethoxysklerol; ***Pol.:*** Aethoxysklerol; ***Spain:*** Etoxisclerol; ***Swed.:*** Aethoxysklerol; ***Switz.:*** Aethoxysklerol; Balmed Hermal Plus; ***Thai.:*** Aethoxysklerol†; ***Turk.:*** Aethoxysklerol; ***Venez.:*** Etoxisclerol.

Multi-ingredient: ***Arg.:*** Nene Dent NF; Solcoseryl Dental†; ***Austral.:*** TAGG†; ***Austria:*** Balneum Plus; Dentinox; Gingivan; Optiderm; Paididont; Prurimix; Solcoseryl Dental; Vonum; ***Belg.:*** Cose-Anal; ***Braz.:*** Nene Dent N; ***Chile:*** Mentobalsam; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; Vatanal; ***Cz.:*** Balneum Hermal Plus; Dentinox N†; Prurimix†; ***Ger.:*** Acoin; Alcos-Anal†; Balneum Plus; Brand- u. Wundgel-Medice N; Collomack†; Corti-Dynexan†; Dentinox N; Haemo-Exhirud†; Hexamon; Inflam†; Meaverin†; Medigel†; Optiderm; Solcoseryl Dental; Tamposit N†; Thesit†; ***Hong Kong:*** Balneum Intensiv Plus; Collomack; Haemoral; Solcoseryl Dental; ***Hung.:*** Dentinox N; ***Indon.:*** Solcoseryl Dental; ***Irl.:*** Balneum Plus; ***Israel:*** Balneum Plus; Derma-Care; ***Ital.:*** Optiderm; Pitiren; ***Malaysia:*** Balneum Intensiv Plus; Collomack†; Solcoseryl Dental; ***Mex.:*** Nene Dent; ***Neth.:*** Epianal; ***Norw.:*** Alcos-Anal; ***Philipp.:*** Solcoseryl Dental; ***Pol.:*** Balneum Hermal Plus; Dentinox N; Optiderm; ***Port.:*** Anacal; Hidratante VV; ***Rus.:*** Hepatrombin H (Гепатромбин Г); Solcoseryl Dental (Солкосерил Дентальная); ***Singapore:*** Balneum Intensiv Plus; Collomack†; Solcoseryl Dental; ***Switz.:*** Balneum Hermal Plus†; Decasept N; Optiderm; Oxydermine; Pruri-med; Ralur†; Remexal; Sclerovein; Solcoseryl Dentaire; Sportusal; Sportusal Spray sine heparino; Venucreme; Venugel; ***Thai.:*** Balneum Intensiv Plus†; Collomack†; Solcoseryl Dental; ***Turk.:*** Dentinox; Kortos; ***UK:*** Anacal; Balneum Plus; E45 Itch Relief; ***Venez.:*** Collomack.

Macrogol Monomethyl Ethers

Éteres monometílicos de polietilenglicol; Macrogol, éteres monometílicos de; Polyethylene Glycol Monomethyl Ethers. α-Methyl-ω-hydroxypoly(oxyethylene).

Полиэтиленгликоля и Метилового Спирта Эфиры

CAS — 9004-74-4.

Pharmacopoeias. In *USNF.*

USNF 26 (Polyethylene Glycol Monomethyl Ether). Addition polymers of ethylene oxide and methyl alcohol, represented by the formula $CH_3(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The name is usually designated by a number that corresponds approximately to its average molecular weight.

As the average molecular weight increases, the water solubility, vapour pressure, hygroscopicity, and solubility in organic solvents decrease while congealing temperature, specific gravity, flash-point, and viscosity increase. Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids with a slight characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material with a consistency similar to beeswax, or as creamy white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethyl acetate, in ethylene glycol monoethyl ether, and in toluene; all grades are insoluble in ether and in hexane. Store in airtight containers.

Profile

Macrogol monomethyl ethers may be used as ointment bases, solvents, and plasticisers.

Macrogol Oleyl Ethers

Macrogol, éteres oleílicos de; Macrogol, éther oléique de; Macrogoli aether oleicum; Macrogoli Aetherum Oleicum; Makrogolio oleilo eteris; Makrogolioleyylieetteri; Makrogol-oleil-éter; Makrogololeyleter; Oletho Compounds.

Полиэтиленгликоля и Олеилового Спирта Эфиры

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Macrogol Oleyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly oleyl alcohol. It may contain some free macrogols and it contains various amounts of free oleyl alcohol. Macrogol oleyl ether with 2 to 5 units of ethylene oxide per molecule is a yellow liquid. Practically insoluble in water and in petroleum spirit; soluble in alcohol. Macrogol oleyl ether with 10 to 20 units of ethylene oxide per molecule is a yellowish-white, waxy mass. Dispersible or soluble in water; soluble in alcohol; practically insoluble in petroleum spirit. Macrogol oleyl ethers should be stored in airtight containers. Protect from light.

Polyoxyl 10 Oleyl Ether

Polioxil 10, éter oleílico de; Polyethylene Glycol Mono-oleyl Ether.

Полиоксиэтиленгликоля и Олеиновой Кислоты Эфир

CAS — 9004-98-2.

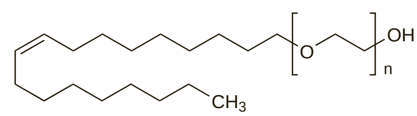

Pharmacopoeias. In *USNF.*

USNF 26 (Polyoxyl 10 Oleyl Ether). A mixture of the monooleyl ethers of mixed macrogols, the average polymer length being equivalent to not less than 9.1 and not more than 10.9 oxyethylene units. It may contain suitable stabilisers.

A soft white semisolid or pale yellow liquid with a bland odour. Soluble in water and in alcohol; dispersible in liquid paraffin and in propylene glycol with possible separation on standing. Store at a temperature of 8° to 15° in airtight containers.

Profile

Macrogol oleyl ethers such as polyoxyl 10 oleyl ether are used as surfactants.

Macrogol Stearates

Ésteres de polietilenglicol; Ésteres de polioxietileno; Macrogol, ésteres del; Macrogol, stéarate de; Macrogoli stearas; Makrogolio stearatas; Makrogolistearaatti; Makrogolstearat; Makrogol-stearát; Makrogol-sztearát; Polyoxyethylene Glycol Stearates; Polyoxyethylene Stearates; Polyoxyl Stearates.

Макрогола Стеараты; Полиэтиленгликоля Стеараты

CAS — 9004-99-3.

Nomenclature. There are two systems of nomenclature used for these compounds; these substances have the general formula $C_{17}H_{35}COO.[O.CH_2CH_2]_n.H$. In the systems used by *BAN* and *USAN* the numbers in the names refer to the approximate polymer length in oxyethylene units whereas in the system used by *INN* the number refers to the average molecular weight of the polymer chain. Thus, the names Macrogol 8 Stearate (*BAN*), Polyoxyl 8 Stearate (*USAN*), and Macrogol Stearate 400 (*rINNM*) all describe the same compound.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Macrogol Stearate). A mixture of the mono- and di-esters of mainly stearic acid and/or palmitic acid and macrogols. It may be obtained by ethoxylation or by esterification of macrogols with stearic acid 50 (type I) or stearic acid 95 (type II). The average polymer length is equivalent to 6 to 100 ethylene oxide units per molecule (nominal value). It may contain free macrogols. White or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Compounds containing 6 to 9 units of ethylene oxide per molecule are practically insoluble but freely dispersible in water; miscible with fatty oils and with waxes. Compounds containing 20 to 100 units of ethylene oxide per molecule are soluble in water; practically insoluble in fatty oils and in waxes. Store in airtight containers.

Polyoxyl 40 Stearate *(USAN)*

Macrogol Stearate 2000 *(rINNM)*; E431; Estearato de macrogol 2000; Estearato de Polioxila 40; Macrogol 40 Stearate *(BAN)*; Macrogol 2000, Stéarate de; Macrogol Ester 2000; Macrogoli Stearas 2000; Polyoxyethylene 40 Stearate; Stearethate 40.

Макрогола 2000 Стеарат

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 26 (Polyoxyl 40 Stearate). A mixture of the mono- and diesters of stearic acid and mixed macrogols, the average polymer length being about 40 oxyethylene units. It contains not less than 17% and not more than 27% of free macrogols. It is a waxy, white to light tan solid, odourless or with a faint fat-like odour. Congealing range 37° to 47°. Soluble in water, in alcohol, in acetone, and in ether; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Incompatibility. Macrogol stearates have been reported to be generally stable with electrolytes and weak acids or bases although strong acids or bases may cause hydrolysis and saponification. Discoloration or precipitation may occur with phenolic substances and complexation with preservatives. Decrease in the antimicrobial activity of bacitracin, chloramphenicol, phenoxymethylpenicillin, and tetracycline has been stated to occur with concentrations of macrogol stearates exceeding 5%.

Profile

Macrogol stearates are macrogol esters that are used as emulsifying and solubilising agents.

Menfegol *(rINN)*

Menfégol; Menfegolum; Menphegol. α-[*p*-(*p*-Menthyl)phenyl]-ω-hydroxypoly(oxyethylene).

Менфегол

CAS — 57821-32-6.

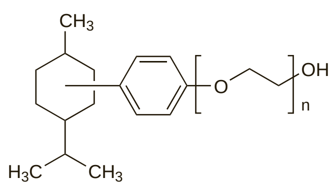

Profile

Menfegol consists of menthylphenyl ethers of macrogols represented by the formula $C_{16}H_{23}(OCH_2CH_2)_nOH$. It is a nonionic surfactant used as a spermicide.

Adverse effects. Frequent use of menfegol in spermicidal foaming tablets has been associated with a high incidence of genital ulceration, which could increase the risk of infection by HIV.[1]

1. Goeman, J. *et al.* Frequent use of menfegol spermicidal vaginal foaming tablets associated with a high incidence of genital lesions. *J Infect Dis* 1995; **171:** 1611–14.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Neo Sampoon; ***Malaysia:*** Neo Sampoon; ***Philipp.:*** Neo Sampoon; ***Singapore:*** Neo Sampoon.

Mono- and Di-glycerides

E471 (mono- and di-glycerides of fatty acids); Mono y diglicéridos.

Моно- и Диглицериды

Pharmacopoeias. In *USNF.*

USNF 26 (Mono- and Di-glycerides). A mixture of glycerol mono- and di-esters, with minor amounts of tri-esters, of fatty acids from edible oils. It contains not less than 40% of monoglycerides. It may contain suitable stabilisers. Store in airtight containers. Protect from light.

Profile

A mixture of mono- and di-glycerides is used as an emulsifying agent and food additive.

Nonoxinols

Macrogol Nonylphenyl Ethers; Nonoxinoles; Nonoxynols. α-(4-Nonylphenyl)-ω-hydroxypoly(oxyethylene).

Ноноксинолы

CAS — 26027-38-3.

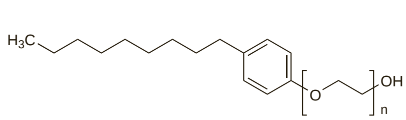

Nomenclature. Nonoxinols are a series of nonylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{15}H_{23}.[O.CH_2.CH_2]_n.OH$.

Nonoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Nonoxynol 4, Nonoxynol 9, Nonoxynol 15, and Nonoxynol 30.

Nonoxinol 9 *(BAN, rINN)*

Nonoksinoli-9; Nonoxinol-9; Nonoxinolum 9; Nonoxynol 9 *(USAN)*. α-(4-Nonylphenyl)-ω-hydroxynona(oxyethylene).

Ноноксинол 9

$C_{33}H_{60}O_{10}$ (nominal) = 616.8.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Nonoxinol 9). A mixture consisting mainly of monononylphenyl ethers of macrogols corresponding to the formula: $C_{15}H_{23}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is 9. A clear, colourless to light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

USP 31 (Nonoxynol 9). An anhydrous liquid mixture consisting chiefly of monononylphenyl ethers of macrogols corresponding to the formula $C_{15}H_{23}.[O.CH_2.CH_2]_n.OH$, in which the average value of *n* is about 9. A clear, colourless to light yellow, viscous liquid. Soluble in water, in alcohol, and in maize oil. Store in airtight containers.

Nonoxinol 10 *(BAN, rINN)*

Nonoxinolum 10; Nonoxynol 10. α-(4-Nonylphenyl)-ω-hydroxydeca(oxyethylene).

Ноноксинол 10

$C_{35}H_{64}O_{11}$ (nominal) = 660.9.

Nonoxinol 11 *(BAN, rINN)*

Nonoxinolum 11; Nonoxynol 11. α-(4-Nonylphenyl)-ω-hydroxyundeca(oxyethylene).

Ноноксинол 11

$C_{37}H_{68}O_{12}$ (nominal) = 704.9.

Adverse Effects and Precautions

Nonoxinols used as vaginal spermicides may cause local irritation.

Genito-urinary infections. Use of spermicidal foam or jelly containing nonoxinol 9 may disturb the normal vaginal flora and predispose to colonisation with *Escherichia coli* and the development of bacteriuria.[1] An increased risk of acute *E. coli* urinary-tract infection has been reported[2] associated with the use of condoms coated with nonoxinol 9. However, another study[3] of women using nonoxinol-9 spermicidal contraceptives showed that most users experienced minimal disruption to the vaginal microbial ecosystem.

For reference to an increased incidence of some sexually transmitted diseases in women using nonoxinol 9, see Antimicrobial Activity, below.

1. Hooton TM, *et al.* Escherichia coli bacteriuria and contraceptive method. *JAMA* 1991; **265:** 64–9.
2. Fihn SD, *et al.* Association between use of spermicide-coated condoms and Escherichia coli urinary tract infection in young women. *Am J Epidemiol* 1996; **144:** 512–20.
3. Schreiber CA, *et al.* Effects of long-term use of nonoxynol-9 on vaginal flora. *Obstet Gynecol* 2006; **107:** 136–43.

Pregnancy. Maternal use of spermicidal contraceptives has been linked to an increased frequency of congenital abnormalities, including trisomy, but it has been suggested that such studies may be flawed by recall bias.[1] Meta-analysis of 9 studies also supported the view that peri- and postconceptual maternal use of spermicides was not associated with adverse fetal outcome.[2]

1. Mishell DR. Contraception. *N Engl J Med* 1989; **320:** 777–87.
2. Einarson TR, *et al.* Maternal spermicide use and adverse reproductive outcome: a meta-analysis. *Am J Obstet Gynecol* 1990; **162:** 655–60.

Toxic shock syndrome. Toxic shock syndrome has been associated with the use of a vaginal contraceptive sponge impregnated with nonoxinol 9. A review[1] of 13 cases reported in the USA up to November 1984 found that in 4 of the cases there were other predisposing conditions: postpartum use, use during menstruation, and prolonged retention.

1. Faich G, *et al.* Toxic shock syndrome and the vaginal contraceptive sponge. *JAMA* 1986; **255:** 216–18.

Uses

Nonoxinols have surface active properties and may be used as solubilising agents. Nonoxinol 9 is used as a spermicide (see Contraception, p.2070).

Antimicrobial activity. Nonoxinol 9 has activity *in vitro* against a number of bacteria and viruses and it was hoped[1,2] that use of spermicidal contraceptives containing nonoxinol 9 might provide some protection against sexually transmitted diseases, including chlamydial, gonococcal, and HIV infection. However, controlled studies involving HIV-negative female sex workers or other high-risk women have found that use of nonoxinol 9 does not reduce the rate of new HIV,[3,4] or gonorrhoea or chlamydia infection;[3,5] meta-analyses[6,7] including these and other studies have come to similar conclusions. Furthermore, nonoxinol 9 has an irritant action and may increase the risk of genital ulceration, leading to an increased risk of infection by HIV. The United Nations,[8] WHO,[9] and FDA[10] have therefore advised against its use by women at high risk.

1. North BB. Vaginal contraceptives: effective protection from sexually transmitted diseases for women? *J Reprod Med* 1988; **33:** 307–311.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; **340:** 211–13.
3. Roddy RE, *et al.* A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med* 1998; **339:** 504–10.
4. Van Damme L, *et al.* Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360:** 971–7. Correction. *ibid.*; 1892.
5. Roddy RE, *et al.* Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydial infection: a randomized controlled trial. *JAMA* 2002; **287:** 1117–22.
6. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of HIV infection by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/04/08).
7. Wilkinson D, *et al.* Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/04/08).
8. Anonymous. UN warns against use of spermicide. *BMJ* 2000; **321:** 194.
9. Anonymous. Nonoxinol 9 ineffective in preventing HIV infection. *WHO Drug Inf* 2002; **16:** 120–1.
10. Food and Drug Administration. FDA mandates new warning for nonoxynol 9 OTC contraceptive products (issued 18/12/07). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01758.html (accessed 21/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Delfen†; Lorophyn; ***Austral.:*** Lubarol; ***Austria:*** Delfen†; Patentex; ***Braz.:*** Pessarios Profilaticos Rendell†; Preserv Nonoxinol-9; ***Canad.:*** Advantage 24†; Delfen; Gynol II†; K-Y Plus Spermicidal Lubricant; Lifestyles; Ortho-Gynol; Ramses; Sheik; Shields†; Today; Trojan; VCF; ***Chile:*** Impidol; Supoviol; VCF†; ***Cz.:*** Delfen†; Patentex Oval N; ***Fin.:*** Patentex; ***Ger.:*** Patentex Oval; Patentex†; ***Hong Kong:*** Patentex; ***Hung.:*** Patentex; ***India:*** Delfen; ***Irl.:*** Delfen†; Gynol II†; Ortho-Creme; ***Israel:*** Delfen†; ***Mex.:*** Lorophyn; ***NZ:*** Lifestyles; Rendells Plus†; ***Pol.:*** Patentex Oval; Secural; ***Port.:*** Delfen†; Rendells; ***Rus.:*** Patentex Oval N (Патентекс Овал Н); ***S.Afr.:*** Delfen; Gynol II; ***Spain:*** Nacha†; ***Swed.:*** Gynol-Plus; ***Switz.:*** C-Film†; Delfen†; Patentex Oval N; Syn-A-Gen; ***Turk.:*** Lorophyn; ***UK:*** Delfen†; Duragel†; Gygel; Gynol II†; Ortho-Creme†; Orthoforms†; Prelude; ***USA:*** Advantage 24; Delfen; Encare; Gynol II; Semicid; Sheik Elite; Shur-Seal; Today; VCF.

Multi-ingredient: ***Arg.:*** Merthiolate Iodopovidona; ***Canad.:*** Protectaid; ***Ger.:*** A-gen 53; ***Hong Kong:*** Protectaid; ***Israel:*** Glovan; ***Mex.:*** Norforms†; Sin-A-Gen; ***Spain:*** Lavolen; ***Turk.:*** Agen; ***UK:*** Protectaid.

Octoxinols

Macrogol Tetramethylbutylphenyl Ethers; Octoxinoles; Octoxynols; Octylphenoxy Polyethoxyethanol. α-[4-(1,1,3,3-Tetramethylbutyl)phenyl]-ω-hydroxypoly(oxyethylene).

Октоксинолы

CAS — 9002-93-1.

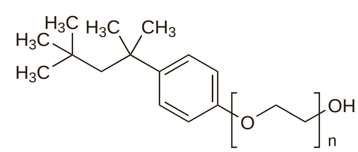

Nomenclature. Octoxinols are a series of tetramethylbutylphenyl ethers of macrogols of differing chain lengths, represented by the formula $C_{14}H_{21}.[O.CH_2.CH_2]_n.OH$.

Octoxinol is *BAN* and *rINN*. The name may be followed by a figure indicating the approximate number of oxyethylene groups in the polyoxyethylene chain. *USAN* specifies Octoxynol 9.

The name *p*-di-isobutyl-phenoxypolyethoxyethanol has been used to describe octoxinol 9 but may have also been applied to other octoxinols.

Octoxinol 9 *(BAN, rINN)*

Octoxinolum 9; Octoxynol 9 *(USAN)*.

Октоксинол 9

$C_{32}H_{58}O_{10}$ (nominal) = 602.8.

Pharmacopoeias. In *USNF.*

USNF 26 (Octoxynol 9). An anhydrous liquid mixture consisting chiefly of mono-octylphenyl ethers of macrogols, corresponding to the formula $C_{14}H_{21}.[O.CH_2.CH_2]_n.OH$, in which the average value of *n* is about 9. A clear, pale yellow, viscous liquid with a faint odour. Miscible with water, with alcohol, and with acetone; soluble in toluene and in benzene; practically insoluble in petroleum spirit. Store in airtight containers.

Octoxinol 10 *(BAN, rINN)*

Octoxinolum 10; Oktoksinoli-10; Oktoksinolis 10; Oktoksynol 10; Oktoxinol-10; Oktoxinol 10.

Октоксинол 10

$C_{34}H_{62}O_{11}$ (nominal) = 646.8.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Octoxinol 10). A mixture consisting mainly of mono-octylphenyl ethers of macrogols corresponding to the formula: $C_{14}H_{21}.(O.CH_2.CH_2)_n.OH$ where the average value of *n* is

The symbol † denotes a preparation no longer actively marketed

10. A clear, colourless or light yellow, viscous liquid. Miscible with water, with alcohol, and with vegetable oils. Store in airtight containers.

Profile

Octoxinols have surface active properties and may be used as solubilising agents. They are also used as spermicides.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Ortho-Gynol; ***NZ:*** Ortho-Gynol; ***USA:*** Ortho-Gynol†.

Multi-ingredient: ***Austral.:*** Summers Eve Feminine; ***Chile:*** Summer's Eve Hierbas†.

Poloxamers

Polioxietilen-propilenglicol; Poloksameerit; Poloksamerai; Poloxamera; Poloxamerek; Poloxamerer; Poloxamères; Poloxámeros; Poloxamery; Polyethylene-polypropylene glycol. α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymer.

Полоксамеры

CAS — 9003-11-6.

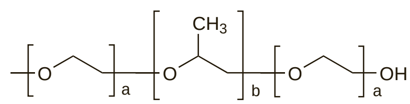

Nomenclature. Poloxamer is *BAN* and *rINN*. The name is followed by a figure, the first 2 digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion. *USAN* specifies Poloxamer 182D, Poloxamer 182LF, Poloxamer 188, Poloxamer 188LF, and Poloxamer 331.
Poloxalene (*BAN*, *USAN*, *rINN*) is also a poloxamer.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Poloxamers). A synthetic block copolymer of ethylene oxide and propylene oxide represented by the general formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antioxidant. Poloxamer 124 is a colourless or almost colourless liquid. Poloxamer 237 and poloxamer 338 are white or almost white, waxy powders, microbeads or flakes; m.p. about 50°. Poloxamers 124, 237, and 338 are very soluble in water and in alcohol; practically insoluble in petroleum spirit (50° to 70°). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.
USNF 26 (Poloxamer). A synthetic block copolymer of ethylene oxide and propylene oxide with the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. It may contain a suitable antoxidant. Poloxamer 124 is a colourless liquid with a mild odour. Poloxamers 237 and 338 are white, prilled or cast solids, odourless or with a mild odour. All poloxamers are freely soluble in water and in alcohol. Poloxamer 124 is freely soluble in isopropyl alcohol and in propylene glycol; poloxamer 237 is sparingly soluble in isopropyl alcohol and in xylene; poloxamer 338 is sparingly soluble in propylene glycol; poloxamer 124 is freely soluble in xylene. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

Incompatibility. Poloxamers have been reported to be incompatible with hydroxybenzoates and phenols.

Poloxalene *(BAN, USAN, rINN)*

Poloxalène; Poloxaleno; Poloxalenum; SKF-18667.

Полоксален

CAS — 9003-11-6.

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Poloxalene). A synthetic block copolymer of ethylene oxide and propylene oxide. A colourless or pale yellow liquid. Soluble in water, in chloroform, and in ethylene dichloride. A 2.5% solution in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature of 8° to 15°. Protect from light.

Poloxamer 188 *(BAN, USAN, rINN)*

Poloxalkol; Poloxamère 188; Poloxámero 188; Poloxamerum 188.

Полоксамер 188

NOTE. Compounded preparations of poloxamer 188 may be represented by the following names:

- Co-danthramer *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Poloxamers). Poloxamer 188 is a poloxamer in which *a* in the general formula given above is 75 to 85 and *b* is 25 to 30; it has an average molecular weight of 7680 to 9510. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50°. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50° to 70°). pH of a 10% solution is 5.0 to 7.5. Store in airtight containers.
USNF 26 (Poloxamer). Poloxamer 118 is a poloxamer in which *a* in the general formula averages 80 and *b* averages 27; it has an average molecular weight of 7680 to 9510. A white prilled or cast solid, odourless or with a very mild odour. M.p. about 52°. Freely soluble in water and in alcohol. Store in airtight containers.

Poloxamer 407 *(BAN, rINN)*

Poloxamère 407; Poloxámero 407; Poloxamerum 407.

Полоксамер 407

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Poloxamers). Poloxamer 407 is a poloxamer in which *a* in the general formula given above is 95 to 105 and *b* is 54 to 60; it has an average molecular weight of 9840 to 14 600. It is a white or almost white, waxy powder, microbeads, or flakes. M.p. about 50°. Very soluble in water and in alcohol; practically insoluble in petroleum spirit (50° to 70°). pH of a 10% solution in water is 5.0 to 7.5. Store in airtight containers.
USNF 26 (Poloxamer). Poloxamer 407 is a poloxamer in which *a* in the general formula averages 101 and *b* averages 56; it has an average molecular weight of 9840 to 14 600. A white, prilled or cast solid, odourless or with a very mild odour. M.p. about 56°. Freely soluble in water, in alcohol, and in isopropyl alcohol. Store in airtight containers.

Precautions

Poloxamers may increase the absorption of liquid paraffin and other fat-soluble substances.

Uses and Administration

Poloxamers are used as emulsifying agents for intravenous fat emulsions, as solubilising agents to maintain clarity in elixirs and syrups, and as wetting agents for antibacterials. They may also be used in ointment or suppository bases and as tablet binders or coaters.

Poloxamer 188 is used as a wetting agent in the treatment of constipation. It is usually given with a laxative such as dantron. It has also been used as an emulsifying agent in fluorocarbon blood substitutes. Poloxamer 188 has been investigated for its ability to improve blood flow in sickle-cell crisis; it has also been tried in myocardial infarction. Other investigational uses include the treatment of burns.

Poloxamer 407 is used in solutions for contact lens care, as is poloxamer 338.

Poloxalene is used as a defoaming agent in the treatment of bloat in ruminants.

◊ References.

1. Orringer EP, *et al.* Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA* 2001; **286:** 2099–2106.
2. Gibbs WJ, Hagemann TM. Purified poloxamer 188 for sickle cell vaso-occlusive crisis. *Ann Pharmacother* 2004; **38:** 320–4.
3. Dumortier G, *et al.* A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006; **23:** 2709–28.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Coloxyl; Pliagel†; ***Canad.:*** Clerz†; ***Fr.:*** Alkenide†; ***NZ:*** Coloxyl; ***S.Afr.:*** Pliagel.

Multi-ingredient: ***Irl.:*** Ailax; Codalax; Cotron; ***NZ:*** Codalax†; Conthram†; ***Thai.:*** Siduol; ***UK:*** Ailax†; Codalax; Danlax; ***USA:*** Baby Orajel Tooth and Gum Cleanser; ControlRx.

Polyoxyl Castor Oils

Aceites de ricino polioxietilenados; Macrogolglycerol Ricinoleate; Macrogolglycérol, ricinoléate de; Macrogolglyceroli ricinoleas; Makrogol-glicerin-éter -ricinoleát; Makrogolglicerolio ricinoleatas; Makrogolglycerolricinoleat; Makrogliglyserolirisiinioleaatti; Makrogologlicerolu rycynooleinian; Polyethoxylated Castor Oils; Polyoxyethylene Castor Oils.

Полиэтиленгликоля Касторовые Масла

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Macrogolglycerol Ricinoleate; Polyoxyl Castor Oil BP 2008). It contains mainly ricinoleyl glycerol ethoxylated with 30 to 50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate and of the corresponding free glycols. It results from the reaction of castor oil with ethylene oxide. A clear, yellow, viscous liquid or semi-solid. Relative density about 1.05; viscosity, at 25°, 500 to 800 mPa s. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Polyoxyl 35 Castor Oil

Aceite de ricino polioxil 35.

Полиэтиленгликоля 35 Касторовое Масло

Pharmacopoeias. In *USNF.*
USNF 26 (Polyoxyl 35 Castor Oil). A mixture of the triricinoleate ester of ethoxylated glycerol with smaller amounts of macrogol ricinoleate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol ricinoleate with about 35 moles of ethylene oxide.
A yellow oily liquid with a faint characteristic odour. Sp. gr. 1.05 to 1.06; viscosity, at 25°, 650 to 850 mPa s. Very soluble in water, producing a practically odourless and colourless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. Store in airtight containers.

Incompatibility. Polyoxyl castor oils are reported to affect polyvinyl chloride containers and apparatus adversely.

Adverse Effects

Polyoxyl castor oils (such as *Cremophor EL*) used as vehicles in intravenous injections have been associated with severe anaphylactoid reactions, hyperlipidaemias, alterations in blood viscosity, and erythrocyte aggregation. They may also lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

◊ References.

1. Bagnarello AG, *et al.* Unusual serum lipoprotein abnormality induced by the vehicle of miconazole. *N Engl J Med* 1977; **296:** 497–9.
2. Forrest ARW, *et al.* Long-term Althesin infusion and hyperlipidaemia. *BMJ* 1977; **2:** 1357–8.
3. Dye D, Watkins J. Suspected anaphylactic reaction to Cremophor EL. *BMJ* 1980; **280:** 1353.
4. Howrie DL, *et al.* Anaphylactoid reactions associated with parenteral cyclosporine use: possible role of Cremophor EL. *Drug Intell Clin Pharm* 1985; **19:** 425–7.
5. Chapuis B, *et al.* Anaphylactic reaction to intravenous cyclosporine. *N Engl J Med* 1985; **312:** 1259.
6. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; **i:** 394.
7. ten Tije AJ, *et al.* Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; **42:** 665–85.
8. Hennenfent KL, Govindan R. Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann Oncol* 2006; **17:** 735–49.

Uses

Polyoxyl castor oils are macrogol esters used as emulsifying and solubilising agents. Polyoxyl 35 castor oil has been used as a solvent in vehicles for various intravenous injections.

Polyoxyl Hydrogenated Castor Oils

Aceites de ricino hidrogenados y polioxietilenados; Macrogolglycerol Hydroxystearate; Macrogolglycérol, hydroxystéarate de; Macrogolglyceroli hydroxystearas; Makrogol-glicerin-éter-hidroxisztearát; Makrogolglicerolio hidroksisteratas; Makrogolglycerolhydroxistearat; Makrogoliglyserolihydroksistearaatti.

Полиэтиленгликоля Касторовые Масла Гидрогенизированные

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Macrogolglycerol Hydroxystearate; Hydrogenated Polyoxyl Castor Oil BP 2008). It contains mainly trihydroxystearyl glycerol ethoxylated with 7 to 60 molecules of ethylene oxide (nominal value), with small amounts of macrogol hydroxystearate and of the corresponding free glycols. It results from the reaction of hydrogenated castor oil with ethylene oxide. Polyoxyl hydrogenated castor oil with less than 10 units of ethylene oxide per molecule is a yellowish, turbid, viscous liquid. Practically insoluble in water; dispersible in alcohol; soluble in acetone. Polyoxyl hydrogenated castor oil with more than 20 units of ethylene oxide per molecule is a white or yellowish, semi-liquid or pasty mass. Freely soluble in water, in alcohol, and in acetone; practically insoluble in petroleum spirit.

Polyoxyl 40 Hydrogenated Castor Oil

Aceite de ricino hidrogenado polioxil 40.

Полиэтиленгликоля 40 Касторовое Масло Гидрогенизированное

Pharmacopoeias. In *USNF.*
USNF 26 (Polyoxyl 40 Hydrogenated Castor Oil). A mixture of mainly the trihydroxystearate ester of ethoxylated glycerol, with smaller amounts of macrogol trihydroxystearate and the corresponding free glycols. It is produced by reacting 1 mole of glycerol trihydroxystearate with about 40 to 45 moles of ethylene oxide.
A white to yellowish paste or pasty liquid with a faint odour. Congealing range 20° to 30°. Very soluble in water, producing an odourless, colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Profile

Polyoxyl hydrogenated castor oils are used as surfactants.

Polysorbates

Polisorbatos.

Полисорбаты

Description. A series of mixtures of fatty acid esters of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Incompatibility. Polysorbates have been reported to be stable with electrolytes and weak acids and bases although saponification may occur in the presence of strong acids and bases. Discoloration or precipitation may occur with phenolic substances. The oleic acid esters are sensitive to oxidation. For reference to the possible incompatibility of polysorbate 80 with hydroxybenzoates, see p.1649.

Polysorbate 20 *(BAN, USAN, rINN)*

E432; Monolaurato de polietileno 20 sorbitano; Monolaurato de polioxietileno 20 sorbitano; Polisorbat 20; Polisorbatas 20; Polisorbato 20; Poliszorbát 20; Polyoxyethylene 20 Sorbitan Monolaurate; Polysorbaatti 20; Polysorbát 20; Polysorbat 20; Polysorbatum 20; Sorbimacrogol Laurate 300; Sorboxaethenum Laurinicum.

Полисорбат 20

$C_{58}H_{114}O_{26}$ (approximate).
CAS — 9005-64-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Polysorbate 20). A mixture of partial esters of fatty acids, mainly lauric acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A clear or slightly opalescent yellowish to brownish-yellow oily liquid. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 26 (Polysorbate 20). A laurate ester of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber liquid with a faint characteristic odour. Soluble in water, in alcohol, in dioxan, in ethyl acetate, and in methyl alcohol; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 40 *(BAN, USAN, rINN)*

E434; Monopalmitato de polietileno 20 sorbitano; Monopalmitato de polioxietileno 20 sorbitano; Polisorbatas 40; Polisorbato 40; Poliszorbát 40; Polyoxyethylene 20 Sorbitan Monopalmitate; Polysorbaatti 40; Polysorbát 40; Polysorbat 40; Polysorbatum 40; Sorbimacrogol Palmitate 300.

Полисорбат 40

$C_{62}H_{122}O_{26}$ (approximate).
CAS — 9005-66-7.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Polysorbate 40). Mixture of partial esters of fatty acids, mainly palmitic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. An oily, viscous, yellowish or brownish-yellow liquid. Relative density about 1.10. Miscible with water, with dehydrated alcohol, with ethyl acetate, and with methyl alcohol; practically insoluble in fatty oils and in liquid paraffin. Store in airtight containers. Protect from light.

The BP 2008 gives Polyoxyethylene 20 Sorbitan Monopalmitate as an approved synonym.

USNF 26 (Polysorbate 40). A palmitate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellow liquid with a faint characteristic odour. Soluble in water and in alcohol; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 60 *(BAN, USAN, rINN)*

E435; Monoestearato de polietileno 20 sorbitano; Monoestearato de polioxietileno 20 sorbitano; Polisorbat 60; Polisorbatas 60; Polisorbato 60; Poliszorbát 60; Polyoxyethylene 20 Sorbitan Monostearate; Polysorbaatti 60; Polysorbát 60; Polysorbat 60; Polysorbatum 60; Sorbimacrogol Stearate 300; Sorboxaethenum Stearinicum.

Полисорбат 60

$C_{64}H_{126}O_{26}$ (approximate).
CAS — 9005-67-8.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Polysorbate 60). A mixture of partial esters of fatty acids, mainly stearic acid 50, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A yellowish-brown gelatinous mass which becomes a clear liquid at temperatures above 25°. Relative density about 1.10. Soluble in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 26 (Polysorbate 60). A mixture of stearate and palmitate esters of sorbitol and its anhydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to orange-coloured oily liquid or semi-gel with a faint characteristic odour. Soluble in water, in ethyl acetate, and in toluene; insoluble in liquid paraffin and in vegetable oils. Store in airtight containers.

Polysorbate 80 *(BAN, USAN, rINN)*

E433; Monooleato de polietileno 20 sorbitano; Monooleato de polioxietileno 20 sorbitano; Olethytan 20; Polisorbat 80; Polisorbatas 80; Polisorbato 80; Poliszorbát 80; Polyäthylenglykol-Sorbitanoleat; Polyoxyethylene 20 Sorbitan Mono-oleate; Polysorbaatti 80; Polysorbát 80; Polysorbat 80; Polysorbatum 80; Polysorbitanum 80 Oleinatum; Sorbimacrogol Oleate 300; Sorboxaethenum Oleinicum; Sorethytan 20 Mono-oleate.

Полисорбат 80

$C_{64}H_{124}O_{26}$ (approximate).
CAS — 9005-65-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *Jpn*. Also in *USNF.*

Ph. Eur. 6.2 (Polysorbate 80). A mixture of partial esters of fatty acids, mainly oleic acid, with sorbitol and its anhydrides ethoxylated with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. An oily, yellowish or brownish-yellow, clear or slightly opalescent liquid. Relative density about 1.10. Dispersible in water, in dehydrated alcohol, in ethyl acetate, and in methyl alcohol; practically insoluble in liquid paraffin and in fatty oils. Store in airtight containers. Protect from light.

USNF 26 (Polysorbate 80). An oleate ester of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. A lemon to amber-coloured oily liquid with a faint characteristic odour. Sp. gr. between 1.06 and 1.09; viscosity, at 25°, between 300 and 500 mPa s. Very soluble in water, producing an odourless and practically colourless solution; soluble in alcohol and in ethyl acetate; insoluble in liquid paraffin. Store in airtight containers.

Polysorbate 85 *(BAN, USAN, rINN)*

Polisorbatas 85; Polisorbato 85; Poliszorbát 85; Polyoxyethylene 20 Sorbitan Trioleate; Polysorbaatti 85; Polysorbat 85; Polysorbát 85; Polysorbatum 85; Sorbimacrogol Trioleate 300; Trioleato de polietileno 20 sorbitano; Trioleato de polioxietileno 20 sorbitano.

Полисорбат 85

$C_{100}H_{188}O_{28}$ (approximate).
CAS — 9005-70-3.

Description. A mixture of mainly trioleate esters of sorbitol and its anhydrides copolymerised with about 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Adverse Effects and Precautions

Polysorbates may increase the absorption of fat-soluble substances.

There have been occasional reports of hypersensitivity after topical application of preparations containing polysorbates.

For discussion of fatalities in low-birth-weight infants associated with the injection of a polysorbate-containing preparation, see below.

Polysorbates used as excipients may also lead to adverse effects due to alterations in the pharmacokinetics of the formulated drug.

◊ References.

1. ten Tije AJ, *et al.* Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. *Clin Pharmacokinet* 2003; **42:** 665–85.

Effects in infants. After the introduction in the USA of an intravenous preparation of vitamin E (*E-Ferol*) there were a number of reports of unusual liver and kidney disorders, with 38 deaths being reported among treated low-birth-weight infants. Affected infants had unexplained hypotension, thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, and metabolic acidosis;[1-3] the preparation was subsequently withdrawn from the market in April 1984 about 5 months after it was introduced. *In-vitro* evidence was produced showing that *E-Ferol* suppressed the response of human lymphocytes to phytohaemagglutinin. However, it was the mixture of polysorbates, polysorbate 20 and in particular polysorbate 80, that was shown to be responsible for this suppression rather than the α-tocopherol acetate component. Despite this *in-vitro* data, overwhelming infection was not a feature in the affected infants.[2] Large doses of polysorbates were unavoidably injected when *E-Ferol* was used and it was suggested that polysorbates may accumulate as a result of an alteration in the metabolism by low-birth-weight infants; polysorbate-induced alteration of membrane fluidity in cells of vessel walls may have led to changes in structure and function.[2]

1. Alade SL, *et al.* Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986; **77:** 593–7.
2. Balistreri WF, *et al.* Lessons from the E-Ferol tragedy. *Pediatrics* 1986; **78:** 503–6.
3. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with inactive ingredients in drug products. *Med Toxicol* 1988; **3:** 128–65 and 209–240.

Hypersensitivity. Local inflammatory reactions after intramuscular injection of a vitamin A preparation were considered[1] to be due to a hypersensitivity reaction to polysorbate 80, included as an excipient. Anaphylactoid reactions which occurred in 2 patients after treatment with omalizumab for 27 and 13 months respectively, were likely to be due to the polysorbate excipient and not to the monoclonal antibody itself.[2] The presence of polysorbate 80 in the injection may also contribute to hypersensitivity reactions to docetaxel (see Adverse Effects of Docetaxel, p.710).

1. Shelley WB, *et al.* Polysorbate 80 hypersensitivity. *Lancet* 1995; **345:** 1312–13.
2. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; **28:** 313–19.

Uses

Polysorbates are hydrophilic nonionic surfactants that are used as emulsifying agents for the preparation of stable oil-in-water emulsions in pharmaceutical products; they are frequently used with a sorbitan ester in varying proportions to produce products with a range of texture and consistency. Polysorbates have also been used in the formulation of insecticide and herbicide sprays, industrial detergents, and cosmetic products. They are also used as emulsifiers in the food industry.

Polysorbates are used as solubilising agents for a variety of substances including essential oils and oil-soluble vitamins such as vitamins A, D, and E, and as wetting agents in the formulation of oral and parenteral suspensions. However, hypersensitivity reactions have been attributed to the presence of polysorbates, see Hypersensitivity, above.

Polysorbates may also be used for their surfactant properties in preparations for the removal of ear wax, and for the management of dry eyes and upper respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sinroncar; ***Belg.:*** Oleosorbate; ***Canad.:*** Diopteаrs; Tears Encore; ***Fr.:*** Cerumenol; ***USA:*** OptiZen; Viva-Drops.

Multi-ingredient: ***Arg.:*** Balsan†; Otoclean Gotas Oticas; ***Fin.:*** Expigen; ***Fr.:*** Peruspray; Fluisedal; Fluisedal sans promethazine; Paroplak; Prorhinel; ***S.Afr.:*** Expigen; ***Switz.:*** Prorhinel; Rhinocure; Rhinocure simplex; ***Turk.:*** Kansilak; Libalaks; ***UK:*** Asonor; ***USA:*** Refresh Dry Eye Therapy; Soothe; Soothe XP.

Propylene Glycol Diacetate

Propilenglicol, diacetato de. Propanediol diacetate.

Диацетат Пропиленгликоля

$C_7H_{12}O_4$ = 160.2.
CAS — 623-84-7 (1,2-isomer); 628-66-0 (1,3-isomer).

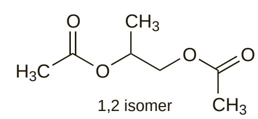

1,2 isomer

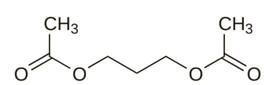

1,3 isomer

Profile

Propylene glycol diacetate is an emulsifying and/or solubilising agent, and a solvent. It is included in some external preparations for ear infection.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Canad.:*** VoSoL HC†; ***NZ:*** VoSoL; ***USA:*** Acetasol; Acetasol HC; VoSoL HC†; VoSoL†.

Propylene Glycol Laurates

E477 (propylene glycol esters of fatty acids); Propilenglicol, laurato de.

Пропиленгликоля Лаураты

Propylene Glycol Dilaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, dilaurato de; Propilenglikolio dilauratas; Propyleeniglykolidilauraatti; Propylene Dilaurate; Propylèneglycol, dilaurate de; Propylenglycoli dilauras; Propylenglykoldilaurat; Propylenglykol-dilaurát.

Пропиленгликоля Дилаурат
CAS — 22788-19-8.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains a minimum of 70% of di-esters and a maximum of 30% of mono-esters. The content of free propylene glycol is not more than 2%. A colourless or slightly yellow, clear oily liquid at 20°. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.

USNF 26 (Propylene Glycol Dilaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains not less than 70.0% of di-esters and not more than 30.0% of mono-esters. Protect from moisture.

Propylene Glycol Monolaurate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monolaurate de; Propilenglikolio monolauratas; Propyleeniglykolimonolauraatti; Propylèneglycol, monolaurate de; Propylenglycoli monolauras; Propylenglykol monolaurát; Propylenglykolmonolaurat.

Пропиленгликоля Монолаурат

CAS — 27194-74-7.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5% (type I) or not more than 1% (type II). A colourless or slightly yellow, clear oily liquid at 20°. Practically insoluble in water; very soluble in alcohol, in methyl alcohol, and in dichloromethane. Protect from moisture.
USNF 26 (Propylene Glycol Monolaurate). A mixture of the propylene glycol mono- and di-esters of lauric acid. It contains 45 to 70% of mono-esters and 30 to 55% of di-esters (type I) or a minimum of 90% of mono-esters and a maximum of 10% of di-esters (type II). The content of free propylene glycol is not more than 5.0% (type I) or not more than 1.0% (type II). Protect from moisture.

Profile

Propylene glycol mono- and dilaurate have similar properties to propylene glycol monopalmitostearate (below) and are used as emulsifying and solubilising agents, including in food.

Propylene Glycol Monopalmitostearate

E477 (propylene glycol esters of fatty acids); Propilenglicol, monopalmitoestearato de; Propilenglikolio monopalmitostearatas; Propilénglikol-monopalmitil-sztearát; Propyleeniglykolimonopalmitostearaatti; Propyleeniglykolimonostearaatti; Propylene Glycol Monostearate; Propylene Glycol Stearate; Propylèneglycol, monopalmitostéarate de; Propylèneglycol (Stéarate de); Propylenglycoli monopalmitostearas; Propylenglycoli Monostearas; Propylenglykolmonopalmitostearat; Propylenglykol-monopalmitostearát; Propylenglykolmonostearat; Prostearin.

Пропиленгликоля Монопальмитостеарат

CAS — 1323-39-3 (propylene glycol monostearate); 29013-28-3 (propylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Propylene Glycol Monopalmitostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains a minimum of 50% of mono-esters produced from the condensation of propylene glycol and stearic acid 50. A white or almost white, waxy solid. M.p. 33° to 40°. Practically insoluble in water; soluble in hot alcohol and in acetone. Protect from light.
USNF 26 (Propylene Glycol Monostearate). A mixture of the propylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 90% of mono-esters of saturated fatty acids, chiefly propylene glycol monostearate and propylene glycol monopalmitate. A white, wax-like solid, beads, or flakes, with a slight agreeable fatty odour. Congealing temperature not less than 45°. Insoluble in water but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble in organic solvents such as alcohol, acetone, ether, benzene, and fixed or mineral oils.

Profile

Propylene glycol monopalmitostearate is used as a stabiliser or emulsifier similarly to glyceryl monostearate (p.1915).

Quillaia

Corteza de Panamá; Corteza de quillay; Corteza palo de jabón; E999 (quillaia extract); Panama Wood; Quilaya; Quillaia Bark; Quillaiae cortex; Quillay; Quillaya, écorce de; Seifenrinde; Soap Bark.

Кора Мыльного Дерева

CAS — 631-01-6 (quillaic acid).

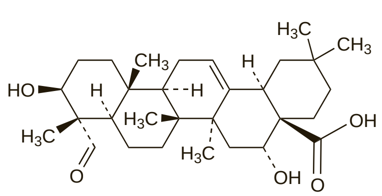

(quillaic acid)

Pharmacopoeias. In *Br., Fr.,* and *Swiss.*
BP 2008 (Quillaia). The dried inner part of the bark of *Quillaja saponaria* and other species of *Quillaja* containing not less than 22% of alcohol (45%)-soluble extractive. It is odourless or almost odourless, but the dust or powder is strongly sternutatory.

Adverse Effects

Quillaia taken by mouth has been reported to produce gastrointestinal irritation. It has been suggested that the ingestion of large amounts may produce liver damage, respiratory failure, convulsions, and coma.

Uses

Quillaia contains 2 amorphous saponin glycosides, quillaic acid and quillaiasapotoxin. It is used as an emulsifying agent and frothing agent, including in foodstuffs; it is often used with tragacanth mucilage or another thickening agent. Quillaia is also used for its surfactant properties in preparations for skin and respiratory-tract disorders.

Preparations

BP 2008: Quillaia Liquid Extract; Quillaia Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Bluderm†; ***Chile:*** Fitotos; Notosil†; Sedotus†; ***Cz.:*** Solutan†; ***Fin.:*** Kvilla; ***Hong Kong:*** Pectoral†; ***Rus.:*** Solutan (Солутан); ***Swed.:*** Quilla simplex; ***Switz.:*** Expectoran Codein†; Expectoran†.

Sorbitan Esters

Sorbitán, ésteres del.

Эфиры Сорбитана

Description. A series of mixtures of the partial esters of sorbitol and its mono- and di-anhydrides with fatty acids.

Sorbitan Laurate *(BAN, rINN)*

E493; Laurato de sorbitán; Monolaurato de sorbitán; Sorbitaanilauraatti; Sorbitan, laurate de; Sorbitan Monolaurate *(USAN)*; Sorbitani lauras; Sorbitanlaurat; Sorbitan-laurát; Sorbitano lauratas; Szorbitán-laurát.

Сорбитана Лаурат

$C_{18}H_{34}O_6$ (approximate).
CAS — 1338-39-2.

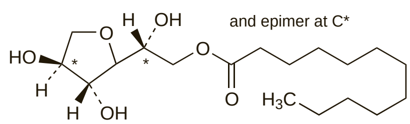

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sorbitan Laurate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with lauric acid. A brownish-yellow viscous liquid. Relative density about 0.98. Practically insoluble but dispersible in water; miscible with alcohol; slightly soluble in cottonseed oil. Protect from light.
USNF 26 (Sorbitan Monolaurate). A partial ester of sorbitol and its mono- and di-anhydrides with lauric acid. A yellow to amber oily liquid with a bland characteristic odour. Insoluble in water; soluble in liquid paraffin; slightly soluble in cottonseed oil and in ethyl acetate. Store in airtight containers.

Sorbitan Oleate *(BAN, rINN)*

E494; Monooleato de sorbitán; NSC-406239; Oleato de sorbitán; Sorbitaanioleaatti; Sorbitan Monooleate *(USAN)*; Sorbitan Mono-oleate; Sorbitan, oléate de; Sorbitani oleas; Sorbitano oleatas; Sorbitanoleat; Sorbitan-oleát; Szorbitán-oleát.

Сорбитана Олеат

$C_{24}H_{44}O_6$ (approximate).
CAS — 1338-43-8.

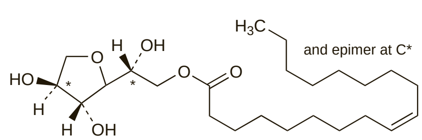

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sorbitan Oleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per mole of oleic acid. A suitable antoxidant may be added. A brownish-yellow viscous liquid. Relative density about 0.99. Practically insoluble but dispersible in water; miscible with alcohol; soluble in fatty oils producing a hazy solution. Protect from light.
USNF 26 (Sorbitan Monooleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, viscous, oily liquid with a bland characteristic odour. Insoluble in water and in propylene glycol; miscible with mineral and vegetable oils. Store in airtight containers.

Sorbitan Palmitate *(BAN, rINN)*

E495; Monopalmitato de sorbitán; Palmitato de sorbitán; Sorbitaanipalmitaatti; Sorbitan Monopalmitate *(USAN)*; Sorbitan, palmitate de; Sorbitani palmitas; Sorbitano palmitatas; Sorbitanpalmitat; Sorbitan-palmitát; Szorbitán-palmitát.

Сорбитана Пальмитат

$C_{22}H_{42}O_6$ (approximate).
CAS — 26266-57-9.

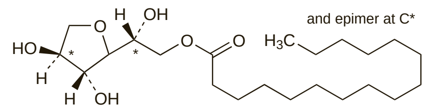

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sorbitan Palmitate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with palmitic acid. A yellowish or yellow powder, waxy flakes, or hard masses. M.p. 44° to 51°. Practically insoluble in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.
USNF 26 (Sorbitan Monopalmitate). A partial ester of sorbitol and its mono- and di-anhydrides with palmitic acid. A cream-coloured, waxy solid with a faint fatty odour. Insoluble in water; soluble in warm dehydrated alcohol; soluble with haze in warm liquid paraffin and in warm arachis oil.

Sorbitan Sesquioleate *(BAN, USAN, rINN)*

Sesquioleato de sorbitán; Sorbitaaniseskvioleaatti; Sorbitan, sesquioléate de; Sorbitani sesquioleas; Sorbitano seskvioleatas; Sorbitanseskvioleat; Sorbitan-seskvioleát; Szorbitán-szeszkvioleát.

Сорбитана Сесквиолеат

$C_{33}H_{60}O_{6.5}$ (approximate).
CAS — 8007-43-0.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Sorbitan Sesquioleate). A mixture usually obtained by esterification of 2 moles of sorbitol and its mono- and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. Relative density about 0.99. A pale yellow or slightly brownish-yellow paste, which becomes a viscous, oily, brownish-yellow liquid at about 25°. Dispersible in water; slightly soluble in dehydrated alcohol; soluble in fatty oils. Protect from light.
USNF 26 (Sorbitan Sesquioleate). A partial oleate ester of sorbitol and its mono- and di-anhydrides. A yellow to amber-coloured, oily viscous liquid. Insoluble in water and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Stearate *(BAN, rINN)*

E491; Estearato de sorbitán; Monoestearato de sorbitán; Sorbitaanistearaatti; Sorbitan Monostearate *(USAN)*; Sorbitan, stéarate de; Sorbitani stearas; Sorbitano stearatas; Sorbitanstearat; Sorbitan-stearát; Szorbitán-sztearát.

Сорбитана Стеарат

$C_{24}H_{46}O_6$ (approximate).
CAS — 1338-41-6.

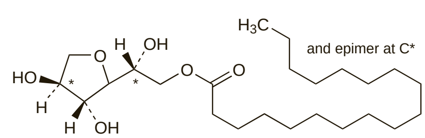

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Sorbitan Stearate). A mixture of the partial esters of sorbitol and its mono- and di-anhydrides with stearic acid. A pale yellow, waxy solid. M.p. 50° to 55°. Practically insoluble but dispersible in water; slightly soluble in alcohol. Protect from light.
USNF 26 (Sorbitan Monostearate). A partial ester of sorbitol and its mono- and di-anhydrides with stearic acid. A cream-coloured to tan, hard, waxy solid with a bland odour. Insoluble in cold water and in acetone; dispersible in warm water; soluble, with haze, above 50° in ethyl acetate and in liquid paraffin.

Sorbitan Trioleate *(BAN, USAN, rINN)*

Sorbitaanitrioleaatti; Sorbitan, trioléate de; Sorbitani trioleas; Sorbitano trioleatas; Sorbitantrioleat; Sorbitan-trioleát; Szorbitán-trioleát; Trioleato de sorbitán.

Сорбитана Триолеат

$C_{60}H_{108}O_8$ (approximate).

CAS — 26266-58-0.

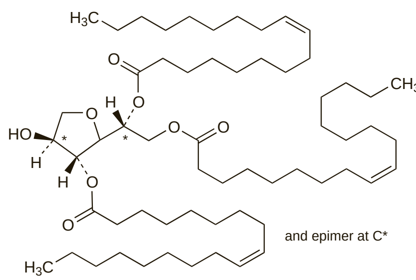

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sorbitan Trioleate). A mixture usually obtained by esterification of 1 mole of sorbitol and its mono- and di-anhydrides per 3 moles of oleic acid. A suitable antoxidant may be added. A pale yellow, light yellowish or brown solid which becomes a brownish-yellow, viscous, oily liquid at about 25°. Relative density about 0.98. Practically insoluble but dispersible in water; slightly soluble in alcohol; soluble in fatty oils. Protect from light.

USNF 26 (Sorbitan Trioleate). A tri-ester of sorbitol and its mono- and di-anhydrides with oleic acid. A yellow to amber-coloured, oily liquid. Insoluble in water, in ethylene glycol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in methyl alcohol, in maize oil, in cottonseed oil, and in liquid paraffin. Store in airtight containers.

Sorbitan Tristearate *(BAN, USAN, rINN)*

E492; Sorbitan, Tristéarate de; Sorbitani Tristearas; Triestearato de sorbitán.

Сорбитана Тристеарат

$C_{60}H_{114}O_8$ (approximate).

CAS — 26658-19-5.

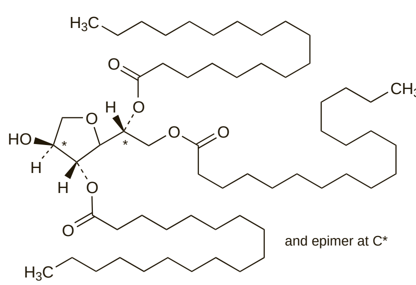

Description. A mixture of the partial tri-esters of sorbitol and its mono- and di-anhydrides with stearic acid.

Adverse Effects

There have been occasional reports of hypersensitive skin reactions after the topical application of creams containing sorbitan esters.

Hypersensitivity. References.

1. Finn OA, Forsyth A. Contact dermatitis due to sorbitan monolaurate. *Contact Dermatitis* 1975; **1:** 318.
2. Hannuksela M, *et al.* Allergy to ingredients of vehicles. *Contact Dermatitis* 1976; **2:** 105–10.
3. Austad J. Allergic contact dermatitis to sorbitan monooleate (Span 80). *Contact Dermatitis* 1982; **8:** 426–7.
4. Boyle J, Kennedy CTC. Contact urticaria and dermatitis to Alphaderm. *Contact Dermatitis* 1984; **10:** 178.
5. Hardy MP, Maibach HI. Contact urticaria syndrome from sorbitan sesquioleate in a corticosteroid ointment. *Contact Dermatitis* 1995; **32:** 114.
6. Wakelin SH, *et al.* Sorbitan mono-oleate: a potential allergen in paste bandages. *Contact Dermatitis* 1996; **35:** 377.
7. de Waard-van der Spek FB, *et al.* Allergic contact dermatitis to sorbitan sesquioleate in Adaptic wound dressing. *Contact Dermatitis* 2007; **57:** 54–6.

Uses

Sorbitan esters are lipophilic nonionic surfactants that are used as emulsifying agents in the preparation of emulsions, creams, and ointments for pharmaceutical and cosmetic use. When used alone they produce stable water-in-oil emulsions but they are frequently used with a polysorbate in varying proportions to produce water-in-oil or oil-in-water emulsions or creams with a variety of different textures and consistencies. Sorbitan esters are also used as emulsifiers and stabilisers in food.

Sucrose Esters

E473 (sucrose esters of fatty acids); Sacarosa, ésteres de; Sacchari monopalmitas (sucrose monoplamitate); Sacchari monostearas (sucrose monostearate); Saccharose, monopalmitate de (sucrose monoplamitate); Saccharose, monostéarate de (sucrose monostearate); Sucroésteres.

Эфиры Сахарозы

Pharmacopoeias. *Eur.* (p.vii) includes Sucrose Monopalmitate and Sucrose Stearate.

Ph. Eur. 6.2 (Sucrose Monopalmitate). A mixture of sucrose monoesters, mainly sucrose monopalmitate, obtained by transesterification of palmitic acid methyl esters of vegetable origin with sucrose. It contains 55.0% monoesters, a maximum 40.0% diesters, and a maximum of 20.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Ph. Eur. 6.2 (Sucrose Stearate). A mixture of sucrose esters, mainly sucrose stearate, obtained by transesterification of stearic acid methyl esters of vegetable origin with sucrose. Sucrose stearate type I contains a minimum 50.0% monoesters, a maximum 40.0% diesters, and a maximum of 25.0% for the sum of triesters and polyesters. Sucrose stearate type II contains 20.0 to 45.0% monoesters, 30.0 to 40.0% diesters, and a maximum of 30.0% for the sum of triesters and polyesters. A white or almost white, unctuous powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from humidity.

Profile

Sucrose esters are nonionic compounds with surface-active properties produced by esterification of 1 or more hydroxyl groups in sucrose with a fatty acid such as stearic or palmitic acid. Commercial sucrose esters are mixtures of the mono-, di-, and tri-esters of palmitic and stearic acids with sucrose; various grades are available. Sucrose esters are used as dispersing, emulsifying, and stabilising agents in food and cosmetic preparations.

Tyloxapol *(BAN, USAN, rINN)*

Superinone; Tiloxapol; Tyloksapoli; Tyloxapolum.

Тилоксапол

CAS — 25301-02-4.

ATC — R05CA01.

ATC Vet — QR05CA01.

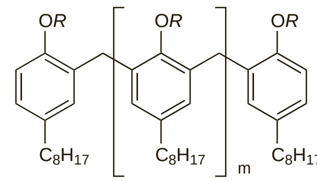

$R = (CH_2CH_2O)_nOH$

n = 8-10

m < 6

Pharmacopoeias. In *US.*

USP 31 (Tyloxapol). A polymer of 4-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide and formaldehyde. A viscous amber liquid, sometimes slightly turbid, with a slight aromatic odour. Slowly but freely miscible with water; soluble in chloroform, in glacial acetic acid, in carbon disulfide, in carbon tetrachloride, in toluene, and in benzene. A 5% solution has a pH of 4.0 to 7.0. Tyloxapol should not be allowed to come into contact with metals. Store in airtight containers.

Adverse Effects

Slight inflammation of the eyelids has been reported after prolonged use of aqueous inhalations of tyloxapol. It has been reported that occasional febrile reactions may occur.

Uses and Administration

Tyloxapol is a nonionic surfactant of the alkyl aryl polyether alcohol type. It is used in solutions for cleansing contact lenses and artificial eyes. Aqueous solutions have been used for inhalation as a mucolytic for tenacious bronchopulmonary secretions. Tyloxapol has also been used as a vehicle for aerosol medication and for antibacterials given in irrigation solutions for pyogenic bone or joint infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Tacholiquin; ***Canad.:*** Enuclene; ***Ger.:*** Enuclen†; Tacholiquin; ***NZ:*** Enuclene; ***USA:*** Enuclene.

Multi-ingredient: *Austral.:* Blink-N-Clean.

The symbol † denotes a preparation no longer actively marketed

Nutritional Agents and Vitamins

Dietary Modification, p.1922
Enteral and Parenteral Nutrition, p.1923
Trace Elements, p.1925
Vitamins, p.1925

The principal constituents of food are carbohydrates, fats, minerals, proteins, vitamins, indigestible fibre, and water. Energy is provided by the metabolism of carbohydrates, fats, surplus protein, and alcohol.

Carbohydrates found in foods may be classified according to their degree of polymerisation into three main groups, namely sugars, oligosaccharides, and polysaccharides; all of these are made up only of carbon, hydrogen, and oxygen. Sugars can be further subdivided into *monosaccharides* (single-molecule sugars), such as fructose and glucose, *disaccharides* (whose molecules consist of two monosaccharides joined together), such as lactose and sucrose, and *sugar alcohols* (polyols) such as sorbitol and mannitol. *Oligosaccharides* typically consist of 3 to 9 monosaccharides joined together, and include malto-oligosaccharides such as maltodextrins. *Polysaccharides* consist of many monosaccharides joined together and include starches and non-starch polysaccharides such as cellulose. Non-starch polysaccharides are the major fraction of dietary fibre, and many authorities now consider this term to be preferable to dietary fibre.

Fats have the same elemental composition as carbohydrates, but with a lower proportion of oxygen. Dietary fat is usually in the form of triglycerides, esters of glycerol with three fatty acid molecules. Essential fatty acids are ones that cannot be made in the body and which must be supplied by the food.

Proteins are made up of carbon, hydrogen, oxygen, and nitrogen; most proteins also contain sulfur and some contain phosphorus. They are required for the regulation of body processes such as growth and tissue maintenance. Excess protein can be converted into carbohydrate and used to provide energy.

Proteins consist of chains of **amino acids** of which there are *essential* and *non-essential* types. Essential amino acids (indispensable amino acids) cannot be synthesised in sufficient amounts in the body and must therefore be present in food; non-essential amino acids can be synthesised in the body. There are eight essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine and histidine are also essential for infant growth while synthesis of cysteine, taurine, and tyrosine may be inadequate in premature infants.

Several inorganic elements, or minerals, are essential dietary constituents; those which are required in relatively small amounts are known as **trace elements** (see below). Their main function is to act as essential cofactors in various enzyme systems.

Vitamins and their general role in health are described below.

Dietary Modification

Infants, children, elderly people, and pregnant or lactating women have particular nutritional requirements, but in most cases, provided that they are in good general health, adjustment to intake is all that is required rather than extensive modification or supplementation.

Dietary modification is important in the management of some disorders. Calorie restriction is fundamental to the management of obesity, although it may be difficult to motivate patients to accept long-term changes to their eating habits, and some fashionable diets are at best of little value.

The role of diet in the aetiology of cardiovascular disorders (such as salt intake in hypertension and fat intake in ischaemic heart disease) is recognised to be of importance and has lead to public health campaigns for healthier eating patterns.

Dietary modification is also an accepted part of the management of diabetes mellitus, while protein restriction is important in the management of uraemia or hepatic encephalopathy.

There are also metabolic disorders such as phenylketonuria, or forms of intolerance to dietary components, such as coeliac disease, in which the diet must be modified to exclude or drastically reduce certain food components.

Amino acid metabolic disorders. Various inborn errors of amino-acid metabolism are known. They are not common but their consequences are often serious or fatal. Although in some cases there is no effective treatment, early diagnosis is important as some conditions can be managed by dietary modification and/or the use of vitamins. Two of the better known syndromes, homocystinuria and phenylketonuria, are discussed briefly below. Cystinosis, another disorder of amino acid metabolism, is discussed on p.2341. Urea cycle disorders are discussed under Hyperammonaemia on p.1929.

Homocystinuria. Homocystinuria in its classical form is an autosomal recessive disorder in which a genetic deficiency of the enzyme cystathionine synthetase (cystathionine β-synthase), results in accumulation of homocysteine (oxidised extracellularly to homocystine).[1,2] Manifestations may include mental retardation, atherosclerosis, thromboembolism, osteoporosis, and ocular symptoms including lens dislocation, glaucoma, cataract, and retinal detachment.[2] Dietary restriction of methionine with cystine supplementation has been used for treatment; some patients may respond to treatment with B vitamins (pyridoxine, cobalamins, and folic acid),[1-3] or to betaine.[2-4] Compliance with betaine is often poor, however; choline, which is converted to betaine by the liver, has also been given, although experience with its use is limited.[3]

Phenylketonuria. Phenylketonuria is an autosomal recessive disorder that is usually due to a defect in the enzyme phenylalanine hydroxylase. This results in raised blood concentrations of phenylalanine in the neonate, and if untreated produces a syndrome of skin rash, depigmentation, hypertonia, seizures, and severe mental retardation.[5,6] Variants of phenylalanine hydroxylase deficiency include atypical or mild phenylketonuria and hyperphenylalaninaemia; some patients have an inherited defect in the metabolism of tetrahydrobiopterin causing a 'malignant phenylketonuria'.[7]

The disease is controlled by use of a diet very low in phenylalanine,[5,8,9] which if started early can permit relatively normal intellectual development. Protein substitutes are recommended, but the optimal dose remains to be determined; there is some evidence that phenylalanine tolerance increases, and blood phenylalanine levels decrease, when total protein intake from the protein substitute is increased.[10] Controversy exists as to whether dietary restrictions may eventually be relaxed,[7,9] and most consider lifelong metabolic control necessary.[5,11] Metabolic control is important in pregnant women as the consequences of fetal exposure to high phenylalanine concentrations include microcephaly, mental deficiency, and congenital heart disease.[5,12,13]

No consensus exists as to optimal blood concentrations of phenylalanine, although frequent monitoring is necessary. In the UK and USA, values between 2 and 6 mg per 100 mL are usually recommended for neonates, children up to age 12, and pregnant women; for patients over 12 years, concentrations between 2 and 10 mg per 100 mL have been advocated.[5]

High-dose tyrosine does not appear to be an effective alternative to a diet low in phenylalanine.[14-18] The active form of tetrahydrobiopterin, sapropterin (p.2383), has been used, with dietary phenylalanine restriction, neurotransmitter replacement, and folinic acid, to treat malignant phenylketonuria;[7,19] it has also shown some promise for the treatment of maternal phenylketonuria.[20] Some have suggested sapropterin may even replace a low-phenylalanine diet in certain patients.[21] Enzyme replacement or substitution are under investigation.[6,7,22]

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Cardiovascular disease. Modification of the diet may be helpful in patients with, or at risk of, cardiovascular disease. In patients with hypertension (p.1171), reduction in salt intake may be tried before starting drug therapy or used as an adjunct to such therapy. Reduction in the total intake of dietary fat, and in particular of saturated fatty acids, is considered important for both the general population and those considered at high risk of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164). An increased intake of long chain n-3 polyunsaturated fatty acids has been recommended and also a restriction on *trans* fatty acids. Dietary cholesterol should be restricted although it may make less of a contribution to plasma cholesterol levels than dietary saturates.[1,2]

For discussion of the possibility that antoxidant vitamins may reduce the risk of ischaemic heart disease see under Vitamins, below. The link between folic acid, homocysteine, and ischaemic heart disease is discussed on p.1941.

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Coeliac disease. Coeliac disease (gluten-sensitive enteropathy; coeliac sprue) is an inflammatory disorder of the small intestine that results from an immunological reaction to the protein fraction of gluten (p.2314). The inflammation leads to mucosal atrophy with subsequent malabsorption, although the extent and severity of mucosal inflammation varies widely, and some patients are asymptomatic. In adults, anaemia and mild gastrointestinal symptoms that may be confused with irritable bowel syndrome are the usual symptoms. In infants and children there may be growth retardation or failure to thrive, and gastrointestinal symptoms may be more marked. Other nutritional deficiencies, including calcium malabsorption leading to osteopenia, may also occur, and mouth ulcers are also common. Provisional diagnosis usually involves serological tests for IgA anti-transglutaminase 2 or antiendomysial antibodies, and multiple intestinal biopsies.

Treatment of coeliac disease involves a strict, life-long, gluten-free diet. Nutritional supplements may be necessary at the start of treatment but can usually be stopped once mucosal recovery has occurred. Diagnosis is confirmed by clinical improvement or normalisation of the mucosa on repeat biopsy after 3 to 4 months. Dermatitis herpetiformis (p.1578) is a non-gastrointestinal manifestation of coeliac disease. Patients may have no gastrointestinal symptoms, although mucosal abnormalities are generally apparent on biopsy. These patients also respond to a gluten-free diet.

Coeliac disease is associated with a number of auto-immune diseases, including type 1 diabetes, thyroid disease, and IgA deficiency. Patients with coeliac disease have an increased incidence of small-bowel lymphoma and a slight increase in the incidence of some other gastrointestinal cancers. There is some evidence that this incidence is reduced in patients maintaining a strict diet.

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Diabetes mellitus. Dietary control is important in both type 1 and type 2 diabetes mellitus (p.431). The goals of dietary modification are to maintain glucose concentrations in the normal range or as close to normal as possible, and a lipid and lipoprotein profile and blood pressure that reduce the risk of macrovascular disease.

Fish odour syndrome. Fish odour syndrome (trimethylaminuria) is an inherited metabolic disorder in which there is impaired hepatic *N*-oxidation of trimethylamine. Trimethylamine is formed in the intestine by bacterial degradation of foods rich in choline and carnitine, and is readily absorbed from the gut. If not oxidised in the liver, it is excreted in the breath, urine, sweat, and vaginal secretions. It smells of rotting fish, and has a high olfactory potency. Treatment involves dietary modification to avoid choline-rich foods such as eggs, liver, peas, soya beans, and sea fish. Short-term treatments to reduce the intestinal flora, and thereby decrease the production of trimethylamine, are occasionally used; examples include metronidazole, neomycin, and lactulose.

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Hepatic encephalopathy. Restriction of dietary protein intake is a mainstay of the treatment of hepatic encephalopathy, but care is required to avoid malnutrition (see p.1697).

Inflammatory bowel disease. In inflammatory bowel diseases (p.1697) dietary modification or **supplementation** may often be necessary to maintain the nutritional status of the patient. Specific nutritional problems include protein deficiency, fluid and electrolyte depletion, iron deficiency, and deficiencies of certain minerals, vitamins and trace elements, such as magnesium, calcium and vitamin D, vitamin K, and folic acid.[1,2] Supplementation may be oral, nasogastric, or parenteral. In general, although they are considered to have equal efficacy,[3] enteral feeding is preferred to parenteral nutrition. The latter is generally reserved for those who cannot tolerate the enteral route, for perioperative use, or for specific clinical circumstances such as bowel obstruction or perforation.[4,5]

Improvement in nutritional status, elimination of dietary antigens, down-regulation of inflammatory cytokines or up-regulation of anti-inflammatory cytokines, or alteration in bacterial flora are also possible mechanisms whereby nutritional therapy may exert a **therapeutic** effect in inflammatory bowel disease.[5-7] Although controversial as primary therapy, enteral feeding, particularly with elemental diets, has been shown to be effective in the treatment of active *Crohn's disease*,[8] but probably less effective than corticosteroids.[9-11] It may also have some benefit in maintaining remission.[12] There are beneficial effects in children with growth failure, which is exacerbated by corticosteroids,[13,14] and some consider enteral nutrition the first choice of management in paediatric patients with Crohn's disease.[3] Combining an elemental diet with low-dose corticosteroids has also been suggested as a therapeutic approach in children, although it is as yet untested.[14] Adult patients with Crohn's disease who are considered candidates for enteral nutrition include those on potentially high cumulative corticosteroid doses, or who are corticosteroid-refractory or corticosteroid-intolerant, or those at high risk for osteoporosis.[5]

Data are considered insufficient to assess the efficacy of enteral nutrition in *ulcerative colitis*.[5,7]

The term **elemental diet** was originally coined to describe diets containing free amino acids and glucose and was often prefixed by the phrase 'chemically defined'. However, it came to embrace diets whose nitrogen sources included peptides and were often also called predigested diets. It was suggested[15] that the term elemental diet could be used for either type but that for those with an amino acid nitrogen source the term chemically defined elemental diet should be used whereas for those with a peptide nitrogen source predigested elemental diet was suitable. The term polymeric diet should be used for those diets with a whole protein nitrogen source (such as milk or soya).

There appears to be little difference between formulas in terms of therapeutic response, although compliance may be better with polymeric feeds due to the unpalatability of elemental diets.[3,5,13] Several different elemental diets are available; some contain long-chain triglycerides as the fat source, but for patients with impaired fat digestion, medium-chain triglycerides are considered preferable.[1] There is some suggestion that the effectiveness of enteral diets in treating active Crohn's disease might relate to the fat rather than nitrogen composition,[1,3,7] with less inflammation occurring with those containing the fewest long-chain triglycerides.[1]

Other potentially beneficial components of diets for Crohn's disease include omega-3 triglycerides, which may have beneficial effects on inflammatory processes, and in achieving remission;[4,14,16] no clinical benefit has been seen with fatty acid or dietary fish oil supplementation in active ulcerative colitis.[17] Short-chain fatty acids have been proposed as a means of increasing butyrate levels, which may have a direct anti-inflammatory effect on the colon; butyrate enemas have shown benefit in ulcerative colitis.[5,13,17] The use of a substrate ('pre-biotic') to deliver short-chain fatty acids, or directly delivering probiotics to the intestine, have also been proposed.[5,17] Glutamine has been suggested as being beneficial for epithelial integrity of the small intestine,[1,16] although useful data are lacking.[1,4,5]

Much interest also surrounds the use of **growth factors** in enteral formulas, such as epidermal growth factor or transforming growth factor-β, which may have anti-inflammatory actions on the gut mucosa.[7]

Elimination diets, whereby foods are slowly reintroduced once remission has been achieved, aim to reduce relapse rates in Crohn's disease, but the process is prolonged and complicated.[1,3] In a study of patients with ulcerative colitis in remission, consumption of red and processed meat, protein, or alcohol increased the likelihood of relapse;[18] these foods are rich sources of sulfur or sulfate, and sulfide toxicity may be important in the pathogenesis of ulcerative colitis.[17] There is also some suggestion that titanium may be harmful in Crohn's disease, and diets low in titanium have been advocated, with preliminary data suggesting a benefit.[3]

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Malignant neoplasms. For a discussion of the possible link between an increased intake of antoxidant vitamins and a reduced risk of developing malignancies, see under Vitamins, below.

Obesity. Obesity is relatively common in the developed world, and is accompanied by an increased risk of cardiovascular disease, diabetes, and other disorders. Methods such as dietary modification, behaviour therapy, and exercise with adjunctive drug therapy, where indicated (see p.2149) can produce weight loss, but the essence of treatment is a reduction in calorific intake, usually by about 300 to 500 kcal daily in patients with a body-mass index (BMI) of 27 to 35, and 500 to 1000 kcal in those with a BMI greater than 35. This would be expected to produce a weight loss of about 0.25 to 1 kg weekly. Very low calorie diets (less than 600 to 800 kcal daily) should only be considered after the failure of determined attempts to lose weight by conventional calorie restriction. For weight loss to be achieved and sustained, eating behaviour must be permanently modified, which may pose difficulties. The proportion of calories from fat in particular, and also alcohol and sugars should be reduced and those from high carbohydrate foods increased. It is obviously important to maintain an adequate intake of essential nutrients.

Artificial sweeteners or other non-sucrose sweeteners are often used as part of weight-reducing diets.

Renal failure. Low-protein diets may be of value in preventing or slowing the progression of chronic renal failure (p.1672). Patients with renal failure who adopt a protein-restricted diet have fewer symptoms of uraemia than those on a normal diet. Some results have also suggested that protein restriction can slow the progression of renal failure, but the value of low-protein diets in delaying the onset of end-stage renal disease has been the subject of much controversy.[1] Two large multicentre studies provided little evidence of a substantial benefit,[2,3] but a systematic review[4] provided support for dietary protein restriction. *Animal* studies suggest that modification of the protein source from animal to soya protein might slow renal disease progression, especially at high intakes.[5]

Generally, low-protein diets providing between 0.6 to 0.8 g/kg daily have been recommended,[1,6-8] although a very low-protein diet providing 0.3 g of vegetable origin protein, supplemented with a mixture of essential amino acids, has been recommended for highly motivated patients with advanced renal failure.[1]

Once the patient starts dialysis, however, protein losses through the dialysis membrane or peritoneum may require an increase of protein intake to between 1.2 and 1.3 g/kg daily.[6,8] Because energy intake needs to remain constant, food selection has to change qualitatively.[6] Sodium, potassium and phosphate intake also need to be controlled.[6,8] During dialysis, restricting dietary phosphate while maintaining sufficient protein intake may be difficult, and modification of the protein source may be necessary.[9]

After kidney transplantation, if renal function stabilises, protein restriction is again advisable;[6] between 1.3 and 1.5 g/kg daily is recommended initially, then 1 g/kg daily for maintenance.[8] However, adverse effects of immunosuppressant drugs may complicate the dietary targets, with the patient at risk of diabetes, dyslipidaemia, and possible hypertension.[6] The importance of salt restriction and reduction of the sodium dialysate content in controlling hypertension in renal patients has been emphasised.[10]

It has been suggested that the benefit of other interventions such as the use of ACE inhibitors,[11] as well as the difficulties in obtaining patient compliance with such a restrictive diet,[12] may have limited the benefits to be obtained from protein restriction, but there is also evidence that response and outcome vary depending on the cause of renal failure.[3,13]

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Enteral and Parenteral Nutrition

Malnutrition of varying degrees is not uncommon in hospitalised patients, and some form of nutritional support is important in patients who cannot eat an adequate normal diet. Such support should provide for the patient's requirements for energy, in the form of carbohydrate and fat, nitrogen as amino acids or protein, water and electrolytes; where appropriate, vitamins and trace elements should also be supplied. Indications for nutritional support may include unconsciousness, obstruction or inability to swallow, inflammatory bowel disease, fistula, short bowel syndrome, and weakness and malnutrition associated with trauma, surgery, or malignant disease. If possible, nutritional support should be by the enteral route; it is easier, more physiological, and less prone to complications than the parenteral route.

Enteral nutrition includes feeding by mouth, by nasogastric or nasoenteric tube, or directly into a gastrostomy or other enterostomy. It may be supplemental, if normal food intake is possible but inadequate, or total. Individual patients vary in their requirements according to age, size, and metabolic state, but a diet supplying 2000 to 3000 kcal of energy and 10 to 15 g of nitrogen (as 60 to 90 g of protein) in 2 to 3 litres of fluid is fairly typical; because absorption from the gastrointestinal tract is incomplete requirements are higher than by the parenteral route. Preparations containing whole protein (often derived from milk or soya) are generally preferred; elemental diets, in which nitrogen is supplied as amino acids or oligopeptides, are less well tolerated and less palatable, although they may have a role in impaired digestion or when a zero-residue diet is desired.

Although preferred to parenteral nutrition, enteral feeding is not without complications. Patients may be at risk of oesophagitis, aspiration, and regurgitation as a result of the tube insertion; other potential problems include diarrhoea, nausea and vomiting, gastric retention, hyperglycaemia, fluid and electrolyte disturbances, and microbial contamination of the feed regimen.

Parenteral nutrition is reserved for situations in which it is impossible to meet nutritional requirements by the enteral route. Like enteral nutrition it may be given supplementally or as the sole source of body requirements (total parenteral nutrition or TPN). It is normally given via a dedicated central venous catheter. However, peripheral veins are increasingly used for short-term feeding. This reduces some complications and insertion is less complex, but because of the risk of thrombophlebitis the feeds used should have low osmolality and neutral pH. Other measures to delay the development of peripheral thrombophlebitis are mentioned under Adverse Effects and Precautions, below.

The formulation of the nutritional solution must be adjusted according to the patient's requirements. The solution should supply sufficient energy to allow for the resting energy expenditure (around 25 kcal/kg in the average adult) but must also take into account any increased energy expenditure of illness. Conversely, starvation can reduce resting metabolism and energy requirements. Various formulae exist for the calculation of energy expenditure in patients. Energy is best supplied in the form of carbohydrate (at least 30%, and preferably 60% of energy requirements should be in this form) and fat. Glucose is the optimal carbohydrate energy source, while fat is supplied as a lipid emulsion, often of soya oil. Nitrogen is supplied as amino acids, but to ensure that these are used for protein synthesis rather than as sources of energy it is important to control the ratio of non-protein energy to nitrogen in the solution. A ratio of 150 to 200 kcal per g of nitrogen is usually considered optimal but in hypercatabolic patients (e.g. in sepsis) lower ratios of 120 kcal per g or less may be appropriate. All essential amino acids are supplied although there is some variation between solutions as to which non-essential amino acids are present.

Parenteral nutrition must also supply the patient's requirements for fluid, essential electrolytes such as sodium, potassium, magnesium, bicarbonate, and calcium (as well as phosphate, since glucose infusion may provoke hypophosphataemia), and, particularly if treatment is prolonged, vitamins and trace elements. If glucose loading produces signs of hyperglycaemia insulin may be added to correct it.

The major complication of parenteral nutrition is bacterial colonisation of the catheter, which can lead to septicaemia. Other problems may include venous thrombosis or air embolism, extravasation due to misplacement of the catheter tip, and metabolic disturbances. Adverse effects of overfeeding include respiratory and hepatic dysfunction. Complications of long-term total parenteral nutrition include gallbladder sludging, gallstones, cholestasis, and abnormal liver function tests.

Stability and compatibility. The complex nature of solutions for parenteral nutrition renders them susceptible to compatibility problems.[1-18] Stability is dependent upon several factors including pH and relative concentrations of the components. Amino acids exert a buffering effect on the overall pH of mixed solutions containing amino acids, glucose, and fat emulsions but amino acids with glucose undergo the Maillard reaction (browning) and the life of combined solutions is therefore limited. Solutions containing electrolytes, particularly divalent cations, are not stable, and aggregation will eventually occur. Additives should be added only if there is known compatibility, and any additions performed aseptically before the start of the infusion.

The most significant cause of precipitation is higher concentrations of calcium and phosphate,[13,18] and the most important factor governing calcium phosphate precipitation is the final pH of the mixture. The pH is itself determined by a number of factors, including the commercial source of the amino acid infusion, and the final amino acid and glucose concentrations. The use of organic phosphate compounds may reduce the likelihood of precipitation. Trace element precipitation may also occur and amino acid infusions can contain detectable quantities of trace elements as contaminants. The most significant cause of chemical instability is the degradation of specific vitamins, through exposure to light or binding with the plastic of the bag or giving sets. Two particular reactions, the oxidation of ascorbic acid, and the reduction of thiamine, are of concern.

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Adverse effects and precautions. *ENTERAL NUTRITION.* Complications of enteral feeding can arise from mechanical, gastrointestinal, metabolic or other causes, such as infection or aspiration.[1] The most common nutritional complication of enteral feeding is failure to meet nutritional requirements, and overzealous feeding may lead to the 'refeeding syndrome' manifested by glucose intolerance, fluid retention, and electrolyte imbalances.[2] High-protein formulas with low water intake may also cause this syndrome.[1] These rapid metabolic and electrolyte changes can lead to severe or even fatal cardiopulmonary and neurological problems.[3] To avoid these problems, low levels of feeding for the first few days have been recommended; about 20 kcal/kg daily has been suggested but even this may be too high, especially in patients with existing electrolyte abnormalities, and about 10 kcal/kg daily may be more suitable for high-risk patients.[4] Mechanical or physical complications include displacement or clogging of the tube, or patient discomfort.[1-5] Many of the problems encountered can be avoided by using a fine bore tube, giving the feed by continuous infusion, and by careful monitoring of the patient for metabolic abnormalities.[6] However, tubes become clogged more often if the calibre of the tube is small, the tube is long, placed in the stomach, the feeding continuous, or if medication is given through the tube.[2,5] Inadequate flushing and protein precipitation may also occur.[3]

Positioning the tube in the small bowel rather than the stomach has been suggested to reduce the incidence of aspiration,[2,5,7] although few studies have been done comparing intraduodenal and intragastric feeding in terms of clinical outcomes, and there are concerns about appropriate placement, infection, and reflux.[8] A meta-analysis[9] failed to find any clinical benefit of post-pyloric feeding over gastric feeding in terms of the incidence of pneumonia, length of stay, and mortality; the study was limited by a relatively small number of patients, and did not include patients considered at high risk of aspiration. Prokinetic drugs such as metoclopramide, or erythromycin, have been used to promote gastric emptying and reduce residual gastric volumes.[7-9]

Complexation of the nutrients with aluminium-containing antacids, also given via the tube, may occur and this deposition of solid masses may cause oesophageal obstruction.[10]

Diarrhoea in patients receiving enteral nutrition may not necessarily be caused by the tube feeding itself;[11,12] malabsorption, infections and microbial contamination, underlying disease, and concomitant drug therapy can be possible contributors.[1,2,4,13,14] However, enteral feeding has been shown to be associated with increased colonic secretion, which can be reversed by infusion of short-chain fatty acids.[15] Because colonic microflora may play a role in the pathogenesis of diarrhoea associated with enteral feeds, manipulation of the microflora using pre- or probiotics has been suggested as a means of reducing the incidence, duration or severity thereof, and some enteral feeding formulas contain prebiotics. However, few studies have investigated the effect on diarrhoea, and further research is warranted.[14]

While enteral tube feeding and the presence of a nasogastric tube are risk factors for infection, optimal nourishment through enteral feeding in high-risk patients unable to tolerate oral nutrition may also improve their immune status.[16]

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PARENTERAL NUTRITION. A common complication of parenteral nutrition is infection of the intravenous feeding catheter site,[1-3] which can lead to septicaemia. Infection and colonisation of central venous catheters may be reduced if the catheter is tunnelled through subcutaneous tissue before emerging through the skin.[4] Strict aseptic techniques should be used[1] for changing the dressing or bags containing the nutrient fluids. Misplacement of the catheter has been reported.[3,5] Precipitation of minerals, lipids, and medications can cause line occlusion.[3]

Thrombophlebitis can occur after the use of either peripheral or central veins. Although it has been suggested that infusion of hyperosmolar solutions via a central line is less likely to produce thrombophlebitis, because the feed is immediately diluted by a large volume of blood, major thrombotic complications such as pulmonary embolism and right atrial thrombosis could be more common than hitherto recognised in children and adolescents receiving long term parenteral nutrition via central catheters.[6,7] The use of a fine-bore silicone catheter peripherally may avoid the need for central vein cannulation[8] and there is a lower incidence of thrombophlebitis when fine-bore silicone catheters rather than teflon ones are used for peripheral parenteral nutrition.[9] The use of giving sets with filters may decrease thrombophlebitis during peripheral infusion.[10,11] The addition of heparin or buffer solutions to the feed, and the use of local hydrocortisone and glyceryl trinitrate, has also been reported to prolong the survival of peripheral infusion sites.[11,12] Extravasation may also be a problem, particularly with hyperosmolar solutions, and has led to severe tissue damage; hyaluronidase or thiomucase may be used in the treatment of such extravasation.[13]

Parenteral nutrition may be associated with atrophic changes in the mucosal structure and enzymic activity of the intestine, leading to increased permeability with a possible increased risk of bacteraemia and endotoxaemia. These changes, which have been attributed to lack of glutamine (which is unstable in solution), can reportedly be prevented by addition of glutamine-releasing dipeptides to solutions for total parenteral nutrition—see p.1947. Some have questioned the extent of this mucosal atrophy or bacterial translocation associated with parenteral feeding.[14,15]

Prolonged parenteral nutrition has been associated with hepatobiliary complications, especially in children;[16,17] cholelithiasis and cholestasis have been reported, with the latter sometimes progressing to liver failure.[18] Although the aetiology is considered multifactorial,[18] contamination of the solution with manganese (see Accumulation under Adverse Effects of Manganese, p.1956) or aluminium[19] has been suggested as one possible cause of the cholestasis.

Aluminium toxicity has also been implicated in the osteomalacia seen in patients on long-term parenteral nutrition.[3,17] Osteopenia and osteoporosis have also been reported;[17] possible mechanisms include calcium, phosphate, or magnesium deficiencies, vitamin D deficiency or toxicity, vitamin K deficiency, or excessive protein.[3] A review, however, considered the risk to be minimal, with little deleterious effect on cortical bone and an improvement on trabecular bone.[5] Other factors implicated in possible metabolic bone disease include calcium deficiency and vitamin D toxicity.[17]

Other metabolic complications associated with parenteral nutrition include hyperglycaemia, hypoglycaemia, hyperlipidaemia, hypercapnia, acid–base disturbances, and 'refeeding syndrome'.[20] Hyperglycaemia may be due to excessive glucose infusion, and can lead to immunodepression and an increased risk of infection; insulin therapy is indicated if it persists. Hypoglycaemia, although less common, may occur if parenteral nutrition is interrupted or as a result of an insulin overdose. Hyperlipidaemia is caused by excessive fatty acid synthesis from glucose, or impaired lipid clearance. The use of a mixture of medium-chain and long-chain triglycerides (rather than long-chain triglyceride emulsions alone) may result in fewer serum lipid abnormalities since medium-chain triglycerides are oxidised faster than long-chain triglycerides. Overfeeding of total calories and glucose can lead to hypercapnia which can cause acute respiratory acidosis.[20] While most acid–base disturbances are related to the underlying condition, excess chloride or acetate in the parenteral nutrition solution may cause metabolic acidosis or alkalosis, respectively.[17] The 'refeeding syndrome' can occur when severely malnourished patients are given rapid nutritional repletion, leading to fluid and electrolyte imbalances, glucose intolerance, and vitamin deficiencies. These may result in significant or even fatal cardiac, pulmonary, renal, gastrointestinal, and neuromuscular complications. Electrolyte disturbances include sodium retention, hypophosphataemia, hypokalaemia, and hypomagnesaemia; thiamine deficiency may lead to Wernicke's encephalopathy in malnourished patients or in thiamine-deficient patients given high carbohydrate loads.[20]

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Uses. Parenteral and enteral nutrition now have an established place either for supplemental use or for providing total nutritional requirements in many conditions. General reviews as well as those pertaining to special groups of patients or disorders have been published.[1-25]

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Trace Elements

Trace elements are inorganic substances found in small amounts in the tissues and required for various metabolic processes; together with the vitamins (see below) they are sometimes referred to as micronutrients. The elements considered essential are chromium, copper, fluorine, iodine, iron, manganese, molybdenum, selenium, and zinc. Iron, in the form of haem, plays an essential role in oxygen transport while iodine is required by the thyroid for the formation of thyroid hormones; most of the other essential trace elements are cofactors for various enzymes. Boron, nickel, silicon, and vanadium may also be essential, and it has been suggested on the basis of *animal* studies that there might be a requirement for tin.

Well-defined deficiency syndromes exist for copper, iodine, iron, selenium, and zinc; although deficiency of other trace elements is possible, their deficiency syndromes are not well defined because of their ubiquity in the diet. Guidance concerning the intake of various trace elements has been published—see also Human Requirements under Vitamins, below.

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Vitamins

Vitamins are organic substances required by the body in small amounts for various metabolic processes. Most are not synthesised in the body, or are synthesised in small or insufficient quantities. Vitamins are sometimes classified as fat soluble or water soluble. Substances in the vitamin A, D, E, and K groups are generally fat soluble, and biotin, folic acid, niacin, pantothenic acid, vitamins B_1, B_2, B_6, and B_{12}, and vitamin C substances are generally water soluble.

Vitamin deficiency may result from an inadequate diet, perhaps due to increased requirements such as during pregnancy, or may be induced by disease or drugs. Vitamins may be used clinically for the prevention and treatment of specific vitamin deficiency states and details of these uses are provided under the individual drug monographs.

Large doses of vitamins (megavitamin therapy) have been proposed for a variety of disorders, but adequate evidence of their value is lacking. Excessive intakes of most water-soluble vitamins have little effect due to their rapid excretion in urine, but excessive intakes of fat-soluble vitamins accumulate in the body and are potentially dangerous.

Stability. Water-soluble vitamins are liable to degrade in solution especially if exposed to light. Addition of vitamin mixtures to infusion solutions for parenteral nutrition should therefore be carried out as soon as possible before infusion. Solutions should be used within 24 hours of preparation and be protected from light.

Carcinogenicity. For mention of an increased risk of lung cancer in patients receiving betacarotene and vitamin A, and an increased incidence of second primary cancers in patients given vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p.1927. For a discussion of possible carcinogenic effects in children given vitamin K intramuscularly, see Carcinogenicity, p.1996.

Effects on mortality. Although vitamin supplements have been widely taken in the hope of improving mortality from various diseases, a large systematic review[1] concluded that there was no evidence that antioxidant vitamin supplements improved mortality, and some, such as vitamin A, betacarotene, and vitamin E, might increase it.

For mention of possible adverse effects on mortality with betacarotene supplementation, see Effects on Mortality, p.1931. For discussion on the effects on mortality with Vitamin A, see p.1972. For mention of possible beneficial effects of high serum ascorbic acid levels on all-cause mortality, see under Vitamin C, p.1984. For mention of possible dose-dependent adverse effects on mortality with use of vitamin E, see Effects on Mortality, p.1993. For discussion of the effects of various antioxidant vitamins on cardiovascular disease and cancer, see Prophylaxis of Ischaemic Heart Disease, below, and Prophylaxis of Malignant Neoplasms, p.1927, below.

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Human requirements. Vitamins and trace elements are essential nutrients and in many countries guidance has been published concerning their intake.

In the UK various terms are used to define intake:[1]

- estimated average requirement (**EAR**) is used for the requirements of energy, proteins, vitamins, or minerals of a group of people and usually about half will need more and half less than the specified figure
- lower reference nutrient intake (**LRNI**) is applied to proteins, vitamins, or minerals and is that amount that is enough for only a few people who have low needs
- reference nutrient intake (**RNI**) is also applied to proteins, vitamins, or minerals and is an amount that is enough, or more than enough, for about 97% of people in a group
- a safe intake is used to indicate an intake or range of intakes where there is not enough information to estimate EAR, LRNI, or RNI, but rather it is an amount enough for almost everyone but is not so large as to cause undesirable effects
- dietary reference value (**DRV**) is used to cover EAR, LRNI, RNI, and safe intake.

It is emphasised in a 1991 report[1] that these intakes are not meant to be recommendations for any individual or group; they do not reflect either a recommendation that such an amount should be taken daily in the diet or as a supplement. They are intended rather as yardsticks for the assessment of dietary surveys and food supply statistics; to provide guidance on appropriate dietary composition and meal provision; or for food labelling purposes in which case it is envisaged that an EAR will be used.

An Expert Group on Vitamins and Minerals, established in the UK to review data on the safe intake of vitamins and minerals from food and food supplements, recommended the use of safe upper levels (**SULs**). These were the doses of vitamins and minerals that individuals could take daily on a lifelong basis without significant risk to health on the basis of available evidence.[2]

In the USA the National Academy of Sciences has traditionally set recommended dietary allowances (**RDAs**),[3] defined as the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged to be adequate to meet the known nutrient needs of practically all healthy persons. The allowances are amounts that are intended to be consumed as part of a normal diet. However, new dietary reference intakes (**DRIs**) have been developed,[4] which include 3 reference values in addition to the traditional RDA as follows:

- the estimated average requirement is the intake that meets the needs of half the individuals in a group
- the adequate intake is the mean intake level that appears to sustain a desired marker of health, and will be set when there is insufficient evidence to establish an RDA
- the tolerable upper intake level is the maximum intake that is not likely to adversely affect health.

Information pertaining to the requirements of specific vitamins and minerals is provided under the individual monographs.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
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Supplementation. An adequate dietary intake of vitamins is necessary for good health but whether vitamin supplementation in the absence of any demonstrable deficiency is beneficial or even worthwhile remains debatable.

It is generally considered that healthy persons eating a normal balanced diet should have no need for vitamin supplementation.[1,2] A review of the topic[1] pointed out that the vitamins that people chose for self medication are often not the ones that are actually present in inadequate amounts in their diets and that the commercial preparations available often do not make it clear whether the amounts they contain are near the physiological requirements or many times greater. Supplementation should concentrate on groups of people at risk of deficiency such as neonates, who need vitamin K; pregnant and lactating women, who need calcium, folic acid, and iron; and certain groups who need vitamin D; vegans and their infants may require vitamin B_{12} supplements. A multivitamin supplement might be considered for some groups such as the elderly and those with reduced calorie intake.[1,3] However, one might have difficulty in finding a good multivitamin preparation containing all 13 vitamins but no non-vitamins. Also with many of the multivitamin preparations the doses and ratios varied inexplicably.[1]

A review[4] of supplementation specifically in children concluded that, provided schoolchildren and adolescents eat a wide variety of foods, there was no need for vitamin supplementation. However, it was recommended that supplementation with vitamins A, C, and D should be given to those between the ages of 6 months and 2 years and preferably up to the age of 5 years. Several authorities in different countries have set upper safety limits for vitamins; these vary considerably.[5]

Vitamin and mineral supplementation has been investigated in various disorders (see below). However, a systematic review for the National Institutes of Health in the USA led to the consensus that evidence was insufficient to recommend either for or against the use of multivitamin and mineral supplements to prevent cancer and chronic disease.[6,7] (For a systematic review that concluded against use of antioxidant supplements see Effects on Mortality, above.)

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EYE DISORDERS. Vitamin therapy has been investigated for the prophylaxis or treatment of various eye disorders. Vitamin A is used in the management of xerophthalmia, see p.1974. There is some suggestion of benefit with vitamin A for retinitis pigmentosa, p.1974; results with vitamin E are conflicting. Vitamin E has been used for the treatment of retinopathy of prematurity, p.1994. For discussion of the effect of vitamins C, E, betacarotene, and zinc on age-related macular degeneration, see under Betacarotene, p.1931.

HIV INFECTION AND AIDS. Low serum micronutrient concentrations are common in HIV-positive individuals, especially in the developing world; malabsorption, anorexia, diarrhoea, and increased energy demands contribute to malnutrition,[1,2] which in turn contributes to immune impairment and increased mortality. Conflicting results have been found with the use of vitamin A in the prevention of vertical transmission, see under Vitamin A, p.1974. A meta-analysis of trials of vitamins to prevent vertical transmission found no strong evidence of benefit and failed to exclude the possibility of harm, having included trials of vitamin A supplementation.[3] A randomised trial found that multivitamin plus selenium supplementation increased CD4 and CD8 cell counts compared with placebo, but also unexpectedly increased the levels of genital HIV-1 shedding.[4] Two other trials have also found that multivitamins, but not vitamin A, increased CD4 and CD8 cell counts;[5,6] delaying the progression of disease in one,[6] and decreasing adverse pregnancy outcomes in the other.[5] While some advise against vitamins as a therapy to prevent vertical transmission,[3] and others recommend it as an adjunctive treatment to antiretroviral therapy,[1,2] most agree that in the setting of poverty and lack of adequate nutrition, provision of food programs and/or supplementation along with antiretroviral treatment for HIV-infected individuals, is vital.[7]

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INFECTION. Vitamin A has an important role in the prevention of complications from measles (see p.1974), but evidence for benefit in respiratory-tract infections is less compelling (see p.1974). Some studies show evidence of benefit for vitamin C in treating the common cold (p.850), but routine high-dose prophylaxis is not considered justified. Vitamin E has shown conflicting results in respiratory-tract infections, see p.1994.

For a discussion of the role of vitamins in HIV infection and AIDS see above.

MENTAL FUNCTION. Giving vitamin and mineral supplements to children was reported in 1988 to increase non-verbal intelligence[1] and the topic has since remained highly controversial. In the next 2 years more studies were published but these failed to substantiate the earlier possible effect and concluded that vitamin supplementation did not improve mental functioning or reasoning in children.[2,3] Suggestions were made shortly after these publications that there might be a subset of children with poor nutritional status who would receive some benefit[4] but this again was disputed.[5]

In 1991 another study was published,[6] this time coinciding with the launch of the proprietary product used in the study, with the publication of a book on the subject, and with the showing on British television of a documentary concerning the study. This study purported to demonstrate that supplementation with exactly the recommended dietary allowances of vitamins improved the IQ of children, a finding that was said not to occur significantly with other quantities of vitamin supplementation. This view attracted extremely harsh criticism[7-9] from physicians, nutritionists, psychologists, and epidemiologists.

Despite conflicting data on the effect of vitamin E intake on cognitive decline, US guidelines have suggested that vitamin E be considered in patients with Alzheimer's disease in an attempt to slow progression of the disease. A subsequent large trial found no benefit for vitamin E over placebo (see Dementia, p.1994). A cohort study found low folate concentrations to be the predominant risk factor for cognitive decline in elderly people.[10] Raised homocysteine concentrations have also been found in patients with cognitive decline and dementia.[11] While a 2-year controlled study found that daily homocysteine-lowering treatment with folate, vitamin B_6, and vitamin B_{12} did not improve cognitive performance,[12] another found that daily folic acid supplementation for 3 years significantly improved measures of cognitive function.[13]

Similarly, low folate concentrations and increased homocysteine concentrations have been implicated in depression, and supplementation has been proposed,[11] both as monotherapy, or as a means of augmenting antidepressant efficacy.[14]

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PREGNANCY. Folic acid protects against the development of neural tube defects (p.1942) and supplementation during pregnancy is advised; vitamin B_{12} supplementation may also be warranted. Vitamin A, however, may be teratogenic and maximum intakes in pregnancy have been recommended, see p.1972. The risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy (see p.1988). Systematic reviews[1,2] of supplementation in pregnancy lacked enough data to indicate whether vitamin C or E, alone or with other supplements, were of benefit. There was some suggestion of decreased risk of developing pre-eclampsia with either vitamin C or E; however, preterm births may have increased with vitamin C supplementation.

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PROPHYLAXIS OF ISCHAEMIC HEART DISEASE. Hypercholesterolaemia is a major risk factor for the development of atherosclerosis and consequently ischaemic heart disease. Since oxidation of lipids, particularly low-density-lipoprotein (LDL) cholesterol,[1] has been proposed as a factor in atherogenesis, the possibility of preventing atherosclerosis by the use of dietary antoxidants such as vitamins E and C and betacarotene has been investigated. A six-year trial of supplementation with vitamins C and E in hypercholesterolaemic patients showed a slowing of atherosclerotic progression, especially in men.[2] Prospective epidemiological studies have revealed a reduced risk of ischaemic heart disease in individuals taking vitamin E supplements,[3,4] and those with a high carotene intake (particularly smokers).[3] In a further prospective cohort study,[5] dietary vitamin E consumption, but not vitamin E supplementation, was associated with decreased risk of death from ischaemic heart disease. Intake of vitamin C, however, did not appear to be associated with a decreased risk of ischaemic heart disease in these studies,[3-5] although another study[6] found a significantly lower risk in those taking vitamin C supplements. Data from some studies assessing serum or fat concentrations also provide evidence that high betacarotene concentrations are associated with decreased cardiovascular disease.[7-9]

However, despite these promising results, randomised placebo-controlled trials have failed to find any benefit for betacarotene supplements in the primary or secondary prevention of ischaemic heart disease, and those for vitamin E supplements are inconclusive. In the Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) study, which monitored cardiovascular disease as a secondary end-point, vitamin E was not associated with a decreased incidence of ischaemic heart disease, and betacarotene was associated with a small increased risk.[10] In further analyses, neither supplement appreciably altered the incidence of angina pectoris,[11] nor showed any beneficial effect on cardiovascular deaths in the subset of men with previous myocardial infarction.[12] It has been suggested that the lack of effect of vitamin E in this study may be due to an insufficiently high dose of tocopherol. Similarly, neither the Betacarotene and Retinol Efficacy Trial (CARET)[13] nor the Skin Cancer Prevention Study[9] found an effect for betacarotene supplementation on the risk of death from cardiovascular disease.

In studies specifically on cardiovascular end-points, no benefit from betacarotene supplements was seen in a large, randomised, placebo-controlled study[14] in healthy men. Studies of supplementation with high-dose vitamin E in patients with evidence of ischaemic heart disease,[15] or after myocardial infarction,[16] failed to show any beneficial effect on cardiovascular deaths, although in one study[15] there was a reduction in non-fatal myocardial infarction and major cardiovascular events. The Heart Outcomes Prevention Evaluation (HOPE) study also showed that vitamin E treatment for 4 to 6 years had no effect on cardiovascular events in high-risk patients;[17] further follow-up[18] raised the possibility of an increased risk of heart failure with vitamin E. Another large-scale study, the Heart Protection Study, assessed the effect of a 'cocktail' of vitamin E, vitamin C, and betacarotene on the development of ischaemic heart disease in high-risk subjects, and again found no evidence of benefit.[19] Another study[20] using a similar cocktail in patients with established heart disease found no effect on clinical outcome. In view of the lack of evidence of benefit with vitamin supplements, it has been recommended that the emphasis should instead be on consuming a balanced diet including antioxidant-rich fruits, vegetables, and whole grains rather than vitamin supplements;[21,22] authors of a meta-analysis[23] of trials of antioxidant vitamins for the prevention of cardiovascular disease concluded that, in view of a possibly harmful effect of betacarotene and inefficacy of vitamin E, the use of these supplements be discouraged. It has been pointed out[24] that differences between the observational and clinical trials may be due to intrinsic differences between individuals who choose to take supplements and the high-risk populations studied in randomised trials, who may be less amenable to cardiovascular risk reduction with antioxidant supplementation.

For a discussion of the possibility that folic acid and vitamin B may reduce ischaemic heart disease through a homocysteine-lowering effect, see p.1941.

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PROPHYLAXIS OF MALIGNANT NEOPLASMS. There is evidence that a diet rich in fruit and vegetables is associated with a lower incidence of malignant disease, particularly of the respiratory and digestive tracts.[1] It has been hypothesised that some of the benefits of such a diet derive from the role of antioxidant vitamins such as the carotenoids and vitamins C and E in scavenging free radicals.[2,3] However, it is by no means certain that these are the only, or necessarily the most important, dietary components responsible for benefit, since components such as dietary fibre may also play a role. In addition, different antioxidants may vary in their properties and efficacy,[3,4] and the appropriate dosage remains largely conjectural, and perhaps as a result the evidence of benefit is often conflicting.

Several clinical studies of the use of **vitamin A** or **betacarotene** in the secondary or primary prevention of malignancy have been reported. Prolongation of disease-free interval in patients with various malignant neoplasms was reported in 1 study of betacarotene,[5] and others reported remission of oral leucoplakia in patients treated with betacarotene and vitamin A,[6,7] or betacarotene alone.[8] Vitamin A alone was reported to reduce the incidence of primary tobacco-related neoplasms in a study of patients treated surgically for lung cancer.[9] In a prospective, cohort study,[10] vitamin A intake, including preformed vitamin A and carotenoids, was associated with a reduced risk of breast cancer among smokers. However, other results have largely failed to substantiate any benefit for secondary prevention. No reduction in the incidence of new skin cancers,[11-13] or in malignant transformation of cervical dysplasia,[14] or in new colorectal adenomas[15] was reported in other studies. In a primary prevention study, a combination of betacarotene, vitamin E, and selenium was associated with a reduction in stomach and oesophageal cancers in a population at high risk of these cancers and with a diet low in micronutrients in China.[16] In contrast, other primary prevention studies have failed to show any benefit, and possibly some harm, from betacarotene supplements in well-nourished populations. A study in smokers[17-19] showed an increase in lung cancer and associated mortality in those receiving betacarotene, but not those receiving vitamin E. Similarly, an increased risk of lung cancer was noted in recipients of betacarotene with vitamin A in another study in individuals at high risk of lung cancer, and this study was stopped early as a result.[20,21] In a 6-year follow-up,[22] this risk was found to persist, albeit at lower and not statistically significant levels. A third study in healthy men found no benefit or harm for betacarotene supplements in terms of incidence of malignant neoplasms, including those of the lung;[23] a subgroup analysis of this study suggested that supplementation may reduce the risk of prostate cancer in those men with low baseline betacarotene levels.[24] Among subjects with colorectal adenoma,[25] who neither smoked nor drank alcohol, betacarotene supplementation was associated with a decrease in the risk of recurrent adenoma, but risk was increased in those who smoked or drank alcohol. A meta-analysis[26] of trials of antioxidant supplementation found that betacarotene had no anticarcinogenic effects on gastrointestinal cancer, and that given alone, it increased mortality. When given with vitamin A and E, mortality increased further. A further systematic review and meta-analysis[27] found that betacarotene supplementation was associated with an increased incidence of cancer among smokers, but not among non-smokers. There was also a trend towards increased cancer mortality with betacarotene supplementation.

Vitamin C has also been proposed for prevention of malignancy but there is no real evidence to justify it. It certainly appears to be ineffective as adjuvant therapy in the treatment of advanced malignancy,[28] and combination with betacarotene and vitamin E failed to show any effect in preventing colorectal adenoma.[15] At physiological concentrations vitamin C is an important antioxidant,[3] but while low serum ascorbic acid concentrations have been inversely related to cancer mortality,[29,30] supplementation is unlikely to be justified in anyone eating a balanced diet.[1]

There is epidemiological evidence that **vitamin D** has protective effects against the development of malignant neoplasms,[31] but evidence from controlled studies is scanty, and it is unclear whether supplementation, and if so to what degree, would be appropriate.

Vitamin E substances are also known to play an important antioxidant role in the body. *Animal* studies have suggested that they should inhibit tumour production, and the Chinese study mentioned above found combined antioxidant therapy including vitamin E to be of benefit in the primary prevention of stomach and oesophageal cancers.[16] Other studies in western populations have generally been disappointing; vitamin E had no effect on lung cancer incidence in those at risk,[17,18] and did not prevent the development of new colorectal adenomas.[15] In a study of patients with head and neck cancer, supplementation with vitamin E led to a higher incidence of second primary cancers and reduced cancer-free survival; patients on supplements had initially also been given betacarotene. While noting the fact that the study population were at high-risk for second primary cancers, the authors cautioned against the use of high-dose vitamin E supplements for cancer prevention.[32] There is also suggestion of increased all-cause mortality with high-dose vitamin E (see p.1993). However, further analysis of the lung-cancer study[33] suggests that vitamin E may have protected against prostate cancer. There is preliminary evidence that selenium (see p.1961) or vitamin E supplementation may reduce the risk of prostate cancer, and a large randomised study is underway to further investigate this.

Results from the Nurses' Health Study have indicated that prolonged use of multivitamins was associated with reduced risk of developing cancer of the colon.[34] This effect was thought to be due to the **folate** component and could be demonstrated after 15 years of use, but not after shorter-term ingestion. Dietary folate was also associated with a modest reduction in risk for colon cancer, and folic acid intake might reduce the risk of breast cancer, especially in those regularly consuming alcohol.[35,36] For the suggestion that folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p.1940.

While a diet involving frequent consumption of fruits and vegetables is likely to be beneficial,[1,37] others have also suggested that these associations may have been overstated, and that weight control and regular exercise should be prioritised.[35]

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31. Ingraham BA, *et al.* Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; **24:** 139–49.
32. Bairati I, *et al.* A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst* 2005; **97:** 481–8.
33. Heinonen OP, *et al.* Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* 1998; **90:** 440–6.
34. Giovannucci E, *et al.* Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med* 1998; **129:** 517–24.
35. Willett WC. Diet and cancer: one view at the start of the millennium. *Cancer Epidemiol Biomarkers Prev* 2001; **10:** 3–8.
36. Zhang S, *et al.* A prospective study of folate intake and the risk of breast cancer. *JAMA* 1999; **281:** 1632–7.
37. US Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med* 2003; **139:** 51–5.

Acesulfame Potassium *(BANM, rINNM)*

Acesulfam draselná sůl; Acesulfam potasowy; Acesulfame K; Acésulfame potassique; Acesulfamkalium; Acesulfamo kalio druska; Acesulfamo potásico; Acesulfamum kalicum; Aceszulfám-kálium; Asesulfaamikalium; E950; H73-3293; H-733293; Hoe-095K; Kalii Acesulfamum. 6-Methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide potassium.

Калия Ацесульфам

$C_4H_4KNO_4S$ = 201.2.

CAS — 55589-62-3.

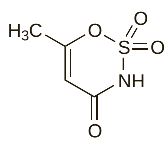

(acesulfame)

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Acesulfame Potassium). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone.

USNF 26 (Acesulfame Potassium). A white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

Profile

Acesulfame potassium is an intense sweetener about 200 times as sweet as sucrose. It is used in beverages, cosmetics, pharmaceuticals, and foods and does not appear to be affected by cooking.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Equalsweet; Genser Sweet; Rondo Sweet; ***Chile:*** Marco Sweet Light; ***UK:*** Sweet 'n Low; ***Venez.:*** Hermesetas Gold; Sweet 'n' Low†.

Alanine *(USAN, rINN)*

A; Ala; Alaniini; Alanin; Alanina; Alaninas; L-Alanine; Alaninum; NSC-206315. L-2-Aminopropionic acid.

Аланин

$C_3H_7NO_2$ = 89.09.

CAS — 56-41-7.

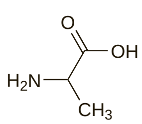

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Alanine). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Alanine). White, odourless, crystals or crystalline powder. Freely soluble in water; slightly soluble in 80% alcohol; insoluble in ether. pH of a 5% solution in water is between 5.5 and 7.0. Store in airtight containers.

Profile

Alanine is an aliphatic non-essential amino acid. It is used as a dietary supplement. The dipeptide *N*(2)-L-alanyl-L-glutamine is used similarly.

Hypoglycaemia. References to the investigational use of alanine in the management of insulin-induced hypoglycaemia.[1-4]

1. Wiethop BV, Cryer PE. Glycemic actions of alanine and terbutaline in IDDM. *Diabetes Care* 1993; **16:** 1124–30.
2. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; **16:** 1131–6.
3. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
4. Evans ML, *et al.* Alanine infusion during hypoglycaemia partly supports cognitive performance in healthy human subjects. *Diabet Med* 2004; **21:** 440–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Abufene; ***Singapore:*** Abufene.

Multi-ingredient: ***Arg.:*** Normoprost Compuesto; ***Ital.:*** Chetonex; ***Spain:*** Tebetane Compuesto.

Alitame *(USAN)*

CP-54802. (3*S*)-Amino-*N*-{(1*R*)-1-[(2,2,4,4-tetramethyl-3-thietanyl) carbamoyl] ethyl} succinamic acid hydrate.

$C_{14}H_{25}N_3O_4S.2\frac{1}{2}H_2O$ = 376.5.

CAS — 80863-62-3 (anhydrous alitame); 99016-42-9 (alitame hydrate).

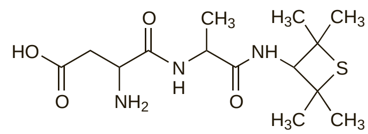

(anhydrous alitame)

Profile

Alitame is an intense sweetener used in foods. It is about 2000 times sweeter than sucrose.

Arginine *(rINN)*

Arg; Argininii; Arginin; Arginina; Argininas; L-Arginine; Argininum; R. L-2-Amino-5-guanidinovaleric acid.

Аргинин

$C_6H_{14}N_4O_2$ = 174.2.

CAS — 74-79-3.

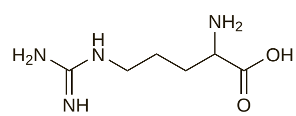

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Arginine). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Arginine). White, practically odourless crystals. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Arginine Aspartate

Arginiiniaspartaatti; Arginina, aspartato de; Argininaspartat; Arginin-aspartát; Arginine, aspartate d'; Arginini aspartas; Arginino aspartatas; Asparginінum. (2*S*)-2-Amino-5-guanidinopentanoic acid (2*S*)-2-aminobutanedioate.

$C_{10}H_{21}N_5O_6$ = 307.3.

CAS — 7675-83-4.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Arginine Aspartate). White or almost white granules or powder. Very soluble in water, practically insoluble in alcohol and in dichloromethane.

Arginine Glutamate *(BAN, USAN, rINNM)*

Arginine, Glutamate d'; Arginini Glutamas; Glutamato de arginina. L-Arginine L-glutamate.

Аргинина Глутамат

$C_6H_{14}N_4O_2,C_5H_9NO_4$ = 321.3.

CAS — 4320-30-3.

ATC — A05BA01.

ATC Vet — QA05BA01.

Arginine Hydrochloride *(USAN, rINNM)*

Arginiinihydrokloridi; Arginine, chlorhydrate d'; L-Arginine Monohydrochloride; Arginin-hidroklorid; Arginin-hydrochlorid; Argininhydroklorid; Arginini hydrochloridum; Arginino hidrochloridas; Hidrocloruro de arginina.

Аргинина Гидрохлорид

$C_6H_{14}N_4O_2,HCl$ = 210.7.

CAS — 1119-34-2.

ATC — B05XB01.

ATC Vet — QB05XB01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Arginine Hydrochloride). A white or almost white crystalline powder, or colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Arginine Hydrochloride). White, practically odourless, crystals or crystalline powder. Freely soluble in water.

Adverse Effects and Precautions

Nausea, vomiting, flushing, headache, numbness, and local venous irritation may occur if arginine solutions are infused too rapidly. Elevated plasma-potassium concentrations have been reported in uraemic patients and arginine should therefore be used with caution in patients with renal disease or anuria. Arginine hydrochloride should be given cautiously to patients with electrolyte disturbances as its high chloride content could lead to the development of hyperchloraemic acidosis.

Extravasation. Full-thickness skin necrosis has been reported[1,2] after extravasation of a 10% solution of arginine hydrochloride. Both osmotic and local hyperkalaemic effects have been proposed as a mechanism for the injury.[1]

1. Bowlby HA, Elanjian SI. Necrosis caused by extravasation of arginine hydrochloride. *Ann Pharmacother* 1992; **26:** 263–4.
2. Salameh Y, Shoufani A. Full-thickness skin necrosis after arginine extravasation—a case report and review of literature. *J Pediatr Surg* 2004; **39:** E9–E11.

Hyperkalaemia. Two alcoholic patients with severe liver disease and moderate renal insufficiency developed severe hyperkalaemia when given arginine hydrochloride and one died.[1] Both patients had received a total of 300 mg of spironolactone some time before arginine hydrochloride, but the contribution of spironolactone to the hyperkalaemia was not known. In a study to investigate the mechanism of metabolic changes due to arginine, plasma-potassium concentrations were found to be significantly higher in diabetic subjects than those for normal subjects, leading the authors to suppose that while arginine-induced hyperkalaemia may be promoted by low insulin blood levels, it could not be attributed to glucagon, pH changes, or aldosterone inhibition.[2]

In another fatal case due to an overdose of arginine,[3] a 21-month-old girl developed an acute metabolic acidosis with transient but severe hyponatraemia, and irreversible brain death; no hyperkalaemia was observed. Unlike the previously reported case, the patient had normal renal function, and the authors supposed the absence of hyperkalaemia to be due to a rapid increase in renal potassium excretion.

1. Bushinsky DA, Gennari FJ. Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 1978; **89:** 632–4.
2. Massara F, *et al.* The risk of pronounced hyperkalaemia after arginine infusion in the diabetic subject. *Diabete Metab* 1981; **7:** 149–53.
3. Gerard JM, Luisiri A. A fatal overdose of arginine hydrochloride. *J Toxicol Clin Toxicol* 1997; **35:** 621–5.

Hypersensitivity. There are 2 reports of anaphylactic reactions shortly after the start of infusions of arginine 5 or 10% given to test growth-hormone output.[1,2] Anaphylaxis to arginine was considered to be a very rare event and only one other apparent allergic reaction had been reported to the manufacturers.

1. Tiwary CM, *et al.* Anaphylactic reaction to arginine infusion. *N Engl J Med* 1973; **288:** 218.
2. Resnick DJ, *et al.* Case report of an anaphylactoid reaction to arginine. *Ann Allergy Asthma Immunol* 2002; **88:** 67–8.

Myocardial infarction. A placebo-controlled trial investigated whether the addition of arginine to standard therapy after myocardial infarction would decrease vascular stiffness and improve left ventricular function. The study was stopped early due to an increased number of deaths in the arginine group. The authors commented that, while the results could be due to chance, nevertheless arginine should not be given to patients after a myocardial infarction.[1]

1. Schulman SP, *et al.* -Arginine therapy in acute myocardial infarction: the Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; **295:** 58–64.

Uses and Administration

Arginine is a basic amino acid that is essential for infant growth. It is used as a dietary supplement.

Arginine stimulates the release of growth hormone by the pituitary gland and may be used instead of, or in addition to, other tests such as insulin-induced hypoglycaemia, for the evaluation of growth disorders; false-positive and false-negative results are relatively common and evaluation therefore should not be made on the basis of a single arginine test. It is used as a 10% solution of the hydrochloride in usual doses of 30 g by intravenous infusion given over 30 minutes; children should be given 500 mg/kg.

Arginine is used in certain conditions accompanied by hyperammonaemia; for further details see below.

Arginine hydrochloride has also been used as an acidifying agent. In severe metabolic alkalosis intravenous doses have been calculated by the formula:

$$\text{intravenous dose (in grams)} = \text{desired decrease in plasma-bicarbonate concentration (mEq or mmol/litre)} \times \text{[patient's body-weight (in kg)/9.6]}$$

In forced acid diuresis to hasten drug elimination after overdose a suggested dose has been 10 g intravenously over 30 minutes. However, this has the potential to cause myoglobinuria with acute renal failure, and is rarely used.

Arginine may also be used in the form of the acetylasparaginate, aspartate, citrate, glutamate, oxoglurate, tidiacicate (thiazolidine-2,4-dicarboxylate), and timonacicate (thiazolidine-4-carboxylate). Formulation as an arginine salt is used to improve the solubility of a number of drugs, notably analgesics and antibacterials.

◊ References.

1. Tapiero H, *et al.* Arginine. *Biomed Pharmacother* 2002; **56:** 439–45.
2. Tong BC, Barbul A. Cellular and physiological effects of arginine. *Mini Rev Med Chem* 2004; **4:** 823–32.

Hyperammonaemia. Hyperammonaemia is a characteristic feature of inborn errors of the urea cycle, caused by defects in the enzymes carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (causing hyperargininaemia), or *N*-acetylglutamate synthase (NAGS).[1,2] During the urea cycle, waste ammonia, in the form of the ammonium ion, is normally condensed with bicarbonate and ATP to form carbamoyl phosphate which undergoes several more reactions, including one leading to the synthesis of arginine, and ultimate transformation to urea for excretion. Thus, in defects of this cycle ammonia accumulates and arginine synthesis is deficient.[3] Hyperammonaemia is most severe when the enzyme defect occurs in the early steps of the urea cycle, such as in CPS or OTC deficiency, and is less severe at later stages, as in ASL or arginase deficiency.[2] Hyperammonaemia is often associated with respiratory alkalosis in patients with urea cycle disorders.[3]

The basis of treatment is dietary protein restriction, to decrease the requirement for waste nitrogen synthesis,[4] and the use of drugs to stimulate alternative pathways of waste nitrogen excretion.[5,6] These include arginine, citrulline, sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. In the initial management of severe hyperammonaemia, haemodialysis is preferred over peritoneal dialysis because it is more effective.[3,7]

Arginine supplements are given except in hyperargininaemia.[5,7] Citrulline may be used in some cases instead;[8] it may be useful for CPS and OTC deficiency (in doses of about 170 mg/kg daily or 3.8 g/m^2 daily),[5,6,9] but it is not recommended for patients with ASS or ASL deficiency, as levels of citrulline are already elevated.[5,10] Some recommend citrulline with arginine in acute hyperammonaemia to aid additional removal of nitrogen.[9] For the treatment of acute hyperammonaemia, some recommend a loading dose of arginine 600 mg/kg over 90 minutes pending definitive diagnosis.[3,10] Alternatively, a loading dose of 200 mg/kg or 4 g/m^2 has been advocated for CPS or OTC deficiency,[6,9,10] and 600 mg/kg or 12 g/m^2 for ASS or ASL deficiency.[6,9,10] The same dose as the loading dose is then given over 24 hours, as a constant maintenance infusion,[6,9,10] until conversion to oral medication is made.[10] For long-term management of ASS or ASL deficiency, doses of arginine ranging from 400 to 700 mg/kg daily have been recommended.[5,6,9,10]

Patients also receive treatment with sodium benzoate and sodium phenylacetate[6,10] or sodium phenylbutyrate.[5,6] ASL deficiency can be managed with protein restriction and arginine alone,[6,11] although some still advocate the use of sodium phenylbutyrate.[5,8] When sodium benzoate is conjugated with glycine and excreted as hippuric acid it provides an alternative pathway of nitrogen excretion, while sodium phenylacetate and sodium phenylbutyrate provide a second and even more effective pathway by conjugation with glutamine.[6,7,10] Some consider intravenous sodium benzoate and sodium phenylacetate the treatment of choice in acute hyperammonaemia; sodium phenylbutyrate is recommended for chronic management.[9] In a 25-year, open-label, uncontrolled study, intravenous therapy with sodium phenylacetate and sodium benzoate clearly improved survival in patients with acute hyperammonaemia, with an overall survival rate of 84%; survival was also related to peak plasma ammonium concentration and age. Haemodialysis was also used to control hyperammonaemia, especially in neonates and older patients who were less responsive to intravenous therapy.[12]

It has been suggested that carnitine supplementation (at 100 mg/kg daily[9] either orally or intravenously) should be added to minimise neurological symptoms and toxicity, but its value is uncertain.[4,13] Low carnitine levels have been reported to be uncommon in patients with urea cycle disorders and, in patients treated with sodium benzoate, benzoyl carnitine may form, negating any potential benefit from carnitine supplementation.[8]

Liver transplantation (p.1815) may achieve long-term correction of urea cycle disorders, even in the very young patient, and gene replacement therapy is under investigation.[14]

Hyperammonaemia and hepatic encephalopathy (p.1697) can also arise from other causes[7,13] for which arginine may not be advocated. Carglumic acid (p.2277) is the treatment of choice for patients with hyperammonaemia arising from NAGS deficiency.

1. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S6–S10.
2. Shih VE. Alternative-pathway therapy for hyperammonemia. *N Engl J Med* 2007; **356:** 2321–2.
3. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S1–S5.
4. Leonard JV. The nutritional management of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S40–S45.
5. Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S56–S61.
6. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl): S46–S55.
7. Leonard JV, Morris AAM. Urea cycle disorders. *Semin Neonatol* 2002; **7:** 27–35.
8. Wilcken B. Problems in the management of urea cycle disorders. *Mol Genet Metab* 2004; **81** (suppl): S86–S91.
9. Kleppe S, *et al.* Urea cycle disorders. *Curr Treat Options Neurol* 2003; **5:** 309–19.
10. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S30–S39.
11. Brusilow SW, *et al.* Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. *N Engl J Med* 1984; **310:** 1630–4.
12. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.
13. Leonard JV, Morris AAM. Inborn errors of metabolism around time of birth. *Lancet* 2000; **356:** 583–7.
14. Lee B, Goss J. Long-term correction of urea cycle disorders. *J Pediatr* 2001; **138** (suppl): S62–S71.

Hypotensive action. Arginine is the physiological precursor of nitric oxide and this has been suggested as an explanation for the hypotensive effect that has been reported in healthy subjects[1-3] and hypertensive patients[1,4] given infusions of arginine, although effects unrelated to nitric oxide generation cannot be excluded.[4]

Oral arginine has also been reported to significantly decrease mean systolic blood pressure in hypertensive patients,[5] in patients on haemodialysis, and in renal transplant recipients.[6] In patients with essential hypertension, a single dose of arginine by mouth had no effect on blood pressure, although it did improve endothelium-dependent flow-mediated dilatation of the brachial artery compared with placebo.[7] In patients with pulmonary hypertension, short-term use of arginine has reduced pulmonary arterial pressure.[8-10]

In pregnant women with pre-eclampsia (see Hypertension, p.1171), plasma-arginine concentrations were found to be markedly reduced compared with control subjects.[11] Arginine infusions of 20 g, given to women with mild to moderate gestational hypertension,[12] and 30 g given to pre-eclamptic women,[13] significantly reduced systolic and diastolic blood pressure, with no adverse effect on fetal heart rate in the one study.[12] In a study of pre-eclamptic women given arginine 12 g daily for 2 days by mouth, no significant differences in diastolic blood pressure were seen compared with those receiving placebo.[14] However, in another study of pre-eclamptic women given 3 g arginine daily for 3 weeks, systolic, diastolic and mean arterial pressure were significantly reduced compared with those taking placebo.[15]

Because of apparent improvement in endothelial function with arginine, some interest has surrounded its potential role in other cardiovascular diseases, such as coronary artery disease and heart failure.[16] Decrease in plasma-cholesterol concentrations has also been reported in 2 hypercholesterolaemic patients given arginine infusions.[17] However, long-term supplementation was found not to be helpful (and possibly harmful) in patients with peripheral arterial disease,[18] and arginine therapy has been implicated in increased mortality when given to patients after myocardial infarction (see under Adverse Effects and Precautions, above).

1. Nakaki T, *et al.* L-arginine-induced hypotension. *Lancet* 1990; **336:** 696.
2. Hishikawa K, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 683–4.
3. Petros AJ, *et al.* L-arginine-induced hypotension. *Lancet* 1991; **337:** 1044–5.
4. Pedrinelli R, *et al.* Pressor, renal and endocrine effects of -arginine in essential hypertensives. *Eur J Clin Pharmacol* 1995; **48:** 195–201.
5. Palloshi A, *et al.* Effect of oral -arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. *Am J Cardiol* 2004; **93:** 933–5.
6. Kelly BS, *et al.* Oral arginine improves blood pressure in renal transplant and hemodialysis patients. *J Parenter Enteral Nutr* 2001; **25:** 194–202.
7. Lekakis JP, *et al.* Oral -arginine improves endothelial dysfunction in patients with essential hypertension. *Int J Cardiol* 2002; **86:** 317–23.
8. Mehta S, *et al.* Short-term pulmonary vasodilation with -arginine in pulmonary hypertension. *Circulation* 1995; **92:** 1539–45.
9. Nagaya N, *et al.* Short-term oral administration of -arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med* 2001; **163:** 887–91.
10. Morris CR, *et al.* Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003; **168:** 63–9.
11. D'Aniello G, *et al.* Plasma -arginine is markedly reduced in pregnant women affected by preeclampsia. *J Chromatogr B Biomed Sci Appl* 2001; **753:** 427–31.
12. Neri I, *et al.* Effects of acute L-arginine infusion on non-stress test in hypertensive pregnant women. *J Matern Fetal Neonatal Med* 2004; **16:** 23–6.
13. Facchinetti F, *et al.* -Arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. *J Soc Gynecol Investig* 1999; **6:** 202–7.
14. Staff AC, *et al.* Dietary supplementation with -arginine or placebo in women with pre-eclampsia. *Acta Obstet Gynecol Scand* 2004; **83:** 103–7.
15. Rytlewski K, *et al.* Effects of prolonged oral supplementation with -arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest* 2005; **35:** 32–7.
16. Cheng JWM, Balwin SN. L-arginine in the management of cardiovascular diseases. *Ann Pharmacother* 2001; **35:** 755–64.
17. Korbut R, *et al.* Effect of -arginine on plasminogen-activator inhibitor in hypertensive patients with hypercholesterolemia. *N Engl J Med* 1993; **328:** 287–8.
18. Wilson AM, *et al.* L-arginine supplementation in peripheral arterial disease: no benefit and possible harm. *Circulation* 2007; **116:** 188–95.

Necrotising enterocolitis. A systematic review[1] considered that although there was evidence suggesting that supplementation of the feed of premature neonates with arginine could prevent the development of necrotising enterocolitis (p.173), it was insufficient to recommend the practice without further study.

1. Shah P, Shah V. Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 24/06/08).

Preparations

BP 2008: Arginine Hydrochloride Intravenous Infusion;
USP 31: Arginine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Inteligen†; Laclorene; ***Austria:*** Sangenor; ***Braz.:*** Reforgan; Targifor; ***Fr.:*** Dynamisan; Energitum†; Eucol; Pargine; Sargenor; Tiadilon; ***Ger.:*** Eubiol†; ***Israel:*** Carginine†; ***Ital.:*** Bioarginina; Dynamisan; Sargenor; Sulfile†; ***Malaysia:*** Arginitric; ***Port.:*** Asparten; Bio-Energol Plus; Pan-Astenico R; Sargenor; Sulfile; ***Spain:*** Potenciator; Sargenor; Sargisthene; Sorbenor; ***Switz.:*** Dynamisan; ***USA:*** R-Gene.

Multi-ingredient: ***Arg.:*** Acrea; Holomagnesio Vital; Inteligen Ginseng†; ***Austria:*** Leberinfusion; Rocmaline; ***Braz.:*** Dinavital C; Ornihepat†; Ornitargin; Targifor C; ***Chile:*** Ureadin 30; ***Cz.:*** Citrargine†; ***Fr.:*** Arginotri-B; Citrarginine†; Epuram†; Fastenyl; Hepagrume; Hepargitol; Rocmaline; Sargenor a la Vitamine C; ***Ger.:*** Glutarsin E†; Polilevo N†; ***Hung.:*** Glutarsin E; Rocmalat†; ***Indon.:*** Sirec; ***Ital.:*** Calciofix; Glutargin†; Ipoazotal Complex; Ipoazotal†; Isoram; Linfoiodine; Polilevo†; Sargenor Plus; Somatron; Tonoplus†; Vitasprint Complex†; ***Spain:*** Dynamogen; Sanieb†; ***Switz.:*** Activital Forte; Arginotri-B; Vitasprint Complex.

Arrowroot

Amylum Marantae; Araruta; Arruruz; Maranta; Pfeilwurzelmehl; Sagú del monte; Yuquilla silvestre.

Profile

Arrowroot consists of the starch granules of the rhizomes of *Maranta arundinacea* (Marantaceae). It has the general properties of starch (p.1968). It has been used as a suspending agent in the preparation of barium meals and has sometimes been used in place of starch in tablet manufacture.

Diarrhoea. In a pilot study in 11 patients with irritable bowel syndrome given 10 mL arrowroot powder three times daily for 1 month, 4 patients reported an improvement in diarrhoea.[1]

1. Cooke C, *et al.* Arrowroot as a treatment for diarrhoea in irritable bowel syndrome patients: a pilot study. *Arq Gastroenterol* 2000; **37:** 20–4.

Asparagine Monohydrate

L-α-Aminosuccinamic Acid Monohydrate; Asparagiinimonohydraatti; Asparagin monohydrát; Asparagina, monohidrato de; Asparaginas monohidratas; L-Asparagine Monohydrate; Asparagine monohydratée; Asparaginmonohydrat; Asparaginum monohydricum; Asparamide; Aspartamic acid; Aspartic acid beta-amide; N (asparagine); NSC-82391. (2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

$C_4H_8N_2O_3,H_2O = 150.1.$

CAS — 70-47-3 (anhydrous asparagine); 5794-13-8 (asparagine monohydrate).

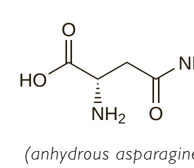

(anhydrous asparagine)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF*, which specifies the anhydrous form or the monohydrate.

Ph. Eur. 6.2 (Asparagine Monohydrate). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.0.
USNF 26 (Asparagine). It is anhydrous or contains one molecule of water of hydration. A white, crystalline powder or white crystals. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. Protect from light.

Profile

Asparagine is a non-essential amino acid.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Acutil Fosforo; Neuralfa; Tiofort; ***Spain:*** Agudil.

Aspartame *(BAN, USAN, rINN)*

APM; Aspartaami; Aspartam; Aspartamas; Aspartamo; Aspartamum; Aszpartám; E951; SC-18862. Methyl *N*-L-α-aspartyl-L-phenylalaninate; 3-Amino-*N*-(α-methoxycarbonylphenethyl)succinamic acid; *N*-L-α-aspartyl-L-phenylalanine, 1-methyl ester.

Аспартам

$C_{14}H_{18}N_2O_5$ = 294.3.
CAS — 22839-47-0.

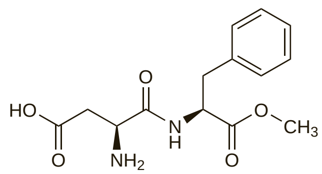

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Aspartame). A white or almost white, slightly hygroscopic, crystalline powder. Sparingly or slightly soluble in water and in alcohol; practically insoluble in dichloromethane and in *n*-hexane. Store in airtight containers.
USNF 26 (Aspartame). White, odourless, crystalline powder having a sweet taste. Sparingly soluble in water; slightly soluble in alcohol. pH of a 0.8% solution in water is about 5.

Stability. In the presence of moisture aspartame hydrolyses to form aspartylphenylalanine and a diketopiperazine derivative, with a resulting loss of sweetness.

Adverse Effects and Precautions

Excessive use of aspartame should be avoided by patients with phenylketonuria since one of its metabolic products is phenylalanine. Aspartame's sweetness is lost during prolonged cooking.

Adverse effects. The safety and adverse effects of aspartame as a pharmaceutical excipient have been reviewed.[1,2]

Aspartame is hydrolysed in the gastrointestinal tract to methyl alcohol, aspartic acid, and phenylalanine. However, even with extraordinary consumption, methyl alcohol toxicity stemming from aspartame use is extremely unlikely. Aspartate concentrations in blood do not rise significantly after a very large dose (50 to 100 mg/kg) and therefore toxicity related to aspartate is also not expected to occur. Despite the similarity of aspartate to glutamate, studies in glutamate-sensitive persons have shown that they are not affected by aspartame consumption. Plasma concentrations of phenylalanine are also unlikely to be markedly elevated after modest consumption of aspartame by healthy persons but persons with phenylketonuria should avoid or limit their use of aspartame.

A number of adverse effects have been reported[1,2] after the use of aspartame, either as spontaneously recorded complaints from consumers or as published case reports in the medical literature. Most frequently reported problems have been headache, neuropsychiatric or behavioural symptoms, seizures, gastrointestinal symptoms, and hypersensitivity or dermatological symptoms. Available data do not provide evidence for serious widespread health consequences attendant upon the use of aspartame but it would appear that certain individuals may have an unusual sensitivity to the product. A safety review[3] by the European Commission Scientific Committee on Food (ECSCF) concluded that no causal link could be established between the consumption of aspartame and the occurrence of epilepsy or seizures, or cognition, mood and behaviour; this included individuals considered sensitive to aspartame.

Studies have confirmed aspartame's lack of effect on children's behaviour or cognitive function.[4,5]

An increased incidence of brain cancer was postulated to be related to aspartame use in one report;[6] however, the FDA[7] and the ECSCF[3] maintained that the available evidence did not support an association. Multiple malignancies have been reported[8] in *rats* given doses lower than the current acceptable daily intake of 40 or 50 mg/kg. The European Food Safety Authority assessed this study and concluded,[9] on the basis of all current available evidence, that the increased incidence of cancers in the *rats* was unrelated to aspartame treatment, and that there was no need to further review the safety of aspartame, nor to revise the established acceptable daily intake for aspartame of 40 mg/kg.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive' ingredients in drug products (part II). *Med Toxicol* 1988; **3:** 209–40.
2. American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; **99:** 268–78.
3. European Commission Health and Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food: update on the safety of aspartame (expressed on 4 December 2002). Available at: http://europa.eu.int/comm/food/fs/sc/scf/out155_en.pdf (accessed 08/11/05)
4. Shaywitz BA, *et al.* Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics* 1994; **93:** 70–5.
5. Wolraich ML, *et al.* Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *N Engl J Med* 1994; **330:** 301–7.
6. Olney JW, *et al.* Increasing brain tumor rates: is there a link to aspartame? *J Neuropathol Exp Neurol* 1996; **55:** 1115–23.
7. Anonymous. Aspartame: no apparent link with brain tumours. *WHO Drug Inf* 1997; **11:** 18–19.
8. Soffritti M, *et al.* First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006; **114:** 379–85.
9. European Food Safety Authority. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a new long-term carcinogenicity study on aspartame. *EFSA J* 2006; **356** 1–44. Available at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_op_ej356_aspartame_en1,2.pdf (accessed 03/03/08)

Breast feeding. Aspartame 50 mg/kg given orally to healthy women resulted in small but significant increases in breast milk aspartate, phenylalanine, and tyrosine concentrations.[1] However, it was noted that these levels were similar to postprandial milk samples and were unlikely to impact upon total amounts of amino acids ingested by the infant. Furthermore, the dose of aspartame given in the study was considerably higher than the projected intake of about 7.5 to 8.5 mg/kg daily, assuming all sucrose intake were replaced by aspartame, and no aspartame abuse. Nonetheless, the American Academy of Pediatrics[2] considers that caution is required when aspartame is ingested by mothers where either the mother or breast-fed infant has phenylketonuria.

1. Stegink LD, *et al.* Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose. *J Nutr* 1979; **109:** 2173–81.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/11/04)

Pharmacokinetics

Aspartame is hydrolysed in the gastrointestinal tract to its 3 primary constituents, methyl alcohol, aspartic acid, and phenylalanine.

Uses

Aspartame is an intense sweetening agent about 180 to 200 times as sweet as sucrose. It is used in foods, beverages, and pharmaceuticals. Each g provides about 17 kJ (4 kcal).

Sickle-cell disease. There is some preliminary evidence that aspartame may have beneficial effects in sickle-cell disease.[1]

1. Manion CV, *et al.* Aspartame effect in sickle cell anemia. *Clin Pharmacol Ther* 2001; **69:** 346–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nutrasweet†; Slap; ***Braz.:*** Dietacil; Dietamina†; Doce Vida†; Finn; ***Canad.:*** Equal; ***Chile:*** Marco Sweett†; Modellsweet†; Naturalist; Originalsweet; Ridersweet†; Valsweet; ***India:*** Lo-Kal†; Low-Cal†; ***Ital.:*** Aspartina; Futura; Suaviter; ***NZ:*** Equal; ***Port.:*** Dolcevita†; ***Rus.:*** Sugarfree (Шугафри); ***Thai.:*** Equal†; Espar; ***Turk.:*** Aspartil; Canderel; Demi Canderel; Diyet Tat; Hermesetas Gold; Nutra-Tat; Sanpa; ***Venez.:*** Dolsiprim†; Dulcolite†; Dulcosil; Edul; Equal†; Hermesetas Gold.

Multi-ingredient: ***Arg.:*** Chuker; Equalsweet; Genser Sweet; Rondo Sweet; Semble; Sucaryl; ***Chile:*** Marco Sweet Light; Nutrasweet†; ***UK:*** Sweet 'n Low; ***Venez.:*** Hermesetas Gold; Sweet 'n' Low†.

Aspartame Acesulfame

L-Phenylalanine, L-α-aspartyl-2-methyl ester, compound with 6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide (1:1).

$C_{18}H_{23}O_9N_3S$ = 457.5.
CAS — 106372-55-8.

Pharmacopoeias. In *USNF.*
USNF 26 (Aspartame Acesulfame). White, odourless, crystalline powder. Slightly soluble in water and in alcohol. It contains not less than 63.0% and not more than 66.0% of aspartame, calculated on the dried basis, and not less than 34.0% and not more than 37.0% of acesulfame, calculated as the acid form on the dried basis.

Profile

Aspartame acesulfame is a compound of aspartame (see above) and acesulfame (see p.1928), and is used similarly in foods. It is an intense sweetener about 350 times as sweet as sucrose.

Aspartic Acid *(USAN, rINN)*

Acide aspartique; Ácido aspártico; Acidum asparticum; Asp; Asparagiinihappo; Asparaginsyra; L-Aspartic Acid; Asparto rūgštis; Aszparaginsav; D; Kwas asparaginowy; Kyselina asparagová. L-Aminosuccinic acid.

Аспарагиновая Кислота

$C_4H_7NO_4$ = 133.1.
CAS — 56-84-8.

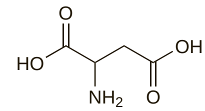

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.
USP 31 (Aspartic Acid). A white or almost white crystalline powder, or colourless crystals. Slightly soluble in water; practically insoluble in alcohol and in ether; soluble in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Aspartic acid is a non-essential amino acid. It is used as a dietary supplement.

Betacarotene *(BAN, rINN)*

all-*trans*-β-Carotene; Beetakaroteeni; Beta Carotene *(USAN)*; Bétacarotène; Betacaroteno; Betacarotenum; Betakaroten; Betakarotenas; Bétakarotin; E160(a); Provitamin A. β,β-Carotene; (*all-E*)-1,1′-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexene].

Бетакаротен

$C_{40}H_{56}$ = 536.9.
CAS — 7235-40-7.
ATC — A11CA02; D02BB01.
ATC Vet — QA11CA02; QA11HA90; QD02BB01.

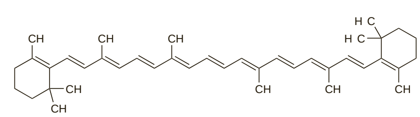

Description. Carotene exists in 3 isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and *animals*. Of the 3 isomers of carotene, the *beta* compound is more active than the *alpha-* or *gamma-*isomers. The vitamin A activity of plants is due to the presence of *alpha-*, *beta-*, and *gamma-*carotenes and to kryptoxanthine; that of *animal* tissues is due to both vitamin A and carotene, while fish-liver oils contain vitamin A but no carotene.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Betacarotene). A brown-red or brownish-red crystalline powder. Practically insoluble in water and in dehydrated alcohol; slightly soluble in cyclohexane. It is sensitive to air, heat and light, especially in solution. Store in airtight containers at a temperature not exceeding 25°. Protect from light.
USP 31 (Beta Carotene). Red or reddish-brown to violet-brown crystals or crystalline powder. Insoluble in water, in acids, and in alkalis; practically insoluble in alcohol and in methyl alcohol; soluble in carbon disulfide, in chloroform, and in benzene; sparingly soluble in ether, in petroleum spirit, and in vegetable oils. Store in airtight containers. Protect from light.

Units

Vitamin A activity in foods is expressed in terms of retinol equivalents: 6 micrograms of betacarotene represents 1 retinol equivalent (or 10 of the former International units for provitamin A—see p.1971).

Adverse Effects and Precautions

Loose stools may occasionally occur during treatment with betacarotene and the skin may assume a slightly yellow discoloration. Bruising, dizziness, and arthralgia have been reported rarely.

Excessive intake of betacarotene does not result in hypervitaminosis A (see Pharmacokinetics, below).

Carcinogenicity. For reference to studies finding an increased incidence of lung cancers in individuals given betacarotene supplements to protect against malignancy, see under Prophylaxis of Malignant Neoplasms, p.1927.

Effects on mortality. A systematic review of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies found that betacarotene, used either singly or with other antioxidants, significantly increased all-cause mortality.[1] In another review and meta-analysis, betacarotene supplementation showed a trend towards increased cancer mortality.[2]

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
2. Bardia A, *et al.* Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc* 2008; **83:** 23–34.

Effects on the skin. Yellow pigmentation of the skin may result from an unusually high consumption of carrots or other source of carotene,[1] or from a defect in the enzyme that normally metabolises betacarotene to vitamin A.[2] Hypercarotenaemia can be distinguished from jaundice by the fact that the sclerae retain their normal white colour. Pigmentation occurs first on the palms and soles and may extend to the nasolabial folds. Although it has been stated that the condition is harmless as the body converts carotene to retinol only as required,[1] others consider that longstanding hypercarotenaemia can have clinical sequelae:[2] neutropenia[3] and amenorrhoea[4] have been reported to be associated with the condition.

1. Sharman IM. Hypercarotenaemia. *BMJ* 1985; **290:** 95.
2. Vaughan Jones SA, Black MM. Metabolic carotenaemia. *Br J Dermatol* 1994; **131:** 145.
3. Shoenfeld Y, *et al.* Neutropenia induced by hypercarotenaemia. *Lancet* 1982; **i:** 1245.
4. Kemmann E, *et al.* Amenorrhoea associated with carotenemia. *JAMA* 1983; **249:** 926–9.

Pharmacokinetics

Gastrointestinal absorption of betacarotene depends on the presence of bile and is increased by dietary fat. About 20 to 60% of betacarotene is metabolised to retinol in the intestinal wall, and a small amount is converted to vitamin A in the liver. The proportion of betacarotene converted to vitamin A decreases as the intake of betacarotene increases, and high doses of betacarotene do not lead to abnormally high serum concentrations of vitamin A. Unchanged betacarotene is distributed to various tissues including fat, the adrenal glands, and ovaries.

◊ References.

1. Wang X-D. Review: absorption and metabolism of β-carotene. *J Am Coll Nutr* 1994; **13:** 314–25.

Human Requirements

Carotenes, of which betacarotene has the highest activity, are major dietary sources of vitamin A—see p.1972.

UK and US recommended dietary intake. There is currently no UK dietary reference value (see p.1925) for betacarotene, and in the USA recommended dietary allowances or dietary reference intakes (see p.1925) have not been set. However, the Expert Group on Vitamins and Minerals[1] has established a safe upper level (SUL) for betacarotene of 7 mg daily, or about 0.11 mg/kg daily for a 60-kg adult.

1. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Uses and Administration

Betacarotene is a carotenoid precursor of vitamin A (p.1971). In the *treatment* of vitamin A deficiency, vitamin A is preferred to betacarotene. However, betacarotene has been used for the *prevention* of vitamin A deficiency at a dose of 6 to 15 mg daily for adults and 3 to 6 mg daily for children.

Betacarotene may be given by mouth to reduce the severity of photosensitivity reactions in patients with erythropoietic protoporphyria (see also Porphyria, below). Doses are in the range of 30 to 300 mg daily for adults and 30 to 150 mg daily for children, depending upon severity; they may be taken as either single daily doses or divided doses but should preferably be taken with meals. The protection offered by betacarotene is not total and generally 2 to 6 weeks of treatment resulting in a yellow coloration of palms and soles is necessary before patients should attempt to increase their exposure to sunlight.

Betacarotene and other carotenoids (alphacarotene and gammacarotene) are used as colouring agents for foods and medicinal products.

Betacarotene has antoxidant activity and has been studied for its possible protective benefit in a number of disorders (but see Effects on Mortality, above).

Age-related macular degeneration. A study in patients with age-related macular degeneration (p.785) indicated that the risk of developing this disorder (a leading cause of irreversible blindness among elderly persons) was markedly decreased amongst those with the highest dietary carotenoid intake;[1] in particular, lutein and zeaxanthin, or green leafy vegetables (which contain high concentrations of these carotenoids) were associated with a lower risk. Increasing the dietary intake of these carotenoids may be of benefit in reducing the development of this disorder. Despite this, systematic reviews found no evidence that antoxidant vitamin and mineral supplementation would either prevent[2,3] or delay the onset of macular degeneration. However, one study[4] has shown modest benefit from vitamin C, vitamin E, betacarotene, and zinc supplementation in those with moderate to severe signs of the disease. A systematic review to assess the effects of antoxidant vitamin or mineral supplementation on the progression of age-related macular degeneration included this study, and noted that the generalisability of these findings to other populations (with differing nutritional status) was unknown. Long-term harm from supplementation could not be ruled out.[5]

1. Seddon JM, *et al.* Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA* 1994; **272:** 1413–20.
2. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 11/03/08).
3. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; **335:** 755–9.
4. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no.8. *Arch Ophthalmol* 2001; **119:** 1417–36.
5. Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/08).

Deficiency states. A study in Senegalese children with vitamin A deficiency found that supplementation with betacarotene (in a single dose equivalent to 200 000 units of vitamin A) was as effective as a single 200 000 unit dose of vitamin A palmitate in reversing ocular changes.[1] Since betacarotene is less toxic than vitamin A itself it would have some advantages for supplementation, either as an oral supplement or by encouraging the consumption of carotenoid-rich fruit and vegetables. A study in anaemic Indonesian women found that a supplement containing betacarotene with iron, vitamin C, and folate improved vitamin A status, whereas an additional daily portion of dark-green leafy vegetables containing a similar amount of betacarotene did not.[2] However, others contended that consumption of food sources of carotenoids were effective in improving vitamin A status in deficiency states,[3,4] and that it might not be appropriate to extrapolate these findings in adults (not necessarily deficient in vitamin A) to vitamin A deficient children.[3,5] WHO policy was to promote dietary adjustment wherever vitamin A deficiency was endemic.[5] Despite further studies confirming improved vitamin A status among those given foods high in betacarotene,[6,7] a review[8] considered the bioavailability of betacarotene from plant foods to be low, and questioned the retinol equivalency determined by WHO (see Units, above). Another study[9] found that increasing dietary fat consumption and eliminating helminthic infection further increased serum retinol concentrations in children given food high in betacarotene.

For a trial reporting improved vitamin A status with betacarotene plus zinc compared with betacarotene or zinc alone, and the suggestion that zinc may have a role in the conversion of betacarotene to retinol, see Vitamin A Deficiency, under Zinc, p.2001.

For further discussion of vitamin A deficiency and the value of supplementation in various disease states, see under Vitamin A Substances, p.1973.

1. Carlier C, *et al.* A randomised controlled trial to test equivalence between retinyl palmitate and β carotene for vitamin A deficiency. *BMJ* 1993; **307:** 1106–10.
2. de Pee S, *et al.* Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 1995; **346:** 75–81.
3. Reddy V. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; **346:** 1634–5.
4. Underwood BA. Vitamin A status and dark green leafy vegetables. *Lancet* 1995; **346:** 1635.
5. WHO. Vitamin A status: is dietary replacement practicable. *WHO Drug Inf* 1995; **9:** 141.
6. Ncube TN, *et al.* Supplementing lactating women with puréed papaya and grated carrots improved vitamin A status in a placebo-controlled trial. *J Nutr* 2001; **131:** 1497–1502.
7. Vuong LT, *et al.* Plasma β-carotene and retinol concentrations of children increase after a 30-d supplementation with the fruit Momordica cochinchinensis (gac). *Am J Clin Nutr* 2002; **75:** 872–9.
8. West CE, *et al.* Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. *J Nutr* 2002; **132** (suppl): 2920S–2926S.
9. Jalal F, *et al.* Serum retinol concentrations in children are affected by food sources of β-carotene, fat intake, and anthelmintic drug treatment. *Am J Clin Nutr* 1998; **68:** 623–9.

Ischaemic heart disease. There are results from epidemiological studies suggesting the potential benefits of dietary betacarotene in preventing ischaemic heart disease, particularly in smokers; however, randomised placebo-controlled studies of betacarotene supplements have returned negative results, as discussed on p.1926.

Malignant neoplasms. Some evidence from epidemiological studies suggested that higher dietary intakes of carotenoids and especially betacarotene had a protective effect against cancer. Consequently several randomised placebo-controlled trials examining the use of betacarotene supplements in the primary or secondary prevention of malignancy were instigated. However, the results of studies so far published have generally been disappointing. Moreover, some results suggest that supplementation with betacarotene may actually be harmful (see Prophylaxis of Malignant Neoplasms, p.1927 and Effects on Mortality, above).

Porphyria. Despite a lack of robust evidence, betacarotene is the most widely used systemic drug for the management of erythropoietic protoporphyria,[1,2] a non-acute porphyria characterised by cutaneous photosensitivity (p.1448). It has been given with canthaxanthin to reduce the skin discoloration caused by betacarotene alone.

1. Todd DJ. Erythropoietic protoporphyria. *Br J Dermatol* 1994; **131:** 751–66.
2. Todd DJ. Therapeutic options for erythropoietic protoporphyria. *Br J Dermatol* 2000; **142:** 826.

Preparations

USP 31: Beta Carotene Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: B-Caroteno; ***Austria:*** Carotaben; ***Braz.:*** Vitcaroten†; Vitizin Beta; Zirvit Beta; ***Cz.:*** Carotaben; ***Ger.:*** Carotaben; Carotana†; Carotinora; ***Ital.:*** Tannisol; ***Switz.:*** Carotaben; ***Turk.:*** Carovit; ***UK:*** Biocarotene.

Multi-ingredient: ***Arg.:*** Bronsul; Natubrown; Sigmasol; Sol Bronce Vital; ***Austral.:*** Antioxidant Forte Tablets; Antioxidant Tablets; Beta A-C; Eye Health Herbal Plus Formula 4; Lifesystem Herbal Plus Formula 5 Eye Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Odourless Garlic†; ***Austria:*** Oleovit A; Oleovit A + D; ***Braz.:*** Purpuralin†; ***Chile:*** Unitone; ***Fr.:*** Difrarel; Phytolongbronze; Phytosolaire; ***Ger.:*** Carotin; ***Hong Kong:*** Purpuralin†; Sanjukei Panax Ginseng; ***India:*** Rovigon†; ***Indon.:*** Bioretin; Lesifit; Matase; Matovit; Nu-Derm Sunblock; Retivit; ***Ital.:*** Agedin Plus; Angstrom Viso; Ecamannan; Keratolip; Levudin†; Mirtilene; Solecin; Tannidin Plus; ***Mex.:*** Unitone; ***Neth.:*** Difrarel; ***Philipp.:*** Pynocare 40 Actisome; ***Pol.:*** Biovision; ***Port.:*** Rilastil Dermo Solar; ***Rus.:*** Strix (Стрикс); ***Spain:*** Aceite Acalorico; Mirtilus; ***Switz.:*** Visaline; ***Turk.:*** Dervanol; ***Venez.:*** Unitone†.

Biotin *(rINN)*

Biotiini; Biotina; Biotinas; Biotine; Biotinum; Coenzyme R; Vitamin H. *cis*-5-(Hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-4-yl)valeric acid.

Биотин

$C_{10}H_{16}N_2O_3S$ = 244.3.
CAS — 58-85-5.
ATC — A11HA05.
ATC Vet — QA11HA05.

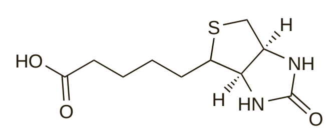

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Biotin). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water and in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Biotin). A practically white crystalline powder. Very slightly soluble in water and in alcohol; insoluble in other common organic solvents. Store in airtight containers.

Profile

Biotin is traditionally considered to be a vitamin B substance. It is an essential coenzyme in fat metabolism and in other carboxylation reactions. Biotin deficiency may result in the urinary excretion of organic acids and changes in skin and hair. Deficiency of biotin is very unlikely in man because of its widespread distribution in food. Egg-yolk and offal are especially good sources. Biotin deficiency has been reported however during long-term parenteral nutrition and in patients with biotinidase deficiency, an inherited metabolic disorder. For dosage in biotinidase or isolated carboxylase deficiency see below. A combination of biotin and chromium tripicolinate (p.1934) has been promoted as an adjunct for the management of diabetes mellitus.

Biotin combines with avidin, a glycoprotein present in raw egg-white, to form an inactive compound.

Adverse effects. For reference to life-threatening eosinophilic pleuropericarditis in a patient receiving biotin and pantothenic acid see p.1959.

Deficiency states. Biotin has been used to treat deficiency of biotinidase or holocarboxylase synthetase, enzymes responsible for the recycling and incorporation of biotin. In the UK, the *BNFC* suggests the following doses:

- for isolated carboxylase defects, biotin may be given to neonates in a dose of 5 mg once daily by mouth or slow intravenous injection, adjusted according to response; older patients may be given 10 mg daily. The usual maintenance dose ranges from 10 to 50 mg daily, though up to 100 mg daily may be needed
- for defects of biotin metabolism, 10 mg once daily may be given by mouth or slow intravenous injection, adjusted according to response. Usual maintenance doses are 5 to 20 mg daily but higher doses may be needed

References.

1. Baumgartner ER, Suormala T. Multiple carboxylase deficiency: inherited and acquired disorders of biotin metabolism. *Int J Vitam Nutr Res* 1997; **67:** 377–84.
2. Tsao CY, Kien CL. Complete biotinidase deficiency presenting as reversible progressive ataxia and sensorineural deafness. *J Child Neurol* 2002; **17:** 146.
3. Wolf B. Biotinidase deficiency: new directions and practical concerns. *Curr Treat Options Neurol* 2003; **5:** 321–8.
4. Seymons K, *et al.* Dermatologic signs of biotin deficiency leading to the diagnosis of multiple carboxylase deficiency. *Pediatr Dermatol* 2004; **21:** 231–5.
5. Grünewald S, *et al.* Biotinidase deficiency: a treatable leukoencephalopathy. *Neuropediatrics* 2004; **35:** 211–16.
6. Puertas Bordallo D, *et al.* Neuropatía óptica por déficit de biotinidasa. *Arch Soc Esp Oftalmol* 2004; **79:** 393–6.
7. Hoffman TL, *et al.* Biotinidase deficiency: the importance of adequate follow-up for an inconclusive newborn screening result. *Eur J Pediatr* 2005; **164:** 298–301.
8. Wilson CJ, *et al.* Severe holocarboxylase synthetase deficiency with incomplete biotin responsiveness resulting in antenatal insult in Samoan neonates. *J Pediatr* 2005; **147:** 115–18.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for biotin although it was considered that an intake of between 10 and 200 micrograms daily was both safe and adequate.[1] Similarly in the USA an adequate intake of 30 micrograms daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aminosam; Panabiotin; ***Austria:*** Bio-H-Tin; Curatin; Medobiotin; Merzbiotin; ***Canad.:*** D Biotin†; ***Chile:*** Hvit; ***Fin.:*** Biotisan; ***Ger.:*** Bio-H-Tin; Biokur†; Biotin-Asmedic; Deacura; Gabunat; Medobiotin†; Natubiotin; Natuderm†; Rombellin†; ***Hung.:*** Bio-H-Tin; ***Ital.:*** Biodermatin; Diathynil; Nebiotin; ***Spain:*** Medebiotin; ***Switz.:*** Bio-H-Tin; Rombellin; ***USA:*** Appearex; Hard Nails.

Multi-ingredient: ***Arg.:*** Folimax B; Megaplus; Tersoderm Anticaspa†; ***Fr.:*** Zeniac LP†; Zeniac†; ***Ger.:*** Carotin; ***Indon.:*** Alicron; ***Spain:*** Doctodermis; Lacerdermol.

Calcium Ferrous Citrate

Ferrous Calcium Citrate. Dicalcium iron(2+) bis(2-hydroxypropane-1,2,3-tricarboxylate).

$C_{12}H_{10}Ca_2FeO_{14}$ = 514.2.
CAS — 53684-61-0.

Profile

Calcium ferrous citrate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Israel: Ferrocal.

Multi-ingredient: ***India:*** Raricap; Raricap L.

Calcium Fluoride

Fluoruro cálcico.

CaF_2 = 78.07.
CAS — 7789-75-5.

Pharmacopoeias. In *Ger.*

Profile

Calcium fluoride is used as a fluoride supplement (see Sodium Fluoride, p.1962) for the prevention of dental caries. Calcium fluoride is also used as a source of calcium.

Homoeopathy. Calcium fluoride has been used in homoeopathic medicines under the following names: Calcarea Fluorica; Calc. Fluor; Calcium Fluoratum; Cal. fl.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Calcifluor†.

Multi-ingredient: ***Cz.:*** Bifluorid†; ***Denm.:*** Bifluorid; ***India:*** Calcinol; ***Ital.:*** Bifluorid†; ***Pol.:*** Bifluorid; ***Swed.:*** Bifluorid.

Calcium Mefolinate

Calcii Mefolinas; Calcio Mefolinato; Calcium L-Methylfolate; Calcium (6*S*)-5-Methyltetrahydrofolate.

Кальция L-Метилфолат

$C_{20}H_{23}CaN_7O_6$ = 497.5.
CAS — 26560-38-3.

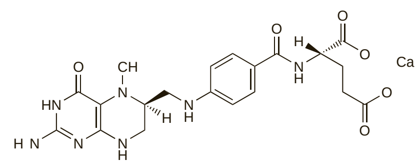

NOTE. Metafolin is a trade name that has been used for calcium mefolinate.

Profile

Calcium mefolinate is the calcium salt of 5-methyltetrahydrofolate, the biologically active metabolite of folic acid (p.1940). It is used as a food supplement and also has similar uses to folic acid.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Biofolic; Furoic; Prefolic; ***USA:*** Deplin.

Multi-ingredient: ***USA:*** Cerefolin; Metanx.

Carnitine Derivatives

Acetylcarnitine Hydrochloride

Acetilcarnitina, hidrocloruro de; Acetyl-L-carnitine Chloride; Levacecarnine Hydrochloride; Levocarnitinum acetilum hydrochloricum; ST-200. (3-Carboxy-2-hydroxypropyl)trimethylammonium acetate (ester) chloride.

$C_9H_{17}NO_4,HCl$ = 239.7.
CAS — 5080-50-2.
ATC — N06BX12.
ATC Vet — QN06BX12.

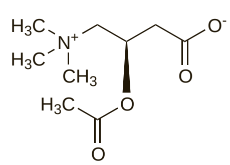

(acetyl-L-carnitine)

Carnitine *(rINN)*

Carnitina; Carnitinum; Karnitin; ST-198; Vitamin B_T. (3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; 3-Hydroxy-4-trimethylammoniobutyrate.

Карнитин

$C_7H_{15}NO_3$ = 161.2.
CAS — 461-06-3.

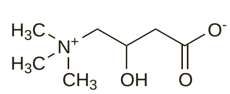

Levocarnitine *(BAN, USAN, rINN)*

L-Carnitine; L-Karnitin; Levocarnitina; Lévocarnitine; Levocarnitinum; Levokarnitiini; Levokarnitin; Levokarnitinas. (*R*)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; (*R*)-3-Hydroxy-4-trimethylammoniobutyrate.

Левокарнитин

$C_7H_{15}NO_3$ = 161.2.
CAS — 541-15-1.
ATC — A16AA01.
ATC Vet — QA16AA01.

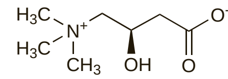

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Levocarnitine). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water; soluble in warm alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 6.5 to 8.5. Store in airtight containers.

USP 31 (Levocarnitine). White, hygroscopic, crystals or crystalline powder. Freely soluble in water and in hot alcohol; practically insoluble in acetone, in ether, and in benzene. pH of a 5% solution in water is between 5.5 and 9.5. Store in airtight containers.

Levocarnitine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de levocarnitina; Lévocarnitine, Chlorhydrate de; Levocarnitini Hydrochloridum. (*R*)-3-Hydroxy-4-trimethylammoniobutyrate hydrochloride.

Левокарнитина Гидрохлорид

$C_7H_{15}NO_3,HCl$ = 197.7.
CAS — 6645-46-1.

Levocarnitine Propionate *(rINNM)*

L-Carnitine propionate; Lévocarnitine, Propionate de; Levocarnitini Propionas; Propionato de levocarnitina; Propionylcarnitine; L-Propionylcarnitine; Propionyl-L-carnitine; ST-261.

Левокарнитина Пропионат

$C_{10}H_{19}NO_4$ = 217.3.
CAS — 20064-19-1.

Levocarnitine Propionate Hydrochloride *(USAN)*

Propionyl-L-carnitine Hydrochloride; STI-261. (2*R*)-3-Carboxy-*N,N,N*-trimethyl-2-(propanoyloxy)propan-1-aminium chloride.

$C_{10}H_{20}ClNO_4$ = 253.7.
CAS — 119793-66-7.

Adverse Effects and Precautions

Gastrointestinal disturbances such as nausea, vomiting, diarrhoea, and abdominal cramps have been reported after the use of levocarnitine. Body odour has also been noticed in some patients, possibly due to the formation of the metabolite trimethylamine (see Fish Odour Syndrome, p.1923). Decreasing the dosage may reduce or eliminate these effects; oral levocarnitine should be consumed slowly to decrease gastrointestinal disturbances. Seizures have been reported.

Patients with severe renal impairment should not be given high oral doses of levocarnitine for long periods, because of the accumulation of the metabolites trimethylamine and trimethylamine-*N*-oxide. This is said not to occur to the same extent after intravenous dosage. Diabetic patients given carnitine while receiving insulin or hypoglycaemic drugs should be monitored for hypoglycaemia.

Renal impairment. Of 30 patients given DL-carnitine intravenously after dialysis sessions 3 developed myasthenia-like symptoms but when these 3 were given only levocarnitine the symptoms did not occur.[1] It was considered that in anuric uraemic patients the D-isomer was not excreted adequately and that accumulation had blocked neuromuscular transmission. It was therefore suggested that levocarnitine, rather than the DL-form, should be used. (High and prolonged oral doses of levocarnitine should, however, be avoided—see above.)

1. Bazzato G, *et al.* Myasthenia-like syndrome after but not -carnitine. *Lancet* 1981; **i:** 1209.

Pharmacokinetics

Oral doses of levocarnitine are absorbed slowly and incompletely from the small intestine. Bioavailability has been reported to be only about 10 to 15%, with peak plasma concentrations attained about 3 to 4 hours after an oral dose. Plasma concentrations after oral doses represent the sum of endogenous and exogenous material. Levocarnitine does not appear to bind to plasma proteins. It is mainly eliminated by the kidneys, undergoing extensive tubular reabsorption. After intravenous doses, levocarnitine appears to undergo minimal metabolism. Levocarnitine given orally may undergo degradation in the gastrointestinal tract, leading to the formation of metabolites such as trimethylamine-*N*-oxide and γ-butyrobetaine, recovered in the urine and faeces, respectively.

◊ References.

1. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. *Clin Pharmacokinet* 2003; **42:** 941–67.
2. Bain MA, *et al.* Disposition and metabolite kinetics of oral L-carnitine in humans. *J Clin Pharmacol* 2006; **46:** 1163–70.
3. Fornasini G, *et al.* A pharmacokinetic model for L-carnitine in patients receiving haemodialysis. *Br J Clin Pharmacol* 2007; **64:** 335–45.

Uses and Administration

Carnitine is an amino acid derivative that is an essential cofactor of fatty acid metabolism.

Carnitine is used in the treatment of primary carnitine deficiency and in carnitine deficiency secondary to a variety of defects of intermediary metabolism or other conditions such as haemodialysis. Both the L- and the DL-isomers have been used, but it is believed that only levocarnitine is effective and in addition, that DL-carnitine supplementation can lead to carnitine deficiency.

In the UK, depending on the condition, up to 200 mg/kg daily of levocarnitine is given orally, in 2 to 4 divided doses. Rarely, higher doses of up to 400 mg/kg daily may be needed. In the USA, lower doses of about 2 to 3 g daily are recommended for adults; the dose given for infants and children is 50 to 100 mg/kg daily in divided doses, to a maximum of 3 g daily.

When given intravenously, up to 100 mg/kg daily is given in 3 to 4 divided doses by slow intravenous injection over 2 to 3 minutes. Higher intravenous doses have been given, but are associated with an increased incidence of adverse effects.

In patients with carnitine deficiency secondary to haemodialysis, the recommended dose of levocarnitine is 10 to 20 mg/kg intravenously after each dialysis session, adjusted according to plasma-carnitine concentrations. An oral maintenance dose of 1 g daily may be considered (but see Adverse Effects and Precautions, above).

Levocarnitine is under investigation for the treatment of zidovudine-induced mitochondrial myopathy. Carnitine derivatives have been used to treat conditions including cardiovascular disease, peripheral arterial disease, cerebrovascular insufficiency, peripheral neuropathies, and neurological disorders, see below.

Carnitine chloride, carnitine hydrochloride, carnitine orotate, and bicarnitine chloride have also been used.

Carnitine supplementation. Carnitine occurs as distinct L- and D-isomers although naturally-occurring carnitine is almost exclusively the L-isomer.[1] Carnitine is an essential co-factor of fatty acid metabolism in the heart, liver, and skeletal muscle.[1,2] It is normally synthesised in the liver, brain, and kidneys in sufficient quantities to meet human requirements but dietary sources such as meat and dairy products also provide carnitine.[1-4] In plasma and tissues carnitine is present in the free form and as acylated esters of which acetylcarnitine is the most abundant.

Although DL-carnitine is the form often present in over-the-counter preparations and dietary supplements, levocarnitine should be preferred, as the two isomers differ in their actions. Levocarnitine acts as a substrate for carnitine acetyltransferase while D-carnitine acts as a competitive inhibitor; also, levocarnitine-induced stimulation of palmitate oxidation is competitively inhibited by D-palmitoylcarnitine. Such differences are believed to account for findings of benefit only with the L-isomer, or unwanted effects when D-carnitine or DL-carnitine was used.[1,5]

Primary **carnitine deficiency** is a disorder of the membrane transport of carnitine and patients have presented with hypoglycaemia and encephalopathy, skeletal myopathy, and cardiomyopathy. Therapy with carnitine in these primary deficiency states is considered to have a rational basis.[2,4-6] Secondary carnitine deficiency occurs in many inherited metabolic disorders, especially in the organic acidurias and disorders of beta-oxidation. The value of carnitine for these conditions is controversial.[2,4,6-8]

Carnitine deficiency may also arise during the long-term use of **drugs** such as valproic acid,[5,9-11] pivampicillin,[12,13] or pivmecillinam,[12] which are conjugated with carnitine. Whether carnitine supplementation can prevent or reverse this type of deficiency is unclear: although treatment with carnitine raised plasma-carnitine concentrations, it had no more effect than placebo on the well-being of children receiving valproic acid therapy in one study,[14] but others have found levocarnitine supplementation of value in attenuating valproate-induced hyperammonaemia after a protein-rich meal,[15] and some paediatric neurologists consider supplementation justified in selected children with epilepsy,[16,17] including those with, or at risk of, valproate-induced hepatotoxicity and hyperammonaemic encephalopathy. There is some suggestion that carbamazepine and phenobarbital can also decrease carnitine concentrations.[10,11] Therapy with cisplatin[18] or ifosfamide[19] has been reported to cause increased urinary excretion of carnitine.

There is also some evidence[5,20] that carnitine supplements may be of benefit to low birth-weight preterm **infants**, but a double-blind study[21] failed to confirm this effect. A systematic review concluded that there are insufficient data to support the use of carnitine supplementation for the treatment of apnoea of prematurity, despite a plausible rationale for such treatment.[22] While some evidence of benefit exists for carnitine supplementation of neonates receiving parenteral nutrition,[5] a systematic review found no evidence of effect on weight gain, fat utilisation, or ketogenesis.[23]

Low concentrations of carnitine have also been reported to occur in a variety of other conditions (see below).

1. Li Wan Po A. Carnitine: a scientifically exciting molecule. *Pharm J* 1990; **245:** 388–9.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631–3.
3. Anonymous. L-carnitine. *Med Lett Drugs Ther* 2004; **46:** 95–6.
4. Scaglia F, Longo N. Primary and secondary alterations of neonatal carnitine metabolism. *Semin Perinatol* 1999; **23:** 152–61.
5. Goa KL, Brogden RN. L-Carnitine: a preliminary review of its pharmacokinetics, and its therapeutic use in ischaemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. *Drugs* 1987; **34:** 1–24.
6. Evangeliou A, Vlassopoulos D. Carnitine metabolism and deficit when supplementation is necessary? *Curr Pharm Biotechnol* 2003; **4:** 211–9.
7. Rinaldo P, *et al.* Effect of treatment with glycine and -carnitine in medium-chain acyl-coenzyme A dehydrogenase deficiency. *J Pediatr* 1993; **122:** 580–4.
8. Winter SC. Treatment of carnitine deficiency. *J Inherit Metab Dis* 2003; **26:** 171–80.
9. Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. *Ann Pharmacother* 2000; **34:** 630–8.
10. Verrotti A, *et al.* Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. *Int J Clin Lab Res* 1999; **29:** 36–40.
11. Castro-Gago M, *et al.* Serum carnitine levels in epileptic children before and during treatment with valproic acid, carbamazepine, and phenobarbital. *J Child Neurol* 1998; **13:** 546–9.
12. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; **ii:** 469–73.
13. Melegh B. Carnitine supplementation in pivampicillin treatment. *Lancet* 1989; **ii:** 1096.
14. Freeman JM, *et al.* Does carnitine administration improve the symptoms attributed to anticonvulsant medications?: a double-blinded, crossover study. *Pediatrics* 1994; **93:** 893–5.
15. Gidal BE, *et al.* Diet- and valproate-induced transient hyperammonemia: effect of -carnitine. *Pediatr Neurol* 1997; **16:** 301–5.
16. De Vivo DC, *et al.* -carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; **39:** 1216–25.
17. Lheureux PER, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005; **9:** 431–40.
18. Heuberger W, *et al.* Increased urinary excretion of carnitine in patients treated with cisplatin. *Eur J Clin Pharmacol* 1998; **54:** 503–8.
19. Marthaler NP, *et al.* Increased urinary losses of carnitine during ifosfamide chemotherapy. *Cancer Chemother Pharmacol* 1999; **44:** 170–2.
20. Shortland GJ, Walter JH. L-carnitine. *Lancet* 1990; **335:** 1215.
21. Shortland GJ, *et al.* Randomised controlled trial of L-carnitine as a nutritional supplement in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F185–F188.
22. Kumar M, *et al.* Carnitine supplementation for preterm infants with recurrent apnea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 08/11/05).
23. Cairns PA, Stalker DJ. Carnitine supplementation of parenterally fed neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 08/11/05).

Cardiovascular disease. There is some evidence that carnitine supplementation may exert a cardioprotective role. Benefit in patients with *cardiomyopathies*,[1-3] reduction of infarct size in patients with *myocardial infarction*,[4] and increased exercise performance in patients with *angina*[5] or *intermittent claudication*,[6-8] have all been described in patients given carnitine. While variable effects on cholesterol and triglyceride plasma concentrations have been described,[5] studies in diabetic[9] and hyperlipoproteinaemic[10] patients have reported reductions in plasma lipoprotein(a) concentrations. However, carnitine supplementation in patients with chronic *heart failure* failed to increase exercise capacity,[11] and its value outside of actual deficiency is still considered uncertain.[5]

1. Winter SC, Buist NRM. Cardiomyopathy in childhood, mitochondrial dysfunction, and the role of L-carnitine. *Am Heart J* 2000; **39** (suppl): S63–S69.
2. Helton E, *et al.* Metabolic aspects of myocardial disease and a role for -carnitine in the treatment of childhood cardiomyopathy. *Pediatrics* 2000; **105:** 1260–70. Correction. *ibid.*; **106:** 623.
3. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000; **139** (suppl): S120–S123.
4. Pauly DF, Pepine CJ. The role of carnitine in myocardial dysfunction. *Am J Kidney Dis* 2003; **41** (suppl): S35–S43.
5. Arsenian MA. Carnitine and its derivatives in cardiovascular disease. *Prog Cardiovasc Dis* 1997; **40:** 265–86.
6. Hiatt WR, *et al.* Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. *Am J Med* 2001; **110:** 616–22.
7. Brevetti G, *et al.* European multicenter study on propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol* 1999; **34:** 1618–24.
8. Wiseman LR, Brogden RN. Propionyl-L-carnitine. *Drugs Aging* 1998; **12:** 243–8.
9. Derosa G, *et al.* The effect of -carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. *Clin Ther* 2003; **25:** 1429–39.
10. Sirtori CR, *et al.* L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a). *Nutr Metab Cardiovasc Dis* 2000; **10:** 247–51.
11. The Investigators of the Study on Propionyl- -Carnitine in Chronic Heart Failure. Study on propionyl- -carnitine in chronic heart failure. *Eur Heart J* 1999; **20:** 70–6.

Exercise performance. Improved exercise performance in patients with angina or peripheral vascular disease has been described in patients given carnitine supplementation (see above). However, evidence of benefit from the use of carnitine in healthy subjects in an attempt to improve athletic performance is lacking.[1,2]

1. Tonda ME, Hart LL. N,N dimethylglycine and -carnitine as performance enhancers in athletes. *Ann Pharmacother* 1992; **26:** 935–7.
2. Brass EP. Supplemental carnitine and exercise. *Am J Clin Nutr* 2000; **72** (suppl): 618S–623S.

Fatigue. Placebo-controlled studies in elderly subjects found that levocarnitine supplementation significantly reduced physical and mental fatigue,[1,2] while an open study in patients with chronic fatigue syndrome reported improvement in mental fatigue with acetylcarnitine, and general fatigue improvement with propionylcarnitine.[3] In a crossover study with amantadine, patients with chronic fatigue syndrome given levocarnitine for 8 weeks showed improvement in 12 out of 18 parameters measuring fatigue; patients who were most ill at the start of the study improved the most.[4] There is also some suggestion that levocarnitine supplementation may be of benefit in alleviating fatigue induced by antineoplastic chemotherapy,[5] or interferon.[6] For reports of carnitine use for fatigue in multiple sclerosis patients, see Neurological Disorders, below.

1. Pistone G, *et al.* Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. *Drugs Aging* 2003; **20:** 761–7.
2. Malaguarnera M, *et al.* L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007; **86:** 1738–44.
3. Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004; **66:** 276–82.
4. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997; **35:** 16–23.
5. Graziano F, *et al.* Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. *Br J Cancer* 2002; **86:** 1854–7.
6. Neri S, *et al.* L-carnitine decreases severity and type of fatigue induced by interferon-α in the treatment of patients with hepatitis C. *Neuropsychobiology* 2003; **47:** 94–7.

Haemodialysis. Carnitine homoeostasis is altered in renal failure[1] and a functional deficiency may develop in patients on dialysis.[2] This dialysis-related carnitine disorder manifests notably as anaemia, intradialytic hypotension, cardiomyopathy, and muscle weakness and fatigability. Treatment with intravenous levocarnitine 20 mg/kg after each dialysis session has been recommended. Clinical response should be evaluated at 3-monthly intervals, and treatment stopped if no improvement is seen within 9 to 12 months.[2] A systematic review suggested a beneficial effect of levocarnitine for the management of anaemia in haemodialysis patients.[3] Since carnitine supplementation has been associated with a reduction[4,5] in the incidence of haemodialysis-induced cramps (p.1671) it has been suggested that these cramps might be due in part to carnitine deficiency.

1. Matera M, *et al.* History of -carnitine: implications for renal disease. *J Ren Nutr* 2003; **13:** 2–14.
2. Eknoyan G, *et al.* Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder: National Kidney Foundation Carnitine Consensus Conference. *Am J Kidney Dis* 2003; **41:** 868–76.
3. Hurot J-M, *et al.* Effects of -carnitine supplementation in maintenance hemodialysis patients: a systematic review. *J Am Soc Nephrol* 2002; **13:** 708–14.
4. Ahmad S, *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients II: clinical and biochemical effects. *Kidney Int* 1990; **38:** 912–18.
5. Sakurauchi Y, *et al.* Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am J Kidney Dis* 1998; **32:** 258–64.

HIV infection. Carnitine deficiency has been reported in HIV-infected patients. Causes may include malabsorption or increased excretion due to a wasting syndrome commonly found in these patients, or toxicity from antiretroviral drugs causing metabolic changes or altered lipid metabolism in the patient.[1] Small, mostly uncontrolled studies have suggested benefit from supplementation with levocarnitine or acetylcarnitine in relieving complications of HIV infection and adverse effects of antiretroviral drugs,[2] notably toxic neuropathy.[3,4]

1. Vilaseca MA, *et al.* Low serum carnitine in HIV-infected children on antiretroviral treatment. *Eur J Clin Nutr* 2003; **57:** 1317–22.
2. Ilias I, *et al.* -Carnitine and acetyl- -carnitine in the treatment of complications associated with HIV infection and antiretroviral therapy. *Mitochondrion* 2004; **4:** 163–8.
3. Herzmann C, *et al.* Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005; **6:** 344–50.
4. Osio M, *et al.* Acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Peripher Nerv Syst* 2006; **11:** 72–6.

Male infertility. Increases in sperm motility have been reported in some infertile men treated with carnitine,[1-3] although clinical benefit needs to be further evaluated.[4]

1. Lenzi A, *et al.* Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. *Fertil Steril* 2003; **79:** 292–300.
2. Lenzi A, *et al.* A placebo-controlled double-blind randomized trial of the use of combined -carnitine and -acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril* 2004; **81:** 1578–84.
3. Vicari E, Calogero AE. Effects of treatment with carnitines in infertile patients with prostato-vesiculo-epididymitis. *Hum Reprod* 2001; **16:** 2338–42.
4. Agarwal A. Carnitines and male infertility. *Reprod Biomed Online* 2004; **8:** 376–84.

Neurological disorders. A meta-analysis of 21 studies concluded that acetylcarnitine improved mild cognitive impairment and prevented deterioration in patients with mild *Alzheimer's disease*.[1] However, a systematic review of 11 of these trials concluded that, although some evidence of benefit on clinical global impression exists, use of acetylcarnitine could not be routinely recommended in the treatment of Alzheimer's disease.[2]

Although no differences were found in serum carnitine concentrations in *multiple sclerosis* patients with or without disabling fatigue,[3] there is some suggestion of benefit with acetylcarnitine treatment for those patients with fatigue.[4] Carnitine has been reported to be of benefit in other cases of fatigue (see above).

In *Rett syndrome*, a severe neurodevelopmental disorder, supplementation with levocarnitine led to improvements in sleep efficiency, energy levels, and communication skills.[5] Parental and medical assessment of patient well-being improved in another study;[6] girls with classical Rett syndrome also improved in motor behaviour as assessed medically.

1. Montgomery SA, *et al.* Meta-analysis of double-blind randomized controlled clinical trials of acetyl- -carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 2003; **18:** 61–71.
2. Hudson S, Tabet N. Acetyl-l-carnitine for dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 08/11/05).
3. Fukazawa T, *et al.* Serum carnitine and disabling fatigue in multiple sclerosis. *Psychiatry Clin Neurosci* 1996; **50:** 323–5.
4. Tomassini V, *et al.* Comparison of the effects of acetyl -carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. *J Neurol Sci* 2004; **218:** 103–8.
5. Ellaway CJ, *et al.* Medium-term open label trial of L-carnitine in Rett syndrome. *Brain Dev* 2001; **23** (suppl): S85–S89.
6. Ellaway C, *et al.* Rett syndrome: randomized controlled trial of -carnitine. *J Child Neurol* 1999; **14:** 162–7.

Preparations

USP 31: Levocarnitine Injection; Levocarnitine Oral Solution; Levocarnitine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Albicar; Fertilix; Neurex; Neuroactil; ***Braz.:*** Levocarnin†; ***Canad.:*** Carnitor; ***Chile:*** Actigeron; Carnicor; ***Fr.:*** Levocarnil; ***Ger.:*** Biocarn; L-Carn; Nefrocarnit; ***Gr.:*** Aveptol; Bitobionil; Carnidose; Carnil; Corubin; Ensial; Frutenor; Growart; Inestom; Intelecta; Koptilan; Levalastine; Levamin; Levars; Levocarnil; Levosan; Lisefor; Listover; Lofostin; Maledrol; Merlit; Mevamyst; Minartine; Minoa; Oskana; Phacovit; Soludamin; Superamin; Tonovit; Trian; Trinalin; ***Hong Kong:*** Carnitene; Carnitor; ***India:*** Carnitor; L-Tine†; ***Ital.:*** Branigen; Branitil; Cardiobil†; Cardiogen†; Carnitene; Carnitolo; Carnitop†; Carnovis†; Carnum†; Carrier†; Dromos; Elleci; Eucar; Eucarnil; Farnitin; Karrer†; Kernit; Lefcar; Levocarvit; Medocarnitin; Megavis; Metina†; Miocardin; Miocor; Miotonal; Neo Cardiol; Nicetile; Normobren; Transfert†; Zibren; ***Mex.:*** Cardispan; Provicar; ***Neth.:*** Nefrocarnit; ***Philipp.:*** Carnicor; ***Pol.:*** Carnivit; ***Port.:*** Cartine; Disocor; Lacetilina; ***Rus.:*** Carniten (Карнитен); Elcar (Элькар); ***Spain:*** Carnicor; Secabiol; ***Turk.:*** Carnitene; ***UK:*** Carnitor; ***USA:*** Carnitor; VitaCarn; ***Venez.:*** Carnisin; Kativil; Lixi; Provicar.

Multi-ingredient: ***Arg.:*** Enlinea†; Garcinol Max; Herbaccion Diet; Metabolic; Reductase; Silueta Plus; Tonekin Plus†; ***Braz.:*** Pepsivit†; ***Chile:*** Grisetin Con Carnitina†; ***Indon.:*** Car-Q; Corsel; Natura DFM; Procardio; Vitaslim; ***Ital.:*** Biocarnil†; Carfosid; Carpantin†; Co-Carnetina B12; Memorandum; ***Mex.:*** Lipovitasi-Or; Redumed; Slim-D; ***Philipp.:*** Fitrum; Godex; Nutrafit; ***Spain:*** Hepadif; Malandil; Pranzo.

Casein

Kazeina.
CAS — 9000-71-9.

Profile

Casein is a protein found in milk and has been used as a source of protein in preparations for enteral and parenteral nutrition; it may be used in the production of protein hydrolysate injection. Calcium caseinate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Secalbum; ***Canad.:*** Casec†; ***Israel:*** Casec; ***Mex.:*** Calsein; Caseincal†; K-Sein; ***USA:*** Casec.

Multi-ingredient: ***Mex.:*** Calciyodina; ***Switz.:*** Cicafissan; Fissan†; Vitafissan N.

Choline Bitartrate

Bitartarato de Colina; Choline Acid Tartrate; Choline Hydrogen Tartrate; Cholinii Tartras; Colina, bitartrato de. 2-Hydroxyethyltrimethylammonium hydrogen tartrate.
$C_9H_{19}NO_7$ = 253.2.
CAS — 87-67-2.

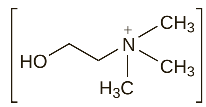

(choline)

Pharmacopoeias. In *US.*

USP 31 (Choline Bitartrate). A white, hygroscopic, crystalline powder; odourless or with a faint trimethylamine odour. Clear and colourless in solution. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 3.0 and 4.0.

Choline Chloride *(rINN)*

Choline, Chlorure de; Cholini Chloridum; Cholinii Chloridum; Choliny chlorek; Cloruro de colina; Koliinikloridi; Kolinklorid. 2-Hydroxyethyltrimethylammonium chloride.
Холина Хлорид
$C_5H_{14}ClNO$ = 139.6.
CAS — 62-49-7 (choline); 67-48-1 (choline chloride).

Pharmacopoeias. In *Fr.* and *US.*

USP 31 (Choline Chloride). Hygroscopic, colourless or white crystals or crystalline powder, usually having a slight odour of trimethylamine. Clear and colourless in solution. Soluble in water and in alcohol. pH of a 10% solution in water is between 4.0 and 7.0.

Profile

Choline is an acetylcholine precursor. It is involved in lipid metabolism and acts as a methyl donor in various other metabolic processes. Choline has traditionally been considered to be a vitamin B substance although its functions do not justify its classification as a vitamin. Choline can be synthesised in the body. However, its absence in total parenteral nutrition causes hepatic steatosis, and it is also thought to be a requirement in the diet of neonates. Sources of choline, which occurs mostly as lecithin, include egg-yolk and vegetable and animal fat.

Choline is used as a dietary supplement and has been used to treat liver disorders such as fatty liver and cirrhosis. It has been tried in the management of Alzheimer's disease (see Dementia, p.362) but without success. Choline is used as the dihydrogen citrate, and orotate salts as well as the bitartrate and the chloride.

Human requirements. In the USA, an adequate intake (see p.1925) of 550 mg daily in men and 425 mg daily in women has been determined for choline.[1] The tolerable upper intake level for adults is 3.5 g daily.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: neurotropan†.

Multi-ingredient: ***Arg.:*** Bil 13; GB 100; ***Austral.:*** Gingo A†; Liv-Detox†; ***Austria:*** Orocholin; ***Braz.:*** Alcafelol†; Aminotox†; Anekron; B-Vesil; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Extrato Hepatico Vitaminado†; Hecrosine B12†; Hepacitron†; Hepalin; Hepatobe†; Hepatotris†; Hepatox; Hormo Hepatico†; Jurubileno†; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B-6; Olocynan†; Olohepat†; Panvitrop; Xantina B12†; Xantinon B12; Xantinon Complex; ***Chile:*** Hepabil; ***Cz.:*** Lipovitan†; ***Fr.:*** Citrocholine; Desintex-Choline; Hepacholine†; Hepagrume; ***Ger.:*** Lipovitan†; ***Hong Kong:*** Bilsan; Hepatofalk; ***India:*** Delphicol; Livocip; Mecolin; Sorbiline; Sorliv; ***Indon.:*** Curliv; Curliv Plus; Hepatin; Lipagent; Methicol; Methioson; Natura DFM; ***S.Afr.:*** Hepavite; Prohep; ***Spain:*** Hepato Fardi†; ***Thai.:*** Liporon; ***UK:*** Lipotropic Factors.

Chondroitin Sulfate–Iron Complex

Chondroitin Sulphate–Iron Complex; Ferropolichondrum; Hierro y sulfato de condroitina, complejo de.
CAS — 54391-57-0.
ATC — B03AB07.
ATC Vet — QB03AB07.

Profile

Chondroitin sulfate-iron complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 900 mg daily, equivalent to up to 90 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Condrofer†; Isairon.

Chromium

Chrom; Chrome; Cromo.
Cr = 51.9961.

Chromium Trichloride

Chromic Chloride; Cromo, tricloruro de.
$CrCl_3,6H_2O$ = 266.4.
CAS — 10025-73-7 (anhydrous chromium trichloride); 10060-12-5 (chromium trichloride hexahydrate).

Pharmacopoeias. In *US.*

USP 31 (Chromic Chloride). Dark green, odourless, slightly deliquescent crystals. Soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in ether. Store in airtight containers.

Chromium Tripicolinate

Chromium Picolinate; Cromo, tripicolinato de.
$C_{18}H_{12}N_3O_6Cr$ = 418.3.

Pharmacopoeias. In *US.*

USP 31 (Chromium Picolinate). Store in airtight containers.

Adverse Effects

Trivalent salts of chromium, such as chromium trichloride, are generally considered to produce few adverse effects. However, hexavalent forms of chromium are notably toxic (see under Chromium Trioxide, p.2281).

Effects on the kidneys. Two cases of renal failure were attributed to ingestion of excessive doses of chromium tripicolinate in women with no history of renal dysfunction.[1,2] Acute renal failure with features of acute tubular necrosis, and requiring haemodialysis, has been reported after ingestion of a chromium picolinate-containing supplement. The amount of chromium in the supplement could not be determined.[3] For mention of decreases in glomerular filtration rate in children receiving chromium-supplemented total parenteral nutrition, see Supplementation, below.

1. Wasser WG, *et al.* Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; **126:** 410.
2. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; **32:** 428–31.
3. Wani S, *et al.* Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *Ann Pharmacother* 2006; **40:** 563–6.

Effects on the skin. There have been rare reports[1,2] of cutaneous reactions to oral chromium tripicolinate, including one of acute generalised exanthematous pustulosis.

1. Young PC, *et al.* Acute generalized exanthematous pustulosis induced by chromium picolinate. *J Am Acad Dermatol* 1999; **41:** 820–3.
2. Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 2000; **65:** 116.

Uses and Administration

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism. Dietary sources rich in chromium include brewers' yeast, meat, whole grains, and nuts. Chromium trichloride has been given as a chromium supplement in total parenteral nutrition. Chromium tripicolinate is used as a chromium supplement, and is being investigated for improving glycaemic control in patients with diabetes mellitus.

Diabetes mellitus. A review[1] of trivalent chromium in the management of diabetes mellitus (p.431) concluded that it may have an adjunctive role. A meta-analysis[2] found no effect of chromium on glucose or insulin concentrations in non-diabetic subjects; data for diabetic patients were inconclusive. A systematic review[3] found no significant effect with chromium supplementation on lipid or glucose metabolism in non-diabetic subjects, but it may have a modest beneficial effect on glycaemia and dyslipidaemia in those patients with diabetes. Meta-analysis was hampered by the overall poor quality and heterogeneity of available studies,[3] and further research was considered necessary.[1-3]

1. Ryan GJ, *et al.* Chromium as adjunctive treatment for type 2 diabetes. *Ann Pharmacother* 2003; **37:** 876–85.
2. Althuis MD, *et al.* Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 2002; **76:** 148–55.
3. Balk EM, *et al.* Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. *Diabetes Care* 2007; **30:** 2154–63.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for chromium although a safe and adequate intake was believed to be above 25 micrograms daily for adults.[1] Similarly, in the USA a recommended dietary allowance has not been published but the adequate intake was estimated to be 35 micrograms daily for young men and 25 micrograms daily for young women.[2] WHO considers that the minimum population mean intake likely to meet normal needs for chromium might be about 33 micrograms daily, and that supplementation of this element should not exceed 250 micrograms daily until more is known.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Chromium. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 155–60.

Supplementation. Although a daily chromium intake of 200 nanograms/kg has been suggested in children given total parenteral nutrition (TPN), a study in 15 children[1] given long-term parenteral nutrition found that supplementation at about this level was associated with serum-chromium concentrations 4 to 42 times higher than the mean value in 15 children not receiving TPN. Raised serum-chromium concentrations were associated with a decrease in glomerular filtration rate; one year after stopping chromium supplementation, which reduced intake to 50 nanograms/kg daily (as contaminants of water and TPN solutions), chromium concentrations, although lower, were still higher than controls and renal function had not altered. The authors subsequently ceased chromium supplementation in both children and adults, since chromium contamination of TPN solutions appeared adequate to prevent deficiency, although it was acknowledged that signs of chromium deficiency might take some years to appear. Chromium contamination in various preparations used in paediatric parenteral nutrition has been studied.[2]

1. Moukarzel AA, *et al*. Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992; **339:** 385–8.
2. Hak EB, *et al*. Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Preparations

USP 31: Chromic Chloride Injection; Chromium Picolinate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: NH4 Silhouette; Ripped Max; Sigmar Lipo; Tonekin; ***Austral.:*** Chrome; ***Chile:*** Edul K-200; ***Fr.:*** Chromasvelt; ***Ital.:*** Croben; ***Mex.:*** Cromifusin†; Ifa Slim†; ***USA:*** Chroma-Pak.

Multi-ingredient: ***Arg.:*** Centellacrom; Cholesterol Reducing Plan†; Garcinia Cambogia Compuesta; Herbaccion Diet; IP-6; Metabolic; Novosual†; Tonekin Plus†; Top Life Diet†; ***Austral.:*** Bioglan 3B Beer Belly Buster; Citri Slim+Trim; Digestaid; Pro-Shape†; ***Indon.:*** Biocholes; Kitoles; Vitaslim; ***Mex.:*** Lipo Slim N†; Slim-D; ***Philipp.:*** Liposorb; Nutrafit.

Citrulline

N^5-(Aminocarbonyl)-L-ornithine; N^δ-Carbamylornithine; Citrulina; L-citrulline; NSC-27425. α-Amino-δ-ureidovaleric acid.

$C_6H_{13}N_3O_3$ = 175.2.
CAS — 372-75-8.

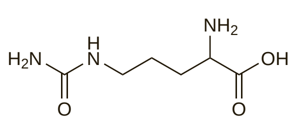

Profile

Citrulline is a non-essential amino acid that is involved in the urea cycle. Citrulline and citrulline malate are used as dietary supplements.

Hyperammonaemia. Citrulline has been given as an alternative to arginine in the management of hyperammonaemia (p.1929) due to **urea cycle disorders**.

Lysinuric protein intolerance is another condition associated with hyperammonaemia and similar neurological sequelae. In this condition there is no deficiency of urea-cycle enzymes but a deficiency of urea-cycle substrate, such as ornithine, which results in reduced synthesis of citrulline. Patients are treated with dietary protein restriction and citrulline supplementation, which improves protein tolerance and nutrition but only slightly ameliorates growth retardation. Osteoporosis may be severe in children with this disorder.[1] A child presenting with osteopenia and diagnosed with lysinuric protein intolerance was given large oral doses of citrulline (up to 5.7 g daily). Aside from a substantial increase in protein tolerance, a striking acceleration in linear growth and bone mass was reported.[2] Lysine deficiency may be implicated in growth retardation,[1] but lysine supplementation may precipitate diarrhoea and malabsorption.[2] Six patients with lysinuric protein intolerance and receiving oral citrulline were supplemented with oral lysine. Larger lysine doses of 0.55 mmol/kg and 1.1 mmol/kg given consecutively, caused profuse diarrhoea, but smaller doses of 0.05 mmol/kg, given three times daily (up to a maximum dose of 2.5 mmol) were well tolerated. Plasma lysine concentrations were normalised with no adverse effects on the urea cycle.[1]

1. Lukkarinen M, *et al*. Oral supplementation corrects plasma lysine concentrations in lysinuric protein intolerance. *Metabolism* 2003; **52:** 935–8.
2. Carpenter TO, *et al*. Lysinuric protein intolerance presenting as childhood osteoporosis: clinical and skeletal response to citrulline therapy. *N Engl J Med* 1985; **312:** 290–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Stimol; ***Indon.:*** Stimol; ***Port.:*** Dynergum; ***Rus.:*** Stimol (Стимол); ***Spain:*** Stimol; ***Switz.:*** Biostimol.

Multi-ingredient: ***Braz.:*** Ornihepat†; Ornitargin; ***Fr.:*** Epuram†; ***Ger.:*** Polilevo N†; ***Ital.:*** Ipoazotal Complex; Ipoazotal†; Polilevo†.

Cod-liver Oil *(BAN)*

Aceite de hígado de bacalao; Balık yağı; Cod Liver Oil; Csukamájolaj; Foie de morue, huile de; Huile de Foie de Morue; Iecoris aselli oleum; Kalanmaksaöljy; Lebertran; Menkių kepenų taukai; Ol. Morrh.; Óleo de Bacalhau; Oleum Jecoris Aselli; Oleum Morrhuae; Olio di Fegato di Merluzzo; Rybí olej; Torskleverolja.

Тресковый Печёночный Жир
CAS — 8001-69-2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Cod-liver Oil (Type A) and Cod-liver Oil (Type B)). Purified fatty oils obtained from the fresh livers of *Gadus morhua* and other species of Gadidae, solid substances being removed by cooling and filtering. The oils contain not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D_3 (colecalciferol) per g. Authorised antioxidants in concentrations not exceeding those prescribed by the competent authority may be added.

Clear yellowish viscous liquids. Practically insoluble in water; slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Store under an inert gas if no antioxidant is added. Protect from light.

USP 31 (Cod Liver Oil). The partially destearinated fixed oil obtained from the fresh livers of *Gadus morrhua* and other species of Gadidae. It contains not less than 600 units (180 micrograms) and not more than 2500 units (750 micrograms) of vitamin A per g and not less than 60 units (1.5 micrograms) and not more than 250 units (6.25 micrograms) of vitamin D per g. It may be flavoured by the addition of not more than 1% of a suitable flavour or a mixture of flavours. A suitable antioxidant may be added.

A thin, oily liquid, having a characteristic, slightly fishy but not rancid odour. Slightly soluble in alcohol; freely soluble in carbon disulfide, in chloroform, in ether, and in ethyl acetate. Store in airtight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Profile

Cod-liver oil is a rich source of vitamin D (p.1986) and a good source of vitamin A (p.1971). It also contains several essential fatty acids.

Cod-liver oil dressings or ointment have been advocated to accelerate healing in burns, ulcers, pressure sores, and superficial wounds, but controlled observations have failed to substantiate claims of their value.

Preparations

USP 31: Cod Liver Oil Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Hypol†; ***Austria:*** Adecaps; Vitapan; ***Ger.:*** Gelovital; Unguentolan; ***Hong Kong:*** Scott's Emulsion; ***India:*** Seaking†; ***Ital.:*** Dermovitamina; ***Pol.:*** Letin-Tran; Masc Tranowa; Naturkaps Tran; Tran; ***Spain:*** Aceite Geve Concentrado; ***Switz.:*** Morrhulan; ***Turk.:*** Seven Seas Pulse; ***Venez.:*** North Sea†; Scott Tradicional; Supercod.

Multi-ingredient: ***Arg.:*** Abanta; Atomoderma A-D; Atomoderma Plus; Eryteal; Hipoglos con Hidrocortisona; Klorane Bebe Eryteal; ***Austral.:*** Covitol; Desitin Nappy Rash Ointment; Hypol; ***Austria:*** Dermilon; Dermowund; Desitin; Leukichtan; Mirfulan; Nuri-Kapseln; Pudan-Lebertran-Zinksalbe; Vulpuran; ***Belg.:*** Mitosyl; Newderm†; Polyseptol; ***Braz.:*** Blumen†; Calciumvit Infantil†; Hiposan; Oxizinco; Topiglos; ***Canad.:*** Desitin; ***Chile:*** Cikavit; Deltisan; Dulinas†; Nenegloss; Pediaderm†; Vatanal; ***Cz.:*** Desitin†; ***Fr.:*** Eryteal†; Halivite†; Magalite; ***Ger.:*** Dermilon; Desitin; Leukona-Wundsalbe†; Mirfulan; Mirfulan Spray N; Mitosyl N; Zinksalbe; ***Gr.:*** Fissan-Pate†; Fissan†; ***Hong Kong:*** Desitin; Scott's Emulsion Orange; ***India:*** Seaking Plus†; ***Indon.:*** Co-Q-10; Scott's Emulsion; ***Irl.:*** Caldease; Morhulin; ***Israel:*** Desitin; Rekasitin; Zincod; ***Ital.:*** Fosfarsile Junior; Neo-Ustiol; Steril Zeta; Trofo 5; ***Mex.:*** Bacnutri; Capent; Desitin; Emulsion de Scott; Glossderm; Sutin†; ***Norw.:*** Aselli; ***Pol.:*** Dehalid†; Rectosec; Tran z Olejem Wiesiolkowym†; Tranvit; ***Port.:*** Mitosyl; ***S.Afr.:*** Achromide; Daromide; SB Universal Ointment; Ung Vernleigh; ***Singapore:*** Seven Seas JointCare High Strength; ***Spain:*** Avril; ***Switz.:*** Keroderm†; Leucen; Radix†; Unguentolan; Vita-Hexin; ***UK:*** Arheumacare; Clogar; JointCare Max; M & M; Morhulin; ***USA:*** A and D Medicated; Caldesene; Clocream; Desitin; Diaper Rash; Dyprotex; ***Venez.:*** Wampole†.

Copper

Cobre; Cuivre; Cuprum; Koppar; Kupari; Kupfer; Miedź.
Cu = 63.546.
CAS — 7440-50-8.

Pharmacopoeias. *Eur.* (see p.vii) includes Copper for Homoeopathic Preparations.

Ph. Eur. 6.2 (Copper for Homoeopathic Preparations; Cuprum ad Praeparationes Homoeopathicae). A reddish-brown powder. Practically insoluble in water and in alcohol; soluble in hydrochloric acid and in nitric acid.

Calcium Copperedetate

Cuproedetato cálcico. Calcium [ethylenediaminetetra-acetato(4−)-*N,N′,O,O′*]copper (II) dihydrate.
$C_{10}H_{12}CaCuN_2O_8,2H_2O$ = 427.9.
CAS — 66317-91-7 (anhydrous calcium copperedetate).

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Calcium Copperedetate). A blue crystalline powder. It contains 9.1 to 9.7% of Ca and 14.4 to 15.3% of Cu. Freely soluble in water, the solution gradually precipitating the tetrahydrate; practically insoluble in alcohol.

Copper Chloride

Cobre, cloruro de; Cupric Chloride; Miedzi chlorek.
$CuCl_2,2H_2O$ = 170.5.
CAS — 7447-39-4 (anhydrous copper chloride); 10125-13-0 (copper chloride dihydrate).

Pharmacopoeias. In *US.*

USP 31 (Cupric Chloride). Bluish-green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Copper Gluconate

Cobre, gluconato de. Copper D-gluconate (1:2); Bis(D-gluconato-O^1,O^2) copper.
$C_{12}H_{22}CuO_{14}$ = 453.8.
CAS — 527-09-3.

Pharmacopoeias. In *US.*

Copper Sulfate

Cobre, sulfato de; Copper Sulph.; Copper Sulphate; Cuivre (Sulfate de); Cuivre, sulfate de; Cupri sulfas; Cupri Sulphas; Cupric Sulfate; Kopparsulfat; Kuparisulfaatti; Kupfersulfat; Miedzi(II) siarczan; Réz(II)-szulfát; Síran měďnatý; Sulfato de Cobre; Vario sulfatas. Copper (II) sulphate pentahydrate.
$CuSO_4,5H_2O$ = 249.7.
CAS — 7758-98-7 (anhydrous copper sulfate); 7758-99-8 (copper sulfate pentahydrate).
ATC — V03AB20.
ATC Vet — QV03AB20.

NOTE. Crude copper sulfate is sometimes known as 'blue copperas', 'blue stone', and 'blue vitriol'.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*
Eur. and *Viet.* also include anhydrous copper sulfate.

Ph. Eur. 6.2 (Copper Sulphate Pentahydrate). A blue crystalline powder or transparent blue crystals. Freely soluble in water; practically insoluble in alcohol; soluble in methyl alcohol.

Ph. Eur. 6.2 (Copper Sulphate, Anhydrous). A greenish-grey, very hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol; slightly soluble in methyl alcohol. Store in airtight containers.

USP 31 (Cupric Sulfate). Deep blue, triclinic crystals, or blue, crystalline granules or powder. It effloresces slowly in dry air. Soluble 1 in 3 of water, 1 in 0.5 of boiling water, 1 in 500 of alcohol, and 1 in 3 of glycerol. Its solutions are acid to litmus. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Treatment

Adverse effects from copper have tended to arise after absorption of the metal from cooking utensils and during dialysis. Ingestion of copper from cooking utensils is associated mainly with hepatotoxicity. Dialysis procedures may supply copper through the water supply or from parts of the equipment and when this happens patients may suffer haemolysis and other haematological reactions, kidney involvement, and hepatotoxicity; the toxicity is generally a result of poor equipment maintenance.

Adverse effects attributed to copper have been reported in women with copper-containing intra-uterine devices. There have been isolated case reports of various effects such as allergy and endometrial changes. However, it is difficult to separate those adverse effects that are due to the device from those due solely to the copper.

The symptoms of Wilson's disease (hepatolenticular degeneration) (see p.1459) are due to an accumulation of copper in various parts of the body.

Copper salts if ingested can produce severe gastrointestinal effects and there may be systemic absorption of copper leading to the effects discussed above. The use of sprays of copper salts in agriculture has been associated with lung changes. Treatment of copper poisoning is symptomatic and may involve the use of a chelating agent to remove any absorbed metal. Dialysis has been tried.

Effects on the liver. Cirrhosis and acute liver failure have been attributed to chronic excessive copper supplement ingestion.[1] Supplementation with 10 mg daily of copper (around the safe upper limit) for 2 months has been reported to be associated with transient mild increases in serum aminotransferase values.[2]

1. O'Donohue J, *et al.* Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur J Gastroenterol Hepatol* 1993; **5:** 561–2.
2. Araya M, *et al.* Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults. *J Nutr* 2005; **135:** 2367–71.

Interactions

Large doses of zinc supplements may inhibit the gastrointestinal absorption of copper.

Uses and Administration

Copper is an essential trace element although severe copper deficiency, which is associated with anaemia, neutropenia, and bone demineralisation, is rare in humans. Copper sulfate is added to parenteral feeds as a source of copper in the prophylaxis and treatment of deficiency states. Doses that have been used for prophylaxis range from 0.5 to 1.5 mg (7.9 to 23.6 micromoles) of copper daily although up to 3 mg daily has been suggested in established deficiency; infants have received 20 micrograms/kg (0.3 micromol/kg) of copper daily. The dose should be governed by the serum-copper concentration, which in healthy adults ranges between 0.7 and 1.6 micrograms/mL (0.01 to 0.025 micromol/mL).

Copper sulfate and other soluble salts of copper have an astringent action on mucous surfaces and in strong solutions they are corrosive. Copper nitrate has been used in preparations for the removal of warts. The uses of copper acetate are discussed on p.2287.

Copper has a contraceptive effect (p.2070) when present in the uterus, and is added to some intra-uterine contraceptive devices; such devices are considered to be effective and safe for several years after insertion, and may be the most effective method for emergency contraception (p.2071). Copper is also reported to have an antimicrobial action.

Copper sulfate has been used to prevent the growth of algae in reservoirs, ponds, and swimming pools and as a molluscicide in the control of fresh-water snails that act as intermediate hosts in the life-cycle of the parasites causing schistosomiasis.

Reagents containing copper sulfate are used in tests for reducing sugars.

In veterinary medicine calcium copperedetate, copper methionate, copper oxide, and cuproxoline are used for the prevention and treatment of copper deficiency.

Copper bracelets are worn as a folk remedy for rheumatic disorders: there is no good evidence to justify such a practice.

Homoeopathy. Copper has been used in homoeopathic medicines under the following names: Cuprum metallicum; Cuprum; Cuprum met.; Cup. met.

Copper sulfate has been used in homoeopathic medicines under the following names: Cuprum sulfuricum; Cuprum sulphuricum; Cup. s.

◊ General references.

1. Wang T, Guo Z. Copper in medicine: homeostasis, chelation therapy and antitumor drug design. *Curr Med Chem* 2006; **13:** 525–37.

Deficiency states. Acquired copper deficiency is very rare and the small number of cases have usually involved patients on total parenteral nutrition or long-term enteral nutrition.[1] Copper deficiency may also be due to malnutrition,[2] malabsorption, or secondary to excessive zinc consumption.[3,4] Clinical manifestations of deficiency include hypocupraemia, hypoceruloplasminaemia, neutropenia, anaemia, osteoporosis, and fracture of the long bones.[2] However, cases may present with neurological signs resembling the subacute combined degeneration normally associated with vitamin B_{12} deficiency.[3,4] Effects on blood may be absent, and zinc concentrations normal;[3] however, hyperzincaemia may be seen even in the absence of exogenous zinc consumption.[4]

Menkes' disease is an X-linked genetic disorder associated with a defect in copper transport, which almost invariably results in death due to progressive cerebral degeneration by the age of 3 years.[5,6] Clinical features include skeletal abnormalities, severe mental retardation, thrombosis, hypothermia, arterial abnormalities, and characteristic facial features.[7] Early parenteral treatment with copper-histidine complex may be of benefit in such children.[5-8] Optimal response to copper therapy appears to occur only in patients who are identified in the newborn period and who have some residual copper-transport activity. More than 3 years of copper replacement therapy may not be necessary or desirable.[6]

1. Masugi J, *et al.* Copper deficiency anemia and prolonged enteral feeding. *Ann Intern Med* 1994; **121:** 386.
2. Cordano A. Clinical manifestations of nutritional copper deficiency in infants and children. *Am J Clin Nutr* 1998; **67** (suppl): 1012S–1016S.
3. Kumar N, *et al.* Copper deficiency myelopathy produces a picture like subacute combined degeneration. *Neurology* 2004; **63:** 33–9.
4. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc* 2006; **81:** 1371–84.
5. Sarkar B, *et al.* Copper-histidine therapy for Menkes' disease. *J Pediatr* 1993; **123:** 828–30.
6. Kaler SG, *et al.* Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med* 2008; **358:** 605–14.
7. Kirodian BG, *et al.* Treatment of Menkes disease with parenteral copper histidine. *Indian Pediatr* 2002; **39:** 183–5.
8. Cox DW. Disorders of copper transport. *Br Med Bull* 1999; **55:** 544–55.

Human requirements. In the UK dietary reference values (see p.1925) have been published for copper.[1] Although an estimated average requirement (EAR) could not be derived a reference nutrient intake (RNI) of 1.2 mg (19 micromoles) daily was set for adults; RNIs of lower values were also specified for infants and children.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for copper of 160 micrograms/kg daily.

In the USA the recommended dietary allowance (RDA) for copper is 900 micrograms daily in adults, and the tolerable upper intake level is 10 mg daily.[3]

WHO has estimated a minimum population mean intake of 1.2 mg daily for women and 1.3 mg daily for men, and safe upper limits of population mean intakes of 10 mg daily for women and 12 mg daily for men;[4] values are also estimated for infants and children.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
4. WHO. Copper. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 123–43.

Schistosomiasis. Although most control programmes for schistosomiasis (p.138) use niclosamide as a molluscicide, and copper salts have largely been abandoned for snail control, WHO noted in 1993 that copper sulfate was still used for this purpose in Egypt.[1]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Preparations

BPC 1973: Compound Ferrous Sulphate Tablets;
USP 31: Cupric Chloride Injection; Cupric Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Multiload; ***Braz.:*** Multiload; ***Canad.:*** Gyne-T†; ***Chile:*** Diupro-tect; Multiload; Safety T; ***Denm.:*** Multiload; ***Fr.:*** Gynelle 375; Ionarthrol†; Metacuprol; Multiload; TT 380; UT 380; ***Ger.:*** femena; Multiload; ***Hong Kong:*** Flexi-T; Multiload; ***Indon.:*** Copper-T; ***Israel:*** Anticon; Mona-Lisa; Multiload; ***Ital.:*** Gravigard; Gynefix; Multiload; No-Gravid; Telo Cypro†; UT 380; ***Malaysia:*** Multiload; ***Mex.:*** Cuprifusin†; Multiload†; ***Neth.:*** Multiload†; ***NZ:*** Multiload; ***Port.:*** Multiload†; ***S.Afr.:*** Cuprocept CCL†; Dalcept†; Multiload†; Tricept†; ***Singapore:*** Multiload; Sof-T†; ***Switz.:*** Multiload; ***Thai.:*** Multiload; ***Turk.:*** Multiload; ***UK:*** Flexi-T; Gynefix; Multiload; ***USA:*** Paragard T380A; ***Venez.:*** Multiload.

Multi-ingredient: ***Arg.:*** Dermalibour; Nova-T; ***Austral.:*** APR Cream†; Ascoxal; ***Braz.:*** Belagin; Micotox†; Sulfato Ferroso Composto; Sulfatofer†; ***Canad.:*** Nova-T; ***Chile:*** Agua Sulfatada Picrica; Cicalfate; Nova-T†; Sebium H2O; ***Fin.:*** Ascoxal†; ***Fr.:*** Atoderm moussant; Cicalfate; Cicaplast; Cu-Zn; Decramp; Dermalibour; Dermo-Sulfuryl; Dermocuivre; Eryase; Nova-T; Oligoderm; Oligorhine; Oligorhine Manganese; Purif-Ac Emulsion; Purif-Ac Gel; Ramet Dalibour; Ramet Pain; Ruboderm Plus; Septalibour†; ***Ger.:*** Nova-T; Solco-Derman; ***Hong Kong:*** Aderma Dermalibour†; Cool Mint Listerine; Nova-T; Solcoderm; ***India:*** Hepatoglobine; ***Indon.:*** Nova-T; ***Irl.:*** Ferrotab†; ***Israel:*** Nova-T; ***Ital.:*** Cuprosodio; Cuprosodio Plus; Emmenoiasi; Inflamase; Nova-T; Rinogutt Atlantic; Sterimar Cu; ***Malaysia:*** Nova-T; Solcoderm†; ***Mex.:*** Ascoxal; Dalidome; Daribur; Nova-T; ***Neth.:*** Nova-T†; ***Norw.:*** Ascoxal†; ***NZ:*** Nova-T; ***Rus.:*** Solcoderm (Солкодерм); ***S.Afr.:*** Ferrous Sulphate Compound; Lotio Pruni Comp cum Cupro; Mister Rub; Nova-T; ***Singapore:*** Nova-T; ***Swed.:*** Ascoxal†; ***Switz.:*** Nova-T; Solcoderm; ***Thai.:*** Nova-T†; ***Turk.:*** Nova-T; ***UK:*** Foresight Iron Formula; Nova-T; ***USA:*** ORA5; ***Venez.:*** Cianofer; Cobalfer; Fercobre†; Folifer B-12; Hepafol con B-12; Nova-T.

Cyclamic Acid *(BAN, USAN)*

Ciclámico, ácido; Cyclam. Acid; E952; Hexamic Acid. *N*-Cyclohexylsulphamic acid.

$C_6H_{13}NO_3S = 179.2.$

CAS — 100-88-9.

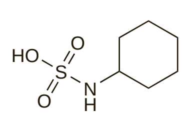

Calcium Cyclamate

Calc. Cyclam.; Calcium Cyclohexanesulfamate; Ciclamato de calcio; Cyclamate Calcium; E952. Calcium *N*-cyclohexylsulphamate dihydrate.

$C_{12}H_{24}CaN_2O_6S_2,2H_2O = 432.6.$

CAS — 139-06-0 (anhydrous calcium cyclamate); 5897-16-5 (calcium cyclamate dihydrate).

Potassium Cyclamate

Cyclamate potassium; HSDB 1239; Monopotassium cyclohexanesulfamate; potassium cyclohexanesulfamate. Potassium *N*-cyclohexysulphamate.

$C_6H_{12}NO_3SK = 217.3.$

CAS — 7758-04-5.

Sodium Cyclamate *(BAN, rINN)*

Ciclamato de sodio; Cyclamate de Sodium; Cyclamate Sodium; E952; Natrii cyclamas; Natrio ciklamatas; Nátrium-ciklamát; Natriumcyklamat; Natrium-cyklamát; Natriumsyklamaatti; Siklamat Sodyum; Sod. Cyclam.; Sodium, cyclamate de; Sodium Cyclohexanesulphamate. Sodium *N*-cyclohexylsulphamate.

Натрия Цикламат

$C_6H_{12}NNaO_3S = 201.2.$

CAS — 139-05-9.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sodium Cyclamate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 5.5 to 7.5.

Profile

Cyclamic acid and its salts are intense sweetening agents. In dilute solutions (up to about 0.17%) sodium cyclamate is about 30 times as sweet as sucrose but this factor decreases at higher concentrations. When the concentration approaches 0.5%, a bitter taste becomes noticeable. It is stable to heat.

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in Great Britain and some other countries because of concern about the metabolite cyclohexylamine. However, after reappraisal their use is now allowed.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Kaldil Diet; ***Braz.:*** Sucaryl; ***Canad.:*** Sucaryl†; ***Turk.:*** Tadalin.

Multi-ingredient: ***Arg.:*** Rondo; Sucaryl; ***Austral.:*** Sucaryl; ***Braz.:*** Finn Cristal; ***Chile:*** Sucaryl†; Sukar-Sin; ***Fr.:*** Sucaryl; ***Israel:*** Sucrin; ***Ital.:*** Diet Sucaryl; ***NZ:*** Sucaryl; ***Port.:*** Dulceril†; ***Rus.:*** Zuckli (Цюкли); ***Turk.:*** Dolce; Dulcaryl.

Cysteine *(rINN)*

C; Cisteína; Cys; Cystéine; L-Cysteine; Cysteinum; E920; L-Cysteina. L-2-Amino-3-mercaptopropionic acid.

Цистеин

$C_3H_7NO_2S = 121.2.$

CAS — 52-90-4.

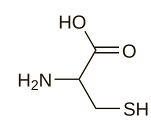

Pharmacopoeias. In *Ger.*

Cysteine Hydrochloride *(rINNM)*

Cisteíno hidrochloridas monohidratas; Cisztein-hidroklorid-monohidrát; Cys Hydrochloride; Cystéine, Chlorhydrate de; Cystéine (chlorhydrate de) monohydraté; L-Cysteine Hydrochloride Monohydrate; Cystein-hydrochlorid monohydrát; Cysteinhydrokloridmonohydrat; Cysteini Hydrochloridum; Cysteini hydrochloridum monohydricum; Hidrocloruro de cisteína; Kysteiinihydrokloridimonohydraatti; L-Cysteiny chlorowodorek. L-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate.

Цистеина Гидрохлорид

$C_3H_7NO_2S,HCl,H_2O = 175.6.$

CAS — 52-89-1 (anhydrous L-cysteine hydrochloride); 7048-04-6 (L-cysteine hydrochloride monohydrate).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Cysteine Hydrochloride Monohydrate; Cysteine Hydrochloride BP 2008). A white or almost white crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Cysteine Hydrochloride). White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Profile

Cysteine is a non-essential amino acid. Cysteine and cysteine hydrochloride are used as dietary supplements.

Cysteine and cysteine hydrochloride are included in preparations used in ophthalmology; eye drops have been used to prevent corneal ulceration after chemical burns.

◊ References.

1. Soghier LM, Brion LP. Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 24/06/08).

Precautions. Cysteine, like other sulfhydryl-containing drugs, could produce a false-positive result in the nitroprusside test for ketone bodies used in diabetes and suspected hepatocellular injury.[1]

1. Csako G, Elin RJ. Unrecognized false-positive ketones from drugs containing free-sulfhydryl group(s). *JAMA* 1993; **269:** 1634.

Preparations

USP 31: Cysteine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Mex.: Fixcanat.

Multi-ingredient: ***Fr.:*** Lobamine-Cysteine; Phakan†; ***Hong Kong:*** Hepatofalk; ***Port.:*** Phakan†; ***S.Afr.:*** Prohep; ***Switz.:*** Phakolen†.

Cystine *(USAN, rINN)*

Cistina; Cistinas; Cisztin; Cystin; L-Cystine; Cystinum; Di(α-aminopropionic)-β-disulphide; β,β′-Dithiodialanine; Kystiini; L-Cystyna. L-3,3′-Dithiobis(2-aminopropionic acid).

Цистин

$C_6H_{12}N_2O_4S_2$ = 240.3.
CAS — 56-89-3.

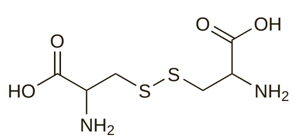

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cystine). A white or almost white crystalline powder. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

Profile

Cystine is a non-essential amino acid. It is used as a dietary supplement.

Low-methionine diets with cystine supplementation have been used in the treatment of congenital homocystinuria (see Amino Acid Metabolic Disorders, p.1922).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Gelucystine; ***Ital.:*** Cistidil; Mavigen Sebo; ***Spain:*** Crecil.

Multi-ingredient: ***Arg.:*** Lohp; Megacistin; Megaplus; ***Austria:*** Gelacet; ***Canad.:*** Amino-Cerv; ***Fr.:*** Cystine B ; Solacy; ***Ger.:*** Gelacet N†; Pantovigar N; ***Rus.:*** Eltacin (Элтацин); ***Switz.:*** Gelacet†; ***USA:*** Amino-Cerv.

Dectaflur *(USAN, rINN)*

Dectafluro; Dectaflurum; SKF-38094. 9-Octadecenylamine hydrofluoride.

Дектафлур

$C_{18}H_{38}NF$ = 287.5.
CAS — 36505-83-6 (nonstereospecific); 1838-19-3 (9-octadecenylamine).

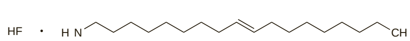

Profile

Dectaflur is used as a source of fluoride (see Sodium Fluoride, p.1962) in the prevention of dental caries. For a report of stomatitis considered to be due to dectaflur, see Hypersensitivity, under Sodium Fluoride, p.1963.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Elmex.

Multi-ingredient: ***Austria:*** Elmex; ***Belg.:*** Elmex; ***Cz.:*** Elmex; ***Fin.:*** Elmex; ***Ger.:*** Elmex; Lawefluor N†; Multifluorid; ***Hung.:*** Elmex; ***Israel:*** Elmex; ***Ital.:*** Elmex; ***Neth.:*** Elmex; ***Switz.:*** Elmex; Paro aux fluorures d'amines Gelee.

Dextrin *(BAN)*

British Gum; Dekstriini; Dekstrinas; Dextrina; Dextrine; Dextrinum; Dextrinum Album; Starch Gum.

$[C_6H_{10}O_5]_n.xH_2O$.
CAS — 9004-53-9.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Dextrin). Maize, potato, or cassava starch partially hydrolysed and modified by heating with or without the presence of acids, alkalis, or pH control agents. A white or almost white, free-flowing powder. Very soluble in boiling water forming a mucilaginous solution; slowly soluble in cold water; practically insoluble in alcohol. A 5% dispersion in water has a pH of 2.0 to 8.0.

USNF 26 (Dextrin). It is starch, or partially hydrolysed starch, modified by heating in a dry state, with or without acids, alkalis, or pH control agents. A white, yellow, or brown free-flowing powder. Its solubility in water varies; it is usually very soluble, but often contains an insoluble portion.

Icodextrin *(BAN, USAN, rINN)*

Icodextrina; Icodextrine; Icodextrinum; Ikodekstriini; Ikodextrin.

Икодекстрин

$[C_6H_{10}O_5]_n$.
CAS — 337376-15-5.

Profile

Dextrin, a glucose polymer, is (1→4)-α-D-glucan derived from the hydrolysis of starch. Icodextrin is dextrin with more than 85% of its molecules with molecular weights between 1640 and 45 000, and a weight-average molecular weight of about 20 000. Dextrin is a source of carbohydrate sometimes used in oral dietary supplements and tube feeding. Glucose is rapidly released in the gastrointestinal tract but because of the high average molecular weight of dextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on dextrin (such as maltodextrin p.1955), and intended for dietary supplementation, usually have a low electrolyte content and are free of lactose and sucrose. These properties make such preparations suitable for dietary supplementation in a variety of diseases including certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Dextrin is used as a tablet and capsule diluent, and as a binding, suspending, and viscosity-increasing agent. It has also been used as an adhesive and stiffening agent for surgical dressings.

Dextrin sulfate intravaginal gel has been investigated in the prophylaxis of HIV infection and AIDS.

Icodextrin is used in dialysis fluids as an alternative to glucose-based solutions (see also below). Icodextrin-based fluids are instilled intraperitoneally to reduce adhesions after gynaecological and other abdominal surgery. They have also been used as vehicles for drugs given via the peritoneal cavity.

Dialysis. Glucose-based solutions are commonly used in dialysis solutions for continuous ambulatory peritoneal dialysis (CAPD). However, there is rapid absorption of glucose across the peritoneal membrane, reducing the duration of ultrafiltration and leading to long-term metabolic complications such as hyperglycaemia, hyperinsulinaemia, hyperlipidaemia and obesity. Other osmotic agents have been investigated. One study reported results in 11 patients[1] receiving CAPD who had suffered repeated fluid overload from glucose-based dialysis solutions, and suggested that replacement of glucose with dextrin as the osmotic agent could reverse fluid overload and possibly reduce the frequency of exchange. However, others[2] considered that the proposed frequency of exchange would not provide adequate removal of urea, and that in addition to underdialysis there would be an accumulation of poorly-metabolisable glucose polymers in the blood.

Icodextrin is another alternative.[3,4] It is a glucose polymer, given in iso-osmolar solution. Studies supported by the manufacturers have found that it can be used in ultrafiltration for up to 12 hours, with lower transperitoneal absorption and potential calorie load than glucose solutions.[5,6] It can also be metabolised by amylases in the blood, so is less likely to accumulate than other glucose polymers if absorbed,[6] although the resultant concentrations of maltose (the primary metabolite) have resulted in falsely elevated blood-glucose measurements with some test methods.[7-9] Licensed product information states that glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase based methods should not be used for this reason. In a study in CAPD patients, icodextrin was well-tolerated and produced at least equivalent ultrafiltration to glucose solutions.[5] Another study found that peritoneal dialysis patients on icodextrin lost weight and had improved fluid status compared with patients on glucose.[10] In a small study of peritoneal dialysis patients with fluid overload and due to be transferred to haemodialysis, substitution of icodextrin for one long-dwell exchange daily significantly increased ultrafiltration and extended technique survival-time.[11]

A combination of icodextrin and glucose has also been investigated as a means to reduce glucose exposure while increasing ultrafiltration.[12,13]

1. Stein A, *et al.* Glucose polymer for ultrafiltration failure in CAPD. *Lancet* 1993; **341:** 1159.
2. Martis L, *et al.* CAPD with dialysis solution containing glucose polymer. *Lancet* 1993; **342:** 176–7.
3. Frampton JE, Plosker GL. Icodextrin: a review of its use in peritoneal dialysis. *Drugs* 2003; **63:** 2079–2105.
4. Hamburger RJ, Kraus MA. Icodextrin fulfills unmet clinical need of PD patients: improved ultrafiltration. *Dialysis Transplant* 2003; **32:** 675–80.
5. Mistry CD, *et al.* A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. *Kidney Int* 1994; **46:** 496–503.
6. Peers E, Gokal R. Icodextrin provides long dwell peritoneal dialysis and maintenance of intraperitoneal volume. *Artif Organs* 1998; **22:** 8–12.
7. Riley SG, *et al.* Spurious hyperglycaemia and icodextrin in peritoneal dialysis fluid. *BMJ* 2003; **327:** 608–9.
8. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 21/07/08)
9. Disse E, Thivolet C. Hypoglycemic coma in a diabetic patient on peritoneal dialysis due to interference of icodextrin metabolites with capillary blood glucose measurements. *Diabetes Care* 2004; **27:** 2279.
10. Davies SJ, *et al.* Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003; **14:** 2338–44.
11. Johnson DW, *et al.* Icodextrin as salvage therapy in peritoneal dialysis patients with refractory fluid overload. *BMC Nephrol* 2001; **2:** 2.
12. Jenkins SB, Wilkie ME. An exploratory study of a novel peritoneal combination dialysate (1.36% glucose/7.5% icodextrin), demonstrating improved ultrafiltration compared to either component studied alone. *Perit Dial Int* 2003; **23:** 475–80.
13. Dallas F, *et al.* Enhanced ultrafiltration using 7.5% icodextrin/1.36% glucose combination dialysate: a pilot study. *Perit Dial Int* 2004; **24:** 542–6.

Hypersensitivity. Skin reactions, sometimes severe and generalised, have occurred in patients given icodextrin.[1-5] Reactions have sometimes been delayed up to about 2 weeks after use.[3]

For the suggestion that recurrent sterile peritonitis in patients receiving icodextrin might be due to a hypersensitivity reaction, see below.

1. Fletcher S, *et al.* Icodextrin allergy in a peritoneal dialysis patient. *Nephrol Dial Transplant* 1998; **13:** 2656–8.
2. Goldsmith D, *et al.* Allergic reactions to the polymeric glucose-based peritoneal dialysis fluid icodextrin in patients with renal failure. *Lancet* 2000; **355:** 897.
3. Queffeulou G, *et al.* Allergy to icodextrin. *Lancet* 2000; **356:** 75.
4. Al-Hoqail IA, Crawford RI. Acute generalized exanthematous pustulosis induced by icodextrin. *Br J Dermatol* 2001; **145:** 1026–7.
5. Valance A, *et al.* Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. *Arch Dermatol* 2001; **137:** 309–10.

Peritonitis. Sterile peritonitis attributed to icodextrin has been reported.[1,2] Subsequently, several batches were withdrawn by the manufacturer in May 2002 because of bacterial contamination with high levels of peptidoglycan.[2,3] However, further incidents of peritonitis have been reported with icodextrin in patients previously exposed to the withdrawn batches,[4-6] prompting theories of sensitisation to icodextrin or peptidoglycans. Concerns were expressed regarding possible cross-sensitisation to dextran polymers in these patients,[6] as well as the possibility that even low levels of peptidoglycans might trigger peritonitis.[7] Histological changes similar to bacterial peritonitis have been found in patients with icodextrin-associated sterile peritonitis.[8] It was suggested that if cloudy dialysate reappeared upon rechallenge, icodextrin should be withdrawn.[8]

In an effort to determine the cause of the aseptic peritonitis, a manufacturer-sponsored analysis determined that recalled batches of dialysis solution were within product and pharmacopoeial specifications for content, safety, and sterility. However, both dialysate solution and icodextrin raw material caused increases in interleukin-6 response *in vitro*, suggesting a non-endotoxin contaminant as the cause of the aseptic peritonitis. Further analysis found peptidoglycan contamination of the raw icodextrin by *Alicyclobacillus acidocaldarius* to be the cause.[3]

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2. MacGinley R, *et al.* Relapsing culture-negative peritonitis in peritoneal dialysis patients exposed to icodextrin solution. *Am J Kidney Dis* 2002; **40:** 1030–5.
3. Martis L, *et al.* Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. *Lancet* 2005; **365:** 588–94.
4. Basile C, *et al.* The impact of relapsing sterile icodextrin-associated peritonitis on peritoneal dialysis outcome. *J Nephrol* 2003; **16:** 384–6.
5. Povlsen JV, *et al.* Exposure to the peptidoglycan contaminant in icodextrin may cause sensitization of the patient maintained on peritoneal dialysis. *Perit Dial Int* 2003; **23:** 509–10.
6. Enia G, *et al.* Sterile icodextrin-associated peritonitis may induce hypersensitivity and recurrent peritonitis on re-challenge. *Nephrol Dial Transplant* 2003; **18:** 626.
7. Seow Y-YT, *et al.* Icodextrin-associated peritonitis among CAPD patients. *Nephrol Dial Transplant* 2003; **18:** 1951–2.
8. Goffin E, *et al.* Icodextrin-associated peritonitis: what conclusions thus far? *Nephrol Dial Transplant* 2003; **18:** 2482–5.

Preparations

USNF 26: Liquid Glucose.

Proprietary Preparations (details are given in Part 3)
Austral.: Poly-Joule; ***Fr.:*** Caloreen; ***Gr.:*** Caloreen†; ***Neth.:*** Dexemel†; ***UK:*** Adept; Caloreen; Dexemel†.

Multi-ingredient: ***Fr.:*** Picot†.

Ferric Ammonium Citrate

381; Ammonium Ferric Citrate; Citrato amónico férrico; Demir III Amonyum sitrat; Ferricum Citricum Ammoniatum; Iron and Ammonium Citrate.

CAS — 1185-57-5.
ATC — V08CA07.
ATC Vet — QV08CA07.

Pharmacopoeias. In *US.*

USP 31 (Ferric Ammonium Citrate). It contains between 16.5% and 18.5% of iron. Store in airtight containers at a temperature of 8° to 15°. Protect from light.

Profile

Ferric ammonium citrate is given orally as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is also used as a food additive, as an acidity regulator, anticaking agent, or source of iron. It has been used as a colouring agent.

Preparations

USP 31: Ferric Ammonium Citrate for Oral Solution.

Proprietary Preparations (details are given in Part 3)
Braz.: Vinho Ferruginoso†; ***Gr.:*** Ferriseltz†; ***India:*** Rubraplex; ***Ital.:*** Sciroppo Fenoglio†; ***Neth.:*** FerriSeltz; ***Port.:*** Cobalti†; ***Spain:*** Ferriseltz; ***Turk.:*** Ferro; Nuklofer Tonik; Samson; Tonoferrin; ***Venez.:*** Dociron†.

Multi-ingredient: ***Arg.:*** ITE B12 Forte; ***Austria:*** Ferrovin-Chinaeisenwein; ***Braz.:*** Ferroben†; Ferrotrat B12 Plus; Ferrotrat B12†; Hematiase B12; Hepavitose†; Regulador Xavier N-2†; Rubrobion†; ***Canad.:*** Maltlevol; ***Ger.:*** Praefeminon plus†; ***Hong Kong:*** Nutroplex; ***India:*** Blosyn; Dexorange; Ferradol; Ferrochelate; Genfol; Globac-Z; Haem Up; Hepatoglobine; Vitamon; ***Ital.:*** Emopon; ***Malaysia:*** Nutroplex†; ***Singapore:*** Nutroplex; ***UK:*** Ironorm; Lexpec with Iron-M†; Lexpec with Iron†; ***USA:*** Geritol; Geritonic; ***Venez.:*** Beferron; Cianofer; Fercobre B-12†; Fercobre†.

Ferric Carboxymaltose *(USAN, rINN)*

Carboximaltosa Férrica; Carboxymaltose Ferrique; Ferricum Carboxymaltosum; VIT-45.

Феррик Карбоксимальтоз

CAS — 9007-72-1.

Profile

Ferric carboxymaltose is used as a source of parenteral iron (p.1949) for iron-deficiency anaemia (p.1951) when oral iron therapy is ineffective or impractical. Dosage should be individualised and the calculated total cumulative dose of iron should not be exceeded. Ferric carboxymaltose is given by intravenous bolus injection over 1 to 2 minutes, in doses supplying up to 200 mg of iron up to 3 times weekly, or diluted in sodium chloride 0.9% by intravenous infusion in a dose of up to 1 g of iron no more than once weekly. It should not be given by intramuscular or subcutaneous injection. In patients on dialysis it may be given undiluted directly into the venous limb of the dialyser. For further information relating to the parenteral use of iron, see Iron Dextran, p.1951.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ferinject; ***Switz.:*** Ferinject; ***UK:*** Ferinject.

Ferric Pyrophosphate

Férrico, pirofosfato; Iron Pyrophosphate.

$Fe_4(P_2O_7)_3$ = 745.2.
CAS — 10058-44-3.

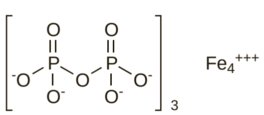

Profile

Ferric pyrophosphate is given orally as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Incremin Iron; ***Chile:*** Incremin†; ***Mex.:*** Incremin Con Hierro; ***USA:*** Vitafol; Vitalize.

Ferritin

Ferritina.

Profile

Ferritin is the major iron storage protein of vertebrates, found mainly in the liver, spleen, intestinal mucosa, and bone marrow and consisting of a soluble protein shell (apoferritin) with a core of crystalline ferric hydroxyphosphate complex. It has been given orally as a source of iron (p.1949) in iron-deficiency anaemias (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Ferrivax; ***Spain:*** Ferroprotina; Hierco†; Kilor; Profer.

Ferrocholinate *(rINN)*

Ferrocholinatum; Ferrocolinato.

Феррохолинат

$C_{11}H_{20}FeNO_9,2H_2O$ = 402.2.
CAS — 1336-80-7.

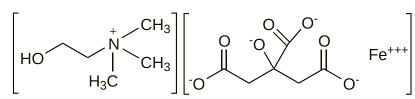

Profile

Ferrocholinate is a chelate prepared by reacting equimolar quantities of freshly precipitated ferric hydroxide with choline dihydrogen citrate. It is given orally as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Podertonic.

Ferrous Ascorbate

Ferroso, ascorbato.

$C_{12}H_{14}FeO_{12}$ = 406.1.
CAS — 24808-52-4.
ATC — B03AA10.
ATC Vet — QB03AA10.

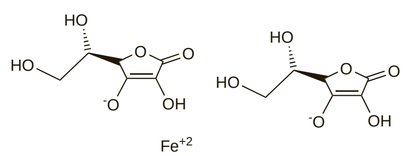

Profile

Ferrous ascorbate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in usual doses of up to 1.47 g daily (equivalent to about 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Ascofer.

Multi-ingredient: ***Austria:*** China-Eisenwein.

Ferrous Aspartate

Ferroso, aspartato.

$C_8H_{12}FeN_2O_8,4H_2O$ = 392.1.
ATC — B03AA09.
ATC Vet — QB03AA09.

Profile

Ferrous aspartate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in usual doses of up to 750 mg daily (equivalent to about 100 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Spartocine†; ***Fin.:*** Spartocine; ***Ger.:*** Spartocine N†; ***USA:*** FE Aspartate.

Ferrous Chloride

Ferroso, cloruro. Iron (II) chloride tetrahydrate.

$FeCl_2,4H_2O$ = 198.8.
CAS — 7758-94-3 (anhydrous ferrous chloride); 13478-10-9 (ferrous chloride tetrahydrate).
ATC — B03AA05.
ATC Vet — QB03AA05.

Profile

Ferrous chloride is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in a usual dosage of about 350 to 700 mg daily in divided doses (equivalent to about 100 to 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Fer UCB; ***Pol.:*** Hemofer; ***Switz.:*** Ferrascorbin.

Multi-ingredient: ***Switz.:*** Ferrascorbin.

Ferrous Fumarate

Demir Fumarat; Ferrofumaraatti; Ferrofumarat; Ferrosi fumaras; Ferroso, fumarato; Fumaran železnatý; Fumarate ferreux; Geležies(II) fumaratas; Vas(II)-fumarát.

$C_4H_2FeO_4$ = 169.9.
CAS — 141-01-5.
ATC — B03AA02.
ATC Vet — QB03AA02; QB03AD02.

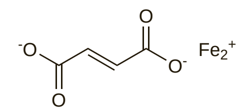

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Ph. Eur. 6.2 (Ferrous Fumarate). A fine, reddish-orange or reddish-brown powder. Slightly soluble in water; very slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Ferrous Fumarate). A reddish-orange to red-brown, odourless powder, which may contain soft lumps that produce a yellow streak when crushed. Slightly soluble in water; very slightly soluble in alcohol. Its solubility in dilute hydrochloric acid is limited by the separation of fumaric acid.

Profile

Ferrous fumarate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in usual doses of up to 600 mg daily (equivalent to about 200 mg of iron daily); doses of up to 1.2 g daily (equivalent to about 400 mg of iron daily) may be used if necessary.

Preparations

BP 2008: Ferrous Fumarate and Folic Acid Tablets; Ferrous Fumarate Capsules; Ferrous Fumarate Oral Suspension; Ferrous Fumarate Tablets;
USP 31: Ferrous Fumarate and Docusate Sodium Extended-release Tablets; Ferrous Fumarate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Ferretab; Ferrobet; ***Braz.:*** Ferroklinge†; ***Canad.:*** Neo-Fer; Palafer; ***Cz.:*** Ferronat; ***Fr.:*** Fumafer; ***Ger.:*** Ferrokapsul†; Ferrum Hausmann; Rulofer N; ***Hung.:*** Feroglobin-B12; ***Indon.:*** Fercee; ***Irl.:*** Galfer; ***Malaysia:*** Firon†; ***Mex.:*** Biofuroso; Croferron; Fernadin; Ferro-Terapina; Ferval; Fumavit; Gestaferron; Medifer; ***Norw.:*** Nycoplus Neo-Fer; ***Singapore:*** Iron Beacons; ***Swed.:*** Erco-Fer; ***Switz.:*** Ferrum Hausmann; Lufer; ***Thai.:*** F-Tab; Femarate; Ferdek; Fermasian; Fermate; ***UK:*** Fersaday; Fersamal; Galfer; ***USA:*** Femiron; Feostat†; Ferretts; Ferro-Dok; Hemaspan†; Hemocyte; Nephro-Fer; Vitron-C; ***Venez.:*** Ferol; Ferroce; Fumafer†.

Multi-ingredient: ***Arg.:*** Anemidox-Ferrum; Anemidox-Solutab; Autrinic Compuesto†; Ferretab Compuesto; Ferrocebrina; Hematon†; Hierro Folico; ***Austral.:*** Bio Iron; Extralife PMS-Care; Medinat PMT-Eze†; ***Austria:*** Ferretab Comp; ***Belg.:*** Gestiferrol; ***Braz.:*** Betozone; Iloban; Rubralong†; ***Canad.:*** Appedrine†; Fortiplex†; Neo-Fer CF; Palafer CF; ***Chile:*** Cronoferril†; Ferranim; Ferro Vitaminico; Folifer; Microfemin†; Orlon; ***Cz.:*** Ferretab Compositum; ***Fin.:*** Matrifolin; ***Ger.:*** Ferrodix†; ***Hong Kong:*** Fortifer; ***India:*** Anemidox; Autrin; Elferri-Z; Fervit†; Globac-Z; Hemsi; Hepasules; Hepatoglobine; Livogen Captab; Livogen-Z; Livogen†; Siderfol; Softeron; Softeron-Z; ***Indon.:*** Calmin-AF; Dasabion; Emineton; Hemarate CE; Hemobion; Natabion; Nichobion; Odiron-C; Prenamia; Prenatin-DF; Rejuvan; Vitachol; Vitalex; Vitamam 2; Vitamam 3; Vitonal-F; ***Irl.:*** Ferrocap F†; Galfer FA; Givitol; ***Israel:*** Folex; Foric; ***Malaysia:*** Ferrovit; Odiron-C†; ***Mex.:*** Autrin†; Dialeli AF; Ferlor AF†; Ferro Grin; Ferrotemp; Fumarol; Yemifer-HE; ***Philipp.:*** Anemicon Plus; Anixon; Appebon with Iron; Beniforte; Essenfer; Fergesol; Ferosal; Ferroplex; Foramefer; Fortifer; Fortifer FA; Fumiron + B; Globifer; Harvifer; Hemarate; Hemobion; Iroplex; Macrobee with Iron; Molvite-OB; Multispec-E; Mulvitron; Nakaron; Trev-Iron; TriHEMIC; Trust Pill; Zoiron; ***Rus.:*** Ferretab Comp (Ферретаб Комп); ***S.Afr.:*** Autrin; Pregamal; ***Singapore:*** Iron Melts; Odiron-C; Wanse; ***Spain:*** Foliferron; ***Switz.:*** Duofer; Duofer Fol; ***Thai.:*** Adnemic F†; Adnemic†; Biocalron; FB Fer; FBC; FBC Plus; FBIC†; Fer-200; Ferli-6; Ferosix; Ferplus-B; Ferropro; Hemarate; Hemolax; Intricon; Obimin-AZ; Polycolvit; Polyvit; Trinsicon†; ***Turk.:*** Vi-Fer; ***UK:*** Galfer FA; Meterfolic; Pregaday; ***USA:*** ABC to Z; Anemagen OB†; Anemagen†; Berocca Plus; Caltrate + Iron & Vitamin D; Certagen; Cevi-Fer†; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Estrostep Fe; Femcon Fe; Ferotrinsic; Ferrogels Forte; Fetrin; Formula B Plus; Fumatinic; Geriot; Gevral T; Hem Fe; Hematinic; Hematinic Plus; Hemocyte Plus; Hemocyte-F; Junel Fe; Livitrinsic-f; Loestrin Fe; Nephro-Fer Rx†; Parvlex; Pronemia Hematinic; Repliva; Tandem; Thera Hematinic; Theragenerix-H; Tilia Fe; Tolfrinic; Tri-Legest; TriHEMIC; Trinsicon; Vitafol; Yelets; Zodeac; ***Venez.:*** Cobalfer; Fefol; Fercor†; Ferroliver; Ferronorm; Folifer B-12; Hepafol con B-12.

Ferrous Gluceptate

Ferroso, gluceptato; Ferrous Glucoheptonate.

$Fe(C_7H_{13}O_8)_2$ = 506.2.
CAS — 25126-38-9.

Profile

Ferrous gluceptate is given orally as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Unifer.

Multi-ingredient: ***Arg.:*** Egestan Hierro; ***Spain:*** Clamarvit†; Normovite Antianemico.

Ferrous Gluconate

E579; Eisen(II)-Gluconat; Ferroglukonaatti; Ferroglukonat; Ferrosi gluconas; Ferrosi Gluconas Hydricus; Ferroso, gluconato; Geležies(II) gliukonatas; Gluconate ferreux; Glukonan železnatý hydrát; Vas(II)-glükonát; Żelaza(II) glukonian. Iron (II) di(D-gluconate).

$C_{12}H_{22}FeO_{14},xH_2O$.

CAS — 299-29-6 (anhydrous ferrous gluconate); 12389-15-0 (ferrous gluconate dihydrate).

ATC — B03AA03.

ATC Vet — QB03AA03.

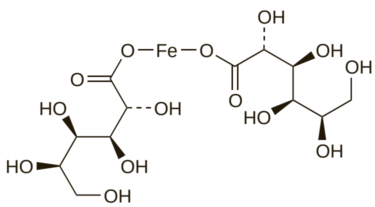

(anhydrous ferrous gluconate)

Pharmacopoeias. In *Eur.* (see p.vii).
Chin. and *US* specify the dihydrate.
Ph. Eur. 6.2 (Ferrous Gluconate). A greenish-yellow to grey powder or granules. It contains not less than 11.8% and not more than 12.5% of ferrous iron calculated with reference to the dried substance. Freely but slowly soluble in water producing a greenish-brown solution, more readily soluble in hot water; practically insoluble in alcohol. A 10% solution in water has a pH of 4.0 to 5.5 three to four hours after preparation. Protect from light.
USP 31 (Ferrous Gluconate). A yellowish-grey or pale greenish-yellow, fine powder or granules having a slight odour resembling that of burnt sugar. Soluble 1 in 5 of water; practically insoluble in alcohol. A 5% solution in water is acid to litmus. Store in airtight containers.

Profile

Ferrous gluconate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.8 g daily (equivalent to up to 210 mg of iron daily).

Preparations

BP 2008: Ferrous Gluconate Tablets;
USP 31: Ferrous Gluconate Capsules; Ferrous Gluconate Elixir; Ferrous Gluconate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Fergon†; ***Austria:*** Losferron; ***Belg.:*** Losferron; ***Canad.:*** Novo-Ferrogluc; ***Chile:*** Glucoferro K; ***Cz.:*** Losferron; ***Ger.:*** Eisen-Sandoz; Ferrum Verla; Losferron; Rulofer G; Vitaferro; ***Israel:*** Ferro; Ferro-Nes; ***Ital.:*** Auxofer; Bioferal; Bioglufer; Blizer; Blustark; Crom; Cromatonferro; Effegyn; Emonorm†; Emoxiron; Eriglobin; Eritropiu; Ferig; Ferro Complex; Ferrogyn; Flexifer†; Gloros; Glucoferro; Losferron; Megafer; Monoferro; Prontoferro; Sidervim; Sustemial; ***Neth.:*** Losferron; ***NZ:*** Fergon†; ***Pol.:*** Ascofer; ***Port.:*** Anemital†; Bioferro; Hemototal; Losferron†; ***Rus.:*** Ferronal (Ферронал); ***Spain:*** Ferrum Sandoz; Losferron; ***Switz.:*** Loesfer†; Lufer; ***Turk.:*** Losferron; ***USA:*** Fergon; ***Venez.:*** Ferroper†; Irolen†; Salfer; Yisafer.

Multi-ingredient: ***Austria:*** Losferron-Fol; ***Fr.:*** Tot'Hema; ***Ger.:*** Biovital Aktiv†; Ferro-C-Calcium; Ferrodix†; Floradix Krauterblut; ***India:*** Elferri†; Gynae-CVP; JP Tone; Livogen Hemtonic; Pentavite†; ***Indon.:*** Adfer; Biosanbe; Diabion; Emibion; Habebion; Inbion; Maltiron; Muveron; Neogobion; Opibion; Sangobion; Sangofer; Sangovitin; Tropifer; Vitabion; ***Malaysia:*** Sangobion; ***Philipp.:*** Sangobion; ***Pol.:*** Additiva Ferrum; ***Port.:*** Tot'Hema; ***Rus.:*** Tot'Hema (Тотема); ***S.Afr.:*** Kiddie Vite†; ***Singapore:*** Neogobion; Sangobion; ***Spain:*** Clamarvit†; ***Switz.:*** Duofer; Duofer Fol; Ferrascorbin; ***Thai.:*** Ferro-Be-Sian; Glufer-C; ***Turk.:*** Ferro-Vital; ***UK:*** Foresight Iron Formula; ***USA:*** Compete; Ferralet Plus†; Hytinic†; Iromin-G; Mission Surgical Supplement†; ***Venez.:*** Gestocal†.

Ferrous Glycine Sulfate

Demir Glisin Sülfat; Ferroglycini Sulfas; Ferroglycinsulfat; Ferroglysiinisulfaatti; Ferroso de glicina, sulfato; Ferrous Aminoacetosulphate; Ferrous Glycine Sulphate.

CAS — 14729-84-1.

ATC — B03AA01.

ATC Vet — QB03AA01.

Profile

Ferrous glycine sulfate is a chelate of ferrous sulfate and glycine used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses containing the equivalent of up to 150 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Neutrofer; ***Chile:*** Cheltin; ***Denm.:*** Glycifer; Niferex; ***Fin.:*** Obsidan; ***Ger.:*** Ferro Sanol; Ferro sanol duodenal; ***Gr.:*** Ferro Sanol; ***Irl.:*** Plesmet; ***Port.:*** Ferrocutid†; Niferex; ***Spain:*** Ferbisol; Ferro Sanol; Glutaferro; ***Swed.:*** Niferex; ***Switz.:*** Ferrosanol duodenal; ***Turk.:*** Ferro Sanol; ***UK:*** Plesmet†; ***USA:*** Gentle Iron; ***Venez.:*** Herronduo.

Multi-ingredient: ***Braz.:*** Neutrofer Folico; ***Fin.:*** Obsidan comp; ***Ger.:*** Ferro sanol comp; Ferro sanol gyn; ***India:*** Fecontin-F; Fecontin-Z; ***Turk.:*** Ferro Sanol B; ***USA:*** Repliva; ***Venez.:*** Herrongyn.

Ferrous Lactate

E585; Ferroso, lactato; Iron Lactate.

$C_6H_{10}FeO_6,3H_2O = 288.0.$

CAS — 5905-52-2 (anhydrous ferrous lactate); 6047-24-1 (ferrous lactate trihydrate).

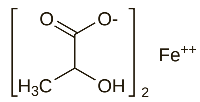

(anhydrous ferrous lactate)

Profile

Ferrous lactate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cromatonbic Ferro†; ***S.Afr.:*** Ferro Drops L; ***Spain:*** Cromatonbic Ferro.

Multi-ingredient: ***Hung.:*** Fagifor†.

Ferrous Oxalate

Ferroso, oxalato; Ferrum Oxalicum Oxydulatum; Iron Protoxalate.

$C_2FeO_4,2H_2O = 179.9.$

CAS — 516-03-0 (anhydrous ferrous oxalate); 6047-25-2 (ferrous oxalate dihydrate).

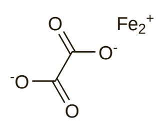

(anhydrous ferrous oxalate)

Profile

Ferrous oxalate has been used as a source of iron (p.1949).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Disulone.

Ferrous Succinate

Ferroso, succinato.

$C_4H_4FeO_4 = 171.9.$

CAS — 10030-90-7.

ATC — B03AA06.

ATC Vet — QB03AA06.

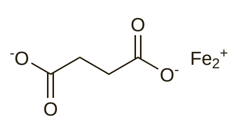

Profile

Ferrous succinate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to about 600 mg daily (equivalent to up to about 200 mg of iron daily).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferdromaco; ***Ger.:*** Ferrlecit 2; ***Swed.:*** Ferromyn S.

Multi-ingredient: ***India:*** Hematrine.

Ferrous Sulfate

Demir Sülfat; Eisen(II)-Sulfat; Ferreux (Sulfate); Ferrosi Sulfas; Ferrosi sulfas heptahydricus; Ferroso, sulfato; Ferrosulfaattiheptahydraatti; Ferrosulfatheptahydrat; Ferrous Sulphate; Ferrum Sulfuricum Oxydulatum; Geležies(II) sulfatas heptahidratas; Iron (II) Sulphate Heptahydrate; Iron Sulphate; Síran železnatý heptahydrát; Sulfate ferreux heptahydraté; Vas(II)-szulfát; Żelaza(II) siarczan.

$FeSO_4,7H_2O = 278.0.$

CAS — 7720-78-7 (anhydrous ferrous sulfate); 7782-63-0 (ferrous sulfate heptahydrate).

ATC — B03AA07.

ATC Vet — QB03AA07; QB03AD03.

NOTE. Crude ferrous sulfate is known as Green Vitriol or Green Copperas.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Swiss also includes ferrous sulfate sesquihydrate.
Ph. Eur. 6.2 (Ferrous Sulphate Heptahydrate). A light green crystalline powder or bluish-green crystals, efflorescent in air. It is oxidised in moist air, becoming brown. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.
USP 31 (Ferrous Sulfate). Pale bluish-green, odourless, crystals or granules. It is efflorescent in dry air and oxidises readily in moist air to form brownish-yellow basic ferric sulfate. Soluble 1 in 1.5 of water and 1 in 0.5 of boiling water; insoluble in alcohol. A 10% solution in water is acid to litmus, having a pH of about 3.7. Store in airtight containers.

Dried Ferrous Sulfate *(USAN)*

Dried Ferrous Sulphate; Exsiccated Ferrous Sulphate; Ferreux (sulfate) desséché; Ferrosi sulfas desiccatus; Ferrosi Sulfas Exsiccatus; Ferroso desecado, sulfato.

CAS — 13463-43-9.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Ferrous Sulphate, Dried). Hydrated ferrous sulphate deprived of part of its water of hydration by drying. A greyish-white powder which is oxidised in moist air, becoming brown. It contains 86.0 to 90.0% of $FeSO_4$. Slowly but freely soluble in water, very soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.
USP 31 (Dried Ferrous Sulfate). A greyish-white to buff-coloured powder consisting primarily of ferrous sulfate monohydrate with varying amounts of ferrous sulfate tetrahydrate. It contains 86.0 to 89.0% of $FeSO_4$. Slowly soluble in water; insoluble in alcohol.

Profile

Ferrous sulfate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally; the dried form is often used in solid dosage forms and the heptahydrate in liquid dosage forms. Usual doses of dried ferrous sulfate are up to 600 mg daily (equivalent to 180 to 195 mg of iron daily, this figure being somewhat variable depending on the purity and water content of the salt).

Ferrous sulfate oxidised with nitric and sulfuric acids yields ferric subsulfate solution, also known as Monsel's solution, which has been used as a haemostatic.

Preparations

BP 2008: Ferrous Sulphate Tablets; Paediatric Ferrous Sulphate Oral Solution; Prolonged-release Ferrous Sulphate Tablets;
BPC 1973: Compound Ferrous Sulphate Tablets;
USP 31: Ferric Subsulfate Solution; Ferrous Sulfate Oral Solution; Ferrous Sulfate Syrup; Ferrous Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Eurofer; Factofer; Feklon; Fer-In-Sol; Ferlea†; Ferricol; Ferrocebrina; Ferromas; Ferrometion; Hemoferrol; Iberol; Medifer; Siderblut; Vitaferro†; ***Austral.:*** Ferro-Gradumet; Ferrograd C; ***Austria:*** Aktiferrin; Ferro-Gradumet; Ferrograd C; Infa-Tardyferon; Tardyferon; ***Belg.:*** Fero-Grad; Fero-Gradumet; ***Braz.:*** Anemiplus†; Cimefer; Fer-In-Sol; Ferrison†; Ferronil; Ferrosol; Ferrototal; Ferrotron†; Hematofer†; Iberol; Ironfer; Lomfer†; Neck-Fer†; Perfer†; Salonfer†; Sulfatofer†; Sulfer Plus; Sulfergan Composto; Sulferro; Sulferrol; Tratfer†; ***Canad.:*** Fer-In-Sol; Fero-Grad; Ferodan; Ferofate; Slow-Fe; ***Chile:*** Ferinsol; Ferrigot; Ferromalt; Iberol Simple†; ***Cz.:*** Aktiferrin; Eisen-Diasporal†; Ferro-Gradumet†; Sorbifer; Tardyferon; ***Denm.:*** Ferro; ***Fin.:*** Duroferon; Retafer; ***Fr.:*** Fero-Grad vitamine C; Timoferol; ***Ger.:*** Aktiferrin N; Ceferro; Dreisafer; Eisendragees-ratiopharm; Eryfer; Ferrogamma; FERROinfant N†; Haemoprotect; Hamatopan; Kendural C; Plastufer; Plastulen; Tardyferon; Vitaferro; ***Gr.:*** Fer-In-Sol†; Microfer; Resoferon; Tardyferon; ***Hong Kong:*** Feospan†; Ferasul; Iron-200; ***Hung.:*** Aktiferrin; Ferro-Gradumet; Sorbifer; Tardyferon; ***Irl.:*** Feospan; Fer-In-Sol; Ferrograd; Ferrograd C; ***Israel:*** Ferro-Gradumet; Slow-Fe; ***Ital.:*** Fer-In-Sol; Ferrograd; Ferrograd C; ***Malaysia:*** Feospan†; Retafer; ***Mex.:*** Fer-In-Sol; Ferifer; Forcil; Hemobion; Valdefer; ***Neth.:*** Fero-Gradumet; Ferrograd; Protiferron; ***Norw.:*** Duroferon; Ferromax; Nycoplus Ferro-Retard; ***NZ:*** Ferro-Gradumet; Ferrograd C; ***Philipp.:*** Feosol; Feovit; Fer-In-Sol; Ferglobin; Ferosal; Sorbifer; United Home Fersulfate Iron; ***Pol.:*** Ferro-Gradumet; Hemofer; Sorbifer; Tardyferon; ***Port.:*** Ferro-Gradumet; Tardyferon; ***Rus.:*** Aktiferrin (Актиферрин); Ferro-Gradumet (Ферроградумет); Ferroplex (Ферроплекс); Hemofer (Гемофер); Sorbifer (Сорбифер); Tardyferon (Тардиферон); ***S.Afr.:*** Fero-Grad; Fesofor; ***Singapore:*** Feospan†; ***Spain:***

Fero-Gradumet; Tardyferon; ***Swed.:*** Duroferon; ***Switz.:*** Actiferrine; Ferro-Gradumet; Resoferon†; ***Thai.:*** Fer-In-Sol; Ferrotabs; Pediron; ***Turk.:*** Oroferon; Tardyferon; ***UAE:*** Kdiron; ***UK:*** Feospan; Ferrograd; Ferrograd C; Ironorm; Slow-Fe†; ***USA:*** Ed-in-Sol†; Fe ; Feosol; Fer-gen-sol; Fer-In-Sol; Fer-Iron†; Feratab; Fero-Grad; Irospan; Slow-Fe; ***Venez.:*** Corsafer†; Fer-In-Sol; Gotafer†; Ironcor†; Mol-Iron†.

Multi-ingredient: ***Arg.:*** Factofer B12; Fefol; Ferro Folic; Hierro Plus; Iberol; Rubiron; Sideralce; Vifortol Prenatal; ***Austral.:*** Fefol; FGF Tabs; Irontona; ***Austria:*** Aktiferrin Compositum; Ferrograd Fol; Ferrum-Quarz; Kephalodoron; Tardyferon-Fol; ***Braz.:*** Anemix†; Anemofer†; Betozone; Cobaldoze; Combiron; Coraben†; Dobiron; Ferrocomplex; Ferroplex; Ferrotonico B12†; Ferrotonico†; Ferrotrat; Iberin Folico; Iberol; Novofer; Paratonico; Rubrargil; Sulfato Ferroso Composto; Sulfatofer†; Tonico Blumen†; ***Canad.:*** Iberet†; Slow-Fe Folic; ***Chile:*** Acomir con hierro; Ferranem; Ferro F-500 Gradumet†; Iberol; Iberol Folico; ***Cz.:*** Aktiferrin Compositum; Ferro-Folgamma; Ferrograd Folic†; Tardyferon-Fol; ***Fr.:*** Tardyferon; Tardyferon B ; ***Ger.:*** Biovital Aktiv†; Eisenkapseln†; Eryfer comp; Ferro-Folgamma; Ferro-Folsan; Hamatopan F; Kendural-Fol-500; Plastulen N; Tardyferon-Fol; ***Gr.:*** Feofol; Fero-Folic; Gyno-Tardyferon; ***Hong Kong:*** Iberet; Iberet-Folic; ***Hung.:*** Biovital†; Ferro-Folgamma; Ferrograd Folic; Tardyferon-Fol; ***India:*** Cofol; Conviron-TR; Fefol; Fefol-Z; Ferrochelate-Z; Fesovit; Iberol; JP Tone-TR; Maxiferon; Plastules; ***Indon.:*** Iberet; Iberet-Folic; ***Irl.:*** Fefol; Ferrograd Folic; Ferrotab†; ***Israel:*** Aktiferrin-F; Ferrograd Folic; Slow-Fe Folic; ***Ital.:*** Ferrograd Folic; ***Malaysia:*** Aktiferrin-F; Iberet-Folic; Iberet†; ***Mex.:*** Ferro Folico; Iberet; Iberol; Orafer Comp; Tardyferon-Fol; ***NZ:*** Ferrograd Folic; ***Philipp.:*** Ameciron; Appebon with Iron; Appetason; Drexabion OB; Dupharon; Femina; Ferlin; Ferosal; Ferro-Folsan Plus; Foralivit; IBC; Iberet; Iberet-Folic; Imefer; Irobon; Mediferron; Mediferron-Vita; Micron-C; Molvite with Iron; Propan with Iron; Regeron-E Plus; Terraferron; ***Pol.:*** Ferrograd Folic; Hemofer F; Tardyferon-Fol; ***Port.:*** Ferro-Folsan†; Ferrograd Folico; Folifer; Tardyferon-Fol; ***Rus.:*** Aktiferrin Compositum (Актиферрин Композитум); Fenules (Фенюльс); Ferro-Folgamma (Ферро-Фольгамма); Gyno-Tardyferon (Гино-тардиферон); ***S.Afr.:*** Fefol; Fefol-Vit; Fero-Folic; Ferrous Sulphate Compound; Foliglobin; ***Singapore:*** Aktiferrin-F; Ferbeaplex; Iberet; Iberet-Folic; Tardyferon B †; ***Switz.:*** Actiferrine-F Nouvelle formule; Fero-Folic; Gyno-Tardyferon; Kendural; Tardyferon; ***Thai.:*** Iberet†; ***Turk.:*** Gyno-Tardyferon; Gynoferon; Natabec; ***UAE:*** Folicron; ***UK:*** Fefol; Ferrograd Folic; Ironorm; Slow-Fe Folic†; ***USA:*** Aqua Ban Plus; Fero-Folic; Generet; Gerivites†; Iberet-Folic†; Iberet†; Slow Fe with Folic Acid; ***Venez.:*** Autrin†; Ferro-Folic; Ferroce con B12.

Ferrous Tartrate

Ferrosi Tartras; Ferroso, tartrato.

$C_4H_4FeO_6,2H_2O = 249.0$.

CAS — 2944-65-2 (anhydrous ferrous tartrate).

ATC — B03AA08.

ATC Vet — QB03AA08.

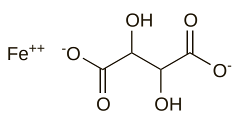

(anhydrous ferrous tartrate)

Profile

Ferrous tartrate has been used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Denm.:*** Ferroplex-frangula.

Ferumoxytol *(USAN)*

Code 7228.

Ферумокситол

CAS — 1309-38-2.

Profile

Ferumoxytol is a superparamagnetic iron oxide that is coated with a low-molecular-weight semisynthetic carbohydrate, polyglucose sorbitol carboxymethyl ether. It is under investigation as a source of iron for iron-deficiency anaemia in patients with chronic kidney disease. Ferumoxytol may potentially be used as a contrast medium in magnetic resonance imaging (p.1474).

◊ References.

1. Landry R, *et al.* Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol* 2005; **25:** 400–10.
2. Spinowitz BS, *et al.* The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. *Kidney Int* 2005; **68:** 1801–7.

Folic Acid *(BAN, rINN)*

Acide folique; Ácido fólico; Acidum folicum; Folacin; Folik Asit; Folinsyre; Folio rūgštis; Folsav; Folsyra; Foolihappo; Kwas foliowy; Kyselina listová; PGA; Pteroylglutamic Acid; Pteroylmonoglutamic Acid; Vitamin B_9; Vitamin B_{11}. *N*-[4-(2-Amino-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

Фолиевая Кислота

$C_{19}H_{19}N_7O_6 = 441.4$.

CAS — 59-30-3 (folic acid); 6484-89-5 (sodium folate).

ATC — B03BB01.

ATC Vet — QB03BB01.

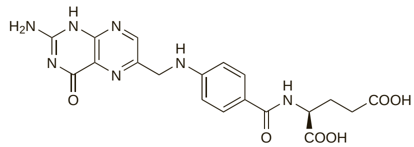

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Folic Acid). A yellowish or orange crystalline powder. Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions. Protect from light.

USP 31 (Folic Acid). A yellow, yellow-brownish, or yellowish-orange, odourless crystalline powder. Very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether. It readily dissolves in dilute solutions of alkali hydroxides and carbonates; soluble in hot, 3N hydrochloric acid and in hot, 2N sulfuric acid; soluble in hydrochloric acid and in sulfuric acid, yielding pale yellow solutions. Protect from light.

Adverse Effects

Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Hypersensitivity. A woman had 3 episodes of hypersensitivity, including anaphylaxis, on exposure to synthetic folic acid. Intradermal testing with folic acid solution was positive and a blinded challenge to folic acid solution led to widespread urticaria. Sensitisation to folic acid may have occurred after supplementation with vitamin B, at which time she had recurrent episodes of urticaria. The patient appeared to tolerate dietary folates, and the authors suggested that foods fortified with folic acid be clearly labelled.[1]

1. Smith J, *et al.* Recurrent anaphylaxis to synthetic folic acid. *Lancet* 2007; **370:** 652.

Precautions

Folic acid should never be given alone or with inadequate amounts of vitamin B_{12} for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B_{12} deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord (see also Vitamin B_{12} Deficiency, below).

Breast feeding. Folic acid is excreted into breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving folic acid, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/01/06)

Carcinogenicity. Follow-up data from a large study of folate supplementation suggested a greater risk of death due to breast cancer in those women randomised to high doses; the association was not statistically significant and further studies were considered necessary.[1] In contrast, other studies suggest a reduced risk of some cancers with folate supplementation, see Prophylaxis of Malignant Neoplasms, p.1927. A large study found that folic acid supplementation did not reduce colorectal adenoma risk; evidence for an increased risk of adenomas with supplementation was equivocal.[2] *Animal* studies suggest that folic acid may have dual modulatory effects on carcinogenesis, depending on dose and timing of supplementation. Folate deficiency may inhibit, whereas supplementation may promote, the progression of established neoplasms. In normal tissue, however, folate deficiency can predispose towards neoplastic transformation and modest amounts of folate may suppress tumour development; supraphysiological doses may enhance tumour progression.[3,4] Thus, use of folate before the existence of preneoplastic lesions may prevent tumour development, whereas use once early lesions are established appears to increase tumorigenesis.[5] However, determining the presence of preneoplastic foci in the general population is almost impossible.[4] Given the tendency for cancer patients to consume more supplements than healthy subjects, the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis should be borne in mind, and research on folate supplementation among patients with cancer is needed.[5] Careful monitoring of the long-term effects of folic acid food fortification is also advised,[3,4] and some have advocated against mandatory fortification on this basis.[6]

1. Charles D, *et al.* Taking folate in pregnancy and risk of maternal breast cancer. *BMJ* 2004; **329:** 1375–6.
2. Cole BF, *et al.* Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; **297:** 2351–9.
3. Kim Y-I. Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr* 2004; **80:** 1123–8.
4. Kim Y-I. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? *Gut* 2006; **55:** 1387–9.
5. Ulrich CM, Potter JD. Folate and cancer—timing is everything. *JAMA* 2007; **297:** 2408–9.
6. Hubner RA, *et al.* Should folic acid fortification be mandatory? No. *BMJ* 2007; **334:** 1253.

Vitamin B_{12} deficiency. The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects (see below) has created debate[1-7] on the amount of fortification and on the risks of masking vitamin B_{12} deficiency, particularly in the elderly. As mentioned in Precautions, above, it is accepted that folic acid should not be used in megaloblastic anaemia due to vitamin B_{12} deficiency, because it will not prevent the neurological manifestations of this deficiency, and may delay the diagnosis. Masking of vitamin B_{12} deficiency has been noted with daily doses of folic acid of 5 mg, and it is generally considered that very low doses do not have this effect. It has also been stated that folic acid may precipitate the neurological manifestations of vitamin B_{12} deficiency; however, a review of the evidence suggests this is unlikely.[8]

Nevertheless, concerns regarding neurological effects of vitamin B_{12} deficiency in the elderly have led to adoption of a level of folic acid fortification in the USA that is accepted will not provide optimum protection against neural tube defects, but that is hoped will minimise any risks.[9] It has been suggested that fortification with vitamin B_{12} as well might also be a solution.[10-12] While some studies of food fortification show no evidence of a deterioration in vitamin B_{12} status in elderly patients,[13,14] there is concern[12,15] that individuals may be consuming folic acid in excess of the upper limit of 1 mg daily (see under Human Requirements, below). Because several countries in the Americas fortify flour, but at varying levels, a technical consultation was convened by the Pan American Health Organization, the March of Dimes, and the CDC, in order to develop guidelines on fortification.[15] It was recommended[16] that all women of reproductive age consume 400 micrograms daily of synthetic folic acid in addition to dietary intake; a minimum additional intake of 200 micrograms daily of folic acid from fortified foods was proposed. A target mean intake of 1 microgram daily of vitamin B_{12} from food fortification was recommended in countries where data are consistent with vitamin B_{12} deficiency; this amount was considered sufficient since, unlike dietary sources of vitamin B_{12}, synthetic vitamin B_{12} is highly bioavailable.

1. Mills JL. Fortification of foods with folic acid—how much is enough? *N Engl J Med* 2000; **342:** 1442–5.
2. Wharton B, Booth I. Fortification of flour with folic acid: a controlled field trial is needed. *BMJ* 2001; **323:** 1198–9.
3. Wald NJ, *et al.* Quantifying the effect of folic acid. *Lancet* 2001; **358:** 2068–73. Correction. *ibid.* 2002; **359:** 630.
4. Oakley GP. Delaying folic acid fortification of flour: governments that do not ensure fortification are committing public health malpractice. *BMJ* 2002; **324:** 1348–9. Correction. *ibid.*; **325:** 259.
5. Reynolds EH. Benefits and risks of folic acid to the nervous system. *J Neurol Neurosurg Psychiatry* 2002; **72:** 567–71.
6. Shane B. Folate fortification: enough already? *Am J Clin Nutr* 2003; **77:** 8–9.
7. Wald NJ, *et al.* Vitamin B-12 and folate deficiency in elderly persons. *Am J Clin Nutr* 2004; **79:** 338.
8. Dickinson CJ. Does folic acid harm people with vitamin B deficiency? *Q J Med* 1995; **88:** 357–64.
9. Tucker KL, *et al.* Folic acid fortification of the food supply: potential benefits and risks for the elderly population. *JAMA* 1996; **276:** 1879–85. Correction. *ibid.* 1997; **277:** 714.
10. Hirsch S, *et al.* The Chilean flour folic acid fortification program reduces serum homocysteine levels and masks vitamin B-12 deficiency in elderly people. *J Nutr* 2002; **132:** 289–91.
11. Ray JG, *et al.* Persistence of vitamin B12 insufficiency among elderly women after folic acid food fortification. *Clin Biochem* 2003; **36:** 387–91.
12. Rampersaud GC, *et al.* Folate: a key to optimizing health and reducing disease risk in the elderly. *J Am Coll Nutr* 2003; **22:** 1–8.
13. Mills JL, *et al.* Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003; **77:** 1474–7.
14. Liu S, *et al.* A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. *BMC Pregnancy Childbirth* 2004; **4:** 20.
15. Freire WB, *et al.* Recommended levels of folic acid and vitamin B fortification: a PAHO/MOD/CDC technical consultation. *Nutr Rev* 2004; **62** (suppl): S1–S2.
16. Allen LH, *et al.* Recommended levels of folic acid and vitamin B fortification: conclusions. *Nutr Rev* 2004; **62** (suppl): S62–S66.

Interactions

Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replacement therapy with folinic acid or folic acid may become necessary in order to prevent megaloblastic anaemia developing; folate supplementation has reportedly decreased serum-phenytoin concentrations in a few cases (see Vitamins, p.500) and there is a possibility that such an effect could also occur with barbiturate antiepileptics.

Antiepileptic-associated folate deficiency is discussed further under Effects on the Blood in Phenytoin, p.495.

◊ References.

1. Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985; **30:** 145–55.

Pharmacokinetics

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.

The principal storage site of folate is the liver; it is also actively concentrated in the CSF.

Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

Human Requirements

Body stores of folate in healthy persons have been reported as being between 5 to 10 mg, but may be much higher. In the UK about 150 to 200 micrograms of folate daily is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their offspring (see below). In the US the recommended dietary allowance is 400 micrograms of dietary folate equivalents (see below) in both men and women. Folate is present, chiefly combined with several L(+)-glutamic acid moieties, in many foods, particularly liver, kidney, yeast, and leafy green vegetables. The vitamin is readily oxidised to unavailable forms and is easily destroyed during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for folate.[1] In the USA recommended dietary allowances (RDAs) had been set, and have recently been reviewed[2] under the programme to set Dietary Reference Intakes (see p.1925). Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the Reference Nutrient Intake (RNI) for adult males and females is 200 micrograms daily and the Estimated Average Requirement (EAR) is 150 micrograms daily. In the USA the RDA is expressed in terms of dietary folate equivalents (DFEs) where 1 microgram DFE is equivalent to 1 microgram folate from natural sources, 0.5 micrograms of a folic acid supplement taken on an empty stomach, or 0.6 micrograms of folic acid from fortified food or as a supplement taken with meals. An RDA of 400 micrograms DFE daily for adult men and women has been set; the EAR is 320 micrograms DFE daily and the tolerable upper intake level is 1 mg daily.

Folate requirements are increased during pregnancy; an RNI of 300 micrograms daily has been suggested for pregnant women in the UK and an RDA of 600 micrograms daily in the USA. In view of the value of folate in preventing neural tube defects, it is now recommended that women planning a pregnancy receive supplemental folic acid before conception and during the first trimester (see Neural Tube Defects, below). To increase the intake in women of child-bearing age, folic acid fortification of grain-based foods has been adopted in the USA, and advocated in other countries including the UK. However, there remains some debate over the appropriate level of fortification to optimise prevention of neural tube defects and to minimise the risks of masking underlying vitamin B_{12} deficiency in the elderly (see Vitamin B_{12} deficiency, above).

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, and in the formation and utilisation of formate. Deficiency, which can result in megaloblastic anaemia (p.1982), develops when the dietary intake is inadequate (as in malnutrition), when there is malabsorption (as in sprue), increased utilisation (as in pregnancy or conditions such as haemolytic anaemia), increased loss (as in haemodialysis), or as a result of the use of folate antagonists and other drugs that interfere with normal folate metabolism (see Interactions, above).

Folic acid is used in the treatment and prevention of the folate deficiency state. It does not correct folate deficiency due to dihydrofolate reductase inhibitors; calcium folinate (p.1944) is used for this purpose. Folic acid is also used in women of child-bearing potential and pregnant women to protect against neural tube defects in their offspring. This is discussed in more detail in Neural Tube Defects, below.

For the treatment of folate-deficient megaloblastic anaemia it is recommended in the UK that folic acid is given orally in doses of 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states. Continued oral dosage with folic acid 5 mg every 1 to 7 days may be necessary in chronic haemolytic states such as thalassaemia major or sickle-cell anaemia, depending on the diet and rate of haemolysis; similar doses may be necessary in some patients receiving renal dialysis in order to prevent deficiency. The *BNFC* recommends an oral dose of 500 micrograms/kg once daily for folate-dependent megaloblastic anaemia in children up to the age of 1 year; older children may be given similar doses to those in adults. For prophylaxis of folate deficiency in children on dialysis it suggests 250 micrograms/kg once daily from 1 month to 12 years of age, and 5 to 10 mg daily in older children.

In the USA the usual recommended therapeutic dose for folate deficiency is lower; oral folic acid 0.25 to 1 mg daily is suggested until a haematopoietic response has been obtained, although some patients require higher doses, especially in malabsorption states. The usual maintenance dose is 400 micrograms daily.

In the prophylaxis of megaloblastic anaemia of pregnancy, the usual dose is 200 to 500 micrograms daily in the UK.

For women of child-bearing potential at high risk of having a pregnancy affected by neural tube defect, the dose of folic acid is 4 or 5 mg daily starting before pregnancy (in the USA the recommendation is 4 weeks before) and continued through the first trimester. For other women of child-bearing potential the dose is 400 micrograms daily.

Folic acid may also be given by intramuscular, intravenous, or subcutaneous injection as the sodium salt.

Cardiovascular disease. Epidemiological studies indicate that individuals with a low serum folate are at increased risk of fatal coronary heart disease,[1] and that those with a high intake of folate,[2] or folic acid and vitamin B_6,[3] from vitamin supplements or food, are at lower risk of ischaemic heart disease or stroke. Vitamin deficiency, especially folic acid deficiency, is a common cause of hyperhomocysteinaemia.[4,5] Elevated blood-homocysteine concentrations may be an independent risk factor for atherosclerosis, ischaemic heart disease (p.1159), venous thrombosis (p.1189), and stroke (p.1185).[4-8] Whether hyperhomocysteinaemia directly causes cardiovascular disease, as concluded by a meta-analysis,[9] or is a possible marker of increased vascular risk,[10] remains controversial.[11,12]

Folic acid reduces blood-homocysteine concentrations;[13-15] vitamin B_{12}, but not B_6, may have an additional effect.[14] The higher the baseline blood-homocysteine concentration, or the lower the baseline value of folate,[14] the greater the effect of folate supplements; reductions were similar with daily doses from 0.5 to 5 mg of folic acid,[14] although a randomised trial[15] found greater effects with a daily 2-mg dose compared with a dose of 0.2 mg. A recent meta-analysis concluded that a daily dose of 0.8 mg or more was needed to achieve maximum reductions in homocysteine concentrations.[16]

Results of studies assessing cardiovascular risk versus folate intake have been variable. Although some have found the risk of hypertension,[17] or stroke[18] to be lower in patients with higher folate intakes (dietary or via supplementation), and there are suggestions that endothelial function is improved by folate supplementation,[19,20] others have reported no association between intake and cardiovascular risk.[21,22] A large open-label study[23] found that, while folic acid supplementation significantly reduced plasma homocysteine concentrations, it did not reduce recurrence of cardiovascular events in patients with stable coronary artery disease. (Most patients had been treated with lipid-lowering therapy, and the authors stated that this might have overshadowed any potential beneficial effects of folic acid.) Similarly, a randomised controlled study, the Vitamin Intervention for Stroke Prevention (VISP) trial,[24] found that high daily doses of folic acid, vitamin B_6 and vitamin B_{12} modestly decreased total homocysteine concentrations compared with low daily doses, but had no treatment effect on recurrent stroke, myocardial infarction, or death. Two further large controlled studies (HOPE-2 and NORVIT) also found no significant beneficial effect of combined treatment with folic acid and vitamins B_6 and B_{12} on cardiovascular disease risk, despite adequate homocysteine-lowering effects;[25,26] such therapy was even suggested to be harmful.[25] While one meta-analysis[27] concluded that folic acid supplementation could effectively reduce the risk of stroke in patients without a history of stroke, another[28] found no reduction in risk of cardiovascular disease, stroke, or all-cause mortality in patients with pre-existing cardiovascular or renal disease. Exclusion of the VISP study from the latter meta-analysis led to a significant protective effect of folic acid supplementation on stroke.[28]

Results of other ongoing studies are considered necessary before definite conclusions can be drawn as to the so-called 'homocysteine hypothesis' of atherothrombotic vascular disease; while some recommend against routine treatment,[4,29,30] others consider homocysteine-lowering treatment in high-risk patients to be justified.[31,32] A meta-analysis[33] of observational studies indicated that the relationship between hyperhomocysteinaemia and ischaemic heart disease and stroke risk in healthy individuals might not be as strong as had previously been suggested, with stronger associations found in retrospective studies than in prospective studies. The American Heart Association has stated[7] that, until the results of more controlled studies become available, routine testing of plasma-homocysteine concentrations cannot be justified; all patients should, however, be encouraged to consume the recommended dietary allowance (RDA) of folate, vitamin B_6 and vitamin B_{12}.

Daily treatment with oral folic acid, vitamin B_6, and vitamin B_{12} significantly decreased restenosis and target-vessel revascularisation after percutaneous coronary angioplasty.[34] In contrast, in another study[35] folic acid, vitamin B_6, and vitamin B_{12}, increased restenosis and target-vessel revascularisation. The studies differed in dosage regimen, patient population, lesion length, and procedure used,[36,37] but the strong proliferative effect of folate on neointimal growth may exceed the positive effect of lowering homocysteine concentrations,[38] and it has been stated[36] that these vitamins should not be routinely used in patients receiving coronary stents.

Patients with renal impairment develop hyperhomocysteinaemia as a result of delayed elimination and altered metabolism; the prevalence of plasma homocysteine levels greater than 15 micromoles/L has been reported to be 80 to 90% in dialysis patients, compared with 5% in the general population. In haemodialysis patients with moderate to severe hyperhomocysteinaemia, intravenous folinic acid 10 mg three times weekly has been reported to dramatically decrease homocysteine concentrations, although normal levels of homocysteine were not attained.[39] In a small study in renal transplant recipients with hyperhomocysteinaemia, vitamin B_6 was effective in reducing post-methionine-loading plasma homocysteine concentrations, and folic acid plus vitamin B_{12} was effective in lowering fasting plasma-homocysteine concentrations. The authors concluded that all three of these B-group vitamins may have a role in reducing atherosclerotic outcomes in this patient group.[40]

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Food fortification. Mandatory fortification of foods with folic acid has caused much controversy, with some advocating this measure as prevention against neural tube defects (below) and others concerned about folic acid supplementation masking vitamin B_{12} deficiency (above) or having possible carcinogenic effects (above).

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Hearing loss. Epidemiological studies have suggested an association between homocysteine and folate concentrations and hearing status. A 3-year controlled study in a country without folic acid food fortification found that supplementation slowed the decline in age-related hearing loss. Further studies were considered necessary to confirm these findings.[1]

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Mental function. For a discussion of the effects of folate supplementation on cognitive function and depression, see Mental Function, p.1926.

Neural tube defects. Failure of the fetal neural tube to fuse normally during the first 4 weeks of pregnancy may result in one of several congenital defects. These include anencephaly (absence of the brain and cranial vault) and spina bifida (failure of the vertebrae to fuse).[1,2] The latter ranges from spina bifida occulta, where neurological abnormalities are rare, to meningocoele or meningomyelocoele, where the meninges, or meninges and spinal cord, herniate outwards through the vertebral defect and which may be associated with hydrocephalus and paralysis of the lower limbs and sphincters.

The reasons for this failure in normal development are not well understood and appear to include both environmental and genetic factors. The risk is increased in certain geographical areas, and in the offspring of parents with previous children who had neural tube defects, or of parents who themselves suffer from the condition.[1]

A defect in the methylenetetrahydrofolate reductase gene has been identified, which is estimated to occur in about 5 to 15% of white populations, and appears to result in an increased requirement for folates, and an increased risk of recurrent early pregnancy loss and neural tube defects.[3,4] Since the 1960s there has been some evidence that the mother's folate status was significant, and in the early 1980s two groups published evidence for claims that oral folic acid, with or without other vitamins, in the period around conception, reduced the incidence of neural tube defect in the offspring of mothers who had previously borne children with the defect.[5,6]

Although criticised on several grounds, the conclusions of these studies were borne out by a large multicentre study initiated by the UK Medical Research Council (MRC).[7] This study was terminated early because of overwhelming evidence that folic acid 4 mg daily taken from before conception until the twelfth week of gestation by women with a history of a previous pregnancy affected by a neural tube defect reduced the incidence of such defect by about two-thirds. Other studies and systematic reviews have since confirmed the benefits of supplementation.[8,9] Multivitamins alone (A, D, B_1, B_2, nicotinamide, B_6, and C) did not demonstrate a similar benefit.

Prevention of recurrence. In the light of the MRC study, it is recommended in the UK that in couples with spina bifida or a history of previous offspring with neural tube defect, all those women who may become pregnant should receive folic acid 5 mg daily (in the absence of a commercially-available 4-mg dosage form) until the twelfth week of pregnancy.[10] In the USA, recommendations are 4 mg of folic acid daily from at least 4 weeks before conception through the first 3 months of pregnancy.[11] It must be borne in mind that only about 60 to 70% of neural tube defects appear to be folate-sensitive, and parents should be counselled appropriately. Similar doses of folic acid have been recommended for women in intermediate- to high-risk categories for neural tube defects in Canada.[12]

The investigators in the MRC trial acknowledged that a 4-mg dose may not be optimal, and both early[5,6] and later[13] studies imply that much lower doses of folic acid may reduce the risk of recurrence, but this has yet to be clearly demonstrated. Furthermore, the optimum length of time that supplements should be given to these women before conception is unknown.

Prevention of occurrence. First occurrences of neural tube defects account for about 95% of cases, and there are obvious public health implications if the benefits of folate in mothers known to be at risk can be extended to the general population. A study in Hungary[14] indicated that folic acid 800 micrograms daily with multivitamins, taken for at least one month before conception and until the third month of gestation decreased the incidence of first occurrence of neural tube defects. A case control study in the USA[15] (where the normal incidence of neural tube defect is much lower than Hungary) suggested that a periconceptional folic acid intake of as little as 400 micrograms daily reduced the occurrence of the disorder by 60%.

With such results in mind the US Public Health Service has recommended that all women of child-bearing age who are capable of pregnancy should receive folic acid 400 micrograms daily although care should be taken to keep folate consumption below 1 mg daily except under medical supervision.[1,16] Such universal coverage would allow for the problem of unplanned pregnancies but would be difficult to achieve, other than by fortification of dietary staples with folate. Food fortification has therefore been adopted in the USA, at a level of 140 micrograms of folic acid per 100 g of cereal-grain product. While this amount will probably be insufficient to provide maximum reduction in the incidence of neural tube defects,[17,18] there is some evidence of benefit,[19] and it was chosen to minimise the risk of masking vitamin B_{12} deficiency in the elderly.[20] Efforts to increase the use of folic acid supplements in women of child-bearing potential are still advocated. In Canada, where food fortification has been associated with a significant reduction in neural tube defects,[21] similar recommendations have been made.[12]

In the UK, the current recommendation is that all women planning a pregnancy should take an extra 400 micrograms of folic acid daily before conception and during the first 12 weeks of pregnancy, bringing the average folate intake to about 600 micrograms daily.[10] In unplanned pregnancies, supplementation should begin as soon as pregnancy is suspected. Some, however, consider this amount to be too low.[22] As in the USA, food fortification has been considered, and the Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that universal fortification of flour at 240 micrograms of folic acid per 100 g in food would significantly reduce the number of neural tube defects.[23] In May 2007, the UK Food Standards Agency agreed that mandatory fortification be introduced. However, there are concerns about possible carcinogenic effects (see Carcinogenicity, above) and results of further studies are awaited. Debate has continued as to the amount, if any, of fortification necessary.[22,24-29] The UK Scientific Advisory Committee on Nutrition reconfirmed[30] the COMA recommendation for fortification of flour but said that further consideration should be given to the amount and form of folate used and also called for better monitoring of vitamin B_{12} in those aged 65 and over. There has also been a renewed call for fortification of foods in Europe,[31-34] and Australia and New Zealand,[35,36] as issuing recommendations on folic acid use has not led to a substantial decrease in the incidence of neural tube defects, and efforts have not reached all the target population. Certainly, mandatory food fortification with folic acid has been shown to dramatically decrease the incidence of neural tube defects in Canada,[37] Chile,[38] and the USA.[39-41] Fears of masking vitamin B_{12} deficiency appear to have not been borne out (see Vitamin B_{12} Deficiency, above).

Patients receiving antiepileptic drugs are at increased risk of neural tube defect and it has been suggested that folic acid supplementation for such patients should be at the level used for prevention of recurrence,[42] i.e. 4 or 5 mg daily.

The mechanism by which folic acid protects against neural tube defects is unknown, but various theories have been postulated including a positive effect in promoting neural tube closure,[43] or a selective abortifacient effect on affected fetuses (terathanasia),[44] although the latter has been disputed.[45] There is some evidence that low maternal vitamin B_{12} concentrations are an independent risk factor for neural tube defects,[46,47] perhaps indicating a role for methionine synthase in their aetiology, and suggesting that additional supplementation with cobalamins may be warranted, or that methionine supplements could be investigated as an alternative to folic acid.[48,49] Some suggest that hyperhomocysteinaemia may be a cause of some neural tube defects and that they may be due to an inborn error of folate and/or homocysteine metabolism; furthermore, a dietary deficiency may trigger a genetic predisposition towards the development of neural tube defects.[2] Interestingly, the results from the Hungarian programme[50,51] and from other studies[52-54] suggest that multivitamin supplements (including folic acid) may also reduce the occurrence of other congenital abnormalities. Maternal folate deficiency has also been associated with an increased risk of adverse birth outcomes, apart from neural tube defects, such as preterm delivery, low infant birth-weight, and fetal growth retardation.[55]

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Osteoporosis. Treatment with folate and vitamin B_{12} can reduce elevated plasma homocysteine concentrations and may subsequently decrease the risk of osteoporosis and hip fracture, see Osteoporosis, under Vitamin B_{12}, p.1983.

Prophylaxis of malignant neoplasms. For reference to suggestions that folate supplements may be associated with reduced risk of certain cancers, see p.1927. However, folic acid may have dual modulatory effects on carcinogenesis, see Carcinogenicity, above.

Preparations

BP 2008: Ferrous Fumarate and Folic Acid Tablets; Folic Acid Tablets;
USP 31: Folic Acid Injection; Folic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acifol; Anemidox Folico; Anfolic; Azolac Folico; Biolfolic; Coflic; Conacid; Dupofol; Edulsan Folic; Egestan; Folaport; Foliagen; Folimax; Folinemic; Galfol; Livifol; Medifol; Ronfolic; Sojar Folico; Suprafol; ***Austral.:*** Megafol; ***Austria:*** Folsan; ***Belg.:*** Folavit; ***Braz.:*** Acfol†; Afopic; Endofolin; Enfol; Folacin; Folin†; Folital; Materfolic; Neo Folico; ***Chile:*** Folacid; Folifemin; Folisanin; ***Denm.:*** Folimet; ***Fin.:*** Folvite; ***Fr.:*** Speciafoldine; ***Ger.:*** DreisaFol; Fol-Asmedic†; Folarell; Folcur; Folgamma Mono; Folsan; Folverlan; Gravi-Fol; Lafol; RubieFol†; ***Gr.:*** Filicine; ***Hung.:*** Feroglobin-B12; Folsav; Huma-Folacid; ***India:*** Folet; Folvite; Ingafol; Rubraplex; Vitafol; ***Indon.:*** Folac; Folacite; Folacom; Folas; Folavit; Folaxin; Nufolic; ***Irl.:*** Cardioguard†; Clonfolic; ***Ital.:*** Fertifol; Folidex; Folina; Folingrav; Serengrav; ***Mex.:*** AF; Folivital; Materfol; Prinac Ac; ***Philipp.:*** Enhansid; Purifol; ***Pol.:*** Acifolik; Folacid; Folifem; Folik; Folimin; Folovit; ***Port.:*** Acfol; Dozefol; Folicil; ***Rus.:*** Folacin (Фолацин); ***Spain:*** Acfol; Zolico; ***Swed.:*** Folacin; ***Switz.:*** Andreafol; Drossafol; Foli-Rivo†; Folvite; ***Thai.:*** Foliamin; Folicare; Folivit; ***Turk.:*** Folbiol; ***UAE:*** Folicum; ***UK:*** Folicare; Lexpec; Preconceive; ***USA:*** Folvite; ***Venez.:*** Afoklin; Folac.

Multi-ingredient: ***Arg.:*** Acifol-B12; Anemidox-Ferrum; Anemidox-Solutab; Blastop; Egestan Hierro; Factofer B12; Fefol; Ferranin Complex; Ferretab Compuesto; Ferro Folic; Ferrocebrina; Folimax B; Hierro Dupofol; Hierro Folico; Hierro Plus; Hierroquick; ITE B12 Forte; Maltofer Fol†; Presterin; QX 10; Rubiron; Sideralce; Siderblut Folic; Tenvic; Vitalix Complex; Yectafer Complex; ***Austral.:*** Antioxidant Forte Tablets; Fefol; FGF Tabs; Pre Natal†; Vita-Preg†; ***Austria:*** Aktiferrin Compositum; Beneuran compositum; Ferretab Comp; Ferrograd Fol; Losferron-Fol; Tardyferon-Fol; ***Belg.:*** Gestiferrol; ***Braz.:*** Anemofer†; Betozone; Coraben†; Ferrini Folico; Ferroplex; Ferrotonico B12†; Ferrotrat; Ferrumvit†; Fol Sang; Folacin; Folifer; Iberin Folico; Iloban; Neutrofer Folico; Noripurum Folico; Vi-Ferrin; ***Canad.:*** Neo-Fer CF; Palafer CF; Slow-Fe Folic; ***Chile:*** Cronoferril†; Ferranem; Ferranim; Ferro F-500 Gradumet†; Ferro Vitaminico; Foli Doce; Folifer; Iberol Folico; Maltofer Fol; ***Cz.:*** Aktiferrin Compositum; Ferretab Compositum; Ferro-Folgamma; Ferrograd Folic†; Maltofer Fol; Tardyferon-Fol; ***Fin.:*** Obsidan comp; ***Fr.:*** Folio; Gynosoja; Tardyferon B ; ***Ger.:*** B Fol-Vicotrat†; Eryfer comp; Ferro sanol comp; Ferro sanol gyn; Ferro-Folgamma; Ferro-Folsan; Folgamma; Folicombin; Hamatopan F; Hepagrisevit Forte-N†; Kendural-Fol-500; Medivitan N; Medyn; MerSol†; Plastulen N; Selectafer N†; Tardyferon-Fol; ***Gr.:*** Dextrifer-Fol; Feofol; Fero-Folic; Ferrum Fol Hausmann; Gyno-Tardyferon; Hemafer fol; ***Hong Kong:*** Eurofer; Hepatofalk; Iberet-Folic; ***Hung.:*** Atherovit; Ferro-Folgamma; Ferrograd Folic; Maltofer Fol; Pregmag; Tardyferon-Fol; ***India:*** Anemidox; Blosyn; Cafe-Kit†; Carboflot†; Cofol; Cofol Z; Conviron-TR; Dexorange; Elferri-Z; Fecontin-F; Fecontin-Z; Fefol; Fefol-Z; Fericip; Ferrochelate; Ferrochelate-Z; Fervit†; Fesovit; Genfol; Globac-Z; Hepasules; Hepatoglobine; Hepofer; Jectocos Plus; JP Tone-TR; Livogen Captab; Livogen Hemtonic; Livogen-Z; Livogen†; Maxiferon; Mumfer-Z†; Mumfer†; Plastules; Probofex; Raricap; Softeron; Softeron-Z; Tonoferon; Vitamon; ***Indon.:*** Adfer; Biosanbe; Folaplus; Hemobion; Iberet-Folic; Maltofer Fol; Natabion; Neogobion; Sangobion; Vomilat; ***Irl.:*** Fefol; Ferrocap F†; Ferrograd Folic; Galfer FA; Givitol; ***Israel:*** Aktiferrin-F; Ferrifol; Ferrograd Folic; Folex; Foric; Slow-Fe Folic; Tricardia; ***Ital.:*** Epargriseovit; Evafer; Ferrograd Folic; Folepar B12; ***Malaysia:*** Aktiferrin-F; Ferrovit; Iberet-Folic; Maltofer; Sangobion; ***Mex.:*** Dialeli AF; Ferlor AF†; Ferranina Fol; Ferricol; Ferro Folico; Forta; Intrafer; Intrafer F-800; Intrafer TF; Ironfol; Orafer Comp; Tardyferon-Fol; Uniferfol; Yemifer-HE; ***NZ:*** Ferrograd Folic; ***Philipp.:*** Ameciron; Anemicon Plus; Anixon; Beniforte; Drexabion OB; Dupharon; Essenfer; Eurofer; Femina; Fergesol; Ferlin; Ferosal; Ferro-Folsan Plus; Foralivit; Foramefer; Fortifer FA; Harvifer; Hemobion; IBC; Iberet-Folic; Imefer; Irobon; Meganerv F-A; Micron-C; Molvite-OB; Nakaron; Sangobion; Terraferron; TriHEMIC; ***Pol.:*** Additiva Ferrum; Ferrograd Folic; Hemofer F; Tardyferon-Fol; ***Port.:*** Ferro-Folsan†; Ferrograd Folico; Ferrum Fol; Folifer; Maltoferfol; Neobefol; Tardyferon-Fol; ***Rus.:*** Aktiferrin Compositum (Актиферрин Композитум); Ferretab Comp (Ферретаб Комп); Ferro-Folgamma (Ферро-Фольгамма); Gyno-Tardyferon (Гино-тардиферон); ***S.Afr.:*** Fefol; Fefol-Vit; Fero-Folic; Ferrimed; Foliglobin; Hepabionta; Pregamal; ***Singapore:*** Aktiferrin-F; Eurofer; Iberet-Folic; Iron Melts; Neogobion; Saferon†; Sangobion; Tardyferon B †; Wanse; ***Spain:*** Foli Doce; Foliferron; Hepa Factor; Normovite Antianemico; ***Switz.:*** Actiferrine-F Nouvelle formule; Duofer Fol; Fero-Folic; Gyno-Tardyferon; Maltofer Fol; ***Thai.:*** Adnemic F†; Eurofer; Ferli-6; Ferosix; Orofer; Trinsicon†; ***Turk.:*** Blood Builder; Epargriseovit; Ferplex Fol; Ferro-Vital; Ferrum Fort Hausmann; Folic Plus; Gyno-Tardyferon; Gynoferon; Maltofer Fol; Vi-Fer; ***UAE:*** Folicron; ***UK:*** Fefol; Ferrograd Folic; Galfer FA; Hematinic; Ironorm; Lexpec with Iron-M†; Lexpec with Iron†; Meterfolic; Pregaday; Slow-Fe Folic†; SoyPlus; ***USA:*** ABC to Z; Berocca Plus; Bevitamel; Centurion A–Z†; Certagen; Cevi-Fer†; Chromagen FA; Chromagen Forte; Compete; Contrin; Fe-Tinic Forte; Feocyte; Fero-Folic; Ferotrinsic; Ferralet Plus†; Ferrex Forte; Ferrex Forte Plus†; Ferrogels Forte; FOLTX; Formula B Plus; Geriot; Geritol Complete; Gevral T; Hematinic; Hematinic Plus; Hemocyte Plus; Hemocyte-F; Iberet-Folic†; Icar-C Plus; Ircon-FA†; Iromin-G; Livitrinsic-f; Nephro-Fer Rx†; Niferex Forte; Nu-Iron V; Parvlex; Poly-Iron Forte; PremesisRx; Pronemia Hematinic; Slow Fe with Folic Acid; Tandem F; Thera Hematinic; Theragenerix-H; Theravee Hematinic; TriHEMIC; Trinsicon; Vitafol; Yelets; Zodeac; ***Venez.:*** Calcibon Natal; Cobalfer; Fefol; Ferganic Folic; Ferro-Folic; Folifer B-12; Hepafol con B-12; Herrongyn; Intaferfol; Maltoferfol.

Folinic Acid *(BAN)*

Citrovorum Factor; Folínico, ácido; Leucovorin. 5-Formyltetrahydropteroylglutamic acid; *N*-[4-(2-Amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxypteridin-6-ylmethylamino)benzoyl]-L(+)-glutamic acid.

Фолиновая Кислота

$C_{20}H_{23}N_7O_7$ = 473.4.

CAS — 58-05-9.

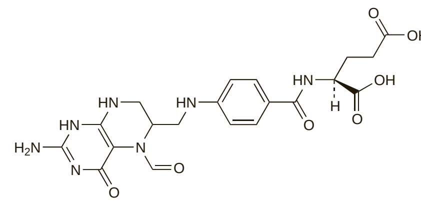

Calcium Folinate *(BANM, rINN)*

Calcii folinas; Calcii Folinas Hydricus; Calcium, folinate de; Calcium Folinate-SF; Calcium Leucovorin; Folinate de Calcium; Folinato cálcico; Kalcio folinatas; Kalciumfolinat; Kalcium-folinát; Kalcium-folinát hydrát; Kalsiumfolinaatti; Kalsiyum Folinat; Kalsiyum Lökovorin; Leucovorin Calcium; NSC-3590. The calcium salt of folinic acid (1:1).

Кальция Фолинат

$C_{20}H_{21}CaN_7O_7$ = 511.5.

CAS — 1492-18-8 (anhydrous calcium folinate); 41927-89-3 (calcium folinate pentahydrate); 6035-45-6 (calcium folinate pentahydrate).

ATC — V03AF03.

ATC Vet — QV03AF03.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Chin. includes the pentahydrate ($C_{20}H_{21}CaN_7O_7,5H_2O$ = 601.6)
.

Ph. Eur. 6.2 (Calcium Folinate). A white or light yellow, amorphous or crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone. A 2.5% solution in water has a pH of 6.8 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Leucovorin Calcium). A yellowish-white or yellow, odourless, powder. Very soluble in water; practically insoluble in alcohol. Protect from light.

Incompatibility. Calcium folinate and fluorouracil, with or without 5% glucose, were incompatible when mixed in various ratios and stored in PVC containers at various temperatures.[1]

1. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.

Calcium Levofolinate *(BAN, rINN)*

Calcii Levofolinas; Calcii levofolinas pentahydricus; Kalcio levofolinatas; Kalciumlevofolinat; Kalcium-levofolinát pentahydrát; Kalcium-levofolinát-pentahidrát; Kalciumlevofolinatpentahydrat; Kalsiumlevofolinaatti; Kalsiumlevofolinaattipentahydraatti; Levofolinate; Lévofolinate calcique pentahydraté; Lévofolinate de Calcium; Levofolinato de calcio; Levoleucovorin Calcium *(USAN)*. The calcium salt of the isomer of *S*-folinic acid (1:1).

Кальция Левофолинат

$C_{20}H_{21}CaN_7O_7,5H_2O$ = 601.6.

CAS — 80433-71-2 (anhydrous calcium levofolinate).

ATC — V03AF04.

ATC Vet — QV03AF04.

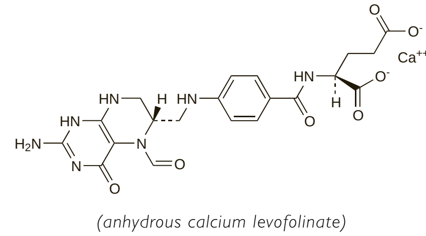

(anhydrous calcium levofolinate)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Calcium Levofolinate Pentahydrate). A white or light yellow, amorphous or crystalline, hygroscopic powder. Slightly soluble in water; practically insoluble in alcohol and in acetone. A 0.8% solution in water has a pH of 7.5 to 8.5. Store in airtight containers. Protect from light.

Sodium Folinate

Disodium folinate *(BANM)*.
Натрия Фолинат
$C_{20}H_{21}N_7O_7Na_2$ = 517.4.
CAS — 42476-21-1 (monosodium folinate).
ATC — V03AF06.
ATC Vet — QV03AF06.

Adverse Effects

Occasional hypersensitivity, including anaphylactic reactions, has been reported; pyrexia has occurred rarely after injections. Gastrointestinal disturbances, insomnia, agitation, and depression have been reported rarely, after high doses.

Precautions

As for Folic Acid, p.1940.

Interactions

As for Folic Acid, p.1940.

Folinic acid should not be used with a folic acid antagonist such as methotrexate as this may nullify the effect of the antagonist. Folinic acid enhances the toxicity, as well as the antineoplastic action, of fluorouracil, especially on the gastrointestinal tract.

Pharmacokinetics

Calcium folinate is well absorbed after oral and intramuscular doses and, unlike folic acid (p.1941), is rapidly converted to biologically active folates. Sodium folinate is considered to be bioequivalent to calcium folinate. Folate is concentrated in the liver and CSF although distribution occurs to all body tissues. Folates are mainly excreted in the urine, with small amounts in the faeces.

◊ References.

1. McGuire BW, *et al.* Pharmacokinetics of leucovorin calcium after intravenous, intramuscular, and oral administration. *Clin Pharm* 1988; **7:** 52–8.
2. Wolfrom C, *et al.* Pharmacokinetic study of methotrexate, folinic acid and their serum metabolites in children treated with high-dose methotrexate and leucovorin rescue. *Eur J Clin Pharmacol* 1990; **39:** 377–83.
3. Zittoun J, *et al.* Pharmacokinetic comparison of leucovorin and levoleucovorin. *Eur J Clin Pharmacol* 1993; **44:** 569–73.
4. Mader RM, *et al.* Pharmacokinetics of rac-leucovorin vs [S]-leucovorin in patients with advanced gastrointestinal cancer. *Br J Clin Pharmacol* 1994; **37:** 243–8.
5. Schmitz JC, *et al.* Disposition of folic acid and its metabolites: a comparison with leucovorin. *Clin Pharmacol Ther* 1994; **55:** 501–8.

Uses and Administration

Folinic acid is the 5-formyl derivative of tetrahydrofolic acid, the active form of folic acid. Folinic acid is used principally as an antidote to folic acid antagonists, such as methotrexate (p.747), which block the conversion of folic acid to tetrahydrofolate by binding the enzyme dihydrofolate reductase. It does not block the antimicrobial action of folate antagonists such as trimethoprim or pyrimethamine, but may reduce their haematological toxicities. It is also used as an adjunct to fluorouracil in the treatment of colorectal cancer.

Folinic acid is given as calcium or sodium folinate, although doses are stated in terms of folinic acid. 1.08 mg of anhydrous calcium folinate, 1.27 mg of calcium folinate pentahydrate, or 1.09 mg of sodium folinate are each equivalent to about 1 mg of folinic acid. Calcium folinate can be given orally, by intramuscular injection, or by intravenous injection or infusion. It has been recommended that oral doses should not be greater than 50 mg, since absorption is saturable. Calcium levofolinate, the active laevo-isomer, is used similarly to calcium folinate; it is given in doses half those recommended for the racemic form. Sodium folinate is given by intravenous injection or infusion; sodium levofolinate is used similarly.

In cases of inadvertent **overdosage of a folic acid antagonist**, folinic acid should be given as soon as possible and preferably within the first hour. Doses equal to or greater than the dose of methotrexate have been recommended. Intravenous injections should be given over several minutes because of their calcium content; the maximum recommended rate is equivalent to folinic acid 160 mg/minute. Alternatively it has been stated that for large doses or overdoses of methotrexate, calcium folinate may be given by intravenous infusion in a dose equivalent to 75 mg of folinic acid within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Although vincristine is not a folic acid antagonist, folinic acid has also been proposed for some manifestations of vincristine toxicity overdosage—see p.787.

Folinic acid is used with high-dose methotrexate antineoplastic therapy to reduce the toxicity of the methotrexate ('**folinic acid rescue**'; 'calcium leucovorin rescue'). Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m^2 and should be considered with methotrexate doses of 100 to 500 mg/m^2. It may sometimes be considered in patients who have received lower doses.

Dosage and duration of folinic acid rescue must be adapted according to the methotrexate regimen and the patient's ability to clear the antineoplastic; many antineoplastic regimens include appropriate rescue protocols. In general, UK licensed drug information recommends that the first dose of calcium folinate is the equivalent of 15 mg folinic acid (6 to 12 mg/m^2) to be given 12 to 24 hours (usually the latter) after the beginning of methotrexate infusion. The same dose is given every 6 hours for 24 hours, initially by intramuscular injection or intravenous injection or infusion, but switching to the oral form after one or more parenteral doses. At the end of this time (48 hours after the start of the original methotrexate infusion) the residual methotrexate concentration should be measured. If this is *less* than a threshold concentration of 0.5 micromoles/litre, the same dose is continued usually for a further 48 hours. If it is *greater* than this value, further calcium folinate dosages should be adapted according to methotrexate concentration as follows, and given every 6 hours for a further 48 hours or until the serum-methotrexate concentration falls below 0.05 micromoles/litre (i.e. one-tenth of the threshold concentration):

- serum methotrexate > 0.5 micromoles/litre: calcium folinate equivalent to 15 mg/m^2 folinic acid
- serum methotrexate > 1 micromole/litre: calcium folinate equivalent to 100 mg/m^2 folinic acid
- serum methotrexate > 2 micromoles/litre: calcium folinate equivalent to 200 mg/m^2 folinic acid

The dose of sodium folinate in rescue therapy is also based on serum-methotrexate concentrations (as measured 24 to 30 hours after beginning methotrexate):

- serum methotrexate 0.01 to 1.5 micromoles/litre: sodium folinate equivalent to 10 to 15 mg/m^2 folinic acid every 6 hours for 48 hours
- serum methotrexate 1.5 to 5 micromoles/litre: sodium folinate equivalent to 30 mg/m^2 folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre
- serum methotrexate > 5 micromoles/litre: sodium folinate equivalent to 60 to 100 mg/m^2 folinic acid every 6 hours until methotrexate concentration is less than 0.05 micromoles/litre

In patients who have received doses of methotrexate below 100 mg, and in whom rescue therapy is considered appropriate, doses of folinic acid 15 mg by mouth every 6 hours for 48 to 72 hours may suffice.

In addition, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of rescue treatment. Renal function should be monitored daily.

Folinic acid is also used **with fluorouracil** to enhance the cytotoxic effect in advanced colorectal cancer. Both high-dose regimens (typically doses of folinic acid 200 mg/m^2, followed by fluorouracil) and low-dose regimens (20 mg/m^2) have been used—for details, see Uses and Administration of Fluorouracil, p.723. Sodium folinate has been used in similar doses. It may also be given at a dose equivalent to folinic acid 500 mg/m^2 by intravenous infusion over 2 hours. An intravenous injection of fluorouracil 600 mg/m^2 is given one hour after the start of the folinate infusion. Alternatively, a continuous infusion of fluorouracil 2.6 g/m^2 is given for 24 hours after the sodium folinate dose. Treatment is given weekly for 6 weeks, and may then be repeated after a 2-week interval; the number of cycles depends on the response of the tumour.

Folinic acid, like folic acid, is effective in the treatment of folate-deficient **megaloblastic anaemia** (see p.1982). Doses of 15 mg daily by mouth have been suggested. If given intramuscularly a dose of up to 1 mg daily has been recommended on the grounds that higher doses have not been proven to be any more effective. It is unsuitable for megaloblastic anaemia secondary to vitamin-B_{12} deficiencies.

Cardiovascular disease. For a report of the use of intravenous folinic acid to reduce levels of homocysteine in haemodialysis patients, see Cardiovascular Disease, under Folic Acid, p.1941.

Deficiency states. Cerebral folate deficiency has been defined as any neurological syndrome associated with low CSF concentrations of 5-methyltetrahydrofolate, the active metabolite of folic acid.[1,2] Neurodevelopmental disorders have been associated with this deficiency, manifest as irritability, sleep disturbances, cerebellar ataxia, spastic paraplegia, dyskinesia, epileptic seizures, and speech difficulties. Dramatic improvements in some symptoms have been noted with oral folinic acid;[1-3] 0.5 to 1 mg/kg folinic acid daily has been used.[1] Analysis of CSF folate metabolites is recommended for patients presenting with movement disorders, mental retardation, or autism.[2,3]

1. Ramaekers VT, Blau N. Cerebral folate deficiency. *Dev Med Child Neurol* 2004; **46:** 843–51.
2. Hansen FJ, Blau N. Cerebral folate deficiency: life-changing supplementation with folinic acid. *Mol Genet Metab* 2005; **84:** 371–3.
3. Moretti P, *et al.* Cerebral folate deficiency with developmental delay, autism, and response to folinic acid. *Neurology* 2005; **64:** 1088–90.

HIV infection and AIDS. Calcium folinate has been used to reduce the toxicity of pyrimethamine and trimethoprim in patients with HIV infection. However, oral calcium folinate given to patients with AIDS receiving co-trimoxazole for the treatment of pneumocystis pneumonia was associated with a higher rate of therapeutic failure and a decrease in survival and did not reduce the frequency of dose-limiting co-trimoxazole toxicity.[1] Calcium folinate also did not reduce the toxicity of co-trimoxazole being used for the primary prophylaxis of PCP.[2] Vitamin B_{12} and folinic acid supplementation in patients with HIV infection did not prevent or reduce zidovudine-induced myelosuppression.[3]

1. Safrin S, *et al.* Adjunctive folinic acid with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis* 1994; **170:** 912–17.
2. Bozzette SA, *et al.* The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
3. Falguera M, *et al.* Study of the role of vitamin B and folinic acid supplementation in preventing hematologic toxicity of zidovudine. *Eur J Haematol* 1995; **55:** 97–102.

Preparations

BP 2008: Calcium Folinate Injection; Calcium Folinate Tablets;
USP 31: Leucovorin Calcium Injection; Leucovorin Calcium Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Asovorin; Cromatonbic Folinico†; Elvefocal; Estroquin; Folinfabra; Leucocalcin; Novizet; Rontafor; ***Austria:*** FOLI-Cell; Isovorin; Rescuvolin; Sodiofolin; ***Belg.:*** Elvorine; Folina-Cell; Ledervorin; Rescuvolin; VoriNa; ***Braz.:*** Calfolin†; Folicorin; Isovorin†; Legifol CS; Lenovor†; Levorin; Nyrin†; Prevax; Rescuvolin†; Tecnovorin; ***Chile:*** Covorit; ***Cz.:*** Antrex†; Levofolic; Sanfcinate†; VoriNa; ***Denm.:*** Isovorin; Rescuvolin†; ***Fin.:*** Antrex; Isovorin; Rescuvolin†; ***Fr.:*** Elvorine; Folinoral; Lederfoline; Osfolate; ***Ger.:*** DeGalin; FOLI-Cell; Lederfolat; Neofolin; O-folin; Oncofolic; Rescuvolin; Ribofolin; VoriNa; ***Gr.:*** Buateron; Calcifolin; Calcivoran; Claro; Durofolin; Esvorin; Fedolen; Folical; Foliment; Folinato; Folivoran; Folmigor; Foxolin; Isovorin; Lizocalcio; Reotan; Rescuvolin; Sanovein; Veravorin; Vivalcid; Zamenit; Zenemia; ***Hong Kong:*** Calciumfolinat; ***Hung.:*** VoriNa; ***India:*** Biovorin; ***Indon.:*** Rescuvolin; ***Irl.:*** Isovorin†; Lederfolin; ***Ital.:*** Calcifolin; Calfolex; Calinat; Citofolin; Divical†; Divifolin; Ecofol; Emovis†; Folanemin; Folaren; Foliben; Folicalgyn†; Folidar; Folinac†; Folinvit†; Foliplus†; Lederfolin; Levofolene; Osfolato; Resfolin†; Sanifolin; Sulton; Tonofolin; ***Jpn:*** Uzel; ***Malaysia:*** Nyrin; Rescuvolin; ***Mex.:*** Dalisol; Flynoken A†; Ifavor; Medsavorina; Precileucin; ***Neth.:*** Rescuvolin; VoriNa; ***Norw.:*** Isovorin; Rescuvolin; ***NZ:*** Rescuvolin†; ***Philipp.:*** Folinoxan; Litacor; Lovorin; Rescuvolin; ***Port.:*** Folinovo; Isovorin; Lederfoline; Medifolin; Raycept; Sodiofolin; VoriNa; ***Rus.:*** Dalisol (Далисол)†; ***S.Afr.:*** Isovorin; Rescuvolin; ***Singapore:*** Rescuvolin†; ***Spain:*** Cromatonbic Folinico; Folaxin; Folidan; Isovorin; Lederfolin; ***Swed.:*** Isovorin; Rescuvolin†; ***Thai.:*** Dalisol; Folina; Rescuvolin; ***Turk.:*** Antrex; Rescuvolin; ***UK:*** Isovorin; Lederfolin†; Refolinon; Sodiofolin; ***Venez.:*** Leuconolver.

Multi-ingredient: ***Gr.:*** Fysiofol; ***Ital.:*** Carfosid; Emazian B12†; Emoantitossina†; Emopon; Eparmefolin; Ferritin Complex; Ferrofolin; Hepa-Factor; Idropan B†; Ipavit†; ***NZ:*** Orzel†.

Folitixorin *(pINN)*

Folitixorina; Folitixorine; Folitixorinum; 5,10-Methylenetetrahydrofolate; 5,10-Methylenetetrahydrofolic acid; Tetrahydromethylenefolate. N-{4-[3-Amino-1,2,5,6,6a,7-hexhydro-1-oxoimidazo(1,5-f)pteridin-8(9H)-yl]benzoyl}-L-glutamic acid.

Фолитиксорин

$C_{20}H_{23}N_7O_6$ = 457.4.

CAS — 3432-99-3.

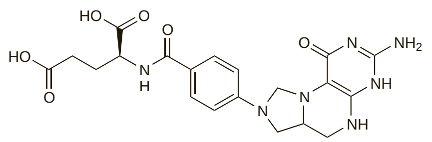

Profile

Folitixorin is an active metabolite of folinic acid. It is under investigation for use with fluorouracil in the treatment of pancreatic cancer and metastatic colorectal cancer.

Fructose

Fructosa; D-Fructose; Fructosum; Fruit Sugar; Fruktoosi; Fruktos; Fruktosa; Fruktóz; Fruktoza; Fruktozė; Laevulose; Laevulosum; Levulose. D-(−)-Fructopyranose.

$C_6H_{12}O_6$ = 180.2.

CAS — 57-48-7.

ATC — V06DC02.

ATC Vet — QV06DC02.

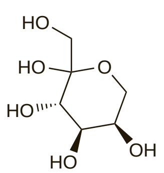

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
USNF includes High Fructose Corn Syrup.

Ph. Eur. 6.2 (Fructose). A white or almost white, crystalline powder with a very sweet taste. Very soluble in water; soluble in alcohol.

USP 31 (Fructose). Colourless crystals or a white crystalline powder. Is odourless and has a sweet taste. Freely soluble in water; soluble 1 in 15 of alcohol and 1 in 14 of methyl alcohol.

USNF 26 (High Fructose Corn Syrup). A sweet, nutritive saccharide mixture prepared as a clear, aqueous solution from high-glucose-equivalent corn starch hydrolysate by the partial enzymatic conversion of glucose to fructose, using an insoluble glucose isomerase enzyme preparation. It is available in two types, 42% and 55%, based on fructose content. Store in airtight containers.

Adverse Effects

Large doses of fructose given by mouth may cause flatulence, abdominal pain, and diarrhoea. Lactic acidosis and hyperuricaemia may follow intravenous infusions; fatalities have occurred.

Gout. Fructose may increase serum concentrations of uric acid, especially in those with existing hyperuricaemia or gout. A large cohort study found that consumption of fructose was associated with an increased risk of gout in men. Fructose-rich fruits or fruit juice may also increase the risk.[1] It has been pointed out that fructose intake has increased in the USA, where soft drinks are usually sweetened with high fructose corn syrup (also known as isoglucose), whereas elsewhere they tend to be sweetened with sucrose.[2]

1. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008; **336:** 309–12.
2. Underwood M. Sugary drinks, fruit, and increased risk of gout. *BMJ* 2008; **336:** 285–6.

Hypersensitivity. Urticaria associated with the ingestion of certain foods by a patient was found to be caused by D-psicose, a minor constituent of high-fructose syrup, which is used as a sweetening agent.[1]

1. Nishioka K, *et al*. Urticaria induced by -psicose. *Lancet* 1983; **ii:** 1417–18.

Precautions

Fructose should not be given to patients with hereditary fructose intolerance.

It should be given with caution to patients with impaired kidney function or severe liver damage.

Intravenous administration. Reiterations of the view that the use of intravenous infusions containing fructose and sorbitol, which remained popular in some countries, should be abandoned.[1,2] Not only can they lead to life-threatening build-up of lactic acid, they have led to fatalities in patients with undiagnosed hereditary fructose intolerance.

1. Collins J. Time for fructose solutions to go. *Lancet* 1993; **341:** 600.
2. Committee on Safety of Medicines/Medicines Control Agency. Reminder: fructose and sorbitol containing parenteral solutions should not be used. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)

Pharmacokinetics

Fructose is absorbed from the gastrointestinal tract but more slowly than glucose. It is metabolised more rapidly than glucose, mainly in the liver where it is phosphorylated and a part is converted to glucose; other metabolites include lactic and pyruvic acid. Although the metabolism of fructose is not dependent on insulin, and insulin is not considered necessary for its removal from the blood, glucose is a metabolic product of fructose and requires the presence of insulin for its further metabolism.

Uses and Administration

Fructose is sweeter than sucrose or sorbitol. It is used as a sweetener in foods for diabetics (although it is not clear it offers any advantage over sucrose); in the UK it has been advised that the intake of fructose be limited to 25 g daily in persons with diabetes mellitus.

Fructose has been used as an alternative to glucose in parenteral nutrition but its use is not recommended because of the risk of lactic acidosis. Use by intravenous infusion in the treatment of severe alcohol poisoning is also no longer recommended.

Solutions of fructose with glucose have been used in the treatment of nausea and vomiting (p.1700) including vomiting of pregnancy. Fructose is also used as a dissolution enhancer and tablet diluent in pharmaceuticals.

Pain. Oral fructose solution was considered to be as effective as oral glucose solution (p.1946) in alleviating mild pain in neonates.[1]

1. Akçam M. Oral fructose solution as an analgesic in the newborn: a randomized, placebo-controlled and masked study. *Pediatr Int* 2004; **46:** 459–62.

Preparations

BP 2008: Fructose Intravenous Infusion;
USP 31: Fructose and Sodium Chloride Injection; Fructose Injection.

Proprietary Preparations (details are given in Part 3)
Hung.: Fructosol; ***Ital.:*** Fructal†; Fructan; Fructofin; Fructopiran†; Fructosil; Laevosan†; ***Spain:*** Levulosado†.

Multi-ingredient: ***Arg.:*** High Energy; ***Austral.:*** Emetrol†; ***Braz.:*** Biofrut†; Dramin B-6 DL; ***Fr.:*** Filigel; ***Hung.:*** Fructosol E†; ***Indon.:*** Gastro-Ad; ***Israel:*** Peptical; ***Ital.:*** Eparema-Levul; Giflorex; Liozim; ***USA:*** Emetrol; Formula EM; Nausetrol.

Gleptoferron *(BAN, USAN, rINN)*

Gleptoferrón; Gleptoferronum; Iron Heptonate.

Глептоферрон

$C_7H_{14}O_8.(C_6H_{10}O_5)_n$.FeOOH.

CAS — 57680-55-4.

ATC Vet — QB03AC91.

Profile

Gleptoferron is a macromolecular complex of ferric hydroxide and dextran-glucoheptonic acid. It has been used for iron-deficiency anaemia in veterinary medicine. It is given by intramuscular injection.

Glucose

Dekstoz Monohidrat; Glucosa; Glukoz; Glukoza; Gukoz.

ATC — B05CX01; V04CA02; V06DC01.

ATC Vet — QB05CX01; QV04CA02; QV06DC01.

Anhydrous Glucose

Anhydrous Dextrose; Anhydrous Glucose; Dextrosum Anhydricum; Gliukozė, bevandenė; Glucosa anhidra; D-Glucose; Glucose anhydre; Glucosum; Glucosum anhydricum; Glukoosi, vedetön; Glukos, vattenfri; Glukosa; Glukoza bezwodna; Vízmentes glükóz. D-(+)-Glucopyranose.

$C_6H_{12}O_6$ = 180.2.

CAS — 50-99-7.

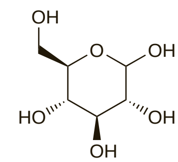

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,*and *Viet.*

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Ph. Eur. 6.2 (Glucose, Anhydrous). A white or almost white, crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

The BP 2008 directs that when Glucose Intravenous Infusion is required as a diluent for official injections or intravenous infusions, Glucose Intravenous Infusion 5% should be used.

USP 31 (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

Glucose Monohydrate

Dextrosum Monohydridicum; Gliukozė monohidratas; Glucosa monohidrato; Glucose monohydraté; D-Glucose Monohydrate; Glucosum monohydricum; Glukoosimonohydraatti; Glukosa monohydrát; Glukosmonohydrat; Glükóz-monohidrát; Glycosum; Grape Sugar. D-(+)-Glucopyranose monohydrate.

$C_6H_{12}O_6,H_2O$ = 198.2.

CAS — 5996-10-1.

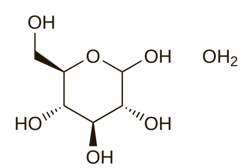

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., US,* and *Viet.*

Some pharmacopoeias include anhydrous glucose and/or glucose monohydrate as separate monographs whereas others permit the anhydrous and/or monohydrate under a single monograph.

Eur. includes Glucose, Liquid and Glucose, Liquid, Spray-dried. *USNF* includes Dextrose Excipient, Liquid Glucose, and Corn Syrup Solids.

Ph. Eur. 6.2 (Glucose Monohydrate; Glucose BP 2008). A white or almost white crystalline powder with a sweet taste. Freely soluble in water; sparingly soluble in alcohol.

Ph. Eur. 6.2 (Glucose, Liquid). A clear, colourless, or brown viscous liquid containing a mixture of glucose, oligosaccharides, and polysaccharides obtained by hydrolysis of starch, in aqueous solution. It contains not less than 70.0% of dry matter. Miscible with water. It may partly or totally solidify at room temperature, liquefying again on heating to 50°.

Ph. Eur. 6.2 (Glucose, Liquid, Spray-dried). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.

USP 31 (Dextrose). It contains one molecule of water of hydration or is anhydrous. Colourless crystals or white, crystalline or granular powder. It is odourless and has a sweet taste. Soluble 1 in 1 of water and 1 in 100 of alcohol; very soluble in boiling water; soluble in boiling alcohol.

USNF 26 (Dextrose Excipient). A sugar usually obtained by hydrolysis of starch. It contains one molecule of water of hydration. Colourless crystals or white, crystalline or granular powder. Freely soluble in water; very soluble in boiling water; slightly soluble in alcohol; sparingly soluble in boiling alcohol.

USNF 26 (Liquid Glucose). It is obtained by incomplete hydrolysis of starch; it consists chiefly of glucose, dextrins, maltose, and water. It is a colourless or yellowish, thick, syrupy, odourless or nearly odourless liquid. Miscible with water; sparingly soluble in alcohol.

USNF 26 (Corn Syrup Solids; Dried Glucose Syrup). A dried mixture of saccharides obtained by partial hydrolysis of edible corn starch by food grade acids and/or enzymes. It contains not less than 20% reducing sugar content (dextrose equivalent) expressed as D-glucose, calculated on the dried basis. A sweet, white to light yellow powder or granules. Soluble in water. Store in airtight containers at a temperature of 8° to 15°.

Adverse Effects and Precautions

Intravenous glucose solutions (particularly hyperosmotic solutions, which also have a low pH) may cause local pain, vein irritation, and thrombophlebitis, and tissue necrosis if extravasation occurs. Some of these reactions may be due to degradation products present after autoclaving or to poor technique in giving the solution. Intravenous infusion can lead to fluid and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia. Prolonged or rapid infusion of large volumes of iso-osmotic solutions may cause oedema or water intoxication; conversely, prolonged or rapid use of hyperosmotic solutions may result in dehydration as a consequence of the induced hyperglycaemia.

The use of hyperosmotic glucose solutions is contra-indicated in patients with anuria, intracranial or intraspinal haemorrhage, and in delirium tremens where there is dehydration. They should be used with caution in patients with diabetes mellitus, as rapid infusion can lead to hyperglycaemia, as well as in those with malnutrition, thiamine deficiency, carbohydrate intolerance, sepsis, shock, or trauma.

It has been suggested that glucose solutions should not be used after acute ischaemic strokes as hyperglycaemia has been implicated in increasing cerebral ischaemic brain damage and in impairing recovery.

Glucose solutions should not be given through the same infusion equipment as whole blood as haemolysis and clumping can occur.

Pregnancy. Glucose solutions are commonly used as hydrating fluids and as vehicles for other drugs. If given during labour it has been suggested that the glucose load on the mother may lead to fetal hyperglycaemia, hyperinsulinaemia, and acidosis, with subsequent neonatal hypoglycaemia and jaundice.[1,2] Others[3] have found no evidence of such an effect, especially if the fetus is well-oxygenated,[4] and note that the number of patients included in such reports is often small and the selection criteria not homogeneous.

A placebo-controlled study[5] in healthy women scheduled for termination of pregnancy at mid-gestation found that giving 100 g of oral glucose 1 hour before termination had no adverse effect on fetal acid–base levels. Fetuses with malformations had been excluded. However, the authors cautioned that, at higher maternal glucose concentrations (as may be found in pregnant diabetics), changes consistent with fetal metabolic acidosis might occur, and that the glucose tolerance test might also be hazardous to fetuses with growth retardation. Late reactions to the acute glucose load could not be studied.

1. Kenepp NB, *et al.* Fetal and neonatal hazards of maternal hydration with 5% dextrose before caesarean section. *Lancet* 1982; **i:** 1150–2.
2. Singhi S, *et al.* Hazards of maternal hydration with 5% dextrose. *Lancet* 1982; **ii:** 335–6.
3. Piquard F, *et al.* Does fetal acidosis develop with maternal glucose infusion during normal labor? *Obstet Gynecol* 1989; **74:** 909–14.
4. Cerri V, *et al.* Intravenous glucose infusion in labor does not affect maternal and fetal acid-base balance. *J Matern Fetal Med* 2000; **9:** 204–8.
5. Weissman A, *et al.* Effect of the 100-g oral glucose tolerance test on fetal acid-base balance. *Prenat Diagn* 2003; **23:** 281–3.

Stroke. Hyperglycaemia may be caused by physiological stress during ischaemic stroke, and this worsens cerebral ischaemic damage and impairs recovery. During cerebral ischaemia, cellular hypoxia causes a shift from aerobic to anaerobic metabolism of glucose leading to intracellular lactic acidosis, which is toxic to the cell. Hyperglycaemia provides more glucose for anaerobic metabolism, further worsening intracellular acidosis. Blood-glucose concentrations should therefore be monitored and hyperglycaemia avoided or treated. Glucose infusions should not be used routinely after ischaemic stroke, unless specifically indicated. Hypoglycaemia must also be avoided and for patients who do require glucose, it should be given by continuous infusion, avoiding large infusions or boluses that can cause hyperglycaemia.[1]

1. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996; **71:** 801–12.

Thiamine deficiency. Giving intravenous glucose to thiamine-deficient patients may precipitate Wernicke's encephalopathy (p.1977).[1,2]

1. Watson AJ, *et al.* Acute Wernickes encephalopathy precipitated by glucose loading. *Ir J Med Sci* 1981; **150:** 301–3.
2. Koguchi K, *et al.* Wernicke's encephalopathy after glucose infusion. *Neurology* 2004; **62:** 512.

Pharmacokinetics

Glucose is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of glucose occur about 40 minutes after oral doses in hypoglycaemic patients. It is metabolised via pyruvic or lactic acid to carbon dioxide and water with the release of energy. All body cells are capable of oxidising glucose and it forms the principal source of energy in cellular metabolism.

Uses and Administration

Glucose, a monosaccharide, is given by mouth or by intravenous infusion in the treatment of carbohydrate and fluid depletion. It is the preferred source of carbohydrate in parenteral nutrition regimens (p.1923) and is used in oral rehydration solutions (p.1672) for the prevention and treatment of dehydration due to acute diarrhoeal diseases (p.1694).

Glucose is also used in the treatment of hypoglycaemia (see below) and is given orally in the glucose tolerance test as a diagnostic aid for diabetes mellitus (see p.431).

The way in which the strengths of glucose solutions for intravenous use are expressed varies in different countries. Both Glucose Intravenous Infusion (BP 2008) and Dextrose Injection (USP 31) may be prepared from either anhydrous glucose or glucose monohydrate. However, the potency of the BP 2008 preparation is expressed in terms of anhydrous glucose whereas that of the USP 31 is expressed in terms of glucose monohydrate. Anhydrous glucose 0.9 g is equivalent to about 1 g of glucose monohydrate. Thus, the term glucose 5% may represent, depending on origin, either 50 g/litre of anhydrous glucose (equivalent to about 55 g/litre of glucose monohydrate) or 50 g/litre of glucose monohydrate (equivalent to about 45 g/litre of anhydrous glucose). As the manner in which such preparations are referred to in the medical literature is sometimes ambiguous, it has not always been possible to state clearly in *Martindale* whether the strengths of glucose solutions mentioned relate to the anhydrous or hydrated form; however, in *Martindale*, unless otherwise specified, glucose injection is a 5% solution to distinguish it from more concentrated forms. For many practical purposes it is probably less important to know the exact way in which the strength of a given concentration is expressed than to avoid confusion between completely different strengths such as 5, 10, and 50% as the more concentrated forms are associated with particular adverse effects and precautions.

Solutions of glucose in water are iso-osmotic with blood at a concentration of anhydrous glucose 5.05% or glucose monohydrate 5.51%. Glucose solution 5% is therefore the strength often employed for fluid depletion; it may be given via a peripheral vein. Glucose solutions with a concentration greater than 5% are hyperosmotic and are generally used as a carbohydrate source; a 50% solution is often used in the treatment of severe hypoglycaemia (but see also Hypoglycaemia, below). Hyperosmotic solutions should generally be given via a central vein although the *American Hospital Formulary Service* suggests that concentrations up to 10% may be given via a large peripheral vein for short periods provided the site is alternated regularly. In the emergency treatment of hypoglycaemia it may be necessary to use a peripheral vein but the solution should be given slowly; a suggested rate for glucose 50% in such circumstances is 3 mL/minute.

The dose of glucose is variable and is dependent on individual patient requirements; serum-glucose concentrations may need to be carefully monitored. The maximum rate of glucose utilisation has been estimated to be about 500 to 800 mg/kg per hour.

Strongly hyperosmotic glucose solutions (25 to 50%) have also been given to reduce cerebrospinal pressure (p.1181) and cerebral oedema caused by delirium tremens or acute alcohol intoxication (see p.1626) although they do not appear to be widely used. Glucose solution (25 to 50%) has also been used as a sclerosing agent in the treatment of varicose veins (p.2347) and as an irritant to produce adhesive pleuritis in the management of pleural effusions and pneumothorax. Liquid glucose is used as a sweetener, binder, or granulating and coating agent in pharmaceuticals.

Ectopic pregnancy. Ectopic pregnancy is now recognised at earlier stages as a result of improved diagnostic techniques. Surgery remains the mainstay of treatment, but although conservative surgical techniques may be used in an attempt to preserve fertility, nonsurgical methods have been increasingly investigated. The best established therapy is with methotrexate (p.749), but hyperosmolar glucose solutions have also been used. Local instillation of 5 to 20 mL of glucose 50% into the gestational sac (salpingocentesis) has been described.[1] It was reported to be more effective than expectant management of early tubal pregnancy[2] but another study was stopped because of a higher failure rate with glucose than local methotrexate.[3]

1. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; **42:** 39–47.
2. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; **76:** 797–800.
3. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; **265:** 82–4.

Glycogen storage disease type I. Starch may be a more acceptable alternative to glucose in the control of the hypoglycaemia of type I glycogen storage disease, see p.1968.

Haemodialysis-induced cramp. Suggestions that haemodialysis-induced cramps (p.1671) are due to hypovolaemia are supported by the efficacy of volume expansion with hypertonic solutions in the management of such cramps. Intravenous infusion of 50 mL of glucose 50% solution has been used as an effective alternative to infusion of sodium chloride or mannitol.[1,2]

1. Milutinovich J, *et al.* Effect of hypertonic glucose on the muscular cramps of hemodialysis. *Ann Intern Med* 1979; **90:** 926–8.
2. Canzanello VJ, *et al.* Comparison of 50% dextrose water, 25% mannitol, and 23.5% saline for the treatment of hemodialysis-associated muscle cramps. *Trans Am Soc Artif Intern Organs* 1991; **37:** 649–52.

Hyperkalaemia. Insulin, together with glucose to prevent hypoglycaemia, is given to stimulate the cellular uptake of potassium in the emergency treatment of moderate to severe hyperkalaemia (p.1669). Usually, 50 mL of glucose 50% is given.

Hypoglycaemia. Glucose is used to correct insulin-induced hypoglycaemia, as discussed on p.447, either by mouth or by infusion of a hypertonic solution (20 or 50%). Glucose 5 or 10% may be used but larger volumes are required. Although 50% glucose solution has been generally used to correct hypoglycaemia in children, some consider that so concentrated a solution is associated with unacceptable morbidity and possible mortality, and that it should be replaced by the 10% solution for this purpose.[1] A 5 or 10% solution is used to prevent the hypoglycaemia associated with insulin infusion for the treatment of diabetic ketoacidosis, once blood-glucose concentrations have fallen below 12.5 mmol/litre (see under Diabetic Emergencies, p.435).

1. Winrow AP, *et al.* Paediatric resuscitation: don't use 50% dextrose. *BMJ* 1993; **306:** 1612.

Myocardial infarction. The value of a glucose, insulin, and potassium combination in patients with myocardial infarction has been investigated (see p.452).

Pain. Oral glucose solution or spray has been used similarly to sucrose solution (p.1970) to alleviate mild pain in neonates,[1-4] and there is some suggestion it may be more effective than topically applied local anaesthetic.[5]

Glucose solutions have been injected for prolotherapy (the local injection of irritant solutions to stimulate proliferation)[6,7] in the management of painful musculoskeletal conditions such as low back pain[7] and groin strain.[8] The value of such treatment has been disputed.

1. Skogsdal Y, *et al.* Analgesia in newborns given oral glucose. *Acta Paediatr Scand* 1997; **86:** 217–20.
2. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; **319:** 1393–7.
3. Carbajal R, *et al.* Crossover trial of analgesic efficacy of glucose and pacifier in very preterm neonates during subcutaneous injections. *Pediatrics* 2002; **110:** 389–93.
4. Akçam M, Örmeci AR. Oral hypertonic glucose spray: a practical alternative for analgesia in the newborn. *Acta Paediatr* 2004; **93:** 1330–3.

5. Gradin M, *et al.* Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics* 2002; **110:** 1053–7.
6. Rabago D, *et al.* A systematic review of prolotherapy for chronic musculoskeletal pain. *Clin J Sport Med* 2005; **15:** 376–80.
7. Dagenais S, *et al.* Prolotherapy injections for chronic low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).
8. Topol GA, *et al.* Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Arch Phys Med Rehabil* 2005; **86:** 697–702.

Preparations

BP 2008: Glucose Intravenous Infusion; Glucose Irrigation Solution; Potassium Chloride and Glucose Intravenous Infusion; Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion; Sodium Chloride and Glucose Intravenous Infusion;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USNF 26: Dextrose Excipient; Liquid Glucose;
USP 31: Alcohol in Dextrose Injection; Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Dextrose and Sodium Chloride Injection; Dextrose Injection; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 3; Multiple Electrolytes and Dextrose Injection Type 4; Potassium Chloride in Dextrose and Sodium Chloride Injection; Potassium Chloride in Dextrose Injection; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Ringer's and Dextrose Injection; Sodium Chloride and Dextrose Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Glucolin; Glucotem; Kissimin; Nutrosa; ***Austral.:*** Insta-Glucose†; ***Austria:*** Glucosteril; ***Canad.:*** Glucodex†; ***Cz.:*** Ardeanutrisol G; Spofagnost†; ***Fin.:*** Glucosteril; ***Ger.:*** Glucosteril; ***Hung.:*** Isodex; ***Indon.:*** Otsu-D5; Wida D5 and D10; ***Ital.:*** Energen; ***Pol.:*** Maltan; ***Port.:*** Glucosada; Glucosado; Glucosteril; ***Rus.:*** Glucosteril (Глюкостерил); ***Spain:*** Apir Glucosado; Biberon; Flebobag Glucosa; Fleboflex Glucosa; Fleboplast Glucosa; Freeflex Glucosa; Glucosmon; Meinvenil Glucosa; Plast Apyr Glucosado; Suero Glucosado Isotonico; ***UK:*** GlucoGel; ***USA:*** Dex4 Glucose; Glutose; Insulin Reaction.

Multi-ingredient: ***Arg.:*** High Energy; Sucaryl; Suimel; ***Austral.:*** BSS Plus; Dexsal; Emetrol†; No Doz Plus; Nyal Chesty Cough†; Vig†; ***Austria:*** BSS Plus; Gluco-Salzlosung; ***Braz.:*** Dramin B-6 DL; Glicofisiologica†; ***Canad.:*** BSS Plus; Sclerodex; ***Fr.:*** BSS Plus; Coramine Glucose; Notabac; ***Ger.:*** BSS Plus; Kochsalz mit Glucose; ***Hong Kong:*** BSS Plus†; ***Hung.:*** BSS Plus; ***India:*** Toniazol†; ***Irl.:*** Venos Expectorant; Venos Honey & Lemon; ***Israel:*** BSS Plus; Peptical; ***Ital.:*** Alcalosio; Apergan; Fosfarsile Forte; ***Malaysia:*** BSS Plus; ***Mex.:*** Combinacion Pl†; ***Norw.:*** Salidex; ***Pol.:*** Glucardiamid; ***Port.:*** Glucosalino; ***Rus.:*** Gluconeodesum (Глюконеодез); ***S.Afr.:*** BSS Plus; ***Singapore:*** BSS Plus; ***Spain:*** Acetuber; Apir Glucosalino; Flebobag Glucosalina; Fleboplast Glucosalina; Freeflex Glucosalina; Glucopotasico; Glucosalina; Glucosalino; Meinvenil Glucosalina; Plast Apyr Glucosalino; Suero Glucosalino; ***Switz.:*** BSS Plus†; Glucosalin; Glucosalin Glycine; Gly-Coramin; ***Thai.:*** BSS Plus; Euro-Collins; Gluco-Calcium; ***UK:*** Buttercup Infant Cough Syrup; Buttercup Syrup (Blackcurrant flavour); Buttercup Syrup (Honey and Lemon flavour); Lockets Medicated Linctus; PEP; Venos Cough Mixture; Venos Expectorant; Venos Honey & Lemon; ***USA:*** BSS Plus; Emetrol; Formula EM; Nausetrol; ***Venez.:*** BSS Plus†; Dextro-Sal†; Glucofisiologica†.

Glutamic Acid *(USAN, rINN)*

Acide glutamique; Ácido glutámico; Acidum glutamicum; E; E620; Glu; L-Glutamic Acid; Glutamiinihappo; Glutaminic Acid; Glutaminsav; Glutaminsyra; Glutamo rūgštis; Kwas glutaminowy; Kyselina glutamová. L-(+)-2-Aminoglutaric acid.

Глутаминовая Кислота

$C_5H_9NO_4$ = 147.1.
CAS — 56-86-0.

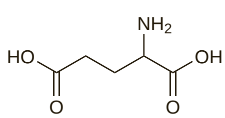

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Glutamic Acid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in boiling water; slightly soluble in cold water; practically insoluble in alcohol, in acetic acid, and in acetone. Protect from light.

Glutamic Acid Hydrochloride *(rINNM)*

Acide Glutamique, Chlorhydrate de; Acidum Glutamicum Hydrochloridum; Aciglumin; Glu Hydrochloride; Hidrocloruro del ácido glutámico. L-(+)-2-Aminoglutaric acid hydrochloride.

Глутаминовой Кислоты Гидрохлорид

$C_5H_9NO_4,HCl$ = 183.6.
CAS — 138-15-8.
ATC — A09AB01.
ATC Vet — QA09AB01.

Pharmacopoeias. In *Ger.*

Glutamine *(USAN, rINN)*

Gln; Glutamina; L-Glutamine; Glutaminum; Levoglutamida; Lévoglutamide; Levoglutamide; Levoglutamidum; Q. L-Glutamic acid 5-amide; L-(+)-2-Aminoglutaramic acid.

Левоглутамид

$C_5H_{10}N_2O_3$ = 146.1.
CAS — 56-85-9.
ATC — A16AA03.
ATC Vet — QA16AA03.

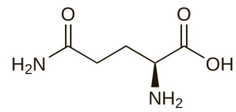

Pharmacopoeias. In *Ger.* and *US.*
USP 31 (Glutamine). White crystals or crystalline powder. Soluble in water; practically insoluble in alcohol and in ether. Store at a mean temperature not exceeding 25°.

Profile

Glutamic acid is a non-essential amino acid which is degraded readily in the body to form glutamine (levoglutamide). Glutamic acid and glutamine are used as dietary supplements. The dipeptides *N*(2)-L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln) are used similarly.

Glutamic acid hydrochloride, which releases hydrochloric acid in the stomach, has been used in the symptomatic treatment of achlorhydria or hypochlorhydria in usual oral doses of 250 to 750 mg with meals.

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis.

Antineoplastic toxicity. Vincristine neurotoxicity has been reduced by the use of oral glutamic acid (see Administration Error, p.787).

Oral supplementation with glutamine may also have a role in alleviating the diarrhoea associated with irinotecan (see Effects on the Gastrointestinal System, p.737).

A glutamine-based oral suspension is under investigation for the treatment of oral mucositis associated with cancer chemotherapy (p.640). In breast cancer patients with moderate to severe oral mucositis glutamine reduced both the incidence and severity of the mucositis.[1] A literature review[2] reported variable results with glutamine supplementation for chemotherapy-induced mucositis, but stated that higher doses may be beneficial.

Oral glutamine was found to be of no benefit in alleviating myalgias or arthralgias associated with paclitaxel therapy.[3]

1. Peterson DE, *et al.* Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer* 2007; **109:** 322–31.
2. Savarese DMF, *et al.* Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev* 2003; **29:** 501–13.
3. Jacobson SD, *et al.* Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* 2003; **1:** 274–8.

Parenteral and enteral nutrition. Evidence that glutamine is involved in the regulation of muscle protein synthesis, maintenance of gut mucosal barrier function, and possibly enhanced immunological response has led to studies of supplementation with glutamine or more stable peptide derivatives in parenteral and enteral nutrition regimens for patients with injury and infection.[1] Although non-essential under normal circumstances, many consider glutamine to be a conditionally essential amino acid in patients with catabolic disease.[2,3]

Supplementation of parenteral nutrition regimens with glutamine has been shown to reduce clinical infection in patients who have undergone bone marrow transplantation[4] or who have suffered multiple trauma.[5] Improved survival has been reported among intensive-care patients given parenteral feeds supplemented with glutamine,[6,7] although a larger study found it difficult to demonstrate benefit.[8] A systematic review,[9] including these studies, inferred that seriously ill patients, with gastrointestinal failure and receiving parenteral nutrition, should receive glutamine supplements for at least 6 days and at a dose of greater than 200 mg/kg daily, in order to derive maximum benefit. Low plasma glutamine concentration upon admission to an intensive-care unit was considered to be an independent risk factor for mortality, and it has been suggested that plasma concentrations be used as an indicator for glutamine supplementation.[10]

In patients undergoing major uncomplicated surgery on the lower gastrointestinal tract, a significantly better postoperative nitrogen balance was achieved in those whose total parenteral nutrition regimen had been supplemented with about 20 g daily of glutamine coupled with alanine (L-alanyl-L-glutamine) (equivalent to about 12 g daily of glutamine) when compared with a control group.[11] Others[12] have shown that supplementation of total parenteral nutrition solutions with a glutamine dipeptide (glycyl-L-glutamine), in quantities equivalent to 230 mg/kg of glutamine daily, prevented the increased intestinal permeability and atrophic changes in the intestinal mucosa associated with unsupplemented solutions. Supplementation of total parenteral nutrition with α-ketoglutarate or a dipeptide, ornithine-α-ketoglutarate, reduced muscle protein depletion in one study,[13] suggesting that this may be a more physiological way of providing glutamine. Although recognising that clinical benefit in terms of infectious complications remained to be established, a review[14] of the use of ornithine-α-ketoglutarate stated that supplementation in the elderly improved clinical outcome in chronic malnutrition, by increasing appetite and body-weight gain and improving healing.

1. Sacks GS. Glutamine supplementation in catabolic patients. *Ann Pharmacother* 1999; **33:** 348–54.
2. Kelly D, Wischmeyer PE. Role of -glutamine in critical illness: new insights. *Curr Opin Clin Nutr Metab Care* 2003; **6:** 217–22.
3. Melis GC, *et al.* Glutamine: recent developments in research on the clinical significance of glutamine. *Curr Opin Clin Nutr Metab Care* 2004; **7:** 59–70.
4. Ziegler TR, *et al.* Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation: a randomized, double-blind, controlled study. *Ann Intern Med* 1992; **116:** 821–8.
5. Houdijk APJ, *et al.* Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998; **352:** 772–6.
6. Griffiths RD, *et al.* Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997; **13:** 295–302.
7. Goeters C, *et al.* Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med* 2002; **30:** 2032–7.
8. Powell-Tuck J, *et al.* A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999; **45:** 82–8.
9. Novak F, *et al.* Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* 2002; **30:** 2022–9.
10. Wernerman J. Glutamine and acute illness. *Crit Care* 2003; **9:** 279–85.
11. Stehle P, *et al.* Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet* 1989; **i:** 231–3.
12. van der Hulst RRWJ, *et al.* Glutamine and the preservation of gut integrity. *Lancet* 1993; **334:** 1363–5.
13. Wernerman J, *et al.* α-Ketoglutarate and postoperative muscle catabolism. *Lancet* 1990; **335:** 701–3.
14. Blonde-Cynober F, *et al.* Use of ornithine α-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; **19:** 73–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dipeptiven; ***Austria:*** Dipeptiven; Neuroglutamin; ***Chile:*** Dipeptiven; ***Cz.:*** Dipeptiven; ***Denm.:*** Dipeptiven; ***Fin.:*** Dipeptiven; Hypochylin; ***Fr.:*** Dipeptiven; ***Ger.:*** Dipeptamin; Glutamin; Gluti-Agil mono; Pepsaletten N; ***Gr.:*** Dipeptiven; ***Hung.:*** Dipeptiven; ***Indon.:*** Dipeptiven; ***Irl.:*** Adamin-G; ***Ital.:*** Dipeptiven; Glutacerebro†; Glutaven; Memoril†; ***Malaysia:*** Dipeptiven; ***Mex.:*** Dipeptiven; ***Neth.:*** Dipeptiven; ***Norw.:*** Dipeptiven; ***Pol.:*** Dipeptiven; ***Port.:*** Cebrotex†; Dipeptiven; ***Rus.:*** Dipeptiven (Дипептивен); ***Spain:*** Dipeptiven; ***Swed.:*** Dipeptiven; Hypochylin; ***Switz.:*** Dipeptiven; ***Thai.:*** Dipeptiven; ***Turk.:*** Dipeptiven; ***UK:*** Dipeptiven.

Multi-ingredient: ***Arg.:*** Normoprost Compuesto; ***Austral.:*** Aspartatol; Bioglan Digestive Zyme; Liv-Detox†; Prozyme†; ***Austria:*** Aslavital; ***Braz.:*** Taludon†; ***Chile:*** Glutacyl Vitaminado; Hexalectol; ***Fr.:*** Phakan†; Vita-Dermacide; YSE Glutamique; ***Ger.:*** Glutarsin E†; Vitasprint B †; ***Hong Kong:*** Dipeptiven; Esafosfina Glutammica; ***Hung.:*** Glutarsin E; ***Indon.:*** Proseval; Stamino; ***Ital.:*** Acutil Fosforo; Briogen†; Esaglut†; Fosfo Plus; Glutamin Fosforo; Memovit B12; Vitasprint Complex†; Vitasprint†; ***Philipp.:*** Glutaphos; Spasmo-Canulase; ***Port.:*** Cebrotex Forte; Espasmo Canulase; Phakan†; Relavit Fosforo; ***Rus.:*** Eltacin (Элтацин); ***S.Afr.:*** Dipeptiven; Lentogesic; Spasmo-Canulase; ***Spain:*** Agudil; Gastroglutal†; Nucleserina; Tebetane Compuesto; ***Switz.:*** Phakolen†; Spasmo-Canulase; Vitasprint Complex; ***Venez.:*** Glutapak; Glutapak-R.

Glycine *(rINN)*

Acidum Aminoaceticum; Aminoacetic Acid; Aminoättiksyra; Aminoetikkahappo; E640 (glycine or glycine sodium); G; Glicin; Glicina; Glicinas; Glicyna; Gly; Glycin; Glycinum; Glycocoll; Glysiini; Sucre de Gélatine.

Глицин

$C_2H_5NO_2$ = 75.07.
CAS — 56-40-6.
ATC — B05CX03.
ATC Vet — QB05CX03.

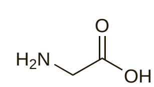

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Glycine). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 5.9 to 6.4.
USP 31 (Glycine). A white, odourless crystalline powder. Soluble 1 in 4 of water at 25°, 1 in 2.6 at 50°, 1 in 1.9 at 75°, and 1 in 1.5 at 100°; soluble 1 in 1254 of alcohol; very slightly soluble in ether. Its solutions are acid to litmus.

Adverse Effects and Precautions

Systemic absorption of glycine irrigation solutions can lead to disturbances of fluid and electrolyte balance and cardiovascular and pulmonary disorders (see below).

Glycine irrigation should be used cautiously in patients with hepatic impairment since any absorption and consequent metabolism may cause hyperammonaemia. The possible effects on fluid and electrolyte balance warrant cautious use in patients with cardiopulmonary or renal dysfunction; glycine irrigation is contraindicated in anuric patients.

Systemic absorption. Absorption of glycine irrigation solution during surgical procedures can cause disturbances of the circulatory and nervous systems.[1-3] Often seen after transurethral resection of the prostate, these symptoms and signs have been referred to as the transurethral resection syndrome,[1] although they have also been described after other urological or gynaecological surgical procedures.[4,5] Hyponatraemia and glycine toxicity are thought to be responsible for the clinical manifestations.[1,2,5]

Symptoms and signs include chest pains, hypertension, hypotension, bradycardia, anuria, dyspnoea, nausea, vomiting, restlessness, confusion, apprehension, irritability, headache, and seizures.[1,3-5] Chills, diarrhoea, and abdominal pain have also been reported,[1] as have visual disturbances and blindness.[3,6] Myocardial infarction,[7,8] coma, and death may occur.[5,7]

Absorption may occur rapidly, through the intravascular route, or, more rarely, slowly via extravascular absorption.[1,2,4] Extravasation should be suspected when abdominal pain and swelling are apparent.[4,9] Ethanol has been added to the irrigation fluid, and ethanol breath tests performed regularly during procedures in order to detect and monitor absorption.[1,2,4,9] However, the syndrome has still occurred despite monitoring;[9] awareness of the pattern of ethanol changes and clinical symptoms associated with extravascular as well as intravascular absorption are considered essential.[4,9]

1. Olsson J, *et al.* Symptoms of the transurethral resection syndrome using glycine as the irrigant. *J Urol (Baltimore)* 1995; **154:** 123–8.
2. Tauzin-Fin P. Complication des liquides d'irrigation à base de glycocolle: le syndrome de résorption. *Therapie* 2002; **57:** 48–54.
3. Radziwill AJ, *et al.* Visual disturbances and transurethral resection of the prostate: the TURP syndrome. *Eur Neurol* 1997; **38:** 7–9.
4. Hahn RG. Transurethral resection syndrome after transurethral resection of bladder tumours. *Can J Anaesth* 1995; **42:** 69–72.
5. Siddiqui MA, *et al.* Glycine irrigant absorption syndrome following cystoscopy. *Clin Nephrol* 1996; **45:** 365–6.
6. Karci A, Erkin Y. Transient blindness following hysteroscopy. *J Int Med Res* 2003; **31:** 152–5.
7. Byard RW, *et al.* Glycine toxicity and unexpected intra-operative death. *J Forensic Sci* 2001; **46:** 1244–6.
8. Hahn RG, Persson P-G. Acute myocardial infarction after prostatectomy. *Lancet* 1996; **347:** 335.
9. Hahn RG. Life-threatening transurethral resection syndrome despite monitoring of fluid absorption with ethanol. *Eur J Anaesthesiol* 1995; **12:** 431–3.

Uses and Administration

Glycine is a non-essential aliphatic amino acid. It is used as a dietary supplement.

Glycine is sometimes used with antacids in the treatment of gastric hyperacidity. It is also used as an ingredient of some aspirin preparations with the object of reducing gastric irritation.

Sterile solutions of glycine 1.5% in water, which are hypotonic and non-conductive, are used as urogenital irrigation solutions during certain surgical procedures, particularly transurethral resection of the prostate.

Glycine hydrochloride has also been used.

Preparations

BP 2008: Glycine Irrigation Solution;
USP 31: Glycine Irrigation.

Proprietary Preparations (details are given in Part 3)
Fr.: Derm Hydralin; Gyn-Hydralin; ***Hong Kong:*** Gyn-Hydralin; ***Mex.:*** Glisuret†.

Multi-ingredient: *Arg.:* Normoprost Compuesto; ***Austral.:*** Cal Alkyline; ***Austria:*** Centramin; ***Braz.:*** B-Vesil; ***Chile:*** Dolotol 12; ***Fr.:*** Cristopal†; Derm'Intim; Item Alphazole; Phakan†; Pruriced; ***India:*** Cotaryl; ***Ital.:*** Detoxicon; Digestivo Antonetto; ***Mex.:*** Segel†; ***Port.:*** Phakan†; ***Rus.:*** Eltacin (Элтацин); ***Spain:*** Sanieb†; Tebetane Compuesto; ***Switz.:*** DAM Antacidum; Phakolen†.

Used as an adjunct in: ***Austral.:*** Cardiprin; Disprin Direct; ***Cz.:*** Godasal; ***Ger.:*** Godamed; Praecineural; ***Hong Kong:*** Cardiprin; Glyprin; ***Indon.:*** Contrexyn; Inzana; Minigrip; ***Israel:*** Lysoprin†; ***Ital.:*** Aspiglicina; Geyfritz†; ***Malaysia:*** Cardiprin; Glyprin; ***NZ:*** Cardiprin†; ***Pol.:*** Alka-Prim; Asprocol; ***Singapore:*** Cardiprin; Glyprin; ***Thai.:*** Caparin; Cardiprin.

Halibut-liver Oil

Aceite de hígado de fletán; Aceite de Higado de Hipogloso; Heilbuttleberöl; Ol. Hippogloss.; Oleum Hippoglossi; Oleum Jecoris Hippoglossi.

Палтусовый Печёночный Жир

CAS — 8001-46-5.

Pharmacopoeias. In *Br.*

BP 2008 (Halibut-liver Oil). The fixed oil extracted from the fresh or suitably preserved liver of the halibut species belonging to the genus *Hippoglossus*. It contains not less than 30 000 units of vitamin A activity per g. Wt per mL 0.915 to 0.925 g. A pale to golden yellow liquid with a fishy, but not rancid, odour and taste. Practically insoluble in alcohol; miscible with chloroform, with ether and with petroleum spirit. Store in well-filled containers. Protect from light.

Profile

Halibut-liver oil is used as a means of giving vitamins A (p.1971) and D (p.1986); the proportion of vitamin A to vitamin D is usually greater in halibut-liver oil than in cod-liver oil (p.1935). It is usually given in capsules.

Preparations

BP 2008: Halibut-liver Oil Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Pancutan Base; ***Canad.:*** Nutrol A; ***Switz.:*** Halibut.

Multi-ingredient: *Arg.:* Eryteal; Klorane Bebe Eryteal; Pancutan; ***Austria:*** Nuri-Kapseln; Vitawund; ***Chile:*** Hipoglos; Mintaglos; Nistaglos; ***Fr.:*** Eryteal†; Preparation H; ***Port.:*** Halibut; ***Switz.:*** A Vogel Capsules polyvitaminees†.

Hetaflur *(BAN, USAN, rINN)*

Cetylamine Hydrofluoride; GA-242; Hétaflur; Hetaflurum; SKF-2208. Hexadecylamine hydrofluoride.

Гетафлур

$C_{16}H_{35}N,HF = 261.5.$

CAS — 3151-59-5.

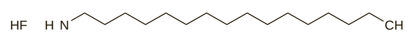

Profile

Hetaflur is used as a source of fluoride (see Sodium Fluoride, p.1962) in the prevention of dental caries.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Israel:* Elmex†.

Histidine *(USAN, rINN)*

H; His; Histidiini; Histidin; Histidina; Histidinas; L-Histidine; Histidinum; Hisztidin; NSC-137773. L-2-Amino-3-(1*H*-imidazol-4-yl)propionic acid.

Гистидин

$C_6H_9N_3O_2 = 155.2.$

CAS — 71-00-1.

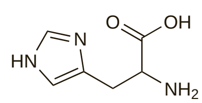

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Histidine). Colourless crystals or a white or almost white crystalline powder. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Histidine). White, odourless crystals. Soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 2% solution in water is between 7.0 and 8.5.

Histidine Hydrochloride

Histidiinihydrokloridimonohydraatti; Histidina, hidrocloruro; Histidine (chlorhydrate d') monohydraté; Histidine Monohydrochloride; Histidin-hydrochlorid monohydrát; Histidinhydrokloridmonohydrat; Histidini hydrochloridum monohydricum; Histidinium Chloride; Histidino hidrochloridas monohidratas; Histydyny monochlorowodorek; Hisztidin-hidroklorid-monohidrát. L-Histidine hydrochloride monohydrate.

$C_6H_9N_3O_2,HCl,H_2O = 209.6.$

CAS — 645-35-2 (anhydrous histidine hydrochloride).

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Histidine Hydrochloride Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 5.0. Protect from light.

Profile

Histidine is a basic amino acid that is essential for infant growth and which may be essential for some other groups, such as patients with uraemia. Histidine and histidine hydrochloride are used as dietary supplements.

Honey

Clarified Honey; Gereinigter Honig; Honung; Hunaja; Madu; Med; Medus; Mel; Mel Depuratum; Mel Despumatum; Miel; Miel Blanc; Miel purificada; Purified Honey; Strained Honey.

Мёд

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Honey; Mel). It is produced by bees (*Apis mellifera*) from the nectar of plants or from secretions of living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store, and leave in the honey comb to ripen and mature. If the bee has been exposed to treatment to prevent or cure diseases or to any substance intended for preventing, destroying, or controlling any pest, unwanted species of plants or animals, appropriate steps are taken to ensure that the levels of residues are as low as possible. It is an almost white to dark brown, viscous liquid which may be partly crystalline.

USNF 26 (Purified Honey). It is obtained by purification of honey from the comb of the bee, *A. mellifera* and all subspecies of *A. mellifera*. The honey is extracted by centrifugation, pressure, or other suitable procedures. Specific gravity 1.400 and 1.435 at 20°. Store in airtight containers. It is not intended for infants under one year of age unless it is free from *Clostridium* spp.

Profile

Honey, which contains about 70 to 80% of glucose and fructose, is used as a demulcent and sweetening agent, especially in linctuses and cough mixtures (p.1547). Preparations containing honey are used in the management of skin ulcers, wounds, and burns.

Contamination. Honey has been identified as a source of *Clostridium botulinum* spores and thus recommendations have been made that honey should not be given to infants under 1 year because of the risk of causing infant botulism.[1,2]

Honey produced from certain species of *Rhododendron* plants has been found to contain grayanotoxins. Grayanotoxin I is responsible for honey poisoning, manifest as bradycardia, cardiac arrhythmias, hypotension, gastrointestinal disturbances, dizziness, loss of consciousness, blurred vision, chills, cyanosis, sweating, and salivation.[3,4] Convulsions have also been reported.[4]

1. Arnon SS, *et al.* Honey and other environmental risk factors for infant botulism. *J Pediatr* 1979; **94:** 331–6.
2. Tanzi MG, Gabay MP. Association between honey consumption and infant botulism. *Pharmacotherapy* 2002; **22:** 1479–83.
3. Özhan H, *et al.* Cardiac emergencies caused by honey ingestion; a single centre experience. *Emerg Med J* 2004; **21:** 742–4.
4. Dilber E, *et al.* A case of mad honey poisoning presenting with convulsion: intoxication instead of alternative therapy. *Turk J Med Sci* 2002; **32:** 361–2.

Wounds. Anecdotal reports and traditional usage dating back to ancient Egypt suggest that honey may be of some value as a wound dressing (p.1585). Its antibacterial properties are attributed both to high osmolality and the liberation of hydrogen peroxide, but may vary with the source:[1-4] in Europe, some of the best activity has been seen with lime-flower honey.[2] Sterilised manuka honey (p.2337) was reported to heal a leg ulcer infected with meticillin-resistant *Staphylococcus aureus*,[5] although a randomised open-label study found no evidence that dressings impregnated with manuka honey improved the healing of venous leg ulcers at 12 weeks compared with usual care.[6] In a preliminary study, honey obtained from the tea plant (see Xanthine-containing Beverages, p.2415) significantly reduced the incidence of grade 3 and 4 radiation-induced oral mucositis.[7]

A group from India[8] has reported that the properties of honey offer a potentially simple and cheap means of preserving skin grafts in developing countries, with 100% uptake of reconstituted grafts stored for up to 6 weeks and 80% uptake of those stored for 7 to 12 weeks. In comparison with sulfadiazine silver, occlusive honey dressings were also found to be more effective for the treatment of superficial partial thickness thermal burns.[9]

However, concern has been expressed since honey may contain not only chemical contaminants but clostridial spores (see also above), and it has been suggested[2] that to be medically acceptable, honey must be sterile, residue-free, and of measured antibacterial activity.

Sugar has been used similarly to honey in treating wounds (see p.1970).

1. Greenwood D. Honey for superficial wounds and ulcers. *Lancet* 1993; **341:** 90–1.
2. Postmes T, *et al.* Honey for wounds, ulcers, and skin graft preservation. *Lancet* 1993; **341:** 756–7.
3. Molan PC. Re-introducing honey in the management of wounds and ulcers - theory and practice. *Ostomy Wound Manage* 2002; **48:** 28–40.
4. Booth S. Are honey and sugar paste alternatives to topical antiseptics? *J Wound Care* 2004; **13:** 31–3.
5. Natarajan S, *et al.* Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. *J Dermatol Treat* 2001; **12:** 33–6.
6. Jull A, *et al.* Honey as Adjuvant Leg Ulcer Therapy trial collaborators. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008; **95:** 175–82.
7. Biswal BM, *et al.* Topical application of honey in the management of radiation mucositis: a preliminary study. *Support Care Cancer* 2003; **11:** 242–8.
8. Subrahmanyam M. Storage of skin grafts in honey. *Lancet* 1993; **341:** 63–4.
9. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns* 1998; **24:** 157–61.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Antibacterial Honey Barrier; ***Ital.:*** Oramil; ***Neth.:*** Melrosum; ***UK:*** Medihoney Antibacterial Wound Gel; Mesitran.

Multi-ingredient: *Arg.:* Expectosan Hierbas y Miel; ***Austral.:*** Logicin Natural Lozenges†; ***Braz.:*** Calmatoss†; Elixir de Inhame†; Expectomel; Melagriao; Melxi†; Peitoral Martel†; ***Canad.:*** Mielocol; ***Chile:*** Fray Romano; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil; Mielax; Mielito; Paltomiel; Paltomiel Plus; Pulmosina; ***Fr.:*** Feromiel; Taido; ***Indon.:*** Pectum; Sirec; ***Irl.:*** Venos Honey & Lemon; ***Ital.:*** Alvear con Ginseng; Apiserum con Telergon 1; Bebimix; Bioton; Fon Wan Eleuthero†; Fon Wan Ginsenergy; Liozim; Nepiros; Nerex; Nutrigel†; Pollingel Ginseng†; ***Mex.:*** Guayalin-Plus†; ***NZ:*** Lemsip Dry Cough†; Robitussin Honey Cough; ***Pol.:*** Babicum; ***Rus.:*** Bronchicum Husten (Бронхикум Сироп от Кашля); ***S.Afr.:*** Choats Extract of Lettuce Cough Mixture; Enzian Anaemodoron Drops; ***Switz.:*** Neo-Angin au miel et citron; ***UK:*** Adult Meltus for Chesty Coughs & Catarrh; Beehive Balsam; Buttercup Syrup (Honey and Lemon flavour); Herb and Honey Cough Elixir; Honey & Molasses; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets; Lockets Medicated Linctus; M & M; Meltus Expectorant; Meltus Honey & Lemon; Potters Children's Cough Pastilles; Potters Gees Linctus; Regina Royal Five; Sanderson's Throat Specific; Throaties Pastilles; Venos Honey & Lemon; Zubes Honey & Lemon; ***Venez.:*** Jengimiel; Jengimiel Sabila; Perebron con Miel†.

Invert Sugar

Azúcar invertido.

CAS — 8013-17-0.

ATC — C05BB03.

ATC Vet — QC05BB03.

Pharmacopoeias. *Br.* and *US* include preparations of invert sugar.

Profile

Invert sugar is an equimolecular mixture of glucose and fructose which may be prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar has similar actions and uses to those of glucose (p.1945) and fructose (p.1945). It has been used as a 10% solution as an alternative to glucose in parenteral nutrition but, as with fructose, such use cannot be recommended.

A syrup of invert sugar is used as a stabilising agent; when mixed with suitable proportions of sucrose-based syrup it will help to prevent crystallisation of the sucrose.

Preparations

BP 2008: Invert Syrup;
USP 31: Invert Sugar Injection; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes and Invert Sugar Injection Type 3.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Emex; ***USA:*** Travert.

Iron

Eisen; Fer; Ferro; Ferrum; Hierro; Ijzer; Järn; Rauta; Żelazo; Železo.

Fe = 55.845.

CAS — 7439-89-6.

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Iron for Homoeopathic Preparations; Ferrum ad Praeparationes Homoeopathicae). A fine, blackish-grey powder, without metallic lustre, obtained by reduction or sublimation. Practically insoluble in water and in alcohol; it dissolves with heating in dilute mineral acids.

Adverse Effects

The astringent action of **oral** iron preparations sometimes produces gastrointestinal irritation and abdominal pain with nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation. Other gastrointestinal effects may include either diarrhoea or constipation. Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach) or by beginning therapy with a small dose and increasing gradually. Modified-release products are claimed to produce fewer adverse effects but this may only reflect the lower availability of iron from these preparations. Oral liquid preparations containing iron salts may blacken the teeth and should be drunk through a straw. The faeces of patients taking iron salts may be coloured black.

The adverse effects associated with iron given **parenterally** are described under iron dextran (see p.1951).

Since absorbed iron is conserved by the body, **iron overload**, with increased storage of iron in various tissues (haemosiderosis), may occur as a result of excessive or mistaken therapy, especially parenteral therapy. Patients with pre-existing iron storage or absorption diseases are also at risk.

Acute iron **overdosage** can be divided into four stages.

- In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- The second phase, which is not always seen, may occur at 6 to 24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation.
- In the third phase, 12 to 48 hours after ingestion, gastrointestinal toxicity recurs together with shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.
- The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that in a young child the equivalent of about 60 mg/kg of iron should be regarded as extremely dangerous. Estimates of acute lethal dosages have ranged from the equivalent of 150 mg/kg of iron upwards. Serum-iron concentrations have also been used as an indication of the severity of overdosage: a peak concentration of 5 micrograms/mL or more is reportedly associated with severe poisoning in many patients.

Effects on the cardiovascular system. For a suggestion that iron overload may contribute to ischaemic heart disease, see Effects in Non-deficient Subjects, below.

Effects on growth. Iron supplementation in iron-replete children has been reported to adversely affect their growth—see Effects in Non-deficient Subjects, below.

Iron overload. Because the body lacks a mechanism for the excretion of excess iron, abnormally high absorption or repeated blood transfusion will result in iron overload (p.1442), leading eventually to haemochromatosis. The consequences of haemochromatosis include pigment deposition in skin and other organs, mild liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, sometimes diabetes and hypothyroidism), and heart disease (pericarditis, heart failure, and arrhythmias). If unchecked, the iron build-up can lead to death, mainly through heart failure or arrhythmia. Where iron overload is due to increased absorption, phlebotomy is the treatment of choice; however, if phlebotomy is not tolerated or in patients who are transfusion-dependent (as in β-thalassaemia—see p.1045) treatment with iron chelators such as desferrioxamine is used to retard accumulation.

Treatment of Adverse Effects

In treating acute iron poisoning, speed is essential to reduce absorption of iron from the gastrointestinal tract. Activated charcoal is ineffective, but gastric lavage should be considered in those who have ingested the equivalent of more than 60 mg/kg of elemental iron within 1 hour of presentation. Serum-iron concentrations may be an aid to estimating the severity of poisoning. Although these do not correlate well with symptoms, the UK Poisons Information Service considers that concentrations taken about 4 hours after ingestion generally indicate the severity of poisoning as follows:

- less than 3 micrograms/mL, mild poisoning
- 3 to 5 micrograms/mL, moderate poisoning
- 5 micrograms/mL or more, severe poisoning

In patients with moderate poisoning, or severe asymptomatic poisoning, the measurement should be repeated after a further 2 hours, and chelation therapy with desferrioxamine (p.1441) should be considered if the concentration is rising. In patients with severe symptomatic poisoning, chelation therapy should be considered straight away.

Other measures include the symptomatic management and therapy of metabolic and cardiovascular disorders.

◊ General references.

1. Proudfoot AT, *et al.* Management of acute iron poisoning. *Med Toxicol* 1986; **i:** 83–100.
2. Mann KV, *et al.* Management of acute iron overdose. *Clin Pharm* 1989; **8:** 428–40.
3. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am* 1994; **12:** 397–413.
4. Fine JS. Iron poisoning. *Curr Probl Pediatr* 2000; **30:** 71–90.

Overdosage. References highlighting the specific problem of iron overdose in children.[1-4] Child-resistant packaging and warning labels may be helpful in reducing the problem.

1. Anonymous. Iron-containing drugs and supplements: accidental poisoning. *WHO Drug Inf* 1995; **9:** 159–60.
2. Fitzpatrick R, Murray V. Iron toxicity: dietary supplements. *Pharm J* 1996; **256:** 666.
3. Committee on Safety of Medicines/Medicines Control Agency. Oral iron supplements: accidental overdose may be fatal in children. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 08/11/05)
4. Singhi SC, *et al.* Acute iron poisoning: clinical picture, intensive care needs and outcome. *Indian Pediatr* 2003; **40:** 1177–82.

Overdosage in pregnancy. Limited data on the treatment of iron overdose in pregnancy from the UK National Teratology Information Service, suggested that treatment with desferrioxamine should not be withheld if clinically indicated.[1-3] Most pregnancies had a normal outcome. A literature review[4] of iron overdose in pregnant women found that women with peak serum-iron concentrations greater than or equal to 4 micrograms/mL were more frequently symptomatic, but that there was no relationship between peak iron level and frequency of spontaneous abortion, preterm delivery, congenital anomalies, or perinatal or maternal death. However, women with stage 3 iron toxicity, defined as those manifesting with hepatic, renal, or cardiac failure, were more likely to spontaneously abort, deliver preterm, or die.

1. McElhatton PR, *et al.* The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 1991; **10:** 251–9.
2. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; **12:** 579.
3. McElhatton PR, *et al.* The outcome of pregnancy following iron overdose by the mother. *Br J Clin Pharmacol* 1998; **45:** 212P–213P.
4. Tran T, *et al.* Intentional iron overdose in pregnancy—management and outcome. *J Emerg Med* 2000; **18:** 225–8.

Precautions

Iron compounds should not be given to patients receiving repeated blood transfusions or to patients with anaemias not produced by iron deficiency unless iron deficiency is also present. Oral and parenteral iron therapy should not be used together. Care should be taken in patients with iron-storage or iron-absorption diseases such as haemochromatosis, haemoglobinopathies, or existing gastrointestinal diseases such as inflammatory bowel disease, intestinal strictures and diverticulae.

Liquid preparations containing iron salts should be well diluted with water and swallowed through a straw to prevent discoloration of the teeth.

Effects in non-deficient subjects. There has been concern about the potential consequences of iron supplementation in individuals and groups who are not actually iron-deficient. Apart from the suggestion that certain populations may be at somewhat increased risk of microbial *infection* after supplementation (see Infections, below), there is some evidence that supplementation in children without iron deficiency may *retard their growth*.[1,2] It has also been proposed that iron may be associated with *ischaemic heart disease*, by modifying low-density lipoprotein in ways which increase its atherogenic potential and by sensitising the myocardium to ischaemic injury.[3,4] However, conclusions of a cohort study[5] and a systematic review[6] did not support any correlation between iron status and coronary heart disease. There is some suggestion that an excess of iron may be *carcinogenic*;[7,8] conclusive studies are lacking.

1. Idjradinata P, *et al.* Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994; **343:** 1252–4.
2. Dewey KG, *et al.* Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. *J Nutr* 2002; **132:** 3249–55.
3. Burt MJ, *et al.* Iron and coronary heart disease: iron's role is undecided. *BMJ* 1993; **307:** 575–6.
4. Sullivan JL. Iron and coronary heart disease: iron makes myocardium vulnerable to ischaemia. *BMJ* 1993; **307:** 1066–7.
5. Sempos CT, *et al.* Serum ferritin and death from all causes and cardiovascular disease: the NHANES II Mortality Study. *Ann Epidemiol* 2000; **10:** 441–8.

6. Danesh J, Appleby P. Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation* 1999; **99:** 852–4.
7. Deugnier Y. Iron and liver cancer. *Alcohol* 2003; **30:** 145–50.
8. Huang X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res* 2003; **533:** 153–71.

INFECTIONS. Iron is not only an essential element for humans but is also essential for many micro-organisms. Thus, it has been suggested that persons with either adequate iron stores or iron overload may provide optimum conditions for microbial growth and therefore be susceptible to an increased incidence and severity of infection; conversely, iron-deficiency anaemia may offer some protection against infections. The topic has been reviewed[1,2] and although there is no evidence that small amounts of iron supplements or iron-fortified food in normal people will render them more prone to infection[3] there is some evidence that in populations with a high prevalence of endemic infectious disease such as malaria, iron therapy may be followed by a higher incidence of infectious complications or by a flare-up of existing low-grade disease. Therefore, the routine use of iron supplements in such communities has been questioned,[4,5] although an increasing number of studies failed to demonstrate a detrimental effect.[6-10] A subsequent systematic review[11] concluded that, while iron supplementation slightly increases the risk of developing diarrhoea, it has no apparent harmful effect on the overall incidence of infectious illnesses in children. More recently, a controlled study found that supplementation with iron and folic acid increased the risk of severe illness and death in pre-school children in a population with high rates of malaria. The authors concluded that, while iron-deficient children can benefit from supplementation in the presence of active prophylaxis and treatment of malaria, supplementation in non-deficient subjects might be harmful.[12] Data conflict on the association between parenteral iron and infection in dialysis patients; some consider that treatment with parenteral iron should be avoided during active infection.[13,14]

1. Hershko C, *et al.* Iron and infection. *BMJ* 1988; **296:** 660–4.
2. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001; **131** (suppl): 616S–633S.
3. Bullen JJ, Ward CG. Iron and infection. *BMJ* 1988; **296:** 1539.
4. Oppenheimer SJ, *et al.* Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1986; **80:** 603–12.
5. Smith AW, *et al.* The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Ann Trop Paediatr* 1989; **9:** 17–23.
6. Harvey PWJ, *et al.* The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *Am J Trop Med Hyg* 1989; **40:** 12–18.
7. Boele van Hensbroek M, *et al.* Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; **89:** 672–6.
8. van den Hombergh J, *et al.* Does iron therapy benefit children with severe malaria-associated anaemia? A clinical trial with 12 weeks supplementation of oral iron in young children from the Turiani Division, Tanzania. *J Trop Pediatr* 1996; **42:** 220–7.
9. Menendez C, *et al.* Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; **350:** 844–50.
10. Mebrahtu T, *et al.* Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children. *J Nutr* 2004; **134:** 3037–41.
11. Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002; **325:** 1142.
12. Sazawal S, *et al.* Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006; **367:** 133–43.
13. Brewster UC, Perazella MA. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial* 2004; **17:** 57–60.
14. Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. *Ann Pharmacother* 2007; **41:** 1476–80.

Interference with diagnostic tests. Although studies *in vitro* found that iron (ferrous sulfate) caused a false-positive result in the Hemoccult test for blood in faeces, this did not occur *in vivo* in persons receiving oral iron therapy.[1-3] An explanation for the difference in these findings was that hydrogen peroxide in the Hemoccult developer converted ferrous ions in solution to ferric ions, which caused oxidation in the test, whereas *in vivo* the iron was probably eliminated in the faeces in the form of non-reactive insoluble iron precipitates.[2]

1. Kulbaski MJ, *et al.* Oral iron and the Hemoccult test: a controversy on the teaching wards. *N Engl J Med* 1989; **320:** 1500.
2. McDonnell M, Elta G. More on oral iron and the Hemoccult test. *N Engl J Med* 1989; **321:** 1684.
3. Anderson GD, *et al.* An investigation into the effects of oral iron supplementation on in vivo Hemoccult stool testing. *Am J Gastroenterol* 1990; **85:** 558–61.

Porphyria. Erythropoietic protoporphyria was exacerbated by oral iron therapy in 4 patients;[1] a further patient had a variable reaction to iron, being able to tolerate it on some occasions but suffering from exacerbation of porphyria on others.[2] Intravenous iron precipitated porphyria cutanea tarda in one patient on haemodialysis.[3]

1. Milligan A, *et al.* Erythropoietic protoporphyria exacerbated by oral iron therapy. *Br J Dermatol* 1988; **119:** 63–6.
2. McClements BM, *et al.* Erythropoietic protoporphyria and iron therapy. *Br J Dermatol* 1990; **122:** 423–6.
3. McKane W, *et al.* Porphyria cutanea tarda precipitated by intravenous iron in a haemodialysis patient. *Nephrol Dial Transplant* 2001; **16:** 1936–8.

Interactions

Iron salts are not well absorbed by mouth, and food may further impair their absorption.

Compounds containing calcium and magnesium, including antacids and mineral supplements, and bicarbonates, carbonates, oxalates, or phosphates, may impair the absorption of iron by the formation of insoluble complexes. Zinc salts may also decrease the absorption of iron. The absorption of both iron salts and tetracyclines is diminished when taken together orally. If treatment with both drugs is required, a time interval of about 2 to 3 hours should be allowed between them. A suitable interval is also advised if an iron supplement is needed in patients given trientine. Iron is chelated by acetohydroxamic acid, reducing the absorption of both. Iron should not be given with dimercaprol as toxic complexes may form.

The response to iron may be delayed in patients receiving systemic chloramphenicol.

Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron.

In addition to those already mentioned, iron salts can also decrease the absorption of other drugs and thus reduce their bioavailability and clinical effect. Drugs so affected include cefdinir, bisphosphonates, entacapone, fluoroquinolones, levodopa, methyldopa, mycophenolate mofetil, and penicillamine. Iron salts may reduce the efficacy of levothyroxine (p.2173).

Interactions with parenteral iron are mentioned under Iron Dextran, p.1952.

◊ Reviews.

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; **31:** 251–5.

Pharmacokinetics

Iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and by some dietary acids (such as ascorbic acid) and occurs more readily when the iron is in the ferrous state or is part of the haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if the body stores are overloaded. Normally only about 5 to 15% of the iron ingested in food is absorbed.

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin; the remainder is contained within the storage forms, ferritin (p.1938) or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin.

Only very small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is re-used. This conservation of body iron, and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive iron therapy or repeated transfusions.

◊ General references.

1. Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet* 1989; **17:** 69–89.

Human Requirements

The body contains about 4 g of iron most of which is present as haemoglobin.

Apart from haemorrhage, iron is mainly lost from the body in the faeces, urine, from skin, and sweat, but the total loss is very small. Iron is also lost in small amounts in breast milk and in menstrual blood. In healthy men and postmenopausal women the loss is replaced by the absorption of about 1 mg of iron daily; about 1.5 to 2 mg needs to be absorbed daily by premenopausal women. In childhood and adolescence, the need is proportionately greater because of growth. Iron absorption is variable but is usually between 5 and 15% and therefore a dietary allowance containing the equivalent of about 10 mg of iron daily is usually sufficient for men and postmenopausal women; up to 15 mg daily may be necessary for premenopausal women with normal menstrual blood losses; some authorities recommend higher amounts or supplements during pregnancy. For further details concerning dietary requirements, see below and for a discussion of prophylactic iron given during pregnancy, see Iron-deficiency Anaemia, under Uses and Administration, below.

Good dietary sources of haem-iron are animal products such as meat and fish; non-haem-iron is also found in animal products and in vegetable products such as legumes and some leafy vegetables, but some vegetable products with a high iron content also contain phosphates or phytates which inhibit absorption by the formation of unabsorbable complexes.

UK and US recommended dietary intake. In the UK, dietary reference values (DRV)[1] and in the USA, recommended dietary allowances (RDA)[2] have been published for iron.

In the UK the estimated average requirement (EAR) for adult males and postmenopausal females is 6.7 mg daily and the reference nutrient intake (RNI) is 8.7 mg daily; for premenopausal females, but without heavy menstrual blood losses, the EAR and RNI are 11.4 and 14.8 mg daily respectively. Amounts for infants, children, and adolescents, which are proportionately higher than those for adults, are also given. No increase is considered necessary during pregnancy or lactation.[1]

In the USA the RDA for adult males and postmenopausal females is 8 mg daily and that for premenopausal women is 18 mg. The tolerable upper intake level is 45 mg daily. Amounts for infants, children, and adolescents, again proportionately higher than for adults, are also provided. The RDA for pregnant women is 27 mg daily. An RDA of 9 mg for lactating adult women has been estimated from the EAR of non-menstruating women plus the average iron content of human milk.[2]

The Food and Agriculture Organization of the United Nations and the WHO have together published guidelines concerning iron requirements and these take into account many factors including bioavailability of iron in the diet.[3]

For the definitions of DRV, EAR, RNI, and RDA, see under Vitamins, p.1925.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. FAO/WHO. *Requirements of vitamin A, iron, folate and vitamin B : report of a joint FAO/WHO expert consultation*. Rome: Food and Agriculture Organization of the United Nations, 1988.

Uses and Administration

Iron is an essential constituent of the body, being necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron deficiency results in defective erythropoiesis and anaemia. Iron and iron salts should only be given for the treatment or prophylaxis of iron-deficiency anaemias (see below). They should not be given for the treatment of other types of anaemia except where iron deficiency is also present. Iron-deficiency anaemias respond readily to iron therapy but the underlying cause of the anaemia should be determined and treated.

The preferred route for giving iron is oral, usually as soluble ferrous salts which are better absorbed than ferric salts. The usual adult dose for the treatment of iron-deficiency anaemia is 100 to 200 mg of iron daily in divided doses. The usual adult prophylactic dose is about 60 to 120 mg of iron daily. There are various recommendations for children's doses and up to 2 mg/kg of iron three times daily for treatment, and 1 to 2 mg/kg daily for prophylaxis of iron-deficiency anaemia (usually to a maximum of 30 mg) has been used. Therapy is generally continued until haemoglobin concentrations reach normal values, which may take some weeks, and then for a further 3 months or more to restore body-iron stores.

Further information concerning the dosage of iron salts and compounds used is provided in the individual monographs; this information, however, tends to reflect the amounts of iron contained in different salts or available commercial preparations and therefore, in some instances, may not be within the general range of iron dosages as quoted above.

The iron content of various iron salts is tabulated in Table 1, below.

Modified-release dosage forms of iron are claimed to result in reduced gastrointestinal adverse effects and have the advantage of once-daily dosage. The preparations are designed to release the iron gradually along the gut but in some instances the iron may not be released until the preparation reaches a part of the gut where absorption is poor thus resulting in sub-optimal dosing.

Iron can also be given parenterally in circumstances where oral therapy cannot be undertaken and such use is typified by iron dextran (see p.1951).

Administration in the elderly. Patients over 80 years of age with iron-deficiency anaemia (below) were randomised to elemental iron therapy in daily doses of 15 mg, 50 mg (as liquid ferrous gluconate), or 150 mg (as tablets of calcium ferrous citrate) and treated for 2 months.[1] Serum haemoglobin and ferritin concentrations increased significantly in all patients, without significant differences between the 3 doses. The authors concluded that, while these results may not apply to patients with iron deficiency due to malabsorption, chronic disease, or untreated *Helicobacter pylori* infection, low-dose therapy is an effective option for elderly patients with iron-deficiency anaemia, in whom the adverse effects of iron could cause considerable morbidity and impaired compliance. Younger patients could also probably be treated effectively with low-dose iron therapy.

1. Rimon E, *et al.* Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; **118:** 1142–7.

Anoxic seizures. Reductions in the frequency of breath-holding episodes in children treated with iron,[1] and especially in those with iron-deficiency anaemia,[2,3] suggest that there might be a relationship between anoxic seizures (p.1221) and iron deficiency.[4]

1. Daoud AS, *et al.* Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997; **130:** 547–50.
2. Mocan H, *et al.* Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; **81:** 261–2.
3. Pedersen KW, Knudsen FU. Skal børn med affektkramper behandles med jern? *Ugeskr Laeger* 2004; **166:** 2789–91.
4. Hannon DW. Breath-holding spells: waiting to inhale, waiting for systole, or waiting for iron therapy? *J Pediatr* 1997; **130:** 510–12.

Cough. In a small study[1] of 19 patients, iron supplementation with ferrous sulfate successfully reduced the cough associated with ACE inhibitors (see p.1194). The authors hypothesised that this effect was due to the inhibition by iron of nitric oxide synthase. However, there are some concerns[2] about the effect of giving a nitric oxide synthase inhibitor to hypertensive patients, as it has been found to increase blood pressure in *animal* studies.

1. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
2. Lev I, Rian AJJT. Iron supplementation in ACE inhibition as a treatment for cough: is it really inoffensive? *Hypertension* 2001; **38:** e38.

Iron-deficiency anaemia. The iron content of the body is normally kept constant by regulation of the amount absorbed to balance the amount lost. If loss is increased, and/or intake inadequate, a negative iron-balance may lead by degrees to depletion of body iron stores, iron deficiency, and eventually to anaemia. Iron requirements are increased during infancy, puberty, pregnancy, and during menstruation, and iron-deficiency anaemias are most common in women and children; the most common cause in adult males and postmenopausal women is blood loss, usually from the gastrointestinal tract.

Iron deficiency usually results in a microcytic, hypochromic anaemia, but the diagnosis of iron deficiency should be confirmed, if there is any doubt, by measurement of serum ferritin, erythrocyte protoporphyrin, or total iron binding capacity (transferrin). Iron therapy can begin once deficiency is confirmed, but the underlying cause of the deficiency should still be sought and treated.

Treatment. The prevention and control of iron-deficiency anaemias has been reviewed.[1-4] Almost all iron-deficiency anaemias respond readily to treatment with iron. The treatment of choice is an oral ferrous salt (ferrous iron is better absorbed than ferric iron).[1] Many iron compounds have been used for this purpose, but do not offer any real advantage over the simple ferrous fumarate, gluconate, or sulfate salts. The usual adult dose is sufficient of these salts to supply about 100 to 200 mg of elemental iron daily (for the elemental iron content of various iron salts, see above), with the aim of increasing haemoglobin concentrations by about 1 g/litre daily or about 20 g/litre every 3 weeks.[1] Haemoglobin response is greatest in the first few weeks of therapy and is proportional to the severity of the original anaemia. Once haemoglobin concentrations have risen to the normal range, iron therapy should be continued for a further 3 months to aid replenishment of iron stores.[1,3] For the view that low-dose iron therapy may be as effective as higher doses, see Administration in the Elderly, above.

Oral iron has been given with agents such as ascorbic acid to enhance iron absorption, and modified-release preparations have been used in patients intolerant of ordinary formulations of iron but the *BNF* considers them to have no therapeutic advantage.

Failure to respond to oral iron after about 3 weeks of therapy may be indicative of non-compliance, continued blood loss with inadequate replacement of iron, malabsorption, wrong diagnosis, or other complicating factors, and the treatment should be reassessed.

Parenteral iron therapy is rarely indicated, may produce severe adverse effects, and should be reserved for patients who are genuinely intolerant of oral iron, persistently non-compliant,[3] who have gastrointestinal disorders exacerbated by oral iron therapy, continuing blood loss too severe for oral treatment to provide sufficient iron, or for those unable to absorb iron adequately from the gastrointestinal tract. Patients with chronic renal failure on haemodialysis (and some on peritoneal dialysis) require regular iron. US guidelines[5] suggest that intravenous use is preferred in haemodialysis patients, but that iron may be given either intravenously or orally in predialysis and peritoneal dialysis patients. The most common parenteral forms are iron dextran, iron sorbitol, iron sucrose, and sodium ferric gluconate complex.

Exceptionally, in patients with profound anaemia, blood transfusion may be necessary to restore dangerously low concentrations of haemoglobin. This may be the case, for example, in cases of worsening angina or severe coexisting pulmonary disease.[1] However, transfusion should always be avoided if possible.

Prophylaxis. Prophylaxis may be desirable in some groups at risk of iron deficiency and consequent anaemia, and may include therapy with oral iron supplements, measures to improve dietary iron intake, fortification of food staples, or control of infection. For the possible problems associated with iron supplementation in those who are not deficient, see Effects in Non-deficient Subjects, under Precautions, above.

WHO[2] recommends that universal supplementation of iron and folic acid should be implemented for pregnant women, starting as soon as possible after gestation starts and continuing for the rest of the pregnancy. WHO also recommends that where anaemia prevalence is above 40%, women of child-bearing age and lactating women should be given 3 months of iron and folic acid supplementation. However, the US Preventive Services Task Force has reviewed the subject of iron supplementation during pregnancy,[6] and concluded that there was insufficient evidence for or against routine supplementation.[7]

Iron supplementation is accepted in menorrhagia, after gastrectomy, and in the management of low birth-weight infants such as the premature. Iron deficiency in infants and children may result in developmental delay or impairment of cognitive function.[2] Breast feeding should be encouraged during the first year of life.[1] WHO has suggested[2] that low birth-weight infants be given universal supplementation. Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%, iron supplementation should be given to all children between 6 and 23 months of age; for children aged 24 months and above, a 3-month course of iron supplementation should be given where the anaemia prevalence is above 40%.

The usual prophylactic dose in adults suggested by WHO is about 60 mg of elemental iron daily. Doses of about 2 mg/kg of elemental iron daily (up to 30 mg) have been suggested for prophylaxis in children (see also Uses and Administration, above).

Dietary measures, such as addition of vitamin-C-rich foods, or other enhancers of iron absorption including iron in the form of haem (found in meat or fish) to the diet, control of parasitic infections such as hookworm (which are responsible for considerable occult blood loss), and malaria prophylaxis are particularly important for the general community in developing countries. Fortification of food staples poses technical problems as iron salts react with food components and may produce rancidity or other undesirable changes on storage. Nonetheless, wheat or maize flour, rice, and milk products have been fortified in some countries, and consideration has also been given to fortification of salt or sugar.

1. Provan D. Iron deficiency anaemia. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Books, 2003: 1–4.
2. World Health Organization. *Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers.* Geneva: WHO, 2001. Available at: http://www.who.int/entity/nutrition/publications/en/ida_assessment_prevention_control.pdf (accessed 11/07/06)
3. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia (issued May 2005). Available at: http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf (accessed 09/11/05)
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; **370:** 511–20.
5. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006; **47** (suppl 3): S16–S85. Correction. *ibid.*; **48:** 518. Also available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm (accessed 04/12/06)
6. US Preventive Services Task Force. Routine iron supplementation during pregnancy: review article. *JAMA* 1993; **270:** 2848–54.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy: policy statement. *JAMA* 1993; **270:** 2846–8.

Restless legs syndrome. Iron deficiency is present in about a quarter of people with restless legs syndrome (see Sleep-associated Movement Disorders, p.958), particularly older people, and serum ferritin concentrations are inversely correlated with the severity of symptoms. Iron may have a role in the pathophysiology of the disorder, and treatment of iron deficiency may reduce symptoms.[1]

1. Medcalf P, Bhatia KP. Restless legs syndrome. *BMJ* 2006; **333:** 457–8.

Table 1. Approximate amounts of different iron salts that supply 60 mg of elemental iron.

Iron salt	Amount
Ferrous ascorbate (anhydrous)	437 mg
Ferrous aspartate (tetrahydrate)	422 mg
Ferrous chloride (tetrahydrate)	214 mg
Ferrous fumarate (anhydrous)	183 mg
Ferrous gluconate (dihydrate)	518 mg
Ferrous succinate (anhydrous)	185 mg
Ferrous sulfate (dried)	186 mg
Ferrous sulfate (heptahydrate)	300 mg

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Celloids IP 82; ***Austria:*** Liquifer†; ***Braz.:*** Ferrini; ***Indon.:*** Ferromia; ***Ital.:*** Liquifer†; Profer; ***Jpn:*** Ferromia; ***Malaysia:*** Ferrocyte; ***Mex.:*** Unifer; ***Singapore:*** Ferrocyte; ***Thai.:*** Ferrocyte; ***USA:*** EZFE; Icar; Ircon.

Multi-ingredient: ***Arg.:*** Hierroquick; ***Austral.:*** Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Clements Iron; Duo Celloids CPIP; Duo Celloids PCIP; Duo Celloids PPIP; Duo Celloids SPIP; Iron Compound†; ***Austria:*** China-Eisenwein; ***Braz.:*** Ferrini Folico; Ferrumvit†; Folifer; Hemofer†; Olohepat†; Sadol; Sangotone†; Vi-Ferrin; ***Cz.:*** Homeovox; ***Ger.:*** Biovital Classic; Ferrodix†; Folicombin; ***Hung.:*** Biovital†; ***India:*** Cafe-Kit†; Carboflot†; Cofol Z; Fexid-Z; Imax; Probofex; Tonoferon; ***Indon.:*** Ferlin; Ferofort; Incremin with Iron; ***Ital.:*** Carfosid; Evafer; ***Mex.:*** Ferricol; Forta; Intrafer; Intrafer F-800; Intrafer TF; Uniferol; ***NZ:*** Incremin with Iron; ***Philipp.:*** Incremin; Odiron; Odiron-C; ***Singapore:*** Memoloba†; ***Switz.:*** Elixir tonique N; ***Thai.:*** Hemo-Cyto-Serum; ***Turk.:*** Blood Builder; ***UK:*** Hematinic; ***USA:*** Centurion A–Z†; Feocyte; FeoGen; Geritol Complete; I-L-X; Icar-C Plus; Ircon-FA†; Renatabs with Iron; Tandem F; Theravee Hematinic; Ultra-Natal.

Iron Dextran

Demir Dekstran; Hierro dextrano; Iron-Dextran Complex.
CAS — 9004-66-4.
ATC Vet — QB03AB90; QB03AC90.

Pharmacopoeias. *Br., Chin.,* and *US* include injections.
BP 2008 (Iron Dextran Injection). A sterile colloidal solution containing a complex of ferric hydroxide and dextrans of weight average molecular weight between 5000 and 7000. It contains 4.75 to 5.25% of iron and 17.0 to 23.0% of dextrans. pH 5.2 to 6.5.
USP 31 (Iron Dextran Injection). A sterile colloidal solution of ferric hydroxide in complex with partially hydrolysed dextran of low molecular weight. It may contain not more than 0.5% of phenol as a preservative. pH 5.2 to 6.5.

Adverse Effects and Treatment

Severe anaphylactoid reactions may occur with iron dextran and fatalities have been reported. It is therefore recommended that it be given where there are facilities for the emergency treatment of such reactions, that certain precautions be observed, and that test doses be used (see Precautions, below).

Rapid intravenous use may be associated with vascular flushing and hypotension. Thrombophlebitis may occur at the site of injection, although the incidence can be reduced by giving iron dextran in sodium chloride 0.9% rather than glucose 5%. Intramuscular injection is associated with local reactions, pain, and staining at the site of injection; leakage along the injection track may occur unless the proper technique is used (see Uses and Administration, below). Cardiovascular effects such as chest pain or tightness, shock, myocardial infarction, hypertension, tachycardia, bradycardia, and arrhythmias may occur with either route. Rashes, urticaria, purpura, and pruritus have been reported. Other reactions include gastrointestinal disturbances, haematuria, dyspnoea, and taste disturbance.

Patients may also experience delayed reactions 1 to 2 days after injection of iron dextran, such as backache, arthralgia, myalgia, lymphadenopathy, chills, fever, paraesthesia, dizziness, malaise, headache, nausea, and vomiting.

Overdose of parenteral iron is unlikely to be associated with any acute manifestations. Unwarranted parenteral iron therapy will result in iron overload and excess storage of iron (haemochromatosis) in the long term. The consequences of this include liver and endocrine dysfunction and heart disease (see Iron Overload, p.1949), and possibly an increased risk of infection (see Infections, under Precautions for Iron, p.1950). Iron overload may require chelation therapy with desferrioxamine (p.1441).

Intramuscular injection of iron complexes such as iron dextran has resulted in sarcomas at the injection site in *animals*. There is some evidence that this may occur in humans.

Effects on the blood. A 1-year-old girl with Down's syndrome and iron-deficiency anaemia was given three intramuscular injections of iron dextran over 6 days (to a total of 30 mg/kg). Pancytopenia developed subsequently, which reappeared when challenged with iron dextran. Tests indicated an allergic pathogenesis for the pancytopenia.[1] For further discussion of hypersensitivity reactions to iron dextran, see under Hypersensitivity, below.

Thrombocytopenia has also been reported after iron dextran[2] and iron sucrose[3] therapy.

1. Hurvitz H, *et al.* Pancytopenia caused by iron-dextran. *Arch Dis Child* 1986; **61:** 194–6.
2. Go RS, *et al.* Thrombocytopenia after iron dextran administration in a patient with severe iron deficiency anemia. *Ann Intern Med* 2000; **132:** 925.
3. Taskapan H, *et al.* Transient severe thrombocytopenia in a patient on CAPD after intravenous iron administration. *Perit Dial Int* 2003; **23:** 408–9.

Hypersensitivity. The Boston Collaborative Drug Surveillance Program monitored consecutively 32 812 medical inpatients. Drug-induced anaphylaxis occurred in 1 of 169 patients given iron dextran (route not stated).[1] An investigation of 481 persons given a total of 2099 intravenous injections of iron dextran found 3 life-threatening immediate anaphylactoid reactions; 8 severe delayed reactions were also observed, and many reactions of a less serious nature.[2] In a more recent series,[3] 10 of 573 patients had anaphylactoid reactions after intravenous iron dextran. Other serious reactions included 1 case of cardiac arrest, and 3 cases of dyspnoea, hypertension, or chest pain.

Test doses are recommended before giving a full therapeutic dose (see Uses and Administration, below) and emergency measures for the treatment of allergic reactions should be available. A desensitisation protocol has been used successfully in a patient who reacted to the test dose[4] and in a patient with a previous life-threatening reaction to iron infusion;[5] methylprednisolone 50 mg was given intravenously at 13 hours, 7 hours, and 1 hour before iron dextran, and diphenhydramine 50 mg and ephedrine 25 mg were given intramuscularly 1 hour before infusion. Dextran 1 (p.1058) was given just before the iron dextran infusion. Approximately 2 g of iron was then given over a period of about 4 days.

It is not clear whether hypersensitivity to iron dextran is due to the dextran or the iron component.[6-8] When compared with lower molecular-weight iron dextran, a higher molecular-weight iron dextran was reported to be associated with significantly higher rates of adverse reactions,[7,9,10] including fatalities and anaphylactoid reactions;[9] some have called for the use of high-molecular-weight iron dextran to be abandoned.[11] Reviews[6,8,12] suggest that parenteral dextran-free iron compounds such as iron sucrose or sodium ferric gluconate complex may be safer alternatives to iron dextran. Iron sucrose has been reported to be well tolerated in patients previously intolerant to iron dextran, sodium ferric gluconate complex, or both.[13] However, adverse reactions have still been reported in patients treated with dextran-free preparations,[8,14] and some have challenged the view that they are safer than iron dextran.[15,16]

In a report of a lupus-like disorder associated with use of iron dextran,[17] the illness resolved with appropriate treatment but recurred on rechallenge.

For discussion of pancytopenia believed to have an underlying allergic pathogenesis, see Effects on the Blood, above.

1. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; **i:** 587–8.
2. Hamstra RD, *et al.* Intravenous iron dextran in clinical medicine. *JAMA* 1980; **243:** 1726–31.
3. Fishbane S, *et al.* The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; **28:** 529–34.
4. Monaghan MS, *et al.* Safe administration of iron dextran to a patient who reacted to the test dose. *South Med J* 1994; **87:** 1010–12.
5. Hickman MA, *et al.* Successful administration of iron dextran in a patient who experienced a life threatening reaction to intravenous iron dextran. *Ann Allergy Asthma Immunol* 2000; **84:** 262–3.
6. Fishbane S. Safety in iron management. *Am J Kidney Dis* 2003; **141** (suppl): S18–S26.
7. McCarthy JT, *et al.* Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—a comparison of two products. *Am J Nephrol* 2000; **20:** 455–62.
8. Fishbane S, Kowalski EA. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. *Semin Dial* 2000; **13:** 381–4.
9. Chertow GM, *et al.* On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; **19:** 1571–5.
10. Auerbach M, *et al.* Clinical update: intravenous iron for anaemia. *Lancet* 2007; **369:** 1502–4.
11. Auerbach M, Rodgers GM. Intravenous iron. *N Engl J Med* 2007; **357:** 93–4.
12. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol* 2004; **76:** 74–8.
13. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** c63–c66.
14. Saadeh CE, Srkalovic G. Acute hypersensitivity reaction to ferric gluconate in a premedicated patient. *Ann Pharmacother* 2005; **39:** 2124–7.
15. Eichbaum Q, *et al.* Is iron gluconate really safer than iron dextran? *Blood* 2003; **101:** 3756–7.
16. Auerbach M, Al Talib K. Low-molecular weight iron dextran and iron sucrose have similar comparative safety profiles in chronic kidney disease. *Kidney Int* 2008; **73:** 528–30.
17. Oh VMS. Iron dextran and systemic lupus erythematosus. *BMJ* 1992; **305:** 1000.

Overdosage. A 29-year-old woman was given 32 mL iron dextran (*Imferon*) intravenously. Twenty-four hours later she developed muscle cramps, bilateral frontal headaches, with subsequent neck stiffness, and marked opisthotonia with photophobia.[1] The haemoglobin concentration did not rise after the infusion of iron which indicated there had been no iron deficiency. Thus, abnormally high concentrations of free iron had followed the iron therapy and this free iron was able to cross into the CSF and was responsible for the meningitic symptoms.

1. Shuttleworth D, *et al.* Meningism due to intravenous iron dextran. *Lancet* 1983; **ii:** 453.

Precautions

Iron dextran is contra-indicated in patients with severe liver damage or acute kidney infection. It is also contra-indicated in persons with a history of hypersensitivity to the preparation. Teratogenicity has been demonstrated in non-anaemic *animals* given the equivalent of about three times the maximum human dose and its use should be avoided in pregnancy if possible.

Additionally, iron dextran should be given with caution to patients with a history of allergic disorders or asthma and in these patients the intramuscular, and not the intravenous, route should be used. Patients with rheumatoid arthritis may develop worsening of symptoms when given iron dextran intravenously. Patients with other inflammatory disorders may be at increased risk of delayed reactions. Large doses of iron dextran by infusion may lead to serum discoloration; this should not be mistaken as evidence of haemolysis. Oral iron salts should be stopped before giving parenteral iron.

A test dose should be given before a full therapeutic dose is given (see Uses and Administration, below) and emergency measures for the treatment of allergic reactions should be available (see Anaphylaxis and Anaphylactic Shock, p.1205). Patients should be kept under observation for at least 1 hour after a test dose or after intravenous doses.

Iron dextran formulated with phenol as a preservative is intended to be given by the intramuscular route only.

Interactions

As for Iron, p.1950.

Enalapril. Enalapril may possibly potentiate the adverse systemic reactions seen with intravenous iron therapy.[1]

1. Rolla G, *et al.* Systemic reactions to intravenous iron therapy in patients receiving angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 1994; **93:** 1074–5.

Pharmacokinetics

After intramuscular injection iron dextran is absorbed primarily through the lymphatic system: most is absorbed after 3 days and the remainder over 3 to 4 weeks. A variable portion may become fixed in the muscle for several weeks or months. After intravenous infusion, iron dextran is taken up by the cells of the reticuloendothelial cells, particularly in the liver and spleen. The reticuloendothelial cells gradually separate iron from the iron-dextran complex; the distribution and elimination of iron is described on p.1950.

Uses and Administration

Iron dextran is given by injection, and should be used only in the treatment of proven iron-deficiency anaemia (p.1951) where oral therapy is ineffective or impracticable.

For iron-deficiency anaemia, total dosage is **calculated** according to the haemoglobin concentration and body-weight of the patient; allowance is also made for additional iron to replenish iron stores. Iron dextran injection is usually supplied with a table from which the recommended dose can be obtained for patients of different weights and haemoglobin (Hb) status. There may be variations between countries in the doses obtained from such tables. Doses can also be calculated from various formulae. A typical formula used for a preparation containing the equivalent of 50 mg/mL of iron is:

$$\text{Dose in mL} = \{0.0442 \times \text{body-weight (kg)} \times [\text{desired Hb level (g/100 mL)} - \text{measured Hb level}]\} + (0.26 \times \text{body-weight})$$

In adults, the calculated lean body-weight should normally be used in this formula rather than the actual body-weight. Note that doses obtained from tables or the above formulae are for iron-deficiency anaemia, and are not suitable for iron replacement for simple blood loss.

Before starting therapy, all patients should receive a **test** dose via the intended route, and should be observed for adverse reactions (see Precautions, above).

The total dose requirement may be given as a series of **intramuscular** injections daily or once or twice weekly. It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted. Before the first therapeutic dose, a test dose should be given and the patient observed for at least 1 hour: a dose of 0.2 mL (10 mg) has been suggested for children weighing less than 10 kg, 0.3 mL (15 mg) for those weighing 10 to 20 kg, and 0.5 mL (25 mg) for adults. A suggested daily maximum dosage for children is: less than 5 kg, up to 0.5 mL (25 mg); 5 to 9 kg, up to 1 mL (50 mg). Larger children and adults normally receive 2 mL (100 mg).

Iron dextran is also given **intravenously** either by total-dose infusion (TDI) or as divided injections. A test dose of 25 mg is given before the first therapeutic dose and the patient is observed for at least 1 hour; if no adverse reactions occur within that time, the remainder of the initial dose may be given. For subsequent doses, the first portion of the dose is given more slowly than the remainder of the dose, during which time the patient is observed for adverse reactions; recommendations for the rate at which this is done may vary in different countries.

In total-dose infusion, the total dose calculated according to the haemoglobin concentration (as outlined above) is given by slow intravenous infusion in about 500 mL of sodium chloride 0.9% or glucose 5%; sodium chloride may be preferable because of the reduced incidence of thrombophlebitis. The first 25 mg of iron should be infused over 15 minutes, and if no adverse reaction has occurred during this time the rate of infusion may be increased progressively to 45 to 60 drops/minute; the infusion usually takes 4 to 6 hours.

For divided intravenous use, the total dose is also calculated according to the haemoglobin concentration. In the UK, the usual recommended dosage schedule is 100 to 200 mg of iron given 2 to 3 times weekly until the total dose has been given. It may be given diluted in 10 to 20 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given slowly over 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the dose is given. Alternatively, 100 to 200 mg may be diluted in 100 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given over 15 minutes and if no adverse reactions occur during this time, the remaining portion of the infusion is given at a rate of not more than 100 mL in 30 minutes. In the USA, the injection may be given undiluted at a rate not exceeding 50 mg iron (1 mL) per minute; maximum daily doses are similar to those given for intramuscular injection.

Preparations

BP 2008: Iron Dextran Injection;
USP 31: Iron Dextran Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fexiron; ***Belg.:*** Fercayl; ***Canad.:*** Dexiron; Infufer; ***Denm.:*** Cosmofer; ***Ger.:*** Cosmofer; ***Gr.:*** Cosmofer†; ***Hong Kong:*** Cosmofer†; ***India:*** Imferon; ***Indon.:*** Hibiron; ***Irl.:*** Cosmofer; ***Mex.:*** Driken; Ferrocel; Ferroin†; Hidex; Irondex; ***Norw.:*** Cosmofer; ***Philipp.:*** Cosmofer; ***Port.:*** Cosmofer; ***Spain:*** Imferon†; ***Switz.:*** Ferrum Hausmann; ***Thai.:*** Cosmofer; ***Turk.:*** Cosmofer; ***UK:*** Cosmofer; ***USA:*** DexFerrum; INFeD; ***Venez.:*** Cosmofer.

Iron Polymaltose

Demir III Hidroksit Polimaltoz; Ferromaltose; Ferrum Polyisomaltose; Hierro polimaltosa.

Profile

Iron polymaltose is a complex of ferric hydroxide and isomaltose. It is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in usual doses containing the equivalent of 100 mg of iron daily although up to 300 mg daily has been given in some countries. It is also given parenterally, the total dose being calculated and given by intravenous infusion or, preferably, as a series of intramuscular injections containing the equivalent of up to 200 mg of iron in a single day; injections are usually given only every few days. For further information relating to the parenteral use of iron, see Iron Dextran, p.1951.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferranin; Maltofer; Siderblut; Vitalix; ***Austral.:*** Ferrosig; Ferrum H; ***Austria:*** Ferrum Hausmann; ***Braz.:*** Noripurum; Ultrafer; ***Chile:*** Ferium; Maltofer; ***Cz.:*** Ferrum; Maltofer; ***Fin.:*** Maltofer; ***Fr.:*** Maltofer†; ***Ger.:*** Ferrum Hausmann; ***Gr.:*** Antianem; Dextrifer; Ferrobest; Ferrum Hausmann; Hemafer; Hydrofer-3; Veltifer; ***Hong Kong:*** Ferrum Hausmann; ***Hung.:*** Maltofer; ***India:*** Fericip; Mumfer; Phosfomin Iron; ***Indon.:*** Maltofer; ***Irl.:*** Ferrum; ***Israel:*** Ferripel; ***Ital.:*** Intrafer; ***Malaysia:*** Maltofer; Saferon; ***Mex.:*** Ferranina; ***NZ:*** Ferrosig; Ferrum H; ***Pol.:*** Ferrum Lek; ***Port.:*** Ferrum Hausmann; Maltofer; ***Rus.:*** Ferrum Lek (Феррум Лек); ***S.Afr.:*** Ferrimed; Ferrimed DS; ***Singapore:*** Ferrum Hausmann; ***Switz.:*** Maltofer; ***Turk.:*** Ferrum Hausmann; Maltofer; ***Venez.:*** Intafer; Maltofer.

Multi-ingredient: ***Arg.:*** Ferranin Complex; Hierro Dupofol; Isis Fe; Maltofer Fol†; Siderblut Folic; Tenvic; Vitalix Complex; ***Braz.:*** Noripurum Folico; Noripurum Vitaminado; ***Chile:*** Maltofer Fol; ***Cz.:*** Maltofer Fol; ***Gr.:*** Dextrifer-Fol; Ferrum Fol Hausmann; Hemafer fol; ***Hong Kong:*** Eurofer; ***Hung.:*** Maltofer Fol; ***India:*** Fericip; Hepofer; Mumfer-Z†; Mumfer†; ***Indon.:*** Feritrin; Maltofer Fol; ***Israel:*** Ferrifol; ***Malaysia:*** Maltofer; ***Mex.:*** Ferranina Complex; Ferranina Fol; Ironfol; ***Philipp.:*** Eurofer; ***Port.:*** Ferrum Fol; Maltoferfol; ***S.Afr.:*** Ferrimed; ***Singapore:*** Eurofer; Saferon†; ***Switz.:*** Maltofer Fol; ***Thai.:*** Eurofer; Orofer; ***Turk.:*** Ferrum Fort Hausmann; Maltofer Fol; ***Venez.:*** Intafer; Intaferfol; Maltoferfol.

Iron Sorbitol

Astra-1572; Demir Sorbitol; Hierro sorbitol; Iron Sorbitex *(USAN)*; Iron-Sorbitol-Citric Acid Complex.

CAS — 1338-16-5.
ATC Vet — QB03AC03.

Pharmacopoeias. *US* includes an injection.

USP 31 (Iron Sorbitex Injection). A sterile solution of a complex of iron, sorbitol, and citric acid that is stabilised with the aid of dextrin and an excess of sorbitol. pH 7.2 to 7.9.

Adverse Effects, Treatment, and Precautions

As for Iron Dextran, p.1951.

There may be severe systemic reactions; cardiac complications, such as complete AV block, ventricular tachycardia, and atrial or ventricular fibrillation, may be fatal. The urine of patients treated with iron sorbitol may become dark on standing.

Iron sorbitol should not be given intravenously. It should preferably be avoided in patients with pre-existing cardiac abnormalities.

Effects on the heart. A description of adverse events in 3 patients with the malabsorption syndrome treated with intramuscular injections of iron sorbitol.[1] Two patients died; in one, findings were consistent with anaphylaxis but in the other cardiac toxicity was considered to be due to a direct effect. In the third patient direct cardiac toxicity was also implicated. In another report,[2] a patient developed cardiac arrhythmia after his seventh injection of iron sorbitol. He was found to have a low serum concentration of alpha-tocopherol, supposed by the authors to be caused by the patient's malabsorption syndrome. This had apparently predisposed the patient to arrhythmia by contributing to myocardial cell sensitivity to lipid peroxidation, which is catalysed by ferrous ions. Insufficient alpha-tocopherol to scavenge the free radicals generated by the iron could also have led to loss of myocardial fatty acids, thereby disturbing membrane function. It was suggested that iron sorbitol was a less stable form of iron than iron dextran, and should be given with extreme caution to patients with malabsorption and low levels of alpha-tocopherol.

1. Karhunen P, *et al*. Reaction to iron sorbitol injection in three cases of malabsorption. *BMJ* 1970; **2:** 521–2.
2. Lindvall S, *et al.* Alpha-tocopherol and cardiac toxicity of iron. *Scand J Haematol* 1980; **25:** 331–8.

Interactions

As for Iron Dextran, p.1952.

Pharmacokinetics

About 66% of iron sorbitol is absorbed within 3 hours of intramuscular injection, most of it directly into the blood circulation, and some via the lymphatic system. Almost all is absorbed within about 10 days. Clearance of iron sorbitol from the plasma is rapid, and is mainly via the reticuloendothelial system, as described for Iron Dextran, p.1952.

Uses and Administration

Iron sorbitol should be used only in the treatment of proven iron-deficiency anaemia (p.1951) where oral therapy is ineffective or impracticable.

It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted.

Total dosage is calculated according to body-weight and the haemoglobin concentration of the blood, and tables are usually provided with iron sorbitol injections for this purpose. The recommended single dose is the equivalent of 1.5 mg/kg of iron up to a maximum of 100 mg daily; these doses are then given daily or every other day until the required haemoglobin concentration has been achieved. Iron sorbitol is not recommended in children weighing under 3 kg.

Iron sorbitol should not be given intravenously.

Preparations

USP 31: Iron Sorbitex Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Yectafer; ***Canad.:*** Jectofer†; ***Ger.:*** Jectofer†; ***India:*** Jectocos; ***Irl.:*** Jectofer†; ***Norw.:*** Jectofer†; ***Turk.:*** Jectofer.

Multi-ingredient: ***Arg.:*** Yectafer Complex; ***India:*** Jectocos Plus.

Iron Succinyl-Protein Complex

Demir III Protein Süksinat; Ferro Proteinsuccinilato; Hierro succinil-proteína, complejo de; Iron Proteinsuccinylate; ITF-282; Proteinsuccinilato de hierro.

CAS — 93615-44-2.
ATC — B03AB09.
ATC Vet — QB03AB09.

Profile

Iron succinyl-protein complex is a source of iron (p.1949) used for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.6 g daily (equivalent to up to 80 mg of iron daily).

◊ References.

1. Köpcke W, Sauerland MC. Meta-analysis of efficacy and tolerability data on iron proteinsuccinylate in patients with iron deficiency anemia of different severity. *Arzneimittelforschung* 1995; **45:** 1211–16.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferplex; ***Braz.:*** Fisiofer†; ***Chile:*** Fisiofer; Legofer; ***Cz.:*** Ferplex; ***Gr.:*** Fysiofer; Legofer; ***Ital.:*** Ferlatum; Ferplex; Ferremon†; Folinemic Ferro†; Legofer†; Pernexin; Proteoferrina; Rekord Ferro; ***Mex.:*** Ferxal; ***Pol.:*** Ferplex; ***Port.:*** Fervit; Fetrival; Legofer; ***Rus.:*** Ferlatum (Ферлатум); ***Spain:*** Ferplex; Ferrocur; Lactoferrina; ***Turk.:*** Ferplex.

Multi-ingredient: ***Gr.:*** Fysiofol; ***Ital.:*** Ferrofolin; ***Turk.:*** Ferplex Fol.

Iron Sucrose *(BAN, USAN)*

Demir Sükroz; Eisenzucker; Ferri oxidum saccharatum; Ferric Hydroxide Sucrose; Ferric Oxide, Saccharated; Ferrique (oxyde) sucré; Ferrum Oxydatum Saccharatum; Hierro sacarosa; Iron (III) hydroxide-sucrose complex; Iron Saccharate; Oxyde de Fer Sucré; Saccharated ferric oxide; Saccharated Iron Oxide; XI-921.

CAS — 8047-67-4.
ATC — B03AB02; B03AC02.
ATC Vet — QB03AB02; QB03AC02.

Pharmacopoeias. In *Swiss.*
US includes an injection.

USP 31 (Iron Sucrose Injection). A sterile, colloidal solution of ferric hydroxide in complex with sucrose in water for injection. Sodium hydroxide may be added to adjust the pH. It contains no antimicrobial agent, chelating agent, dextran, gluconate, or other added substances. pH 10.5 to 11.1 at 20°. It is intended for intravenous use only. When given by intravenous infusion, it should be diluted with 0.9% sodium chloride injection to a concentration of 0.5 to 2.0 mg of elemental iron/mL. Do not allow to freeze.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p.1951. Iron sucrose injection is strongly alkaline and must not be given subcutaneously or intramuscularly. UK (but not US) licensed drug information contra-indicates its use in patients with a history of asthma, eczema, anaphylaxis, or other allergic disorders.

Effects on the blood. For a report of thrombocytopenia associated with iron sucrose, see under Iron Dextran, p.1952.

Hypersensitivity. For a discussion of whether iron sucrose may be a safer alternative to iron dextran, see p.1952.

Pharmacokinetics

Iron sucrose is rapidly cleared from the plasma after intravenous injection with a terminal half-life of about 6 hours. A competitive exchange of iron takes place from the iron sucrose complex to the iron-binding protein transferrin. About 5% of a dose is eliminated via the kidneys in the first 4 hours after a dose.

Uses and Administration

Iron sucrose is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given when oral iron therapy is ineffective or impractical, by slow intravenous injection, or intravenous infusion; when used in haemodialysis patients, it may be given into the venous limb of the dialyser. The dose is calculated according to body-weight and iron deficit. In the UK the cumulative dose is given in single doses of 100 mg of iron not more than three times weekly; if rapid delivery is required, the dose may be increased up to 200 mg not more than three times weekly. The dose may be given undiluted at a rate of 20 mg/minute, after a test dose of 20 mg of iron has been given over 1 to 2 minutes. Alternatively, 100 mg is diluted in a maximum of 100 mL of sodium chloride 0.9% and the first 25 mg given as a test dose over 15 minutes; the remaining portion is given at a rate not exceeding 50 mL per 15 minutes.

In the USA, a similar dose is given for haemodialysis patients receiving supplemental erythropoietin therapy, to a total cumulative dose of 1 g. For peritoneal dialysis patients on erythropoietin, two infusions of 300 mg over 1.5 hours are given 14 days apart, followed by an infusion of 400 mg over 2.5 hours 14 days later. The doses are diluted in a maximum of 250 mL of sodium chloride 0.9%. For patients not on dialysis, a total cumulative dose of 1 g is given over a 14-day period, as a 200 mg slow undiluted intravenous injection over 2 to 5 minutes on 5 separate occasions within this time. Iron sucrose has also been given orally.

Anaemia of chronic renal failure. References.

1. Charytan C, *et al.* Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 2001; **37:** 300–7.
2. Stoves J, *et al.* A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; **16:** 967–74.
3. Chandler G, *et al.* Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001; **38:** 988–91.
4. Blaustein DA, *et al.* The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease. *Kidney Int* 2003; (suppl): S72–S77.
5. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** 63–6.
6. Leijn E, *et al.* Intravenous iron supplementation in children on hemodialysis. *J Nephrol* 2004; **17:** 423–6.
7. Aronoff GR, *et al.* Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. *Kidney Int* 2004; **66:** 1193–8.
8. Van Wyck DB, *et al.* The United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; **68:** 2846–56.
9. Hollands JM, *et al.* Safety of high-dose iron sucrose infusion in hospitalized patients with chronic kidney disease. *Am J Health-Syst Pharm* 2006; **63:** 731–4.

Preparations

USP 31: Iron Sucrose Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Energavit; Ferricrine; Sucrox; Venofer; ***Austral.:*** Venofer; ***Belg.:*** Venofer; ***Canad.:*** Venofer; ***Chile:*** Rafofer; Venofer; ***Cz.:*** Ferrologic; Ferrum; Venofer; ***Denm.:*** Venofer; ***Fin.:*** Venofer; ***Fr.:*** Venofer; ***Ger.:*** FERROinfant Neu†; Venofer; ***Gr.:*** Anemifer; Felix; Ferroprol; Ferrovin; Venofer; ***Hong Kong:*** Venofer; ***Hung.:*** Venofer; ***Indon.:*** Venofer; ***Israel:*** Venofer; ***Ital.:***

Ferrum Hausmann; Unifer†; ***Malaysia:*** Venofer; ***Mex.:*** Venoferrum; ***Neth.:*** Venofer; ***Norw.:*** Venofer; ***NZ:*** Venofer; ***Port.:*** Venofer; ***S.Afr.:*** Venofer; ***Singapore:*** Venofer; ***Spain:*** Feriv; Venofer; ***Swed.:*** Venofer; ***Switz.:*** Venofer; ***Thai.:*** Venofer; ***Turk.:*** Venofer; ***UK:*** Venofer; ***USA:*** Venofer; ***Venez.:*** Venofer.

Multi-ingredient: ***Ger.:*** Hicoton†; Junisana†; Selectafer N†.

Isoleucine *(USAN, rINN)*

I; Ile; Isoleucin; Isoleucina; L-Isoleucine; Isoleucinum; Isoleusiini; Izoleucin; Izoleucinas. L-2-Amino-3-methylvaleric acid.

Изолейцин

$C_6H_{13}NO_2$ = 131.2.

CAS — 73-32-5.

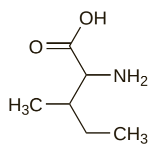

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Isoleucine). A white or almost white, crystalline powder or flakes. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Isoleucine). White, practically odourless crystals. Soluble in water; slightly soluble in hot alcohol; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0.

Profile

Isoleucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Bramin-hepa†; Falkamin; ***Ital.:*** Falkamin†; Isobranch; Isoram.

Isomalt *(BAN)*

Bay-i-3930; E953; Isomalta; Isomalti; Isomaltitol; Isomaltum; Izomalt; Izomaltas; Palatinit.

CAS — 64519-82-0.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Isomalt). A mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol ($C_{12}H_{24}O_{11}$ = 344.3) and 1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate ($C_{12}H_{24}O_{11},2H_2O$ = 380.3) and neither of the two components is less than 3%, calculated with reference to the anhydrous substance. A white or almost white powder or granules. Freely soluble in water; practically insoluble in dehydrated alcohol.

USNF 26 (Isomalt). 6-*O*-α-D-Glucopyranosyl-D-glucitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0% of the mixture, calculated on the anhydrous basis.

Profile

Isomalt is a sugar alcohol (polyol) used as a bulk sweetener in foods. The ingestion of large quantities may produce flatulence and have a laxative effect.

Metabolism. Isomalt is partly metabolised in the small intestine to glucose, mannitol, and sorbitol and the remaining isomalt is completely metabolised by the flora of the large intestine.[1] The Australian manufacturers have commented that the hydrolysis and absorption is minimal and does not significantly affect blood-sugar or insulin concentrations; they consider isomalt to be suitable for use by diabetic patients.[2]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-ninth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 733* 1986.
2. Barnes JA. Martindale and isomalt. *Aust J Pharm* 1994; **75:** 183.

Lactose

Lactosa; Lactosum; Laktoosi; Laktos; Laktosa; Laktóz; Laktoza; Laktozė; Lattosio; Milk Sugar; Saccharum Lactis; Saccharum Lactis.

CAS — 63-42-3 (anhydrous lactose); 5989-81-1 (lactose monohydrate); 10039-26-6 (lactose monohydrate, cyclic); 64044-51-5 (lactose monohydrate, open form).

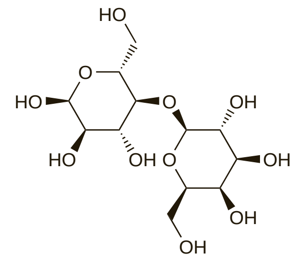

(anhydrous lactose)

Description. Lactose is a disaccharide obtained from the whey of milk. It may exist in a number of distinct forms depending upon the crystallisation and drying processes employed. The forms can vary in the contents of crystalline and amorphous lactose, the amounts of α-lactose (*O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose) and β-lactose (*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose), and in their hydration states. The α-form of lactose exists in either the anhydrous ($C_{12}H_{22}O_{11}$ = 342.3) or monohydrate ($C_{12}H_{22}O_{11},H_2O$ = 360.3) state whereas the β-form exists only in the anhydrous state. Commercial lactose is mainly the α-monohydrate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *Viet.* Also in *USNF.* Some pharmacopoeias include separate monographs for anhydrous lactose and lactose monohydrate.

Ph. Eur. 6.2 (Lactose, Anhydrous). It is β-lactose or a mixture of α-lactose and β-lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol.

Ph. Eur. 6.2 (Lactose Monohydrate; Lactose BP 2008). It is the monohydrate of α-lactose. It may be modified as to its physical characteristics and may contain varying proportions of amorphous lactose. A white or almost white, crystalline powder. Freely but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 26 (Anhydrous Lactose). It is β-lactose or a mixture of α- and β-lactose. It is a white or almost white powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USNF 26 (Lactose Monohydrate). It is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety. It may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose. It is a white, free-flowing powder. Freely, but slowly soluble in water; practically insoluble in alcohol. Store in airtight containers.

Adverse Effects and Precautions

Lactose intolerance occurs due to a deficiency of the intestinal enzyme lactase. Ingestion of lactose by patients with lactase deficiency leads to a clinical syndrome of abdominal pain, diarrhoea, distension, and flatulence; symptoms may also occur in persons without such a deficiency who have ingested excessive amounts of lactose.

Lactose is contra-indicated in patients with galactosaemia, the glucose-galactose malabsorption syndrome, or lactase deficiency.

Lactose intolerance. Reviews of lactose intolerance.[1-3] The capacity of the infant intestine to produce lactase, the enzyme responsible for digesting lactose, is retained into adulthood only by a minority of the world's population, mostly in those of north European descent; in Africa and Asia more than 90% of the population are lactase deficient. Because of the ubiquity of lactose in the diet and the consequent frequency of abdominal symptoms, attempts have been made to treat lactose intolerance by dietary exclusion (which need not be complete since lactase deficiency is rarely absolute). An alternative is enzyme replacement therapy with β-galactosidase from micro-organisms (see Tilactase, p.2402), but the role of such therapy has yet to be fully determined. The findings of one study[4] suggested that, in adults with lactose intolerance, the use of lactose-digestive aids is unnecessary if lactose intake is limited to the equivalent of 240 mL of milk or less daily.

There has been concern that lactose might be contaminated with protein from milk, and it has been recommended that children with cow's milk allergy avoid lactose-containing foods. However, a small study[5] found that children allergic to cow's milk could still tolerate lactose.

For the use of soya in infants intolerant to cow's milk, see Food Intolerance, p.1967.

1. Anonymous. Lactose intolerance. *Lancet* 1991; **338:** 663–4.
2. Vesa TH, *et al.* Lactose intolerance. *J Am Coll Nutr* 2000; **19** (suppl): 165S–175S.
3. Heyman MB. Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics* 2006; **118:** 1279–86.
4. Suarez FL, *et al.* A comparison of symptoms after the consumption of milk or lactose-hydrolysed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995; **333:** 1–4.
5. Fiocchi A, *et al.* Clinical tolerance to lactose in children with cows' milk allergy. *Pediatrics* 2003; **112:** 359–62.

Pharmacokinetics

Lactose is hydrolysed by lactase in the small intestine to glucose and galactose, which are then absorbed.

Uses and Administration

Lactose, the carbohydrate component of milk, is less sweet than sucrose.

Lactose is widely used as an excipient in pharmaceutical manufacturing. In the production of capsules or tablets it may be used as a diluent, bulking agent, or filler, and in powders as a bulking agent. Lactose is also used as a carrier for drugs in dry powder inhalers. Characteristics such as particle size or flow characteristics make different grades of lactose suitable for different applications.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Ichth-Oestren; ***Fr.:*** Tavag.

Leucine *(USAN, rINN)*

α-Aminoisocaproic Acid; L; Leu; Leucin; Leucina; Leucinas; L-Leucine; Leucinum; Leucyna; Leusiini. L-2-Amino-4-methylvaleric acid.

Лейцин

$C_6H_{13}NO_2$ = 131.2.

CAS — 61-90-5.

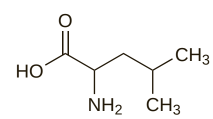

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Leucine). A white or almost white, crystalline powder or shiny flakes. Sparingly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Leucine). White, practically odourless crystals. Sparingly soluble in water; insoluble in ether. pH of a 1% solution in water is between 5.5 and 7.0.

Profile

Leucine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Revitalose; ***Ger.:*** Bramin-hepa†; Falkamin; ***Ital.:*** Falkamin†; Isobranch; Isoram.

Lutein

E161(b); Xanthophyll. (3*R*,3′*R*,6′*R*)-β,ε-Carotene-3,3′-diol.

Лютеин

$C_{40}H_{56}O_2$ = 568.9.

CAS — 127-40-2.

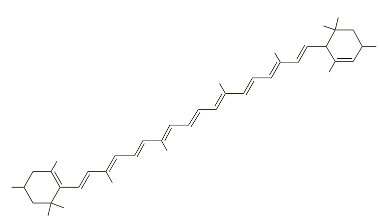

Pharmacopoeias. In *US.*

US. also includes Lutein Preparation.

USP 31 (Lutein). A red crystalline powder. Soluble in dehydrated alcohol, in dichloromethane, and in ethyl acetate; partially soluble in hexane. Store at 8° to 15° in tightly-sealed, airtight containers. Protect from light and oxygen.

Profile

Lutein is a naturally occurring carotenoid that has been investigated for its supposed role in a number of conditions including age-related macular degeneration (p.785), cataracts, cardiovascular disease, and cancer.

Lutein is also used as a colouring agent.

◊ References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; **132** (suppl): 518S–524S.
2. Granado F, *et al.* Nutritional and clinical relevance of lutein in human health. *Br J Nutr* 2003; **90:** 487–502.
3. Mozaffarieh M, *et al.* The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J* 2003; **2:** 20.
4. Trumbo PR, Ellwood KC. Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: an evaluation using the Food and Drug Administration's evidence-based review system for health claims. *Am J Clin Nutr* 2006; **84:** 971–4.
5. Cho E, *et al.* Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. *Am J Clin Nutr* 2008; **87:** 1837–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Lutebiol.

Multi-ingredient: ***Indon.:*** Eyevit; Lutevision; Lutevision Extra; Lutevit; Matovit Fifty; Nuvision; Oculex; Optha-LL; Optimax; Reticopen; Retivit; Vita-Vision; ***Israel:*** Opti-safe; Opti-safe AREDS; ***Mex.:*** Snelvit; ***Philipp.:*** Nutrotal.

Lysine *(USAN, rINN)*

K; Lisina; Lys; L-Lysine; Lysinum. L-2,6-Diaminohexanoic acid.

Лизин

$C_6H_{14}N_2O_2$ = 146.2.
CAS — 56-87-1.
ATC — B05XB03.
ATC Vet — QB05XB03.

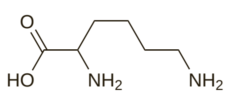

Pharmacopoeias. In *Ger.* as the monohydrate.

Lysine Acetate *(rINNM)*

Acetato de lisina; Lizino acetatas; Lizyny octan; Lys Acetate; Lysiiniasetaatti; Lysinacetat; Lysin-acetát; Lysine, acétate de; L-Lysine Monoacetate; Lysini acetas. L-2,6-Diaminohexanoic acid acetate.

Лизина Ацетат

$C_6H_{14}N_2O_2,C_2H_4O_2$ = 206.2.
CAS — 57282-49-2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Lysine Acetate). A white or almost white, crystalline powder or colourless crystals. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. Protect from light.
USP 31 (Lysine Acetate). White, odourless crystals or crystalline powder. Freely soluble in water.

Lysine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lisina; Lizin-hidroklorid; Lizino hidrochloridas; Lys Hydrochloride; Lysiinihydrokloridi; Lysine, chlorhydrate de; L-Lysine Monohydrochloride; Lysin-hydrochlorid; Lysinhydroklorid; Lysini hydrochloridum. L-2,6-Diaminohexanoic acid hydrochloride.

Лизина Гидрохлорид

$C_6H_{14}N_2O_2,HCl$ = 182.6.
CAS — 657-27-2.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Lysine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. Protect from light.
USP 31 (Lysine Hydrochloride). A white, odourless powder. Freely soluble in water.

Profile

Lysine is a basic amino acid that is an essential constituent of the diet. Lysine acetate and lysine hydrochloride are used as dietary supplements.

Lysinuric protein intolerance. For mention of the use of lysine to correct lysine deficiency in lysinuric protein intolerance, see Hyperammonaemia, under Citrulline, p.1935.

Preparations

USP 31: Lysine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Port.: Incremin†.

Multi-ingredient: ***Arg.:*** Latlas; ***Austral.:*** Cold Sore Relief†; Vitaline†; ***Fr.:*** Curasten; Revitalose; ***Hong Kong:*** Digezym; ***India:*** Ferrochelate; Logical; Tonoferon; ***Indon.:*** Champs C with Lysine; ***Ital.:*** Biocarnil†; Calciofix; ***Mex.:*** Corpotasin CL; ***Singapore:*** Champs C with Lysine; ***Spain:*** Euzymina Lisina I; Euzymina Lisina II; Malandil; Pranzo; ***USA:*** Klorvess.

Magnesium Fluoride

Фторид Магния

MgF_2 = 62.30.
CAS — 7783-40-6.

Profile

Magnesium fluoride is used as a fluoride supplement (see Sodium Fluoride, p.1962) for the prevention of dental caries. Magnesium fluoride is also used as a source of magnesium.

Homoeopathy. Magnesium fluoride has been used in homoeopathic medicines under the following names: Magnesia Fluorata; Magnesium Fluoratum; Magnesia Fluoricum.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Magnesium Pyre; Magnogene.

Maize Oil

Aceite de maíz; Corn Oil; Huile de Maïs; Kukoricamagolaj; Kukuřičný olej; Kukurūzų aliejus; Maïs, huile de; Maissiöljy; Majsolja; Maydis oleum; Ol. Mayd.; Olej kukurydziany; Oleum Maydis.

Pharmacopoeias. In *Chin., Eur* (see p.vii), and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Maize Oil, Refined; Maydis Oleum Raffinatum). The refined fatty oil obtained from the seeds of *Zea mays*. A clear, light yellow or yellow oil. Practically insoluble in water and in alcohol; miscible with dichloromethane and with petroleum spirit (b.p.: 40° to 60°). Store at a temperature not exceeding 25°. Protect from light.
USNF 26 (Corn Oil). The refined fixed oil obtained from the embryos of *Zea mays* (Gramineae). A clear, light yellow, oily liquid having a faint characteristic odour. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Maize oil is a fixed oil with a high content of unsaturated acids, and has been used to replace saturated acids in the diets of patients with familial hypercholesterolaemia. It is also used as an oily vehicle in pharmaceutical formulations.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Gal-Vit†.

Multi-ingredient: ***Fr.:*** Preservation; ***USA:*** Lipomul.

Malt Extract

Extractum Bynes; Malta, extracto de.

Profile

Malt extract contains 50% or more of maltose, with dextrin, glucose, and small amounts of other carbohydrates, and protein. It is prepared from malted grain of barley (*Hordeum distichon*, *H. vulgare*) or a mixture of this with not more than 33% of malted grain of wheat (*Triticum aestivum* or *T. turgidum*).

Malt extract has nutritive properties. It is chiefly used as a vehicle in preparations containing cod-liver oil (p.1935) and halibut-liver oil (p.1948). It is a useful flavouring agent for masking bitter tastes.

A product known as malt soup extract, obtained from barley grains, and containing 73% maltose with 12% other polymeric carbohydrates as well as small amounts of proteins, electrolytes, and vitamins, is sometimes used as a laxative.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Maltin; ***USA:*** Maltsupex.

Multi-ingredient: ***Fr.:*** Galactogil; ***S.Afr.:*** Cough Elixir.

Maltitol *(BAN)*

E965; Hydrogenated Maltose; D-Maltitol; Maltitoli; Maltitolis; Maltitolum. α-D-Glucopyranosyl-1,4-D-glucitol.

$C_{12}H_{24}O_{11}$ = 344.3.
CAS — 585-88-6.

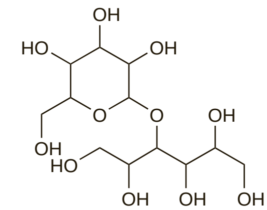

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Maltitol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.
USNF 26 (Maltitol). A white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol.

Maltitol Syrup

E965; Hydrogenated Glucose Syrup; Hydrogenated High Maltose-glucose Syrup; Liquid Maltitol; Maltitol ciekły; Maltitol, flytande; Maltitol, jarabe de; Maltitol liquide; Maltitol roztok; Maltitol Solution; Maltitoli, nestemäinen; Maltitolum liquidum; Maltitszirup; Skystasis maltitolis.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Maltitol, Liquid). An aqueous solution of a hydrogenated, part hydrolysed starch, containing not less than 68.0% w/w and not more than 85.0% w/w of anhydrous substance composed of a mixture of mainly D-maltitol with D-sorbitol and hydrogenated oligo- and polysaccharides. It contains not less than 50.0% w/w of D-maltitol and not more than 8.0% w/w of D-sorbitol, both calculated with reference to the anhydrous substance. A clear, colourless, syrupy liquid. Miscible with water and with glycerol.
USNF 26 (Maltitol Solution). A water solution containing, on the anhydrous basis, not less than 50.0% of D-maltitol (w/w) and not more than 8.0% of D-sorbitol (w/w).

Nomenclature. Hydrogenated glucose syrup is a generic term encompassing products of widely varying composition and it was concluded that such products containing up to 90% of maltitol should more properly be called maltitol syrup.[1] This was subsequently amended to include products containing up to 98% maltitol.[2] Preparations containing a minimum of 98% of maltitol were assigned the title maltitol.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989.
2. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993.

Profile

Maltitol and maltitol syrup are bulk sweeteners used in foods and pharmaceuticals; they are considered to be less cariogenic than sucrose. The ingestion of large quantities may produce flatulence and diarrhoea.

Maltodextrin

Maltodekstriini; Maltodekstrinas; Maltodextrina; Maltodextrine; Maltodextrinum.
CAS — 9050-36-6.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Maltodextrin). A mixture of glucose, disaccharides, and polysaccharides, obtained by the partial hydrolysis of starch. The degree of hydrolysis, expressed as dextrose equivalent (DE) is not more than 20 (nominal value). A white or almost white, slightly hygroscopic powder or granules. Freely soluble in water.
USNF 26 (Maltodextrin). A nonsweet, nutritive saccharide mixture of polymers that consists of D-glucose units with a dextrose equivalent of less than 20. It is prepared by the partial hydrolysis of food grade starch with suitable acids and/or enzymes. White, hygroscopic powder or granules. Freely soluble or readily dispersible in water; slightly soluble to insoluble in dehydrated alcohol. pH of a 20% solution in water is between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 30° and a relative humidity not exceeding 50%.

Profile

Maltodextrin, a glucose polymer (malto-oligosaccharide), is a source of carbohydrate often used in oral dietary supplements and tube feeding. It rapidly releases glucose in the gastrointestinal tract but because of the high average molecular weight of maltodextrin, solutions have a lower osmolarity than isocaloric solutions of glucose. Additionally, preparations based on maltodextrin and intended for dietary supplementation usually have a low electrolyte content and are free of other sugars such as fructose, galactose, lactose, and sucrose. These properties make such preparations suitable for dietary supplementation in a variety of diseases including certain gastrointestinal disorders where malabsorption is a problem, in disaccharide intolerance (without isomaltose intolerance), and in acute and chronic hepatic and renal diseases where protein, mineral, and fluid restriction are often necessary.

Maltodextrin is also employed as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Carbohidrato 100; MC Modulo Calorico; ***Austral.:*** Maxijul; ***Braz.:*** Nidex; Oligossac†; ***Canad.:*** Moducal†; ***Chile:*** Modulo Calorico; ***Cz.:*** Fantomalt†; ***Fin.:*** Fantomalt; ***Hong Kong:*** Fiber Basics; ***Ital.:*** Energen; Fantomalt; Maltovis; Nidex; ***NZ:*** Moducal; ***Port.:*** Fantomalt†; Moducal†; ***USA:*** Moducal; ***Venez.:*** Fantomalt.

Multi-ingredient: *Chile:* Nutrasweet†; ***Fr.:*** Gumilk; ***Indon.:*** Fantomalt; ***Ital.:*** Giflorex; ***Pol.:*** Fantomalt; ***Venez.:*** Glutapak; Glutapak-R; Hermesetas Gold; Modulo Calorico; Multidex.

Maltose

D-maltose; Maltobiose; Maltosa. 4-*O*-α-D-Glucopyranosyl-β-D-glucopyranose.

$C_{12}H_{22}O_{11}$ = 342.3.

CAS — 69-79-4 (anhydrous maltose); 6363-53-7 (maltose monohydrate).

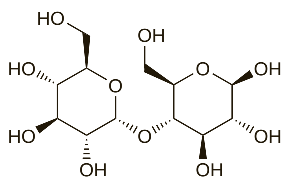

(anhydrous maltose)

Pharmacopoeias. *Jpn* includes the monohydrate. *USNF* permits the anhydrous and monohydrate forms.

USNF 26 (Maltose). It contains one molecule of water of hydration or is anhydrous. A white, odourless, crystalline powder that has a sweet taste. Freely soluble in water; very soluble in dehydrated alcohol; practically insoluble in ether; slightly soluble in methyl alcohol. pH of a 10% solution in water is between 3.7 and 4.7 (anhydrous form) and between 4.0 and 5.5 (monohydrate form).

Profile

Maltose, a disaccharide composed of two glucose molecules, is less sweet than sucrose. It is obtained from starch by hydrolysis with amylase. Maltose is often present with other sugars in mixtures used as carbohydrate sources. It is also used as a pharmaceutical excipient.

Adverse effects. Hyponatraemia developed after intravenous infusion of normal immunoglobulin in 10% maltose in a patient with acute renal failure after liver transplantation.[1] The effect, which recurred on each of four successive infusions, resembled that of hyperglycaemia and was thought to be due to accumulation of maltose and other osmotically active metabolites in the extracellular fluid.

1. Palevsky PM, *et al.* Maltose-induced hyponatremia. *Ann Intern Med* 1993; **118:** 526–8.

Precautions. Preparations that contain, or are metabolised to, maltose may interfere with the results from glucose tests (p.2314). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2] The problem may also occur with icodextrin, which produces maltose as a metabolite (see Dialysis, p.1937).

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/cber/safety/maltose110405.htm (accessed 01/07/08)

Preparations

USNF 26: Liquid Glucose.

Proprietary Preparations (details are given in Part 3)
Indon.: Martos; ***Jpn:*** Martos.

Multi-ingredient: *Fr.:* Picot†.

Manganese

Mangan; Manganèse; Manganeso; Manganum.

Mn = 54.938045.

CAS — 7439-96-5.

Manganese Chloride

Manganeso, cloruro de.

$MnCl_2.4H_2O$ = 197.9.

CAS — 7773-01-5 (anhydrous manganese chloride); 13446-34-9 (manganese chloride tetrahydrate).

Pharmacopoeias. In *US.*

USP 31 (Manganese Chloride). Large, irregular, pink, odourless, translucent crystals. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. pH of a 5% solution in water is between 3.5 and 6.0.

Manganese Gluconate

Manganèse, gluconate de; Manganeso, gluconato de; Mangani gluconas. Bis(D-gluconato-O^1,O^2) manganese; Manganese D-gluconate.

$C_{12}H_{22}MnO_{14}$ = 445.2.

Pharmacopoeias. In *Eur.* (see p.vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.

Ph. Eur. 6.2 (Manganese Gluconate). A white or pale pink, slightly hygroscopic, crystalline powder. Soluble in water; practically insoluble in anhydrous ethanol; insoluble in dichloromethane. Store in non-metallic, airtight containers.

USP 31 (Manganese Gluconate).

Manganese Sulfate

Mangaanisulfaattimonohydraatti; Manganèse (sulfate de) monohydraté; Manganese Sulphate; Manganeso, sulfato de; Mangani Sulfas; Mangani sulfas monohydricum; Mangán(II)-szulfát-monohidrát; Mangano sulfatas; Mangansulfatmonohydrat; Manganu siarczan; Síran manganatý. Manganese (II) sulphate monohydrate.

$MnSO_4,H_2O$ = 169.0.

CAS — 7785-87-7 (anhydrous manganese sulfate); 10034-96-5 (manganese sulfate monohydrate); 10101-68-5 (manganese sulfate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US. Br.* and *Fr.* also include the tetrahydrate.

BP 2008 (Manganese Sulphate). The tetrahydrate occurs as pale pink, odourless or almost odourless, crystals or crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Ph. Eur. 6.2 (Manganese Sulphate Monohydrate). It occurs as a pale pink, slightly hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

USP 31 (Manganese Sulfate). The monohydrate occurs as pale red, slightly efflorescent crystals, or as a purple, odourless powder. Soluble in water; insoluble in alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

Acute poisoning due to ingestion of manganese or manganese salts is rare. The main symptoms of chronic poisoning, either from injection or usually inhalation of manganese dust or fumes in air, include extrapyramidal effects which may be followed by progressive deterioration in the CNS. Parenteral manganese should be used cautiously in patients with reduced biliary excretion, especially in cholestatic liver disease. When the duration of total parenteral nutrition is likely to exceed 1 month, serum-manganese concentration and liver function should be checked before starting treatment and regularly during treatment; additives containing manganese should be stopped if serum-manganese concentrations are raised or cholestasis develops.

Accumulation. There are reports of cholestatic liver disease, and possibly changes in the basal ganglia, associated with hypermanganesaemia in children given long-term parenteral nutrition;[1,2] manganese accumulation may be secondary to impaired biliary excretion.[3] Manganese supplementation in such patients requires re-appraisal and whole blood manganese concentrations should be monitored regularly. A low-dose regimen of not more than 1 microgram/kg (0.018 micromoles/kg) daily has been suggested,[2,3] a dose that was also recommended by the American Society for Parenteral and Enteral Nutrition.[4] Hypermanganesaemia and basal ganglia manganese deposition resolved over time in 2 children when the manganese dose in their parenteral nutrition was reduced.[5] Manganese accumulation in the basal ganglia has been seen in patients with liver cirrhosis,[6,7] and may be associated with parkinsonism[7,8] (for reference to the use of aminosalicylic acid in the treatment of manganese-induced parkinsonism, see p.202). Concern has been expressed[9] at the high levels of manganese contained in infant formulas.

1. Reynolds AP, *et al.* Manganese in long term paediatric parenteral nutrition. *Arch Dis Child* 1994; **71:** 527–8.
2. Fell JME, *et al.* Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996; **347:** 1218–21.
3. Beath SV, *et al.* Manganese toxicity and parenteral nutrition. *Lancet* 1996; **347:** 1773–4. Correction. *ibid.* **348:** 416.
4. Mirtallo J, *et al.* American Society for Parenteral and Enteral Nutrition. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr* 2004; **28:** S39–S70.
5. Kafritsa Y, *et al.* Long term outcome of brain manganese deposition in patients on home parenteral nutrition. *Arch Dis Child* 1998; **79:** 263–5.
6. Krieger D, *et al.* Manganese and chronic hepatic encephalopathy. *Lancet* 1995; **346:** 270–4.
7. Burkhard PR, *et al.* Chronic parkinsonism associated with cirrhosis. *Arch Neurol* 2003; **60:** 521–8.
8. Zatta P, *et al.* The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. *Brain Res Bull* 2003; **62:** 15–28.
9. Hozyasz KK, Ruszczynska A. High manganese levels in milk-based infant formulas. *Neurotoxicology* 2004; **25:** 733.

Pharmacokinetics

Absorption of manganese from the gastrointestinal tract is variable, ranging from 3 to 50%. There is some evidence that the amount absorbed decreases as intake increases, suggesting a homoeostatic response. In the circulation, manganese is bound to transmanganin, a beta-1-globulin. Manganese is stored in the brain, kidneys, pancreas, and liver. It is excreted in bile, and undergoes enterohepatic circulation.

Uses and Administration

Manganese is an essential trace element and small amounts of a salt such as the chloride or sulfate are sometimes added to solutions for total parenteral nutrition. Suggested doses are 275 micrograms (5 micromoles) elemental manganese daily for adults and children over 40 kg, and 1 microgram/kg (0.0182 micromol/kg) daily for infants and children to a maximum of 15 micrograms (see also Accumulation, above).

Manganese compounds or salts that have been used in therapeutics in addition to those mentioned above include manganese amino acid chelate, manganese dioxide, manganese gluconate, and manganese hydrogen citrate.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1925) has been set for manganese although a safe intake for adults was believed to lie above 1.4 mg (26 micromoles) daily.[1] Similarly, in the USA a recommended dietary allowance has not been published, although an adequate intake has been estimated to be 2.3 mg daily for men and 1.8 mg daily for women.[2] A tolerable upper intake level of 11 mg has also been set.[2] WHO has not proposed a safe range of mean population intakes for manganese since neither intakes resulting in deficiency nor threshold toxicity levels have been established.[3] Diets high in unrefined cereals, nuts, leafy vegetables, and tea will be high in manganese.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Manganese. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996; 163–7.

Preparations

BPC 1973: Compound Ferrous Sulphate Tablets;
USP 31: Manganese Chloride for Oral Solution; Manganese Chloride Injection; Manganese Sulfate Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Mangaplexe†; ***Mex.:*** MN-Fusin†.

Multi-ingredient: *Austral.:* Bio Magnesium; Bioglan Joint Mobility; ***Braz.:*** Eviprostat†; Xantina B12†; Xantinon B12; ***Fr.:*** Cicaplast; Oligoderm; Oligorhine Manganese; ***Ger.:*** Algosteril Trionic†; ***Indon.:*** Eviprostat; Fitbon; Fitbon Plus; ***Irl.:*** Ferrotab†; ***Ital.:*** Sterimar Mn; ***Mex.:*** Actiman; ***Philipp.:*** Ruflex; ***Rus.:*** Tot'Hema (Тотема); ***S.Afr.:*** Ferrous Sulphate Compound; ***Singapore:*** Arthro-Flex; Eviprostat.

Medium-chain Triglycerides

Keskipitkäketjuiset tyydyttyneet triglyseridit; Triacylglyceroly střední nasycené; Trigliceridai, vidutinės grandinės; Trigliceridek, közepes szénláncú zsírsavaké; Triglicéridos de cadena media; Triglycerida saturata media; Triglycerider, medellångkedjiga; Triglycérides à chaîne moyenne.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Triglycerides, Medium-chain). They are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis.* They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2$ = 172.3). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in well-filled containers. Protect from light.

USNF 26 (Medium-Chain Triglycerides). They are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis.* They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2$ = 172.3). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Medium-chain triglycerides are used for enteral and parenteral nutrition (p.1923) in conditions associated with malabsorption of fat, such as cystic fibrosis, enteritis, and steatorrhoea, and after intestinal resection. Medium-chain triglycerides are more readily hydrolysed than long-chain triglycerides and are not dependent upon biliary or pancreatic secretions for absorption from the gastrointestinal tract. They provide 35 kJ (8.3 kcal) per g. They do not provide essential fatty acids.

Medium-chain triglycerides have also been used as bases for pharmaceutical preparations.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Teceeme; ***Austral.:*** Liquigen; MCT Oil; ***Canad.:*** MCT Oil†; ***Fin.:*** Liquigen; MCT Oljy; ***Fr.:*** Liquigen; ***Gr.:*** MCT Oil; ***Hung.:*** Structolipid; ***Israel:*** MCT; ***Ital.:*** MCT; Mytic 810; ***Malaysia:*** MCT Oil†; ***NZ:*** Liquigen; MCT Oil; ***Port.:*** MCT Oil; ***Singapore:*** MCT†; ***UK:*** Alembicol D; MCT Oil; ***USA:*** MCT.

Multi-ingredient: ***Arg.:*** Lipofundin MCT/LCT-E; Lipofundin MCT/LCT†; ***Austral.:*** Caprilon; MCT Duocal; ***Austria:*** Lipofundin mit MCT; SMOFlipid; Structolipid; ***Belg.:*** Medialipide†; ***Chile:*** Lipofundin MCT/LCT; Lipovenos MCT/LCT; ***Cz.:*** Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; ***Denm.:*** SMOFlipid; Structolipid; ***Fin.:*** Lipoplus; Nutriflex Lipid; Structolipid; Vasolipid; ***Fr.:*** Liprocil; Medialipide; Structolipide; ***Ger.:*** Gleitgelen; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; SMOFlipid; Visine Trockene Augen; ***Gr.:*** Lipofundin MCT/LCT; SMOFlipid; Structolipid; ***Hong Kong:*** Lipofundin MCT/LCT; Nutriflex Lipid; ***Hung.:*** Lipofundin MCT; Lipovenos PLR†; SMOFlipid; ***Indon.:*** Lipofundin MCT/LCT; ***Irl.:*** Caprilon; Liquigen; MCT Duocal†; ***Israel:*** Lipofundin MCT/LCT; ***Ital.:*** Caprilon; Lipofundin MCT; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; Structolipid; ***Mex.:*** Lipofundin MCT/LCT; Lipovenoes MCT†; ***Neth.:*** Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; ***Norw.:*** Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; ***NZ:*** Structolipid; ***Pol.:*** Lipofundin MCT/LCT; SMOFlipid; ***Port.:*** Lipofundina MCT/LCT; Lipoplus; Nutribraun; Structolipid; ***S.Afr.:*** Lipofundin MCT/LCT; ***Singapore:*** Lipofundin MCT/LCT†; ***Spain:*** Lipofundina MCT/LCT; Nutriflex Lipid; Structolipid; ***Swed.:*** Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; ***Switz.:*** Lipofundin MCT/LCT; Nutriflex Lipid; Structolipid; ***Thai.:*** Lipofundin MCT/LCT; Structolipid; ***Turk.:*** Lipofundin MCT/LCT; ***UK:*** Caprilon; Imuderm; Lipidem; Lipofundin MCT/LCT; Liquigen; MCT Duocal; SMOFlipid; Structolipid; ***Venez.:*** Lipofundin MCT/LCT; Propol†.

Molybdenum

Molibdeno; Molybdän; Molybdène.

Mo = 95.96.

Ammonium Molybdate

Amonowy molibdenian; Molibdato de amonio. Hexaammonium molybdate tetrahydrate.

$(NH_4)_6Mo_7O_{24},4H_2O$ = 1236.0.

CAS — 12054-85-2.

Pharmacopoeias. In *US.*

USP 31 (Ammonium Molybdate). Colourless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Sodium Molybdate

Molibdato de sodio; Molybdenan sodný dihydrát; Natrii molybdas dihydricus; Natrio molibdatas dihidratas; Nátrium-molibdenát-dihidrát; Natriummolybdaattidihydraatti; Natriummolybdatdihydrat; Sodium (molybdate de) dihydraté; Sodu molibdenian.

$Na_2MoO_4,2H_2O$ = 242.0.

Pharmacopoeias. In *Eur.* (see p.vii). *Ger.* also includes a monograph for the anhydrous substance.

Ph. Eur. 6.2 (Sodium Molybdate Dihydrate). A white or almost white powder or colourless crystals. Freely soluble in water.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for total parenteral nutrition. A suggested dose is about 20 to 120 micrograms (0.2 to 1.2 micromoles) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.1925) has been set for molybdenum although a safe intake was believed to be between 50 and 400 micrograms (0.5 and 4 micromoles) daily for adults.[1] In the USA, the recommended dietary allowance is 45 micrograms daily for adults.[2] The tolerable upper intake level is 2 mg daily.[2] WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 micrograms daily,[3] corresponding to approximately 400 nanograms/kg.

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health.* Geneva: WHO, 1996; 144–54.

Preparations

USP 31: Ammonium Molybdate Injection.

Proprietary Preparations (details are given in Part 3)

Fr.: Molybdene Injectable; ***USA:*** Molypen.

Neohesperidin Dihydrochalcone

E959; Neohesperidiinidihydrokalkoni; Neohesperidin DC; Neohesperidin-dihidrochalkonas; Neohesperidin-dihydrochalconum; Neohesperidin-dihydrochalkon; Neohesperidindivätekalkon; Neohesperidine DC; Néohespéridine-dihydrochalcone; Neoheszperidin-dihidro-kalkon; NHDC. 3,5-Dihydroxy-4-[3-(3-hydroxy-4-methoxyphenyl)propionyl]phenyl 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside.

$C_{28}H_{36}O_{15}$ = 612.6.

CAS — 13241-33-3 (neohesperidin); 20702-77-6 (neohesperidin dihydrochalcone); 18916-17-1 (naringin dihydrochalcone); 65520-51-6 (neoeriocitrin dihydrochalcone).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Neohesperidin-dihydrochalcone). A white or yellowish-white powder. Practically insoluble in water and in dichloromethane; freely soluble in dimethyl sulfoxide; soluble in methyl alcohol. Protect from light.

Profile

Neohesperidin dihydrochalcone is an intense sweetener derived from naringin, a flavonoid present in citrus peel. It is about 1000 to 1500 times as sweet as sucrose and is used in foods, beverages, and pharmaceuticals. It has a synergistic sweetening effect when used with other sweeteners.

Neotame

Neotamo. *N*-[*N*-(3,3-Dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

$C_{20}H_{30}N_2O_5$ = 378.5.

CAS — 165450-17-9.

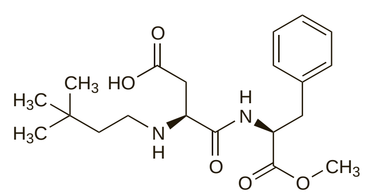

Pharmacopoeias. In *USNF.*

USNF 26 (Neotame). Store in a dry place at a temperature not exceeding 40°.

Profile

Neotame is an intense sweetener used in foods and beverages. It has between 7000 and 13 000 times the sweetening power of sucrose and is stable to heat.

◊ References.

1. Anonymous. Neotame—a new artificial sweetener. *Med Lett Drugs Ther* 2002; **44:** 73–4.

Nicotinamide Ascorbate *(rINNM)*

Ascorbato de nicotinamida; Niacinamide Ascorbate; Nicoscorbine; Nicotinamide, Ascorbate de; Nicotinamidi Ascorbas.

Никотинамида Аскорбат

$C_{12}H_{14}N_2O_7$ = 298.2.

CAS — 1987-71-9.

Profile

Nicotinamide ascorbate is a complex of nicotinamide (p.1957) with ascorbic acid (p.1983) that is used in multivitamin preparations. It has also been given with betaine glucuronate and diolamine glucuronate for liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Jetepar; ***Ital.:*** Ietepar†; ***Malaysia:*** Jetepar; ***Philipp.:*** Jetepar; ***Singapore:*** Jetepar.

Nicotinic Acid *(rINN)*

375; Acide nicotinique; Ácido nicotínico; Acidum nicotinicum; Kwas nikotynowy; Kyselina nikotinová; Niacin; Nikotiinihappo; Nikotinik Asit; Nikotino rūgštis; Nikotinsäure; Nikotinsav; Nikotinsyra. Pyridine-3-carboxylic acid.

Никотиновая Кислота

$C_6H_5NO_2$ = 123.1.

CAS — 59-67-6.

ATC — C04AC01; C10AD02.

ATC Vet — QC04AC01; QC10AD02.

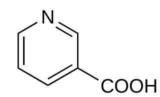

NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Nicotinic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water and in boiling alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. Protect from light.

USP 31 (Niacin). White crystals or crystalline powder, odourless or has a slight odour. Soluble 1 in 60 of water; freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; practically insoluble in ether.

Nicotinamide *(rINN)*

Niacinamide; Nicotinamida; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Nikotiiniamidi; Nikotinamid; Nikotinamidas; Nikotynamid; Vitamin B_3; Vitamin PP. Pyridine-3-carboxamide.

Никотинамид

$C_6H_6N_2O$ = 122.1.

CAS — 98-92-0.

ATC — A11HA01.

ATC Vet — QA11HA01.

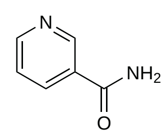

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Nicotinamide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 6.0 to 7.5.

USP 31 (Niacinamide). A white crystalline powder, odourless or practically so. Soluble 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; soluble in glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given by mouth or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. Flushing may be accompanied by dizziness, tachycardia, palpitations, dyspnoea, sweating, chills, or oedema. These symptoms are transient and various strategies have been proposed to reduce them (see Incidence of Adverse Effects, below). Nicotinamide does not have a vasodilator action.

Other adverse effects that have been reported, especially after high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, cramps, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, amblyopia, jaundice and impairment of liver function, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug. Hypophosphataemia, a reduction in platelet counts, and prolongation of prothrombin time have also been reported. Insomnia, myalgia, hypotension, and rhinitis may occur rarely.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation. Frequency of application should be reduced if these effects occur.

◊ References.

1. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; **99** (suppl 1): S22–S31.

Incidence of adverse effects. Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.[1,2] Dermal and gastrointestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical trials; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before the nicotinic acid, or simply by giving nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. Flushing may be less common with modified-release formulations.[2]

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2:** 10–32.
2. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.[1] The effects appeared to be dose-related and reversible. In 2 patients treatment was stopped because of symptoms suggestive of cystoid macular oedema. Other cases of nicotinic acid maculopathy have been reported.[2,3]

1. Fraunfelder FW, *et al.* Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79:** 54–6.
2. Callanan D, *et al.* Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279:** 1702.
3. Spirn MJ, *et al.* Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol* 2003; **135:** 913–14.

Effects on glucose tolerance. Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,[1,2] although it has been investigated in the prevention of diabetes mellitus (see below).

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.
2. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.

Effects on the liver. Hepatotoxicity may occur with nicotinic acid.[1-6] Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. It has been suggested[7] that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.[8] However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms[4,9,10] it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. Some manufacturers of modified-release preparations have stated that cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when patients have substituted modified-release dosage forms for immediate-release crystalline preparations at equivalent doses. There is also a suggestion that not all modified-release preparations are alike in their effects.[11]

1. Henkin Y, *et al.* Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264:** 241–3.
2. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264:** 181.
3. Etchason JA, *et al.* Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66:** 23–8.
4. Rader JI, *et al.* Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92:** 77–81.
5. Coppola A, *et al.* Niacin-induced hepatotoxicity: unusual presentations. *South Med J* 1994; **87:** 30–2.
6. Gavilán JC, *et al.* Hepatitis inducida por niacina. *Med Clin (Barc)* 2002; **118:** 558.
7. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66:** 112–13.
8. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97:** 313–16.
9. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
10. Gray DR, *et al.* Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121:** 252–8.
11. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272:** 513–14.

Effects on the muscles. Myopathy has been noted with nicotinic acid.[1,2] Rhabdomyolysis has occurred when nicotinic acid was given with lovastatin (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1393).

1. Litin SC, Anderson CF. Nicotinic-acid associated myopathy: a report of three cases. *Am J Med* 1989; **86:** 481–3.
2. Gharavi AG, *et al.* Niacin-induced myopathy. *Am J Cardiol* 1994; **74:** 841–2.

Hyperuricaemia. Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.[1]

1. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54:** 2815–19.

Precautions

Nicotinic acid should be given cautiously to patients with a history of peptic ulcer disease, and to those with diabetes mellitus, gout, or hepatic impairment. Modified-release preparations should not be substituted for equivalent doses of immediate-release crystalline nicotinic acid preparations, as cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred. Liver function tests and plasma glucose should be frequently monitored.

Interactions

There may be an increased risk of myopathy or rhabdomyolysis when nicotinic acid is used with statins (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1393). Nicotinic acid may increase the requirements for insulin or oral hypoglycaemics. Aspirin may reduce the clearance of nicotinic acid. *In vitro* studies suggest that colestipol and colestyramine may reduce the availability of nicotinic acid, and some licensed product information recommends an interval of at least 4 to 6 hours between giving nicotinic acid and bile-acid binding resins.

Antiepileptics. For the effect of nicotinamide on *carbamazepine*, see Vitamins, p.475.

Nicotine. A patient started to have flushing and dizziness after her usual doses of nicotinic acid when transdermal nicotine patches were added to her therapy.[1] She had experienced such reactions 3 years previously on starting nicotinic acid therapy, but not since, and it was suggested that on this occasion an interaction might have been responsible.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* 1993; **27:** 1283–4.

Pharmacokinetics

Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to *N*-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

◊ References.

1. Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. *Am J Health-Syst Pharm* 2003; **60** (Suppl 2): S9–14.

Human Requirements

The daily human requirement of nicotinic acid, though not definitely known, is probably about 15 to 20 mg. Yeast, meat, fish, potatoes, legumes, and wholemeal cereals are good sources of nicotinic acid and nicotinamide. However they may be present in a bound, unabsorbable form in cereals, especially maize. Nicotinic acid can also be obtained from the conversion of tryptophan in the body, 60 mg of dietary tryptophan being considered equivalent to 1 mg of dietary nicotinic acid, so requirements are influenced by dietary protein intake and if protein intake is adequate there is little need for any preformed vitamin in the diet. There is generally little loss of nicotinic acid from foods during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for nicotinic acid[1] and in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK the reference nutrient intake (RNI) is 6.6 mg niacin equivalent per 1000 kcal daily and the estimated average requirement (EAR) is 5.5 mg niacin equivalent per 1000 kcal daily for adult males and females. One niacin equivalent is equal to 1 mg of dietary nicotinic acid or 60 mg of dietary tryptophan. In the US the RDAs are also expressed in niacin equivalents and are 16 mg daily for adult males and 14 mg daily for adult females; the EAR is 12 mg daily in males and 11 mg daily in females. The tolerable upper intake level for adults is 35 mg daily.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (nadide, p.2350) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra, characterised by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, loss of appetite, headache, lethargy, and mental and neurological disturbances. Nicotinic acid deficiency may occur with other vitamin B-complex deficiency states, for example in alcoholism.

Nicotinic acid and nicotinamide are used in the treatment and prevention of **nicotinic acid deficiency**. Nicotinamide is preferred as it does not cause vasodilatation. They are usually given orally, the preferred route, but may also be given by the intramuscular route or by slow intravenous injection. Doses of up to 500 mg daily (of either compound) in divided doses have been recommended.

Nicotinic acid has been used for its **vasodilator** action in the treatment of a variety of disorders; its value is not considered to be established.

In high doses, nicotinic acid has beneficial effects on blood lipid profiles, and has been used, with dietary modification and often with other lipid regulating drugs, in **hyperlipidaemias** (see below). For the immediate-release preparations, up to 600 mg daily in 3 divided oral doses has been given initially, gradually increased over 2 to 4 weeks to doses of up to 6 g daily; adverse effects may be a limiting factor. Alternatively, initial doses of 375 or 500 mg at night have been given as a modified-release preparation and gradually increased according to response to a maintenance dose of 1 to 2 g at bedtime. The daily dose should not be increased by more than 500 mg in any 4-week period. A combination preparation containing nicotinic acid with laropiprant, a prostaglandin D_2 antagonist that inhibits nicotinic acid-induced flushing, may also be used.

Topical nicotinamide is used in the treatment of mild to moderate inflammatory **acne** (see below), typically as a 4% gel applied twice daily.

Nicotinamide has been shown to inhibit the destruction of pancreatic beta cells *in vitro* and is therefore being investigated in the prevention and treatment of type 1 **diabetes mellitus** (see below).

Acne. Topical nicotinamide may be used in the treatment of inflammatory acne (p.1577); nicotinamide 4% was as effective as clindamycin 1% when applied topically twice daily for 8 weeks.[1]

1. Shalita AR, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34:** 434–7.

Diabetes mellitus. Nicotinic acid can affect glucose tolerance and should be used with care in established diabetes (see Effects on Glucose Tolerance, above). However, the drug has been used successfully in patients with diabetes. Nicotinamide has been reported to induce remission in patients with newly diagnosed type 1 diabetes mellitus (p.431), and may delay the onset of disease.[1,2]

However, a randomised trial found modified-release nicotinamide at 1.2 g/m^2 daily (to a maximum of 3 g daily) to be ineffective in preventing the onset of diabetes mellitus in first-degree relatives of patients with the disease.[3] Nicotinic acid can also raise high-density lipoprotein (HDL)-cholesterol concentrations (see below);[4,5] changes in glucose tolerance were mild enough for the drug to be considered as an alternative to statins and fibrates in diabetic patients.

1. Elliott RB, Chase HP. Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 1991; **34:** 362–5.
2. Pozzilli P, *et al.* Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996; **19:** 1357–63.
3. European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type I diabetes. *Lancet* 2004; **363:** 925–31.
4. Elam MB, *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *JAMA* 2000; **284:** 1263–70.
5. Grundy SM, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002; **162:** 1568–76.

Hyperlipidaemias. The first-line treatment for hyperlipidaemias remains dietary and lifestyle modification; where this fails, drug therapy may be considered (p.1169). Nicotinic acid is reported to have a favourable effect on blood-lipid profiles, raising high-density lipoprotein (HDL)-cholesterol and lowering low-density lipoprotein (LDL)-cholesterol.[1-3] Nicotinic acid is used particularly in familial hypertriglyceridaemia, or in familial combined hyperlipidaemia when both triglyceride and cholesterol concentrations are similarly elevated. Nicotinic acid was less effective than lovastatin at reducing LDL-cholesterol in patients with primary hypercholesterolaemia, but more effective at increasing HDL-cholesterol; lovastatin was better tolerated.[4] A combination of nicotinic acid with lovastatin was found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, and more effective than either atorvastatin or simvastatin in increasing HDL-cholesterol, in a study of patients with dyslipidaemia.[5] Some have recommended that nicotinic acid be substituted for a statin to lower LDL-cholesterol when patients cannot tolerate a statin.[2] Combination therapy is recommended when the reduction in LDL-cholesterol is insufficient with statin monotherapy,[2,6] or when raising HDL-cholesterol would be beneficial,[7-9] as in patients with type 2 diabetes mellitus, or the metabolic syndrome.[8] The risk of muscle toxicity with this combination is not considered to be significantly different to that with statin monotherapy.[7]

1. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271:** 672–7.
2. McKenney J. Niacin for dyslipidemia: considerations in product selection. *Am J Health-Syst Pharm* 2003; **60:** 995–1005.
3. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* 2005; **65:** 2719–40.
4. Illingworth DR, *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. *Arch Intern Med* 1994; **154:** 1586–95.
5. Bays HE, *et al.* Comparison of once-daily, Niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; **91:** 667–72.
6. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003; **78:** 735–42.
7. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004; **164:** 697–705.
8. Chapman MJ, *et al.* Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; **20:** 1253–68.
9. Yim BT, Chong PH. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. *Ann Pharmacother* 2003; **37:** 106–15.

Pemphigus. Oral treatment with nicotinamide and a tetracycline[1-6] has controlled lesions in pemphigus and pemphigoid (p.1582), including persistent pemphigoid gestationis,[5] and ocular cicatricial pemphigoid.[6]

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132:** 668–70.
2. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133:** 88–90.
3. Reiche L, *et al.* Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; **23:** 254–7.
4. Goon ATJ, *et al.* Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000; **41:** 327–30.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13:** 143–6.
6. Dragan L, *et al.* Tetracycline and niacinamide: treatment alternatives in ocular cicatricial pemphigoid. *Cutis* 1999; **63:** 181–3.

Preparations

BP 2008: Nicotinamide Tablets; Nicotinic Acid Tablets; Vitamins B and C Injection;
BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;
USP 31: Niacin Injection; Niacin Tablets; Niacinamide Injection; Niacinamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: NB-3; Niaspan; Nicozinc; ***Austria:*** Direktan; Nicovitol; ***Belg.:*** Ucemine PP; ***Braz.:*** Papuless; ***Canad.:*** Niaspan; ***Chile:*** Cotina; Niacex; Niaspan; Vectidan†; ***Fin.:*** Niaspan; ***Fr.:*** Niaspan; Nicobion; ***Ger.:*** Niaspan; Nicobion; ***Hong Kong:*** Niaspan; ***India:*** Nialip; ***Indon.:*** Niacef; Niaspan; ***Irl.:*** Niaspan; Nicam; ***Mex.:*** Hipocol; Nacro; Pepevit; ***Neth.:*** Niaspan; ***Philipp.:*** Niaspan; ***Port.:*** Niaspan; ***Singapore:*** Niaspan; ***Swed.:*** Niaspan; Nicangin; ***Thai.:*** Nicotabs; ***UK:*** Freederm; Niaspan; Nicam; ***USA:*** Endur-acin; Niaspan; Nicotinex†; Slo-Niacin; ***Venez.:*** Niaspan.

Multi-ingredient: ***Arg.:*** Antikatarata†; Centella Asiatica Compuesta; IP-6; Nicozinc; Parencias†; ***Austral.:*** Bioglan Cirflo†; Chilblain Formula†; Gingo A†; Prochol†; Silybum Complex†; ***Austria:*** Beneuran Vit B-Komplex†; Diligan; Pertrombon; Spasmocor; ***Belg.:*** Trihistalex; ***Braz.:*** Gaba†; Nicopaverina B6†; Nicopaverina†; ***Canad.:*** PML Crono†; ***Chile:*** Cicapost; Perfungol; Ureadin Forte; Ureadin Rx PS; Ureadin Rx RD; ***Fin.:*** Neurovitan; Vertipam; ***Fr.:*** TTD-B -B ; Vita-Dermacide; ***Ger.:*** Eukalisan N; Hepagrisevit Forte-N†; MerSol†; Peteha†; Telbibur N†; ***Hung.:*** Paniverin; ***India:*** Diligan; Hepa-Merz; Nutrozyme; Sioneuron; Unienzyme; ***Indon.:*** Biocholes; Cereton; Kitoles; Sotens; ***Irl.:*** Effaclar AI; ***Israel:*** Babyzim; ***Ital.:*** Emazian B12†; Emoantitossina†; Emopon; Epargriseovit; Fisioreve; Folepar B12; Fosforilasi; Neuroftal†; Novostatin; Solvobil; Vit-Porphyrin†; ***Mon.:*** Monasens; ***Philipp.:*** Jetepar; ***Pol.:*** Dernilan; ***Port.:*** Diligan†; Ureadin Forte; ***Rus.:*** Lidevine (Лидевин); Oftan Catachrom (Офтан Катахром); ***S.Afr.:*** Cosaldon†; ***Singapore:*** Erase; ***Spain:*** Depurativo Richelet; Euzymina Lisina I; Euzymina Lisina II; Vitaphakol; ***Swed.:*** Theranyl†; ***Thai.:*** B-100 Complex; ***Turk.:*** Epargriseovit; ***UK:*** Crampex; Quiet Life; S.P.H.P.; ***USA:*** Advicor; Simcor.

Olaflur *(BAN, USAN, rINN)*

Amine Fluoride 297; GA-297; Olaflurum; SKF-38095. 2,2′-(3-[*N*-(2-Hydroxyethyl)octadecylamino]propylimino)diethanol dihydrofluoride.

Олафлур

$C_{27}H_{60}F_2N_2O_3$ = 498.8.

CAS — 6818-37-7.

ATC — A01AA03.

ATC Vet — QA01AA03.

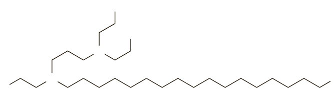

Profile

Olaflur is used as a source of fluoride (see Sodium Fluoride, p.1962) in the prevention of dental caries. For a report of stomatitis considered to be due to olaflur, see Hypersensitivity, under Sodium Fluoride, p.1963.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Elmex†; ***Israel:*** Elmex†; ***Pol.:*** Fluormex; ***Port.:*** Elmex.

Multi-ingredient: ***Austria:*** Elmex; ***Belg.:*** Elmex; ***Cz.:*** Elmex; ***Fin.:*** Elmex; ***Fr.:*** Elmex Sensitive†; Elmex†; Meridol†; ***Ger.:*** Elmex; Lawefluor N†; Multifluorid; ***Hung.:*** Elmex; ***Israel:*** Elmex; Meridol; ***Ital.:*** Elmex; ***Neth.:*** Elmex; ***Pol.:*** Fluormex; ***Switz.:*** Elmex; Paro aux fluorures d'amines Gelee.

Ornithine *(rINN)*

α,δ-Diaminovaleric Acid; Orn; L-Ornithine; Ornithinum; Ornitina. L-2,5-Diaminovaleric acid.

Орнитин

$C_5H_{12}N_2O_2$ = 132.2.

CAS — 70-26-8.

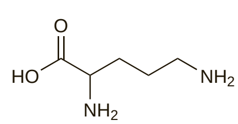

Pharmacopoeias. *Ger.* includes Ornithine Aspartate and Ornithine Hydrochloride.

Profile

Ornithine is an aliphatic non-essential amino acid. It is used as a dietary supplement.

The aspartate, hydrochloride, and oxoglurate (ornithine ketoglutarate, see also Parenteral and Enteral Nutrition under Glutamic Acid, p.1947) have been used in various indications including the treatment of hyperammonaemia (p.1929) and hepatic encephalopathy (p.1697).

◊ References.

1. Rapport L, Lockwood B. Ornithine ketoglutarate. *Pharm J* 2001; **266:** 688–90.
2. Coudray-Lucas C, *et al.* Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med* 2000; **28:** 1772–6.
3. Kircheis G, *et al.* Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002; **17:** 453–62.
4. Blonde-Cynober F, *et al.* Use of ornithine alpha-ketoglutarate in clinical nutrition of elderly patients. *Nutrition* 2003; **19:** 73–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cere; Hepa; Ornicetil; ***Chile:*** Hepa-Merz†; ***Cz.:*** Hepa-Merz†; ***Fr.:*** Cetornan; Ornicetil; ***Ger.:*** Hepa-Merz; Hepa-Merz KT; Hepa-Vibolex; ***Hong Kong:*** Hepa-Merz; ***Hung.:*** Hepa-Merz; ***India:*** Hepa-Merz; ***Indon.:*** Hepa-Merz; Hevtin; ***Ital.:*** Ornicetil†; Ornil; Ornil KGF; ***Mex.:*** Hepa-Merz; ***Philipp.:*** Hepa-Merz; ***Pol.:*** Hepatil.

Multi-ingredient: ***Braz.:*** Ornihepat†; Ornitargin; ***Fr.:*** Epuram†; Ornitaine; ***Ger.:*** Polilevo N†; ***India:*** Biohep†; Hepa-Merz; ***Ital.:*** Ipoazotal Complex; Ipoazotal†; Polilevo†; Somatron; ***Pol.:*** Hepa-Merz.

Pantothenic Acid *(BAN)*

Pantoténico, ácido; Vitamin B_5. (+)-(*R*)-3-(2,4-Dihydroxy-3,3-dimethylbutyramido)propionic acid.

Пантотеновая Кислота; Витамин B5

$C_9H_{17}NO_5$ = 219.2.

CAS — 79-83-4 (D-pantothenic acid); 599-54-2 (DL-pantothenic acid).

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

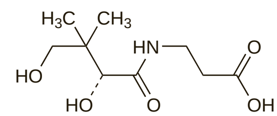

(D-pantothenic acid)

Calcium Pantothenate *(BANM, rINN)*

Calcii pantothenas; Calcium, pantothénate de; Dextro Calcium Pantothenate; Kalcio pantotenatas; Kalciumpantotenat; Kalcium-pantotenát; Kalsiumpantotenaatti; Pantotenato de calcio; Pantothenan vápenatý; Pantothénate de Calcium; Wapnia pantotenian.

Кальция Пантотенат

$(C_9H_{16}NO_5)_2Ca$ = 476.5.

CAS — 137-08-6 (calcium D-pantothenate); 6381-63-1 (calcium DL-pantothenate);.

ATC — A11HA31; D03AX04.

ATC Vet — QA11HA31; QD03AX04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*
US also has a monograph for Racemic Calcium Pantothenate.
Ger. also includes Sodium Pantothenate.

Ph. Eur. 6.2 (Calcium Pantothenate). A white or almost white, slightly hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution has a pH of 6.8 to 8.0. Store in airtight containers.

USP 31 (Calcium Pantothenate). The calcium salt of the dextrorotatory isomer of pantothenic acid. A white, odourless, slightly hygroscopic powder. Soluble 1 in 3 of water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Store in airtight containers.

USP 31 (Racemic Calcium Pantothenate). A mixture of the calcium salts of the dextrorotatory and laevorotatory isomers of pantothenic acid. The physiological activity of Racemic Calcium Pantothenate is about one-half that of Calcium Pantothenate. A white, slightly hygroscopic powder, having a faint characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether; soluble in glycerol. Its solutions are neutral or alkaline to litmus. Store in airtight containers.

Adverse Effects

Pantothenic acid is reported to be generally non-toxic.

Eosinophilia. A report of life-threatening eosinophilic pleuropericarditis associated with the use of biotin and pantothenic acid.[1] Symptoms resolved on stopping the vitamins.

1. Debourdeau PM, *et al.* Life-threatening eosinophilic pleuropericardial effusion related to vitamins B and H. *Ann Pharmacother* 2001; **35:** 424–6.

Pharmacokinetics

Pantothenic acid is readily absorbed from the gastrointestinal tract after oral doses. It is widely distributed in the body tissues and appears in breast milk. About 70% of pantothenic acid is excreted unchanged in the urine and about 30% in the faeces.

Human Requirements

Pantothenic acid is widely distributed in foods. Meat, legumes, and whole grain cereals are particularly rich sources; other good sources include eggs, milk, vegetables, and fruits.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) has been set (see p.1925) for pantothenic acid although an intake of 3 to 7 mg daily for adults was believed to be adequate.[1] Similarly, in the USA a recommended dietary allowance has not been published but an adequate intake for adults was believed to be 5 mg daily, increased to 6 mg in pregnancy and 7 mg during lactation.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Pantothenic acid is traditionally considered to be a vitamin B substance. It is a component of coenzyme A which is essential in the metabolism of carbohydrate, fat, and protein.

Deficiency of pantothenic acid is unlikely in man because of its widespread distribution in food.

Pantothenic acid has no accepted therapeutic uses in human medicine, though it has been given by mouth as a nutritional supplement, often as the calcium salt and usually with other vitamins of the B group.

Preparations

USP 31: Calcium Pantothenate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cidermex; ***Austral.:*** Pantonate; ***Ger.:*** Kerato Biciron; ***Mex.:*** Span Plex; ***Rus.:*** Zorex (Зорекс); ***Switz.:*** Pantothen.

Multi-ingredient: ***Arg.:*** Bifena; Cellskinlab Hydragel B5; Culuflex H; Guarana Diates; Megaplus; Valeriana Relax Diates; ***Austral.:*** Bioglan Zn-A-C; Hair and Skin Formula†; ***Austria:*** Lemuval; ***Belg.:*** Sili-Met-San; ***Braz.:*** Gaba†; Pantevit; Varizol†; ***Chile:*** Foltene Research Anticaspa; Hydrating B5 Gel; Modane; ***Fr.:*** Modane; ***Ger.:*** Azupanthenol†; Carotin; Pantovigar N; Potsilo N; Regepithel; ***Hong Kong:*** Regepithel†; ***India:*** Sioneuron; ***Indon.:*** Proimbus; ***Ital.:*** Esaglut†; Nuleron; Silisan; Vitecaf; ***Malaysia:*** Vitamin C-500 YSP; ***Mex.:*** Espaven; Modaton; ***Spain:*** Calcio 20 Complex; Hubergrip†; Lacerdermol; Lupidon; Pantenil; Pulmofasa; Tri Hachemina; ***Switz.:*** Cortifluid N; Decasept N; Sili-Met-San†.

Phenylalanine *(USAN, rINN)*

α-Aminohydrocinnamic Acid; F; Fenilalanin; Fenilalanina; Fenilalaninas; Fenylalanin; Fenyloalanina; Fenyylialaniini; Phe; Phénylalanine; L-Phenylalanine; Phenylalaninum. L-2-Amino-3-phenylpropionic acid.

Фенилаланин

$C_9H_{11}NO_2$ = 165.2.

CAS — 63-91-2.

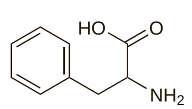

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Phenylalanine). A white or almost white, crystalline powder, or shiny, white flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Phenylalanine). White, odourless crystals. Sparingly soluble in water; very slightly soluble in alcohol, in methyl alcohol, and in dilute mineral acids. pH of a 1% solution in water is between 5.4 and 6.0.

Profile

Phenylalanine is an aromatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Phenylalanine intake should be restricted in patients with phenylketonuria (see Amino Acid Metabolic Disorders, p.1922).

Vitiligo. There is no totally effective treatment for vitiligo (localised hypopigmentation, p.1582). Oral or topical photochemotherapy with psoralens is generally considered to be the best available treatment, but experimental therapy includes UVA phototherapy with phenylalanine. Use of phenylalanine in oral doses of up to 100 mg/kg with UVA/sunlight led to beneficial results in more than 90% of 200 patients with vitiligo.[1] Greatest benefit was noted in early disease, but prolonged use still induced repigmentation in long-standing cases. Repigmentation occurred mainly in areas rich in follicles. Such therapy is contra-indicated in phenylketonuria and in pregnancy.

Similarly a further open study reported responses in 94 of 149 patients receiving 50 to 100 mg/kg daily of phenylalanine plus twice weekly UVA treatment.[2] However, only 22% of responders had repigmentation in more than 60% of the affected area. Higher doses did not seem to be more effective than 50 mg/kg daily. Another group reported on 6 years of experience of treatment of vitiligo using 50 or 100 mg/kg daily of phenylalanine, with application of 10% phenylalanine gel and daily sun exposure.[3] Although not ideal, they considered the treatment useful, especially for its ability to rapidly repigment the face. The same group performed an open study, adding topical 0.025% clobetasol propionate, and ultraviolet exposure during autumn and winter; 65.5% of patients achieved 100% repigmentation on the face.[4]

1. Cormane RH, *et al.* Treatment of vitiligo with -phenylalanine and light. *Br J Dermatol* 1986; **115:** 587.
2. Siddiqui AH, *et al.* L-Phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology* 1994; **188:** 215–18.
3. Camacho F, Mazuecos J. Treatment of vitiligo with oral and topical phenylalanine: 6 years of experience. *Arch Dermatol* 1999; **135:** 216–17.
4. Camacho F, Mazuecos J. Oral and topical L-phenylalanine, clobetasol propionate, and UVA/sunlight - a new study for the treatment of vitiligo. *J Drugs Dermatol* 2002; **2:** 127–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** KLB6 Fruit Diet; ***Fr.:*** Revitalose.

Polysaccharide-Iron Complex

Polisacárido hierro, complejo.

Profile

Polysaccharide-iron complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses containing the equivalent of up to 300 mg of iron daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Ferricure; ***Chile:*** Niferex†; ***Hong Kong:*** Niferex; ***Norw.:*** Niferex; ***Pol.:*** Venofer; ***UK:*** Niferex; ***USA:*** Fe-Tinic; Ferrex; Ferrex Plus; Hytinic†; Niferex; Nu-Iron†; Poly-Iron.

Multi-ingredient: ***USA:*** Fe-Tinic Forte; Ferrex Forte; Ferrex Forte Plus†; Ferrex PC; Hemocyte-F; Niferex Forte; Nu-Iron V; Poly-Iron Forte; Tandem.

Proline *(USAN, rINN)*

P; Pro; Proliini; Prolin; Prolina; Prolinas; L-Proline; Prolinum. L-Pyrrolidine-2-carboxylic acid.

Пролин

$C_5H_9NO_2$ = 115.1.

CAS — 147-85-3.

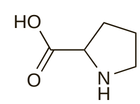

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Proline). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Proline). White, odourless crystals. Freely soluble in water and in dehydrated alcohol; insoluble in butyl alcohol, in ether, and in isopropyl alcohol.

Profile

Proline is a cyclic non-essential amino acid. It is used as a dietary supplement.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Port.:*** Creme Laser Hidrante.

Saccharin

Benzoic Acid Sulphimide; Benzoic Sulfimide; Benzosulphimide; E954; Gluside; Sacarina; Saccarina; Saccharine; Saccharinum; Sacharin; Sacharinas; Sacharyna; Sackarin; Sakkariini; *o*-Sulfobenzimide; Szacharin; Zaharina. 1,2-Benzisothiazolin-3-one 1,1-dioxide.

$C_7H_5NO_3S$ = 183.2.

CAS — 81-07-2.

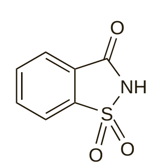

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*. Also in *USNF.*

Ph. Eur. 6.2 (Saccharin). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in cold water; sparingly soluble in boiling water and in alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. A saturated solution, prepared without heating, is acid to litmus.

USNF 26 (Saccharin). White crystals or white, crystalline powder. Is odourless or has a faint, aromatic odour. In dilute solutions, it is intensely sweet. Soluble 1 in 290 of water, 1 in 25 of boiling water, and 1 in 31 of alcohol; slightly soluble in chloroform and in ether; is readily dissolved by dilute solutions of ammonia, by solutions of alkali hydroxides, and by solutions of alkali carbonates with the evolution of carbon dioxide. Its solutions are acid to litmus.

Saccharin Calcium

Calcium Benzosulphimide; Calcium Saccharin; E954; Sacarina cálcica; Saccharine calcique; Saccharinum calcicum.

$C_{14}H_8CaN_2O_6S_2,3\frac{1}{2}H_2O$ = 467.5.

CAS — 6485-34-3 (anhydrous saccharin calcium); 6381-91-5 (hydrated saccharin calcium).

Pharmacopoeias. In *US.*

USP 31 (Saccharin Calcium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. Soluble 1 in 2.6 of water and 1 in 4.7 of alcohol.

Saccharin Potassium

E954; Potassium Benzosulphimide; Potassium Saccharin.

$C_7H_5NO_3SK$ = 222.3.

CAS — 10332-51-1.

Saccharin Sodium

E954; Sacarina sódica; Saccharin Sod.; Saccharine sodique; Saccharinnatrium; Saccharinum natricum; Saccharoidum Natricum; Sacharin sodná sůl; Sacharino natrio druska; Sacharyna sodowa; Sackarinnatrium; Sakkariininatrium; Sodium Benzosulphimide; Sodium Saccharin; Soluble Gluside; Soluble Saccharin; Szacharin-nátrium.

$C_7H_4NNaO_3S$ = 205.2.

CAS — 128-44-9 (anhydrous saccharin sodium); 6155-57-3 (saccharin sodium dihydrate).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.* Some pharmacopoeias specify the dihydrate but it may contain a variable quantity of water as a result of efflorescence.

Ph. Eur. 6.2 (Saccharin Sodium). A white or almost white, crystalline powder or colourless crystals. It may contain a variable quantity of water. Efflorescent in dry air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

USP 31 (Saccharin Sodium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. When in powdered form, it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence. Soluble 1 in 1.5 of water and 1 in 50 of alcohol.

Adverse Effects

There have been rare reports of hypersensitivity and photosensitivity reactions with saccharin.

Saccharin-associated bladder tumours in *rats* given high doses have been the cause of much concern and investigation. However, it is now generally accepted that these findings are not relevant to the use of saccharin as a sweetener in man.

Effects on the liver. Elevated liver enzyme values in an elderly woman followed use of two different medications sweetened with saccharin sodium.[1] Findings resolved on stopping all preparations containing saccharin, and recurred on rechallenge with a small amount of saccharin sodium.

1. Negro F, *et al.* Hepatotoxicity of saccharin. *N Engl J Med* 1994; **331:** 134–5.

Pharmacokinetics

Saccharin is readily absorbed from the gastrointestinal tract. It is almost all excreted unchanged in the urine within 24 to 48 hours.

Uses and Administration

Saccharin and its salts are intense sweeteners, a dilute solution having about 300 times the sweetening power of sucrose. They are used in pharmaceuticals and in foods and beverages and are heat stable. They have no food value. The salts are more often used than saccharin itself as they are considered to be more palatable.

Preparations

USP 31: Saccharin Sodium Oral Solution; Saccharin Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Dul-Suc; Sukar-Sin; ***Fr.:*** Sucredulcor†; ***NZ:*** Sactabs; ***Turk.:*** Hermesetas; ***Venez.:*** Hermesetas.

Multi-ingredient: ***Arg.:*** Chuker; Rondo; Semble; Sucaryl; Suimel; ***Austral.:*** Sucaryl; ***Braz.:*** Finn Cristal; ***Chile:*** Sucaryl†; Sukar-Sin; ***Fr.:*** Sucaryl; ***Israel:*** Sucrin; ***Ital.:*** Diet Sucaryl; ***NZ:*** Sucaryl; ***Port.:*** Dulceril†; ***Rus.:*** Zuckli (Цюкли); ***Turk.:*** Dolce.

Safflower Oil

Aceite de alazor; Aceite de cártamo; Carthame (huile de) raffinée; Carthami oleum raffinatum; Dygminų aliejus, rafinuotas; Safflorolja, raffinerad; Saflorioljy, puhdistettu; Světlicový olej čištěný.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Chin., Eur. (see p.vii), and *Jpn* include Safflower, the flower of *Carthamus tinctorius.*

Ph. Eur. 6.2 (Safflower Flower; Carthami Flos). Dried flower of

Carthamus tinctorius. It contains not less than 1% of total flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Safflower Oil, Refined). The fatty oil obtained from seeds of *Carthamus tinctorius* (type I) or from seeds of hybrids of *C. tinctorius* (type II), by expression and/or extraction followed by refining. Type II refined safflower oil is rich in oleic acid. It may contain a suitable antioxidant. A clear, viscous, yellow to pale yellow liquid. Relative density about 0.922 (type I) and about 0.914 (type II). Practically insoluble in alcohol; miscible with petroleum spirit (b.p.: 40° to 60°). Store in well-filled airtight containers. Protect from light.

USP 31 (Safflower Oil). The refined fixed oil yielded from the seed of *Carthamus tinctorius* (Compositae). A light yellow oil. It thickens and becomes rancid on prolonged exposure to air. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Safflower oil is the refined fixed oil obtained from the seeds of the safflower, or false (bastard) saffron, *Carthamus tinctorius* (Compositae). It contains about 75% of linoleic acid as well as various saturated fatty acids.

Safflower oil has similar actions and uses to those of soya oil, p.1965. Emulsions containing a mixture of safflower oil 5% and soya oil 5%, or 10% and 10% respectively, are given as part of total parenteral nutrition regimens.

Adverse effects. For reference to the association of safflower oil-based emulsion, as part of a parenteral nutrition regimen, with the development of sinus bradycardia, see Effects on the Cardiovascular System, under Soya Oil, p.1966.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lipidos†.

Multi-ingredient: ***Canad.:*** Microlipid; ***Chile:*** Liposyn†; ***Denm.:*** Liposyn†; ***Fin.:*** Liposyn†; ***Ger.:*** Abbolipid†; ***Israel:*** Liposyn; ***Ital.:*** Liposyn†; ***Mex.:*** Liposyn; ***Swed.:*** Liposyn†; ***Switz.:*** A Vogel Capsules polyvitaminees†; ***Turk.:*** Liposyn; ***USA:*** Liposyn II; Microlipid.

Selenium

Selen; Selenio; Sélénium.
Se = 78.96.

Selenious Acid

Kwas selenawy; Selenioso, ácido. Monohydrated selenium dioxide .
H_2SeO_3 = 129.0.
CAS — 7783-00-8.

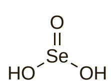

Pharmacopoeias. In *US.*

USP 31 (Selenious Acid). Store in airtight containers.

Potassium Selenate

Selenato potásico.
K_2SeO_4 = 221.2.
CAS — 7790-59-2.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Potassium Selenate). Colourless crystals or a white crystalline powder. Freely soluble in water.

Sodium Selenate

Disodium Selenate; Natriumseleniat; NSC-378348; Selenato sódico; Sodium Selenium Oxide.
Na_2SeO_4 = 188.9.
CAS — 13410-01-0.
ATC — A12CE01.
ATC Vet — QA12CE01.

Sodium Selenite

Natrii selenis pentahydricus; Natrio selenitas pentahidratas; Natriumseleniittipentahydraatti; Natriumselenitpentahydrat; Seleničitan sodný pentahydrát; Selenito sódico; Sodium (sélénite de) pentahydraté; Sodu selenin pięciowodny; Sodyum Selenit.
$Na_2SeO_3,5H_2O$ = 263.0.
CAS — 10102-18-8.
ATC — A12CE02.
ATC Vet — QA12CE02.

Pharmacopoeias. In *Eur.* (see p.vii). *BP(Vet)* includes anhydrous sodium selenite.

Ph. Eur. 6.2 (Sodium Selenite Pentahydrate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP(Vet) 2008 (Sodium Selenite). A white to slightly greyish pink granular powder. Freely soluble in water; practically insoluble in alcohol and ether.

Adverse Effects

Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, metallic taste, garlic odour of breath, irritability, fatigue, and peripheral neuropathy.

Effects on mortality. A systematic review[1] of the effect of antoxidant supplements on mortality in randomised primary and secondary prevention studies considered that selenium had no significant effect on mortality, either beneficial or harmful; however, it was recommended that future studies should be monitored closely for harm.

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Toxicity. *Chronic* exposure to high amounts of selenium has been reported to cause toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis. There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis. Studies have had conflicting results, and different inorganic and organic forms may vary greatly in biological activity, toxicity, and nutritional importance.[1]

Acute toxicity has also been reported; characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death.[1-3] A man who had taken vitamin tablets containing between 500 and 1000 times the amount of selenium labelled on the bottle developed generalised alopecia, changes in nail colour, diarrhoea, worsening fatigue, and paraesthesias. Two weeks after stopping the vitamins, early regrowth of hair and yellowish-white and red transverse lines on his nails were noted.[2] In another case, an elderly man who was concerned that he might have prostate cancer ingested 10 g of sodium selenite. He developed significant abdominal pain, vomiting and diarrhoea, hypotension, and ventricular tachycardia. Blood tests showed acidosis, hypokalaemia and an excessive selenium concentration. Despite symptomatic therapy, he suffered a cardiac arrest and died.[3]

1. Vinceti M, *et al.* Adverse health effects of selenium in humans. *Rev Environ Health* 2001; **16:** 233–51.
2. Clark RF, *et al.* Selenium poisoning from a nutritional supplement. *JAMA* 1996; **275:** 1087–8.
3. See KA, *et al.* Accidental death from acute selenium poisoning. *Med J Aust* 2006; **185:** 388–9.

Pharmacokinetics

Selenium compounds are generally readily absorbed from the gastrointestinal tract. Selenium is stored in red blood cells, the liver, spleen, heart, and nails. It is converted in tissues to its metabolically active forms. Selenium is excreted in the urine, and to a lesser extent in the faeces.

Uses and Administration

Selenium is an essential trace element. It is an integral part of the enzyme system glutathione peroxidase, which protects intracellular structures against oxidative damage. Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease, seen in certain areas of China. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy, which causes a severe deformity of the joints. Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine and derivatives.

Selenious acid and its sodium salt, sodium selenite, are used as a source of selenium, especially for patients with deficiency states after prolonged parenteral nutrition. Suggested doses for addition to total parenteral nutrition are 31.5 micrograms elemental selenium daily for adults and children greater than 40 kg, and 2 micrograms/kg daily for infants and children to a maximum of 30 micrograms daily. Sodium selenate has also been used.

For proven selenium deficiency that cannot be offset from food sources, selenium may be given orally, or by intramuscular or intravenous injection, usually in the form of sodium selenite pentahydrate, to provide doses of about 100 to 200 micrograms selenium daily; if necessary this can be increased to 500 micrograms daily.

Selenate and selenite salts are used for selenium deficiency states in veterinary medicine.

Action. References.

1. Rayman MP. The importance of selenium to human health. *Lancet* 2000; **356:** 233–41.

Administration in neonates. The low selenium plasma concentrations in preterm neonates have been suggested to be a potential risk factor for neonatal respiratory disorders and retinopathy of prematurity. A systematic review[1] found that supplementation with selenium did not reduce the incidence of these complications, nor is it associated with improved survival. However, it is associated with benefit in terms of reduction in the number of episodes of late-onset sepsis in very preterm infants. There was evidence that recommended doses in this group might be inadequate for some populations.

1. Darlow BA, Austin NC. Selenium supplementation to prevent short-term morbidity in preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 10/11/05).

HIV infection and AIDS. A randomised controlled study found that oral supplementation with selenium 200 micrograms daily for 9 months suppressed the progression in HIV-1 viral load and provided indirect improvement of the CD4 count.[1] For a study reporting increased CD4 and CD8 counts, but increased genital HIV-1 shedding with multivitamin plus selenium supplementation, see HIV Infection and AIDS, p.1926.

1. Hurwitz BE, *et al.* Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. *Arch Intern Med* 2007; **167:** 148–54.

Human requirements. In the UK dietary reference values (see p.1925)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for selenium.

In the UK the reference nutrient intake for adults is 75 and 60 micrograms daily for men and women respectively; values are also given for infants and children of varying ages and for lactating women. The UK report also noted that there was no convincing evidence that high intakes protected against cancer or cardiovascular disease; indeed, there was even some evidence that high intakes disturbed selenium homoeostasis and it was recommended that the maximum safe intake from all sources should be set at 450 micrograms daily for adult males. The Expert Group on Vitamins and Minerals[3] have since established a safe upper level (SUL) for selenium of 450 micrograms daily.

In the USA, the RDA for adult males and females is 55 micrograms daily, and again values are also given for infants and children as well as pregnant and lactating women. The tolerable upper intake level is 400 micrograms daily.[2]

WHO have recommended a lower limit of the safe range of population mean intakes of dietary selenium of 40 micrograms daily for adult males and 30 micrograms daily for adult females.[4] A maximum daily safe dietary selenium intake of 400 micrograms was suggested for adults.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 10/11/05)
4. WHO. Selenium. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 105–22.

Prophylaxis of malignant neoplasms. Selenium supplementation did not protect against the development of new basal or squamous cell carcinomas of the skin in a study of patients with a history of these cancers.[1] Further follow-up data[2] showed a statistically significant increased risk of squamous cell carcinoma and of total non-melanoma skin cancer with selenium supplementation. However, analysis of secondary end-points at the first report indicated a reduced incidence of various other cancers in this study group.[1]

Subsequent study has suggested, in particular, an association between low selenium intake and the risk of prostate cancer; incidence was reduced by 63% in patients receiving the supplement.[3] Further follow-up confirmed this inverse association, but found that only men with low baseline selenium concentrations were likely to benefit.[4] Another group has also reported an inverse correlation between surrogate measurements of long-term selenium intake and the risk of advanced prostate cancer.[5] A case-control study[6] found an inverse association between pre-diagnostic plasma selenium concentrations and the subsequent risk of advanced prostate cancer, but not of localised prostate cancer. Higher pre-diagnostic selenium levels were associated with a lower risk of prostate cancer only for subjects with increased baseline prostate-specific antigen (PSA) concentrations (above 4 nanograms/mL). The authors hypothesised that selenium may influence tumour progression. Trials of selenium supplementation with prostate cancer detection as primary end-points are ongoing.

Similarly, an inverse association between selenium concentrations and the risk of bladder cancer has been reported, although results from case-control studies are inconsistent. Controlled studies investigating the effect of selenium on bladder cancer recurrence and prognosis are planned.[7]

For a finding that selenium supplementation had no beneficial effect on overall mortality, see Effects on Mortality, above.

1. Clark LC, *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996; **276:** 1957–63. Correction. *ibid.* 1997; **277:** 1520.
2. Duffield-Lillico AJ, *et al.* Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1477–81.
3. Clark LC, *et al.* Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998; **81:** 730–4.
4. Duffield-Lillico AJ, *et al.* Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* 2003; **91:** 608–12.

5. Yoshizawa K, *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; **90:** 1219–24.
6. Li H, *et al.* A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004; **96:** 696–703.
7. Brinkman M, *et al.* Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006; **7:** 766–74.

Preparations

USP 31: Selenious Acid Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Selebound; ***Austria:*** Selen; Selenase; ***Cz.:*** Selenase; ***Fr.:*** Plexium; Selenion; ***Ger.:*** Cefasel; Seleject; Selemun†; Selen-loges; Selenase; Seltrans; ***Hong Kong:*** Selepen; ***Mex.:*** Selefusin†; ***Neth.:*** Selenase; ***Pol.:*** Cerosel; ***Port.:*** Selenase; ***Switz.:*** Selenase; ***Turk.:*** Selenase; ***UK:*** Selenase; ***USA:*** Sele-Pak; Selepen.

Multi-ingredient: ***Arg.:*** Centella Asiatica Compuesta; ***Canad.:*** Selenium Plus; ***Chile:*** Natursel-C; ***Fr.:*** Bio-Selenium; Phytosolaire; Selenium-ACE; ***Indon.:*** Ekinase; Imulan; Stacare; ***Irl.:*** Antox; ***Ital.:*** Fosfarsile Forte; Influ-Zinc; Longevital; Neomyrt Plus; Selenium-ACE; Tannidin Plus; ***Port.:*** Rilastil Dermo Solar; Selenium-ACE†; ***Thai.:*** Bio-Selenium Zinc; ***UK:*** Se-Power; Selene-Activ; ***Venez.:*** Kalsis.

Serine *(USAN, rINN)*

β-Hydroxyalanine; S; Ser; Seriini; Serin; Serina; Serinas; Sérine; L-Serine; Serinum; Seryna; Szerin. L-2-Amino-3-hydroxypropionic acid.

Серин

$C_3H_7NO_3$ = 105.1.
CAS — 56-45-1 (serine); 302-84-1 (DL-serine).

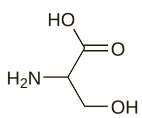

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Serine). White or almost white crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. Protect from light.
USP 31 (Serine). White, odourless crystals. Soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Serine is a non-essential amino acid. It is used as a dietary supplement.

The racemic form (DL-serine) has been included in iron supplements to increase iron absorption.

Preparations

Proprietary Preparations (details are given in Part 3)
Used as an adjunct in: ***Austria:*** Aktiferrin; Aktiferrin Compositum; ***Cz.:*** Aktiferrin; Aktiferrin Compositum; ***Hung.:*** Aktiferrin; ***Israel:*** Aktiferrin-F; ***Malaysia:*** Aktiferrin-F; ***Rus.:*** Aktiferrin (Актиферрин); Aktiferrin Compositum (Актиферрин Композитум); ***Singapore:*** Aktiferrin-F; ***Switz.:*** Actiferrine; Actiferrine-F Nouvelle formule.

Sodium Feredetate *(BAN, rINN)*

Ferédétate de Sodium; Feredetato sódico; Natrii Feredetas; Sodium Ironedetate. The monohydrated iron chelate of the monosodium salt of ethylenediamine-*NNN′N′*-tetra-acetic acid; Iron (III) sodium ethylenediaminetetra-acetate monohydrate.

Натрия Фередетат

$C_{10}H_{12}FeN_2NaO_8,H_2O$ = 385.1.
CAS — 15708-41-5 (anhydrous sodium feredetate).
ATC — B03AB03.
ATC Vet — QB03AB03.

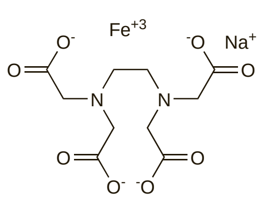

(anhydrous sodium feredetate)

Pharmacopoeias. In *Br.*
BP 2008 (Sodium Feredetate). A yellow or yellowish brown, hygroscopic, crystalline powder. A 1% solution in water has a pH of 4.0 to 6.5. Store in airtight containers.

Profile

Sodium feredetate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.42 g daily (equivalent to up to about 205 mg of iron daily).

Preparations

BP 2008: Sodium Feredetate Oral Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Ferrostrane; ***Philipp.:*** Ferrosmate; ***UK:*** Sytron.

Sodium Ferric Gluconate Complex *(USAN)*

Ferric Sodium Gluconate; D-Gluconic acid, iron (3+) sodium salt; Hierro gluconato sódico, complejo de; Iron Gluconate; Natrii ferrigluconas; Sodium Ferric Gluconate; Sodium ferrigluconate; Sodium-Iron(III) Gluconate Complex.

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_x$.
CAS — 34089-81-1.
ATC Vet — QB03AC07.

NOTE. Distinguish from Ferrous Gluconate.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p.1951.

Hypersensitivity. For a discussion as to whether sodium ferric gluconate complex may be a safer alternative to iron dextran, see p.1952.

Pharmacokinetics

Peak concentrations vary with the dose and rate at which sodium ferric gluconate complex is given. The volume of distribution does not appear to vary according to dose or rate. Elimination half-life varies by dose, and has been reported to be 0.85 hours for a dose of 62.5 mg and 1.45 hours for a dose of 125 mg; doses were given by slow intravenous injection.

Uses and Administration

Sodium ferric gluconate complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. The recommended dose for haemodialysis patients who are receiving epoetin therapy is 125 mg iron (10 mL) diluted in 100 mL sodium chloride 0.9%, and given as an intravenous infusion over 1 hour; it may also be given undiluted as a slow intravenous injection (at a rate of 12.5 mg/minute) during dialysis. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response. Children 6 years of age and older may be given 1.5 mg/kg of elemental iron (0.12 mL/kg), diluted in 25 mL sodium chloride 0.9% and infused over 1 hour, up to a maximum of 125 mg per dose.

Anaemia of chronic renal failure. References.

1. Yorgin PD, *et al.* Sodium ferric gluconate therapy in renal transplant and renal failure patients. *Pediatr Nephrol* 2000; **15:** 171–5.
2. Fishbane S, Wagner J. Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 2001; **37:** 879–83.
3. Folkert VW, *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; **41:** 651–7.
4. Michael B, *et al.* Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; **19:** 1576–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Pentaferr; ***Cz.:*** Ferrlecit; ***Ger.:*** Ferrlecit; ***Hung.:*** Ferrlecit; ***India:*** Efecient; ***Israel:*** Ferrlecit; ***Ital.:*** Actiferro†; Epaplex 40†; Extrafer; Ferlixit; Ferri-Emina†; Ferritin Oti; Ferrosprint; Fevital Simplex†; Hemocromo; Inferil†; Rossepar; Rubroferrina†; Sanifer; ***USA:*** Ferrlecit.

Multi-ingredient: ***Ital.:*** Ferritin Complex; ***Port.:*** Ferritin Oti.

Sodium Fluoride

Fluorid sodný; Fluoruro sódico; Natrii fluoridum; Natrio fluoridas; Natrium Fluoratum; Natriumfluorid; Nátrium-fluorid; Natriumfluoridi; Sodium, fluorure de; Sodu fluorek; Sodyum Fluorür.

NaF = 41.99.
CAS — 7681-49-4.
ATC — A01AA01; A12CD01.
ATC Vet — QA01AA01; QA12CD01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Sodium Fluoride). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol.
USP 31 (Sodium Fluoride). A white, odourless powder. Soluble 1 in 25 of water; insoluble in alcohol.

Adverse Effects and Treatment

In the controlled amounts recommended for fluoridation of drinking water and at the recommended doses used in dentistry for caries prophylaxis, sodium fluoride has not been shown to have significant adverse effects.

In **acute** poisoning, sodium fluoride taken by mouth is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastrointestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcaemia, hypomagnesaemia, hyperkalaemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Death may occur within 2 to 4 hours. Although there is much interindividual variation, a single oral dose of 5 to 10 g of sodium fluoride would be considered lethal in an untreated adult by most authorities. However, severe poisoning has been reported after oral doses of less than 1 g, and the minimum dose that can cause possibly fatal toxicity in children has been suggested to be 5 mg/kg of fluoride ion.

Treatment of acute poisoning involves gastric lavage with lime water or a weak solution of another calcium salt to precipitate fluoride, maintenance of high urine output, slow intravenous injections of calcium gluconate 10% for hypocalcaemia and tetany, and symptomatic and supportive measures. Magnesium sulfate may be given to correct hypomagnesaemia, and aluminium hydroxide may also reduce fluoride absorption. Haemodialysis may be considered.

Chronic fluoride poisoning may result in skeletal fluorosis, manifestations of which include increased density and coarsened trabeculation of bone and calcification in ligaments, tendons, and muscle insertions. Clinical signs are bone pain, stiffness, limited movement, and in severe cases, crippling deformities. Prolonged excessive intake by children during the period of tooth development before eruption can result in dental fluorosis characterised by mottled enamel. At fluoride concentrations in drinking water of 1 to 2 ppm (1 to 2 mg/litre) dental fluorosis is mild with white opaque flecks on the teeth. At higher concentrations, enamel defects become more severe with brown to black staining and the teeth have a pitted corroded appearance.

The **fluoridation** of water (below) has been a subject of considerable controversy. Suggestions that it increases the incidence of thyroid disorders, chromosome aberrations, and cancer have not been substantiated.

◊ Reviews of the toxic effects of fluoride salts.

1. WHO. Fluorine and Fluorides. *Environmental Health Criteria 36*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc36.htm (accessed 08/11/05)
2. Whitford GM. The physiological and toxicological characteristics of fluoride. *J Dent Res* 1990; **69** (Spec Iss): 539–49.
3. Whitford GM. The metabolism and toxicity of fluoride. *Monogr Oral Sci* 1996; **16:** 1–153.
4. WHO. Fluorides. *Environmental Health Criteria 227*. Geneva: WHO, 2002. Available at: http://www.inchem.org/documents/ehc/ehc/ehc227.htm (accessed 08/11/05)

Carcinogenicity. Based on comparisons of cancer mortality rates for communities residing in fluoridated and non-fluoridated cities, it was alleged that artificial fluoridation of water might be associated with an increased risk of cancer.[1] Re-examination of these data by others did not confirm the relationship, nor did further studies in a number of countries.[2] In Great Britain, the Working Party on Fluoridation of Water and Cancer[3] found nothing that could lead them to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, was capable of inducing cancer, or of increasing the mortality from cancer. In this respect, fluoridation of drinking water was considered safe. Further study in *animal* models by the USA National Toxicology Programme[4] found no evidence of carcinogenicity in female *rats* or in *mice* of either sex. A small number of osteosarcomas was found in male *rats* in the medium- and high-dose groups, although the association between sodium fluoride and the tumour was uncertain. A review of epidemiological evidence of possible carcinogens in drinking water stated that additional data gathered since 1990 did not support an association between the risk of osteosarcoma, or any other cancer, and the fluoride in drinking water.[5]

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumours.[6]

1. Yiamouyiannis J, Burk D. Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977; **10**: 102–25S.
2. Clemmesen J. The alleged association between artificial fluoridation of water supplies and cancer: a review. *Bull WHO* 1983; **61:** 871–83.

3. DHSS. *Fluoridation of water and cancer: a review of the epidemiological evidence: report of the working party.* London: HMSO, 1985.
4. Public Health Service report on fluoride benefits and risks. *JAMA* 1991; **266:** 1061–2, 1066–7.
5. Cantor KP. Drinking water and cancer. *Cancer Causes Control* 1997; **8:** 292–308.
6. Grandjean P, Olsen JH. Extended follow-up of cancer incidence in fluoride-exposed workers. *J Natl Cancer Inst* 2004; **96:** 802–3.

Effects on bones and joints. Exacerbation of **rheumatoid arthritis** in a 68-year-old woman was attributed to sodium fluoride given in a dose equivalent to 22 mg of fluorine daily for osteoporosis.[1]

An increased risk of **hip fracture** in the elderly has been suggested as being associated with fluoridated water;[2] another study[3] reported that this association was confined to fluoride concentrations of more than 110 micrograms/litre. However, a large case-control study[4] found no increase in the risk of hip fracture for people ingesting fluoridated water at concentrations of about 1 mg/litre (1 ppm). Similarly, a large prospective study[5] in older white women found no increase in the risk of fractures with long-term exposure to fluoridated drinking water, and even a suggestion of a reduction in the risk of fractures of the hip and vertebrae, due to increased bone mineral density of the femoral neck and lumbar spine, in those women continuously exposed to fluoridation. An epidemiological study in a large rural Chinese population determined that long-term fluoride exposure from drinking water containing 4.32 ppm or more increased the risk of overall fracture as well as hip fracture. Water containing 1 to 1.06 ppm decreased the risk of overall fractures relative to areas with negligible water fluoridation; a similar protective effect on the risk of hip fractures was not seen. Although the number of hip fractures were small, the authors suggested that this supported other findings that fluoride concentrations of about 1 ppm in drinking water do not increase the risk of hip fracture.[6] For comment on the influence of therapeutic doses of fluoride on the incidence of fractures, see below under Osteoporosis in Uses and Administration.

Use of fluoride, particularly in doses of 40 mg or more daily, may be associated with a **peripheral pain syndrome**, usually manifested as bone pain in the distal lower limbs, but sometimes involving the upper limbs and axial skeleton. The cause is uncertain: both stress fractures and increased bone growth at the site of pain have been proposed.[7]

Fluoride-related **bone disease** (skeletal fluorosis) manifesting as osteomalacia or osteosclerosis, has been reported after excessive consumption of tea (brewed, bottled, or iced).[8,9] Some bottled teas were found to have fluoride concentrations above the FDA's limit of 2.4 ppm for bottled beverages.[9]

1. Duell PB, Chesnut CH. Exacerbation of rheumatoid arthritis by sodium fluoride treatment of osteoporosis. *Arch Intern Med* 1991; **151:** 783–4.
2. Danielson C, *et al.* Hip fractures and fluoridation in Utah's elderly population. *JAMA* 1992; **268**: 746–8.
3. Jacqmin-Gadda H, *et al.* Fluorine concentration in drinking water and fractures in the elderly. *JAMA* 1995; **273:** 775–6.
4. Hillier S, *et al.* Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet* 2000; **355:** 265–9.
5. Phipps KR, *et al.* Community water fluoridation, bone mineral density, and fractures: prospective study of effects in older women. *BMJ* 2000; **321:** 860–4.
6. Li Y, *et al.* Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *J Bone Miner Res* 2001; **16:** 932–9.
7. Jones G, Sambrook PN. Drug-induced disorders of bone metabolism: incidence, management and avoidance. *Drug Safety* 1994; **10:** 480–9.
8. Hallanger Johnson JE, *et al.* Fluoride-related bone disease associated with habitual tea consumption. *Mayo Clin Proc* 2007; **82:** 719–24. Correction. *ibid.*; 1017. [dosage error]
9. Whyte MP. Fluoride levels in bottled teas. *Am J Med* 2006; **119:** 189–90.

Effects on the kidneys. Nephrotoxicity has been associated with high plasma concentrations of fluoride during anaesthesia with fluorine-containing anaesthetics such as methoxyflurane (p.1789). Elevated fluoride ion concentrations have also been noted in the plasma of patients receiving enflurane or isoflurane, although no clinical effect on renal function was found (see Effects on the Kidneys, p.1782 and Metabolism, p.1786).

Fluorosis. Discussions of chronic fluorosis.[1-5] In a 1994 report, WHO considered that in temperate climates, *teeth* seemed not to be affected if fluoride concentrations in drinking water were not greatly above 1 ppm; fluorosis affecting bone had not been detected at concentrations of 4 to 8 ppm in temperate regions, although it could occur at concentrations of more than 6 ppm in tropical areas.[6] However, a later systematic review[7] of the effects of water fluoridation, which included 214 studies worldwide, considered that at a concentration of 1 ppm, an estimated 12.5% of exposed people would develop sufficient fluorosis of their teeth to cause aesthetic concern. Swallowing of fluoridated toothpaste by young children has been implicated as a risk factor for fluorosis.[4,8] Higher concentrations of fluoride in toothpaste have been associated with less caries, but with higher levels of fluorosis,[9] and toothpastes with lower concentrations of fluoride have been recommended for use in children.[8,9] The use of infant formula feeds reconstituted with fluoridated water may result in ingestion of large amounts of fluoride[5] and subsequent fluorosis;[3] bottled water may also contain fluoride.[5]

Skeletal fluorosis associated with excess tea consumption has also been reported (see Effects on Bones and Joints, above).

1. Anonymous. Chronic fluorosis. *BMJ* 1981; **282:** 253–4.
2. Mason JO. A message to health professionals about fluorosis. *JAMA* 1991; **265**: 2939.
3. Horowitz HS. Proper use of fluoride products in fluoridated communities. *Lancet* 1999; **353:** 1462.
4. Whelton HP, *et al.* A review of fluorosis in the European Union: prevalence, risk factors and aesthetic issues. *Community Dent Oral Epidemiol* 2004; **32** (suppl): 9–18.
5. Levy SM. An update on fluorides and fluorosis. *J Can Dent Assoc* 2003; **69:** 286–91.
6. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994.
7. McDonagh MS, *et al.* Systematic review of water fluoridation. *BMJ* 2000; **321:** 855–9.
8. Rock WP, Sabieha AM. The relationship between reported toothpaste usage in infancy and fluorosis of permanent incisors. *Br Dent J* 1997; **183:** 165–70.
9. Steiner M, *et al.* Effect of 1000 ppm relative to 250 ppm fluoride toothpaste: a meta-analysis. *Am J Dent* 2004; **17:** 85–8.

Gum disease. In the Davangere district of India, the fluoride concentration in the drinking water ranges from 1.5 to 3 ppm; there is virtually no dental care. In a study of patients with dental fluorosis in this district, a strong association was found between the occurrence of periodontal disease and the severity of fluorosis; periodontitis was also high in subjects with poor oral hygiene. Gingivitis reduced as the degree of fluorosis increased. Fluoride may have a role in the etiology and pathogenesis of gum disease.[1]

1. Vandana KL, Reddy MS. Assessment of periodontal status in dental fluorosis subjects using community periodontal index of treatment needs. *Indian J Dent Res* 2007; **18:** 67–71.

Hypersensitivity. Dermatitis, urticaria, headaches, gastrointestinal reactions, stomatitis, and mouth ulcers have all been reported as hypersensitivity reactions after use of fluoride-containing toothpastes, tablets, drops or drinking water.[1] Topical treatment of the teeth with a sodium fluoride preparation has been reported to cause severe disseminated acute urticaria and facial angioedema, requiring hospitalisation.[2] However, 2 other cases of reaction to the same commercial preparation were considered to be due to colophony (p.2286) contained in the preparation.[3] It has been suggested that, in cases of probable toothpaste allergy, lack of response to patch tests on the skin may be because fluoride crosses the oral mucous membrane more easily than the skin.[4]

Stomatitis has also been reported after use of gels containing olaflur and dectaflur.[5]

1. Mummery RV. Claimed fluoride allergy. *Br Dent J* 1984; **157:** 48.
2. Camarasa JG, *et al.* Contact urticaria from sodium fluoride. *Contact Dermatitis* 1993; **28:** 294.
3. Isaksson M, *et al.* Contact allergy to Duraphat. *Scand J Dent Res* 1993; **101:** 49–51.
4. Brun R. Recurrent benign aphthous stomatitis and fluoride allergy. *Dermatology* 2004; **208:** 181.
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Overdosage. References.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5:** 79–85.
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4. Shulman JD, Wells LM. Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. *J Public Health Dent* 1997; **57:** 150–8.

Precautions

When considering fluoride supplementation, allowance should be made for fluorides ingested from other sources; fluoride supplements in children are not generally recommended when the fluoride content of drinking water is over 0.7 ppm (0.6 ppm in the USA) (see also Uses and Administration, below). Care should be taken to prevent children swallowing excessive fluoride after topical application to teeth.

Patients with impaired renal function may be particularly susceptible to fluorosis. Regular dialysis with fluoridated water may result in additional fluoride absorption; a maximum concentration of 0.2 ppm of fluoride in the dialysate has been recommended. Dialysis patients not using deionised water are at risk from changes in the fluoride content of the water supply.

Interactions

Aluminium, calcium, and magnesium salts may decrease the absorption of fluoride.

Pharmacokinetics

Sodium fluoride and other soluble fluorides are readily absorbed from the gastrointestinal tract. Inhaled fluorides (from industrial fumes and dusts) are absorbed through the lungs. Fluoride is deposited mainly in the bones and teeth. It is principally excreted in the urine but small amounts may also be excreted in faeces and sweat. It crosses the placenta and is present in saliva, nails, and hair. There is some evidence of distribution into breast milk.

Uses and Administration

Sodium fluoride is used to prevent dental caries and may be used to increase bone density in osteoporosis (see below). Sodium fluoride is used as a source of fluoride in total parenteral nutrition.

The content of sodium fluoride is usually expressed in terms of the fluoride; 2.2 mg of sodium fluoride is equivalent to about 1 mg of fluoride. Each g provides about 23.8 mmol of sodium and fluoride.

For **dental caries prophylaxis**, sodium fluoride is used as an adjunct to diet and oral hygiene. It may render the enamel of teeth more resistant to acid, promote remineralisation, or reduce microbial acid production. Fluoride can be given by *fluoridation* of the public water supply (below) to achieve a usual fluoride concentration of 1 ppm in temperate regions. The concentration may vary from 0.6 to 1.2 ppm depending on the climatic temperature with the lower concentrations being used in hotter regions where more water is likely to be consumed. Fluoridation of salt at a minimum concentration of 200 mg of fluoride per kg of salt is an alternative. Fluoridation of milk has been tried in some countries.

Alternatively, sodium fluoride may be given as an *oral supplement* to children considered to be at high risk of caries. The daily dosage should be adjusted for the fluoride content of the drinking water, for fluorides ingested from other sources such as the diet, and for the age of the child. Guidelines in the USA and the UK both suggest that, where the drinking water contains less than 0.3 ppm of fluoride, children may be given the following doses according to age:

- under 6 months, not recommended
- 6 months to 3 years, sodium fluoride 0.55 mg (equivalent to 0.25 mg of fluoride) daily
- 3 to 6 years, 1.1 mg (equivalent to 0.5 mg of fluoride) daily
- 6 years and over, 2.2 mg (equivalent to 1 mg of fluoride) daily.

When drinking water contains 0.3 to 0.7 ppm (0.3 to 0.6 ppm in the USA) of fluoride lower doses should be considered. Specifically, it is recommended that no additional fluoride should be given to children less than 3 years of age and for older children the above doses should be halved. If the water contains more than 0.7 ppm (0.6 ppm in the USA) of fluoride, supplementation is not recommended. Tablets should be sucked or chewed before swallowing since the topical action of fluoride on enamel and plaque is considered to be more important than the systemic effect. The value of giving fluoride during pregnancy, to benefit the child, is not established. Dental benefits from the use of dietary fluoride supplements by adults are unsubstantiated.

After tooth eruption, *local application* of fluoride is effective. Daily mouth-rinses of sodium fluoride 0.05% (about 225 ppm fluoride) or weekly mouth-rinses of sodium fluoride 0.2% (900 ppm) may be used, but are not recommended for children aged under 6 years because they are unable to effectively spit the rinse out after use. Sodium fluoride 2% (about 9090 ppm) solution is available for topical use, under professional supervision. Fluoridated toothpastes are now widely available and are a convenient source of fluoride. In the UK, the maximum permitted fluoride level in conventional toothpastes is sodium fluoride 0.32% (0.15% or 1500 ppm fluoride); higher concentrations of sodium fluoride 0.619% (2800 ppm fluoride) are available under professional supervision. Formulations for children under 7 years of age typically contain sodium fluoride 0.11% (500 ppm); higher concentrations may be used, but the amount applied should be supervised to avoid excessive use or ingestion. Sodium fluoride has also been applied topically as a varnish under professional supervision. Alternatively, sodium fluoride solutions or gels acidified with phosphoric acid (commonly known as acidulated phosphate fluoride preparations) may be used. These preparations are considered to increase the fluoride uptake by the enamel and protect the enamel from demineralisation. For maximum benefit, eating, drinking, or rinsing should be avoided for at least 15 to 30 minutes after topical fluoride application.

Other fluoride compounds used in oral hygiene products and toothpastes include aluminium fluoride, ammonium fluoride, calcium fluoride (p.1932), dectaflur (p.1937), magnesium fluoride (p.1955) nicomethanol hydrofluoride, olaflur (p.1959), potassium fluoride, sodium monofluorophosphate (p.1964), and stannous fluoride (p.1967). Other fluorides used in the fluoridation of water supplies include sodium silicofluoride (p.1965).

Sodium fluoride has also been used, like some other fluoride compounds, in **rodenticides** and **insecticides**.

Dental caries prophylaxis. There is strong and consistent evidence in favour of the effectiveness of fluoride in preventing or reducing the incidence of dental caries. However, there is no strong evidence that one form of topical fluoride is more effective than another.

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1. WHO. Fluorides and oral health: report of a WHO expert committee on oral health status and fluoride use. *WHO Tech Rep Ser 846* 1994.
2. Anonymous. Fluoride supplement dosage: a statement by the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry. *Br Dent J* 1997; **182:** 6–7.
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6. Marinho VCC, *et al.* Fluoride varnishes for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 08/11/05).
7. Marinho VCC, *et al.* Fluoride toothpastes for preventing dental caries in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 08/11/05).
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9. Twetman S, *et al.* Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odontol Scand* 2003; **61:** 347–55.
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12. Petersson LG, *et al.* Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. *Acta Odontol Scand* 2004; **62:** 170–6.
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14. Jones S, *et al.* The effective use of fluorides in public health. *Bull WHO* 2005; **83:** 670–6.
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16. WHO/FDI World Dental Federation/International Association for Dental Research. Beijing declaration: call to action to promote oral health by using fluoride in China and Southeast Asia (issued September 2007). Available at: http://www.fdiworldental.org/public_health/assets/Fluoride_Consultation/Beijing_Declaration_English.pdf (accessed 10/03/08)

Fluoridation of water. Some countries add fluoride to water supplies to prevent dental caries. This has been the subject of much controversy.

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3. Cheng KK, *et al.* Adding fluoride to water supplies. *BMJ* 2007; **335:** 699–702.

Human requirements. In the USA dietary reference intakes have been set for fluoride. These propose an adequate intake (see p.1925) for dental caries prevention to be 4 mg daily in adult men and 3 mg in women;[1] lower values are suggested in children and adolescents, depending on age. The tolerable upper intake level is 10 mg daily in adults.[1]

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Osteoporosis. Fluoride has been used in the treatment of osteoporosis (p.1084) to improve bone strength by inducing subclinical fluorosis. The main effect of fluoride on the skeleton is to stimulate osteoblasts and increase trabecular bone mass. Because antiresorptive drugs cannot restore lost bone mass, this is potentially valuable in the treatment of osteoporosis. However, too much fluoride can increase bone fragility, and the overall effect of sodium fluoride on the incidence of fracture has not been established.

A controlled study in patients with postmenopausal osteoporosis[1] found that sodium fluoride 75 mg daily with a calcium supplement increased trabecular bone mass of the spine but did not reduce the incidence of vertebral fractures. Patients given sodium fluoride also had a higher incidence of nonvertebral fractures. An extension and re-analysis of the study,[2] however, showed that gradual increases in bone mass observed in patients taking lower doses of sodium fluoride (down to about 40 mg daily) were associated with a decrease in the incidence of fractures. A previous study[3] had reported a beneficial effect in vertebral fracture rate in patients with primary osteoporosis and at least one vertebral crush fracture. In this study sodium fluoride was given in a daily dose of 50 mg; calcium and vitamin D were also given. Interim analysis of a subsequent study using a slow-release formulation of sodium fluoride 50 mg daily taken intermittently with a regular calcium supplement showed a decrease in vertebral fractures of 50% at 2.5 years.[4] At 4 years the beneficial effect was sustained, the main effect being seen in a reduced incidence of new vertebral fractures;[5] no reduction was seen in the incidence of recurrent fractures but this study found no evidence of an increase in nonvertebral fractures. Some consider that low-dose fluoride can be of benefit in established postmenopausal osteoporosis, but the therapeutic window is narrow, and calcium and vitamin D must also be given to meet the calcium demand and avoid resorption of established bone.[6] A further double-blind study failed to show a reduction in vertebral fracture rates in women with osteoporosis treated with fluoride, and calcium and vitamin D compared with women who received only calcium and vitamin D.[7] This was despite a significant increase in bone mass density of the spine in the fluoride-treated groups. Fluoride regimens consisted of 50 mg enteric-coated sodium fluoride daily, or 150 or 200 mg sodium monofluorophosphate daily. In contrast, a further 4-year study found a decrease in vertebral fracture rates in women with moderate osteoporosis treated with sodium monofluorophosphate 156 mg daily plus calcium compared with those receiving calcium alone.[8]

A systematic review of 11 studies concluded that fluoride can increase bone mineral density at the lumbar spine, but this does not reduce the rate of vertebral fractures.[9] The authors of this review considered that fluoride should not be used in the first-line therapy of postmenopausal osteoporosis.

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2. Riggs BL, *et al.* Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. *J Bone Miner Res* 1994; **9:** 265–75.
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4. Pak CYC, *et al.* Slow-release sodium fluoride in the management of postmenopausal osteoporosis: a randomized controlled trial. *Ann Intern Med* 1994; **120:** 625–32.
5. Pak CYC, *et al.* Treatment of postmenopausal osteoporosis with slow-release sodium fluoride: final report of a randomized controlled trial. *Ann Intern Med* 1995; **123:** 401–8.
6. Anonymous. New drugs for osteoporosis. *Med Lett Drugs Ther* 1996; **38:** 1–3.
7. Meunier PJ, *et al.* Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVOStudy. *Osteoporosis Int* 1998; **8:** 4–12.
8. Reginster JY, *et al.* The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis: a randomized, controlled trial. *Ann Intern Med* 1998; **129:** 1–8.
9. Haguenauer D, *et al.* Fluoride for treating postmenopausal osteoporosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 08/11/05).

Preparations

BP 2008: Sodium Fluoride Mouthwash; Sodium Fluoride Oral Drops; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets;
USP 31: Sodium Fluoride and Acidulated Phosphate Topical Solution; Sodium Fluoride and Phosphoric Acid Gel; Sodium Fluoride Oral Solution; Sodium Fluoride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Elgydium Junior; Elgydium Proteccion; Fluordent; Fluorogel; Fluorogel 2001; Fluoroplat; Naf Buches; Nafluor†; Pentafresh†; ***Austral.:*** Fluor†; Flurets; Neutrafluor; ***Austria:*** Duraphat; Fluodont; Zymafluor; ***Belg.:*** Fluodontyl†; Fluor; Procal†; Z-Fluor; ***Braz.:*** Fluornatrium†; Fluotrat; Primafluor†; ***Canad.:*** Fluor-A-Day; Fluoridrops†; Fluorinse; Fluoritabs†; Fluotic; Karidium†; Oral-B Anti-Cavity Dental Rinse; Oro-NaF; PDF; ***Chile:*** Caristop; Fluocaril Bi-Fluore; Gengisyl; Vitaflur; Vitis Pasta; ***Cz.:*** Fluocaril†; Fluossen†; Ossin†; Zymafluor; ***Denm.:*** Duraphat; Fluorette; ***Fin.:*** Duraphat; Fludent; Fluorilette; ***Fr.:*** Elgydium Junior; Elgydium Protection Caries; Elgyfluor Junior†; Elgyfluor†; Fluodontyl; Fluogum; Fluoplexe; Fluor Microsol†; Fluorex; Sanogyl†; Zymafluor; ***Ger.:*** Duraphat; Fluoretten; Fluoros; NaFril†; Ossin; Zymafluor; ***Gr.:*** Apoflux†; Duraphat; ***Hung.:*** Arthrofluor; Dentocar; Zymafluor; ***India:*** Otoflour; ***Indon.:*** Listermint; ***Israel:*** Denticare†; Dentix; Duraphat; Fluden; Fluvium; Teeth Tough; Zymafluor; ***Ital.:*** AZ Verde; Dentosan Extra Fluor; Dentosan Prevent†; Duraphat; Eburdent; Fluor Verde; Fluor-In; Listerine Difesa; Oral-B Collutorio Protezione Anti-Carie Fluorinse; Zymafluor; ***Mex.:*** Audifluor; ***Neth.:*** Dentigel; En-De-Kay; Osteofluor; Zymafluor; ***Norw.:*** Duraphat; Fluorette; Flux; ***Philipp.:*** Infaflor; ***Pol.:*** Fluossen; Zymafluor; ***Port.:*** Duraphat; Elmex; Fluor-In; Maxfluor; Medusit†; Oratol F†; Zymafluor; ***Rus.:*** Ossin (Оссин)†; ***S.Afr.:*** Listerfluor; Zymafluor; ***Spain:*** Fluodontyl; Fluor; Zymafluor†; ***Swed.:*** Dentan; Dentirol Fluor; Duraphat†; Fludent; Fluorette; Top dent fluor; ***Switz.:*** Duraphat; Fluocaril†; Ossin; Ossofluor; Zymafluor; ***Thai.:*** Zymafluor; ***Turk.:*** Fluoxytil; Zymafluor; ***UK:*** Duraphat; En-De-Kay; Fluor-A-Day; Fluorigard; Sensodyne Mint; ***USA:*** ACT; APF†; Denta Plus; DentaGel; EtheDent; Fluorigard; Fluorinse; Fluoritab; Flura; Karidium; Karigel; Karigel-N; Listerine Tooth Defense; Luride; Minute-Gel; MouthKote F/R; NeutraGard Advanced; OrthoWash; Pediaflor; Pharmaflur; Phos-Flur; Point-Two; Prevident; SF Gel; Thera-Flur.

Multi-ingredient: *Arg.:* ADC Fluor; Buclorhex; Cal-C-Vita Fluor; Desensyl; Elgydium; Elgydium Dientes Sensibles; Elgyfluor†; Emoform Total; Esmedent con Fluor; Fluordent PX; Fluorexidina†; Fluorogel 2001 Chiquitos; Fluorogel 2001 para Dientes Sensibles; Hyper Sensitive; Odol Control Sarro†; Odol Med Antiplaca†; Odol Tratamiento de Encias†; Oral-B Dientes Sensibles con Fluor†; Oral-B Enjuague Bucal†; Parodontax Fluor; Sens-Out†; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Proteccion Total; Squam; Tri-Vi-Fluor; ***Austral.:*** Macleans Sensitive; Oral-B Sensitive†; ***Austria:*** Elmex; Ossiplex; ***Belg.:*** Elmex; Fluocaril; Sedemol; Sulfa-Sedemol; ***Braz.:*** Calcifix B12; Calcifix Irradiado; Calcigenol; Calcinol Complexo; Malvatricin; Malvatricin Branqueador; Malvatricin Natural; Poly-Vi-Fluor; Proplax†; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool; Sensodyne Fresh Mint; Sensodyne Protecao Total; Tri-Vi-Fluor; ***Canad.:*** Cepacol with Fluoride; Oral Plan†; Oral-B Anti-Bacterial with Fluoride; Oral-B Sensitive†; Sensodyne-F; Tri-Vi-Flor†; ***Chile:*** Cariax; Caristop; FKD; Kariax†; Listermint Con Fluor; Oralgene; Orthokin; Ortodent†; Sensaid; Vitis Encias Pasta; ***Cz.:*** Bifluorid†; Blend-a-Med†; Elmex; Fluocaril Bi-Fluore Vitamin E†; Fluocaril Bi-Fluore†; Natabec F†; Ossiplex†; ***Denm.:*** Bifluorid; ***Fin.:*** Elmex; Xerodent; ***Fr.:*** Elgydium Dents Sensibiles; Elgyfluor†; Elmex Sensitive†; Elmex†; Fluocaril Bi-Fluore; Fluocaril dents sensibles; Fluocaril Junior and Fluocaril Kids; Fluogel; Fluoselgine; Fluosterol; Listerine protection dents et gencives; Parogencyl prevention gencives; Paroplak; Sanogyl Fluo†; Sanogyl Junior†; Sanogyl†; Sensigel; Zymaduo; ***Ger.:*** D-Fluoretten; Elmex; Fluor-Vigantoletten; Lawefluor N†; Multifluorid; Natabec F†; Ossiplex; Ossofortin Plus; Zymafluor D; ***Hong Kong:*** Listerine Teeth and Gum Defence; ***Hung.:*** Elmex; Ossiplex†; ***Israel:*** Elmex; ***Ital.:*** Actifluor†; Actisens†; Aqua Emoform†; AZ Protezione Gengive; AZ Tartar Control; Benodent; Bifluorid†; Broxo al Fluoro; Broxodin†; Colgate Total; Dentosan Junior; Dentosan Placca & Carie; Dentosan Sensibile; Eburdent F; Elmex; Emoform Actisens†; Emoform-Tat†; Eudent con Glysan†; Fluocaril; Fluocaril Bi-Fluore; Lacalut; Oral-B Collutorio per la Protezione di Denti e Gengive; Oral-B Sensitive; Ossiplex†; Otofluor; Plax†; Ridiodent; ***Mex.:*** Fluoxytil; ***Neth.:*** Elmex; ***Norw.:*** Xerodent; ***Philipp.:*** Listerine Teeth & Gum Defense; Poly-Vi-Flor; Xylorinse; ***Pol.:*** Bifluorid; Fluormex; Fluoro-zel; ***Port.:*** Bexident; Biofluor Ortodoncia†; Biofluor Plus†; Biofluor Prevencao†; Biofluor Sensitive†; Fluocaril Bi-Fluore; ***Rus.:*** Elgyfluor (Эльгифлуор); Sensigel (Сенсигель); ***S.Afr.:*** Ossiplex; ***Singapore:*** 2Sensitive†; Elgyfluor; Sensigel; ***Spain:*** Vitagama Fluor; ***Swed.:*** Bifluorid; Xerodent; ***Switz.:*** Elmex; Fluocaril Bi-Fluore†; Paro aux fluorures d'amines Gelee; Parodontax F†; ***Thai.:*** Poly-Vi-Flor; ***Turk.:*** D-Flor; Kalsifluor; Nesgarin; Sensodyne-F Gel; ***UK:*** Dentyl pH; Hydrotab; Listermint with Fluoride; Macleans Mouthguard; Saliva Orthana; Sensodyne-F; ***USA:*** Adeflor M†; Apatate with Fluoride†; ControlRx; Florical; Fluoridex Daily Defense Sensitivity Relief; Mulvidren-F Softab; Poly-Vi-Flor; Polytabs-F; Sensitivity Protection Crest; Soluvite; Tri Vit with Fluoride†; Tri-Vi-Flor; Trivitamin Fluoride Drops; Vi-Daylin/F; ***Venez.:*** Sensodyne.

Sodium Monofluorophosphate

MFP Sodium; Monofluorofosfato sódico; Natrii Monofluorophosphas; Natriummonofluorfosfat; Natriummonofluorifosfaatti; Sodium Fluorophosphate. Disodium phosphorofluoridate.

Na_2PO_3F = 143.9.

CAS — 10163-15-2.

ATC — A01AA02; A12CD02.

ATC Vet — QA01AA02; QA12CD02.

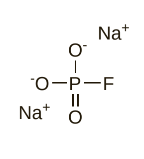

Pharmacopoeias. In *US.*

USP 31 (Sodium Monofluorophosphate). A white to slightly grey, odourless powder. Freely soluble in water. pH of a 2% solution in water is between 6.5 and 8.0.

Profile

Sodium monofluorophosphate is used as a source of fluoride (see Sodium Fluoride, p.1962) in toothpastes for the prevention of dental caries. It may also be given by mouth in the management of osteoporosis.

In the UK, the maximum permitted fluoride level in toothpastes is 1.14% of sodium monofluorophosphate (0.15% or 1500 ppm of fluoride). Formulations for children under 7 years of age typically contain sodium monofluorophosphate 0.38% (500 ppm fluoride); higher concentrations may be used, but the amount applied should be supervised to avoid excessive use or ingestion.

Other monofluorophosphate salts permitted for use in oral hygiene products and dentifrices include ammonium monofluorophosphate, calcium monofluorophosphate, and potassium monofluorophosphate. Glutamine monofluorophosphate has been used for osteoporosis.

Osteoporosis. For reference to the use of fluorides, including sodium monofluorophosphate, in the treatment of osteoporosis, see under Uses of Sodium Fluoride, p.1964.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Osteomar†; ***Austral.:*** Fluorocare; ***Austria:*** Osteopro; ***Braz.:*** Emoform AP; Malvatricin Antitartaro; Unique Plus; ***Chile:*** Fluocaril Bi-Fluore; Gengisyl; Oralfresh; ***Cz.:*** Difluena†; ***Ger.:*** Mono-Tridin; ***Ital.:*** Clinomyn; Isifluor; Neo Emoform†; Neo Fluostomygen; Platinum.

Multi-ingredient: ***Arg.:*** Desensyl; Emoform Total; Fluocalcic†; Fluordent PX; Hexiben; Hexiben Plus†; Negaporosis; Odol Med Antiplaca†; Sensodyne-F; Squam; ***Austria:*** Fluocalcic; ***Belg.:*** Fluocalcic†; Fluocaril; ***Braz.:*** Emoform AT; Fluomint; Malvatricin Antiplaca; Malvatricin Branqueador; Malvatricin Dentes Sensiveis; Malvatricin Natural; Malvatricin Natural Organic; Malvatricin Natural Soft; Malvatricin Plus; Sensodyne-F; ***Canad.:*** Viadent†; ***Chile:*** Caristop; Gingilacer†; Sensilacer†; Tridin†; ***Cz.:*** Fluocalcic†; Fluocaril Bi-Fluore Vitamin E†; Fluocaril Bi-Fluore†; Tridin; ***Fr.:*** Emoform Dents Sensibles; Fluocaril Bi-Fluore; Fluocaril blancheur; Fluocaril Junior and Fluocaril Kids; Sanogyl Fluo†; Sanogyl Junior†; Sanogyl†; ***Ger.:*** Calcivit F†; Fluoril; Tridin; Tridin Forte; ***Hong Kong:*** Tridin; ***Hung.:*** Tridin; ***Ital.:*** Aqua Emoform†; Biogreen; Broxo al Fluoro; Broxodin†; Calcitridin†; Dentosan Carie & Alito†; Dentosan Junior; Emoform-Tat†; Eudent con Glysan†; Fluocaril Bi-Fluore; Formedico; Neo-Stomygen; Orosanyl†; Periogard Plus; Stomygen; Tridin; ***Mex.:*** Dentsiblen; Fluoxytil; Periodentyl; ***Pol.:*** Fluoro-zel; ***Port.:*** Fluocaril Bi-Fluore; ***Switz.:*** Emoform-F au fluor; Fluo-calc†; Fluocaril Bi-Fluore†; ***Turk.:*** Sensodyne-F; ***USA:*** Monocal; Optimoist; Sensodyne-F; ***Venez.:*** Sensident†; Topdent†.

Sodium Silicofluoride

Fluosilicato sódico; Sodium Fluorosilicate; Sodium Fluosilicate; Sodium Hexafluorosilicate.

Na_2SiF_6 = 188.1.

CAS — 16893-85-9.

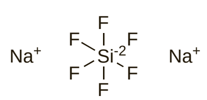

Profile

Sodium silicofluoride is used as a source of fluoride (see Sodium Fluoride, p.1962) for the fluoridation of drinking water. It has also been considered for inclusion in oral hygiene products.

Other silicofluoride (fluorosilicate) salts permitted for use in oral hygiene products include ammonium silicofluoride, magnesium silicofluoride, and potassium silicofluoride.

Sodium silicofluoride has also been used in insecticides.

Sorbitol

E420; D-Sorbitol; Sorbitoli; Sorbitolis; Sorbitolum; Szorbit. D-Glucitol.

$C_6H_{14}O_6$ = 182.2.

CAS — 50-70-4.

ATC — A06AD18; A06AG07; B05CX02; V04CC01.

ATC Vet — QA06AD18; QA06AG07; QB05CX02; QV04CC01.

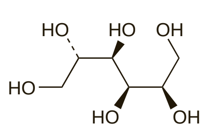

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *Viet.* Also in *USNF.*

US includes only Sorbitol Solution.

Ph. Eur. 6.2 (Sorbitol). A white or almost white crystalline powder. It exhibits polymorphism. Very soluble in water; practically insoluble in alcohol.

USNF 26 (Sorbitol). White, odourless, hygroscopic powder, granules, or crystalline masses having a sweet taste with a cold sensation. Soluble 1 in 0.45 of water; sparingly soluble in alcohol; practically insoluble in solvent ether. pH of a 10% w/w solution in water is between 3.5 and 7.0.

Incompatibility. For reference to the incompatibility of sorbitol with hydroxybenzoates, see p.1649.

Adverse Effects and Precautions

As for Fructose, p.1945.

Effects on electrolyte balance. Sorbitol is used as a vehicle in some proprietary preparations of activated charcoal intended to reduce drug absorption after poisoning; the sorbitol increases the palatability of the preparation and also produces an osmotic diarrhoea that facilitates elimination of the activated charcoal and adsorbed drug. Repeated doses of such preparations are often advocated but there have been reports[1-3] of severe sorbitol-induced hypernatraemia in adults and children. In all cases, charcoal in a 70% sorbitol suspension had been given. It has been recommended that fluid and electrolyte balance be monitored closely, and that preparations with lower concentrations of sorbitol be used if possible.[2,3] For debate about such multiple dose therapy see Poisoning, under Activated Charcoal, p.1436.

1. Gazda-Smith E, Synhavsky A. Hypernatraemia following treatment of theophylline toxicity with activated charcoal and sorbitol. *Arch Intern Med* 1990; **150:** 689 and 692.
2. Allerton JP, Strom JA. Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis* 1991; **17:** 581–4.
3. Farley TA. Severe hypernatremic dehydration after use of an activated charcoal-sorbitol suspension. *J Pediatr* 1986; **109:** 719–22.

Effects on the gastrointestinal tract. Sorbitol is often used as a sweetener in sugar-free preparations and the risk of sorbitol-induced diarrhoea associated with such products has been highlighted.[1-4] Chronic sorbitol-induced diarrhoea with associated pneumatosis intestinalis has been reported in a child given 21.7 g sorbitol daily in liquid medications.[5] Colonic and upper gastrointestinal necrosis, including some fatalities, have been reported after use of sodium polystyrene sulfonate in sorbitol, and may have been associated with the sorbitol component, see p.1465.

It has also been suggested that sorbitol contributed to the morbidity in a patient who developed septicaemia as a complication of intestinal pseudo-obstruction, after the use of charcoal with sorbitol to treat self-poisoning with theophylline.[6] It was suggested that gaseous distension after bacterial metabolism of sorbitol had rendered the bowel wall ischaemic, facilitating passage of bacteria or of endotoxin into the systemic circulation.

1. Brown AM, Masson E. 'Hidden' sorbitol in proprietary medicines - a cause for concern? *Pharm J* 1990; **245:** 211.
2. Edes TE, *et al.* Diarrhea in tube-fed patients: feeding formula not necessarily the cause. *Am J Med* 1990; **88:** 91–3.
3. Johnston KR, *et al.* Gastrointestinal effects of sorbitol as an additive in liquid medications. *Am J Med* 1994; **97:** 185–91.
4. Bauditz J, *et al.* Severe weight loss caused by chewing gum. *BMJ* 2008; **336:** 96–7.
5. Duncan B, *et al.* Medication-induced pneumatosis intestinalis. *Pediatrics* 1997; **99:** 633–6.
6. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7:** 74–7.

Pharmacokinetics

Sorbitol is poorly absorbed from the gastrointestinal tract after oral or rectal use. It is metabolised mainly in the liver, to fructose (see p.1945), a reaction catalysed by the enzyme sorbitol dehydrogenase. Some sorbitol may be converted directly to glucose by the enzyme aldose reductase.

Uses and Administration

Sorbitol is a polyhydric sugar alcohol (polyol) with half the sweetening power of sucrose. It occurs naturally in many fruits and vegetables and is prepared commercially by the reduction of glucose.

It has been given as a 30% solution as an alternative to glucose in parenteral nutrition (p.1923) but its use is not recommended because of the risk of lactic acidosis.

Sorbitol may be given orally or rectally as an osmotic laxative in the management of constipation (p.1693); doses of 20 to 50 g have been suggested.

Solutions containing about 3% of sorbitol are used as irrigating fluids in transurethral surgical procedures.

Sorbitol was formerly given intravenously as a 50% solution as an osmotic diuretic.

Sorbitol also acts as a bulk sweetening agent. It is used in limited quantities as a sweetener in energy-reduced diabetic food products. It is also used as an alternative to sucrose in many sugar-free oral liquid preparations and in sugar-free foods as it is less likely to cause dental caries.

Sorbitol also has humectant and stabilising properties and is used in various pharmaceutical and cosmetic products including toothpaste.

Preparations

Ph. Eur.: Sorbitol, Liquid (Crystallising); Sorbitol, Liquid (Non-crystallising); Sorbitol, Liquid, Partially Dehydrated;
USNF 26: Noncrystallizing Sorbitol Solution;
USP 31: Sorbitol Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Progras†; ***Austral.:*** Sorbilax; ***Braz.:*** Minilax; ***Cz.:*** Ardeanutrisol SO†; ***Hung.:*** Szorbit†; ***Swed.:*** Cystosol†; Resulax.

Multi-ingredient: ***Arg.:*** Humectante Bucal; Micronema; ***Austral.:*** Aquae; Carbosorb S; Fleet Micro-Enema; Medevac†; Microlax; ***Austria:*** Glandosane; Lemazol; Microklist; Resectal; Trommgallol; Yal; ***Belg.:*** Microlax; Spagulax Sorbitol; ***Braz.:*** Anekron; Biliflux†; Colachofra; Hepalin; Hepatobe†; Hepatox; Hormo Hepatico†; ***Canad.:*** Charac Tol; Charcodote; Microlax; Salivart; ***Chile:*** Salivart†; Secand; Tabletas Phillips; ***Cz.:*** Yal; ***Denm.:*** Klyx; ***Fin.:*** Klyx; Microlax; Somanol + Ethanol; ***Fr.:*** Apilaxe†; Artisial; Exova†; Hepacholine†; Hepagrume; Hepargitol; Microlax; Nivabetol; Ornitaine; Parapsyllium; Schoum; Spagulax au Sorbitol; SST; ***Ger.:*** Flacar; Freka-Drainjet Purisole; Glandosane; Klysma Sorbit; Microklist; Tutofusin S†; Yal; ***Hong Kong:*** Aquae; Glandosane; Microlax; Salivart; ***Hung.:*** Balansol; Yal†; ***India:*** Alkasol-P; Livocip; Mecolin; Sorbiline; Sorliv; ***Indon.:*** Laxarec; Microlax; ***Israel:*** Charcodote; Spray Mint; ***Ital.:*** Citroepatina; Macrolax; Magisbile†; Novilax; Sorbiclis; ***Malaysia:*** Microlax†; ***Mex.:*** Clyss-Go; ***Neth.:*** Klyx; Microlax; ***Norw.:*** Klyx; Microlax; ***NZ:*** Carbosorb S†; Carbosorb XS; Medevac†; Microlax; ***Pol.:*** Purisole SM; Rektiolax; ***Port.:*** Clyss-Go; Glandosane; Purisole; ***Rus.:*** Microlax (Микролакс); ***S.Afr.:*** Agofell; Microlax†; ***Spain:*** Sugarbil; Vitaphakol; ***Swed.:*** Klyx; Microlax; Vi-Siblin S; ***Switz.:*** Agarol Soft; Cital†; Glandosane; Microklist; Pursana; Yal; ***Thai.:*** Glandosane†; ***Turk.:*** Charflo Sorbitol; Kansilak; Libalaks; Sabalax; ***UK:*** Glandosane; Luborant; Relaxit; Saliva Natura; SST; ***USA:*** Actidose with Sorbitol; Moi-Stir; Numoisyn; Plax; Salivart; ***Venez.:*** Clys-Go†.

Soya Bean

Habas de soja; Soja Bean; Soyabean; Soybean.

Description. Soya bean is the seed of the soya plant *Glycine max* (*G. hispida*; *G. soja* (L.) Merr.). It is a source of soya oil and soya protein.*G.soja* Siebold & Zucc. is wild soybean.

Soya Oil

Aceite de soja; Soiae Oleum; Soijaöljy; Soja Bean Oil; Soja, huile de; Sojae oleum; Sojaolja; Sójový olej; Sojų aliejus; Soya Yağı; Soyabean Oil; Soya-bean Oil; Soybean Oil; Szójababolaj.

Pharmacopoeias. In *Chin., Jpn,* and *US.*

Eur. (see p.vii) includes both hydrogenated and refined oils. *Ger.* also includes a partially hydrogenated oil. *USNF* includes the hydrogenated oil.

Ph. Eur. 6.2 (Soya-bean Oil, Refined; Soiae Oleum Raffinatum). It is the fatty oil obtained from seeds of *Glycine soja* and *G. max* (*G. hispida*) by extraction and subsequent refining. It may contain a suitable antoxidant and is a clear, pale yellow liquid. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled containers at a temperature not exceeding 25°. Protect from light.

The BP 2008 directs that when Soya Oil, Soyabean Oil, or Soyabean Oil is demanded, Refined Soya Oil shall be supplied.

Ph. Eur. 6.2 (Soya-bean Oil, Hydrogenated; Soiae Oleum Hydrogenatum). It is obtained by refining, bleaching, hydrogenation, and deodorisation of soya oil. It consists mainly of triglycerides of palmitic and stearic acids and is a white or almost white mass or powder which melts to a clear, pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Protect from light.

USP 31: (Soybean Oil). The refined fixed oil obtained from the seeds of the soya plant *Glycine max* (Fabaceae). It may contain suitable antoxidants. A clear, pale yellow, oily liquid having a characteristic odour. Insoluble in water; miscible with chloroform and with ether. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

USNF 26 (Hydrogenated Soybean Oil). The product obtained by refining, bleaching, hydrogenation, and deodorisation of oil obtained from seeds of the soya plant, *Glycine max* (Fabaceae). It consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. between 66° and 72°. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane, in petroleum spirit after heating, and in toluene. Store in airtight containers. Protect from light.

Incompatibility. For mention of the compatibility and stability of solutions and emulsions for parenteral nutrition see under Enteral and Parenteral Nutrition, p.1924.

Adverse Effects

Hypersensitivity reactions including fever and chills have been reported after the infusion of soya oil emulsion although they are considered to be fairly rare. Other rare immediate reactions include dyspnoea, cyanosis, hyperlipidaemia, hypercoagulability, nausea, vomiting, headache, and chest and back pain. Delayed reactions include hepatomegaly, splenomegaly, jaundice due to cholestasis, thrombocytopenia, leucopenia, and transient increases in liver function tests.

Prolonged or too rapid infusion of soya oil emulsion or its use in patients with impaired fat metabolism has been associated with the 'overload syndrome'. This is manifested by anaemia, leucocytopenia, thrombocytopenia, and impaired coagulation, hepatosplenomegaly, hyperlipidaemia, fever, focal seizures, shock, and coma. Metabolic acidosis has been associated with severe overdosage especially if carbohydrates are not also given. Pigmentation of tissues in the reticuloendothelial system after prolonged therapy with lipid emulsion infusions has also been reported.

Soya protein-based infant feeds can be antigenic and cause gastrointestinal adverse effects in sensitive individuals.

Bacteraemia. A strong association has been found between giving lipids through peripheral venous catheters made of Teflon and development of coagulase-negative staphylococcal bacteraemia in neonates.[1] It was suggested that investigation of catheters made of other materials, or other delivery systems, might reduce the opportunity for coagulase-negative staphylococci to adhere and come into contact with nutrient-rich growth media in the form of lipid emulsions. Others also took the view that this work should not lead to the abandonment of parenteral lipids in premature infants.[2]

1. Freeman J, *et al.* Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990; **323:** 301–8.
2. Klein JO. From harmless commensal to invasive pathogen: coagulase-negative staphylococci. *N Engl J Med* 1990; **323:** 339–40.

Effects on the cardiovascular system. Sinus bradycardia has been reported in a patient receiving total parenteral nutrition that included soya oil-based emulsion via a central line.[1] The authors suggested that it might be wise to give fat emulsion only through a peripheral vein. However, sinus bradycardia has been reported after a safflower oil-based emulsion given via a peripheral vein as part of a TPN regimen.[2]

1. Sternberg A, *et al.* Intralipid-induced transient sinus bradycardia. *N Engl J Med* 1981; **304:** 422–3.
2. Traub SL, *et al.* Sinus bradycardia associated with peripheral lipids and total parenteral nutrition. *J Parenter Enteral Nutr* 1985; **9:** 358–60.

Effects on the endocrine system. Soya bean is a rich source of phytoestrogens including isoflavones, and it has been found that infants fed soya-based formula have high serum concentrations of these substances,[1] which has brought the safety of soya-based formulas into question. *Animal* and *in vitro* data suggest that isoflavones such as genistein have pharmacological effects on growth and development.[2] However, genistein and daidzein are less potent than endogenous oestrogens and have less binding affinity to oestrogen receptors.[3] It is not known to what extent infants are able to metabolise and deconjugate soya isoflavones.[4] A small retrospective study[5] observed no oestrogenic effects in children fed soya protein formula for at least 6 months. A larger retrospective cohort study[6] in adults observed no statistically significant differences between those who had been fed soya formula and those fed cow's milk formula as infants.

As yet, there is insufficient evidence of harm from soya-based formulas,[7] although further studies are deemed necessary to assess long-term effects.[2,4] The American Academy of Pediatrics[8] considers soya protein-based formulas to be safe and effective in healthy term infants, while providing no advantage over cow's milk protein-based formulas. However, soya-based formulas are not recommended for use in low birth-weight preterm infants because of concerns about poorer growth rates compared with infants given formulas based on cow's milk protein.

Before their supplementation with iodine, there had been reports of hypothyroidism associated with soya formula feeds. Abnormal thyroid function tests have since been reported in infants fed with soya formulas, and a retrospective analysis of infants with congenital hypothyroidism found those fed with soya took longer for their thyroid stimulating hormone levels to normalise.[9]

1. Setchell KDR, *et al.* Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 1997; **350:** 23–7.
2. Chen A, Rogan WJ. Isoflavones in soy infant formula: a review of evidence for endocrine and other activity in infants. *Annu Rev Nutr* 2004; **24:** 33–54.
3. Miniello VL, *et al.* Soy-based formulas and phyto-oestrogens: a safety profile. *Acta Paediatr Suppl* 2003; **91:** 93–100.
4. Mendez MA, *et al.* Soy-based formulae and infant growth and development: a review. *J Nutr* 2002; **132:** 2127–30.
5. Giampietro PG, *et al.* Soy protein formulas in children; no hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab* 2004; **17:** 191–6.
6. Strom BL, *et al.* Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001; **286:** 807–14.
7. Tuohy PG. Soy infant formula and phytoestrogens. *J Paediatr Child Health* 2003; **39:** 401–5.
8. American Academy of Pediatrics Committee on Nutrition. Soy protein-based formulas: recommendations for use in infant feeding. *Pediatrics* 1998; **101:** 148–53. Also available at: http://www.pediatrics.org/cgi/content/full/101/1/148 (accessed 08/11/05)
9. Conrad SC, *et al.* Soy formula complicates management of congenital hypothyroidism. *Arch Dis Child* 2004; **89:** 37–40.

Effects on the nervous system. CNS disorders in 2 patients given infusions of fractionated soya emulsion included convulsions and coma; cortical blindness developed in one young woman.[1] A similar case was attributed to fat embolism,[2] but, occurring after what the manufacturers pointed out was a faster than recommended infusion,[3] may perhaps have represented a fat-overload syndrome. Neurological complications can be the presenting and principal signs of fat overload; focal and generalised seizures, weakness, and encephalopathy have been reported.[4]

Migraine with visual aura has also been reported in a 57-year old man taking soya beans, soya milk, and a soya protein supplement.[5]

1. Jellinek EH. Dangers of intravenous fat infusions. *Lancet* 1976; **ii:** 967.
2. Estebe JP, Malledant Y. Fat embolism after lipid emulsion infusion. *Lancet* 1991; **337:** 673.
3. McCracken M. Fat embolism after lipid emulsion infusion. *Lancet* 1991; **337:** 983.
4. Schulz PE, *et al.* Neurological complications from fat emulsion therapy. *Ann Neurol* 1994; **35:** 628–30.
5. Engel PA. New onset migraine associated with use of soy isoflavone supplements. *Neurology* 2002; **59:** 1289–90.

Hypersensitivity. Urticaria has been reported in 2 patients after the intravenous use of soya oil emulsions.[1,2] In one case the patient had previously received the emulsion for 19 days without ill-effect.[1]

Anaphylactic reactions have been documented after the ingestion of several foods or foodstuffs containing, or prepared from, soya beans, although the exact allergen remains unknown. In one patient who suffered anaphylactic attacks after eating such products a specific IgE-antibody response to the allergen Kunitz soybean trypsin inhibitor was demonstrated.[3] This was not, however, the only allergen present in soya beans as other patients who had a negative response to this allergen had positive responses in whole soya bean tests. A type I reaction to soya bean protein has been described in patients given parenteral lipid emulsions containing soya bean lecithin as the emulsifier.[4] A patient who ingested a soya protein drink experienced exercise-induced anaphylaxis; skin prick tests were positive to soya, but specific IgE antibodies to soya were undetectable.[5]

IgE antibodies to soya bean antigens have also been found in workers who suffered from asthma after handling soya beans[6,7] leading to the suggestion that an allergic mechanism had been responsible; the asthma was believed to have been due to the dust released during the handling of the beans.

1. Kamath KR, *et al.* Acute hypersensitivity reaction to Intralipid. *N Engl J Med* 1981; **304:** 360.
2. Hiyama DT, *et al.* Hypersensitivity following lipid emulsion infusion in an adult patient. *J Parenter Enteral Nutr* 1989; **13:** 318–20.
3. Moroz LA, Yang WH. Kunitz soybean trypsin inhibitor: a specific allergen in food anaphylaxis. *N Engl J Med* 1980; **302:** 1126–8.
4. Weidmann B, *et al.* Hypersensitivity reactions to parenteral lipid solutions. *Support Care Cancer* 1997; **5:** 504–5.
5. Taramarcaz P, *et al.* Soy anaphylaxis. *Allergy* 2001; **56:** 792.
6. Sunyer J, *et al.* Case-control study of serum immunoglobulin-E antibodies reactive with soybean in epidemic asthma. *Lancet* 1989; **i:** 179–82.
7. Hernando L, *et al.* Asthma epidemics and soybean in Cartagena (Spain). *Lancet* 1989; **i:** 502.

Pulmonary fat emboli. Pulmonary fat emboli or microemboli, sometimes fatal, have occurred in several infants who received infusions of fat emulsions based on soya oil.[1-3]

In one case[3] the patient's serum, which contained a high concentration of C-reactive protein, agglutinated the fat emulsion and this finding was considered to support the hypothesis that microemboli are formed by agglutination of fat emulsion in the blood by C-reactive protein. The authors of this report did not consider the precise pathogenesis to be clear, nor did they know whether the condition was preventable, but did suggest that it might be prudent either to ensure that the C-reactive protein concentration was normal (less than 10 mg/litre) or to perform a creaming test to determine which babies may embolise the infused fat emulsion. However, another study,[4] while not excluding a role of C-reactive protein in agglutination, failed to find any correlation between raised concentrations of this protein and the rate of agglutination. A review[5] classified fat embolism into those derived from direct entry of depot fat into the blood (e.g. after trauma), and those derived from agglutination of endogenous or exogenous fat. High concentrations of C-reactive protein were considered to be responsible for the agglutination of the liposomes of fat emulsions; chylomicrons and very low-density lipoproteins in the blood may also agglutinate, contributing to fat embolism.

1. Barson AJ, *et al.* Fat embolism in infancy after intravenous fat infusions. *Arch Dis Child* 1978; **53:** 218–23.
2. Levene MI, *et al.* Pulmonary fat accumulation after Intralipid infusion in the preterm infant. *Lancet* 1980; **ii:** 815–8.
3. Hulman G, Levene M. Intralipid microemboli. *Arch Dis Child* 1986; **61:** 702–3.
4. Zagara G, *et al.* C-reactive protein and serum agglutination in vivo of intravenous fat emulsions. *Lancet* 1989; **i:** 733.
5. Hulman G. The pathogenesis of fat embolism. *J Pathol* 1995; **176:** 3–9.

Precautions

Intravenous soya oil emulsion should not be given to patients with severe liver disease, acute shock, or severe or pathological hyperlipidaemia, or when the ability to metabolise fat may otherwise be impaired. Caution has also been advised in patients with pulmonary disease, renal insufficiency, uncompensated diabetes mellitus, metabolic disorders, sepsis, anaemia, and some disorders of blood coagulation. If given to such patients, the elimination of fat should be monitored daily.

Intravenous soya oil emulsion may interfere with some laboratory tests if blood is taken before fat has adequately cleared; this may take 4 to 6 hours.

Egg-yolk phospholipids may be used as emulsifiers in some preparations, which should not be given to patients with severe egg allergy.

Fat emulsions may extract phthalate plasticisers from bags and giving sets and non-phthalate containing equipment should be used wherever possible.

Soya-based infant feeds should be avoided in infants with documented cow's milk protein-induced enteropathy or enterocolitis, as these infants are often also sensitive to soya protein.

Neonatal hyperbilirubinaemia. In neonates with hyperbilirubinaemia, intravenous lipid emulsions should be used with caution because of the risk of displacing bilirubin from albumin. The risk appears to be higher in preterm infants,[1] at higher doses,[1] and with intermittent rather than continuous dosing.[2]

1. Spear ML, *et al.* The effect of 15-hour fat infusions of varying dosage on bilirubin binding to albumin. *J Parenter Enteral Nutr* 1985; **9:** 144–7.
2. Brans YW, *et al.* Influence of intravenous fat emulsion on serum bilirubin in very low birthweight neonates. *Arch Dis Child* 1987; **62:** 156–60.

Uses and Administration

Emulsions of fractionated soya oil containing 10, 20, or 30% are given by slow intravenous infusion as part of total parenteral nutrition regimens (p.1923), usually with amino acid and carbohydrate solutions. The solutions and emulsions may be given at separate sites, at the same site through a Y-connector, or combined in one admixture. Fat emulsions provide a high energy intake in a relatively small volume. They may also be used to prevent or correct essential fatty acid deficiency. When used as a calorie source the dose of the emulsion is determined by the energy requirements and clinical status of the patient; the amount of total carbohydrate, generally, should not comprise more than 60% of patients' total calorie intake. For the prevention and correction of fatty acid deficiency about 5 to 10% of total calorific intake should be as an intravenous fat emulsion.

The composition and dosage recommendations of commercial preparations do differ slightly but they should be started slowly. Suggested initial rates for the 10% and 20% products are 1 mL/minute and 0.5 mL/minute respectively for 15 to 30 minutes. The rate may then be increased and up to about 500 mL (or 10 mL/kg) of 10% or 250 mL (or 5 mL/kg) of 20% emulsion may be given on the first day. The total daily dosage may then be increased gradually on subsequent days; suggested daily dose ranges are 500 to 1500 mL of a 10% or 500 to 1000 mL of a 20% emulsion and suggested rates of infusion are 500 mL of a 10% emulsion over a period of not less than 3 hours, and 500 mL of a 20% emulsion over not less than 5 hours. Where a 30% emulsion is used, a dose of 333 mL or about 4.75 mL/kg has been recommended, given over 5 hours or more; the first dose should not exceed 3 mL/kg.

Soya oil also has emollient properties and is used as a bath additive in the treatment of dry skin conditions.

Preparations made from whole soya beans, containing soya oil and soya protein, are used as the basis of lactose-free vegetable milks for infants and patients with lactose or similar disaccharide intolerance or with an allergy to cow's milk protein (see also below).

Administration. It has been suggested[1] that it is the concentration of phospholipid solubilisers, and particularly the excess present as free phospholipid liposomes, that determines the effect of lipid emulsions on plasma-lipid concentrations. In 20 premature infants requiring parenteral nutrition, infusion of up to 4 g/kg of fat daily as a 20% emulsion had less effect on plasma lipid concentrations than 2 g/kg daily as a 10% emulsion; the difference was thought to be due to the fact that the 20% emulsion was relatively liposome-poor, with a ratio of phospholipids to triglycerides of 0.06, whereas the liposome-rich 10% emulsion had a ratio of 0.12. The authors suggested that the 10% emulsion should not be used in preterm infants. Others noted similar results;[2] a 10% lipid emulsion with a reduced phospholipid content has, however, been reported to be relatively well tolerated in premature infants.[3]

For mention of the risk of kernicterus if lipid infusions are given to hyperbilirubinaemic neonates, see under Precautions, above.

1. Haumont D, *et al.* Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992; **121:** 759–63.
2. Cairns PA, *et al.* Tolerance of mixed lipid emulsion in neonates: effect of concentration. *Arch Dis Child Fetal Neonatal Ed* 1996; **75:** F113–F116.
3. Gohlke BC, *et al.* Serum lipids during parenteral nutrition with a 10% lipid emulsion with reduced phospholipid emulsifier content in premature infants. *J Pediatr Endocrinol Metab* 1997; **10:** 505–9.

Food intolerance. The American Academy of Pediatrics has recommended[1] that soya-based infant feeds are appropriate for use in galactosaemia and hereditary lactase deficiency, and documented allergy to cow's milk protein. However, infants with documented cow's milk protein enteropathy or enterocolitis should receive hydrolysed protein formula, as they are likely to be sensitive to soya protein. They concluded that soya-based infant feeds have no proven role in the prevention of atopic disease or in the management of infantile colic. In infants and children at high risk for developing food allergies or intolerance, a systematic review[2] found that there was no evidence that feeding with a soy formula compared to a cow's milk formula reduced the incidence of food allergies or intolerance.

The FDA has warned against the use of soya-based drinks intended for adults as the sole source for nutrition for infants.[3] It was stated that soya drinks can lead to severe protein and calorie malnutrition, multiple vitamin and mineral deficiency, and death in infants who receive no other source of nourishment, and should not be confused with soya-based infant formulas, which are specially formulated to meet the nutritional needs of infants.

For reference to the use of soya-based foods themselves causing allergic reactions, see under Hypersensitivity, above.

1. American Academy of Pediatrics. Soy protein-based formulas: recommendations for use in infant feeding. *Pediatrics* 1998; **101:** 148–53.
2. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/11/05).
3. Nightingale S. Warnings issued about practices, products: soy drink warning. *JAMA* 1985; **254:** 1428.

Hyperlipidaemias. Soya protein has been tried in the treatment of hyperlipidaemia (p.1169). Soya isoflavones such as genistein (p.2391) and daidzein (p.2391) can mimic oestrogen and should therefore have a beneficial effect on blood lipids.[1,2] Other constituents of soya protein, including fytic acid and saponins, may also contribute and thus intact soya protein may provide the maximum cholesterol-lowering effect.[2,3] A meta-analysis of controlled trials found that the substitution of soya protein for animal protein in the diet resulted in significant decreases in serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride concentrations.[4] A subsequent systematic review of studies reached similar conclusions,[1] and the FDA considered that a low-fat diet including 25 g daily of soya protein might reduce the risk of ischaemic heart disease.[2] A later analysis by the American Heart Association[5] considered that cardiovascular benefit was very modest and appeared only when large amounts of animal protein were substituted with soya protein. The effect appeared to be more to do with a broader modification of diet than any effect of soya isoflavones. Soya protein does not appear to have a cholesterol-lowering effect in subjects with normal cholesterol concentrations,[2] although a small study found it to be beneficial in type 2 diabetes patients with near-normal lipid concentrations.[6]

1. Costa RL, Summa MA. Soy protein in the management of hyperlipidemia. *Ann Pharmacother* 2000; **34:** 931–5.
2. Erdman JW. Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. *Circulation* 2000; **102:** 2555–9.
3. Demonty I, *et al.* Role of isoflavones in the hypocholesterolemic effect of soy. *Nutr Rev* 2003; **61:** 189–203.
4. Anderson JW, *et al.* Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995; **333:** 276–82.
5. Sacks FM, *et al.* Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* 2006; **113:** 1034–44.
6. Hermansen K, *et al.* Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. *Diabetes Care* 2001; **24:** 228–33.

Menopausal disorders. Soya contains phytoestrogens in the form of isoflavones, in particular genistein (p.2391) and daidzein (p.2391), which have been investigated for their oestrogen-modulating effects in the treatment of menopausal symptoms (p.2077).[1] It is thought that genistein may exert oestrogenic effects in the presence of low oestrogen concentrations, but that it may be anti-oestrogenic when concentrations of oestrogen are high.[2]

A small reduction in the incidence of hot flushes has been noted with soya isoflavone extract.[3] A systematic review,[4] however, concluded that phytoestrogens available as soya foods, soya extracts, or red clover extracts (p.2285) do not improve hot flushes or other menopausal symptoms.

Isoflavones may have a beneficial effect on cholesterol and lipid concentrations (see Hyperlipidaemias, above). Some epidemiological studies and *animal* data suggest that they may also provide protection against breast cancer.[1,2,5] However, phytoestrogens could also stimulate breast tumour growth due to oestrogenic activity.[6] These stimulating and inhibitory effects may be concentration-dependent; soya products contain only small amounts of phytoestrogens and it may be difficult to consume enough soy to have any beneficial effect on breast cancer growth.[7] A meta-analysis[8] concluded that soya intake may be associated with a small reduction in breast cancer risk, but that this result should be interpreted with caution due to confounding factors and a lack of dose response. Given the possibility of adverse effects, recommendations for high-dose soya isoflavone supplementation to prevent breast cancer or its recurrence are premature.

A few small studies have shown that soya isoflavones can decrease bone turnover, leading to speculation that they could be used to prevent osteoporosis (p.1084).[1] The effects of these isoflavones should be investigated in larger trials before they can be recommended as alternatives to conventional HRT.[5-7,9] (For the view that they may lack cardiovascular benefits see Hyperlipidaemias, above.) In a trial to investigate effects on cognitive function, bone mineral density, and plasma lipids in postmenopausal women, no differences were noted between soya protein containing isoflavones, and placebo.[10]

1. Vincent A, Fitzpatrick LA. Soy isoflavones: are they useful in menopause? *Mayo Clin Proc* 2000; **75:** 1174–84.
2. Goldwyn S, *et al.* Promotion of health by soy isoflavones: efficacy, benefit and safety concerns. *Drug Metabol Drug Interact* 2000; **17:** 261–89.
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4. Krebs EE, *et al.* Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstet Gynecol* 2004; **104:** 824–36.
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6. Mason P. Isoflavones. *Pharm J* 2001; **266:** 16–19.
7. de Lemos ML. Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother* 2001; **35:** 1118–21.
8. Trock BJ, *et al.* Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 2006; **98:** 459–71.
9. Anonymous. The role of isoflavones in menopausal health: consensus opinion of the North American Menopause Society. *Menopause* 2000; **7:** 215–29.
10. Kreijkamp-Kaspers S, *et al.* Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004; **292:** 65–74.

Preparations

USP 31: Lipid Injectable Emulsion.

Proprietary Preparations (details are given in Part 3)

Arg.: Ivelip; Lipofundin N; Lipovenos; Piascledine; Sojar Pro; Soyacal; ***Austral.:*** Intralipid; Ivelip†; ***Austria:*** Balneum; Elolipid; Intralipid; Lipovenos; Olbad Cordes; ***Belg.:*** Gynosoya; ***Braz.:*** Endolipid†; Fisiogen; Isofarma†; ***Canad.:*** Intralipid; ***Chile:*** Lipofundin; Lipovenos; ***Cz.:*** Balneum Hermal; Elolipid†; Intralipid; Ivelip†; Lipofundin N†; Lipovenoes; Soyacal; ***Denm.:*** Intralipid; ***Fin.:*** Intralipid; ***Fr.:*** Endolipide†; Gastro'Aid; Gydrelle Phyto; Gynalpha; Intralipide; Ivelip; Phyto Soya; ***Ger.:*** Allergika†; Balneoconzen N; Balneovit; Balneum; Deltalipid; Eucerin Omega Olbad†; Intralipid; Lipofundin N; Lipopharm; Lipostabil; Lipovenos; Olbad Cordes; Penatoel†; salvilipid; Soyacal; ***Gr.:*** Intralipid; Lipovenoes†; ***Hong Kong:*** Intralipid; Lipofundin N; ***Hung.:*** Intralipid; Lipofundin; Lipovenos†; Structolipid; ***Indon.:*** Intralipos; ***Irl.:*** Balneum; Intralipid; ***Israel:*** Balneum; Intralipid; Ivelip; ***Ital.:*** Balneum Hermal; Elolipid; Intralipid; Ivelip†; Lipofundin S; Lipovenos; Soyacal†; ***Jpn:*** Intrafat†; ***Malaysia:*** Intralipid; Intralipos†; ***Mex.:*** Ivelip†; Lipofundin N; Lipovenoes; ***Neth.:*** Intralipid; Lipovenos; ***Norw.:*** Intralipid; ***NZ:*** Intralipid; Ivelip; ***Philipp.:*** Soyacal; ***Pol.:*** Balneum Hermal; Intralipid; Ivelip; Lipofundin N; Soya Meno; Soyfem; ***Port.:*** Banholeum; Emulsao de Lipidos; Endolipide; Intralipid; Lipovenoes; Soyacal; ***Singapore:*** Intralipid; Intralipos; ***Spain:*** Aquiflav; Bluna; Fitoladius; Flavodrei; Intralipid; Isodonna; Ivelip; Lipovenos; Malena; Phyto Soya; Pleginer; Primsoja; Soyacal; ***Swed.:*** Intralipid; Lipovenos†; ***Switz.:*** Balmed Hermal; Balmed Hermal Plus; Balneum Hermal†; Intralipid; Lipovenos; ***Thai.:*** Intralipid; Intralipos†; Ivelip; Lipofundin N; Lipofundin S; Lipovenoes†; ***Turk.:*** Intralipid; Ivelip; Lipovenos; ***UK:*** Balneum; Intralipid; Ivelip; Lipofundin; ***USA:*** Intralipid; Liposyn III; ***Venez.:*** Intralipid†; Ivelip; Lipofundin N†.

Multi-ingredient: ***Arg.:*** Clinoleic; Derrumal; Kabiven; Lipofundin MCT/LCT-E; Lipofundin MCT/LCT†; Liposomas; Sigmafem; Sojar Plus-Calcio; ***Austral.:*** Bioglan Mens Super Soy/Clover; Bioglan Soy Power Plus; Extralife Meno-Care; Hypol; Lifechange Menopause Formula†; PhytoLife; Soy Forte with Black Cohosh†; ***Austria:*** Balneum Plus; Clinoleic; Clinomel; Compleven†; Gesamtnahrlosung; KabiMix; Kabiven; Lipofundin mit MCT; Nutriflex Lipid; Olbad Cordes comp; Oleosint; OliClinomel; PE-Mix; SMOFlipid; Structolipid; TriMix; Vitromix; ***Belg.:*** Medialipide†; ***Braz.:*** Borag; Piascledine; ***Chile:*** Kabiven; Lipofundin MCT/LCT; Liposyn†; Lipovenos MCT/LCT; ***Cz.:*** Balneum Hermal Plus; Clinoleic; Clinomel†; Kabiven; Lipofundin MCT/LCT; Lipoplus; Nutralipid MCT†; Nutralipid P†; Nutriflex Lipid; OliClinomel; Piascledine; SMOFlipid; ***Denm.:*** Clinoleic; Kabiven; Liposyn†; OliClinomel; SMOFlipid; Vitrimix†; ***Fin.:*** Clinoleic; Compleven†; Kabiven; Lipoplus; Liposyn†; Nutriflex Lipid; OliClinomel; Structolipid; Vamin Glukos Combi†; Vasolipid; ***Fr.:*** Biopause; Biopause solution intime; Clinoleic; Clinomel†; Gynosoja; KabiMix†; Kabiven; Medialipide; Nutriflex Lipide; OliClinomel; Perikabiven; Piascledine; StructoKabiven; Structolipide; Vitrimix KV; ***Ger.:*** Abbolipid†; Balneum Plus; Clinoleic; Clinomel†; Compleven†; Kabiven; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; Oleobal; OliClinomel; SMOFlipid; Sulfo-Olbad Cordes†; Windol Basisbad†; ***Gr.:*** Clinoleic; Clinomel; Kabiven; Lipofundin MCT/LCT; Nutriflex Lipid; OliClinomel; SMOFlipid; ***Hong Kong:*** Apaisac; Kabiven; Lipofundin MCT/LCT; Nutriflex Lipid; Sawmetto Vivo-Livo†; Vitrimix KV; ***Hung.:*** Clinomel†; Kabiven; Lipofundin MCT; Lipovenos PLR†; OliClinomel; SMOFlipid; ***Indon.:*** Hepabion; Ivelip; Kabiven; Lanaven; Lipofundin MCT/LCT; Lipovenoes; Maxitrin; Vitrimix; ***Irl.:*** Balneum Plus; Vitrimix KV; ***Israel:*** Balneum Plus; Clinoleic; Kabiven; Lipofundin MCT/LCT; Liposyn; ***Ital.:*** Acumel; Climil Complex; Climil-80; Clinoleic; Clinomel†; Demalit; Fitogen; Ginil; KabiMix†; Kabiven; Lipofundin MCT; Liposyn†; Nutriperi Lipid; Nutriplus Lipid; Nutrispecial Lipid; OliClinomel; Periven; Piascledine; Pluvio; Pulsalux; Sojyam†; Soymen; Structolipid; Triacid; Trivemil†; ***Malaysia:*** Kabiven; Vitrimix KV†; ***Mex.:*** Bano Coloide; Caltrate + S; Clinoleic†; Clinomel†; Kabiven; Lipofundin MCT/LCT; Liposyn; Lipovenoes MCT†; Piascledine; Riban; Soyaloid; Soyaloid Apruri; Soydex; Sy-Clinomel†; ***Neth.:*** Clinoleic; KabiMix†; Kabiven; Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; OliClinomel; SMOFlipid; Structolipid; Vitrimix KV; ***Norw.:*** Ivamix†; KabiMix†; Kabiven; Nutriflex Lipid; SMOFlipid; Vasolipid; Vitrimix†; ***NZ:*** Kabiven; ***Philipp.:*** Her Soy Plus; ***Pol.:*** Balneum Hermal Plus; Clinoleic; Clinomel; Compleven; Kabiven; Lecigal†; Lipofundin MCT/LCT; Naturapia Menopauza; Piascledine; SMOFlipid; ***Port.:*** Banholeum Composto; Banholeum Gele; Clinoleic; Lipofundina MCT/LCT; Lipoplus; Nutribraun; Nutriplasmal; OliClinomel; Structolipid; Vitrimix; ***Rus.:*** Kabiven (Кабивен); Piascledine (Пиаскледин); ***S.Afr.:*** Clinomel; Lipofundin MCT/LCT; ***Singapore:*** Celatrac; Kabiven; Lipofundin MCT/LCT†; ***Spain:*** Clinoleic; Clinomel†; Fitogyn; KabiMix†; Kabiven; Lipofundina MCT/LCT; Nutriflex Lipid; Nutriplasmal†; OliClinomel; Structolipid; ***Swed.:*** Clinoleic; Clinomel†; Compleven†; KabiMix†; Kabiven; Lipoplus; Liposyn†; Nutriflex Lipid; OliClinomel; SMOFlipid; Structolipid; Vasolipid; Vitrimix†; ***Switz.:*** Antidry; Balneum Hermal Plus†; Clinoleic; Lipofundin MCT/LCT; Nutriflex Lipid; OliClinomel; Structolipid; ***Thai.:*** Kabiven; Lipofundin MCT/LCT; OliClinomel; Vitrimix; ***Turk.:*** Lipofundin MCT/LCT; Liposyn; Vitrimix; ***UK:*** Balneum Plus; Clinoleic; Compleven†; Kabiven; Lipidem; Lipofundin MCT/LCT; OliClinomel; Phytolife Plus; SMOFlipid; Structolipid; Vitrimix KV†; Ymea; ***USA:*** Liposyn II; Tucks; ***Venez.:*** Lipofundin MCT/LCT.

Stannous Fluoride

Fluoruro estañoso; Stannosi Fluoridum. Tin fluoride.

SnF_2 = 156.7.

CAS — 7783-47-3.

ATC — A01AA04.

ATC Vet — QA01AA04.

Pharmacopoeias. In *US.*

USP 31 (Stannous Fluoride). A white crystalline powder. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a freshly prepared 0.4% solution in water is between 2.8 and 3.5.

Stability. Aqueous solutions of stannous fluoride decompose within a few hours with the formation of a white precipitate; they slowly attack glass.

Profile

Stannous fluoride is used as a source of fluoride (see Sodium Fluoride, p.1962) for the prophylaxis of dental caries. Dental gels containing concentrations of stannous fluoride 0.4% are available for daily use. Higher concentrations have been applied under professional supervision. Stannous fluoride has also been used in dentifrices and mouth rinses.

Stannous fluoride has an unpleasant taste.

Preparations

USP 31: Stannous Fluoride Gel.

Proprietary Preparations (details are given in Part 3)

Fr.: Emoform; ***Ital.:*** Fluorigard Gel-Kam; Gel-Kam†; Oral-B Pasta Dentifricia Denti e Gengive; ***Switz.:*** Parocare†; ***UK:*** Fluorigard Gel-Kam; ***USA:*** Gel Kam; Gel-Kam; Gel-Tin; PerioMed; Stop.

Multi-ingredient: ***Fr.:*** Meridol†; ***Israel:*** Meridol; ***Ital.:*** Actifluor†.

Starch

Almidón; Amido; Amidon; Amidon de blé (wheat starch); Amidon de maïs (maize starch); Amidon de pomme de terre (potato starch); Amidon de riz (rice starch); Amidon prégélatinisé (pregelatinised starch); Amilo; Amylum; Amylum pregelificatum (pregelatinised starch); Bulvių krakmolas (potato starch); Burgonyakeményítő (potato starch); Búzakeményítő (wheat starch); Hidegenduzzadó keményítő (pregelatinised starch); Kukoricakeményítő (maize starch); Kukurūzų krakmolas (maize starch); Kviečių krakmolas (wheat starch); Maissitärkkelys (maize starch); Majsstärkelse (maize starch); Maydis amylum (maize starch); Oryzae amylum (rice starch); Perunatärkkelys (potato starch); Potatisstärkelse (potato starch); Pregelifikuotas krakmolas (pregelatinised starch); Pšeničný škrob (wheat starch); Riisitärkkelys (rice starch); Risstärkelse (rice starch); Rizskeményítő (rice starch); Ryžių krakmolas (rice starch); Škrob bramborový (potato starch); Škrob kukuřičný (maize starch); Škrob předbobtnalý (pregelatinised starch); Škrob rýžový (rice starch); Skrobia kukurydziana (maize starch); Skrobia pszeniczna (wheat starch); Skrobia ziemniaaczana (potato starch); Solani amylum (potato starch); Stärke; Tritici amylum (wheat starch); Vehnätärkkelys (wheat starch); Vetestärkelse (wheat starch).

CAS — 9005-25-8 (starch); 9005-82-7 (α-amylose); 9004-34-6 (β-amylose); 9037-22-3 (amylopectin).

Description. Starch consists of polysaccharide granules obtained from the caryopsis of maize, *Zea mays*, rice, *Oryza sativa*, wheat, *Triticum aestivum* (*T. vulgare*), from the tubers of potato, *Solanum tuberosum* or from the rhizomes of cassava, *Manihot utilissima*. Maize starch is also known as corn starch. Starch contains amylose and amylopectin, both polysaccharides based on α-glucose.

Pharmacopoeias. Some or all of the starches described are included in *Chin., Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Chin. and *Eur.* also include Pregelatinised Starch, *USNF* also includes Pregelatinized Starch, Modified Starch, and Pregelatinized Modified Starch. *US* includes Absorbable Dusting Powder and Topical Starch.

Ph. Eur. 6.2 (Maize Starch; Maydis Amylum). It is obtained from the caryopsis of *Zea mays*. It is a tasteless, matt, white to slightly yellowish, very fine powder that creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. Store in airtight containers.

Ph. Eur. 6.2 (Potato Starch; Solani Amylum). It is obtained from the tuber of *Solanum tuberosum*. It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 5.0 to 8.0. Store in airtight containers.

Ph. Eur. 6.2 (Rice Starch; Oryzae Amylum). It is obtained from the caryopsis of *Oryza sativa*. It is a tasteless, very fine, white or almost white powder which creaks when pressed between the fingers. The presence of granules with cracks or irregularities on the edge is exceptional. Practically insoluble in cold water and in alcohol. Store in airtight containers.

Ph. Eur. 6.2 (Wheat Starch; Tritici Amylum). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). It is a very fine, white or almost white powder which creaks when pressed between the fingers. It does not contain starch grains of any other origin but may contain a minute quantity, if any, of fragments of the tissue of the original plant. Practically insoluble in cold water and in alcohol. The pH of a 20% mixture in water after 15 minutes is 4.5 to 7.0. Store in airtight containers.

Ph. Eur. 6.2 (Pregelatinised Starch; Amylum Pregelificatum). It is prepared from maize starch, potato starch, or rice starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules, and subsequent drying. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics. It is a white or yellowish white powder that swells in cold water.

BP 2008 (Tapioca Starch). It is obtained from the rhizomes of *Manihot utilissima*. It is a very fine powder which creaks when pressed between the fingers. Practically insoluble in cold water and in alcohol. Store in airtight containers.

The BP 2008 gives Cassava Starch as an approved synonym.

The BP 2008 directs that when starch is specified and the type is not indicated, Maize Starch, Potato Starch, Rice Starch, Wheat Starch, or in tropical countries where these are not available, Tapioca Starch may be supplied or used.

USNF 26 (Corn Starch). It consists of the starch granules separated from the mature grain of corn, *Zea mays* (Gramineae). Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.0 to 7.0.

USNF 26 (Potato Starch). It is obtained from the tuber of *Solanum tuberosum*. Irregular, angular, white masses or fine powder. Is odourless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 5.0 to 8.0.

USNF 26 (Tapioca Starch). Granules separated from the tubers of tapioca (cassava), *Manihot utilissima* (Euphorbiaceae). Irregular, angular, white to pale yellow masses or fine powder. Insoluble in cold water and in alcohol. A 20% slurry in water after 5 minutes of continuous agitation has a pH of 4.5 to 7.0.

USNF 26 (Wheat Starch). It is obtained from the caryopsis of *Triticum aestivum* (*T. vulgare*). Irregular, angular, white masses or fine powder. Is odourless and has a slight, characteristic taste. Insoluble in cold water and in alcohol. A 20% slurry in water, allowed to stand for 15 minutes after 1 minute of moderate agitation, has a pH of 4.5 to 7.0.

USNF 26 (Pregelatinized Starch). It is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. It may be modified to render it compressible and flowable.

USNF 26 (Modified Starch). It is starch modified by chemical means. Food starch may be acid-modified, bleached, oxidised, esterified, etherified, or treated enzymatically to change its functional properties. A 20% slurry in water, after 5 minutes stirring at a moderate rate, has a pH of 3.0 to 9.0.

USNF 26 (Pregelatinized Modified Starch). It is Modified Starch that has been chemically or mechanically processed, or both, to rupture all or part of the granules to produce a product that swells in cold water. Moderately coarse to fine, white to off-white powder. It is odourless and has a slight, characteristic taste. Slightly soluble to soluble in cold water; insoluble in alcohol.

Adverse Effects

Effects of cassava. In 1985 WHO added *malnutrition-related diabetes* (which included the type previously known as tropical diabetes) to its classification of diabetes mellitus.[1] Epidemiological evidence had suggested an association between fibrocalculous pancreatic diabetes (a subclass of malnutrition-related diabetes) and the consumption of cassava root (tapioca, manioc), which for many people living in tropical developing countries, where protein intake was low, was the main source of food energy.

Cassava root contains several cyanogenic substances and although food preparation and processing could reduce the cyanide content, there was the possibility that in persons with an inadequate protein intake, particularly if deficient in sulfur-containing amino acids which are involved in detoxification pathways, accumulation of cyanides might occur. WHO, however, did consider that further research was necessary to firmly establish any relation between this type of diabetes and high levels of cassava consumption. In a review that appeared in the following year[2] the cassava/malnutrition hypothesis was thought to be attractive, but unproven; also there was strong evidence against it being the only cause.

WHO deleted malnutrition-related diabetes from its most recent report on the classification of diabetes.[3] Fibrocalculous pancreatic diabetes is now fibrocalculous pancreatopathy, a disease which may cause diabetic mellitus but is not considered a form of diabetes.

Konzo, an upper motor neurone disease characterised by spastic paraparesis,[4] and commonly associated with optic neuropathy,[5] has been reported to be caused by dietary exposure to cyanide after ingestion of cassava root. *Growth retardation* has also been associated with consumption of inadequately processed cassava.[6]

1. WHO. Diabetes mellitus: report of a WHO study group. *WHO Tech Rep Ser 727* 1985.
2. Abu-Bakare A, *et al.* Tropical or malnutrition-related diabetes: a real syndrome? *Lancet* 1986; **i:** 1135–8.
3. Alberti KGMM, Zimmet PZ. Definition, diagnosis, and classification of diabetes mellitus and its complications. Part I: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; **15:** 539–53.
4. Ernesto M, *et al.* Persistent konzo and cyanogen toxicity from cassava in northern Mozambique. *Acta Trop* 2002; **82:** 357–62.
5. Mwanza J-C, *et al.* Neuro-ophthalmologic findings in konzo, an upper motor neuron disorder in Africa. *Eur J Ophthalmol* 2003; **13:** 383–9.
6. Banea-Mayambu J-P, *et al.* Dietary cyanide from insufficiently processed cassava and growth retardation in children in the Democratic Republic of Congo (formerly Zaire). *Ann Trop Paediatr* 2000; **20:** 34–40.

Glove powder. The use of starch glove powders by surgeons has resulted in contamination of surgical wounds by starch and in the development of complications such as inflammation, adhesions, and granulomatous lesions. In addition, glove starch powder may be a risk factor in the development of latex allergy, and may act as a vector for bacterial pathogens. Because of these risks, it has been proposed that the use of powder in latex gloves be banned.[1-4]

1. Haglund U, Junghanns K, eds. Glove powder—the hazards which demand a ban. *Eur J Surg* 1997; **163** (suppl 579): 1–55.
2. AAAAI and ACAAI joint statement concerning the use of powdered and non-powdered natural latex gloves. *Ann Allergy Asthma Immunol* 1997; **79:** 487.
3. Dave J, *et al.* Glove powder: implications for infection control. *J Hosp Infect* 1999; **42:** 282–5.
4. Edlich RF, Reddy VR. A call to ban glove cornstarch. *Arch Surg* 2001; **136:** 116.

Uses and Administration

Starch is absorbent and is widely used in dusting powders, either alone or mixed with zinc oxide or other similar substances. Starch is used as a surgical glove powder, but such use has been discouraged (see above). It is incorporated in many tablets as a binder, diluent, or disintegrating agent. Pregelatinised starch is used similarly as a tablet binder.

Starch mucilage is given by mouth in the treatment of iodine poisoning; it has been used topically as a skin emollient.

Rice-based solutions may be used in the prevention and treatment of dehydration due to acute diarrhoeal diseases (p.1694).

Glycogen storage disease type I. Type I glycogen storage disease is an autosomal recessive metabolic disorder in which glucose-6-phosphatase is not expressed, resulting in hypoglycaemia due to lack of glucose production. Accumulation of glycogen and other metabolic derangements can lead to complications including renal impairment, hepatomegaly and hepatic adenoma, hyperuricaemia, hyperlipidaemias, and lactic acidosis. The condition has been successfully managed by continuous nocturnal nasogastric infusion of glucose and frequent daytime feedings. However, such a regimen requires good patient compliance and monitoring of the night-time infusions.[1] As an alternative, a more standard diet together with uncooked corn starch suspensions prepared with tap water at room temperature and taken every 6 hours in doses of 1.75 to 2.5 g/kg have been reported[2] to be very satisfactory in maintaining normoglycaemia. In one infant, in whom starch was unsatisfactory, the lack of response was considered to be due to inadequate pancreatic amylase activity and although it was subsequently reported[3] that addition of a pancreatic enzyme concentrate had produced some improvement, the response was still inadequate to maintain normoglycaemia for more than 2 hours. It was considered that other amylase preparations should be identified for possible use in such patients. A small study of 7 young adults with glycogen storage disease type I found that a single dose of uncooked corn starch maintained plasma glucose concentrations for 7 hours in 5 of the patients.[4] A long-term study of the effects of corn starch therapy found that complications were less among patients with near normal metabolic control and in those having started therapy at a younger age, but other factors appeared to be involved in the pathogenesis.[5] Corn starch therapy has nonetheless been reported to have caused the amelioration of proximal renal tubular dysfunction in 3 patients who had previously only received frequent daytime feeding as therapy. In 16 other patients who had previously received treatment with corn starch or glucose infusions such renal dysfunction was not identified and it was considered that the rapid response to therapy may explain why renal tubular dysfunction is not found more frequently in these patients.[6]

Because optimal metabolic control reduces the risk of developing long-term complications, an attempt has been made to define guidelines for long-term management of the disease.[7] Continuous nocturnal nasogastric feeding with a glucose or glucose polymer or a sucrose-free maltodextrin formula low in lactose may be introduced in very young infants. Uncooked corn starch should not be started in patients under 1 year of age as pancreatic amylase activity may be immature. Thereafter, since no significant differences in growth or biochemical parameters have been found between the use of nocturnal nasogastric infusions and uncooked corn starch overnight, corn starch may be started at a dose of 250 mg/kg and increased slowly to prevent adverse effects. It is recommended that the corn starch be mixed with water in a ratio of 1:2 and that an uncooked corn starch tolerance test be performed to establish the duration of the fasting period. The total dietary plan should aim to provide 60 to 65% of the total energy intake from carbohydrates, 10 to 15% from protein, and the remainder from fat, preferably vegetable oils with a high linoleic acid content. Lactose, fructose, and sucrose should be restricted. Drug therapy for metabolic complications may be necessary, such as allopurinol for hyperuricaemia, and bicarbonate for correction of lactic acidosis.[7]

For mention of the possible role of starch in glycogen storage disease type V, see under Sucrose, p.1970.

For a brief description of glycogen storage disease type II, see under Acid Alpha Glucosidase, p.2245.

1. Goldberg T, Slonim AE. Nutrition therapy for hepatic glycogen storage diseases. *J Am Diet Assoc* 1993; **93:** 1423–30.
2. Chen Y-T, *et al.* Cornstarch therapy in type 1 glycogen-storage disease. *N Engl J Med* 1984; **310:** 171–5.
3. Chen Y-T, Sidbury JB. Cornstarch therapy in type 1 glycogen-storage disease. *N Engl J Med* 1984; **311:** 128–9.
4. Wolfsdorf JI, Crigler JF. Cornstarch regimens for nocturnal treatment of young adults with type I glycogen storage disease. *Am J Clin Nutr* 1997; **65:** 1507–11.
5. Weinstein DA, Wolfsdorf JI. Effect of continuous glucose therapy with uncooked cornstarch on the long-term clinical course of type 1a glycogen storage disease. *Eur J Pediatr* 2002; **161** (suppl): S35–S39.

6. Chen Y-T, *et al.* Amelioration of proximal renal tubular dysfunction in type I glycogen storage disease with dietary therapy. *N Engl J Med* 1990; **323:** 590–3.
7. Rake JP, *et al.* Guidelines for management of glycogen storage disease type I - European study on glycogen storage disease type I (ESGSD I). *Eur J Pediatr* 2002; **161** (suppl): S112–S119.

Preparations

BP 2008: Compound Zinc Paste; Dithranol Paste; Talc Dusting Powder; ***USP 31:*** Absorbable Dusting Powder; Topical Starch.

Proprietary Preparations (details are given in Part 3)
Austral.: Karicare Food Thickener; ***Mex.:*** Panaline†; ***NZ:*** Karicare Food Thickener.

Multi-ingredient: ***Austral.:*** Nucolox; ZSC; ***Braz.:*** Talco Alivio†; ***Fr.:*** Magic Mix; Poudre du Marcheur; ***India:*** Feel Chill; ***Israel:*** Baby Paste; ***Ital.:*** Lenipasta†; ***NZ:*** Lamisil Odor Eze; Nucolox†; ***Port.:*** Cuidaderma; ***S.Afr.:*** SB Universal Ointment; ***UK:*** Herbheal Ointment; Psorasolv; Skin Clear; ***USA:*** Balmex Baby; Desitin with Zinc Oxide; Diaparene Corn Starch; Mexsana; Norforms†; Paladin; Yeast-X†.

Stevioside

Esteviósido; Eupatorin; Rebaudin; Stevin; Steviosin.
$C_{38}H_{60}O_{18}$ = 804.9.
CAS — 57817-89-7.

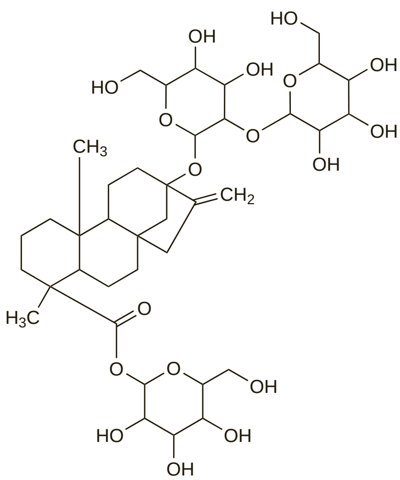

Pharmacopoeias. In *Chin.*

Profile

Stevioside is a glycoside extracted from the leaves of yerba dulce, *Stevia rebaudiana* (Compositae). It has about 300 times the sweetness of sucrose and has been used as a sweetening agent in foods. Both the related glycoside rebaudioside A (rebiana), and an extract of the leaves of *Stevia rebaudiana* which contains these and other glycosides, have been used similarly. The use of stevioside or stevia leaves as a sweetener has been banned in some countries due to concerns about genotoxicity and possible effects on fertility.

◊ References.

1. Geuns JM. Stevioside. *Phytochemistry* 2003; **64:** 913–21.

Hypertension. The antihypertensive action of stevioside has been investigated. An oral dose of 250 mg three times daily was found to lower blood pressure in patients with mild to moderate hypertension,[1] and 500 mg three times daily decreased blood pressure and the incidence of left ventricular hypertrophy in patients with mild hypertension.[2]

1. Chan P, *et al.* A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. *Br J Clin Pharmacol* 2000; **50:** 215–20.
2. Hsieh M-H, *et al.* Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clin Ther* 2003; **25:** 2797–2808.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Edulsan; Steviadulri.

Multi-ingredient: ***Chile:*** Nature Complex Reduct-Te.

Sucralose *(BAN)*

Sucralosa; Sucralosum; TGS; Trichlorogalactosucrose. 1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl 4-chloro-4-deoxy-α-D-galactopyranoside.
$C_{12}H_{19}Cl_3O_8$ = 397.6.
CAS — 56038-13-2.

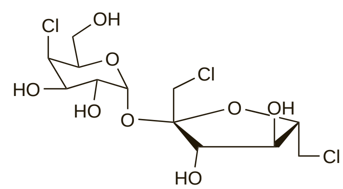

Pharmacopoeias. In *USNF.*

USNF 26 (Sucralose). A white to off-white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in ethyl acetate. Store in a cool, dry place at a temperature not exceeding 21°.

Profile

Sucralose is used as a sweetening agent in foods, beverages, and pharmaceuticals. It has between about 300 and 1000 times the sweetening power of sucrose and is stable to heat. It has no food value and is noncariogenic.

◊ References.

1. Anonymous. Sucralose—a new artificial sweetener. *Med Lett Drugs Ther* 1998; **40:** 67–8.
2. Roberts A, *et al.* Sucralose metabolism and pharmacokinetics in man. *Food Chem Toxicol* 2000; **38** (suppl): S31–S41.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Sugafor.

Sucrose

Azúcar; Cane Sugar; Refined Sugar; Sacarosa; Saccharose; Saccharosum; Saccharum; Sacharosa; Sacharoza; Sacharozė; Sackaros; Sakkaroosi; Sucre; Sucrosum; Szacharóz; Zucker. β-D-Fructofuranosyl-α-D-glucopyranoside.
$C_{12}H_{22}O_{11}$ = 342.3.
CAS — 57-50-1.

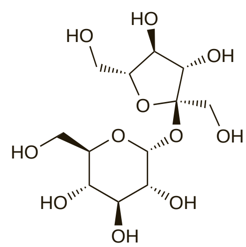

Description. Sucrose is obtained from sugar-cane, *Saccharum officinarum* (Gramineae), sugar-beet, *Beta vulgaris* (Chenopodiaceae), and other sources.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *Viet.* Also in *USNF.*
Br. also contains Compressible Sugar.
Eur. also includes Sugar Spheres.
USNF also includes Compressible Sugar, Confectioner's Sugar, and Sugar Spheres.

Ph. Eur. 6.2 (Sucrose). A white or almost white, crystalline powder or shiny, colourless or white or almost white crystals. Very soluble in water; slightly soluble in alcohol; practically insoluble in dehydrated alcohol.

USNF 26 (Sucrose). A sugar obtained from *Saccharum officinarum* (Gramineae), *Beta vulgaris* (Chenopodiaceae), and other sources. White, crystalline powder or lustrous, dry, colourless or white crystals. Soluble 1 in 0.5 of water, 1 in 0.2 of boiling water, and 1 in 170 of alcohol; practically insoluble in dehydrated alcohol.

Incompatibility. Sucrose may be contaminated by traces of heavy metals or sulfites and this can lead to incompatibility with other ingredients when it is used as a pharmaceutical excipient. Syrup preserved with hydroxybenzoates has been reported to be incompatible with a range of compounds.

Adverse Effects and Precautions

Sucrose consumption increases the incidence of dental caries.

Sucrose use should be avoided in patients with the glucose-galactose malabsorption syndrome, fructose intolerance, or sucrase-isomaltase deficiency. The intake of sucrose from dietary and other sources must be controlled in patients with diabetes mellitus.

Dietary sugar. The Panel on Dietary Sugars reviewed the evidence relating to sugars in the diet and the health of the population in the UK.[1]

No evidence was found that the consumption of most sugars naturally incorporated into the cellular structure of foods (intrinsic sugars) represented a threat to health and consideration was therefore mainly directed towards the dietary use of sugars not so incorporated (extrinsic sugars), of which sucrose was the principal non-milk extrinsic sugar.

There was extensive evidence suggesting that sugars were the most important dietary factor in the cause of dental caries and it was recommended that consumption of non-milk extrinsic sugars should be decreased.

It was considered that dietary sugars may contribute to the development of obesity, a condition which plays an important part in the aetiology of a number of diseases. For the majority of the population, who had normal plasma lipids and normal glucose tolerance, the consumption of sugars within the present range carried no special metabolic risks but those persons consuming more than about 200 g daily should replace the excess with starch. It was, however, recommended that those with special medical problems such as diabetes or hypertriglyceridaemia should restrict non-milk extrinsic sugar to less than about 20 to 50 g daily unless otherwise instructed by their own physician or dietitian. It was also concluded that current consumption of sugars, particularly sucrose, played no direct causal role in the development of cardiovascular (atherosclerotic coronary, peripheral, or cerebral vascular) disease, essential hypertension, or diabetes mellitus, and also had no significant specific effects on behaviour or psychological function. Although links between sucrose intake and certain other diseases (such as colorectal cancer, renal and biliary calculi, and Crohn's disease) had been proposed it was not felt that the evidence was adequate to justify any general dietary recommendations.

The conclusions of a joint FAO/WHO consultation on carbohydrates in human nutrition[2] were broadly in agreement with the above. However, they noted that the terms intrinsic and extrinsic sugars had not gained wide acceptance, either in the UK or other countries in the world, and they recommended against the use of these terms.

1. DoH. Dietary sugars and human disease: report of the panel on dietary sugars of the committee on medical aspects of food policy. *Report on health and social subjects 37.* London: HMSO, 1989.
2. FAO/WHO. *Carbohydrates in human nutrition: report of a joint FAO/WHO expert consultation. FAO Food and Nutrition 66.* Rome: Food and Agriculture Organization of the United Nations, 1998.

Effects on the kidneys. Acute renal failure with severe hyponatraemia has followed the use of granulated sugar to treat an infected pneumonectomy wound cavity.[1] It was noted that intravenous sucrose had long been known to be nephrotoxic in both *animal* models and man and that mild renal insufficiency before sucrose intoxication might have contributed to the nephrosis. Others, however, considered that the nephrotoxicity might have been caused by gentamicin, a solution of which had been used to irrigate the cavity before packing the wound.[2] Intravenous immunoglobulin preparations containing sucrose (as a stabilising agent) have also caused acute renal failure.[3,4]

1. Debure A, *et al.* Acute renal failure after use of granulated sugar in deep infected wound. *Lancet* 1987; **i:** 1034–5.
2. Archer H, *et al.* Toxicity of topical sugar. *Lancet* 1987; **i:** 1485–6.
3. Ahsan N, *et al.* Intravenous immunoglobulin-induced osmotic nephrosis. *Arch Intern Med* 1994; **154:** 1985–7.
4. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; **93:** 901–4.

Pharmacokinetics

Sucrose is hydrolysed in the small intestine by the enzyme sucrase to glucose and fructose, which are then absorbed. Sucrose is excreted unchanged in the urine when given intravenously.

Uses and Administration

Sucrose, a disaccharide, is used as a sweetening agent. It is commonly used as household sugar. If the sweetness of sucrose is taken as 100, fructose has a value of about 173, glucose 74, maltose 32, galactose 32, and lactose 16.

Sucrose is used as a tablet excipient and lozenge basis, and as a suspending and viscosity-increasing agent. Syrups prepared from concentrated solutions of sucrose form the basis of many linctuses. Treacle (molasses), a byproduct of sugar production that contains sucrose and minerals, has also been used.

Sucrose 30% eye drops have been used as a hypertonic agent for clearing corneal oedema.

Cough. Sucrose syrups are used as demulcents in linctuses used for treating cough (p.1547).

Diagnostic test for gastrointestinal damage. Sucrose is not absorbed from the healthy gastrointestinal tract. It has been proposed that the absorption of sucrose could be used as a diagnostic test of gastric damage.[1-3]

1. Sutherland LR, *et al.* A simple non-invasive marker of gastric damage: sucrose permeability. *Lancet* 1994; **343:** 998–1000.
2. Meddings JB, *et al.* Sucrose permeability: a novel means of detecting gastroduodenal damage noninvasively. *Am J Ther* 1995; **2:** 843–9.
3. Kawabata H, *et al.* Sucrose permeability as a means of detecting diseases of the upper digestive tract. *J Gastroenterol Hepatol* 1998; **13:** 1002–6.

Gastrointestinal spasm. For mention of a beneficial effect of sucrose solution in infant colic, see p.1696.

Glycogen storage disease type V. Glycogen storage disease type V (McArdle's disease) is a rare autosomal recessive disorder characterised by mutations in the gene for myophosphorylase, an enzyme essential for glycogenolysis.[1,2] Patients present with exercise-induced pain, cramps, fatigue, and myoglobinuria which, if severe, can cause acute renal failure.[2] Low-dose creatine supplementation (60 mg/kg daily) produced modest benefits during ischaemic exercise testing, but higher doses (150 mg/kg daily) worsened symptoms.[2] Sucrose 75 g by mouth improved exercise tolerance in 12 patients in a randomised crossover study.[1] Uncooked corn starch, either alone or with sucrose, has been suggested as an alternative in order to avoid any pronounced increase in serum insulin,[3] but this has been rejected on the basis that the necessary rapid increase in blood glucose will not be produced.[4]

1. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med* 2003; **349:** 2503–9.
2. Quinlivan R, Beynon RJ. Pharmacological and nutritional treatment for McArdle's disease (glycogen storage disease type V). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).
3. Gaglia JL, Wolfsdorf JI. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; **350:** 1575.
4. Vissing J, Haller RG. Oral sucrose and exercise tolerance in McArdle's disease. *N Engl J Med* 2004; **350:** 1575–6.

Hiccup. Giving a teaspoon of dry granulated sugar resulted in the immediate cessation of hiccup in 19 of 20 patients;[1] 12 of the patients had suffered from hiccup for less than 6 hours but in the remaining 8 persistent hiccup had been present for 24 hours to 6 weeks. The effect may be due to stimulation of the pharynx. An early protocol for the treatment of intractable hiccup (p.976) suggests that swallowing dry granulated sugar is one of the first treatments that should be tried.

1. Engleman EG, *et al.* Granulated sugar as treatment for hiccups in conscious patients. *N Engl J Med* 1971; **285:** 1489.

Pain. A systematic review[1] concluded that sucrose solutions could reduce physiological and behavioural indicators of stress and pain in neonates undergoing painful procedures although there had been some doubt expressed[2] over whether this indicated effective analgesia. The review[1] was unable to determine an optimal dose, but 1 mL of a 25% solution or 2 mL of a 50% solution has been reported to reduce crying time in premature[3] and full-term[4] infants, respectively, when given 2 minutes before heel-prick sampling. Similarly, 2 mL of a 75% sucrose solution by mouth reduced crying time in infants given intramuscular vaccines,[5] and 2 mL of oral sucrose 24% reduced pain scores in premature infants undergoing eye examinations for retinopathy of prematurity.[6] One literature review[7] suggested that a dose of 500 mg sucrose provided effective analgesia for neonates. However, a randomised study found pacifiers (dummies) to have a better analgesic effect than 2 mL of a 30% sucrose solution; a synergistic effect was found with a combination of sucrose and pacifiers.[8] Another review[9] recommended that, along with a pacifier, 0.1 to 0.4 mL of a 24% sucrose solution be given to premature infants, and up to 2 mL be given to term infants. Others have recommended the use of 0.5 mL/kg of a 33% sucrose solution (about 170 mg/kg), stating that more dilute solutions carry a risk of bacterial contamination.[10] The route by which sucrose solution is given may also be important: a reduced pain response was only noted after intraoral doses; giving it via a nasogastric tube was ineffective.[11]

A study in preterm infants found that, while there were no differences on neurobehavioural developmental outcomes between infants given repeated sucrose analgesia or placebo, higher number of doses of sucrose predicted lower scores in motor development, vigour, alertness and orientation. The authors postulated that repeated stimulation by sucrose may interfere with normal functioning and maturation of the preterm infant's endogenous opiate system, and cautioned against the routine use of sucrose analgesia in this population.[12] For choice of analgesic in children, see p.3.

1. Stevens B, *et al.* Sucrose for analgesia in newborn infants undergoing painful procedures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 08/11/05).
2. Anonymous. Pacifiers, passive behaviour, and pain. *Lancet* 1992; **339:** 275–6.
3. Ramenghi LA, *et al.* Reduction of pain response in premature infants using intraoral sucrose. *Arch Dis Child* 1996; **74:** F126–F128.
4. Haouari N, *et al.* The analgesic effect of sucrose in full term infants: a randomised controlled trial. *BMJ* 1995; **310:** 1498–1500.
5. Lewindon PJ, *et al.* Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. *Arch Dis Child* 1998; **78:** 453–6.
6. Gal P, *et al.* Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* 2005; **39:** 1029–33.
7. Masters-Harte LD, Abdel-Rahman SM. Sucrose analgesia for minor procedures in newborn infants. *Ann Pharmacother* 2001; **35:** 947–52.
8. Carbajal R, *et al.* Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates. *BMJ* 1999; **319:** 1393–7.
9. Prince WL, *et al.* Treatment of neonatal pain without a gold standard: the case for caregiving interventions and sucrose administration. *Neonatal Netw* 2004; **23:** 33–45.
10. Shann F. Suckling and sugar reduce pain in babies. *Lancet* 2007; **369:** 721–3.
11. Ramenghi LA, *et al.* "Sucrose analgesia": absorptive mechanism or taste perception. *Arch Dis Child Fetal Neonatal Ed* 1999; **80:** F146–F147.
12. Johnston CC, *et al.* Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics* 2002; **110:** 523–8.

Wound healing. Sugar, either in the form of granulated sugar[1-5] or pastes composed of caster sugar and icing sugar,[6,7] has been used successfully in the treatment of wounds (p.1585) including mediastinitis after cardiac surgery,[1,3] large abscesses and bed sores,[6,7] diabetic ulcers,[2,4] and recurrent bone infections after surgical debridement in patients with leprosy.[5] Debridement of the wound is believed to be due partly to the osmotic effect of sugar and partly to the mechanical cleansing action but it is not known how sugar stimulates granulation tissue to form.[6,7] Once granulation tissue is well established and the wound is shrinking, an alternative wound preparation, such as an alginate, hydrocolloid, or hydrogel, should be used as sugar pastes cause bleeding.[8] Sugar is also effective at deodorising malodorous wounds. The use of the combined caster and icing sugar pastes, of which details of the formulas used are provided in the original publications,[6,7] has been advocated as a way to overcome the problems of possible non-sterility and contamination of commercial granulated sugar.[6,7]

Honey (p.1948) has been used similarly.

1. Trouillet JL, *et al.* Use of granulated sugar in treatment of open mediastinitis after cardiac surgery. *Lancet* 1985; **ii:** 180–4.
2. Quatraro A, *et al.* Sugar and wound healing. *Lancet* 1985; **ii:** 664.
3. De Feo M, *et al.* Treatment of recurrent postoperative mediastinitis with granulated sugar. *J Cardiovasc Surg* 2000; **41:** 715–19.
4. Kilic A. Healing of diabetic ulcers with granulated sugar. *Plast Reconstr Surg* 2001; **108:** 585.
5. Grauwin MY, *et al.* Comment guérir les ostéites et ostéo-arthrites des extrémités des anciens malades de la lèpre par le sucre cristallisé alimentaire? *Acta Leprol* 1999; **11:** 147–52.
6. Gordon H, *et al.* Sugar and wound healing. *Lancet* 1985; **ii:** 663–4.
7. Middleton KR, Seal D. Sugar as an aid to wound healing. *Pharm J* 1985; **235:** 757–8.
8. Seal DV, Middleton K. Healing of cavity wounds with sugar. *Lancet* 1991; **338:** 571–2.

Preparations

BP 2008: Compressible Sugar; Syrup;
Ph. Eur.: Sugar Spheres;
USNF 26: Compressible Sugar; Confectioner's Sugar; Sugar Spheres; Syrup.

Proprietary Preparations (details are given in Part 3)
Fr.: Gelodiet.

Multi-ingredient: ***Arg.:*** Equalsweet; Sucaryl; ***Austral.:*** Nyal Chesty Cough†; ***Irl.:*** Venos Expectorant; ***Jpn:*** U-Pasta; ***S.Afr.:*** Emetrol; ***UK:*** Honey & Molasses; Venos Cough Mixture; Venos Expectorant.

Sucrose Polyesters

Sacarosa, poliésteres de la.

Profile

A sucrose polyester that is a mixture of hexa-, hepta-, and octa-fatty acid esters of sucrose is used as a nondigestible fat substitute by the food industry. Fat substitutes have been promoted as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

Possible adverse effects of sucrose polyesters are flatulence, anal leakage, abdominal cramps, and loose bowel movements. They may also reduce the absorption of fat-soluble vitamins.

◊ References.

1. Cotton JR, *et al.* Replacement of dietary fat with sucrose polyester: effects on energy intake and appetite control in non-obese males. *Am J Clin Nutr* 1996; **63:** 891–6.
2. Goldman P. Olestra: assessing its potential to interact with drugs in the gastrointestinal tract. *Clin Pharmacol Ther* 1997; **61:** 613–18.
3. Cheskin LJ, *et al.* Gastrointestinal symptoms following consumption of olestra or regular triglyceride potato chips: a controlled comparison. *JAMA* 1998; **279:** 150–2.
4. Sandler RS, *et al.* Gastrointestinal symptoms in 3181 volunteers ingesting snack foods containing olestra or triglycerides. *Ann Intern Med* 1999; **130:** 253–61.
5. Bray GA, *et al.* A 9-mo randomized clinical trial comparing fat-substituted and fat-reduced diets in healthy obese men: the Ole Study. *Am J Clin Nutr* 2002; **76:** 928–34.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Heartfelt†.

Sunflower Oil

Aceite de girasol; Auringonkukkaöljy; Helianthi annui oleum; Helianthi Oleum; Huile de Tournesol; Napraforgóolaj; Olej słonecznikowy; Oleum Helianthi; Saulėgrąžų aliejus; Slunečnicový olej; Solrosolja; Sonnenblumenöl; Sunflowerseed Oil; Tournesol, huile de.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sunflower Oil, Refined; Helianthi Annui Oleum Raffinatum). The fatty oil obtained from the seeds of *Helianthus annuus* by mechanical expression or by extraction and then refined. A suitable antioxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40° to 60°). Store in well-filled airtight containers. Protect from light.

USNF 26 (Sunflower Oil). A refined fixed oil obtained from the seeds of the sunflower plant *Helianthus annuus* (Asteraceae alt. Compositae). Specific gravity between 0.914 and 0.924 at 20°. Store in airtight containers. Protect from light.

Profile

Sunflower oil is the fixed oil expressed from the fruits of *Helianthus annuus*. It is used as a salad oil and in pharmaceutical preparations. It is rich in linoleic acid (p.2308).

Multiple sclerosis. As discussed on p.892, the role of dietary lipids in multiple sclerosis remains to be proven,[1] although many patients modify their diets and take supplements of sunflower and other oils. One study showed a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil).[2] Another[3] reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[4] of the relationship between dietary interventions (including linoleic acid given as sunflower oils) and multiple sclerosis concluded that there was insufficient evidence to determine their benefits or risks.

1. Anonymous. Lipids and multiple sclerosis. *Lancet* 1990; **336:** 25–6.
2. Millar JHD, *et al.* Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; **1:** 765–8.
3. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; **336:** 37–9.
4. Farinotti M, *et al.* Dietary interventions for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Oleoban†.

Multi-ingredient: ***Arg.:*** Alofresh†; Prueboi†; ***Austral.:*** Snor-Away†; ***Austria:*** Pelsana Med; Piniment; ***Fr.:*** Oropur; ***Hong Kong:*** Sanjukei Panax Ginseng; ***India:*** Efaderm; ***Ital.:*** DHA; ***NZ:*** Snorenz; ***Port.:*** Oleoban Composto†; Oleoban Gel†; ***Switz.:*** Huile de millepertuis A. Vogel (huile de St. Jean); Pelsano; ***UK:*** Goodnight StopSnore; Snor-Away.

Tagatose

D-*lyxo*-hexulose; D-Tagatose; Tagatosum; Tagatoza.

$C_6H_{12}O_6$ = 180.2.

CAS — 87-81-0 (tagatose); 17598-81-1 (DL-tagatose).

Pharmacopoeias. In *USNF.*

USNF 26 (Tagatose). Tagatose is a ketohexose, an epimer of fructose inverted at C-4. It is obtained from galactose by isomerisation under alkaline conditions in the presence of calcium. White or almost white crystals, having a sweet taste. Very soluble in water; very slightly soluble in alcohol.

Profile

Tagatose is a naturally occurring monosaccharide, produced commercially from lactose. It is 92% as sweet as sucrose, but contains fewer calories. It may be used as a sweetener in foods, beverages, toothpaste, mouthwashes, and medicines.

Thaumatin *(BAN)*

E957; Katemfe; Taumatina.

CAS — 53850-34-3.

Profile

Thaumatin is a protein extracted from the fruit of *Thaumatococcus daniellii* (Marantaceae); it is a mixture of polypeptides thaumatin I and thaumatin II, each consisting of 207 amino acid residues and having a molecular weight of about 22 000. The amino-acid range excludes histidine. Thaumatin is an odourless, cream-coloured powder with an intensely sweet taste. The sweetness builds up gradually but persists for up to an hour, and is considered to be by far the sweetest of such compounds in use, having 2000 to 3000 times the sweetness of sucrose. It is approved as a sweetener and flavour modifier in foods, beverages, and pharmaceuticals.

Threonine *(USAN, rINN)*

β-Methylserine; T; Thr; Threonin; Thréonine; L-Threonine; Threoninum; Treoniini; Treonin; Treonina; Treoninas. L-2-Amino-3-hydroxybutyric acid.

Треонин

$C_4H_9NO_3$ = 119.1.

CAS — 72-19-5.

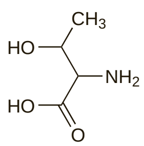

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Threonine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 2.5% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Threonine). White, odourless crystals. Freely soluble in water; insoluble in dehydrated alcohol, in chloroform, and in ether. pH of a 5% solution in water is between 5.0 and 6.5.

Profile

Threonine is an amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

Threonine has been investigated for the treatment of various spastic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Stimolfit.

Tyrosine *(USAN, rINN)*

Tirosina; Tirozin; Tirozinas; Tyr; Tyrosiini; Tyrosin; L-Tyrosine; Tyrosinum; Tyrozyna; Y. L-2-Amino-3-(4-hydroxyphenyl)propionic acid.

Тирозин

$C_9H_{11}NO_3$ = 181.2.

CAS — 60-18-4.

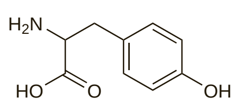

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Tyrosine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Tyrosine). White, odourless crystals or crystalline powder. Very slightly soluble in water; insoluble in alcohol and in ether.

Profile

Tyrosine is an aromatic non-essential amino acid. It is used as a dietary supplement.

Phenylketonuria. Tyrosine was not an effective alternative to a diet low in phenylalanine in patients with phenylketonuria, see under Amino Acid Metabolic Disorders, p.1922.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Aussie Tan Pre-Tan; Bioglan Zellulean with Escin; Tyroseng†; ***India:*** Placentrex; ***Port.:*** Rilastil Dermo Solar.

Valine *(USAN, rINN)*

α-Aminoisovaleric Acid; V; Val; Valiini; Valin; Valina; Valinas; L-Valine; Valinum. (*S*)-2-Amino-3-methylbutanoic acid.

Валин

$C_5H_{11}NO_2$ = 117.1.

CAS — 72-18-4.

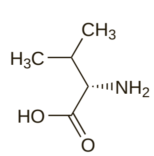

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Valine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. Protect from light.

USP 31 (Valine). White, odourless crystals. Soluble in water; practically insoluble in alcohol, in acetone, and in ether. pH of a 5% solution in water is between 5.5 and 7.0.

Profile

Valine is a branched-chain aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement. It is also an ingredient of several preparations that have been promoted for disorders of the liver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Revitalose; ***Ger.:*** Bramin-hepa†; Falkamin; ***Ital.:*** Falkamin†; Isobranch; Isoram.

Vitamin A *(USAN)*

Retinol *(BAN, rINN)*; Antixerophthalmic Vitamin; A-vitamiini; A-vitamin; Axerophtholum; Oleovitamin A; Rétinol; Retinolum; Vitamin A Alcohol; Vitaminas A; Vitamine A; Vitaminum A; Witamina A. 15-Apo-β-caroten-15-ol; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraen-1-ol.

Ретинол

$C_{20}H_{30}O$ = 286.5.

CAS — 68-26-8.

ATC — A11CA01; D10AD02; R01AX02; S01XA02.

ATC Vet — QA11CA01; QD10AD02; QR01AX02; QS01XA02.

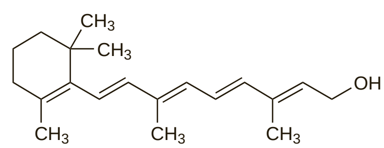

Description. Vitamin A is generally used in the form of esters, such as the acetate, palmitate, and propionate.

Vitamin A Acetate. Retinol Acetate; Retinyl Acetate; $C_{22}H_{32}O_2$ = 328.5; CAS — 127-47-9

Vitamin A Palmitate. Retinol Palmitate; Retinyl Palmitate; $C_{36}H_{60}O_2$ = 524.9; CAS — 79-81-2

Vitamin A Propionate. Retinol Propionate; Retinyl Propionate; $C_{23}H_{34}O_2$ = 342.5; CAS — 7069-42-3.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*, which permit retinol or its esters.

Chin. includes a monograph for the acetate. *Jpn* includes monographs for the acetate and the palmitate.

Br. includes a monograph for a natural ester concentrate.

Eur. also includes monographs for synthetic concentrates in an oily form, a powder form, and a solubilisate/emulsion.

Int. includes an oily concentrated form.

The BP 2008 states that the term 'Retinol' is used within BP titles for preparations containing synthetic ester(s) and the term 'Vitamin A' within the BP title for the preparation containing material of natural origin.

Ph. Eur. 6.2 (Vitamin A). Under the name Vitamin A are included a number of substances of very similar structure (including (*Z*)-isomers) found in animal tissues and possessing similar activity. The principal and biologically most active substance is all-(*E*) retinol.

Vitamin A is generally used in the form of esters such as the acetate, propionate, and palmitate. Synthetic retinol ester refers to an ester (acetate, propionate, or palmitate) or a mixture of synthetic retinol esters.

Retinol acetate occurs as pale yellow crystals. M.p. about 60°; once melted it tends to yield a supercooled melt. Retinol propionate occurs as a reddish-brown oily liquid. Retinol palmitate occurs as a fat-like, light yellow solid, or as a yellow oily liquid, if melted. M.p. about 26°. All retinol esters are practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Oily Form), Synthetic; Vitaminum A Densatum Oleosum; Synthetic Retinol Concentrate (Oily Form) BP 2008). It is prepared from synthetic retinol ester as is or by dilution with a suitable vegetable oil. It contains not less than 500 000 units of vitamin A per g. It is a yellow or brownish-yellow, oily liquid; practically insoluble in water; soluble or partly soluble in dehydrated alcohol; miscible with organic solvents. Partial crystallisation may occur in highly concentrated solutions.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Powder Form), Synthetic; Vitaminum A Pulvis; Synthetic Retinol Concentrate (Powder Form) BP 2008). It is obtained by dispersing a synthetic retinol ester in a matrix of gelatin or acacia or other suitable material. It contains not less than 250 000 units of vitamin A per g. It is a yellowish powder usually in the form of particles of almost uniform size. Practically insoluble in water or may swell or form an emulsion, depending on formulation.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

Ph. Eur. 6.2 (Vitamin A Concentrate (Solubilisate/Emulsion), Synthetic; Vitaminum A in Aqua Dispergibile; Synthetic Retinol Concentrate, Solubilisate/Emulsion BP 2008). It is a liquid form (water is generally used as solvent) of synthetic retinol ester and a suitable solubiliser. It contains not less than 100 000 units of vitamin A per g. It is a yellow or yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or take the form of a gel. A mixture of 1 g with 10 mL of water previously warmed to 50° gives after cooling to 20°, a uniform, slightly opalescent and slightly yellow dispersion.

Store in airtight containers. Protect from light. Once the container has been opened, its contents should be used as soon as possible and any part of the contents not used at once should be protected by an atmosphere of inert gas.

BP 2008 (Natural Vitamin A Ester Concentrate). It consists of a natural ester or a mixture of natural esters of retinol or of a solution of the ester or mixture of esters in arachis oil or other suitable vegetable oil. It contains not less than 485 000 units of vitamin A per g. It is a yellow oil or a mixture of oil and crystalline material, with a faint odour. Practically insoluble in water; soluble or partly soluble in alcohol; miscible with chloroform, with ether, and with petroleum spirit. Store in airtight containers at 8° to 15°. Protect from light.

USP 31 (Vitamin A). It may consist of retinol or its esters formed from edible fatty acids, principally acetic and palmitic acids. In liquid form, it is a light yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. It may be practically odourless or may have a mild fishy odour but no rancid odour or taste. It is unstable in air and light. In liquid form, it is insoluble in water and in glycerol; soluble in dehydrated alcohol and in vegetable oils; very soluble in chloroform and in ether. In solid form, may be dispersible in water. Store in airtight containers, preferably under an atmosphere of inert gas. Protect from light.

Units

The International Standards for vitamin A and for provitamin A were discontinued in 1954 and 1956 respectively but the International units for these substances have continued to be widely used. In 1960–1, the WHO Expert Committee on Biological Standardization stated that the International unit for vitamin A is equivalent to the activity of 0.000344 mg of pure all-*trans* vitamin A acetate and the International unit for provitamin A is equivalent to the activity of 0.0006 mg of pure all-*trans* β-carotene.

The activity of one International unit is contained in 0.0003 mg of all-*trans* retinol, in 0.00055 mg of all-*trans* retinol palmitate, and in 0.000359 mg of all-*trans* retinol propionate.

The USP 31 defines 1 USP unit as equal to the biological activity of 0.0003 mg of the all-*trans* isomer of retinol, and is equivalent to the International unit.

Vitamin A activity in foods is currently expressed in terms of retinol equivalents: 1 retinol equivalent is defined as 1 microgram of all-*trans* retinol, 6 micrograms of all-*trans* beta carotene, or 12 micrograms of other provitamin A carotenoids.

Adverse Effects and Precautions

The use of excessive amounts of vitamin A substances over long periods can lead to toxicity. Rarely, acute toxicity may also occur with very high doses.

- Hypervitaminosis A (chronic toxicity) is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low-grade fever, hepatomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), pruritus, alopecia, dry hair, cracking and bleeding lips, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia, and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, and visual disturbances which may be severe. Symptoms usually clear on withdrawal of vitamin A, but in children premature closure of the epiphyses of the long bones may result in arrested bone growth.

- Acute vitamin A intoxication is characterised by sedation, dizziness, confusion, diarrhoea and vomiting, sore mouth, bleeding gums, desquamation, and increased intracranial pressure (resulting in bulging fontanelle in infants or severe headache in adults). Hepatomegaly and visual disturbances may occur; irritability may be severe.

Hypervitaminosis A does not appear to be a problem with large doses of carotenoids (see Pharmacokinetics under Betacarotene, p.1931).

Enhanced susceptibility to the effects of vitamin A may be seen in children and in patients with liver disease.

Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects; for further details see Pregnancy, below.

Gastrointestinal absorption of vitamin A may be impaired in cholestatic jaundice and fat-malabsorption conditions.

Benign intracranial hypertension. High doses of vitamin A cause increased intracranial pressure, and, in infants, this is manifested as bulging of the fontanelle. In one study,[1] 11.5% of infants receiving 3 doses of 50 000 units of vitamin A at monthly intervals had bulging fontanelle, compared with 1% of infants receiving placebo. The bulging lasted between 24 and 72 hours and subsided without treatment,[1] and did not appear to be associated with any physical or developmental abnormalities on long-term follow-up.[2] In another study in neonates, bulging fontanelle occurred in 4.6% of recipients of vitamin A 50 000 units and 2.7% of placebo recipients 24 hours after the dose.[3] In contrast, less than 1% of infants given 3 doses of 25 000 units of vitamin A at monthly intervals had bulging fontanelle in a further study.[4]

1. de Francisco A, *et al.* Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993; **342:** 526–7.
2. van Dillen J, *et al.* Long-term effect of vitamin A with vaccines. *Lancet* 1996; **347:** 1705.
3. Agoestina T, *et al.* Safety of one 52 micromol (50 000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994; **72:** 859–68.
4. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid.* 1999; **353:** 154.

Carcinogenicity. For mention of the *increased* risk of lung cancer in high-risk individuals receiving betacarotene and vitamin A, when compared with placebo, in a study investigating vitamins in lung cancer prevention, see Prophylaxis of Malignant Neoplasms, p.1927.

Effects on the blood. Normochromic macrocytic anaemia developed in a patient who had been receiving vitamin A 150 000 units daily by mouth for several months.[1] The patient's haemoglobin returned to normal when vitamin A was stopped, and the accompanying symptoms of perioral dermatitis and glossitis also disappeared. Similarly, normochromic normocytic anaemia and thrombocytopenia in an infant given 62 000 units daily for 80 days, resolved on stopping vitamin A.[2] In contrast, vitamin A has been reported to have a beneficial effect on anaemia, see under Deficiency states, below.

1. White JM. Vitamin-A-induced anaemia. *Lancet* 1984; **ii:** 573.
2. Perrotta S, *et al.* Infant hypervitaminosis A causes severe anemia and thrombocytopenia: evidence of a retinol-dependent bone marrow cell growth inhibition. *Blood* 2002; **99:** 2017–22.

Effects on bone. Excessive dietary intake of vitamin A may be associated with osteoporosis. In an epidemiological study,[1] a dietary intake of retinol greater than 1500 micrograms daily (5000 units) doubled the risk of hip fracture compared with an intake of less than 500 micrograms daily (about 1670 units) in women (odds ratio, 2.1; 95% confidence interval 1.1 to 4.0). These data were confirmed by the Nurses' Health Study,[2] which found that postmenopausal women with the highest vitamin A and retinol intakes were at increased risk for hip fracture, irrespective of whether the intakes were from food plus supplements, or food alone. Women with daily retinol intakes of more than 1500 micrograms had a relative risk for hip fracture of 1.64 compared with those consuming less than 500 micrograms daily. Betacarotene intake, however, did not correlate significantly with an increased risk of fracture. A large cohort study[3] of men found that the overall risk of any fracture, including hip fractures, was substantially increased among men with the highest concentrations of serum retinol; there was no association between serum betacarotene levels and the risk of fracture. Subsequently, routine supplementation and the fortification of food with vitamin A in western countries has been questioned.[4] A report[5] from the UK Government's Scientific Advisory Committee on Nutrition cautions against the intake of more than 1.5 mg of vitamin A daily in those at increased risk of osteoporosis, such as postmenopausal women and the elderly. However, results from a cohort study in the elderly[6] suggest a U-shaped dose relationship, in that both high and low intakes of vitamin A were associated with reduced bone mineral density, and another study[7] in women aged between 50 and 74 years, found both high and low serum vitamin A concentrations to be associated with an increased risk of hip fracture.

1. Melhus H, *et al.* Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 1998; **129:** 770–8.
2. Feskanich D, *et al.* Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002; **287:** 47–54.
3. Michaëlsson K, *et al.* Serum retinol levels and the risk of fracture. *N Engl J Med* 2003; **348:** 287–94.
4. Lips P. Hypervitaminosis A and fractures. *N Engl J Med* 2003; **348:** 347–9.
5. Scientific Advisory Committee on Nutrition. *Review of dietary advice on vitamin A.* London: The Stationery Office, 2005. Also available at: http://www.sacn.gov.uk/pdfs/sacn_vita_report.pdf (accessed 21/07/08)
6. Promislow JHE, *et al.* Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. *J Bone Miner Res* 2002; **17:** 1349–58.
7. Opotowsky AR, Bilezikian JP. Serum vitamin A concentration and the risk of hip fracture among women 50 to 74 years old in the United States: a prospective analysis of the NHANES I Follow-up Study. *Am J Med* 2004; **117:** 169–74.

Effects on the immune system. Vitamin A deficiency is generally associated with impaired immunity, and treatment of deficiency results in reductions in morbidity and mortality from a number of infectious diseases (see under Deficiency States, below). However, a few studies have shown increased prevalence of diarrhoea and/or respiratory-tract infections with high doses of vitamin A. There is a possibility that high single doses of vitamin A may temporarily attenuate the immune response in non-deficient children.[1] For the effect of high-dose vitamin A supplements on the response to measles vaccine in some studies, see p.2222.

1. Anonymous. Childhood morbidity, immunity and micronutrients. *WHO Drug Inf* 1996; **10:** 12–16.

Effects on the liver. Vitamin A is stored in the Dissë space of liver cells and excessive dosage can lead to fibrosis and obstruction of sinusoidal blood flow, causing non-cirrhotic portal hypertension and hepatocellular dysfunction.[1] Although hepatotoxicity has typically been reported with habitual ingestion of doses of vitamin A greater than 50 000 units daily, a case of severe hepatic fibrosis, with jaundice and hepatomegaly, has been reported in a patient who had been taking 25 000 units daily for at least 6 years in a multivitamin supplement.[2]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Kowalski TE, *et al.* Vitamin A hepatotoxicity: a cautionary note regarding 25,000 IU supplements. *Am J Med* 1994; **97:** 523–8.

Effects on mortality. Vitamin A supplementation has been reported to have beneficial effects on childhood mortality, especially in developing countries, see Deficiency States, below *et seq.* However, a systematic review of antoxidant supplementation in adults concluded that vitamin A either singly or with other antioxidants increased mortality.[1]

1. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Hypersensitivity. Local inflammatory reactions and severe anaphylactoid reactions have occurred in patients receiving vitamin A injections, and are usually attributed to solubilisers such as polyoxyl castor oils (p.1918), and, less commonly, polysorbates (p.1919).

A case of cutaneous hypersensitivity to retinol palmitate itself has been described.[1]

1. Shelley WB, *et al.* Hypersensitivity to retinol palmitate injection. *BMJ* 1995; **311:** 232.

Overdosage. Although no clinical manifestations of toxicity were seen in 3 boys who ingested large amounts of vitamin A, their serum retinol concentrations continued to rise over about 3 weeks, and took several months to normalise; the authors cautioned that the use of chewable vitamins resembling confectionery may increase the risk of overdose in children.[1]

1. Lam HS, *et al.* Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. *Pediatrics* 2006; **118:** 820–4.

Pregnancy. The fact that synthetic vitamin A derivatives such as isotretinoin are teratogenic (p.1601) has prompted concern about the potential teratogenicity of high doses of vitamin A.

A prospective cohort study found that a total daily intake of vitamin A from all sources of greater than 15 000 units during early pregnancy was associated with a significantly increased risk of birth defects of structures arising from the cranial neural crest.[1] When vitamin A intake from supplements was analysed separately, an apparent vitamin A threshold dose for the development of birth defects of 10 000 units daily was suggested. However, this study has been criticised[2,3] and some suggest the data allows for a higher threshold dose.[3] A further study found no significant difference in birth defect rates between women consuming greater than 8000 or 10 000 units of vitamin A daily in the period around conception (as supplements and fortified cereals) and those consuming less than 5000 units daily.[4]

After earlier case reports in the USA suggesting that large doses of vitamin A (equivalent to about ten times the daily recommended dietary allowance of 2250 units) taken in early pregnancy may cause birth defects, the UK Chief Medical Officer cautioned women against the use of vitamin A supplements except under medical supervision.[5] Additionally, advice was given that liver or liver products should not be eaten because high concentrations of vitamin A had been detected in some samples of animal liver. However, others thought that the avoidance of liver or liver products might result in inadequate nutrition in some and that a less alarmist view might have been to suggest a limitation on intake rather than total prohibition.[6,7]

The American College of Obstetricians and Gynecologists has recommended that women who are pregnant or planning pregnancy should ensure that any vitamin supplements they take contain a daily dose of vitamin A of no more than 5000 units.[8] The Australian Adverse Drug Reactions Advisory Committee has advised women in this category to avoid vitamin A supplements and to not exceed the recommended daily allowance of 2500 units from all sources.[9]

1. Rothman KJ, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1995; **333:** 1369–73.
2. Werler MM, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1195–6.
3. Watkins M, *et al.* Teratogenicity of high vitamin A intake. *N Engl J Med* 1996; **334:** 1196.
4. Mills JL, *et al.* Vitamin A and birth defects. *Am J Obstet Gynecol* 1997; **177:** 31–6.
5. Department of Health. *Women cautioned: watch your vitamin A intake.* London: Department of Health, 1990 (18 October).
6. Nelson M. Vitamin A, liver consumption, and risk of birth defects. *BMJ* 1990; **301:** 1176.
7. Sanders TAB. Vitamin A and pregnancy. *Lancet* 1990; **336:** 1375.
8. American College of Obstetricians and Gynecologists. ACOG committee opinion: vitamin A supplementation during pregnancy. Number 196, January 1998 (replaces No. 157, September 1995). *Int J Gynaecol Obstet* 1998; **61:** 205–6.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Vitamin A and birth defects. *Aust Adverse Drug React Bull* 1996; **15:** 14–15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 21/07/08)

Interactions

Absorption of vitamin A from the gastrointestinal tract may be reduced by the presence of neomycin, colestyramine, or liquid paraffin.

There is an increased risk of hypervitaminosis A if vitamin A is given with synthetic retinoids such as acitretin, isotretinoin, and tretinoin.

There is conflicting evidence regarding the effect of vitamin A on the response to measles vaccine (see p.2222).

Pharmacokinetics

Vitamin A substances are readily absorbed from the gastrointestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake, or impaired liver or pancreatic function. Vitamin A esters are hydrolysed by pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. It is released from the liver bound to a specific α_1-globulin (retinol-binding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid; these and other metabolites are excreted in urine and faeces. Vitamin A does not readily diffuse across the placenta (but see Pregnancy, above), but is present in breast milk.

◊ References.

1. Hartmann D, *et al.* Pharmacokinetic modelling of the plasma concentration-time profile of the vitamin retinyl palmitate following intramuscular administration. *Biopharm Drug Dispos* 1990; **11:** 689–700.
2. Reinersdorff DV, *et al.* Plasma kinetics of vitamin A in humans after a single oral dose of [8,9,19-] retinyl palmitate. *J Lipid Res* 1996; **37:** 1875–85.
3. Harrison EH, Hussain MM. Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *J Nutr* 2001; **131:** 1405–8.

Human Requirements

Dietary vitamin A is derived from 2 sources, *preformed retinoids* from animal sources such as liver, kidney, dairy produce, and eggs (fish-liver oils are the most concentrated natural source), and *provitamin carotenoids* which can be obtained from many plants; the latter are converted to retinol in the body but are less effectively utilised. Carotenes (α, β, and γ) are major sources and of these, β-carotene (betacarotene—see p.1930) has the highest vitamin A activity and is the most plentiful in food. Variable amounts of β-carotenes are found in carrots and dark green or yellow vegetables. Red palm oil is a good source of α- and β-carotenes.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published[1] for vitamin A and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women (but see Pregnancy, above). In the UK the reference nutrient intake (RNI) for adult males and females is 700 and 600 micrograms retinol equivalents (about 2330 and 2000 units) daily, respectively and the estimated average requirement (EAR) is 500 and 400 micrograms retinol equivalents (about 1660 and 1330 units) daily, respectively. This UK report[1] also highlighted the toxicity associated with large doses of vitamin A and recommended that regular intakes should not exceed 9000 micrograms (30 000 units) daily in adult men and 7500 micrograms (25 000 units) daily in adult women. (A later report[3] was unable to establish a safe upper level for vitamin A intake, but considered that total intakes above 1500 micrograms retinol equivalents daily might be inappropriate.) Figures were also given in the earlier report for infants and children who were said to be more sensitive to the effects of vitamin A. These limits did not apply to therapeutic doses of vitamin A used under medical supervision.[1] In pregnancy the RNI is 700 micrograms retinol equivalents (2330 units) daily and in nursing mothers 950 micrograms (3160 units) daily. In the USA the RDA for adults is 900 micrograms daily for men and 700 micrograms daily for women.[2] The tolerable upper intake level is 3000 micrograms daily.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 06/01/06)

Uses and Administration

Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency develops when the dietary intake is inadequate and is seen more frequently in young children than in adults. It is rare in developed countries but remains a major problem in many developing countries. Prolonged deficiency leads to xerophthalmia or 'dry eye', the initial symptom of which is night blindness which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

Vitamin A is used in the treatment and prevention of vitamin A deficiency. It may be given orally in an oil- or water-based form, the oil-based generally being the preferred type. It can also be given by intramuscular injection of a water-miscible form; oil-miscible preparations of vitamin A are poorly absorbed from injection sites after intramuscular injection and are not usually given by this route. For further details concerning vitamin A supplementation, including doses for the treatment and prophylaxis of xerophthalmia, see below.

Vitamin A supplements are often given to patients with primary biliary cirrhosis or chronic cholestatic liver disease as deficiencies are common in these disorders. An intramuscular dose of 100 000 units every 2 to 4 months has been suggested.

Vitamins A and D have been used together in creams or ointments in the treatment of minor skin disorders including abrasions. Vitamin A has also been used alone to treat various skin disorders including acne and psoriasis. It has been tried in patients with retinitis pigmentosa to retard the decline in retinal function.

Deficiency states. Vitamin A deficiency is relatively rare in developed countries and is usually only seen in certain medical conditions such as biliary cirrhosis or cholestatic jaundice. However, it is a continuing problem in many developing countries and children appear to be particularly vulnerable.

In **developing countries** where dietary intake is often less than desirable, infections such as measles, acute respiratory diseases, and diarrhoea can be major precipitating factors of vitamin A deficiency. Thus WHO have targeted elimination of vitamin A deficiency as an important strategy in child health,[1,2] and as part of the Expanded Programme on Immunization. They recommend the use of vitamin A supplements in the treatment of vitamin A deficiency and to prevent vitamin A deficiency where the periodic use of supplements is determined to be the most feasible and effective method of improving vitamin A status.

- In *universal distribution programmes*,[2,3] supplemental doses are given to all children up to the age of 5 at a dose of 200 000 units every 4 to 6 months, with infants between the ages of 6 and 12 months receiving half this dose. Infants aged less than 6 months may receive 50 000 units if they are not breast fed or if they are breast fed and their mothers have not received supplemental vitamin A. If clinical signs of vitamin A deficiency are evident at the time of routine supplementation, treatment should be given as described under Xerophthalmia, below. Mothers should receive 200 000 units within 6 weeks of delivery of a child.
- *Targeted distribution programmes* involve vitamin A supplementation to children and pregnant women in specific high-risk areas.[2] Doses used in children are similar to those used in universal programmes, but doses used in pregnant women should not exceed 10 000 units daily, or 25 000 units weekly.[2]

A number of studies have indicated that general supplementation with vitamin A decreases both mortality rates and morbidity among children in developing countries with a high prevalence of vitamin A deficiency.[4-7] Although not all studies have confirmed these findings,[8,9] two meta-analyses concur that the effect is likely to be genuine especially as regards measles infection,[10,11] (see Measles, below) and researchers and commentators have agreed that overall improvement of vitamin A status is worthwhile and necessary.[12-14] A study in children given half the dose of vitamin A recommended by WHO found that it provided equally good or better protection against mortality, but not against morbidity.[15] Supplementation with vitamin A 23 300 units weekly, or the equivalent amount of betacarotene, in women of child-bearing age reduced pregnancy-related mortality.[16] Some studies have evaluated mortality specifically in infants less than 6 months of age. In one study there was no overall benefit on early infant mortality with a tendency for the relative risk of mortality to increase with improved nutritional status,[17] whereas others reported decreases in mortality at 6 months[18] and 1 year[19] of age. A further study found no sustained benefit of vitamin A supplements on vitamin A status or morbidity beyond the age of 6 months, in infants receiving supplements with immunisation at 6, 10, and 14 weeks.[20] A study in vitamin-A-deficient children has demonstrated abnormalities in T-cell subsets which are corrected by vitamin A supplementation,[21] and it has been proposed that the apparent effects of vitamin A on morbidity and mortality may be due to modulation of immune function (see also Effects on the Immune System, above).

In **other countries** in which vitamin A deficiency is not widespread some form of supplementation may still be considered. Preterm infants have low vitamin A status at birth, which may increase their risk of developing chronic lung disease.[22] A meta-analysis of studies in low birth-weight infants found that vitamin A supplementation was associated with a reduced requirement for oxygen at 36 weeks postmenstrual age.[22] While studies of vitamin A supplementation to prevent chronic lung disease in very low birth-weight infants have had conflicting results,[23,24] some have commented that differences in patient population, postnatal therapies, and dosage of vitamin A could explain these discrepancies, and consider optimal supplementation necessary.[25] Others have called for further studies in preterm infants to define optimal dosage and mode of delivery of vitamin A; research should include quantification of hepatic stores, assessment of retinal function, and long-term clinical outcome.[26]

1. Potter AR. Reducing vitamin A deficiency: could save the eyesight and lives of countless children. *BMJ* 1997; **314:** 317–18.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
3. WHO. Integration of vitamin A supplementation with immunization. *Wkly Epidem Rec* 1999; **74:** 1–6.
4. Rahmathullah L, *et al.* Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929–35.
5. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
6. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
7. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
8. Herrera MG, *et al.* Vitamin A supplementation and child survival. *Lancet* 1992; **340:** 267–71.
9. Gupta P, Indrayan A. Effect of vitamin A supplementation on childhood morbidity and mortality: critical review of Indian studies. *Indian Pediatr* 2002; **39:** 1099–1118.
10. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
11. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
12. Anonymous. Vitamin A and malnutrition/infection complex in developing countries. *Lancet* 1990; **336:** 1349–51.
13. Humphrey JH, Rice AL. Vitamin A supplementation of young infants. *Lancet* 2000; **356:** 422–4.
14. Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. *J Infect Dis* 2000; **182** (suppl): S122–S133.
15. Benn CS, *et al.* Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005; **331:** 1428–32.
16. West KP, *et al.* Double blind, cluster randomised trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal. *BMJ* 1999; **318:** 570–5. Correction. *ibid.*; 1386.
17. West KP, *et al.* Mortality of infants <6 mo of age supplemented with vitamin A: a randomized double-masked trial in Nepal. *Am J Clin Nutr* 1995; **62:** 143–8.
18. Rahmathullah L, *et al.* Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003; **327:** 254–7.
19. Humphrey JH, *et al.* Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr* 1996; **128:** 489–96.
20. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998; **352:** 1257–63. Correction. *ibid.* 1999; **353:** 154.
21. Semba RD, *et al.* Abnormal T-cell subset proportions in vitamin-A-deficient children. *Lancet* 1993; **341:** 5–8.
22. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/07/08).
23. Tyson JE, *et al.* Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med* 1999; **340:** 1962–8.
24. Wardle SP, *et al.* Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F9–F13.
25. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rationale and evidence. *Pediatrics* 1999; **104:** 1369–74.
26. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F103–F108.

ANAEMIA. A study among pregnant Indonesian women with nutritional anaemia (see Iron-Deficiency Anaemia, p.1951) found a beneficial effect for vitamin A on haemoglobin when given with iron supplementation.[1] Similarly, in anaemic children given iron,[2] or adolescents given iron plus folic acid,[3] greater improvements in haemoglobin concentrations were seen with addition of vitamin A to supplementation. Vitamin A is considered essential for haematopoiesis; it has been suggested that vitamin A is required for the mobilisation and utilisation of iron for haemoglobin synthesis.[4] However, there are reports of anaemia caused by vitamin A supplementation, see Effects on the Blood, above.

1. Suharno D, *et al.* Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993; **342:** 1325–8.
2. Mwanri L, *et al.* Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. *J Nutr* 2000; **130:** 2691–6.
3. Ahmed F, *et al.* Concomitant supplemental vitamin A enhances the response to weekly supplemental iron and folic acid in anemic teenagers in urban Bangladesh. *Am J Clin Nutr* 2001; **74:** 108–15.
4. van den Broek N. Anaemia and micronutrient deficiencies. *Br Med Bull* 2003; **67:** 149–60.

DIARRHOEA. Although oral rehydration therapy remains the mainstay of the management of diarrhoea (p.1694) once it develops, it has been suggested that vitamin A supplementation may be of use in reducing the incidence and mortality of diarrhoea during childhood. Several large mortality studies reported that vitamin A supplementation was associated with reduced mortality attributed to diarrhoea,[1-3] although another did not.[4] The effect on morbidity from diarrhoea is even less clear. A reduction in the severity, but not the incidence, of diarrhoea has been noted in two studies.[5,6] However, in one study in children with subclinical vitamin A deficiency, there was an increased prevalence of diarrhoea for 2 weeks after vitamin A supplementation,[7] and in another study, vitamin A increased the incidence of diarrhoea in children aged less than 30 months.[8] A meta-analysis[9] concluded that vitamin A supplementation has no consistent overall protective effect on the incidence of diarrhoea. While severity was not examined, they noted that the decrease in diarrhoea mortality rates but not incidence can be reconciled if vitamin A reduces diarrhoea severity and not susceptibility to infection. This is possibly supported by a study that found that a single high-dose vitamin A supplement, given with standard antibacterial treatment, reduced the severity of acute shigellosis in children in Bangladesh.[10] One group[11] proposed that the inconsistent findings on morbidity of vitamin A supplementation may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. They found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone (see Vitamin A Deficiency, under Zinc, p.2001).

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.

4. Vijayaraghavan K, *et al.* Effect of massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; **336:** 1342–5.
5. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; **344:** 228–31.
6. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; **309:** 1404–7.
7. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
8. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
9. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
10. Hossain S, *et al.* Single dose vitamin A treatment in acute shigellosis in Bangladeshi children: randomised double blind controlled trial. *BMJ* 1998; **316:** 422–6.
11. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.

HIV INFECTION AND AIDS. A study in Malawi found that the rates of vertical transmission of HIV infection (birth of seropositive infants to seropositive mothers) were inversely related to maternal vitamin A status;[1] vitamin A deficiency during pregnancy was associated with a threefold to fourfold increased risk of mother-to-child transmission of HIV. This was not incompatible with the role of vitamin A in immunity and maintenance of mucosal surfaces, and since both HIV infection and pregnancy are risk factors for vitamin A deficiency, it was suggested that nutritional intervention to reduce vitamin A deficiency might help combat mother-to-child transmission. A South African study[2] found, in contrast, that supplementing HIV-infected pregnant women with vitamin A and betacarotene did not reduce the overall risk of vertical transmission to neonates. Supplementation did reduce the incidence of preterm births, and among these neonates, risk of perinatal HIV transmission was lower in those whose mothers had been supplemented. Vitamin A supplementation actually increased the risk of HIV transmission through breast feeding, with no effect on mortality at 24 months, in a Tanzanian trial.[3] Yet another study,[4] again in Tanzania, for which vertical transmission data were not available, found no evidence of an effect of vitamin A on birth outcomes in HIV-infected women and the authors pointed out that serum concentrations of vitamin A might be a marker of the stage of HIV disease rather than being causally related to outcome. The study did however find that multivitamin supplements reduced the risk of low birth-weight and size for age, and of premature birth, in the offspring of these women.[4] Interestingly, another trial in Tanzania found little difference between vitamin A supplementation and placebo on the progression of HIV disease and mortality. Multivitamin (excluding vitamin A) supplementation delayed disease progression and was associated with decreased mortality; addition of vitamin A to the multivitamin regimen reduced this benefit.[5] This is in contrast to 2 studies in Tanzania[6] and Uganda,[7] which found that vitamin A supplementation decreased mortality in children infected with HIV; however these results were not considered generalisable to communities with access to better healthcare and nutrition.

A systematic review and meta-analysis,[8] which included some of these conflicting trials, did not support the use of vitamin A supplementation to reduce the risk of vertical transmission and concluded that it may in fact increase the risk. Maternal vitamin A supplementation was not considered to decrease childhood mortality at 1 year. In addition, multivitamin supplementation was considered to have no effect on reduction of childhood mortality at 1 year, nor on prevention of preterm delivery.

Means of reducing the risk of HIV infection in neonates are discussed under HIV Infection Prophylaxis, p.858.

1. Semba RD, *et al.* Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994; **343:** 1593–7.
2. Coutsoudis A, *et al.* Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. *AIDS* 1999; **13:** 1517–24.
3. Fawzi WW, *et al.* Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* 2002; **16:** 1935–44.
4. Fawzi WW, *et al.* Randomised trial of effects of vitamin supplements on pregnancy outcomes and T-cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; **351:** 1477–82.
5. Fawzi WW, *et al.* A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; **351:** 23–32.
6. Fawzi WW, *et al.* A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. *Pediatr Infect Dis J* 1999; **18:** 127–33.
7. Semba RD, *et al.* Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. *Nutrition* 2005; **21:** 25–31.
8. Mills EJ, *et al.* Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of RCTs including more than 2800 women. *AIDS Res Ther* 2005; **2:** 4.

MEASLES. Vitamin A supplementation has an important role in the prevention of complications from measles.[1,2] Two studies specifically addressing vitamin A status and measles have found that complications such as pneumonia and diarrhoea were less common in children who had received supplements at the time of diagnosis than in those given a placebo.[3,4] WHO has recommended treating children in populations where vitamin A deficiency is common with high-dose vitamin A supplements during episodes of measles as follows:[5]

- all children over 12 months of age—200 000 units
- those between 6 and 12 months of age—100 000 units
- infants less than 6 months of age—50 000 units

Doses are given on 2 consecutive days and followed by a third dose at least 2 weeks later.

Studies in the USA have indicated that even among well-nourished children from a developed country, vitamin A deficiency in measles patients is not uncommon,[6,7] and vitamin A supplementation needs to be considered in children at risk.[8]

1. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; **306:** 366–70.
2. Fawzi WW, *et al.* Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993; **269:** 898–903.
3. Barclay AJG, *et al.* Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; **294:** 294–6.
4. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160–4.
5. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
6. Arrieta AC, *et al.* Vitamin A levels in children with measles in Long Beach, California. *J Pediatr* 1992; **121:** 75–8.
7. Butler JC, *et al.* Measles severity and serum retinol (vitamin A) concentration among children in the United States. *Pediatrics* 1993; **91:** 1176–81.
8. Committee on Infectious Diseases of the American Academy of Pediatrics. Vitamin A treatment of measles. *Pediatrics* 1993; **91:** 1014–15.

PREMATURITY. The fetus accumulates vitamin A in the third trimester, and most premature infants have low plasma vitamin A concentrations. Inadequate vitamin A supplementation after birth may exacerbate the problem, and contribute to an increased risk of developing chronic lung disease. A systematic review found that supplementing very low birth-weight infants with vitamin A was associated with a reduction in death or oxygen requirement at 1 month of age.[1]

1. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/03/08).

RESPIRATORY-TRACT INFECTIONS. Mortality studies did not show a consistent impact for vitamin A supplementation on death from non-measles-related respiratory infections.[1-3] Similarly, other studies have found no benefit of vitamin A on subsequent respiratory morbidity.[4-6] A meta-analysis of studies reporting pneumonia morbidity and mortality found no overall benefit or harm from vitamin A supplementation.[7] However, an increased prevalence of symptoms of respiratory infections associated with vitamin A supplementation has been noted in two studies,[8,9] particularly in children with adequate nutritional status. A meta-analysis of the effect of vitamin A supplementation on childhood morbidity found an increased incidence of respiratory-tract infections; since most trials had excluded children with overt vitamin A deficiency, the authors speculated that high-dose vitamin A given to children with adequate vitamin A stores might cause a temporary decline in immune status, increasing their susceptibility to infection.[10] A systematic review concluded that vitamin A should not be given to all children for *prevention* of acute lower respiratory-tract infections, but noted that children with vitamin A deficiency or poor nutritional status might benefit from supplementation in this respect.[11]

Vitamin A was not effective for the *treatment* of childhood non-measles-related lower respiratory-tract infections[12] or pneumonia.[13] Similarly, there was no benefit from vitamin A in the treatment of RSV infection in children in 2 studies.[14,15] In one of these studies there was a tendency for vitamin A to improve outcomes in the subgroup of severely ill children,[14] and in the other there was a slight increase in duration of hospitalisation in low-risk children receiving vitamin A.[15] A meta-analysis found no evidence that adjunctive treatment with high-dose vitamin A alters the course of pneumonia in children.[16]

1. West KP, *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.
2. Daulaire NMP, *et al.* Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.
3. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; **342:** 7–12.
4. Barreto ML, *et al.* Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; **344:** 228–31.
5. Bhandari N, *et al.* Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *BMJ* 1994; **309:** 1404–7.
6. Kartasasmita CB, *et al.* Plasma retinol level, vitamin A supplementation and acute respiratory infections in children of 1-5 years old in a developing country. *Tubercle Lung Dis* 1995; **76:** 563–9.
7. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull WHO* 1995; **73:** 609–19.
8. Stansfield SK, *et al.* Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 1993; **342:** 578–82.
9. Dibley MJ, *et al.* Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; **126:** 434–42.
10. Grotto I, *et al.* Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003; **142:** 297–304.
11. Chen H, *et al.* Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 12/03/08).
12. Kjolhede CL, *et al.* Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995; **126:** 807–12.
13. Nacul LC, *et al.* Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia. *BMJ* 1997; **315:** 505–10.
14. Dowell SF, *et al.* Treatment of respiratory syncytial virus infection with vitamin A: a randomized placebo-controlled trial in Santiago, Chile. *Pediatr Infect Dis J* 1996; **15:** 782–6.
15. Bresee JS, *et al.* Vitamin A therapy for children with respiratory syncytial virus infection: a multicenter trial in the United States. *Pediatr Infect Dis J* 1996; **15:** 777–82.
16. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: a meta-analysis. *Acta Paediatr* 2004; **93:** 1437–42.

XEROPHTHALMIA. Vitamin A deficiency is responsible in many developing countries for visual problems that may culminate in xerophthalmia and blindness.[1] Supplementation with vitamin A as recommended by WHO and discussed under Deficiency states, above, will raise the vitamin A status of the individual and act prophylactically against the development of xerophthalmia. For the treatment of xerophthalmia (which includes night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia) WHO have stated[2] that oral doses of vitamin A, preferably in an oil-based preparation, are the treatment of choice and should be given immediately the disorder is recognised in the following doses:

- patients over 1 year of age (with the exception of women of reproductive age)—200 000 units
- infants aged 6 to 12 months—100 000 units
- those aged less than 6 months—50 000 units

Doses should be repeated the next day, and again at least 2 weeks later.

In *women of reproductive age* there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant (see Pregnancy, above) with the serious consequences of xerophthalmia. WHO recommend that when there are severe signs of active xerophthalmia (i.e. acute corneal lesions) high-dose vitamin A treatment should be given as described above for those aged over 1 year. When only less severe signs are present (night blindness, Bitot's spots), women of reproductive age should receive a daily oral dose of 5000 to 10 000 units for at least 4 weeks. Alternatively, a weekly dose of not more than 25 000 units may be substituted.

Although xerophthalmia is far less common in developed countries, vitamin A deficiency should be considered in all patients with recurrent conjunctival or corneal disorders associated with gastrointestinal or liver disease.[3]

1. Smith J, Steinemann TL. Vitamin A deficiency and the eye. *Int Ophthalmol Clin* 2000; **40:** 83–91.
2. WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*. 2nd ed. Geneva: WHO, 1997.
3. Watson NJ, *et al.* Vitamin A deficiency and xerophthalmia in the United Kingdom. *BMJ* 1995; **310:** 1050–1. Correction. *ibid.*: 1320.

Malignant neoplasms. Epidemiological studies suggest that antoxidant vitamins such as the vitamin A substances may play a role in preventing the development of malignancy but there is currently little evidence from prospective studies that supplementation is helpful, and even some evidence of harm (see p.1927). Conversely, synthetic retinoids such as tretinoin (all-*trans*-retinoic acid) have an established role in treating some cancers (see p.1619).

Retinitis pigmentosa. Retinitis pigmentosa is the name applied to a group of slowly progressive hereditary degenerative diseases of the retina[1] that often result in blindness in adulthood. The rod and cone photoreceptors in the retina are primarily affected and initial symptoms include night blindness and intolerance to light. Later signs include infiltration of pigment from the retinal pigmentary epithelium into the retinal layers. Various treatments have been tried but none appear to have any proven benefit. Results of one large double-blind study[2] suggest that whereas treatment with vitamin A might slow the decline in visual acuity treatment with vitamin E appears to have a deleterious effect on the rate of decline. Vitamin E did appear to delay the rate of vision decline in 3 patients with retinitis pigmentosa and a defect in α-tocopherol-transfer protein associated with vitamin E deficiency.[3] Supplementation with 15 000 units of vitamin A daily for up to 12 years was considered to be safe in a study in adults with retinitis pigmentosa; no clinical manifestations of hepatotoxicity were apparent.[4] Docosahexaenoic acid has also been investigated, with variable results; some consider that vitamin A and oily fish in the diet could be beneficial in terms of visual preservation.[1] Transplantation of the retina is being investigated as a treatment for retinitis pigmentosa.[1,5] Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed.[1]

1. Hartong DT, *et al.* Retinitis pigmentosa. *Lancet* 2006; **368:** 1795–1809.
2. Berson EL, *et al.* A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* 1993; **111:** 761–2.
3. Yokota T, *et al.* Retinitis pigmentosa and ataxia caused by a mutation in the gene for the α-tocopherol-transfer protein. *N Engl J Med* 1996; **335:** 1770–1.
4. Sibulesky L, *et al.* Safety of <7500 RE (<25 000 IU) vitamin A daily in adults with retinitis pigmentosa. *Am J Clin Nutr* 1999; **69:** 656–63.
5. Anonymous. Transplantation as a therapy for retinitis pigmentosa? *Br J Ophthalmol* 1997; **81:** 430.

Retinopathy of prematurity. There is some suggestion that vitamin A supplementation may reduce the incidence of retinopathy of prematurity (p.1994).

Preparations

BP 2008: Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Vitamins A and D Capsules;
USP 31: Oleovitamin A and D; Oleovitamin A and D Capsules; Vitamin A Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: A-Vitel; Adermicina A Mama; Amenite A†; Andrioderma; Arovit; Atomoderma A; Bagovit A; Cazmar; Domsedan; Fiosen-A†; Flavostat†; Masivol; Metabolite-A†; Midermus†; Rogadermis†; Skinderm A; ***Austral.:*** Ungvita; ***Austria:*** Arcavit A†; Avitol; Oleovit A; ***Belg.:*** Vitamuruine; ***Braz.:*** Arovit; Avitan†; Biocrin†; Lacrigel A; Retinar; ***Canad.:*** Arovit; ***Chile:*** Avitana; Bagovit A; Microret; ***Cz.:*** A-Mulsin†; Axerophthol; ***Denm.:*** A-vitamin; ***Fin.:*** A-Vitamiini†; ***Fr.:*** A 313; Arovit†; Avibon; ***Ger.:*** A-Mulsin†; A-Vicotrat†; Augenschutz NA; Oculotect; Oculotect sine; Solan-M; Vitadral; Vitafluid; Vitagel; ***Hung.:*** Oculotect; ***Israel:*** Avipur; ***Ital.:*** Arovit; Euvitol; Repervit†; Vit-A-N; ***Malaysia:*** Fairy ADE; ***Mex.:*** A Grin; A-Vicon†; Acon; Avinal-Ex†; Dermotin A; Microret; Microvita; Palmicaps†; Retigel-A; ***Neth.:*** Dagravit A Forte†; ***NZ:*** Dermalife; Ungvita; ***Philipp.:*** Afaxin; Alici-A; Hypotears; ***Pol.:*** Aksoderm; Dermosavit; Dermovit A; Masc Ochronna z Witamina A; Masc Witaminowa Ochronna; ***Port.:*** A-Vite; Vitaminoftalmina; ***Rus.:*** Vita-POS (Вита-ПОС); ***S.Afr.:*** Arovit; ***Spain:*** Auxina A Masiva; Biominol A; Dif Vitamin A Masivo†; Rinocusi Vitaminico; Rinovitex; ***Swed.:*** Arovit; ***Switz.:*** Arovit†; Oculotect; ***Turk.:*** Avicap; Avigen; Carovigen; ***UK:*** Biovit-A; ***USA:*** Aquasol A; Palmitate-A; Pedi-Vit-A; Retinol-A; ***Venez.:*** Alfa-Mon; Retiva.

Multi-ingredient: ***Arg.:*** A-D-C; A-Vitel E; AD Shock; Adermicina; Adermicina A; Atomoderma A-D; Atomoderma A-E; Aulo Gelio Pie; Baby-Tex; Bagovit A Plus; Bagovit Avant Piel; Calcusan Bebe; Celuvital†; Crema De Ordene; Derivoco†; Dermanova; Dermosan; Epitheliale A-Derma; Factor Vit AE; Glossderm†; Herbaccion Nutriderm†; Hipoglos; Hipoglos con Hidrocortisona; Masivol Urea; Medicreme; Nemegel†; O-Biol; Palan†; Panoxi; Platsul A; Puraloe Nutritivo; Redoxon A; Revital; Salvicutan†; Sulfadiazina de Plata; Sulfaplat; Ulcevarin†; Vagicural; Vansame; Vansame Plus; Vitapelen†; Zoodermina Cream; ***Austral.:*** Althaea Complex; Arthriforte; Bioglan Micelle A plus E; Bioglan Zn-A-C; Dermalife Plus; ER Cream†; Garlic, Horseradish, A & C Capsules†; Hydrastis Complex†; John Plunketts Protective Day Cream; Macro Natural Vitamin E Cream; Proyeast†; Sambucus Complex†; Trifolium Complex†; Verbascum Complex†; ***Austria:*** A-E-Mulsin; Arcavit A/E; Coldistop; Gelacet; Gerogelat; Lemuval; Oleovit; Oleovit A; Oleovit A + D; Regenerin†; Rovigon; Ultren; Vasovitol; ***Belg.:*** Neo-Cutigenol; Newderm†; Rovigon; Vita-Mefren†; ***Braz.:*** AD-Til; ADE 2 (Adedois); Adecal; Adederme; Adeforte; Aderogil D3; Babymed; Cariderm†; Dermalisan; Dermoden; Epitezan; Gaduol†; Glossaliv; Hipoderme; Hipodermon; Hipodex; Hipoglos; Licovit; Multiderme; Pronenen; Regencel; Regenom; Sensibaby; Solemil†; Suavederm; Vitadesan; ***Canad.:*** A & D; A & D Ointment†; Antiseptic Skin Cream†; Lubriderm Advanced Moisture†; Nutrol A D; ***Chile:*** Brexon†; Dermaglos; Dermaglos Plus†; Droxel; Microret K; Negloss; Panthoderm-A; Pediaderm†; Platsul A; Pomada Vitaminica; Povin; Rovigon; Sanoderm; ***Cz.:*** A-E-Mulsin†; Coldastop; Hypotears; Infadolan; ***Fin.:*** A-Vita; Aesol; Oftan A-Pant; Wicarba; Wicnevit; ***Fr.:*** Alpha 5 DS†; Cirkan a la Prednacinolone; Pommade Lelong†; Rovigon†; Seborheane; Solacy; ***Ger.:*** A + E Thilo†; A-E-Mulsin†; Coldastop; duraultra; Gelacet N†; Hewekzem novo N; Kwim†; Oculotect; Regepithel; Remederm; Rovigon G†; Salus Augenschutz-Kapseln NA†; Tears Again; Unguentacid; Vita-POS; ***Gr.:*** Aquasol A+D; Aquasol A†; Avegon; Eviol-A; Novaquasol-A; ***Hong Kong:*** Aderma Epitheliale†; Hypotears†; Regepithel†; ***Hung.:*** Alksebor; Caldea†; Coldastop; Neogranormon; Vita-Merfen†; ***India:*** Medithane; Ossivite; Sclerobion; Sharkomalt; Sharkovit; ***Indon.:*** Oculotect; Scott's E Vita; Visivit; Vita-Vision; ***Israel:*** Aquitol†; Aronal Forte; Baby A + D; Neocutan Silver; Oleovit A + D †; Vita-Merfen NF; Vitamidyne A and D; ***Ital.:*** AD Pabyrn; Adisterolo; Babysteril; Derman-Oil; Dermana Crema; Dermana Pasta; Dicalcium†; Evitex; Granoleina†; Midium; Neoceuticals Spot Treatment; Provitamin A-E; Retinovit; Rinopanteina; Rovigon; Tocalfa; ***Mex.:*** Adekals; Adekon; Adekon C; Adeloren†; Adibal; Aquasol AD; Capent; Hipoglos; Hipoglos Cremoso; Kamiloderm; Microka; Microret K; Nutrem; Quinoret; Sutin†; Vidamil; Vitalorange; ***Neth.:*** Dagravit A-E Forte†; Halitran; ***Philipp.:*** Remederm; Rovigon; Vandol; ***Pol.:*** Alantavit; Capivit A + E; Oculotect; Tokovit A + E; Tranvit; ***Port.:*** Bacitracina Zimaia; Dermabut; Esclerobion; Rovigon; Synchrovit; ***S.Afr.:*** Vandol†; ***Spain:*** Adiod; Antihemorroidal†; Auxina A + E; Biominol A D; Calcio 20 Complex; Cicatral; Dermo Halibut; Epitelizante; Evitex A E Fuerte; Gramoce A; Grietalgen; Grietalgen Hidrocort†; Halibut; Halibut Hidrocortisona; Hubergrip†; Lacerdermol; Lacerdermol Complex; Mastiol; Mitosyl; Vicomin A C; Vitaber A E; Wobenzimal†; ***Swed.:*** AD-vitamin; ***Switz.:*** Alphastria; Antikeloides Creme; Carbamide Creme; Coldistop; Gelacet†; Leniderm†; Malvedrin; Oravil; Riccovitan†; Rovigon; Sanhelios Capsules a la vitamine A†; Unatol; Unguentolan; Vita-Hexin; Vita-Merfen; ***Turk.:*** Balya; ***UK:*** S.P.H.P.; Se-Power; ***USA:*** A and D Medicated; Aloe Grande; Clocream; Diaper Guard; Lazercreme; Lobana Derm-Aide; Lobana Peri-Garde; Paladin; Phicon; ***Venez.:*** A-D-Vit; Adaderm; Ademina; Adenar; Dicalcico†; Hipoglos†; Vandol; Vitenol†.

Vitamin B Substances

Vitamina B, grupo de la.

The B vitamin group includes the B$_1$ substances (thiamine and its derivatives), B$_2$ (riboflavin), B$_6$ (pyridoxine and derivatives), and B$_{12}$ (the cobalamins). In addition, nicotinic acid and its derivatives (p.1957) and folic acid (p.1940) are held to be part of the group, as is pantothenic acid (p.1959), but these latter substances are not generally referred to by their traditional B nomenclature.

Preparations

Proprietary Preparations (details are given in Part 3)

Philipp.: Vaneular.

Multi-ingredient: ***Braz.:*** Plex B; Xantina B12†; Xantinon B12; ***India:*** Elferri†; Hycibex; JP Tone; Livogen†; Lupizyme; Terramycin SF; Toniazol†; Vitexid; ***Indon.:*** Gunabion; Lesifit; Tonikum; ***Malaysia:*** Hepavite; Time Release Nutrition Mega B + C Complex†; ***Philipp.:*** IBC; ***Singapore:*** Hepavite.

Used as an adjunct in: ***Philipp.:*** Trisofort.

Vitamin B$_1$ Substances

Vitamina B$_1$.

Acetiamine Hydrochloride *(rINNM)*

Acethiamine Hydrochloride; Acétiamine, Chlorhydrate d'; Acetiamini Hydrochloridum; Diacethiamine Hydrochloride; Hidrocloruro de acetiamina. *N*-(5-Acetoxy-3-acetylthiopent-2-en-2-yl)-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide hydrochloride monohydrate.

Ацетиамина Гидрохлорид

$C_{16}H_{22}N_4O_4S,HCl,H_2O = 420.9.$

CAS — 299-89-8 (acetiamine).

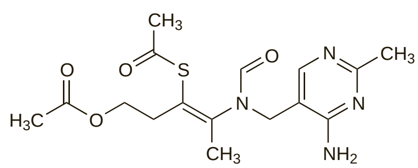

(acetiamine)

Benfotiamine *(rINN)*

Benfotiamina; Benfotiaminum; *S*-Benzoylthiamine *O*-Monophosphate. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(2-benzoylthio-4-dihydroxyphosphinyloxy-1-methylbut-1-enyl)formamide.

Бенфотиамин

$C_{19}H_{23}N_4O_6PS = 466.4.$

CAS — 22457-89-2.
ATC — A11DA03.
ATC Vet — QA11DA03.

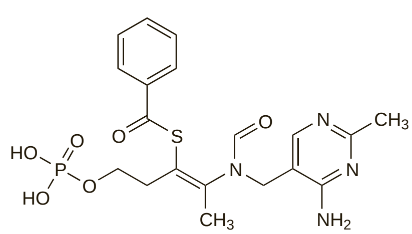

Bisbentiamine *(rINN)*

O-Benzoylthiamine Disulphide; Bisbentiamina; Bisbentiaminum. *NN'*-{Dithiobis[2-(2-benzoyloxyethyl)-1-methylvinylene]}bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide].

Бисбентиамин

$C_{38}H_{42}N_8O_6S_2 = 770.9.$

CAS — 2667-89-2.

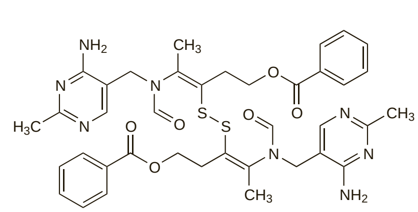

Cocarboxylase *(BAN, rINN)*

Cocarboxilasa; Co-carboxylase; Cocarboxylasum; Diphosphothiamine; Pyruvodehydrase; Thiamine Pyrophosphate. 3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-{2-[dihydroxyphosphinyloxy-(hydroxy)phosphinyloxy]ethyl}-4-methylthiazolium hydroxide.

Кокарбоксилаза

$C_{12}H_{20}N_4O_8P_2S$ (hydroxide form) = 442.3.

CAS — 154-87-0 (cocarboxylase chloride).

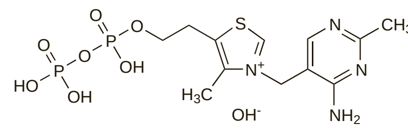

Pharmacopoeias. *Pol.* includes the chloride.

Cycotiamine *(rINN)*

CCT; Cicotiamina; Cyclocarbothiamine; Cycotiaminum. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[1-(2-oxo-1,3-oxathian-4-ylidene)ethyl]formamide.

Цикотиамин

$C_{13}H_{16}N_4O_3S = 308.4.$

CAS — 6092-18-8.

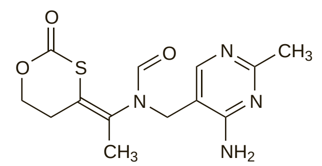

Fursultiamine *(rINN)*

Fursultiamina; Fursultiaminum; Thiamine Tetrahydrofurfuryl Disulphide; TTFD. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-[4-hydroxy-1-methyl-2-(tetrahydrofurfuryldithio)but-1-enyl]formamide.

Фурсультиамин

$C_{17}H_{26}N_4O_3S_2 = 398.5.$

CAS — 804-30-8.

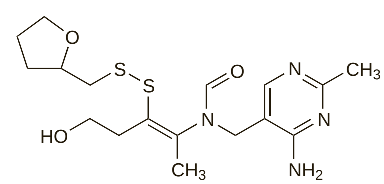

Octotiamine *(rINN)*

Octotiamina; Octotiaminum; Oktotiamiini; Oktotiamin; TATD; Thioctothiamine. *N*-[2-(3-Acetylthio-7-methoxycarbonylheptyldithio)-4-hydroxy-1-methylbut-1-enyl]-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide.

Октотиамин

$C_{23}H_{36}N_4O_5S_3 = 544.8.$

CAS — 137-86-0.

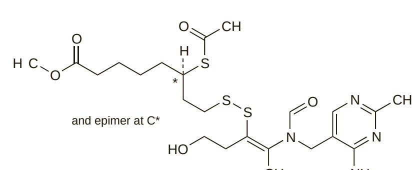

Prosultiamine *(rINN)*

DTPT; Prosultiamina; Prosultiamine; Prosultiaminum; Thiamine Propyl Disulphide. *N*-(4-Amino-2-methylpyrimidin-5-ylmethyl)-*N*-(4-hydroxy-1-methyl-2-propyldithiobut-1-enyl)formamide.

Просультиамин

$C_{15}H_{24}N_4O_2S_2$ = 356.5.

CAS — 59-58-5.

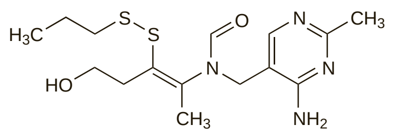

Sulbutiamine *(rINN)*

Bisibutiamine; *O*-Isobutyrylthiamine Disulphide; Sulbutiamina; Sulbutiaminum. *NN'*-{Dithiobis[2-(2-isobutyryloxyethyl)-1-methylvinylene]}bis[*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)-formamide].

Сульбутиамин

$C_{32}H_{46}N_8O_6S_2$ = 702.9.

CAS — 3286-46-2.

ATC — A11DA02.

ATC Vet — QA11DA02.

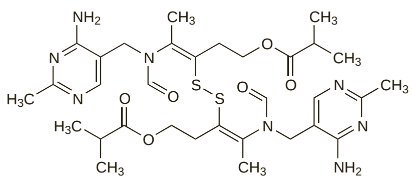

Thiamine Hydrochloride *(BANM, rINNM)*

Aneurine Hydrochloride; Hidrocloruro de tiamina; Thiamin Hydrochloride; Thiamine, chlorhydrate de; Thiamine Chloride; Thiamin-hydrochlorid; Thiamini hydrochloridum; Thiaminii Chloridum; Tiamiinihydrokloridi; Tiamin-hidroklorid; Tiaminhydroklorid; Tiamino hidrochloridas; Tiaminy chlorowodorek; Vitamin B_1. 3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride.

Тиамина Гидрохлорид

$C_{12}H_{17}ClN_4OS,HCl$ = 337.3.

CAS — 59-43-8 (thiamine); 67-03-8 (thiamine hydrochloride).

ATC — A11DA01.

ATC Vet — QA11DA01.

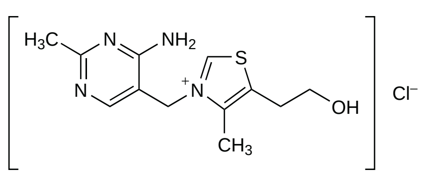

(thiamine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Thiamine hydrobromide is included in *Int.*

Ph. Eur. 6.2 (Thiamine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol; soluble in glycerol. A 2.5% solution in water has a pH of 2.7 to 3.3. Store in nonmetallic containers. Protect from light.

USP 31 (Thiamine Hydrochloride). White crystals or crystalline powder, usually having a slight, characteristic odour. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Soluble 1 in 1 of water and 1 in 170 of alcohol; insoluble in ether and in benzene; soluble in glycerol. pH of a 1% solution in water is between 2.7 and 3.4. Store in airtight containers. Protect from light.

Stability. Sterile thiamine hydrochloride solutions of pH 4 or less lose activity only very slowly but neutral or alkaline solutions deteriorate rapidly, especially in contact with air.

Thiamine Nitrate *(BANM, rINNM)*

Aneurine Mononitrate; Nitrato de tiamina; Thiamine Mononitrate; Thiamine, nitrate de; Thiamini nitras; Thiamin-nitrát; Tiamiininitraatti; Tiaminnitrat; Tiamin-nitrát; Tiamino nitratas; Tiaminy azotan; Vitamin B_1 Mononitrate. 3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium nitrate.

Тиамина Нитрат

$C_{12}H_{17}N_5O_4S$ = 327.4.

CAS — 532-43-4.

ATC — A11DA01.

ATC Vet — QA11DA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Thiamine Nitrate). A white or almost white, crystalline powder or small, colourless crystals. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in alcohol and in methyl alcohol. A 2% solution in water has a pH of 6.8 to 7.6. Store in nonmetallic containers. Protect from light.

USP 31 (Thiamine Mononitrate). White crystals or crystalline powder, usually having a slight characteristic odour. Soluble 1 in 44 of water; slightly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 6.0 and 7.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Adverse effects with thiamine are rare, but hypersensitivity reactions have occurred, mainly after parenteral doses. These reactions have ranged in severity from very mild to, very rarely, fatal anaphylactic shock (see below).

Breast feeding. Supplementation did not significantly affect thiamine concentration in breast milk of healthy, well-nourished women when compared with those not given thiamine; the authors supposed that absorptive capacity of the mammary gland may be saturable.[1] Based on this, the American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Nail PA, *et al.* The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; **33:** 198–204.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Hypersensitivity. The UK CSM had received, between 1970 and July 1988, 90 reports of adverse reactions associated with the use of an injection containing high doses of vitamins B and C. The most frequent reactions were anaphylaxis (41 cases, including 2 fatalities), dyspnoea or bronchospasm (13 cases), and rash or flushing (22 cases); 78 of the reactions occurred during, or shortly after, intravenous injection and the other 12 after intramuscular injection.[1] They recommended that parenteral treatment be used only when essential, and that, when given, facilities for treating anaphylaxis should be available. They also recommended that, when the intravenous route was used, the injection be given slowly (over 10 minutes). Various authors[2,3] have noted that parenteral treatment is *essential* for the prophylaxis and treatment of Wernicke's encephalopathy (see below). However, further reports of anaphylaxis to parenteral thiamine have since been described,[4-6] including one with a fatal outcome.[4]

1. Committee on Safety of Medicines. Parentrovite & allergic reactions. *Current Problems 24* 1989.
2. Wrenn KD, Slovis CM. Is intravenous thiamine safe? *Am J Emerg Med* 1992; **10:** 165.
3. Thomson AD, Cook CCH. Parenteral thiamine and Wernicke's encephalopathy: the balance of risks and concerns. *Alcohol Alcohol* 1997; **32:** 207–9.
4. Van Haecke P, *et al.* Thiamine-induced anaphylactic shock. *Am J Emerg Med* 1995; **13:** 371–2.
5. Morinville V, *et al.* Anaphylaxis to parenteral thiamine (vitamin B1). *Schweiz Med Wochenschr* 1998; **128:** 1743–4.
6. Johri S, *et al.* Anaphylaxis from intravenous thiamine—long forgotten? *Am J Emerg Med* 2000; **18:** 642–3.

Pharmacokinetics

Small amounts of thiamine are well absorbed from the gastrointestinal tract after oral doses, but the absorption of doses larger than about 5 mg is limited. It is also rapidly absorbed on intramuscular injection. It is widely distributed to most body tissues, and appears in breast milk. Within the cell, thiamine is mostly present as the diphosphate. Thiamine is not stored to any appreciable extent in the body and amounts in excess of the body's requirements are excreted in the urine unchanged or as metabolites.

◊ References.

1. Weber W, *et al.* Nonlinear kinetics of the thiamine cation in humans: saturation of nonrenal clearance and tubular reabsorption. *J Pharmacokinet Biopharm* 1990; **18:** 501–23.
2. Tallaksen CME, *et al.* Kinetics of thiamin and thiamin phosphate esters in human blood, plasma and urine after 50 mg intravenously or orally. *Eur J Clin Pharmacol* 1993; **44:** 73–8.
3. Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. *Int J Clin Pharmacol Ther* 1996; **34:** 47–50.
4. Greb A, Bitsch R. Comparative bioavailability of various thiamine derivatives after oral administration. *Int J Clin Pharmacol Ther* 1998; **36:** 216–21.
5. Frank T, *et al.* High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol* 2000; **56:** 251–7.
6. Drewe J, *et al.* Effect of intravenous infusions of thiamine on the disposition kinetics of thiamine and its pyrophosphate. *J Clin Pharm Ther* 2003; **28:** 47–51.

Human Requirements

Thiamine requirements are directly related to the carbohydrate intake and the metabolic rate. A daily dietary intake of about 0.9 to 1.5 mg of thiamine is recommended for healthy men and about 0.8 to 1.1 mg for healthy women. Cereals, nuts, peas, beans, yeast, and pork are rich sources of thiamine. Some other meats especially liver or kidneys, and also fish, contain significant amounts. Flour and bakery products are often enriched with thiamine. Considerable losses of thiamine may result from cooking processes.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for thiamine[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] In the UK for adult males and females the reference nutrient intake (RNI) is 0.4 mg per 1000 kcal daily and the estimated average requirement (EAR) is 0.3 mg per 1000 kcal daily. In the USA an RDA of 1.2 mg daily in adult males and 1.1 mg daily in females is recommended.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Thiamine is a water-soluble vitamin, although some of its derivatives have greater lipophilicity. It is an essential coenzyme for carbohydrate metabolism in the form of the diphosphate (thiamine pyrophosphate, cocarboxylase). Thiamine deficiency develops when the dietary intake is inadequate; severe deficiency leads to the development of a syndrome known as beri-beri. Chronic 'dry' beri-beri is characterised by peripheral neuropathy, muscle wasting and muscle weakness, and paralysis. Acute 'wet' beri-beri is characterised by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe cases of thiamine deficiency notably in association with chronic alcoholism. Severe thiamine deficiency, characterised by lactic acidosis and neurological deterioration, has been reported within a relatively short time of starting thiamine-free total parenteral nutrition; some deaths have occurred.

Thiamine is used in the treatment and prevention of thiamine deficiency. It is given orally, the preferred route, or if necessary by the intramuscular or intravenous routes (but see Hypersensitivity, above); intravenous injections should be given slowly over 30 minutes. In the treatment of mild chronic thiamine deficiency usual oral doses of 10 to 25 mg daily, in single or divided doses, have been recommended. In severe thiamine deficiency doses of up to 300 mg daily are given, and even higher daily doses may be used in Wernicke-Korsakoff syndrome by the intravenous route.

Thiamine is usually given as either the hydrochloride or nitrate salts although other salts such as the dicamsylate, disulfide, monophosphate (monophosphothiamine) or pyrophosphate (cocarboxylase) may be used.

Other compounds that possess vitamin B_1 activity and may be given as alternatives to thiamine include benfotiamine, cycotiamine, octotiamine, prosultiamine, and sulbutiamine. Acetiamine, bisbentiamine, and fursultiamine have also been used.

Diabetes mellitus. Low plasma thiamine concentrations have been found[1] in patients with type 1 and type 2 diabetes mellitus (p.431). In a small placebo-controlled study, benfotiamine

100 mg given four times daily by mouth significantly improved neuropathic pain in patients with diabetic polyneuropathy (see p.6).[2]

1. Thornalley PJ, *et al.* High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; **50:** 2164–70.
2. Haupt E, *et al.* Benfotiamine in the treatment of diabetic polyneuropathy—a three-week randomized, controlled pilot study (BEDIP Study). *Int J Clin Pharmacol Ther* 2005; **43:** 71–7.

Wernicke-Korsakoff syndrome. The Wernicke-Korsakoff syndrome is a manifestation of thiamine deficiency seen particularly in alcoholics, but which may accompany other conditions including starvation or prolonged fasting, or persistent vomiting. It was originally classified as two separate disorders, Wernicke's encephalopathy and Korsakoff's syndrome, but these are now thought to represent aspects of a single pathological process.[1,2]

Classical Wernicke's symptoms comprise confusion, ataxia, ophthalmoplegia, and nystagmus. Ophthalmoplegia and ataxia may precede the mental symptoms by some days. Hypothermia may be seen, and collapse and sudden death may occur in some patients. The manifestations of Korsakoff's syndrome are short-term memory loss, learning deficits, and confabulation. The conditions are associated with demyelination and glial proliferation, as well as haemorrhagic lesions, mainly in the periventricular regions of the brain; characteristic biochemical abnormalities include raised serum-pyruvate concentration, which has been postulated as a cause of encephalopathy.[3]

Early recognition and treatment is important, both because of the risk of collapse and sudden death,[4] and to prevent irreversible damage to the CNS. Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy,[5] and may indeed only become evident on treatment.

Treatment is with parenteral thiamine, preferably intravenously, to ensure adequate absorption; any risks of parenteral treatment are considered justifiable.[1,2,6,7] Although as little as 2 or 3 mg may be enough to reverse the ocular symptoms, which generally begin to improve in 1 to 6 hours, doses of at least 100 mg should be given initially. (In practice a typical dose is 500 mg given intravenously with other vitamins every 8 hours, for 2 days if symptoms persist, and followed by 100 mg twice daily orally, or 250 mg daily intravenously until the patient can take oral thiamine.[6,8]) The ataxia and acute confusional state may also resolve dramatically although improvement may not be noted for days or months. Even several months after the onset of symptoms, treatment with high doses of thiamine has occasionally resulted in recovery.[9] The effects of the syndrome on memory are much harder to reverse. Some 25% of patients make a full, and 50% a partial, recovery.[5]

1. Cook CCH, *et al.* B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol* 1998; **33:** 317–36.
2. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 2–7.
3. Petrie WM, Ban TA. Vitamins in psychiatry: do they have a role? *Drugs* 1985; **30:** 58–65.
4. Reuler JB, *et al.* Wernicke's encephalopathy. *N Engl J Med* 1985; **312:** 1035–9.
5. Anonymous. Korsakoff's syndrome. *Lancet* 1990; **336:** 912–13.
6. Cook CCH, Thomson AD. B-complex vitamins in the prophylaxis and treatment of Wernicke-Korsakoff syndrome. *Br J Hosp Med* 1997; **57:** 461–5.
7. Cook CCH. Prevention and treatment of Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 2000; **35** (suppl): 19–20.
8. Chataway J, Hardman E. Thiamine doses for alcohol withdrawal. *Br J Hosp Med* 1994; **51:** 615.
9. Carota A, Schnider A. Dramatic recovery from prolonged Wernicke-Korsakoff disease. *Eur Neurol* 2005; **53:** 45–6.

Preparations

BP 2008: Thiamine Injection; Thiamine Tablets; Vitamins B and C Injection;
BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;
USP 31: Thiamine Hydrochloride Elixir; Thiamine Hydrochloride Injection; Thiamine Hydrochloride Tablets; Thiamine Mononitrate Elixir.

Proprietary Preparations (details are given in Part 3)
Arg.: Megastene; ***Austral.:*** Beta-Sol†; Betamin; ***Austria:*** Beneuran; Bevitol; Diclo-B; ***Belg.:*** Benerva; Beneurol; Betamine; ***Braz.:*** Arcalion; Benerva; Beneum; Neurivit; ***Canad.:*** Betaxin†; ***Chile:*** Arcalion; Betamin†; ***Cz.:*** Benfogamma; Thiabene; ***Fin.:*** Neuramin; Vita-B1; ***Fr.:*** Arcalion; Benerva; Bevitine; ***Ger.:*** Aneurin†; B1-ASmedic; B Vicotrat†; Betabion; Milgamma mono; ***Gr.:*** Arcalion; Benerva; ***Hong Kong:*** Arcalion; Super B1; ***Hung.:*** Benfogamma; Beres B1; ***India:*** Arcalion; Benalgis; ***Indon.:*** Alinamin; Arcalion; Beston; Licobevit; ***Irl.:*** Benerva†; ***Ital.:*** Benerva; Bivitasi†; ***Jpn:*** Alinamin-F; Neuvita; ***Malaysia:*** Arcalion; ***Mex.:*** Benal; Benerva; Carzilasa; Fortical; MTX-2 Alf; TTC†; X-2; ***Philipp.:*** Arcalion; Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Supraneuron; Vineuron; ***Pol.:*** Benfogamma; ***Port.:*** Arcalion; Trifosfaneurina; Vitanidia; ***Rus.:*** Benfogamma (Бенфогамма); Enerion (Энерион); ***Singapore:*** Arcalion; ***Spain:*** Arcalion; Benerva; Neurostop; Surmenalit; ***Swed.:*** Benerva; Betabion; ***Switz.:*** Arcalion; Benerva; Nicobrevin N†; ***Thai.:*** Alinamin-F; Arcalion; Menamin†; ***Turk.:*** Arcalion; Bevigen; ***UAE:*** Thiavit; ***UK:*** Benerva; Tyvera; ***Venez.:*** Arcalion; Beplus.

Multi-ingredient: ***Arg.:*** Algio Nervomax; Algio Nervomax Fuerte; Co-Tioctan; Cobenexol Forte; Cobenexol Fuerte; CVP B1 B6 B12†; Dexabion; Dolo Nervobion; Dolo Nervobion 10000; Dorixina B1 B6 B12; Dr Calm†; Klosidol B1 B6 B12; Nervobion Fuerte; Nervomax TB12; Valeriana Diates; Venostasin; ***Austral.:*** Berberis Complex; ***Austria:*** Ambene N; Arca-Be; Beneuran compositum; Beneuran Vit B-Komplex†; Calcisan B + C; Diclovit; Dilaescol; Dolo-Neurobion; Neurobion; Neuromerck; Neuromultivit; Pronerv; ***Belg.:*** Betapyr; Neurobion; Vioneurin†; ***Braz.:*** Aminocid†; Bicavine; Cianotrat-Dexa; Citoneurin; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacobal; Dexador; Dexadoze; Dexagil; Dexaneurin; Dexanevral†; Doxal; Dozeneurin; Espasmocron; Fol Sang; Lisan†; Sulfato Ferroso Composto; Sulfatofer†; Trirubin†; Venofortan†; Venostasin†; Vitaneuron†; Vitatonus; ***Canad.:*** Penta-3B; Penta-3B + C; Penta-Thion; ***Chile:*** Betonvit†; Dolotol 12; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; ***Cz.:*** Milgamma; Milgamma N; Neuromultivit; ***Fin.:*** Neurobion; Neurovitan; ***Fr.:*** Hexaquine; Vitathion; ***Ger.:*** B-Komplex forte; Bevit Forte; Dolo-Neurobion forte†; Dolo-Neurobion N†; Hewedolor neuro; Medivitan N Neuro; Milgamma; Milgamma N; Milgamma-NA; Milneuron NA; Neuralysan S†; Neuro; Neuro uno; Neuro-AS N†; neuro-B forte; Neuro-Effekton B; Neuro-Lichtenstein M; Neuro-Lichtenstein N; Neuro-ratiopharm N; Neuro-ratiopharm†; Neuro-Vibolex; Neurobion; Neurobion N; Neurotrat S; Novirell B Duo; Pantovigar N; Pleomix-B; Regepithel; Vitaject†; Vitamin B duo; ***Gr.:*** Neurobion; ***Hong Kong:*** 3B; Alinamin-F; Childrens Coltalin with Vit B †; Coltalin with Vit B †; Magesto; Milgamma; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Fort; Regepithel†; Tonterin†; Vibion; Vida Neurotab; Vidaclofen-Plus; ***Hung.:*** Milgamma; Milgamma N; Neurobion; ***India:*** Sioneuron; Vitneurin; ***Indon.:*** Abajos; Arsinal; Betrion; Bicitron; Biocombin; Biomega; Biomex; Butamidon; Corobion; Corsaneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; Lapibion; Licobion; Mersibion; Nervitone; Nervitone E; Neuralgin RX; Neuro Panstop; Neuro-Beston; Neurobat; Neurobat A; Neurobion; Neurobiovit; Neurodex; Neurogen; Neurohax; Neurophil; Neuropyramin; Neurosanbe; Neurosanbe Plus; Neurotrat; Neurotropic Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Primabion; Pritagesic; Scanneuron; Sohobion; Solaneuron; Stileran; Supranal; Tocobion; Trimate-E; Tropineuron; ***Israel:*** Calmanervin; Tribemin; ***Ital.:*** Adenobeta†; Adenoplex; Adenovit†; Antiadiposo; Benexol B12; Dobetin con Vitamina B1; Dobetin Totale; Emazian B12†; Emoantitossina†; Emopon; Esaglut†; Fibronevrina; Folepar B12; Fosforilasi; Fosfoutipi Vitaminico†; Mionevrasi; Neuraben; Neuroftal†; Odontalgico Dr. Knapp con Vit. B1; Rubjovit; Trinevrina B6; ***Jpn:*** Neurovitan†; ***Malaysia:*** 3B; Alinamin B12†; Flavettes Neuroforte; Fundamin-E; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Fort; Re-B; Vitabion; ***Mex.:*** Ariflam Forte; B1-12-15; Bedocil†; Benexol B12; Betrox; Cobotiaxina; Dexabion; Diclovith-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiaminal; Doxemina; Duciclon; Ferrotemp; Forvin; Innobion; Lipovitasi-Or; Macrox-5; Neuralin; Neurobion; Nuro-B; Odexan; Ofzim; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Revitaliv-C; Selectadoce; Suma-B; Tiabexol; Tiamidexal; Tiaminal B ; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; ***Neth.:*** Neurobion; Princi B1 + B6; ***Philipp.:*** Dolo-Neurobion; Glutaphos; Hinuron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Vitanerv; ***Pol.:*** Milgamma N; ***Port.:*** Cebrotex Forte; Linamin Plus†; Neurobion; ***Rus.:*** Aescusan (Эскузан); Benalgin (Бенальгин); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); ***S.Afr.:*** Kiddie Vite†; Neurobion; ***Singapore:*** Alinamin B12†; Alinamin-F; Daneuron; Neurobion; Neurodex; Neuroforte; Neurorubine; Neurovit; Neuroxel; Nevramin; Princi-B Fort; ***Spain:*** Acetuber; Antineurina; Benexol B1 B6 B12; Bester Complex; Calmante Vitaminado PG; Calmante Vitaminado PG Efervescente; Calmante Vitaminado Rinver; Dalamon†; Hidroxil B12 B6 B1; Inzitan; Mederebro; Meloka; Menalgil B6; Nervobion; Neuromade; Neurostop Complex; Pazbronquial; Quimpedor; Refulgin; Viadetres†; ***Swed.:*** Neurobion; ***Switz.:*** Benexol B12; Neurorubin; Trilagavit; ***Thai.:*** 3B; Alinamin B12†; Alinamin-F; B-100 Complex; Beromin; Cydoxmine-B†; Cyriamine; Diasgest; Digestin; Douzabox; Endogest†; Genavit; Hemolax; Mesto-Of; Neubee; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvit; Princi-B; Re-B Forte; Tribesian; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; ***Turk.:*** Benexol; Benol; Benoral; Bevitab; Bevitol; Nerox-B; Neurogriseovit; Neurovit; Neuvitan; Tribeksol; ***UAE:*** 3V; ***UK:*** Don't Bug Me; Labiton†; Quiet Life; ***Venez.:*** Bedoyecta; Befosfin; Briomet; Deca-Lentermina Complex; Dobetin Compuesto; Mega-Neubion; Miovit; Neubion; Neuribe; Rubrinal; Rubrinex; Tres-Be.

Used as an adjunct in: ***Indon.:*** Nufadoxin.

Vitamin B_2 Substances

Vitamina B_2.

Riboflavin *(BAN, rINN)*

E101; Lactoflavin; Riboflaviini; Riboflavina; Riboflavinas; Riboflavine; Riboflavinum; Ryboflawina; Vitamin B_2; Vitamin G. 7,8-Dimethyl-10-(1′-D-ribityl)isoalloxazine; 3,10-Dihydro-7,8-dimethyl-10-(D-*ribo*-2,3,4,5-tetrahydroxypentyl)benzopteridine-2,4-dione.

Рибофлавин

$C_{17}H_{20}N_4O_6$ = 376.4.
CAS — 83-88-5.
ATC — A11HA04.
ATC Vet — QA11HA04.

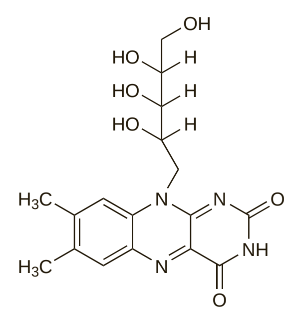

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Riboflavin). A yellow or orange-yellow crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light. Solutions deteriorate on exposure to light, especially in the presence of alkali.

USP 31 (Riboflavin). A yellow to orange-yellow crystalline powder, having a slight odour. When dry, it is not appreciably affected by diffused light, but in solution light induces quite rapid deterioration, especially in the presence of alkalis. Very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; insoluble in chloroform and in ether; soluble in dilute solutions of alkalis. Its saturated solution in water is neutral to litmus. Store in airtight containers. Protect from light.

Riboflavin Sodium Phosphate *(BANM, rINNM)*

Fosfato sódico de riboflavina; Natrii Riboflavini Phosphas; Riboflaviininatriumfosfaatti; Riboflavin fosfát sodná sůl; Riboflavin 5′-Phosphate Sodium; Riboflavine, phosphate sodique de; Riboflavine Phosphate (Sodium Salt); Riboflavine Sodium Phosphate; Riboflavin-foszfát-nátrium; Riboflavini natrii phosphas; Riboflavinnatriumfosfat; Riboflavino natrio fosfatas; Vitamin B_2 Phosphate.

The sodium salt of riboflavin 5′-phosphate.

Натрия Рибофлавина Фосфат

$C_{17}H_{20}N_4NaO_9P$ = 478.3.
CAS — 130-40-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Chin. and *US* specify the dihydrate salt.

Ph. Eur. 6.2 (Riboflavin Sodium Phosphate). A yellow or orange-yellow, hygroscopic, crystalline powder. Soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Riboflavin 5′-Phosphate Sodium). A fine, orange-yellow, hygroscopic, crystalline powder, having a slight odour. When dry, it is not affected by diffused light, but when in solution light induces rapid deterioration. Sparingly soluble in water. pH of a 1% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Large doses of riboflavin result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests.

Breast feeding. Supplementation significantly increased riboflavin concentration in the breast milk of women compared with those not given riboflavin. Significant differences between the two groups decreased over the period from 1 to 6 weeks postpartum; both groups of women had breast milk concentrations above previously reported normal values, and the authors concluded that supplementation was not necessary in healthy, well-nourished women.[1] The American Academy of Pediatrics considers the use of riboflavin to be usually compatible with breast feeding.[2]

1. Nail PA, *et al.* The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *Am J Clin Nutr* 1980; **33:** 198–204.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Pharmacokinetics

Riboflavin is readily absorbed from the gastrointestinal tract. Although riboflavin is widely distributed to body tissues little is stored in the body.

Riboflavin is converted in the body to the coenzyme flavine mononucleotide (FMN; riboflavin 5′-phosphate) and then to another coenzyme flavine adenine dinucleotide (FAD). About 60% of FMN and FAD are bound to plasma proteins. Riboflavin is excreted in urine, partly as metabolites. As the dose increases, larger amounts are excreted unchanged. Riboflavin crosses the placenta and is distributed into breast milk.

Human Requirements

The riboflavin requirement is often related to the energy intake but it appears to be more closely related to resting metabolic requirements. A daily dietary intake of about 1.1 to 1.8 mg of riboflavin is recommended. Liver, kidney, fish, eggs, milk, cheese, yeast, and some green vegetables such as broccoli and spinach are the richest sources of riboflavin. In general, little loss of riboflavin occurs during cooking, but considerable losses may occur if foods, especially milk, are exposed to sunlight.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) have been published for riboflavin[1] and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females of varying ages, and for pregnant and lactating women; the differences between age groups are intended to reflect the changes in caloric intakes at these ages. In the UK the reference nutrient intake (RNI) is 1.3 mg daily and 1.1 mg daily for adult males and females respectively; the estimated average requirement (EAR) is 1.0 mg daily and 0.9 mg daily respectively. In the USA the RDAs for adult males and females are 1.3 and 1.1 mg daily respectively.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Riboflavin, a water-soluble vitamin, is essential for the utilisation of energy from food. The active, phosphorylated forms, flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD), are involved as coenzymes in oxidative/reductive metabolic reactions. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.

Riboflavin deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as ariboflavinosis, characterised by cheilosis, angular stomatitis, glossitis, keratitis, surface lesions of the genitalia, and seborrhoeic dermatitis. There may also be normocytic anaemia and ocular symptoms including itching and burning of the eyes, and corneal vascularisation. Some of these symptoms may, in fact, be due to other vitamins such as pyridoxine or nicotinic acid which do not function correctly in the absence of riboflavin. Riboflavin deficiency may also occur with other vitamin B-complex deficiency states such as pellagra.

Riboflavin is used in the treatment and prevention of riboflavin deficiency. It is usually given in oral doses of 1 or 2 mg for prophylaxis; up to 30 mg daily in divided doses is used for treatment. Riboflavin, as the sodium phosphate, is also a component of intramuscular or intravenous vitamins B and C injections; riboflavin sodium phosphate 1.27 g is equivalent to about 1 g of riboflavin.

Riboflavin tetrabutyrate has also been used.

Riboflavin is also used as a colouring agent for food.

Glutaric aciduria. Milder forms of glutaric aciduria type II (p.1451) may respond to riboflavin.[1] Treatment with riboflavin 50 mg daily resulted in progressive improvement in a 4-year-old boy, with full recovery after 1 year. His brother, who had sustained permanent brain damage after epileptic seizures, showed moderate clinical improvement with riboflavin therapy.[2] In an adult patient with a history of recurrent pancreatitis and exercise intolerance, treatment with riboflavin 120 mg daily and levocarnitine resulted in no further episodes, although abnormal concentrations of amino acids were still apparent in her urine.[3]

1. Gregersen N, *et al*. Riboflavin responsive glutaric aciduria type II. *Prog Clin Biol Res* 1990; **321:** 477–94.
2. Uziel G, *et al*. Riboflavin-responsive glutaric aciduria type II presenting as a leukodystrophy. *Pediatr Neurol* 1995; **13:** 333–5.
3. Liang W-C, *et al*. Riboflavin-responsive glutaric aciduria type II with recurrent pancreatitis. *Pediatr Neurol* 2004; **31:** 218–21.

Migraine. Results from open studies[1,2] and a placebo-controlled trial[3] have suggested that riboflavin in high doses (400 mg daily) might be of some benefit in the prophylaxis of migraine attacks (p.616).

1. Schoenen J, *et al*. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. *Cephalalgia* 1994; **14:** 328–9.
2. Boehnke C, *et al*. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur J Neurol* 2004; **11:** 475–7.
3. Schoenen J, *et al*. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. *Neurology* 1998; **50:** 466–70.

Preparations

BP 2008: Vitamins B and C Injection;
BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;
USP 31: Riboflavin Injection; Riboflavin Tablets.

Proprietary Preparations (details are given in Part 3)

Belg.: Berivine; Ribon; ***Fin.:*** Vita-B2; ***Fr.:*** Beflavine; ***Ger.:*** B2-ASmedic; ***Hong Kong:*** FAD Ophthalmic Soln; Hibon; ***Indon.:*** Alinamin; ***Thai.:*** Boflavin.

Multi-ingredient: ***Austral.:*** Antioxidant Forte Tablets; Antioxidant Tablets; Extralife Eye-Care; Liv-Detox†; ***Austria:*** Beneuran Vit B-Komplex†; ***Braz.:*** Sulfatofer†; ***Ger.:*** Kwim†; ***Hong Kong:*** Alinamin-F; ***India:*** Hepa-Merz; ***Indon.:*** Matase; ***Ital.:*** Emazian B12†; Emoantitossina†; Facovit; Fosforilasi; Neuroftal†; ***Jpn:*** Neurovitan†; ***Mex.:*** Pangavit Pediatrico; ***Philipp.:*** Godex; ***Pol.:*** Biovision; ***Singapore:*** Alinamin-F; ***Spain:*** Aftasone B C; ***Thai.:*** Alinamin-F; B-100 Complex; ***Turk.:*** Neuvitan; ***UK:*** Quiet Life; Se-Power; ***USA:*** Cerefolin.

Vitamin B_6 Substances

Vitamina B_6.

Vitamin B_6 is usually available as pyridoxine but the term is also used to refer to the related compounds, pyridoxal and pyridoxamine.

Metadoxine

Metadoxina; Pyridoxine Pidolate. Pyridoxine *l*-5-oxopyrrolidine-2-carboxylate.

$C_8H_{11}NO_3,C_5H_7NO_3$ = 298.3.
CAS — 74536-44-0.

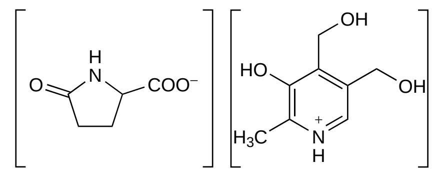

Pyridoxal Phosphate

Codecarboxylase; MC-I; Piridoxal, fosfato de; Pyridoxal 5-Phosphate. 3-Hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5′-phosphate.

$C_8H_{10}NO_6P$ = 247.1.
CAS — 54-47-7.
ATC — A11HA06.
ATC Vet — QA11HA06.

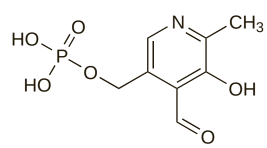

Pyridoxamine Hydrochloride

Piridoxamina, hidrocloruro de; Pyridoxamine Dihydrochloride. 4-Aminomethyl-5-hydroxy-6-methyl-3-pyridinemethanol hydrochloride.

$C_8H_{12}N_2O_2,2HCl$ = 241.1.
CAS — 524-36-7.

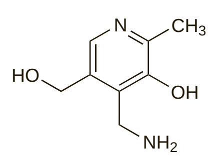

(pyridoxamine)

Pyridoxine Hydrochloride *(BANM, rINNM)*

Adermine Hydrochloride; Hidrocloruro de piridoxina; Piridoksin Hidroklorür; Piridoksino hidrochloridas; Piridossina Cloridrato; Piridoxin-hidroklorid; Pirydoksyny chlorowodorek; Pyridoksiinihydrokloridi; Pyridoxine, chlorhydrate de; Pyridoxin-hydrochlorid; Pyridoxinhydroklorid; Pyridoxini hydrochloridum; Pyridoxinii Chloridum; Pyridoxinium Chloride; Pyridoxol Hydrochloride; Vitamin B_6. 3-Hydroxy-4,5-bis(hydroxymethyl)-2-picoline hydrochloride.

Пиридоксина Гидрохлорид

$C_8H_{11}NO_3,HCl$ = 205.6.
CAS — 65-23-6 (pyridoxine); 58-56-0 (pyridoxine hydrochloride).
ATC — A11HA02.
ATC Vet — QA11HA02.

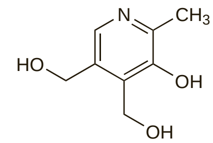

(pyridoxine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Pyridoxine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.4 to 3.0. Protect from light.

USP 31 (Pyridoxine Hydrochloride). White or practically white crystals or crystalline powder. Soluble 1 in 5 of water and 1 in 115 of alcohol; insoluble in ether. Its solutions in water have a pH of about 3. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies; the dose at which these occur is controversial (see below).

Breast feeding. Vitamin B_6 is excreted into breast milk.[1,2] While some have expressed concern over the inhibition of breast milk secretion by pyridoxine,[3] others have cautioned that pyridoxine deficiency may cause seizures in the neonate.[4] The American Academy of Pediatrics considers the use of pyridoxine to be usually compatible with breast feeding.[5]

1. West KD, Kirksey A. Influence of vitamin B intake on the content of the vitamin in human milk. *Am J Clin Nutr* 1976; **29:** 961–9.
2. Roepke JLB, Kirksey A. Vitamin B nutriture during pregnancy and lactation: 1. Vitamin B intake, levels of the vitamin in biological fluids, and condition of the infant at birth. *Am J Clin Nutr* 1979; **32:** 2249–56.
3. Greentree LB. Dangers of vitamin B in nursing mothers. *N Engl J Med* 1979; **300:** 141–2.
4. Lande NI. More on dangers of vitamin B in nursing mothers. *N Engl J Med* 1979; **300:** 926–7.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Effects on the nervous system. Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months.[1] There has, however, been debate as to whether smaller doses can produce such effects. Some contend that amounts of pyridoxine below this level are unlikely to produce toxic effects.[2,3] However, there have been some case reports[4,5] with amounts up to about 500 mg daily and prolonged use of even lower doses (about 200 mg daily or less) may also cause sensory peripheral neuropathy.[6] After a review of the possible toxicity associated with lower doses of pyridoxine, proposals were put forward in the UK to limit the dose freely available in dietary supplements to 10 mg daily; products supplying up to 50 mg daily would continue to be available from pharmacies and higher doses would only be available on prescription.[7] These proposals were heavily contested.[7,8] An upper limit of 100 mg daily has been suggested in the USA.[8]

1. Schaumburg H, *et al*. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 1983; **309:** 445–8.
2. Pauling L. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310:** 197.
3. Baker H, Frank O. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **310:** 197.
4. Berger A, Schaumburg HH. More on neuropathy from pyridoxine abuse. *N Engl J Med* 1984; **311:** 986.
5. Waterston JA, Gilligan BS. Pyridoxine neuropathy. *Med J Aust* 1987; **146:** 640–2.
6. Dordain G, Deffond D. Neuropathies à la pyridoxine: revue de la littérature. *Therapie* 1994; **49:** 333–7.
7. Collier J. Vitamin B-6: food or medicine? *BMJ* 1998; **317:** 92–3.
8. Anonymous. Still time for rational debate about vitamin B . *Lancet* 1998; **351:** 1523.

Interactions

Pyridoxine reduces the effects of levodopa (see p.808), but this does not occur if a dopa decarboxylase inhibitor is also given. Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbital (p.494) and phenytoin (p.500). Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine, isoniazid, penicillamine, and oral contraceptives.

Pharmacokinetics

Pyridoxine, pyridoxal, and pyridoxamine are readily absorbed from the gastrointestinal tract after oral doses and are converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk.

Human Requirements

For adults, the daily requirement of pyridoxine is probably about 1.5 to 2 mg and this amount is present in most normal diets. The requirement tends to increase as protein intake increases due to the role of the vitamin in amino acid metabolism. Meats, especially chicken, kidney, and liver, cereals, eggs, fish, and certain vegetables and fruits are good sources of pyridoxine.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p.1925) have been published for vitamin B_6 and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and during pregnancy and lactation. In the UK the reference nutrient intake (RNI) is 15 micrograms per g of protein daily for adult males and females and the estimated average requirement (EAR) is 13 micrograms per g of protein daily for the same group. In the USA the RDA for adult men ranges from 1.3 to 1.7 mg daily and that for adult women ranges from 1.3 to 1.5 mg daily.[2] The tolerable upper intake level is 100 mg daily.[2] The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for vitamin B_6 of 170 micrograms/kg daily.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)

Uses and Administration

Pyridoxine, a water-soluble vitamin, is involved mainly in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. It is also required for the formation of haemoglobin.

Deficiency of pyridoxine is rare in humans because of its widespread distribution in foods. Pyridoxine deficiency may however be drug-induced and can occur, for instance, during isoniazid therapy. Inadequate utilisation of pyridoxine may result from certain inborn errors of metabolism. Pyridoxine deficiency may lead to anaemia, dermatitis, cheilosis, and neurological symptoms such as peripheral neuritis, and convulsions.

Pyridoxine is used in the treatment and prevention of pyridoxine deficiency states. It is usually given orally, the preferred route, but may also be given by the subcutaneous, intramuscular, or intravenous routes. Doses of pyridoxine hydrochloride up to 150 mg daily are used in general deficiency states; higher doses of up to 400 mg daily are used in the treatment of sideroblastic anaemias (see below); and similar high doses have been used to treat certain metabolic disorders such as homocystinuria (see Amino Acid Metabolic Disorders, below) or primary hyperoxaluria (below). Pyridoxine has also been used to treat seizures due to hereditary syndromes of pyridoxine deficiency or dependency in infants.

Pyridoxine has also been tried in the treatment of many other disorders, including depression and other symptoms associated with the premenstrual syndrome (see below) and the use of oral contraceptives, although its efficacy has been questioned.

Pyridoxine is usually given as the hydrochloride although other salts such as the citrate, oxoglurate, phosphate, and phosphoserinate, have also been used. Metadoxine, the pidolate, has been investigated in alcoholism (see below).

For the use of pyridoxine in the prophylaxis of isoniazid-induced peripheral neuritis and for the treatment of acute isoniazid toxicity, see Treatment of Adverse Effects, under Isoniazid, p.289.

Pyridoxal phosphate may be used to treat vitamin B_6 deficiency. Pyridoxamine has also been given.

◊ Reviews.

1. Bender DA. Non-nutritional uses of vitamin B . *Br J Nutr* 1999; **81:** 7–20.
2. Lheureux P, *et al.* Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med* 2005; **12:** 78–85.

Alcoholism and alcohol poisoning. Pyridoxine and its pidolate, known as metadoxine, have been tried in the treatment of alcohol poisoning and alcoholism.[1] One study showed pyridoxine to be ineffective in acute alcohol poisoning[2] but another[3] suggested that the pidolate might be of benefit as an adjunct in the management of alcohol withdrawal (p.1626). In patients treated for alcoholic fatty liver, liver function returned to normal more quickly with metadoxine, even in patients who did not completely abstain from alcohol.[4]

1. Addolorato G, *et al.* Metadoxine in the treatment of acute and chronic alcoholism: a review. *Int J Immunopathol Pharmacol* 2003; **16:** 207–14.
2. Mardel S, *et al.* Intravenous pyridoxine in acute ethanol intoxication. *Hum Exp Toxicol* 1994; **13:** 321–3.
3. Rizzo A, *et al.* Uso terapeutico della metadoxina nell'alcolismo cronico: studio clinico in doppio cieco su pazienti ricoverati in un reparto di medicina generale. *Clin Ter* 1993; **142:** 243–50.
4. Caballería J, *et al.* Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-control trial. *J Hepatol* 1998; **28:** 54–60.

Amino acid metabolic disorders. Pyridoxine has been used in various inborn errors of amino acid metabolism, such as homocystinuria (p.1922), with or without cobalamins and folate. Relatively high doses may need to be given (see above). For children with metabolic disorders such as homocystinuria and cystathioninuria, the *BNFC* suggests pyridoxine in an oral dose of 50 to 100 mg once or twice daily for neonates, and 50 to 250 mg once or twice daily in patients aged 1 month to 18 years. For the use of pyridoxine in primary hyperoxaluria, another inherited metabolic disorder, see below.

Anaemias. Some patients with acquired or hereditary sideroblastic anaemia (p.1044) that is severe enough to require treatment will respond to high doses (up to 400 mg daily) of pyridoxine, and a trial is considered worthwhile in all patients.

Cardiovascular disease. For mention of the possible link between vitamin B_6, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid, p.1941. Pyridoxal phosphate is thought to prevent cellular calcium overload in ischaemia-reperfusion injury, but a large multicentre study[1] investigating doses of 250 mg daily orally given 3 to 10 hours before coronary artery bypass graft surgery in intermediate- to high-risk patients, and for a further 30 days after the procedure, found it did not reduce the incidence of cardiovascular death or non-fatal myocardial infarction.

1. Alexander JH, *et al.* MEND-CABG II Investigators. Efficacy and safety of pyridoxal 5′-phosphate (MC-1) in high-risk patients undergoing coronary artery bypass graft surgery: the MEND-CABG II randomized clinical trial. *JAMA* 2008; **299:** 1777–87.

Carpal tunnel syndrome. Pyridoxine has been advocated by some[1] for patients with carpal tunnel syndrome (see Soft-tissue Rheumatism, p.13), but evidence of efficacy is considered to be limited.[2] In most studies reporting improvement with pyridoxine, doses have ranged from 50 to 300 mg daily for 12 weeks; a review concluded that treatment should be stopped if there is no apparent response after this period.[3]

1. Lewis PJ. Pyridoxine supplements may help patients with carpal tunnel syndrome. *BMJ* 1995; **310:** 1534.
2. O'Connor D, *et al.* Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 09/01/06).
3. Aufiero E, *et al.* Pyridoxine hydrochloride treatment of carpal tunnel syndrome; a review. *Nutr Rev* 2004; **62:** 96–104.

Epilepsy. Pyridoxine-dependent epilepsy is an autosomal recessive disorder associated with decreased central γ-aminobutyric acid (GABA) concentrations and elevated cerebral glutamate concentrations. Untreated patients suffer from progressive encephalopathy, mental retardation, and intractable epilepsy; lifelong supplementation with pyridoxine can control epileptic symptoms but mental retardation may still develop. An epidemiological study[1] defined cases as those children with recurrent seizures that ceased within 7 days of oral pyridoxine at a usual dose of 30 mg/kg daily (minimum dose 15 mg/kg daily; maximum dose 1000 mg/kg daily), or within 30 minutes of intravenous pyridoxine (usual dose 100 mg; minimum dose 50 mg), that recurred when supplementation was withdrawn, and ceased again upon dosage as before. The study found that, despite their rarity, pyridoxine-dependent seizures frequently present atypically, and the author suggested that pyridoxine be given to all children with intractable seizures beginning before 3 years of age, including neonates with suspected hypoxic-ischaemic encephalopathy.

Test doses of pyridoxine intravenously, repeated at intervals of 10 minutes up to a total of 500 mg if necessary, have been suggested in the diagnosis of pyridoxine-dependent epilepsy; if the patient responds then a daily oral dose of 5 mg/kg is suggested although there is no real consensus on the appropriate dosage.[2] The *BNFC* suggests an intravenous test dose of 50 to 100 mg; in those who respond, oral doses of 50 to 100 mg once daily in neonates or 20 to 50 mg once or twice daily in older children, are suggested, adjusted as required. Alternatively, in patients with recurrent seizures refractory to conventional anticonvulsant therapy, oral pyridoxine supplementation of 15 mg/kg daily should lead to resolution of clinical seizures within a week in those with the condition; however, in some patients the daily dose required may be lower.[3]

A study in one patient[4] found that although pyridoxine 5 mg/kg reduced glutamate concentrations in CSF from the untreated value of 200 times normal limits, it did so only to 10 times the normal value, despite remission of symptoms. Doses of 10 mg/kg daily were required to normalise CSF glutamate, and it was suggested that this was a more appropriate target for therapy. In some children, pyridoxal phosphate has been suggested to be more effective than pyridoxine in controlling seizures.[5]

1. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. *Arch Dis Child* 1999; **81:** 431–3.
2. Gospe SM. Current perspectives on pyridoxine-dependent seizures. *J Pediatr* 1998; **132:** 919–23.
3. Gospe SM. Pyridoxine-dependent seizures: findings from recent studies pose new questions. *Pediatr Neurol* 2002; **26:** 181–5.
4. Baumeister FAM, *et al.* Glutamate in pyridoxine-dependent epilepsy: neurotoxic glutamate concentration in the cerebrospinal fluid and its normalization by pyridoxine. *Pediatrics* 1994; **94:** 318–21.
5. Wang H-S, *et al.* Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Arch Dis Child* 2005; **90:** 512–15.

Palmar-plantar erythrodysesthesia syndrome. Pyridoxine, in doses of 100 to 300 mg daily, has been used successfully[1] for treating and preventing palmar-plantar erythrodysesthesia syndrome associated with antineoplastic therapy (see p.639).

1. Nagore E, *et al.* Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; **1:** 225–34.

Premenstrual syndrome. Pyridoxine has been widely used in the premenstrual syndrome (p.2099) despite controversy over its effectiveness. Some consider that depressive symptoms may be provoked by pyridoxine deficiency because of its role as a coenzyme in the production of certain neurotransmitters, but it is difficult to attribute any of the other symptoms of the premenstrual syndrome to pyridoxine deficiency and doses of 50 mg are no more effective than a placebo.[1] A systematic review found that although treatment with pyridoxine was more effective than placebo, there was insufficient high-quality evidence to recommend its routine use in premenstrual syndrome.[2] If pyridoxine is used, the dosage should be restricted (see Effects on the Nervous System, above) because of concerns about neurotoxicity.[3]

1. West CP. The premenstrual syndrome. *Prescribers' J* 1987; **27** (2): 9–15.
2. Wyatt KM, *et al.* Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999; **318:** 1375–81.
3. Severino SK, Moline ML. Premenstrual syndrome: identification and management. *Drugs* 1995; **49:** 71–82.

Primary hyperoxaluria. Primary hyperoxaluria (as distinct from the various forms secondary to other disorders) is a genetic disorder characterised by excessive synthesis and urinary excretion of oxalic acid. Two forms are known, type I (hyperglycolic aciduria) and type II (L-glyceric aciduria), associated with different enzyme defects. They are marked by recurrent calcium oxalate kidney stones, or nephrocalcinosis, leading to renal failure, together with extrarenal deposition of calcium oxalate and frequently severe peripheral vascular insufficiency. Treatment with high doses of pyridoxine may help decrease oxalate excretion particularly in type I disease,[1,2] although response is variable.[3] A few patients may respond to lower (physiological) doses.[4] Such treatment can be used with an oral orthophosphate supplement, which helps reduce renal deposition of calcium oxalate, and the combination appears to preserve renal function.[5] Therapy with magnesium salts, potassium citrate, and thiazide diuretics has also been suggested.[2] In patients in whom renal failure develops, the results of kidney transplantation have been disappointing, due to deposition of calcium oxalate in the new kidney, although transplanting the liver as well can correct the enzyme defect.[1,6] Pre-emptive liver transplantation, performed before renal failure or systemic oxalosis has occurred, may be an option.[2]

1. Cochat P, Basmaison O. Current approaches to the management of primary hyperoxaluria. *Arch Dis Child* 2000; **82:** 470–3.
2. Marangella M, *et al.* The primary hyperoxalurias. *Contrib Nephrol* 2001; **136:** 11–32.
3. Toussaint C. Pyridoxine-responsive PH1: treatment. *J Nephrol* 1998; **11** (suppl 1): 49–50.
4. Yendt ER, Cohanim M. Response to a physiologic dose of pyridoxine in type I primary hyperoxaluria. *N Engl J Med* 1985; **312:** 953–7.
5. Milliner DS, *et al.* Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *N Engl J Med* 1994; **331:** 1553–8.
6. Watts RWE, *et al.* Combined hepatic and renal transplantation in primary hyperoxaluria type I: clinical report of nine cases. *Am J Med* 1991; **90:** 179–88.

Tardive dyskinesia. In a double-blind, controlled, crossover study,[1] daily oral doses of vitamin B_6 1.2 g effectively reduced the symptoms of tardive dyskinesia (see Extrapyramidal Disorders, p.971).

1. Lerner V, *et al.* Vitamin B treatment for tardive dyskinesia: a randomized, double-blind, placebo-controlled, crossover study. *J Clin Psychiatry* 2007; **68:** 1648–54.

Preparations

BP 2008: Pyridoxine Tablets; Vitamins B and C Injection;
BPC 1973: Strong Compound Vitamin B Tablets;
USP 31: Pyridoxine Hydrochloride Injection; Pyridoxine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Benadon; ***Austral.:*** Pyroxin; ***Austria:*** Diclo-B; ***Belg.:*** Bedoxine; ***Braz.:*** Dimedril†; Fonto-Vit B6; Neuri B6; Seis-B; ***Canad.:*** Carthamex; ***Chile:*** Metadoxil†; Vitabe; ***Fin.:*** Heksavit; Vita-B6; ***Fr.:*** Becilan; Dermo 6; ***Ger.:*** B6-ASmedic; B Vicotrat; Bonasanit; Hexobion; ***Gr.:*** Besix; ***Hung.:*** Beres B6; Metadoxil; ***India:*** Pyricontin; ***Indon.:*** Liconam; Stopmun; ***Irl.:*** Complement Continus; ***Israel:*** Anacrodyne; B-Six; ***Ital.:*** Benadon; Memosprint†; Metadoxil; Xanturenasi; ***Mex.:*** Abrixone; Fortical; Metasin; Valpirina; ***Philipp.:*** Drexabion; Hybutin; Jaga; Lixtress; Meganerv; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Supraneuron; Vineuron; ***Port.:*** Benadon; Metadoxil†; ***Rus.:*** Metadoxil (Метадоксил); ***S.Afr.:*** Beesix; Lactosec; ***Spain:*** Benadon; Conductasa; Godabion B6†; ***Swed.:*** Benadon; ***Switz.:*** Benadon; Complement Continus†; ***Thai.:*** B-6; Metadoxil; ***Turk.:*** B Vigen; Libavit B ; Postadoxine; ***USA:*** Vitelle Nestrex†; ***Venez.:*** Benadon†; Beplus; Biprin; Clodoxin; Suprabion; Vibralen†.

Multi-ingredient: ***Arg.:*** 6 Copin; Algio Nervomax; Algio Nervomax Fuerte; Blastop; Butineuron; Cadencial Plus; Calcimax Magnesio; Centella Incaico; Cobenexol Forte; Cobenexol Fuerte; CVP B1 B6 B12†; Dexabion; Dolo Nervobion; Dolo Nervobion 10000; Dorixina B1 B6 B12; Flexicamin B12; Flogiatrin B12; Holomagnesio B6; KLB6 Fruit Diet; Klosidol B1 B6 B12; Lohp; Magnebe; Megacistin; Megaplus; Nervobion Fuerte; Nervomax TB12; Neuronal Vascular†; Plenovit Melatonina; Presterin; QX 10; Sindrolen†; Total Magnesiano B6; ***Austral.:*** Bio Magnesium; Extralife Flow-Care; Extralife Fluid-Care; Extralife PMS-Care; Extralife Uri-Care; Liv-Detox†; Mag-Oro; Medinat PMT-Eze†; Zinc Zenith; ***Austria:*** Arca-Be; Aslavital; Astronautal; Beneuran compositum; Beneuran Vit B-Komplex†; Contravert B ; Diclovit; Dolo-Neurobion; Echnatol B ; Neurobion; Neuromerck; Neuromultivit; Pronerv; Sigmalin B ; Sigmalin B forte; Sigmalin B ohne Coffein; Vertirosan Vitamin B ; ***Belg.:*** Betapyr; Neurobion; Vioneurin†; ***Braz.:*** Alergo Filinal; Aminocid†; Aminotox†; Anekron; Benistina†; Betaliver†; Bicavine; Biohepax; Bronquitos; Cianotrat-Dexa; Citoneurin; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacobal; Dexador; Dexadoze; Dexagil; Dexaneurin; Dexanevral†; Diagrin†; Doxal; Dramavit B6†; Dramin B-6; Dramin B-6 DL; Emetrol†; Enjool†; Epativan; Epocler; Estac†; Gabax; Hepacitron†; Hepatobe†; Hepatox; Hormo Hepatico†; Levordiol; Megestran†; Monotrean B6; Nausicalm; Nausilon B6; Necro B-6; Nicopaverina B6†; Pantevit; Plagon; Trirubin†; Vitatonus; Vominil†; Xantinon Complex; ***Canad.:*** Diclectin; Penta-3B; Penta-3B + C; ProstGard†; ***Chile:*** Activator†; Betonvit†; Dolotol 12; Ferro Vitaminico; Gamalate B6; Glutacyl Vitaminado; Hexalectol; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; ***Cz.:*** Magne-B ; Milgamma N; Neuromultivit; ***Fin.:*** Neurobion; Neurovitan; Wicnecarb; Wicnevit; ***Fr.:*** Arthrolib; Catarstat; Cysti-Z†; Cystine B ; Lyso-6; Magne-B ; Phakan†; Uvimag B ; ***Ger.:*** B-Komplex forte; Bevit Forte; Bramin-hepa†; Dolo-Neurobion forte†; Dolo-Neurobion N†; Hepagrisevit Forte-N†; Hewedolor neuro; Medivitan N; Medivitan N Neuro; Medyn; Milgamma; Milgamma N; Milgamma-NA; Milneuron NA; Neuralysan S†; Neuro; Neuro uno; Neuro-AS N†; neuro-B forte; Neuro-Effekton B; Neuro-Lichtenstein M; Neuro-Lichtenstein N; Neuro-ratiopharm N; Neuro-ratiopharm†; Neuro-Vibolex; Neurobion; Neurobion N; Neurotrat S; Nifurantin B 6; Novirell B Duo; Pleomix-B; Reisegold†; Telbibur N†; Vitaject†; Vitamin B duo; ***Gr.:*** Lyso-6; Neurobion; ***Hong Kong:*** 3B; C-Sik†; Milgamma; Navidoxine; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Fort; Vibion; Vida Neurotab; Vidaclofen-Plus; ***Hung.:*** Atherovit; Beres Magnezium + B ; Magne-B ; Magurlit†; Milgamma N; Neurobion; Pregmag; Vitacalc†; ***India:*** Blosyn; Conviron-TR; Cx-3; Cx-4; Cx-5; Doxinate; Eternex; Gocox Compound; Gocox-4†; Ipcacin Kid; Ipcazide; Isokin-300; Rifa; Rifa E; Sclerobion; Sioneuron; Vitneurin; Vominate; Wokex-2; Wokex-3; Wokex-4; ***Indon.:*** Abajos; Anvomer B6; Arsinal; Avogin; Betrion; Bicitron; Biocombin; Biomega; Biomex; Corobion; Corsaneuron; Daneuron; Deprex; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Dramasine; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; Lapibion; Licobion; Mediamer B6; Mersibion; Myoviton; Nervitone; Nervitone E; Neuralgin RX; Neuro Panstop; Neuro-Beston; Neurobat; Neurobat A; Neurobion; Neurobiovit; Neurodex; Neurohax; Neurophil; Neuropyramin; Neurosanbe; Neurosanbe Plus; Neurotrat; Neurotropic Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Pregnasea; Pregvomit; Primabion; Pritagesic; Scanneuron; Sohobion; Solaneuron; Stileran; Tocobion; Trimate-E; Tropineuron; Vitap; Vomilat; ***Israel:*** Calmanervin; Tribemin; Tricardia; ***Ital.:*** Acutil Fosforo; Adenoplex; Adenovit†; Alcalosio; Benexol B12; Coxantenurasi; Dobetin Totale; Emoantitossina†; Esaglut†; Fosforilasi; Miazide B6†; Midium; Mionevrasi; Neuraben; Sedofit; Trinevrina B6; ***Jpn:*** Neurovitan†; ***Malaysia:*** 3B; Becoloxin†; Flavettes Neuroforte; Fundamin-E; Navidoxine†; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Fort; Re-B; Vitabion; ***Mex.:*** Ariflam Forte; Benexol B12; Betrox; Bomine; Bonadoxina; Bonalen; Bonazin; Cobotiaxina; Dexabion; Diclovith-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiamial; Doxemina; Duciclon; Emediba; Forvin; Innobion; Lecifar-K†; Liatriz; Macrox-5; Meclifar; Meclison; Neuralin; Neurobion; Nuro-B; Odexan; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Pidoxina; Revitaliv-C; Selectadoce; Suma-B; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; Vo-Remi; ***Neth.:*** Emesafene; Neurobion; Princi B1 + B6; ***Philipp.:*** Catarstat; Dolo-Neurobion; Godex; Hinuron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Vitanerv; ***Pol.:*** Filomag B ; Maglek B ; Magne-B ; Magnefar B ; Magsolvit B ; Magvit B ; MBE; Milgamma N; Slow-Mag B ; ***Port.:*** Detoxergon; Esclerobion; Linamin Plus†; Nausefe; Neurobion; Phakan†; ***Rus.:*** Lysobact (Лизобакт); Magne B6 (Магне В6); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); Vectrum Calcium (Вектрум Кальций); ***S.Afr.:*** Asic; Neurobion; Vomifene; ***Singapore:*** Daneuron; Navidoxine†; Neurobion; Neurodex; Neuroforte; Neurorubine; Neurovit; Neuroxel; Nevramin; Princi-B Fort; ***Spain:*** Acetuber; Aftasone B C; Agudil; Antineurina; Benexol B1 B6 B12; Bester Complex; Biodramina Cafeina; Cariban; Cefabol; Dalamon†; Dorken; Duplicalcio 150†; Gamalate B6; Hidroxil B12 B6 B1; Mederebro; Menalgil B6; Nervobion; Neuromade; Neurostop Complex; Nuclesenina; Pazbronquial; Pleocortex B6†; Quimpedor; Redutona; Sirodina†; Taurobetina†; Tepazepan; ***Swed.:*** Neurobion; ***Switz.:*** Acne Gel; Antemin compositum; Benexol B12; Catarstat; Itinerol B ; Linervidol†; Lyso-6†; Neurorubin; Phakolen†; Suracton†; Trawell compositum; Trilagavit; ***Thai.:*** 3B; B-100 Complex; Beromin; Cydoxmine-B†; Cyriamine; Douzabox; Ferli-6; Ferosix; Genavit; Hemolax; Neubee; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvit; Princi-B; Re-B Forte; Roxine; Tribesian; Tricortin†; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; ***Turk.:*** Benexol; Benol; Benoral; Bevitab; Bevitol; Nerox-B; Neurogriseovit; Neurovit; Tribeksol; ***UAE:*** 3V; ***UK:*** HealthAid Boldo-Plus; Kelp Plus 3; ***USA:*** Beelith; Cerefolin; FOLTX; KLB6; Lurline PMS; Marlyn Formula 50; Metanx; PremesisRx; Releaf for PMS; ***Venez.:*** Bedoyecta; Bonadoxina; Briomet; Deca-Lentermina Complex; Dermagran; Dobetin Compuesto; Etizil†; Lecivar Plus; Lentermina Complex; Mebax†; Mega-Neubion; Miovit; Neubion; Neuribe; Rubrinal; Rubrinex; Tres-Be.

Used as an adjunct in: ***Ger.:*** Isozid comp N; tebesium; ***India:*** Rifacomb†; ***Indon.:*** bacbutINH; Erabutol Plus; INH-Ciba; INHA; Inoxin; Medinh-OD; Meditam-6; Mycothambin-INH; Niacifort-6; Niazitol; Pulmolin; Pulna; Pyravit; Pyrifort; Santibi Plus; Suprazid; TB Vit 6; ***Ital.:*** Etanicozid B6; ***Philipp.:*** CombiKids; Comprilex; Curazid (Reformulated); Ethamizid; Ethi 400; Eurocoxin; Isodexid; Isoxin; Kidz Kit 2; Kidz Kit 3; Nicetal; Odinah; Refam Duo; Refam Pedia Kit; Sthamizide; SVM-Polypac-A; Techxafort; Terozid; Vamsoxid; ***Pol.:*** Laktomag B ; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Protiocomb (Протиокомб); Repin B (Репин В); Rifacomb (Рифакомб); ***Spain:*** Cemidon B6; Tisobrif; ***Turk.:*** Isovit.

Vitamin B_{12} Substances

Vitamina B_{12}.

Vitamin B_{12} is the name generally used for a group of related cobalt-containing compounds, also known as cobalamins, of which cyanocobalamin and hydroxocobalamin are the principal forms in clinical use.

Cobamamide *(pINN)*

Adenosylcobalamin; Cobamamida; Cobamamidum; Coenzyme B_{12}; Dibencozide; Dibenzcozamide; Dimebenzcozamide; Kobamamid. Inner salt of the *Co*-(5′-deoxyadenosine-5′) derivative of the 3′-ester of cinobinamide phosphate with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole.

Кобамамид

$C_{72}H_{100}CoN_{18}O_{17}P$ = 1579.6.
CAS — 13870-90-1.
ATC — B03BA04.
ATC Vet — QB03BA04.

Pharmacopoeias. In *Chin.*

Cyanocobalamin *(BAN, rINN)*

Cianocobalamina; Cianokobalamin; Cianokobalaminas; Cobamin; Cyanocobalamine; Cyanocobalaminum; Cyanokobalamin; Cycobemin; Cyjanokobalamina; Kyanokobalamin; Siyanokobalamin; Syanokobalamiini. *Co*α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co*β-cyanocobamide.

Цианокобаламин

$C_{63}H_{88}CoN_{14}O_{14}P$ = 1355.4.
CAS — 68-19-9.
ATC — B03BA01.
ATC Vet — QB03BA01.

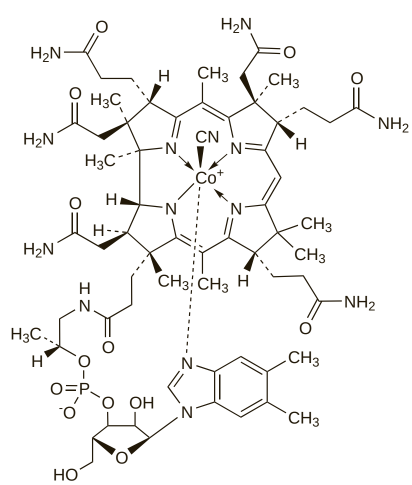

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Cyanocobalamin). A dark red, crystalline powder or dark red crystals. The anhydrous substance is very hygroscopic. Sparingly soluble in water and in alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.
USP 31 (Cyanocobalamin). Dark red crystals or amorphous or crystalline red powder. In the anhydrous form it is very hygroscopic and when exposed to air it may absorb about 12% of water. Soluble 1 in 80 of water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Hydroxocobalamin *(BAN, USAN, rINN)*

Hidroksokobalaminas; Hidroxocobalamina; Hydroksikobalamiini; Hydroxikobalamin; Hydroxocobalamine; Hydroxocobalaminum; Hydroxycobalaminum; Idrossocobalamina. *Co*α-[α-(5,6-Dimethylbenzimidazolyl)]-*Co*β-hydroxocobamide.

Гидроксокобаламин

$C_{62}H_{89}CoN_{13}O_{15}P$ = 1346.4.
CAS — 13422-51-0.
ATC — B03BA03; V03AB33.
ATC Vet — QB03BA03; QV03AB33.

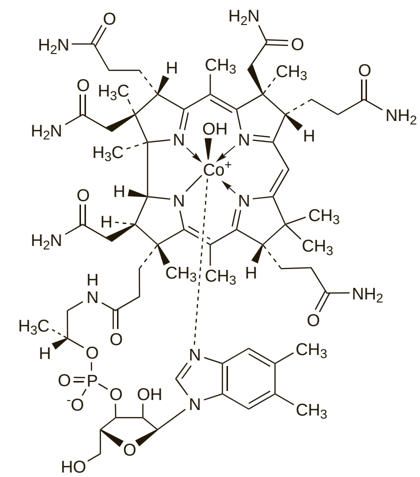

NOTE. The hydrated form of hydroxocobalamin has been referred to as aquocobalamin.

Pharmacopoeias. In *Int.* and *US.*
USP 31 (Hydroxocobalamin). Dark red crystals or red crystalline powder. Is odourless or has not more than a slight acetone odour. The anhydrous form is very hygroscopic. Soluble 1 in 50 of water and 1 in 100 of alcohol; practically insoluble in acetone, in chloroform, in ether, and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 8.0 and 10.0. Store in airtight containers at a temperature of 8° to 15°. Protect from light.

Hydroxocobalamin Acetate *(BANM, rINNM)*

Acetato de hidroxocobalamina; Acetatocobalamin; Hidroksokobalamino acetatas; Hidroxokobalamin-acetát; Hydroksokobalamiiniasetaatti; Hydroxocobalamine, acétate d'; Hydroxocobalamini acetas; Hydroxokobalamin acetát; Hydroxokobalamina-cetat.

Гидроксокобаламина Ацетат

$C_{64}H_{93}CoN_{13}O_{17}P$ = 1406.4.
CAS — 22465-48-1.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn,* and *Viet.*
Ph. Eur. 6.2 (Hydroxocobalamin Acetate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2° and 8° in airtight containers. Protect from light.

Hydroxocobalamin Chloride *(BANM, rINNM)*

Cloruro de hidroxocobalamina; Hidroksokobalamino chloridas; Hidroxokobalamin-klorid; Hydroksokobalamiinikloridi; Hydroxocobalamine, chlorure d'; Hydroxocobalamini chloridum; Hydroxocobalamini Hydrochloridum; Hydroxokobalamin hydrochlorid; Hydroxokobalaminklorid.

Гидроксокобаламина Хлорид

$C_{62}H_{90}ClCoN_{13}O_{15}P$ = 1382.8.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.,* and *Viet.*
Ph. Eur. 6.2 (Hydroxocobalamin Chloride). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2° and 8° in airtight containers. Protect from light.

Hydroxocobalamin Sulfate *(BANM, rINNM)*

Hidroksokobalamino sulfatas; Hidroxokobalamin-szulfát; Hydroksokobalamiinisulfaatti; Hydroxocobalamin Sulphate; Hydroxocobalamine, sulfate d'; Hydroxocobalamini sulfas; Hydroxokobalamin sulfát; Hydroxokobalaminsulfat; Sulfato de hidroxocobalamina.

Гидроксокобаламина Сульфат

$C_{124}H_{180}Co_2N_{26}O_{34}P_2S$ = 2790.8.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Viet.*

Ph. Eur. 6.2 (Hydroxocobalamin Sulphate). A dark red, very hygroscopic, crystalline powder or dark red crystals. Soluble in water. Some decomposition may occur on drying. Store at a temperature between 2° and 8° in airtight containers. Protect from light.

Mecobalamin *(BAN, USAN, pINN)*

Mecobalamina; Mécobalamine; Mecobalaminum; Methylcobalamin. Coα-[α-(5,6-Dimethylbenzimidazolyl)]-Coβ-methylcobamide.

Мекобаламин

$C_{63}H_{91}CoN_{13}O_{14}P$ = 1344.4.
CAS — 13422-55-4.
ATC — B03BA05.
ATC Vet — QB03BA05.

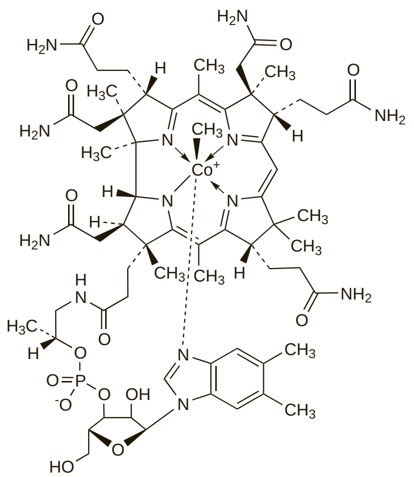

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Allergic hypersensitivity reactions have occurred rarely after parenteral doses of the vitamin B_{12} compounds cyanocobalamin and hydroxocobalamin. Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy.

Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin.

Intranasal cyanocobalamin may cause rhinitis, nausea, and headache.

Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable. Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B_{12} deficiency (see p.1940).

Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Breast feeding. Vitamin B_{12} is distributed into breast milk.[1] The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.[2]

1. Samson RR, McClelland DBL. Vitamin B in human colostrum and milk. *Acta Paediatr Scand* 1980; **69:** 93–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Hypersensitivity. Analysis, by the Boston Collaborative Drug Surveillance Program, of data on 15 438 patients hospitalised between 1975 and 1982 detected 3 allergic skin reactions attributed to cyanocobalamin among 168 recipients of the drug.[1] For the purposes of the study, reactions were defined as being generalised morbilliform exanthems, urticaria, or generalised pruritus only.

In a patient with a generalised pruritic reaction to hydroxocobalamin (with subsequent urticaria, bronchospasm, and oropharyngeal angioedema), cyanocobalamin was relatively well-tolerated, with only one episode of delayed urticaria.[2]

1. Bigby M, *et al*. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
2. Heyworth-Smith D, Hogan PG. Allergy to hydroxycobalamin, with tolerance of cyanocobalamin. *Med J Aust* 2002; **177:** 162–3.

Local reactions. After 3 years of monthly intramuscular vitamin B_{12} injections, a patient presented with a sclerotic plaque at the injection site, which was successfully treated by excision and local fat transfer. It was unclear as to whether the patient had reacted to the vehicle, the preservative, or to the cyanocobalamin.[1] Fascial haematoma after vitamin B_{12} injection leading to local compression (posterior arm compartment syndrome) has also been reported.[2]

1. Ho J, *et al*. Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; **30:** 1252–5.
2. Knapke D, Truumees E. Posterior arm and deltoid compartment syndrome after vitamin B12 injection. *Orthopedics* 2004; **27:** 520–1.

Interactions

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H_2-antagonists, omeprazole, and colchicine. Serum concentrations may be decreased by use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations. Parenteral chloramphenicol may attenuate the effect of vitamin B_{12} in anaemia.

Pharmacokinetics

Vitamin B_{12} substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

Vitamin B_{12} is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B_{12} is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.

Retention in the body. After injection of cyanocobalamin a large proportion is excreted in the urine within 24 hours; the body retains only 55% of a 100-microgram dose and 15% of a 1000-microgram dose. Body stores of vitamin B_{12} amount to 2000 to 3000 micrograms which is believed to be enough for 3 to 4 years. If 1000 micrograms is injected monthly, the 150 micrograms retained lasts for about 1 month. Hydroxocobalamin is better retained than cyanocobalamin; 90% of a 100-microgram dose and 30% of a 1000-microgram dose are retained and that range is believed to be enough for 2 to 10 months.[1]

1. Anonymous. Time to drop cyanocobalamin? *Drug Ther Bull* 1984; **22:** 43.

Human Requirements

For adults, the daily requirement of vitamin B_{12} is probably about 1 to 2 micrograms and this amount is present in most normal diets. Vitamin B_{12} occurs only in animal products; it does not occur in vegetables, therefore strict vegetarian (vegan) diets that exclude dairy products may provide an inadequate amount although it has been said that many years of vegetarianism are necessary before a deficiency is produced, if at all. Meats, especially liver and kidney, milk, eggs, and other dairy products, and fish are good sources of vitamin B_{12}.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p.1925) have been published for vitamin B_{12} and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, adults and pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 1.5 micrograms daily for adult males and females and the estimated average requirement (EAR) is 1.25 micrograms daily. In the USA the RDA for adults is 2.4 micrograms daily.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B , folate, vitamin B , pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309065542 (accessed 21/07/08)

Uses and Administration

Vitamin B_{12}, a water-soluble vitamin, occurs in the body mainly as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide) and hydroxocobalamin. Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis. Mecobalamin is also closely involved with folic acid in several important metabolic pathways.

Vitamin B_{12} deficiency can occur in strict vegetarians with an inadequate dietary intake, although it may take many years before a deficiency is produced. Deficiency is more likely in patients with malabsorption syndromes or metabolic disorders, nitrous oxide-induced megaloblastosis, or after gastrectomy or extensive ileal resection. Deficiency leads to the development of megaloblastic anaemias and demyelination and other neurological damage. A specific anaemia known as pernicious anaemia develops in patients with an absence of the intrinsic factor necessary for good absorption of the vitamin from dietary sources.

Vitamin B_{12} preparations are used in the treatment and prevention of vitamin B_{12} deficiency. It is essential to identify the exact cause of deficiency, preferably before starting therapy. Hydroxocobalamin is generally preferred to cyanocobalamin; it binds more firmly to plasma proteins and is retained in the body longer (see under Pharmacokinetics, above). Cyanocobalamin and hydroxocobalamin are generally given by the intramuscular route, although cyanocobalamin may be given orally or subcutaneously, or intranasally (see also under Administration, below). Oral cyanocobalamin may be used in treating or preventing vitamin B_{12} deficiency of dietary origin.

In the UK, recommended doses for **pernicious anaemia** and other macrocytic anaemias *without neurological involvement* are hydroxocobalamin (or cyanocobalamin) 250 to 1000 micrograms intramuscularly on alternate days for 1 to 2 weeks, then 250 micrograms weekly until the blood count returns to normal. Maintenance doses of 1000 micrograms of hydroxocobalamin are given every 2 to 3 months (or monthly for cyanocobalamin). If there is *neurological involvement*, hydroxocobalamin or cyanocobalamin may be given in doses of 1000 micrograms on alternate days and continued for as long as improvement occurs. For the *prophylaxis* of anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy or malabsorption syndromes hydroxocobalamin may be given in doses of 1000 micrograms intramuscularly every 2 or 3 months or cyanocobalamin in doses of 250 to 1000 micrograms intramuscularly each month. For vitamin B_{12} deficiency of *dietary* origin, oral cyanocobalamin 50 to 150 micrograms may be taken daily between meals.

Lower doses of both cyanocobalamin and hydroxocobalamin are recommended in the USA. For the *treatment* of deficiency, the usual intramuscular or subcutaneous dose of cyanocobalamin is 100 micrograms daily for 7 days, then on alternate days for 7 further doses, then every 3 to 4 days for 2 to 3 weeks. For hydroxocobalamin the usual intramuscular dose is 30 micrograms daily for 5 to 10 days. For *maintenance*, both cyanocobalamin and hydroxocobalamin are given at a dose of 100 to 200 micrograms monthly, based on haematological monitoring. Intranasal preparations of cyanocobalamin are also available for maintenance therapy, the recommended dose being 500 micrograms once weekly. Oral doses of up to 1000 micrograms of cyanocobalamin have also been used. In patients with normal gastrointestinal absorption, doses of 1 to 25 micrograms daily are considered sufficient as a *dietary supplement.*

Treatment usually results in rapid haematological improvement and a striking clinical response. However, neurological symptoms respond more slowly and in some cases remission may not be complete.

Cobamamide and mecobalamin may also be used for vitamin B_{12} deficiency.

Hydroxocobalamin may also be given in the treatment of **tobacco amblyopia** and **Leber's optic atrophy**; initial doses are 1000 micrograms daily for 2 weeks intramuscularly followed by 1000 micrograms twice weekly for as long as improvement occurs. Thereafter, 1000 micrograms is given every 1 to 3 months.

Hydroxocobalamin is also used for the treatment of known or suspected **cyanide toxicity** (see below). Each 2.5 g vial of hydroxocobalamin is reconstituted with 100 mL of diluent, preferably sodium chloride 0.9%. The starting dose for adults is 5 g intravenously over 15 minutes. Depending on the severity of the toxicity and the clinical response, a second dose of 5 g may be infused over 15 minutes to 2 hours.

Cyanocobalamin and hydroxocobalamin are also used in the **Schilling test** to investigate vitamin B_{12} absorption and deficiency states. They are given in a non-radioactive form together with cyanocobalamin radioactively-labelled with cobalt-57 (p.2053) or cobalt-58 (p.2053) and the amount of radioactivity excreted in the urine can be used to assess absorption status. A differential Schilling test, in which the forms of cyanocobalamin are given under different conditions (such as with intrinsic factor, antibacterials, or pancreatic enzymes) can provide information concerning the cause of the malabsorption.

Administration. The small amounts of vitamin B_{12} present in the diet are absorbed from the gastrointestinal tract by an active process that involves binding with intrinsic factor. As intrinsic factor is absent in patients who have developed pernicious anaemia it has often been assumed that oral vitamin B_{12} preparations will therefore be ineffective. However, about 1% of an oral dose is absorbed by passive diffusion, and with large doses this amount may be sufficient for therapy. Thus attention has been given again to the use of oral cobalamins for the treatment of pernicious anaemia.[1-3] Oral cyanocobalamin 2000 micrograms daily was as effective as intramuscular therapy in patients with vitamin B_{12} deficiency in a comparative study.[4] Some now consider that oral doses of 1000 micrograms daily,[3,5] or every 2 weeks for children,[6] are a suitable alternative to injections given at monthly or so intervals; others still deem oral use to be unjustified on the grounds of negligible oral absorption.[7] A systematic review[8] of 2 studies found some evidence for a satisfactory haematological, biochemical, and clinical short-term response to oral replacement in some patients with conditions associated with malabsorption. Another review[9] concluded that, while there is substantial evidence to support the use of 1000 to 2000 micrograms daily of oral cobalamin as maintenance therapy, parenteral therapy is preferable for initial treatment of those with neurological symptoms. Cyanocobalamin is also effective when given intranasally,[10] with peak plasma concentrations greater than those achievable orally, and this may offer another alternative to injection. The intranasal absorption of hydroxocobalamin has been studied.[11,12] Cobalamin has also been given sublingually. Normalisation of serum cobalamin concentration has been reported in 18 patients given cyanocobalamin 2000 micrograms sublingually for 7 to 12 days;[13] 500 micrograms sublingually was found to be as effective as the same dose given orally in correcting cobalamin deficiency.[14]

1. Lederle FA. Oral cobalamin for pernicious anemia: medicine's best kept secret? *JAMA* 1991; **265:** 94–5.
2. Hathcock JN, Troendle GJ. Oral cobalamin for treatment of pernicious anemia? *JAMA* 1991; **265:** 96–7.
3. Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998; **352:** 1721–2.
4. Kuzminski AM, *et al.* Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; **92:** 1191–8.
5. Andrès E, *et al.* Usefulness of oral cyanocobalamin therapy in severe hematologic manifestations related to vitamin B deficiency. *Ann Pharmacother* 2004; **38:** 1086–7.
6. Çetin M, Altay C. Efficacy of oral vitamin B treatment in children. *J Pediatr* 2001; **139:** 754.
7. Van der Kuy P-HM, *et al.* Bioavailability of oral hydroxocobalamin. *Br J Clin Pharmacol* 2000; **49:** 395P–396P.
8. Vidal-Alaball J, *et al.* Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 05/09/06).
9. Lane LA, Rojas-Fernandez C. Treatment of Vitamin B -deficiency anemia: oral versus parenteral therapy. *Ann Pharmacother* 2002; **36:** 1268–72.
10. Romeo VD, *et al.* Intranasal cyanocobalamin. *JAMA* 1992; **268:** 1268–9.
11. van Asselt DZB, *et al.* Nasal absorption of hydroxocobalamin in healthy elderly adults. *Br J Clin Pharmacol* 1998; **45:** 83–6.
12. Slot WB, *et al.* Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. *Gastroenterology* 1997; **113:** 430–3.
13. Delpre G, *et al.* Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation. *Lancet* 1999; **354:** 740–1.
14. Sharabi A, *et al.* Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol* 2003; **56:** 635–8.

Amino acid metabolic disorders. References to the use of hydroxocobalamin in the treatment of inborn errors of vitamin B_{12} metabolism.[1-3] Some patients with homocystinuria (p.1922) or methylmalonic aciduria have responded to cobalamins—the *BNFC* suggests an initial intramuscular dose of 1 mg daily, for 5 to 7 days, in patients from one month of age; this is reduced, according to response, to 1 mg once or twice weekly. Some children respond to maintenance with 5 to 10 mg once or twice weekly by mouth.

1. Linnell JC, Bhatt HR. Inherited errors of cobalamin metabolism and their management. *Baillieres Clin Haematol* 1995; **8:** 567–601.
2. Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). *J Pediatr* 1998; **132:** 121–4.
3. Smith DL, Bodamer OA. Practical management of combined methylmalonicaciduria and homocystinuria. *J Child Neurol* 2002; **17:** 353–6.

Cardiovascular disease. For mention of the possible link between vitamin B_{12}, hyperhomocysteinaemia, and cardiovascular disease, see under Folic Acid p.1941.

Cyanide toxicity. Hydroxocobalamin combines with cyanide to form cyanocobalamin, and thus may be used as an antidote to cyanide toxicity (p.2045). Hydroxocobalamin is reported to be effective in controlling cyanide toxicity due to nitroprusside infusion,[1] and after exposure to inhaled combustion products in residential fires.[2]

It has been hypothesised that the amount of cyanocobalamin formed is limited by the number of cyanide ions present and the amount of hydroxocobalamin given. For a given dose of hydroxocobalamin a maximum concentration of cyanocobalamin would be reached, allowing measurement of cyanocobalamin as a surrogate emergency marker for cyanide levels, which are difficult and time-consuming to measure. For a 5-g dose of hydroxocobalamin given intravenously over 30 minutes, the authors of one study considered a cyanocobalamin concentration of about 300 micromoles/litre a sign that all the hydroxocobalamin had been used, and more should be given.[2] They cautioned, however, that, unless antidote regimen and blood sampling were similar to that in their study, this concentration should not be extrapolated to other patient populations.

In another patient given hydroxocobalamin 5 g intravenously over 2 hours,[3] plasma concentrations of cyanide rose 1 hour after treatment with hydroxocobalamin. The authors attributed this to hydroxocobalamin extracting cyanide from red blood cells to form cyanocobalamin in plasma, which was then measured as cyanide.

1. Zerbe NF, Wagner BKJ. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med* 1993; **21:** 465–7.
2. Houeto P, *et al.* Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. *Lancet* 1995; **346:** 605–8.
3. Weng T-I, *et al.* Elevated plasma cyanide after hydroxocobalamin infusion for cyanide poisoning. *Am J Emerg Med* 2004; **22:** 492–3.

Deficiency states. The emergence of newer metabolic assays for homocysteine and methylmalonic acid has led to the identification of subtle vitamin B_{12} deficiency[1-3] without the overt manifestations of megaloblastic anaemia (see below) or neurological disease; this condition appears to be particularly common in the elderly.[1,4-6] At present, there is no clear clinical rationale for treating subtle deficiency.[1,7] A study in elderly patients suggested that food-cobalamin malabsorption, a disorder characterised by the inability to release vitamin B_{12} from food or its binding protein, might be to blame for this subtle deficiency; these patients had some neurological or haematological abnormalities, and treatment with oral or parenteral vitamin B_{12} was found to be effective.[6] There have also been suggestions that deficiency may be linked to some immunological impairment, identified as impaired antibody responses to pneumococcal vaccine.[8] Moreover, raised homocysteine concentrations have been identified as a risk factor for atherosclerosis and ischaemic heart disease, and there is increasing interest in the potential of B vitamins, including B_{12}, to reduce homocysteine concentrations and therefore atherosclerotic outcomes (see Cardiovascular Disease, under Uses of Folic Acid, p.1941). Evidence that hyperhomocysteinaemia may be a risk factor for dementia is limited.[5] A systematic review concluded that evidence for efficacy of vitamin B_{12} in improving cognitive function of people with dementia (and low serum vitamin B_{12} concentrations) was lacking.[9]

Dietary vitamin B_{12} deficiency in infants may lead to developmental abnormalities.[10,11]

The issue of fortification of food with folic acid to reduce the number of infants born with neural tube defects has created debate on the risks of masking vitamin B_{12} deficiency, and fortification with vitamin B_{12} has also been recommended, see under Folic Acid, p.1940.

1. Carmel R. Subtle cobalamin deficiency. *Ann Intern Med* 1996; **124:** 338–40.
2. Green R. Screening for vitamin B deficiency: caveat emptor. *Ann Intern Med* 1996; **124:** 509–11.
3. Carmel R, *et al.* Update on cobalamin, folate, and homocysteine. *Hematology (Am Soc Hematol Educ Program)* 2003; 62–81.
4. Andrès E, *et al.* Vitamin B (cobalamin) deficiency in elderly patients. *Can Med Assoc J* 2004; **171:** 251–9.
5. Clarke R. Prevention of vitamin B-12 deficiency in old age. *Am J Clin Nutr* 2001; **73:** 151–2.
6. Andrès E, *et al.* Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med* 2005; **118:** 1154–9.
7. Metz J. What's the use of oral vitamin B ? A neglected but valid treatment route may have new uses in the future. *Med J Aust* 1999; **170:** 407.
8. Fata FT, *et al.* Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B levels. *Ann Intern Med* 1996; **124:** 299–304.
9. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 09/01/06).
10. Emery ES, *et al.* Vitamin B12 deficiency: a cause of abnormal movements in infants. *Pediatrics* 1997; **99:** 255–6.
11. von Schenck U, *et al.* Persistence of neurological damage induced by dietary vitamin B-12 deficiency in infancy. *Arch Dis Child* 1997; **77:** 137–9.

Eczema. A small study found that topical application of a preparation containing vitamin B_{12} was more effective than placebo in patients with atopic eczema.[1]

1. Stücker M, *et al.* Topical vitamin B —a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004; **150:** 977–83.

Megaloblastic anaemia. The megaloblastic anaemias are characterised by macrocytosis (an increased mean cell volume) and the production of distinctive morphological changes and abnormal maturation in developing haematopoietic cells in the bone marrow: white cell and platelet lines are affected as well as erythroid precursors, and in severe cases anaemia may be associated with leucopenia and thrombocytopenia. Megaloblastic anaemia is a consequence of impaired DNA biosynthesis in the bone marrow, usually due to a deficiency of vitamin B_{12} (cobalamins) or folate, both of which are essential for this process. Although the haematological symptoms of B_{12} deficiency and folate deficiency are similar it is important to distinguish between them since the use of folate alone in B_{12}-deficient megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known.

Vitamin B_{12} deficiency anaemia. Vitamin B_{12} deficiency and its associated symptoms may be due to malabsorption (including following gastrectomy), dietary deficiency (mainly in strict vegetarians), competition with intestinal bacteria or parasites, or to the effect of drugs such as nitrous oxide. In populations of northern European origin, pernicious anaemia, in which atrophy of the gastric mucosa results in a lack of the intrinsic factor essential for B_{12} absorption, is the most frequent cause. As body stores of the vitamin are large, it may take several years for signs of deficiency to manifest once the defect in absorption occurs.

In addition to megaloblastic anaemia, vitamin B_{12} deficiency may result in neurological damage, including peripheral neuropathy and effects on mental function ranging from mild neurosis to dementia.

TREATMENT. The treatment is with vitamin B_{12}, almost always by the intramuscular or sometimes the deep subcutaneous route since in most patients absorption from the gastrointestinal tract is inadequate. Hydroxocobalamin is generally preferred to cyanocobalamin since it need be given less often. Regimens may vary, but hydroxocobalamin 1 mg every few days for 6 doses will restore normal body stores of the vitamin (see also Uses and Administration, above). Dosage has not been well established in children; the *BNFC* recommends similar doses to those licensed in adults. The haematological response to therapy is rapid, with improvement in most parameters and symptoms beginning within 48 hours. Neurological abnormalities may take much longer to respond, and may not do so completely.

PROPHYLAXIS. Where the defect in B_{12} handling is irreversible, as in pernicious anaemia, maintenance therapy must continue for life to prevent a recurrence of the deficiency. Therapy must also be given prophylactically after total gastrectomy or total ileal resection, or where gastrointestinal surgery is shown to have impaired absorption of the vitamin. Typically, injection of hydroxocobalamin 1 mg every 3 months is used. In patients whose diet supplies inadequate B_{12}, deficiency may be prevented, in the absence of other causes, by much lower oral doses given as a supplement; up to 150 micrograms of cyanocobalamin daily has been recommended.

Folate-deficiency anaemia. Deficiency of folate may be due to inadequate diet, or malabsorption syndromes (such as coeliac disease or sprue), to increased need (as in pregnancy, one of the most common causes of megaloblastic anaemia, or the increased haematopoiesis of haemolytic syndromes), to increased urinary loss or loss due to haemodialysis, or to an adverse effect of alcohol, antiepileptics, or other drugs.

The clinical features of folate-deficient megaloblastic anaemia are similar to those of disease due to vitamin-B_{12} deficiency except that the accompanying severe neuropathy does not occur, and deficiency may develop much more rapidly. Deficiency may also be associated with neural tube defects (p.1942) if it occurs in pregnancy.

TREATMENT. Once folate deficiency has been established the usual treatment in the UK is folic acid 5 mg by mouth daily. Lower doses of up to 1 mg are suggested in the USA. It is customary to continue therapy for at least 4 months, the time necessary for complete red cell replacement. In patients with malabsorption, therapy may require higher doses, up to 15 mg of folic acid daily. As in B_{12}-deficiency anaemia, the response to therapy is rapid.

PROPHYLAXIS. Long-term maintenance is rarely needed, except in a few patients in whom the underlying cause of folate deficiency cannot be treated (for example in some severe haemolytic syndromes). Doses of 5 mg daily or even weekly have been suggested for prophylaxis in patients undergoing dialysis or with chronic haemolytic states, depending on the diet and rate of haemolysis; a dose of 400 micrograms daily is recommended in the USA.

For primary prophylaxis of megaloblastic anaemia in pregnancy, folic acid is given in the UK in usual doses of 200 to 500 micrograms daily, often with a ferrous salt for prophylaxis of iron deficiency.

Drugs that act as inhibitors of dihydrofolate reductase, such as methotrexate, may produce severe megaloblastic anaemia which cannot be reversed by therapy with folic acid. The adverse effects of such drugs may be largely prevented or reversed by therapy with folinic acid, which can be incorporated into folate metabolism without the need for reduction by the inhibited enzyme. For details of such 'folinic acid rescue', see under Folinic Acid, p.1944.

General references.

1. Wickramasinghe SN. Folate and vitamin B deficiency and supplementation. *Prescribers' J* 1997; **37:** 88–95.
2. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. *Semin Hematol* 1999; **36:** 3–18.
3. Rasmussen SA, *et al.* Vitamin B deficiency in children and adolescents. *J Pediatr* 2001; **138:** 10–17.
4. Hoffbrand V, Provan D. Macrocytic anaemias. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Publishing Group, 2003.
5. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. *Annu Rev Nutr* 2004; **24:** 299–326.

Neural tube defects. There is abnormality in homocysteine metabolism in many women who give birth to children with neural tube defects (p.1942); the enzyme methionine synthase, which converts homocysteine to methionine, requires both folate and vitamin B_{12} as cofactors, and low maternal vitamin B_{12} concentrations may be an independent risk factor for neural tube defects.[1] A case-control study found elevated mid-trimester methylmalonic acid concentrations in women with pregnancies affected by neural tube defects, suggesting that abnormalities of cobalamin metabolism, and subsequent methylation, may be involved in the aetiology of neural tube defects.[2] Decreased vitamin B_{12} concentrations, but no folate deficiency, were found in 3 women with pregnancies affected by neural tube defects.[3] A review[4] of case-control studies found a moderate association between low maternal vitamin B_{12} status and the risk of fetal neural tube defects. If confirmed, this would suggest that additional supplementation with cobalamins may be warranted.[3-5]

1. Mills JL, *et al.* Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet* 1995; **345:** 149–51.
2. Adams MJ, *et al.* Elevated midtrimester serum methylmalonic acid levels as a risk factor for neural tube defects. *Teratology* 1995; **51:** 311–17.
3. Candito M, *et al.* Anomalies du tube neural et vitamine B12: à propos de trois cas. *Ann Biol Clin (Paris)* 2004; **62:** 235–8.
4. Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. *Q J Med* 2003; **96:** 289–95.
5. Refsum H. Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *Br J Nutr* 2001; **85** (suppl): S109–S113.

Osteoporosis. An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women.[1-3] Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations (see Cardiovascular Disease, under Folic Acid, p.1941). In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture),[4] those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies,[3,5] and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.[3,6]

1. van Meurs JBJ, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004; **350:** 2033–41.
2. McLean RR, *et al.* Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med* 2004; **350:** 2042–9.
3. van Meurs JBJ, Uitterlinden AG. Homocysteine and fracture prevention. *JAMA* 2005; **293:** 1121–2.
4. Sato Y, *et al.* Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; **293:** 1082–8. Correction. *ibid.* 2006; **296:** 396.
5. Dhonukshe-Rutten RAM, *et al.* Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. *J Nutr* 2003; **133:** 801–7.
6. Sugiyama T, *et al.* Folate and vitamin B for hip fracture prevention after stroke. *JAMA* 2005; **294:** 792.

Rhinitis. A sublingual formulation of cyanocobalamin (*PreHistin; Cobalis, USA*) has been reported to be under investigation in the management of seasonal allergic rhinitis, but published studies are lacking.

Preparations

BP 2008: Cyanocobalamin Tablets; Hydroxocobalamin Injection;
USP 31: Cyanocobalamin Injection; Hydroxocobalamin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Benzoral†; Difenac Forte; Lisoneurin B12; Methycobal†; Reedvit†; SL B12; Vitam Doce; ***Austral.:*** Cytamen; Neo-Cytamen; ***Austria:*** Diclo-B; Erycytol; Hepavit; ***Belg.:*** Forta B†; ***Braz.:*** Bedozil; Cianon B12; Cronobe; Enzicoba; Rubranova; Vitadoze†; Zinabol†; ***Canad.:*** Bedoz†; ***Cz.:*** B Ankermann†; Neurobene; ***Denm.:*** Betolvex; Vibeden; ***Fin.:*** Betolvex; Cohemin; ***Fr.:*** Cobanzyme; Cyanokit; Dodecavit; Epithea; ***Ger.:*** Ambe 12; Aquo-Cytobion†; B 12-L 90†; B12 Depot-Rotexmedica; B12 Rotexmedica; B12 Steigerwald; B Ankermann; B Depot-Hevert; B Vicotrat†; B -AS-medic; Cytobion; Hamo-Vibolex†; Lophakomp-B 12; Lophakomp-B 12 Depot; Novidroxin†; Novirell B Mono; Vicapan N†; ***Gr.:*** Articlox; Idroxocobalamina†; ***Hong Kong:*** Cobamin; Cyanokit; Methycobal; ***Hung.:*** Feroglobin-B12; ***India:*** Mecovit; Methycobal; Myelogen†; ***Indon.:*** Arcored; Berthyco; Cobazim; Ethigobal; Kalmeco; Lapibal; Meconeuro; Megabal; Methycobal; Metifer; Mevrabal; Nerfeco; Neulamin; Nufacobal; Scanmecob; Sohobal; ***Irl.:*** Cytacon; Cytamen; Neo-Cytamen; ***Israel:*** Bedodeka; Bevitex; Nascobal; ***Ital.:*** Cobaforte; Dobetin; Eritrovit B12†; Indusil; Neo-Cytamen; OH B12; ***Jpn:*** Methycobal; ***Malaysia:*** Methycobal; Neuromethyn; ***Mex.:*** Axofor; Biocobal; Biotrefon L; Bissel 12; Compensal; Droxivit†; Duradoce; Exorvit; Fortical; Hidroxovit†; Leo-Doce; Maxibol; Nebal; Neribax†; Neurofor; Rubrina†; Sanovit; Selectofort†; Valamin 12†; ***Neth.:*** Hydrocobamine; ***Norw.:*** Betolvex; ***NZ:*** Neo-B12; Neo-Cytamen; ***Philipp.:*** Drexabion; Heraclene; Hybutin; Jaga; Lixtress; Mecovit; Meganerv; Methycobal; Nervafil; Nervilan; Neuro-B's; Neurobexol; Neurobion; Neurolink; Polynerv; Rubramin; Supraneuron; Vineuron; ***Port.:*** Algobaz†; Bedoze†; Co-Vibedoze; Cobamet†; Cobaxid; Dozefol; Jaba B ; OH B12; Permadoze; Tridocemine†; ***S.Afr.:*** Cobalatec; Norivite-12†; ***Singapore:*** Hidomin†; Methycobal; Neuromethyn; ***Spain:*** Asimil B12†; Cromatonbic B12; Isopto B 12; Megamilbedoce; Optovite B12; Reticulogen Fortificado†; Zimadoce; ***Swed.:*** Behepan; Betolvex; Betolvidon; ***Switz.:*** Betolvex; Vitarubin; ***Thai.:*** Ampavit; Hitocobamin; Mecobal; Merabin; Methycobal; Neuromet; Redisol†; Sicobal†; ***Turk.:*** Aktibol; Dodex; ***UAE:*** Cynovit; ***UK:*** Cobalin-H; Cytacon; Cytamen; Neo-Cytamen; ***USA:*** CaloMist; Crystamine; Crysti 1000; Cyanokit; Cyomin; Hydro Cobex; Hydro-Crysti-12; LA-12†; Nascobal; Twelve Resin-K; ***Venez.:*** Bedovit Simple; Beplus; Cristadoce; Dobetin; Docebe B12†; Droxofor†; Hidro-Doce; Ibedox; Maxibol.

Multi-ingredient: ***Arg.:*** Acifol-B12; Algio Nervomax; Algio Nervomax Fuerte; Anemidox-Ferrum; Anemidox-Solutab; Betametasona B12; Bioneural B12†; Blastop; Blokium B12; Buta Rut B12; Cobenexol Forte; Cobenexol Fuerte; Corteroid Gesic; CVP B1 B6 B12†; Dastonil; Delta Tomanil B12; Dexabion; Diclogesic Plus B12; Dioxaflex B12; Dolo Nervobion; Dolo Nervobion 10000; Dorixina B1 B6 B12; Doxtran B12; Factofer B12; Ferranin Complex; Ferrocebrina; Flexicamin B12; Flogiatrin B12; Hierro Folico; ITE B12 Forte; Klosidol B1 B6 B12; Nervobion Fuerte; Nervomax TB12; Nucleo CMP†; Oxa B12; Presterin; QX 10; Rodinac B12; Rubiron; Siderblut Folic; Sindrolen†; Tenvic; Tunik B12; Vesalion B12; Virobron B12 NF; Vitalix Complex; Xedenol B12; Yectafer Complex; ***Austral.:*** Medinat PMT-Eze†; ***Austria:*** Ambene; Ambene N; Arca-Be; Beneuran compositum; Diclovit; Neurobion; Neuromerck; Neuromultivit; Pronerv; Rheumesser; ***Belg.:*** Neurobion; Vioneurin†; ***Braz.:*** Aminocid†; Anemofer†; Bicavine; Calcifix B12; Calcinol Complexo; Cianotrat-Dexa; Citoneurin; Cobactin; Cobaglobal; Cobavit; Cobavital; Coraben†; Dexa-Citoneurin; Dexa-Cronobe; Dexa-Neuriberi†; Dexacobal; Dexador; Dexadoze; Dexagil; Dexalgen; Dexaneurin; Dexanevral†; Dozeneurin; Ferroplex; Ferrotrat; Fol Sang; Hematiase B12; Hepatotris†; Iloban; Lisan†; Lisotox; Metiocolin B12; Metiocolin Composto; Nucleo CMP; Trirubin†; Vi-Ferrin; Vitaneuron†; Vitatonus; Xantinon Complex; ***Canad.:*** Acti-B ; Fortiplex†; Penta-3B; Penta-3B + C; ***Chile:*** Betonvit†; Citoneuron; Cronoferril†; Dolotol 12; Ferranem; Ferranim; Foli Doce; Folifer; Nefersil B; Neurobionta; Neurocam; Tol 12; Tol 12 Plus; ***Cz.:*** Aktiferrin Compositum; Dicopac†; Ferro-Folgamma; Milgamma; Milgamma N; Neuromultivit; ***Fin.:*** Neurobion; Neurovitan; ***Ger.:*** Ambene Comp†; B-Komplex forte; B Fol-Vicotrat†; Dolo-Neurobion forte†; Eryfer comp; Eukalisan N; Ferro sanol comp; Ferro-Folgamma; Folgamma; Hepagrisevit Forte-N†; Medivitan N; Medyn; Milgamma N; Neuro-ratiopharm†; Neurobion; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Selectafer N†; Telbibur N†; Vitaject†; Vitasprint B †; ***Gr.:*** Neurobion; ***Hong Kong:*** 3B; Neuro B1-6-12†; Neurobion; Neuromin; Neurorubine; Nevramin; Princi-B Fort; Vibion; Vida Neurotab; Vidaclofen-Plus; ***Hung.:*** Atherovit; Ferro-Folgamma; Milgamma; Milgamma N; Neurobion; ***India:*** Alcrin-M; Anemidox; Blosyn; Calcinol; Carboflot†; Conviron-TR; Delphicol; Dexorange; Elferri-Z; Ferrochelate; Fervit†; Genfol; Globac-Z; Hepasules; Hepatoglobine; Jectocos Plus; Macalvit; Omilcal; Ostocalcium B-12; Plastules; Sigmacalvit; Sioneuron; Softeron; Tonoferon; Vitamon; Vitneurin; ***Indon.:*** Abajos; Adfer; Arsinal; Betrion; Bicitron; Biocombin; Biomega; Biomex; Biosanbe; Corobion; Corsaneuron; Daneuron; Dolo Scanneuron; Dolo-Licobion; Dolo-Neurobion; Dolofenac; Farbion; Foraneural; Fundamin-E; Goralgin; Ikaneuron; Ikaneuron Plus; LaktaFit; Lapibion; Licobion; Mecola; Moloco + B12; Neogobion; Nervitone; Nervitone E; Neuralgin RX; Neuro Panstop; Neuro-Beston; Neurobat; Neurobat A; Neurobion; Neurobiovit; Neurodex; Neurohax; Neurophil; Neuropyramin; Neurosanbe; Neurosanbe Plus; Neurotrat; Neurotropic Plus; Neurovit E; Nevradin; Nevramin; Penagon; Ponconeuron; Primabion; Pritagesic; Remasal; Sangobion; Scanneuron; Sohobion; Solaneuron; Stileran; Tocobion; Trimate-E; Tropineuron; ***Israel:*** Tribemin; Tricardia; ***Ital.:*** Adenobeta†; Adenoplex; Adenovit†; Benexol B12; Briogen†; Calcio Dobetin; Co-Carnetina B12; Dobetin con Vitamina B1; Dobetin Totale; Emazian B12†; Emoantitossina†; Emopon; Epargriseovit; Eparmefolin; Fibronevrina; Folepar B12; Fosfo Plus; Fosfoutipi Vitaminico†; Gluta Complex†; Glutamin Fosforo; Hepa-Factor; Hepatos B12; Memovisus†; Memovit B12; Mionevrasi; Neo-Eparbiol†; Neuraben; Porfirin 12; Tonogen; Tricortin; Trinevrina B6; Vitasprint Complex†; Vitasprint†; ***Jpn:*** Neurovitan†; ***Malaysia:*** 3B; Alinamin B12†; Ferrovit; Flavettes Neuroforte; Fundamin-E; Neuro B†; Neurobion; Neurorubine; Neurovit†; Nevramin; Princi-B Fort; Re-B; Sangobion; Vitabion; ***Mex.:*** Ariflam Forte; B1-12-15; Bedoce-Cal; Bedocil†; Benexol B12; Betrox; Ciprolisina; Cobotiaxina; Dexabion; Diclovith-B; Dodemina Tri; Dolo-Neurobion; Dolo-Pangavit; Dolo-Tiaminal; Doxemina; Duciclon; Forvin; Gonakor; Innobion; Intrafer F-800; Iodarsolo B12†; Macrox-5; Milbeta; Neuralin; Neurobion; Neuroflax; Nuro-B; Odexan; Orafer Comp; Pangavit B; Pangavit Hypak; Pangavit Pediatrico; Revitaliv-C; Selectadoce; Suma-B; Tiabexol; Tiamidexal; Tiaminal B ; Tiaminal B Trivalente; Tribedoce; Tribedoce Compuesto; Tribedoxyl†; Trineurovita; Trineurovita Compuesto; Uni-Dox; ***Neth.:*** Neurobion; ***Philipp.:*** Beniforte; Dolo-Neurobion; Essenfer; Glutaphos; Godex; Harvifer; Hinuron-E; Meganerv F-A; Neuroforte-E; Nevramin; Nuron-E; Osteo-4; Sangobion; TriHEMIC; Vitanerv; ***Pol.:*** Additiva Ferrum; Milgamma N; Vegevit B ; ***Port.:*** Linamin Plus†; Neobefol; Neurobion; ***Rus.:*** Ambene (Амбене); Ferro-Folgamma (Ферро-Фольгамма); Milgamma (Мильгамма); Neuromultivit (Нейромультивит); ***S.Afr.:*** Foliglobin; Neurobion; Prohep; Sentinel Ulcer Mixture; ***Singapore:*** Aktiferrin-F; Alinamin B12†; Daneuron; Iron Melts; Neogobion; Neurobion; Neurodex; Neuroforte; Neurorubine; Neurovit; Neuroxel; Nevramin; Princi-B Fort; Sangobion; Wanse; ***Spain:*** Antineurina; Benexol B1 B6 B12; Bester Complex; Calcio 20 Complex; Covitasa B12; Dalamon†; Duplicalcio B12; Enoton; Foli Doce; Hepa Factor; Hidroxil B12 B6 B1; Inzitan; Malandil; Mederebro; Menalgil B6; Nervobion; Neuromade; Neurostop Complex; Refulgin; Rubrocortin†; Taurobetina†; Tonico Juventus; Trofalgon; Viadetres†; Vitafardi C B12; ***Swed.:*** Neurobion; ***Switz.:*** Benexol B12; Neurorubin; Trilagavit; Vitasprint Complex; ***Thai.:*** 3B; Alinamin B12†; Beromin; Cydoxmine-B†; Cyriamine; Douzabox; Genavit; Hemolax; Neubee; Neurobex; Neurobion; Nevramin; Nuro-B; Nuvit; Ostone-B12; Princi-B; Re-B Forte; Trabit†; Tribesian; Tricortin†; Trinsicon†; Trivit-B; Vita-B; Vitabion; Vitamedin†; Vitron; ***Turk.:*** Blood Builder; Epargriseovit; Neurogriseovit; Tribeksol; ***UAE:*** 3V; ***UK:*** Dicopac; Hematinic; ***USA:*** Anemagen†; Bevitamel; Cerefolin; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Fe-Tinic Forte; FeoGen; Ferotrinsic; Ferralet Plus†; Ferrex Forte; Ferrex Forte Plus†; Ferrogels Forte; Fetrin; FOLTX; Fumatinic; Hem Fe; Hemocyte-F; Icar-C Plus; Livitrinsic-f; Metanx; Niferex Forte; Poly-Iron Forte; PremesisRx; Pronemia Hematinic; Tolfrinic; TriHEMIC; Trinsicon; ***Venez.:*** Autrin†; Bedoyecta; Beferron; Befosfin; Briomet; Cianofer; Cobalfer; Deca-Lentermina Complex; Dobetin Compuesto; Fefol; Fercobre B-12†; Fercor†; Ferroce con B12; Folifer B-12; Hepafol; Hepafol con B-12; Intafer; Lentermina Complex; Mega-Neubion; Miovit; Neubion; Neuribe; Rubrinal; Rubrinex; Tres-Be.

Vitamin C Substances

Vitamina C.

Several substances have vitamin C activity, notably ascorbic acid and its calcium and sodium salts. Natural products with a high vitamin C content include black currant (p.2267), lemon (p.2332), sweet orange (p.2357), and rose fruit (p.2381).

Ascorbic Acid *(BAN, rINN)*

Acide ascorbique; Ácido ascórbico; Acidum ascorbicum; L-Ascorbic Acid; Askorbiinihappo; Askorbik Asit; Askorbinsyra; Askorbo rūgštis; Aszkorbinsav; Cevitamic Acid; E300; Kwas askorbowy; Kyselina askorbová; Vitamin C. The enolic form of 3-oxo-L-gulofuranolactone; 2,3-Didehydro-L-*threo*-hexono-1,4-lactone.

Аскорбиновая кислота

$C_6H_8O_6$ = 176.1.
CAS — 50-81-7.
ATC — A11GA01; G01AD03; S01XA15.
ATC Vet — QA11GA01; QG01AD03; QS01XA15.

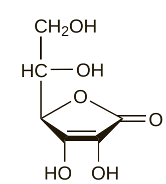

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US*, and *Viet.*

Ph. Eur. 6.2 (Ascorbic Acid). A white or almost white crystalline powder or colourless crystals becoming discoloured on exposure to air and moisture. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.1 to 2.6. Store in nonmetallic containers. Protect from light.

USP 31 (Ascorbic Acid). White or slightly yellow crystals or powder. On exposure to light, it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidises. Soluble 1 in 3 of water and 1 in 40 of alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Calcium Ascorbate *(BANM, rINNM)*

Ascorbate de Calcium; Ascorbato cálcico; Askorban vápenatý dihydrát; Calcii ascorbas; Calcii Ascorbas Dihydricus; Calcium, ascorbate de; E302; Kalcio askorbatas; Kalciumaskorbat; Kalcium-aszkorbát; Kalsiumaskorbaatti.

Кальций Аскорбат

$(C_6H_7O_6)_2Ca,2H_2O$ = 426.3.

CAS — 5743-27-1.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Calcium Ascorbate). A white or slightly yellowish crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH between 6.8 and 7.4. Store in nonmetallic containers. Protect from light.

USP 31 (Calcium Ascorbate). A white to slightly yellow, practically odourless, powder. Freely soluble in water (about 1 in 2); slightly soluble in alcohol; insoluble in ether. pH of a 10% solution in water is between 6.8 and 7.4. Store in airtight containers. Protect from light.

Sodium Ascorbate *(BANM, rINN)*

Ascorbate de sodium; Ascorbate sodique; Ascorbato de sodio; Askorban sodný; E301; Monosodium L-Ascorbate; Natrii ascorbas; Natrio askorbatas; Natriumaskorbaatti; Natriumaskorbat; Nátrium-aszkorbát. 3-Oxo-L-gulofuranolactone sodium enolate.

Натрия Аскорбат

$C_6H_7NaO_6$ = 198.1.

CAS — 134-03-2.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Sodium Ascorbate). A white or yellowish crystalline powder or crystals. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 7.0 to 8.0. Store in nonmetallic containers. Protect from light.

USP 31 (Sodium Ascorbate). White or very faintly yellow, odourless or practically odourless, crystals or crystalline powder. On exposure to light it gradually darkens. Soluble 1 in 1.3 of water; very slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Ascorbic acid is usually well tolerated. Large doses are reported to cause diarrhoea and other gastrointestinal disturbances. It has also been stated that large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi and ascorbic acid should therefore be given with care to patients with hyperoxaluria (see Effects on the Kidneys, below). Tolerance may be induced with prolonged use of large doses, resulting in symptoms of deficiency when intake is reduced to normal. Prolonged or excessive use of chewable vitamin C preparations may cause erosion of tooth enamel.

Large doses of ascorbic acid have resulted in haemolysis in patients with G6PD deficiency (see Effects on the Blood, below).

Breast feeding. Vitamin C is excreted into breast milk and thus supplied to breast-feeding infants. Lactating women in developing countries have significantly lower concentrations of ascorbic acid in their breast milk compared with lactating women in developed countries,[1] and seasonal variation in consumption of foods rich in vitamin C leads to variable amounts of ascorbic acid in breast milk.[2] Supplementation with high-dose ascorbic acid (1 g daily for 10 days) led to significant increases in breast-milk concentrations in both European and African women;[1] however, the overall effect was modest in European women compared with a threefold increase observed in African women. Lower doses of 100 mg daily for 10 days approximately doubled the ascorbic acid breast milk content in the latter, as did supplementation with orange juice 3 or 5 times a week; a significant day-to-day effect was also noted, indicating that the ascorbic acid content of breast milk is regulated. In a small study[2] involving four different doses of ascorbic acid supplements, women in West Africa showed that increased intake caused an increase in the ascorbate concentration of breast milk, but concentrations approached a plateau at higher intakes; it was concluded that about 100 to 120 mg of vitamin C daily was needed to achieve acceptable plasma and breast-milk ascorbate concentrations in this population.

1. Daneel-Otterbech S, *et al.* Ascorbic acid supplementation and regular consumption of fresh orange juice increase the ascorbic acid content of human milk: studies in European and African lactating women. *Am J Clin Nutr* 2005; **81:** 1088–93.
2. Bates CJ, *et al.* The effect of vitamin C supplementation on lactating women in Keneba, a West African rural community. *Int J Vitam Nutr Res* 1983; **53:** 68–76.

Effects on the blood. There are reports of haemolysis in patients with G6PD deficiency after large doses of ascorbic acid either intravenously[1,2] or in soft drinks.[3] There has also been a report[4] of a patient with paroxysmal nocturnal haemoglobinuria suffering haemolysis after taking large amounts of ascorbic acid in a soft drink. There is concern that the large quantities of vitamin C in feeds for premature neonates may have a pro-oxidant effect, and lead to haemolysis. However, a double-blind study found no increase in erythrocyte destruction or hyperbilirubinaemia in premature neonates receiving vitamin C.[5]

1. Campbell GD, *et al.* Ascorbic acid-induced hemolysis in G-6-PD deficiency. *Ann Intern Med* 1975; **82:** 810.
2. Rees DC, *et al.* Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *BMJ* 1993; **306:** 841–2.
3. Mehta JB, *et al.* Ascorbic-acid-induced haemolysis in G-6-PD deficiency. *Lancet* 1990; **336:** 944.
4. Iwamoto N, *et al.* Haemolysis induced by ascorbic acid in paroxysmal nocturnal haemoglobinuria. *Lancet* 1994; **343:** 357.
5. Doyle J, *et al.* Does vitamin C cause hemolysis in premature newborn infants? Results of a multicenter double-blind, randomized, controlled trial. *J Pediatr* 1997; **130:** 103–9.

Effects on the kidneys. Although renal impairment associated with excessive oxalate excretion has been reported with large doses of ascorbic acid[1-3] it has been considered that healthy persons can ingest large amounts of ascorbic acid with relatively small increases in oxalate excretion[4-6] and without an increased risk of oxalate stone formation. A study of vitamin C supplementation with 1 or 2 g given daily for 3 days in calcium stone-forming patients, and 1 g given daily for 3 days in healthy subjects, found that urinary oxalate excretion and the risk of calcium oxalate crystallisation increased significantly in all groups.[7] A prospective cohort study found that increased vitamin C intake (over 1 g daily) was positively associated with the risk of stone formation; an increased risk was observed even at lower intakes of about 90 to 250 mg daily. The risk was raised for both dietary and supplemental vitamin C intake. However, the relation between vitamin C intake and stone formation had emerged only after the inclusion of dietary potassium in the analysis, with potassium intake positively associated with dietary vitamin C intake, but inversely associated with stone formation. This led the authors to conclude that, while limiting dietary vitamin C intake in men with calcium oxalate nephrolithiasis was unwarranted (because of the high potassium content of vitamin C-rich foods), supplemental vitamin C should be avoided.[8]

1. Reznik VM, *et al.* Does high-dose ascorbic acid accelerate renal failure? *N Engl J Med* 1980; **302:** 1418–19.
2. Swartz RD, *et al.* Hyperoxaluria and renal insufficiency due to ascorbic acid administration during total parenteral nutrition. *Ann Intern Med* 1984; **100:** 530–1.
3. Balcke P, *et al.* Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic hemodialysis. *Ann Intern Med* 1984; **101:** 344–5.
4. Tsao CS. Ascorbic acid administration and urinary oxalate. *Ann Intern Med* 1984; **101:** 405–6.
5. Wandzilak TR, *et al.* Effect of high dose vitamin C on urinary oxalate levels. *J Urol (Baltimore)* 1994; **151:** 834–7.
6. Curhan GC, *et al.* Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999; **10:** 840–5.
7. Baxmann AC, *et al.* Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 2003; **63:** 1066–71.
8. Taylor EN, *et al.* Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol* 2004; **15:** 3225–32.

Effects on mortality. There is some suggestion that serum ascorbic acid concentrations are inversely related to all-cause mortality;[1-4] serum levels were also inversely related to cancer mortality in men but not in women.[1-3] However, a meta-analysis of 3 studies found vitamin C supplementation to have no benefit on mortality in elderly people.[5] A systematic review of antioxidant supplementation in adults also found no significant effect on mortality from studies in which vitamin C was used either singly or with other antioxidants;[6] small beneficial effects or large harmful effects could not be excluded, and since vitamin C can also act as a pro-oxidant, further studies should monitor closely for any harm.

1. Loria CM, *et al.* Vitamin C status and mortality in US adults. *Am J Clin Nutr* 2000; **72:** 139–45.
2. Simon JA, *et al.* Relation of serum ascorbic acid to mortality among US adults. *J Am Coll Nutr* 2001; **20:** 255–63.
3. Khaw K-T, *et al.* Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet* 2001; **357:** 657–63.
4. Fletcher AE, *et al.* Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr* 2003; **78:** 999–1010.
5. Ness A, *et al.* Role of antioxidant vitamins in prevention of cardiovascular diseases. *BMJ* 1999; **319:** 577.
6. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).

Effects on the teeth. A report of dental enamel erosion attributed to the daily ingestion of chewable ascorbic acid tablets over a period of 3 years.[1] The tablets lowered the pH of the saliva to a level at which calcium was lost from the tooth enamel.

1. Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; **107:** 253–6.

Interference with laboratory tests. Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely-elevated or false-negative test results may be obtained from plasma, faeces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used.

Interactions

For the effect of ascorbic acid on various drugs see under desferrioxamine (p.1440), hormonal contraceptives (p.2068), HRT (p.2076), fluphenazine (under Chlorpromazine, p.975), and warfarin (p.1432). Ascorbic acid may increase the absorption of iron in iron-deficiency states. Omeprazole may affect the bioavailability of dietary vitamin C (see Malabsorption, under Omeprazole, p.1754).

Pharmacokinetics

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine. Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by haemodialysis.

Human Requirements

A daily dietary intake of about 30 to 100 mg of vitamin C has been recommended for adults. There is, however, wide variation in individual requirements. Humans are unable to form their own ascorbic acid and so a dietary source is necessary. Most dietary ascorbic acid is obtained from fruit and vegetable sources; only small amounts are present in milk and animal tissues. Relatively rich sources include rose hips (rose fruit), black currant, citrus fruits, leafy vegetables, tomatoes, potatoes, and green and red peppers.

Ascorbic acid is readily destroyed during cooking processes. Considerable losses may also occur during storage.

UK and US recommended dietary intake. In the UK[1] dietary reference values (see p.1925) have been published for vitamin C and similarly in the USA recommended dietary allowances (RDAs) have been set.[2] Differing amounts are recommended for infants and children of varying ages, for adult males and females, and for pregnant and lactating women. In the UK the reference nutrient intake (RNI) is 40 mg daily for adult males and females and the estimated average requirement (EAR) is 30 mg daily. In general the amount recommended in the USA for all ages and groups is higher than that set in the UK; the RDA is 90 mg daily for men and 75 mg daily for women.[2] The RDA is increased in smokers by 35 mg daily. The tolerable upper intake level is 2 g daily.[2] The EAR is 75 mg daily for men and 60 mg daily for women.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Uses and Administration

Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intercellular material. Vitamin C deficiency develops when the dietary intake is inadequate. It is rare in adults, but may occur in infants, alcoholics, or the elderly. Deficiency leads to the development of a well-defined syndrome known as scurvy. This is characterised by capillary fragility, bleeding (especially from small blood vessels and the gums), normocytic or macrocytic anaemia, cartilage and bone lesions, and slow healing of wounds.

Vitamin C is used in the treatment and prevention of deficiency. It completely reverses symptoms of deficiency. It is usually given orally, the preferred route, as ascorbic acid, and has been given to children in the form of a suitable fruit juice such as orange juice or as black currant or rose hip syrups. Ascorbic acid or sodium ascorbate may be given parenterally, preferably by the intramuscular route, but also by the intravenous or subcutaneous routes. Doses of 25 to 75 mg daily in the prevention of deficiency, and 250 mg or more daily in divided doses for the treatment of deficiency, have been recommended.

Ascorbic acid 100 to 200 mg daily may be given with desferrioxamine in the treatment of patients with thalassaemia, to improve the chelating action of desferrioxamine, thereby increasing the excretion of iron (see p.1441). In iron deficiency states ascorbic acid may increase gastrointestinal iron absorption and ascorbic acid or ascorbate salts are therefore included in some oral iron preparations. Ascorbic acid or sodium ascorbate have been used in treating methaemoglobinaemia. Ascorbic acid has been used to acidify urine. It has also been tried in the treatment of many other disorders (see below) but there is little evidence of beneficial effect.

Eye drops containing potassium ascorbate (ascorbic acid 10%) have been used for the treatment of chemical eye burns (p.1674); they may be used with sodium citrate eye drops (see Uses of Bicarbonate, p.1674).

Ascorbic acid and calcium and sodium ascorbates are used as antoxidants in pharmaceutical manufacturing and in the food industry.

Non-deficiency disorders. A beneficial effect of vitamin C therapy has been claimed for an extraordinary number of conditions, including age-related macular degeneration (under Betacarotene, p.1931) Alzheimer's disease (see Dementia, under Vitamin E, p.1994), atherosclerosis (see Prophylaxis of Ischaemic Heart Disease, p.1926), cancer (see Prophylaxis of Malignant Neoplasms, p.1927), the common cold (p.850), and idiopathic thrombocytopenic purpura (p.1505). Other conditions claimed to benefit include asthma, wound healing, psychiatric disorders, infections due to abnormal leucocyte function, infertility, osteogenesis imperfecta, pain in Paget's disease, and opioid withdrawal. Generally there are few properly controlled studies to substantiate these claims. Although preliminary evidence suggested a benefit in pre-eclampsia, this was not confirmed in later studies (see Hypertension, p.1171).

Preparations

BP 2008: Ascorbic Acid Injection; Ascorbic Acid Tablets; Paediatric Vitamins A, C and D Oral Drops; Vitamins B and C Injection;
USP 31: Ascorbic Acid Injection; Ascorbic Acid Oral Solution; Ascorbic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cebion†; Cellskinlab Serum 15; Cewin; Citrocola; Citrovita; Gynefix; Redoxon; Urosedac; Vicenrik; Vitafizz C; ***Austral.:*** Bioglan Cal C; Pro-C†; Redoxon†; Sugarless C; Supa C†; Vicks Vital†; Vita C†; ***Austria:*** Ascorbin; C-Vit; Calcascorbin; Ce-Limo; Cebion; Cetebe; Cevitol; Iroviton Vitamin C; Iroviton-Irocovit-C†; Mel-C; Redoxon; ***Belg.:*** C-Dose†; C-Will; Cetamine; Cevi-drops; Ophtavit C; Redoxon; Upsa C; Upsavit C; ***Braz.:*** Active C; Bio-C; Cebion; Ceklin†; Cenevit; Cetivit; Cetozone; Cevita; Ceviton; Cewin; Citron†; Citroplex; Citrovit; Energil C; Energrip C†; Fonto-Vit C; Redoxon; Vagi C; Vi-Ce; Vitabase Vitamina C†; Vitacitrus†; Vitageyer C†; Vitamice; Vitergyl C; ***Canad.:*** Action; Ascorbex†; Balanced C Complex†; Ester-C; Kamu Jay†; Kyolic Formula 103; Nutrol C; Proflavanol C; Redoxon; Revitalose C†; Revitonus C; Super C; Vita-C†; ***Chile:*** Cebion; Crevet; Crevet L; Esvit C; Mintavit-C; Necta C; Redoxon†; Vitac; Vitaseve; ***Cz.:*** Additiva; Apo-C†; C-Vitamin; Cebion†; Celaskon; Linamon†; ***Fin.:*** Ascorbin; Bio-C-Vitamin; C-Tabs; C-vimin; Ceerexin†; Cevi-Tabs; Poremax-C; Puru-C; Vita-C; ***Fr.:*** Arkovital C; Doliactic; Laroscorbine; Midy Vitamine C; Vitascorbol; ***Ger.:*** Ascorell; Ascorvit; C-L90†; Cebion; Cebion N†; Cetebe; Forum C; Hermes Cevitt; Macalvit; Synum C†; Vagi-C; ***Gr.:*** Ascorbine†; Cebion†; Vitorange; ***Hong Kong:*** Cecap; Cegrovit; Celin†; Cetrinets; Champs Junior; Delrosa; Flavettes; Redoxon; Vicemex†; Vorange; ***Hung.:*** Beres C; Cebion; Cetebe; Hermes Cevitt; Vitascor; ***India:*** Cecon; Celin; Limcee; Sukcee; ***Indon.:*** Askorbin; Bekamin C; Biferce; Cebion; Champs C; Ever Ce; Extrace; Fit-C; Flavettes; Sweeta C; Vicee; Vitacimin; Vitalong C TRC; Vitamex C; Xon-Ce; ***Irl.:*** Redoxon; Rubex; ***Israel:*** C-Tamin; C500; Cereon†; Redoxon; Vi-C; ***Ital.:*** Additiva; Agrumina†; Agruvit; Bio-Ci; C Monovit; C-Lisa†; C-Tard; Cebion; Cimille; Duo-C; Dynaphos-C; Grumivit†; Redoxon; Univit; Vici; ***Jpn:*** Hicee; ***Malaysia:*** Ascorbin; Cecap; Ceelin; Cetrinets†; Chewette C; Citrex Vitamin C; Dumovit C†; Orange C†; Upha C; Vita C; ***Mex.:*** Ce-Vi-Sol; Cemina†; Cevalin; Dermoskin C†; Femiprim; Gomas Garde G; Oxital C; Poly C; Ramy CE; Redoxon; Sinesmin; ***Neth.:*** C-Will; Dayvital; Redoxon†; ***Norw.:*** Bio-C; Nycoplus C-vitamin; ***NZ:*** Citravite†; Redoxon; ***Philipp.:*** Asconvita; Ascorcee; Bonalet-Cee; C-4-Kids; Calcebone; CareZee; Ce-Vi-Sol; Cecon; Ceelin; Cetrasol; Cetrinets; Chilcee; Chilvit-Cee; Cixtor; Daycee; Esvicee; Incee-Vit; Nutricee; Pedcee; Pediafortan-C; Poten-Cee; Provit-Cee; Supravit-C; Vamcee; Zerrucee; ***Pol.:*** Ascorgem; Cebion; Cetebe; Cevikap; Juvit; Monovitan C; Vicefar; ***Port.:*** Anti-rugas C; C'Nergil; Cebiolon; Cebion; Cecon; Cecrisina; Cetebe†; Citavi†; Prevegyne†; Redoxon; Vitaminac Retard; Vivin C; ***Rus.:*** Celascon (Целаскон); Citravit (Цитравит); Plivit C (Пливит С)†; ***S.Afr.:*** Chewy C†; Rovit C†; Scorbex; Vitaforce C; Vitaforce Massif-C; ***Singapore:*** Active C; Ascorbin; Cebion; Cetrinets†; Champs C; Dancimin-C; Dumovit C†; Flavettes; High-C; Redoxon; Vorange; ***Spain:*** Cebion; Citrovit; Redoxon; Unimicebrina†; ***Swed.:*** C-vimin; Ido-C; ***Switz.:*** Cegrovit†; Cetebe; Demovit C; Neutra-C†; Nicobrevin N†; Redoxon; Vicemex†; Viforcit†; Vita-Ce†; ***Thai.:*** Bio-C; C Mon†; C-Will; Hicee; Med-C; Mita-C; Sweetcee; Teddy-C†; Vit C-Mile; Vitacimin; ***Turk.:*** C-plan; Ester Vit; Redoxon; Vitabiol C; ***UK:*** Buffered C; Buffered C 500; Haliborange Halibonbons; Redoxon; ***USA:*** Asco-Caps; Ascocid; Ascor; Cecon; Cenolate; Cevi-Bid; Chew-C; Dull-C; N'ice Vitamin C; Sunkist; Vita-C; ***Venez.:*** Cebion; Cevax; Cevit; Mirinda†; Oranvit†; Redoxon†; Vitadyn C; Vitrexon.

Multi-ingredient: ***Arg.:*** A-D-C; Ajo 1000 + C; Ajo Forte; Ascoxal†; Aseptobron Antigripal; Bayaspirina C; Bio Grip C; Bio Grip Plus; Bio-Grip C; Calcium C; Cardiax; Cellskinlab C + AHA; Cellskinlab C + E; Citrovita; Coriovaccine; Corizina; Corvita C; CVP B1 B6 B12†; CVP Duo; CVP Flebo; CVP Forte; Cyclo 3; Daygrip; Dristan Analgesico†; Dristan Compuesto; Epiteliol-C; Expectosan Hierbas y Miel; Factus; Fiblast; Finagrip†; Flucalin; Fullgrip; Gripanil C; Inmunogrip C; IP-6; Isalax Fibras; Kacerutin; Mejoral Grip T Descongestivo; Melagel; Mudagrip†; Nectar G; Nervigenol Magnesio†; Nilflux; Nulagrip C†; Parageniol Grip Caliente; Parencias†; Pirinace; Potasio C; Provacsin Oral; Redoxon A; Redoxon Doble Accion; Rumisedan; Sigma CE; Sigmace Plus; Uridon; Venart; Venidium; Venter; Viclor Grip; Vita-C Derms's; Wilpan Antigripal; Wilpan C†; ***Austral.:*** Action Cold & Flu; Anthogenol; Antioxidant Forte Tablets; Antioxidant Tablets; Ascoxal; Beta A-C; Bio C; Bio Magnesium; Bio-C Complex; Bioglan Cirflo†; Bioglan Mega C; Bioglan Super Cal C; Bioglan Zn-A-C; C Supa + Bioflavonoids†; Cold & Flu Tablets Non Drowsy; Cold and Flu Relief†; Cold Sore Relief†; Cranberry Complex; Echinacea 4000; Echinacea Lozenge; Extralife Leg-Care; Extralife Uri-Care; Eye Health Herbal Plus Formula 4; Flavons; Garlic and Horseradish + C Complex; Garlic, Horseradish, A & C Capsules†; Gentle C with Bioflavonoids†; Glycoprep-C; Hair and Skin Formula†; Infant Tonic†; Irontona; Lifesystem Herbal Plus Formula 5 Eye Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Logicin Natural Lozenges†; Macro C†; Neo-C; Procold†; Proyeast†; Redoxon Double Strength; Slow Release Mega C†; Sore Throat Chewing Gum†; Strepsils Zinc Cold Relief; Super Cal-C Bio; Sustained Release C; Verbascum Complex†; Vitatona; Zinc + C250†; Zinc C Plus†; Zinc Zenith; Zinvit C; ***Austria:*** Ado C; Adolorin ASS/Vit C; Adoquick Vit C; Ascorbisal; Aspirin + C; Aspro mit Vitamin C; ASS + C; ASS plus Vit C; Calcipot C; Calcisan B + C; Calcisan C; Ce-Limo-Calcium; Cebion plus Rutin; Grippinon; Grippostad C; Helopyrin; Iromin-Chinin-C; Lemazol; Macalvit; Mexa-Vit C; Neo Citran; Nisicur; Ossiplex; Phlebodril; Ruticalzon; Rutiscorbin†; Seltoc; Tetesept; Thomapyrin mit Vitamin C; Trimedil; Ultren; ViCetamol; Vit-C-Lutsch; Waldheim Influvidon; ***Belg.:*** Afebryl; Aspirine C; Efferalgan C†; Guronsan; Medica Junior; Perdogrip†; Perdolan Mono C†; Redoxon + Zink; Sandoz Calcium + Vitamine C†; Sedergine C†; Strepsils Vit C; ***Braz.:*** Algice; Amigdalol; Analgin C-R; Aspirina C; Baldin-CE†; Biofrut†; Bromil; Broncopinol†; Calcium-Sandoz + Vitamina C; Castanha de India Composta†; Cebion Calcio; Cebion Plus Com Minerais†; Cebion Plus Magnesio†; Cebion Zinco; Coldrin; Coquevit†; Dactil OB; Dinavital C; Eucaliptan†; Folacin; Forgrip†; Gingilone; Gripanil†; Gripcaps C†; Gripen; Gripen F; Gripion†; Gripomatine†; Griponia†; Gripsay; Griptol†; Killgrip†; Lima C; Limao Bravo com Vitamina C†; Limao Bravo†; Melhoral C†; Nogripe; Pulmorien†; Redoxon Zinco; Resfry; Resprax; Suprasten†; Targifor C; Termogripe C†; Trimedal; Vick Pyrena; Vita Grip; Vitercal C; ***Canad.:*** Citron Chaud DM; Cran-C†; Hot Lemon; Hot Lemon Relief; Hot Lemon Relief for Cough and Cold; Neo Citran A†; Neo Citran†; One A Day Cold Season†; Penta-3B + C; Penta-Thion; Swiss Herb Cough Drops; Timed Release Ester C; Zinc Plus; ***Chile:*** Aspirina C; C-1000-C†; Calcigran; Captus; Citro-C; Congestex; Cotibin Flu†; Crevet Calcio + D3 + C; Droxel; Duo-CVP; Elcal-C Magnesio†; Eniflex†; Gripexin Limonada Caliente; Gripexin Nueva Formula Compuesto†; Hemoplex†; Kitadol Flu Noche†; Kitadol Flu†; Primacy C+AHA†; Skin C†; Tapsin Compuesto; Tapsin Compuesto con Clorfenamina; Tapsin Compuesto Dia/Noche Plus; Tapsin Compuesto DN; Tapsin Limonada D.N.†; Tapsin Limonada Dia†; Tapsin Limonada Noche†; Trio-D†; ***Cz.:*** Acylpyrin + C; Ascorutin; Aspirin C; Aspro C†; Calcium C Neo; Calcium C†; Cemaquin†; Coldrex; Coldrex Hotrem; Coldrex MaxGrip; Cyclo 3 Fort; Efferalgan Vitamin C; Febrisan; Fervex; Grippostad C; Grippostad Horky Napoj; Magnesium Pharmavit; Mexavit; Ossiplex†; Paraskorbin†; Redoxon Double Action; Rhinoval C†; Ring N†; Strepsils Vitamin C; Tetesept Angidin†; Tomapyrin C†; Trigrip; Upsarin C†; ***Fin.:*** Ascoxal†; Aspirin C; Burana-C; Cellavie†; Coldrex; Finrexin; Posinova; Posivil†; ***Fr.:*** Acti 5; Adena C†; Afebryl†; Aphtoral; Ascortonyl; Aspirine vitamine C; Aspro vitamine C; Bicirkan; Broncorinol maux de gorge†; Ca-C†; Catalgine Vitamine C†; Cequinyl; Cirkan; Codetricine vitamine C†; Cyclo 3 Fort; Detoxalgine†; Efferalgan Vitamine C; Fastenyl; Fervex; Guronsan; Humex Mal de Gorge sans sucre; Moviprep; Nicoprive; Ophtadil†; Phakan†; Revitalose; Rhinofebral; Sargenor a la Vitamine C; Strepsils Vitamine C; Tonicalcium; Vascocitrol; Veinobiase; Veinostase; Venyl†; Vitathion; ***Ger.:*** Aspirin plus C; ASS + C; Boxazin plus C; Cebion Erkaltungs†; Ferro-C-Calcium; Fibrex Hot Drink†; Fomagrippin N†; Grippostad C; Jasimenth CN; NeyDop N (Revitorgan-Dilutionen N Nr 97)†; NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; Ossiplex; ratioGrippal + C; Ring N; Ruticalzon VC†; Thomapyrin C; Togal Kopfschmerzbrause + Vitamin C; Tyrosolvetten-C†; Vitamin C-Calcium†; Wick Daymed Erkaltungs; ***Gr.:*** Apotel C-500; Aspirin C; Cyclo 3 Forte; Depon+Vit. C; Flavobion-C; Gluta-calcium†; Panadol+C; Salospir C-500; ***Hong Kong:*** Beechams Hot Lemon†; Ca-C†; Callimon; Cemaquin†; Coldrex†; Flavo-C; Lemsip†; Neozep; Panadol Cold & Flu Day; Panadol Cold & Flu Extra; Panadol Cold & Flu Hot Remedy; Panadol Cold and Flu; Phenahist; Poly C†; Pregnacare; Procosamine†; Proflavanol†; Redoxon Double Action; Vitacimin Sweetlet; Welsan Lipocream; ***Hung.:*** Aspirin plus C; Aspro C; ASS + C; Blackcurrant Coldrex Hot†; Calcium-Sandoz + Vitamin C; Coldrex; Coldrex MaxGrip; Efferalgan C†; Fervex; Grippostad C; Lemon Coldrex†; Magnezium†; Neo Citran; Ossiplex†; Rhinoval C†; Rutascorbin; Strepsils Vitamin C; Upsarin C†; ViCetamol; Vitacalc†; ***India:*** Cadisper C; Citravite; CKP; CVP; Fervit†; Gynae-CVP; Hepasules; Kalpastic; Livogen†; Siochrome; Styptocid; Styptocip†; ***Indon.:*** Agrippin; Aptivium Optimum Joint Formula; Calcium-Sandoz Vit C; Champs C with Lysine; Decolgen; Deprex; Flutamol; Jointfit; Juvelon-C; Matase; Neozep; Phenadex; Proza; Redoxon Double Action; Sentril; Stamino; StarMuno; Stop Cold; Vitaslim; ***Irl.:*** Beechams Flu-Plus†; Beechams Hot Lemon Decongestant†; Beechams Hot Remedies†; Lemsip Cold & Flu; Lemsip Pharmacy Flu Strength; Lemsip Pharmacy with Phenylephrine†; Panadol Cold & Flu; Redoxon Double Action; Strepsils Vitamin C; ***Israel:*** Aspirin C; Calcium-Sandoz + Vit C; Strepsils with Vitamin C; ***Ital.:*** Asapiuci; Aspirina C; Aspro C; Benagol Vitamina C; Bronchenolo Antiflu; Capill; Centella Complex; Coryfin C; Ecamannan; Efferalgan C; Epargriseovit; Idro P2†; Idroskin C; Influ-Zinc; Influvit; Istantal; Jodo Calcio Vitaminico; Levital Plus; Lipaven; Neo Borocillina C; Neo Uniplus C†; Neomyrt Plus; Ossiplex†; Raffreddoremed; Rubjovit; Rutisan CE†; Salicina; Sargenor Plus; Sinegrip; Tachiflu; Tachifludec; Varicofit; Vivin C; Zerinoflu; ***Malaysia:*** Calcium-Sandoz + Vitamin C; Chitosan C†; Nat-C; Proflavanol; Time Release Nutrition Mega B + C Complex†; Vitamin C-500 YSP; ***Mex.:*** Actiman; Adekon C; Ascoxal; C-1000-C; Cal-Rutina; Clorfriol†; Fabroven; Flavit; Gripaleta†; Guayalin-Plus†; Noxivid; Nutrem; Pharbrix; Proflavanol; Rosavit C; Vidamil; Vitanumonyl C; ***Neth.:*** Aflukin C; Antigrippine; Aspirine C; Buckleys Kinderhoestsiroop; Citrosan; Finimal C; Hot Coldrex; Strepsils Sinaasappel en Vitamine C; ***Norw.:*** Ascoxal†; ***NZ:*** Botanica Hayfever; Lemsip Flu Strength; Redoxon Double Action; Strepsils Echinacea Defence; Strepsils with Vitamin C; Strepsils Zinc Defence; ***Philipp.:*** Bo-D-Fense; Delrosa; Liposorb; Osteo-4; Pynocare 40 Actisome; Time-Cee; ***Pol.:*** Apap C Plus; Ascalcin Plus; Ascorutical; Aspirin C; Bioaron C; Biovision; Calcium 500D; Calcium C; Calcium-Sandoz + Vitamin C; Cerutin; Coldrex HotRem; Coldrex MaxGrip; Coldrex MaxGrip C; Cyclo 3 Fort; Efferalgan Vitamin C; Effervit Calcium; Febrisan; Fervex; Grippostad C; Gryпostop Mix; MaxFlu; Polopiryna C; Rutinacea; Rutinoscorbin; Rutokal C; Rutovit C; Scorbolamid; Sebidin; Tetesept; Tiliros; Troxescorbin; Upsarin C; V-piryna; ***Port.:*** Afebryl; Aspirina C; Ca-C; Cegripe; Codiasp; Cortigripe; Cyclo 3; Gripetral; Guronsan; Ilvico N; Lipoforte†; Medifon; Paramolan C; Phakan†; Rinogan†; Rutinice Fortissimo; ***Rus.:*** Antigrippin-ANVI (Антигриппин-АНВИ); Ascorutical (Аскорутикаль); Aspirin C (Аспирин-С); Coldrex HotRem Lemon (Колдрекс ХотРем со Вкусом Лимона); Coldrex MaxGrip Lemon (Колдрекс МаксГрипп со Вкусом Лимона)†; Cyclo 3 Fort (Цикло-3 Форт); Daleron C (Далерон С); Grippostad (Гриппостад); Grippostad C (Гриппостад С); Herbion Plantain Syrup (Гербион Сироп Подорожника); Maxicold (Максиколд); Mexavit (Мексавит); Midol C (Мидол С); Paracetamol-C (Парацетамол-С); Prophylactin C (Профилактин С); Sebidin (Себидин); TheraFlu Flu and Cold (ТераФлю от Гриппа и Простуды Экстра); Vectrum Calcium (Вектрум Кальций); ***S.Afr.:*** Borstol Cold and Flu Powders with Vitamin C; Colcaps; Coldvico; Colstat; Corenza C; Coryx; Degoran C; Endcol Cold & Flu; Expectussin C†; Famucaps; Flu-Stat; Flusin C; Flusin DM; Flusin S; Flutex; Flutex Cold and Flu; Grippon; Histamed Compound; Ilvico; Med-Lemon Hot Medication with Vitamin C; Med-Lemon Hot Medication-Lemon Menthol; Merck-Flu; Nitroflu†; Ossiplex; Panado Medsip; Paracetacod; Sandoz Calcium-C†; Strepsils Orange-C; Vitaplus C Plus; ***Singapore:*** Ca-C; Cartipro; Champs C with Lysine; Cyclo 3 Fort; Febs; Flexeze†; Memoloba†; Panadol Cold & Flu Hot Remedy; Poly C; Proflavanol; Proza; Redoxon All Day Defence; Redoxon Double Action; ***Spain:*** Acyflox; Aftasone B C; Alergical; Algidol; Aspirina C; Beecham Lemon; Calcio 20 Complex; Calmagrip; Calmante Vitaminado PG Efervescente; Clamarvit†; Coricidin†; Cortafriol C; Couldina C; Desenfriol C; Dolmen; Efferalgan Vit C; Fabroven; Fluxal†; Frenadol Complex; Gingilone; Gramoce A; Guronsan; Lema C; Odontocromil c Sulfamida†; Pastillas Antisep Garg L; Propalgina Plus; Redoxon Calciovit; Rimagrip; Rinomicine; Sedergine C; Strepsils con Vitamina C; Vicomin A C; Vitafardi C B12; ***Swed.:*** Ascoxal†; Macalvit; ***Switz.:*** Alca-C; Ascosal; Aspirine C; C-Calcium; Ca-C†; Calcium D Sauter; Callimon†; Cemaquin; Contre-Douleurs C; Dafalgan plus C; Demogripal C; Desaquick extra fresh†; Desaquick forte†; Desaquick fresh†; DoloCitran C; Esberitop; Escogripp sans codeine; Gramipan†; Grippostad C†; Influbene C; Instacyl; Neo Citran Grippe/refroidissement; Neo-Angin avec vitamin C sans sucre; Neo-Codion N; No Grip C†; Panadol C; Phakolen†; Pretuval C; Redoxon + Zinc; Rhinofebral†; Treupel Grippe; Treupel simplex†; Visaline; Zolben C; ***Thai.:*** Biocalron; Blackmores Naturetime Buffered C; Ca-C; Cyclo 3 Fort; Detoch†; Nat-C Medicrafts; Rhinophen-C†; Sentril; Strepsils Plus Vit C; ***Turk.:*** Afebryl; Aspirin plus C; Calcium-Sandoz C; Epargriseovit; Mentimol; Sedergine Vit-C; Strepsils C; Vicks Pastil; Zinco C; ***UK:*** Beechams Cold & Flu; Beechams Flu-Plus; Beechams for Natural Defence; Boots Cold & Flu Relief; Boots Cold & Flu Relief Hot Lemon; Cold Relief; Goodypops; Hacks; Hacks Blackcurrant; Hematinic; Lemsip Cold & Flu Breathe Easy; Lemsip Cold & Flu Max Strength; Lemsip Cold & Flu Original; Lemsip Non-Decongestant†; Moviprep; Olbas Powerflu plus Vitamin C; Paracets Cold Relief; Redoxon Double Action; Resolve; Strepsils with Vitamin C; Strepsils Zinc Defence†; Top C; Uniflu with Gregovite C; Vicks Vital†; ***USA:*** Amino-Opti-C; C Factors "1000" Plus; Citrus-flav C; Ester-C Plus; Ester-C Plus Multi-Mineral; Hemocyte Plus; Pan C; Peridin-C; Proflavanol; Span C; Sucrets Defense Kids Formula; ***Venez.:*** Calcebion; Cepin; Dremo-K†; Kalsis; Multidex; Ro-C-Var; Terace Zinc.

Used as an adjunct in: ***Arg.:*** Anemidox-Ferrum; Anemidox-Solutab; Ferro Folic; Ferrocebrina; Hierro Folico; Hierro Plus; Iberol; Rubiron; Sideralce; ***Austral.:*** Bio Iron; Ferrograd C; ***Austria:*** Ferretab; Ferrograd C; Liquifer†; Losferron; Losferron-Fol; ***Belg.:*** Fero-Grad; Losferron; ***Braz.:*** Anemofer†; Cobaldoze; Combiron; Dobiron; Ferrocomplex; Ferroplex; Ferrotonico B12†; Iberin Folico; Iberol; Iloban; Novofer; Rubralong†; Rubrargil; Sulfato Ferroso Composto; ***Canad.:*** Fero-Grad; Iberet†; Neo-Fer CF; Palafer CF; ***Chile:*** Confer; Cronoferril†; Ferranem; Ferrinam; Ferro F-500 Gradumet†; Ferro Vitaminico; Folifer; Iberol; Iberol Folico; ***Cz.:*** Ferro-Folgamma; Losferron; Sorbifer; Tardyferon; Tardyferon-Fol; ***Fin.:*** Duroferon; ***Fr.:*** Fero-Grad vitamine C; Tardyferon; Tardyferon B ; Timoferol; ***Ger.:*** Ferro-Folgamma; Kendural C; Kendural-Fol-500; Losferron; Tardyferon; Tardyferon-Fol; ***Hong Kong:*** Iberet; Iberet-Folic; ***Hung.:*** Ferro-Folgamma; Sorbifer; Tardyferon-Fol; ***India:*** Anemidox; Autrin; Conviron-TR; Raricap; Siderfol; Softeron; ***Indon.:*** Adfer; Biosanbe; Dasabion; Emibion; Emineton; Fercee; Feritrin; Ferofort; Habebion; Hemarate CE; Hemobion; Iberet; Iberet-Folic; Inbion; Natabion; Neogobion; Nichobion; Odiron-C; Opibion; Prenamia; Sangobion; Sangofer; Sangovitin; Tropifer; Viliron; Vitabion; Vitalex; Vitonal-F; ***Irl.:*** Ferrograd C; ***Ital.:*** Auxofer; Bioferal; Bioglufer; Blizer; Blustark; Crom; Cromatonferro; Effegyn; Emonorm†; Eriglobin; Eritropiu; Ferig; Ferro Complex; Ferrograd C; Ferrograd Folic; Ferrogyn; Flexifer†; Gloros; Liquifer†; Losferron; Megafer; Monoferro; Prontoferro; Sidervim; ***Malaysia:*** Iberet-Folic; Iberet†; Odiron-C†; Sangobion; ***Mex.:*** Autrin†; Ferro Folico; Fumarol; Iberet; Iberol; ***Neth.:*** Losferron; ***Norw.:*** Duroferon; ***NZ:*** Ferrograd C; ***Philipp.:*** Iberet; Iberet-Folic; Imefer; Macrobee with Iron; Magniferron; Micron-C; Molvite with Iron; Mulvitron; Odiron-C; Sangobion; Sorbifer; Terraferon; TriHEMIC; ***Pol.:*** Additiva Ferrum; Ascofer; Sorbifer; Tardyferon; Tardyferon-Fol; ***Rus.:*** Fenules (Фенюльс); Ferro-Folgamma (Ферро-Фольгамма); Ferroplex (Ферроплекс); Gyno-Tardyferon (Гино-тардиферон); Sorbifer (Сорбифер); ***S.Afr.:*** Autrin; Fero-Folic; Fero-Grad; Foliglobin; ***Singapore:*** Iberet; Iberet-Folic; Iron Melts; Neogobion; Odiron-C; Sangobion; ***Switz.:*** Duofer; Duofer Fol; Fero-Folic; Ferrascorbin; Kendural; Loesfer†; Lufer; ***Thai.:*** Glufer-C; Iberet†; Trinsicon†; ***Turk.:*** Ferro-Vital; Gyno-Tardyferon; Vi-Fer; ***UK:*** Ferrograd C; ***USA:*** Anemagen†; Cevi-Fer†; Chromagen; Chromagen FA; Chromagen Forte; Contrin; Feocyte; FeoGen; Fero-Folic; Fero-Grad; Ferotrinsic; Ferralet Plus†; Ferrex Forte Plus†; Ferrex Plus; Ferrogels Forte; Fetrin; Fumatinic; Hem Fe; Hemaspan†; Hematinic Plus; I-L-X; Iberet-Folic†; Iberet†; Icar-C Plus; Irospan; Livitrinsic-f; Niferex; Niferex Forte; Pronemia Hematinic; Tolfrinic; TriHEMIC; Trinsicon; Vitron-C; ***Venez.:*** Autrin†; Fefol; Fercor†; Ferro-Folic; Ferroce; Ferroce con B12; Ferronorm; Hepafol con B-12; Iberol C.

Vitamin D Substances

Vitamina D.

The term vitamin D is used for a range of closely related sterol compounds including alfacalcidol, calcifediol, calcitriol, colecalciferol, dihydrotachysterol, and ergocalciferol. Newer vitamin D analogues include doxercalciferol, falecalcitriol, maxacalcitol, and paricalcitol.

Alfacalcidol *(BAN, rINN)*

Alfacalcidolum; Alfakalcidol; Alfakalcidolis; Alfakalsidol; Alfakalsidoli; EB-644; 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3; 1α-OHD_3. (5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β-diol.

Альфакальцидол

$C_{27}H_{44}O_2$ = 400.6.
CAS — 41294-56-8.
ATC — A11CC03.
ATC Vet — QA11CC03.

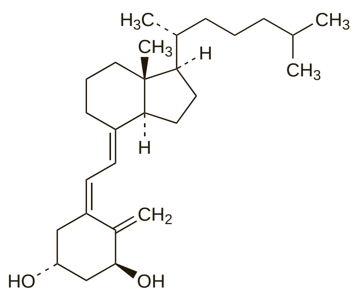

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Alfacalcidol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-alfacalcidol takes place in solution, depending on temperature and time. Activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.

Calcifediol *(BAN, USAN, rINN)*

Calcidiol; Calcifédiol; Calcifediolum; Calcifediolum Monohydricum; 25-Hydroxycholecalciferol; 25-Hydroxyvitamin D_3; Kalcifediol; Kalcifediol monohydrát; Kalcifediolis; Kalcyfediol; Kalsifedioli; 25-$(OH)D_3$; U-32070E. (5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-3β,25-diol monohydrate.

Кальцифедиол

$C_{27}H_{44}O_2,H_2O$ = 418.7.
CAS — 19356-17-3 (anhydrous calcifediol); 63283-36-3 (calcifediol monohydrate).
ATC — A11CC06.
ATC Vet — QA11CC06.

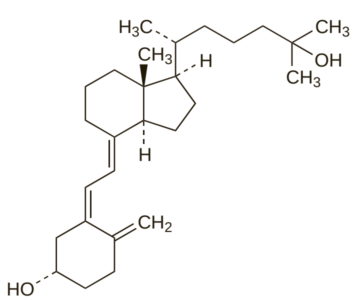

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Calcifediol). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Reversible isomerisation to pre-calcifediol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.
USP 31 (Calcifediol). Store in airtight containers. Protect from light.

Calcitriol *(BAN, USAN, rINN)*

Calcitriolum; 1,25-Dihydroxycholecalciferol; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D_3; Kalcitriol; Kalcitriolis; Kalsitriol; Kalsitrioli; 1α,25$(OH)_2D_3$; Ro-21-5535. (5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

Кальцитриол

$C_{27}H_{44}O_3$ = 416.6.
CAS — 32222-06-3 (anhydrous); 77326-95-5 (monohydrate).
ATC — A11CC04; D05AX03.
ATC Vet — QA11CC04; QD05AX03.

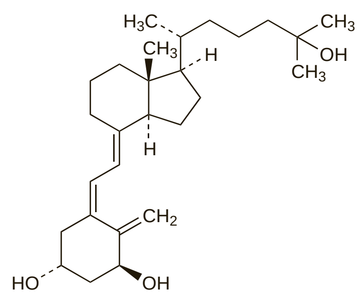

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Calcitriol). White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. It is sensitive to air, heat, and light. A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store at 2° to 8° under an atmosphere of nitrogen in airtight containers. The contents of an opened container should be used immediately. Protect from light.
USP 31 (Calcitriol). It may be anhydrous or contain one molecule of hydration. White or almost white crystals. Practically insoluble in water; freely soluble in alcohol; soluble in ether and in fatty oils. Store in airtight containers. Protect from light.

Colecalciferol *(BAN, rINN)*

Activated 7-Dehydrocholesterol; Cholécalciférol; Cholecalciferol; Cholecalciferolum; Cholekalciferol; Cholekalciferolis; Cholekalcyferol; Colécalciférol; Colecalciferolum; Kolekalciferol; Kolekalsiferol; Kolekalsiferoli; Vitamin D_3. (5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-trien-3β-ol.

Колекальциферол

$C_{27}H_{44}O$ = 384.6.
CAS — 67-97-0.
ATC — A11CC05.
ATC Vet — QA11CC05.

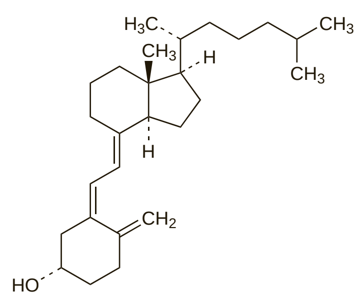

Description. Colecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Eur. also includes monographs for concentrates in an oily form, a powder form, and a water-dispersible form. *US* also includes a solution.
Ph. Eur. 6.2 (Cholecalciferol; Colecalciferol BP 2008). White or almost white crystals which are sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in trimethylpentane and in fatty oils. Solutions in solvents without an antioxidant are unstable and should be used immediately. A reversible isomerisation to pre-colecalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2° to 8°. The contents of an opened container should be used immediately. Protect from light.
The BP 2008 directs that when calciferol or vitamin D is prescribed or demanded, Colecalciferol or Ergocalciferol shall be dispensed or supplied.
Ph. Eur. 6.2 (Cholecalciferol Concentrate (Oily Form); Cholecalciferolum Densatum Oleosum; Colecalciferol Concentrate (Oily Form) BP 2008). A solution of colecalciferol in a suitable vegetable oil. It contains not less than 500 000 units/g. It may contain suitable stabilisers such as antoxidants. A clear, yellow liquid. Practically insoluble in water; slightly soluble in dehydrated alcohol; miscible with solvents of fats. Partial solidification may occur, depending on the temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.
Ph. Eur. 6.2 (Cholecalciferol Concentrate (Powder Form); Cholecalciferoli Pulvis; Colecalciferol Concentrate (Powder Form) BP 2008). It is obtained by dispersing an oily solution of colecalciferol in an appropriate matrix which is usually based on a combination of gelatin and carbohydrates of suitable quality. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. White or yellowish-white, small particles. Depending on their formulation, it may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of nitrogen.
Ph. Eur. 6.2 (Cholecalciferol Concentrate (Water-dispersible Form); Cholecalciferolum in Aqua Dispergibile; Colecalciferol Concentrate (Water-dispersible Form) BP 2008). A solution of colecalciferol in a suitable vegetable oil to which suitable solubilisers have been added. It contains not less than 100 000 units/g. It may contain suitable stabilisers such as antoxidants. A slightly yellowish liquid of variable opalescence and viscosity. Highly concentrated solutions may become cloudy at low temperatures or form a gel at room temperature. Store in well-filled airtight containers. Protect from light. The contents of an opened container are to be used as soon as possible; any unused part is to be protected by an atmosphere of inert gas.
USP 31 (Cholecalciferol). White, odourless crystals. Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils. M.p. about 85°. It is affected by air and light. Store under nitrogen in hermetically sealed containers at a temperature of 8° to 15°. Protect from light.
USP 31 (Cholecalciferol Solution). A solution of colecalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. Store in airtight containers. Protect from light.

Dihydrotachysterol *(BAN, rINN)*

Dichysterol; Dihidrotakisterol; Dihidrotaquisterol; Dihydrotachystérol; Dihydrotachysterolum; Dihydrotakisterol; Dihydrotakysterol; Dihydrotakysteroli. (5*E*,7*E*,22*E*)-10α-9,10-Secoergosta-5,7,22-trien-3β-ol.

Дигидротахистерол

$C_{28}H_{46}O$ = 398.7.
CAS — 67-96-9.
ATC — A11CC02.
ATC Vet — QA11CC02.

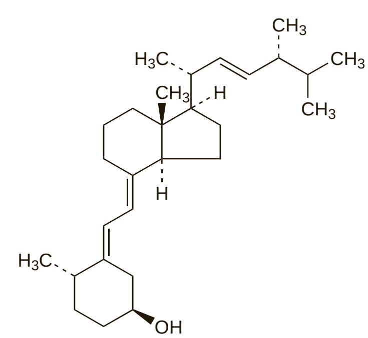

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Dihydrotachysterol). Colourless crystals, or a white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in *n*-hexane. Store under an inert gas in airtight containers at 2° to 8°.
USP 31 (Dihydrotachysterol). Colourless or white, odourless crystals, or white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform and in ether; sparingly soluble in vegetable oils. Store in hermetic glass containers from which the air has been displaced by an inert gas. Protect from light.

Doxercalciferol *(USAN, rINN)*

Doxercalciférol; Doxercalciferolum; 1α-Hydroxyergocalciferol; 1α-Hydroxyvitamin D_2; 1α-OH-D_2. (5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraene-1α,3β-diol.

Доксэркальциферол

$C_{28}H_{44}O_2$ = 412.6.

CAS — 54573-75-0.

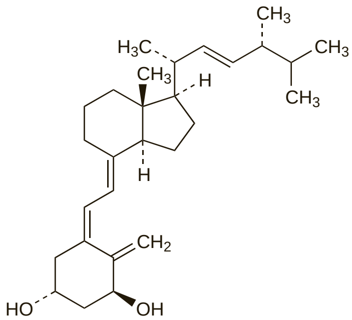

Ergocalciferol *(BAN, rINN)*

Calciferol; Ergocalciférol; Ergocalciferolum; Ergokalciferol; Ergokalciferolis; Ergokalsiferol; Ergokalsiferoli; Irradiated Ergosterol; Viosterol; Vitamin D_2. (5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3β-ol.

Эргокальциферол

$C_{28}H_{44}O$ = 396.6.

CAS — 50-14-6.

ATC — A11CC01.

ATC Vet — QA11CC01.

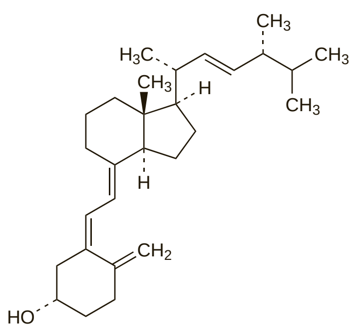

Description. Ergocalciferol is an antirachitic substance obtained from ergosterol, a sterol present in fungi and yeasts, by ultraviolet irradiation.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Ergocalciferol). White or almost white, crystals or white or slightly yellowish crystalline powder. It is sensitive to air, heat, and light. Practically insoluble in water; freely soluble in alcohol; soluble in fatty oils. Solutions in volatile solvents are unstable and should be used immediately. A reversible isomerisation to pre-ergocalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds. Store under nitrogen in airtight containers at a temperature of 2° to 8°. The contents of an opened container should be used immediately. Protect from light.

The BP 2008 directs that when calciferol or vitamin D is prescribed or demanded, Ergocalciferol or Colecalciferol shall be dispensed or supplied.

USP 31 (Ergocalciferol). White, odourless crystals. It is affected by air and light. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils. Store in hermetically sealed containers under nitrogen at a temperature of 8° to 15°. Protect from light.

Falecalcitriol *(rINN)*

Falécalcitriol; Falecalcitriolum; Flocalcitriol; Hexafluorocalcitriol; Ro-23-4194; ST-630. (+)-(5*Z*,7*E*)-26,26,26,27,27,27-Hexafluoro-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

Фалекальцитриол

$C_{27}H_{38}F_6O_3$ = 524.6.

CAS — 83805-11-2.

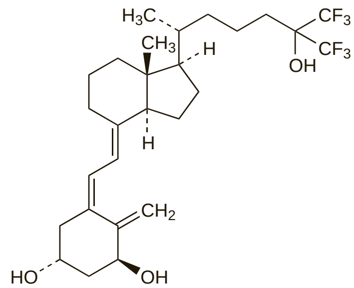

Maxacalcitol *(USAN, rINN)*

1α,25-Dihydroxy-22-oxavitamin D_3; Maxacalcitolum; OCT; 22-Oxacalcitriol; Sch-209579. (+)-(5*Z*,7*E*,20*S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol.

Максакальцитол

$C_{26}H_{42}O_4$ = 418.6.

CAS — 103909-75-7.

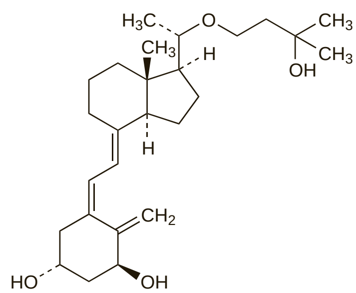

Paricalcitol *(USAN, rINN)*

ABT-358; Compound 49510; Paracalcin; Paricalcitolum. (7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol.

Парикальцитол

$C_{27}H_{44}O_3$ = 416.6.

CAS — 131918-61-1.

ATC — A11CC07.

ATC Vet — QA11CC07.

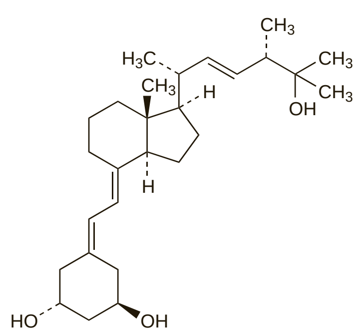

Pharmacopoeias. In *US.*

USP 31 (Paricalcitol). A white to almost white powder. Insoluble in water; soluble in alcohol. Store under argon in airtight containers at a temperature of −25° to −10°.

Units

The Second International Standard Preparation (1949) of vitamin D consisted of bottles containing about 6 g of a solution of colecalciferol in vegetable oil (1000 units/g). This standard has now been discontinued.

NOTE. Pharmacopoeias consider that one unit of vitamin D is contained in 25 nanograms of colecalciferol or ergocalciferol (i.e. 1 mg of colecalciferol or ergocalciferol is equivalent to 40 000 units of vitamin D as determined by bioassay in *rats*), but see below.

Equivalence. It has been proposed that units of vitamin D be defined in moles or molecules rather than weight terms; in which case, 1 unit of colecalciferol and ergocalciferol would be equivalent to 25 nanograms and 25.78 nanograms, respectively. This inequivalence in units might confound optimal vitamin D dosing recommendations.[1] For the view that colecalciferol is more potent than ergocalciferol, and should be preferred for vitamin D supplementation, see Administration, below.

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D) as a vitamin supplement. *Am J Clin Nutr* 2006; **84:** 694–7.

Adverse Effects and Treatment

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage (for a discussion of vitamin-D mediated hypercalcaemia and its treatment, see p.1668). Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal.

Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

Hypercalcaemia. Vitamin D is the most likely of all vitamins to cause overt toxicity. Doses of 60 000 units daily can cause hypercalcaemia (p.1668), with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.[1,2] A number of reports of accidental overdosage, leading to hypercalcaemia or nephrocalcinosis, occurred in the UK after introduction of a concentrated alfacalcidol oral solution that was 10 times stronger than the former presentation.[3]

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.[4]

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol.[5] Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol.[6]

Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies.[7] For reference to the effect of other vitamin D analogues used in psoriasis on calcium homoeostasis, see p.1591.

1. Anonymous. Toxic effects of vitamin overdosage. *Med Lett Drugs Ther* 1984; **26:** 73–4.
2. Chiricone D, *et al.* Unusual cases of chronic intoxication by vitamin D. *J Nephrol* 2003; **16:** 917–21.
3. Committee on Safety of Medicines/Medicines Control Agency. Accidental overdose with alfacalcidol (One-Alpha drops). *Current Problems* 2001; **27:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 09/01/06)
4. Jibani M, Hodges NH. Prolonged hypercalcaemia after industrial exposure to vitamin D . *BMJ* 1985; **290:** 748–9.
5. Hodson EM, *et al.* Treatment of childhood renal osteodystrophy with calcitriol or ergocalciferol. *Clin Nephrol* 1985; **24:** 192–200.
6. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124:** 520–8.
7. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135:** 347–54.

Precautions

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity (see above). Similar monitoring is recommended in infants if they are breast fed by mothers receiving pharmacological doses of vitamin D (see below).

Breast feeding. Vitamin D is distributed into breast milk,[1] and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.[2] The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding,[3] although they and others[4] recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

1. Rothberg AD, *et al.* Maternal-infant vitamin D relationships during breast-feeding. *J Pediatr* 1982; **101:** 500–503.
2. Cancela L, *et al.* Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breast-fed infants. *J Endocrinol* 1986; **110:** 43–50.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)
4. Greer FR, *et al.* High concentrations of vitamin D in human milk associated with pharmacologic doses of vitamin D . *J Pediatr* 1984; **105:** 61–4.

Pregnancy. Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy. Indeed, one report noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism;[1] the dose needed tended to increase during the second half of pregnancy. In one woman in whom the dose of calcitriol remained raised after delivery (in an attempt to allow for the calcium loss involved in breast feeding) hypercalcaemia developed; this did not occur in 2 women who did not breast feed and in whom the dose of the vitamin D preparations was reduced soon after delivery.[1] For discussions regarding vitamin D requirements during pregnancy, see UK and US recommended dietary intake, p.1988, and Pregnancy and the Neonate, p.1991, below.

1. Caplan RH, Beguin EA. Hypercalcemia in a calcitriol-treated hypoparathyroid woman during lactation. *Obstet Gynecol* 1990; **76:** 485–9.

Interactions

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D. Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

Danazol. A report of hypercalcaemia associated with danazol in a patient maintained on alfacalcidol therapy for hypoparathyroidism.[1] Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol.

1. Hepburn NC, *et al.* Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism. *Postgrad Med J* 1989; **65:** 849–50.

Levothyroxine. Three patients taking dihydrotachysterol and calcium, for postoperative hypoparathyroidism after thyroidectomy, as well as levothyroxine, developed hypercalcaemia when the latter was stopped before a radio-iodine scan.[1] The dose of dihydrotachysterol should be reduced and serum-calcium concentrations should be monitored when thyroid treatment is interrupted, since elimination of dihydrotachysterol may be delayed in hypothyroidism.

1. Lamberg B-A, Tikkanen MJ. Hypercalcaemia due to dihydrotachysterol treatment in patients with hypothyroidism after thyroidectomy. *BMJ* 1981; **283:** 461–2.

Pharmacokinetics

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and colecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Colecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol, dihydrotachysterol, and doxercalciferol are converted directly in the liver to their active metabolites (calcitriol, 25-hydroxydihydrotachysterol, and 1,25-dihydroxyergocalciferol respectively).

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

Human Requirements

The daily requirements of vitamin D in adults are small and may be met mainly by exposure to sunlight and/or obtained from the diet. A daily dietary intake of about 200 to 400 units (5 to 10 micrograms of colecalciferol or ergocalciferol) of vitamin D is generally considered adequate for healthy adults. In comparison with older adults (in the age range of 25 years upwards) the requirements per kg body-weight are greater in infants, children, and young adults and during pregnancy and lactation. Requirements may also be higher in people who are not exposed to adequate sunlight such as the elderly or housebound.

Vitamin D is present in few foods. Fish-liver oils, especially cod-liver oil, are good sources of vitamin D. Other sources, which contain much smaller amounts, include butter, eggs, and liver. Some foods are fortified with vitamin D, and milk and margarine may therefore also supply the vitamin. Cooking processes do not appear to affect the activity of vitamin D.

UK and US recommended dietary intake. In the UK dietary reference values (see p.1925) for vitamin D have only been published for selected groups of the population.[1] In the USA recommended dietary allowances had been set, and were subsequently replaced by dietary reference intakes[2] (see p.1925). Differing amounts are recommended for infants and children of varying ages, for adults, and for pregnant and lactating women. In the UK a dietary intake was considered unnecessary for adults living a normal lifestyle who were being exposed to solar radiation; for those confined indoors a reference nutrient intake (RNI) of 10 micrograms (400 units) [as colecalciferol or ergocalciferol] daily was set. This RNI of 10 micrograms daily was also considered to be applicable to all persons aged 65 years or more and to pregnant and lactating women. RNIs were set for children up to the age of 3 years; dietary intake was considered unnecessary for older children. Mention was made that in order to achieve the above reference nutrient intakes, supplementation of the diet may actually be required and supplementation was also recommended for Asian [i.e. from the Indian subcontinent] women and children in the UK (see also Pregnancy and the Neonate, below). In the USA,[2] adequate intakes for vitamin D are: 5 micrograms (200 units) daily (as colecalciferol) for all persons from birth through to age 50 years, including pregnant or lactating women; 10 micrograms daily for adults aged 51 to 70 years; and 15 micrograms daily for those aged greater than 70 years. The tolerable upper intake level is 50 micrograms (2000 units) daily. The 2005 Dietary Guidelines for Americans (published jointly by the US Department of Health and Human Services, and the US Department of Agriculture) recommend that high-risk groups including the elderly, those with dark skin, and those exposed to insufficient UV radiation, consume daily intakes of 25 micrograms (1000 units) daily.[3] The definition of vitamin D deficiency and vitamin D insufficiency remains controversial in terms of serum vitamin D concentrations.[4,5] Because vitamin D insufficiency is considered to be common in northern latitudes,[5] and deficiency is increasing worldwide,[4] higher intakes than those mentioned above have been recommended. Some have called for the establishment of an estimated average requirement (EAR) in North America,[4] and estimate a recommended dietary allowance (RDA) of greater than 12.5 micrograms (500 units). Others[5] suggest that the adequate intake be increased to at least 20 to 25 micrograms (800 to 1000 units) daily. A risk assessment analysis concluded that the tolerable upper intake level of vitamin D could be increased to 250 micrograms (10 000 units) daily for the general healthy population.[6]

The consensus of over 300 scientists from 23 countries at a vitamin D workshop was that governmental guidelines, in all countries, with respect to daily vitamin D requirements (to maintain bone health and health in general) were too low and did not reflect advances in vitamin D research over the preceding decade. Eating vitamin D-rich foods does not solve vitamin D deficiency for most adults; fortification of food should be significantly improved and implemented. Recommendations were made that blood concentrations of vitamin D should be at least 20 nanograms/mL, and that the tolerable upper intake level of 50 micrograms (2000 units) be re-evaluated in light of new data.[7]

For the view that colecalciferol is more potent than ergocalciferol, and should be the preferred form of vitamin D supplementation, see Administration, below.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)
3. US Department of Health and Human Services/US Department of Agriculture. Dietary Guidelines for Americans 2005. Available at: http://www.health.gov/DIETARYGUIDELINES/dga2005/document/pdf/DGA2005.pdf (accessed 10/09/07)
4. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005; **135:** 304–9.
5. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr* 2005; **135:** 332–7.
6. Hathcock JN, *et al.* Risk assessment for vitamin D. *Am J Clin Nutr* 2007; **85:** 6–18.
7. Norman AW, *et al.* 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; **103:** 204–5.

Uses and Administration

Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homoeostasis and bone mineralisation.

Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of the vitamin in the diet. Deficiency generally takes a long time to develop because of slow release of the vitamin from body stores. It may occur in some infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to light may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency.

Deficiency leads to the development of a syndrome characterised by hypocalcaemia, hypophosphataemia, undermineralisation or demineralisation of bone, bone pain, bone fractures, and muscle weakness, known in adults as osteomalacia (see below). In children, in whom there may be growth retardation and skeletal deformity, especially of the long bones, it is known as rickets.

Vitamin D compounds are used in the treatment and prevention of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism, as indicated by the cross-references given below.

Many forms and analogues of vitamin D are available, and the choice of agent depends on the cause of the condition to be treated and the relative properties of the available agents. Colecalciferol and ergocalciferol are traditionally considered equal in potency (but see Administration, below), and have a slow onset and relatively prolonged duration of action. Dihydrotachysterol has relatively weak antirachitic activity, but its actions are faster in onset and less persistent than those of the calciferols and it does not require renal hydroxylation. Calcifediol, an intermediate metabolite, has some action of its own but is also converted to the more potent 1,25-dihydroxycholecalciferol (calcitriol); calcitriol and its analogue alfacalcidol are the most potent and rapidly acting of the vitamin D substances.

- For the treatment of simple nutritional deficiencies **colecalciferol** or **ergocalciferol** are generally preferred. They are usually given orally, but may also be given by intramuscular injection. A dose of 10 micrograms (400 units) daily is generally sufficient in adults for the prevention of simple deficiency states; in the UK, 20 micrograms (800 units) daily is recommended in those whose exposure to sunlight is limited, in those whose diet is deficient in vitamin D, and in housebound or institutionalised elderly people. Deficiency due to malabsorption states or liver disease often requires higher doses for treatment, of up to 1 mg (40 000 units) daily. Doses of up to 5 mg (200 000 units) daily may be used in the treatment of hypocalcaemia due to hypoparathyroidism.
- Where large doses are required it may be preferable to use one of the more potent derivatives. In particular, when renal function is impaired as in secondary hyperparathyroidism associated with chronic renal failure, with consequent reduction in the conversion of calciferols to their active metabolites, then a drug such as alfacalcidol, calcitriol, doxercalciferol, maxacalcitol, or paricalcitol, which does not require renal hydroxylation, should be given.

  Calcitriol is given orally or by intravenous injection. Usual initial adult oral doses of 250 nanograms daily or on alternate days are given, increased if necessary, in steps of 250 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 1 microgram daily. Initial doses intravenously are usually 500 nanograms three times a week increased if necessary in steps of 250 to 500 nanograms at intervals of 2 to 4 weeks, to a usual dose of 0.5 to 3 micrograms three times a week. For moderate to severe secondary hyperparathyroidism in dialysis patients initial doses of 0.5 to 4 micrograms have been given three times a week, increased if necessary in steps of 250 nanograms to 1 microgram at intervals of 2 to 4 weeks to a maximum of 8 micrograms given three times a week.

  Alternatively, **alfacalcidol** is given in initial oral doses of 1 microgram daily, or 500 nanograms for elderly patients. Doses of 0.25 to 1 microgram daily may be given for maintenance. Suggested doses for children under 20 kg are 50 nanograms/kg daily and for premature infants and neonates a dose of 50 to 100 nanograms/kg daily. Doses of alfacalcidol may also be given by intravenous injection over 30 seconds.

  Doxercalciferol is given orally or by intravenous injection. The initial oral dose is 10 micrograms three times weekly at dialysis, increased by increments of 2.5 micrograms after 8 weeks if necessary. The maximum recommended oral dose is 20 micrograms three times weekly. The initial intravenous dose is 4 micrograms given three times weekly at dialysis, and increased after 8 weeks in increments of 1 to 2 micrograms if required. Doses are titrated according to parathyroid hormone concentrations.

  Maxacalcitol is given intravenously at a dose of 2.5 to 10 micrograms three times weekly; the dose may be gradually increased if necessary, to a maximum of 20 micrograms three times weekly.

  Paricalcitol is given intravenously in the USA at a dose of 40 to 100 nanograms/kg on alternate days or less frequently; in the UK the initial dose (in micrograms) is calculated by dividing the baseline intact parathyroid hormone concentration (in picograms/mL) by 80. The dose may be increased or decreased if necessary by 2 to 4 micrograms at intervals of 2 to 4 weeks, based on parathyroid hormone concentrations. Paricalcitol is also given orally either as a daily dose or three times weekly (no more frequently than every other day). Again, the initial dose is based on baseline intact parathyroid hormone concentrations. If these are 500 picograms/mL or less, paricalcitol is given at a dose of 1 microgram daily, or 2 micrograms three times weekly; if they are above 500 picograms/mL, paricalcitol 2 micrograms daily, or 4 micrograms three times weekly is suggested. Doses are titrated according to parathyroid hormone concentrations.
- Of the other available forms, **calcifediol**, the 25-hydroxylated metabolite of colecalciferol, has been given in usual adult oral doses of 50 to 100 micrograms daily or 100 to 200 micrograms on alternate days. For hypocalcaemic tetany due to hypoparathyroidism, **dihydrotachysterol** is given in initial adult oral doses of 250 to 2400 micrograms daily, depending on severity, for about three days. Maintenance doses have ranged from 250 micrograms weekly to 1000 micrograms daily.

When vitamin D substances are given in pharmacological doses, dosage must be individualised for each patient, and should be based on regular monitoring of plasma-calcium concentrations (initially once or twice weekly), to optimise clinical response and avoid hypercalcaemia.

Vitamin D, usually in the form of calcitriol, may be used in the treatment of osteoporosis (see below). In established postmenopausal osteoporosis, calcitriol 0.25 micrograms twice daily is recommended. Vitamin D and calcium supplements are often given as adjuncts to other therapies in osteoporosis.

Calcitriol has been used in the management of psoriasis (see below).

Calciferol derivatives are used as rodenticides.

◊ General references.

1. Thomas MK, Demay MB. Vitamin D deficiency and disorders of vitamin D metabolism. *Endocrinol Metab Clin North Am* 2000; **29:** 611–27.
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3. Holick MF. Vitamin D: a millenium perspective. *J Cell Biochem* 2003; **88:** 296–307.
4. Holick MF. Vitamin D: importance in the prevention of cancers, type I diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004; **79:** 362–71.
5. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89:** 552–72.
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9. Calvo MS, *et al.* Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135:** 310–16.
10. Bandeira F, *et al.* Vitamin D deficiency: a global perspective. *Arq Bras Endocrinol Metabol* 2006; **50:** 640–6.
11. Mason P. Vitamin D—function and uses. *Pharm J* 2006; **277:** 227–30.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357:** 266–81.
13. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87:** 1080S–1086S.

Administration. Minor differences in the chemistry of the side-chains of ergocalciferol and colecalciferol lead to the production of different metabolites (see Pharmacokinetics, above).[1] Colecalciferol has been reported to raise serum vitamin D concentrations more effectively than ergocalciferol,[2,3] perhaps because of higher affinities of colecalciferol and its metabolites for liver enzymes, plasma vitamin D binding protein, and vitamin D receptors.[1] It has been suggested that 50 000 units of ergocalciferol should be considered equivalent to no more than 15 000 units of colecalciferol, and perhaps closer to 5000 units; the tolerable upper intake level (see UK and US recommended dietary intake, p.1988) ought not to be applied to ergocalciferol.[3] These differences and the inequivalence in units (see Equivalence, under Units, above) may confound optimal vitamin D dosing recommendations.[1,3] The form of vitamin D used in studies should be specified.[2] While ergocalciferol is effective in treating vitamin D deficiency, the differences in potency have led some to suggest that colecalciferol be used as the preferred form of vitamin D.[1,3]

1. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D) as a vitamin supplement. *Am J Clin Nutr* 2006; **84:** 694–7.
2. Trang HM, *et al.* Evidence that vitamin D increases serum 25-hydroxyvitamin D more efficiently than does vitamin D . *Am J Clin Nutr* 1998; **68:** 854–8.
3. Armas LAG, *et al.* Vitamin D is much less effective than vitamin D in humans. *J Clin Endocrinol Metab* 2004; **89:** 5387–91.

Administration in the elderly. Vitamin D deficiency is common in the elderly,[1-3] especially in housebound patients, and during wintertime.[4] Deficiency is aggravated by a diet low in calcium,[1] lack of sunlight exposure, and decreasing ability of the skin to synthesise vitamin D with advancing age.[3,5] Elderly patients are therefore at risk of secondary hyperparathyroidism, bone loss and osteoporosis, and fractures.[1,6,7] Low serum vitamin D has been associated with increased fracture rates, and there is some evidence from *animal* studies that vitamin D may promote bone healing after fracture, increasing the mechanical strength of bone by promoting mineralisation.[7] Poor muscle strength and weakness may be associated with vitamin D deficiency, and may increase the risk of falling in the elderly.[2,8,9] A meta-analysis[10] of 5 studies found that vitamin D supplementation reduced the risk of falls in the elderly by 22% compared with calcium or placebo. Vitamin D deficiency in the elderly may be less prevalent in the USA, due to fortification of food.[1] Food fortification has therefore been recommended,[1] or supplementation with doses in the region of 10 to 20 micrograms (400 to 800 units) daily;[1,4] 20 micrograms (800 units) daily is considered necessary for reduction of falls and fractures in the elderly.[2,7,11] The 2005 Dietary Guidelines for Americans recommend that elderly people should consume 25 micrograms (1000 units) daily; the upper level of 50 micrograms (2000 units) should not be exceeded.[5] See also Osteomalacia, and Osteoporosis, below.

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; **22:** 477–501.
2. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. *BMJ* 2005; **330:** 524–6.
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6. Passeri G, *et al.* Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Endocrinol Metab* 2003; **88:** 5109–15.
7. Simon J, *et al.* Fractures in the elderly and vitamin D. *J Nutr Health Aging* 2002; **6:** 406–12.
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9. Janssen HCJP, *et al.* Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002; **75:** 611–15.
10. Bischoff-Ferrari HA, *et al.* Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004; **291:** 1999–2006.
11. Bischoff-Ferrari HA, *et al.* Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; **293:** 2257–64.

Cardiovascular disease. Myocardial tissue contains a vitamin D-dependent calcium-binding protein, indicating a role for vitamin D in the regulation of myocardial contractility.[1,2] Lack of vitamin D is considered to play a role in the aetiology and pathogenesis of cardiovascular disease such as congestive heart failure;[2] case reports have shown that vitamin D treatment reduced blood pressure and myocardial hypertrophy.[3] However, there is currently no rationale to prescribe specific vitamin D analogues for patients with congestive heart failure.[2]

1. Luong KVQ, Nguyen LTH. Vitamin D and cardiovascular disease. *Curr Med Chem* 2006; **13:** 2443–7.
2. Zittermann A, *et al.* Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; **11:** 25–33.
3. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; **92:** 39–48.

Diabetes mellitus. Vitamin D has a role in glucose homoeostasis and in the mechanism of insulin release.[1] Cohort studies[2,3] have suggested that supplementation with vitamin D may have a beneficial role in reducing the risk for developing both type 1 and type 2 diabetes mellitus. However, another study[4] found no significant differences in vitamin D status in Finnish or Karelian children, 2 neighbouring geographical areas with vastly differing incidences of type 1 diabetes.

1. Reis AF, *et al.* Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease: a review of evidence. *Diabetes Metab* 2005; **31:** 318–25.
2. Hyppönen E, *et al.* Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001; **358:** 1500–1503.
3. Pittas AG, *et al.* Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; **29:** 650–6.
4. Viskari H, *et al.* Circulating vitamin D concentrations in two neighboring populations with markedly different incidence of type 1 diabetes. *Diabetes Care* 2006; **29:** 1458–9.

Hyperparathyroidism. Vitamin D has been used for certain forms of hyperparathyroidism (p.1087). The **secondary hyperparathyroidism** of renal osteodystrophy (p.1086) may respond to treatment with calcitriol, or its analogue alfacalcidol,[1,2] which do not require renal hydroxylation for activation. Calcitriol has been used orally,[3] intravenously,[3,4] and intraperitoneally;[5] percutaneous injection directly into the parathyroid gland has also been reported to be safe and effective.[6-8] However, doses capable of suppressing parathyroid hormone secretion may lead to hypercalcaemia,[1-3,5,9,10] hyperphosphataemia,[1,2,5,9,10] and a decline in renal function;[11] the increase in calcium and phosphate may promote soft tissue and vascular calcification,[1,2] see Hypercalcaemia, under Adverse Effects, above.

Newer analogues for this indication include paricalcitol,[12-15] doxercalciferol,[16-18] falecalcitriol,[19] and maxacalcitol.[20-25] These are reported to have less effect on calcium and phosphate concentrations, while retaining the suppressive effect on parathyroid hormone;[1,5,9,10] however, some[2,18] consider clinically relevant benefit to be lacking. Paricalcitol was found to have a faster effect and cause less hypercalcaemia than calcitriol in patients on haemodialysis,[15] as well as offering a significant survival advantage over calcitriol.[13] A review considered paricalcitol to be as effective and as well tolerated as calcitriol.[14] Maxacalcitol and calcitriol were considered equally effective when given intravenously to haemodialysis patients,[25] while oral falecalcitriol was considered better than oral alfacalcidol at reducing parathyroid hormone concentrations.[19] Intravenous doxercalciferol appears to be safer than oral doxercalciferol;[1] comparative data are lacking.[2,18] A meta-analysis found that the use of vitamin D in chronic kidney disease did not consistently reduce parathyroid hormone concentrations.[26]

Some have cautioned against vitamin D supplementation in **primary hyperparathyroidism** because of concerns about exacerbation of hypercalcaemia and hypercalciuria. However, in a small study in patients with mild primary hyperparathyroidism, correction of vitamin D deficiency did not exacerbate hypercalcaemia, and decreased parathyroid hormone concentrations and bone turnover.[27]

1. Brown AJ, Coyne DW. Vitamin D analogs: new therapeutic agents for secondary hyperparathyroidism. *Treat Endocrinol* 2002; **1:** 313–27.
2. Cunningham J. New vitamin D analogues for osteodystrophy in chronic kidney disease. *Pediatr Nephrol* 2004; **19:** 705–8.
3. Quarles LD, *et al.* Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 1994; **45:** 1710–21.
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5. Dusso AS, *et al.* Vitamin D receptor and analogs. *Semin Nephrol* 2004; **24:** 10–16.
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7. Shiizaki K, *et al.* Effect of percutaneous calcitriol injection therapy on secondary hyperparathyroidism in uraemic patients. *Nephrol Dial Transplant* 2003; **18** (suppl): iii42–iii46.
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11. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124:** 520–8.
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17. Coburn JW, *et al.* Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004; **43:** 877–90.
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19. Akiba T, *et al.* Controlled trial of falecalcitriol versus alfacalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1998; **32:** 238–46.
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21. Yasuda M, *et al.* Multicenter clinical trial of 22-oxa-1,25-dihydroxyvitamin D3 for chronic dialysis patients. *Am J Kidney Dis* 2003; **41** (suppl 1): S108–S111.
22. Doi S, *et al.* Effect of 22-oxacalcitriol on secondary hyperparathyroidism in hemodialysis patients. *Intern Med* 2003; **42:** 955–9.
23. Kubota M, *et al.* The effect of intraperitoneal 22-oxacalcitriol on secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients (IPOX Study). *Adv Perit Dial* 2003; **19:** 227–30.
24. Murakami K, *et al.* Suppression of parathyroid hormone secretion in CAPD patients by intraperitoneal administration of maxacalcitol. *Clin Exp Nephrol* 2004; **8:** 134–8.
25. Hayashi M, *et al.* Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial. *Nephrol Dial Transplant* 2004; **19:** 2067–73.
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Hypoparathyroidism. Although parenteral calcium salts may be given acutely for hypocalcaemic tetany, long-term treatment of hypoparathyroidism (p.1087) usually aims at correction of associated hypocalcaemia with oral calcium salts and oral vitamin D compounds, which increase the intestinal absorption of calcium.

Hypoparathyroidism in *pregnancy* poses severe risks of fetal hyperparathyroidism with neonatal hypocalcaemic rickets, which may be fatal. Treatment with calcium and either colecalciferol or ergocalciferol in doses of 1.25 to 2.5 mg daily, or dihydrotachysterol 0.25 to 1.0 mg daily is essential.[1] Calcitriol, in doses of between 0.25 to 3 micrograms daily, with calcium supplementation, has also been suggested; the dosage is adjusted to physiological requirements during pregnancy.[2]

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2. Callies F, *et al.* Management of hypoparathyroidism during pregnancy - report of twelve cases. *Eur J Endocrinol* 1998; **139:** 284–9.

Inflammatory bowel disease. Some studies have found a high prevalence of vitamin D deficiency in patients with inflammatory bowel disease (IBD). The aetiology of this is not entirely clear and may be multifactorial.[1,2] Patients with IBD may have decreased exposure to sunlight since the incidence and prevalence of IBD are greatest in northern latitudes. Patients might also have inadequate dietary intake of vitamin D, since IBD patients may avoid foods, such as dairy products, that are generally fortified with this vitamin. Deficiency might also be due to malabsorption, especially in IBD patients that have undergone small-bowel resection, although intestinal absorption was normal in many IBD patients with low vitamin D concentrations. The use of drugs such as colestyramine, and disturbed enterohepatic circulation of vitamin D metabolites have also been proposed as mechanisms for hypovitaminosis D in patients with IBD, as has an increased loss of vitamin D through protein-losing enteropathy.[1,2] A study[3] in children and young adults with IBD also found a high prevalence of vitamin D deficiency in this patient population. Predisposing factors included dark-skinned complexion, winter season, lack of vitamin D supplementation, early stage of disease, more severe disease, and upper gastrointestinal tract involvement in patients with Crohn's disease. Vitamin D concentrations were positively correlated with serum albumin concentrations, leading the authors to conclude protein-losing enteropathy was a leading mechanism for deficiency. If this were so, both enteral and parenteral supplementation of vitamin D might prove inadequate at the usual dose, and in patients with active disease.

However, the American Gastroenterological Association concluded, in a review of osteoporosis in gastrointestinal diseases,[4] that osteomalacia and vitamin D deficiency were not common in IBD patients (including Crohn's disease) and were unlikely to be causes of most cases of diminished bone mineral density in patients with IBD.

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2. Pappa HM, *et al.* Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease.*Inflamm Bowel Dis* 2006; **12:** 1162–74.
3. Pappa HM, *et al.* Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics* 2006; **118:** 1950–61.
4. Bernstein CN, *et al.* American Gastroenterological Association Clinical Practice Committee. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003; **124:** 795–841.

Malignant neoplasms. The active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol) has been found to promote tissue differentiation and to inhibit cellular proliferation *in vitro*. These findings have prompted investigation into the potential role and efficacy of vitamin D metabolites or analogues (sometimes referred to as deltanoids) in malignant neoplasms and in other disorders of cell growth such as psoriasis (see below).

There is laboratory evidence that vitamin D compounds can inhibit the growth of cancer cells, including those of the breast,[1,2] colon,[3] and prostate.[4,5] Epidemiological studies have suggested that vitamin D deficiency may be associated with higher risks of cancer.[6-9] Furthermore, increased sun exposure may be associated with improved survival for some cancers.[7,9] Phase I and II studies of calcitriol either alone, or with antineoplastics, have shown promising results.[10,11] A study in humans has been performed with the calcitriol derivative calcipotriol (p.1591); in this trial calcipotriol used topically in advanced or cutaneous metastatic breast cancer was considered to exert some positive effects and further investigation was considered warranted.[12] Regression of T-cell lymphoma of the skin (mycosis fungoides, p.657) has been reported after application of calcipotriol,[13] and after systemic treatment with calcitriol and a retinoid in a patient who failed to respond to topical calcipotriol.[14] However, 3 other patients with cutaneous T-cell lymphoma failed to respond to calcitriol and isotretinoin,[15] which may have been because of the phenotype or stage of the disease.[16] In a 7-year study in 36 282 postmenopausal women, of whom 18 176 received vitamin D_3 (400 units daily) and calcium, supplementation had no effect on the incidence of colorectal cancer.[17] This study has raised debate as to whether the dose of vitamin D used was insufficient.[7] A later analysis[18] of the study results suggested that supplementation had been of benefit in women in the placebo arms of the study but that this had been offset by an increase in risk in women also taking oestrogens. A smaller 4-year study[19] involving 1179 postmenopausal women given calcium with or without vitamin D_3 1100 units daily, or placebo, found that supplementation reduced all-cancer risk, and baseline and treatment-modified serum concentrations of vitamin D were strong predictors of cancer risk.

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Multiple sclerosis. Multiple sclerosis (p.892) is more common in regions further from the equator, and it has been suggested that sunlight exposure and vitamin D exert a protective effect. Studies have also found lower vitamin D concentrations in patients with multiple sclerosis. Results from two large prospective cohorts found an inverse relationship between intake of vitamin D from supplements and risk of the disease; no association was found between vitamin D intake from food and incidence of multiple sclerosis.[1] A prospective, case-control study[2] found that, among whites, the risk of multiple sclerosis significantly decreased with increasing concentrations of vitamin D; no significant association was found among blacks and Hispanics. However, the sample size in the latter groups were smaller and concentrations of vitamin D are lower among blacks. A review[3] found little evidence to support the effectiveness of vitamin D in the treatment of multiple sclerosis; although uncontrolled studies suggest vitamin D may be beneficial, small patient populations and confounding variables have limited the usefulness of the data.

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2. Munger KL, *et al.* Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296:** 2832–8.
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Osteomalacia and rickets. Treatment of osteomalacia and rickets (p.1084) primarily aims at correcting any underlying deficiency states, and vitamin D substances, calcium, or phosphate supplements may be given orally as necessary.

Where **rickets** is due to impaired synthesis of 1,25-dihydroxycholecalciferol (type I pseudodeficiency) or receptor resistance (type II pseudodeficiency) replacement therapy with calcitriol may be indicated (in the latter case with very high dose calcium),[1] while X-linked hypophosphataemic rickets is generally treated with phosphate supplementation and calcitriol.[2] The use of single large doses of a vitamin D substance (Stosstherapie), for the prophylaxis of rickets, is highly controversial because of problems with toxicity, although it may be effective in patients with rickets due to proven[3] or recalcitrant[4] vitamin D deficiency. Factors contributing to reported resurgences in rickets[2,4-8] include increased breast feeding without sufficient vitamin D supplementation, and less exposure to sunlight. A major risk factor for infants is maternal vitamin D deficiency (see Pregnancy and the Neonate, below). In the UK, the Department of Health advises that children aged 5 years and under be supplemented with 7 micrograms (280 units) daily,[8] but renewed public health campaigns have been called for, along with supplementation of infants from high-risk groups with 400 units of vitamin D daily.[6] Similar recommendations have been made in Australia and New Zealand.[4] In the USA, the American Academy of Pediatrics has recommended that all infants have a minimum intake of 200 units daily.[9] Others have commented that even 200 units daily may not be enough as a preventive measure,[2,10] and that, in those children with good exposure to sunlight, calcium supplementation may also be necessary.[11]

In adults, vitamin D deficiency may be asymptomatic. Most patients who present clinically do so because of muscle weakness, or muscles aches and pains.[12] Even severe vitamin D deficiency may result in a syndrome of persistent, non-specific musculoskeletal pain, before the onset of the clinical presentation of **osteomalacia**.[13] However, others[14] have queried the association.

For discussion on doses of vitamin D considered sufficient for prophylaxis, see UK and US Recommended Dietary Intake, above; for treatment, see Uses and Administration, above. Because the process of ageing decreases the skin's ability to synthesise vitamin D, elderly people may be at risk of deficiency (see Administration in the Elderly, above).

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5. Kreiter SR, *et al.* Nutritional rickets in African American breast-fed infants. *J Pediatr* 2000; **137:** 153–7.
6. Shaw NJ, Pal BR. Vitamin D deficiency in UK Asian families: activating a new concern. *Arch Dis Child* 2002; **86:** 147–9.
7. Welch TR, *et al.* Vitamin D-deficient rickets: the reemergence of a once-conquered disease. *J Pediatr* 2000; **137:** 143–5.
8. Anonymous. Primary vitamin D deficiency in children. *Drug Ther Bull* 2006; **44:** 12–16.
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14. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 2004; **79:** 1585–6.

PREGNANCY AND THE NEONATE. It has been supposed that most infants receive adequate calcium and vitamin D during pregnancy and during breast feeding or bottle feeding to prevent the development of rickets. However, this has been disputed;[1,2] even infants born to vitamin D replete mothers become vitamin D deficient after 8 weeks if not supplemented, and those born to vitamin D deficient mothers will reach a deficient state more quickly. In many populations where sun exposure is severely limited and there is inadequate corrective vitamin D supplementation, there is also a high prevalence of vitamin D deficiency in nursing mothers.[3] It is accepted that there are certain groups of women whose infants may be at special risk of neonatal rickets; these include those suffering economic deprivation, those living at high latitudes, and Asian immigrants [i.e. from the Indian subcontinent] in northern Europe, especially in winter. It is therefore suggested that pregnant women in such circumstances should receive supplements as the diet and sunshine exposure may not be providing adequate calcium (1 to 1.2 g daily) or vitamin D (400 units daily).[4] Alternatively, 1000 units vitamin D daily during the third trimester, or a single dose of 100 000 to 200 000 units of ergocalciferol during the sixth or seventh month, has been proposed.[5] The Committee on Medical Aspects of Food Policy (COMA) in the UK recommended[6] in 1991 that pregnant women receive supplementary vitamin D to achieve an intake of 10 micrograms daily. However, a 2003 report commissioned by the NICE found insufficient evidence to assess the effectiveness of vitamin D in pregnancy and has recommended against routine vitamin D supplementation in healthy pregnant women.[7] A review[2] of dietary vitamin D requirements during pregnancy and lactation has stated that women who were vitamin D deficient at the beginning of their pregnancy remained deficient despite supplementation with 800 to 1600 units daily. The authors suggested that current recommendations in the UK and the USA were grossly inadequate during pregnancy, especially for ethnic minorities (see UK and US recommended dietary intake, above). Instead, they suggested that doses of about 2000 to 10 000 units daily would be needed in order to achieve normal vitamin D concentrations. Furthermore, routine vitamin D supplementation of infants in high-risk groups has been recommended (see Osteomalacia, above).

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Osteopetrosis. For mention of the use of high-dose calcitriol in the management of osteopetrosis, see under Corticosteroids, p.1509.

Osteoporosis. Vitamin D concentrations have been found to correlate positively with bone mineral density (BMD),[1] and supplementation with vitamin D and calcium has led to beneficial increases in BMD in most trials.[2] Sufficient intake of vitamin D and calcium is recommended for prevention of osteoporosis (p.1084), and supplementation is an accepted baseline adjunctive treatment.[2,3] The age-related increase in fracture risk is influenced by BMD changes and an increased propensity to falls, attributable in part to a loss of muscular strength. In addition to its role in calcium homoeostasis, vitamin D status has also been correlated to muscular strength in older people.[3]

Studies using vitamin D (with or without calcium) for the prevention of fractures have produced conflicting results.[4-11] However, in elderly patients, in whom dietary deficiencies are common, calcium and vitamin D supplements are recommended (see Administration in the Elderly, above). Supplementation is also recommended in elderly institutionalised patients.[12] A meta-analysis[13] of fracture prevention trials found that oral vitamin D supplementation with between 700 to 800 units daily reduced the risk of hip and non-vertebral fractures in elderly patients. However, a systematic review[6] has stated that the effectiveness of vitamin D alone in fracture prevention remains unclear. Calcium may be necessary to optimise the clinical efficacy of vitamin D supplementation in terms of reducing fracture risk.[3] A meta-analysis[14] found that oral vitamin D appeared to reduce the risk of hip fractures only when calcium supplementation was added. However, another meta-analysis[15] found that the difference in relative risk reduction for all fracture types when vitamin D was added to calcium supplementation, was very small and statistically insignificant, although those with low vitamin D serum concentrations tended to have a greater risk reduction than those with normal vitamin D concentrations. A significant difference was seen between the effects of different vitamin D doses. While noting that this could be due to statistical artifact, the authors noted that their analysis had been limited by the scarcity of data for vitamin D doses higher than 800 units, and that it was possible that vitamin D would have a beneficial effect if the dose were greater than 800 units daily. It has been suggested[16] that the vitamin D analogues alfacalcidol and calcitriol are more effective for osteoporosis than ergocalciferol or colecalciferol. However, a systematic review[6] found no evidence of benefit for analogues compared with vitamin D.

Vitamin D is also recommended for the prevention of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p.1491).

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10. Jackson RD, *et al.* Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; **354:** 669–83. Correction. *ibid.*; 1102.
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12. Anonymous. Lifestyle advice for fracture prevention. *Drug Ther Bull* 2002; **40:** 83–6.
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14. Boonen S, *et al.* Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007; **92:** 1415–23.
15. Tang BMP, *et al.* Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; **370:** 657–66.
16. Ringe JD, Schacht E. Prevention and therapy of osteoporosis: the roles of plain vitamin D and alfacalcidol. *Rheumatol Int* 2004; **24:** 189–97.

Psoriasis. A vitamin D analogue, calcipotriol (p.1591), is often used as an alternative to more traditional topical drugs in the initial management of mild to moderate psoriasis (p.1583). Another vitamin D analogue, tacalcitol (p.1615), is used similarly. Initial studies with topical maxacalcitol,[1] falecalcitriol,[2] and paricalcitol[3] suggest they are safe and effective for psoriasis. Calcitriol itself has been tried, both topically[4-6] and orally.[7] Calcitriol ointment has been found to be as effective as calcipotriol ointment[8] and short-contact dithranol cream; skin irritation was less with calcitriol compared with dithranol.[9] While global improvement and severity scores were found to be better with betamethasone dipropionate ointment, remission times were longer with calcitriol treatment.[10]

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3. Durakovic C, *et al.* Topical paricalcitol (19-nor-1α,25-dihydroxyvitamin D) is a novel, safe and effective treatment for plaque psoriasis: a pilot study. *Br J Dermatol* 2004; **151:** 190–5.
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10. Camarasa JM, *et al.* Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. *J Dermatol Treat* 2003; **14:** 8–13.

Renal osteodystrophy. See under Hyperparathyroidism, above.

Rheumatoid arthritis. A large cohort study[1] found an inverse correlation between vitamin D intake and the risk of developing rheumatoid arthritis. However, a small study[2] of serum vitamin D concentrations in patients with rheumatoid arthritis who had donated blood before the onset of symptoms, found no association between vitamin D deficiency and later development of rheumatoid arthritis, suggesting that vitamin D does not have an important role in the pathogenesis of rheumatoid arthritis.

1. Merlino LA, *et al.* Vitamin D intake is inversely associated with rheumatoid arthritis. *Arthritis Rheum* 2004; **50:** 72–7.
2. Nielen MMJ, *et al.* Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. *Arthritis Rheum* 2006; **54:** 3719–20.

Rickets. See Osteomalacia and Rickets, above.

Preparations

BP 2008: Calcitriol Capsules; Calcium and Colecalciferol Tablets; Calcium and Ergocalciferol Tablets; Colecalciferol Injection; Colecalciferol Tablets; Ergocalciferol Injection; Ergocalciferol Tablets; Paediatric Vitamins A, C and D Oral Drops;
BPC 1973: Calcium with Vitamin D Tablets; Vitamins A and D Capsules;
USP 31: Calcifediol Capsules; Calcitriol Injection; Calcium with Vitamin D Tablets; Dihydrotachysterol Capsules; Dihydrotachysterol Oral Solution; Dihydrotachysterol Tablets; Ergocalciferol Capsules; Ergocalciferol Oral Solution; Ergocalciferol Tablets; Oleovitamin A and D; Oleovitamin A and D Capsules; Paricalcitol Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Aderosol; Alfa Calcimax†; Alpha D3; Dexiven; Findeclin Combi; Ostelin; Raquiferol; Rexamat†; Silcor†; Sterogyl; Vita D; ***Austral.:*** Calcijex; Citrihexal; Kosteo; Ostelin; Rocaltrol; Sitriol; Zemplar; ***Austria:*** AT 10; Bocatriol; Calcijex; Etalpha; Laevovit D ; Oleovit D ; Rocaltrol; Silkis; Vi-De ; Zemplar; ***Belg.:*** 1-Alpha; AT 10†; D-Cure; Dedrogyl; Rocaltrol; Silkis; ***Braz.:*** Alfad†; Calcijex; Innosfen; Ostriol†; Rocaltrol; Sigmacalcidol; Sigmatriol; Silkis; ***Canad.:*** Calcijex; D-Vi-Sol; Drisdol; Hectorol; Hytakerol†; One-Alpha; Ostoforte; Riva D; Rocaltrol; Zemplar; ***Chile:*** Acuode; Alfa D†; Etalpha; Genevis D2†; Genevis†; Rocaltrol; Silkis; ***Cz.:*** Alpha D3; Calciferol; Calcijex; Infadin; OsteoD; Rocaltrol; Silkis; Tachystin; Vigantol; Zemplar; ***Denm.:*** Bocatriol; Dygratyl; Etalpha; Rocaltrol†; ***Fin.:*** Calcijex†; Deetipat; Devitol; Dygratyl; Etalpha; Jekovit; Silkis; Zemplar; ***Fr.:*** Adrigyl†; Dedrogyl; Densical vitamine D ; Rocaltrol; Silkis; Sterogyl; Un-Alfa; Uvedose; Uvesterol D; Zyma-D2†; Zymad; ***Ger.:*** AT 10; Bocatriol; Bondiol; D Vicotrat; Decostriol; Dedrei; Dedrogyl; Dekristol; Doss; EinsAlpha; Ospur D ; Osteotriol; Rocaltrol; Silkis; Tachystin; Vigantol; Vigantoletten; Zemplar; ***Gr.:*** A-Calcid; A-Ostin-D3; Abbocalcijex; Alcidolin; Alestopor; Alfacalcil; Alfadel; Alpha D3; Alpha-Due; Alpha-Plus; Alphabikal; Alphacal; Alphasidol; Alphazol; Antebe; Axelanol; Baludol; Biovit; Calcidrops; Calcodol-D3; Calfadol; Calinol; Caltrioject; D-Triol; Dedrogyl; Didrogyl; Emarfen; Helposteol; Iasvest; Lifercal; Losefan; Mega-Alpha; One-Alpha; Ossidrol; Ostelin; Osteovile; Ostitriol; Otari; Silkis; Sterogyl; V-D-Bone; Vitocalcit; Votrace; Zemplar; ***Hong Kong:*** Alpha D3; Bon-One; Calcijex; Decostriol; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Hung.:*** Alpha D3; AT 10†; Calcijex; Laevovit D †; Osteo D; Rocaltrol; Silkis; Tachystin; Vigantol; Zemplar; ***India:*** Alfacip; Alpha D3; Alphadol; Arachitol; Aristrol†; Calcirol; Minroset; Rolsical; ***Indon.:*** Bon-One; Calcijex; Calcit; Ecatrol; One-Alpha; Oscal; Osteofem; Ostovell; Ostriol; Ro-

caltrol; ***Irl.:*** Calcijex†; One-Alpha; Rocaltrol; Silkis; Zemplar; ***Israel:*** Alpha D3; Calcijex; One-Alpha; ***Ital.:*** Alpha D3; Atiten; Calcijex; Dediol; Deril; Dibase; Didrogyl; Difix; Diseon; Diserinal; Geniad; Ostelin; Ostidil-D3; Rocaltrol; Sefal; Silkis; Tridelta; Trikal; Zemplar; ***Jpn:*** Alfarol; Hornel; Onealfa; Oxarol; Rocaltrol; ***Malaysia:*** Calcijex; Fairy ADE; One-Alpha; Osteocap; Rocaltrol; Roical; Zemplar; ***Mex.:*** Alfad; Altrical; Altrol; Calciofem; Geldex; Lemytriol; Rocaltrol; Silkis; Tirocal; Zemplar; Zygium; ***Neth.:*** Calcijex; Devaron; Dihydral; Etalpha; Rocaltrol; Silkis; Zemplar; ***Norw.:*** AFI-D ; Calcijex; Etalpha; Rocaltrol; Silkis; Zemplar; ***NZ:*** CalD; One-Alpha; Rocaltrol; ***Philipp.:*** Bon-One; Osteomeg; Rocaltrol; Silkis; ***Pol.:*** Alfadiol; Calcijex; Devikap; Devisol; Juvit D ; Kalcytriol; Rocaltrol; Silkis; Vigantol; Vigantoletten; ***Port.:*** Calcijex; Dedrogyl; Etalpha; Rocaltrol; Silkis; Vigantol; Zemplar; ***Rus.:*** Alpha D3 (Альфа Д3-тев); Aquadetrim (Аквадетрим); Etalpha (Этальфа); Osteotriol (Остеотриол)†; Tachystin (Тахистин); Vigantol (Вигантол); ***S.Afr.:*** AT 10; One-Alpha; Rocaltrol; ***Singapore:*** Alpha D3; Bon-One; Bongreen†; Calcijex; One-Alpha; Rocaltrol†; Roical; Silkis; Zemplar; ***Spain:*** Calcijex; Etalpha; Hidroferol; Oseofort; Rocaltrol; Silkis; Zemplar; ***Swed.:*** Calcijex; Devitre†; Dygratyl; Etalpha; Rocaltrol; Zemplar; ***Switz.:*** AT 10; Bocatriol†; Calcijex; Rocaltrol; Silkis; Vi-De ; Zemplar; ***Thai.:*** Alpha D3; Bon-One; Calcit; Decostriol; Meditrol; One-Alpha; OsteoD; Rocaltrol; ***Turk.:*** Alpha D3; Calcijex; Devit-3; One-Alpha; Osteo-D; Rocaltrol; ***UK:*** AT 10; Calcijex; One-Alpha; Rocaltrol; Silkis; Zemplar; ***USA:*** Calciferol; Calcijex; Calderol; Delta-D; DHT; Drisdol; Hectorol; Hytakerol†; Maximum D3; Rocaltrol; Zemplar; ***Venez.:*** Alpha D3; Rocaltrol; Silkis; Zemplar.

Multi-ingredient: ***Arg.:*** A-D-C; AD Shock; Adermicina; Anartrit; Atomoderma A-D; Calcimax D3; Calcimax Magnesio; Calcio Cit; Calcio Masticable; Calcional D3; Calcium D†; Calnier-D; Caltrate + D; Cavirox; Cavirox Cit; Citramar D; Dermosan; Dr Selby; Femorel Max; Fosamax Plus; Full Calcio; Glossderm†; Magnesio Incaico; Ostram D3; Regenesis Max; Regucal D; Ribastamin Duo; Sinamida Cicatrizante†; Snella; Taxus; Ultracalcium D3; Vitapelen†; ***Austral.:*** Bio Magnesium; Caltrate + Vitamin D; Caltrate Plus; FAB Tri-Cal; Fosamax Plus; Prosteo†; Soy Forte with Black Cohosh†; ***Austria:*** Cacit mit Vitamin D ; Cal-D-or; Cal-D-Vita; Cal-De; Calcichew D ; Calcimagon-D3; Calcipot D ; Calcisan D; Calcium Plus; Calcium-D-Sandoz; Kombi-Kalz; Maxi-Kalz Vit D3; Oleovit A + D; Ruticalzon; ***Belg.:*** Cacit Vitamine D ; D-Vital; Fosavance; Newderm†; Sandoz Ca-D; Steovit D3; Topcal D3†; ***Braz.:*** AD-Til; ADE 2 (Adedois); Adecal; Adederme; Adeforte; Aderogil D3; Alendil Calcio D; Babymed; Calcifix B12; Calcifix Irradiado; Calcinol Complexo; Calcium D3; Calde; Caltrate + D; Caltrate + M; Cariderm†; Dermalisan; Dermoden; Gaduol†; Glossaliv; Hipoderme; Hipodermon; Hipodex; Hipoglos; Maxicalc-D; Miocalven D; Multiderme; Natecal D†; Os-Cal + D; Ossocal-D; OsteoNutri; Pronenen; Reposcal D; Sensibaby; Solemil†; Suavederm; Vitadesan; ***Canad.:*** A & D; A & D Ointment†; Antiseptic Skin Cream†; Cal D; Calburst†; Calcia; Calcite D; Calcium D; Calcium Magnesium Plus†; Caltrate Plus; Caltrate Select; Caltrate with Vitamin D; Mega Cal Calcium†; Neo Cal D; Nu Cal D; Nutrol A D; Os-Cal D; Viactiv; ***Chile:*** Aplical-D†; Brexon†; Cadevit; Calcefor D; Calcigran; Calcigran D; Calcimax D3; Calcio Day D†; Calcio Nil Forte†; Calciovit Puro; Calcium Forte D; Calcium-Sandoz + D; Calcium-Sandoz Forte D; Calcivorin D; Caldar-D; Caldeval; Caprimida D; Caprimida D Balance; Crevet Calcio + D3 + C; Dermaglos Plus†; Dical-D†; Elcal-D; Kaplus-D; Levucal D; Macrocal-D; Natecal D; Nenegloss; Oseofort; Osteocaps; Ostram D3; Pediaderm†; Platsul A; Pomada Vitaminica; Povin; Sanidecal-D; Sanoderm; Trical-D; ***Cz.:*** Adrovance; Calcichew D ; Caltrate Plus; Fosavance; Ideos; Infadolan; Kombi-Kalz; Osteocare; Vita-Calc†; Vitacalcin D†; ***Denm.:*** Calcichew D ; CaviD; Ideos†; ***Fin.:*** Calcichew D ; D-Calsor; Fosavance; Ideos; Kalcipos-D; Ostram-Vit D †; ***Fr.:*** Actonelcombi; Adrovance; Arthrolib; Cacit Vitamine D ; Calcidose Vitamine D; Calciforte Vitamin D ; Calciprat D ; Calcos Vitamine D ; Calperos D ; Caltrate Vitamine D ; Eptavit; Estrofort; Fixical Vitamine D ; Fluosterol; Fosavance; Frubiose Vitamine D†; Ideos; Metocalcium; Osseans D3; Osteocal D3; Ostram Vitamine D ; Zymaduo; ***Ger.:*** CalciAPS D3; Calcigen D; Calcilac KT; Calcimagon-D3; Calcimed D ; Calcium D ; Calcium Verla D; Calcium-D-Sandoz†; Calcium-dura Vit D ; Calcium-Sandoz D Osteo; Calcivit D; calcivitase†; D-Fluoretten; Fluor-Vigantoletten; Fosavance; Frubiase Calcium forte 500; Ideos; Ossofortin D; Ossofortin forte; Ossofortin Plus; Ossofortin†; Osspulvit D ; Osspulvit S†; Osteoplus; Ostocavid; Remicalcin + D ; Sandocal-D; Strafortin†; Zymafluor D; ***Gr.:*** Adrovance; Aquasol A+D; Cal+D; Calcidina; Calcioral D3; Calcium-D-Sandoz; Cald 3-Therapy; Caldesil; Calvidin; D-Calcium; Decal; Dioflam; Flavobion-C; Fosavance; Ideos; Natecal D3; Taminol; Videcalcio; ***Hong Kong:*** Calcichew D †; Calcioday-D; Calperos D ; Caltrate + D; Caltrate + Soy; Caltrate Plus; Citracal + D; Doctor's Choice Fortified Bone Support; Flavettes Cal D3; Fosamax Plus; Mega-Cal with Vit D; Os-Cal + D; Osteocare; ***Hung.:*** Actonel Trio; Calcichew D ; Calcisedron-D; Calcium-D-Sandoz; Calcivid; Caldea†; Fosavance; Ideos; Neogranormon; Osteocare; Vitacalc†; ***India:*** Alfacip Plus; Anemidox; Aristrol Forte†; Cafe-Kit†; Cal-Aid; Calcigen; Calcinol; Calcom; Calfa-Plus; Calmix†; Cipcal; Cipcal M; Incad; Kalzana; Kemicetine Antiozena; Logical; Macalvit; Milical; Milical-XP†; Minrosetc; Omilcal; Ossivite; Ostebon; Ostebon-M; Ostocalcium; Ostocalcium B-12; Sandocal with Vit D ; Sharkomalt; Sharkovit; Sigmacalvit; Styptocid; Trical-D; ***Indon.:*** Cal-95; Calc-Os; Calcidin; Calosbon; Calporosis D; Calsical; Cavit D3; CDR Fortos; Day-Cal; Dumocalcin Plus; Epocaldi; Fosamax Plus; Hi-Bone; Hical; Jointfit; Licokalk Plus; Menoxa; Osfit; Ossovit; Osteocal Plus; Osteocare; Osteopor; Scott's E Vita; Steopor; Vitacal-D; ***Irl.:*** Bio-Calcium + D ; Bio-Calcium + D + K; Calcichew D ; Calvidin; Chocovite; Decal; Fosavance; Ideos; Osteofos D3; ***Israel:*** Aquitol†; Baby A + D; Calcichew D ; Calcium Citrate; Caltrate + Vit D; Oleovit A + D †; Vitamidyne A and D; ***Ital.:*** AD Pabyrn; Adisterolo; Biocalcium D3; Cacit Vitamina D3; Cadtre; Calcicold3; Calcidon; Calciozim†; Calcium-D3-Sandoz; Calciumcafe; Calisvit; Calma D3; CalplusD3; Caltrate; Carbo D3; Cartago; Dicalcium†; Ditrevit; Ditrost; Effercal D3; Eurocal D3; Fitogen; Fosavance; Foscald3; Granoleina†; Ideos; Kalaz D3; Metocal Vitamina D; Natecal; Orotre; Osteofos D3; Ostram D ; Tonacal D3; Urtotre; ***Malaysia:*** Adult Citrex Cal-Mag-D3; Bio-Enhanced Calcium Plus; Calcioday-D†; Caltrate + D; Caltrate Plus; Citracal + D†; Dumocalcin†; Effcal; Fosamax Plus; Junior Citrex Cal-Mag-D3; Milical; Os-Cal + D†; Revital Calcium D3; Vitacal + D†; ***Mex.:*** Adekals; Adekon; Adekon C; Adeloren†; Adibal; Alfem; Aquasol AD; Caltrate + D; Caltrate + M; Caltrate + S; Caltrec†; Capent; Dical; Fosamax Plus; Minerbon; Os-Cal + D; Osteocalcio; Osteomin D; Posture D; Sandoz Calcium + D; Sutin†; Valmetrol-3; Vidamil; Vitalorange; ***Neth.:*** CaD; Calci-Chew D3; Calisvit; Halitran; Ideos; Sandoz Ca-D; ***Norw.:*** Calcigran; Ideos; Nycoplus Calcigran; ***NZ:*** Fosamax Plus; ***Philipp.:*** Agre-Calvit; Calciday; Caltrate Plus; Calvit; Esvical; Fosavance; Her Soy Plus; Osteo-4; Osteo-D; Osteocare; Vandol; ***Pol.:*** Alantavit; Calcium 500D; Calderin; Caltrate + Witamina D; Caltrate Plus; Ideos; Orocal D ; Ostowap D ; Tranvit; Vicalvit D; ***Port.:*** Bidiam; Cacit; Calcigenol; Calcior-D; Calcitab D; Calcium 600†; Calcium D; Calcium-D-Sandoz; Caltrate Plus Mastigavel†; Caltrate Plus†; Decalcit; Densical D; Dermabut; Fosavance; Ideos; Natecal D; Ostram D3†; Osvical; ***Rus.:*** Calcemin (Кальцемин); Calcemin Advance (Кальцемин Адванс); Calcium-D3 Nycomed (Кальций-Д3 Никомед); Ideos (Идеос); Natecal D (Натекаль Д); Vectrum Calcium (Вектрум Кальций); ***S.Afr.:*** Phytopause BSF; Vandol†; ***Singapore:*** BoneCare; Cal-D3†; Calcioday-D†; Calcium-D; Caltrate + Soy; Caltrate + Vit D; Caltrate Plus; Cavit-D3; Citracal + D; Dumocalcin; Effcal; Fosamax Plus; Glucocal; Os-Cal + D; Vitacal; Vitacal + D†; ***Spain:*** Adiod; Biominol A D; Calcial D; Calcio 20 Complex; Calcio 20 Fuerte; Calcio D; Calcium-Sandoz Forte D; Caosina D; Carbocal D; Cicatral; Cimascal D; Creacal†; Disnal; Fosavance; Grietalgen; Grietalgen Hidrocort†; Ibercal D; Ideos; Mastical D; Maxbon; Mencalisvit; Metafisol; Mitosyl; Natecal D; Osteomerck; Ostine; Osvical D; Redoxon Calciovit; Tepox Cal D; Trabex; Veriscal D; ***Swed.:*** AD-vitamin; Cal-D-Vita; Calcichew D ; Ideos; Kalcipos-D; ***Switz.:*** Cal-De†; Calcimagon-D3; Calcium D Sauter; Calcium-Sandoz D3; Calcivit; Calperos D ; Decalcit; Malvedrin; Osteocal D3; Phytopharma Calcium; Riccovitan†; ***Thai.:*** Bio-Calcium + D3 + K; Cal-D-Vita; Calcalcin; Calcioday-D†; Calcium D; Caldoxon; Caltab W/Vitamin D; Caltrate + D; Caltrate Plus; Calvin Plus; Combi-Cal†; Effcal; Fortica; Ostone-B12; Prima-Cal Plus Vit D; ***Turk.:*** Balya; Cal-D-Vita; Calcidine; Calcimax D3; Calcium-D-Sandoz; Caltrate; D-Flor; Folic Plus; Fosfokalsiyum; Kalsifluor; Nature Made Oyster Shell Calcium; Osteocare; ***UK:*** Actonel Combi; Adcal-D ; Cacit D3; Calceos; Calcichew D ; Calcium and Ergocalciferol Tablets; Calfovit D3; Caltrate Plus; Crampex; Fosavance; Haliborange Calcium Plus Vitamin D; Natecal D3; Osteo-Life; Osteocare; S.P.H.P.; ***USA:*** A and D Medicated; Calcarb with Vitamin D; Calcet; Calcium 600 + D; Calel-D; Caltrate + Iron & Vitamin D; Caltrate + Vitamin D; Caltrate Plus; Calvite P & D; Citracal + D; Citracal Creamy Bites†; Citracal Plus with Magnesium; Clocream; Desert Pure Calcium; Diaper Guard; Fosamax Plus; Fosteum; Lobana Derm-Aide; Lobana Peri-Garde; Os-Cal + D; Oyster Calcium with Vitamin D; Paladin; Posture-D; ***Venez.:*** A-D-Vit; Adaderm; Adenar; Brocalcio D3; Cal.Cell; Calcibon D; Calcibon D Magnesio; Calcibon D Soya; Calcibon Natal; Calcinor D; Calcio Ostelin; Calciofar D; Calciogenol; Calcion D Plus; Calcitrex D3; Calpal D†; Caltrate + D; Citracal D; Dicalcico†; Hipoglos†; Ideos; Kidcal; Maltocalcine; Oscal D; Vandol; Vitenol†.

Vitamin E Substances

Vitamina E.

ATC — A11HA03.

ATC Vet — QA11HA03.

NOTE. The food additive number E306 is used for tocopherols.

Vitamin E is a generic term applied to a large number of natural or synthetic compounds. The most important substances are the **tocopherols** of which **alpha tocopherols** are the most active and widely distributed in nature; other naturally occurring tocopherols include beta, gamma, and delta tocopherols, but these are not used in therapeutics. The other group of compounds with vitamin E activity are the tocotrienols.

Alpha tocopherols occur naturally in the *d* optical isomer form, which is more active than the synthetic racemic *dl* form; for further details concerning the comparative activities of the different forms and isomers of vitamin E compounds, see under Units, below.

d-Alpha Tocopherol

d-Alfa Tokoferol; (+)-Alpha-Tocopherol; *RRR*-alpha-Tocophérol; *RRR*-alpha-Tocopherolum; Natural Alpha Tocopherol; Natural α-Tocopherol; RRR-α-Tocopherolum; RRR-α-Tokoferol; D-α-Tocoferol; *RRR*-α-Tocopherol; *d*-α-Tocopherol; *RRR*-α-tocopherolum; *RRR*-α-tokoferol; *RRR*-α-Tokoferoli; *RRR*-α-Tokoferolis. (+)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.

$C_{29}H_{50}O_2$ = 430.7.

CAS — 59-02-9.

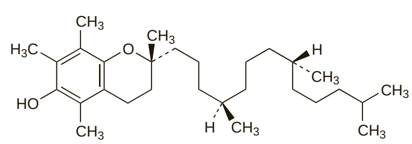

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (*RRR*-α-Tocopherol; *RRR*-Alpha-Tocopherol BP 2008). A clear, colourless, or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas in airtight containers. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

dl-Alpha Tocopherol

all-rac-α-Tokoferol; all-*rac*-α-Tocopherol; Alpha Tocopherol; (±)-Alpha-Tocopherol; E307; int-rac-α-Tocopherolum; int-*rac*-α-Tocopherolum; Synthetic Alpha Tocopherol; Synthetic α-Tocopherol; DL-α-Tocoferol; Tocoferolum Alfa; α-Tocopherol; *dl*-α-Tocopherol; α-Tocopherolum; α-Tokoferol; Tokoferol-alfa; tout-*rac*-α-Tocophérol; Visų racematų α-Tokoferolis. (±)-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol.

$C_{29}H_{50}O_2$ = 430.7.

CAS — 10191-41-0.

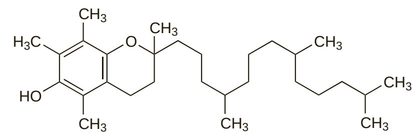

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (all-*rac*-α-Tocopherol; all-*rac*-Alpha Tocopherol BP 2008). A clear, colourless or yellowish-brown viscous oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in dichloromethane, and in fatty oils. Store under an inert gas. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is unstable to air and light, particularly in alkaline media. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store under an inert gas in airtight containers. Protect from light.

d-Alpha Tocoferil Acetate

d-Alpha Tocopheryl Acetate; (+)-Alpha-Tocopherol Acetate; (+)-Alpha-Tocopheryl Acetate; *RRR*-alpha-Tocophéryle, acétate de; *RRR*-alpha-Tocopherylis acetas; RRR-α-Tocopherylis acetas; RRR-α-Tokoferylu octan; D-α-Tocoferilo, acetato de; Tocoferoli Alfa *RRR* Acetas; *RRR*-α-Tocopheroli Acetas; *d*-α-Tocopheryl Acetate; *RRR*-α-Tocopheryl Acetate; *RRR*-α-Tocopherylis Acetas; *RRR*-α-Tokoferilio acetatas; *RRR*-α-Tokoferol-acetát; Tokoferol-acetát alfa *RRR*; Tokoferol-alfa-*RRR*-acetát; *RRR*-α-Tokoferylacetat; *RRR*-α-Tokoferyyliasetaatti. (+)-α-Tocopherol acetate.

$C_{31}H_{52}O_3$ = 472.7.

CAS — 58-95-7.

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (*RRR*-α-Tocopheryl Acetate; *RRR*-Alpha-Tocopheryl Acetate BP 2008). A clear, colourless or slightly greenish-yellow, viscous oily liquid. Practically insoluble in water; soluble in alcohol; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It may solidify in the cold. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acetate

dl-Alfa Tokoferil Asetat; all-rac-α-Tokoferylu octan; all-*rac*-α-Tocopheryl Acetate; Alpha Tocopheryl Acetate; *dl*-Alpha Tocopheryl Acetate; (±)-Alpha-Tocopherol acetate; int-rac-α-Tocopherylis acetas; int-*rac*-α-Tocopherylis Acetas; DL-α-Tocoferilo, acetato de; Tocoferoli Alfa Acetas; α-Tocopherol Acetate; α-Tocopheroli Acetas; *dl*-α-Tocopheryl Acetate; Tokoferol alfa-acetát; Tokoferolu octan; tout-*rac*-α-Tocophéryle, acétate de; Visų racematų α-Tokoferilio acetatas. (±)-α-Tocopherol acetate.

$C_{31}H_{52}O_3$ = 472.7.

CAS — 7695-91-2; 52225-20-4.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn. US* allows it under the title Vitamin E.

Eur. also has a monograph for the concentrated powdered form.

Ph. Eur. 6.2 (all-*rac*-α-Tocopheryl Acetate; all-*rac*-Alpha Tocopheryl Acetate BP 2008). A clear, colourless or slightly greenish-yellow, viscous, oily liquid. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in fatty oils. Protect from light.

Ph. Eur. 6.2 (α-Tocopheryl Acetate Concentrate (Powder Form); α-Tocopherylis Acetatis Pulvis; Alpha Tocopheryl Acetate Concentrate (Powder Form) BP 2008). It is prepared either by finely dispersing *dl*-alpha tocoferil acetate in a suitable carrier (e.g. gelatin, acacia, carbohydrates, lactoproteins, or a mixture of these) or by adsorbing *dl*-alpha tocoferil acetate on to silicic acid. The concentrate contains not less than 25% of *dl*-alpha tocoferil acetate. Almost white, yellowish, or light-brown small particles. Depending on the formulation, the powder may be practically insoluble in water or may swell or form a dispersion. Store in well-filled airtight containers. Protect from light.

USP 31 (Vitamin E). A clear, yellow, or greenish-yellow, practically odourless, viscous oil. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol; miscible with acetone, with chloroform, with ether, and with vegetable oils. Store in airtight containers. Protect from light.

d-Alpha Tocoferil Acid Succinate

d-Alpha Tocopheryl Acid Succinate; *d*-Alpha-Tocopherol acid succinate; *RRR*-alpha-Tocophéryle, hydrogénosuccinate de; *RRR*-alpha-Tocopherylis hydrogenosuccinas; D-α-Tocoferilo, succinato ácido; Tocoferoli Alfa *RRR* Hydrogenosuccinas; *RRR*-α-Tocopheroli Hydrogenosuccinas; *d*-α-Tocopheryl Acid Succinate; *RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-α-Tocopherylis Hydrogenosuccinas; *RRR*-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa-*RRR*-hydrogen-sukcinát; *RRR*-α-Tokoferol-hidrogén-szukcinát; *RRR*-α-Tokoferylvätesuccinat; *RRR*-α-Tokoferyylivetysuksinaatti. (+)-α-Tocopherol hydrogen succinate.

$C_{33}H_{54}O_5$ = 530.8.

CAS — 4345-03-3.

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

US also includes Vitamin E Polyethylene Glycol Succinate, a mixture formed by the esterification of *d*-alpha tocoferil acid succinate with a macrogol.

Ph. Eur. 6.2 (*RRR*-α-Tocopheryl Hydrogen Succinate; *RRR*-Alpha Tocopheryl Hydrogen Succinate BP 2008). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 31 (Vitamin E). A white, practically odourless, powder. M.p. about 75°; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

dl-Alpha Tocoferil Acid Succinate

dl-Alpha Tocopheryl Acid Succinate; Alpha Tocopheryl Hydrogen Succinate; DL-alpha-Tocophéryle, hydrogénosuccinate de; DL-alpha-Tocopherylis hydrogenosuccinas; DL-α-Tocoferilo, succinato ácido; Tocoferoli Alfa Hydrogenosuccinas; DL-α-Tocopheroli Hydrogenosuccinas; *dl*-α-Tocopheryl Acid Succinate; DL-α-Tocopheryl Hydrogen Succinate; DL-α-tocopherylis Hydrogenosuccinas; DL-α-Tokoferilio-vandenilio sukcinatas; Tokoferol-alfa hydrogen sukcinát; DL-α-tokoferol-hidrogén-szukcinát; DL-α-Tokoferylvätesuccinat; DL-α-Tokoferyylivetysuksinaatti. (±)-α-Tocopherol hydrogen succinate.

$C_{33}H_{54}O_5$ = 530.8.

CAS — 17407-37-3.

Pharmacopoeias. In *Eur.* (see p.vii). *US* allows it under the title Vitamin E.

Ph. Eur. 6.2 (DL-α-Tocopheryl Hydrogen Succinate; Alpha Tocopheryl Hydrogen Succinate BP 2008). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol and in acetone; very soluble in dichloromethane. Protect from light.

USP 31 (Vitamin E). A white, practically odourless, powder. M.p. about 70°; it is unstable when held molten. It is stable to air and light, but unstable to alkali. Insoluble in water; soluble in alcohol, in acetone, in ether, and in vegetable oils; very soluble in chloroform; slightly soluble in alkaline solution. Store in airtight containers. Protect from light.

Units

Though the potency of preparations of vitamin E is still sometimes expressed in units, the International Standard for vitamin E was discontinued in 1956. The International Unit was the activity contained in 1 mg of a standard preparation of *dl*-alpha-tocoferil acetate. Past editions of the USP have stated that in expressing vitamin E activity of tocopherol products, the following equivalents of 1 mg were to be used:

- *d*-alpha tocopherol, 1.49 units
- *dl*-alpha tocopherol, 1.1 units
- *d*-alpha tocoferil acetate, 1.36 units
- *dl*-alpha tocoferil acetate, 1 unit
- *d*-alpha tocoferil acid succinate, 1.21 units
- *dl*-alpha tocoferil acid succinate, 0.89 unit.

For dietary purposes, vitamin-E activity may now be expressed in terms of alpha tocopherol equivalents (α-TEs). One α-TE is the activity contained in:

- 1 mg of *d*-alpha tocopherol (natural alpha tocopherol; *RRR*-α-tocopherol)
- 1.4 mg *dl*-alpha tocopherol
- 1.1 mg *d*-alpha tocoferil acetate
- 1.5 mg *dl*-alpha tocoferil acetate
- 1.2 mg *d*-alpha tocoferil acid succinate
- 1.7 mg *dl*-alpha tocoferil acid succinate.

Adverse Effects and Precautions

Vitamin E is usually well tolerated. Large doses may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances, and have also been reported to cause blurred vision, dizziness, fatigue and weakness. Contact dermatitis has occurred after topical application.

Large doses of vitamin E have been reported to increase bleeding tendency in vitamin-K deficient patients such as those taking oral anticoagulants. However, it has also been suggested that it may increase the risk of thrombosis in some patients, such as those taking oestrogens. The clinical significance of these effects is not known.

A higher incidence of necrotising enterocolitis has been noted in premature infants weighing less than 1.5 kg treated with vitamin E.

Carcinogenicity. For mention of an *increased* incidence of second primary cancers and reduced cancer-free survival in patients with head and neck cancer receiving vitamin E (and betacarotene initially), see Prophylaxis of Malignant Neoplasms, p.1927.

Effects on mortality. While some studies of antioxidants, including vitamin E, have suggested beneficial effects on the progression of cardiovascular disease and cancer, other studies (including large randomised studies such as the Women's Health Study[1]) have shown little or no effect.[2] Vitamin E may even cause an increased risk of heart failure, or incidence of cancer (see Prophylaxis of Ischaemic Heart Disease, p.1926, and Prophylaxis of Malignant Neoplasms, p.1927). A meta-analysis[3] and a systematic review[4] of vitamin E supplementation found no benefit in terms of mortality. Another meta-analysis[5] found no effect for vitamin E supplementation on all-cause mortality overall. However, in dose-response analysis, high-dosage vitamin E (greater than 400 units daily) showed a significantly increased risk; there was some suggestion of a decreased risk with low doses (less than 400 units daily); all-cause mortality progressively increased for doses greater than 150 units daily. (Such an effect was not seen in the Women's Health Study, in which participants received 600 units on alternate days.) Some have commented[6] that the meta-analysis may not have isolated the effects of vitamin E, since in many of the trials studied, other nutritional supplements had been given, including betacarotene, itself possibly associated with an increased risk of death; however, the use of high-dose vitamin E was considered unjustified. A systematic review of antoxidant supplementation found that vitamin E, either singly or with other antioxidants, increased mortality.[7] A large cohort study in a population aged 65 years or older, after adjustment for age and sex, found that there was no association between vitamin E use and mortality. However, mortality was increased in vitamin E users who had a history of cardiovascular disease, or who were taking nitrates, warfarin, and diuretics. There was a consistent trend towards reduced mortality in vitamin E users without cardiovascular disease or taking these drugs. The authors concluded that vitamin E should be used with caution in those with cardiovascular disease, and that further investigation of the potential interaction between vitamin E and particular drugs was warranted.[8]

1. Lee I-M, *et al.* Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294:** 56–65.
2. Brown BG, Crowley J. Is there any hope for vitamin E? *JAMA* 2005; **293:** 1387–90.
3. Vivekananthan DP, *et al.* Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361:** 2017–23.
4. Shekelle PG, *et al.* Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med* 2004; **19:** 380–9.
5. Miller ER, *et al.* Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142:** 37–46.
6. Greenberg ER. Vitamin E supplements: good in theory, but is the theory good? *Ann Intern Med* 2005; **142:** 75–6.
7. Bjelakovic G, *et al.* Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 18/06/08).
8. Hayden KM, *et al.* Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med* 2007; **120:** 180–4.

Neonatal toxicity. For a review and discussion of liver and kidney toxicity in premature neonates associated with an intravenous preparation of vitamin E (E-Ferol) and attributed to the inclusion of polysorbates, see Effects in Infants, p.1919.

Interactions

Various drugs may interfere with the absorption of vitamin E including colestyramine, colestipol, and orlistat. High doses of vitamin E may increase the effects of oral anticoagulants.

Pharmacokinetics

Absorption of vitamin E from the gastrointestinal tract is dependent on the presence of bile and on normal pancreatic function. The amount of vitamin E absorbed varies widely between about 20% and 80% and appears to decrease as the dose is increased. It enters the blood via the chylomicrons in the lymph and is bound to beta lipoproteins. It is widely distributed to all tissues, and stored in adipose tissue. Some vitamin E is metabolised in the liver to glucuronides of tocopheronic acid and its γ-lactone. Some is excreted in the urine, but most of a dose is slowly excreted in the bile. Vitamin E appears in breast milk but is poorly transferred across the placenta.

Human Requirements

The daily requirement of vitamin E has not been clearly defined but is probably about 3 to 12 mg of *d*-alpha tocopherol or the equivalent of other vitamin E substances. Requirements increase with increased dietary amounts of polyunsaturated fatty acids. There appears to be no evidence that supplements are required in subjects on balanced diets.

Vitamin E is widely distributed in food. The richest sources are vegetable oils especially wheat-germ oil (p.2415), sunflower oil, and cottonseed oil; cereals and nuts are also good sources. Significant losses of vitamin E from food may occur during cooking and storage.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI—see p.1925) nor an estimated average requirement (EAR) has been set for vitamin E although daily intakes of 4 mg and 3 mg α-tocopherol equivalents (see under Units, above) were considered adequate for men and women, respectively.[1] The Expert Group on Vitamins and Minerals[2] have established a safe upper level (SUL) for vitamin E of 800 units or 540 mg of *d*-alpha tocopherol daily.

In the USA the recommended dietary allowance for adults is 15 mg daily of alpha tocopherol, and the tolerable upper intake level is 1000 mg daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41.* London: HMSO, 1991.
2. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 09/01/06)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington DC: National Academy Press, 2000. Also available at: http://www.nap.edu/openbook.php?isbn=0309069351 (accessed 21/07/08)

Uses and Administration

Vitamin E, a fat-soluble vitamin, prevents the oxidation of polyunsaturated fatty acids. It reacts with free radicals, which are the cause of oxidative damage to cell membranes, without the formation of another free radical in the process.

Vitamin E deficiency is rare but develops when the dietary intake is inadequate. In children with cystic fibrosis or biliary atresia, malabsorption of fat may lead to a vitamin E deficiency; deficiency may also occur in children with abnormalities of lipid transport, as in abetalipoproteinaemia. Low vitamin E concentrations are also found in premature, very low birth-weight infants. In previously healthy adults malabsorption and low intake of vitamin E must continue for a number of years before signs of deficiency appear. The major signs of vitamin E deficiency are the development of myopathic and neurological disorders.

Vitamin E is used in the treatment and prevention of vitamin E deficiency. It is usually given orally, generally the preferred route, but has also been given by intramuscular or intravenous routes. It may be given as *d*- or *dl*-alpha tocopherol or as the respective acetates or acid succinates.

Recommended doses vary, in part because of differences in the activity of different preparations; however, a daily dose of several times the recommended dietary allowance (RDA), or around 40 to 50 mg of *d*-alpha tocopherol, has been suggested for deficiency syndromes; somewhat higher daily doses have been given in cystic fibrosis (100 to 200 mg of *dl*-alpha tocoferil acetate, or about 67 to 135 mg of *d*-alpha tocopherol) and much higher daily doses in abetalipoproteinaemia (50 to 100 mg/kg of *dl*-alpha tocoferil acetate, or about 33 to 67 mg/kg *d*-alpha tocopherol).

Vitamin E has also been tried in retinopathy of prematurity and intraventricular haemorrhage in neonates (see Perinatal Disorders, below), and in many other disorders, for which the evidence of value is generally lacking (see Prophylaxis of Ischaemic Heart Disease, p.1926, and Prophylaxis of Malignant Neoplasms, p.1927).

Other substances with vitamin-E activity that have been used include *dl*-alpha tocoferil palmitate and tocofersolan (tocophersolan), a water-soluble substance which is *d*-alpha tocoferil acid succinate combined with a macrogol. Wheat-germ oil (p.2415) is also widely used as a source of vitamin E.

Vitamin E is often used as an antioxidant in pharmaceutical manufacturing.

◊ General reviews.

1. Meydani M. Vitamin E. *Lancet* 1995; **345:** 170–5.
2. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. *J Physiol Biochem* 2001; **57:** 43–56.
3. Brigelius-Flohé R, *et al.* The European perspective on vitamin E: current knowledge and future research. *Am J Clin Nutr* 2002; **76:** 703–16.
4. Dutta A, Dutta SK. Vitamin E and its role in the prevention of atherosclerosis and carcinogenesis: a review. *J Am Coll Nutr* 2003; **22:** 258–68.
5. Sung L, *et al.* Vitamin E: the evidence for multiple roles in cancer. *Nutr Cancer* 2003; **46:** 1–14.

Age-related macular degeneration. Dietary supplementation with antioxidants including vitamin E has been promoted for age-related macular degeneration. For further details, see under Betacarotene, p.1931.

Chemotherapy-induced toxicity. A small pilot study[1] found that oral vitamin E 600 mg daily given during chemotherapy and for 3 months afterwards reduced chemotherapy-induced neuropathy in patients given regimens based on platinum (carboplatin or cisplatin), or paclitaxel, or both. The authors considered that similarities exist between neuropathy induced by cisplatin (and possibly paclitaxel) and that seen in vitamin E deficiency states, (see below). Oral vitamin E 300 mg daily alleviated palmar-plantar erythrodysesthesia in 5 patients given capecitabine and docetaxel.[2] In 4 of these patients, chemotherapy was continued without interruption or dose reduction. Improvement was generally noticed after 7 to 10 days of treatment.

1. Argyriou AA, *et al.* Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005; **64:** 26–31.
2. Kara IO, *et al.* Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. *Breast* 2006; **15:** 414–24.

Deficiency states. Vitamin E deficiency may cause neurological damage characterised by sensory loss, ataxia and retinitis pigmentosa. In 2 patients with common variable immunodeficiency and an associated enteropathy, vitamin E deficiency developed. Treatment with intramuscular or oral vitamin E led to objective neurological improvement.[1]

1. Aslam A, *et al.* Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. *Clin Immunol* 2004; **112:** 24–9.

Dementia. A hypothesis that free radicals may initiate and maintain mechanisms responsible for neurodegeneration in Alzheimer's disease (p.362) has prompted the investigation of various drugs for antioxidant therapy.[1] Preliminary studies[1,2] have suggested that alpha tocopherol might possibly slow progression. A prospective cohort study found that self-administration of combined vitamin C and vitamin E was associated with a lower risk of vascular dementia in elderly men,[3] although no significant protective effect was seen against Alzheimer's disease. However, other studies have suggested that high intake of vitamins C and E, whether from diet[4] or supplements,[5] may reduce the risk of Alzheimer's disease. Yet another study suggested that dietary vitamin E, but not vitamin C, intake reduced the risk of Alzheimer's disease;[6] a population-based study found vitamin E intake from food and supplements to be associated with reduced cognitive decline.[7] US guidelines suggested[8] that vitamin E 1000 units twice daily by mouth be considered in patients with Alzheimer's disease in an attempt to slow progression of the disease. However, a large randomised trial in patients with amnestic mild cognitive impairment found that vitamin E 2000 units daily provided no benefit over placebo in terms of probability of progression to Alzheimer's disease.[9] Reviewers[10,11] have recommended against the use of vitamin E for Alzheimer's disease.

1. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs* 2004; **18:** 807–25.
2. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; **336:** 1216–22.
3. Masaki KH, *et al.* Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 2000; **54:** 1265–72.
4. Engelhart MJ, *et al.* Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002; **287:** 3223–9.
5. Zandi PP, *et al.* Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County study. *Arch Neurol* 2004; **61:** 82–8.
6. Morris MC, *et al.* Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002; **287:** 3230–7.
7. Morris MC, *et al.* Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002; **59:** 1125–32.
8. Doody RS, *et al.* Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56:** 1154–66. Also available at: http://www.neurology.org/cgi/reprint/56/9/1154.pdf (accessed 09/01/06)
9. Petersen RC, *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; **352:** 2379–88.
10. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.
11. Boothby LA, Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 2005; **39:** 2073–80.

Ischaemic heart disease. For a discussion of studies involving vitamin E in the prophylaxis of ischaemic heart disease, see p.1926.

Malignant neoplasms. For a discussion of studies involving vitamin E in the prophylaxis of malignant neoplasms, see p.1927.

Motor neurone disease. A prospective analysis found that regular use of vitamin E supplements was associated with a decreased risk of amyotrophic lateral sclerosis.[1] However, further studies were considered necessary and significant evidence to support the benefit of antioxidants in motor neurone disease (p.2380) is lacking.[2]

1. Ascherio A, *et al.* Vitamin E intake and risk of amyotrophic lateral sclerosis. *Ann Neurol* 2005; **57:** 104–10.
2. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 20/06/08).

Muscle spasm. Vitamin E is one of several drugs that have been tried in the management of nocturnal cramps (p.1887) but there is little convincing evidence to support its use.[1,2] It has, however, been found to have similar efficacy to quinine for haemodialysis-induced cramp (p.1671).[3] A small study found the combination of vitamins E and C to be more effective than either vitamin alone for reducing haemodialysis-induced cramps; prolonged use was not evaluated.[4]

1. Connolly PS, *et al.* Treatment of nocturnal leg cramps: a crossover trial of quinine vs vitamin E. *Arch Intern Med* 1992; **152:** 1877–80.
2. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
3. Roca AO, *et al.* Dialysis leg cramps: efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.
4. Khajehdehi P, *et al.* A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrol Dial Transplant* 2001; **16:** 1448–51.

Muscular dystrophies. Vitamin E substances have been used in some countries in the management of muscular dystrophies, but controlled studies[1] have failed to demonstrate any benefit.

1. Örndahl G, *et al.* Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy: a placebo-controlled study. *J Intern Med* 1994; **235:** 205–10.

Parkinsonism. Vitamin E has been tried (as *dl*-alpha tocopherol) in an attempt to slow neurodegeneration in patients with Parkinson's disease (p.791) but has proved ineffective.[1]

1. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

Perinatal disorders. The primary biological action of vitamin E is known to be the protection of polyunsaturated fatty acids, and thus membranes, from oxidation. Two disorders that may particularly affect premature and very low birth-weight infants are *retinopathy of prematurity* (below) and *intraventricular haemorrhage* (p.1050) and as both may have some association with the occurrence of excess oxygen or oxidant stress, there has been interest in the possibility that vitamin E might have a role in their prevention.

Pre-eclampsia. Although preliminary evidence has suggested[1] that women supplemented with vitamin E (with other supplements) may be at decreased risk of developing clinical pre-eclampsia (see Hypertension in Pregnancy, p.1171), large studies[2,3] in women given combined vitamin C and vitamin E supplements failed to show any benefit.

1. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/01/06).
2. Poston L, *et al.* Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006; **367:** 1145–54.
3. Rumbold AR, *et al.* ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006; **354:** 1796–1806.

Respiratory-tract infections. A randomised study in elderly patients found that supplementation with vitamin E had no effect on the incidence of lower respiratory-tract infections in elderly nursing home residents, although there was some suggestion of benefit from supplementation on upper respiratory-tract infections, particularly the common cold.[1] In contrast, another study found that, among elderly non-institutionalised people with an acute respiratory-tract infection, vitamin E supplementation increased illness duration, number of symptoms, frequency of fever, and restricted activity.[2]

1. Meydani SN, *et al.* Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004; **292:** 828–36. Correction. *ibid.*; 1305.
2. Graat JM, *et al.* Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002; **288:** 715–21.

Retinitis pigmentosa. Vitamin E has been tried in retinitis pigmentosa (p.1974) with conflicting results.

Retinopathy of prematurity. Retinopathy of prematurity (retrolental fibroplasia) is a disease associated with immature vascularisation of the retina. Formation of retinal lesions may interfere with normal development, resulting in neovascularisation and fibrovascular proliferation. Some cases regress spontaneously but advanced cases can lead to tractional retinal detachment and loss of vision. The pathogenesis of retinopathy of prematurity is not clearly understood, but is likely to be multifactorial;[1,2] greater immaturity, lower birth-weight, and male gender are associated with more severe disease.[3]

After the acknowledgement of a link between retinopathy of prematurity and oxygen therapy, the use of oxygen was reduced and the incidence of this disorder declined. A subsequent rise in incidence probably reflected the increased survival rate of extremely premature infants due to improved neonatal care, and certainly, variations in incidence between countries, or indeed areas, may reflect varying levels of available postnatal care.[2] Despite extensive research (see p.1690), a safe concentration of arterial oxygen has not been defined and antioxidants such as vitamin E have been used prophylactically for several decades. However, this use is controversial. Studies assessing the efficacy of vitamin E prophylaxis have not produced clear results.[4] Some considered that vitamin E prophylaxis had a beneficial effect and recommended[5] routine prophylaxis as soon as possible after birth for infants less than 1.5 kg. However, others feel that there is no data to support prophylaxis with vitamin E[4,6,7] and that antioxidants cannot be recommended for routine use.[1] The various studies have been re-evaluated by meta-analysis, the results of which suggest that vitamin E may reduce the incidence of stage 3+ retinopathy of prematurity,[8] a conclusion supported by a systematic review[9] which noted, however, that supplementation increased the risk of sepsis and could therefore not be recommended. The authors of the meta-analysis recommended that a well-controlled study should be conducted.[8] A systematic review of vitamin A supplementation in very low birth-weight infants concluded that vitamin A may reduce the incidence of retinopathy of prematurity, and that further investigation was warranted.[10]

Other agents tried for prophylaxis include penicillamine and antenatal dexamethasone, with some suggestion of benefit.[11,12] Reduction in ambient-light exposure did not alter the incidence of retinopathy of prematurity.[13,14] Inositol supplementation has also been tried, with conflicting results.[4]

1. Holmström G. Retinopathy of prematurity. *BMJ* 1993; **307:** 694–5.
2. Wheatley CM, *et al.* Retinopathy of prematurity: recent advances in our understanding. *Arch Dis Child Fetal Neonatal Ed* 2002; **87:** F78–F82.
3. Darlow BA, *et al.* Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics* 2005; **115:** 990–6.
4. Reynolds JD. The management of retinopathy of prematurity. *Paediatr Drugs* 2001; **3:** 263–72.
5. Johnson L, *et al.* Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. *J Pediatr* 1989; **114:** 827–38.
6. Law MR, *et al.* Is routine vitamin E administration justified in very low-birthweight infants? *Dev Med Child Neurol* 1990; **32:** 442–50.
7. Ehrenkranz RA. Vitamin E and retinopathy of prematurity: still controversial. *J Pediatr* 1989; **114:** 801–3.
8. Raju TNK, *et al.* Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr* 1997; **131:** 844–50.
9. Brion LP, *et al.* Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 20/06/08).
10. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/03/08).
11. Higgins RD, *et al.* Antenatal dexamethasone and decreased severity of retinopathy of prematurity. *Arch Ophthalmol* 1998; **116:** 601–5.

12. Phelps DL, *et al.* D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).
13. Reynolds JD, *et al.* Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998; **338:** 1572–6.
14. Phelps DL, Watts JL. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).

Tardive dyskinesia. Reviews[1,2] on the use of vitamin E in the management of antipsychotic-induced tardive dyskinesia (see under Extrapyramidal Disorders, p.971) concluded that evidence of benefit has generally come from small studies with methodological problems. One review[1] concluded that whereas vitamin E may protect against deterioration of tardive dyskinesia there was no evidence that it produced symptomatic improvement. It was suggested[2] that vitamin E therapy may be most beneficial in those patients with tardive dyskinesia of less than 5-years duration. Some recommend vitamin E as a treatment option in patients with newly diagnosed disease.[3] Further large-scale studies are required to establish its place in treatment.

1. Soares KVS, McGrath JJ. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 09/01/06).
2. Boomershine KH, *et al.* Vitamin E in the treatment of tardive dyskinesia. *Ann Pharmacother* 1999; **33:** 1195–1202.
3. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. *Ann Pharmacother* 2005; **39:** 2065–72.

Preparations

BP 2008: Alpha Tocopheryl Succinate Tablets;
USNF 26: Tocopherols Excipient;
USP 31: Vitamin E Capsules; Vitamin E Preparation.

Proprietary Preparations (details are given in Part 3)

Arg.: Antioxidante Natural; E-devit Protectora; Ephynal; Etec; Evion; Risordan†; Senexon E†; Tonovital E; ***Austral.:*** Bioglan Micelle E; Bioglan Natural E; Bioglan Water Soluble E; Chew-E; Dal-E; Macro E†; Mega E†; Vita E†; ***Austria:*** Avigilen; Ephynal; Etocomed; Evitol; Tocovenos; ***Belg.:*** Docviteee; Ephynal; Optovit E; ***Braz.:*** E Plus; E Radicaps; E-Mil†; E-Tabs; Efherol†; Ema-ma; Ephynal; Fonto-Vit E; Fort E; Teutovit-E; Vieta; Vita-E; Vitizin E; Zirvit E; ***Canad.:*** Aquasol E; Kyolic Formula 106; Novo E; Nutrol E; One A Day Cholesterol Health†; Organex†; ***Chile:*** Crevet-E; Egogyn; Etec; ***Cz.:*** Biogelat Vitamin E†; Erevit; Evit†; Sant-E-Gal†; ***Fin.:*** Bio-E-Vitamin; Equiday; Esol†; Ido-E; Tokovitan; Vita-E†; ***Fr.:*** Dermorelle; Ephynal†; Toco; Tocolion; Tocopa; ***Ger.:*** Antioxidans E; Biopto-E; Biosan E; Detulin; E-Mulsin†; E-Tonil; E-Vicotrat; Elex E; Embial†; Ephynal†; Eplonat; Eusovit; Evion; Flexal Vitamin E; Malton E; Mowivit; Optovit; Puncto E; Sanavitan S; Spondyvit; Tocorell; Tocovital; Togasan; Uno-Vit; Vibolex E; Vita-E; Vitagutt Vitamin E†; Vitazell E; ***Gr.:*** E-Vicotrat; Ephynal†; Eviol; ***Hong Kong:*** Clinic†; Keri Vit E; Myra 300-E; Natopherol; Topher-E; ***India:*** Ecap; EEE; Evion; Evitam; Greenpearl†; ***Indon.:*** Bio-E; Dalfarol; Edoti; Evion; Evipon; Lanturol; Natopherol; Natur-E; Naturol; Prima-E; Proxidan; Santa-E; Tocopherine; Vinpo-E; Vitaferol; ***Irl.:*** Ephynal†; ***Israel:*** Ephynal†; Evitex; Evitol; ***Ital.:*** E-Vitum; Ephynal; Evasen Crema; Evion; Natovit; Rigentex; Sursum; ***Malaysia:*** Citrex Vitamin E; E Vita†; Fairy ADE; Juvela†; Natopherol; Toco-E; ***Mex.:*** Bacferol†; E-Fertoc; Egrin; EPH; Eugerminol†; Ixopolet; Revitare E; Vit-E-Far; Vitalle†; ***Norw.:*** Bio-E-Vitamin; Ido-E; Nycoplus E; ***NZ:*** Micelle E; ***Philipp.:*** Enat; Enervon-E; Evion; Myra; Zyme E; ***Pol.:*** Dermovit E; Tokovit E; Vitole E; ***Port.:*** Ephynal; Ve; ***Rus.:*** Evitol (Эвитол); ***S.Afr.:*** Ephynal; Vitaforce E; ***Singapore:*** Myra 300-E; Natopherol; Naturee; ***Spain:*** Auxina E; Ephynal; ***Swed.:*** E-vidon; E-vimin; Ido-E; ***Switz.:*** ecobiosan; Ephynal; Evit; Lipo E†; Optovit; ***Thai.:*** Bio-E; E-Drops; ***Turk.:*** Eforol; Ephynal; Evicap; Evigen; Evon; Grandpherol; Natural E; Natural Wealth; ***UK:*** Ephynal; Prairie Gold; Vita-E; ***USA:*** Aqua-E; Aquasol E; Aquavit-E; E-Gems; Nutr-E-Sol; Vita-Plus E; Vitec; ***Venez.:*** Best; Ecogyn†; Egogyn; Ephynal†; Epol; Missecap; Nat-E; Vit-E-Nat; Vit-E-Var; Vitae; Viteral.

Multi-ingredient: ***Arg.:*** A-Vitel E; Abanta; Acilac; Atomoderma A-E; Brunavera; Cardiax; Cellskinlab C + E; Centella Asiatica Diates; Centella Asiatica Vital; Centellase de Centella Queen; Crema De Ordene; Culuflex H; Dermanova; E-devit; Epitheliale A-Derma; Estri-Atlas; Eurocolor Broncea-dor; Factor Vit AE; Lipofundin MCT/LCT-E; Liposomas; Nectar G; Oxidermos; Redudiet; SCV 300; Sigmafem; Snella; Snella Vag; Sojasterol†; Solenil Post Solar; Vansame; VNS 45; ***Austral.:*** Althaea Complex; Antioxidant Forte Tablets; Antioxidant Tablets; Arthriforte; Beta A-C; Bioglan Bioage Peripheral; Bioglan Micelle A plus E; Bioglan Primrose-E; Curash Baby Wipes; Curash Babycare; ER Cream†; Eye Health Herbal Plus Formula 4; Ginkgo Complex†; Hair and Skin Formula†; Lifechange Circulation Aid†; Lifesystem Herbal Plus Formula 5 Eye Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Macro Natural Vitamin E Cream; ML 20†; Sambucus Complex†; Serenoa Complex†; ***Austria:*** A-E-Mulsin; Arcavit A/E; Coldistop; Droxaryl; Gerogelat; Mamellin; Pasuma-Dragees; Regenerin†; Rovigon; Ulcurilen; Vasovitol; ***Belg.:*** Rovigon; ***Braz.:*** Adeforte; Licovit; ***Canad.:*** Bionagre plus E; Lubriderm Advanced Moisture†; PML Crono†; ***Chile:*** Dermaglos; Dermaglos Plus†; Rovigon; ***Cz.:*** A-E-Mulsin†; Coldastop; Dr Theiss Beinwell Salbe†; Fluocaril Bi-Fluore Vitamin E†; Lipovitan†; Vitazulen†; ***Fin.:*** Aesol; Cellavie†; ***Fr.:*** Alpha 5 DS†; Bakol; BiaZinc†; Bio-Selenium; Cicatryl; Cirkan a la Prednacinolone; Difrarel E; Ophtadil†; Phytolongbronze; Phytosolaire; Reti-Nat; Rovigon†; Seborheane; Tonimer; Topialyse; Topialyse Fluide; Topialyse Plus; ***Ger.:*** A + E Thilo†; A-E-Mulsin†; anabol-loges; Coldastop; Dynef†; Hewekzem novo N; Lipidavit; Lipovitan†; Magnesium Tonil mit Vitamin E; Magnesium-Plus-Hevert; Mapurit; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Protecor; Remederm; Rovigon G†; RubieMag + E†; Salus Herz-Schutz-Kapseln†; Saluscor Herz-Schutz; Tears Again; Ulcurilen N†; Unguentacid; Ureata S†; Vaso-E-Bion; ***Gr.:*** Avegon; Eviol-A; ***Hong Kong:*** Aderma Epitheliale†; Apaisac; Basikol; Difrarel E; Doctor's Choice Omega 3; DS Emulsion; E-Prime†; Eye Q; Pilelife; Pregnacare; Sanjukei Panax Ginseng; Welsan Lipocream; ***Hung.:*** Alksebor; Coldastop; Difrarel E; Magnevital; ***India:*** Cadvion; Elovera; Elovera-SPF; Rovigon†; Sclerobion; Seaking Plus†; Sofderm; Vitexid; ***Indon.:*** Fundamin-E; Garlic-Plus; Hepamax; Jointfit; Juvelon-C; Lanakeloid-E; Lapibion; Legreskin; Lesifit; Lycoq; Nervitone E; Remasal; RG-Q; Tocobion; Trimate-E; Velostin; Voldilex; ***Ital.:*** Angstrom Viso; Apogeo; Babysteril; Capill; Colesterase; Coqun; Derman-Oil; Dermana Crema; Dermana Pasta; Ecamannan; Efagel; Emortrofine; Ener-E†; Eurogel; Forticrin; Granoleina†; Ictom 3†; Midium; Migel; Mirtilene; Pasta Dicofarm; Provitamin A-E; Retinovit; Rovigon; Royal E; Rutisan CE†; Skarflex; Tannidin Plus; Tocalfa; Ultravisin; Vasopt; Vit Eparin; ***Malaysia:*** Balance Elastin E†; Boots Antenatal Massage Cream†; Elovera; Natopherol Dermal-Day†; Prim E; Salonpas; Tocovid; ***Mex.:*** Aveendix; Cardioprotect; Cetopic; Emolin Neo; Hipoglos Cremoso; Nutrem; Panaline†; Periodentyl; ***Neth.:*** Dagravit A-E Forte†; ***NZ:*** Chap Stick; ***Philipp.:*** Elovera; Hinuron-E; Neuroforte-E; Nuron-E; Pynocare 40 Actisome; Remederm; Rovigon; ***Pol.:*** Capivit A + E; Dehalid†; Lecytyna E; MBE; Tokovit A + E; ***Port.:*** Alkagin; Antiestrias; Creme Laser Hidrante; Esclerobion; Nutraisdin; Rilastil Dermo Solar; Rovigon; Synchrorose; Synchrovit; Zolium†; ***Singapore:*** Desitin Creamy†; E-Prime; Erase; ***Spain:*** Auxina A + E; Vitaber A E; Wobenzimal†; ***Switz.:*** Alphastria; Coldistop; Leniderm†; Oravil; Rovigon; Visaline; ***Thai.:*** Men Hormone; Siduol; ***UK:*** Octacosanol; Se-Power; ***USA:*** Aloe Grande; Diaper Guard; Lactinol-E; Lazercreme; Lobana Derm-Aide; Lobana Peri-Garde; Phicon; Tucks; Wound Cleanser; Ze Caps†; ***Venez.:*** Ademina; Kalsis.

Vitamin K Substances

Vitamina K.

The term vitamin K is used for a range of naphthoquinone compounds that includes: acetomenaphthone, menadiol, menadione, menatetrenone, and phytomenadione.

Acetomenaphthone *(BAN)*

Acetomenadione; Acetomenaftona; Acetomenaph.; Menadiol Diacetate; Vitamin K_4 Diacetate. 2-Methyl-1,4-naphthylene diacetate.

$C_{15}H_{14}O_4$ = 258.3.
CAS — 573-20-6.

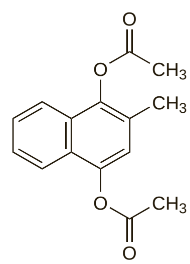

Pharmacopoeias. In *Chin.*

Menadiol Sodium Phosphate *(BANM)*

Menadiol, fosfato sódico de; Menadiol Sodium Diphosphate; Menadiolum Solubile; Vitamin K_4 Sodium Phosphate. 2-Methylnaphthalene-1,4-diyl bis(disodium phosphate) hexahydrate.

$C_{11}H_8Na_4O_8P_2,6H_2O$ = 530.2.
CAS — 481-85-6 (menadiol); 131-13-5 (anhydrous menadiol sodium phosphate); 6700-42-1 (menadiol sodium phosphate hexahydrate); 84-98-0 (menadiol diphosphate).

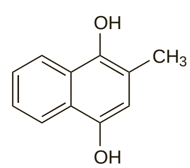

(menadiol)

NOTE. Menadiol Potassium Sulfate (Potassium Menaphthosulfate) is *BAN* and Menadiol Sodium Sulfate is *rINN.*

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Menadiol Sodium Phosphate). A white to pink, hygroscopic, crystalline powder with a characteristic odour. Very soluble in water; practically insoluble in alcohol.

USP 31 (Menadiol Sodium Diphosphate). A white to pink, hygroscopic, powder having a characteristic odour. Very soluble in water; insoluble in alcohol. Its solutions in water are neutral or slightly alkaline to litmus having a pH of about 8. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Menadione *(BAN)*

Menadion; Menadiona; Menadionas; Ménadione; Menadioni; Menadionum; Menaph.; Menaphthene; Menaphthone; Methylnaphthochinonum; Vitamin K_3. 2-Methyl-1,4-naphthoquinone.

$C_{11}H_8O_2$ = 172.2.
CAS — 58-27-5.
ATC — B02BA02.
ATC Vet — QB02BA02.

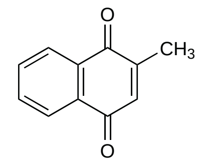

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Menadione). A pale yellow crystalline powder. It is unstable in light. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in toluene. Protect from light.

USP 31 (Menadione). A bright yellow, practically odourless, crystalline powder. It is affected by sunlight. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 50 of vegetable oils, and 1 in 10 of benzene; sparingly soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Handling. Menadione powder is irritating to the respiratory tract and to the skin. The alcoholic solution has vesicant properties.

Menadione Sodium Bisulfite *(rINN)*

Bisulfito sódico de menadiona; Kavitanum; Menadiol Sodyum Bisülfit; Ménadione, Bisulfite Sodique de; Menadione Sodium Bisulphite *(BANM)*; Menadioni Natrii Bisulfis; Menadioninatriumbisulfiitti; Menadionnatriumbisulfit; Menadionu wodorosiarczyn sodowy; Menaph. Sod. Bisulphite; Menaphthone Sodium Bisulphite; Methylnaphthochinonumnatrium Bisulfurosum; Vikasolum; Vitamin K_3 Sodium Bisulphite. Sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxonaphthalene-2-sulphonate trihydrate.

Менадиона Натрия Бисульфит

$C_{11}H_8O_2NaHSO_3,3H_2O$ = 330.3.
CAS — 130-37-0 (anhydrous menadione sodium bisulfite); 6147-37-1 (menadione sodium bisulfite trihydrate).

Pharmacopoeias. In *Chin.* and *Pol.*

Menatetrenone *(rINN)*

E-3100; Ea-0167; Menaquinone-4; Menaquinone 4; Menaquinone K4; Menatetren; Menatetrenona; Ménatétrénone; Menatetrenonum; MK-4; Vitamin $K_{2(20)}$; Vitamin MK 4. 2-Methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadeca-tetraenyl)-1,4-naphthoquinone.

Менатетренон

$C_{31}H_{40}O_2$ = 444.6.
CAS — 863-61-6.

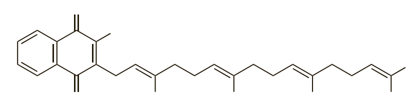

Pharmacopoeias. In *Jpn.*

Phytomenadione *(BAN, rINN)*

Fitomenadion; Fitomenadiona; Fitomenadionas; Fytomenadion; Fytomenadioni; Methylphytylnaphthochinonum; Phylloquinone; Phytomenad.; Phytoménadione; Phytomenadionum; Phytonadione; Vitamin K_1. 2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione.

Фитоменадион

$C_{31}H_{46}O_2$ = 450.7.
CAS — 84-80-0.
ATC — B02BA01.
ATC Vet — QB02BA01.

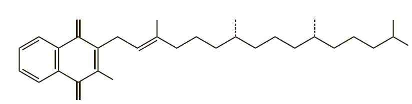

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Phytomenadione). A mixture of the *trans* (*E*) and *cis* (*Z*) isomers. It contains not less than 75% of *trans*-phytomenadione, and also allows not more than 4% of *trans*-epoxyphytomenadione.

A clear, intense yellow, viscous, oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils. Protect from light.

USP 31 (Phytonadione). A mixture of the *E* and *Z* isomers. It contains not more than 21% of the *Z* isomer. A clear, yellow to amber, very viscous, odourless or practically odourless, liquid. It is stable in air, but decomposes on exposure to sunlight. Insoluble in water; slightly soluble in alcohol; soluble in dehydrated alcohol, in chloroform, in ether, in vegetable oils, and in benzene. Store in airtight containers. Protect from light.

Stability. A polyoxyl castor oil formulation of phytomenadione was stable for at least 30 days at room temperature when repackaged in amber glass dropper bottles.[1] When refrigerated at 4° to 8°, it was stable in both plastic and amber glass bottles.

1. Wong VK, Ho PC. Stability of Konakion repacked in dropper bottles for oral administration. *Aust J Hosp Pharm* 1996; **26:** 641–4.

Adverse Effects and Precautions

Intravenous doses of *phytomenadione* have caused severe reactions resembling hypersensitivity or anaphylaxis. Symptoms have included facial flushing, sweating, chest constriction and chest pain, dyspnoea, cyanosis, and cardiovascular collapse; fatalities have been reported. Anaphylactic reactions have generally been associated with an overly rapid rate of infusion but have also been reported even when the solution was diluted and infused slowly. They are generally thought to be due to polyoxyl castor oil which is present as a surfactant in some parenteral formulations; reports of such reactions with formulations that do not contain polyoxyl castor oil are rare (but see Hypersensitivity, below).

Pain, swelling, and phlebitis may occur at the injection site when phytomenadione is given. Localised skin reactions including atrophy or necrosis have been reported after intramuscular or subcutaneous injection of phytomenadione.

Phytomenadione formulations solubilised with lecithin and a bile salt should be given with caution to patients with severely impaired liver function and to premature neonates weighing less than 2.5 kg, since the bile salt may displace bilirubin.

Giving *menadione* and *menadiol sodium phosphate* to neonates, especially premature infants, or to the mother during late pregnancy has been associated with the development in the infant of haemolytic anaemia, hyperbilirubinaemia, and kernicterus, and such use is not recommended. Phytomenadione has a lower risk of haemolysis. Menadione and menadiol sodium phosphate have also been reported to cause haemolysis in patients with G6PD deficiency or vitamin E deficiency.

Breast feeding. Vitamin K is variably distributed into breast milk; a study found phytomenadione concentrations in the first 10 mL of expressed milk ("fore milk") to be lower than those in the last 10 mL ("hind milk"). These changes may be related to the lipid concentration, which is higher in hind milk. Lipid composition also changes over the course of lactation, with pronounced changes in the first week, and the authors proposed that a mechanism exists whereby vitamin K concentration in milk is higher in the first few days of life so as to meet the neonate's nutritional requirements at a time when vitamin K status is precarious.[1] The American Academy of Pediatrics considers[2] that, as no adverse effects have been seen in breast-fed infants whose mothers were receiving phytomenadione, its use is therefore usually compatible with breast feeding.

1. von Kries R, *et al.* Vitamin K content of maternal milk: influence of the stage of lactation, lipid composition, and vitamin K supplements given to the mother. *Pediatr Res* 1987; **22:** 513–17.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 09/01/06)

Carcinogenicity. A case-control study from the UK[1] suggested an increased risk of cancer in children who had received vitamin K at birth for the prevention of vitamin K deficiency bleeding (see below). A further study[2] by the same authors indicated that this risk was associated with intramuscular, but not oral, dosage, and was strongest for childhood leukaemia. In response to these data, the British Paediatric Association recommended that the oral route should be preferred for prophylaxis,[3] whereas the American Academy of Pediatrics continued to advocate the intramuscular route,[4] and still does so, concluding there is no association between this route and childhood leukaemia or other cancers.[5]

Subsequent studies from the USA,[6] Sweden,[7] Denmark,[7,8] Germany,[9] and England[10] did not confirm an increased risk of childhood cancer, including leukaemias, after the use of intramuscular vitamin K. More recently, 4 further studies were published.[11-14] Two of these, a case-control study in Scotland[11] and an ecological study in Britain,[12] showed no increased risk of any cancers with the use of intramuscular vitamin K. A third case-control study in England and Wales[13] found a borderline association between intramuscular vitamin K and cancers, particularly leukaemia. In the fourth study, a case-control study in northern England,[14] there was an increased risk (odds ratio 1.79) of acute lymphoblastic leukaemia developing 1 to 6 years after birth in children who had received intramuscular vitamin K. In 1998 a review[15] by an expert working group of the UK CSM concluded that there was no increased risk of solid tumours with vitamin K, and that, although an increased risk of leukaemia could not be excluded, observed results were compatible with chance. Moreover, they could not identify a plausible mechanism for a carcinogenic effect of vitamin K. Since then, a pooled analysis of case-control studies in Great Britain and Germany[16] found no convincing evidence that vitamin K given intramuscularly was associated with childhood leukaemia. A national case-control study in the UK[17] concluded there was no evidence that vitamin K, irrespective of the route, influenced the risk of children developing leukaemia or any other cancer. If there is any increased risk, it is likely to manifest only in a very small subpopulation who are at high risk for some as-yet-unidentified biological reason.[18] The UK Department of Health[19] advocates either oral or intramuscular prophylaxis, and recommends that the parents should be involved in the decision on which route is used.

1. Golding J, *et al.* Factors associated with childhood cancer in a national cohort study. *Br J Cancer* 1990; **62:** 304–8.
2. Golding J, *et al.* Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992; **305:** 341–6.
3. British Paediatric Association. *Vitamin K prophylaxis in infancy.* London, 1992: British Paediatric Association.
4. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–3.
5. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2.
6. Klebanoff MA, *et al.* The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993; **329:** 905–8.
7. Ekelund H, *et al.* Administration of vitamin K to newborn infants and childhood cancer. *BMJ* 1993; **307:** 89–91.
8. Olsen JH, *et al.* Vitamin K regimens and incidence of childhood cancer in Denmark. *BMJ* 1994; **308:** 895–6.
9. von Kries R, *et al.* Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. *BMJ* 1996; **313:** 199–203.
10. Ansell P, *et al.* Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. *BMJ* 1996; **313:** 204–5.
11. McKinney PA, *et al.* Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. *BMJ* 1998; **316:** 173–7.
12. Passmore SJ, *et al.* Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. *BMJ* 1998; **316:** 184–9.
13. Passmore SJ, *et al.* Case-control studies of relation between childhood cancer and neonatal vitamin K administration. *BMJ* 1998; **316:** 178–184.
14. Parker L, *et al.* Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study. *BMJ* 1998; **316:** 189–93.
15. Committee on Safety of Medicines/Medicines Control Agency. Safety of intramuscular vitamin K (Konakion). *Current Problems* 1998; **24:** 3–4. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 21/07/08)
16. Roman E, *et al.* Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *Br J Cancer* 2002; **86:** 63–9.
17. Fear NT, *et al.* Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003; **89:** 1228–31.
18. Ross JA, Davies SM. Vitamin K prophylaxis and childhood cancer. *Med Pediatr Oncol* 2000; **34:** 434–7.
19. Department of Health. *Vitamin K for newborn babies.* London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=7634&Rendition=Web (accessed 21/07/08)

Effects on the blood. Cerebral arterial thrombosis developed in 2 patients with malabsorption syndromes due to coeliac disease during treatment with vitamin K for severe deficiency of vitamin-K-dependent coagulation factors. An increased tendency to thrombotic events had previously been reported to be present in patients with intestinal inflammatory disorders. It was suggested that if bleeding did occur in such patients treatment should be with plasma infusions or small doses of vitamin K but that vitamin K deficiency should not be specifically treated since a gluten-free diet or corticosteroids given for the gastrointestinal disorder will result in a gradual correction.[1]

1. Florholmen J, *et al.* Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. *BMJ* 1980; **281:** 541.

Hypersensitivity. Hypersensitivity reactions have been reported after subcutaneous,[1-3] intramuscular,[4] intravenous,[5-7] and oral[7] use of vitamin K, although the incidence is low.[6,7]

Subcutaneous doses are considered to pose less risk of **anaphylaxis** than the intravenous route;[5] fatalities have been reported with intravenous use,[7] even after low doses, given slowly, and by dilute infusion.[5,7] There has also been a fatality associated with oral use.[7] While anaphylactoid reactions have been attributed to the polyoxyl castor oil vehicle,[6,7] a direct immune mechanism has also been proposed.[7]

Vitamin K itself appears to be the antigen causing adverse **cutaneous reactions**.[3] Two types of cutaneous reactions have been described: pruritic, erythematous, eczematous plaques usually occurring up to 2 weeks after a dose, and sclerodermoid morphea-like plaques, with or without eczema, which may be delayed.[1,3,4] In addition, there have been rare reports of diffuse maculopapular eruption, but the relationship of this reaction to vitamin K use has been questioned.[3] Despite reports that the eczematous reactions resolve faster than the sclerodermatous reactions,[1] persistent eczema[4] or pruritus has occurred.[3]

Treatment has been largely symptomatic; topical and systemic corticosteroids and antihistamines have been used.[1,3,4] For patients who have previously reacted to phytomenadione injections, the use of menadione either by injection or by mouth has been suggested;[3] cross-reactivity was not anticipated to be a problem. However, cross-reactions on patch testing have been reported.[4] It has been suggested that reactions to vitamin K in patients might signify underlying hepatic disease,[1] although others believe the condition is seen more frequently in patients with liver disease since they are often those requiring vitamin K.[3]

1. Gettler SL, Fung MA. Indurated plaques on the arms of a 52-year-old man. *Arch Dermatol* 2001; **137:** 957–62.
2. Bui L, *et al.* Skin reaction to subcutaneous phytonadione injections. *Am J Health-Syst Pharm* 2004; **61:** 407.
3. Wilkins K, *et al.* Cutaneous reactions associated with vitamin K . *J Cutan Med Surg* 2000; **4:** 163–7.
4. Sommer S, *et al.* Type IV hypersensitivity to vitamin K. *Contact Dermatitis* 2002; **46:** 94–6.
5. Wjasow C, McNamara R. Anaphylaxis after low dose intravenous vitamin K. *J Emerg Med* 2003; **24:** 169–72.
6. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K): a 5-year retrospective review. *Ann Allergy Asthma Immunol* 2002; **89:** 400–406.
7. Fiore LD, *et al.* Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001; **11:** 175–83.

Overdosage. UK licensed product information states that, while there is no known clinical syndrome attributable to hypervitaminosis of phytomenadione, adverse effects have been reported after overdose in neonates and infants. These include jaundice, hyperbilirubinaemia, increases in liver enzyme values, abdominal pain, constipation, soft stools, malaise, agitation, and skin eruptions. Most adverse events were not considered to be serious, and resolved without any treatment.

Interactions

Vitamin K decreases the effects of oral anticoagulants (see p.1432), and is used to counteract excessive effects of these drugs, see Uses and Administration, below. Vitamin K may reduce the response to resumed therapy with anticoagulants for a week or more.

Pharmacokinetics

The fat-soluble vitamin K compounds phytomenadione and menadione require the presence of bile for their absorption from the gastrointestinal tract; the water-soluble derivatives can be absorbed in the absence of bile. Vitamin K accumulates mainly in the liver but is stored in the body only for short periods of time. Vitamin K does not appear to cross the placenta readily and it is variably distributed into breast milk. Phytomenadione is rapidly metabolised to more polar metabolites and is excreted in bile and urine as glucuronide and sulfate conjugates.

Absorption. Absorption of phytomenadione from the colloidal (micellar) preparation was more irregular and unpredictable after intramuscular than intravenous dosage in healthy adults;[1] when used as an antidote to anticoagulant, this formulation should be given intravenously. In neonates, plasma phytomenadione concentrations were within or above the adult fasting plasma range 24 days after receiving a single dose of the colloidal preparation either orally (3 mg) or intramuscularly (1.5 mg).[2]

1. Soedirman JR, *et al.* Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K) mixed micelles formulation. *Br J Clin Pharmacol* 1996; **41:** 517–23.
2. Schubiger G, *et al.* Vitamin K concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. *J Pediatr Gastroenterol Nutr* 1993; **16:** 435–9.

Human Requirements

The minimum daily requirements of vitamin K are not clearly defined but an intake of about 1 microgram/kg daily appears to be adequate. Vitamin K requirements in normal adults can be met from the average diet and from the synthesis of menaquinones (also known as vitamin K_2) by bacterial action in the intestine. Vitamin K occurs naturally as phytomenadione (vitamin K_1), which is present in many foods, especially leafy green vegetables such as cabbage and spinach, and is also present in avocado, meat, cow's milk, egg-yolk, and some cereals.

UK and US recommended dietary intake. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR—see p.1925) has been set for vitamin K although an intake of 1 microgram/kg daily was considered to be both safe and adequate for adults; a higher intake of 10 micrograms daily (about 2 micrograms/kg daily) was believed to be justified in infants because of the absence of hepatic menaquinones in early life and reliance on dietary vitamin K alone. It was stated that all babies should receive prophylactic vitamin K at birth[1] and for further details concerning neonatal use, see Vitamin K Deficiency Bleeding, below.

In the USA, adequate intake levels have been determined to be 120 micrograms daily for adult men and 90 micrograms daily for adult women.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)

Uses and Administration

Vitamin K is an essential cofactor in the hepatic synthesis of prothrombin (factor II) and other blood clotting factors (factors VII, IX, and X, and proteins C and S) and in the function of proteins such as osteocalcin important for bone development.

Vitamin K deficiency may develop in neonates, but is uncommon in adults, although it may occur in patients with malabsorption syndromes, obstructive jaundice or hepatic disease. Deficiency leads to the development of hypoprothrombinaemia, in which the clotting time of the blood is prolonged and spontaneous bleeding can occur. Coumarin anticoagulants interfere with vitamin K metabolism, and their effects can be antagonised by giving vitamin K.

Vitamin K compounds are used in the treatment and prevention of haemorrhage associated with vitamin K deficiency. The dose of vitamin K should be carefully controlled by prothrombin-time estimations.

Phytomenadione is a naturally occurring vitamin K substance. It is the only vitamin K compound used to reverse hypoprothrombinaemia and haemorrhage caused by anticoagulant therapy. It is not effective as a heparin antidote. For **over-anticoagulation**, the dose depends on the international normalised ratio (INR) and the degree of haemorrhage. Typical doses of phytomenadione are 0.5 to 5 mg by slow intravenous injection or up to 5 mg orally (see also Over-anticoagulation, below). Depending on the solubilising agents used, some formulations of phytomenadione are more suitable for intravenous use than others, and dosage details vary. Phytomenadione has also been used in hypoprothrombinaemia due to certain cephalosporins (see Cefamandole, Adverse Effects, p.221).

In the treatment of **vitamin K deficiency bleeding** in neonates, phytomenadione may be given in a dose of 1 mg intravenously, subcutaneously, or intramuscularly; further doses may be given if necessary. As a prophylactic measure, a single dose of 0.5 to 1 mg may be given intramuscularly to the newborn infant, or 2 mg orally followed by a second dose of 2 mg after 4 to 7 days; for further details see below.

Menadiol sodium phosphate is a water-soluble derivative of menadione, a synthetic lipid-soluble vitamin K analogue. It may be used for the prevention of vitamin K deficiency in patients with malabsorption syndromes in whom oral phytomenadione may be inefficiently absorbed. It is given in usual doses equivalent to 10 to 40 mg of menadiol phosphate daily by mouth.

Menadiol dibutyrate has also been used; menatetrenone is used in the management of osteoporosis. Acetomenaphthone has been used in preparations promoted for the relief of chilblains.

◊ General reviews.

1. Shearer MJ. Vitamin K. *Lancet* 1995; **345:** 229–34.
2. Vermeer C, Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. *Hematol Oncol Clin North Am* 2000; **14:** 339–53.
3. Vermeer C, *et al.* Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. *Eur J Nutr* 2004; **43:** 325–35.

Action. References to the action of vitamin K and the role of vitamin K-dependent coagulation proteins and carboxyglutamate-containing proteins such as osteocalcin.

1. Friedman PA. Vitamin K-dependent proteins. *N Engl J Med* 1984; **310:** 1458–60.
2. Rick ME. Protein C and protein S: vitamin K-dependent inhibitors of blood coagulation. *JAMA* 1990; **263:** 701–3.
3. Nelsestuen GL, *et al.* Vitamin K-dependent proteins. *Vitam Horm* 2000; **58:** 355–89.
4. Saxena SP, *et al.* Novel vitamin K-dependent pathways regulating cell survival. *Apoptosis* 2001; **6:** 57–68.

Malignant neoplasms. In a small study in women with viral cirrhosis of the liver to establish the effects of vitamin K on bone loss, those given menatetrenone were found to have a lower incidence of hepatocellular carcinoma; larger controlled studies were advocated, with prevention of carcinoma by menatetrenone as a primary end-point.[1] Another study[2] reported reduced recurrence of hepatocellular carcinoma in patients given menatetrenone.

1. Habu D, *et al.* Role of vitamin K in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; **292:** 358–61.
2. Mizuta T, Ozaki I. Hepatocellular carcinoma and vitamin K. *Vitam Horm* 2008; **78:** 435–42.

Neonatal intraventricular haemorrhage. Vitamin K crosses the placenta slowly and to a limited extent, but sufficiently so to warrant studies to assess whether giving phytomenadione to the mother can reduce the incidence or severity of intraventricular haemorrhage (p.1050) in the preterm neonate. Studies have shown conflicting results. A systematic review concluded that vitamin K given to the mother before birth did not significantly prevent periventricular haemorrhage, and could not be recommended for routine clinical use.[1]

1. Crowther CA, Henderson-Smart DJ. Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/01/06).

Osteoporosis. The effects of vitamin K on bone, and its role in osteoporosis (p.1084) have been reviewed.[1-3] It is widely prescribed for the management of osteoporosis in Japan.[3] A reduced risk of vertebral[4] and nonvertebral[5] fracture has been reported from 2 studies in postmenopausal women given menatetrenone 45 mg daily by mouth. Vitamin K_2 (menaquinones such as menatetrenone) appears to have more marked effects on bone than vitamin K_1 (phytomenadione).[3] A systematic review[6] to assess whether vitamin K supplementation can reduce bone loss and prevent fractures identified 13 studies with data on bone loss; 7 reported fracture data. Most studies were conducted in Japan among postmenopausal women. Vitamin K supplements increased bone mineral density (BMD) in all but 1 study. Meta-analyses of the 7 studies with fracture data showed a reduced fracture incidence with menatetrenone supplementation, especially at the hip. The authors advised caution in interpretation of the data, since the studies were not designed to show fracture effects, and quality of many of the trials was poor. In addition, dietary differences in Japan might confound findings. While patients at risk of fracture should be encouraged to consume a diet high in vitamin K, routine supplementation is not justified until these results can be confirmed in a large randomised study with fracture as a primary outcome.

1. Iwamoto J, *et al.* Effects of vitamin K2 on osteoporosis. *Curr Pharm Des* 2004; **10:** 2557–76.
2. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health-Syst Pharm* 2005; **62:** 1574–81.
3. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. *Altern Med Rev* 2005; **10:** 24–35.
4. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *Am J Med* 2004; **117:** 549–55.
5. Sato Y, *et al.* Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. *Bone* 2005; **36:** 61–8.
6. Cockayne S, *et al.* Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 1256–61.

Over-anticoagulation. Doses of vitamin K for over-anticoagulation with warfarin have traditionally been large, and this continues to be reflected in licensed product information for these products, where recommended oral or parenteral doses range from 2.5 to 25 mg initially, with a maximum dose of 40 to 50 mg. However, large doses of vitamin K may result in overcorrection, and increase the delay before resumed anticoagulant therapy becomes effective. In addition, the time to onset of action is a minimum of 1 to 2 hours, irrespective of dose. There is increasing evidence that lower doses of vitamin K are effective in over-anticoagulation,[1-3] and this is reflected in current guidelines (see Treatment of Adverse Effects of Warfarin, p.1426). The use of vitamin K lowers the elevated INR faster than witholding warfarin alone. However, for patients on phenprocoumon, vitamin K had insufficient effect, and no benefit for those on acenocoumarol; stopping therapy is more effective.[3] The route by which vitamin K is given may also be significant. A meta-analysis[4] of studies of vitamin K for the treatment of over-anticoagulation found that oral or intravenous vitamin K therapy was more effective for warfarin than simply stopping the anticoagulant; however, subcutaneous therapy was not effective. A review[5] noted that over-anticoagulated patients present with a wide range of INR values, and may respond differently to fixed dosing regimens of vitamin K, leaving them outside their target INR 24 hours after treatment and at risk for either haemorrhage or thromboembolism. Patient factors that affect response to vitamin K include age, body-weight, co-morbidity or health status, warfarin daily dose, and genetic polymorphism. The authors called for a more individualised approach to the reversal of over-anticoagulation.

A study has shown that dietary vitamin K intake is an important factor in anticoagulation instability; even brief periods of increased or decreased intake had significant effects on anticoagulation.[6] A high intake of green, leafy vegetables or selected oil-based foods can readily provide a dietary intake of 0.5 mg of vitamin K. Instead of restricting dietary vitamin K, maintenance of a stable intake may result in improved maintenance of therapeutic anticoagulation.[7]

Concern has also been expressed about possible effects on patients taking warfarin if vitamin K is included in their parenteral nutrition.[8]

1. Weibert RT, *et al.* Correction of excessive anticoagulation with low-dose oral vitamin K . *Ann Intern Med* 1997; **125:** 959–62.
2. Fetrow CW, *et al.* Antagonism of warfarin-induced hypoprothrombinemia with use of low-dose subcutaneous vitamin K . *J Clin Pharmacol* 1997; **37:** 751–7.
3. Hanslik T, Prinseau J. The use of vitamin K in patients on anticoagulant therapy: a practical guide. *Am J Cardiovasc Drugs* 2004; **4:** 43–55.
4. DeZee KJ, *et al.* Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006; **166:** 391–7.
5. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol* 2006; **77:** 457–62.
6. Franco V, *et al.* Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med* 2004; **116:** 651–6.
7. Bovill EG, *et al.* Vitamin K and oral anticoagulation: thought for food. *Am J Med* 2004; **116:** 711–13.
8. Bern M. Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy. *J Parenter Enteral Nutr* 2004; **28:** 388–98.

Vitamin K deficiency bleeding. Vitamin K deficiency bleeding (VKDB; haemorrhagic disease of the newborn; HDN), of which 3 types have been recognised, is associated with a clotting defect due to vitamin K deficiency.[1,2]

- In early VKDB bleeding occurs at the time of delivery or during the first 24 hours of life and is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism such as warfarin, some antiepileptics, rifampicin, or isoniazid.
- Classic VKDB, the most common type, usually occurs at 2 to 5 days of age and breast feeding is an important factor as human breast milk has a much lower content of vitamin K than either cow's milk or infant formulas.
- Late VKDB presents frequently as intracranial haemorrhage in infants over one month of age. The vitamin-K deficiency in these cases can be either idiopathic (usually in breast-fed infants who did not receive vitamin K at birth) and/or can be a secondary manifestation of other disorders such as chronic diarrhoea, cystic fibrosis or other malabsorption syndromes, biliary atresia, or α_1-antitrypsin deficiency.

Treatment of VKDB involves use of parenteral phytomenadione, usually 1 mg initially with further doses depending on response. More immediate treatment, in the form of blood transfusion or blood clotting factors, may be needed to compensate for severe blood loss and delayed response to vitamin K. VKDB, particularly the late type, carries a high risk of morbidity or death; therefore, the emphasis has been on prevention. It has long been known that giving vitamin K to the neonate soon after birth can reduce the incidence of VKDB. Menadiol sodium phosphate was formerly used, but reports in the 1950s of jaundice and kernicterus in infants given this vitamin K analogue caused concern, and led to the preferential use of phytomenadione either intramuscularly or orally. Giving phytomenadione, usually as a single intramuscular injection, has been standard practice for neonates considered at high risk of VKDB, such as those who had a complicated delivery, those born prematurely, and those whose mothers were receiving antiepileptic therapy. Since it is not possible to selectively identify all neonates that are at risk for VKDB, the routine use of phytomenadione in all neonates has been advocated. However, such practice has been controversial, particularly as regards the route.[2-4] Some have considered that oral dosage is less invasive and more acceptable to parents.[4] However, there has also been concern about the adequacy of absorption of oral phytomenadione, and the lack of a suitable oral formulation. In addition, there was some evidence[2,5-7] to suggest that a single intramuscular dose was more effective than a single oral dose in preventing late VKDB, and that repeated oral doses might be required, which may be less convenient and carry the risk of poor compliance. More recently, a possible increased risk of childhood cancer in neonates treated with intramuscular, but not oral, phytomenadione has been reported (see Carcinogenicity, above). Although the association remains controversial, it led to recommendations for the preferential use of oral vitamin K in neonates at low-risk of VKDB in some countries, including the UK[8] and Germany,[9] whereas other countries, including the USA,[10,11] still preferred the intramuscular route for all neonates.

There is still no agreement on the most effective oral dose and frequency, and study of this has been complicated by the lack of a suitable oral preparation of phytomenadione.[12,13] Options currently available for oral use include the polyoxyl castor oil and polysorbate-80 containing preparations (unlicensed for oral use) and the colloidal, micelle formulation (licensed for oral use in some countries). These preparations are packaged in glass ampoules, therefore are unsuitable for parents to give at home.

The 1992 recommendations of the British Paediatric Society[8] for oral use of the polyoxyl castor oil formulation suggested a single dose of 500 micrograms on the day of birth. For breast-fed babies, additional doses of 500 micrograms at 7 to 10 days and at 4 to 6 weeks, or 200 micrograms at weekly intervals for 26 weeks, or 50 micrograms daily for 26 weeks, were recommended. Current UK doses[14] for the colloidal preparation in healthy term neonates are 2 mg soon after birth, then 2 mg at 4 to 7 days. Exclusively breast-fed infants should be given a third oral dose of 2 mg one month after birth. Further monthly doses of 2 mg have been recommended while the infant remains exclusively breast-fed. A report[15] of the failure of prophylaxis in 3 breast-fed babies (2 of whom had unidentified cholestatic liver disease) who received 2 doses of this formulation, as recommended in Switzerland, emphasises the importance of the third, and possibly, other, follow-up doses. Plasma vitamin K concentrations in breast-fed infants receiving 3 oral doses of this formulation were at least equal to concentrations in those receiving a single intramuscular dose.[16] A study in Germany, however, found the mixed micellar oral formulation to be no more efficacious than older vitamin K preparations,[17] and a pharmacokinetic study found its absorption to be unreliable in infants with conjugated hyperbilirubinaemia;[18] the authors suggest that even 3 oral doses may not provide sufficient protection against VKDB in infants with latent cholestasis. The most recent advice from the UK Department of Health[14] advocates that all newborn infants should receive vitamin K prophylaxis, both oral and intramuscular routes should be available, and that parents should be involved in the decision on which route is used.

Other oral regimens have been investigated or are in use. In the Netherlands a regimen of 1 mg orally or intramuscularly at birth, followed by 25 micrograms daily or 1 mg weekly by mouth from 1 week to 3 months of age has been found satisfactory.[19,20] In Germany[9,20] and Australia[20] the suggested oral regimen for the polyoxyl castor oil formulation was 1 mg at birth, at 3 to 10 days and at weeks 3 to 6, although some failures have been reported in babies receiving this regimen,[9] and the Australian data confirm it is less effective than a single intramuscular dose.[20] One hospital in the USA has satisfactorily used, for many years, a single 2-mg dose given via nasogastric tube to neonates after birth,[21] although the American Academy of Pediatrics still advocates use of the intramuscular route.[11] In Denmark, a 2-mg dose at birth followed by a weekly dose of 1 mg during the first 3 months of life has effectively prevented any late VKDB in healthy breast-fed babies.[22] In France, for formula-fed neonates at no risk of haemorrhage, 2 mg is given orally at birth, followed by a second dose between day 2 and 7; infants who are breast-fed are given weekly oral doses of 2 mg until cessation of exclusive breast feeding. For neonates at high risk of haemorrhage, however, the first dose is given intramuscularly, or even by slow intravenous injection, according to the clinical state of the infant.[2]

Although phytomenadione crosses the placenta slowly and to a limited extent, it is nevertheless recommended that pregnant women receiving drugs that are vitamin K antagonists (particularly antiepileptics) should receive phytomenadione 10 to 20 mg daily from 36 weeks gestation.[2,23] This is in addition to the requirement that their neonates, who are at high risk of VKDB, receive intramuscular phytomenadione soon after birth. Maternal phytomenadione has been investigated as a means of improving vitamin K status in breast-fed neonates. In 1 study,[24] 5 mg daily for 12 weeks was effective for this purpose.

1. Hathaway WE. Haemostatic disorders in the newborn. In: Bloom AL, Thomas DP, eds. *Haemostasis and thrombosis*. 2nd ed. Edinburgh: Churchill Livingstone, 1987: 554–69.
2. Autret-Leca E, Jonville-Béra A-P. Vitamin K in neonates: how to administer, when and to whom. *Paediatr Drugs* 2001; **3:** 1–8.
3. Tripp JH, McNinch AW. Haemorrhagic disease and vitamin K. *Arch Dis Child* 1987; **62:** 436–7.
4. Brown SG, *et al.* Should intramuscular vitamin K prophylaxis for haemorrhagic disease of the newborn be continued? A decision analysis. *N Z Med J* 1989; **102:** 3–5.
5. Clarkson PM, James AG. Parenteral vitamin K : the effective prophylaxis against haemorrhagic disease for all newborn infants. *N Z Med J* 1990; **103:** 95–6.
6. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. *BMJ* 1991; **303:** 1105–9.
7. Von Kries R. Neonatal vitamin K. *BMJ* 1991; **303:** 1083–4.
8. British Paediatric Association. *Vitamin K prophylaxis in infancy.* London, 1992: British Paediatric Association.
9. von Kries R, *et al.* Repeated oral vitamin K prophylaxis in West Germany: acceptance and efficacy. *BMJ* 1995; **310:** 1097–8.
10. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. *Pediatrics* 1993; **91:** 1001–3.
11. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. *Pediatrics* 2003; **112:** 191–2.
12. Barton JS, *et al.* Neonatal vitamin K prophylaxis in the British Isles: current practice and trends. *BMJ* 1995; **310:** 632–3.
13. Rennie JM, Kelsall AWR. Vitamin K prophylaxis in the newborn—again. *Arch Dis Child* 1994; **70:** 248–51.
14. Department of Health. *Vitamin K for newborn babies.* London, 1998: Department of Health. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Professionalletters/Chiefmedicalofficerletters/DH_4004993?IdcService=GET_FILE&dID=7634&Rendition=Web (accessed 21/07/08)
15. Baenziger O, *et al.* Oral vitamin K prophylaxis for newborn infants: safe enough? *Lancet* 1996; **348:** 1456.
16. Greer FR, *et al.* A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. *Arch Dis Child* 1998; **79:** 300–5.
17. von Kries R, *et al.* Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F109–F112.
18. Pereira SP, *et al.* Intestinal absorption of mixed micellar phylloquinone (vitamin K) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F113–F118.
19. Cornelissen M, Hirasing R. Vitamin K for neonates. *BMJ* 1994; **309:** 1441–2.
20. Cornelissen M, *et al.* Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr* 1997; **156:** 126–30.
21. Clark FI, James EJP. Twenty-seven years of experience with oral vitamin K therapy in neonates. *J Pediatr* 1995; **127:** 301–4.
22. Nørgaard Hansen K, Ebbesen F. Neonatal vitamin K prophylaxis in Denmark: three years' experience with oral administration during the first three months of life compared with one oral administration at birth. *Acta Paediatr Scand* 1996; **85:** 1137–9.
23. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992; **42** (suppl 5): 149–60.
24. Greer FR, *et al.* Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997; **99:** 88–92.

Preparations

BP 2008: Menadiol Phosphate Injection; Menadiol Phosphate Tablets; Phytomenadione Injection; Phytomenadione Tablets;
USP 31: Menadiol Sodium Diphosphate Injection; Menadiol Sodium Diphosphate Tablets; Menadione Injection; Phytonadione Injectable Emulsion; Phytonadione Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: K1; Konakion; Mestil-Ka; Rupek; ***Austral.:*** K Thrombin†; Konakion; ***Austria:*** Kavitol; Konakion; ***Belg.:*** Konakion; Vitamon K; ***Braz.:*** Kanakion; Kavit; Vikatron; Vita K; ***Chile:*** Auriderm K2; Fitoquinona†; Konakion; ***Cz.:*** Kanavit; ***Denm.:*** Konakion; Menadion; ***Fin.:*** Konakion; ***Ger.:*** Kanavit; Konakion; ***Gr.:*** Konakion; ***Hong Kong:*** Auriderm K2; Konakion; ***Hung.:*** Konakion; ***India:*** Kenadion; ***Indon.:*** Neo-K; ***Irl.:*** Konakion; ***Israel:*** Konakion; ***Ital.:*** Konakion; Vitak; ***Jpn:*** Glakay; Kaytwo; ***Malaysia:*** Konakion; ***Mex.:*** K-50; Konakion; Royken; ***Neth.:*** Konakion; ***Norw.:*** Konakion; ***NZ:*** K-Thrombin; Konakion; ***Philipp.:*** Clotigen; Cycomin; Hema-K; Hemadone; Hemo-K; Konakion; ***Pol.:*** Vitacon; ***Port.:*** Kanakion; ***S.Afr.:*** Konakion; ***Spain:*** Kaergona Hidrosoluble; Konakion; ***Swed.:*** Konakion; ***Switz.:*** Konakion; ***Thai.:*** Glakay; Konakion; KP†; ***Turk.:*** Konakion MM; Libavit K; ***UK:*** Konakion; ***USA:*** Aquamephyton†; Mephyton.

Multi-ingredient: ***Arg.:*** Antidiar†; Estreptocarbocaftiazol; Kacerutin; ***Austral.:*** Chilblain Formula†; ***Chile:*** Hepabil; Katin; Microret K; ***India:*** Cadisper C; CKP; Gynae-CVP; K5 Hair Tincture†; Kalpastic; Siochrome; Styptocid; Styptocip†; ***Indon.:*** Hi-Bone; ***Irl.:*** Bio-Calcium + D + K; ***Mex.:*** Hemosin-K; Microka; Microret K; ***Rus.:*** Vectrum Calcium (Вектрум Кальций); ***Spain:*** Caprofides Hemostatico; Cromoxin K†; ***Thai.:*** Bio-Calcium + D3 + K; Siduol; ***Venez.:*** Dremo-K†.

Xylitol *(BAN)*

E967; Ksilitolis; Ksylitol; Ksylitoli; Xilit; Xilitol; Xylit; *meso*-Xylitol; Xylitolum.

$C_5H_{12}O_5$ = 152.1.
CAS — 87-99-0 (xylitol); 16277-71-7 (D-xylitol).

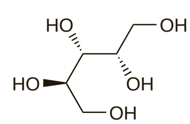

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Xylitol). A white or almost white crystalline powder or crystals. M.p. 92° to 96°. Very soluble in water; sparingly soluble in alcohol.

USNF 26 (Xylitol). White crystals or crystalline powder. Crystalline xylitol has a melting range between 92° and 96°. It has a sweet taste and produces a cooling sensation in the mouth. Soluble 1 in about 0.65 of water; sparingly soluble in alcohol.

Adverse Effects

Large amounts of xylitol taken orally may cause diarrhoea and flatulence. Hyperoxaluria, which can occur with intravenous infusion, is unlikely after oral use. Hyperuricaemia, changes in liver-function tests, and acidosis (including lactic acidosis) have occurred after intravenous infusion.

Hypersensitivity. A report of oral erosions caused by contact hypersensitivity to xylitol-containing chewing gum.[1]

1. Hanakawa Y, *et al.* Xylitol as a causative agent of oral erosive eczema. *Br J Dermatol* 2005; **152:** 821–2.

Uses and Administration

Xylitol is a polyhydric alcohol (polyol) related to the pentose sugar, xylose (p.2416). It is used as a bulk sweetener in foods and as a sweetener or excipient in pharmaceuticals. Xylitol is also used as a sweetening agent in sugar-free preparations as it is non-cariogenic and is less likely to cause dental caries than sucrose. It is under investigation for the prevention of dental caries and acute otitis media. It was formerly considered as a substitute for glucose in intravenous nutrition but such use has generally been abandoned due to adverse effects.

Dental caries. Chewing-gum containing xylitol appears to have a useful role in the prevention of dental caries (p.180).[1-5]

1. Edgar WM. Sugar substitutes, chewing gum and dental caries—a review. *Br Dent J* 1998; **184:** 29–32.
2. Gales MA, Nguyen T-M. Sorbitol compared with xylitol in prevention of dental caries. *Ann Pharmacother* 2000; **34:** 98–100.
3. Maguire A, Rugg-Gunn AJ. Xylitol and caries prevention—is it a magic bullet? *Br Dent J* 2003; **194:** 429–36.
4. van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? *Caries Res* 2004; **38:** 286–93.
5. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. *J Am Dent Assoc* 2006; **137:** 190–6. Correction. *ibid.*; 447.

Otitis media. It has been suggested that xylitol chewing gum[1,2] and xylitol syrup[2,3] may have a preventative effect against acute otitis media (p.182). However, a randomised study[4] found xylitol to be ineffective when given only during an acute respiratory-tract infection.

1. Uhari M, *et al.* Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996; **313:** 1180–4.
2. Uhari M, *et al.* A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 1998; **102:** 879–84.
3. Uhari M, *et al.* Xylitol in preventing acute otitis media. *Vaccine* 2001; **19:** S144–S147.
4. Tapiainen T, *et al.* Xylitol administered only during respiratory infections failed to prevent acute otitis media. Abstract: *Pediatrics* 2002; **109:** 302. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e19 (accessed 08/11/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Trident; ***Ger.:*** Xylit; ***Philipp.:*** Xylogel.

Multi-ingredient: ***Arg.:*** Emoform Total; Fluorogel 2001 Chiquitos; Fluorogel 2001 para Dientes Sensibles; Hyper Sensitive; Periobacter; Periodent; Solucion Oral; ***Chile:*** Oralgene; ***Fr.:*** Exova†; ***Ger.:*** Cardioplegin N†; Kalium-Magnesium-Asparaginat†; Saseem; ***Mex.:*** Dentsiblen; Fluoxytil; Periodentyl; Perioxidin; ***Philipp.:*** Xylorinse; ***UK:*** Biotene Oralbalance; BioXtra†; Saliva Natura; Saliva Orthana; ***USA:*** Optimoist.

Dried Yeast

Brewers' Yeast; Cerevisiae Fermentum Siccatum; Faex Siccata; Fermento de Cerveja; Levadura desecada; Levedura Sêca; Levure de Bière; Saccharomyces Siccum; Trockenhefe.

Сушёные Дрожжи

Pharmacopoeias. In *Jpn.*

Profile

Dried yeast consists of unicellular fungi belonging to the family Saccharomycetaceae, dried by a process that avoids decomposition of the vitamins present. The chief species are *Saccharomyces cerevisiae*, *S. carlsbergensis*, and *S. monacensis*. Dried yeast contains thiamine, nicotinic acid, riboflavin, pyridoxine, pantothenic acid, biotin, folic acid, cyanocobalamin, aminobenzoic acid, inositol, and chromium.

Dried yeast is a rich source of vitamins of the B group. It has been used for the prevention and treatment of vitamin B deficiency in doses of 1 to 8 g daily by mouth. Yeast is an ingredient of some preparations for treating haemorrhoids, and some preparations intended to restore normal gastrointestinal flora. Yeast is widely used in brewing.

Antibiotic-associated colitis. Although other organisms, including *Candida* spp., have been implicated in antibiotic-associated diarrhoea, colonisation of the colon with *Clostridium difficile*, a toxin-producing Gram-positive anaerobe, is the most common identifiable cause of antibiotic-associated colitis (p.171) and pseudomembranous colitis. There are reports of benefit with dried yeast in patients with *C. difficile*-associated diarrhoea;[1,2] commercially available brewers' yeast tablets were used, at a dose of 3 tablets three times daily (strength unspecified), in 3 patients refractory to standard treatment,[1] or as adjunctive therapy in 11 patients, using the same dose.[2]

1. Schellenberg D, *et al.* Treatment of Clostridium difficile diarrhoea with brewer's yeast. *Lancet* 1994; **343:** 171–2.
2. Barthram J, *et al.* Further research warranted. *Pharm J* 1997; **259:** 371.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Bioflorin†; Florax†; Ginoflorax†; Levedo; Lomvit†; ***Fr.:*** Microlev†; ***Ger.:*** AgioStop; Furunkulosin†; Hamadin N; Imoflora; Levurinetten N†; Omniflora Akut; Perocur; Santax S; Yomogi; ***India:*** Laviest; ***Ital.:*** Nutrivit†; Zimocel; ***Mex.:*** Levifusa; ***Port.:*** Lio-Levedura†; ***Thai.:*** Brewers Yeast; ***UK:*** Bio-Strath.

Multi-ingredient: ***Arg.:*** Bifena; Karbonetas; ***Austral.:*** ML 20†; Plantiodine Plus†; Preparation H†; ***Austria:*** Levurinetten; Sperti Praparation H; ***Braz.:*** Composto Emagrecedor†; Emagrevit†; Manolio†; ***Canad.:*** Preparation H; ***Chile:*** Sperti Preparation H; ***Cz.:*** Preparation H; ***Fr.:*** Actisoufre; Calciforte; Calciforte Vitamin D ; Carbolevure; D'Contract; Levure Or; Phytophanere; Preparation H; Solacy; Spasmag; ***Ger.:*** Pantovigar N; Sperti Praparation H†; ***Gr.:*** Preparation H; ***India:*** Elferri†; Livogen†; Medithane; Plastules; Softeron-Z; ***Irl.:*** Preparation H; ***Israel:*** Preparation H; ***Ital.:*** Bifilact; Eurogel; Florelax; Lactisporin; Lactivis; Lactolife; Levudin†; Lievitosohn;

Lievitovit; Preparazione H; Sillix C†; Sillix†; ***Neth.:*** Sperti Preparation H; ***Pol.:*** Preparation H†; Vegevit B ; ***Port.:*** Bioregime Fort†; Sperti Preparacao H; ***Rus.:*** Preparation H (Препарейшн Эйч); ***S.Afr.:*** Preparation H; ***Spain:*** Preparacion H; ***Switz.:*** A Vogel Capsules polyvitaminees†; Carbolevure; Sperti Preparation H; ***UK:*** Bio-Strath Artichoke Formula; Bio-Strath Valerian Formula; Bio-Strath Willow Formula; Brewers Yeast; Preparation H; Tonic Yeast; Yeast Vite; ***USA:*** Medicone†; Preparation H; Rectagene Medicated Balm; Wyanoids Relief Factor; ***Venez.:*** Wampole†.

Zeaxanthin

Anchovyxanthin; Zeaxanthol. (3*R*,3′*R*)-β,β-Carotene-3,3′-diol.

Зеаксантин

$C_{40}H_{56}O_2$ = 568.9.

CAS — 144-68-3.

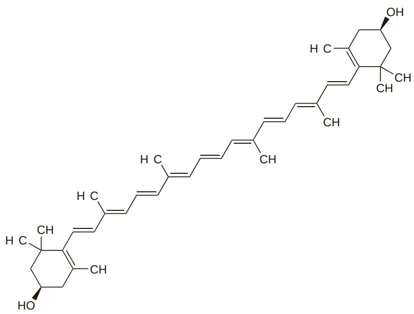

Profile

Zeaxanthin is a naturally occurring carotenoid that is promoted as a dietary supplement for age-related macular degeneration (p.785).

◊ References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; **132** (suppl): 518S–524S.
2. Mozaffarieh M, *et al.* The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J* 2003; **2:** 20.
3. Hartmann D, *et al.* Plasma kinetics of zeaxanthin and 3′-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. *Am J Clin Nutr* 2004; **79:** 410–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Indon.:* Eyevit; Matovit Fifty; Nuvision; ***Mex.:*** Snelvit.

Zinc

Cynk; Zincum; Zink.

Zn = 65.38.

CAS — 7440-66-6.

Zinc Acetate

Cink-acetát-dihidrát; Cinko acetatas dihidratas; Cynku octan; E650; Octan zinečnatý dihydrát; Sinkkiasetaatti; Zinc (acétate de) dihydraté; Zinc, acetato de; Zinci Acetas; Zinci acetas dihydricus; Zinkacetat.

$(CH_3CO_2)_2Zn,2H_2O$ = 219.5.

CAS — 557-34-6 (anhydrous zinc acetate); 5970-45-6 (zinc acetate dihydrate).

ATC — A16AX05.

ATC Vet — QA16AX05.

NOTE. Zinc Acetate, Basic is *rINN*.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Zinc Acetate Dihydrate; Zinc Acetate BP 2008). A white or almost white, crystalline powder or leaflets. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 5.8 to 7.0. Store in nonmetallic containers.

USP 31 (Zinc Acetate). White crystals or granules having a slight acetous odour. Is slightly efflorescent. Soluble 1 in 2.5 of water and 1 in 30 of alcohol; freely soluble in boiling alcohol. pH of a 5% solution in water is between 6.0 and 8.0. Store in airtight containers.

Zinc Chloride

Chlorid zinečnatý; Cink-klorid; Cinko chloridas; Cynku chlorek; Sinkkikloridi; Zinc, chlorure de; Zinc, cloruro de; Zinci chloridum; Zincum Chloratum; Zinkklorid.

$ZnCl_2$ = 136.3.

CAS — 7646-85-7.

ATC — B05XA12.

ATC Vet — QB05XA12.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Zinc Chloride). A white or almost white, deliquescent, crystalline powder or cast in white or almost white sticks. Very soluble in water; freely soluble in alcohol and in glycerol. An approximately 10% solution in water has a pH of 4.6 to 5.5. Store in nonmetallic containers.

USP 31 (Zinc Chloride). A white or practically white, odourless, crystalline powder, or white or practically white crystalline granules. May also be in porcelain-like masses or moulded into cylinders. It is very deliquescent. Soluble 1 in 0.5 of water, 1 in 1.5 of alcohol, and 1 in 2 of glycerol. Its solution in water or in alcohol is usually slightly turbid, but the turbidity disappears when a small quantity of hydrochloric acid is added. A 10% solution in water is acid to litmus. Store in airtight containers.

Turbidity. Zinc chloride almost always contains some oxychloride which produces a slightly turbid aqueous solution. Turbid solutions, except when intended for ophthalmic use, may be cleared by adding gradually a small amount of dilute hydrochloric acid. Solutions of zinc chloride should be filtered through asbestos or sintered glass, since they dissolve paper and cotton wool.

Zinc Citrate

Zinc Citrate Trihydrate. 2-Hydroxy-1,2,3-propanetricarboxylic acid zinc salt.

Цитрат Цинка

$C_{12}H_{10}O_{14}Zn_3,3H_2O$ = 628.4.

CAS — 546-46-3.

Pharmacopoeias. In *Chin.*

Zinc Gluconate

Zinc, gluconate de; Zinc, gluconato de; Zinci gluconas.

$C_{12}H_{22}O_{14}Zn$ = 455.7.

CAS — 4468-02-4.

ATC — A12CB02.

ATC Vet — QA12CB02.

Pharmacopoeias. In *Chin.* and *US*.

USP 31 (Zinc Gluconate). White or practically white powder or granules. Soluble in water; very slightly soluble in alcohol. pH of a 1% solution in water is between 5.5 and 7.5.

Zinc Sulfate

Çinko Sülfat; Cinko sulfatas; Cink-szulfát; Cynku siarczan; Sinkkisulfaatti; Síran zinečnatý; Zinc, sulfate de; Zinc, sulfato de; Zinc Sulphate; Zinci sulfas; Zincum Sulfuricum; Zinksulfat.

$ZnSO_4,7H_2O$ = 287.5.

CAS — 7733-02-0 (anhydrous zinc sulfate); 7446-20-0 (zinc sulfate heptahydrate).

ATC — A12CB01.

ATC Vet — QA12CB01.

NOTE. 'White vitriol' or 'white copperas' is crude zinc sulfate.

ZSU is a code approved by the BP 2008 for use on single unit doses of eye drops containing zinc sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *Viet.*

Eur. also includes the monohydrate and the hexahydrate.

US includes the monohydrate and the heptahydrate in one monograph.

Ph. Eur. 6.2 (Zinc Sulphate Heptahydrate; Zinci Sulfas Heptahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 6.2 (Zinc Sulphate Hexahydrate; Zinci Sulfas Hexahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 6.2 (Zinc Sulphate Monohydrate; Zinci Sulfas Monohydricus). Colourless, transparent, crystals or a white or almost white crystalline powder. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic containers.

USP 31 (Zinc Sulfate). It contains one or seven molecules of water of hydration. Colourless, transparent, prisms, or small needles. May occur as a white, granular, crystalline powder. It is odourless and is efflorescent in dry air. Very soluble in water (heptahydrate); freely soluble in water (monohydrate); practically insoluble in alcohol (monohydrate); insoluble in alcohol (heptahydrate); freely soluble in glycerol (heptahydrate). Its solutions are acid to litmus. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of zinc salts (the gluconate and sulfate) given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals.

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Prolonged use of high doses of zinc supplements, orally or parenterally, leads to copper deficiency with associated sideroblastic anaemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in haemodialysis solutions. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate (p.1462).

Metal fume fever is an occupational disease associated with inhalation of freshly-oxidised metal fumes, most commonly from zinc, iron or copper. It is characterised by chills, fever, cough, dyspnoea, myalgia, and chest pain, and is generally self-limiting and does not appear to be associated with long-term sequelae.

Effects on the blood. There have been reports[1-3] of anaemia, leucopenia, and neutropenia in patients consuming excessive amounts of zinc supplements for acne. A patient given zinc-containing enteral feeds as well as zinc supplementation was diagnosed with sideroblastic anaemia due to zinc toxicity.[4] All patients were copper-deficient,[1-4] despite supplementation with copper in one case.[4]

1. Porea TJ, *et al.* Zinc-induced anemia and neutropenia in an adolescent. *J Pediatr* 2000; **136:** 688–90.
2. Igic PG, *et al.* Toxic effects associated with consumption of zinc. *Mayo Clin Proc* 2002; **77:** 713–16.
3. Salzman MB, *et al.* Excessive oral zinc supplementation. *J Pediatr Hematol Oncol* 2002; **24:** 582–4.
4. Irving JA, *et al.* Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. *Can Med Assoc J* 2003; **169:** 129–31.

Hypersensitivity. Report of a patient who developed palmoplantar pustulosis about 1 year after receiving dental fillings containing zinc.[1] Zinc hypersensitivity was confirmed by *in vitro* and patch testing. Complete remission occurred on replacing the dental fillings.

1. Yanagi T, *et al.* Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005; **366:** 1050.

Parenteral nutrition. Zinc was found to be a common contaminant of various components used for total parenteral nutrition (TPN), and rubber stoppers or glass may have been the source.[1] Levels of zinc found may exceed daily requirements even before the addition of supplementary zinc. The authors suggested it may be important to routinely monitor zinc status in patients receiving long-term TPN, particularly infants and children.

1. Hak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Interactions

The absorption of zinc may be reduced by iron supplements (see also Absorption, under Pharmacokinetics, below) , penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones (see Antacids and Metal Ions, under Interactions of Ciprofloxacin, p.246), iron, penicillamine, and tetracyclines (p.348).

Pharmacokinetics

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

Absorption. Although zinc deficiency (see Deficiency States, under Uses and Administration, below) in some cases may be due to inadequate dietary intake, inhibitors of zinc absorption may also be causative.[1] *Phytates*, which are present in cereals, corn, legumes, and rice, inhibit zinc absorption. The animal *protein* in beef, eggs, and cheese counteracts the inhibitory effect of phytate, whereas the casein in milk decreases zinc absorption. Proteins also often contain other constituents such as inorganic *phosphate* that can negatively affect zinc absorption. Long-term use of *calcium* supplements has no effect on zinc status, but dietary calcium may form insoluble complexes with phytate and zinc, thus decreasing the absorption of zinc. *Iron* can reduce zinc absorption, although the effect is apparent only at a very high ratio of iron to zinc, and in aqueous solution, which suggests that iron fortification of foods will not affect zinc absorption. Although it is possible that iron supplementation could affect mechanisms of zinc uptake and transport, studies have not found such an effect, and long-term iron supplementation is not considered to impair zinc status.

Zinc can form complexes with ligands or chelators; if the complex is readily absorbed, this can increase zinc absorption. *Edetic acid* has been found to have variable effects on zinc status depending on the ratio of edetic acid to other cations and phytate, which compete for complex formation with zinc. *Histidine* also chelates with zinc and can increase plasma zinc concentrations; however, the ratio of histidine to zinc is important because high doses of histidine may enhance the urinary excretion of zinc. *Methionine* may improve zinc absorption, although evidence is limited. Adding organic acids such as *citrate* to foods can enhance zinc absorption; zinc citrate has been used as a dietary supplement.

1. Lönnerdal B. Dietary factors influencing zinc absorption. *J Nutr* 2000; **130:** 1378S–1383S.

Human Requirements

UK and US recommended dietary intake. In the UK dietary reference values (DRV)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for zinc (see p.1925 for an explanation of these terms). In the UK the reference nutrient intake (RNI) for adult males and females is 9.5 and 7.0 mg daily respectively; values are also given for infants and children of varying ages and for lactating women. The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for zinc of 25 mg daily. In the USA the RDA for adults is 11 mg daily for men and 8 mg daily for women.[2] The tolerable upper intake level is 40 mg daily.

WHO recommend lower limits of the safe ranges of population mean intakes of dietary zinc for 3 categories of diets based on high, moderate, and low zinc bioavailability: values are 4.0, 6.5, and 13.1 mg dietary zinc daily for women, and 5.6, 9.4, and 18.7 mg dietary zinc daily for men, respectively.[4] They recommend an upper limit of the safe range of population mean intakes of zinc of 35 mg daily for women, and 45 mg daily for men.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 14/11/05)
4. WHO. Zinc. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 72–104.

Uses and Administration

Zinc is an essential element of nutrition and traces are present in a wide range of foods. It is a constituent of many enzyme systems and is present in all tissues. Features of zinc deficiency include growth retardation and defects of rapidly-dividing tissues such as the skin, the immune system, and the intestinal mucosa. Water-soluble zinc salts are used as supplements to correct zinc deficiency; for example, in malabsorption syndromes, during parenteral feeding, in conditions with increased body losses (trauma, burns, and protein-losing states), and in acrodermatitis enteropathica (a rare genetic disorder characterised by severe zinc deficiency). They have been tried in the treatment of a large number of conditions that may be related to zinc deficiency.

Doses of zinc salts are usually expressed in terms of elemental zinc, and the following salts contain about 50 mg of zinc:

- zinc acetate (dihydrate) 168 mg
- zinc chloride 104 mg
- zinc citrate (trihydrate) 160 mg
- zinc gluconate 348 mg
- zinc sulfate (heptahydrate) 220 mg

The approximate number of millimoles of zinc contained in these salts are:

- 4.6 mmol in 1 g zinc acetate (dihydrate)
- 7.3 mmol in 1 g zinc chloride
- 4.8 mmol in 1 g zinc citrate (trihydrate)
- 2.2 mmol in 1 g zinc gluconate
- 3.5 mmol in 1 g zinc sulfate (heptahydrate)

In **deficiency states**, zinc is usually given orally as the sulfate, the sulfate monohydrate, or the gluconate, in doses of up to 50 mg of elemental zinc three times daily. When intravenous supplements are required, zinc chloride or zinc sulfate may be given; a suggested dose for parenteral nutrition is 6.5 mg of elemental zinc (100 micromoles) daily.

Oral zinc salts, commonly the acetate, may be used as copper absorption inhibitors in **Wilson's disease** (p.1459). The usual adult dose is 50 mg three times daily up to a maximum of five times daily. Children from 1 to 6 years may be given 25 mg twice daily; those from 6 to 16 years and with a body-weight under 57 kg are given 25 mg three times daily. Adolescents from 16 years of age, or with a body-weight of above 57 kg are given 50 mg three times daily. An effective dose in pregnant women is usually 25 mg three times daily; however, dosage is adjusted based on copper concentrations.

Zinc sulfate is used topically in a variety of skin conditions mainly for its **astringent** properties. The insoluble zinc salts, commonly the oxide (p.1621), are used similarly. A 1.2% solution of zinc acetate is used topically with erythromycin in the treatment of acne vulgaris (p.1577). Zinc sulfate is also used as an astringent in eye drops. Zinc chloride has been used for its powerful caustic and astringent properties, usually in very dilute solution, in, for example, mouthwashes. Zinc citrate has been used in preparations for oral care and as a dietary supplement.

Age-related macular degeneration. High doses of dietary supplements such as betacarotene, vitamin C, vitamin E, and zinc are being promoted for preservation of vision in the elderly but there are no data to suggest any benefit for patients who do not have age-related macular degeneration or have only mild disease and such treatment is not necessarily harmless.[1] For further details, see under Betacarotene, p.1931.

1. Anonymous. Antioxidant vitamins and zinc for macular degeneration. *Med Lett Drugs Ther* 2003; **45:** 45–46.

Common cold. Zinc salts, in the form of lozenges, have been tried in the treatment of the common cold (p.850) with variable results.[1-4] A systematic review of randomised trials found that there was no strong evidence to recommend their use.[5] Similarly, variable results have been obtained with intranasal preparations of zinc gluconate;[6-8] intranasal zinc sulfate has proven ineffective.[9]

1. Mossad SB, *et al.* Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996; **125:** 81–8.
2. Macknin ML, *et al.* Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998; **279:** 1962–7.
3. Prasad AS, *et al.* Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 245–52.
4. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000; **31:** 1202–8.
5. Marshall I. Zinc for the common cold. [Withdrawn and awaiting update]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 21/07/08).
6. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001; **33:** 1865–70.
7. Hirt M, *et al.* Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000; **79:** 778–82.
8. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *Q J Med* 2003; **96:** 35–43.
9. Belongia EA, *et al.* A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; **111:** 103–8.

Deficiency states. General references.

1. Hambidge M. Human zinc deficiency. *J Nutr* 2000; **130** (suppl): 1344S–1349S.
2. Prasad AS. Zinc deficiency: has been known of for 40 years but ignored by global health organisations. *BMJ* 2003; **326:** 409–10.
3. Shrimpton R, *et al.* Zinc deficiency: what are the most appropriate interventions? *BMJ* 2005; **330:** 347–9.
4. Mason P. Physiological and medicinal zinc. *Pharm J* 2006; **276:** 271–4.

DIAGNOSIS AND TESTING. A loss of taste acuity is a sign of zinc deficiency (see Taste Disorders, below) and this has been used as a test for the condition: patients who do not immediately perceive a strong flavour on tasting a dilute (typically 0.1 or 0.2%) solution of zinc sulfate are considered likely to benefit from supplementation. However, a study in pregnant women failed to confirm that the ability to taste such a solution was related to zinc deficiency.[1]

Authors of a small study of Japanese children with short stature evaluated body zinc clearance, and considered those patients with high clearance values but normal serum zinc concentrations to have marginal zinc deficiency.[2]

1. Mahomed K, *et al.* Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **48:** 169–75.
2. Kaji M, *et al.* Studies to determine the usefulness of the zinc clearance test to diagnose marginal zinc deficiency and the effects of oral zinc supplementation for short children. *J Am Coll Nutr* 1998; **17:** 388–91.

DIARRHOEA. Chronic diarrhoea can be a sign of zinc deficiency, and diarrhoea can lead to excessive zinc losses and zinc deficiency when dietary zinc is inadequate. Zinc supplements have been shown to reduce the incidence, intensity, or duration of acute diarrhoea (p.1694) in children in developing countries.[1-5] Beneficial effects have also been seen with zinc supplementation for persistent diarrhoea.[4,5] A WHO report concluded that zinc supplementation at a dose of about 10 to 20 mg daily for 14 days is efficacious in significantly reducing the severity and duration of diarrhoea; the type of zinc salt does not appear to influence efficacy, although the best formulation should be determined to minimise adverse effects such as vomiting.[6] A further report[7] concluded that there was sufficient evidence to recommend the inclusion of zinc as adjunctive therapy to oral rehydration salts in the standard management of both dysenteric and non-dysenteric acute diarrhoea.

For a report of increased efficacy in reducing persistent diarrhoea and dysentery when zinc is used with vitamin A, see Diarrhoea, under Deficiency states, p.1973. For suggestions that zinc potentiates the effect of vitamin A, see Vitamin A deficiency, below.

1. Bhutta ZA, *et al.* Zinc Investigators' Collaborative Group. Prevention of diarrhea and pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Bhutta ZA, *et al.* Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; **72:** 1516–22.
3. Aggarwal R, *et al.* Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics* 2007; **119:** 1120–30.
4. Lukacik M, *et al.* A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics* 2008; **121:** 326–36.
5. Fischer Walker CL, Black RE. Micronutrients and diarrheal disease. *Clin Infect Dis* 2007; **45** (suppl 1): S73–S77.
6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *J Health Popul Nutr* 2001; **19:** 338–46.
7. Robberstad B, *et al.* Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. *Bull WHO* 2004; **82:** 523–31.

GROWTH RETARDATION. Growth retardation in a group of short Japanese children without endocrine abnormalities was found to be associated with mild to moderate zinc deficiency; supplementation with oral zinc sulfate 5 mg/kg daily over 6 months resulted in an improvement in growth velocity despite unchanged growth hormone production.[1] Similarly, supplementation with 10 mg zinc daily for 6 days of each week, for 6 months, increased the growth rate of stunted Ethiopian infants; weight also increased in both stunted and non-stunted children, and the authors commented that these effects were at least partly due to improvements in appetite, and reduced morbidity from infection.[2] Results from a meta-analysis of these 2 studies and 31 others indicated that zinc supplementation resulted in a highly significant increase in both linear growth and weight gain of prepubertal children; weight-for-height index was not affected. Significant increases in serum zinc concentrations were also noted with supplementation, but additional studies were considered necessary in order to determine whether mean serum zinc concentration could accurately predict response to supplementation.[3]

1. Nakamura T, *et al.* Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. *J Pediatr* 1993; **123:** 65–9.
2. Umeta M, *et al.* Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet* 2000; **355:** 2021–6.
3. Brown KH, *et al.* Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; **75:** 1062–71.

PNEUMONIA. A pooled analysis[1] of 10 studies performed in developing countries found that zinc supplementation reduced the incidence of pneumonia in children by 41%. A randomised study in Bangladesh, in 270 children aged 2 to 23 months, found that 20 mg daily of elemental zinc, given by mouth and adjuvant to standard antimicrobial therapy, accelerated recovery from pneumonia when compared with placebo; children aged 12 months or older resolved their respiratory illness earlier than younger infants.[2] Another study in Bangladesh[3], involving 1621 children 2 to 12 months old, found that prophylaxis with 70 mg of oral zinc acetate [about 20 mg of zinc] given weekly reduced the incidence of pneumonia compared with placebo and also reduced subsequent pneumonia-related mortality; a small reduction in the incidence of diarrhoea was also seen.

1. Bhutta ZA, *et al.* Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Brooks WA, *et al.* Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet* 2004; **363:** 1683–8.
3. Brooks WA, *et al.* Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005; **366:** 999–1004.

PREGNANCY. Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45 mg daily) during pregnancy may have beneficial effects on fetal growth and development, and lead to improved pregnancy outcomes.[1] A controlled study in Peru found that addition of oral zinc (25 mg of zinc daily as zinc sulfate) to iron and folate supplementation improved fetal bone growth, as measured by femur length.[2] A systematic review[3] concluded that, while zinc supplementation during pregnancy appears to reduce preterm delivery, there was no convincing evidence that it resulted in other useful benefits. Since the association with preterm birth might reflect poor nutrition, improvement in the overall nutritional status of impoverished populations would be more beneficial than zinc supplementation in isolation.

1. Favier M, Hininger-Favier I. Zinc et grossesse. *Gynecol Obstet Fertil* 2005; **33:** 253–8.
2. Merialdi M, *et al.* Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr* 2004; **79:** 826–30.
3. Mahomed K, *et al.* Zinc supplementation for improving pregnancy and infant outcome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 05/03/08).

TASTE DISORDERS. Zinc appears to be effective for the treatment of taste disturbances (p.977) associated with zinc deficiency but there is insufficient evidence to determine its efficacy for taste dysfunction secondary to conditions that do not involve low serum zinc concentrations.[1] Zinc picolinate was found to significantly improve objective measurement of taste when compared with placebo, both in patients with zinc deficiency and in those with idiopathic taste disorders (and normal serum zinc concentrations); there were no differences in subjective assessment of taste.[2] A later study[3] also found oral zinc gluconate 140 mg daily [about 20 mg of zinc] to be of benefit in idiopathic dysgeusia.

1. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
2. Sakai F, *et al.* Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. *Acta Otolaryngol* 2002; (suppl 546): 129–33.
3. Heckmann SM, *et al.* Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. *J Dent Res* 2005; **84:** 35–8. Correction. *ibid.*; 382.

Vitamin A deficiency. It has been proposed[1] that the inconsistent effects on morbidity of vitamin A supplementation (see Diarrhoea, under Deficiency States, p.1973) may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. The authors found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone. There is also some suggestion that zinc may potentiate the effects of vitamin A in the treatment of night blindness,[2] but only in those patients already deficient in zinc. A study in Bangladesh[3] found that the proportional improvement in vitamin A status in vitamin A-deficient children was larger in those given zinc with vitamin A than in those given vitamin A or zinc alone, suggesting a synergistic effect. Similarly, a study in Indonesia[4] of supplementation in pregnant women found that betacarotene with zinc, but not betacarotene or zinc alone, improved vitamin A status in both mothers and infants at 6 months postpartum; the authors suggested that zinc may have a specific role in the conversion of betacarotene to retinol.

1. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.
2. Christian P, *et al.* Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *Am J Clin Nutr* 2001; **73:** 1045–51.
3. Rahman MM, *et al.* Synergistic effect of zinc and vitamin A on the biochemical indexes of vitamin A nutrition in children. *Am J Clin Nutr* 2002; **75:** 92–8.
4. Dijkhuizen MA, *et al.* Zinc plus β-carotene supplementation of pregnant women is superior to β-carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr* 2004; **80:** 1299–1307.

Wilson's disease. References.

1. Anderson LA, *et al.* Zinc acetate treatment in Wilson's disease. *Ann Pharmacother* 1998; **32:** 78–87.
2. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc: XV long-term follow-up studies. *J Lab Clin Med* 1998; **132:** 264–78.
3. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc: XVII: treatment during pregnancy. *Hepatology* 2000; **31:** 364–70.
4. Brewer GJ. Zinc acetate for the treatment of Wilson's disease. *Expert Opin Pharmacother* 2001; **2:** 1473–7.

Preparations

BP 2008: Erythromycin and Zinc Acetate Lotion; Zinc Sulphate Eye Drops; Zinc Sulphate Lotion;
USP 31: Zinc Chloride Injection; Zinc Sulfate Injection; Zinc Sulfate Ophthalmic Solution; Zinc Sulfate Oral Solution; Zinc Sulfate Tablets; Zinc Sulfide Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Galzin; Z-Kraft†; ***Austral.:*** Bioglan Zinc Chelate; Zincaps; ***Austria:*** Zinkamin†; ***Braz.:*** Zincopan; ZN Xampu; ***Canad.:*** Anu-Aide†; Anusol; Anuzinc; Egozinc; Rivasol; ***Chile:*** Num-Zit; ***Cz.:*** Wilzin; Zincteral; Zinek-AlO†; Zinkorotat-POS; ***Fr.:*** Effizinc; Rubozinc; Wilzin; Zymizinc†; ***Ger.:*** Biolectra Zink; Biosan Zink†; Cefazink; Curazink; Nefro-Zinc; Ophtopur-Z; Solvezink†; Unizink; Virudermin; Vitazink; Wilzin; Zink beta; Zink Verla; Zink-D Longoral; Zink-Ratiopharm; Zink-Sandoz; Zinkamin; Zinkaspart; Zinkbrause; Zinkit; Zinkorot; Zinkotase; ***Hong Kong:*** Egozinc; Eye Glo Relief; Zincaps; ***Irl.:*** Solvazinc; ***Israel:*** Avazinc; Zincol; ***Ital.:*** Pontefix; Troca Flu Rino; Wilzin; ***Mex.:*** Tersaken†; Unguento del Bebe; Z-Crim; Zn-Fusin†; ***Neth.:*** Wilzin; ***Norw.:*** Solvezink; ***NZ:*** Elemental Zinc†; Zincaps; ***Philipp.:*** Immuzinc; Prozinc; Zinbee; ***Pol.:*** Wilzin; Zincas; Zincteral; ***Port.:*** Wilzin; ***Spain:*** Wilzin; ***Swed.:*** Solvezink; ***Switz.:*** Collazin; Virudermin; ***Thai.:*** Zincaps; Zinctab†; ***Turk.:*** Zinco; ***UK:*** Solvazinc; Tartar Control Listerine; Wilzin; Zincomed; Zincosol; ***USA:*** Dermadrox; Galzin; Halls Zinc Defense; Ivy Dry; Orazinc; Verazinc; Zinca-Pak; Zincate.

Multi-ingredient: ***Arg.:*** Caladryl Incoloro; Callicida; Citrovita; Clean-AC; Cleanance; Crema de Ordene; Crema Para Paspaduras; Dermalibour; Kelual Zinc; Lacto-Cev Zn; Lactocrem Bebe; Lagrimas de Santa Lucia†; Litiofarm†; Megaplus; Negacne; Ninderm; Redoxon Doble Accion; Sigma CE; Sigmace Plus; Zineryt; ***Austral.:*** Antioxidant Forte Tablets; Antioxidant Tablets; APR Cream†; Beta A-C; Bioglan Joint Mobility; Bioglan The Blue One; Bioglan Zn-A-C; Caprilate; Cold and Flu Relief†; Cold Sore Relief†; Echinacea 4000; Echinacea ACE + Zinc; Echinacea Complex; Extralife Eye-Care; Extralife Flow-Care; Galium Complex†; Goodnight Formula†; In A Wink†; Lifechange Mens Complex with Saw Palmetto†; Lifesystem Herbal Plus Formula 8 Echinacea†; Logicin Natural Lozenges†; Odourless Garlic†; Proyeast†; Redoxon Double Strength; Serenoa Complex†; Strepsils Zinc Cold Relief; Trifolium Complex†; Urapro†; Visine Allergy†; Zinc + C250†; Zinc C Plus†; Zinc Plus; Zinc Supplement†; Zinc Zenith; Zincfrin; Zinvit; Zinvit C; Zinvit G; ***Austria:*** Efalith; Lipactin; Ophtaguttal; Zeller-Augenwasser; ***Belg.:*** Efalith; Lipactin; Redoxon + Zink; Zincfrin; Zincfrin Antihistaminicum†; Zineryt; ***Braz.:*** Antiseptin†; Babymed; Belagin; Cariderm†; Cebion Zinco; Colirio Legrand; Colirio Moura Brasil; Colirio Teuto; Fluo-Vaso; Kalloplast†; Maxibell; Mirabel; Mirorroidin†; Redoxon Zinco; Sensibaby; Stilux; Suavederm; Visiplex; Visolon; Visual†; Zincolok; ***Canad.:*** Anodan-HC; Anugesic-HC; Anusol Plus; Anusol-HC; Anuzinc HC; Anuzinc HC Plus; Anuzinc Plus; Clear Eyes Allergy; Egozinc-HC; Hemorrhoid Ointment; Lipactin; Listerine Antiseptic Tartar Control; One A Day Cold Season†; Onguent Hemorrhoidal; Orajel Mouth Sore Medicine; Polysporin Itch Relief; Proctodan-HC; ProstGard†; ratio-Hemcort-HC; Rectogel; Rectogel HC; Rivasol HC; Visine Allergy; Zinc Plus; Zincfrin; Zincfrin-A; ***Chile:*** Agua Sulfatada Picrica; Astrijesan; Caladryl Clear; Cicalfate; Clean-AC; Cleanance; Deltisan; Gingilacer†; Oculosan; Orajel Compuesto†; Oralfresh Citrus; Orthokin; Ortodent†; Pomada Antihemorroidal†; Primacy C+AHA†; Sebium AKN; Sebium H2O; ***Cz.:*** Acne Lotio†; Curiosin†; Osteocare; Redoxon Double Action; Zineryt; ***Denm.:*** Zincfrin; ***Fin.:*** Lipactin; Wicnelact; Zincfrin-A†; Zincfrin†; ***Fr.:*** Aftagel; Atoderm moussant; Cicalfate; Cicaplast; Clean-AC; Cleanance; Cleanance K; Cu-Zn; Cystel Shampooing Antiseborrheique†; Cysti-Z†; D'Contract; Dermalibour; Dermo-Sulfuryl; Evosebor Li-Zn; Kelual Zinc; Keralac Plus†; Purif-Ac Emulsion; Purif-Ac Gel; Ramet Dalibour; Ramet Pain; Ruboderm Plus; Sebium AKN; Seborheane; Septalibour†; Serozinc; Supro; YSE; YSE Glutamique; Zeniac LP†; Zeniac†; ***Ger.:*** Algosteril Trionic†; Efadermin; Gehwol Nagelpilz†; Lipactin; Oculosan N; Zincfrin; Zineryt; ***Gr.:*** Oculosan; Zabysept; ***Hong Kong:*** Aderma Dermalibour†; Hemcort HC†; Listerine Tartar Control; Nazin; Oculosan; Osteocare; Redoxon Double Action; Visine AC; ***Hung.:*** Osteocare; Vition; Zineryt; ***India:*** Andre; Aristrol Forte†; Cofol Z; Elferri-Z; Fecontin-Z; Fefol-Z; Ferrochelate-Z; Globac-Z; JP Tone-TR; Livogen-Z; Mumfer-Z†; New Eye Lotion; Ocurest-Z; Zad-G; Zinco Sulpha; ***Indon.:*** Artriox; Biostrum; Climadan; Enerbex; Ilefrin; Imboost; Imboost Force; Imudator; Indofrin; Indofrin-A; Isotic Frizin; Oculosan; Osteocare; Proza; Redoxon Double Action; Soprost; Stacare; StarMuno; Zincopto; ***Irl.:*** Efalith; Redoxon Double Action; Zineryt; ***Israel:*** Hemo; Visine AC; ***Ital.:*** Acnesan†; Bagno Oculare†; Cuprosodio; Cuprosodio Plus; Emmenoiasi; Forbrand; Formedico; Ginsana Ton; Indaco; Inflamase; Influ-Zinc; Influ-Zinc Gola; Listerine Tartar Control; Meziv†; Novostatin; Periogard Plus; Zinc-Imizol; Zincometil; Zineryt; ***Malaysia:*** Adult Citrex; Oculosan†; Zincfrin†; ***Mex.:*** Afazol Z; Caladryl Clear; Dalidome; Daribur; Exastrin; Gripaleta†; Micostatin Baby; Periodentyl; Soyaloid Apruri; Tokolirio; Unguento Cruz; Unguento de la Madre; Unguento Sulfatiazol Rojtier; Z Frin; Zincfrin; Zincfrin-A; ***Neth.:*** Zineryt; ***NZ:*** Clear Eyes ACR†; Listerine Tartar Control; Redoxon Double Action; Strepsils Zinc Defence; Zincfrin; ***Philipp.:*** Bo-D-Fense; Listerine Tartar Control; Oculosan; Osteocare; ***Pol.:*** Biherpan; Cincol; Hemcort HC; Naturapia Prostata; Oculosan; Zincuprin; Zineryt; ***Port.:*** Bioclin Sebo Care†; Kemphor; Oralbiotico; Oratol; Zineryt; ***Rus.:*** Anusol (Анузол); Relief Ultra (Релиф Ультра); Zineryt (Зинерит); ***S.Afr.:*** Nazene Z; Oculoforte†; Oculosan; Tartar Control Listerine Antiseptic; Zincfrin-A; Zineryt; ***Singapore:*** Listerine Tartar Control; New Daigaku†; Proza; Redoxon All Day Defence; Redoxon Double Action; Vita Calmag Zn†; ***Spain:*** Buco Regis; Cloram Zinc; Coliriocilina Adren Astr; Odamida; Odontocromil c Sulfamida†; Zincfrin†; Zineryt; ***Swed.:*** Mezinc; Zincfrin; ***Switz.:*** Acne Lotion; Collypan; Eau pour les yeux; Efalith; Hima-Pasta; Lipactin; Oculosan; Redoxon + Zinc; ***Thai.:*** Bio-Selenium Zinc; Oculosan; Opplin†; Visotone; ***Turk.:*** Osteocare; Zinco C; ***UK:*** Brushtox; Dispello; Flavo-Zinc; Lypsyl Cold Sore Gel; Osteocare; Redoxon Double Action; Se-Power; Strepsils Zinc Defence†; Vicks Vital†; Zineryt; ***USA:*** Amerigel; Anti-Itch; Benadryl Itch; Better Prostate†; Caladryl Clear; Cholesterol Support; Clear Eyes Seasonal Relief; Dermadrox; Dermasept Antifungal; Fosteum; Gets-It; Nasal-Ease; Orajel Mouth Aid; Prostate Support; Sucrets Defense Kids Formula; Sulpho-Lac; Super Ivy Dry; VasoClear A; Visine Allergy Relief; Wound Cleanser; Ze Caps†; Zincfrin; ***Venez.:*** Calasyl Transparente; Dermagran; Sebium AKN; Terace Zinc.

Obstetric Drugs

Obstetric Drug Groups, p.2002
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Prostaglandins, p.2002
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Lactation inhibition and induction, p.2003
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Termination of pregnancy, p.2004

This chapter includes a number of drugs used in obstetrics for the management of labour and postpartum haemorrhage, including various prostaglandins, oxytocics, ergot alkaloids, and tocolytics. Some of these drugs have also been used to terminate pregnancy, as has the antiprogestogen mifepristone (p.2011).

Other drugs with important roles in obstetric management to be found elsewhere in *Martindale* include local anaesthetics (p.1850), opioid analgesics (p.101), and medical gases such as oxygen (p.1690) and nitrous oxide (p.1789). For drugs used in the management of perinatal bacterial infection, see Antibacterials (p.158).

Obstetric Drug Groups

Ergot alkaloids

Some ergot alkaloids have a powerful action on the uterus, causing uterine contractions that are utilised in the active management of the third stage of labour, and to prevent or treat postpartum and postabortal haemorrhage.

Described in this chapter are

Ergometrine, p.2009	Ergotoxine, p.2010
Ergot, p.2010	Methylergometrine, p.2011

Oxytocics

Oxytocics cause contraction of the uterus and may be used for the induction and augmentation of labour, in the management of the third stage of labour, and to prevent and treat postpartum haemorrhage.

Described in this chapter are

Carbetocin, p.2005	Oxytocin, p.2015
Demoxytocin, p.2006	

Prostaglandins

Some prostaglandins soften and dilate the cervix and induce contraction of the uterus. They may be used in labour induction, termination of pregnancy, and the treatment of postpartum haemorrhage.

Described in this chapter are

Carboprost, p.2006	Meteneprost, p.2010
Dinoprost, p.2006	Misoprostol, p.2013
Dinoprostone, p.2007	Sulprostone, p.2018
Gemeprost, p.2010	

Tocolytics

Tocolytics inhibit uterine contractions and are used in premature labour to delay early delivery. Beta agonists other than ritodrine have also been used, and details on salbutamol (p.1131) and terbutaline (p.1138) can be found in the chapter on Bronchodilators and Anti-asthma Drugs. Other drugs that have been tried for their tocolytic actions include calcium-channel blockers (see Nifedipine, p.1350), glyceryl trinitrate (p.1296), magnesium sulfate (p.1679), and NSAIDs (see Indometacin, p.66).

Described in this chapter are

Atosiban, p.2005	Ritodrine, p.2017

Management of Obstetric Conditions

The management of some obstetric conditions is discussed below.

Labour induction and augmentation

The uterus is normally spontaneously contractile but during pregnancy various physiological mechanisms maintain it in a quiescent state; retention of the fetus is also aided by a firm and contracted cervix. During the final 4 to 5 weeks of pregnancy the cervix normally undergoes a 'ripening' process in which it becomes softened and dilated, so that at parturition it is not a barrier to delivery of the fetus. Endogenous prostaglandins play an important role in this process, and also sensitise the uterus in preparation for labour.

- Labour usually begins spontaneously but in some cases it may be necessary to induce labour, for example in pregnancies that go beyond term or where rupture of the membranes occurs without labour. In other cases there may be indications for early delivery such as maternal hypertensive states, antepartum haemorrhage, intra-amniotic infection (chorioamnionitis), or intra-uterine fetal death.[1,2]
- Once labour has started, augmentation of uterine activity may be necessary if contractions fail to progress satisfactorily. A process of active management of labour, including early oxytocin augmentation, has been used in nulliparous women with a single fetus presenting head-first at term and showing no evidence of fetal compromise. Although it may shorten labour without increasing maternal or neonatal harm, it has not been shown to reduce the rate of caesarean section.[3]

Various techniques are available for **induction of labour**, and the choice may be influenced by the ripeness of the cervix and whether the membranes are intact or have ruptured. Mechanical methods are commonly used and may be all that is needed to induce labour. UK guidelines suggest that sweeping of the membranes (manually separating the lower membrane portion from the uterine wall during vaginal examination) should be offered to women at term. It increases the likelihood of spontaneous labour within 48 hours and birth within one week, and reduces the frequency of formal induction of labour.[4] However, it may cause maternal discomfort, irregular contractions, and bleeding.[5] Laminaria tents or hygroscopic cervical dilators may be used to stimulate cervical ripening.[1] Amniotomy (deliberate rupture of the membranes and release of amniotic fluid) may also be used to stimulate labour, once the cervix becomes favourable.[2] When pharmacological induction of labour is required, a prostaglandin or oxytocin is generally used. UK guidelines[4] suggest that, regardless of cervical status, prostaglandins are preferred to oxytocin in all women with intact membranes, but either may be used in women who have ruptured membranes as neither method then offers any particular advantage. However, others[1,2,6] suggest that a ripened cervix improves the chance of successful labour induction, and WHO[7] recommends oxytocin alone if the cervix is favourable but that a prostaglandin or a mechanical method (Foley catheter) should be used to ripen an unfavourable cervix before induction.

As prostaglandins can both ripen the cervix and initiate uterine activity, they induce labour that is similar to spontaneous labour.[1] Overall, compared with oxytocin, prostaglandins seem to improve the rate of successful vaginal delivery, lower the rate of caesarean section, reduce the need for epidural analgesia, and be associated with improved maternal satisfaction.[4] The intravenous and oral routes have been associated with frequent adverse, particularly gastrointestinal, effects[8,9] and intravaginal dosage is now preferred. The intracervical route is no more effective than the intravaginal route, and is no longer recommended.[4] Dinoprostone (prostaglandin E_2) is the most widely used prostaglandin and has been given by various routes. It is usually given intravaginally as gel, vaginal tablets, or pessaries, and a systematic review[10] considered the clinical benefits equivalent; UK guidelines favour use of vaginal tablets.[4]

Whenever possible, amniotomy should be performed in women with intact membranes before giving oxytocin.[4] If vaginal prostaglandins have already been given, usually to ripen the cervix,[2,7] oxytocin should not be started for at least 6 hours.[4] Oxytocin is given by slow intravenous infusion, adjusted according to response.[2,7] Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/minute, dose increases of 1 to 6 milliunits/minute, and intervals between increases of 15 to 40 minutes.[1] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but cause more uterine hyperstimulation.[1] Low-dose regimens are now generally advocated.[1,4,7] There has been some interest in pulsed administration of oxytocin for induction to mimic the pulsatile secretion of endogenous oxytocin that occurs during spontaneous labour, but such use has not been established.[1]

Misoprostol has also been investigated.[1,6,11] Most studies have used the intravaginal route and have suggested it may be more effective than standard methods of labour induction.[12] Oral misoprostol may have a similar efficacy to intravaginal use.[13] However, the risk of uterine hyperstimulation may be increased with misoprostol and there is as yet insufficient evidence of its safety to recommend routine use.

The antiprogestogen mifepristone also produces cervical dilatation and stimulates uterine contraction and has been tried for cervical ripening and for induction of labour. A systematic review of studies found that it may be effective, but its place in therapy has yet to be established.[14]

In pregnancies at term, premature rupture of the fetal membranes may be treated with early induction of labour or expectant management (waiting for labour to occur naturally, which will start within 24 hours in most women[15]). There have been concerns that prolonged rupture of membranes may result in higher rates of maternal and neonatal infection, but that induction may result in more caesarean deliveries.[11] A systematic review[15] of studies in women with premature rupture of membranes at 37 weeks or later, comparing induction (oxytocin infusion or intravaginal dinoprostone) with expectant management found no difference in rates of caesarean section or instrumental vaginal births. There were lower rates of chorioamnionitis and endometritis in women treated with induction. In neonates, there was no difference in infection rate, but fewer admissions to the intensive care unit after oxytocin use. Women were also more satisfied with induction than expectant management. Oral and vaginal misoprostol have also been investigated in this group, and may have a similar efficacy to oxytocin and dinoprostone.[11]

Labour augmentation may be started when labour is abnormally slow (dystocia) due to atony. Oxytocin is generally used, in similar doses to those for induction.[7] As for induction, both high- and low-dose regimens have been described, with higher doses reducing the duration of labour and rate of caesarean deliveries, but causing more hyperstimulation.[3] Augmentation using oxytocin results in normal vaginal delivery in about half of all women treated.[16]

Intravaginal dinoprostone has also been used for augmentation of labour. A placebo-controlled study[17] in women with slow cervical dilatation found doses of 1 or 2 mg to be effective for improving cervical dilatation and reducing the time to delivery; women given the higher dose were less likely to require oxytocin augmentation after 6 hours, but were at greater risk of hyperstimulation.

Once delivery has successfully been initiated, management of the third stage of labour may be considered to reduce the risks of postpartum haemorrhage (see below).

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Lactation inhibition and induction

Lactation is the physiological secretion of milk post partum. Milk production by the breast is induced by prolactin while oxytocin promotes milk ejection into the milk ducts; both prolactin and oxytocin secretion are stimulated by suckling.

Lactation inhibition. The breast engorgement with consequent discomfort and galactorrhoea triggered by prolactin secretion post partum can be problematic in women who choose not to breast feed or are unable to do so. Nonsteroidal or synthetic oestrogens were historically used to suppress lactation in such women, but this use is now considered inappropriate because of an increased risk of thromboembolism. Bromocriptine is a potent inhibitor of prolactin secretion: it has been given post partum in short treatment courses (about 14 days) to suppress lactation. However, it has also been associated with severe adverse effects, and its use for lactation suppression is no longer advocated in a number of countries. Other dopaminergics with similar actions such as cabergoline, lisuride, metergoline, and quinagolide have also been used to suppress lactation. Although it has been suggested that cabergoline, which is generally better tolerated than bromocriptine, may be a better choice for lactation inhibition,[1] the same general objections as for bromocriptine apply to all these drugs. A study in HIV-infected women requiring lactation suppression (in order to prevent mother-to-child transmission from breast milk) found that a combined oral contraceptive was as effective as bromocriptine.[2] Non-pharmacological methods include warm showers to induce milk leakage and reduce pressure, ice packs to reduce local pain and swelling, and a well fitting supportive brassiere. The removal of just enough milk to reduce the pressure but not enough to empty the breasts may help to reduce milk production gradually. Active treatments including mild analgesics such as ibuprofen or paracetamol are also advocated.[3] However, a review[4] noted that few non-pharmacological methods were well evaluated, and that mild analgesia might not be enough to prevent the considerable pain experienced by many women.

Lactation induction. Drug therapy has sometimes been used to help stimulate lactation, although mechanical stimulation of the nipple remains the primary method.[5] Dopamine antagonists, of which metoclopramide has been the most widely used, can produce modest increases in breast milk production but carry a risk of adverse effects including dystonias. If used, such therapy should be limited to 1 or 2 weeks; there has also been some concern about the presence of these drugs in breast milk.[5,6] The efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.[7] Domperidone has also been reported to increase milk production,[6,8] and may cause fewer adverse central effects than metoclopramide. Nevertheless, the FDA has warned against the use of domperidone because of the potential risks of adverse effects in both mother and infant.[9] Protirelin has been given intranasally to stimulate lactation by increasing serum prolactin concentrations, but is expensive, and a suitable commercial preparation is unavailable.[5] Although oxytocin nasal spray has been tried to promote milk ejection, a double-blind, placebo-controlled study[10] of women expressing milk for preterm infants found that although milk production increased marginally in the first 2 days with oxytocin, there was no difference overall after 5 days. Most mothers also believed that they were receiving the active spray suggesting a significant placebo effect. Others[5] warn that its use may interfere with the mother's ability to learn to eject milk naturally, resulting in some becoming dependent upon its action.

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Postpartum haemorrhage

If the uterus fails to contract adequately after delivery (uterine atony), or if retained placental remnants prevent retraction of the placental bed, postpartum haemorrhage may occur. These two causes account for about 80% of cases of postpartum haemorrhage; in the remainder it is usually due to trauma of the genital tract or coagulopathy. *Primary postpartum haemorrhage* has traditionally been defined as vaginal bleeding of more than 500 mL within 24 hours after childbirth. However, the volume of blood loss is often underestimated and the ability of a woman to cope with blood loss may be affected by her previous health, anaemia, and hypovolaemia.[1-3]

Postpartum haemorrhage may be fatal to the mother unless promptly dealt with, and **management** generally involves:

- removal of the placenta if it has not been expelled
- the use of oxytocics to contract the uterus
- transfusion if blood loss is severe

Parenteral oxytocin, or an ergot alkaloid (ergometrine or methylergometrine), is the oxytocic generally used to control bleeding due to uterine atony,[1,2] and oxytocin infusion may be used to maintain uterine contraction.[3] Prostaglandins such as carboprost or dinoprostone may be used for primary postpartum haemorrhage[1,2] that has not been controlled by oxytocin and ergot preparations.[3] Rectal misoprostol has also been shown to be effective,[4] but a subsequent review[5] found that the original study was not large enough to evaluate the effects on maternal mortality, serious morbidity, or hysterectomy rates, and that there was insufficient evidence to support the use of misoprostol instead of a combination of oxytocin and ergometrine. However, there is considerable interest in the use of misoprostol, particularly for developing countries, because of its better stability and ease of administration;[3] further research has been encouraged.[6,7] Surgery may be required if medical management does not control bleeding.[2,3]

Secondary postpartum haemorrhage occurs between 24 hours and 12 weeks after delivery and although associated with maternal morbidity rather than death in developed countries, it is a major contributor to maternal death in developing countries. Antibacterials, oxytocics, hormone therapy, and a variety of surgical treatments are used,[1,2,8] but a systematic review[8] concluded that evidence for the best treatment is lacking.

Risk factors for postpartum haemorrhage include prolonged labour, augmented labour, overdistended uterus (for example in multiple pregnancy), and a history of postpartum haemorrhage.[2] However, atonic postpartum haemorrhage occurs in many women without identifiable risk factors, and authorities recommend that **prophylaxis** should be offered to all women during childbirth.[9,10] *Active management of the third stage of labour* involves prophylactic use of an oxytocic, cord clamping before placental delivery, controlled cord traction, and uterine massage after delivery of the placenta.

The routine use of active management, with oxytocics usually given after delivery of the anterior shoulder or immediately after delivery of the baby, reduces blood loss, the risk of postpartum haemorrhage, and the risk of prolonged third stage of labour.[11] However, despite the widespread use of oxytocics there is limited evidence of high quality comparing different drugs. Oxytocin[12] and ergot alkaloids[13] (usually ergometrine) can both reduce postpartum blood loss and appear to be equally effective,[12] while the fixed combination *Syntometrine* (oxytocin and ergometrine) may be more effective than oxytocin alone in reducing the risk of moderate postpartum haemorrhage (500 to 1000 mL).[14] However, ergot alkaloids and *Syntometrine* cause more adverse effects than oxytocin, particularly nausea, vomiting, and raised blood pressure.[12,14] Although the quality of evidence is low, WHO recommends that oxytocin is generally preferred for prevention of postpartum haemorrhage; an ergot alkaloid (ergometrine or methylergometrine) or *Syntometrine* may be used if oxytocin is not available.[10]

Prostaglandins have also been investigated as an alternative for the routine management of the third stage of labour, and there has been particular interest in misoprostol. Although oral or sublingual misoprostol may reduce the risk of severe postpartum haemorrhage (more than 1000 mL), it is less effective than conventional injectable oxytocics.[15] Data on other prostaglandins are scarce.[15] Based on these findings, a systematic review[15] has suggested that prostaglandins are not preferrable to oxytocin, but that misoprostol may be used where no injectable oxytocic is available. Others have also argued that although misoprostol may be less effective, it would still be useful in developing countries where there are no alternatives,[16] and some authorities include misoprostol as an option when other oxytocics are not available or the birth attendant's skills are limited.[7,9,10]

Where a skilled attendant is not available to provide active management, an appropriately trained healthcare worker may give oxytocin or misoprostol alone for the prevention of postpartum haemorrhage.[10]

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Premature labour

Premature labour (preterm labour) is the onset of labour before the expected date, resulting in delivery of an immature infant. Conventionally the definition includes women giving birth before 37 weeks of gestation but in practice most problems arise with births before 32 to 34 weeks.[1-3] Risk factors for premature labour include infection, premature rupture of the membranes, cervical incompetence, and multiple pregnancy. There are few proven measures to *prevent premature labour*, but cervical cerclage (temporary surgical closure of the cervix) may be used for cervical incompetence,[4] and treatment of infections is being investigated.[5] In women with premature rupture of the membranes who have not gone into spontaneous labour there is some evidence that antibacterial therapy may be effective in delaying delivery and improving outcomes (see Premature Labour, p.188). The value of prophylactic tocolysis, using drugs to prevent the onset of uterine contractions, is unclear[6,7] and such therapy is not recommended.[8] In women who have a history of spontaneous premature delivery, there is some evidence to suggest that a prophylactic progestogen such as hydroxyprogesterone caproate may reduce the risk for premature delivery in subsequent pregnancies.[9,10]

A diagnosis of premature labour is not always easy to make and evidence of cervical change should usually be present in addition to uterine activity.[2,3,11] Once a diagnosis has been established, a decision must be made as to whether to postpone delivery by *acute tocolysis*, using drugs that inhibit uterine contractions. It may not be considered appropriate to stop labour in some women. However, in patients of about 24 to 34 weeks of gestation without complications, attempts to postpone delivery are usually worth trying, if only in the short-term, to allow emergency treatment such as corticosteroids to be given to the mother to enhance the maturation of the fetal respiratory system (see Neonatal Respiratory Distress Syndrome, p.1508) and to enable the patient to be transferred to a specialised unit for preterm delivery.[1-3,11] In the presence of ruptured membranes, tocolysis is rarely considered necessary after this time (some recommend 32 weeks of gestation[2] while others recommend 36 weeks[3]).

- The commonest tocolytics have historically been the beta-adrenoceptor agonists, which relax the smooth muscle of the uterus by stimulation of beta$_2$-adrenoceptors.[12] Nonselective agonists, for example orciprenaline and isoxsuprine, have been replaced by more selective beta$_2$ agonists such as ritodrine, salbutamol, and terbutaline. These can postpone labour for a few days[13,14] and the preferred route for starting treatment is subcutaneous or intravenous infusion.[12] Oral or subcutaneous maintenance therapy with beta$_2$ agonists after successful treatment of an episode of acute premature labour produces no further benefit[15,16] (see also Maintenance Therapy, below). There is little evidence that beta$_2$ agonists significantly reduce perinatal mortality rates.[17] The patient may experience adverse cardiovascular and metabolic effects and, in particular, pulmonary oedema has been reported in some women given beta$_2$ agonists intravenously to suppress labour (see p.1132). It is therefore essential that the patient's heart rate and state of hydration are carefully monitored throughout infusion. In the event of caesarean section beta blockers may be needed to combat an increased tendency to uterine bleeding.
- More recently, calcium-channel blockers have been shown to be effective tocolytics, presumably by their action on myometrial calcium.[12] Most experience concerns nifedipine, which has been reported to be at least as effective as, and possibly better than, beta$_2$ agonists or magnesium in delaying labour,[18-20] although a systematic review[21] considered the quality of many of the studies reporting efficacy to be poor. It has the advantage that it can be given orally,[12] and some favour its use as a first-line drug,[1,19] although it is not licensed in the UK for this use. Nicardipine has also produced favourable results.[22] Others have expressed concern about the safety of calcium-channel blockers,[23] and some suggest that they should be used with caution.[2,3]
- Atosiban is a peptide analogue of oxytocin with oxytocin antagonist properties. A pooled analysis[24] of three controlled studies, and a systematic review,[25] found atosiban to be as effective as beta agonists in the management of premature labour, with fewer maternal cardiovascular adverse effects. These findings were supported by a large open-label study[26] of women treated with atosiban or usual care (usually a beta agonist). Some clinicians favour atosiban as a first-line tocolytic in preference to the traditional drugs.[1-3]
- In the USA, magnesium sulfate is the most widely used parenteral tocolytic, and is thought to act by calcium antagonism at the neuromuscular junction.[12] Although it has been generally considered to be as effective as the beta$_2$ agonists,[12] a systematic review[27] concluded that it was ineffective at delaying birth or preventing preterm birth, and it has been suggested that tocolytic use of magnesium may be associated with increased paediatric mortality—see p.1681. To decrease the risk of overdose, magnesium sulfate should only be given from a controlled pump.[12] Oral magnesium has been tried but has not been shown to be effective.[12] Although magnesium sulfate is widely used, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[11] It is not recommended in Europe,[3] and some in the USA have called for such use to be stopped.[28,29]
- Prostaglandins have a role in the induction of labour as mediators of uterine contractions and cervical softening and dilatation. Cyclo-oxygenase (prostaglandin synthetase) inhibitors, particularly indometacin, have therefore been given orally or rectally to inhibit premature labour.[12,30] Although this treatment may be as effective as ritodrine,[31,32] adverse effects on the fetus have been reported, such as oligohydramnios, intraventricular haemorrhage, necrotising enterocolitis, and oliguria.[30] The most widely reported complication has been constriction of the fetal ductus arteriosus; pulmonary vascular hypertrophy can develop after prolonged constriction. Sensitivity of the ductus arteriosus appears to increase with gestational age, and indometacin therapy should therefore be limited to gestations of less than 32 weeks. If therapy is to continue for longer than 72 hours, the ductus arteriosus should be monitored for evidence of constriction. An increased incidence of persistent patent ductus arteriosus in the newborn has also been reported after indometacin tocolysis, although an association has been questioned.[30] A systematic review[33] of observational and randomised studies found no significant increase overall in the risk of neonatal complications in infants who had been exposed to indometacin tocolysis compared with infants who had not. However, the data had limited statistical power and the review was unable to exclude the possibility that indometacin may increase the risk of adverse neonatal outcomes. The evidence for efficacy of cyclo-oxygenase inhibitors is based on small studies,[34] and because of the potential for adverse effects, indometacin is generally reserved as a second-line drug or given with other tocolytics for an additive effect.[12] More recently it has been suggested that the enzyme isoform cyclo-oxygenase-2 is associated with labour, while cyclo-oxygenase-1 is responsible for constant prostaglandin synthesis in body tissues. The role of cyclo-oxygenase-2 inhibitors in the treatment or prevention of premature labour remains investigational.
- Other drugs are under investigation. Application of patches of the nitric oxide donor glyceryl trinitrate to the abdomen to produce uterine relaxation was reported to be as effective as ritodrine treatment.[35] However, another study[36] found transdermal glyceryl trinitrate to be less effective than beta agonists, and a systematic review[37] concluded that there was insufficient evidence to support its routine use.

When acute tocolysis has successfully suppressed uterine activity, the use of *maintenance therapy* has been tried to prevent recurrent episodes of premature labour. However, a systematic review[38] found that although there was a small but significant increase in the number of days gained before delivery, maintenance therapy did not reduce the incidence of premature birth or recurrent premature labour; there was also a non-significant trend towards an increase in adverse perinatal outcomes. Maintenance therapy is not recommended for routine use.[1,3,11]

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Termination of pregnancy

Termination of pregnancy can be achieved medically or surgically. Uterine aspiration is a common method used for *surgical termination*; before 13 weeks of pregnancy it is usually termed suction or vacuum curettage, and after 13 weeks as dilatation and evacuation.[1] Cervical dilatation becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.[2,3] It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,[1,3] mifepristone, or a prostaglandin such as gemeprost or misoprostol.[1-3] Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring about successful termination when used alone, but the high doses required can cause significant adverse effects.[4-6] The most commonly used prostaglandins are gemeprost and misoprostol;[3,4] others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.[3] The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.[3-5,7] The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.[4,5] Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.[1]

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,[1,2] local anaesthesia using paracervical block,[1-3] or general anaesthesia.[2] Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.[3,4] Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.[6] Generally, bleeding lasts longer after medical termination than after vacuum aspiration.[6] With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.[1,6]

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.[2,6] Methotrexate followed by a prostaglandin is an alternative at this early stage,[1,5] but expulsion can take several days or weeks.[4] Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses[4,5] so a vaginal prostaglandin is preferred.[2,5,6]
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.[2]
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.[2,3]

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after pregnancy failure or early fetal death. Surgical evacuation is effective but associated with a higher risk of infection than expectant management.[8] Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.[9] For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, above.

1. Stubblefield PG, *et al.* Methods for induced abortion. *Obstet Gynecol* 2004; **104:** 174–85.
2. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/induced_abortionfull.pdf (accessed 30/06/08)
3. Lalitkumar S, *et al.* Mid-trimester induced abortion: a review. *Hum Reprod Update* 2007; **13:** 37–52.
4. Hamoda H, Flett GMM. Medical termination of pregnancy in the early first trimester. *J Fam Plann Reprod Health Care* 2005; **31:** 10–14.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, issued October 2005). *Obstet Gynecol* 2005; **106:** 871–82.
6. WHO. Frequently asked clinical questions about medical abortion (2006). Available at: http://www.who.int/reproductive-health/publications/medical_abortion/faq.pdf (accessed 30/06/08)
7. Kulier R, *et al.* Medical methods for first trimester abortion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
8. Nanda K, *et al.* Expectant care versus surgical treatment for miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
9. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Aglepristone *(rINN)*

Aglepristona; Aglépristone; Aglepristonum; RU-46534. 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-[(*Z*)-propenyl]estra-4,9-dien-3-one.

Аглепристон

$C_{29}H_{37}NO_2$ = 431.6.

CAS — 124478-60-0.

ATC Vet — QG03XB90.

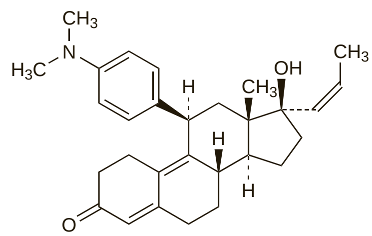

Profile

Aglepristone has antiprogestogenic activity and is used in veterinary medicine as an abortifacient in *dogs*.

Atosiban *(BAN, USAN, rINN)*

Atosibaani; Atosibanum; ORF-22164; RWJ-22164. 1-(3-Mercaptopropionic acid)-2-[3-(*p*-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfanylpropanoyl),2-(4-*O*-ethyltyrosine),4-L-threonine-8-L-ornithine]oxytocin.

Атозибан

$C_{43}H_{67}N_{11}O_{12}S_2$ = 994.2.

CAS — 90779-69-4.

ATC — G02CX01.

ATC Vet — QG02CX01.

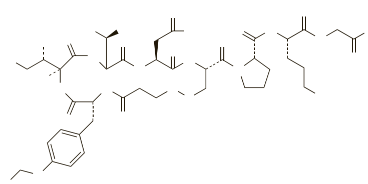

Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where gestational age is below 24 or over 33 weeks, in eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p.2015) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p.2003). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

1. Romero R, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182:** 1173–83.
2. Valenzuela GJ, *et al.* Maintenance treatment of preterm labor with the oxytocin antagonist atosiban: the Atosiban PTL-098 Study Group. *Am J Obstet Gynecol* 2000; **182:** 1184–90.
3. Moutquin JM, *et al.* Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000; **182:** 1191–9.
4. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001; **108:** 133–42.
5. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001; **80:** 413–22.
6. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 177–85.
7. Coomarasamy A, *et al.* Oxytocin antagonists for tocolysis in preterm labour—a systematic review. *Med Sci Monit* 2002; **8:** RA268–73.
8. Tsatsaris V, *et al.* Atosiban for preterm labour. *Drugs* 2004; **64:** 375–82.
9. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; **35:** 305–13.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tractocile; ***Austria:*** Tractocile; ***Belg.:*** Tractocile; ***Braz.:*** Tractocile†; ***Cz.:*** Tractocile; ***Denm.:*** Tractocile; ***Fin.:*** Tractocile; ***Fr.:*** Tractocile; ***Ger.:*** Tractocile; ***Gr.:*** Tractocile; ***Hong Kong:*** Tractocile; ***Hung.:*** Tractocile; ***Irl.:*** Tractocile; ***Ital.:*** Tractocile; ***Malaysia:*** Tractocile; ***Mex.:*** Tractocile; ***Neth.:*** Tractocile; ***Norw.:*** Tractocile; ***NZ:*** Tractocile; ***Pol.:*** Tractocile; ***Port.:*** Tractocile; ***S.Afr.:*** Tractocile; ***Spain:*** Tractocile; ***Swed.:*** Tractocile; ***Switz.:*** Tractocile; ***UK:*** Tractocile.

Carbetocin *(BAN, rINN)*

Carbetocina; Carbétocine; Carbetocinum; Karbetocin; Karbetosiini. 2,1-Desamino-4,1-desthio-$O^{4,2}$-methyl[1-homocysteine]-oxytocin; 1-Butyric acid-2-[3-(*p*-methoxyphenyl)-L-alanine]oxytocin.

Карбетоцин

$C_{45}H_{69}N_{11}O_{12}S$ = 988.2.

CAS — 37025-55-1.

ATC — H01BB03.

ATC Vet — QH01BB03.

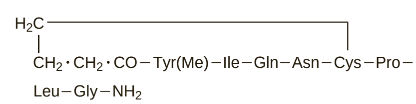

Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p.2015). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.[1] The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The American Academy of Pediatrics considers that the use of carbetocin is usually compatible with breast feeding.[2]

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82:** 456–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/08)

Interactions

Although reports are lacking, carbetocin may be involved in similar interactions to those that can occur with oxytocin (p.2016).

Pharmacokinetics

After intravenous injection of carbetocin, firm uterine contraction occurs within 2 minutes and lasts for several hours. Carbetocin undergoes a biphasic elimination, with a terminal elimination half-life of about 40 minutes. Less than 1% of a dose is excreted unchanged by the kidney. Carbetocin is distributed into breast milk.

Uses and Administration

Carbetocin is a synthetic analogue of oxytocin (p.2016) reported to have a longer duration of action. For the prevention of uterine atony and excessive bleeding after caesarean section under epidural or spinal anaesthesia, a single dose of 100 micrograms may be given by slow intravenous injection over 1 minute. Carbetocin must only be given after delivery of the infant, preferably before removal of the placenta.

◊ References.

1. Hunter DJS, *et al.* Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. *Clin Pharmacol Ther* 1992; **52:** 60–7.
2. Dansereau J, *et al.* Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol* 1999; **180:** 670–6.
3. Boucher M, *et al.* Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynaecol Can* 2004; **26:** 481–8.
4. Leung SW, *et al.* A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006; **113:** 1459–64.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Duratocin; ***Austral.:*** Duratocin; ***Canad.:*** Duratocin; ***Fr.:*** Pabal; ***Hong Kong:*** Duratocin; ***Hung.:*** Pabal; ***Malaysia:*** Duratocin; ***Mex.:*** Lonactene; ***Port.:*** Pabal; ***Singapore:*** Duratocin; ***UK:*** Pabal.

Multi-ingredient: ***Cz.:*** Duratocin.

Carboprost *(BAN, USAN, rINN)*

Carboprostum; 15-Me-PGF$_{2α}$; Methyldinoprost; (15S)-15-Methylprostaglandin F$_{2α}$; U-32921. (5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxy-15-methylprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl}hept-5-enoic acid.

Карбопрост

$C_{21}H_{36}O_5$ = 368.5.
CAS — 35700-23-3.
ATC — G02AD04.
ATC Vet — QG02AD04.

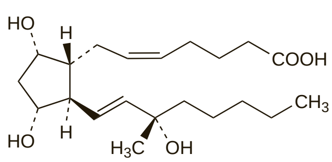

Carboprost Methyl *(BANM, USAN, rINNM)*

Carboprost Méthyle; Carboprostum Methylis; Methyl Carboprost; Metil carboprost; U-36384. The methyl ester of carboprost.

Карбопрост Метил

$C_{22}H_{38}O_5$ = 382.5.
CAS — 35700-21-1.
ATC — G02AD04.
ATC Vet — QG02AD04.

Pharmacopoeias. In *Chin.*

Carboprost Trometamol *(BANM, rINNM)*

Carboprost trométamol; Carboprost Tromethamine *(USAN)*; Carboprostum Trometamoli; Carboprostum trometamolum; Kaboprosttrometamol; Karboprost z trometamolem; Karboprostas trometamolis; Karboprostitrometamoli; Karboprost-trometamol; U-32921E.

Карбопрост Трометамол

$C_{21}H_{36}O_5,C_4H_{11}NO_3$ = 489.6.
CAS — 58551-69-2.
ATC — G02AD04.
ATC Vet — QG02AD04.

Description. Carboprost trometamol is a compound of carboprost with trometamol in a ratio of 1:1.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Carboprost Trometamol). A white or almost white powder. Soluble in water. Store at a temperature below −15°.

USP 31 (Carboprost Tromethamine). A white to off-white powder. Soluble in water. Store at −25° to −10°.

Adverse Effects and Precautions

As for Dinoprostone, p.2007.

Carboprost may cause bronchospasm and, less frequently, dyspnoea and pulmonary oedema. Patients with cardiopulmonary disorders should be monitored for reductions in arterial-oxygen content.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including carboprost (see under Dinoprostone, p.2007).

Effects on the neonate. For a report of inadvertent intramuscular administration of carboprost to a neonate, see under Dinoprostone, p.2007.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including carboprost, for termination of pregnancy or induction of labour, see Dinoprostone, p.2007.

Uses and Administration

Carboprost is a synthetic 15-methyl analogue of dinoprost (prostaglandin F$_{2α}$; below). It is a uterine stimulant with a more prolonged action than dinoprost; the presence of the methyl group delays inactivation by enzymic dehydrogenation.

Carboprost is used for the termination of pregnancy (p.2004) and for the treatment of refractory postpartum haemorrhage due to uterine atony (p.2003) that is not controlled by oxytocin and ergot preparations. It is usually given intramuscularly as the trometamol salt but doses are expressed in terms of carboprost. Carboprost trometamol 1.3 micrograms is equivalent to about 1 microgram of carboprost.

For the **termination** of second trimester pregnancy (between 13 and 20 weeks of gestation) the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection and repeated every 1½ to 3½ hours depending on the uterine response. If necessary the dose may be increased to 500 micrograms, but the total dose given should not exceed 12 mg, and continuous use for more than 2 days is not recommended. If preferred, a test dose of 100 micrograms may be given initially. Carboprost trometamol has also been given intra-amniotically in a dose equivalent to 1 mg of carboprost over five minutes; this dose may be repeated after 24 hours if termination has not occurred and the membranes are intact. A total dose of 5 mg should not be exceeded.

Carboprost methyl given as vaginal pessaries has been tried for termination of pregnancy in the second trimester.

For the treatment of **postpartum haemorrhage** the equivalent of 250 micrograms of carboprost is given by deep intramuscular injection as the trometamol salt at intervals of about 90 minutes; the interval may be reduced if necessary, but should not be less than 15 minutes. A total dose of 2 mg should not be exceeded.

Haemorrhagic cystitis. Carboprost trometamol instilled into the bladder successfully controlled cyclophosphamide-induced haemorrhagic cystitis (p.702) in 15 of 24 bone marrow transplant patients.[1] The dose consisted of 50 mL of solutions containing 2 to 10 micrograms/mL instilled four times daily for 7 days.

1. Ippoliti C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46:** 811–15.

Preparations

USP 31: Carboprost Tromethamine Injection.

Proprietary Preparations (details are given in Part 3)
Belg.: Prostin/15M; ***Canad.:*** Hemabate; ***Cz.:*** Prostin 15M; ***Denm.:*** Prostinfenem; ***India:*** Prostodin; ***Neth.:*** Prostin/15M; ***NZ:*** Prostin 15M; ***Swed.:*** Prostinfenem; ***UK:*** Hemabate; ***USA:*** Hemabate.

Demoxytocin *(rINN)*

Deamino-oxytocin; Demoksitosiini; Demoxitocina; Démoxytocine; Demoxytocinum; Desaminocitocina; Desamino-oxytocin; ODA-914. 1-(3-Mercaptopropionic acid)-oxytocin.

Демокситоцин

$C_{43}H_{65}N_{11}O_{12}S_2$ = 992.2.
CAS — 113-78-0.
ATC — H01BB01.
ATC Vet — QH01BB01.

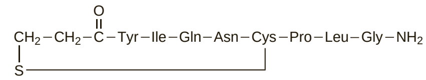

Profile

Demoxytocin is a synthetic analogue of oxytocin (p.2015) and has similar properties. It has been given as buccal tablets for the induction and augmentation of labour. It has also been given before nursing to stimulate milk ejection, although it is generally recommended that oxytocics should not be used for this purpose (see p.2003).

Dinoprost *(BAN, USAN, rINN)*

Dinoprosti; Dinoprostum; PGF$_{2α}$; Prostaglandin F$_{2α}$; U-14583. (5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-9,11,15-Trihydroxyprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl}hept-5-enoic acid.

Динопрост

$C_{20}H_{34}O_5$ = 354.5.
CAS — 551-11-1.
ATC — G02AD01.
ATC Vet — QG02AD01.

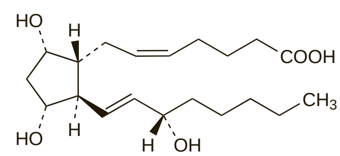

NOTE. In *Martindale* the term dinoprost is used for the exogenous substance and prostaglandin F$_{2α}$ for the endogenous substance.

Pharmacopoeias. In *Jpn.*

Dinoprost Trometamol *(BANM, rINNM)*

Dinoprost trométamol; Dinoprost Tromethamine *(USAN)*; Dinoprostas trometamolis; Dinoprostitrometamoli; Dinoprost-trometamol; Dinoprost-trometamol; Dinoprostum Trometamoli; Dinoprostum trometamolum; Dinoproszt-trometamol; PGF$_{2α}$ THAM; Prostaglandin F$_{2α}$ Trometamol; U-14583E.

Динопрост Трометамол

$C_{20}H_{34}O_5,C_4H_{11}NO_3$ = 475.6.
CAS — 38562-01-5.
ATC — G02AD01.
ATC Vet — QG02AD01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dinoprost Trometamol). A white or almost white powder. Very soluble in water; freely soluble in alcohol; practically insoluble in acetonitrile.

USP 31 (Dinoprost Tromethamine). A white to off-white crystalline powder. Very soluble in water; slightly soluble in chloroform; freely soluble in dimethylformamide; soluble in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Dinoprostone, p.2007.

Dinoprost can cause bronchoconstriction, and bronchospasm with wheezing and dyspnoea has occurred, especially in asthmatic patients.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Interactions

As for Dinoprostone, p.2008. Alcohol and beta agonists may reduce the efficacy of dinoprost.

◊ For a report of a severe reaction after the use of oxytocin, methylergometrine, and dinoprost, see under Dinoprostone, p.2008.

Uses and Administration

Dinoprost is a prostaglandin of the F series (p.2374) with actions on smooth muscle; the endogenous substance is termed prostaglandin F$_{2α}$ and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasoconstrictor on blood vessels and as a bronchoconstrictor on bronchial muscle.

Dinoprost is used principally for the termination of pregnancy (p.2004). It may also be used for missed abortion, hydatidiform mole, and intra-uterine fetal death. Dinoprost has also been given for the induction of labour but has a higher incidence of adverse effects than dinoprostone, and is no longer routinely recommended; more appropriate treatment is discussed on p.2002.

Dinoprost is usually given intra-amniotically for termination of pregnancy. It has been given intravenously, but with a high incidence of adverse effects. The extra-amniotic route has also been used. Dinoprost is given as the trometamol salt, but doses are described in terms of the base; 1.3 mg of dinoprost trometamol is equivalent to about 1 mg of dinoprost.

For the termination of pregnancy during the second trimester 40 mg of dinoprost is given intra-amniotically by slowly injecting 8 mL of a solution containing 5 mg/mL into the amniotic sac. A further dose of 10 to 40 mg may be given after 24 hours if the termination process has not been established or completed and the membranes are still intact. It should not be given continuously for more than 2 days.

Ileus. Ileus induced by vinca alkaloids in 3 patients with carcinoma of the lung was successfully relieved by the intravenous infusion of dinoprost 300 to 500 nanograms/kg per minute for 2 hours twice daily.[1]

1. Saito H, *et al.* Prostaglandin F in the treatment of vinca alkaloid-induced ileus. *Am J Med* 1993; **95:** 549–51.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Prostin F2 Alpha; ***Cz.:*** Enzaprost F; ***Ger.:*** Minprostin F α; ***Gr.:*** Enzaprost; ***Hong Kong:*** Prostin F2 Alpha; ***Hung.:*** Enzaprost F; ***Irl.:*** Prostin F2†; ***Israel:*** Prostin F2 Alpha; ***NZ:*** Prostin F2 Alpha; ***Pol.:*** Enzaprost; ***Rus.:*** Enzaprost F (Энзапрост Ф); Prostin F2 Alfa (Простин F2-Альфа)†; ***S.Afr.:*** Prostin F2 Alpha.

Dinoprostone *(BAN, USAN, rINN)*

Dinoproston; Dinoprostona; Dinoprostonas; Dinoprostoni; Dinoprostonum; Dinoproszton; PGE_2; Prostaglandin E_2; U-12062. (5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}hept-5-enoic acid.

Динопростон

$C_{20}H_{32}O_5$ = 352.5.

CAS — 363-24-6.

ATC — G02AD02.

ATC Vet — QG02AD02.

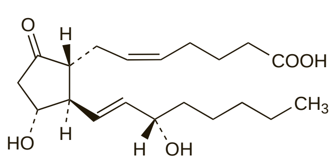

NOTE. In *Martindale* the term dinoprostone is used for the exogenous substance and prostaglandin E_2 for the endogenous substance.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dinoprostone). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Store at a temperature not exceeding −15°.

USP 31 (Dinoprostone). A white to off-white, crystalline powder. Freely soluble in alcohol, in acetone, in dichloromethane, in ether, in ethyl acetate, in isopropyl alcohol, in methyl alcohol; soluble in diisopropyl ether and in toluene; practically insoluble in hexanes. Protect from light.

Adverse Effects

The incidence and severity of adverse reactions to dinoprostone are dose-related and also depend to some extent on the route; the intravenous route has been associated with a high incidence of adverse effects. Nausea, vomiting, diarrhoea, and abdominal pain are common by all routes. Back pain and rash can occur. Transient cardiovascular (vasovagal) symptoms have included flushing, shivering, headache, dizziness, and hypotension; there have been rare reports of myocardial infarction and cardiac arrest. Hypertension has also been reported. Convulsions and EEG changes have occurred rarely. Local tissue irritation and erythema, as well as pyrexia and raised white cell count, may follow intravenous doses but generally revert to normal after termination of the infusion. Transient pyrexia and raised white cell count may also occur after intravaginal use. Local infection may follow intra- or extra-amniotic therapy. Excessive uterine activity may occur and there have been occasional reports of uterine rupture after the use of prostaglandins to terminate pregnancy or induce labour; fetal distress and, rarely, fetal death have occurred during induction. Disseminated intravascular coagulation has occurred rarely.

Dinoprostone, although generally acting as a bronchodilator, may cause bronchoconstriction in some individuals. Hypersensitivity reactions have occurred.

Incidence of adverse effects. Adverse effects were evaluated in 626 patients[1] undergoing abortion (usually in the second trimester), using extra-amniotic or intra-amniotic dinoprost or dinoprostone, often with oxytocin. Vomiting occurred in 291, diarrhoea in 28, pyrexia in 34, transient hypotension (fall in systolic blood pressure of at least 20 mmHg) in 25, transient bronchospasm in 2 patients given extra-amniotic dinoprost, and blood loss exceeding 250 mL in 68 (38 lost more than 500 mL). No patients had convulsions even though 8 were being treated for epilepsy. Three patients sustained lacerations to the cervix. Five patients complained of breast soreness or lactation; these symptoms may have been under-reported. Overall 14 patients were re-admitted; 13 because of excessive vaginal bleeding and 1 because of pelvic infection.

A later report describes the cumulative experience in 3313 pregnancies[2] in which dinoprostone gel was used for induction of term labour or cervical ripening. Adverse effects were rare. Vomiting, fever, and diarrhoea occurred in about 0.2% of mothers and were difficult to distinguish from the effects of concurrent drug therapy. Detectable myometrial activity was dose-related and more common after intravaginal than after intracervical use. Myometrial activity was reported in 0.6 to 6% of patients following intravaginal application and hyperstimulation was virtually non-existent at an intracervical dose of 500 micrograms. Fetal effects were negligible in the absence of uterine hyperstimulation.

1. MacKenzie IZ, *et al.* Prostaglandin-induced abortion: assessment of operative complications and early morbidity. *BMJ* 1974; **4:** 683–6.
2. Rayburn WF. Prostaglandin E gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol* 1989; **160:** 529–34.

Effects on the bones. Reversible periosteal reactions of the long bones and bone thickening have occurred in infants receiving long-term therapy with prostaglandins of the E series (see Alprostadil, p.2183). In addition, reversible widening of cranial sutures was reported[1] in 2 neonates given dinoprostone intravenously for 95 and 97 days respectively.

1. Hoevels-Guerich H, *et al.* Widening of cranial sutures after long-term prostaglandin E therapy in two newborn infants. *J Pediatr* 1984; **105:** 72–4.

Effects on the cardiovascular system. Cardiovascular adverse effects are most common after intravenous dinoprostone but may also occur with other routes. Severe cardiovascular disorders reported with the intra-amniotic or intravaginal use of dinoprost or dinoprostone have included: cardiac arrhythmias in 3 patients,[1,2] fatal in 2 of them;[2] hypotension, tachypnoea, and tachycardia in 3 patients[3,4] with associated pyrexias in 2 patients;[3] and fatal myocardial infarction in a patient who had several high-risk factors for ischaemic heart disease.[5]

Severe hypertension occurred in a patient[6] who received dinoprostone by direct myometrial injection and by intravenous infusion concomitantly for postpartum haemorrhage.

Adverse cardiovascular effects have also been reported with other prostaglandins used in gynaecological or obstetric indications (see under Gemeprost, p.2010, and Sulprostone, p.2018).

1. Burt RL, *et al.* Hypokalemia and cardiac arrhythmia associated with prostaglandin-induced abortion. *Obstet Gynecol* 1977; **50:** 45S–46S.
2. Cates W, Jordaan HVF. Sudden collapse and death of women obtaining abortions induced with prostaglandin F . *Am J Obstet Gynecol* 1979; **133:** 398–400.
3. Phelan JP, *et al.* Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E . *Am J Obstet Gynecol* 1978; **132:** 28–32.
4. Cameron IT, Baird DT. Sudden collapse after intra-amniotic prostaglandin E injection. *Lancet* 1984; **ii:** 1046.
5. Patterson SP, *et al.* A maternal death associated with prostaglandin E . *Obstet Gynecol* 1979; **54:** 123–4.
6. Veber B, *et al.* Severe hypertension during postpartum haemorrhage after i.v. administration of prostaglandin E2. *Br J Anaesth* 1992; **68:** 623–4.

Effects on the fetus. A woman who failed to abort despite receiving carboprost intravaginally 7 weeks after conception gave birth at 34 weeks of gestation to an infant with hydrocephalus and abnormal digits.[1] There have been reports of 2 infants born, without congenital abnormality, to women who continued with the pregnancy after attempted mid-trimester termination using intravaginal gemeprost.[2,3] However, abnormalities including limb deformities, cleft palate, anencephaly, cerebellar atrophy, and heart malformation were reported in a review[4] of 71 cases of pregnancy that were continued after attempted termination using mifepristone either alone or with a prostaglandin. Of the 8 cases of abnormality that were reported, 7 occurred in the group of 10 women who had been given intravaginal gemeprost. A case of cerebellar agenesis has also been described[5] after a failed medical termination using mifepristone and gemeprost. For abnormalities reported after the failed misuse of misoprostol alone for termination of pregnancy, see p.2013.

For reports of adverse effects on the fetus due to hyperstimulation of the uterus during labour, see under Effects on the Uterus, below.

1. Collins FS, Mahoney MJ. Hydrocephalus and abnormal digits after failed first-trimester prostaglandin abortion attempt. *J Pediatr* 1983; **102:** 620–1.
2. Lakasing L, Spencer JAD. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 1999; **106:** 1319–20.
3. Rolland P, Sinha A. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 2000; **107:** 1184.
4. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.
5. Afadapa FK, Elsapagh K. Isolated one-sided cerebellar agenesis following an attempted medical termination of pregnancy. *J Obstet Gynaecol* 2006; **26:** 581–2.

Effects on the gastrointestinal system. Necrotising enterocolitis has been associated with the use of intravenous[1] or oral[2] dinoprostone, or intravenous alprostadil,[2] in infants with symptomatic congenital heart disease. It has been suggested that induced hypotension and apnoea may be responsible,[1] although others[3] did not support this view, or that pulmonary vasodilatation may produce systemic to pulmonary shunting, rendering the gastrointestinal tract relatively ischaemic.[2]

1. Leung MP, *et al.* Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. *J Pediatr* 1988; **113:** 1044–6.
2. Singh GK, *et al.* Study of low dosage prostaglandin—usages and complications. *Eur Heart J* 1994; **15:** 377–81.
3. Miller MJS, Clark DA. Congenital heart disease and necrotizing enterocolitis. *J Pediatr* 1989; **115:** 335–6.

Effects on the neonate. Aspiration of the undissolved remnants of a dinoprostone vaginal tablet caused neonatal respiratory distress due to mechanical obstruction of the airways; there was no evidence to suggest absorption of dinoprostone from the tablet matrix.[1]

Inadvertent intramuscular injection of carboprost 250 micrograms caused hypertension, bronchospasm, diarrhoea, and hyperthermia in a neonate. There was also an adverse neurological effect that was either a dystonic reaction or seizure activity. The neonate was treated symptomatically and discharged 24 hours later; neurological and developmental examinations were normal at 3 months of age.[2] The authors of this report also learned of 2 other cases that had been reported to the manufacturer, in which neonates given injections of 125 micrograms and 63 micrograms remained asymptomatic.

1. Andersson S, *et al.* Neonatal respiratory distress caused by aspiration of a vaginal tablet containing prostaglandin. *BMJ* 1987; **295:** 25–6.
2. Mrvos R, *et al.* Carboprost exposure in a newborn with recovery. *J Toxicol Clin Toxicol* 1999; **37:** 865–7.

Effects on the nervous system. Convulsions and EEG changes have been occasionally reported during the use of prostaglandins for termination of pregnancy. Convulsions occurred[1] in 5 of 320 women after intra-amniotic dinoprost, but in other large series[2-4] of patients given dinoprost or dinoprostone by various routes no problems occurred despite the inclusion of patients with a history of epilepsy. However, convulsions were reported[5] in 3 of 4 epileptic patients given sulprostone intramuscularly.

1. Lyneham RC, *et al.* Convulsions and electroencephalogram abnormalities after intra-amniotic prostaglandin F . *Lancet* 1973; **ii:** 1003–5.
2. MacKenzie IZ, *et al.* Convulsions and prostaglandin-induced abortion. *Lancet* 1973; **ii:** 1323.
3. Thiery M, *et al.* Prostaglandins and convulsions. *Lancet* 1974; **i:** 218.
4. Fraser IS, Gray C. Electroencephalogram changes after prostaglandin. *Lancet* 1974; **i:** 360.
5. Brandenburg H, *et al.* Convulsions in epileptic women after administration of prostaglandin E derivative. *Lancet* 1990; **336:** 1138.

Effects on the uterus. Use of prostaglandins to induce labour or to terminate pregnancy is associated with an increased risk of hyperstimulation of the uterus. Uterine rupture has occurred with carboprost,[1] dinoprost or dinoprostone,[2-7] gemeprost,[8-10] misoprostol,[11-14] and sulprostone.[15-17] These effects have been reported with parenteral, local, and oral dosage. The risk of rupture and associated complications is increased in grand multiparae[4] and those with uterine scarring from previous caesarean section.[5,7] Studies have reported relative risks of between 6 and 10 times those of spontaneous labour after labour induction with dinoprostone in the latter group.[5,7] In addition to rupture, with the risk of potentially fatal maternal haemorrhage, hyperstimulation has been associated with fetal distress and death,[18-20] and maternal death due to amniotic fluid embolism.[18,21]

1. Vergote I, *et al.* Uterine rupture due to 15-methyl prostaglandin F . *Lancet* 1982; **ii:** 1402.
2. Claman P, *et al.* Uterine rupture with the use of vaginal prostaglandin E for induction of labor. *Am J Obstet Gynecol* 1984; **150:** 889–90.
3. Keller F, Joyce TH. Uterine rupture associated with the use of vaginal prostaglandin E suppositories. *Can Anaesth Soc J* 1984; **31:** 80–2.

4. Larsen JV, *et al.* Uterine hyperstimulation and rupture after induction of labour with prostaglandin E . *S Afr Med J* 1984; **65:** 615–16.
5. Ravasia DJ, *et al.* Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol* 2000; **183:** 1176–9.
6. Rabl M, *et al.* A randomized trial of vaginal prostaglandin E for induction of labor: insert vs tablet. *J Reprod Med* 2002; **47:** 115–19.
7. Taylor DR, *et al.* Uterine rupture with the use of PGE vaginal inserts for labor induction in women with previous cesarean sections. *J Reprod Med* 2002; **47:** 549–54.
8. Thavarasah AS, Achanna KS. Uterine rupture with the use of Cervagem (prostaglandin E1) for induction of labour on account of intrauterine death. *Singapore Med J* 1988; **29:** 351–2.
9. Byrne P, Onyekwuluje T. Uterine rupture after termination of pregnancy with gemeprost. *BMJ* 1991; **302:** 852.
10. Vine SJ, *et al.* Transverse posterior cervicoisthmic rupture after gemeprost pessaries for termination. *BMJ* 1992; **305:** 1332.
11. Blanchette HA, *et al.* Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E) with those of dinoprostone (prostaglandin E) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol* 1999; **180:** 1551–9.
12. Mathews JE, *et al.* Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *Int J Gynaecol Obstet* 2000; **68:** 43–4.
13. Khabbaz AY, *et al.* Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *J Matern Fetal Med* 2001; **10:** 141–5.
14. Nayki U, *et al.* Uterine rupture during second trimester abortion with misoprostol. *Fetal Diagn Ther* 2005; **20:** 469–71.
15. Larue L, *et al.* Rupture d'un utérus sain lors d'une interruption de grossesse par prostaglandines au deuxième trimestre. *J Gynecol Obstet Biol Reprod (Paris)* 1991; **20:** 269–72.
16. Prasad RNV, Ratnam SS. Uterine rupture after induction of labour for intrauterine death using the prostaglandin E analogue sulprostone. *Aust N Z J Obstet Gynaecol* 1992; **32:** 282–3.
17. de Boer MA, *et al.* Low dose sulprostone for termination of second and third trimester pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2001; **99:** 244–8.
18. Stronge J, *et al.* A neonatal and maternal death following the administration of intravaginal prostaglandin. *J Obstet Gynaecol* 1987; **7:** 271–2.
19. Quinn MA, Murphy AJ. Fetal death following extra-amniotic prostaglandin gel: report of two cases. *Br J Obstet Gynaecol* 1981; **88:** 650–1.
20. Simmons K, Savage W. Neonatal death associated with induction of labour with intravaginal prostaglandin E : case report. *Br J Obstet Gynaecol* 1984; **91:** 598–9.
21. Less A, *et al.* Vaginal prostaglandin E and fatal amniotic fluid embolus. *JAMA* 1990; **263:** 3259–60.

Overdosage. Severe adverse effects associated with intra-amniotic prostaglandins have been attributed to absorption into the systemic circulation of doses higher than would normally be given systemically. Rigors, vomiting, severe abdominal pain, and an intense desire to urinate and defaecate occurred[1] in 3 patients given dinoprostone intra-amniotically for mid-trimester abortion; one patient had peripheral vasoconstriction and a rapid low-volume pulse, with hypotension, and another had peripheral cyanosis. It was suggested[2] that this might have been due to displacement of the needle or cannula outside the amniotic sac. In 2 of the patients prior use of urea may have increased the rate of absorption of prostaglandins from the amniotic cavity. In a further report[3] flushing, severe headache, and nausea immediately after a test dose of dinoprost 2.5 mg was also thought to be due to incorrect positioning of the needle and consequent injection into the systemic circulation; at least part of the dose might have been injected into the peritoneal cavity.[4]

Severe reactions have also been reported with prostaglandins given to abort hydatidiform moles. A 20-year-old woman given 20 mg of dinoprostone by injection into the uterine cavity developed profound hypotension, bradycardia, and rigors, followed by nausea, vomiting, suprapubic pain, an increased pulse rate, pyrexia, and generalised flushing.[5] Since there are no fetal membranes in a molar pregnancy, intra-uterine administration is similar to extra-amniotic administration and the dose used was 100 times higher than the usual extra-amniotic dose.[4] However, in a similar patient[6] 'extra-amniotic' instillation of dinoprostone 200 micrograms was followed immediately by nausea, retching, severe abdominal pain, dizziness, difficulty in breathing and the production of frothy blood-stained sputum, an imperceptible pulse, and hypotension; the dinoprostone had probably been injected directly into the maternal circulation.

1. Ross AH, Whitehouse WL. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **1:** 642.
2. Craft I, Bowen-Simpkins P. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **2:** 446.
3. Brown R. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382.
4. Karim SMM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **3:** 347.
5. Smith AM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382–3.
6. McNicol E, Gray H. Adverse reaction to extra-amniotic prostaglandin E . *Br J Obstet Gynaecol* 1977; **84:** 229–30.

Precautions

Dinoprostone should not be given to patients in whom oxytocic drugs are generally contra-indicated (see also Oxytocin, p.2016), because spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia, or fetal distress. It should not be used where there is a predisposition to uterine rupture, as in high parity or the presence of a uterine scar from previous caesarean section or major uterine surgery, or in those with a history of pelvic inflammatory disease. Since prostaglandins enhance the effects of oxytocin, use of these drugs together or in sequence should be carefully monitored.

Dinoprostone is contra-indicated in active cardiac, pulmonary, renal, or hepatic disease. It should be used with caution in patients with glaucoma or raised intra-ocular pressure, a history of asthma or epilepsy, hepatic or renal impairment, or cardiovascular disease.

In the induction of labour cephalopelvic relationships should be carefully evaluated before use. During use uterine activity, fetal status, and the progress of cervical dilatation should be carefully monitored to detect adverse responses, such as hypertonus, sustained uterine contractions, or fetal distress. In patients with a history of hypertonic uterine contractility or tetanic uterine contractions, uterine activity and the state of the fetus should be continuously monitored throughout labour. Where high-tone myometrial contractions are sustained the possibility of uterine rupture should be considered.

Dinoprostone should not be given by the myometrial route, since there is a possible association with cardiac arrest in severely ill patients. The extra-amniotic route should not be used in patients with cervicitis or vaginal infections. Vaginal preparations of dinoprostone should not be used in the induction of labour once the membranes are ruptured. In some countries, intravenous prostaglandins are considered to be contra-indicated in women who smoke.

Dinoprostone should be used with caution in women over 35 years of age, those with complications during pregnancy, such as gestational diabetes, hypertension, or hypothyroidism, and in those past the fortieth week of pregnancy as their condition may further enhance the increased risk of disseminated intravascular coagulation in the immediate postpartum period associated with pharmacologically induced labour.

In the therapeutic termination of pregnancy, fetal damage has been seen in cases of incomplete termination and the appropriate treatment for complete evacuation of the uterus should therefore be instituted whenever termination is unsuccessful or incomplete. Dinoprostone should not be used for termination in patients with pelvic infection, unless adequate treatment has already been started.

Administration. For the hazards of unintentional systemic absorption of prostaglandins after intra-uterine use for the termination of pregnancy and abortion of hydatidiform moles, see Overdosage in Adverse Effects, above.

Interactions

Dinoprostone enhances the effects of oxytocin on the uterus. There is a theoretical risk that prostaglandin synthetase inhibitors, such as aspirin and NSAIDs, might alter the efficacy of dinoprostone.

Uterine stimulants. Marked hypertension, vomiting, and severe dyspnoea occurred after the sequential use of *oxytocin*, *methylergometrine*, and *dinoprost* within the space of 10 minutes to a woman with postpartum haemorrhage.[1]

1. Cohen S, *et al.* Severe systemic reactions following administration of different ureotonic [uterotonic] drugs. *N Y State J Med* 1983; **83:** 1060–1.

Uses and Administration

Dinoprostone is a prostaglandin of the E series (p.2374) with actions on smooth muscle; the endogenous substance is termed prostaglandin E_2 and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasodilator and as a bronchodilator. In the UK, dinoprostone is used principally in the induction of labour (p.2002); it may also be used for the termination of pregnancy (p.2004), missed abortion, hydatidiform mole, and intra-uterine fetal death.

Dinoprostone is usually given vaginally. It may also be given intravenously, extra-amniotically, or orally, but the intravenous route has been associated with a high incidence of adverse effects and is generally only used for missed abortion or hydatidiform mole; continuous use for more than 2 days is not recommended.

For the **induction of labour** dinoprostone is used to ripen (soften and dilate) the cervix before the membranes are ruptured and to induce labour at term. The cervical gel used for cervical ripening contains 500 micrograms in 2.5 mL, whereas the vaginal gel used for induction of labour contains 1 or 2 mg in 2.5 mL; the vaginal gel should not be used in the cervical canal. Pessaries are also available for both cervical ripening and labour induction. These are not bioequivalent to the gels and their dosage is different.

To soften and dilate the cervix before induction of labour dinoprostone 500 micrograms is given as *cervical gel*. This dose may be repeated after 6 hours if there was no response to the initial dose; in some cases a third dose may be used to a maximum cumulative dose of 1.5 mg in 24 hours.

For induction of labour the dose as *vaginal gel* is 1 mg (or 2 mg in primigravid patients with unfavourable induction features) followed, if necessary, by a further 1 or 2 mg after 6 hours; a total dose of 3 mg (or 4 mg in unfavourable primigravid patients) should not be exceeded. Alternatively a *vaginal pessary* containing 3 mg may be used and this may be followed, if necessary, by a further 3 mg after 6 to 8 hours; a total dose of 6 mg should not be exceeded.

A *modified-release vaginal pessary* containing 10 mg and delivering about 300 micrograms/hour can be used for cervical ripening and subsequent labour induction. If satisfactory cervical ripening does not occur within 12 or 24 hours, depending on the preparation, then it should be removed.

Dinoprostone may be given *orally* for the induction of labour in an initial dose of 500 micrograms, repeated hourly, and increased if necessary to 1 mg hourly until an adequate response is achieved; single doses of 1.5 mg should not be exceeded. Oral use has, however, generally been replaced by intravaginal dosage since the latter is associated with fewer gastrointestinal adverse effects.

Dinoprostone has been given *intravenously* for the induction of labour but is no longer recommended for routine use by most authorities. A suggested intravenous dosage has been 250 nanograms/minute infused as a solution containing 1.5 micrograms/mL for 30 minutes, the dose being subsequently maintained or increased according to the patient's response; in intra-uterine fetal death higher doses may be required and an initial rate of 500 nanograms/minute has been used with increases at intervals of not less than 1 hour.

For the **termination of pregnancy** in the second trimester 1 mL of a solution containing dinoprostone 100 micrograms/mL may be instilled *extra-amniotically* through a suitable Foley catheter, with subsequent doses of 1 or 2 mL given at intervals usually of 2 hours, according to response. Dinoprostone has also been given *intravenously* for the termination of pregnancy and for missed abortion or hydatidiform mole. A solution containing 5 micrograms/mL may be infused at a rate of 2.5 micrograms/minute for 30 minutes, the infusion then being maintained or increased to a rate of 5 micrograms/minute; this rate should be maintained for at least 4 hours before making further increases.

In the USA dinoprostone pessaries are used for the termination of second trimester pregnancy. A dose of 20 mg is given *intravaginally* and repeated every 3 to 5 hours according to response for up to 2 days; a total dose of 240 mg should not be exceeded. Pessaries are also used in the USA in missed abortion, intra-uterine fetal death, and benign hydatidiform mole.

Dinoprostone is used in some centres to maintain the patency of the ductus arteriosus (see below).

Haemorrhagic cystitis. Dinoprostone instilled into the bladder for 4 hours and repeated for 4 days successfully improved severe cyclophosphamide-induced haemorrhagic cystitis (p.702) in a bone marrow transplant recipient.[1] Similar results were obtained in another series of 10 patients.[2]

1. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E . *Ann Intern Med* 1984; **101:** 142.
2. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.

Hepatic disorders. See under Alprostadil, p.2184, for reference to the use of prostaglandins, including dinoprostone, in the treatment of viral hepatitis.

Patent ductus arteriosus. Prostaglandins, particularly alprostadil (p.2184) and dinoprostone, may be used to maintain the patency of the ductus arteriosus in infants with congenital heart disease until surgery can be performed to correct the malformation. Treatment for a longer period, especially with oral dinoprostone, may facilitate later surgery by allowing growth of the infants and their pulmonary arteries.

Beneficial responses to long-term use of dinoprostone have been reported.[1,2] Dinoprostone has been given orally in an initial dose of 20 to 25 micrograms/kg hourly, decreasing the frequency of doses after the first week; it was suggested that treatment should be continued for up to 4 weeks initially and a decision then made whether to proceed with surgery or to plan a longer course of treatment to encourage further growth. When gastrointestinal absorption is expected to be poor or when oral treatment is ineffective, dinoprostone has been given by intravenous infusion. The *BNFC* recommends an initial dose of 5 to 10 nanograms/kg per minute increased as necessary, in steps of 5 nanograms/kg per minute, to 20 nanograms/kg per minute; further increases may be needed and doses of up to 100 nanograms/kg per minute have been used, however, these are associated with an increased risk of adverse effects.

1. Silove ED, *et al.* Evaluation of oral and low dose intravenous prostaglandin E in management of ductus dependent congenital heart disease. *Arch Dis Child* 1985; **60:** 1025–30.
2. Thanopoulos BD, *et al.* Prostaglandin E administration in infants with ductus-dependent cyanotic congenital heart disease. *Eur J Pediatr* 1987; **146:** 279–82.

Pemphigus. Erosive oral lesions in 3 patients[1] with pemphigus vulgaris (p.1582), that had previously been refractory to standard corticosteroid therapy, resolved on sucking oral dinoprostone tablets 1.5 to 3 mg daily. Symptoms recurred within weeks of ceasing dinoprostone but could be controlled by courses of 0.5 to 1 mg daily for 1 to 2 weeks, when required. In a group of 10 patients,[2] topical dinoprostone produced similar results in 6 patients, but disease was exacerbated in the others; the dinoprostone was applied twice daily, but details of the dosage form and dose were not reported.

1. Morita H, *et al.* Clinical trial of prostaglandin E on the oral lesions of pemphigus vulgaris. *Br J Dermatol* 1995; **132:** 165–6.
2. Kumaran MS, Kanwar AJ. Efficacy of topical PGE2 in recalcitrant oral lesions of pemphigus vulgaris: a clinical trial. *J Eur Acad Dermatol Venereol* 2006; **20:** 898–9.

Peripheral vascular disease. Various prostaglandins have been used in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy.

Postpartum haemorrhage. Dinoprostone and other prostaglandins have been used to control severe postpartum haemorrhage (p.2003) unresponsive to ergometrine and oxytocin.

Beneficial response to continuous intra-uterine irrigation with dinoprostone solution 1.5 micrograms/mL was seen in 22 patients with postpartum haemorrhage unresponsive to other treatment.[1] Postpartum haemorrhage was controlled in another patient using a dinoprostone 3-mg vaginal suppository held against the uterine wall.[2]

1. Peyser MR, Kupfermine MJ. Management of severe postpartum hemorrhage by intrauterine irrigation with prostaglandin E . *Am J Obstet Gynecol* 1990; **162:** 694–6.
2. Markos AR. Prostaglandin E intrauterine suppositories in the treatment of secondary postpartum hemorrhage. *J R Soc Med* 1989; **82:** 504–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prolisina E2; Propess; ***Austral.:*** Cervidil; Prostin E2; ***Austria:*** Prepidil; Propess; Prostin E2; ***Belg.:*** Prepidil; Prostin E2; ***Canad.:*** Cervidil; Prepidil; Prostin E2; ***Cz.:*** Prepidil; Propess; Prostin E2; ***Denm.:*** Minprostin; ***Fin.:*** Minprostin; Propess; ***Fr.:*** Prepidil; Propess; Prostine E ; ***Ger.:*** Minprostin E ; Prepidil; Propess; ***Gr.:*** Minprostin; Propess; Prostin E2; ***Hong Kong:*** Prostin E2; ***Hung.:*** Prepidil; Propess†; Prostin E2; ***India:*** Cerviprime; Primiprost; ***Indon.:*** Prostin E2; ***Irl.:*** Prostin E2; ***Israel:*** Prepidil; Propess; Prostin E2; ***Ital.:*** Prepidil; Propess; Prostin E2; ***Malaysia:*** Prostin E2; ***Mex.:*** Prepidil; Propess; ***Neth.:*** Prepidil; Propess; Prostin E2; ***Norw.:*** Minprostin; ***NZ:*** Cervidil; Prostin E2; ***Pol.:*** Prepidil; Propess; ***Port.:*** Propess; Prostin E2; ***Rus.:*** Prepidil (Препидил); Prostin E2 (Простин Е2)†; ***S.Afr.:*** Prandin E ; Prepidil; Propess; Prostin E2; ***Singapore:*** Prostin E2; ***Spain:*** Prepidil; Propess; ***Swed.:*** Minprostin; Propess; ***Switz.:*** Prepidil†; Propess; Prostin E2; ***Thai.:*** Prostin E2; ***UK:*** Propess; Prostin E2; ***USA:*** Cervidil; Prepidil; Prostin E2.

Ergometrine Maleate *(BANM, rINNM)*

Ergobasine Maleate; Ergometriinimaleaatti; Ergométrine, maléate d'; Ergometrinhydrogenmaleat; Ergometrini maleas; Ergometrin-maleat; Ergometrin-maleát; Ergometrin-maleinát; Ergometrino maleatas; Ergonovine Bimaleate; Ergonovine Maleate; Ergostetrine Maleate; Ergotocine Maleate; Maleato de ergobasina; Maleato de ergometrina; Maleato de Ergonovina. *N*-[(*S*)-2-Hydroxy-1-methylethyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

Эргометрина Малеат

$C_{19}H_{23}N_3O_2,C_4H_4O_4$ = 441.5.

CAS — 60-79-7 (ergometrine); 129-51-1 (ergometrine maleate).

ATC — G02AB03.

ATC Vet — QG02AB03.

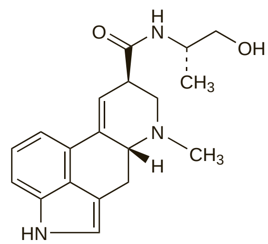

(ergometrine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ergometrine Maleate). A white or almost white or slightly coloured, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 3.6 to 4.4. Store in airtight glass containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Ergonovine Maleate). A white to greyish-white or faintly yellow, odourless, microcrystalline powder. It darkens with age and on exposure to light. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. Deterioration and degradation of ergometrine-containing injections has been seen when exposed to high temperatures in the tropics.[1-4] The mean loss in one study[3] of ergometrine injection under shipment to the tropics was 5.8%, but in some individual samples the loss was more marked: 18 of 80 test samples contained less than 80% of the stated content, and in 3 cases the content was less than 60%. A similar but much less significant pattern was seen with methylergometrine: the content varied from 98.6 to 99.5% of the labelled amount. Tablets of ergometrine and methylergometrine were also shown to be unstable under simulated tropical conditions, with humidity as the main adverse factor.[5]

1. Walker GJA, *et al.* Potency of ergometrine in tropical countries. *Lancet* 1988; **ii:** 393.
2. Abu-Reid IO, *et al.* Stability of drugs in the tropics. *Int Pharm J* 1990; **4:** 6–10.
3. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–12.
4. Hogerzeil HV, Walker GJ. Instability of (methyl)ergometrine in tropical climates: an overview. *Eur J Obstet Gynecol Reprod Biol* 1996; **69:** 25–9.
5. de Goot ANJA, *et al.* Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. *J Clin Pharm Ther* 1995; **20:** 109–13.

Adverse Effects and Treatment

Nausea and vomiting, abdominal pain, diarrhoea, headache, dizziness, tinnitus, chest pain, palpitations, bradycardia and other cardiac arrhythmias, coronary artery vasospasm, myocardial infarction, dyspnoea, and pulmonary oedema have been reported after use of ergometrine. Hypertension may occur, particularly after rapid intravenous dosage; hypotension has also been reported. Hypersensitivity reactions, including shock, have occurred. Ergometrine shows less tendency to produce gangrene than ergotamine, but ergotism has been reported and symptoms of acute poisoning are similar (see p.620).

Adverse effects should be treated as for ergotamine, p.620.

Effects on the respiratory system. Bronchospasm has been reported after use of ergometrine.[1] Although studies *in vitro* on *canine* bronchi have suggested a direct action on smooth muscle, this could not be confirmed in studies using human bronchi.

1. Hill H, *et al.* Ergometrine and bronchospasm. *Anaesthesia* 1987; **42:** 1115–16.

Overdosage. Ergometrine maleate has been given accidentally in adult doses to neonates,[1-5] sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, encephalopathy, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance. When given with oxytocin, water intoxication has also been reported.[1] In all of these cases, recovery occurred after intensive symptomatic treatment including assisted ventilation and anticonvulsants. However, deaths have also been recorded.[5] The long-term outcome of ergometrine overdosage has been reported for 6 infants.[5] Their ages at follow-up ranged from 18 months to 5 years; all had normal physical and behavioural development and neurological outcomes.

1. Whitfield MF, Salfield SAW. Accidental administration of Syntometrine in adult dosage to the newborn. *Arch Dis Child* 1980; **55:** 68–70.
2. Pandey SK, Haines CI. Accidental administration of ergometrine to newborn infant. *BMJ* 1982; **285:** 693.
3. Mitchell AA, *et al.* Accidental administration of ergonovine to a newborn. *JAMA* 1983; **250:** 730–1.
4. Donatini B, *et al.* Inadvertent administration of uterotonics to neonates. *Lancet* 1993; **341:** 839–40.
5. Dargaville PA, Campbell NT. Overdose of ergometrine in the newborn infant: acute symptomatology and long-term outcome. *J Paediatr Child Health* 1998; **34:** 83–9.

Precautions

As for Ergotamine Tartrate, p.620. Ergometrine should also be used with caution in patients with veno-atrial shunts or mitral valve stenosis. Ergometrine is contra-indicated for the induction of labour or for use during the first stage of labour. If used at the end of the second stage of labour, before delivery of the placenta, there must be expert obstetric supervision. Its use should be avoided in patients with pre-eclampsia, eclampsia, or threatened spontaneous abortion.

Porphyria. Ergometrine maleate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Ergotamine Tartrate, p.621. Halothane has been considered to diminish the effects of ergometrine on the uterus.

Sympathomimetics. Use of *dopamine* in a patient treated with ergometrine was associated with subsequent development of gangrene in both hands and feet.[1] In another case,[2] the use of ergometrine with *noradrenaline* resulted in cyanosis of the hands and necrosis in some of the fingers.

1. Buchanan N, *et al.* Symmetrical gangrene of the extremities associated with the use of dopamine subsequent to ergometrine administration. *Intensive Care Med* 1977; **3:** 55–6.
2. Chuang S-S. Finger ischemia secondary to the synergistic agonist effect of norepinephrine and ergonovine and in a burn patient. *Burns* 2003; **29:** 92–4.

Pharmacokinetics

Ergometrine is reported to be rapidly absorbed after doses by mouth and by intramuscular injection, with onset of uterine contractions in about 5 to 15 minutes and 2 to 7 minutes, respectively. Elimination appears to be principally by hepatic metabolism.

Uses and Administration

Ergometrine has a much more powerful action on the uterus than most other ergot alkaloids, especially on the puerperal uterus. Its main action is the production of intense contractions, which at higher doses are sustained, in contrast to the more physiological rhythmic uterine contractions induced by oxytocin; its action is more prolonged than that of oxytocin.

Ergometrine maleate is used in the active management of the third stage of labour, and to prevent or treat postpartum or postabortal haemorrhage (p.2003) caused by uterine atony; by maintaining uterine contraction and tone, blood vessels in the uterine wall are compressed, and blood flow reduced.

In the **active management of the third stage of labour**, ergometrine maleate and oxytocin are given together under full obstetric supervision. A dose of ergometrine maleate 500 micrograms and oxytocin 5 units is injected intramuscularly after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant; contractions are reported to occur within 2 to 7 minutes. Delivery of the placenta is actively assisted while the uterus is firmly contracted.

In the prevention or treatment of **postpartum haemorrhage**, a similar dose of ergometrine maleate with oxytocin is given intramuscularly following delivery of the placenta or when bleeding occurs. A combined intravenous preparation of ergometrine maleate with oxytocin has been used but is no longer recommended. Ergometrine maleate alone is used for prevention or treatment of postpartum or postabortal haemorrhage in a usual intramuscular dose of 200 micrograms. The dose may be repeated in severe bleeding, but is rarely needed more often than once in 2 to 4 hours. In emergencies such as excessive uterine bleeding, ergometrine maleate has been given intravenously in a dose of 200 micrograms; single doses of 250 to 500 micrograms have also been used. Intravenous doses should be given over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. Parenteral treatment of haemorrhage may be followed by ergometrine maleate 200 to 400 micrograms orally 2 to 4 times daily until the danger of atony and haemorrhage has passed, which is usually 48 hours. Tablets have also been given sublingually.

In the treatment of mild secondary postpartum haemorrhage, ergometrine maleate has been given orally.

Ergometrine tartrate was formerly used.

Diagnosis and testing. Ergometrine maleate[1-8] or methylergometrine maleate[9,10] have been used in a provocation test for the diagnosis of Prinzmetal's angina (variant angina) (p.1157).

1. Waters DD, *et al.* Ergonovine testing in a coronary care unit. *Am J Cardiol* 1980; **46:** 922–30.
2. Health and Public Policy Committee, American College of Physicians. Performance of ergonovine provocative testing for coronary artery spasm. *Ann Intern Med* 1984; **100:** 151–2.
3. Song J-K, *et al.* Safety and clinical impact of ergonovine stress echocardiography for diagnosis of coronary vasospasm. *J Am Coll Cardiol* 2000; **35:** 1850–6.
4. Kashima K, *et al.* Long-term outcome of patients with ergonovine induced coronary constriction not associated with ischemic electrocardiographic changes. *J Cardiol* 2001; **37:** 301–8.
5. Palinkas A, *et al.* Safety of ergot stress echocardiography for non-invasive detection of coronary vasospasm. *Coron Artery Dis* 2001; **12:** 649–54.
6. Song JK, *et al.* Prognostic implication of ergonovine echocardiography in patients with near normal coronary angiogram or negative stress test for significant fixed stenosis. *J Am Soc Echocardiogr* 2002; **15:** 1346–52.
7. Sueda S, *et al.* Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. *Coron Artery Dis* 2004; **15:** 491–7.
8. Coma-Canella I, *et al.* Ergonovine test in angina with normal coronary arteries: is it worth doing it? *Int J Cardiol* 2006; **107:** 200–6.
9. Bertrand ME, *et al.* Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; **65:** 1299–1306.
10. Lablanche JM, *et al.* Réflexions d'un comité d'experts de la Société française de cardiologie concernant l'usage du maléate de méthylergométrine (Methergin) dans la détection d'une vasomotricité coronaire anormale. *Arch Mal Coeur Vaiss* 1995; **88:** 247–53.

Preparations

BP 2008: Ergometrine and Oxytocin Injection; Ergometrine Injection; Ergometrine Tablets;
USP 31: Ergonovine Maleate Injection; Ergonovine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Evina; Metrergina; ***Braz.:*** Ergotrate†; ***Gr.:*** Mitrotan; ***Mex.:*** Ergotrate; ***Thai.:*** Gynaemine; ***USA:*** Ergotrate.

Multi-ingredient: ***Austral.:*** Syntometrine; ***Hong Kong:*** Syntometrine†; ***Irl.:*** Syntometrine; ***Malaysia:*** Syntometrine; ***NZ:*** Syntometrine; ***S.Afr.:*** Syntometrine; ***UK:*** Syntometrine.

Ergot

Cornezuelo del centeno; Secale Cornutum.

Спорынья

Description. Ergot consists of the sclerotium of the fungus *Claviceps purpurea* (Hypocreaceae) developed in the ovary of the rye, *Secale cereale* (Gramineae). It contains not less than 0.15% of total alkaloids, calculated as ergotoxine, and not less than 0.01% of water-soluble alkaloids, calculated as ergometrine. Some authorities have expressed alkaloidal content in terms of ergotamine and ergometrine.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p.620.

Epidemic ergot poisoning, arising from the ingestion of ergotised rye bread, is now seldom seen. Two forms of epidemic toxicity, which rarely occur together, have been described: a gangrenous form characterised by agonising pain of the extremities of the body followed by dry gangrene of the peripheral parts, and a rarer nervous type giving rise to paroxysmal epileptiform convulsions.

Poisoning. A report of an outbreak of ergotism, attributed to the ingestion of infected wild oats (*Avena abyssinica*), in Ethiopia.[1]

1. King B. Outbreak of ergotism in Wollo, Ethiopia. *Lancet* 1979; **ii:** 1411.

Uses and Administration

Ergot has the vasoconstricting and oxytocic actions of its constituent alkaloids, especially ergotamine (p.620) and ergometrine (above). A liquid extract or tablets of prepared ergot were formerly used as an oxytocic. Preparations containing ergot extracts have been promoted for use in dyspepsia and nervous disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Ergotab.

Ergotoxine

Ecboline; Ergotoxina.

Эрготоксин

CAS — 8006-25-5 (ergotoxine); 8047-28-7 (ergotoxine esilate); 8047-29-8 (ergotoxine phosphate); 564-36-3 (ergocornine); 511-08-0 (ergocristine); 511-09-1 (α-ergocryptine); 20315-46-2 (β-ergocryptine).

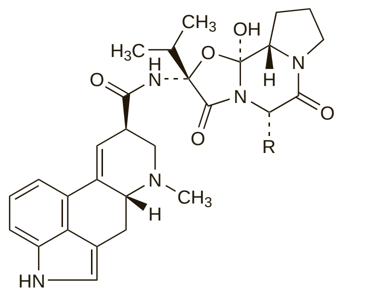

Ergocornine	R = $CH(CH_3)_2$
Ergocristine	R = $CH_2C_6H_5$
α-Ergocryptine	R = $CH_2CH(CH_3)_2$
β-Ergocryptine	R = $CH(CH_3)CH_2CH_3$

Profile

Ergotoxine is a mixture of naturally occurring ergot alkaloids. It contains equal proportions of ergocornine ($C_{31}H_{39}N_5O_5$ = 561.7), ergocristine ($C_{35}H_{39}N_5O_5$ = 609.7), and ergocryptine ($C_{32}H_{41}N_5O_5$ = 575.7) as the α- and β-isomers. The esilate was formerly used as an oxytocic and in the treatment of migraine. Ergotoxine phosphate has also been used.

Gemeprost *(BAN, USAN, rINN)*

16,16-Dimethyl-*trans*-Δ^2-prostaglandin E_1 methyl ester; Géméprost; Gemeprosti; Gemeprostum; ONO-802; SC-37681. Methyl (2*E*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dienoate; Methyl (*E*)-7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-oxocyclopentyl}hept-2-enoate.

Гемепрост

$C_{23}H_{38}O_5$ = 394.5.
CAS — 64318-79-2.
ATC — G02AD03.
ATC Vet — QG02AD03.

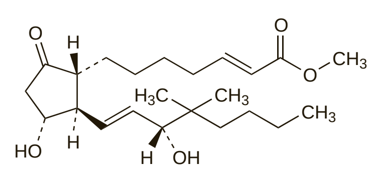

Adverse Effects and Precautions

As for Dinoprostone, p.2007. Vaginal bleeding and mild uterine pain may occur. Pulse and blood pressure should be monitored in patients given gemeprost.

The effects of gemeprost on the fetus are not known. Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Incidence of adverse effects. The incidence of vomiting (19 or 35%) and diarrhoea (12 or 19%) in 2 studies of patients treated with gemeprost pessaries was similar to that seen with other prostaglandins, but gemeprost was reported to cause less uterine pain.[1,2]

1. Cameron IT, Baird DT. The use of 16,16-dimethyl-trans-Δ prostaglandin E methyl ester (gemeprost) vaginal pessaries for the termination of pregnancy in the early second trimester: a comparison with extra-amniotic prostaglandin E . *Br J Obstet Gynaecol* 1984; **91:** 1136–40.
2. Andersen LF, *et al.* Termination of second trimester pregnancy with gemeprost vaginal pessaries and intra-amniotic PGF : a comparative study. *Eur J Obstet Gynecol Reprod Biol* 1989; **31:** 1–7.

Effects on the cardiovascular system. Periods of ventricular standstill of up to 6 seconds were seen in a patient during treatment with gemeprost vaginal pessaries.[1] The patient required temporary cardiac pacing, but no persistent cardiac rhythm disturbances were detected on follow-up. Severe cardiogenic shock due to vasospasm, and subsequent stroke, has been reported in a patient who had received gemeprost pessaries some hours earlier; myocardial infarction ensuing from coronary spasm was reported in a second patient.[2]

1. Kalra PA, *et al.* Cardiac standstill induced by prostaglandin pessaries. *Lancet* 1989; **i:** 1460–1.
2. Schulte-Sasse U. Life threatening myocardial ischaemia associated with the use of prostaglandin E to induce abortion. *Br J Obstet Gynaecol* 2000; **107:** 700–2.

Effects on the fetus. Congenital abnormalities have been reported in pregnancies carried to term after failed termination using prostaglandins, including gemeprost (see under Dinoprostone, p.2007).

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including gemeprost, for termination of pregnancy or induction of labour, see under Dinoprostone, p.2007.

Interactions

As for Dinoprostone, p.2008.

Uses and Administration

Gemeprost is a synthetic analogue of alprostadil (prostaglandin E_1; p.2183). It is used to soften and dilate the cervix and as a uterine stimulant in the termination of pregnancy (p.2004). In the first trimester, a pessary containing gemeprost 1 mg is inserted into the vagina 3 hours before surgery to ripen the cervix. Gemeprost may also be used for termination of pregnancy in the second trimester when a 1-mg pessary is inserted every 3 hours to a maximum of 5 pessaries. If this is ineffective, one further course may be given starting 24 hours after the beginning of the first course. If termination is not well established after 10 pessaries, alternative treatment should be used to complete uterine evacuation. In the case of intra-uterine fetal death in the second trimester, only one course of up to 5 pessaries should be given. Vaginal gemeprost is also used after oral mifepristone (p.2012) in the termination of pregnancy.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cervagem; ***Denm.:*** Cervagem; ***Fin.:*** Cervagem†; ***Fr.:*** Cervageme; ***Ger.:*** Cergem; ***Hong Kong:*** Cervagem†; ***Ital.:*** Cervidil; ***Jpn:*** Preglandin; ***Malaysia:*** Cervagem; ***Norw.:*** Cervagem†; ***NZ:*** Cervagem; ***Singapore:*** Cervagem; ***Swed.:*** Cervagem.

Meteneprost *(USAN, rINN)*

9-Deoxo-16,16-dimethyl-9-methylene-prostaglandin E_2; Méténéprost; Meteneprostum; U-46785. (5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*R*)-11,15-Dihydroxy-16,16-dimethyl-9-methyleneprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyloct-1-enyl]-5-methylenecyclopentyl}hept-5-enoic acid.

Метенепрост

$C_{23}H_{38}O_4$ = 378.5.
CAS — 61263-35-2.

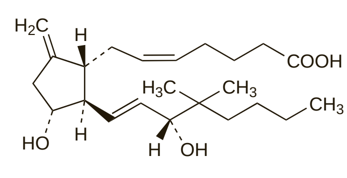

Profile

Meteneprost is a synthetic derivative of dinoprostone (prostaglandin E_2; p.2007). It is a uterine stimulant and has been studied for the termination of pregnancy.

◊ References.

1. Takkar D, *et al.* Early abortion by mifepristone (RU 486) followed by vaginal gel (meteneprost) versus oral (misoprostol) prostaglandin. *Adv Contracept* 1999; **15:** 163–73.
2. An ICMR Task Force Study. A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE gel (meteneprost) or 600 μg oral PGE (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. *Contraception* 2000; **62:** 125–30.

Methylergometrine Maleate *(BANM, rINNM)*

Maleato de metilergometrina; Methylergobasine Maleate; Méthylergométrine, hydrogénomaléate de; Méthylergométrine, Maléate de; Methylergometrini hydrogenomaleas; Methylergometrini Maleas; Methylergonovine Maleate; Metilergobazin Maleat; Metilergometrin Maleat. *N*-[(*S*)-1-(Hydroxymethyl)propyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

Метилэргометрина Малеат

$C_{20}H_{25}N_3O_2,C_4H_4O_4$ = 455.5.

CAS — 113-42-8 (methylergometrine); 57432-61-8 (methylergometrine maleate).

ATC — G02AB01.

ATC Vet — QG02AB01.

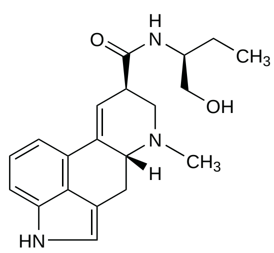

(methylergometrine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Methylergometrine Maleate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; slightly soluble in anhydrous alcohol. pH of a 0.5% solution is 4.4 to 5.2. Store in airtight containers. Protect from light.

USP 31 (Methylergonovine Maleate). A white to pinkish-tan, odourless, microcrystalline powder. Soluble 1 in 100 of water, 1 in 175 of alcohol, 1 in 1900 of chloroform, and 1 in 8400 of ether. pH of a 0.02% solution in water is between 4.4 and 5.2. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. For mention of slight variations in the methylergometrine content of the injection after transport to a tropical climate, see under Ergometrine Maleate, p.2009.

Adverse Effects, Treatment, and Precautions

As for Ergometrine Maleate, p.2009.

Overdosage. References.

1. Aeby A, *et al.* Methylergometrine poisoning in children: review of 34 cases. *J Toxicol Clin Toxicol* 2003; **41:** 249–53.
2. Bangh SA, *et al.* Neonatal ergot poisoning: a persistent iatrogenic illness. *Am J Perinatol* 2005; **22:** 239–43.

Pharmacokinetics

Methylergometrine maleate is reported to be rapidly absorbed when given orally or intramuscularly, with onset of uterine contractions in about 5 to 15 minutes and 2 to 5 minutes, respectively. Oral bioavailability may show considerable interindividual variation. It undergoes extensive first-pass hepatic metabolism and only small amounts of unchanged drug are excreted in the urine. The elimination half-life is reported to be about 2 to 3 hours.

◊ The pharmacokinetics of methylergometrine maleate have been studied after oral doses in healthy subjects[1,2] and in postpartum women.[3] Small amounts of methylergometrine have been detected in breast milk.[4,5]

1. Mäntylä R, *et al.* Methylergometrine (methylergonovine) concentrations in the human plasma and urine. *Int J Clin Pharmacol Biopharm* 1978; **16:** 254–7.
2. de Groot ANJA, *et al.* Comparison of the bioavailability and pharmacokinetics of oral methylergometrine in men and women. *Int J Clin Pharmacol Ther* 1995; **33:** 328–32.
3. Allonen H, *et al.* Methylergometrine: comparison of plasma concentrations and clinical response of two brands. *Int J Clin Pharmacol Biopharm* 1978; **16:** 340–2.
4. Erkkola R, *et al.* Excretion of methylergometrine (methylergonovine) into the human breast milk. *Int J Clin Pharmacol Biopharm* 1978; **16:** 579–80.
5. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Uses and Administration

Methylergometrine maleate has an action on the uterus similar to that of ergometrine maleate (p.2009) and is used similarly in the active management of the third stage of labour, and in the prevention and treatment of postpartum or postabortal haemorrhage (p.2003). In the management of the third stage of labour, it may be given in a dose of 200 micrograms intramuscularly after delivery of the anterior shoulder or, at the latest, immediately after delivery of the infant. The same dose may be used for the prevention or treatment of postpartum or postabortal haemorrhage, and may be repeated every 2 to 4 hours as necessary up to a maximum of 5 doses. In emergencies it may be given in similar doses by slow intravenous injection over at least 1 minute to reduce the risk of adverse effects, particularly hypertension. During the puerperium, methylergometrine maleate has been given in oral doses of 200 micrograms 3 or 4 times daily for up to a week or 125 to 250 micrograms up to 3 times daily.

Methylergometrine is a metabolite of methysergide (p.623).

Diagnosis and testing. For reference to the use of methylergometrine maleate in the diagnosis of variant angina, see Ergometrine Maleate, p.2010.

Preparations

USP 31: Methylergonovine Maleate Injection; Methylergonovine Maleate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Basofortina; ***Austria:*** Methergin; ***Belg.:*** Methergin; ***Braz.:*** Ergometrin; Methergin; ***Chile:*** Methergin†; ***Denm.:*** Methergin; ***Fin.:*** Methergin; ***Fr.:*** Methergin; ***Ger.:*** Methergin; Methylergobrevin; ***Gr.:*** Demergin; Methergin; ***Hong Kong:*** Methergin†; ***India:*** Ergogin; Ingagen-M; Methergin; Utergin; ***Indon.:*** Bledstop; Glomethyl; Methergin; Metherinal; Methovin; Metilat; Metvell; Myomergin; Myotonic; Pospargin; ***Israel:*** Methergin; ***Ital.:*** Methergin; ***Malaysia:*** Methergin; ***Mex.:*** Methergin; ***Neth.:*** Methergin; ***Philipp.:*** Medisyl; Mergot; Mergotrex; Methergin; Myometril; Usamema; ***Port.:*** Methergin; ***Spain:*** Methergin; ***Swed.:*** Methergin; ***Switz.:*** Methergin; ***Thai.:*** Ergotyl; Expogin; Metrine; Nathergen†; ***Turk.:*** Methergin; Metiler; Uterjin; ***USA:*** Methergine; ***Venez.:*** Methergin.

Multi-ingredient: ***Ger.:*** Syntometrin†.

Mifepristone *(BAN, USAN, rINN)*

C-1073; Mifepriston; Mifepristona; Mifépristone; Mifepristoni; Mifepristonum; RU-486; RU-38486. 11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-prop-1-ynylestra-4,9-dien-3-one.

Мифепристон

$C_{29}H_{35}NO_2$ = 429.6.

CAS — 84371-65-3.

ATC — G03XB01.

ATC Vet — QG03XB01.

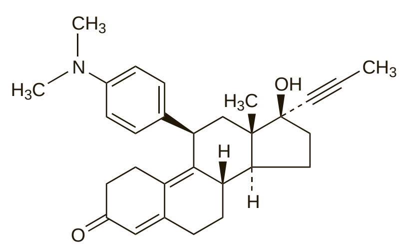

Pharmacopoeias. In *Chin.*

Adverse Effects

Uterine bleeding and cramps often occur after the use of mifepristone in procedures for the termination of pregnancy, and will occur in almost all patients after the addition of a prostaglandin. Bleeding typically continues for about 9 to 16 days, and may be severe enough to warrant curettage and transfusion in a small proportion of patients. However, prolonged heavy bleeding may also be a sign of incomplete abortion or other complications that require medical or surgical intervention. Other adverse effects of mifepristone include malaise, dizziness, chills, fever, headache, diarrhoea, nausea, vomiting, skin rashes, and urticaria; although some of these effects may be caused by the prostaglandin given after mifepristone.

Serious, sometimes fatal, infections have occurred in women undergoing abortion, although no causal relationship has been established between these events and the use of mifepristone.

Effects on the cardiovascular system. For a report of a woman who died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone, see p.2018.

Effects on the fetus. Studies in *rabbits*, but not *rats* or *mice*, suggest mifepristone causes fetal malformation. There have been reports of normal fetal development after the use of mifepristone alone in mothers who subsequently decided to continue their pregnancy.[1,2] However, in two reports, use of mifepristone was possibly related to malformations of the fetus including sirenomelia.[2,3] Cerebellar agenesis has been reported after a failed medical termination using mifepristone and gemeprost (see under Dinoprostone, p.2007).

1. Lim BH, *et al.* Normal development after exposure to mifepristone in early pregnancy. *Lancet* 1990; **336:** 257–8.
2. Pons J-C, *et al.* Development after exposure to mifepristone in early pregnancy. *Lancet* 1991; **338:** 763.
3. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.

Toxic shock syndrome. Fatal toxic shock syndrome occurred in 5 women who underwent medical termination of pregnancy using mifepristone and misoprostol.[1,2] In 4 cases it was specified that mifepristone 200 mg had been given orally, followed by misoprostol 800 micrograms vaginally.[2] Within a week of termination, these patients presented with signs and symptoms that included abdominal pain, nausea and vomiting, tachycardia, hypotension, oedema, haemoconcentration, profound leucocytosis, and absence of fever. Postmortem examination found evidence of endometritis and toxic shock syndrome that was attributed to *Clostridium sordellii* infection. This is an infrequent human pathogen, but the authors of one report[2] noted that *C. sordellii* infection of the genital tract had also been reported in 8 women after delivery, suggesting that pregnancy, childbirth, or termination of pregnancy may predispose a small number of women to acquire this organism, and that associated dilatation of the cervix may allow for ascending infection. Although there has also been some speculation about the possible mechanisms, both pharmacological[3] and physical,[4] by which oral mifepristone or vaginal misoprostol might potentiate *C. sordellii* infection, a causal relationship between these drugs and the 5 reported deaths has not been established.[5]

1. Sinave C, *et al.* Toxic shock syndrome due to Clostridium sordellii: a dramatic postpartum and postabortion disease. *Clin Infect Dis* 2002; **35:** 1441–3.
2. Fischer M, *et al.* Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. *N Engl J Med* 2005; **353:** 2352–60.
3. Miech RP. Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 1483–8.
4. Sicard D, Chauvelot-Moachon L. Comment: pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii. *Ann Pharmacother* 2005; **39:** 2142–3.
5. FDA. Questions and answers on Mifeprex (mifepristone) November 4, 2005. Available at: http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa20050719.htm (accessed 30/06/08)

Precautions

The use of mifepristone is contra-indicated in women with a confirmed or suspected ectopic pregnancy, because medical termination using mifepristone and a prostaglandin will not be effective (for use with methotrexate, see below). The expected symptoms of a medical termination may also be similar to those of a ruptured ectopic pregnancy. Mifepristone is also contra-indicated in patients with chronic adrenal failure or severe uncontrolled asthma. Use in those with renal or hepatic impairment is also not recommended. Mifepristone should be given with care to patients with less severe asthma or with chronic obstructive airways diseases, haemorrhagic or cardiovascular disease or associated risk factors, or anaemia. Therapy may need to be adjusted in patients receiving long-term corticosteroid treatment; a corticosteroid may need to be given if acute adrenal suppression is suspected. Care is also required in patients receiving anticoagulants because of the increased risk of severe bleeding. Patients with prosthetic heart valves or those with a history of infective endocarditis should be given chemoprophylaxis when undergoing pregnancy termination. As with other means of terminating pregnancy, rhesus-negative women who have not been rhesus immunised will require protection with anti-D immunoglobulin.

Porphyria. Mifepristone is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

The metabolism of mifepristone is mediated by the cytochrome P450 isoenzyme CYP3A4. Theoretically, use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of mifepristone. *In-vitro* studies indicate that mifepristone itself inhibits CYP3A4; it should be used cautiously with CYP3A4 substrates that have a narrow therapeutic index.

NSAIDs. The effects of mifepristone on the uterus and cervix may be mediated by increased prostanoid synthesis resulting from its inhibitory effect on progesterone. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of mifepristone. However, a placebo-controlled study[1] in 28 women found that in the 13 given *naproxen* 500 mg orally 60, 48, 36, 24, and 12 hours before surgical termination of pregnancy the efficacy of mifepristone 100 mg given orally to soften the cervix was not reduced. Also, NSAIDs did not affect medical termination using mifepristone followed by misoprostol (see p.2013).

1. Rådestad A, Bygdeman M. Cervical softening with mifepristone (RU 486) after pretreatment with naproxen: a double-blind randomized study. *Contraception* 1992; **45:** 221–7.

Pharmacokinetics

After oral doses peak plasma concentrations of mifepristone occur after about 1 to 2 hours; bioavailability is about 70%. Mifepristone is about 98% bound to plasma proteins, mainly α_1-acid glycoprotein. Elimination is biphasic; a slow phase is followed by a more rapid terminal phase, with an elimination half-life of about 18 hours. Mifepristone undergoes hepatic oxidative metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and metabolites are excreted in the bile and eliminated in the faeces. Only a small fraction is detected in the urine.

◊ Reviews.

1. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynecol Reprod Biol* 2002; **101:** 113–20.

Uses and Administration

Mifepristone is a steroid derived from norethisterone that has potent antiprogestogenic activity. It is used in termination of pregnancy (see below), for either medical termination or for softening and dilatation of the cervix before surgical termination of pregnancy. Mifepristone is also used for labour induction after intra-uterine fetal death (see below).

In the UK the licensed regimen for the **termination** of pregnancies of up to 49 days is a single oral dose of 600 mg of mifepristone followed by a prostaglandin 36 to 48 hours later; prostaglandin treatment may be with either misoprostol 400 micrograms orally or gemeprost 1 mg vaginally. Alternatively, 200 mg of mifepristone may be given as a single dose followed, 36 to 48 hours later, by gemeprost 1 mg vaginally. Regimens containing vaginal gemeprost may also be used for the termination of pregnancies of up to 63 days. In the USA the licensed regimen for the termination of pregnancies up to 49 days of gestation is a single oral dose of 600 mg of mifepristone followed 2 days later by 400 micrograms of misoprostol orally, unless abortion has already been completed. As an adjunct to prostaglandin termination of pregnancy beyond the first trimester, the licensed dose in the UK is a single oral dose of mifepristone 600 mg; this is given 36 to 48 hours before scheduled prostaglandin administration, thus shortening the duration of the procedure and reducing the dose of prostaglandin required.

For **softening** and **dilatation of the cervix** before surgical termination of pregnancy during the first trimester, a single 200-mg dose of mifepristone is given 36 to 48 hours before the procedure.

For labour induction following intra-uterine **fetal death**, mifepristone 600 mg is given daily for 2 consecutive days; if labour has not started within 72 hours of the first dose, other methods of induction should be used.

Mifepristone has been tried for **other uses** such as postcoital contraception, endometriosis, uterine fibroids (leiomyomas), and for progestogen-dependent neoplasms such as meningiomas (see below). Mifepristone also has anti-glucocorticoid activity so it has been used in the treatment of Cushing's syndrome (below), and is under investigation in psychotic major depression (below).

◊ General references.

1. Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 1997; **33:** 7–17.
2. Mahajan DK, London SN. Mifepristone (RU486): a review. *Fertil Steril* 1997; **68:** 967–76.
3. Koide SS. Mifepristone: auxiliary therapeutic use in cancer and related disorders. *J Reprod Med* 1998; **43:** 551–60.
4. DeHart RM, Morehead MS. Mifepristone. *Ann Pharmacother* 2001; **35:** 707–19.
5. Weingertner A-S, *et al.* Utilisations actuelles et potentielles de la mifépristone en gynécologie-obstétrique et dans les autres disciplines médicales. *J Gynecol Obstet Biol Reprod (Paris)* 2004; **33:** 692–702.
6. Tang OS, Ho PC. Clinical applications of mifepristone. *Gynecol Endocrinol* 2006; **22:** 655–9.

Contraception. Mifepristone has been established as an effective emergency contraceptive (p.2071). Initial studies found a dose of 600 mg given within 72 hours of coitus to be effective.[1,2] Subsequently lower doses, given up to 120 hours after coitus, have been shown to be well tolerated and as effective as standard emergency contraceptive regimens.[3-5] Studies[3,5,6] and meta-analyses[7,8] have confirmed the effectiveness of a dose of 10 mg. There was some evidence of a slight dose-response effect; it was calculated that there would be 1 extra pregnancy per 146 women treated if the dose were reduced from 25 to 10 mg, but the associated increase in availability of the drug might outweigh this.[8]

The development of a mifepristone-based standard contraceptive (p.2070) has been less successful. Regimens based on daily,[9] weekly,[10,11] or monthly[12,13] doses of mifepristone have been investigated.

1. Glasier A, *et al.* Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception. *N Engl J Med* 1992; **327:** 1041–4.
2. Webb AMC, *et al.* Comparison of Yuzpe regimen, danazol, and mifepristone (RU 486) in oral postcoital contraception. *BMJ* 1992; **305:** 927–31.
3. von Hertzen H, *et al.* Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; **360:** 1803–10.
4. Ashok PW, *et al.* Mifepristone versus the Yuzpe regimen (PC4) for emergency contraception. *Int J Gynecol Obstet* 2004; **87:** 188–93.
5. Hamoda H, *et al.* A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. *Obstet Gynecol* 2004; **104:** 1307–13.
6. Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. *Lancet* 1999; **353:** 697–702.
7. Piaggio G, *et al.* Combined estimates of effectiveness of mifepristone 10 mg in emergency contraception. *Contraception* 2003; **68:** 439–46.
8. Piaggio G, *et al.* Meta-analyses of randomized trials comparing different doses of mifepristone in emergency contraception. *Contraception* 2003; **68:** 447–52.
9. Brown A, *et al.* Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J Clin Endocrinol Metab* 2002; **87:** 63–70.
10. Godfrey EM, *et al.* Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. *Contraception* 2004; **70:** 41–6.
11. Pei K, *et al.* Weekly contraception with mifepristone. *Contraception* 2007; **75:** 40–4.
12. Hapangama DK, *et al.* Feasibility of administering mifepristone as a once a month contraceptive pill. *Hum Reprod* 2001; **16:** 1145–50.
13. Narvekar N, *et al.* Toward developing a once-a-month pill: a double-blind, randomized, controlled trial of the effect of three single doses of mifepristone given at midcycle on the pattern of menstrual bleeding. *Fertil Steril* 2006; **86:** 819–24.

Cushing's syndrome. Mifepristone may be useful in Cushing's syndrome (p.2344) because of its glucocorticoid antagonist effects.

References.

1. Nieman LK, *et al.* Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 1985; **61:** 536–40.
2. van der Lely A-J, *et al.* Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* 1991; **114:** 143–4.
3. Sartor O, Cutler GB. Mifepristone: treatment of Cushing's syndrome. *Clin Obstet Gynecol* 1996; **39:** 506–10.
4. Chu JW, *et al.* Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab* 2001; **86:** 3568–73.

Depression. Mifepristone has been investigated in the management of depression (p.373) with psychotic features;[1-4] preliminary results suggest some benefit.

1. Belanoff JK, *et al.* An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 2002; **52:** 386–92.
2. Simpson GM, *et al.* An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005; **66:** 598–602.
3. Flores BH, *et al.* Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 2006; **31:** 628–36.
4. DeBattista C, *et al.* Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biol Psychiatry* 2006; **60:** 1343–9.

Ectopic pregnancy. Methotrexate with mifepristone may be more effective than methotrexate alone[1,2] for the medical treatment of ectopic pregnancy (p.749), although some have not found the combination to produce any benefit over methotrexate alone in the majority of women.[3]

1. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; **13:** 1987–90.
2. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; **179:** 640–3.
3. Rozenberg P, *et al.* Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate-mifepristone and methotrexate-placebo. *Hum Reprod* 2003; **18:** 1802–8.

Endometriosis. Some results[1,2] have suggested that mifepristone, which is capable of suppressing ovarian function, may be of benefit in patients with endometriosis (p.2091).

1. Kettel LM, *et al.* Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. *Fertil Steril* 1991; **56:** 402–7.
2. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; **178:** 1151–6.

Fibroids. Mifepristone has been reported to produce significant decreases in uterine and leiomyoma volumes, and to reduce symptoms such as dysmenorrhoea and menorrhagia, when given to patients with fibroids (p.2107). However, data are from small uncontrolled studies using oral doses ranging from 5 to 50 mg daily, and endometrial hyperplasia has been noted.[1]

1. Steinauer J, *et al.* Systematic review of mifepristone for the treatment of uterine leiomyomata. *Obstet Gynecol* 2004; **103:** 1331–6.

Labour induction. A few studies[1-4] have reported that mifepristone was effective for cervical ripening and labour induction (p.2002) at term. A systematic review[5] considered that mifepristone was better than placebo but that there was still insufficient evidence to support its use. A later dose-finding study[6] found that single oral doses ranging from 50 to 600 mg were no more effective than placebo for inducing labour.

Mifepristone is used for cervical ripening and labour induction where intra-uterine fetal death has occurred,[7] usually in oral doses of 600 mg given daily for 2 days. The effective use of a lower single dose of 200 mg, followed by misoprostol given orally and/or vaginally, has also been described.[8,9]

1. Frydman R, *et al.* Labor induction in women at term with mifepristone (RU486): a double-blind, randomized, placebo-controlled study. *Obstet Gynecol* 1992; **80:** 972–5.
2. Giacalone PL, *et al.* Cervical ripening with mifepristone before labor induction: a randomized study. *Obstet Gynecol* 1998; **92:** 487–92.
3. Elliott CL, *et al.* The effects of mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol* 1998; **92:** 804–9.
4. Stenlund PM, *et al.* Induction of labor with mifepristone—a randomized, double-blind study versus placebo. *Acta Obstet Gynecol Scand* 1999; **78:** 793–8.
5. Neilson JP. Mifepristone for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 30/06/08).
6. Berkane N, *et al.* Use of mifepristone to ripen the cervix and induce labor in term pregnancies. *Am J Obstet Gynecol* 2005; **192:** 114–20.
7. Cabrol D, *et al.* Induction of labor with mifepristone (RU 486) in intrauterine fetal death. *Am J Obstet Gynecol* 1990; **163:** 540–2.
8. Wagaarachchi PT, *et al.* Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *BJOG* 2002; **109:** 443–7.
9. Väyrynen W, *et al.* Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. *Acta Obstet Gynecol Scand* 2007; **86:** 701–5.

Malignant neoplasms. Mifepristone has been used successfully in some patients with inoperable meningioma,[1-4] a brain tumour that may be progestogen-receptor positive. It has been given long term in oral doses of 200 mg daily, in some cases for more than 10 years. Adverse effects from long-term therapy have included fatigue, hot flushes, nausea, and depression; gynaecomastia has occurred in men and breast tenderness in women. Cessation of menstruation during mifepristone therapy occurs in premenopausal women, and there have been isolated cases of endometrial hyperplasia in pre- and postmenopausal women.

1. Grunberg SM, *et al.* Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991; **74:** 861–6.
2. Lamberts SWJ, *et al.* Mifepristone (RU 486) treatment of meningiomas. *J Neurol Neurosurg Psychiatry* 1992; **55:** 486–90.
3. Spitz IM, *et al.* Management of patients receiving long-term treatment with mifepristone. *Fertil Steril* 2005; **84:** 1719–26.
4. Grunberg SM, *et al.* Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006; **24:** 727–33.

Termination of pregnancy. Mifepristone sensitises the myometrium to prostaglandins, increases uterine contractility, and softens and dilates the cervix.[1] It is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with prostaglandins for the termination of pregnancy (p.2004). Mifepristone has also been tried with methotrexate in the treatment of ectopic pregnancy (see above) and may be used to induce labour where intra-uterine fetal death has occurred (see above).

Mifepristone, followed 36 to 48 hours later by a prostaglandin, is an effective medical alternative to surgical methods for the termination of pregnancy in the *first trimester*.[1] Efficacy decreases with increasing gestational age, and the success rate may be affected by the choice of prostaglandin, its dose, and route of administration. Termination success rates are highest for gestations of up to 49 days; after this the success rate for mifepristone with oral misoprostol tends to decrease compared with other regimens.[2] Vaginal gemeprost may be used with mifepristone for gestations of up to 63 days.[1] The usual dose of oral mifepristone is 600 mg, although lower doses of 200 and 400 mg have been studied in various regimens with prostaglandins and found to be as effective. However, a further reduction to 50 mg significantly reduced efficacy.[1,3]

Although surgical termination is commonly used for pregnancies of 9 to 13 weeks, there is increasing evidence to support the use of medical termination using mifepristone followed by misoprostol. A regimen using oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, has been described.[4,5] Two further vaginal doses of misoprostol 400 micrograms were given at intervals of 3 hours if the products of conception had not been passed (these doses could be given orally if vaginal bleeding was heavier than a normal period[5]). Surgical evacuation was then used if necessary. In a large case series of 1076 women,[6] medical abortion was successful in 95.8%. A regimen of oral mifepristone 200 mg, followed 36 to 48 hours later by misoprostol 800 micrograms vaginally (or 600 micrograms sublingually), was used, with up to 5 further doses of misoprostol 400 micrograms (vaginally or sublingually) given at intervals of 3 hours if needed. The mean number of misoprostol doses used was 2.31.

Mifepristone is also used to ripen the cervix before vacuum aspiration for surgical termination in the first trimester. Oral doses of 600 mg have been used, but lower doses were also found to be more effective than placebo[7,8] and as effective as prostaglandins;[9-11] consequently, a dose of 200 mg is now often used.

Mifepristone followed by a prostaglandin may also be used for medical termination in the *second trimester* (mid-trimester termination; gestation of 13 to 24 weeks).[12,13] Similarly to early termination, a study found mifepristone 200 mg orally to be as effective as 600 mg when followed by misoprostol.[14] Further retrospective reviews have also reported mifepristone 200 mg followed by misoprostol[15] or gemeprost[16] to be effective.

In the UK the Royal College of Obstetricians and Gynaecologists' guidelines[17] for both early and mid-trimester terminations include the following regimens:

- for gestation up to 63 days (9 weeks), mifepristone 200 mg orally followed 24 to 72 hours later by misoprostol 800 micrograms vaginally; if abortion has not occurred 4 hours after administration of misoprostol in women at 49 to 63 days of gestation, a further dose of misoprostol 400 micrograms may be given orally or vaginally
- for gestation between 9 and 13 weeks, mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally; a maximum of 4 further doses of misoprostol 400 micrograms may be given every 3 hours, orally or vaginally, if necessary
- for mid-trimester termination (13 to 24 weeks), mifepristone 200 mg orally followed 36 to 48 hours later by misoprostol 800 micrograms vaginally, then up to 4 further doses of misoprostol 400 micrograms given every 3 hours orally

Mifepristone followed by a prostaglandin has also been used as an effective alternative to surgical evacuation[18,19] in the management of first trimester *pregnancy failure*. As for termination, mifepristone doses of 200 and 600 mg orally, followed by misoprostol, appear to be equally effective,[20] although some studies[21,22] suggest that pretreatment with mifepristone does not improve the expulsion rate compared with vaginal or oral misoprostol alone.

1. Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. *Contraception* 2006; **74:** 66–86.
2. Kahn JG, *et al.* The efficacy of medical abortion: a meta analysis. *Contraception* 2000; **61:** 29–40.
3. Marions L. Mifepristone dose in the regimen with misoprostol for medical abortion. *Contraception* 2006; **74:** 21–5.
4. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **352:** 542–3.
5. Ashok PW, *et al.* A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. *Hum Reprod* 2002; **17:** 92–8.
6. Hamoda H, *et al.* Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. *Contraception* 2005; **71:** 327–32.
7. WHO. The use of mifepristone (RU 486) for cervical preparation in first trimester pregnancy termination by vacuum aspiration. *Br J Obstet Gynaecol* 1990: **97:** 260–6.
8. World Health Organization Task Force on Postovulatory Methods of Fertility Regulation. Cervical ripening with mifepristone (RU 486) in late first trimester abortion. *Contraception* 1994; **50:** 461–75.
9. Henshaw RC, Templeton AA. Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486). *Br J Obstet Gynaecol* 1991; **98:** 1025–30.
10. Ngai SW, *et al.* Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study. *Br J Obstet Gynaecol* 1996; **103:** 1120–3.
11. Ashok PW, *et al.* Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study. *Am J Obstet Gynecol* 2000; **183:** 998–1002.
12. Rodger M, Baird D. Pretreatment with mifepristone (RU486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* 1990; **97:** 41–5.
13. Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. *Br J Obstet Gynaecol* 1993; **100:** 758–61.
14. Webster D, *et al.* A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996; **103:** 706–9.
15. Ashok PW, *et al.* Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception* 2004; **69:** 51–8.
16. Tang OS, *et al.* Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception* 2001; **64:** 29–32.
17. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/induced_abortionfull.pdf (accessed 30/06/08)
18. Chia KV, Ogbo VI. Medical termination of missed abortion. *J Obstet Gynaecol* 2002; **22:** 184–6.
19. Niinimäki M, *et al.* A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. *Fertil Steril* 2006; **86:** 367–72.
20. Coughlin LB, *et al.* Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? *J Obstet Gynaecol* 2004; **24:** 69–71.
21. Grønlund A, *et al.* Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation: a multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynecol Scand* 2002; **81:** 1060–5.
22. Stockheim D, *et al.* A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. *Fertil Steril* 2006; **86:** 956–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mifegyne; ***Denm.:*** Mifegyne; ***Fin.:*** Mifegyne; ***Fr.:*** Mifegyne; ***Ger.:*** Mifegyne; ***Gr.:*** Mifegyne; ***India:*** Mifegest; MT Pill; ***Israel:*** Mifegyne; ***Neth.:*** Mifegyne; ***Norw.:*** Mifegyne; ***NZ:*** Mifegyne; ***Port.:*** Mifegyne; ***Rus.:*** Pencrofton (Пенкрофтон); ***S.Afr.:*** Mifegyne; ***Spain:*** Mifegyne; ***Swed.:*** Mifegyne; ***Switz.:*** Mifegyne; ***UK:*** Mifegyne; ***USA:*** Mifeprex.

Misoprostol *(BAN, USAN, rINN)*

Misoprostoli; Misoprostolum; Mizoprostol; SC-29333. (±)-Methyl 7-{(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl}heptanoate; (±)-Methyl (13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate.

Мизопростол

$C_{22}H_{38}O_5$ = 382.5.

CAS — 59122-46-2.

ATC — A02BB01; G02AD06.

ATC Vet — QA02BB01; QG02AD06.

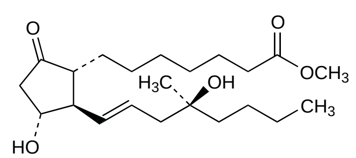

(11*R*, 16*S*)-Form

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Misoprostol). A clear, colourless or yellowish, hygroscopic, oily liquid. Practically insoluble in water; soluble in alcohol; sparingly soluble in acetonitrile. Store in airtight containers at –20°.

Adverse Effects

The commonest adverse effect of misoprostol is diarrhoea. Other gastrointestinal effects include abdominal pain, dyspepsia, flatulence, and nausea and vomiting. Increased uterine contractility and abnormal vaginal bleeding (including menorrhagia and intermenstrual bleeding) have been reported. Other adverse effects include skin rashes, headache, and dizziness. Hypotension is rarely seen at doses recommended for peptic ulcer disease.

Incidence of adverse effects. Data on misoprostol presented to the FDA have been summarised.[1] During controlled studies the most common adverse effect was diarrhoea (8.2% compared with 3.1% for placebo); it was dose-related but usually mild, only 8 of 2003 subjects receiving misoprostol having withdrawn because of incapacitating diarrhoea. Headaches and abdominal discomfort were also reported. The effects of misoprostol on the uterus and the potential risks of uterine bleeding or abortion in pregnant women were of more concern. In nonpregnant women taking part in the controlled studies there were menstrual complaints in 15 of 410 (3.7%) receiving misoprostol compared with 2 of 115 (1.7%) given placebo. In a study in pregnant women who had elected to undergo first trimester abortion, all 6 who had a spontaneous expulsion of the uterine contents had received 1 or 2 doses of misoprostol 400 micrograms the previous evening, while none of those given placebo aborted spontaneously; overall 25 of the 56 women given misoprostol had uterine bleeding compared with only 2 of 55 on placebo.

1. Lewis JH. Summary of the 29th meeting of the Gastrointestinal Drugs Advisory Committee, Food and Drug Administration—June 10, 1985. *Am J Gastroenterol* 1985; **80:** 743–5.

Effects on the fetus. Misoprostol on its own is only a weak abortifacient and is often ineffective when used alone for the termination of pregnancy (see below). However, it has been widely misused for this purpose in some countries, notably Brazil,[1,2] and anecdotal reports have associated congenital malformations with such misuse during the first trimester of pregnancy. A systematic review[3] of 4 case-control studies confirmed that misoprostol was associated with an increased risk of congenital abnormality, particularly Möbius syndrome and terminal transverse limb defects.

1. Costa SH, Vessey MP. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. *Lancet* 1993; **341:** 1258–61.
2. Coêlho HLL, *et al.* Misoprostol and illegal abortion in Fortaleza, Brazil. *Lancet* 1993; **341:** 1261–3. Correction. *ibid.*; 1486.
3. da Silva Dal Pizzol T, *et al.* Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. *Reprod Toxicol* 2006; **22:** 666–71.

Effects on the uterus. For reference to uterine rupture in women given misoprostol to induce labour or terminate pregnancy, see under Dinoprostone, p.2007.

Toxic shock syndrome. Fatal toxic shock syndrome has occurred in a few women who underwent medical termination of pregnancy using oral mifepristone and vaginal misoprostol, although a causal relationship between these drugs and the deaths has not been established (see under Mifepristone, p.2011).

Precautions

Misoprostol should not be used to treat peptic ulcer disease in patients who are pregnant or who may become pregnant because it can cause uterine contraction. It should be used with caution in patients in whom hypotension might cause severe complications. Patients with conditions such as inflammatory bowel disease, for whom profound diarrhoea could be dangerous, should be monitored carefully if misoprostol is given.

Like other prostaglandins used in the termination of pregnancy (see Dinoprostone, p.2008), misoprostol should not be used in women at increased risk of uterine rupture, such as those with multiple pregnancy or a uterus scarred by previous caesarean section. Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Breast feeding. Misoprostol acid was detected in the breast milk of 10 women given a single oral dose of misoprostol for postpartum uterine atony.[1] The concentration rose rapidly, peaked at about 1 hour, and had fallen towards the detection limit by about 5 hours after the dose. Product information for misoprostol licensed for use in gastric ulceration advises that it should not be given to breast-feeding women because misoprostol acid could potentially cause diarrhoea in the infant.

1. Vogel D, *et al.* Misoprostol versus methylergometrine: pharmacokinetics in human milk. *Am J Obstet Gynecol* 2004; **191:** 2168–73.

Inflammatory bowel disease. Life-threatening diarrhoea was reported in a patient with unrecognised Crohn's disease after 6 doses of misoprostol.[1] Abdominal cramps, pain, and profuse watery diarrhoea also occurred after 3 doses of misoprostol in a woman with Crohn's disease.[2] In a cohort study of misoprostol taken with NSAIDs for arthritis there were 13 patients with a history of inflammatory bowel disease; 7 did not develop diarrhoea, 3 developed mild diarrhoea, 1 developed severe diarrhoea that stopped when misoprostol was withdrawn, and 2 developed bloody diarrhoea.[3]

1. Kornbluth A, *et al.* Life-threatening diarrhea after short-term misoprostol use in a patient with Crohn ileocolitis. *Ann Intern Med* 1990; **113:** 474–5.
2. Johnson JS, *et al.* Profuse diarrhea after misoprostol use in a patient with a history of Crohn's disease. *Ann Pharmacother* 1992; **26:** 1092–3.
3. Faich GA, *et al.* Diarrhea after misoprostol in Crohn disease. *Ann Intern Med* 1991; **114:** 342.

Interactions

NSAIDs. It has been suggested that *aspirin* and *NSAIDs*, which are prostaglandin synthetase inhibitors, might alter the efficacy of misoprostol used for termination of pregnancy by inhibiting uterine cramping. However, studies in women undergoing medical[1] or surgical[2] termination found that NSAIDs did not reduce the efficacy of misoprostol. In another study,[3] *diclofenac* did not reduce the efficacy of medical termination using mifepristone followed by misoprostol.

1. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. *Contraception* 1997; **56:** 165–8.
2. Li CFI, *et al.* A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. *Contraception* 2003; **67:** 101–5. Correction. *ibid.*; 339.
3. Fiala C, *et al.* The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. *Hum Reprod* 2005; **20:** 3072–7.

Pharmacokinetics

Misoprostol is reported to be rapidly absorbed and metabolised to its active form (misoprostol acid; SC-30695) after oral doses; peak plasma concentrations of misoprostol acid occur after about 15 to 30 minutes. Food reduces the rate but not the extent of absorption. Misoprostol acid is further metabolised by oxidation in a number of body organs and is excreted mainly in the urine. The plasma elimination half-life is reported to be between 20 and 40 minutes. Misoprostol acid is distributed into breast milk.

◊ References.

1. Schoenhard G, *et al.* Metabolism and pharmacokinetic studies of misoprostol. *Dig Dis Sci* 1985; **30** (suppl): 126S–128S.
2. Karim A, *et al.* Effects of food and antacid on oral absorption of misoprostol, a synthetic prostaglandin E analog. *J Clin Pharmacol* 1989; **29:** 439–43.
3. Foote EF, *et al.* Disposition of misoprostol and its active metabolite in patients with normal and impaired renal function. *J Clin Pharmacol* 1995; **35:** 384–9.
4. Zieman M, *et al.* Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; **90:** 88–92.
5. Khan R-U, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol* 2003; **101:** 968–74.
6. Khan R-U, *et al.* Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol* 2004; **103:** 866–70.
7. Schaff EA, *et al.* Comparison of misoprostol plasma concentrations following buccal and sublingual administration. *Contraception* 2005; **71:** 22–5.

Uses and Administration

Misoprostol is a synthetic analogue of alprostadil (prostaglandin E_1; p.2183).

It is used in the treatment of benign gastric and duodenal **ulceration** (below) including that associated with NSAIDs. The usual oral dose is 800 micrograms daily in two to four divided doses with food. Treatment is initially given for at least 4 weeks, even if symptoms are relieved sooner, and may continue for up to 8 weeks if necessary. Further courses may be used to treat relapse.

Misoprostol is also used prophylactically with NSAIDs to prevent NSAID-induced ulcers. The usual oral dose is 200 micrograms two to four times daily. A dose of 100 micrograms four times daily may be used in patients not tolerating the higher dose. Some preparations of NSAIDs contain misoprostol in an attempt to limit their adverse effects on the gastrointestinal mucosa.

Misoprostol may be used to ripen the cervix before surgical **termination of pregnancy** (below) in the first trimester. A single oral dose of misoprostol 400 micrograms is given 3 to 4 hours before surgery. It may also be used for medical termination of pregnancy at up to 49 days of amenorrhoea, in a single oral dose of 400 micrograms given 36 to 48 hours after mifepristone. Misoprostol has also been used for induction of labour and in the management of postpartum haemorrhage (see below).

◊ General reviews.

1. Goldberg AB, *et al.* Misoprostol and pregnancy. *N Engl J Med* 2000; **344:** 38–47.
2. Blanchard K, *et al.* Misoprostol for women's health: a review. *Obstet Gynecol* 2002; **99:** 316–32.
3. Lokugamage AU, *et al.* Misoprostol and pregnancy: ever-increasing indications of effective usage. *Curr Opin Obstet Gynecol* 2003; **15:** 513–18.
4. Chong YS, *et al.* Misoprostol: a quarter century of use, abuse, and creative misuse. *Obstet Gynecol Surv* 2004; **59:** 128–40.

Labour induction and augmentation. Prostaglandins are well established for the induction of labour (p.2002) and misoprostol has been widely investigated for this indication. A systematic review[1] of studies of misoprostol given *vaginally* found that it increased cervical ripening and induced labour. It was more effective than vaginal or intracervical dinoprostone, reducing the need for oxytocin augmentation and improving the rate of vaginal delivery achieved within 24 hours. It was also found to be more effective than intravenous oxytocin. Most studies used misoprostol tablets in a dose of 50 micrograms vaginally every 4 hours, but reported doses have varied from 25 micrograms every 2 to 3 hours, to 100 micrograms every 6 to 12 hours. Low doses of misoprostol resulted in more use of oxytocin, but caused less uterine hyperstimulation. Although unlicensed, misoprostol is reported to be used outside clinical studies particularly in the USA, and the American College of Obstetricians and Gynecologists has recommended a dose of 25 micrograms intravaginally every 3 to 6 hours.[2] Misoprostol has also been given *orally* but this route is less well established. A wide range of doses have been reported but most studies have used 50 micrograms every 4 hours. Some reviews have found oral to be less effective than vaginal misoprostol.[2,3] However, others[4] have concluded that oral use produces similar outcomes to vaginal misoprostol, with less hyperstimulation, but that comparison is complicated by the wide variation in doses. Overall, oral misoprostol appears to be at least as effective as vaginal dinoprostone, but because of limited data it should be used with caution.[4] The risk of uterine hyperstimulation may be increased with misoprostol by either route, particularly at higher doses,[1,4] and it should not be used in women with scarred uteri from previous caesarean delivery or uterine surgery[2] (see also Effects on the Uterus, under Adverse Effects of Dinoprostone, p.2007). There has also been some limited investigation of misoprostol given *sublingually*.[3,5,6]

Misoprostol has been tried for labour induction after intra-uterine fetal death, generally in higher doses than those used for labour at term. It has been used successfully in doses of 400 micrograms every 4 hours orally[7] and 400 micrograms every 12 hours vaginally.[8] A comparison of 200 micrograms given either orally or vaginally every 6 hours, to a maximum of 4 doses or until labour was established, found the time from induction to delivery to be shorter, and fewer women needed oxytocin augmentation, with vaginal use.[9]

Misoprostol may also be used for active management of the third stage of labour (see Postpartum Haemorrhage, below).

1. Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 30/06/08).
2. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Safety* 2002; **25:** 665–76.
3. Bartusevicius A, *et al.* Oral, vaginal and sublingual misoprostol for induction of labor. *Int J Gynecol Obstet* 2005; **91:** 2–9.
4. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
5. Shetty A, *et al.* Sublingual misoprostol for the induction of labor at term. *Am J Obstet Gynecol* 2002; **186:** 72–6.
6. Shetty A, *et al.* Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *Br J Obstet Gynaecol* 2002; **109:** 645–50.
7. Pongsatha S, Tongsong T. Therapeutic termination of second trimester pregnancies with intrauterine fetal death with 400 micrograms of oral misoprostol. *J Obstet Gynaecol Res* 2004; **30:** 217–20.
8. Fawole AO, *et al.* Experience with intravaginal misoprostol in the management of intra-uterine fetal death. *Afr J Med Med Sci* 2004; **33:** 105–8.
9. Nyende L, *et al.* Comparison of vaginal and oral misoprostol, for the induction of labour in women with intra-uterine foetal death. *East Afr Med J* 2004; **81:** 179–82.

Organ and tissue transplantation. Misoprostol 200 micrograms orally four times daily improved renal function in ciclosporin-treated recipients of renal transplants.[1] The number of patients who had acute graft rejection was lower in the misoprostol group than in the placebo group. However, another study[2] did not indicate any difference in the incidence of rejection episodes or in renal function when misoprostol was added to immunosuppressant regimens for kidney transplantation, and misoprostol does not appear to have gained a role in the usual management of renal transplantation (p.1813).

1. Moran M, *et al.* Prevention of acute graft rejection by the prostaglandin E analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. *N Engl J Med* 1990; **322:** 1183–8.
2. Pouteil-Noble C, *et al.* Misoprostol in renal transplant recipients: a prospective, randomized, controlled study on the prevention of acute rejection episodes and cyclosporin A nephrotoxicity. *Nephrol Dial Transplant* 1994; **9:** 552–5.

Peptic ulcer disease. Misoprostol is used in the prophylaxis and treatment of peptic ulceration (p.1702) in patients taking NSAIDs. There is good evidence that misoprostol can reduce the risk of gastric and duodenal ulcer formation in patients on long-term NSAID treatment,[1-4] and it appears more effective in this respect than histamine H_2-antagonists,[1] for which evidence of benefit against gastric injury is less persuasive. However, misoprostol's abdominal adverse effects, particularly diarrhoea and abdominal cramps, may limit its usefulness and patient acceptability. Omeprazole, which is equally effective in preventing NSAID-induced ulceration, is better tolerated.[3] Improved formulations, in which the active isomer of misoprostol is bound to a polymer, may reduce adverse effects.[5]

1. Koch M, *et al.* Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury: a meta-analysis of randomized controlled clinical trials. *Arch Intern Med* 1996; **156:** 2321–32.
2. Champion GD, *et al.* NSAID-induced gastrointestinal damage: epidemiology, risk and prevention, with an evaluation of the role of misoprostol: an Asia-Pacific perspective and consensus. *Drugs* 1997; **53:** 6–19.
3. Hawkey CJ, *et al.* Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1998; **338:** 727–34.
4. Rostom A, *et al.* Prevention of NSAID-induced gastroduodenal ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 30/06/08).
5. Chen D, *et al.* Stabilization and sustained-release effect of misoprostol with methacrylate copolymer. *Int J Pharmaceutics* 2000; **203:** 141–8.

Postpartum haemorrhage. Prostaglandins, usually given parenterally, have an accepted role in the management of established postpartum haemorrhage (p.2003) not controlled by oxytocin and ergot preparations. There have been reports[1-3] of the successful use of rectal misoprostol to control postpartum haemorrhage, using single doses of 800 or 1000 micrograms. A review[4] found that there was some evidence for reduced blood loss with lower doses of misoprostol, and suggested that oral, sublingual, rectal, or a combination of these, might be the most effective routes; possible regimens were 200 to 400 micrograms sublingually or rectally, or similar doses plus 200 micrograms orally. It also suggested that the oral dose of misoprostol should not exceed 600 micrograms because of the risk of hyperpyrexia. There have also been a few cases in which intra-uterine misoprostol 800 micrograms has controlled refractory secondary postpartum haemorrhage.[5,6]

Misoprostol has also been given immediately after delivery in the active management of third-stage labour. In a study[7] of more than 18 500 women treated in hospital, which compared oral misoprostol 600 micrograms with intramuscular or intravenous oxytocin, a higher proportion of women who received misoprostol had blood loss of at least 1000 mL and required additional oxytocics. Misoprostol was also associated with significantly more shivering and pyrexia. The results of this large study suggest that parenteral oxytocin is preferred for active management, but it has been argued that misoprostol may be particularly useful in preventing postpartum haemorrhage in developing countries where there is limited access to healthcare facilities and parenteral oxytocics.[8-10] Two placebo-controlled studies have addressed this argument, reporting that oral[11] or sublingual[12] misoprostol used in rural primary healthcare settings reduced postpartum haemorrhage, particularly severe haemorrhage (1000 mL or more). A systematic review[13] concluded that oral misoprostol was less effective than injectable oxytocics in reducing blood loss and the use of additional oxytocics, but that it may be used where no injectable uterotonic is available.

1. O'Brien P, *et al.* Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 1998; **92:** 212–4.
2. Lokugamage AU, *et al.* A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; **80:** 835–9.
3. Shojai R, *et al.* Le misoprostol par voie rectale dans l'hémorragie de la délivrance: rectal misoprostol for postpartum hemorrhage. *Gynecol Obstet Fertil* 2004; **32:** 703–7.
4. Hofmeyr GJ, *et al.* Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; **112:** 547–53.
5. Adekanmi OA, *et al.* Intrauterine misoprostol for the treatment of severe recurrent atonic secondary postpartum haemorrhage. *BJOG* 2001; **108:** 541–2.
6. Oboro VO, *et al.* Intrauterine misoprostol for refractory postpartum hemorrhage. *Int J Gynecol Obstet* 2003; **80:** 67–8.
7. Gülmezoglu AM, *et al.* WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; **358:** 689–95.
8. Darney PD. Misoprostol: a boon to safe motherhood...or not? *Lancet* 2001; **358:** 682–3.
9. Shannon C, Winikoff B. Use of misoprostol in third stage of labour. *Lancet* 2002; **359:** 709.
10. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. *Int J Gynecol Obstet* 2006; **92:** 10–18.
11. Derman RJ, *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet* 2006; **368:** 1248–53.
12. Høj L, *et al.* Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. Abridged version: *BMJ* 2005; **331:** 723–7. Full version: http://www.bmj.com/cgi/content/full/331/7519/723 (accessed 30/06/08)
13. Gülmezoglu AM, *et al.* Prostaglandins for preventing postpartum haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).

Termination of pregnancy. Prostaglandins are widely used for the termination of pregnancy (p.2004) and misoprostol has been studied both for cervical preparation and for inducing uterine contractions.

In the *first trimester*, misoprostol is used for cervical ripening before surgical termination; it has been reported to be effective when given orally, sublingually, or vaginally,[1-4] usually in a dose of 400 micrograms. Oral misoprostol (400 micrograms) given after mifepristone is effective in medical termination of early pregnancy of up to 63 days, and especially so at up to 49 days.[5,6] Misoprostol 800 micrograms has also been given vaginally after mifepristone,[7-10] and a regimen of 2 or 3 doses of sublingual misoprostol after oral mifepristone has been reported to be effective.[11] Successful use of vaginal misoprostol with intramuscular or oral methotrexate has also been described.[12-15]

Misoprostol on its own is only a weak abortifacient, particularly when given orally, and congenital malformations have been reported after failed abortion attempts using misoprostol alone (see Effects on the Fetus, above). However, there is interest in finding a regimen that is effective, particularly in countries where mifepristone is unavailable. A dose of 800 micrograms vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.[16,17] A large study[18] has also reported that 800 micrograms given every 12 hours for 3 doses was less effective when given sublingually than vaginally; the routes were equally effective when misoprostol was given every 3 hours, but sublingual administration caused more adverse effects such as fever, chills, shivering, and diarrhoea.

Misoprostol has also been studied for termination of pregnancy during the *second trimester*. It has been used in various regimens to induce medical termination, given either alone[19,20] or after oral mifepristone,[21,22] and reported to be effective when given vaginally, sublingually, or orally. The time to complete abortion may depend on the dose, dosage interval, and route of administration. Compared with other prostaglandins, intravaginal misoprostol alone (generally as a single dose of 200 micrograms or repeated after 12 hours if necessary) has been reported to be as effective as dinoprostone for medical termination.[23] Another study[24] found 400 micrograms intravaginally every 3 hours, up to 5 doses, to be at least as effective as intra-amniotic carboprost. The use of buccal misoprostol to prepare the cervix before surgical termination has also been described.[25]

In the management of first trimester *pregnancy failure*, intravaginal misoprostol has been proposed as an alternative to surgery for evacuation of the uterus.[26] Doses have ranged from 400 to 800 micrograms, but the lower doses tend to be less effective.[27] Misoprostol has also been used with mifepristone for uterine evacuation after pregnancy failure (see Termination of Pregnancy, p.2012) and to induce labour where late *intra-uterine fetal death* has occurred (see Labour Induction, p.2012).

1. Ngai SW, *et al.* The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. *Hum Reprod* 1999; **14:** 2139–42.
2. Saxena P, *et al.* Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions. *Hum Reprod* 2004; **19:** 77–80.
3. Vimala N, *et al.* Cervical priming with sublingual misoprostol vs. 15-methyl-prostaglandin F2α prior to surgical abortion. *Int J Gynecol Obstet* 2005; **88:** 134–7.
4. Carbonell Esteve JL, *et al.* Sublingual versus vaginal misoprostol (400 μg) for cervical priming in first-trimester abortion: a randomized trial. *Contraception* 2006; **74:** 328–33.
5. Peyron R, *et al.* Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; **328:** 1509–13.
6. Spitz IM, *et al.* Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998; **338:** 1241–7.
7. El-Refaey H, *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995; **332:** 983–7.
8. Ashok PW, *et al.* Termination of pregnancy at 9-13 weeks' amenorrhoea with mifepristone and misoprostol. *Lancet* 1998; **52:** 542–3.
9. Schaff EA, *et al.* Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. *JAMA* 2000; **284:** 1948–53.
10. Shannon C, *et al.* Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. *BJOG* 2006; **113:** 621–8.
11. Hamoda H, *et al.* A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005; **112:** 1102–8.
12. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; **90:** 611–16.
13. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; **57:** 83–8.
14. Borgatta L, *et al.* Early medical abortion with methotrexate and misoprostol. *Obstet Gynecol* 2001; **97:** 11–16.
15. Aldrich T, Winikoff B. Does methotrexate confer a significant advantage over misoprostol alone for early medical abortion? A retrospective analysis of 8678 abortions. *BJOG* 2007; **114:** 555–62.
16. Philip NM, *et al.* A consensus regimen for early abortion with misoprostol. *Int J Gynecol Obstet* 2004; **87:** 281–3.
17. Blanchard K, *et al.* Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception* 2005; **72:** 91–7.
18. von Hertzen H, *et al.* WHO Research Group on Postovulatory Methods of Fertility Regulation. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. *Lancet* 2007; **369:** 1938–46.
19. Tang OS, *et al.* A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004; **111:** 1001–5.
20. Caliskan E, *et al.* Randomized comparison of 3 misoprostol protocols for abortion induction at 13–20 weeks of gestation. *J Reprod Med* 2005; **50:** 173–80. Correction. *ibid.*; 732. [dose]
21. Hamoda H, *et al.* A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. *Hum Reprod* 2005; **20:** 2348–54.
22. Tang OS, *et al.* A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005; **20:** 3062–6.
23. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E for termination of second-trimester pregnancy. *N Engl J Med* 1994; **331:** 290–3.
24. Su L-L, *et al.* A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for midtrimester termination of pregnancy. *Am J Obstet Gynecol* 2005; **193:** 1410–14.
25. Patel A, *et al.* Planned Parenthood Federation of America Buccal Misoprostol Waiver Group. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. *Contraception* 2006; **73:** 420–30.
26. Zhang J, *et al.* A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005; **353:** 761–9.
27. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Cytotec; ***Austria:*** Cyprostol; ***Belg.:*** Cytotec; ***Braz.:*** Cytotec; ***Canad.:*** Cytotec†; ***Chile:*** Misotrol; ***Cz.:*** Cytotec†; ***Denm.:*** Cytotec; ***Fin.:*** Cytotec; ***Fr.:*** Cytotec; Gymiso; ***Ger.:*** Cytotec†; ***Gr.:*** Cytotec; ***Hong Kong:*** Cytotec; ***India:*** Cytolog; Misoprost; ***Indon.:*** Cytotec; Gastrul; Noprostol; ***Irl.:*** Cytotec; ***Israel:*** Cytotec; ***Ital.:*** Cytotec; Misodex; ***Malaysia:*** Cytotec; ***Mex.:*** Cytotec; ***Neth.:*** Cytotec; ***Norw.:*** Cytotec; ***NZ:*** Cytotec; ***Pol.:*** Cytotec; ***Port.:*** Cytotec; ***Rus.:*** Cytotec (Сайтотек)†; ***S.Afr.:*** Cytotec; ***Singapore:*** Cytotec; ***Spain:*** Cytotec; Glefos†; ***Swed.:*** Cytotec; ***Switz.:*** Cytotec; ***Thai.:*** Cytotec; ***Turk.:*** Cytotec; ***UK:*** Cytotec; ***USA:*** Cytotec; ***Venez.:*** Cytotec.

Used as an adjunct in: ***Arg.:*** Oxaprost; ***Austral.:*** Arthrotec; ***Austria:*** Arthrotec; ***Belg.:*** Arthrotec; ***Canad.:*** Arthrotec; ***Cz.:*** Arthrotec†; ***Denm.:*** Arthrotec; ***Fin.:*** Arthrotec; ***Fr.:*** Artotec; ***Ger.:*** Arthotec; ***Gr.:*** Arthrotec; ***Hong Kong:*** Arthrotec; ***Irl.:*** Arthrotec; ***Israel:*** Arthrotec; ***Ital.:*** Artrotec; Misofenac; ***Mex.:*** Artrenac Pro; Artrene; Artrotec; ***Neth.:*** Arthrotec; Artrotec; Misofenac; Normulen; ***Norw.:*** Arthrotec; ***Pol.:*** Arthrotec; ***Port.:*** Arthrotec; Diclotec; ***Rus.:*** Arthrotec (Артротек)†; ***S.Afr.:*** Arthrotec; ***Spain:*** Artrotec; Normulen; ***Swed.:*** Arthrotec; ***Switz.:*** Arthrotec; ***Thai.:*** Arthrotec†; ***UK:*** Arthrotec; Napratec; ***USA:*** Arthrotec; ***Venez.:*** Arthrotec.

Oxytocin *(BAN, rINN)*

Alpha-hypophamine; Hipofamina; Ocitocina; Oksitocinas; Oksitosiini; Oksitosin; Oxitocin; Oxitocina; Oxytocine; Oxytocinum. Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 cyclic (1→6) disulphide; [2-Leucine,7-isoleucine]vasopressin.

Окситоцин

$C_{43}H_{66}N_{12}O_{12}S_2$ = 1007.2.

CAS — 50-56-6.

ATC — H01BB02.

ATC Vet — QH01BB02.

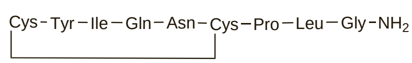

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Oxytocin). A cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary that stimulates contraction of the uterus and milk ejection in receptive mammals. It is obtained by chemical synthesis and is available in the freeze-dried form as an acetate. A white or almost white, hygroscopic powder. Very soluble in water and in dilute solutions of dehydrated alcohol and of acetic acid. A 2% solution in water has a pH of 3.0 to 6.0. Store at 2° to 8° in airtight containers. Protect from light.

Ph. Eur. 6.2 (Oxytocin Concentrated Solution). A solution of oxytocin with a concentration of not less than 250 micrograms of oxytocin per mL. It may contain a suitable antimicrobial preservative. A clear colourless liquid with a pH of 3.0 to 5.0. Store at 2° to 8°. Protect from light.

USP 31 (Oxytocin). A nonapeptide hormone having the property of causing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary glands. It is prepared by synthesis or obtained from the posterior lobe of the pituitary of healthy domestic animals used for food by man. Its oxytocic activity is not less than 400 units/mg. Store in airtight containers at 2° to 8°.

Units

12.5 units of oxytocin for bioassay are contained in about 21.4 micrograms of synthetic peptide (with human albumin 5 mg and citric acid) in one ampoule of the fourth International Standard (1978).

Adverse Effects

Oxytocin given in high doses, or to women who are hypersensitive to it, may cause uterine hyperstimulation with hypertonic or tetanic contractions, leading to uterine rupture and soft tissue damage. Effects in the fetus include bradycardia, arrhythmias, asphyxiation, and perhaps death.

Maternal deaths from severe hypertension and subarachnoid haemorrhage have occurred. Rapid intravenous injection of oxytocin has produced acute transient hypotension with flushing and reflex tachycardia. Postpartum haemorrhage, fatal afibrinogenaemia, and disseminated intravascular coagulation have been reported, but may be due to complications of labour induction rather than oxytocin itself.

High doses of oxytocin infused over prolonged periods can also cause water retention leading to hyponatraemia and intoxication, which may progress to convulsions, coma, and even death. Vasopressin-like activity (see p.2412) is more likely with oxytocin of natural origin but may occur even with the synthetic peptide.

Other adverse effects include headache, nausea and vomiting, skin rashes, cardiac arrhythmias, pelvic haematoma, and anaphylactic and other hypersensitivity reactions.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

Adverse effects after intranasal use of oxytocin have included nasal irritation, rhinorrhoea, lachrymation, uterine bleeding, and violent uterine contractions.

Inappropriate use. In a 1988 comment on the misuse of oxytocin in labour,[1] it was noted that statements on the management of labour were often misinterpreted as meaning that all women who failed to make adequate progress in terms of cervical dilatation should be given oxytocin. This was only true if poor progress was due to poor uterine action, and would be dangerous where there was disproportion; the decision to use oxytocin required careful assessment by an experienced obstetrician. In the previous 2 years the authors had seen one case of fractured pelvis, 2 of ruptured uterus, and 7 of cerebral palsy from fetal hypoxia, all of which were thought to be due to the ill-advised use of oxytocin to augment labour. More than a decade later the injudicious use of oxytocin during labour, with adverse outcomes including neonatal brain damage and death, continues to be reported. A review[2] of obstetric malpractice claims in Sweden found that the incorrect use of oxytocin was obvious in 37 of 54 cases; often, the oxytocin infusion had been increased despite a non-reassuring fetal heart-rate pattern with or without overly frequent uterine contractions, or fetal monitoring was inadequate and hence fetal distress not recognised.

For reference to haemorrhage and to neonatal hyperbilirubinaemia occurring after an oxytocin challenge test, see under Uses and Administration, below.

1. Taylor RW, Taylor M. Misuse of oxytocin in labour. *Lancet* 1988; **i:** 352.
2. Jonsson M, *et al.* Analysis of malpractice claims with a focus on oxytocin use in labour. *Acta Obstet Gynecol Scand* 2007; **86:** 315–19.

Neonatal jaundice. Analysis of neonatal jaundice in 12 461 single births confirmed a higher incidence of jaundice in offspring of mothers given oxytocin, independent of gestational age at birth, sex, race, epidural analgesia, method of delivery, and birth-weight, which were also associated with jaundice.[1] A later review[2] of 12 023 single births also found some of these factors to be associated with neonatal hyperbilirubinaemia, but not epidural analgesia or the use of oxytocin. Another smaller population study[3] also concluded that oxytocin was not significantly related to neonatal jaundice. In a total of 90 infants born to mothers after oxytocin-induced labour in 2 studies,[4,5] haematological disturbances were noted. These included erythrocyte fragility or reduction in erythrocyte deformability, hyponatraemia, hypo-osmolality, and an increase in serum-bilirubin concentration. Glucose injection, used as a vehicle for oxytocin may have further aggravated these changes.[5] A comparison[6] of women who received oxytocin infusion in either glucose 5% or sodium chloride 0.9% found the use of glucose to be associated with more cases of hyponatraemia in cord plasma, and neonatal hyperbilirubinaemia. In contrast, another study[7] found no difference between these diluents, but did report that neonatal bilirubin concentrations were higher when oxytocin had been used for augmentation of labour, compared with labour induction.

See also under Oxytocin Challenge Test in Uses and Administration, below.

1. Friedman L, *et al.* Factors influencing the incidence of neonatal jaundice. *BMJ* 1978; **1:** 1235–7.
2. Linn S, *et al.* Epidemiology of neonatal hyperbilirubinemia. *Pediatrics* 1985; **75:** 770–4.
3. Seidman DS, *et al.* Predicting the risk of jaundice in fullterm healthy newborns: a prospective population-based study. *J Perinatol* 1999; **19:** 564–7.
4. Buchan PC. Pathogenesis of neonatal hyperbilirubinaemia after induction of labour with oxytocin. *BMJ* 1979; **2:** 1255–7.
5. Singhi S, Singh M. Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia. *Arch Dis Child* 1979; **54:** 400–2.
6. Omigbodun AO, *et al.* Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. *Int J Gynecol Obstet* 1993; **40:** 235–9.
7. Oral E, *et al.* Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. *Arch Gynecol Obstet* 2003; **267:** 117–20.

The symbol † denotes a preparation no longer actively marketed

Water intoxication. Oxytocin-induced water intoxication is most likely to arise as a result of prolonged attempts to empty the uterus in missed abortion or mid-trimester termination of pregnancy, but it has also been described after oxytocin infusion in other conditions including induction of labour.[1] Irrespective of the oxytocin concentration, patients in virtually all the reported cases have received more than 3.5 litres of infused fluid. Convulsions and somnolence associated with hyponatraemia have also been reported in a patient who was drinking more than 5 litres of herbal tea daily while using intranasal oxytocin 8 times or more daily.[2]

Another factor contributing to hyponatraemia is the antidiuretic effect of the pethidine and morphine commonly used for analgesia with oxytocin infusions. Water intoxication usually presents with fits and loss of consciousness but in some cases there may be preceding signs such as raised venous pressure, bounding pulse, and tachycardia. Diagnosis is confirmed by profound hyponatraemia; the mechanism appears to be more complex than simply haemodilution by the infused water. Treatment consists of controlling convulsions and maintaining an airway; oxytocin infusion must be stopped and isotonic, or even hypertonic, saline may be infused. Diuresis may then be assisted with furosemide. The prime objective, however, should be prevention; no patient should receive more than 3 litres of fluid containing oxytocin, and a careful fluid balance record is essential.

1. Feeney JG. Water intoxication and oxytocin. *BMJ* 1982; **285:** 243.
2. Mayer-Hubner B. Pseudotumour cerebri from intranasal oxytocin and excessive fluid intake. *Lancet* 1996; **347:** 623.

Precautions

Oxytocin should not be given where spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia or vasa praevia, placental abruption, cord presentation or prolapse, mechanical obstruction to delivery, fetal distress or hypertonic uterine contractions. It should not be used where there is a predisposition to uterine rupture, as in multiple pregnancy or high parity, polyhydramnios, or the presence of a uterine scar from previous caesarean section. Oxytocin should not be used for prolonged periods in resistant uterine inertia, severe pre-eclampsia, or severe cardiovascular disorders.

When given for induction or enhancement of labour particular care is needed in borderline cephalopelvic disproportion, less severe degrees of cardiovascular disease, and in patients over 35 years of age or with other risk factors. Careful monitoring of fetal heart rate and uterine motility is essential so that dosage of oxytocin can be adjusted to individual response; the drug should be given by intravenous infusion, preferably by means of an infusion pump. Infusion should be stopped immediately if fetal distress or uterine hyperactivity occur.

Over-vigorous labour should be avoided in cases of intra-uterine fetal death, or where there is meconium-stained amniotic fluid, because there is a risk of amniotic fluid embolism.

The risk of water intoxication should be borne in mind, particularly when high doses of oxytocin are given over a long time. Infusion volumes should be kept low, and in such circumstances an electrolyte-based infusion fluid should be used rather than glucose solution. Fluid intake by mouth should be restricted and a fluid balance chart maintained; serum electrolytes should be measured if electrolyte imbalance is suspected.

Oxytocin challenge test. For the suggestion that oxytocin challenge testing should be used with caution in women whose offspring might be at risk of hyperbilirubinaemia, see under Uses and Administration, below.

Interactions

Oxytocin may enhance the vasopressor effects of sympathomimetics. Some inhalational anaesthetics, such as cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic effect; cardiac arrhythmias may occur. Prostaglandins and oxytocin may potentiate the effects of each other on the uterus; the UK licensed product information for oxytocin states that it should not be started for 6 hours after use of vaginal prostaglandins.

Pharmacokinetics

Oxytocin undergoes enzymatic destruction in the gastrointestinal tract but it is rapidly absorbed from the mucous membranes when given intranasally. It is metabolised by the liver and kidneys with a plasma half-life of only a few minutes. Only small amounts are excreted unchanged in the urine.

◊ References.

1. Seitchik J, *et al*. Oxytocin augmentation of dysfunctional labor IV: oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; **150:** 225–8.
2. Perry RL, *et al*. The pharmacokinetics of oxytocin as they apply to labor induction. *Am J Obstet Gynecol* 1996; **174:** 1590–3.

Uses and Administration

Oxytocin is a cyclic nonapeptide secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis.

Oxytocin causes contraction of the uterus, the effect increasing with the duration of pregnancy due to proliferation of oxytocin receptors. Small doses increase the tone and amplitude of the uterine contractions; large or repeated doses result in tetany. Oxytocin also stimulates the smooth muscle associated with the secretory epithelium of the lactating breast causing the ejection of milk but having no direct effect on milk secretion. It has a weak antidiuretic action.

Oxytocin is used for the induction and augmentation of labour, to control postpartum bleeding and uterine hypotonicity in the third stage of labour, and to promote lactation in cases of faulty milk ejection. It is also used in missed abortions, but other measures may be preferred.

For the **induction** or **augmentation of labour** (below) oxytocin may be given by slow intravenous infusion preferably by means of an infusion pump. A solution containing 5 units in 500 mL of a physiological electrolyte solution such as sodium chloride 0.9% has been recommended but more concentrated solutions may be given via infusion pump, and current UK guidelines suggest 10 or 30 units in 500 mL of diluent. Infusion is begun at a recommended initial rate of 1 to 2 milliunits/minute and then gradually increased at intervals of at least 30 minutes, until a maximum of 3 or 4 contractions are occurring every 10 minutes. A rate of up to 6 milliunits/minute is reported to produce plasma oxytocin concentrations comparable to those in natural labour, and 12 milliunits/minute is usually the most that is needed but doses of up to 20 milliunits/minute or more may be required. UK guidelines suggest that 32 milliunits/minute should not be exceeded, and no more than a total of 5 units should be given in 1 day. Oxytocin should not be started for 6 hours after vaginal prostaglandins have been given. Fetal heart rate and uterine contractions should be monitored continuously. Once labour is progressing, oxytocin infusion may be gradually withdrawn.

For the treatment and prevention of **postpartum haemorrhage** (below) oxytocin may be given by slow intravenous injection in a dose of 5 units; this may be followed in severe cases by intravenous infusion of 5 to 20 units in 500 mL of a suitable non-hydrating diluent. The *BNF* suggests that in the treatment of uterine bleeding, higher doses may also be considered: a single dose of 10 units by slow intravenous injection may be used, followed if necessary by an infusion containing up to 30 units in 500 mL. A single dose of 5 units by slow intravenous injection has also been given during caesarean section, immediately after delivery of the child. An alternative for the prophylaxis of postpartum haemorrhage in the routine management of the third stage of labour is the intramuscular injection of oxytocin 5 units with ergometrine maleate 500 micrograms after delivery of the anterior shoulder, or, at the latest, immediately after delivery of the infant; the *BNF* suggests a single intramuscular dose of oxytocin 10 units used alone if ergometrine is contra-indicated. In the USA a dose of 10 units of oxytocin, by intravenous infusion at a rate of 20 to 40 milliunits/minute, or as an intramuscular injection, has been recommended for treatment of postpartum haemorrhage.

In **missed abortion** a suggested dose in the UK is 5 units by slow intravenous injection, followed if necessary by intravenous infusion at a rate of 20 to 40 milliunits/minute or higher.

Oxytocin nasal spray is used to facilitate **lactation**; a dose of one spray, delivering 4 units, into one nostril 5 minutes before suckling has been used. However, evidence for its efficacy is limited and there is a danger that the mother may become dependent upon its action; such usage is not generally recommended (see p.2003).

An **oxytocin challenge test** (below) has been used to evaluate fetal distress in pregnant patients at high risk.

Synthetic derivatives of oxytocin such as demoxytocin (p.2006) have been used similarly.

Labour induction and augmentation. Oxytocin infusions have proved to be one of the most successful agents for induction and augmentation of labour, as discussed on p.2002. There have been numerous studies on the dosage of oxytocin required to induce or augment labour. Various dosage regimens have been tried, and studies have reported using initial doses ranging from 0.5 to 6 milliunits/minute, dose increases of 1 to 6 milliunits/minute, and intervals between increases of 15 to 40 minutes.[1] Higher doses and shorter intervals between increases can shorten labour and reduce rates of intra-amniotic infection and caesarean delivery, but result in more uterine hyperstimulation and emergency caesarean deliveries for fetal distress.[1] Low-dose regimens are now generally advocated; for example, UK guidelines[2] favour a starting dose of 1 to 2 milliunits/minute, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 32 milliunits/minute. WHO[3] suggests a starting dose of 2.5 milliunits/minute, increased at intervals of 30 minutes, and titrated against contractions to a maximum of 60 milliunits/minute. However, it has been pointed out that no one regimen has been clearly proved superior.[1,4,5]

1. Stubbs TM. Oxytocin for labor induction. *Clin Obstet Gynecol* 2000; **43:** 489–94.
2. Royal College of Obstetricians and Gynaecologists. Induction of labour: evidence-based clinical guideline number 9 (issued June 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/inductionoflabourrcogrep.pdf (accessed 30/06/08)
3. Department of Reproductive Health and Research. Induction and augmentation of labour. In: WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors*. Geneva: WHO, 2003: P17–P26. Also available at: http://www.who.int/reproductive-health/impac/Procedures/Induction_P17_P25.html (accessed 30/06/08)
4. Patka JH, *et al*. High- versus low-dose oxytocin for augmentation or induction of labor. *Ann Pharmacother* 2005; **39:** 95–101.
5. Smith JG, Merrill DC. Oxytocin for induction of labor. *Clin Obstet Gynecol* 2006; **49:** 594–608.

Oxytocin challenge test. The oxytocin challenge test (OCT) is designed to detect placental insufficiency, and identify fetuses at risk of still-birth or complications during labour. In a study, it was performed on 399 occasions in 305 women with pregnancies at risk and a gestational age of 36 weeks or more.[1] Oxytocin 1 milliunit/minute was given by infusion pump and increased every 5 to 10 minutes until a contraction rate of 3 per 10 minutes was achieved. Less than 10% of late or variable decelerations of fetal heart rate (FHR) was judged negative; 10 to 29% was judged equivocal; and 30% or more was judged positive. The finding of a positive or equivocal response to the OCT was considered a prediction of decelerations of the FHR during parturition, though the type of risk might vary. After 100 OCTs in 90 pregnant women considered at risk[2] it was concluded that a negative result is a reliable test of fetal well-being which should encourage obstetricians to await spontaneous onset of labour in preference to intervention. However, there have been reports of fetal death occurring despite a negative response to the OCT.[3-5] Another study[6] found that in 239 women with an unequivocal OCT result, a negative response was a reliable test for a good outcome, but that a positive result was not a reliable predictor of poor outcome.

Adverse effects associated with the OCT have included haemorrhage occurring in a patient after the second of two tests (the patient was found to have a major placenta praevia)[7] and neonatal hyperbilirubinaemia.[8] The latter effect led to the suggestion that the OCT should be used with caution in women whose babies might be at risk from hyperbilirubinaemia.

1. Schulman H, *et al*. Quantitative analysis in the oxytocin challenge test. *Am J Obstet Gynecol* 1977; **129:** 239–44.
2. Sellappah S, Wagman H. Oxytocin challenge test as an out patient procedure. *Br J Clin Pract* 1984; **38:** 255–8.
3. Marcum RG. False negative oxytocin challenge test. *Am J Obstet Gynecol* 1977; **127:** 894.
4. Lorenz RP, Pagano JS. A case of intrauterine fetal death after a negative oxytocin challenge test. *Am J Obstet Gynecol* 1978; **130:** 232.
5. Dittman R, Belcher J. False-negative oxytocin challenge test. *N Engl J Med* 1978; **298:** 56.

6. Ocak V, *et al.* The predictive value of fetal heart rate monitoring: a retrospective analysis of 2165 high-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1992; **44:** 53–8.
7. Ng KH, Wong WP. Risk of haemorrhage in oxytocin stress test. *BMJ* 1976; **2:** 698–9.
8. Peleg D, Goldman JA. Oxytocin challenge test and neonatal hyperbilirubinaemia. *Lancet* 1976; **ii:** 1026.

Postpartum haemorrhage. Oxytocin is used for the prophylaxis and treatment of postpartum haemorrhage (p.2003). In the active management of the third stage of labour, the combination of oxytocin and ergometrine may be associated with a small reduction in the risk of postpartum haemorrhage compared with oxytocin alone, but a higher incidence of nausea, vomiting, and hypertension.

Retained placenta. Oxytocin injected into the vein of the umbilical cord has been used to assist the removal of retained placenta. A meta-analysis[1] of 12 studies found evidence that oxytocin reduced the incidence of manual removal of the retained placenta, although there was no apparent benefit in terms of other measures including blood loss, curettage, and infection. The removal of the placenta is important to allow contraction of the myometrium and prevention of excessive blood loss, and is one reason for the use of oxytocin in the active management of the third stage of labour, as discussed under Postpartum Haemorrhage—see above and on p.2003.

1. Carroli G, Bergel E. Umbilical vein injection for management of retained placenta. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 30/06/08).

Preparations

BP 2008: Ergometrine and Oxytocin Injection; Oxytocin Injection;
USP 31: Oxytocin Injection; Oxytocin Nasal Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Hipofisina; Syntocinon; Veracuril; ***Austral.:*** Syntocinon; ***Austria:*** Syntocinon; ***Belg.:*** Syntocinon; ***Braz.:*** Naox; Orastina; Oxiton; Syntocinon; ***Chile:*** Syntocinon; ***Denm.:*** Syntocinon; ***Fin.:*** Syntocinon; ***Fr.:*** Syntocinon; ***Ger.:*** Orasthin†; Syntocinon; ***Hong Kong:*** Syntocinon; ***India:*** Gynotocin; Pitocin; Syntocinon; ***Indon.:*** Induxin; Pitogin; Piton-S; Syntocinon; ***Irl.:*** Syntocinon; ***Ital.:*** Syntocinon; ***Malaysia:*** Syntocinon; ***Mex.:*** Oxitopisa; Syntocinon; Xitocin; ***Neth.:*** Piton-S†; Syntocinon; ***Norw.:*** Syntocinon; ***NZ:*** Syntocinon; ***Philipp.:*** Estima; Fetusin; NeOxyn; Obcin; Oxitone; Oxtimon; Solvoxine; Syntocinon; Tranoxy; ***Port.:*** Syntocinon; ***S.Afr.:*** Syntocinon; ***Singapore:*** Syntocinon; ***Spain:*** Syntocinon; ***Swed.:*** Syntocinon; ***Switz.:*** Syntocinon; ***Turk.:*** Postuitrin; Synpitan; ***UK:*** Syntocinon; ***USA:*** Pitocin; ***Venez.:*** Pitocin†; Syntocinon.

Multi-ingredient: ***Austral.:*** Syntometrine; ***Ger.:*** Syntometrin†; ***Hong Kong:*** Syntometrine†; ***Irl.:*** Syntometrine; ***Malaysia:*** Syntometrine; ***NZ:*** Syntometrine; ***S.Afr.:*** Syntometrine; ***UK:*** Syntometrine.

Prolactin

Galactin; Galactina; Hormona lactogénica; Hormona luteotrópica; Lactoestimulina; Lactogen; Lactogenic Hormone; Lactógeno; Lactotropin; LMTH; LTH; Luteomammotropic Hormone; Luteotrophic Hormone; Luteotropin; Luteotropina; Mammotropin; Mamotropina; Prolactina.

Пролактин

CAS — 9002-62-4; 12585-34-1 (sheep); 56832-36-1 (ox); 9046-05-3 (pig).

Profile

Prolactin is a water-soluble protein from the anterior pituitary; it is structurally related to growth hormone (p.1799). In *animals*, prolactin has many actions and is involved in reproduction, parental care, feeding of the young, electrolyte balance, and growth and development. In humans it has a definite role in inducing milk production; oxytocin (p.2016) stimulates milk ejection. Relatively high concentrations of prolactin have been found in amniotic fluid. Placental lactogen has been shown to have prolactin-like activity. Prolactin secretion is stimulated by suckling and, for a few months after delivery, it has an inhibitory effect on the ovaries, acting as a natural contraceptive.

The hypothalamus can both stimulate and inhibit prolactin secretion by the anterior pituitary; the inhibitory influence is predominant and is mediated through a dopaminergic system. Dopamine binds to the lactotrope D_2 receptor to inhibit prolactin synthesis and release. Noradrenaline and gamma-aminobutyric acid are also inhibitory as are dopaminergic drugs such as bromocriptine. Although protirelin (p.2176) has prolactin-releasing activity, there is evidence for the existence of a separate hypothalamic releasing factor (PRF). Prolactin secretion may also be stimulated by methyldopa, metoclopramide, reserpine, opioid analgesics, and phenothiazine or butyrophenone antipsychotics.

Hyperprolactinaemia, which is associated with a variety of other endocrine disorders, is discussed on p.2079.

Prolactin has been given by intramuscular injection in the management of lactation disorders and some forms of menstrual disturbance.

Ritodrine Hydrochloride

(BANM, USAN, rINNM) ⊗

DU-21220 (ritodrine); Hidrocloruro de ritodrina; Ritodrin Hidroklorür; Ritodrine, Chlorhydrate de; Ritodrini Hydrochloridum. *erythro*-2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl)propan-1-ol hydrochloride.

Ритодрина Гидрохлорид

$C_{17}H_{21}NO_3$,HCl = 323.8.

CAS — 26652-09-5 (ritodrine); 23239-51-2 (ritodrine hydrochloride).

ATC — G02CA01.

ATC Vet — QG02CA01.

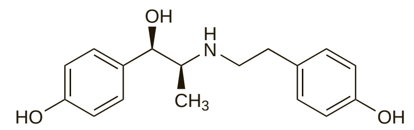

(ritodrine)

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2008 (Ritodrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in acetone and in ether. A 2% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 31 (Ritodrine Hydrochloride). A white to nearly white, odourless or practically odourless, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in ether; soluble in propyl alcohol. pH of a 2% solution in water is between 4.5 and 6.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for Salbutamol Sulfate, p.1131. Leucopenia or agranulocytosis has been reported occasionally with prolonged intravenous use.

In women given ritodrine for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p.1132, apply.

Effects on the eyes. Ritodrine and to a lesser extent salbutamol have been implicated in retinopathy in the premature infant when used for premature labour.[1]

1. Michie CA, *et al.* Do maternal β-sympathomimetics influence the development of retinopathy in the premature infant? *Arch Dis Child* 1994; **71:** F149.

Effects on the heart. Myocardial ischaemia or signs of myocardial ischaemia have been reported in patients given ritodrine.[1-3] Sinus tachycardia and ST-segment depression commonly occur in patients given ritodrine, but the relationship between these changes and ischaemia remains unclear.[3]

1. Brosset P, *et al*. Cardiac complications of ritodrine in mother and baby. *Lancet* 1982; **i:** 1468.
2. Ben-Shlomo I, *et al.* Myocardial ischaemia during intravenous ritodrine treatment: is it so rare? *Lancet* 1986; **ii:** 917–18.
3. Verhaert D, Van Acker R. Acute myocardial infarction during pregnancy. *Acta Cardiol* 2004; **59:** 331–9.

Effects on skeletal muscle. Elevated serum-creatine kinase concentrations have been found in women given ritodrine tocolysis,[1] and there have been rare reports of rhabdomyolysis.[1,2]

1. Matsuda Y, *et al.* Evaluation of creatine kinase level during long-term tocolysis. *J Perinat Med* 2002; **30:** 476–9.
2. Nasu K, *et al.* Rhabdomyolysis caused by tocolysis with oral ritodrine hydrochloride in a pregnant patient with myotonic dystrophy. *Gynecol Obstet Invest* 2006; **61:** 53–5.

Pulmonary oedema. Several cases of pulmonary oedema have been reported in patients given a $beta_2$ agonist, including ritodrine, for premature labour.[1-4] In 1995 the UK CSM[4] commented that it had received 10 reports of pulmonary oedema, fatal in 2 patients. The CSM considered that fluid overload was the most important predisposing factor. Other risk factors included multiple pregnancies, a history of cardiac disease, and maternal infection. For further discussion of the precautions necessary in the use of $beta_2$ agonists to treat premature labour, and the risk factors involved, see Salbutamol, p.1132.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.
2. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med* 1989; **110:** 714–18.
3. Clesham GJ, *et al.* β Adrenergic agonists and pulmonary oedema in preterm labour. *BMJ* 1994; **308:** 260–2.
4. Committee on Safety of Medicines/Medicines Control Agency. Reminder: ritodrine and pulmonary oedema. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)

Interactions

As for Salbutamol Sulfate, p.1132.

Pharmacokinetics

Ritodrine is rapidly absorbed from the gastrointestinal tract but is subject to fairly extensive first-pass metabolism; about 30% of an oral dose is bioavailable. It is metabolised in the liver primarily by conjugation with glucuronic acid or sulfate and excreted in urine as unchanged drug and metabolites. About 70 to 90% of a dose is reported to be excreted in the urine within 10 to 12 hours. It crosses the placenta.

◊ References.

1. Gandar R, *et al.* Serum level of ritodrine in man. *Eur J Clin Pharmacol* 1980; **17:** 117–22.
2. Gross AS, Brown KF. Plasma protein binding of ritodrine at parturition and in nonpregnant women. *Eur J Clin Pharmacol* 1985; **28:** 479–81.
3. Kuhnert BR, *et al.* Ritodrine pharmacokinetics. *Clin Pharmacol Ther* 1986; **40:** 656–64.
4. Caritis SN, *et al.* Pharmacokinetics of orally administered ritodrine. *Am J Obstet Gynecol* 1989; **161:** 32–5.
5. Caritis SN, *et al*. Pharmacokinetics of ritodrine administered intravenously: recommendations for changes in the current regimen. *Am J Obstet Gynecol* 1990; **162:** 429–37.
6. Caritis SN, *et al.* Pharmacokinetics and pharmacodynamics of ritodrine after intramuscular administration to pregnant women. *Am J Obstet Gynecol* 1990; **162:** 1215–19.
7. Pacifici GM, *et al*. Sulphation and glucuronidation of ritodrine in human foetal and adult tissues. *Eur J Clin Pharmacol* 1993; **44:** 259–64.
8. Pacifici GM, *et al.* Ritodrine sulphation in the human liver and duodenal mucosa: interindividual variability. *Eur J Drug Metab Pharmacokinet* 1998; **23:** 67–74.

Uses and Administration

Ritodrine hydrochloride is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has general properties similar to those of salbutamol (see p.1133). It decreases uterine contractility and is used to arrest premature labour (p.2003).

Ritodrine hydrochloride is usually given by intravenous infusion. Where possible this should be with the aid of a **syringe pump**, when the concentration should be 3 mg/mL, using glucose 5% as the diluent. A recommended initial rate of infusion is 50 micrograms/minute increased at intervals of 10 minutes by increments of 50 micrograms/minute until there is evidence of patient response, which is usually at a rate of 150 to 350 micrograms/minute, the latter figure being the maximum recommended rate. If no syringe pump is available then the infusion may be made using a **controlled infusion device** to deliver a more dilute solution of 300 micrograms/mL, with glucose 5% being used once again as the diluent. The same dose is used as with the syringe pump.

The maternal pulse should be monitored throughout the infusion and the rate adjusted to avoid a maternal heart rate of more than 140 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. The infusion should be continued for 12 to 48 hours after the contractions have stopped. Ritodrine hydrochloride may subsequently be given **by mouth** in an initial dose of 10 mg every 2 hours for 24 hours, starting 30 minutes before the end of the intravenous infusion. Thereafter, 10 to 20 mg may be given every 4 to 6 hours according to the patient's response. The total daily oral dose should not exceed 120 mg.

If intravenous infusion is inappropriate, 10 mg may be given **intramuscularly** every 3 to 8 hours and continued for 12 to 48 hours after the contractions have stopped.

◊ Reviews.

1. Yaju Y, Nakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. *Pharmacoepidemiol Drug Safety* 2006; **15:** 813–22.

Preparations

BP 2008: Ritodrine Injection; Ritodrine Tablets;
USP 31: Ritodrine Hydrochloride Injection; Ritodrine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ritopar; ***Belg.:*** Pre-Par; ***Braz.:*** Miodrina; ***Chile:*** Materlac†; ***Cz.:*** Pre-Par†; ***Gr.:*** Pre-Par†; Yutopar; ***Hong Kong:*** Yutopar†; ***India:*** Yutopar;

Indon.: Yutopar; ***Israel:*** Ritopar; ***Ital.:*** Miolene; ***Port.:*** Pre-Par†; ***Spain:*** Pre-Par; ***Turk.:*** Pre-Par; ***UK:*** Yutopar.

Sulprostone *(USAN, rINN)*

CP-34089; 16-Phenoxy-ω-17,18,19,20-tetranor-prostaglandin E_2-methylsulfonylamide; SHB-286; Sulproston; Sulprostona; Sulprostoni; Sulprostonum; ZK-57671. (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxybut-1-enyl]-5-oxocyclopentyl}-*N*-(methylsulphonyl)hept-5-enamide.

Сульпростон

$C_{23}H_{31}NO_7S$ = 465.6.
CAS — 60325-46-4.
ATC — G02AD05.
ATC Vet — QG02AD05.

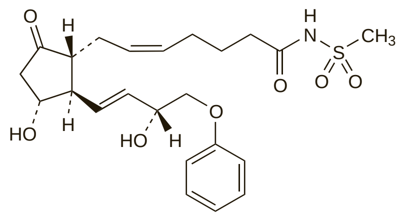

Adverse Effects and Precautions

As for Dinoprostone, p.2007. In some countries, such as France, the licensed product information for sulprostone contra-indicates its use in smokers or those who have smoked in the last 2 years, and in women over 35 years of age.

Once a prostaglandin has been given to terminate pregnancy it is essential that termination take place; if the prostaglandin is unsuccessful other measures should be used.

Effects on the cardiovascular system. A 31-year-old woman died from cardiovascular shock during an abortion induced by mifepristone followed by sulprostone. She had 12 children, one previous abortion, and was a heavy cigarette smoker.[1] Four other deaths with sulprostone had not been associated with abortion. Other reported cases that did not result in death have included myocardial infarction in a 32-year-old woman given sulprostone for intra-uterine fetal death,[2] and cardiac arrest in a 38-year-old woman, with no history of smoking, after sulprostone was given by both intramyometrial and intravenous bolus injection for postpartum haemorrhage;[3] in both cases the authors suggested that sulprostone had caused coronary artery spasm.

Inadvertent subcutaneous infusion of sulprostone was thought to have caused arterial spasm with pain and oedema in the arm of a woman being treated for postpartum haemorrhage; she recovered after treatment with iloprost infusion.[4]

1. Anonymous. A death associated with mifepristone/sulprostone. *Lancet* 1991; **337:** 969–70.
2. Fliers E, *et al.* A prostaglandin analogue as a probable cause of myocardial infarction in a young woman. *BMJ* 1991; **302:** 416.
3. Chen FG, *et al.* Cardiac arrest associated with sulprostone use during caesarean section. *Anaesth Intensive Care* 1998; **26:** 298–301.
4. de Koning YWCM, *et al.* Critical limb ischemia after accidental subcutaneous infusion of sulprostone. *Eur J Obstet Gynecol Reprod Biol* 1995; **61:** 171–3.

Effects on the nervous system. For a report of convulsions in epileptic patients given sulprostone, see under Dinoprostone, p.2007.

Effects on the uterus. For reference to hyperstimulation and uterine rupture after use of prostaglandins, including sulprostone, for termination of pregnancy or induction of labour, see under Dinoprostone, p.2007.

Interactions

As for Dinoprostone, p.2008.

Uses and Administration

Sulprostone is a synthetic derivative of dinoprostone (prostaglandin E_2; p.2007) that has uterine stimulant effects. It is used for dilatation of the cervix before surgical termination of pregnancy in the first trimester, for medical termination of pregnancy in the second trimester (p.2004), and to empty the uterus in missed abortion, hydatidiform mole, and intra-uterine fetal death. It is also used to control postpartum haemorrhage (p.2003).

Sulprostone is given by intravenous infusion. A dose of 500 micrograms over 3 to 6 hours is used for cervical dilatation in the first trimester. For termination of pregnancy in the second trimester, or to empty the uterus, sulprostone is infused at a rate of 100 micrograms/hour for up to 10 hours; if necessary the infusion rate may be increased to up to 500 micrograms/hour, to a maximum total dose of 1.5 mg in 24 hours. If termination is unsuccessful the course may be repeated once, 12 to 24 hours after the end of the first infusion.

To control postpartum haemorrhage, an initial infusion of 100 micrograms/hour is given. This may be increased to 500 micrograms/hour if necessary to control bleeding, then reduced to a maintenance dose of 100 micrograms/hour. A total dose of 1.5 mg in 24 hours should not be exceeded.

Sulprostone has also been given extra-amniotically and locally into the cervix. It has also been given by the intramuscular route, but this is no longer recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Nalador; ***Fin.:*** Nalador†; ***Fr.:*** Nalador; ***Ger.:*** Nalador; ***Hong Kong:*** Nalador; ***Hung.:*** Nalador†; ***Ital.:*** Nalador; ***Neth.:*** Nalador; ***Port.:*** Nalador; ***Switz.:*** Nalador; ***Thai.:*** Nalador.

Organic Solvents

Most of the solvents described in this chapter have no specific therapeutic use. Additional solvents used in pharmacy and described in other chapters include alcohols, chlorinated hydrocarbons such as chloroform and trichloroethylene, fixed oils, glycols, paraffins, and water.

Organic solvents are widely used in industry and toxicity has been associated with acute or chronic exposure. due to inhalation, ingestion, or absorption through the skin. Organic solvents are irritant to the skin and mucous membranes, and often affect the CNS. They may sensitise the myocardium to catecholamines and cardiac arrhythmias may occur. Chronic exposure may lead to central and peripheral neurotoxicity, as well as to renal toxicity and hepatotoxicity.

◊ References.

1. White RF, Proctor SP. Solvents and neurotoxicity. *Lancet* 1997; **349:** 1239–43.

Abuse. Since they are volatile liquids and have CNS effects many organic solvents are implicated in volatile substance abuse. Clinical features of intoxication are similar to those of alcohol intoxication, with initial CNS stimulation followed by CNS depression, which may progress to delirium, convulsions, coma, and death. Sudden death due to cardiac arrhythmias has also been reported.

References.

1. Proceedings of a meeting on substance abuse. *Hum Toxicol* 1989; **8:** 253–334.
2. Ashton CH. Solvent abuse. *BMJ* 1990; **300:** 135–6.

Acetone

Aceton; Acetona; Acetonas; Acétone; Acetonum; Asetoni; Dimethyl Ketone; Propanone; 2-Propanone.

Ацетон

$C_3H_6O = 58.08.$

CAS — 67-64-1.

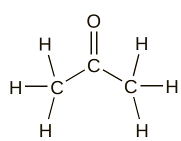

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Acetone). A volatile, clear, colourless liquid; the vapour is flammable. Miscible with water and with alcohol. Protect from light.

USNF 26 (Acetone). A transparent, colourless, mobile, volatile, very flammable liquid, having a characteristic odour. Sp. gr. not more than 0.789. Miscible with water, with alcohol, with chloroform, with ether, and with most volatile oils. A 50% solution in water is neutral to litmus. Store in airtight containers remote from fire.

Adverse Effects and Treatment

Inhalation of acetone vapour causes excitement followed by CNS depression with headache, restlessness, fatigue, and possibly convulsions, leading to coma and respiratory depression in severe cases. Vomiting and haematemesis may occur. There may be a latent period before the onset of symptoms of acetone poisoning. Similar symptoms may be seen after ingestion of acetone although hyperglycaemia has also been reported. The vapour is irritant to mucous membranes in high concentrations.

Acetone is commonly implicated in volatile substance abuse (see above).

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

◊ For the possible effect of acetone on the metabolism of acetonitrile, see under Acetonitrile, below.

Pharmacokinetics

Acetone is absorbed through the lungs after inhalation. Some absorption occurs from the gastrointestinal tract. It is mostly excreted unchanged, predominantly through the lungs and also in the urine.

Uses

Acetone is widely used as an industrial, pharmaceutical, and domestic solvent; it is also used as an extraction solvent in food processing.

Acetonitrile

Acetonitrilo; Acetonitryl; Ethanenitrile; Methyl Cyanide.

Ацетонитрил

$C_2H_3N = 41.05.$

CAS — 75-05-8.

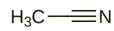

Description. Acetonitrile is a colourless liquid with an aromatic odour. Wt per mL about 0.79 g. B.p. about 81°. It emits highly toxic fumes of hydrogen cyanide when heated to decomposition or when reacted with acids or oxidising agents. Store in airtight containers.

Adverse Effects and Treatment

As for cyanides (see Hydrocyanic Acid, p.2045).

◊ Cyanide poisoning, including a fatality, has been reported[1,2] in a number of infants after ingestion of artificial nail removers containing acetonitrile. As acetonitrile is slowly metabolised to cyanide, serious toxic effects may not occur until several hours after ingestion and there is the danger that these products may be confused with acetone-based nail polish removers which are less toxic. In a report[3] of an adult who died after ingestion of acetonitrile, the onset of symptoms was delayed for 24 hours. It was considered that concomitant ingestion of acetone had slowed the metabolism of acetonitrile. In another case[4] vomiting, diarrhoea, convulsions, and reduced consciousness developed in a 35-year-old man 15 hours after occupational exposure to acetonitrile. Despite treatment for cyanide poisoning, acute renal failure and rhabdomyolysis subsequently developed.

1. Caravati EM, Litovitz TL. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *JAMA* 1988; **260:** 3470–3.
2. Losek JD, *et al.* Cyanide poisoning from a cosmetic nail remover. *Pediatrics* 1991; **88:** 337–40.
3. Boggild MD, *et al.* Acetonitrile ingestion: delayed onset of cyanide poisoning due to concurrent ingestion of acetone. *Postgrad Med J* 1990; **66:** 40–1.
4. Muraki K, *et al.* Massive rhabdomyolysis and acute renal failure after acetonitrile exposure. *Intern Med* 2001; **40:** 936–9.

Pharmacokinetics

Acetonitrile is absorbed by inhalation, ingestion, and through the skin. It undergoes metabolism to cyanide, which is responsible for the toxicity of acetonitrile.

Uses

Acetonitrile is used as an industrial solvent. It may also be present in artificial nail removers.

Amyl Acetate

Acetato de amilo.

Амилацетат

$C_7H_{14}O_2 = 130.2.$

CAS — 123-92-2 (iso-amyl acetate); 53496-15-4 (sec-amyl acetate); 628-63-7 (n-amyl acetate).

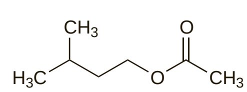

iso-amyl acetate

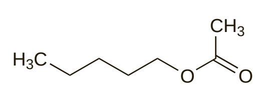

n-amyl acetate

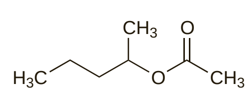

sec-amyl acetate

Description. Amyl acetate is a mixture of isomers, principally *iso*-, *sec*-, and *n*-amyl acetate. *iso*-Amyl acetate is a clear colourless liquid with a sharp, fruity odour. Wt per mL about 0.87 g. B.p. about 140°. Slightly soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Adverse Effects and Treatment

Prolonged exposure to amyl acetate may produce headache, fatigue, and depression of the CNS. Irritation of mucous membranes may also occur.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

Effects on the heart. A 27-year-old man developed headache, nausea, and vomiting after using a paint containing amyl acetate as the solvent in an unventilated room.[1] Some days later chest pain and dyspnoea developed; he was admitted to hospital 2 weeks after exposure with heart failure which slowly responded to treatment.

1. Weissberg PL, Green ID. Methyl-cellulose paint possibly causing heart failure. *BMJ* 1979; **ii:** 1113–14.

Uses

Amyl acetate is used as a pharmaceutical and industrial solvent.

Amylene Hydrate

Aethyldimethylmethanolum; Dimethylethyl Carbinol; Hidrato de amileno; Tertiary Amyl Alcohol. 2-Methylbutan-2-ol.

Амилгидрат

$C_5H_{12}O = 88.15.$

CAS — 75-85-4.

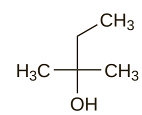

Pharmacopoeias. In *USNF.*

USNF 26 (Amylene Hydrate). A clear, colourless liquid having a camphoraceous odour. Sp. gr. 0.803 to 0.807. Distilling range 97° to 103°. Freely soluble in water; miscible with alcohol, with chloroform, with ether, and with glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects

Amylene hydrate is irritant and has a depressant effect on the CNS.

Uses

Amylene hydrate is used as a pharmaceutical solvent. It was formerly used as a hypnotic.

Aniline

Anilina; Phenylamine.

Анилин

$C_6H_7N = 93.13.$

CAS — 62-53-3.

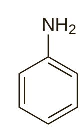

Description. Aniline is a colourless or pale yellow oily liquid with a characteristic odour, readily darkening to brown on exposure to air and light. Wt per mL about 1.02 g. B.p. about 183°. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Inhalation, ingestion, or cutaneous absorption of aniline results in methaemoglobinaemia, with cyanosis, headache, weakness, stupor, convulsions, and coma. Irritation of the skin or mucous membranes, nausea and vomiting, and cardiac arrhythmias may occur. Haemolysis has been reported and may give rise to renal damage or jaundice. Death is usually a result of cardiovascular collapse.

Treatment may involve oxygen, methylthioninium chloride (p.1451), transfusions, or possibly haemodialysis. Gastric aspiration or activated charcoal may be considered in patients who present within 1 hour of ingestion.

Bladder papillomas have been reported in workers previously exposed to aniline. Commercial aniline may be contaminated with β-naphthylamine, a potential carcinogen.

Handling. Suitable precautions should be taken to avoid skin contact with aniline as it can penetrate skin and produce systemic toxicity.

Uses

Aniline is a solvent with wide industrial applications.

Benzene

Benceno; Benzen; Phenyl Hydride.

Бензол

C_6H_6 = 78.11.

CAS — 71-43-2.

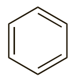

NOTE. Benzene may be known as 'benzina', 'benzol', 'benzole', or 'benzolum'. However, 'benzol' is also used to describe a mixture of hydrocarbons and 'benzin' or 'benzine' is used as a name for a petroleum distillate (see also Petroleum Spirit, p.2026).

Description. Benzene is a clear colourless flammable liquid with a characteristic aromatic odour. Wt per mL about 0.88 g. B.p. about 80°. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Symptoms of acute poisoning after inhalation or ingestion of benzene include initial excitement or euphoria followed by CNS depression with headache, dizziness, blurred vision, and ataxia, which in severe cases may progress to coma (accompanied by hyperactive reflexes), convulsions, and death from respiratory failure. Other symptoms include nausea and irritation of the mucous membranes; ventricular arrhythmias may occur. Direct skin contact with liquid benzene may result in marked irritation, and dermatitis may develop on prolonged or repeated exposure.

Prolonged industrial exposure to benzene vapour has been associated with adverse effects on the gastrointestinal tract and the CNS but in particular with marked effects on the bone marrow and blood. Decreases in the numbers of red or white blood cells or of platelets may occur, producing symptoms of headache, fatigue, anorexia, pallor, and petechiae. In severe cases pancytopenia or aplastic anaemia may develop. Leukaemia, particularly acute myeloid leukaemia, has also developed, often many years after exposure to benzene has ceased. These effects have been reported in workers exposed to relatively high concentrations of the vapour (around 200 ppm or more) but reduced red blood cell counts and anaemia have also been reported at lower concentrations. Chromosome abnormalities have been observed after prolonged exposure to benzene, particularly at the higher concentrations associated with blood dyscrasias; however, the significance of these abnormalities in the development of leukaemia is unclear.

Treatment of poisoning consists of symptomatic and supportive measures. The UK National Poisons Information Service considers that gut decontamination (gastric lavage) is contra-indicated because it may increase the risk of aspiration. In chronic poisoning, repeated blood transfusions may be necessary. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

◊ Reviews.

1. Health and Safety Executive. Benzene. *Toxicity Review 4.* London: HMSO, 1982.
2. WHO. Benzene. *Environmental Health Criteria 150.* Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc150.htm (accessed 29/06/04)

Malignant neoplasms. Epidemiological data support an association between benzene exposure and acute myeloid leukaemia, but the risk after low levels of exposure (1 to 10 ppm) is less clear.[1] However, a large cohort study[2] suggested that there is an increased risk of acute myeloid leukaemia and of non-Hodgkin's lymphoma with benzene exposure at levels below 10 ppm.

1. Austin H, *et al.* Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 1988; **127:** 419–39.
2. Hayes RB, *et al.* Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997; **89:** 1065–71.

Pregnancy. An evaluation of the USA National Natality and Fetal Mortality Survey noted that maternal or paternal occupational exposure to agents such as benzene was associated with an increased risk of still-birth and that paternal exposure to benzene increased the risk of low-birth-weight infants.[1]

1. Savitz DA, *et al.* Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol* 1989; **129:** 1201–18.

Pharmacokinetics

Benzene is absorbed after inhalation and ingestion, but is not significantly absorbed through the skin. Some is excreted unchanged from the lungs. Oxidation to phenol and related quinol compounds occurs, the metabolites being excreted in the urine as conjugates of sulfuric or glucuronic acid.

Uses

Benzene was formerly applied as a pediculicide. Its use as an industrial solvent is decreasing.

Butyl Acetate

Acetato de butilo; Butylu octan. *n*-Butyl acetate.

Бутилацетат

$C_6H_{12}O_2$ = 116.2.

CAS — 123-86-4.

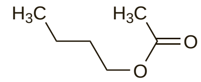

Description. Butyl acetate is a clear, colourless flammable liquid with a strong fruity odour. Wt per mL about 0.88 g. B.p. 123° to 126°. Slightly soluble in water; miscible with alcohol. Store in airtight containers.

Adverse Effects

Butyl acetate is irritant. High concentrations may cause CNS depression.

Uses

Butyl acetate is used as an industrial solvent and as an extraction solvent in food processing.

Butyl Alcohol

Alcohol butílico; *n*-Butanol; *n*-Butyl Alcohol. Butan-1-ol.

Бутиловый Спирт

$C_4H_{10}O$ = 74.12.

CAS — 71-36-3.

Pharmacopoeias. In *USNF.*

USNF 26 (Butyl Alcohol). A clear, colourless, mobile liquid having a characteristic, penetrating vinous odour. Sp. gr. 0.807 to 0.809. It distils within a range of 1.5°, including 117.7°. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers at a temperature not exceeding 40°.

Adverse Effects and Precautions

Butyl alcohol may be irritant and may cause mild CNS depression with headache, dizziness, and drowsiness.

◊ References to the toxicity of butyl alcohol.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 29/06/04)
2. WHO. 1-Butanol health and safety guide. *IPCS Health and Safety Guide 3.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg003.htm (accessed 29/06/04)

Handling. Suitable precautions should be taken to avoid skin contact with butyl alcohol as it can penetrate skin and produce systemic toxicity.

Uses

Butyl alcohol is used as an industrial and pharmaceutical solvent and as an extraction solvent in food processing.

Butylamine

Butilamina; *n*-Butylamine; Butyloamina.

Бутиламин

$C_4H_{11}N$ = 73.14.

CAS — 109-73-9.

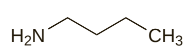

Description. Butylamine is a colourless to pale yellow flammable liquid with an ammoniacal odour. Wt per mL about 0.744 g. B.p. about 78°. Miscible with water, with alcohol, and with ether. Store in airtight containers.

Adverse Effects and Precautions

Butylamine is irritant. Symptoms of CNS depression may be observed after exposure to high concentrations of the vapour.

Handling. Suitable precautions should be taken to avoid skin contact with butylamine as it can penetrate skin and produce systemic toxicity.

Uses

Butylamine is used as a solvent.

Carbon Disulfide

Carbon Bisulphide; Carbon Disulphide; Carbonei Sulfidum; Carboneum Bisulfuratum; Carboneum Sulfuratum; Disulfuro de carbono; Schwefelkohlenstoff; Węgla disiarczek.

Сероуглерод

CS_2 = 76.14.

CAS — 75-15-0.

S=C=S

Description. Carbon disulfide is a clear, colourless, volatile, flammable liquid with a chloroform-like odour. Commercial grades have an unpleasant odour described by some as being reminiscent of decaying radishes. Wt per mL about 1.26 g. B.p. about 46°. Store in airtight containers.

Stability. The vapour of carbon disulfide when mixed with air in the proportions of 1 to 50% is highly explosive.

Adverse Effects, Treatment, and Precautions

Carbon disulfide is irritant. Toxic effects may occur as a result of inhalation, ingestion, or absorption through the skin.

Acute poisoning may result in gastrointestinal disturbances and euphoria, followed by CNS depression. Symptoms include headache, dizziness, mood changes, and in severe cases, manic psychoses, delirium, hallucinations, coma, convulsions, and death due to respiratory failure.

Chronic poisoning has been associated with occupational exposure to carbon disulfide vapour for prolonged periods. It is characterised by peripheral neuropathies; CNS effects such as headache, fatigue, insomnia, tremor, emotional lability, extrapyramidal disorders, bipolar disorder, and encephalopathy; gastrointestinal effects including anorexia, dyspepsia, and ulcerative changes; and effects on the eye. Occupational exposure to carbon disulfide has been shown to be associated with an increased incidence of mortality from coronary heart disease. The action of carbon disulfide on endocrine function has resulted in menstrual irregularities, an increased incidence of spontaneous abortions and premature births, loss of libido, sperm abnormalities, and decreased serum-thyroxine concentrations; there is limited evidence of impaired glucose tolerance.

Treatment consists of removal from exposure and general supportive and symptomatic measures. Gastric lavage should be avoided. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias. Peripheral neuropathies may be only slowly reversible.

◊ Reviews of the toxicity of carbon disulfide.

1. WHO. Carbon Disulfide. *Environmental Health Criteria 10.* Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc010.htm (accessed 29/06/04)
2. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
3. Health and Safety Executive. Carbon disulphide. *Toxicity Review 3.* London: HMSO, 1981.
4. Beauchamp RO, *et al.* A critical review of the literature on carbon disulfide toxicity. *Crit Rev Toxicol* 1983; **11:** 169–278.

Effects on endocrine function. The effects of exposure to carbon disulfide were studied retrospectively in 265 female workers in the rayon industry exposed for at least 1 year, and 291 non-exposed female workers.[1] Levels of exposure varied over the study period from 0.7 to 30.6 mg/m^3. Women exposed to carbon disulfide had a higher risk of menstrual disturbances than non-exposed women. However, there was no difference between the 2 groups in incidence of toxaemia, emesis gravidarum, spontaneous abortion, premature or overdue delivery, or congenital malformation.

1. Zhou SY, *et al.* Effects of occupational exposure to low-level carbon disulfide (CS) on menstruation and pregnancy. *Ind Health* 1988; **26:** 203–14.

Effects on the heart. An increased incidence of mortality from cardiovascular disease has been found in workers occupationally exposed to carbon disulfide.[1-3] The evidence suggested that the risk decreases after cessation of exposure. However, the association has been critically reviewed.[4]

1. Nurminen M, Hernberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. *Br J Ind Med* 1985; **42:** 32–5.
2. Sweetnam PM, *et al.* Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Br J Ind Med* 1987; **44:** 220–7.
3. MacMahon B, Monson RR. Mortality in the US rayon industry. *J Occup Med* 1988; **30:** 698–705.
4. Sulsky SI, *et al.* Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. *Int Arch Occup Environ Health* 2002; **75:** 365–80.

Handling. Suitable precautions should be taken to avoid skin contact with carbon disulfide as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Carbon disulfide is rapidly absorbed after inhalation and ingestion, and is also absorbed through intact skin. It is excreted unchanged through the lungs and in the urine mainly as metabolites.

Uses
Carbon disulfide is used as an industrial solvent and has been used, in the vapour form, as an insecticide.

Carbon Tetrachloride
Tetracloruro de carbono; Węgla tetrachlorek. Tetrachloromethane.

Четырёххлористый Углерод

CCl_4 = 153.8.

CAS — 56-23-5.

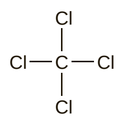

Description. Carbon tetrachloride is a clear, colourless, mobile, liquid with a chloroform-like odour. Sp. gr. 1.588 to 1.590. B.p. 76° to 78°. Practically insoluble in water; miscible with alcohol, chloroform, ether, petroleum spirit, and fixed and volatile oils. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Handling. Avoid contact with carbon tetrachloride; the vapour and liquid are poisonous. Care should be taken not to vaporise carbon tetrachloride in the presence of a flame because of the production of harmful gases, mainly phosgene.

Adverse Effects
Individual response to carbon tetrachloride varies widely; inhalation or ingestion of a few mL of carbon tetrachloride has proved fatal and its toxicity appears to be increased by alcohol. Poisoning may follow inhalation, ingestion, or topical application but develops more rapidly after inhalation.

Carbon tetrachloride is irritant; repeated application of carbon tetrachloride to the skin may result in dermatitis. Aspiration may result in pulmonary oedema.

Adverse effects after acute exposure from any route include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and CNS disturbances such as headache, dizziness, and drowsiness, with progression to convulsions, coma, and death from respiratory depression or circulatory collapse. Death may also occur as a result of ventricular arrhythmia. Hepatic and renal cellular necrosis can occur and are associated with free radical production; symptoms usually begin a few days or up to 2 weeks after acute exposure to carbon tetrachloride. Renal damage may present as oliguria, progressing to proteinuria, anuria, weight gain, and oedema. Symptoms of hepatic damage include anorexia, jaundice, and hepatomegaly. If hepatorenal necrosis is not fatal recovery is eventually complete.

Symptoms of chronic poisoning are similar to those of acute poisoning; in addition, paraesthesias, visual disturbances, anaemia, and aplastic anaemia have occurred. Carcinogenicity has been demonstrated in *animals.*

◊ References.

1. Melamed E, Lavy S. Parkinsonism associated with chronic inhalation of carbon tetrachloride. *Lancet* 1977; **i:** 1015.
2. Johnson BP, *et al.* Cerebellar dysfunction after acute carbon tetrachloride poisoning. *Lancet* 1983; **ii:** 968.
3. Perez AJ, *et al.* Acute renal failure after topical application of carbon tetrachloride. *Lancet* 1987; **i:** 515–6.
4. Health and Safety Executive. Carbon tetrachloride, chloroform. *Toxicity Review 23*. London: HMSO, 1992.
5. Manno M, Rezzadore M. Critical role of ethanol abuse in carbon tetrachloride poisoning. *Lancet* 1994; **343:** 232.
6. WHO. Carbon tetrachloride health and safety guide. *IPCS Health and Safety Guide 108*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg108.htm (accessed 29/06/04)

Treatment of Adverse Effects
If carbon tetrachloride vapour has been inhaled the patient should be removed to the fresh air. Clothing contaminated by liquid should be removed and the skin washed. If carbon tetrachloride has been ingested gastric lavage may be performed if the patient presents within 1 hour and activated charcoal may be given.

The usual symptomatic and supportive measures should be instituted. Hepatic and renal function should be monitored closely. Haemodialysis or peritoneal dialysis may be needed if renal function is impaired. Adrenaline or other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Acetylcysteine (p.1550) may be given to patients recently exposed to carbon tetrachloride in an attempt to prevent or modify hepatic and renal damage.

Pharmacokinetics
Carbon tetrachloride is readily absorbed after inhalation and ingestion. It is also absorbed through the skin. Metabolism to reactive free radicals is thought to account for the hepatorenal toxicity of carbon tetrachloride.

Carbon tetrachloride is slowly excreted from the body via the lungs and the urine.

Uses
Carbon tetrachloride is employed in industry as a solvent and degreaser. It was formerly used in certain types of fire extinguisher and as an industrial and domestic dry cleaner but has been largely replaced for this purpose by less toxic substances. Carbon tetrachloride has also been used for the fumigation of cereals.

Carbon tetrachloride was formerly given orally as an anthelmintic but it has been superseded by equally effective and less toxic drugs.

Cyclohexane
Ciclohexano; Cykloheksan; Hexahydrobenzene; Hexamethylene.

Циклогексан

C_6H_{12} = 84.16.

CAS — 110-82-7.

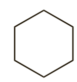

Description. Cyclohexane is a colourless, flammable liquid. Wt per mL about 0.78 g. B.p. about 81°. Store in airtight containers.

Adverse Effects
Cyclohexane is irritant, and may also have effects on the CNS.

◊ Reviews of the toxicity of cyclohexane.

1. Health and Safety Executive. Cyclohexane, cumene, para-dichlorobenzene (p-DCB), chlorodifluoromethane (CFC 22). *Toxicity Review 25*. London: HMSO, 1991.

Uses
Cyclohexane is used as an industrial solvent.

Dichloromethane
Cloruro de metileno; Dichlormethan; Diclorometano; Diklórmetán; Methylene Chloride; Méthylène, chlorure de; Methyleni chloridum; Metileno chloridas; Metyleenikloridi; Metylenklorid; Metylenu chlorek.

Дихлорметан

CH_2Cl_2 = 84.93.

CAS — 75-09-2.

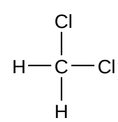

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Methylene Chloride; Dichloromethane BP 2008). A clear, colourless, volatile liquid. Relative density 1.320 to 1.332. It may contain not more than 2% of alcohol and/or not more than 0.03% of 2-methylbut-2-ene as stabiliser. Sparingly soluble in water; miscible with alcohol. Store in airtight containers. Protect from light.

USNF 26 (Methylene Chloride). A clear, colourless, mobile liquid having an odour resembling chloroform. Sp. gr. 1.318 to 1.322. Miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers.

Stability. Phosgene is produced on heating of dichloromethane.

Adverse Effects and Treatment
Acute exposure to dichloromethane vapour may depress the CNS; symptoms progress from headache and dizziness to coma and death in severe cases. Pulmonary oedema has been reported. Significant exposure may result in raised blood concentrations of carboxyhaemoglobin and symptoms of carbon monoxide poisoning. Cardiovascular effects have been attributed to hypoxia secondary to carboxyhaemoglobinaemia. There has been a report of haemolysis after acute ingestion of dichloromethane.

Chronic occupational exposure to dichloromethane vapour has produced gastrointestinal disturbances in addition to symptoms observed after acute poisoning. Dichloromethane is a common constituent of paint strippers and may be implicated in volatile substance abuse (p.2019).

The liquid is irritant and high concentrations of the vapour are irritant to the eyes.

Treatment of acute poisoning consists of removal from exposure and supportive and symptomatic measures. Carboxyhaemoglobinaemia should be managed as for carbon monoxide poisoning (p.1688) by giving 100% oxygen; hyperbaric oxygen may be indicated. After ingestion gastric lavage or activated charcoal are generally contra-indicated, although gastric aspiration may be considered in serious cases if the airway can be protected. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias.

◊ References.

1. WHO. Methylene Chloride. *Environmental Health Criteria 32*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc32.htm (accessed 29/06/04)
2. Health and Safety Executive. Dichloromethane (methylene chloride). *Toxicity Review 12*. London: HMSO, 1985.
3. WHO. Methylene chloride health and safety guide. *IPCS Health and Safety Guide 6*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg006.htm (accessed 29/06/04)
4. Rioux JP, Myers RAM. Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 1988; **6:** 227–38.
5. Manno M, *et al.* Double fatal inhalation of dichloromethane. *Hum Exp Toxicol* 1992; **11:** 540–5.
6. Dhillon S, Von Burg R. Methylene chloride. *J Appl Toxicol* 1995; **15:** 329–35.
7. Chang YL, *et al.* Diverse manifestations of oral methylene chloride poisoning: report of 6 cases. *J Toxicol Clin Toxicol* 1999; **37:** 497–504.
8. Jacubovich RM, *et al.* Facial nerve palsy after acute exposure to dichloromethane. *Am J Ind Med* 2005; **48:** 389–92.

Pharmacokinetics
Dichloromethane is rapidly absorbed after inhalation and is also absorbed after ingestion and slowly through intact skin. It appears to be partially metabolised to carbon dioxide and carbon monoxide which are exhaled, although significant blood-carboxyhaemoglobin concentrations may be attained. Some unchanged dichloromethane is exhaled and small amounts are excreted in the urine.

Uses
Dichloromethane is used as a pharmaceutical and industrial solvent. It is also employed as an extraction solvent in food processing.

Dichloromethane is widely used in paint strippers.

Dichloropropane
Dicloropropano; Propylene Dichloride. 1,2-Dichloropropane.

Дихлорпропан

$C_3H_6Cl_2$ = 113.0.

CAS — 78-87-5.

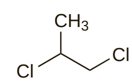

Description. Dichloropropane is a colourless, mobile, flammable liquid. Wt per mL about 1.16 g. B.p. about 96°. Store in airtight containers.

Adverse Effects
Dichloropropane is irritant; high concentrations may result in CNS depression.

◊ Acute renal failure, haemolytic anaemia, acute liver disease, and disseminated intravascular coagulation has been reported[1] after intentional inhalation of a stain remover containing dichloropropane; the patient recovered after blood transfusions and haemodialysis.

1. Locatelli F, Pozzi C. Relapsing haemolytic-uraemic syndrome after organic solvent sniffing. *Lancet* 1983; **ii:** 220.

Uses
Dichloropropane is used as an industrial solvent, dry cleaning agent, and agricultural defumigant.

Diethyl Phthalate
Diéthyle, phtalate de; Diethyl-ftalát; Diethylis phthalas; Dietilftalát; Dietilo ftalatas; Dietylftalat; Dietyyliftalaatti; Ethyl Phthalate; Ftalato de dietilo. Benzene-1,2-dicarboxylic acid diethyl ester.

Диэтилфталат

$C_{12}H_{14}O_4$ = 222.2.

CAS — 84-66-2.

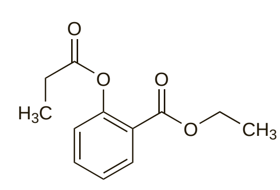

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Diethyl Phthalate). A clear, colourless or very slightly yellow, oily liquid. Relative density 1.117 to 1.121. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 26 (Diethyl Phthalate). A colourless, practically odourless, oily liquid. Sp. gr. 1.118 to 1.122 at 20°. Insoluble in water; miscible with alcohol, with ether, and with other usual organic solvents. Store in airtight containers.

Adverse Effects

Diethyl phthalate is irritant and, in high concentrations, causes CNS depression. There has been concern about potential toxicity resulting from exposure to phthalates used as plasticisers.

◊ References.

1. Health and Safety Executive. Review of the toxicity of the esters of o-phthalic acid (phthalate esters). *Toxicity Review 14*. London: HMSO, 1986.
2. Kamrin MA, Mayor GH. Diethyl phthalate: a perspective. *J Clin Pharmacol* 1991; **31:** 484–9.
3. Shea KM, *et al.* American Academy of Pediatrics Technical Report. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 2003; **111:** 1467–74. [Re-affirmed May 2007]

Uses

Diethyl phthalate is used as a denaturant of alcohol, for example in surgical spirit, and as a solvent and plasticiser.

Dimethyl Sulfoxide *(BAN, USAN, rINN)*

Dimethyl Sulphoxide; Dimethyli Sulfoxidum; Dimethylis sulfoxidum; Dimethylsulfoxid; Diméthylsulfoxyde; Dimetil sulfóxido; Dimetilsulfoksidas; Dimetil-szulfoxid; Dimetylosulfotlenek; Dimetylsulfoxid; Dimetyylisulfoksidi; DMSO; Methyl Sulphoxide; NSC-763; SQ-9453; Sulphinylbismethane.

Диметилсульфоксид

C_2H_6OS = 78.13.
CAS — 67-68-5.
ATC — G04BX13; M02AX03.
ATC Vet — QG04BX13; QM02AX03.

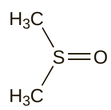

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dimethyl Sulfoxide). A colourless hygroscopic liquid or crystals. F.p. not lower than 18.3°. Relative density 1.100 to 1.104. Miscible with water and with alcohol. Store in airtight glass containers. Protect from light.

USP 31 (Dimethyl Sulfoxide). A clear, colourless, odourless, hygroscopic liquid. M.p. about 18.4°. Sp. gr. 1.095 to 1.097. Soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

High concentrations of dimethyl sulfoxide applied to the skin may cause burning discomfort, itching, erythema, vesiculation, and urticaria. Continued use may result in scaling.

Systemic effects, including gastrointestinal disturbances, drowsiness, headache, and hypersensitivity reactions, may occur after use by any route. A garlic-like odour on the breath and skin is attributed to the formation of dimethyl sulfide (see Pharmacokinetics, below). Intravascular haemolysis has followed intravenous use. Local discomfort and spasm may occur when given by bladder instillation.

Treatment of adverse effects consists of symptomatic and supportive measures. Gastric lavage may be helpful after acute ingestion, although it should be remembered that absorption is rapid.

◊ Reviews.

1. Brobyn RD. The human toxicology of dimethyl sulfoxide. *Ann N Y Acad Sci* 1975; **243:** 497–506.
2. Willhite CC, Katz PI. Toxicology updates: dimethyl sulfoxide. *J Appl Toxicol* 1984; **4:** 155–60.

◊ Dimethyl sulfoxide given by intravenous infusion for spinal cord injury to 14 patients caused transient haemolysis and haemoglobinuria.[1] Infusion strengths greater than 10% were associated with grossly discoloured urine but there was no evidence of renal damage. In 2 patients, raised liver and muscle enzyme concentrations, mild jaundice, and evidence of haemolysis developed when given dimethyl sulfoxide intravenously for arthritis.[2] One also developed acute renal tubular necrosis, deterioration in level of consciousness, and evidence of cerebral infarction. Acute, reversible neurological deterioration in a patient has been associated with intravenous dimethyl sulfoxide.[3]

Adverse effects have also been reported in patients given haematopoietic stem cells cryopreserved in dimethyl sulfoxide. A patient with pre-existing diabetes insipidus[4] developed serum hyperosmolality when given stem cells after chemotherapy for a malignant germ-cell tumour; symptoms included severe headache, confusion, and abdominal pain. Acute neurotoxicity has also been reported,[5,6] although it appears to be rare;[5] 2 patients also had myocardial damage.[6]

1. Muther RS, Bennett WM. Effects of dimethyl sulfoxide on renal function in man. *JAMA* 1980; **244:** 2081–3.
2. Yellowlees P, *et al.* Dimethylsulphoxide-induced toxicity. *Lancet* 1980; **ii:** 1004–6.
3. Bond GR, *et al.* Dimethylsulphoxide-induced encephalopathy. *Lancet* 1989; **i:** 1134–5.
4. Thomé S, *et al.* Dimethylsulphoxide-induced serum hyperosmolality after cryopreserved stem-cell graft. *Lancet* 1994; **344:** 1431–2.
5. Mueller LP, *et al.* Neurotoxicity upon infusion of dimethylsulfoxide-cryopreserved peripheral blood stem cells in patients with and without pre-existing cerebral disease. *Eur J Haematol* 2007; **78:** 527–31.
6. Chen-Plotkin AS, *et al.* Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation. *Neurology* 2007; **68:** 859–61.

Precautions

When used as a penetrating basis for other drugs applied topically, dimethyl sulfoxide may enhance their toxic effects.

Since dimethyl sulfoxide has been associated with lens changes in *animals*, licensed product information recommends assessment of ophthalmic function every 6 months during long-term treatment of cystitis with intravesical instillation of dimethyl sulfoxide. Hepatic and renal function should also be assessed at intervals of 6 months. Bladder instillation may be harmful in patients with urinary-tract malignancy because of vasodilatation.

Interactions

◊ For mention of an interaction between dimethyl sulfoxide and *sulindac*, see p.127.

Pharmacokinetics

Dimethyl sulfoxide is readily absorbed by all routes. It is metabolised by oxidation to dimethyl sulfone (p.2294) and by reduction to dimethyl sulfide. Dimethyl sulfoxide and the sulfone metabolite are excreted in the urine and faeces. Dimethyl sulfide is excreted through the lungs and skin and is responsible for the characteristic odour from patients.

Uses and Administration

Dimethyl sulfoxide is a highly polar substance with exceptional solvent properties for both organic and inorganic chemicals, and is widely used as an industrial solvent.

It has been reported to have a wide spectrum of pharmacological activity including membrane penetration, anti-inflammatory effects, local analgesia, weak bacteriostasis, diuresis, vasodilatation, dissolution of collagen, and free-radical scavenging.

The principal use of dimethyl sulfoxide is as a vehicle for drugs such as idoxuridine (p.881); it aids penetration of the drug into the skin, and so may enhance the drug's effect. It is also used as a 50% aqueous solution for bladder instillation for the symptomatic relief of interstitial cystitis; doses of 50 mL are instilled and allowed to remain for 15 minutes. Treatment is repeated every 2 weeks initially.

Dimethyl sulfoxide has been given orally, intravenously, or topically for a wide range of indications including cutaneous and musculoskeletal disorders, but evidence of beneficial effects is limited.

Dimethyl sulfoxide is used as a cryoprotectant for various human tissues.

Amyloidosis. Oral or local dimethyl sulfoxide has been tried[1-3] as part of the management of some forms of amyloidosis (p.743).

1. Ichida M, *et al.* Successful treatment of multiple myeloma-associated amyloidosis by interferon-alpha, dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol* 2000; **72:** 491–3.
2. Malek RS, *et al.* Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. *J Urol (Baltimore)* 2002; **168:** 1018–20.
3. Amemori S, *et al.* Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J Gastroenterol* 2006; **41:** 444–9.

Cryopreservation. Dimethyl sulfoxide is used as a cryoprotectant in various assisted conception techniques.[1] Adverse effects have been reported in patients receiving haematopoietic stem cells cryopreserved in dimethyl sulfoxide (see under Adverse Effects, above).

1. Trounson AO. Cryopreservation. *Br Med Bull* 1990; **46:** 695–708.

Extravasation of antineoplastics. Several reports have suggested a role for topical dimethyl sulfoxide in the treatment of anthracycline extravasation.[1-4] The problem of antineoplastic extravasation and its management is discussed further on p.640.

1. Lawrence HJ, Goodnight SH. Dimethyl sulfoxide and extravasation of anthracycline agents. *Ann Intern Med* 1983; **98:** 1025.
2. Olver IN, *et al.* A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol* 1988; **6:** 1732–5.
3. Rospond RM, Engel LM. Dimethyl sulfoxide for treating anthracycline extravasation. *Clin Pharm* 1993; **12:** 560–1.
4. Bertelli G, *et al.* Dimethylsulphoxide and cooling after extravasation of antitumour agents. *Lancet* 1993; **341:** 1098.

Gallstones. For mention of the use of a mixture containing dimethyl sulfoxide to dissolve gallstones, see Methyl *tert*-Butyl Ether, p.2025.

Interstitial cystitis. Bladder instillation of dimethyl sulfoxide is used[1,2] in the symptomatic management of interstitial cystitis (p.2179). Treatment usually consists of 50 mL of a 50% aqueous solution that is retained in the bladder for 15 minutes. This may be repeated every 1 to 2 weeks for 4 to 8 treatments, and overall response rates of 50 to 90% have been reported. Although relapse rates after a 4 to 8 week course of treatment are high (35 to 40%), about half of these patients will respond to additional dimethyl sulfoxide treatment. Maintenance therapy on either a regular or intermittent basis may be used.[1]

1. Parkin J, *et al.* Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. *Urology* 1997; **49** (suppl 5A): 105–7.
2. Rössberger J, *et al.* Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol* 2005; **39:** 73–7.

Dimethylacetamide

Acetyldimethylamine; Dimethylacetamid; Diméthylacétamide; Dimethylacetamidum; Dimetilacetamida; Dimetilacetamidas; Dimetylacetamid; Dimetyloacetamid; Dimetyyliasetamidi; DMAC. *NN*-Dimethylacetamide.

Диметилацетамид

C_4H_9NO = 87.12.
CAS — 127-19-5.

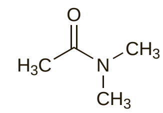

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dimethylacetamide). A clear, colourless, slightly hygroscopic liquid. Relative density 0.941 to 0.944. B.p. about 165°. Miscible with water, with alcohol, and with most common organic solvents. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Dimethylformamide (below), although a disulfiram-like reaction with alcohol has not been reported.

◊ A review[1] of the toxicology of dimethylacetamide with reference to its use as a vehicle for antineoplastics.

1. Kim S-N. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; **19:** 345–68.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylacetamide as it can penetrate skin and produce systemic toxicity.

Uses

Dimethylacetamide is used as an industrial and pharmaceutical solvent.

Dimethylformamide

Dimetilformamida; Dimetyloformamid; DMF. *NN*-Dimethylformamide.

Диметилформамид

C_3H_7NO = 73.09.
CAS — 68-12-2.

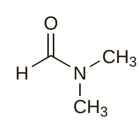

Description. Dimethylformamide is a colourless liquid. Wt per mL about 0.95 g. B.p. about 153°.

Adverse Effects and Precautions

Dimethylformamide is irritant. Gastrointestinal effects including nausea, vomiting, loss of appetite, and abdominal pain, CNS effects such as headache, dizziness, and weakness, and liver damage have been reported in workers occupationally exposed to the liquid or vapour. Some workers exposed to dimethylformamide have experienced a disulfiram-like effect after consumption of alcohol.

◊ Reviews of the adverse effects of dimethylformamide.

1. WHO. Dimethylformamide. *Environmental Health Criteria 114*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc114.htm (accessed 30/06/04)

Effects on the liver. Exposure to dimethylformamide was considered to be the most likely cause of elevated liver enzyme values in 36 of 58 (62%) workers in a fabric coating factory.[1] Symptoms reported were generally mild and included anorexia, abdominal pain, nausea, headache, dizziness, and a disulfiram-type reaction to alcohol.

Hepatotoxicity has occurred after acute poisoning with a veterinary drug formulated in dimethylformamide. There were only minor increases in liver enzyme values in a patient who was treated early with acetylcysteine.[2]

1. Redlich CA, *et al.* Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988; **108:** 680–6.
2. Buylaert W, *et al.* Hepatotoxicity of N,N-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Hum Exp Toxicol* 1996; **15:** 607–11.

Handling. Suitable precautions should be taken to avoid skin contact with dimethylformamide as it can penetrate skin and produce systemic toxicity.

Malignant neoplasms. There have been reports of testicular cancer in men occupationally exposed to dimethylformamide.[1] Such an association could not, however, be substantiated by epidemiological data[2] on 3859 male employees exposed to dimethylformamide between 1950 and 1970 and followed up to 1984. It has been suggested that although dimethylformamide may not itself be carcinogenic, it may increase absorption through the skin of heavy metal carcinogens, possibly including chromates.[3]

1. Levin SM, *et al.* Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* 1987; **ii:** 1153.
2. Chen JL, Kennedy GL. Dimethylformamide and testicular cancer. *Lancet* 1988; **i:** 55.
3. Ducatman AM. Dimethylformamide, metal dyes, and testicular cancer. *Lancet* 1989; **i:** 911.

Pharmacokinetics

Dimethylformamide is absorbed after inhalation and through intact skin. It is excreted mainly in the urine as metabolites.

Uses

Dimethylformamide is used as an industrial solvent.

Dioxan

Diethylene Dioxide; Diethylene Ether; Dioksan; Dioxane; Dioxano. 1,4-Dioxane.

Диоксан

$C_4H_8O_2$ = 88.11.

CAS — 123-91-1.

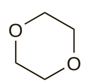

NOTE. Do not confuse dioxan and dioxin (p.2295).

Description. Dioxan is a colourless flammable liquid with an ethereal odour. Wt per mL about 1.03 g. B.p. about 101°. Store in airtight containers.

Stability. It is dangerous to distil or evaporate dioxan unless precautions have been taken to remove explosive peroxides.

Adverse Effects, Treatment, and Precautions

Dioxan vapour is irritant to mucous membranes. High concentrations may cause nausea and vomiting, and CNS depression with headache, dizziness, drowsiness, and in severe cases unconsciousness. On repeated exposure, severe hepatic and renal damage, including necrotic changes, can occur and may be fatal. Direct contact with liquid dioxan can result in dermatitis. Dioxan has been shown to be carcinogenic in *animals.*

Treatment consists of removal from exposure and general supportive and symptomatic measures.

Handling. Suitable precautions should be taken to avoid skin contact with dioxan as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Dioxan is absorbed after inhalation and through the skin. It is metabolised by oxidation to β-hydroxyethoxy-acetic acid.

Uses

Dioxan is used as an industrial solvent.

Epichlorohydrin

Epiclorhidrina. 1-Chloro-2,3-epoxypropane.

Эпихлоргидрин

C_3H_5ClO = 92.52.

CAS — 106-89-8.

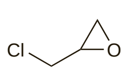

Description. Epichlorohydrin is a colourless, flammable liquid. Wt per mL about 1.18 g. B.p. 115° to 118°. Store in airtight containers.

Stability. The vapour of epichlorohydrin forms explosive mixtures with air. Harmful gases including phosgene are liberated on heating of epichlorohydrin.

Adverse Effects and Precautions

Epichlorohydrin is irritant. It has been shown to be carcinogenic in *animals.*

◊ References to the toxicity of epichlorohydrin.

1. WHO. Epichlorohydrin. *Environmental Health Criteria 33.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc33.htm (accessed 30/06/04)
2. WHO. Epichlorohydrin health and safety guide. *IPCS Health and Safety Guide 8.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg008.htm (accessed 30/06/04)
3. Health and Safety Executive. Ammonia, 1-chloro-2,3-epoxypropane (epichlorohydrin), carcinogenicity of cadmium and its compounds. *Toxicity Review 24.* London: HMSO, 1991.
4. Kolman A, *et al.* Genotoxic effects of ethylene oxide, propylene oxide and epichlorohydrin in humans: update review (1990–2001). *Mutat Res* 2002; **512:** 173–94.

Handling. Suitable precautions should be taken to avoid skin contact with epichlorohydrin as it can penetrate skin and produce systemic toxicity.

Uses

Epichlorohydrin is used as an industrial solvent.

Solvent Ether

Aether; Aether Aethylicus; Aether Solvens; Diethyl Ether; Eetteri; Éter; Eter; Éter disolvente; Eteris; Éther; Ether; Éther rectifié; Ethyl Ether; Ethyl Oxide.

Диэтиловый Эфир; Этиловый Эфир

$(C_2H_5)_2O$ = 74.12.

CAS — 60-29-7.

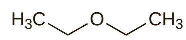

NOTE. Solvent ether is not intended for anaesthesia; only ether of a suitable quality (see p.1783) should be so used.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ether). A colourless, clear, volatile, highly flammable liquid. It may contain a suitable non-volatile antioxidant at a suitable concentration. Relative density 0.714 to 0.716. Distillation range 34° to 35°. Soluble in water; miscible with alcohol, with dichloromethane, and with fatty oils. Store at 8° to 15° in airtight containers. Protect from light.

USP 31 (Ether). A colourless, mobile, volatile, flammable liquid, having a characteristic sweet, pungent odour. It is slowly oxidised by the action of air and light, with the formation of peroxides. B.p. about 35°. Sp. gr. 0.713 to 0.716. Soluble 1 in 12 of water; miscible with alcohol, with chloroform, with dichloromethane, with petroleum spirit, with benzene, and with fixed and volatile oils; soluble in hydrochloric acid. Store in partly filled airtight containers at a temperature not exceeding 30° and remote from fire. Protect from light.

Stability. Though ether is one of the lightest of liquids, its vapour is very heavy, being 2⁄ times heavier than air.

Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark; precautions should be taken against the production of static electrical discharge. Explosive peroxides are generated by the atmospheric oxidation of solvent ether and it is dangerous to distil a sample which contains peroxides.

Adverse Effects

As for Anaesthetic Ether, p.1783. Ingestion of 30 to 60 mL may be fatal.

Uses

Solvent ether is widely used as a pharmaceutical and industrial solvent, and is used as an extraction solvent in food processing.

Ethyl Acetate

Acetato de etilo; Acetic Ether; Aethylis Acetas; Aethylium Aceticum; Ethyl Ethanoate; Ethyl-acetát; Éthyle, acétate d'; Ethylis acetas; Etil-acetát; Etilacetatas; Etylacetat; Etylu octan; Etyyliasetaatti.

Этилацетат

$C_4H_8O_2$ = 88.11.

CAS — 141-78-6.

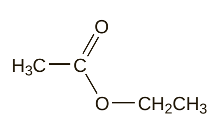

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Ethyl Acetate). A colourless, clear, volatile liquid. Relative density 0.898 to 0.902. B.p. 76° to 78°. Soluble in water; miscible with alcohol, with acetone, and with dichloromethane. Store at a temperature not exceeding 30°. Protect from light.

USNF 26 (Ethyl Acetate). A transparent, colourless, flammable liquid having a fragrant, refreshing, slightly acetous odour. Sp. gr. 0.894 to 0.898. Soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers at a temperature not exceeding 40°.

Adverse Effects

Ethyl acetate is irritant to mucous membranes. High concentrations may cause CNS depression. Ethyl acetate may be implicated in volatile substance abuse (p.2019).

◊ For discussion of neurotoxicity after occupational exposure to solvents and the absence of such an effect with ethyl acetate, see under Toluene, p.2026.

Uses

Ethyl acetate is used as a flavour and solvent in pharmaceutical preparations. It is also used in industry as a solvent and as an extraction solvent in food processing.

Formamide

Carbamaldehyde; Formamid; Formamida; Methanamide.

Формамид

CH_3NO = 45.04.

CAS — 75-12-7.

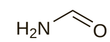

Description. Formamide is a colourless, oily liquid. B.p. 210°. Wt per mL, about 1.13 g.

Profile

Formamide is used as an industrial solvent. It is reported to be irritant.

Glycerol Formal

Glycérol formal; Glycerol-formalum. A mixture of the two isomers 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane present in a constant ratio of 40:60 respectively.

Глицерол Формаль

$C_4H_8O_3$ = 104.1.

CAS — 4740-78-7 (5-hydroxy-1,3-dioxane); 5464-28-8 (4-hydroxymethyl-1,3-dioxolane).

(5-hydroxy-1,3-dioxane) (4-hydroxymethyl-1,3-dioxolane)

Profile

Glycerol formal is used as a pharmaceutical solvent.

Glycofurol

Glicofurol; Glycofural; Glycofurol 75; Tetrahydrofurfuryl Alcohol Polyethylene Glycol Ether. α-(Tetrahydrofuranyl)-ω-hydroxypoly(oxyethylene).

Гликофурфурол

$C_5H_9O.(C_2H_4O)_n.OH$.

CAS — 9004-76-6; 31692-85-0.

Description. Glycofurol is a clear, colourless, almost odourless liquid. Wt per mL about 1.08 g. B.p. 80° to 100°. Incompatible with oxidising agents. Store under nitrogen in airtight containers. Protect from light.

Profile

Glycofurol is used as a pharmaceutical solvent for injections.

Hexachloroethane

Hexacloroetano.

Гексахлорэтан

C_2Cl_6 = 236.7.

CAS — 67-72-1.

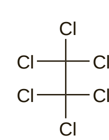

Profile

Hexachloroethane is a chlorinated hydrocarbon used in industry as a solvent. Eye irritation and photophobia have resulted from industrial exposure to the vapour. It was formerly used in veterinary medicine as an anthelmintic, but has been superseded by less toxic drugs.

n-Hexane

n-Hexano.

н-Гексан

C_6H_{14} = 86.18.

CAS — 110-54-3.

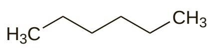

Description. *n*-Hexane is a colourless, flammable, volatile liquid with a faint odour. Wt per mL about 0.66 g. B.p. about 69°. Store in airtight containers.

Adverse Effects

n-Hexane is irritant. Acute exposure to the vapour may result in CNS depression with headache, drowsiness, dizziness, and in severe cases unconsciousness. Chronic occupational exposure and abuse of *n*-hexane have been associated with the development of peripheral neuropathies. *n*-Hexane is a constituent of some adhesives and may be implicated in volatile substance abuse (p.2019). Some adverse effects of petrol have been attributed to its content of *n*-hexane.

◊ References.

1. Health and Safety Executive. *n*-Hexane. *Toxicity Review 18*. London: HMSO, 1987.
2. WHO. *n*-Hexane. *Environmental Health Criteria 122*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc122.htm (accessed 30/06/04)
3. WHO. *n*-Hexane health and safety guide. *IPCS Health and Safety Guide 59*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg059.htm (accessed 30/06/04)

Effects on the nervous system. There have been many reports of peripheral neuropathy attributed to the abuse of, and occupational exposure to, *n*-hexane, although symptoms tend to be milder in the latter.[1] Tetraplegia has occurred in severe cases. There is typically a clinical deterioration several weeks after exposure followed by a slow recovery which, in severe cases, may not be complete. It has been suggested that methyl ethyl ketone potentiates the peripheral neuropathy induced by *n*-hexane. Occupational exposure to *n*-hexane has also been associated with cranial nerve neuropathy.

Parkinsonism in a leather worker, possibly associated with exposure to solvents, mainly *n*-hexane, has been noted.[2]

For further discussion of neurotoxicity after occupational exposure to solvents including *n*-hexane, see under Toluene, p.2026.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.
2. Pezzoli G, *et al.* Parkinsonism due to n-hexane exposure. *Lancet* 1989; **ii:** 874.

Pharmacokinetics

n-Hexane is absorbed after inhalation and to a limited extent through the skin. Oxidative metabolites, including 2,5-hexanedione are excreted in the urine largely as conjugates. Some unchanged *n*-hexane is excreted via the lungs.

Uses

n-Hexane is widely used as an industrial solvent, as a solvent in glues, and as an extraction solvent in food processing.

Isobutyl Alcohol

Alcohol isobutílico; Isobutanol.

Изобутиловый Спирт

$C_4H_{10}O$ = 74.12.

CAS — 78-83-1.

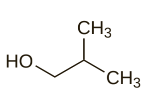

Profile

Isobutyl alcohol is used as an industrial solvent. It is also used as an anaesthetic in the American lobster, *Homarus americanus*.

◊ References.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 30/06/04)
2. WHO. Isobutanol health and safety guide. *IPCS Health and Safety Guide 9*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg009.htm (accessed 30/06/04)

Kerosene

Kerosine; 'Paraffin'; Queroseno.

Керосин

CAS — 8008-20-6.

Description. Kerosene is a mixture of hydrocarbons, chiefly members of the alkane series, distilled from petroleum. It is a clear, colourless liquid with a characteristic odour. Sp. gr. about 0.8 g. B.p. 180° to 300°. An odourless grade is available. Store in airtight containers.

Adverse Effects

The chief danger from ingestion of kerosene is pneumonitis and attendant pulmonary complications resulting from aspiration. Spontaneous or induced vomiting increases the risk of aspiration. Ingestion of kerosene results in a burning sensation in the mouth and throat, gastrointestinal disturbances, and possibly cough, dyspnoea, and transient cyanosis. There may be excitation followed by CNS depression, with weakness, dizziness, drowsiness, confusion, incoordination, and restlessness progressing to convulsions, coma, and respiratory depression in severe cases. Cardiac arrhythmias have been reported.

The course of poisoning from inhalation is similar to that following ingestion although CNS and cardiac effects are more likely. Kerosene is irritant.

Abuse. A case of volatile substance abuse (p.2019) involving inhalation and ingestion of kerosene has been reported.[1]

1. Das PS, *et al.* Kerosene abuse by inhalation and ingestion. *Am J Psychiatry* 1992; **149:** 710.

Treatment of Adverse Effects

Treatment of kerosene poisoning is supportive and symptomatic. Every precaution should be taken to avoid aspiration of kerosene into the lungs. The UK National Poisons Information Service considers that gastric lavage should not be used. If large amounts have been taken or there is concern about another toxin, gastric aspiration may be considered if it can be carried out within 1 hour of ingestion and the airway can be protected. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias.

Uses

Kerosene is used as a degreaser and cleaner and as an illuminating and fuel oil in kerosene ('paraffin') lamps and stoves. The odourless grade has been used as a solvent in the preparation of some insecticide sprays.

2-Methoxyethanol

Eter monometylowy glikolu etylenowego; Ethylene Glycol Monomethyl Ether; 2-Metoxietanol.

2-Метоксиэтанол

$C_3H_8O_2$ = 76.09.

CAS — 109-86-4.

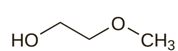

Description. 2-Methoxyethanol is a clear, colourless to slightly yellow liquid. Wt per mL about 0.96 g. B.p. about 125°. Miscible with water, with alcohol, with acetone, with dimethylformamide, with ether, and with glycerol. Store in airtight containers.

Adverse Effects and Precautions

2-Methoxyethanol is irritant to mucous membranes. Ingestion may result in CNS depression with confusion, weakness, and in severe cases coma and death from respiratory depression. Nausea, metabolic acidosis, and renal damage may also occur. Prolonged industrial exposure to the vapour has been associated with severe effects on the CNS characterised by headache, dizziness, lethargy, weakness, ataxia, tremor, disorientation, mental changes, weight loss, and visual disturbances. Anaemia has also been reported. There has been concern about the potential for reproductive toxicity.

◊ References to the toxicity of 2-methoxyethanol and other glycol ethers.

1. Health and Safety Executive. Glycol ethers. *Toxicity Review 10*. London: HMSO, 1985.
2. WHO. 2-Methoxyethanol, 2-ethoxyethanol, and their acetates. *Environmental Health Criteria 115*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc115.htm (accessed 30/06/04)
3. Browning RG, Curry SC. Clinical toxicology of ethylene glycol monoalkyl ethers. *Hum Exp Toxicol* 1994; **13:** 325–35.
4. Johanson G. Toxicity review of ethylene glycol monomethyl ether and its acetate ester. *Crit Rev Toxicol* 2000; **30:** 307–45.
5. Bagchi G, Waxman DJ. Toxicity of ethylene glycol monomethyl ether: impact on testicular gene expression. *Int J Androl* 2008; **31:** 269–74.

Handling. Suitable precautions should be taken to avoid skin contact with 2-methoxyethanol as it can penetrate skin and produce systemic toxicity.

Uses

2-Methoxyethanol is used as an industrial solvent.

Methyl Alcohol

Metanol; Metanoli; Metanolis; Méthanol; Methanol; Methanolum.

Метиловый Спирт

CH_3OH = 32.04.

CAS — 67-56-1.

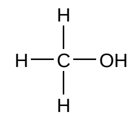

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Methanol). A colourless, clear, volatile, hygroscopic liquid. It is flammable. B.p. about 64°. Relative density 0.791 to 0.793. Miscible with water and with dichloromethane. Store in airtight containers.

The BP 2008 gives Methyl Alcohol as an approved synonym.

USNF 26 (Methyl Alcohol). A clear, colourless, flammable liquid having a characteristic odour. Miscible with water, with alcohol, with ether, with benzene, and with most other organic solvents. Store in airtight containers remote from heat, sparks, and open flames.

Adverse Effects

Immediate signs of acute poisoning after ingestion of methyl alcohol resemble those of ethanol (alcohol; ethyl alcohol) intoxication (see p.1625), but are milder. Characteristic symptoms of methyl alcohol poisoning are caused by toxic metabolites and develop after a latent period of about 12 to 24 hours, or longer if taken with ethanol. The outstanding features of poisoning are metabolic acidosis with rapid, shallow breathing, visual disturbances which often proceed to irreversible blindness, and severe abdominal pain. Other symptoms include headache, gastrointestinal disturbances, pain in the back and extremities, and coma which in severe cases may result in death due to respiratory failure or, rarely, to circulatory collapse. Mania and convulsions occasionally occur. Individual response to methyl alcohol varies widely. Ingestion of 30 mL is considered to be potentially fatal.

Absorption of methyl alcohol through the skin or inhalation of the vapour may also lead to toxic systemic effects.

◊ References to the adverse effects of methyl alcohol.

1. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings: mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; **1:** 309–34.
2. Anderson TJ, *et al.* Neurologic sequelae of methanol poisoning. *Can Med Assoc J* 1987; **136:** 1177–9.
3. Cavalli A, *et al.* Severe reversible cardiac failure associated with methanol intoxication. *Postgrad Med J* 1987; **63:** 867–8.
4. Shapiro L, *et al.* Unusual case of methanol poisoning. *Lancet* 1993; **341:** 112.
5. Medinsky MA, Dorman DC. Recent developments in methanol toxicity. *Toxicol Lett* 1995; **82–83:** 707–11.
6. McKellar MJ, *et al.* Acute ocular methanol toxicity: clinical and electrophysiological features. *Aust N Z J Ophthalmol* 1997; **25:** 225–30.
7. Williams GF, *et al.* Methanol poisoning: a review and case study of four patients from central Australia. *Aust Crit Care* 1997; **10:** 113–18.
8. Shelby M, *et al.* NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. *Reprod Toxicol* 2004; **18:** 303–90.
9. Hantson PE. Intoxication aiguë par le méthanol : physiopathologie, pronostic et traitement. *Bull Mem Acad R Med Belg* 2006; **161:** 425–34.

Handling. Suitable precautions should be taken to avoid skin contact with methyl alcohol as it can penetrate skin and produce systemic toxicity.

Treatment of Adverse Effects

Gastric aspiration may be considered if the patient presents within 1 hour of ingesting methyl alcohol. Activated charcoal is probably of little use as it does not absorb significant amounts of methyl alcohol. Metabolic acidosis (p.1667) should be corrected immediately with intravenous sodium bicarbonate. If significant amounts of methyl alcohol have been ingested, early treatment with an antidote (ethanol or fomepizole) is recommended. Ethanol delays the oxidation of methyl alcohol to its toxic metabolites formaldehyde and formic acid; dosage is adjusted to achieve and maintain a blood-ethanol concentration of 1 to 1.5 mg/mL. An **oral** dose for a 70-kg adult of about 150 mL of an ethanolic solution containing 40% v/v of C_2H_5OH has been suggested. Alcoholic spirits (such as whisky, gin, or vodka) may often be of the suitable strength. If required, an ethanolic **infusion** containing 10% v/v of C_2H_5OH may then be given as maintenance for which the following doses have been used:

- for an average adult, 1.38 mL/kg per hour
- for a non-drinker or child, 0.83 mL/kg per hour
- for a chronic drinker, 1.96 mL/kg per hour

The infusion should be continued until methyl alcohol concentrations are undetectable, or fall below 50 micrograms/mL with resolution of systemic toxicity.

Fomepizole (p.1446), an inhibitor of alcohol dehydrogenase, is also used; it inhibits the metabolism of methyl alcohol to its toxic metabolites.

Haemodialysis may be indicated to increase the removal of methyl alcohol and its toxic metabolites. Peritoneal dialysis has been used but is less efficient. Haemodialysis may be considered if the blood-methyl alcohol concentration is greater than 500 micrograms/mL, if there is severe metabolic acidosis unresponsive to sodium bicarbonate, or there is visual disturbance, CNS toxicity, renal failure, or severe electrolyte disturbance. If haemodialysis is used, a constant blood-ethanol concentration may be ensured either by increasing the ethanol infusion rate or by addition of ethanol to the dialysate fluid.

Treatment should not be stopped prematurely since oxidation and excretion of methyl alcohol may continue for several days; patients should, therefore, be closely observed and monitored. Suitable supportive treatment should be carried out as required.

Folinic acid and folic acid have been given in the treatment of methyl alcohol toxicity because they may enhance the metabolism of formic acid.

◊ References.

1. Barceloux DG, *et al.* American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40:** 415–46.

Pharmacokinetics

Methyl alcohol is readily absorbed from the gastrointestinal tract and distributed throughout the body fluids. It may also be absorbed after inhalation or through large areas of skin. Oxidation by alcohol dehydrogenase with formation of formaldehyde and formic acid takes place mainly in the liver and also in the kidneys. These metabolites are thought to be largely responsible for the characteristic symptoms of methyl alcohol poisoning. Metabolism is much slower than for ethanol, which competitively inhibits the metabolism of methyl alcohol. Oxidation and excretion may continue for several days after ingestion. Elimination of unchanged methyl alcohol via the lungs and in the urine is a minor route of excretion.

Uses

Methyl alcohol is used as a pharmaceutical and industrial solvent. It is also used as 'wood naphtha' to denature ethanol in the preparation of industrial methylated spirits. Methyl alcohol is also used as an extraction solvent in food processing.

Methyl *tert*-Butyl Ether

Éter metilterbutílico; Methyl Terbutyl Ether; Methyl Tertiary Butyl Ether; MTBE. 2-Methoxy-2-methylpropane.

Метил-трет-бутиловый Эфир

$C_5H_{12}O$ = 88.15.

CAS — 1634-04-4.

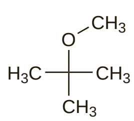

Description. Methyl *tert*-butyl ether is a volatile, flammable liquid. Wt per mL about 0.74 g. B.p. about 55°. Store in airtight containers.

Stability. Explosive peroxides may be generated by the atmospheric oxidation of methyl tert-butyl ether, but the risk is lower than with solvent ether.

Adverse Effects

Methyl *tert*-butyl ether is irritant and may cause CNS depression. Adverse effects that have been reported after use as a gallstone solvent are described under Uses and Administration, below.

Uses and Administration

Methyl *tert*-butyl ether is a solvent that has been used for the rapid dissolution of cholesterol gallstones.

Gallstones. An alternative to bile acid therapy in patients with gallstones (p.2409) who are not considered suitable for surgery is direct instillation of a solvent into the gallbladder.

Methyl *tert*-butyl ether has been used to dissolve cholesterol gallstones; stones rich in calcium or pigments are not dissolved.[1] Unfortunately incomplete dissolution and residual debris can lead to recurrence of stone formation.[2] The solvent is usually instilled via a percutaneous transhepatic catheter,[1,3] although other routes have been used.[4] Gallbladder stones were treated in 75 patients with continuous infusion and aspiration of methyl *tert*-butyl ether 4 to 6 times/minute for an average of 5 hours daily for 1 to 3 days.[1] At least 95% of the stone mass was dissolved in 72 patients. Gallbladder stones recurred in 4 patients between 6 and 16 months after the procedure; 7 of 51 patients with residual stone fragments had an episode of biliary colic during 6 to 42 months of follow-up. Nausea, sometimes with emesis, occurred in about one-third of patients. Overflow of solvent from the gallbladder can result in absorption from the gastrointestinal tract; methyl *tert*-butyl ether is detected on the breath and sedation can occur. One patient in whom overflow occurred developed ulcerative duodenitis and intravascular haemolysis. Coma and acute renal failure have also complicated treatment and have been attributed to leakage alongside the catheter rather than overflow of solvent.[5] Other workers[6,7] have obtained similar results for the dissolution of gallstones. One group[6] found that nausea and vomiting could be reduced if the treatment time was kept short and the perfusion volume was kept as low as possible; they also managed to prevent bile leakage and haemorrhage using a tissue adhesive or subcutaneous ceruletide to contract the gallbladder. Dissolution of gallbladder stones with methyl *tert*-butyl ether is likely to remain confined to specialist centres for use in patients unsuitable for surgical treatment.[1,8] A combination of litholytic modalities such as dissolution with solvents or bile acids, or lithotripsy may overcome some of the disadvantages of individual treatments.[9]

Methyl *tert*-butyl ether has been instilled via a nasobiliary catheter to dissolve stones in the common bile duct. Although effective in some cases,[10] further study has indicated disappointing overall results.[1,11]

Various combinations of drugs have been investigated to dissolve pigment-rich or mixed stones. For common bile-duct stones these include a cocktail of dimethyl sulfoxide 60%, methyl *tert*-butyl ether 20%, and sodium bicarbonate 20%, and a regimen of alternating infusions of pentyl ether and edetic acid-urea 10%.[12] A similar regimen of methyl hexyl ether and edetic acid-urea has been used successfully in 2 patients with calcified gallbladder stones.[13]

1. Bouchier IAD. Gall stones. *BMJ* 1990; **300:** 592–7.
2. Maudgal DP, Northfield TC. A practical guide to the nonsurgical treatment of gallstones. *Drugs* 1991; **41:** 185–92.
3. Thistle JL, *et al.* Dissolution of cholesterol gallbladder stones by methyl *tert*-butyl ether administered by percutaneous transhepatic catheter. *N Engl J Med* 1989; **320:** 633–9.
4. Foerster E-Ch, *et al.* Direct dissolution of gallbladder stones. *Lancet* 1989; **i:** 954.
5. Ponchon T, *et al.* Renal failure during dissolution of gallstones by methyl-*tert*-butyl ether. *Lancet* 1988; **ii:** 276–7.
6. Hellstern A, *et al.* Gall stone dissolution with methyl tert-butyl ether: how to avoid complications. *Gut* 1990; **31:** 922–5.
7. McNulty J, *et al.* Dissolution of cholesterol gall stones using methyltertbutyl ether: a safe effective treatment. *Gut* 1991; **32:** 1550–3.
8. Hetzer FH, *et al.* Kontaktlitholyse von Gallensteinen mit Methyltertbutyläther bei Risikopatienten—eine Fallbeschreibung. *Swiss Surg* 2001; **7:** 39–42.
9. Salen G, Tint GS. Nonsurgical treatment of gallstones. *N Engl J Med* 1989; **320:** 665–6.
10. Murray WR, *et al.* Choledocholithiasis—in vivo stone dissolution using methyl tertiary butyl ether (MTBE). *Gut* 1988; **29:** 143–5.
11. Neoptolemos JP, *et al.* How good is methyl tert-butyl (MTBE) for common bile duct (CBD) stone dissolution? *Gut* 1989; **30:** A736–7.
12. Anonymous. Gallstones, bile acids, and the liver. *Lancet* 1989; **ii:** 249–51.
13. Swobodnik W, *et al.* Dissolution of calcified gallbladder stones by treatment with methyl-hexyl ether and urea-EDTA. *Lancet* 1988; **ii:** 216.

Methyl Butyl Ketone

2-Hexanone; Methyl *n*-Butyl Ketone; Metilbutilcetona; Propylacetone. Hexan-2-one.

Метилбутилкетон

$C_6H_{12}O$ = 100.2.

CAS — 591-78-6.

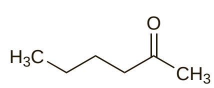

Description. Methyl butyl ketone is a colourless, volatile liquid. Wt per mL about 0.82 g. B.p. about 127°. Store in airtight containers.

Methyl Isobutyl Ketone

Hexone; Isobutilmetilcetona; Isopropylacetone; Metilisobutilcetona; MIBK. 4-Methylpentan-2-one.

Метилизобутилкетон

$C_6H_{12}O$ = 100.2.

CAS — 108-10-1.

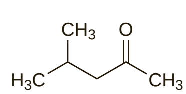

Pharmacopoeias. In *USNF.*

USNF 26 (Methyl Isobutyl Ketone). A transparent, colourless, mobile, volatile liquid having a faint ketonic and camphoraceous odour. Sp. gr. not more than 0.799. Distilling range 114° to 117°. Slightly soluble in water; miscible with alcohol, with ether, and with benzene. Store in airtight containers.

Adverse Effects and Precautions

Methyl butyl ketone and methyl isobutyl ketone may depress the CNS in high concentrations. Their vapours are irritating to mucous membranes. Methyl isobutyl ketone may be implicated in volatile substance abuse (p.2019).

◊ References.

1. WHO. Methyl isobutyl ketone. *Environmental Health Criteria 117*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc117.htm (accessed 30/06/04)
2. WHO. Methyl isobutyl ketone health and safety guide. *IPCS Health and Safety Guide 58*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg058.htm (accessed 30/06/04)

Effects on the nervous system. Peripheral neuropathy[1] has occurred after occupational exposure to methyl butyl ketone, particularly an outbreak of neuropathy in a printing plant after the replacement of methyl isobutyl ketone by methyl butyl ketone in a solvent mixture with methyl ethyl ketone. Methyl ethyl ketone may have potentiated the neurotoxicity induced by methyl butyl ketone.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl butyl ketone, see under Toluene, p.2026.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.

Handling. Suitable precautions should be taken to avoid skin contact with methyl butyl ketone or methyl isobutyl ketone as they can penetrate skin and produce systemic toxicity.

Uses

Methyl isobutyl ketone is used as an industrial and pharmaceutical solvent and also as an alcohol denaturant. Methyl butyl ketone is used as an industrial solvent.

Methyl Chloride

Cloruro de metilo; Monochloromethane. Chloromethane.

Метилхлорид

CH_3Cl = 50.49.

CAS — 74-87-3.

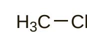

Description. Methyl chloride is a colourless gas compressed to a colourless liquid with an ethereal odour. B.p. about –24°. Store in airtight containers.

Adverse Effects and Treatment

Symptoms of methyl chloride intoxication often appear after a latent period of several hours and are similar after acute or chronic exposure to the vapour. Symptoms include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and signs of CNS depression including headache, weakness, drowsiness, confusion, visual disturbances, and incoordination progressing to convulsions, coma, and death from respiratory depression in severe cases. There have been a few reports of hepatic and renal damage.

Treatment consists of removal from exposure and supportive and symptomatic measures. Neurological effects may persist for many months.

◊ References to the toxicity of methyl chloride.

1. Repko JD, Lasley SM. Behavioral, neurological, and toxic effects of methyl chloride: a review of the literature. *CRC Crit Rev Toxicol* 1979; **6:** 283–302.

Uses

Methyl chloride is used as an industrial solvent. It has been used as an aerosol propellant and refrigerant and was formerly used as a local anaesthetic.

Methyl Ethyl Ketone

Ethyl Methyl Ketone; Etylometyloketon; MEK; Metiletilcetona; Metyloetyloketon. Butan-2-one.

Метилэтилкетон

C_4H_8O = 72.11.

CAS — 78-93-3.

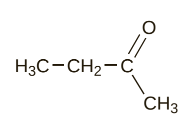

Description. Methyl ethyl ketone is a colourless flammable liquid with an acetone-like odour. Wt per mL about 0.81 g. B.p. 79° to 81°. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Adverse Effects

Methyl ethyl ketone is irritant. Inhalation may result in mild CNS effects including headache and dizziness; nausea and vomiting may also occur.

Methyl ethyl ketone may be implicated in volatile substance abuse (p.2019).

◊ References.

1. WHO. Methyl ethyl ketone. *Environmental Health Criteria 143*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc143.htm (accessed 30/06/04)

Effects on the nervous system. There are isolated reports of neurotoxicity produced by methyl ethyl ketone alone.[1] These include 1 of retrobulbar neuritis and 1 of peripheral neuropathy. It has been suggested, however, that methyl ethyl ketone potentiates the peripheral neuropathy induced by methyl butyl ketone and *n*-hexane.

For further discussion of neurotoxicity after occupational exposure to solvents including methyl ethyl ketone, see under Toluene, p.2026.

1. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.

Uses

Methyl ethyl ketone is used as an industrial solvent and as an extraction solvent in food processing.

Octyldodecanol

Octildodecanol; Octyldodécanol; Octyldodecanolum; Oktildodekanol; Oktildodekanolis; Oktyldodekanol; Oktylododekanol; Oktyylidodekanoli.

Октилдодеканол

$C_{20}H_{42}O = 298.5$.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Octyldodecanol). A condensation product of saturated liquid fatty alcohols. It contains not less than 90% of (*RS*)-2-octyldodecan-1-ol, the remainder consisting mainly of related alcohols. A clear, colourless to yellowish, oily liquid. Relative density 0.830 to 0.850. Practically insoluble in water; miscible with alcohol. Protect from light.

USNF 26 (Octyldodecanol). It contains not less than 90% of 2-octyldodecanol, the remainder consisting chiefly of related alcohols. A clear, water-white, free-flowing liquid. Insoluble in water; soluble in alcohol and in ether. Store in airtight containers.

Profile

Octyldodecanol is used as a pharmaceutical solvent.

Pentane

Amyl Hydride; Pentan; *n*-Pentane.

Пентан

$C_5H_{12} = 72.15$.

CAS — 109-66-0.

Profile

Pentane is used as a solvent and as a fuel. It is highly volatile and has also been used topically for its cooling effects.

◊ References.

1. McKee R, *et al.* Toxicology of n-pentane (CAS no. 109-66-0). *J Appl Toxicol* 1998; **18:** 431–42.

Petroleum Spirit

Benzyna; Éter de petróleo; Light Petroleum; Petroleum Benzin; Petroleum Ether; Solvent Hexane.

Бензин; Петролейный Эфир

Description. Petroleum spirit is a purified distillate of petroleum, consisting of a mixture of the lower members of the paraffin series of hydrocarbons. It is a colourless, transparent, very volatile, highly flammable liquid with a characteristic odour. It is available in a variety of boiling ranges.

Pharmacopoeias. In *Ger.*, *Jpn.*, and *Pol*. Various boiling ranges are specified.

Swiss describes Benzinum Medicinale, consisting mainly of hexane and heptane.

◊ NOTE. The motor fuel termed 'petrol' in the UK and 'gasoline' in the USA is a mixture of volatile hydrocarbons of variable composition containing paraffins (alkanes), olefins (alkenes), cycloparaffins, and aromatic compounds.

Adverse Effects and Treatment

As for Kerosene, p.2024. Petroleum spirit and petrol, being more volatile and of lower viscosity than kerosene, are more likely to be inhaled and to cause aspiration pneumonitis. The toxicity of petrol varies with its composition; some adverse effects have been attributed to lead additives or to the content of *n*-hexane or benzene. Petrol may be implicated in volatile solvent abuse (p.2019).

◊ References to the toxicity of petroleum spirit.[1-3]

For discussion of neurotoxicity after occupational exposure to solvents including petrol, see under Toluene, p.2026.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)
2. Daniels AM, Latcham RW. Petrol sniffing and schizophrenia in a Pacific island paradise. *Lancet* 1984; **i:** 389.
3. Eastwell HD. Elevated lead levels in petrol "sniffers". *Med J Aust* 1985; **143** (suppl): S63–4.

Uses

Petroleum spirit and other petroleum distillates are used as pharmaceutical solvents.

Propylene Carbonate

Carbonato de propileno. 4-Methyl-1,3-dioxolan-2-one.

Пропиленкарбонат

$C_4H_6O_3 = 102.1$.

CAS — 108-32-7.

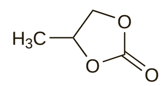

Description. Propylene carbonate is a clear colourless mobile liquid. Freely soluble in water; miscible with alcohol and with chloroform; practically insoluble in petroleum spirit.

Pharmacopoeias. In *USNF.*

USNF 26 (Propylene Carbonate). Sp. gr. 1.203 to 1.210 at 20°. Store in airtight containers.

Profile

Propylene carbonate is used as a solvent in oral and topical pharmaceuticals and for cellulose-based polymers and plasticisers. It has been used as a nonvolatile, stabilising liquid carrier in hard gelatin capsules.

Tetrachloroethane

Acetylene Tetrachloride; Tetrachloroetan; Tetracloroetano. 1,1,2,2-Tetrachloroethane.

Тетрахлорэтан

$C_2H_2Cl_4 = 167.8$.

CAS — 79-34-5.

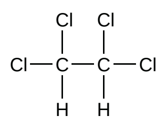

Description. Tetrachloroethane is a colourless liquid with a chloroform-like odour. B.p. about 146°. Wt per mL about 1.59 g. Store in airtight containers.

Adverse Effects and Treatment

As for Carbon Tetrachloride, p.2021. Tetrachloroethane is probably the most toxic of the chlorinated hydrocarbons. Poisoning can occur through percutaneous absorption as well as after ingestion or inhalation.

Handling. Suitable precautions should be taken to avoid skin contact with tetrachloroethane as it can penetrate skin and produce systemic toxicity.

Uses

Tetrachloroethane is used as an industrial solvent.

Tetrachloroethylene

Perchloroethylene; Tetrachloroethene; Tetrachloroethylenum; Tetracloroetileno.

Тетрахлорэтилен

$C_2Cl_4 = 165.8$.

CAS — 127-18-4.

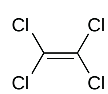

Adverse Effects and Treatment

As for Carbon Tetrachloride, p.2021. Symptoms, especially after ingestion, are less severe with tetrachloroethylene than with carbon tetrachloride.

The vapour or liquid may be irritating to skin or mucous membranes.

Tetrachloroethylene may be implicated in volatile substance abuse (p.2019). Dependence may follow habitual inhalation of small quantities of tetrachloroethylene vapour.

◊ References to adverse effects of tetrachloroethylene.

1. Bagnell PC, Ellenberger HA. Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. *Can Med Assoc J* 1977; **117:** 1047–8.
2. WHO. Tetrachloroethylene. *Environmental Health Criteria 31*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc31.htm (accessed 30/06/04)
3. WHO. Tetrachloroethylene health and safety guide. *IPCS Health and Safety Guide 10*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg010.htm (accessed 30/06/04)
4. Health and Safety Executive. Tetrachloroethylene (tetrachloroethene, perchloroethylene). *Toxicity Review 17*. London: HMSO, 1987.
5. Mutti A, *et al.* Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet* 1992; **340:** 189–93.

Pharmacokinetics

Tetrachloroethylene is slightly absorbed from the gastrointestinal tract; absorption is increased in the presence of alcohol and fats or oils. It is absorbed after inhalation and after direct contact with the skin. It is excreted unchanged in expired air; initial elimination is rapid but a proportion may be retained and excreted slowly.

Metabolites of tetrachloroethylene, mainly trichloroacetic acid, have been found in the urine.

Uses and Administration

Tetrachloroethylene is a chlorinated hydrocarbon widely used as a solvent in industry. It was formerly given orally as an anthelmintic, but has been superseded by equally effective and less toxic drugs.

Toluene

Methylbenzene; Phenylmethane; Toluen; Tolueno; Toluol; Toluole.

Толуол

$C_7H_8 = 92.14$.

CAS — 108-88-3.

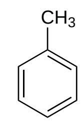

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of toluene:

Tolley; Tolly; Tooly.

Description. Toluene is a colourless, volatile, flammable liquid with a characteristic odour. Wt per mL about 0.87 g. B.p. about 111°. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Toluene has similar acute toxicity to benzene (p.2020) but is a less serious industrial hazard. Adverse effects are treated similarly to benzene. It is a common constituent of adhesives and is frequently implicated in volatile substance abuse (p.2019). Commercial toluene may contain benzene, and this may perhaps influence the pattern of adverse effects. In addition to acute toxic effects, toluene abuse has been associated with damage to the nervous system, kidneys, liver, heart, and lungs (see below). Chronic poisoning caused by occupational exposure to toluene has resulted mainly in nervous system disorders.

◊ Reviews.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. WHO. Toluene. *Environmental Health Criteria 52*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc52.htm (accessed 30/06/04)
3. Health and Safety Executive. Toluene. *Toxicity Review 20*. London: HMSO, 1989.

◊ The non-neurological toxicity after volatile substance abuse has been reviewed.[1] Chronic toluene abuse may result in damage to the *kidneys*; renal tubular acidosis and glomerulonephritis have been described, although evidence for the latter is only circumstantial. Renal tubular acidosis has been regarded as reversible; however, there are reports suggesting that damage to renal tubules is permanent.

The few reports linking chronic toluene abuse with *liver* damage cover hepatomegaly and hepatorenal failure. Effects on the *heart* are usually acute; sudden death has resulted from ventricular arrhythmias. Chronic myocarditis with fibrosis has been reported. Chronic toluene inhalation can cause damage to the *lungs.* Autopsies in a few patients have shown changes indicative of emphysema.

Nervous system toxicity has also been reviewed.[2,3] Cerebellar dysfunction has occurred after toluene abuse; an acute intoxication phase, which usually subsides within weeks of abstinence, is followed by a chronic phase which may be permanent. Diffuse CNS disease such as encephalopathy, dementia, and multifocal brain injury may also develop. An association between toluene abuse and peripheral neuropathy has not been confirmed; muscle weakness may be a result of electrolyte and fluid disturbances. Choreoathetosis, epilepsy, and optic atrophy with anosmia and deafness have been reported after toluene abuse. Some of these neurological effects, particularly cerebellar effects and diffuse

CNS disease have also occurred after occupational exposure to toluene.

Some studies have noted an excess mortality from motor neurone diseases among leather workers,[4] although this has not been confirmed by others.[5] Occupational exposure to solvents has been postulated as the cause.[4] Of the many agents currently used in leather work, those with known or probable neurotoxic effects are *n*-hexane, methyl butyl ketone, toluene, and methyl ethyl ketone. Ethyl acetate is commonly used but has no recognised neurological adverse effects.[4] A Swedish study of workers in a range of occupations has found some support for an increased risk of amyotrophic lateral sclerosis after occupational exposure to solvents, probably toluene and petrol.[6] Another Swedish study found an association between multiple sclerosis and occupational exposure to solvents, especially white spirit and petrol.[6]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Lolin Y. Chronic neurological toxicity associated with exposure to volatile substances. *Hum Toxicol* 1989; **8:** 293–300.
3. Filley CM, *et al.* The effects of toluene on the central nervous system. *J Neuropathol Exp Neurol* 2004; **63:** 1–12.
4. Hawkes CH, *et al.* Motoneuron disease: a disorder secondary to solvent exposure? *Lancet* 1989; **i:** 73–6.
5. Martyn CN. Motoneuron disease and exposure to solvents. *Lancet* 1989; **i:** 394.
6. Gunnarsson L-G, Lindberg G. Amyotrophic lateral sclerosis in Sweden 1970-83 and solvent exposure. *Lancet* 1989; **i:** 958.

Handling. Suitable precautions should be taken to avoid skin contact with toluene as it can penetrate skin and produce systemic toxicity.

Pregnancy. Retrospective surveys of pregnancies in mothers with a history of solvent abuse suggested that toluene abuse during pregnancy can cause preterm delivery and perinatal death. It was suggested that toluene may be teratogenic as intra-uterine exposure was associated with prenatal and postnatal growth retardation, microcephaly, impairment of mental development, and facial dysmorphia.[1-3] It is uncertain if these results can be extrapolated to cover occupational exposure. Although some studies of occupational exposure to solvents during pregnancy have suggested an association,[4,5] exposure is usually to a number of solvents[5] and there is little consistent evidence to link exposure to any particular one with spontaneous abortion, retarded fetal development, still-birth, or congenital malformation.[6]

1. Wilkins-Haug L, Gabow PA. Toluene abuse during pregnancy: obstetric complications and perinatal outcomes. *Obstet Gynecol* 1991; **77:** 504–9.
2. Pearson MA, *et al.* Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 1994; **93:** 211–15.
3. Arnold GL, *et al.* Toluene embryopathy: clinical delineation and developmental follow-up. *Pediatrics* 1994; **93:** 216–20.
4. McDonald JC, *et al.* Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med* 1987; **44:** 527–33.
5. Khattak S, *et al.* Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA* 1999; **281:** 1106–9.
6. Scott A. *BMJ* 1992; **304:** 369.

Pharmacokinetics

Toluene is absorbed after inhalation and ingestion, and to some extent through the skin. It is rapidly metabolised mainly by oxidation to benzoic acid which is excreted in the urine largely as the glycine conjugate hippuric acid; *o*-, *m*-, and *p*-cresol are minor urinary metabolites. Some unchanged toluene is excreted through the lungs.

Uses

Toluene is widely used as an industrial solvent.

Tri-*n*-butyl Phosphate

Fosfato de tributilo; Tributyl Phosphate; Tributyl-fosfát; Tributylis Phosphas; Tri-*n*-butylis Phosphas; Tri(*n*-butyl)phosphate; Tri-n-butilo fosfatas; Tri-n-butyle, phosphate de; Tri-n-butylfosfat; Tri-n-butylis phosphas; Tri-n-butyylifosfaatti. Phosphoric acid tributyl ester.

Три-н-бутилфосфат

$C_{12}H_{27}O_4P$ = 266.3.

CAS — 126-73-8.

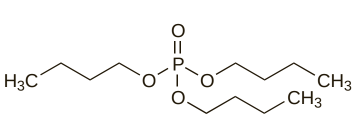

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tri-*n*-butyl Phosphate; Tributyl Phosphate BP 2008). A clear, colourless to pale yellow liquid. Slightly soluble in water; miscible with alcohol. Protect from light.

Profile

Tri-*n*-butyl phosphate is an organophosphate that is used as a solvent and plasticiser.

◊ References.

1. WHO. Tri-*n*-butyl phosphate. *Environmental Health Criteria 112*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc112.htm (accessed 29/06/04)

Trichloroethane

Methylchloroform; α-Trichloroethane; Tricloroetano. 1,1,1-Trichloroethane.

Трихлорэтан

$C_2H_3Cl_3$ = 133.4.

CAS — 71-55-6.

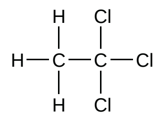

Description. Trichloroethane is a colourless, slightly hygroscopic liquid. Sp. gr. about 1.31. B.p. about 74°. Practically insoluble in water; miscible with alcohol, with chloroform, and with ether. Non-flammable. Store in airtight containers.

Adverse Effects and Treatment

Acute intoxication with trichloroethane may result in initial excitement followed by CNS depression with dizziness, drowsiness, headache, lightheadedness, and ataxia, progressing to coma and death from respiratory depression in severe cases. Death may also occur from ventricular arrhythmias. Fatalities have occurred after accidental exposure to high concentrations of trichloroethane in confined spaces. Trichloroethane is commonly used in dry cleaning, type correction fluids, and as a solvent for plaster removal and is frequently implicated in volatile substance abuse (p.2019).

Nausea, vomiting, and diarrhoea have been reported after ingestion. Trichloroethane is a mild irritant.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures. Activated charcoal is unlikely to be of benefit after ingestion and gastric lavage is contra-indicated. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

◊ Reviews.

1. Health and Safety Executive. 1,1,1-Trichloroethane. *Toxicity Review 9*. London: HMSO, 1984.
2. WHO. 1,1,1-Trichloroethane. *Environmental Health Criteria 136*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc136.htm (accessed 30/06/04)

Effects on the heart. Effects on the heart of trichloroethane abuse were considered usually to be acute, and sudden death from ventricular arrhythmias had occurred in abusers. There have, however, been a few cases of chronic cardiac toxicity after both abuse and occupational exposure.[1]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.

Effects on the liver. According to a brief review of non-neurological toxicity from volatile substance abuse,[1] there were no reports of damage to the liver after the abuse of trichloroethane. There was a report of hepatotoxicity after acute occupational exposure, but this might have been a hypersensitivity reaction. There was another report[2] of fatty liver disease in 4 patients with a history of occupational exposure to trichloroethane although there has been some debate over the validity of the association for 2 of these cases.[3,4] Chronic active hepatitis associated with trichloroethane exposure has since been reported.[5]

1. Marjot R, McLeod AA. Chronic non-neurological toxicity from volatile substance abuse. *Hum Toxicol* 1989; **8:** 301–6.
2. Hodgson MJ, *et al.* Liver disease associated with exposure to 1,1,1-trichloroethane. *Arch Intern Med* 1989; **149:** 1793–8.
3. Guzelian PS. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2321–2.
4. Hodgson MJ, Vanthiel DH. 1,1,1-Trichloroethane and the liver. *Arch Intern Med* 1991; **151:** 2322 and 2325–6.
5. Croquet V, *et al.* Hépatite chronique active probablement induite par le 1,1, 1-trichloroéthane. *Gastroenterol Clin Biol* 2003; **27:** 120–2.

Effects on the skin. Scleroderma has been reported[1] in 3 patients occupationally exposed to trichloroethylene and, in 2 cases, also to trichloroethane.

1. Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67:** 263–4.

Pharmacokinetics

Trichloroethane is absorbed after inhalation and ingestion, and through intact skin. Small amounts are metabolised to trichloroethanol and trichloroacetic acid and excreted in the urine, but it is largely excreted unchanged through the lungs over a period of days.

Uses

Trichloroethane has wide applications as an industrial solvent. It is commonly used in dry cleaning, typewriter correction fluids, and as a solvent for plaster removal.

White Spirit

Stoddard Solvent; Trementina.

Уайтспирит

CAS — 64742-82-1 (white spirit type 1); 64741-92-0 (white spirit type 2); 64742-48-9 (white spirit type 3); 64742-88-7 (white spirit type 0); 8052-41-3 (Stoddard solvent).

Description. White spirit is a mixture of hydrocarbons available as a colourless liquid. Store in airtight containers.

Adverse Effects and Treatment

As for Kerosene, p.2024.

◊ References to the toxicity of white spirit.[1]

For discussion of neurotoxicity after occupational exposure to solvents including white spirit, see under Toluene, p.2026.

1. WHO. Selected petroleum products. *Environmental Health Criteria 20*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc020.htm (accessed 30/06/04)

Uses

White spirit is used as an industrial solvent. It is available in various grades. One grade available in the USA is known as Stoddard solvent.

Xylene

Dimethylbenzene; Ksylen; Xileno; Xylol; Xylole.

Ксилол

C_8H_{10} = 106.2.

CAS — 1330-20-7; 108-38-3 (m-xylene); 95-47-6 (o-xylene); 106-42-3 (p-xylene).

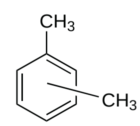

Description. Xylene is a mixture of the *o*-, *m*-, and *p*-isomers in which the *m*-isomer predominates. It is a colourless, volatile, flammable liquid. Wt per mL about 0.86 g. B.p. about 138° to 142°. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

The acute toxicity of xylene is similar to that of benzene (p.2020) but is less marked. Adverse effects are treated similarly to benzene.

Xylene has been implicated in volatile substance abuse (p.2019). Commercial xylene may contain benzene, and this may perhaps influence the pattern of adverse effects.

Xylene should not be used to dissolve ear wax if the tympanic membrane is perforated.

◊ References.

1. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
2. Health and Safety Executive. Xylenes. *Toxicity Review 26*. London: HMSO, 1992.
3. WHO. Xylenes. *Environmental Health Criteria 190*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc190.htm (accessed 30/06/04)

Effects on the eyes. Eye injuries due to accidental contact with paints containing xylene have been reported.[1] The injuries resembled alkali burns and were treated in a similar manner. Xylene-induced keratopathy has been reviewed.[2]

1. Ansari EA. Ocular injury with xylene - a report of two cases. *Hum Exp Toxicol* 1997; **16:** 273–5.
2. Trujillo F, *et al.* Xylene keratopathy: a case report and review of the literature. *Cornea* 2003; **22:** 88–90.

Effects on the nervous system. References to the adverse effects of xylene on the nervous system.

1. Arthur LJH, Curnock DA. Xylene-induced epilepsy following innocent glue sniffing. *BMJ* 1982; **284:** 1787.
2. Roberts FP, *et al.* Near-pure xylene causing reversible neuropsychiatric disturbance. *Lancet* 1988; **ii:** 273.

Handling. Suitable precautions should be taken to avoid skin contact with xylene as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Xylene is absorbed after inhalation, ingestion, and to some extent through the skin. It is rapidly metabolised by oxidation to the corresponding *o*-, *m*-, or *p*-methylbenzoic (toluic) acids and excreted in the urine largely as the glycine conjugate, methylhippuric acid (toluric acid). Xylenols are minor metabolites and are excreted in the urine as the glucuronide and sulfate conjugates. Some unchanged xylene is excreted through the lungs.

Uses

Xylene is used as an industrial and pharmaceutical solvent and in preparations to dissolve ear wax.

Paraffins and Similar Bases

This chapter includes substances used mainly as bases for the preparation of creams, ointments, other topical preparations, and suppositories. They may act as inert carriers for drugs or have emulsifying and emollient properties. Some are also used to improve the texture, stability, or water repellent properties of the final preparation. The bases discussed include petroleum hydrocarbons, animal fats and waxes, vegetable oils, and silicones. Other substances used in the preparation of bases can be found in Soaps and other Anionic Surfactants (p.2138) and in Nonionic Surfactants (p.1914).

Alkyl Benzoate

Alkyl (C12-15) Benzoate; Benzoato de alquilo.

Алкил Бензоат

CAS — 68411-27-8 (C_{12}-C_{15} alkyl ester).

Pharmacopoeias. In *USNF.*

USNF 26 (Alkyl (C12-15) Benzoate). It consists of esters of a mixture of C_{12} to C_{15} primary and branched alcohols and benzoic acid (average molecular formula $C_{20}H_{32}O_2$ = 304.5). It is a clear, practically colourless, oily liquid. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in ethyl acetate, in isopropyl alcohol, in isopropyl myristate, in isopropyl palmitate, in liquid paraffin, in vegetable oils, in volatile silicones, and in wool fat. Store in airtight containers. Protect from light.

Profile

Alkyl benzoate has emollient properties. It may be used as an oily vehicle.

White Beeswax

Baltasis vaškas; Bleached Wax; Cera alba; Cera Blanca; Cêra Branca; Cera de abejas; Cire Blanche; Cire d'abeille blanche; E901; Fehér viasz; Gebleichtes Wachs; Valkovaha; Vax, vitt; Vosk bílý; White Wax; Wosk biały.

Осветлённый Пчелиный Воск

CAS — 8012-89-3.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Beeswax, White). It is bleached yellow beeswax. It occurs as white or yellowish-white pieces or plates, translucent when thin, with an odour similar to that of yellow beeswax, though fainter and never rancid, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61° to 66°. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 26 (White Wax). It is bleached and purified yellow beeswax. A yellowish-white solid, somewhat translucent in thin layers. It has a faint characteristic odour and is free from rancidity. M.p. 62° to 65°. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30°.

Yellow Beeswax

Cêra Amarela; Cera Amarilla; Cera de abejas amarilla; Cera flava; Cire d'abeille jaune; Cire Jaune; E901; Gelbes Wachs; Geltonasis vaškas; Keltavaha; Refined Wax; Sárga viasz; Vax, gult; Vosk žlutý; Wosk żółty; Yellow Wax.

Жёлтый Пчелиный Воск

CAS — 8012-89-3.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Beeswax, Yellow). The wax obtained by melting with hot water the walls of the honeycomb of the bee, *Apis mellifera*, and removing the foreign matter. It occurs as yellow or light brown pieces or plates with a faint and characteristic odour of honey, and with a fine-grained, matt and non-crystalline fracture, becoming soft and malleable when warmed in the hand. Drop point 61° to 66°. Practically insoluble in water; partially soluble in hot alcohol; completely soluble in fatty and essential oils.

USNF 26 (Yellow Wax). The purified wax from the honeycomb of the bee, *Apis mellifera* (Apidae). It is a solid, varying in colour from yellow to greyish-brown with an agreeable honey-like odour, somewhat brittle when cold, pliable when warmed in the hand, and presenting a dull, granular, noncrystalline fracture when broken. M.p. 62° to 65°. Insoluble in water; sparingly soluble in cold alcohol; boiling alcohol dissolves the cerotic acid and a portion of the myricin that are constituents of the wax; completely soluble in chloroform, in ether, in fixed oils, and in volatile oils; partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30°.

Profile

Yellow beeswax is used as a stiffening agent in ointments and creams, and enables water to be incorporated to produce water-in-oil emulsions. It is also used as a coating in the manufacture of modified-release oral preparations. White beeswax has similar uses; it is occasionally used to adjust the melting-point of suppositories.

A sterile preparation of white beeswax, hard paraffin, and isopropyl palmitate (Sterile Surgical Bone Wax) is used to control bleeding from damaged bone during surgery. It should not be confused with Aseptic Surgical Wax (BPC 1949), also known as Horsley's Wax, which contained yellow beeswax, olive oil, and phenol in a mercuric chloride solution and was used to control haemorrhage in bone or cranial surgery.

Beeswaxes are also used in foods and cosmetics.

Hypersensitivity to beeswax has been reported.

Granuloma formation. Use of surgical bone wax has been associated with an inflammatory response in some patients. Formation of granuloma tissue at the site of application to the orbit,[1] foot,[2] and sternum[3] has been reported. Seven patients developed local pain and tenderness after use of bone wax in foot surgery; further surgery to remove granulomatous tissue 4 to 52 months later resolved pain in 5 patients.[2] In an autopsy study of 18 cadavers with evidence of sternotomy, 17 of which had macroscopic evidence of bone wax use, signs of inflammation or granuloma formation were found in all but one. The authors concluded that bone wax is non-resorbable and can cause chronic inflammation up to 10 years after application.[3]

1. Katz SE, Rootman J. Adverse effects of bone wax in surgery of the orbit. *Ophthal Plast Reconstr Surg* 1996; **12:** 121–6.
2. Anfinsen O-G, *et al.* Complications secondary to the use of standard bone wax in seven patients. *J Foot Ankle Surg* 1993; **32:** 505–8.
3. Sudmann B, *et al.* Histologically verified bone wax (beeswax) granuloma after median sternotomy in 17 of 18 autopsy cases. *Pathology* 2006; **38:** 138–41.

Hypersensitivity. Sensitivity reactions to topical beeswax products have been reported rarely. Contact dermatitis from use of a beeswax-based nipple protector has been reported,[1] and cheilitis from a beeswax lip product has also occurred.[2]

1. García M, *et al.* Allergic contact dermatitis from a beeswax nipple-protective. *Contact Dermatitis* 1995; **33:** 440–1.
2. Lucente P, *et al.* Contact cheilitis due to beeswax. *Contact Dermatitis* 1996; **35:** 258.

Preparations

BP 2008: Paraffin Ointment;
USP 31: Rose Water Ointment; White Ointment; Yellow Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Aqualane; Cold Cream Naturel†; Zoodermina Cream; ***Austria:*** Tiroler Steinol; ***Braz.:*** Balmex; ***Chile:*** Cold Cream Avene; ***Fr.:*** Cerat Inalterable; Cold Cream Naturel; ***USA:*** Paladin.

Candelilla Wax

E902.

Канделильский Воск

CAS — 8006-44-8.

Pharmacopoeias. In *USNF.*

USNF 26 (Candelilla Wax). The purified wax from the leaves of the plant *Euphorbia antisyphilitica*. It is a hard, yellowish-brown, opaque to translucent wax. M.p. between 68.5° and 72.5°. Insoluble in water; soluble in chloroform and in toluene.

Profile

Candelilla wax is used as a pharmaceutical excipient and in the food industry.

Cetostearyl Alcohol

Alcohol cetoestearílico; Alcohol cetylicus et stearylicus; Alcohol Cetylstearylicus; Alcool Cetostearilico; Alkohol cetostearylowy; Cetearyl Alcohol; Cetil-sztearil-alkohol; Cetostearilo alkoholis; Cetostearyl Alc.; Cetostearylalkohol; Cétostéarylique alcool; Cétostéarylique, alcool; Cetylstearylalkohol; Setostearyylialkoholi.

Цетостеариловый Спирт

CAS — 8005-44-5; 67762-27-0.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Cetostearyl Alcohol). A mixture of solid aliphatic alcohols, mainly stearyl alcohol and cetyl alcohol. It contains not less than 90% of stearyl plus cetyl alcohols and not less than 40% of stearyl alcohol. A white or pale yellow wax-like mass, plates, flakes, or granules. M.p. 49° to 56°. Practically insoluble in water; soluble in alcohol and in petroleum spirit. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.

Ph. Eur. 6.2 (Cetostearyl Alcohol (Type A), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans A). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium cetostearyl sulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, wax-like mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; slightly soluble in alcohol.

Ph. Eur. 6.2 (Cetostearyl Alcohol (Type B), Emulsifying; Alcohol Cetylicus et Stearylicus Emulsificans B). A mixture containing not less than 80% cetostearyl alcohol and not less than 7% sodium laurilsulfate, both calculated with reference to the anhydrous substance. A suitable buffer may be added. White or pale yellow, wax-like mass, plates, flakes, or granules. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; slightly soluble in alcohol.

USNF 26 (Cetostearyl Alcohol). It contains not less than 40% of stearyl alcohol ($C_{18}H_{38}O$ = 270.5) and the sum of the stearyl alcohol content and the cetyl alcohol ($C_{16}H_{34}O$ = 242.4) content is not less than 90%. Unctuous, white flakes or granules, having a faint, characteristic odour. M.p. 48° to 55°. Insoluble in water; soluble in alcohol and in ether.

Profile

Cetostearyl alcohol is used in creams, ointments, and other topical preparations as a stiffening agent and emulsion stabiliser. Used with suitable hydrophilic substances, as in Emulsifying Wax, it produces oil-in-water emulsions that are stable over a wide pH range. It is also used to improve the emollient properties of paraffin ointments. It is used in the formulation of modified-release oral preparations.

Cetostearyl alcohol can cause hypersensitivity.

Hypersensitivity. Sensitivity reactions to cetostearyl alcohol in topical preparations have been reported rarely.[1-3]

1. Pecegueiro M, *et al.* Contact dermatitis to Hirudoid cream. *Contact Dermatitis* 1987; **17:** 290–3.
2. Marston S. Contact dermatitis from cetostearyl alcohol in hydrocortisone butyrate lipocream, and from lanolin. *Contact Dermatitis* 1991; **24:** 372.
3. Rademaker M, *et al.* Contact dermatitis from cetostearyl alcohol. *Australas J Dermatol* 1997; **38:** 220–1.

Preparations

BP 2008: Cetomacrogol Emulsifying Wax; Cetrimide Emulsifying Ointment; Emulsifying Wax;
USNF 26: Emulsifying Wax.

Cetyl Alcohol

Alcohol cetílico; Alcohol cetylicus; Alcohol Hexadecílico; Álcool Cetílico; Alkohol cetylowy; Cetanol; Cetil-alkohol; Cetilo alkoholis; Cetylalkohol; Cétylique, alcool; Ethal; Ethol; 1-Hexadecanol; Hexadecan-1-ol; Hexadecyl Alcohol; *n*-Hexadecyl Alcohol; Palmityl Alcohol; Setyylialkoholi.

Цетиловый Спирт

$C_{16}H_{34}O$ = 242.4.

CAS — 36653-82-4; 124-29-8.

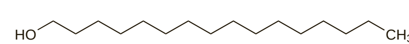

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Cetyl Alcohol). A mixture of solid alcohols, mainly cetyl alcohol, of animal or vegetable origin. It occurs as a white or almost white, unctuous mass, powder, flakes, or granules. M.p. 46° to 52°. Practically insoluble in water; freely to sparingly soluble in alcohol; miscible when melted with animal and vegetable oils, with liquid paraffin, and with melted wool fat.

USNF 26 (Cetyl Alcohol). A mixture containing not less than 90% of cetyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes, cubes, granules, or castings, with a faint characteristic odour. M.p. 45° to 50°. Insoluble in water; soluble in alcohol and in ether, the solubility increasing with increasing temperature.

Profile

Cetyl alcohol is used in topical preparations for its emollient, water absorptive, stiffening, and weak emulsifying properties. It may be incorporated into suppositories to raise the melting-point and may be used in the coating of modified-release solid dose forms. It is also used in cosmetics.

Cetyl alcohol can cause hypersensitivity.

Hypersensitivity. Hypersensitivity reactions have occasionally been attributed to the presence of cetyl alcohol in topical preparations.[1-4] One report suggested that minor impurities in the cetyl alcohol may be responsible.[1]

1. Komamura H, *et al.* A case of contact dermatitis due to impurities of cetyl alcohol. *Contact Dermatitis* 1997; **36:** 44–6.

2. Oiso N, *et al.* Concomitant allergic reaction to cetyl alcohol and crotamiton. *Contact Dermatitis* 2003; **49:** 261.
3. Soga F, *et al.* Contact dermatitis due to lanoconazole, cetyl alcohol and diethyl sebacate in lanoconazole cream. *Contact Dermatitis* 2004; **50:** 49–50.
4. Kiec-Swierczynska M, *et al.* Photoallergic and allergic reaction to 2-hydroxy-4-methoxybenzophenone (sunscreen) and allergy to cetyl alcohol in cosmetic cream. *Contact Dermatitis* 2005; **53:** 170–1.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lactopan†.

Multi-ingredient: *Arg.:* Caien; ***Hong Kong:*** Ego Skin Cream; ***Malaysia:*** Ego Skin Cream; ***NZ:*** Ego Skin Cream; ***Philipp.:*** Dermalin; Sebo Fluid; ***Singapore:*** Ego Skin Cream.

Cetyl Esters Wax

Cera Cetyla; Cera de ésteres cetílicos; Cera de ésteres del alcohol cetílico; Esperma de ballena sintético; Spermaceti Wax Replacement; Synthetic Spermaceti.

Воск Сложных Цетиловых Эфиров

CAS — 85566-24-1.

Pharmacopoeias. In *Int.* Also in *USNF.*
USNF 26 (Cetyl Esters Wax). A mixture consisting primarily of esters of saturated fatty alcohols (C_{14} to C_{18}) and saturated fatty acids (C_{14} to C_{18}). White to off-white somewhat translucent flakes with a crystalline structure and a pearly lustre when caked; it has a faint odour and is free from rancidity. M.p. 43° to 47°. Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, in chloroform, in ether, and in fixed and volatile oils; slightly soluble in cold petroleum spirit. Store in a dry place at a temperature not exceeding 40°.

Profile

Cetyl esters wax is used mainly as a stiffening agent and emollient in creams and ointments. It is also used in the coating of some oral dosage forms. It is a synthetic replacement for natural spermaceti obtained from the sperm whale and the bottle-nosed whale.

Preparations

USP 31: Rose Water Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Arg.:* Cold Cream Naturel†.

Cholesterol

Cholesterin; Cholestérol; Cholesterolis; Cholesterolum; Colesterina; Colesterol; Kolesterol; Kolesteroli; Koleszterin; Koleszterin. Cholest-5-en-3β-ol.

Холестерин; Холестерол

$C_{27}H_{46}O = 386.7.$
CAS — 57-88-5.

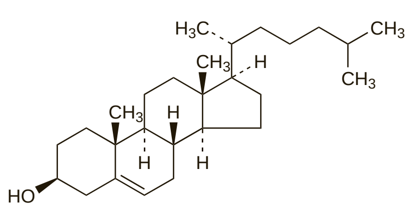

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Cholesterol). A white or almost white, crystalline powder. It is sensitive to light. M.p. 147° to 150°. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.
USNF 26 (Cholesterol). White or faintly yellow, practically odourless, pearly leaflets, needles, powder, or granules. It acquires a yellow to pale tan colour on prolonged exposure to light. M.p. 147° to 150°. Insoluble in water; slowly soluble 1 in 100 of alcohol; soluble 1 in 50 of dehydrated alcohol; soluble in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, in petroleum spirit, and in vegetable oils. Protect from light.

Profile

Cholesterol imparts water-absorbing power to pharmaceutical preparations and is used as an emulsifying agent. It has emollient activity and is used mainly in topical preparations. It is also used in ophthalmic and vaginal formulations, and in preparations for parenteral use.

Cholesteryl benzoate has been used as an ingredient in dermatological preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Senophile†.

Multi-ingredient: *Arg.:* Liposomas; ***Belg.:*** Senophile; ***Chile:*** Perfungol.

Coconut Oil

Aceite de coco; Coco (huile de) raffinée; Cocois oleum raffinatum; Coconut Butter; Copra Oil; Finomított kókuszolaj; Hindistancevizi Yağı; Kokosolja, raffinerad; Kokosový olej čištěný; Kokosų aliejus, rafinuotas; Kookosöljy, puhdistettu; Oleum Cocois; Oleum Cocos Raffinatum; Oleum Cocosis.

Кокосовое Масло

CAS — 8001-31-8.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn.*, and *USNF.*
Ph. Eur. 6.2 (Coconut Oil, Refined). The refined fatty oil obtained from the dried, solid part of the endosperm of *Cocos nucifera*. A white or almost white, unctuous mass. M.p. 23° to 26°. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65° to 70°). Store in well-filled containers. Protect from light.
USNF 26 (Coconut oil). The refined fixed oil obtained from the seeds of *Cocos nucifera*. A clear, white to light yellow-tan, viscous liquid. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in light petroleum. M.p. 23° to 26°. Store in airtight, well-filled containers. Protect from light.

Profile

Coconut oil is used as a basis for topical creams and ointments, in rectal and vaginal suppositories, and in solid dosage forms. It is also used in food manufacturing. Topical preparations have been used for pediculosis.

Fractionated coconut oil (thin vegetable oil) is used as a source of medium-chain triglycerides (p.1956).

Hypersensitivity. Sensitivity reactions to coconut products, including coconut oil,[1] have been reported rarely. Cases of anaphylaxis have been reported.[2,3]

1. Couturier P, *et al.* Un cas d'allergie à l'huile de noix de coco chez un nourrisson: responsabilité des laits materrisés. *Allerg Immunol (Paris)* 1994; **26:** 386–7.
2. Rosado A, *et al.* Anaphylaxis to coconut. *Allergy* 2002; **57:** 182–3.
3. Nguyen SA, *et al.* Cross-reactivity between coconut and hazelnut proteins in a patient with coconut anaphylaxis. *Ann Allergy Asthma Immunol* 2004; **92:** 281–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Aesculo Gel L; ***UK:*** Nitlotion.

Multi-ingredient: *Arg.:* Tersoderm Cabellos Grasos†; ***Cz.:*** Nutralipid MCT†; ***Fr.:*** Biostop; ***Indon.:*** Minyak Telon; Minyak Telon Cap Tiga Anak; Yanthi Baby Oil; ***Mex.:*** Nutegen G†; ***NZ:*** Mr Nits; ***Turk.:*** Kataljin.

Emulsifying Wax

Anionic Emulsifying Wax; Cera emulgente; Cera Emulsificans; Cera emulsionante; Cetylanum; Emulsif. Wax.

Эмульгирующий Воск

CAS — 8014-38-8.

Pharmacopoeias. In *Br.* Also in *USNF.*
BP 2008 (Emulsifying Wax). It is prepared from 9 parts of cetostearyl alcohol and 1 part of sodium laurilsulfate or sodium salts of similar sulfated higher primary aliphatic alcohols. An almost white or pale yellow, waxy solid or flakes, becoming plastic when warmed, with a faint characteristic odour. Practically insoluble in water, forming an emulsion; partly soluble in alcohol.
USNF 26 (Emulsifying Wax). It is prepared from cetostearyl alcohol containing a polyoxyethylene derivative of a fatty acid ester of sorbitan. M.p. 50° to 54°. It is a creamy-white, wax-like solid, with a mild characteristic odour. Insoluble in water; soluble in alcohol; freely soluble in chloroform, in ether, in most hydrocarbon solvents, and in aerosol propellants.

Profile

Emulsifying wax added to fatty or paraffin bases facilitates the preparation of oil-in-water emulsions which are absorbed and are nongreasy when rubbed into the skin. It is a constituent of many hydrophilic ointment bases for so-called 'washable' ointments, and is also used in rectal preparations, and in cosmetics.

Sunscreen activity. Emulsifying ointment, which contains emulsifying wax with white soft paraffin and liquid paraffin, was found to have major sunscreen activity in clinically normal skin.[1] It should not be used before phototherapy or in phototesting procedures.

1. Cox NH, Sharpe G. Emollients, salicylic acid, and ultraviolet erythema. *Lancet* 1990; **335:** 53–4.

Preparations

BP 2008: Aqueous Cream; Emulsifying Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *UK:* Epaderm; Hydromol.

Hard Fat

Adeps Neutralis; Adeps solidus; Glicéridos semisintéticos sólidos; Glycérides hémi-synthétiques solides; Glycérides Semi-synthétiques Solides; Grasa sólida; Hårdfett; Hartfett; Kietieji riebalai; Kovarasva; Massa Estearínica; Neutralfett; Szilárd zsír; Tuk ztužený; Tłuszcz obojętny.

Твёрдый Жир

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*
Ph. Eur. 6.2 (Hard Fat). A mixture of triglycerides, diglycerides, and monoglycerides obtained either by esterification of fatty acids of natural origin with glycerol or by transesterification of natural fats. A white or almost white, waxy, brittle mass. M.p. 30° to 45°; it does not differ by more than 2° from the nominal value. Practically insoluble in water; slightly soluble in dehydrated alcohol. When heated to 50°, it melts giving a colourless or slightly yellowish liquid. Protect from light and heat.
USNF 26 (Hard Fat). A mixture of glycerides of saturated fatty acids. A white mass, almost odourless and free from rancid odour, and greasy to the touch. M.p. is between 27° and 44° and does not differ by more than 2° from the nominal value. The melted substance is colourless or slightly yellowish and forms a white emulsion when shaken with an equal amount of hot water. Practically insoluble in water; slightly soluble in alcohol; freely soluble in ether. Store in airtight containers at a temperature 5° or more below the melting-point.

Profile

The name Hard Fat is applied to a range of bases with varying degrees of hardness and differing melting ranges used for the preparation of suppositories and vaginal pessaries. Hard fat is also used in some topical preparations.

Isopropyl Myristate *(USAN)*

Isopropyl myristát; Isopropyle, myristate d'; Isopropylis myristas; Isopropylmyristat; Isopropyylimyristaatti; Izopropil-mirisztát; Izopropilo miristatas; Izopropylu mirystynian; Miristato de isopropilo. Tetradecanoic acid 1-methylethyl ester; Isopropyl tetradecanoate.

Изопропилмиристат

$C_{17}H_{34}O_2 = 270.5.$
CAS — 110-27-0.

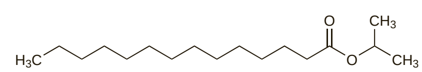

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Isopropyl Myristate). A clear, colourless, oily liquid. Relative density about 0.853. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.
USNF 26 (Isopropyl Myristate). A clear practically colourless, almost odourless, oily liquid; congeals at about 5°. Insoluble in water, in glycerol and in propylene glycol; freely soluble in alcohol. Miscible with most organic solvents and with fixed oils. Store in airtight containers. Protect from light.

Incompatibility. Isopropyl myristate is incompatible with hard paraffin.

Profile

Isopropyl myristate is resistant to oxidation and hydrolysis and does not become rancid. It is absorbed fairly readily by the skin and is used as a basis for relatively nongreasy emollient ointments and creams. It is also used as a penetration enhancer for many substances applied externally as creams, sprays, or transdermal patches.

Other isopropyl fatty acid esters, including di-isopropyl adipate, isopropyl laurate, isopropyl linoleate, and isopropyl palmitate (below) have similar properties and are used for similar purposes to those of isopropyl myristate.

Hypersensitivity. A case of sensitivity to isopropyl myristate has been reported[1] in a 64-year-old woman. She developed a rash after using a sunscreen containing isopropyl myristate for 3 days, and patch testing confirmed a sensitivity both to this substance and to isohexadecane (a mixture of C_{16} paraffins).

1. Bharati A, King CM. Allergic contact dermatitis from isohexadecane and isopropyl myristate. *Contact Dermatitis* 2004; **50:** 256–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Nucoa.

Multi-ingredient: *Hong Kong:* Hydromol†; ***Irl.:*** Emulsiderm; Hydromol†; ***Israel:*** Emulsiderm; ***UK:*** Dermol; Diprobath; Doublebase; Emulsiderm; Full Marks Solution; Hydromol.

Isopropyl Palmitate

Isopropyl palmitát; Isopropyle, palmitate d'; Isopropylis palmitas; Isopropylpalmitat; Isopropyylipalmitaatti; Izopropilo palmitatas; Izopropil-palmitát; Palmitato de isopropilo. Hexadecanoic acid 1-methylethyl ester; Isopropyl hexadecanoate.

Изопропилпальмитат

$C_{19}H_{38}O_2$ = 298.5.

CAS — 142-91-6.

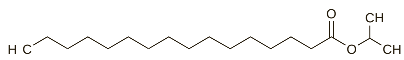

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Isopropyl Palmitate). A clear, colourless, oily liquid. Relative density about 0.854. Immiscible with water; miscible with alcohol, with dichloromethane, with fatty oils, and with liquid paraffin. Protect from light.

USNF 26 (Isopropyl Palmitate). A colourless, mobile, liquid with a very slight odour. Insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in acetone, in castor oil, in chloroform, in cottonseed oil, in ethyl acetate, and in mineral oil. Store in airtight containers. Protect from light.

Profile

Isopropyl palmitate has properties and uses similar to those of isopropyl myristate (above).

Hypersensitivity. Sensitivity reactions to isopropyl palmitate have been reported rarely.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Fotoprotector Isdin Extrem.

Laurocapram *(USAN, rINN)*

Azone; Laurocapramum; N-0252. 1-Dodecylazacycloheptan-2-one; 1-Dodecylhexahydro-2*H*-azepin-2-one.

Лаурокапрам

$C_{18}H_{35}NO$ = 281.5.

CAS — 59227-89-3.

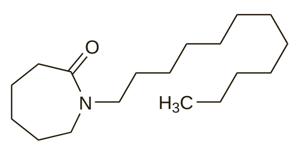

Pharmacopoeias. In *Chin.*

Profile

Laurocapram has been investigated for enhancing the penetration of drugs through the skin.

Microcrystalline Wax

Amorphous Wax; Cera microcristalina; Cerum microcrystallinum; Cire microcristalline; E905; Petroleum Ceresin; Petroleum Wax (microcrystalline).

Микрокристаллический Воск

CAS — 63231-60-7.

Pharmacopoeias. In *USNF.*

USNF 26 (Microcrystalline Wax). A mixture of straight-chain, branched-chain, and cyclic hydrocarbons, obtained by solvent fractionation of the still bottom fraction of petroleum by suitable dewaxing or de-oiling means. A white or cream-coloured odourless waxy solid. Melting range 54° to 102°. Insoluble in water; sparingly soluble in dehydrated alcohol; soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. Store in airtight containers.

Profile

Microcrystalline wax is used as a stiffening agent in creams and ointments and as a coating agent for solid dosage forms, including modified-release preparations. Microcrystalline wax is also used in foods and cosmetics.

Oleic Acid

Acide oléique; Acidum oleicum; Elaic Acid; Kwas oleinowy; Kyselina olejová; Olajsav; Oleico, ácido; Oleinic Acid; Oleino rūgštis; Oljesyra; Öljyhappo; Ölsäure. (*Z*)-9-Octadecanoic acid.

Масляная Кислота; Олеиновая Кислота

$C_{18}H_{34}O_2$ = 282.5.

CAS — 112-80-1.

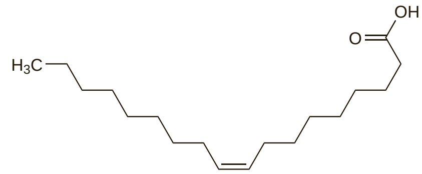

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Oleic Acid). It contains 65 to 88% of oleic acid together with varying amounts of saturated and other unsaturated fatty acids. It may contain a suitable antoxidant. It is a clear, yellowish or brownish, oily liquid. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in well-filled airtight containers. Protect from light.

USNF 26 (Oleic Acid). It is manufactured from fats and oils derived from edible sources, animal or vegetable, and consists chiefly of oleic acid. It may contain suitable stabilisers. Oleic acid solely for external use is exempt from the requirement that it be prepared from edible sources. It is a colourless to pale yellow oily liquid when freshly prepared with a characteristic lard-like odour. On exposure to air it gradually absorbs oxygen and darkens in colour. When strongly heated in air, it is decomposed with the production of acid vapours. Congealing point between 3° and 10° for oleic acid from animal sources and between 10° and 16° for oleic acid from vegetable sources. Practically insoluble in water; miscible with alcohol, with chloroform, with ether, with benzene and with fixed and volatile oils. Store in airtight containers.

Profile

Oleic acid forms soaps with alkaline substances and is used as an emulsifying or solubilising agent. It occurs in edible fats and oils which are used as foods or food components. Oleic acid is used in topical preparations, including transdermal films and patches, and in oral and inhalation preparations. It has also been used as a choleretic.

Preparations

BP 2008: Chloroxylenol Solution; White Liniment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Glavit; Primoris; ***Chile:*** Acnoxyl Jabon†.

Oleyl Alcohol

Alcohol oleico; Alcohol oleicus; *cis*-9-Octadecen-1-ol; Oleic Alcohol; Oleilo alkoholis; Oléique (alcool); Oleo Alcohol; Oleol; Oleylalkohol; Oleyylialkoholi. (*Z*)-Octadec-9-en-1-ol.

Олеиловый Спирт

$C_{18}H_{36}O$ = 268.5.

CAS — 143-28-2.

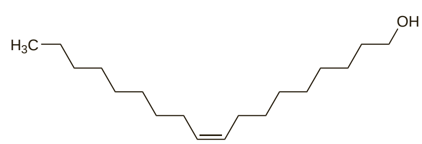

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Oleyl Alcohol). A mixture of unsaturated and saturated long-chain fatty alcohols consisting mainly of oleyl alcohol and elaidyl alcohol; (*E*-octadec-9-en-1-ol; *trans*-9-octadecenol) It may be of vegetable or animal origin. A colourless or light yellow liquid.

USNF 26 (Oleyl Alcohol). A mixture of unsaturated and saturated high molecular weight fatty alcohols consisting chiefly of oleyl alcohol. A clear, colourless to light yellow, oily liquid with a faint characteristic odour. Insoluble in water; soluble in alcohol, in ether, in isopropyl alcohol, and in light liquid paraffin. Store in well-filled airtight containers at a temperature not exceeding 25°.

Profile

Oleyl alcohol is used as an emollient, as an emulsifying and solubilising agent, and as a penetration enhancer in substances applied externally, including some delivered via transdermal patches. Oleyl alcohol has also been used in aerosol preparations for rectal use. The acetate has also been used.

Fractionated Palm Kernel Oil

Aceite de palma refinado.

Масло Пальмовое Косточковое Фракционированное; Фракционированное Пальмоядровое Масло

Pharmacopoeias. In *Br.*

BP 2008 (Fractionated Palm Kernel Oil). It is obtained by expression of the natural oil from the kernels of *Elaeis guineensis* followed by selective solvent fractionation and hydrogenation. A white, odourless or almost odourless, solid, brittle fat. M.p. 31° to 36°. Practically insoluble in water and in alcohol; miscible with chloroform, with ether, and with petroleum spirit (boiling range, 40° to 60°). Store at a temperature not exceeding 25°.

Profile

Fractionated palm kernel oil is used as a basis for suppositories. It is also used in food manufacturing. The unfractionated oil has been used as an emollient and as an ointment basis.

The oil obtained from the flesh of the fruit is known as palm oil and is also used in cooking; the composition and properties of these 2 oils are, however, different.

Hard Paraffin

Cera de parafina; Hard Wax; Hartparaffin; Kietasis parafinas; Paraff. Dur.; Paraffin; Paraffin, fast; Paraffin Wax; Paraffine solide; Paraffinum Durum; Paraffinum solidum; Parafiini, kiinteä; Parafin tvrdý; Parafina sólida; Parafina stała; Szilárd paraffin.

Твёрдый Парафин

CAS — 8002-74-2.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

USNF also includes Synthetic Paraffin.

Ph. Eur. 6.2 (Paraffin, Hard). A purified mixture of solid saturated hydrocarbons, generally obtained from petroleum. M.p. 50° to 61°. It is a colourless or white mass. The melted substance is free from fluorescence in daylight. Practically insoluble in water and in alcohol; freely soluble in dichloromethane. Protect from light.

USNF 26 (Paraffin). A purified mixture of solid saturated hydrocarbons obtained from petroleum. It may contain suitable antoxidants. It is a colourless or white, odourless, more or less translucent mass showing a crystalline structure, and is slightly greasy to the touch. It has a congealing range of 47° to 65°. Insoluble in water and in alcohol; slightly soluble in dehydrated alcohol; freely soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. An alcoholic extract is neutral to litmus. Store at a temperature not exceeding 40°. Protect from light.

USNF 26 (Synthetic Paraffin). A very hard odourless white wax containing mostly long-chain, unbranched, saturated hydrocarbons, with a small amount of branched hydrocarbons. The average molecular weight may range from 400 to 1400. Insoluble in water; very slightly soluble in aliphatic, oxygenated, and halogenated hydrocarbon solvents; slightly soluble in aromatic and normal paraffinic solvents.

Profile

Hard paraffin is used mainly as a stiffening agent in ointment bases. It is also used in creams, and as a coating for capsules and tablets.

Hard paraffin is used in physiotherapy in the form of paraffin-wax baths for the relief of pain in inflamed joints and sprains.

The injection of paraffins may produce granulomatous reactions.

Preparations

BP 2008: Paraffin Ointment; Simple Ointment; Wool Alcohols Ointment.

Proprietary Preparations (details are given in Part 3)

Fr.: Cuticerin.

Multi-ingredient: ***Fr.:*** Grassolind Neutral; ***UK:*** Melrose.

Liquid Paraffin

905 (mineral hydrocarbons); Aceite de parafina; Aceite de vaselina; Aceite mineral; Aceite mineral blanco; Dickflüssiges Paraffin; Folyékony paraffin; Heavy Liquid Petrolatum; Heavy Mineral Oil; Huile de Vaseline Épaisse; Liquid Petrolatum; Mineral Oil; Oleum Petrolei; Oleum Vaselini; Paraffin, flytande; Paraffin Oil; Paraffine liquide; Paraffinum liquidum; Paraffinum Subliquidum; Parafiini, nestemäinen; Parafin tekutý; Parafina ciekła; Parafina líquida; Skystasis parafinas; Sıvı Parafin; Vaselinöl; Vaselinum Liquidum; White Mineral Oil.

Вазелиновое Масло; Жидкий Вазелин; Медицинское Парафиновое Масло; Парафин Жидкий

CAS — 8012-95-1.

ATC — A06AA01.

ATC Vet — QA06AA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Paraffin, Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.827 to 0.890. Viscosity 110 to 230 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USP 31 (Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is a transparent, colourless, odourless or almost odourless, oily liquid, free, or practically free, from fluorescence. Insoluble in water and in alcohol; soluble in volatile oils; miscible with fixed oils (except castor oil). Store in airtight containers. Protect from light.

Light Liquid Paraffin

Dünnflüssiges Paraffin; Hígan folyó paraffin; Huile de Vaseline Fluide; Light Liquid Petrolatum; Light Mineral Oil; Light White Mineral Oil; Paraff. Liq. Lev.; Paraffin, lättflytande; Paraffine liquide légère; Paraffinum Liquidum Leve; Paraffinum Liquidum Tenue; Paraffinum perliquidum; Parafiini, kevyt nestemäinen; Parafín tekutý lehký; Skystasis lengvas parafinas; Spray Paraffin; Vaselina líquida.

ATC — A06AA01.
ATC Vet — QA06AA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF. US* also includes Topical Light Mineral Oil .

Ph. Eur. 6.2 (Paraffin, Light Liquid). A purified mixture of liquid saturated hydrocarbons obtained from petroleum. It is a transparent, colourless, oily liquid, free from fluorescence in daylight. Relative density 0.810 to 0.875. Viscosity 25 to 80 mPa s. Practically insoluble in water; slightly soluble in alcohol; miscible with hydrocarbons. Protect from light.

USNF 26 (Light Mineral Oil). A purified mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It has similar characteristics to Mineral Oil but a lower kinematic viscosity. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Excessive oral or rectal dosage with liquid paraffin may result in anal seepage and irritation, excessive purgation, and watery diarrhoea. Liquid paraffin is absorbed to a slight extent and may give rise to foreign-body granulomatous reactions. Similar reactions have followed the injection of liquid paraffin and may be considerably delayed in onset. Injection may also cause vasospasm and prompt surgical removal may be required to prevent severe damage. Lipoid pneumonia has been reported after aspiration of liquid paraffin. Because of the risk of aspiration, oral liquid paraffin should not be given to patients who have difficulty swallowing, or to those with impaired neurodevelopment.

Some licensed product information warns that chronic ingestion of liquid paraffin may rarely be associated with impaired absorption of fat-soluble vitamins and possibly other compounds. There is little published evidence to support this. Prolonged use should, however, be avoided. Liquid paraffin should not be used when abdominal pain, nausea, or vomiting is present. The UK CSM considers that it should not be used in children under 3 years of age.

Granuloma. References.

1. Di Benedetto G, *et al.* Paraffin oil injection in the body: an obsolete and destructive procedure. *Ann Plast Surg* 2002; **49:** 391–6.

Lipoid pneumonia. References.

1. Becton DL, *et al.* Lipoid pneumonia in an adolescent girl secondary to use of lip gloss. *J Pediatr* 1984; **105:** 421–3.
2. Ohwada A, *et al.* Exogenous lipoid pneumonia following ingestion of liquid paraffin. *Intern Med* 2002; **41:** 483–6.
3. Karacan O, *et al.* Fire-eater's pneumonia after aspiration of liquid paraffin. *Turk J Pediatr* 2006; **48:** 85–8.
4. Meltzer E, *et al.* Lipoid pneumonia: a preventable complication. *Isr Med Assoc J* 2006; **8:** 33–5.

Uses and Administration

Taken orally, liquid paraffin acts as a lubricant and, since it keeps the stools soft, it has been used in the symptomatic treatment of constipation (p.1693), although it should be used with caution because of its adverse effects. The recommended daily oral dose is 10 to 30 mL in divided doses, preferably before breakfast and at night. An emulsion of liquid paraffin may also be used in a dose of 10 to 30 mL at night. Liquid paraffin and its preparations should not, however, be taken immediately before going to bed. Liquid paraffin is an ingredient of several preparations that contain other laxatives such as cascara, magnesium hydroxide, or phenolphthalein. It has also been given as an enema in a usual dose of 120 mL.

Externally, liquid paraffin may be used as an ingredient of ointment bases, as an emollient and cleanser in certain skin conditions, and as an ophthalmic lubricant in the management of dry eye (p.2140).

Light liquid paraffin has similar uses to liquid paraffin.

Administration in children. UK licensed product information gives the following oral doses of liquid paraffin for constipation in children, to be taken at night:

- under 3 years: not recommended
- 3 to 5 years: 2.5 to 5 mL
- 5 to 12 years: 5 to 10 mL
- over 12 years: as for adults

For light liquid paraffin, the *BNFC* recommends a daily oral dose of 0.5 to 1 mL/kg, up to a maximum of 45 mL, for children aged 3 to 18 years. It should be taken after the evening meal but not immediately before going to bed, and may be mixed with ice-cream or yogurt to improve palatability.

The *BNFC* gives the following oral doses of liquid paraffin emulsion, to be taken once daily but not immediately before going to bed:

- under 3 years: not recommended
- 3 to 12 years: 0.5 to 1 mL/kg, up to a maximum of 30 mL
- 12 to 18 years: as for adults

Preparations

BP 2008: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Light Liquid Paraffin Eye Drops; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion; Liquid Paraffin Oral Emulsion; Simple Eye Ointment; Wool Alcohols Ointment;
USP 31: Bland Lubricating Ophthalmic Ointment; Mineral Oil Emulsion; Mineral Oil, Rectal; Topical Light Mineral Oil.

Proprietary Preparations (details are given in Part 3)
Arg.: Babix; Lansoyl; Lax Ewe Jalea; Laxante Arceli; Laxuave Enteral; Laxuave Jalea; Lexavite†; Lubritina Franklin; Modaton NI; Oilatum; ***Austral.:*** Agarol; Hamilton Skin Therapy; Oilatum Bar; Oilatum Emollient; Oilatum Shower Gel; ***Belg.:*** Lansoyl; ***Braz.:*** Nujol; ***Canad.:*** Fleet Enema Mineral Oil; Lansoyl; Nujol; ***Chile:*** Laxonarol; ***Cz.:*** Oilatum Emollient; Oilatum Gel; ***Fr.:*** Lansoyl; Laxamalt†; Lubentyl; Oilatum Emollient; Oilatum Soap†; Restrical; ***Ger.:*** Agarol N†; Obstinol M; ***Gr.:*** Agarol Plain; Nujol; Paragel; ***Hong Kong:*** Agarol; Hamilton Body Wash; Keri; Oilatum Bar; Oilatum Emollient; Oilatum Gel; Vigarol; ***Indon.:*** Oilatum Bar; Oilatum Gel; ***Irl.:*** Alcoderm†; Oilatum Gel; Oilatum Junior; Oilatum Soap; ***Ital.:*** Agarol CM†; Duratirs†; ***Malaysia:*** Balneum; Egozite Protective Baby Lotion; Laxaron†; Oilatum; ***NZ:*** Fleet Mineral Enema†; Oilatum; ***Philipp.:*** Oilatum; ***Pol.:*** Oilatum; ***S.Afr.:*** Oilatum Bar; Oilatum Emollient; ***Singapore:*** Balneum; Laxarol; Nutraderm†; Oilatum Bar; Oilatum Emollient; Oilatum Gel; ***Spain:*** Emuliquen Simple; Hodernal; ***Switz.:*** Lansoyl; Laxamalt; Paragol N; ***Thai.:*** Agarol; Oilatum Bar; Oilatum Emollient; Oilatum Gel; ***Turk.:*** Duratears; Sokol; ***UK:*** Cetraben Emollient; Dermamist; Keri; Oilatum Bath Formula; Oilatum Fragrance Free; Oilatum Gel; Oilatum Junior; Oilatum Soap; Zerobase; ***USA:*** Kondremul; Liqui-Doss.

Multi-ingredient: ***Arg.:*** Agarol; Alcon Lagrimas; Aqualane; Cold Cream Naturel†; Mil-Par; Usar Fibras†; ***Austral.:*** Alpha Keri; DermaVeen Shower & Bath; Dermeze; Duratears; E45; Egozite Baby Cream; Granugen; Hamilton Body Lotion†; Hamilton Cleansing Lotion†; Hamilton Dry Skin; Lacri-Lube; Oilatum Plus; Parachoc; Pinetarsol; Rikoderm†; Soov Prickly Heat; ***Austria:*** Balneum F; Neda Fruchtewurfel; ***Belg.:*** Duratears; Lacrytube; Tulle Vaseline†; ***Braz.:*** Agarol; Balmex; Fenogar†; Parapsyl; ***Canad.:*** Agarol Plain; Akwa Tears; Alpha Keri†; Duolube; Duratears†; Episec; Huile de Bain Therapeutique; Hypotears; Lubriderm Advanced Moisture†; Lubriderm†; Magnolax; Oilatum; Optilube; Penederm†; Puralube†; Refresh Lacri-Lube; Tears Naturale PM; Therapeutic Bath Oil†; Therapeutic Skin Lotion†; ***Chile:*** Acnaid; Acnoxyl Jabon†; Agarol; Cold Cream Avene; Durasolets; Duratears; Lacri-Lube; ***Cz.:*** Balmandol; Balneum Hermal F; Oilatum Plus; ***Denm.:*** Ojensalve Neutral; ***Fin.:*** Lacri-Lube; ***Fr.:*** Cerat Inalterable; Cold Cream Naturel; Dexeryl; Lubentyl a la Magnesie; Melaxose; Oilatum Body Oil†; Oilatum Cream†; Parapsyllium; Transulose; ***Ger.:*** Allergika†; Balneum F; Cellosorb; Coliquifilm; Excipial; Gleitgelen; Oleobal; Parfenac Basisbad†; Vita-POS; Windol Basisbad†; ***Gr.:*** Duratears; ***Hong Kong:*** Alpha Keri; Balneum; Duratears; Ego Skin Cream; Egozite Baby Cream; Hydromol†; Oilatum Cream; Oilatum Plus; Polytar Emollient; Soov Prickly Heat; ***India:*** Agarol†; Cetraben; Cremaffin; Easylax; ***Indon.:*** Laxadine; Oilatum Plus; Yanthi Baby Oil; ***Irl.:*** Emulsiderm; Hydromol†; Lacri-Lube; Oilatum Emollient; Oilatum Junior; Oilatum Junior Flare-Up; Oilatum Plus; Polytar Emollient†; ***Israel:*** Balneum F; CleanEars; Duratears; Emulsiderm; Lacrimol; ***Ital.:*** Balneum Hermal Forte; Duolaxan†; Lacrilube; ***Malaysia:*** Balneum; Duratears Naturale; Ego Skin Cream; Egozite Baby Cream; Lacrilube†; Oilatum; Oilatum Plus Antibacterial; QV Flare Up; Soov Prickly Heat†; ***Mex.:*** Acuafil†; Milpar; ***Neth.:*** Duratears Z; Transulose; ***Norw.:*** Simplex; ***NZ:*** Alpha Keri; BK; DP; DP Lotion - HC; Ego Skin Cream; Egozite Baby; Hydroderm; Karicare Breast and Body Cream†; Lacrilube; Oilatum Plus; Poly-Visc; Polytar Emollient; ***Philipp.:*** Oilatum; Oilatum Plus; ***Pol.:*** Amfobase; Balneum Hermal F; Diprobase; E45; Mentho-Paraffinol; Oilatum Plus; Unibasis; ***Port.:*** Banholeum Gele; Betacade†; Melaxose; Oleoban Gel†; ***S.Afr.:*** Oilatum Plus; ***Singapore:*** Balneum; DermaVeen Shower & Bath; Duratears; Ego Skin Cream; Egozite Baby Cream; Egozite Protective Baby Lotion†; Lacrilube; Oilatum Plus; QV Flare Up; Soov Prickly Heat†; ***Spain:*** Aceite Acalorico; Emuliquen Laxante; Lubrifilm; Vaselatum; ***Switz.:*** Antidry; Balmandol; Balmed Hermal F; Balneum Hermal F†; Coliquifilm; Paragar; Woloderma†; ***Thai.:*** Balneum†; Duratears; Emulax; Oilatum Cream; Oilatum Plus; ***Turk.:*** Balmandol; ***UK:*** 50:50; Alpha Keri; Ashbourne Emollient Medicinal Bath Oil†; Cetraben Emollient; Dermalo; Dermol; Diprobase; Diprobath; Doublebase; Emollin; Emulsiderm; Epaderm; Hydromol; Imuderm; Infaderm; Lacri-Lube; Lubri-Tears; Mil-Par; Oilatum Cream; Oilatum Emollient; Oilatum Junior; Oilatum Junior Flare-Up†; Oilatum Plus; Polytar Emollient; ***USA:*** Agoral; Akwa Tears; Alpha Keri; Bodi Care Lotion; Bodi Oil; Desitin Creamy; Dry Eyes; Duratears Naturale; Geri-Silk; Haley's M-O; Hemorid For Women; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; Lacticare; LubriFresh PM; LubriTears; Paladin; Puralube; Refresh PM; Soothe XP; Stye; Tears Again; Tears Renewed; Throat Discs; Vagisil; ***Venez.:*** Agarol†; Lacrimart†; Mil-Par; Milcor†; Oleoderm.

White Soft Paraffin

905 (mineral hydrocarbons); Minkštasis baltas parafinas; Paraff. Moll. Alb.; Paraffinum Molle Album; Parafina blanda blanca; Valkovaseliini; Vaselin, vitt; Vaselina blanca; Vaselina Branca; Vaselina filante; Vaseline blanche; Vaseline Officinale; Vaselinum album; Vazelína bílá; Wazelina biała; White Petrolatum; White Petroleum Jelly.

Белый Вазелин

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Many pharmacopoeias use the title Vaselinum Album; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 6.2 (Paraffin, White Soft). Purified and wholly or nearly decolorised mixture of semi-solid hydrocarbons, obtained from petroleum. It may contain a suitable antioxidant. It is not suitable for oral use. A white or almost white, translucent, soft unctuous mass, slightly fluorescent in daylight when melted. Drop point 35° to 70°. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

The BP 2008 gives White Petroleum Jelly as an approved synonym.

USP 31 (White Petrolatum). A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorised. It may contain a suitable stabiliser. A white or faintly yellowish unctuous mass, transparent in thin layers even after cooling to 0°. Insoluble in water; slightly soluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in chloroform, in benzene, and in carbon disulfide; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Yellow Soft Paraffin

Keltavaseliini; Minkštasis geltonas parafinas; Paraff. Moll. Flav.; Paraffinum Molle Flavum; Petrolatum; Petroleum Jelly; Sárga vazelin; Vaselin, gult; Vaselina Amarela; Vaselina amarilla; Vaselina filante amarilla; Vaseline jaune; Vaselinum flavum; Vazelína žlutá; Wazelina żółta; Yellow Petrolatum; Yellow Petroleum Jelly.

Жёлтый Вазелин

CAS — 8009-03-8.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Many pharmacopoeias use the title Vaselinum Flavum; in some countries the name 'Vaseline' is a trade-mark.

Ph. Eur. 6.2 (Paraffin, Yellow Soft). A purified mixture of semi-solid hydrocarbons obtained from petroleum. A yellow, translucent, unctuous mass, slightly fluorescent in daylight when melted. It has a drop point of 40° to 60°. Practically insoluble in water, in alcohol, and in glycerol; slightly soluble in dichloromethane. Protect from light.

USP 31 (Petrolatum). A purified mixture of semi-solid hydrocarbons obtained from petroleum. It may contain a suitable stabiliser. It is an unctuous yellowish to light amber mass, having not more than a slight fluorescence even after being melted. It is transparent in thin layers. It is free or practically free from odour. M.p. 38° to 60°. Insoluble in water; practically insoluble in cold or hot alcohol and in cold dehydrated alcohol; freely soluble in benzene, in carbon disulfide, in chloroform, and in turpentine oil; soluble in ether, in petroleum spirit, and in most fixed and volatile oils.

Adverse Effects

Adverse effects of soft paraffin are rare when used in topical preparations, but sensitivity reactions and acne have been reported after topical use. Granulomatous reactions after absorption or injection and lipoid pneumonia after aspiration have occurred.

Fire risk. Burns to the scalp, face, and hands have been reported[1] in 5 patients who accidentally ignited their hair after the application of paraffin-based hair grease. Four patients suffered inhalation injury, 2 of whom required intubation. The death of a patient who, while smoking, ignited bandages covering a paraffin-based ointment for psoriasis,[2] prompted the *BNF* to recommend that patients should be told not to smoke and to keep away from flames when using paraffin-based emollients.

1. Bascom R, *et al.* Inhalation injury related to use of petrolatum-based hair grease. *J Burn Care Rehabil* 1984; **5:** 327–30.
2. National Patient Safety Agency. Skin treatment fire risk. *Patient Safety Bulletin* 2007 (Jan.); 4. Available at: http://www.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=6341 (accessed 29/08/08)

Hypersensitivity. The allergenicity of soft paraffin products has been investigated.[1-4] Considering their widespread use there are very few reports of sensitivity;[4] of nearly 80 000 patients patch tested with white soft paraffin, only 29 showed a positive reaction. White soft paraffin is generally less sensitising than yellow soft paraffin, although allergenicity differs from product to product. The allergenic components are probably polycyclic aromatic hydrocarbons present as impurities and quantities found in a particular paraffin depend on the source and purification method. Only the purest forms should be used in pharmaceuticals, cosmetics, and for patch testing, and highly purified white soft paraffin is preferred to yellow soft paraffin.

1. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (I). Sensitising capacity of different brands of yellow and white petrolatums. *Contact Dermatitis* 1983; **9:** 175–85.
2. Dooms-Goossens A, Degreef H. Contact allergy to petrolatums (II). Attempts to identify the nature of the allergens. *Contact Dermatitis* 1983; **9:** 247–56.
3. Dooms-Goossens A, Dooms M. Contact allergy to petrolatums (III). Allergenicity prediction and pharmacopoeial requirements. *Contact Dermatitis* 1983; **9:** 352–9.
4. Schnuch A, *et al.* White petrolatum (Ph. Eur.) is virtually non-sensitizing: analysis of IVDK data on 80 000 patients tested between 1992 and 2004 and short discussion of identification and designation of allergens. *Contact Dermatitis* 2006; **54:** 338–43.

Lipoid pneumonia. Various uses of soft paraffin have been associated with lipoid pneumonia, including topical facial use to treat psoriasis,[1] long-term intranasal application for a dry nose,[2] and use as a lubricant during nasogastric intubation.[3]

1. Cohen MA, *et al.* Exogenous lipoid pneumonia caused by facial application of petrolatum. *J Am Acad Dermatol* 2003; **49:** 1128–30.
2. Brown AC, *et al.* Exogenous lipoid pneumonia due to nasal application of petroleum jelly. *Chest* 1994; **105:** 968–9.
3. Bernabeu Mora R, *et al.* Neumonía lipoidea aguda debiba a la aspiración accidental de vaselina utilizada en un sondaje nasogástrico. *Arch Bronconeumol* 2000; **36:** 485–7.

Uses and Administration

Soft paraffin is used as an ointment basis and as an emollient in the management of skin disorders. It is not readily absorbed by the skin. Sterile dressings containing soft paraffin are used for wound dressing and as a packing material. Soft paraffin is also included in ointments used as ophthalmic lubricants in the management of dry eye (p.2140). Application of soft paraffin has been used for the eradication of pubic lice from the eyelashes (see Pediculosis, p.2034). It has been used as a contact medium to reduce pain during extracorporeal shock wave lithotripsy. Soft paraffin is also used in food manufacturing.

Preparations

BP 2008: Cetomacrogol Emulsifying Ointment; Cetrimide Emulsifying Ointment; Emulsifying Ointment; Paraffin Ointment; Simple Eye Ointment; Simple Ointment; Wool Alcohols Ointment;
USP 31: Bland Lubricating Ophthalmic Ointment; Hydrophilic Ointment; Hydrophilic Petrolatum; Petrolatum Gauze; White Ointment; Yellow Ointment.

Proprietary Preparations (details are given in Part 3)
Austral.: Jelonet; Uni Salve†; Unitulle†; ***Braz.:*** Vaselina; ***Canad.:*** Prevex; Vaseline; ***Fr.:*** Cuticerin; Jelonet; Tulle Gras; Vaselitulle; ***Ger.:*** Oleo Tull; ***Gr.:*** Vaseline Pur; ***Irl.:*** Dermamist; ***Ital.:*** Adaptic; Jelonet; Lomatuell H; ***Mex.:*** Formula Dermica; Lubrilin; ***Philipp.:*** Apollo; ***Rus.:*** Kliotex (Клиотекс); ***S.Afr.:*** Jelonet; ***Spain:*** Lacrilube; ***Turk.:*** Duratears; ***UK:*** Dermamist; Jelonet; Paratulle†; Vaseline; ***USA:*** Ocu-Lube.

Multi-ingredient: ***Arg.:*** Alcon Lagrimas; Aqualane; Benzalcrem; ***Austral.:*** DermaVeen Moisturising; Dermeze; E45; Gold Cross Skin Basics Zinc Cream†; Lacri-Lube; Poly Visc; ***Austria:*** Tiroler Steinol; ***Belg.:*** Duratears; Lacrytube; Tulle Vaseline†; ***Canad.:*** A & D Ointment; Akwa Tears; Chapstick Medicated Lip Balm†; Duolube; Duratears†; Hydrophil; Hypotears; Moisturel; Optilube; Puralube†; Refresh Lacri-Lube; Tears Naturale PM; ***Chile:*** Chapstick Medicated; Durasolets; Duratears; Lacri-Lube; Pasta Lassar; ***Denm.:*** Ojensalve Neutral; ***Fin.:*** Lacri-Lube; ***Fr.:*** Cellosorb; Codexial Zinc; Dexeryl; Grassolind Neutral; Ictyane; Ictyane HD; Oilatum Cream†; Transulose; ***Ger.:*** Allergika†; Cellosorb; Coliquifilm; Sofra-Tull sine; Vita-POS; ***Gr.:*** Duratears; Vaseline Borique; Vaseline Oxyde Zinc; ***Hong Kong:*** Balneum; Duratears; Dyprotex†; Oilatum Cream; ***India:*** Cetraben; ***Irl.:*** Lacri-Lube; Oilatum Junior; ***Israel:*** Duratears; Kamil Blue; Lacrimol; ***Ital.:*** Lacrilube; ***Malaysia:*** Balneum; Duratears Naturale; Lacrilube†; Oilatum; ***Neth.:*** Duratears Z; Transulose; ***Norw.:*** Simplex; ***NZ:*** Lacrilube; Poly-Visc; ***Philipp.:*** Oilatum; ***Pol.:*** Amfobase; Diprobase; E45; Unibasis; ***Singapore:*** Balneum; Duratears; Lacrilube; ***Spain:*** Lubrifilm; Tears Lubricante†; Vaselina Boricada; Vaselina Mentolada†; ***Switz.:*** Coliquifilm; ***Thai.:*** Balneum†; Duratears; Oilatum Cream; ***Turk.:*** Cinkos; ***UK:*** 50:50; Cetraben Emollient; Diprobase; Emollin; Epaderm; Hewletts; Hydromol; Imuderm; Lacri-Lube; Lubri-Tears; Melrose; Oilatum Cream; Oilatum Junior; ***USA:*** Akwa Tears; Bodi Care Lotion; Bottom Better; Chapstick Medicated Lip Balm; Desitin Creamy; Diaper Guard; Dry Eyes; Duratears Naturale; Formulation R; Hemorid For Women; Hydrocerin; Hypotears; Lacri-Gel; Lacri-Lube; Lubri-Fresh PM; LubriTears; Paladin; Puralube; Refresh PM; Stye; Tears Again; Tears Renewed; ***Venez.:*** Lacrimart†.

Shea Butter

Manteca de Karité.

Карите; Масло Ши

Profile

Shea butter is a natural fat obtained from the kernel of the fruit of *Vitellaria paradoxa* (*Butyrospermum parkii*) (Sapotaceae) indigenous to West Africa. It is used as an ointment and cream basis. Shea butter is widely used in cosmetics. It is also used in cooking oil, and as a substitute for theobroma oil in chocolate manufacturing.

Preparations

Silicones

Siliconas.

Силиконы

ATC — A03AX13.
ATC Vet — QA03AX13.

Description. Silicones are polymers with a structure consisting of alternate atoms of silicon and oxygen, with organic groups attached to the silicon atoms. As the degree of polymerisation increases, the products become more viscous and the various grades are distinguished by a number, approximately corresponding to the viscosity of the particular grade. Silicones may be fluids, greases, waxes, resins, or rubbers depending on the degree of polymerisation.

Cyclomethicone

Dimethylcyclopolysiloxane.

Циклометикон

$(C_2H_6OSi)_n$.
CAS — 69430-24-6.

Pharmacopoeias. In *USNF.*
USNF 26 (Cyclomethicone). A fully methylated cyclic siloxane containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, in which *n* is 4, 5, or 6, or a mixture of them. Store in airtight containers.

Dimeticone *(BAN, rINN)*

Dimethicone *(USAN)*; Dimethyl Silicone Fluid; Dimethylpolysiloxane; Dimethylsiloxane; Dimeticona; Diméticone; Dimeticonum; Dimetikon; Dimetikonas; Dimetikoni; Dimetilpolisiloxano; Dimetykon; E900; Huile de Silicone; Methyl Polysiloxane; Metilpolisiloksan; Metilpolisiloxano; Permethylpolysiloxane; Polidimetilsiloxano; Silicone Oil; Siliconum Liquidum. Poly(dimethylsiloxane).

Диметикон

$CH_3.[Si(CH_3)_2.O]_nSi(CH_3)_3$.
CAS — 9006-65-9.
ATC — A03AX13.
ATC Vet — QA03AX13.

Description. Dimeticones are fluid silicones in which the organic group is a methyl radical.
Simeticone (activated dimeticone), a mixture of liquid dimeticones with silicon dioxide, is described on p.1770.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Dimeticone). The degree of polymerisation is such that the kinematic viscosities are nominally between 20 and 1300 mm^2/second; dimeticones with a nominal viscosity of 50 mm^2/second or lower are intended for external use only. Dimeticones are clear, colourless, liquids of various viscosities. Practically insoluble in water; very slightly soluble to practically insoluble in dehydrated alcohol; miscible with ethyl acetate, with methyl ethyl ketone, and with toluene.
USNF 26 (Dimethicone). A mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilised with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, wherein *n* has an average value such that the corresponding nominal viscosity is in a discrete range between 20 and 30 000 centistokes. It is a clear colourless, odourless liquid. Insoluble in water, in alcohol, in acetone, and in methyl alcohol; very slightly soluble in isopropyl alcohol; soluble in amyl acetate, in chlorinated hydrocarbons, in ether, in *n*-hexane, in petroleum spirit, in benzene, in toluene, and in xylene. Store in airtight containers.

Adverse Effects and Precautions

Adverse effects from the clinical use of silicones appear to be rare. Foreign-body reactions have been reported after their use as joint implants. Other implants, notably breast implants used for reconstruction after mastectomy or for cosmetic purposes, carry the risk of migration of silicone with cyst formation and other complications; accidental intravascular injection has been fatal. Late adverse ocular effects can follow the intravitreal injection of liquid silicone in the management of retinal detachment (see below).

Breast feeding. Concern has been raised regarding the possible effects on infants of mothers with silicone breast implants who breast feed. Oesophageal dysfunction has been reported in a number of such children,[1] although this finding has not been confirmed by subsequent reports. The American Academy of Pediatrics therefore states[2] that the current evidence does not justify classifying silicone implants as a contra-indication to breast feeding.

1. Levine JJ, Ilowite NT. Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants. *JAMA* 1994; **271:** 213–6. Correction. *ibid.*; **272:** 770.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 20/11/07)

Connective tissue disorders. Since the introduction of silicone breast implants in the early 1960s there have been numerous anecdotal reports of connective tissue disorders in women who have undergone breast reconstruction or augmentation with these implants. Scleroderma has been the most frequently reported disorder; others have included SLE, rheumatoid arthritis, and inflammatory myopathies. A syndrome of vague musculoskeletal symptoms, fever, and fatigue has also been reported. These cases led the FDA to call for a moratorium in the USA on the use of silicone breast implants in January 1992. However, with the exception of one study of self-reported symptoms which showed only a small increase in risk,[1] large epidemiological studies,[2-5] meta-analyses,[6-8] and a review by the Medical Devices Agency in the UK have so far failed to show any association between silicone breast implants and connective tissue disorders. After conducting a review of the evidence, the FDA in 2006 re-approved the sale of silicone breast implants, for use in women of all ages for breast reconstruction, and for cosmetic use in women aged 22 years or more;[9] the approval obliges the manufacturers to conduct a 10-year post-approval safety study.

1. Hennekens CH, *et al.* Self-reported breast implants and connective-tissue diseases in female health professionals: a retrospective cohort study. *JAMA* 1996; **275:** 616–21.
2. Gabriel SE, *et al.* Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994; **330:** 1697–1702.
3. Sánchez-Guerrero J, *et al.* Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med* 1995; **332:** 1666–70.
4. Silverman BG, *et al.* Reported complications of silicone gel breast implants: an epidemiologic review. *Ann Intern Med* 1996; **124:** 744–56.
5. Nyrén O, *et al.* Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 1998; **316:** 417–22.
6. Janowsky EC, *et al.* Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *N Engl J Med* 2000; **342:** 781–90.
7. Lipworth L, *et al.* Silicone breast implants and connective tissue disease: an updated review of the epidemiologic evidence. *Ann Plast Surg* 2004; **52:** 598–601.
8. Lipworth L, *et al.* Breast implants and fibromyalgia: a review of the epidemiologic evidence. *Ann Plast Surg* 2004; **52:** 284–7.
9. Food and Drug Administration. FDA approves silicone gel-filled breast implants after in-depth evaluation (issued 17/11/06). Available at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01512.html (accessed 20/11/07)

Uses and Administration

Dimeticones and other silicones are water-repellent and have a low surface tension. They are used in topical barrier preparations for protecting the skin against water-soluble irritants. Creams, lotions, and ointments containing a dimeticone are used for the prevention of bedsores and napkin rash and to protect the skin against trauma due to incontinence or stoma discharge. A 4% solution of dimeticone is used for the treatment of head pediculosis in adults and children aged over 6 months. Silicone preparations should not be applied where free drainage is necessary or to inflamed or abraded skin. Silicones, usually a dimeticone, are also used topically as wound dressings, and to reduce scar elevation and pigmentation. They are also used in oral solid dosage forms, including modified-release preparations.

Silicones have also been used for arthroplasty in rheumatic disorders, by intravitreal injection for retinal detachment, and by subcutaneous injection or implantation in reconstructive or cosmetic surgery.

Dimeticones, in particular simeticone (activated dimeticone) (p.1770), are used in the treatment of flatulence.

Retinal detachment. Retinal detachment is separation of the retina from the underlying retinal pigmentary epithelium and usually requires surgical repair. Intravitreal injection of liquid silicone, either alone or with a gas,[1] is used for retinal tamponade with or after surgery in complicated or persistent detachment of the retina.[2] In most cases, the silicone fluid is later removed from the eye.[3] High-density silicone fluids are increasingly being used.[4] Use of silicone fluid is reported to trigger a local inflammatory response, which may persist after the fluid is removed.[5] Other late complications after its use may include cataract, glaucoma, and keratopathy.

1. Rizzo S, *et al.* Long-term vitreous replacement with perfluorohexyloctane and silicone oil: preliminary reports of a multicentric study. *Ophthalmologica* 2005; **219:** 147–53.
2. Quiram PA, *et al.* Outcomes of vitrectomy with inferior retinectomy in patients with recurrent rhegmatogenous retinal detachments and proliferative vitreoretinopathy. *Ophthalmology* 2006; **113:** 2041–7.
3. Szurman P, *et al.* Primary silicone oil tamponade in the management of severe intraocular foreign body injuries: an 8-year follow-up. *Retina* 2007; **27:** 304–11.
4. Herbrig E, *et al.* Anatomical and functional results of endotamponade with heavy silicone oil – Densiron 68 – in complicated retinal detachment. *Ophthalmic Res* 2007; **39:** 198–206.
5. Wickham LJ, *et al.* Immunopathology of intraocular silicone oil: retina and epiretinal membranes. *Br J Ophthalmol* 2007; **91:** 258–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aerogal; Atoderm†; Europiel; Finescar; Kurapel; Skinderm SIL; ***Austral.:*** Dermatix; Egozite Protective Baby Lotion; Instru-Safe†; Rosken Skin Repair; Silic 15; ***Canad.:*** Barrier Cream†; Barriere; Dermatix Si; ***Chile:*** Cadinol†; Epi-Derm; Lomprax; Neogasol; Para; ***Fr.:*** Cica-Care; Dermatix; Ophtasiloxane; ***Ger.:*** Dermatix; Jaikin N†; Mepiform; Mepilex; Mepitel; Symadal M; ***Hong Kong:*** Egozite Protective Baby Lotion; Silic 15; Skin Repair; ***Hung.:*** Fomarex†; ***Irl.:*** Dermatix; ***Israel:*** Adato-Sil Ol†; ***Ital.:*** Cica-Care; Mepiform; Mepitel; ***Malaysia:*** Dermatix; Egozite Protective Baby Lotion; Silic 15; ***Neth.:*** SIL-1000, -5000; ***NZ:*** Aquim†; DP Barrier Cream; Egozite Protective Baby Lotion; Silicare†; ***Philipp.:*** Cica-Care; Dermatix; ***Pol.:*** Silol; ***Singapore:*** Baritex; Dermatix; Silic 15; Skin Repair; ***UK:*** Cica-Care; Dermatix; Hedrin; Mepiform; Silgel; ***USA:*** Mentholatum Softlips; Pro-Q.

Multi-ingredient: ***Arg.:*** Sumo Full Contact; ***Austral.:*** Dermalife Plus; Dimethicream; Eczema Cream; Egozite Baby Cream; Hamilton Pine Tar with Menthol; Hamilton Skin Repair†; Nappy-Mate†; Silcon†; ***Austria:*** Ceolat Compositum; Evalgan; ***Braz.:*** Balmex; ***Canad.:*** Blistex Lip Balm; Blistex Ultra Protection Lip Balm; Complex 15†; Moisturel; Zilactin-Lip; ***Chile:*** Aero Itan; Balsamo Analgesico con Fenilbutazona; Blisprotex; Neopankreoflat; Ureadin 30; Xeragel; ***Denm.:*** Silan; ***Fr.:*** Supro; ***Hong Kong:*** DS Emulsion; Dyprotex†; Egozite Baby Cream; Hamilton Skin Repair; ***India:*** Siloderm; Tinidafyl Plus; ***Irl.:*** Conotrane†; Siopel†; Sprilon; Vasogen; ***Israel:*** Kamil Blue; Kelo-Cote; ***Ital.:*** Angstrom Viso; Rikospray; ***Malaysia:*** Egozite Baby Cream; Palmer's Cocoa Butter Formula Scar Serum; ***Mex.:*** Hidribet†; ***NZ:*** Egoderm; Egozite Baby; Karicare Barrier Cream†; Rosken Skin Repair; Silic; ***S.Afr.:*** Arola Rosebalm; Siopel; ***Singapore:*** Egozite Baby Cream; Egozite Protective Baby Lotion†; Scarfade†; ***Spain:*** Dermo Halibut; Proskin; Silidermil; ***Swed.:*** Silon; ***UK:*** Conotrane; Cymex; Full Marks Solution; Siopel; Sprilon; Vasogen; ***USA:*** Blistex Lip Balm; ControlRx; Diaper Guard; Dyprotex; Gold Bond Medicated Triple Action Relief; Herpecin-L; Maxilube; Mentholatum Cherry Ice; Mentholatum Natural Ice; Mentholatum Softlips Lipbalm; Mentholatum Softlips Lipbalm (UV); Soothe & Cool; ***Venez.:*** Hidribet.

Squalane

Cosbiol; Dodecahydrosqualene; Escualano; Perhidroescualeno; Perhydrosqualène; Skvalaani; Skvalan; Skvalanas; Skwalan; Spinacane; Squalanum; Szkvalán. 2,6,10,15,19,23-Hexamethyltetracosane.

Сквалан

$C_{30}H_{62}$ = 422.8.
CAS — 111-01-3.

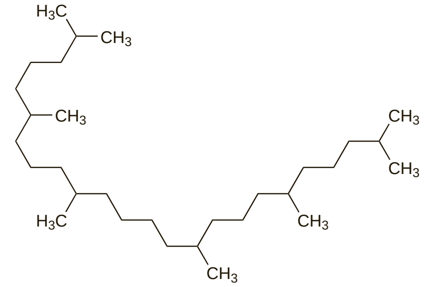

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Squalane). A clear, colourless, oily liquid. Relative density about 0.815. It may be of vegetable (unsaponifiable matter of olive oil) or animal (shark liver oil) origin. Practically insoluble in water and in alcohol; freely soluble in acetone and in cyclohexane; miscible with most fats and oils.
USNF 26 (Squalane). A saturated hydrocarbon obtained by hydrogenation of squalene, an aliphatic triterpene occurring in some fish oils. It is a colourless, almost odourless, transparent oil. Insoluble in water; very slightly soluble in dehydrated alcohol; miscible with chloroform and with ether; slightly soluble in acetone. Store in airtight containers.

Profile

Squalane is a saturated derivative of squalene, a constituent of human sebum. It is miscible with human sebum and is included in topical preparations to increase skin permeability. It is also used as an emollient.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cremisona†; ***Hong Kong:*** Apaisac; Physiogel; ***Israel:*** CleanEars; ***Port.:*** Creme Laser Hidrante; Lactonico†.

Stearyl Alcohol

Alcohol estearílico; Alcohol octadecílico; Alcohol stearylicus; Alcool Stéarylique; Alkohol stearylowy; 1-Octadecanol; Octadecan-1-ol; Octadecyl Alcohol; Stearilo alkoholis; Stearylalkohol; Stéarylique, alcool; Stearyylialkoholi; Sztearil-alkohol.

Стеариловый Спирт

$C_{18}H_{38}O = 270.5.$
CAS — 112-92-5.

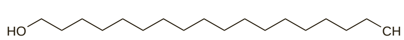

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Stearyl Alcohol). A mixture of solid alcohols; it contains not less than 95.0% of stearyl alcohol. White or almost white, unctuous flakes, granules, or mass. M.p. 57° to 60°. Practically insoluble in water; soluble in alcohol. When melted, it is miscible with fatty oils, with liquid paraffin, and with melted wool fat.
USNF 26 (Stearyl Alcohol). It contains not less than 90% of stearyl alcohol the remainder consisting chiefly of related alcohols. White unctuous flakes or granules with a faint characteristic odour. M.p. 55° to 60°. Insoluble in water; soluble in alcohol and in ether.

Profile

Stearyl alcohol is used to thicken topical and vaginal ointments and creams, and to increase their water-holding capacity; it has emollient and weak emulsifying properties. Stearyl alcohol is also used in oral solid dosage forms, including modified-release preparations.

Stearyl alcohol can cause hypersensitivity.

Hypersensitivity. Stearyl alcohol is usually considered to have a low potential for sensitisation although there have been isolated case reports of contact dermatitis to topical products containing it.[1-3]

1. Black H. Contact dermatitis from stearyl alcohol in Metosyn (fluocinonide) cream. *Contact Dermatitis* 1975; **1:** 125.
2. de Berker D, *et al.* Contact sensitivity to the stearyl alcohol in Efudix cream (5-fluorouracil). *Contact Dermatitis* 1992; **26:** 138.
3. Yesudian PD, King CM. Allergic contact dermatitis from stearyl alcohol in Efudix cream. *Contact Dermatitis* 2001; **45:** 313–14.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: SFC Lotion.

Multi-ingredient: ***Arg.:*** Caien.

Theobroma Oil

Beurre de Cacao; Burro di Cacao; Butyrum Cacao; Cacao Butter; Cacao Oleum; Cocoa Butter; Kakaobutter; Kakaový olej; Manteca de cacao; Manteiga de Cacau; Ol. Theobrom.; Olej kakaowy; Oleum Cacao; Oleum Theobromatis.

Какао-Масло; Масло Какао

CAS — 8002-31-1.

Pharmacopoeias. In *Br., Fr., Ger., Jpn,* and *Pol.* Also in *USNF.*
BP 2008 (Theobroma Oil). The solid fat obtained from the roasted seeds of *Theobroma cacao.* A yellowish-white, somewhat brittle, solid fat, with a slight odour of cocoa. M.p. 31° to 34°. Slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit (boiling range, 40° to 60°). Store at a temperature not exceeding 25°.
USNF 26 (Cocoa Butter). A fat obtained from the seeds of *Theobroma cacao* (Sterculiaceae). It is a yellowish-white, usually brittle solid with a faint agreeable odour. M.p. 31° to 35°. Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in chloroform and in ether.

Profile

Theobroma oil is used as a basis for suppositories. If it is heated to more than 36° during preparation the solidification point will be appreciably lowered due to the formation of metastable states; this leads to subsequent difficulty in setting. Theobroma oil is a major ingredient of chocolate.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Lapiz Gras†.

Multi-ingredient: ***Malaysia:*** Palmer's Cocoa Butter Formula; Palmer's Cocoa Butter Formula Scar Serum.

Wool Alcohols

Alcoholes adipis lanae; Alcoholes de lana; Alcoholes de lanolina; Alcoholia Lanae; Alcolanum; Alcools de graisse de laine; Alkoholy tuku z ovčí vlny; Gyapjúviaszalkoholok; Lanalcolum; Lanolin Alcohols; Ullfettalkoholer; Villa-alkoholit; Vilnų riebalų alkoholiai; Wollwachsalkohole; Wool Wax Alcohols.

Спирты Шерстяного Жира

CAS — 8027-33-6.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Wool Alcohols). A mixture of sterols and higher aliphatic alcohols obtained from wool fat and containing not less than 30.0% of cholesterol. It may contain not more than 200 ppm of butylated hydroxytoluene. A pale yellow to brownish-yellow, brittle mass becoming plastic on heating. M.p. not lower than 58°. Practically insoluble in water; slightly soluble in alcohol (90%); soluble in boiling dehydrated alcohol, and in dichloromethane. Store in well-filled containers. Protect from light.
USNF 26 (Lanolin Alcohols). A mixture of sterols, aliphatic alcohols, and triterpenoid alcohols obtained by the hydrolysis of wool fat. It may contain not more than 0.1% of a suitable antioxidant. It is a hard, waxy amber solid with a characteristic odour. M.p. not below 56°. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform, in ether, and in petroleum spirit. Store at a temperature not exceeding 25°. Protect from light.

Incompatibility. Wool alcohols is incompatible with coal tar, ichthammol, resorcinol, and phenol.

Profile

Wool alcohols is an emulsifying agent and emulsion stabiliser used in the preparation of water-in-oil creams and ointments. It increases the water absorbing capacity of hydrocarbon mixtures; the addition of 5% of wool alcohols permits a threefold increase in the amount of water that can be incorporated in soft paraffin and such emulsions are not 'cracked' by the addition of weak acids.

It has an emollient action on the skin and is used in preparations for dry skin and dry eyes.

Derivatives of wool alcohols with similar uses include acetylated wool alcohols and ethoxylated wool alcohols.

Wool alcohols may cause hypersensitivity (but see also under Wool Fat, below).

Preparations

BP 2008: Wool Alcohols Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Macoderm; ***Canad.:*** Refresh Lacri-Lube; ***Fin.:*** Lacri-Lube; ***Ger.:*** Coliquifilm; ***Irl.:*** Oilatum Emollient; ***Israel:*** Adinol; ***Ital.:*** Lacrilube; ***NZ:*** Lacrilube; ***Switz.:*** Coliquifilm; ***UK:*** Ashbourne Emollient Medicinal Bath Oil†; Dermalo; Lacri-Lube; Oilatum Emollient; ***USA:*** Hydrocerin; Refresh PM.

Wool Fat

Adeps lanae; Adeps lanae hydrogenatus (wool fat, hydrogenated); Anhydrous Lanolin; Cera Lanae; Graisse de laine; Graisse de laine hydrogénée (wool fat, hydrogenated); Graisse de Suint Purifiée; Gyapjúviasz; Lanoléine; Lanolin; Lanolina; Lanolina anhidra; Lanolinum; Purified Lanolin; Refined Wool Fat; Suarda; Tuk z ovčí vlny; Tuk z ovčí vlny hydrogenovaný (wool fat, hydrogenated); Ullfett; Villarasva; Vilnų riebalai; Wollfett; Wollwachs.

Ланолин; Шерстяной Жир

CAS — 8006-54-0.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.* Some pharmacopoeias include Hydrous Wool Fat which is prepared by the addition of water to wool fat.
Eur. also includes Hydrogenated Wool Fat.
US also includes Modified Lanolin.
Ph. Eur. 6.2 (Wool Fat). A purified, anhydrous, waxy material obtained from the wool of the sheep (*Ovis aries*). It may contain not more than 200 ppm of butylated hydroxytoluene. A yellow, unctuous substance. When melted, it is a clear or almost clear, yellow liquid. Drop point 38° to 44°. 10 g absorbs not less than 20 mL of water. Practically insoluble in water; slightly soluble in boiling dehydrated alcohol; it forms an opalescent solution in petroleum spirit. Store at a temperature not exceeding 25°.
Ph. Eur. 6.2 (Wool Fat, Hydrogenated; Adeps Lanae Hydrogenatus). A mixture of higher aliphatic alcohols and sterols obtained from the direct, high-pressure, high-temperature hydrogenation of anhydrous wool fat during which the esters and acids present are reduced to corresponding alcohols. It may contain butylated hydroxytoluene. A white or pale yellow, unctuous substance. M.p. 45° to 55°. Practically insoluble in water; soluble in boiling alcohol and in petroleum spirit. Store in well-filled containers. Protect from light.
Ph. Eur. 6.2 (Wool Fat, Hydrous; Adeps Lanae Cum Aqua). A mixture of 75% of wool fat and 25% of water. It may contain not more than 150 ppm of butylated hydroxytoluene. A pale yellow, unctuous substance. Drop point 38° to 44°. Store at a temperature not exceeding 25°.
USP 31 (Lanolin). A purified wax-like substance obtained from the wool of the sheep, *Ovis aries* (Bovidae). It is a yellow tenacious unctuous mass with a slight characteristic odour. Melting range 38° to 44°. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Insoluble in water, but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in chloroform and in ether. Store at a temperature preferably between 15° and 30°.
USP 31 (Modified Lanolin). It is Lanolin that has been processed to reduce the contents of free lanolin alcohols and detergent and pesticide residues. It contains not more than 0.25% of water. It may contain not more than 0.02% of a suitable antoxidant. Store in airtight, preferably rust-proof, containers and preferably at a temperature of 15° to 30°.

Profile

Wool fat is used in the formulation of water-in-oil creams and ointments. When mixed with a suitable vegetable oil or with soft paraffin it gives emollient creams that penetrate the skin. It can absorb about 30% of water. Wool fat is also used in other topical, vaginal, rectal, and ophthalmic preparations.

Derivatives and modifications of wool fat include hydrogenated wool fat (hydrogenated lanolin), hydrous wool fat (hydrous lanolin), poloxyl lanolin (ethoxylated lanolin), isopropyl lanolate, lanolin oil, and lanolin wax.

Wool fat can cause sensitivity reactions.

Hypersensitivity. Wool fat is widely regarded as a common sensitising agent, but the true extent of allergy to it is controversial. Suspected sensitivity reactions have proved difficult to reproduce in skin patch testing.[1] The allergens are unknown but are thought to be in the alcoholic fraction. A retrospective study[2] of more than 24 000 patients with eczema who received skin patch testing found that sensitivity reactions to a standard patch reagent of wool alcohols 30% in soft paraffin were rare; an average of 1.7% of patients per year showed sensitivity.

1. Wolf R. The lanolin paradox. *Dermatology* 1996; **192:** 198–202.
2. Wakelin SH, *et al.* A retrospective analysis of contact allergy to lanolin. *Br J Dermatol* 2001; **145:** 28–31.

Pesticide residues. Concerns have been raised in the past about pesticide residues in wool fat,[1-3] because of the possible risk to breast-fed infants whose mothers were using wool fat-based nipple ointments. Official published standards such as Ph. Eur. and USP now include limits for pesticide levels in wool fat.

1. Copeland CA, *et al.* Pesticide residue in lanolin. *JAMA* 1989; **261:** 242.
2. Cade PH. Pesticide in lanolin. *JAMA* 1989; **262:** 613.
3. Copeland CA, Wagner SL. Pesticide in lanolin. *JAMA* 1989; **262:** 613.

Preparations

BP 2008: Simple Eye Ointment; Simple Ointment;
USP 31: Modified Lanolin.

Proprietary Preparations (details are given in Part 3)

Austral.: Lansinoh†; ***Canad.:*** Lansinoh†; PureLan; ***Ger.:*** Oleo Tull; ***Port.:*** Lansinoh; Multi-Mam Lanolina†; ***S.Afr.:*** Duratears; ***Turk.:*** Duratears.

Multi-ingredient: ***Arg.:*** Alcon Lagrimas; Crema Para Paspaduras; Dr Selby; Ninderm; Quem Plus†; ***Austral.:*** Alpha Keri; Duratears; E45; Lacri-Lube; Poly Visc; Rikoderm†; Silcon†; Soothe'n Heal; ***Austria:*** Tiroler Steinol; ***Belg.:*** Duratears; Lacrytube; ***Canad.:*** A & D Ointment; Akwa Tears; Alpha Keri†; Duratears†; Huile de Bain Therapeutique; Lubriderm†; Optilube; Tears Naturale PM; Therapeutic Bath Oil†; Therapeutic Skin Lotion†; ***Chile:*** Duratears; Lacri-Lube; Pasta Lassar; ***Fr.:*** Grassolind Neutral; ***Ger.:*** Sofra-Tull sine; Vita-POS; ***Gr.:*** Duratears; Fissan-Pate†; ***Hong Kong:*** Alpha Keri; Balneum; Duratears; ***Indon.:*** Yanthi Baby Oil; ***Irl.:*** Lacri-Lube; ***Israel:*** Duratears; Kamil Blue; Lacrimol; Pedisol; ***Malaysia:*** Balneum; Duratears Naturale; Lacrilube†; ***Mex.:*** Acuafil†; ***Neth.:*** Duratears Z; ***NZ:*** Alpha Keri; BK; DP; DP Lotion - HC; Hydroderm; Oralife Peppermint; ***Pol.:*** E45; ***Singapore:*** Balneum; Duratears; Lacrilube; ***Spain:*** Lubrifilm; Tears Lubricante†; ***Thai.:*** Balneum†; Duratears; ***UK:*** Alpha Keri; Hewletts; Lubri-Tears; Melrose; ***USA:*** Akwa Tears; Alpha Keri; Bodi Oil; Bottom Better; Dermadrox; Dry Eyes; Duratears Naturale; Geri-Silk; Lacri-Gel; Lacri-Lube; LubriFresh PM; LubriTears; Paladin; ***Venez.:*** Lacrimart†; Oleoderm.

The symbol † denotes a preparation no longer actively marketed

Pesticides and Repellents

Pediculosis, p.2034
Scabies, p.2035
Vector control, p.2035

This chapter describes compounds used as pesticides and as insect repellents. The term pesticide covers fungicides, herbicides, insecticides (including acaricides), molluscicides, and rodenticides, among others. Most of the pesticides included here are used in clinical or veterinary practice or in vector control against human or animal disease. Some are used primarily in an agricultural or horticultural setting and are included because of their potential toxicity.

Pesticides can be absorbed during application, by consumption of treated or contaminated products or by accidental contamination, and they may be stored or retained in the tissues. International regulations and controls operate to reduce the risk to both public and user. Values for acceptable daily intakes of pesticides have been published by the Food and Agriculture Organization of the United Nations and the WHO Health Organization (WHO) through the WHO Technical Report series of publications or through *Pesticides Residues in Food: yearly evaluations*, FAO Plant Production and Protection Papers, Rome.

Classification of the main pesticides included in this chapter is given in Table 1 below.

The **fungicides** included in this chapter are some of those used in the management of plant disease.

Herbicides are used for weed control both in the domestic setting and professionally in agriculture and horticulture. Those here have been included primarily because they are toxic and have been associated with many cases of poisoning.

Insect repellents can help to avoid insect bites and the unpleasant reactions they may produce. Perhaps more importantly, the correct use of insect repellents plays a major role in personal protection against a number of communicable diseases transmitted by insect vectors. Examples are babesiosis (ticks), Lyme disease (ticks), malaria (mosquitoes), relapsing fevers (lice and ticks), spotted fevers (ticks), and typhus fever (fleas, lice, and mites). Some compounds, such as diethyltoluamide and dimethyl phthalate, are effective as repellents while others, such as benzyl benzoate and some of the pyrethroids, are effective both as repellents and as insecticides.

Insecticides have numerous applications. They are used in the treatment of ectoparasitic infections such as pediculosis (lice infections) (below) and in the vector control (below) of a number of communicable diseases that are spread by insects. Acaricides are used to treat scabies (mite infections) (see, below) and are included within the broad classification of insecticides, although acari (mites) are not, technically, insects. Insecticides are also widely used in veterinary practice and in agriculture and horticulture.

The insecticides used in veterinary practice are often classified as topical or systemic ectoparasiticides. Topical ectoparasiticides are applied topically to the host animal (such as dogs or cats) to kill its ectoparasites (such as fleas). In the case of systemic ectoparasiticides the term 'systemic' refers to the ingestion of the insecticide by the ectoparasite from the host's blood; the insecticide may be present in the host's blood either as a result of absorption through the skin after topical application or after systemic dosage.

Table 1. Classification of pesticides.

Fungicides	Benomyl, cicloheximide, copper naphthenate, hexachlorobenzene, pentachlorophenol
Herbicides	Dichlorophenoxyacetic acid, dinitro-*o*-cresol, dinitrophenol, diquat, glyphosate, paraquat, pentachlorophenol, trichlorophenoxyacetic acid
Insect repellents	Butopyronoxyl, dibutyl phthalate, diethyltoluamide, dimethyl phthalate, dioctyl adipate, ethohexadiol, piperonal
Insecticides	
Carbamate	Bendiocarb, carbaryl, carbosulfan, methomyl, propoxur
Chlorinated	Chlordane, clofenotane, dieldrin, endosulfan, endrin, heptachlor, lindane, methoxychlor
Organophosphorus	Azamethiphos, bromophos, chlorpyrifos, clofenvinfos, coumafos, cythioate, dichlorvos, dimethoate, dimpylate, dioxation, ethion, famphur, fenitrothion, fenthion, heptenophos, iodofenphos, malathion, naled, parathion, phosmet, phoxim, pirimiphos-methyl, propetamphos, pyraclofos, temefos
Pyrethroid	Alpha-cypermethrin, bioallethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esdepallethrine, etofenprox, fenvalerate, flumethrin, permethrin, phenothrin, pyrethrum flower, resmethrin, tetramethrin
Miscellaneous	Amitraz, benzyl benzoate, chloropicrin, copper oleate, cymiazole, cyromazine, diflubenzuron, emamectin, ethylene dibromide, ethylene dichloride, fipronil, fluazuron, fluvalinate, lufenuron, methoprene, methyl bromide, pyriproxyfen, rotenone, sulfiram, triflumuron
Molluscicides	Endod, metaldehyde, pentachlorophenol
Rodenticides	Aluminium phosphide, antu, brodifacoum, bromadiolone, chloralose, chlorophacinone, coumatetralyl, difenacoum, diphenadione, flocoumafen, fluoroacetamide, norbormide, red squill, sodium fluoroacetate

Molluscicides are used in agriculture or horticulture or in the domestic garden to control snail and slug pests. Additionally, molluscicides such as niclosamide (described in the Anthelmintics chapter on p.151) are used against the freshwater snail vector *Bulinus* in the control of schistosomiasis.

Rodenticides may be used to exterminate rats and mice which may be vectors for diseases such as leptospirosis, plague, rat-bite fever, and some haemorrhagic fevers. Many rodenticides are anticoagulants. Warfarin (p.1425) is a commonly used rodenticide.

Clinical Uses of Pesticides and Repellents

Pediculosis

Two species of louse cause pediculosis[1-7] in man; these are *Pediculus humanus* with its two varieties, *Pediculus humanus capitis* (the head louse) and *Pediculus humanus humanus* (the body louse), and *Pthirus pubis* (*Phthirus pubis*) (the pubic or crab louse). Unlike the head louse, the body louse is an important vector for a number of infections including epidemic typhus (p.198), trench fever (p.196), and relapsing fever (p.189).

Insecticides used in the treatment of head lice include the organophosphate malathion, and some pyrethroids such as bioallethrin, permethrin, phenothrin, and tetramethrin. The carbamate, carbaryl, is also effective, although there has been some concern over a theoretical risk of carcinogenicity. Lindane has been used but is no longer recommended as a first-line treatment due to its neurotoxicity and resistance. To be effective insecticide products need to be applied correctly; a quantity of 50 to 100 mL should be applied thoroughly to the hair from hair root to the tip and left on for 8 to 12 hours. Insecticide products kill only adult lice and not the ova, therefore treatment is usually repeated 7 days later. Close contacts should be screened and if infected with living lice should also receive treatment.

Resistance has been reported to the currently used insecticides. Resistance is considered to be most likely to pyrethroids, intermediate to malathion, and least likely to carbaryl. In the UK the policy of rotating insecticides on a district-wide basis in order to overcome the development of resistance is now considered outdated. The current recommendation in the case of suspected resistance and treatment failure is to use an insecticide from a different class for the next course. Lotions are preferred to shampoos for head lice since contact time with the insecticide is longer and treatment is thus more effective. A head louse repellent containing piperonal is available. Non-insecticide treatments include a 4% dimeticone lotion[8] (see p.2032) and wet-combing (also called 'bug-busting') with conditioner.[9] Dimeticone is thought to act by disrupting the ability of the lice to manage their water balance. Dimeticone is applied similarly to the insecticide products and 2 treatments are also required to kill any newly hatched nymphs. A dry-on, suffocation-based pediculicide has also been claimed to be effective,[10,11] although some have questioned the claims.[12]

Infestations of crab lice and body lice respond to the same insecticides as head lice. Aqueous solutions are generally preferred to alcoholic for crab louse infestations, since the latter may irritate excoriated skin and genitalia.

Malathion has also been suggested for treatment of infestation of the eye lashes and brows with pubic lice (pthiriasis or phthiriasis palpebrarum). Other treatments have included the application of a thick layer of yellow soft paraffin or application of yellow mercuric oxide 1% eye ointment twice daily for about 7 or 8 days or a single application of fluorescein eye drops.

Body louse infestations in the developed world are mainly seen in homeless individuals, and often respond to the provision of opportunities for simple hygiene. Clothing and bed linen of persons with body lice should be washed at high temperature or dry cleaned or treated with insecticides. There is some evidence that oral ivermectin may be effective in killing body lice.

Topical or systemic antimicrobials should be given as necessary for secondary infections.

1. Burgess IF. Human lice and their management. *Adv Parasitol* 1995; **36:** 271–342.
2. Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355:** 819–26.
3. Roos TC, *et al.* Pharmacotherapy of ectoparasitic infections. *Drugs* 2001; **61:** 1067–88.
4. Burkhart CG. Relationship of treatment-resistant head lice to the safety and efficacy of pediculicides. *Mayo Clin Proc* 2004; **79:** 661–6.
5. Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol* 2005; **4:** 207–11.
6. Chuard C. Les pédiculoses. *Rev Med Suisse* 2007; **3:** 2266–72.
7. Leone PA. Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clin Infect Dis* 2007; **44** (suppl 3): S153–S159.
8. Pearlman DL. A simple treatment for head lice: dry-on, suffocation-based pediculicide. *Pediatrics* 2004; **114:** e275–e279.
9. Burgess IF, *et al.* Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; **330:** 1423–5.
10. Hill N, *et al.* Single blind, randomised, comparative study of the Bug Buster kit and over the counter pediculicide treatments against head lice in the United Kingdom. *BMJ* 2005; **331:** 384–6.
11. Pearlman D. Cetaphil cleanser (Nuvo lotion) cures head lice. *Pediatrics* 2005; **116:** 1612.
12. Roberts RJ, Burgess IF. New head-lice treatments: hope or hype? *Lancet* 2005; **365:** 8–10.

Scabies

Scabies is a parasitic infection of the skin by the mite *Sarcoptes scabiei*. The main symptom is pruritus, which is caused by an allergic reaction to the parasite and may not occur until several weeks after infection for the first time. Subsequent infections usually result in pruritus after a few days. Pruritus may persist for some months after effective treatment with an acaricide, but is not necessarily an indication for further acaricidal treatment; rather, antipruritics should be used. A severe crusted form (Norwegian scabies) may occur rarely, particularly in immunocompromised or incapacitated patients.

Treatment is with the acaricides permethrin or malathion applied, preferably as aqueous lotions, to clean, cool, dry skin over the entire body and left on for 8 to 24 hours, depending upon the preparation. The preparation should be reapplied to the hands whenever they are washed during this period. In adults, it is not usually necessary to treat the face and scalp, but these areas should be treated in young children or patients with atypical or crusted scabies. A single treatment may be effective, but treatment is usually repeated after 7 to 10 days if necessary. Other drugs used topically in the treatment of scabies include benzyl benzoate, crotamiton, lindane, and sulfur; sulfiram is used with benzyl benzoate. A single oral dose of ivermectin may be effective. Close family and personal contacts should be treated at the same time and all clothes, towels, and bedding used by the infected person 2 days before treatment should be washed in hot water and dried in a hot dryer.

In addition to treatment with an acaricide, symptomatic treatment of the itching with crotamiton, calamine lotion, or systemic antihistamines or corticosteroids may be required.

References.

1. Elgart ML. A risk-benefit assessment of agents used in the treatment of scabies. *Drug Safety* 1996; **14:** 386–93.
2. Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355:** 819–26.
3. Roos TC, *et al.* Pharmacotherapy of ectoparasitic infections. *Drugs* 2001; **61:** 1067–88.
4. Chosidow O. Scabies. *N Engl J Med* 2006; **354:** 1718–27.
5. Heukelbach J, Feldmeier H. Scabies. *Lancet* 2006; **367:** 1767–74.
6. Strong M, Johnstone PW. Interventions for treating scabies. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/09/07).

Vector control

Many pests are involved in the transmission of communicable diseases, and vector control[1,2] is an important part of the fight against such diseases. Insecticides are used in the control of filariasis (p.137) (*Aedes*, *Anopheles*, *Culex*, and *Mansonia* mosquitoes);[3] leishmaniasis (p.824) (*Phlebotomus* or *Lutzomyia* sandflies);[4] malaria (p.594) (*Anopheles* mosquitoes);[5-8] dengue fever (see Haemorrhagic Fevers, p.850) (*Aedes* mosquitoes);[9,10] onchocerciasis (p.137) (*Simulium* blackflies);[11] African trypanosomiasis (p.827) (*Glossina* tsetse flies);[12] and American trypanosomiasis (p.827) (*Triatoma* bugs).[13] The insecticide temefos is useful in dracunculiasis (p.136) (crustacean host to the guinea worm larvae). In some cases, as in filariasis or onchocerciasis, the insecticides used act mainly against the larval stage of the insect vector, whereas in other situations, as in malaria, activity is against the adult insect; in trypanosomiasis, activity is directed against both adult and immature stages. The majority of the experience gained in insecticidal vector control has probably been in malaria, and, for instance, a positive effect seen in the control of leishmaniasis has been considered to be mainly a byproduct of the concomitant malaria control programmes.

Insect repellents can provide personal protection against many insect vectors. For example, in malaria, insect repellents as well as the use of insecticides are important in preventing mosquito bites.

Molluscicides are used in the control of schistosomiasis (p.138) (*Bulinus* snails).[14]

Rodenticides are also extremely valuable in the vector control of some diseases such as leptospirosis (p.177), plague (p.186), rat-bite fever (p.164), and some haemorrhagic fevers (p.850).

1. Chavasse DC, Yap HH, eds. *Chemical methods for the control of vectors and pests of public health importance.* Geneva: WHO, 1997.
2. Rozendaal JA. *Vector control: methods for use by individuals and communities.* Geneva: WHO, 1997.
3. WHO. Lymphatic filariasis: the disease and its control. *WHO Tech Rep Ser 821* 1992. Available at: http://libdoc.who.int/trs/WHO_TRS_821.pdf (accessed 21/07/08)
4. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 21/07/08)
5. WHO. Vector control for malaria and other mosquito-borne diseases. *WHO Tech Rep Ser 857* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_857.pdf (accessed 21/07/08)
6. WHO. *Malaria vector control: insecticides for indoor residual spraying.* Geneva: WHO, 2001.
7. WHO. *International travel and health.* 2008 ed. Available at: http://www.who.int/ith/ (accessed 17/04/08)
8. Lengeler C. Insecticide-treated bednets and curtains for preventing malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/08/05).
9. WHO. *Prevention and control of dengue and dengue haemorrhagic fever: comprehensive guidelines.* New Delhi: WHO, 1999. Also available at: http://www.searo.who.int/LinkFiles/Regional_Guidelines_on_Dengue_DHF_prevention_&_control_searo-29.pdf (accessed 10/10/05)
10. Lloyd LS. *Best practices for dengue prevention and control in the Americas.* Washington DC: Environmental Health Project, 2003. Also available at: http://www.ehproject.org/PDF/Strategic_papers/SR7-BestPractice.pdf (accessed 10/10/05)
11. WHO. Report of a WHO expert committee on onchocerciasis control. *WHO Tech Rep Ser 852* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 21/07/08)
12. WHO. Control and surveillance of African trypanosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 881* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_881.pdf (accessed 21/07/08)
13. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 21/07/08)
14. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 21/07/08)

Aluminium Phosphide

Aluminum Phosphide; Fosfuro de aluminio.

$AlP = 57.96$.

CAS — 20859-73-8 (aluminium phosphide); 7803-51-2 (phosphine); 1314-84-7 (zinc phosphide).

Profile

Aluminium phosphide is used for the fumigation of grain and as a rodenticide. It releases phosphine (PH_3) in the presence of moisture and this accounts for its pesticidal activity. Phosphine gas has a garlic-like odour repulsive to man and domestic animals but apparently not to *rats*. Zinc phosphide is used similarly.

◊ References to poisoning associated with aluminium phosphide.

1. Wilson R, *et al.* Acute phosphine poisoning aboard a grain freighter. *JAMA* 1980; **244:** 148–50.
2. Singh S, *et al.* Aluminium phosphide ingestion. *BMJ* 1985; **290:** 1110–11.
3. Anger F, *et al.* Fatal aluminium phosphide poisoning. *J Anal Toxicol* 2000; **24:** 90–2.
4. Nocera A, *et al.* Dangerous bodies: a case of fatal aluminium phosphide poisoning. *Med J Aust* 2000; **173:** 133–5.
5. Popp W, *et al.* Phosphine poisoning in a German office. *Lancet* 2002; **359:** 1574.
6. Bogle RG, *et al.* Aluminium phosphide poisoning. *Emerg Med J* 2006; **23:** e3.
7. Memiş D, *et al.* Fatal aluminium phosphide poisoning. *Eur J Anaesthesiol* 2007; **24:** 292–3.
8. Shadnia S, *et al.* Unintentional poisoning by phosphine released from aluminum phosphide. *Hum Exp Toxicol* 2008; **27:** 87–9.

Amitraz *(BAN, USAN, pINN)*

Amitratsi; Amitrazum; U-36059. *N,N′*-[(Methylimino)dimethylidyne]di-2,4-xylidine.

Амитраз

$C_{19}H_{23}N_3 = 293.4$.

CAS — 33089-61-1.

ATC Vet — QP53AD01.

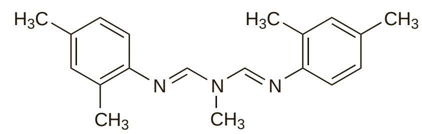

Pharmacopoeias. In *BP(Vet)*. Also in *US* for veterinary use only.

BP(Vet) 2008 (Amitraz). A white to buff powder. Practically insoluble in water; decomposes slowly in alcohol; freely soluble in acetone.

Profile

Amitraz is used as a topical ectoparasiticide in veterinary practice. It is effective against various lice, mites, and ticks.

◊ References to poisoning with amitraz.

1. Jorens PG, *et al.* An unusual poisoning with the unusual pesticide amitraz. *Hum Exp Toxicol* 1997; **16:** 600–1.
2. Aydin K, *et al.* Amitraz poisoning in children: clinical and laboratory findings of eight cases. *Hum Exp Toxicol* 1997; **16:** 680–2.
3. Leung VK, *et al.* Amitraz poisoning in humans. *J Toxicol Clin Toxicol* 1999; **37:** 513–14.
4. Yaramis A, *et al.* Amitraz poisoning in children. *Hum Exp Toxicol* 2000; **19:** 431–3.
5. Yilmaz HL, Yildizdas DR. Amitraz poisoning, an emerging problem: epidemiology, clinical features, management, and preventive strategies. *Arch Dis Child* 2003; **88:** 130–4.
6. Proudfoot AT. Poisoning with amitraz. *Toxicol Rev* 2003; **22:** 71–4.
7. Gursoy S, *et al.* Intravenous amitraz poisoning. *Clin Toxicol* 2005; **43:** 113–16.
8. Elinav E, *et al.* Near-fatal amitraz intoxication: the overlooked pesticide. *Basic Clin Pharmacol Toxicol* 2005; **97:** 185–7.
9. Avsarogullari L, *et al.* Acute amitraz poisoning in adults: clinical features, laboratory findings, and management. *Clin Toxicol* 2006; **44:** 19–23.
10. Demirel Y, *et al.* Acute amitraz intoxication: retrospective analysis of 45 cases. *Hum Exp Toxicol* 2006; **25:** 613–17.

Azamethiphos *(BAN)*

Azametifós; CGA-18809; OMS-1825. *S*-[(6-Chloro-2,3-dihydro-2-oxo-1,3-oxazolo[4,5-*b*]pyridin-3-yl)methyl] *O,O*-dimethyl phosphorothioate.

$C_9H_{10}ClN_2O_5PS = 324.7$.

CAS — 35575-96-3.

ATC Vet — QP53AF17.

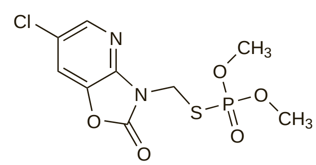

Profile

Azamethiphos is an organophosphorus insecticide (p.2047) used in veterinary practice for the control of sea-lice infestation in salmon and for the control of ectoparasites in the environment.

Bendiocarb

2,3-Isopropylidenedioxyphenyl methylcarbamate.

$C_{11}H_{13}NO_4 = 223.2$.

CAS — 22781-23-3.

ATC Vet — QP53AE03.

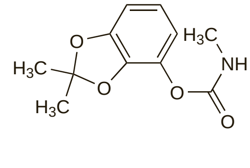

Profile

Bendiocarb is a carbamate insecticide (p.2037) for agricultural and household use.

Benomyl

Benomilo. Methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate.

$C_{14}H_{18}N_4O_3$ = 290.3.
CAS — 17804-35-2.

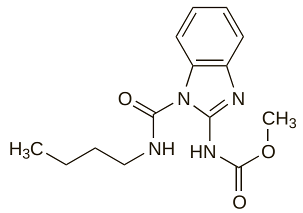

Profile

Benomyl is a fungicide used for the treatment and control of fungal plant diseases.

◊ References.

1. WHO. Benomyl. *Environmental Health Criteria 148*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc148.htm (accessed 23/04/04)
2. WHO. Benomyl health and safety guide. *IPCS Health and Safety Guide 81*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg81_e.htm (accessed 23/04/04)

Toxicity. Although experimental evidence in *animals* has suggested a possible link between benomyl and congenital eye defects (anophthalmia) the association could not be confirmed in humans.[1-4]

1. Gilbert R. "Clusters" of anophthalmia in Britain. *BMJ* 1993; **307:** 340–1.
2. Bianchi F, *et al.* Clusters of anophthalmia. *BMJ* 1994; **308:** 205.
3. Kristensen P, Irgens LM. Clusters of anophthalmia. *BMJ* 1994; **308:** 205–6.
4. Castilla EE. Clusters of anophthalmia. *BMJ* 1994; **308:** 206.

Benzyl Benzoate

Bencilo, benzoato de; Bensylbensoat; Bentsyylibentsoaatti; Benzil Benzoat; Benzil-benzoát; Benzilbenzoatas; Benzoato de bencilo; Benzoato de Benzilo; Benzoesäurebenzylester; Benzyl Benz.; Benzyl-benzoát; Benzyle, benzoate de; Benzylis benzoas; Benzylu benzoesan.

$C_6H_5.CO.O.CH_2.C_6H_5$ = 212.2.
CAS — 120-51-4.
ATC — P03AX01.
ATC Vet — QP53AX11.

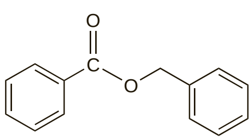

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Benzyl Benzoate). Colourless or almost colourless crystals, or a colourless or almost colourless oily liquid. F.p. is not below 17°. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with fatty and essential oils. Store in well-filled airtight containers. Protect from light.

USP 31 (Benzyl Benzoate). A clear, colourless, oily liquid with a slight aromatic odour. Practically insoluble in water and in glycerol; miscible with alcohol, with chloroform, and with ether. Store at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Adverse Effects and Treatment

Benzyl benzoate is irritant to the eyes and mucous membranes and it may be irritant to the skin. Hypersensitivity reactions have been reported. If ingested, benzyl benzoate may cause stimulation of the CNS and convulsions. Systemic symptoms have been reported on excessive topical use. For poisoning associated with topical use the skin should be washed. Appropriate symptomatic measures should also be instituted.

Uses and Administration

Benzyl benzoate is an acaricide used in the treatment of scabies (p.2035) although other treatments are generally preferred. A 25% emulsion is applied to the whole body, usually from the neck down (although the *BNF* considers that application should be extended to the scalp, neck, face, and ears). If the application is thorough, one treatment may suffice, although the possibility of failure is lessened by a second application within 5 days. Alternatively, three applications at 12-hour intervals, without bathing, may be made, followed by bathing 12 hours after the last application. The *BNF* recommends one application to the whole body, repeated, without bathing, on the next day, and washed off 24 hours later; a third application may sometimes be necessary. Benzyl benzoate is not generally recommended for infants and children, but if used the application should be diluted to minimise the risk of irritation, although this also reduces efficacy.

Benzyl benzoate has also been used as a pediculicide.

Benzyl benzoate is also used as a solubilising agent.

Preparations

BP 2008: Benzyl Benzoate Application;
USP 31: Benzyl Benzoate Lotion.

Proprietary Preparations (details are given in Part 3)
Austral.: Ascabiol; Benzemul; ***Braz.:*** Acarsan; Bencocan; Benzibel†; Benzin†; Benzoax; Benzoben†; Benzocan†; Benzolato†; Benzolina†; Benzolom†; Benzotisan; Miticocan; Parasimed; Pruridol; Sanasar; Sarnaton†; Sarnezan†; Sarnilab; Sarnodex; Scabenzil; Scabioid; Zilaben; ***Ger.:*** Acaril†; Acarosan†; Antiscabiosum; ***Gr.:*** Benzogal; ***Irl.:*** Ascabiol†; ***Israel:*** Scabiex; ***Ital.:*** Mom Lozione Preventiva; ***Mex.:*** Ansar; Hastilan; ***Pol.:*** Novoscabin; ***Port.:*** Acarilbial; Neo-Acarina†; Piozil; ***S.Afr.:*** Ascabiol; ***UK:*** Ascabiol; ***Venez.:*** Benzalcor; Benzo-Bencil; Benzodit†; Niostal†.

Multi-ingredient: ***Arg.:*** Anusol Duo S; Anusol-A; Amecrem†; Bencil Scab; Detebencil; Hexabencil; Perbel; Permecil; Sapucai†; Scabioderm; ***Austral.:*** Anusol; ***Belg.:*** Pulmex; Pulmex Baby; ***Braz.:*** Anusol-HC; ***Fr.:*** Allerbiocid S†; Ascabiol; Sanytol†; ***Hong Kong:*** Anusol-HC†; ***Hung.:*** Novascabin; ***Irl.:*** Anugesic-HC; Anusol-HC; ***Ital.:*** Antiscabbia Candioli al DDT Terapeutico; Antiscabbia CM; Dekar 2; Prurex; Skab 2; ***Malaysia:*** Anucare; Anusol; ***NZ:*** Anusol; ***Pol.:*** Cetriscabin; ***S.Afr.:*** Anugesic; ***Singapore:*** Anusol; ***Spain:*** Tulgrasum Cicatrizante; Yacutin; ***Swed.:*** Tenutex; ***Thai.:*** Anusol; ***UK:*** Anugesic-HC; Anusol-HC, Plus HC; Sudocrem; ***USA:*** Anumed; Anumed HC; Hemril; ***Venez.:*** Kertyol.

Bioallethrin *(BAN)*

Allethrin I; Bioaletrina; Depallethrin. (*RS*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)-cyclopropanecarboxylate.

$C_{19}H_{26}O_3$ = 302.4.
CAS — 584-79-2.
ATC — P03AC02.
ATC Vet — QP53AC02.

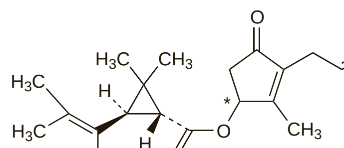

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Profile

Bioallethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049). It is used topically, with the synergist piperonyl butoxide (p.2049), in the treatment of pediculosis (p.2034). It is also used in anti-mosquito devices and for the control of household insect pests.

◊ References.

1. WHO. Allethrins. *Environmental Health Criteria 87*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc87.htm (accessed 23/04/04)
2. WHO. Allethrins health and safety guide. *IPCS Health and Safety Guide 24*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg024.htm (accessed 23/04/04)

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Actomite.

Multi-ingredient: ***Arg.:*** Limpacid; Para Piojicida; Scabioderm; ***Austral.:*** Paralice†; ***Belg.:*** Para; ***Braz.:*** Sarnapen†; ***Canad.:*** Para†; ***Fr.:*** Para Special Poux; ***Ger.:*** Jacutin N; Spregal; ***Israel:*** Monocide; ***Ital.:*** Cruzzy; ***Neth.:*** Para-Speciaal.

Brodifacoum

Brodifacum; WBA-8119. 3-[3-(4′-Bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarin.

$C_{31}H_{23}BrO_3$ = 523.4.
CAS — 56073-10-0.

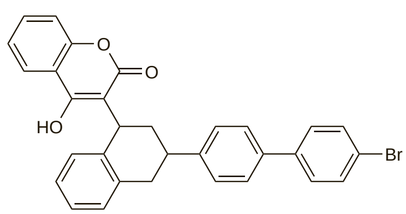

Profile

Brodifacoum is an anticoagulant rodenticide. It is reported to be effective in warfarin-resistant strains of rodents.

◊ References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Brodifacoum health and safety guide. *IPCS Health and Safety Guide 93*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg093.htm (accessed 23/04/04)

Toxicity. Brodifacoum, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with brodifacoum.[2-10]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Watts RG, *et al.* Accidental poisoning with a superwarfarin compound (brodifacoum) in a child. *Pediatrics* 1990; **86:** 883–7.
3. Ross GS, *et al.* An acquired hemorrhagic disorder from long-acting rodenticide ingestion. *Arch Intern Med* 1992; **152:** 410–12.
4. Kruse JA, Carlson RW. Fatal rodenticide poisoning with brodifacoum. *Ann Emerg Med* 1992; **21:** 331–6.
5. Tecimer C, Yam LT. Surreptitious superwarfarin poisoning with brodifacoum. *South Med J* 1997; **90:** 1053–5.
6. Corke PJ. Superwarfarin (brodifacoum) poisoning. *Anaesth Intensive Care* 1997; **25:** 707–9.
7. La Rosa FG, *et al.* Brodifacoum intoxication with marijuana smoking. *Arch Pathol Lab Med* 1997; **121:** 67–9.
8. Miller MA, *et al.* Rapid identification of surreptitious brodifacoum poisoning by analysis of vitamin K-dependent factor activity. *Am J Emerg Med* 2006; **24:** 383.
9. Olmos V, López CM. Brodifacoum poisoning with toxicokinetic data. *Clin Toxicol* 2007; **45:** 487–9.
10. Kapadia P, Bona R. Acquired deficiency of vitamin K-dependent clotting factors due to brodifacoum ingestion. *Conn Med* 2008; **72:** 207–9.

Bromadiolone

Bromadiolona. 3-[3-(4′-Bromobiphenyl-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxycoumarin.

$C_{30}H_{23}BrO_4$ = 527.4.
CAS — 28772-56-7.

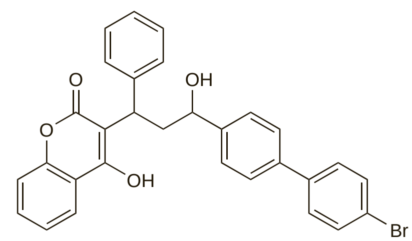

Profile

Bromadiolone is an anticoagulant rodenticide.

◊ References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 23/04/04)
2. WHO. Bromadiolone health and safety guide. *IPCS Health and Safety Guide 94*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg094.htm (accessed 23/04/04)

Toxicity. Bromadiolone, a second-generation anticoagulant rodenticide, inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with bromadiolone.[2-5]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Greeff MC, *et al.* "Superwarfarin" (bromodialone) poisoning in two children resulting in prolonged anticoagulation. *Lancet* 1987; **ii:** 1269.
3. Chow EY, *et al.* A case of bromadiolone (superwarfarin) ingestion. *CMAJ* 1992; **147:** 60–2.
4. Grobosch T, *et al.* Acute bromadiolone intoxication. *J Anal Toxicol* 2006; **30:** 281–6.
5. Lo VM, *et al.* Bromadiolone toxicokinetics: diagnosis and treatment implications. *Clin Toxicol* 2008; 1–8.

Bromophos

Bromofós; Bromofos; OMS-658. *O*-4-Bromo-2,5-dichlorophenyl *O,O*-dimethyl phosphorothioate.

$C_8H_8BrCl_2O_3PS$ = 366.0.

CAS — 2104-96-3.

ATC Vet — QP53AF11.

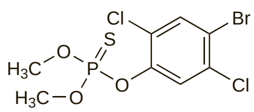

Profile

Bromophos is an organophosphorus insecticide (p.2047) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide.

Butopyronoxyl

Butopiroxinilo; Indalone. Butyl 3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-carboxylate.

$C_{12}H_{18}O_4$ = 226.3.

CAS — 532-34-3.

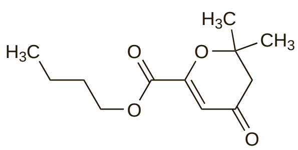

Profile

Butopyronoxyl has been used as an insect repellent.

Carbamate Insecticides

Insecticidas del grupo de los carbamatos.

Description. The carbamate insecticides are *N*-substituted esters of carbamic acid.

◊ References.

1. WHO. Carbamate pesticides: a general introduction. *Environmental Health Criteria 64*. Geneva: WHO, 1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc64.htm (accessed 24/07/08)

Adverse Effects

As for Organophosphorus Insecticides, p.2047.

The carbamates are cholinesterase inhibitors, differing from the organophosphorus insecticides in that the inhibition they produce is generally less intense and more rapidly reversible. In addition, they do not appear to enter the CNS as readily and severe central effects are therefore uncommon.

Treatment of Adverse Effects

If substantial amounts of carbamate insecticides have been ingested the use of gastric lavage should be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive and includes atropine, but this may not always be necessary due to the rapidly reversible nature of the cholinesterase inhibition produced. Pralidoxime is thought to be generally unnecessary; some *animal* studies have suggested that it may increase the toxicity of carbamates.

◊ References.

1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.

Carbaryl *(BAN)*

Carbaril *(pINN)*; Carbarilo; Carbarilum; Karbaril; OMS-29. 1-Naphthyl methylcarbamate.

Карбарил

$C_{12}H_{11}NO_2$ = 201.2.

CAS — 63-25-2.

ATC Vet — QP53AE01.

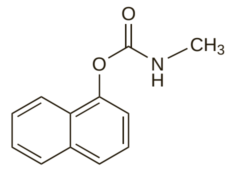

Pharmacopoeias. In *Br.*

BP 2008 (Carbaryl). A white to off-white or light grey powder which darkens on exposure to light. Very slightly soluble in water; soluble in alcohol and in acetone. Store at a temperature not exceeding 25°. Protect from light.

Adverse Effects and Treatment

As for Carbamate Insecticides, above. Carbaryl may be absorbed after ingestion, inhalation, or skin contamination.

Carbaryl has been reported to produce neoplasms in *mice* and *rats* and in late 1995 the UK DoH advised that it would be prudent to consider carbaryl as a potential human carcinogen; its medicinal use was limited to prescription only. However, the DoH emphasised that the risk was a theoretical one and that any risk from the intermittent use of head lice preparations was likely to be very small.

Uses and Administration

Carbaryl is a carbamate insecticide (above). It is used as a 0.5 or 1.0% lotion or shampoo in the treatment of head and pubic pediculosis (p.2034). Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Carbaryl is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

◊ References.

1. WHO. Carbaryl health and safety guide. *IPCS Health and Safety Guide 78*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/hsg/hsg/hsg78_e.htm (accessed 23/04/04)
2. WHO. Carbaryl. *Environmental Health Criteria 153*. Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc153.htm (accessed 23/04/04)

Preparations

BP 2008: Carbaryl Lotion.

Proprietary Preparations (details are given in Part 3)

Israel: Hafif; ***UK:*** Carylderm.

Carbosulfan

Carbosulfán. 2,3-Dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate.

$C_{20}H_{32}N_2O_3S$ = 380.5.

CAS — 55285-14-8.

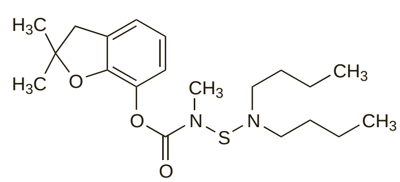

Profile

Carbosulfan is a carbamate insecticide (p.2037) used in agriculture and for the larvicidal treatment of rivers in the control of onchocerciasis (p.137).

Chloralose *(rINN)*

Alphachloralose; Chloralosane; α-Chloralose; Chloralosum; Cloralosa; Glucochloral. (*R*)-1,2-*O*-(2,2,2-Trichloroethylidene)-α-D-glucofuranose.

Хлоралоза

$C_8H_{11}Cl_3O_6$ = 309.5.

CAS — 15879-93-3.

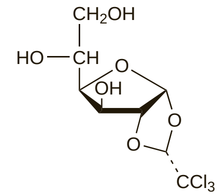

Profile

Chloralose has general properties similar to those of cloral hydrate (p.979), of which it is a derivative. It is used as a rodenticide. It was formerly used for its hypnotic properties.

Chlordane

Chlordan; Clordano. 1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene.

$C_{10}H_6Cl_8$ = 409.8.

CAS — 57-74-9.

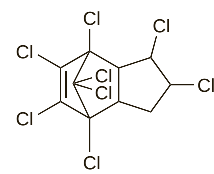

Profile

Chlordane is a chlorinated insecticide (p.2037). Its use is limited, or even prohibited, in some countries because of toxicity due to its persistent nature.

◊ References.

1. Kutz FW, *et al.* A fatal chlordane poisoning. *J Toxicol Clin Toxicol* 1983; **20:** 167–74.
2. Olanoff LS, *et al.* Acute chlordane intoxication. *J Toxicol Clin Toxicol* 1983; **20:** 291–306.
3. WHO. Chlordane. *Environmental Health Criteria 34*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc34.htm (accessed 23/04/04)
4. WHO. Chlordane health and safety guide. *IPCS Health and Safety Guide 13*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg013.htm (accessed 23/04/04)

Chlorinated Insecticides

Insecticidas clorados.

Adverse Effects

Chlorinated or organochlorine insecticides form a very wide group and the toxicity of individual members varies considerably. In general these insecticides produce symptoms consistent with CNS stimulation. They may be absorbed through the respiratory and gastrointestinal tracts and through the skin.

Symptoms of acute poisoning include nausea and vomiting, paraesthesia, giddiness, tremors, convulsions, coma, and respiratory failure. Liver, kidney, and myocardial toxicity have been reported. Effects on the blood include agranulocytosis and aplastic anaemia. Symptoms may be complicated by the effects of the solvent.

Chlorinated insecticides have been reported to enhance microsomal hepatic enzyme activity. Skin reactions can occur after contact.

Polychlorinated biphenyl (PCB) and terphenyl compounds were formerly used as insecticides in many countries. They accumulate in body fat and are not readily excreted, although they are distributed into breast milk and possibly cross the placenta; because of this and because of accidental contamination they remain a cause for concern. The related polybrominated biphenyl compounds (PBB), which have no insecticidal uses, have also been absorbed by humans after accidental contamination of the food chain.

Some chlorinated insecticides have weak oestrogenic effects; it has been proposed that exposure may increase the risk of breast cancer.

Treatment of Adverse Effects

If chlorinated insecticides have been ingested gastric lavage or activated charcoal may be considered if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Treatment is largely symptomatic and supportive with treatment of CNS stimulation such as hyperactivity and convulsions.

◊ References.

1. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
2. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Uses

The chlorinated or organochlorine insecticides were widely used but, because of persistence in man, many have been banned or restricted.

◊ References.

1. WHO. Polychlorinated biphenyls and terphenyls. *Environmental Health Criteria 140*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc140.htm (accessed 28/05/04)
2. WHO. Polychlorinated biphenyls and polychlorinated terphenyls (PCBs and PCTs) health and safety guide. *IPCS Health and Safety Guide 68*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg68.htm (accessed 28/05/04)

Chlorophacinone

Clorofacinona; LM-91. 2-[2-(4-Chlorophenyl)-2-phenylacetyl]indane-1,3-dione.

$C_{23}H_{15}ClO_3$ = 374.8.
CAS — 3691-35-8.

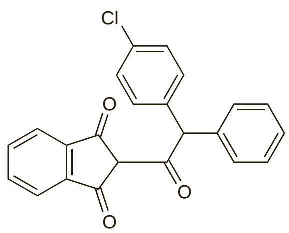

Profile

Chlorophacinone is an indanedione derivative used as an anticoagulant rodenticide. It is also reported to uncouple oxidative phosphorylation with consequent stimulation of cellular metabolism which may contribute to its toxicity.

◊ References.

1. Burucoa C, *et al.* Chlorophacinone intoxication: biological and toxicological study. *J Toxicol Clin Toxicol* 1989; **27:** 79–89.
2. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)
3. Lagrange F, *et al.* Toxicological management of chlorophacinone poisoning. *Acta Clin Belg Suppl* 1999; **1:** 13–16.
4. Papin F, *et al.* Lethal paradoxical cerebral vein thrombosis due to suspicious anticoagulant rodenticide intoxication with chlorophacinone. *Forensic Sci Int* 2007; **166:** 85–90.

Chloropicrin

Cloropicrina; Nitrochloroform. Trichloronitromethane.

CCl_3NO_2 = 164.4.
CAS — 76-06-2.

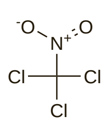

Profile

Chloropicrin is a lachrymatory agent with an intense odour. It is intensely irritating to the skin and mucous membranes. It is an insecticide and is used for fumigating stored grain and soil. Chloropicrin is also added to other fumigants as a warning gas.

Chlorpyrifos *(BAN)*

Clorpirifós. *O,O*-Diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate.

$C_9H_{11}Cl_3NO_3PS$ = 350.6.
CAS — 2921-88-2.

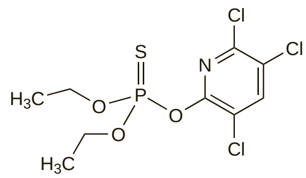

Profile

Chlorpyrifos is an organophosphorus insecticide (p.2047) used in agriculture.

Cicloheximide *(rINN)*

Cicloheximida; Cicloheximidum; Cycloheximide *(USAN)*; U-4527. 3-{(2*R*)-2-[(1*S*,3*S*,5*S*)-3,5-Dimethyl-2-oxocyclohexyl]-2-hydroxyethyl}glutarimide.

Циклогексимид

$C_{15}H_{23}NO_4$ = 281.3.
CAS — 66-81-9.

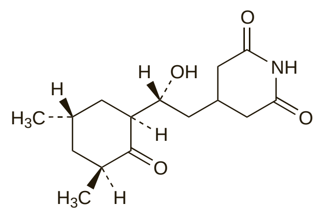

Profile

Cicloheximide is an antimicrobial substance produced by strains of *Streptomyces griseus*. It has antifungal properties and has been used for the treatment and control of certain mycotic plant diseases.

Clofenotane *(rINN)*

Chlorofenotano; Chlorophenothane; Chlorphenothanum; Clofénotane; Clofenotano; Clofenotanum; DDT; Dichlorodiphenyltrichloroethane; Dichophanum; Dicophane; Klofenotaani; Klofenotan. 1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane.

Клофенотан

$C_{14}H_9Cl_5$ = 354.5.
CAS — 50-29-3.
ATC — P03AB01.
ATC Vet — QP53AB01.

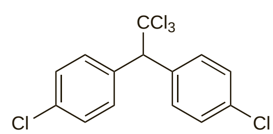

Pharmacopoeias. In *It.*

Adverse Effects and Treatment

As for Chlorinated Insecticides, p.2037.

◊ References.

1. WHO. DDT and its derivatives. *Environmental Health Criteria 9*. Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc009.htm (accessed 28/05/04)
2. WHO. DDT and its derivatives—environmental aspects. *Environmental Health Criteria 83*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc83.htm (accessed 28/05/04)

Carcinogenicity. Some small epidemiological studies have suggested that certain organochlorines, namely 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), a metabolite of clofenotane, and polychlorinated biphenyls (PCBs), might increase the risk of breast cancer in women. However, re-analysis[1,2] of the available data indicated that an association with breast cancer was unlikely for clofenotane; there was no evidence for an association with the PCBs. Any link between exposure to clofenotane and the development of testicular cancer in men was also refuted[3] after long-term monitoring of populations in Scandinavia.

1. Key T, Reeves G. Organochlorines in the environment and breast cancer. *BMJ* 1994; **308:** 1520–1.
2. van't Veer P, *et al.* DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. *BMJ* 1997; **315:** 81–5.
3. Ekbom A, *et al.* DDT and testicular cancer. *Lancet* 1996; **347:** 553–4.

Effects on fertility. A metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), was reported[1] to have anti-androgenic properties in *rats* and exposure to clofenotane might account for a previously reported decline in male fertility and an increase in male reproductive abnormalities.

1. Keke WR, *et al.* Persistent DDT metabolite p,p′-DDE is a potent androgen receptor antagonist. *Nature* 1995; **375:** 581–5.

Effects on the nervous system. A retrospective study[1] found that retired malaria workers exposed long-term to clofenotane did less well in neurobehavioural tests than a control group, and had an increase in neuropsychological and psychiatric symptoms.

1. van Wendel de Joode B, *et al.* Chronic nervous-system effects of long-term occupational exposure to DDT. *Lancet* 2001; **357:** 1014–16.

Pregnancy. In a large prospective study[1] of children born between 1959 and 1966, an association was found between preterm births and small-for-gestational-age babies, and maternal concentrations of a metabolite of clofenotane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) measured in serum samples which had been stored during pregnancy.

1. Longnecker MP, *et al.* Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet* 2001; **358:** 110–14.

Pharmacokinetics

Clofenotane may be absorbed after ingestion or inhalation or through the skin. Clofenotane is stored in the body, particularly in body fat, and is very slowly eliminated. It crosses the placenta and appears in breast milk. It is metabolised in the body to the ethylene derivative, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE); the acetic acid derivative (DDA) also appears in the urine.

Uses

Clofenotane is a chlorinated insecticide (p.2037). It is a stomach and contact poison and retains its activity for long periods under a variety of conditions. It is effective against disease vectors such as fleas, lice, and mosquitoes and has been applied topically for pediculosis (p.2034) and scabies (p.2035), although more suitable alternatives exist.

Because of the extreme persistence of clofenotane, concern over its effect in the environment, and the problem of resistance, the widespread use of clofenotane is now generally discouraged. It is no longer used in some countries while in others its use is limited.

◊ Despite reservations regarding the use of clofenotane for vector control, many countries have relied on it for the control of both malaria and visceral leishmaniasis. WHO has concluded[1,2] that clofenotane might be used provided:

- that it was used only for indoor spraying
- that it was known to be effective
- that it was manufactured to WHO's specifications
- that the necessary safety precautions were taken in its use and disposal

However, they recommended further investigation of the effects of clofenotane in breast milk and of suspected carcinogenicity, as well as clarification of the significance of the reduced density of muscarinic receptors caused by clofenotane.

1. WHO. WHO expert committee on malaria: twentieth report. *WHO Tech Rep Ser 892* 2000. Available at: http://libdoc.who.int/trs/WHO_TRS_892.pdf (accessed 21/07/08)
2. WHO Global Malaria Programme. Indoor residual spraying: use of indoor residual spraying for scaling up global malaria control and elimination 2006. Available at: http://malaria.who.int/docs/IRS-position.pdf (accessed 21/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Antiscabbia Candioli al DDT Terapeutico.

Clofenvinfos *(BAN, rINN)*

Chlorfenvinphos; Chlorofenwinfos; Clofenvinfós; Clofenvinfosum. 2-Chloro-1-(2,4-dichlorophenyl)vinyl diethyl phosphate.

Клофенвинфос

$C_{12}H_{14}Cl_3O_4P$ = 359.6.
CAS — 470-90-6.

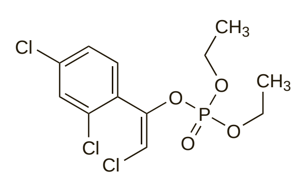

Profile

Clofenvinfos is an organophosphorus insecticide (p.2047) used in agriculture.

Copper Naphthenate

Cobre, naftenato de.
CAS — 1338-02-9.

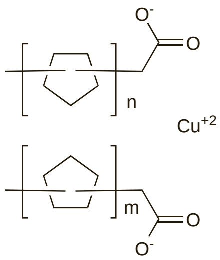

Profile

Copper naphthenate is the copper salt of naphthenic acid and is classified as a general use pesticide. It is used to preserve wood against a broad spectrum of fungi, termites, and other wood-destroying insects. Copper naphthenate has also been used as a topical antifungal in veterinary medicine.

Copper Oleate

Cobre, oleato de.
$Cu(C_{18}H_{33}O_2)_2$ = 626.5.
CAS — 1120-44-1.

Profile

Copper oleate has been used topically as an insecticide for the treatment of pediculosis (p.2034).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Plus & Plus.

Coumafos *(BAN, rINN)*

Bayer-21199; Coumafosum; Coumaphos; Cumafós; Kumafoosi; Kumafos. *O*-3-Chloro-4-methyl-7-coumarinyl *O,O*-diethyl phosphorothioate.
Кумафос
$C_{14}H_{16}ClO_5PS$ = 362.8.
CAS — 56-72-4.
ATC Vet — QP53AF08.

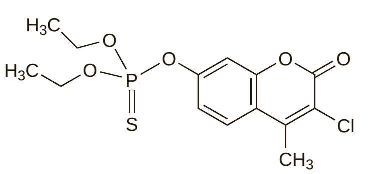

Profile

Coumafos is an organophosphorus insecticide (p.2047) used as a topical ectoparasiticide in veterinary practice.

Coumatetralyl

Cumatetralilo. 4-Hydroxy-3-(1,2,3,4-tetrahydro-1-naphthyl)coumarin.
$C_{19}H_{16}O_3$ = 292.3.
CAS — 5836-29-3.

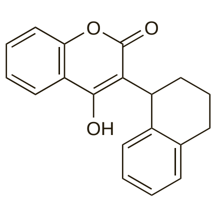

Profile

Coumatetralyl is an anticoagulant rodenticide.

◊ References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 28/05/04)

Cyfluthrin *(BAN)*

Bay-VI-1704; Ciflutrina; Cyfluthin. (*RS*)-α-Cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{18}Cl_2FNO_3$ = 434.3.
CAS — 68359-37-5.
ATC — P03BA01.
ATC Vet — QP53AC12.

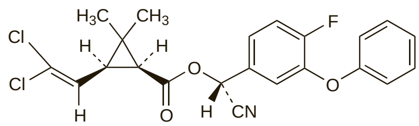

(1S,3S-isomer)

Profile

Cyfluthrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in agriculture and veterinary practice, and in the vector control of malaria (p.594).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Responsar†; Solfac.

Cyhalothrin *(BAN)*

Cihalotrina; Cyhalotryna; PP-563. (*RS*)-α-Cyano-3-phenoxybenzyl (*Z*)-(1*RS*,3*RS*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{23}H_{19}ClF_3NO_3$ = 449.9.
CAS — 68085-85-8.
ATC Vet — QP53AC06.

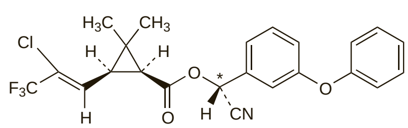

and enantioner plus epimer at c*

Profile

Cyhalothrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) that is used, particularly as a mixture of the (*Z*)-(1*R*,3*R*) *S* ester and the (*Z*)-(1*S*,3*S*) *R* ester (known as lambda-cyhalothrin), for the control of insect pests in public health. It has also been used in agriculture and in veterinary practice.

◊ References.

1. WHO. Cyhalothrin. *Environmental Health Criteria 99*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc99.htm (accessed 23/04/04)
2. WHO. Cyhalothrin and lambda-cyhalothrin health and safety guide. *IPCS Health and Safety Guide 38.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg038.htm (accessed 23/04/04)

Cymiazole

CGA-50439; CGA-192357 (cymiazole hydrochloride); Cimiazol; Cymiazol; Cymiazolum; Symiatsoli; Xymiazole. 2,4-Dimethyl-*N*-(3-methyl-2(3*H*)-thiazolylidene)benzenamine.
$C_{12}H_{14}N_2S$ = 218.3.
CAS — 61676-87-7 (cymiazole); 121034-85-3 (cymiazole hydrochloride).
ATC Vet — QP53AA02.

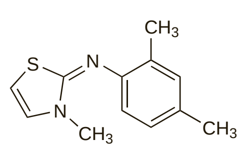

Profile

Cymiazole is a pesticide used in beekeeping.

Cypermethrin *(BAN)*

Cipermetrina; Cypermetryna; NRDC-149. (*RS*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Cl_2NO_3$ = 416.3.
CAS — 52315-07-8.
ATC — P03BA02.
ATC Vet — QP53AC08.

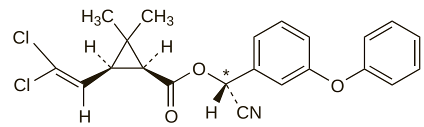

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Alpha-cypermethrin *(BAN)*

Alfacipermetrina. (*SR*)-α-Cyano-3-phenoxybenzyl (1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
$C_{22}H_{19}Cl_2NO_3$ = 416.3.
CAS — 67375-30-8.

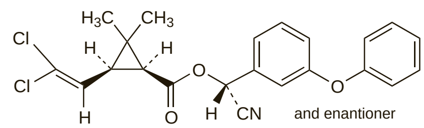

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Profile

Cypermethrin, an isomeric mixture containing alpha-cypermethrin, is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in veterinary practice as a topical ectoparasiticide and to control sea-lice infestation in salmon. It is used in agriculture. Zeta-cypermethrin is also used. Alpha-cypermethrin is used in agriculture and for vector control in the management of malaria (p.594).

◊ References.

1. WHO. Cypermethrin. *Environmental Health Criteria 82.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc82.htm (accessed 23/04/04)
2. WHO. Cypermethrin health and safety guide. *IPCS Health and Safety Guide 22.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg022.htm (accessed 23/04/04)
3. WHO. Alpha-cypermethrin. *Environmental Health Criteria 142.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc142.htm (accessed 23/04/04)

Cyromazine *(BAN, rINN)*

CGA-72662; Ciromazina; Cyromazinum. *N*-Cyclopropyl-1,3,5-triazine-2,4,6-triamine.
Циромазин
$C_6H_{10}N_6$ = 166.2.
CAS — 66215-27-8.

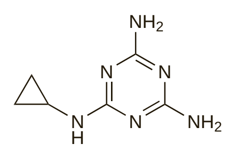

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Cyromazine). A white or off-white, odourless, crystalline powder. Slightly soluble in water and in methyl alcohol.

Profile

Cyromazine is used as a topical ectoparasiticide in veterinary practice.

Cythioate *(BAN)*

Citioato. *O,O*-Dimethyl *O*-(4-sulphamoylphenyl) phosphorothioate.
$C_8H_{12}NO_5PS_2$ = 297.3.
CAS — 115-93-5.
ATC Vet — QP53AF10; QP53BB01.

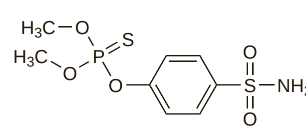

Profile

Cythioate is an organophosphorus insecticide (p.2047) used as a systemic ectoparasiticide in veterinary practice; it is given orally to the host animal.

Daminozide

Daminozida. *N*-Dimethylaminosuccinamic acid.

$C_6H_{12}N_2O_3$ = 160.2.

CAS — 1596-84-5.

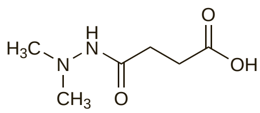

Profile

Daminozide is a plant growth regulator that has been used in pesticides to improve fruit crops. There have been concerns about residues of the chemical in the fruit.

Deltamethrin (BAN)

Decamethrin; Deltamethrinum; Deltametriini; Deltametrin; Deltametrina; Deltametryna; NRDC-161. (*S*)-α-Cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate.

$C_{22}H_{19}Br_2NO_3$ = 505.2.

CAS — 52918-63-5.

ATC — P03BA03.

ATC Vet — QP53AC11.

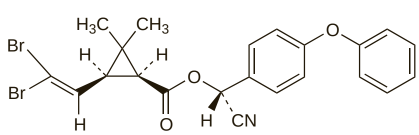

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Deltamethrin). A white to buff-coloured crystalline powder. Insoluble in water; soluble in alcohol and in acetone.

Profile

Deltamethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in the vector control of malaria (p.594). It is also used as a topical ectoparasiticide in veterinary practice and as an agricultural and household insecticide.

◊ References.

1. WHO. Deltamethrin health and safety guide. *IPCS Health and Safety Guide 30*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg030.htm (accessed 26/04/04)
2. WHO. Deltamethrin. *Environmental Health Criteria 97*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc97.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Del-Lend†; Deltacid; Deltalab; Deltamitren†; Deltapio†; Deltasay†; Deotrin; Hexafen†; Neolend†; Pediderm; Sifdel†; ***Fr.:*** Cinq sur Cinq; Pharmavoyage Moustiquaires; ***Mex.:*** Difexon†; ***Venez.:*** Nopucid.

Multi-ingredient: ***Arg.:*** Capitis†; Deca-Scab†; Hexa-Defital NF; Nopucid Compuesto; ***Braz.:*** Deltacid Plus; ***Chile:*** Launol.

Dibromochloropropane

Dibromocloropropano. 1,2-Dibromo-3-chloropropane.

$C_3H_5Br_2Cl$ = 236.3.

CAS — 96-12-8.

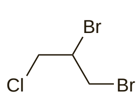

Profile

Dibromochloropropane has been used as a pesticide. Low sperm counts and evidence of testicular damage have occurred in workers exposed to dibromochloropropane.

Dibutyl Phthalate

Butyl Phthalate; DBP; Dibutil-ftalát; Dibutilo ftalatas; Dibutilo, ftalato de; Dibutyle, phtalate de; Dibutylftalat; Dibutyl-ftalát; Dibutylis phthalas; Dibutylu ftalan; Dibutyyliftalaatti. Dibutyl benzene-1,2-dicarboxylate.

$C_{16}H_{22}O_4$ = 278.3.

CAS — 84-74-2.

ATC — P03BX03.

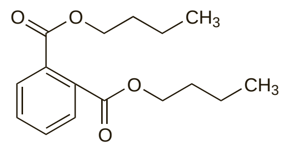

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Dibutyl Phthalate). A clear, oily, colourless or very slightly yellow liquid. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 26 (Dibutyl Phthalate). A clear, oily, colourless or very slightly yellow liquid. Practically insoluble in water; miscible with alcohol and with ether. Store in airtight containers.

Adverse Effects and Precautions

Dibutyl phthalate has occasionally caused hypersensitivity reactions. As with other phthalates contact with plastics should be avoided.

Uses and Administration

Dibutyl phthalate has been used as an insect repellent although it is slightly less effective than dimethyl phthalate (p.2041). It is less volatile and less easily removed by washing than dimethyl phthalate, and its chief use therefore has been for the impregnation of clothing.

Dibutyl phthalate has also been used as a plasticiser.

◊ References.

1. WHO. Di-*n*-butyl phthalate. *Environmental Health Criteria 189*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc189.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Mylol†.

Dichlorophenoxyacetic Acid

2,4-D; Diclorofenoxiacético, ácido. 2,4-Dichlorophenoxyacetic acid.

$C_8H_6Cl_2O_3$ = 221.0.

CAS — 94-75-7.

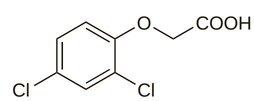

Adverse Effects, Treatment, and Precautions

Most cases of poisoning with dichlorophenoxyacetic acid have involved its ingestion with other herbicides; the solvent may also play a part in any toxicity. There is little pattern to the range of adverse effects that may occur after ingestion, inhalation, or topical exposure.

Adverse effects have involved the CNS and peripheral nervous system, muscles, and the cardiovascular system. Gastrointestinal effects are common with poisoning. Hepatotoxicity, nephrotoxicity, and pulmonary disorders have occurred but it is not clear that dichlorophenoxyacetic acid contributed to the toxicity. The role of phenoxyacetic acids in cancer is discussed under trichlorophenoxyacetic acid (p.2051).

Activated charcoal or possibly gastric lavage should be considered after ingestion of substantial amounts if the patient presents within 1 hour. Contaminated clothing should be removed and the skin washed with soap and water. Forced alkaline diuresis or haemodialysis have been reported to be effective in removing dichlorophenoxyacetic acid; the latter is considered more effective. Further treatment is symptomatic.

◊ References.

1. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D). *Environmental Health Criteria 29*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc29.htm (accessed 26/04/04)
2. WHO. 2,4-Dichlorophenoxyacetic (2,4-D) health and safety guide. *IPCS Health and Safety Guide 5*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg005.htm (accessed 26/04/04)
3. WHO. 2,4-Dichlorophenoxyacetic acid (2,4-D)—environmental aspects. *Environmental Health Criteria 84*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc84.htm (accessed 26/04/04)
4. Bradberry SM, *et al.* Mechanisms of toxicology, clinical features, and management of acute chlorophenoxy herbicide poisoning: a review. *J Toxicol Clin Toxicol* 2000; **38:** 111–22.

Uses

Dichlorophenoxyacetic acid is a herbicide widely used for weed control in cereals and other crops. It is usually used as its salts or esters with other herbicides.

Dichlorvos (BAN, USAN, rINN)

DDVP; Dichlorfos; Dichlorvosum; Diclorvós; NSC-6738; OMS-14; SD-1750. 2,2-Dichlorovinyl dimethyl phosphate.

Дихлорвос

$C_4H_7Cl_2O_4P$ = 221.0.

CAS — 62-73-7.

ATC Vet — QP52AB03; QP53AF04.

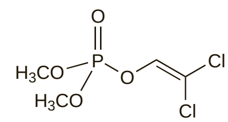

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Dichlorvos is an organophosphorus insecticide (p.2047) of short persistence, effective against a wide range of insects. It is sometimes used as a fumigant. It has been used for the extermination of insects in aircraft (disinsection). It is also used as a topical ectoparasiticide and as an anthelmintic in veterinary practice. Concern has been expressed over its possible carcinogenicity.

◊ References.

1. WHO. Dichlorvos health and safety guide. *IPCS Health and Safety Guide 18*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg018.htm (accessed 26/04/04)
2. WHO. Dichlorvos. *Environmental Health Criteria 79*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc79.htm (accessed 26/04/04)
3. Van Maele-Fabry G, *et al.* Dichlorvos and carcinogenicity: a systematic approach to a regulatory decision. *Regul Toxicol Pharmacol* 2000; **31:** 13–21.
4. Ishmael J, *et al.* Dichlorvos—a comprehensive review of 11 rodent carcinogenicity studies. *Regul Toxicol Pharmacol* 2006; **44:** 238–48.
5. Booth ED, *et al.* Review of the in vitro and in vivo genotoxicity of dichlorvos. *Regul Toxicol Pharmacol* 2007; **49:** 316–26.

Dieldrin (BAN, pINN)

Dieldrina; Dieldrine; Dieldrinum; Dieldryna.

Диэлдрин

CAS — 60-57-1 (HEOD).

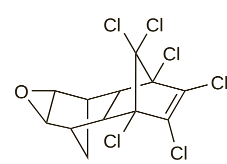

(HEOD)

Description. Dieldrin contains about 85% of (1*R*,4*S*,5*S*,8*R*)-1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4:5,8-dimethanonaphthalene (HEOD), $C_{12}H_8Cl_6O$ = 380.9. The remaining 15% is mainly chlorinated organic compounds related to HEOD.

Adverse Effects and Treatment

As for Chlorinated Insecticides, p.2037.

Dieldrin is more toxic than clofenotane (p.2038) and is readily absorbed through the skin.

◊ References.

1. WHO. Aldrin and dieldrin. *Environmental Health Criteria 91*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc91.htm (accessed 26/04/04)
2. WHO. Aldrin and dieldrin health and safety guide. *IPCS Health and Safety Guide 21*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg021.htm (accessed 26/04/04)
3. Høyer AP, *et al.* Organochlorine exposure and risk of breast cancer. *Lancet* 1998; **352:** 1816–20.
4. Jorgenson JL. Aldrin and dieldrin: a review of research on their production, environmental deposition and fate, bioaccumulation, toxicology, and epidemiology in the United States. *Environ Health Perspect* 2001; **109** (suppl 1): 113–39.

Uses

Dieldrin is a chlorinated insecticide (p.2037) formerly used as a sheepdip. Its use is now limited to a few specified purposes such as termite control.

Diethyltoluamide *(BAN, rINN)*

DEET; *N,N*-Diethyl-3-methylbenzamide; Diéthyltoluamide; Diethyltoluamidum; Dietiltoluamida; Dietiltoluamida. *NN*-Diethyl-*m*-toluamide.

Диэтилтолуамид

$C_{12}H_{17}NO$ = 191.3.
CAS — 134-62-3.
ATC — P03BX01.
ATC Vet — QP53GX01.

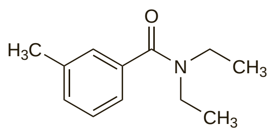

Pharmacopoeias. In *Int.* and *US.*

USP 31 (Diethyltoluamide). A colourless liquid with a faint pleasant odour. Practically insoluble in water and in glycerol; miscible with alcohol, with carbon disulfide, with chloroform, with ether, and with isopropyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

Occasional hypersensitivity to diethyltoluamide has been reported. Diethyltoluamide should not be applied near the eyes, to mucous membranes, to broken skin, or to areas of skin flexion, as irritation or blistering may occur. Systemic toxicity has been reported after application of large topical doses, particularly in children.

◊ Hypersensitivity and anaphylaxis has been described in a patient after exposure to diethyltoluamide.[1] Toxic encephalopathy has been noted in children given liberal applications of this compound;[2] seizures have also been reported,[3] and there have been cases of manic psychosis[4] and cardiovascular toxicity (sinus bradycardia and orthostatic hypotension)[5] associated with topical application. An assessment[6] of both published and unpublished data concluded that there had been remarkably few problems considering the widespread use of diethyltoluamide and that the encephalopathy in children had not been substantiated by detailed surveillance; however, another case analysis[7] did find an association with encephalopathy in children.

Toxic reactions, including death, have been reported after the ingestion of large amounts of diethyltoluamide-containing insect repellents.[8]

1. Miller JD. Anaphylaxis associated with insect repellent. *N Engl J Med* 1982; **307:** 1341–2.
2. Roland EH, *et al.* Toxic encephalopathy in a child after brief exposure to insect repellents. *Can Med Assoc J* 1985; **132:** 155–6.
3. Anonymous. Seizures temporally associated with use of DEET insect repellent—New York and Connecticut. *Arch Dermatol* 1989; **125:** 1619–20.
4. Snyder JW, *et al.* Acute manic psychosis following the dermal application of N,N-diethyl-m-toluamide (DEET) in an adult. *J Toxicol Clin Toxicol* 1986; **24:** 429–39.
5. Clem JR, *et al.* Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult. *Ann Pharmacother* 1993; **27:** 289–93.
6. Goodyer L, Behrens RH. Short report: the safety and toxicity of insect repellents. *Am J Trop Med Hyg* 1998; **59:** 323–4.
7. Briassoulis G, *et al.* Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children. *Hum Exp Toxicol* 2001; **20:** 8–14.
8. Tenenbein M. Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents. *JAMA* 1987; **258:** 1509–11.

Uses

Diethyltoluamide is an insect repellent that is effective against mosquitoes as well as blackflies, harvest-bugs or chiggers, midges, ticks, and fleas. It is considered to be of value for personal protection against malaria (p.594). It has also been used as a repellent against leeches. It may be applied to skin and clothing.

Preparations

USP 31: Diethyltoluamide Topical Solution.

Proprietary Preparations (details are given in Part 3)

Austral.: Apex Repel Super; ***Belg.:*** Mouskito Tropical; ***Canad.:*** Bens†; Bug zzz Away†; Cutter†; Deep Woods OFF†; Konk†; Muskol†; Off; Off Skintastic; Ungava; ***Fr.:*** Insect Ecran; Item Antipoux; ***NZ:*** Apex Repel Super; ***S.Afr.:*** Mylol†; ***UK:*** Bens; Jungle Formula Insect Repellent; Mijex.

Multi-ingredient: ***Arg.:*** Standard XXI; ***Austral.:*** Apex Repel Super; Apex Repel Ultra; ***Belg.:*** Mouskito Sun; Mouskito Travel Milk; Mouskito Travel Stick; ***Canad.:*** Coppertone Bug & Sunblock†; Muskol with Sunblock†; Off Skintastic with Sunscreen†; ***Fr.:*** Mousticologne; Moustidose Adult et Enfant; Tiq'Aouta; ***Hong Kong:*** Pellit†; ***Israel:*** Yatushan Plus†; ***Ital.:*** Esoklin; Sinezan; ***Jpn:*** Una Repellent; ***NZ:*** Apex Repel Super; Apex Repel Ultra; ***S.Afr.:*** Mylol†; No-Bite†; ***Thai.:*** Pellit†.

Difenacoum

Difenacum. 3-(3-Biphenyl-4-yl-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxycoumarin.

$C_{31}H_{24}O_3$ = 444.5.
CAS — 56073-07-5.

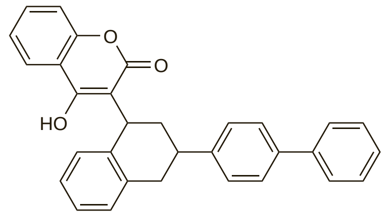

Profile

Difenacoum is an anticoagulant rodenticide.

◊ References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)
2. WHO. Difenacoum health and safety guide. *IPCS Health and Safety Guide 95.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg095.htm (accessed 26/04/04)

Toxicity. Difenacoum, a second-generation anticoagulant rodenticide inhibits prothrombin synthesis to cause bleeding that may be occult.[1] It is absorbed from the gastrointestinal tract; dermal absorption is possible. Poisons containing 100 mg in each kg of bait are not hazardous to man; more concentrated forms are particularly hazardous and their availability should be restricted. Baits, which should be prepared only by trained personnel, should contain a suitable marker-dye.

There have been reports of poisoning with difenacoum.[2-4]

1. WHO. Safe use of pesticides: ninth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 720* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_720.pdf (accessed 21/07/08)
2. Barlow AM, *et al.* Difenacoum (Neosorexa) poisoning. *BMJ* 1982; **285:** 541.
3. Butcher GP, *et al.* Difenacoum poisoning as a cause of haematuria. *Hum Exp Toxicol* 1992; **11:** 553–4.
4. McCarthy PT, *et al.* Covert poisoning with difenacoum: clinical and toxicological observations. *Hum Exp Toxicol* 1997; **16:** 166–70.

Diflubenzuron

1-(4-Chlorophenyl)-3-(2,6-difluorobenzoyl)urea.

$C_{14}H_9ClF_2N_2O_2$ = 310.7.
CAS — 35367-38-5.
ATC Vet — QP53BC02.

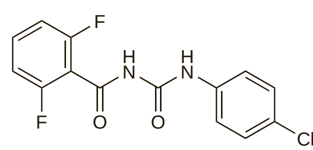

Profile

Diflubenzuron is an insecticide and larvicide that acts as a growth regulator by interfering with the formation of cuticle. It is used in agriculture and for the control of disease vectors.

Diflubenzuron possesses residual activity against mosquito larvae.

◊ References.

1. WHO. Diflubenzuron. health and safety guide. *IPCS Health and Safety Guide 99.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg099.htm (accessed 26/04/04)
2. WHO. Diflubenzuron. *Environmental Health Criteria 184.* Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc184.htm (accessed 26/04/04)

Dimethoate

Dimetoato; Fosfamid. *O,O*-Dimethyl *S*-methylcarbamoylmethyl phosphorodithioate.

$C_5H_{12}NO_3PS_2$ = 229.3.
CAS — 60-51-5.

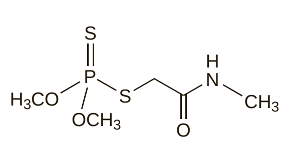

Profile

Dimethoate is an organophosphorus insecticide (p.2047) used in agriculture.

◊ References.

1. WHO. Dimethoate health and safety guide. *IPCS Health and Safety Guide 20.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg020.htm (accessed 28/05/04)
2. WHO. Dimethoate. *Environmental Health Criteria 90.* Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc90.htm (accessed 28/05/04)
3. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; **9:** 49–51.
4. Hoffmann U, Papendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; **32:** 464–8.

Dimethyl Phthalate

Dimetilo, ftalato de; DMP; Methyl Phthalate. Dimethyl benzene-1,2-dicarboxylate.

$C_{10}H_{10}O_4$ = 194.2.
CAS — 131-11-3.
ATC — P03BX02.
ATC Vet — QP53GX02.

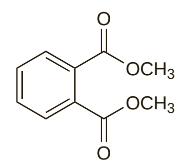

Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Dimethyl Phthalate). A colourless or faintly coloured liquid, odourless or almost odourless. Slightly soluble in water; miscible with alcohol, with ether, and with most organic solvents.

Adverse Effects and Precautions

Dimethyl phthalate may cause temporary smarting and should not be applied near the eyes or to mucous membranes. As with other phthalates contact with plastics should be avoided.

Uses

Dimethyl phthalate is an insect repellent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** SVR Creme Antimoustique†; Tiq'Aouta; ***Hong Kong:*** Pellit†; ***Hung.:*** Novascabin; ***Israel:*** Yatushan Plus†; ***S.Afr.:*** Mylol†; ***Thai.:*** Pellit†.

Dimpylate *(BAN, rINN)*

Diazinon; Diazynon; Dimpilato; Dimpylaatti; Dimpylat; Dimpylatum. *O,O*-Diethyl *O*-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate.

Димпилат

$C_{12}H_{21}N_2O_3PS$ = 304.3.
CAS — 333-41-5.
ATC Vet — QP53AF03.

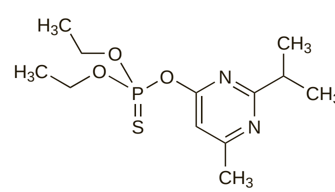

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Dimpylate). A clear, yellowish-brown, slightly viscous liquid. Practically insoluble in water; miscible with alcohol, with ether, and with most organic solvents.

Profile

Dimpylate is an organophosphorus insecticide (p.2047) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It is also used as an insecticide in agriculture and horticulture.

◊ References.

1. Wagner SL, Orwick DL. Chronic organophosphate exposure associated with transient hypertonia in an infant. *Pediatrics* 1994; **94:** 94–7.

Dinitro-o-cresol

DNOC. 4,6-Dinitro-o-cresol.

$C_7H_6N_2O_5$ = 198.1.

CAS — 534-52-1.

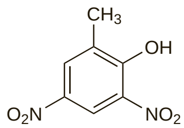

Profile

Dinitro-*o*-cresol is a dinitrophenol formerly used as an insecticide and herbicide. It increases metabolism by uncoupling oxidative phosphorylation and was also formerly used in obesity. Fatal poisoning has occurred.

◊ References.

1. WHO. Dinitro-ortho-cresol. *Environmental Health Criteria 220.* Geneva: WHO, 2000. Available at: http://www.inchem.org/documents/ehc/ehc/ehc220.htm (accessed 26/04/04)

Dinitrophenol

Dinitrofenol. 2,4-Dinitrophenol.

$C_6H_4N_2O_5$ = 184.1.

CAS — 51-28-5.

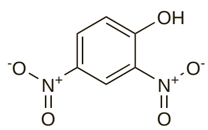

Profile

Dinitrophenol has been used as a herbicide. Since dinitrophenol increases metabolism by uncoupling oxidative phosphorylation it was formerly used in the treatment of obesity. Fatal poisoning has occurred.

Dioctyl Adipate

DEHA; Di-(2-ethylhexyl)adipate; Dioctilo, adipato de.

$C_{22}H_{42}O_4$ = 370.6.

Profile

Dioctyl adipate is used as an insect repellent. It is also used as a plasticiser by the plastics industry; concern about the migration of this and other plasticisers into foodstuffs from polythene films used to wrap them ('cling film') have led to its use at lower concentrations.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Protec.

Dioxation *(BAN, rINN)*

Dioxathion; Dioxatión; Dioxationum. It consists mainly of *cis* and *trans* isomers of *S,S*′-1,4-dioxan-2,3-diyl bis(*O,O*-diethyl phosphorodithioate).

Диоксатион

$C_{12}H_{26}O_6P_2S_4$ = 456.5.

CAS — 78-34-2.

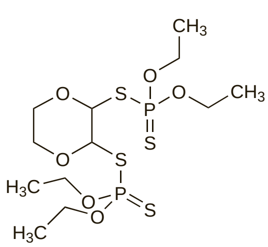

Profile

Dioxation is an organophosphorus insecticide (p.2047) that has been used in agriculture and as a topical ectoparasiticide in veterinary practice.

Diphenadione *(BAN, pINN)*

Difenadiona; Diphacinone; Diphénadione; Diphenadionum. 2-(Diphenylacetyl)indan-1,3-dione.

Дифенадион

$C_{23}H_{16}O_3$ = 340.4.

CAS — 82-66-6.

ATC — B01AA10.

ATC Vet — QB01AA10.

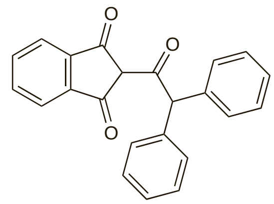

Profile

Diphenadione is used as an anticoagulant rodenticide.

Diquat Dibromide

Diquat, dibromuro de. 9,10-Dihydro-8a,10a-diazoniaphenanthrene dibromide; 1,1′-Ethylene-2,2′-bipyridyldiylium dibromide.

$C_{12}H_{12}Br_2N_2$ = 344.0.

CAS — 2764-72-9 (diquat); 85-00-7 (diquat dibromide).

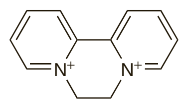

(diquat)

Profile

Diquat dibromide is a contact herbicide used in agriculture and horticulture. It has similar adverse effects to those of paraquat (p.2047).

◊ References.

1. WHO. Paraquat and diquat. *Environmental Health Criteria 39.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. WHO. Diquat health and safety guide. *IPCS Health and Safety Guide 52.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg052.htm (accessed 26/04/04)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.
4. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. *J Toxicol Clin Toxicol* 2000; **38:** 123–8.

Emamectin

Emamectina. A mixture of (4″-*R*)-5-*O*-Demethyl-4″-deoxy-4″-(methylamino)avermectin A_{1a} and (4″-*R*)-5-*O*-Demethyl-25-de(1-methylpropyl)-4″-deoxy-4″-(methylamino)-25-(1-methylethyl)avermectin A_{1a} in the ratio of 9:1.

CAS — 121124-29-6 (major component); 121424-52-0 (minor component); 137335-79-6.

ATC Vet — QP54AA06.

Profile

Emamectin is an avermectin insecticide used for the control of sea-lice infestation in salmon.

Endod

Profile

Endod is obtained from the dried fruits of *Phytolacca dodecandra* (Phytolaccaceae) and has molluscicidal properties. It has been investigated for the control of the snail vector of schistosomiasis.

Endosulfan

Endosulfán. 1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-en-2,3-ylenebismethylene sulphite.

$C_9H_6Cl_6O_3S$ = 406.9.

CAS — 115-29-7.

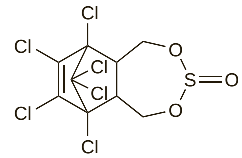

Profile

Endosulfan is a chlorinated insecticide (p.2037) used in agriculture.

◊ References.

1. WHO. Endosulfan. *Environmental Health Criteria 40.* Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc40.htm (accessed 26/04/04)
2. WHO. Endosulfan health and safety guide. *IPCS Health and Safety Guide 17.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg017.htm (accessed 26/04/04)
3. Blanco-Coronado JL, *et al.* Acute intoxication by endosulfan. *J Toxicol Clin Toxicol* 1992; **30:** 575–83.
4. Boereboom FT, *et al.* Nonaccidental endosulfan intoxication: a case report with toxicokinetic calculations and tissue concentrations. *J Toxicol Clin Toxicol* 1998; **36:** 345–52.
5. Chugh SN, *et al.* Endosulfan poisoning in Northern India: a report of 18 cases. *Int J Clin Pharmacol Ther* 1998; **36:** 474–7.
6. Venkateswarlu K, *et al.* Endosulfan poisoning—a clinical profile. *J Assoc Physicians India* 2000; **48:** 323–5.
7. Karatas AD, *et al.* Characteristics of endosulfan poisoning: a study of 23 cases. *Singapore Med J* 2006; **47:** 1030–2.
8. Bektas M, *et al.* Management of acute endosulfan poisoning in an organophosphate poisoning clinic. *Clin Toxicol* 2007; **45:** 563–4.

Endrin

Endrín; Endryna. (1*R*,4*S*,4a*S*,5*S*,6*S*,7*R*,8*R*,8a*R*)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene.

$C_{12}H_8Cl_6O$ = 380.9.

CAS — 72-20-8.

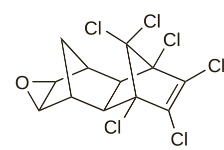

Profile

Endrin is a chlorinated insecticide (p.2037), but its use was prohibited, at least in some countries, because of toxicity and persistence in the environment.

◊ General references to endrin,[1-4] including reports of poisoning.[2,3]

1. Anonymous. Acute convulsions associated with endrin poisoning—Pakistan. *JAMA* 1985; **253:** 334–5.
2. Runhaar EA, *et al.* A case of fatal endrin poisoning. *Hum Toxicol* 1985; **4:** 241–7.
3. WHO. Endrin health and safety guide. *IPCS Health and Safety Guide 60.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg060.htm (accessed 26/04/04)
4. WHO. Endrin. *Environmental Health Criteria 130.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc130.htm (accessed 26/04/04)

Esdepallethrine

Esdepaletrina. (*S*)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)-cyclopropanecarboxylate.

$C_{19}H_{26}O_3$ = 302.4.

CAS — 28434-00-6.

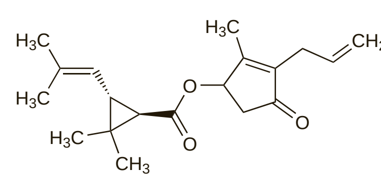

Profile

Esdepallethrine is a pyrethroid insecticide (see Pyrethrum Flower, p.2049). It is used as an acaricide with piperonyl butoxide (p.2049) in the topical treatment of scabies (p.2035).

Esdepallethrine is also used in devices and sprays to control insects, including mosquitoes.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cinq sur Cinq; Mousticologne.

Multi-ingredient: ***Arg.:*** Acardust†; ***Canad.:*** Scabene†; ***Fr.:*** A-Par; Acardust; Cinq sur Cinq; Spregal; ***Gr.:*** Spregal; ***Israel:*** Acardust; ***Neth.:*** Spregal; ***Rus.:*** Spregal (Спрегаль); ***S.Afr.:*** Spregal.

Ethion

Diethion; Etión; Etion. *O,O,O′,O′*-Tetraethyl *S,S′*-methylenediphosphorodithioate.
$C_9H_{22}O_4P_2S_4$ = 384.5.
CAS — 563-12-2.

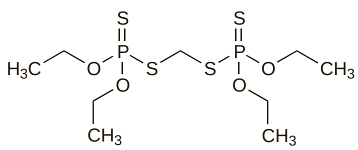

Profile

Ethion is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Ethohexadiol

Ethylhexanediol; Etohexadiol. 2-Ethylhexane-1,3-diol.
$C_8H_{18}O_2$ = 146.2.
CAS — 94-96-2.
ATC — P03BX06.
ATC Vet — QP53GX04.

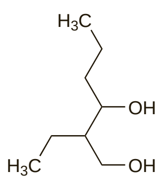

Profile

Ethohexadiol is an insect repellent. It may be applied topically to the skin and to clothing. It has been used with dimethyl phthalate.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Moustidose Adult et Enfant.

Ethyl Butylacetylaminopropionate

EBAAP; IR-3535; Merck-3535; Repellent 3535. (*N*-Butyl-*N*-acetyl)-3-ethylaminopropionate; *N*-Acetyl-*N*-butyl-beta-alanine ethyl ester; .
$C_{11}H_{21}NO_3$ = 215.3.
CAS — 52304-36-6.

Profile

Ethyl butylacetylaminopropionate is used as an insect repellent; it may be applied to the skin.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mouskito; Shampoux Repel; ***Braz.:*** Johnson's Baby Locao Anti-Mosquito; ***Fr.:*** Cinq sur Cinq; Prebutix; ***Thai.:*** Johnson's Baby Clear†; ***UK:*** Mijex Extra.

Multi-ingredient: ***Arg.:*** Standard XXI; ***Austral.:*** Apex Repel Super; Apex Repel Ultra; ***Belg.:*** Mouskito Sun; ***Fr.:*** Guep'Away†; Mousticologne; Moustidose Bebe-Nourrisson; Prebutix; ***NZ:*** Apex Repel Super; Apex Repel Ultra.

Ethylene Dibromide

EDB; Etileno, dibromuro de. 1,2-Dibromoethane.
$C_2H_4Br_2$ = 187.9.
CAS — 106-93-4.

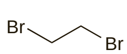

Profile

Ethylene dibromide is an insecticidal fumigant and a lead scavenger used in the petroleum industry. Its use has been restricted in certain areas because of carcinogenicity in *animals* and because of evidence of persistence in fruit and cereals that have undergone fumigation.

Ethylene dibromide is more toxic than carbon tetrachloride or ethylene dichloride. It is irritant to the eyes, skin, and mucous membranes. Inhalation leads to drowsiness, CNS depression, and possibly pulmonary oedema. Contact with the skin causes blistering and it is readily absorbed. Kidney and liver damage may occur.

◊ Reports of poisoning due to ethylene dibromide.

1. Letz GA, *et al.* Two fatalities after acute occupational exposure to ethylene dibromide. *JAMA* 1984; **252:** 2428–31.
2. Singh S, *et al.* Non-fatal ethylene dibromide ingestion. *Hum Exp Toxicol* 2000; **19:** 152–3.
3. Mehrotra P, *et al.* Two cases of ethylene dibromide poisoning. *Vet Hum Toxicol* 2001; **43:** 91–2.
4. Singh N, *et al.* Outcome of sixty four cases of ethylene dibromide ingestion treated in tertiary care hospital. *J Assoc Physicians India* 2007; **55:** 842–5.

Ethylene Dichloride

Brocide; Dutch Liquid; Etileno, dicloruro de. 1,2-Dichloroethane.
$C_2H_4Cl_2$ = 98.96.
CAS — 107-06-2.

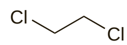

Profile

Ethylene dichloride is an insecticidal fumigant. It is also used in the petroleum industry and as an industrial solvent. Exposure to the vapour may cause lachrymation and corneal clouding, nasal irritation, and vertigo due to the depressant effect on the CNS. Contact with the skin may cause dermatitis. Kidney and liver damage, hypotension and cardiac impairment, gastrointestinal disturbances, haemorrhage, coma, and pulmonary oedema may follow absorption after inhalation, topical application, or ingestion.

Ethylene dichloride has been reported to be carcinogenic in *animals.*

◊ References.

1. WHO. 1,2 Dichloroethane. *Environmental Health Criteria 176.* Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc176.htm (accessed 06/06/06)
2. WHO. 1,2-Dichloroethane health and safety guide. *IPCS Health and Safety Guide 55.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg055.htm (accessed 26/04/04)
3. Proudfoot A, ed. Pesticide poisoning: notes for the guidance of medical practitioners. 2nd ed. London: DoH, The Stationery Office, 1996.

Etofenprox *(rINN)*

Étofenprox; Etofenproxum. α-[(*p*-Ethoxy-β,β-dimethylphenethyl)oxy]-*m*-phenoxytoluene.
Этофенпрокс
$C_{25}H_{28}O_3$ = 376.5.
CAS — 80844-07-1.

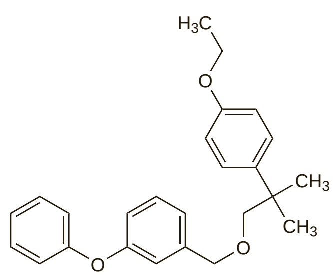

Profile

Etofenprox is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in the vector control of malaria (p.594).

Famphur

Famfur; Famophos.
$C_{10}H_{16}NO_5PS_2$ = 325.3.
CAS — 52-85-7.

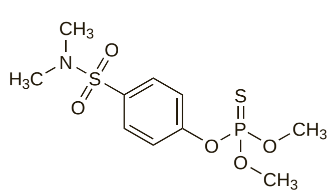

Profile

Famphur is an organophosphorus insecticide (p.2047) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal.

Fenitrothion *(BAN)*

Fenitrotión. *O,O*-Dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate.
$C_9H_{12}NO_5PS$ = 277.2.
CAS — 122-14-5.

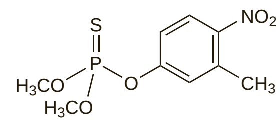

Profile

Fenitrothion is an organophosphorus insecticide (p.2047) used as a topical ectoparasiticide in veterinary practice. It is also used as an agricultural insecticide.

◊ References.

1. WHO. Fenitrothion health and safety guide. *IPCS Health and Safety Guide 65.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg065.htm (accessed 26/04/04)
2. WHO. Fenitrothion. *Environmental Health Criteria 133.* Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc133.htm (accessed 26/04/04)
3. Bouma MJ, Nesbit R. Fenitrothion intoxication during spraying operations in the malaria programme for Afghan refugees in North West Frontier Province of Pakistan. *Trop Geogr Med* 1995; **47:** 12–14.
4. Inoue S, *et al.* Prognostic factors and toxicokinetics in acute fenitrothion self-poisoning requiring intensive care. *Clin Toxicol* 2008; **46:** 528–33.

Fenthion *(BAN)*

Bayer-29493; Fentión; S-752. *O,O*-Dimethyl *O*-4-methylthio-*m*-tolyl phosphorothioate.
$C_{10}H_{15}O_3PS_2$ = 278.3.
CAS — 55-38-9.
ATC Vet — QP53BB02.

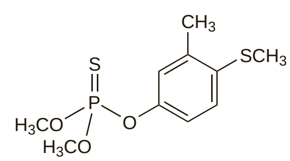

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Fenthion). A yellowish-brown oily substance. Immiscible with water; miscible with alcohol and with chloroform.

Profile

Fenthion is an organophosphorus insecticide (p.2047) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. Fenthion has also been used in agriculture.

Toxicity. Macular changes have been detected in the eyes of workers regularly exposed to fenthion.[1] It was considered that there was a need for long-term studies on subjects exposed to different organophosphorus compounds to assess their role in producing macular changes.

1. Misra UK, *et al.* Some observations on the macula of pesticide workers. *Hum Toxicol* 1985; **4:** 135–45.

Fenvalerate *(BAN)*

Fenvalerato; Fenwalerianian; OMS-2000; Pydrin; S-5602; SD-43775; WL-43775. (*RS*)-α-Cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)-3-methylbutyrate.
$C_{25}H_{22}ClNO_3$ = 419.9.
CAS — 51630-58-1.
ATC Vet — QP53AC14; QP53AX02.

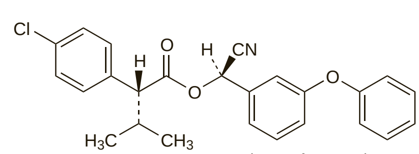

mixture of 4 stereoisomers

Profile

Fenvalerate is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used as a topical ectoparasiticide in veterinary practice. It has also been used as an insecticide in agriculture and horticulture.

Esfenvalerate, one of the stereoisomers of fenvalerate, is also used as an agricultural insecticide.

◊ References.

1. WHO. Fenvalerate health and safety guide. *IPCS Health and Safety Guide 34*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg034.htm (accessed 26/04/04)
2. WHO. Fenvalerate. *Environmental Health Criteria 95*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc95.htm (accessed 26/04/04)

Fipronil *(BAN)*

Fiproniili; Fipronilo; MB-46030; RM-1601. (*RS*)-5-Amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(trifluoromethylsulfinyl)pyrazole-3-carbonitrile.

$C_{12}H_4Cl_2F_6N_4OS$ = 437.1.

CAS — 120068-37-3.

ATC Vet — QP53AX15.

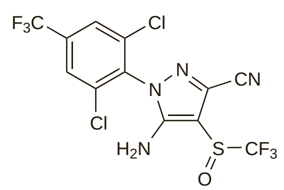

Profile

Fipronil is used as a topical ectoparasiticide in veterinary practice. It has also been investigated for the treatment of head lice.

Flocoumafen

Flocoumafene; Flocumafeno; OMS-3047. 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin.

$C_{33}H_{25}F_3O_4$ = 542.5.

CAS — 90035-08-8.

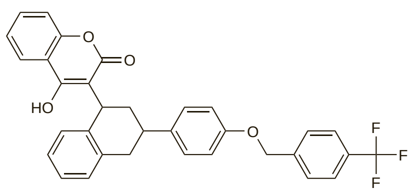

Profile

Flocoumafen is a coumarin derivative used as an anticoagulant rodenticide. It is said to be effective in rodents resistant to other anticoagulant rodenticides.

◊ References.

1. WHO. Anticoagulant rodenticides. *Environmental Health Criteria 175*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc175.htm (accessed 26/04/04)

Fluazuron *(rINN)*

CGA-157419; Fluazurón; Fluazuronum. 1-(4-Chloro-3-{[3-chloro-5-(trifluoromethyl)-2-pyridyl]oxy}phenyl)-3-(2,6-difluorobenzoyl)urea.

Флуазурон

$C_{20}H_{10}Cl_2F_5N_3O_3$ = 506.2.

CAS — 86811-58-7.

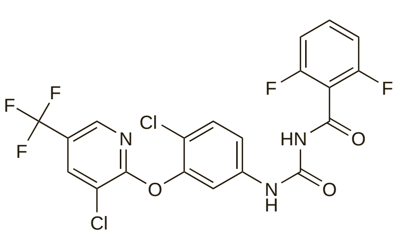

Profile

Fluazuron is used as a topical ectoparasiticide in veterinary practice.

Flumethrin *(BAN)*

Flumethrinum; Flumetriini; Flumetrin; Flumetrina. α-Cyano-4-fluoro-3-phenoxybenzyl 3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate.

$C_{28}H_{22}Cl_2FNO_3$ = 510.4.

CAS — 69770-45-2.

ATC Vet — QP53AC05.

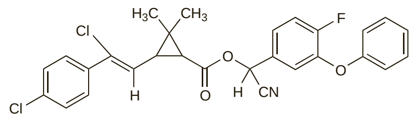

Profile

Flumethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used as a topical ectoparasiticide in veterinary practice.

◊ Reports of poisoning with flumethrin.

1. Box SA, Lee MR. A systemic reaction following exposure to a pyrethroid insecticide. *Hum Exp Toxicol* 1996; **15:** 389–90.

Fluoroacetamide

Compound 1081; Fluoroacetamida.

$FCH_2.CONH_2$ = 77.06.

CAS — 640-19-7.

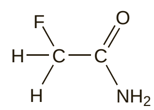

Profile

Fluoroacetamide is a rodenticide and produces adverse effects similar to those of sodium fluoroacetate (p.2050).

Fluvalinate

Fluvalinato; ZR-3210. Cyano(3-phenoxyphenyl)methyl ester of *N*-[2-chloro-4-(trifluoromethyl)phenyl]-DL-valine.

$C_{26}H_{22}ClF_3N_2O_3$ = 502.9.

CAS — 69409-94-5.

ATC Vet — QP53AC10.

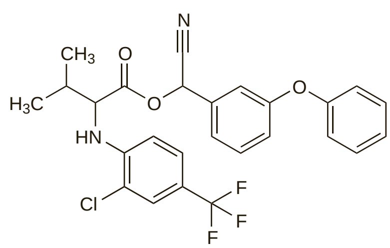

Profile

Fluvalinate is a pesticide used in beekeeping.

Glyphosate

Glifosato. *N*-(Phosphonomethyl)glycine.

$C_3H_8NO_5P$ = 169.1.

CAS — 1071-83-6.

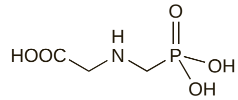

Profile

Glyphosate is used as a herbicide.

◊ References.

1. WHO. Glyphosate. *Environmental Health Criteria 159*. Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/ehc/ehc/ehc159.htm (accessed 26/04/04)

Toxicity. Reports[1-3] and reviews[4] of poisoning with glyphosate products, prognostic factors,[5] guidelines for treatment[6] have been published. The toxicity has been believed to be largely due to the inclusion of surfactants, particularly polyoxyethyleneamine, in the herbicide (Roundup) formulation but products vary considerably as to the surfactant contained and the concentration and salt of glyphosate used, and the evidence that surfactants potentiate glyphosate toxicity is unclear.[6]

1. Sawada Y, *et al.* Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. *Lancet* 1988; **i:** 299.
2. Talbot AR, *et al.* Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. *Hum Exp Toxicol* 1991; **10:** 1–8.
3. Menkes DB, *et al.* Intentional self-poisoning with glyphosate-containing herbicides. *Hum Exp Toxicol* 1991; **10:** 103–7.
4. Bradberry SM, *et al.* Glyphosate poisoning. *Toxicol Rev* 2004; **23:** 159–67.
5. Lee CH, *et al.* The early prognostic factors of glyphosate-surfactant intoxication. *Am J Emerg Med* 2008; **26:** 275–81.
6. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners.* 2nd ed. London: DoH, The Stationery Office, 1996.

Heptachlor

Heptacloro. 1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene.

$C_{10}H_5Cl_7$ = 373.3.

CAS — 76-44-8.

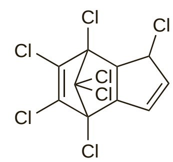

Profile

Heptachlor is a chlorinated insecticide (p.2037), but its use was prohibited, at least in some countries, because of its persistent nature.

◊ References.

1. WHO. Heptachlor. *Environmental Health Criteria 38*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc38.htm (accessed 26/04/04)
2. WHO. Heptachlor health and safety guide. *IPCS Health and Safety Guide 14*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg014.htm (accessed 26/04/04)

Heptenophos

Heptenofós; Hoe-02982. 7-Chlorobicyclo[3.2.0]hepta-2,6-dien-6-yl dimethyl phosphate.

$C_9H_{12}ClO_4P$ = 250.6.

CAS — 23560-59-0.

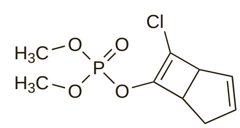

Profile

Heptenophos is an organophosphorus insecticide (p.2047) that has been used in veterinary practice for the control of ectoparasites. It is also used in agriculture.

Hexachlorobenzene

HCB; Heksachlorobenzen; Hexaclorobenceno.

C_6Cl_6 = 284.8.

CAS — 118-74-1.

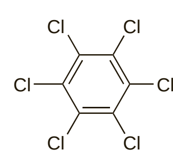

NOTE. Hexachlorobenzene should not be confused with gamma benzene hexachloride (lindane).

Profile

Hexachlorobenzene has been used as an agricultural fungicide. It is not biodegradable to any significant extent and hexachlorobenzene residues in food have arisen as a result of its occurrence in industrial wastes as well as its use as a fungicide; its use is banned in some countries.

Hexachlorobenzene is reported to be distributed into breast milk.

◊ References.

1. WHO. Hexachlorobenzene. *Environmental Health Criteria 195*. Geneva: WHO, 1997. Available at: http://www.inchem.org/documents/ehc/ehc/ehc195.htm (accessed 26/04/04)
2. WHO. Hexachlorobenzene health and safety guide. *IPCS Health and Safety Guide 107*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg107.htm (accessed 26/04/04)

Toxicity. Porphyria cutanea tarda[1] and parkinsonism[2] have both been reported in subjects who had ingested seed crops treated with hexachlorobenzene. In a further report the symptoms of porphyria in some patients have been said to persist for many years.[3]

1. Cam C, Nigogosyan G. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. *JAMA* 1963; **183:** 88–91.
2. Chapman LJ, *et al.* Parkinsonism and industrial chemicals. *Lancet* 1987; **i:** 332–3.
3. Cripps DJ, *et al.* Porphyria turcica due to hexachlorobenzene: a 20 to 30 year follow-up study on 204 patients. *Br J Dermatol* 1984; **111:** 413–22.

Hydrocyanic Acid

Cianhídrico, ácido; Prussic Acid.

CAS — 74-90-8.

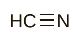

Description. Hydrocyanic acid is an aqueous solution containing hydrogen cyanide, HCN = 27.03. A colourless liquid with a characteristic almond odour.

Adverse Effects and Precautions

Hydrocyanic acid and its vapour are intensely poisonous. Cyanides interfere with the oxygen uptake of cells by inhibition of cytochrome oxidase, an enzyme necessary for cellular oxygen transport.

Poisoning by cyanides may occur from inhalation of the vapour, ingestion, or absorption through the skin. Poisoning may arise from cyanide pesticides, industrial accidental exposure, or the inhalation of fumes from some burning plastics. Poisoning may also occur from cyanide-containing plants or fruits.

When large doses of hydrocyanic acid are taken, unconsciousness occurs within a few seconds and death within a few minutes. With smaller toxic doses the symptoms, which occur within a few minutes, may include constriction of the throat, nausea, vomiting, giddiness, headache, palpitation, hyperpnoea then dyspnoea, bradycardia (although initially there may be tachycardia), unconsciousness, and violent convulsions, followed by death. The characteristic smell of bitter almonds may not be obvious and not all individuals can detect it. Cyanosis is not prominent. Similar but usually slower effects occur with cyanide salts.

The fatal dose of hydrocyanic acid for man is considered to be about 50 mg and of the cyanides about 250 mg.

Treatment of Adverse Effects

Treatment must be given rapidly but should not involve the use of antidotes unless it is certain that cyanide has been absorbed and poisoning is severe.

Cyanide is absorbed very rapidly on inhalation and the poisoned patient should be removed from the area and given oxygen. Steps should be taken to ensure that the airway is adequate. Contaminated clothing should be removed and skin washed. If the patient is conscious, amyl nitrite may be inhaled for up to 30 seconds in every minute but the value of this practice is questionable. Should the patient be unconscious or nearly so, then in the UK and some other countries it is the practice to give dicobalt edetate (p.1443) by injection since it forms a stable complex with the cyanide ion. However, cyanide poisoning should be confirmed, as absence of cyanide puts the patient at risk from the adverse effects of dicobalt edetate. The recommended dose of dicobalt edetate is 300 mg given intravenously over about 1 to 5 minutes, depending on the severity of the poisoning, and repeated once or twice depending on the response. It is customary to give 50 mL of glucose 50% intravenously after each injection. In the USA cyanide antidote kits containing amyl nitrite, sodium nitrite, and sodium thiosulfate are available. After the use of inhaled amyl nitrite, 10 mL of sodium nitrite injection (3%) is given intravenously over 5 to 20 minutes, then, using the same needle and vein, an injection of 12.5 g of sodium thiosulfate (50 mL of a 25% solution or 25 mL of a 50% solution) is given over a period of about 10 minutes. The nitrite components from amyl nitrite and sodium nitrite convert haemoglobin to methaemoglobin which competes with cytochrome oxidase for cyanide, with the formation of cyanmethaemoglobin; sodium thiosulfate acts as a sulfur donor and aids the conversion or inactivation of cyanide from cyanmethaemoglobin to thiocyanate. If toxic symptoms recur, the injections of nitrite and thiosulfate may be repeated at half the initial doses. Appropriate measures should be instituted to correct hypotension and acidosis. The methaemoglobinaemia induced by the nitrites in the antidote kits can be dangerous and fatalities have been reported.

Hydroxocobalamin may be used for the management of cyanide toxicity. The usual dose is 70 mg/kg by intravenous infusion, repeated once or twice according to severity. Alternatively, hydroxocobalamin 5 g may be given by intravenous infusion over 15 minutes, followed if necessary by a second dose of 5 g intravenously, infused over 15 minutes to 2 hours.

If cyanide has been ingested, one of the above procedures should be used. Activated charcoal or gastric lavage may be considered if the patient presents within 1 hour.

◊ Some references concerning the management of cyanide poisoning.[1-4] The use of solutions A and B (15.8% ferrous sulfate in 0.3% citric acid, and 6% sodium carbonate respectively) as so called oral antidotes in persons exposed to cyanide has been condemned as ineffective and lacking scientific evidence.[2]

1. Langford RM, Armstrong RF. Algorithm for managing injury from smoke inhalation. *BMJ* 1989; **299:** 902–5.
2. Koizumi A. Fighting myths. *Lancet* 1994; **344:** 559–60.
3. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
4. Geller RJ, *et al.* Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics* 2006; **118:** 2146–58.

Uses

Cyanides have various industrial applications. Hydrocyanic acid and cyanide salts produce hydrogen cyanide, which has been used as a gas for the eradication of rabbits, rodents, and some other pests. Cyanide salts that might be encountered include calcium cyanide, mercuric cyanide, potassium cyanide, potassium ferricyanide, potassium sodium cyanide, and sodium cyanide.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Oftalmol Ocular.

Imidacloprid

Bay-NTN-33893. 1-[(6-Chloro-3-pyridinyl)methyl]-4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine.

$C_9H_{10}ClN_5O_2$ = 255.7.

CAS — 105827-78-9; 138261-41-3.

ATC Vet — QP53AX17.

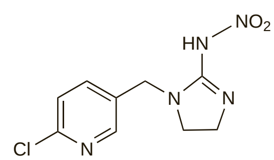

Profile

Imidacloprid is used as a topical ectoparasiticide in veterinary practice, and as an insecticide in agriculture. It has also been investigated for use in the treatment of head lice.

Iodofenphos *(BAN)*

Iodofenfós; Jodfenphos. *O*-2,5-Dichloro-4-iodophenyl *O,O*-dimethyl phosphorothioate.

$C_8H_8Cl_2IO_3PS$ = 413.0.

CAS — 18181-70-9.

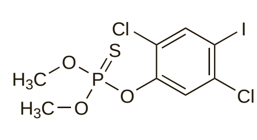

Profile

Iodofenphos is an organophosphorus insecticide (p.2047) used in veterinary practice for the control of ectoparasites in the environment. It has also been used as an agricultural insecticide. It is an effective mosquito larvicide.

Iodopropynyl Butyl Carbamate

3-Iodo-2-propynyl-*N*-butyl carbamate.

$C_8H_{12}INO_2$ = 281.1.

CAS — 55406-53-6.

Profile

Iodopropynyl butyl carbamate is a carbamate pesticide (p.2037). It is used as a preservative in cosmetic preparations; contact sensitisation has been reported. It is also used as a wood preservative.

◊ References.

1. Bryld LE, *et al.* Iodopropynyl butylcarbamate: a new contact allergen. *Contact Dermatitis* 1997; **36:** 156–8.
2. Badreshia S, Marks JG. Iodopropynyl butylcarbamate. *Am J Contact Dermat* 2002; **13:** 77–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Irl.: Saliker†.

Multi-ingredient: ***Arg.:*** Pityval†; Saliker†; ***Braz.:*** Effaclar; Pityval; Saliker; ***Fr.:*** Effaclar; Pityval; Saliker†; ***Irl.:*** Effaclar; Effaclar AI; Effaclar K.

Lindane *(BAN, USAN, rINN)*

666; Benhexachlor; Gamma Benzene Hexachloride; Gamma-BHC; Gamma-HCH; HCH; Hexicide; Lindaani; Lindán; Lindan; Lindanas; Lindano; Lindanum. 1α,2α,3β,4α,5α,6β-Hexachlorocyclohexane.

Линдан

$C_6H_6Cl_6$ = 290.8.

CAS — 58-89-9.

ATC — P03AB02.

ATC Vet — QP53AB02; QS02QA01.

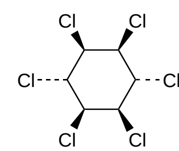

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Lindane). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. Protect from light.

USP 31 (Lindane). A white, crystalline powder with a slight musty odour. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in chloroform; sparingly soluble in ether; slightly soluble in ethylene glycol.

Adverse Effects, Treatment, and Precautions

As for Chlorinated Insecticides, p.2037.

Serious adverse effects, including seizures and deaths, have been reported in patients who have used higher than recommended concentrations of lindane, or after a second application of lindane to the skin in the treatment of scabies and pediculosis: lindane should not be used as a first-line treatment in the management of the latter conditions. Babies, children, the elderly and people weighing less than 50 kg are considered to be particularly at risk. Lindane should not be used in patients who have a body-weight less than 50 kg, a history of epilepsy, have open or crusted sores on the skin around the head and neck or broken skin around the treatment areas, or skin conditions such as psoriasis or atopic dermatitis. Lindane is excreted into the breast milk but the amount excreted is not considered to be clinically significant; breastfeeding should, however, be avoided for at least 4 days after stopping treatment. There is limited human data on the use of lindane in pregnancy and *animal* data indicate a low risk for congenital defects, but because of its serious toxic potential safer alternative products are recommended.

◊ Seizures have been reported after the topical use of lindane.[1] In reply, one of the manufacturers stated that up to the end of 1983 they were aware of 21 cases of convulsive disorders apparently associated with the use of their product; it had been used by over 40 million people. Of the 21 cases, the seizures were definitely or probably caused by the product in 11, but in 9 the seizures were associated with ingestion or excessive use.[2] From 1998 to 2003, 870 cases of unintentional lindane ingestion were reported in the USA.[3] Signs and symptoms of illness after ingestion included abdominal cramps, confusion, cough, headache, nausea, oral irritation, seizures, and vomiting.

Isolated reports of adverse effects associated with lindane include disseminated intravascular coagulation and subsequent death after oral ingestion[4] and aplastic anaemia after prolonged topical exposure (twice daily application for 3 weeks).[5]

1. Etherington JD. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; **289:** 228.
2. Kelly VT. Major epileptic seizures and topical gammabenzene hexachloride. *BMJ* 1984; **289:** 837.
3. CDC. Unintentional topical lindane ingestions—United States, 1998–2003. *MMWR* 2005; **54:** 533–5. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5421a2.htm (accessed 22/04/08)
4. Rao CVSR, *et al.* Disseminated intravascular coagulation in a case of fatal lindane poisoning. *Vet Hum Toxicol* 1988; **30:** 132–4.
5. Rauch AE, *et al.* Lindane (Kwell)-induced aplastic anemia. *Arch Intern Med* 1990; **150:** 2393–5.

Uses and Administration

Lindane is a chlorinated insecticide (p.2037). It has been used topically in a concentration of 1% for scabies (p.2035) in selected patients and has also been used in pediculosis (p.2034), but use for head lice is restricted by resistance.

The symbol † denotes a preparation no longer actively marketed

Lindane has been used for the control of disease vectors including mosquitoes, lice, and fleas, but resistance has developed. It has also been used as an agricultural and a horticultural insecticide, but its use is prohibited or restricted in many countries.

◊ References.

1. WHO. Lindane. *Environmental Health Criteria 124*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc124.htm (accessed 26/04/04)
2. WHO. Lindane health and safety guide. *IPCS Health and Safety Guide 54*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg054.htm (accessed 26/04/04)

Preparations

USP 31: Lindane Cream; Lindane Lotion; Lindane Shampoo.

Proprietary Preparations (details are given in Part 3)
Arg.: Gamma-Scab; Hexa-Defital; ***Austria:*** Jacutin; ***Braz.:*** Escabron†; Pediletan; Pilensar; ***Canad.:*** Hexit; ***Chile:*** Plomurol; Scabexyl†; ***Cz.:*** Jacutin†; Skabicid†; ***Fr.:*** Scabecid†; ***Ger.:*** Delitex N; InfectoPedicul; Jacutin; ***Hung.:*** Jacutin; ***India:*** Ascabiol; Gab; Nit-N-Mite; Scaboma; ***Indon.:*** Obat Kutu Rambut Cap Dua Jempol; ***Irl.:*** Quellada†; ***Israel:*** Bicide; ***Malaysia:*** Jacutin; ***Mex.:*** Herklin; ***NZ:*** Benhex; ***Pol.:*** Jacutin; ***Port.:*** Musside†; Sarcoderma†; ***S.Afr.:*** Gambex; Quellada†; ***Singapore:*** Jacutin; ***Switz.:*** Jacutin; ***Thai.:*** Jacutin; ***Venez.:*** Demar†; Somergan.

Multi-ingredient: ***Arg.:*** Gamma-Scab; Hexa-Defital; Lyndan; ***Fr.:*** Elenol; ***India:*** Emscab; Nit-N-Mite†; Scabine; Scaboma; Scarab; ***Indon.:*** Scabicid; Topicide; ***Mex.:*** Herklin; ***Spain:*** Yacutin.

Lufenuron *(BAN, rINN)*

CGA-184699; Lufenurón; Lufénurone; Lufenuronum. 1-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea; (*RS*)-*N*-[2,5-Dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenylcarbamoyl]-2,6-difluorobenzamide.

Луфенурон

$C_{17}H_8Cl_2F_8N_2O_3$ = 511.2.
CAS — 103055-07-8.
ATC Vet — QP53BC01.

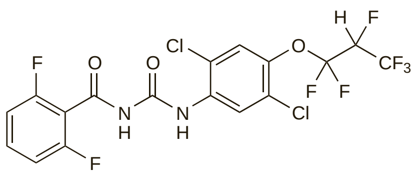

Profile

Lufenuron is used as a systemic ectoparasiticide in veterinary practice; it is given by mouth or injection to the host animal.

Malathion *(BAN)*

Carbofos; Compound 4047; Malathionum; Malatión; Malation; Malationas; Malationi; OMS-1. Diethyl 2-(dimethoxyphosphinothioylthio)succinate.

$C_{10}H_{19}O_6PS_2$ = 330.4.
CAS — 121-75-5.
ATC — P03AX03.
ATC Vet — QP53AF12.

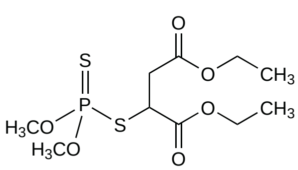

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Malathion). A clear, colourless or slightly yellowish liquid. It freezes at about 3°. Slightly soluble in water; miscible with alcohol, with acetone, with cyclohexane, and with vegetable oils. Store in airtight containers. Protect from light.

USP 31 (Malathion). A clear, colourless, or slightly yellowish liquid with a characteristic odour. Congeals at about 2.9°. Slightly soluble in water; miscible with alcohols, with ethers, with esters, with ketones, with aromatic and alkylated aromatic hydrocarbons, and with vegetable oils. Store in airtight containers. Protect from light.

Stability. The manufacturers have reported that malathion is sensitive to heat and is degraded at temperatures above 30°.

Adverse Effects and Treatment

As for Organophosphorus Insecticides, p.2047.

Malathion is one of the safer organophosphorus insecticides but its toxicity may be increased by the presence of impurities.

◊ Acute renal insufficiency has been described in a patient associated with excessive exposure to a malathion spray.[1] The condition resolved without specific treatment. Renal toxicity had not previously been associated with organophosphorus pesticides. In a second case of acute poisoning,[2] due to ingestion of malathion, mild transient renal insufficiency and proteinuria with several other late complications including cardiac arrhythmias, pulmonary oedema, diffuse interstitial fibrosis, and muscle weakness due to peripheral neuropathy, were seen subsequent to recovery from the initial cholinergic toxicity.

1. Albright RK, *et al*. Malathion exposure associated with acute renal failure. *JAMA* 1983; **250:** 2469.
2. Dive A, *et al*. Unusual manifestations after malathion poisoning. *Hum Exp Toxicol* 1994; **13:** 271–4.

Uses and Administration

Malathion is an organophosphorus insecticide (p.2047). It is used in the treatment of head and pubic pediculosis (p.2034) and in scabies (p.2035); lotions of 0.5% and shampoos of 1% are commonly available. Lotions are generally preferred to shampoos as the contact time is longer. Aqueous lotions are preferred to treat pubic lice and scabies because alcoholic lotions are irritant to excoriated skin and the genitalia; aqueous lotions may also be preferable in asthmatic subjects or children to avoid alcoholic fumes. Skin or hair treated with an alcohol-based preparation should be allowed to dry naturally.

Malathion is also used in veterinary practice, agriculture, and horticulture. It is widely used for adult and larval mosquito control although resistance occurs.

Preparations

USP 31: Malathion Lotion.

Proprietary Preparations (details are given in Part 3)
Austral.: Lice Rid†; ***Belg.:*** Prioderm; Radikal; ***Denm.:*** Prioderm; ***Fin.:*** Prioderm; ***Fr.:*** Prioderm; ***Gr.:*** Sicaril; Specifthir†; ***Irl.:*** Derbac-M; Prioderm; Quellada M; ***Israel:*** Prioderm; ***Ital.:*** Aftir Gel; ***Neth.:*** Noury Hoofdlotion; Prioderm; ***Norw.:*** Prioderm; ***NZ:*** A-Lices; Derbac-M; Prioderm; ***Port.:*** Olicide†; ***Rus.:*** Pedilin (Педилин); ***Singapore:*** A-Lices; Lice Care; ***Swed.:*** Prioderm; ***Switz.:*** Lusap†; Prioderm; ***UK:*** Derbac-M; Prioderm; Quellada M; Suleo-M†; ***USA:*** Ovide.

Multi-ingredient: ***Arg.:*** Aero Helpp Forte†; Para Plus; ***Belg.:*** Para Plus; ***Fr.:*** Para Plus; ***Gr.:*** Para-plus; ***Israel:*** Para Plus; ***NZ:*** Para Plus; ***Rus.:*** Para Plus (Пара Плюс).

Metaldehyde

Metaldehído.

$(C_2H_4O)_x$.
CAS — 9002-91-9.

Description. Metaldehyde is a cyclic polymer of acetaldehyde.

Adverse Effects and Treatment

Symptoms of poisoning by metaldehyde, which may be delayed, include vomiting and diarrhoea, fever, drowsiness, convulsions, and coma. Death from respiratory failure may occur within 48 hours. Kidney and liver damage may occur.

Treatment is symptomatic, although activated charcoal may be considered if more than 50 mg/kg has been ingested within the preceding hour.

◊ References.

1. Longstreth WT, Pierson DJ. Metaldehyde poisoning from slug bait ingestion. *West J Med* 1982; **137:** 134–7.
2. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
3. Bleakley C, *et al*. Self-poisoning with metaldehyde. *Emerg Med J* 2008; **25:** 381–2.

Uses

Metaldehyde is a molluscicide used in pellets against slugs and snails. It is an ingredient of some firelighters.

'Meta' is compressed metaldehyde which has been used as a solid fuel burning with a non-luminous carbon-free flame.

Methomyl

Metomilo. *S*-Methyl *N*-(methylcarbamoyloxy)thioacetimidate.

$C_5H_{10}N_2O_2S$ = 162.2.
CAS — 16752-77-5.

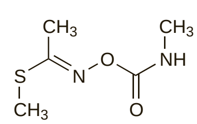

Profile

Methomyl is a carbamate insecticide (p.2037) that has been used in agriculture.

◊ References.

1. WHO. Methomyl health and safety guide. *IPCS Health and Safety Guide 97*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/hsg/hsg/hsg097.htm (accessed 26/04/04)
2. WHO. Methomyl. *Environmental Health Criteria 178*. Geneva: WHO, 1996. Available at: http://www.inchem.org/documents/ehc/ehc/ehc178.htm (accessed 26/04/04)

◊ Reports of poisoning with methomyl and its management.

1. Martinez-Chuecos J, *et al*. Management of methomyl poisoning. *Hum Exp Toxicol* 1990; **9:** 251–4.
2. Buchholz U, *et al*. An outbreak of food-borne illness associated with methomyl-contaminated salt. *JAMA* 2002; **288:** 604–10.

Methoprene *(rINN)*

Méthoprène; Methoprenum; Metopreno; ZR-515. Isopropyl 11-methoxy-3,7,11-trimethyldodeca-2(*E*),4(*E*)-dienoate.

Метопрен

$C_{19}H_{34}O_3$ = 310.5.
CAS — 40596-69-8.
ATC Vet — QP53BD01.

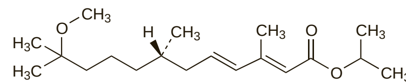

Profile

Methoprene is an insect growth regulator which mimics the action of insect juvenile hormones and, if it is applied at the appropriate period of sensitivity, it causes death by preventing the transformation of larva to pupa. It is used against a variety of insects including fleas and mosquitoes. It is used in veterinary practice for the control of ectoparasites in the environment, rather than being applied to the animals themselves. It is also used in agriculture.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Aspipur.

Methoxychlor

Methoxy-DDT; Metoksychlor; Metoxicloro. 1,1,1-Trichloro-2-2-bis(*p*-methoxyphenyl)-ethane.

$C_{16}H_{15}Cl_3O_2$ = 345.6.
CAS — 72-43-5.

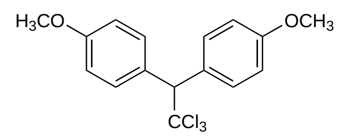

Profile

Methoxychlor is a chlorinated insecticide (p.2037) used in agriculture, horticulture, and veterinary practice.

Methyl Bromide

Metilo, bromuro de. Bromomethane; Monobromomethane.

CH_3Br = 94.94.
CAS — 74-83-9.

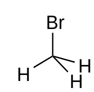

Adverse Effects, Treatment, and Precautions

Methyl bromide is a vesicant. Toxic effects after inhalation or percutaneous absorption are mainly due to neurotoxicity and include dizziness, headache, vomiting, blurred vision, weakness, ataxia, confusion, mania, hallucinations, mental depression, convulsions, pulmonary oedema, and coma. Renal and hepatic toxicity may also occur and death may be due to circulatory collapse or respiratory failure. Onset of symptoms may be preceded by a latent period. Concentrations of 1% or more are irritant to the eyes. Treatment is symptomatic although dimercaprol or acetylcysteine therapy has been tried.

Rubber absorbs and retains methyl bromide and should not therefore be used in protective clothing.

◊ References to toxicity of methyl bromide including reports of poisoning.

1. Chavez CT, *et al*. Methyl bromide optic atrophy. *Am J Ophthalmol* 1985; **99:** 715–19.
2. Langard S, *et al*. Fatal accident resulting from methyl bromide poisoning after fumigation of a neighbouring house: leakage through sewage pipes. *J Appl Toxicol* 1996; **16:** 445–8.
3. De Haro L, *et al*. Central and peripheral neurotoxic effects of chronic methyl bromide intoxication. *J Toxicol Clin Toxicol* 1997; **35:** 29–34.
4. Michalodimitrakis MN, *et al*. Death following intentional methyl bromide poisoning: toxicological data and literature review. *Vet Hum Toxicol* 1997; **39:** 30–4.
5. Horowitz BZ, *et al*. An unusual exposure to methyl bromide leading to fatality. *J Toxicol Clin Toxicol* 1998; **36:** 353–7.

6. Lifshitz M, Gavrilov V. Central nervous system toxicity and early peripheral neuropathy following dermal exposure to methyl bromide. *J Toxicol Clin Toxicol* 2000; **38:** 799–801.
7. Yamano Y, *et al.* Three cases of acute methyl bromide poisoning in a seedling farm family. *Ind Health* 2001; **39:** 353–8.
8. Hoizey G, *et al.* An unusual case of methyl bromide poisoning. *J Toxicol Clin Toxicol* 2002; **40:** 817–21.
9. Geyer HL, *et al.* Methyl bromide intoxication causes reversible symmetric brainstem and cerebellar MRI lesions. *Neurology* 2005; **64:** 1279–81.

Uses

Methyl bromide has been used as an insecticidal fumigant for soil and some foodstuffs.

When supplied for fumigation it usually contains chloropicrin as a lachrymatory warning agent.

Methyl bromide has been used as a gaseous disinfectant; it has low antimicrobial activity but good penetrating power.

Methyl bromide was formerly used with carbon tetrachloride in some fire extinguishers. It has also been used as a refrigerant.

◊ General references.

1. WHO. Methyl bromide (bromoethane) health and safety guide. *IPCS Health and Safety Guide 86*. Geneva: WHO, 1994. Available at: http://www.inchem.org/documents/hsg/hsg/hsg86_e.htm (accessed 26/04/04)
2. WHO. Methyl bromide. *Environmental Health Criteria 166*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc166.htm (accessed 26/04/04)

Naled

Bromchlophos. Dimethyl 1,2-dibromo-2,2-dichloroethyl phosphate.

$C_4H_7Br_2Cl_2O_4P$ = 380.8.

CAS — 300-76-5.

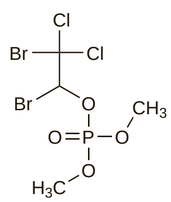

Profile

Naled is an organophosphorus insecticide used as a topical ectoparasiticide in veterinary practice.

Naphthalene

Naftalen; Naftaleno; Naphthalin.

$C_{10}H_8$ = 128.2.

CAS — 91-20-3.

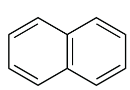

Adverse Effects, Treatment, and Precautions

Ingestion of naphthalene can produce headache, nausea and vomiting, diarrhoea, profuse sweating, dysuria, coma, and convulsions. Less than one naphthalene mothball (200 to 500 mg) may cause haemolysis. Ingestion of 5 to 15 g is considered lethal for adults and a dose as low as 74 mg/kg has proved fatal. In children ingestion of 100 mg/kg is lethal. Doses as low as 2 g and 80 mg/kg ingested over 2 days have proved fatal in young children. Treatment is symptomatic; lavage may be considered if the patient presents within 1 hour of ingestion. The vapour is irritating to the eyes; chronic exposure has led to cataract formation. Haemolytic anaemia and haematuria leading to acute renal failure may occur particularly in persons with G6PD deficiency. Blood transfusions may be required.

Pregnancy. Haemolytic anaemia in a neonate has been attributed to inhalation of naphthalene by the mother during the twenty-eighth week of pregnancy.[1]

1. Athanasion M, *et al.* Hemolytic anemia in a female newborn infant whose mother inhaled naphthalene before delivery. *J Pediatr* 1997; **130:** 680–1.

Uses

Naphthalene has been used in lavatory deodorant discs and in mothballs. It has also been used as a soil fumigant.

Norbormide

McN-1025; Norbormida. 5-[α-Hydroxy-α-(2-pyridyl)benzyl]-7-[α-(2-pyridyl)benzylidene]-8,9,10-trinorborn-5-ene-2,3-dicarboximide.

$C_{33}H_{25}N_3O_3$ = 511.6.

CAS — 991-42-4.

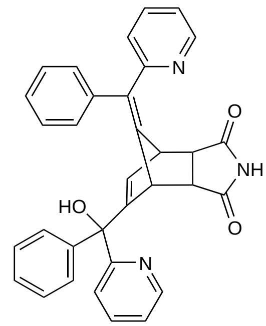

Profile

Norbormide is a selective rodenticide effective against most species of *rats*, in which it produces extreme irreversible peripheral vasoconstriction. It is not very toxic to other rodents.

Organophosphorus Insecticides

Insecticidas organofosforados; Organofosforlu İnsektisitler.

Description. The organophosphorus or organophosphate insecticides may be esters, amides, or thiol derivatives of phosphoric, phosphonic, phosphorothioic, or phosphonothioic acids.

◊ References.

1. WHO. Organophosphorus insecticides: a general introduction. *Environmental Health Criteria 63*. Geneva: WHO, 1986. Available at: http://www.inchem.org/documents/ehc/ehc/ehc63.htm (accessed 19/07/04)

Adverse Effects

Organophosphorus insecticides are potent cholinesterase inhibitors and can be very toxic. This inhibition results in both muscarinic and nicotinic effects with some central involvement.

Toxic effects may include abdominal cramps, nausea, vomiting, diarrhoea, pancreatitis, urinary incontinence, miosis or mydriasis, weakness, respiratory disturbances, lachrymation, increased salivation and sweating, bradycardia or tachycardia, hypotension or hypertension, cyanosis, muscular twitching, and convulsions. Some organophosphorus compounds cause delayed neuropathy. CNS symptoms include restlessness, anxiety, dizziness, confusion, coma, and depression of the respiratory or cardiovascular system. Patients may experience mental disturbances. Inhalation or external contact can cause local as well as systemic effects.

Repeated exposure may have a cumulative effect though the organophosphorus insecticides are, in contrast to the chlorinated insecticides, rapidly metabolised and excreted and are not appreciably stored in body tissues.

◊ References to the adverse effects and poisoning encountered with organophosphorus compounds such as insecticides (including sheepdips).

1. Minton NA, Murray VSG. A review of organophosphate poisoning. *Med Toxicol* 1988; **3:** 350–75.
2. Karalliedde L, Senanayake N. Organophosphorus insecticide poisoning. *Br J Anaesth* 1989; **63:** 736–50.
3. Öztürk MA, *et al.* Anticholinesterase poisoning in Turkey—clinical, laboratory and radiologic evaluation of 269 cases. *Hum Exp Toxicol* 1990; **9:** 273–9.
4. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 24/07/08)
5. Casey P, Vale JA. Deaths from pesticide poisoning in England and Wales: 1945–1989. *Hum Exp Toxicol* 1994; **13:** 95–101.
6. Eyer P. Neuropsychopathological changes by organophosphorus compounds—a review. *Hum Exp Toxicol* 1995; **14:** 857–64.
7. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
8. Steenland K. Chronic neurological effects of organophosphate pesticides. *BMJ* 1996; **312:** 1312–13.
9. Brown AA, Brix KA. Review of health consequences from high-, intermediate- and low-level exposure to organophosphorus nerve agents. *J Appl Toxicol* 1998; **18:** 393–408.
10. Koksal N, *et al.* Organophosphate intoxication as a consequence of mouth-to-mouth breathing from an affected case. *Chest* 2002; **122:** 740–1.
11. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ* 2007; **334:** 629–34.
12. Aardema H, *et al.* Organophosphorus pesticide poisoning: cases and developments. *Neth J Med* 2008; **66:** 149–53.

Treatment of Adverse Effects

Rapid treatment for poisoning with organophosphorus insecticides is essential. Use of gastric lavage may be considered if a substantial amount has been ingested within 1 to 2 hours of presentation, unless the product is formulated in a hydrocarbon solvent (as there is a high risk of fatal aspiration pneumonia). Contaminated clothing should be removed and the skin, including any areas contaminated by vomiting or hypersecretion, should receive copious and prolonged washing with soap and water. Contamination of the eye is treated by washing of the conjunctiva. The patient should be treated with atropine (see Poisoning, p.1221) and either pralidoxime (p.1460) or obidoxime (p.1456) and symptomatic treatment should be instituted. Diazepam is sometimes given; it may be necessary to give it parenterally in moderate to severe poisoning to control muscle fasciculations and convulsions; oral dosage in mild poisoning may be helpful in relieving anxiety. The patient should be observed for signs of deterioration due to delayed absorption.

Paraquat

Parakuat. 1,1′-Dimethyl-4,4′-bipyridyldiylium ion.

$C_{12}H_{14}N_2$ = 186.3.

CAS — 4685-14-7.

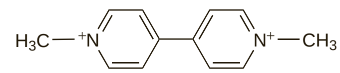

Paraquat Dichloride

Paraquat, dicloruro de.

$C_{12}H_{14}Cl_2N_2$ = 257.2.

CAS — 1910-42-5.

Adverse Effects

Concentrated solutions of paraquat may cause irritation, inflammation, and possibly blistering of the skin, cracking and shedding of the nails, and delayed healing of cuts and wounds. It is not significantly absorbed from undamaged skin. A few fatalities have occurred after skin contact, but these appear to have been associated with prolonged contact and concentrated solutions.

Splashes in the eye cause severe inflammation, which may be delayed for 12 to 24 hours, corneal oedema, reduced visual acuity, and extensive superficial stripping of the corneal and conjunctival epithelium, which usually slowly heals. Inhalation of dust or spray may cause nasal bleeding.

Paraquat weedkillers available for use in domestic gardens contain 2.5% w/v paraquat, sometimes with other herbicides such as diquat. While this strength of paraquat can cause nausea and vomiting as well as some respiratory changes when ingested, it is not considered to be a lethal form.

Most of the cases of severe poisoning follow the ingestion or sometimes injection of the concentrated forms of paraquat herbicide (20% w/v), the distribution of which is restricted to agriculturalists and horticulturalists. Ingestion of, or dermal exposure to small amounts of concentrated paraquat may result in severe pulmonary fibrosis and death within 24 hours. A dose of 10 to 15 mL of the concentrate (20% w/v) is considered to be lethal. Most, but not all patients who ingest 20 to 40 mg of paraquat ion/kg (7.5 to 15 mL of the concentrate) die within 2 or 3 weeks after ingestion. Ingestion of doses of more than 40 mg of paraquat ion/kg (more than 15 mL of concentrate) usually results in death within 1 to 7 days after ingestion. The irritant effects of paraquat are reflected in oesophageal ulceration and gastrointestinal effects. There is widespread organ damage, most notably involving the kidneys and lungs. In such poisoning death is virtually certain and occurs rapidly.

Preparations of paraquat may contain an emetic or a laxative and some contain a malodorous agent to deter ingestion.

◊ General references concerning paraquat toxicity and its treatment.

1. WHO. Paraquat and diquat. *Environmental Health Criteria 39*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc39.htm (accessed 26/04/04)
2. Bismuth C, *et al.* Paraquat poisoning. *Drug Safety* 1990; **5:** 243–51.
3. Pond SM. Manifestations and management of paraquat poisoning. *Med J Aust* 1990; **152:** 256–9.
4. Paraquat health and safety guide. *Health and Safety Guide 51*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg051.htm (accessed 26/04/04)
5. WHO. Safe use of pesticides: fourteenth report of the WHO expert committee on vector biology and control. *WHO Tech Rep Ser 813* 1991. Available at: http://libdoc.who.int/trs/WHO_TRS_813.pdf (accessed 21/07/08)
6. Proudfoot A, ed. *Pesticide poisoning: notes for the guidance of medical practitioners*. 2nd ed. London: DoH, The Stationery Office, 1996.
7. Eddleston M, *et al.* Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review. *QJM* 2003; **96:** 809–24.
8. Dinis-Oliveira RJ, *et al.* Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *Crit Rev Toxicol* 2008; **38:** 13–71.

Treatment of Adverse Effects

After contact with paraquat, contaminated clothing should be removed and the skin washed with soap and water. The eyes, if splashed, should be irrigated; later topical therapy may involve the symptomatic use of antibacterials or corticosteroids.

There is no specific treatment for paraquat poisoning and the immediate aim is to remove or inactivate the paraquat. Although the benefit of gastric decontamination is uncertain, if the patient presents less than 6 hours after ingestion the initial management involves giving an oral adsorbent, preferably activated charcoal in a dose of 100 g and followed by 50 g every 2 hours for up to 6 hours post ingestion. Fuller's earth (often as a 15% suspension) and bentonite (as a 7% suspension) are alternative oral adsorbents and are given in similar doses to those of charcoal. When none of these adsorbents is available, a suspension of clay or of uncontaminated soil should be considered if medical attention is likely to be delayed. An osmotic laxative may be used with the first dose of the adsorbent in order to hasten bowel evacuation and prevent obstruction due to the adsorbent. Patients may require intensive supportive therapy, but oxygen should not be given initially as it appears to enhance the pulmonary toxicity of paraquat; however, it may be needed in later stages as part of palliative care.

Methods aimed at hastening elimination such as forced diuresis, peritoneal dialysis, haemodialysis, and haemoperfusion have been tried but the first three appear to be ineffective and results with the last method have varied; no method is of proven value.

◊ For some general references concerning the treatment of paraquat toxicity, see under Adverse Effects, above.

Once paraquat has been absorbed, moderate to severe poisoning may result in acute renal failure, hepatitis, and pulmonary fibrosis; death may occur after 2 to 3 weeks. Pulse therapy with cyclophosphamide and methylprednisolone might be of benefit in such patients but not in those with fulminant poisoning.[1,2]

1. Lin J-L, *et al.* Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax* 1996; **51:** 661–3.
2. Lin J-L, *et al.* A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat poisoned patients. *Am J Respir Crit Care Med* 1999; **159:** 357–60. Correction to the dose of cyclophosphamide. *ibid.* 2001; **163:** 292.

Uses

Paraquat is a contact herbicide widely used as the dichloride in agriculture and horticulture. Liquid concentrates are supplied in the UK only to approved users.

Parathion

Paratión. *O,O*-Diethyl *O*-4-nitrophenyl phosphorothioate.

$C_{10}H_{14}NO_5PS$ = 291.3.

CAS — 56-38-2.

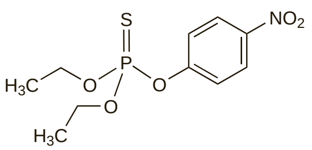

Profile

Parathion is an organophosphorus insecticide (p.2047) that has been used in agriculture and horticulture. Its metabolite diethyl nitrophenyl phosphate (paraoxon, p.1883) contributes to its toxicity.

◊ References.

1. WHO. Parathion health and safety guide. *IPCS Health and Safety Guide 74*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg74.htm (accessed 26/04/04)

◊ Reports of poisoning with parathion.

1. Anastassiades CJ, Ioannides M. Organophosphate poisoning and auricular fibrillation. *BMJ* 1984; **289:** 290.
2. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; **4:** 339–40.
3. Clifford NJ, Nies AS. Organophosphate poisoning from wearing a laundered uniform previously contaminated with parathion. *JAMA* 1989; **262:** 3035–6.
4. Wang M-H, *et al.* Q-T interval prolongation and pleomorphic ventricular tachyarrhythmia ('Torsade de pointes') in organophosphate poisoning: report of a case. *Hum Exp Toxicol* 1998; **17:** 587–90.
5. Eyer F, *et al.* Human parathion poisoning: a toxicokinetic analysis. *Toxicol Rev* 2003; **22:** 143–63.
6. Lund CM, Iversen G. Bladanforgiftning forekommer endnu. *Ugeskr Laeger* 2005; **167:** 3195–6.
7. Hoffmann U, Papendorf T. Organophosphate poisonings with parathion and dimethoate. *Intensive Care Med* 2006; **32:** 464–8.

Pentachlorophenol

PCP; Penta; Pentaclorofenol.

C_6HCl_5O = 266.3.

CAS — 87-86-5.

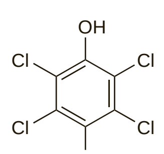

NOTE. The name PCP has also been used as a synonym for phencyclidine hydrochloride.

Adverse Effects, Treatment, and Precautions

Pentachlorophenol may be absorbed in toxic amounts through the skin or by inhalation, as well as by ingestion. Pentachlorophenol and its aqueous solutions are irritant to the eyes, mucous membranes, and to the skin, and may produce caustic burns. The systemic effects are due to uncoupling of oxidative phosphorylation with consequent stimulation of cellular metabolism. Acute poisoning with pentachlorophenol increases metabolic rate, leading to raised temperature with copious sweating and thirst, restlessness, fatigue, increased rate and depth of respiration, and tachycardia. There may be abdominal pain and nausea, and death has occurred from respiratory failure. Symptoms of subacute or chronic poisoning include hyperpyrexia and CNS, haematological, renal, reproductive, respiratory, and skin disorders.

Treatment is symptomatic. Raised body temperature should be treated by physical means; the use of antipyretics is not recommended since they can increase toxicity.

◊ Reviews of the toxicity of pentachlorophenol.

1. Health and Safety Executive. Pentachlorophenol. *Toxicity Review 5*. London: HMSO, 1982.
2. WHO. Pentachlorophenol. *Environmental Health Criteria 71*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc71.htm (accessed 26/04/04)
3. Pentachlorophenol health and safety guide. *Health and Safety Guide 19*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg019.htm (accessed 26/04/04)
4. Jorens PG, Schepens PJC. Human pentachlorophenol poisoning. *Hum Exp Toxicol* 1993; **12:** 479–95.
5. Proudfoot AT. Pentachlorophenol poisoning. *Toxicol Rev* 2003; **22:** 3–11.

◊ There have been reports of malignant neoplasms,[1,2] aplastic anaemia,[3] pancreatitis,[4] intravascular haemolysis,[5] and urticaria[6] associated with exposure to pentachlorophenol.

1. Greene MH, *et al.* Familial and sporadic Hodgkin's disease associated with occupational wood exposure. *Lancet* 1978; **ii:** 626–7.
2. Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet* 1979; **i:** 55–6.
3. Roberts HJ. Aplastic anemia due to pentachlorophenol. *N Engl J Med* 1981; **305:** 1650–1.
4. Cooper RG, Macaulay MB. Pentachlorophenol pancreatitis. *Lancet* 1982; **i:** 517.
5. Hassan AB, *et al.* Intravascular haemolysis induced by pentachlorophenol. *BMJ* 1985; **291:** 21–2.
6. Kentor PM. Urticaria from contact with pentachlorophenate. *JAMA* 1986; **256:** 3350.

Pharmacokinetics

Pentachlorophenol may be absorbed after ingestion or inhalation or through the skin. After ingestion, the majority of a dose is eliminated in the urine as unchanged pentachlorophenol and its glucuronide, with small amounts appearing in the faeces.

Uses

Pentachlorophenol has been used mainly as the sodium salt (C_6Cl_5NaO = 288.3), as a preservative for a wide range of industrial and agricultural products, including wood and other building materials, textiles, glues, and starch. It has also been used for the control of slime and algae, and as a molluscicide, fungicide, and herbicide.

Permethrin *(BAN, USAN, rINN)*

Perméthrine; Permethrinum; Permetriini; Permetrin; Permetrina; Permetryna. 3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

Перметрин

$C_{21}H_{20}Cl_2O_3$ = 391.3.

CAS — 52645-53-1.

ATC — P03AC04.

ATC Vet — QP53AC04.

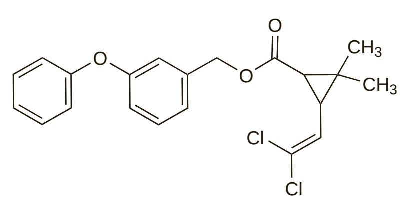

Profile

Permethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049). It is used in the treatment of head pediculosis (p.2034) as a 1% application; there have been signs of resistance. It is also used as a 5% cream for pubic pediculosis and as an acaricide in the treatment of scabies (p.2035).

Permethrin is also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide.

Permethrin is active against mosquitoes and is widely used for the impregnation of bednets and curtains in the control of malaria (p.594). It is also active against blackflies in the adult and larval stages and is used for the larvicidal treatment of rivers in the control of onchocerciasis (p.137). It is also active against tsetse flies.

Permethrin is suitable for aircraft disinsection.

◊ References.

1. WHO. Permethrin health and safety guide. *IPCS Health and Safety Guide 33*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg033.htm (accessed 26/04/04)
2. WHO. Permethrin. *Environmental Health Criteria 94*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc94.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Assy Crema de Enjuague; Assy Espuma; B-Jen; Blum; Capitis; Dermoper; Duncankil†; Fripi; Hairclin†; Helpp; Kinderval; Kwell; Lumat†; Nopucid; Pelo Libre; Percapyl†; Quitoso NF; Sapucai†; Witty; ***Austral.:*** Lyclear; Pyrifoam; Quellada; ***Belg.:*** Mouskito Textile; Nix; Zalvor; ***Braz.:*** Clean Hair; Keltrina; Kwell; Lendrex†; Nedax; Nedax Plus; Permetel†; Permetrix†; Piodrex; Pioletal; Piolhol Plus†; Piostop†; Pluritin†; Toppyc†; Wellcid†; ***Canad.:*** Kwellada-P; Nix; ***Chile:*** Assy Espuma†; Kilnits; ***Cz.:*** Infectoscab; ***Denm.:*** Nix; ***Fin.:*** Nix; ***Fr.:*** Insect Ecran; Modul'Aid†; Mousticologne; Moustidose; Nix; Pharmavoyage Moustiquaires; ***Ger.:*** InfectoPedicul; Infectoscab; ***Gr.:*** Nix; ***Hong Kong:*** Quellada; ***India:*** Perlice; Permite; ***Indon.:*** Scabimite; ***Irl.:*** Lyclear; ***Israel:*** Lyclear; Mite-X; New-Nok; Nok†; Zehu-Ze; ***Ital.:*** Nix; Pre Clean Mom; ***Mex.:*** Novo-Herklin 2000; Scabisan; Scabisan Plus; ***Neth.:*** Loxazol; ***Norw.:*** Nix; ***NZ:*** Lyderm; Pyrifoam; ***Philipp.:*** Kwell Reformulated; Pyrifoam; ***Port.:*** Desintan P†; Nix; Quitoso; ***Rus.:*** Nix (Никс); ***S.Afr.:*** Lyclear; ***Spain:*** Sarcop; ***Swed.:*** Nix; ***Switz.:*** Loxazol; ***Turk.:*** Kwellada; Niksen; Zalvor; ***UK:*** Lyclear; Residex P55; ***USA:*** Acticin; Elimite; Nix; ***Venez.:*** Piokil Plus.

Multi-ingredient: ***Arg.:*** Aero Helpp Forte†; Arnecrem†; Bencil Scab; Detebencil; Detebencil Nit; Hexa-Defital Plus; Hexabencil; Para Plus; Pedicrem; Perbel; Permecil; Sapucai†; ***Belg.:*** Para Plus; Shampoux; ***Braz.:*** Piolhol†; ***Cz.:*** Charlieu Anti-Poux†; ***Fr.:*** Anti-Ac†; Aspipur; Charlieu Anti-Poux; Para Plus; Pyreflor; Sanytol†; ***Gr.:*** Para-plus; ***Israel:*** Para Plus; ***Ital.:*** Antiscabbia CM; ***NZ:*** Para Plus; ***Rus.:*** Para Plus (Пара Плюс); ***S.Afr.:*** Nitagon.

Phenothrin *(BAN, rINN)*

Fenotrin; Fenotrina; Phénothrine; Phenothrinum; S-2539. 3-Phenoxybenzyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

Фенотрин

$C_{23}H_{26}O_3$ = 350.5.

CAS — 26002-80-2.

ATC — P03AC03.

ATC Vet — QP53AC03.

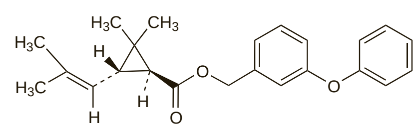

Profile

Phenothrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049). It is used for the treatment of head and pubic pediculosis (p.2034) as a 0.2% alcoholic or 0.5% aqueous lotion, or as a 0.5% alcoholic foam; as with permethrin there have been signs of resistance.

Phenothrin is also used in veterinary practice as a topical ectoparasiticide, as a household insecticide, and for the disinsection of public areas and aircraft.

◊ References.

1. WHO. d-Phenothrin health and safety guide. *IPCS Health and Safety Guide 32*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg032.htm (accessed 26/04/04)
2. WHO. d-Phenothrin. *Environmental Health Criteria 96*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc96.htm (accessed 26/04/04)

Aircraft disinsection. References.

1. Russell RC, Paton R. In-flight disinsection as an efficacious procedure for preventing international transport of insects of public health importance. *Bull WHO* 1989; **67:** 543–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nopucid MC; Sumo; ***Cz.:*** Parasidose; ***Fr.:*** Itax Antipoux; Item Antipoux; Parasidose; ***Gr.:*** Ivaliten; Pubex; Sitem; ***Irl.:*** Headmaster; ***Israel:*** Sof-Sof†; ***Ital.:*** Cruzzy Shampoo Potenziato alla Sumitrina; Mediker; Mom Gel; Mom Shampoo Schiuma; Neo Mom; Ottocid; ***Mex.:*** Herklin NF; ***NZ:*** Full Marks; Parasidose; ***Rus.:*** Anti-Bit (Анти-Бит); Itax (Итакс); ***Turk.:*** Anti-Bit; ***UK:*** Full Marks; ***USA:*** Pronto.

Multi-ingredient: ***Fr.:*** Sanytol†; ***Gr.:*** Cif Candioli; ***Ital.:*** Mom Shampoo Antiparassitario; Neo Mom; ***Mex.:*** Herklin NF; ***Neth.:*** Zinkan.

Phosmet *(BAN)*

Fosmet. *O,O*-Dimethyl phthalimidomethyl phosphorodithioate.
$C_{11}H_{12}NO_4PS_2$ = 317.3.
CAS — 732-11-6.
ATC Vet — QP53AF06; QP53BB03.

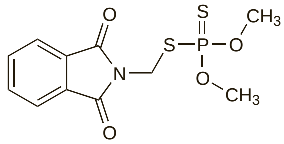

Profile

Phosmet is an organophosphorus insecticide (p.2047) used as a systemic ectoparasiticide in veterinary practice; it is applied topically to the host animal. It has also been used in agriculture and horticulture.

Phoxim *(BAN, pINN)*

Bayer-9053; Foksiimi; Foxim; Foxima; Phoxime; Phoximum. 2-(Diethoxyphosphinothioyloxyimino)-2-phenylacetonitrile.
Фоксим
$C_{12}H_{15}N_2O_3PS$ = 298.3.
CAS — 14816-18-3.
ATC Vet — QP53AF01.

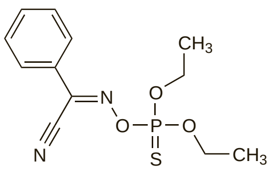

Profile

Phoxim is an organophosphorus insecticide (p.2047) used as a topical ectoparasiticide in veterinary practice. It is also used for the larvicidal treatment of rivers in the control of onchocerciasis (p.137).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Baythion EC†.

Piperonal

Heliotropin; Piperonylaldehyde. 1,3-Benzodioxole-5-carboxaldehyde.
$C_8H_6O_3$ = 150.1.
CAS — 120-57-0.

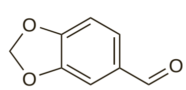

Profile

Piperonal is used as an insect repellent against head lice (see Pediculosis, p.2034).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Para Repulsif; ***UK:*** Rappell.

Piperonyl Butoxide *(BAN)*

Piperonil Butoksit; Piperonilo, butóxido de. 5-[2-(2-Butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole.
$C_{19}H_{30}O_5$ = 338.4.
CAS — 51-03-6.

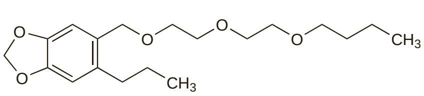

Pharmacopoeias. In *BP(Vet)*.
BP(Vet) 2008 (Piperonyl Butoxide). A yellow or pale brown oily liquid. Very slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with petroleum oils.

Profile

Piperonyl butoxide is used as a synergist for pyrethrin and pyrethroid insecticides. Mixtures of piperonyl butoxide and pyrethrins or pyrethroids are used in the treatment of pediculosis (p.2034).

Piperonyl butoxide is considered to cause a variety of gastrointestinal effects as well as mild CNS depression.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Acardust†; Aero Helpp Forte†; Capitis†; Deca-Scab†; Hexa-Defital NF; Limpacid; Nopucid Compuesto; Para Piojicida; Para Plus; Quitoso†; Scabioderm; ***Austral.:*** Banlice; Paralice†; ***Belg.:*** Para; Para Plus; Shampoux; ***Braz.:*** Deltacid Plus; Piolhol†; Sarnapen†; ***Canad.:*** Licetrol†; Para†; Pronto; R & C; Scabene†; ***Chile:*** Launol; ***Cz.:*** Charlieu Anti-Poux†; ***Fr.:*** A-Par; Acardust; Anti-Ac†; Aspipur; Charlieu Anti-Poux; Para Plus; Para Special Poux; Pyreflor; Spray-Pax; Spregal; ***Ger.:*** Goldgeist; Jacutin N; Spregal; ***Gr.:*** Para-plus; Runde; Spregal; ***Israel:*** A-200†; Acardust; Kin Soff; Para Plus; ***Ital.:*** Baygon; Cruzzy; Milice; Mom Piretro Emulsione†; Sinezan; ***Neth.:*** Para-Speciaal; Spregal; Zinkan; ***NZ:*** Para Plus; ***Port.:*** Para-Pio†; ***Rus.:*** Para Plus (Пара Плюс); Pedilin Ko (Педилин Ко); Spray-Pax (Спрей-пакс); Spregal (Спрегаль); ***S.Afr.:*** Nitagon; Spregal; ***Turk.:*** Kwell-P; ***UK:*** Fortefog; Prevent; ***USA:*** Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pirimiphos-Methyl

Metilpirimifós. *O*-2-Diethylamino-6-methylpyrimidin-4-yl *O,O*-dimethyl phosphorothioate.
$C_{11}H_{20}N_3O_3PS$ = 305.3.
CAS — 29232-93-7.

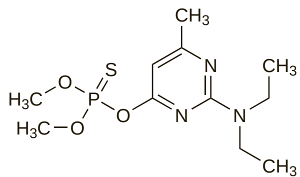

Profile

Pirimiphos-methyl is an organophosphorus insecticide (p.2047). It is used in agriculture and domestically.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Anti-Ac†.

Propetamphos *(BAN)*

Propetamfós; Propetamfos. Isopropyl (*E*)-3-[(ethylamino)(methoxy)phosphinothio-oxy]but-2-enoate.
$C_{10}H_{20}NO_4PS$ = 281.3.
CAS — 31218-83-4.
ATC Vet — QP53AF09.

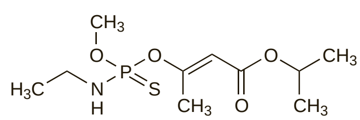

Profile

Propetamphos is an organophosphorus insecticide (p.2047) used as a topical ectoparasiticide in veterinary practice.

Propoxur *(BAN)*

2-Isopropoxyphenyl methylcarbamate.
$C_{11}H_{15}NO_3$ = 209.2.
CAS — 114-26-1.
ATC Vet — QP53AE02.

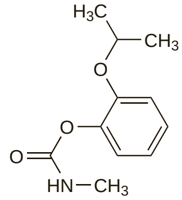

Profile

Propoxur is a carbamate insecticide (p.2037) used as a topical ectoparasiticide in veterinary practice. It is also used as a fumigant in agriculture.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Baygon.

Pyraclofos

Piraclofós. (*RS*)-[*O*-1-(4-Chlorophenyl)pyrazol-4-yl *O*-ethyl *S*-propyl phosphorothioate].
$C_{14}H_{18}ClN_2O_3PS$ = 360.8.
CAS — 77458-01-6.

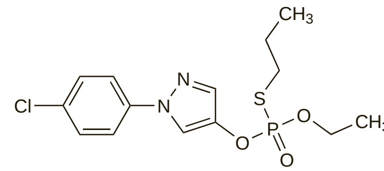

Profile

Pyraclofos is an organophosphorus insecticide (p.2047) used for the larvicidal treatment of rivers in the control of onchocerciasis (p.137).

Pyrethrum Flower

Chrysanthème Insecticide; Dalmatian Insect Flowers; Flor del pelitre; Insect Flowers; Insektenblüten; Piretro; Pyrethri Flos.
CAS — 8003-34-7 (pyrethrum); 121-21-1 (pyrethrin I); 121-29-9 (pyrethrin II); 25402-06-6 (cinerin I); 121-20-0 (cinerin II).
ATC — P03AC01.
ATC Vet — QP53AC01.

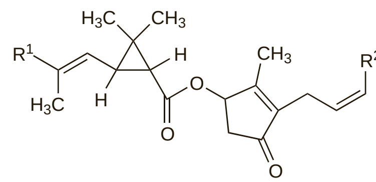

	R^1	R^2
Pyrethrin-I	CH_3	$CH{=}CH_2$
Pyrethrin-II	$COOCH_3$	$CH{=}CH_2$
Cinerin-I	CH_3	CH_3
Cinerin-II	$COOCH_3$	CH_3

Pharmacopoeias. In *BP(Vet)*, which also includes the extract. *US* includes only the extract.
BP(Vet) 2008 (Pyrethrum Flower). The dried flowerheads of *Chrysanthemum cinerariaefolium* containing not less than 1% of pyrethrins of which not less than one-half consists of pyrethrin I. It has a faint but characteristic odour.
BP(Vet) 2008 (Pyrethrum Extract). An extract prepared from Pyrethrum Flower. It contains 24.5 to 25.5% of pyrethrins, of which not less than half consists of pyrethrin I. A dark olive green or brown viscous liquid or, if decolourised, a pale amber liquid. Store in a well-filled container. Protect from light. It should be thoroughly stirred before use.
USP 31 (Pyrethrum Extract). A mixture of three naturally occurring, closely related insecticidal esters of chrysanthemic acid (pyrethrins I: jasmolin I, cinerin I, and pyrethrin I) and three closely related esters of pyrethric acid (pyrethrins II: jasmolin II, cinerin II, and pyrethrin II). The ratio of pyrethrins I to pyrethrins II is not less than 0.8 and not more than 2.8. It may contain pigments characteristic of chrysanthemum species, triglyceride oils, terpenoids, and carotenoid. It may also contain suitable solvents and antioxidants. It contains no other added substances. It is a pale yellow liquid having a bland, flowery odour. Insoluble in water; soluble in liquid paraffin and in most organic solvents. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Pyrethrum is irritant to the eyes and mucosa. Hypersensitivity reactions have been reported.

◊ References to the potential for toxicity of pyrethrin and pyrethroid insecticides.

1. Ray DE, Forshaw PJ. Pyrethroid insecticides: poisoning syndromes, synergies, and therapy. *J Toxicol Clin Toxicol* 2000; **38:** 95–101.
2. Bateman DN. Management of pyrethroid exposure. *J Toxicol Clin Toxicol* 2000; **38:** 107–9.
3. Bradberry SM, *et al.* Poisoning due to pyrethroids. *Toxicol Rev* 2005; **24:** 93–106.
4. Proudfoot AT. Poisoning due to pyrethrins. *Toxicol Rev* 2005; **24:** 107–13.
5. Ray DE, Fry JR. A reassessment of the neurotoxicity of pyrethroid insecticides. *Pharmacol Ther* 2006; **111:** 174–93.

Uses

Pyrethrum flower is mainly used for the preparation of pyrethrum extracts containing a mixture of chrysanthemic acid and pyrethric acid esters (pyrethrins I and II).

Pyrethrins in the form of pyrethrum extract have a long history of use as insecticides. Pyrethrum is rapidly toxic to many insects. It has a much quicker knock-down effect than clofenotane or lindane, but it is less persistent and less stable. Its action can be enhanced by certain substances such as piperonyl butoxide (p.2049), and pyrethrins with piperonyl butoxide are used clinically in the treatment of pediculosis (p.2034).

Pyrethroid insecticides (synthetic analogues of pyrethrins), such as permethrin and phenothrin, are also used clinically; deltamethrin and permethrin are among those used for the vector control of malaria.

Pyrethrum, pyrethrins, and pyrethroids are also used as topical ectoparasiticides in veterinary practice and as agricultural, horticultural, and household insecticides.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Pearsol; SH3.

Multi-ingredient: *Arg.:* Quitoso†; ***Austral.:*** Banlice; ***Canad.:*** Licetrol†; Pronto; R & C; ***Fr.:*** Spray-Pax; ***Ger.:*** Goldgeist; ***Israel:*** A-200†; Kin Soff; ***Ital.:*** Milice; Sinezan; ***Port.:*** Para-Pio†; ***Rus.:*** Bubil (Бубил); Spray-Pax (Спрей-пакс); ***Turk.:*** Kwell-P; ***UK:*** Fortefog; Prevent; ***USA:*** Blue; Licide; Pronto; Pyrinyl II; Pyrinyl Plus; RID; Tisit.

Pyriproxyfen

Piriproxifeno; Pyriproksifeeni; Pyriproxifen; Pyriproxifène; Pyriproxifenum; Pyriproxyfenum; S-9318; S-31183. 2-[1-Methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine.

$C_{20}H_{19}NO_3$ = 321.4.

CAS — 95737-68-1.

ATC Vet — QP53AX23.

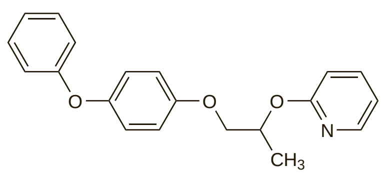

Profile

Pyriproxyfen is used as a topical ectoparasiticide in veterinary practice.

Red Squill

Esquila.

CAS — 507-60-8 (scilliroside).

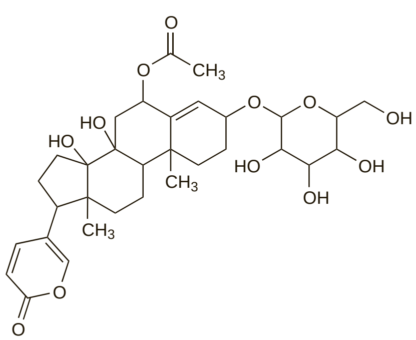

(scilliroside)

Profile

Red squill is a red variety of *Urginea maritima*, which contains, in addition to cardiac glycosides, an active principle, scilliroside. It is very toxic to *rats* and has been incorporated in rat poisons; it has neurotoxic and cardiotoxic properties.

Resmethrin

Resmetrina. 5-Benzyl-3-furylmethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

$C_{22}H_{26}O_3$ = 338.4.

CAS — 10453-86-8.

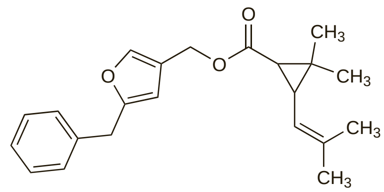

Profile

Resmethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in veterinary practice for the control of ectoparasites in the environment. Resmethrin is also used as an agricultural, horticultural, and household insecticide, but is not synergised by pyrethrum synergists such as piperonyl butoxide (p.2049).

◊ References.

1. WHO. Resmethrins. *Environmental Health Criteria 92*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc092.htm (accessed 26/04/04)
2. WHO. Resmethrins health and safety guide. *IPCS Health and Safety Guide 25*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg025.htm (accessed 26/04/04)

Rotenone

Rotenona; Rotenonum. (2*R*,6a*S*,12a*S*)-1,2,6,6a,12,12a-Hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-*b*]furo[2,3-*h*]-chromen-6-one.

$C_{23}H_{22}O_6$ = 394.4.

CAS — 83-79-4.

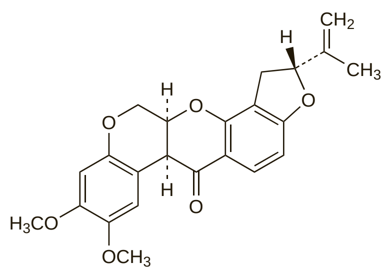

Profile

Rotenone is a non-systemic insecticide used in agriculture and in horticulture.

Rotenone is the active ingredient of derris (the dried rhizome and roots of *Derris elliptica*; also known as tuba root or aker-tuba) and of lonchocarpus (the dried root of *Lonchocarpus utilis*; also known as cube root, timbo, or barbusco). Powdered forms of derris and of lonchocarpus have been used as insecticides and fish poisons.

◊ References.

1. WHO. Rotenone health and safety guide. *IPCS Health and Safety Guide 73*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/hsg/hsg/hsg073.htm (accessed 26/04/04)

Sodium Fluoroacetate

Compound 1080; Fluoroacetato sódico; Sodium Monofluoroacetate.

$FCH_2.CO_2Na$ = 100.0.

CAS — 62-74-8.

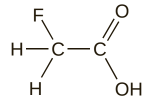

(fluoroacetic acid)

Adverse Effects, Treatment, and Precautions

Sodium fluoroacetate is highly toxic, the lethal dose if ingested being about 1 to 5 mg/kg. Toxic effects may be delayed for several hours after absorption by mouth or inhalation, and include nausea and vomiting, apprehension, muscle twitching, cardiac irregularities, convulsions, respiratory failure, coma, and death usually due to ventricular fibrillation.

Treatment is generally supportive and symptomatic.

◊ References to sodium fluoroacetate toxicity.

1. Chi CH, *et al*. Clinical presentation and prognostic factors in sodium monofluoroacetate intoxication. *J Toxicol Clin Toxicol* 1996; **34:** 707–12.
2. Chi CH, *et al*. Hemodynamic abnormalities in sodium monofluoroacetate intoxication. *Hum Exp Toxicol* 1999; **18:** 351–3.
3. Goncharov NV, *et al*. Toxicology of fluoroacetate: a review, with possible directions for therapy research. *J Appl Toxicol* 2006; **26:** 148–61.
4. Proudfoot AT, *et al*. Sodium fluoroacetate poisoning. *Toxicol Rev* 2006; **25:** 213–19.

Uses

Sodium fluoroacetate is a highly effective rodenticide but must be used with great caution because of its toxicity to other animals and to man.

Sulfiram *(BAN, rINN)*

Monosulfiram; Sulfiramum. Tetraethylthiuram monosulphide.

Сульфирам

$C_{10}H_{20}N_2S_3$ = 264.5.

CAS — 95-05-6.

ATC Vet — QS02QA02.

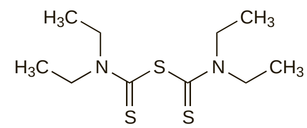

Adverse Effects and Precautions

An erythematous rash has occasionally been reported. Sulfiram produces effects similar to those of disulfiram (p.2296) if ingested with alcohol. As there may be a risk of absorption after application of sulfiram to the whole body, patients are advised to abstain from alcohol for at least 48 hours.

◊ The reactions to alcohol occasionally reported in patients who have applied sulfiram solution[1,2] resemble those seen with disulfiram. Analysis has shown that sulfiram solutions exposed to room light undergo photochemical conversion to disulfiram, and that the concentration of disulfiram, and the ability of the solution to inhibit aldehyde dehydrogenase and hence the metabolism of alcohol, increases with the duration of such storage.[3,4] Whether patients who have applied sulfiram solution should avoid direct light immediately afterwards has not been elucidated.[4]

1. Blanc D, Deprez P. Unusual adverse reaction to an acaricide. *Lancet* 1990; **335:** 1291–2.
2. Burgess I. Adverse reactions to monosulfiram. *Lancet* 1990; **336:** 873.
3. Mays DC, *et al*. Photolysis of monosulfiram: a mechanism for its disulfiram-like reaction. *Clin Pharmacol Ther* 1994; **55:** 191.
4. Lipsky JJ, *et al*. Monosulfiram, disulfiram, and light. *Lancet* 1994; **343:** 304.

Uses and Administration

Sulfiram is a pesticide that has been used as an acaricide, either alone or with benzyl benzoate, in the treatment of scabies (p.2035), although other treatments are now preferred.

Sulfiram has also been used as a pesticide in veterinary practice.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Sarfiram; Sulfitrat†; Tetmosol; Valfiran; ***India:*** Tetmosol; ***Mex.:*** Tetmosol†; ***Port.:*** Thiosan†; ***S.Afr.:*** Tetmosol; ***Singapore:*** Tetmosol†.

Multi-ingredient: *Fr.:* Ascabiol.

Temefos *(USAN, rINN)*

27165; Téméfos; Temefós; Temefosum; Temephos. *O,O′*-(Thiodi-*p*-phenylene) *O,O,O′,O′*-tetramethyl bis(phosphorothioate).

Темефос

$C_{16}H_{20}O_6P_2S_3$ = 466.5.

CAS — 3383-96-8.

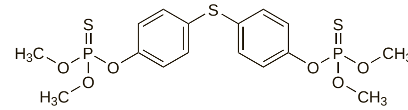

Profile

Temefos is an organophosphorus insecticide (p.2047). It is effective against the larvae of mosquitoes, blackflies, and other insects, and is used for the larvicidal treatment of rivers in the control of onchocerciasis (p.137). It is also effective against the crustacean host to the larvae of the guinea worm and is used in the control of dracunculiasis (p.136); treatment of drinking water is both effective and acceptable.

Tetrachlorvinphos

ENT-25841; SD-8447; Tetrachlorowinfos; Tetraclorvinfós. 2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate.

$C_{10}H_9Cl_4O_4P$ = 366.0.

CAS — 961-11-5; 22248-79-9 (Z-tetrachlorvinphos); 22350-76-1 (E-tetrachlorvinphos).

ATC Vet — QP53AF14.

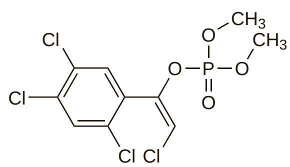

Profile

Tetrachlorvinphos is an organophosphorus insecticide (p.2047) used as an ectoparasiticide in veterinary practice.

Tetramethrin *(rINN)*

Tétraméthrine; Tetramethrinum; Tetrametrina. Cyclohex-1-ene-1,2-dicarboximidomethyl (1*RS*,3*RS*)-(1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

Тетраметрин

$C_{19}H_{25}NO_4$ = 331.4.

CAS — 7696-12-0.

ATC — P03BA04.

ATC Vet — QP53AC13.

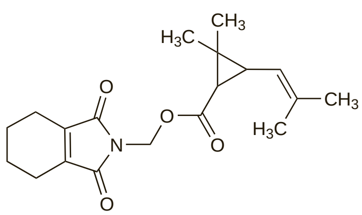

Profile

Tetramethrin is a pyrethroid insecticide (see Pyrethrum Flower, p.2049) used in the treatment of pediculosis (p.2034). It is also used in veterinary practice for the control of ectoparasites in the environment and as a household insecticide.

◊ References.

1. WHO. Tetramethrin health and safety guide. *IPCS Health and Safety Guide 31*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/hsg/hsg/hsg031.htm (accessed 26/04/04)
2. WHO. Tetramethrin. *Environmental Health Criteria 98*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc98.htm (accessed 26/04/04)

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Aspipur; ***Gr.:*** Cif Candioli; Runde; ***Ital.:*** Baygon; Mom Piretro Emulsione†; Mom Shampoo Antiparassitario; Neo Mom; ***Rus.:*** Pedilin Ko (Педилин Ко).

Trichlorophenoxyacetic Acid

2,4,5-T; Triclorofenoxiacético, ácido. 2,4,5-Trichlorophenoxyacetic acid.

$C_8H_5Cl_3O_3$ = 255.5.

CAS — 35915-18-5.

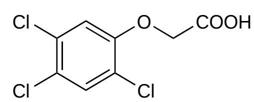

Profile

Trichlorophenoxyacetic acid is a selective herbicide with similar actions to dichlorophenoxyacetic acid (p.2040). It is usually used in ester formulations. It was used with dichlorophenoxyacetic acid as a defoliating agent in the Vietnam war.

Toxicity. The phenoxy herbicides were used for defoliation in Vietnam as Agent Orange, which consisted of a mixture of dichlorophenoxyacetic acid, trichlorophenoxyacetic acid, and the impurity TCDD (dioxin), and concern has been expressed that they may have contributed to an increased incidence of cancer among exposed subjects as well as an adverse effect on the offspring of those subjects. This has been a matter of considerable debate,[1] prompting a series of biennial reassessments of the health effects of Agent Orange by the US National Academy of Sciences' Institute of Medicine.[2] To date the Institute has concluded[3] that there is evidence of increased incidence of chronic lymphocytic leukaemia, soft tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, and chloracne, with phenoxy herbicides.

1. McCarthy M. Agent Orange. *Lancet* 1993; **342:** 362.
2. Stephenson J. New IOM report links Agent Orange exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; **275:** 1066–7.
3. Institute of Medicine. *Veterans and Agent Orange: update 2002 (2003).* Washington: The National Academies Press. Also available at: http://www.nap.edu/openbook.php?isbn=0309086167 (accessed 24/07/08)

Triflumuron

Triflumurón; Trifluron. 2-Chloro-*N*-([{4-(trifluoromethoxy)phenyl}amino]carbonyl)benzamide.

$C_{15}H_{10}ClF_3N_2O_3$ = 358.7.

CAS — 64628-44-0.

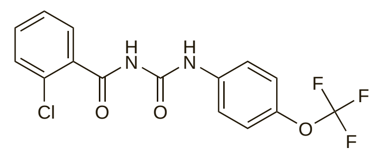

Profile

Triflumuron is an insecticide used in agriculture and as a topical ectoparasiticide in veterinary practice.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Baycidal†.

Radiopharmaceuticals

Radioactive compounds are used in medicine as sources of radiation for radiotherapy and for diagnostic purposes. They have numerous uses in research and industry.

Sealed radioactive sources are bonded or encapsulated to prevent the escape of the radioactive material and are used as supplied. Unsealed sources, on the other hand, are radioactive materials usually in liquid, particulate, or gaseous form that are removed from their containers for application. Radiopharmaceuticals come within this category.

The aim of this chapter is to provide background information on the radionuclides that are used as radiopharmaceuticals. Care is required in the preparation, handling, use, and disposal of these compounds; they are thus best dealt with by those with suitable experience and training.

Atomic Structure

An atom may be viewed as a central positively charged nucleus around which negatively charged electrons revolve in orbits. The electrons are arranged round the atomic nucleus in a series of 'shells' in each of which is a limited number of orbits.

The nucleus consists of 2 main kinds of particles known as protons, each of unit positive charge, and neutrons, which are uncharged; the total number of these particles in the nucleus is known as the *mass number.*

Each electron carries a negative charge which is of the same size as the positive charge of the proton, so that in the neutral atom the number of electrons is equal to the number of protons in the nucleus.

The number of protons in the nucleus is known as the *atomic number*, and this determines the number of electrons in the extranuclear structure. All the atoms of a particular chemical element have the same atomic number, but while the number of protons is constant, the number of neutrons in the atoms, and thus their masses (mass numbers), may vary. These different forms of the same element are known as isotopes of the element and these isotopes differ in some of their physical properties.

Some isotopes may be stable, the differences between them arising solely from their difference in mass; others may be radioactive (*radioisotopes*), their nuclei changing spontaneously and emitting particles or electromagnetic waves, or both.

Most of the naturally occurring isotopes are stable, though there are a number which are unstable and therefore radioactive, for example, uranium-235. In addition, artificial radionuclides are prepared by converting stable nuclei into unstable forms or naturally occurring radionuclides may be prepared by artificial means.

The symbol used for a nuclide is a development of the chemical symbol for the atom, with the mass number as a superscript and the atomic number as a subscript; thus the symbols for the 3 hydrogen isotopes—common hydrogen, deuterium, and tritium—are ${}^{1}_{1}H$, ${}^{2}_{1}H$, and ${}^{3}_{1}H$, and the symbols for the 3 naturally occurring uranium isotopes are ${}^{234}_{92}U$, ${}^{235}_{92}U$, and ${}^{238}_{92}U$; as the atomic number can be inferred from the chemical symbol it is the usual practice to omit the subscript. It is also common practice to write out the full name of the element followed by the mass number, e.g. chromium-51 for ${}^{51}Cr$.

Emissions from Radioisotopes

The 3 main types of emission from radioactive substances are *alpha particles, beta particles,* and *gamma-rays.* Most sources emit more than one type of radiation.

Alpha particles are positively charged particles (helium nuclei), each consisting of 2 protons and 2 neutrons.

Beta particles (β^- or β^+) are identical to electrons or positrons but arise from the nucleus. They are emitted with great velocity and their energies are spread over a spectrum. Positrons are similar to electrons, having a similar mass but a positive charge.

Gamma-rays are electromagnetic radiations or *photons* with wavelengths much shorter than those of light.

In certain cases, e.g. chromium-51, *electron capture* (EC) occurs, an electron from an inner shell being absorbed by the nucleus with the production of an *X-ray* characteristic of the daughter atom or emission of an *Auger electron.*

The type of emission from a radionuclide largely determines its usefulness in medicine. Those emitting alpha particles are very little used partly because detection and measurement are difficult. Positron-emitters, such as carbon-11, fluorine-18, nitrogen-13, and oxygen-15, have become more popular in recent years and are used in positron-emission tomography (PET) where the radiation is measured from within the body, as opposed to computed tomography (CT) where the energy is supplied from an external source. Single photon emission tomography (SPECT) is another technique like positron-emission tomography that provides views of slices through the body and this technique uses gamma-ray emitting radionuclides which are the most accessible and the most common radiation source in radiopharmaceuticals.

Decay of Radionuclides

A radionuclide will consist of atoms in several forms, including: unstable atoms, which will at some time undergo an energy change with the emission of ionising radiation; those that are actually undergoing this change; and those that have undergone the change. In quantitative terms this transition occurs at a rate that is characteristic of the radionuclide and it is expressed as its half-life—the time required for the activity to fall by one-half. Many radionuclides have complex decay characteristics with several possible energies of emitted particles and radiation. Some radionuclides may be in an excited or metastable state denoted by the suffix m attached to the mass number (e.g. technetium-99m) and undergo *isomeric transition* (IT) with the release of gamma-rays.

The activity of radionuclides is measured in terms of the rate of transformation or disintegration. The unit is the becquerel (Bq) = 1 transformation/second; the curie (Ci) was formerly used as the unit of activity; $1\ Ci = 3.7 \times 10^{10}\ Bq$.

Supply, Preparation, and Control

A wide range of radionuclides and specially formulated radiopharmaceuticals is available from specialised manufacturers. However, there are national controls on the use, transport, storage, and disposal of such compounds. Authority and guidance should be sought from the relevant bodies and authorities before using such compounds.

Generators are special features in the supply of radionuclides. They are receptacles containing a parent and daughter nuclide in equilibrium and from which the daughter nuclide, which usually has a short half-life, may be eluted. Generators are available for the production of indium-113m, krypton-81m, and technetium-99m. Generators are also available for some positron-emitters.

Storage conditions for radiopharmaceuticals should be such as to prevent the inadvertent emission of radioactivity as well as to meet the storage requirements for the pharmaceutical that has been labelled. Thus due account still has to be paid, for instance, to the effects of temperature and light. Radiopharmaceuticals are liable to decomposition by self-irradiation effects which may cause degradation of solvent, preservative, or other compounds. There can also be a continuous formation of oxidising and reducing chemical species arising from the effect of the radioactivity on any chemical substances present in the radiopharmaceutical, even in minute amounts.

Adverse Effects

The internal irradiation of tissues after the use of radionuclides carries similar dangers to exposure to ionising radiation from an external source, and locally high radiation doses may arise if these nuclides are concentrated in a tissue. The most serious danger is genetic damage prior to and during the reproductive period. Tissues whose cells are in a continuous state of multiplication are particularly sensitive to the effects of radiation.

Untoward effects of exposure to the larger doses of irradiation include leucopenia, anaemia, inflammation of the skin, radiation sickness, and neoplasms.

In considering the effect of a given radionuclide it is usual to calculate the dose to the organ most critically affected, and also the dose to the whole body.

In considering the adverse effects of radiopharmaceuticals one should not forget the effects that might arise from the carrier or from contaminants.

General Uses

Radiopharmaceuticals are used widely in many branches of medicine and surgery, mainly for the diagnosis and sometimes for the treatment of disease. They can provide information not available using other diagnostic techniques such as contrast media, ultrasound, and computed tomography or other external irradiation. Highly specific information may be derived using monoclonal antibodies tagged with radionuclides.

Many investigations involve oral or parenteral doses of radionuclides or labelled compounds followed usually by an imaging procedure. Some investigations involve the measurement of radioactive concentrations in organs, tissues, blood, urine, or faeces. The quantities used are always the smallest that will give the desired accuracy of image or of measurement.

Radiological Terms

- Alpha particles–nuclei of helium atoms emitted by radioactive atomic nuclei
- annihilation–the interaction and disappearance of a positive and a negative electron with the conversion of their energy into electromagnetic radiation
- atomic number (Z)–the number of protons in the atomic nucleus
- Auger effect–the emission of an electron from an atom due to the filling of a vacancy in an inner electron shell
- becquerel (Bq)–the SI unit of activity, defined as 1 transformation/second. The curie was formerly used as the unit of activity. $1\ Bq = 2.7 \times 10^{-11}\ Ci$
- beta particles–electrons or positrons emitted by radioactive atomic nuclei
- carrier-free–a preparation in which substantially all the atoms of the activated element present are radioactive. Material of high specific activity is often loosely referred to as 'carrier-free'
- curie (Ci)–now superseded as a unit of activity by the becquerel. A curie (Ci) represented 3.7×10^{10} transformations/second. $1\ Ci = 3.7 \times 10^{10}\ Bq$
- daughter–of a given nuclide, any nuclide that originates from it by radioactive decay

- electron capture (EC)–a mode of radioactivity decay involving the capture of an orbital electron by its nucleus
- gamma-radiation–electromagnetic radiation emitted in the process of a change in configuration of a nucleus or particle annihilation and having wavelengths shorter than those of X-rays
- gray (Gy)–the SI unit of absorbed dose, defined as 1 J/kg. The rad was formerly used as the unit of absorbed dose. 1 Gy = 100 rads
- isomeric transition (IT)–the decay of one isomer to another having a lower energy state. The transition is accompanied by the emission of gamma-radiation
- isomers–nuclides with the same mass number and atomic number but with nuclei having different energy states
- isotopes–nuclides with the same atomic number but different mass numbers
- nuclide–a species of atom having a specific mass number, atomic number, and nuclear energy state
- photon–a quantum of electromagnetic radiation
- positron–a positive beta particle
- rad (radiation absorbed dose)–now superseded as a unit of absorbed dose by the gray. A rad is equal to 10^{-2} J/kg. The röntgen and the rad in soft tissue are approximately equivalent in magnitude for moderate energies. 1 rad = 10^{-2} Gy
- radioactive decay–the spontaneous change of a nucleus resulting in the emission of a particle or a photon
- radioactivity–the property of certain nuclides of spontaneously emitting particles or photons or of undergoing spontaneous fission
- radioisotope–an isotope that is radioactive
- radionuclide–a nuclide that is radioactive
- rem (röntgen-equivalent-man)–now superseded as a unit of dose equivalent by the sievert (Sv). A rem is numerically equal to the absorbed dose in rads multiplied by the appropriate quality factor defining the biological effect and by any other modifying factors. The sievert is the joule/kg (J kg^{-1}) equal to 100 rem
- röntgen (R)–a unit of exposure of X- or gamma-radiation, equal to 2.58×10^{-4} coulombs/kg in air; superseded by the SI unit of exposure, the coulomb/kg (C kg^{-1}). 1 C kg^{-1} = 3.876×10^3 R
- sievert (Sv)–the SI unit of dose equivalent numerically equal to the absorbed dose in grays multiplied by the appropriate quality factor defining the biological effect and by any other modifying factors expressed in J/kg
- specific activity–the activity per unit mass of a material containing a radioactive substance
- X-rays–electromagnetic radiation other than annihilation radiation originating in the extranuclear part of the atom and having wavelengths much shorter than those of visible light

Carbon-11

Carbono 11.

CAS — 14333-33-6.

HALF-LIFE. 20.4 minutes.

Profile

Carbon-11 is a positron-emitter that is used in positron-emission tomography (see Emissions from Radioisotopes, p.2052). Compounds that have been labelled with carbon-11 include L-methionine for the detection of malignant neoplasms, acetic and palmitic acids for the study of myocardial metabolism, raclopride and mespiperone for the study of CNS dopaminergic D_2 receptors, and flumazenil for the study of GABA receptors. Labelled carbon monoxide may be used to assess blood volume.

Preparations

Ph. Eur.: -Methionine ((C)Methyl) Injection; Flumazenil (N-(C)Methyl) Injection; Raclopride ((C)Methoxy) Injection; Sodium Acetate ((1- C)) Injection;
USP 31: Carbon Monoxide C 11; Flumazenil C 11 Injection; Mespiperone C 11 Injection; Methionine C 11 Injection; Raclopride C 11 Injection; Sodium Acetate C 11 Injection.

Carbon-14

Carbono 14.

CAS — 14762-75-5.

HALF-LIFE. 5730 years.

Profile

Carbon-14 has been used to label many organic compounds that may be employed in breath tests.

Urea (p.1620) labelled with carbon-14 is used in a breath test to detect *Helicobacter pylori* as an aid in the diagnosis of peptic ulcer disease (p.1702).

Preparations

USP 31: Urea C 14 Capsules.

Proprietary Preparations (details are given in Part 3)
Cz.: HeliCap; ***Neth.:*** HeliCap; ***Port.:*** HeliCap; ***USA:*** Pytest.

Chromium-51

Cromo 51.

CAS — 14392-02-0.
ATC — V09CX04 (chromium edetate (^{51}Cr)).
ATC Vet — QV09CX04 (chromium edetate (^{51}Cr)); QV09GX03 (chromate labelled cells (^{51}Cr)).

HALF-LIFE. 27.7 days.

Profile

Chromium-51, as sodium chromate (^{51}Cr), is used to label red blood cells so that red cell survival and red cell volume can be measured. Chromium-51 activity in the faeces can be used to estimate gastrointestinal blood losses. Red blood cells labelled with chromium-51 and damaged by heat before re-injection have been used for spleen scanning.

As chromium edetate (^{51}Cr) given intravenously, chromium-51 is used in the determination of the glomerular filtration rate.

As chromic chloride (^{51}Cr), chromium-51 has been given intravenously for the determination of loss of serum protein into the gastrointestinal tract.

Preparations

Ph. Eur.: Chromium(Cr) Edetate Injection; Sodium Chromate(Cr) Sterile Solution;
USP 31: Chromium Cr 51 Edetate Injection; Sodium Chromate Cr 51 Injection.

Cobalt-57

Cobalto 57.

CAS — 13981-50-5.
ATC — V09XX01 (cobalt cyanocobalamin (^{57}Co)).
ATC Vet — QV09XX01 (cobalt cyanocobalamin (^{57}Co)).

HALF-LIFE. 271 days.

Profile

Cobalt-57, in the form of an aqueous solution or capsules of cyanocobalamin (^{57}Co), is given orally for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes. It is also used with cyanocobalamin (^{58}Co), see below.

Preparations

Ph. Eur.: Cyanocobalamin(Co) Capsules; Cyanocobalamin(Co) Solution;
USP 31: Cyanocobalamin Co 57 Capsules; Cyanocobalamin Co 57 Oral Solution.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Cz.:* Dicopac†; ***UK:*** Dicopac.

Cobalt-58

Cobalto 58.

CAS — 13981-38-9.
ATC — V09XX02 (cobalt cyanocobalamin (^{58}Co)).
ATC Vet — QV09XX02 (cobalt cyanocobalamin (^{58}Co)).

HALF-LIFE. 70.8 days.

Profile

Cobalt-58, in the form of an aqueous solution or capsules of cyanocobalamin (^{58}Co), is given orally for the measurement of absorption of vitamin B_{12} in the diagnosis of pernicious anaemia and other malabsorption syndromes.

The different emissions of cobalt-57 and cobalt-58 allow the isotopes to be distinguished. This can be used to differentiate between failure of absorption due to lack of intrinsic factor (pernicious anaemia) and that due to ileal malabsorption, by giving both free cyanocobalamin (^{58}Co) and cyanocobalamin (^{57}Co) bound to intrinsic factor. A dual isotope kit has been used for this purpose.

Preparations

Ph. Eur.: Cyanocobalamin(Co) Capsules; Cyanocobalamin(Co) Solution;
USP 31: Cyanocobalamin Co 58 Capsules.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Cz.:* Dicopac†; ***UK:*** Dicopac.

Erbium-169

CAS — 15840-13-8.
ATC — V10AX04 (erbium citrate colloid (^{169}Er)).
ATC Vet — QV10AX04 (erbium citrate colloid (^{169}Er)).

HALF-LIFE. 9.4 days.

Profile

Erbium-169 is a radionuclide that has been used in the treatment of arthritic conditions particularly of the small joints.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ermm-1.

Fluorine-18

Flúor 18.

CAS — 13981-56-1.
ATC — V09IX04 (fludeoxyglucose (^{18}F)).
ATC Vet — QV09IX04 (fludeoxyglucose (^{18}F)).

HALF-LIFE. 110 minutes.

Profile

Fluorine-18 is a positron-emitting radionuclide that is used in positron-emission tomography (see Emissions from Radioisotopes, p.2052).

Fludeoxyglucose (^{18}F) (2-deoxy-2-fluoro-^{18}F-α-D-glucopyranose; ^{18}F-fluorodeoxyglucose) is given by intravenous injection for the assessment of cerebral and myocardial glucose metabolism in various physiological or pathological states including stroke and myocardial ischaemia. It is also used for the detection of malignant tumours including those of the brain, liver, lung, and thyroid gland. Fluorodopa (^{18}F) is also used in cerebral imaging. Sodium fluoride (^{18}F) is used in bone scanning.

Preparations

Ph. Eur.: Fludeoxyglucose (F) Injection; Sodium Fluoride (F) Injection;
USP 31: Fludeoxyglucose F 18 Injection; Fluorodopa F 18 Injection; Sodium Fluoride F 18 Injection.

Proprietary Preparations (details are given in Part 3)
Austria: 18F-FDG; Efdege; Flucis; ***Cz.:*** Efdege; FDG Scan; ***Hung.:*** Pozitron-Scan-FDG; ***Neth.:*** Efdege; Flucis; Glucotrace; ***Port.:*** Contracer; Flucis; Steripet; ***Spain:*** Farna FDG; FDG Scan; Fluodos; Fluorscan; Fluotracer.

Gallium-67

Galio 67.

CAS — 14119-09-6.
ATC — V09HX01 (gallium citrate (^{67}Ga)).
ATC Vet — QV09HX01 (gallium citrate (^{67}Ga)).

HALF-LIFE. 3.26 days.

Profile

Gallium-67 is used in the form of an intravenous injection of gallium citrate (^{67}Ga).

Gallium citrate (^{67}Ga) is concentrated in some malignant tumours of the lymphatic system, as well as in some other tissues, and is used for tumour visualisation. Concentration also occurs in inflammatory lesions and the injection is therefore used for the localisation of focal inflammatory sites, such as may occur in abscesses, osteomyelitis, or sarcoidosis. Gallium scans have proved useful for the detection of the various infections and malignancies that may be encountered in patients with AIDS.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to gallium-67 since radioactivity has been reported to be present in breast milk for 2 weeks.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Ph. Eur.: Gallium(Ga) Citrate Injection;
USP 31: Gallium Citrate Ga 67 Injection.

Gold-198

Oro 198.

CAS — 10043-49-9.
ATC — V10AX06 (colloidal gold (^{198}Au)).
ATC Vet — QV10AX06 (colloidal gold (^{198}Au)).

HALF-LIFE. 65 hours (2.7 days).

Profile

Gold-198, as colloidal gold (^{198}Au) with most of the activity associated with particles of diameter 5 to 20 nm, has been used by intrapleural or intraperitoneal injection in the treatment of malignant ascites and malignant pleural effusion, and by intravenous injection for the measurement of liver blood flow, in liver scanning, and for general investigations of the reticuloendothelial system. Since the gamma-ray energies are not particularly good for scanning and the radiation dose to the patient is relatively high, it has generally been superseded by more suitable agents such as technetium-99m-labelled compounds.

Indium-111

Indio 111.

CAS — 15750-15-9.

ATC — V09AX01 (indium pentetate (^{111}In)); V09GX02 (indium imciromab (^{111}In)); V09HB01 (indium oxinate labelled cells (^{111}In)); V09HB02 (indium tropolonate labelled cells (^{111}In)); V09IB01 (indium pentetreotide (^{111}In)); V09IB02 (indium satumomab pendetide (^{111}In)); V09IB03 (indium antiovariumcarcinoma antibody (^{111}In)); V09IB04 (indium capromab pendetide (^{111}In)).

ATC Vet — QV09AX01 (indium pentetate (^{111}In)); QV09GX02 (indium imciromab (^{111}In)); QV09HB01 (indium oxinate labelled cells (^{111}In)); QV09HB02 (indium tropolonate labelled cells (^{111}In)); QV09IB01 (indium pentetreotide (^{111}In)); QV09IB02 (indium satumomab pendetide (^{111}In)); QV09IB03 (indium antiovariumcarcinoma antibody (^{111}In)); QV09IB04 (indium capromab pendetide (^{111}In)).

HALF-LIFE. 67 hours (2.8 days).

Profile

Indium-111 as indium (^{111}In) complexed with pentetic acid (pentetate) is used diagnostically in CSF studies.

Leucocytes labelled with indium (^{111}In) hydroxyquinoline are used for the location of inflammatory lesions; applications have been the detection or localisation of abscesses, infections (including those occurring in patients with AIDS), inflammatory bowel diseases such as Crohn's disease or ulcerative colitis, and transplant rejection. Platelets have been similarly labelled and used for the detection of thrombi and for the investigation of thrombocytopenia. Labelled erythrocytes have been used to investigate gastrointestinal haemorrhage.

Colloids have been prepared using indium chloride (^{111}In) and have been used for investigation of the lymphatic system. Indium (^{111}In) bleomycin has been given by intravenous injection for the detection of tumours. Indium (^{111}In) pentetreotide is used for the detection and localisation of tumours originating from neuroendocrine cells.

Several different monoclonal antibodies, such as altumomab pentetate, capromab pendetide, ibritumomab tiuxetan, imciromab pentetate, and satumomab pendetide, have been labelled with indium-111. Uses include the detection, diagnosis, and evaluation of malignant neoplasms of the colon, rectum, prostate, and ovaries as well as the detection and localisation of myocardial infarction.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to indium-111 since a very small amount of radioactivity has been reported to be present in breast milk for 20 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Ph. Eur.: Indium(In) Chloride Solution; Indium(In) Oxine Solution; Indium(In) Pentetate Injection;
USP 31: Indium In 111 Capromab Pentetide Injection; Indium In 111 Chloride Solution; Indium In 111 Ibritumomab Tiuxetan Injection; Indium In 111 Oxyquinoline Solution; Indium In 111 Pentetate Injection; Indium In 111 Pentetreotide Injection; Indium In 111 Satumomab Pendetide Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Octreoscan; ***Cz.:*** Myoscint†; Octreoscan; OncoScint†; ***Israel:*** Prostascint Kit; ***Ital.:*** Octreoscan; ***Neth.:*** OctreoScan; ***Port.:*** Octreoscan; ***Spain:*** OncoScint CR 103†; ***USA:*** Octreoscan; OncoScint CR/OV†.

Indium-113m

Indio 113m.

CAS — 14885-78-0 (indium-113).

HALF-LIFE. 99.5 minutes.

Profile

Indium-113m is a daughter of tin-113 (^{113}Sn, half-life 115 days) and because of its short half-life is normally prepared just before use by elution from a sterile generator consisting of tin-113 adsorbed on an ion-exchange material contained in a column.

Indium-113m may be used for labelling a variety of materials with differing physical properties including particles and colloids suited to scanning procedures for various organs and tissues. Chelates with pentetic acid have also been used. The short half-life of indium-113m and its lack of beta-emission have allowed large doses to be given with a small radiation dose to the patient. High count rates for scanning are therefore achieved.

Iodine-123

Iodo 123.

CAS — 15715-08-9.

ATC — V09AB01 (iodine iofetamine (^{123}I)); V09AB02 (iodine iolopride (^{123}I)); V09AB03 (iodine ioflupane (^{123}I)); V09CX01 (sodium iodohippurate (^{123}I)); V09FX02 (sodium iodide (^{123}I)); V09IX01 (iobenguane (^{123}I)).

ATC Vet — QV09AB01 (iodine iofetamine (^{123}I)); QV09AB02 (iodine iolopride (^{123}I)); QV09AB03 (iodine ioflupane (^{123}I)); QV09CX01 (sodium iodohippurate (^{123}I)); QV09FX02 (sodium iodide (^{123}I)); QV09IX01 (iobenguane (^{123}I)).

HALF-LIFE. 13.2 hours.

Profile

Iodine-123 has similar adverse effects and precautions to those of iodine-131 (see below).

Its principal use is in thyroid uptake tests and thyroid imaging when it is given orally or by intravenous injection as sodium iodide (^{123}I).

Sodium iodohippurate (^{123}I) is given intravenously in tests of renal function and in renal imaging.

Iobenguane (^{123}I) (*m*-iodobenzylguanidine (^{123}I)) is given intravenously for the localisation of certain tumours, for example phaeochromocytomas, and for the evaluation of neuroblastoma. It is also used for functional studies of the adrenal medulla and myocardium.

Ioflupane (^{123}I) is given intravenously to detect loss of functioning dopaminergic neurones in the differential diagnosis of tremor and parkinsonism.

Various monoclonal antibodies have been labelled with iodine-123; potential applications include the detection of malignant neoplasms.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to iodine-123 since radioactivity has been reported to be present in breast milk for up to 36 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Ph. Eur.: Sodium Iodide(I) Injection; Sodium Iodide(I) Solution for Radiolabelling; Sodium Iodohippurate(I) Injection;
USP 31: Iobenguane I 123 Injection; Iodohippurate Sodium I 123 Injection; Sodium Iodide I 123 Capsules; Sodium Iodide I 123 Solution.

Proprietary Preparations (details are given in Part 3)
Cz.: DaTSCAN; Hippuran; ***Fr.:*** DaTSCAN; ***Ital.:*** DaTSCAN; ***Neth.:*** AdreView; DaTSCAN; Hippuran; ***Port.:*** DaTSCAN; ***UK:*** DaTSCAN.

Iodine-125

Iodo 125.

CAS — 14158-31-7.

ATC — V09CX03 (sodium iotalamate (^{125}I)); V09GB01 (fibrinogen (^{125}I)); V09GB02 (iodinated human albumin (^{125}I)); V09IX03 (iodine CC49 monoclonal antibody (^{125}I)).

ATC Vet — QV09CX03 (sodium iotalamate (^{125}I)); QV09GB01 (fibrinogen (^{125}I)); QV09GB02 (iodinated human albumin (^{125}I)); QV09IX03 (iodine CC49 monoclonal antibody (^{125}I)).

HALF-LIFE. 60.1 days.

Profile

Iodine-125 has similar adverse effects and precautions to those of iodine-131 (see below).

Iodine-125 is not very suitable for the external counting of radioactivity in the thyroid gland because its gamma-energy is weak and tissue absorption is high. However, it is very suitable for radio-immunoassays *in vitro* and because it has a long half-life it is preferred as a label for many compounds to detect and estimate drugs and hormones in body fluids.

Iodine-125 has been used orally as sodium iodide (^{125}I) in the diagnosis of thyroid disorders.

Sodium iotalamate (^{125}I) has been used intravenously in the determination of glomerular filtration rate and sodium iodohippurate (^{125}I) intravenously for the measurement of effective renal plasma flow.

Iodine-125, as iodinated (^{125}I) human fibrinogen, has been used intravenously to demonstrate and locate deep-vein thrombosis of the leg. Iodinated (^{125}I) fibrinogen has also been used in the measurement of fibrinogen metabolism in certain disturbances of blood coagulation.

Human albumin iodinated with iodine-125 has been used for the determination of blood or plasma volume.

Iodine-125 implants have been used for the local treatment of cancers (brachytherapy). Titanium capsules containing iodine-125 adsorbed onto a silver rod have been used in the treatment of cancers of the head and neck, lung, pancreas, and prostate. Brain tumours have been treated with titanium capsules containing iodine-125 adsorbed onto anion exchange resin spheres.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to iodine-125 since radioactivity has been reported to be present in breast milk for 12 days.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Preparations

Ph. Eur.: Human Albumin Injection, Iodinated (I);
USP 31: Iodinated I 125 Albumin Injection; Iothalamate Sodium I 125 Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: OncoSeeds; Rapid Strand; ***USA:*** Glofil.

Iodine-131

Iodo 131.

CAS — 10043-66-0.

ATC — V09CX02 (sodium iodohippurate (^{131}I)); V09FX03 (sodium iodide (^{131}I)); V09IX02 (iobenguane (^{131}I)); V09XA01 (iodine norcholesterol (^{131}I)); V09XA02 (iodocholesterol (^{131}I)); V09XA03 (iodinated human albumin (^{131}I)); V10XA01 (sodium iodide (^{131}I)); V10XA02 (iobenguane (^{131}I)); V10XA53 (iodine tositumomab (^{131}I)).

ATC Vet — QV09CX02 (sodium iodohippurate (^{131}I)); QV09FX03 (sodium iodide (^{131}I)); QV09IX02 (iobenguane (^{131}I)); QV09XA01 (iodine norcholesterol (^{131}I)); QV09XA02 (iodocholesterol (^{131}I)); QV09XA03 (iodinated human albumin (^{131}I)); QV10XA01 (sodium iodide (^{131}I)); QV10XA02 (iobenguane (^{131}I)); QV10XA53 (iodine tositumomab (^{131}I)).

HALF-LIFE. 8.04 days.

Adverse Effects

A percentage of patients treated with iodine-131 for hyperthyroidism become hypothyroid each year, depending on the dose given, and eventually most patients will require thyroid replacement therapy. Hypoparathyroidism has also been reported. Radiation thyroiditis with soreness may develop shortly after treatment. There may be severe and potentially dangerous swelling of the thyroid especially in patients with large goitres and this has on rare occasions produced asphyxiation. Leukaemia and carcinoma of the thyroid have occasionally been reported, particularly in young patients. Retrospective studies have shown an increased incidence of thyroid cancer in adults after iodine-131 treatment for hyperthyroidism. However, the absolute risk of thyroid cancer is small and the underlying thyroid disease may play a role.

In the treatment of thyroid carcinoma, the larger doses of radioactive iodine sometimes cause nausea and vomiting a few days after ingestion, which may be due to gastritis as iodine-131 is also concentrated in gastric mucosa. Salivary gland toxicity may also occur. Large doses depress the bone marrow.

◊ References.

1. Ron E, *et al.* Cancer mortality following treatment for adult hyperthyroidism. *JAMA* 1998; **280:** 347–55.
2. Franklyn JA, *et al.* Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999; **353:** 2111–15.
3. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. *Pediatrics* 2003; **111:** 745–9.

Precautions

The use of sodium iodide (^{131}I) is contra-indicated, even in diagnostic doses, during pregnancy. Sodium iodide (^{131}I) should not be given to patients with large toxic nodular goitres or to patients with severe thyrotoxic heart disease. There is some controversy as to whether radio-iodine therapy exacerbates Graves' ophthalmopathy (see Hyperthyroidism, p.2165).

Many drugs have been reported to interfere with thyroid- or other organ-function studies and checks should be made on any treatment the patient might be receiving before any estimations are carried out.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to iodine-131 since radioactivity has been reported to be present in breast milk for 2 to 14 days; high doses used for the treatment of thyroid cancer may prolong exposure to the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Uses and Administration

Iodine radioisotopes are mainly used in studies of thyroid function and in the treatment of hyperthyroidism (p.2165) and some forms of thyroid carcinoma (p.674).

Iodine radioisotopes can be incorporated into many compounds including liothyronine and levothyroxine, triglycerides and fatty acids, such as glyceryl trioleate and oleic acid, and proteins, such as iodinated human albumin, with varying degrees of stability and with little or no change in the biological activity of the labelled molecule. It is common practice to saturate the thyroid with non-radioactive iodine when uptake of radiation by the gland is not desired (see Radiation Protection, p.2171).

Sodium iodide (^{131}I) is given orally and by intravenous injection in studies of thyroid function, particularly in measurements of the uptake of iodine by the thyroid, and in thyroid scanning. It is also used in the treatment of hyperthyroidism and in the treatment of malignant neoplasms of the thyroid.

Injections containing iobenguane (^{131}I) (*m*-iodobenzylguanidine (^{131}I)) may be used for the localisation and treatment of phaeochromocytoma (p.1179) and neuroblastoma (p.674).

Human albumin iodinated with iodine-131 is used in the determination of the blood or plasma volume.

Sodium iodohippurate (^{131}I) is used intravenously for renal-function tests and for renal imaging.

Rose bengal sodium (^{131}I) has been given intravenously in tests of liver function.

Iodinated (^{131}I) norcholesterol (6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (^{131}I)) has been used for adrenal scintigraphy by slow intravenous injection.

Various monoclonal antibodies labelled with iodine-131 are used for the detection of malignant neoplasms and some are used for therapeutic purposes, such as iodine (^{131}I) tositumomab for non-Hodgkin's lymphoma.

Preparations

Ph. Eur.: Iobenguane(I) Injection for Diagnostic Use; Iobenguane(I) Injection for Therapeutic Use; Iodinated(I) Norcholesterol Injection; Sodium Iodide(I) Capsules for Diagnostic Use; Sodium Iodide(I) Capsules for Therapeutic Use; Sodium Iodide(I) Solution; Sodium Iodide(I) Solution for Radiolabelling; Sodium Iodohippurate(I) Injection;
USP 31: Iobenguane I 131 Injection; Iodinated I 131 Albumin Aggregated Injection; Iodinated I 131 Albumin Injection; Iodohippurate Sodium I 131 Injection; Rose Bengal Sodium I 131 Injection; Sodium Iodide I 131 Capsules; Sodium Iodide I 131 Solution.

Proprietary Preparations (details are given in Part 3)
Cz.: Capsion; Curicap; Hippuran; Lipiocis†; Theracap; ***Neth.:*** Capsion; Jobenguaan; MIBG; Theracap; ***Port.:*** Capsion; Curicap; Theracap; ***Spain:*** Curicap; ***UK:*** Capsion; Theracap; ***USA:*** Bexxar; Hicon; Iodotope.

Iron-59

Hierro 59.
CAS — 14596-12-4.
ATC — V09XX04 (ferric citrate (^{59}Fe)).
ATC Vet — QV09XX04 (ferric citrate (^{59}Fe)).

HALF-LIFE. 44.6 days.

Profile

Iron-59, in the form of ferrous citrate (^{59}Fe) or ferric citrate (^{59}Fe), has been used by intravenous injection in the measurement of iron absorption and utilisation. Ferric chloride (^{59}Fe) has been given for the same purpose.

Krypton-81m

Criptón 81m.
CAS — 15678-91-8.
ATC — V09EX01 (krypton gas (^{81m}Kr)).
ATC Vet — QV09EX01 (krypton gas (^{81m}Kr)).

HALF-LIFE. 13.1 seconds.

Profile

Krypton-81m is a daughter of rubidium-81 (^{81}Rb, half-life 4.58 hours), and is prepared immediately before use by elution from a generator containing rubidium-81 adsorbed on a suitable ion-exchange column using air or oxygen as the eluent. Krypton-81m is used as a gas in lung ventilation studies. Such ventilation studies can be combined with lung perfusion studies to diagnose pulmonary embolism.

Preparations

Ph. Eur.: Krypton(Kr) Inhalation Gas;
USP 31: Krypton Kr 81m.

Proprietary Preparations (details are given in Part 3)
Cz.: KryptoScan; ***Neth.:*** KryptoScan.

Nitrogen-13

Nitrógeno 13.
CAS — 13981-22-1.

HALF-LIFE. 9.96 minutes.

Profile

Nitrogen-13 is a positron-emitting radionuclide that is used in positron-emission tomography (see Emissions from Radioisotopes, p.2052). In the form of ammonia (^{13}N) it is given intravenously for imaging blood flow in organs such as the heart, brain, and liver. Nitrogen gas (^{13}N) may be used for pulmonary ventilation studies.

Preparations

Ph. Eur.: Ammonia(N) Injection;
USP 31: Ammonia N 13 Injection.

Oxygen-15

Oxígeno 15.
CAS — 13982-43-9.

HALF-LIFE. 2 minutes.

Profile

Oxygen-15 is a positron-emitting radionuclide used in positron-emission tomography (see Emissions from Radioisotopes, p.2052). It is used in the form of water (^{15}O) and is given intravenously to study cerebral and myocardial perfusion.

Oxygen gas, carbon dioxide, and carbon monoxide have also been labelled with oxygen-15.

Preparations

Ph. Eur.: Carbon Monoxide(O); Oxygen(O); Water(O) Injection;
USP 31: Water O 15 Injection.

Phosphorus-32

Fósforo 32.
CAS — 14596-37-3.
ATC — V10AX01 (phosphorus chromic phosphate colloid (^{32}P)); V10XX01 (sodium phosphate (^{32}P)).
ATC Vet — QV10AX01 (phosphorus chromic phosphate colloid (^{32}P)); QV10XX01 (sodium phosphate (^{32}P)).

HALF-LIFE. 14.3 days.

Profile

Phosphorus-32, given as sodium phosphate (^{32}P), is used intravenously in the treatment of polycythaemia vera (p.654). Phosphorus-32 is taken up by the rapidly proliferating haematopoietic cells sufficiently to reduce their reproduction. Sodium phosphate (^{32}P) has also been used intravenously in the treatment of chronic myeloid (p.653) and chronic lymphocytic leukaemia (p.653) and in the palliative treatment of bone metastases.

Chromic phosphate (^{32}P) is given intraperitoneally or intrapleurally in the treatment of malignant effusions (p.659); it may also be given by interstitial injection for the treatment of ovarian (p.670) or prostatic carcinoma (p.671).

Preparations

Ph. Eur.: Sodium Phosphate(P) Injection;
USP 31: Chromic Phosphate P 32 Suspension; Sodium Phosphate P 32 Solution.

Proprietary Preparations (details are given in Part 3)
USA: Phosphocol.

Rhenium-186

Renio 186.
CAS — 14998-63-1.
ATC — V10AX05 (rhenium sulfide colloid (^{186}Re)); V10BX03 (rhenium etidronate (^{186}Re)).
ATC Vet — QV10AX05 (rhenium sulfide colloid (^{186}Re)); QV10BX03 (rhenium etidronate (^{186}Re)).

HALF-LIFE. 90.6 hours.

Profile

Rhenium-186 has been used in colloidal form for the treatment of arthritic joint conditions. Rhenium (^{186}Re) etidronate is used for the palliation of painful bone metastases of prostate cancer. Etidronate labelled with another isotope, rhenium-188, has also been used. Monoclonal antibodies labelled with rhenium-186 have been investigated for the treatment of various malignant neoplasms.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Nanocis; RE-186-MM-1; Re-Bone.

Rubidium-82

Rubidio 82.
CAS — 14391-63-0.

HALF-LIFE. 75 seconds.

Profile

Rubidium-82 is a positron-emitting radionuclide that is used in positron-emission tomography (see Emissions from Radioisotopes, p.2052). Rubidium chloride (^{82}Rb) is given intravenously for cardiac imaging.

Preparations

USP 31: Rubidium Chloride Rb 82 Injection.

Samarium-153

Samario 153.
CAS — 15766-00-4.
ATC — V10AX02 (samarium hydroxyapatite colloid (^{153}Sm)); V10BX02 (samarium lexidronam (^{153}Sm)).
ATC Vet — QV10AX02 (samarium hydroxyapatite colloid (^{153}Sm)); QV10BX02 (samarium lexidronam (^{153}Sm)).

HALF-LIFE. 47 hours.

Profile

Samarium-153, in the form of samarium (^{153}Sm) lexidronam (samarium (^{153}Sm) EDTMP) is used for the palliative treatment of painful bone metastases (p.660). It is given by intravenous injection.

◊ References.

1. Sartor O, *et al.* Samarium-153-lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004; **63:** 940–5.

Preparations

USP 31: Samarium Sm 153 Lexidronam Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Quadramet†; ***Cz.:*** Quadramet; ***Fr.:*** Quadramet†; ***Ital.:*** Quadramet; ***Neth.:*** Quadramet; ***Port.:*** Quadramet; ***Spain:*** Quadramet; ***UK:*** Quadramet; ***USA:*** Quadramet.

Selenium-75

Selenio 75.
CAS — 14265-71-5.
ATC — V09DX01 (selenium tauroselcholic acid (^{75}Se)); V09XX03 (selenium norcholesterol (^{75}Se)).
ATC Vet — QV09DX01 (selenium tauroselcholic acid (^{75}Se)); QV09XX03 (selenium norcholesterol (^{75}Se)).

HALF-LIFE. 118.5 days.

Profile

Selenium-75 in the form of tauroselcholic acid (^{75}Se) (^{75}SeHCAT) is used orally in the measurement of bile acid absorption for the assessment of ileal function.

Selenium-75 in the form of 6β-[(methyl[^{75}Se]seleno)methyl]-19-norcholest-5(10)-en-3β-ol (selenonorcholestenol (^{75}Se)) has been used intravenously in adrenal scintigraphy.

Preparations

Proprietary Preparations (details are given in Part 3)
Neth.: SeHCAT; ***UK:*** Scintadren.

Strontium-89

Estroncio 89.
CAS — 14158-27-1.
ATC — V10BX01 (strontium chloride (^{89}Sr)).
ATC Vet — QV10BX01 (strontium chloride (^{89}Sr)).

HALF-LIFE. 50.5 days.

Profile

Strontium-89, in the form of strontium chloride (^{89}Sr), is used for the palliation of pain in patients with bone metastases (p.660); it is given intravenously.

◊ References.

1. Robinson RG, *et al.* Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995; **274:** 420–4.

Preparations

Ph. Eur.: Strontium(Sr) Chloride Injection;
USP 31: Strontium Chloride Sr 89 Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Metastron; ***Austria:*** Metastron; ***Cz.:*** Metastron; ***Fr.:*** Metastron; ***Ital.:*** Metastron; ***Neth.:*** Metastron; ***Port.:*** Metastron; ***Spain:*** Metastron; ***UK:*** Metastron; ***USA:*** Metastron.

Technetium-99m

Tecnecio 99m.
CAS — 14133-76-7 (technetium-99).
ATC — V09AA01 (technetium exametazime (^{99m}Tc)); V09AA02 (technetium bicisate (^{99m}Tc)); V09BA01 (technetium oxidronate (^{99m}Tc)); V09BA02 (technetium medronate (^{99m}Tc)); V09BA03 (technetium pyrophosphate (^{99m}Tc)); V09BA04 (technetium butedronate (^{99m}Tc)); V09CA01 (technetium pentetate (^{99m}Tc)); V09CA02 (technetium succimer (^{99m}Tc)); V09CA03 (technetium mertiatide (^{99m}Tc)); V09CA04 (technetium gluceptate (^{99m}Tc)); V09CA05 (technetium gluconate (^{99m}Tc)); V09DA01 (technetium disofenin (^{99m}Tc)); V09DA02 (technetium etifenin (^{99m}Tc)); V09DA03 (technetium lidofenin (^{99m}Tc)); V09DA04 (technetium mebrofenin (^{99m}Tc)); V09DA05 (technetium galtifenin (^{99m}Tc)); V09DB01 (technetium nanocolloid (^{99m}Tc)); V09DB02 (technetium microcolloid (^{99m}Tc)); V09DB03 (technetium millimicrospheres (^{99m}Tc)); V09DB04 (technetium tin colloid (^{99m}Tc)); V09DB05 (technetium sulfur colloid (^{99m}Tc)); V09DB06 (technetium rhenium sulfide colloid (^{99m}Tc)); V09DB07 (technetium phytate (^{99m}Tc)); V09EA01 (technetium pentetate (^{99m}Tc)); V09EA02 (technetium technegas (^{99m}Tc)); V09EA03 (technetium nanocolloid (^{99m}Tc)); V09EB01 (technetium macrosalb (^{99m}Tc)); V09EB02 (technetium microspheres (^{99m}Tc)); V09FX01 (technetium pertechnetate (^{99m}Tc)); V09GA01 (technetium sestamibi (^{99m}Tc)); V09GA02 (technetium tetrofosmin (^{99m}Tc)); V09GA03 (technetium teboroxime (^{99m}Tc)); V09GA04 (technetium human albumin (^{99m}Tc)); V09GA05 (technetium furifosmin (^{99m}Tc)); V09GA06 (technetium stannous agent labelled cells (^{99m}Tc)); V09GA07 (technetium apcitide (^{99m}Tc)); V09HA01 (technetium human immunoglobulin (^{99m}Tc)); V09HA02 (technetium exametazime labelled cells

(^{99m}Tc)); V09HA03 (technetium antigranulocyte antibody (^{99m}Tc)); V09HA04 (technetium sulesomab (^{99m}Tc)); V09IA01 (technetium antiCEA antibody (^{99m}Tc)); V09IA02 (technetium antimelanoma antibody (^{99m}Tc)); V09IA03 (technetium pentavalent succimer (^{99m}Tc)); V09IA04 (technetium votumumab (^{99m}Tc)); V09IA05 (technetium depreotide (^{99m}Tc)); V09IA06 (technetium arcitumomab (^{99m}Tc)).

ATC Vet — QV09AA01 (technetium exametazime (^{99m}Tc)); QV09AA02 (technetium bicisate (^{99m}Tc)); QV09BA01 (technetium oxidronate (^{99m}Tc)); QV09BA02 (technetium medronate (^{99m}Tc)); QV09BA03 (technetium pyrophosphate (^{99m}Tc)); QV09BA04 (technetium butedronate (^{99m}Tc)); QV09CA01 (technetium pentetate (^{99m}Tc)); QV09CA02 (technetium succimer (^{99m}Tc)); QV09CA03 (technetium mertiatide (^{99m}Tc)); QV09CA04 (technetium gluceptate (^{99m}Tc)); QV09CA05 (technetium gluconate (^{99m}Tc)); QV09DA01 (technetium disofenin (^{99m}Tc)); QV09DA02 (technetium etifenin (^{99m}Tc)); QV09DA03 (technetium lidofenin (^{99m}Tc)); QV09DA04 (technetium mebrofenin (^{99m}Tc)); QV09DA05 (technetium galtifenin (^{99m}Tc)); QV09DB01 (technetium nanocolloid (^{99m}Tc)); QV09DB02 (technetium microcolloid (^{99m}Tc)); QV09DB03 (technetium millimicrospheres (^{99m}Tc)); QV09DB04 (technetium tin colloid (^{99m}Tc)); QV09DB05 (technetium sulfur colloid (^{99m}Tc)); QV09DB06 (technetium rhenium sulfide colloid (^{99m}Tc)); QV09DB07 (technetium phytate (^{99m}Tc)); QV09EA01 (technetium pentetate (^{99m}Tc)); QV09EA02 (technetium technegas (^{99m}Tc)); QV09EA03 (technetium nanocolloid (^{99m}Tc)); QV09EB01 (technetium macrosalb (^{99m}Tc)); QV09EB02 (technetium microspheres (^{99m}Tc)); QV09FX01 (technetium pertechnetate (^{99m}Tc)); QV09GA01 (technetium sestamibi (^{99m}Tc)); QV09GA02 (technetium tetrofosmin (^{99m}Tc)); QV09GA03 (technetium teboroxime (^{99m}Tc)); QV09GA04 (technetium human albumin (^{99m}Tc)); QV09GA05 (technetium furifosmin (^{99m}Tc)); QV09GA06 (technetium stannous agent labelled cells (^{99m}Tc)); QV09GA07 (technetium apcitide (^{99m}Tc)); QV09HA01 (technetium human immunoglobulin (^{99m}Tc)); QV09HA02 (technetium exametazime labelled cells (^{99m}Tc)); QV09HA03 (technetium antigranulocyte antibody (^{99m}Tc)); QV09HA04 (technetium sulesomab (^{99m}Tc)); QV09IA01 (technetium antiCEA antibody (^{99m}Tc)); QV09IA02 (technetium antimelanoma antibody (^{99m}Tc)); QV09IA03 (technetium pentavalent succimer (^{99m}Tc)); QV09IA04 (technetium votumumab (^{99m}Tc)); QV09IA05 (technetium depreotide (^{99m}Tc)); QV09IA06 (technetium arcitumomab (^{99m}Tc)).

HALF-LIFE. 6.02 hours.

Adverse Effects and Precautions

Hypersensitivity reactions have been reported with technetium-99m preparations.

Breast feeding. The American Academy of Pediatrics has stated[1] that temporary cessation of breast feeding is required after exposure to technetium-99m since radioactivity has been reported to be present in breast milk for 15 to 72 hours.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/07/04)

Uses and Administration

Technetium-99m is a daughter of molybdenum-99 (^{99}Mo, half-life 66.2 hours) and because of its short half-life is normally prepared just before use by elution from a sterile generator consisting of molybdenum-99 adsorbed onto alumina in a glass column. Technetium-99m as pertechnetate ($^{99m}TcO_4^-$) is obtained by elution with a sterile solution of sodium chloride 0.9%. Radiopharmaceuticals of technetium-99m are prepared shortly after elution to reduce loss by decay.

Because it has a short half-life and can be given in relatively large doses, and because the energy of its gamma-emission is readily detected, technetium-99m is very widely used, either as the pertechnetate or in the form of various labelled compounds, particles, and colloids for scanning bone and organs such as the brain, heart, kidney, liver, lung, spleen, and thyroid.

Sodium pertechnetate (^{99m}Tc) is used intravenously for angiography and for imaging blood pools, brain, salivary glands, and thyroid gland; the oral route may also be used for brain and thyroid imaging. Topical application to the eye is used for studying nasolachrymal drainage and the intraurethral route for imaging the urinary tract. Potassium perchlorate may be given before the pertechnetate to prevent uptake in the thyroid or choroid plexus and thus enhance visualisation in other organs.

Macroaggregates of human albumin labelled with technetium-99m [macrosalb (^{99m}Tc)] are used in lung scanning for the detection of abnormal lung perfusion patterns; after intravenous injection of a suspension of suitable particle size, usually 10 to 100 micrometres, the particles become trapped in the lung capillaries enabling ischaemic areas to be defined. Labelled albumin microspheres of particle size 10 to 50 micrometres are used similarly. Labelled macroaggregates of albumin have also been used in venography for the detection of deep-vein thrombosis of the legs. Technetium (^{99m}Tc) apcitide is a labelled peptide that binds to the glycoprotein IIb/IIIa receptor of activated platelets, and is also used for imaging of deep-vein thrombosis.

When technetium-99m bound to human serum albumin is given intravenously it becomes evenly distributed in the circulation and highly vascular organs or pools of blood may be readily located. Such a preparation is used in the examination of the heart.

Technetium-99m in the form of a colloid, such as albumin, sulfur, antimony sulfide, or tin, is used intravenously for the examination of the liver, spleen, and bone marrow. Sulfur colloid (^{99m}Tc) may be given orally for oesophageal and gastrointestinal imaging. Albumin colloid (^{99m}Tc) may be given subcutaneously for scanning of the lymphatic system. Colloidal rhenium sulfide (^{99m}Tc) has been used for sentinel lymph node detection in patients with malignancies.

Technetium-99m complexes of iminodiacetic acid derivatives, such as disofenin, etifenin, lidofenin, and mebrofenin are used intravenously in the investigation of hepatic function and in the imaging of the hepatobiliary system.

Agents used intravenously in both brain and renal imaging are technetium-99m-labelled gluconate, gluceptate, and pentetate. Other technetium-99m-labelled compounds are used in brain and kidney scanning; for instance, labelled bicisate and exametazime have been used in brain imaging and betiatide, mertiatide, and succimer have been used in kidney studies. The pentetate is also given by inhalation for lung ventilation imaging, and orally for studies of gastro-oesophageal reflux and gastric emptying.

For bone scanning various labelled phosphate compounds may be used and include medronate, oxidronate, and pyrophosphate, all given intravenously. Technetium-99m as the pyrophosphate is also used in cardiac scintigraphy. Technetium-99m as the medronate and pyrophosphate are also used to label red blood cells for use in blood pool scintigraphy, cardiac scintigraphy, detection of gastrointestinal bleeding, and testicular scintigraphy.

Compounds used intravenously in cardiac imaging include technetium-99m-labelled sestamibi, teboroxime, and tetrofosmin. Technetium (^{99m}Tc) sestamibi is also used for breast imaging.

Technetium-99m-labelled leucocytes (prepared using exametazime) are used for localisation of sites of inflammation or infection.

Monoclonal antibodies labelled with technetium-99m, such as arcitumomab and nofetumomab merpentan, are used for the detection and localisation of malignant neoplasms. Labelled sulesomab is used in the detection of osteomyelitis. Labelled fanolesomab was used in the diagnosis of appendicitis but was withdrawn from the market due to severe adverse effects. Technetium (^{99m}Tc) depreotide is a labelled peptide used intravenously for imaging of pulmonary malignancy.

Many other technetium-99m-labelled compounds have been prepared and used in different clinical studies for the examination of different organs or systems. Use with other radionuclides includes subtraction scanning with thallium-201 to detect parathyroid tumours.

Preparations

Ph. Eur.: Sodium Pertechnetate(Tc) Injection (Fission); Sodium Pertechnetate(Tc) Injection (Non-fission); Technetium(Tc) Bicisate Injection; Technetium(Tc) Colloidal Rhenium Sulphide Injection; Technetium(Tc) Colloidal Sulphur Injection; Technetium(Tc) Colloidal Tin Injection; Technetium(Tc) Etifenin Injection; Technetium(Tc) Exametazime Injection; Technetium(Tc) Gluconate Injection; Technetium(Tc) Human Albumin Injection; Technetium(Tc) Macrosalb Injection; Technetium(Tc) Medronate Injection; Technetium(Tc) Mertiatide Injection; Technetium(Tc) Microspheres Injection; Technetium(Tc) Pentetate Injection; Technetium(Tc) Sestamibi Injection; Technetium(Tc) Succimer Injection; Technetium(Tc) Tin Pyrophosphate Injection;
USP 31: Sodium Pertechnetate Tc 99m Injection; Technetium Tc Fanolesomab Injection; Technetium Tc 99m (Pyro- and trimeta-) Phosphates Injection; Technetium Tc 99m Albumin Aggregated Injection; Technetium Tc 99m Albumin Colloid Injection; Technetium Tc 99m Albumin Injection; Technetium Tc 99m Apcitide Injection; Technetium Tc 99m Arcitumomab Injection; Technetium Tc 99m Bicisate Injection; Technetium Tc 99m Depreotide Injection; Technetium Tc 99m Disofenin Injection; Technetium Tc 99m Etidronate Injection; Technetium Tc 99m Exametazime Injection; Technetium Tc 99m Gluceptate Injection; Technetium Tc 99m Lidofenin Injection; Technetium Tc 99m Mebrofenin Injection; Technetium Tc 99m Medronate Injection; Technetium Tc 99m Mertiatide Injection; Technetium Tc 99m Nofetumomab Merpentan Injection; Technetium Tc 99m Oxidronate Injection; Technetium Tc 99m Pentetate Injection; Technetium Tc 99m Pyrophosphate Injection; Technetium Tc 99m Red Blood Cells Injection; Technetium Tc 99m Sestamibi Injection; Technetium Tc 99m Succimer Injection; Technetium Tc 99m Sulfur Colloid Injection; Technetium Tc 99m Tetrofosmin Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Cardiolite; Ceretec; Myoview; Neurolite; ***Austria:*** Cardiolite; Ceretec; Myoview; TechneScan HDP; TechneScan LyoMAA; TechneScan MAG3; ***Belg.:*** Cardiolite†; Neurolite†; ***Cz.:*** 6-MDP; 8-MDP; Amerscan DMSA†; Amerscan Hepatate; Amerscan Medronate; Amerscan Pentetate†; Amerscan Pulmonate†; Amerscan Stannous; Amertec†; Anti-Granulocyte BW†; Brain-Spect; Cardio-Spect; Cardiolite; CEA-Scan†; Ceretec; DTPA; Hibida; HM-PAO Kit; Leuco-Scint; LeukoScan; Lymphoscint†; Macro-Albumon; Macrotec; Mag 3; Myoview; Nano-Albumon; Nanocoll; Neospect; Neurolite; Neuroscan; Osteocis†; Pulmocis; Rotop Mag-3†; Scintimun; Senti-Scint; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan HIG; TechneScan HSA; TechneScan Lyomaa; TechneScan MAG3; TechneScan PYP; TechneScan Q12†; Trimetyl-HIDA; Ultra Technekow FM; UltraTag RBC; ***Fr.:*** Cardiolite†; Myoview; Neurolite†; ***Irl.:*** Cardiolite†; ***Ital.:*** Cardiolite; CEA-Scan; Ceretec; LeukoScan; Myoview; Neospect; Neurolite; TechneScan MAG3; ***Neth.:*** Amerscan DMSA†; Amerscan Hepatate; Amerscan Medronate; Amerscan Pentetate†; Amerscan Stannous; Bridatec; Cardiolite; Ceretec; Cholediam; DraxImage MAA; DraxImage MDP; Drytec; Elumatic; LeukoScan; Maasol; Myoview; NeoSpect; Neurolite; Osteocis; Osteosol†; Phytacis; Pulmocis; Pulmotec; Teceos; TechneScan DMSA; TechneScan DTPA; TechneScan HDP; TechneScan HSA; TechneScan LyoMAA; TechneScan MAG3; TechneScan PYP; Ultra TechneKow; UltraTag; Venticoll; ***Port.:*** Angiocis; Bridatec; Cardiolite; Ceretec; Elumatic; LeukoScan; Macrotec; Mertioscan; Myoview; Nanocoll; NeoSpect; Neurolite; Osteocis; Pentacis; Phytacis; Pulmotec; Renocis; TechneScan DTPA; TechneScan HDP; TechneScan MAG3; Ultra TechneKow FM; ***Spain:*** Cardiolite; CEA-Scan; Ceretec; Drytec; Macrotec; Myoview; Neospect; Neurolite; TechneScan HDP; TechneScan Lyomaa; TechneScan MAG3; ***UK:*** Amerscan DMSA; Amerscan Hepatate; Amerscan Medronate; Amerscan Pentetate; Amerscan Pulmonate; Amerscan Stannous; Amertec; Angiocis; Cardiolite; CEA-Scan; Ceretec; Cholecis; Medrocis†; Myoview; Nanocoll; Osteocis; Pentacis; Pulmocis; Renocis; ***USA:*** AcuTect; Cardiolite; CEA-Scan; Choletec; Miraluma; NeoTect; NeutroSpec†; TechneScan HDP.

Thallium-201

Talio 201.

CAS — 15064-65-0.
ATC — V09GX01 (thallium chloride (^{201}Tl)).
ATC Vet — QV09GX01 (thallium chloride (^{201}Tl)).

HALF-LIFE. 73.1 hours.

Profile

Thallium-201, in the form of thallous chloride (^{201}Tl), is given by intravenous injection for scanning the myocardium in the investigation of acute myocardial infarction. It is also used for myocardial perfusion imaging in cardiac stress testing of patients with ischaemic heart disease. Adenosine (see Ischaemic Heart Disease, p.1203), dipyridamole (see Myocardial Imaging, p.1268), or dobutamine (see Diagnosis and Testing, p.1272) may be used to induce pharmacological stress in those patients unable to tolerate exercise.

Other uses include muscle perfusion scintigraphy in peripheral vascular disorders, visualisation of brain and thyroid tumours and metastases, and the localisation of parathyroid adenomas and hyperplasia by thallium-201 and technetium-99m subtraction scanning.

Preparations

Ph. Eur.: Thallous(Tl) Chloride Injection;
USP 31: Thallous Chloride Tl 201 Injection.

Proprietary Preparations (details are given in Part 3)
Austria: DRN 8103.

Tritium

Hydrogen-3; Tritio.

CAS — 10028-17-8.

HALF-LIFE. 12.3 years.

Profile

Tritium, in the form of tritiated water, has been used to determine the total body water by a dilution technique.

Preparations

Ph. Eur.: Tritiated(H) Water Injection.

Xenon-127

Xenón 127.

CAS — 13994-19-9.
ATC — V09EX02 (xenon gas (^{127}Xe)).
ATC Vet — QV09EX02 (xenon gas (^{127}Xe)).

HALF-LIFE. 36.41 days.

Profile

Xenon-127 has similar physical properties to those of xenon-133 (see below) and is also used by inhalation for pulmonary function studies and lung imaging.

Preparations

USP 31: Xenon Xe 127.

Xenon-133

Xenón 133.

CAS — 14932-42-4.
ATC — V09EX03 (xenon gas (^{133}Xe)).
ATC Vet — QV09EX03 (xenon gas (^{133}Xe)).

HALF-LIFE. 5.25 days.

Profile

Xenon-133 is an inert gas with relatively low solubility in plasma. In the gaseous form, it is mixed with air or oxygen in a bag or in a closed or open circuit spirometer. When the gas is stopped, xenon-133 is excreted promptly and completely through the lungs. It is used by inhalation in pulmonary function studies and lung imaging as well as in cerebral blood flow studies. It has also been used for these purposes in the form of an injection in sodium chloride 0.9%.

Preparations

Ph. Eur.: Xenon(Xe) Injection;
USP 31: Xenon Xe 133; Xenon Xe 133 Injection.

Yttrium-90

Itrio 90.

CAS — 10098-91-6.

ATC — V10AA01 (yttrium citrate colloid (^{90}Y)); V10AA02 (yttrium ferrihydroxide colloid (^{90}Y)); V10AA03 (yttrium silicate colloid (^{90}Y)); V10XX02 (ibritumomab tiuxetan (^{90}Y)).

ATC Vet — QV10AA01 (yttrium citrate colloid (^{90}Y)); QV10AA02 (yttrium ferrihydroxide colloid (^{90}Y)); QV10AA03 (yttrium silicate colloid (^{90}Y)); QV10XX02 (ibritumomab tiuxetan (^{90}Y)).

HALF-LIFE. 64.1 hours.

Yttrium-90 conjugated to ibritumomab tiuxetan (p.730) is used in the treatment of non-Hodgkin's lymphoma. Conjugates with various other monoclonal antibodies and compounds are also under investigation for malignant neoplasms.

Yttrium-90, in the form of a colloidal suspension of yttrium silicate (^{90}Y) has been used for instillation into pleural or peritoneal cavities in the treatment of malignant pleural effusion (p.659) or malignant ascites.

Yttrium-90, as either yttrium citrate (^{90}Y) or yttrium silicate (^{90}Y), has also been used in the treatment of arthritic conditions of joints.

Yttrium-90 enclosed in glass microspheres has been used for the local treatment of malignant neoplasms of the liver.

Preparations

USP 31: Yttrium Y 90 Ibritumomab Tiuxetan Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Ytracis; Yttriga; ***Hung.:*** Ytracis; ***Neth.:*** Theryttrex†; Ytracis; ***Port.:*** Ytracis; ***Spain:*** Ytracis; ***UK:*** Ytracis.

Sex Hormones and their Modulators

The male and female sex organs, the adrenal cortex, and the placenta produce steroidal hormones that influence the development and maintenance of structures directly and indirectly associated with reproduction. The secretion of these sex hormones is controlled by gonadotrophic hormones of the anterior lobe of the pituitary gland (and in pregnancy, from the placenta); the secretion of pituitary gonadotrophic hormones is in turn influenced by the hypothalamus and also by the concentration of circulating sex hormones. There are 3 groups of endogenous sex hormones, androgens, oestrogens, and progestogens, all of which are derived from the same steroidal precursors. The progestogenic hormone, progesterone, is formed from pregnenolone, and both of these compounds may be converted to androgen precursors such as androstenedione. Androstenedione is converted to the androgenic hormone testosterone by hydroxysteroid dehydrogenases. Oestrogenic hormones are synthesised from androstenedione (and also from testosterone) by the action of aromatase.

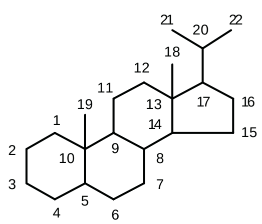

steroidal skeleton

Testosterone is the main androgenic hormone formed in the interstitial (Leydig) cells of the testes. A small proportion of circulating testosterone is also derived from the metabolism of less potent androgens secreted by the adrenal cortex and ovaries. In many target tissues testosterone is then converted to the more active dihydrotestosterone by 5α-reductase. Some testosterone also undergoes peripheral conversion to oestradiol.

Testosterone controls the development and maintenance of the male sex organs and the male secondary sex characteristics. It also produces systemic anabolic effects, such as increased retention of nitrogen, calcium, sodium, potassium, chloride, and phosphate. This leads to an increase in water retention and bone growth. The skin becomes more vascular and less fatty and erythropoiesis is increased.

Numerous derivatives of testosterone have been developed. Alkylation at the 17α position results in derivatives that are orally active, but associated with a risk of hepatotoxicity (see Table 1, below). Esterification of the 17β-hydroxyl group increases lipid solubility and is used to prepare long-acting intramuscular preparations (e.g. testosterone enantate). Removal of the 19-methyl group is reported to improve the anabolic to androgenic ratio (e.g. nandrolone). The derivatives also vary in their plasma protein binding affinity, and degree of conversion to dihydrotestosterone and aromatic conversion to oestrogen. Numerous other structural modifications have been made.

Oestradiol is the most active of the naturally occurring oestrogens formed from androgen precursors in the ovarian follicles of premenopausal women. In men and postmenopausal women (and to an insignificant extent in premenopausal women) oestrogens are also formed in adipose tissue from adrenal androgens.

Table 1. 17α-Alkylated testosterone derivatives

Danazol	Norethandrolone
Ethylestrenol	Oxandrolone
Fluoxymesterone	Oxymetholone
Methandienone	Stanozolol
Methyltestosterone	

Oestrogens control the development and maintenance of the female sex organs, secondary sex characteristics, and mammary glands as well as certain functions of the uterus and its accessory organs (particularly the proliferation of the endometrium, the development of the decidua, and the cyclic changes in the cervix and vagina). Large amounts of oestradiol are also formed in the placenta; in late pregnancy, this increases the spontaneous activity of the uterine muscle and its response to oxytocic drugs. The additional activity of progesterone is essential for the complete biological function of the female sex organs. Oestrogens also have some direct effects on metabolic processes, including those affecting bone mass, lipids, carbohydrates, and proteins.

A number of oestrogens are used therapeutically. Ethinyl substitution at the C17 position has led to the development of synthetic oestrogens such as ethinylestradiol and mestranol, which have greatly improved potency and oral activity. Oral activity of natural oestrogens is improved by esterification (e.g. estradiol valerate) or by conjugation (e.g. estrone sulfate). Esterification also increases solubility in lipid vehicles and is used to prepare long-acting intramuscular preparations.

A number of nonsteroidal oestrogens, including chlorotrianisene, dienestrol, and diethylstilbestrol, have also been used.

Progesterone is the main hormone secreted by the corpus luteum. It acts on the endometrium by converting the proliferative phase induced by oestrogen to a secretory phase thereby preparing the uterus to receive the fertilised ovum. Progesterone has a catabolic action and causes a slight rise in basal body temperature during the secretory phase of menstruation. During pregnancy the placenta produces large quantities of progesterone, which suppresses uterine motility and is responsible for the further development of the breasts.

Progestogens (gestagens, progestagens, progestins) are synthetic compounds with actions similar to those of progesterone. They are either progesterone derivatives or 19-nortestosterone analogues. The 19-nortestosterone analogues (such as norethisterone and norgestrel) possess some androgenic activity, but some newer norgestrel derivatives (desogestrel, gestodene, and norgestimate) have little androgenic activity. The progesterone derivatives dydrogesterone, hydroxyprogesterone, and medroxyprogesterone are less androgenic than the 19-nortestosterone analogues. The progesterone derivatives chlormadinone, and particularly cyproterone, have anti-androgenic activity.

The principal natural and synthetic sex hormones covered in this chapter are thus:

- **androgens and anabolic steroids**, typified by testosterone (p.2129)
- **oestrogens**, typified by estradiol (p.2097)
- **progestogens**, typified by progesterone (p.2125)

Other related substances also described in this chapter are:

- drugs with mainly **weak androgenic** properties such as danazol and gestrinone
- drugs that combine **oestrogenic and progestogenic** properties such as tibolone
- drugs with mainly **anti-androgenic** properties including the progesterone derivative cyproterone acetate. Those anti-androgens used principally in the hormonal treatment of prostate cancer are covered in the Antineoplastics chapter; they include the nonsteroidal drugs bicalutamide (p.686), flutamide (p.725), and nilutamide (p.756). The nonsteroidal 5α-reductase inhibitors finasteride (p.2188) and dutasteride (p.2188) and the plant extract saw palmetto (p.2192), used in the treatment of benign prostatic hyperplasia, are covered in the Urological Drugs chapter
- drugs with mainly **anti-oestrogenic** properties. These include the nonsteroidal anti-oestrogens clomifene, cyclofenil, and the more selective nonsteroidal anti-oestrogens ormeloxifene and raloxifene. Those anti-oestrogens used principally in the hormonal treatment of breast cancer are covered in the Antineoplastics chapter; they include the oestrogen receptor antagonists tamoxifen (p.772) and toremifene (p.781), and various aromatase inhibitors such as formestane (p.726) and anastrozole (p.681)
- **gonad-regulating hormones** (see below for more detail) include endogenous and recombinant forms of luteinising and follicle-stimulating hormones, and their releasing hormone gonadorelin and its analogues.

The therapeutic applications of sex hormones and related substances are broad and cover many circumstances where hormonal manipulation is desirable. Major applications are the use of oestrogens and progestogens for **contraception** (p.2070) and for the alleviation of **menopausal symptoms** (p.2077). A physiological application is the use of sex hormones or gonad-regulating hormones in the management of **delayed puberty** (p.2079) and **hypogonadism** (p.2079). Other clinical applications include the management of **benign prostatic hyperplasia** (p.2178), **endometriosis** (p.2091), **gynaecomastia** (p.2092), **hirsutism** (p.2089), **infertility** (p.2080), **mastalgia** (p.2092), **menorrhagia** (p.2126), and **premenstrual syndrome** (p.2099). Hormonal manipulation also has an important role in the treatment of **malignant neoplasms** of the breast (p.661), prostate (p.671), and endometrium (p.663).

Hormonal Contraceptives

Anticonceptivos hormonales; Contraceptifs Hormonaux; Hormonale Kontrazeptiva.

Гормональный Контрацептивы

Types of Contraceptive

Hormonal contraceptives are currently only available for women although preparations for men are being evaluated. Oral hormonal contraceptives for women are divided into 2 main types: 'combined' (containing an oestrogen and a progestogen) and 'progestogen-only'. Parenteral preparations have also been developed and include subcutaneous implants and depot intramuscular injections. Progestogen-releasing intra-uterine devices and a combined hormonal contraceptive vaginal ring are available. A combined hormonal transdermal patch has also been developed.

Parenteral progestogen-only contraceptives provide reliable suppression of ovulation by suppressing the necessary mid-cycle surge of luteinising hormone. However, the low doses in progestogen-only oral contraceptives do not suppress it reliably in all cycles. Contraceptive efficacy is instead achieved by thickening the cervical mucus so that it is not readily penetrated by sperm, and by preventing proliferation of the endometrium so that it remains unfavourable for implantation of any fertilised ova. Intra-uterine progestogen-only devices act similarly; the physical presence of the system in the uterus may also contribute to overall contraceptive efficacy.

Oestrogens inhibit ovulation by suppressing the mid-cycle release of follicle-stimulating hormone. They act synergistically with progestogens in combined oral contraceptives to provide regular and consistent suppression of ovulation.

Oral preparations are also available for *emergency contraception* after unprotected coitus; they prevent implantation of any fertilised ova.

Adverse Effects

Many reports have been published of adverse effects associated with the use of **combined oral contraceptives**. The data have mostly been gained retrospectively and often involve older preparations containing higher doses of oestrogen and progestogen than are used currently.

There may be gastrointestinal adverse effects such as nausea or vomiting, chloasma (melasma) and other skin or hair changes, headache, water retention, weight gain, breast tenderness, and changes in libido.

Menstrual irregularities such as spotting, breakthrough bleeding, or amenorrhoea can occur during treatment. These effects may result from the relative balance of oestrogenic and progestogenic effects of particular products and their incidence may be reduced by changing to a different product. For example, early or mid-cycle spotting or absence of withdrawal bleeding may require a preparation with a greater oestrogen to progestogen ratio or less progestogen as in multiphasic preparations.

Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients. Some patients may experience depression and other mental changes. Preparations containing a progestogen with androgenic properties such as levonorgestrel or norgestrel may be associated with increased oiliness of the skin and acne. Conversely, acne may be improved with progestogens such as norgestimate or desogestrel.

There is an increased risk of cardiovascular disease and associated mortality related, at least in part, to the oestrogen content of combined oral contraceptives. The incidence of cardiovascular adverse effects is probably less with the newer lower-dose preparations than with the older higher-dose preparations. Increased mortality from myocardial infarction is much greater with increased age and in cigarette smokers, although some evidence suggests that healthy women aged over 35 years who do not smoke are not at increased risk. Other risk factors include a family history of arterial disease, diabetes mellitus, hypertension, obesity, and migraine. Thrombosis may be more common when factor V Leiden is present or in patients with blood groups A, B, or AB. Specific risk factors for venous thromboembolism include varicose veins, long-term immobilisation, obesity, and a family history of venous thromboembolism. Recent evidence has also indicated that the risk of venous thromboembolism varies according to the progestogen component of combined oral contraceptives; a higher incidence has been associated with desogestrel and gestodene than with levonorgestrel, norethisterone, and etynodiol. For further discussion see Venous Thromboembolism, below.

Combined oral contraceptives may cause hypertension and there may be reduced glucose tolerance and changes in lipid metabolism. Liver function can be impaired, although jaundice is rare. There appears to be a marked increase (though the incidence is still very low) in the relative risk of benign liver tumours. Malignant liver tumours have also been reported.

Combined oral contraceptives are reported to slightly increase the risk of cervical cancer (although other factors may be involved) and breast cancer, but to protect against ovarian cancer and endometrial cancer. For further discussion, see Carcinogenicity, below.

As with combined oral contraceptives, **progestogen-only contraceptives** may cause nausea, vomiting, headache, breast discomfort, depression, skin disorders, and weight gain. Menstrual irregularities such as amenorrhoea, breakthrough bleeding, spotting, and menorrhagia are more common with progestogen-only contraceptives, and are particularly common with parenteral preparations. Available progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives.

Carcinogenicity. Concern has often been expressed as to whether the use of hormonal contraceptives by normally healthy women may either cause or increase the risk of developing malignant neoplasms. To investigate any possible link between such use and cancer, two main types of study have been used by epidemiologists, namely the prospective study and the case-control study. Many factors have made direct comparison of results difficult and such factors include the type and composition of oral contraceptive used (which has changed over the years), the age of the patient, the age at which use first began, and the sexual and obstetric history of the patient. Overall the evidence indicates that combined oral contraceptives in fact exert a protective effect against the development of endometrial and ovarian carcinoma. However, there is a small increase in risk of breast cancer during use and for 10 years after discontinuation. In addition, there does appear to be a slight risk of cervical cancer with the prolonged use of combined oral contraceptives and a negligible risk of liver cancer. For further details concerning the effects on individual organs, see the following sections. It should be noted that even where the relative risk has been shown to be substantially increased this will not translate into many new cases of a rare cancer, and this contributes to the difficulties of assessing clinical relevance.

In the long-term Oxford Family Planning Association contraceptive study, the beneficial effects of oral contraceptives on the uterus and ovary were calculated to outweigh the adverse effect on the cervix.[1] This large cohort study also found no increased risk of breast cancer although the data could not exclude a small increase in risk with current use that declined after stopping. Long-term follow-up of the prospective Royal College of General Practitioners' study has found no overall increased risk of cancer.[2] It is also worthy of note that two large prospective cohort studies (the Nurses' Health Study and the Royal College of General Practitioners' study) found no evidence of a difference in overall mortality between women who had used oral contraceptives and those who had not.[3,4] Some general reviews on hormonal contraceptives and cancer are cited below.[5-9]

1. Vessey M, Painter R. Oral contraceptive use and cancer: findings in a large cohort study, 1968–2004. *Br J Cancer* 2006; **95:** 385–9.
2. Hannaford PC, *et al.* Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. Abridged version: *BMJ* 2007; **335:** 651–4. Full version: http://www.bmj.com/cgi/reprint/335/7621/651.pdf (accessed 14/01/08)
3. Colditz GA, *et al.* Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; **120:** 821–6.
4. Beral V, *et al.* Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; **318:** 96–100.
5. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
6. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; **14:** 260–72.
7. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
8. IARC/WHO. Combined estrogen-progestogen contraceptives. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 91* 2005. Available at: http://monographs.iarc.fr/ENG/Meetings/91-contraceptives.pdf (accessed 14/01/08)
9. Lech MM, Ostrowska L. Risk of cancer development in relation to oral contraception. *Eur J Contracept Reprod Health Care* 2006; **11:** 162–8.

BREAST. Numerous epidemiological studies have been published on the potential link between hormonal contraceptives and breast cancer. Most of these data relate to **combined oral contraceptives**, which are the most widely used form. The breast cancer risk from use of these contraceptives will require monitoring for some time to come as the first users of oral contraceptives continue to age, and because of the changing patterns of use.

Early studies from the 1980s variously failed to show any significant increase in risk of breast cancer in women who had ever used hormonal contraceptives compared with those who had never done so,[1-4] or showed an increase in risk,[5] or identified a risk in specific sub-groups of users.[6-12] Potential identified risk factors, for which much of the evidence was conflicting, included current use,[10] duration of use,[7,11] age at first use,[6] duration of use before a first full-term pregnancy,[7,8] nulliparity,[9] high-dose preparations,[11] and family history of breast cancer.[12] It was also reported that use of oral contraceptives might lead to an accelerated presentation of breast cancer,[13] or an increased risk of invasive cancer.[4]

In response to these studies, the UK CSM,[14] the FDA in the USA,[15] and the International Committee for Research in Reproduction[16] issued advice that the available evidence did not require a change in prescribing practice. This advice has not been subsequently changed, although patients should be informed of the possible small increase in risk of breast cancer, which has to be weighed against established benefits of therapy.[17]

A Collaborative Group on Hormonal Factors in Breast Cancer was set up to re-analyse all the worldwide epidemiological evidence on breast cancer risk and hormonal contraceptives. The group identified individual data on 53 297 women with breast cancer, and 100 239 controls (women without breast cancer) from 54 studies, and published a summary of their findings,[18] and a further detailed review.[19] They reported that women currently using oral contraceptives have a slight increase in the relative risk of breast cancer (1.24; 95% confidence intervals 1.15 to 1.33), and that this risk decreases after stopping use, and is no longer significant after 10 or more years. There was a weak trend towards an increase in risk with increasing duration of use. Thus, it appears that the risk of breast cancer

- increases soon after first exposure
- does not increase with duration of exposure
- returns to normal 10 years after cessation of exposure.[18]

Reviews[20,21] of major studies published between 1990 and 2000, including that of the Collaborative Group, have also indicated that, in general, there is some excess breast cancer risk in current or recent users of oral contraceptives, but that excess risk does not persist in the long term after cessation of oral contraceptive use, regardless of duration of use.

The Collaborative Group found that cancers diagnosed in those who had ever used hormonal contraceptives were clinically less advanced than in those who had never done so.[18] Further information is required on whether this is related to earlier diagnosis or a biological effect of the hormones. In addition, data on breast cancer mortality are required.

When analysed by *age at first use*, the risk was largest in those women who started use as teenagers. Because of the trend towards earlier use, further review of long-term data is required.[18] The most important risk factor is, however, the *age at which women discontinue* the contraceptive; the greater the age at stopping, the more breast cancers are diagnosed.[17]

Data from the collaborative group suggested that there was no difference in risk with *parity* when comparing nulliparous women, parous women who began use of oral contraceptives before their first child, and parous women who began use of oral contraceptives after the birth of their first child.[18] However, a later meta-analysis[22] reported higher risks in parous women, particularly those who used oral contraceptives for 4 or more years before first full-term pregnancy.

Low-dose oral contraceptives were not associated with a decreased risk of breast cancer.[18] When preparations were grouped according to oestrogen dose (< 50 micrograms, 50 micrograms, and >50 micrograms), there was, if anything, a decrease in breast cancer risk with increasing dose among women who had stopped use 10 or more years before, largely due to a reduction in breast cancer risk in those who had used the highest dose preparations.

The Collaborative Group's analysis did not note any difference in risk according to *family history.*[18] However, a subsequent cohort study found an increased risk of breast cancer among women with a strong family history of the disease who used earlier formulations of oral contraceptives.[23] Another cohort study[24] provided support for the Collaborative Group's findings, reporting no statistical difference in the risk with oral contraceptive use in women with a family history of breast cancer; there was actually a trend towards a reduction in risk of breast cancer with long-term use. Women carrying mutations in the BRCA1 or BRCA2 genes are at increased risk of developing breast cancer; any additional risk from oral contraceptives is of particular concern because these women may be encouraged to take them to reduce their risk of ovarian cancer (see Ovary, below). However, results from studies in known carriers of these mutations have been mixed. A modest increase in the risk of breast cancer in BRCA1 carriers has been reported with ever use of oral contraceptives,[25] but another study[26] found a reduced risk in carriers who used current preparations containing lower oestrogen doses than those available before 1975. Further study is needed in these women.

There are far fewer data on risk of breast cancer with **progestogen-only contraceptives**, which are less frequently used than combined preparations.

A WHO study published in 1991 indicated that, overall, depot medroxyprogesterone acetate did not increase the risk of breast cancer (relative risk compared with never users 1.21; 95% confidence intervals 0.96 to 1.53) and that risk did not increase with duration of use.[27] However, there appeared to be a slight increase in risk within the first 4 years of use, especially in women under 35 years of age. These findings agreed with those of a smaller study[28] in which women who had used depot medroxyprogesterone acetate for 2 years or longer before the age of 25 had a relative risk of 4.6. Pooled analysis of these 2 studies indicated that current or recent use was the key factor.[29] The relative risk of breast cancer in women who had used medroxyprogesterone acetate in the last 5 years was 2.0, and there was no increased risk in women who had ceased use more than 5 years previously, regardless of their duration of use. Another small study[30] reported no increase in risk overall in women who had ever used medroxyprogesterone acetate; there was an increase for current use in the subgroup of women aged 35 to 44 (relative risk 2.3), but this was no longer the case 4 years after stopping.

The Collaborative Group on Hormonal Factors in Breast Cancer reported that there was some evidence of an increased risk of breast cancer for use of oral or injectable progestogens in the previous 5 years (relative risk 1.17), and no risk 10 or more years after stopping use.[18] These findings were broadly similar to those for combined preparations. As for combined preparations, the most important factor is the *age at discontinuation.* For women who stop by age 30 after 5 years use of a progestogen-only preparation there would be an estimated increase from 44 to 46 or 47 cases per 10 000 compared with those who have never used a hormonal contraceptive. For 5 years use stopping by age 40 there would be an estimated increase from 160 to 170 cases diagnosed in the following 10 years.[17]

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2. Paul C, *et al.* Oral contraceptives and breast cancer: a national study. *BMJ* 1986; **293:** 723–6.
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7. Meirik O, *et al.* Oral contraceptive use and breast cancer in young women: a joint national case-control study in Sweden and Norway. *Lancet* 1986; **ii:** 650–4.
8. McPherson K, *et al.* Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 1987; **56:** 653–60.
9. Meirik O, *et al.* Breast cancer and oral contraceptives: patterns of risk among parous and nulliparous women—further analysis of the Swedish-Norwegian material. *Contraception* 1989; **39:** 471–5.
10. Romieu I, *et al.* Prospective study of oral contraceptive use and risk of breast cancer in women. *J Natl Cancer Inst* 1989; **81:** 1313–21.
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15. Anonymous. Cancer risks of oral contraception. *Lancet* 1989; **i:** 84.
16. International Committee for Research in Reproduction. Oral contraceptives and breast cancer. *JAMA* 1989; **262:** 206–7.
17. CSM/MCA. Oral contraceptives and breast cancer. *Current Problems* 1998; **24:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023232&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)
18. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347:** 1713–27.
19. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996; **54** (suppl): 1S–106S.
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21. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
22. Kahlenborn C, *et al.* Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. *Mayo Clin Proc* 2006; **81:** 1290–1302.
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24. Silvera SAN, *et al.* Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. *Cancer Causes Control* 2005; **16:** 1059–63.
25. Narod SA, *et al.* Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2002; **94:** 1773–9.
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29. Skegg DCG, *et al.* Depot medroxyprogesterone acetate and breast cancer: a pooled analysis of the World Health Organization and New Zealand studies. *JAMA* 1995; **273:** 799–804.
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CERVIX. It is often considered difficult to carry out satisfactory epidemiological studies on the relationship between hormonal contraceptives and cervical cancer because of the many known variables that can influence the development of this type of neoplasm. For example, sexual activity *per se,* and multiple sexual partners (both of the woman and her partner) increase the risk, while the use of other non-hormonal barrier methods of contraception may offer some protection against cervical neoplasia. Nevertheless, there have been some suggestions that the use of oral contraceptives may be associated with an increased risk.

Two UK cohort studies from the 1980s revealed an increased risk of cervical cancer in women receiving oral contraceptives that was shown to increase with increasing duration of use.[1,2]

In 1992, WHO reviewed[3] these cohort data, and data from 18 case-controlled studies carried out up to 1990. They concluded that use of oral contraceptives for more than 5 years was associated with a modest increase in the relative risk of cervical squamous cell carcinoma (in the order of 1.3 to 1.8). Additional potential risk factors included recent or current use and high oestrogen dose. Of known risk factors for cervical cancer, women with multiple sexual partners, genital infection, or high parity had enhanced risks associated with oral contraceptives.[3] Later reviews came to similar conclusions.[4,5]

Most cervical cancers are squamous cell carcinomas, but it has been proposed that oral contraceptive use might be a particular risk factor for the rarer adenocarcinoma of the cervix, the incidence of which has risen in younger women. Reviewing studies up to 1990, WHO concluded that data were insufficient to draw firm conclusions on links between oral contraceptives and the risk of cervical adenocarcinoma.[3] A case-controlled study from 1994 found an increased risk of adenocarcinoma of the cervix in users of oral contraceptives.[6] Any use of oral contraceptives was associated with an approximate doubling of risk, and use for more than 12 years was associated with a relative risk 4.4 times greater than that in women who never used an oral contraceptive. In 1996, a WHO study reported that the strength of the observed relationship for cervical adenocarcinomas and adenosquamous carcinomas and oral contraceptives was about the same as that for invasive squamous cell cervical carcinomas.[7]

Human papillomavirus (HPV) has a role in the aetiology of cervical cancer; women who are HPV positive and using oral contraceptives may be at increased risk of cervical neoplasm.[8,9] A pooled analysis of 8 case-control studies in women who tested positive for HPV DNA suggested risk of invasive squamous cervical cancer or carcinoma *in situ* was increased about threefold in those who used oral contraceptives for 5 years or more.[10]

Data on the risk of cervical cancer with **progestogen-only contraceptives** are limited. WHO have investigated any possible link between the use of medroxyprogesterone acetate as a long-acting injectable contraceptive and cervical neoplasia. Analysis showed a small non-significant elevated risk (1.11; 95% confidence interval 0.9 to 1.29), and no clear association with duration of use.[11] A later case-control study[12] found no significant association between injectable progestogen contraceptives and invasive cervical cancer risk.

1. Vessey MP, *et al.* Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. *Lancet* 1983; **ii:** 930–4.
2. Beral V, *et al.* Oral contraceptive use, and malignancies of the genital tract: results from the Royal College of General Practitioners' oral contraception study. *Lancet* 1988; **ii:** 1331–5.
3. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
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9. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
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11. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. *Contraception* 1992; **45:** 299–312.
12. Shapiro S, *et al.* Risk of invasive cancer of the cervix in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen oral contraceptives (South Africa). *Cancer Causes Control* 2003; **14:** 485–95.

ENDOMETRIUM. It has been shown that **combined oral contraceptives** decrease the risk of endometrial cancer. WHO analysed data from case-control and cohort studies published up to 1990,[1] including data from the large Cancer and Steroid Hormone Study (CASH) in the USA,[2] and reported that there was a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of combined oral contraceptives. The reduction in risk was estimated to be 20% after 1 year and 50% after 4 years of use.[1] The protective effect was observed for endometrial cancer with and without squamous elements,[1,2] and was found to persist for at least 15 years after cessation of use.[2] More recent studies with longer term follow-up have indicated that the protection persists for at least 20 years.[3,4] Further follow-up is required to determine the true duration of protection; data from one study[5] suggested that the reduction in risk was more pronounced in women who had stopped contraceptive use more than 25 years before, but another study[4] suggested that any protective effect may no longer be present 30 years after stopping combined oral contraceptive use.

The results of the WHO Collaborative Study on Neoplasia and Steroid Contraceptives suggested that protection may be greater with preparations containing high-dose progestogen.[6] However, another study found that risk of endometrial cancer was unrelated to progestogen potency of the oral contraceptive, although this study also reported no protective effect for less than 5 years of use.[7] Further analysis of the CASH study data[8] found that although preparations containing high and low doses of progestogen had a similar protective effect overall, it was greatest for high-dose progestogen preparations in women with a higher BMI.

Unopposed menopausal oestrogen replacement therapy is known to increase the risk of endometrial cancer (see p.2072), and there is some evidence[3,7] that it reduces the protective effect of previous oral contraception.

There are limited data on the effect of **progestogen-only contraceptives** on the risk of endometrial cancer, although they would be expected to be protective. Results from the WHO Collaborative Study[9] suggest that depot medroxyprogesterone acetate reduced the risk of endometrial cancer; the estimated relative risk in users was 0.21. However, many of the women in this study received supplemental oestrogen to control menstrual irregularity, and were therefore technically taking a form of combined therapy.[10] There was some evidence that the protective effect of medroxyprogesterone acetate was greater in women who had not received oestrogen,[10] although this remains to be proven.

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GASTROINTESTINAL TRACT. A link between female sex hormones and the risk of colorectal cancer has been postulated. Epidemiological studies have variously shown a possible increased risk of rectal cancer,[1] a possible decreased risk of colorectal cancer[2] in women ever having used oral contraceptives, and no association between past oral contraceptive use and colorectal cancer.[3] A meta-analysis,[4] which included these 3 studies, found a reduction in the risk of colorectal cancer for women who had ever used oral contraceptives. Duration of use was not related to risk reduction, but the effect was apparently stronger for recent contraceptive use although this was based on limited data. Subsequent studies have produced similar results. A reduction in risk has been associated with ever use of oral contraceptives in one report,[5] while others have found no effect statistically but a trend towards protection with current or recent use.[6,7]. (See also under Hormone Replacement Therapy, p.2073.)

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2. Fernandez E, *et al.* Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer. *Br J Cancer* 1996; **73:** 1431–5.
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5. Lin J, *et al.* Oral contraceptives, reproductive factors, and risk of colorectal cancer among women in a prospective cohort study. *Am J Epidemiol* 2007; **165:** 794–801.
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7. Nichols HB, *et al.* Oral contraceptive use, reproductive factors, and colorectal cancer risk: findings from Wisconsin. *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 1212–18.

LIVER. The use of **combined oral contraceptives** has been rarely associated with liver tumours, both benign (hepatic adenomas and focal nodular hyperplasia)[1] and malignant (hepatocellular carcinoma).[1,2]

Early studies of *hepatic adenoma* found that risk increased with the duration of use of oral contraceptives, and appeared to be higher in women who had used preparations with a high oestrogen content.[1] There are also case reports of adenoma that has regressed after stopping oral contraceptive use.[3] However, a study[4] in the 1990s found no increase in risk associated with contraceptive use, and the authors considered that lower doses of oestrogens might explain the different findings. The association between oral contraceptive use and *focal nodular hyperplasia* has also been studied. One case-control study[4] found a slight increase in risk associated with use for 10 years or more. Another study[5] that followed a series of patients for about 2 years after diagnosis found no correlation between oral contraceptive use and lesion size or number, and no increase in lesion size in those patients who continued to use hormonal contraception.

Hepatocellular carcinomas are associated with hepatitis B, and are relatively common in countries where this is endemic but rare elsewhere. Case-control studies in populations at high risk for hepatocellular carcinoma suggest that the use of oral contraceptives does not significantly affect the risk, although long-term data are scanty.[6,7] However, survival after curative treatment is better in women than men, and a retrospective study from Hong Kong has suggested that this may be associated with a history of oral contraceptive use.[8] In contrast, case-control studies in countries where the prevalence of hepatitis B is low have shown an increased risk of hepatocellular carcinoma among users of oral contraceptives, particularly after long-term use (reviewed by WHO[1] and La Vecchia[2,9]). However, because the malignancy is so rare, this increased risk may be negligible.[2] For example, there has been no increase in mortality from liver cancer in young women in the UK since the introduction and use of oral contraceptives.[10] Similar findings have been reported for the USA and Sweden.[11]

There are limited data specifically on **progestogen-only contraceptives**. Results from a WHO study[12] provided no evidence that use of medroxyprogesterone acetate as a long-acting injectable contraceptive altered the risk of developing liver cancer but the power of the study to detect small alterations in risk was low.

1. WHO. Oral contraceptives and neoplasia: report of a WHO scientific group. *WHO Tech Rep Ser 817* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_817.pdf (accessed 14/01/08)
2. La Vecchia C, *et al.* Oral contraceptives and cancer: a review of the evidence. *Drug Safety* 1996; **14:** 260–72.
3. Aseni P, *et al.* Rapid disappearance of hepatic adenoma after contraceptive withdrawal. *J Clin Gastroenterol* 2001; **33:** 234–6.
4. Heinemann LAJ, *et al.* Modern oral contraceptive use and benign liver tumors: the German benign liver tumor case—control study. *Eur J Contracept Reprod Health Care* 1998; **3:** 194–200.
5. Mathieu D, *et al.* Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology* 2000; **118:** 560–4.
6. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Combined oral contraceptives and liver cancer. *Int J Cancer* 1989; **43:** 254–9.
7. Kew MC, *et al.* Contraceptive steroids as a risk factor for hepatocellular carcinoma: a case/control study in South African black women. *Hepatology* 1990; **11:** 298–302.
8. Lam CM, *et al.* Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *J Clin Gastroenterol* 2005; **39:** 533–9.
9. La Vecchia C, *et al.* Oral contraceptives and cancer: an update. *Drug Safety* 2001; **24:** 741–54.
10. Mant JWF, Vessey MP. Trends in mortality from primary liver cancer in England and Wales 1975-1992: influence of oral contraceptives. *Br J Cancer* 1995; **72:** 800–3.
11. Waetjen LE, Grimes DA. Oral contraceptives and primary liver cancer: temporal trends in three countries. *Obstet Gynecol* 1996; **88:** 945–9.
12. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1986; **64:** 375–82.

OVARY. There is convincing evidence that **combined oral contraceptives** reduce the risk of ovarian cancer,[1,2] possibly as a function of their inhibition of ovulation. Relative risks for ovarian cancer have variously been reported as 0.4 to 0.8 in those who have ever used oral contraceptives, and decrease with increasing duration of use. There is evidence that there may be a delay of several years before the protective effect becomes apparent,[3] but that it persists for as long as 20 or 30 years after cessation of use.[3-5] The protective effect has been noted for both malignant and borderline malignant tumours[6] and for each of the major histological subtypes of epithelial ovarian cancer, although there have been conflicting data for mucinous tumours.[5]

It has been suggested that newer lower-dose oestrogen preparations may be slightly less protective than higher-dose preparations.[7] The relative risk for use of high-dose preparations was 0.68, and for low-dose preparations was 0.81, but it was noted that this difference could have occurred by chance. A later study[4] reported that risk reduction was not affected by oral contraceptive formulation. In contrast, another study[8] found a greater risk reduction associated with low-dose contraceptives than older high-dose preparations (odds ratio of 0.24 versus 0.70). The authors speculated that the accompanying changes in progestogen content might have played a role. This was examined using the data from the Cancer and Steroid Hormone (CASH) study, which suggested that higher progestogen potency provided greater risk reduction than lower progestogen potency, regardless of oestrogen dose.[9] Androgenicity of the progestogen does not appear to influence the protective effect of combined oral contraceptives.[10]

The protective effect against ovarian cancer may have significant implications for public health. There have been substantial declines in ovarian cancer incidence and mortality in younger women in countries where oral contraceptives have become widely used; it is estimated that 3000 to 5000 cases (and consequently 2000 to 3000 deaths) are avoided each year in Europe; similar numbers are quoted in North America.[11]

There are few data on the effects of **progestogen-only contraceptives** on the risk of ovarian cancer. WHO have investigated the effect of depot medroxyprogesterone acetate on ovarian cancer, and found that it was not associated with either a decrease or increase in risk (relative risk 1.07; 95% confidence interval 0.6 to 1.8).[12] This is perhaps surprising since the preparation, like combined oral contraceptives, inhibits ovulation.

Women carrying mutations in either the BRCA1 or BRCA2 gene are at increased risk of ovarian cancer, and the effect of oral contraceptives in these women has been evaluated. Although there was no protective effect in one study,[13] others have found a risk reduction with contraceptive use similar to that reported for noncarriers.[14-17] It has been suggested that oral contraceptives might be used prophylactically to protect against ovarian cancer in women with these mutations, but this must be considered in the context of their increased risk of breast cancer (see Breast, above). Women with endometriosis may also be at increased risk of ovarian cancer, and an analysis[18] of the pooled data from 4 studies suggested that long-term use of oral contraceptives may also be protective in this group.

1. Whittemore AS, *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies II: invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992; **136:** 1184–1203.
2. Bosetti C, *et al.* Long-term effects of oral contraceptives on ovarian cancer risk. *Int J Cancer* 2002; **102:** 262–5.
3. Rosenberg L, *et al.* A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol* 1994; **139:** 654–61.
4. Ness RB, *et al.* Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. *Am J Epidemiol* 2000; **152:** 233–41.
5. Riman T, *et al.* Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. *Am J Epidemiol* 2002; **156:** 363–73.
6. Kumle M, *et al.* Risk for invasive and borderline epithelial ovarian neoplasias following use of hormonal contraceptives: the Norwegian-Swedish Women's Lifestyle and Health Cohort Study. *Br J Cancer* 2004; **90:** 1386–91.
7. Rosenblatt KA, *et al.* High-dose and low-dose combined oral contraceptives: protection against epithelial ovarian cancer and the length of the protective effect. *Eur J Cancer* 1992; **28A:** 1872–6.
8. Royar J, *et al.* Low-dose oral contraceptives: protective effect on ovarian cancer risk. *Int J Cancer* 2001; **95:** 370–4.
9. Schildkraut JM, *et al.* Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst* 2002; **94:** 32–8.
10. Greer JB, *et al.* Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. *Obstet Gynecol* 2005; **105:** 731–40.
11. La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998–2004. *Eur J Cancer Prev* 2006; **15:** 117–24.
12. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *Int J Cancer* 1991; **49:** 191–5.
13. Modan B, *et al.* Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001; **345:** 235–40.
14. Narod SA, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998; **339:** 424–8.
15. McGuire V, *et al.* Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 2004; **160:** 613–18.
16. Whittemore AS, *et al.* Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 2004; **91:** 1911–15.
17. McLaughlin JR, *et al.* Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet Oncol* 2007; **8:** 26–34.
18. Modugno F, *et al.* Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004; **191:** 733–40.

SKIN. Although there have been some suggestions of a possible association between the use of oral contraceptives and the development of malignant melanoma[1-4] most studies, including analyses of relatively large numbers of women suffering from malignant melanoma, found no such association with either current or prior use of oral contraceptive preparations.[5-12] A meta-analysis of 18 case-control studies confirmed the lack of association.[13]

1. Beral V, *et al.* Malignant melanoma and oral contraceptive use among women in California. *Br J Cancer* 1977; **36:** 804–9.
2. Lerner AB, *et al.* Effects of oral contraceptives and pregnancy on melanomas. *N Engl J Med* 1979; **301:** 47.
3. Beral V, *et al.* Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* 1984; **50:** 681–5.
4. Feskanich D, *et al.* Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer* 1999; **81:** 918–23.
5. Bain C, *et al.* Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* 1982; **68:** 537–9.
6. Helmrich SP, *et al.* Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. *J Natl Cancer Inst* 1984; **72:** 617–20.
7. Green A, Bain C. Hormonal factors and melanoma in women. *Med J Aust* 1985; **142:** 446–8.
8. Østerlind A, *et al.* The Danish case-control study of cutaneous malignant melanoma III: hormonal and reproductive factors in women. *Int J Cancer* 1988; **42:** 821–4.
9. Palmer JR, *et al.* Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* 1992; **3:** 547–54.
10. Holly EA, *et al.* Cutaneous melanoma in women III: reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; **141:** 943–50.
11. Smith MA, *et al.* Hormonal and reproductive influences and risk of melanoma in women. *Int J Epidemiol* 1998; **27:** 751–7.
12. Naldi L, *et al.* Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005; **15:** 545–50.
13. Gefeller O, *et al.* Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998; **138:** 122–4.

Ectopic pregnancy. All methods of contraception effectively reduce the risk of ectopic pregnancy overall by reducing the rate of pregnancy. However, when contraception fails the proportion of pregnancies that are ectopic is higher for users of oral and intra-uterine **progestogen-only contraceptives** and levonorgestrel implants than in the general population.[1] There is no increase in the proportion of ectopic pregnancies for methods that inhibit ovulation more reliably, such as combined oral contraceptives[1] and medroxyprogesterone acetate depot injection.[2]

A small number of cases of ectopic pregnancy after failure of **emergency contraception**, with both the Yuzpe regimen (oestrogen plus progestogen)[3] and progestogen-only contraception,[4] have been reported. However, data from clinical studies[5] and postmarketing surveillance[6] have shown that when levonorgestrel emergency contraception does rarely fail, there is no increase in the chance of ectopic pregnancy occurring.

1. Furlong L-A. Ectopic pregnancy risk when contraception fails: a review. *J Reprod Med* 2002; **47:** 881–5.
2. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
3. Nielsen CL, Miller L. Ectopic gestation following emergency contraceptive pill administration. *Contraception* 2000; **62:** 275–6.
4. Harrison-Woolrych M, Woolley J. Progestogen-only emergency contraception and ectopic pregnancy. *J Fam Plann Reprod Health Care* 2003; **29**(1): 5–6.
5. Trussell J, *et al.* Ectopic pregnancy following use of progestin-only ECPs. *J Fam Plann Reprod Health Care* 2003; **29:** 249.
6. Gainer E, *et al.* Progestogen-only emergency contraception. *J Fam Plann Reprod Health Care* 2003; **29**(2): 60. Correction. *ibid.*; 159.

Effects on body-weight. Weight gain has been reported as an adverse effect of combined oral contraceptives, but there is no strong evidence from clinical studies to confirm that they have a significant effect on weight.[1,2] However, there is some evidence that weight gain might be associated with medroxyprogesterone acetate when given as a long-acting injectable contraceptive. There have been reports of both weight gain[3] over 5 years, and no change in weight[4] over 10 years, in women using medroxyprogesterone compared with those using a copper IUD. Studies[5,6] in adolescents using medroxyprogesterone or an oral contraceptive for 12 or 18 months have reported more weight gain in those using medroxyprogesterone, and that significant weight gain was more likely in those who were overweight when contraception was started. The risk of weight gain, however, may be confounded by a number of factors including age, race, diet, exercise, and prior pregnancy.

For discussion of a possible association between obesity and oral contraceptive failure, see Obesity, under Precautions, below.

1. Gupta S. Weight gain on the combined pill—is it real? *Hum Reprod Update* 2000; **6:** 427–31.
2. Gallo MF, *et al.* Combination contraceptives: effects on weight. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 14/01/08).
3. Bahamondes L, *et al.* Comparison of weight increase in users of depot medroxyprogesterone acetate and copper IUD up to 5 years. *Contraception* 2001; **64:** 223–5.
4. Taneepanichskul S, *et al.* Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; **59:** 301–3.
5. Mangan SA, *et al.* Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol* 2002; **15:** 79–82.
6. Bonny AE, *et al.* Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Arch Pediatr Adolesc Med* 2006; **160:** 40–5.

Effects on carbohydrate metabolism. The potential effects of oral contraceptives on carbohydrate metabolism are of concern because impaired glucose tolerance, hyperinsulinism, and insulin resistance contribute to atherogenesis and cardiovascular disease.[1] Early studies suggested that the prevalence of abnormal glucose tolerance in oral contraceptive users was increased from about 4 to 35%.[2] This decreased glucose tolerance was found to be related to oestrogen dose, particularly those greater than 75 micrograms daily, and to the type of progestogen. Marked hyperglycaemia has been associated with contraceptives containing high doses of oestrogen but is not seen with combined oral contraceptives used currently, which contain lower doses of oestrogen.[1] Progestogens have little effect on glucose tolerance, but are associated with hyperinsulinaemia. This effect is dose-dependent, and levonorgestrel has the most potent effect, with desogestrel, gestodene, and norethisterone reported to have less effect.[1] Combined oral contraceptives can also induce insulin resistance;[1] it is believed that the oestrogen is responsible and that the progestogen modifies this effect.[3]

Despite evidence of these effects, more recent studies of lower-dose preparations containing desogestrel, levonorgestrel, or norethisterone have found little or no effect on various measurements of carbohydrate metabolism;[4-6] this lack of effect has also been confirmed in a meta-analysis[7] of studies of hormonal contraceptive use in non-diabetic women although it was noted that no strong statement could be made since few studies compared the same types of contraceptives and some had large drop out rates. Also, data from the Nurses' Health Study indicate that oral contraceptive use does not appear to increase the risk of developing type 2 diabetes mellitus.[8,9] However, a study in the USA of breast-feeding women of Hispanic origin who had experienced recent gestational diabetes, suggested that the use of progestogen-only, but not combined, contraceptives was associated with an increased risk of developing type 2 diabetes mellitus in this group.[10]

Injectable progestogen-only contraceptives have been reported in epidemiological studies to be associated with an increase in the incidence of type 2 diabetes mellitus. However, metabolic studies in lean, non-diabetic women have generally found no effect on glucose concentrations, suggesting that obesity or weight gain associated with injectable progestogen-only contraceptive use may play a role.[11]

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201.
2. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
3. Godsland IF, *et al.* Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; **74:** 64–70.
4. Kim C, *et al.* Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA study. *Diabetes Care* 2002; **25:** 1027–32.
5. Troisi RJ, *et al.* Oral contraceptive use and glucose metabolism in a national sample of women in the United States. *Am J Obstet Gynecol* 2000; **183:** 389–95.
6. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
7. Lopez LM, *et al.* Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 14/01/08).
8. Rimm EB, *et al.* Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 1992; **35:** 967–72.
9. Chasan-Taber L, *et al.* A prospective study of oral contraceptives and NIDDM among US women. *Diabetes Care* 1997; **20:** 330–5.
10. Kjos SL, *et al.* Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *JAMA* 1998; **280:** 533–8.
11. Kahn HS, *et al.* Effects of injectable or implantable progestin-only contraceptives on insulin-glucose metabolism and diabetes risk. *Diabetes Care* 2003; **26:** 216–25.

Effects on the cardiovascular system. Soon after their introduction in the 1960s it became apparent that **combined oral contraceptives** were associated with an increased risk of cardiovascular effects including *hypertension, venous thromboembolism, myocardial infarction*, and *stroke*. Consequently, there are a number of contra-indications and precautions relating to their use in women with risk factors for cardiovascular disease (see under Precautions, below).

Changing patterns of use, and a progressive reduction in doses, have meant a continued need to evaluate the risks associated with oral contraceptives.

Current use of lower-dose combined oral contraceptives (less than 50 micrograms oestrogen) increases blood pressure in many women, and also results in a small but significant increased risk of venous thromboembolism. Any increased risk of myocardial infarction and stroke is low in women aged less than 35 years who do not smoke and who do not have pre-existing hypertension. Further details of these adverse effects are covered in the sections below.

The effect of progestogens on the cardiovascular risk profile of oral contraceptives has not been established. Some of the newer progestogens have been reported to have more favourable effects on plasma lipids (see Effects on Lipids, below) and there is some suggestion that they may have a lower risk of myocardial infarction, but there are insufficient data to confirm or refute this. However, it has been reported that desogestrel and gestodene are associated with a higher risk of venous thromboembolism than older progestogens.

The Nurses' Health Study found no association between ever having used oral contraceptives and death from cardiovascular disease.[1] The Royal College of General Practitioners' study reported an increase in death from cerebrovascular disease with current or recent (within 10 years) use of oral contraceptives, but not for past use (greater than 10 years).[2]

Some general reviews are cited below.[3-7]

1. Colditz GA, *et al.* Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. *Ann Intern Med* 1994; **120:** 821–6.
2. Beral V, *et al.* Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 1999; **318:** 96–100.
3. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptive: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
4. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. *Ann Intern Med* 1998; **128:** 467–77.
5. WHO. Cardiovascular disease and steroid hormone contraception. *WHO Tech Rep Ser 877* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_877.pdf (accessed 14/01/08)
6. Hannaford P. Cardiovascular events associated with different combined oral contraceptives: a review of current data. *Drug Safety* 2000; **22:** 361–71.
7. Godsland IF, *et al.* Occlusive vascular diseases in oral contraceptive users: epidemiology, pathology and mechanisms. *Drugs* 2000; **60:** 721–869.

HYPERTENSION. In a one-year prospective multicentre study[1] involving 704 women under the age of 35 using a **combined oral contraceptive** containing levonorgestrel 250 micrograms and ethinylestradiol 50 micrograms and 703 women using a non-hormonal intra-uterine contraceptive device, those using the oral contraceptive developed higher systolic and diastolic blood pressures (systolic pressures were 3.6 to 5.0 mmHg higher, diastolic pressures were 1.9 to 2.7 mmHg higher). Only 4 women receiving oral contraceptives developed hypertension. A similar increase in blood pressure was noted in a study[2] involving 222 users of combined oral contraceptives containing 30 micrograms ethinylestradiol. There was a greater increase in blood pressure for those preparations containing 250 micrograms levonorgestrel than those containing 150 micrograms levonorgestrel.

More recently, data from the Nurses' Health Study[3] showed an increased risk (relative risk 1.8) for the development of hypertension in women taking lower-dose combined oral contraceptives. Increasing doses of progestogen were positively associated with hypertension, and the lowest risk occurred in women receiving triphasic preparations, which have the lowest total dose of progestogen. A UK study[4] found a small increase in blood pressure of 2.3/1.6 mmHg associated with the use of combined oral contraceptives. In this study, oral **progestogen-only contraceptives** were not associated with an increase in blood pressure. A more recent review[5] also found no evidence that use of progestogen-only contraception for up to 2 to 3 years was associated with high blood pressure. Similarly, depot medroxyprogesterone acetate does not raise blood pressure.[6]

1. WHO Task Force on Oral Contraceptives. The WHO multicentre trial of the vasopressor effects of combined oral contraceptives 1: comparisons with IUD. *Contraception* 1989; **40:** 129–45.
2. Khaw K-T, Peart WS. Blood pressure and contraceptive use. *BMJ* 1982; **285:** 403–7.
3. Chasan-Taber L, *et al.* Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996; **94:** 483–9.
4. Dong W, *et al.* Blood pressure in women using oral contraceptives: results from the Health Survey for England 1994. *J Hypertens* 1997; **15:** 1063–8.
5. Hussain SF. Progestogen-only pills and high blood pressure: is there an association? A literature review. *Contraception* 2004; **69:** 89–97.
6. Taneepanichskul S, *et al.* Effects of DMPA on weight and blood pressure in long term acceptors. *Contraception* 1999; **59:** 301–3.

MYOCARDIAL INFARCTION. Case-control studies from the 1970s and early 1980s revealed an increased risk of acute myocardial infarction in users of oral contraceptives (generally of the high-dose type) relative to those never having used them.[1,2] Several large cohort studies have provided similar findings.[3-6] Among current users the reported[1-3,5,6] relative risk of myocardial infarction has varied between about 1.8 and 6.4, whereas in women having used oral contraceptives in the past the reported[2-5] relative risk has varied between about 0.8 and 2.5. Women who *smoke* while using oral contraceptives are at a greatly increased risk,[1,5,7] those smoking more than 15 to 25 cigarettes daily having at least a twentyfold increased risk of myocardial infarction compared with non-smoking non-oral contraceptive users.[1,5]

These studies have principally been from the USA or the UK. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception has reported the findings of an international multicentre case-control study.[8] The overall odds ratio for acute myocardial infarction in current users of combined oral contraceptives was 5.01 in Europe and 4.78 in Africa, Asia, and Latin America. This increase in risk reflected use in women who had coexistent risk factors such as smoking, and who had not had their blood pressure checked before use. Thus, when the background incidence of acute myocardial infarction is taken into account, use of combined oral contraceptives in non-smoking women aged less than 35 years is associated with an excess of 3 per million women-years, and this is likely to be lower in those women who have their blood pressure screened before and during use. However, in older women who smoke, the excess risk associated with the use of combined oral contraceptives is substantial (400 per million women-years). There was no increase in risk associated with past use of oral contraceptives irrespective of duration of use.

There has been interest in the effect of different progestogen components on the risk of myocardial infarction. Limited data from the WHO study[8] and from the USA[9] and the UK[10] suggested no difference in risk between desogestrel or gestodene compared with levonorgestrel. Analysis of European data[11] suggested a reduction in risk with gestodene- and desogestrel-containing products compared with other progestogens (0.28; 95% confidence intervals 0.09 to 0.86). A WHO Scientific Group meeting concluded that available data did not allow the conclusion that risk of myocardial infarction was related to progestogen type.[12]

More recently, data on combined oral contraceptives that have lower oestrogen doses have revealed at most small and non-significant increases in risk of acute myocardial infarction associated with oral contraceptive use,[10,13-15] although case-control studies have suggested that again, there may be a greatly increased risk in women who smoke more than 20 to 25 cigarettes daily.[10,16] However, subsequent meta-analyses including these and other studies have concluded that, overall, there was an increased risk of myocardial infarction with current use of low-dose combined oral contraceptives (oestrogen less than 50 micrograms). Subgroup analyses of progestogen type found that there was an increased risk in users of second generation contraceptives (generally containing levonorgestrel) compared with non-users; calculated odds ratios were 2.18 (1.62 to 2.94),[17] 2.17 (1.76 to 2.69),[18] and 1.85 (1.03 to 3.32).[19] However, the risk was not increased in users of third generation contraceptives (generally containing desogestrel or gestodene) compared with non-users.[17-19] Clinically, although the risk of myocardial infarction may be increased, the absolute risk is very low in healthy young women who do not smoke and do not have cardiovascular risk factors. Despite reassuring data for these newer progestogens regarding the risk of myocardial infarction, there is probably a small increased risk of venous thromboembolism associated with desogestrel or gestodene (see below).

1. Shapiro S, *et al.* Oral-contraceptive use in relation to myocardial infarction. *Lancet* 1979; **i:** 743–7.
2. Slone D, *et al.* Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981; **305:** 420–4.
3. Royal College of General Practitioners' Oral Contraception Study. Further analyses of mortality in oral contraceptive users. *Lancet* 1981; **i:** 541–6.
4. Stampfer MJ, *et al.* A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med* 1988; **319:** 1313–17.
5. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. *BMJ* 1989; **298:** 165–8.
6. Vessey MP, *et al.* Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. *BMJ* 1989; **299:** 1487–91.
7. Goldbaum GM, *et al.* The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA* 1987; **258:** 1339–42.
8. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 1997; **349:** 1202–9.
9. Jick H, *et al.* Risk of acute myocardial infarction and low-dose combined oral contraceptives. *Lancet* 1996; **347:** 627–8.
10. Dunn N, *et al.* Oral contraceptives and myocardial infarction: results of the MICA case-control study. *BMJ* 1999; **318:** 1579–83.
11. Lewis MA, *et al.* The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the transnational study on oral contraceptives and the health of young women. *Contraception* 1997; **56:** 129–40.
12. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
13. Thorogood M, *et al.* Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study. *Br J Obstet Gynaecol* 1991; **98:** 1245–53.
14. Sidney S, *et al.* Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. *Circulation* 1998; **98:** 1058–63.
15. Tanis BC, *et al.* Oral contraceptives and the risk of myocardial infarction. *N Engl J Med* 2001; **345:** 1787–93.
16. Rosenberg L, *et al.* Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med* 2001; **161:** 1065–70.
17. Spitzer WO, *et al.* Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. *Hum Reprod* 2002; **17:** 2307–14.
18. Khader YS, *et al.* Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception* 2003; **68:** 11–17.
19. Baillargeon J-P, *et al.* Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

STROKE. Current use of **combined oral contraceptives** has been associated with an increased risk of stroke, with most data relating to older high-dose oestrogen preparations. In general this association has been strongest for ischaemic stroke, and relatively weak for haemorrhagic stroke.[1] A Danish study found that low-dose oral contraceptives (30 to 40 micrograms of oestrogen) were associated with a lower risk of cerebral thromboembolism than preparations containing 50 micrograms oestrogen.[2]

Data on 2198 cases of stroke (haemorrhagic, ischaemic, and unclassified) and 6086 controls have been reported from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.[3,4] For all strokes combined, odds ratios for the current use of lower-dose (less than 50 micrograms oestrogen) and higher-dose preparations were, respectively, 1.41 (95% confidence intervals 0.90 to 2.20) and 2.71 (1.70 to 4.32) in Europe, and 1.86 (1.49 to 2.33) and 1.92 (1.48 to 2.50) in Africa, Asia, and Latin America. In Europe, it was estimated that the incidence rate of stroke in women aged 20 to 44 years was 4.8 per 100 000 women-years, and that this was increased to 6.7 per 100 000 in users of lower-dose preparations and 12.9 per 100 000 in users of higher-dose preparations.[3]

The risk of haemorrhagic stroke was significant only in women aged greater than 35 years, those who had a history of hypertension, and those who were current smokers.[3]

The overall odds ratio for ischaemic stroke was 2.99 (1.65 to 5.40) in Europe and 2.93 (2.15 to 4.00) in Africa, Asia, and Latin America.[4] Odds ratios were lower in women aged less than 35 years, those who did not smoke, those with no history of hypertension, and those who reported that their blood pressure had been checked before use. Duration of current use and past use were unrelated to risk.[4] A similar overall odds ratio of 2.3 (1.15 to 4.59) has been reported from the UK.[5] Similar findings have also been published from the USA.[6] Low-dose preparations (less than 50 micrograms oestrogen) were associated with a non-significant increase in ischaemic stroke; the odds ratio was 1.18 (0.54 to 2.59); a later meta-analysis considered the association between low-dose combined oral contraceptives and stroke to be tenuous at best, and possibly non-existent.[7]

A meta-analysis[8] of studies of ischaemic stroke found that there was an overall increased risk associated with the current use of oral contraceptives. However, the risk was less elevated with lower oestrogen doses, and in studies that controlled for smoking and hypertension.

As regards the effect of the type of progestogen on risk of stroke, one case-control study[9] reported that there was no significant difference in risk of ischaemic stroke between low-dose oral contraceptives containing second generation progestogens and those containing desogestrel, gestodene, or norgestimate. However, another study[10,11] found that levonorgestrel- or norgestimate-containing preparations were associated with a higher risk of cerebral thrombosis than preparations containing desogestrel or gestodene. A re-analysis of the WHO data led to the cautious conclusion that the risk for stroke between second and third generation progestogens was similar,[12] and this was also supported by analysis of the General Practice Research Database[13] and a Dutch case-control study.[14] Meta-analyses[8,15] also found no significant difference between progestogen generations in the risk of ischaemic stroke.

Data for **progestogen-only contraceptives** are limited. The Danish study reported no increase in cerebral thromboembolic attacks in users of oral progestogen-only contraceptives; the odds ratio was 0.9 (0.4 to 2.4).[2]

1. Vessey MP, *et al*. Oral contraceptives and stroke: findings in a large prospective study. *BMJ* 1984; **289:** 530–1.
2. Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993; **306:** 956–63.
3. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 505–10.
4. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 1996; **348:** 498–505.
5. Nightingale AL, Farmer RDT. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke* 2004; **35:** 1574–8.
6. Petitti DB, *et al*. Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996; **335:** 8–15.
7. Chan W-S, *et al*. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med* 2004; **164:** 741–7.
8. Gillum LA, *et al*. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; **284:** 72–8.
9. Heinemann LAJ, *et al*. Case-control study of oral contraceptives and risk of thromboembolic stroke: results from international study on oral contraceptives and health of young women. *BMJ* 1997; **315:** 1502–4.
10. Lidegaard Ø, Kreiner S. Cerebral thrombosis and oral contraceptives: a case-control study. *Contraception* 1998; **57:** 303–14.
11. Lidegaard Ø, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception* 2002; **65:** 197–205.
12. Poulter NR, *et al*. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. *Lancet* 1999; **354:** 301–2.
13. Jick SS, *et al*. Risk of idiopathic cerebral haemorrhage in women on oral contraceptives with differing progestagen components. *Lancet* 1999; **354:** 302–3.
14. Kemmeren JM, *et al*. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002; **33:** 1202–8.
15. Baillargeon J-P, *et al*. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 3863–70.

Venous thromboembolism. Use of **combined oral contraceptives** has long been known to be associated with an increased risk of venous thromboembolic events, particularly deep-vein thrombosis and pulmonary embolism. This increased risk applies both to idiopathic events and events associated with surgery or trauma, is limited to current users and is probably highest in the first year of use. Most early data relate to high-dose combined preparations, and it has been suggested by some studies,[1] but not others,[2,3] that preparations containing lower doses of oestrogen may be associated with a lower risk. More recently, reports have identified an increased risk of cerebral-vein thrombosis with oral contraceptives.[4]

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception reported data from over 10 times more cases than any previous study.[5] The increased risk of idiopathic deep-vein thrombosis and/or pulmonary embolism associated with current use of combined oral contraceptives was 4.15 (95% confidence intervals 3.09 to 5.57) in Europe and 3.25 (2.59 to 4.08) in Africa, Asia, and Latin America. The increased risk was apparent within 4 months of starting use, was unaffected by duration of use, and had disappeared within 3 months of stopping use. Risk was unaffected by age, hypertension, or smoking (in contrast to myocardial infarction, see above), but was increased in those with a body-mass index greater than 25 kg/m^2 and in those with a history of hypertension of pregnancy. Of preparations containing progestogens of the norethisterone or norgestrel type, risk was non-significantly less with lower-dose oestrogen than with high-dose oestrogen.

The progestogen component has generally been considered to be unrelated to thromboembolic events; therefore, it came as a surprise when WHO found a higher risk in combined oral contraceptives containing *desogestrel* or *gestodene* than in those containing older progestogens.[5] These risk data were the subject of a separate report,[6] and were subsequently confirmed by 3 further case-control studies.[7-9] The increased risk varied from 4.8 to 9.1 compared with non-users, and was found to be 1.5 to 2.6 times higher than for preparations containing levonorgestrel or other progestogens. The incidence of venous thromboembolic disease has been estimated to be 25 per 100 000 users per year for desogestrel- and gestodene-containing products and 15 per 100 000 users per year for products containing low-dose oestrogen with other progestogens, compared with 5 per 100 000 per year for non-users. The risk was especially high in women with the factor V Leiden mutation,[8] who are at increased risk of thrombosis, but screening to exclude these women from using oral contraceptives was not considered necessary.[10,11] Despite much debate about possible bias and confounding in these results,[12,13] and the ambiguous or contradictory results of subsequent studies,[14-16] many sources seem now to agree with the 1997 conclusion of a WHO scientific group meeting[17] that there is a modestly increased risk of venous thromboembolism associated with the use of products containing desogestrel or gestodene, compared with levonorgestrel. The extent of any risk associated with combined products containing *drospirenone* has also been questioned. Data from a prescription event monitoring study suggested that it was associated with a high incidence of deep-vein thrombosis and pulmonary embolism,[18] but the authors acknowledged potential bias that may have affected the result. Subsequent large cohort studies[19,20] reported that the risk of venous thromboembolism was similar to that for users of other combined oral contraceptives, including levonorgestrel-containing preparations. It is unclear to what extent products containing *cyproterone* are associated with increased risk (see Effects on the Cardiovascular System, under Cyproterone Acetate, p.2088).

Regulatory agencies have reacted in different ways to these data. The UK CSM has advised caution in prescribing of these products (see Cardiovascular Disease under Precautions, below), as have some other European authorities.

The mechanism behind differences in thrombotic potential is not known, but there is evidence that oral contraceptives may increase concentrations of prothrombin and factor VIII, and induce a resistance to the blood's natural anticoagulation system.[11] These effects may be greater with products containing desogestrel and gestodene compared with older progestogens.[11] Thrombophilias, including factor V Leiden, further increase the risk of thromboembolism from hormonal contraceptives.[21]

There has also been some concern about a possible increase in cardiovascular risk with a **transdermal patch** that releases ethinylestradiol and norelgestromin, because users are exposed to about 60% more total oestrogen than users of an oral contraceptive containing ethinylestradiol 35 micrograms (peak serum concentrations are lower but steady-state concentrations are higher). However, 2 studies comparing the patch with a combined oral contraceptive (ethinylestradiol plus norgestimate) came to different conclusions; one found the risk of venous thromboembolism to be similar,[22] while the other found a twofold increase in risk with the patch.[23] Further study is needed to explain this discrepancy, and to determine whether there is any effect on the risks of myocardial infarction and stroke.

1. Vessey M, *et al*. Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
2. Kierkegaard A. Deep vein thrombosis and the oestrogen content in oral contraceptives—an epidemiological analysis. *Contraception* 1985; **31:** 29–41.
3. Helmrich SP, *et al*. Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 1987; **69:** 91–5.
4. Dentali F, *et al*. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006; **107:** 2766–73.
5. WHO Collaborative Study Group. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; **346:** 1575–82.
6. WHO Collaborative Study Group. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995; **346:** 1582–8.
7. Jick H, *et al*. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346:** 1589–93.
8. Bloemenkamp KWM, *et al*. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995; **346:** 1593–6.
9. Spitzer WO, *et al*. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; **312:** 83–8.
10. Vandenbroucke JP, *et al*. Factor V Leiden: should we screen oral contraceptive users and pregnant women? *BMJ* 1996; **313:** 1127–30.
11. Vandenbroucke JP, *et al*. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344:** 1527–35.
12. Lewis MA, *et al*. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. *Contraception* 1996; **54:** 5–13.
13. Farley TMM, *et al*. Oral contraceptives and thrombotic diseases: impact of new epidemiologic studies. *Contraception* 1996; **54:** 193–5.
14. Farmer RDT, *et al*. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349:** 83–8.
15. Farmer RDT, *et al*. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. *BMJ* 2000; **321:** 477–9.
16. Jick H, *et al*. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000; **321:** 1190–5. Correction. *ibid*. 2001; **322:** 28.
17. WHO. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: summary of conclusions. *Wkly Epidem Rec* 1997; **72:** 361–3.
18. Pearce HM, *et al*. Deep vein thrombosis and pulmonary embolism reported in the Prescription Event Monitoring Study of Yasmin . *Br J Clin Pharmacol* 2005; **60:** 98–102.
19. Dinger JC, *et al*. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contraception* 2007; **75:** 344–54.
20. Seeger JD, *et al*. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007; **110:** 587–93.
21. Wu O, *et al*. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.
22. Jick SS, *et al*. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. *Contraception* 2006; **73:** 223–8.
23. Cole JA, *et al*. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol* 2007; **109:** 339–46.

Effects on the ears. In the Royal College of General Practitioners' study of oral contraception in the UK,[1] by 1981 there had been 13 cases of newly occurring otosclerosis in each of the groups of oral contraceptive users (101 985 woman-years) and controls (146 534 woman-years); this showed a non-significant relative risk of 1.29. Although, by analogy with pregnancy, it may be prudent to suppose that oral contraceptives could exacerbate pre-existing otosclerosis, the data do not support the view that the condition is associated with their use. Similarly, the Oxford Family Planning Association contraceptive study[2] of 17 032 women followed for up to 26 years found no association between oral contraceptive use and the development of a range of ear diseases, including otosclerosis.

1. Kay CR, Wingrave SJ. Oral contraceptives and otosclerosis. *BMJ* 1984; **288:** 1164.
2. Vessey M, Painter R. Oral contraception and ear disease: findings in a large cohort study. *Contraception* 2001; **63:** 61–3.

Effects on the eyes. Analysis of data from 2 large UK cohort studies suggested that oral contraceptive use does not increase the risk of eye disease, with the possible exception of retinal vascular lesions.[1] Retinal vein thrombosis has also been reported after the use of emergency contraception.[2] The patient presented with a 10-day history of blurred vision that started the day after taking a regimen of ethinylestradiol with norgestrel; the condition resolved after 2 months of treatment with low-dose aspirin.

1. Vessey MP, *et al*. Oral contraception and eye disease: findings in two large cohort studies. *Br J Ophthalmol* 1998; **82:** 538–42.
2. Lake SR, Vernon SA. Emergency contraception and retinal vein thrombosis. *Br J Ophthalmol* 1999; **83:** 630–1.

Effects on fertility. After stopping hormonal contraceptives some patients may experience amenorrhoea, anovulation, and infertility. This infertility, however, has been shown by most studies to be only temporary.

Data from the Oxford Family Planning Association study[1] have indicated that impairment of fertility after oral contraceptives was only very slight and short-lived in women who had previously had a baby. In nulliparous women aged 25 to 29 years impairment of fertility was more pronounced but the effect had almost entirely disappeared after 48 months. In nulliparous women aged 30 to 34 years the duration of impairment was longer but, again, this was not permanent as by 72 months after stopping oral contraceptive use the numbers of women who had not conceived were similar to a group who had previously used non-hormonal methods of contraception. In contrast to women using intra-uterine devices, in whom long-term use was associated with greater impairment of fertility than short-term (less than 42 months) use, there appears to be no association between fertility and duration of oral contraceptive use.[2] However, a later survey,[3] although concurring that the effects were transient, did find a relationship between duration of use of combined oral contraceptives and subsequent time to pregnancy.

Oral progestogen-only preparations do not appear to have a significant effect on fertility.[3] Smaller studies have also indicated that injectable progestogen-only contraceptives have no long-lasting effects on fertility;[3,4] but it has been suggested that a return to ovulation occurs significantly earlier in prior norethisterone enantate users than in medroxyprogesterone users.[5]

Infertility may also be related to the presence of pelvic inflammatory disease; for further details concerning the role of oral contraceptives in this disorder, see Pelvic Inflammatory Disease, below.

1. Anonymous. "Pill" use appears to impair fertility in a certain group of women. *Pharm J* 1986; **236:** 227.
2. Doll H, *et al.* Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. *Br J Obstet Gynaecol* 2001; **108:** 304–14.
3. Hassan MAM, Killick SR. Is previous use of hormonal contraception associated with a detrimental effect on subsequent fecundity? *Hum Reprod* 2004; **19:** 344–51.
4. Fotherby K, *et al.* Return of ovulation and fertility in women using norethisterone enanthate. *Contraception* 1984; **29:** 447–55.
5. Garza-Flores J, *et al.* Return to ovulation following the use of long-acting injectable contraceptives: a comparative study. *Contraception* 1985; **31:** 361–6.

Effects on the gallbladder. Data from the Royal College of General Practitioners' (RCGP) oral contraception study accumulated up to December 1979 revealed no overall increased risk of gallbladder disease in the long-term, despite the indications of earlier data and other studies relating to short-term use.[1] Further studies[2,3] have identified an increased risk of gallbladder disease in oral contraceptive users under the age of 30 or 20, respectively. A systematic review[4] also found that oral contraceptives were associated with a slightly and transiently increased risk of gallbladder disease. However, the results of separate studies varied considerably and the reviewers highlighted a number of possible confounding factors and biases, nonetheless, it was concluded that newer low-dose contraceptives (less than 50 micrograms of oestrogen) were less likely to cause problems than older formulations. Later data from the RCGP study showed an increase in risk of mild hepatitis during the first 4 years of oral contraceptive use, possibly reflecting gallstone-associated cholestasis.[5] This risk then decreased to less than that seen in women who had never used oral contraceptives.

1. Wingrave SJ, Kay CR. Oral contraceptives and gallbladder disease: Royal College of General Practitioners' oral contraception study. *Lancet* 1982; **ii:** 957–9.
2. Scragg RKR, *et al.* Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease—a case-control study. *BMJ* 1984; **288:** 1795–9.
3. Strom BL, *et al.* Oral contraceptives and other risk factors for gallbladder disease. *Clin Pharmacol Ther* 1986; **39:** 335–41.
4. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health* 1993; **83:** 1113–20.
5. Hannaford PC, *et al.* Combined oral contraceptives and liver disease. *Contraception* 1997; **55:** 145–51.

Effects on the gastrointestinal tract. Several studies,[1-3] epidemiological data,[4] and a meta-analysis,[5] have shown a weak association between oral contraceptive use and the onset of Crohn's disease or ulcerative colitis. However, the suggestion that oral contraceptives have an aetiological role in chronic inflammatory bowel disease cannot be regarded as established.

The rate of relapse of Crohn's disease in women taking oral contraceptives has also been studied. Although one study[6] reported an increased risk of relapse in women who had taken oral contraceptives in the past, both this study and another prospective cohort study[7] found no increase in risk in current users. These results may have been influenced by smoking, or changes in oestrogen dose and progestogen content.

Women with inflammatory bowel disease may be offered the same contraceptive choices as other women, although oral contraceptive absorption, and hence efficacy, may be reduced when there is small bowel involvement or malabsorption.[8]

1. Corrao G, *et al.* Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. *Int J Epidemiol* 1998; **27:** 397–404.
2. Sicilia B, *et al.* Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis* 2001; **33:** 762–7.
3. García Rodríguez LA, *et al.* Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005; **22:** 309–15.
4. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease. *Gut* 2000; **46:** 140.
5. Godet PG, *et al.* Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995; **37:** 668–73.
6. Timmer A, *et al.* Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. *Gastroenterology* 1998; **114:** 1143–50.
7. Cosnes J, *et al.* Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. *Gut* 1999; **45:** 218–22.
8. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (July 2003): contraceptive choices for women with inflammatory bowel disease. *J Fam Plann Reprod Health Care* 2003; **29:** 127–34. Also available at: http://www.ffprhc.org.uk/admin/uploads/IBD%20final%20pdf.pdf (accessed 15/01/08)

Effects on lipids. Combined oral contraceptives have been reported to be associated with an excess risk of various adverse cardiovascular events (see above). Because other epidemiological evidence suggests that the composition of blood lipids may be one of several factors involved in the aetiology of some of these disorders, many workers have investigated the biochemical profiles of women taking various formulations of oral contraceptives. Results have often been conflicting as the net effect is the result of opposing actions of the oestrogen and the progestogen components, and depends on the ratio between these. In general, the oestrogen component increases triglycerides, but decreases low-density lipoproteins, whereas the progestogen component tends to decrease high-density lipoproteins and increase low-density lipoproteins, particularly if it is androgenic (19-nortestosterone-derived progestogens). Newer non-androgenic progestogens such as desogestrel and gestodene appear to have a less detrimental effect on serum lipids. However, the contribution of these lipid changes to the incidence of cardiovascular disease in oral contraceptive users is uncertain. In particular, contrary to expectations, desogestrel and gestodene appear to be associated with a higher risk of venous thromboembolism than older progestogens (see above).

Some references to the effects of various oral contraceptives on serum lipid profiles are given below.[1-4]

For further details concerning the proposed role of the various serum lipids and subfractions in the aetiology of cardiovascular disease, see Hyperlipidaemias, p.1169.

For reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives, see below.

1. Crook D, Godsland I. Safety evaluation of modern oral contraceptives: effects on lipoprotein and carbohydrate metabolism. *Contraception* 1998; **57:** 189–201. Correction. *ibid.*: 420.
2. Knopp RH, *et al.* Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001; **63:** 1–11.
3. Graff-Iversen S, Tonstad S. Use of progestogen-only contraceptives/medications and lipid parameters in women age 40 to 42 years: results of a population-based cross-sectional Norwegian Survey. *Contraception* 2002; **66:** 7–13.
4. Gaspard U, *et al.* A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. *Contraception* 2004; **69:** 271–8.

Effects on the liver. The use of combined oral contraceptives has been rarely associated with the benign liver tumours, hepatic adenoma and focal nodular hyperplasia (see under Carcinogenicity, above).

Hepatitis possibly associated with gallstones has also been reported (see Effects on the Gallbladder, above).

Effects on mental state. Changes in mood and affect have been reported with oral contraceptives, and the onset of depression is a common reason given for stopping use. Nonetheless, a review[1] concluded that most women taking oral contraceptives actually experienced beneficial effects, with less variability in affect across the menstrual cycle and less negative affect during the menstrual phase compared with non-users. However, there may be a subgroup of women predisposed to negative changes in mood and affect because of factors such as a history of depression, premenstrual mood symptoms before oral contraceptive use, a history of mood symptoms related to pregnancy, or a family history of mood complaints related to oral contraceptives. A lower ratio of progestogen to oestrogen was associated with more negative mood changes in women with a history of premenstrual emotional symptoms, while a higher ratio was associated with negative changes in women without such a history. In addition, monophasic regimens appeared to have a greater stabilising effect than triphasic preparations. A number of possible mechanisms have been suggested to explain how combined hormonal contraceptives might influence mood.[2]

Cohort studies of injectable[3] and implantable[4] progestogen-only contraceptives found no overall change in depressive symptom score. A small increase in depressive score noted at the 2-year follow-up of implant users was found to occur in women who also had a decrease in relationship satisfaction, which the authors concluded was independent of contraceptive use. Another study[5] found an association between injectable medroxyprogesterone acetate and depressive symptoms, but other factors that might have influenced this result were also identified and another explanation could not be ruled out.

1. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002; **70:** 229–40.
2. Kurshan N, Epperson CN. Oral contraceptives and mood in women with and without premenstrual dysphoria: a theoretical model. *Arch Womens Ment Health* 2006; **9:** 1–14.
3. Westhoff C, *et al.* Depressive symptoms and Depo-Provera . *Contraception* 1998; **57:** 237–40.
4. Westhoff C, *et al.* Depressive symptoms and Norplant contraceptive implants. *Contraception* 1998; **57:** 241–5.
5. Civic D, *et al.* Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. *Contraception* 2000; **61:** 385–90.

Effects on the musculoskeletal system. ***BONE DENSITY.*** Combined oral contraceptives are generally considered not to have a detrimental effect on bone mineral density but study results have been inconsistent and any clinical significance unclear. However, overall, combined oral contraceptives appear not to affect bone mineral density or biochemical markers of bone turnover.[1]

Reviews of studies in different age groups have found that bone mineral density in healthy premenopausal women does not appear to be significantly affected.[2,3] However, there is limited evidence that adolescents and young women (less than 23 years of age) using oral combined contraceptives have a lower bone mineral density than non-users; it is unclear whether contraceptives might prevent young women from reaching their peak bone mass and put them at increased risk of osteoporosis later in life.[3] There is some evidence of a positive effect on bone mineral density in perimenopausal[2,3] and postmenopausal women[3] taking combined oral contraceptives, but past use in postmenopausal women appeared to have no effect. Although bone mineral density is used as an indicator of fracture risk, the true effects of combined oral contraceptives on this clinical outcome are unclear;[1] there is a particular lack of data in older women, in whom osteoporotic fractures are most common.[3]

There is stronger evidence that bone mineral density is reduced in current users of the depot progestogen-only contraceptive, medroxyprogesterone acetate. Recovery occurs after stopping treatment,[4,5] but it is still unclear whether adult women can regain baseline bone mineral density levels, and whether adolescents can reach peak bone mass.[4] There is also a lack of data on the clinical outcome of fracture in both current and former users of all ages.[1,4]

As adolescence is an age at which bone mineral density is normally increasing there is some concern about the possible long-term effects of medroxyprogesterone. The UK CSM has advised that in adolescents it should only be used if other methods of contraception are unsuitable or unacceptable, and that there should be a re-evaluation of risks and benefits for women of all ages who wish to continue use beyond 2 years.[6] The FDA has also advised[7] that, for all women, medroxyprogesterone should only be used as a long-term contraceptive, giving an example of more than 2 years, if other contraceptive methods are inadequate. In contrast, however, WHO[8] advises that there should be no restriction, including duration of use, on the use of medroxyprogesterone in women aged 18 to 45 who are otherwise eligible to use it; in adolescents and women over 45, the advantages generally outweigh the theoretical risks of fracture, but because of limited data on long-term use the overall risks and benefits should be reconsidered over time with the individual user. Others[9] offer similar recommendations in support, pointing out that further research is needed.

There is some evidence that oestrogen supplementation may reduce or prevent the reduction in bone mineral density caused by medroxyprogesterone acetate.[10,11] Although such supplementation could be considered in medroxyprogesterone users who have osteopenia or are at high risk, the optimal dose, route, and extent of benefit has not been established.[9]

1. Lopez LM, *et al.* Steroidal contraceptives: effect on bone fractures in women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 14/01/08).
2. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. *Br J Sports Med* 2006; **40:** 11–24.
3. Martins SL, *et al.* Combined hormonal contraception and bone health: a systematic review. *Contraception* 2006; **73:** 445–69.
4. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. *Contraception* 2006; **73:** 470–87.
5. Kaunitz AM, *et al.* Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. *Contraception* 2006; **74:** 90–9.
6. MHRA. Updated prescribing advice on the effect of Depo-Provera contraception on bones. Message from Professor G Duff, Chairman of CSM (issued 16th November, 2004). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con019478&RevisionSelectionMethod=Latest (accessed 14/01/08)
7. FDA. Black box warning added concerning long-term use of Depo-Provera contraceptive injection (issued November 17, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01325.html (accessed 14/01/08)
8. WHO. WHO statement on hormonal contraception and bone health (issued July 2005). Available at: http://www.who.int/reproductive-health/family_planning/docs/hormonal_contraception_bone_health.pdf (accessed 14/01/08)
9. Cromer BA, *et al.* Depot medroxyprogesterone acetate and bone mineral density in adolescents—the Black Box Warning: a Position Paper of the Society for Adolescent Medicine. *J Adolesc Health* 2006; **39:** 296–301.
10. Cundy T, *et al.* A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab* 2003; **88:** 78–81.
11. Cromer BA, *et al.* Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. *Am J Obstet Gynecol* 2005; **192:** 42–7.

RHEUMATOID ARTHRITIS. There have been rare reports of arthritis or arthropathies attributed to oral contraceptives, and some large studies have investigated the incidence of rheumatoid arthritis in oral contraceptive users. A negative association between the use of oral contraceptives and the development of rheumatoid arthritis has been reported in some studies thus giving rise to the suggestion that oral contraceptive use may, in fact, have some sort of protective role. These findings were not, however, substantiated by a recent, large, long-term cohort study[1] which found no association, either beneficial or detrimental, between the use of oral contraceptives and the later development of rheumatoid arthritis. An earlier meta-analysis also found no conclusive evidence of a protective effect of oral contraceptives on rheumatoid arthritis risk.[2] There is limited information about the effect of oral contraceptives on pre-existing rheumatoid arthritis. One study[3] found that there was no significant influence on the progression of the disease, but there was a trend towards less radiographic joint damage and disability with long-term oral contraceptive use.

1. Karlson EW, *et al.* Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; **50:** 3458–67.
2. Pladevall-Vila M, *et al.* Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. *Am J Epidemiol* 1996; **144:** 1–14.
3. Drossaers-Bakker KW, *et al.* Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. *Ann Rheum Dis* 2002; **61:** 405–8.

Effects on the nervous system. *Headache* is reported as a common adverse effect and frequent reason for stopping combined oral contraceptives. However, a systematic review[1] found that although study results could not be pooled, there was no strong evidence associating combined oral contraceptive use with headache. There may have been an increase in headache in the early cycles, but this tended to improve with continued use; for most women there was no effect on headache activity and some actually reported improvement. Headache also appeared to be associated with oestrogen withdrawal during the tablet-free week of the cycle, but there was no evidence that headache was improved by changing to a preparation with a lower dose of oestrogen. However, some women appeared to be at higher risk, such as those with a strong personal or family history of troublesome headaches, particularly migraine. Combined oral contraceptives are not contra-indicated in women with non-migrainous headache, but they should be used with caution or avoided in women with migraine because of the increased risk of stroke (see Migraine, under Precautions, below).

Chorea has been reported in women using combined oral contraceptives. Reviews of the literature have reported the onset of chorea to range from 1 week to 11 months,[2] with an average of 3 months,[3] and resolution of symptoms after stopping the contraceptive to occur after 1 week to 5 months[2] or an average of 5 weeks.[3] The mechanism of this effect is unclear. Some cases occurred in patients with no history of neurological disease,[2,3] but others had a history of rheumatic fever, often with Sydenham chorea, or chorea gravidarum, chorea secondary to other conditions, or congenital heart disease.[3] There is some evidence that chorea could be mediated by the production of antiphospholipid antibodies, as either a primary antiphospholipid syndrome or secondary to SLE.[4,5] It has been suggested that the production of these antibodies could be aggravated by the oestrogen component of combined oral contraceptives.[4] In another case report[6] it was suggested that the presence of anti-basal ganglia antibodies might have played a role in the development of chorea by making the basal ganglia more susceptible to the effects of the oestrogen component of an oral contraceptive.

It is generally advised that combined oral contraceptives should be used with caution or avoided in women with antiphospholipid antibodies because they are at increased risk of venous thromboembolism, see Cardiovascular Disease, under Precautions, below.

1. Loder EW, *et al.* Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol* 2005; **193:** 636–49.
2. Wadlington WB, *et al.* Chorea associated with the use of oral contraceptives: report of a case and review of the literature. *Clin Pediatr (Phila)* 1981; **20:** 804–6.
3. Galimberti D. Chorea induced by the use of oral contraceptives: report of a case and review of the literature. *Ital J Neurol Sci* 1987; **8:** 383–6.
4. Omdal R, Roalsø S. Chorea gravidarum and chorea associated with oral contraceptives—diseases due to antiphospholipid antibodies? *Acta Neurol Scand* 1992; **86:** 219–20.
5. Cervera R, *et al.* Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine (Baltimore)* 1997; **76:** 203–12.
6. Miranda M, *et al.* Oral contraceptive induced chorea: another condition associated with anti-basal ganglia antibodies. *J Neurol Neurosurg Psychiatry* 2004; **75:** 327–8.

Effects on the pancreas. There have been reports of pancreatitis secondary to hyperlipidaemia associated with the use of combined oral contraceptives.[1,2]

1. Parker WA. Estrogen-induced pancreatitis. *Clin Pharm* 1983; **2:** 75–9.
2. Stuyt PMJ, *et al.* Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *BMJ* 1986; **293:** 734.

Effects on the skin. Oral contraceptives may cause chloasma, and those containing androgenic progestogens may cause or aggravate acne and hirsutism. More rarely, oral contraceptives have been implicated in photosensitivity reactions[1] and photosensitivity associated with drug-induced lupus erythematosus.[2] A survey of people using UVA sunbeds at commercial premises in the UK revealed that the prevalence of pruritus, nausea, and skin rashes as adverse reactions to sunbed use was higher in women taking oral contraceptives than in women receiving no medication.[3] There has been a report of hidradenitis suppurativa, a condition resulting in the recurrence of boils at the axillary apocrine sweat glands, anogenital region, and breasts, occurring in 7 women using oral contraceptives.[4] Sweet's syndrome (acute febrile neutrophilic dermatosis) has been described very rarely with hormonal contraceptives. In one case,[5] the reaction started 10 days after beginning a combined oral contraceptive and resolved after stopping the contraceptive and treating with oral and topical corticosteroids. The woman reported that a similar reaction had occurred 6 months earlier with a different combined oral contraceptive. Sweet's syndrome has also occurred 1 month after insertion of a levonorgestrel IUD; the condition was controlled with corticosteroids, but only resolved completely after removal of the IUD.[6]

For mention of the refuted association between oral contraceptives and malignant melanoma, see Skin under Carcinogenicity above. Auto-immune progesterone dermatitis has been reported in women with a history of oral contraceptive use (see p.2125).

1. Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. *Br J Dermatol* 2001; **144:** 641–2.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; (Jun.): 508–11.
3. Diffey BL. Use of UV-A sunbeds for cosmetic tanning. *Br J Dermatol* 1986; **115:** 67–76.
4. Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ* 1989; **298:** 28–9.
5. Sáez M, *et al.* Sweet's syndrome induced by oral contraceptive. *Dermatology* 2002; **204:** 84.
6. Hamill M, *et al.* Sweet's syndrome and a Mirena intrauterine system. *J Fam Plann Reprod Health Care* 2004; **30:** 115–16.

Effects on the uterus. The Oxford Family Planning Association study found that the risk of developing uterine leiomyomas (uterine fibroids) was reduced by the use of oral contraceptives[1] by about 17% with each 5 years of oral contraceptive use. This was not thought to be due to selective prescribing.[2,3] The authors hypothesised that unopposed oestrogen may be a risk factor for uterine fibroids, and that the reduced risk with oral contraceptives might be analogous to the reduction in endometrial carcinoma seen with these drugs (see above).[1] Other studies[4,5] have also reported a reduced risk of uterine leiomyomas in current users of oral contraceptives, while past users have a risk similar to that in women who have never used oral contraceptives. However, one study[4] did suggest that in women who had first used oral contraceptives at an early age (13 to 16 years) there was a modestly elevated risk. Another case-control study involving 390 women with leiomyomas failed to find a protective (or detrimental) effect with oral contraceptive use.[6] A further cohort study[7] also found no association between oral contraceptive use and leiomyoma formation, but did report a reduced risk with current use of medroxyprogesterone acetate depot injection.

1. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 359–62.
2. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
3. Ross RK, *et al.* Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *BMJ* 1986; **293:** 1027.
4. Marshall LM, *et al.* A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril* 1998; **70:** 432–9.
5. Chiaffarino F, *et al.* Use of oral contraceptives and uterine fibroids: results from a case-control study. *Br J Obstet Gynaecol* 1999; **106:** 857–60.
6. Parazzini F, *et al.* Oral contraceptive use and risk of uterine fibroids. *Obstet Gynecol* 1992; **79:** 430–3.
7. Wise LA, *et al.* Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. *Am J Epidemiol* 2004; **159:** 113–23.

Pelvic inflammatory disease. It has been suggested that oral contraceptives protect against pelvic inflammatory disease. However, although oral contraceptives are thought to reduce the risk of developing acute pelvic inflammatory disease, higher rates of infection of the lower genital tract by *Chlamydia trachomatis*,[1] and, more tentatively, *Neisseria gonorrhoeae*,[2] have been reported. Other studies[3,4] have suggested that oral contraceptive use is associated with reduced symptom severity, but absence of symptoms is not the same as absence of disease: oral contraceptives might reduce the inflammatory reaction to infection, resulting in unrecognised disease and subsequent complications such as tubal infertility and ectopic pregnancy.[5] There is evidence that users of older oral contraceptives containing more than 50 micrograms of oestrogen may have been at increased risk of tubal infertility, particularly if first used before 20 years of age.[6] No increased risk, or an active decrease in risk (depending on age at first use) was reported for formulations containing 50 micrograms or less of oestrogen, which are now favoured.

The possible effects of depot medroxyprogesterone acetate have also been examined and one study[7] suggested that it was associated with an increase in cervical chlamydial and gonococcal infections. However, confounding factors in this study such as sexual practices, a history of infection, and the background pool of infectivity in sexual partners, have been highlighted[8,9] and cast doubt on a true causal relationship between medroxyprogesterone acetate and risk of infection.

1. Washington AE, *et al.* Oral contraceptives, Chlamydia trachomatis infection, and pelvic inflammatory disease: a word of caution about protection. *JAMA* 1985; **253:** 2246–50.
2. Louv WC, *et al.* Oral contraceptive use and the risk of chlamydial and gonococcal infections. *Am J Obstet Gynecol* 1989; **160:** 396–402.
3. Wølner-Hanssen P, *et al.* Decreased risk of symptomatic chlamydial pelvic inflammatory disease associated with oral contraceptive use. *JAMA* 1990; **263:** 54–9.
4. Ness RB, *et al.* Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) study. *Am J Obstet Gynecol* 2001; **185:** 121–7.
5. Henry-Suchet J. Hormonal contraception and pelvic inflammatory disease. *Eur J Contracept Reprod Health Care* 1997; **2:** 263–7.
6. Cramer DW, *et al.* The relationship of tubal infertility to barrier method and oral contraceptive use. *JAMA* 1987; **257:** 2446–50.
7. Morrison CS, *et al.* Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. *Sex Transm Dis* 2004; **31:** 561–7.
8. Dayan L, Donovan B. Chlamydia, gonorrhoea, and injectable progesterone. *Lancet* 2004; **364:** 1387–8.
9. Warner P. Concerns regarding design, analysis, and interpretation of the Morrison study on hormonal contraceptive use and acquisition of cervical infections. *Sex Transm Dis* 2005; **32:** 644.

Precautions

Before hormonal contraceptives are given, the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use. The contraceptive effectiveness of combined and progestogen-only preparations may be reduced during episodes of vomiting or diarrhoea and extra contraceptive measures may be necessary during and for 7 days after recovery. For precautions to be taken if a 'pill' is missed, see Uses and Administration, below.

Combined oral contraceptives are *contra-indicated* in women with markedly impaired liver function or cholestasis, the Dubin-Johnson or Rotor syndromes, hepatic adenoma, oestrogen-dependent neoplasms such as breast or endometrial cancer, cardiovascular disease (see also below) including previous or current thromboembolic disorders or high risk of them, and arterial disease or multiple risk factors for it, disorders of lipid metabolism, undiagnosed vaginal bleeding, possible pregnancy, or a history during pregnancy of pruritus or cholestatic jaundice, chorea, herpes gestationis, pemphigoid gestationis, or deteriorating otosclerosis. They are also contra-indicated in severe or focal migraine (or where there are other risk factors for cardiovascular disease) and should be used with caution in other forms of migraine (for further details, see below). They should be *given with caution* to women with a history of clinical depression, gallbladder disease, sickle-cell disease, or conditions influenced by fluid retention. Oral contraceptive absorption, and hence efficacy, may be reduced in women with inflammatory bowel disease when there is small bowel involvement or malabsorption. They should also be used with caution in those with varicose veins (and should be avoided where the restrictions outlined under Venous Thromboembolism apply, see Cardiovascular Disease, below). Where not actually contra-indicated, they should also be used with caution in those with a risk factor for cardiovascular disease such as diabetes mellitus, smoking, obesity, hypertension, or a family history of cardiovascular disorders (see also below). Current opinion is that low-dose combined oral contraceptives may be used in women over the age of 35 years provided they do not smoke and have no other risk factors for cardiovascular disease, but that they should be avoided over the age of 50 years. Use by those undergoing surgery or prolonged bed rest may increase the risk of thromboembolic episodes and it is generally recommended that combined oral contraceptives should be stopped 4 weeks before major elective surgery (but see also below). Combined oral contraceptives should not be used after recent evacuation of a hydatidiform mole until urine and plasma gonadotrophin concentrations have returned to normal. Contact lenses may irritate. The use of combined oral contraceptives may influence the results of certain laboratory tests including liver, thyroid, adrenal, and renal-function tests, plasma concentrations of binding proteins and lipid/lipoprotein fractions, and fibrinolysis and coagulation parameters.

Combined oral contraceptives should be *stopped immediately*, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 100 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during oral contraception or pregnancy.

Progestogen-only contraceptives, whether oral or injectable, may be used when oestrogen-containing preparations are contra-indicated but certain contra-indications and precautions must still be observed. They are contra-indicated in women with undiagnosed vaginal bleeding, possible pregnancy, severe arterial disease, hormone-dependent neoplasms, and severe liver disease such as hepatic adenoma.

Like combined oral contraceptives they should not be used after recent evacuation of a hydatidiform mole. Progestogen-only contraceptives should be used with caution in women with heart disease, malabsorption syndromes, liver dysfunction including recurrent cholestatic jaundice, or a history of jaundice in pregnancy. Oral progestogen-only contraceptives should also be used with caution in past ectopic pregnancy (see above) or functional ovarian cysts. Despite unsatisfactory evidence of hazard, other suggested cautions for progestogen-only contraceptives include diabetes mellitus, hypertension, migraine, and thromboembolic disorders.

Breast feeding. Progestogen-only contraceptives are the hormonal contraceptives of choice for breast-feeding women because they do not affect lactation,[1] but recommendations vary about when they can or should be started, and may not match licensed product information. Some guidelines[2] recommend that all progestogen-only methods can be started 6 weeks after birth. Others[3] suggest that oral preparations can be started any time in breast-feeding women, although they are not needed before 3 weeks postpartum; the *BNF* also warns that there is an increased risk of breakthrough bleeding if progestogen-only oral contraceptives are started before 3 weeks postpartum. Progestogen-only parenteral contraceptives, such as medroxyprogesterone acetate, are usually not given until 6 weeks postpartum;[1-3] troublesome bleeding can occur before this time.[3] The etonogestrel implant may be used 3 weeks postpartum and the levonorgestrel IUD may be inserted 4 weeks postpartum.[3]

Combined oral contraceptives can reduce the volume of breast milk and are therefore avoided in breast-feeding women for the first 6 weeks after birth.[1,3] In general, they are not recommended for 6 months or until weaning,[2,3] but some suggest[3] that they may be considered between 6 weeks and 6 months postpartum if breast feeding is established and other contraceptive methods are unacceptable.

Very small amounts of oestrogens and progestogens from hormonal contraceptives are distributed into breast milk, but there is no indication that this adversely affects development of the breast-fed infant.[3,4] The American Academy of Pediatrics[5] has also reviewed the use of hormonal contraceptives during lactation, commenting that early information was based on the use of high-dose contraceptives. It was noted that there might be a decrease in milk production, but that there was insufficient information to confirm that there was any alteration in the composition of breast milk, and that although there had been rare cases of gynaecomastia in breast-fed infants of mothers who received high-dose contraceptives, there was no consistent evidence of long-term adverse effects on the infant. A later study[6] of 48 children whose mothers had received high-dose combined oral contraceptives during breast feeding found no effect on these children compared with controls, up to 8 years of age. The Academy therefore considers[7] that combined oral contraceptives are usually compatible with breast feeding.

Breast feeding itself suppresses ovulation and can be used, if started immediately postpartum, as the lactational amenorrhoea method of contraception; for further details, see Contraception, p.2070.

1. Queenan JT. Contraception and breastfeeding. *Clin Obstet Gynecol* 2004; **47:** 734–9.
2. Hatcher RA, *et al. The essentials of contraceptive technology: a handbook for clinical staff*. Baltimore: John Hopkins Bloomberg School of Public Health, Population Information Program, 2003. Also available at: http://www.infoforhealth.org/pubs/ect/ (accessed 14/01/08)
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (July 2004): contraceptive choices for breastfeeding women. *J Fam Plann Reprod Health Care* 2004; **30:** 181–9. Also available at: http://www.ffprhc.org.uk/admin/uploads/breastfeeding.pdf (accessed 14/01/08)
4. Fraser IS. A review of the use of progestogen-only minipills for contraception during lactation. *Reprod Fertil Dev* 1991; **3:** 245–54.
5. American Academy of Pediatrics Committee on Drugs. Breastfeeding and contraception. *Pediatrics* 1981; **68:** 138–40. Also available at: http://pediatrics.aappublications.org/cgi/reprint/68/1/138.pdf (accessed 14/01/08)
6. Nilsson S, *et al.* Long-term follow-up of children breast-fed by mothers using oral contraceptives. *Contraception* 1986; **34:** 443–57.
7. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 14/01/08)

Cardiovascular disease. Combined oral contraceptives are associated with a number of arterial and venous risks. Progestogen-only contraceptives are associated with fewer risks, although they still need to be avoided when arterial disease is severe.

Arterial disease. In the UK the *BNF* has recommended that combined oral contraceptives may be used with **caution** if any **one** of the following factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of arterial disease* in first-degree relative aged under 45 years (avoid if there is also an atherogenic lipid profile)
- *diabetes mellitus* (avoid if diabetic complications are present)
- *hypertension* (avoid if blood pressure is above 160/100 mmHg)
- *smoking* (avoid if 40 or more cigarettes are smoked daily)
- *age over 35 years* (avoid if over 50 years)
- *obesity*—body-mass index above 30 kg/m^2 (avoid if body-mass index exceeds 39 kg/m^2)
- *migraine,* see under Migraine, below.

Venous thromboembolism. Combined oral contraceptives increase the risk of venous thromboembolism and should not be used in women with a personal history of venous or arterial thrombosis. In addition they should be used with **caution** if any **one** of the following risk factors are present, but should be **avoided** if **two or more** factors are present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid if there is a known prothrombotic coagulation abnormality such as antiphospholipid antibodies, which may occur in patients with SLE, or factor V Leiden)
- *long-term immobilisation* such as wheelchair use (avoid if confined to bed or with a leg in plaster)
- *varicose veins* (avoid during sclerosing treatment)
- *obesity*—body-mass index above 30 kg/m^2 (avoid if body-mass index greater than 39 kg/m^2).

The *BNF* also advises that women taking combined oral contraceptives may be at an increased risk of deep-vein thrombosis during *travel* involving prolonged periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing graduated compression hosiery.

In the light of evidence indicating an increased risk of venous thromboembolism with combined oral contraceptives containing *desogestrel* or *gestodene* (see Venous Thromboembolism, under Effects on the Cardiovascular System, above), the UK CSM advised additional precautions for these products. As well as the usual precautions, it was initially advised they should not be used by obese women (body-mass index greater than 30 kg/m^2), those with varicose veins, or those with a history of thrombosis of any cause. Moreover, it was also recommended that they should be used only by women who were intolerant of other combined oral contraceptives and who were prepared to accept an increased risk of venous thromboembolism. Subsequently the CSM[1] modified its advice as follows: they recommended that these products should be avoided in women with known risk factors for venous thromboembolism. However, in women without contra-indications, the type of combined contraceptive was considered a matter of clinical judgement and personal choice, as long as the woman was fully informed of the small excess risk associated with desogestrel- and gestodene-containing products.

1. CSM/MCA. Combined oral contraceptives containing desogestrel or gestodene and the risk of venous thromboembolism. *Current Problems* 1999; **25:** 12. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 14/01/08)

Lupus erythematosus. SLE is an auto-immune disease that is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that oral contraceptive use may be associated with a slightly increased risk in the onset of SLE.[1-3] There are also reports and studies of the effect of contraceptives on disease exacerbation, although there has been an apparent reduction in reports which has coincided with the lowering of oestrogen content in contraceptive preparations.[2] More recently, controlled studies[4,5] have found that disease activity and flares over 12 months in women with stable SLE were similar whether they were given a combined oral contraceptive (containing ethinylestradiol 30 or 35 micrograms), a progestogen-only oral preparation, placebo, or copper IUD. However, patients with major disease, such as lupus nephritis, could be at greater risk of exacerbation. It is also generally advised that combined oral contraceptives should be avoided in women with antiphospholipid antibodies (which includes about a third of all patients with SLE) because they are at increased risk of venous thromboembolism.[1,2]

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Sánchez-Guerrero J, *et al.* A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2539–49.
5. Petri M, *et al.* Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2550–8.

Migraine. Both migraine and the use of combined oral contraceptives have been identified as risk factors for ischaemic stroke. A systematic review[1] concluded that in women with a history of migraine, users of combined oral contraceptives were 2 to 4 times more likely to have an ischaemic stroke than non-users. It was unclear, however, whether this increase in relative risk was due to independent effects of contraceptives and migraine, or whether contraceptive use had a greater effect in women with a history of migraine than in those without.

In the UK the *BNF* has recommended that combined oral contraceptives be **contra-indicated** in:

- migraine with typical focal aura
- severe migraine regularly lasting longer than 72 hours despite treatment
- migraine treated with an ergot derivative

It also recommends **caution** in migraine without focal aura and migraine controlled with a serotonin (5-HT$_1$) agonist. A woman receiving a combined oral contraceptive should report any increase in headache frequency or the onset of focal symptoms. If focal neurological symptoms not typical of aura persist for longer than one hour the combined oral contraceptive should be discontinued and the woman referred urgently to a neurologist.

Other risk factors for arterial disease should also be considered in women with a history of migraine (see Cardiovascular Disease, above).

1. Curtis KM, *et al.* Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006; **73:** 189–94.

Obesity. It has been suggested that higher body-weight or BMI might be associated with a greater risk of oral contraceptive failure. A number of cohort and case-control studies have evaluated this association, with mixed results that may have been confounded by recall bias, inaccuracy of reported body-weight, non-compliance, and change in oestrogen dose over time. Some studies have suggested that there is an increased risk of contraceptive failure,[1,2] while others have found no association.[3] In addition, some have found a weak association that was no longer statistically significant when results were adjusted for confounders such as education, income, and ethnicity.[4,5] It is therefore unclear whether an association exists, but obesity is a risk factor for cardiovascular disease and combined oral contraceptives should be used with caution, or avoided, in these women (see Cardiovascular Disease, above).

1. Holt VL, *et al.* Body weight and risk of oral contraceptive failure. *Obstet Gynecol* 2002; **99:** 820–7.
2. Holt VL, *et al.* Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol* 2005; **105:** 46–52.
3. Vessey M, Painter R. Oral contraceptive failures and body weight: findings in a large cohort study. *J Fam Plann Reprod Health Care* 2001; **27:** 90–1.
4. Brunner LR, Hogue CJ. The role of body weight in oral contraceptive failure: results from the 1995 national survey of family growth. *Ann Epidemiol* 2005; **15:** 492–9.
5. Brunner Huber LR, *et al.* Body mass index and risk for oral contraceptive failure: a case-cohort study in South Carolina. *Ann Epidemiol* 2006; **16:** 637–43.

Porphyria. Oral contraceptives have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients. The progestogen content is considered more hazardous than the oestrogen content. A progestogen-only contraceptive may be used with extreme caution if non-hormonal contraception is inappropriate and potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

Pregnancy. In contrast to the numerous cases of congenital malformations reported after the use of high doses of sex hormones for hormonal pregnancy tests, there have been only a few suggestions that continued use of oral contraceptives during early pregnancy may result in congenital limb reduction deformities,[1-3] and one case of neonatal choreoathetosis after prenatal exposure to oral contraceptives.[4]

Many studies, conversely, have shown no evidence that the use of oral contraceptives is associated with congenital malformations or teratogenic effects, whether past use (stopped before conception), use after the last menstrual period, or known use in early pregnancy. A meta-analysis[5] confirmed this; the relative risk for all malformations with use of oral contraceptives was estimated to be 0.99 (95% confidence intervals 0.83 to 1.19). The use of oral contraceptives in early pregnancy also appears unlikely to increase the risk of hypospadia in male fetuses[6,7] (see also under Precautions of Estradiol, p.2098).

Depot intramuscular medroxyprogesterone acetate is a highly effective contraceptive, but failures do occur rarely. A review[8] of such failures had limited data on birth outcome in 100 women who continued the pregnancy, but no abnormalities or fetal anomalies were reported.

In 25 pregnancies that were continued after the failure of levonorgestrel-based emergency contraception,[9] there was 1 case of gastro-oesophageal reflux requiring medical treatment and 1 case of nasolachrymal duct obstruction that was surgically drained, but compared with a control group and expected baseline risk there was no increased risk of congenital or genital abnormalities.

For a discussion of the ectopic pregnancy risk in users of hormonal contraceptives, see above.

1. Janerich DT, *et al.* Oral contraceptives and congenital limb reduction defects. *N Engl J Med* 1974; **291:** 697–700.
2. McCredie J, *et al.* Congenital limb defects and the pill. *Lancet* 1983; **ii:** 623.
3. Kricker A, *et al.* Congenital limb reduction deformities and use of oral contraceptives. *Am J Obstet Gynecol* 1986; **155:** 1072–8.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.
5. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* 1990; **76:** 552–7.
6. Raman-Wilms L, *et al.* Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. *Obstet Gynecol* 1995; **85:** 141–9.
7. Wogelius P, *et al.* Maternal use of oral contraceptives and risk of hypospadias—a population-based case-control study. *Eur J Epidemiol* 2006; **21:** 777–81.
8. Borgatta L, *et al.* Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002; **66:** 169–72.
9. De Santis M, *et al.* Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. *Fertil Steril* 2005; **84:** 296–9.

Sickle-cell disease. *Sickle-cell disease* and oral contraceptive use are both associated with an increased risk of thrombosis but it is by no means certain that the two risks are additive. Study of a small number of women with sickle-cell disease found that combined and progestogen-only contraceptives had no effect on red cell deformability.[1] Licensed product information for some preparations has specifically warned against the use of combined oral contraceptives in sickle-cell disease. However, there is a lack of strong clinical evidence to support such a contra-indication,[2,3] and there is some suggestion that progestogen-only contraception may be associated with improvements in clinical symptoms and sickle-cell crises.[4] WHO considers[5] that in women with sickle-cell disease the benefits generally outweigh the risks for low-dose combined oral contraceptives (35 micrograms or less of ethinylestradiol) and other forms of combined hormonal contraceptives (injectable, transdermal patch, and vaginal ring), and that there is no restriction for the use of progestogen-only contraceptives (oral, depot injection, implant, and intra-uterine device).

For *sickle-cell trait* there is no increased risk of thrombosis and no contra-indication to the use of a combined or progestogen-only preparation. Many women with sickle-cell trait have, unnecessarily, been denied the use of oral contraceptives in the mistaken belief that advice for sickle-cell disease applies to the trait.[6]

1. Yoong WC, *et al.* Red cell deformability in oral contraceptive pill users with sickle cell anaemia. *Br J Haematol* 1999; **104:** 868–70.
2. Freie HMP. Sickle cell diseases and hormonal contraception. *Acta Obstet Gynecol Scand* 1983; **62:** 211–17.
3. Howard RJ, *et al.* Contraceptives, counselling, and pregnancy in women with sickle cell disease. *BMJ* 1993; **306:** 1735–7.
4. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; **73:** 195–204.
5. WHO. *Medical eligibility criteria for contraceptive use.* Third ed. Geneva: WHO, 2004. Available at: http://www.who.int/reproductive-health/publications/mec/index.htm (accessed 14/01/08)
6. Evans DIK. Should patients who say that they have "sickle cells" be prescribed the contraceptive pill? *BMJ* 1984; **289:** 425.

Surgery. Case reports and epidemiological studies showing an increased risk of idiopathic deep-vein thrombosis and pulmonary embolism in young women taking **combined oral contraceptives** (see above) led to the widespread belief that oral contraceptives may predispose to deep-vein thrombosis postoperatively. In consequence, the advice commonly given in the UK has been that, if possible, combined oral contraceptives should be stopped 4 weeks before major elective surgery and all surgery of the legs, and that prophylactic heparin should be considered where this was not possible.[1] They can normally be started again at the first menses occurring at least 2 weeks after full mobilisation. However, estimates of the size of the risk are variable;[2-5] one report[2] found that the incidence of deep-vein thrombosis postoperatively in young women taking combined oral contraceptives was about twice that of women not taking contraceptives but the difference was not statistically significant. Some have considered[6] that the risk to young women of becoming pregnant after stopping oral contraceptives, or of developing adverse effects from heparin prophylaxis, may be greater than the risk of developing postoperative deep-vein thrombosis. This is in line with the views of the Thromboembolic Risk Factors (THRIFT) Consensus Group.[7] They suggested that unless there were other risk factors there was insufficient evidence to support a policy of routinely stopping combined oral contraceptives before major surgery. Additionally, there was insufficient evidence to support routine specific thromboembolic prophylaxis in women without additional risk factors. A review[8] has subsequently recommended that women for whom major elective surgery was planned should continue taking the combined oral contraceptive but should receive thromboprophylaxis in the perioperative period. It has also been pointed out[9,10] that for patients awaiting surgery who require contraception, a progestogen-only oral contraceptive or an injection of medroxyprogesterone acetate may be suitable since neither preparation increases the risk of thrombosis.

1. Guillebaud J. Surgery and the pill. *BMJ* 1985; **291:** 498–9.
2. Vessey M, *et al.* Oral contraceptives and venous thromboembolism: findings in a large prospective study. *BMJ* 1986; **292:** 526.
3. Tso SC, *et al.* Deep vein thrombosis and changes in coagulation and fibrinolysis after gynaecological operations in Chinese: the effect of oral contraceptives and malignant disease. *Br J Haematol* 1980; **46:** 603–12.
4. Gallus AS, *et al.* Oral contraceptives and surgery: reduced antithrombin and antifactor XA levels without postoperative venous thrombosis in low-risk patients. *Thromb Res* 1984; **35:** 513–26.
5. Sagar S, *et al.* Oral contraceptives, antithrombin III activity, and postoperative deep-vein thrombosis. *Lancet* 1976; **i:** 509–11.
6. Sue-Ling H, Hughes LE. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 447–8.
7. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; **305:** 567–74.
8. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.
9. Guillebaud J. Should the pill be stopped preoperatively? *BMJ* 1988; **296:** 786–7.
10. Guillebaud J, Robinson GE. Stopping the pill. *BMJ* 1991; **302:** 789.

Travel. For a warning that women taking oral contraceptives may be at increased risk of deep-vein thrombosis from travel involving prolonged immobility see Cardiovascular Disease, above.

Interactions

Enzyme-inducing drugs can cause combined oral contraceptives to fail by increasing their metabolism and clearance. This effect is well established for a number of *antiepileptics*, *griseofulvin*, and *rifamycin antibacterials*, and has also been suggested for some *antivirals* and for *modafinil*. Although less well documented, these interactions would also be expected to apply to progestogen-only contraceptives. The *BNF* has provided recommendations for contraception in women taking enzyme-inducing drugs.

- When a short course of an enzyme-inducing drug is taken, the dose of a combined oral contraceptive should be adjusted to provide ethinylestradiol 50 micrograms or more daily. Additional non-hormonal contraceptive methods should be used during the course and for 4 weeks after stopping it.
- For women requiring long-term treatment with an enzyme-inducing drug, an alternative method of contraception that is unaffected by the enzyme-inducing drug should be considered. However, if a combined oral contraceptive is used, a regimen that provides ethinylestradiol 50 micrograms or more daily should be used. 'Tricycling' has also been recommended where 3 or 4 cycles of monophasic tablets are taken without any breaks, followed by a short tablet-free interval of 4 days; the efficacy of this regimen is uncertain however. Enzyme activity may not return to normal for several weeks after stopping long-term treatment, and appropriate contraceptive measures should be continued for 4 to 8 weeks. These measures are not sufficient for long-term use of rifamycins, and an alternative method such as an IUD is always recommended.
- For women using a contraceptive transdermal patch, additional non-hormonal contraceptive methods should be used during a short-term course of an enzyme-inducing drug and for 4 weeks after stopping. If concomitant use runs beyond the 3 weeks of patch treatment, a new treatment cycle should be started immediately without a patch-free interval. For women taking an enzyme-inducing drug long-term, another form of contraception should be considered.
- Progestogen-only oral contraceptives and injectable preparations containing norethisterone or etonogestrel (but not medroxyprogesterone) may be affected by enzyme-inducing drugs, and an additional or alternative method of contraception is recommended during treatment and for at least 4 weeks after stopping. An alternative method of contraception should be considered if long-term treatment with an enzyme-inducing drug is required. Intra-uterine progestogen-only contraceptives are unlikely to be affected by enzyme-inducing drugs.
- An increased dose of postcoital (emergency) contraception, as a single oral dose of levonorgestrel 3 mg, has been suggested for women receiving enzyme-inducing drugs. Alternatively, a copper IUD may be used.

Rarely, *broad-spectrum antibacterials* have been associated with combined oral contraceptive failure, possibly by reducing enterohepatic recycling of the oestrogen component. As the doses of oestrogen and progestogen in oral contraceptives have decreased, reports of menstrual irregularities and unintended pregnancies attributed to these drug interactions have increased.

Further details of drugs affecting hormonal contraceptives are given below under specific headings.

Oral contraceptives may also *affect other drugs*. Compounds undergoing oxidative metabolism can have their plasma concentration raised by oral contraceptives through an inhibitory action. Conversely, oral contraceptives appear to induce glucuronidation of some drugs thus reducing their plasma concentration. Oral contraceptives can also antagonise the actions of a number of drugs. Drugs affected include:

- some analgesics (increased clearance of paracetamol and morphine)
- anticoagulants (increased and decreased effects reported; see p.1431)
- some antidepressants (reduced effectiveness, but also increased toxicity; see p.380)
- antidiabetics (antagonism of effect)
- the antiepileptic lamotrigine (decreased plasma concentrations; see p.486)
- antihypertensives (antagonism of effect)
- benzodiazepines (increased or decreased clearance; see p.991)
- ciclosporin (increased toxicity; see p.1828)
- clofibrate (increased clearance and antagonism of effect)
- corticosteroids (enhanced effect; see p.1495)
- levothyroxine (reduced free fraction due to increased binding globulin concentration; see p.2173)
- lidocaine (increased free fraction due to altered protein binding; see Protein Binding, under Pharmacokinetics, p.1864)
- selegiline (decreased clearance; see p.817)
- xanthines (decreased clearance; see p.1145)

◊ Reviews.

1. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; **18:** 472–84.
2. Shenfield GM. Oral contraceptives: are drug interactions of clinical significance? *Drug Safety* 1993; **9:** 21–37.

3. Quereux C, Bory JP. Interaction médicamenteuse et contraception orale. *Contracept Fertil Sex* 1998; **26:** 129–31.
4. Schwartz JB. Oral contraceptive therapy in women: drug interactions and unwanted outcomes. *J Gend Specif Med* 1999; **2:** 26–9.
5. Elliman A. Interactions with hormonal contraception. *Br J Fam Plann* 2000; **26:** 109–11. Correction. *ibid.*; 151.
6. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (April 2005): drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31:** 139–51. Also available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 14/01/08)

Antibacterials. An interaction between the *rifamycins (rifampicin* and *rifabutin)* and oral contraceptives is well established and alternative contraceptive measures are necessary (see Rifamycins, below).

A variety of *broad-spectrum antibacterials* have also been reported to decrease oral contraceptive efficacy. Some studies have pointed to interference with intestinal flora involved in enterohepatic circulation of oestrogens as being a likely mechanism for this interaction. Although up until 1985 there had been 32 reports[1] of unintended pregnancies in women receiving *penicillins* (25 of them with *ampicillin*) the ability of antibacterials to inhibit oral contraceptive efficacy remains unproven. The data are consistent, however, with the supposition that efficacy is occasionally impaired.[2] Several cases of unintended pregnancies have been reported after the use of *tetracyclines*. It is recommended that additional contraceptive precautions should be used while taking, and for 7 days after stopping, a short course of any broad-spectrum antibacterial. If these 7 days run into the last 7 days of the cycle, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next cycle of tablets started immediately. If the course of antibacterial exceeds 3 weeks the intestinal flora develop resistance and additional precautions become unnecessary.

With regard to other antibacterials, in theory any one with significant effects on intestinal flora could affect contraceptive efficacy. Isolated cases of pregnancy have been reported following the use of *cephalosporins, chloramphenicol, dapsone, isoniazid, nitrofurantoin, sulfonamides,* and *co-trimoxazole* but it is impossible to determine which, if any, of these interactions is real.

1. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
2. Dickinson BD, *et al.* Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; **98:** 853–60.

RIFAMYCINS. *Rifampicin* regularly results in menstrual irregularities and occasionally in unintended pregnancies in women receiving oral contraceptives. It is a potent enzyme inducer and considerably enhances the metabolism of oral contraceptives. For short courses of rifampicin, additional contraceptive precautions should be taken during the course and for 4 weeks after stopping. A non-hormonal method of contraception such as an IUD is recommended during, and for 4 to 8 weeks after stopping, long-term rifampicin therapy.

Similar precautions are recommended during *rifabutin* therapy.

Contraceptive failure, resulting in an ectopic pregnancy, has also been reported in a woman who started rifampicin therapy 3 months after placement of an etonogestrel implant.[1]

1. Patni S, *et al.* Ectopic pregnancy with Implanon . *J Fam Plann Reprod Health Care* 2006; **32:** 115.

TROLEANDOMYCIN. Severe pruritus and jaundice may occur if oral contraceptives and troleandomycin are given together.[1] It has been suggested that their hepatic effects may be additive or synergistic, and that concurrent use should be avoided.

1. Miguet J-P, *et al.* Jaundice from troleandomycin and oral contraceptives. *Ann Intern Med* 1980; **92:** 434.

Antidepressants. *St John's wort* may decrease blood concentrations of oral contraceptives by enzyme induction.[1-3] There have been reports of intermenstrual bleeding and altered menstrual bleeding in women on long-term oral contraceptives who started taking St John's wort.[4] Several pregnancies have also been reported.[5,6]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

1. Hall SD, *et al.* The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003; **74:** 525–35.
2. Pfrunder A, *et al.* Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* 2003; **56:** 683–90.
3. Murphy PA, *et al.* Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005; **71:** 402–8.
4. Yue Q-Y, *et al.* Safety of St. John's wort (Hypericum perforatum). *Lancet* 2000; **355:** 576–7.
5. Läkemedelsverket (Medical Products Agency—Sweden). Minskad effekt av p-piller vid samtidig användning av johannesört har lett till oönskad graviditet (issued 4th February, 2002). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage____580.aspx (accessed 14/01/08)
6. Schwarz UI, *et al.* Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *Br J Clin Pharmacol* 2003; **55:** 112–13.

Antidiabetics. *Troglitazone* is an enzyme inducer and increases the clearance of oestrogens and progestogens. A high-dose oral contraceptive, or an alternative method of contraception should be considered in women receiving troglitazone and requiring contraception.[1] However, *rosiglitazone* is not an enzyme inducer and is not expected to affect the efficacy of oral contraceptives.[2]

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

1. Loi C-M, *et al.* Effect of troglitazone on the pharmacokinetics of an oral contraceptive agent. *J Clin Pharmacol* 1999; **39:** 410–17.
2. Inglis AML, *et al.* Lack of effect of rosiglitazone on the pharmacokinetics of oral contraceptives in healthy female volunteers. *J Clin Pharmacol* 2001; **41:** 683–90.

Antiepileptics. Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during antiepileptic therapy.[1,2] *Phenytoin*, barbiturates such as *phenobarbital* and *primidone*, and *carbamazepine* have been most frequently implicated, and *oxcarbazepine*, *felbamate*, and *topiramate* may interact similarly.[3] These drugs increase the clearance of both oestrogens and progestogens by enzyme induction, so diminishing their effects. Contraceptive methods that are not affected by enzyme induction include a copper or levonorgestrel IUD, or intramuscular depot medroxyprogesterone acetate.[4,5] If these are unsuitable, a combined oral contraceptive with an increased oestrogen content equivalent to ethinylestradiol 50 micrograms or more, and a corresponding increase in progestogen, is generally recommended. In addition, the use of a monophasic preparation given for 3 cycles without a break followed by a tablet-free interval of 4 days (tricycling) has also been suggested.[4] The importance of the progestogen in suppressing ovulation has also been discussed, with the suggestion that ethinylestradiol doses of less than 50 micrograms could be used provided the dose of progestogen is at least 1 mg of norethisterone, 150 micrograms of levonorgestrel, or 300 micrograms of norgestrel.[5] Biphasic, triphasic, and progestogen-only oral contraceptives are not recommended.[5]

Lamotrigine may also reduce contraceptive efficacy, and is markedly affected in turn by the contraceptive (see p.486).

For the effects of oral contraceptives on *valproate*, see p.511.

The efficacy of postcoital hormonal contraception (emergency contraception) is also reduced by enzyme-inducing antiepileptic drugs,[4] and an increased dose has been suggested (see above).

Antiepileptics that are reported not to interact with hormonal contraceptives include *ethosuximide*, *gabapentin*, *levetiracetam*, *tiagabine*, *valproate*, and *vigabatrin*.[4,5]

1. Mattson RH, Cramer JA. Epilepsy, sex hormones, and antiepileptic drugs. *Epilepsia* 1985; **26** (suppl 1): S40–S51.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Wilbur K, Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. *Clin Pharmacokinet* 2000; **38:** 355–65.
4. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. *Epilepsia* 2006; **47:** 1419–22.
5. Thorneycroft I, *et al.* The impact of antiepileptic drug therapy on steroidal contraceptive efficacy. *Epilepsy Behav* 2006; **9:** 31–9.

Antifungals. Menstrual irregularities and pregnancies have been reported in women receiving oral contraceptives and *griseofulvin*,[1,2] which is known to be an inducer of hepatic enzymes and may increase the metabolism of hormonal contraceptives. Additional contraceptive measures should be considered during concomitant use and after stopping griseofulvin; for general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above. There have also been anecdotal reports[3-5] of menstrual irregularities and contraceptive failure with *fluconazole*, *itraconazole*, and *ketoconazole*, and similar advice applies to these if pregnancy is to be avoided with certainty.

1. van Dijke CPH, Weber JCP. Interaction between oral contraceptives and griseofulvin. *BMJ* 1984; **288:** 1125–6.
2. Back DJ, *et al.* Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 1988; **25:** 527–32.
3. Pillans PI, Sparrow MJ. Pregnancy associated with a combined oral contraceptive and itraconazole. *N Z Med J* 1993; **106:** 436.
4. Meyboom RHB, *et al.* Disturbance of withdrawal bleeding during concomitant use of itraconazole and oral contraceptives. *N Z Med J* 1997; **110:** 300.
5. van Puijenbroek EP, *et al.* Verstoring van de pilcyclus tijdens het gelijktijdig gebruik van itraconazol en orale anticonceptiva. *Ned Tijdschr Geneeskd* 1998; **142:** 146–9.

Antivirals. A number of antivirals are likely to accelerate the metabolism of oestrogens and progestogens; theoretically therefore, they may decrease the efficacy of hormonal contraceptives. This has been suggested for HIV-protease inhibitors such as *nelfinavir*,[1] *ritonavir*,[2] and ritonavir-boosted HIV-protease inhibitors, and for the NNRTI *nevirapine*.[3] An alternative form of contraception should be considered. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

Conversely, the area under the plasma-concentration-time curve for ethinylestradiol is reported to be increased by HIV-protease inhibitors such as *amprenavir*, *atazanavir*, and *indinavir*, and the NNRTIs *delavirdine* and *efavirenz*. Although the clinical implications are unknown, the licensed product information recommends alternative or additional contraception.

The *BNF* suggests that the use of condoms with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of infection.

1. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* 2004; **37:** 1219–20.
2. Ouellet D, *et al.* Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998; **46:** 111–16.
3. Mildvan D, *et al.* Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* 2002; **29:** 471–7.

Endothelin receptor antagonists. In a pharmacokinetic study of healthy women[1] the area under the concentration-time curve (AUC) of both ethinylestradiol and norethisterone were reduced by *bosentan*, probably by enzyme induction. The possibility of contraceptive failure should be considered, and licensed product information for bosentan suggests that an additional or alternative method of contraception should be used during bosentan therapy. For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see above.

In contrast, *sitaxentan* is an inhibitor of some cytochrome P450 isoenzymes, and it has increased exposure to ethinylestradiol and norethisterone in women taking a combined oral contraceptive. An increase in oestrogen exposure may possibly increase the risk of thromboembolism.

1. van Giersbergen PLM, *et al.* Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol Ther* 2006; **44:** 113–18.

Retinoids. One woman taking an oral progestogen-only contraceptive (levonorgestrel 30 micrograms daily) showed a significant increase in plasma-progestogen while receiving *acitretin*, which indicated ovulation had occurred.[1] However, progestogen-only contraceptives do not suppress ovulation in all cycles, and this is not thought to be their primary mechanism of contraceptive efficacy (see Types of Contraceptive, p.2058). Nevertheless, because it is imperative that women receiving retinoids do not conceive, some have concluded that oral progestogen-only contraceptives are not suitable for use with retinoids.[2]

The anti-ovulatory efficacy of combined oral contraceptives was not affected by acitretin in 8 women in the study above,[1] or by *etretinate* in a study[3] in 12 women. Other studies have reported that *isotretinoin* did not significantly change plasma concentrations or adversely affect contraceptive efficacy of ethinylestradiol and levonorgestrel in 9 women,[4] or ethinylestradiol and norethisterone in 26 women.[5] It has been concluded that, unless otherwise contra-indicated, oral combined contraceptives are the contraceptive method of choice for women undergoing retinoid treatment.[2] Licensed product information for retinoids, including isotretinoin, reminds prescribers that two effective forms of contraception such as a combined oral contraceptive with a barrier method should be used during and after retinoid treatment (see also Pregnancy, under Isotretinoin, p.1601).

Both isotretinoin and combined oral contraceptives can have adverse effects on plasma lipids;[6] it has therefore been recommended that plasma lipids should be monitored during concurrent retinoid and oral contraceptive therapy, and that an oral contraceptive containing a non-androgenic progestogen is preferred,[2] since these have less detrimental effects on lipids (p.2064).

1. Berbis P, *et al.* Acitretin (RO10-1670) and oral contraceptives: interaction study. *Arch Dermatol Res* 1988; **280:** 388–9.
2. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; **184:** 161–70.
3. Berbis P, *et al.* Study on the influence of etretinate on biologic activity of oral contraceptives. *J Am Acad Dermatol* 1987; **17:** 302–3.
4. Orme M, *et al.* Isotretinoin and contraception. *Lancet* 1984; **ii:** 752–3.
5. Hendrix CW, *et al.* The effect of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 2004; **75:** 464–75.
6. Chen Y, *et al.* Elevation of serum triglyceride and cholesterol levels from isotretinoin therapy with concomitant oral contraceptives. *Pharmacoepidemiol Drug Safety* 1995; **4:** 91–6.

Stimulants. *Modafinil* induces hepatic enzymes and may reduce the efficacy of oral contraceptives.[1] Licensed product information for modafinil suggests that alternative or additional methods of contraception are needed; US information recommends that this is also continued for 1 month after stopping modafinil, but in the UK it is recommended for 2 months.

For general recommendations on the use of hormonal contraceptives with enzyme-inducing drugs, see Interactions, above.

1. Robertson P, *et al.* Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 2002; **71:** 46–56.

Vitamins. Large supplements of *vitamin C* have been reported to increase serum ethinylestradiol concentrations in women taking oral contraceptives,[1] but a further study showed no effect on either ethinylestradiol[2] or levonorgestrel.[3]

1. Back DJ, *et al.* Interaction of ethinyloestradiol with ascorbic acid in man. *BMJ* 1981; **282:** 1516.

2. Zamah NM, *et al.* Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993; **48:** 377–91.
3. Kuhnz W, *et al.* Influence of high doses of vitamin C on the bioavailability and the serum protein binding of levonorgestrel in women using a combination oral contraceptive. *Contraception* 1995; **51:** 111–16.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p.2098 and Progesterone, p.2126, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

◊ Reference to the effects of hormonal contraceptives on binding proteins.[1]

1. Fotherby K. Interactions of contraceptive steroids with binding proteins and the clinical implications. *Ann N Y Acad Sci* 1988; **538:** 313–20.

Uses and Administration

The main use of hormonal contraceptives is for contraception, but combined oral contraceptives are also commonly used in menstrual disorders such as dysmenorrhoea (p.6), premenstrual syndrome (p.2099), and menorrhagia (p.2126), particularly where contraception is also required. Combined oral contraceptives are also used in polycystic ovary syndrome (p.2080) and Turner's syndrome (p.2081), and may be used in endometriosis (p.2091); those containing non-androgenic progestogens may be used in acne (p.2070) and hirsutism (p.2089).

Combined oral contraceptives containing both an oestrogen and a progestogen are the most effective type of oral contraceptive for general use. The synthetic ethinyl derivatives ethinylestradiol and mestranol are the oestrogens typically used in such preparations. The progestogenic component is usually a 19-nortestosterone derivative such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestrenol, norethisterone, norethisterone acetate, norgestimate, or norgestrel. Preparations may be *monophasic* (containing a fixed dose of oestrogen and progestogen), or *biphasic* or *triphasic* (when the dose of progestogen, or both the progestogen and oestrogen, are varied through the cycle). Phased preparations are designed to mimic more closely the pattern of endogenous hormone secretion and may provide better cycle control than monophasic preparations. More rarely, *sequential* preparations are used, which contain an oestrogen alone for part of the cycle. Most combined oral contraceptives are taken for 21 days followed by an interval of 7 days when menstrual bleeding will occur. Some preparations include 21 active tablets plus 7 inert tablets to remove the need for counting days ('every day' preparations). Variations on this 28-day cycle include 22 days of active tablets followed by a 6-day interval for bleeding, and 24 days of active tablets followed by a 4-day interval. Long- or extended-cycle preparations are also available: some preparations may be taken continuously for 84 days, followed by 7 days of inert tablets or a lower dose of oestrogen alone (such as ethinylestradiol 10 micrograms). More recently, a preparation containing active tablets to be taken every day without any tablet-free interval has been introduced. The oestrogen content of most preparations is currently ethinylestradiol 20 to 40 micrograms daily; in some preparations a lower dose of 15 micrograms is used and in others up to 50 micrograms is available (even higher doses were often formerly used). A formulation containing the lowest dose of oestrogen compatible with good cycle control should be chosen, considering the following:

- *low-strength* preparations (ethinylestradiol 20 micrograms) are most appropriate for women with risk factors for cardiovascular disease (see under Precautions, above), provided a combined oral contraceptive is considered otherwise suitable
- *standard-strength* preparations (ethinylestradiol 30 or 35 micrograms or mestranol 50 micrograms if monophasic, or ethinylestradiol 30 to 40 micrograms if phased) are appropriate for most other women
- *high-strength* preparations (ethinylestradiol 50 micrograms) are generally used only in circumstances where bioavailability of the oestrogen is reduced, such as concomitant use of some enzyme-inducing drugs (see Interactions, above)

When first **starting** combined oral contraceptives, if the first tablet is taken on the first day of the menstrual cycle (the first day of bleeding) additional contraceptive precautions are unnecessary. If the first tablet is taken on the fourth day of the cycle or later, additional contraceptive precautions should be undertaken for 7 days (or 14 days for 'every day' preparations in case the inert tablets are inadvertently taken first). If amenorrhoea is present and pregnancy has been excluded, combined oral contraceptives may be started on any day, but additional precautions should be used for the first 7 days. In the case of abortion or miscarriage combined oral contraceptives should be started on the same day. In women not breast feeding, they may be started 3 weeks postpartum, but additional contraceptive precautions should be taken for the first 7 days if the combined oral contraceptive is started later than 3 weeks postpartum; progestogen-only contraceptives are preferred in breast-feeding women (see under Precautions, above).

When **changing** to a combined preparation containing a different progestogen, the new preparation should be started on the day after the last active tablet of the old preparation. If a tablet-free interval is taken then extra contraceptive precautions are necessary for the first 7 days of the new preparation. In the case of 'every day' preparations, to allow for the fact that the inert tablets may inadvertently be taken first, extra contraceptive precautions are necessary during the first 14 days. Meticulous regularity of dosage is essential and contraceptive protection may be lost if a dose is not taken at the proper time or is missed, especially if the missed dose is at the beginning or end of a cycle.

If a tablet is **missed** the risk of pregnancy is greatest when this happens at the beginning or at the end of a cycle, which lengthens the tablet-free interval. Over time, advice for dealing with missed tablets has changed and varies between countries and preparations. In 2004, WHO issued recommendations based on how many combined oral contraceptive tablets have been missed and when.

- If 1 or 2 tablets containing 30 or 35 micrograms of ethinylestradiol (or 1 tablet of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; no additional contraceptive protection or emergency contraception is needed. This advice also applies if a new course of tablets has been started 1 or 2 days late for 30- or 35-microgram tablets, or 1 day late for 20-microgram tablets.
- If 3 or more tablets containing 30 or 35 micrograms of ethinylestradiol (or 2 or more tablets of 20 micrograms) have been missed at any time, the most recent missed tablet should be taken as soon as possible, and the rest of the course should be taken as normal; the woman should also use condoms or abstain from intercourse until she has taken active tablets for 7 days in a row. This advice also applies if a new course of tablets has been started 3 or more days late for 30- or 35-microgram tablets, or 2 or more days late for 20-microgram tablets. In addition, emergency contraception should be considered if the tablets were missed in the first week of the course and she had unprotected intercourse during the tablet-free interval or in the first week. If the tablets were missed in the third week of the course, then the tablet-free interval (or the 7 inert tablets) should be omitted and the next course of tablets started immediately after the last.

If the woman has missed more than 1 tablet, she can take the first missed tablet and then either continue taking the rest of the missed tablets or discard them to stay on schedule. Depending on when she realises that she has missed a tablet, she may take 2 tablets on the same day or even at the same time.

For extended-cycle preparations, licensed product information gives similar advice regarding missed tablets (or starting a course late), in that the course should be resumed as soon as possible. If 1 tablet has been missed, additional contraception is not needed, but if 2 or more tablets have been missed, additional contraception should be used until 7 days of active tablets have been taken.

Similarly, extra contraceptive measures may be needed during, and after recovery from, vomiting or diarrhoea. WHO recommends that if the woman vomits within 2 hours after taking a tablet, she should take another tablet. If there is severe vomiting or diarrhoea for more than 24 hours she should continue taking the course if she can, and if it continues for 2 or more days she should follow the advice for missed tablets.

Progestogen-only oral contraceptives are suitable for women when an oestrogen component is contra-indicated. They are taken continuously, usually **starting** on day one of the menstrual cycle, with no interval during menstrual bleeding. They are associated with a higher failure rate than the combined preparations. Regularity in taking the doses is even more important with this type of preparation; contraceptive efficacy is reduced if a dose is delayed by more than 3 hours (a delay of up to 12 hours is acceptable for desogestrel). Commonly used progestogens include the 19-nortestosterone derivatives etynodiol diacetate, levonorgestrel or norgestrel, and norethisterone.

When **changing** from a combined oral contraceptive preparation to an oral progestogen-only contraceptive, the new tablets should be started immediately with no tablet-free interval (or, in the case of 'every day' preparations, omitting the inert tablets).

If a **missed tablet** is delayed by more than 3 hours (or 12 hours for desogestrel), it should be taken as soon as possible and the next tablet taken at the correct time. Although some UK licensed product information suggests that additional contraceptive methods should be used for the next 7 or 14 days, depending on the product, WHO suggests that extra contraception is only required for the next 2 days. Postcoital hormonal contraception (emergency contraception) should be considered if unprotected intercourse has occurred before 2 further tablets have been taken correctly. Additional contraceptive methods may also be needed during, and after recovery from, vomiting or diarrhoea, and WHO gives the same advice as that for combined oral contraceptives described above.

Progestogens are also used alone as **parenteral contraceptives** and provide a very high level of contraceptive efficacy. They are usually given within the first 5 days of the menstrual cycle. Injectable contraceptives are usually used to provide short-term protection for several months or are used in women unable to use other methods. Medroxyprogesterone acetate is given by intramuscular or subcutaneous injection as a long-acting depot preparation to provide contraception for at least 12 weeks. Norethisterone enantate is used similarly by intramuscular injection to provide protection for up to 8 weeks. Levonorgestrel is used in the form of a subcutaneous implant providing contraception for up to 5 years. A contraceptive implant containing etonogestrel, effective for 3 years, is also available. A combined parenteral contraceptive containing the oestrogen estradiol cipionate with medroxyprogesterone acetate, and given monthly by intramuscular injection, has been developed.

Hormonal **intra-uterine contraceptive devices** are also available. One such device releases progesterone to provide contraception for 1 year; another releases levonorgestrel for 5 years. These are usually inserted within 7 days of the onset of menstruation. A contraceptive **vaginal ring**, which releases ethinylestradiol and etonogestrel, is retained in the vagina for 3 weeks; it is then removed for a one-week interval after which a new ring is inserted.

A contraceptive **transdermal patch**, which releases ethinylestradiol and norelgestromin, has been developed. A new patch is applied each week for 3 weeks, followed by a one-week patch-free interval. If the patch becomes partly or completely detached, or there is a delay in its application, contraceptive efficacy can be reduced or lost.

- If the patch has been detached for less than 24 hours, it should be re-applied if it is still sufficiently adhesive, or replaced with a new patch; no additional contraceptive method is needed and the following patch should be applied on the usual day. If it has been detached for 24 hours or more, a new 4-week cycle should be started and a new patch applied; additional contraceptive precautions should be taken for the first 7 days.
- If application of the first patch of a new cycle is delayed after the patch-free interval, it should be applied as soon as remembered and this day used as the first day of the new cycle; additional contraceptive precautions should be used for 7 days, and if unprotected intercourse has occurred during the patch-free interval then the possibility of fertilisation should be considered.
- When the patch is changed in the middle of the cycle (week 2 and 3), if there is a delay of up to 48 hours the new patch should be applied immediately, with the next patch applied on the usual day; no additional contraceptive precaution is needed. If the delay is more than 48 hours, the new patch should be applied and a new 4-week cycle started; additional contraceptive precautions should be taken for 7 days.
- If there is a delay in removing the third patch, before the patch-free interval, it should be removed as soon as possible and the next cycle started on the usual day; no additional contraception is required.

Postcoital hormonal contraceptives (emergency contraception) should be taken within 72 hours after unprotected intercourse to be most effective (for details see Emergency Contraception, below). A single oral dose of levonorgestrel 1.5 mg may be given within 72 hours of intercourse, or it may be given as a dose of 750 micrograms within 72 hours of intercourse followed by a second dose 12 hours later. An alternative preparation available for such use consists of tablets each containing ethinylestradiol 50 micrograms and norgestrel 500 micrograms or levonorgestrel 250 micrograms. Two tablets should be taken within 72 hours and a further 2 tablets 12 hours later. UK licensed product information for levonorgestrel-only preparations suggests that if vomiting occurs within 3 hours of any dose it can be repeated. However, WHO considers that 2 hours is probably sufficient for hormone absorption and that no action is needed if vomiting occurs after this time. WHO also considers that combined hormonal preparations are more likely to cause nausea and vomiting, and that the use of an antiemetic may be considered before repeating a dose. The efficacy of postcoital hormonal contraception may be reduced in women who are being treated with enzyme-inducing drugs, and a higher dose of levonorgestrel has been suggested (see Interactions, above).

◊ Reviews and guidelines.

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5. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC guidance (issued July 2006, updated January 2007): first prescription of combined oral contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJan06.pdf (accessed 14/01/08)

Acne. Oral contraceptives have been shown to be effective[1,2] in reducing inflammatory and non-inflammatory lesions in women with acne (p.1577) who require contraception, probably by a multifactorial action on circulating androgens. Studies have used combinations of ethinylestradiol with various progestogens; a systematic review[2] considered that combinations with chlormadinone or cyproterone acetate were more effective than those with levonorgestrel, but noted that this was based on limited evidence. Combination preparations based on cyproterone acetate, that also have a contraceptive effect, have traditionally been favoured for acne management (see also p.2089).

1. Huber J, Walch K. Treating acne with oral contraceptives: use of lower doses. *Contraception* 2006; **73:** 23–9.
2. Arowojolu AO, *et al.* Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/01/08).

Contraception. Contraception is used for fertility control, and some methods have additional non-contraceptive health benefits. There are a wide variety of regular methods including periodic abstinence (natural family planning), male and female barrier methods, intra-uterine devices (IUDs), female hormonal contraceptives, and female or male sterilisation. In addition, female hormonal contraceptives and copper IUDs are available for emergency (postcoital) contraception. The methods used for contraceptive purposes can be grouped into three categories: those that prevent ovulation, those that prevent fertilisation of the ovum, and those that prevent implantation of the fertilised ovum. None of the available contraceptive methods are effective once implantation of a fertilised ovum has occurred, i.e. they are not abortifacients.

A large number of factors will influence the choice of contraceptive method. Those relating to the woman include age (and therefore likely fertility), parity, medical disorders, risk of sexually transmitted diseases, smoking status, breast feeding, and cultural and religious considerations. Those relating to the method include its failure rate, reversibility, ease of use, mechanism of action, adverse effects, and non-contraceptive benefits.

The most reliable reversible methods for contraception are those for which there can be no 'user' failure such as *progestogen injections* and *implants*, and progestogen or copper *intra-uterine devices* (IUDs). When used perfectly, these methods have reported failure rates of between 0.05 and 0.6% during the first year of use; higher rates had been reported with older IUDs. The duration of action of the various progestogen injections is up to 2 or 3 months, whereas progestogen implants and progestogen IUDs can be effective for 1 to 5 years, depending on the preparation. These long-acting progestogen preparations thicken cervical mucus, so preventing sperm penetration, and suppress the endometrium, so preventing implantation. In addition, they suppress ovulation; the degree of suppression is complete for injectable preparations, about 50% for implants, and low for the progestogen IUDs. Copper IUDs were traditionally thought to act by preventing implantation, but it is now thought that the biochemical changes which they produce in the uterus also prevent fertilisation. They are effective and have a prolonged action (up to 5 or 10 years). There is an increased risk of pelvic infection in the 20 days after insertion of an IUD, but the risk is the same as non-IUD users thereafter. An IUD must not be used in women with a current sexually transmitted infection or pelvic inflammatory disease, but it may be considered in those who are no longer at risk after an infection has been treated. For women at increased risk of infection, prophylactic antibacterial therapy may be given before IUD insertion if screening test results are not yet available. In the past, it was recommended that IUDs were not suitable for nulliparous women because of a risk of impaired fertility after removal. However, this may have been biased by other factors such as the increased risk of sexually transmitted infection associated with sexual behaviour in younger women. Nulliparity alone is therefore no longer considered a contra-indication to IUD use, and indeed some IUDs have been designed specifically for this group of women. Although IUDs are effective at preventing pregnancy, in the uncommon event of IUD failure, the risk of ectopic pregnancy is increased and can occur in 6 to 8% of these pregnancies.

Of methods subject to 'user' failure, *combined oral contraceptives* are the most effective. They have a reported failure rate during the first year of 0.3% if used perfectly, but 8% in typical practice. Their principal mechanism of action is to prevent ovulation, and they also decrease the chances of fertilisation and implantation. Combined oral contraceptives offer the non-contraceptive advantages of avoidance of dysmenorrhoea, premenstrual tension, and iron-deficiency anaemia, and in the long-term they protect against endometrial and ovarian cancer. However, they do not protect against sexually transmitted diseases, they are unsuitable for older women who smoke, and long-term use carries a slight increased risk of breast cancer. Other forms of combined contraceptive which have been developed recently include *monthly injection*, *vaginal ring*, and *transdermal patch*.

Progestogen-only oral contraceptives are considered to have a slightly higher failure rate than that for combined preparations because of the need for more accurate dosage timing. A 0.9% failure rate has been given for the first year of use if taken correctly, but in practice failure rates of up to 10% have been reported. Failure rates are lower in women taking these contraceptives during breast feeding, as breast feeding itself provides additional contraception (see also Natural Family Planning Methods, below). Regularity in taking them is essential; a dose should not be delayed for more than 3 hours (up to 12 hours for desogestrel). They act primarily to decrease the chance of fertilisation and implantation since they prevent ovulation in only 14 to 50% of cycles, although desogestrel is said to reliably inhibit ovulation. They are useful for women who are breast feeding, for those who smoke and are more than 35 years of age, and if medical conditions contra-indicate the use of oestrogens.

Barrier methods, including both male and female condoms, vaginal sponges containing spermicide, and diaphragms and cervical caps used with spermicide, act as a mechanical barrier to prevent fertilisation, and inactivate sperm. Barrier methods decrease the risk of sexually transmitted diseases and a shift towards their use has occurred since the emergence of HIV infection in particular. However, barrier methods are not as effective in preventing conception as hormonal contraception and IUDs. Even when used correctly, failure rates in the first year of use vary from 2% for the male condom, to 6% for the diaphragm with spermicide, to 20% for the vaginal sponge in parous women. Spermicides, such as nonoxinol 9, may be used as foam, cream, jelly, dissolvable vaginal tablets or pessaries, or as a spermicide-containing polyvinyl alcohol film placed over the cervix. However, they are generally considered relatively ineffective when used as the sole method of contraception, and such use is not recommended.

Natural family planning methods such as periodic abstinence using the calendar, temperature, cervical mucus ('Billings') or sympto-thermal methods require high motivation to learn and practice effectively. However, they may be the only acceptable method to some people. More recently, daily measurement of urine hormone concentrations has been used as a predictor of the timing of ovulation and hence the risk of becoming pregnant; on 'unsafe' days abstinence or barrier methods are required. Traditional methods such as withdrawal (coitus interruptus) are widely used in some areas, but are considered relatively ineffective. The lactational amenorrhoea method of contraception can be used during breast feeding for up to 6 months after childbirth. For it to be an effective contraceptive method, breast feeding must start immediately after birth, the infant must be fully or nearly fully breast-fed, feedings must be no more than 4 to 6 hours apart, and menstruation must not have restarted. When carried out consistently and correctly, this method has a failure rate of 0.9% in the first 6 months.

Various other methods of contraception are under investigation including the use of the antiprogestogen mifepristone, selective sex-hormone receptor modulators, and contraceptive vaccines. There has also been some investigation of **male contraception**. Weekly intramuscular injection of high-dose testosterone or nandrolone to produce azoospermia has been investigated with some success, but development of an oral contraceptive dosage form for males has been slow. Use of a progestogen with testosterone is being studied, as is the use of implants of synthetic androgens such as trestolone (7-α-methyl-19-nortestosterone; MENT).

The available irreversible methods of contraception are surgical male or female *sterilisation*. The use of mepacrine for non-surgical female sterilisation has been attempted but has proved extremely controversial.

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Emergency contraception. Emergency contraception (postcoital contraception) can be used after unprotected intercourse but before a fertilised ovum has been implanted. Methods that act after implantation are considered abortifacients. The two most commonly used emergency contraceptives are *oral contraceptives* and *copper IUDs*.

Oral contraceptive regimens (the so-called ‘morning after pill’) have historically used a preparation containing high-dose oestrogen with a progestogen, taken within 72 hours of intercourse, and repeated 12 hours later (the Yuzpe regimen). This preparation is thought to act by a variety of mechanisms, which may depend on when in the menstrual cycle it is used. It may prevent implantation, prevent or delay ovulation, disrupt ovum transport, and alter corpus luteum function. However, levonorgestrel alone (without an oestrogen) is now widely recommended as an emergency contraceptive. A large WHO multicentre study found that levonorgestrel 750 micrograms alone within 72 hours of intercourse and repeated after 12 hours was more effective than the Yuzpe regimen and better tolerated.[1] Both regimens were most effective when given within 24 hours of intercourse.[1,2] A small observational study[3] of the Yuzpe method used between 72 and 120 hours after unprotected intercourse reported a trend towards decrease in effectiveness. A further large study[4] by WHO found that for up to 120 hours after intercourse, a single dose of levonorgestrel 1.5 mg was as effective as two doses of 750 micrograms given 12 hours apart, with a pregnancy rate of about 1.5%.

Efficacy rates vary between studies, but the Yuzpe method has been shown to reduce the risk of pregnancy by about 75% and levonorgestrel by about 89%.[5] Based on its greater efficacy and better tolerability, levonorgestrel is now generally recommended as the hormonal emergency contraceptive of choice that can be offered up to 120 hours after intercourse.[5-9]

Copper, but not progestogen, IUDs can be inserted up to 120 hours after unprotected intercourse for postcoital contraception. They have a failure rate of no more than 1% when used for emergency contraception.[9] Thus, when efficacy is a priority the IUD is the emergency contraceptive method of choice.

Mifepristone is under investigation as an emergency contraceptive. Its action appears to depend on inhibiting ovulation or, if ovulation has occurred, preventing implantation. Early studies used a single dose of 600 mg, but later studies have found 10 mg to be equally effective. Mifepristone also appears to be at least as effective as levonorgestrel but it can delay the onset of subsequent menstruation, which might cause anxiety in some women.[10,11]

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Malignant neoplasms. The prophylactic use of oral contraceptives may protect against ovarian cancer in women with mutations of the BRCA1 or BRCA2 genes, but must be balanced against the risk of breast cancer in these women (see Ovary, under Carcinogenicity, p.2061).

Hormone Replacement Therapy

Hormonersatztherapie; HRT; THS; Traitement Hormonal Substitutif; Tratamiento hormonal restitutivo.
Гормонозаместительная Терапия

The Menopause

The menopause is defined as the permanent cessation of cyclical menstruation due to loss of ovarian follicular activity. It is therefore determined in retrospect, conventionally after 1 year without menstruation. In the few years before the menopause (the menopausal transition), ovarian oestradiol secretion declines, sometimes in a fluctuating manner, and there is a resultant increase in pituitary follicle-stimulating hormone (FSH) secretion. The menopausal transition may be characterised by irregular menstrual cycles and dysfunctional uterine bleeding, and fertility is much reduced compared with the early reproductive years. The term perimenopause is used to cover the menopausal transition and the first year after the menopause, and may last 6 years or more. It has sometimes been referred to as the climacteric. Oestrogen concentrations reach their minimum and FSH concentrations their maximum about 4 years after the menopause. After the menopause the ovaries may continue to produce some androgens; adrenal and ovarian androgens are aromatised to oestrogens (predominantly oestrone) in the periphery, but oestrogen concentrations are much lower than in premenopausal women. The median age for the natural menopause is about 51 years. If the menopause occurs in women aged 40 years or less, it is considered premature. The menopause may be induced by surgical removal of both ovaries, or sometimes by antineoplastic drugs or radiotherapy.

The decline in oestrogen concentrations during the perimenopause may be associated with both acute and long-term effects. However, some of these may be difficult to differentiate from the effects of ageing, and the incidence varies geographically. Established *acute symptoms* can include vasomotor instability, manifesting as hot flushes and night sweats, and vaginal atrophy and dyspareunia. Non-specific symptoms include palpitations, headache, backache, and psychological symptoms such as tiredness, lack of concentration, loss of libido, irritability, insomnia, and depression. Insomnia may occur secondary to night sweats. There is little evidence that depressive illness is disproportionately increased at the menopause. Urinary problems are common in ageing women, and may occur in the perimenopause, but the extent that these are due to lack of oestrogens has not been determined. An established *long-term consequence* of the decline in oestrogen concentrations is an increased risk of bone fractures resulting from an increase in the rate of bone resorption. In addition, decline in oestrogen concentrations is associated with adverse effects on blood lipoproteins, and this may be a risk factor for cardiovascular disease.

Acute and longer-term effects of the menopause may be managed by using hormone replacement therapy (HRT) with oestrogens, with or without progestogens, and nonhormonal therapies (see Menopausal Disorders, p.2077).

Adverse Effects of HRT

When oestrogens are used for menopausal HRT, adverse effects include nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, altered blood lipids, cholestatic jaundice, glucose intolerance, rashes and chloasma (melasma), changes in libido, migraine, dizziness, depression, mood changes, headache, leg cramps, vaginal candidiasis, and decreased tolerance of contact lenses. Transdermal delivery systems may cause contact sensitisation (possibly severe hypersensitivity reactions on continued exposure), and nasal sprays may cause local irritation, rhinorrhoea, and epistaxis. Headache has been reported on vigorous exercise. Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma (see below). The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. Current use of menopausal HRT is associated with an increased risk of venous thromboembolism and breast cancer (see below).

◊ Reviews.

1. Winship KA. Unopposed oestrogens. *Adverse Drug React Acute Poisoning Rev* 1987; **1:** 37–66.
2. Evans MP, *et al.* Hormone replacement therapy: management of common problems. *Mayo Clin Proc* 1995; **70:** 800–5.

Carcinogenicity. Use of unopposed oestrogen as menopausal HRT in women with a uterus increases the risk of endometrial cancer, irrespective of the route of administration. This risk is reduced, although possibly not eliminated completely, by the concomitant use of a progestogen. There is also evidence that use of HRT, as oestrogen alone or with a progestogen, increases the risk of breast cancer.

Because of continuing modifications in regimens for HRT there is a continuing need to monitor the incidence of various cancers in users of this therapy.

The carcinogenicity of combined menopausal HRT has been reviewed.[1]

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BREAST. Early age at menarche and late age at menopause increase the risk of breast cancer, and surgical oophorectomy at an early age decreases the risk of breast cancer. In addition, higher concentrations of unbound endogenous oestrogens in postmenopausal women appear to increase the risk of developing breast cancer.[1] Such risk factors have prompted concerns that menopausal HRT might be associated with an increased risk of breast cancer.

Reviews and analyses[2-4] of studies published during the 1970s and/or 1980s on the use of **unopposed oestrogen** replacement therapy in postmenopausal women have generally shown that there is an associated moderate increase in the risk of breast cancer; figures for overall relative risk compared with non-oestrogen users ranged from under 1 to up to 2. One of these,[3] a meta-analysis of studies from 1976 to 1989, further showed that although the relative risk of breast cancer rose to 1.3 after 15 years of oestrogen use, it did not appear to rise at all until after 5 years of use. A similar meta-analysis[4] differentiated between low-dose oestrogens and high-dose oestrogens; those taking 625 micrograms daily of conjugated oestrogens had a risk of breast cancer 1.08 times higher than non-oestrogen users, whereas the relative risk in those taking 1.25 mg daily or more was up to 2.0. A subsequent meta-analysis[5] differentiated between current use of HRT, duration of use, and use at any time. The highest relative risk of breast cancer was associated with current use (1.4); use for 10 years or more was associated with a relative risk of about 1.2, and having ever used HRT was not associated with an increased risk. In 1997 the Collaborative Group on Hormonal Factors in Breast Cancer reanalysed about 90% of the worldwide evidence on breast cancer and the use of HRT.[6] They reported that the relative risk of having breast cancer diagnosed was increased by a factor of 1.023 for each year of use, being 1.35 for 5 or more years of use. However, this effect was reduced on cessation of use, and had largely disappeared after about 5 years. In women who started therapy at age 50, the cumulative excess number of breast cancers diagnosed per 1000 women between age 50 and 70 were estimated to be 2, 6, and 12 for 5, 10, and 15 years of use, respectively, from a baseline of 45 per 1000 in never-users.[6] In contrast, the arm of the Women’s Health Initiative[7] that compared conjugated oestrogens with placebo over an average of about 7 years found a trend towards a reduction in breast cancer risk with HRT. A Finnish cohort study[8] also found no increase in risk with less than 5 years of oral estradiol or estriol therapy. For women taking unopposed oestrogen in the Nurses’ Health Study[9] cohort the linear increase in risk with increasing duration of use did not become statistically significant until current use exceeded 20 years.

Most data relate to the use of unopposed oestrogen. There has been speculation both that the concomitant use of progestogen in HRT could reduce the risk of breast cancer and that it might increase it. Bergkvist *et al.*[10] suggested an increased relative risk of

4.4 in the small subgroup using long-term **combined therapy**, but because of the large confidence intervals they considered these results inconclusive. Analysis of the Nurses' Health Study cohort has provided evidence that current use of oestrogen and progestogen is associated with a similar increased relative risk of breast cancer to that of unopposed oestrogen (1.4 versus 1.3).[11] The Collaborative Group on Hormonal Factors in Breast Cancer[6] found no evidence of marked differences between preparations containing oestrogens alone and those containing oestrogens and progestogens. However, in a randomised study, oestrogen plus progestogen was associated with greater increases in radiographic breast density than unopposed oestrogen.[12] The results of further cohort studies[13,14] and case-control studies[15,16] also suggest that the risk of breast cancer may be higher for current or recent use of combined HRT compared with oestrogen alone, and a cohort study[17] of over 1 million women (the Million Women Study) found relative risks of 1.3 for users of oestrogen alone, and 2.0 for combined HRT, compared with never-users. After an average follow-up of about 5 years the Women's Health Initiative,[18] comparing combined HRT with placebo in more than 16 000 women, was stopped early because of an increased rate of invasive breast cancer in women given HRT.

The public health perspective on the **implications** of any increased risk of breast cancer will depend on the background risk. This is high in western countries, so a small increased relative risk would equate to a large absolute increase in number of cases.[19]

If menopausal oestrogen therapy increases the risk of breast cancer, there is a need to ascertain whether these cancers can be detected early, how aggressive they are, and what the mortality rate from them is. Currently, there are limited data on these points.

- There is evidence[20,21] that the use of HRT decreases the sensitivity and specificity of screening mammography (resulting in more false positives and more false negatives), apparently because it increases radiographic breast density[22,23] or slows the natural change from dense patterns to fatty patterns,[24] so decreasing the ability to interpret the mammogram. This is of concern for the success of screening programmes, and has been suggested as a factor in the increased detection of interval cancers (those detected between screening appointments).[25] In addition, HRT-associated increases in radiographic breast density could actually be a marker for risk of breast cancer.[12,26]
- Some data suggest that breast cancers in women on HRT may be of better prognostic grade.[27,28] The Collaborative Group on Hormonal Factors in Breast Cancer reported that breast cancers were more likely to be localised in current or recent users of HRT, but that there was evidence of an increased risk of metastasis with increasing duration of use.[6] However, the Women's Health Initiative[26] did not confirm previous findings of favourable prognosis, and found breast cancers in combined HRT users to be larger, more likely to be node positive, and at a more advanced stage at diagnosis. The likelihood of good prognostic grade in women on HRT may depend on the histological type of any lesion that develops: invasive lobular and tubular cancers are more strongly associated with current use of HRT than invasive ductal cancer.[29]
- Follow-up of most studies is currently insufficient to give a clear indication of mortality risk with long-term use. Early data from a UK cohort study[30] suggested a decreased risk of breast cancer mortality, but after further follow-up the risk was no longer reduced.[31] Similarly, a study in 2614 women with breast cancer followed up for up to 22 years found that the use of HRT at the time of diagnosis was associated with a reduction in mortality, but the effect waned over time.[32] In contrast, data[11] from the Nurses' Health Study cohort suggest an increase in risk of death from breast cancer in women who have currently used HRT for 5 years or more (1.45). Similarly, although mortality was lower overall, a trend towards an increased risk of death from breast cancer (1.9; 95% confidence interval 0.4 to 8.4) was seen in a study of long-term use (mean of 17 years).[33]

The risk of breast cancer may be increased further by the use of HRT in women who are already at an increased risk. Although a study found a modest increase in risk in these women, it was not significantly higher, and there was a reduced total mortality rate.[34] It is unclear whether use of HRT in breast cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, below).

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9. Chen WY, *et al.* Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006; **166:** 1027–32.
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11. Colditz GA, *et al.* The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; **332:** 1589–93.
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28. Gapstur SM, *et al.* Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA* 1999; **281:** 2091–7.
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31. Hunt K, *et al.* Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol* 1990; **97:** 1080–6.
32. Schairer C, *et al.* Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst* 1999; **91:** 264–70.
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34. Sellers TA, *et al.* The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med* 1997; **127:** 973–80.

CERVIX. Studies of the effect of HRT on cervical cancer risk are likely to be subject to the potential confounding of other risk factors such as sexual activity. There are few data on this risk; one study[1] suggested oestrogens do not increase, and may decrease, the risk of cervical cancer, but another[2] suggested that unopposed oestrogen might increase the risk of adenocarcinoma. Therapy with combined HRT did not significantly affect the incidence of cytological abnormalities found in annual cervical smears in women in the Heart and Estrogen/progestin Replacement Study (HERS).[3] In the Women's Health Initiative study,[4] however, there was an overall increase in the incidence of new abnormalities in women given combined HRT, compared with placebo, although the incidence of high-grade squamous intra-epithelial lesion and cervical cancer was not affected.

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2. Lacey JV, *et al.* Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. *Gynecol Oncol* 2000; **77:** 149–54.
3. Sawaya GF, *et al.* The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *Ann Intern Med* 2000; **133:** 942–50.
4. Yasmeen S, *et al.* Incidence of cervical cytological abnormalities with aging in the Women's Health Initiative: a randomized controlled trial. *Obstet Gynecol* 2006; **108:** 410–19.

ENDOMETRIUM. The increased incidence of endometrial hyperplasia and risk of cancer in women receiving unopposed oestrogen replacement therapy is well established. An analysis of case control studies published during the 1970s and 1980s revealed a relative risk of developing endometrial cancer of 1.4 to 7.6 in women who had ever used oestrogen, and a relative risk of 3.1 to 15 in long-term users, compared with nonusers.[1] Risk was also increased with higher doses of oestrogens. In general, endometrial cancer in oestrogen users was of a better prognostic stage, and survival rates were better, than in nonusers.[1] An elevated risk of endometrial cancer persists for a number of years after stopping unopposed oestrogen therapy.[2]

Addition of a progestogen to oestrogen replacement therapy reduces the incidence of endometrial hyperplasia[3] and cancer. However, the extent to which this alters the risks and benefits of oestrogen replacement therapy, and the optimum progestogen type, and dose and duration, have not been fully elucidated.

As regards risk of endometrial cancer, preliminary data from a cohort study revealed that the addition of cyclical progestogen to oestrogen therapy reduced this risk compared with oestrogen therapy alone.[4] A further case-control study confirmed that progestogens decreased the relative risk, and that the reduction in risk was greater when progestogens were used for 10 or more days per month than when they were used for less than 10 days per month.[5] Two much larger case-control studies have confirmed these findings.[6,7] However, 1 of these studies[6] reported that in long-term users the addition of a progestogen did not reduce the risk of endometrial cancer to that seen in nonusers—after 5 years of use, the relative risk of endometrial cancer with HRT containing 10 or more days of progestogen per month was 2.5 (95% confidence intervals 1.1 to 5.5). This finding remains to be confirmed.

Use of progestogens for 10 days of an 84-day cycle (long cycle) has been suggested to improve acceptability of combined HRT. However, one study of a long-cycle regimen was stopped because of an increased risk of endometrial hyperplasia and atypia compared with a conventional monthly cycle regimen.[8]

Some newer regimens of HRT use continuous low doses of progestogen with oestrogen, which avoid withdrawal bleeding. Data on the incidence of endometrial hyperplasia from randomised trials of these regimens have been reassuring.[3,9,10] Continuous norethisterone plus ethinylestradiol,[9] and continuous medroxyprogesterone plus conjugated oestrogens,[10] protected the endometrium against the hyperplasia seen with the oestrogen alone. Continuous therapy was as effective as cyclical therapy containing 12 days of progestogen,[10] and there is a suggestion from meta-analysis[3] that continuous therapy may even be more effective than sequential when given over a prolonged period, although this remains to be confirmed. The first data on endometrial cancer risk from continuous combined HRT suggest that it is as protective as sequential therapy with the progestogen given for 10 or more days per month (odds ratio 1.07 per 5 years of use for both regimens).[7] The Women's Health Initiative reported[11] that although the rate of endometrial cancer for continuous combined HRT was reduced, it was not significantly different to placebo over 5 years. However, in the analysis of endometrial cancer in the Million Women cohort study,[12] in which 55% of the 716 738 women had not used HRT, there was a lower risk of endometrial cancer with continuous combined HRT, whereas it was not altered for cyclic combined HRT, and was higher for oestrogen-only HRT and tibolone. The beneficial effects of combined HRT were also found to be greatest in obese women.

It is unclear whether use of HRT in endometrial cancer survivors increases the risk of subsequent recurrence and associated mortality (see also Malignant Neoplasms under Precautions, below).

1. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. *Am J Obstet Gynecol* 1989; **161:** 1859–64.
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4. Persson I, *et al.* Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *BMJ* 1989; **298:** 147–51.
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Gastrointestinal tract. Evidence of an effect of oestrogen replacement therapy on colorectal cancer is ambiguous, since studies have reported both an increased and a decreased incidence; a meta-analysis in 1995 suggested no overall effect.[1] However, subsequent cohort studies did suggest a lower incidence of colon cancer in those who had received oestrogens.[2,3] This was most pronounced in current users in whom the relative risk was about one-third to one-half of that for women who had never taken oestrogen. Similarly, a large case-control study also reported a significant reduction in colon cancer, but not rectal cancer.[4] A later meta-analysis[5] concluded that the risk of colon cancer might be decreased among women who have recently used HRT, and that the risk of death from colon cancer might also be reduced. The Women's Health Initiative,[6] a placebo-controlled study of combined HRT in more than 16 000 women, found that those taking HRT had a decreased risk of developing colorectal cancer, but that at diagnosis there was greater lymph node involvement and it was at a more advanced stage.

There is less information on the effect of HRT on death from colorectal cancer. In the Nurses' Health Study cohort[7] there were decreased risks of death from colorectal cancer and death overall for women taking HRT when cancer was diagnosed, compared with those who had never taken HRT. However, this benefit was limited to women who had been taking HRT for no more than 5 years before diagnosis; longer duration of use and past use had no effect on survival.

1. MacLennan SC, *et al.* Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995; **162:** 491–3.
2. Calle EE, *et al.* Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995; **87:** 517–23.
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4. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995; **87:** 1067–71.
5. Nanda K, *et al.* Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; **93:** 880–8.
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Ovary. There was no clear evidence that the use of oestrogen replacement therapy altered the risk of invasive ovarian cancer in various case-control studies reviewed by the Collaborative Ovarian Cancer Group.[1] However, subsequent study of a large cohort has suggested that long-term oestrogen replacement therapy may increase the risk of fatal ovarian cancer.[2,3] Similarly, a meta-analysis indicated an increased risk for invasive epithelial ovarian cancer, especially after long-term use of HRT.[4] Another, later, cohort study[5] also reported that there was an increased risk of ovarian cancer with oestrogen replacement therapy, particularly when given for 10 years or more, but found no increase for combined HRT. A Swedish case-control study[6] looked at different types of HRT and also found that the risk was increased with oestrogen replacement therapy. For combined HRT, however, the risk was increased for women who had used sequential combined HRT (continuous oestrogen plus cyclical progestogen), but not for those who had used continuous combined HRT. Similarly, in the Women's Health Initiative,[7] a placebo-controlled study of continuous combined HRT in more than 16 000 women, the increased incidence of ovarian cancer was not significant during 5.6 years of follow-up. Further cohort data support an association with long-term current use of unopposed oestrogen replacement therapy,[8-10] but the role of progestogen remains less clear; the Million Women Study[10] also found increased risks with combined HRT, but the Nurses' Health Study[9] found no association. In the cohort NIH-AARP Diet and Health Study[8] the risk of ovarian cancer was also increased overall for 5 or more years of combined HRT use, and found to be higher for users of sequential compared with continuous combined HRT.

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3. Rodriguez C, *et al.* Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001; **285:** 1460–5.
4. Garg PP, *et al.* Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; **92:** 472–9.
5. Lacey JV, *et al.* Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; **288:** 334–41. Correction. *ibid.*; 2544.
6. Riman T, *et al.* Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* 2002; **94:** 497–504.
7. Anderson GL, *et al.* Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; **290:** 1739–48.
8. Lacey JV, *et al.* Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 2006; **98:** 1397–1405.
9. Danforth KN, *et al.* A prospective study of postmenopausal hormone use and ovarian cancer risk. *Br J Cancer* 2007; **96:** 151–6.
10. Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2007; **369:** 1703–10.

Effects on carbohydrate metabolism. Data from a survey of postmenopausal women showed that diabetic women who were currently taking HRT had better glycaemic control than those who had never taken HRT or were previous users.[1] In the Heart and Estrogen/Progestin Replacement study[2] in postmenopausal women with ischaemic heart disease, there was no significant change in fasting glucose concentrations after 4 years of combined HRT in women with or without diabetes compared with a rise in women given placebo. There was also a lower risk of developing diabetes in those given HRT (cumulative incidence 6.2%) compared with placebo (9.5%). The Women's Health Initiative study[3] reported changes in fasting glucose and insulin concentrations, indicating a fall in insulin resistance, in women treated with combined HRT. During an average 5.6 years of follow-up there was a lower incidence of diabetes in women given HRT (3.5%) compared with placebo (4.2%). This represented an absolute reduction of 15 cases of treated diabetes per 10 000 women per year of HRT treatment.

Although HRT may improve glycaemic control in diabetic postmenopausal women, it is generally used with caution in this group. Diabetic patients are already at increased risk of cardiovascular disease, and HRT may be associated with an increased risk of ischaemic heart disease (see below).

1. Crespo CJ, *et al.* Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2002; **25:** 1675–80.
2. Kanaya AM, *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003; **138:** 1–9.
3. Margolis KL, *et al.* Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; **47:** 1175–87.

Effects on the cardiovascular system. Various facts support the theory that endogenous oestrogens may be cardioprotective. For example, mortality rates for cardiovascular disease in women are lower than those in men at all ages. In addition, women who have a surgically induced menopause at a young age are at increased risk of ischaemic heart disease compared with women who have a natural menopause.

Conversely, use of high doses of oestrogens for malignant disease is associated with an increased risk of cardiovascular events. Similarly, use of oestrogens in combined oral contraceptives carries a small increased risk of cardiovascular disease (see p.2062). Moreover, an early study in men surviving a myocardial infarction found that high doses of conjugated oestrogens (5 mg daily) were associated with a higher incidence of subsequent coronary events than placebo (see Effects on the Cardiovascular System, in Conjugated Oestrogens, p.2087).

In practice, a number of large observational studies found a decreased risk of ischaemic heart disease and mortality in women receiving menopausal HRT compared with those who have never received this therapy (see below). The reduction in risk was estimated as 30 to 50%, but biases such as the healthy user effect seem to play a part in this estimate; unfortunately, results from controlled studies have cast doubt on the extent of any reduction in risk. There is also evidence to show that HRT *increases* the risk of stroke (see below) and venous thromboembolism (see below).

The mechanisms by which oestrogen exerts its cardiovascular effects are not fully understood.[1] Oestrogen has beneficial effects on lipoproteins, but adverse effects on triglycerides (see below). Similarly, it has beneficial effects on some, and adverse effects on other, mediators of thrombosis. Oestrogen may also have a direct beneficial effect on the coronary vasculature. Progestogens may reduce the beneficial effects of oestrogens on some lipids, although observational data has suggested that this is not sufficient to reverse potential benefit.

1. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; **340:** 1801–11.

Hypertension. Although high doses of oestrogens have been associated with increased blood pressure, use of menopausal HRT in normotensive and hypertensive women has little effect on blood pressure or may be associated with a small decrease.[1-4] An observational study[5] of normotensive postmenopausal women also found that, over time, the average increase in systolic blood pressure was significantly less in women who were taking HRT.

1. Affinito P, *et al.* Effects of hormonal replacement therapy in postmenopausal hypertensive patients. *Maturitas* 2001; **40:** 75–83.
2. Mueck AO, Seeger H. Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women. *Maturitas* 2004; **49:** 189–203.
3. Steiner AZ, *et al.* Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: the Estrogen in the Prevention of Atherosclerosis Trial. *Menopause* 2005; **12:** 728–33.
4. Karalis I, *et al.* Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Pressure* 2005; **14:** 38–44.
5. Scuteri A, *et al.* Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. *Ann Intern Med* 2001; **135:** 229–38.

Ischaemic heart disease. In 1991, Stampfer and Colditz reviewed 31 case-control and cohort studies on the risk of ischaemic heart disease in women using menopausal HRT.[1] Four studies showed an adverse trend, 2 showed no effect on risk, and 25 showed a trend to **reduction in risk** or a significant reduction in risk. The summary relative risk was 0.56, with estimated 95% confidence intervals of 0.50 to 0.61. Other reviews have reported similar reductions in risk.[2,3] Much of the data relate to the use of unopposed oestrogen, which is no longer recommended in women with a uterus because of the risk of endometrial cancer (see above).

There was concern that the **addition of progestogen** might negate or reduce the cardiovascular benefits of oestrogens by reducing the oestrogen-induced rise in serum high-density-lipoprotein cholesterol concentrations. It was postulated that this might be particularly true for progestogens derived from nortestosterone rather than progesterone. Results from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) indicated that the beneficial effects on blood lipoproteins and fibrinogen, although greatest with unopposed oestrogen, were still present when combined with medroxyprogesterone or micronised progesterone (micronised progesterone was preferable to medroxyprogesterone).[4] Moreover, the UK Medical Research Council Study reported a fairly even balance between possibly beneficial and adverse effects on lipid concentrations and coagulability when conjugated oestrogens alone were compared with conjugated oestrogens plus norgestrel (a nortestosterone derivative).[5] Similar results were reported in the CHART study for ethinylestradiol with or without norethisterone.[6] Although reassuring, these 3 studies provided information only on surrogate endpoints.

Data from the Nurses' Health Study cohort[7] showed a greater reduction in the risk of major ischaemic heart disease among women receiving an oestrogen plus a progestogen (relative risk 0.4) than those receiving an oestrogen alone (0.6), as compared with the risk in women not using hormones. *In-vitro* data suggest that progestogens may actually protect against atherosclerosis via inhibition of smooth muscle cell proliferation.[8]

As regards **duration of HRT use**, current use appeared to be the most important factor for cardiovascular risk reduction. Users with coronary risk factors appeared to derive greater benefit from HRT than those at low risk of coronary artery disease.[9] Of concern, the Nurses' Health Study reported that the apparent benefit from HRT decreased with increasing duration of use beyond 10 years because of an increase in mortality from breast cancer.[9]

However, a number of studies have now found **no beneficial effect** on risk of heart disease. In contrast to previous findings, a retrospective case-control study[10] did not find a decreased risk of myocardial infarction in women currently using combined HRT or oestrogens alone. The authors of this study suggested that the benefit of HRT may not be as large as has been estimated in some qualitative overviews, and emphasised the need for data from randomised studies.[10] This has been confirmed by results[11] of the Heart and Estrogen/Progestin Replacement Study, a randomised placebo-controlled study in women with established ischaemic heart disease. Combined HRT with conjugated oestrogens plus medroxyprogesterone produced no overall reduction in the occurrence of myocardial infarction or death due to ischaemic heart disease in these women. This overall lack of effect was due to an initial increase in cardiac events during the first year, with a later beneficial effect in years 3 to 5. During unblinded follow-up[12] of 2.7 years, these late beneficial effects did not persist and the risk of cardiovascular events was not reduced. Observational data from the Nurses' Health Study cohort[13] also noted a trend towards an initial increase in cardiac events followed by a decrease in risk with long-term use of HRT, in women with a history of ischaemic heart disease. Other studies found that HRT did not affect the progression of existing coronary atherosclerosis as measured by angiography.[14,15] Oestrogen therapy for 2 years also had no effect on the risk of further cardiac events in postmenopausal women who had survived a myocardial infarction.[16] There is also some evidence that the risks and benefits of HRT may vary according to the presence or absence of particular prothrombotic mutations.[17]

These worrying results have suggested that HRT should **not** be used for secondary prevention in women with heart disease, in contrast to some earlier suggestions (see also Cardiovascular Disorders under Uses and Administration, below).

In women without pre-existing heart disease, observational data from the Nurses' Health Study[18] showed a reduced risk of major coronary events in users of HRT, compared with never-users. However, there were increased rates of coronary events at an average follow-up of about 5 years in the Women's Health Initiative,[19] a primary prevention study comparing combined HRT with placebo in over 16 000 women. The risk was highest in the first year of HRT but decreased to a smaller non-significant excess risk in the following years.[20] The arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy found that over an average of 7 years there was no difference in the risk of ischaemic heart disease.[21,22] These results suggest that HRT should also **not** be used for primary prevention of ischaemic heart disease.

There is continuing debate about the effect of HRT on ischaemic heart disease, and how it might be influenced by age. The generalisability of some study results, such as in the Women's Health Initiative, has been questioned because the mean age of the study group has been much older than women who generally take HRT for vasomotor symptoms in their 50s. A meta-analysis[23] has compared data from younger and older women, and found that for younger women (less than 10 years since menopause or under 60 years of age) there was a reduced risk of myocardial infarction or cardiac death with HRT. In older women, however, events increased in the first year then decreased after 2 years, resulting in a neutral effect over time. Secondary analysis[24] of the Women's Health Initiative data found that for women who started HRT closer to menopause (aged 50 to 59 years or less than 10 years since menopause) there was a trend towards reduced risks of ischaemic heart disease and death, while risk increased with age and time since menopause. One factor might be the reduction by HRT of atherosclerotic calcification in the coronary arteries.[25] Further studies are underway to examine the effect of HRT, started soon after menopause, in the prevention of atherosclerosis.

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; **20:** 47–63.
2. Grady D, *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; **117:** 1016–37.
3. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA* 1991; **265:** 1861–7.
4. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; **273:** 199–208. Correction. *ibid.*; **274:** 1676.
5. Medical Research Council's General Practice Research Framework. Randomised comparison of oestrogen versus oestrogen plus progestogen hormone replacement therapy in women with hysterectomy. *BMJ* 1996; **312:** 473–8.
6. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; **276:** 1397–1403.
7. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.*; 1046.
8. Lee W-S, *et al.* Progesterone inhibits arterial smooth muscle cell proliferation. *Nature Med* 1997; **3:** 1005–1008.
9. Grodstein F, *et al.* Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; **336:** 1769–75.
10. Sidney S, *et al.* Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med* 1997; **127:** 501–8.
11. Hulley S, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280:** 605–13.
12. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.*; 1064.
13. Grodstein F, *et al.* Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: a prospective, observational study. *Ann Intern Med* 2001; **135:** 1–8.
14. Herrington DM, *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000; **343:** 522–9.
15. Hodis HN, *et al.* Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003; **349:** 535–45.
16. The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; **360:** 2001–8.
17. Psaty BM, *et al.* Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001; **285:** 906–13.
18. Grodstein F, *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133:** 933–41.
19. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
20. Manson JE, *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349:** 523–34.
21. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
22. Hsia J, *et al.* Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; **166:** 357–65.
23. Salpeter SR, *et al.* Coronary heart disease events associated with hormone therapy in younger and older women. *J Gen Intern Med* 2006; **21:** 363–6.
24. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
25. Manson JE, *et al.* WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; **356:** 2591–2602.

STROKE. The Framingham Study suggested a more than twofold increased risk of stroke in women using menopausal HRT.[1] However, subsequent studies reporting risk of stroke separately from other cardiovascular events showed either no effect on risk[2] or a decreased risk in the order of 30 to 50%.[3,4]

Data from the Nurses' Health Study cohort[5] revealed little association between the risk of stroke of any type and current use of unopposed oestrogens or oestrogen plus progestogen. However, they reported a trend towards an increased risk of stroke in current users of high-dose oestrogen therapy (1.25 mg or higher). Similarly, a large Danish case-control study found that unopposed oestrogens or oestrogen plus progestogen had no effect on the risk of non-fatal haemorrhagic or thromboembolic stroke,[6] and data from the Heart and Estrogen/Progestin Replacement Study indicated that combined HRT in women with pre-existing ischaemic heart disease had no effect on risk of stroke.[7,8] In contrast to these results, the Women's Health Initiative, a placebo-controlled study of over 16 000 healthy women, found that combined HRT increased the risk of ischaemic stroke, and that the increase in risk became apparent after about 1 year of starting HRT.[9] Furthermore, the arm of the Women's Health Initiative that compared unopposed conjugated oestrogens with placebo in more than 10 000 women with prior hysterectomy also found an increased risk of stroke;[10] additional data and analysis also confirmed that the increased risk was for ischaemic stroke, and appeared after about 4 years.[11] Although the numbers of haemorrhagic strokes were small in both Women's Health Initiative studies, the combined data showed no significant effect of hormone therapy.[11] A systematic review,[12] which was dominated by the results of the Women's Health Initiative, found that HRT was associated with an increase in stroke. This was attributed largely to ischaemic stroke, whereas there was no significant change in the risks of haemorrhagic stroke, fatal stroke, or transient ischaemic attack. A poor outcome (death or dependency) was also found to be more likely with HRT. Secondary analysis[13] of the Women's Health Initiative data also found that the risk of stroke was increased regardless of years since menopause.

In a controlled study in postmenopausal women who had recently had a stroke or transient ischaemic attack, the use of unopposed oestrogen had no significant effect on mortality or the recurrence of stroke.[14]

1. Wilson PWF, *et al.* Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham study. *N Engl J Med* 1985; **313:** 1038–43.
2. Stampfer MJ, *et al.* Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991; **325:** 756–62.
3. Paganini-Hill A, *et al.* Postmenopausal oestrogen treatment and stroke: a prospective study. *BMJ* 1988; **297:** 519–22.
4. Finucane FF, *et al.* Decreased risk of stroke among postmenopausal hormone users: results from a national cohort. *Arch Intern Med* 1993; **153:** 73–9.
5. Grodstein F, *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:** 453–61. Correction. *ibid.*; 1406.
6. Tønnes Pedersen A, *et al.* Hormone replacement therapy and risk of non-fatal stroke. *Lancet* 1997; **350:** 1277–83.
7. Simon JA, *et al.* Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001; **103:** 638–42.
8. Grady D, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 49–57. Correction. *ibid.*; 1064.
9. Wassertheil-Smoller S, *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; **289:** 2673–84.
10. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; **291:** 1701–12.
11. Hendrix SL, *et al.* Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006; **113:** 2425–34.
12. Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005; **330:** 342–4.
13. Rossouw JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; **297:** 1465–77. Correction. *ibid.* 2008; **299:** 1426.
14. Viscoli CM, *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; **345:** 1243–9.

VENOUS THROMBOEMBOLISM. Traditionally it has been assumed that, unlike combined oral contraceptives, menopausal HRT is not associated with an increased risk of venous thromboembolism.

However, observational studies have provided substantial evidence that there is an increased risk of deep-vein thrombosis and/or pulmonary embolism in women receiving HRT.[1-4] The relative risk of venous thromboembolism was found to be 2.1 to 3.6 in current users compared with past-users or those who had never received HRT. This equates to an excess of 16 to 23 cases per 100 000 women per year. One study found that the increase in risk was restricted to the first year of use.[4] Another reported an increased risk with increasing oestrogen dose.[2]

Evidence from later randomised placebo-controlled studies[5-8] supports the findings of the observational studies above. Results from the Women's Health Initiative also suggest that the risk is higher with combined HRT than oestrogen alone.[9] It has been suggested that transdermal HRT might be preferable in women with a history of thromboembolism (see Administration, below) and a case-control study[10] reported that unlike oral preparations, transdermal oestrogen was not associated with an increased risk of venous thromboembolism.

The UK CSM considers that the absolute risk of venous thromboembolism in all women using HRT is higher than was originally suggested, and that the risks are higher particularly in older women and in women with predisposing factors, such as a history of venous thromboembolism.[11] Women with the factor V Leiden thrombophilia are at high risk of developing venous thromboembolism when taking HRT. The pooled results of 2 studies showed[12] that in the presence of this thrombophilia alone the odds ratio of developing venous thromboembolism was 3.58, and for HRT alone was 3.16, but women who had both these risk factors had a much higher risk of 13.16.

1. Daly E, *et al.* Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996; **348:** 977–80.
2. Jick H, *et al.* Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; **348:** 981–83.
3. Grodstein F, *et al.* Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; **348:** 983–7.
4. Pérez Gutthann S, *et al.* Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ* 1997; **314:** 796–800.
5. Grady D, *et al.* Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000; **132:** 689–96. Correction. *ibid.* 2001; **134:** 81.
6. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
7. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.
8. Cushman M, *et al.* Women's Health Initiative Investigation. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; **292:** 1573–80.
9. Curb JD, *et al.* Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006; **166:** 772–80.
10. Canonico M, *et al.* Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; **115:** 840–5.
11. CSM/MCA. New product information for hormone replacement therapy. *Current Problems* 2002; **28:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 23/01/08)
12. Wu O, *et al.* Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost* 2005; **94:** 17–25.

Effects on the eyes. The risk of dry eye increases with age, when tear production normally decreases. The incidence is higher in women, but it is unclear whether sex hormone changes in perimenopausal and postmenopausal women play a role in ocular surface dysfunction.[1] The effects of HRT on the incidence and management of dry eye have been debated. Relief of symptoms has occurred in some women given HRT[1] and improvements in tests of tear function and conjunctival epithelium have been reported.[2] However, a large cohort study[3] found a higher prevalence of dry eye syndrome in women taking HRT, particularly oestrogen alone, than in those not taking HRT.

1. Versura P, Campos EC. Menopause and dry eye: a possible relationship. *Gynecol Endocrinol* 2005; **20:** 289–98.
2. Pelit A, *et al.* Tear function tests and conjunctival impression cytology before and after hormone replacement therapy in postmenopausal women. *Eur J Ophthalmol* 2003; **13:** 337–42.
3. Schaumberg DA, *et al.* Hormone replacement therapy and dry eye syndrome. *JAMA* 2001; **286:** 2114–19.

Effects on the gallbladder. The use of HRT is reported to increase the risk of gallstone formation and cholecystectomy in postmenopausal women.[1-4]

1. Uhler ML, *et al.* Estrogen replacement therapy and gallbladder disease in postmenopausal women. *Menopause* 2000; **7:** 162–7.
2. Simon JA, *et al.* Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2001; **135:** 493–501.
3. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
4. Cirillo DJ, *et al.* Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; **293:** 330–9.

Effects on lipids. Oestrogens increase serum high-density-lipoprotein cholesterol and decrease low-density-lipoprotein cholesterol concentrations, effects that are considered favourable and may be a mechanism behind their apparent reduction in ischaemic heart disease in postmenopausal women, although controlled studies have not found combined HRT to reduce coronary events (see Effects on the Cardiovascular System, above). Oestrogens may also increase serum triglyceride concentrations, which is undesirable. Severe hypertriglyceridaemia and pancreatitis have occurred in women with hypertriglyceridaemia treated with oestrogens.[1,2] Use of concomitant progestogen reduces oestrogen-induced hypertriglyceridaemia.[2]

1. Glueck CJ, *et al.* Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994; **123:** 59–64.
2. Isley WL, Oki J. Estrogen-induced pancreatitis after discontinuation of concomitant medroxyprogesterone therapy. *Am J Med* 1997; **102:** 416–17.

Effects on mental function. For results suggesting that HRT may increase the risk of developing dementia see under Uses and Administration, below.

Effects on the pancreas. Unopposed oestrogen has been associated with pancreatitis in women with hypertriglyceridaemia (see Effects on Lipids, above). There have also been a few cases of pancreatitis, attributed to HRT, in which triglyceride concentrations were within the normal range.[1,2]

1. Blake WED, Pitcher ME. Estrogen-related pancreatitis in the setting of normal plasma lipids: case report. *Menopause* 2003; **10:** 99–101.
2. Trenque-Tessereau M-GB, *et al.* Combined estradiol/gestodene and acute pancreatitis. *Ann Pharmacother* 2005; **39:** 1953–4.

Precautions

Before menopausal HRT is given the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use.

HRT should be avoided in women with active thrombophlebitis or thromboembolic disease; it should not be given to those with a history of recurrent thromboembolism unless they are already receiving anticoagulant treatment.

HRT should not be given to those with undiagnosed abnormal vaginal bleeding, and abnormal vaginal bleeding during therapy should be investigated (see below). HRT is also contra-indicated in women with oestrogen-dependent neoplasms such as those of the breast or endometrium, and is usually considered contra-indicated in women with a history of these conditions although this has been debated (see below). Active liver disease and Dubin-Johnson or Rotor syndromes are also generally considered to be contra-indications.

Prolonged exposure to unopposed oestrogens increases the risk of endometrial cancer whatever the route of administration (see above). HRT should be used with caution in women with antiphospholipid antibodies or predisposing factors to thromboembolism (see also Venous Thromboembolism, above), and in migraine, a history of breast nodules or fibrocystic disease, uterine fibroids, or a history of endometriosis. HRT should also be used with caution in women with diabetes because of the increased risk of heart disease. Consideration should be given to temporarily stopping HRT 4 to 6 weeks before elective surgery (but see also below).

HRT should be stopped immediately, and appropriate investigations and treatment carried out, if any of the following occur:

- sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
- unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident
- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 100 mmHg diastolic)
- clear exacerbation of other conditions known to be capable of deteriorating during HRT or pregnancy.

Although evidence is in many cases less well established, HRT should perhaps also be used with caution in diseases which may be exacerbated during pregnancy or oestrogen therapy including asthma, epilepsy, hypertension, renal disease, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and SLE.

Doses of oestrogen in HRT are insufficient to provide contraception. HRT is contra-indicated in known or suspected pregnancy, and in women who are breast feeding.

Endometriosis. Women with endometriosis who are treated with hysterectomy and bilateral oophorectomy undergo a surgically-induced menopause and can experience acute menopausal symptoms; they are also at risk of conditions such as osteoporosis from long-term oestrogen deficiency. HRT until about 50 years of age has been recommended for women who undergo premature menopause, but disease reactivation and malignant transformation to adenocarcinoma in residual foci have been reported in women with a history of endometriosis, particularly with unopposed oestrogen. Although there are limited data to quantify the risks from HRT, they appear to be small. Nevertheless, recurrent disease may be more severe, with a greater chance of causing ureteric obstruction and consequent renal damage. To minimise the risks of reactivation and malignancy, women with a history of endometriosis should probably be given continuous combined HRT at the lowest effective dose. Although withholding HRT for a few months to wait for endometriosis to regress after surgery has been recommended, there is limited supporting evidence and others suggest that HRT may be started soon after surgery.[1]

1. Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006; **9:** 325–35.

Lupus erythematosus. SLE is an auto-immune disease which is far more common in women than in men, and usually has a peak onset for women in their 20s and 30s. There is some evidence to suggest that menopausal HRT use may be associated with a slightly increased risk in the onset of SLE in older women.[1-3] In women with pre-existing SLE, small studies found no apparent effect of HRT on disease flares.[2] In a larger study of 351 women, who were given either combined HRT or placebo for 12 months, severe flares were rare in both groups but mild to moderate flares were increased in the HRT group.[4]

Women with SLE are at increased risk of thromboembolic disease, and it has been suggested that transdermal oestrogen HRT may have less of a thrombogenic effect than oral HRT.[5] Women with antiphospholipid antibodies (which includes about a third of all patients with SLE) are at the highest risk and some[5] suggest that HRT should be avoided altogether in patients with persistent antibodies.

1. Petri M. Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus* 2001; **10:** 222–6.
2. Mok CC, *et al.* Use of exogenous estrogens in systemic lupus erythematosus. *Semin Arthritis Rheum* 2001; **30:** 426–35.
3. Costenbader KH, *et al.* Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; **56:** 1251–62.
4. Buyon JP, *et al.* The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005; **142:** 953–62.
5. Gompel A, Piette JC. Systemic lupus erythematosus and hormone replacement therapy. *Menopause Int* 2007; **13:** 65–70.

Malignant neoplasms. HRT is usually avoided in women who have been treated for *breast cancer* because of the concern that oestrogen will stimulate cancer recurrence. A retrospective observational study[1] and a retrospective case-control study[2] among women diagnosed with breast cancer did not find any evidence of an adverse effect in those who began HRT after diagnosis. A systematic review[3] of studies of HRT in breast cancer survivors reached a similar conclusion, but also noted that these studies were small, not randomised, and many were uncontrolled. More recently, an open randomised study[4] was stopped early when it was found that 2 years of HRT increased the risk of breast cancer (local recurrence, contralateral cancer, or distant metastases); this has cast doubt on the safety of HRT in these patients. A similar study, however, found that about 4 years of HRT did not increase the risk of cancer recurrence.[5] Comparing these two results, the authors suggested that the increased risk may have been due to the use of combined HRT that included continuous progestogen, rather than cyclic or long-cycle regimens. A systematic review[6] of 20 studies, including these two, highlighted the many differences in design such as HRT regimens used, and concluded that in the absence of sufficient evidence of safety HRT should not be used in women with a history of breast cancer. Other reviewers[7] have also recommended a cautious approach, suggesting that HRT should not be used for first-line management of menopausal symptoms in these women, but may be justified when other treatments have failed. The safety of different HRT regimens requires further study,[6,7] and the use of tibolone is under investigation.[8]

Similarly, HRT is usually avoided in patients who have been treated for *endometrial cancer*, because of the theoretical risk of stimulating tumour recurrence.[9] There is a lack of well-designed studies on this subject, but some data suggest that HRT might not increase the rate of recurrence or death.[10,11]

Women who carry *mutations of the BRCA1 and BRCA2 genes* are at greatly increased risk of breast and ovarian cancers, and prophylactic oophorectomy after child-bearing may be considered as a means of reducing this risk. The use of HRT to manage the subsequent menopausal symptoms has been controversial because of concerns that it may adversely affect the risk of breast cancer. One study[12] that used a decision analytical model concluded that HRT did not negate the benefits of oophorectomy; the degree of life expectancy loss or gain was relatively small and influenced by length of HRT use, age at oophorectomy, and presence or absence of concurrent mastectomy. The authors suggested that the decision to use short-term HRT should be based on quality of life issues rather than life expectancy, and that HRT should be stopped at or before the expected age of natural menopause. A subsequent cohort study[13] also found that the use of HRT did not negate the protective effect of prophylactic oophorectomy against breast cancer in BRCA1/2 mutation carriers. Despite these reassuring results, data are limited and further studies are needed to determine appropriate formulations and the optimal timing and duration of HRT for these women.[14]

1. Durna EM, *et al.* Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust* 2002; **177:** 347–51.
2. O'Meara ES, *et al.* Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001; **93:** 754–62.
3. Col NF, *et al.* Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001; **19:** 2357–63.
4. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet* 2004; **363:** 453–5.
5. von Schoultz E, *et al.* Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 2005; **97:** 533–5.
6. Antoine C, *et al.* Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007; **22:** 616–22.
7. Hickey M, *et al.* Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncol* 2005; **6:** 687–95.
8. Baber R, *et al.* Therapy for menopausal symptoms during and after treatment for breast cancer: safety considerations. *Drug Safety* 2005; **28:** 1085–1100.
9. Committee on Gynecologic Practice. ACOG committee opinion: hormone replacement therapy in women treated for endometrial cancer (number 235, May 2000). *Int J Gynecol Obstet* 2001; **73:** 283–4.
10. Suriano KA, *et al.* Estrogen replacement therapy in endometrial cancer patients: a matched control study. *Obstet Gynecol* 2001; **97:** 555–60.
11. Barakat RR, *et al.* Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2006; **24:** 587–92.
12. Armstrong K, *et al.* Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004; **22:** 1045–54.
13. Rebbeck TR, *et al.* Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005; **23:** 7804–10.
14. Rubinstein WS. Surgical management of BRCA1 and BRCA2 carriers: bitter choices slightly sweetened. *J Clin Oncol* 2005; **23:** 7772–4.

Porphyria. HRT should be used with caution in patients with porphyria.

Surgery. A review[1] recommended that women receiving HRT and due to have major elective surgery or leg surgery should continue taking the HRT and should routinely receive thromboprophylaxis (e.g. subcutaneous low-molecular-weight heparins and the use of graduated elastic compression stockings) in the perioperative period. Similar management was proposed when undergoing emergency surgery but prophylaxis was considered unnecessary with minor surgery. These conclusions were based on the advice of specialist groups but it was noted that there was some conflict with recommendations of manufacturers and those of the *BNF*. The *BNF* states that it may be prudent to stop HRT 4 to 6 weeks before major surgery; failing that, prophylaxis as above is recommended. HRT should only be restarted after full mobilisation.

1. Anonymous. Drugs in the peri-operative period: hormonal contraceptives and hormone replacement therapy. *Drug Ther Bull* 1999; **37:** 78–80.

Vaginal bleeding. Menopausal HRT is contra-indicated in patients with undiagnosed abnormal vaginal bleeding, which may be a symptom of endometrial carcinoma. The causes of abnormal vaginal bleeding in women receiving HRT and guidelines on their investigation and treatment have been reviewed.[1-3]

1. Good AE. Diagnostic options for assessment of postmenopausal bleeding. *Mayo Clin Proc* 1997; **72:** 345–9.
2. Spencer CP, *et al.* Management of abnormal bleeding in women receiving hormone replacement therapy. *BMJ* 1997; **315:** 37–42.
3. Oehler MK, *et al.* Assessment of abnormal bleeding in menopausal women: an update. *J Br Menopause Soc* 2003; **9:** 117–21.

Withdrawal. Although it is now generally recommended that menopausal HRT used to relieve vasomotor and vaginal symptoms should be given at the lowest effective dose for no longer than necessary (see Menopausal Disorders, p.2077), there has been little study of how to effectively withdraw HRT without a recurrence of menopausal symptoms. When the Women's Health Initiative (WHI) study was stopped prematurely, the effect of HRT withdrawal was assessed in 8405 of the women in this study who were receiving either combined HRT or placebo at the time.[1] A range of menopausal symptoms were reported in both groups. Moderate to severe vasomotor symptoms (hot flushes and night sweats) occurred in 21.2% of women who stopped HRT, compared with 4.8% stopping placebo; younger women were more likely to develop symptoms. Pain and stiffness was reported by about 37% who stopped HRT, with a similar incidence across age groups. Having these symptoms at study entry was the strongest factor for recurrence when treatment ended.

Once the WHI study was stopped, many other women were also advised, or independently chose, to stop HRT; retrospective studies in smaller groups have reported the recurrence of troublesome menopausal symptoms in 30% or more.[2-4] There also appeared to be no advantage to tapering the withdrawal of HRT, compared with stopping abruptly.[2,3] Women reported using various measures to manage recurrent menopausal symptoms,[1,3,4] including lifestyle management such as exercise and drinking more fluids, vaginal oestrogen therapy, antidepressants, and preparations such as cimicifuga (black cohosh), soya, or red clover; in some cases women restarted HRT.

1. Ockene JK, *et al.* Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005; **294:** 183–93.
2. Grady D, *et al.* Predictors of difficulty when discontinuing postmenopausal hormone therapy. *Obstet Gynecol* 2003; **102:** 1233–9.
3. Haskell SG. After the Women's Health Initiative: postmenopausal women's experiences with discontinuing estrogen replacement therapy. *J Womens Health (Larchmt)* 2004; **13:** 438–42.
4. Ness J, *et al.* Menopausal symptoms after cessation of hormone replacement therapy. *Maturitas* 2006; **53:** 356–61.

Interactions

Drugs that increase the hepatic metabolism of oestrogens and progestogens have been associated with failure of the combined oral contraceptive (see p.2067). Important examples include rifamycins, some antiepileptics, and griseofulvin. It is not unreasonable to assume that these drugs would also be associated with decreased effectiveness of HRT, but there appears to be little information on this (for one report, see Antiepileptics, below).

Although oral contraceptives alter the effects of a number of drugs (see p.2067), the lower doses of oestrogens used in HRT are considered less likely to induce interactions, although the possibility remains.

◊ A study[1] in 12 healthy women aged 20 to 25 years, using bupropion as a probe reaction, found that HRT (estradiol valerate with levonorgestrel) was an inhibitor of the cytochrome P450 isoenzyme CYP2B6.

1. Palovaara S, *et al.* Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2003; **74:** 326–33.

Alcohol. Acute ingestion of an alcoholic beverage led to a threefold increase in circulating estradiol in a study of women on menopausal HRT.[1] Another study[2] that included 309 women taking HRT found that about half had low serum-oestradiol concentrations, and that moderate alcohol consumption was one of the factors associated with achieving therapeutic concentrations.

Both alcohol consumption and HRT are risk factors for breast cancer, and cohort studies[3,4] have suggested that the risk from the combination may be higher than the individual risks alone.

1. Ginsburg ES, *et al.* Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996; **276:** 1747–51.
2. Gavaler JS. Oral hormone replacement therapy: factors that influence the estradiol concentrations achieved in a multiracial study population. *J Clin Pharmacol* 2002; **42:** 137–44.
3. Chen WY, *et al.* Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002; **137:** 798–804.
4. Zhang SM, *et al.* Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol* 2007; **165:** 667–76.

Antiepileptics. *Phenytoin* was reported to reduce the effect of conjugated oestrogens in a menopausal woman.[1]

1. Notelovitz M, *et al.* Interaction between estrogen and Dilantin in a menopausal woman. *N Engl J Med* 1981; **304:** 788–9.

Levothyroxine. Increased doses of levothyroxine may be needed in hypothyroid women who receive oestrogens for postmenopausal HRT—see p.2173.

Tacrine. HRT may increase plasma concentrations of tacrine—see p.370.

Vitamins. The effect of oral *ascorbic acid* (500 mg twice daily) on plasma concentrations of oestradiol was studied in 25 postmenopausal women stabilised on transdermal estradiol gel.[1] After 1 month, oestradiol concentrations had risen for the group overall by about 21%. The greatest responses were in those who initially had low plasma concentrations of ascorbic acid or oestradiol. The authors suggested that the antioxidant effect of ascorbic acid might reverse the oxidation of oestrogens, but that these results did not support the general use of ascorbic acid as an adjuvant to HRT.

1. Vihtamäki T, *et al.* Oral ascorbic acid increases plasma oestradiol during postmenopausal hormone replacement therapy. *Maturitas* 2002; **42:** 129–35.

Pharmacokinetics

For a discussion of the pharmacokinetics of oestrogens and progestogens, see Estradiol, p.2098 and Progesterone, p.2126, respectively. The extent of binding of progestogens to serum sex-hormone binding globulin may be altered when they are given with an oestrogen. Oestrogens increase serum concentrations of sex-hormone binding globulin, and progestogens differ in their ability to suppress this effect.

Uses and Administration

The term *hormone replacement therapy* (HRT) is often used to represent the use of an oestrogen, with or without a progestogen, in peri- and postmenopausal women. HRT is used for the management of acute menopausal symptoms such as vasomotor symptoms and atrophic vaginitis, and can be used long-term in women with premature or surgically-induced menopause until the normal age of menopause. HRT may also be used for postmenopausal osteoporosis in selected women, when other preferred drugs cannot be used or have been ineffective. The most commonly used oestrogens in menopausal HRT are natural oestrogens such as estradiol, and conjugated oestrogens. Dosages of oestrogens used in HRT are generally lower than those used in combined oral contraceptives, and do not therefore provide contraception.

Oestrogens for HRT are available as oral tablets, intranasal sprays, subcutaneous implants, topical applications for vulvovaginal use, intravaginal rings, and transdermal patches and gels. Generally, if prolonged therapy (for more than 2 to 4 weeks) with an oestrogen by any route is envisaged in a woman with an intact uterus, a progestogen is required to prevent endometrial proliferation. This may be given by mouth cyclically for 10 to 14 days per cycle or continuously; transdermal preparations that supply both oestrogen and progestogen are now also available. Both progesterone derivatives such as medroxyprogesterone and dydrogesterone, and 19-nortestosterone analogues such as norethisterone, norgestrel, and levonorgestrel are used. Doses of progestogens for HRT are similar to those used in combined oral contraceptives.

Administration. In a discussion of the relative merits of oral and transdermal oestrogen therapy[1] it was suggested that there was circumstantial and theoretical evidence to suppose that transdermal therapy might be preferable in women who smoke, who suffer from migraine, hepatobiliary disease, or hypertriglyceridaemia, or who have a history of thromboembolism. In contrast, oral HRT might be preferable in patients with hypercholesterolaemia. However, studies to examine these suppositions were needed. Although there have been further studies comparing cardiovascular risk markers in women given oral or transdermal HRT, data on clinical outcome are scarce[2] (see also Venous Thromboembolism, under Adverse Effects, above). Various alternatives to oral oestrogen therapy have been reviewed.[3-5] For reviews of estradiol given as implants or transdermally, see p.2099.

1. Lufkin EG, Ory SJ. Relative value of transdermal and oral estrogen therapy in various clinical situations. *Mayo Clin Proc* 1994; **69:** 131–5.
2. Modena MG, *et al.* New evidence regarding hormone replacement therapies is urgently required: transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas* 2005; **52:** 1–10.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, and other methods of delivery. *Obstet Gynecol Clin North Am* 1994; **21:** 271–97.
4. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; **67:** 1–12.
5. Yoo J-W, Lee CH. Drug delivery systems for hormone therapy. *J Control Release* 2006; **112:** 1–14.

Cardiovascular disorders. Observational studies have shown a decreased risk of ischaemic heart disease and consequent mortality in women receiving menopausal HRT and oestrogens are known to have some beneficial effects on the plasma lipid profile (see Effects on Lipids, above). However, results from randomised placebo-controlled studies of combined HRT for primary or secondary prevention of ischaemic heart disease have shown no overall benefit from HRT, and possibly an increased risk of coronary events (see Ischaemic Heart Disease, under Adverse Effects, above). It has therefore been recommended that HRT should not be used for prevention of cardiovascular disease.[1] Cardiovascular risk reduction, including management of blood lipids, is discussed on p.1164.

1. Mosca L, *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004; **109:** 672–93.

Dementia. Several observational studies[1-3] have suggested that oestrogens can reduce the risk and delay the onset of Alzheimer's disease (p.362) in postmenopausal women receiving HRT. However, subsequent meta-analyses[4,5] concluded that studies conducted so far had substantial methodological problems and that results were conflicting. A further observational study[6] has also reported improved global cognition, and a slower rate of decline over 3 years in women receiving HRT. This study also found[7] that previous HRT use reduced the risk of developing dementia, but that current HRT use had no effect unless it was taken for more than 10 years. In contrast, another observational study (a substudy of the Nurse's Health Study[8] including 13 807 women) found no association between HRT use and cognitive performance over 2 years, and a suggestion that long-term use or initiation at older ages may increase the risk of cognitive decline. Any apparent benefits of HRT have also been thrown into question by the results of two large controlled studies of women who received conjugated oestrogens with medroxyprogesterone, or placebo, for about 4 years. At the end of the Heart and Estrogen/Progestin Replacement Study of women with coronary disease, there was no difference in cognitive function tests between those receiving HRT or placebo.[9] In the Women's Health Initiative Memory Study of over 4000 women aged 65 years and older, HRT had no clinically significant effect on global cognitive function, but the risk of suffering a substantial decline was higher for the HRT group.[10] Also, HRT did not prevent the development of mild cognitive impairment, and actually doubled the risk of dementia.[11] The absolute risk of dementia is small, however, and this increase is equivalent to 45 cases of dementia per year for every 10 000 women taking HRT compared with 22 cases for placebo. Similar effects were found for conjugated oestrogens alone in women with a prior hysterectomy who were studied in a separate arm of the Women's Health Initiative.[12,13] Pooling of data from both the oestrogen alone and combined HRT arms of this study suggested that HRT had an adverse effect on cognition,[13] increased the risk for both dementia and mild cognitive impairment, and should not be used to prevent dementia or cognitive decline.[12] A substudy of the Women's Health Initiative examined changes in specific cognitive domains, particularly memory and affect, in 1416 women given combined HRT or placebo.[14] After an average of 4 to 5 years, combined HRT had a negative effect on verbal memory, but a trend to a positive effect on figural memory; there was no significant influence on other cognitive domains and affect.

It has been suggested that age might provide an explanation for the conflict between results of observational and controlled studies. A review that compared results from controlled studies in younger women (less than 65 years old) and older women (65 or older) found that younger women may not be at risk from oestrogen alone and may benefit in verbal memory and attention.[15] However, the reviewer noted that there were limited data available on oestrogen alone in younger women and a lack of studies of combined HRT. A case-control study[16] has also reported a reduced risk of Alzheimer's disease in younger women (50 to 63 years old), but not older women, given HRT.

Some reports[17-19] suggest that treatment with oestrogens may be of benefit in women who already have Alzheimer's disease. However, in a controlled trial in women with mild to moderate Alzheimer's disease, oestrogen replacement therapy for one year did not slow the progression of disease or improve global, cognitive, or functional outcomes.[20] Further analysis of the range of hormone concentrations measured in this study[21] found no association between plasma concentrations of estradiol and estrone, and cognitive function.

1. Tang M-X, *et al.* Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996; **348:** 429–32.
2. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med* 1996; **156:** 2213–17.
3. Kawas C, *et al.* A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997; **48:** 1517–21.
4. Yaffe K, *et al.* Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; **279:** 688–95.
5. LeBlanc ES, *et al.* Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001; **285:** 1489–99.
6. Carlson MC, *et al.* Hormone replacement therapy and reduced cognitive decline in older women: the Cache county study. *Neurology* 2001; **57:** 2210–16.
7. Zandi PP, *et al.* Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache county study. *JAMA* 2002; **288:** 2123–9.
8. Kang JH, *et al.* Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology* 2004; **63:** 101–7.
9. Grady D, *et al.* Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002; **113:** 543–8.
10. Rapp SR, *et al.* Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289:** 2663–72.
11. Shumaker SA, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289:** 2651–62.

12. Shumaker SA, *et al.* Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291:** 2947–58.
13. Espeland MA, *et al.* Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291:** 2959–68.
14. Resnick SM, *et al.* Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006; **91:** 1802–10.
15. Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci* 2005; **1052:** 182–97.
16. Henderson VW, *et al.* MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005; **76:** 103–5.
17. Ohkura T, *et al.* Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. *Dementia* 1995; **6:** 99–107.
18. Schneider LS, *et al.* Potential role for estrogen replacement in the treatment of Alzheimer's dementia. *Am J Med* 1997; **103** (suppl 3A): 46S–50S.
19. Asthana S, *et al.* High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* 2001; **57:** 605–12.
20. Mulnard RA, *et al.* Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000; **283:** 1007–15. Correction. *ibid.*; **284:** 2597.
21. Thal LJ, *et al.* Estrogen levels do not correlate with improvement in cognition. *Arch Neurol* 2003; **60:** 209–12.

Hyperparathyroidism. The effects of HRT have been studied in postmenopausal women with mild primary hyperparathyroidism (p.1087). Oestrogens have been reported to reduce the rate of bone turnover and plasma concentrations of calcium in these patients, as well as increase bone mineral density.[1-4]

1. Marcus R, *et al.* Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. *Ann Intern Med* 1984; **100:** 633–40.
2. Selby PL, Peacock M. Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. *N Engl J Med* 1986; **314:** 1481–5.
3. Grey AB, *et al.* Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism: a randomized, controlled trial. *Ann Intern Med* 1996; **125:** 360–8.
4. Orr-Walker BJ, *et al.* Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. *Arch Intern Med* 2000; **160:** 2161–6.

Menopausal disorders. The menopause (p.2071) is a natural process that occurs in women with normal ageing. For some, the only noticeable change during the perimenopause is irregular menstrual periods that eventually stop, but for others vasomotor symptoms and atrophic vaginitis can cause significant discomfort; effects vary not only between women, but also for the individual woman as she progresses through the menopausal transition. Menopausal effects can be more sudden and intense in women who have the abrupt loss of oestrogen associated with menopause induced by surgery, chemotherapy, or radiotherapy. Many reviews and guidelines have been published on management of the menopause including the use of HRT.

Acute menopausal symptoms. There are a number of strategies that may be tried for the management of acute menopausal symptoms.

- In postmenopausal women with only *vaginal symptoms*, non-hormonal vaginal lubricants and moisturisers can be tried first.[1] If these are inadequate, locally-acting vaginal oestrogen therapy may be effective;[1,2] improvement typically occurs within a few weeks, but may take 4 to 6 weeks. Oestrogen therapy may continue for as long as required for symptomatic relief, but data on the effects of long-term use are lacking.[1] Systemic exposure from vaginal preparations is believed to be limited, and the addition of a progestogen to protect against endometrial hyperplasia in women with a uterus is generally not indicated when low-dose local oestrogen therapy is used.[1] Nevertheless, studies have reported cases of endometrial hyperplasia and overstimulation; a systematic review found that there were insufficient data to confirm whether a progestogen should be given when vaginal oestrogens are used for more than 6 months.[2] Women using a cream may be at higher risk of systemic absorption since dosing relies on the amount of cream measured by the woman, which may be variable compared with vaginal tablets. (Some vaginal preparations are designed to deliver sufficient systemic oestrogen to treat vasomotor symptoms—see below.)
- Mild *vasomotor symptoms* may be adequately managed with lifestyle changes such as maintaining a lower core body temperature, physical activity, and relaxation techniques.[3] Moderate to severe symptoms can be controlled with HRT,[3-9] usually given orally or transdermally; some vaginal rings also deliver sufficient oestrogen to the circulation to treat vasomotor symptoms. The lowest dose that controls symptoms is given short term, generally for no more than 5 years. Women without a uterus, and who have not had endometriosis, may receive continuous oestrogen alone.[6,7] Women with a uterus should also receive a progestogen to reduce the risk of endometrial hyperplasia and cancer associated with unopposed oestrogen therapy[3,4,6,9] (for a discussion of the risks of endometrial cancer with HRT, see under Adverse Effects, above). In women who are postmenopausal (more than 12 months) continuous combined HRT may be used.[7] However, continuous combined HRT can cause irregular bleeding in perimenopausal women, so they are usually given a cyclical progestogen orally or transdermally, which will cause regular withdrawal bleeding; an alternative is the levonorgestrel intrauterine device. Vaginal progesterone or oral long-cycle regimens (progestogen for 12 to 14 days every 3 to 6 months) have been used to reduce adverse effects, but it is not clear that these provide adequate endometrial protection.[9]

  Perimenopausal women are still potentially fertile and HRT does not provide contraception. It is now considered that women free of all risk factors for venous and arterial disease may use a low-dose combined oral contraceptive (p.2069) to provide both relief of menopausal symptoms and contraception.[3] However, it is recommended that they should stop the oral contraceptive at the age of 50, so that the menstrual cycle and menopausal status can be assessed. Non-hormonal contraceptives or the progestogen-only oral contraceptive (see p.2070) may be used if contraception is required in perimenopausal women using HRT, and continued to the age of 55 when natural sterility can be assumed.[10]

  Alternative hormonal therapies for vasomotor symptoms include the progestogens megestrol and medroxyprogesterone.[3,6,11] Tibolone, which has oestrogenic, progestogenic, and androgenic properties, is another option for postmenopausal women.[4,7,12,13]

  Non-hormonal therapies have also been tried although evidence for the efficacy of these is less conclusive than that for HRT.[3,6,11,14] The antidepressants fluoxetine, paroxetine, and venlafaxine have shown some benefit in small trials, and low doses of gabapentin have been reported to be effective. Clonidine or veralipride may be considered when HRT is not suitable, but the use of these can be limited by adverse effects. Other therapies have been used to manage vasomotor symptoms based on anecdotal reports of benefit, but they have generally not been effective when studied in placebo-controlled trials. These include isoflavones from soya or red clover, evening primrose oil, cimicifuga (black cohosh), *Angelica sinensis* (dong quai), and vitamin E.
- *Non-specific symptoms* may also improve in women given HRT, but good evidence is somewhat scanty and HRT should not be used solely for these indications. Oestrogens might reduce recurrent urinary-tract infections in susceptible women,[7] but incontinence can worsen (see below). Many women report improved mood and well-being when given oestrogens, although it is unclear to what extent this is due to relief of other symptoms. Two large controlled studies[15,16] have found that combined HRT improved some quality of life measures in postmenopausal women with vasomotor symptoms, but that asymptomatic women in general received no benefit. There is insufficient evidence to support the use of oestrogen, alone or in combined HRT, for the treatment of depression.[9] Moreover, the addition of progestogens carries some risk of adverse effects on mood such as depression, anxiety, and irritability. Androgens such as testosterone are sometimes used as adjuncts to HRT to improve psychological well-being and libido,[17] particularly in women with surgically-induced menopause.[6]

Initiation of HRT. There is increasing discussion about when to start HRT, as the timing of treatment after menopause seems to relate to long-term health outcomes. There has been interest particularly in how the effect of HRT on ischaemic heart disease might be affected by age, considering that many women who took part in studies of HRT were older than those who generally take HRT for vasomotor symptoms in their 50s (see Ischaemic Heart Disease under Effects on the Cardiovascular System, above). The benefit-risk ratio is more likely to be acceptable for short-term symptomatic management in younger women around the age of typical natural menopause (about 51 years). It is also now generally advised that, unless there is a compelling indication, HRT should not be started in women older than 60 who have had a natural menopause at the typical age because they will usually have higher baseline risks of cardiovascular disease and breast cancer.[9] It is also generally agreed that all women who have had a *premature natural or induced menopause* should be offered HRT or a combined oral contraceptive until about 50 years of age, unless there are specific contra-indications to therapy. These women may need higher doses of HRT than those normally used to control vasomotor symptoms. Adjunctive androgen therapy may also be considered, particularly in oophorectomised women.[18] Considerations as to how long they need to continue HRT after the usual age for the menopause are probably the same as for other women.

Long-term use of HRT. There are extensive data from observational studies on the beneficial effects on fracture rates and cardiovascular disease, on the risks for development of breast cancer and endometrial cancer, and on the possible effects on overall mortality. However, the women receiving HRT in these studies may differ from women not receiving HRT, and the extent of any bias resulting from this is unclear.[19] Randomised prospective studies have confirmed the increased risk of breast cancer, venous thromboembolism, stroke, and dementia associated with combined HRT (see under Adverse Effects, above). Contrary to the anticipated benefits for preventing ischaemic heart disease, these studies also found an increase in coronary events, and such use is now not recommended (see Cardiovascular Disorders, above). These results have led to recommendations that HRT should not be used long term solely for the prevention of chronic disease in generally healthy postmenopausal women.[6,20,21] However, although other treatments are now preferred for the prevention and treatment of osteoporosis (p.1084), long-term HRT may be suitable for some women (see also below).

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Osteoporosis. Oestrogens may be used in selected patients for the treatment and prevention of postmenopausal osteoporosis (p.1084). They have a direct antiresorptive effect on bone, and will increase bone mass density (BMD). However, data from the Heart and Estrogen/Progestin Replacement Study (HERS) have called into question the benefit of HRT in reducing the incidence of fractures.[1,2] A meta-analysis[3] including the initial HERS data,[1] most of which were from women without osteoporosis, consequently found only non-significant reduction in fracture risk in older women although overall the risk of fracture was reduced by between 20 and 30%. Subsequent results from the Women's Health Initiative[4] showed that, contrary to the results of this meta-analysis, combined HRT did reduce the risk of fracture in healthy postmenopausal women. Similarly, cohort data from 138 737 women in the Million Women Study[5] showed that current use of HRT reduced fracture risk, but that this protection wore off rapidly after stopping HRT. Other studies have also reported that protection against loss of bone mineral density[6] and fracture[7] is not retained after stopping HRT.

Despite the probable benefits, there is substantial evidence to show that HRT is associated with an increased risk of cancer, particularly breast cancer (see Breast under Carcinogenicity, above), and some cardiovascular diseases such as stroke and venous thromboembolism (see Effects on the Cardiovascular System, above). It is now generally recommended by authorities, such as the UK CSM,[8] that the risk to benefit ratio of HRT is unfavourable for the prevention of osteoporosis as first-line therapy, and that it should not be used in this way for women over 50 years of age. HRT does, however, remain an option when other osteoporosis prevention therapies are unsuitable. Younger women who have experienced premature menopause may be given HRT for menopausal symptoms and to prevent osteoporosis until the age of 50, after which its use should be reviewed and considered a second-line choice.

Suggested minimum daily doses are 625 micrograms of oral conjugated oestrogens, 2 mg of oral estradiol or 50 micrograms transdermally, and 15 micrograms of oral ethinylestradiol; lower doses may also be effective,[9-15] and a transdermal patch supplying 14 micrograms of estradiol daily is licensed for the prevention of osteoporosis in the USA. Addition of a progestogen (required to prevent endometrial hyperplasia in women with a uterus) does not impair the beneficial effect of oestrogens on BMD, whether given cyclically or continuously,[16,17] and may provide a further reduction in risk of fractures.[18] Although current, long-term use of HRT can increase BMD and reduce fracture risk, unresolved issues are the duration of therapy required to prevent fractures in old age, and the ideal age to start therapy to obtain the maximum benefits to the bone with the minimum risk of breast cancer.[18-20]

Oestrogens may also be used in women to reduce the risk of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p.1491).

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Urinary incontinence. Urinary incontinence (p.2180) may be one of a number of acute symptoms associated with a decline in oestrogen levels at the menopause (see Menopausal Disorders, above). Studies[1,2] suggest that oestrogens used with alpha-adrenoceptor agonists are effective in the management of female stress incontinence and this combination has been advocated for use in postmenopausal patients with mild symptoms. Unfortunately addition of a progestogen to treatment to reduce the risk of endometrial carcinoma in women with an intact uterus might exacerbate the incontinence.[3] The value of oestrogens used without an alpha-adrenoceptor agonist in urinary incontinence is less clear. One study[4] reported that oestrogen therapy and pelvic floor exercises for 18 months was more effective than exercises alone in women with mild stress incontinence. However, a placebo-controlled study[5] found no improvement after 6 months of oestrogen therapy.

Some consider that oestrogens may be of use for symptoms of urgency, frequency, and nocturia in postmenopausal patients with urge incontinence, particularly if given locally;[6] it has been suggested that hypoestrogenism may reduce the sensory threshold of the bladder.[7] A meta-analysis of 23 studies concluded that oestrogen therapy subjectively improved urinary incontinence in postmenopausal women but many of the studies examined were considered to be deficient in some respect.[8] Later well-designed studies[9,10] of women with stress, urge, or mixed incontinence found that HRT did not improve, or even worsened, measures of incontinence, although there was the possibility that concomitant progestogen therapy might have affected efficacy. Furthermore, the placebo-controlled Women's Health Initiative[11] found that both oestrogen alone and combination HRT increased the overall risk of developing stress, urge, or mixed incontinence, and worsened incontinence in women who were symptomatic before starting HRT. Another placebo-controlled study[12] also found that combination HRT increased the risk of developing stress or urge incontinence, and the large Nurses' Health Study cohort reported[13] that the current use of HRT increased the risk of developing urinary incontinence.

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Gonad-regulating Hormones

The Hypothalamic-Pituitary-Gonadal Axis

The regulation of sexual function involves the so-called hypothalamic-pituitary-gonadal axis.

The pituitary gland or hypophysis is composed in humans of 2 parts, the anterior lobe or adenohypophysis, and the posterior lobe (neurohypophysis) and neural stalk, above which lies the hypothalamus. Both parts of the pituitary secrete hormones: posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve fibres to the pituitary where they are stored until required, whereas anterior pituitary hormones are synthesised *in situ* by specialised cells, but are subject to complex hormonal control by hypothalamic regulatory hormones and target organ hormones, as well as excitatory and inhibitory impulses from the brain. These interacting systems are collectively known as the hypothalamic-pituitary-endocrine axes.

The anterior pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) are collectively known as **gonadotrophic hormones** or gonadotrophins. They are glycoproteins secreted by specialised pituitary cells (gonadotropes) that stimulate gonadal function and sex hormone production. In men, LH stimulates the synthesis of testosterone and other androgens, while in women, FSH and LH regulate production of oestradiol and synthesis of progesterone in a complex and interacting manner. A third substance with gonadotrophic (primarily luteinising) actions, chorionic gonadotrophin, is secreted by the placenta.

The synthesis and secretion of pituitary gonadotrophic hormones is in turn stimulated by a hypothalamic releasing hormone, **gonadotrophin-releasing hormone** (GnRH). In post-pubertal subjects, GnRH is secreted from the hypothalamus at regular intervals determined by an internal 'clock' or neuronal pulse generator in the arcuate nucleus, and enters the blood of the portal vascular system that links the hypothalamus to the anterior pituitary. This results in pulsatile release of the gonadotrophic hormones, which is essential for normal gonadal function. More prolonged and continuous exposure to GnRH leads to desensitisation and downregulation of its receptors on pituitary gonadotropes, and hence, after an initial surge, to suppression of gonadotrophic hormone secretion.

The sex hormones themselves produce negative feedback effects at both hypothalamic and pituitary levels. In general, both oestrogen and progesterone reduce the amplitude (i.e. the amount) of gonadotrophic hormone released; progesterone also reduces the frequency of the pulses. Testosterone is thought to act by conversion to oestrogen via aromatase, although it also has some direct action. The gonads also produce a hormone, inhibin, that selectively inhibits FSH secretion from the pituitary without affecting LH, and its biological opposite, activin, which stimulates pituitary FSH secretion.

Types of Gonad-regulating Hormone

Gonad-regulating hormones in clinical use may be divided into 3 major groups.

- Endogenous follicle-stimulating and luteinising hormones are available from urinary sources as human menopausal gonadotrophins or menotrophin (p.2109) and as urofollitropin (p.2136), and in recombinant forms such as follitropins alfa and beta (p.2104) and lutropin alfa (p.2112). Chorionic gonadotrophin and its recombinant form choriogonadotropin alfa (p.2085) are also used.
- The hypothalamic releasing hormone gonadorelin (p.2106), and its longer-acting analogues such as buserelin (p.2083), deslorelin (p.2093), goserelin (p.2108), histrelin (p.2109), leuprorelin (p.2111), nafarelin (p.2117), and triptorelin (p.2135) are widely used to stimulate or inhibit the hypothalamic-pituitary-gonadal axis.
- More recently, direct gonadotrophin-releasing hormone antagonists have become available, such as abarelix (p.2081), cetrorelix (p.2084), and ganirelix (p.2105).

Use of Gonad-regulating Hormones

The gonad-regulating hormones play an important role in the management of a number of endocrine disorders, as discussed in the reviews below and elsewhere in this chapter. They also play an important role in the management of endocrine-sensitive malignant neoplasms (see p.643).

Amenorrhoea

Amenorrhoea is the absence of menstruation: a break in menstruation of 6 months or more is considered pathological in an adult woman who is not pregnant, lactating, or menopausal. Amenorrhoea occurring from the time of puberty is known as primary, while amenorrhoea developing later in life is referred to as secondary. Pathological amenorrhoea is usually associated with infertility (see also below). Hirsutism (p.2089) may also be present.

The causes of amenorrhoea (or oligomenorrhoea—infrequent and erratic periods) are most often ovarian or hypothalamic/pituitary in origin. Ovarian causes include failure of normal gonadal development, as in Turner's syndrome (below); premature ovarian failure including that due to trauma, drugs, radiotherapy, or autoimmunity; and conditions such as the polycystic ovary syndrome (below). Hypothalamic or pituitary causes include reduced production of gonadotrophins due to inadequate nutrition, excessive exercise, or pituitary trauma (see also Hypogonadism, below); or excess prolactin production (see Hyperprolactinaemia, below). Other causes, including adrenal disorders, thyroid disorders, abnormalities of the vagina or uterus, or testicular feminisation, may be found rarely.

The management of amenorrhoea essentially involves the identification of any underlying disorder and its correction, if possible. When the cause cannot be corrected, oestrogen replacement therapy, usually in the form of an oral contraceptive, is appropriate to minimise the consequences of long-term oestrogen deficiency.

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Cryptorchidism

The testes are formed within the abdomen and subsequently descend the inguinal canal to the scrotum. Failure of the testes to descend (cryptorchidism) occurs in about 3 to 6% of newborn males but in many the testes descend during the first year of life decreasing the prevalence to about 1%. In children with cryptorchidism, pathological testicular damage has been noted by the age of 1 year, and may result in subsequent infertility; cryptorchidism also significantly increases the risk of testicular cancer. Abnormalities of the testes and anatomical abnormalities such as inguinal hernia may contribute to maldescent, and both primary testicular disease and gonadotrophin deficiency may be associated with cryptorchidism. For discussions of Hypogonadism and Infertility, see below. Cryptorchidism should be distinguished from retractile testes in which the testes develop normally and for which treatment is usually not required.

Although cryptorchidism is common, there is no consensus on the best treatment: surgery is commonly used in the USA whereas primary hormonal treatment is more popular in Europe.[1,2]

Surgery is successful in almost all cases, and is usually undertaken at around 1 year of age.[1,2] Primary hormonal therapy generally uses chorionic gonadotrophin or a gonadorelin analogue to stimulate androgen production. Success rates vary but reports are difficult to compare because of differences in patient age and treatment regimens, and the possible inclusion of retractile testes. Systematic reviews[3,4] suggest that gonadorelin and chorionic gonadotrophin are more effective than placebo with a success rate of about 20% overall, although this may be considerably lower if care is taken to exclude retractile testes. The lower the position of the undescended testis, the more likely benefit from hormonal therapy appears to be.[3,5] Treatment may also be less successful as boys grow older, and treatment before 12 to 18 months[6] or 2 years of age[4] has been recommended. Some reports suggest that results may be improved by combined therapy with gonadorelin and chorionic gonadotrophin,[7] but others have found no advantage over single drug therapy.[8,9] Surgery is used second-line when hormonal treatment is unsuccessful. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[6] Chorionic gonadotrophin may also be useful as an adjuvant before surgery, in order to cause a non-palpable testis to become palpable;[10] however, changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Even after successful treatment, however, there may still be impaired fertility. Similarly, the risk of testicular cancer is not necessarily reduced, but orchidopexy does enable early detection and all patients should be monitored.[1,2]

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Delayed puberty

The onset of puberty is associated with an increase in the secretion of luteinising hormone. There is a subsequent increase in concentrations of sex hormones, the development of secondary sexual characteristics, and an associated growth spurt. Delayed puberty is diagnosed when there is no breast development by 13.4 years of age in girls, and no testicular enlargement by 14 in boys. In addition to the various causes of hypogonadism (see below), some of which may be difficult to diagnose, severe systemic illness such as asthma or diabetes, or hypothyroidism, may cause delay in sexual maturation. Where no apparent cause can be found a family history of delayed maturation may suggest constitutional delayed puberty, in which normal pubertal development can eventually be expected.

Where pubertal delay is secondary to some other condition appropriate management of the precipitating cause is required. In constitutional delayed puberty small doses of oestrogens in girls, or androgens (such as oxandrolone or a testosterone ester) in boys, may be given to promote growth and sexual development if psychological problems are apparent. Care is required as overly aggressive therapy with sex hormones may lead to premature closure of the epiphyses and compromise final adult height. Treatment should be interrupted periodically to see if spontaneous pubertal development has begun. The use of chorionic gonadotrophin or a gonadorelin analogue has no advantage in such patients, although they have a role in hypogonadotrophic hypogonadism, which may be difficult to distinguish from constitutional delay.

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Endometriosis

Gonadorelin analogues are used in the management of endometriosis (see p.2091) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy, with concomitant hormone replacement, can be used to prevent this.

Hyperprolactinaemia

Hyperprolactinaemia is a condition of elevated circulating prolactin concentrations. It occurs for physiological reasons in pregnancy or after mechanical stimulation of the nipple, as in suckling. However, hyperprolactinaemia may also be an adverse effect of drugs that inhibit dopaminergic function, such as antipsychotics and metoclopramide; other drugs causing hyperprolactinaemia include opioid analgesics, methyldopa, reserpine, oestrogens, SSRIs, and verapamil. Furthermore, pathological hyperprolactinaemia may be associated with prolactin-secreting pituitary adenomas (prolactinomas), damage to the pituitary stalk or hypothalamus (including that caused by non-secreting tumours), or trauma to the chest wall; it may also be associated with disorders such as Cushing's syndrome or hypothyroidism. Prolactinomas are amongst the commonest pathological causes, and so-called idiopathic hyperprolactinaemia, in which no apparent cause is found, may in fact represent undetected microadenoma.

The consequences of hyperprolactinaemia include suppression of ovarian function in women, leading to erratic cycles or amenorrhoea, and infertility (see also above and below respectively); in men, in whom the condition is less common, reduced gonadotrophin production leads to testosterone deficiency, diminished libido, and impotence. Both sexes may develop unwanted milk flow (galactorrhoea), although this also requires the presence of oestrogens; men may rarely develop gynaecomastia (p.2092) due to the change in oestrogen/androgen balance.

Management of hyperprolactinaemia depends on its cause. Pathological hyperprolactinaemia must be distinguished from physiological, and where it is secondary to another disease this should be managed appropriately; any drug thought likely to be causative should be withdrawn if possible. Some patients are asymptomatic, or are untroubled by their symptoms; whether such patients should be treated has been a matter of some controversy, although the risk of osteoporosis in women with prolonged suppression of ovarian function has been cited as a reason for such treatment.[1]

In many cases hyperprolactinaemia will be secondary to a prolactinoma. These are generally classified as microadenomas (less than 10 mm in size) or macroadenomas (over 10 mm in size); macroadenomas are often associated with prolactin concentrations more than 10 times the normal upper limit and their rapid expansion may result in visual defects and headache. Initially a course of treatment with a dopamine agonist such as bromocriptine, while rarely curative, is extremely effective in controlling hyperprolactinaemia and restoring gonadal function.[2,3] Surgical removal is now rarely indicated, although transsphenoidal decompression may be necessary for macroadenomas despite bromocriptine therapy, and ultimately radiotherapy may also be required.

The most extensively used dopamine agonist is bromocriptine; it decreases prolactin secretion and reduces tumour size in the majority of patients.[2] There are reports of maintained normoprolactinaemia and reduced tumour size when bromocriptine has been withdrawn after about 2 to 4 years of treatment.[4] However, this occurs in only a minority of patients, and macroadenomas in particular can re-expand, sometimes rapidly, when treatment is stopped.[2] It has been suggested[3] that when the prolactin concentration has been normal for 2 years and the tumour has decreased by at least 50%, the dose of bromocriptine can be gradually reduced, with close follow-up to detect tumour enlargement. The short half-life and the adverse effects of bromocriptine may pose problems, although depot formulations can minimise these. Giving oral prednisolone with intramuscular depot bromocriptine has been reported to reduce the incidence of adverse effects.[5]

Treatment of hyperprolactinaemia restores ovulation in the majority of female patients. In those who become pregnant it is generally advised that fetal exposure to the dopamine agonist should be as short as possible, and therefore stopped when pregnancy is confirmed. Bromocriptine is the drug of choice for patients who are planning pregnancy, because most experience exists with its use compared with other dopamine agonists. The hyperoestrogenic state of pregnancy itself can stimulate prolactinoma growth and patients must be carefully monitored throughout gestation. If symptomatic tumour growth occurs, bromocriptine may be restarted, which is probably less harmful to the mother and fetus than surgery. Surgical debulking before pregnancy has been advocated by some, but may not prevent symptomatic tumour enlargement during pregnancy.[2,6]

Alternative dopaminergic treatments include cabergoline and quinagolide.[2,7] Cabergoline appears to be more effective, and better tolerated, than bromocriptine, and can also be effective in patients who do not respond to bromocriptine. It is considered by some to be a first-line alternative, although bromocriptine is favoured in women who wish to become pregnant. Quinagolide appears to be of similar efficacy to bromocriptine, and may be useful in patients intolerant of or unresponsive to other drugs. Pergolide has also been tried, with similar efficacy to bromocriptine, but it is not licensed for such use.

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Hypogonadism

Hypogonadism (decreased or absent gonadal function) may occur in both men and women, and may be either primary, due to some dysfunction of the gonads themselves, or secondary, due to hypopituitarism or some other cause of decreased gonadotrophic stimulation.

Primary ovarian dysfunction may be due to failure of the ovaries to form normally, as in Turner's syndrome (see below), or their degeneration before puberty; there may be premature failure, effectively an early menopause, due to low initial follicle numbers or to destruction of follicles by autoantibodies, chemotherapy, radiotherapy, infection, or trauma. Primary testicular dysfunction may be due to congenital disorders such as Klinefelter's syndrome (associated with an XXY chromosome constitution); the effects of chemotherapy, radiotherapy, infections (particularly mumps), or trauma; and a few other conditions such as testicular degeneration.

Secondary hypogonadism may be due to general hypopituitarism, or to a specific deficiency of gonadotrophin production, or gonadorelin production. Kallmann's syndrome is a congenital disorder of hypogonadotrophic hypogonadism due to gonadorelin deficiency associated with anosmia or hyposmia. The causes of pituitary or hypothalamic failure include neoplasms, radiotherapy to the head and neck, trauma, or infiltrative granulomatous diseases such as tuberculosis. Gonadotrophin production may also be suppressed by various drugs (notably exogenous sex steroids and continuous, rather than pulsatile, use of gonadorelin analogues), by weight loss or inadequate nutrition, by excessive exercise, by severe systemic illness, and by hyperprolactinaemia (see above).

The fundamental treatment for primary hypogonadism is replacement therapy with sex hormones to produce appropriate sexual development and activity and counteract effects such as osteoporosis, but fertility cannot usually be restored. In prepubertal children, the induction of secondary sexual characteristics must be balanced against a possible reduction in final height due to premature closure of the bone epiphyses. Women are generally given an oestrogen with a progestogen, and men are treated with androgens, often in the form of a long-acting testosterone ester such as the cipionate or enantate given intramuscularly. Transdermal testosterone is also effective.

The cause of secondary hypogonadism should be determined and managed appropriately if possible. In some cases this may be adequate to restore gonadal function but in other cases sex hormone replacement therapy as in primary hypogonadism will be required. Where there is no fundamental defect in gonadal function the possibility of using a gonadotrophic hormone or stimulating the release of gonadotrophins also exists. In general, however, such therapy is often reserved for attempts to restore fertility (see under Infertility, below), since it is inconvenient and expensive.

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Infertility

Although about one couple in 6 may experience sufficient difficulty in conceiving children to seek medical help, most are subfertile rather than infertile, and may eventually conceive, with or without treatment. A number of possible treatments are available, but which is used depends upon the cause of the problem. Reduced fertility can have its origins in the male or the female partner or may be due to a combination of factors from both.

The most obvious cause of infertility is a failure of either ovulation in the female or spermatogenesis in the male. Such failures may be due to damage or abnormal formation of the gonads, a failure of hypothalamic/pituitary stimulation, abnormal feedback as in the polycystic ovary syndrome, or suppression of gonadal function as in hyperprolactinaemia. These conditions and their management are briefly discussed under Hypogonadism (above), Polycystic Ovary Syndrome (PCOS; below), and Hyperprolactinaemia (above).

Female factors. The primary problem in about 20% of infertile women is ovulatory dysfunction, and most of these women will have PCOS. *Clomifene* is often used first-line to stimulate ovulation in women with hypothalamic dysfunction, as in PCOS,[1-4] and has been reported to produce ovulation in about 70% of anovulatory women. Women with PCOS who do not respond to clomifene may be treated with ovarian drilling (laparoscopic diathermy).[2,4] Those who do ovulate with clomifene but have not become pregnant within 6 months may be offered intra-uterine insemination in addition to clomifene.[4] In overweight women with PCOS, metformin may be added when clomifene alone has not been effective.[1-4] The addition of a mid-cycle injection of chorionic gonadotrophin has also been tried for women who fail to ovulate with clomifene,[1] and to define the optimal time for intra-uterine insemination,[2] but such a regimen has not been proven to be better. Some women with clomifene-resistant anovulation may benefit from the sequential use of clomifene and a gonadotrophin that has follicle-stimulating activity.[2] In women with elevated dehydroepiandrosterone concentrations, the addition of a corticosteroid to clomifene may improve the ovulation rate.[1,2] Because of concerns about a possibly increased risk of ovarian cancer, opinion varies as to the maximum number of cycles for which clomifene should be used, but is usually either 6 or 12 cycles (see Carcinogenicity, p.2086). *Tamoxifen* is an alternative in those who cannot tolerate clomifene.[3,4] Aromatase inhibitors such as *letrozole* have also been tried, and seem to be at least as effective as clomifene in inducing ovulation,[5] although concerns about the potential for maternal or fetal toxicity remain to be assuaged.

Gonadotrophins with follicle-stimulating activity can be given directly to women with PCOS who have not ovulated with clomifene or tamoxifen; human menopausal gonadotrophin, urofollitropin, and recombinant follicle-stimulating hormone are considered to be equally effective.[4] Women with hypothalamic anovulation or hypogonadotrophic hypogonadism generally require gonadotrophins that also have luteinising hormone activity, because of low endogenous levels.[4,6] There is growing interest in the use of recombinant luteinising hormone in these patients.[6] Various regimens have been used but in general, follicle-stimulating hormone is given until a dominant follicle is suitably mature, and then chorionic gonadotrophin is given to trigger ovulation and provide luteal support.[6] The risks of ovarian hyperstimulation syndrome and multiple pregnancies are considerable however, particularly in PCOS, and close monitoring is mandatory using ovarian ultrasound to assess follicle development.[3,4]

Another method used for anovulation is pulsatile *gonadorelin*[4] (gonadotrophin-releasing hormone) or its analogues. It is primarily indicated in women with hypothalamic causes of anovulation; it is less effective in women with PCOS than in hypogonadotrophic patients.

Where anovulation is secondary to hyperprolactinaemia treatment with dopamine agonists such as bromocriptine can restore fertility (see Hyperprolactinaemia, above).

Where infertility is due to obstruction of the fallopian tubes or intra-uterine adhesions, surgery may be effective for some women.[4] Where infection is the cause, appropriate anti-infective agents may be useful. (See also under Pelvic Inflammatory Disease, p.184.)

Endometriosis (p.2091) is another important cause of infertility in women, although the reason for the association is not fully understood. Medical treatment of endometriosis does not enhance fertility, although conservative surgery may do so.[4]

In the absence of the above disorders and when infertility is otherwise unexplained the UK guidelines[4] indicate that treatment with clomifene should be offered.

Various other drugs have been used, on a more or less empirical basis. Growth hormone or one of its analogues has been used as an adjunct to ovarian stimulation with gonadotrophins but is not considered to improve pregnancy rates.[4]

Assisted reproduction may be considered when other methods fail. IVF is the most commonly used technique, in which oocytes are retrieved from the ovaries, fertilised *in vitro*, and resulting embryos are selected for transfer to the uterus. Less common techniques include transfer into a fallopian tube of gametes (an unfertilised egg and sperm) or a zygote (fertilised egg). Unlike ovulation induction described above, assisted reproduction techniques intentionally use ovarian hyperstimulation regimens to produce multiple oocytes for retrieval; women are therefore at risk of the ovarian hyperstimulation syndrome and should be monitored appropriately. Women with risk factors for ovarian hyperstimulation syndrome, such as those with PCOS, should not be given chorionic gonadotrophin for oocyte maturation or luteal support.[4] The most commonly used regimens are the 'long protocols' in which a gonadorelin agonist is started in the midluteal phase of the menstrual cycle to desensitise the pituitary and prevent a premature surge of luteinising hormone. When pituitary and ovulation suppression has been achieved, gonadotrophins (human menopausal gonadotrophins or follicle-stimulating hormone) are given to stimulate follicle production. At the appropriate stage of follicular development, a single dose of chorionic gonadotrophin is given to trigger ovulation. These 'long protocols' appear to give better results than short ('flare-up') or ultrashort regimens, in which gonadorelin agonists are given for less time, although short regimens may be useful in poor responders.[6] Meta-analysis indicates that recombinant follicle-stimulating hormone, urofollitropin, and human menopausal gonadotrophins are equally effective.[4] *Gonadorelin antagonists*, such as cetrorelix and ganirelix, have been used as an alternative to gonadorelin agonists. Pituitary desensitisation occurs more rapidly and shorter treatment regimens are used, but they may be associated with reduced pregnancy rates.[4,6,7] *Progesterone* is the preferred drug for luteal support for IVF procedures because of the increased likelihood of ovarian hyperstimulation syndrome with chorionic gonadotrophin.[4]

Male factors. Impaired male fertility may result from urogenital abnormalities, infections of the genital tract, increased scrotal temperature associated with varicocele, endocrine disturbances, genetic abnormalities, and immunological factors, but around 70% of cases may be idiopathic, where no causal factor is found.[8] Some forms of obstructive azoospermia can be corrected surgically. Varicocele repair with surgery or percutaneous embolisation may be considered in some men but the effects on fertility outcome are unclear.[8-10]

In men with hypogonadotrophic hypogonadism, replacement therapy with a gonadotrophin that has luteinising hormone activity, such as chorionic gonadotrophin, is given to stimulate testosterone production. Menopausal gonadotrophins, or the more specific follicle-stimulating hormone, are then added to stimulate spermatogenesis.[8,9] Spermatozoa may appear in the ejaculate after about 6 to 9 months of treatment, but may take considerably longer in some men.[9] Pulsatile gonadorelin may restore gonadotrophin secretion and correct infertility in men with hypogonadotrophic hypogonadism of hypothalamic origin, such as those with Kallmann's syndrome;[8,9] therapy for 1 to 2 years may be necessary to achieve adequate sperm production in some patients who have not previously received gonadotrophins or gonadorelin.[8]

In idiopathic oligospermia, results of drug therapy have been disappointing. Studies of gonadorelin have produced contradictory results and gonadotrophins have not been effective.[8] The antioestrogens, clomifene and tamoxifen, have been used in subfertile men,[9] but there is limited convincing evidence of benefit.[4,8] Corticosteroids have been used in men with autoantibodies to spermatozoa, but efficacy is unproven and corticosteroids are generally not recommended[4,8,9] although they might be considered in men with autoantibodies who have failed assisted reproduction techniques.[9] However, corticosteroids may have a beneficial effect on infertility associated with auto-immune orchitis.[9] Various other drugs have been used on an empirical basis for idiopathic male infertility but evidence for their efficacy is either limited or lacking.[8,9]

When other methods fail, assisted reproduction may be considered. Techniques for male infertility include intra-uterine insemination and intracytoplasmic sperm injection.[4,8-10]

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Polycystic ovary syndrome

The polycystic ovary syndrome comprises enlargement of the ovaries with multiple follicular cysts and a thickened, whitish, capsule; there is persistent elevation of serum luteinising hormone concentrations, with a tendency to increased androgen concentrations. Women typically present with erratic menstruation, hirsutism, and obesity, although not all these features may be present; fertility is often impaired. Associated metabolic changes include hyperinsulinaemia with insulin resistance, and increased risk of developing hyperlipidaemia, hypertension, and ischaemic heart disease. The risk of endometrial cancer is also increased.

Management is essentially symptomatic. Patients should be encouraged to modify their lifestyle, to correct lipid abnormalities, and to lose weight if obese;[1,2] weight loss alone may be sufficient to improve menstrual regularity, hirsutism, and fertility. Symptoms of hyperandrogenism can be treated with an anti-androgen, such as cyproterone acetate or spironolactone, with an oestrogen or a combined contraceptive pill.[1-5] Flutamide and finasteride have also been used in these patients (see also the discussion of the management of hirsutism, p.2089).[5] In women who do not desire pregnancy, an oral contraceptive is also the recommended treatment for amenorrhoea or oligomenorrhoea.[2,5-7] Alternatively a progestogen that lacks androgenic properties may be given cyclically, in order to induce withdrawal bleeding (anovular women who do not receive hormonal treatment may be at increased risk of endometrial cancer).[3,6,7] Metformin may also improve metabolic abnormalities and menstrual regularity (see also below), and endocrinologists in the USA have suggested that it may be considered particularly for women who are overweight or obese.[1] However, other practitioners have argued that weight reduction is more effective and should be the initial management for obese women with polycystic ovary syndrome.[2]

In patients who wish to conceive, clomifene citrate is used to induce ovulation. In patients who do not respond, gonadotrophins or laparoscopic ovarian diathermy may be tried. The effects of metformin on ovulation induction are also under investigation (see below).[2,3,6,7] Patients must be monitored carefully during any therapy to induce ovulation, as women with polycystic ovaries are more prone to multiple follicle development and ovarian hyperstimulation. For further details on ovulation induction and assisted reproduction, see Infertility, above.

Insulin resistance is a feature of polycystic ovary syndrome, particularly in obese women. Small non-randomised studies of metformin have reported improvements in insulin metabolism, a reduction in circulating androgen concentrations, small reductions in body-mass index or waist/hip ratio, and improvements in menstrual cycles.[8] Previous controlled studies have found that metformin alone improved ovulation rates and menstrual cycles, and that rates could be improved further when given with clomifene citrate.[8,9] However, more recently, 2 large, placebo-controlled studies have found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[2] Metformin may also improve responses to ovulation induction using follicle-stimulating hormone.[8] Long-term effects of metformin in polycystic ovary syndrome have not been studied, however, and any reduction in cardiovascular risks is yet to be established.[10] There has also been some interest in the use of thiazolidinediones, such as rosiglitazone, but these drugs can increase body-mass, which is undesirable in women who are already overweight.[5,8] Their use is considered investigational.[1]

Bromocriptine[4] may be useful in women with polycystic ovary syndrome and associated hyperprolactinaemia (see above).

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Precocious puberty

Precocious puberty is commonly understood to mean the development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys; it is four to five times more common in girls. However, the age limit used to define precocious puberty in girls has been questioned.[1] Recent data from the United States suggests that puberty is occurring earlier in girls, at age 7 years for white girls, and 6 years for African-American girls. Precocious puberty is either central, due to premature activation of the hypothalamic-pituitary-gonadal axis, or peripheral, due to secretion of extrapituitary gonadotrophins or gonadal steroids independent of gonadorelin secretion from the hypothalamus or pituitary gonadotrophins. In many cases the cause is not apparent, and they are classified as idiopathic. A small proportion of cases are due to tumours. Central precocious puberty may be caused by CNS lesions secondary to diseases such as encephalitis, meningitis, or granuloma, or due to head trauma. Peripheral precocious puberty can be associated with congenital or familial syndromes such as McCune-Albright syndrome or familial testotoxicosis (familial male precocious puberty). Congenital adrenal hyperplasia (see p.1502) can also produce premature sexual development in boys and virilisation in girls.

Apart from early sexual maturation and the associated emotional distress, the chief clinical consequence of precocious puberty is short stature as an adult, due to premature closure of the epiphyses under the influence of sex steroids.[2,3] Age, emotional impact and final height potential should be considered in deciding when to begin and end treatment.[2]

Gonadorelin analogues are the treatment of choice in central precocious puberty.[2,3] The use of continuous rather than pulsatile gonadorelin can paradoxically suppress gonadotrophin secretion by desensitisation and down regulation of pituitary receptors. Cyproterone acetate has been given at the beginning of treatment to prevent the initial stimulatory effect of the gonadorelin analogue.[2] Although originally given daily, by subcutaneous injection or nasal insufflation, intramuscular and subcutaneous depot preparations of gonadorelin analogues are more convenient, and are now more widely used.[2,3] Treatment suppresses sexual development and skeletal maturation, and most studies have reported an improvement in final height.[3,4] However, the treatment of girls with borderline early puberty (between 6 and 8 years of age) has been questioned, as studies suggest that most will reach adult height within the normal range without treatment.[1] Such girls with idiopathic slowly progressing puberty, and no evidence of advanced bone age, may not require gonadorelin therapy, but should be monitored for an onset of rapid pubertal development.[1,5] Children with concomitant growth hormone deficiency (for example after cranial irradiation) may need additional therapy with somatropin or its analogues for maximum benefit.[6] Somatropin has also been used in children who do not have growth hormone deficiency but who have a poor response to gonadorelin analogue therapy; evidence for a beneficial effect is limited.[7]

In the peripheral forms of precocious puberty the gonadorelin analogues are ineffective. Any underlying condition such as a gonadal or adrenal neoplasm should be sought and treated appropriately. Otherwise, therapy is aimed at suppressing premature sexual maturation, and drugs such as cyproterone and medroxyprogesterone have been used.[8] In girls with precocious puberty associated with the McCune-Albright syndrome, the aromatase inhibitor testolactone has been used with some success to block oestrogen biosynthesis,[9,10] ketoconazole has been used in 2 cases,[11] and tamoxifen has been reported to be beneficial.[12] Although ineffective when given alone, testolactone was reported to be of benefit when used with the anti-androgen, spironolactone, in boys with testotoxicosis;[13] a reduction in the rate of bone maturation was reported. Response diminished with long-term treatment, but could be restored by the addition of a gonadorelin analogue, deslorelin, to therapy.[14] This regimen has also been reported[15] to improve predicted adult height. Ketoconazole, which has anti-androgenic properties, has also been tried in boys with familial male precocious puberty; it had beneficial effects on testosterone concentrations and adult height reported in a series of 5 patients.[16]

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14. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
15. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.
16. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.

Premenstrual syndrome

Gonadorelin analogues have been used to treat patients with severe symptoms attributable to the premenstrual syndrome (p.2099), with 'add-back' therapy with oestrogen plus progestogen to prevent the symptoms of oestrogen deficiency.

Turner's syndrome

Turner's syndrome is a congenital disorder associated with the absence of an X or Y chromosome, resulting in an individual with only a single X chromosome who is female in phenotype but in whom the ovaries do not develop. In addition to this gonadal dysgenesis, which results in infertility and primary amenorrhoea, various physical abnormalities may be present including short stature, a short webbed neck and characteristic facial appearance, shield-like chest, multiple naevi, and certain renal and cardiovascular abnormalities. Hypothyroidism and glucose intolerance may occur.

As with other forms of ovarian failure, HRT with oestrogen and intermittent progestogen is indicated in women with Turner's syndrome, in order to produce sexual maturation and the development of secondary sexual characteristics as well as to avoid complications such as osteoporosis. Clinical opinion has generally been that therapy should begin with low doses of oestrogen in girls of prepubertal age, gradually increasing the dose to promote slow development of secondary sexual characteristics and eventual breakthrough bleeding, at which point a cyclic progestogen should be added to oestrogen maintenance to minimise the risk of endometrial hyperplasia and cancer. In general, therapy is started around 14 to 15 years of age, but may be started as early as 12 years of age in girls who have reached a satisfactory height, especially those who have been treated with growth hormone.[1-3] There is no consensus on which oestrogen is preferred for these patients; conjugated oestrogens, ethinylestradiol, and estradiol have all been used. An oral contraceptive may be used for maintenance therapy.[3]

A minority of patients with Turner's syndrome have some residual ovarian function, and there are a few reports of pregnancy in such patients. In women without ovaries it may be possible to maintain pregnancy by appropriate endocrine replacement after implantation of a fertilised donor egg.[1]

Short stature is the most common clinical manifestation of Turner's syndrome. Growth hormone therapy has been widely used and may be considered from as early as 2 years of age,[2] but there is considerable debate about the extent of the benefit in terms of final height. Results from 622 girls enrolled in the National Cooperative Growth Study[4] suggested a mean height gain of 6.4 ± 4.9 cm, and another cohort database[5] of 485 girls found that when treatment was started before puberty a mean increase in final height of 5 cm or more would be expected. A systematic review[6] of 4 controlled studies found that growth hormone increased short-term growth, but that there was limited controlled data on final height. It has been suggested[1] that a final height of 150 cm is an achievable goal for most patients. Growth hormone therapy during childhood and adolescence may also be important in maximising bone mass and reducing the risk of osteoporosis.[7] Although it is generally recommended that oestrogen replacement be delayed where growth promotion is a priority,[1,2] optimal oestrogen replacement therapy may also be important in maximising final height. In a comparison[8] of the introduction of conjugated oestrogen therapy at 12 or 15 years of age, the combination of growth hormone and oestrogen initially stimulated growth velocity and bone maturation more than growth hormone alone, but subsequently declined after about 2 years. Patients who received growth hormone for a longer period before starting oestrogen therapy attained greater adult height, a finding also noted in another study;[9] it was suggested that early use of growth hormone could allow oestrogen therapy to be begun at a more appropriate, younger age without compromising final height. However, the use of low-dose oestrogen from an even earlier age (as young as 8 years) to stimulate linear growth does not add to the effect of growth hormone therapy and may even reduce final height.[10] Combination of growth hormone with a non-aromatisable anabolic steroid such as oxandrolone is recommended as an option in girls aged 8 to 12 years if therapy is begun late,[1] or if response to growth hormone is inadequate.[2]

Adult women with Turner's syndrome require multidisciplinary management including cardiovascular monitoring, psychological support, and a programme of prevention for diabetes, osteoporosis, and hypertension.[1,2]

1. Saenger P, *et al.* Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001; **86:** 3061–9.
2. Frías JL, *et al.* Health supervision for children with Turner syndrome. *Pediatrics* 2003; **111:** 692–702.
3. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351:** 1227–38.
4. Plotnick L, *et al.* Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. *Pediatrics* 1998; **102:** 479–81.
5. Betts PR, *et al.* A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; **80:** 221–5.
6. Cave CB, *et al.* Recombinant growth hormone in children and adolescents with Turner syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. *Pediatrics* 1998; **102** (suppl): 481–5.
8. Chernausek SD, *et al.* Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. *J Clin Endocrinol Metab* 2000; **85:** 2439–45.
9. Reiter EO, *et al.* Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001; **86:** 1936–41.
10. Quigley CA, *et al.* Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002; **87:** 2033–41.

Abarelix *(USAN, rINN)*

Abarélix; Abarelixum; PPI-149; R-3827. *N*-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide.

Абареликс

$C_{72}H_{95}ClN_{14}O_{14}$ = 1416.1.
CAS — 183552-38-7.
ATC — L02BX01.
ATC Vet — QL02BX01.

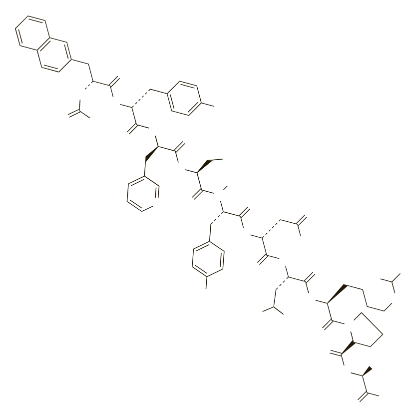

Adverse Effects and Precautions

Immediate hypersensitivity reactions, including urticaria, pruritus, hypotension, and syncope, can occur with abarelix, and the cumulative risk of such a reaction increases with repeated doses. Patients should be monitored for at least 30 minutes after each injection. Hot flushes, sleep disturbance, breast enlargement and tenderness may result from testosterone reduction. Prolongation of the QT interval has occurred in patients receiving abarelix.

Elevations in transaminase concentrations have occurred, and liver function should be monitored before starting treatment, and periodically during treatment. The effectiveness of abarelix in the management of prostate cancer decreases with duration of therapy, and may be further reduced in patients weighing more than about 100 kg (225 pounds). The serum concentration of testosterone should be measured on day 29 of therapy and then every 8 weeks, to monitor for treatment failure.

Pharmacokinetics

Abarelix is absorbed slowly after intramuscular injection, with a peak concentration in serum reached after about 3 days. It is metabolised by hydrolysis and has an elimination half-life of about 13 days with intramuscular use.

◊ References.

1. Wong SL, *et al.* Pharmacokinetics and pharmacodynamics of a novel depot formulation of abarelix, a gonadotropin-releasing hormone (GnRH) antagonist, in healthy men ages 50 to 75. *J Clin Pharmacol* 2004; **44:** 495–502.

Uses and Administration

Like cetrorelix (p.2084), abarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used to reduce testosterone concentrations in the palliative hormonal therapy of prostate cancer (p.671). A dose of abarelix 100 mg is given intramuscularly on days 1, 15, and 29, and then every 4 weeks thereafter.

Abarelix has been investigated for the treatment of endometriosis.

Malignant neoplasms. References.

1. Tomera K, *et al.* The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol (Baltimore)* 2001; **165:** 1585–9.
2. McLeod D, *et al.* A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 2001; **58:** 756–61.
3. Trachtenberg J, *et al.* A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol (Baltimore)* 2002; **167:** 1670–4.
4. Koch M, *et al.* An open-label study of abarelix in men with symptomatic prostate cancer at risk of treatment with LHRH agonists. *Urology* 2003; **62:** 877–82.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Plenaxis.

Alfatradiol *(rINN)* ⊗

Alfatradiolum; Alpha-estradiol; Epiestradiol; 17α-Estradiol; NSC-20293. Estra-1,3,5(10)-triene-3,17α-diol.

Альфатрадиол

$C_{18}H_{24}O_2$ = 272.4.
CAS — 57-91-0.

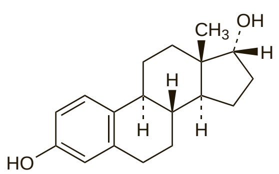

Profile

Alfatradiol is the 17-α isomer of estradiol (p.2097) but has much weaker oestrogenic actions. It is a 5α-reductase inhibitor and is used topically as a 0.025% solution for alopecia androgenetica (p.1577).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avixis; ***Ger.:*** Ell-Cranell alpha; Pantostin; ***Mex.:*** Avixis.
Multi-ingredient: *Ger.:* Ell-Cranell dexa.

Algestone Acetophenide *(USAN, rINNM)*

Acetofenido de alfasona; Acetofenido de algestona; Acetofenido de dihidroxiprogesterona; Algestone, Acétophenide d'; Algestoni Acetophenidum; Alphasone Acetophenide; Dihydroxyprogesterone Acetophenide; SQ-15101. 16α,17α-(1-Phenylethylidenedioxy)pregn-4-ene-3,20-dione; 16α,17α-Isopropylidenedioxypregn-4-ene-3,20-dione.

Альгестона Ацетофенид

$C_{29}H_{36}O_4$ = 448.6.
CAS — 595-77-7 (algestone); 24356-94-3 (algestone acetophenide).

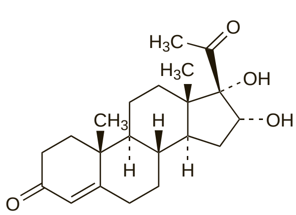

(algestone)

Profile

Algestone acetophenide is a progestogen (see Progesterone, p.2125) that is given by intramuscular injection in monthly doses of 150 mg, with estradiol enantate, as a hormonal contraceptive (see p.2058). It has also been applied topically in the treatment of acne.

◊ References.

1. Martínez GH, *et al.* Vaginal bleeding patterns in users of Perlutal, a once-a-month injectable contraceptive consisting of 10 mg estradiol enanthate combined with 150 mg dihydroxyprogesterone acetophenide: a trial of 5462 woman-months. *Contraception* 1998; **58:** 21–7.
2. Coutinho EM, *et al.* Efficacy, acceptability, and clinical effects of a low-dose injectable contraceptive combination of dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2000; **61:** 277–80.
3. Coutinho EM, *et al.* Comparison of two regimens of a monthly injectable contraceptive containing dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2006; **73:** 249–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Arg.:* Atrimon; Perlutal; ***Braz.:*** Femineo†; Perlutan; Preg-Less; Unalmes†; Uno-Ciclo†; ***Chile:*** Agurin†; Unalmes; ***Mex.:*** Anafertin; Ginoplan†; Patector; Perludil; Perlutal; Yectames; ***Port.:*** Cicnor†; ***Singapore:*** Unijab; ***Spain:*** Topasel.

Allylestrenol *(BAN, rINN)*

Alilestrenol; Allylestrénol; Allylestrenolum; Allyloestrenol; Allylöstrenol; Allyyliestrenoli. 17α-Allylestr-4-en-17β-ol.

Аллилэстренол

$C_{21}H_{32}O$ = 300.5.
CAS — 432-60-0.
ATC — G03DC01.
ATC Vet — QG03DC01.

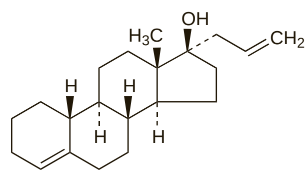

Profile

Allylestrenol is a progestogen (see Progesterone, p.2125) structurally related to progesterone that has been given in threatened and recurrent miscarriage, and to prevent premature labour. However, with the exception of proven progesterone deficiency, such use is no longer recommended. In threatened miscarriage in progesterone-deficient women a suggested oral dose is 5 mg three times daily for 5 to 7 days.

Pregnancy. A case-control study of allylestrenol use in pregnancy during 1980 to 1984 in Hungary indicated that it was not teratogenic.[1]

1. Czeizel A, Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. *Clin Ther* 1988; **10:** 725–39.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Turinal†; ***Hong Kong:*** Turinal; ***India:*** Maintane; Profar; ***Indon.:*** Gravynon; Lestron; Preabor; Pregtenol; Premaston; Prenolin; Prestrenol; Progeston; ***Malaysia:*** Turinal†; ***Philipp.:*** Turinal; ***Rus.:*** Turinal (Туринал); ***Singapore:*** Turinal.

Altrenogest *(BAN, USAN, rINN)*

A-35957; A-41300; Altrénogest; Altrenogesti; Altrenogestum; RH-2267; RU-2267. 17α-Allyl-17β-hydroxy-19-norandrosta-4,9,11-trien-3-one; 17β-Hydroxy-19,21,24-trinorchola-4,9,11,22-tetraen-3-one.

Альтреногест

$C_{21}H_{26}O_2$ = 310.4.
CAS — 850-52-2.
ATC Vet — QG03DX90.

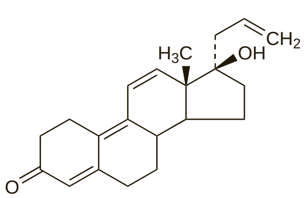

Profile

Altrenogest is a progestogen (see Progesterone, p.2125) used in veterinary medicine.

Androstanolone *(BAN, rINN)* ⊗

Androstanolo; Androstanolon; Androstanolona; Androstanoloni; Androstanolonum; Dihidrotestosterona; Dihydrotestosterone; Estanolona; Stanolon; Stanolone. 17β-Hydroxy-5α-androstan-3-one.

Андростанолон

$C_{19}H_{30}O_2$ = 290.4.
CAS — 521-18-6.
ATC — A14AA01; G03BB02.
ATC Vet — QA14AA01; QG03BB02.

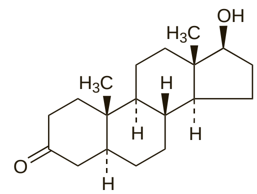

Profile

Androstanolone is formed naturally in the body from testosterone (p.2129) by the action of 5α-reductase, and is more active than the parent compound. It has anabolic and androgenic properties and is applied topically in the form of a 2.5% gel for male hypogonadism and gynaecomastia, and for lichen sclerosus in both men and women.

◊ References.

1. Wang C, Swerdloff RS. Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J Clin Endocrinol Metab* 2002; **87:** 1462–6.

Lichen sclerosus. For references to the use of androgens such as androstanolone in lichen sclerosus, see under Testosterone, p.2133.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Andractim; ***Fr.:*** Andractim; ***Thai.:*** Andractim†.

Androstenedione ⊗

Androstenodiona. Androst-4-ene-3,17-dione.

Андростендион

$C_{19}H_{26}O_2$ = 286.4.
CAS — 63-05-8.

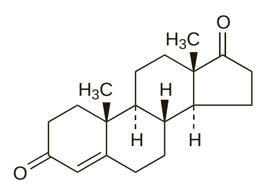

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of androstenedione:
Andro.

Profile

Androstenedione is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens (see p.2058). It has been used in an attempt to enhance athletic performance and as hormone replacement for men. In March 2004 the FDA banned the distribution of dietary supplements containing androstenedione, considering them to be adulterated and warning that they did not meet safety requirements.

Action. The effects of androstenedione have been studied in groups of young (under 40 years of age) and older (up to 65 years) men with normal serum testosterone concentrations.[1-4] Testosterone concentrations were reported to remain unchanged[1,4] as well as increase,[2,3] although they returned to baseline in the longer study of 12 weeks.[3] In 3 of the studies, oestrogens (oestradiol and oestrone) increased.[1-3] Changes in lipid profiles were also noted, particularly a decrease in high-density lipoprotein (HDL) cholesterol.[1,3] Androstenedione did not enhance the effects of resistance training.[1,3]

There has been a report of impotence and severe oligospermia associated with ingestion of androstenedione by a bodybuilder.[5] Priapism has also been reported.[6]

1. King DS, *et al.* Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. *JAMA* 1999; **281:** 2020–8.
2. Leder BZ, *et al.* Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA* 2000; **283:** 779–82.
3. Broeder CE, *et al.* The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. *Arch Intern Med* 2000; **160:** 3093–3104.
4. Beckham SG, Earnest CP. Four weeks of androstenedione supplementation diminishes the treatment response in middle aged men. *Br J Sports Med* 2003; **37:** 212–8.
5. Ritter RH, *et al.* Oral androstenedione-induced impotence and severe oligospermia. *Fertil Steril* 2005; **84:** 217.e7–e8.
6. Kachhi PN, Henderson SO. Priapism after androstenedione intake for athletic performance enhancement. *Ann Emerg Med* 2000; **35:** 391–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Thai.:*** Metharmon-F.

Bazedoxifene Acetate *(USAN, rINNM)* ⊗

Acetato de bazedoxifeno; Bazédoxifène, Acétate de; Bazedoxifeni Acetas; TSE-424; WAY-140424; WAY-TSE-424. 1-{*p*-[2-(Hexahydro-1*H*-azepin-1-yl)ethoxy]benzyl}-2-(*p*-hydroxyphenyl)-3-methylindol-5-ol monoacetate.

Базедоксифена Ацетат

$C_{30}H_{34}N_2O_3,C_2H_4O_2$ = 530.7.

CAS — 198481-32-2 (bazedoxifene); 198481-33-3 (bazedoxifene acetate).

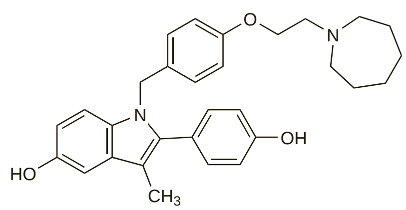

(bazedoxifene)

Profile

Bazedoxifene acetate is a selective oestrogen receptor modulator. It is under investigation in the prevention and treatment of postmenopausal osteoporosis, and with conjugated oestrogens in the management of menopausal vasomotor symptoms, atrophic vaginitis, and postmenopausal osteoporosis.

◊ Reviews.

1. Stump AL, *et al.* Bazedoxifene: a third-generation selective estrogen receptor modulator for treatment of postmenopausal osteoporosis. *Ann Pharmacother* 2007; **41:** 833–9.
2. Lewiecki EM. Bazedoxifene and bazedoxifene combined with conjugated estrogens for the management of postmenopausal osteoporosis. *Expert Opin Invest Drugs* 2007; **16:** 1663–72.

Boldenone Undecenoate *(BANM, rINNM)* ⊗

Ba-29038; Boldenone Undecylenate *(USAN)*; Boldénone, Undécylénate de; Boldenoni Undecylenas; 1-Dehydrotestosterone (boldenone); Undecilenato de boldenona. 17β-Hydroxyandrosta-1,4-dien-3-one 17-(undec-10-enoate).

Болденона Ундециленат

$C_{30}H_{44}O_3$ = 452.7.

CAS — 846-48-0 (boldenone); 13103-34-9 (boldenone undecenoate).

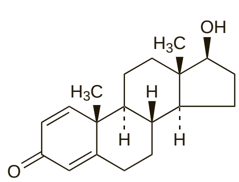

(boldenone)

Profile

Boldenone undecenoate is an anabolic steroid (see Testosterone, p.2129) that has been used in veterinary practice. It has been subject to abuse in sport.

Buserelin *(BAN, rINN)* ⊗

Busereliini; Buserelina; Buserelinas; Busériline; Buserelinum; Buszerelin; S74-6766. (6-*O*-*tert*-Butyl-D-serine)-des-10-glycinamidegonadorelin ethylamide; 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

Бусерелин

$C_{60}H_{86}N_{16}O_{13}$ = 1239.4.

CAS — 57982-77-1.

ATC — L02AE01.

ATC Vet — QH01CA90; QL02AE01.

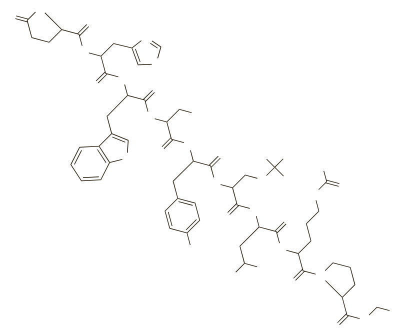

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Buserelin). A white or slightly yellowish hygroscopic powder. Sparingly soluble in water and in dilute acids. Store at 2° to 8°. Protect from light and moisture.

Buserelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de buserelina; Buserelin Asetat; Busériline, Acétate de; Buserelini Acetas; Hoe-766; D-Ser (Bu^t)^6 Pro^9 NEt LHRH acetate.

Бусерелина Ацетат

$C_{60}H_{86}N_{16}O_{13},C_2H_4O_2$ = 1299.5.

CAS — 68630-75-1.

ATC — L02AE01.

ATC Vet — QL02AE01.

Adverse Effects and Precautions

As for Gonadorelin, p.2106.

Interactions

As for Gonadorelin, p.2107.

Pharmacokinetics

Buserelin is completely absorbed after subcutaneous injection, with peak plasma concentrations occurring about 1 hour after a dose. It accumulates in liver and kidneys as well as in the anterior pituitary. It is metabolised by tissue peptidases and is excreted in urine and bile as unchanged drug and metabolites. The half-life after injection is stated to be about 80 minutes.

Uses and Administration

Buserelin is an analogue of gonadorelin (p.2107) with similar properties. It is used for the suppression of testosterone in the treatment of malignant neoplasms of the prostate; it is also used in the treatment of endometriosis and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. It has been used in precocious puberty and tried in the treatment of uterine fibroids (see below). Buserelin is usually given as the acetate but doses are expressed in terms of the base; 105 micrograms of buserelin acetate is equivalent to about 100 micrograms of buserelin.

In advanced **prostatic carcinoma** doses of 500 micrograms are injected subcutaneously every 8 hours for 7 days. On the eighth day treatment is changed to the nasal route; 100 micrograms is sprayed into each nostril 6 times daily (usually before and after meals). An acceptable response should be achieved within 4 to 6 weeks. Since there is an initial increase in circulating testosterone, an anti-androgen such as cyproterone acetate may be given for at least 3 days before beginning buserelin therapy, and continued for at least 3 weeks, to avoid the risk of a disease flare. Long-acting subcutaneous depot preparations that release buserelin over a 2- or 3-month period are also available.

In **endometriosis** a dose of 150 micrograms is sprayed into each nostril three times daily. The usual duration of therapy is 6 months, which should not be exceeded.

In **infertility**, pituitary desensitisation before ovulation induction with gonadotrophins is achieved by giving 150 micrograms intranasally four times daily, beginning either in the early follicular phase (day 1) or midluteal phase (day 21) of the menstrual cycle. Alternatively, 200 to 500 micrograms may be given daily as a subcutaneous injection. Therapy should be continued until pituitary downregulation occurs, which normally takes 1 to 3 weeks; if necessary 300 micrograms four times daily intranasally, or 500 micrograms twice daily subcutaneously may be given. Gonadotrophin treatment is then added to buserelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

◊ General reviews.

1. Brogden RN, *et al.* Buserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical profile. *Drugs* 1990; **39:** 399–437.

Endometriosis. Gonadorelin analogues such as buserelin have a role in the management of endometriosis (p.2091), but the need for long-term therapy limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lemay A, *et al.* Efficacy of intranasal or subcutaneous luteinizing hormone-releasing hormone agonist inhibition of ovarian function in the treatment of endometriosis. *Am J Obstet Gynecol* 1988; **158:** 233–6.
2. Donnez J, *et al.* Administration of nasal buserelin as compared with subcutaneous buserelin implant for endometriosis. *Fertil Steril* 1989; **52:** 27–30.
3. Nieto A, *et al.* Long term follow-up of endometriosis after two different therapies (gestrinone and buserelin). *Clin Exp Obstet Gynecol* 1996; **23:** 198–204.
4. Regidor P-A, *et al.* Long-term follow-up on the treatment of endometriosis with the GnRH-agonist buserelin acetate. *Eur J Obstet Gynecol Reprod Biol* 1997; **73:** 153–60.
5. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.

Fibroids. Like other gonadorelin analogues (see also p.2107) buserelin has been used to reduce the volume of uterine fibroids.

References.

1. Maheux R, *et al.* Use of intranasal luteinizing hormone-releasing hormone agonist in uterine leiomyomas. *Fertil Steril* 1987; **47:** 229–33.
2. Matta WHM, *et al.* Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin. *Br J Obstet Gynaecol* 1989; **96:** 200–6.
3. Fedele L, *et al.* Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. *Eur J Obstet Gynecol Reprod Biol* 1991; **38:** 53–7.
4. Ueki M, *et al.* Endocrinological and histological changes after treatment of uterine leiomyomas with danazol or buserelin. *J Obstet Gynaecol* 1995; **21:** 1–7.

Infertility. Buserelin is given with gonadotrophic hormone therapy for induction of ovulation and as an aid to improving IVF procedures. Buserelin with gonadotrophic hormones has been found to result in pregnancies in women previously unresponsive to clomifene citrate,[1,2] although there may be a greater risk of multiple births.[3]

The regimens used in IVF may be characterised according to how long the gonadorelin analogue is given for:

- long, 2 weeks or more
- short, 8 to 10 days
- ultrashort, 3 days

A comparative study of such regimens found that the best results in all age groups were consistently associated with the long buserelin protocol.[4] The timing of buserelin dosage may also be important. Starting buserelin in the midluteal phase of the cycle has been reported to produce more rapid pituitary down regulation and higher pregnancy rates from IVF than when buserelin was begun in the early follicular phase.[5]

For a general discussion of the management of infertility, see p.2080.

1. Armitage M, *et al.* Successful treatment of infertility due to polycystic ovary disease using a combination of luteinising hormone releasing hormone agonist and low dosage menotrophin. *BMJ* 1987; **295:** 96.
2. Owen EJ, *et al.* The use of a short regimen of buserelin, a gonadotrophin-releasing hormone agonist, and human menopausal gonadotrophin in assisted conception cycles. *Hum Reprod* 1989; **4:** 749–53.
3. Rutherford AJ, *et al.* Improvement of in vitro fertilisation after treatment with buserelin, an agonist of luteinising hormone releasing hormone. *BMJ* 1988; **296:** 1765–8.
4. Tan S-L, *et al.* Cumulative conception and live-birth rates after in vitro fertilization with and without the use of long, short, and ultrashort regimens of the gonadotrophin-releasing hormone agonist buserelin. *Am J Obstet Gynecol* 1994; **171:** 513–20.
5. Urbancsek J, Witthaus E. Midluteal buserelin is superior to early follicular phase buserelin in combined gonadotropin-releasing hormone analog and gonadotropin stimulation in in vitro fertilization. *Fertil Steril* 1996; **65:** 966–71.

Malignant neoplasms. The long-term use of buserelin in men decreases the testicular concentration of testosterone. For this reason it is used in the treatment of prostatic cancer (p.671), which is androgen-dependent.[1] Gonadorelin analogues are an effective alternative to orchidectomy, sometimes combined with an anti-androgen for enhanced effect, and play a major role in the management of advanced, incurable disease.

Other reports of malignant neoplasms treated with buserelin include its use in metastatic breast cancer[2,3] (p.661).

1. de Voogt HJ, *et al.* The use of the LHRH-analogue buserelin in the treatment of prostatic cancer: a 10-year review on 1522 patients treated in 119 centers on 4 continents. *Scand J Urol Nephrol Suppl* 1991; **138:** 131–6.
2. Falkson CI, *et al.* Cyclophosphamide, doxorubicin and fluorouracil (CAF) plus depo-buserelin in the treatment of premenopausal women with metastatic breast cancer. *Ann Oncol* 1992; **3:** 849–53.
3. Klijn JG, *et al.* Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst* 2000; **92:** 903–11.

Porphyria. Buserelin given with medroxyprogesterone acetate suppressed cyclic and premenstrual exacerbations of porphyria (p.1448) in 2 patients. Doses used were 300 micrograms buserelin intranasally in the evenings of days 1 to 21 of the menstrual cycle and 10 mg medroxyprogesterone acetate daily by mouth from day 12 to 21. Both patients were free from porphyric attacks during the reported 11 months of treatment.[1] Intranasal buserelin has also been used in 1 patient to prevent premenstrual exacerbation of coproporphyria.[2] The initial dose of 900 micrograms daily could be tapered to 150 micrograms daily, with only 1 minor attack in 5 years of treatment. The authors of this report also noted a number of case reports of buserelin used in acute intermittent porphyria.

1. Bargetzi MJ, *et al.* Premenstrual exacerbations in hepatic porphyria: prevention by intermittent administration of an LH-RH agonist in combination with a gestagen. *JAMA* 1989; **261:** 864.
2. Yamamori I, *et al.* Prevention of premenstrual exacerbation of hereditary coproporphyria by gonadotropin-releasing hormone analogue. *Intern Med* 1999; **38:** 365–8.

Precocious puberty. The gonadorelin analogues have largely replaced other treatments in the management of central precocious puberty (p.2081). References to the use of buserelin.

1. Drop SLS, *et al.* The effect of treatment with an LH-RH agonist (buserelin) on gonadal activity growth and bone maturation in children with central precocious puberty. *Eur J Pediatr* 1987; **146:** 272–8.
2. Cacciari E, *et al.* Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994; **148:** 1194–9.
3. Juul A, *et al.* Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). *J Clin Endocrinol Metab* 1995; **80:** 3059–67.
4. Bertelloni S, *et al.* Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 1998; **157:** 363–7.
5. Tuvemo T, *et al.* Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Horm Res* 2002; **57:** 27–31.

Premenstrual syndrome. For reference to the use of buserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p.2108.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Suprefact; ***Austria:*** Suprecur; Suprefact; ***Belg.:*** Suprefact; ***Braz.:*** Suprefact; ***Canad.:*** Suprefact; ***Cz.:*** Suprecur†; Suprefact†; ***Denm.:*** Suprecur; Suprefact; ***Fin.:*** Suprecur; Suprefact; ***Fr.:*** Bigonist; Suprefact; ***Ger.:*** Profact; Suprecur; ***Gr.:*** Suprefact; ***Hong Kong:*** Suprecur; ***Hung.:*** Suprefact; ***Irl.:*** Suprecur; Suprefact; ***Israel:*** Suprefact; ***Ital.:*** Suprefact; ***Jpn:*** Suprecur; ***Malaysia:*** Suprefact; ***Mex.:*** Suprefact; ***Neth.:*** Suprecur†; Suprefact; ***Norw.:*** Suprecur; Suprefact; ***NZ:*** Suprefact; ***Port.:*** Suprefact; ***S.Afr.:*** Suprefact; ***Singapore:*** Suprefact; ***Spain:*** Suprefact; ***Swed.:*** Suprecur; Suprefact; ***Switz.:*** Suprefact; ***Thai.:*** Suprefact; ***Turk.:*** Suprecur; Suprefact; ***UK:*** Suprecur; Suprefact.

Cetrorelix Acetate *(BANM, USAN, rINNM)*

Acetato de cetrorelix; Cétrorélix, Acétate de; Cetrorelixi Acetas; D-20761; NS-75A; SB-75 (cetrorelix); SB-075 (cetrorelix). *N*-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-carbamoyl-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide acetate.

Цетрореликса Ацетат

$C_{70}H_{92}ClN_{17}O_{14},xC_2H_4O_2$ = 1431.0 (cetrorelix).
CAS — 120287-85-6 (cetrorelix); 145672-81-7 (cetrorelix acetate).
ATC — H01CC02.
ATC Vet — QH01CC02.

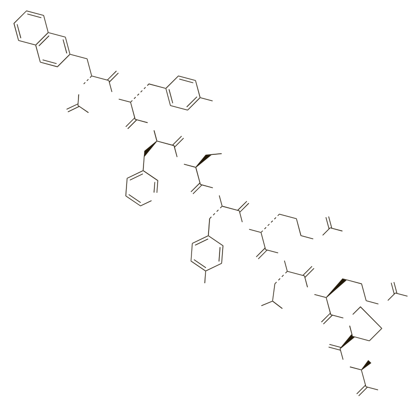

(cetrorelix)

Adverse Effects and Precautions

Transient reactions at the injection site, including erythema, pruritus, and swelling, may occur. Nausea and headache have been reported occasionally. Systemic hypersensitivity reactions have been reported rarely.

Cetrorelix should not be used in patients with moderate to severe renal or hepatic impairment.

Pharmacokinetics

The bioavailability of cetrorelix after subcutaneous injection is about 85%. The mean terminal half-life after a subcutaneous injection of 3 mg is about 60 hours; it is less with lower doses (about 5 and 20 hours respectively after single and multiple doses of 250 micrograms).

◊ References.

1. Pechstein B, *et al.* Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 266–74.
2. Nagaraja NV, *et al.* Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women. *Clin Pharmacol Ther* 2000; **68:** 617–25.

Uses and Administration

Cetrorelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p.2080); it is used to prevent luteinising hormone surges and premature ovulation. It has also been tried in benign prostatic hyperplasia, malignant neoplasms of the prostate, endometriosis, and for uterine fibroids. Cetrorelix is given by subcutaneous injection as the acetate; an intramuscular depot formulation containing cetrorelix embonate is reported to be under development. For assisted reproduction, doses of cetrorelix acetate equivalent to cetrorelix 250 micrograms daily may be given either in the morning beginning on day 5 or 6 of ovarian stimulation or in the evening beginning on day 5, and continued until ovulation induction. Alternatively a single dose equivalent to 3 mg of cetrorelix may be given on day 7; if follicle growth does not allow ovulation induction within 4 days, additional doses of cetrorelix 250 micrograms once daily may be given until the day of ovulation induction.

◊ References.

1. Gonzalez-Barcena D, *et al.* Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist cetrorelix. *Hum Reprod* 1997; **12:** 2028–35.
2. Comaru-Schally AM, *et al.* Efficacy and safety of luteinizing hormone-releasing hormone antagonist cetrorelix in the treatment of symptomatic benign prostatic hyperplasia. *J Clin Endocrinol Metab* 1998; **83:** 3826–31.
3. Felberbaum RE, *et al.* Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist cetrorelix. *Hum Reprod* 1998; **13:** 1660–8.
4. Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; **358:** 1793–1803.
5. Ludwig M, *et al.* Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol: meta-analysis. *Arch Gynecol Obstet* 2001; **265:** 175–82.
6. Roulier R, *et al.* Depot GnRH agonist versus the single dose GnRH antagonist regimen (cetrorelix, 3 mg) in patients undergoing assisted reproduction treatment. *Reprod Biomed Online* 2003; **7:** 185–9.
7. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
8. Al-Inany HG, *et al.* Gonadotrophin-releasing hormone antagonists for assisted conception. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/07/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cetrotide; ***Austral.:*** Cetrotide; ***Austria:*** Cetrotide; ***Belg.:*** Cetrotide; ***Braz.:*** Cetrotide; ***Canad.:*** Cetrotide; ***Chile:*** Cetrotide; ***Cz.:*** Cetrotide; ***Denm.:*** Cetrotide; ***Fin.:*** Cetrotide; ***Fr.:*** Cetrotide; ***Ger.:*** Cetrotide; ***Gr.:*** Cetrotide; ***Hong Kong:*** Cetrotide; ***Hung.:*** Cetrotide; ***India:*** Cetrotide; ***Indon.:*** Cetrotide; ***Irl.:*** Cetrotide; ***Israel:*** Cetrotide; ***Ital.:*** Cetrotide; ***Malaysia:*** Cetrotide; ***Mex.:*** Cetrotide; ***Neth.:*** Cetrotide; ***Norw.:*** Cetrotide; ***NZ:*** Cetrotide; ***Philipp.:*** Cetrotide; ***Pol.:*** Cetrotide; ***Port.:*** Cetrotide; ***Rus.:*** Cetrotide (Цетротид); ***Singapore:*** Cetrotide; ***Spain:*** Cetrotide; ***Swed.:*** Cetrotide; ***Switz.:*** Cetrotide; ***Thai.:*** Cetrotide; ***Turk.:*** Cetrotide; ***UK:*** Cetrotide; ***USA:*** Cetrotide; ***Venez.:*** Cetrotide.

Chlormadinone Acetate *(BANM, USAN, rINNM)*

Acetato de clormadinona; Chlormadinone, Acétate de; Chlormadinoni Acetas; NSC-92338. 6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate.

Хлормадинона Ацетат

$C_{23}H_{29}ClO_4$ = 404.9.
CAS — 1961-77-9 (chlormadinone); 302-22-7 (chlormadinone acetate).
ATC — G03DB06.
ATC Vet — QG03DB06.

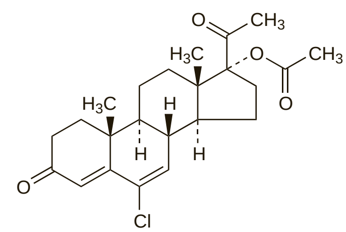

Pharmacopoeias. In *Chin., Fr.,* and *Jpn.*

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Effects on the skin. A report of auto-immune dermatitis in a patient associated with chlormadinone acetate.[1]

1. Katayama I, Nishioka K. Autoimmune progesterone dermatitis with persistent amenorrhoea. *Br J Dermatol* 1985; **112:** 487–91.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Uses and Administration

Chlormadinone acetate is a progestogen structurally related to progesterone (p.2126) that has anti-androgenic activity. It is given either alone or with an oestrogen in the treatment of menstrual disorders such as menorrhagia (p.2126) and endometriosis (p.2091) in oral doses of 2 to 10 mg daily either cyclically or continuously. It may also be used as the progestogen component of combined oral contraceptives (see p.2069) at a dose of 1 to 2 mg daily, particularly in women with androgen-dependent conditions such as acne and hirsutism. Chlormadinone acetate has been used in some countries in the management of prostatic hyperplasia and prostate cancer; oral doses of 25 or 50 mg, respectively have been given twice daily.

◊ Reviews.

1. Curran MP, Wagstaff AJ. Ethinylestradiol/chlormadinone acetate. *Drugs* 2004; **64:** 751–60.
2. Bouchard P. Chlormadinone acetate (CMA) in oral contraception—a new opportunity. *Eur J Contracept Reprod Health Care* 2005; **10** (suppl 1): 7–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Luteran; ***Ger.:*** Gestafortin†; ***Jpn:*** Prostal; ***Mex.:*** Lutoral.

Multi-ingredient: ***Chile:*** Belara; Lovinda; ***Cz.:*** Belara; ***Fr.:*** Belara; ***Ger.:*** Balanca; Belara; Esticia; Gestamestrol N†; Neo-Eunomin; Ovosiston†; ***Hung.:*** Belara; ***Israel:*** Belara; ***Ital.:*** Belara; ***Mex.:*** Belara; Lutoral-E; Secuentex-21; ***Port.:*** Belara; Libeli; ***Rus.:*** Belara (Белара); ***Spain:*** Belara; ***Switz.:*** Belara; ***Venez.:*** Belara.

Chlorotrianisene *(BAN, rINN)*

Chlorotrianisène; Chlorotrianisenum; Clorotrianiseno; Klooritrianiseeni; Klortrianisen; NSC-10108; Tri-*p*-anisylchloroethylene. Chlorotris(4-methoxyphenyl)ethylene.

Хлортрианизен

$C_{23}H_{21}ClO_3$ = 380.9.
CAS — 569-57-3.
ATC — G03CA06.
ATC Vet — QG03CA06.

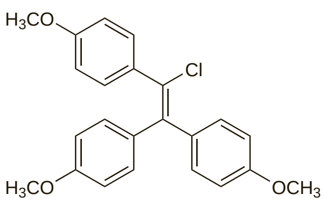

Pharmacopoeias. In *Chin.*

Profile

Chlorotrianisene is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p.2094). It has a prolonged action, and has been given orally for the treatment of menopausal symptoms, female hypogonadism, and prostatic carcinoma.

Chorionic Gonadotrophin *(BAN, rINN)* ⊗

CG; Choriogonadotrophin; Chorionic Gonadotropin; Chorioninis gonadotropinas; Gonadotrofina coriónica; Gonadotrophine Chorionique; Gonadotrophinum Chorionicum; Gonadotropin choriový; Gonadotropine chorionique; Gonadotropinum chorionicum; hCG; Human Chorionic Gonadotrophin; Koriongonadotropiini; Koriongonadotropin; Korion-gonadotropin; Koriyonik Gonadotrofin; Pregnancy-urine Hormone; PU.

Гонадотропин Хорионический

CAS — 9002-61-3.
ATC — G03GA01.
ATC Vet — QG03GA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Gonadotrophin, Chorionic). A dry preparation of placental glycoproteins extracted from the urine of pregnant women. The potency is not less than 2500 units/mg. A white to yellowish-white, amorphous powder. Soluble in water. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Chorionic Gonadotropin). A gonad-stimulating polypeptide hormone obtained from the urine of pregnant women. It has a potency of not less than 1500 USP units/mg. A white or practically white, amorphous powder. Freely soluble in water. Store in airtight containers at 2° to 8°.

Choriogonadotropin Alfa *(BAN, USAN, rINN)* ⊗

Choriogonadotropine Alfa; Choriogonadotropinum Alfa; Coriogonadotropina alfa.

Хориогонадотропин Альфа

CAS — 177073-44-8 (choriogonadotropin alfa); 56832-30-5 (α subunit); 56832-34-9 (β subunit).
ATC — G03GA08.
ATC Vet — QG03GA08.

Adverse Effects and Precautions

Adverse effects that have been reported with chorionic gonadotrophin include headache, tiredness, changes in mood, depression, restlessness, oedema (especially in males), and pain on injection. Treatment for cryptorchidism may produce premature epiphyseal closure or precocious puberty. Gynaecomastia has been reported. Ovarian hyperstimulation may occur, with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock, and thromboembolic disorders in severe cases.

Chorionic gonadotrophin should be given with care to patients in whom androgen-induced fluid retention might be a hazard as in asthma, epilepsy, migraine, or cardiovascular disorders, including hypertension, or renal disorders. Hypersensitivity reactions may occur and it is recommended that patients suspected to be susceptible should be given skin tests before treatment. It should not be given to patients with disorders that might be exacerbated by androgen release such as carcinoma of the prostate or precocious puberty. Use should also be avoided in the presence of breast, uterine, ovarian, and testicular tumours, as well as tumours of the hypothalamus, pituitary, thyroid, and adrenal glands.

Pharmacokinetics

Peak concentrations of chorionic gonadotrophin occur about 6 hours after an intramuscular dose and 16 to 20 hours after a subcutaneous injection. It is distributed primarily to the gonads. Blood concentrations decline in a biphasic manner, with half-lives of about 6 to 11 hours and 23 to 38 hours, respectively. Chorionic gonadotrophin is metabolised mainly in the kidneys. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours.

After subcutaneous doses, choriogonadotropin alfa has a bioavailability of about 40%. It is metabolised and excreted similarly to chorionic gonadotrophin.

Uses and Administration

Chorionic gonadotrophin is a hormone produced by the placenta and obtained from the urine of pregnant women. Its effects are mainly those of the gonadotrophin, luteinising hormone (p.2112), which is responsible for triggering ovulation and formation of the corpus luteum in women, and stimulates the production of testosterone by the testes in men. It is usually given by intramuscular injection although the subcutaneous route has also been used. Choriogonadotropin alfa is a recombinant form of chorionic gonadotrophin.

In *women* with **anovulatory infertility** due to absent or low concentrations of gonadotrophins, chorionic gonadotrophin is given to induce ovulation after follicular development has been stimulated with follicle-stimulating hormone or human menopausal gonadotrophins. A single dose of 5000 to 10 000 units of chorionic gonadotrophin is given by intramuscular injection to mimic the midcycle peak of luteinising hormone which normally stimulates ovulation. Up to 3 repeat injections of up to 5000 units each may be given within the next 9 days to prevent insufficiency of the corpus luteum. Chorionic gonadotrophin is also given with menotrophin as an adjunct to IVF procedures and other assisted conception techniques involving superovulation and oocyte collection.

Choriogonadotropin alfa is used similarly to induce ovulation in the treatment of anovulatory infertility, or as an adjunct to IVF procedures and other assisted conception techniques. A single dose of 250 micrograms is given, by subcutaneous injection, when optimal stimulation of follicular growth is achieved.

In *males*, chorionic gonadotrophin has been used in the treatment of prepubertal **cryptorchidism**. Regimens vary widely, but doses usually range from 500 to 4000 units three times weekly by intramuscular injection. Treatment should continue for 1 to 2 months after testicular descent.

Chorionic gonadotrophin is also given for male infertility associated with hypogonadotrophic **hypogonadism**. Again, there is considerable variation in the dosage regimen, and doses have varied from 500 to 4000 units two or three times weekly by intramuscular injection. A drug with follicle-stimulating activity such as menotrophin is often added to enable normal spermatogenesis.

In the treatment of **delayed puberty** associated with hypogonadism in males, an initial dose of chorionic gonadotrophin 500 to 1500 units is given twice weekly by intramuscular injection; the dose should be titrated against plasma-testosterone concentration.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with chorionic gonadotrophin is widely used for cryptorchidism (p.2079). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[3] Chorionic gonadotrophin may also be used as an adjuvant before surgery, to render the testes palpable,[4] but changes suggestive of inflammation in the testis have been reported following such treatment.[5]

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (issued March 2008). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Paediatric%20Urology.pdf (accessed 31/03/08)
4. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10-year experience. *J Urol (Baltimore)* 1996; **156:** 804–6.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19:** 293–8.

Delayed puberty. Use of chorionic gonadotrophin may be appropriate in boys with delayed puberty due to hypogonadotrophic hypogonadism (p.2079).

Infertility. In women with anovulatory infertility chorionic gonadotrophin and choriogonadotropin alfa can be used to provoke ovulation and provide luteal support once maturation of a suitable number of follicles has been stimulated by other means. They are used similarly in the various protocols for assisted reproduction. However, use is not recommended for assisted reproduction in patients at risk of ovarian hyperstimulation, such as those with polycystic ovary syndrome. In men with hypogonadotrophic hypogonadism chorionic gonadotrophin is used to stimulate and maintain spermatogenesis. The management of male and female infertility, including the role of chorionic gonadotrophin, is discussed on p.2080.

Malignant neoplasms. Control of Kaposi's sarcoma (p.675) has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but regrowth occurred when dosage was reduced or withdrawn.[1] Another study, using lower doses, was stopped due to toxicity and lack of benefit,[2] but others have confirmed benefit after intralesional injection.[3] There is some suggestion that preparations vary in their activity against the tumour and that it is not chorionic gonadotrophin itself, but some impurity (perhaps a ribonuclease[4] or the degradation product of the β-subunit[5]), that is the active principle.[3,6,7] Some contaminants may have a stimulant effect on the neoplasm, which might also contribute to the variable results.[5]

1. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; **346:** 118–19.
2. Bower M, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642.
3. Gill PS, *et al.* The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. *N Engl J Med* 1996; **335:** 1261–9. Correction. *ibid.* 1997; **336:** 1115.
4. Griffiths SJ, *et al.* Ribonuclease inhibits Kaposi's sarcoma. *Nature* 1997; **390:** 568.
5. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; **204:** 330–3.
6. Gill PS, *et al.* Intralesional human chorionic gonadotropin for Kaposi's sarcoma. *N Engl J Med* 1997; **336:** 1188.
7. von Overbeck J, *et al.* Human chorionic gonadotropin for AIDS-related Kaposi's sarcoma. *Lancet* 1995; **346:** 642–3.

Obesity. A meta-analysis[1] involving 24 studies concluded that there was no evidence that chorionic gonadotrophin was effective in the treatment of obesity (p.2149).

1. Lijesen GKS, *et al.* The effect of human chorionic gonadotropin (HCG) in the treatment of obesity by means of the Simeons therapy: a criteria-based meta-analysis. *Br J Clin Pharmacol* 1995; **40:** 237–43.

Testicular function. Chorionic gonadotrophin is used in the assessment of testicular function in suspected primary hypogonadism and incomplete masculinisation. The *BNFC* states that for children 1 month to 18 years of age a dose of 1500 to 2000 units may be given once daily for 3 days (short stimulation test) or twice weekly for 3 weeks (prolonged test).

Preparations

BP 2008: Chorionic Gonadotrophin Injection;
USP 31: Chorionic Gonadotropin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Dinaron; Endocorion; Gonacor; Ovidrel; Pregnyl; Profasi†; ***Austral.:*** Ovidrel; Pregnyl; Profasi; ***Austria:*** Pregnyl; Profasi; ***Belg.:*** Choragon; Ovitrelle; Pregnyl; ***Braz.:*** Choragon†; Ovidrel; Pregnyl; Profasi HP; ***Canad.:*** Pregnyl†; Profasi HP; ***Chile:*** APL†; Gonacor; Ovidrel†; Pregnyl; Profasi†; ***Cz.:*** Ovitrelle; Praedyn†; Pregnyl; Profasi†; ***Denm.:*** Ovitrelle; Pregnyl; Profasi†; ***Fin.:*** Ovitrelle; Pregnyl; Profasi†; ***Fr.:*** Ovitrelle; ***Ger.:*** Choragon; Ovitrelle; Predalon; Pregnesin†; Primogonyl†; ***Gr.:*** Ovitrelle; Pregnyl; Profasi†; ***Hong Kong:*** Choragon; Choriomon; Ovidrel; Pregnyl; Profasi; ***Hung.:*** Choragon; Ovitrelle; Pregnyl; Profasi†; ***India:*** Corion; Profasi; Proligon†; Provigil; Pubergen; ***Indon.:*** Ovidrel; Pregnyl; ***Irl.:*** Ovitrelle; Pregnyl; Profasi; ***Israel:*** Chorigon†; Ovitrelle; Pregnyl; ***Ital.:*** Gonasi HP; Ovitrelle; Pregnyl; Profasi HP†; ***Malaysia:*** Choragon; Ovidrel; Pregnyl; Profasi†; ***Mex.:*** Choragon; Choriomon; Gonadotropyl C†; Ovidrel; Pregnyl; Profasi HP†; ***Neth.:*** Choragon; Ovitrelle; Pregnyl; Profasi†; ***Norw.:*** Ovitrelle; Pregnyl; Profasi†; ***NZ:*** Ovidrel; Profasi; ***Philipp.:*** Ovidrel; Pregnyl; ***Pol.:*** Choragon; Ovitrelle; Pregnyl; ***Port.:*** Ovitrelle; Pregnyl; Profasi HP†; ***Rus.:*** Choragon (Хорагон); Ovitrelle (Овитрель); Pregnyl (Прегнил); ***S.Afr.:*** APL; Pregnyl; Profasi; ***Singapore:*** Ovidrel; Pregnyl; Profasi†; ***Spain:*** Ovitrelle; Profasi HP†; ***Swed.:*** Ovitrelle; Pregnyl; Profasi†; ***Switz.:*** Choriomon; Ovitrelle; Pregnyl; Profasi†; ***Thai.:*** IVF-C; Ovidrel; Pregnyl; Profasi†; ***Turk.:*** Choragon; Ovitrelle; Pregnyl;

Profasi; ***UK:*** Choragon; Ovitrelle; Pregnyl; ***USA:*** Chorex†; Choron; Gonic; Novarel; Ovidrel; Pregnyl; Profasi; ***Venez.:*** Ovidrel; Pregnyl; Profasi†.

Multi-ingredient: ***Ger.:*** NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; ***Mex.:*** Gonakor.

Clomifene Citrate *(BANM, rINNM)* ⊗

Chloramiphene Citrate; Citrato de clomifeno; Clomifène, citrate de; Clomifeni citras; Clomiphene Citrate *(USAN)*; Klomifeenisitraatti; Klomifen Sitrat; Klomifencitrat; Klomifén-citrát; Klomifen-citrát; Klomifeno citratas; MER-41; MRL-41; NSC-35770. A mixture of the *E* and *Z* isomers of 2-[4-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate.

Кломифена Цитрат

$C_{26}H_{28}ClNO,C_6H_8O_7 = 598.1.$

CAS — 911-45-5 (clomifene); 15690-57-0 ((E)-clomifene); 15690-55-8 ((Z)-clomifene); 50-41-9 (clomifene citrate); 7599-79-3 ((E)-clomifene citrate); 7619-53-6 ((Z)-clomifene citrate).

ATC — G03GB02.

ATC Vet — QG03GB02.

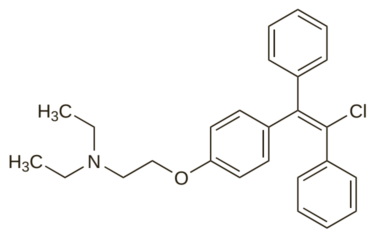

(clomifene)

NOTE. Clomifene may be separated into its *Z*- and *E*-isomers, zuclomifene and enclomifene.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Clomifene Citrate). A white or pale yellow, crystalline powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Clomiphene Citrate). A white to pale yellow, essentially odourless powder. It contains 30 to 50% of the *Z* isomer. Slightly soluble in water and in chloroform; sparingly soluble in alcohol; insoluble in ether; freely soluble in methyl alcohol.

Adverse Effects

The incidence and severity of adverse effects of clomifene citrate tend to be related to the dose used. The most commonly reported adverse effects are reversible ovarian enlargement and cyst formation, vasomotor flushes resembling menopausal symptoms, and abdominal or pelvic discomfort or pain, sometimes with nausea or vomiting. Ovarian hyperstimulation syndrome has occurred. Breast tenderness, abnormal uterine bleeding, weight gain, headache, and endometriosis have also been reported. Transient visual disturbances such as spots or flashes, after-images, and blurring of vision may occur, and there have been rare reports of cataracts and optic neuritis. Skin reactions such as allergic rashes and urticaria have occasionally been reported and reversible hair loss has been reported rarely. CNS disturbances have included convulsions, dizziness, lightheadedness, nervous tension, fatigue, vertigo, insomnia, and depression. Abnormalities in liver function tests and jaundice have sometimes been reported.

There is an increased risk of multiple births with clomifene therapy, but rarely more than twins. There is also an increased risk of ectopic pregnancy. Although there have been reports of congenital disorders such as neural tube defects or Down's syndrome in infants born to women treated with clomifene, the role of the drug in the causation of these defects has not been established and the incidence is reported to be similar to that for the general population.

Carcinogenicity. There have been a number of reports suggesting an association between drug therapy to treat infertility by stimulating ovulation and the subsequent development of ovarian cancer.[1-5] Concern has focused in particular on the use of clomifene citrate and gonadotrophins, and a study has reported an increased risk of ovarian cancer in women who had prolonged clomifene therapy (for one year or more) although not in those who received the drug for a shorter period.[6] No association between gonadotrophin therapy and ovarian cancer was noted in this study. The conclusions of this study were only tentative, since the numbers who developed ovarian cancer were small; it has been pointed out that a successfully achieved pregnancy may reduce the risk of some other cancers, and that the risks and benefits of the procedure are not easy to balance.[7] A review[8] of epidemiological and cohort studies concluded that clomifene was not associated with any increase in the risk of ovarian cancer when used for less than 12 cycles, but noted conflicting results, limitations of the data, and the need to control for infertility and nulliparity as risk factors for ovarian cancer. Further cohort[9,10] and case-control[11] studies, and pooled analyses,[12,13] have also found no association between use of clomifene and ovarian cancer.

As a matter of prudence the UK CSM has recommended that clomifene should not normally be used for more than 6 cycles.[14] However, the UK guidelines[15] on the treatment of infertility considered that the limit of 6 cycles related to one course of treatment only. In practice many women required more than one course and it was considered that benefit may be derived from use of up to 12 cycles.

1. Fishel S, Jackson P. Follicular stimulation for high tech pregnancies: are we playing it safe? *BMJ* 1989; **299:** 309–11.
2. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. *BMJ* 1989; **299:** 740.
3. Dietl J. Ovulation and ovarian cancer. *Lancet* 1991; **338:** 445.
4. Willemsen W, *et al.* Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993; **341:** 986–8.
5. Tewari K, *et al.* Fertility drugs and malignant germ-cell tumour of ovary in pregnancy. *Lancet* 1998; **351:** 957–8.
6. Rossing MA, *et al.* Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994; **331:** 77–6.
7. Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994; **331:** 805–6.
8. Duckitt K, Templeton AA. Cancer in women with infertility. *Curr Opin Obstet Gynecol* 1998; **10:** 199–203.
9. Potashnik G, *et al.* Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; **71:** 853–9.
10. Brinton LA, *et al.* Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 2004; **103:** 1194–1203.
11. Rossing MA, *et al.* A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; **160:** 1070–8.
12. Ness RB, *et al.* Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; **155:** 217–24.
13. Kashyap S, *et al.* Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 2004; **103:** 785–94.
14. CSM/MCA. Clomiphene (Clomid, Serophene): possible association with ovarian cancer. *Current Problems* 1995; **21:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 30/06/08)
15. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (issued February 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/Fertility_full.pdf (accessed 30/06/08) or http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 30/06/08)

Effects on the CNS. An infertile woman had convulsions when given clomifene citrate;[1] only 5 other cases had been reported since 1963.

1. Rimmington MR, *et al.* Convulsions after clomiphene citrate. *BMJ* 1994; **309:** 512.

Effects on the eyes. As mentioned above, clomifene may cause visual disturbances, which resolve on stopping treatment. However, visual symptoms have persisted in a few cases.[1]

1. Purvin VA. Visual disturbance secondary to clomiphene citrate. *Arch Ophthalmol* 1995; **113:** 482–4.

Effects on the fetus. After reports of neural tube defects in fetuses conceived after ovulation induction, analyses of congenital defect registers and follow-up studies of clomifene use suggested that the drug might possibly be associated with an increase in risk.[1-5] However, subsequent studies reported no increased risk,[6-8] and a pooled analysis[9] of 10 epidemiological studies found no strong evidence to confirm an association. Further studies have also reported no increased risk of neural tube defects[10] or hypospadias in male offspring[11] after exposure to fertility treatment. However, another case-control study[12] did find a potential association between clomifene and neural tube defects, but noted that because of the low baseline prevalence of the malformation, the absolute risk difference would be small. It is not clear whether the underlying infertility itself affects the risk of congenital defects and whether it may confound the calculated risk associated with clomifene.[9]

1. Cornel MC, *et al.* Ovulation induction and neural tube defects. *Lancet* 1989; **i:** 1386.
2. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 167.
3. Cuckle H, Wald N. Ovulation induction and neural tube defects. *Lancet* 1989; **ii:** 1281.
4. Cornel MC, *et al.* Ovulation induction, in-vitro fertilisation, and neural tube defects. *Lancet* 1989; **ii:** 1530.
5. Vollset SE. Ovulation induction and neural tube defects. *Lancet* 1990; **337:** 178.
6. Mills JL, *et al.* Risk of neural tube defects in relation to maternal fertility and fertility drug use. *Lancet* 1990; **336:** 103–4.
7. Rosa F. Ovulation induction and neural tube defects. *Lancet* 1990; **336:** 1327.
8. Werler MM, *et al.* Ovulation induction and risk of neural tube defects. *Lancet* 1994; **344:** 445–6.
9. Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 1995; **64:** 936–41.
10. Whiteman D, *et al.* Reproductive factors, subfertility, and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *Am J Epidemiol* 2000; **152:** 823–8.
11. Sørensen HT, *et al.* Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study. *BMJ* 2005; **330:** 126–7.
12. Wu YW, *et al.* Potential association between infertility and spinal neural tube defects in offspring. *Birth Defects Res A Clin Mol Teratol* 2006; **76:** 718–22.

Effects on mental function. Acute psychotic reactions with paranoid tendencies have occurred rarely during clomifene use.[1,2]

1. Siedentopf F, *et al.* Clomiphene citrate as a possible cause of a psychotic reaction during infertility treatment. *Hum Reprod* 1997; **12:** 706–7.
2. Oyffe I, *et al.* Clomiphene-induced psychosis. *Am J Psychiatry* 1997; **154:** 1169–70.

Precautions

Clomifene is contra-indicated in patients with liver disease or a history of liver dysfunction. It should not be used in pregnancy. Clomifene should not be used in women with uterine bleeding that is undiagnosed or caused by hormone-dependent tumours, or in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation. Patients should be warned of the possibility of multiple births.

Clomifene should not be given to women with ovarian cysts, except those with polycystic ovary syndrome, and the lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have an exaggerated response to usual doses of clomifene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomifene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced. Clomifene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Treatment should be stopped if visual disturbances develop and the patient warned that this might affect their ability to drive or operate machinery. Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer: a maximum of 6 cycles of treatment has generally been advised, but see also under Carcinogenicity, above.

Pharmacokinetics

Clomifene citrate is absorbed from the gastrointestinal tract. It is metabolised in the liver and slowly excreted via the bile. Unchanged drug and metabolites are excreted in the faeces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Enterohepatic recirculation takes place. The *E*-isomer is reported to be less well absorbed and more rapidly eliminated than the *Z*-isomer.

◊ References.

1. Szutu M, *et al.* Pharmacokinetics of intravenous clomiphene isomers. *Br J Clin Pharmacol* 1989; **27:** 639–40.

Uses and Administration

Clomifene is a nonsteroidal compound that has both oestrogenic and anti-oestrogenic properties, the latter residing principally in the *E*-isomer. Its action in stimulating ovulation is believed to be related to its anti-oestrogenic properties. It stimulates the secretion of pituitary gonadotrophic hormones, probably by blocking the negative feedback effect of oestrogens at receptor sites in the hypothalamus and pituitary.

Clomifene is the most widely used drug in the treatment of anovulatory infertility (p.2080). Therapy with clomifene will not be successful unless the woman, though anovulatory, is capable of ovulation and her partner is fertile. It is ineffective in primary pituitary or primary ovarian failure. The usual oral dose is 50 mg of clomifene citrate daily for 5 days, starting on or about the 5th day of the menstrual cycle or at any time if there is amenorrhoea. If ovulation does not occur, a course of 100 mg daily for 5 days may be given starting as early as 30 days after the previous one. Women should be examined for pregnancy and ovarian enlargement or cysts between treatment cycles. In general, 3 courses of therapy are adequate to assess whether ovulation is obtainable. If ovulation has not occurred, the diagnosis should be re-evaluated. Once ovulation is established, each treatment cycle of clomifene should be started on or about the 5th day of the menstrual cycle. If pregnancy has not occurred after a total of about 6 treatment cycles, licensed product information recommends that no further clomifene therapy should be given (but see also Carcinogenicity, above). Clomifene has also been used with gonadotrophins.

Clomifene has been used in the treatment of male infertility due to oligospermia to stimulate gonadotrophin release and enhance spermatogenesis, but there is limited convincing evidence of benefit.

Infertility. Reviews.

1. Homburg R. Clomiphene citrate—end of an era? a mini-review. *Hum Reprod* 2005; **20:** 2043–51.
2. Cèdrin-Durnerin I. Contre l'utilisation du citrate de clomifène dans les infertilités inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 61–5.
3. Merviel P. Pour une utilisation raisonnable du citrate de clomifène dans les infertilitiés inexpliquées. *Gynecol Obstet Fertil* 2006; **34:** 66–9.
4. The Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; **86** (5 suppl): S187–S193.

Preparations

BP 2008: Clomifene Tablets;
USP 31: Clomiphene Citrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Genozym; Serofene; ***Austral.:*** Clomhexal; Clomid; Fermil; Serophene; ***Austria:*** Serophene; ***Belg.:*** Clomid; Pergotime; ***Braz.:*** Clomid; Indux; Serophene; ***Canad.:*** Clomid; Serophene; ***Chile:*** Serofene†; Zimaquin; ***Cz.:*** Clomhexal; Clostilbegyt; Serophene†; ***Denm.:*** Pergotime; ***Fin.:*** Clomifen; ***Fr.:*** Clomid; Pergotime; ***Ger.:*** Clomhexal; ***Gr.:*** Serpafar; ***Hong Kong:*** Clomid†; Clostilbegyt; Duinum†; Fertilan; Ova-Mit; Serophene; ***Hung.:*** Clostilbegyt; Serophene†; ***India:*** Clofert; Clopreg; Fertomid; Ovipreg; Ovofar; Siphene; ***Indon.:*** Blesifen; Clomifil; Clovertil; Fensipros; Fertilphen; Fertin; Genoclom; Mestrolin; Ofertil; Pinfetil; Profertil; Provula; ***Irl.:*** Clomid; ***Israel:*** Ikaclomin; ***Ital.:*** Clomid; Prolifen; Serofene; ***Malaysia:*** Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate; Serophene†; ***Mex.:*** Omifin; Serophene†; ***Neth.:*** Clomid; Serophene; ***Norw.:*** Pergotime; ***NZ:*** Phenate; Serophene; ***Philipp.:*** Clomid; Clostil; I-Clom; Ova-Mit; ***Pol.:*** Clostilbegyt; ***Port.:*** Dufine; ***Rus.:*** Clostilbegyt (Клостилбегит); ***S.Afr.:*** Clomid; Clomihexal; Fertomid; Serophene†; ***Singapore:*** Clomid; Clostilbegyt; Duinum; Ova-Mit; Ovinum; Phenate†; Serophene; ***Spain:*** Clomifeno†; Omifin; ***Swed.:*** Pergotime; ***Switz.:*** Clomid; Serophene; ***Thai.:*** Clomid; Duinum; Ova-Mit; Ovinum; Serophene; ***Turk.:*** Fertilin; Gonaphene; Klomen; Serophene; ***UK:*** Clomid; ***USA:*** Clomid; Serophene; ***Venez.:*** Serophene.

Clostebol Acetate *(BAN, rINNM)* ⊗

Acetato de clostebol; 4-Chlorotestosterone Acetate; Chlortestosterone Acetate; Clostébol, Acétate de; Closteboli Acetas. 4-Chloro-3-oxoandrost-4-en-17β-yl acetate; 4-Chloro-17β-hydroxyandrost-4-en-3-one acetate.

Клостебола Ацетат

$C_{21}H_{29}ClO_3$ = 364.9.

CAS — 1093-58-9 (clostebol); 855-19-6 (clostebol acetate).

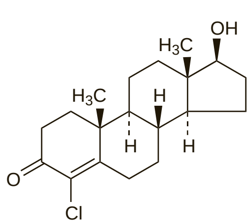

(clostebol)

Profile

Clostebol acetate has anabolic properties (see Testosterone, p.2129) and has been given by intramuscular injection and orally. It has also been applied topically to wounds and ulcers, and has been used as an ophthalmological preparation.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Trofodermin; ***Ger.:*** Megagrisevit†; ***Mex.:*** Trofodermin-S†.

Multi-ingredient: ***Braz.:*** Novaderm; Trofodermin; ***Chile:*** Trofodermin Neomicina; ***Ital.:*** Trofodermin; ***Mex.:*** Neobol; ***Thai.:*** Trofodermin†.

Conjugated Oestrogens

Conjugated Estrogens; Estrogeenit, konjugoidut; Estrogena Coniugata; Estrogenai, konjuguoti; Estrogener, konjugerade; Estrogènes conjugués; Estrogeni Coniunct; Estrogeni coniuncti; Estrógenos conjugados; Estrogeny konjugované; Konjugált ösztrogének; Konjüge Östrojen.

Эстрогены Конъюгированные

ATC — G03CA57.

ATC Vet — QG03CA57.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Estrogens, Conjugated). A mixture of various conjugated forms of oestrogens obtained from the urine of pregnant mares or by synthesis, dispersed in a suitable powdered diluent. It contains two principal components, 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the combined two is 79.5 to 88.0%. It also contains 2.5 to 9.5% of sodium 17α-estradiol sulfate, 13.5 to 19.5% of sodium 17α-dihydroequilin sulfate, and 0.5 to 4.0% of sodium 17β-dihydroequilin sulfate. All percentages are related to the labelled content.

An almost white brownish amorphous powder.

USP 31 (Conjugated Estrogens). A mixture of sodium estrone sulfate and sodium equilin sulfate, derived wholly or in part from equine urine or synthetically from estrone and equilin. It contains other conjugated oestrogenic substances of the type excreted by pregnant mares. It contains 52.5 to 61.5% of sodium estrone sulfate and 22.5 to 30.5% of sodium equilin sulfate; the total of the two combined should comprise 79.5 to 88.0% of the labelled content of conjugated oestrogens. It should contain, as sulfate conjugates, 13.5 to 19.5% of 17α-dihydroequilin, 2.5 to 9.5% of 17α-estradiol, and 0.5 to 4.0% of 17β-dihydroequilin, relative to the labelled content of conjugated oestrogens.

If it is obtained from natural sources it is a buff-coloured amorphous powder which is odourless or has a slight characteristic odour; the synthetic form is a white to light buff-coloured crystalline or amorphous powder, odourless or with a slight odour. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Synthetic Conjugated Estrogens, A

Synthetic Conjugated Oestrogens, A.

Синтетические Конъюгированные Эстрогены, A

Synthetic Conjugated Estrogens, B *(USAN)*

CE-10; Synthetic Conjugated Oestrogens, B.

Синтетические Конъюгированные Эстрогены, B

CAS — 746658-13-9.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormone Replacement Therapy, p.2071.

Effects on the cardiovascular system. In an early study of *men* with a previous myocardial infarction, treatment with conjugated oestrogens 5 mg daily was stopped because of a higher incidence of subsequent coronary events.[1] Moreover, treatment with the lower 2.5 mg dose was later also stopped because of suggestions of adverse trends including a greater incidence of venous thromboembolism.[2]

For the cardiovascular effects of HRT, including conjugated oestrogens, in women, see p.2073.

1. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA* 1970; **214:** 1303–13.
2. Coronary Drug Project Research Group. The Coronary Drug Project: findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973; **226:** 652–7.

Effects on the nervous system. Reversible chorea has been described in 2 women given conjugated oestrogens with a progestogen as postmenopausal HRT;[1,2] in 1 case the patient had a history of migraine and Sydenham's chorea.[1] Chorea also recurred in a postmenopausal woman with a history of chorea gravidarum when she was given vaginal conjugated oestrogens.[3]

1. Steiger MJ, Quinn NP. Hormone replacement therapy induced chorea. *BMJ* 1991; **302:** 762.
2. Suchowersky O, Muthipeedika J. A case of late-onset chorea. *Nat Clin Pract Neurol* 2005; **1:** 113–16.
3. Caviness JN, Muenter MD. An unusual cause of recurrent chorea. *Mov Disord* 1991; **6:** 355–7.

Hypersensitivity. An anaphylactic reaction after intravenous conjugated oestrogens has been reported.[1]

1. Searcy CJ, *et al.* Anaphylactic reaction to intravenous conjugated estrogens. *Clin Pharm* 1987; **6:** 74–6.

Interactions

See under Hormone Replacement Therapy, p.2076.

Pharmacokinetics

Conjugated oestrogens taken orally are hydrolysed by enzymes present in the intestine that remove the sulfate group and allow absorption of the unconjugated oestrogen. Metabolism occurs primarily in the liver; there is some enterohepatic recycling (see also under Estradiol, p.2098).

Uses and Administration

Conjugated oestrogens have actions and uses similar to those described for estradiol (see p.2098).

When used as menopausal HRT (p.2076) doses of 0.3 to 1.25 mg daily are given orally either cyclically or continuously, with a progestogen either cyclically or continuously in women with a uterus. Doses of 0.3 to 1.25 mg may also be used for the prevention of postmenopausal osteoporosis, but oestrogen therapy is generally reserved for women who are at significant risk and who cannot be given non-hormonal treatment. Topical vaginal therapy may be used specifically for menopausal atrophic vaginitis, atrophic urethritis, and kraurosis vulvae; 0.5 to 2 g of a 0.0625% cream may be used daily for 3 weeks of a 4-week cycle. For women with a uterus, the addition of cyclical progestogen is generally not required during topical vaginal oestrogen therapy. However, the use of a progestogen may be considered, and during long-term therapy these women should be monitored for evidence of endometrial hyperplasia.

When given as replacement therapy on a cyclical basis, oral doses of 1.25 mg daily are used for primary ovarian failure, adjusted according to response. Doses of 300 to 625 micrograms daily are usually given for female hypogonadism, although higher doses were formerly used.

For the palliative treatment of prostatic carcinoma (p.671), an oral dose of 1.25 to 2.5 mg three times daily has been used. A dose of 10 mg three times daily for at least 3 months has been used for palliative treatment of breast carcinoma in men (p.663) and postmenopausal women (p.661).

Abnormal uterine bleeding has been treated acutely by giving 25 mg of conjugated oestrogens by slow intravenous injection, repeated if required after 6 to 12 hours; the intramuscular route has also been used.

Synthetic conjugated oestrogens are derived from plant material, and are not a generic equivalent of Conjugated Estrogens described in USP 31 (see above). Synthetic conjugated estrogens, A, contains a mixture of nine derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.45 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. A dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative topical therapy should be considered if this is the only symptom being treated. Synthetic conjugated estrogens, B, contains a mixture of ten derivatives of estrone, equilin, estradiol, and equilenin. It is used in oral doses of 0.3 to 1.25 mg daily for the relief of vasomotor symptoms associated with the menopause. A dose of 300 micrograms daily may be used for menopausal vulvar and vaginal atrophy, but an alternative topical therapy should be considered if this is the only symptom being treated.

Administration in children. Conjugated oestrogens have been used to reduce final height in girls with constitutional tall stature (see Growth Disorders, under Estradiol, p.2099). They have also been used in children for some haemorrhagic disorders (below).

Haemorrhagic disorders. Case reports and small studies have described the use of high-dose conjugated oestrogens in the management of haemorrhagic disorders associated with renal failure,[1-5] although it is unclear how oestrogens might reduce prolonged bleeding times in these patients.[6] Treatment has been given orally, but an intravenous dose of 600 micrograms/kg given over 30 to 40 minutes, once daily for 5 days, has been reported most often.[6]

Conjugated oestrogens have also been used in various doses in the management of haemorrhagic cystitis (p.2178), particularly that caused by high-dose cyclophosphamide therapy (p.702). The successful use of 25 mg intravenously for 2 consecutive days has been reported,[7] as has a regimen consisting of a 1 mg/kg intravenous dose followed by 5 mg orally for 3 weeks.[8] A report[9] of treatment in 10 patients described the use of oral conjugated oestrogens in doses of 6 to 12 mg daily, usually in three divided doses, for durations of 5 days to 16 weeks.[9] Another report[10] of therapy in 10 children aged between 8 and 19 years described intravenous doses of 12.5 to 50 mg twice daily, often for 2 or 3 days, followed by oral doses ranging from 2.5 mg twice daily to 5 mg four times daily for durations of a few days to about 3 weeks.

Oestrogens have also been used in the treatment of other bleeding disorders (see Estradiol, p.2099).

1. Liu YK, *et al.* Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984; **ii:** 887–90.
2. Livio M, *et al.* Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; **315:** 731–5.
3. Seth S, Geier TM. Use of conjugated estrogens to control gastrointestinal tract bleeding in two patients with chronic renal failure. *Clin Pharm* 1988; **7:** 906–9.
4. Shemin D, *et al.* Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990; **89:** 436–40.
5. Heunisch C, *et al.* Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998; **18:** 210–7.
6. Hedges SJ, *et al.* Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; **3:** 138–53.
7. Kopterides P, *et al.* Cyclophosphamide-induced hemorrhagic cystitis successfully treated with conjugated estrogens. *Am J Hematol* 2005; **80:** 166–7.
8. Rodriguez Luna JM, *et al.* Control of massive hematuria in idiopathic hemorrhagic cystitis after administration of conjugated estrogen. *J Urol (Baltimore)* 1992; **148:** 1524–5.
9. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen–report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
10. Heath JA, *et al.* Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; **37:** 523–6.

Preparations

USP 31: Conjugated Estrogens Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Belestar; Livomarin; Premarin; ***Austral.:*** Premarin; ***Austria:*** Conjugen†; Oestro-Feminal†; Premarin; ***Belg.:*** Premarin†; ***Braz.:*** Estrogenon; Estroplus; Gestrocon; Menoprin; Menosedan†; Prem; Premarin; Repogen; ***Canad.:*** CES; Congest; Premarin; ***Chile:*** Climatrol E; Conpremin; Estrarona; Profemina; ***Cz.:*** Oestrofeminal†; Premarin†; Presomen†; ***Denm.:*** Premarin†; ***Fin.:*** Premarin†; ***Fr.:*** Premarin†; ***Ger.:*** Climarest†; Climopax mono; Femavit†; Oestrofeminal†; Presomen; Transannon†; ***Gr.:*** Premarin; ***Hong Kong:*** Equin; Premarin; ***Hung.:*** Premarin†; ***India:*** Espauz; Estrin; Premarin; ***Irl.:*** Premarin; ***Israel:*** Premaril†; Prevagin-Premaril†; ***Ital.:*** Emopremarin†; Premarin†; ***Malaysia:*** Premarin; ***Mex.:*** Equifan; Fahifem; Neradin; Premarin; Six Din; Sultrona; Terapova; ***Neth.:*** Dagynil; Premarin†; PremarinLite†; ***NZ:*** Premarin; ***Philipp.:*** Menpoz; Premarin; ***S.Afr.:*** Premarin; ***Singapore:*** Equin; Premarin; Longaplex; Premarin†; ***Swed.:*** Premarina†; ***Switz.:*** Premarin; Transannon†; ***Thai.:*** Estromon; Premarin; ***Turk.:*** Premarin; ***UK:*** Premarin; ***USA:*** Cenestin; Enjuvia; Premarin; ***Venez.:*** Biostrogen; Climatrol E; Menostat; Premarin.

Multi-ingredient: ***Arg.:*** Periofem Ciclico†; Periofem Continuo†; Premelle Ciclico†; Premelle Continuo†; ***Austral.:*** Menoprem†; Premia; Premia Continuous; Premia Low†; Provelle†; ***Austria:*** Perennia; Premarin compositum†; Premarin Plus; Sequennia; ***Belg.:*** Premelle Cycle†; Premelle†; Premplus†; ***Braz.:*** Menosedan Ciclo†; Menosedan Fase†; Menosedan MPA†; Menotensil; Premarin MPA†; Premelle; Premelle Ciclo; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.:*** Premplus; ***Chile:*** Climatrol Continuo; Climatrol HT; Climatrol HT Continuo; Conpremin Pak; Conpremin Pak Plus; Novafac; Novafac 30; Novafac CC; Prempak†; Profemina CC†; Profemina MP; ***Cz.:*** Cyclo-Premella†; Premella†; Presomen Compositum†; ***Ger.:*** Climopax; Climopax Cyclo; Presomen Compositum; ***Gr.:*** Premelle; Premelle Cycle; ***Hong Kong:*** Premelle; Premelle Cycle; Prempak†; ***Hung.:*** Cyclo-Premella†; Premella†; ***Irl.:*** Premique; Premique Cycle; Prempak-C; ***Israel:*** Premaril MP†; Premaril Plus MP†; ***Ital.:*** Premelle Combinato; Premelle S†; Premelle Sequenziale†; Prempak†; ***Malaysia:*** Plentiva Cycle 5†; Plentiva†; Premelle; Prempak†; ***Mex.:*** Premelle; ***Neth.:*** Premarin Plus†; Premelle Cycle†; Premelle†; PremelleLite†; Prempak-C†; ***NZ:*** Menoprem†; Premia Continuous; Premia†; Prempak-C†; ***Philipp.:*** Premelle; Premelle Cycle; ***Port.:*** Premarin Plus†; Premelle Cycle†; Premelle†; ***S.Afr.:*** Premelle; Premelle Cycle; Prempak N; ***Singapore:*** Premelle Cycle†; Premelle†; Prempak-C; ***Spain:*** Premelle; Premelle Ciclico; ***Swed.:*** Premelle Sekvens†; Premelle†; ***Switz.:*** Cyclo-Premella ST; Premarin Plus†; Premella; Premia†; ***Thai.:*** Premelle Cycle†; Premelle†; ***Turk.:*** Premelle; Premelle Cycle; ***UK:*** Premique; Premique Cycle; Prempak-C; ***USA:*** Premphase; Prempro; ***Venez.:*** Climatrol HT Ciclico; Climatrol HT Continuo; Cyclogesterin†; Premelle Ciclico†; Premelle Continuo; Premelle Plus Continuo†.

Cyclofenil *(BAN, rINN)* ⊗

Ciclofenilo; Cyclofénil; Cyclofenilum; Cyklofenil; F-6066; H-3452; ICI-48213; Siklofenil; Syklofeniili. 4,4′-(Cyclohexylidenemethylene)bis(phenyl acetate).

Циклофенил

$C_{23}H_{24}O_4$ = 364.4.

CAS — 2624-43-3.

ATC — G03GB01.

ATC Vet — QG03GB01.

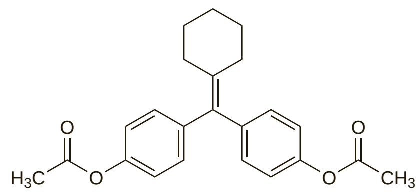

Profile

Cyclofenil is a nonsteroidal anti-oestrogen that has been used in the treatment of menstrual disturbances and anovulatory infertility due to hypothalamic-pituitary dysfunction.

It has been given orally in doses of 200 mg three times daily for 5 days, in a cyclical regimen for 3 or 4 cycles. It has also been given for menopausal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Menopax; ***Ital.:*** Neoclym; ***Mex.:*** Fertodur†; ***Turk.:*** Fertodur.

Cyproterone Acetate *(BANM, USAN, rINNM)*

Acetato de ciproterona; Ciproteron-acetát; Ciproterono acetatas; Cyproteronacetat; Cyproteron-acetát; Cyprotérone, acétate de; Cyproteroni acetas; NSC-81430; SH-714; SH-881 (cyproterone); Siproteron Asetat; Syproteroniasetaatti. 6-Chloro-1β,2β-dihydro-17α-hydroxy-3′*H*-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione acetate.

Ципротерона Ацетат

$C_{24}H_{29}ClO_4$ = 416.9.

CAS — 2098-66-0 (cyproterone); 427-51-0 (cyproterone acetate).

ATC — G03HA01.

ATC Vet — QG03HA01.

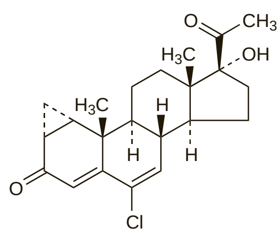

(cyproterone)

NOTE. Compounded preparations of cyproterone acetate may be represented by the following names:

- Co-cyprindiol (*BAN*)—cyproterone acetate 2000 parts and ethinylestradiol 35 parts (w/w).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cyproterone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone; very soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects

When given to men cyproterone reduces libido, inhibits spermatogenesis, reduces the volume of ejaculate, and causes infertility. There may be azoospermia after 8 weeks and slight atrophy of the seminiferous tubules, but these changes are slowly reversible and spermatogenesis usually recovers to pre-treatment levels about 3 to 5 months after stopping cyproterone. Abnormal spermatozoa may be produced. Gynaecomastia is common and permanent enlargement of the mammary glands may occur; galactorrhoea and benign nodules have been reported rarely. Fatigue and weakness are common and depressive mood changes can occur occasionally. Patients may experience weight changes, alterations in hair pattern, dry skin, and rarely rashes or hypersensitivity. Shortness of breath may occur, and anaemia and osteoporosis have been reported rarely. Liver function tests may be altered; there have also been reports of hepatitis, jaundice, and hepatic failure, sometimes fatal, developing usually after several months of high-dose cyproterone therapy, but an association with liver cancer is uncertain.

When low-dose cyproterone is given with ethinylestradiol to women, adverse effects associated with combined oral contraceptives (see p.2059) may occur.

Carcinogenicity. See Effects on the Liver, below.

Effects on the cardiovascular system. Combined oral contraceptives are associated with a small increased risk of cardiovascular disease (see p.2062). A case-control study suggested that the risk of venous thromboembolism may be further increased for women taking combined contraceptives containing cyproterone compared with levonorgestrel.[1] A review by the authorities in New Zealand considered the risk to be at least as great as with third-generation oral contraceptives,[2] a conclusion further supported by a study in that country of the contraceptives used by women discharged from hospital with a diagnosis of deep-vein thrombosis or pulmonary embolism.[3] In 2002, the UK CSM[4] warned that preparations containing cyproterone and ethinylestradiol should not be used solely for contraception, but for treatment of severe acne that had not responded to oral antibacterials, or for moderately severe hirsutism, and that they should be withdrawn 3 or 4 cycles after the treated condition has completely resolved. However, others[5,6] have questioned some study results, concluding that preparations containing cyproterone are not associated with a risk in excess of that associated with conventional combined oral contraceptives including those containing levonorgestrel. Some[7] have also called for the removal of the CSM recommendation to limit the duration of therapy, particularly as acne and hirsutism frequently recur after stopping cyproterone therapy. In 2008, the CHM (formerly the CSM) reconfirmed its 2002 advice on the use of cyproterone with ethinylestradiol.[8] However, it added that for women with severe hyperandrogenism, in whom symptoms usually recur when treatment is stopped, therapy could be continued with regular specialist review until the symptoms were judged unlikely to recur. It was also recommended that, for all women, treatment can be restarted at any time if acne or hirsutism recurs after stopping therapy.

The study of any association may be confounded by the adverse cardiovascular risk associated with polycystic ovary disease, an underlying condition in many women given cyproterone with ethinylestradiol to manage acne and hirsutism.[6]

1. Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001; **358:** 1427–9.
2. Savage R. New Zealand Medicines and Medical Devices Safety Authority. Venous thromboembolism with Diane 35 and Estelle 35 (issued March 2002). Available at: http://www.medsafe.govt.nz/Profs/PUarticles/VTEwithCPA.htm (accessed 27/06/08)
3. Heuser P, *et al.* Specific oral contraceptive use and venous thromboembolism resulting in hospital admission. *N Z Med J* 2004; **117:** U1176. Available at: http://www.nzma.org.nz/journal/117-1206/1176/content.pdf (accessed 27/06/08)
4. CSM/MCA. Cyproterone acetate (Dianette): risk of venous thromboembolism (VTE). *Current Problems* 2002; **28:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
5. Spitzer WO. Cyproterone acetate with ethinylestradiol as a risk factor for venous thromboembolism: an epidemiological evaluation. *J Obstet Gynaecol Can* 2003; **25:** 1011–18.
6. Seaman HE, *et al.* Venous thromboembolism associated with cyproterone acetate in combination with ethinyloestradiol (Dianette): observational studies using the UK General Practice Research Database. *Pharmacoepidemiol Drug Safety* 2004; **13:** 427–36.
7. Franks S, *et al.* Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy. *Hum Reprod* 2008; **23:** 231–2.
8. MHRA/CHM. Cyproterone acetate with ethinylestradiol (co-cyprindiol): recommended duration of use. *Drug Safety Update* 2008; **1** (9): 4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)

Effects on the eyes. Bilateral optic atrophy in an elderly male patient was thought to be associated with cyproterone.[1] The authors could find no other cases from the published literature or the manufacturers' records. Central retinal vein occlusion occurred in a 28-year-old woman given cyproterone for the treatment of hair loss.[2]

1. Markus H, *et al.* Visual loss and optic atrophy associated with cyproterone acetate. *BMJ* 1992; **305:** 159.
2. Zaoui M, *et al.* Occlusion de la veine centrale de la rétine sous anti-androgènes. *J Fr Ophtalmol* 2000; **23:** 42–4.

Effects on the liver. There have been numerous reports of hepatic reactions associated with cyproterone acetate. In February 1995, the UK CSM noted that it had received 96 reports of reactions including hepatitis, cholestatic jaundice, and hepatic failure, following cyproterone treatment;[1] 33 cases had led to fatalities. Nearly all cases (91 of 96) were in elderly men typically receiving high doses (300 mg daily) for prostatic cancer, and toxicity usually developed after several months of treatment. In view of this it was recommended that the use of cyproterone acetate in prostatic cancer be restricted to short courses for the testosterone flare associated with the commencement of gonadorelin analogue therapy, or for hot flushes after surgical or chemical castration, or for patients unresponsive to, or intolerant of, other treatments. A retrospective analysis[2] of data from 105 patients with advanced prostate cancer, who had received cyproterone acetate 150 mg daily, found mild to moderate hepatotoxicity in 6 patients and severe toxicity in 4. There was a higher occurrence of hepatotoxicity (19 cases out of 124 patients) in a similar group that had been given flutamide. Fourteen published case reports have also been briefly reviewed.[3] Patients with chronic viral hepatitis might be at higher risk of developing hepatotoxicity from cyproterone therapy.[4]

Although there is little doubt of the risk of hepatotoxicity, suggestions of an association between cyproterone therapy and the development of liver cancer remain contentious. There are individual reports of hepatocellular carcinoma developing in patients receiving cyproterone,[5,6] and some evidence *in vitro* of the formation of DNA adducts in exposed hepatocytes,[7] but there does not seem to be clinical evidence to support any association between use of cyproterone acetate and the development of liver tumours.[7,8]

1. CSM/MCA. Hepatic reactions with cyproterone acetate (Cyprostat, Androcur). *Current Problems* 1995; **21:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 27/06/08)
2. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66:** 735–40.
3. Savidou I, *et al.* Hepatotoxicity induced by cyproterone acetate: a report of three cases. *World J Gastroenterol* 2006; **12:** 7551–5.
4. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36:** 293–7.
5. Watanabe S, *et al.* Three cases of hepatocellular carcinoma among cyproterone users. *Lancet* 1994; **344:** 1567–8.
6. Rüdiger T, *et al.* Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinyloestradiol. *Lancet* 1995; **345:** 452–3.
7. Lewis S. Warning on cyproterone. *Lancet* 1995; **345:** 247.
8. Rabe T, *et al.* Liver tumours in women on oral contraceptives. *Lancet* 1994; **344:** 1568–9.

Precautions

When used for hypersexuality, cyproterone is contra-indicated in men with liver diseases or malignant or wasting diseases. In addition, it should not be given to men with severe chronic depression, severe diabetes with vascular changes, sickle-cell anaemia, or to those with a history of thromboembolic disorders. It may delay bone maturation and testicular development and so should not be given to immature youths. When used for prostate cancer, there are no absolute contra-indications to the use of cyproterone, but the above conditions should prompt cautious consideration of the risks and benefits.

In men treated with cyproterone, liver function should be monitored before starting, and regularly during, treatment, and whenever any symptoms or signs suggestive of hepatotoxicity occur. If cyproterone-induced hepatotoxicity occurs, treatment should be withdrawn. In men with prostate cancer, it may be advisable to limit the duration of treatment (see Effects on the Liver, above). Men with diabetes require careful monitoring of diabetic control. Since anaemia has been seen, regular blood counts are recommended before and during treatment. Adrenocortical suppression has been reported and function should be monitored regularly during treatment. Patients should be advised that fatigue and weakness are common and may interfere with driving and the operation of machinery.

When cyproterone is given with ethinylestradiol to women the precautions for combined oral contraceptives (see p.2065) should be observed.

Pregnancy. Use of cyproterone during pregnancy might carry a risk of feminisation of a male fetus. However, there are a few case reports of healthy male infants born to mothers who had inadvertently taken a combination of cyproterone acetate and ethinylestradiol during the early stages of pregnancy,[1,2] and of a male fetus that was found to have no malformations after abortion was induced.[3] For further information on oral contraceptive use in pregnancy, see p.2067.

1. Statham BN, *et al*. Conception during 'Diane' therapy—a successful outcome. *Br J Dermatol* 1985; **113:** 374.
2. Bye P. Comments on 'conception during "Diane" therapy—a successful outcome'. *Br J Dermatol* 1986; **114:** 516.
3. Bergh T, Bakos O. Exposure to antiandrogen during pregnancy: case report. *BMJ* 1987; **294:** 677–8.

Interactions

UK licensed product information states that alcohol may reduce the effectiveness of cyproterone acetate as it is ineffective in chronic alcoholics. Dosage requirements of oral antidiabetics and insulin may be altered because of cyproterone's effects on carbohydrate metabolism.

When given with ethinylestradiol to women, interactions similar to those for combined oral contraceptives (see p.2067) might be anticipated.

Pharmacokinetics

Cyproterone acetate is slowly absorbed from the gastrointestinal tract with peak plasma concentrations being achieved in about 3 hours. It is about 96% bound to plasma proteins, mainly albumin. The terminal elimination half-life is about 43 hours. Cyproterone is metabolised by various pathways including hydroxylation and conjugation; about 35% of a dose is excreted in urine, the remainder being excreted in the bile. The principal metabolite, 15β-hydroxycyproterone, has anti-androgenic activity.

The elderly. In a study[1] of healthy men, a decrease in hepatic clearance of cyproterone acetate was found in elderly men and thought to be due to an age-related reduction in liver volume.

1. Kuhnz W, *et al.* Investigation into the age-dependence of the pharmacokinetics of cyproterone acetate in healthy male volunteers. *Eur J Clin Pharmacol* 1997; **53:** 75–80.

Uses and Administration

Cyproterone acetate is a progestogen (see Progesterone, p.2126) with anti-androgenic properties.

It is used for the **control of libido** in severe hypersexuality or sexual deviation in men (see Disturbed Behaviour, p.954). The usual oral dose is 50 mg twice daily after meals.

It is also used for the palliative treatment of **prostatic carcinoma** (p.671), to control disease flare or hot flushes associated with gonadorelin analogue therapy, and to control hot flushes associated with orchidectomy. In palliative treatment where gonadorelin analogues or surgery are contra-indicated, not tolerated, or where oral therapy is preferred, doses of 200 to 300 mg daily are given in 2 or 3 divided doses after meals. The usual initial dose for disease flare is 300 mg daily in 2 or 3 divided doses after meals, which may be reduced to 200 mg daily if the higher dose is not tolerated. For the treatment of hot flushes, a dose of 50 mg daily is used; this may be increased up to 150 mg daily in 3 divided doses if necessary.

Cyproterone acetate may be used with ethinylestradiol in women for the control of **acne** and **hirsutism** (see below). The usual oral doses are 2 mg of cyproterone acetate with 35 micrograms of ethinylestradiol given daily for 21 days of each menstrual cycle; the first treatment course is started on the first day of the menstrual cycle and each subsequent course is started after 7 tablet-free days have followed the preceding course. This regimen also provides contraception, and patients relying on this effect should be given the same advice regarding missed doses and reduced efficacy due to vomiting and diarrhoea as that given for combined oral contraceptives (see p.2069). Treatment should be withdrawn 3 or 4 cycles after the androgen-dependent condition has completely resolved, but repeat courses may be given if it recurs.

Cyproterone acetate has also been given by depot intramuscular injection. A dose of 300 mg given once every 10 to 14 days has been used to control libido; once a satisfactory effect has been obtained, the dose may be reduced by gradually increasing the interval between injections until a stable maintenance dose is reached. In palliative therapy of prostatic carcinoma, 300 mg may be given once every 2 weeks after orchidectomy, or once weekly without orchidectomy.

Dose-related hepatotoxicity has occurred with cyproterone, particularly in men treated for prostate cancer (see Effects on the Liver and Precautions, above).

Acne. Cyproterone acetate may be used in the management of acne (p.1577), generally in women with signs of hyperandrogenism. An oral combination of cyproterone acetate 2 mg with ethinylestradiol 35 micrograms, which also provides contraception, is often used in women whose condition is moderately severe, and may be considered in women with mild acne who wish to use hormonal contraception. In more severe disease, higher doses of cyproterone may be added to this low-dose regimen; examples include giving cyproterone acetate 50 mg daily for 10 or 21 days of each cycle.[1] A systematic review[2] considered that a combination of ethinylestradiol with low-dose cyproterone acetate was more effective in the treatment of acne than combined oral contraceptives containing levonorgestrel, but noted that this was based on limited evidence.

1. Beylot C, *et al.* Oral contraceptives and cyproterone acetate in female acne treatment. *Dermatology* 1998; **196:** 148–52.
2. Arowojolu AO, *et al.* Combined oral contraceptive pills for treatment of acne. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).

Alopecia. Cyproterone acetate has been tried in the treatment of female-pattern alopecia (p.1577). In premenopausal women, oral doses of 50 or 100 mg daily have usually been given in sequential regimens with an oestrogen or combined oral contraceptive; continuous treatment using 50 mg daily has been given to postmenopausal women. It has generally been considered that women with other signs of hyperandrogenism, such as acne and seborrhoea, as well as hair loss are most likely to benefit from cyproterone but results from small studies have been mixed.[1-3]

1. Vexiau P, *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146:** 992–9.
2. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril* 2003; **79:** 91–5.
3. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.

Gender reassignment. Cyproterone acetate is used for its anti-androgenic effects in male-to-female transsexuals.[1,2] An oral dose of 50 mg twice daily is usually given with an oestrogen (see Estradiol, p.2099).

1. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
2. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Hidradenitis suppurativa. Beneficial responses to cyproterone acetate with ethinylestradiol have been seen[1-3] in women with hidradenitis suppurativa, an androgen-dependent disorder of the skin and hair in the pubic and axillary regions.

1. Mortimer PS, *et al.* A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; **115:** 263–8.
2. Sawers RS, *et al.* Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; **115:** 269–74.
3. Mortimer PS, *et al.* Mediation of hidradenitis suppurativa by androgens. *BMJ* 1986; **292:** 961.

Hirsutism. Hirsutism is an abnormal growth in females of coarse pigmented terminal hair in an adult male pattern, and is one of the clinical expressions of hyperandrogenism. Most women with hirsutism have increased concentrations of circulating androgens from the ovaries associated with polycystic ovary syndrome (p.2080). In rare cases, the adrenal gland is the primary source of increased androgens, for example, in congenital adrenal hyperplasia (p.1502). In a few cases, severe hirsutism is associated with frank virilisation due to massively increased circulating androgen concentrations from an androgen-secreting tumour. Hirsutism is an adverse effect of androgenic progestogens, such as norgestrel, used in hormonal contraceptives and HRT. Androgens and anabolic steroids may also cause hirsutism in females.

Treatment for hirsutism uses topical cosmetic treatments such as bleaching, shaving, plucking, electrolysis, and laser hair removal, and in the mildest cases this may be all that is required. However, such mechanical means of treatment are more usually combined with drug therapy to prevent further conversion of vellus to terminal hair, and to slow the regrowth of terminal hair, which may become lighter and softer. Because the growth cycle of hair is long, a response to therapy may not be seen for 6 to 12 months.[1-3]

Combined *hormonal contraceptives* containing non-androgenic progestogens are widely used for hirsutism but their effects are generally limited.[1-3] The mainstay of oral drug therapy for hirsutism is an anti-androgen, the most commonly used being the steroidal anti-androgens *cyproterone acetate* and *spironolactone*. To increase efficacy (by suppressing ovarian androgen production) and minimise the chance of conception (because of the risk of feminisation of a male fetus), cyclical ethinylestradiol is commonly used with cyproterone acetate. Combined non-androgenic hormonal contraceptives are commonly used with spironolactone, which has no progestogenic activity. Cyproterone acetate may be used in a low-dose combined preparation containing cyproterone acetate 2 mg with ethinylestradiol 35 micrograms.[2-4] In more severe hirsutism, the two drugs may be prescribed separately in a 'reversed sequential regimen'. High-dose regimens[2] have used cyproterone acetate 100 mg daily given on days 5 to 14 of the menstrual cycle with ethinylestradiol 50 micrograms on days 5 to 24. However, lower doses are also effective, with fewer adverse effects; such regimens include[4] cyproterone acetate 50 mg (days 5 to 15) with ethinylestradiol 20 micrograms (days 5 to 25), or cyproterone acetate 12.5 mg (days 5 to 15) with ethinylestradiol 10 to 20 micrograms (days 5 to 25). Alternatively,[2] cyproterone acetate 25 to 50 mg daily may be added to the first 10 days of any low-dose combined oral contraceptive. When a satisfactory response has been achieved, the cyproterone dosage is gradually reduced, and eventually the low-dose combination preparation may be sufficient.

In some countries spironolactone is the drug of choice for the treatment of hirsutism, particularly if there is associated obesity and hypertension; doses of 100 to 200 mg daily are generally used.[1,2,4] Despite its wide use, however, evidence of benefit is considered scanty.[5] *Flutamide*, *finasteride*, and *leuprorelin* have also been shown to be effective, although some consider finasteride to be less active.[4] The condition has also been reported to respond to *ketoconazole*. *Eflornithine* is used topically for the reduction of facial hair.[1,3,4] It is thought to slow hair growth by the inhibition of ornithine decarboxylase in hair follicles.

Corticosteroids can suppress adrenal androgen production, but results with *dexamethasone* have been disappointing and the addition of an anti-androgen is usually needed.[4] Corticosteroids may have a limited role in managing hirsutism associated with congenital adrenal hyperplasia.[1,2]

1. Rosenfield RL. Hirsutism. *N Engl J Med* 2005; **353:** 2578–88.
2. Claman P, *et al.* Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines no. 110, January 2002: Hirsutism: evaluation and treatment. *J Obstet Gynaecol Can* 2002; **24:** 62–7. Also available at: http://www.sogc.org/guidelines/public/110E-CPG-January2002.pdf (accessed 27/06/08)
3. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. *Best Pract Res Clin Endocrinol Metab* 2006; **20:** 221–34.
4. Carmina E. A risk-benefit assessment of pharmacological therapies for hirsutism. *Drug Safety* 2001; **24:** 267–76.
5. Farquhar C, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 27/06/08).

Precocious puberty. Although cyproterone acetate has been used for the treatment of central precocious puberty (p.2081), it has generally been superseded and is now given in a short course to prevent the initial stimulatory effect of gonadorelin analogue therapy. The use of an oral dose of cyproterone acetate 50 mg twice daily, given from 3 weeks before to 2 weeks after starting the gonadorelin analogue, has been reported.[1] Menstrual-like bleeding may occur in girls after stopping cyproterone, depending on the degree of precocity. Gonadorelin analogue therapy does not control adrenal production of sex hormones, which, if overactive, can stimulate adrenarche and advancement of bone age; cyproterone acetate in usual doses of 10 to 20 mg twice daily has been used to treat this.[1]

Cyproterone acetate may sometimes be used to suppress sexual maturation in the management of peripheral forms of precocious puberty. Although it is not licensed for this, the *BNFC* includes an initial oral dose of 25 mg twice daily, adjusted according to response.

1. Laron Z, Kauli R. Experience with cyproterone acetate in the treatment of precocious puberty. *J Pediatr Endocrinol Metab* 2000; **13** (suppl): 805–10.

Preparations

BP 2008: Cyproterone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Androcur; Androstat; Asisdun†; Asoteron; Ceprater; Ciclamil; Ciprofarma; Ciproplex; CPD†; Kebirterona; Omnigeriat; Purfilx; Rubidox†; ***Austral.:*** Androcur; Cyprohexal; Cyprone; Cyprostat; Procur; ***Austria:*** Andro-Diane; Androcur; Curandron; ***Belg.:*** Androcur; Cyproplex; ***Braz.:*** Andelux; Androcur; Androneo; Androsteron; Bioterona†; Cetoteron; Ciprostat; ***Canad.:*** Alti-CPA†; Androcur; ***Chile:*** Ciproviron†; ***Cz.:*** Androcur; Cyproplex; Minerva; ***Denm.:*** Androcur; ***Fin.:*** Androcur; ***Fr.:*** Androcur; Kaliale; ***Ger.:*** Androcur; Virilit; ***Gr.:*** Androcur; ***Hong Kong:*** Androcur; ***Hung.:*** Androcur; ***Indon.:*** Androcur; ***Irl.:*** Androcur; ***Israel:*** Androcur; Armocur†; Cypron; ***Ital.:*** Androcur; ***Malaysia:*** Androcur; Cyproplex; ***Mex.:*** Androcur; Neoproxil; ***Neth.:*** Androcur; Curandron; ***Norw.:*** Androcur; ***NZ:*** Androcur; Procur; Siterone; ***Philipp.:*** Androcur; ***Pol.:*** Androcur; ***Port.:*** Androcur; ***Rus.:*** Androcur (Андрокур); ***S.Afr.:*** Androcur; Cyproplex; ***Singapore:*** Androcur; ***Spain:*** Androcur; ***Swed.:*** Androcur; Diane; ***Switz.:*** Androcur; Elleacnelle; ***Thai.:*** Androcur; ***Turk.:*** Androcur; ***UK:*** Androcur; Cyprostat; ***Venez.:*** Androcur; Asoteron.

Multi-ingredient: ***Arg.:*** Avancel; Biofem 35; Climene; Diane; Mileva; ***Austral.:*** Brenda-35 ED; Climen; Diane; Estelle; Juliet†; ***Austria:*** Bellgyn; Climen; Dialuna; Diane; Femogyn; Midane; Minerva; Sterigynon; Xylia; ***Belg.:*** Claudia; Climen; Co-Cyproterone; Cyprodiol; Daphne; Diane; Docyproestra; Gratiella; Merckelisa; Ratiopharmeva; ***Braz.:*** Artemidis; Ciprane; Climene; Diane; Elamax; Ferane 35; Repopil; Selene; Tess; ***Canad.:*** Diane; ***Chile:*** Anuar; Climene; Diane; Dixi-35; Drina; Evilin; Lady-Ten 35; ***Cz.:*** Chloe; Climen; Diane; Vreya; ***Denm.:*** Climen; Dianova; Feminil; ***Fin.:*** Cypretyl; Diane; Femilar; ***Fr.:*** Climene; Diane; Evepar; Holgyeme; Lumalia; Minerva; ***Ger.:*** Attempta; Bella; Clevia; Climen; Cyproderm; Cypronette; Diane; Ergalea; Juliette; ***Gr.:*** Gynofen 35; ***Hong Kong:*** Climen 28; Diane; ***Hung.:*** Climen; Cypromix; Diane; Minerva; ***India:*** Diane; Ginette; ***Indon.:*** Climen 28; Diane; ***Irl.:*** Dianette; ***Israel:*** Diane; Estelle; ***Ital.:*** Climen; Diane; Pausene; Visofid; ***Malaysia:*** Climen; Diane; Estelle; ***Mex.:*** Climene; Diane; Eunice 35-ED; Mileva; ***Neth.:*** Climene; Diane; ***Norw.:*** Climen†; Diane; ***NZ:*** Diane; Estelle; ***Philipp.:*** Althea; Climen 28; Diane; ***Pol.:*** Climen; Cyprest; Diane; ***Port.:*** Climen; Diane; ***Rus.:*** Climen (Климен); Diane (Диане); ***S.Afr.:*** Climen; Diane; Diva; Ginette; Minerva; ***Singapore:*** Climen; Diane; Estelle; ***Spain:*** Climen; Clisin†; Diane; ***Switz.:*** Climen; Cypestra; Diane; Feminac; Minerva; ***Thai.:*** Climen; Diane; Helen†; Lady-35; Manoane; Preme†; Sucee; ***Turk.:*** Climen; Diane; ***UK:*** Acnocin; Cicafem; Clairette; Dianette; Diva; ***Venez.:*** Climene; Diane; Dixi.

Danazol *(BAN, USAN, pINN)* ⊗

Danatsoli; Danazolum; Win-17757. 17α-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17β-ol.

Даназол

$C_{22}H_{27}NO_2$ = 337.5.

CAS — 17230-88-5.

ATC — G03XA01.

ATC Vet — QG03XA01.

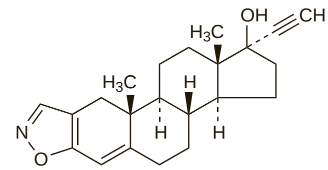

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Danazol). A white to pale yellow crystalline powder. Practically insoluble or insoluble in water and in petroleum spirit; sparingly soluble in alcohol and in benzene; soluble in acetone; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects of danazol that reflect inhibition of the pituitary-ovarian axis include menstrual disturbances and amenorrhoea (occasionally persistent), hot flushes, sweating, reduction in breast size, changes in libido, vaginal dryness and irritation, emotional lability, and nervousness.

Adverse effects attributable to androgenic activity include acne, oily skin or hair, mild hirsutism, oedema, weight gain, deepening of the voice, androgenic alopecia, and rarely clitoral hypertrophy. Testicular atrophy and a reduction in spermatogenesis may occur.

Other adverse effects include gastrointestinal disturbances, increased or decreased blood cell counts, thrombotic events, headache, backache, dizziness, tremor, depression, fatigue, sleep disorders, muscle spasm or cramp, skin rash, hyperglucagonaemia, abnormal glucose tolerance, decreased serum high-density-lipoprotein cholesterol, increased serum low-density-lipoprotein cholesterol, and elevation of liver-function test values and rarely cholestatic jaundice. Some patients may experience palpitations, tachycardia, and hypertension. Benign intracranial hypertension and visual disturbances have occurred.

Effects on carbohydrate metabolism. Diabetes mellitus developed in a patient given danazol 400 mg twice daily for endometriosis.[1] The diabetes developed 8 weeks after starting danazol therapy and resolved completely after the drug was stopped.

1. Seifer DB, *et al.* Insulin-dependent diabetes mellitus associated with danazol. *Am J Obstet Gynecol* 1990; **162:** 474–5.

Effects on the liver. As with other 17α-alkylated steroids (see p.2130), hepatic adverse effects have been associated with danazol, including hepatitis[1] and cholestasis.[2,3] Hepatic adenoma has occurred after long-term danazol use.[4-7] Adenomas are often removed surgically because of the risks of haemorrhage and malignant transformation, but regression over 18 months and 2 years after stopping danazol has been described in 2 patients.[6] There have also been rare reports of focal nodular hyperplasia,[7,8] hepatocellular carcinoma,[9] and peliosis hepatis.[10]

A case of acute hepatic failure has been attributed to danazol in a patient already taking ciclosporin (see below).

1. Ohsawa T, Iwashita S. Hepatitis associated with danazol. *Drug Intell Clin Pharm* 1986; **20:** 889.
2. Boue F, *et al.* Danazol and cholestatic hepatitis. *Ann Intern Med* 1986; **105:** 139–40.
3. Bray GP. *et al.* Resolution of danazol-induced cholestasis with S-adenosylmethionine. *Postgrad Med J* 1993; **69:** 237–9.
4. Fermand JP, *et al.* Danazol-induced hepatocellular adenoma. *Am J Med* 1990; **88:** 529–30.
5. Bork K, *et al.* Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999; **353:** 1066–7.
6. Bork K, Schneiders V. Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. *J Hepatol* 2002; **36:** 707–9.
7. Bartley J, *et al.* Hepatocellular adenoma and focal nodular hyperplasia after long-term use of danazol for endometriosis: a case report. *Arch Gynecol Obstet* 2004; **269:** 290–3.
8. Helsing P, Nielsen EW. Hepatocellular focal nodular hyperplasia after danazol treatment for hereditary angio-oedema. *Acta Derm Venereol* 2006; **86:** 272–3.
9. Confavreux C, *et al.* Danazol-induced hepatocellular carcinoma. *QJM* 2003; **96:** 317–18.
10. Makdisi WJ, *et al.* Fatal peliosis of the liver and spleen in a patient with agnogenic myeloid metaplasia treated with danazol. *Am J Gastroenterol* 1995; **90:** 317–8.

Effects on the pancreas. There have been reports of pancreatitis in patients receiving danazol.[1,2]

1. Chevalier X, *et al.* Danazol induced pancreatitis and hepatitis. *Clin Rheumatol* 1990; **9:** 239–41.
2. Balasch J, *et al.* Acute pancreatitis associated with danazol treatment for endometriosis. *Hum Reprod* 1994; **9:** 1163–5.

Effects on the skin and hair. There have been isolated reports of erythema multiforme occurring in patients given danazol. In 3 cases the reaction developed about 2 weeks after starting danazol, and was effectively managed by stopping danazol and treating with corticosteroids.[1,2]

Hirsutism is a recognised adverse effect of danazol, but is usually mild. Excessive facial hair growth of sudden onset, sufficient to cause distress, has been described in a woman given danazol for mastalgia. The hirsutism improved after stopping the danazol.[3]

1. Gately LE, Andes WA. Danazol and erythema multiforme. *Ann Intern Med* 1988; **109:** 85.
2. Reynolds NJ, Sansom JE. Erythema multiforme during danazol therapy. *Clin Exp Dermatol* 1992; **17:** 140.
3. Zawar V, Sankalecha C. Facial hirsutism following danazol therapy. *Cutis* 2004; **74:** 301–3.

Precautions

Danazol should be used with caution in conditions that may be adversely affected by fluid retention, such as in cardiovascular, hepatic, and renal disorders; it should be avoided in marked dysfunction. It should also be used with care in patients with diabetes mellitus, polycythaemia, abnormal blood lipids, migraine, or epilepsy. Danazol should not be given to patients with undiagnosed genital bleeding or androgen-dependent tumours. As with other 17α-alkylated compounds, there is an increased risk of liver disorders and liver function should be monitored during therapy. It should not be used in patients with a thromboembolic disorder or a history of thrombosis.

Danazol should not be given during pregnancy because of a possible androgenic effect on the female fetus (see below), and non-hormonal contraception is recommended during treatment. Caution is required in children and adolescents since precocious sexual development may occur in boys and virilisation in girls, and premature epiphyseal closure may occur in both sexes.

In the event of androgenic effects, danazol should be withdrawn, as they may prove irreversible on continued use.

Breast feeding. Licensed product information warns that danazol should be avoided in breast-feeding women because of the theoretical potential for androgenic effects in the infant.

Porphyria. Danazol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Reports of masculinisation of female infants born to mothers who had received danazol during pregnancy.[1-3]

1. Shaw RW, Farquhar JW. Female pseudohermaphroditism associated with danazol exposure in utero: case report. *Br J Obstet Gynaecol* 1984; **91:** 386–9.
2. Kingsbury AC. Danazol and fetal masculinization: a warning. *Med J Aust* 1985; **143:** 410–11.
3. Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol* 1992; **99:** 212–15.

Interactions

Therapy with danazol may inhibit the hepatic metabolism of a number of drugs including carbamazepine (see p.475), ciclosporin (see below), and possibly tacrolimus (see p.1845). Danazol may also enhance the effects of warfarin (see Sex Hormones under Warfarin, p.1431). Introduction of danazol appeared to reduce the maintenance requirement for alfacalcidol (see p.1988). Rhabdomyolysis has been attributed to use of danazol with statins (see p.1393).

Ciclosporin. Danazol may raise ciclosporin concentrations (see p.1828), possibly by inhibiting its metabolism.

A case of fatal acute hepatic failure due to centrilobular massive hepatic necrosis was attributed to danazol in a patient already taking ciclosporin.[1] Danazol may have raised the ciclosporin concentrations in this case, but the authors speculated that an alternative interaction between the two drugs might have played a role in this reaction to danazol.

1. Hayashi T, *et al.* Fatal acute hepatic failure induced by danazol in a patient with endometriosis and aplastic anemia. *J Gastroenterol* 2001; **36:** 783–6.

Pharmacokinetics

Danazol is absorbed from the gastrointestinal tract and metabolised in the liver; absorption is markedly increased if it is taken with food. A plasma elimination half-life of 3 to 6 hours has been reported after a single dose, but is increased to about 26 hours with repeated dosing. Ethisterone, 2-hydroxymethylethisterone, and 17-hydroxymethylethisterone are the major metabolites, though none have pituitary inhibiting activity. Danazol and its metabolites may undergo enterohepatic circulation. Metabolites are excreted in the urine and faeces.

Uses and Administration

Danazol suppresses the pituitary-ovarian axis by inhibiting pituitary output of gonadotrophins. It has weak androgenic activity.

Danazol has been given orally in the treatment of a variety of conditions including endometriosis, some benign breast disorders such as mastalgia and fibrocystic breast disease, gynaecomastia, menorrhagia associated with dysfunctional uterine bleeding, and prevention of hereditary angioedema. It may also be used for the pre-operative thinning of the endometrium prior to hysteroscopic endometrial ablation, and has been tried in other conditions including various blood disorders.

When given to women, treatment with danazol should be started on day 1 of the menstrual cycle or after pregnancy has been otherwise excluded.

In **endometriosis** the usual dose is 200 to 800 mg daily in 2 to 4 divided doses, adjusted according to the response. Therapy is given for 3 to 6 months or continued for up to 9 months if necessary.

In the treatment of **benign breast disorders** the usual initial dose is 100 to 400 mg daily in 2 divided doses, adjusted according to response, and continued for 3 to 6 months. For **gynaecomastia** 200 mg daily has been given to male adolescents, increased after 2 months to 400 mg daily if no response occurs; adult men have been given 400 mg daily initially, in up to 4 divided doses. Daily doses of up to 800 mg have been used, and therapy is usually tried for 6 months.

In dysfunctional uterine bleeding manifesting as **menorrhagia** doses of 200 mg daily have been given and treatment is reviewed after 3 months.

In the management of **hereditary angioedema** initial doses of 200 mg two or three times daily are given, and then reduced according to the patient's response.

For **pre-operative thinning** of the endometrium danazol has been given in a dose of 400 to 800 mg daily in up to 4 divided doses, for 3 to 6 weeks.

Blood disorders. Although danazol may produce thrombocytopenia and leucopenia its use has also been investigated in some blood disorders. Increased platelet counts have been reported in patients with *idiopathic thrombocytopenic purpura* (p.1505). Small cohort studies have reported response rates of about 60 to 70%, including both partial and complete responses,[1-3] with a mean or median time to response of about 3 months.[1,2] Analysis of data from 96 patients suggested that age, sex, and spleen status may affect the response to danazol.[2] The response in men was not affected by age, but was better in splenectomised patients. However, in women there was a better response rate with advancing age in unsplenectomised patients, and the benefit of splenectomy on rates of response to danazol was only seen in younger women (45 years or younger). A better overall response rate in older patients (60 years and older) was also reported in another group.[4] However, others have found only a trend to less frequent response in younger patients, and no apparent relationship between response and sex or prior splenectomy.[1] *Thrombocytopenia associated with rheumatic disorders*, such as SLE, the antiphospholipid antibody syndrome, and rheumatoid arthritis has also been reported to respond to treatment with danazol.[5-7] For mention of the use of danazol in *Henoch-Schönlein purpura* see Hypersensitivity Vasculitis, p.1505.

Additionally there have been reports of response to danazol therapy in patients with *auto-immune haemolytic anaemia*[8,9] (p.1043), anaemia of *myelofibrosis with myeloid metaplasia*,[10] *paroxysmal nocturnal haemoglobinuria*,[11] *hereditary haemorrhagic telangiectasia*,[12] and *Evan's syndrome* due to SLE.[13] There have been conflicting reports in patients with *myelodysplastic syndromes*.[14-18]

1. Maloisel F, *et al.* Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. *Am J Med* 2004; **116:** 590–4.
2. Ahn YS, *et al.* Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann Intern Med* 1989; **111:** 723–9.
3. Zimmer J, *et al.* Current management of adult idiopathic thrombocytopenic purpura in practice: a cohort study of 201 patients from a single center. *Clin Lab Haematol* 2004; **26:** 137–42.
4. Andrès E, *et al.* Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. *Drugs Aging* 2003; **20:** 841–6.
5. Blanco R, *et al.* Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. *Br J Rheumatol* 1997; **36:** 1095–9.
6. Arnal C, *et al.* Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002; **29:** 75–83.
7. Aviña-Zubieta JA, *et al.* Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus. *Lupus* 2003; **12:** 52–7.
8. Ahn YS, *et al.* Danazol therapy for autoimmune hemolytic anemia. *Ann Intern Med* 1985; **102:** 298–301.
9. Tan AM, *et al.* Danazol for treatment of refractory autoimmune hemolytic anaemia. *Ann Acad Med Singapore* 1989; **18:** 707–9.
10. Cervantes F, *et al.* Efficacy and tolerability of danazol as a treatment for the anaemia of myelofibrosis with myeloid metaplasia: long-term results in 30 patients. *Br J Haematol* 2005; **129:** 771–5.
11. Harrington WJ, *et al.* Danazol for paroxysmal nocturnal hemoglobinuria. *Am J Hematol* 1997; **54:** 149–54.
12. Haq AU, *et al.* Hereditary hemorrhagic telangiectasia and danazol. *Ann Intern Med* 1988; **109:** 171.
13. Aranegui P, *et al.* Danazol for Evan's syndrome due to SLE. *DICP Ann Pharmacother* 1990; **24:** 641–2.
14. Wattel E, *et al.* Androgen therapy in myelodysplastic syndromes with thrombocytopenia: a report on 20 cases. *Br J Haematol* 1994; **87:** 205–8.
15. Chabannon C, *et al.* A review of 76 patients with myelodysplastic syndromes treated with danazol. *Cancer* 1994; **73:** 3073–80.
16. Letendre L, *et al.* Myelodysplastic syndrome treatment with danazol and cis-retinoic acid. *Am J Hematol* 1995; **48:** 233–6.
17. Viniou N, *et al.* Danazol therapy for thrombocytopenia in patients with myelodysplastic syndromes. *Acta Haematol (Basel)* 2002; **107:** 234–6.
18. Chan G, *et al.* Danazol for the treatment of thrombocytopenia in patients with myelodysplastic syndrome. *Am J Hematol* 2002; **71:** 166–71.

Endometriosis. Endometriosis is a condition affecting women mainly in their reproductive years, and caused by endometrial tissue developing outside the uterine cavity. It occurs most often in the pelvic peritoneal cavity and occasionally elsewhere such as the thoracic cavity. The aetiology is uncertain, although it is widely believed that retrograde flow of menstrual tissue introduces endometrial cells into the pelvic cavity, and that the implantation and growth of these cells may be influenced by genetic, immunologic, hormonal, and environmental factors.[1,2]

The presentation of endometriosis is variable, and while symptoms can range from mild to severe, many affected women are asymptomatic.[3] There is considerable overlap of symptoms with other conditions such as irritable bowel syndrome and pelvic inflammatory disease, but a definitive diagnosis of endometriosis can be made by visualisation at laparoscopy. The most common symptom is pain, usually manifesting as secondary dysmenorrhoea, dyspareunia, or cyclical back or pelvic pain. Pain may occur on micturition or defaecation if endometriosis affects the bladder or bowel; fibrosis and adhesions can develop. Endometriosis is also strongly associated with infertility. Severe endometriosis can distort the pelvic anatomy and thereby reduce fecundity, but how minimal and mild disease might affect fertility is unclear.[1,4] Management will depend in part on the presenting complaint, the extent of disease, and whether fertility is an issue. Conservative laparoscopic surgery or drug therapy may be used, but disease recurrence is common and long-term management is usually needed.[1,5] Nevertheless, spontaneous regression may occur in about a third of patients.[4,5]

Where **infertility** is the presenting symptom, surgery is generally performed in more severe disease, based on the assumption that correction of anatomical defects should improve fecundity although there is a lack of controlled studies to confirm this.[2,3,6,7] There is also limited evidence to suggest that surgery may improve fertility in mild disease,[3] but it is likely that the effect is small.[7] Assisted reproductive techniques such as IVF (see Infertility, p.2080) offer the best chance of conception in more severe disease.[6,7] The extent of benefit in mild or moderate endometriosis is less clear.[6] Superovulation with intra-uterine insemination may be considered in such cases, with IVF an alternative for women aged 35 or more, and postoperative expectant management another option in younger women.[7]

Drug therapy has not been shown to be of direct value for infertility.[7,8] Also, because the drugs used for endometriosis tend to suppress ovulation and are potentially contraceptive, they will delay the opportunity for conception during treatment.[3,6,9] Pre- and postoperative drug therapy have also been tried, but there is insufficient evidence to show that these are any more effective than surgery alone.[10]

For patients whose primary symptom is **pain**, drug treatments that cause anovulatory hypoestrogenism (to induce atrophy and shrinkage of the hormonally sensitive ectopic endometrial deposits) are effective and are the mainstay of treatment.[4] One of the most widely used treatments has been *danazol*, which produces subjective improvement in symptoms of pain and reduction of some pelvic abnormalities and tissue implants.[1,11] Its androgenic effects can be a problem and there is concern about its effect on blood lipids, therefore therapy is restricted to 6 months, or rarely up to 9 months. *Gestrinone* has been shown to be equally effective and may be a useful alternative.[3,8,12] *Progestogens* such as medroxyprogesterone acetate, dydrogesterone, or norethisterone acetate are also commonly used. They appear to be as effective as danazol in relieving pain symptoms[12] and tend to be better tolerated.[1,4] The use of local levonorgestrel from an intra-uterine device is also under investigation.[2]

Combined oral contraceptives are often used to relieve endometriosis pain, although the evidence for their benefit is largely observational[1] and data from controlled studies remain scanty.[13] They have been used in a continuous fashion to induce amenorrhoea, as well as the usual cyclical regimens, but it is unclear which is most effective.[3,8]

The other major group of drugs that are used in endometriosis are *gonadorelin* and its analogues such as buserelin, goserelin, leuprorelin, nafarelin, and triptorelin, which are as effective as danazol.[1,6] Long-term use is limited by the risk of osteoporosis, but concomitant 'add-back' therapy such as low-dose oestrogen and progestogen HRT,[1,3,6,8] or tibolone,[1,3] can be used to prevent this. Adverse effects resembling menopausal symptoms can also be relieved by 'add-back' therapy, which may make gonadorelin analogues more tolerable than danazol.[4] Parathyroid hormone[14,15] may also be effective for 'add-back' therapy to prevent bone loss.

Investigational drugs include the *antiprogestogens* such as mifepristone,[16] and *aromatase inhibitors* such as anastrozole.[17]

There is some evidence that laparoscopic ablation can also reduce pain but controlled studies are limited.[4,6] Ideally, endometrial deposits found during diagnostic laparoscopy should be removed during the procedure.[3,8,18] There is a lack of comparison between surgery and drug treatment. Although there are reports of improved pain control using postoperative medical therapy,[18] study results have been mixed and there is insufficient evidence to confirm whether a combination of surgery and drug therapy has any additional benefit.[6,10]

There is a relatively high recurrence rate of endometriosis after conservative surgery and drug therapy. In women who can accept loss of child-bearing potential, definitive therapy is surgical oophorectomy and hysterectomy with complete excision or ablation of endometrial deposits.[3,8,18] Oestrogen replacement therapy is given, but carries a risk of recurrence of the disease; some have suggested that combined HRT may be preferable (see p.2075).

1. Crosignani P, *et al.* Advances in the management of endometriosis: an update for clinicians. *Hum Reprod Update* 2006; **12:** 179–89.
2. Hompes PGA, Mijatovic V. Endometriosis: the way forward. *Gynecol Endocrinol* 2007; **23:** 5–12.
3. Royal College of Obstetricians and Gynaecologists. The investigation and management of endometriosis (green-top guideline no. 24, issued October 2006). Available at: http://www.rcog.org.uk/resources/Public/pdf/endometriosis_gt_24_2006.pdf (accessed 30/06/08)
4. Child TJ, Tan SL. Endometriosis: aetiology, pathogenesis and treatment. *Drugs* 2001; **61:** 1735–50.
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6. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. *Ann N Y Acad Sci* 2002; **955:** 360–72.
7. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2006; **86** (suppl 4): S156–S160.
8. European Society for Human Reproduction and Embryology. ESHRE guideline for the diagnosis and treatment of endometriosis (last updated 30th June, 2007). Available at: http://guidelines.endometriosis.org/index.html (accessed 30/06/08)
9. Hughes E, *et al.* Ovulation suppression for endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
10. Yap C, *et al.* Pre and post operative medical therapy for endometriosis surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 30/06/08).
11. Selak V, *et al.* Danazol for pelvic pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/06/08).
12. Prentice A, *et al.* Progestagens and anti-progestagens for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 30/06/08).
13. Davis L, *et al.* Modern combined oral contraceptives for pain associated with endometriosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
14. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
15. Finkelstein JS, *et al.* Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
16. Kettel LM, *et al.* Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU 486). *Am J Obstet Gynecol* 1998; **178:** 1151–6.
17. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; **84:** 300–304.
18. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril* 2006; **86** (suppl 4): S18–S27.

Gynaecomastia. Gynaecomastia is a common benign glandular enlargement of the male breast, caused either by increased oestrogenic activity or decreased androgenic activity. Examples of gynaecomastia caused by increased oestrogenic activity include oestrogen-secreting malignancies, increased aromatisation of androgens into oestrogens (associated with an increase in adipose tissue), and exposure to drugs with oestrogenic activity such as digitoxin. Neonatal and pubertal gynaecomastia also come into this category, the former due to exposure to maternal oestrogens and the latter because oestrogen levels increase before androgens do. Gynaecomastia caused by decreased androgenic activity may be associated with the natural decline of testosterone concentrations in ageing men, various forms of hypogonadism, increased metabolism of androgens (for example in alcoholism), and exposure to drugs with anti-androgenic properties such as spironolactone, cimetidine, ketoconazole, cyproterone acetate, or flutamide. Some systemic disorders may also be associated with gynaecomastia, including cirrhosis of the liver, hyperthyroidism, and renal failure; it may also occur on refeeding after starvation.

Gynaecomastia has a high rate of spontaneous regression, and specific therapy (other than the removal of any cause) need only be considered if the enlarged breast tissue causes sufficient pain, embarrassment, or emotional discomfort to interfere with the patient's daily life.[1-3] Drug therapy is only likely to be of benefit while tissue is still proliferating; once glandular tissue has become inactive and fibrotic (usually after more than 12 months) a complete response is unlikely.[2,3]

Except in primary hypogonadism,[3] testosterone itself is unlikely to be of benefit (and may be aromatised to oestradiol, exacerbating the situation),[2] but a non-aromatisable androgen such as *androstanolone* (dihydrotestosterone) may produce some benefit.[2,4] *Danazol* has produced marked responses in some patients,[4] but adverse effects may limit its usefulness.[2] Quite good responses have also been reported with *tamoxifen*,[4-6] and this has been recommended as a drug of choice.[2,3] A retrospective review[7] of men treated for idiopathic gynaecomastia found that a complete response occurred in 18 of 23 men treated with tamoxifen, but in only 8 of 20 who received danazol. The decrease in pain was similar for both groups, but relapse occurred in 5 of the men treated with tamoxifen. The use of other drugs with anti-oestrogen effects, such as *clomifene*[8,9] and *raloxifene*,[6] has also been described in small numbers of boys with pubertal gynaecomastia. Aromatase inhibitors have been investigated for their potential to prevent the peripheral aromatisation of androgens to oestrogens. Improvement in pubertal gynaecomastia has been reported with *testolactone*,[10] but a controlled study[11] in 80 boys found 6 months of treatment with *anastrozole* to be no better than placebo. Studies in men being treated for prostate cancer also found anastrozole to be ineffective for the prevention[12,13] and treatment[12] of gynaecomastia associated with bicalutamide therapy; in comparison, tamoxifen was effective in both studies.

Where drug therapy is unsuccessful, or the breast enlargement is long-standing, surgical removal of breast tissue is advocated.[2,3] Prophylactic low-dose radiotherapy to the breast can significantly reduce the risk of gynaecomastia and breast pain in men undergoing anti-androgen treatment for prostate cancer,[2] although comparative studies suggest that it may be less effective than tamoxifen.[14,15]

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9. Plourde PV, *et al.* Clomiphene in the treatment of adolescent gynecomastia: clinical and endocrine studies. *Am J Dis Child* 1983; **137:** 1080–2.
10. Zachmann M, *et al.* Treatment of pubertal gynaecomastia with testolactone. *Acta Endocrinol (Copenh)* 1986; **279** (suppl): 218–26.
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13. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; **23:** 808–15.
14. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; **6:** 295–300.
15. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; **174:** 2197–2203.

Hereditary angioedema. Danazol has been used successfully[1,2] to prevent attacks of hereditary angioedema (p.1081). Patients with lupus erythematosus-like syndromes associated with hereditary angioedema have also benefited from danazol therapy.[3-5]

1. Bowen T, *et al.* Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004; **114:** 629–37.
2. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]
3. Masse R, *et al.* Reversal of lupus-erythematosus-like disease with danazol. *Lancet* 1980; **ii:** 651.
4. Donaldson VH, Hess EV. Effect of danazol on lupus-erythematosus-like disease in hereditary angioneurotic oedema. *Lancet* 1980; **ii:** 1145.
5. Duhra P, *et al.* Discoid lupus erythematosus associated with hereditary angioneurotic oedema. *Br J Dermatol* 1990; **123:** 241–4.

Mastalgia. Mastalgia may occur alone or be associated with nodularity or other fibrocystic changes in the female breast. It is usually divided into cyclical mastalgia, which accounts for about two-thirds of all cases, non-cyclical mastalgia, and chest-wall or costochondral pain (Tietze's syndrome). Cyclical mastalgia has a temporal association with the menstrual cycle and is most common in the third decade of life, with a chronic relapsing course thereafter; it usually resolves at the menopause. Non-cyclical mastalgia tends to present later in life as constant or intermittent pain that is not associated with the menstrual cycle.

Once clear pathological causes of pain have been excluded most patients can be managed by simple reassurance.[1-3] In the management of mild mastalgia, simple measures such as wearing a properly fitting brassiere and the use of relaxation techniques are widely recommended.[1-3] Warm compresses or ice packs and gentle massage may provide relief, particularly when the pain is cyclic or intermittent and of short duration.[1] There is some evidence that a low-fat diet may reduce symptoms of mastalgia, but the evidence to support a restriction of dietary caffeine intake is inconsistent and such a measure is not generally recommended.[1,3] Although few studies have been done to confirm a beneficial effect, many women are likely to self-medicate as required with simple analgesics such as paracetamol and oral or topical NSAIDs.[1] Patients who take an oral contraceptive or HRT may find that symptoms improve on reducing the estrogen dose or stopping treatment.[1,3]

Women with moderate to severe mastalgia that has lasted for more than 6 months may require specific drug treatment. *Danazol* is probably the most effective drug for mastalgia, and studies suggest that it is of benefit in about 70% or more of patients with cyclical mastalgia,[1-3] and somewhat fewer with the non-cyclical form.[2] However, adverse effects may force the dose to be reduced or stopped. Danazol given only during the luteal phase (days 14 to 28) has been reported to be effective in cyclical mastalgia, and to cause few adverse effects.[4] *Gestrinone* has also been reported to be effective in cyclical mastalgia.[1] Although effective in cyclical mastalgia,[3,5] *bromocriptine* is not as effective as danazol, and its use is similarly limited by adverse effects.[1,2] A small study[6] has reported that *lisuride* was effective in cyclical mastalgia.

Gamolenic acid (usually as evening primrose oil) has been widely used in cyclical mastalgia because of early studies suggesting that it was an effective treatment with few adverse effects. Although further studies have produced conflicting results and there is now doubt about its efficacy,[2,3,5] some still suggest that it can be tried as there may be a beneficial effect with minimal risk.[1]

In refractory cyclical or non-cyclical mastalgia *tamoxifen*[3,5] has been shown to be effective; controlled trials have reported efficacy rates of up to 96% in cyclical mastalgia and 56% in non-cyclical mastalgia.[1] However, the concept of using tamoxifen in otherwise healthy premenopausal women has produced some concern.[7-9] *Toremifene* has been reported to be of benefit.[10,11] *Goserelin* has also been shown to be effective,[12,13] but there is limited experience with the use of gonadorelin analogues and severe adverse effects are likely to limit their use.[1] Injection of a *local anaesthetic* with a *corticosteroid* has proved effective for the pain of non-cyclical mastalgia.[14]

Other drugs that have been used for cyclical mastalgia include antibacterials, diuretics, and various vitamins but there is no evidence that they are any better than placebo.[1]

1. Smith RL, *et al.* Evaluation and management of breast pain. *Mayo Clin Proc* 2004; **79:** 353–72.
2. Gumm R, *et al.* Evidence for the management of mastalgia. *Curr Med Res Opin* 2004; **20:** 681–4.
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4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; **180:** 18–23.
5. Srivastava A, *et al.* Evidence-based management of mastalgia: a meta-analysis of randomised trials. *Breast* 2007; **16:** 503–12.
6. Kaleli S, *et al.* Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.
7. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; **i:** 305.
8. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; **i:** 680–1.
9. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; **i:** 681.
10. Gong C, *et al.* A double-blind randomized controlled trial of toremifen therapy for mastalgia. *Arch Surg* 2006; **141:** 43–7.
11. Oksa S, *et al.* Toremifene for premenstrual mastalgia: a randomised, placebo-controlled crossover study. *BJOG* 2006; **113:** 713–18.
12. Hamed H, *et al.* LHRH analogue for treatment of recurrent and refractory mastalgia. *Ann R Coll Surg Engl* 1990; **72:** 221–4.
13. Mansel RE, *et al.* European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. *Am J Obstet Gynecol* 2004; **191:** 1942–9.
14. Khan HN, *et al.* Local anaesthetic and steroid combined injection therapy in the management of non-cyclical mastalgia. *Breast* 2004; **13:** 129–32.

Menorrhagia. Danazol is effective in the treatment of menorrhagia (p.2126) but it is only used short term because of its adverse effects.[1] It may also be used for pre-operative endometrial thinning.[2]

1. Beaumont H, *et al.* Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/06/08).
2. Sowter MC, *et al.* Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 30/06/08).

Premenstrual syndrome. Danazol may be useful[1-3] in the management of the premenstrual syndrome (p.2099), but some have found it to be of value only for cyclical mastalgia rather than for general symptoms,[4] and in any case adverse effects limit its long-term use.

1. Halbreich U, *et al.* Elimination of ovulation and menstrual cyclicity (with danazol) improves dysphoric premenstrual syndromes. *Fertil Steril* 1991; **56:** 1066–9.
2. Deeny M, *et al.* Low dose danazol in the treatment of the premenstrual syndrome. *Postgrad Med J* 1991; **67:** 450–4.
3. Hahn PM, *et al.* A randomized, placebo-controlled, crossover trial of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology* 1995; **20:** 193–209.
4. O'Brien PMS, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol* 1999; **180:** 18–23.

Skin disorders. Danazol has been reported to relieve pruritus (p.1582) refractory to usual treatment with antihistamines; underlying conditions have included cholinergic urticaria,[1,2] chronic actinic dermatitis,[3] myeloproliferative disorders,[4] and autoimmune disorders.[4] In 2 reports, the skin disorder had been associated with low plasma concentrations of antiprotease.[1,3] Danazol has generally been given in oral doses of 200 to 800 mg daily.[4] Maintenance treatment may be needed, and relapse can occur when the dose is reduced or treatment is withdrawn.

Danazol was also reported to reduce induration and pain in a man with lipodermatosclerosis.[5]

1. Berth-Jones J, Graham-Brown RAC. Cholinergic pruritus, erythema and urticaria: a disease spectrum responding to danazol. *Br J Dermatol* 1989; **121:** 235–7.
2. La Shell MS, England RW. Severe refractory cholinergic urticaria treated with danazol. *J Drugs Dermatol* 2006; **5:** 664–7.
3. Humbert P, *et al.* Chronic actinic dermatitis responding to danazol. *Br J Dermatol* 1991; **124:** 195–7.
4. Kolodny L, *et al.* Danazol relieves refractory pruritus associated with myeloproliferative disorders and other diseases. *Am J Hematol* 1996; **51:** 112–16.
5. Hafner C, *et al.* Lipodermatosclerosis: successful treatment with danazol. *Acta Derm Venereol* 2005; **85:** 365–6.

Preparations

USP 31: Danazol Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Ladogal; ***Austral.:*** Azol; Danocrine; ***Austria:*** Danokrin; ***Belg.:*** Danatrol; ***Braz.:*** Ladogal; ***Canad.:*** Cyclomen; ***Chile:*** Danogar†; ***Cz.:*** Anargil†; Danol†; Danoval; ***Denm.:*** Danocrine†; ***Fin.:*** Danocrine†; ***Fr.:*** Danatrol; ***Gr.:*** Danatrol; ***Hong Kong:*** Anargil; Danocrine; ***Hung.:*** Danoval; ***India:*** Danogen; Gonablok; Zendol; ***Indon.:*** Azol; Danocrine; ***Irl.:*** Danazant†; Danol; ***Israel:*** Danol; ***Ital.:*** Danatrol; ***Jpn:*** Bonzol†; ***Malaysia:*** Anargil; Azol; Ladogal; Vabon†; ***Mex.:*** Danalem; Kendazol†; Ladogal; Novaprin; Zoldan-A†; ***Neth.:*** Danatrol; ***Norw.:*** Danocrine†; ***NZ:*** D-Zol; Danocrine†; ***Philipp.:*** Ladogal; ***Port.:*** Danatrol; Mastodanatrol†; ***Rus.:*** Danoval (Дановал); ***S.Afr.:*** Danogen; Ladazol; ***Singapore:*** Azol; Ladogal; ***Spain:*** Danatrol; ***Swed.:*** Danocrine†; ***Switz.:*** Danatrol; ***Thai.:*** Anargil; Ectopal; Ladogal; Vabon; ***Turk.:*** Danasin; ***UK:*** Danol; ***USA:*** Danocrine†; ***Venez.:*** Danogen; Ladogal.

Degarelix *(USAN, rINN)*

Dégarélix; Degarelixum; FE-200486 (degarelix acetate). *N*-Acetyl-3-(naphthalen-2-yl)-D-alanyl-4-chloro-D-phenylalanyl-3-(pyridin-3-yl)-D-alanyl-L-seryl-4-({[(4S)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl}amino)-L-phenylalanyl-4-(carbamoylamino)-Dphenylalanyl-L-leucyl-N^6-(1-methylethyl)-L-lysyl-Lprolyl-D-alaninamide.

Дегареликс

$C_{82}H_{103}ClN_{18}O_{16}$ = 1632.3.

CAS — 214766-78-6.

Profile

Like cetrorelix (p.2084), degarelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is under investigation to reduce testosterone concentrations in hormonal therapy of prostate cancer.

Delmadinone Acetate *(BANM, USAN, rINNM)*

Acetato de delmadinona; Delmadinonacetat; Delmadinone, Acétate de; Delmadinoni Acetas; Delmadinoniasetaatti; RS-1301. 6-Chloro-17α-hydroxypregna-1,4,6-triene-3,20-dione acetate.

Дельмадинона Ацетат

$C_{23}H_{27}ClO_4$ = 402.9.

CAS — 15262-77-8 (delmadinone); 13698-49-2 (delmadinone acetate).

ATC Vet — QG03DX91.

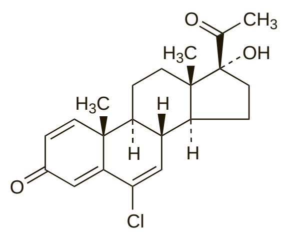

(delmadinone)

Profile

Delmadinone acetate is a progestogen with anti-androgenic and anti-oestrogenic activity. It is used as an anti-androgen in veterinary practice.

Deslorelin *(BAN, USAN, rINN)* ⊗

Deslorelina; Desloréline; Deslorelinum; D-Trp LHRH-PEA. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

Дезлорелин

$C_{64}H_{83}N_{17}O_{12}$ = 1282.5.

CAS — 57773-65-6.

ATC Vet — QH01CA93.

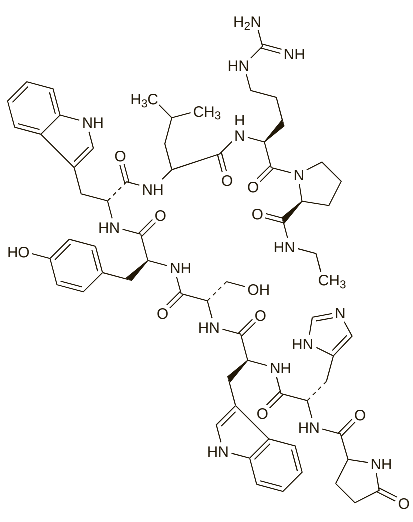

Profile

Deslorelin is an analogue of gonadorelin (p.2106) that has been investigated in the treatment of precocious puberty, short stature, prostate cancer, and endometriosis.

◊ References.

1. Anonymous. Deslorelin: D-Trp-LHRH-PEA, LHRH agonist analogue, Somagard. *Drugs R D* 1999; **2:** 420–2.
2. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
3. Yanovski JA, *et al.* Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003; **348:** 908–17.

Desogestrel *(BAN, USAN, rINN)*

Desogestreeli; Désogestrel; Desogestrelum; Dezogestrel; Org-2969. 13β-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17β-ol.

Дезогестрел

$C_{22}H_{30}O$ = 310.5.

CAS — 54024-22-5.

ATC — G03AC09.

ATC Vet — QG03AC09.

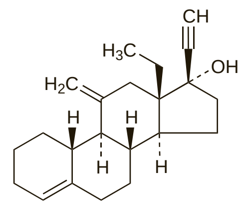

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Desogestrel). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane; very soluble in methyl alcohol.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. When used as a progestogen-only contraceptive, irregular bleeding is more common with desogestrel than with other progestogen-only preparations. Desogestrel is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that desogestrel-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p.2063, and for precautions, see p.2066).

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Pharmacokinetics

After oral doses, desogestrel undergoes oxidative transformation in the intestinal mucosa and liver to its active metabolite 3-keto-desogestrel (etonogestrel—see p.2103).

◊ References.

1. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by the intestinal mucosa. *Br J Clin Pharmacol* 1989; **27:** 295–9.
2. Madden S, *et al.* Metabolism of the contraceptive steroid desogestrel by human liver in vitro. *J Steroid Biochem* 1990; **35:** 281–8.
3. Kuhnz W, *et al.* Protein binding of the contraceptive steroids gestodene, 3-keto-desogestrel and ethinyloestradiol in human serum. *J Steroid Biochem* 1990; **35:** 313–18.
4. Kuhnz W, *et al.* Pharmacokinetics and serum protein binding of 3-keto-desogestrel in women during three cycles of treatment with a low-dose combination oral contraceptive. *Arzneimittelforschung* 1992; **42:** 1142–6.
5. Timmer CJ, *et al.* Bioavailability and bioequivalence of etonogestrel from two oral formulations of desogestrel: Cerazette and Liseta. *Eur J Drug Metab Pharmacokinet* 1999; **24:** 335–43.
6. Verhoeven CH, *et al.* Excretion and metabolism of desogestrel in healthy postmenopausal women. *J Steroid Biochem Mol Biol* 2001; **78:** 471–80.
7. Korhonen T, *et al.* The role of CYP2C and CYP3A in the disposition of 3-keto-desogestrel after administration of desogestrel. *Br J Clin Pharmacol* 2005; **60:** 69–75.

Uses and Administration

Desogestrel is a progestogen (see Progesterone, p.2126) structurally related to levonorgestrel that is used as a hormonal contraceptive (see p.2069). A typical daily dose of 150 micrograms is used as the progestogenic component of monophasic combined oral contraceptive preparations. Doses of 50 to 150 micrograms daily may be used in triphasic combined preparations. A dose of 75 micrograms daily is used as an oral progestogen-only contraceptive; unlike traditional progestogen-only contraceptives, desogestrel is said to reliably inhibit ovulation. Progestogen-only contraceptive efficacy is reduced if a dose of desogestrel is delayed by more than 12 hours.

Contraception. The effects of a progestogen-only contraceptive containing desogestrel have been reported.[1-3] Oral desogestrel has also been investigated as a male contraceptive, combined with testosterone given by intramuscular injection,[4] subcutaneous implant,[5,6] or transdermal patch.[7]

1. Collaborative study group on the desogestrel-containing progestogen-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. *Eur J Contracept Reprod Health Care* 1998; **3:** 169–78.
2. Rice CF, *et al.* A comparison of the inhibition of ovulation achieved by desogestrel 75 μg and levonorgestrel 30 μg daily. *Hum Reprod* 1999; **14:** 982–5.
3. Korver T, *et al.* Maintenance of ovulation inhibition with the 75-μg desogestrel-only contraceptive pill (Cerazette) after scheduled 12-h delays in tablet intake. *Contraception* 2005; **71:** 8–13.
4. Wu FCW, *et al.* Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. *J Clin Endocrinol Metab* 1999; **84:** 112–22.
5. Kinniburgh D, *et al.* Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. *Hum Reprod* 2002; **17:** 1490–1501.
6. Anderson RA, *et al.* Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone. *Hum Reprod* 2002; **17:** 2869–77.
7. Hair WM, *et al.* A novel male contraceptive pill-patch combination: oral desogestrel and transdermal testosterone in the suppression of spermatogenesis in normal men. *J Clin Endocrinol Metab* 2001; **86:** 5201–9.

Preparations

USP 31: Desogestrel and Ethinyl Estradiol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cerazette; ***Austria:*** Cerazette; ***Belg.:*** Cerazette; ***Braz.:*** Cerazette; Kelly; ***Chile:*** Arlette; Cerazette; Nogesta; Vanish; ***Cz.:*** Azalia; Cerazette; ***Denm.:*** Cerazette; ***Fin.:*** Cerazette; ***Fr.:*** Cerazette; ***Ger.:*** Cerazette; ***Gr.:*** Cerazette; ***Hung.:*** Cerazette; ***Indon.:*** Cerazette; ***Israel:*** Cerazette; ***Ital.:*** Cerazette; ***Mex.:*** Cerazette; ***Neth.:*** Cerazette; ***Norw.:*** Cerazette; ***NZ:*** Cerazette; ***Philipp.:*** Cerazette; ***Pol.:*** Cerazette; ***Port.:*** Cerazette; ***Rus.:*** Cerazette (Чарозетта); ***Spain:*** Cerazet; ***Swed.:*** Cerazette; ***Switz.:*** Cerazette; ***UK:*** Cerazette; ***Venez.:*** Arlette; Cerazette.

Multi-ingredient: ***Arg.:*** Marvelon; Mercilon; ***Austral.:*** Marvelon; ***Austria:*** Gracial; Laurina; Liberel; Liseta†; Marvelon; Mercilon; ***Belg.:*** Desorelle; Gracial; Marvelon; Mercilon; Ovidol; ***Braz.:*** Femina; Gestradiol; Gracial; Malu; Mercilon; Mercilon Conti; Microdiol; Minian; Novial; Primera; ***Canad.:*** Marvelon; Ortho-Cept; ***Chile:*** Ciclidon; Dal; Desoren; Gracial; Gynostat; Marvelon; Midalet; Miniestrel; Neolette; ***Cz.:*** Gracial; Jenetten†; Laurina; Marvelon; Mercilon; Novynette; Regulon; Vilonet†; ***Denm.:*** Desorelle; Gracial; Marvelon; Mercilon; Novynette; ***Fin.:*** Gracial; Marvelon; Mercilon; ***Fr.:*** Cycleane; Mercilon; Varnoline; ***Ger.:*** Biviol; Cyclosa; Desmin; Lamuna; Lovelle; Marvelon; Novial; Oviol; ***Gr.:*** Gracial; Laurina; Marvelon; Mercilon; ***Hong Kong:*** Gracial; Marvelon; Mercilon; Novynette; ***Hung.:*** Gracial; Marvelon; Mercilon; Novynette; Regulon; ***India:*** Femilon; Novelon; ***Indon.:*** Marvelon; Mercilon; ***Irl.:*** Marviol; Mercilon; ***Israel:*** Feminet; Mercilon; Microdiol; ***Ital.:*** Dueva; Gracial; Mercilon; Planum; Practil; Securgin; ***Malaysia:*** Marvelon; Mercilon; Novynette; Regulon; ***Mex.:*** Marvelon; Mercilon; Novial; ***Neth.:*** Gracial; Marvelon; Mercilon; Ovidol; ***Norw.:*** Marvelon; ***NZ:*** Marvelon; Mercilon; Trimiron†; ***Philipp.:*** Gracial; Marvelon; Mercilon; ***Pol.:*** Marvelon; Mercilon; Novynette; Regulon; ***Port.:*** Gracial; Laurina; Marvelon; Mercilon; Novynette; Regulon; ***Rus.:*** Marvelon (Марвелон); Mercilon (Мерсилон); Novynette (Новинет); Regulon (Регулон); Tri-Merci (Три-Мерси); ***S.Afr.:*** Marvelon; Mercilon; ***Singapore:*** Marvelon; Mercilon; ***Spain:*** Gracial; Microdiol; Suavuret; ***Swed.:*** Desolett; Mercilon; Trimiron; ***Switz.:*** Gracial; Marvelon; Mercilon; ***Thai.:*** Marvelon; Mercilon; Oilezz; ***Turk.:*** Desolett; Myralon; ***UK:*** Marvelon; Mercilon; ***USA:*** Apri; Cesia; Cyclessa; Desogen; Kariva; Mircette; Ortho-Cept; Reclipsen; Solia; Velivet; ***Venez.:*** Ciclidon; Marvelon; Mercilon; Mipil; Novial.

Dienestrol *(BAN, rINN)*

Dehydrostilbestrol; Diènestrol; Dienestroli; Dienestrolis; Dienestrolum; Dienoestrol; Dienoestrolum; Dienösztrol; Oestrodienolum. *(E,E)*-4,4′-[Di(ethylidene)ethylene]diphenol; 4,4′-(1,2-Diethylidene-1,2-ethanediyl)bisphenol.

Диенэстрол

$C_{18}H_{18}O_2$ = 266.3.

CAS — 84-17-3 (dienestrol); 13029-44-2 ((E,E)-dienestrol).

ATC — G03CB01.

ATC Vet — QG03CB01; QG03CC02.

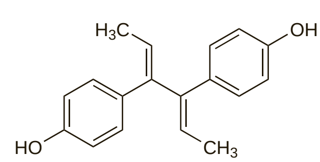

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dienestrol). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Dienestrol). Colourless, white, or practically white needle-like crystals, or white or practically white crystalline powder. It is odourless. Practically insoluble in water; soluble in alcohol, in acetone, in ether, in methyl alcohol, in propylene glycol, and in solutions of alkali hydroxides; slightly soluble in chloroform and in fatty oils.

Profile

Dienestrol is a synthetic nonsteroidal oestrogen structurally related to diethylstilbestrol (p.2094). It has been used as a 0.01% cream in the treatment of menopausal atrophic vaginitis. If used on a long-term basis in women with a uterus a progestogen is required.

Dienestrol diacetate has been used as an ingredient of topical preparations for skin disorders.

Porphyria. Dienestrol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

USP 31: Dienestrol Cream.

Proprietary Preparations (details are given in Part 3)
Denm.: Sexadien†; ***USA:*** Ortho-Dienestrol.

Dienogest *(BAN, USAN, rINN)*

Diénogest; Dienogesti; Dienogestum; STS-557. 17-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile.

Диеногест

$C_{20}H_{25}NO_2$ = 311.4.
CAS — 65928-58-7.

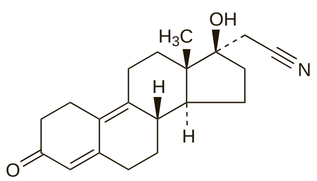

Profile

Dienogest is a nonethinylated progestogen (see Progesterone, p.2125) structurally related to nortestosterone. It is reported to have anti-androgenic properties. Dienogest is used as the progestogen component of some combined oral contraceptives (see p.2058); a typical daily dose is 2 mg. It is also used as the progestogen component in menopausal HRT (see p.2071) in a daily dose of 2 mg.

◊ Reviews.

1. Foster RH, Wilde MI. Dienogest. *Drugs* 1998; **56:** 825–33.
2. Wellington K, Perry CM. Estradiol valerate/dienogest. *Drugs* 2002; **62:** 491–504.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Jeanine.

Multi-ingredient: ***Austral.:*** Valette; ***Austria:*** Climodien; Jeanine; Lafamme; Valette; ***Belg.:*** Climodien; ***Cz.:*** Jeanine; Klimodien; ***Denm.:*** Climodien; ***Fr.:*** Climodiene; ***Ger.:*** Climodien; Lafamme; Valette; ***Gr.:*** Climodien†; ***Hung.:*** Klimodien†; ***Neth.:*** Climodien; Lafamme; ***Norw.:*** Climodien; ***Pol.:*** Jeanine; ***Port.:*** Climodien; Lafamme; Valette; ***Rus.:*** Climodien (Климодиен); Jeanine (Жанин); ***Spain:*** Climodien; Mevaren; ***Swed.:*** Climodien; ***Turk.:*** Climodien.

Diethylstilbestrol *(BAN, rINN)*

DES; Diéthylstilbestrol; Diethylstilbestrolum; Diethylstilboestrol; Dietilestilbestrol; Dietilstilbestrolis; Dietilstilbösztrol; Dietylstilbestrol; Dietyylistilbestroli; NSC-3070; Stilbestrol; Stilboestrol. (*E*)-αβ-Diethylstilbene-4-4′-diol.

Диэтилстильбэстрол

$C_{18}H_{20}O_2$ = 268.4.
CAS — 56-53-1.
ATC — G03CB02; L02AA01.
ATC Vet — QG03CB02; QG03CC05; QL02AA01.

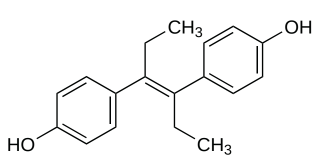

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Diethylstilbestrol). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Diethylstilbestrol). A white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, in fatty oils, and in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Diethylstilbestrol Dipropionate *(BANM, rINNM)*

Diéthylstilbestrol, Dipropionate de; Diethylstilbestroli Dipropionas; Dipropionato de dietilestilbestrol; Stilboestrol Dipropionate. (*E*)-αβ-Diethylstilbene-4,4′-diol dipropionate.

Диэтилстильбэстрола Дипропионат

$C_{24}H_{28}O_4$ = 380.5.
CAS — 130-80-3.
ATC — G03CB02; L02AA01.
ATC Vet — QG03CB02; QL02AA01.

Adverse Effects and Precautions

Dose-related adverse effects of diethylstilbestrol include nausea, fluid retention, and arterial and venous thrombosis, and these effects are common at the doses used for palliation of cancer. Impotence and gynaecomastia occur in men, and withdrawal bleeding may occur in women, as may hypercalcaemia and bone pain in women treated for breast cancer. Diethylstilbestrol should be used with caution in those with cardiovascular disease or renal or hepatic impairment. Use of diethylstilbestrol is contra-indicated if pregnancy is suspected.

Adverse effects and precautions of oestrogens in general (steroidal compounds) are covered under Estradiol, on p.2097.

Historically, high doses of diethylstilbestrol and related substances were used for 'hormonal support' in pregnant women to try to prevent miscarriages and preterm births, most commonly in the USA. This practice was later shown to be ineffective. Adverse effects on the genito-urinary tract of offspring of these women have been noted. In particular, an increased incidence of changes in the cervix and vagina including adenosis and rarely clear-cell adenocarcinoma has been seen in postpubertal daughters of women who received diethylstilbestrol or related substances during pregnancy (see below). A possible increased incidence of abnormalities of the genital tract and of abnormal spermatozoa has been reported in male offspring similarly exposed (see below). The recipients themselves appear to be at a small increased risk of breast cancer (see below).

Carcinogenicity. *BREAST.* No statistically significant difference in the incidence of breast cancer was found among a group of 693 women given diethylstilbestrol during pregnancy 25 years earlier compared with a control group of 668 who were not.[1] This finding was, however, criticised[2] on the basis that the study lacked the statistical power to reject the null hypothesis. In another study[3] the incidence of breast cancer in 3033 women who had taken diethylstilbestrol in pregnancy during the period 1940 to 1960 was compared with the incidence in a comparable group of unexposed women. This study involved over 85 000 women-years of follow-up in each group and it was found that the incidence of breast cancer per 100 000 women-years was 134 in the exposed group and 93 in the unexposed group (a relative risk of 1.4). The authors concluded that in those women given diethylstilbestrol there was a moderately increased incidence of breast cancer but that some unrecognised concomitant of exposure could not be excluded as a possibility for the increase. Although this study suggested that the risk increased over time, subsequent follow-up,[4] while confirming a modest increase in risk overall, did not confirm a higher risk in these women as time went on. Further follow-up and analysis[5] of the combined data from these cohort studies[1,3,4] confirmed a modest increase in risk of breast cancer associated with diethylstilbestrol (relative risk 1.27, 95% confidence interval 1.07 to 1.52). Another large population cohort study[6] suggested that the risk of fatal breast cancer might also be increased in women who had been given diethylstilbestrol.

Two cases of breast cancer[7] in premenopausal women exposed to diethylstilbestrol *in utero* have raised the possibility that the risk of breast cancer may be increased in these women, in addition to the known genito-urinary risk (see below under Pregnancy, Effects on Female Offspring). However, a cohort study[8] involving 4536 women exposed *in utero* found no increased risk of other cancers overall, and did not show an increased risk of breast cancer (relative risk 1.18; 95% confidence intervals 0.56 to 2.49). A later study[9] of further follow-up of this cohort, plus additional data from another group, found that although the risk overall and for younger women was not increased, from the age of 40 years the risk increased to 1.91 (95% confidence interval 1.09 to 3.33). The risk appeared to increase further with greater age, but the relatively small number of cases in women aged 50 years and over made this harder to establish.

1. Bibbo M, *et al.* A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. *N Engl J Med* 1978; **298:** 763–7.
2. Clark LC, Portier KM. Diethylstilbestrol and the risk of cancer. *N Engl J Med* 1979; **300:** 263–4.
3. Greenberg ER, *et al.* Breast cancer in mothers given diethylstilbestrol in pregnancy. *N Engl J Med* 1984; **311:** 1393–8.
4. Colton T, *et al.* Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *JAMA* 1993; **269:** 2096–2100.
5. Titus-Ernstoff L, *et al.* Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001; **84:** 126–33.
6. Calle EE, *et al.* Diethylstilbestrol and risk of fatal breast cancer in a prospective cohort of US women. *Am J Epidemiol* 1996; **144:** 645–52.
7. Huckell C, *et al.* Premenopausal breast cancer after in-utero exposure to stilboestrol. *Lancet* 1996; **348:** 331.
8. Hatch EE, *et al.* Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 1998; **280:** 630–4.
9. Palmer JR, *et al.* Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 1509–14.

GENITO-URINARY TRACT. See below under Pregnancy, Effects on Female Offspring.

KIDNEY. Renal carcinoma was associated with the long-term use of diethylstilbestrol for prostate cancer in 2 men.[1]

1. Nissenkorn I, *et al.* Oestrogen-induced renal carcinoma. *Br J Urol* 1979; **51:** 6–9.

LIVER. Hepatic angiosarcoma developed in a 76-year-old man who had received diethylstilbestrol 3 mg daily for 12 years.[1] Hepatoma developed in another elderly man who had received a similar dose for 4.5 years.[2]

1. Hoch-Ligeti C. Angiosarcoma of the liver associated with diethylstilbestrol. *JAMA* 1978; **240:** 1510–11.
2. Brooks JJ. Hepatoma associated with diethylstilbestrol therapy for prostate carcinoma. *J Urol (Baltimore)* 1982; **128:** 1044–5.

Effects on the blood. Adverse haematological effects reported with diethylstilbestrol have included severe bone-marrow changes in a 71-year-old man given diethylstilbestrol in a massive dose of 150 mg daily for 7 years[1] and fatal immune haemolytic anaemia in a 69-year-old man given weekly infusions of diethylstilbestrol 1 g for 9 weeks.[2] The latter reaction was due to an IgG antibody specific for diethylstilbestrol.

1. Anderson AL, Lynch EC. Myelodyspoietic syndrome associated with diethylstilbestrol therapy. *Arch Intern Med* 1980; **140:** 976–7.
2. Rosenfeld CS, *et al.* Diethylstilbestrol-associated hemolytic anemia with a positive direct antiglobulin test result. *Am J Med* 1989; **86:** 617–18.

Pregnancy. *EFFECTS ON FEMALE OFFSPRING.* The DESAD (Diethylstilbestrol and Adenosis) Project carried out by the National Cancer Institute in the USA led to several reports linking exposure to diethylstilbestrol *in utero* to adverse genital-tract effects.[1-3] It was reported that of nearly 300 young females with clear-cell adenocarcinoma of the genital tract, more than 80% had been exposed *in utero* to diethylstilbestrol-type hormones.[1] Patients had been aged 7 to 28 years at the time of diagnosis. Doses and duration of treatment varied widely; the association existed for both 1.5 mg of diethylstilbestrol daily throughout pregnancy and variable amounts for a week or more during the first trimester. Vaginal adenosis, rare in unexposed young women, was present in about a third of those exposed in the first 4 months of pregnancy, and cervical ectropion in more than two-thirds. Vaginal epithelial changes were most closely associated with early exposure to diethylstilbestrol, with the total dose, and with the duration of exposure; their incidence decreased with age. The risk of cancer in the first 25 years after exposure was small.[2] Fertility did not appear to be impaired in women who had been exposed *in utero* to diethylstilbestrol but the relative risk of an unfavourable outcome of pregnancy in such a group was 1.69. However, of the women who became pregnant, 81% of those exposed to diethylstilbestrol and 95% of control subjects had at least one full-term live birth.[3] In a review of vaginal adenosis and its association with maternal diethylstilbestrol ingestion during pregnancy[4] it was noted that the link between diethylstilbestrol and particularly the benign changes in the vagina and cervix (adenosis) seemed well established. The association between this drug and the development of genital malignancies was less clear, and the very low incidence in the prospective studies in the USA supported this concept. The problem was rare in the UK, but clinicians should be aware that it existed. Cases of vaginal adenosis in young women should be investigated and screened appropriately, and preferably referred to centres where colposcopic expertise was available. Treatment of simple vaginal adenosis should be avoided.

Later reviews[5,6] have highlighted the fact that adverse effects were still emerging in women who had been exposed to diethylstilbestrol *in utero* several decades before. The need for thorough medical screening of such women was emphasised; genital-tract examination was particularly important. It was pointed out[6] that many women exposed to diethylstilbestrol *in utero* were in the reproductive stage of their lives and warranted special observation since a diethylstilbestrol-damaged genital tract posed a potential problem during pregnancy.[5,6] It has also been suggested, for example, that such women are at increased risk of developing pre-eclampsia.[7,8]

There has been concern about the possibility of transgenerational effects on the grandchildren of women given diethylstilbestrol during pregnancy. There has been very little reported on *female offspring of exposed women*, but there were no breast or gynaecological abnormalities found on examination of 28 daughters (over 15 years of age) of women who had been exposed *in utero* and had in many cases cervical and/or vaginal changes characteristic of diethylstilbestrol exposure.[9] Limited data from a Dutch cohort[10] of 16 284 mothers and 8934 sons suggested that the *male offspring of exposed women* may in turn be at greatly increased risk of hypospadias, although the absolute risk was small. A case-control study[11] also found an increased risk, but of a much smaller magnitude, and another cohort study[12] (including DESAD data) found no support for a greatly increased risk of hypospadias. The earlier cohort study that reported the greatly increased risk may have been affected by factors related to infertility, as the study was done in a cohort of subfertile women, about half of whom had undergone IVF.

Further information on the adverse effects of diethylstilbestrol in females exposed to the drug *in utero* can be obtained from the references listed below.[13-23] For mention of the possible increased risk of breast cancer in these women, see Carcinogenicity, above.

1. Professional and Public Relations Committee of the DESAD (Diethylstilbestrol and Adenosis) Project of the Division of Cancer Control and Rehabilitation. Exposure in utero to diethylstilbestrol and related synthetic hormones: association with vaginal and cervical cancers and other abnormalities. *JAMA* 1976; **236:** 1107–9.
2. O'Brien PC, *et al.* Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. *Obstet Gynecol* 1979; **53:** 300–8.
3. Barnes AB, *et al.* Fertility and outcome of pregnancy in women exposed in utero to diethylstilbestrol. *N Engl J Med* 1980; **302:** 609–13.
4. Emens M. Vaginal adenosis and diethylstilboestrol. *Br J Hosp Med* 1984; **31:** 42–8.
5. Anonymous. Diethylstilboestrol—effects of exposure in utero. *Drug Ther Bull* 1991; **29:** 49–50.
6. Wingfield M. The daughters of stilboestrol. *BMJ* 1991; **302:** 1414–15.
7. Mittendorf R, Williams MA. Stilboestrol exposure in utero and risk of pre-eclampsia. *Lancet* 1995; **345:** 265–6.
8. Troisi R, *et al.* Preeclampsia risk in women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2007; **110:** 113–20.
9. Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. *Obstet Gynecol* 2002; **99:** 197–200.
10. Klip H, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 2002; **359:** 1102–7.
11. Brouwers MM, *et al.* Hypospadias: a transgenerational effect of diethylstilbestrol? *Hum Reprod* 2006; **21:** 666–9.
12. Palmer JR, *et al.* Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology* 2005; **16:** 583–6.
13. Herbst AL, *et al.* Prenatal exposure to stilbestrol: a prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 1975; **292:** 334–9.
14. Herbst AL, *et al.* Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Am J Obstet Gynecol* 1977; **128:** 43–50.
15. Kaufman RH, *et al.* Upper genital tract changes associated with in-utero exposure to diethylstilbestrol. *Am J Obstet Gynecol* 1977; **128:** 51–9.
16. Fowler WC, Edelman DA. In utero exposure to DES: evaluation and followup of 199 women. *Obstet Gynecol* 1978; **51:** 459–63.
17. Anderson B, *et al.* Development of DES-associated clear-cell carcinoma: the importance of regular screening. *Obstet Gynecol* 1979; **53:** 293–9.
18. Noller KL, *et al.* Maturation of vaginal and cervical epithelium in women exposed in utero to diethylstilbestrol (DESAD project). *Am J Obstet Gynecol* 1983; **146:** 279–85.
19. Robboy SJ, *et al.* Increased incidence of cervical and vaginal dysplasia in 3980 diethylstilbestrol-exposed young women: experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 1984; **252:** 2979–83.
20. Kaufman RH, *et al.* Upper genital tract changes and infertility in diethylstilbestrol-exposed women. *Am J Obstet Gynecol* 1986; **154:** 1312–18.
21. Melnick S, *et al.* Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix—an update. *N Engl J Med* 1987; **316:** 514–16.
22. Helmerhorst TJM, *et al.* Colposcopic findings and intraepithelial neoplasia in diethylstilbestrol-exposed offspring: the Dutch experience. *Am J Obstet Gynecol* 1989; **161:** 1191–4.
23. Giusti RM, *et al.* Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995; **122:** 778–88.

Effects on male offspring. The effects of exposure to diethylstilbestrol *in utero* have been studied in male offspring.[1-4] Problems in passing urine and abnormalities of the penile urethra were found to be more common in young males exposed to diethylstilbestrol *in utero* than in controls in one study.[1] In another,[2] genital tract abnormalities such as epididymal cysts, capsular induration, and defective testicles occurred in 41 of 163 diethylstilbestrol-exposed men compared with 11 of 168 controls; sperm counts and motility were also reduced in exposed males. In contrast, comparison of 828 men exposed to diethylstilbestrol *in utero* with 676 unexposed men suggested that, overall, diethylstilbestrol exposure did not result in an increased risk of genito-urinary abnormalities, infertility, or testicular cancer.[3] It was suggested that previously reported increased frequencies of such abnormalities may have resulted from a selection bias and/or from a difference in diethylstilbestrol usage. Another study[4] in 253 exposed men found that although there was an increased incidence of congenital malformations of the genitalia (18 cases compared with 5 of 241 controls), this was not associated with any decrease in fertility or impairment of sexual function. An analysis[5] of the combined data from 4 cohorts suggested that there was a small increase in the risk of infertility (relative risk 1.3, 95% confidence interval 1.0 to 1.6) in men who had been exposed to diethylstilbestrol, but that overall this was not associated with an increased likelihood of never fathering a pregnancy or live births, and did not affect the number of pregnancies or live births. Data from these 4 cohorts was also analysed[6] for the development of cancer. The overall rates of cancer were similar to those in unexposed men and to national rates. The rate of testicular cancer was increased in men who had been exposed to diethylstilbestrol *in utero*, but this finding did not reach statistical significance and was limited to only one of the cohorts. Further follow-up will be needed as these men approach the age at which most cancers are diagnosed.

For reference to possible effects on the male *grandchildren* of women who took diethylstilbestrol (the offspring of women exposed *in utero*) see Effects on Female Offspring, above.

1. Henderson BE, *et al.* Urogenital tract abnormalities in sons of women treated with diethylstilbestrol. *Pediatrics* 1976; **58:** 505–7.
2. Anonymous. Offspring of women given DES remains under study. *JAMA* 1977; **238:** 932.
3. Leary FJ, *et al.* Males exposed in utero to diethylstilbestrol. *JAMA* 1984; **252:** 2984–9.
4. Wilcox AJ, *et al.* Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995; **332:** 1411–16.
5. Perez KM, *et al.* National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril* 2005; **84:** 1649–56.
6. Strohsnitter WC, *et al.* Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst* 2001; **93:** 545–51.

Veterinary use. In the EU, the use of diethylstilbestrol or other stilbenes in veterinary medicine is banned unless prior steps are taken to ensure the treated animal and its products are not available for human or animal consumption.

Pharmacokinetics

Diethylstilbestrol is readily absorbed from the gastrointestinal tract. It is slowly metabolised in the liver and excreted in the urine and faeces, mainly as the glucuronide.

Uses and Administration

Diethylstilbestrol is a synthetic nonsteroidal oestrogen that has been used in the palliation of breast and prostate cancer.

Daily oral doses of 10 to 20 mg are occasionally used in the palliative treatment of malignant neoplasms of the breast in postmenopausal women (p.661). The usual oral dose in carcinoma of the prostate (p.671) is 1 to 3 mg daily; higher doses were formerly given. Diethylstilbestrol has also been used in the treatment of prostatic carcinoma in the form of its diphosphate salts (see Fosfestrol, p.2104).

Diethylstilbestrol has been used as pessaries in the short-term management of menopausal atrophic vaginitis.

Preparations

BP 2008: Diethylstilbestrol Pessaries; Diethylstilbestrol Tablets;
USP 31: Diethylstilbestrol Injection; Diethylstilbestrol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Novo Fosfostilben; ***Braz.:*** Destilbenol; ***Fr.:*** Distilbene; ***Irl.:*** Boestrol; ***Mex.:*** Dimeprost.

Drospirenone *(BAN, USAN, rINN)*

Dihydrospirenone; Drospirenon; Drospirenona; Drospirénone; Drospirenoni; Drospirenonum; SH-470; ZK-30595. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione.

Дроспиренон

$C_{24}H_{30}O_3$ = 366.5.

CAS — 67392-87-4.

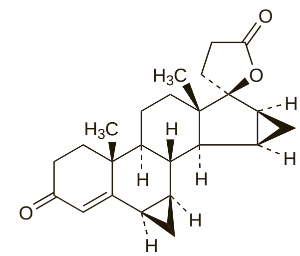

Pharmacopoeias. In *US.*

USP 31 (Drospirenone). A white to off-white powder. Practically insoluble in water and in hexane; sparingly soluble in alcohol and in ethyl acetate; soluble in methyl alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Drospirenone has antimineralocorticoid activity and therefore should not be used in patients at risk of hyperkalaemia, such as those with renal or hepatic impairment or adrenal insufficiency.

◊ Reviews.

1. Heinemann LAJ, Dinger J. Safety of a new oral contraceptive containing drospirenone. *Drug Safety* 2004; **27:** 1001–18.

Effects on the cardiovascular system. As with combined oral contraceptives containing other progestogens, there are reports[1-4] of thrombotic and ischaemic events in patients taking a preparation of ethinylestradiol and drospirenone. The extent of risk associated with hormonal contraceptives that contain drospirenone is mentioned under Venous Thromboembolism, p.2063.

1. Vayá A, *et al.* Transient ischaemic attack associated with the new contraceptive Yasmin. *Thromb Res* 2003; **112:** 121.
2. van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003; **326:** 257.
3. Ortí G, *et al.* Acute myocardial infarction associated with Yasmin oral contraceptive. *Clin Appl Thromb Hemost* 2007; **13:** 336–7.
4. Girolami A, *et al.* Retinal central artery occlusion in a young woman after ten days of a drospirenone-containing oral contraceptive (Yasmin). *Thromb Haemost* 2007; **98:** 473–4.

Renal impairment. US licensed product information for preparations containing drospirenone contra-indicates its use in renal impairment, and in the UK it is contra-indicated in severe impairment. A study[1] of women with renal impairment that was mild (creatinine clearance 50 to 80 mL/minute) or moderate (30 to 50 mL/min) found a trend toward increasing drospirenone exposure with decreasing creatinine clearance. Serum-potassium concentrations were not significantly altered by drospirenone, despite the concomitant use of other drugs that can also potentially increase potassium concentrations including beta blockers and ACE inhibitors.

1. Schürmann R, *et al.* Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *J Clin Pharmacol* 2006; **46:** 867–75.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067, and Hormone Replacement Therapy, p.2076. Because drospirenone has antimineralocorticoid activity, it may potentially exacerbate the effects of drugs that can increase serum-potassium, such as ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, potassium-sparing diuretics, or NSAIDs. Drospirenone may also reduce blood pressure, such that antihypertensive treatment may require adjustment.

Diuretics. The pharmacokinetics of hydrochlorothiazide were not affected by the addition of drospirenone and estradiol in a placebo-controlled study of 36 hypertensive postmenopausal women.[1] However, those given the combination in this study developed lower blood pressure and higher serum-potassium concentrations, which was attributed to the antimineralocorticoid effect of drospirenone.[2] Nontheless, there were no cases of hyperkalaemia. It has been suggested that these potential antihypertensive and potassium-sparing effects might be beneficial in women requiring treatment for both menopausal symptoms and hypertension (see also Menopausal Disorders, below).

1. Karara AH, *et al.* Pharmacokinetics and pharmacodynamics of drospirenone-estradiol combination hormone therapy product coadministered with hydrochlorothiazide in hypertensive postmenopausal women. *J Clin Pharmacol* 2007; **47:** 1292–1302.
2. Preston RA, *et al.* Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance in hypertensive postmenopausal women receiving hydrochlorothiazide. *Menopause* 2007; **14:** 408–14.

NSAIDs. Drospirenone has the potential to exacerbate the effects of other drugs, such as NSAIDs, that can increase serum potassium. Licensed product information suggests that a clinical effect is unlikely in practice, although the use of a number of such drugs together or the presence of renal impairment may increase the risk. In a small study[1] of healthy postmenopausal women, there was no evidence that potassium concentrations were any higher during concomitant use of *indometacin* with a combination of drospirenone plus estradiol compared with indometacin alone.

1. Schütt B, *et al.* Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol* 2007; **47:** 774–81.

Pharmacokinetics

After oral doses, drospirenone is rapidly absorbed with a bioavailability of about 76%. It is about 97% bound to plasma proteins, though it does not bind to sex hormone binding globulin or corticosteroid binding globulin. It is extensively metabolised with a terminal half-life of about 30 to 40 hours. The metabolites are excreted in the urine and faeces.

Uses and Administration

Drospirenone is a structural analogue of spironolactone (p.1400); it has the effects of a progestogen (see Progesterone, p.2126) with antimineralocorticoid and anti-androgenic activity. It is used as the progestogenic component of combined oral contraceptives (see p.2069), usually in a dose of 3 mg daily with ethinylestradiol 30 micrograms, for 21 days of each 28-day cycle. A combination of drospirenone 3 mg with ethinylestradiol 20 micrograms, given daily for 24 days of each 28-day cycle, may also be used for contraception and for the management of premenstrual dysphoric disorder (see below) or moderate acne (p.1577) in women who also require an oral contraceptive. Drospirenone is also used as the progestogenic component of menopausal HRT (see below) in a continuous dosage regimen of 0.5 or 2 mg daily.

◊ Reviews.

1. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000; **62:** 29–38.
2. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. *Climacteric* 2005; **8** (suppl 3): 4–12.
3. Oelkers WH. Drospirenone in combination with estrogens: for contraception and hormone replacement therapy. *Climacteric* 2005; **8** (suppl 3): 19–27.
4. Fenton C, *et al.* Drospirenone/ethinylestradiol 3mg/20μg (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. *Drugs* 2007; **67:** 1749–65.

Contraception. References.

1. Huber J, *et al.* Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. *Eur J Contracept Reprod Health Care* 2000; **5:** 25–34.
2. Foidart JM, *et al.* A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care* 2000; **5:** 124–34. Correction. *ibid.* 2001; **6:** 63.
3. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception* 2000; **61:** 105–11.
4. Oelkers W, *et al.* Effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; **14:** 204–13.
5. Bachmann G, *et al.* Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 μg ethinylestradiol and 3 mg drospirenone. *Contraception* 2004; **70:** 191–8.
6. Gruber DM, *et al.* A comparison of the cycle control, safety, and efficacy profile of a 21-day regimen of ethinylestradiol 20μg and drospirenone 3mg with a 21-day regimen of ethinylestradiol 20μg and desogestrel 150μg. *Treat Endocrinol* 2006; **5:** 115–21.
7. Cibula D, *et al.* Efficacy and safety of a low-dose 21-day combined oral contraceptive containing ethinylestradiol 20μg and drospirenone 3mg. *Clin Drug Investig* 2006; **26:** 143–50.

Menopausal disorders. Drospirenone is used as the progestogenic component of menopausal HRT[1-3] (p.2076). The antimineralocorticoid effect of drospirenone has also been investigated and found to lower blood pressure in postmenopausal women with treated and untreated hypertension.[4]

1. Schürmann R, *et al.* Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004; **7:** 189–96.
2. Whitehead M. Hormone replacement therapy with estradiol and drospirenone: an overview of the clinical data. *J Br Menopause Soc* 2006; **12** (suppl 1): 4–7.
3. Archer DF, *et al.* Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause* 2005; **12:** 716–27.
4. Mallareddy M, *et al.* Drospirenone, a new progestogen, for postmenopausal women with hypertension. *Drugs Aging* 2007; **24:** 453–66.

Premenstrual syndrome. The combination of drospirenone with ethinylestradiol has been studied in the management of premenstrual syndrome (p.2099). A systematic review[1] of 5 studies found some evidence that the combination may be useful in the treatment of premenstrual dysphoric disorder. However, it was not known whether the effect lasted beyond 3 cycles of treatment, whether the combination was effective for less severe symptoms, or whether combinations using drospirenone were any better than combined contraceptives containing other progestogens.

1. Lopez LM, *et al.* Oral contraceptives containing drospirenone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Diva Total.

Multi-ingredient: ***Arg.:*** Angeliq; Damsel; Diva; Divina; Equifem; Gadofem; Isis; Isis Fe; Kala; Kirumelle; Maxima; Yasmin; Yasminelle; ***Austral.:*** Angeliq; Yasmin; ***Austria:*** Allurene; Angeliq; Yasmin; Yirala; ***Belg.:*** Angeliq; Yasmin; ***Braz.:*** Angeliq; Elani; Yasmin; YAZ; ***Canad.:*** Yasmin; ***Chile:*** Angeliq; Dahlia; Femelle; Yasmin; ***Cz.:*** Angeliq; Belanette; Yadine; Yasminelle; ***Denm.:*** Angemin; Yasmin; ***Fin.:*** Angeliq; Yasmin; ***Fr.:*** Angeliq; Jasmine; Jasminelle; ***Ger.:*** Angeliq; Petibelle; Yasmin; ***Gr.:*** Angeliq; Yasmin; ***Hong Kong:*** Angeliq; Yasmin; ***Hung.:*** Angeliq; Yadine; Yasminelle; ***Indon.:*** Angeliq; Yasmin; ***Irl.:*** Angeliq; Yasmin; ***Israel:*** Angeliq; Yasmin; ***Ital.:*** Angeliq; Yasmin; ***Malaysia:*** Yasmin; ***Mex.:*** Angeliq; Yasmin; ***Neth.:*** Allurene; Angeliq; Belanette; Liofora; Yasmin; Yasminelle; Yira; ***Norw.:*** Yasmin; ***NZ:*** Yasmin; ***Philipp.:*** Angeliq; Yasmin; ***Pol.:*** Angeliq; Yasmin; Yasminelle; ***Port.:*** Angeliq; Petibelle; Yasmin; Yasminelle; ***Rus.:*** Angeliq (Анжелик); Yarina (Ярина); ***S.Afr.:*** Angeliq; Yasmin; ***Singapore:*** Yasmin; ***Spain:*** Angeliq; Yasmin; Yira†; ***Swed.:*** Angemin; Yasmin; ***Switz.:*** Yasmin; ***Thai.:*** Angeliq; Yasmin; ***Turk.:*** Angeliq; Yasmin; ***UK:*** Angeliq; Yasmin; ***USA:*** Angeliq; Yasmin; YAZ; ***Venez.:*** Yasmin.

Drostanolone Propionate *(BANM, rINNM)* ⊗

Compound 32379; Dromostanolone Propionate *(USAN)*; Drostanolone, Propionate de; Drostanoloni Propionas; 2α-Methyldihydrotestosterone Propionate; NSC-12198; Propionato de drostanolona. 17β-Hydroxy-2α-methyl-5α-androstan-3-one propionate.

Дростанолона Пропионат

$C_{23}H_{36}O_3$ = 360.5.

CAS — 58-19-5 (drostanolone); 521-12-0 (drostanolone propionate).

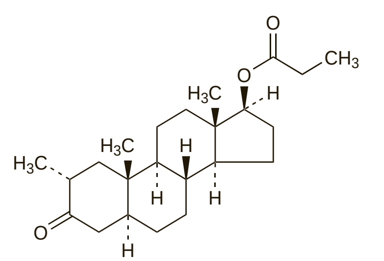

Profile

Drostanolone propionate has anabolic and androgenic properties (see Testosterone, p.2129) and has been used in the treatment of advanced malignant neoplasms of the breast in postmenopausal women. It has been subject to abuse in sport.

Dydrogesterone *(BAN, USAN, rINN)*

6-Dehydro-*retro*-progesterone; 6-Dehydro-9β,10α-progesterone; Didrogesteron; Didrogesterona; Dydrogesteron; Dydrogestérone; Dydrogesteroni; Dydrogesteronum; Isopregnenone; NSC-92336. 9β,10α-Pregna-4,6-diene-3,20-dione.

Дидрогестерон

$C_{21}H_{28}O_2$ = 312.4.

CAS — 152-62-5.

ATC — G03DB01.

ATC Vet — QG03DB01.

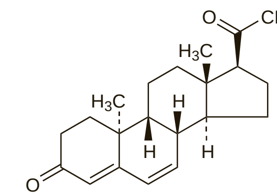

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Dydrogesterone). A white or almost white crystalline powder; odourless or almost odourless. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in chloroform; slightly soluble in ether and in fixed oils. Protect from light.

USP 31 (Dydrogesterone). A white to pale yellow crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 2 of chloroform, and 1 in 200 of ether.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormone Replacement Therapy, p.2071.

Porphyria. Dydrogesterone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Anomalies (non-virilising) of the genito-urinary tract were found in a 4-month-old baby whose mother had taken dydrogesterone 20 mg daily from the eighth to twentieth week of pregnancy and 10 mg daily from then until term.[1] She had also been given hydroxyprogesterone caproate 250 mg by intramuscular injection weekly from the eighth to the twentieth week.

1. Roberts IF, West RJ. Teratogenesis and maternal progesterone. *Lancet* 1977; **ii:** 982.

Interactions

As for progestogens in general (see Progesterone, p.2126).

Uses and Administration

Dydrogesterone is a progestogen structurally related to progesterone (p.2126). It does not have oestrogenic or androgenic properties.

Dydrogesterone has been given orally in the treatment of menstrual disorders such as menorrhagia (p.2126), usually in a dose of 10 mg twice daily in a cyclical regimen, and for the treatment of endometriosis (p.2091) in a dose of 10 mg two or three times daily cyclically or continuously. It has also been given cyclically in doses of 10 mg once or twice daily, or continuously in doses of 5 mg daily, for endometrial protection during menopausal HRT (p.2076).

In threatened miscarriage suggested doses have been 40 mg initially followed by 10 mg or more every 8 hours, continued for a week after symptoms cease then gradually reduced unless symptoms return. In recurrent miscarriage suggested doses have been 10 mg twice daily given cyclically until conception then continuously until week 20 of pregnancy, the dose may then be gradually reduced. However, such use is not recommended unless there is proven progesterone deficiency. Cyclical dydrogesterone has also been used in infertility (p.2080) in doses of 10 mg twice daily.

Preparations

BP 2008: Dydrogesterone Tablets;
USP 31: Dydrogesterone Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Duphaston; ***Austria:*** Duphaston; ***Belg.:*** Duphaston; ***Braz.:*** Duphaston; ***Chile:*** Duphaston; ***Cz.:*** Duphaston; ***Fin.:*** Terolut; ***Fr.:*** Duphaston; ***Ger.:*** Duphaston; ***Gr.:*** Duphaston; ***Hong Kong:*** Duphaston; ***Hung.:*** Duphaston; ***India:*** Duphaston; ***Indon.:*** Duphaston; ***Irl.:*** Duphaston; ***Israel:*** Biphaston†; Duphaston; ***Ital.:*** Dufaston; ***Malaysia:*** Duphaston; ***Neth.:*** Duphaston; ***NZ:*** Duphaston; ***Philipp.:*** Duphaston; ***Pol.:*** Duphaston; ***Port.:*** Duphaston; ***Rus.:*** Duphaston (Дюфастон); ***S.Afr.:*** Duphaston; ***Singapore:*** Duphaston; ***Swed.:*** Duphaston; ***Switz.:*** Duphaston; ***Thai.:*** Duphaston; ***Turk.:*** Duphaston; ***UK:*** Duphaston†; ***Venez.:*** Duphaston.

Multi-ingredient: ***Austral.:*** Femoston; ***Austria:*** Femoston; Femoston Conti; Femphascyl; Femphascyl conti; ***Belg.:*** Femoston; Femoston Conti; ***Braz.:*** Femoston; Femoston Conti; ***Chile:*** Femoston; Femoston Conti; ***Cz.:*** Femoston; Femoston Conti; ***Fin.:*** Femoston; Femoston Conti; ***Fr.:*** Climaston; ***Ger.:*** Femoston; Femoston Conti; ***Gr.:*** Femaston; ***Hong Kong:*** Femoston; ***Hung.:*** Femoston; ***Irl.:*** Femoston; Femoston Conti; ***Ital.:*** Femoston; Femoston Conti; ***Malaysia:*** Femoston; Femoston Conti; ***Mex.:*** Lutalmin; ***Neth.:*** Climaston Continu; Femoston; Femoston Continu; Femphascyl Continu; ***Philipp.:*** Femoston; ***Pol.:*** Femoston; Femoston Conti; ***Port.:*** Femoston; Femoston 1/5; Femphascyl†; ***Rus.:*** Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); ***S.Afr.:*** Femoston; Femoston Conti; ***Singapore:*** Femoston; Femoston Conti; ***Switz.:*** Femoston; Femoston Conti; ***Thai.:*** Femoston 1/10; Femoston Conti; ***UK:*** Femapak; Femoston; Femoston Conti; ***Venez.:*** Femoston; Femoston Conti.

Elcometrine

Elcometrina; 16-Methylene-17-alpha-acetoxy-19 Norprogesterone; ST-1435.

$C_{23}H_{30}O_4$ = 370.5.

CAS — 7759-35-5.

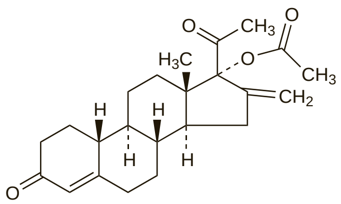

Profile

Elcometrine is a synthetic progestogen that is being developed for use in contraception and menopausal HRT, and in the management of endometriosis.

◊ References.

1. Ylänen K, *et al.* Subdermal progestin implant (Nestorone) in the treatment of endometriosis: clinical response to various doses. *Acta Obstet Gynecol Scand* 2003; **82:** 167–72.
2. Sitruk-Ware R, *et al.* Nestorone : clinical applications for contraception and HRT. *Steroids* 2003; **68:** 907–13.
3. Sivin I, *et al.* Two-year performance of a Nestorone -releasing contraceptive implant: a three-center study of 300 women. *Contraception* 2004; **69:** 137–44.
4. Sivin I, *et al.* Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. *Contraception* 2005; **71:** 122–9.
5. Fraser IS, *et al.* Serum Nestorone and ethinyl estradiol levels, and ovulation inhibition in women using three different dosage combinations of a Nestorone progestogen-ethinyl estradiol contraceptive vaginal ring on a bleeding-signaled regimen. *Contraception* 2005; **72:** 40–5.
6. Weisberg E, *et al.* Clinical performance and menstrual bleeding patterns with three dosage combinations of a Nestorone progestogen/ethinyl estradiol contraceptive vaginal ring used on a bleeding-signaled regimen. *Contraception* 2005; **72:** 46–52.
7. Croxatto HB, *et al.* Feasibility study of Nestorone -ethinylestradiol vaginal contraceptive ring for emergency contraception. *Contraception* 2006; **73:** 46–52.

Equilin

Equilina. 3-Hydroxyestra-1,3,5(10),7-tetraen-17-one.

$C_{18}H_{20}O_2$ = 268.4.

CAS — 474-86-2.

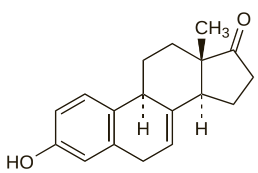

Pharmacopoeias. In *US.*

USP 31 (Equilin). Store in airtight containers. Protect from light.

Profile

Equilin is a natural oestrogenic hormone found in horses. Sodium equilin sulfate is one of the components of both conjugated oestrogens (p.2087) and esterified oestrogens (see below) used for menopausal HRT.

Esterified Oestrogens

Esterified Estrogens; Estrógenos esterificados.

Эстрогены Этерифицированные

Pharmacopoeias. In *US.*

USP 31 (Esterified Estrogens). A mixture of the sodium salts of the sulfate esters of the oestrogenic substances, principally estrone. It contains 75 to 85% of sodium estrone sulfate and 6 to 15% of sodium equilin sulfate, in such a proportion that the total of these two components is not less than 90%, of the labelled amount of esterified oestrogens. A white or buff-coloured amorphous powder; odourless or having a slight characteristic odour. Store in airtight containers.

Profile

Esterified oestrogens have actions and uses similar to those described for estradiol (see below). They are used for the same purposes (principally menopausal HRT), and in a similar oral dosage, as conjugated oestrogens (see p.2087), although higher cyclical doses of 2.5 to 7.5 mg daily are still licensed for use in female hypogonadism.

Preparations

USP 31: Esterified Estrogens Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Menest†; ***Chile:*** Femibel; ***Switz.:*** Oestro-Feminal†; ***USA:*** Estratab; Menest.

Multi-ingredient: ***Chile:*** Delitan; Feminova-T; ***USA:*** Covaryx; Estratest; Syntest.

Estradiol *(BAN, rINN)*

Beta-oestradiol; Dihidrofoliculina; Dihidroxiestratrieno; Dihidroxiestrina; Dihydrofolliculin; Dihydrotheelin; Dihydroxyoestrin; Estradioli; Estradiolis; Estradiolum; NSC-9895; Oestradiol; Östradiol; Ösztradiol. Estra-1,3,5(10)-triene-3,17β-diol.

Эстрадиол

$C_{18}H_{24}O_2$ = 272.4.

CAS — 50-28-2 (anhydrous estradiol).

ATC — G03CA03.

ATC Vet — QG03CA03.

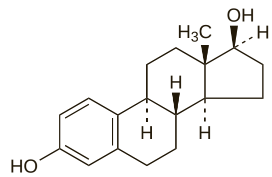

NOTE. In *Martindale* the term oestradiol is used for the endogenous substance.

Pharmacopoeias. In *Chin.* and *US.*

Eur. (see p.vii) includes the hemihydrate.

Ph. Eur. 6.2 (Estradiol Hemihydrate). A white or almost white crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

USP 31 (Estradiol). White or creamy-white, odourless, hygroscopic small crystals or crystalline powder. Practically insoluble in water; soluble 1 in 28 of alcohol, 1 in 435 of chloroform, and 1 in 150 of ether; soluble in acetone, in dioxan, and in solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Estradiol Acetate *(BANM, USAN, rINNM)*

Acetato de estradiol; E-3A; Estradiol, Acétate d'; Estradiol-3-acetate; Estradioli Acetas; Oestradiol Acetate. Estra-1,3,5(10)-triene-3,17β-diol 3-acetate.

Эстрадиола Ацетат

$C_{20}H_{26}O_3$ = 314.4.

CAS — 4245-41-4.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Benzoate *(BANM, rINNM)*

Benzoato de estradiol; Beta-oestradiol Benzoate; Dihydroxyoestrin Monobenzoate; Estradiol, benzoate d'; Estradiolbensoat; Estradiol-benzoát; Estradioli benzoas; Estradiolibentsoaatti; Estradiolio benzoatas; Estradiolu benzoesan; NSC-9566; Oestradiol Benzoate; Östradiol Benzoat; Ösztradiol-benzoát. Estra-1,3,5(10)-triene-3,17β-diol 3-benzoate.

Эстрадиола Бензоат

$C_{25}H_{28}O_3$ = 376.5.

CAS — 50-50-0.

ATC — G03CA03.

ATC Vet — QG03CA03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Estradiol Benzoate). An almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in acetone; freely soluble in dichloromethane; slightly soluble in methyl alcohol.

USP 31 (Estradiol Benzoate). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in acetone; slightly soluble in ether. Store in airtight containers. Protect from light.

Estradiol Cipionate *(BANM, rINNM)*

Cipionato de estradiol; Estradiol, Cipionate d'; Estradiol Cypionate; Estradioli Cipionas; Oestradiol Cyclopentylpropionate; Oestradiol Cypionate. Estra-1,3,5(10)-triene-3,17β-diol 17-(3-cyclopentylpropionate).

Эстрадиола Ципионат

$C_{26}H_{36}O_3$ = 396.6.

CAS — 313-06-4.

ATC — G03CA03.

ATC Vet — QG03CA03.

Pharmacopoeias. In *US.*

USP 31 (Estradiol Cypionate). A white to practically white crystalline powder, odourless or has a slight odour. Insoluble in water; soluble 1 in 40 of alcohol, 1 in 7 of chloroform, and 1 in 2800 of ether; soluble in acetone and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers. Protect from light.

Estradiol Dipropionate *(BANM, rINNM)*

Dihydroxyoestrin Dipropionate; Dipropionato de estradiol; Estradiol, Dipropionate d'; Estradioli Dipropionas; Oestradiol Dipropionate. Estra-1,3,5(10)-triene-3,17β-diol dipropionate.

Эстрадиола Дипропионат

$C_{24}H_{32}O_4$ = 384.5.

CAS — 113-38-2.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Enantate *(BANM, rINNM)*

Enantato de estradiol; Estradiol, Enantate d'; Estradiol Enanthate *(USAN)*; Estradioli Enantas; Oestradiol Enanthate; Oestradiol 17-Heptanoate; SQ-16150. Estra-1,3,5(10)-triene-3,17β-diol 17-heptanoate.

Эстрадиола Энантат

$C_{25}H_{36}O_3$ = 384.6.

CAS — 4956-37-0.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Hexahydrobenzoate *(BANM, rINNM)*

Estradiol, Hexahydrobenzoate d'; Estradioli Hexahydrobenzoas; Hexahidrobenzoato de estradiol; Oestradiol Hexahydrobenzoate. Estra-1,3,5(10)-triene-3,17β-diol 17-cyclohexanecarboxylate.

Эстрадиола Гексагидробензоат

$C_{25}H_{34}O_3$ = 382.5.

CAS — 15140-27-9.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Phenylpropionate *(BANM, rINNM)*

Estradiol, Phénylpropionate de; Estradioli Phenylpropionas; Fenilpropionato de estradiol; Oestradiol Phenylpropionate; Östradiol Fenilpropiyonat. Estra-1,3,5(10)-triene-3,17β-diol 17-(3-phenylpropionate).

Эстрадиола Фенилпропионат

$C_{27}H_{32}O_3$ = 404.5.

ATC — G03CA03.

ATC Vet — QG03CA03.

Estradiol Valerate *(BANM, rINN)*

Estradiol, valérate d'; Estradioli valeras; Estradiolio valeratas; Estradiolivaleraatti; Estradiolvalerat; Estradiol-valerát; NSC-17590; Oestradiol Valerate; Östradiol-17-Valerat; Ösztradiol-valerát; Valerato de estradiol. Estra-1,3,5(10)-triene-3,17β-diol 17-valerate.

Эстрадиола Валерат

$C_{23}H_{32}O_3$ = 356.5.

CAS — 979-32-8.

ATC — G03CA03.

ATC Vet — QG03CA03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Estradiol Valerate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 31 (Estradiol Valerate). A white crystalline powder which is usually odourless or may have a faint fatty odour. Practically insoluble in water; soluble in benzyl benzoate, in dioxan, in methyl alcohol, and in castor oil; sparingly soluble in arachis oil and in sesame oil. Store in airtight containers. Protect from light.

Adverse Effects

The adverse effects of estradiol and other oestrogens are related, in part, to dose and duration of therapy, and to the gender and age of the recipient. In addition, adverse effects may be modified by a progestogen in combined oral contraceptives or menopausal HRT. Whether adverse effects of natural and synthetic oestrogens differ, and whether the dosage route has an effect, is less clear.

The adverse effects of oestrogens used in hormonal contraceptives are considered in detail starting on p.2059. Those of oestrogens used in HRT are considered in detail starting on p.2071.

The use of oestrogens in children may cause premature closure of the epiphyses resulting in decreased final adult height.

Large doses of oestrogens used in palliation of cancers have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, they cause impotence and feminising effects such as gynaecomastia. In women, they may cause withdrawal bleeding, and, when used for breast cancer, they have caused hypercalcaemia and bone pain.

Effects on the skin. Transdermal patches in which estradiol is dissolved in the adhesive matrix may cause fewer skin reactions than those releasing estradiol from an alcoholic reservoir.

1. Ross D. Randomised crossover comparison of skin irritation with two transdermal oestradiol patches. *BMJ* 1997; **315:** 288.

Precautions

The precautions for the use of estradiol and other oestrogens used as menopausal HRT are considered in detail starting on p.2075. Those for oestrogens used in hormonal contraceptives are considered in detail starting on p.2065.

High doses of oestrogen used in treating malignant disease should be used cautiously in patients with cerebrovascular disorders, coronary artery disease, or venous thromboembolism. They may exacerbate hypercalcaemia of malignancy.

Oestrogens should be used with caution in children because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature.

Oestrogens have been reported to interfere with some diagnostic tests such as those for thyroid function and glucose tolerance.

Breast feeding. Estradiol has been detected in breast milk after the use of pessaries containing 50 or 100 mg of estradiol.[1] The American Academy of Pediatrics considers that estradiol is usually compatible with breast feeding.[2]

1. Nilsson S, *et al.* Transfer of estradiol to human milk. *Am J Obstet Gynecol* 1978; **132:** 653–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Cosmetic use. Use of cosmetic products containing oestrogens has led to adverse effects such as precocious puberty in children[1,2] and gynaecomastia or postmenopausal bleeding in adults.[1] Such products have been used by a greater proportion of African Americans than any other ethnic group in the USA, and it has been hypothesised that this may have contributed to the observations of earlier onset of puberty in girls[3,4] and increased risk of breast cancer in young women.[4]

1. Anonymous. Estrogens in cosmetics. *Med Lett Drugs Ther* 1985; **27:** 54–5.
2. Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. *Clin Pediatr (Phila)* 1998; **37:** 733–9.
3. Li S-T, *et al.* Hormone-containing hair product use in prepubertal children. *Arch Pediatr Adolesc Med* 2002; **156:** 85–6.
4. Donovan M, *et al.* Personal care products that contain estrogens or xenoestrogens may increase breast cancer risk. *Med Hypotheses* 2007; **68:** 756–66.

Porphyria. Oestrogens are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Pregnancy. Although gross abnormalities of the genito-urinary tract have been reported in the male offspring of women who took diethylstilbestrol during pregnancy there is conflicting evidence as to whether the oestrogen produced an increased risk of abnormalities, infertility, or testicular cancer in such offspring (see p.2095). The male fetus is normally protected from the feminising effects of the natural oestrogens in the uterine environment by the early development of the testes and the secretion of male hormones.[1] However, there has been considerable concern about a rising incidence of disorders of the male reproductive tract, and a reduction in sperm counts, which has been noted in the last 20 to 30 years. It has been hypothesised that overexposure of male fetuses to environmental oestrogens derived from pollutants such as pesticides and plastics may be responsible for this decline,[2,3] although some dispute this.[4] A systematic review[5] of epidemiological data found no strong evidence to link fetal exposure to oestrogens (as pharmaceuticals or pollutants) with reduced sperm count, cryptorchidism, or hypospadias, although there was some evidence to support a possible link with testicular cancer.

For discussion of the lack of effects of hormonal contraceptives on the fetus, including evidence that they are unlikely to increase the risk of hypospadia in the male fetus, see Pregnancy, under Precautions of Hormonal Contraceptives, p.2067.

1. Mittwoch U, *et al.* Male sexual development in "a sea of oestrogen". *Lancet* 1993; **342:** 123–4.
2. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993; **341:** 1392–5.
3. de Kretser DM. Declining sperm counts. *BMJ* 1996; **312:** 457–8.
4. Thomas JA. Falling sperm counts. *Lancet* 1995; **346:** 635.
5. Storgaard L, *et al.* Male reproductive disorders in humans and prenatal indicators of estrogen exposure: a review of published epidemiological studies. *Reprod Toxicol* 2006; **21:** 4–15.

Veterinary use. An FAO/WHO expert committee examining the risks from residues of veterinary drugs in foodstuffs established an acceptable daily intake for estradiol, but concluded that there would be no need to specify a numerical maximum residue limit for estradiol in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as oestrogens in veterinary practice is restricted, and their use as growth promotors is banned.

There is concern about the effect of environmental oestrogens on male fertility and development, see Pregnancy, above.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Interactions involving estradiol and other oestrogens used in menopausal HRT are covered on p.2076. Interactions for oestrogens used in hormonal contraceptives are covered on p.2067.

Pharmacokinetics

In general, estradiol and other oestrogens are readily absorbed from the gastrointestinal tract and through the skin or mucous membranes. However, the natural unconjugated oestrogens such as estradiol undergo extensive first-pass metabolism in the gastrointestinal tract and liver after oral doses. They are, therefore, generally not orally active, although a micronised preparation of estradiol has sufficient bioavailability (3 to 5%) to be orally active. Estradiol is metabolised in part to less active oestrogens such as estriol and estrone. Synthetic oestrogens produced by alkylation of the C17 position, such as ethinylestradiol, are more slowly metabolised and are therefore orally active. Conjugated oestrogens, which are essentially oestrogen metabolites, are also orally active because they are hydrolysed by enzymes in the lower gastrointestinal tract allowing absorption of the active oestrogen. Vaginal, transdermal, intranasal, or parenteral use of oestrogens also avoids first-pass hepatic metabolism. Plasma-estradiol concentrations are reported to reach a peak 1.5 to 2 hours after an oral dose, and again at about 8 hours due to enterohepatic recycling. Estradiol esters are rapidly hydrolysed to free estradiol when given orally. After intramuscular injection of the esters, absorption is prolonged.

Oestrogens are extensively bound to plasma proteins. Naturally occurring oestrogens such as estradiol are principally bound to sex-hormone binding globulin. Conversely, ethinylestradiol is mostly bound to albumin.

Oestrogens are metabolised in the liver. A variety of sulfate and glucuronide conjugates are formed, and these are excreted in the urine and the bile. Those excreted in the bile undergo enterohepatic recycling or are excreted in the faeces.

◊ References to the pharmacokinetics of estradiol[1-4] and other oestrogens.[5,6]

1. Kuhnz W, *et al.* Pharmacokinetics of estradiol, free and total estrone, in young women following single intravenous and oral administration of 17β-estradiol. *Arzneimittelforschung* 1993; **43:** 966–73.
2. Schubert W, *et al.* Pharmacokinetic evaluation of oral 17β-oestradiol and two different fat soluble analogues in ovariectomized women. *Eur J Clin Pharmacol* 1993; **44:** 563–8.
3. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, other methods of delivery. *Obstet Gynecol Clin North Am* 1994; **21:** 271–9.
4. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17β-estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
5. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol* 1990; **75** (suppl): 9S–14S.
6. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995; **35** (suppl): 18S–24S.

Uses and Administration

Estradiol is the most active of the naturally occurring oestrogens (for further details, see p.2058). Estradiol and its semisynthetic esters and other natural oestrogens are primarily used as menopausal HRT (see p.2076) whereas synthetic derivatives such as ethinylestradiol and mestranol have a major role as components of combined oral contraceptives (see Hormonal Contraceptives, p.2069). Estradiol may also be used as replacement therapy for female hypogonadism or primary ovarian failure (p.2079). Replacement therapy ('add-back' therapy) may also be given to women in whom the pituitary-ovarian axis is suppressed by therapy with gonadorelin or its analogues.

Estradiol hemihydrate 1.03 mg is equivalent to about 1 mg of the anhydrous substance.

For **menopausal HRT** oral preparations or transdermal patches of estradiol are commonly used. Other transdermal formulations, subcutaneous implants, and a nasal spray are also available. Intramuscular injections were formerly used. In women with a uterus, a progestogen is also required, given cyclically or continuously, usually by mouth although some combined transdermal preparations are available. Local vaginal estradiol preparations are used specifically for the treatment of menopausal atrophic vaginitis; these are generally recommended for short-term use only, if given without a progestogen in women with a uterus, although specific recommendations vary between products.

For use *by mouth* estradiol or estradiol valerate are normally given; doses are 1 or 2 mg daily cyclically or more often continuously. Estradiol acetate may be given in an initial dose of 450 micrograms daily, increasing if necessary to 0.9 or 1.8 mg once daily.

Estradiol may be used topically as *transdermal skin patches* to provide a systemic effect; a variety of patches are available which release between 25 and 100 micrograms of estradiol every 24 hours. A low-dose patch supplying 14 micrograms daily is also available specifically for the prevention of postmenopausal osteoporosis in women at significant risk; with this low dose, the addition of a 14-day course of progestogen in women with a uterus is only required once every 6 to 12 months. Depending on the preparation, patches are replaced once or twice weekly. Each new patch is applied to a different area of skin in rotation, usually below the waistline; patches should not be applied on or near the breasts. *Topical gel* preparations are also used for systemic effect. The usual applied dose is 0.25 to 1.5 mg of estradiol daily, depending on the preparation, but up to 3 mg daily may be required for control of menopausal symptoms in some women. The gel should not be applied on the face or on or near the breasts, vagina, or vulval region. A *topical emulsion* is also available; estradiol hemihydrate 8.7 mg is applied daily to provide a systemic estradiol dose of about 50 micrograms. A *transdermal spray* has also been developed, delivering a single dose of estradiol 1.53 mg onto the skin. It should be applied to the skin of the inner surface of the forearm, and the dose may be increased up to 3 sprays once daily in the morning, at separate sites on the forearm, according to response.

A *nasal spray* is available, delivering 150 micrograms of estradiol hemihydrate per spray. The usual initial dose is 150 micrograms daily (1 spray in 1 nostril). After 2 or 3 cycles the dose may be adjusted according to response; the usual maintenance dose is 300 micrograms daily (1 spray in each nostril once daily) but may range from 150 micrograms once daily up to 450 to 600 micrograms daily in 2 divided doses.

In order to prolong the duration of action *subcutaneous implants* of estradiol may be used. The dose of estradiol is generally 25 to 100 mg with a new implant being given after about 4 to 8 months according to oestrogen concentrations.

Estradiol may be used locally either as 25-microgram *vaginal tablets*, at an initial dose of one tablet daily for 2 weeks followed by a maintenance dose of one tablet twice a week, or as a 0.01% *vaginal cream*, in initial amounts of 2 to 4 g of cream daily for 1 to 2 weeks followed by half the initial dose for a similar period, then a maintenance dose of 1 g up to 3 times weekly. A local delivery system using a 3-month *vaginal ring* contains 2 mg of estradiol hemihydrate, and delivers about 7.5 micrograms of estradiol per 24 hours. Another 3-month vaginal ring system, which contains estradiol acetate, releases either 50 or 100 micrograms of estradiol daily, and is used for the relief of both local and systemic postmenopausal symptoms.

Intramuscular injections of estradiol benzoate or valerate esters have been used as oily depot solutions, usually given once every 3 to 4 weeks. The cipionate, dipropionate, enantate, hexahydrobenzoate, phenylpropionate, and undecylate esters have been used similarly. The enantate and cipionate esters are used as the oestrogen component of combined injectable **contraceptives**.

Estradiol and other oestrogens have sometimes been used in higher doses for palliative treatment in **prostate cancer** (p.671) and **breast cancer** in men and postmenopausal women (p.661).

Administration. ***BUCCAL AND SUBLINGUAL ADMINISTRATION.*** Estradiol is absorbed through the *buccal* route, and has been reported to improve postmenopausal vasomotor symptoms.[1] A pharmacokinetic study[2] of micronised estradiol found the *sublingual* route resulted in more rapid absorption, a higher peak concentration, and more rapid elimination, than oral dosage. Sublingual micronised estradiol has been studied for the management of postpartum depression.[3]

1. Gass MS, *et al.* A short study in the treatment of hot flashes with buccal administration of 17-β estradiol. *Maturitas* 2004; **49:** 140–7.
2. Price TM, *et al.* Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 β-estradiol. *Obstet Gynecol* 1997; **89:** 340–5.
3. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.

IMPLANTS. There may be a striking interpatient variation in blood-estradiol concentrations in women receiving estradiol implants,[1] and symptoms of oestrogen deficiency have re-appeared in some patients even though serum-estradiol concentrations were within or above the physiological range.[2] After debate on the appropriateness of using serum concentrations of estradiol as a guide to implant use, rather than symptoms,[3-7] it is now recommended that estradiol concentration should be monitored during therapy.

Cyclical progestogen may be required for a prolonged period after removal of estradiol implants in women with a uterus.[7]

1. Guirgis RR. Oestradiol implants: what dose, how often? *Lancet* 1987; **ii:** 856.
2. Gangar K, *et al.* Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989; **299:** 601–2.
3. Ginsburg J, Hardiman P. Oestrogen deficiency and oestradiol implants. *BMJ* 1989; **299:** 1031.
4. Studd J, *et al.* Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1400–1.
5. Swyer GIM. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
6. Tobias JH, Chambers TJ. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 854.
7. Wardle P, Fox R. Symptoms of oestrogen deficiency in women with oestradiol implants. *BMJ* 1989; **299:** 1102.

INTRANASAL ADMINISTRATION. The intranasal route for estradiol HRT has been reviewed.[1] It appears to be comparable in efficacy to oral[2] or transdermal use[3,4] in the treatment of menopausal symptoms. As with transdermal application, the intranasal route avoids intestinal and hepatic first-pass metabolism.

1. Dooley M, *et al.* Estradiol-intranasal: a review of its use in the management of menopause. *Drugs* 2001; **61:** 2243–62.
2. Studd J, *et al.* Efficacy and acceptability of intranasal 17β-oestradiol for menopausal symptoms: randomised dose-response study. *Lancet* 1999; **353:** 1574–8. Correction. *ibid.*; **354:** 780.
3. Lopes P, *et al.* Randomized comparison of intranasal and transdermal estradiol. *Obstet Gynecol* 2000; **96:** 906–12.
4. Davis SR, *et al.* Intranasal versus transdermal matrix oestrogen replacement in Australasian women. *Maturitas* 2005; **51:** 163–71.

TRANSDERMAL ADMINISTRATION. Transdermal estradiol given via *patches* applied to the skin has been reviewed.[1-3] This method of delivery has certain advantages over the oral route in that gastrointestinal and hepatic first-pass metabolism is avoided, liver enzymes are not stimulated (although this may also mean that beneficial effects on serum lipids are absent), and the prolonged drug release from the patch means less frequent application is necessary and hence patient compliance may be improved. For oestrogen replacement in menopausal and postmenopausal women estradiol patches are used continuously or in a cyclical manner, with added progestogen for part of the cycle in those women with an intact uterus. This does not lead to drug accumulation and produces blood-estradiol concentrations and estradiol to estrone ratios similar to those normally observed in premenopausal women. The patch is well tolerated with skin irritation being the main problem. Patches are as effective as oral oestrogens in treating menopausal and postmenopausal symptoms such as flushing and vaginal atrophy and in preventing osteoporosis. Combined HRT patches, providing both estradiol and a progestogen, have also been developed.[4]

Estradiol is also effective when applied topically to the skin as a *gel*[5] or *emulsion*.[6]

1. Balfour JA, Heel RC. Transdermal estradiol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs* 1990; **40:** 561–82.
2. Cheang A, *et al.* A risk-benefit appraisal of transdermal estradiol therapy. *Drug Safety* 1993; **9:** 365–79.
3. Jewelewicz R. New developments in topical estrogen therapy. *Fertil Steril* 1997; **67:** 1–12.
4. Dando TM, Perry CM. 17 β-Estradiol/levonorgestrel transdermal system. *Treat Endocrinol* 2004; **3:** 319–24.
5. Naunton M, *et al.* Estradiol gel: review of the pharmacology, pharmacokinetics, efficacy, and safety in menopausal women. *Menopause* 2006; **13:** 517–27.
6. Simon JA. ESTRASORB Study Group. Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause* 2006; **13:** 222–31.

Depression. The use of oestrogen therapy in the treatment of premenopausal women with **postnatal** depression has been shown to be effective.[1,2] However, although such therapy could be a useful adjunct to conventional treatment (see Depression, p.373), the risk of serious adverse effects including thrombosis may limit its value.[3]

Whether oestrogens are of benefit in older women, typically with depression associated with the **menopause** (p.2077), is less clear. Some studies of transdermal estradiol have reported benefit,[4-6] whereas other studies of transdermal[7] or oral[8] dosage have not found it to be effective. Whether the presence of a progestogen in combination HRT would reduce any purported benefit is also unclear. Antidepressants remain the standard of care in perimenopausal or postmenopausal women with clinical depression.

1. Gregoire AJP, *et al.* Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; **347:** 930–3.
2. Ahokas A, *et al.* Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17β-estradiol: a preliminary study. *J Clin Psychiatry* 2001; **62:** 332–6.
3. Dennis CL, *et al.* Oestrogens and progestins for preventing and treating postpartum depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 27/06/08).
4. Soares C de N, *et al.* Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women. *Arch Gen Psychiatry* 2001; **58:** 529–34.
5. Cohen LS, *et al.* Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003; **160:** 1519–22.
6. Schiff R, *et al.* Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women: a randomised placebo controlled pilot cross-over study. *Psychoneuroendocrinology* 2005; **30:** 309–15.
7. Morrison MF, *et al.* Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004; **55:** 406–12.
8. Almeida OP, *et al.* A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiol Aging* 2006; **27:** 141–9.

Gender reassignment. Oestrogens are used in male-to-female transsexuals to develop and maintain secondary sexual characteristics. Although ethinylestradiol and conjugated oestrogens have been used for this purpose, and there is some evidence that such use can improve vascular function,[1] others consider ethinylestradiol too thrombogenic at the doses required [typically 50 to 100 micrograms daily or more] and suggest that estradiol, as the valerate in oral doses of 2 to 4 mg daily, or transdermally as a patch supplying 100 micrograms daily, is the oestrogen of choice.[2,3] Cyproterone acetate is usually also given for its antiandrogenic effect (see p.2089).

1. New G, *et al.* Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997; **29:** 1437–44.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Growth disorders. Supraphysiological doses of oestrogens inhibit somatic growth and have been used, with a cyclical progestogen, to reduce final height in girls with constitutional tall stature, although such treatment has declined markedly with changing social norms.[1] In early reports, diethylstilbestrol was used, but this is an unsuitable choice because of the increased risk of cancer. Ethinylestradiol has been given in the past in doses of up to 500 micrograms daily, but doses of 50 to 100 micrograms daily came to be preferred, although lower doses may be equally effective.[2,3] Conjugated oestrogens have also been used, and a study[4] reported that doses of 7.5 to 11.25 mg daily resulted in an average decrease of about 5 cm from final predicted height. In practice, doses as low as 625 micrograms daily have been used.[3] Reported height reductions have ranged from 2 to 10 cm but studies are difficult to compare. Treatment has generally been continued until closure of the epiphyses, but the effects of oestrogen therapy may be influenced by both chronological and bone age at the onset of treatment, duration of treatment, the oestrogen used and its dose, and the point of final height assessment.[2] High-dose oestrogen therapy is also associated with adverse effects such as weight gain, headache, nausea, and pigmentation of the areolae or nipples,[2,3] and there can be adverse changes to haemostatic and lipid measures.[2] A retrospective cohort review[5] has also reported that girls who had been treated with high-dose oestrogens were more likely to report fertility problems in later life than similar girls who had not been treated.

Oestrogen therapy has occasionally been used to help promote growth in girls with constitutional delayed puberty (see p.2079).

1. Lee JM, Howell JD. Tall girls: the social shaping of a medical therapy. *Arch Pediatr Adolesc Med* 2006; **160:** 1035–9.
2. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
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Haemorrhagic disorders. Limited evidence supports the use of oestrogens in various bleeding disorders. There have been mixed results from small studies of oestrogens, given alone or with a progestogen, in patients with hereditary haemorrhagic telangiectasia;[1,2] the use of a combined oral contraceptive has been suggested as a suitable option for fertile women with symptomatic epistaxis.[3] There are also some reports[2,4,5] of bleeding being reduced in patients with gastrointestinal vascular malformations from other causes. Conjugated oestrogens have been used in haemorrhagic disorders associated with chronic renal failure and haemorrhagic cystitis (see p.2087).

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Lactation inhibition. Synthetic oestrogens (e.g. quinestrol) and nonsteroidal oestrogens (e.g. diethylstilbestrol) were historically used to suppress lactation (p.2003). However, this use is now considered inappropriate because of an increased risk of puerperal thromboembolism.

Premenstrual syndrome. Premenstrual syndrome (PMS) presents as a variable combination of psychological and somatic symptoms occurring during the luteal phase of the menstrual cycle, which resolve during, and immediately after, menstruation. Another term, premenstrual dysphoric disorder, has been proposed to cover severe cyclical mood disorder that is functionally incapacitating.[1,2] Whereas about 20 to 40% of women have complaints that may be classified as PMS, only 3 to 8% meet criteria for premenstrual dysphoric disorder.[2] The term premenstrual tension (PMT) has sometimes been applied to the psychological symptoms. Many symptoms of PMS are the same as normal premenstrual symptoms, but are more severe. The aetiology of PMS is not fully understood, although it is thought that affected women may be more sensitive to the effects of normal hormonal fluctuations on CNS neurotransmitter function.[2]

Initial management includes non-medical interventions[3] such as education and support, counselling, stress management, relaxation techniques, and exercise; caffeine and salt restriction are of unproven benefit. The herbal remedy agnus castus has been found to be of benefit.[4] For patients with moderate to severe symptoms, a number of drugs have been tried with varying degrees of success; objective assessment of efficacy has been hampered by varying diagnostic criteria, a marked placebo response, and difficulties in obtaining reproducible responses. Treatment may be aimed at modifying the menstrual cycle or treating specific symptoms.

In women with mainly psychological symptoms, *SSRIs* can be helpful.[1,3,5,6] Fluoxetine and sertraline have been shown in controlled studies to alleviate both psychological and somatic symptoms in women with PMS, and may be given intermittently (only in the luteal phase) or continuously. If treatment with one SSRI is ineffective or not tolerated, another SSRI or *venlafaxine* may be substituted.[1,3,6] There is limited information on the use of SSRIs for PMS in adolescents, and precautions regarding suicidal ideation in young adults should be considered.[2] *Clomipramine*, a nonselective serotonin reuptake inhibitor, has been tried for PMS with some success. The anxiolytic *alprazolam* has also been used, but use of this and other benzodiazepines should be restricted to the luteal phase of the cycle in selected patients to minimise the risk of dependence and tolerance.[7]

Abdominal bloating and swelling associated with PMS has traditionally been thought to be due to sodium and water retention. However, in most women with these symptoms there is no evidence of an increase in body-weight or in body sodium or total water, and use of *diuretics* is therefore not justified.[8] Nevertheless, in women with appreciable weight gain and abdominal bloating in the luteal phase, the aldosterone antagonist spironolactone may be useful.[1,6,9] Another symptom of PMS, cyclical mastalgia, is discussed on p.2092.

Pyridoxine has been tried on the basis that it is a cofactor in neurotransmitter (specifically serotonin) synthesis, and has been found to relieve depression induced by oral contraceptives in selected patients. However, its efficacy in PMS is equivocal, and high daily doses have been associated with neurotoxicity.[10] *Calcium* supplementation may relieve symptoms of PMS.[6,11]

Treatments that modify the menstrual cycle have often been used in women with PMS. In general, drugs with proven efficacy such as danazol, oestrogen implants, and gonadorelin analogues are reserved for women with severe PMS unresponsive to other treatments, because of their adverse effects. *Progestogen* therapy was once popular, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground. In addition, a systematic review[12] of clinical trials found no evidence to support the use of progesterone or progestogens for PMS. *Combined oral contraceptives* have met with limited success.[2] They may be useful in some women for the control of somatic symptoms, but in others, PMS is caused or exacerbated by them. There is some suggestion that combined contraceptives containing drospirenone may be more effective in managing PMS than those containing progestogens such as levonorgestrel or norethisterone.[3] Consideration should be given to continuous rather than cyclical use.[3] Perimenopausal women may benefit from *oestrogen* delivered from transdermal patches. In women with a uterus, use with a cyclical progestogen is required to avoid endometrial hyperplasia; unfortunately, the progestogen may be associated with the return of symptoms. Possible strategies to minimise this include the use of a less androgenic progestogen, reducing the frequency with which it is given, or using an intra-uterine device to deliver the progestogen locally.[13] *Danazol* can be useful,[1,3] but there is concern over its adverse effects on lipids during long-term use and over the risk of masculinisation of a female fetus should pregnancy occur. For patients with severe symptoms not amenable to other treatments, gonadorelin analogues such as *goserelin* can be used to eliminate ovarian function, 'add-back' treatment with oestrogen plus progestogen being given to protect against the adverse effects of oestrogen deficiency including osteoporosis.[3] This treatment is very effective for both physical and psychological symptoms.[14] Short-term use (3 months) of a gonadorelin analogue alone has been used to confirm the diagnosis of PMS, or to predict the response to bilateral oophorectomy.[1,3]

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Preparations

BP 2008: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Estradiol Injection; Estradiol Transdermal Patches; ***USP 31:*** Estradiol and Norethindrone Acetate Tablets; Estradiol Cypionate Injection; Estradiol Injectable Suspension; Estradiol Pellets; Estradiol Tablets; Estradiol Transdermal System; Estradiol Vaginal Cream; Estradiol Valerate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Aerodiol; Climaderm†; Disequens; Estraderm; Estradot; Estreva†; Estring†; Estrofem; Etrosteron; Eutocol; Evorel; Fem 7†; Ginatex; Ginediol; Hormodiol; Lindisc; Oestro Gel; Progynon; Progynova; Replasyn†; Ronfase; Rontagel; Transdiol†; Trial Gel; Trial Sat; ***Austral.:*** Aerodiol; Climara; Dermestril†; Estraderm; Estradot; Estrofem; Femtran; Menorest; Primogyn Depot; Progynova; Sandrena; Vagifem; Zumenon; ***Austria:*** Aerodiol; Climara; Cycloderm; Dermestril; Duokliman; Estracutan; Estraderm; Estradot; Estramon; Estring; Estrofem; Estrogel; FemSeven; FemSieben; Klimapur; Klimareduct; Linoladiol; Menorest; Merimono; Progynon; Progynova; Sterigin; Systen; Vagifem; Zerella†; Zumenon; ***Belg.:*** Aerodiol; Climara; Dermestril; Estraderm; Estreva; Estrofem; Feminova; Meno-Implant; Oestrogel; Progynova; Systen; Vagifem; Vivelle; Zumenon; ***Braz.:*** Aerodiol; Avaden; Avicis; Benzo-Ginoestril; Climaderm; Estradelle; Estraderm†; Estradot; Estreva; Estrofem; Fem 7; Ginedisc†; Hormodose; Lindisc; Menorest†; Merimono; Natifa; Oestrogel; Primogyna; Riselle; Sandrena; Systen; ***Canad.:*** Climara; Delestrogen†; Estrace; Estraderm; Estradot; Estring; Estrogel; Oesclim; Vagifem; Vivelle†; ***Chile:*** Climaderm; Cyclobiol†; Dermatrans; Enadiol; Epiestrol; Estranova E; Estreva; Farlutes; Fem 7; Femalon; Femiderm; Femidot; Ginoderm; Mirion; Oesclim†; Primaquin; Primofol Depot†; Primogyna†; Progynova; Sandrena; Transvital; Vagifem; ***Cz.:*** Agofollin; Climara; Dermestril; Divigel; Elleste†; Estrace†; Estraderm; Estradot; Estrahexal; Estrapatch; Estreva†; Estrimax; Estring†; Estrofem; Fem 7†; Linoladiol N; Menorest†; Neofollin; Octodiol; Oesclim†; Oestrogel; Riselle; Systen; Vagifem; ***Denm.:*** Aerodiol; Climara; Divigel; Estraderm†; Estring; Estrofem; Estrogel; Evorel; Femanest; Progynon; Sandrena; Vagifem; Vivelle Dot; ***Fin.:*** Climara; Dermestril; Divigel; Estraderm†; Estradot; Estrena; Estring; Estrofem; Estrogel; Evorel; FemSeven; Menorest†; Merimono; Progynova; Vagifem; Zumenon; ***Fr.:*** Aerodiol; Climara; Delidose; Dermestril; Estraderm; Estrapatch; Estrofem; Evafilm†; Menorest; Oesclim; Oestrodose; Oestrogel; Oromone; Progynova; Provames; Systen; Thais; Vivelledot; ***Ger.:*** Aerodiol; Cerella†; Cutanum; Dermestril; Ephelia†; Estrabeta; Estraderm; Estradot; Estramon; Estreva; Estrifam; Estring; Estronorm; Evorel†; Fem 7; Femoston mono; Gynokadin; GynPolar; Linoladiol N; Menorest†; Merimono; Progynon Depot 10†; Progynova; Sandrena; Sisare mono; Tradelia; Vagifem; ***Gr.:*** Aerodiol†; Dermestril; Estraderm TTS†; Estradot; Estramon; Estring†; Estrofem†; Estrogel; Menorest; Oesclim†; Oestrogel; Vagifem; ***Hong Kong:*** Aerodiol†; Dermestril; Estraderm; Estreva; Estrofem; Fem 7†; Oestrogel; Progynova; Vagifem; ***Hung.:*** Calidiol; Dermestril; Divigel; Estraderm; Estradot†; Estramon; Estrapatch; Estrimax; Estrofem; FemSeven; Linoladiol N; Oesclim†; Oestrogel; Systen†; Vagifem; ***India:*** Divigel; Estraderm†; ***Indon.:*** Estreva; Fem 7; Progynova; ***Irl.:*** Aerodiol; Climara; Dermestril†; Divigel; Epiestrol†; Estraderm; Estradot; Estrofem; Evorel; Fematab; Menorest†; Oestrogel†; Vagifem; ***Israel:*** Dermestril; Estraderm; Estrofem; Evorel; Meno-Patch†; Oestrodose; Oestrogel; Progynova; Vagifem; ***Ital.:*** Aerodiol; Armonil; Climara; Dermestril; Ephelia; Epiestrol; Esclima; Estraderm; Estroclim; Estrodose; Estrofem; FemSeven; Gelestra; Ginaikos; Menorest; Progynova; Sandrena; Sprediol; Systen; Vagifem; Zerella; ***Malaysia:*** Divigel; Estrofem†; Oestrogel; Progynova; Trisequens†; ***Mex.:*** Armistor; Benzo-Ginestryl; Climaderm; Essventia; Estraderm; Estramon; Estreva; Evorel; Fem 7; Ginedisc; Oestrogel; Primogyn; Sandrena; Systen; ***Mon.:*** Femsept; ***Neth.:*** Aerodiol; Climara; Dermestril; Estraderm; Estradot; Estreva; Estrofem; Fem 7; Femring†; Meno-Implant; Menorest; Ovestal; Progynova; Sandrena; Systen; Vagifem; Zumenon; ***Norw.:*** Climara; Estraderm†; Estradot; Estring; Evorel; Progynova; Vagifem; ***NZ:*** Aerodiol; Climara; Estraderm; Estrofem; Femtran; Progynova; Sandrena†; Vagifem; ***Philipp.:*** Climara; Estrofem; Progynova; Vagifem; ***Pol.:*** Calidiol; Climara; Divigel; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Estroplast; Fem 7; Oesclim; Progynova; Systen; Vagifem; ***Port.:*** Climara; Crinohermal; Dermestril; Epiestrol; Estraderm; Estradot; Estrapatch; Estreva; Estrofem; Estronar†; Feminova; Femring; Femsete; Menorest†; Vagifem; Zumenon; ***Rus.:*** Climara (Климара); Divigel (Дивигель); Estrimax (Эстримакс); Estrofem (Эстрофем); Oestrogel (Эстрожель); Progynova (Прогинова); ***S.Afr.:*** Climara; Estraderm; Estradot; Estring; Estro-Pause; Estrofem; Evorel; Femigel; Primogyn Depot; Progynova; Vagifem; ***Singapore:*** Divigel; Estraderm; Estreva; Estrofem; Fem 7†; Oestrogel†; Progynova; Vagifem; ***Spain:*** Absorlent; Alcis; Cliogan; Dermestril; Endomina; Esprasone; Estraderm; Estradot; Estroffik; Evopad; Menorest†; Meriestra; Oestraclin; Oestrodose†; Progynova; Vagifem; ***Swed.:*** Climara; Divigel; Estraderm†; Estradot; Evorel; Femanest; FemSeven; Menorest†; Oesclim; Oestring; Progynon; Vagifem; ***Switz.:*** Aerodiol; Cerina†; Climara; Dermestril†; Divigel; Epiestrol†; Estraderm; Estradot; Estramon; Estreva†; Estring; Estrofem N; Fem 7; FemSeven†; Menorest†; Oestrogel; Progynova; Sandrena; Systen; Vagifem; Zumenon; ***Thai.:*** Climara; Divigel; Estrofem; Oestrogel; Progynon; Progynova; Vagifem; ***Turk.:*** Aerodiol; Akrofolline; Climara; Estraderm; Estramon; Estreva; Vagifem; ***UK:*** Aerodiol†; Bedol; Climaval; Elleste-Solo; Estraderm; Estradot; Estring; Evorel; Fematrix; FemSeven; FemTab†; Menorest†; Menoring†; Oestrogel; Progynova; Sandrena; Vagifem; Zumenon; ***USA:*** Alora; Climara; Delestrogen; depGynogen; Depogen; Divigel; Elestrin; Esclim; Estrace; Estraderm; Estrasorb; Estring; Estrogel; Evamist; FemPatch; Femring; Femtrace; Gynodiol; Menostar; Vagifem; Valergen; Vivelle; ***Venez.:*** Aerodiol; Climaderm; Estraderm†; Estradot; Estrogel; FemSeven; Progynova.

Multi-ingredient: ***Arg.:*** Activelle; Angeliq; Atrimon; Ciclocur; Climene; Cristerona; Dilena†; Dos Dias N; Equifem; Estalis; Estalis Sequi; Estracomb; Estragest; Evorel Conti; Evorel Sequi; Farludiol; Farludiol Ciclo; Fem 7 Combi†; Fempack; Gadofem; Gynodian Depot; Hosterona; Kliogest; Lubriderm; Menstrogen; Mesigyna; Perlutal; Plenifem†; Prefest; Primosiston; Supligol NF; Supligol†; Totelle Ciclico; Totelle Continuo; Trial Combi; Trial Gest; Trial Pack†; Trisequens; ***Austral.:*** Angeliq; Climen; Estalis Continuous; Estalis Sequi; Estracombi; Femoston; Kliogest; Kliovance; Trisequens; ***Austria:*** Activelle; Allurene; Angeliq; Climabelle†; Climen; Climodien; Cyclacur; Estalis; Estalis Sequens; Estracomb; Femipak; Femoston; Femoston Conti; Femphascyl; Femphascyl conti; FemSeven Combi; Filena†; Gynodian Depot; Ichth-Oestren; Kliogest; Lafamme; Liseta†; Mericomb; Merigest; Minique†; Novofem; Perikliman; Trisequens; ***Belg.:*** Activelle; Angeliq; Climen; Climodien; Cyclocur; Dimenformon; Diviplus; Diviva; Estalis; Estracombi; Feminova Plus; Femoston; Femoston Conti; Kliogest; Novofem; Totelle Cycle†; Trisequens; Trivina†; ***Braz.:*** Activelle; Angeliq; Cicloprimogyna; Cliane; Climene; Cyclofemina; Dilena; Elamax; Estalis; Estalis SQ; Estandron P; Estracomb†; Estragest; Femineo†; Femoston; Femoston Conti; Gestadinona; Gineane; Ginecoside†; Ginedisc 50 Plus†; Kliogest; Lindisc Duo†; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Normomensil†; Perlutan; Postoval†; Prefest; Preg-Less; Suprema; Systen Conti; Systen Sequi; Totelle; Totelle Ciclo; Trinestril; Trisequens; Unalmes†; Uno-Ciclo†; ***Canad.:*** Climacteron; Estalis; Estalis Sequi; Estracomb; ***Chile:*** Activelle; Agurin†; Angeliq; Avaden; Cliane; Climene; Cyclofem†; Enadiol CC; Enadiol MP; Enadiol Neta; Estandron Prolongado; Estracomb; Estragest; Estranova 30 Simple; Estranova CC; Farlupost; Fem 7 Combi; Femoston; Femoston Conti; Ginefolin; Gravidinona†; Gynodian Depot; Kilios; Kliogest; Mesigyna; Novafem; Postoval†; Primaquin MP; Primaquin MP Continuo; Progyluton; Totelle; Totelle Continuo; Trisequens; Unalmes; ***Cz.:*** Activelle; Aknefug†; Alpicort F; Angeliq; Avaden†; Climara Duo†; Climen; Convaden†; Cyclo-Menorette†; CycloOstrogynal†; Divina; Diviseq; Estalis; Estalis Sequi; Estrace Plus†; Estrace-C†; Estracomb†; Estragest†; Femoston; Femoston Conti; Folivirin; Gynodian Depot; Indivina; Kliane; Klimodien; Klimonorm; Kliogest; Linoladiol-H N†; Novofem; Pausogest; Sequidot; Systen Conti; Systen Sequi; Triaklim†; Trisequens; ***Denm.:*** Activelle; Angemin; Climen; Climodien; Cyclo-Progynon; Divina; Divina Plus; Estracomb; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Indivina; Klimalet; Klimaxil†; Kliogest; Novofem; Nuvelle; Ostranorm†; Totelle†; Trevina; Trinorm†; Trisekvens; ***Fin.:*** Activelle; Angeliq; Climara Duo†; Cyclabil; Divina; Divitren; Estalis; Estalis Sekvens; Estracomb†; Evorel Conti; Evorel Sequi; Femilar; Femoston; Femoston Conti; FemSeven Combi; Indivina; Kliogest; Mericomb; Merigest; Novofem; Senikolp†; Totelle Sekvens†; Trisekvens; ***Fr.:*** Activelle; Angeliq; Avadene; Climaston; Climene; Climodiene; Divina; Diviseq; Duova; Kliogest; Novofemme; Successia†; Trisequens; ***Ger.:*** Activelle; Aknefug-Emulsion†; Alpicort F; Androfemon†; Angeliq; Climen; Climodien; Clionara; Crinohermal fem; Cyclo-Menorette; Cyclo-Progynova; CycloOstrogynal; Estalis Sequi; Estracomb†; Estrafemol; Estragest; Fem 7 Combi; Femoston; Femoston Conti; Gianda; Gravibinon†; Gynamon; Gynodian Depot; Indivina; Jephagynon†; Klimonorm; Kliogest N; Lafamme; Linoladiol-H N; Mericomb; Merigest; NeoOstrogynal†; NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; Novofem; Osmil; Ostronara; Procyclo; Sisare; Sisare 28; Syngynon†; Trisequens; Vitrena†; ***Gr.:*** Activelle†; Angeliq; Climodien†; Cyclacur; Divina; Estalis; Estopause; Estracomb TTS; Femaston; Kliogest; Nuvelle†; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong:*** Activelle; Angeliq; Climen 28; Dilena; Estracomb; Femoston; Hormonin; Klimonorm†; Kliogest; Novofem; Trisequens; ***Hung.:*** Activelle; Alpicort F; Angeliq; Climen; Cyclo-Menorette†; Divina; Divitren†; Estracomb; Estragest; Femoston; FemSeven Combi; Indivina; Klimodien†; Klimonorm; Kliogest; Linoladiol-H N†; Pausogest; Triaklim; Trisequens; Tulita; ***India:*** Kemicetine Antiozena; Mixogen; ***Indon.:*** Angeliq; Climen 28; Cyclo-Progynova; Cyclofem; Mediol; Renodiol; ***Irl.:*** Activelle; Angeliq; Diviseq†; Estalis; Estalis Sequi; Estracombi; Estrapak†; Evorel Conti; Femoston; Femoston Conti; Indivina; Kliogest; Novofem; Nuvelle†; Trisequens; ***Israel:*** Activelle; Angeliq; Evorel Conti; Evorel Sequi; Kliogest; Meno-MPA†; Meno-Net†; Novofem; Progyluton; Trisequens; ***Ital.:*** Activelle; Angeliq; Biormon†; Climen; Combiseven; Estalis Sequi; Estracomb; Femity; Femoston; Femoston Conti; Filena; Gravibinan†; Gynodian Depot; Kliogest; Menovis; Naemis; Nuvelle; Nuvelle TS†; Pausene; Totelle†; Trisequens; ***Malaysia:*** Activelle; Climen; Duogynon; Femoston; Femoston Conti; Klimonorm†; Kliogest†; Progyluton; ***Mex.:*** Anafertin; Angeliq; Avaden; Binodian; Cliane; Climene; Cyclofemina; Damax; Despamen; Dilena; Estalis; Estracomb; Evorel Conti; Genofort; Ginoplan†; Gravidinona; Lutalmin; Lutoginestryl F; Mesigyna; Metrigen Fuerte; Nostidyn; Ominol†; Patector; Perludil; Perlutal; Prefest; Primosiston†; Primoson-F; Progediol†; Proger-F; Progyluton; Totelle Continuo; Totelle Secuencial; Xofemina; Yectames; ***Mon.:*** FemseptCombi; Naemis; ***Neth.:*** Activelle; Allurene; Angeliq; Avaden†; Climaston Continu; Climene; Climodien; Cyclocur; Divina†; Estalis; Estalis Sequi; Estandron Prolongatum; Estracomb; Fem 7 Sequi; Femoston; Femoston Continu; Femphascyl Continu; Kliogest; Lafamme; Naemis; Novofem; Trisequens; ***Norw.:*** Activelle; Climen†; Climodien; Cyclabil; Diviseq†; Estalis; Estalis Sekvens; Indivina; Kliogest; Novofem; Totelle Sekvens†; Trisekvens; ***NZ:*** Cliane; Estrapak†; Kliogest; Kliovance; Nuvelle; Trisequens; ***Philipp.:*** Angeliq; Climen 28; Femoston; Kliogest; ***Pol.:*** Activelle; Alpicort E; Angeliq; Climen; Cyclo-Progynova; Divina; Diviseq; Estalis; Estalis Sequi; Estracomb; Fem 7 Combi; Femoston; Femoston Conti; Gynodian Depot; Indivina; Klimonorm; Kliogest; Novofem; Systen Conti; Systen Sequi; Trisequens; ***Port.:*** Activelle; Angeliq; Avadene; Cicnor†; Climara Duo†; Climen; Climodien; Dilena; Emmenovis†; Estalis; Estalis Sequi; Estracomb; Femoston; Femoston 1/5; Femsete Combi; Femsete Evo; Kliogest; Lafamme; Naemis; Novofem; Nuvelle; Progyluton; Trisequens; ***Rus.:*** Angeliq (Анжелик); Climen (Климен); Climodien (Климодиен); Cyclo-Progynova (Цикло-прогинова); Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен); Femoston (Фемостон); Femoston 1/5 (Фемостон 1/5); Gynodian Depot (Гинодиан Депо); Indivina (Индивина); Klimonorm (Климонорм); Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.:*** Activelle; Angeliq; Climen; Divina; Estracombi; Estro-Pause N; Evorel Conti; Evorel Sequi; Femoston; Femoston Conti; Kliogest; Mixogen; Novofem; Postoval; Prefesta; Primodian Depot; Trisequens; Trivina; ***Singapore:*** Activelle; Climen; Estracomb; Femoston; Femoston Conti; Kliogest; Progyluton; Trisequens; ***Spain:*** Absorlent Plus; Activelle; Angeliq; Auroclim; Climen; Climodien; Clisin†; Duofemme; Endomina Plus; Estalis; Estalis Sequi; Estracomb; Merigest; Merigest Sequi; Mevaren; Nuvelle; Perifem; Progyluton; Topasel; Trisequens; ***Swed.:*** Activelle; Angemin; Climodien; Cyclabil; Divina Plus; Divina†; Estalis; Estalis Sekvens; Estracomb†; Evorel Micronor; Femanor; Femasekvens; Indivina; Kliogest; Novofem; Totelle Sekvens†; Totelle†; Trisekvens; Trivina; ***Switz.:*** Activelle; Alpicort F; Climen; Cyclacur; Diviseq; Estalis; Estalis Sequi; Estracomb; Estragest; Fem 7 Combi; Femoston; Femoston Conti; Gynodian Depot; Indivina; Kliogest N; Linoladiol†; Mericomb; Merigest; Novofem; OestroTabs Plus Cyclic†; Primosiston†; Systen Conti; Systen Sequi; Triaval; Trisequens; ***Thai.:*** Activelle; Angeliq; Climen; Cyclo-Progynova; Diviseq; Duoton; Femoston 1/10; Femoston Conti; Indivina; Klimonorm; Phenokinon-F; Primodian Depot; ***Turk.:*** Activelle; Angeliq; Climen; Climodien; Cyclo-Progynova; Di-Pro; Divina; Estandron Prolongatum; Estracombi; Kliogest; Mesigyna; Trisequens; ***UK:*** Angeliq; Climagest; Climesse; Clinorette; Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Elleste Duet Conti; Elleste-Duet; Estracombi; Estrapak†; Evorel Conti; Evorel Pak†; Evorel Sequi; Femapak; Femoston; Femoston Conti; FemSeven Conti; FemSeven Sequi; FemTab Continuous†; FemTab Sequi†; Hormonin; Indivina; Kliofem; Kliovance; Novofem; Nuvelle; Nuvelle Continuous; Tridestra; Trisequens; ***USA:*** Activella; Angeliq; ClimaraPro; CombiPatch; Depo-Testadiol; Depotestogen; Lunelle†; Prefest; ***Venez.:*** Avaden; Cliane; Climene; Estracomb†; Estragest; Femoston; Femoston Conti; Ginecosid; Gynodian Depot; Mesigyna; Primosiston†; Progyluton; Totelle Ciclico; Totelle Continuo.

Estrapronicate *(rINN)*

Estrapronicato; Estrapronicatum. Oestradiol 17-nicotinate 3-propionate.

Эстрапроникат

$C_{27}H_{31}NO_4$ = 433.5.

CAS — 4140-20-9.

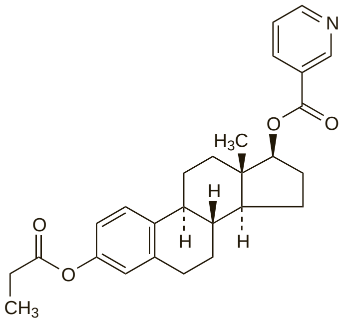

Profile

Estrapronicate is a derivative of estradiol (p.2097) with nicotinic acid. It has been used as an ingredient of a combined preparation with an anabolic steroid and a progestogen for osteoporosis.

Estriol *(BAN, rINNM)*

Estrioli; Estriolis; Estriolum; Follicular Hormone Hydrate; Oestriol; Östriol; Ösztriol; Theelol. Estra-1,3,5(10)-triene-3,16α,17β-triol.

Эстриол

$C_{18}H_{24}O_3$ = 288.4.

CAS — 50-27-1.

ATC — G03CA04.

ATC Vet — QG03CA04; QG03CC06.

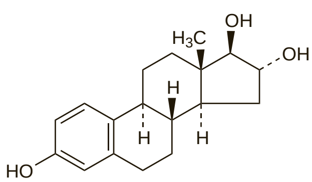

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Estriol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol.

USP 31 (Estriol). A white or practically white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, in dioxan, in ether, and in vegetable oils. Store in airtight containers.

Estriol Sodium Succinate *(BAN, rINNM)*

Estriol, Succinate Sodique d'; Estrioli Natrii Succinas; Oestriol Sodium Succinate; Succinato sódico de estriol. Disodium 3-hydroxyestra-1,3,5(10)-triene-16α,17β-diyl disuccinate.

Эстриола Натрия Сукцинат

$C_{26}H_{30}Na_2O_9$ = 532.5.

CAS — 113-22-4.

ATC — G03CA04.

ATC Vet — QG03CA04.

Estriol Succinate *(BAN, rINN)*

Estriol, Succinate d'; Estrioli Succinas; Estriolisuksinaatti; Estriolsuccinat; Oestriol Succinate; Succinato de estriol. 3-Hydroxyestra-1,3,5(10)-triene-16α,17β-diyl di(hydrogen succinate).

Эстриола Сукцинат

$C_{26}H_{32}O_9$ = 488.5.

CAS — 514-68-1.

ATC — G03CA04.

ATC Vet — QG03CA04.

Profile

Estriol is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (p.2097). It is claimed to have only a mild proliferative effect on the endometrium.

It is used for menopausal HRT (p.2071). When oestrogens are given to women with a uterus, a progestogen is required, particularly if used long term. For short-term treatment, oral doses of estriol have been 0.5 to 3 mg daily given for one month followed by 0.5 to 1 mg daily. Estriol has also been given with other natural oestrogens such as estradiol and estrone (see below); usual doses of estriol have ranged from about 0.25 to 2 mg daily. Estriol may be used intravaginally for the short-term treatment of menopausal atrophic vaginitis and kraurosis vulvae. A dose of 500 micrograms may be given as a 0.01% or 0.1% cream or as a pessary; initial treatment may be given once daily, then reduced to twice each week.

Estriol has also been given orally for infertility (p.2080) caused by poor cervical penetration, in a dose of 0.25 to 1 mg daily on days 6 to 15 of the menstrual cycle.

Estriol succinate has also been given orally in the treatment of menopausal disorders. The sodium succinate salt has been used parenterally in the treatment of haemorrhage and thrombocytopenia.

Preparations

BP 2008: Estriol Cream.

Proprietary Preparations (details are given in Part 3)

Arg.: Colpoestriol; Orgestriol; ***Austral.:*** Ovestin; ***Austria:*** Ortho-Gynest; Ovestin; Styptanon; ***Belg.:*** Aacifemine; Ortho-Gynest; ***Braz.:*** Estriopax; Hormocervix; Hormoniol; Ovestrion; Styptanon; ***Chile:*** Ovestin; Sinapause; Vacidox; ***Cz.:*** Ortho-Gynest; Ovestin; ***Denm.:*** Ovestin; ***Fin.:*** Ovestin; Pausanol; ***Fr.:*** Gydrelle; Physiogine; Trophicreme; ***Ger.:*** Cordes Estriol; Gynasan†; OeKolp; Oestro-Gynaedron M; Ortho-Gynest; Ovestin; Synapause E; Xapro; ***Gr.:*** Ovestin; ***Hong Kong:*** Ovestin†; ***Hung.:*** Estrokad; Ortho-Gynest; Ovestin; ***India:*** Evalon; ***Indon.:*** Ovestin; ***Irl.:*** Ortho-Gynest†; ***Israel:*** Ortho-Gynest; Ovestin; ***Ital.:*** Colpogyn; Ortho Gynest Depot; Ovestin; Trofogin; ***Jpn:*** Estriel; ***Mex.:*** Ortho-Gynest; Ovestin; Sinapause; ***Neth.:*** Synapause-E ; ***Norw.:*** Ovesterin; ***NZ:*** Ovestin; ***Philipp.:*** Ovestin; ***Pol.:*** Oekolp; Ortho-Gynest; Ovestin; ***Port.:*** Ovestin; Pausigin; Synapausa†; ***Rus.:*** Ovestin (Овестин); ***S.Afr.:*** Synapause; ***Spain:*** Ovestinon; ***Swed.:*** Ovesterin; ***Switz.:*** Oestro-Gynaedron Nouveau; Ortho-Gynest; Ovestin; ***Thai.:*** Ovestin†; ***Turk.:*** Estrofem; Ovestin; ***UK:*** Ortho-Gynest; Ovestin; ***Venez.:*** Ortho-Gynest; Ovestin.

Multi-ingredient: ***Arg.:*** Tropivag Plus; ***Austria:*** Gynoflor; ***Belg.:*** Gynoflor; ***Cz.:*** Cyclo-Menorette†; CycloOstrognal†; Gynoflor; ***Fr.:*** Florgynal; Trophigil; ***Ger.:*** Cyclo-Menorette; CycloOstrognal; Gynoflor; NeoOstrognal†; Oestrugol N†; ***Hong Kong:*** Hormonin; ***Hung.:*** Cyclo-Menorette†; Gynoflor; ***Port.:*** Gynoflor; ***Switz.:*** Gynoflor; ***Turk.:*** Gynoflor; ***UK:*** Hormonin.

Estrone *(BAN, rINN)*

Estron; Estrona; Estroni; Estronum; Foliculina; Follicular Hormone; Folliculin; Ketohydroxyoestrin; Oestrone; Östron. 3-Hydroxyestra-1,3,5(10)-trien-17-one.

Эстрон

$C_{18}H_{22}O_2$ = 270.4.

CAS — 53-16-7.

ATC — G03CA07.

ATC Vet — QG03CA07; QG03CC04.

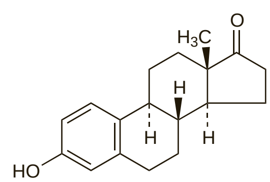

Pharmacopoeias. In *US.*

USP 31 (Estrone). Odourless, small white crystals or white to creamy-white crystalline powder. Practically insoluble in water; soluble 1 in 250 of alcohol and 1 in 110 of chloroform at 15°; soluble 1 in 50 of boiling alcohol, 1 in 33 of boiling acetone, 1 in 145 of boiling benzene, and 1 in 80 of boiling chloroform; soluble 1 in 50 of acetone at 50°; soluble in dioxan and in vegetable oils; slightly soluble in solutions of fixed alkali hydroxides. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Estrone is a naturally occurring oestrogen with actions and uses similar to those described for estradiol (see p.2097).

For menopausal HRT (see p.2071) estrone has been given orally at a dose of 1.4 to 2.8 mg daily in a cyclical or continuous regimen, as a combination product with estradiol and estriol (see above). Estrone has also been given by intramuscular injection in oily solutions and aqueous suspensions. When used specifically for menopausal atrophic vaginitis, estrone has been given vaginally. If used in women with a uterus, estrone by any route should be given with a progestogen.

Preparations

USP 31: Estrone Injectable Suspension; Estrone Injection.

Proprietary Preparations (details are given in Part 3)

USA: Kestrone.

Multi-ingredient: ***Braz.:*** Gineburno†; ***Fin.:*** Senikolp†; ***Fr.:*** Synergon; ***Hong Kong:*** Hormonin; ***Spain:*** Cicatral; Grietalgen; Grietalgen Hidrocort†; ***Thai.:*** Metharmon-F; ***Turk.:*** Synergon; ***UK:*** Hormonin.

Estropipate *(BAN)*

Estropipato; Piperazine Estrone Sulfate; Piperazine Oestrone Sulphate. Piperazine 17-oxoestra-1,3,5-(10)-trien-3-yl hydrogen sulphate.

Эстропипате

$C_{18}H_{22}O_5S,C_4H_{10}N_2$ = 436.6.

CAS — 7280-37-7.

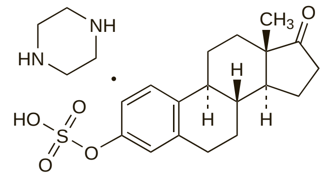

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Estropipate). A white or almost white crystalline powder. Very slightly soluble in water, in alcohol, in chloroform, and in ether.

USP 31 (Estropipate). A white to yellowish-white fine crystalline powder, odourless or may have a slight odour. Very slightly soluble in water, in alcohol, in chloroform, and in ether; soluble 1 in 500 of warm alcohol; soluble in warm water. Store in airtight containers.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormone Replacement Therapy, p.2071.

Interactions

See under Hormone Replacement Therapy, p.2076.

Uses and Administration

Estropipate is a semisynthetic conjugate of estrone with piperazine that is used for menopausal HRT (see p.2076). Its action is due to estrone (see above) to which it is hydrolysed in the body.

Estropipate is given orally for the short-term treatment of menopausal symptoms; suggested doses have ranged from 0.75 to 3 mg daily, given cyclically or continuously; doses up to 6 mg daily have also been given cyclically. When used longer term for the prevention of postmenopausal osteoporosis a daily dose of 0.75 or 1.5 mg is given cyclically or continuously. In women with a uterus estropipate should be used with a progestogen. Estropipate has also been used short term for menopausal atrophic vaginitis as a vaginal cream containing 0.15%; 2 to 4 g of cream is applied daily. It is also given orally in the treatment of female hypogonadism, castration, and primary ovarian failure in doses of 1.5 to 3 mg daily, in a cyclical regimen; higher doses of up to 9 mg daily given cyclically have also been used.

Preparations

BP 2008: Estropipate Tablets;
USP 31: Estropipate Tablets; Estropipate Vaginal Cream.

Proprietary Preparations (details are given in Part 3)

Austral.: Genoral; Ogen; ***Canad.:*** Ogen; ***Indon.:*** Ogen; ***Irl.:*** Harmogen†; ***Mex.:*** Ogen†; ***S.Afr.:*** Ortho-Est; ***UK:*** Harmogen; ***USA:*** Ogen; Ortho-Est†.

Ethinylestradiol *(BAN, rINN)*

Aethinyloestradiolum; Ethinyl Estradiol; Éthinylestradiol; Ethinylestradiolum; Ethinyloestradiol; Etinilestradiol; Etinilestradiolis; Etinilöstradiol; Etinilösztradiol; Etinylestradiol; Etinyyliestradioli; Etynyloestradiol; NSC-10973. 17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol; 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol.

Этинилэстрадиол

$C_{20}H_{24}O_2$ = 296.4.

CAS — 57-63-6.

ATC — G03CA01; L02AA03.

ATC Vet — QG03CA01; QL02AA03.

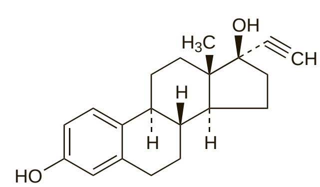

NOTE. Compounded preparations of ethinylestradiol may be represented by the following names:

- Co-cyprindiol (*BAN*)—ethinylestradiol 35 parts and cyproterone acetate 2000 parts (w/w).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Ethinylestradiol). A white to slightly yellowish-white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; dissolves in dilute alkaline solutions. Protect from light.

USP 31 (Ethinyl Estradiol). A white to creamy white, odourless, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides. Store in nonmetallic airtight containers. Protect from light.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormonal Contraceptives, p.2059.

Effects on calcium homoeostasis. Two patients with metastatic breast cancer given ethinylestradiol developed rapidly progressive irreversible and fatal hypercalcaemia, considered to be due to stimulation of osteolysis by the oestrogen.[1]

1. Cornbleet M, *et al*. Fatal irreversible hypercalcaemia in breast cancer. *BMJ* 1977; **1:** 145.

Effects on the liver. Cholestasis and pruritus developed in a liver transplant recipient receiving ethinylestradiol at a dose of 50 micrograms daily for the treatment of menorrhagia.[1] Symptoms subsided on withdrawal of ethinylestradiol but returned on its re-introduction.

1. Fedorkow DM, *et al*. Cholestasis induced by oestrogen after liver transplantation. *BMJ* 1989; **299:** 1080–1.

Interactions

See under Hormonal Contraceptives, p.2067.

◊ Reviews.

1. Zhang H, *et al*. Pharmacokinetic drug interactions involving 17α-ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet* 2007; **46:** 133–57.

Pharmacokinetics

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active by mouth, but there is some initial conjugation by the gut wall, and the systemic bioavailability is only about 40%. Ethinylestradiol is highly protein bound, but unlike naturally occurring oestrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. It is metabolised in the liver, initially by aromatic hydroxylation catalysed by the cytochrome P450 isoenzyme CYP3A4, to form 2-hydroxyethinylestradiol and various conjugated metabolites. These are excreted in urine and faeces. Metabolites undergo enterohepatic recycling.

◊ References.

1. Back DJ, *et al*. The gut wall metabolism of ethinyloestradiol and its contribution to the pre-systemic metabolism of ethinyloestradiol in humans. *Br J Clin Pharmacol* 1982; **13:** 325–30.
2. Guengerich FP. Metabolism of 17 α-ethynylestradiol in humans. *Life Sci* 1990; **47:** 1981–8.
3. van den Heuvel MW, *et al*. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005; **72:** 168–74.

Uses and Administration

Ethinylestradiol is a synthetic oestrogen with actions similar to those of estradiol (see p.2098).

It is frequently used as the oestrogenic component of combined oral **contraceptive** preparations; a typical daily dose is 20 to 40 micrograms (for guidance on appropriate dose, see p.2069). Ethinylestradiol betadex clathrate has been used similarly in combined oral contraceptives. Ethinylestradiol is also used in a combined contraceptive transdermal patch. A dose of 20 micrograms ethinylestradiol is released daily with norelgestromin. A new patch is applied each week for 3 weeks of a 4-week cycle. Oestrogen exposure from such a patch may be higher than with a comparable oral contraceptive. A combined contraceptive vaginal ring device delivering an average of 15 micrograms ethinylestradiol daily with etonogestrel is also available; it remains in the vagina for 3 weeks and is then removed for a one-week break, after which a new ring is inserted. Ethinylestradiol has also been used orally as an emergency contraceptive (p.2071) combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne (p.1577) and hirsutism (p.2089), particularly when contraception is also required (see Uses and Administration, under Cyproterone Acetate, p.2089).

Ethinylestradiol has also been used for **menopausal HRT** (p.2076), although natural oestrogens are usually preferred. Oral doses of 10 to 50 micrograms daily have been given cyclically (with a progestogen in women with a uterus), but preparations providing lower doses of 2.5 or 5 micrograms daily are also available.

For the treatment of female **hypogonadism**, doses of 10 to 50 micrograms daily on a cyclical basis have been used.

For the palliative treatment of **prostate cancer** (p.671) doses of 150 micrograms to 3 mg have been given daily. For palliation of malignant neoplasms of the **breast** (p.661) in postmenopausal women doses of 100 micrograms to 1 mg three times daily have been used.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include doses of ethinylestradiol. An initial oral dose of 2 micrograms daily may be used in the management of **delayed puberty** (p.2079) in girls. This may be increased every 6 months to 5 micrograms, then to 10 micrograms, then to 20 micrograms daily, according to response. After 12 to 18 months of treatment, a progestogen should be added for 7 days of each 28-day cycle. A daily dose of ethinylestradiol 20 micrograms with cyclical progestogen may then be used to maintain sexual maturation. For the prevention of constitutional **tall stature**, ethinylestradiol may be given to girls aged 2 to 12 years old in a dose of 20 to 50 micrograms daily (see also Growth Disorders in Estradiol, p.2099).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p.1798). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using ethinylestradiol has been tried in both boys and girls in order to increase responsiveness to the test,[1,2] although there appears to be no consensus on such use.[3] The *BNFC* includes an oral dose of 100 micrograms daily for 3 days before the test, for girls with a bone age above 10 years.

1. Loche S, *et al*. The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82:** 861–4.
2. Coutant R, *et al*. Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86:** 5805–12.
3. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 22/08/08)

Preparations

BP 2008: Ethinylestradiol Tablets; Levonorgestrel and Ethinylestradiol Tablets;
USP 31: Desogestrel and Ethinyl Estradiol Tablets; Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Levonorgestrel and Ethinyl Estradiol Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norgestimate and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Diva Total; ***Austria:*** Progynon C†; ***Cz.:*** Minerva; ***Ger.:*** Progynon C†; Turisteron†; ***Hung.:*** Mikrofollin†; ***India:*** Lynoral; ***Indon.:*** Lynoral; ***Israel:*** Progynon C†; ***Neth.:*** Lynoral; ***Port.:*** Jeanine; ***Rus.:*** Microfollin (Микрофоллин); ***S.Afr.:*** Estinyl†; ***Swed.:*** Diane; ***Switz.:*** Elleacnelle; ***Thai.:*** Manodiol; ***USA:*** Estinyl.

Multi-ingredient: ***Arg.:*** Afrodita; Aleli; Anubis; April; Avancel; Biofem; Biofem 35; Cilest; Cuarcic; Cuidafem; Damsel; Diane; Diva; Divina; Dos Dias N; Evelea; Evra; Femexin; Femiane; Ginelea; Ginelea T; Gynovin; Harmonet; Isis; Isis Fe; Kala; Kirumelle; Lindiol†; Livianne; Loette; Lutogynestryl; Marvelon; Maxima; Mercilon; Mesconcept; Microfem; Microgynon; Microvlar; Mileva; Minesse; Minulet; Miranova; Mirelle; Neogynon; Nordette; Nordiol†; Norgestrel Minor; Norgestrel Plus; Ovral†; Secret 28; Tridestan N; Tridette; Trinordiol; Triquilar; Venisse; Yasmin; Yasminelle; ***Austral.:*** Biphasil†; Brenda-35 ED; Brevinor; Diane; Estelle; Femoden ED; Improvil; Juliet†; Levlen ED; Loette; Logynon ED; Marvelon; Microgynon; Microlevlen ED; Minulet; Monofeme; Nordette; Nordiol†; Norimin; NuvaRing; Sequilar ED; Synphasic; Tri-Minulet†; Trifeme; Trioden; Triphasil; Triquilar; Valette; Yasmin; ***Austria:*** Bellgyn; Cileste; Dialuna; Diane; Donnina; FemHRT†; Femogyn; Gracial; Gynovin; Harmonette; Jeanine; Laurina; Liberel; Loette; Madonella; Marvelon; Meliane; Mercilon; Microgynon; Midane; Minerva; Minesse; Minulet; Mirelle; Myvlar; Neo-Stediril; Neogynon†; NuvaRing; Ovranette; Ovysmen; Perikursal; Primosiston; Sequilar; Stediril D; Sterigynon; Tri-Minulet; TriCilest; Trigynon; Trinordiol; Trinovum; Triodena; Valette; Vivelle; Xylia; Yasmin; Yirala; Yris; ***Belg.:*** Binordiol†; Cilest; Claudia; Co-Cyproterone; Cyprodiol; Daphne; Desorelle; Diane; Doccyproestra; Evra; Femodene; Gestodelle; Gestofeme; Gracial; Gratiella; Harmonet; Lowette; Marvelon; Meliane; Mercilon; Merckelisa; Microgynon; Minestril†; Minulet; Mirelle; Neo-Stediril†; Neogynon†; NuvaRing; Ovidol; Ovysmen; Ratiopharmeva; Stediril 30; Stediril D†; Tri-Minulet; Trigynon; Trinordiol; Trinovum; Triodene; Yasmin; ***Braz.:*** Adoless; Alexa; Allestra; Anacyclin†; Anfertil; Artemidis; Ciclo; Ciclofemme; Ciclon†; Ciclovulon; Ciprane; Concepnor; Diane; Diminut; Elani; Evanor; Evra; Femiane; Femina; Ferane 35; Fertnon; Gestinol; Gestradiol; Gestrelan; Ginesse; Gracial; Gynera; Harmonet; Level; Levordiol; Lovelle; Malu; Mercilon; Mercilon Conti; Microdiol; Micropil; Microvlar; Minesse; Minian; Minima; Minulet; Mirelle; Neovlar; Nociclin; Nordette; Normamor; Novial; NuvaRing; Ovoresta; Previane; Primera; Primosiston; Repopil; Selene; Siblima; Tamisa; Tess; Trinordiol; Trinovum†; Triquilar; Yasmin; YAZ; ***Canad.:*** Alesse; Brevicon; Cyclen; Demulen; Diane; Evra; FemHRT; Loestrin 1.5/30; Marvelon; Min-Ovral; Minestrin; NuvaRing; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Cept; Ovral; Select 1/35; Synphasic; Tri-Cyclen; Triphasil; Triquilar; Yasmin; ***Chile:*** Alesse; Anovulatorio Micro-Dosis; Anuar; Anulette; Belara; Careza; Ciclidon; Ciclomex; Dahlia; Dal; Desoren; Diane; Dixi-35; Drina; Evilin; Evra; Farlutal Estrogeno†; Femelle; Feminol; Femitres; Gracial; Gynera; Gynostat; Harmonet; Innova Cd; Lady-Ten 35; Loette†; Lovinda; Mactex; Marvelon; Microfemin†; Microgen; Microgynon; Midalet; Minesse; Miniestrel; Minigest; Minulet; Mirelle; Modutrol; Neofam; Neolette; Nordette; Nordiol; Norvetal; NuvaRing; Orlon; Primosiston; Tri-Ciclomex; Tri-Mactex; Trifas†; Trinordiol; Triquilar; Trolit; Yasmin; ***Cz.:*** Anteovin†; Belanette; Belara; Chloe; Cilest; Diane; Evra; Femoden; Gracial; Gravistat; Harmonet; Jeanine; Jenetten†; Katya; Laurina; Lindynette; Loette; Logest; Lunafem; Marvelon; Mercilon; Microgynon; Milligest; Milvane†; Minesse; Minisiston; Minulet; Mirelle; Non-Ovlon†; Novynette; NuvaRing; Pramino; Regulon; Restovar†; Stediril†; Sunya; Tri-Minulet; Tri-Regol; Trinordiol; Trinovum; Triquilar; Trisiston†; Vilonet†; Vreya; Yadine; Yasminelle; ***Denm.:*** Cilest; Desorelle; Diane; Dianova; Econ†; Evra; Feminil; Fironetta†; Gestonette; Gracial; Gynatrol†; Gynera; Harmonet; Lindynette; Malonetta; Marvelon; Meloden; Mercilon; Microgyn; Milvane; Minulet; Neogentrol†; Neogynon; Novynette; NuvaRing; Tetragynon†; Tri-Minulet†; Triminetta; Trinordiol; Trinovum; Triquilar; Yasmin; ***Fin.:*** Cilest; Cypretyl; Diane; Evra; Femoden; Gracial; Harmonet; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Mirelle; Neo-Primovlar†; NuvaRing; Tri-Femoden; Tri-Minulet†; Trikvilar; Trinordiol†; Yasmin; ***Fr.:*** Adepal; Belara; Cilest; Cycleane; Daily; Diane; Effiprev; Evepar; Evra; Harmonet; Holgyeme; Jasmine; Jasminelle; Ludeal; Lumalia; Meliane; Melodia; Mercilon; Minerva; Minesse; Minidril; Miniphase; Minulet; Moneva; NuvaRing; Ortho-Novum 1/35; Phaeva; Planor†; Stediril; Tetragynon†; Tri-Minulet; Triafemi; TriCilest; Triella; Trinordiol; Varnoline; ***Ger.:*** Attempta; Balanca; Belara; Bella; Biviol; Cilest; Clevia; Conceplan M; Cyclosa; Cyproderm; Cypronette; Desmin; Diane; Ergalea; Eve; Evra; Femigoa; Femovan; Femranette mikro†; Gravistat; Juliette; Lamuna; Leios; Lovelle; Lyn-ratiopharm-Sequenz; Marvelon; Microgynon; Minisiston; Minulet; Miranova; MonoStep; Neo-Eunomin; Neo-Stediril†; Neogynon†; Non-Ovlon†; Nora-ratiopharm†; NovaStep; Novial; NuvaRing; Ostro-Primolut†; Oviol; Ovoresta M; Ovysmen†; Perikursal†; Petibelle; Pramino; Primosiston†; Prosiston†; Sequilar†; Sequostat†; Sinovula†; Stediril 30†; Stediril D†; Stediril†; Synphasec; Tetragynon†; Triette†; Trigoa; Trinordiol†; Trinovum; Triquilar; Trisiston; TriStep†; Valette; Yasmin; ***Gr.:*** Evra; Gracial; Gynera; Gynofen 35; Harmonette; Laurina; Loette; Marvelon; Meliane; Mercilon; Minulet; Neogynon†; Nordette†; Nordiol†; NuvaRing; Ovral†; Tri-Minulet; Trigynera; Trinordiol†; Triquilar†; Yasmin; ***Hong Kong:*** Brevinor; Diane; Eugynon; Evra; Gracial; Gynera; Harmonet; Marvelon; Meliane; Mercilon; Microgynon; Minulet†; Neogynon†; Nordette; Norimin†; Novynette; Rigevidon; Synphase†; Tri-Regol; Trinordiol†; Trinovum†; Triquilar†; Yasmin; ***Hung.:*** Anteovin; Belara; Cilest; Cypromix; Diane; Evra; Femoden; Gracial; Harmonet; Lindynette; Loette; Marvelon; Meliane; Mercilon; Milligest; Minerva; Minesse; Minulet; Miranova†; Novynette; NuvaRing; Ovidon; Regulon; Rigevidon; Tri-Minulet†; Tri-Regol; Trinordiol; Triodena; Triquilar; Yadine; Yasminelle; ***India:*** Diane; Duoluton-L; Femilon; Ginette; Mixogen; Novelon; Ovilow†; Ovipauz-L†; Ovral; Triquilar; ***Indon.:*** Diane; Gynera; Marvelon; Mercilon; Microdiol; Microgynon; Pil Keluarga Berencana; Planak; Trinordiol; Triquilar; Yasmin; ***Irl.:*** Brevinor; Cilest; Dianette; Evra; Femodene†; Logynon; Marviol; Mercilon; Microgynon 30†; Microlite; Minulet; NuvaRing; Ovran†; Ovranette; Tri-Minulet; Trinordiol; Triodene†; Yasmin; ***Israel:*** Belara; Diane; Estelle; Evra; Feminet; Gynera; Harmonet; Logynon†; Meliane; Mercilon; Microdiol; Microgynon; Minesse; Minulet; Neogynon†; Nordette; Ortho Cyclen; Trinordiol†; Yasmin; ***Ital.:*** Arianna; Belara; Diane; Dueva; Egogyn; Eugynon†; Evanor-D†; Evra; Fedra; Ginoden; Gracial; Harmonet; Loette; Mercilon; Microgynon; Milvane; Minesse; Minulet; Miranova; Novogyn; NuvaRing; Ovranet†; Planum; Practil; Securgin; Tri-Minulet; Trigynon; Trinordiol†; Visofid; Yasmin; ***Jpn:*** Ange; Ortho 777; ***Malaysia:*** Diane; Estelle; Gynera; Lindynette; Loette; Marvelon; Meliane; Mercilon; Microgynon 30; Minulet; Nordette; Novynette; Regulon; Rigevidon; Tri-Regol†; Trinordiol; Triquilar†; Yasmin; ***Mex.:*** Alesse; Belara; Cilest; Diane; Eunice 35-ED; Evra; Femexin; Ginelea; Gynovin; Letinnov; Marvelon; Mercilon; Microgynon; Mileva; Minesse; Minulet; Neogynon; Nordet; Nordiol; Novial; NuvaRing; Ortho-Novum 1/35; Ovral; Secret 28; Trinordiol; Triquilar; Yasmin; ***Neth.:*** Alesse; Belanette; Cilest; Diane; Evra; Femodeen; Gracial; Harmonet†; Levlen†; Logynon; Lovette; Lyndiol†; Marvelon; Meliane; Mercilon; Microgynon; Ministat; Minulet; Miranova; Modicon; Neocon; Neogynon; NuvaRing; Ovidol; Ovostat†; Rigevidon; Stediril; Tri-Minulet†; Trigynon; Trinordiol; Trinovum; Triodeen; Yasmin; Yasminelle; Yira; ***Norw.:*** Diane; Evra; Follimin†; Loette; Marvelon; Microgynon; NuvaRing; Synfase; Tetragynon†; Trinordiol; Trionetta; Yasmin; ***NZ:*** Brevinor; Diane; Estelle; Femodene; Levlen ED; Loette; Marvelon; Melodene; Mercilon; Microgynon; Minulet; Monofeme; Nordette; Nordiol†; Norimin; Ovral†; Synphasic; Trifeme; Trimiron†; Triphasil; Triquilar; Yasmin; ***Philipp.:*** Althea; Diane; Evra; Femenal; Gracial; Gynera; Lady; Logynon; Marvelon; Meliane; Mercilon; Microgynon; Micropil; Minulet; Nordette; Nordiol; Rigevidon; Seif; Trinordiol; Trust Pill; Yasmin; ***Pol.:*** Anteovin; Cilest; Cyprest; Diane; Evra; Femoden; Gravistat; Harmonet; Jeanine; Logest; Marvelon; Mercilon; Microgynon; Milvane; Minisiston; Minulet; Mirelle; Novynette; Regulon; Rigevidon; Stediril; Tri-Minulet; Tri-Regol; Trinordiol; Trinovum; Triquilar; Trisiston; Yasmin; Yasminelle; ***Port.:*** Belara; Diane; Effiplen; Estinette; Evra; Femphascyl†; Gracial; Gynera; Harmonet; Laurina; Libeli; Marvelon; Mercilon; Microgeste; Microginon; Minesse; Minigeste; Minulet; Miranova; Neomonovar†; Novynette; NuvaRing; Petibelle; Regulon; Tetragynon; Tri-Gynera; Tri-Minulet; Trinordiol; Triquilar; Valette; Yasmin; Yasminelle; ***Rus.:*** Anteovin (Антеовин); Belara (Белара); Cilest (Силест); Diane (Диане); Evra (Евра); Femoden (Фемоден); Jeanine (Жанин); Lindynette (Линдинет); Logest (Логест); Marvelon (Марвелон); Mercilon (Мерсилон); Microgynon (Микрогинон); Minisiston (Минизистон); Non-Ovlon (Нон-овлон); Novynette (Новинет); NuvaRing (НоваРинг); Ovidon (Овидон); Regulon (Регулон); Rigevidon (Ригевидон); Tri-Merci (Три-Мерси); Tri-Regol (Три-Регол); Triquilar (Триквилар); Trisiston (Тризистон); Yarina (Ярина); ***S.Afr.:*** Biphasil; Brevinor†; Cilest; Diane; Diva; E-Gen-C; Evra; Femodene ED; Ginette; Harmonet; Loette; Logynon ED; Marvelon; Melodene; Menoflush; Mercilon; Minerva; Minesse; Minulette; Miranova; Mirelle; Nordette; Nordiol; Ovral; Tri-Minulet; TriCilest; Trinovum; Triodene; Triphasil; Yasmin; ***Singapore:*** Diane; Estelle; Evra; Gynera; Loette; Marvelon; Meliane; Mercilon; Microgynon; Minulet; Nordette; Trinordiol; Triquilar†; Yasmin; ***Spain:*** Belara; Diane; Evra; Gracial; Gynovin; Harmonet; Loette; Meliane; Melodene 15; Microdiol; Microgynon; Minesse; Minulet; Neogynona; NuvaRing; Ovoplex; Suavuret; Tri-Minulet; Triagynon; Triciclor; Trigynovin; Yasmin; Yira†; ***Swed.:*** Cilest; Desolett; Evra; Follimin; Follinett; Mercilon; Neovletta; NuvaRing; Orthonett Novum; Restovar; Synfase; Trimiron; Trinordiol; Trinovum; Trionetta; Triregol; Yasmin; ***Switz.:*** Belara; Binordiol†; Cilest; Cypestra; Diane; Evra; Feminac; Gracial; Gynera; Harmonet; Marvelon; Meloden; Mercilon; Microgynon; Milvane; Minerva; Minesse; Minulet; Miranova; Mirelle; Neogynon†; NuvaRing; Ologyn; Ovysmen; Primosiston; Stediril 30; Stediril D; Tetragynon; Tri-Minulet; Trinordiol; Trinovum; Triquilar; Yasmin; ***Thai.:*** Anna†; Cilest; Diane; Eugynon 250†; Evra; FMP†; Gynera; Helen†; Hormone Multicap†; Horon†; Jeny-FMP†; Lady-35; Lyndiol†; Manoane; Marvelon; Meliane; Mercilon; Microgest; Microgynon; Microlenyn; Minulet†; Nordette; Oilezz; Preme†; R-Den†; Riget; Rigevidon; Sucee; TriCilest; Triquilar; Yasmin; ***Turk.:*** Desolett; Diane; Ginera; Lo-Ovral; Microgynon; Minulet; Miranova; Myralon; Preven; Triquilar; Yasmin; ***UK:*** Acnocin; Binovum; Brevinor; Cicafem; Cilest; Clairette; Dianette; Diva; Eugynon 30†; Evra; Femodene; Femodette; Katya; Loestrin; Logynon; Marvelon; Mercilon; Microgynon 30; Minulet†; Norimin; Ovran 30; Ovranette; Ovysmen; Sunya; Synphase; Tri-Minulet†; Triadene; Trinordiol†; Trinovum; Yasmin; ***USA:*** Alesse; Apri; Aranelle; Aviane; Balziva; Brevicon; Cesia; Cryselle; Cyclessa; Demulen†; Desogen; Enpresse; Estrostep Fe; Estrostep†; Femcon Fe; FemHRT; Jolessa; Junel Fe; Kariva; Kelnor; Leena; Lessina; Levlen; Levlite; Levora; Lo/Ovral; Loestrin; Loestrin Fe; Lutera; Lybrel; Mircette; Modicon; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Nordette; Norinyl 1 + 35; NuvaRing; Ortho Cyclen; Ortho Evra; Ortho Tri-Cyclen; Ortho-Cept; Ortho-Novum 1/35; Ortho-Novum 10/11; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Ovral; Portia; Preven†; Previfem; Quasense; Reclipsen; Seasonale; Seasonique; Solia; Sprintec; Sronyx; Tilia Fe; Tri-Legest; Tri-Levlen; Tri-Norinyl; Tri-Previfem; Tri-Sprintec; TriNessa; Triphasil; Trivora; Velivet; Yasmin; YAZ; Zenchent; Zovia; ***Venez.:*** Alesse; Belara; Ciclidon; Diane; Dixi; Evra; Femiane; Gynera; Harmonet; Marvelon; Mercilon; Minesse; Minigynon; Minulet; Mipil; Mirelle; Neogynon; Nordette; Nordiol; Novial; Ortrel; Ovral; Primosiston†; Rigevidon; Tri-Regol; Trinordiol; Triquilar; Yasmin.

Ethylestrenol *(BAN, USAN, rINN)* ⊗

Éthylestrénol; Ethylestrenolum; Ethyloestrenol; Etilestrenol; Etylestrenol; Etyyliestrenoli. 17α-Ethylestr-4-en-17β-ol; 19-Nor-17α-pregn-4-en-17β-ol.

Этилэстренол

$C_{20}H_{32}O$ = 288.5.
CAS — 965-90-2.
ATC — A14AB02.
ATC Vet — QA14AB02.

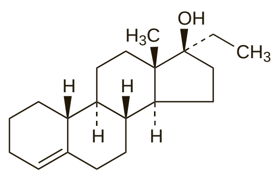

Profile

Ethylestrenol is a 17α-alkylated anabolic steroid (see Testosterone, p.2129) with little androgenic effect and slight progestogenic activity. It has been used for the promotion of growth in boys with short stature or delayed bone growth. It is used in veterinary medicine.

Etonogestrel *(BAN, USAN, rINN)*

Etonogestreeli; Étonogestrel; Etonogestrelum; 3-keto-Desogestrel; Org-3236. 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one; 17β-Hydroxy-11-methylene-18-homo-19-nor-17α-pregn-4-en-20-yn-3-one.

Этоногестрел

$C_{22}H_{28}O_2$ = 324.5.
CAS — 54048-10-1.
ATC — G03AC08.
ATC Vet — QG03AC08.

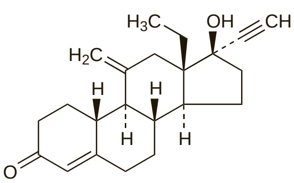

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Breast feeding. Etonogestrel was found in the breast milk of 42 women given a contraceptive etonogestrel implant. Over the 4-month study, compared with a group who used an intra-uterine non-hormonal device, etonogestrel did not affect the volume or composition of breast milk, or the growth of the breast-fed infants.[1] At 3 years of age there was no difference in growth between these 2 groups of children.[2]

1. Reinprayoon D, *et al.* Effects of the etonogestrel-releasing contraceptive implant (Implanon) on parameters of breastfeeding compared to those of an intrauterine device. *Contraception* 2000; **62:** 239–46.
2. Taneepanichskul S, *et al.* Effects of the etonogestrel-releasing implant Implanon and a nonmedicated intrauterine device on the growth of breast-fed infants. *Contraception* 2006; **73:** 368–71.

Vaginal bleeding. Prolonged vaginal bleeding, lasting from 2 to 26 weeks, has been reported with the use of etonogestrel subdermal implants. Blood transfusion was needed in the management of one patient.[1] Heavy bleeding has been described in 2 women after the implant had broken while in place.[2,3]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Implanon and vaginal bleeding. *Aust Adverse Drug React Bull* 2003; **22:** 11–12. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0306.pdf (accessed 27/06/08)
2. Pickard S, Bacon L. Persistent vaginal bleeding in a patient with a broken Implanon . *J Fam Plann Reprod Health Care* 2002; **28:** 207–8.
3. Agrawal A, Robinson C. Spontaneous snapping of an Implanon in two halves in situ. *J Fam Plann Reprod Health Care* 2003; **29:** 238.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Etonogestrel is highly bound to plasma proteins; about 32% is bound to sex hormone binding globulin and 66% to albumin. It is metabolised by the cytochrome P450 isoenzyme CYP3A4, and both metabolites and unchanged drug are excreted in the urine and faeces. The elimination half-life is about 25 to 30 hours. Etonogestrel is distributed into breast milk.

◊ References.

1. Timmer CJ, Mulders TMT. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinet* 2000; **39:** 233–42.
2. Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. *Eur J Contracept Reprod Health Care* 2000; **5** (suppl 2): 12–20.

Uses and Administration

Etonogestrel, the active metabolite of desogestrel (p.2093), is used as a hormonal contraceptive (see p.2069). A subdermal implant containing 68 mg of etonogestrel is used as a progestogen-only contraceptive that is effective for 3 years. Etonogestrel is also used as the progestogen component of a combined contraceptive delivered via a vaginal ring device. The ring releases an average of 120 micrograms daily of etonogestrel and 15 micrograms daily of ethinylestradiol and remains in the vagina for 3 weeks; it is then removed for a one-week break after which a new ring is inserted.

Etonogestrel is under investigation as a male contraceptive, given orally or by implant, with testosterone implants or injections.

◊ References.

1. Edwards JE, Moore A. Implanon: a review of clinical studies. *Br J Fam Plann* 1999; **24:** 3–16.
2. Le J, Tsourounis C. Implanon: a critical review. *Ann Pharmacother* 2001; **35:** 329–36.
3. Roumen F. Contraceptive efficacy and tolerability with a novel combined contraceptive vaginal ring, NuvaRing. *Eur J Contracept Reprod Health Care* 2002; **7** (suppl 2): 19–24.
4. Meirik O, *et al.* WHO Consultation on Implantable Contraceptives for Women. Implantable contraceptives for women. *Hum Reprod Update* 2003; **9:** 49–59.
5. Sarkar NN. The combined contraceptive vaginal device (NuvaRing): a comprehensive review. *Eur J Contracept Reprod Health Care* 2005; **10:** 73–8.
6. Roumen FJ. The contraceptive vaginal ring compared with the combined oral contraceptive pill: a comprehensive review of randomized controlled trials. *Contraception* 2007; **75:** 420–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Implanon†; ***Austral.:*** Implanon; ***Austria:*** Implanon; ***Belg.:*** Implanon; ***Braz.:*** Implanon; ***Chile:*** Implanon; ***Cz.:*** Implanon; ***Denm.:*** Implanon; ***Fin.:*** Implanon; ***Fr.:*** Implanon; ***Ger.:*** Implanon; ***Gr.:*** Implanon†; ***Hung.:*** Implanon; ***Indon.:*** Implanon; ***Irl.:*** Implanon; ***Ital.:*** Implanon†; ***Malaysia:*** Implanon; ***Mex.:*** Implanon; ***Neth.:*** Implanon; ***Norw.:*** Implanon; ***Port.:*** Implanon; ***Singapore:*** Implanon; ***Spain:*** Implanon; ***Swed.:*** Implanon; ***Switz.:*** Implanon; ***Thai.:*** Implanon; ***Turk.:*** Implanon; ***UK:*** Implanon; ***USA:*** Implanon; ***Venez.:*** Implanon.

Multi-ingredient: ***Austral.:*** NuvaRing; ***Austria:*** NuvaRing; ***Belg.:*** NuvaRing; ***Braz.:*** NuvaRing; ***Canad.:*** NuvaRing; ***Chile:*** NuvaRing; ***Cz.:*** NuvaRing; ***Denm.:*** NuvaRing; ***Fin.:*** NuvaRing; ***Fr.:*** NuvaRing; ***Ger.:*** NuvaRing; ***Gr.:*** NuvaRing; ***Hung.:*** NuvaRing; ***Irl.:*** NuvaRing; ***Ital.:*** NuvaRing; ***Mex.:*** NuvaRing; ***Neth.:*** NuvaRing; ***Norw.:*** NuvaRing; ***Port.:*** NuvaRing; ***Rus.:*** NuvaRing (НоваРинг); ***Spain:*** NuvaRing; ***Swed.:*** NuvaRing; ***Switz.:*** NuvaRing; ***USA:*** NuvaRing.

Etynodiol Diacetate *(BANM, pINNM)*

Aethynodiolum Diaceticum; Diacetato de etinodiol; Ethynodiol Diacetate *(USAN)*; Étynodiol, Diacetate d'; Etynodioli Diacetas; SC-11800. 19-Nor-17α-pregn-4-en-20-yne-3β,17β-diol diacetate.

Этинодиола Диацетат

$C_{24}H_{32}O_4$ = 384.5.
CAS — 1231-93-2 (etynodiol); 297-76-7 (etynodiol diacetate).
ATC — G03DC06.
ATC Vet — QG03DC06.

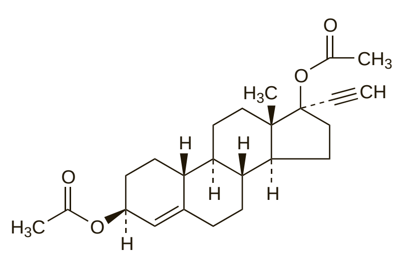

Pharmacopoeias. In *Br.*, *Pol.*, and *US.*

BP 2008 (Etynodiol Diacetate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Protect from light.

USP 31 (Ethynodiol Diacetate). A white, odourless, crystalline powder. Insoluble in water; soluble in alcohol; very soluble in chloroform; freely soluble in ether; sparingly soluble in fixed oils. Protect from light.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Pregnancy. Fetal adrenal cytomegaly in a 17-week-old fetus was associated with the maternal ingestion of an oral contraceptive containing etynodiol diacetate 2 mg and mestranol 100 micrograms from the sixth to the fourteenth week of pregnancy.[1]

1. Gau GS, Bennett MJ. Fetal adrenal cytomegaly. *J Clin Pathol* 1979; **32:** 305–6.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Etynodiol diacetate is readily absorbed from the gastrointestinal tract and rapidly metabolised, largely to norethisterone (p.2119). About 60% of a dose is stated to be excreted in urine and about 30% in faeces; the half-life in plasma is about 25 hours.

Uses and Administration

Etynodiol diacetate is a progestogen (see Progesterone, p.2126) that is used as the progestogenic component of combined oral contraceptives and also alone as an oral progestogen-only contraceptive (see p.2069); typical daily doses are 1 or 2 mg in combination products and 500 micrograms for progestogen-only contraceptives.

Preparations

USP 31: Ethynodiol Diacetate and Ethinyl Estradiol Tablets; Ethynodiol Diacetate and Mestranol Tablets.

Proprietary Preparations (details are given in Part 3)
Cz.: Femulen†; ***Hung.:*** Continuin†; ***Israel:*** Femulen†; ***NZ:*** Femulen; ***UK:*** Femulen.

Multi-ingredient: ***Arg.:*** Soluna; ***Canad.:*** Demulen; ***USA:*** Demulen†; Kelnor; Zovia.

Flugestone Acetate *(BANM, rINNM)*

Acetato de flugestona; Flugestone, Acétate de; Flugestoni Acetas; Flurogestone Acetate *(USAN)*; NSC-65411; SC-9880. 9α-Fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione 17-acetate.

Флугестона Ацетат

$C_{23}H_{31}FO_5$ = 406.5.
CAS — 337-03-1 (flugestone); 2529-45-5 (flugestone acetate).

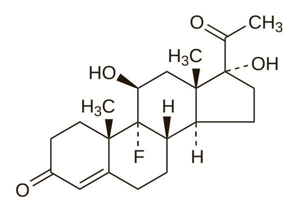

(flugestone)

Profile

Flugestone acetate is a progestogen (see Progesterone, p.2125) used in veterinary medicine.

Fluoxymesterone *(BAN, rINN)* ⊗

Fluoksimesteroni; Fluoximesteron; Fluoximesterona; Fluoxymestérone; Fluoxymesteronum; Fluximesterona; NSC-12165. 9α-Fluoro-11β,17β-dihydroxy-17α-methylandrost-4-en-3-one.

Флуоксиместерон

$C_{20}H_{29}FO_3$ = 336.4.
CAS — 76-43-7.
ATC — G03BA01.
ATC Vet — QG03BA01.

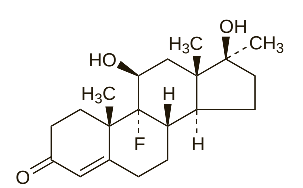

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Fluoxymesterone). A white or practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Protect from light.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

As with other 17α-alkylated compounds fluoxymesterone may cause hepatotoxicity, and is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

Uses and Administration

Fluoxymesterone has androgenic properties (see Testosterone, p.2131). It is effective when given orally and is more potent than methyltestosterone.

In the treatment of male hypogonadism (p.2079), fluoxymesterone has been given in a dosage of 5 to 20 mg daily. For the use of fluoxymesterone in boys with delayed puberty, see Administration in Children, below. In the palliation of inoperable neoplasms of the breast in postmenopausal women (p.661) it has been given in daily doses of up to 40 mg. Fluoxymesterone has also been used in the treatment of aplastic anaemia.

Administration in children. In the treatment of delayed puberty (p.2079) in boys fluoxymesterone has been given orally in usual daily doses of 2.5 to 10 mg, adjusted according to response (doses up to 20 mg daily have been used). Care is necessary because of the risk of epiphyseal closure and treatment is generally only given for 4 to 6 months.

Preparations

USP 31: Fluoxymesterone Tablets.

Proprietary Preparations (details are given in Part 3)
Hong Kong: Halotestin†; ***Mex.:*** Stenox; ***Thai.:*** Halotestin†; ***USA:*** Androxy.

Multi-ingredient: *Arg.:* Ferona.

Follicle-stimulating Hormone ⊗

Folitropina; FSH.
ATC Vet — QG03GA90.

Follitropin Alfa *(BAN, rINN)* ⊗

Folitropin Alfa; Folitropina alfa; Follitropine Alfa; Follitropinum Alfa.

Фоллитропин Альфа

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit).
CAS — 9002-68-0 (follitropin alfa); 56832-30-5 (α- subunit); 110909-60-9 (β-subunit); 146479-72-3 (follitropin alfa).
ATC — G03GA05.
ATC Vet — QG03GA05.

Follitropin Beta *(BAN, rINN)* ⊗

Folitropin Beta; Folitropina beta; Follitropine Bêta; Follitropinum Beta; Org-32489.

Фоллитропин Бета

$C_{437}H_{682}N_{122}O_{134}S_{13}$ = 10 206 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ = 12 485 (β-subunit).
CAS — 169108-34-3 (follitropin beta); 150490-84-9 (follitropin beta); 56832-30-5 (α-subunit); 110909-60-9 (β-subunit).
ATC — G03GA06.
ATC Vet — QG03GA06.

Units

80 units of human pituitary follicle-stimulating hormone are contained in about 4.17 micrograms (with 5 mg of mannitol and 1 mg human serum albumin) in one ampoule of the first International Standard (1986).

138 units of recombinant human follicle-stimulating hormone for bioassay are contained in one ampoule of the first International Standard (1995).

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

Spongiform encephalopathies. In a few countries, gonadotrophins derived from cadaver pituitary glands have been used in the treatment of infertility, and a small number of patients are reported to have acquired Creutzfeldt-Jakob disease from such preparations.[1] However, most countries have preferred to use gonadotrophins derived from urine,[1] and these in their turn are being replaced with recombinant products;[2] such preparations appear to carry negligible risk of transmitting prion disease.[3-5]

1. Healy DL, Evans J. Creutzfeldt-Jakob disease after pituitary gonadotrophins. *BMJ* 1993; **307:** 517–18.
2. Eshkol A, Page ML. Human gonadotrophin preparations. *BMJ* 1994; **308:** 789.
3. Matorras R, Rodríguez-Escudero FJ. Bye-bye urinary gonadotrophins? The use of urinary gonadotrophins should be discouraged. *Hum Reprod* 2002; **17:** 1675.
4. Balen A. Is there a risk of prion disease after the administration of urinary-derived gonadotrophins? *Hum Reprod* 2002; **17:** 1676–80.
5. Jansen C. Bye-bye urinary gonadotrophins? Reply to debate. *Hum Reprod* 2003; **18:** 895–6.

Pharmacokinetics

Follitropins alfa and beta are slowly absorbed after subcutaneous or intramuscular injection, with an absolute bioavailability of about 70 to 80%. Peak plasma concentrations of follitropin beta have been stated to occur about 12 hours after subcutaneous or intramuscular injection. Accumulation occurs with repeated doses, reaching a steady state within 3 to 5 days. Follitropins are slowly eliminated from the body, with a terminal half-life ranging from 12 to 70 hours. About one-eighth of a dose of follitropin alfa is reported to be excreted in the urine.

◊ References.

1. Karlsson MO, *et al*. The population pharmacokinetics of recombinant- and urinary-human follicle stimulating hormone in women. *Br J Clin Pharmacol* 1998; **45:** 13–20.

Uses and Administration

Follicle-stimulating hormone is secreted by the anterior lobe of the pituitary gland, with another gonadotrophin, luteinising hormone (p.2112).

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova; in men it has a role in spermatogenesis.

Recombinant human follicle-stimulating hormones (follitropins alfa or beta) are used in the treatment of female infertility due to anovulation, in women who have not responded to clomifene therapy. Follitropins are also used for the stimulation of spermatogenesis in the management of male infertility caused by hypogonadotrophic hypogonadism (see Infertility, p.2080).

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle.

- Treatment is usually begun with 75 to 150 units daily by subcutaneous or intramuscular injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation.

It has been suggested in UK licensed product information for follitropin alfa that a daily dose of 225 units is the usual maximum, and that if a patient fails to respond adequately after 4 weeks of treatment that cycle should be abandoned and the patient should subsequently begin the next cycle at a higher starting dose.

Follitropins are also used as part of IVF or other assisted reproductive technologies.

- For this purpose doses of 150 to 225 units daily are generally given, for at least 4 days, commencing on the second or third day of the menstrual cycle. Thereafter the dose may be adjusted individually based on ovarian response to a usual maximum of about 450 units; adequate follicular development generally occurs within about 5 to 10 days of treatment.
- Pituitary downregulation with a gonadorelin analogue may be used with follitropin therapy, in which case the gonadorelin analogue is generally begun about 2 weeks before follitropin, and the 2 are then continued together until follicular development is adequate.
- A single dose of up to 10 000 units of chorionic gonadotrophin is then given to induce final follicular maturation and oocyte retrieval performed about 35 hours later.

Follitropins are used for the stimulation of spermatogenesis in the management of **male infertility** caused by hypogonadotrophic hypogonadism. Before starting follitropin therapy, chorionic gonadotrophin is given to raise serum testosterone concentrations to the normal range, which may take 3 to 6 months. A dose of follitropin alfa or beta of 150 units subcutaneously three times weekly is then used, with continued chorionic gonadotrophin; doses of follitropin alfa up to 300 units three times weekly may be required. Treatment is continued for at least 4 months, and more than 18 months of treatment may be needed. A dose of follitropin beta 75 units daily or two or three times weekly, by subcutaneous or intramuscular injection, has been used similarly.

Other substances with follicle-stimulating activity are used similarly: these include human menopausal gonadotrophins (p.2109), which have both luteinising and follicle-stimulating activity, and urofollitropin (p.2136).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gonal-F; Puregon; ***Austral.:*** Gonal-F; Puregon; ***Austria:*** Gonal-F; Puregon; ***Belg.:*** Gonal-F; Puregon; ***Braz.:*** Gonal-F; Puregon; ***Canad.:*** Gonal-F; Puregon; ***Chile:*** Gonal-F†; Puregon; ***Cz.:*** Gonal-F; Puregon; ***Denm.:*** Gonal-F; Puregon; ***Fin.:*** Gonal-F; Puregon; ***Fr.:*** Gonal-F; Puregon; ***Ger.:*** Gonal-F; Puregon; ***Gr.:*** Gonal-F; Puregon; ***Hong Kong:*** Gonal-F; Puregon; ***Hung.:*** Gonal-F; Puregon; ***India:*** Gonal-F; ***Indon.:*** Gonal-F; Puregon; ***Irl.:*** Gonal-F; Puregon; ***Israel:*** Gonal-F; Puregon; ***Ital.:*** Gonal-F; Puregon; ***Malaysia:*** Gonal-F; Puregon; ***Mex.:*** Gonal-F; Puregon; ***Neth.:*** Gonal-F; Puregon; ***Norw.:*** Gonal-F; Puregon; ***NZ:*** Gonal-F; Puregon; ***Philipp.:*** Gonal-F; Puregon; ***Pol.:*** Gonal-F; Puregon; ***Port.:*** Gonal-F; Puregon; ***Rus.:*** Gonal-F (Гонал-Ф); Puregon (Пурегон); ***S.Afr.:*** Gonal-F; Puregon†; ***Singapore:*** Gonal-F; Puregon; ***Spain:*** Gonal-F; Puregon; ***Swed.:*** Gonal-F; Puregon; ***Switz.:*** Gonal-F; Puregon; ***Thai.:*** Gonal-F; Puregon; ***Turk.:*** Gonal-F; Puregon; ***UK:*** Gonal-F; Puregon; ***USA:*** Follistim; Gonal-F; ***Venez.:*** Gonal-F; Puregon.

Multi-ingredient: *Cz.:* Pergoveris; ***Port.:*** Pergoveris; ***UK:*** Pergoveris.

Formebolone *(BAN, rINN)* ⊗

Formebolona; Formébolone; Formebolonum; Formyldienolone.
11α,17β-Dihydroxy-17β-methyl-3-oxoandrosta-1,4-diene-2-carbaldehyde.

Формеболон

$C_{21}H_{28}O_4$ = 344.4.
CAS — 2454-11-7.

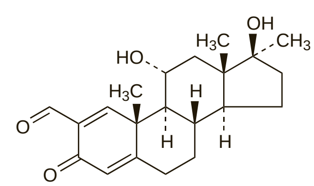

Profile

Formebolone has been used for its anabolic properties (see Testosterone, p.2129). It appears to be widely abused by body-builders.

Fosfestrol *(BAN, rINN)*

Diethylstilbestrol Diphosphate; Fosfestroli; Fosfestrolum; Phosphoestrolum; Stilboestrol Diphosphate. (*E*)-α,α′-Diethylstilbene-4,4′-diol bis(dihydrogen phosphate); (*E*)-4,4′-(1,2-Diethylvinylene)bis(phenyl dihydrogen orthophosphate).

Фосфэстрол

$C_{18}H_{22}O_8P_2$ = 428.3.
CAS — 522-40-7.
ATC — L02AA04.
ATC Vet — QL02AA04.

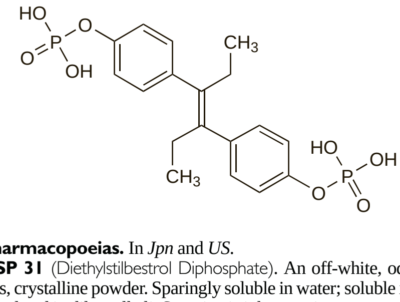

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Diethylstilbestrol Diphosphate). An off-white, odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol and in dilute alkali. Store in airtight containers at a temperature not exceeding 21°.

Fosfestrol Sodium *(BANM, rINNM)*

Fosfestrol sódico; Fosfestrol Sodique; Natrii Fosfestrolum.

Натрий Фосфэстрол

$C_{18}H_{18}Na_4O_8P_2$ = 516.2.

CAS — 23519-26-8 (fosfestrol tetrasodium xH_2O); 4719-75-9 (anhydrous fosfestrol tetrasodium).

ATC — L02AA04.

ATC Vet — QL02AA04.

Pharmacopoeias. In *Br.*, which specifies xH_2O.

BP 2008 (Fosfestrol Sodium). A white or almost white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. A 5% solution in water has a pH of 7.0 to 9.0. Protect from light.

Adverse Effects and Precautions

As for Diethylstilbestrol, see p.2094.

After intravenous injection of fosfestrol sodium there may be a temporary burning sensation in the perineal region and pain at the site of bony metastases. Slow infusion is not recommended as cytotoxic concentrations of the drug may not be achieved.

Uses and Administration

Fosfestrol is a synthetic nonsteroidal oestrogen that requires dephosphorylation to diethylstilbestrol (p.2094) before it is active. It is used in the treatment of malignant neoplasms of the prostate (p.671).

Fosfestrol and its sodium salt have both been used, and doses of fosfestrol sodium may be expressed in terms of either the base or the salt; anhydrous fosfestrol sodium 300 mg is equivalent to about 250 mg of fosfestrol. Expressed in terms of fosfestrol sodium, initial doses of 600 to 1200 mg daily by slow intravenous injection over about 1 hour may be given for 5 to 10 days, followed by 300 mg daily for 10 to 20 days. Injections should be given preferably with the patient lying down. Maintenance intravenous doses of fosfestrol sodium 300 to 600 mg may be given, reduced gradually over several months from dosing 4 times a week to once weekly. Fosfestrol sodium may also be given orally. If initial doses cannot be given intravenously, doses of 360 to 480 mg three times daily have been given orally. For maintenance therapy, doses of 120 to 240 mg three times daily may be used, and gradually reduced to 240 mg daily.

Preparations

BP 2008: Fosfestrol Injection; Fosfestrol Tablets;
USP 31: Diethylstilbestrol Diphosphate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fosfostilben†; Honvan†; ***Austria:*** Honvan; ***Belg.:*** Honvan†; ***Braz.:*** Ronvan†; ***Canad.:*** Honvol; ***Fr.:*** ST-52†; ***Ger.:*** Honvan†; ***Gr.:*** Honvan; ***Hong Kong:*** Honvan†; ***India:*** Honvan; ***Mex.:*** Honvan†; ***Neth.:*** Honvan†; ***Port.:*** Honvan†; ***Spain:*** Honvan†; ***Switz.:*** Honvan†.

Ganirelix Acetate *(BANM, USAN, rINNM)*

Acetato de ganirelix; Ganirélix, Acétate de; Ganirelixi Acetas; Org-37462; RS-26306. *N*-Acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-(*N*,*N*′-diethylamidino)-D-lysyl-L-leucyl-N^6-(*N*,*N*′-diethylamidino)-L-lysyl-L-prolyl-D-alaninamide acetate.

Ганиреликса Ацетат

$C_{80}H_{113}ClN_{18}O_{13},2C_2H_4O_2$ = 1690.4.

CAS — 124904-93-4 (ganirelix); 129311-55-3 (ganirelix acetate).

ATC — H01CC01.

ATC Vet — QH01CC01.

Adverse Effects and Precautions

As for Cetrorelix, p.2084.

Pharmacokinetics

Ganirelix is rapidly absorbed after subcutaneous injection, with a bioavailability of about 91%. It is metabolised by enzymatic hydrolysis and about 75% of a dose is excreted as metabolites in the faeces. Unchanged drug is found in the urine. The elimination half-life of ganirelix is about 13 hours.

◊ References.

1. Oberyé JJL, *et al*. Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutron) part I: absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. *Fertil Steril* 1999; **72:** 1001–5.

Uses and Administration

Like cetrorelix (p.2084), ganirelix is a gonadorelin (gonadotrophin-releasing hormone) antagonist. It is used as a component of ovarian stimulation regimens for assisted reproduction in infertility (p.2080); ganirelix acetate is given by subcutaneous injection to prevent premature luteinising hormone surges. Doses are expressed in terms of the acetate or the equivalent amount of base. Ganirelix acetate 108 mg is equivalent to about 100 mg of ganirelix. In the UK a dose equivalent to ganirelix 250 micrograms is given once daily, starting on day 6 of ovarian stimulation and continued until ovulation induction. In the USA a dose of ganirelix acetate 250 micrograms is used similarly.

◊ References.

1. Gillies PS, *et al*. Ganirelix. *Drugs* 2000; **59:** 107–11.
2. The European Orgalutran Study Group, *et al*. Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. *Hum Reprod* 2000; **15:** 1490–8. Correction. *ibid.*; 1877.
3. The North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. *Fertil Steril* 2001; **75:** 38–45.
4. European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. *Hum Reprod* 2001; **16:** 644–51.
5. Griesinger G, *et al*. Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
6. Out HJ, *et al*. A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction. *Hum Reprod* 2004; **19:** 90–5.
7. Wilcox J, *et al*. CAP IV Investigator Group. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril* 2005; **84:** 108–17.
8. Lambalk CB, *et al*. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. *Hum Reprod* 2006; **21:** 632–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Orgalutran; ***Austral.:*** Orgalutran; ***Belg.:*** Orgalutran; ***Braz.:*** Orgalutran; ***Canad.:*** Orgalutran; ***Chile:*** Orgalutran; ***Cz.:*** Orgalutran; ***Denm.:*** Orgalutran; ***Fin.:*** Orgalutran; ***Fr.:*** Orgalutran; ***Ger.:*** Orgalutran; ***Gr.:*** Orgalutran; ***Hong Kong:*** Orgalutran; ***Hung.:*** Orgalutran; ***Irl.:*** Orgalutran; ***Israel:*** Orgalutran; ***Ital.:*** Orgalutran; ***Malaysia:*** Orgalutran; ***Mex.:*** Orgalutran; ***Norw.:*** Orgalutran; ***NZ:*** Orgalutran; ***Philipp.:*** Orgalutran; ***Port.:*** Orgalutran; ***Rus.:*** Orgalutran (Оргалутран); ***Singapore:*** Orgalutran; ***Spain:*** Orgalutran; ***Swed.:*** Orgalutran; ***Switz.:*** Orgalutran; ***Thai.:*** Orgalutran; ***Turk.:*** Orgalutran; ***UK:*** Orgalutran; ***USA:*** Antagon†; ***Venez.:*** Orgalutran.

Gestodene *(BAN, USAN, rINN)*

Gestodeeni; Gestoden; Gestodène; Gestodeno; Gestodenum; SH-B-331. 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one.

Гестоден

$C_{21}H_{26}O_2$ = 310.4.

CAS — 60282-87-3.

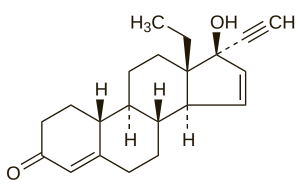

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Gestodene is reported to have few androgenic effects, and to have less adverse effect on the serum lipid profile than older 19-nortestosterone derivatives. However, there is some evidence that gestodene-containing combined oral contraceptives are associated with a small increased risk of venous thromboembolism (see p.2063, and for precautions, see under Cardiovascular Disease, p.2066).

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Antiepileptics. *Felbamate* significantly increased gestodene clearance from a low-dose combined oral contraceptive, and might decrease contraceptive efficacy.[1] See also p.2068.

1. Saano V, *et al*. Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. *Clin Pharmacol Ther* 1995; **58:** 523–31.

Pharmacokinetics

Gestodene is well absorbed with a high bioavailability when given orally. It is extensively bound to plasma proteins; 75 to 87% to sex hormone binding globulin, and 13 to 24% to albumin. Gestodene is metabolised in the liver, less than 1% of a dose being excreted in the urine unchanged. After multiple doses with ethinylestradiol, gestodene has an elimination half-life of about 20 hours.

Uses and Administration

Gestodene is a progestogen (see Progesterone, p.2125) structurally related to levonorgestrel. It is used as the progestogenic component of combined oral contraceptives (see p.2069); a typical daily dose is 75 micrograms in monophasic preparations, and 50 to 100 micrograms in triphasic preparations. Gestodene is also used orally as the progestogenic component of menopausal HRT (see p.2076) in a regimen of 25 or 50 micrograms daily for 12 days of a 28-day cycle.

◊ Reviews.

1. Anonymous. Femodene/Minulet—how different is gestodene? *Drug Ther Bull* 1990; **28:** 41–2.
2. Wilde MI, Balfour JA. Gestodene: a review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. *Drugs* 1995; **50:** 364–95.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Avaden.

Multi-ingredient: *Arg.:* Aleli; Biofem; Cuidafem; Femiane; Ginelea; Ginelea T; Gynovin; Harmonet; Livianne; Mesconcept; Minesse; Minulet; Mirelle; Secret 28; Venisse; ***Austral.:*** Femoden ED; Minulet; Tri-Minulet†; Trioden; ***Austria:*** Gynovin; Harmonette; Meliane; Minesse; Minulet; Mirelle; Myvlar; Tri-Minulet; Triodena; Yris; ***Belg.:*** Femodene; Gestodelle; Gestofeme; Harmonet; Meliane; Minulet; Mirelle; Tri-Minulet; Triodene; ***Braz.:*** Adoless; Alexa; Allestra; Diminut; Femiane; Fertnon; Gestinol; Ginesse; Gynera; Harmonet; Micropil; Minesse; Minima; Minulet; Mirelle; Previane; Siblima; Tamisa; ***Chile:*** Avaden; Careza; Ciclomex; Feminol; Gynera; Harmonet; Microgen; Minesse; Minigest; Minulet; Mirelle; Tri-Ciclomex; ***Cz.:*** Avaden†; Convaden†; Femoden; Harmonet; Katya; Lindynette; Logest; Lunafem; Milligest; Milvane†; Minesse; Minulet; Mirelle; Sunya; Tri-Minulet; ***Denm.:*** Gestonette; Gynera; Harmonet; Lindynette; Meloden; Milvane; Minulet; Tri-Minulet†; ***Fin.:*** Femoden; Harmonet; Meliane; Minulet; Mirelle; Tri-Femoden; Tri-Minulet†; ***Fr.:*** Avadene; Harmonet; Meliane; Melodia; Minesse; Minulet; Moneva; Phaeva; Successia†; Tri-Minulet; ***Ger.:*** Femovan; Minulet; ***Gr.:*** Gynera; Harmonette; Meliane; Minulet; Tri-Minulet; Trigynera; ***Hong Kong:*** Gynera; Harmonet; Meliane; Minulet†; ***Hung.:*** Femoden; Harmonet; Lindynette; Meliane; Milligest; Minesse; Minulet; Tri-Minulet†; Triodena; ***Indon.:*** Gynera; ***Irl.:*** Femodene†; Minulet; Tri-Minulet; Triodene†; ***Israel:*** Gynera; Harmonet; Meliane; Minesse; Minulet; ***Ital.:*** Arianna; Fedra; Ginoden; Harmonet; Milvane; Minesse; Minulet; Tri-Minulet; ***Malaysia:*** Gynera; Lindynette; Meliane; Minulet; ***Mex.:*** Avaden; Ginelea; Gynovin; Minesse; Minulet; Secret 28; ***Neth.:*** Avaden†; Femodeen; Harmonet†; Meliane; Minulet; Tri-Minulet†; Triodeen; ***NZ:*** Femodene; Melodene; Minulet; ***Philipp.:*** Gynera; Meliane; Minulet; ***Pol.:*** Femoden; Harmonet; Logest; Milvane; Minulet; Mirelle; Tri-Minulet; ***Port.:*** Avadene; Effiplen; Estinette; Gynera; Harmonet; Microgeste; Minesse; Minigeste; Minulet; Tri-Gynera; Tri-Minulet; ***Rus.:*** Femoden (Фемоден); Lindynette (Линдинет); Logest (Логест); ***S.Afr.:*** Femodene ED; Harmonet; Melodene; Minesse; Minulette; Mirelle; Tri-Minulet; Triodene; ***Singapore:*** Gynera; Meliane; Minulet; ***Spain:*** Gynovin; Harmonet; Meliane; Melodene 15; Minesse; Minulet; Tri-Minulet; Trigynovin; ***Switz.:*** Gynera; Harmonet; Meloden; Milvane; Minesse; Minulet; Mirelle; Tri-Minulet; ***Thai.:*** Gynera; Meliane; Minulet†; ***Turk.:*** Ginera; Minulet; ***UK:*** Femodene; Femodette; Katya; Minulet†; Sunya; Tri-Minulet†; Triadene; ***Venez.:*** Avaden; Femiane; Gynera; Harmonet; Minesse; Minulet; Mirelle.

Gestonorone Caproate *(BANM, USAN, rINN)*

Caproato de gestonorona; Caproato de gestronol; Gestonorone, caproate de; Gestonoroni caproas; Gestronol Hexanoate; Hexanoato de gestonorona; Hexanoato de gestronol; NSC-84054; SH-582. 17α-Hydroxy-19-norpregn-4-ene-3,20-dione hexanoate.

Гестонорона Капроат

$C_{26}H_{38}O_4$ = 414.6.

CAS — 1253-28-7.

ATC — G03DA01; L02AB03.

ATC Vet — QG03DA01; QL02AB03.

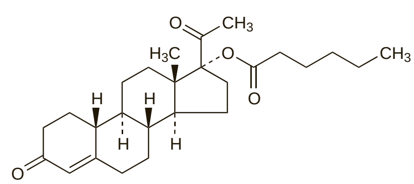

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125).

Local reactions have occurred at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may develop during or immediately after injection but can be avoided by injecting gestonorone very slowly. In males, spermatogenesis is temporarily inhibited.

Interactions

As for progestogens in general (see Progesterone, p.2126).

Uses and Administration

Gestonorone caproate is a long-acting potent progestogen structurally related to progesterone (p.2126). It has been given in an oily solution by intramuscular injection in doses of 200 to 400 mg every 5 to 7 days for the adjunctive treatment of endometrial carcinoma (p.663). It has also been used in the management of benign prostatic hyperplasia (p.2178) in doses of 200 mg weekly, increased to 300 to 400 mg weekly if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Depostat; ***Ger.:*** Depostat†; ***Ital.:*** Depostat†; ***Mex.:*** Primostat; ***Rus.:*** Depostat (Депостат); ***Spain:*** Depostat†; ***Switz.:*** Depostat†.

Gestrinone *(BAN, USAN, rINN)* ⊗

A-46745; Ethylnorgestrienone; Gestrinon; Gestrinona; Gestrinoni; Gestrinonum; R-2323; RU-2323. 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,9,11-trien-20-yn-3-one.

Гестринон

$C_{21}H_{24}O_2$ = 308.4.

CAS — 16320-04-0; 40542-65-2.

ATC — G03XA02.

ATC Vet — QG03XA02.

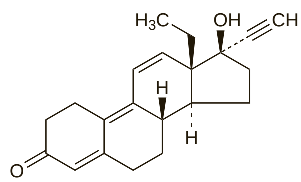

Adverse Effects and Precautions

As for Danazol, p.2090.

Interactions

Antiepileptic drugs and rifampicin may accelerate the metabolism of gestrinone.

Pharmacokinetics

Gestrinone is well absorbed after oral doses with negligible first-pass hepatic metabolism. Peak plasma concentrations occur about 3 hours after a dose. The plasma half-life is about 24 hours. Gestrinone is metabolised in the liver to form conjugated metabolites.

Uses and Administration

Gestrinone is a synthetic steroidal hormone reported to have antiprogestogenic properties, with some androgenic and anti-oestrogenic activity; it inhibits pituitary gonadotrophin release. It is used in the treatment of endometriosis (p.2091) in oral doses of 2.5 mg twice weekly; the first dose is taken on the first day of the menstrual cycle with the second dose taken three days later; thereafter the doses should be taken on the same two days of each week, usually for a period of 6 months. If a dose is missed it should be given as soon as possible and the original dose sequence maintained thereafter; if 2 or more doses are missed gestrinone should be stopped and restarted on the first day of a new cycle after a negative pregnancy test.

Gestrinone has been studied in the management of cyclical mastalgia (p.2092) and uterine fibroids (p.2107).

◊ References.

1. Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. *BMJ* 1987; **294:** 272–4.
2. Brosens IA, *et al.* The morphologic effect of short-term medical therapy of endometriosis. *Am J Obstet Gynecol* 1987; **157:** 1215–21.
3. Coutinho EM, Azadian-Boulanger G. Treatment of endometriosis by vaginal administration of gestrinone. *Fertil Steril* 1988; **49:** 418–22.
4. Hornstein MD, *et al.* A randomized double-blind prospective trial of two doses of gestrinone in the treatment of endometriosis. *Fertil Steril* 1990; **53:** 237–41.
5. Peters F. Multicentre study of gestrinone in cyclical breast pain. *Lancet* 1992; **339:** 205–8.
6. Worthington M, *et al.* A randomized comparative study of the metabolic effects of two regimens of gestrinone in the treatment of endometriosis. *Fertil Steril* 1993; **59:** 522–6.
7. Gestrinone Italian Study Group. Gestrinone versus a gonadotropin-releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomized, double-blind study. *Fertil Steril* 1996; **66:** 911–19.
8. Dawood MY, *et al.* Clinical, endocrine, and metabolic effects of two doses of gestrinone in treatment of pelvic endometriosis. *Am J Obstet Gynecol* 1997; **176:** 387–94.
9. La Marca A, *et al.* Gestrinone in the treatment of uterine leiomyomata: effects on uterine blood supply. *Fertil Steril* 2004; **82:** 1694–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nemestran; ***Austral.:*** Dimetriose; ***Braz.:*** Dimetrose; ***Cz.:*** Nemestran†; ***Ital.:*** Dimetrose; ***Malaysia:*** Dimetriose; ***Mex.:*** Nemestran; ***Neth.:*** Nemestran; ***NZ:*** Dimetriose; ***Port.:*** Dimetriose; ***S.Afr.:*** Tridomose; ***Singapore:*** Dimetriose; ***Spain:*** Nemestran†; ***Switz.:*** Nemestran; ***Thai.:*** Dimetriose; ***UK:*** Dimetriose.

Gonadorelin *(BAN, rINN)* ⊗

Follicle Stimulating Hormone-releasing Factor; GnRH; Gonadoliberin; Gonadoreliini; Gonadorelina; Gonadoréline; Gonadorelinum; Gonadotrophin-releasing Hormone; Hoe-471; LH/FSH-RF; LH/FSH-RH; LH-RF; LH-RH; Luliberin; Luteinising Hormone-releasing Factor. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosylglycyl-L-leucyl-L-arginyl-L-prolylglycinamide.

Гонадорелин

$C_{55}H_{75}N_{17}O_{13}$ = 1182.3.

CAS — 33515-09-2.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

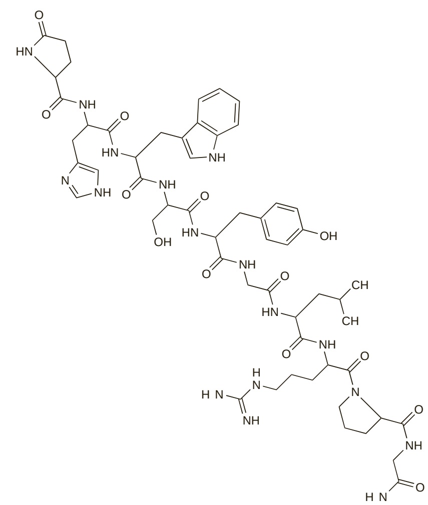

Gonadorelin Acetate *(BANM, USAN, rINNM)* ⊗

Abbott-41070; Acetato de gonadorelina; Gonadolrelin-acetát; Gonadoreliiniasetaatti; Gonadorelinacetat; Gonadorelin-acetát; Gonadoréline, acétate de; Gonadorelini acetas; Gonadorelino acetatas.

Гонадорелина Ацетат

$C_{55}H_{75}N_{17}O_{13},xC_2H_4O_2,yH_2O$.

CAS — 34973-08-5 (anhydrous gonadorelin diacetate); 52699-48-6 (gonadorelin diacetate tetrahydrate).

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US* for veterinary use only.

USP 31 (Gonadorelin Acetate). A white to slightly yellowish powder. Soluble in water; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of not more than 8°.

Ph. Eur. 6.2 (Gonadorelin Acetate). The acetate form of a hypothalamic peptide that stimulates the release of follicle-stimulating hormone and luteinising hormone from the pituitary gland. It is obtained by chemical synthesis. A white or slightly yellowish powder; soluble in water and in 1% v/v glacial acetic acid; sparingly soluble in methyl alcohol. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Gonadorelin Hydrochloride *(BANM, USAN, rINNM)* ⊗

AY-24031; Gonadoréline, Chlorhydrate de; Gonadorelini Hydrochloridum; Hidrocloruro de gonadorelina.

Гонадорелина Гидрохлорид

$C_{55}H_{75}N_{17}O_{13},2HCl$ = 1255.2.

CAS — 51952-41-1.

ATC — H01CA01; V04CM01.

ATC Vet — QH01CA01; QV04CM01.

Pharmacopoeias. In *US.*

USP 31 (Gonadorelin Hydrochloride). A synthetic polypeptide hormone having the property of stimulating the release of the luteinising hormone from the hypothalamus. It is extremely hygroscopic. Protect from exposure to moisture and store in airtight well-sealed containers, in a desiccator.

Adverse Effects

Gonadorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with gonadorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction can occur, and breast swelling and tenderness have been reported infrequently with gonadorelin analogues. Long-term treatment can also cause a loss of bone mineral density in men. Other adverse effects reportedly associated with gonadorelin analogue therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, changes in scalp and body hair, alterations in liver function tests and blood lipids, and decreased glucose tolerance. Arthralgia and paraesthesias have been reported. Ovarian hyperstimulation (as seen with chorionic gonadotrophin, p.2085), although rare, has occurred in women given gonadorelin.

Reactions or pain may occur at the site of injection with rash (local or generalised), thrombophlebitis, swelling, or pruritus. Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported.

Other effects may be a consequence of the particular use of gonadorelin or its analogues. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment for cancer of the prostate and prophylactic anti-androgen therapy may be added. Flare may manifest as an increase in bone pain; occasionally there has been spinal cord compression, or a worsening of urinary-tract symptoms with haematuria and urinary obstruction. Acute degeneration of submucous fibroids with severe bleeding has been reported following use of leuprorelin. An initial increase in signs and symptoms has also been reported in women with breast cancer receiving gonadorelin analogues; hypercalcaemia has occurred in those with metastatic disease. In girls being treated for precocious puberty, vaginal bleeding may occur in the first month of treatment because of initial ovarian stimulation followed by treatment-induced oestrogen withdrawal.

Hypersensitivity. Acquired hypersensitivity led to an anaphylactic reaction after an intravenous dose of gonadorelin in a man who had been receiving pulsatile subcutaneous gonadorelin therapy for 10 weeks.[1]

1. Potashnik G, *et al.* Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993; **328:** 815.

Osteoporosis. Long-term use of a gonadorelin analogue results in oestrogen deficiency-associated osteoporosis and various drugs have been investigated for their ability to reduce this effect. Parathyroid hormone has been reported to prevent bone loss in small studies of young women receiving nafarelin.[1,2] 'Add-back' therapy with tibolone[3,4] or oestrogen plus progestogen[5,6] has also had beneficial effects on bone mineral density in women receiving gonadorelin analogues. However, studies have used various combination regimens and it is not possible to determine which is most effective.[6,7] There is less information available about the management of osteoporosis in men receiving gonadorelin analogues as androgen deprivation therapy, but measures have included supplemental calcium and vitamin D, and the use of bisphosphonates.[8] Raloxifene is also under investigation in both women[9] and men.[10]

1. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; **331:** 1618–23.
2. Finkelstein JS, *et al.* Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998; **280:** 1067–73.
3. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
4. Palomba S, *et al.* A clinical trial of the effects of tibolone administered with gonadorelin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
5. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.

6. Sagsveen M, *et al.* Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Surrey ES, the Add-back Consensus Working Group. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.
8. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer* 2003; **97** (suppl): 789–95.
9. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
10. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Pituitary apoplexy. Pituitary apoplexy has been reported after endocrine stimulation testing using gonadorelin. A review[1] of 14 cases found that 2 patients had received gonadorelin alone but most had also received protirelin (thyrotropin-releasing hormone). The onset of initial symptoms was within 2 hours and pituitary tumour haemorrhage was much more common than infarction alone.

1. Matsuura I, *et al.* Infarction followed by hemorrhage in pituitary adenoma due to endocrine stimulation test. *Endocr J* 2001; **48:** 493–8.

Precautions

Gonadorelin or its analogues should not generally be used in patients with pituitary adenoma as haemorrhagic infarction (pituitary apoplexy) has sometimes occurred. It has also been recommended that patients with weight-related amenorrhoea should not receive these drugs until their weight is corrected. Although at least one manufacturer recommends that gonadorelin should not be used in women with polycystic ovary disease or with endometriotic cysts, gonadorelin and its analogues have been used for ovulation induction in polycystic disease and produced improvement in uterine fibroids; gonadorelin analogues have also been used with benefit in endometriosis. Gonadorelin analogues may increase cervical resistance, making it difficult to dilate the cervix for intra-uterine surgical procedures. Gonadorelin or its analogues should be stopped if the patient becomes pregnant. Contraceptive measures should be taken to protect against unwanted ovulation. Men at risk from tumour flare should be carefully monitored in the first month of therapy.

Interactions

Drugs affecting pituitary secretion of gonadotrophins may alter the response to gonadorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

Pharmacokinetics

Gonadorelin is poorly absorbed from the gastrointestinal tract. It has a terminal plasma half-life of only 10 to 40 minutes after intravenous injection. It is hydrolysed in the plasma and excreted in the urine as inactive metabolites.

Gonadorelin analogues are absorbed after oral, intramuscular, intranasal, or rectal doses and have a longer half-life.

Uses and Administration

Gonadorelin is a synthetic form of hypothalamic gonadotrophin-releasing hormone. It stimulates the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. The secretion of endogenous gonadotrophin-releasing hormone is pulsatile and is controlled by several factors including circulating sex hormones. Gonadotrophic hormones (gonadotrophins), released from the pituitary gland in response to gonadorelin, stimulate secretion of sex hormones from the gonads. A single dose of gonadorelin or one of its analogues has the effect of increasing circulating sex hormones; continued use leads to down-regulation of gonadorelin-receptor synthesis in the pituitary and results in a paradoxical reduction in sex-hormone secretion.

Gonadorelin may be given as the base, acetate, or hydrochloride, and the dose may be expressed in terms of any of these.

Gonadorelin is used in the **diagnosis of hypothalamic-pituitary-gonadal dysfunction**. Assessment is usually based on the response to a dose of gonadorelin of 100 micrograms by intravenous or subcutaneous injection. In females, where possible, it should be given early in the follicular stage of the menstrual cycle. In the UK, the *BNFC* includes a single dose of 2.5 micrograms/kg, to a maximum of 100 micrograms, for children from the age of 1 year.

Gonadorelin is also used in the treatment of **amenorrhoea** and **infertility** associated with hypogonadotrophic hypogonadism. Weight-related amenorrhoea should have been corrected by diet. Treatment in such conditions is based on an intermittent pulse pump providing 5 to 20 micrograms over one minute every 90 minutes, either subcutaneously or intravenously, for up to 6 months or until conception.

Gonadorelin or, more usually, its analogues such as buserelin, goserelin, leuprorelin, nafarelin, and triptorelin (which are more potent and have a longer duration of action) are used in cryptorchidism, malignant neoplasms (especially of the prostate), and in delayed and precocious puberty.

Benign prostatic hyperplasia. The gonadorelin analogues have been tried in the management of benign prostatic hyperplasia (p.2178) but are considered unsatisfactory for indefinite use. See also under Leuprorelin Acetate, p.2111, and Nafarelin Acetate, p.2118.

Cryptorchidism. Although surgery remains the treatment with the best success rate, primary hormonal therapy with gonadorelin or an analogue is widely used for cryptorchidism (p.2079). Systematic reviews[1,2] suggest a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[3]

1. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
2. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
3. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (issued March 2008). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Paediatric%20Urology.pdf (accessed 31/03/08)

Delayed and precocious puberty. For mention of the use of gonadorelin or its analogues in delayed and precocious puberty, see p.2079 and p.2081 respectively. Benefit in delayed puberty is most likely in those cases where it is secondary to hypogonadism (see p.2079).

Diagnosis of hypothalamic and pituitary dysfunction. Gonadorelin may be used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction such as in hypogonadism, delayed puberty, and precocious puberty.[1,2]

1. Eckert KL, *et al.* A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996; **97:** 517–19.
2. De Martino MU, *et al.* Dynamic testing in the evaluation of male gonadal function. *J Endocrinol Invest* 2003; **26** (suppl): 107–13.

Disturbed behaviour. Gonadorelin analogues such as leuprorelin (p.2111) or triptorelin (p.2136) may be tried in men with paraphilias.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p.2091), but the need for long-term therapy to prevent recurrence limits their value, because of the risk of osteoporosis. 'Add-back' therapy (hormone replacement) may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms.

Some references to gonadorelin analogues in endometriosis are listed below. For further references, see Buserelin Acetate, p.2083, Goserelin Acetate, p.2108, Leuprorelin Acetate, p.2112, and Nafarelin Acetate, p.2118.

1. Gargiulo AR, Hornstein MD. The role of GnRH agonists plus add-back therapy in the treatment of endometriosis. *Semin Reprod Endocrinol* 1997; **15:** 273–84.
2. Hemmings R. Combined treatment of endometriosis: GnRH agonists and laparoscopic surgery. *J Reprod Med* 1998; **43** (suppl 3): 316–20.
3. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
4. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? *Fertil Steril* 1999; **71:** 420–4.

Fibroids. Uterine fibroids (leiomyomas) are benign tumours of uterine smooth muscle.[1,2] They are found in about 25% of women, most of whom are aged in their 30s or 40s when the condition becomes symptomatic. Fibroids may give rise to menstrual problems, particularly menorrhagia, pelvic discomfort, infertility, and miscarriage. Although small fibroids may not require treatment, the management of symptomatic fibroids has traditionally been surgical. However, because fibroids are oestrogen responsive, gonadorelin analogues have also been tried as medical treatment for their ability to induce a hypogonadotrophic hypogonadal state. These drugs produce a significant reduction in uterine and fibroid volume, and amenorrhoea, but when treatment stops uterine and fibroid volume tend to return to pretreatment values. The hypoestrogenism produced during treatment also causes menopausal symptoms such as hot flushes and vaginal dryness, and bone loss may occur. Giving oestrogens or progestogens, once the uterine fibroid size has significantly reduced, has been tried as 'add-back' therapy to counteract these adverse effects.[3,4] Tibolone has also been reported to reduce bone loss and vasomotor symptoms.[2] Subcutaneous injection of long-acting depot preparations of gonadorelin or its analogues appears to be the preferred method and is considered a valuable pre-operative adjunct to surgery, simplifying the procedure by reducing uterine and fibroid volume and intra-operative blood loss, as well as correcting pre-operative iron-deficiency anaemia.[5,6] However, concern has been expressed that the use of gonadorelin analogues for treating fibroids may complicate the differentiation of benign and malignant growths.[7]

For further references to use of gonadorelin analogues in the treatment of fibroids, see Buserelin Acetate, p.2083, Goserelin Acetate, p.2108, Leuprorelin Acetate, p.2112, Nafarelin Acetate, p.2118, and Triptorelin, p.2136.

Other drugs that are under investigation for fibroids include gonadorelin antagonists such as cetrorelix and ganirelix, and mifepristone. Danazol and gestrinone have also been tried in a small number of patients.[2]

1. Stewart EA. Uterine fibroids. *Lancet* 2001; **357:** 293–8.
2. De Leo V, *et al.* A benefit-risk assessment of medical treatment for uterine leiomyomas. *Drug Safety* 2002; **25:** 759–79.
3. Friedman AJ, *et al.* Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonists: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1990; **163:** 1114–19.
4. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? *Br J Obstet Gynaecol* 1998; **105:** 475–85.
5. Lethaby A, *et al.* Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 15/09/05).
6. Agence Française de Sécurité Sanitaire des Produits de Santé. Les traitements médicamenteux du fibrome utérin - octobre 2004. Available at: http://afssaps.sante.fr/pdf/5/rbp/fibrorec.pdf (accessed 15/09/05)
7. Mesia AF, *et al.* Aborted leiomyosarcoma after treatment with leuprolide acetate. *Obstet Gynecol* 1998; **92:** 664–6.

Growth retardation. The use of a gonadorelin analogue to delay precocious puberty may improve the final height of children with the disorder. However, the use of a gonadorelin analogue with growth hormone in short but otherwise normal children is controversial—see under Triptorelin, p.2136.

Hirsutism. For reference to the use of gonadorelin analogues such as leuprorelin in the treatment of hirsutism, see p.2112.

Infertility. Gonadorelin and its analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both women and men (p.2080). Some further references are given below. See also under Buserelin Acetate, p.2083, Leuprorelin Acetate, p.2112, and Nafarelin Acetate, p.2118.

For mention of the use of gonadorelin and its analogues in the management of infertility in polycystic ovary syndrome, see below.

1. Lingle L, Hart LL. Gonadotropin-releasing hormone in infertility. *DICP Ann Pharmacother* 1989; **23:** 246–8.
2. Thomas AK, *et al.* Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: correlation with body weight and other parameters. *Fertil Steril* 1989; **51:** 786–90.
3. Homburg R, *et al.* One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. *BMJ* 1989; **298:** 809–12.
4. Kovacs GT, *et al.* Induction of ovulation with gonadotrophin-releasing hormone—life-table analysis of 50 courses of treatment. *Med J Aust* 1989; **151:** 21–6.
5. Santoro N. Efficacy and safety of intravenous pulsatile gonadotropin-releasing hormone: Lutrepulse for injection. *Am J Obstet Gynecol* 1990; **163:** 1759–64.
6. Nachtigall LB, *et al.* Adult-onset idiopathic hypogonadotropic hypogonadism–a treatable form of male infertility. *N Engl J Med* 1997; **336:** 410–15.

Malignant neoplasms. Gonadorelin analogues are used in the treatment of prostatic cancer (p.671) where they provide an alternative to orchidectomy in the management of advanced disease. They may also be used for ovarian ablation in premenopausal women with breast cancer (p.661). Gonadorelin analogues have been tried in neoplasms of the endometrium (p.663) and ovary, but their use is much less well established.

Analogues used include buserelin (p.2084), goserelin (p.2108), leuprorelin (p.2112), and triptorelin (p.2136).

Mastalgia. Gonadorelin analogues such as goserelin may be effective in severe refractory mastalgia (p.2092).

Polycystic ovary syndrome. Gonadorelin and its analogues have been used in the management of infertility associated with polycystic ovary syndrome (see Infertility, p.2080), even though some product information contra-indicates their use in this syndrome.

Pulsatile gonadorelin has been tried for ovulation induction but rates of ovulation and pregnancy are poor when it is used alone in women with polycystic ovary syndrome. Pretreatment with a gonadorelin analogue for pituitary desensitisation before starting pulsatile gonadorelin has shown some benefit in patients with polycystic ovary syndrome who have high levels of luteinising hormone.[1] However, there is only limited clinical data from small short-term trials and case series on the use of pulsatile gonadorelin in these women.[2]

Gonadorelin analogues may be used for pituitary desensitisation before the use of gonadotrophins for ovulation induction, and there is a suggestion that this strategy may improve pregnancy rates compared with gonadotrophins alone in women with polycystic ovary syndrome.[3] Gonadorelin analogues are used also in ovarian stimulation protocols for assisted reproduction techniques.[1]

Women with polycystic ovary syndrome are at increased risk of ovarian hyperstimulation syndrome and must be carefully monitored throughout the use of ovulation induction regimens.[1]

1. Buckett WM, Tan SL. Use of luteinizing hormone releasing hormone agonists in polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1998; **12:** 593–606.
2. Bayram N, *et al.* Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 15/09/05).
3. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 15/09/05).

Porphyria. For mention of the use of gonadorelin analogues to suppress cyclic premenstrual exacerbations of acute porphyria, see Buserelin, p.2084, Nafarelin, p.2118, and Triptorelin, p.2136.

Premenstrual syndrome. In women in whom other drug treatments for premenstrual syndrome (p.2099) are ineffective, use of a gonadorelin analogue, usually with HRT as 'add-back' therapy to prevent menopausal symptoms, may be considered.[1] Short-term therapy (3 months) has been used to confirm the diagnosis of premenstrual syndrome, or to predict the response to bilateral oophorectomy when this is being considered. Some references to the use of gonadorelin analogues in premenstrual syndrome are given below.[2-7]

1. Wyatt KM, *et al.* The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. *Br J Obstet Gynaecol* 2004; **111:** 585–93.
2. Hussain SY, *et al.* Buserelin in premenstrual syndrome. *Gynecol Endocrinol* 1992; **6:** 57–64.
3. Mezrow G, *et al.* Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril* 1994; **62:** 932–7.
4. Brown CS, *et al.* Efficacy of depot leuprolide in premenstrual syndrome: effect of symptom severity and type in a controlled trial. *Obstet Gynecol* 1994; **84:** 779–86.
5. West CP, Hillier H. Ovarian suppression with the gonadotrophin-releasing hormone agonist goserelin (Zoladex) in management of the premenstrual tension syndrome. *Hum Reprod* 1994; **9:** 1058–63.
6. Leather AT, *et al.* The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. *Gynecol Endocrinol* 1999; **13:** 48–55.
7. Di Carlo C, *et al.* Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Preparations

USP 31: Gonadorelin for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Luteoliberina; ***Austria:*** Kryptocur; Lutrelef; Relefact LH-RH; ***Belg.:*** HRF; ***Braz.:*** Parlib†; ***Canad.:*** Lutrepulse; ***Cz.:*** Relefact LH-RH†; ***Fr.:*** Lutrelef; Stimu-LH; ***Ger.:*** Kryptocur; Lutrelef; Relefact LH-RH; ***Gr.:*** Relefact LH-RH; ***Hong Kong:*** Relisorm L†; ***Hung.:*** Relisorm I†; ***Irl.:*** HRF; ***Israel:*** Lutrelef†; Relefact LH-RH; ***Ital.:*** Kryptocur; Lutrelef; ***Neth.:*** Cryptocur; HRF; Lutrelef; Relefact LH-RH; ***NZ:*** HRF†; ***S.Afr.:*** HRF; ***Spain:*** Luforan†; ***Swed.:*** Lutrelef; ***Switz.:*** Kryptocur; Lutrelef; Relisorm L†; ***UK:*** HRF; ***USA:*** Factrel.

Goserelin *(BAN, USAN, rINN)* ⊗

Gosereliini; Goserelina; Goserelinas; Goséréline; Goserelinum; Goszerelin; ICI-118630. 3-[5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-*O-tert*-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl]carbazamide.

Гозерелин

$C_{59}H_{84}N_{18}O_{14}$ = 1269.4.

CAS — 65807-02-5.

ATC — L02AE03.

ATC Vet — QL02AE03.

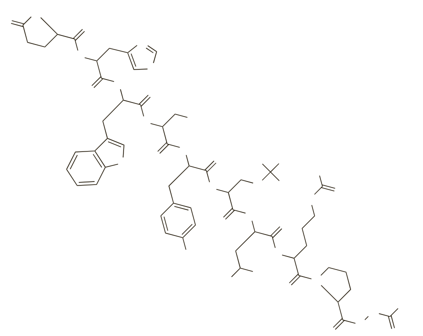

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Goserelin). A nonapeptide analogue of the hypothalamic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white powder. Soluble in water; freely soluble in glacial acetic acid. It dissolves in dilute solutions of mineral acids and alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

Goserelin Acetate *(BANM, rINNM)* ⊗

Acetato de goserelina; Goséréline, Acétate de; Goserelini Acetas; D-Ser (Bu^t)^6 Azgly^{10}-LHRH Acetate.

Гозерелина Ацетат

$C_{59}H_{84}N_{18}O_{14}$, $C_2H_4O_2$ = 1329.5.

CAS — 145781-92-6.

ATC — L02AE03.

ATC Vet — QL02AE03.

Adverse Effects and Precautions

As for Gonadorelin, p.2106. Some women may have vaginal bleeding during initial therapy, which normally resolves spontaneously.

Pituitary apoplexy. Pituitary apoplexy (a clinical syndrome caused by haemorrhage and infarction of a pituitary adenoma) occurred in a few elderly patients with a symptomless pituitary adenoma who were given goserelin for advanced prostate cancer.[1,2] Symptoms included headache, vomiting, visual disturbances, gradual impairment of consciousness, intermittent fever, and progressive hyponatraemia. Symptoms were treated with corticosteroid replacement therapy.

1. Ando S, *et al.* Pituitary apoplexy after goserelin. *Lancet* 1995; **345:** 458.
2. Eaton HJ, *et al.* Rapid onset of pituitary apoplexy after goserelin implant for prostate cancer: need for heightened awareness. *Intern Med J* 2001; **31:** 313–14.

Pharmacokinetics

Goserelin is almost completely absorbed after subcutaneous injection, and has a serum elimination half-life of 2 to 4 hours, which may be increased in renal impairment. More than 90% of a dose is excreted in urine, as unchanged drug and metabolites.

◊ Reviews.

1. Cockshott ID. Clinical pharmacokinetics of goserelin. *Clin Pharmacokinet* 2000; **39:** 27–48.

Uses and Administration

Goserelin is an analogue of gonadorelin (p.2107) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in breast cancer in pre- and peri-menopausal women, and in the management of endometriosis and uterine fibroids. It is also given before surgery for endometrial reduction and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility. Goserelin is usually given as the acetate but doses are expressed in terms of the base; 10.5 mg of goserelin acetate is equivalent to about 10 mg of goserelin.

Goserelin acetate is available as depot preparations; with one such preparation a dose equivalent to 3.6 mg of goserelin injected subcutaneously into the anterior abdominal wall provides effective suppression of oestradiol or testosterone for 28 days. A full response should be achieved by the end of this period and treatment is continued with repeated doses at 28-day intervals; in endometriosis, therapy is given for up to 6 months, while in women with anaemia as a result of uterine fibroids it is continued, with iron supplementation, for up to 3 months before surgery. In men with prostate cancer, preparations supplying the equivalent of 10.8 mg of goserelin, given every 12 weeks, may also be used.

In the treatment of prostatic cancer an anti-androgen such as cyproterone acetate may be given for several days before beginning goserelin therapy and continued for at least 3 weeks, to avoid the risk of a disease flare.

Regimens for oocyte collection for IVF use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins. The equivalent of 3.6 mg of goserelin is given as a subcutaneous depot injection and serum-oestradiol concentrations monitored until they decline to levels similar to those in the early follicular phase, a process which usually takes 7 to 21 days. Once downregulation occurs gonadotrophin (follicle stimulating) therapy is begun until an appropriate stage of follicular development, when it is withdrawn and chorionic gonadotrophin is given to induce ovulation.

Goserelin has also been given in other sex-hormone-related conditions.

◊ Reviews of goserelin.

1. Chrisp P, Goa KL. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical use in sex hormone-related conditions. *Drugs* 1991; **41:** 254–88.
2. Perry CM, Brogden RN. Goserelin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynaecological disorders. *Drugs* 1996; **51:** 319–46.

Endometriosis. Gonadorelin analogues such as goserelin are effective in the management of endometriosis (p.2091), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis. 'Add-back' therapy, with concomitant hormone replacement, may be given in an attempt to reduce bone mineral density loss and vasomotor symptoms in women receiving goserelin.

References.

1. Shaw RW, *et al.* An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. *Fertil Steril* 1992; **58:** 265–72.
2. Schlaff WD. Extending the treatment boundaries: Zoladex and add-back. *Int J Gynaecol Obstet* 1999; **64** (suppl 1): S25–S31.
3. Franke HR, *et al.* Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. *Fertil Steril* 2000; **74:** 534–9.
4. Pierce SJ, *et al.* Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. *Fertil Steril* 2000; **74:** 964–8.

Fibroids. Gonadorelin analogues such as goserelin have been tried as an adjunct or an alternative to surgery in the treatment of uterine fibroids (p.2107) although there has been some concern that this might complicate the diagnosis of malignancy. Some further references are listed below.

1. Lumsden MA, *et al.* Treatment with the gonadotrophin releasing hormone-agonist goserelin before hysterectomy for uterine fibroids. *Br J Obstet Gynaecol* 1994; **101:** 438–42.
2. Benagiano G, *et al.* Zoladex (goserelin acetate) and the anemic patient: results of a multicenter fibroid study. *Fertil Steril* 1996; **66:** 223–9.
3. Parazzini F, *et al.* Goserelin acetate to avoid hysterectomy in pre-menopausal women with fibroids requiring surgery. *Eur J Obstet Gynecol Reprod Biol* 1999; **87:** 31–3.

Malignant neoplasms. Goserelin is effective in the treatment of prostate cancer (p.671). It has produced a response similar to that of orchidectomy (surgical removal of the testes) in patients with metastatic prostate cancer.[1] Goserelin has been combined with an anti-androgen such as flutamide to provide maximum androgen blockade, but this appears to produce modest additional benefits at most. There is some evidence that adjuvant therapy with goserelin may improve survival in patients with localised or locally advanced prostate cancer when combined with radiotherapy or radical prostatectomy, and adjuvant use of goserelin appears to be more beneficial than neoadjuvant use.[2]

Goserelin may also be used as hormonal therapy in premenopausal women with advanced breast cancer (p.661); it seems to be as effective as oophorectomy,[3] and use with tamoxifen is more effective than goserelin alone.[4] It is also used as an alternative or addition to adjuvant chemotherapy in pre- or peri-menopausal women with oestrogen-receptor positive early breast cancer.[5-9]

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77. Correction. *ibid.* 2005; **143:** 764–5.

2. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. *BJU Int* 2004; **93:** 42–6.
3. Taylor CW, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998; **16:** 994–9.
4. Klijn JGM, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; **19:** 343–53.
5. Jakesz R, *et al.* Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; **20:** 4621–7.
6. Jonat W, *et al.* Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; **20:** 4628–35.
7. International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003; **95:** 1833–46.
8. Cheer SM, *et al.* Goserelin: a review of its use in the treatment of early breast cancer in premenopausal and perimenopausal women. *Drugs* 2005; **65:** 2639–55.
9. Baum M, *et al.* ZIPP International Collaborators' Group. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur J Cancer* 2006; **42:** 895–904.

Mastalgia. For reference to the use of goserelin in mastalgia, see under Danazol, p.2092.

Premenstrual syndrome. For reference to the use of goserelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug treatment, see under Gonadorelin, p.2108.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Larmadex; Zoladex; ***Austral.:*** Zoladex; ***Austria:*** Zoladex; ***Belg.:*** Zoladex; ***Braz.:*** Zoladex; ***Canad.:*** Zoladex; ***Chile:*** Vacromil; Zoladex; ***Cz.:*** Zoladex; ***Denm.:*** Zoladex; ***Fin.:*** Zoladex; ***Fr.:*** Zoladex; ***Ger.:*** Zoladex; ***Gr.:*** Zoladex; ***Hong Kong:*** Zoladex; ***Hung.:*** Zoladex; ***Indon.:*** Zoladex; ***Irl.:*** Zoladex; ***Israel:*** Zoladex; ***Ital.:*** Zoladex; ***Malaysia:*** Zoladex; ***Mex.:*** Zoladex; ***Neth.:*** Zoladex; ***Norw.:*** Zoladex; ***NZ:*** Zoladex; ***Philipp.:*** Zoladex; ***Pol.:*** Zoladex; ***Port.:*** Zoladex; ***Rus.:*** Zoladex (Золадекс); ***S.Afr.:*** Zoladex; ***Singapore:*** Zoladex; ***Spain:*** Zoladex; ***Swed.:*** Zoladex; ***Switz.:*** Zoladex; ***Thai.:*** Zoladex; ***Turk.:*** Zoladex; ***UK:*** Zoladex; ***USA:*** Zoladex; ***Venez.:*** Zoladex.

Multi-ingredient: *Austral.:* Zolacos CP.

Hexestrol *(rINN)*

Dihydrodiethylstilboestrol; Dihydrostilboestrol; Hexanoestrol; Hexestrolum; Hexoestrol; NSC-9894; Synestrol; Synoestrol. 4,4′-(1,2-Diethylethylene)diphenol.

Гексэстрол

$C_{18}H_{22}O_2$ = 270.4.

CAS — 5635-50-7 (hexestrol); 84-16-2 (meso-hexestrol).

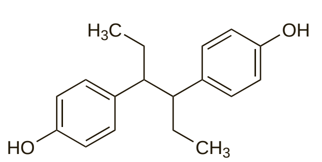

Profile

Hexestrol is a synthetic nonsteroidal oestrogen that is used in the treatment of malignant neoplasms and gynaecological disorders.

Histrelin *(USAN, rINN)* ⊗

Histrelina; Histréline; Histrelinum; ORF-17070; RWJ-17070. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*N*-benzyl-D-histidyl-L-leucyl-L-argininyl-*N*-ethyl-L-prolinamide.

Гистрелин

$C_{66}H_{86}N_{18}O_{12}$ = 1323.5.

CAS — 76712-82-8.

ATC — H01CA03.

ATC Vet — QH01CA03.

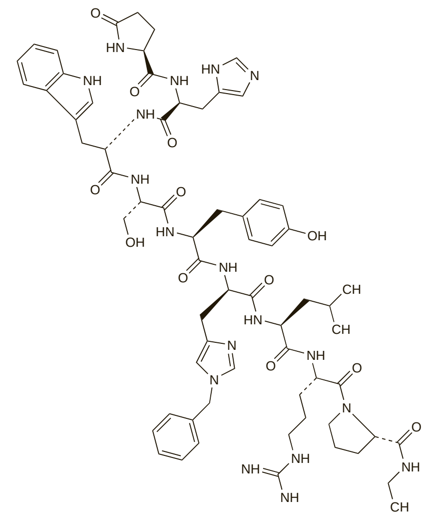

Histrelin Acetate *(rINNM)* ⊗

Acetato de histrelina; Histréline, Acétate d'; Histrelini Acetas.

Гистрелина Ацетат

$C_{66}H_{86}N_{18}O_{12},xC_2H_4O_2,yH_2O$.

CAS — 220810-26-4.

ATC — H01CA03.

ATC Vet — QH01CA03.

Adverse Effects and Precautions

As for Gonadorelin, p.2106.

Uses and Administration

Histrelin is an analogue of gonadorelin (p.2107) with similar properties. A subcutaneous implant containing histrelin acetate 50 mg, and designed to release histrelin 50 to 60 micrograms daily for 12 months, is used in the palliative treatment of advanced prostate cancer (p.671).

Histrelin is used in the treatment of precocious puberty in children (see below). It has also been investigated in disorders related to the menstrual cycle, and in the treatment of acute porphyrias.

◊ References.

1. Anderson KE, *et al.* A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. *Arch Intern Med* 1990; **150:** 1469–74.
2. Mortola JF, *et al.* Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab* 1991; **72:** 252A–F.
3. Cheung AP, Chang RJ. Pituitary responsiveness to gonadotrophin-releasing hormone agonist stimulation: a dose-response comparison of luteinizing hormone/follicle-stimulating hormone secretion in women with polycystic ovary syndrome and normal women. *Hum Reprod* 1995; **10:** 1054–9.
4. Chertin B, *et al.* An implant releasing the gonadotropin hormone-releasing hormone agonist histrelin maintains medical castration for up to 30 months in metastatic prostate cancer. *J Urol (Baltimore)* 2000; **163:** 838–44.
5. Schlegel PN, *et al.* Effective long-term androgen suppression in men with prostate cancer using a hydrogel implant with the GnRH agonist histrelin. *Urology* 2001; **58:** 578–82.
6. Dineen MK, *et al.* An evaluation of the pharmacokinetics and pharmacodynamics of the histrelin implant for the palliative treatment of prostate cancer. *J Clin Pharmacol* 2005; **45:** 1245–9.
7. Schlegel PN. Histrelin Study Group. Efficacy and safety of histrelin subdermal implant in patients with advanced prostate cancer. *J Urol (Baltimore)* 2006; **175:** 1353–8.

Administration in children. For the suppression of gonadal sex hormone production in children with central precocious puberty (p.2081), histrelin acetate has been given by subcutaneous injection in usual doses equivalent to histrelin 10 micrograms/kg daily. Alternatively, a subcutaneous implant containing histrelin acetate 50 mg and designed to release histrelin acetate 65 micrograms daily for 12 months may be used. The implant is not recommended for children under 2 years of age.

References.

1. Barradell LB, McTavish D. Histrelin: a review of its pharmacological properties and therapeutic role in central precocious puberty. *Drugs* 1993; **45:** 570–88.
2. Feuillan PP, *et al.* Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 1999; **84:** 44–9.
3. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
4. Hirsch HJ, *et al.* The histrelin implant: a novel treatment for central precocious puberty. Abstract: *Pediatrics* 2005; **116:** 1534–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/116/6/e798 (accessed 04/12/07)
5. Eugster EA, *et al.* Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab* 2007; **92:** 1697–1704.

Preparations

Proprietary Preparations (details are given in Part 3)

Malaysia: Vantas; ***USA:*** Supprelin; Vantas.

Human Menopausal Gonadotrophins *(BAN)* ⊗

Gonadotropina menopáusica humana; HMG; Org-31338; Urogonadotrophin.

ATC — G03GA02.

ATC Vet — QG03GA02.

Description. A purified extract of human postmenopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH); the relative *in-vivo* activity is expressed as a ratio. Human menopausal gonadotrophins with a ratio of FSH:LH of 1:1 are known as menotrophin (see below).

Menotrophin *(BAN)* ⊗

Menotropiini; Menotropin; Menotropina; Menotropins *(USAN)*; Menotropinum.

CAS — 9002-68-0.

Pharmacopoeias. In *Br., Chin., Jpn,* and *US.*

BP 2008 (Menotrophin). A dry preparation containing glycoprotein gonadotrophins possessing follicle-stimulating and luteinising activities. It contains not less than 40 units of follicle-stimulating hormone activity per mg. The ratio of units of luteinising hormone activity to units of follicle-stimulating hormone activity is about 1. The preparation is exclusively or predominantly of pituitary origin and obtained from the urine of postmenopausal women but, when necessary, chorionic gonadotrophin obtained from the urine of pregnant women may be added to achieve the above ratio. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers. Protect from light.

USP 31 (Menotropins). An extract of human postmenopausal urine containing both follicle-stimulating hormone and luteinising hormone. It has a potency of not less than 40 follicle-stimulating hormone units and not less than 40 luteinising hormone units per mg. The ratio of units is about 1. Chorionic Gonadotropin obtained from the urine of pregnant women may be added to achieve this ratio. Not more than 30% of the luteinising hormone activity is contributed by Chorionic Gonadotropin. Store in airtight containers at 2° to 8°.

Adverse Effects

Human menopausal gonadotrophins may cause dose-related ovarian hyperstimulation varying from mild ovarian enlargement and abdominal discomfort to severe hyperstimulation with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported.

Hypersensitivity reactions and local reactions at the injection site may occur. Nausea and vomiting, joint pains and fever have been reported; gynaecomastia, acne, and weight gain have occurred in men.

Carcinogenicity. In a case-control study of 4575 women with primary invasive breast cancer, an evaluation of risk factors found that, overall, the use of infertility drugs was not associated with an increased risk of breast cancer.[1] However, subgroup analysis of individual drugs found that the use of human menopausal gonadotrophins for at least 6 months or 6 treatment cycles was associated with a risk of breast cancer that was 2 to 3 times greater than for women who had never received any fertility treatment. The authors of this study noted that these results were based on small numbers and that other studies had failed to show an association between fertility treatment and breast cancer.

1. Burkman RT, *et al.* Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; **79:** 844–51.

Effects on the ovary. Ovarian hyperstimulation syndrome after use of human menopausal gonadotrophins in 4 women progressed to acute adnexal torsion.[1] Deep-vein thrombosis has also been a rare complication of ovarian hyperstimulation syndrome associated with the use of human menopausal gonadotrophins plus chorionic gonadotrophin.[2,3] In another case in which thrombosis followed the use of human menopausal gonadotrophins alone, hereditary activated protein C resistance and smoking may have been contributing factors.[4]

1. Kemmann E, *et al.* Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol* 1990; **76:** 403–6.
2. Kaaja R, *et al.* Severe ovarian hyperstimulation syndrome and deep venous thrombosis. *Lancet* 1989; **ii:** 1043.
3. Sobande AA, *et al.* Ovarian hyperstimulation syndrome and deep vein thrombosis. *Saudi Med J* 2000; **21:** 783–4.
4. Ludwig M, *et al.* Deep vein thrombosis during administration of HMG for ovarian stimulation. *Arch Gynecol Obstet* 2000; **263:** 139–41.

Precautions

Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who experience ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk.

There is a risk of multiple births.

Interactions

In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Uses and Administration

Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity (see p.2104) and luteinising hormone (LH) activity (see p.2112).

Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are given to induce follicular maturation and are followed by treatment with chorionic gonadotrophin to stimulate ovulation and corpus luteum formation, a topic discussed further on p.2080.

The dosage and schedule of treatment for **female infertility** must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles, or both. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by single doses of chorionic gonadotrophin 5000 to 10 000 units (see p.2085). In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks although in the US the manufacturers recommend that an individual course should not exceed 12 days. This course may be repeated at least twice more if necessary.

An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose.

In IVF and other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later.

In **men with infertility** due to hypogonadotrophic hypogonadism (see Infertility, p.2080), spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Infertility. Systematic reviews have not found evidence of a significant difference in efficacy for human menopausal gonadotrophins compared with urinary-derived gonadotrophins in women with anovulatory infertility[1] (p.2080), or compared with recombinant follicle-stimulating hormone in assisted reproduction cycles.[2] UK guidelines[3] consider that human menopausal gonadotrophins, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy for women with ovulatory disorders, such as polycystic ovary syndrome, and for IVF treatment.

1. Nugent D, *et al.* Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2000 (accessed 16/09/05).
2. Van Wely M, *et al.* Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. National Collaborating Centre for Women's and Children's Health/NICE. Fertility: assessment and treatment for people with fertility problems. February 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 28/07/08)

Preparations

BP 2008: Menotrophin Injection;
USP 31: Menotropins for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: HMG Ferring; Lifecell; Menopur; Pergonal†; ***Austral.:*** Humegon; ***Austria:*** Menopur; ***Belg.:*** Menopur; ***Braz.:*** Menogon†; Menopur†; Merional-HMG†; Pergonal; ***Canad.:*** Humegon†; Pergonal†; Repronex; ***Chile:*** Menopur; Pergonal†; ***Cz.:*** Humegon†; Menogon; Menopur; Merional; ***Denm.:*** Menogon†; Menopur; ***Fin.:*** Menogon†; Menopur; ***Fr.:*** Menopur; ***Ger.:*** Humegon†; Menogon; ***Gr.:*** Altermon; Menogon; Menopur; Merional; Pergogreen†; Pergonal†; ***Hong Kong:*** Menogon; Menopur; Merional; Pergonal; ***Hung.:*** Menogon†; Menopur; Merional; ***India:*** Eventin; Pergonal; Pregnorm; ***Irl.:*** Humegon; Menogon†; Menopur; ***Israel:*** Humegon†; Menogon; Menopur; Pergonal†; ***Ital.:*** Humegon†; Menogon; Meropur; ***Jpn:*** Gonadoryl; ***Malaysia:*** Menopur; ***Mex.:*** Humegon†; Merapur HP; Merional; Pergonal†; ***Neth.:*** Humegon; Menogon; Menopur; Pergonal†; ***Norw.:*** Menopur; ***Pol.:*** Menopur; ***Port.:*** Humegon†; ***Rus.:*** Menogon (Меногон); Menopur (Менопур); Pergonal (Пергонал); ***S.Afr.:*** Humegon†; Pergonal†; ***Singapore:*** Menogon; ***Spain:*** HMG; Menopur; Pergonal†; ***Swed.:*** Menopur; ***Switz.:*** Menogon†; Menopur; Merional; Pergonal†; ***Thai.:*** IVF-M; Menogon; ***Turk.:*** Menogon; Pergonal; ***UK:*** Menogon†; Menopur; Merional; ***USA:*** Humegon; Menopur; Pergonal†; Repronex; ***Venez.:*** Pergonal†.

Hydroxyestrone Diacetate

Hidroxiestrona, diacetato de; 16α-Hydroxyoestrone Diacetate. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.

$C_{22}H_{26}O_5$ = 370.4.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (hydroxyestrone diacetate).

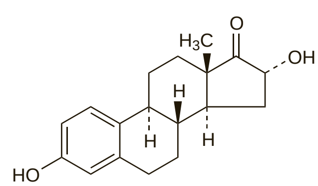

(hydroxyestrone)

Profile

Hydroxyestrone diacetate is an oestrogen (see Estradiol, p.2097). It has been given in vulvovaginal disorders and for female infertility.

Hydroxyprogesterone Caproate *(BANM, rINN)*

17-AHPC; Caproate d'hydroxyprogestirone; Caproato de hidroxiprogesterona; Hidroksiprogesteron Heksanoat; Hidroksiprogesteron Kaproat; Hydroxyprogesterone Hexanoate; Hydroxyprogesteroni Caproas; NSC-17592. 3,20-Dioxopregn-4-en-17α-yl hexanoate; 17α-Hydroxypregn-4-ene-3,20-dione hexanoate.

Гидроксипрогестерона Капроат

$C_{27}H_{40}O_4$ = 428.6.

CAS — 68-96-2 (hydroxyprogesterone); 630-56-8 (hydroxyprogesterone caproate).
ATC — G03DA03.
ATC Vet — QG03DA03.

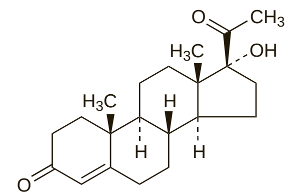

(hydroxyprogesterone)

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Hydroxyprogesterone Caproate). A white or creamy-white, crystalline powder. Odourless or having a slight odour. Insoluble in water; soluble in ether; slightly soluble in benzene. Protect from light. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125).

There may be local reactions at the site of injection. Rarely, coughing, dyspnoea, and circulatory disturbances may occur during or immediately after injection of hydroxyprogesterone caproate but can be avoided by injecting the drug very slowly.

Pregnancy. Abnormalities reported in infants born to mothers who had received hydroxyprogesterone during pregnancy have included tetralogy of Fallot in one infant,[1] genito-urinary abnormalities in 2 infants,[2] and adrenocortical carcinoma in one infant.[3]

1. Heinonen OP, *et al.* Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 1977; **296:** 67–70.
2. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.
3. Mann JR, *et al.* Transplacental carcinogenesis (adrenocortical carcinoma) associated with hydroxyprogesterone hexanoate. *Lancet* 1983; **ii:** 580.

Interactions

As for progestogens in general (see Progesterone, p.2126).

Uses and Administration

Hydroxyprogesterone caproate is a progestogen structurally related to progesterone (p.2125) that has been used for recurrent miscarriage and various menstrual disorders. In recurrent miscarriage associated with proven progesterone deficiency, doses of 250 to 500 mg weekly by intramuscular injection have been given during the first half of pregnancy. Hydroxyprogesterone caproate has also been used to prevent premature labour (see below).

The acetate and the enantate have also been used.

Premature labour. In women who have a history of spontaneous premature delivery (p.2003), there is some evidence to suggest that prophylactic progesterone, may reduce the risk for premature delivery in subsequent pregnancies. A placebo-controlled study[1] has used intramuscular injections of hydroxyprogesterone caproate, starting in weeks 16 to 20 of gestation and continuing until delivery or week 36. The risk of delivery at less than 37 weeks was reduced in women given hydroxyprogesterone, but the rate was still high at 36.3% of 306 women compared with 54.9% of 153 given placebo. Vaginal progesterone has been found to reduce the frequency of uterine contractions and the rate of preterm delivery in women at high risk,[2] and to reduce preterm delivery in women with a short cervix at mid-gestation.[3] The best timing of therapy is unclear, although two retrospective analyses[4,5] found that rates of preterm delivery were similar for two groups of women started on hydroxyprogesterone prophylaxis at either 16 to 20.9 weeks of gestation or 21 to 26.9 weeks. Another retrospective study[6] suggested that early cessation of hydroxyprogesterone was associated with an increased risk of spontaneous recurrent preterm delivery and that treatment should continue until 36 weeks of gestation.

Systematic reviews[7,8] of studies using progestogens (mainly hydroxyprogesterone) have concluded that prophylaxis does reduce the risk of preterm delivery and low birth-weight (less than 2.5 kg). However, further study is required, particularly to identify the optimal timing, route, and dose of treatment, and long-term effects on infant health.[8] Based on limited data, an expert committee in the USA has recommended[9] that the use of progesterone and hydroxyprogesterone should be restricted to women with a history of previous spontaneous delivery at less than 37 weeks. In Canada,[10] a history of preterm labour is considered an indication for intramuscular hydroxyprogesterone caproate 250 mg weekly, or vaginal progesterone 100 mg daily, given from 20 weeks of gestation until the risk of prematurity is low. For women with a short cervix (less than 15 mm at 22 to 26 weeks of gestation), vaginal progesterone 200 mg daily may be used.

There is an increased risk of preterm delivery in twin gestations, but the use of hydroxyprogesterone does not appear to be of benefit.[11]

1. Meis PJ, *et al.* Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003; **348:** 2379–85.
2. da Fonseca EB, *et al.* Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003; **188:** 419–24.
3. Fonseca EB, *et al.* Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; **357:** 462–9.
4. González-Quintero VH, *et al.* Gestational age at initiation of 17α-hydroxyprogesterone caproate (17P) and recurrent preterm delivery. *J Matern Fetal Neonatal Med* 2007; **20:** 249–52.
5. How HY, *et al.* Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? *Am J Obstet Gynecol* 2007; **197:** 260.e1–4.
6. Rebarber A, *et al.* Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol* 2007; **196:** 224.e1–4.
7. Sanchez-Ramos L, *et al.* Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol* 2005; **105:** 273–9.
8. Dodd JM, *et al.* Prenatal administration of progesterone for preventing preterm birth. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 27/06/08).
9. American College of Obstetrics and Gynecologist Committee on Obstetric Practice. Use of progesterone to reduce preterm birth (ACOG committee opinion number 291, issued November 2003). *Int J Gynecol Obstet* 2004; **84:** 93–4.
10. Farine D, *et al.* Society of Obstetricians and Gynaecologists of Canada. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can* 2008; **30:** 67–71. Also available at: http://www.sogc.org/guidelines/documents/guiJOGC202TU0801.pdf (accessed 27/06/08)
11. Rouse DJ, *et al.* A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; **357:** 454–61.

Preparations

USP 31: Hydroxyprogesterone Caproate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Gestageno; Proluton Depot; ***Austria:*** Proluton Depot; ***Chile:*** Primolut Depot†; ***Cz.:*** Neolutin Forte; ***Fr.:*** Progesterone-retard Pharlon; ***Ger.:*** Progesteron-Depot; Proluton Depot; ***Gr.:*** Proluton Depot; ***India:*** Maintane; NT-Natal; Proluton Depot; ***Israel:*** Depolut†; Proluton Depot; ***Ital.:*** Lentogest; Proluton; ***Malaysia:*** Jenaprogon†; Proluton Depot; ***Mex.:*** Caposten; Primolut Depot; ***Neth.:*** Proluton Depot†; ***Philipp.:*** Proluton Depot; ***Pol.:*** Kaprogest; ***Singapore:*** Proluton Depot; ***Thai.:*** Proluton Depot; ***Turk.:*** Proluton Depo; ***USA:*** Hylutin†.

Multi-ingredient: ***Arg.:*** Dos Dias N; Primosiston; ***Braz.:*** Gestadinona; Trinestril; ***Chile:*** Gravidinona†; ***Ger.:*** Gravibinon†; Syngynon†; ***Ital.:*** Gravibinan†; ***Mex.:*** Gravidinona; Primosiston†; ***Switz.:*** Primosiston†; ***Venez.:*** Primosiston†.

Leuprorelin *(BAN, rINN)* ⊗

Leuprolide; Leuproreliini; Leuprorelina; Leuprorelinas; Leuproréline; Leuprorelinum. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

Лейпрорелин

$C_{59}H_{84}N_{16}O_{12}$ = 1209.4.

CAS — 53714-56-0.

ATC — L02AE02.

ATC Vet — QL02AE02.

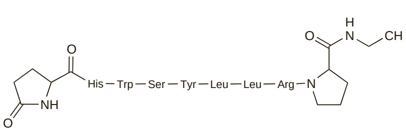

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Leuprorelin). A synthetic nonapeptide analogue of the hypothalamic peptide gonadorelin. It is obtained by chemical synthesis and is available as an acetate. A white or almost white, hygroscopic, powder. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Leuprorelin Acetate *(BANM, rINNM)* ⊗

Abbott-43818; Acetato de leuprorelina; Leuprolide Acetate *(USAN)*; Leuproreliiniasetaatti; Leuprorelinacetat; Leuproréline, Acétate de; Leuprorelini Acetas; Löprorelin Asetat; TAP-144.

Лейпрорелина Ацетат

$C_{59}H_{84}N_{16}O_{12},C_2H_4O_2$ = 1269.5.

CAS — 74381-53-6.

ATC — L02AE02.

ATC Vet — QL02AE02.

Pharmacopoeias. In *US.*

USP 31 (Leuprolide Acetate). Store in airtight containers at a temperature not exceeding 30°.

Adverse Effects and Precautions

As for Gonadorelin, p.2106. Thrombocytopenia and leucopenia have been reported rarely.

Benign intracranial hypertension. Increased intracranial pressure associated with leuprorelin treatment has been reported in a few isolated cases.[1,2]

1. Arber N, *et al.* Pseudotumor cerebri associated with leuprorelin acetate. *Lancet* 1990; **335:** 668.
2. Boot JH. Pseudotumour cerebri as a side effect of leuprorelin acetate. *Ir J Med Sci* 1996; **165:** 60.

Effects on the eyes. Leuprorelin may be associated with blurred vision, usually lasting 1 to 2 hours after injection, but in rare instances longer.[1] Haemorrhage or occlusion of intra-ocular blood vessels, ocular pain, and lid oedema have also been reported but the association is less well established.

1. Fraunfelder FT, Edwards R. Possible ocular adverse effects associated with leuprolide injections. *JAMA* 1995; **273:** 773–4.

Hypersensitivity. An anaphylactic reaction started within 5 minutes of the injection of a leuprorelin depot formulation in a patient with prostate cancer.[1] Recurrent anaphylaxis developed in another patient given a depot injection of leuprorelin acetate for endometriosis, requiring both acute and chronic management.[2]

1. Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Aust* 1994; **161:** 455.
2. Letterie GS, *et al.* Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991; **78:** 943–6.

Local reactions. Local reactions, including erythema, pain, induration, granulomas, and sterile abscess are particularly associated with depot injections of gonadorelin analogues such as leuprorelin and triptorelin;[1-5] they may also occur with subcutaneous daily injection.[1] It has been suggested that the depot vehicle, a lactic acid-glycolic acid copolymer, may be responsible for many, although not all, such reactions.[1-5] Reactions are claimed to be more prevalent in children than in adults:[4] an incidence of about 5% of patients has been suggested. Reactions are apparently idiosyncratic and may occur at any time during therapy, may be intermittent, or may never recur.[4]

1. Manasco PK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 334–5.
2. Neely EK, *et al.* Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123:** 335.
3. Tonini G, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159.
4. Neely EK, *et al.* Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; **126:** 159–60.
5. Yasukawa K, *et al.* Leuprorelin acetate granulomas: case reports and review of the literature. *Br J Dermatol* 2005; **152:** 1045–7.

Pituitary apoplexy. Pituitary apoplexy occurred shortly after the injection of a depot formulation of leuprorelin for the treatment of prostate cancer in 2 patients with occult pituitary adenomas.[1,2] In a woman receiving leuprorelin daily in preparation for oocyte donation, symptoms began after the third dose.[3] Signs and symptoms in these cases included headache, visual disturbances, generalised weakness, nausea and vomiting, and haemorrhagic necrosis of the macroadenoma.

1. Morsi A, *et al.* Pituitary apoplexy after leuprolide administration for carcinoma of the prostate. *Clin Endocrinol (Oxf)* 1996; **44:** 121–4.
2. Reznik Y, *et al.* Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest* 1997; **20:** 566–8.
3. Engel G, *et al.* Pituitary apoplexy after leuprolide injection for ovum donation. *J Adolesc Health* 2003; **32:** 89–93.

Interactions

As for Gonadorelin, p.2107.

Pharmacokinetics

Leuprorelin acetate is not active when given orally but is well absorbed on subcutaneous or intramuscular injection. After a parenteral dose it has an elimination half-life of about 3 hours.

◊ References.

1. Sennello LT, *et al.* Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. *J Pharm Sci* 1986; **75:** 158–60.
2. Periti P, *et al.* Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet* 2002; **41:** 485–504.

Uses and Administration

Leuprorelin is an analogue of gonadorelin (p.2107) with similar properties. Continuous administration is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in central precocious puberty, and in the management of endometriosis and uterine fibroids. It is also given before uterine surgery for endometrial reduction, and may be used in the treatment of breast cancer in premenopausal women. Leuprorelin is used as the acetate.

In the palliative treatment of **advanced prostate cancer**, leuprorelin acetate may be given by subcutaneous injection in a usual single daily dose of 1 mg. It is also given subcutaneously or intramuscularly as depot preparations but the dosage and route of these may differ between countries. In the USA, the dose is 7.5 mg monthly, 22.5 mg every 3 months, or 30 mg every 4 months, given subcutaneously or intramuscularly, depending on the preparation. A depot preparation of 45 mg given subcutaneously once every 6 months is also used. In the UK, leuprorelin acetate may also be used in advanced prostate cancer, as well as medical treatment of locally advanced cancer, as an adjuvant to surgery in locally advanced cancer at high risk of progression, or as an adjuvant to radiotherapy in high-risk localised or locally advanced disease. A dose of 3.75 mg may be given once a month, by subcutaneous or intramuscular injection, or 11.25 mg may be given subcutaneously every 3 months. A nonbiodegradable titanium alloy implant, which is inserted subcutaneously into the inner part of the upper arm, is also available in the USA for advanced disease. It contains 72 mg of leuprorelin acetate and delivers the drug at a controlled rate of 120 micrograms daily. After 12 months it must be removed, but can be replaced by another implant to continue therapy. An anti-androgen such as cyproterone acetate may be given for several days before beginning leuprorelin therapy and continued for about 3 weeks, to avoid the risk of a disease flare.

For the management of **endometriosis** and **uterine fibroids**, leuprorelin acetate 3.75 mg monthly may be given as a single depot injection, intramuscularly or subcutaneously. Alternatively, 11.25 mg may be given as an intramuscular depot every 3 months. Treatment is begun during the first 5 days of the menstrual cycle, and may be continued for up to 6 months for endometriosis, while in women with anaemia due to uterine fibroids it is continued, with iron supplementation, usually for up to 3 months. To prepare for uterine surgery including endometrial ablation or resection, a single 3.75 mg depot injection may be given 5 to 6 weeks before the procedure, or monthly for 3 to 4 months before surgery for uterine fibroids.

In the management of central **precocious puberty** leuprorelin acetate has been given by intramuscular depot injection in a dose of 300 micrograms/kg every 4 weeks, adjusted according to response. Doses of 50 micrograms/kg daily by subcutaneous injection, adjusted according to response, have also been used.

Leuprorelin acetate has also been given in other sex-hormone-related disorders.

◊ General references.

1. Plosker GL, Brogden RN. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs* 1994; **48:** 930–67.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p.2178.

References to the use of leuprorelin.

1. Gabrilove JL, *et al.* Effect of long-acting gonadotropin-releasing hormone analog (leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. *J Clin Endocrinol Metab* 1989; **69:** 629–32.
2. Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic hyperplasia. *J Urol (Baltimore)* 1993; **150:** 359–64.
3. Eri LM, Tveter KJ. Safety, side effects and patient acceptance of the luteinizing hormone releasing hormone agonist leuprolide in treatment of benign prostatic hyperplasia. *J Urol (Baltimore)* 1994; **152:** 448–52.
4. Eri LM, *et al.* Effects on the endocrine system of long-term treatment with the luteinizing hormone-releasing hormone agonist leuprolide in patients with benign prostatic hyperplasia. *Scand J Clin Lab Invest* 1996; **56:** 319–25.

Disturbed behaviour. Leuprorelin has been used in the treatment of men with paraphilias (p.954). Case series have reported reductions in abnormal sexual thoughts and behaviours.[1-3]

1. Briken P, *et al.* Treatment of paraphilia with luteinizing hormone-releasing hormone agonists. *J Sex Marital Ther* 2001; **27:** 45–55.

2. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. *Arch Sex Behav* 2001; **30:** 409–22.
3. Saleh FM, *et al.* Treatment of paraphilia in young adults with leuprolide acetate: a preliminary case report series. *J Forensic Sci* 2004; **49:** 1343–8.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p.2091) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' hormone replacement therapy can be used to prevent this.

References to the use of leuprorelin.

1. Hornstein MD, *et al.* Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998; **91:** 16–24.
2. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999; **93:** 51–8.
3. Takeuchi H, *et al.* A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. *J Obstet Gynaecol Res* 2000; **26:** 325–31.
4. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002; **99:** 709–19.
5. Rotondi M, *et al.* Depot leuprorelin acetate versus danazol in the treatment of infertile women with symptomatic endometriosis. *Eur J Gynaecol Oncol* 2002; **23:** 523–6.

Fibroids. Gonadorelin analogues may be of some benefit as an adjunct or alternative to surgery in women with uterine fibroids (p.2107), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of leuprorelin.

1. Friedman AJ, *et al.* Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. *Obstet Gynecol* 1991; **77:** 720–5.
2. Friedman AJ, *et al.* Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. *Hum Reprod* 1994; **9:** 1618–25.
3. Zullo F, *et al.* A prospective randomized study to evaluate leuprolide acetate treatment before laparoscopic myomectomy: efficacy and ultrasonographic predictors. *Am J Obstet Gynecol* 1998; **178:** 108–112.
4. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil Steril* 2000; **74:** 540–6.
5. Jasonni VM, *et al.* Randomized double-blind study evaluating the efficacy on uterine fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate depot treatment before myomectomy. *Acta Obstet Gynecol Scand* 2001; **80:** 956–8.

Hirsutism. The mainstay of drug treatment for hirsutism (p.2089) has been an anti-androgen, usually cyproterone acetate or spironolactone. Although gonadorelin analogues have been used, and are effective, they must be given parenterally or nasally and may produce menopausal effects, notably osteoporosis.

References to the use of leuprorelin.

1. Elkind-Hirsch KE, *et al.* Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. *Fertil Steril* 1995; **63:** 970–8.
2. Azziz R, *et al.* Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J Clin Endocrinol Metab* 1995; **80:** 3406–11.
3. Ciotta L, *et al.* Clinical and hormonal effects of gonadotropin-releasing hormone agonist plus an oral contraceptive in severely hirsute patients with polycystic ovary disease. *Fertil Steril* 1996; **65:** 61–7.
4. Bayhan G, *et al.* A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol* 2000; **27:** 203–6.

Infertility. Gonadorelin analogues are used in the treatment of infertility—see p.2080.

References to the use of leuprorelin.

1. Stone BA, *et al.* Gonadotrophin and estradiol levels during ovarian stimulation in women treated with leuprolide acetate. *Obstet Gynecol* 1989; **73:** 990–5.
2. Sathanandan M, *et al.* Adjuvant leuprolide in normal, abnormal, and poor responders to controlled ovarian hyperstimulation for in vitro fertilization/gamete intrafallopian transfer. *Fertil Steril* 1989; **51:** 998–1006.
3. Filicori M, *et al.* Different gonadotropin and leuprorelin ovulation induction regimens markedly affect follicular fluid hormone levels and folliculogenesis. *Fertil Steril* 1996; **65:** 387–93.
4. Surrey ES, *et al.* Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002; **78:** 699–704.

Malignant neoplasms. Gonadorelin analogues are used as an alternative to orchidectomy in the management of advanced malignant neoplasms of the prostate (p.671). Such therapy is as effective as orchidectomy in prolonging survival;[1] combination of leuprorelin or other gonadorelin analogues with nonsteroidal anti-androgens to produce maximal androgen blockade produces only modest additional benefit.[2] Intermittent maximal androgen blockade is being studied in an attempt to improve results, and leuprorelin is also under investigation as neoadjuvant therapy in localised disease.[3] Leuprorelin is also used for ovarian ablation[4] in premenopausal women with breast cancer (p.661).

There are also isolated reports of endometrial cancer (p.663),[5] and ovarian cancer[6] responding to leuprorelin, but the role of the gonadorelin analogues in these conditions is much less well established.

1. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77.
2. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1491–8.
3. Persad R. Leuprorelin acetate in prostate cancer: a European update. *Int J Clin Pract* 2002; **56:** 389–96.
4. Schmid P, *et al.* Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). *Anticancer Res* 2002; **22:** 2325–32.
5. Noci I, *et al.* Longstanding survival without cancer progression in a patient affected by endometrial carcinoma treated primarily with leuprolide. *Br J Cancer* 2001; **85:** 333–6.
6. Paskeviciute L, *et al.* No rules without exception: long-term complete remission observed in a study using a LH-RH agonist in platinum-refractory ovarian cancer. *Gynecol Oncol* 2002; **86:** 297–301.

Precocious puberty. The gonadorelin analogues have replaced other agents as the drugs of choice for the treatment of central precocious puberty (p.2081).

References to the use of leuprorelin.

1. Lee PA, *et al.* Effects of leuprolide in the treatment of central precocious puberty. *J Pediatr* 1989; **114:** 321–4.
2. Clemons RD, *et al.* Long-term effectiveness of depot gonadotropin-releasing hormone analogue in the treatment of children with central precocious puberty. *Am J Dis Child* 1993; **147:** 653–7.
3. Carel JC, *et al.* Treatment of central precocious puberty with depot leuprorelin. *Eur J Endocrinol* 1995; **132:** 699–704.
4. Carel J-C, *et al.* Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). *J Clin Endocrinol Metab* 2002; **87:** 4111–16.
5. Tanaka T, *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function: the TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab* 2005; **90:** 1371–6.

Premenstrual syndrome. For reference to the use of leuprorelin or other gonadorelin analogues (with HRT to prevent menopausal symptoms) in women unresponsive to other drug therapy, see under Gonadorelin, p.2108.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Eligard; Lectrum; Lupron; Reliser†; ***Austral.:*** Eligard; Lucrin; ***Austria:*** Enantone; Trenantone; ***Belg.:*** Depo-Eligard; Lucrin; ***Braz.:*** Lectrum; Lorelin; Lupron; Reliser; ***Canad.:*** Eligard; Lupron; ***Chile:*** Lupron; ***Cz.:*** Eligard; Lucrin; ***Denm.:*** Enanton†; Procren; ***Fin.:*** Eligard; Enanton; Procren; ***Fr.:*** Eligard; Enantone; Lucrin†; ***Ger.:*** Eligard; Enantone; Enantone-Gyn; Trenantone; Uno-Enantone†; ***Gr.:*** Daronda; Elityran; Leuprol; ***Hong Kong:*** Enantone; Lorelin; Lucrin†; ***Hung.:*** Eligard; Lucrin; ***India:*** Lupride; ***Indon.:*** Endrolin; Lectrum; Tapros; ***Irl.:*** Prostap; ***Israel:*** Lucrin; ***Ital.:*** Enantone; ***Jpn:*** Leuplin; Lupron; ***Malaysia:*** Lucrin; ***Mex.:*** Lectrum; Lorelin; Lucrin; Reliser†; ***Neth.:*** Daronda; Eligard; Lucrin; ***Norw.:*** Enanton; Procren; ***NZ:*** Eligard; Lucrin; ***Philipp.:*** Luprolex; ***Pol.:*** Eligard; Lucrin Depot; ***Port.:*** Eligard; Lucrin; ***Rus.:*** Lucrin (Люкрин); ***S.Afr.:*** Lucrin; ***Singapore:*** Lucrin; ***Spain:*** Eligard; Ginecrin; Procrin; ***Swed.:*** Eligard; Enanton; Procren; ***Switz.:*** Eligard; Lucrin; ***Thai.:*** Enantone; ***Turk.:*** Lucrin; ***UK:*** Prostap; ***USA:*** Eligard; Lupron; Viadur†; ***Venez.:*** Lupron; Reliser†.

Luteinising Hormone ⊗

Human Interstitial-cell-stimulating Hormone; ICSH; LH; Lutropin; Lutropina.

CAS — 9002-67-9; 39341-83-8 (human).

Lutropin Alfa *(BAN, USAN, rINN)* ⊗

Lutropina alfa; Lutropine Alfa; Lutropinum Alfa.

Лутропин Альфа

CAS — 152923-57-4 (lutropin alfa); 56832-30-5 (α subunit); 53664-53-2 (β subunit).
ATC — G03GA07.
ATC Vet — QG03GA07.

Units

35 units of human pituitary luteinising hormone are contained in about 5.8 micrograms (with 1 mg of human albumin, 5 mg of mannitol, and 1 mg of sodium chloride) in one ampoule of the second International Standard (1988).

10 units of the alpha subunit of human pituitary luteinising hormone are contained in about 10 micrograms (with 0.5 mg of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

10 units of the beta subunit of human pituitary luteinising hormone are contained in 10 micrograms (with 0.5 mg of human albumin, 2.5 mg of lactose, and 45 micrograms of sodium chloride) in one ampoule of the first International Standard (1984).

189 units of recombinant human luteinising hormone are contained in about 8.8 micrograms (with 2 mg of human albumin, 10 mg of lactose, and 8.9 mg of sodium chloride) in one ampoule of the first International Standard (2003).

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

Pharmacokinetics

The absolute bioavailability of lutropin alfa after subcutaneous doses is about 60%, and the terminal half-life is at least 10 to 12 hours.

Uses and Administration

Luteinising hormone (LH) is secreted with follicle-stimulating hormone (FSH) (p.2104), another gonadotrophin, by the anterior pituitary lobe.

These gonadotrophins stimulate the normal functioning of the gonads and the secretion of sex hormones in both men and women. In women, follicle-stimulating hormone stimulates the development and maturation of the follicles and ova. As the follicle develops it produces oestrogen in increasing amounts which at mid-cycle stimulates the release of LH. This causes rupture of the follicle with ovulation and converts the follicle into the corpus luteum which secretes progesterone. In men, luteinising hormone stimulates the interstitial cells of the testis to secrete testosterone, which in turn has a direct effect on the seminiferous tubules.

Gonadotrophic substances with luteinising or follicle-stimulating activity or both are used in the treatment of infertility (p.2080), chiefly in females but also in males. Such substances include chorionic gonadotrophin (p.2085) which possesses LH activity and human menopausal gonadotrophins (p.2110) which possess both LH and FSH activity.

Lutropin alfa is a recombinant human luteinising hormone used to induce ovulation in women with severe deficiency of luteinising and follicle-stimulating hormones. It is used at the same time as a preparation with follicle-stimulating activity, usually follitropin alfa. The dosage and schedule of treatment must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles or both. Treatment is usually begun with 75 units of lutropin alfa daily by subcutaneous injection for 7 to 14 days, accompanied by FSH. If there is no response, the FSH dosage may be increased at 7- or 14-day intervals until an adequate but not excessive response is achieved. A treatment cycle of up to 5 weeks may be needed. Treatment is then stopped and followed after 1 or 2 days by a single dose of chorionic gonadotrophin 5000 to 10 000 units to induce ovulation. These patients are generally amenorrhoeic and treatment may be started at any time.

◊ References.

1. The European Recombinant Human LH Study Group. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: a dose-finding study. *J Clin Endocrinol Metab* 1998; **83:** 1507–14.
2. Burgués S, The Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain. *Hum Reprod* 2001; **16:** 2525–32.
3. The European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. *J Clin Endocrinol Metab* 2001; **86:** 2607–18.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Luveris; ***Austral.:*** Luveris; ***Belg.:*** Luveris†; ***Braz.:*** Luveris; ***Chile:*** Luveris†; ***Cz.:*** Luveris; ***Denm.:*** Luveris; ***Fin.:*** Luveris; ***Fr.:*** Luveris; ***Ger.:*** Luveris; ***Gr.:*** Luveris; ***Hong Kong:*** Luveris; ***Hung.:*** Luveris; ***Indon.:*** Luveris; ***Irl.:*** Luveris; ***Israel:*** Luveris; ***Ital.:*** Luveris; ***Malaysia:*** Luveris; ***Mex.:*** Luveris; ***Neth.:*** Luveris; ***Norw.:*** Luveris; ***NZ:*** Luveris; ***Philipp.:*** Luveris; ***Pol.:*** Luveris; ***Port.:*** Luveris; ***Rus.:*** Luveris (Луверис); ***Singapore:*** Luveris; ***Spain:*** Luveris; ***Swed.:*** Luveris; ***Switz.:*** Luveris; ***Thai.:*** Luveris; ***Turk.:*** Luveris; ***UK:*** Luveris; ***USA:*** Luveris; ***Venez.:*** Luveris.

Multi-ingredient: ***Cz.:*** Pergoveris; ***Port.:*** Pergoveris; ***UK:*** Pergoveris.

Lynestrenol *(BAN, USAN, rINN)*

Ethinylestrenol; Etinilestrenol; Linestrenol; Linestrenolis; Lynesztrenol; Linoestrenol; Lynenol; Lynestrénol; Lynestrenoli; Lynestrenolum; Lynoestrenol; NSC-37725. 19-Nor-17α-pregn-4-en-20-yn-17β-ol.

Линэстренол

$C_{20}H_{28}O$ = 284.4.
CAS — 52-76-6.
ATC — G03AC02; G03DC03.
ATC Vet — QG03AC02; QG03DC03.

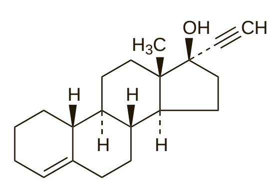

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lynestrenol). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol and in acetone. Protect from light.

Profile

Lynestrenol is a progestogen (see Progesterone, p.2125) structurally related to norethisterone that is used alone or as the progestogenic component of oral contraceptives (see p.2058). Typical oral daily doses for contraception are 500 micrograms when used as a progestogen-only preparation, and 0.75 or 2.5 mg when combined with an oestrogen. When used alone for menstrual disorders, doses of 5 to 10 mg daily are given, often as cyclical regimens.

Porphyria. Lynestrenol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Exluton; ***Austria:*** Orgametril; ***Belg.:*** Orgametril; ***Braz.:*** Exluton; ***Chile:*** Exluton; Linosun; Normalac; ***Cz.:*** Exluton†; Orgametril; ***Denm.:*** Orgametril; ***Fin.:*** Exluton†; Orgametril; ***Fr.:*** Orgametril; ***Ger.:*** Orgametril; ***Gr.:*** Orgametril†; ***Hung.:*** Orgametril; ***Indon.:*** Endometril; Exluton; ***Mex.:*** Exluton; ***Neth.:*** Exluton; Orgametril; ***Norw.:*** Exlutona†; ***Philipp.:*** Daphne; Exluton; ***Pol.:*** Orgametril; ***Port.:*** Exluton†; Orgametril†; ***Rus.:*** Exluton (Эксклютон); ***S.Afr.:*** Exluton†; ***Spain:*** Orgametril; ***Swed.:*** Exlutena; Orgametril; ***Thai.:*** Exluton; ***Turk.:*** Orgametril; ***Venez.:*** Exluton; Normalac.

Multi-ingredient: ***Arg.:*** Lindiol†; ***Braz.:*** Anacyclin†; Ovoresta; ***Chile:*** Anovulatorios; ***Cz.:*** Restovar†; ***Ger.:*** Lyn-ratiopharm-Sequenz; Ovoresta M; ***Neth.:*** Lyndiol†; Ministat; Ovostat†; ***Swed.:*** Restovar; ***Thai.:*** Lyndiol†.

Medrogestone *(BAN, USAN, rINN)*

AY-62022; Medrogeston; Medrogestona; Médrogestone; Medrogestoni; Medrogestonum; Metrogestone; NSC-123018; R-13-615. 6,17α-Dimethylpregna-4,6-diene-3,20-dione.

Медрогестон

$C_{23}H_{32}O_2$ = 340.5.
CAS — 977-79-7.
ATC — G03DB03.
ATC Vet — QG03DB03.

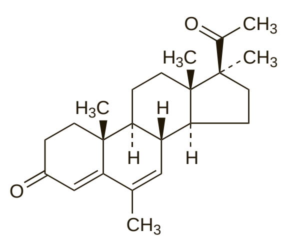

Profile

Medrogestone is a progestogen structurally related to progesterone (p.2125) that is used in the treatment of menstrual disorders, and as the progestogen in menopausal HRT (see p.2071). It is usually given orally in daily doses of 5 to 10 mg, generally in a cyclical regimen. Higher doses were used in the treatment of endometrial carcinoma, prostatic hyperplasia, and breast disorders including carcinoma. It has also been used for threatened or recurrent miscarriage, but such use is not recommended unless there is proven progesterone deficiency.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Colpron; ***Belg.:*** Colpro†; ***Fr.:*** Colprone; ***Ger.:*** Prothil; ***Hong Kong:*** Colprone†; ***Ital.:*** Colprone†; ***S.Afr.:*** Colpro†; ***Spain:*** Colpro†; ***Switz.:*** Colpro†.

Multi-ingredient: ***Austria:*** Premarin compositum†; Premarin Plus; ***Belg.:*** Premplus†; ***Cz.:*** Presomen Compositum†; ***Ger.:*** Presomen Compositum; ***Hong Kong:*** Prempak†; ***Ital.:*** Prempak†; ***Malaysia:*** Prempak†; ***Neth.:*** Premarin Plus†; ***Port.:*** Premarin Plus†; ***S.Afr.:*** Prempak N; ***Switz.:*** Premarin Plus†.

Medroxyprogesterone Acetate

(BANM, rINNM)

Acetato de medroxiprogesterona; Medroksiprogesteron Asetat; Medroksiprogesteroniasetaatti; Medroksiprogesterono acetatas; Medroxyprogesteronu octan; Medroxiprogesteronacetat; Medroxiprogeszteron-acetát; Medroxyprogesteron-acetát; Médroxyprogestérone, acétate de; Medroxyprogesteroni acetas; Methylacetoxyprogesterone; Metipregnone; NSC-26386. 6α-Methyl-3,20-dioxopregn-4-en-17α-yl acetate; 17α-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate.

Медроксипрогестерона Ацетат

$C_{24}H_{34}O_4$ = 386.5.
CAS — 520-85-4 (medroxyprogesterone); 71-58-9 (medroxyprogesterone acetate).
ATC — G03AC06; G03DA02; L02AB02.
ATC Vet — QG03AC06; QG03DA02; QL02AB02.

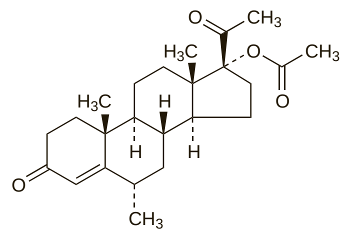

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Medroxyprogesterone Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Medroxyprogesterone Acetate). A white to off-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in dioxan; freely soluble in chloroform; slightly soluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059. Medroxyprogesterone acetate may have glucocorticoid effects when given long term at high doses.

Breast feeding. Medroxyprogesterone is reported to be distributed into breast milk when given as a depot progestogen-only contraceptive.[1] No adverse effects have been seen in breast-fed infants of mothers given medroxyprogesterone, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding. Progestogen-only parenteral contraceptives should not be used until 6 weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p.2066).

1. Schwallie PC. The effect of depot-medroxyprogesterone acetate on the fetus and nursing infant: a review. *Contraception* 1981; **23:** 375–86.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Carcinogenicity. The risk of various cancers associated with the use of depot medroxyprogesterone acetate as a contraceptive has been evaluated by WHO.[1] Overall, there was no increase in risk of breast cancer, although there is some evidence that current or recent use may be associated with a slight increase in risk (see also p.2059). There was no significant increased risk of cervical cancer (see also p.2060), and a protective effect against endometrial cancer (see p.2060). In contrast to combined oral contraceptives, there was no evidence of a protective effect against ovarian cancer (p.2061).

1. Anonymous. Depot-medroxyprogesterone acetate (DMPA) and cancer: memorandum from a WHO meeting. *Bull WHO* 1993; **71:** 669–76.

Effects on bone density. Use of medroxyprogesterone acetate as a parenteral progestogen-only contraceptive has been associated with reductions in bone density (see under Effects on the Musculoskeletal System, p.2064). This effect has also been reported after oral doses for menstrual disorders,[1] and is thought to be due to medroxyprogesterone-induced oestrogen deficiency.

1. Cundy T, *et al.* Short-term effects of high dose oral medroxyprogesterone acetate on bone density in premenopausal women. *J Clin Endocrinol Metab* 1996; **81:** 1014–17.

Effects on the skin. Acute local skin necrosis has been reported[1] after the intramuscular injection of medroxyprogesterone acetate as a depot contraceptive. A case of pigmented purpura on the lower legs, occurring about 4 months after starting medroxyprogesterone acetate injections, has been described.[2]

1. Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera . *Br J Dermatol* 2000; **143:** 1356–7.
2. Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; **43:** 308–10.

Glucocorticoid effects. There have been reports of Cushing's syndrome induced by medroxyprogesterone acetate in patients receiving long-term therapy with high doses for the treatment of malignant neoplasms[1-5] or paraphilia.[6] Cushingoid symptoms regressed when treatment was stopped. Medroxyprogesterone possesses glucocorticoid activity and there is a risk of adrenal insufficiency during periods of stress or after sudden withdrawal of treatment. Some[4] consider that patients should be monitored for glucose intolerance and adrenal insufficiency during treatment.

1. Siminoski K, *et al.* The Cushing syndrome induced by medroxyprogesterone acetate. *Ann Intern Med* 1989; **111:** 758–60.
2. Donckier JE, *et al.* Cushing syndrome and medroxyprogesterone acetate. *Lancet* 1990; **335:** 1094.
3. Grenfell A, *et al.* Cushing's syndrome and medroxyprogesterone acetate. *Lancet* 1990; **336:** 256.
4. Merrin PK, Alexander WD. Cushing's syndrome induced by medroxyprogesterone. *BMJ* 1990; **301:** 345.
5. Shotliff K, Nussey SS. Medroxyprogesterone acetate induced Cushing's syndrome. *Br J Clin Pharmacol* 1997; **44:** 304.
6. Krueger RB, *et al.* Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse* 2006; **18:** 227–8.

Porphyria. Medroxyprogesterone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients. However, for a reference to the use of medroxyprogesterone acetate with buserelin acetate in the prevention of premenstrual exacerbations of porphyria in 2 women, see p.2084.

Interactions

As for progestogens in general (see Progesterone, p.2126). Aminoglutethimide markedly reduces plasma concentrations of medroxyprogesterone so that an increase in medroxyprogesterone dosage is likely to be required.

Pharmacokinetics

Medroxyprogesterone is absorbed from the gastrointestinal tract. In the blood, it is highly protein bound, principally to albumin. It is metabolised in the liver and excreted mainly as glucuronide conjugates in the urine and faeces. It has a half-life of about 16 to 30 hours after oral doses; the half-life may be as long as 50 days after intramuscular injection. Medroxyprogesterone is reported to be distributed into breast milk.

Uses and Administration

Medroxyprogesterone acetate is a progestogen structurally related to progesterone, with actions and uses similar to those of the progestogens in general (see Progesterone, p.2126). It is given orally or, for prolonged action, as an aqueous suspension by intramuscular or subcutaneous injection, depending on the product.

It is used for the treatment of **menorrhagia** (p.2126) and **secondary amenorrhoea** in oral doses of 2.5 to 10 mg daily for 5 to 10 days starting on the assumed or calculated 16th to 21st day of the menstrual cycle, although treatment may begin on any day in secondary amenorrhoea.

In the treatment of mild to moderate **endometriosis** (p.2091) usual oral doses are 10 mg three times daily for 90 consecutive days, or 50 mg weekly or 100 mg every 2 weeks by intramuscular injection for at least 6 months. An alternative formulation used for the treatment of pain associated with endometriosis is given in a dose of 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

Medroxyprogesterone acetate is also given by injection as a **contraceptive** (see under Hormonal Contraceptives, p.2069). As a progestogen-only contraceptive an intramuscular dose of 150 mg is given every 12 or 13 weeks. A combined contraceptive injection containing medroxyprogesterone acetate 25 mg with estradiol cipionate 5 mg is given monthly as an intramuscular injection. An alternative formulation used as a progestogen-only contraceptive is given as a dose of medroxyprogesterone acetate 104 mg in 0.65 mL by subcutaneous injection once every 12 to 14 weeks.

When used as the progestogen component of **menopausal HRT** (see p.2076), medroxyprogesterone acetate is given orally in a variety of regimens including 1.5, 2.5, or 5 mg daily continuously, 5 or 10 mg daily for 12 to 14 days of a 28-day cycle, and 20 mg daily for 14 days of a 91-day cycle.

Medroxyprogesterone acetate may also be used in the palliative treatment of some hormone-dependent malignant neoplasms. In **breast carcinoma** (see below) oral doses of 0.4 to 1.5 g daily may be given, although doses up to 2 g daily have been used in the past. Intramuscular medroxyprogesterone acetate has been given in initial doses of 500 mg daily for 4 weeks, then in maintenance doses twice weekly. In **endometrial** (below) and **renal carcinoma** (p.667) oral doses have ranged from 200 to 600 mg daily. Initial doses of 0.6 to 1.2 g weekly have been given by intramuscular injection, reducing to a maintenance schedule of as little as 450 mg monthly. In **prostatic carcinoma** (p.671) oral doses have been 100 to 600 mg daily; 500 mg has also been given by intramuscular injection, initially twice weekly for 3 months then once weekly for maintenance.

Cachexia. Medroxyprogesterone may improve appetite and food intake, and prevent loss of body-weight in cachexia (p.2115) associated with severe chronic disorders,[1,2] although information is limited.

1. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996; **14:** 1077–84.
2. Simons JPFHA, *et al.* Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer* 1998; **82:** 553–60.

Contraception. Medroxyprogesterone acetate has an established use as a parenteral progestogen-only contraceptive (p.2070). It has also been developed as the progestogenic component of a combined injectable contraceptive and has been investigated as a component of hormonal contraceptives for men. References.

1. Garza-Flores J, *et al.* Introduction of Cyclofem once-a-month injectable contraceptive in Mexico. *Contraception* 1998; **58:** 7–12.
2. Kaunitz AM, *et al.* Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). *Contraception* 1999; **60:** 179–87.
3. Kaunitz AM. Current concepts regarding use of DMPA. *J Reprod Med* 2002; **47** (suppl): 785–9.
4. Turner L, *et al.* Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab* 2003; **88:** 4659–67.
5. Gu YQ, *et al.* Male hormonal contraception: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week intervals in Chinese men. *J Clin Endocrinol Metab* 2004; **89:** 2254–62.
6. Page ST, *et al.* Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab* 2006; **91:** 4374–80.

Epilepsy. Early findings[1] suggested that medroxyprogesterone acetate might be of value in the management of catamenial epilepsy (p.465). In a later review[2] it was suggested that hormonal manipulation with drugs such as medroxyprogesterone should be reserved for highly selected groups under close supervision.

1. Mattson RH, *et al.* Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology* 1984; **34:** 1255–8.
2. Herkes GK. Drug treatment of catamenial epilepsy. *CNS Drugs* 1995; **3:** 260–6.

Male hypersexuality. The anti-androgenic action of medroxyprogesterone has been used for suppression of libido in the control of men with deviant or disinhibited sexual behaviour[1-8] (see Disturbed Behaviour, p.954). Most have received intramuscular medroxyprogesterone acetate; doses of about 300 mg weekly have been used,[3] but ranged from 100 mg each month to 500 mg each week in one report of 5 cases,[8] and up to 750 mg each week in another case.[6] Oral treatment with 30 mg daily was also successful in 1 case.[5]

1. Kiersch TA. Treatment of sex offenders with Depo-Provera. *Bull Am Acad Psychiatry Law* 1990; **18:** 179–87.
2. Weiner MF, *et al.* Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. *Lancet* 1992; **339:** 1121–2.
3. Kravitz HM, *et al.* Medroxyprogesterone treatment for paraphiliacs. *Bull Am Acad Psychiatry Law* 1995; **23:** 19–33.
4. Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behaviour in traumatic brain injury. *Brain Inj* 1998; **12:** 703–7.
5. Brooks JO, Waikar MV. Inappropriate masturbation and schizophrenia. *J Clin Psychiatry* 2000; **61:** 451.
6. Stewart JT. Optimizing antilibidinal treatment with medroxyprogesterone acetate. *J Am Geriatr Soc* 2005; **53:** 359–60.
7. Maletzky BM, *et al.* The Oregon depo-Provera program: a five-year follow-up. *Sex Abuse* 2006; **18:** 303–16.
8. Light SA, Holroyd S. The use of medroxyprogesterone acetate for the treatment of sexually inappropriate behaviour in patients with dementia. *J Psychiatry Neurosci* 2006; **31:** 132–4.

Malignant neoplasms. *BREAST.* Progestogens are used as second- or third-choice drugs in the hormonal therapy of advanced breast cancer (p.661). Some references to the use of medroxyprogesterone acetate in advanced breast cancer are cited below.[1-8] Comparative studies have shown that patients respond equally well to medroxyprogesterone and either mepitiostane,[1] aminoglutethimide,[2] or oophorectomy.[3]

1. Izuo M, *et al.* A phase III trial of oral high-dose medroxyprogesterone acetate (MPA) versus mepitiostane in advanced postmenopausal breast cancer. *Cancer* 1985; **56:** 2576–9.
2. Canney PA, *et al.* Randomized trial comparing aminoglutethimide with high-dose medroxyprogesterone acetate in therapy for advanced breast carcinoma. *J Natl Cancer Inst* 1988; **80:** 1147–51.
3. Martoni A, *et al.* High-dose medroxyprogesterone acetate versus oophorectomy as first-line therapy of advanced breast cancer in premenopausal patients. *Oncology* 1991; **48:** 1–6.
4. Muss HB, *et al.* Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol* 1994; **12:** 1630–8.
5. Clinton OP, *et al.* A prospective randomized trial to evaluate different oral dose regimens of medroxyprogesterone acetate in women with advanced breast cancer. *Clin Oncol* 1995; **7:** 251–6.
6. Byrne MJ, *et al.* Medroxyprogesterone acetate addition or substitution for tamoxifen in advanced tamoxifen-resistant breast cancer: a phase III randomized trial. *J Clin Oncol* 1997; **15:** 3141–8.
7. Koyama H, *et al.* A randomized controlled comparative study of oral medroxyprogesterone acetate 1,200 and 600 mg in patients with advanced or recurrent breast cancer. *Oncology* 1999; **56:** 283–90.
8. Kloke O, *et al.* Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. *Breast Cancer Res Treat* 1999; **55:** 51–9.

ENDOMETRIUM. Progestogens are used in the treatment of advanced endometrial carcinoma (p.663) but there are doubts about their value in the earlier stages of disease.[1] Medroxyprogesterone acetate was effective in a rare case of low-grade endometrial stromal sarcoma.[2] It has also been used in a few patients as adjuvant therapy after surgery[3] and for the treatment of metastatic disease.[4]

1. Martin-Hirsch PL, *et al.* Progestagens for endometrial cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/06/08).
2. Rand RJ, Lowe JW. Low-grade endometrial stromal sarcoma treated with a progestogen. *Br J Hosp Med* 1990; **43:** 154–6.
3. Amant F, *et al.* Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br J Cancer* 2007; **97:** 1194–9.
4. Pink D, *et al.* Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol* 2006; **101:** 464–9.

Respiratory disorders. Reviews of the use of medroxyprogesterone acetate in obstructive sleep apnoea have concluded that it has a limited role.[1,2]

Progesterone and, more commonly, medroxyprogesterone acetate are used in the treatment of pulmonary lymphangioleiomyomatosis, a rare disease affecting only women.[3-7] Anecdotal evidence suggests some patients improve or stabilise on treatment, possibly those with chylous effusions or chylous ascites.[8] However, a more rapid decline in lung function has also been observed with progestogen therapy in some groups.[5,6]

Medroxyprogesterone acetate was reported to be effective in treating congenital central hypoventilation syndrome in 2 children.[9] It has also been used in adults with central hypoventilation resulting from brainstem stroke[10] and other causes.[11] Medroxyprogesterone has also been investigated for its effects on respiration in chronic obstructive pulmonary disease, sometimes with acetazolamide.[12-14]

1. Millman RP. Medroxyprogesterone and obstructive sleep apnea. *Chest* 1989; **96:** 225–6.
2. Terra SG, Oberg KC. Medroxyprogesterone acetate in the treatment of obstructive sleep apnea. *Ann Pharmacother* 1997; **31:** 776–8.
3. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999; **54:** 254–64.
4. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; **55:** 1052–7.
5. Johnson SR, *et al.* Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; **59:** 800–3.
6. Taveira-DaSilva AM, *et al.* Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; **126:** 1867–74.
7. Schiavina M, *et al.* Efficacy of hormonal manipulation in lymphangioleiomyomatosis: a 20-year-experience in 36 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2007; **24:** 39–50.
8. Taylor JR, *et al.* Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990; **323:** 1254–60.
9. Milerad J, *et al.* Alveolar hypoventilation treated with medroxyprogesterone. *Arch Dis Child* 1985; **60:** 150–5.
10. Smyth A, Riley M. Chronic respiratory failure: an unusual cause and treatment. *Thorax* 2002; **57:** 835–6.
11. Bootsma GP, *et al.* Chronic respiratory failure. *Thorax* 2003; **58:** 281.
12. Wagenaar M, *et al.* Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20:** 1130–7.
13. Wagenaar M, *et al.* Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. *Chest* 2003; **123:** 1450–9.
14. Saaresranta T, *et al.* Medroxyprogesterone improves nocturnal breathing in postmenopausal women with chronic obstructive pulmonary disease. *Respir Res* 2005; **6:** 28.

Sickle-cell disease. The frequency of painful crises has been reduced in women with homozygous sickle-cell disease (p.1044) given intramuscular depot medroxyprogesterone acetate,[1,2] and it is now considered to be a suitable contraceptive for this group (see also Sickle-cell Disease, under Precautions of Hormonal Contraceptives, p.2067).

1. de Ceulaer K, *et al.* Medroxyprogesterone acetate and homozygous sickle-cell disease. *Lancet* 1982; **ii:** 229–31.
2. de Abood M, *et al.* Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. *Contraception* 1997; **56:** 313–16.

Preparations

BP 2008: Medroxyprogesterone Injection; Medroxyprogesterone Tablets; ***USP 31:*** Medroxyprogesterone Acetate Injectable Suspension; Medroxyprogesterone Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cycrin†; Depo-Provera†; Farlutale; Livomedrox; Map An; Medrosterona; Veraplex; ***Austral.:*** Depo-Provera; Depo-Ralovera; Medroxyhexal; Provera; Ralovera; ***Austria:*** Depocon; Farlutal; Prodafem; Provera†; ***Belg.:*** Depo-Provera; Farlutal; Provera; Veraplex; ***Braz.:*** Acemedrox; Acetoflux; Contracep; Cycrin; Depo-Provera; Farlutal; Medroxitest; Medroxon; Progesan†; Provera; Tricilon†; ***Canad.:*** Alti-MPA†; Apo-Medroxy; Depo-Provera; Gen-Medroxy; Novo-Medrone; Provera; ratio-MPA; ***Chile:*** Depo-Prodasone; Farlutal; Farlutes; Prodasone; Provera; Sicrit†; ***Cz.:*** Depo-Provera; Femihexal; Medroplex; Provera; Sayana; ***Denm.:*** Depo-Provera; Perlutex; Provera; ***Fin.:*** Depo-Provera; Farlutal; Gestapuran; Lutopolar†; Mepastat; Provera; ***Fr.:*** Depo-Prodasone; Depo-Provera; Farlutal; Gestoral†; ***Ger.:*** Clinofem; Clinovir; Depo-Clinovir; Farlutal†; G-Farlutal†; MPA; MPA Gyn; MPA-beta; MPA-Noury†; ***Gr.:*** Depo-Provera; Farlutal; Gestoral†; Progevera; Provera; ***Hong Kong:*** Depo-Provera; Farlutal; Provera; ***Hung.:*** Depo-Provera; Provera; ***India:*** Depo-Provera; Meprate; ***Indon.:*** Planibu; Prothyra; Provera; Triclofem; Veraplex; ***Irl.:*** Depo-Provera; Provera; ***Israel:*** Aragest; Depo-Provera; Provera; ***Ital.:*** Depo-Provera; Farlutal; Provera; ***Jpn:*** Hysron; ***Malaysia:*** Condep; Depo-Provera; Farlutal†; Non-Preg; Petogen†; Provera; Veraplex; ***Mex.:*** Ciclotal; Cycrin†; Depo-Provera†; Farlutal†; Megestrin†; Megestron; Provera; ***Neth.:*** Depo-Provera; Farlutal†; Megestron; Provera; ***Norw.:*** Depo-Provera; Farlutal; Perlutex; Provera; ***NZ:*** Depo-Provera; Farlutal†; Provera; ***Philipp.:*** Depo-Provera; Depotrust; Lyndavel; Provera; ***Pol.:*** Depo-Provera; Gestomikron; Provera; ***Port.:*** Depo-Provera; Provera; ***Rus.:*** Ciclotal (Циклотал); Depo-Provera (Депо-провера); Veraplex (Вераплекс); ***S.Afr.:*** Depo-Provera; Petogen; Provera; ***Singapore:*** Depo-Provera; Farlutal†; Provera; ***Spain:*** Depo-Progevera; Farlutal; Progevera; Progevera 250; ***Swed.:*** Depo-Provera; Farlutal†; Gestapuran; Provera; ***Switz.:*** Depo-Provera; Farlutal; Prodafem; ***Thai.:*** Contracep†; Depo-Gestin; Depo-M; Depo-Progesno; Depo-Progesta; Depo-Provera†; Enaf; Farlutal; Manodepo; Medeton; Pheno-M; Provera; ***Turk.:*** Depo-Provera; Farlutal; ***UK:*** Climanor; Depo-Provera; Farlutal†; Provera; ***USA:*** Amen†; Cycrin†; Depo-Provera; Depo-subQ Provera; Provera; ***Venez.:*** Depo-Provera; Farlutal†; Provera.

Multi-ingredient: ***Arg.:*** Dilena†; Farludiol; Farludiol Ciclo; Periofem Ciclico†; Periofem Continuo†; Premelle Ciclico†; Premelle Continuo†; ***Austral.:*** Menoprem†; Premia; Premia Continuous; Premia Low†; Provelle†; ***Austria:*** Femipak; Filena†; Perennia; Sequennia; ***Belg.:*** Diviplus; Diviva; Premelle Cycle†; Premelle†; Trivina†; ***Braz.:*** Cyclofemina; Dilena; Menosedan Ciclo†; Menosedan Fase†; Menosedan MPA†; Premarin MPA†; Premelle; Premelle Ciclo; Prempro Bifasico; Prempro Monofasico; Repogen Ciclo; Repogen Conti; Selecta; ***Canad.:*** Premplus; ***Chile:*** Climatrol Continuo; Climatrol HT; Climatrol HT Continuo; Conpremin Pak; Conpremin Pak Plus; Cyclofem†; Enadiol CC; Enadiol MP; Estranova 30 Simple; Estranova CC; Farlupost; Farlutal Estrogeno†; Kilios; Novafac; Novafac 30; Novafac CC; Novafem; Prempak†; Primaquin MP; Primaquin MP Continuo; Profemina CC†; Profemina MP; ***Cz.:*** Cyclo-Premella†; Divina; Diviseq; Indivina; Premella†; ***Denm.:*** Divina; Divina Plus; Indivina; Klimalet; Klimaxil†; Trevina; ***Fin.:*** Divina; Divitren; Indivina; ***Fr.:*** Divina; Diviseq; Duova; Precyclan; ***Ger.:*** Climopax; Climopax Cyclo; Estrafemol; Gianda; Indivina; Osmil; Procyclo; Sisare; Sisare 28; Vitrena†; ***Gr.:*** Divina; Estopause; Premelle; Premelle Cycle; ***Hong Kong:*** Dilena; Premelle; Premelle Cycle; ***Hung.:*** Cyclo-Premella†; Divina; Divitren†; Indivina; Premella†; ***Indon.:*** Cyclofem; ***Irl.:*** Diviseq†; Indivina; Premique; Premique Cycle; ***Israel:*** Meno-MPA†; Premaril MP†; Premaril Plus MP†; ***Ital.:*** Filena; Premelle Combinato; Premelle S†; Premelle Sequenziale†; ***Malaysia:*** Plentiva Cycle 5†; Plentiva†; Premelle; ***Mex.:*** Cyclofemina; Dilena; Premelle; Xofemina; ***Neth.:*** Divina†; Premelle Cycle†; Premelle†; PremelleLite†; ***Norw.:*** Diviseq†; Indivina; ***NZ:*** Menoprem†; Premia Continuous; Premia†; ***Philipp.:*** Premelle; Premelle Cycle; ***Pol.:*** Divina; Diviseq; Indivina; ***Port.:*** Dilena; Medrivas Antibiotico; Premelle Cycle†; Premelle†; ***Rus.:*** Divina (Дивина); Diviseq (Дивисек); Divitren (Дивитрен); Indivina (Индивина); ***S.Afr.:*** Divina; Premelle; Premelle Cycle; Trivina; ***Singapore:*** Premelle Cycle†; Premelle†; ***Spain:*** Medrivas; Medrivas Antib; Perifem; Premelle; Premelle Ciclico; ***Swed.:*** Divina Plus; Divina†; Indivina; Premelle Sekvens†; Premelle†; Trivina; ***Switz.:*** Cyclo-Premella ST; Diviseq; Indivina; OestroTabs Plus Cyclic†; Premella; Premia†; Triaval; ***Thai.:*** Diviseq; Indivina; Premelle Cycle†; Premelle†; ***Turk.:*** Divina; Premelle; Premelle Cycle; ***UK:*** Indivina; Premique; Premique Cycle; Tridestra; ***USA:*** Lunelle†; Premphase; Prempro; ***Venez.:*** Climatrol HT Ciclico; Climatrol HT Continuo; Premelle Ciclico†; Premelle Continuo; Premelle Plus Continuo†.

Megestrol Acetate *(BANM, USAN, rINNM)*

Acetato de megestrol; BDH-1298; Compound 5071; Megestol Asetat; Mégestrol, acétate de; Megestrolacetat; Megestrol-acetát; Megestroli acetas; Megestroliasetaatti; Megestrolio acetatas; Megesztrol-acetát; NSC-71423; SC-10363. 6-Methyl-3,20-dioxopregna-4,6-dien-17α-yl acetate; 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

Мегестрола Ацетат

$C_{24}H_{32}O_4$ = 384.5.

CAS — 3562-63-8 (megestrol); 595-33-5 (megestrol acetate).

ATC — G03AC05; G03DB02; L02AB01.

ATC Vet — QG03AC05; QG03DB02; QL02AB01.

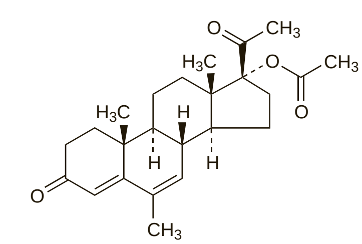

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Megestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone. Protect from light.

USP 31 (Megestrol Acetate). A white to creamy-white, essentially odourless, crystalline powder. Insoluble in water; sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform; slightly soluble in ether and in fixed oils. Protect from light.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). The weight gain that may occur with megestrol acetate appears to be associated with an increased appetite and food intake rather than with fluid retention. Megestrol acetate may have glucocorticoid effects when given long term.

Effects on carbohydrate metabolism. Megestrol therapy has been associated with hyperglycaemia[1-3] or diabetes mellitus[4] in AIDS patients being treated for cachexia. It has been suggested that megestrol produces peripheral insulin resistance due to a glucocorticoid action.[5]

1. Panwalker AP. Hyperglycemia induced by megestrol acetate. *Ann Intern Med* 1992; **116:** 878.
2. Bornemann M, Johnson AC. Endocrine effects of HIV infection. *N Engl J Med* 1993; **328:** 890.
3. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **17:** 46–50.
4. Henry K, *et al.* Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med* 1992; **116:** 53–4.
5. Leinung MC, *et al.* Induction of adrenal suppression by megestrol acetate in patients with AIDS. *Ann Intern Med* 1995; **122:** 843–5.

Effects on the musculoskeletal system. Severe pain of the hands similar to carpal tunnel syndrome occurred in 4 women while taking megestrol acetate and melphalan;[1] megestrol appeared to be responsible.

Osteoporosis and vertebral compression fractures occurred in 2 postmenopausal women taking megestrol for anorexia.[2] In both cases there was evidence of adrenocortical insufficiency that recovered after megestrol therapy was stopped, suggesting that the glucocorticoid effect of megestrol may have contributed to the development of osteoporosis.

1. DiSaia PJ, Morrow CP. Unusual side effect of megestrol acetate. *Am J Obstet Gynecol* 1977; **129:** 460–1.
2. Wermers RA, *et al.* Osteoporosis associated with megestrol acetate. *Mayo Clin Proc* 2004; **79:** 1557–61.

Effects on the respiratory system. Hyperpnoea occurred in 2 patients given megestrol acetate 80 mg three times daily.[1]

1. Fessel WJ. Megestrol acetate and hyperpnea. *Ann Intern Med* 1989; **110:** 1034–5.

Glucocorticoid effects. Megestrol has glucocorticoid-like properties that can cause adrenocortical suppression in a significant number of patients.[1-4] There are also reports of adrenal insufficiency severe enough to require replacement therapy with hydrocortisone.[3,5,6]

1. Naing KK, *et al.* Megestrol acetate therapy and secondary adrenal suppression. *Cancer* 1999; **86:** 1044–9.
2. Ron IG, *et al.* A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy. *Eur J Cancer* 2002; **38:** 1490–4.
3. Orme LM, *et al.* Megestrol acetate in pediatric oncology patients may lead to severe, symptomatic adrenal suppression. *Cancer* 2003; **98:** 397–405.
4. Chidakel AR, *et al.* High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. *J Endocrinol Invest* 2006; **29:** 136–40.
5. Mann M, *et al.* Glucocorticoidlike activity of megestrol: a summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med* 1997; **157:** 1651–6.
6. Stockheim JA, *et al.* Adrenal suppression in children with the human immunodeficiency virus treated with megestrol acetate. *J Pediatr* 1999; **134:** 368–70.

Porphyria. Megestrol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals.*

Interactions

As for progestogens in general (see Progesterone, p.2126).

Pharmacokinetics

Megestrol acetate is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Megestrol acetate is highly protein bound in plasma. It undergoes hepatic metabolism, with 57 to 78% of a dose being excreted in the urine and 8 to 30% in the faeces.

Uses and Administration

Megestrol acetate is a progestogen structurally related to progesterone (p.2125).

It is used for the palliative treatment of some hormone-dependent malignant neoplasms (see below). Oral doses of 40 to 320 mg daily in divided doses may be given in **endometrial carcinoma**, and doses of 40 mg four times daily or 160 mg once daily may be used in **breast cancer**.

Megestrol acetate is also used in the treatment of **anorexia** and **cachexia** (see below) in patients with cancer or AIDS. The usual dose is 400 to 800 mg daily, as tablets or oral suspension. A suspension of megestrol acetate that has an increased bioavailability is also available (*Megace ES; Par Pharmaceutical, USA*) and is given in a dose of 625 mg in 5 mL daily for anorexia, cachexia, or unexplained significant weight loss in patients with AIDS.

Cachexia. In some patients with severe chronic disorders or malignant neoplasms, anorexia (loss of appetite) forms part of a syndrome of metabolic abnormalities and progressive physical wasting known as cachexia. Improved nutrition and dietary counselling are usually insufficient to reverse cachexia, and drug therapy has been tried to stimulate appetite and promote weight gain.

In **cancer-related cachexia**, corticosteroids are frequently used for appetite stimulation in patients with advanced malignancies, although they do not appear to promote weight gain. However, because their effect is usually temporary, and adverse effects occur with prolonged use,[1-3] they tend to be reserved for short-term treatment in patients with a limited life expectancy of weeks.[4] Megestrol has produced weight gain in some randomised controlled studies,[5] although some of this may result from increase in fat mass rather than increase in lean body-mass.[2,3] It is generally used in patients with a longer life expectancy of months.[4] Similar properties have been reported with medroxyprogesterone.[1] A systematic review[6] concluded that only corticosteroids and the progestogens megestrol and medroxyprogesterone had sufficient evidence to support their use in cancer-related anorexia. Anabolic steroids have also been tried, but further evaluation is necessary:[1,7] a comparison of megestrol or dexamethasone with fluoxymesterone found the latter to be less effective than the progestogen or the corticosteroid.[8] Prokinetic drugs such as metoclopramide may be useful in patients whose symptoms are secondary to decreased gastrointestinal motility,[1,2] although relief of nausea may not necessarily lead to improved caloric intake or appetite.[6] It has been suggested that NSAIDs might inhibit the effects of pro-inflammatory cytokines associated with weight loss in cancer patients. The addition of ibuprofen improved the response to megestrol in one small study,[9] but more work is needed. There has also been interest in the effects of eicosapentaenoic acid, which may inhibit muscle protein degradation, but study results have been mixed[3] and a systematic review[10] concluded that there was insufficient evidence to recommend the use of eicosapentaenoic acid. Further investigation is needed to confirm its clinical effects, possibly using higher doses or treating for longer periods than have been so far reported.[6] Thalidomide was found to attenuate weight loss in a study[11] of patients with advanced pancreatic cancer, but quality of life and duration of survival were not significantly improved. Other drugs studied but with little, if any, benefit include cannabinoids, cyproheptadine and hydrazine.[1,2,6] Other compounds under investigation include the endogenous hormones ghrelin and melatonin.[7]

High-dose megestrol[12-14] or oxandrolone[15-17] are effective in **HIV-related cachexia**, a topic discussed under HIV-associated Wasting, p.858.

1. Mantovani G, *et al.* Managing cancer-related anorexia/cachexia. *Drugs* 2001; **61:** 499–514.
2. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin* 2002; **52:** 72–91.
3. Tisdale MJ. Clinical anticachexia treatments. *Nutr Clin Pract* 2006; **21:** 168–74.
4. Jatoi A. Pharmacologic therapy for the cancer anorexia/weight loss syndrome: a data-driven, practical approach. *J Support Oncol* 2006; **4:** 499–502.
5. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 27/06/08).
6. Yavuzsen T, *et al.* Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005; **23:** 8500–11.
7. Bossola M, *et al.* Cancer cachexia: it's time for more clinical trials. *Ann Surg Oncol* 2007; **14:** 276–85.
8. Loprinzi CL, *et al.* Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999; **17:** 3299–3306.
9. McMillan DC, *et al.* A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br J Cancer* 1999; **79:** 495–500.
10. Dewey A, *et al.* Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Gordon JN, *et al.* Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54:** 540–5.
12. Von Roenn JH, *et al.* Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994; **121:** 393–9.
13. Oster MH, *et al.* Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med* 1994; **121:** 400–408.
14. Clarick RH, *et al.* Megestrol acetate treatment of growth failure in children infected with human immunodeficiency virus. *Pediatrics* 1997; **99:** 354–7.
15. Strawford A, *et al.* Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. *JAMA* 1999; **281:** 1282–90.
16. Mwamburi DM, *et al.* Comparing megestrol acetate therapy with oxandrolone therapy for HIV-related weight loss: similar results in 2 months. *Clin Infect Dis* 2004; **38:** 895–902.
17. Grunfeld C, *et al.* Oxandrolone in the treatment of HIV-associated weight loss in men: a randomized, double-blind, placebo-controlled study. *J Acquir Immune Defic Syndr* 2006; **41:** 304–14.

Hot flushes. Megestrol has been used to treat hot flushes in women with breast cancer (to avoid the potentially tumour-stimulating effects of an oestrogen—see Malignant Neoplasms, under Precautions of HRT, p.2075), as well as in men with hot flushes after orchidectomy or anti-androgen therapy for prostate cancer.[1] Therapy, which involved low oral doses of 20 mg twice daily, was associated with a decrease in frequency of flushes of 50% or more in about three-quarters of all patients. About 3 years after the study had finished, these patients were asked about any ongoing use of megestrol and the occurrence of hot flushes.[2] Although symptoms still occurred in many of the patients taking megestrol, they were less common and less severe than in those who had stopped therapy, which included some who had stopped because of no perceived benefit. In patients taking megestrol, most were on doses of 20 mg or less daily. Information collected about adverse effects of megestrol revealed unexpected reports of chills, but these were described as being not as disabling as the hot flushes had been.

1. Loprinzi CL, *et al.* Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994; **331:** 347–52.
2. Quella SK, *et al.* Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer* 1998; **82:** 1784–8.

Malignant neoplasms. Like some other progestogens megestrol acetate is used in endometrial cancer (p.663), and it has been reported to have similar efficacy to anastrozole[1] and tamoxifen[2] in postmenopausal women with advanced breast cancer (p.661). There was no advantage in terms of response or survival in escalating the standard dose of megestrol (160 mg daily) to 800 or 1600 mg daily in a randomised study in women with breast cancer.[3]

1. Buzdar A, *et al.* Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996; **14:** 2000–11.
2. Stuart NSA, *et al.* A randomised phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer. *Eur J Cancer* 1996; **32A:** 1888–92.
3. Abrams J, *et al.* Dose-response trial of megestrol acetate in advanced breast cancer: cancer and Leukemia Group B phase III study 8741. *J Clin Oncol* 1999; **17:** 64–73.

Preparations

BP 2008: Megestrol Tablets;
USP 31: Megestrol Acetate Oral Suspension; Megestrol Acetate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Megace†; Megacorp; Meltonar; Varigestrol; ***Austral.:*** Megace; ***Austria:*** Megace; ***Belg.:*** Megace; ***Braz.:*** Femigestrol; Gynodal; Megestat; ***Canad.:*** Megace; ***Chile:*** Megace; Mestrel†; ***Cz.:*** Megace; Megaplex; ***Denm.:*** Megace; ***Fin.:*** Megace; Megestin†; ***Fr.:*** Megace; ***Ger.:*** Megestat; ***Gr.:*** Megace; ***Hong Kong:*** Megace; ***Hung.:*** Megace; Megesin; ***India:*** Endace; ***Indon.:*** Megace; Megaplex; ***Irl.:*** Megace; ***Israel:*** Megace†; ***Ital.:*** Megace; Megestil; Meprogest†; ***Malaysia:*** Megace; ***Mex.:*** Megace; Mestrel; ***Neth.:*** Megace; ***Norw.:*** Megace; ***NZ:*** Megace; ***Philipp.:*** Megace; ***Pol.:*** Cachexan; Gestar; Megace; Megalia; Megesin; ***Port.:*** Acestrol; Megace; ***Rus.:*** Megaplex (Мегаплекс); ***Singapore:*** Megace; ***Spain:*** Borea; Maygace; Megefren; Megostat†; ***Swed.:*** Megace; ***Switz.:*** Megestat; ***Thai.:*** Megace; Megaplex; Mestrel; ***Turk.:*** Megace; ***UK:*** Megace; ***USA:*** Megace; ***Venez.:*** Megase.

Melengestrol Acetate *(BANM, USAN, rINNM)*

5373; Acetato de melengestrol; BDH-1921; Mélengestrol, Acétate de; Melengestroli Acetas; NSC-70968. 17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate.

Меленгестрола Ацетат

$C_{25}H_{32}O_4$ = 396.5.

CAS — 5633-18-1 (melengestrol); 2919-66-6 (melengestrol acetate).

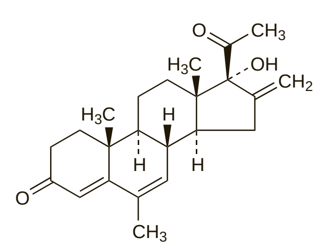

(melengestrol)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Melengestrol Acetate). A white to light yellow, crystalline powder. Insoluble in water; slightly soluble in alcohol; freely soluble in chloroform and in ethyl acetate. Store in airtight containers. Protect from light.

The symbol † denotes a preparation no longer actively marketed

Profile

Melengestrol acetate is a progestogen that is used as an animal feed in beef heifers to improve feed efficiency, increase the rate of body-weight gain, and suppress oestrus.

◊ WHO specifies an acceptable daily intake of melengestrol acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of melengestrol acetate and other steroidal hormones as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: sixty-sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 939* 2006. Also available at: http://libdoc.who.int/publications/2006/9241209399_eng.pdf (accessed 24/06/08)

Mepitiostane *(rINN)* ⊗

Mépitiostane; Mepitiostano; Mepitiostanum; S-10364. 17β-(1-Methoxycyclopentyloxy)-2α,3α-epithio-5α-androstane; Cyclopentanone 2α,3α-epithio-5α-androstan-17β-yl methyl acetal.

Мепитиостан

$C_{25}H_{40}O_2S$ = 404.6.
CAS — 21362-69-6.

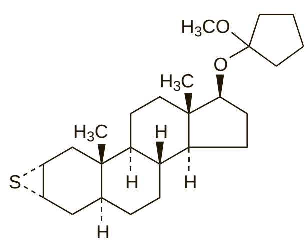

Pharmacopoeias. In *Jpn.*

Profile

Mepitiostane has androgenic and anabolic properties (see Testosterone, p.2129) and is given in usual oral doses of 10 mg twice daily for the management of neoplasms of the breast and anaemia associated with renal failure.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Thioderon.

Mesterolone *(BAN, USAN, rINN)* ⊗

Mesterolon; Mesterolona; Mesterolonas; Mestérolone; Mesteroloni; Mesterolonum; Meszterolon; NSC-75054; SH-723. 17β-Hydroxy-1α-methyl-5α-androstan-3-one.

Местеролон

$C_{20}H_{32}O_2$ = 304.5.
CAS — 1424-00-6.
ATC — G03BB01.
ATC Vet — QG03BB01.

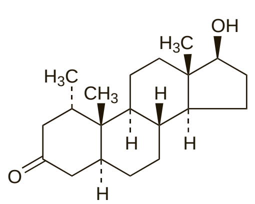

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Mesterolone). A white or yellowish crystalline powder. Practically insoluble in water; sparingly soluble in acetone, in ethyl acetate, and in methyl alcohol.

Adverse Effects and Precautions

As for androgens in general (see Testosterone, p.2130).

Mesterolone is reported not to inhibit gonadotrophin secretion or spermatogenesis.

Pharmacokinetics

Mesterolone is rapidly and almost completely absorbed after an oral dose, producing maximum serum concentrations after about 1.6 hours. It is rapidly metabolised, with an absolute bioavailability of about 3% of the oral dose, and a terminal half-life of 12 to 13 hours. Unlike other androgens (see Testosterone, p.2131), mesterolone is not metabolised to oestrogenic compounds. Mesterolone is bound to serum proteins; about 40% to albumin and 58% to sex-hormone binding globulin. About 77% of the metabolites are excreted in the urine, and about 13% in the faeces.

Uses and Administration

Mesterolone has androgenic properties (see Testosterone, p.2131) but is reported to have less inhibitory effect on intrinsic testicular function than testosterone.

Mesterolone is given orally in the treatment of androgen deficiency or male infertility associated with hypogonadism (p.2079) in initial doses of 75 to 100 mg daily followed by doses of 50 to 75 mg daily for maintenance, in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Proviron; ***Austria:*** Proviron; ***Belg.:*** Proviron; ***Braz.:*** Proviron; ***Chile:*** Proviron; ***Cz.:*** Proviron; ***Denm.:*** Mestoranum†; ***Fin.:*** Proviron†; ***Ger.:*** Proviron†; Vistimon†; ***Gr.:*** Proviron; ***Hong Kong:*** Proviron†; ***Hung.:*** Proviron; ***India:*** Provironum; ***Indon.:*** Androlon; Infelon; Proviron; ***Israel:*** Proviron; ***Ital.:*** Proviron; ***Malaysia:*** Provironum†; Vistimon†; ***Mex.:*** Proviron; ***Neth.:*** Proviron; ***Philipp.:*** Proviron; ***Pol.:*** Proviron; ***Port.:*** Proviron; ***S.Afr.:*** Proviron; ***Singapore:*** Provironum; ***Spain:*** Proviron; ***Thai.:*** Provironum; ***Turk.:*** Proviron; ***UK:*** Proviron; ***Venez.:*** Proviron.

Mestranol *(BAN, USAN, rINN)*

Compound 33355; EE_3ME; Ethinyloestradiol-3-methyl Ether; Mestranoli; Mestranolis; Mestranolum; Mesztranol. 3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

Местранол

$C_{21}H_{26}O_2$ = 310.4.
CAS — 72-33-3.

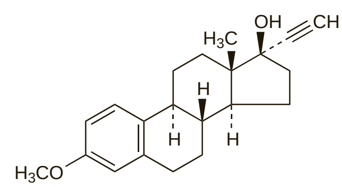

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Mestranol). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Mestranol). A white to creamy-white, odourless, crystalline powder. Insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in chloroform; soluble in dioxan; slightly soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). See also under Hormonal Contraceptives, p.2059.

Porphyria. Mestranol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

See under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Mestranol is readily absorbed from the gastrointestinal tract, and about 70% is rapidly metabolised in the liver to ethinylestradiol (p.2102).

Uses and Administration

Mestranol is a synthetic oestrogen prodrug that is rapidly metabolised to ethinylestradiol; it therefore has actions similar to those of estradiol (see p.2098). It is used as the oestrogen component of combined oral contraceptive preparations (see p.2069) in a usual dose of 50 micrograms daily. The progestogen component is often norethisterone. Mestranol has also been used as the oestrogen component of some preparations for menopausal HRT (see p.2076), although natural oestrogens are often preferred. It has been given in a sequential regimen in a dose of 50 micrograms daily, with a cyclical progestogen.

Preparations

USP 31: Ethynodiol Diacetate and Mestranol Tablets; Norethindrone and Mestranol Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Norinyl-1; ***Braz.:*** Biofim†; Megestran†; ***Canad.:*** Ortho-Novum 1/50†; ***Chile:*** Anovulatorios; ***Cz.:*** Menophase†; ***Ger.:*** Esticia; Gestamestrol N†; Ovosiston†; ***Hong Kong:*** Norinyl-1; ***Mex.:*** Lutoral-E; Norace; Norinyl; Ortho-Novum†; Secuentex-21; ***NZ:*** Norinyl-1; ***S.Afr.:*** Norinyl-1/28; ***Thai.:*** Anamai†; ***UK:*** Norinyl-1; ***USA:*** Necon 1/50; Norinyl 1 + 50; Ortho-Novum 1/50.

Metenolone *(BAN, rINN)* ⊗

Metenolon; Metenolona; Méténolone; Metenoloni; Metenolonum; Methenolone. 17β-Hydroxy-1-methyl-5α-androst-1-en-3-one.

Метенолон

$C_{20}H_{30}O_2$ = 302.5.
CAS — 153-00-4.
ATC — A14AA04.
ATC Vet — QA14AA04.

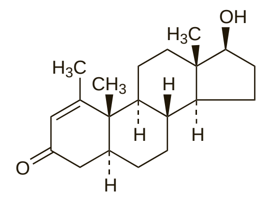

Metenolone Acetate *(BANM, rINNM)* ⊗

Acetato de metenolona; Acetato de metilandrostenolona; Méténolone, Acétate de; Metenoloni Acetas; Methenolone Acetate *(USAN)*; NSC-74226; SH-567; SQ-16496. 17β-Hydroxy-1-methyl-5α-androst-1-en-3-one acetate.

Метенолона Ацетат

$C_{22}H_{32}O_3$ = 344.5.
CAS — 434-05-9.
ATC — A14AA04.
ATC Vet — QA14AA04.

Pharmacopoeias. In *Jpn.*

Metenolone Enantate *(BANM, rINNM)* ⊗

Enantato de metenolona; Enantato de metilandrostenolona; Méténolone, Enantate de; Metenoloni Enantas; Methenolone Enanthate *(USAN)*; Methenolone Oenanthate; NSC-64967; SH-601; SQ-16374. 17β-Hydroxy-1-methyl-5α-androst-1-en-3-one heptanoate.

Метенолона Энантат

$C_{27}H_{42}O_3$ = 414.6.
CAS — 303-42-4.
ATC — A14AA04.
ATC Vet — QA14AA04.

Pharmacopoeias. In *Jpn.*

Profile

Metenolone is an anabolic steroid (see Testosterone, p.2129) that has been used in treating aplastic anaemia, breast cancer, and postmenopausal osteoporosis. Metenolone acetate has been given in oral doses of 100 to 150 mg daily for aplastic anaemia. Intramuscular depot injections of metenolone enantate have been given for osteoporosis in doses of 100 mg every 2 weeks, reducing to once every 3 to 4 weeks after an initial response. The acetate was also used orally in the past for osteoporosis. Intramuscular injections of 100 mg of the enantate every 1 to 2 weeks, or 200 mg every 2 to 3 weeks, have been used in progressive breast cancer.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Primobolan; ***Ger.:*** Primobolan†; ***Gr.:*** Primobolan Depot†; ***Mex.:*** Primobolan; ***S.Afr.:*** Primobolan; ***Spain:*** Primobolan Depot.

Multi-ingredient: ***Ger.:*** NeyPulpin N (Revitorgan-Dilutionen N Nr 10)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†.

Methandienone *(BAN)* ⊗

Metandienone *(pINN)*; Metandienon; Metandienona; Métandiénone; Metandienoni; Metandienonum; Methandrostenolone; NSC-42722. 17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one.

Метандиенон

$C_{20}H_{28}O_2$ = 300.4.
CAS — 72-63-9.
ATC — A14AA03; D11AE01.
ATC Vet — QA14AA03; QD11AE01.

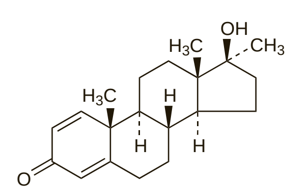

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methandienone:
Iron Brew.

Pharmacopoeias. In *Pol.*

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

As with other 17α-alkylated compounds, methandienone is associated with hepatotoxicity and hepatic function should be monitored during therapy. It should probably be avoided in patients with hepatic impairment, and certainly if this is severe.

Uses and Administration

Methandienone has anabolic and some androgenic properties (see Testosterone, p.2131). It has little progestogenic activity. Methandienone has been given orally as an anabolic drug.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Metanabol; ***Thai.:*** Anabol; Danabol†; Melic.

Methyl-1-testosterone ⊗

17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one; M1T.

Метил-1-тестостерон

$C_{20}H_{30}O_2$ = 302.5.

CAS — 65-04-3.

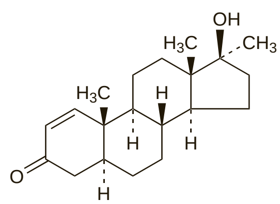

Profile

Methyl-1-testosterone is an anabolic steroid (see Testosterone, p.2129) that appears to be widely abused by body-builders.

◊ References.

1. Health Canada. Health Canada warns consumers not to use supplements containing methyl-1-testosterone due to potential serious health risks (issued February 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_06_e.html (accessed 13/11/07)

Methyltestosterone *(BAN, rINN)* ⊗

Methyltestosteron; Méthyltestostérone; Methyltestosteronum; Metiltestosterona; Metiltestosteronas; Metiltesztoszteron; Metylotestosteron; Metyltestosteron; Metyylitestosteroni; NSC-9701.
17β-Hydroxy-17α-methylandrost-4-en-3-one.

Метилтестостерон

$C_{20}H_{30}O_2$ = 302.5.

CAS — 58-18-4.

ATC — G03BA02.

ATC Vet — QG03BA02; QG03EK01.

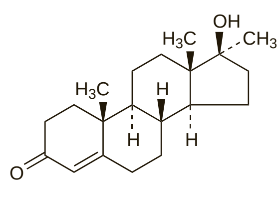

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Methyltestosterone). A white or slightly yellowish-white, crystalline powder. Practically insoluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Methyltestosterone). White or creamy-white, odourless, slightly hygroscopic, crystals or crystalline powder. Practically insoluble in water; soluble in alcohol, in ether, in methyl alcohol, and in other organic solvents; sparingly soluble in vegetable oils. Protect from light.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

As with other 17α-alkylated compounds, methyltestosterone can produce a cholestatic hepatitis with jaundice, and has caused peliosis hepatis and hepatic neoplasms (see below). Methyltestosterone should be used with caution in patients with liver impairment, and is probably best avoided if this is severe. Liver function should be monitored during therapy.

Effects on the liver. Reports of peliosis hepatis[1] and liver damage[2-4] associated with methyltestosterone.

See also under Malignant Neoplasms, below.

1. Bagheri SA, *et al.* Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med* 1974; **81:** 610–18.
2. Westaby D, *et al.* Liver damage from long-term methyltestosterone. *Lancet* 1977; **ii:** 261–3.
3. Lowdell CP, Murray-Lyon IM. Reversal of liver damage due to long term methyltestosterone and safety of non-17 α-alkylated androgens. *BMJ* 1985; **291:** 637.
4. Borhan-Manesh F, Farnum JB. Methyltestosterone-induced cholestasis: the importance of disproportionately low serum alkaline phosphatase level. *Arch Intern Med* 1989; **124:** 2127–9.

Malignant neoplasms. Hepatocellular carcinoma[1-7] and hepatic adenoma[5,8] have been associated with methyltestosterone. A review[9] of reports of liver tumours associated with anabolic androgens found that methyltestosterone was an androgen that had been commonly implicated, and that the majority of tumours were hepatocellular carcinomas.

1. Johnson FL, *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; **ii:** 1273–6.
2. Henderson JT, *et al.* Androgenic-anabolic steroid therapy and hepatocellular carcinoma. *Lancet* 1973; **i:** 934.
3. Farrell GC, *et al.* Androgen-induced hepatoma. *Lancet* 1975; **i:** 430–2.
4. Goodman MA, Laden AMJ. Hepatocellular carcinoma in association with androgen therapy. *Med J Aust* 1977; **1:** 220–1.
5. Boyd PR, Mark GJ. Multiple hepatic adenomas and a hepatocellular carcinoma in a man on oral methyl testosterone for eleven years. *Cancer* 1977; **40:** 1765–70.
6. Cocks JR. Methyltestosterone-induced liver-cell tumours. *Med J Aust* 1981; **2:** 617–19.
7. Gleeson D, *et al.* Androgen associated hepatocellular carcinoma with an aggressive course. *Gut* 1991; **32:** 1084–6.
8. Coombes GB, *et al.* An androgen-associated hepatic adenoma in a trans-sexual. *Br J Surg* 1978; **65:** 869–70.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.

Pregnancy. For reference to virilisation of a female fetus whose mother received methyltestosterone during pregnancy, see p.2131.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p.2131).

Pharmacokinetics

Methyltestosterone is absorbed from the gastrointestinal tract and from the oral mucosa. It undergoes less extensive first-pass hepatic metabolism than testosterone after oral doses, and has a longer half-life.

Uses and Administration

As for androgens and anabolic steroids in general (see Testosterone, p.2131).

Methyltestosterone is effective when given orally; its effect is increased about twofold when given buccally, as this avoids first-pass hepatic metabolism.

Suggested doses of methyltestosterone for androgen replacement therapy in male hypogonadism (p.2079) have been 10 to 50 mg daily orally or 5 to 25 mg daily buccally. Doses of 50 to 200 mg daily orally or 25 to 100 mg daily buccally have been given for metastatic breast carcinoma (p.661) in postmenopausal women. Oral doses of 1.25 to 2.5 mg daily, for 21 days of a 28-day cycle, have been given with oestrogens for the short-term treatment of menopausal vasomotor symptoms (p.2077) unresponsive to oestrogens alone.

Preparations

USP 31: Methyltestosterone Capsules; Methyltestosterone Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Android; Testred; Virilon.

Multi-ingredient: ***Austria:*** Pasuma-Dragees; ***Braz.:*** Gabecon M†; Testonus†; ***Chile:*** Delitan; Feminova-T; ***Fin.:*** Potentol†; ***Hong Kong:*** Wari-Procomil; ***India:*** Mixogen; ***Mex.:*** Bigenol; ***Thai.:*** Hormone Multicap†; Horon†; Men Hormone; Wari-Procomil†; ***UK:*** Prowess; ***USA:*** Covaryx; Estratest; Syntest.

Mibolerone *(BAN, USAN, rINN)* ⊗

Mibolerona; Mibolérone; Miboleronum; NSC-72260; U-10997.
17β-Hydroxy-7α,17-dimethylestr-4-en-3-one.

Миболерон

$C_{20}H_{30}O_2$ = 302.5.

CAS — 3704-09-4.

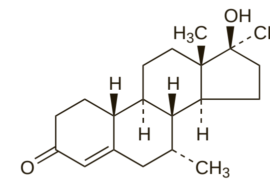

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Mibolerone). A white to off-white powder. Practically insoluble in water; slightly soluble in chloroform, in dioxan, and in dichloromethane.

Profile

Mibolerone is an androgen that is used in veterinary practice as a contraceptive for female dogs. It also has anabolic properties.

Nafarelin Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de nafarelina; Nafareliiniasetaatti; Nafarelin Asetat; Nafarelinacetat; Nafaréline, Acétate de; Nafarelini Acetas; D-Nal(2)^6-LHRH acetate hydrate; RS-94991298. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolylglycinamide acetate hydrate.

Нафарелина Ацетат

$C_{66}H_{83}N_{17}O_{13},xC_2H_4O_2,yH_2O$.

CAS — 76932-56-4 (nafarelin); 86220-42-0 (nafarelin acetate).

ATC — H01CA02.

ATC Vet — QH01CA02.

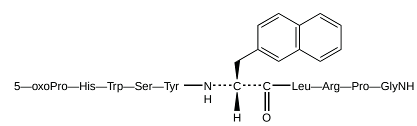

(nafarelin)

Adverse Effects and Precautions

As for Gonadorelin, p.2106.

Effects on electrolytes. Severe hyperkalaemia occurred in a woman receiving nafarelin therapy for uterine fibroids.[1] Despite serum-potassium greater than 10 mmol/litre she had no symptoms and the electrocardiogram was normal. Hyperkalaemia resolved without treatment on stopping nafarelin.

1. Hata T, *et al.* Severe hyperkalaemia with nafarelin. *Lancet* 1996; **347:** 333.

Interactions

As for Gonadorelin, p.2107.

Pharmacokinetics

Nafarelin is rapidly absorbed on intranasal use with peak plasma concentrations achieved within 20 minutes of a dose, although bioavailability is only about 3%. The plasma half-life is about 3 to 4 hours. Nafarelin is metabolised by peptidases in the body; after subcutaneous dosage it is excreted in urine, as metabolites and a small amount of unchanged drug, and in the faeces.

Uses and Administration

Nafarelin acetate is an analogue of gonadorelin (p.2107) with similar properties. It is used in the treatment of endometriosis and central precocious puberty, and as an adjunct to ovulation induction with gonadotrophins in the treatment of infertility.

For **endometriosis** it is given in usual doses equivalent to 200 micrograms of nafarelin twice daily intranasally, doubled after 2 months if amenorrhoea has not occurred. Treatment should begin on days 2 to 4 of the menstrual cycle, and may be continued for up to 6 months.

For central **precocious puberty** the usual dose is the equivalent of nafarelin 800 micrograms intranasally (400 micrograms in each nostril) twice daily. If adequate suppression is not achieved at this dose it may be increased to 600 micrograms three times daily in alternate nostrils (1800 micrograms daily).

Regimens for **oocyte collection for IVF** use gonadorelin analogues for pituitary desensitisation before ovulation induction with gonadotrophins; the equivalent of 400 micrograms of nafarelin is given intranasally twice daily, beginning either in the early follicular phase (day 2) or midluteal phase (day 21) of the menstrual cycle. Therapy should be continued until downregulation is achieved; if this does not occur within 12 weeks therapy should be withdrawn. Once downregulation occurs gonadotrophin treatment is added to nafarelin therapy until an appropriate stage of follicular development, when both are withdrawn and chorionic gonadotrophin is given to induce ovulation.

Nafarelin has also been given in other sex hormone-related conditions.

Benign prostatic hyperplasia. For a discussion of the management of benign prostatic hyperplasia, including mention of the use of gonadorelin analogues and the view that they are unsatisfactory for indefinite therapy, see p.2178.

Prostate size decreased by a mean of 24.2% in 9 men treated for benign prostatic hyperplasia for 6 months with nafarelin acetate 400 micrograms daily subcutaneously.[1] Six months after the end of treatment, prostate size approached that of pretreatment values.

1. Peters CA, Walsh PC. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. *N Engl J Med* 1987; **317:** 599–604.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p.2091), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References to the use of nafarelin.

1. Henzl MR, *et al.* Administration of nasal nafarelin as compared with oral danazol for endometriosis: a multicenter double-blind comparative clinical trial. *N Engl J Med* 1988; **318:** 485–9.
2. Burry KA. Nafarelin in the management of endometriosis: quality of life assessment. *Am J Obstet Gynecol* 1992; **166:** 735–9.
3. Hornstein MD, *et al.* Retreatment with nafarelin for recurrent endometriosis symptoms: efficacy, safety, and bone mineral density. *Fertil Steril* 1997; **67:** 1013–18.
4. Adamson GD, *et al.* Therapeutic efficacy and bone mineral density response during and following a three-month re-treatment of endometriosis with nafarelin (Synarel). *Am J Obstet Gynecol* 1997; **177:** 1413–18.
5. Agarwal SK, *et al.* Nafarelin vs. leuprolide acetate depot for endometriosis: changes in bone mineral density and vasomotor symptoms. *J Reprod Med* 1997; **42:** 413–23.
6. Zhao SZ, *et al.* Impact of nafarelin and leuprolide for endometriosis on quality of life and subjective clinical measures. *J Reprod Med* 1999; **44:** 1000–1006.
7. Bergqvist A, *et al.* A comparative study of the acceptability and effect of goserelin and nafarelin on endometriosis. *Gynecol Endocrinol* 2000; **14:** 425–32.

Fibroids. Gonadorelin analogues have been tried as an adjunct or alternative to surgery in the treatment of uterine fibroids (see p.2107), although there has been some concern that this might complicate the diagnosis of malignancy.

References to the use of nafarelin.

1. Minaguchi H, *et al.* Clinical use of nafarelin in the treatment of leiomyomas: a review of the literature. *J Reprod Med* 2000; **45:** 481–9.

Infertility. Gonadorelin analogues are used in the treatment of infertility (p.2080). As well as being used directly they are employed in regimens to induce superovulation to enable ova collection and IVF. A meta-analysis[1] found that the outcome of IVF treatment using nafarelin was equivalent to that using other gonadorelin analogues, but that nafarelin was associated with a shorter time needed for ovarian stimulation and a reduced gonadotrophin requirement.

1. Wong JM, *et al.* Efficacy of nafarelin in assisted reproductive technology: a meta-analysis. *Hum Reprod Update* 2001; **7:** 92–101.

Porphyria. Nafarelin nasal spray was used to prevent menstrual exacerbations of acute intermittent porphyria (p.1448) in 2 sisters.[1]

1. McNulty SJ, Hardy KJ. Two patients with acute intermittent porphyria treated with nafarelin to prevent menstrual exacerbations. *J R Soc Med* 2000; **93:** 429–30.

Precocious puberty. Nafarelin preserved adult height potential in girls with idiopathic precocious puberty (p.2081) having a poor initial height prognosis.[1] However, reviewers have noted that results from earlier studies into other features of precocious puberty have been equivocal.[2]

1. Kreiter M, *et al.* Preserving adult height potential in girls with idiopathic true precocious puberty. *J Pediatr* 1990; **117:** 364–70.
2. Chrisp P, Goa KL. Nafarelin: a review of its pharmacodynamic and pharmacokinetic properties, and clinical potential in sex hormone-related conditions. *Drugs* 1990; **39:** 523–51.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Synrelin; ***Austral.:*** Synarel; ***Braz.:*** Synarel; ***Canad.:*** Synarel; ***Cz.:*** Synarel; ***Denm.:*** Synarela; ***Fin.:*** Synarela; ***Fr.:*** Synarel; ***Ger.:*** Synarela; ***Hong Kong:*** Synarel†; ***Hung.:*** Synarel†; ***India:*** Nasarel; ***Irl.:*** Synarel; ***Israel:*** Synarel; ***Mex.:*** Synarel†; ***Neth.:*** Synarel; ***Norw.:*** Synarela; ***NZ:*** Synarel†; ***Pol.:*** Synarel; ***S.Afr.:*** Synarel; ***Spain:*** Synarel; ***Swed.:*** Synarela; ***Switz.:*** Synrelina; ***Turk.:*** Synarel; ***UK:*** Synarel; ***USA:*** Synarel.

Nandrolone *(BAN, rINN)* ⊗

Estrenolona; Hidroxiestrenona; Nandrolon; Nandrolona; Nandroloni; Nandrolonum; Norandrostenolona; 19-Nortestosterone; Nortestrionato. 17β-Hydroxyestr-4-en-3-one; 3-Oxoestr-4-en-17β-yl.

Нандролон

$C_{18}H_{26}O_2$ = 274.4.
CAS — 434-22-0.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

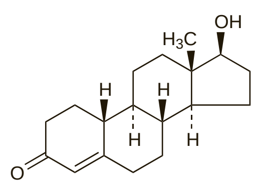

Nandrolone Cyclohexylpropionate *(BANM, rINNM)* ⊗

Ciclohexilpropionato de nandrolona; Nandrolone Cyclohexanepropionate; Nandrolone, Cyclohexylpropionate de; Nandroloni Cyclohexylpropionas; Nortestosterone Cyclohexylpropionate. 3-Oxoestr-4-en-17β-yl 3-cyclohexylpropionate; 17β-Hydroxyestr-4-en-3-one cyclohexylpropionate.

Нандролона Циклогексилпропионат

$C_{27}H_{40}O_3$ = 412.6.
CAS — 912-57-2.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Nandrolone Decanoate *(BANM, USAN, rINNM)* ⊗

Decanoato de nandrolona; Nandrolon-dekanoát; Nandrolone, décanoate de; Nandroloni decanoas; Nandrolonu dekanonian; Nortestosterone Decanoate; Nortestosterone Decylate. 3-Oxoestr-4-en-17β-yl decanoate; 17β-Hydroxyestr-4-en-3-one decanoate.

Нандролона Деканоат

$C_{28}H_{44}O_3$ = 428.6.
CAS — 360-70-3.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Nandrolone Decanoate). A white or almost white, crystalline powder. M.p. 34° to 38°. Practically insoluble in water; very soluble in alcohol and in dichloromethane. Store under nitrogen at 2° to 8°. Protect from light.

USP 31 (Nandrolone Decanoate). A white to creamy-white fine crystalline powder, odourless or may have a slight odour. Practically insoluble in water; soluble in alcohol, in acetone, in chloroform, and in vegetable oils. Store at 2° to 8° in airtight containers. Protect from light.

Nandrolone Laurate *(BANM, rINNM)* ⊗

Dodecanoato de nandrolona; Laurato de nandrolona; Nandrolone Dodecanoate; Nandrolone, Laurate de; Nandroloni Lauras; Nortestosterone Laurate. 3-Oxoestr-4-en-17β-yl dodecanoate; 17β-Hydroxyestr-4-en-3-one dodecanoate.

Нандролона Лаурат

$C_{30}H_{48}O_3$ = 456.7.
CAS — 26490-31-3.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Nandrolone Laurate). A white to creamy-white crystalline powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, in ether, in fixed oils, and in esters of fatty acids. Store at 2° to 8°. Protect from light.

Nandrolone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de nandrolona; Nandrolone Hydrocinnamate; Nandrolone Phenpropionate; Nandrolone, Phénylpropionate de; Nandroloni Phenylpropionas; Nandrolonu fenylopropionian; 19-Norandrostenolone Phenylpropionate; Nortestosterone Phenylpropionate; NSC-23162. 3-Oxoestr-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyestr-4-en-3-one 3-phenylpropionate.

Нандролона Фенилпропионат

$C_{27}H_{34}O_3$ = 406.6.
CAS — 62-90-8.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nandrolone phenylpropionate:
Iron Brew.

Pharmacopoeias. In *Br., Chin., Pol.,* and *US.*

BP 2008 (Nandrolone Phenylpropionate). A white to creamy-white crystalline powder with a characteristic odour. Practically insoluble in water; soluble in alcohol. Protect from light.

USP 31 (Nandrolone Phenpropionate). Store in airtight containers. Protect from light.

Nandrolone Sodium Sulfate *(rINNM)* ⊗

Nandrolone Sodium Sulphate *(BANM)*; Nandrolone, Sulfate Sodique de; Nandroloni Natrii Sulfas; Nortestosterone Sodium Sulphate; Sulfato sódico de nandrolona. 3-Oxoestr-4-en-17β-yl sodium sulphate; 17β-Hydroxyestr-4-en-3-one sodium sulphate.

Нандролона Натрия Сульфат

$C_{18}H_{25}O_5SNa$ = 376.4.
CAS — 60672-82-4.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Nandrolone Undecylate *(rINNM)* ⊗

Nandrolone Undecanoate *(BANM)*; Nandrolone, Undécylate de; Nandroloni Undecylas; Nortestosterone Undecanoate; Undecilato de nandrolona. 3-Oxoestr-4-en-17β-yl undecanoate; 17β-Hydroxyestr-4-en-3-one undecanoate.

Нандролона Ундесилат

$C_{29}H_{46}O_3$ = 442.7.
CAS — 862-89-5.
ATC — A14AB01; S01XA11.
ATC Vet — QA14AB01; QS01XA11.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

Abuse. Nandrolone, like other anabolic compounds, has been abused by athletes and bodybuilders. However, controversy has arisen over the methods used to detect abuse, and there is some evidence that metabolites of nandrolone may be produced endogenously (see under Precautions of Testosterone, p.2131).

Effects on the liver. Intrahepatic cholestasis occurred in a patient receiving nandrolone cyclohexylpropionate.[1]

1. Gil VG, *et al.* A non-C17-alkylated steroid and long-term cholestasis. *Ann Intern Med* 1986; **104:** 135–6.

Porphyria. Nandrolone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p.2131).

Uses and Administration

Nandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p.2131). It is usually given as the decanoate ester in the form of oily intramuscular injections. The hexyloxyphenylpropionate, propionate, phenylpropionate, and undecylate esters have also been used.

Doses of nandrolone decanoate 25 to 100 mg once every 3 to 4 weeks have been used as an anabolic after debilitating illness, for postmenopausal osteoporosis, and for postmenopausal metastatic breast carcinoma. Doses of between 50 and 200 mg weekly have been suggested for the treatment of anaemia of chronic renal failure, and doses of 50 to 150 mg weekly for aplastic anaemia.

Nandrolone sodium sulfate has been used topically in the treatment of corneal damage.

Nandrolone cyclohexylpropionate, laurate, and phenylpropionate are used in veterinary medicine.

Cachexia. Nandrolone increased lean body-mass in patients with HIV-associated wasting[1-4] (p.858) and in one study[5] was found to have greater effect than testosterone on body-weight and BMI but a similar effect on lean body-mass. Nandrolone has also increased lean body-mass in patients with end-stage renal failure undergoing dialysis.[6,7] Although caution is generally advised with the use of androgenic and anabolic steroids in patients with renal impairment (see Testosterone, p.2131), a study[8] of nandrolone given for 3 months to patients with predialysis chronic renal impairment found that lean body-mass increased without fluid retention or adverse effect on renal function or serum-lipids. In these reports, intramuscular doses of nandrolone decanoate have ranged from 100 mg once every 2 weeks[4] up to 600 mg weekly,[2] and treatment has generally been given for 12 to 24 weeks.

1. Gold J, *et al.* Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. *AIDS* 1996 **10:** 745–52.
2. Sattler FR, *et al.* Effects of pharmacological doses of nandrolone decanoate and progressive resistance training in immunodeficient patients infected with human immunodeficiency virus. *J Clin Endocrinol Metab* 1999; **84:** 1268–76.
3. Storer TW, *et al.* A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *J Clin Endocrinol Metab* 2005; **90:** 4474–82.
4. Mulligan K, *et al.* Effect of nandrolone decanoate therapy on weight and lean body mass in HIV-infected women with weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 2005; **165:** 578–85.
5. Gold J, *et al.* Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. *HIV Med* 2006; **7:** 146–55.
6. Johansen KL, *et al.* Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *JAMA* 1999; **281:** 1275–81.
7. Johansen KL, *et al.* Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol* 2006; **17:** 2307–14.
8. Eiam-Ong S, *et al.* Nutritional effect of nandrolone decanoate in predialysis patients with chronic kidney disease. *J Ren Nutr* 2007; **17:** 173–8.

Male contraception. Preliminary findings showed that nandrolone suppressed spermatogenesis,[1-3] suggesting potential as a male contraceptive (p.2070), but later studies seem to have favoured other androgens.

1. Schürmeyer T, *et al.* Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. *Lancet* 1984; **i:** 417–20.
2. Knuth UA, *et al.* Combination of 19-nortestosterone-hexyloxyphenyl-propionate (Anadur) and depot-medroxyprogesterone-acetate (Clinovir) for male contraception. *Fertil Steril* 1989; **51:** 1011–18.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. *Fertil Steril* 1993; **60:** 1062–8.

Preparations

BP 2008: Nandrolone Decanoate Injection; Nandrolone Phenylpropionate Injection;
USP 31: Nandrolone Decanoate Injection; Nandrolone Phenpropionate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Deca-Durabolin; Keratyl†; ***Austral.:*** Deca-Durabolin; ***Austria:*** Deca-Durabolin; ***Belg.:*** Deca-Durabolin; ***Braz.:*** Deca-Durabolin; ***Canad.:*** Deca-Durabolin; ***Chile:*** Anaprolina; Deca-Durabolin; Nandrosande; ***Cz.:*** Deca-Durabolin†; Keratyl†; Superanabolon; ***Fin.:*** Deca-Durabolin; ***Fr.:*** Keratyl†; ***Ger.:*** Deca-Durabolin; Keratyl†; ***Gr.:*** Anaboline Depot; Deca-Durabolin; Extraboline; Nurezan†; ***Hong Kong:*** Deca-Durabolin; ***Hung.:*** Retabolil; ***India:*** Deca-Durabolin; Deceneurabol†; Durabolin; Metabol; Metadec; Neurabol; ***Indon.:*** Deca-Durabolin; ***Ital.:*** Deca-Durabolin; Dynabolon†; ***Malaysia:*** Deca-Durabolin; ***Mex.:*** Deca-Durabolin; ***Neth.:*** Deca-Durabolin; Durabolin; ***Norw.:*** Deca-Durabolin; ***NZ:*** Deca-Durabolin; ***Pol.:*** Deca-Durabolin; ***Port.:*** Deca-Durabolin; Nandain†; ***Rus.:*** Retabolil (Ретаболил); ***S.Afr.:*** Deca-Durabolin; ***Singapore:*** Deca-Durabolin; ***Spain:*** Deca-Durabolin; ***Swed.:*** Deca-Durabol; ***Switz.:*** Deca-Durabolin; Keratyl; ***Thai.:*** Deca-Durabolin; Keratyl; ***UK:*** Deca-Durabolin; ***USA:*** Androlone-D; Deca-Durabolin; Durabolin; Hybolin; Neo-Durabolic; ***Venez.:*** Deca-Durabolin.

Multi-ingredient: ***Arg.:*** Dexatopic†; ***Indon.:*** Dexatopic; ***Neth.:*** Dexatopic†.

Nomegestrol Acetate *(BANM, rINNM)*

Acetato de nomegestrol; Nomegestrol acetát; Nomégestrol, acétate de; Nomegestrol Asetat; Nomegestrolacetat; Nomegestroli acetas; Nomegestroliasetaatti; Nomegestrolio acetatas; Nomegesztrol-acetát. 17-Hydroxy-6-methyl-19-norpregna-4,6-diene-3,20-dione acetate.

Номегестрола Ацетат

$C_{23}H_{30}O_4$ = 370.5.
CAS — 58691-88-6 (nomegestrol); 58652-20-3 (nomegestrol acetate).
ATC — G03DB04.
ATC Vet — QG03DB04.

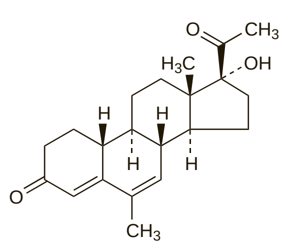

(nomegestrol)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Nomegestrol Acetate). A white or almost white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Protect from light.

Profile

Nomegestrol acetate is a progestogen structurally related to progesterone (p.2125) that has been used in the treatment of menstrual disorders and as the progestogen component of menopausal HRT (p.2071). Typical oral doses are 5 mg daily for 10 to 14 days of a 28-day cycle. A subdermal implant is under investigation as a long-acting progestogen-only contraceptive.

◊ References.

1. Coutinho EM, *et al.* Multicenter clinical trial on the efficacy and acceptability of a single contraceptive implant of nomegestrol acetate, Uniplant. *Contraception* 1996; **53:** 121–5.
2. Devoto L, *et al.* Hormonal profile, endometrial histology and ovarian ultrasound assessment during 1 year of nomegestrol acetate implant (Uniplant). *Hum Reprod* 1997; **12:** 708–13.
3. Barbosa IC, *et al.* Carbohydrate metabolism in sickle cell patients using a subdermal implant containing nomegestrol acetate (Uniplant). *Contraception* 2001; **63:** 263–5.
4. Arowojolu AO, Ladipo OA. Nonmenstrual adverse events associated with subdermal contraceptive implants containing normegestrel [sic] and levonorgestrel. *Afr J Med Med Sci* 2003; **32:** 27–31.
5. Barbosa IC, *et al.* Effects of a single Silastic contraceptive implant containing nomegestrol acetate (Uniplant) on endometrial morphology and ovarian function for 1 year. *Contraception* 2006; **74:** 492–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lutenyl; ***Belg.:*** Lutenyl; ***Braz.:*** Lutenil; ***Chile:*** Lutenyl; ***Cz.:*** Lutenyl†; ***Hong Kong:*** Lutenyl; ***Indon.:*** Lutenyl; ***Ital.:*** Lutenyl; ***Mex.:*** Luvenyl; ***Mon.:*** Lutenyl; ***Pol.:*** Lutenyl; ***Port.:*** Lutenyl; ***Turk.:*** Lutenyl; ***Venez.:*** Lutenyl†.

Multi-ingredient: ***Ital.:*** Naemis; ***Mon.:*** Naemis; ***Neth.:*** Naemis; ***Port.:*** Naemis.

Norelgestromin *(BAN, USAN, rINN)*

17-Deacylnorgestimate; Norelgestromiini; Norelgestromina; Norelgestromine; Norelgestrominum; RWJ-10553. 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime.

Норэльгестромин

$C_{21}H_{29}NO_2$ = 327.5.
CAS — 53016-31-2.

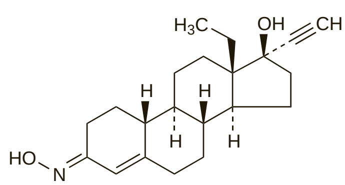

Profile

Norelgestromin is a progestogen (see Progesterone, p.2125); it is the primary active metabolite of norgestimate (p.2121). Norelgestromin is used as the progestogenic component of a combined contraceptive transdermal patch. A dose of 150 micrograms of norelgestromin is released daily with ethinylestradiol. A new patch is applied each week for 3 weeks of a 4-week cycle. Norelgestromin exposure from such a patch may be greater than that resulting from a comparable oral contraceptive.

◊ References.

1. Audet M-C, *et al.* Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. *JAMA* 2001; **285:** 2347–54.
2. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. *J Clin Pharmacol* 2001; **41:** 1232–7.
3. Abrams LS, *et al.* Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra /Evra) under conditions of heat, humidity, and exercise. *J Clin Pharmacol* 2001; **41:** 1301–9.
4. Abrams LS, *et al.* Pharmacokinetics of a contraceptive patch (Evra /Ortho Evra) containing norelgestromin and ethinyloestradiol at four application sites. *Br J Clin Pharmacol* 2002; **53:** 141–6.
5. Burkman RT. The transdermal contraceptive system. *Am J Obstet Gynecol* 2004; **190** (suppl): S49–S53.
6. Devineni D, *et al.* Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol* 2007; **47:** 497–509.
7. Jick S, *et al.* Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol. *Contraception* 2007; **76:** 4–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Evra; ***Belg.:*** Evra; ***Braz.:*** Evra; ***Canad.:*** Evra; ***Chile:*** Evra; ***Cz.:*** Evra; ***Denm.:*** Evra; ***Fin.:*** Evra; ***Fr.:*** Evra; ***Ger.:*** Evra; ***Gr.:*** Evra; ***Hong Kong:*** Evra; ***Hung.:*** Evra; ***Irl.:*** Evra; ***Israel:*** Evra; ***Ital.:*** Evra; ***Mex.:*** Evra; ***Neth.:*** Evra; ***Norw.:*** Evra; ***Philipp.:*** Evra; ***Pol.:*** Evra; ***Port.:*** Evra; ***Rus.:*** Evra (Евра); ***S.Afr.:*** Evra; ***Singapore:*** Evra; ***Spain:*** Evra; ***Swed.:*** Evra; ***Switz.:*** Evra; ***Thai.:*** Evra; ***UK:*** Evra; ***USA:*** Ortho Evra; ***Venez.:*** Evra.

Norethandrolone *(BAN, rINN)* ⊗

17α-Ethyl-17β-hydroxyestr-4-en-3-one; 17β-Hydroxy-19-nor-17α-pregn-4-en-3-one; Noretandrolona; Noréthandrolone; Norethandrolonum.

Норэтандролон

$C_{20}H_{30}O_2$ = 302.5.
CAS — 52-78-8.
ATC — A14AA09.
ATC Vet — QA14AA09.

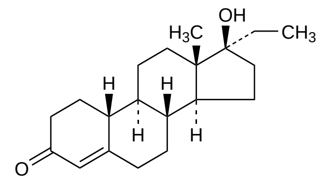

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130). As with other 17α-alkylated compounds, norethandrolone may produce hepatotoxicity and liver function should be monitored. It should probably be avoided in patients with impaired liver function, and certainly if this is severe.

Uses and Administration

Norethandrolone is an anabolic steroid with some androgenic properties (see Testosterone, p.2131). It is given in the treatment of aplastic anaemia in an oral dose of 0.25 to 2 mg/kg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Nilevar.

Norethisterone *(BAN, pINN)*

Ethinylnortestosterone; Etinil hidroxiestrona; Etinilnortestosterona; Norethindrone; Norethisteron; Noréthistérone; Norethisteronum; Noretindrona; Noretisteron; Noretisterona; Noretisteronas; Noretisterone; Noretisteroni; Noretiszteron; Noretysteron; Norpregneninolona; Norpregneninolone; NSC-9564. 17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one.

Норэтистерон

$C_{20}H_{26}O_2$ = 298.4.
CAS — 68-22-4.
ATC — G03AC01; G03DC02.
ATC Vet — QG03AC01; QG03DC02.

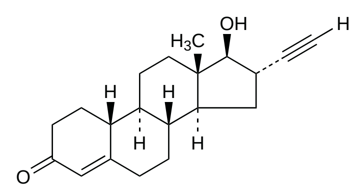

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Norethisterone). A white or yellowish-white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in acetone; soluble in dichloromethane.
USP 31 (Norethindrone). A white to creamy-white odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in chloroform and in dioxan; slightly soluble in ether.

Norethisterone Acetate *(BANM, pINNM)*

Acetato de noretisterona; Norethindrone Acetate; Norethisteron-acetát; Noréthistérone, acétate de; Norethisteroni acetas; Noretisteron Asetat; Noretisteronacetat; Noretisteroniasetaatti; Noretisterono acetatas; Noretiszteron-acetát. 17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate; 3-Oxo-19-nor-17α-pregn-4-en-20-yn-17β-yl acetate.

Норэтистерона Ацетат

$C_{22}H_{28}O_3$ = 340.5.
CAS — 51-98-9.
ATC — G03AC01; G03DC02.
ATC Vet — QG03AC01; QG03DC02.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Norethisterone Acetate). A white or yellowish-white crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichlo-

romethane. Protect from light.

USP 31 (Norethindrone Acetate). A white to creamy-white odourless crystalline powder. Practically insoluble in water; soluble 1 in 10 of alcohol, 1 in less than 1 of chloroform, 1 in 2 of dioxan, and 1 in 18 of ether.

Norethisterone Enantate *(BANM, pINNM)*

Enantato de noretisterona; Norestisteron Enantat; Norethindrone Enanthate; Noréthistérone, Enantate de; Norethisterone Enanthate; Norethisterone Heptanoate; Norethisteroni Enantas. 17β-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate.

Норэтистерона Энантат

$C_{27}H_{38}O_3$ = 410.6.

CAS — 3836-23-5.

ATC — G03AC01; G03DC02.

ATC Vet — QG03AC01; QG03DC02.

Pharmacopoeias. In *Int.*

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Effects on the liver. There were 6 cases of jaundice among 107 patients with breast cancer treated with high-dose norethisterone acetate;[1] the jaundice was reversible and of an obstructive type. A retrospective analysis[2] found that the use of norethisterone to prevent menstrual haemorrhage during the thrombocytopenic phase of allogeneic bone marrow transplantation was a significant risk factor for hepatic veno-occlusive disease.

1. Langlands AO, Martin WMC. Jaundice associated with norethisterone-acetate treatment of breast cancer. *Lancet* 1975; **i:** 584–5.
2. Hägglund H, *et al.* Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood* 1998; **92:** 4568–72.

Porphyria. Norethisterone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Abnormalities seen in the offspring of women given norethisterone during pregnancy (either alone or with ethinylestradiol) included: hypospadias,[1] masculinisation of female infants,[2] meningomyelocele or hydrocephalus,[3] and neonatal choreoathetosis associated with oral contraceptive use.[4] For reference to the fact that oral contraceptives have not generally been associated with teratogenicity, even when used inadvertently in pregnancy, see p.2067.

1. Aarskog D. Clinical and cytogenetic studies in hypospadias. *Acta Paediatr Scand* 1970; (suppl 203): 1–62.
2. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.
3. Gal I, *et al.* Hormonal pregnancy tests and congenital malformation. *Nature* 1967; **216:** 83.
4. Profumo R, *et al.* Neonatal choreoathetosis following prenatal exposure to oral contraceptives. *Pediatrics* 1990; **86:** 648–9.

Venous thromboembolism. For mention that combined oral contraceptives containing older progestogens such as norethisterone appear to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p.2063.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Norethisterone is absorbed from the gastrointestinal tract, undergoing first-pass hepatic metabolism, with peak plasma concentrations occurring 1 to 2 hours after an oral dose. It exhibits biphasic pharmacokinetics; an initial distribution phase is followed by a prolonged elimination phase with a half-life of about 8 hours or more. Norethisterone is highly protein bound; about 60% to albumin and 35% to sex hormone binding globulin. Use with an oestrogen increases the proportion bound to sex hormone binding globulin. It is metabolised in the liver with 50 to 80% of a dose being excreted in the urine and up to 40% appearing in the faeces.

Norethisterone acetate is rapidly hydrolysed to norethisterone, principally by intestinal tissue.

After intramuscular injection of norethisterone enantate peak concentrations of norethisterone in plasma are not attained for several days.

Uses and Administration

Norethisterone and its acetate and enantate esters are progestogens (see Progesterone, p.2126) derived from nortestosterone that have weak oestrogenic and androgenic properties. They are commonly used as **hormonal contraceptives** (see p.2069). Norethisterone and norethisterone acetate are both given orally. Typical daily doses are 350 micrograms for norethisterone and 600 micrograms for norethisterone acetate when used alone, or 0.5 to 1 mg for norethisterone and 1 to 1.5 mg for norethisterone acetate when used with an oestrogen. Norethisterone enantate is given by intramuscular injection; a dose of 200 mg provides contraception for 8 weeks. An intramuscular injection containing norethisterone enantate 50 mg with estradiol valerate 5 mg is given once each month.

Norethisterone and norethisterone acetate are used as the progestogen component of **menopausal HRT** (see p.2076). Typical regimens have included either continuous daily doses of norethisterone 700 micrograms or norethisterone acetate 0.5 to 1 mg, or cyclical regimens of norethisterone or norethisterone acetate 1 mg daily for 10 to 12 days of a 28-day cycle. Norethisterone acetate is also available as transdermal patches supplying 140, 170, or 250 micrograms in 24 hours, that are applied twice weekly for 2 weeks of a 4-week cycle; the lower strengths may also be applied twice weekly on a continuous basis.

Norethisterone and norethisterone acetate may be given orally, usually in divided doses, for the treatment of conditions such as **menorrhagia** (below) and **endometriosis** (p.2091). In menorrhagia (dysfunctional uterine bleeding), norethisterone is given in usual doses of 10 to 15 mg daily and norethisterone acetate in doses of 2.5 to 10 mg daily, in a cyclical regimen. In endometriosis the dosage of norethisterone is 10 to 25 mg daily and of norethisterone acetate 5 to 15 mg daily. Treatment of endometriosis is usually continuous for 4 to 9 months.

Norethisterone has been used in daily doses of up to 15 mg orally in a cyclical regimen in the treatment of **premenstrual syndrome** (p.2099).

In **breast cancer** (p.661) oral doses of up to 60 mg daily of norethisterone have been used.

Administration in children. Although unlicensed in the UK for use in children, the *BNFC* does include norethisterone for the management of delayed puberty (p.2079) in girls. It is added after 12 to 24 months of oestrogen therapy to establish a menstrual cycle and maintain sexual maturation, in an oral dose of 5 mg once daily for the last 7 days of a 28-day cycle.

Menorrhagia. Although cyclical norethisterone has been widely used for menorrhagia (p.2126), it is of limited efficacy during ovulatory cycles[1] being most effective for anovulatory bleeding, which occurs in a minority of women with menorrhagia.

1. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).

Preparations

BP 2008: Estradiol and Norethisterone Acetate Tablets; Estradiol and Norethisterone Tablets; Norethisterone Tablets;
USP 31: Estradiol and Norethindrone Acetate Tablets; Norethindrone Acetate and Ethinyl Estradiol Tablets; Norethindrone Acetate Tablets; Norethindrone and Ethinyl Estradiol Tablets; Norethindrone and Mestranol Tablets; Norethindrone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Ginediol; Primolut-Nor; Selectan; ***Austral.:*** Locilan; Micronor; Noriday; Primolut N; ***Austria:*** Duokliman; Micronovum; Primolut-Nor; ***Belg.:*** Primolut-Nor; ***Braz.:*** Micronor; Norestin; Primolut-Nor; ***Canad.:*** Micronor; Norlutate†; ***Chile:*** Primolut-Nor; ***Cz.:*** Primolut-Nor†; ***Denm.:*** Mini-Pe; ***Fin.:*** Mini-Pill; Primolut N; Primolut-Nor; ***Fr.:*** Milligynon; Primolut-Nor; ***Ger.:*** Gestakadin; Noristerat; Primolut-Nor; Sovel†; ***Gr.:*** Fortilut; Primolut-Nor; ***Hong Kong:*** Norcolut; Primolut N; ***Hung.:*** Norcolut; ***India:*** Cycloreg; Noristerat; Norlut; Primolut N; Styptin; ***Indon.:*** Anore; Norelut; Primolut N; Regumen; ***Irl.:*** Noriday; Primolut N; ***Israel:*** Primolut-Nor; ***Ital.:*** Primolut-Nor; ***Malaysia:*** Depocon; Norcolut; Noriday; Noristerat; Primolut N; Sunolut; Trisequens†; ***Mex.:*** Noristerat; Primolut-Nor; ***Neth.:*** Primolut N; ***Norw.:*** Conludag; Primolut N; ***NZ:*** Noriday; Primolut N; ***Philipp.:*** Noristerat; Primolut N; ***Pol.:*** Primolut-Nor; ***Port.:*** Primolut-Nor; ***Rus.:*** Primolut-Nor (Примолют-нор); ***S.Afr.:*** Micronovum; Nur-Isterate; Primolut N; ***Singapore:*** Norcolut; Noristerat†; Primolut N; ***Spain:*** Primolut-Nor; ***Swed.:*** Mini-Pe; Primolut-Nor; ***Switz.:*** Micronovum; Primolut N; ***Thai.:*** Noristerat†; Primolut N; Steron; ***Turk.:*** Primolut N; ***UK:*** Micronor; Micronor HRT†; Noriday; Noristerat; Primolut N; Utovlan; ***USA:*** Aygestin; Jolivette; Nor-QD; Ortho Micronor.

Multi-ingredient: ***Arg.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Estragest; Evorel Conti; Evorel Sequi; Kliogest; Mesigyna; Trial Combi; Trial Gest; Trial Pack†; Trisequens; ***Austral.:*** Brevinor; Estalis Continuous; Estalis Sequi; Estracombi; Improvil; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Austria:*** Activelle; Estalis; Estalis Sequens; Estracomb; FemHRT†; Kliogest; Mericomb; Merigest; Novofem; Ovysmen; Perikliman; Primosiston; Trinovum; Trisequens; ***Belg.:*** Activelle; Estalis; Estracombi; Kliogest; Minestril†; Novofem; Ovysmen; Trinovum; Trisequens; ***Braz.:*** Activelle; Biofim†; Ciclovulon; Cliane; Estalis; Estalis SQ; Estracomb†; Estragest; Gineane; Ginedisc 50 Plus†; Kliogest; Megestran†; Mericomb; Merigest; Mesigyna; Natifa Pro; Noregyna; Primosiston; Suprema; Systen Conti; Systen Sequi; Trinovum†; Trisequens; ***Canad.:*** Brevicon; Estalis; Estalis Sequi; Estracomb; FemHRT; Loestrin 1.5/30; Minestrin; Ortho 0.5/35; Ortho 1/35; Ortho 7/7/7; Ortho-Novum 1/50†; Select 1/35; Synphasic; ***Chile:*** Activelle; Cliane; Enadiol Neta; Estracomb; Estragest; Ginefolin; Kliogest; Mesigyna; Primosiston; Trisequens; ***Cz.:*** Activelle; Estalis; Estalis Sequi; Estrace Plus†; Estrace-C†; Estracomb†; Estragest†; Kliane; Kliogest; Menophase†; Non-Ovlon†; Novofem; Pausogest; Sequidot; Systen Conti; Systen Sequi; Triaklim†; Trinovum; Trisequens; ***Denm.:*** Activelle; Econ†; Estracomb; Evo-Conti; Evo-Sequi; Femanor; Femasekvens; Kliogest; Novofem; Ostranorm†; Trinorm†; Trinovum; Trisekvens; ***Fin.:*** Activelle; Estalis; Estalis Sekvens; Estracomb†; Evorel Conti; Evorel Sequi; Kliogest; Mericomb; Merigest; Novofem; Trisekvens; ***Fr.:*** Activelle; Kliogest; Miniphase; Novofemme; Ortho-Novum 1/35; Triella; Trisequens; ***Ger.:*** Activelle; Clionara; Conceplan M; Estalis Sequi; Estracomb†; Estragest; Eve; Gynamon; Kliogest N; Mericomb; Merigest; Non-Ovlon†; Nora-ratiopharm†; Novofem; Ostro-Primolut†; Ovysmen†; Primosiston†; Prosiston†; Sequostat†; Sinovula†; Synphasec; Trinovum; Trisequens; ***Gr.:*** Activelle†; Estalis; Estracomb TTS; Kliogest; Systen Conti; Systen Sequi; Trisequens; ***Hong Kong:*** Activelle; Brevinor; Estracomb; Kliogest; Norimin†; Norinyl-1; Novofem; Synphase†; Trinovum†; Trisequens; ***Hung.:*** Activelle; Estracomb; Estragest; Kliogest; Pausogest; Triaklim; Trisequens; Tulita; ***Irl.:*** Activelle; Brevinor; Estalis; Estalis Sequi; Estracombi; Estrapak†; Evorel Conti; Kliogest; Novofem; Trisequens; ***Israel:*** Activelle; Evorel Conti; Evorel Sequi; Kliogest; Meno-Net†; Novofem; Trisequens; ***Ital.:*** Activelle; Estalis Sequi; Estracomb; Kliogest; Trisequens; ***Jpn:*** Ortho 777; ***Malaysia:*** Activelle; Kliogest†; ***Mex.:*** Cliane; Estalis; Estracomb; Evorel Conti; Mesigyna; Norace; Norinyl; Nostidyn; Ortho-Novum 1/35; Ortho-Novum†; ***Neth.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Modicon; Neocon; Novofem; Trinovum; Trisequens; ***Norw.:*** Activelle; Estalis; Estalis Sekvens; Kliogest; Novofem; Synfase; Trisekvens; ***NZ:*** Brevinor; Cliane; Estrapak†; Kliogest; Kliovance; Norimin; Norinyl-1; Synphasic; Trisequens; ***Philipp.:*** Kliogest; Micropil; ***Pol.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Novofem; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Port.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Kliogest; Novofem; Trisequens; ***Rus.:*** Non-Ovlon (Нон-овлон); Pausogest (Паузогест); Triaklim (Триаклим); Trisequens (Трисеквенс); ***S.Afr.:*** Activelle; Brevinor†; Estracombi; Estro-Pause N; Evorel Conti; Evorel Sequi; Kliogest; Norinyl-1/28; Novofem; Trinovum; Trisequens; ***Singapore:*** Activelle; Estracomb; Kliogest; Trisequens; ***Spain:*** Absorlent Plus; Activelle; Duofemme; Endomina Plus; Estalis; Estalis Sequi; Estracomb; Merigest; Merigest Sequi; Trisequens; ***Swed.:*** Activelle; Estalis; Estalis Sekvens; Estracomb†; Evorel Micronor; Femanor; Femasekvens; Kliogest; Novofem; Orthonett Novum; Synfase; Trinovum; Trisekvens; ***Switz.:*** Activelle; Estalis; Estalis Sequi; Estracomb; Estragest; Kliogest N; Mericomb; Merigest; Novofem; Ovysmen; Primosiston; Systen Conti; Systen Sequi; Trinovum; Trisequens; ***Thai.:*** Activelle; Anamai†; ***Turk.:*** Activelle; Estracombi; Kliogest; Mesigyna; Trisequens; ***UK:*** Binovum; Brevinor; Climagest; Climesse; Clinorette; Elleste Duet Conti; Elleste-Duet; Estracombi; Estrapak†; Evorel Conti; Evorel Pak†; Evorel Sequi; FemTab Continuous†; Kliofem; Kliovance; Loestrin; Norimin; Norinyl-1; Novofem; Nuvelle Continuous; Ovysmen; Synphase; Trinovum; Trisequens; ***USA:*** Activella; Aranelle; Balziva; Brevicon; CombiPatch; Estrostep Fe; Estrostep†; Femcon Fe; FemHRT; Junel Fe; Leena; Loestrin; Loestrin Fe; Modicon; Necon 1/50; Necon 10/11; Necon 0.5/35, 1/35; NEE 1/35; Norinyl 1 + 35; Norinyl 1 + 50; Ortho-Novum 1/35; Ortho-Novum 1/50; Ortho-Novum 10/11; Ortho-Novum 7/7/7; Ovcon 35; Ovcon 50; Tilia Fe; Tri-Legest; Tri-Norinyl; Zenchent; ***Venez.:*** Cliane; Estracomb†; Estragest; Mesigyna; Primosiston†.

Noretynodrel *(BAN, rINN)*

Norethynodrel *(USAN)*; Noretinodrel; Noretynodreeli; Norétynodrel; Noretynodrelum; NSC-15432; SC-4642. 17β-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

Норэтинодрел

$C_{20}H_{26}O_2$ = 298.4.

CAS — 68-23-5.

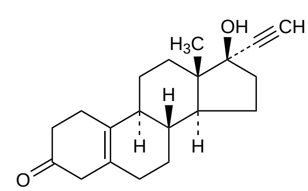

Pharmacopoeias. In *US.*

USP 31 (Norethynodrel). A white or practically white, odourless, crystalline powder. Very slightly soluble in water and in petroleum spirit; sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform.

Profile

Noretynodrel is a progestogen (see Progesterone, p.2125) structurally related to norethisterone that has been given orally with an oestrogen such as mestranol for the treatment of various menstrual disorders and endometriosis.

Breast feeding. About 1% of an oral dose of radiolabelled noretynodrel was detected in breast milk in a study of 4 women.[1] No adverse effects have been seen in breast-fed infants of mothers given noretynodrel, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Laumas KR, *et al.* Radioactivity in the breast milk of lactating women after oral administration of H-norethynodrel. *Am J Obstet Gynecol* 1967; **98:** 411–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Porphyria. Noretynodrel is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Pregnancy. A woman given noretynodrel during pregnancy to prevent threatened miscarriage gave birth to a female infant showing signs of masculinisation.[1]

1. Wilkins L. Masculinization of female fetus due to use of orally given progestins. *JAMA* 1960; **172:** 1028–32.

Norgestimate *(BAN, USAN, rINN)*

D-138; Dexnorgestrel Acetime; Norgestimaatti; Norgestimat; Norgestimato; Norgestimatum; ORF-10131; RWJ-10131. 13β-Ethyl-3-hydroxyimino-18,19-dinor-17α-pregn-4-en-20-yn-17β-yl acetate.

Норгестимат

$C_{23}H_{31}NO_3$ = 369.5.

CAS — 35189-28-7.

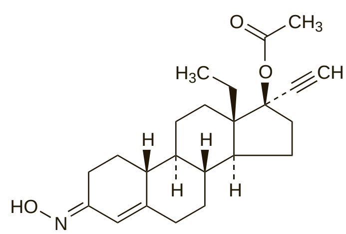

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Norgestimate). A white or almost white powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in acetone.

USP 31 (Norgestimate). A mixture of (*E*)- and (*Z*)-isomers having a ratio of (*E*)- to (*Z*)-isomer between 1.27 and 1.78. A white to pale yellow powder. Insoluble in water; sparingly soluble in acetonitrile; freely to very soluble in dichloromethane.

Profile

Norgestimate is a progestogen (see Progesterone, p.2125) structurally related to levonorgestrel (to which it is partly metabolised) that is used as the progestogenic component of combined oral contraceptives (see p.2058) and in menopausal HRT (see p.2071). A typical daily dose is 250 micrograms in monophasic contraceptive preparations, and 180 to 250 micrograms in triphasic preparations. For HRT, a regimen of estradiol daily for 3 days followed by estradiol with norgestimate 90 micrograms daily for 3 days is used; this 6-day cycle is repeated continuously without interruption.

Preparations

USP 31: Norgestimate and Ethinyl Estradiol Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cilest; Prefest; Tridette; ***Austria:*** Cileste; Tri-Cilest; Vivelle; ***Belg.:*** Cilest; ***Braz.:*** Prefest; ***Canad.:*** Cyclen; Tri-Cyclen; ***Chile:*** Mactex; Neofam; Orlon; Tri-Mactex; Trifas†; ***Cz.:*** Cilest; Pramino; ***Denm.:*** Cilest; ***Fin.:*** Cilest; ***Fr.:*** Cilest; Effiprev; Triafemi; TriCilest; ***Ger.:*** Cilest; Pramino; ***Hung.:*** Cilest; ***Irl.:*** Cilest; ***Israel:*** Ortho Cyclen; ***Mex.:*** Cilest; Prefest; ***Neth.:*** Cilest; ***Pol.:*** Cilest; ***Rus.:*** Cilest (Силест); ***S.Afr.:*** Cilest; Prefesta; TriCilest; ***Swed.:*** Cilest; ***Switz.:*** Cilest; ***Thai.:*** Cilest; Tri-Cilest; ***UK:*** Cilest; ***USA:*** Ortho Cyclen; Ortho Tri-Cyclen; Prefest; Previfem; Sprintec; Tri-Previfem; Tri-Sprintec; TriNessa; ***Venez.:*** Ortrel.

Norgestomet *(BAN, USAN, rINN)*

Norgestometum; SC-21009. 11β-Methyl-3,20-dioxo-19-norpregn-4-en-17α-yl acetate.

Норгестомет

$C_{23}H_{32}O_4$ = 372.5.

CAS — 25092-41-5.

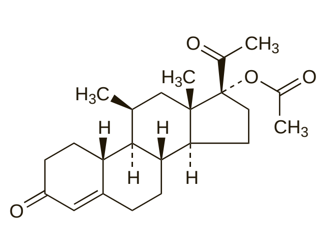

Profile

Norgestomet is a progestogen (see Progesterone, p.2125) used in veterinary medicine with estradiol.

Norgestrel *(BAN, USAN, rINN)*

Norgestreeli; *dl*-Norgestrel; DL-Norgestrel; Norgestrelis; Norgestrelum; Norgesztrel; Wy-3707. (±)-13-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Норгестрел

$C_{21}H_{28}O_2$ = 312.4.

CAS — 6533-00-2.

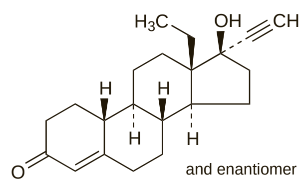

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Norgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Norgestrel). A white or practically white, practically odourless crystalline powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform.

Levonorgestrel *(BAN, USAN, rINN)*

Levonorgestreeli; Lévonorgestrel; Levonorgestrelis; Levonorgestrelum; Levonorgesztrel; D-Norgestrel; Wy-5104. (−)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

Левоноргестрел

CAS — 797-63-7.

ATC — G03AC03.

ATC Vet — QG03AC03.

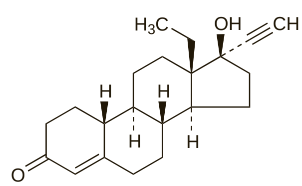

NOTE. The name Dexnorgestrel has also been used.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *US.*

Ph. Eur. 6.2 (Levonorgestrel). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Levonorgestrel). A white or practically white, odourless powder. Practically insoluble in water; slightly soluble in alcohol; soluble in chloroform. Protect from light.

Adverse Effects and Precautions

As for progestogens in general (see Progesterone, p.2125). See also under Hormonal Contraceptives, p.2059.

Incidence of adverse effects. After the introduction of levonorgestrel in a subdermal implant formulation in February 1991, the US FDA had received about 5800 reports of adverse effects as of December 1993 (out of an estimated 891 000 implants distributed).[1] Serious adverse effects associated with the implant included 24 cases of infection related to insertion of the implant, 15 cases of stroke and 39 of benign intracranial hypertension, 3 cases of thrombocytopenic purpura and 6 of thrombocytopenia (1 fatal). None of the reporting rates for these disorders exceeded the expected rate in this population. In a 5-year cohort study[2] of more than 16 000 women who received either a levonorgestrel implant or an IUD (not progestogen-releasing), or underwent sterilisation, there was no significant risk of major morbidity associated with the implant, although there were moderately elevated risks of gallbladder disease and raised blood pressure in current users.

1. Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995; **85:** 538–42.
2. Meirik O, *et al.* Safety and efficacy of levonorgestrel implant, intrauterine device, and sterilization. *Obstet Gynecol* 2001; **97:** 539–47.

Benign intracranial hypertension. Intracranial hypertension, presenting as headaches, vomiting, and visual obscuration associated with florid bilateral papilloedema developed in 2 patients 4 to 5 months after subdermal implantation of levonorgestrel.[1] Despite a further 56 cases reported to various drug monitoring centres, and 70 cases known to the manufacturers,[2] it remained unclear whether the drug actually caused intracranial hypertension, but removal of implants was recommended in patients in whom intracranial pressure increased.

1. Alder JB, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1720–1.
2. Weber ME, *et al.* Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995; **332:** 1721.

Breast feeding. Levonorgestrel was detected in breast milk and the circulation of breast-fed infants during the use of either a levonorgestrel IUD, subcutaneous implant, or progestogen-only oral contraceptive.[1] A review[2] of studies of a levonorgestrel implant used during lactation concluded that it did not adversely affect the duration of lactation, infant growth or development. Further studies of a levonorgestrel IUD[3] and implant[4] also found no adverse effect on lactation or infant growth. The implant study[4] did find an increased incidence of mild respiratory, skin, and eye diseases in infants in the first year of life, but the possibility of bias or chance could not be excluded. The American Academy of Pediatrics considers that levonorgestrel is usually compatible with breast feeding.[5] Progestogen-only contraceptives should not be started until several weeks after birth if the woman is breast feeding (see Breast Feeding under Hormonal Contraceptives, p.2066).

In a pharmacokinetic study[6] using a single oral dose of levonorgestrel 1.5 mg, the drug concentration peaked between 2 and 4 hours in breast milk and then fell rapidly. The authors suggested that breast-feeding women who are given this dose of levonorgestrel for emergency contraception should be advised to breast feed immediately before the dose, then discard milk for at least 8 hours but not more than 24 hours.

1. Shikary ZK, *et al.* Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. *Contraception* 1987; **35:** 477–86.
2. Díaz S. Contraceptive implants and lactation. *Contraception* 2002; **65:** 39–46.
3. Shaamash AH, *et al.* A comparative study of the levonorgestrel-releasing intrauterine system Mirena versus the copper T380A intrauterine device during lactation: breast-feeding performance, infant growth and infant development. *Contraception* 2005; **72:** 346–51.
4. Schiappacasse V, *et al.* Health and growth of infants breastfed by Norplant contraceptive implants users: a six-year follow-up study. *Contraception* 2002; **66:** 57–65.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)
6. Gainer E, *et al.* Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. *Hum Reprod* 2007; **22:** 1578–84.

Effects on the blood. Studies[1-3] of women who had been given different levonorgestrel subcutaneous implants found that over 5 years there were various changes in blood clotting factors, fibrinolytic activity, and platelet number and aggregation, some of which persisted even 6 months after removal of the implants. However, these haemostatic changes did not result in activation of the coagulation system or a state of hypercoagulation.

1. Singh K, *et al.* Evaluation of hemostatic function following Norplant implant removal. *Adv Contracept* 1993; **9:** 49–58.
2. Singh K, *et al.* Evaluation of hemostatic function following Norplant-2 rods removal. *Adv Contracept* 1993; **9:** 241–50.
3. Koh SCL, *et al.* A prospective study on the effects of reformulated 2-rod Norplant implant on haemostasis after five years of use. *J Obstet Gynaecol Res* 1999; **25:** 177–83.

Effects on carbohydrate metabolism. For a mention that levonorgestrel has been reported to be the most potent progestogen associated with hyperinsulinaemia when used as a combined oral contraceptive, see p.2061.

Glucocorticoid effects. Reference to the minimal suppressive effect of subdermal levonorgestrel on adrenal function.[1]

1. Toppozada MK, *et al.* Effect of Norplant implants on the pituitary-adrenal axis function and reserve capacity. *Contraception* 1997; **55:** 7–10.

Myasthenia gravis. Myasthenia gravis occurring after insertion of a levonorgestrel implant improved on removal of the implant.[1]

1. Brittain J, Lange LS. Myasthenia gravis and levonorgestrel implant. *Lancet* 1995; **346:** 1556.

Porphyria. Levonorgestrel has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Adverse effects in infants whose mothers had received oral contraceptives containing norgestrel during early pregnancy have included tracheo-oesophageal fistula in one infant[1] and inoperable hepatoblastoma in another.[2] However, many epidemiological studies have failed to show any association between fetal malformations and oral contraceptives, even when used inadvertently during pregnancy, see p.2067.

1. Frost O. Tracheo-oesophageal fistula associated with hormonal contraception during pregnancy. *BMJ* 1976; **2:** 978.
2. Otten J, *et al.* Hepatoblastoma in an infant after contraceptive intake during pregnancy. *N Engl J Med* 1977; **297:** 222.

Venous thromboembolism. For mention that levonorgestrel-containing combined oral contraceptives appeared to be associated with a lower incidence of venous thromboembolism than desogestrel- or gestodene-containing preparations, see p.2063. See also Effects on the Blood, above.

Interactions

As for progestogens in general (see Progesterone, p.2126). See also under Hormonal Contraceptives, p.2067.

Pharmacokinetics

Levonorgestrel is rapidly and almost completely absorbed after an oral dose, and undergoes little first-pass hepatic metabolism. It is highly bound to plasma proteins; 42 to 68% to sex hormone binding globulin and 30 to 56% to albumin. The proportion bound to sex hormone binding globulin is higher when it is given with an oestrogen. Levonorgestrel and norgestrel are metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine and to a lesser extent in the faeces. Levonorgestrel is distributed into breast milk.

◊ References.

1. Fotherby K. Levonorgestrel: clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 203–15.

Uses and Administration

Norgestrel and its active (–)-isomer levonorgestrel are progestogens (see Progesterone, p.2126) derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. For example, levonorgestrel 37.5 micrograms is equivalent to norgestrel 75 micrograms.

They are both used as **hormonal contraceptives** (see p.2069). The typical daily dose is the equivalent of:

- 30 or 37.5 micrograms of levonorgestrel as an oral progestogen-only contraceptive
- 150 micrograms of levonorgestrel in monophasic combined oral contraceptives (doses may range from a low dose of 100 micrograms of levonorgestrel in some preparations up to 250 micrograms in others; a preparation containing 90 micrograms of levonorgestrel for continuous use without a tablet-free interval is also available)
- 50 to 125 micrograms of levonorgestrel in triphasic preparations

Subcutaneous implants containing levonorgestrel may be used for long-acting progestogen-only contraception. Insertion and removal must be carried out by personnel fully trained in the technique. One available product consists of 2 implants, each containing 75 mg of levonorgestrel. It should be inserted under the skin within the first 7 days of the menstrual cycle, and is effective for up to 5 years. Another product consisting of 6 implants, which also provided up to 5 years of contraception, is no longer widely marketed. Each implant contained 36 mg of levonorgestrel. Uterine, cervical, and vaginal devices containing levonorgestrel have also been investigated. An intra-uterine device is available for contraception or **menorrhagia**, containing a total of 52 mg of levonorgestrel which is released at an initial rate of 20 micrograms per 24 hours. The device is effective for 5 years.

For **emergency contraception** (p.2071), levonorgestrel may be given alone in a single oral dose of 1.5 mg within 72 hours of coitus (preferably as soon as possible). Alternatively, a dose of 750 micrograms is given within 72 hours of coitus (preferably as soon as possible), and repeated after 12 hours. Another regimen uses levonorgestrel 500 micrograms plus ethinylestradiol 100 micrograms, given within 72 hours of coitus and repeated after 12 hours.

Both levonorgestrel and norgestrel are used as the progestogenic component of **menopausal HRT** (see p.2076). Typical regimens are the equivalent of 75 to 250 micrograms of levonorgestrel orally for 10 to 12 days of a 28-day cycle. Levonorgestrel may also be given via a combined transdermal patch, releasing 10 micrograms per 24 hours, which is applied once weekly for 2 weeks of a 4-week cycle. Alternatively, a patch releasing 7 or 15 micrograms per 24 hours with an oestrogen is applied once weekly for continuous HRT. The intra-uterine levonorgestrel device described above may be used for up to 4 years with oestrogen replacement therapy.

Administration. ***IMPLANTS.*** Some references to the use of levonorgestrel by subcutaneous implant for hormonal contraception.[1-3]

1. Coukell AJ, Balfour JA. Levonorgestrel subdermal implants: a review of contraceptive efficacy and acceptability. *Drugs* 1998; **55:** 861–87.
2. Sivin I. Risks and benefits, advantages and disadvantages of levonorgestrel-releasing contraceptive implants. *Drug Safety* 2003; **26:** 303–35.
3. Power J, *et al.* Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).

INTRA-UTERINE DEVICES. Some references to the use of levonorgestrel-releasing intra-uterine devices for contraception[1-7] and menopausal HRT.[8,9]

1. Backman T, *et al.* Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nation-wide study of 17,360 users. *Br J Obstet Gynaecol* 2000; **107:** 335–9.
2. French RS, *et al.* Levonorgestrel-releasing (20 microgram/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. *Br J Obstet Gynaecol* 2000; **107:** 1218–25.
3. Backman T. Benefit-risk assessment of the levonorgestrel intrauterine system in contraception. *Drug Safety* 2004; **27:** 1185–1204.
4. Guillebaud J. The levonorgestrel intrauterine system: a clinical perspective from the UK. *Ann N Y Acad Sci* 2003; **997:** 185–93.
5. Jensen JT. Contraceptive and therapeutic effects of the levonorgestrel intrauterine system: an overview. *Obstet Gynecol Surv* 2005; **60:** 604–12.
6. Peled Y, *et al.* Levonorgestrel-releasing intrauterine system as an adjunct to estrogen for the treatment of menopausal symptoms—a review. *Menopause* 2007; **14:** 550–4.
7. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. FSRH guidance (November 2007): intrauterine contraception. Available at: http://www.ffprhc.org.uk/admin/uploads/CEUGuidanceIntrauterineContraceptionNov07.pdf (accessed 18/07/08)
8. Sitruk-Ware R. The levonorgestrel intrauterine system for use in peri- and postmenopausal women. *Contraception* 2007; **75** (suppl): S155–S160.
9. Chrisman C, *et al.* The levonorgestrel-releasing intrauterine system: an updated review of the contraceptive and noncontraceptive uses. *Clin Obstet Gynecol* 2007; **50:** 886–97.

Menorrhagia. Although oral cyclical progestogens have limited efficacy in the treatment of menorrhagia (p.2126), the levonorgestrel-containing intra-uterine device appears to be particularly useful in reducing menstrual blood loss. The *BNF* notes that another treatment should be considered if bleeding does not improve within 3 to 6 months of insertion. The use of levonorgestrel has been systematically reviewed.[1]

1. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).

Preparations

BP 2008: Levonorgestrel and Ethinylestradiol Tablets; Levonorgestrel Tablets; Norgestrel Tablets;
USP 31: Levonorgestrel and Ethinyl Estradiol Tablets; Norgestrel and Ethinyl Estradiol Tablets; Norgestrel Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Imediat N†; Microlut; Mirena†; Norgeal†; Norgestrel Continuo; Norgestrel Max; Ovulol; Postinor-2; Segurite; ***Austral.:*** Microlut; Microval; Mirena; Postinor-2; ***Austria:*** Mirena; Postinor; Vikela; ***Belg.:*** Microlut; Microval†; Mirena; Norlevo; Postinor; ***Braz.:*** Minipil; Minipil-2 Post; Mirena; Norlevo†; Nortrel; Pilem; Poslov; Postinor Uno; Postinor-2; Pozato; Prevyol-2; ***Canad.:*** Mirena; Norplant†; Plan B; ***Chile:*** Microlut†; Microval; Mirena; Postinor-2†; Tace; ***Cz.:*** Escapelle; Mirena; Norplant†; Postinor; ***Denm.:*** Levonova; Microluton; Norlevo; Postinor; ***Fin.:*** Jadelle; Levonova†; Microluton; Mirena; Norlevo; Postinor†; ***Fr.:*** Microval; Mirena; Norlevo; Vikela†; ***Ger.:*** 28 mini; Duofem; Levogynon; Microlut; Mikro-30†; Mirena; ***Gr.:*** Mirena; Norlevo; Postinor; ***Hong Kong:*** Mirena; Postinor-2; ***Hung.:*** Escapelle; Mirena; Rigesoft; ***India:*** Ecee2; Norlevo; Pill 72; ***Indon.:*** Mirena; Norplant; Postinor-2; ***Irl.:*** Levonelle; Mirena; Norlevo; ***Israel:*** Mirena; Postinor-2; ***Ital.:*** Levonelle; Mirena; Norlevo; ***Malaysia:*** Escapelle; Madonna; Mirena; Norplant†; Postinor; ***Mex.:*** Glanique; Hispatrel; Microlut; Mirena; Post-Day; Postinor-2; Silogin; ***Neth.:*** Jadelle; Mirena; Norlevo; Postinor; Vikela; ***Norw.:*** Jadelle; Levonova; Microluton†; Norlevo; Postinor; ***NZ:*** Levonelle; Microlut; Microval†; Mirena; Postinor-2; ***Philipp.:*** Mirena; ***Pol.:*** Escapelle; Mirena; Postinor-Duo; ***Port.:*** Jadelle; Levonelle; Mirena; Norlevo; Postinor; ***Rus.:*** Escapelle (Эскапел); Microlut (Микролют); Mirena (Мирена); Postinor (Постинор); ***S.Afr.:*** Microval; Mirena; Norlevo; ***Singapore:*** Mirena; Norplant†; Postinor; ***Spain:*** Jadelle; Mirena; Norlevo; Postinor; ***Swed.:*** Follistrel; Jadelle; Levonova; Norlevo; Norplant†; Postinor; ***Switz.:*** Microlut; Mirena; Norlevo; ***Thai.:*** Jadelle; Madonna; Mirena; Norplant; Postinor; ***Turk.:*** Mirena; Norlevo; ***UK:*** Levonelle; Microval†; Mirena; Neogest†; Norgeston; Postinor-2; ***USA:*** Mirena; Ovrette†; Plan B; ***Venez.:*** Jadelle; Microval; Mirena; Norlevo; Postinor-2.

Multi-ingredient: *Arg.:* Afrodita; Anubis; April; Ciclocur; Cuarcic; Dos Dias N; Evelea; Fem 7 Combi†; Femexin; Loette; Microfem; Microgynon; Microvlar; Miranova; Neogynon; Nordette; Nordiol†; Norgestrel Minor; Norgestrel Plus; Ovral†; Plenifem†; Tridestan N; Trinordiol; Triquilar; ***Austral.:*** Biphasil†; Levlen ED; Loette; Logynon ED; Microgynon; Microlevlen ED; Monofeme; Nordette; Nordiol†; Sequilar ED; Trifeme; Triphasil; Triquilar; ***Austria:*** Climabelle†; Cyclacur; Donnina; FemSeven Combi; Loette; Madonella; Microgynon; Neo-Stediril; Neogynon†; Ovranette; Perikursal; Sequilar; Stediril D; Trigynon; Trinordiol; ***Belg.:*** Binordiol†; Cyclocur; Feminova Plus; Lowette; Microgynon; Neo-Stediril†; Neogynon†; Stediril 30; Stediril D†; Trigynon; Trinordiol; ***Braz.:*** Anfertil; Ciclo; Ciclofemme; Ciclon†; Cicloprimogyna; Concepnor; Evanor; Gestrelan; Level; Levordiol; Lindisc Duo†; Lovelle; Microvlar; Neovlar; Nociclin; Nordette; Normamor; Postoval†; Trinordiol; Triquilar; ***Canad.:*** Alesse; Min-Ovral; Ovral; Triphasil; Triquilar; ***Chile:*** Alesse; Anovulatorio Micro-Dosis; Anulette; Fem 7 Combi; Femitres; Innova Cd; Loette†; Microfemin†; Microgynon; Modutrol; Nordette; Nordiol; Norvetal; Postoval†; Progyluton; Trinordiol; Triquilar; Trolit; ***Cz.:*** Anteovin†; Climara Duo†; Cyclo-Menorette†; CycloOstrogynal†; Gravistat; Klimonorm; Loette; Microgynon; Minisiston; Stediril†; Tri-Regol; Trinordiol; Triquilar; Trisiston†; ***Denm.:*** Cyclo-Progynon; Fironetta†; Gynatrol†; Malonetta; Microgyn; Neogentrol†; Neogynon; Nuvelle; Tetragynon†; Triminetta; Trinordiol; Triquilar; ***Fin.:*** Climara Duo†; Cyclabil; FemSeven Combi; Microgynon; Neo-Primovlar†; Trikvilar; Trinordiol†; ***Fr.:*** Adepal; Daily; Ludeal; Minidril; Stediril; Tetragynon†; Trinordiol; ***Ger.:*** Cyclo-Menorette; Cyclo-Progynova; CycloOstrogynal; Fem 7 Combi; Femigoa; Femranette mikro†; Gravistat; Klimonorm; Leios; Microgynon; Minisiston; Miranova; MonoStep; Neo-Stediril†; Neogynon†; NovaStep; Ostronara; Perikursal†; Sequilar†; Stediril 30†; Stediril D†; Stediril†; Tetragynon†; Triette†; Trigoa; Trinordiol†; Triquilar; Trisiston; TriStep†; ***Gr.:*** Cyclacur; Loette; Neogynon†; Nordette†; Nordiol†; Nuvelle†; Ovral†; Trinordiol†; Triquilar†; ***Hong Kong:*** Eugynon; Klimonorm†; Microgynon; Neogynon†; Nordette; Rigevidon; Tri-Regol; Trinordiol†; Triquilar†; ***Hung.:*** Anteovin; Cyclo-Menorette†; FemSeven Combi; Klimonorm; Loette; Miranova†; Ovidon; Rigevidon; Tri-Regol; Trinordiol; Triquilar; ***India:*** Duoluton-L; Ovilow†; Ovipauz-L†; Ovral; Triquilar; ***Indon.:*** Cyclo-Progynova; Microdiol; Microgynon; Pil Keluarga Berencana; Planak; Trinordiol; Triquilar; ***Irl.:*** Logynon; Microgynon 30†; Microlite; Nuvelle†; Ovran†; Ovranette; Prempak-C; Trinordiol; ***Israel:*** Logynon†; Microgynon; Neogynon†; Nordette; Progyluton; Trinordiol†; ***Ital.:*** Combiseven; Egogyn; Eugynon†; Evanor-D†; Femity; Loette; Microgynon; Miranova; Novogyn; Nuvelle; Nuvelle TS†; Ovranet†; Trigynon; Trinordiol†; ***Jpn:*** Ange; ***Malaysia:*** Klimonorm†; Loette; Microgynon 30; Nordette; Progyluton; Rigevidon; Tri-Regol†; Trinordiol; Triquilar†; ***Mex.:*** Alesse; Femexin; Letinnov; Microgynon; Neogynon; Nordet; Nordiol; Ovral; Progyluton; Trinordiol; Triquilar; ***Mon.:*** FemseptCombi; ***Neth.:*** Alesse; Cyclocur; Fem 7 Sequi; Levlen†; Logynon; Lovette; Microgynon; Miranova; Neogynon; Prempak-C†; Rigevidon; Stediril; Trigynon; Trinordiol; ***Norw.:*** Cyclabil; Follimin†; Loette; Microgynon; Tetragynon†; Trinordiol; Trionetta; ***NZ:*** Levlen ED; Loette; Microgynon; Monofeme; Nordette; Nordiol†; Nuvelle; Ovral†; Prempak-C†; Trifeme; Triphasil; Triquilar; ***Philipp.:*** Femenal; Lady; Logynon; Microgynon; Nordette; Nordiol; Rigevidon; Seif; Trinordiol; Trust Pill; ***Pol.:*** Anteovin; Cyclo-Progynova; Fem 7 Combi; Gravistat; Klimonorm; Microgynon; Minisiston; Rigevidon; Stediril; Tri-Regol; Trinordiol; Triquilar; Trisiston; ***Port.:*** Climara Duo†; Femsete Combi; Femsete Evo; Microginon; Miranova; Neomonovar†; Nuvelle; Progyluton; Tetragynon; Trinordiol; Triquilar; ***Rus.:*** Anteovin (Антеовин); Cyclo-Progynova (Цикло-прогинова); Klimonorm (Климонорм); Microgynon (Микрогинон); Minisiston (Минизистон); Ovidon (Овидон); Rigevidon (Ригевидон); Tri-Regol (Три-Регол); Triquilar (Триквилар); Trisiston (Тризистон); ***S.Afr.:*** Biphasil; E-Gen-C; Loette; Logynon ED; Miranova; Nordette; Nordiol; Ovral; Postoval; Triphasil; ***Singapore:*** Loette; Microgynon; Nordette; Prempak-C; Progyluton; Trinordiol; Triquilar†; ***Spain:*** Auroclim; Loette; Microgynon; Neogynona; Nuvelle; Ovoplex; Progyluton; Triagynon; Triciclor; ***Swed.:*** Cyclabil; Follimin; Follinett; Neovletta; Trinordiol; Trionetta; Triregol; ***Switz.:*** Binordiol†; Cyclacur; Fem 7 Combi; Microgynon; Miranova; Neogynon†; Ologyn; Stediril 30; Stediril D; Tetragynon; Trinordiol; Triquilar; ***Thai.:*** Anna†; Cyclo-Progynova; Eugynon 250†; FMP†; Jeny-FMP†; Klimonorm; Microgest; Microgynon; Microlenyn; Nordette; R-Den†; Riget; Rigevidon; Triquilar; ***Turk.:*** Cyclo-Progynova; Lo-Ovral; Microgynon; Miranova; Preven; Triquilar; ***UK:*** Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Eugynon 30†; FemSeven Conti; FemSeven Sequi; FemTab Sequi†; Logynon; Microgynon 30; Nuvelle; Ovran 30; Ovranette; Prempak-C; Trinordiol†; ***USA:*** Alesse; Aviane; ClimaraPro; Cryselle; Enpresse; Jolessa; Lessina; Levlen; Levlite; Levora; Lo/Ovral; Lutera; Lybrel; Nordette; Ovral; Portia; Preven†; Quasense; Seasonale; Seasonique; Sronyx; Tri-Levlen; Triphasil; Trivora; ***Venez.:*** Alesse; Minigynon; Neogynon; Nordette; Nordiol; Ovral; Progyluton; Rigevidon; Tri-Regol; Trinordiol; Triquilar.

Norgestrienone *(rINN)*

Norgestrienona; Norgestriénone; Norgestrienonum. 17β-Hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yn-3-one.

Норгестриенон

$C_{20}H_{22}O_2$ = 294.4.
CAS — 848-21-5.
ATC — G03AC07.
ATC Vet — QG03AC07.

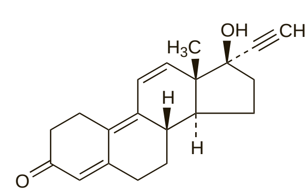

Profile

Norgestrienone is a progestogen (see Progesterone, p.2125) structurally related to norethisterone that has been used as an oral contraceptive (see p.2058). Typical doses have been 2 mg daily with an oestrogen, and 350 micrograms daily when used alone.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Fr.:* Planor†.

Normethandrone ⊗

Methylestrenolone; Methylestrenolonum; Methylnortestosterone; 17α-Methyl-19-nortestosterone; Metylöstrenolon; Metyyliestrenoloni; Normethandrolone; NSC-10039. 17β-Hydroxy-17α-methylestr-4-en-3-one.

Норметандрон

$C_{19}H_{28}O_2$ = 288.4.
CAS — 514-61-4.
ATC — G03DC31.
ATC Vet — QG03DC31.

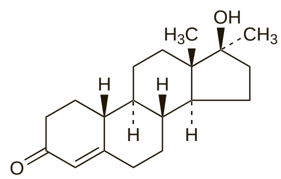

Profile

Normethandrone is a progestogen that also has androgenic and anabolic properties. It has been given orally with an oestrogen for the treatment of amenorrhoea and menopausal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Braz.:*** Ginecoside†; ***Indon.:*** Mediol; Renodiol; ***Venez.:*** Ginecosid.

Ormeloxifene *(rINN)* ⊗

Centchroman; Orméloxifène; Ormeloxifeno; Ormeloxifenum. *trans*-1-{2-[4-(3,4-Dihydro-7-methoxy-2,2-dimethyl-3-phenyl-2*H*-1-benzopyran-4-yl)phenoxy]ethyl}pyrrolidine.

Ормелоксифен

$C_{30}H_{35}NO_3$ = 457.6.
CAS — 31477-60-8.

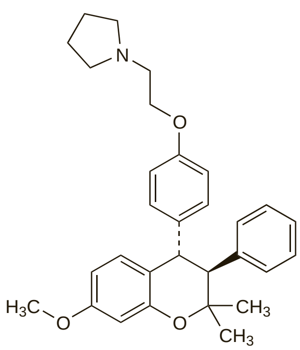

Profile

Ormeloxifene is a selective oestrogen receptor modulator with anti-oestrogenic actions and weak oestrogenic activity. It has been given weekly as an oral contraceptive and used for dysfunctional uterine bleeding, and has been investigated in the management of benign breast diseases such as mastalgia. The *l*-isomer, levormeloxifene, which has oestrogenic effects, has been investigated in the management of postmenopausal osteoporosis, but development appears to have been discontinued because of adverse effects.

◊ References.

1. Kamboj VP, *et al.* New products: centchroman. *Drugs Today* 1992; **28:** 227–32.
2. Gupta RC, *et al.* Centchroman: a new non-steroidal oral contraceptive in human milk. *Contraception* 1995; **52:** 301–5.
3. Lal J, *et al.* Pharmacokinetics of centchroman in healthy female subjects after oral administration. *Contraception* 1995; **52:** 297–300.
4. Lal J, *et al.* Optimization of contraceptive dosage regimen of centchroman. *Contraception* 2001; **63:** 47–51.
5. Alexandersen P, *et al.* Efficacy of levormeloxifene in the prevention of postmenopausal bone loss and on the lipid profile compared to low dose hormone replacement therapy. *J Clin Endocrinol Metab* 2001; **86:** 755–60.
6. Skrumsager BK, *et al.* Levormeloxifene: safety, pharmacodynamics and pharmacokinetics in healthy postmenopausal women following single and multiple doses of a new selective oestrogen receptor modulator. *Br J Clin Pharmacol* 2002; **53:** 284–95.
7. Ravn P, *et al.* What can be learned from the levormeloxifene experience? *Acta Obstet Gynecol Scand* 2006; **85:** 135–42.
8. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg* 2007; **31:** 1178–84.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Centron.

Ovary Extracts

Extractos de ovario; Ovarian Extracts.

Profile

Ovary extracts of animal origin (usually porcine or bovine) have been used for a variety of disorders including gynaecological and menopausal disorders. They have often been used in preparations containing other mammalian tissue extracts or herbal medicines.

Oxandrolone *(BAN, USAN, rINN)* ⊗

NSC-67068; Oxandrolona; Oxandrolonum; SC-11585. 17β-Hydroxy-17α-methyl-2-oxa-5α-androstan-3-one.

Оксандролон

$C_{19}H_{30}O_3$ = 306.4.
CAS — 53-39-4.
ATC — A14AA08.
ATC Vet — QA14AA08.

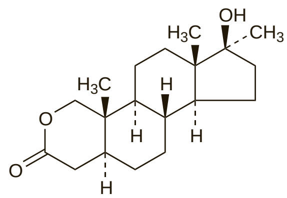

Pharmacopoeias. In *US.*

USP 31 (Oxandrolone). A white odourless crystalline powder. Soluble 1 in 5200 of water, 1 in 57 of alcohol, 1 in 69 of acetone, 1 in less than 5 of chloroform, and 1 in 860 of ether. Protect from light.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130). As with other 17α-alkylated compounds, oxandrolone may cause hepatotoxicity, and liver function should be monitored. It should be avoided if hepatic impairment is severe.

Interactions

As for androgens and anabolic steroids in general (see Testosterone, p.2131).

Pharmacokinetics

Oxandrolone is rapidly absorbed from the gastrointestinal tract, and extensively bound to plasma proteins. It is excreted mainly in the urine as unchanged oxandrolone and some metabolites, with an elimination half-life of about 9 to 10 hours. A small amount is excreted in the faeces.

Uses and Administration

Oxandrolone has anabolic and androgenic properties (see Testosterone, p.2131) and is given as adjunctive therapy to promote weight gain in oral doses of 2.5 to 20 mg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required. Elderly patients may be more susceptible to the adverse effects of oxandrolone, and a dose of up to 5 mg twice daily is recommended. See below for doses of oxandrolone used in children.

Administration in children. Oxandrolone has been given to children as adjunctive therapy to promote weight gain in oral doses of up to 100 micrograms/kg daily in 2 to 4 divided doses. Treatment is usually given as a course of 2 to 4 weeks, which may be repeated intermittently as required.

For the promotion of growth in boys with constitutional delay of growth and puberty, and in girls with Turner's syndrome, usual daily doses of 100 micrograms/kg have been used. Treatment may be given for up to a year, but bone age must be assessed during therapy to avoid the risk of premature epiphyseal closure (see also below).

Cachexia. Oxandrolone has been used for its protein anabolic effect in a number of conditions associated with cachexia (p.2115) or wasting,[1] including alcoholic hepatitis, burn injury, HIV-infection, and muscular dystrophy (p.1507).

1. Orr R, Singh MF. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs* 2004; **64:** 725–50.

Growth retardation. A beneficial effect of oxandrolone on growth rate in *boys* with constitutional delay of growth and puberty (p.2079) has been shown in various studies,[1-6] two of which[2,5] were placebo-controlled. Doses used have included 1.25 or 2.5 mg daily[1-3] and 50 or 100 micrograms/kg daily,[4-6] generally for 3 to 12 months. Although a slight advance in bone age has been noted,[1,4,5] final predicted height[5] and actual adult height[3] was not compromised by oxandrolone therapy. Oxandrolone did not affect the rate of pubertal progression and as the aim of such therapy is primarily to relieve psychosocial difficulties associated with short stature and sexual immaturity, it is not clear that it achieves this.[5]

Oxandrolone is also used for the promotion of growth in *girls* with Turner's syndrome (p.2081), usually added to growth hormone therapy.[7-9]

1. Stanhope R, Brook CGD. Oxandrolone in low dose for constitutional delay of growth and puberty in boys. *Arch Dis Child* 1985; **60:** 379–81.
2. Stanhope R, *et al.* Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988; **63:** 501–5.
3. Tse W-Y, *et al.* Long-term outcome of oxandrolone treatment in boys with constitutional delay of growth and puberty. *J Pediatr* 1990; **117:** 588–91.
4. Papadimitriou A, *et al.* Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone. *Arch Dis Child* 1991; **66:** 841–3.
5. Wilson DM, *et al.* Oxandrolone therapy in constitutionally delayed growth and puberty. *Pediatrics* 1995; **96:** 1095–1100.
6. Lampit M, Hochberg Z. Androgen therapy in constitutional delay of growth. *Horm Res* 2003; **59:** 270–5.
7. Nilsson KO, *et al.* Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996; **81:** 635–40.
8. Ranke MB, *et al.* KIGS International Board. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab* 2000; **85:** 4212–18.
9. Stahnke N, *et al.* Favorable final height outcome in girls with Ullrich-Turner syndrome treated with low-dose growth hormone together with oxandrolone despite starting treatment after 10 years of age. *J Pediatr Endocrinol Metab* 2002; **15:** 129–38.

Preparations

USP 31: Oxandrolone Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Oxandrin; ***Israel:*** Lonavar; ***Mex.:*** Xtendrol; ***USA:*** Oxandrin.

Oxymetholone *(BAN, USAN, rINN)* ⊗

CI-406; HMD; Oksimetolon; Oksimetoloni; Oximetolon; Oximetolona; Oxymétholone; Oxymetholonum. 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one.

Оксиметолон

$C_{21}H_{32}O_3$ = 332.5.
CAS — 434-07-1.
ATC — A14AA05.
ATC Vet — QA14AA05.

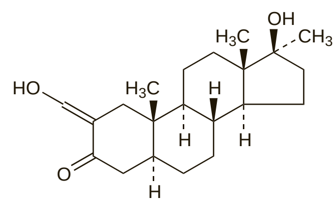

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Oxymetholone). A white to creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light. Avoid contact with ferrous metals.

USP 31 (Oxymetholone). A white to creamy-white, odourless crystalline powder. Practically insoluble in water; soluble 1 in 40 of alcohol, 1 in 5 of chloroform, 1 in 82 of ether, and 1 in 14 of dioxan.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130).

Liver disturbances and jaundice are common with normal doses and hepatic neoplasms have also been reported (see below). Liver function should be monitored during therapy. As with other 17α-alkylated compounds, oxymetholone should probably be avoided in patients with liver impairment, and certainly if this is severe.

Effects on carbohydrate metabolism. Pronounced hyperglucagonaemia developed in 6 patients receiving oxymetholone.[1]

1. Williams G, *et al.* Severe hyperglucagonaemia during treatment with oxymetholone. *BMJ* 1986; **292:** 1637–8.

Effects on the liver. Peliosis hepatis[1-4] and various liver tumours[4-8] has been associated with oxymetholone use. A review[9] of reports of liver tumours associated with anabolic androgens found that oxymetholone was the androgen most often implicated, and that the majority of tumours were hepatocellular carcinomas.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. *Ann Intern Med* 1974; **81:** 610–18.
2. McDonald EC, Speicher CE. Peliosis hepatis associated with administration of oxymetholone. *JAMA* 1978; **240:** 243–4.
3. Hirose H, *et al.* Fatal splenic rupture in anabolic steroid-induced peliosis in a patient with myelodysplastic syndrome. *Br J Haematol* 1991; **78:** 128–9.

4. Linares M, *et al.* Hepatocellular carcinoma and squamous cell carcinoma in a patent with Fanconi's anemia. *Ann Hematol* 1991; **63:** 54–5.
5. Lesna M, *et al.* Liver nodules and androgens. *Lancet* 1976; **i:** 1124.
6. Mokrohisky ST, *et al.* Fulminant hepatic neoplasia after androgen therapy. *N Engl J Med* 1977; **296:** 1411–12.
7. Kosaka A, *et al.* Hepatocellular carcinoma associated with anabolic steroid therapy: report of a case and review of the Japanese literature. *J Gastroenterol* 1996; **31:** 450–4.
8. Nakao A, *et al.* Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol* 2000; **35:** 557–62.
9. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.

Effects on the nervous system. Toxic confusional state and choreiform movements developed in an elderly man given oxymetholone 200 to 300 mg daily.[1]

1. Tilzey A, *et al.* Toxic confusional state and choreiform movements after treatment with anabolic steroids. *BMJ* 1981; **283:** 349–50.

Uses and Administration

Oxymetholone has anabolic and androgenic properties (see Testosterone, p.2131). It has been used mainly in the treatment of anaemias such as aplastic anaemia at a usual oral dose of 1 to 5 mg/kg daily. Treatment for 3 to 6 months has been suggested, with the drug either withdrawn gradually on remission or reduced to an appropriate maintenance dose.

◊ Reviews.

1. Pavlatos AM, *et al.* Review of oxymetholone: a 17α-alkylated anabolic-androgenic steroid. *Clin Ther* 2001; **23:** 789–801.

Aplastic anaemia. There have been mixed results[1-5] with oxymetholone in the treatment of aplastic anaemia (p.1042); generally, the response and survival rates have been disappointing. Although it was used extensively in the past, oxymetholone is now generally reserved for patients who have failed, or cannot tolerate, immunosuppressant therapy.

1. Davis S, Rubin AD. Treatment and prognosis in aplastic anaemia. *Lancet* 1972; **i:** 871–3.
2. Mir MA, Delamore IW. Oxymetholone in aplastic anaemia. *Postgrad Med J* 1974; **50:** 166–71.
3. Camitta BM, *et al.* A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood* 1979; **53:** 504–14.
4. Mir MA, Geary CG. Aplastic anaemia: an analysis of 174 patients. *Postgrad Med J* 1980; **56:** 322–9.
5. Webb DKH, *et al.* Acquired aplastic anaemia: still a serious disease. *Arch Dis Child* 1991; **66:** 858–61.

Preparations

BP 2008: Oxymetholone Tablets;
USP 31: Oxymetholone Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Hemogenin; ***India:*** Adroyd; ***Thai.:*** Androlic; ***Turk.:*** Anapolon; ***USA:*** Anadrol.

Polyestradiol Phosphate *(BAN, rINN)*

Fosfato de poliestradiol; Leo-114; Polyestradiol, Phosphate de; Polyestradiolfosfat; Polyestradioli Phosphas; Polyestradiolifosfaatti; Polyoestradiol Phosphate. A water-soluble polymeric ester of estradiol and phosphoric acid with a molecular weight of about 26 000.

Полиэстрадиола Фосфат

CAS — 28014-46-2.
ATC — L02AA02.
ATC Vet — QL02AA02.

Adverse Effects and Precautions

As for oestrogens in general (see Estradiol, p.2097). Pain may occur at the site of injection, and mepivacaine is included in some preparations to minimise this.

Pharmacokinetics

After intramuscular injection polyestradiol phosphate is released slowly into the bloodstream where it is slowly metabolised to estradiol.

Uses and Administration

Polyestradiol phosphate is a polymer of estradiol (see p.2097) that has a prolonged duration of action, and is used in the treatment of metastatic prostatic carcinoma (p.671). It has been given by deep intramuscular injection in initial doses of 80 to 160 mg every 4 weeks for 2 to 3 months, reduced to 40 to 80 mg every 4 weeks for maintenance. Higher initial doses of 320 mg and maintenance doses of 160 mg have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Estradurin; ***Belg.:*** Estradurine; ***Denm.:*** Estradurin; ***Fin.:*** Estradurin; ***Ger.:*** Estradurin†; ***Neth.:*** Estradurin; ***Norw.:*** Estradurin; ***Rus.:*** Estradurin (Эстрадурин)†; ***Swed.:*** Estradurin; ***Switz.:*** Estradurin.

Prasterone *(rINN)* ⊗

Dehydroandrosterone; Dehydroepiandrosteron; Dehydroepiandrosterone; Dehydroepiandrosteroni; Dehydroepiandrosteronum; Dehydroisoandrosterone; DHEA; GL-701; Prasterona; Prastérone; Prasteronum. 3β-Hydroxyandrost-5-en-17-one.

Прастерон

$C_{19}H_{28}O_2$ = 288.4.
CAS — 53-43-0.
ATC — A14AA07.
ATC Vet — QA14AA07.

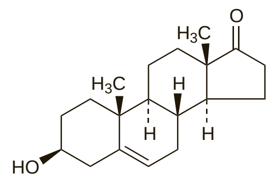

Pharmacopoeias. In *Fr.*

Prasterone Enantate *(rINNM)* ⊗

Dehydroepiandrosterone Enanthate; EDHEA; Enantato de prasterona; Prastérone, Enantate de; Prasterone Enanthate; Prasteroni Enantas. 3β-Hydroxyandrost-5-en-17-one heptanoate.

Прастерона Энантат

$C_{26}H_{40}O_3$ = 400.6.
CAS — 23983-43-9.
ATC — A14AA07.
ATC Vet — QA14AA07.

Prasterone Sodium Sulfate *(rINNM)* ⊗

Dehydroepiandrosterone Sulphate Sodium; DHA-S (prasterone sulfate); DHEAS (prasterone sulfate); PB-005; Prasterone Sodium Sulphate; Prastérone, Sulfate Sodique de; Prasteroni Natrii Sulfas; Sulfato sódico de prasterona. 3β-Hydroxyandrost-5-en-17-one hydrogen sulphate sodium.

Прастерона Натрия Сульфат

$C_{19}H_{27}NaO_5S$ = 390.5.
CAS — 651-48-9 (prasterone sulfate); 1099-87-2 (prasterone sodium sulfate).
ATC — A14AA07.
ATC Vet — QA14AA07.

Pharmacopoeias. *Chin.* and *Jpn* include the dihydrate.

Profile

Prasterone is a naturally occurring adrenal androgen that is a precursor of androgens and oestrogens. Prasterone enantate, in a dose of 200 mg every 4 weeks, is given by intramuscular depot injection with estradiol valerate as menopausal HRT (p.2076). Prasterone is also being investigated in adrenal insufficiency and in SLE, and the sodium sulfate has been investigated for the treatment of burns and acute asthma.

◊ General reviews.

1. Kroboth PD, *et al.* DHEA and DHEA-S: a review. *J Clin Pharmacol* 1999; **39:** 327–48.
2. Pepping J. DHEA: dehydroepiandrosterone. *Am J Health-Syst Pharm* 2000; **57:** 2048–56.
3. Cameron DR, Braunstein GD. The use of dehydroepiandrosterone therapy in clinical practice. *Treat Endocrinol* 2005; **4:** 95–114.

HIV infection and AIDS. Plasma concentrations of endogenous prasterone are reported to be abnormally low in patients with AIDS, and it has been suggested that use of prasterone might be of benefit; however, large controlled studies are lacking.[1] Small controlled studies have confirmed that oral use increases circulating concentrations of prasterone and its sulfated form, and have reported improvements in quality of life measures[2] and reductions in symptoms of mild depression,[3] but no beneficial antiviral or immunomodulatory effects.[4] Also, there were no significant changes in measures of serum lipids, insulin, growth hormone, or the overall function of the gonadal or hypothalamic-pituitary-adrenal axes.[5]

1. Centurelli MA, *et al.* The role of dehydroepiandrosterone in AIDS. *Ann Pharmacother* 1997; **31:** 639–42.
2. Piketty C, *et al.* Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease. *Clin Endocrinol (Oxf)* 2001; **55:** 325–30.
3. Rabkin JG, *et al.* Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry* 2006; **163:** 59–66.
4. Abrams DI, *et al.* Dehydroepiandrosterone (DHEA) effects on HIV replication and host immunity: a randomized placebo-controlled study. *AIDS Res Hum Retroviruses* 2007; **23:** 77–85.
5. Poretsky L, *et al.* Endocrine effects of oral dehydroepiandrosterone in men with HIV infection: a prospective, randomized, double-blind, placebo-controlled trial. *Metabolism* 2006; **55:** 858–70.

Replacement therapy. There has been much speculation about the physiological role and importance of prasterone, which is the most abundant steroid hormone in the circulation. It is produced by the adrenal gland and is a precursor of androgens and oestrogens. Serum concentrations peak at about 20 years then gradually decline with age. Epidemiological and *animal* studies suggest that certain age-related diseases may be linked to this decline, including reduced immunocompetence, obesity, diabetes, and cancers.[1] It has been suggested, therefore, that replacement therapy with prasterone might alleviate some of the problems of ageing. Prasterone has been studied for its effect on cognition and memory, sexual function, insulin sensitivity, cardiovascular risk factors, muscle strength and body composition, bone loss, and immune function, but results have generally been conflicting,[1,2] and there is insufficient evidence of safety and efficacy to recommend such use. A systematic review[3] of studies in healthy adults taking prasterone supplementation found no support for an improvement in cognitive function. A review[4] of the use of prasterone as a 'food supplement' noted that although it was being taken in the belief that it could reverse some of the effects of ageing there was no good evidence of this. Various androgenic effects, including hirsutism and voice changes, have been reported in women taking prasterone and there is a theoretical possibility that it might promote growth of hormone-sensitive tumours in both sexes.[1,4]

Prasterone has also been studied as replacement therapy for patients with adrenal insufficiency, who have subnormal levels of prasterone. Such therapy, usually in oral doses of 50 mg daily, has been reported to raise serum levels of prasterone to normal, and improve measures of well-being, mood, and fatigue.[1,5-7] There have been mixed results from studies of the effects of prasterone on carbohydrate metabolism with reports of either no effect[8,9] or increased insulin sensitivity.[10]

1. Dhatariya KK, Nair KS. Dehydroepiandrosterone: is there a role for replacement? *Mayo Clin Proc* 2003; **78:** 1257–73.
2. GISEG (Italian Study Group on Geriatric Endocrinology). Consensus document on substitution therapy with DHEA in the elderly. *Aging Clin Exp Res* 2006; **18:** 277–300. Also available at: http://www.kurtis.it/abs/index.cfm?id_articolo_numero=2297 (accessed 13/11/07)
3. Grimley Evans J, *et al.* Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 13/11/07).
4. Anonymous. Dehydroepiandrosterone (DHEA). *Med Lett Drugs Ther* 1996; **38:** 91–2.
5. Arlt W, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341:** 1013–20.
6. Hunt PJ, *et al.* Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 2000; **85:** 4650–6.
7. Brooke AM, *et al.* Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab* 2006; **91:** 3773–9.
8. Callies F, *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. *J Clin Endocrinol Metab* 2001; **86:** 1968–72.
9. Libè R, *et al.* Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 2004; **27:** 736–41.
10. Dhatariya K, *et al.* Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005; **54:** 765–9.

Systemic lupus erythematosus. In a number of small studies carried out by one group,[1-5] there was symptomatic improvement in SLE (p.1513), and a reduction in corticosteroid dosage, in women who received oral prasterone 200 mg daily for several months. Although they considered that there was clear evidence of benefit,[6] larger studies[7-9] have produced more statistically ambiguous results. They suggested that prasterone might stabilise or improve disease, and reduce corticosteroid requirements and time to disease flare, but only in patients with active disease. Nested data from one of these studies[10] also showed that prasterone treatment for up to a year improved bone mineral density of the lumbar spine and hip. The results of a larger study designed to confirm this effect on bone were not statistically significant in favour of prasterone, but an open-label 1-year extension study does suggest that long-term treatment might maintain or improve bone mineral density; the full results of these latter studies are yet to be published.[11] In a study[12] of lumbar spine bone mineral density in women with quiescent SLE, prasterone may have had a protective effect in postmenopausal women who were not otherwise treated with oestrogens or bisphosphonates, but there was no change in premenopausal women.

1. van Vollenhoven RF, *et al.* An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1994; **37:** 1305–10.
2. van Vollenhoven RF, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 1995; **38:** 1826–31.
3. van Vollenhoven RF, *et al.* Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 1998; **25:** 285–9.
4. Barry NN, *et al.* Dehydroepiandrosterone in systemic lupus erythematosus: relationship between dosage, serum levels, and clinical response. *J Rheumatol* 1998; **25:** 2352–6.
5. van Vollenhoven RF, *et al.* A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 1999; **8:** 181–7.
6. van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; **26:** 349–62.
7. Petri MA, *et al.* Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1820–9.

8. Chang D-M, *et al.* Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus. *Arthritis Rheum* 2002; **46:** 2924–7.
9. Petri MA, *et al.* Effects of prasterone on disease activity and symptoms in women with active systemic lupus erythematosus: results of a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; **50:** 2858–68.
10. Mease PJ, *et al.* Effects of prasterone on bone mineral density in women with systemic lupus erythematosus receiving chronic glucocorticoid therapy. *J Rheumatol* 2005; **32:** 616–21.
11. Genelabs Technologies Inc., USA. Genelabs updates development options for its investigational lupus drug after FDA meeting (issued January 13, 2006). Available at: http://www.genelabs.com/pressReleases/011306.html (accessed 13/11/07)
12. Hartkamp A, *et al.* The effect of dehydroepiandrosterone on lumbar spine bone mineral density in patients with quiescent systemic lupus erythematosus. *Arthritis Rheum* 2004; **50:** 3591–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Biolaif; ***Pol.:*** Biosteron; ***Port.:*** Dinistenile†.

Multi-ingredient: ***Arg.:*** Dastonil; Gynodian Depot; Supligol NF; ***Austria:*** Gynodian Depot; ***Chile:*** Gynodian Depot; ***Cz.:*** Gynodian Depot; ***Ger.:*** Gynodian Depot; ***Ital.:*** Gynodian Depot; ***Mex.:*** Binodian; Sten; ***Pol.:*** Gynodian Depot; ***Rus.:*** Gynodian Depot (Гинодиан Депо); ***Switz.:*** Gynodian Depot; ***Venez.:*** Gynodian Depot.

Progesterone *(BAN, rINN)*

Corpus Luteum Hormone; Luteal Hormone; Luteine; Luteohormone; NSC-9704; Pregnenedione; Pregnenodiona; Progesteron; Progesterona; Progesteronas; Progestérone; Progesteroni; Progesteronum; Progestina; Progeszteron. Pregn-4-ene-3,20-dione.

Прогестерон

$C_{21}H_{30}O_2$ = 314.5.
CAS — 57-83-0.
ATC — G03DA04.
ATC Vet — QG03DA04.

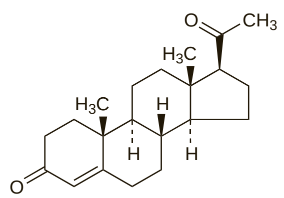

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Progesterone). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol; sparingly soluble in acetone and in fatty oils. Protect from light.

USP 31 (Progesterone). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in dioxan; sparingly soluble in vegetable oils. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely. Alterations in the serum lipid profile may occur, and rarely alterations in liver-function tests and jaundice. Pain, diarrhoea, and flatulence have followed rectal use. Injection-site reactions have followed parenteral use.

Adverse effects vary depending on the dose and type of progestogen. For example, androgenic effects such as acne and hirsutism are more likely to occur with nortestosterone derivatives such as norethisterone and norgestrel. These derivatives may also be more likely to adversely affect serum lipids. Conversely, adverse effects on serum lipids appear less likely with gestodene and desogestrel, but these 2 drugs have been associated with a higher incidence of thromboembolism than norethisterone and norgestrel when used in combined oral contraceptives (see p.2063). High doses of progestogens such as those used in treating cancer have also been associated with thromboembolism. For a discussion of the effect of progestogens on the cardiovascular risk profile of menopausal HRT see p.2073. Breakthrough uterine bleeding is more common with oral progestogen-only contraceptives than when progestogens are used for menstrual irregularities or as part of menopausal HRT.

Some progestogens when given during pregnancy have been reported to cause virilisation of a female fetus. This appears to have been associated with those progestogens with more pronounced androgenic activity such as norethisterone; the natural progestogenic hormone progesterone and its derivatives such as dydrogesterone and medroxyprogesterone do not appear to have been associated with such effects.

For the adverse effects of progestogens when administered either alone or with oestrogens as contraceptives, see p.2059. For those of menopausal HRT, see p.2071.

Carcinogenicity. In a cohort study[1] of women aged 40 to 64 years, the premenopausal use of oral progestogens alone, mainly for benign breast, uterine, and ovarian conditions, and irregular menstruation, was not associated with an increased risk of breast cancer. However, the data did suggest that there was an increased risk for current users of progestogens for longer than 4.5 years (relative risk 1.44, 95% confidence interval 1.03 to 2.00) compared with women who had never used progestogens. Limitations of this study included the lack of analysis of different progestogens or a record of the reasons for progestogen treatment.

1. Fabre A, *et al.* Oral progestagens before menopause and breast cancer risk. *Br J Cancer* 2007; **96:** 841–4.

Effects on the skin. Auto-immune progesterone dermatitis includes reactions such as eczema, urticaria, and angioedema that usually begin 3 to 10 days before the onset of menstrual flow and end 1 to 2 days into menses, which correlates with raised endogenous progesterone concentrations during the luteal phase of the menstrual cycle. The onset of the condition can be as early as menarche, and many women have never been exposed to exogenous progesterone, but it has also occurred in women with a history of oral contraceptive use. Management has been based on the suppression of endogenous progesterone secretion and oral contraceptives are usually tried first, although they appear to have limited success possibly because of the progestogen component. Other drugs that have been used include corticosteroids, conjugated oestrogens, gonadorelin analogues, androgens, and tamoxifen, but all have significant adverse effects associated with long-term use. Bilateral oophorectomy has been used in severe cases, when drug therapy has been unsuccessful.[1]

A woman with a history of auto-immune progesterone dermatitis developed pruritic, pink, oedematous plaques and macules on the upper thighs, axillae, and buttocks after the use of vaginal progestogen gel during infertility treatment.[2] The reaction was managed with topical corticosteroids. In another woman, with a history of chronic urticaria exacerbated by progesterone, the use of progesterone and various other progestogens as a component of HRT after oophorectomy caused urticaria and angioedema.[3] Desensitisation using micronised progesterone was successful in this case.

1. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy* 2004; **2:** 10.
2. Jenkins J, *et al.* Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol* 2008; **58:** 353–5.
3. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol. *J Allergy Clin Immunol* 2004; **114:** 456–7.

Precautions

Progesterone and the progestogens should be used with caution in patients with hypertension, cardiac or renal impairment, asthma, epilepsy, and migraine, or other conditions which may be aggravated by fluid retention. Progestogens can decrease glucose tolerance and diabetic patients should be carefully monitored. They should also be used with care in persons with a history of depression. High doses should be used with caution in patients susceptible to thromboembolism.

Progesterone and the progestogens should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history or current high risk of arterial disease and should generally be avoided in hepatic impairment, especially if severe. Unless progestogens are being used as part of the management of breast or genital-tract carcinoma they should not be given to patients with these conditions.

Although progestogens have been given as hormonal support during early pregnancy such use is not now generally advised. However, the use of a progesterone-type progestogen might still be considered for women who are progesterone-deficient. Such use may prevent spontaneous evacuation of a dead fetus, therefore careful monitoring of pregnancy is required. Progestogens should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

For precautions to be observed when progestogens are used as contraceptives, see p.2065. For those to be observed when progestogens are used in preparations for menopausal HRT, see p.2075.

Abuse. A case report of abuse of and dependency on progesterone.[1]

1. Keefe DL, Sarrel P. Dependency on progesterone in woman with self-diagnosed premenstrual syndrome. *Lancet* 1996; **347:** 1182.

Breast feeding. A large study[1] compared a contraceptive progesterone-releasing vaginal ring and a copper IUD for 1 year in breast-feeding women. There was little difference in infant weight gain during the study, although at 12 months the infants of mothers using the IUD were breast-fed less frequently, receiving more supplementary feeding, and were heavier. There was no adverse effect of progesterone on lactation or infant growth. Further smaller studies[2,3] have also found no adverse effect on lactation or infant growth. The American Academy of Pediatrics has found no reports of adverse effects in breast-fed infants of mothers given progesterone, and therefore considers it to be usually compatible with breast feeding.[4]

1. Sivin I, *et al.* Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the copper T 380A IUD. *Contraception* 1997; **55:** 225–32.
2. Díaz S, *et al.* Fertility regulation in nursing women: IX contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and copper T 380-A intrauterine devices. *Contraception* 1997; **56:** 223–32.
3. Massai R, *et al.* Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* 1999; **60:** 9–14.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/06/08)

Porphyria. Progesterone and progestogens have been associated with acute attacks of porphyria and are considered unsafe in patients with porphyria (but medroxyprogesterone has been used with buserelin to suppress premenstrual exacerbations of porphyria, see p.2084). Progestogens should generally be avoided by all women with porphyria; however, where non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs the risk. The risk of an acute attack is greatest in women who have had a previous attack or are under 30 years of age. Long-acting progestogen preparations should never be used in those at risk.

Pregnancy. In Hungary, where 30% of all pregnant women were given hormonal support therapy with progestogens during the early 1980s, a case-control study suggested that there was a causal relationship between such treatment and hypospadias in their offspring.[1] Mixed results have been reported in other studies of the association between maternal progestogen use and the risk of hypospadias, but the indications and types of progestogens used in early pregnancy have also changed over time (for example, withdrawal bleeding induced by progestogens as a form of pregnancy testing is no longer used, and progestogen luteal support in early pregnancy is no longer recommended for routine use; see also Miscarriage, below). Nevertheless, results from a more recent case-control study[2] of deliveries between October 1997 and December 2000 suggested an increase in risk of at least twofold.

There have also been reports of nongenital malformations, including limb reduction defects, neural tube defects, and congenital heart malformations, following intra-uterine exposure to progestogens in early pregnancy. However, numerous analyses of accumulated data have found no evidence of a recognisable malformation syndrome.[3]

For details of individual case reports, see Pregnancy under Dydrogesterone (p.2096), Hydroxyprogesterone (p.2110), Norethisterone (p.2120), and Noretynodrel (p.2121). For the effects of hormonal contraceptive use during early pregnancy, see p.2067. For the risk of ectopic pregnancy with progestogen-only contraceptives, see p.2061.

1. Czeizel A. Increasing trends in congenital malformations of male external genitalia. *Lancet* 1985; **i:** 462–3.
2. Carmichael SL, *et al.* Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005; **159:** 957–62.
3. Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 906–18.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for progesterone, but concluded that there would be no need to specify a numerical maximum residue limit for progesterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that in the EU the use of steroidal hormones such as progestogens in veterinary practice is restricted, and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 27/06/08)

Interactions

Enzyme-inducing drugs such as carbamazepine, griseofulvin, phenobarbital, phenytoin, and rifampicin may enhance the clearance of progesterone and the progestogens. These interactions are likely to reduce the efficacy of progestogen-only contraceptives (see p.2067), and additional or alternative contraceptive measures are recommended.

Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect; an increase in progestogen dose is likely to be required.

Since progesterone and other progestogens can influence diabetic control an adjustment in antidiabetic dosage could be required. Progestogens may inhibit ciclosporin metabolism leading to increased plasma-ciclosporin concentrations and a risk of toxicity (see p.1828).

Pharmacokinetics

Progesterone has a short elimination half-life and undergoes extensive first-pass hepatic metabolism when given orally; oral bioavailability is very low although it may be increased somewhat by an oily vehicle and by micronisation. Progesterone is absorbed when given buccally, rectally, or vaginally, and rapidly absorbed from the site of an oily intramuscular injection.

Various derivatives have been produced to extend the duration of action and to improve oral activity. Esters of progesterone derivatives such as hydroxyprogesterone caproate are used intramuscularly, and megestrol acetate is orally active. The ester medroxyprogesterone acetate is used orally and parenterally. 19-Nortestosterone progestogens have good oral activity because the 17-ethinyl substituent slows hepatic metabolism.

Progesterone and the progestogens are highly protein bound; progesterone is bound to albumin and corticosteroid binding globulin; esters such as medroxyprogesterone acetate are principally bound to albumin; and 19-nortestosterone analogues are bound to sex-steroid binding globulin and albumin. Progesterone is metabolised in the liver to various metabolites including pregnanediol, which are excreted in the urine as sulfate and glucuronide conjugates. Similarly, progestogens undergo hepatic metabolism to various conjugates, which are excreted in the urine. Progesterone is distributed into breast milk.

◊ Reviews.

1. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996; **51:** 188–215.
2. Stanczyk FZ. Structure-function relationships, metabolism, pharmacokinetics and potency of progestins. *Drugs Today* 1996; **32** (suppl H): 1–14.
3. Schindler AE, *et al.* Classification and pharmacology of progestins. *Maturitas* 2003; **46** (suppl 1): S7–S16.

Uses and Administration

Progesterone is a natural hormone whereas progestogens are synthetic compounds, derived from progesterone or 19-nortestosterone, with actions similar to those of progesterone (for further details, see p.2058).

Progestogens derived from 19-nortestosterone are used as **hormonal contraceptives** (see p.2069), either alone or combined with an oestrogen. The progesterone derivative medroxyprogesterone acetate is also used, and progesterone itself has been used.

Progestogens, and sometimes progesterone, are used with oestrogens for **menopausal HRT** (p.2076) to reduce the increased risk of endometrial hyperplasia and carcinoma that occurs when long-term oestrogen therapy is unopposed.

Similarly, drugs with progestogenic actions may be used in **menstrual disorders** such as dysmenorrhoea (p.6) and menorrhagia associated with dysfunctional uterine bleeding (below). Progestogens may also be used in the management of endometriosis (p.2091). Although progestogens and progesterone have been used for the management of the premenstrual syndrome (below), such a practice is of debatable value.

Progestogens may be valuable in advanced **endometrial cancer** (p.663) and have been tried in some other malignancies. The progestogens typically used for malignant disease include medroxyprogesterone acetate, megestrol, and norethisterone. Some progestogens such as megestrol and medroxyprogesterone are used for the **cachexia** or wasting associated with severe illness including cancer and AIDS (p.2115).

Progestogens have been widely advocated for either the prevention of **recurrent miscarriage** or the treatment of threatened miscarriage (below). However, there is little evidence of any benefit from such a practice and the use of progestogens in early pregnancy is not now generally advised, with the exception of the use of progesterone or a progesterone derivative in women who are progesterone deficient (see also Precautions, above). Progesterone is, however, the preferred drug for luteal support in women undergoing **assisted reproductive techniques** such as IVF (see Infertility, p.2080).

USES AND ADMINISTRATION OF PROGESTERONE. Progesterone is usually given as an oily intramuscular injection, a vaginal gel or pessaries, or as suppositories. Preparations containing micronised progesterone are also available for oral and vaginal use.

In dysfunctional uterine bleeding or amenorrhoea 5 to 10 mg daily of progesterone may be given by intramuscular injection for about 5 to 10 days until 2 days before the anticipated onset of menstruation. Alternatively, progesterone may be given for amenorrhoea as a vaginal gel at a usual dose of 45 mg on alternate days for up to 6 doses; the dose may be increased to 90 mg in those who do not respond to the lower dose. An oral dose of 400 mg given daily at bedtime for 10 days may also be used for amenorrhoea.

In women with a history of recurrent miscarriage and proven progesterone deficiency, twice weekly intramuscular injection (increased to daily if necessary) of 25 to 100 mg of progesterone, from about day 15 of the pregnancy until 8 to 16 weeks, has been used. The dose may be increased to 200 mg daily if necessary. Vaginal doses of micronised progesterone 200 to 400 mg daily, in 2 divided doses, have also been given until week 12 of pregnancy. A similar intramuscular schedule has been used for luteal support in IVF or gamete intra-fallopian transfer techniques with treatment beginning on the day of transfer of embryo or gametes. Alternatively, progesterone may be given vaginally in assisted reproduction, but doses can vary widely depending on the preparation. A vaginal gel may be given at a dose of 90 mg daily; it is given for 30 days if pregnancy occurs, and may be continued until there is placental autonomy (up to 10 to 12 weeks). A dose of 90 mg twice daily has been used in women with ovarian failure. A vaginal tablet containing micronised progesterone 100 mg may be given 2 or 3 times daily; treatment is started at oocyte retrieval and continued for up to 10 weeks. Some soft capsules containing micronised progesterone may also be suitable for intravaginal use in a dose of 400 to 600 mg daily, in 2 or 3 divided doses, from the day of gonadotrophin administration until week 12 of pregnancy.

Progesterone may be given vaginally or rectally in doses of 200 mg daily to 400 mg twice daily for the management of the premenstrual syndrome. Treatment usually starts on day 12 to 14 of the menstrual cycle and continues until the onset of menstruation. Similar vaginal or rectal doses have also been used in the treatment of puerperal (post-natal) depression.

Progesterone has been given as the progestogen component of menopausal HRT. Soft capsules containing micronised progesterone are available in some countries for oral use, given in a dose of 200 mg daily at bedtime for 12 to 14 days of each month. Alternatively, a dose of 100 mg daily may be given from day 1 to 25 of each cycle, resulting in less withdrawal bleeding.

A progesterone-releasing intra-uterine device has been used as a hormonal contraceptive; the device contains 38 mg of progesterone and is effective for up to 12 months. A vaginal ring device that releases 10 mg of progesterone daily is used in some countries for contraception in lactating women. The first ring is inserted 6 weeks after delivery, then replaced every 90 days.

Administration. A number of progesterone creams for *topical* application to the skin are promoted in various countries for the management of menopausal symptoms and conditions associated with progesterone deficiency. These are sometimes described as containing 'natural' progesterone or phytoprogesterone from plant sources. However, many of these products are available without prescription or medical consultation and there has been some concern about their safety and efficacy. Reviews[1,2] have found early studies reporting that absorption of progesterone from these creams was minimal. However, a later study[3] using liquid chromatography-tandem spectrometry of whole blood reported that steady-state progesterone exposure was similar for women given either oral micronised progesterone or topical cream.[3] The authors suggested that the differences between their results and previous studies were likely to have been caused by the use of different analytical techniques, and that women using these creams may in fact be exposed to higher systemic concentrations of progesterone than previously thought. Some proponents of topical progesterone therapy have questioned the importance of using serum concentrations as a marker for absorption. A review[4] concluded that available serum-progesterone concentrations probably remain low after topical use and that further studies on the pharmacokinetics of topical progesterone are needed. In terms of efficacy, a number of small controlled studies have not shown progesterone cream to be any better than placebo for the management of menopausal vasomotor symptoms or the prevention of bone loss, and mixed results have been reported regarding the prevention of endometrial proliferation associated with oestrogen therapy.[1,2,4]

1. Anonymous. 'Natural' progesterone creams for postmenopausal women. *Drug Ther Bull* 2001; **39:** 10–11.
2. Wren BG. Transdermal progesterone creams for postmenopausal women: more hype than hope? *Med J Aust* 2005; **182:** 237–9.
3. Hermann AC, *et al.* Over-the-counter progesterone cream produces significant drug exposure compared to a Food and Drug Administration-approved oral progesterone product. *J Clin Pharmacol* 2005; **45:** 614–19.
4. Elshafie MAA, Ewies AAA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynaecol* 2007; **27:** 655–9.

Menorrhagia. Menorrhagia, or excessive menstrual bleeding, is usually defined as a blood loss exceeding 80 mL per menstrual period,[1,2] compared with a normal loss of about 30 mL. However, many women consider losses below 80 mL to be excessive particularly if 'flooding' occurs. Although not life-threatening, menorrhagia can lead to iron deficiency anaemia and considerably impair quality of life. Menorrhagia may be associated with pelvic disorders such as fibroids or endometriosis, the use of copper IUDs, or some systemic disorders.[1-3] However, most commonly it is associated with dysfunctional uterine bleeding;[1] a term used to denote frequent, prolonged or heavy uterine bleeding for which no specific cause is found (essential, idiopathic, or primary menorrhagia). Both ovulatory (regular) and anovulatory cycles may give rise to dysfunctional uterine bleeding.[2] In general, medical treatment is used initially in women with no underlying uterine abnormalities.[3] The most commonly used drugs are NSAIDs, tranexamic acid, combined oral contraceptives, and progestogens, and choice of therapy may be influenced by the contraceptive needs of the patient.[1-3] Surgery can be used if medical management is ineffective, and may be considered for first-line treatment in selected patients.[3]

NSAIDs such as mefenamic acid, ibuprofen, and naproxen have been widely used. They reduce menstrual blood loss by about 20 to 50%, and there does not seem to be evidence to suggest that one NSAID is more effective than another.[1] They are taken only during the menstrual phase, which reduces adverse effects, and probably improves patient compliance; they also have the benefit of relieving dysmenorrhoea (p.6).[1] Systematic review[4] suggests that NSAIDs are less effective than tranexamic acid, danazol, and intra-uterine levonorgestrel in reducing bleeding. NSAIDs are considered a suitable option when hormonal therapy is not acceptable. They should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds them to be beneficial.[3]

Given during menstruation *tranexamic acid* reduces menstrual blood loss by about half;[1] the benefits of tranexamic therapy have been confirmed by systematic review.[5] Like NSAIDs, tranexamic acid is considered a suitable option when hormonal therapy is not acceptable. It should be stopped if symptoms do not improve within three menstrual cycles, but can be used for as long as the patient finds it to be beneficial.[3] *Etamsylate* has been used for menorrhagia, but it is less effective than NSAIDs and tranexamic acid, and is no longer recommended.[1,3]

In women who require contraception, a *combined oral contraceptive* appears to be effective,[1,3] although good evidence of this is actually lacking.[6] It has been suggested that extended-cycle regimens should be considered for women with menorrhagia, as there are fewer bleeding episodes per year of treatment.[2] Traditional therapy with *progestogens* such as norethisterone or medroxyprogesterone given during the luteal phase appears to be ineffective in women with normal ovulatory cycles,[1,3,7] although cyclical therapy may be of benefit in anovulatory patients as it imposes a cycle.[2] Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss,[1,3,7] but is associated with adverse effects that may limit its acceptability. Long-acting injectable progestogens, such as medroxyprogesterone acetate, reduce menstrual blood loss or induce amenorrhoea when they are used as contraceptives. They have therefore been used for menorrhagia, although specific studies for this indication are lacking.[1,3]

More recently, a contraceptive *levonorgestrel-containing IUD* has been shown to be very effective in reducing menstrual blood loss in menorrhagia.[1,2] UK guidelines[3] suggest that it should be considered first when either hormonal or non-hormonal treatment is acceptable and long-term use is anticipated, although comparative data are scanty.[8] There is also some evidence that it may be an effective alternative to surgery, but data from long-term follow-up are needed.[9] As there can be changes in bleeding pattern associated with this device, particularly in the first few cycles, use for at least 6 months is advised to enable full assessment of benefit.[3]

Danazol is also effective,[10] producing about a 50% reduction in menstrual blood loss,[1] but has significant adverse effects and treatment is usually limited to 3 to 6 months. *Gonadorelin analogues* are effective for menorrhagia associated with fibroids (p.2107).[1] When used pre-operatively for endometrial thinning, they produce more consistent results than danazol.[11] Gonadorelin analogues may therefore be considered before surgery or when other options for fibroids are contra-indicated, but 'add-back' hormone replacement is recommended for the management of adverse effects from oestrogen deficiency or if they are used for more than 6 months.[3]

In patients who fail to respond to drug treatment, or in whom such therapy is inappropriate, various *surgical options* exist. Conservative surgical techniques, where the endometrium is ablated or resected, are increasingly being used, and are an effective alternative to hysterectomy.[3,12] Hysterectomy is the ultimate therapy, but is associated with significant morbidity.

1. Roy SN, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. *Drug Safety* 2004; **27:** 75–90.
2. Nelson AL, Teal SB. Medical therapies for chronic menorrhagia. *Obstet Gynecol Surv* 2007; **62:** 272–81.
3. National Collaborating Centre for Women's and Children's Health/NICE. Heavy menstrual bleeding (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf (accessed 27/06/08)
4. Lethaby A, *et al.* Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).
5. Lethaby A, *et al.* Antifibrinolytics for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 27/06/08).
6. Iyer V, *et al.* Oral contraceptive pills for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1997 (accessed 27/06/08).
7. Lethaby A, *et al.* Cyclical progestogens for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/06/08).
8. Lethaby AE, *et al.* Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 27/06/08).
9. Marjoribanks J, *et al.* Surgery versus medical therapy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 27/06/08).
10. Beaumont H, *et al.* Danazol for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
11. Sowter MC, *et al.* Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 27/06/08).
12. Lethaby A, *et al.* Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 27/06/08).

Miscarriage. Threatened miscarriage is a common complication of pregnancy that presents before 20 weeks of gestation as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable. Endogenous progesterone is normally produced by the corpus luteum to maintain pregnancy, and low concentrations have been associated with pregnancy loss. Progestogen therapy has therefore been widely used in the treatment of threatened miscarriage,[1] but there is a paucity of clinical study data to support routine use.[2] Similarly, progestogens have been used prophylactically to prevent miscarriage, but studies have suffered from various limitations.[3] A systematic review[4] found no evidence to support routine use, but there was limited evidence to suggest that women with a history of recurrent miscarriage (3 or more consecutive miscarriages) might gain some benefit. The *BNF* advises that progestogen prophylaxis in women with a history of recurrent miscarriage is not recommended. (See also Pregnancy, above, for reports of hypospadias in the offspring of women given hormonal support therapy.)

1. Sotiriadis A, *et al.* Threatened miscarriage: evaluation and management. *BMJ* 2004; **329:** 152–5.
2. Wahabi HA, *et al.* Progestogen for treating threatened miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).
3. Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. *Best Pract Res Clin Obstet Gynaecol* 2008; **22:** 375–89.
4. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 27/06/08).

Premature labour. Recommendations have been made regarding progesterone therapy for the prevention of premature birth in women at risk of preterm delivery (see under Hydroxyprogesterone Caproate, p.2110).

Premenstrual syndrome. Progestogen therapy was once popular for premenstrual syndrome, but beneficial responses have not been universally achieved and the theory that progesterone was necessary to correct a hormone imbalance is now losing ground (see p.2099). Progesterone has been given orally, vaginally, and rectally, in continuous and luteal phase regimens. However, systematic reviews[1,2] have found no convincing evidence to support its use.

1. Wyatt K, *et al.* Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; **323:** 776–80.
2. Ford O, *et al.* Progesterone for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/06/08).

Preparations

BP 2008: Progesterone Injection;
USP 31: Progesterone Injectable Suspension; Progesterone Injection; Progesterone Intrauterine Contraceptive System; Progesterone Vaginal Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Crinone; Faselut†; Gester; Mafel; Progest; Proluton; Utrogestan; ***Austral.:*** Crinone; Proluton; ***Austria:*** Utrogestan; ***Belg.:*** Crinone; Progestogel; Utrogestan; ***Braz.:*** Crinone; Evocanil; Utrogestan; ***Canad.:*** Crinone; Prometrium; ***Chile:*** Crinone†; Hormoral; Progendo; Progering; ***Cz.:*** Agolutin; Crinone; Utrogestan; ***Denm.:*** Crinone; ***Fin.:*** Crinone; Lugesteron; ***Fr.:*** Estima; Evapause†; Progestogel; Utrogestan; ***Ger.:*** Crinone; Progestogel; Utrogest; ***Gr.:*** Crinone; Promenorea; Utrogestan; ***Hong Kong:*** Crinone; Cyclogest; Endometrin; Progestogel; Utrogestan; ***Hung.:*** Utrogestan; ***India:*** Crinone; Dubagest; Naturogest; Profine†; Progest†; Remens; Uterone; ***Indon.:*** Crinone; ***Irl.:*** Crinone; Utrogestan; ***Israel:*** Crinone; Endometrin; Gestone; Utrogestan; ***Ital.:*** Crinone; Esolut; Lutogin†; Progeffik; Progestogel†; Progestol†; Prometrium; Prontogest; ***Malaysia:*** Crinone; Cyclogest; Utrogestan†; ***Mex.:*** Crinone; Cuerpo Amarillo Fuerte; Gepromi; Geslutin; Gestageno; Premastan; Prosphere; Utrogestan; ***Neth.:*** Progestan; ***Norw.:*** Crinone; ***NZ:*** Crinone; Gestone; ***Philipp.:*** Crinone; ***Pol.:*** Luteina; ***Port.:*** Crinone; Progenar†; Progestogel; Utrogestan; ***Rus.:*** Crinone (Крайнон); Progestogel (Прожестожель); Utrogestan (Утрожестан); ***S.Afr.:*** Crinone; Cyclogest; Utrogestan; ***Singapore:*** Crinone; Cyclogest; Utrogestan†; ***Spain:*** Crinone; Darstin; Progeffik; Progestogel†; Progestosol; Utrogestan; ***Swed.:*** Crinone; ***Switz.:*** Crinone; Progestogel; Utrogestan; ***Thai.:*** Crinone; Cyclogest; Gestone†; Progestogel; Utrogestan; ***Turk.:*** Crinone; Cyclogest; Progestan; ***UK:*** Crinone; Cyclogest; Gestone; Utrogestan; ***USA:*** Crinone; Endometrin; Prochieve; Progestasert†; Prometrium; ***Venez.:*** Crinone; Progendo; Progestogel; Utrogestan.

Multi-ingredient: ***Arg.:*** Cristerona; Fempack; Hosterona; Lubriderm; Menstrogen; Tropivag Plus; ***Braz.:*** Ginecoside†; Normomensil†; ***Fr.:*** Florgynal; Synergon; Trophigil; ***Ger.:*** Jephagynon†; ***Ital.:*** Biormon†; Menovis; ***Malaysia:*** Duogynon; ***Mex.:*** Damax; Genofort; Lutoginestryl F; Metrigen Fuerte; Ominol†; Primoson-F; Progediol†; Proger-F; ***Port.:*** Emmenovis†; ***Thai.:*** Duoton; Phenokinon-F; ***Turk.:*** Di-Pro; Synergon; ***Venez.:*** Cyclogesterin†; Ginecosid.

Proligestone *(BAN, rINN)*

Proligeston; Proligestona; Proligestoni; Proligestonum. 14a,17α-Propylidene dioxypregn-4-ene-3,20-dione.

Пролигестон

$C_{24}H_{34}O_4$ = 386.5.
CAS — 23873-85-0.
ATC Vet — QG03DA90.

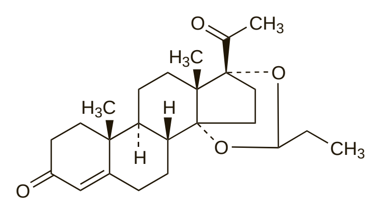

Profile

Proligestone is a progestogen used in veterinary medicine.

Promegestone *(rINN)*

Promegestona; Promégestone; Promegestonum; R-5020. 17α-Methyl-17-propionylestra-4,9-dien-3-one.

Промегестон

$C_{22}H_{30}O_2$ = 326.5.
CAS — 34184-77-5.
ATC — G03DB07.
ATC Vet — QG03DB07.

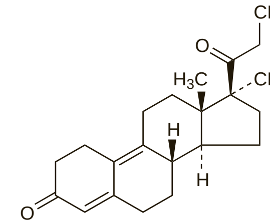

Profile

Promegestone is a progestogen structurally related to progesterone (p.2125). It has been given orally on a cyclical basis, in doses of 125 to 500 micrograms daily, in the treatment of menstrual disorders and mastalgia, and as the progestogen component of menopausal HRT.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Surgestone; ***Port.:*** Surgestone.

Promestriene *(rINN)*

Promestrien; Promestriène; Promestrieno; Promestrienum. 17β-Methoxy-3-propoxyestra-1,3,5(10)-triene.

Прометриен

$C_{22}H_{32}O_2$ = 328.5.
CAS — 39219-28-8.
ATC — G03CA09.
ATC Vet — QG03CA09.

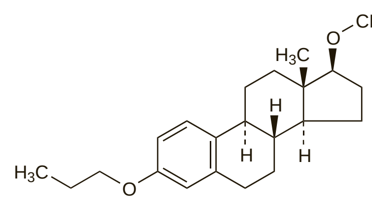

Profile

Promestriene is a derivative of estradiol (p.2097) that has been used topically in menopausal atrophic vaginitis, and in seborrhoea and acne.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Colpotrophine; ***Braz.:*** Colpotrofine; ***Cz.:*** Colpotrophine†; ***Hong Kong:*** Colpotrophine; ***Ital.:*** Colpotrophine; ***Mex.:*** Colpotrophine; ***Port.:*** Colpotrophine; ***Singapore:*** Colpotrophine; ***Spain:*** Colpotrofin; Delipoderm; ***Switz.:*** Colpotrophine; ***Turk.:*** Colpotrophine; ***Venez.:*** Colpotrofina†.

Multi-ingredient: ***Cz.:*** Colposeptine†; ***Hong Kong:*** Colposeptine; ***Port.:*** Trophoseptine; ***Turk.:*** Colposeptine.

Quinestradol *(BAN, rINN)*

Oestriol 3-Cyclopentyl Ether; Quinestradiol; Quinestradolum. 3-Cyclopentyloxyestra-1,3,5(10)-triene-16α,17β-diol.

Хинэстрадол

$C_{23}H_{32}O_3$ = 356.5.
CAS — 1169-79-5.

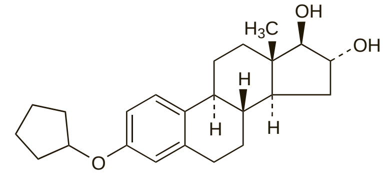

Profile

Quinestradol is a synthetic oestrogen that has been given orally for the treatment of menopausal vaginal symptoms.

Quinestrol *(BAN, USAN, rINN)*

17α-Ethinyloestradiol 3-cyclopentyl Ether; Quinestrolum; W-3566. 3-Cyclopentyloxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol.

Хинэстрол

$C_{25}H_{32}O_2$ = 364.5.

CAS — 152-43-2.

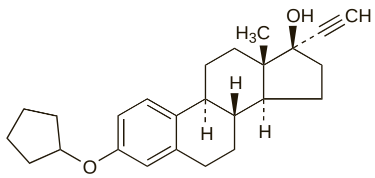

Pharmacopoeias. In *Chin.*

Profile

Quinestrol is a synthetic oestrogen that has a prolonged duration of action and is metabolised to ethinylestradiol (p.2101). Quinestrol has been given orally for the treatment of menopausal symptoms and other conditions arising from oestrogen deficiency. It has also been used as the oestrogen component of combined oral contraceptive preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Qui-Lea.
Multi-ingredient: *Arg.:* Soluna.

Raloxifene Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de keoxifeno; Hidrocloruro de raloxifeno; Keoxifene Hydrochloride; LY-156758; LY-139481 (raloxifene); Raloksifen Hidroklorür; Raloxifène, chlorhydrate de; Raloxifeni hydrochloridum. 6-Hydroxy-2-(*p*-hydroxyphenyl)benzo[*b*]thien-3-yl-*p*-(2-piperidinoethoxy)phenyl ketone hydrochloride.

Ралоксифена Гидрохлорид

$C_{28}H_{27}NO_4S,HCl$ = 510.0.

CAS — 84449-90-1 (raloxifene); 82640-04-8 (raloxifene hydrochloride).

ATC — G03XC01.

ATC Vet — QG03XC01.

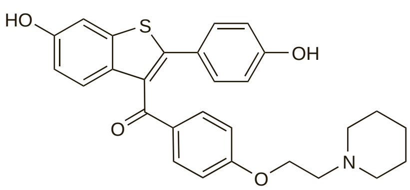

(raloxifene)

Pharmacopoeias. In *US.*

USP 31 (Raloxifene Hydrochloride). An almost white to pale yellow powder. Very slightly soluble in water, in isopropyl alcohol, and in octanol; slightly soluble in alcohol; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; practically insoluble in ether and in ethyl acetate.

Adverse Effects

The most common adverse effects of raloxifene are hot flushes, leg cramps, and a flu-like syndrome. Raloxifene is associated with an increased risk of venous thromboembolic events, particularly during the first 4 months of treatment. Peripheral oedema has also been reported. Rashes, gastrointestinal disturbances, thrombocytopenia, increased blood pressure, headache including migraine, and mild breast symptoms such as pain, enlargement, and tenderness have occurred very rarely.

Incidence of adverse effects. An observational cohort study[1] examined postmarketing adverse events that occurred during raloxifene use in primary care in England. The cohort of 13 987 patients consisted largely of women aged about 62 years, who were receiving raloxifene for the prevention or treatment of osteoporosis. Of the 461 events reported, the most common included flushing, headache or migraine, malaise or lassitude, cramp, oedema, sweating, depression, weight gain, and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, and diarrhoea. Other less common effects included mastalgia and other breast symptoms, vaginal bleeding, thrombophlebitis, and visual disturbances. Rare events included cerebrovascular attack, transient ischaemic attack, pulmonary embolus, deep-vein thrombosis, bullous eruption, leucopenia, thrombocytopenia, upper gastrointestinal haemorrhage, and perforated duodenal ulcer.

The incidence of *cardiovascular* effects associated with raloxifene treatment was examined in the 4-year Multiple Outcomes of Raloxifene Evaluation (MORE), which studied its effects in postmenopausal women with osteoporosis, and in a subsequent 4-year follow-up (Continuing Outcomes Relevant to Evista; CORE).[2] There were 7705 women in the MORE study, of whom 4011 were enrolled in CORE. Overall no significant differences were seen between active treatment and placebo for any cardiovascular event over the 8 years; the calculated incidence was 72 per 10 000 woman-years in those taking raloxifene and 62 per 10 000 in the placebo group. Another large placebo-controlled study[3] (Raloxifene Use for The Heart: RUTH) investigated the cardiovascular effects of raloxifene in postmenopausal women with, or at increased risk of, ischaemic heart disease. After treatment for about 5 years there was no significant difference between the groups for overall cardiovascular events and related deaths. However, in those given raloxifene there was an increased risk of fatal stroke (absolute risk increase, 0.7 per 1000 women-years) and venous thromboembolism (1.2 per 1000 women-years).

1. Layton D, *et al.* Safety profile of raloxifene as used in general practice in England: results of a prescription-event monitoring study. *Osteoporosis Int* 2005; **16:** 490–500.
2. Ensrud K, *et al.* Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol* 2006; **97:** 520–7.
3. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.

Effects on the liver. Hepatitis, probably associated with the drug, occurred in a woman a month after starting raloxifene.[1] Non-alcoholic steatohepatitis was associated with raloxifene in a woman with minor liver dysfunction, a fatty liver, and a family history of cryptogenic liver cirrhosis.[2] Her liver function worsened during the 3 months after starting the drug, and had returned to baseline 3 months after stopping.

1. Vilches AR, *et al.* Raloxifene-associated hepatitis. *Lancet* 1998; **352:** 1524–5.
2. Takamura T, *et al.* Selective estrogen receptor modulator raloxifene-associated aggravation of nonalcoholic steatohepatitis. *Intern Med* 2007; **46:** 579–81.

Precautions

Raloxifene should be avoided in women with active venous thromboembolism, or a history of thromboembolic disorders. It should be stopped at least 72 hours before periods of prolonged immobilisation, such as post-surgical recovery. Raloxifene should be used with caution in women with risk factors for venous thromboembolism including congestive heart failure or active malignancy, or risk factors for stroke such as transient ischaemic attack or atrial fibrillation. It should be avoided in hepatic and severe renal impairment, and used with caution in moderate renal impairment (but see also Administration in Renal Impairment, below).

Raloxifene had adverse effects in *animal* teratogenicity studies and should not be used in women who are or may become pregnant. It should not be given to women with undiagnosed uterine bleeding. An increase in triglycerides has been reported in some women with a history of hypertriglyceridaemia caused by oestrogen therapy.

Interactions

Colestyramine reduces the absorption and enterohepatic recycling of raloxifene, and they should not be given together. Raloxifene may decrease the efficacy of warfarin.

Fibrates. Cholestasis developed when *fenofibrate* was given to a woman who had been on raloxifene therapy for about 3 years.[1] The authors reviewed other rare reports of liver reactions to either raloxifene or fibrates and suggested that the reaction was likely to be due to an interaction, although the mechanism was not clear.

1. Lucena MI, *et al.* Prolonged cholestasis after raloxifene and fenofibrate interaction: a case report. *World J Gastroenterol* 2006; **12:** 5244–6.

Pharmacokinetics

Raloxifene is absorbed from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism to the glucuronide conjugates. It is highly bound to plasma proteins, principally albumin and α_1-acid glycoprotein. Raloxifene undergoes enterohepatic recycling, and has a half-life of about 27 hours. It is excreted almost entirely in the faeces.

Renal impairment. The pharmacokinetics of raloxifene are not expected to be affected by renal impairment because the renally excreted fraction is only about 6% in healthy subjects. However, a study[1] in male subjects found the clearance of a single oral dose of 120 mg to be significantly reduced in 10 men with renal impairment (creatinine clearance 24 to 51 mL/minute) compared with a group of 10 with normal renal function. It was calculated that steady-state concentrations could be about 2.3 times higher in patients with renal impairment. The authors suggested that this unexpected observation might be caused by reduced metabolic clearance in the renal tubules or by impairment of biliary excretion of raloxifene glucuronides by uraemic toxins.

1. Czock D, *et al.* Raloxifene pharmacokinetics in males with normal and impaired renal function. *Br J Clin Pharmacol* 2005; **59:** 479–82.

Uses and Administration

Raloxifene hydrochloride is a selective oestrogen receptor modulator; it is a benzothiophene that appears to have oestrogen agonist effects on bone and antagonist effects in uterine and breast tissue. It is used, in oral doses of 60 mg daily, for the prevention and treatment of postmenopausal osteoporosis (below). The same dose is also used to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or are at high risk of invasive breast cancer (below).

◊ Reviews.

1. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med* 1999; **130:** 431–9.
2. Snyder KR, *et al.* Raloxifene hydrochloride. *Am J Health-Syst Pharm* 2000; **57:** 1669–75.
3. Barrett-Connor E. Raloxifene: risks and benefits. *Ann N Y Acad Sci* 2001; **949:** 295–303.
4. Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. *Int J Clin Pharmacol Ther* 2003; **41:** 331–45.
5. Trémollières F, Ribot C. Indications du raloxifène chez la femme ménopausée. *Gynecol Obstet Fertil* 2006; **34:** 147–53.

Administration in renal impairment. Although unexpected, renal impairment reduced raloxifene clearance in a pharmacokinetic study (see above). Licensed product information in the UK contra-indicates the use of raloxifene in severe renal impairment, and in the USA it advises caution in moderate and severe impairment. Nevertheless, raloxifene has been studied in postmenopausal women with renal impairment and severe osteopenia or osteoporosis. An oral dose of 60 mg daily for 1 year was given to 25 women on haemodialysis and found to improve bone mineral density of the lumbar spine, compared with 25 women given placebo; there were no reported adverse effects.[1]

1. Hernández E, *et al.* Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; **63:** 2269–74.

Hyperparathyroidism. The effects of raloxifene have been reported in postmenopausal women with mild primary hyperparathyroidism (p.1087). Reductions in markers of bone turnover and plasma concentrations of calcium have been described in an observational report[1] and a small, short-term, placebo-controlled study.[2] An increase in bone mineral density was also detected after 12 months of treatment with raloxifene.[1]

1. Zanchetta JR, Bogado CE. Raloxifene reverses bone loss in postmenopausal women with mild asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 189–90.
2. Rubin MR, *et al.* Raloxifene lowers serum calcium and markers of bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 1174–8.

Malignant neoplasms of the breast. Studies have found raloxifene to be effective for the prophylaxis of breast cancer (p.662). In a placebo-controlled study[1] of postmenopausal women with osteoporosis and no history of breast cancer (MORE), the use of raloxifene for about 3 years reduced the risk of developing breast cancer. This was seen as a reduction in the risk of invasive oestrogen-receptor positive breast cancer, as there was no effect on the risk of oestrogen-receptor negative disease. The reduction in risk was maintained in an extension[2] of this study (CORE) to a total of 8 years of treatment. Similar results were reported in a large placebo-controlled study (RUTH)[3] of postmenopausal women who were treated for about 5 years. Both MORE/CORE[4] and RUTH[3] reported risk reduction in women at either high or low risk, but the MORE study[4] found the effect to be greater in women with a family history of breast cancer.

In a study[5] of postmenopausal women with a predicted increased risk of breast cancer (STAR), prophylactic raloxifene for up to 5 years was found to be as effective as tamoxifen in reducing the risk of invasive breast cancer.

1. Cummings SR, *et al.* The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA* 1999; **281:** 2189–97. Correction. *ibid.*; **282:** 2124.
2. Martino S, *et al.* Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; **96:** 1751–61.

3. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; **355:** 125–37.
4. Lippman ME, *et al.* Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. *Clin Cancer Res* 2006; **12:** 5242–7.
5. Vogel VG, *et al.* Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006; **295:** 2727–41. Corrections. *ibid.*; **296:** 2926 and *ibid.* 2007; **298:** 973.

Osteoporosis. Raloxifene partially mimics the effects of oestrogens in bone to increase bone mineral density in postmenopausal women.[1,2] The MORE study in 7705 postmenopausal women with osteoporosis (p.1084) found that up to 4 years of raloxifene treatment reduced the risk of vertebral fracture,[3-6] but the risk of nonvertebral fracture did not differ significantly from that in women given placebo.[3,5] A meta-analysis[7] of data from this and other smaller studies concluded that raloxifene reduced the risk of vertebral fracture by between 40 and 49% in postmenopausal women with osteoporosis.

Small studies suggest that raloxifene may be effective as 'add-back' therapy to prevent the loss of bone mineral density associated with gonadorelin analogue therapy in women[8,9] and men.[10]

1. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs* 2000; **60:** 379–411.
2. Cranney A, Adachi JD. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. *Drug Safety* 2005; **28:** 721–30.
3. Ettinger B, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; **282:** 637–45.
4. Maricic M, *et al.* Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002; **162:** 1140–3.
5. Delmas PD, *et al.* Multiple Outcomes of Raloxifene Evaluation Investigators. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002; **87:** 3609–17.
6. Qu Y, *et al.* The effect of raloxifene therapy on the risk of new clinical vertebral fractures at three and six months: a secondary analysis of the MORE trial. *Curr Med Res Opin* 2005; **21:** 1955–9.
7. Seeman E, *et al.* Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos Int* 2006; **17:** 313–16.
8. Palomba S, *et al.* Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. *J Clin Endocrinol Metab* 2002; **87:** 4476–81.
9. Palomba S, *et al.* Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. *Hum Reprod* 2004; **19:** 1308–14.
10. Smith MR, *et al.* Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3841–6.

Preparations

USP 31: Raloxifene Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Biofem†; Ciclotran†; Evista; Ketidin; Loxifen†; Oseofem; Raxeto; ***Austral.:*** Evista; ***Austria:*** Evista; ***Belg.:*** Evista; ***Braz.:*** Evista; ***Canad.:*** Evista; ***Chile:*** Evista; ***Cz.:*** Evista; Optruma; ***Denm.:*** Evista; ***Fin.:*** Evista; Optruma†; ***Fr.:*** Evista; Optruma; ***Ger.:*** Evista; Optruma; ***Gr.:*** Evista; ***Hong Kong:*** Evista; ***Hung.:*** Evista; ***India:*** Bonmax; Estroact; Ralista; ***Indon.:*** Evista; ***Irl.:*** Evista; ***Israel:*** Evista; ***Ital.:*** Evista; Optruma; ***Jpn:*** Evista; ***Malaysia:*** Evista; ***Mex.:*** Evista; ***Neth.:*** Evista; Optruma; ***Norw.:*** Evista; ***NZ:*** Evista; ***Philipp.:*** Evista; ***Pol.:*** Evista; ***Port.:*** Evista; Optruma; ***S.Afr.:*** Evista; ***Singapore:*** Evista; ***Spain:*** Evista; Optruma; ***Swed.:*** Evista; ***Switz.:*** Evista; ***Thai.:*** Celvista; ***Turk.:*** Evista; ***UK:*** Evista; ***USA:*** Evista; ***Venez.:*** Evista.

Stanozolol *(BAN, USAN, rINN)* ⊗

Androstanazol; Androstanazole; Estanazol; Estanozolol; Methylstanazole; Metistanazol; NSC-43193; Stanotsololi; Stanozololis; Stanozololum; Stanozolum; Sztanozolol; Win-14833. 17α-Methyl-2′*H*-5α-androst-2-eno[3,2-*c*]pyrazol-17β-ol.

Станозолол

$C_{21}H_{32}N_2O$ = 328.5.
CAS — 10418-03-8.
ATC — A14AA02.
ATC Vet — QA14AA02.

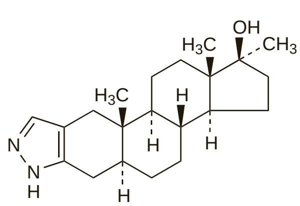

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of stanozolol:
Iron Brew.

Pharmacopoeias. In *Chin.* and *US.*
USP 31 (Stanozolol). An odourless crystalline powder occurring in 2 forms; needles melt at about 155° and prisms at about 235°. Insoluble in water; soluble 1 in 41 of alcohol, 1 in 74 of chloroform, and 1 in 370 of ether; slightly soluble in acetone and in ethyl acetate; soluble in dimethylformamide; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for androgens and anabolic steroids in general (see Testosterone, p.2130). As with other 17α-alkylated compounds stanozolol may produce hepatotoxicity, and liver function should be monitored. It is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Haematocrit and haemoglobin concentrations should also be monitored.

Because of its androgenic effects it has been recommended that stanozolol should not be used to treat hereditary angioedema in premenopausal women except in life-threatening situations.

Effects on the kidney. Renal failure with cholestatic jaundice has been reported with stanozolol (see below).

Effects on the liver. Cholestatic jaundice has been reported with stanozolol,[1-3] in some cases with acute tubular necrosis and renal failure.[4]

1. Slater SD, *et al.* Jaundice induced by stanozolol hypersensitivity. *Postgrad Med J* 1976; **52:** 229–32.
2. Evely RS, *et al.* Severe cholestasis associated with stanozolol. *BMJ* 1987; **294:** 612–13.
3. Martínez B, *et al.* Colestasis inducida por consumo de estanozolol. *Rev Esp Enferm Dig* 2006; **98:** 219–20.
4. Yoshida EM, *et al.* At what price, glory? Severe cholestasis and acute renal failure in an athlete abusing stanozolol. *Can Med Assoc J* 1994; **151:** 791–3.

Effects on the nervous system. Benign intracranial hypertension developed in an elderly woman receiving stanozolol; CSF pressure returned to normal after stanozolol was stopped.[1]

1. Tully MP, *et al.* Intracranial hypertension associated with stanozolol. *DICP Ann Pharmacother* 1990; **24:** 1234.

Porphyria. Stanozolol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As mentioned under Testosterone, p.2131, anabolic steroids may enhance the activity of a number of drugs. For the effect of stanozolol on some anticoagulants, see p.1431.

Uses and Administration

Stanozolol has anabolic and androgenic properties (see Testosterone, p.2131). As with other anabolic steroids, stanozolol has been used for breast cancer in postmenopausal women, and for anaemias, osteoporosis, and catabolic disorders. It has been given in oral doses of 2 mg every 8 to 12 hours, or 50 mg by intramuscular injection every 2 or 3 weeks.

In the management of hereditary angioedema, an initial oral dose of 2.5 to 10 mg daily has been given to prevent attacks. The dosage may then be reduced, according to the patient's response; maintenance doses of 2 mg daily or on alternate days, or 2.5 mg three times weekly have been used successfully. For doses that have been used in children, see below.

Administration in children. Androgens are usually avoided in children with hereditary angioedema (below) because of their adverse effects, but they have been used when other treatments are ineffective. In the USA oral doses of stanozolol 1 mg daily, given only during an attack, have been used in children under 6 years of age, and up to 2 mg daily in those aged 6 to 12 years. Slightly higher doses have been permitted in children in the UK.

Hereditary angioedema. Stanozolol raises serum concentrations of C1 esterase inhibitor and has been used successfully to prevent attacks of hereditary angioedema (p.1081).

References.

1. Bowen T, *et al.* Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004; **114:** 629–37.
2. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.
3. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]

Vascular disorders. Stanozolol has been used in the treatment of vascular manifestations of Behçet's syndrome. It has also been reported to promote fibrinolysis in vascular disorders, and has been tried in various conditions. However, most studies have been noncomparative and in small numbers of patients, and results have been variable.

Preparations

BP 2008: Stanozolol Tablets;
USP 31: Stanozolol Tablets.

Proprietary Preparations (details are given in Part 3)
Gr.: Stromba; ***India:*** Menabol; Neurabol; ***Irl.:*** Stromba†; ***Spain:*** Winstrol; ***Thai.:*** Stanol†; ***USA:*** Winstrol†.

Multi-ingredient: ***Thai.:*** Cetabon.

Testis Extracts ⊗

Extractos testiculares; Testicular Extracts.

Тестикулярный Экстракт

Profile

Testis extracts are usually of bovine origin and have been used in a variety of disorders. They have been given to elderly men as androgenic supplements. They have also been used topically, often in preparations containing other mammalian tissue extracts, in the treatment of peripheral circulatory or musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Orchibion†.

Multi-ingredient: ***Canad.:*** ratio-Heracline; ***Ger.:*** poliomyelan†; tactunerval†; ***Hong Kong:*** Wari-Procomil; ***Thai.:*** Wari-Procomil†.

Testosterone *(BAN, rINN)* ⊗

Testosteron; Testosterona; Testosteronas; Testostérone; Testosteroni; Testosteronum; Tesztoszteron. 17β-Hydroxyandrost-4-en-3-one.

Тестостерон

$C_{19}H_{28}O_2$ = 288.4.
CAS — 58-22-0.
ATC — G03BA03.
ATC Vet — QG03BA03.

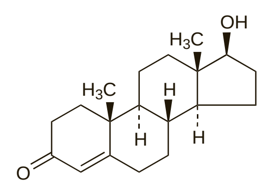

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of testosterone:
T-Stoff.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Testosterone). A white or almost white, crystalline powder, or colourless or yellowish-white crystals. Practically insoluble in water and in fatty oils; freely soluble in alcohol and in dichloromethane. Protect from light.
USP 31 (Testosterone). White or slightly creamy-white, odourless, crystals or crystalline powder. Practically insoluble in water; soluble 1 in 6 of dehydrated alcohol, 1 in 2 of chloroform, and 1 in 100 of ether; soluble in dioxan and in vegetable oils. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Testosterone Cipionate *(BANM, rINNM)* ⊗

Cipionato de testosterona; Testostérone, Cipionate de; Testosterone Cyclopentylpropionate; Testosterone Cypionate; Testosteroni Cipionas. 3-Oxoandrost-4-en-17β-yl 3-cyclopentylpropionate; 17β-Hydroxyandrost-4-en-3-one cyclopentanepropionate; 17β-(3-Cyclopentyl-1-oxopropoxy)androst-4-en-3-one.

Тестостерона Ципионат

$C_{27}H_{40}O_3$ = 412.6.
CAS — 58-20-8.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *US.*
USP 31 (Testosterone Cypionate). A white or creamy-white, crystalline powder, odourless or has a slight odour. Insoluble in water; freely soluble in alcohol, in chloroform, in dioxan, and in ether; soluble in vegetable oils. Protect from light.

Testosterone Decanoate *(BANM, rINNM)* ⊗

Decanoato de testosterona; Testosteron Dekanoat; Testostérone, décanoate de; Testosteroni decanoas. 3-Oxoandrost-4-en-17β-yl decanoate; 17β-Hydroxyandrost-4-en-3-one decanoate.

Тестостерона Деканоат

$C_{29}H_{46}O_3$ = 442.7.
CAS — 5721-91-5.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Testosterone Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in anhydrous alcohol, in acetone, and in dichloromethane; freely soluble in fatty oils. Store at a temperature of 2° to 8°.

Testosterone Enantate *(BANM, rINNM)* ⊗

Enantato de testosterona; NSC-17591; Testosteron enantát; Testostérone, enantate de; Testosterone Enanthate; Testosterone Heptanoate; Testosterone Heptylate; Testosteronenantat; Testosteroni enantas; Testosteronienantaatti; Testosterono enantatas; Testosteronu enantan; Tesztoszteronönantát. 3-Oxoandrost-4-en-17β-yl heptanoate; 17β-Hydroxyandrost-4-en-3-one heptanoate.

Тестостерона Энантат

$C_{26}H_{40}O_3$ = 400.6.
CAS — 315-37-7.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Testosterone Enantate). A white or yellowish-white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in fatty oils. Store at a temperature of 2° to 8°. Protect from light.

USP 31 (Testosterone Enanthate). A white or creamy-white crystalline powder. It is odourless or has a faint odour characteristic of heptanoic acid. Insoluble in water; very soluble in ether; soluble in vegetable oils. Store in a cool place.

Testosterone Isocaproate *(BANM, rINNM)* ⊗

Isocaproato de testosterona; Testosteron Isokaproat; Testostérone, isocaproate de; Testosterone Isohexanoate; Testosteroni isocaproas. 3-Oxoandrost-4-en-17β-yl 4-methylpentanoate; 17β-Hydroxyandrost-4-en-3-one 4-methylpentanoate.

Тестостерона Изокапронат

$C_{25}H_{38}O_3$ = 386.6.
CAS — 15262-86-9.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Testosterone Isocaproate). A white or almost white powder. Practically insoluble in water; very soluble in acetone and in dichloromethane; freely soluble in fatty oils.

Testosterone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de testosterona; Testosteron Fenilpropiyonat; Téstosterone, Phénylpropionate de; Testosteroni Phenylpropionas. 3-Oxoandrost-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyandrost-4-en-3-one 3-phenylpropionate.

Тестостерона Фенилпропионат

$C_{28}H_{36}O_3$ = 420.6.
CAS — 1255-49-8.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Testosterone Phenylpropionate). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

Testosterone Propionate *(BANM, rINNM)* ⊗

NSC-9166; Propionato de testosterona; Testosteron Propiyonat; Testostérone, propionate de; Testosteroni propionas; Testosteronipropionaatti; Testosterono propionatas; Testosteronpropionat; Testosteron-propionát; Testosteronu propionian; Tesztoszteronpropionát. 3-Oxoandrost-4-en-17β-yl propionate; 17β-Hydroxyandrost-4-en-3-one propionate.

Тестостерона Пропионат

$C_{22}H_{32}O_3$ = 344.5.
CAS — 57-85-2.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Testosterone Propionate). A white or almost white powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in fatty oils.

USP 31 (Testosterone Propionate). White or creamy-white, odourless, crystals or crystalline powder. Insoluble in water; freely soluble in alcohol, in dioxan, in ether, and in other organic solvents; soluble in vegetable oils. Protect from light.

Testosterone Undecylate *(rINNM)* ⊗

Org-538; Testosteron Undekanoat; Testosterone Undecanoate *(BANM, USAN)*; Testostérone, Undécylate de; Testosteroni Undecylas; Undecilato de testosterona. 3-Oxoandrost-4-en-17β-yl undecanoate; 17β-Hydroxyandrost-4-en-3-one undecanoate.

Тестостерона Ундесилат

$C_{30}H_{48}O_3$ = 456.7.
CAS — 5949-44-0.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Chin.*

Adverse Effects

Testosterone and other **androgens** may give rise to adverse effects related to their androgenic or anabolic activities. These include increased retention of sodium and water, oedema, hypercalcaemia, and impaired glucose tolerance. Other effects include increased low-density-lipoprotein cholesterol, decreased high-density-lipoprotein cholesterol, increased haematocrit, and suppression of clotting factors. Androgens may cause headache, depression, and gastrointestinal bleeding. It has been suggested that androgens may induce sleep apnoea in susceptible patients.

Abnormal liver function tests may occur and there have been reports of liver toxicity including jaundice and cholestatic hepatitis. There have also been reports of peliosis hepatis and hepatic tumours in patients who have received high doses over prolonged periods. These adverse hepatic effects have occurred primarily with the 17α-alkylated derivatives (e.g. methyltestosterone, stanozolol).

In men, large doses suppress spermatogenesis and cause testicular atrophy. Epididymitis and bladder irritability can occur. Priapism is a sign of excessive dosage and may occur especially in elderly males. Gynaecomastia may occur. Androgens may cause prostatic hyperplasia and accelerate the growth of malignant neoplasms of the prostate.

In women, the inhibitory action of androgens on the activity of the anterior pituitary results in the suppression of ovarian activity and menstruation. Continued use produces symptoms of virilism, such as hirsutism or male-pattern baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, and hypertrophy of the clitoris. Virilisation may not be reversible, even after stopping therapy.

Large and repeated doses in early puberty may cause closure of the epiphyses and stop linear growth. Children may experience symptoms of virilisation: in boys there may be precocious sexual development with phallic enlargement and increased frequency of erection, and in girls, clitoral enlargement. Gynaecomastia may also occur in boys.

Masculinisation of the external genitalia of the female fetus may occur if androgens are given during pregnancy.

After transdermal application of testosterone, skin reactions may include irritation, erythema, allergic contact dermatitis, and sometimes burn-like lesions. Skin reactions are more common with patches that contain permeation enhancers.

The **anabolic steroids**, because they generally retain some androgenic activity, share the adverse effects of the androgens described above, but their virilising effects, especially in women, are usually less. There have been reports of adverse psychiatric effects in athletes taking large doses to try and improve performance. For adverse effects following the misuse of anabolic steroids, see Abuse under Precautions, below.

Carcinogenicity. Testosterone therapy is used in healthy older men with low or low-normal serum-testosterone concentrations (see Hypogonadism, under Uses and Administration, below), but there is some concern about a possible associated increase in prostate cancer risk. This concern is based on the fact that, regardless of any treatment, the incidence of prostate cancer increases with age, that normal prostate growth is dependent on androgens, and that androgen deprivation causes regression of advanced prostate cancer.[1] However, the relationship between androgens and the onset of prostate cancer is far from clear. Some data show that low serum-testosterone can predict more aggressive high-grade tumours, with a higher likelihood of metastatic disease and poorer outcome.[1,2] Although there have been reports of prostate cancer developing in men who have been treated with testosterone,[3] small clinical studies have, overall, not shown an increase in the risk of prostate cancer.[4] The effect of 6 months of testosterone enantate therapy on the prostate has been studied in 21 ageing men.[5] Although low serum-testosterone concentrations were normalised, there were no significant changes in androgen concentrations in prostate tissue, prostate volume, prostate specific antigen, or prostate cancer incidence. Further study of longer duration in larger numbers of men is needed to confirm the safety of this therapy.

In men with a history of prostate cancer, testosterone therapy for hypogonadism is generally contra-indicated because of the presumed risk of tumour recurrence. However, there are a small number of reports of testosterone being used safely after curative surgery, suggesting that testosterone therapy with close monitoring may be considered in such men with symptomatic hypogonadism.[6] There is even less data on the use of testosterone for hypogonadism in men who have been treated with radiotherapy with curative intent, or with androgen ablation by gonadorelin analogue therapy. Testosterone has also been used for hypogonadism in a small number of men with high-grade intra-epithelial neoplasia, a precancerous lesion, without increasing the risk of cancer development.[6]

For reference to hepatic malignancies associated with androgens and anabolic steroids, see Effects on the Liver, below. Renal cell carcinoma has also been reported after their abuse (see under Precautions, below).

1. Raynaud J-P. Prostate cancer risk in testosterone-treated men. *J Steroid Biochem Mol Biol* 2006; **102:** 261–6.
2. Barqawi A, Crawford ED. Testosterone replacement therapy and the risk of prostate cancer: is there a link? *Int J Impot Res* 2006; **18:** 323–8.
3. Brand TC, *et al.* Testosterone replacement therapy and prostate cancer: a word of caution. *Curr Urol Rep* 2007; **8:** 185–9.
4. Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? *Prostate Cancer Prostatic Dis* 2006; **9:** 14–18.
5. Marks LS, *et al.* Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; **296:** 2351–61.
6. Kaufman J. A rational approach to androgen therapy for hypogonadal men with prostate cancer. *Int J Impot Res* 2006; **18:** 26–31.

Effects on the cardiovascular system. A cerebrovascular accident has been reported in a young man after the overzealous self-administration of testosterone enantate intramuscularly for hypogonadism.[1] It was noted that thromboembolic complications are not generally recognised as adverse effects of androgen therapy although there is some experimental evidence that testosterone stimulates thrombus formation. A systematic review[2] found evidence concerning cardiovascular events in studies of testosterone given to men with low or normal testosterone concentrations to be of poor quality, but some data to suggest that alterations in plasma lipid concentrations and blood pressure were not significant.

1. Nagelberg SB, *et al.* Cerebrovascular accident associated with testosterone therapy in a 21-year-old hypogonadal man. *N Engl J Med* 1986; **314:** 649–50.
2. Haddad RM, *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 29–39.

Effects on the liver. Hepatotoxicity, including elevations in liver enzymes, hepatic cholestasis and jaundice, and rarely peliosis hepatis and hepatic tumours, has occurred with androgens and anabolic steroids, particularly the 17α-alkylated derivatives. Prolonged treatment and high doses may be significant contributory factors. Tumours have included hepatocellular carcinomas, benign adenomas, and less commonly angiosarcomas and cholangiocarcinomas. Tumours and peliosis may regress on stopping therapy, but they can also progress to liver failure and death. Some reviews of the hepatic effects of androgens and anabolic steroids are cited below.[1-5] There has been a specific report of benign hepatic adenoma in a patient treated with testosterone enantate for 11 years,[6] and of hepatocellular carcinoma in a patient given testosterone enantate and methyltestosterone.[7] Further specific references may be found under individual drug monographs.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy. *Ann Intern Med* 1974; **81:** 610–18.
2. Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis* 1987; **7:** 230–6.
3. Søe KL, *et al.* Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 1992; **12:** 73–9.
4. Touraine RL, *et al.* Hepatic tumours during androgen therapy in Fanconi anaemia. *Eur J Pediatr* 1993; **152:** 691–3.
5. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.
6. Carrasco D, *et al.* Hepatic adenomata and androgen treatment. *Ann Intern Med* 1984; **100:** 316.
7. Johnson FL. *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; **ii:** 1273–6.

Effects on sexual function. Priapism has occurred after the use of testosterone for the management of delayed puberty[1-4] or hypogonadism.[5-7]

1. Zelissen PMJ, Stricker BHC. Severe priapism as a complication of testosterone substitution therapy. *Am J Med* 1988; **85:** 273–4.
2. Ruch W, Jenny P. Priapism following testosterone administration for delayed male puberty. *Am J Med* 1989; **86:** 256.
3. Madrid Garcia FJ, *et al.* Priapismo secundario a la administración de testosterona en el tratamiento del retraso puberal. *Arch Esp Urol* 2001; **54:** 703–5.
4. Arrigo T, *et al.* High-flow priapism in testosterone-treated boys with constitutional delay of growth and puberty may occur even when very low doses are used. *J Endocrinol Invest* 2005; **28:** 390–1.
5. Zargooshi J. Priapism as a complication of high dose testosterone therapy in a man with hypogonadism. *J Urol (Baltimore)* 2000; **163:** 907.
6. Shergill IS, *et al.* Testosterone induced priapism in Kallmann's syndrome. *J Urol (Baltimore)* 2003; **169:** 1089.
7. Ichioka K, *et al.* Testosterone-induced priapism in Klinefelter syndrome. *Urology* 2006; **67:** e17–e18.

Precautions

Testosterone and other androgens and anabolic steroids should be used cautiously in patients with cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possible fluid retention or oedema caused. They should not be given to patients with hypercalcaemia or hypercalciuria, and should be used cautiously in conditions in which there is a risk of these developing such as skeletal metastases. The use of the 17α-alkylated derivatives, which are associated with an increased risk of hepatotoxicity, is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

In men, androgens and anabolic steroids should not be given to those with carcinoma of the breast or prostate (although in women they have been used in the treatment of certain breast carcinomas; see also Carcinogenicity, above, regarding the use of testosterone in men with a history of prostate cancer). The prostate should be examined regularly during treatment.

Androgens and anabolic steroids should not be given during pregnancy because of the risk of virilisation of the female fetus.

Androgens and anabolic steroids should be used with extreme care in children because of the masculinising effects and also because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature. Skeletal maturation should be monitored during therapy.

Androgens and anabolic steroids may interfere with a number of clinical laboratory tests such as those for glucose tolerance and thyroid function.

Abuse. The adverse effects arising from the illicit use of androgens and anabolic steroids by athletes, often taken together at doses well in excess of those used therapeutically, have been discussed.[1-4] Such misuse is associated with potentially serious health risks. Effects have included abnormal liver function and hepatic neoplasms (see also Effects on the Liver, above), an atherogenic blood lipid profile and increased risk of cardiovascular disease, and reduced glucose tolerance. Hypogonadal states are commonly induced (azoospermia or oligospermia and testicular atrophy in men, and amenorrhoea or oligomenorrhoea in women). Gynaecomastia is relatively common in men, and virilisation in women. Psychiatric disturbances such as mania, hypomania, depression, aggression, and emotional lability, have been described. There is also some evidence that dependence associated with an acute withdrawal syndrome can occur. Rare reports include alterations in immune response, tendon damage, renal cell carcinoma, and peliosis hepatis.

There has been some dispute about the methods used to detect abuse of certain anabolic steroids in athletes. A study in healthy subjects has apparently confirmed endogenous production of small amounts of nandrolone metabolites;[5] a number of different factors might have an influence including genetics, intense exercise, trauma, and hypoglycaemic stress.[6]

1. Pärssinen M, Seppälä T. Steroid use and long-term health risks in former athletes. *Sports Med* 2002; **32:** 83–94.
2. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004; **34:** 513–54.
3. Maravelias C, *et al.* Adverse effects of anabolic steroids in athletes: a constant threat. *Toxicol Lett* 2005; **158:** 167–75.
4. Trenton AJ, Currier GW. Behavioural manifestations of anabolic steroid use. *CNS Drugs* 2005; **19:** 571–95.
5. Reznik Y, *et al.* Urinary nandrolone metabolites of endogenous origin in man: a confirmation by output regulation under human chorionic gonadotropin stimulation. *J Clin Endocrinol Metab* 2001; **86:** 146–50.
6. Kohler RMN, Lambert MI. Urine nandrolone metabolites: false positive doping test? *Br J Sports Med* 2002; **36:** 325–9.

Breast feeding. It is not known whether testosterone is distributed into breast milk, but it should be avoided in women who are breast feeding because of the theoretical potential androgenic effect on the infant. High doses of testosterone can suppress lactation.

Porphyria. Androgens are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

A female patient with acute intermittent porphyria (p.1448) who suffered from severe attacks pre-menstrually was successfully managed with subcutaneous implants of testosterone when suppression of the menstrual cycle with buserelin met with limited success.[1]

1. Savage MW, *et al.* Acute intermittent porphyria treated by testosterone implant. *Postgrad Med J* 1992; **68:** 479–81.

Pregnancy. Reports of female fetal virilisation after maternal use of testosterone[1] or methyltestosterone[2] during pregnancy.

1. Reschini E, *et al.* Female pseudohermaphroditism due to maternal androgen administration: 25-year follow-up. *Lancet* 1985; **i:** 1226.
2. Dewhurst J, Gordon RR. Fertility following change of sex. *Lancet* 1984; **ii:** 1461.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for testosterone, but concluded that there would be no need to specify a numerical maximum residue limit for testosterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that, in the EU, the use of androgens in veterinary practice is restricted and their use as growth promotors is banned. In addition, the use of anabolic steroids is banned in animals intended for human consumption.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 09/07/08)

Interactions

Testosterone and other androgens and anabolic steroids have been reported to enhance the activity of a number of drugs, with resulting increases in toxicity. Drugs affected include ciclosporin (see p.1828), levothyroxine (see p.2173), and anticoagulants such as warfarin (see p.1431). Resistance to the effects of neuromuscular blockers (p.1905) has also been reported. As androgens and anabolic steroids can alter glucose metabolism, doses of insulin or oral antidiabetics may need adjustment.

Pharmacokinetics

Testosterone is absorbed from the gastrointestinal tract, the skin, and the oral mucosa. However, testosterone undergoes extensive first-pass hepatic metabolism when given orally and is therefore usually given intramuscularly, subcutaneously, or transdermally. In addition, the basic molecule of testosterone has been modified to produce orally active compounds and to extend the duration of action. Alkylation of the 17α position produces compounds that are more slowly metabolised by the liver, and hence may be administered orally. Esterification of the 17β hydroxyl group increases lipid solubility and results in slower systemic absorption following intramuscular injection. The rate of absorption of the esters is related to the size of the ester group. The undecylate ester undergoes less complete inactivation after oral doses because of distribution into the lymphatic system. Testosterone esters are hydrolysed to testosterone after absorption.

Testosterone is about 80% bound to sex-hormone binding globulin. Derivatives of 19-nortestosterone and 17-α-methylated compounds have reduced binding to this globulin. The plasma half-life of testosterone is reported to range from about 10 to 100 minutes. It is largely metabolised in the liver via oxidation at the 17-OH group with the formation of androstenedione, which is further metabolised to the weakly androgenic androsterone and inactive etiocholanolone which are excreted in the urine mainly as glucuronides and sulfates. About 6% is excreted unchanged in the faeces after undergoing enterohepatic recirculation. Testosterone is converted to the more active dihydrotestosterone in some target organs by 5α-reductase. 19-Nortestosterone derivatives appear to be less susceptible to this enzyme. Small amounts of testosterone are aromatised to form oestrogenic derivatives, particularly oestradiol. Compounds with a saturated A-ring, such as mesterolone, appear to be less likely to be aromatised to oestrogen.

◊ References to the pharmacokinetics of subcutaneous testosterone pellets,[1] scrotal[2,3] and non-scrotal[4-7] transdermal patches, gel,[8,9] and a buccal preparation,[10,11] are given below.

1. Handelsman DJ, *et al.* Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990; **71:** 216–22.
2. Findlay JC, *et al.* Transdermal delivery of testosterone. *J Clin Endocrinol Metab* 1987; **64:** 266–8.
3. Cunningham GR, *et al.* Testosterone replacement with transdermal therapeutic systems: physiological serum testosterone and elevated dihydrotestosterone levels. *JAMA* 1989; **261:** 2525–30.
4. Meikle AW, *et al.* Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site. *J Clin Endocrinol Metab* 1996; **81:** 1832–40.
5. Yu Z, *et al.* Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol* 1997; **37:** 1129–38.
6. Dobs AS, *et al.* Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; **84:** 3469–78.
7. Singh AB, *et al.* Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab* 2001; **86:** 2437–45.
8. Swerdloff RS, *et al.* Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000; **85:** 4500–10.
9. Marbury T, *et al.* Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim , compared to AndroGel . *Biopharm Drug Dispos* 2003; **24:** 115–20.
10. Korbonits M, *et al.* A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrinol Metab* 2004; **89:** 2039–43.
11. Wang C, *et al.* New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. *J Clin Endocrinol Metab* 2004; **89:** 3821–9.

Uses and Administration

The natural hormone testosterone and its derivatives have anabolic and androgenic properties (for further details, see p.2058).

The primary indication for androgens, such as testosterone or its esters, is as replacement therapy in **male hypogonadal disorders** (below) caused by either pituitary or testicular disorders or in hypogonadism following orchidectomy. Testosterone may be used as a subcutaneous implant in a dose of 100 to 600 mg; plasma concentrations of testosterone are usually maintained within the physiological range for 4 to 5 months with a dose of 600 mg. It may also be given by transdermal delivery systems. Patches are applied to the back, abdomen, thighs or upper arms to supply 2.5 to 7.5 mg daily. A scrotal patch containing 10 or 15 mg of testosterone and supplying about 4 or 6 mg of testosterone in 24 hours has been used, but is no longer widely available. Hydroalcoholic gels containing 1 or 2% testosterone are also used; they are applied daily to the shoulders and upper arms, abdomen, or thighs, depending on the preparation. About 10% of the applied dose is absorbed across the skin to provide a systemic dose of testosterone 5 to 10 mg. A sustained-release adhesive buccal system that contains testosterone 30 mg is applied twice daily; by this route the systemic dose is about 3 mg. Testosterone has also been given by intramuscular injection in a dose of up to 50 mg two or three times weekly, but testosterone esters are generally preferred by this route.

The testosterone esters are usually formulated as oily solutions for intramuscular use to give a prolonged duration of action. Doses that have been used for the various esters are:

- testosterone cipionate 50 to 400 mg every 2 to 4 weeks

- testosterone enantate 50 to 400 mg every 2 to 4 weeks, or an initial dose of 250 mg every 2 to 3 weeks followed by maintenance dosing every 3 to 6 weeks
- testosterone propionate up to 50 mg two or three times weekly
- testosterone undecylate 1 g every 10 to 14 weeks

The isocaproate, phenylpropionate, and propionate esters may be given as a combined intramuscular preparation, sometimes also containing testosterone decanoate. Testosterone hexahydrobenzoate, testosterone hexahydrobenzylcarbonate, and testosterone isobutyrate have also been used. The undecylate ester is also given orally in an initial dose of 120 to 160 mg daily, in 2 divided doses, for 2 to 3 weeks, followed by a maintenance dose of 40 to 120 mg daily. See below for some doses of testosterone used in children.

Androgens and anabolic steroids have sometimes been used with oestrogens in the management of certain menopausal disorders, but the use of androgens and anabolic steroids in women with osteoporosis is no longer advocated because their adverse effects essentially outweigh any benefit they may produce. In the UK menopausal women are sometimes given implants of testosterone in a dose of 50 to 100 mg every 4 to 8 months as an adjunct to menopausal HRT for symptoms such as decreased libido. In the USA, preparations containing an androgen and an oestrogen are available for the treatment of menopausal vasomotor symptoms; intramuscular doses of testosterone cipionate 50 mg with estradiol cipionate 2 mg have been given once every 4 weeks, with attempts to taper treatment at 3 to 6 month intervals. However, there are concerns about the use of these preparations and conflicting opinion as to their usefulness (see below). More recently a transdermal patch has become available for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause (bilateral oophorectomy and hysterectomy) who are receiving oestrogen therapy. The patch is applied twice weekly and delivers a daily systemic dose of testosterone 300 micrograms; the initial response to therapy should be evaluated after 3 to 6 months and reassessed every 6 months. In postmenopausal women androgens, and sometimes anabolic steroids are occasionally used in the hormonal therapy of disseminated breast carcinoma but care should be taken to choose a compound with a lower masculinising effect; the short-acting synthetic compounds are usually preferred for such purposes. Testosterone enantate has been used in doses of 200 to 400 mg every 2 to 4 weeks by intramuscular injection.

Anabolic steroids, and sometimes androgens, have been used in the treatment of refractory anaemias characterised by deficient red cell production, such as aplastic anaemia. Anabolic steroids and synthetic androgens with an attenuated action (sometimes known as 'attenuated androgens') such as danazol are also used in the management of hereditary angioedema.

Topical androgens may be used in the treatment of lichen sclerosus.

Androgens and anabolic steroids have been used for their anabolic properties in various catabolic states.

Testosterone hemisuccinate is an ingredient of preparations that have been promoted for the management of cataracts.

◊ General reviews of androgens and anabolic steroids.

1. Hickson RC, *et al.* Adverse effects of anabolic steroids. *Med Toxicol Adverse Drug Exp* 1989; **4:** 254–71.
2. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996; **334:** 707–14.
3. Conway AJ, *et al.* Use, misuse and abuse of androgens: the Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; **172:** 220–4. Correction. *ibid.*; 334. Also available at: http://www.mja.com.au/public/issues/172_05_060300/conway/conway.html (accessed 13/11/07)
4. Handelsman DJ. Testosterone: use, misuse and abuse. *Med J Aust* 2006; **185:** 436–9.

Administration in children. Testosterone is used in adolescent males with hypogonadism, and has been used in constitutionally delayed puberty (see below). It has also been used to reduce final height in boys with constitutional tall stature (see below).

For the induction and maintenance of **sexual maturation** in boys over 12 years of age, the *BNFC* includes doses of testosterone undecylate 40 mg orally on alternate days, increasing up to 120 mg daily according to response. Alternatively, testosterone enantate or propionate may be given by deep intramuscular injection in doses of 25 to 50 mg/m^2 every month, increasing every 6 to 12 months according to response. An injection containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg) has also been given intramuscularly, once each month for 3 doses, for delayed puberty. For boys over 15 years, the adult dose of a transdermal patch may be used, and an implant may be suitable for maintenance in hypogonadal males over 16 years (see above for doses). However, great care is necessary when using androgens for such conditions as bone growth and final height may be inhibited by the early fusion of the epiphyses. Extemporaneously prepared testosterone cream has been applied topically in the management of microphallus (the alcohol in proprietary gels can cause irritation).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p.1798). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using testosterone has been tried in boys in order to increase responsiveness to the test,[1-3] although there appears to be no consensus on such use.[4] The *BNFC* includes a single intramuscular dose of a product containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg), given 3 to 5 days before the test.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82:** 861–4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86:** 5805–12.
3. Gönç EN, *et al.* Comparison of stimulated growth hormone levels in primed versus unprimed provocative tests: effect of various testosterone doses on growth hormone levels. *Horm Res* 2001; **56:** 32–7.
4. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 22/08/08)

Anabolic effects. The androgens generally possess anabolic activity and were formerly used to increase weight in patients suffering from emaciation or debilitating diseases but effectiveness was doubtful. The anabolic steroids were developed in order to enhance the ability to build proteins and diminish the virilising and masculinising effects of the natural androgens, but all anabolics retain some androgenic activity. The anabolic steroids have again, like the androgens, been used in an attempt to produce weight gain in cachexia and wasting diseases (p.2115).

The anabolic steroids and androgens have been the subject of much misuse and abuse by athletes, sports persons, and body builders (see under Precautions, above) in an attempt to increase muscle mass and body-weight but such use cannot be justified.

References to the anabolic effects of testosterone.

1. Bhasin S, *et al.* The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; **335:** 1–7.
2. Basaria S, *et al.* Anabolic-androgenic steroid therapy in the treatment of chronic diseases. *J Clin Endocrinol Metab* 2001; **86:** 5108–17.
3. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *Lancet Infect Dis* 2002; **2:** 692–9.
4. Johns K, *et al.* Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).

Antineoplastic-induced infertility. For reference to the use of testosterone to preserve gonadal function during cyclophosphamide therapy, see Effects on Reproductive Potential, p.702.

Constitutionally delayed puberty. Testosterone enantate given by intramuscular injection every 1 to 2 months for periods ranging from 3 months to several years, produced beneficial effects in boys with constitutionally delayed puberty and growth;[1,2] growth rate increased, sexual and skeletal maturation were stimulated, and full height potential did not appear to be compromised. However, it has been pointed out that repeated intramuscular injections are painful and are disliked by adolescents;[3] oral testosterone undecylate or oxandrolone have been shown to be effective in the treatment of delayed puberty and growth in boys,[4,5] and may be preferred.[3] It should be noted that giving androgens to boys with constitutional delay of growth and puberty is controversial (see p.2079). For reference to the use of testosterone in boys with delayed puberty due to hypogonadism see below.

1. Donaldson MDC, Savage DCL. Testosterone therapy in boys with delayed puberty. *Arch Dis Child* 1987; **62:** 647–8.
2. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med* 1988; **319:** 1563–7.
3. Kelnar CJH. Treatment of the short, sexually immature adolescent boy. *Arch Dis Child* 1994; **71:** 285–7.
4. Albanese A, *et al.* Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child* 1994; **71:** 315–17.
5. Brown DC, *et al.* A double blind, placebo controlled study of the effects of low dose testosterone undecanoate on the growth of small for age, prepubertal boys. *Arch Dis Child* 1995; **73:** 131–5.

Constitutionally tall stature. Supraphysiological doses of androgens have been used to *reduce* final height in tall adolescent boys. Testosterone esters in monthly doses of up to 1000 mg by intramuscular injection have been used.[1] Preliminary evidence after a mean of 10 years follow-up suggests that there was no long-term effect on reproductive function.[2] For reference to the use of testosterone to *increase* growth rate, see Constitutionally Delayed Puberty, above.

1. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
2. de Waal WJ, *et al.* Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child* 1995; **73:** 311–15.

Dementia. There has been some suggestion that age-related reduction in endogenous testosterone may have a role in cognitive decline in men (see Dementia, p.362). In a longitudinal study[1] of 574 men who were followed for about 19 years, a lower calculated concentration of free testosterone was found to be one of a number of risk factors associated with the development of Alzheimer's disease. A possible role for testosterone treatment has therefore been proposed and some preliminary studies have been undertaken. A small short-term study[2] of older men with Alzheimer's disease or mild cognitive impairment reported improvements in some measures of cognitive function in patients given intramuscular testosterone. In another study,[3] however, testosterone applied as a topical gel was reported to improve quality of life as scored by the caregivers of men with mild Alzheimer's disease, but to have no significant effect on quality of life in healthy elderly men or on cognitive function in either group.

1. Moffat SD, *et al.* Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004; **62:** 188–93.
2. Cherrier MM, *et al.* Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005; **64:** 2063–8.
3. Lu PH, *et al.* Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol* 2006; **63:** 177–85.

Erectile dysfunction. Although testosterone is known to enhance libido its physiological role in erection is still not fully understood. Studies have produced mixed results, but suggest that men with sexual or erectile dysfunction (p.2179) and low baseline concentrations of testosterone may derive some benefit from testosterone monotherapy;[1,2] the use of testosterone may also have some benefit in those who have responded poorly to phosphodiesterase type-5 inhibitors.[1,3] However, because of limited evidence and the potential for adverse effects, therapy should probably be limited to men with severe hypogonadism[1,2] (see also Hypogonadism, below).

For reference to the use of a cream containing testosterone, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

1. Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006; **119:** 373–82.
2. Boloña ER, *et al.* Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 20–8.
3. Shabsigh R, *et al.* The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract* 2006; **60:** 1087–92.

Gender reassignment. Testosterone is used in female-to-male transsexuals to develop and maintain secondary sexual characteristics.[1,2] A testosterone ester, or a combination of esters, is usually given by intramuscular injection in doses of 200 to 250 mg every 2 weeks, adjusted according to response.[2,3] Alternatively, testosterone undecylate 1 g may be given once every 10 to 12 weeks.[3] Oral or transdermal testosterone is less commonly used, and the addition of a progestogen may be needed to fully suppress menstruation in non-oophorectomised patients.[2]

1. Moore E, *et al.* Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 2003; **88:** 3467–73.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Heart failure. Low serum-testosterone concentrations have been reported in men with chronic heart failure (p.1165). A study in men with moderate heart failure and low or low-normal testosterone concentrations found that 12 months of transdermal testosterone therapy improved symptoms of heart failure and exercise capacity.[1] The mechanism of benefit was unclear.

1. Malkin CJ, *et al.* Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006; **27:** 57–64.

Hypogonadism. Replacement therapy with testosterone or a testosterone ester is the standard treatment for *primary hypogonadism* in men (see p.2079). The androgen is often given as an intramuscular depot injection of one of the esters, although subcutaneous implants, oral formulations, transdermal systems, topical gel, and a buccal preparation are also used (for doses see above).[1-3] Testosterone is also used to promote masculinisation in hypogonadal adolescent boys,[4,5] and is of value in the prevention of osteoporosis in hypogonadal men.[6,7] Testosterone has a negative feedback effect on gonadotrophin secretion, therefore any remaining spermatogenesis is generally suppressed; androgens are thus rarely useful in reversing male infertility (p.2080). Recommendations for monitoring therapy have been made.[3,8]

Transdermal testosterone may possibly be of benefit as an adjunct to oestrogen replacement in *women* who have undergone hysterectomy and oophorectomy (see Menopausal Hormone Replacement Therapy, below).

There has also been growing interest in the use of testosterone therapy in *healthy older men*, although there is limited evidence to prove a direct association between clinical changes and the natural decline of endogenous hormone concentrations with age.[9] This aspect of ageing is increasingly being described as the andropause, but the fall in testosterone concentrations is gradual, and not a rapid and significant decline of hormones with loss of fertility like that which occurs in the female menopause[9,10] (p.2071); other terms such as partial androgen deficiency or late-onset hypogonadism have also been proposed.[9] Testosterone therapy has been studied in healthy older men with normal or low-normal serum-testosterone concentrations. Modest beneficial changes in body composition (increased lean body-mass and decreased fat-mass) have been reported, but many studies have found no associated improvement in muscle strength, mobility, or functional autonomy, or a reduced risk of falls. Results are also inconsistent or negative from studies measuring skeletal effects, sexual function, cognitive function, mood, and quality of life.[9] A meta-analysis[11] of 8 studies suggested that intramuscular testosterone might be more effective than transdermal administration for increasing lumbar bone mineral density. There are concerns about potential adverse effects of testosterone on the prostate (see Carcinogenicity, above) and the cardiovascular system, and high doses have been reported to cause or exacerbate sleep apnoea.[9,12] Although recommendations have been made for the use and monitoring of testosterone therapy in healthy older men with androgen deficiency,[12-14] many caution that until further clinical studies have been done it should only be used in those with confirmed hypogonadism.[9,10]

1. Gooren LJG, Bunck MCM. Androgen replacement therapy: present and future. *Drugs* 2004; **64:** 1861–91.
2. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol (Oxf)* 2006; **65:** 275–81.
3. Bhasin S, *et al.* Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 1995–2010. Also available at: http://www.endo-society.org/guidelines/final/upload/AndrogensMenGuideline053006.pdf (accessed 22/08/08)
4. Moorthy B, *et al.* Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height. *Arch Dis Child* 1991; **66:** 197–9.
5. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Arch Dis Child* 1997; **76:** 495–9.
6. Wang C, *et al.* Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 2001; **54:** 739–50.
7. Zacharin MR, *et al.* Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol (Oxf)* 2003; **58:** 691–5.
8. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350:** 482–92.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26:** 833–76.
10. Juul A, Skakkebæk NE. Androgens and the ageing male. *Hum Reprod Update* 2002; **8:** 423–33.
11. Tracz MJ, *et al.* Testosterone use in men and its effects on bone health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab* 2006; **91:** 2011–16.
12. Liu PY, *et al.* The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab* 2004; **89:** 4789–96.
13. Nieschlag E, *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *J Androl* 2006; **27:** 135–7. Also published in *Eur Urol* 2005; **48:** 1–4. and *Int J Androl* 2005; **28:** 125–7.
14. Wald M, *et al.* Testosterone replacement therapy for older men. *J Androl* 2006; **27:** 126–32.

Lichen sclerosus. Topical androgens such as androstanolone and testosterone have been used to treat vulvar lichen sclerosus (p.1580) in postmenopausal women.[1-4] However, virilisation can occur and a topical corticosteroid is generally preferred.[5]

1. Paslin D. Treatment of lichen sclerosus with topical dihydrotestosterone. *Obstet Gynecol* 1991; **78:** 1046–9.
2. Bracco GL, *et al.* Clinical and histologic effects of topical treatments of vulval lichen sclerosus: a critical evaluation. *J Reprod Med* 1993; **38:** 37–40.
3. Paslin D. Androgens in the topical treatment of lichen sclerosus. *Int J Dermatol* 1996; **35:** 298–301.
4. Joura EA, *et al.* Short-term effects of topical testosterone in vulvar lichen sclerosus. *Obstet Gynecol* 1997; **89:** 297–9.
5. Neill SM, *et al.* British Association of Dermatologists. Guidelines for the management of lichen sclerosus. *Br J Dermatol* 2002; **147:** 640–9. Also available at: http://www.bad.org.uk/healthcare/guidelines/Lichen_Sclerosus.pdf (accessed 13/11/07)

Male contraception. In male contraceptive studies it was found that high-dose testosterone severely reduced sperm production.[1] In those in whom azoospermia was not induced there was oligozoospermia with remaining sperm having a markedly reduced fertilising capacity. In a multicentre study carried out by WHO[2] involving 271 healthy fertile men, weekly intramuscular injection of testosterone enantate 200 mg produced azoospermia in 157 men within 6 months. In a subsequent 12-month study of these azoospermic men, during which time testosterone enantate was the only contraceptive measure used, there was only 1 pregnancy. Spermatogenesis was re-established on withdrawal of testosterone. These findings have been confirmed in a larger study of the same regimen, which additionally assessed contraceptive efficacy in men who achieved oligozoospermia (less than 3×10^6/mL).[3] No pregnancies occurred in couples where the man was azoospermic. However, the pregnancy rate was 8.1 per 100-person-years in the subgroup of couples where the man was oligozoospermic. This rate is sixfold higher than is generally seen with hormonal contraceptives in women.[4] Both studies found that consistent azoospermia was achieved in a higher percentage of Asian men (95%) than Western men (70%).[4] Testosterone undecylate has also been studied as a longer-acting intramuscular injection. In a study[5] involving Chinese men, a loading dose of 1000 mg followed by monthly maintenance doses of 500 mg effectively and persistently suppressed spermatogenesis in about 95% of 296 men who had initially responded; pregnancy occurred in the partner of 1 of the 6 men with sperm rebound.

An alternative approach being investigated is the use of testosterone with a progestogen, which enhances the suppression of spermatogenesis and may allow lower doses of androgen to be used with fewer adverse effects. Progestogens under investigation include cyproterone, desogestrel, etonogestrel, levonorgestrel, medroxyprogesterone, and norethisterone.[6,7]

For a general discussion on choice of contraceptive method, including mention of male contraception, see p.2070.

1. Matsumoto AM. Is high dosage testosterone an effective male contraceptive agent? *Fertil Steril* 1988; **50:** 324–8.
2. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* 1990; **336:** 955–9.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril* 1996; **65:** 821–9.
4. Anonymous. An androgen contraceptive for men: preliminary findings. *WHO Drug Inf* 1996; **10:** 50–3.
5. Gu Y-Q, *et al.* A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab* 2003; **88:** 562–8.
6. Amory JK, *et al.* Drug insight: Recent advances in male hormonal contraception. *Nat Clin Pract Endocrinol Metab* 2006; **2:** 32–41.
7. Grimes DA, *et al.* Steroid hormones for contraception in men. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/11/07).

Menopausal hormone replacement therapy. Menopause does not necessarily result in androgen deficiency in women, and androgen replacement is therefore not routinely required (see Menopausal Disorders, p.2077). In the UK menopausal women may nonetheless sometimes be given implants of testosterone as an adjunct to menopausal HRT. In the USA, injectable preparations containing an androgen and an oestrogen are available for the treatment of menopausal vasomotor symptoms, but there is conflicting opinion as to their usefulness, and further data are needed.[1] In Canada, a preparation containing estradiol and testosterone esters for intramuscular injection (*Climacteron; Sabex, Canad.*) was discontinued in 2005 because of concerns that testosterone is partially metabolised to oestrogen, which should be opposed by a progestogen in women with a uterus, and that there was no established dose of progestogen that could be recommended in this situation.[2] A study[3] in healthy postmenopausal women found that oral testosterone alone did not stimulate endometrial proliferation as estradiol did, and that it appeared to reduce the effect of estradiol when they were used together. However, therapy was given for only 3 months and long-term effects need further study. Improvements in mood and libido have been shown when androgens were given to postmenopausal women with an established cause of androgen deficiency such as surgically induced menopause.[4] A systematic review of the addition of testosterone to postmenopausal HRT considered that there was some evidence of benefit on sexual function, but that studies varied too much to estimate the effect of any particular combination.[5] More recently, a number of placebo-controlled studies in women with surgically induced[6-9] or natural[10] menopause have reported improvements in sexual activity and desire with transdermal testosterone. A product (*Intrinsa; Proctor and Gamble, UK*) has been licensed for use in the UK for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause who are also receiving oestrogen replacement therapy, but the FDA has not licensed it in the USA and has expressed concern about the lack of data on long-term safety.[11] However, the North American Menopause Society[12] has recommended that testosterone therapy may be considered for postmenopausal women who present with symptoms of decreased sexual desire associated with personal distress and who have no other identifiable cause for their sexual concerns. Nevertheless, they warn that use of testosterone without estrogen cannot be recommended because there is no information on safety and efficacy in this situation, that topical preparations are preferred over oral products, that the lowest dose should be used for the shortest time, and that there is insufficient efficacy and safety data for therapy beyond 6 months.

The Endocrine Society[13] has evaluated data on the use of testosterone in various groups of women, including those with menopausal symptoms, and advises that although there is some evidence for efficacy in selected populations, such as surgically menopausal women, it cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.

The use of transdermal testosterone, with oestrogen and progestogen replacement therapy, is also being investigated in young women with spontaneous premature ovarian failure.[14]

1. Abraham D, Carpenter PC. Issues concerning androgen replacement therapy in postmenopausal women. *Mayo Clin Proc* 1997; **72:** 1051–5.
2. Sandoz Canada. Discontinuation of Climacteron Injection (estradiol dienanthate/estradiol benzoate and testosterone enanthate benzilic acid hydrazone injection in corn oil) (issued 23rd November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps-eng.pdf (accessed 22/08/08)
3. Zang H, *et al.* Effects of testosterone treatment on endometrial proliferation in postmenopausal women. *J Clin Endocrinol Metab* 2007; **92:** 2169–75.
4. Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154:** 1–11.
5. Somboonporn W, *et al.* Testosterone for peri- and postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).
6. Shifren JL, *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000; **343:** 682–8.
7. Simon J, *et al.* Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005; **90:** 5226–33.
8. Braunstein GD, *et al.* Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005; **165:** 1582–9.
9. Buster JE, *et al.* Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005; **105:** 944–52.
10. Shifren JL, *et al.* Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause* 2006; **13:** 770–9.
11. Moynihan R. FDA panel rejects testosterone patch for women on safety grounds. *BMJ* 2004; **329:** 1363.
12. North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2005; **12:** 497–511. Also available at: http://www.menopause.org/aboutmeno/PStestosterone.pdf (accessed 13/11/07)
13. Wierman ME, *et al.* Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 3697–3710. Also available at: http://www.endo-society.org/guidelines/final/upload/Androgens_in_Women_CG.pdf (accessed 22/08/08)
14. Kalantaridou SN, *et al.* A pilot study of an investigational testosterone transdermal patch system in young women with spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 2005; **90:** 6549–52.

Rheumatoid arthritis. A hypogonadal condition characterised by low serum-testosterone concentrations appears to be associated with at least the active stages of rheumatoid arthritis (p.11) in men.[1] Clinical improvement and reductions in IgM rheumatoid factor concentration, tender joint count, and the daily dosage of NSAIDs required, were observed in a small study[1] of men with rheumatoid arthritis and low serum-testosterone concentrations given oral testosterone undecylate 40 mg three times daily for 6 months. Improvements in rheumatoid arthritis were also seen in 12 of 36 postmenopausal women treated with intramuscular testosterone 50 mg plus a low dose of progesterone (2.5 mg) once every 2 weeks compared with 2 of 32 women receiving placebo.[2] However, a placebo-controlled study[3] in 30 men with normal serum-testosterone concentrations found no beneficial effect from intramuscular testosterone enantate on measures of disease activity.

1. Cutolo M, *et al.* Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum* 1991; **34:** 1–5.
2. Booij A, *et al.* Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis* 1996; **55:** 811–15.
3. Hall GM, *et al.* A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 1996; **35:** 568–73.

Preparations

BP 2008: Testosterone Implants; Testosterone Propionate Injection;
USP 31: Testosterone Cypionate Injection; Testosterone Enanthate Injection; Testosterone Injectable Suspension; Testosterone Propionate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Androlone; Androtag; Nebido; Sustanon 250; Testoviron Depot 100; Testoviron Depot 250; Undestor; ***Austral.:*** Andriol; Androderm; Primoteston Depot; Reandron; Sustanon 100; Sustanon 250; Testogel; ***Austria:*** Andriol; Nebido; Reandron; Testoderm; Testoviron 250; ***Belg.:*** AndroGel; Sustanon 250; Testim; Testocaps; Undestor†; ***Braz.:*** Androxon; Deposteron; Nebido; ***Canad.:*** Andriol; Androderm; AndroGel; Delatestryl; ***Chile:*** Actiser-T; Nebido; Primoniat Depot; Sustenan; Sustenan 250; Testocaps; ***Cz.:*** Agovirin; AndroGel; Intrinsa; Livensa; Nebido; Sustanon; Testopatch; Tostran; Undestor; ***Denm.:*** Andriol; Nebido; Restandol; Testogel; Testoviron Depot 135; Testoviron Depot 250; ***Fin.:*** Atmos; Nebido; Panteston; Sustanon 250; Testim; Testogel; ***Fr.:*** AndroGel; Androtardyl; Intrinsa; Nebido; Pantestone; Testopatch; ***Ger.:*** Andriol; Androderm†; Androtop; Nebido; Striant; Testim; Testogel; Testoviron Depot 250; ***Gr.:*** Androderm; Andropatch; Nebido; Restandol; Testim; Testoviron; ***Hong Kong:*** Andriol; Sustanon; Testoviron Depot; ***Hung.:*** Andriol; Nebido; ***India:*** Aquaviron; Nuvir; Sustanon 100; Sustanon 250; Testanon 25; Testanon 50; Testoviron Depot; ***Indon.:*** Andriol Testocaps; Nebido; Sustanon 250; ***Irl.:*** Andropatch; Nebido; Restandol; Striant; Sustanon 100; Sustanon 250; Testim; Tes-

The symbol † denotes a preparation no longer actively marketed

togel; ***Israel:*** AndroGel; Androxon; Sustanon 250; Testoviron Depot; ***Ital.:*** Andriol; Androderm†; AndroGel; Sustanon; Testim; Testo-Enant; Testogel; Testovis; ***Malaysia:*** Andriol; Jenasteron†; Nebido; ***Mex.:*** Andriol; Nebido; Primoteston Depot; Sostenon; Testoprim-D; ***Neth.:*** Andriol; AndroGel; Nebido; Striant; Sustanon 100; Sustanon 250; Testim; Testogel; Testoviron Depot†; ***Norw.:*** Andriol; Androxon†; Atmos; Nebido; Testogel; ***NZ:*** Androderm; Panteston; Primoteston Depot; Sustanon; ***Philipp.:*** Andriol; Nebido; ***Pol.:*** Nebido; Omnadren; Testosteronum Prolongatum; Undestor; ***Port.:*** Andriol; AndroGel; Intrinsa; Livensa; Nebido; Striant; Testim; Testogel; Testopatch; Testoviron Depot; Tostran; ***Rus.:*** Andriol (Андриол); AndroGel (Андрогель); Nebido (Небидо); Omnadren (Омнадрен); ***S.Afr.:*** Androxon; Depotrone; Sustanon 250; ***Singapore:*** Andriol; Sustanon 250; ***Spain:*** Androderm; Numanis; Reandron; Testex; Testim; Testogel; Testoviron Depot 250; ***Swed.:*** Atmos; Nebido; Testim; Testogel; Testoviron Depot; Testrex; Undestor; ***Switz.:*** Andriol; Androderm; Nebido; Testoderm†; Testogel; Testoviron Depot; ***Thai.:*** Andriol; Testoviron 100†; Testoviron Depot; Virormone†; ***Turk.:*** Afro; Sustanon 250; Virigen; ***UK:*** Andropatch; Intrinsa; Nebido; Restandol; Striant; Sustanon 100; Sustanon 250; Testim; Testogel; Testosterone Implants; Tostran; Virormone; ***USA:*** Androderm; AndroGel; Delatestryl; Striant; Testim; Testoderm†; Testopel; Virilon†; ***Venez.:*** Andriol; AndroGel; Polysterone 250; Proviron Depot.

Multi-ingredient: ***Arg.:*** Supligol†; ***Braz.:*** Durateston; Estandron P; Trinestril; ***Canad.:*** Climacteron; ***Chile:*** Estandron Prolongado; ***Cz.:*** Folivirin; ***Ger.:*** Androfemon†; Testoviron Depot 100†; Testoviron Depot 50†; ***India:*** Mixogen; ***Ital.:*** Facovit; Testoviron; ***Malaysia:*** Sustanon 250; ***Mex.:*** Despamen; Sten; ***Neth.:*** Estandron Prolongatum; ***Norw.:*** Primoteston Depot; ***Port.:*** Sustenon 250; ***S.Afr.:*** Mixogen; Primodian Depot; ***Spain:*** Testoviron Depot 100; ***Thai.:*** Metharmon-F; Primodian Depot; ***Turk.:*** Estandron Prolongatum; ***USA:*** Depo-Testadiol; Depotestogen.

Tetrahydrogestrinone ⊗

THG. 18a-Homo-pregna-4,9,11-trien-17β-ol-3-one; .

$C_{21}H_{28}O_2$ = 312.4.

CAS — 618903-56-3.

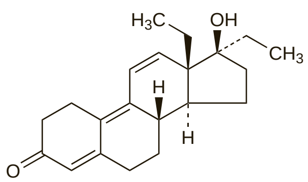

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of tetrahydrogestrinone: The Clear.

Profile

Tetrahydrogestrinone is a synthetic anabolic steroid that is structurally related to gestrinone (p.2106) and trenbolone (p.2135). It has been subject to abuse in sport.

Action. Tetrahydrogestrinone had androgenic and progestogenic activity in a yeast-based *in-vitro* bioassay study.[1] The anabolic and androgenic properties of tetrahydrogestrinone have also been studied in *animals*.[2-4]

1. Death AK, *et al.* Tetrahydrogestrinone is a potent androgen and progestin. *J Clin Endocrinol Metab* 2004; **89:** 2498–2500.
2. Labrie F, *et al.* Tetrahydrogestrinone induces a genomic signature typical of a potent anabolic steroid. *J Endocrinol* 2005; **184:** 427–33.
3. Jasuja R, *et al.* Tetrahydrogestrinone is an androgenic steroid that stimulates androgen receptor-mediated, myogenic differentiation in C3H10T1/2 multipotent mesenchymal cells and promotes muscle accretion in orchidectomized male rats. *Endocrinology* 2005; **146:** 4472–8.
4. Friedel A, *et al.* Tetrahydrogestrinone is a potent but unselective binding steroid and affects glucocorticoid signalling in the liver. *Toxicol Lett* 2006; **164:** 16–23.

Tibolone *(BAN, USAN, rINN)* ⊗

7α-Methylnorethynodrel; Org-OD-14; Tibolon; Tibolona; Tiboloni; Tibolonum. 17β-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

Тиболон

$C_{21}H_{28}O_2$ = 312.4.

CAS — 5630-53-5.

ATC — G03CX01.

ATC Vet — QG03CX01.

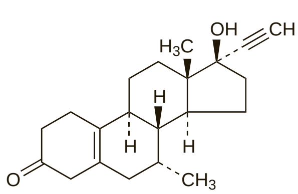

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tibolone). A white or almost white, crystalline powder or crystals. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store at a temperature of 2° to 8°.

Adverse Effects

Irregular vaginal bleeding or spotting may occur with tibolone, mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HRT (p.2071), tibolone does not produce regular withdrawal bleeding. Other effects on the genital tract may include leucorrhoea, pruritus, candidiasis, and vaginitis. Other adverse effects have included breast pain, weight gain, oedema, dizziness, skin reactions, headache, migraine, visual disturbances, gastrointestinal disturbances, hypertrichosis, altered liver function, depression, and arthralgia or myalgia.

Incidence of adverse effects. In 1994, the UK CSM had received reports of 2796 suspected adverse reactions with tibolone over 3 years, out of about 666 000 prescriptions.[1] The commonest reported effects were headache, dizziness, nausea, rash, itching, and weight gain. Vaginal bleeding appeared to occur in about 8 to 9% of recipients. There had also been 52 reports of migraine, 4 of exacerbation of migraine, and 49 reports of visual disturbances, some suggestive of migraine.

1. CSM/MCA. Tibolone (Livial). *Current Problems* 1994; **20:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 18/08/08)

Carcinogenicity. *BREAST.* The large cohort Million Women study[1] examined breast cancer incidence and mortality in relation to HRT use. After an average follow-up of 2.6 years for incidence, and 4.1 years for mortality, data were available for a group of 18 186 women who had used tibolone. There were 184 cases of invasive breast cancer equating to an overall risk of 1.45 (95% confidence interval 1.25 to 1.68) relative to women who had never used HRT. This was between the relative risks calculated for oestrogen-only HRT (1.30) and combined HRT (2.00). The risk was raised for current but not past use of tibolone, and increased with total duration of use.

For comment on the risk of recurrence in women with a history of breast cancer see Malignant Neoplasms under Precautions, below.

1. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362:** 419–27. Correction. *ibid.*; 1160.

ENDOMETRIUM. Endometrial hyperplasia and endometrial carcinoma have been rarely reported after investigation of uterine bleeding in women receiving tibolone therapy,[1-3] as has exacerbation of adenomyosis.[4] Some of these women had previously received oestrogens.

A cohort and nested case-control study[5] found that tibolone might have been associated with an increased risk of endometrial cancer compared with conventional forms of combined HRT, but the data were weak and might have been affected by bias and uncontrolled confounding factors. The large cohort Million Women Study[6] of HRT included a group of 28 028 who had used tibolone for an average of about 3 years. The risk of endometrial cancer was increased to 1.79 (95% confidence interval 1.43 to 2.25) in those who had used tibolone, compared with women who had never used HRT, and the risk was higher with more than 3 years of use compared with shorter durations. In contrast, a smaller randomised study[7] comparing tibolone with combined HRT recorded no cases of endometrial hyperplasia or carcinoma in 1317 women given tibolone for up to 2 years.

1. von Dadelszen P, *et al.* Endometrial hyperplasia and adenocarcinoma during tibolone (Livial) therapy. *Br J Obstet Gynaecol* 1994; **101:** 158–61.
2. Ginsburg J, Prelevic GM. Cause of vaginal bleeding in postmenopausal women taking tibolone. *Maturitas* 1996; **24:** 107–10.
3. Yazigi R, *et al.* Carcinoma of the endometrium in patients treated with tibolone. *Gynecol Oncol* 2004; **93:** 568–70.
4. Prys Davies A, Oram D. Exacerbation of adenomyosis in a postmenopausal woman taking tibolone associated with an elevation in serum CA 125. *Br J Obstet Gynaecol* 1994; **101:** 632–3.
5. de Vries CS, *et al.* Tibolone and endometrial cancer: a cohort and nested case-control study in the UK. *Drug Safety* 2005; **28:** 241–9.
6. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365:** 1543–51.
7. Archer DF, *et al.* Endometrial effects of tibolone. *J Clin Endocrinol Metab* 2007; **92:** 911–18.

Effects on the cardiovascular system. A study[1,2] of tibolone in the treatment of osteoporosis in postmenopausal women found that although it reduced the risk of fracture there was an increased risk of stroke.

1. Grobbee DE. LIFT study to continue as planned. *BMJ* 2005; **331:** 843.
2. Cummings SR. LIFT study is discontinued. *BMJ* 2006; **332:** 667.

Precautions

Tibolone is contra-indicated in women with hormone-dependent tumours, cardiovascular or cerebrovascular disorders including thrombophlebitis, thromboembolic processes, or a history of these conditions, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, porphyria, and severe liver disorders. It should not be given to pregnant women and is not intended for use in premenopausal women, except those being treated with a gonadorelin analogue. Use of tibolone within 12 months of a natural menopause is also not recommended because irregular vaginal bleeding is likely. In postmenopausal women, vaginal bleeding starting after 3 months or more of treatment, or recurrent or persistent bleeding, should be investigated.

Care should be taken when giving tibolone to patients with uterine fibroids, endometriosis, liver disease, disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction, hypertension, epilepsy, or migraine, or with a history of these conditions. It should also be given with caution to patients with dyslipidaemia or diabetes mellitus. Tibolone should be stopped if there are signs of thromboembolism, a significant increase in blood pressure, new onset of migraine-type headache, or if abnormal liver function tests or cholestatic jaundice occur. Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely.

Malignant neoplasms. Licensed product information for tibolone advises that it is contra-indicated in women with a history of hormone-dependent tumours. However, the risk of cancer recurrence associated with tibolone has not been determined and there have been a few reports of its use for menopausal symptoms in such patients. An observational study[1] and a case-control study[2] of women who had been treated for breast cancer found no evidence that tumour recurrence was higher in those subsequently given tibolone than in those who were not. Case-control studies have also suggested that tibolone does not increase the risk of recurrence of treated endometrial[3] or ovarian[4] cancers. Although promising, these data are limited and further studies are needed to confirm the safety of tibolone in these groups of patients, particularly as there is some evidence[5] that in UK general practice it may have been prescribed preferentially to women at increased risk of breast and endometrial cancers, including women with a history of breast cancer.

For reports of the incidence of breast and endometrial cancers in women given tibolone, see Carcinogenicity, above.

1. Dimitrakakis C, *et al.* Clinical effects of tibolone in postmenopausal women after 5 years of tamoxifen therapy for breast cancer. *Climacteric* 2005; **8:** 342–51.
2. Goutzioulis M, *et al.* Tibolone therapy in breast cancer survivors: a retrospective study. *J Obstet Gynaecol Res* 2007; **33:** 68–73.
3. Lee K-B, *et al.* Endometrial cancer patients and tibolone: a matched case-control study. *Maturitas* 2006; **55:** 264–9.
4. Lee K-B, *et al.* The safety of tibolone in epithelial ovarian cancer patients. *Maturitas* 2006; **55:** 156–61.
5. Velthuis-te Wierik EJM, *et al.* Preferential prescribing of tibolone and combined estrogen plus progestogen therapy in postmenopausal women. *Menopause* 2007; **14:** 518–27.

Interactions

Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity.

For reference to the effect of tibolone on the activity of oral anticoagulants, see Sex Hormones under Warfarin, p.1431.

Pharmacokinetics

Tibolone is rapidly and extensively absorbed after oral doses and quickly metabolised into three active metabolites, two of which have mainly oestrogenic activity while the third, like the parent compound, has progestogenic and androgenic activity. Peak concentrations of tibolone and its metabolites occur after about 1 to 1.5 hours, and the two main metabolites have an elimination half-life of about 7 hours. Metabolites are excreted in the bile and eliminated in the faeces. About 30% of a dose is excreted in the urine.

◊ References.

1. Timmer CJ, Doorstam DP. Effect of renal impairment on the pharmacokinetics of a single oral dose of tibolone 2.5 mg in early postmenopausal women. *Pharmacotherapy* 2002; **22:** 148–53.
2. Timmer CJ, Huisman JA. Effect of a standardized meal on the bioavailability of a single oral dose of tibolone 2.5 mg in healthy postmenopausal women. *Pharmacotherapy* 2002; **22:** 310–15.
3. Timmer CJ, *et al.* Pharmacokinetics of tibolone in early and late postmenopausal women. *Br J Clin Pharmacol* 2002; **54:** 101–6.
4. Verheul HAM, *et al.* Pharmacokinetic parameters of sulfated tibolone metabolites in postmenopausal women after single and multiple doses of tibolone. *Clin Pharmacol Ther* 2007; **81:** 573–9.

Uses and Administration

Tibolone is a steroid derived from noretynodrel that has oestrogenic, progestogenic, and weak androgenic properties. It is used as menopausal HRT (below) for oestrogen deficiency symptoms, including vasomotor symptoms, in postmenopausal women. Tibolone may also be used in the prevention of postmenopausal osteoporosis in women at high risk of fracture who cannot be treated with other therapy. The usual oral dose is 2.5 mg daily in a continuous regimen. Tibolone should not be started for at least 12 months after the last menstrual period of a natural menopause, but may be started immediately in women who have undergone a surgical menopause or who are being treated with a gonadorelin analogue. Unlike oestrogen-based HRT, a progestogen is not added to tibolone therapy for women with an intact uterus.

In women with a uterus who are transferring from an oestrogen-only form of HRT to tibolone, it is suggested that a withdrawal bleed be induced with a progestogen before starting tibolone, and in those transferring from a cyclical combined HRT, tibolone should be started the day after finishing a full cycle. Women taking continuous combined HRT can be transferred to tibolone at any time.

'Add-back' therapy. Tibolone reduces the vasomotor symptoms and bone loss caused by gonadorelin analogues, without impairing their efficacy in the treatment of endometriosis[1,2] (p.2091) and fibroids[3] (p.2107). Tibolone also reduced vasomotor symptoms in a short-term study of women being treated with leuprorelin for premenstrual syndrome[4] (p.2099).

1. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapetyl). *Fertil Steril* 1996; **65:** 342–8.
2. Taskin O, *et al.* Effectiveness of tibolone on hypoestrogenic symptoms induced by goserelin treatment in patients with endometriosis. *Fertil Steril* 1997; **67:** 40–5.
3. Palomba S, *et al.* A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 1998; **70:** 111–18.
4. Di Carlo C, *et al.* Use of leuprolide acetate plus tibolone in the treatment of severe premenstrual syndrome. *Fertil Steril* 2001; **75:** 380–4.

Menopausal disorders. The oestrogenic effects of tibolone make it effective in the management of menopausal disorders (p.2077) such as vasomotor symptoms and vaginal atrophy. It may also be used for the prevention of postmenopausal bone loss, and there is some evidence that it may be useful for treating postmenopausal osteoporosis and reducing fracture risk. The progestogenic effects of tibolone are thought to be sufficient to prevent endometrial proliferation, so that, unlike the oestrogens that are generally used for menopausal HRT (p.2076), a progestogen is not added to tibolone therapy for women with an intact uterus.

Reviews.

1. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. *J Clin Endocrinol Metab* 2002; **87:** 16–23.
2. Swegle JM, Kelly MW. Tibolone: a unique version of hormone replacement therapy. *Ann Pharmacother* 2004; **38:** 874–81.
3. Kenemans P, Speroff L. Tibolone: clinical recommendations and practical guidelines: a report of the International Tibolone Consensus Group. *Maturitas* 2005; **51:** 21–8.
4. Ettinger B. Tibolone for prevention and treatment of postmenopausal osteoporosis. *Maturitas* 2007; **57:** 35–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Climatix; Discretal; Paraclim; Senalina; Tiboclim; Tibofem; Tirovarina; Tocline; ***Austral.:*** Livial; ***Austria:*** Liviel; ***Belg.:*** Livial; ***Braz.:*** Donna†; Klimater; Libiam; Livial; Livolon; Reduclim; Tibial; ***Chile:*** Climafen; Lifar†; Lirex; Livial; Plenovid; Tinox; Tobe; ***Cz.:*** Ladybon; Livial; Tibolvivax; ***Denm.:*** Livial; ***Fin.:*** Livial; ***Fr.:*** Livial; ***Ger.:*** Liviella; ***Gr.:*** Livial; ***Hong Kong:*** Livial; ***Hung.:*** Livial; ***India:*** Livial; Tibofem; Tibomax; ***Indon.:*** Livial; ***Irl.:*** Livial; ***Israel:*** Livial; ***Ital.:*** Livial; ***Malaysia:*** Livial; ***Mex.:*** Livial; ***Neth.:*** Livial; ***Norw.:*** Livial; ***NZ:*** Livial; ***Philipp.:*** Livial; ***Pol.:*** Livial; ***Port.:*** Clitax; Goldar; Livial; Ulcinil; ***Rus.:*** Livial (Ливиал); ***S.Afr.:*** Livifem; ***Singapore:*** Livial; ***Spain:*** Boltin; ***Swed.:*** Livial; ***Switz.:*** Livial; ***Thai.:*** Livial; ***Turk.:*** Livial; ***UK:*** Livial; ***Venez.:*** Femsel; Fomene; Livial; Tinox.

Trenbolone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de trenbolona; RU-1697; Trenbolone, Acétate de; Trenboloni Acetas; Trienbolone Acetate. 17β-Hydroxyestra-4,9,11-trien-3-one acetate.

Тренболона Ацетат

$C_{20}H_{24}O_3$ = 312.4.

CAS — 10161-33-8 (trenbolone); 10161-34-9 (trenbolone acetate).

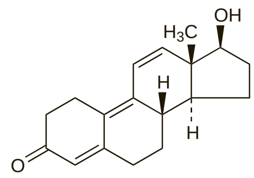

(trenbolone)

Pharmacopoeias. In *US*, for veterinary use only.

USP 31 (Trenbolone Acetate). Store in airtight containers at a temperature of 2° to 8°.

Profile

Trenbolone acetate has been used as an anabolic agent in veterinary practice. The hexahydrobenzylcarbonate has also been used for its anabolic properties.

◊ WHO specifies an acceptable daily intake of trenbolone acetate as a residue in foods, and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the EU the use of trenbolone acetate and other anabolic steroids is restricted to certain therapeutic indications in non-food producing animals and their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: thirty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 788* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_788.pdf (accessed 13/11/07)

Trimegestone *(BAN, USAN, rINN)*

RU-27987; Trimegeston; Trimegestona; Trimégestone; Trimegestoni; Trimegestonum. 17β-(*S*)-Lactoyl-17-methylestra-4,9-dien-3-one; 17β-[(*S*)-2-Hydroxypropionyl]-17α-methylestra-4,9-dien-3-one.

Тримегестон

$C_{22}H_{30}O_3$ = 342.5.

CAS — 74513-62-5.

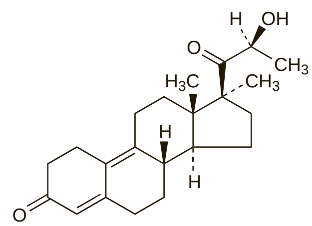

Profile

Trimegestone is a progestogen (see Progesterone, p.2125) used as the progestogenic component of menopausal HRT (see p.2071). It is given orally in daily doses of 250 or 500 micrograms in a cyclical regimen, or 125 micrograms in a continuous regimen. Trimegestone is also under investigation as a component of a combined oral contraceptive.

◊ Reviews.

1. Grubb G, *et al.* Clinical experience with trimegestone as a new progestin in HRT. *Steroids* 2003; **68:** 921–6.
2. Sitruk-Ware R, *et al.* Preclinical and clinical properties of trimegestone: a potent and selective progestin. *Gynecol Endocrinol* 2007; **23:** 310–19.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Totelle Ciclico; Totelle Continuo; ***Austria:*** Minique†; ***Belg.:*** Totelle Cycle†; ***Braz.:*** Totelle; Totelle Ciclo; ***Chile:*** Totelle; Totelle Continuo; ***Denm.:*** Totelle†; ***Fin.:*** Totelle Sekvens†; ***Ital.:*** Totelle†; ***Mex.:*** Totelle Continuo; Totelle Secuencial; ***Norw.:*** Totelle Sekvens†; ***Swed.:*** Totelle Sekvens†; Totelle†; ***Venez.:*** Totelle Ciclico; Totelle Continuo.

Triptorelin *(BAN, USAN, rINN)* ⊗

AY-25650; BIM-21003; BN-52014; CL-118532; Triptorelina; Triptoréline; Triptoreline; Triptorelinum; D-Trp[6]-LHRH; [6-D-Tryptophan] luteinising hormone-releasing factor. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide.

Трипторелин

$C_{64}H_{82}N_{18}O_{13}$ = 1311.4.

CAS — 57773-63-4.

ATC — L02AE04.

ATC Vet — QL02AE04.

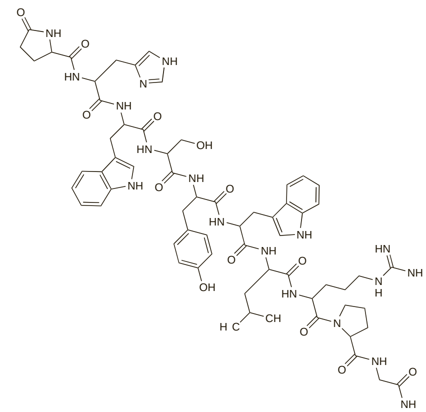

Triptorelin Acetate *(BANM, rINNM)* ⊗

Acetato de triptorelina; Triptoreliiniasetaatti; Triptorelin Asetat; Triptorelinacetat; Triptoréline, Acétate de; Triptorelini Acetas.

Трипторелина Ацетат

$C_{64}H_{82}N_{18}O_{13}$, $C_2H_4O_2$ = 1371.5.

CAS — 140194-24-7.

ATC — L02AE04.

ATC Vet — QL02AE04.

Triptorelin Diacetate *(BANM, rINNM)* ⊗

Diacetato de triptorelina; Triptoréline, Diacetate de; Triptorelini Diacetas.

Трипторелина Диацетат

$C_{64}H_{82}N_{18}O_{13}$,$2C_2H_4O_2$ = 1431.6.

CAS — 105581-02-0.

ATC — L02AE04.

ATC Vet — QL02AE04.

Triptorelin Embonate *(BANM, rINNM)* ⊗

Embonato de triptorelina; Triptorelin Pamoate *(USAN)*; Triptoréline, Embonate de; Triptorelini Embonas.

Трипторелина Эмбонат

$C_{64}H_{82}N_{18}O_{13}$,$C_{23}H_{16}O_6$ = 1699.8.

CAS — 124508-66-3.

ATC — L02AE04.

ATC Vet — QL02AE04.

Adverse Effects and Precautions

As for Gonadorelin, p.2106.

Local reactions. For reference to local reactions occurring following injection of gonadorelin analogues, including triptorelin, see Leuprorelin Acetate, p.2111.

Sepsis. A report of 2 patients in whom triptorelin therapy led to sepsis caused by expulsion of necrotic fibroids through the cervix.[1]

1. Ellenbogen A, *et al.* Complication of triptorelin treatment for uterine myomas. *Lancet* 1989; **ii:** 167–8.

Interactions

As for Gonadorelin, p.2107.

Pharmacokinetics

Triptorelin is rapidly absorbed after subcutaneous injection, with peak plasma concentrations achieved about 40 minutes after a dose. The biological half-life has been stated to be about 7.5 hours, although longer half-lives have been reported in patients with prostate cancer, and shorter half-lives in some groups of healthy subjects.

◊ References.

1. Müller FO, *et al.* Pharmacokinetics of triptorelin after intravenous bolus administration in healthy males and in males with renal or hepatic insufficiency. *Br J Clin Pharmacol* 1997; **44:** 335–41.

Uses and Administration

Triptorelin is an analogue of gonadorelin (p.2107) with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, deviant sexual behaviour in men, precocious puberty, and in the management of endometriosis, female infertility, and uterine fibroids. Triptorelin may be given as the base, acetate, diacetate, or embonate, although for some preparations stated to contain the acetate or diacetate it is not always clear which has actually been used. Doses are usually given in terms of the base, and the following are each equivalent to about 1 mg of triptorelin:

- triptorelin acetate, 1.05 mg
- triptorelin diacetate, 1.09 mg
- triptorelin embonate, 1.30 mg

Triptorelin is given as a daily subcutaneous injection, or as an intramuscular or subcutaneous depot preparation lasting a month or longer.

In the palliative treatment of advanced **prostate cancer**, a dose equivalent to triptorelin 3 or 3.75 mg is given intramuscularly as a depot preparation every 4 weeks; the first dose may be preceded by 100 micrograms daily for 7 days by subcutaneous injection. In some countries, depot preparations containing 3.75 mg may be given subcutaneously instead. A longer-acting depot preparation that contains the equivalent of triptorelin 11.25 mg is given once every 12 to 13 weeks. In some countries, depot doses of 3 mg once every 4 weeks or 11.25 mg once every 12 to 13 weeks may also be used for medical therapy in locally advanced disease. An anti-androgen such as cyproterone acetate may be given for several days before beginning therapy with triptorelin and continued for about 3 weeks to avoid the risk of a disease flare.

An 11.25-mg intramuscular depot preparation, given every 12 weeks, may be used in the management of **deviant sexual behaviour** in men. The addition of an anti-androgen should be considered when starting therapy, to counteract the initial rise in serum-testosterone concentrations.

Similar doses of the 3- or 3.75-mg depot preparations may be given for up to 6 months in the management of **endometriosis** or **uterine fibroids**, with treatment begun during the first 5 days of the menstrual cycle. The 11.25-mg depot may be used as an alternative for endometriosis. In the management of female infertility doses of 100 micrograms subcutaneously daily, with gonadotrophins, have been recommended from the second day of the menstrual cycle for about 10 to 12 days.

In children with **precocious puberty** a dose equivalent to triptorelin 50 micrograms/kg from the 3-mg depot preparation may be given intramuscularly every 4 weeks. Alternatively, using the 3.75-mg preparation, doses of 1.875 mg for children weighing less than 20 kg, 2.5 mg for children of 20 to 30 kg, or 3.75 mg for children of more than 30 kg may be given intramuscularly or subcutaneously; the first 3 doses should be given at 14-day intervals, with further doses given every 4 weeks. The longer acting 11.25-mg depot preparation, given intramuscularly once every 3 months, is another alternative.

Delayed and precocious puberty. Gonadorelin analogues such as triptorelin[1-6] are used in the management of central precocious puberty (p.2081). They may also be effective in delayed puberty (p.2079) although they are most likely to be helpful where this is due to hypogonadism. Triptorelin has been used to differentiate gonadotrophin deficiency from constitutional delayed puberty,[7,8] although one study[9] found it to be less accurate than a test using human chorionic gonadotrophin.

1. Oostdijk W, *et al.* Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 1996; **75:** 292–7.
2. Cassio A, *et al.* Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5—8.5 years. *Arch Dis Child* 1999; **81:** 329–32.
3. Heger S, *et al.* Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 1999; **84:** 4583–90.
4. Carel J-C, *et al.* Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab* 1999; **84:** 1973–8.
5. Mul D, *et al.* Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. *Horm Res* 2002; **58:** 1–7.
6. Carel JC, *et al.* Triptorelin 3-month CPP Study Group. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. *Eur J Endocrinol* 2006; **154:** 119–24.
7. Zamboni G, *et al.* Use of the gonadotropin-releasing hormone agonist triptorelin in the diagnosis of delayed puberty in boys. *J Pediatr* 1995; **126:** 756–8.
8. Kauschansky A, *et al.* Use of GnRH agonists and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. *Clin Endocrinol (Oxf)* 2002; **56:** 603–7.
9. Degros V, *et al.* The human chorionic gonadotropin test is more powerful than the gonadotropin-releasing hormone agonist test to discriminate male isolated hypogonadotropic hypogonadism from constitutional delayed puberty. *Eur J Endocrinol* 2003; **149:** 23–9.

Disturbed behaviour. Combined therapy with triptorelin, which suppressed testosterone secretion by inhibiting the pituitary-gonadal axis, and supportive psychotherapy, has been tried in the treatment of men with paraphilias (see p.954): a reduction in abnormal sexual thoughts and behaviours has been reported, although the study was uncontrolled.[1]

1. Rösler A, Witztum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. *N Engl J Med* 1998; **338:** 416–22.

Endometriosis. Gonadorelin analogues are effective in the management of endometriosis (p.2091), but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy (hormone replacement) can be used to prevent this.

References.

1. Lindsay PC, *et al.* The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). *Fertil Steril* 1996; **65:** 342–8.
2. Bergqvist A, *et al.* Effects of triptorelin versus placebo on the symptoms of endometriosis. *Fertil Steril* 1998; **69:** 702–8.
3. Donnez J, *et al.* Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis. *Fertil Steril* 2004; **81:** 297–304.
4. Wong AY, Tang L. An open and randomized study comparing the efficacy of standard danazol and modified triptorelin regimens for postoperative disease management of moderate to severe endometriosis. *Fertil Steril* 2004; **81:** 1522–7.

Fibroids. Gonadorelin analogues have been used as an alternative to surgery in the treatment of uterine fibroids (see p.2107), despite some concern that this may complicate the diagnosis of malignancy.

References to the use of triptorelin.

1. van Leusden HA. Symptom-free interval after triptorelin treatment of uterine fibroids: long-term results. *Gynecol Endocrinol* 1992; **6:** 189–98.
2. Golan A, *et al.* Pre-operative gonadotrophin-releasing hormone agonist treatment in surgery for uterine leiomyomata. *Hum Reprod* 1993; **8:** 450–2.
3. Broekmans FJ, *et al.* Two-step gonadotropin-releasing hormone agonist treatment of uterine leiomyomas: standard-dose therapy followed by reduced-dose therapy. *Am J Obstet Gynecol* 1996; **175:** 1208–16.
4. Vercellini P, *et al.* Treatment with a gonadotrophin releasing hormone agonist before hysterectomy for leiomyomas: results of a multicentre, randomised controlled trial. *Br J Obstet Gynaecol* 1998; **105:** 1148–54.
5. Seracchioli R, *et al.* GnRH agonist treatment before total laparoscopic hysterectomy for large uteri. *J Am Assoc Gynecol Laparosc* 2003; **10:** 316–19.

Growth retardation. As discussed on p.1798 gonadorelin analogues have been given with growth hormone to short girls without growth hormone deficiency, in an attempt to delay puberty and bone maturation and thus maximise the final height achieved. Use in growth hormone-deficient children has also been investigated. However, there is some doubt about the extent of benefit, and in any case the concept of such treatment in children who are not clinically deficient in growth hormone is controversial, and some authorities do not consider it appropriate.

References to the use of triptorelin.

1. Saggese G, *et al.* Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. *J Pediatr* 1995; **126:** 468–73.
2. Kamp GA, *et al.* A randomized controlled trial of three years growth hormone and gonadotropin-releasing hormone agonist treatment in children with idiopathic short stature and intrauterine growth retardation. *J Clin Endocrinol Metab* 2001; **86:** 2969–75.
3. Tauber M, *et al.* Can some growth hormone (GH)-deficient children benefit from combined therapy with gonadotropin-releasing hormone analogs and GH? Results of a retrospective study. *J Clin Endocrinol Metab* 2003; **88:** 1179–83.

Infertility. Gonadorelin analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both men and women. For a discussion of infertility and its management, including the role of gonadorelin analogues, see p.2080.

Malignant neoplasms. Triptorelin, like other gonadorelin analogues, may be used in the production of androgen blockade in patients with prostate cancer (p.671).

References.

1. Klippel KF, *et al.* Wirksamkeit und Vertraglichkeit von 2 Applikationsformen (s.c. und i.m.) von Decapeptyl Depot bei Patienten mit fortgeschrittenem Prostatakarzinom. *Urologe* 1999; **38:** 270–5.
2. Heyns CF, *et al.* Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU Int* 2003; **92:** 226–31.

Porphyria. Triptorelin has been used successfully to suppress premenstrual exacerbations of acute intermittent porphyria (p.1448), in doses of 3.75 mg by intramuscular depot injection given monthly.[1,2] To reduce the risk of osteoporosis, 'add-back' therapy with topical oestrogen and oral calcium was used in one case,[1] and tibolone in another.[2]

1. De Block CEM, *et al.* Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects – a case report. *Eur J Endocrinol* 1999; **141:** 50–4.
2. Castelo-Branco C, *et al.* Use of gonadotropin-releasing hormone analog with tibolone to prevent cyclic attacks of acute intermittent porphyria. *Metabolism* 2001; **50:** 995–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Decapeptyl; Gonapeptyl; ***Austria:*** Decapeptyl; Pamorelin; ***Belg.:*** Decapeptyl; ***Braz.:*** Neo Decapeptyl; ***Chile:*** Decapeptyl; ***Cz.:*** Decapeptyl; Diphereline; ***Denm.:*** Decapeptyl; Pamorelin; ***Fin.:*** Decapeptyl; ***Fr.:*** Decapeptyl; Gonapeptyl; ***Ger.:*** Decapeptyl; Pamorelin; ***Gr.:*** Arvekap; Gonapeptyl; ***Hong Kong:*** Decapeptyl; Diphereline; ***Hung.:*** Decapeptyl; Diphereline; ***India:*** Decapeptyl; ***Irl.:*** Decapeptyl; Gonapeptyl; ***Israel:*** Decapeptyl; Diphereline; ***Ital.:*** Decapeptyl; Gonapeptyl; ***Malaysia:*** Decapeptyl; ***Mex.:*** Trelstar†; ***Neth.:*** Decapeptyl; Gonapeptyl; Pamorelin; ***Pol.:*** Decapeptyl; Diphereline; ***Port.:*** Decapeptyl; ***Rus.:*** Decapeptyl (Декапептил); Diphereline (Диферелин); ***S.Afr.:*** Decapeptyl; ***Singapore:*** Decapeptyl; ***Spain:*** Decapeptyl; Gonapeptyl; ***Swed.:*** Decapeptyl; Moapar; ***Switz.:*** Decapeptyl; ***Thai.:*** Decapeptyl; Diphereline; ***Turk.:*** Decapeptyl; ***UK:*** Decapeptyl; Gonapeptyl; ***USA:*** Trelstar; ***Venez.:*** Decapeptyl.

Urofollitropin *(BAN, USAN, rINN)* ⊗

Ürofolitropin; Urofolitropin; Urofolitropina; Urofolitropinas; Urofollitrophin; Urofollitropiini; Urofollitropine; Urofollitropinum.

Урофоллитропин

CAS — 97048-13-0.

ATC — G03GA04.

ATC Vet — QG03GA04.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Urofollitropin). A dry preparation containing menopausal gonadotrophin obtained from the urine of postmenopausal women. It has follicle-stimulating activity and no or virtually no luteinising activity. The potency is not less than 90 units of follicle-stimulating hormone per mg; the ratio of units of luteinising hormone to units of follicle-stimulating hormone is not more than 1:60. An almost white or slightly yellow powder. Soluble in water. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

As for Human Menopausal Gonadotrophins, p.2109.

Pharmacokinetics

After multiple intramuscular or subcutaneous dosing of urofollitropin, the maximum plasma concentration of follicle-stimulating hormone occurs about 10 hours after a dose, and has an elimination half-life of about 15 or 20 hours respectively.

Uses and Administration

Urofollitropin is a gonadotrophin, obtained from the urine of postmenopausal women, possessing follicle-stimulating hormone (FSH) activity but virtually no luteinising activity. For details of the actions of FSH, see p.2104.

Urofollitropin is used similarly to human menopausal gonadotrophins (p.2110) in the treatment of **female infertility** with the exception that, being without luteinising hormone activity, it can be used in patients where any increase in luteinising hormone activity is not required, as in polycystic ovarian disease. Urofollitropin is given subcutaneously or intramuscularly in a dosage adjusted according to the patient's response. Usually a dose providing 75 to 150 units of FSH daily is given initially. When an adequate response is achieved, as determined by oestrogen monitoring or ultrasonic visualisation of follicles, treatment is stopped and after 1 or 2 days a single dose of chorionic gonadotrophin 5000 to 10 000 units is given to induce ovulation. Treatment with urofollitropin should be stopped if there is no response after 4 weeks although treatment may be attempted again in future cycles. US product information has recommended that a maximum daily dose of 450 units should not be exceeded, and that courses of treatment should be no longer than 12 days.

Urofollitropin is also used with other drugs as part of IVF procedures. It is typically given in a dose providing 150 to 225 units of FSH daily, usually beginning from day 2 or 3 of the menstrual cycle. Alternatively, therapy has been begun with clomifene citrate and continued with urofollitropin, or urofollitropin may be given after suppression of gonadotrophin release with a gonadorelin analogue. Treatment is continued until an adequate response is obtained and the final injection of urofollitropin is followed 1 to 2 days later by 5000 to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is performed 34 to 35 hours later.

Urofollitropin is also used with chorionic gonadotrophin to stimulate spermatogenesis in the treatment of **male infertility**, although a preparation with combined luteinising activity, such as human menopausal gonadotrophins, may be preferred. The usual dose of urofollitropin provides 150 units of FSH three times a week. Treatment with urofollitropin and chorionic gonadotrophin should be continued for at least 4 months. For a brief discussion of hypogonadism see p.2079.

Infertility. For reference to the use of preparations with follicle-stimulating hormone activity in infertility, see p.2080.

References to the use of urofollitropin.

1. McFaul PB, *et al.* Treatment of clomiphene citrate-resistant polycystic ovarian syndrome with pure follicle-stimulating hormone or human menopausal gonadotropin. *Fertil Steril* 1990; **53:** 792–7.
2. European Metrodin HP Study Group. Efficacy and safety of highly purified urinary follicle-stimulating hormone with human chorionic gonadotropin for treating men with isolated hypogonadotropic hypogonadism. *Fertil Steril* 1998; **70:** 256–62.
3. Crain JL, *et al.* Outcome comparison of in vitro fertilization treatment with highly purified subcutaneous follicle-stimulating hormone (Fertinex, a urofollitropin) versus intramuscular menotropins. *Am J Obstet Gynecol* 1998; **179:** 299–307.
4. Lenton E, *et al.* Induction of ovulation in women undergoing assisted reproductive techniques: recombinant human FSH (follitropin alpha) versus highly purified urinary FSH (urofollitropin HP). *Hum Reprod* 2000; **15:** 1021–7.
5. Mohamed MA, *et al.* Urinary follicle-stimulating hormone (FSH) is more effective than recombinant FSH in older women in a controlled randomized study. *Fertil Steril* 2006; **85:** 1398–1403.

Preparations

BP 2008: Urofollitropin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Follitrin; Fostimon; ***Austral.:*** Metrodin; ***Braz.:*** Metrodin; ***Canad.:*** Bravelle; Fertinorm†; ***Chile:*** Follitrin; ***Cz.:*** Fostimon; Metrodin†; ***Fr.:*** Fostimon; ***Gr.:*** Bravelle; Metrodin†; ***Hong Kong:*** Follimon†; Fostimon; Metrodin†; ***Hung.:*** Fostimon; Metrodin†; ***India:*** Gonotrop F; Metrodin; Neogentin; ***Irl.:*** Metrodin†; ***Israel:*** Metrodin†; ***Ital.:*** Fostimon; Metrodin†; ***Mex.:*** Fostimon; ***Neth.:*** Bravelle; Metrodin†; ***Port.:*** Bravelle; Fostimon; Metrodin; ***Rus.:*** Metrodin (Метродин); ***S.Afr.:*** Metrodin†; ***Singapore:*** Metrodin†; ***Spain:*** Neo Fertinorm†; ***Switz.:*** Fostimon; Metrodin†; ***Thai.:*** Follimon; ***Turk.:*** Metrodin; ***UK:*** Fostimon; ***USA:*** Bravelle; Fertinex; Metrodin.

Zeranol *(BAN, USAN, rINN)* ⊗

MK-188; P-1496; THFES (HM); Zearalanol; Zéranol; Zeranolum.
(3*S*,7*R*)-3,4,5,6,7,8,9,10,11,12-Decahydro-7,14,16-trihydroxy-3-methyl-1*H*-2-benzoxacyclotetradecin-1-one.
Зеранол
$C_{18}H_{26}O_5$ = 322.4.
CAS — 26538-44-3.

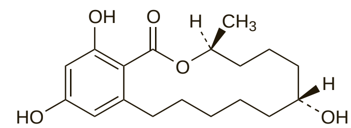

Profile

Zeranol is a nonsteroidal oestrogen that has been used for the management of menopausal and menstrual disorders. It has also been used as a growth promotor in veterinary practice. Its anabolic properties may be subject to abuse in sport.

◊ WHO specifies an acceptable daily intake of zeranol as a residue in foods and recommends maximum residue limits in various animal tissues.[1] However, it should be noted that, in the European Union the use of zeranol in veterinary medicine is prohibited. Certain other steroidal hormones are permitted for restricted use but their use as growth promotors is banned.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: thirty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 763* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_763.pdf (accessed 30/06/08)

Soaps and Other Anionic Surfactants

Soaps and other anionic surfactants dissociate in aqueous solution to form an anion, which is responsible for the surface activity, and a cation which is devoid of surface-active properties. They are widely used for their emulsifying and cleansing properties. The term **detergent** is used to describe a surface-active agent with such properties that concentrates at oil-water interfaces. Anionic surfactants used in pharmaceutical preparations include:

- **Alkali-metal** and **ammonium soaps** (monovalent alkyl carboxylates) which are the sodium, potassium, and ammonium salts of the higher fatty acids
- **Metallic soaps** (polyvalent alkyl carboxylates), the calcium, zinc, magnesium, and aluminium salts of the higher fatty acids; they produce water-in-oil emulsions and are often formed by chemical reaction during the preparation of the emulsion
- **Amine soaps**, which are salts of amines with fatty acids
- **Alkyl sulfates** or **sulfated fatty alcohols**, salts of the sulfuric acid esters of the higher fatty alcohols
- **Alkyl ether sulfates** or **ethoxylated alkyl sulfates**, formed by sulfating ethoxylated alcohols.
- **Sulfated oils**, which are prepared by treating fixed oils with sulfuric acid and neutralising with sodium hydroxide solution.

Many **sulfonated compounds** have been produced that possess surface-active properties and are used as detergents; they include alkyl sulfonates, alkyl aryl sulfonates, and amide sulfonates. Docusate sodium (p.1725), a sulfonated dibasic acid ester, has medicinal and pharmaceutical uses.

Ampholytic (or amphoteric) surfactants possess at least one anionic group and at least one cationic group in the molecule and can therefore have anionic, nonionic, or cationic properties depending on the pH. When the strength of the cationic portion of the molecule is equivalent to that of the anionic portion the isoelectric point occurs at pH 7 and the molecule is said to be balanced. Ampholytic surfactants have the detergent properties of anionic surfactants and the disinfectant properties of cationic surfactants. Their activity depends on the pH of the media in which they are used. Compounds used include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, and dodicin. Long-chain betaines are sometimes classed as ampholytic surfactants.

Balanced ampholytic surfactants are reputed to be non-irritant to the eyes and skin and have therefore been used in baby shampoos.

Aluminium Monostearate

Aluminii monostearas; Aluminium, monostéarate de; Aluminum Monostearate; Glinu monostearynian; Monoestearato de aluminio; Monostearato de aluminio. Dihydroxy(octadecanoato-*O*-)aluminium; Dihydroxy(stearato)aluminium.

Алюминия Моностеарат

CAS — 7047-84-9.

Pharmacopoeias. In *Jpn* and *Pol.* Also in *USNF.*

USNF 26 (Aluminum Monostearate). A compound of aluminium with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of aluminium monostearate and aluminium monopalmitate. A fine, white to yellowish-white, bulky powder with a faint characteristic odour. Insoluble in water, in alcohol, and in ether.

Profile

Aluminium monostearate is used as a gelling agent in oil-based cosmetic and pharmaceutical formulations. It may also be used as a stabiliser in cosmetic emulsions.

Calcium Stearate

Calcii stearas; Calcium, stéarate de; Estearato de calcio; Kalcio stearatas; Kalciumstearat; Kalcium-sztearát; Kalsiumstearaatti; Stearan vápenatý. Calcium octadecanoate.

Кальция Стеарат

CAS — 542-42-7 (calcium palmitate); 1592-23-0 (calcium stearate).

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Calcium Stearate). A mixture of calcium salts of different fatty acids consisting mainly of stearic acid ($C_{36}H_{70}CaO_4$ = 607.0) and palmitic acid ($C_{32}H_{62}CaO_4$ = 550.9) with minor proportions of other fatty acids. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acids is not less than 90.0%. A fine, white or almost white, crystalline powder. Practically insoluble in water and in alcohol.

USNF 26 (Calcium Stearate). A compound of calcium with a mixture of solid organic acids obtained from fats, consisting mainly of variable proportions of calcium stearate ($C_{36}H_{70}CaO_4$ = 607.0) and calcium palmitate ($C_{32}H_{62}CaO_4$ = 550.9). A fine, white to yellowish-white bulky, unctuous powder, free from grittiness with a slight characteristic odour. Insoluble in water, in alcohol, and in ether.

Profile

Calcium stearate is added to granules as a lubricant in the manufacture of tablets and capsules.

Adverse effects. Acute eosinophilic pneumonia in 1 patient has been attributed to the presence of calcium stearate used as an additive in an antihistamine tablet formulation.[1]

1. Kurai J, *et al.* Acute eosinophilic pneumonia caused by calcium stearate, an additive agent for an oral antihistaminic medication. *Intern Med* 2006; **45:** 1011–16.

Calcium Stearoyl-lactylate

Calcium Stearoyl-2-lactylate; E482. Calcium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctodecanoate.

Стеароиллактилат Кальция

CAS — 5793-94-2.

Sodium Stearoyl-lactylate

E481; Sodium Stearoyl-2-lactylate. Sodium 2-(1-Carboxyethoxy)-1-methyl-2-oxoethyloctadecanoate sodium salt.

Стеароиллактилат Натрия

CAS — 25383-99-7.

Profile

Sodium stearoyl-lactylate has anionic surfactant properties and is used as an emulsifier and stabilising and suspending agent in the food industry, including in foods for special diets. The calcium salt is used similarly.

Magnesium Stearate

572; Estearato de magnesio; Magnesii stearas; Magnésium, stéarate de; Magnesiumstearaatti; Magnesiumstearat; Magnézium-sztearát; Magnezu stearynian; Magnio stearatas; Stearan hořečnatý.

Стеарат Магния

CAS — 1555-53-9 (magnesium oleate); 2601-98-1 (magnesium palmitate); 557-04-0 (magnesium stearate).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Magnesium Stearate). A mixture of the magnesium salts of different fatty acids consisting mainly of stearic acid ($C_{36}H_{70}MgO_4$ = 591.2) and palmitic acid ($C_{32}H_{62}MgO_4$ = 535.1) and in minor proportions other fatty acids. The fatty acid fraction contains not less than 40.0% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90.0%. A white or almost white, very fine, light powder, greasy to the touch. Practically insoluble in water and in dehydrated alcohol.

USNF 26 (Magnesium Stearate). A compound of magnesium with a mixture of solid organic acids, and consisting mainly of variable proportions of magnesium stearate ($C_{36}H_{70}MgO_4$ = 591.2) and magnesium palmitate ($C_{32}H_{62}MgO_4$ = 535.1). It is a very fine, light, white powder, slippery to touch. Insoluble in water, in alcohol, and in ether.

Profile

Magnesium stearate is added to granules as a lubricant in the manufacture of tablets and capsules. It has also been used as a dusting powder and in barrier creams.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Philipp.:*** Johnson's Baby Double Protection Powder.

Sodium Cetostearyl Sulfate

Cetoestearilsulfato de sodio; Cétostéaryle (sulfate de) sodique; Cetylstearylschwefelsaures Natrium; Natrii cetylo- et stearylosulfas; Natrio cetostearilo sulfatas; Natrium Cetylosulphuricum; Natrium Cetylstearylosulphuricum; Nátrium-cetil-sztearil-szulfát; Natriumcetostearylsulfat; Natrium-cetylstearyl-sulfát; Natriumsetostearyylisulfaatti; Sodium Cetostearyl Sulphate; Sodu cetostearylosiarczan.

Натрия Цетостеарилсульфат

CAS — 1120-01-0 (sodium cetyl sulfate); 1120-04-3 (sodium stearyl sulfate).

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Cetostearyl Sulphate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaO_4S$ = 344.5) and sodium stearyl sulfate ($C_{18}H_{37}NaO_4S$ = 372.5). A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

USNF 26 (Sodium Cetostearyl Sulfate). A mixture of sodium cetyl sulfate ($C_{16}H_{33}NaSO_4$ = 344.5) and sodium stearyl sulfate ($C_{18}H_{37}NaSO_4$ = 372.5). It contains not less than 40% of sodium cetyl sulfate and the sum of the sodium cetyl sulfate content and sodium stearyl sulfate content is not less than 90%, both contents calculated on the anhydrous basis. A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; practically insoluble in cold water; partly soluble in alcohol.

Profile

Sodium cetostearyl sulfate is an anionic emulsifying agent. It is used as a detergent and wetting agent.

Sodium Cocoyl Isetionate

Sodium Cocoyl Isethionate.

Кокоил Изетионат Натрия

CAS — 61789-32-0.

Profile

Sodium cocoyl isetionate is the sodium salt of a sulfonated ester of coconut oil fatty acids. It is an anionic surfactant used as a soap substitute. Sodium cocoyl sarcosinate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Physiogel; ***Hong Kong:*** Physiogel; ***Indon.:*** Physiogel; ***Ital.:*** Physiogel; ***Malaysia:*** Physiogel; ***Singapore:*** Physiogel; ***Thai.:*** Physiogel.

Multi-ingredient: ***Fr.:*** Oilatum AD†; ***Mex.:*** Bonaven; ***Philipp.:*** Physiogel.

Sodium Laurilsulfate *(pINNM)*

Laurilsulfate de Sodium; Laurilsulfato de sodio; Natrii laurilsulfas; Natrio laurilsulfatas; Natrium Lauryl Sulphuricum; Natriumlaurilsulfat; Nátrium-lauril-szulfát; Natrium-lauryl-sulfát; Natriumlauryylisulfaatti; Sodium Dodecyl Sulphate; Sodium, laurilsulfate de; Sodium Lauryl Sulfate; Sodium Lauryl Sulphate; Sodu dodecylosiarczan patrz: Sodu laurylosiarczan; Sodu laurylosiarczan.

Натрий Лаурилсульфат

CAS — 151-21-3.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Sodium Laurilsulfate; Sodium Lauryl Sulphate BP 2008). A mixture of sodium alkyl sulfates, consisting mainly of sodium dodecyl sulfate ($C_{12}H_{25}NaO_4S$ = 288.4). It contains not less than 85% of sodium alkyl sulfates and not more than a total of 8% of sodium chloride and sodium sulfate. A white or pale yellow powder or crystals. Freely soluble in water giving an opalescent solution; partly soluble in alcohol.

USNF 26 (Sodium Lauryl Sulfate). A mixture of sodium alkyl sulfates, consisting mainly of sodium laurilsulfate ($C_{12}H_{25}NaO_4S$ = 288.4). The combined content of sodium chloride and sodium sulfate is not more than 8%. Small, white or light yellow crystals with a slight, characteristic odour. Soluble 1 in 10 of water giving an opalescent solution.

Incompatibility. Sodium laurilsulfate interacts with cationic surfactants such as cetrimide, resulting in a loss of activity. It is also incompatible with salts of polyvalent metal ions (e.g. aluminium, lead, tin, or zinc) and with acids of pH below 2.5. It is not affected by hard water because of the solubility of the corresponding calcium and magnesium salts.

Profile

Sodium laurilsulfate is an anionic emulsifying agent. It is a detergent and wetting agent, effective in both acid and alkaline solution and in hard water. It is used in medicated shampoos and as a skin cleanser and in toothpastes. It is used in the preparation of Emulsifying Wax (p.2029). Prolonged exposure to sodium laurilsulfate may irritate the skin or mucous membranes.

Other salts of laurilsulfate have been used for their surfactant properties. These include monoethanolamine, diolamine, and trolamine laurilsulfates, and magnesium and ammonium laurilsulfates. Similar surfactants include sodium lauril ether sulfate and sodium alkyl sulfoacetates such as sodium lauril sulfoacetate.

Sodium laurilsulfate and related surfactants are also included in some combination preparations used rectally for the management of constipation.

Preparations

BP 2008: Emulsifying Wax.

Proprietary Preparations (details are given in Part 3)

Arg.: Euroclear; Limectant; ***Chile:*** Solucion Detergente; ***Fr.:*** Gyalme†; Saforelle; ***Hong Kong:*** Lowila Cake; ***Mex.:*** Aquanil; ***Spain:*** Anticerumen.

Multi-ingredient: ***Arg.:*** Caien; Micronema; Nigalax; Plus & Plus; ***Austral.:*** Fleet Micro-Enema; Microlax; Pinetarsol; ***Austria:*** Microklist; ***Belg.:*** Microlax; Neo-Sabenyl; ***Canad.:*** Microlax; Plax; ***Cz.:*** Dermofug; ***Denm.:*** Microlax; ***Fin.:*** Microlax; ***Fr.:*** Bactident; Microlax; Ysol 206; ***Ger.:*** Dermowas; Microklist; ***Gr.:*** Sabenyl†; ***Hong Kong:*** Fleet Micro-Enema†; Microlax; ***Indon.:*** Laxarec; Microlax; ***Irl.:*** Micolette; Microlax; ***Israel:*** Microlet; ***Ital.:*** Eso Zim; Novilax; ***Malaysia:*** Dentinox Cradle Cap; Lorasil Feminine Hygeine†; Microlax†; ***Mex.:*** Microlax; ***Neth.:*** Casen Mikroklysma; Microlax; ***Norw.:*** Microlax; ***NZ:*** Fleet Micro-Enema†; Microlax; ***Pol.:*** Rektiolax; ***Port.:*** Fleet Micro-Enema; Microlax; ***Rus.:*** Microlax (Микролакс); ***S.Afr.:*** Medigel; Microlax†; ***Singapore:*** Dentinox Cradle Cap; Microlax; ***Spain:*** Clisteran; Micralax; ***Swed.:*** Fleet Micro†; Microlax; ***Switz.:*** Microklist; ***UK:*** Dentinox Cradle Cap; Micolette; Micralax; Relaxit; ***USA:*** Bodi Kleen; Cetaklenz; Geri-Lav Free; Klout; Maxilube; Summers Eve Post-Menstrual; Trichotine; Trimo-San; ***Venez.:*** Novafix; Vitar†.

Sodium Oleate

Oleato de sodio.

Олеиновокислый Натрий

CAS — 143-19-1.

Profile

Sodium oleate is an anionic surfactant used as an ingredient in preparations for the symptomatic relief of haemorrhoids and pruritus ani.

Zinc oleate and potassium oleate have also been used in skin preparations, while the sodium, potassium, and calcium salts have had applications as food additives.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Cose-Anal; ***Ger.:*** Alcos-Anal†; Neo-Ballistol†; ***Neth.:*** Epianal; ***Norw.:*** Alcos-Anal; ***Swed.:*** Alcos-Anal.

Sodium Stearate

Estearato de sodio; Natrii stearas; Natrio stearatas; Natriumstearaatti; Natriumstearat; Sodium, stéarate de; Sodu stearynian; Stearan sodný.

Стеарат Натрия

CAS — 408-35-5 (sodium palmitate); 822-16-2 (sodium stearate).

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Stearate). A mixture of sodium salts of different fatty acids consisting mainly of stearic acid ($C_{18}H_{35}O_2Na$ = 306.5) and palmitic acid ($C_{16}H_{31}O_2Na$ = 278.4). It contains 7.4 to 8.5% of sodium, calculated with reference to the dried substance. The fatty acid fraction contains not less than 40% of stearic acid and the sum of stearic acid and palmitic acid is not less than 90%. A white or yellowish, fine powder, with a greasy touch. Slightly soluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 26 (Sodium Stearate). A mixture containing not less than 90% of sodium stearate ($C_{18}H_{35}NaO_2$ = 306.5) and sodium palmitate ($C_{16}H_{31}NaO_2$ = 278.4); the content of sodium stearate is not less than 40% of the total. It contains small amounts of the sodium salts of other fatty acids. A fine, white powder, soapy to the touch, usually with a slight tallow-like odour. Slowly soluble in cold water and in cold alcohol; readily soluble in hot water and in hot alcohol. Protect from light.

Profile

Sodium stearate is an emulsifying and stiffening agent used in a variety of topical and rectal preparations.

Sodium Stearyl Fumarate

Fumarato de estearilo y sodio; Natrii stearylis fumaras; Natrio stearilfumaratas; Natriumstearylfumarat; Natrium-stearyl-fumarát; Natriumstearyylifumaraatti; Nátrium-sztearil-fumarát; Stéaryle (fumarate de) sodique.

Натрия Стеарилфумарат

$C_{22}H_{39}NaO_4$ = 390.5.

CAS — 4070-80-8.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Stearyl Fumarate). A fine, white or almost white powder with agglomerates of flat, circular shaped particles. Practically insoluble in water, in alcohol, and in acetone; slightly soluble in methyl alcohol.

USNF 26 (Sodium Stearyl Fumarate). A fine white powder. Practically insoluble in water; slightly soluble in methyl alcohol.

Profile

Sodium stearyl fumarate is used as a lubricant in the manufacture of tablets and capsules.

Sodium Tetradecyl Sulfate *(rINN)*

Natrii Tetradecylis Sulfas; Natriumtetradecylsulfat; Natriumtetradekyylisulfaatti; Sodium Tetradecyl Sulphate; Tetradecilsulfato de sodio; Tétradécyl Sulfate de Sodium. Sodium 4-ethyl-1-isobutyloctyl sulfate.

Натрия Тетрадецил Сульфат

$C_{14}H_{29}NaO_4S$ = 316.4.

CAS — 139-88-8.

ATC — C05BB04.

ATC Vet — QC05BB04.

Pharmacopoeias. *Br.* includes as a concentrated form.

BP 2008 (Sodium Tetradecyl Sulphate Concentrate). A clear, colourless gel. Store at a temperature not exceeding 25°. Protect from light.

Adverse Effects and Precautions

The complications of injection sclerotherapy with sclerosants such as sodium tetradecyl sulfate are discussed under Monoethanolamine Oleate, p.2346.

Uses and Administration

Sodium tetradecyl sulfate is an anionic surfactant. It has sclerosing properties and is used in the treatment of varicose veins (p.2347). It has also been given in the management of bleeding oesophageal varices (p.2346), and tried in endoscopic injection therapy for nonvariceal bleeding associated with peptic ulcer disease (p.1702).

For sclerotherapy of varicose veins a solution of sodium tetradecyl sulfate is injected slowly into the lumen of an isolated segment of an emptied superficial vein, followed by compression. Solutions are available in a variety of strengths (0.2 to 3%); doses depend on the site and condition being treated. A test dose is advisable in patients with a history of allergy. Facilities for treating anaphylaxis should be available.

Preparations

BP 2008: Sodium Tetradecyl Sulphate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Fibro-Vein; ***Austral.:*** Fibro-Vein†; ***Canad.:*** Trombojet; Trombovar†; ***Cz.:*** Fibro-Vein†; ***Fr.:*** Trombovar; ***Hung.:*** Fibro-Vein; ***Irl.:*** Fibro-Vein; ***Ital.:*** Fibro-Vein; Trombovar; ***Malaysia:*** Trombovar†; ***Neth.:*** Trombovar; ***NZ:*** Fibro-Vein; ***Rus.:*** Trombovar (Тромбовар); ***S.Afr.:*** Fibrovein; STD; ***UK:*** Fibro-Vein; ***USA:*** Sotradecol.

Soft Soap

Green Soap; Jabón blando; Jabón de potasa; Jabón verde; Medicinal Soft Soap; Mydło potasowe; Potassium Soap; Sabão Mole; Sapo Mollis.

Зелёное Мыло; Калиевое Мыло

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*

BP 2008 (Soft Soap). It is made by the interaction of potassium hydroxide or sodium hydroxide with a suitable vegetable oil or oils or their fatty acids. It may be coloured with chlorophyll or not more than 0.015% of a suitable green soap dye. A yellowish-white to green or brown, unctuous substance. Soluble in water and in alcohol.

USP 31 (Green Soap). It is made by the saponification of suitable vegetable oils, excluding coconut oil and palm kernel oil, without the removal of glycerol. The method given in the USP 31 involves mixing the oil with oleic acid and to the heated mixture adding potassium hydroxide dissolved in glycerol and water. The homogeneous emulsion is then adjusted to weight with hot water. A yellowish-white to brownish- or greenish-yellow, transparent to translucent, soft unctuous mass with a slight, characteristic odour.

Adverse Effects and Treatment

Soaps and anionic detergents, in general, may be irritant to the skin by removing natural oils and may produce redness, soreness, cracking and scaling, and papular dermatitis. There may be some irritation of the mucous membranes and this limits the use of soap enemas; marked irritation may occur if soaps or detergents enter the eye. Ingestion of anionic detergents may cause gastrointestinal irritation with nausea, diarrhoea, intestinal distension, and occasionally vomiting. Treatment is symptomatic.

Uses

Soft soap is used to remove incrustations in chronic scaly skin diseases such as psoriasis (p.1583) and to cleanse the scalp before the application of lotions. A solution of soft soap in warm water has been used as an enema to soften impacted faeces but should be avoided as it may inflame the colonic mucosa; other measures are now preferred (see Constipation, p.1693). Alcoholic solutions of soft soap, such as Soap Spirit (BP 2008) and Green Soap Tincture (USP 31), are used as skin cleansers and detergents.

Potash soap (linseed oil soap) has been used in the preparation of liquid soaps. Hard soap (castile soap) and curd soap were formerly used as pill excipients and hard soap was also formerly used in the preparation of plasters.

Preparations

BP 2008: Soap Spirit;
USP 31: Green Soap; Green Soap Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Waldheim Abfuhrdragees forte; Waldheim Abfuhrdragees mild; ***Spain:*** Linimento Naion; ***USA:*** Therevac Plus; Therevac SB.

Sulfated Castor Oil

Aceite de ricino sulfatado; Ol. Ricin. Sulphat.; Oleum Ricini Sulphatum; Red Oil; Sulfonated Castor Oil; Sulphated Castor Oil; Turkey-red Oil.

Ализариновое Масло; Сульфированное Касторовое Масло

CAS — 8002-33-3.

Profile

Sulfated castor oil is a detergent and wetting agent derived from castor oil (p.2278); it has been used as a skin cleanser and emulsifying agent. Sodium ricinoleate has been used similarly.

Sulfated hydrogenated castor oil (hydroxystearin sulfate) has been used in the manufacture of hydrophilic ointment bases and other emulsions.

Zinc Stearate

Cinko stearatas; Cink-sztearát; Cynku stearynian; Estearato de zinc; Sinkkistearaatti; Stearan zinečnatý; Zinc, stéarate de; Zinci stearas; Zinkstearat.

Стеарат Цинка

CAS — 4991-47-3 (zinc palmitate); 557-05-1 (zinc stearate).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Zinc Stearate). Zinc stearate [$(C_{17}H_{35}CO_2)_2Zn$ = 632.3] may contain varying proportions of zinc palmitate [$(C_{15}H_{31}CO_2)_2Zn$ = 576.2] and zinc oleate [$(C_{17}H_{33}CO_2)_2Zn$ = 628.3]. A light, white or almost white, amorphous powder, free from gritty particles. Practically insoluble in water and in dehydrated alcohol.

USP 31 (Zinc Stearate). A compound of zinc with a mixture of solid organic acids obtained from fats and consisting mainly of variable proportions of zinc stearate [$(C_{17}H_{35}CO_2)_2Zn$ = 632.3] and zinc palmitate [$(C_{15}H_{31}CO_2)_2Zn$ = 576.2]. A fine, white, bulky powder, free from grittiness, with a faint characteristic odour. Insoluble in water, in alcohol, and in ether.

Adverse Effects

Zinc stearate inhalation has caused fatal pneumonitis, particularly in infants.

Uses

Zinc stearate is added to granules as a lubricant in the manufacture of tablets and capsules.

Zinc stearate has also been used as a soothing and protective application in the treatment of skin inflammation. It may be used either alone or with other powders or in the form of a cream.

Preparations

USP 31: Compound Clioquinol Topical Powder.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Prurisedan; ***Ital.:*** Steril Zeta; ***Switz.:*** Hydrocortisone compositum; ***Thai.:*** Banocin; ***UK:*** Simpsons.

Stabilising and Suspending Agents

The stabilising and suspending agents described in this chapter have the property of increasing the viscosity of water when dissolved or dispersed. The rheological properties of the dispersions can vary widely from thin liquids to thick gels.

They have wide applications both in pharmaceutical manufacturing and in the food industry. As well as being used as thickening and suspending agents many are used in emulsions as stabilisers and in some cases as emulsifying agents; some are also used in the manufacture of tablets as disintegrants, binding and granulating agents, and for film or enteric coating.

Some are used in artificial tear and artificial saliva preparations which are used in the management of dry eye and dry mouth respectively. Those most commonly used are carbomers, cellulose ethers such as carmellose and hypromellose, polyvinyl alcohol, and povidone. Some, such as the alginates and methylcellulose, are also used in gastrointestinal disorders.

Dry eye

Dry eye is a chronic condition caused by instability of the tear film covering the eye; the tear film breaks up to leave dry spots rather than being maintained between blinks. Tears consist of a slightly alkaline fluid that is spread across the eye by blinking and is lost via the lachrymal ducts or by evaporation. Mucus secreted by the conjunctiva is also required to maintain tear film stability and dry eye can result from reduced production of either tears or conjunctival mucus. Reduced tear secretion is common in the elderly, but also occurs in some systemic disorders or as an adverse effect of drugs such as those, like tricyclic antidepressants, that have antimuscarinic effects. Tear film instability may also result from increased tear evaporation, for example due to corneal exposure in thyroid disease, or from lid, corneal, or other eye disorders.

The main symptoms of dry eye are discomfort, typically with a chronic gritty sensation, visual disturbances, and sometimes photophobia. If left untreated corneal ulceration and eventual loss of sight may occur. Keratoconjunctivitis sicca (corneal inflammation) may result from severe dry eye in Sjögren's syndrome (see below).

Treatment of dry eye is primarily symptomatic using 'artificial tears' preparations; eye drops containing hypromellose or other cellulose ethers (carmellose, hyetellose, methylcellulose), polyvinyl alcohol, or povidone are used. Carbomer, in liquid gel formulations, and ointments containing soft or liquid paraffins are also used. Ointments have a longer duration of action than drops, but tend to blur the vision and are most suitable for use at night. Drops should be used as frequently as required, up to hourly or more often if necessary. Frequent use of eye drops may cause sensitivity to the preservative, in which case preservative-free preparations should be considered. An alternative in patients needing very frequent instillation of drops is a slow-release ophthalmic insert of hyprolose. Punctal occlusion with gelatin rods or collagen implants is used diagnostically to block tear outflow and treatment by permanent occlusion may be considered. Mucus build-up due to reduced tear production may respond to topical mucolytics such as acetylcysteine or bromhexine. Topical immunosuppressants such as ciclosporin may be of benefit in some patients with keratoconjunctivitis sicca;[1] combination of topical ciclosporin with punctal occlusion has been tried.[2]

Sjögren's syndrome is an auto-immune inflammatory disease primarily affecting the lachrymal and salivary glands, and manifests as dry eye and dry mouth. It is often secondary to an auto-immune disorder such as rheumatoid arthritis.[3] Treatment is mainly symptomatic[4] using artificial tears and topical mucolytics for dry eye; dry mouth is treated with artificial saliva as outlined below. Oral pilocarpine may be of benefit for both dry eye and dry mouth;[5,6] systemic treatment with the mucolytic bromhexine has produced conflicting results.[7-9] Corticosteroids and immunosuppressants may have a role in patients with CNS involvement.[10]

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8. Tapper-Jones LM, *et al.* Sjögren's syndrome treated with bromhexine: a reassessment. *BMJ* 1980; **280:** 1356.
9. Prause JU, *et al.* Lacrimal and salivary secretion in Sjögren's syndrome: the effect of systemic treatment with bromhexine. *Acta Ophthalmol (Copenh)* 1984; **62:** 489–97.
10. Rogers SJ, *et al.* Myelopathy in Sjögren's syndrome: role of nonsteroidal immunosuppressants. *Drugs* 2004; **64:** 123–32.

Dry mouth

Dryness of the mouth (xerostomia) resulting from decreased salivary secretion is often an adverse effect of therapy with drugs such as antimuscarinics, antihistamines, tricyclic antidepressants, and diuretics. Other causes include dehydration, anxiety, Sjögren's syndrome (see Dry Eye, above), and radiotherapy of the head and neck. Dry mouth can cause eating difficulties and lead to oral disease such as candidiasis, dental caries, and bacterial infections.[1,2] Where possible any underlying disorder should be treated first.

Frequent sips of fluids help to relieve dry mouth. Artificial saliva products are also important in the symptomatic treatment of dry mouth. They aim to mimic normal saliva and generally contain viscosity-increasing agents, such as mucins or cellulose derivatives such as carmellose,[3,4] as well as electrolytes, including fluoride; they seldom relieve symptoms for more than 1 or 2 hours. It may be possible to stimulate saliva production with sialogogues such as sugarless chewing gum or citrus products but the low pH of the latter can damage the teeth. Malic acid has also been used as a sialogogue.

A number of systemic therapies have also been tried. Pilocarpine is an effective sialogogue, increasing salivary production where some function remains,[5] and is used in dry mouth following radiotherapy; it may also be effective in Sjögren's syndrome or other causes of dry mouth. Adverse effects, particularly increased sweating, may, however, limit its use.[6] Carbachol has been suggested as an alternative to pilocarpine with a study[7] reporting comparable efficacy but less sweating. Anethole trithione and cevimeline have been used similarly. Amifostine is used for the prevention of dry mouth associated with radiotherapy.

1. Fox PC. Management of dry mouth. *Dent Clin North Am* 1997; **41:** 863–75.
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Acacia

Acac.; Acaciae gummi; Akaasiakumi; Akaciagummi; Arabmézga; Arabská klovatina; E414; Goma arábiga; Gomme arabique; Gomme de Sénégal; Gum Acacia; Gum Arabic; Guma arabska; Gumiarabikas; Gummi Africanum; Gummi Arabicum; Gummi Mimosae.

CAS — 9000-01-5.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Acacia). The air-hardened gummy exudate from the trunk and branches of *Acacia senegal*, other species of *Acacia* of African origin, and *Acacia seyal*. Yellowish-white, yellow, or pale amber tears, sometimes with a pinkish tint. It is friable, opaque, frequently with a cracked surface, easily broken into irregular, whitish or slightly yellowish angular fragments with conchoidal fracture and a glassy and transparent appearance. Very slowly but almost completely soluble, after about 2 hours, in twice its mass of water leaving only a very small residue of vegetable particles; the liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

Ph. Eur. 6.2 (Acacia, Spray-dried; Acaciae Gummi Dispersione Desiccatum). It is obtained from a solution of acacia. Dissolves, rapidly and completely, after about 20 minutes, in twice its mass of water. The liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent, and weakly acid to blue litmus paper. Practically insoluble in alcohol. Protect from light.

USNF 26 (Acacia). The dried gummy exudate from the stems and branches of *Acacia senegal* (Leguminosae) or of other related African species of *Acacia*. Spheroidal tears or angular fragments of white to yellowish-white colour. It is translucent or somewhat opaque from the presence of numerous minute fissures. It is very brittle, the fractured surface is glassy and occasionally iridescent. It is also available as flakes, powder, granules, or as a spray-dried form. It is practically odourless. Insoluble in alcohol. Store in airtight containers.

Incompatibility. Incompatibilities of acacia have been reported with a number of substances including alcohol, aminophenazone, apomorphine, cresol, ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin. Acacia contains an oxidising enzyme that may affect preparations containing easily oxidised substances; the enzyme may be inactivated by heating at 100° for a short time.

Adverse Effects

Hypersensitivity reactions have occurred rarely after inhalation or ingestion of acacia.

Uses

Acacia is used in pharmaceutical manufacturing as a suspending and emulsifying agent, as a tablet binder, and in pastilles. It is often used with tragacanth.

It is used as an emulsifier and stabiliser in the food industry.

Preparations

USNF 26: Acacia Syrup.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Norflam.

Agar

Agar-agar; Agaras; Colle du Japon; E406; Gelosa; Gélose; Japanese Isinglass; Layor Carang.

CAS — 9002-18-0.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Agar). Polysaccharides extracted from various species of Rhodophyceae algae, mainly those belonging to the genus *Gelidium*. It is prepared by treating the algae with boiling water; the extract is filtered while hot, concentrated, and dried. Colourless to pale yellow translucent strips, flakes, or powder; tough when damp but becoming more brittle on drying.

USNF 26 (Agar). The dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Gelidiaceae), *Gracilaria confervoides* (Sphaerococcaceae), and related red algae (Class Rhodophyceae). It usually consists of thin, membranous, agglutinated strips, but may occur in cut, flaked, or granulated forms. May be weak yellowish-orange, yellowish-grey to pale yellow, or colourless. It is tough when damp, brittle when dry. Odourless or has a slight odour. Insoluble in cold water; soluble in boiling water.

Uses and Administration

Agar is used as a suspending or thickening agent in pharmaceutical manufacturing and as an emulsifying and stabilising agent in the food industry.

It was formerly used similarly to methylcellulose (p.2145) as a bulk laxative. Preparations containing agar with liquid paraffin and phenolphthalein are available to treat constipation, but the relatively small amount of agar in these probably acts solely as an emulsion stabiliser.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Agarol; Usar Fibras†; ***Austral.:*** Lexat†; ***Braz.:*** Agarol; Fenogar†; ***Chile:*** Agarol; ***Fr.:*** Pseudophage; ***India:*** Agarol†; ***Port.:*** Byl†; ***Switz.:*** Paragar; ***USA:*** Agoral; ***Venez.:*** Agarol†.

Alginic Acid

Acide alginique; Acidum alginicum; Algiinihappo; Algínico, ácido; Algino rūgštis; Alginsav; Alginsyra; Aljinik Asit; E400; Kyselina alginová; Polymannuronic Acid.

CAS — 9005-32-7.
ATC — A02BX13.
ATC Vet — QA02BX13.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Alginic Acid). A mixture of polyuronic acids composed of residues of D-mannuronic and L-guluronic acids extracted from algae belonging to the Phaeophyceae. A white or pale yellowish-brown, crystalline or amorphous powder. It swells in water. Very slightly soluble or practically insoluble in alcohol; practically insoluble in organic solvents; dissolves in solutions of alkali hydroxides.

USNF 26 (Alginic Acid). A hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (Phaeophyceae). A white to yellowish-white, odourless or practically odourless, fibrous powder. Insoluble in water and in organic solvents; soluble in alkaline solutions. pH of a 3% dispersion in water is between 1.5 and 3.5.

Propylene Glycol Alginate

E405; Propilenglicol, alginato de. Propane-1,2-diol Alginate.
ATC — A02BX13.
ATC Vet — QA02BX13.

Pharmacopoeias. In *USNF.*

USNF 26 (Propylene Glycol Alginate). A white to yellowish, practically odourless, fibrous or granular powder. Soluble in water, in solutions of dilute organic acids, and, depending on the degree of esterification, in hydroalcoholic mixtures containing up to 60% by weight of alcohol, to form stable, viscous colloidal solutions at a pH of 3.

Sodium Alginate

Algin; Alginato sódico; E401; Natrii alginas; Natrio alginatas; Natriumalginaatti; Natriumalginat; Nátrium-alginát; Natrium-alginát; Sodium, alginate de; Sodium Polymannuronate; Sodyum Aljinat.
CAS — 9005-38-3.
ATC — A02BX13.
ATC Vet — QA02BX13.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Alginate). It consists chiefly of the sodium salt of alginic acid. A white or pale yellowish-brown powder. Slowly soluble in water, forming a viscous, colloidal solution; practically insoluble in alcohol.

USNF 26 (Sodium Alginate). A yellowish-white, practically odourless, coarse or fine powder. Soluble in water, forming a viscous, colloidal solution; insoluble in alcohol, in chloroform, and in ether, in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight, and in acids when the pH of the resulting solution becomes lower than about 3. Store in airtight containers.

Incompatibility. Incompatibilities of sodium alginate have been observed with acridine derivatives, methylrosanilinium chloride, phenylmercuric acetate and nitrate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals. High concentrations of electrolytes cause an increase in viscosity until salting-out of sodium alginate occurs; salting-out occurs if more than 4% of sodium chloride is present.

Uses and Administration

Alginic acid and alginates such as propylene glycol alginate and sodium alginate are used in pharmaceutical manufacturing as suspending and thickening agents. They may be used as stabilisers for oil-in-water emulsions and as binding and disintegrating agents in tablets. Various grades are usually available commercially for different applications and yield solutions of varying viscosity. A reduction in viscosity has been said to occur following sterilisation by autoclaving of sodium alginate solutions.

Alginic acid and alginates (ammonium alginate, calcium alginate (p.1058), potassium alginate, propylene glycol alginate, and sodium alginate) are also used as emulsifiers and stabilisers in the food industry.

Alginic acid or the alginates, magnesium alginate and sodium alginate, are given, usually formulated with an antacid, in the management of gastro-oesophageal reflux disease (p.1696). Alginic acid or the alginate reacts with gastric acid to form a viscous gel (often termed a raft) that floats on top of the gastric contents. This raft then acts as a mechanical barrier to reduce reflux.

Alginic acid is also used, usually in the form of a mixed calcium-sodium salt, as a haemostatic and wound dressing; it is employed in the form of a fibre made into a dressing or packing material.

Preparations

BP 2008: Alginate Raft-forming Oral Suspension; Compound Alginate Antacid Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Nu-Gel Hidrogel con Alginato; ***Austral.:*** Kaltostat†; ***Canad.:*** Kaltostat; Restore CalciCare; Tegagen†; ***Fr.:*** Nu-Gel; ***Irl.:*** Kaltostat; ***Israel:*** Nu-Gel; ***Ital.:*** Flaminal; Kaltostat; Nu-Gel; ***NZ:*** Gaviscon; ***Port.:*** Biafine; ***Rus.:*** Alginatol (Альгинатол); Natalsid (Натальсид); ***S.Afr.:*** Gaviscon; Gaviscon Advance; Kaltostat; ***UK:*** Comfeel SeaSorb.

Multi-ingredient: ***Arg.:*** Comfeel SeaSorb†; Gaviscon†; Glicalox†; Mylanta Reflux; Redudiet; Rennie; Seasorb; ***Austral.:*** Gaviscon; Gaviscon Double Strength; Infant Gaviscon; Meracote†; Mylanta Heartburn Relief†; ***Austria:*** Rennie Duo; ***Belg.:*** Gastriphar; Gaviscon; Gaviscon Advance; ***Canad.:*** Carboflex†; Gastrifom; Gaviscon Heartburn Relief; Heartburn Relief†; Maalox HRF; ***Chile:*** Algicote; Gaviscon; ***Cz.:*** Alginete†; Gaviscon; ***Denm.:*** Gaviscon; ***Fin.:*** Gaviscon; ***Fr.:*** Gaviscon; Gavisconell; Hyalogran; Pseudophage; Release Ag; Topaal; Topalkan; ***Ger.:*** Gaviscon; Gaviscon Advance; Nu-Gel†; Recatol Algin; ***Hong Kong:*** Gaviscon; ***India:*** Acigon†; Gaviscon; Raftace; Visco; ***Irl.:*** Acidex; Algicon†; Gaviscon; Gaviscon Advance; Gaviscon Infant; Gaviscon Lemon; Pyrogastrone; Rennie Duo†; ***Israel:*** Algical Kalzarevet; Kaltocarb; Kaltostat; ***Ital.:*** Digerall†; Gastrotuss; Gaviscon; Gaviscon Advance; Silvercel; ***Malaysia:*** Gaviscon; Gaviscon Advance; ***Mex.:*** Algicon†; ***Neth.:*** Aciflux; Algicon; Gaviscon; Rennie Duo; Rennie Refluxine; ***Norw.:*** Gaviscon; ***NZ:*** Gaviscon; Mylanta Heartburn Relief; ***Pol.:*** Gealcid; ***Port.:*** Carboflex†; Kaltostat; Rennie Duo; ***S.Afr.:*** Gaviscon; Gelacid; Infant Gaviscon; ***Singapore:*** Gaviscon; Gaviscon Advance; ***Spain:*** Dolcopin; ***Swed.:*** Gaviscon; ***Switz.:*** Gaviscon†; Refluxine†; ***Turk.:*** Gaviscon; Rennie Duo; ***UK:*** Acidex; Algicon†; Bisodol Extra; Bisodol Heartburn Relief; Gastrocote; Gaviscon Advance; Gaviscon Cool; Gaviscon Double Action; Gaviscon Infant; Gaviscon†; Peptac; Pyrogastrone†; Raft-Eze; Rennie Duo; Setlers Heartburn & Indigestion Liquid; Topal; ***USA:*** Foamicon†; Gaviscon; Genaton; Pretts Diet Aid.

Aluminium Magnesium Silicate

Aliuminio-magnio silikatas; Alumiinimagnesiumsilikaatti; Aluminii magnesii silicas; Aluminium (silicate d') et de magnésium; Aluminiummagnesiumsilikat; Alumínium-magnézium-szilikát; Aluminosilicato magnésico; Křemičitan hořečnato-hlinitý; Magnesium Aluminium Silicate; Magnesium Aluminum Silicate; Saponite.
CAS — 1327-43-1; 12511-31-8.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF. USNF* also includes Magnesium Aluminosilicate and Magnesium Aluminometasilicate.

Ph. Eur. 6.2 (Aluminium Magnesium Silicate). A mixture of colloidal-size particles of montmorillonite and saponite, free from grit and nonswellable ore. Almost white powder, granules, or plates. Practically insoluble in water and in organic solvents; swells in water to form a colloidal dispersion. A 5% dispersion in water has a pH of 9.0 to 10.0.

USNF 26 (Magnesium Aluminum Silicate). A blend of colloidal montmorillonite and saponite that has been processed to remove grit and nonswellable ore components. There are several types, differing in viscosity and in ratio of aluminium content to magnesium content. It is an odourless, fine (micronised) powder, small cream to tan granules, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol; swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

USNF 26 (Magnesium Aluminosilicate). A synthetic material that contains 20.5 to 27.7% of magnesium oxide, 27.0 to 34.3% of aluminium oxide, and 14.4 to 21.7% of silicon dioxide, calculated on the dried basis. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 8.5 to 10.5. Store at a temperature not exceeding 40° in airtight containers.

USNF 26 (Magnesium Aluminometasilicate). A synthetic material that contains 29.1 to 35.5% of aluminium oxide, 11.4 to 14.0% of magnesium oxide, and 29.2 to 35.6% of silicon dioxide, calculated on the dried basis. It exists in two forms, Type I-A and Type I-B. A white powder or granules having an amorphous structure. Practically insoluble in water and in alcohol; partially soluble in acids and alkalis. A 4% suspension in water has a pH of 6.5 to 8.5 (Type I-A) and 8.5 to 10.5 (Type I-B). Store at a temperature not exceeding 40° in airtight containers.

Uses

Aluminium magnesium silicate has a variety of pharmaceutical uses, including use as a suspending and thickening agent, as an emulsion stabiliser, and as a binder and disintegrating agent in tablets.

Other forms of aluminium magnesium silicate include an artificial hydrate known as almasilate (p.1705), which is used as an antacid, and attapulgite (p.1709), a purified native hydrated aluminium magnesium silicate that is highly adsorbent and is used in a wide range of products including fertilisers and pesticides. Activated attapulgite, which is attapulgite that has been carefully heated to increase its adsorptive capacity, is used in preparations for diarrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Neusilin.

Multi-ingredient: ***Denm.:*** Alkasid†; ***India:*** Digene; ***Indon.:*** Flatucid; Stomadon; ***Jpn:*** Cabe 2; ***Thai.:*** Diasgest; ***UAE:*** Alkasid.

Bentonite

Bentoniitti; Bentonit; Bentonita; Bentonitas; Bentonitum; E558; Mineral Soap; Soap Clay; Wilkinite.
CAS — 1302-78-9.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF*, which also includes a purified form.

Ph. Eur. 6.2 (Bentonite). A natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms may be replaced by other atoms such as magnesium and iron. A very fine, homogeneous, greyish-white powder with a more or less yellowish or pinkish tint. Practically insoluble in water and in aqueous solutions, but swells with a little water forming a malleable mass.

USNF 26 (Bentonite). A native, colloidal, hydrated aluminium silicate. A very fine, odourless, hygroscopic, pale buff or cream-coloured to greyish powder, free from grit. Insoluble in water, but swells to about 12 times its volume when added to water; insoluble in, and does not swell in, organic solvents. pH of a 2% suspension in water, mixed vigorously to facilitate wetting, is between 9.5 and 10.5. Store in airtight containers.

USNF 26 (Purified Bentonite). A colloidal montmorillonite that has been processed to remove grit and nonswellable ore components. An odourless, fine, micronised powder, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerol. pH of a 5% suspension in water is between 9.0 and 10.0. Store in airtight containers.

Uses

Bentonite absorbs water readily to form sols or gels, depending on its concentration. It is used in pharmaceutical manufacturing as a suspending and stabilising agent and as an adsorbent or clarifying agent. It is also used as an anticaking agent in the food industry.

Bentonite may be used as an oral adsorbent in paraquat poisoning (p.2047).

Preparations

USNF 26: Bentonite Magma.

Proprietary Preparations (details are given in Part 3)
Gr.: Bentonine†.

Multi-ingredient: ***Indon.:*** Stomagel; ***Malaysia:*** Clearasil Pimple Treatment; ***S.Afr.:*** Clearasil T; ***Singapore:*** Clearasil Pimple Treatment.

Carbomers

Acrylic Acid Polymers; Carbomera; Carbomères; Carbómeros; Carbopols; Carboxypolymethylene; Carboxyvinyl Polymers; Karbomeerit; Karbomerai; Karbomerek; Karbomerer; Karbomerler; Karbomery; Poliakrilic Asit; Polyacrylic Acid.
CAS — 9003-01-4; 54182-57-9.

NOTE. Carbomer is *BAN, USAN*, and *rINN*.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Int. USNF* has separate monographs for a range of carbomers.
USNF also includes Carbomer Copolymer and Carbomer Interpolymer.

Ph. Eur. 6.2 (Carbomers). High-molecular-weight polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols. They are produced in several grades characterised by the viscosity of a defined solution. White or almost white, fluffy, hygroscopic powders. They swell in water and in other polar solvents after dispersion and neutralisation with sodium hydroxide solution. Store in airtight containers.

USNF 26 (Carbomer 934; Carbomer 934P; Carbomer 940; Carbomer 941; Carbomer 1342). Carbomers are high-molecular-weight polymers of acrylic acid cross-linked with allyl ethers of pentaerythritol. The viscosity of a neutralised aqueous dispersion for each carbomer is:

- Carbomer 934 (0.5%), 30 500 to 39 400 cP
- Carbomer 934P (0.5%), 29 400 to 39 400 cP
- Carbomer 940 (0.5%), 40 000 to 60 000 cP
- Carbomer 941 (0.5%), 4000 to 11 000 cP
- Carbomer 1342 (1.0%), 9500 to 26 500 cP

They are white, fluffy, hygroscopic powders having a slight characteristic odour. pH of a 1% dispersion in water is about 3. When neutralised with alkali hydroxides or with amines, they dissolve in water, in alcohol, and in glycerol. Store in airtight containers.

USNF 26 (Carbomer Copolymer). A high-molecular-weight copolymer of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of polyalcohols. Different types of Carbomer Copolymer are characterised by the viscosity of a defined solution. Carbomer Copolymer does not constitute the official title when benzene is used in the manufacturing process, in which case the name will be Carbomer 1342 if it complies with the requirements of that monograph. Store in airtight containers at a temperature not exceeding 45°.

USNF 26 (Carbomer Interpolymer). A carbomer homopolymer or copolymer that contains a block copolymer of macrogol and a long chain alkyl acid ester. Different types of Carbomer Interpolymer are characterised by the viscosity of a defined solution. Store in airtight containers at a temperature not exceeding 45°.

Uses and Administration

Carbomers are used in pharmaceutical manufacturing as suspending agents, gel bases, emulsifiers, and binding agents in tablets.

Carbomers, in liquid gel formulations containing typically 0.2 or 0.3%, are used topically as tear substitutes in the management of dry eye (p.2140).

Preparations

BP 2008: Carbomer Eye Drops.

Proprietary Preparations (details are given in Part 3)
Arg.: Acrylarm; Lacryvisc†; Liposic; Refresh Gel; Siccafluid; Teargel†; Viscotears; ***Austral.:*** Poly Gel; Viscotears; ***Austria:*** AquaTears; Liposic; Tears Naturale; Vidisic; ***Belg.:*** Alcon Eye Gel; Lacrinorm; Liposic; Ocugel; Thilo Tears; Vidisic; ***Braz.:*** Refresh Gel; Vidisic†; Viscotears; ***Canad.:*** Lacrinorm†; Tear-Gel; ***Chile:*** Feels; Lacryvisc; Nicotears; Viscotears; ***Cz.:*** Lacryvisc†; Oftagel; Vidisic; ***Denm.:*** Oftagel; Viscotears; ***Fin.:*** Oftagel; Viscotears; ***Fr.:***

Aqualarm; Civigel; Gel-Larmes; Lacrinorm; Lacryvisc; Liposic; Siccafluid; ***Ger.:*** Arufil C; Liposic; Liquigel; Siccapos; Thilo-Tears; Vidisic; Visc-Ophtal; ***Gr.:*** Dacrio Gel; Liposic; Tear drops†; Thilogel; Viscoter; ***Hong Kong:*** Lacryvisc; Liposic; Viscotears; ***Hung.:*** Oftagel; Vidisic; ***Irl.:*** GelTears; Liquivisc; Vidisic; ***Israel:*** Viscotears; ***Ital.:*** Dacriogel; Dropgel; Lacrigel; Lacrinorm; Lipovisc; Siccafluid; Viscotirs; ***Malaysia:*** Vidisic†; ***Mex.:*** Conforgel; Lacryvisc; Lipolac; Refresh; Viscotears; ***Neth.:*** Dry Eye Gel; Lacrinorm; Liposic; Siccafluid; Thilo-Tears; Vidisic; ***Norw.:*** Oftagel; Viscotears; ***NZ:*** Viscotears; ***Philipp.:*** Lacryvisc; Lipolin; Siccafluid; Vidisic; ***Pol.:*** Oftagel; Oftipan; Vidisic; ***Port.:*** Lacryvisc; Liposic; Siccafluid; Vidisic; ***Rus.:*** Oftagel (Офтагель); Vidisic (Видисик); ***S.Afr.:*** Teargel; ***Singapore:*** Lacryvisc; Vidisic; ***Spain:*** Lacryvisc; Lipolac; Siccafluid; Viscotears; ***Swed.:*** Oftagel; Viscotears; ***Switz.:*** Lacrinorm; Lacryvisc; Siccafluid; Viscotears; ***Thai.:*** Lacryvisc; Vidisic; ***Turk.:*** Lacryvisc; Siccapos; Thilo-Tears; Viscotears; ***UK:*** GelTears; Liposic; Liquivisc; Viscotears; ***Venez.:*** Acrylarm; Lacryvisc; Siccafluid; Viscotears.

Multi-ingredient: ***Arg.:*** Latlas; ***Austral.:*** Genteal Moisturising; ***Chile:*** Gelsolets; ***Cz.:*** Hypotears; ***Hong Kong:*** Clinac OC; Hypotears†; ***Indon.:*** Genteal; Oculotect; ***Irl.:*** Liposic; ***Ital.:*** Dropyal; ***Pol.:*** Oculotect; ***Port.:*** Hidratante VG; ***Switz.:*** Lacrycon; ***USA:*** Maxilube; ***Venez.:*** Genteal.

Carmellose *(rINN)*

Carboxymethylcellulose; Carmellosum; Carmelosa; CMC; E466.

Кармеллоза

CAS — 9000-11-7.

Pharmacopoeias. In *Jpn.*

Carmellose Calcium *(rINNM)*

Calcii Carmellosum; Calcium Carboxymethylcellulose; Carboxymethylcellulose Calcium; Carmellose calcique; Carmellosum calcicum; Carmellosum Calcium; Carmelosa cálcica; Karmeliozės kalcio druska; Karmelloosikalsium; Karmelloskalcium; Karmellóz-kalcium; Karmelosa vápenatá sůl.

Кальций Кармеллоза

CAS — 9050-04-8.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Carmellose Calcium). A white or yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, and in toluene. Store in airtight containers.

USNF 26 (Carboxymethylcellulose Calcium). A white to yellowish-white, hygroscopic powder. It swells in water to form a suspension; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 1% suspension in water is between 4.5 and 6.0. Store in airtight containers.

Carmellose Sodium *(BAN, rINNM)*

Carboxymethylcellulose Sodium; Carboxymethylcellulosum Natricum; Carmellose sodique; Carmellosum natricum; Carmelosa sódica; Cellulose Gum; E466; Karmeliozės natrio druska; Karmelloosinatrium; Karmellosnatrium; Karmellóz-nátrium; Karmelosa sodná sůl; Karmeloza sodowa; Natrii Carmellosum; SCMC; Sodium Carboxymethylcellulose; Sodium Cellulose Glycollate.

Натрий Кармеллоза

CAS — 9004-32-4.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Eur. and *USNF* also include low-substituted carmellose sodium.

USNF also includes Carboxymethylcellulose Sodium 12.

Eur also includes a mixture of microcrystalline cellulose with carmellose sodium.

Ph. Eur. 6.2 (Carmellose Sodium). A white or almost white, hygroscopic granular powder. It has a sodium content of 6.5 to 10.8% calculated on the dry substance. Easily dispersed in water forming colloidal solutions; practically insoluble in dehydrated alcohol, in acetone, in ether, and in toluene. A 1% colloidal solution in water has a pH of 6.0 to 8.0.

Ph. Eur. 6.2 (Carmellose Sodium, Low-substituted; Carmellosum Natricum, Substitutum Humile). It contains not less than 2.0% and not more than 4.5% of sodium, calculated with reference to the dried substance. A white or almost white powder or short fibres. It swells in water to form a gel; practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 6.0 to 8.5.

Ph. Eur. 6.2 (Microcrystalline Cellulose and Carmellose Sodium). A colloid-forming, powdered mixture of microcrystalline cellulose with 5 to 22% of carmellose sodium. It contains 75 to 125% of the nominal amount of carmellose sodium, calculated with reference to the dried substance. A white or off-white, coarse or fine powder. Dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids. pH of a 2% dispersion in water is 6 to 8.

USP 31 (Carboxymethylcellulose Sodium). A white to cream-coloured, hygroscopic powder or granules. It contains not less than 6.5% and not more than 9.5% of sodium, calculated on the dried basis. Easily dispersed in water to form colloidal solutions; insoluble in alcohol, in ether, and in most other organic solvents. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

USNF 26 (Low-Substituted Carboxymethylcellulose Sodium). It has a sodium content of 2.0 to 4.5%, calculated on the dried basis. A white or almost white powder or short fibres. Practically insoluble in alcohol, in acetone, and in toluene. It swells in water to form a gel. pH of a 1% suspension in water is between 6.0 and 8.5. Store in airtight containers.

USNF 26 (Carboxymethylcellulose Sodium 12). A colourless or white to off-white, odourless, powder or granules. Water solubility depends on degree of substitution (easily dispersed in water at all temperatures, forming a clear, colloidal solution). Insoluble in alcohol, in acetone, in ether, and in toluene. It has a sodium content of 10.4 to 12.0%, calculated on the dry substance. Store in airtight containers.

Incompatibility. Incompatibilities of carmellose sodium have been reported with strongly acidic solutions, with soluble salts of iron and some other metals, and with xanthan gum.

Croscarmellose Sodium *(USAN)*

Carmellosum natricum conexum; Croscarmellose sodique; Croscarmelosa sódica; Crosslinked Carboxymethylcellulose Sodium; E468; Kroskarmeliozės natrio druska; Kroskarmelloosi natrium; Kroskarmellosnatrium; Kroskarmelosa sodná sůl; Kroskarmeloza sodowa; Kroszkarmellóz-nátrium; Modified Cellulose Gum.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Croscarmellose Sodium). A cross-linked polymer of carmellose sodium. A white or greyish-white powder. Practically insoluble in dehydrated alcohol, in acetone, and in toluene. A 1% suspension in water has a pH of 5.0 to 7.0.

USNF 26 (Croscarmellose Sodium). The sodium salt of a cross-linked partly *O*-(carboxymethylated) cellulose. A white, free-flowing powder. Partially soluble in water; insoluble in alcohol, in ether, and in other organic solvents. pH of a dispersion containing 1 g mixed with 100 mL of water for 5 minutes is between 5.0 and 7.0.

Uses and Administration

Carmellose calcium and carmellose sodium have a variety of pharmaceutical uses, including use as suspending, thickening, and emulsifying agents, and as disintegrants, binders, and coating agents in tablets. Carmellose sodium is also used as an emulsifier or stabiliser in the food industry. Croscarmellose sodium is used as a tablet disintegrant.

Carmellose sodium is used topically as an ingredient of protective preparations for stoma care, in the management of wounds, and for the mechanical protection of oral and perioral lesions, such as mouth ulceration (p.1700). It is also used, in concentrations of up to 1%, in artificial saliva preparations for the treatment of dry mouth (p.2140), and in eye drops for the management of dry eye (p.2140).

Carmellose sodium given orally absorbs water and acts as a bulk-forming agent; the volume of faeces is increased and peristalsis promoted. It is used in the treatment of constipation (p.1693). Carmellose sodium has been included in preparations to control appetite in the management of obesity (p.2149) but there is little evidence of efficacy. For precautions to be observed with bulk-forming agents, see under Methylcellulose, p.2145.

Preparations

BP 2008: Carmellose Sodium Eye Drops;
USP 31: Carboxymethylcellulose Sodium Paste; Carboxymethylcellulose Sodium Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aqua Lent Lagrima†; Aqua Lent Lubricante; Aquacel; Aucic; Cellufresh†; Celluvisc†; Comfeel; Comfeel Plus Transparente; Natura Fresh; Nu-Derm Hidrocoloide; Refresh Liquigel; Refresh Tears; ***Austral.:*** Aquacel†; Cellufresh; Celluvisc; Refresh Liquigel; Refresh Tears Plus†; ***Austria:*** Celluvisc; ***Belg.:*** Gelilact; ***Braz.:*** Cellufresh; Ecofilm; Fresh Tears; Lacrifilm; Salivan; ***Canad.:*** Aquacel†; Refresh Celluvisc; Refresh Liquigel; Refresh Plus; Refresh Tears; ***Chile:*** Refresh Liquigel; Refresh Tears; ***Cz.:*** Cellufluid; ***Denm.:*** Celluvisc; ***Fin.:*** Celluvisc; ***Fr.:*** Aquacel; Askina Biofilm†; Biatain; Celluvisc; Clip Ampoules; Clip Brulures; Comfeel; Hydrocoll; Physiotulle; Sureskin; Urgomed; Urgotul; ***Ger.:*** Algoplaque; Alione; Cellufresh; Cellumed; Celluvisc; Comfeel Plus Transparenter; Physiotulle; Urgotul; ***Gr.:*** Cellufluid; Celluvisc; ***Hong Kong:*** Refresh; ***Irl.:*** Celluvisc; ***Israel:*** Refresh Tears; ***Ital.:*** Cellufresh; Celluvisc; Lacrilens; ***Malaysia:*** Refresh Plus†; Refresh Tears†; ***Mex.:*** Celluvisc†; Novafix Ultra Fuerte; Refresh Liquigel; Refresh Tears; Thera Tears†; ***Neth.:*** Celluvisc; ***NZ:*** Cellufresh†; Celluvisc†; Refresh Tears Plus; ***Philipp.:*** Cellufresh; Celluvisc; ***Port.:*** Aquacel†; Askina Biofilm†; Cellufluid; Celluvisc; ***S.Afr.:*** Cellufresh; Celluvisc; Comfeel; Refresh Liquigel; Refresh Tears; ***Singapore:*** Celluvisc; Refresh Plus†; Refresh Tears†; ***Spain:*** Cellufresh; Celluvisc; Viscofresh; ***Swed.:*** Celluvisc; ***Switz.:*** Cellufluid; Celluvisc; ***Thai.:*** Cellufresh; Celluvisc; ***UK:*** Celluvisc; Comfeel; Intrasite; Physiotulle; ***USA:*** Celluvisc; Clear Eyes for Dry Eyes; Optive; Refresh Plus; Refresh Tears; Tears Again; TheraTears; ***Venez.:*** Refresh Liquigel; Refresh Tears.

Multi-ingredient: ***Arg.:*** Comfeel Plus; Comfeel Purilon†; Comfeel Sea-Sorb†; Humectante Bucal; Mucobase; Purilon; Razagleda Plus†; Seasorb; ***Austral.:*** Aquae; Orabase; Orahesive†; SoloSite; Stomahesive†; ***Austria:*** Glandosane; Sialin; ***Braz.:*** Chofranina; ***Canad.:*** Appedrine†; Carboflex†; Orabase†; Orahesive†; Salivart; Tegasorb; ***Chile:*** Delgadol Fibra; K.C.M.C; Novafix Extra Fuerte; Reducform-F; Salivart†; ***Cz.:*** Alginete†; Spofax; ***Fr.:*** Altreet Ag; Amivia†; Aquacel Ag; Artisial; Askina Sorb†; Biatain Argent; Cellosorb; Clip Hemo; Intrasite; Melgisorb; Purilon; Release Ag; Seasorb; Urgosorb; Urgotul S.Ag; ***Ger.:*** Cellosorb; Comfeel Plus; Glandosane; Lary-Phary; Nu-Gel†; Purilon; Recatol Algin; SeaSorb Soft; ***Hong Kong:*** Aquae; Glandosane; Salivart; ***India:*** Digene; ***Irl.:*** Orabase; ***Israel:*** Orabase†; ***Ital.:*** Aquacel Ag; ***NZ:*** Orabase; Stomahesive; ***Port.:*** Askina Sorb†; Carboflex†; Glandosane; Varihesive†; ***S.Afr.:*** Granuflex; Granugel; Orabase; ***Spain:*** Laxvital; ***Switz.:*** Glandosane; ***Thai.:*** Bisolax; Emulax; Glandosane†; ***UK:*** Comfeel Plus; Glandosane; Luborant; Orabase; Orahesive; Physiotulle-Ag; SeaSorb Soft; Seprafilm; Stomahesive; ***USA:*** Entertainer's Secret; Moi-Stir; Pretts Diet Aid; Salivart; Seprafilm; Surgel; ***Venez.:*** Klincosal; Novafix; Polantac.

Carrageenan

Carrageenanum; Carrageenin; Carragenina; Carraghénanes; Carraghénates; Chondrus Extract; E407; Irish Moss Extract.

CAS — 9000-07-1 (carrageenan); 11114-20-8 (κ-carrageenan); 9064-57-7 (λ-carrageenan).

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 26 (Carrageenan). The hydrocolloid obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweeds). It consists chiefly of a mixture of the ammonium, calcium, magnesium, potassium, and sodium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. The prevalent copolymers in the hydrocolloids are κ-carrageenan, ι-carrageenan, and λ-carrageenan.

A yellowish or tan to white, coarse to fine, practically odourless, powder. Soluble in water at 80° forming a viscous, clear or slightly opalescent solution that flows readily. It disperses more readily in water if first moistened with alcohol, with glycerol, or with a saturated solution of glucose in water. Store in airtight containers at a temperature of 8° to 15°.

Uses and Administration

Carrageenan is used in pharmaceutical manufacturing and the food industry as a suspending and gelling agent.

It has been used as a bulk-forming laxative to treat constipation; for precautions to be observed with bulk-forming laxatives, see under Methylcellulose, p.2145. Carrageenan is also included in topical preparations for the symptomatic relief of anorectal disorders. A gel containing carrageenan has been investigated as a topical microbicide.

A degraded form of carrageenan was formerly used in gastrointestinal disorders but it was associated with lesions in *animals* and is no longer used.

Irish moss (*Chondrus crispus*), a source of carrageenan, is used in herbal medicine.

◊ Refined non-degraded carrageenan and furcellaran, a similar extract from Rhodophyceae that is included in the specifications for food-grade carrageenan, have generally been considered safe for use as food additives, although this may not be the case with degraded and 'semi-refined' forms.[1] However, in the UK the Food Advisory Committee has recommended that carrageenan should not be permitted as an additive for infant formulas because of the possibility of immunological consequences after absorption from the immature gut.[2] Carrageenans affect the immune system of experimental *animals* after parenteral or oral use, and small amounts of food-grade carrageenan cross the intestinal epithelium in *rats* and are taken up by gut-associated lymphoid tissue.[3]

1. FAO/WHO. Evaluation of certain food additives and contaminants: twenty-eighth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 710* 1984.
2. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. FdAC/REP/12. London: HMSO, 1992.
3. MAFF. Food Advisory Committee: report on the review of the emulsifiers and stabilisers in food regulations. FdAC/REP/11. London: HMSO, 1992.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Coreine.

Multi-ingredient: ***Austral.:*** Bonningtons Irish Moss; ***Austria:*** Anoreine; Anoreine mit Lidocain; ***Cz.:*** Titanoreine†; ***Fr.:*** Anoreine; Titanoreine; Titanoreine Lidocaine; ***Ger.:*** Saseem; ***Ital.:*** Resource Gelificata; ***NZ:*** Bonningtons Irish Moss; ***Pol.:*** Tytanoreina†; ***Spain:*** Titanorein; ***Switz.:*** Flogecyl; Titanoreine†; ***UK:*** Fam-Lax Senna.

Cellacefate *(BAN, rINN)*

CAP; Celacefát; Celacefat; Celacefato; Celiuliozės acetatas-ftalatas; Cellacéfate; Cellacefatum; Cellacephate; Cellulosaacetatftalat; Cellulose, acétate phtalate de; Cellulose Acetate Phthalate; Cellulosi acetas phthalas; Cellulosum Acetylphthalicum; Cellulóz-acetát-ftalát; Celophthalum; Selluloosa-asetaattiftalaatti.

Целлацефат

CAS — 9004-38-0.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Cellulose Acetate Phthalate; Cellacefate BP 2008). Cellulose in which some of the hydroxyl groups are acetylated (21.5 to 26.0%) and some are phthalylated (30.0 to 36.0%), both calculated with reference to the anhydrous, acid-free substance.

A hygroscopic, white or almost white, free-flowing powder or colourless flakes. Practically insoluble in water, in dehydrated alcohol, and in dichloromethane; freely soluble in acetone; soluble in diethylene glycol; it dissolves in dilute solutions of alkalis. Store in airtight containers.

USNF 26 (Cellacefate). A reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains 21.5 to 26.0% of acetyl groups, and 30.0 to 36.0% of phthalyl(*o*-carboxy-benzoyl) groups, calculated on the anhydrous, acid-free basis. A white, free-flowing powder that may have a slight odour of acetic acid. Insoluble in water and in alcohol; soluble in acetone and in dioxan. Store in airtight containers.

Uses

Cellacefate is unaffected by immersion in acid media in the stomach but softens and swells in intestinal fluid. It is used in pharmaceutical manufacturing as an enteric-coating material for tablets and capsules, usually with a plasticiser. Films of cellacefate are reported to be permeable to some ionic substances such as ammonium chloride and potassium iodide, and such substances require a sealing coat.

Cellulose

Celulosa.

Description. Cellulose is an unbranched polysaccharide polymer consisting of 1,4-β-linked glucopyranose units. It is the chief constituent of fibrous plant material.

Dispersible Cellulose *(BAN)*

Cellulose microcristalline et carmellose sodique; Cellulosum microcristallinum et carmellosum natricum; Celulosa dispersable; Microcrystalline Cellulose and Carboxymethylcellulose Sodium; Microcrystalline Cellulose and Carmellose Sodium.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2008 (Dispersible Cellulose). An odourless or almost odourless, white or off-white, coarse or fine powder consisting of a colloid-forming attrited mixture of microcrystalline cellulose and carmellose sodium. Disperses in water to produce a white, opaque dispersion or gel; practically insoluble in organic solvents and in dilute acids. Store at a temperature between 8° and 15°.

USNF 26(Microcrystalline Cellulose and Carboxymethylcellulose Sodium). A colloid-forming, attrited mixture of microcrystalline cellulose and carmellose sodium. A white to off-white, odourless, coarse to fine, powder. It swells in water, producing, when dispersed, a white, opaque dispersion or gel; insoluble in organic solvents and in dilute acids. Store in airtight containers in a dry place, and at a temperature not exceeding 40°.

Microcrystalline Cellulose

Celiuliozė, mikrokristalinė; Cellulosa Microgranulare; Cellulosa, mikrokristallin; Cellulose Gel; Cellulose microcristalline; Cellulosum microcristallinum; Cellulosum Microcrystallinum; Cellulosum Microristallinum; Celulosa microcristalina; Celulosa mikrokrystalická; Celuloza mikrokrystaliczna; Crystalline Cellulose; E460; Mikrokristályos cellulóz; Selluloosa, mikrokiteinen.

CAS — 9004-34-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *Jpn.* Also in *USNF.*

Eur also includes a mixture of microcrystalline cellulose with carmellose sodium.

Ph. Eur. 6.2 (Cellulose, Microcrystalline). A purified, partly depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant materials, with mineral acids. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in dilute acids, and in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is 5.0 to 7.5.

Ph. Eur. 6.2 (Microcrystalline Cellulose and Carmellose Sodium). A colloid-forming, powdered mixture of microcrystalline cellulose with 5 to 22% of carmellose sodium. It contains 75 to 125% of the nominal amount of carmellose sodium, calculated with reference to the dried substance. A white or off-white, coarse or fine powder. Dispersible in water producing a white, opaque colloidal dispersion; practically insoluble in organic solvents and in dilute acids. pH of a 2% dispersion in water is 6 to 8.

USNF 26 (Microcrystalline Cellulose). A purified, partially depolymerised cellulose, prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It is a fine, white or almost white powder consisting of free-flowing, nonfibrous particles. Insoluble in water, in dilute acids, and in most organic solvents; practically insoluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid obtained from a 12.5% mixture in water after 20 minutes of shaking is between 5.0 and 7.5. Store in airtight containers.

Powdered Cellulose

Celiuliozės milteliai; Cellulosapulver; Cellulose en poudre; Cellulose Powder; Cellulosi pulvis; Cellulózpor; Celulosa en polvo; Celulosový prášek; E460; Selluloosajauhe.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Cellulose, Powdered). A purified mechanically disintegrated cellulose prepared from alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white, fine or granular powder. Practically insoluble in water, in dehydrated alcohol, in acetone, in toluene, in most organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation.

USNF 26 (Powdered Cellulose). A purified, mechanically disintegrated cellulose prepared by processing alpha-cellulose obtained as a pulp from fibrous plant materials. It is a white or almost white powder. Exhibits degrees of fineness ranging from a free-flowing, dense powder to a coarse, fluffy, nonflowing material. Insoluble in water, in nearly all organic solvents, and in dilute acids; slightly soluble in sodium hydroxide solution (1 in 20). The pH of the supernatant liquid of an 11.1% mixture in water is between 5.0 and 7.5 one hour after preparation. Store in airtight containers.

Uses and Administration

Powdered cellulose and microcrystalline cellulose are used in pharmaceutical manufacturing as tablet binders and disintegrants and as capsule and tablet diluents. These two forms of cellulose are also used in the food industry. Dispersible cellulose (which also contains some carmellose sodium) forms a thixotropic gel with water and is used pharmaceutically as a suspending and thickening agent.

Various forms of cellulose have been included in preparations used in the management of constipation and obesity. Cellulose is also used in adsorbent powder preparations used for skin disorders including hyperhidrosis.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Fibrasan; ***UK:*** Nasaleze; Sterigel; ***USA:*** Unifiber.

Multi-ingredient: ***Arg.:*** Usar Fibras†; ZeaSorb; ***Austral.:*** ZeaSorb; ***Canad.:*** ZeaSorb; ***Chile:*** ZeaSorb†; ***Cz.:*** Systogen†; ***Fr.:*** Gelopectose; Hydroclean; ZeaSorb; ***Irl.:*** ZeaSorb; ***Israel:*** Celluspan; ***Thai.:*** ZeaSorb; ***UK:*** ZeaSorb.

Ceratonia

Carob Bean Gum; Carob Gum; Cerat.; Ceratonia Gum; E410; Goma de garrofín; Gomme de Caroube; Guma z nasion Carobe; Locust Bean Gum.

CAS — 9000-40-2.
ATC — A07XA02.
ATC Vet — QA07XA02.

Uses

Ceratonia consists of the endosperms separated from the seeds of the locust bean tree, *Ceratonia siliqua* (Leguminosae). It is used as a thickening agent and stabiliser in the food industry.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Arobon; ***Irl.:*** Carobel; ***Ital.:*** Arobon; ***Switz.:*** Nestargel; ***UK:*** Carobel; Nestargel.

Multi-ingredient: ***Austria:*** China-Eisenwein; ***Belg.:*** Kestomatine Baby†; ***Fr.:*** Gumilk; ***Indon.:*** Polysilane; ***Switz.:*** Kestomatine Bebe†.

Dextrates *(USAN)*

Dextratos.

CAS — 39404-33-6.

Pharmacopoeias. In *USNF.*

USNF 26 (Dextrates). A purified, anhydrous or hydrated, mixture of saccharides obtained by the controlled enzymatic hydrolysis of starch. Free-flowing, porous, white, odourless, spherical granules consisting of aggregates of microcrystals. Freely soluble in water (heating increases its solubility in water); soluble in dilute acids and alkalis and in basic organic solvents such as pyridine; insoluble in the common organic solvents. pH of a 20% solution in water is between 3.8 and 5.8. Store in a dry place at a temperature of 8° to 15°.

Uses

Dextrates is used as a capsule and tablet diluent and as a tablet binding agent.

Ethylcellulose *(rINN)*

Cellulose Ethyl Ether; E462; Éthylcellulose; Ethylcellulosum; Ethylcelulosa; Etilceliuliozė; Etilcellulóz; Etilcelulosa; Etylcellulosa; Etyyliselluloosa.

Этилцеллюлоза

CAS — 9004-57-3.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44 to 51% of ethoxy ($-OC_2H_5$) groups, calculated on the dried basis. A white to yellowish-white, odourless or almost odourless, powder or granular powder. Solutions of ethylcellulose may show a slight opalescence. Practically insoluble in water, in glycerol (85%), and in propylene glycol; soluble in dichloromethane and in a mixture of 20 parts alcohol and 80 parts toluene (w/w); slightly soluble in ethyl acetate and methyl alcohol.

USNF 26 (Ethylcellulose). A partly *O*-ethylated cellulose. It contains 44.0 to 51.0% of ethoxy groups, calculated with reference to the dried substance. A free-flowing white to light tan powder. Its aqueous suspensions are neutral to litmus. Insoluble in water, in glycerol, and in propylene glycol. Ethylcellulose containing less than 46.5% of ethoxy groups is freely soluble in chloroform, in methyl acetate, in tetrahydrofuran, and in mixtures of aromatic hydrocarbons with alcohol; ethylcellulose containing 46.5% or more of ethoxy groups is freely soluble in alcohol, in chloroform, in ethyl acetate, in methyl alcohol, and in toluene.

Uses

Ethylcellulose is used as a binder in tablets and as a coating material for tablets, granules, and microcapsules. It is also used as a thickening agent.

Preparations

USNF 26: Ethylcellulose Aqueous Dispersion.

Gastric Mucin *(BAN)*

Mucina gástrica.

Uses and Administration

Gastric mucin is a high-molecular-weight glycoprotein precipitated by alcohol (60%) after digestion of hogs' stomach linings by pepsin and hydrochloric acid. It is used in artificial saliva formulations for dry mouth (p.2140) as an oral spray containing 3.5% or as lozenges.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Saliva medac; ***Neth.:*** Saliva Orthana.

Multi-ingredient: ***UK:*** Saliva Orthana.

Hyetellose *(rINN)*

Hidroksietilceliuliozė; Hidroxietilcellulóz; Hidroxietilcelulosa; Hydroksietyyliselluloosa; Hydroksyetyloceluloza; Hydroxietylcellulosa; Hydroxyethyl Cellulose; Hydroxyéthylcellulose; Hydroxyethylcellulose; Hydroxyethylcellulosum; Hyétellose; Hyetellosum; Hyetelosa.

Гиетэллоза

CAS — 9004-62-0.

NOTE. HECL is a code approved by the BP 2008 for use on single unit doses of eye drops containing hyetellose and sodium chloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Hydroxyethylcellulose). A partially substituted 2-hydroxyethyl ether of cellulose. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% solution measured at 25°. A white, yellowish-white, or greyish-white, powder or granules. Soluble in cold or hot water, forming colloidal solutions; practically insoluble in alcohol, in acetone, and in toluene. A 1% solution in water has a pH of 5.5 to 8.5.

USNF 26 (Hydroxyethyl Cellulose). A partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve their dispersion in water. It may contain suitable anticaking agents. A white to light tan, practically odourless, hygroscopic, powder. Soluble in cold or hot water, giving a colloidal solution; practically insoluble in alcohol and in most organic solvents. pH of a 1% solution in water is between 6.0 and 8.5.

Uses and Administration

Hyetellose is used in pharmaceutical manufacturing as a thickener and stabiliser and as a tablet coating and binding agent. It is present in lubricant preparations for dry eye (p.2140), contact lens care (p.1622), and dry mouth (p.2140).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Rohto Zi Contact†; ***Ger.:*** Lacrigel; ***Israel:*** V-Tears; ***USA:*** Comfort Tears; Gonioscopic; TearGard.

Multi-ingredient: ***Arg.:*** Hidratagel; ***Austral.:*** Minims Artificial Tears†; ***Fr.:*** Premicia; ***Ger.:*** Lubrikano; Nu-Gel†; ***Irl.:*** Minims Artificial Tears; ***Israel:*** V-Crima; ***Turk.:*** Gleitgelen; ***UK:*** Minims Artificial Tears; ***USA:*** Biotene with Calcium; Optimoist.

Hymetellose *(rINN)*

HEMC; Hidroxietilmetilcelulosa; Hydroxyethyl Methylcellulose; Hydroxyethylmethylcellulose; Hymétellose; Hymetellosum; Méthylhydroxyéthylcellulose; Methylhydroxyethylcellulose; Methylhydroxyethylcellulosum; Metilhidroksietilceliuliozė; Metilhidroxietilcellulóz; Metylhydroxietylcellulosa; Metyylihydroksietyyliselluloosa.

Гимэтеллоза

CAS — 9032-42-2.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Methylhydroxyethylcellulose; Hydroxyethylmethylcellulose BP 2008). A partially substituted ether of cellulose containing methoxyl and 2-hydroxyethyl groups. Various grades are available and are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20°. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water forming a colloidal solution. A 1% w/w solution in water has a pH of 5.5 to 8.0.

USNF 26 (Hymetellose). A partly *O*-(methylated) and *O*-(2-hydroxyethylated) cellulose. Various grades are available, labelled with the viscosity of a 2% w/w solution measured at 20°. A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Insoluble in hot water, in alcohol, in acetone, in ether, and in toluene; dissolves in cold water forming a colloidal solution. pH of a 1% w/w solution in water is between 5.5 and 8.0.

Uses

Hymetellose is used similarly to other cellulose ethers, such as methylcellulose (p.2145), as a pharmaceutical excipient.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Cellobexon.

Multi-ingredient: ***Fr.:*** Pharmatex.

Hyprolose *(rINN)*

E463; Hidroksipropilceliuliozė; Hidroxipropilcellulóz; Hidroxipropilcelulosa; Hydroksipropyyliselluloosa; Hydroxipropylcellulosa; Hydroxypropyl Cellulose; Hydroxypropylcellulose; Hydroxypropylcellulosum; Hydroxypropylcelulosa; Hyprolosum.

Гипролоза

CAS — 9004-64-2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn*. Also in *USNF* which has two separate monographs, for Hydroxypropyl Cellulose and for Low-substituted Hydroxypropyl Cellulose.

Ph. Eur. 6.2 (Hydroxypropylcellulose). A partially substituted 2-hydroxypropyl ether of cellulose. Various grades are available and may be distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20°. White or yellowish-white, granules or powder; hygroscopic after drying. Soluble in cold water, in dehydrated alcohol, in glacial acetic acid, in methyl alcohol, in propylene glycol, and in a mixture of 10 parts methyl alcohol and 90 parts dichloromethane, forming colloidal solutions; practically insoluble in hot water, in ethylene glycol, and in toluene; sparingly soluble or slightly soluble in acetone. A 1% w/w solution in water has a pH of 5.0 to 8.5.

USNF 26 (Hydroxypropyl Cellulose). A partially substituted poly(hydroxypropyl) ether of cellulose. When dried at 105° for 1 hour, it contains not more than 80.5% of hydroxypropoxy groups. It may contain not more than 0.60% of silica or other suitable anticaking agent. A white to cream-coloured, practically odourless, granular solid or powder, hygroscopic after drying. Soluble in cold water, in alcohol, in chloroform, and in propylene glycol, giving a colloidal solution; insoluble in hot water. pH of a 1% solution in water is between 5.0 and 8.0.

USNF 26 (Low-Substituted Hydroxypropyl Cellulose). It contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups. A white to yellowish-white, practically odourless, hygroscopic, fibrous or granular powder. Practically insoluble in dehydrated alcohol and in ether; dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution; swells in water, in sodium carbonate, and in 2N hydrochloric acid. pH of the suspension obtained by shaking 1.0 g with 100 mL of water is between 5.0 and 7.5. Store in airtight containers.

Adverse Effects

Hyprolose used as a solid ocular insert may result in blurred vision and ocular discomfort or irritation including hypersensitivity and oedema of the eyelids.

Hypersensitivity. Allergic contact dermatitis was reported in a patient, associated with the hyprolose present in the reservoir layer of a transdermal estradiol patch.[1]

1. Schwartz BK, Clendenning WE. Allergic contact dermatitis from hydroxypropyl cellulose in a transdermal estradiol patch. *Contact Dermatitis* 1988; **18:** 106–7.

Uses and Administration

Hyprolose is used in pharmaceutical manufacturing in the film coating of tablets, as a tablet excipient, as a thickener, and in microencapsulation. It is used as an emulsifier and stabiliser in the food industry.

Hyprolose is also used as a modified-release solid ophthalmic insert in the management of dry eye (p.2140).

Preparations

USP 31: Hydroxypropyl Cellulose Ocular System.

Proprietary Preparations (details are given in Part 3)

Austral.: Lacrisert†; ***Canad.:*** Lacrisert; ***Fin.:*** Lacrisert; ***Fr.:*** Lacrisert; ***Neth.:*** Lacrisert; ***Norw.:*** Lacrisert†; ***Swed.:*** Lacrisert; ***USA:*** Lacrisert.

Hypromellose *(BAN, rINN)*

E464; Hipromeliozė; Hipromellóz; Hipromelosa; Hipromeloz; Hydroxypropyl Methylcellulose; Hydroxypropylmethylcellulose; Hypromelloosi; Hypromellos; Hypromellosum; Hypromelosa; Hypromeloza; Methyl Hydroxypropyl Cellulose; Methylcellulose Propylene Glycol Ether; Methylhydroxypropylcellulose; Methylhydroxypropylcellulosum.

Гипромеллоза

CAS — 8063-82-9; 9004-65-3.
ATC — S01KA02.
ATC Vet — QS01KA02.

NOTE. HPRM is a code approved by the BP 2008 for use on single unit doses of eye drops containing hypromellose where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Hypromellose). A mixed ether of cellulose containing a variable proportion of methoxy and 2-hydroxypropoxy groups. Various grades are available (see Labelling, below). A white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Dissolves in cold water, forming a colloidal solution; practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene. A 1% w/w solution in water has a pH of 5.0 to 8.0.

USP 31 (Hypromellose). A methyl and hydroxypropyl mixed ether of cellulose It contains methoxy and hydroxypropoxy groups conforming to the limits for the types 1828, 2208, 2906, and 2910, calculated on the dried basis (see Labelling, below). A white to slightly off-white fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture; insoluble in dehydrated alcohol, in chloroform, and in ether.

Labelling. In Europe, grades of hypromellose are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20° (e.g. hypromellose 4500). In the USA, they are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of methoxy groups, and the third and fourth digits the approximate percentage content of hydroxypropoxy groups.

Hypromellose Phthalate *(BANM, rINNM)*

Ftalát hypromelosy; Ftalato de hipromelosa; Hipromeliozės ftalatas; Hipromellóz-ftalát; Hydroxypropyl Methylcellulose Phthalate; Hypromelloosiftalaatti; Hypromellose, phtalate d'; Hypromellosftalat; Hypromellosi phthalas; Methylhydroxypropylcellulose Phthalate; Methylhydroxypropylcellulosi Phthalas.

Гипромеллозы Фталат

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Hypromellose Phthalate). A monophthalic acid ester of hypromellose containing methoxy, 2-hydroxypropoxy, and phthalyl groups, calculated with reference to the anhydrous substance. White or slightly off-white, free-flowing flakes or a granular powder. Practically insoluble in water and in dehydrated alcohol; very slightly soluble in acetone and in toluene; soluble in a mixture of equal volumes of acetone and methyl alcohol, and of dichloromethane and methyl alcohol. Store in airtight containers.

USNF 26 (Hypromellose Phthalate). A monophthalic acid ester of hypromellose. It contains methoxy, hydroxypropoxy, and phthalyl groups. It contains 21.0 to 35.0% of phthalyl groups, calculated on the anhydrous basis. Store in airtight containers. A white, odourless, powder or granules. Practically insoluble in water, in dehydrated alcohol, and in hexane; produces a viscous solution in a mixture of dehydrated alcohol and acetone (1:1), or in a mixture of methyl alcohol and dichloromethane (1:1); dissolves in 1N sodium hydroxide. Store in airtight containers.

Labelling. Different grades of hypromellose phthalate in the USA are distinguished by appending a number in which the first 2 digits represent the approximate percentage content of the methoxy groups, the next 2 digits the approximate percentage content of hydroxypropoxy groups, and the last 2 digits the approximate percentage content of the phthalyl groups. Another system of nomenclature involves appending a number which indicates the pH value (× 10) at which the polymer dissolves in aqueous buffer solutions; letters such as S or F may also be used to indicate grades of high molecular-weight or small particle size respectively.

Uses and Administration

Hypromellose has properties similar to those of methylcellulose (below). It is used in pharmaceutical manufacturing for film-coating tablets, as a tablet binder, as a modified-release matrix, and as an emulsifier, suspending agent, and stabiliser in topical gels and ointments. Hypromellose may also be used as an emulsifier and stabiliser in the food industry.

Hypromellose phthalate is used to provide enteric coating for tablets and granules, for the preparation of modified-release granules, and as a coating to mask the unpleasant taste of some tablets.

Hypromellose is widely used clinically in ophthalmic solutions; it is preferred to methylcellulose since mucilages of hypromellose have greater clarity and usually contain fewer undispersed fibres. Hypromellose is used to prolong the action of medicated eye drops and, either alone or with other viscosity-increasing agents, in artificial tears preparations for the management of dry eye (p.2140); solutions containing 0.3 to 1% of hypromellose are commonly used. Solutions for contact lens care (p.1622) and for lubricating artificial eyes contain similar concentrations. Hypromellose is also used intra-ocularly, usually as a 2% solution, as an adjunct in ophthalmic surgery (below) and concentrations of up to 2.5% may be used topically to protect the cornea during gonioscopy procedures.

Hypromellose has been included in artificial saliva preparations used in the management of dry mouth (p.2140), but other drugs are usually preferred.

Ophthalmic surgery. Intra-ocular hypromellose may be used as a visco-elastic agent to protect the eye during surgery. In cataract extraction it is used to maintain the anterior chamber and to coat the intra-ocular lens to facilitate its implantation. Although intra-ocular hypromellose is generally considered to be well tolerated, some[1] have reported an increased incidence of pupil abnormalities (non-reactive semi-dilated pupils) after such use; others[2] did not confirm this. There has also been a report[3] of corneal opacities in a number of patients after use of intra-ocular hypromellose.

1. Tan AKK, Humphry RC. The fixed dilated pupil after cataract surgery—is it related to intraocular use of hypromellose? *Br J Ophthalmol* 1993; **77:** 639–41.
2. Eason J, Seward HC. Pupil size and reactivity following hydroxypropyl methylcellulose and sodium hyaluronate. *Br J Ophthalmol* 1995; **79:** 541–3.
3. Newton JN, *et al.* Corneal opacities after cataract surgery with hypromellose. *Lancet* 2000; **355:** 290.

Preparations

BP 2008: Hypromellose Eye Drops;
USP 31: Hypromellose Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Artelac; Cool Tears; Genteal; Lacrisifi†; Lagrima Dorf; Natura Lagrimas; Oftalook Plus; ***Austral.:*** Genteal Lubricant; Isopto Tears†; Methopt†; ***Austria:*** Artelac; Okuzell; Prosicca; ***Belg.:*** Artelac; Isopto Tears; ***Braz.:*** Artelac†; Filmcel; Genteal; Lubrik†; ***Canad.:*** Eyelube; Genteal; Isopto Tears; Lacril; Visine Advance True Tears; Visine Contact Lens; ***Chile:*** Genteal; ***Cz.:*** Isopto Tears†; Lacrisyn†; ***Denm.:*** Artelac; ***Fin.:*** Artelac; Isopto Alkaline; Isopto Plain; ***Fr.:*** Artelac; ***Ger.:*** Artelac; Berberil Dry Eye; Cellugel; Celoftal; Genteal; HPMC-Ophtal†; Methocel; Sic-Ophtal; Sicca-Stulln; ***Gr.:*** Lubrilac; Vidilac; ***Hong Kong:*** Blueye; Eye Glo Moist; Genteal; Isopto Tears; Lac-Oph; Methocel†; ***Hung.:*** Artelac†; Humalac B; Lacrisyn†; ***India:*** Hyprosol; Moisol; Nova Vizol; Occu System†; Sanvisc; ***Indon.:*** Genteal; ***Irl.:*** Artelac; Isopto Alkaline; Isopto Plain; ***Israel:*** Adato-Cel†; Genteal; Ocucoat; ***Ital.:*** Gel 4000; Genteal; Lacrimill†; Lacrisifi; Lacrisol; Methocel; ***Malaysia:*** Cellugel; Eye Glo Moist; ***Mex.:*** Artelac; Celulose; Filmexil†; Genteal; Luvistar; Meticel; ***Norw.:*** Artelac; ***NZ:*** Genteal; Methopt; ***Philipp.:*** Artelac; Genteal; Methopt; ***Pol.:*** Artelac; ***Port.:*** Artelac; Davilose; Hidrocil†; ***Rus.:*** Defislez (Дефислёз); Lacrisifi (Лакрисифи); Lacrisyn (Лакрисин); ***S.Afr.:*** Cellugel; Methocel; Spersatear; Viscotraan; ***Singapore:*** Eye Mo Moist†; Genteal; Lacrisifi†; Methocel†; ***Spain:*** Acuolens; Artific; ***Swed.:*** Artelac; Isopto Plain; ***Switz.:*** Isopto Tears; Methocel; ***Thai.:*** Genteal; Isopto Tears; Lac-Oph; Natear; Opsil Tears; Simoph Tears†; ***Turk.:*** Lacrisifi; ***UK:*** Artelac; Brolene Cool Eyes; Isopto Alkaline; Isopto Plain; ***USA:*** Artificial Tears; Entrocel; Genteal; Gonak; Goniosoft; Goniosol; Isopto Plain; Isopto Tears; Lacril; Ocucoat; Tearisol; Tears Again MC; Ultra Tears; ***Venez.:*** Celoftal†; Genteal.

Multi-ingredient: ***Arg.:*** Alcon Lagrimas; Irix Lagrimas; Kalopsis Lagrimas; Oxysept Comfort; Phoenix Lagrimas; Solucion Oral; Tears Naturale; Visine Lagrimas; ***Austral.:*** Bion Tears; Blink-N-Clean; Genteal Moisturising; Opti-Free Comfort†; Poly-Tears; Tears Naturale; Visine True Tears†; ***Austria:*** Lacrisic; ***Belg.:*** Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.:*** Lacribell; Lacrima Plus; Lacrima†; Opti-Tears; Trisorb; ***Canad.:*** Artificial Tears; Bion Tears; Moisture Drops†; Tears Naturale; Tears Naturale Forte; ***Chile:*** Lagrimas Artificiales; Nico Drops; Nicotears; Novo-Tears; Tears Naturale; ***Cz.:*** Tears Naturale; ***Denm.:*** Dacriosol; ***Ger.:*** Gelipur; Isopto Naturale; Lacrisic; Oculotect; ***Gr.:*** Tears Naturale; ***Hong Kong:*** Bion Tears; Tears Naturale Forte; Visine for Contacts; ***Hung.:*** Dacrolux; Tears Naturale; ***Indon.:*** Genteal; Isotic Tearin; Tears; Tears Naturale II; ***Irl.:*** Ilube; Tears Naturale; ***Israel:*** Tears Naturale; ***Ital.:*** Dacriosol; Hamamilla†; Ipragocce†; Tirs; ***Malaysia:*** Bion Tears; Dacrolux; Tears Naturale; ***Mex.:*** Lacrima Plus; Naphacel; Naphtears; Naturalag; Tears Naturale; ***Neth.:*** Duratears; ***Norw.:*** Tears Naturale; ***NZ:*** Poly-Tears; Tears Naturale; ***Philipp.:*** Gentle Tears; Tears Naturale; Visine Refresh; ***Pol.:*** Tears Naturale; ***Port.:*** Tears Naturale†; ***Rus.:*** Tears Naturale (Слеза Натуральная); ***S.Afr.:*** Moisture Drops†; Tears Naturale; ***Singapore:*** Bion Tears; Dacrolux†; Tears Naturale; ***Spain:*** Dacrolux; Humectante; Tears Humectante; ***Swed.:*** Bion Tears; ***Switz.:*** Tears Naturale; ***Thai.:*** Bion Tears; Tears Naturale; ***Turk.:*** Dacrolux; Tears Naturale; ***UK:*** Ilube; Tears Naturale; Uvistat Eye Drops; ***USA:*** Bion Tears; Clear Eyes CLR; Lacri-Tears; LubriTears; Maximum Strength Allergy Drops; Moisture Drops; Nature's Tears; Ocucoat; Tears Naturale; Tears Renewed; Visine Pure Tears; Visine Tears; ***Venez.:*** Genteal; Optifresh.

Magnesium Silicate

E553(a); Silicato de magnesio.

CAS — 1343-88-0.
ATC — A02AA05.
ATC Vet — QA02AA05.

NOTE. The code E553(a) has also been applied to magnesium trisilicate.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

USNF 26 (Magnesium Silicate). A compound of magnesium oxide and silicon dioxide. It contains not less than 15.0% of magnesium oxide and not less than 67.0% of silicon dioxide, calculated on the ignited basis. It is a fine, white, odourless powder, free from grittiness. Insoluble in water and in alcohol. It is readily decomposed by mineral acids. pH of a well-mixed 10% suspension in water is between 7.0 and 10.8.

Uses

Magnesium silicate is used in the food industry and in pharmaceutical manufacturing as an anticaking agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Acnoil Free.

Multi-ingredient: ***Braz.:*** Cutisanol; ***Fr.:*** ZeaSorb; ***Port.:*** Mucal†.

Methylcellulose *(rINN)*

E461; Méthylcellulose; Methylcellulosum; Methylcelulosa; Metilceliuliozė; Metilcellulóz; Metilcelulosa; Metylcellulosa; Metyloceluloza; Metyyliselluloosa.

Метилцеллюлоза

CAS — 9004-67-5.
ATC — A06AC06.
ATC Vet — QA06AC06.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Methylcellulose). A cellulose having some of the hydroxyl groups in the form of the methyl ether. Various grades of methylcellulose are available and are distinguished by appending a number indicating the apparent viscosity in millipascal seconds of a 2% w/w solution at 20°. It is a white, yellowish-white, or greyish-white powder or granules; hygroscopic after drying. Practically insoluble in hot water, in dehydrated alcohol, in acetone, and in toluene; dissolves in cold water, forming a colloidal solution. A 1% w/w solution in water has a pH of 5.0 to 8.0.

USP 31 (Methylcellulose). A methyl ether of cellulose. When dried at 105° for 2 hours, it contains 27.5 to 31.5% of methoxy groups. It is a white, fibrous powder or granules. It swells in water and produces a clear to opalescent, viscous, colloidal suspension; insoluble in alcohol, in chloroform, and in ether; soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform. Its aqueous suspensions are neutral to litmus.

Incompatibility. Incompatibilities of methylcellulose have been reported with a number of compounds including chlorocresol, hydroxybenzoates, and phenol. Large amounts of electrolytes increase the viscosity of methylcellulose mucilages owing to salting-out of the methylcellulose; in very high concentrations of electrolytes, the methylcellulose may be completely precipitated.

Adverse Effects

Large quantities of methylcellulose may temporarily increase flatulence and distension and there is a risk of intestinal obstruction. Oesophageal obstruction may occur if compounds such as methylcellulose are swallowed dry.

Precautions

Methylcellulose and other bulk-forming agents should not be given to patients with intestinal obstruction or conditions likely to lead to intestinal obstruction. They should be taken with sufficient fluid to prevent faecal impaction or oesophageal obstruction, and should not be taken immediately before going to bed. Methylcellulose should not be used in infective bowel disease.

Interactions

Bulk laxatives such as methylcellulose lower the transit time through the gut and could affect the absorption of other drugs.

Uses and Administration

The various grades of methylcellulose are widely used in pharmaceutical manufacturing as emulsifying, suspending, and thickening agents and as binding, disintegrating, and coating agents in tablet manufacturing. Low-viscosity grades are preferred for use as emulsifying agents as the surface tension produced is lower than with the higher-viscosity grades. Low-viscosity grades may also be used as suspending or thickening agents for liquid oral dosage forms and solutions of methylcellulose may be used as replacements for sugar-based syrups or other suspension bases. For thickening topically applied products such as gels and creams a high-viscosity grade is usually used. In tablet technology low- or medium-viscosity grades are used as binding agents while high-viscosity grades act as tablet disintegrants by swelling on contact with the disintegration medium. For tablet coating, highly substituted low-viscosity grades are usually used. Methylcellulose may also be included in modified-release tablet formulations.

Methylcellulose is also used as an emulsifier and stabiliser in the food industry.

Methylcellulose is used clinically as a bulk-forming agent. Medium- or high-viscosity grades are used as bulk laxatives in the treatment of constipation (p.1693); by taking up moisture they increase the volume of the faeces and promote peristalsis. Methylcellulose is usually given in an oral dosage of up to 6 g daily in divided doses, taken with plenty of fluid. In the UK, the *BNFC* recommends a dose of 1 g twice daily for children aged from 7 to 12 years. Methylcellulose is also given in similar doses but with a minimum amount of water for the control of diarrhoea (p.1694) and for the control of faecal consistency in ostomies. It is also used in the management of diverticular disease (p.1695). Methylcellulose has also been used as an aid to appetite control in the management of obesity (p.2149) but there is little evidence of efficacy.

Solutions of high-viscosity grade methylcellulose (usually 0.5 to 1%) have been used as a vehicle for eye drops, as artificial tears, and in contact lens care, but hypromellose (above) is now generally preferred for this purpose.

Preparations

BP 2008: Methylcellulose Granules; Methylcellulose Tablets;
USP 31: Methylcellulose Ophthalmic Solution; Methylcellulose Oral Solution; Methylcellulose Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Bulk; ***Fr.:*** Dacryolarmes†; ***Irl.:*** Celevac; ***Ital.:*** Lacrimart; ***Malaysia:*** Methocel†; ***Spain:*** Muciplasma; ***UK:*** Celevac; ***USA:*** Citrucel; Murocel.

Multi-ingredient: ***Austral.:*** Bioglan 3B Beer Belly Buster; Citri Slim+Trim; Le Trim-BM†; Neo-Trim Fibre†; Parachoc; Pro-Shape†; ***Braz.:*** Kolantyl; Kolantyl DMP; ***S.Afr.:*** Kolantyl; Medigel; Merasyn.

Pectin

E440 (amidated pectin or pectin); Pectina; Pektin.

CAS — 9000-69-5.
ATC — A07BC01.
ATC Vet — QA07BC01.

Pharmacopoeias. In *US.*

USP 31 (Pectin). A purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace; it consists mainly of partially methoxylated polygalacturonic acids. A yellowish-white, almost odourless, coarse or fine powder. Almost completely soluble in 1 in 20 of water, forming a viscous, opalescent, colloidal solution which flows readily and is acid to litmus; practically insoluble in alcohol or in diluted alcohol and in other organic solvents. It dissolves more readily in water if first moistened with alcohol, glycerol, or simple syrup, or if mixed with 3 or more parts of sucrose. Store in airtight containers.

Interactions

Bulk-forming agents such as dietary fibre lower the transit time through the gut and may affect the absorption of other drugs.

Lipid regulating drugs. Pectin, used as a source of fibre, with a lipid-lowering diet and *lovastatin*, has resulted in a paradoxical increase in low-density lipoprotein (LDL)-cholesterol in patients with hypercholesterolaemia. It was believed the pectin reduced the absorption of lovastatin from the gut.[1]

1. Richter WO, *et al.* Interaction between fibre and lovastatin. *Lancet* 1991; **338:** 706.

Uses and Administration

Pectins are used as emulsifiers and stabilisers in the food industry. They are non-starch polysaccharide constituents of dietary fibre (see under Dietary Role in Bran, p.1713).

Pectin is an adsorbent and bulk-forming agent and is present in multi-ingredient preparations for the management of diarrhoea, constipation, and obesity. Pectin has also been tried for reducing or slowing carbohydrate absorption in the dumping syndrome (p.1695).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Kaogel†; ***Fr.:*** Arhemapectine Antihemorragique†; Hydrocoll.

Multi-ingredient: ***Arg.:*** Bismuto con Pectina; Crema De Bismuto; Endomicina†; Mucobase; Opocler†; ***Austral.:*** Betaine Digestive Aid; Bioglan 3B Beer Belly Buster; Bioglan Psylli-Mucil Plus; Bioglan Zellulean with Escin; Bis-Pectin†; Citri Slim+Trim; Diarcalm; Diareze; Donnagel; Kaomagma with Pectin†; Orabase; Orahesive†; PC Regulax†; Pro-Shape†; Stomahesive†; ***Austria:*** Diarrhoesan; ***Belg.:*** Tanalone; ***Braz.:*** Atalin†; Atapec†; Enterobion†; Kaomagma; Kaopectin†; Parenterin; Sanadiar†; ***Canad.:*** Orabase†; Orahesive†; Tegasorb; ***Chile:*** Enterol; Furazolidona; ***Fr.:*** Gelopectose; ***Ger.:*** Diarrhoesan; Kaoprompt-H; ***Gr.:*** Kaopectate†; ***Hong Kong:*** Enterocin Compound; Uni-Kaotin; ***Indon.:*** Andikap; Arcapec; Diagit; Entrogard; Kaopectate; Licopec; Molagit; Neo Diaform; Neo Diastop; Neo Entrostop; Neo Kaocitin; Neo Kaolana; Neo Kaominal; Neo Koniform; ***Irl.:*** Kaopectate†; Orabase; ***Israel:*** Kaopectin; Kapectin Forte†; Orabase†; ***Ital.:*** Cruscasohn; Streptomagma; ***Malaysia:*** Beakopectin†; Kaopectate†; ***Mex.:*** Ameban; Caopecfar; Colfur; Contefur†; Coralzul; Depofin; Dia-Par Compuesto; Dibapec Compuesto; Estibal; Exofur; Facetin-D; Farpectol; Furoxona CP; Fuzotyl†; Hidromagma†; Isocar; K-Omistron; Kaomycin; Kaopectate; Kapecfuran; Kediar; Lactopectin; Neokap; Neoxil; Olam; Optazol; Quimefuran; Suyodil; Tapzol con Neomicina†; Treda; Trilor†; Yodozona; ***NZ:*** Orabase; Stomahesive; ***Port.:*** Cloranpectina†; Varihesive†; ***S.Afr.:*** Betapect; Bipectinol; Biskapect; Chloropect; Collodene; Enterolyte; Gastropect; Granuflex; Granugel; Kantrexil; Kao†; Kaopectin†; Kaostatex; Orabase; Pectin-K; Pectrolyte; ***Singapore:*** Beakopectin; Kaopectate†; ***Spain:*** Dextrinca; Estreptoenterol†; ***Switz.:*** HEC; ***Thai.:*** Biodan†; Carbonpectate; Cenopec; Di-Su-Frone†; Difuran; Disento PF; Furasian; Furopectin†; Kaopectal; Med-Kafuzone†; ***Turk.:*** Streptomagma; ***UAE:*** Kaptin; ***UK:*** Goodypops; KLN; Orabase; Orahesive; Stomahesive; ***USA:*** K-C; Kao-Paverin; Kao-Spen; Kaodene Non-Narcotic; Sucrets Herbal; ***Venez.:*** Kaopecon†; Kaopectate†; Klincosal; Micyn-2; Mycin-2†; Parepectolin†; Pec-Kao†; Sendafur†; Strediazin c Atapulguita†; Streptomagma.

Polyethylene Oxide

Polietileno, óxido de.

Pharmacopoeias. In *USNF.*

USNF 26 (Polyethylene Oxide). A nonionic homopolymer of ethylene oxide, represented by the formula $(OCH_2CH_2)_n$, in which *n* represents the average number of oxyethylene groups (about 2000 to over 100 000). It is obtainable in several grades, varying in viscosity profile in an aqueous isopropyl alcohol solution. It may contain not more than 3% of silicon dioxide. A white to off-white powder. Miscible with water; freely soluble in acetonitrile, in dichloromethane, in ethylene dichloride, and in trichloroethylene; insoluble in aliphatic hydrocarbons, in ethylene glycol, in diethylene glycol, and in glycerol. Store in airtight containers. Protect from light.

Uses

Polyethylene oxide is used as a tablet binder and as a suspending and thickening agent in pharmaceutical preparations. Polyethylene oxide has been used in hydrogel wound dressings.

Preparations

Polyvinyl Acetate

Poli(vinil-acetát); Polivinilacetatas; Poly(acétate de vinyle); Poly(vinylacetat); Polyvinyl-acetát; Polyvinylis Acetas; Poly(vinylis acetas); Poly(vinyyliasetaatti).

CAS — 9003-20-7.

Pharmacopoeias. In *Eur.* (see p.vii). *Eur.* also includes a 30% dispersion.

Ph. Eur. 6.2 (Poly(vinyl acetate)). A white or almost white powder or colourless granules or beads. Practically insoluble in water; soluble in alcohol; freely soluble in ethyl acetate. It is hygroscopic and swells in water. It softens at temperatures above 40° to 50°.

Ph. Eur. 6.2 (Poly(Vinyl Acetate) Dispersion 30 per cent). A dispersion in water of polyvinyl acetate having a mean relative molecular mass of about 450 000. It may contain povidone and a suitable surface-active agent, such as sodium laurilsulfate, as stabilisers.

An opaque, white or almost white, slightly viscous liquid. Miscible with water and with alcohol. It is sensitive to spoilage by microbial contaminants. Store at a temperature of 5° to 30°.

Polyvinyl Acetate Phthalate

Polivinilo, acetato ftalato de.

Pharmacopoeias. In *USNF.*

USNF 26 (Polyvinyl Acetate Phthalate). A reaction product of phthalic anhydride and a partially hydrolysed polyvinyl acetate. It contains 55.0 to 62.0% of phthalyl groups, calculated on an anhydrous acid-free basis. It is a free-flowing white powder that may have a slight odour of acetic acid. Insoluble in water, in chloroform, and in dichloromethane; soluble in alcohol and in methyl alcohol. Store in airtight containers.

Uses

Polyvinyl acetate phthalate is a viscosity-modifying agent that is used in the manufacture of enteric coating for tablets. Polyvinyl acetate is used in tablet coating; it is also widely used as a glue.

Polyvinyl Alcohol

Alcohol polivinílico; Alcohol Polyvinylicus; Alkohol poliwinylowy; Polivinil Alkol; Poli(vinil-alkohol); Polivinilo alkoholis; Poly(alcohol vinylicus); Poly(alcool vinylique); Polyvinylalkohol; Poly(vinylalkohol); Poly(vinyylialkoholi).

CAS — 9002-89-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Poly(Vinyl Alcohol)). It is obtained by polymerisation of vinyl acetate followed by partial or complete hydrolysis of polyvinyl acetate in the presence of catalytic amounts of alkali or mineral acids. Various grades are available and they differ in their degree of polymerisation and their degree of hydrolysis, which determine the physical properties of the different grades. They are characterised by the viscosity and the ester value of the substance. The mean relative molecular mass lies between 20 000 and 150 000. The viscosity is 3 to 70 millipascal seconds. The ester value, which characterises the degree of hydrolysis, is not greater than 280.

Polyvinyl alcohol occurs as a yellowish-white powder or translucent granules. Soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 4% solution in water has a pH of 4.5 to 6.5.

USP 31 (Polyvinyl Alcohol). A synthetic resin represented by the formula $(CH_2CHOH)_n$, where the average value of *n* is 500 to 5000. It is prepared by 85 to 89% hydrolysis of polyvinyl acetate. White to cream-coloured, odourless, granules or powder. Freely soluble in water at room temperature; solution may be effected more rapidly at somewhat higher temperatures. pH of a 4% solution in water is between 5.0 and 8.0.

Uses and Administration

Polyvinyl alcohol is a nonionic surfactant that is used in pharmaceutical manufacturing as a stabilising agent and as a viscosity-increasing agent and lubricant.

Polyvinyl alcohol has also been used in the preparation of jellies that dry rapidly when applied to the skin to form a soluble plastic film.

Polyvinyl alcohols of various grades are used for a wide variety of industrial applications.

Polyvinyl alcohol has been used to increase the viscosity of ophthalmic preparations thus prolonging contact of the active ingredient with the eye. It is included in artificial tears preparations used for dry eye (p.2140) and in contact lens solutions (p.1622). For dry eye it is often used in a concentration of 1.4% with or without povidone.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Bio Tears; Lagrima Artificial; Lagrima Humectante†; Lentisol; Lersan; Liquifilm Lagrimas†; Natura Wet; Total Solucion; ***Austral.:*** Liquifilm; PVA†; ***Belg.:*** Liquifilm; ***Braz.:*** Duracare†; Lacril; Totalens†; ***Canad.:*** Artificial Tears; Hypotears; Liquifilm; Optilube PVA; Scheinpharm Artificial Tears†; Total†; ***Chile:*** Lagrimas Artificiales; Liquifilm Lagrimas†; Visidic; ***Cz.:*** Liquifilm†; ***Denm.:*** Lacril; ***Fin.:*** Liquifilm; Oftan; ***Ger.:*** Lacrimal†; Liquifilm; Vistil; ***Gr.:*** Liquifilm Tears; ***Hong Kong:*** Liquifilm; PMS-Artificial Tears; ***Hung.:*** Humalac A and C; ***India:*** Aquatears; ***Indon.:*** Optifresh; ***Irl.:*** Liquifilm; Sno Tears; ***Israel:*** Hypotears†; Liquifilm Tears; ***Ital.:*** Lacrilux; Vistil; ***Malaysia:*** Liquifilm†; ***Mex.:*** Acuafil Ofteno; Lubrik; ***Norw.:*** Ocufri; ***NZ:*** Liquifilm; ***Pol.:*** Lacrimal; ***Port.:*** Liquifilm; ***S.Afr.:*** Liquifilm Tears; ***Singapore:*** Hypotears; Liquifilm Tears; ***Spain:*** Hypo Tears; Liquifilm Lagrimas; ***Swed.:*** Sincon; ***Switz.:*** Liquifilm†; Liquitears; ***Thai.:*** Liquifilm Tears; ***Turk.:*** Liquifilm; ***UK:*** Liquifilm Tears; Refresh; Sno Tears; ***USA:*** Akwa Tears; Dry Eyes; Liquifilm; Nu-Tears; Ocu-Tears; Puralube; Tears Again; ***Venez.:*** Acuafil Ofteno; Lacril.

Multi-ingredient: ***Arg.:*** Consil; Latlas; Panoptic Lagrimas; Refresh Free†; Soquette; ***Austral.:*** Murine Revital Eyes; Murine Tears for Eyes; Refresh; Tears Plus; ***Austria:*** Siccaprotect; ***Braz.:*** Refresh; ***Canad.:*** Artificial Tears Extra; Artificial Tears Plus; Murine; Refresh; Scheinpharm Artificial Tears Plus†; Teardrops; Tears Plus; ***Chile:*** Red Off Aqua; ***Cz.:*** Siccaprotect; ***Fr.:*** Refresh; ***Ger.:*** Dispatenol; Lacrimal OK; Liquifilm OK; Siccaprotect; ***Gr.:*** Onufrid; Refresh; ***Hong Kong:*** Hypotears; ***India:*** I-Lube; ***Israel:*** Refresh; ***Ital.:*** Collyria†; Hypotears; ***Malaysia:*** Hypotears; Murine NTF†; Murine Plus†; Refresh†; ***Mex.:*** Lagrifilm Plus; Soltrictor con Lagrifilm; ***Neth.:*** Tears Plus; ***NZ:*** Refresh; Tears Plus†; ***S.Afr.:*** Refresh; Tears Plus; ***Singapore:*** Refresh†; ***Spain:*** Liquifresh; ***Switz.:*** Collylarm; Hypotears; Siccaprotect; Tears Plus†; ***Thai.:*** Refresh; ***Turk.:*** Refresh; Siccaprotect; ***UK:*** Blink; Hypotears†; ***USA:*** Hypotears; Murine; Murine Plus; Nu-Tears II; Refresh Classic; Tears Plus; VasoClear†.

Povidone *(BAN, USAN, rINN)*

E1201; Polivinilpirolidon; Polyvidone; Polyvidonum; Polyvinylpyrrolidone; Povidon; Povidona; Povidonas; Povidoni; Povidonum; Powidon; PVP; Vinylpyrrolidinone Polymer. Poly (2-oxopyrrolidin-1-ylethylene).

Повидон

$(C_6H_9NO)_n$.

CAS — 9003-39-8.
ATC — A07BC03.
ATC Vet — QA07BC03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Povidone). Linear polymers of 1-ethenylpyrrolidin-2-one. The different types of povidone are characterised by their viscosity in solution. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in methyl alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 3.0 to 7.0 depending on the viscosity. Store in airtight containers.

USP 31 (Povidone). A synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerisation of which results in polymers of various molecular weights. The different types of povidone are characterised by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. A white to slightly creamy-white, hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in acetone; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 7.0. Store in airtight containers.

Copovidone

Copolyvidone; Copolyvidonum; Copovidona; Copovidonum; Kopovidon; Kopovidonas; Kopovidoni.

ATC — A07BC03.
ATC Vet — QA07BC03.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Copovidone). A copolymer of 1-vinylpyrrolidin-2-one and vinyl acetate in the mass proportion 3:2. A white or yellowish-white, hygroscopic powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane. Protect from moisture.

USNF 26 (Copovidone). A copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a mass proportion of 3:2. A white to yellowish-white, hygroscopic, powder or flakes. Freely soluble in water, in alcohol, and in dichloromethane; practically insoluble in ether. Store in airtight containers.

Crospovidone *(BAN, rINN)*

Crospovidona; Crospovidonum; Krospovidon; Krospovidonas; Krospovidoni; Kroszpovidon; Polyplasdone XL.

Кросповидон

CAS — 9003-39-8.
ATC — A07BC03.
ATC Vet — QA07BC03.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Crospovidone). A cross-linked homopolymer of 1-vinylpyrrolidin-2-one. A white or yellowish-white, hygroscopic powder or flakes. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from moisture.

USNF 26 (Crospovidone). A synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. A white to creamy-white, hygroscopic powder having a faint odour. Insoluble in water and in ordinary organic solvents. pH of a 1% suspension in water is between 5.0 and 8.0. Store in airtight containers.

Adverse Effects

Some products intended for parenteral use contain povidone as an excipient and injection has led to deposition of povidone in the tissues with consequent lesions and pain. There have been occasional reports of liver involvement.

◊ Reviews of adverse effects associated with pharmaceutical excipients including povidone.

1. Golightly LK, *et al.* Pharmaceutical excipients: adverse effects associated with 'inactive ingredients' in drug products (part II). *Med Toxicol* 1988; **3:** 209–40.

Hypersensitivity. For reference to anaphylaxis caused by the povidone component of povidone-iodine, see p.1659.

Uses and Administration

Povidone is used in pharmaceutical manufacturing as a suspending and dispersing agent and as a tablet binding, granulating, and coating agent. It is used as a carrier for iodine (see Povidone-Iodine, p.1659). An insoluble cross-linked form of povidone known as crospovidone is used as a tablet disintegrant. Copovidone, a copolymer with vinyl acetate, is used as a tablet binding and coating agent.

Povidone is included in artificial tears preparations used in the management of dry eye (p.2140) and in solutions for contact lens care (p.1622). For dry eye it is often used in a concentration of 0.6% with other viscosity-increasing agents (such as polyvinyl alcohol); it may also be used alone in solutions containing 1.5 to 5%.

Povidone has also been used as an adsorbent in gastrointestinal disorders.

Povidone was formerly used as a plasma expander but other compounds are now preferred.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Hypotears Plus; Megatears†; Sol-O-Flex; ***Austral.:*** In A Wink Moisturing†; Rohto Zi Fresh†; Spray-on Bande†; ***Austria:*** Oculotect; Protagent; ***Belg.:*** Oculotect; Siccagent; ***Braz.:*** Hypotears Plus; ***Chile:*** Lepex; Oculotec; ***Cz.:*** Arufil; Hypotears Plus; ***Denm.:*** Oculac; ***Fin.:*** Oculac; ***Fr.:*** Bolinan; Dulcilarmes; Fluidabak; Larmecran; Nu-Gel†; Nutrivisc; Unifluid; ***Ger.:*** Aloclair; Arufil; Lacophtal; Lacri-Stulln; Oculotect Fluid; Protagent; Vidirakt S; Vidisept; Wet-COMOD; Yxin Tears; ***Gr.:*** Oculotect; Protagent; ***Hong Kong:*** Hypotears Plus; Protagent; ***Hung.:*** Arufil; Oculotect; ***Israel:*** Hypotears E; Lacrimol; ***Ital.:*** Clarover; Nu-Gel; Protagent†; Wet-COMOD; ***Malaysia:*** Oculotect; Vidisept N†; ***Mex.:*** Hypotears Plus; Logical; Renu Plus; ***Neth.:*** Duratears Free; Oculotect; Protagens; Vidisic PVP; ***Norw.:*** Oculac; ***Philipp.:*** Oculotect; Vidisept N; ***Pol.:*** Oculotect; Vidisept; ***Port.:*** Oculotect; ***Rus.:*** Vid-COMOD (Вид-КОМОД); ***S.Afr.:*** Hypotears; ***Singapore:*** Oculotect; Vidisept N; ***Spain:*** Oculotect; ***Swed.:*** Oculac; ***Switz.:*** Oculac; Protagent; ***Thai.:*** Hypotears Plus; ***Turk.:*** Oculotect; Protagent; ***UK:*** Aloclair; Oculotect; ***Venez.:*** Hipotears Plus†; Hypotears Plus.

Multi-ingredient: ***Arg.:*** Maxilac; Panoptic Lagrimas; Refresh Free†; Visine Plus; ***Austral.:*** Murine Revital Eyes; Murine Tears for Eyes; Refresh; Tears Plus; Visine Advanced Relief; ***Austria:*** Lacrisic; ***Braz.:*** Refresh; ***Canad.:*** Artificial Tears Extra; Artificial Tears Plus; Moisture Drops†; Murine; Refresh; Scheinpharm Artificial Tears Plus†; Teardrops; Tears Plus; Visine Advance Triple Action; ***Fr.:*** Poly-Karaya; Refresh; ***Ger.:*** Lacrimal OK; Lacrisic; Liquifilm OK; Visine Trockene Augen; ***Gr.:*** Onufrid; Refresh; ***India:*** I-Lube; ***Israel:*** Aphtagone; Aptha-X; Gelclair†; Refresh; V-Crima; ***Ital.:*** Filmabak; ***Malaysia:*** Murine NTF†; Murine Plus†; Refresh†; ***Mex.:*** Lagrifilm Plus; Soyaloid; Soydex; Visine Extra; ***Neth.:*** Tears Plus; ***NZ:*** Refresh; Tears Plus†; Visine Advanced Relief; ***Rus.:*** Gluconeodesum (Глюконеодез); Haemodez-N (Гемодез-Н); ***S.Afr.:*** Moisture Drops†; Refresh; Tears Plus; ***Singapore:*** Refresh†; ***Spain:*** Liquifresh; ***Switz.:*** Collylarm; Tears Plus†; ***Thai.:*** Refresh; ***Turk.:*** Refresh; ***UK:*** Gelclair; ***USA:*** Advanced Relief Visine; Gelclair; Murine; Murine Plus; Refresh Classic; Tears Plus.

Silicas

Silice.

Purified Siliceous Earth

Diatomaceous Earth; Diatomite; Purified Infusorial Earth; Purified Kieselguhr; Terra Silicea Purificada; Tierra de diatomeas; Ziemia okrzemkowa.

CAS — 7631-86-9.

Pharmacopoeias. In *USNF.*

USNF 26 (Purified Siliceous Earth). A form of silicon dioxide consisting of frustules and fragments of diatoms purified by calcining. A very fine, white, light grey, or pale buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite. It is gritty and readily absorbs moisture, and retains about four times its weight of water before becoming fluid. Insoluble in water, in acids, and in dilute solutions of alkali hydroxides.

Silicon Dioxide

Colloidal Hydrated Silica; E551; Kiseldioxid, kolloidal, hydratiserad; Koloidinis silicio dioksidas, hidratuotas; Oxid křemičitý koloidní hydratovaný; Piidioksidi, kolloidinen, hydratoitu; Precipitated Silica; Silica colloidalis hydrica; Silica Gel; Silice colloïdale hydratée; Silicio, dióxido de; Víztartalmú, kolloid szilicium-dioxid.

$SiO_2.xH_2O$ = 60.08 (anhydrous).
CAS — 63231-67-4; 7631-86-9.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF. Eur.* and *USNF* also include dental-type silica.

Ph. Eur. 6.2 (Silica, Colloidal Hydrated). A light, fine, white or almost white, amorphous powder. Practically insoluble in water, and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides.

Ph. Eur. 6.2 (Silica, Dental Type). An amorphous silica (precipitated, gel, or obtained by flame hydrolysis). A white or almost white, light, fine amorphous powder. Practically insoluble in water and in mineral acids; dissolves in hydrofluoric acid and in hot solutions of alkali hydroxides.

USNF 26 (Silicon Dioxide). It is obtained by insolubilising the dissolved silica in sodium silicate solution. Where obtained by the addition of sodium silicate to a mineral acid, the product is termed silica gel; where obtained by the destabilisation of a solution of sodium silicate in such a manner as to yield very fine particles, the product is termed precipitated silica. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 2 to 10 micrometres. Insoluble in water, in alcohol, and in other organic solvents; soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.0. Store in airtight containers. Protect from moisture.

USNF 26 (Dental-Type Silica). It is obtained from sodium silicate solution by destabilising with acid in such a way as to yield very fine particles. A fine, white, odourless, hygroscopic, amorphous powder in which the diameter of the average particles ranges from 0.5 to 40 micrometres. Insoluble in water, in alcohol, and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of 5% slurry in water is between 4.0 and 8.5. Store in airtight containers.

Colloidal Silicon Dioxide

Acidum Silicicum Colloidale; Colloidal Anhydrous Silica; Colloidal Silica; Hochdisperses Silicumdioxid; Kiseldioxid, kolloidal, vattenfri; Koloidinis silicio dioksidas, bevandenis; Krzemu dwutlenek koloidalny; Oxid křemičitý koloidní bezvodý; Piidioksidi, kolloidinen, vedetön; Silica colloidalis anhydrica; Silice colloïdale anhydre; Silicii Dioxidum Colloidalle; Silicio coloidal, dióxido de; Vízmentes, kolloid, szilicium-dioxid.

SiO_2 = 60.08.
CAS — 7631-86-9.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Eur. and *USNF* also include hydrophobic colloidal silica.

Ph. Eur. 6.2 (Silica, Colloidal Anhydrous). A light, fine, white or almost white, amorphous powder. It has a particle size of about 15 nm. Practically insoluble in water and in mineral acids except hydrofluoric acid; dissolves in hot solutions of alkali hydroxides. A 3.3% suspension in water has a pH of 3.5 to 5.5.

Ph. Eur. 6.2 (Silica, Hydrophobic Colloidal; Silica Hydrophobica Colloidalis). Colloidal silicon dioxide partly alkylated for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and mineral acids except hydrofluoric acid. It dissolves slowly in hot solutions of alkali hydroxides.

USNF 26 (Colloidal Silicon Dioxide). A submicroscopic fumed silicon dioxide, prepared by the vapour-phase hydrolysis of a silicon compound. A light, white, non-gritty powder of extremely fine particle size (about 15 nm). Insoluble in water and in acid (except hydrofluoric acid); soluble in hot solutions of alkali hydroxides. pH of a 4% dispersion in water is between 3.5 and 5.5.

USNF 26 (Hydrophobic Colloidal Silica). Prepared by partial alkylation for hydrophobation. A light, fine, white or almost white, amorphous powder, not wettable by water. Practically insoluble in water and in mineral acids, except hydrofluoric acid; dissolves slowly in hot solutions of alkali hydroxides.

Adverse Effects

Prolonged inhalation of some forms of silica dust may be associated with the development of fibrosis of the lung (silicosis). The forms of silica described here and used as pharmaceutical excipients may cause irritation of the respiratory tract if inhaled but do not appear to be associated with silicosis.

Uses

The different forms of silica have various pharmaceutical uses. Purified siliceous earth is used as a filtering medium and adsorbent. Silicon dioxide is used as a suspending and thickening agent and, in the form of silica gel, as a desiccant. Colloidal silicon dioxide is used as a suspending agent and thickener, as a stabiliser in emulsions, and as an anticaking agent and desiccant. Silicon dioxide is also used as an anticaking agent in the food industry.

Homoeopathy. Silicon dioxide has been used in homoeopathic medicines under the following names: Acidum silicicum; Silicea; Sil.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Celloids S 79; ***Cz.:*** Original Silicea Balsam†; ***Ger.:*** Entero-Teknosal; Gela†; Sklerosol N†; ***NZ:*** Biosil†; ***Rus.:*** Polysorb (Полисорб); ***UK:*** Aerosil.

Multi-ingredient: ***Austral.:*** Bio-Disc; Duo Celloids SCF; Duo Celloids SPS; Duo Celloids SSS; Silicic Complex†; ***Austria:*** CO Granulat; Kephalodoron; ***Chile:*** Cartilago T-500; Xeragel; ***Cz.:*** Acne Cream†; CO Granulat†; ***Fin.:*** Wicne; ***Fr.:*** Gelopectose; Topaal; Topalkan; ***Ger.:*** Aplona; CO Granulat†; Equisil N; Rosatum Heilsalbe; ***Gr.:*** Gastrovison†; ***Hong Kong:*** Disflatyl; ***Israel:*** Adinol; Kelo-Cote; ***Ital.:*** Lacalut; ***Malaysia:*** Rowarolan; ***NZ:*** Lamisil Odor Eze; ***Philipp.:*** BioSil; ***S.Afr.:*** Lotio Pruni Comp cum Cupro; ***Singapore:*** Disflatyl; ***Switz.:*** Acne Creme; Fissan†.

Sodium Starch Glycolate

Carboxyméthylamidon sodique; Carboxymethylamylum natricum; Glicolato sódico de almidón; Karboksymetyloskrobia sodowa; Karboximetilkeményítő-nátrium; Karboxymethylškrob sodná sůl; Natriumstärkelseglykolat; Natriumtärkkelysglykolaatti; Sodium Carboxymethyl Starch; Sodium Starch Glycollate; Starch Sodium Glycolate.

CAS — 9063-38-1.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Starch Glycolate (Type A); Carboxymethylamylum Natricum A). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.8 to 4.2% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Sodium Starch Glycolate (Type B); Carboxymethylamylum Natricum B). The sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.0 to 3.4% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent suspension in water; practically insoluble in dichloromethane. pH of a 3.33% dispersion in water is 3.0 to 5.0. Store in airtight containers. Protect from light.

Ph. Eur. 6.2 (Sodium Starch Glycolate (Type C); Carboxymethylamylum Natricum C). The sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch. It contains 2.8 to 5.0% of sodium, calculated with reference to the substance washed with alcohol (80%) and dried. A fine, white or almost white, very hygroscopic, free-flowing powder. It forms a translucent gel-like product in water; practically insoluble in dichloromethane. pH of a 3.33% gel in water is 5.5 to 7.5. Store in airtight containers. Protect from light.

USNF 26 (Sodium Starch Glycolate). The sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0% of sodium chloride. The sodium content is 2.8 to 4.2% (Type A) or 2.0 to 3.4% (Type B). pH of a 1 g in 30 mL suspension in water is between 5.5 and 7.5 (Type A) or between 3.0 and 5.0 (Type B).

A white, odourless, relatively free-flowing powder available in several different viscosity grades. A 2% dispersion in cold water settles, on standing, in the form of a highly hydrated layer. Protect from wide variations in temperature and humidity which may cause caking.

Uses

Sodium starch glycolate is used as a disintegrating agent in tablet manufacture.

Tragacanth

Dragant; E413; Goma Alcatira; Goma de tragacanto; Gomme adragante; Gum Dragon; Gum Tragacanth; Trag.; Tragacanta; Tragacantha; Tragacanto; Tragakanta; Tragakantas; Tragant; Tragantti.

CAS — 9000-65-1.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Tragacanth). The air-hardened gummy exudation flowing naturally or obtained by incision from the trunk and branches of *Astragalus gummifer* and some other species of *Astragalus* (Leguminosae) from western Asia. It occurs as thin, flattened, ribbon-like, white or pale yellow, translucent, horny strips. When reduced to a powder it forms a mucilaginous gel with about ten times its weight of water. Protect from light.

USNF 26 (Tragacanth). The dried gummy exudation from *Astragalus gummifer* or other Asiatic species of *Astragalus* (Leguminosae). It occurs as odourless, flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces. It is white to weak yellow, translucent, and horny in texture. Powdered tragacanth is white to yellowish-white.

Adverse Effects

Hypersensitivity reactions, sometimes severe, have occurred rarely after the ingestion of products containing tragacanth. Contact dermatitis has been reported following the external use of tragacanth.

Uses

Tragacanth forms viscous solutions or gels with water, depending on the concentration. It is used in pharmaceutical manufacturing as a suspending agent and as an emulsifying agent. In dispensing aqueous preparations of tragacanth, the powdered tragacanth is first dispersed in a wetting agent, such as alcohol, to prevent agglomeration on the addition of water.

Tragacanth is also used for similar purposes in the food industry.

Xanthan Gum

Corn Sugar Gum; E415; Goma de xantána; Gomme xanthane; Ksantaanikumi; Ksantano lipai; Polysaccharide B 1459; Xantán gumi; Xantangummi; Xantham Gum; Xanthani gummi; Xanthanová klovatina.

CAS — 11138-66-2.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Xanthan Gum). A gum produced by fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It is the sodium, potassium, or calcium salt of a high-molecular-weight polysaccharide containing D-glucose, mannose, and glucuronic acid. It also contains not less than 1.5% of pyruvic acid, calculated with reference to the dried substance. A white or yellowish-white, free-flowing powder. Soluble in water giving a highly viscous solution; practically insoluble in organic solvents. A 1% solution in water has a pH of 6.0 to 8.0.

USNF 26 (Xanthan Gum). A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris* and purified. It contains D-glucose, D-mannose, and D-glucuronic acid. It is prepared as the sodium, potassium, or calcium salt. A cream-coloured powder. Soluble in hot or cold water. Its solutions are neutral to litmus.

Uses

Xanthan gum is used in pharmaceutical manufacturing as a suspending, stabilising, thickening, and emulsifying agent. It is also used similarly in the food industry.

◊ Suspensions of crushed tablets or insoluble powders made with xanthan gum were reported to be preferable to those made with tragacanth.[1]

The stability was generally good and only a small number of drugs had been found to be incompatible (amitriptyline, tamoxifen, and verapamil).[1] For extemporaneous dispensing, a 1% solution of xanthan gum with hydroxybenzoate, prepared in advance, was diluted to 0.5% with water when preparing the suspension.

Xanthan gum was found to be a suitable suspending vehicle for delivering antispasmodics topically along the length of the oesophagus in patients with oesophageal spasm.[2] Coagulation of the gum had been observed when it was used for suspensions of certain film-coated tablets.

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Preparations

USNF 26: Xanthan Gum Solution.

Proprietary Preparations (details are given in Part 3)
Ger.: Ronfnyl; ***Malaysia:*** Ronfnyl†; ***Switz.:*** TenderWet†.

Multi-ingredient: ***Ital.:*** Resource Gelificata.

Stimulants and Anorectics

Hyperactivity, p.2148
Narcoleptic syndrome, p.2148
Obesity, p.2149
Prader-Willi syndrome, p.2149

This chapter includes compounds used, generally under specialist supervision, for their central stimulant or their anorectic effects. Many are sympathomimetics and are subject to extensive abuse, which has led to strict limitations on their availability.

Hyperactivity

Attention deficit hyperactivity disorder (ADHD) is a syndrome of developmentally inappropriate and socially disruptive behaviour beginning in childhood and characterised by varying degrees of hyperactivity, inattention, and impulsiveness. Children with ADHD are easily distracted and have difficulty in completing tasks. Associated features may include low frustration tolerance, mood lability, and defiance. Some children continue to have symptoms throughout adolescence and into adulthood. The terms hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction, attention deficit disorder, and attention deficit disorder with hyperactivity have sometimes been used synonymously for ADHD, but patients described as having these disorders do not necessarily satisfy the diagnostic criteria for ADHD.

Both drug and behaviour therapy may be used for the management of ADHD. Drug therapy is useful for the control of symptoms but is not curative. In the USA drug treatment for ADHD is quite common even in mild forms, and in the hands of specialists appears superior to behavioural therapy, but in the UK drugs are generally reserved for the more severely affected child who fails to respond to counselling and behaviour therapy.

Dexamfetamine and methylphenidate are usually the drugs of first choice but there is no consensus on which is the more effective; some also recommend the use of the selective noradrenaline reuptake inhibitor atomoxetine. Pemoline has been used but is associated with hepatotoxicity. Most children who benefit from drug therapy appear to require several years of treatment. Prolonged use of central stimulants can retard growth and some recommend occasional drug holidays to allow catch-up growth and determine whether continued therapy is necessary; many authorities consider that young children should not receive stimulants. Stimulants appear to be of use when the disorder persists into adulthood.

Tricyclic antidepressants such as imipramine and desipramine are also used for ADHD in both children and adults and their effect appears to be independent of their antidepressant action. However, they tend to be reserved for patients who fail to respond to, or are intolerant of, central stimulants. Tricyclic antidepressants may be useful in patients with co-existing Tourette's syndrome or in those with a family history of the disorder, as stimulants are believed to precipitate or exacerbate associated tics (p.954). Tricyclic antidepressants might also be preferred in patients with co-existing anxiety, depression, or enuresis, or in those with a history of drug abuse. Use with central stimulants has been studied but careful monitoring is advised (see also Interactions under Dexamfetamine, p.2153). MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use. SSRIs such as fluoxetine have produced beneficial results as an adjunct to central stimulants in a small number of patients with associated depression or obsessive-compulsive disorder, but their value in ADHD alone is unclear. Bupropion has shown promising results in controlled studies in children but may exacerbate tics and increase the risk of seizures in predisposed patients. Venlafaxine has been effective in open trials in a small number of adult patients.

There is some evidence that carbamazepine may be an effective alternative to central stimulants. Clonidine has been used successfully with stimulants in children with an inadequate response to stimulants alone. However, there have been reports of adverse cardiac events associated with such combinations. Antipsychotics can produce severe adverse effects and are probably only warranted as adjunctive therapy to central stimulants in severe cases or when there is also extremely violent or destructive behaviour. Dopaminergics such as levodopa or pergolide have been tried with beneficial results for the treatment of restless legs syndrome and periodic limb movements in sleep associated with ADHD; some improvements in ADHD symptoms were also noted on resolution of the parasomnias.

Much controversy has surrounded the hypothesis that certain synthetic food additives including preservatives and artificial flavours and colours are aetiological agents in ADHD. Controlled studies have not proved the efficacy of dietary manipulation.

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Narcoleptic syndrome

Narcolepsy is characterised by excessive daytime sleepiness and irresistible sleep attacks that last from a few minutes to hours. The narcoleptic syndrome often includes **cataplexy**, a sudden short-lived loss of muscle tone and paralysis of voluntary muscles induced by strong emotions. The severity of the attack can vary and some patients experience complete collapse but there is no loss of consciousness. **Sleep paralysis** consists of transient episodes of complete paralysis while falling asleep or during waking; respiration is unaffected. Some patients also have vivid auditory or visual hallucinations while falling asleep (**hypnagogic hallucinations**) or disturbed sleep.

For the management of narcoleptic syndrome the patient is initially encouraged to take planned regular short periods of sleep during the day and to avoid stressful events that may provoke attacks. If drug treatment is required then central stimulants are the main drugs used for the sleep attacks of narcolepsy. However, most are ineffective against cataplexy. The selection, dose, and timing of these drugs needs to be titrated for each patient, and drug holidays have been suggested to reduce the risk of developing tolerance. Amfetamines were the first drugs used. However, methylphenidate is often preferred to dexamfetamine as it has a rapid action and is considered to have fewer adverse effects. Alternative non-amfetamine stimulants used in the treatment of narcolepsy include mazindol, which also appears to be effective in cataplexy, and modafinil. Selegiline has been reported to improve excessive daytime sleepiness and cataplexy. There is a wide range of other drugs for which there is anecdotal or other limited evidence of efficacy in narcolepsy but there appears to be no evidence that they are superior to the central stimulants.

Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis. However, a recent systematic review concluded that evidence supporting the use of antidepressants in cataplexy is scarce. Imipramine and clomipramine appear to have been widely used (some consider that clomipramine is the most effective of the tricyclics for this indication); desipramine and protriptyline have also been given. The onset of action is quicker, and the effective doses seem to be lower, than when tricyclics are used for depression, although tolerance to the effect may develop after 6 to 8 months, requiring an increase in dose. The daily dose should be titrated to provide maximal protection for the time of day when symptoms usually occur.

The use of sodium oxybate at night with stimulants during the day has been reported to improve the symptoms of patients with narcoleptic syndrome.

Patients requiring treatment for both narcolepsy and cataplexy may be given central stimulants and tricyclic antidepressants but require careful monitoring as the combination may produce serious adverse effects such as cardiac arrhythmias or hypertension; see also Interactions of Dexamfetamine, p.2153.

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Obesity

Obesity results from an imbalance between energy intake and energy expenditure and increases the risk of cardiovascular disease, diabetes mellitus, gallstones, respiratory disease, osteoarthritis, and some forms of cancer. The prevalence of obesity is increasing especially in developed countries. Obesity may be defined in terms of the body-mass index (BMI), which is the weight (kg) divided by the square of the height (m^2):

- BMI 25.0 to 29.9: overweight
- BMI 30.0 to 34.9: obese, moderate risk of co-morbidity
- BMI 35.0 to 39.9: obese, severe risk of co-morbidity
- BMI 40.0 or more: obese, very severe risk of co-morbidity

Weight loss appears to improve control of diabetes mellitus and hypertension, and to reduce cardiovascular risk factors but long-term benefits are difficult to assess as weight is often regained.

Initial management involves dietary modification and includes calorie restriction and changes in the dietary proportions of fat, protein, and carbohydrates. Physical activity should also be increased and excess alcohol avoided. These measures should be followed for at least 3 months. If there has then been less than 10% reduction in weight and the BMI is still above 30, drug treatment may be considered. For patients with associated risk factors such as diabetes mellitus, ischaemic heart disease, hyperlipidaemias, hypertension, or sleep apnoea, drugs may be considered when the BMI is 27 or 28. Combination drug therapy is not recommended. Drugs should be given initially for 12 weeks. If weight loss is less than 5% then they should be considered a failure and stopped. If weight loss is more than 5% they may be continued and the patient monitored at monthly intervals. Treatment should be stopped once the BMI falls below 30 (or 27/28 as appropriate, see above), or if weight is regained, or there is any suspicion of toxicity.

Many drugs are capable of reducing appetite and have been used as such in the treatment of obesity. Both centrally acting (appetite suppressant, anorectic) drugs and those with a local action on the gastrointestinal tract have been used. However, toxicity has been a major problem with centrally acting drugs and very few are still in current use.

Appetite suppressants can be divided into two main groups: central stimulants that act on central catecholamine pathways and drugs acting on central serotonin pathways. Stimulants such as the amfetamines and phenmetrazine are no longer recommended because of their addictive potential. Other stimulants that have been used include diethylpropion, phentermine, mazindol, and phenylpropanolamine but they are also no longer recommended. The serotonergic drugs dexfenfluramine and fenfluramine were formerly used in long-term therapy (up to 1 year) but have both been associated with valvular heart defects and have generally been withdrawn worldwide. There have also been reports of valvular heart defects in patients receiving combinations of anorectics. UK and US guidelines therefore emphasise the centrally acting serotonin and noradrenaline reuptake inhibitor sibutramine, and the gastric lipase inhibitor orlistat, as appropriate choices for the drug treatment of obesity, in combination with diet and exercise. Rimonabant, a cannabinoid type-1 receptor antagonist, is also used as an adjunct in the treatment of obesity (although it was not mentioned in the guidelines). A systematic review of long-term studies (1 year or more) found orlistat, rimonabant, and sibutramine to be modestly effective in reducing weight; however, further studies, particularly on safety, are warranted.

Many other drugs have been tried, including fluoxetine, which has met with some success, and ephedrine with caffeine. The antiepileptics topiramate and zonisamide have also been investigated. Bulk-forming drugs such as methylcellulose and sterculia have been used in an attempt to control appetite by the local effect they might exert when they swell in the gastrointestinal tract, but there is little evidence of efficacy. Nondigestible fat substitutes such as sucrose polyesters have been promoted by the food industry, as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

The control of appetite and the mechanisms of obesity are under investigation. A gene, called the ob-gene, and its protein product, leptin, have been identified and appear to be involved in regulation of food intake.

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Prader-Willi syndrome

Compulsive eating and a voracious appetite are two of the many clinical features of Prader-Willi syndrome, a congenital disorder characterised by infantile hypotonia, hypogonadism, and facial dysmorphism, with subsequent development of abnormalities of behaviour and intellect.[1,2] Supervision and restricted access to food are the mainstay in preventing obesity, but are commonly not sufficient. Fluoxetine may decrease food intake in some patients. It has also been tried for associated self-mutilatory behaviour (skin picking) with variable results.[3,4] Growth hormone may be of benefit in increasing associated short stature and decreasing percentage body fat,[5-11] but close surveillance of glucose homoeostasis is advisable and there have been reports of fatalities in patients with severe obesity or risk factors for respiratory impairment or obstruction.[12] Anorectics have been ineffective.[2]

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9. Eiholzer U, *et al.* Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. *J Pediatr* 2004; **144:** 753–8.
10. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; **145:** 744–9.
11. Mogul HR, *et al.* Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab* 2008; **93:** 1238–45.
12. Stafler P, Wallis C. Prader-Willi syndrome: who can have growth hormone? *Arch Dis Child* 2008; **93:** 341–5.

Adrafinil *(rINN)* ⊗

Adrafinilo; Adrafinilum; CRL-40028. 2-[(Diphenylmethyl)sulfinyl]acetohydroxamic acid.

Адрафинил

$C_{15}H_{15}NO_3S$ = 289.3.
CAS — 63547-13-7.
ATC — N06BX17.
ATC Vet — QN06BX17.

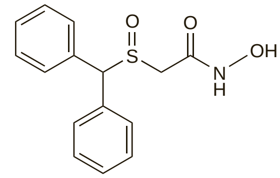

Profile

Adrafinil is a central stimulant and alpha$_1$-adrenergic agonist chemically related to modafinil (p.2160). It is given orally for mental function impairment in the elderly in doses of 600 mg to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Olmifon.

Almitrine Dimesilate *(BANM, rINNM)*

Almitrine Bismesylate; Almitrine, Dimésilate d'; Almitrine Dimesylate; Almitrine Mesylate *(USAN)*; Almitrini Dimesilas; Dimesilato de almitrina; S-2620 (almitrine or almitrine dimesilate). *NN'*-Diallyl-6-[4-(4,4'-difluorobenzhydryl)piperazin-1-yl]-1,3,5-triazine-2,4-diyldiamine bis(methanesulphonate).

Альмитрина Димезилат

$C_{26}H_{29}F_2N_7,2CH_4SO_3$ = 669.8.
CAS — 27469-53-0 (almitrine); 29608-49-9 (almitrine dimesilate).
ATC — R07AB07.
ATC Vet — QR07AB07.

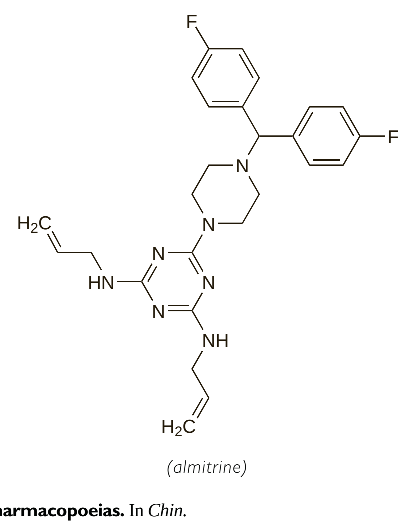

(almitrine)

Pharmacopoeias. In *Chin.*

Profile

Almitrine dimesilate has been used as a respiratory stimulant in acute respiratory failure associated with conditions such as chronic obstructive pulmonary disease. Usual oral doses range from 50 to 100 mg daily and treatment may be intermittent. Up to 3 mg/kg has been given daily by intravenous infusion in 2 or 3 divided doses, each dose being infused over 2 hours. It is also available in a compound preparation with raubasine for mental function impairment in the elderly.

Mental impairment. References.

1. Poitrenaud J, *et al.* Almitrine-raubasine and cognitive impairment in the elderly: results of a 6-month controlled multicenter study. *Clin Neuropharmacol* 1990; **13** (suppl 3): S100–S108.
2. Poitrenaud J, *et al.* Time course of age-associated memory impairment in 8037 patients treated with Duxil for 6 months. *Rev Geriatr* 1994; **19:** 531–8.
3. Poitrenaud J, *et al.* Memory disorders in 8037 elderly patients with age-associated memory impairment: multicenter trial with a 6-month follow-up under almitrine-raubasine. *Eur Neurol* 1995; **35** (suppl 1): 43–6.
4. Allain H, Bentue-Ferrer D. Clinical efficacy of almitrine-raubasine: an overview. *Eur Neurol* 1998; **39** (suppl 1): 39–44.

Respiratory system disorders. Respiratory stimulants (such as almitrine) have a limited and short-term role in acute respiratory failure in chronic obstructive pulmonary disease (p.1112). Almitrine has been reported[1-4] to improve ventilation and blood oxygenation, and to decrease the number of episodes of dyspnoea and hospital admissions, although others[5] have failed to note benefit. There are also reports[6,7] of beneficial effects when used with inhaled nitric oxide in patients with severe hypoxaemic acute respiratory distress syndrome (p.1498) as well as in patients with hypoxia caused by focal lung lesions.[8] However, any modest benefits may be outweighed by the adverse effects, which have included peripheral paraesthesia and weight loss,[1] and headache, urticaria, breathlessness, diarrhoea, chest pain, nausea, and vomiting.[3] The peripheral neuropathy that sometimes occurs during long-term use of almitrine[9,10] may be due to an underlying feature of the pulmonary disease being treated,[11-13] although some disagree with this.[14]

1. Watanabe S, *et al.* Long-term effect of almitrine bismesylate in patients with hypoxemic chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; **140:** 1269–73.
2. Daskalopoulou E, *et al.* Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease. *Thorax* 1990; **45:** 666–9.
3. Bakran I, *et al.* Double-blind placebo controlled clinical trial of almitrine bismesylate in patients with chronic respiratory insufficiency. *Eur J Clin Pharmacol* 1990; **38:** 249–53.
4. Górecka D, *et al.* Effects of almitrine bismesylate on arterial blood gases in patients with chronic obstructive pulmonary disease and moderate hypoxaemia: a multicentre, randomised, double-blind, placebo-controlled study. *Respiration* 2003; **70:** 275–83.
5. Sans-Torres J, *et al.* Long-term effects of almitrine bismesylate in COPD patients with chronic hypoxaemia. *Respir Med* 2003; **97:** 599–605. Correction. *ibid.*; 1243.
6. Jolliet P, *et al.* Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in acute respiratory distress syndrome. *Crit Care Med* 1997; **25:** 786–94.
7. Gallart L, *et al.* The NO Almitrine Study Group. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; **158:** 1770–7.
8. Payen D, *et al.* Inhaled nitric oxide, almitrine infusion, or their coadministration as a treatment of severe hypoxemic focal lung lesions. *Anesthesiology* 1998; **89:** 1157–65.
9. Chedru F, *et al.* Peripheral neuropathy during treatment with almitrine. *BMJ* 1985; **290:** 896.
10. Gherardi R, *et al.* Peripheral neuropathy in patients treated with almitrine dimesylate. *Lancet* 1985; **i:** 1247–50.
11. Suggett AJ, *et al.* Almitrine and peripheral neuropathy. *Lancet* 1985; **ii:** 830–1.
12. Alani SM, *et al.* Almitrine and peripheral neuropathy. *Lancet* 1985; **ii:** 1251.
13. Moore N, *et al.* Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985; **ii:** 1311.
14. Louarn F, Gherardi R. Almitrine and peripheral neuropathy. *Lancet* 1985; **ii:** 1068.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Vectarion†; ***Braz.:*** Vectarion; ***Denm.:*** Vectarion; ***Fr.:*** Vectarion; ***Irl.:*** Vectarion; ***Pol.:*** Armanor; ***Port.:*** Vectarion; ***Rus.:*** Armanor (Арманор); ***Spain:*** Vectarion.

Multi-ingredient: ***Fr.:*** Duxil†; ***Hong Kong:*** Duxaril; ***Philipp.:*** Duxaril; ***Port.:*** Duxil; Transoxyl†; ***Singapore:*** Duxaril; ***Spain:*** Duxor†; ***Thai.:*** Duxaril.

Amfetamine *(BAN, rINN)* ⊗

Amfetamiini; Amfetamin; Amfétamine; Amfetaminum; Amphetamine; Amphetaminum; Anfetamina; Racemic Desoxynorephedrine. (*R,S*)-α-Methylphenethylamine.

Амфетамин

$C_9H_{13}N$ = 135.2.

CAS — 300-62-9 (amfetamine); 139-10-6 (amfetamine phosphate).

ATC — N06BA01.

ATC Vet — QN06BA01.

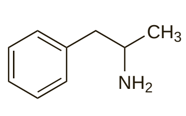

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amfetamine:

A; Affe; Aimies; Amf; Amfa; Amfis; Amp; Amph; Amphes; Amphet; Anfes; Anfetas; A-Plus; Back dex; Bam; Bambinos; Bass; B-bombs; Beans; Bennie; Bennies; Benny and the Jets; Bens; Benz; Benzedrine; Benzidrine; Berick; Billy; Billy Whizz; Biphetamine; Bippies; Black beauties; Black birds; Black bombers; Black cadillacs; Black hollies; Black mollies; Black and white; Blacks; Blue belly; Blue boy; Blue mollies; Bolt; Bombido; Bombita; Bombitas; Boostant; Bottles; Brain pills; Brain ticklers; Brownies; Browns; Bumblebees; Candy; Cartwheels; Chalk; Chicken powder; Chocolate; Christina; Christmas tree; Clear rocks; Coast to coast; Coasts to coasts; Colorado Rockies; Co-pilot; Crank; Crisscross; Croke; Cross tops; Cross-tops; Crossroads; Crystal; Crystal methadrine; Debs; Dex; Dexadrine; Dexedrine; Dexies; Diamonds; Diet Coke; Diet pills; Dolls; Dominoes; Double cross; Drivers; Eve; Eye opener; Eye openers; Fast; Fast balls; Fastin; Fives; Fly Boys; Football; Footballs; Forwards; French blue; French blues; Gaggler; Gas; GB's; Glass; Go; Go-ee; Goey; Greenies; Halloo-Wach; Hanyak; Head drugs; Head fruit; Hearts; Hi speeds; High speed; Hööpkipulveri; Horse heads; Hydro; Iboga; Ice; Inbetweens; Jam; Jam cecil; Jelly baby; Jelly bean; Jelly beans; Johnny go fast; Jolly bean; Jolly beans; Jugs; Khat; L.A.; La Glass; LA ice; LA turnarounds; Leapers; Lid poppers; Lid proppers; Lightning; Lip poppers; Little bomb; Little Guys; Louee; Louie; Macka; 357 Magnum; 357 Magnums; MAO; Marathons; Marching Powder; Meth; Methedrine; Methlies Quik; Mini beans; Mini berries; Minibennie; Mollies; Monoamine oxidase; Morning shoot; Morning shot; Nineteen; Nitro; Nugget; Oranges; Peaches; Pep; Pep pills; Pervitiini; Pink hearts; Pixies; Pollutants; Powder; Proszek; Pulver; Purple hearts; Rhythm; Rippers; Road dope; Rosa; Roses; Shight; Shighty; Slammin'; Slamming; Slipvins; Snap; Snow; Snow pallets; Sparkle plenty; Sparklers; Speckled birds; Speckled eggs; Speed; Speed ball; Speed balls; Speed cristal; Speedball; Spivias; Splash; Splivins; Sprinkles; Star; Strawberry shortcake; Sulph; Sulphate; Sulphates; Sweeties; Sweets; Tens; The C; Thrusters; Toffee whizz; Topette; TR-6s; Truck drivers; Turkey; Turnabout; Turnarounds; Tweak; Tweek; Up; Uppers; Uppies; U.S.P.; Wake amine; Wake ups; Water; West Coast turnarounds; Wheels; Whiffle dust; Whiffledust; White; White Cross; White Crunch; Whites; Whiz; Whizz; Wire; X; X-mas tree; Zoomers.

Amfetamine Sulfate *(rINNM)* ⊗

Amfetamiinisulfaatti; Amfétamine, sulfate d'; Amfetamine Sulphate *(BANM)*; Amfetamini sulfas; Amfetamino sulfatas; Amfetaminsulfat; Amfetamin-sulfát; Amfetamin-szulfát; Amphetamine Sulfate; Amphetamine Sulphate; Amphetamini Sulfas; Phenaminum; Phenylaminopropanum Racemicum Sulfuricum; Sulfato de anfetamina. (*R,S*)-α-Methylphenethylamine sulphate.

Амфетамина Сульфат

$(C_9H_{13}N)_2,H_2SO_4$ = 368.5.

CAS — 60-13-9.

ATC — N06BA01.

ATC Vet — QN06BA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Amfetamine Sulphate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Amphetamine Sulfate). A white odourless crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. Its solutions are acid to litmus, having a pH of 5 to 6.

Incompatibility. Amfetamine sulfate is incompatible with alkalis and calcium salts.

Profile

Amfetamine is an indirect-acting sympathomimetic with actions and uses similar to those of its isomer dexamfetamine (p.2153). Amfetamine, amfetamine sulfate, and amfetamine aspartate are given orally in doses similar to those of dexamfetamine sulfate. The laevo-isomer, levamfetamine was formerly used in a similar manner. Amfetamine, being volatile, was formerly given by inhalation.

Breast feeding. Amfetamine is concentrated in breast milk and the American Academy of Pediatrics has stated[1] that it has caused irritability and poor sleep pattern in breast-feeding infants when used as a drug of abuse by mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/04/04)

Preparations

USP 31: Amphetamine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Epipropane; ***Canad.:*** Adderall; ***USA:*** Adderall.

Amfetaminil *(rINN)* ⊗

Amfétaminil; Amfetaminilum; Amphetaminil; Anfetaminilo. α-(α-Methylphenethylamino)-α-phenylacetonitrile.

Амфетаминил

$C_{17}H_{18}N_2$ = 250.3.

CAS — 17590-01-1.

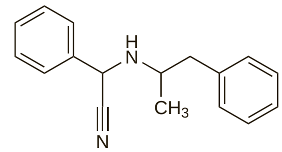

Profile

Amfetaminil is a central stimulant that has been given orally in the treatment of narcolepsy.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: AN 1†.

Amiphenazole Hydrochloride *(BANM, rINNM)* ⊗

Amiphénazol, Chlorhydrate d'; Amiphenazole Chloride; Amiphenazoli Hydrochloridum; Hidrocloruro de amifenazol. 5-Phenylthiazole-2,4-diamine hydrochloride.

Амифеназола Гидрохлорид

$C_9H_9N_3S,HCl$ = 227.7.

CAS — 490-55-1 (amiphenazole); 942-31-4 (amiphenazole hydrochloride).

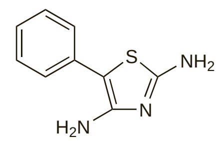

(amiphenazole)

Profile

Amiphenazole hydrochloride has properties similar to those of doxapram hydrochloride (p.2155) and has been used intramuscularly or intravenously as a respiratory stimulant.

Lichenoid reactions have been reported in addition to those reactions expected from its central activity.

Ammonium Camphocarbonate

Canfocarbonato de amonio.

$C_{11}H_{19}NO_3$ = 213.3.

CAS — 5972-75-8.

Profile

Ammonium camphocarbonate has been used in preparations for the treatment of respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Pulmofasa.

Armodafinil *(USAN, rINN)* ⊗

Armodafinilo; Armodafinilum; CEP-10953; CRL-40982. 2-[(*R*)-(Diphenylmethyl)sulfinyl]acetamide.

Армодафинил

$C_{15}H_{15}NO_2S$ = 273.4.

CAS — 112111-43-0.

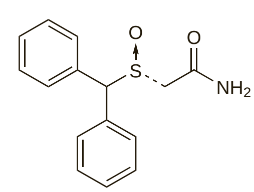

Profile

Armodafinil is the *R*-enantiomer of modafinil (p.2160) and is used similarly in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p.2148), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, armodafinil is given orally in a single dose of 150 or 250 mg in the morning. For the management of shift-work sleep disorder, the daily dose is 150 mg taken as a single dose 1 hour before starting work. Reduced doses are recommended in the elderly and in patients with severe hepatic impairment.

◊ References.

1. Harsh JR, *et al.* The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin* 2006; **22:** 761–74.
2. Roth T, *et al.* Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther* 2006; **28:** 689–706.
3. Hirshkowitz M, *et al.* Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 2007; **101:** 616–27.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Nuvigil.

Atomoxetine Hydrochloride *(BANM, USAN, rINNM)*

Atomoxétine, Chlorhydrate d'; Atomoxetini Hydrochloridum; Hidrocloruro de tomoxetina; LY-135252; LY-139602; LY-139603; Tomoxetine Hydrochloride. (−)-*N*-Methyl-γ-(2-methylphenoxy)-benzenepropanamine hydrochloride.

Томоксетина Гидрохлорид

$C_{17}H_{21}NO,HCl = 291.8.$

CAS — 83015-26-3 (atomoxetine); 82248-59-7 (atomoxetine hydrochloride).

ATC — N06BA09.

ATC Vet — QN06BA09.

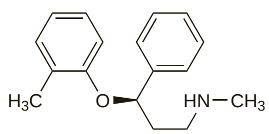

(atomoxetine)

Adverse Effects and Precautions

Adverse effects reported in patients receiving atomoxetine include dyspepsia and other gastrointestinal disturbances, anorexia and weight loss, fatigue, sleep disturbances, dizziness, irritability and emotional lability, cough, sinusitis or rhinorrhoea, urinary hesitancy or retention, decreased libido and sexual dysfunction, priapism, skin rashes, increased sweating, and hot flushes. Suicidal behaviour has been reported in children (see Effects on Mental State, below). Hypersensitivity reactions have occurred rarely. There have also been rare reports of severe hepatotoxicity (see Effects on the Liver, below).

There may be increases in blood pressure and heart rate, and atomoxetine should be given with caution to patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease (see also Effects on the Cardiovascular System, under Dexamfetamine Sulfate, p.2153). Orthostatic hypotension and syncope have also been reported. QT prolongation has been associated with atomoxetine therapy and it should be used with caution in patients with known or suspected prolonged QT interval. Use with drugs liable to inhibit the cytochrome P450 isoenzyme CYP2D6, other drugs that may prolong the QT interval, or drugs likely to cause electrolyte imbalance may also increase the risk (see Interactions, below). Sudden death, stroke, and myocardial infarction have also been reported in patients given atomoxetine. All patients should be assessed for cardiovascular disease before treatment is started. Atomoxetine should generally not be used in those with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems

Seizures are a potential risk with atomoxetine therapy and it should be used with caution in patients with a history of seizures; treatment may need to be stopped in those who develop seizures or have an increase in seizure frequency.

Atomoxetine is contra-indicated in patients with angle-closure glaucoma as it may increase the risk of mydriasis.

The weight and height gain of children receiving atomoxetine has been reported to lag behind that of the predicted norm for about the first 9 to 12 months of treatment and generally normalises within about 3 years of treatment; licensed product information recommends that growth be monitored and consideration given to dose reduction or interrupting treatment in patients who are not growing or gaining weight satisfactorily.

Poor metabolisers of atomoxetine (see Pharmacokinetics, below) may have an increased risk of adverse reactions.

Effects on the liver. In December 2004, the US manufacturer stated that 2 cases of severe hepatotoxicity had been reported with atomoxetine treatment since the drug was launched in 2002.[1] In both cases the patients recovered; however, because of the risk of acute hepatic failure resulting in death or the need for transplantation, it was recommended that atomoxetine should be permanently discontinued in patients with jaundice or markedly increased liver enzyme values.

Similar advice has also been issued in the UK by the CSM.[2] Up to February 2005, the CSM were aware of 3 reports of hepatic disorders (one each of hepatitis, jaundice, and increased bilirubin) with atomoxetine treatment in the UK; a total of 41 reports of hepatic disorders had been received worldwide.

1. Eisenberg P. Safety data on Strattera (atomoxetine hydrochloride)–hepatic effects. Available at: http://www.strattera.com/pdf/dear_hcp.pdf (accessed 31/01/05)
2. MHRA. Strattera (atomoxetine)–risk of hepatic disorders. Message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 02/02/05). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019459&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)

Effects on mental state. Irritability and mood swings have been reported with the use of atomoxetine in children. In an observational study of 153 children, irritability, aggression, mania, or hypomania were associated with atomoxetine in 51 cases. Of these, 31 had a family history, and 41 a personal history, of mood disorders; 27 had both and 6 had neither. The authors therefore recommended that all patients receiving atomoxetine should be monitored closely.[1]

Subsequently, the FDA[2] requested the US manufacturer (*Eli Lilly*) to conduct an analysis of adverse events from 12 clinical trials involving 2208 patients. The risk of suicidal behaviour during the first few months of treatment was found to be 0.4% in children receiving atomoxetine compared with no risk in those on placebo; no suicides were reported although there was one unsuccessful suicide attempt in the atomoxetine-treated group. This finding resulted in the inclusion of a warning in US labelling about the increased risk of suicidal ideation in children and adolescents being treated with atomoxetine; it was also recommended that changes in behaviour must be closely monitored, particularly during the initial months of therapy or when the dose is changed. Similar warnings have been issued by the UK CSM[3] and regulatory authorities in other countries.[4]

In light of these concerns a review of available data in Europe was conducted; it was considered that the overall risk to benefit ratio of atomoxetine in children remained favourable.[5]

1. Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. *Pediatrics* 2004; **114:** 895–6.
2. FDA. FDA alert for healthcare professionals: atomoxetine (marketed as Strattera)–suicidal thinking in children and adolescents (issued 29th September, 2005). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/atomoxetinehcp.pdf (accessed 19/04/06)
3. MHRA. Strattera (atomoxetine): risk of suicidal thoughts/behaviour. Message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 29th September, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2018039.pdf (accessed 11/08/08)
4. Lilly, Canada. WARNING for atomoxetine regarding the potential for behavioural and emotional changes, including risk of self-harm (issued 28th September 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/mede-ff/strattera_hpc-cps-eng.pdf (accessed 08/08/08)
5. MHRA. Updated warnings on the attention deficit hyperactivity disorder drug Strattera: information for healthcare professionals. Message from Professor G Duff, Chairman of Commission on Human Medicines (issued 16th February, 2006). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023222&ssTargetNodeId=221 (accessed 19/04/06)

Handling. Atomoxetine is an ocular irritant and atomoxetine capsules should not therefore be opened. If the capsule contents do accidentally come into contact with the eye, the affected eye must be flushed immediately with water; hands and other potentially contaminated surfaces should be washed as soon as possible.

Interactions

Atomoxetine should not be taken with an MAOI, or within 2 weeks of stopping MAOI therapy, nor should MAOI therapy be started for 2 weeks after stopping atomoxetine. Care should be taken if given with other drugs that raise blood pressure, because of a possible additive affect; the actions of salbutamol on the cardiovascular system may be potentiated. In addition, there is a risk of cardiac events in patients receiving atomoxetine who are also taking drugs that affect cardiac conduction or electrolyte balance, or that inhibit the cytochrome P450 isoenzyme CYP2D6 (see below).

Seizures have been noted with atomoxetine and caution is advised when used with drugs known to lower the seizure threshold.

Atomoxetine is metabolised via the isoenzyme CYP2D6 and inhibitors of this enzyme such as paroxetine, fluoxetine, and quinidine may increase plasma concentrations of atomoxetine in extensive, but not poor, metabolisers.

Antidepressants. *Paroxetine* was found to inhibit atomoxetine's metabolism by cytochrome P450 isoenzyme CYP2D6 in extensive metabolisers resulting in pharmacokinetics for atomoxetine similar to those in poor metabolisers.[1]

1. Belle DJ, *et al.* Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. *J Clin Pharmacol* 2002; **42:** 1219–27.

Pharmacokinetics

Atomoxetine is well absorbed after oral doses, with peak plasma concentrations being achieved 1 to 2 hours later. Bioavailability is about 94% in poor metabolisers but only 63% in extensive metabolisers. Atomoxetine is about 98% bound to plasma proteins. Atomoxetine is metabolised primarily via the cytochrome P450 isoenzyme CYP2D6 to the active metabolite 4-hydroxyatomoxetine; a minority of the population are poor metabolisers and experience plasma concentrations about 5 times those in extensive metabolisers. It is excreted in the urine as glucuronide metabolites and a small amount of unchanged drug; less than 17% of a dose is excreted in the faeces. The half-life of atomoxetine is about 5.2 hours in extensive and 21.6 hours in poor metabolisers.

◊ References.

1. Sauer J-M, *et al.* Clinical pharmacokinetics of atomoxetine. *Clin Pharmacokinet* 2005; **44:** 571–90.
2. Cui YM, *et al.* Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. *Br J Clin Pharmacol* 2007; **64:** 445–9.

Uses and Administration

Atomoxetine hydrochloride is a selective noradrenaline reuptake inhibitor used in the treatment of attention deficit hyperactivity disorder (p.2148) in adults and children aged 6 years and over. It is given as the hydrochloride although doses are expressed in terms of the base; atomoxetine hydrochloride 11.4 mg is equivalent to about 10 mg of atomoxetine.

In *adults and adolescents and children weighing over 70 kg*, the initial dose is the equivalent of 40 mg daily, gradually increased after at least 7 days to 80 mg daily; in the USA an increase in dose may be made after a minimum of 3 days. A further increase to a maximum of 100 mg daily may be made after 2 to 4 weeks. In *children and adolescents of 70 kg and under*, the initial dose is the equivalent of about 500 micrograms/kg daily; this may be gradually increased to about 1.2 mg/kg daily. The total daily dose in this group should not exceed 1.4 mg/kg or 100 mg, whichever is less. Doses may be given as either a single dose in the morning or as equally divided doses in the morning and late afternoon or early evening.

Reduced doses are recommended in patients with hepatic impairment, see below. A lower initial dose and slower titration of atomoxetine may be required in patients who are poor CYP2D6 metabolisers (see Adverse Effects and Precautions, and Pharmacokinetics, above) and in those also taking CYP2D6 inhibitors (see Interactions, above). US licensed product information recommends increasing to the usual target dose only if symptoms fail to improve after 4 weeks and the initial dose is well tolerated in these patients.

◊ References.

1. Michelson D, *et al.* Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Abstract: *Pediatrics* 2001; **108:** 1197. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/5/e83 (accessed 15/04/04)
2. Simpson D, Plosker GL. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. *Drugs* 2004; **64:** 205–22.
3. Kelsey DK, *et al.* Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. Abstract: *Pediatrics* 2004; **114:** 240. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/1/e1 (accessed 14/05/08)
4. Eiland LS, Guest AL. Atomoxetine treatment of attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2004; **38:** 86–90.
5. Corman SL, *et al.* Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. *Am J Health-Syst Pharm* 2004; **61:** 2391–9.
6. Barton J. Atomoxetine: a new pharmacotherapeutic approach in the management of attention deficit/hyperactivity disorder. *Arch Dis Child* 2005; **90** (Suppl 1): i26–i29.
7. Gibson AP, *et al.* Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; **40:** 1134–41.
8. Wilens TE, *et al.* Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr* 2006; **149:** 112–19.
9. Newcorn JH, *et al.* Low-dose atomoxetine for maintenance treatment of attention-deficit/hyperactivity disorder. Abstract: *Pediatrics* 2006; **118:** 2527. Full version: http://pediatrics.aappublications.org/cgi/reprint/118/6/e1701 (accessed 14/05/08)

Administration in hepatic impairment. In patients with moderate hepatic impairment the dose of atomoxetine (see above) should be reduced by 50%, while in those with severe impairment it should be reduced by 75%.

References.

1. Chalon SA, *et al.* Effect of hepatic impairment on the pharmacokinetics of atomoxetine and its metabolites. *Clin Pharmacol Ther* 2003; **73:** 178–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Recit; Strattera; ***Austral.:*** Strattera; ***Belg.:*** Strattera; ***Canad.:*** Strattera; ***Chile:*** Deaten; Strattera; ***Cz.:*** Strattera; ***Ger.:*** Strattera; ***Gr.:*** Strattera; ***Hong Kong:*** Strattera; ***Malaysia:*** Strattera; ***Mex.:*** Strattera; ***Neth.:*** Strattera; ***Norw.:*** Strattera; ***NZ:*** Strattera; ***Philipp.:*** Strattera; ***Port.:*** Strattera; ***Rus.:*** Strattera (Страттера); ***S.Afr.:*** Strattera; ***Singapore:*** Strattera; ***Thai.:*** Strattera; ***UK:*** Strattera; ***USA:*** Strattera.

Bemegride *(BAN, rINN)*

Bemegrida; Bémégride; Bemegridum. 3-Ethyl-3-methylglutarimide; 4-Ethyl-4-methylpiperidine-2,6-dione.

Бемегрид

$C_8H_{13}NO_2$ = 155.2.
CAS — 64-65-3.
ATC — R07AB05.
ATC Vet — QR07AB05.

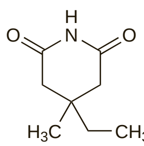

Profile

Bemegride has properties similar to those of doxapram (p.2155). It has been given intravenously as a respiratory stimulant.

Porphyria. Bemegride has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Benzfetamine Hydrochloride *(BANM, rINNM)* ⊗

Benzfétamine, Chlorhydrate de; Benzfetamini Hydrochloridum; Benzphetamine Hydrochloride; Hidrocloruro de benzfetamina. (+)-*N*-Benzyl-*N*,α-dimethylphenethylamine hydrochloride.

Бензфетамина Гидрохлорид

$C_{17}H_{21}N,HCl$ = 275.8.
CAS — 156-08-1 (benzfetamine); 5411-22-3 (benzfetamine hydrochloride).

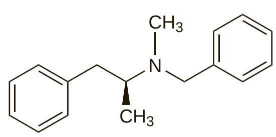

(benzfetamine)

Profile

Benzfetamine hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (below). It has been used as an anorectic in the treatment of obesity (p.2149), although amfetamines are no longer recommended for this indication. The usual initial oral dose is 25 to 50 mg given once daily, subsequently adjusted, according to requirements, to a dose of 25 to 50 mg up to three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Didrex.

Benzylpiperazine ⊗

N-Benzylpiperazine; 1-Benzylpiperazine. 1-(Phenylmethyl)piperazine.

Бензилпиперазин

$C_{11}H_{16}N_2$ = 176.3.
CAS — 2759-28-6.

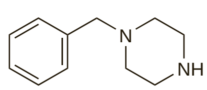

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of benzylpiperazine:
A2; Blast; BZP; Charge; Charlie; Cosmic Kelly; ESP; Euphoria; Exodus; Frenzy; Legal E; Legal X; Nemesis; Pep; Pep Love; Pep Stoned; Pep Twisted; Rapture; The Good Stuff.

Profile

Benzylpiperazine is reported to produce CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p.2153) and is subject to abuse.

Other piperazine derivatives subject to abuse include:

- 1-(3,4-methylenedioxybenzyl)piperazine (MDBP)
- 1-(3-trifluoromethylphenyl)piperazine (TFMPP)
- 1-(3-chlorophenyl)piperazine (mCPP)
- 1-(4-methoxyphenyl)piperazine (MeOPP)

◊ References.

1. Gee P, *et al.* Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand. *N Z Med J* 2005; **118:** U1784.
2. Staack RF. Piperazine designer drugs of abuse. *Lancet* 2007; **369:** 1411–13.
3. Johnstone AC, *et al.* Benzylpiperazine: a drug of abuse? *J Psychopharmacol* 2007; **21:** 888–94.
4. Wood DM, *et al.* Collapse, reported seizure—and an unexpected pill. *Lancet* 2007; **369:** 1490.

Catha ⊗

Abyssinian, African, or Arabian Tea; Kat; Kath; Khat; Miraa; Qat; Somali Tea.

Description. Catha consists of the leaves of *Catha edulis* (Celastraceae), and contains cathine, cathinone, celastrin, choline, tannins, and inorganic salts.
The following terms have been used as 'street names' (see p.vi) or slang names for various forms of catha:
Cat; Chat; Feline; Kat; Miraa; Pootie; Qat; Quaadka.

Cathine *(pINN)* ⊗

Cathinum; Catina; (+)-Norpseudoephedrine. *threo*-2-Amino-1-phenylpropan-1-ol.

Катин

$C_9H_{13}NO$ = 151.2.
CAS — 492-39-7; 36393-56-3.
ATC — A08AA07.
ATC Vet — QA08AA07.

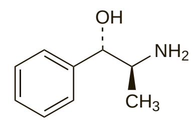

Cathinone *(pINN)* ⊗

Cathinonum; Catinona. (*S*)-2-Aminopropiophenone.

Катинон

$C_9H_{11}NO$ = 149.2.
CAS — 71031-15-7.

Profile

Catha, the leaves of *Catha edulis* (Celastraceae), is used for its stimulant properties among some cultures of Africa and the Middle East, usually by chewing the leaves. Its effects are reported to resemble those of the amfetamines (see Dexamfetamine Sulfate, below), and are thought to be largely due to the content of cathinone. Dependence and psychotic reactions have been reported. Cathine, another constituent, has been used as the hydrochloride as an anorectic.

◊ References to the pharmacology and pharmacokinetics of catha and its constituents[1-8] and reports of adverse effects.[9-15]

1. Brenneisen R, *et al.* Metabolism of cathinone to (–)-norephedrine and (–)-norpseudoephedrine. *J Pharm Pharmacol* 1986; **38:** 298–300.
2. Brenneisen R, *et al.* Amphetamine-like effects in humans of the khat alkaloid cathinone. *Br J Clin Pharmacol* 1990; **30:** 825–8.
3. Kalix P. Pharmacological properties of the stimulant khat. *Pharmacol Ther* 1990; **48:** 397–416.
4. Kalix P. Chewing khat, an old drug habit that is new in Europe. *Int J Risk Safety Med* 1992; **3:** 143–56.
5. Kalix P. Cathinone, a natural amphetamine. *Pharmacol Toxicol* 1992; **70:** 77–86.
6. Widler P, *et al.* Pharmacodynamics and pharmacokinetics of khat: a controlled study. *Clin Pharmacol Ther* 1994; **55:** 556–62.
7. Kalix P. Catha edulis, a plant that has amphetamine effects. *Pharm World Sci* 1996; **18:** 69–73.
8. Toennes SW, *et al.* Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. *Br J Clin Pharmacol* 2003; **56:** 125–30.
9. Rumpf KW, *et al.* Rhabdomyolysis after ingestion of an appetite suppressant. *JAMA* 1983; **250:** 2112.
10. Gough SP, Cookson IB. Khat-induced schizophreniform psychosis in UK. *Lancet* 1984; **i:** 455.
11. Roper JP. The presumed neurotoxic effects of Catha edulis—an exotic plant now available in the United Kingdom. *Br J Ophthalmol* 1986; **70:** 779–81.
12. Zureikat N, *et al.* Chewing khat slows the orocaecal transit time. *Gut* 1992; **33** (suppl): S23.
13. Yousef G, *et al.* Khat chewing as a cause of psychosis. *Br J Hosp Med* 1995; **54:** 322–6.
14. Al-Motarreb A, *et al.* Khat chewing and acute myocardial infarction. *Heart* 2002; **87:** 279–280.
15. Al-Motarreb A, *et al.* Khat chewing is a risk factor for acute myocardial infarction: a case-control study. *Br J Clin Pharmacol* 2005; **59:** 574–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Antiadipositum X-112 T; ***S.Afr.:*** Dietene; Eetless; Leanor; Nobese No. 1; Slim 'n Trim; Thinz; ***Switz.:*** Antiadipositum X-112; Belloform†; Limit-X†; Miniscap†; ***Thai.:*** Mirapront N†.

Multi-ingredient: ***Mex.:*** Redotex; Redotex NF.

Clobenzorex Hydrochloride *(rINNM)* ⊗

Clobenzorex, Chlorhydrate de; Clobenzorexi Hydrochloridum; Hidrocloruro de clobenzorex; SD-271-12. (+)-*N*-(2-Chlorobenzyl)-α-methylphenethylamine hydrochloride.

Клобензорекса Гидрохлорид

$C_{16}H_{18}ClN,HCl$ = 296.2.
CAS — 13364-32-4 (clobenzorex); 5843-53-8 (clobenzorex hydrochloride).
ATC — A08AA08.
ATC Vet — QA08AA08.

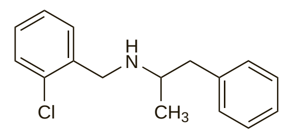

(clobenzorex)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of clobenzorex:
Dinintels.

Profile

Clobenzorex hydrochloride is a central stimulant and sympathomimetic with properties similar to those of dexamfetamine (below). It has been used as an anorectic in the treatment of obesity (p.2149) but regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Asenlix; Itravil; Obeclox; Redicres.

Deanol *(BAN)* ⊗

Démanol. 2-Dimethylaminoethanol.

$C_4H_{11}NO$ = 89.14.
CAS — 108-01-0 (deanol); 3342-61-8 (deanol aceglumate); 3635-74-3 (deanol acetamidobenzoate); 968-46-7 (deanol benzilate); 71-79-4 (deanol benzilate hydrochloride); 15585-86-1 (deanol cyclohexylpropionate); 5988-51-2 (deanol tartrate).
ATC — N06BX04.
ATC Vet — QN06BX04.

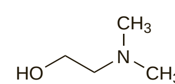

NOTE. Deanol Aceglumate is *pINN.*

Profile

Deanol, a precursor of choline, may enhance central acetylcholine formation. It has been used as a central stimulant in the treatment of hyperactivity in children but its efficacy is not proven. It has been included in preparations used as tonics and for the management of impaired mental function.

It has been used as a variety of salts and esters including deanol aceglumate, deanol acetamidobenzoate, deanol bisorcate, deanol cyclohexylpropionate (cyprodenate; cyprodemanol), deanol hemisuccinate, deanol pidolate, and deanol tartrate. Deanol benzilate (deanol diphenylglycolate; benzacine) has been used as the hydrochloride in antispasmodic preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: DM Active; ***Belg.:*** Actebral†; ***Fr.:*** Astyl†; ***Ger.:*** Risatarun; ***Ital.:*** Rischiaril†; ***Pol.:*** Bimanol; ***Port.:*** Tonibral†; ***Rus.:*** Nooclerin (Нооклерин).

Multi-ingredient: ***Fr.:*** Acti 5; Debrumyl; ***Ger.:*** Rowachol comp†; ***Port.:*** Actilam; Debrumyl; Forticol; Tonice; ***Spain:*** Anti Anorex Triple; Denubil; ***Switz.:*** Vigoran†.

Dexamfetamine Sulfate *(pINNM)* ⊗

Deksamfetamin Sülfat; Dexamfétamine, Sulfate de; Dexamfetamine Sulphate *(BANM)*; Dexamfetamini Sulfas; Dexamphetamine Sulphate; Dexamphetamini Sulfas; Dextro Amphetamine Sulphate; Dextroamphetamine Sulfate; NSC-73713 (dexamfetamine); Sulfato de dexanfetamina. (*S*)-α-Methylphenethylammonium sulphate; (+)-α-Methylphenethylamine sulphate.

Дексамфетамина Сульфат

$(C_9H_{13}N)_2,H_2SO_4$ = 368.5.

CAS — 51-64-9 (dexamfetamine); 7528-00-9 (dexamfetamine phosphate); 51-63-8 (dexamfetamine sulfate).
ATC — N06BA02.
ATC Vet — QN06BA02.

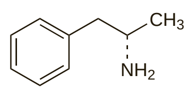

(dexamfetamine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dexamfetamine:
Dex; Dexies; Dexy; Oranges; Panama; Peaches.

Pharmacopoeias. In *Br.*, *Swiss*, and *US.*

BP 2008 (Dexamfetamine Sulphate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether.

USP 31 (Dextroamphetamine Sulfate). A white, odourless, crystalline powder. Soluble 1 in 10 of water and 1 in 800 of alcohol; insoluble in ether. pH of a 5% solution in water is between 5.0 and 6.0.

Adverse Effects

The adverse effects of dexamfetamine are commonly symptoms of overstimulation of the CNS and include insomnia, night terrors, nervousness, restlessness, irritability, and euphoria that may be followed by fatigue and depression. There may be dryness of the mouth, anorexia, abdominal cramps and other gastrointestinal disturbances, headache, dizziness, tremor, sweating, tachycardia, palpitations, myocardial infarction, increased or sometimes decreased blood pressure, altered libido, and impotence. Psychotic reactions, such as hallucinations and delusional thinking, mania, seizures, and stroke have occurred, as has muscle damage with associated rhabdomyolysis and renal complications. Rarely, cardiomyopathy has occurred with chronic use. Sudden death has been reported in patients with structural cardiac abnormalities (see also Effects on the Cardiovascular System, below). In addition in children, growth retardation may occur during prolonged treatment.

In *acute overdosage*, the adverse effects are accentuated and may be accompanied by hyperpyrexia, mydriasis, hyperreflexia, chest pain, cardiac arrhythmias, confusion, panic states, aggressive behaviour, hallucinations, delirium, convulsions, respiratory depression, coma, circulatory collapse, and death. Individual patient response may vary widely and toxic manifestations may occur with quite small overdoses.

Tolerance can develop to some of dexamfetamine's central effects leading to increased doses and habituation. Abrupt cessation after prolonged treatment or abuse of amfetamines has been associated with extreme fatigue, hyperphagia, and depression. However, it is generally accepted that the amfetamines, although widely abused, are not associated with substantial physical dependence.

Abuse of amfetamines for their euphoriant effects has resulted in personality changes, compulsive and stereotyped behaviour, and may induce a toxic psychosis with auditory and visual hallucinations and paranoid delusions.

Abuse. Abuse of amfetamines can lead to toxicity affecting many organs or body systems. There have been reports of *intracerebral haemorrhage*[1-3] and of *cardiomyopathy*.[4-6] *Acute myocardial infarction* has also occurred.[7]

A syndrome characterised by *circulatory collapse, fever, leukaemoid reaction, disseminated intravascular coagulation*, and *rhabdomyolysis* with *diffuse myalgias* and *muscle tenderness* has been described[8] in 5 drug abusers who had used amfetamines or phenmetrazine intravenously. In an earlier study,[9] *necrotising angiitis* was associated with intravenous metamfetamine abuse. A 30-year-old man who had ingested 50 amfetamine sulfate tablets developed *rhabdomyolysis* and *myoglobinuric renal failure*, possibly secondary to a crush syndrome, but in the absence of prolonged coma or other major myotoxic factors.[10] However, *acute interstitial nephritis* and *acute renal failure* have followed oral amfetamine abuse without the associated factors of rhabdomyolysis, hyperpyrexia, or necrotising angiitis.[11]

Chronic use may result in adverse effects such as *hallucinations*, a *delusional disorder* resembling *paranoid schizophrenia*, *stereotyped behaviour*, and *movement disorders*.[12] Although chronic intoxication is the most common precondition for psychosis, individual sensitivities are an important aspect of the drug reaction.

Increased serum concentrations of *levothyroxine* have been associated with heavy amfetamine abuse in 4 psychiatric patients.[13]

Abrupt cessation after prolonged treatment or abuse of amfetamines may cause *extreme fatigue, hyperphagia*, and *depression*. *Depressive stupor* has been reported in 3 long-term abusers of amfetamine after sudden withdrawal.[14]

1. Delaney P, Estes M. Intracranial hemorrhage with amphetamine abuse. *Neurology* 1980; **30:** 1125–8.
2. Harrington H, *et al.* Intracerebral hemorrhage and oral amphetamine. *Arch Neurol* 1983; **40:** 503–7.
3. Salanova V, Taubner R. Intracerebral haemorrhage and vasculitis secondary to amphetamine use. *Postgrad Med J* 1984; **60:** 429–30.
4. Smith HJ, *et al.* Cardiomyopathy associated with amphetamine administration. *Am Heart J* 1976; **91:** 792–7.
5. Call TD, *et al.* Acute cardiomyopathy secondary to intravenous amphetamine abuse. *Ann Intern Med* 1982; **97:** 559–60.
6. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265:** 1152–4.
7. Waksman J, *et al.* Acute myocardial infarction associated with amphetamine use. *Mayo Clin Proc* 2001; **76:** 323–6.
8. Kendrick WC, *et al.* Rhabdomyolysis and shock after intravenous amphetamine administration. *Ann Intern Med* 1977; **86:** 381–7.
9. Citron BP, *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; **283:** 1003–11.
10. Scandling J, Spital A. Amphetamine-associated myoglobinuric renal failure. *South Med J* 1982; **75:** 237–40.
11. Foley RJ, *et al.* Amphetamine-induced acute renal failure. *South Med J* 1984; **77:** 258–60.
12. Ellinwood EH, Kilbey MM. Fundamental mechanisms underlying altered behavior following chronic administration of psychomotor stimulants. *Biol Psychiatry* 1980; **15:** 749–57.
13. Morley JE, *et al.* Amphetamine-induced hyperthyroxinemia. *Ann Intern Med* 1980; **93:** 707–9.
14. Tuma TA. Depressive stupor following amphetamine withdrawal. *Br J Hosp Med* 1993; **49:** 361–3.

Effects on the cardiovascular system. There have been very rare reports of sudden death in children and adults taking *Adderall* (*Shire*), a combination preparation of amfetamine salts. In February 2005 Health Canada[1] reported that, worldwide, there have been 20 cases of sudden death in patients taking the product at usual recommended doses; 14 of these deaths occurred in children. In some cases there was no history of cardiac disorders nor any structural abnormalities. Health Canada considered the incidence of fatal adverse effects to be greater with this combination preparation than with other stimulants and consequently withdrew the product from the Canadian market. However, a subsequent independent review committee recommended[2] that *Adderall* be allowed back onto the Canadian market although they did warn that it should not be used in patients with structural cardiac abnormalities.[3]

The committee also recommended that all stimulants used in attention deficit hyperactivity disorder undergo enhanced postmarketing surveillance and consequently, in May 2006, Health Canada[4] revised the labelling of amfetamine, atomoxetine, dexamfetamine, dexmethylphenidate, and methylphenidate to include warnings about their effects on the cardiovascular system. However, it was also noted that the incidence or reporting rates of serious cardiovascular adverse effects with these drugs, including fatal cases, were no greater than background rates.

1. Health Canada. Health Canada has suspended market authorization of ADDERALL XR (amphetamine salts), a drug approved for Attention Deficit Hyperactivity Disorder (ADHD) in children (issued 9th February, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr_hpc-cps-eng.pdf (accessed 11/08/08)
2. Health Canada. Report of the "Adderall XR New Drug Committee" (issued 26th August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ndca_rep_cnma_rap_2005-08-25-eng.pdf (accessed 11/08/08)
3. Shire, Canada. ADDERALL XR and serious adverse events (issued 31st August, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adderall_xr2_hpc-cps-eng.pdf (accessed 11/08/08)
4. Health Canada. Attention deficit hyperactivity disorder (ADHD) drugs: updated and standardized labelling regarding very rare cardiac-related adverse events (issued May 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/adhd-tdah_medic_hpc-cps_e.pdf (accessed 21/09/06)

Effects on growth. The Pediatric Subcommittee of the FDA Psychopharmacologic Drugs Advisory Committee reviewed the growth-suppressing effects of stimulant medication in hyperkinetic children.[1] There was reasonable evidence that stimulant drugs, particularly in higher doses, moderately suppressed growth in weight and might have a minor suppressing effect on growth in stature. There were indications that some growth caught up during drug holidays, and that early growth suppression was not evident in adulthood. Careful monitoring during treatment was recommended.

See also under Methylphenidate Hydrochloride, p.2159.

1. Roche AF, *et al.* The effects of stimulant medication on the growth of hyperkinetic children. *Pediatrics* 1979; **63:** 847–50.

Treatment of Adverse Effects

Activated charcoal may be given to delay absorption if the patient presents within 1 hour; gastric lavage may be considered in recent large ingestions. In general the management of overdosage with amfetamines involves supportive and symptomatic therapy. Sedation is usually sufficient. Forced acid diuresis has been advocated to increase amfetamine excretion but is seldom necessary and should only be considered in severely poisoned patients; it requires close supervision and monitoring.

Precautions

Dexamfetamine is contra-indicated in patients with cardiovascular disease including moderate to severe hypertension and those with structural cardiac abnormalities, cardiomyopathy, or advanced arteriosclerosis. It should also not be used in patients with hyperthyroidism, glaucoma, hyperexcitability, or agitated states. Dexamfetamine should not be given to those with a history of drug or alcohol abuse and it should be avoided in pregnant or breast-feeding women.

It should be given with caution to patients with mild hypertension, renal impairment, bipolar disorder, or unstable personality. Behavioural disturbances and thought disorders may be exacerbated in psychotic patients.

Height and weight in children should be monitored as growth retardation may occur.

Care may be needed in certain patients predisposed to tics or Tourette's syndrome as symptoms may be provoked. Dexamfetamine is likely to reduce the convulsive threshold; caution is therefore advised in patients with epilepsy. However, it appears that in some countries amfetamines have been included in antiepileptic preparations containing phenytoin or phenobarbital in an attempt to increase their antiepileptic action. Amfetamines may impair patients' ability to drive or to operate machinery.

Diabetic control should be monitored when central stimulants are used for the control of obesity.

Prolonged high doses may need gradual withdrawal as abrupt cessation may produce fatigue and mental depression.

Abuse. Dexamfetamine is subject to extensive abuse and for this reason its availability is severely curtailed. For adverse effects associated with abuse, see above.

Porphyria. Amfetamines are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity. Metamfetamine has been associated with acute attacks of porphyria.

Pregnancy. No difference was found in the incidence of severe congenital anomalies between 1824 children of mothers prescribed amfetamines or phenmetrazine during pregnancy and 8989 children of mothers who had not received these drugs.[1] Though an excess of oral clefts was noted in the offspring of mothers prescribed amfetamines, there was no excess of congenital heart disease.[1] This was contrary to a previous suggestion[2] in which congenital heart disease in 184 infants had been studied and a link to maternal dexamfetamine exposure postulated. There has been a report of a bradycardia followed by death in a fetus due to maternal intravenous self-administration of 500 mg of amfetamine.[3]

1. Milkovich L, van den Berg BJ. Effects of antenatal exposure to anorectic drugs. *Am J Obstet Gynecol* 1977; **129:** 637–42.
2. Nora JJ, *et al.* Dexamphetamine: a possible environmental trigger in cardiovascular malformations. *Lancet* 1970; **i:** 1290–1.
3. Dearlove JC, Betteridge TJ. Stillbirth due to intravenous amphetamine. *BMJ* 1992; **304:** 548.

Tourette's syndrome. A review[1] of clinical reports concluded that there was virtually no evidence that central stimulants caused or provoked Tourette's syndrome and weak or inadequate evidence that clinically appropriate doses of central stimulants caused tics in previously asymptomatic patients or exacerbated pre-existing symptoms. However, the authors suggested that there was evidence that high or toxic doses might exacerbate or provoke tics in predisposed patients. Long-term methylphenidate therapy did not appear to exacerbate motor or vocal tics in a study[2] of 34 children with ADHD and chronic multiple tic disorder who were followed up for 2 years. However, the authors did point out that careful clinical monitoring is essential to eliminate the possibility of drug-induced exacerbation in individual patients. In contrast, a report[3] on 15 children who developed Tourette's syndrome while receiving stimulant medication for hyperactivity considered that such therapy was contra-indicated in children with motor tics or diagnosed Tourette's syndrome and should be used with caution in children with a family history of these symptoms. In addition, it suggested that the development of motor tic symptoms in any child given stimulants should be a clear indication for stopping immediately to minimise the possibility of eliciting a full-blown Tourette's syndrome.

1. Shapiro AK, Shapiro E. Do stimulants provoke, cause, or exacerbate tics and Tourette syndrome? *Compr Psychiatry* 1981; **22:** 265–73.
2. Gadow KD, *et al.* Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Arch Gen Psychiatry* 1999; **56:** 330–6.
3. Lowe TL, *et al.* Stimulant medications precipitate Tourette's syndrome. *JAMA* 1982; **247:** 1729–31.

Interactions

Dexamfetamine is an indirect-acting sympathomimetic and may interact with a number of other drugs. To avoid precipitating a hypertensive crisis, it should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment. Use of beta blockers with amfetamines may produce severe hypertension. Dexamfetamine may also diminish the effects of other antihypertensives, including guanethidine and similar drugs, and concurrent use should be avoided. Patients receiving amfetamines and tricyclic antidepressants require careful monitoring as the risk of cardiovascular effects including arrhythmias may be increased. The urinary excretion of amfetamines is reduced by urinary alkalinisers, which may enhance or prolong their effects; excretion is increased by urinary acidifiers.

Amfetamines may delay the absorption of ethosuximide, phenobarbital, and phenytoin. The stimulant effects of amfetamines are inhibited by chlorpromazine, haloperidol, and lithium. Disulfiram may inhibit the metabolism and excretion of amfetamines.

Use of sympathomimetics with volatile liquid anaesthetics such as halothane is associated with an increased risk of cardiac arrhythmias.

Pharmacokinetics

Amfetamines are readily absorbed from the gastrointestinal tract and are distributed into most body tissues with high concentrations in the brain and CSF. They are partially metabolised in the liver but a considerable fraction may be excreted in the urine unchanged. Urinary elimination is pH-dependent and enhanced in acid urine. Amfetamines are distributed into breast milk.

◊ References.

1. Steiner E, *et al*. Amphetamine secretion in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 123–4.
2. de la Torre R, *et al*. Clinical pharmacokinetics of amfetamine and related substances: monitoring in conventional and non-conventional matrices. *Clin Pharmacokinet* 2004; **43:** 157–85.
3. Ilett KF, *et al*. Transfer of dexamphetamine into breast milk during treatment for attention deficit hyperactivity disorder. *Br J Clin Pharmacol* 2007; **63:** 371–5.

Uses and Administration

Dexamfetamine, the dextrorotatory isomer of amfetamine, is an indirect-acting sympathomimetic with alpha- and beta-adrenergic agonist activity. It has a marked stimulant effect on the CNS, particularly the cerebral cortex.

Dexamfetamine is used in the treatment of narcolepsy (p.2148). It is also used in the treatment of attention deficit hyperactivity disorder (p.2148); in the UK, this use is limited to refractory hyperactivity disorders in children. Dexamfetamine has been given in the treatment of obesity (p.2149), although amfetamines are no longer recommended for this indication. Amfetamines have also been used to overcome fatigue but, again, such use is considered undesirable. In some countries dexamfetamine has been tried for motion sickness (p.1700), but safer drugs are available.

Dexamfetamine is generally used as the sulfate and is given by mouth.

In the treatment of **narcolepsy**, the usual initial dose is 5 to 10 mg daily in divided doses, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily. The lower initial dose of 5 mg daily is recommended for the elderly and any weekly increments should also be restricted to 5 mg in such patients.

In children with **hyperactivity** individualisation of treatment is especially important. Children aged 6 years and over usually start with a dose of 5 mg once or twice daily; the dose may be increased if necessary by 5 mg at weekly intervals to an upper limit of 20 mg daily, although older children might require up to 40 mg or more daily. Although dexamfetamine is licensed for the treatment of children younger than 6 years of age in some countries, including the UK and the USA, many authorities consider that stimulants should not be used in young children.

In the USA, an immediate-release, combination preparation containing dexamfetamine sulfate and saccharate, with amfetamine sulfate and amfetamine aspartate monohydrate (*Adderall, Shire*), is licensed for the treatment of narcolepsy and attention deficit hyperactivity disorder. This formulation is given by mouth in doses similar to those for dexamfetamine (see above). A modified-release formulation is also available for the treatment of attention deficit hyperactivity disorder in adults and children. The initial dose in adults is 20 mg of total amfetamine salts once daily. In children, it is given as for dexamfetamine in initial doses of 10 mg of total amfetamine salts once daily increased gradually up to a maximum of 30 mg daily; in older children aged 13 to 17 years the dose may be increased to a maximum of 20 mg once daily after 1 week if necessary.

Preparations

BP 2008: Dexamfetamine Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Dexedrine; ***Switz.:*** Dexamin†; ***UK:*** Dexedrine; ***USA:*** Dexedrine; Dextrostat.

Multi-ingredient: *Canad.:* Adderall; ***USA:*** Adderall.

Dexfenfluramine Hydrochloride

(BANM, USAN, rINNM) ⊗

Deksfenfluramiinihydrokloridi; Dexfenfluramine, Chlorhydrate de; Dexfenfluraminhydroklorid; Dexfenfluramini Hydrochloridum; Hidrocloruro de dexfenfluramina; S-5614 (dexfenfluramine). (*S*)-*N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

Дексфенфлурамина Гидрохлорид

$C_{12}H_{16}F_3N,HCl = 267.7.$

CAS — 3239-44-9 (dexfenfluramine); 3239-45-0 (dexfenfluramine hydrochloride).

ATC — A08AA04.

ATC Vet — QA08AA04.

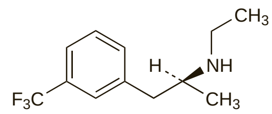

(dexfenfluramine)

Profile

Dexfenfluramine is the *S*-isomer of fenfluramine (p.2156). It stimulates the release of serotonin and selectively inhibits its reuptake, but differs from fenfluramine in not possessing any catecholamine agonist activity.

Dexfenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but, like fenfluramine, was withdrawn worldwide after reports of valvular heart defects.

Porphyria. Dexfenfluramine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Isolipan†; ***Hung.:*** Isolipan†.

Dexmethylphenidate Hydrochloride

(USAN, rINNM) ⊗

Dexméthylphénidate, Chlorhydrate de; Dexmethylphenidati Hydrochloridum; d-MPH; Hidrocloruro de dexmetilfenidato; *d-threo*-Methylphenidate; *d*-Methylphenidate Hydrochloride. Methyl (2*R*)-phenyl[(2*R*)-piperidin-2-yl]acetate hydrochloride.

Дексметилфенидата Гидрохлорид

$C_{14}H_{19}NO_2,HCl = 269.8.$

CAS — 40431-64-9 (dexmethylphenidate); 19262-68-1 (dexmethylphenidate hydrochloride).

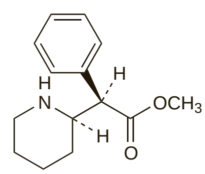

(dexmethylphenidate)

Profile

Dexmethylphenidate hydrochloride is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride (p.2159). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders.

Dexmethylphenidate hydrochloride is licensed for use in children aged 6 years and older. For patients new to methylphenidate the starting dose of dexmethylphenidate hydrochloride is 2.5 mg twice daily. Each dose should be given at least four hours apart. Dosage may be adjusted in 2.5 to 5 mg increments weekly to a maximum of 10 mg twice daily.

For patients currently using methylphenidate the starting dose of dexmethylphenidate hydrochloride is half the dose of the racemic substance. The maximum recommended dose is 10 mg twice daily.

A modified-release formulation is also available for once-daily dosing.

Dexmethylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond to assess the patient's condition.

◊ References.

1. Robinson DM, Keating GM. Dexmethylphenidate extended release: in attention-deficit hyperactivity disorder. *Drugs* 2006; **66:** 661–8.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Focalin.

Diethylaminoethanol ⊗

Dietilaminoetanol. 2-Diethylaminoethanol.

$C_6H_{15}NO = 117.2.$

CAS — 100-37-8.

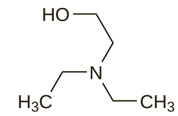

Profile

Diethylaminoethanol is an analogue of deanol (p.2152) and has been used similarly as the malate. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Durobion.

Multi-ingredient: *Austria:* Barokaton.

Diethylpropion Hydrochloride *(BANM)* ⊗

Amfepramone Hydrochloride *(pINNM)*; Amfépramone, Chlorhydrate d'; Amfepramoni Hydrochloridum; Hidrocloruro de anfepramona. *N*-(1-Benzoylethyl)-*NN*-diethylammonium chloride; 2-Diethylaminopropiophenone hydrochloride; (*RS*)-α-Diethylaminopropiophenone hydrochloride.

Амфепрамона Гидрохлорид

$C_{13}H_{19}NO,HCl = 241.8.$

CAS — 90-84-6 (diethylpropion); 134-80-5 (diethylpropion hydrochloride).

ATC — A08AA03.

ATC Vet — QA08AA03.

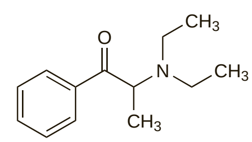

(diethylpropion)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diethylpropion:
Blue; Blues.

Pharmacopoeias. In *US.*

USP 31 (Diethylpropion Hydrochloride). A white to off-white, fine crystalline powder. Is odourless or has a slight characteristic odour. It may contain tartaric acid as a stabilising agent. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, and 1 in 3 of chloroform; practically insoluble in ether. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153. In addition gynaecomastia has been reported rarely. The incidence of central adverse effects may be lower with diethylpropion than with dexamfetamine. Diethylpropion should not be given to patients with emotional instability or a history of psychiatric illness. It should be avoided in children and the elderly. Diethylpropion hydrochloride is subject to abuse.

Porphyria. Diethylpropion is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Diethylpropion is an indirect-acting sympathomimetic and, similarly to dexamfetamine (p.2153), may interact with a number of other drugs.

Pharmacokinetics

Diethylpropion is readily absorbed from the gastrointestinal tract. It is extensively metabolised in the liver and possibly the gastrointestinal tract and is excreted in the urine. Diethylpropion crosses the blood-brain barrier and the placenta. Diethylpropion and its metabolites are distributed into breast milk.

Uses and Administration

Diethylpropion hydrochloride is a central stimulant and indirect-acting sympathomimetic with the actions of dexamfetamine (p.2154). It is used as an oral anorectic in the short-term treatment of obesity (p.2149), although stimulants are not generally recommended for this indication.

Doses of 25 mg three times daily 1 hour before meals or 75 mg once daily in mid-morning as a modified-release preparation, are given. To reduce the risk of dependence, diethylpropion should not be given for more than a few weeks at a time.

Regulatory authorities in the EU have called for the withdrawal of diethylpropion from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

USP 31: Diethylpropion Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Tenuate; ***Braz.:*** Dualid S; Hipofagin S; Inibex S; ***Canad.:*** Tenuate; ***Chile:*** Sacin; ***Denm.:*** Regenon; ***Ger.:*** Regenon; ***Hong Kong:*** Atractil; Prothin; ***Mex.:*** Ifa Norex; Neobes; ***NZ:*** Tenuate Dospan; ***S.Afr.:*** Tenuate Dospan; ***Switz.:*** Prefamone†; Regenon; ***Thai.:*** Atractil; Dietil; Regenon†; ***USA:*** Tenuate†.

Multi-ingredient: ***Arg.:*** Tratobes; ***Indon.:*** Apisate.

Dimefline Hydrochloride *(BANM, USAN, rINNM)*

Diméfline, Chlorhydrate de; Dimeflini Hydrochloridum; DW-62; Hidrocloruro de dimeflina; NSC-114650; Rec-7/0267. 8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenylchromen-4-one hydrochloride.

Димефлина Гидрохлорид

$C_{20}H_{21}NO_3,HCl = 359.8.$

CAS — 1165-48-6 (dimefline); 2740-04-7 (dimefline hydrochloride).

ATC — R07AB08.

ATC Vet — QR07AB08.

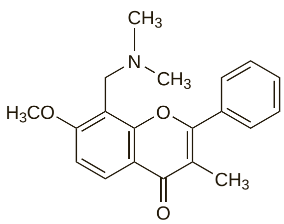

(dimefline)

Profile

Dimefline has actions similar to those of doxapram (below) and has been used orally as the hydrochloride and parenterally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Remeflin.

Doxapram Hydrochloride *(BANM, USAN, rINNM)*

AHR-619; Doksapraamihydrokloridi; Doksapram Hidroklorür; Doksapramo hidrochloridas; Doxapram, chlorhydrate de; Doxaprám-hidroklorid; Doxapram-hydrochlorid monohydrát; Doxapramhydroklorid; Doxaprami hydrochloridum; Doxaprami Hydrochloridum Monohydricum; Hidrocloruro de doxapram. 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate.

Доксапрама Гидрохлорид

$C_{24}H_{30}N_2O_2,HCl,H_2O = 433.0.$

CAS — 309-29-5 (doxapram); 113-07-5 (anhydrous doxapram hydrochloride); 7081-53-0 (doxapram hydrochloride monohydrate).

ATC — R07AB01.

ATC Vet — QR07AB01.

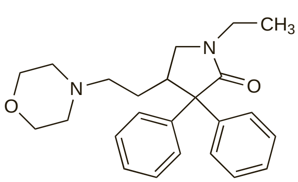

(doxapram)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Doxapram Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water, in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.0.

USP 31 (Doxapram Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 50 of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 5.0. Store in airtight containers.

Incompatibility. The commercial injection of doxapram hydrochloride is reported to be incompatible with alkaline solutions such as aminophylline, furosemide, or thiopental sodium.

Adverse Effects

As with other respiratory stimulants, there is a risk that doxapram will produce adverse effects due to general stimulation of the CNS.

Doxapram may produce dyspnoea and other respiratory problems such as coughing, bronchospasm, laryngospasm, hiccup, hyperventilation, and rebound hypoventilation. Muscle involvement may range from fasciculations to spasticity. Convulsions, headache, dizziness, hyperactivity, and confusion can occur as can sweating, flushing, fever or a sensation of warmth, particularly in the genital or perineal regions. Hallucinations may occur rarely. There may be nausea, vomiting, diarrhoea, and problems with urination. Cardiovascular effects include hypertension and various arrhythmias although sudden hypotension may also occur.

Thrombophlebitis may follow extravasation of doxapram during injection.

Effects on the heart. Second-degree AV block caused by prolongation of the QT interval has been associated with doxapram use in 3 neonates.[1] Although the preparation used contained benzyl alcohol this was not considered to play a role in the adverse effect. A prospective study[2] involving 40 premature infants given doxapram for apnoea of prematurity also found QT interval lengthening at 48 and 72 hours of treatment, even when the drug plasma concentrations were kept within therapeutic ranges. In 6 infants, the QT interval lengthened to a degree considered to be life-threatening. There was also a trend towards moderate increases in blood pressure. The authors recommended heart monitoring when doxapram was given to premature infants.

1. De Villiers GS, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998; **133:** 149–50.
2. Maillard C, *et al.* QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001; **70:** 540–5.

Effects on the liver. Acute hepatic necrosis in a patient was attributed to a 24-hour infusion of doxapram.[1] Liver function tests returned to normal over 3 weeks.

1. Fancourt GJ, *et al.* Hepatic necrosis with doxapram hydrochloride. *Postgrad Med J* 1985; **61:** 833–5.

Precautions

Doxapram should not be given to patients with epilepsy or other convulsive disorders, cerebral oedema, cerebrovascular accident, head injury, acute severe asthma, physical obstruction of the airway, severe hypertension, ischaemic heart disease, hyperthyroidism, or phaeochromocytoma. Caution is also advisable if doxapram is used in patients with less severe degrees of hypertension or impaired cardiac reserve. It should be given with care to patients with significant hepatic or renal impairment.

Patients should be carefully supervised during use of doxapram; special attention should be paid to changes in blood gas measurements. Doxapram should be given with oxygen in severe irreversible airways obstruction or severely decreased lung compliance because of the increased work of breathing. A $beta_2$ agonist should also be given to patients with bronchoconstriction.

Interactions

Additive pressor effects may occur when doxapram is used with sympathomimetics or MAOIs. Cardiac arrhythmias may occur when doxapram is given with anaesthetics known to sensitise the myocardium, such as halothane, enflurane, and isoflurane; it has been recommended that doxapram should not be given for at least 10 minutes after stopping these anaesthetics. Doxapram may temporarily mask the residual effects of neuromuscular blockers. The manufacturers have reported that there may be an interaction between doxapram and aminophylline manifested by agitation and increased skeletal muscle activity.

Pharmacokinetics

After intravenous doses doxapram is rapidly distributed into the tissues. Onset of respiratory stimulation usually occurs in 20 to 40 seconds, with a peak effect achieved in 1 to 2 minutes. Duration of effect following a single dose varies from 5 to 12 minutes. Doxapram is extensively metabolised in the liver. The major route of excretion of metabolites and a small amount of unchanged drug is thought to be via bile to the faeces. It is also excreted in the urine.

Some absorption occurs when doxapram is given orally.

◊ References.

1. Robson RH, Prescott LF. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol* 1978; **7:** 81–7.
2. Baker JR, *et al.* Normal pharmacokinetics of doxapram in a patient with renal failure and hypothyroidism. *Br J Clin Pharmacol* 1981; **11:** 305–6.

Uses and Administration

Doxapram hydrochloride is a central and respiratory stimulant with a brief duration of action. It acts by stimulation of peripheral chemoreceptors and central respiratory centres; at higher doses, it stimulates other parts of the brain and spinal cord. Doxapram has a pressor action and may also increase catecholamine release.

Doxapram has limited uses in the treatment of acute respiratory failure (for example where this is superimposed on chronic obstructive pulmonary disease), and of postoperative respiratory depression (see Respiratory Failure under Oxygen, p.1691).

Doxapram hydrochloride may be infused at a rate of 1.5 to 4 mg/minute in the treatment of acute respiratory failure.

For postoperative respiratory depression it has been given in a dose of 0.5 to 1.5 mg/kg by intravenous injection over a period of at least 30 seconds. This dose may be repeated at hourly intervals. It may also be given by intravenous infusion, initially at a rate of 2 to 5 mg/minute and then reduced, according to response, to 1 to 3 mg/minute; a recommended maximum total dosage is 4 mg/kg.

Doxapram hydrochloride has also been used to treat respiratory and CNS depression following drug overdose but its use for this indication is no longer recommended.

Chronic obstructive pulmonary disease. Respiratory stimulants such as doxapram have a limited and short-term role in hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (p.1112). Benefit has been reported in such patients in whom doxapram was used as an alternative to intubation.[1,2] However, a systematic review suggested that despite short-term improvements in blood-gas exchange with doxapram, techniques such as non-invasive ventilation might be more effective.[3]

1. Hirshberg AJ, *et al.* Use of doxapram hydrochloride injection as an alternative to intubation to treat chronic obstructive pulmonary disease patients with hypercapnia. *Ann Emerg Med* 1994; **24:** 701–3.
2. Kerr HD. Doxapram in hypercapnic chronic obstructive pulmonary disease with respiratory failure. *J Emerg Med* 1997; **15:** 513–15.
3. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).

Neonatal apnoea. Doxapram is effective in neonatal apnoea (p.1118) and may be considered as an alternative, or in addition, to xanthines in infants with apnoea that does not respond to xanthine therapy alone. However, it is less convenient to use as it must be given by continuous intravenous infusion and blood pressure must be monitored (although it has also been suggested that the oral route may be used after the initial intravenous dose—see *BNFC* doses below). Additionally, some preparations may contain benzyl alcohol as a preservative making them unsuitable for use in neonates. It has been used in intravenous doses of 2.5 mg/kg per hour.[1-3] Adverse CNS effects have been reported.[3] Lower doses of 0.25 or 1.5 mg/kg per hour have been shown to be effective.[4,5] However, use of low doses of 500 micrograms/kg per hour in very low birth-weight premature infants produced higher than expected plasma-doxapram concentrations and a greater increase in systolic blood pressure compared with controls.[6] A systematic review[7] concluded that the place of doxapram in the management of neonatal apnoea had not yet been properly established.

Although unlicensed, the *BNFC* suggests giving neonates doxapram hydrochloride intravenously in an initial dose of 2.5 mg/kg over 5 to 10 minutes followed by 300 micrograms/kg per hour by continuous infusion, adjusted according to response, to a maximum dose of 1.5 mg/kg per hour; alternatively, 6 mg/kg may be given orally 4 times daily after the initial intravenous dose.

1. Sagi E, *et al.* Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Arch Dis Child* 1984; **59:** 281–3.
2. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
3. Dear PRF, Wheeler D. Doxapram and neonatal apnoea. *Arch Dis Child* 1984; **59:** 903–4.
4. Bairam A, Vert P. Low-dose doxapram for apnoea of prematurity. *Lancet* 1986; **i:** 793–4.
5. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
6. Huon C, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomized, double-blind study. *Acta Paediatr* 1998; **87:** 1180–4.
7. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/10/07).

Respiratory depression. References to the use of doxapram in postoperative respiratory depression.

1. Jansen JE, *et al.* Effect of doxapram on postoperative pulmonary complications after upper abdominal surgery in high-risk patients. *Lancet* 1990; **335:** 936–8.
2. Thangathurai D, *et al.* Doxapram for respiratory depression after epidural morphine. *Anaesthesia* 1990; **45:** 64–5.
3. Sajjad T. Comparison of the effects of doxapram or carbon dioxide on ventilatory frequency and tidal volume during induction of anaesthesia with propofol, *Br J Anaesth* 1994; **73:** 266P.
4. Alexander-Williams M, *et al.* Doxapram and the prevention of postoperative hypoxaemia. *Br J Anaesth* 1995; **75:** 233P.

Shivering. Doxapram is one of a number of drugs that have been used in postoperative shivering, see p.1779.

References.

1. Sarma V, Fry ENS. Doxapram after general anaesthesia: its role in stopping shivering during recovery. *Anaesthesia* 1991; **46:** 460–1.
2. Singh P, *et al.* Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71:** 685–8.
3. Wrench IJ, *et al.* The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52:** 32–6.

Preparations

BP 2008: Doxapram Injection;
USP 31: Doxapram Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Dopram†; ***Austria:*** Dopram; ***Belg.:*** Dopram; ***Denm.:*** Dopram; ***Fin.:*** Dopram; ***Fr.:*** Dopram; ***Ger.:*** Dopram; ***Gr.:*** Dopram; ***Hong Kong:*** Dopram†; ***Irl.:*** Dopram; ***Neth.:*** Dopram; ***Norw.:*** Dopram; ***NZ:*** Dopram†; ***S.Afr.:*** Dopram; ***Spain:*** Docatone†; ***Switz.:*** Dopram†; ***UK:*** Dopram; ***USA:*** Dopram.

Etamivan *(BAN, rINN)* ⊗

Etamivaani; Étamivan; Etamiván; Etamivanum; Ethamivan *(USAN)*; NSC-406087; Vanillic Acid Diethylamide; Vanillic Diethylamide. *N,N*-Diethylvanillamide.

Этамиван

$C_{12}H_{17}NO_3$ = 223.3.
CAS — 304-84-7.
ATC — R07AB04.
ATC Vet — QR07AB04.

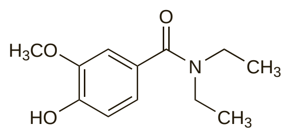

Profile

Etamivan has actions similar to those of doxapram (above). It was formerly used as a respiratory stimulant, but the risk of toxicity associated with effective doses is now considered to be unacceptable.

Etamivan is available in oral compound preparations for cerebrovascular and circulatory disorders and hypotension, but such use is not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Dosulfin Bronquial; ***Austria:*** Cinnarplus; Instenon; ***Ger.:*** Normotin-R†; ***Hong Kong:*** Instenon; ***Rus.:*** Instenon (Инстенон); ***Thai.:*** Instenon†.

Etilamfetamine Hydrochloride *(rINNM)* ⊗

Ethylamphetamine Hydrochloride; Étilamfétamine, Chlorhydrate d'; Etilamfetamini Hydrochloridum; Hidrocloruro de etilanfetamina. *N*-Ethyl-α-methylphenethylamine hydrochloride.

Этиламфетамина Гидрохлорид

$C_{11}H_{17}N,HCl$ = 199.7.
CAS — 457-87-4 (etilamfetamine); 1858-47-5 (etilamfetamine hydrochloride).
ATC — A08AA06.
ATC Vet — QA08AA06.

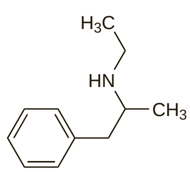

(etilamfetamine)

Profile

Etilamfetamine hydrochloride is a central stimulant with properties similar to those of dexamfetamine (p.2153). It has been used as an anorectic in the treatment of obesity.

Fencamfamin Hydrochloride *(BANM, rINNM)* ⊗

Fencamfamine, Chlorhydrate de; Fencamfamini Hydrochloridum; H-610; Hidrocloruro de fencanfamina. *N*-Ethyl-3-phenylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

Фенкамфамина Гидрохлорид

$C_{15}H_{21}N,HCl$ = 251.8.
CAS — 1209-98-9 (fencamfamin); 2240-14-4 (fencamfamin hydrochloride).
ATC — N06BA06.
ATC Vet — QN06BA06.

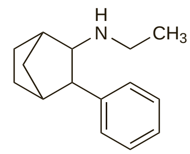

(fencamfamin)

Profile

Fencamfamin hydrochloride has been given orally as a central stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***S.Afr.:*** Reactivan.

Fenetylline Hydrochloride *(BANM, rINNM)* ⊗

Amfetyline Hydrochloride; 7-Ethyltheophylline Amphetamine Hydrochloride; Fenethylline Hydrochloride *(USAN)*; Fénétylline, Chlorhydrate de; Fenetyllini Hydrochloridum; H-814; Hidrocloruro de fenetilina; R-720-11. 7-[2-(α-Methylphenethylamino)ethyl]theophylline hydrochloride.

Фенетиллина Гидрохлорид

$C_{18}H_{23}N_5O_2,HCl$ = 377.9.
CAS — 3736-08-1 (fenetylline); 1892-80-4 (fenetylline hydrochloride).
ATC — N06BA10.
ATC Vet — QN06BA10.

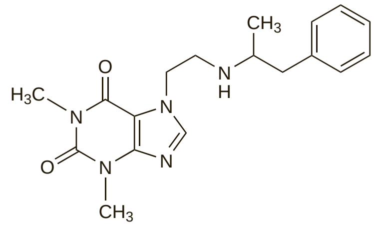

(fenetylline)

Profile

Fenetylline is a theophylline derivative of amfetamine with properties similar to those of dexamfetamine (p.2153). It is given orally in the management of narcolepsy in an initial dose of 25 mg daily, increased to usual maintenance doses of 50 to 100 mg daily in 2 divided doses; no more than 150 mg daily should be used. It has also been used in the management of hyperactivity disorders. Fenetylline is subject to abuse.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Captagon; ***Ger.:*** Captagon†.

Fenfluramine Hydrochloride *(BANM, USAN, rINNM)* ⊗

AHR-3002; Fenfluramine, Chlorhydrate de; Fenfluramini Hydrochloridum; Hidrocloruro de fenfluramina; S-768. *N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

Фенфлюрамина Гидрохлорид

$C_{12}H_{16}F_3N,HCl$ = 267.7.
CAS — 458-24-2 (fenfluramine); 404-82-0 (fenfluramine hydrochloride).
ATC — A08AA02.
ATC Vet — QA08AA02.

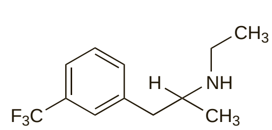

(fenfluramine)

Adverse Effects and Precautions

As for Dexamfetamine, p.2153, but fenfluramine usually depresses rather than stimulates the CNS. Fenfluramine has been associated with serious cardiovascular toxicity. Pulmonary hypertension led to certain precautions being imposed upon its use and subsequent reports of valvular heart defects led to its general withdrawal worldwide.

Effects on the cardiovascular system. The association of primary *pulmonary hypertension* with the use of anorectics including fenfluramine, dexfenfluramine, and phentermine is well recognised.[1-3] Both reversible and irreversible cases have been reported and in some cases it has proved fatal.[1,4-9] The condition appears to be linked to prolonged or repeated therapy.[1,10] In 1992 the UK CSM advised that treatment should not exceed 3 months[1] but later in 1997 it revised its recommendations for fenfluramine and dexfenfluramine allowing treatment for up to 12 months under certain conditions.[2] The CSM stated that treatment could be continued beyond 3 months only if there had been a satisfactory response (more than 10% weight loss) and that this loss was maintained. Patients should also be monitored for symptoms of pulmonary hypertension. For other anorectics such as phentermine the maximum duration of treatment remained 3 months.

However, shortly after this, a report was published[11] that outlined an association between the use of a fenfluramine-phentermine combination and the development of *valvular heart disease* in 24 patients. Initially, the response by the CSM was to advise against the use of combinations of anorectics[12] although subsequently fenfluramine, along with dexfenfluramine, was withdrawn from the world market after more cases became known.[13,14] By September 1997 the FDA in the USA[14] had received 144 reports of valvulopathy, including the original 24, associated with fenfluramine or dexfenfluramine, with or without phentermine; none were associated with phentermine treatment alone. As a consequence the US authorities made recommendations[14] for the screening of all patients who had previously received fenfluramine or dexfenfluramine in order to detect heart valve lesions and to provide optimal care. Further studies[15-20] have supported the association with valvular abnormalities, and suggested that prolonged exposure or exposure to high doses of dexfenfluramine or fenfluramine increased the risk; clinically important disease would probably not develop in most patients with only short-term exposure.[21]

In 2000, the European Commission called for the withdrawal of all anorectics from the European market. Those anorectics involved in the decision included clobenzorex, diethylpropion, fenproporex, mazindol, mefenorex, phendimetrazine, phenmetrazine, and phentermine. However in 2002, after an appeal by some manufacturers, the European Court ruled that the Commission did not have the authority to withdraw marketing authorisations. Subsequently, some anorectics have been allowed back onto the European market.

1. CSM. Fenfluramine (Ponderax Pacaps), dexfenfluramine (Adifax) and pulmonary hypertension. *Current Problems 34* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService= GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. CSM/MCA. Anorectic agents: risks and benefits. *Current Problems* 1997; **23:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
3. Abenhaim L, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; **335:** 609–16.
4. Douglas JG, *et al.* Pulmonary hypertension and fenfluramine. *BMJ* 1981; **283:** 881–3.
5. McMurray J, *et al.* Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986; **292:** 239–40.
6. Fotiadis I, *et al.* Fenfluramine-induced irreversible pulmonary hypertension. *Postgrad Med J* 1991; **67:** 776–7.
7. Atanassoff PG, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436.
8. Cacoub P, *et al.* Pulmonary hypertension and dexfenfluramine. *Eur J Clin Pharmacol* 1995; **48:** 81–3.
9. Roche N, *et al.* Pulmonary hypertension and dexfenfluramine. *Lancet* 1992; **339:** 436–7.
10. Thomas SHL, *et al.* Appetite suppressants and primary pulmonary hypertension in the United Kingdom. *Br Heart J* 1995; **74:** 600–63.
11. Connolly HM, *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; **337:** 581–8. Correction. *ibid.*; 1783.
12. CSM/MCA. Anorectic agents and valvular heart disease. *Current Problems* 1997; **23:** 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
13. CSM/MCA. Fenfluramine and dexfenfluramine withdrawn. *Current Problems* 1997; **23:** 13–14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
14. Anonymous. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR* 1997; **46:** 1061–6.
15. Khan MA, *et al.* The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998; **339:** 713–18.
16. Jick H, *et al.* A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med* 1998; **339:** 719–24.
17. Weissman NJ, *et al.* An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998; **339:** 725–32.
18. Gardin JM, *et al.* Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; **283:** 1703–9.
19. Lepor NE, *et al.* Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol* 2000; **86:** 107–10.
20. Jollis JG, *et al.* Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000; **101:** 2071–7.
21. Devereux RB. Appetite suppressants and valvular heart disease. *N Engl J Med* 1998; **339:** 765–6.

Effects on the liver. The UK MHRA had warned[1] that there had been cases of hepatotoxicity associated with adulteration of traditional Chinese slimming medicines with fenfluramine and/or nitrosofenfluramine. Nitrosofenfluramine was known to be hepatotoxic.

1. Medicines and Healthcare products Regulatory Agency (MHRA). Shubao slimming capsules containing fenfluramine and nitrosofenfluramine (issued 28th April, 2004). Available at: http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con009291.pdf (accessed 11/08/08)

Porphyria. Fenfluramine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Uses and Administration

Fenfluramine is an indirect-acting sympathomimetic related to amfetamine, but at standard doses it usually depresses rather than stimulates the CNS. It appears to stimulate the release of serotonin and selectively inhibits its reuptake resulting in increased CNS serotonin concentrations. It may also increase glucose utilisation and lower blood-glucose concentrations.

Fenfluramine was formerly given by mouth as the hydrochloride in the treatment of obesity (p.2149) but was generally withdrawn worldwide after reports of valvular heart defects.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Megaval†.

Fenproporex Hydrochloride *(rINNM)* ⊗

N-2-Cyanoethylamphetamine Hydrochloride; Fenproporex, Chlorhydrate de; Fenproporexi Hydrochloridum; Hidrocloruro de fenproporex. (±)-3-(α-Methylphenethylamino)propionitrile hydrochloride.

Фенпропорекса Гидрохлорид

$C_{12}H_{16}N_2,HCl = 224.7.$

CAS — 15686-61-0 (fenproporex); 18305-29-8 (fenproporex hydrochloride).

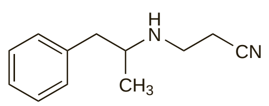

(fenproporex)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fenproporex:
Pasexes.

Profile

Fenproporex is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2153). After oral doses it is reported to be metabolised to amfetamine. Fenproporex has been given as the hydrochloride, the diphenylacetate, and as a resinate.

Fenproporex hydrochloride has been used as an anorectic in the treatment of obesity (p.2149) although the use of stimulants in this way is no longer recommended. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Desobesi-M; Lipomax†; ***Chile:*** Salcal; Sinapet†; ***Mex.:*** Feprorex; Ifa-Diety.

Multi-ingredient: ***Arg.:*** Tratobes; ***Mex.:*** Esbelcaps.

Lisdexamfetamine Mesilate *(rINNM)* ⊗

Lisdexamfetamine Dimesylate *(USAN)*; Lisdexamfétamine, Mésilate de; Lisdexamfetamini Mesilas; Mesilato de lisdexanfetamina; NRP-104. (2*S*)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate.

Лисдексамфетамина Мезилат

$C_{15}H_{25}N_3O,(CH_4O_3S)_2 = 455.6.$

CAS — 608137-32-2 (lisdexamfetamine); 608137-33-3 (lisdexamfetamine mesilate).

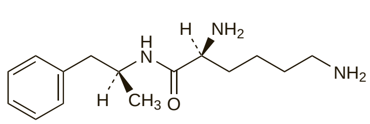

(lisdexamfetamine)

Profile

Lisdexamfetamine is a prodrug of dexamfetamine (p.2153). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders (p.2148).

Lisdexamfetamine is given orally as the mesilate and doses are expressed in terms of this salt. For adults, and children between 6 and 12 years of age, the starting dose is 30 mg once daily in the morning, increased if necessary in increments of 10 or 20 mg daily at approximately weekly intervals, up to a total maximum dose of 70 mg daily. If therapy is continued for longer than 4 weeks, use of lisdexamfetamine should be periodically stopped to evaluate the necessity for continued administration.

◊ References.

1. Blick SK, Keating GM. Lisdexamfetamine. *Paediatr Drugs* 2007; **9:** 129–35.
2. Biederman J, *et al.* Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther* 2007; **29:** 450–63.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Vyvanse.

Lobelia

Indian Tobacco.

Description. Lobelia consists of the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent.

Lobeline Hydrochloride *(BANM, rINNM)* ⊗

Alpha-lobeline Hydrochloride; Hidrocloruro de lobelina; Lobeliinihydrokloridi; Lobéline, chlorhydrate de; Lobelin-hidroklorid; Lobelin-hydrochlorid; Lobelinhydroklorid; Lobelini hydrochloridum; Lobelino hidrochloridas. 2-[6-(β-Hydroxyphenethyl)-1-methyl-2-piperidyl]acetophenone hydrochloride.

Лобелина Гидрохлорид

$C_{22}H_{27}NO_2,HCl = 373.9.$

CAS — 90-69-7 (lobeline); 134-63-4 (lobeline hydrochloride).

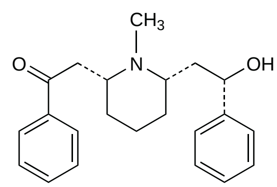

(lobeline)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Lobeline Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water; freely soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.6 to 6.4. Protect from light.

Lobeline Sulfate *(rINNM)* ⊗

Lobéline, Sulfate de; Lobeline Sulphate *(BANM)*; Lobelini Sulfas; Sulfato de lobelina.

Лобелина Сульфат

$(C_{22}H_{27}NO_2)_2,H_2SO_4 = 773.0.$

CAS — 134-64-5.

Adverse Effects

Adverse effects of lobelia and lobeline include nausea and vomiting, coughing, tremor, and dizziness. Symptoms of overdosage include profuse diaphoresis, paresis, tachycardia, hypothermia, hypotension, and coma; fatalities have occurred.

Uses and Administration

Lobelia is the dried aerial parts of *Lobelia inflata* (Lobeliaceae). Lobeline is the main alkaloidal constituent and has peripheral and central effects similar to those of nicotine (p.2352).

Lobelia has been used mainly in preparations aimed at relieving respiratory-tract disorders. Lobeline has been given by mouth as the hydrochloride or sulfate as a smoking deterrent (see Smoking Cessation, p.2354). Lobelia has been used similarly given either orally or incorporated into herbal cigarettes.

Smoking cessation. Reviews of smoking cessation therapy generally consider lobeline to have little benefit compared with placebo.[1-3]

1. Nunn-Thompson CL, Simon PA. Pharmacotherapy for smoking cessation. *Clin Pharm* 1989; **8:** 710–20.
2. Gourlay SG, McNeil JJ. Antismoking products. *Med J Aust* 1990; **153:** 699–707.
3. Stead LF, Hughes JR. Lobeline for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 16/05/05).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cig-Ridettes†; ***Canad.:*** Butt-Out; ***Spain:*** Smokeless.

Multi-ingredient: ***Austral.:*** Potassium Iodide and Stramonium Compound†; ***Belg.:*** Kamfeine†; ***Braz.:*** Asmatiron†; Bronquidex; Brontoss; Expectobron†; Expectol†; Iodeto de Potassio†; Iol†; Iolin†; MM Expectorante; Pulmoforte†; Sedatux†; Xarope Peitoral de Ameixa Composto†; ***Chile:*** Paltomiel Plus; Pulmagol; Ramistos; ***Spain:*** Pazbronquial; ***UK:*** Antibron; Asthma & Catarrh Relief; Balm of Gilead; Chest Mixture; Herbelix; Horehound and Aniseed Cough Mixture; Modern Herbals Cold & Congestion; Vegetable Cough Remover; ***Venez.:*** Novacodin.

Mazindol *(BAN, USAN, rINN)* ⊗

42-548; AN-448; Matsindoli; Mazindolum; SaH-42548. 5-(4-Chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol.

Мазиндол

$C_{16}H_{13}ClN_2O = 284.7.$

CAS — 22232-71-9.
ATC — A08AA05.
ATC Vet — QA08AA05.

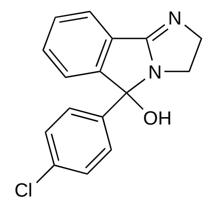

Pharmacopoeias. In *US.*
USP 31 (Mazindol). A white to off-white crystalline powder, having not more than a faint odour. Insoluble in water; slightly soluble in chloroform and in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153.

Effects on the testes. Testicular pain developed in 8 men after taking mazindol.[1]

1. McEwen J, Meyboom RHB. Testicular pain caused by mazindol. *BMJ* 1983; **287:** 1763–4.

Interactions

As for Dexamfetamine Sulfate, p.2153.

Lithium. For a report of mazindol interacting with lithium to cause lithium toxicity, see Central Stimulants, p.405.

Pharmacokinetics

Mazindol is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as metabolites.

Uses and Administration

Mazindol is a central stimulant with actions similar to those of dexamfetamine (p.2154), although structurally the two compounds are unrelated. It appears to inhibit reuptake of dopamine and noradrenaline. It has been used as an anorectic, given orally in the treatment of obesity (p.2149), although stimulants are no longer recommended for this indication. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Mazindol has been investigated in the treatment of Duchenne muscular dystrophy.

Narcolepsy. Mazindol has been reported[1-4] to be beneficial in patients with narcolepsy and associated cataplexy (p.2148). A wide range of doses has been used: 3 to 8 mg daily in one study,[1] 1 mg weekly to 16 mg daily in another;[3] children have been given 1 to 2 mg daily.[4]

1. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurol Scand* 1979; **60:** 250–4.
2. Shindler J, *et al.* Amphetamine, mazindol, and fencamfamin in narcolepsy. *BMJ* 1985; **290:** 1167–70.
3. Alvarez B, *et al.* Mazindol in long-term treatment of narcolepsy. *Lancet* 1991; **337:** 1293–4.
4. Allsopp MR, Zaiwalla Z. Narcolepsy. *Arch Dis Child* 1992; **67:** 302–6.

Preparations

USP 31: Mazindol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afilan; Dimagrir; Dimagrir Triac†; Fagolip Plus; Samonter; ***Braz.:*** Absten S; Fagolipo; ***Canad.:*** Sanorex†; ***Hong Kong:*** Qualizindol; ***Hung.:*** Teronac†; ***Indon.:*** Teronac; ***Mex.:*** Diestet; Ifa Lose; Ilezol; Liofindol†; Obendol; Sanorex†; Solucaps; ***Singapore:*** Teronac; ***Switz.:*** Teronac†.

Multi-ingredient: ***Arg.:*** Maxitratobes; ***Braz.:*** Dobesix†; Moderine.

Mefenorex Hydrochloride (USAN, pINNM) ⊗

Hidrocloruro de mefenorex; Méfénorex, Chlorhydrate de; Mefenorexi Hydrochloridum; Ro-4-5282. *N*-(3-Chloropropyl)-α-methylphenethylamine hydrochloride.

Мефенорекса Гидрохлорид

$C_{12}H_{18}ClN,HCl = 248.2.$

CAS — 17243-57-1 (mefenorex); 5586-87-8 (mefenorex hydrochloride).
ATC — A08AA09.
ATC Vet — QA08AA09.

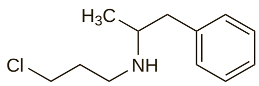

(mefenorex)

Profile

Mefenorex hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2153). It has been used as an anorectic in the treatment of obesity although stimulants are no longer recommended for this indication. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Mesocarb (rINN) ⊗

Mésocarb; Mesocarbo; Mesocarbum. 3-(α-Methylphenethyl)-*N*-(phenylcarbamoyl)syndnone imine.

Мезокарб

$C_{18}H_{18}N_4O_2 = 322.4.$

CAS — 34262-84-5.

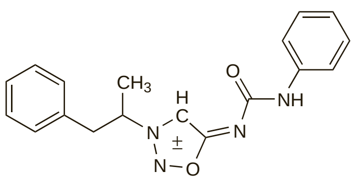

Profile

Mesocarb is reported to be a central stimulant.

Metamfetamine Hydrochloride (rINNM) ⊗

d-Deoxyephedrine Hydrochloride; *d*-Desoxyephedrine Hydrochloride; Hidrocloruro de metanfetamina; Métamfétamine, Chlorhydrate de; Metamfetamini Hydrochloridum; Methamphetamine Hydrochloride; Methamphetamini Hydrochloridum; Methylamphetamine Hydrochloride; Phenylmethylaminopropane Hydrochloride. (+)-*N*,α-Dimethylphenethylamine hydrochloride.

Метамфетамина Гидрохлорид

$C_{10}H_{15}N,HCl = 185.7.$

CAS — 537-46-2 (metamfetamine); 51-57-0 (metamfetamine hydrochloride).
ATC — N06BA03.
ATC Vet — QN06BA03.

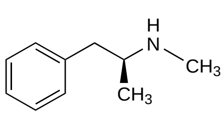

(metamfetamine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of metamfetamine:
20/20; 222; Agua; Albino Poo; Alffy; All tweakend long; Amp; Anny; Anything going on; Bache knock; Bache rock; Bag chasers; Baggers; Barney dope; Batak; Bathtub crank; Bato; Batu; Batu kilat; Batunas; Batuwhore; Beannies; Beegokes; Bianca; Bikerdope; Billy; Bitch; Biznack; Black; Black beauty; Blade; Blanco; Bling; Blizzard; Blue acid; Blue belly; Blue devils; Blue funk; Blue meth; Bomb; Bombita; Bombitas; Boo; Booger; Boorit-Cebuano; Boo-Yah!; Brian Ed; Brown; Buff stick; Bugger sugar; Buggs; Bump; Bumps; Buzzard dust; Caca; Cale Gerst; Candy; Cankinstien; Cartwheels; CC; ChaChaCha; Chach; Chalk; Chalk dust; Champagne; Chank; Cheebah; Cheese; Chicken; Chicken feed; Chicken flippin; Chikin; Chimichanga; Chingadera; Chittle; Chizel; Chiznad; Choad; Chris; Chrissy; Christal; Christina; Christine; Christmas tree; Christy; Cinnamon; Clavo; Clear; Coco; Coffee; Colorado Rockies; Cookies; CR; Crack Whore; Crank; Cranster Gansters; Cri, cri; Criddle; Criddy; Cringe; Crink; Crip; Cris; Crisco; Crissie; Crissy; Cristina; Cristy; Critty; Crizzy; Croak; Crossles; Crothch dope; Crow; Crunk; Crypto; Crystal; Crystal glass; Crystal meth; Crystal methadrine; Crystalight; Crystals; Cube; D; Debbie; Desocsins; Desogtion; Devil dust; Devils dandruff; Devils drug; Dingles; Dirt; Dirty; Dizzy D; D-Monic; Do da; Doody; Doo-my-lau; Dope; Drano; Dummy dust; Dyno; El Gato Diablo; Epimethrine; Epod; Eraser dust; Ethyl-M; Evil yellow; Fast; Fatch; Fedrin; Fil-layed; Fizz whizz; Fizz Wizz; Flash; Fluff; Future; G; Gackle-a Fackle-a; Gab; Gak; Gas; Gear; Geek; Geep; Geeter; Gemini; Get geared up; Getgo; Glass; Go; Go-ey; Go Fast; Go-fast; Go-go; Go-go juice; Gonzales; Goop; Go Pills; Goose-Egg; Got anything; Grads; Granulated orange; Grit; Gumption; Gyp; Haiwaiian salt; Hank; Hanyak; Hard Crystal; Hawaiis finest; High speed chicken feed; Highthen; Hillbilly crack; Hippy crack; Hironpon; Hiropon; Holy Smoke; Homework; Hoo; Horse mumpy; Hot Ice; Hydro; Hypes; Ibski; Ice; Ice cream; Icee; Ink; Ish; Izice; Jab; Jasmine; Jenny Crank; Jenny Crank Program; Jet fuel; Jetfuel; Jib; Jib nugget; Jibb Tech Warrier; Jibber jabbin; Jinga; Juddha; Juice; Junk; Kaksonjae; Kibble; Killer; KooLAID; Kryptonite; L.A.; LA Glass; L.A. glass; la glass; L.A. ice; LA Ice; Lamer; Laundry detergent; Leapers; Lemon drop; Life; Lily; Linda; Linga; Load of Laundry; Lost weekend; Love; Low; Lucille; M man; Magic; Maui-wowie; Meth; Meth amps; Meth monsters; Methaine; Methandfriend; Methandfriendsofmine; Methanfelony; Methatrim; Methedrine; Methlies Quik; Methmood; Method; Mexican crack; Minibennies; Motivation; Motorcycle crack; Moving on G; Nazi crank; Nazi dope; Nazi vitamens; Nazimeth; Ned; Newday; No doze; Nose candy; On a good one; Orange; OZs; P; Patsie; Peaking; Peanut butter; Peel dope; Pervatine; Pervitin; Phazers; Phets; Philopon; Pieta; Piko; Pink; Pink elephants; Pink hearts; Poison; Poof; Poop; Poop'd out; Poor man's cocaine; Poor man's coke; Poot; Pootananny; Poppers; Powder; Powder monkeys; Powder point; Project propellant; Puddle; Pump; Pure; Q'd; Quartz; Quick; Quill; Rachet jaw; Rails; Rank; Red; Red devils; Red phosphorus; Redneck cocaine; Redneck heroin; Richie Rich; Rip; Rippers; Rock; Rock crank; Rocket fuel; Rocky mountain high; Rosebud; Rudy; Rudy's; Rumdumb; Running Pizo; Sack; Sam's sniff; Sarahs; Satan dust; Scante; Scap; Schlep rock; Schmiz; Sciznac; Scooby snax; Scootie; Scud; Scwadge; Sean; Sha-bang; Shab; Shabs; Shabu; Shamers; Shards; Shit; Shiznac; Shiznack; Shiznastica; Shiznit; Shiznittlebang; Shiznitty; Shizzo; Shnizzie snort; Shwack; Skeech; Sketch; Ski; Skitz; Sky rocks; Sliggers; Smiley smile; Smurf dope; Smzl; Snaps; Sniff; Snow; Soap; Soap dope; Space food; Spaceman; Spackle; Spagack; Sparacked; Sparked; Sparkle; Speckled birds; Speed; Speed racer; Spin, spin, spin; Spinack; Spindarella; Spinney Boo; Spinning; Spishak; Splash; Spook; Spoosh; Sprack; Sprizzlefracked; Sprung; Spun Ducky Woo; Squawk; Stallar; Sto-Pid; Stove top; Styels; Sugar; Suger; Super ice; Sweetness; Swerve; Syabu; Ta'doww; Talkie; Tanner; Tasmanian Devil; T.D.; Teena; Tenner; Terry; Texas Tea; The New Prozac; The White House; Tic; Tical; Tick tick; Tik; Tina; Tink Dust; Tish; Tobats; Tootie; Toots; Torqued; Trash; Trippin Trip; Tubbytoast; Tuk; Tuk-tuk; Tutu; Twack; Twacked out; Tweak; Tweedle Doo; Tweek; Tweezwasabi; Twiz; Twizacked; Ugly Dust; Upside-down b; Uppers; Vanilla Pheromones; Wake; Wash; Water; Way; We We We; Wet; Whacked; White; White bitch; White Cross; White Crosses; White Crunch; White ink; White junk; White lady; White pony; Whiz; Whizz; Who-Ha; Wigg; Work; Working man's cocaine; Xaing; YAMA; Ya Ba; Yaaba; Yaba; Yammer Bammer; Yank; Yankee; Yay; Yead Out; Yellow bam; Yellow barn; Yellow jackets; Yellow powder; Zingin; Zip; Zoiks; Zoom.

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Methamphetamine Hydrochloride). White, odourless or practically odourless, crystals or crystalline powder. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in ether. Its solutions in water have a pH of about 6. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153.

Metamfetamine is subject to extensive abuse.

Abuse. Pulmonary oedema,[1,2] cardiomyopathy,[2,3] and choreoathetosis and rhabdomyolysis[4] have occurred after smoking of metamfetamine crystals. It is also abused orally and intravenously, and has been associated with fatalities.[5] Dental problems such as rampant caries and tooth wear and fracture, colloquially termed "meth mouth", have been reported with long-term abuse.[6,7] A marked increase in prevalence of abuse in recent years, particularly in the USA, has led to increased research into the consequences of such abuse and methods for management.[8-11]

A study of former users suggests that metamfetamine abuse may cause long-term neuronal damage.[12]

1. Nestor TA, *et al.* Acute pulmonary oedema caused by crystalline methamphetamine. *Lancet* 1989; **ii:** 1277–8.
2. Hong R, *et al.* Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265:** 1152–4.
3. Yeo K-K, *et al.* The association of methamphetamine use and cardiomyopathy in young patients. *Am J Med* 2007; **120:** 165–71.
4. Sperling LS, Horowitz JL. Methamphetamine-induced choreoathetosis and rhabdomyolysis. *Ann Intern Med* 1994; **121:** 986.
5. Albertson TE, *et al.* Methamphetamine and the expanding complications of amphetamines. *West J Med* 1999; **170:** 214–19.
6. Curtis EK. Meth mouth: a review of methamphetamine abuse and its oral manifestations. *Gen Dent* 2006; **54:** 125–9.
7. Donaldson M, Goodchild JH. Oral health of the methamphetamine abuser. *Am J Health-Syst Pharm* 2006; **63:** 2078–82. Correction. *ibid.*; 2180.
8. Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. *J Addict Dis* 2002; **21:** 21–34.
9. Rawson RA, *et al.* Treatment of methamphetamine use disorders: an update. *J Subst Abuse Treat* 2002; **23:** 145–50.
10. Cretzmeyer M, *et al.* Treatment of methamphetamine abuse: research findings and clinical directions. *J Subst Abuse Treat* 2003; **24:** 267–77.
11. Lineberry TW, Bostwick JM. Methamphetamine abuse: a perfect storm of complications. *Mayo Clin Proc* 2006; **81:** 77–84.
12. Ernst T, *et al.* Evidence for long-term neurotoxicity associated with methamphetamine abuse: a H MRS study. *Neurology* 2000; **54:** 1344–9.

Porphyria. Metamfetamine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Dexamfetamine Sulfate, p.2153.

Pharmacokinetics

Like most amfetamines (see Dexamfetamine Sulfate, p.2154) metamfetamine is readily absorbed from the gastrointestinal tract and is distributed into most body tissues. It is partially metabolised in the liver and excreted in the urine.

◊ References.

1. Shappell SA, *et al.* Chronopharmacokinetics and chronopharmacodynamics of dextromethamphetamine in man. *J Clin Pharmacol* 1996; **36:** 1051–63.
2. Harris DS, *et al.* The bioavailability of intranasal and smoked methamphetamine. *Clin Pharmacol Ther* 2003; **74:** 475–86.

Uses and Administration

Metamfetamine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p.2154).

It has been given orally in the treatment of attention deficit hyperactivity disorder in children aged 6 years and over, although dexamfetamine and methylphenidate are the main stimulants used (p.2148). Initial doses are 5 mg once or twice daily, increased if necessary by 5 mg at weekly intervals to the optimum effective dose, usually 20 to 25 mg daily given in 2 divided doses.

Metamfetamine hydrochloride has also been used as an anorectic in the management of obesity (p.2149), although amfetamines are no longer recommended for this indication. A dose of 5 mg before each meal has been given orally. Treatment should be for no longer than a few weeks.

Metamfetamine hydrochloride has also been used parenterally as a pressor agent.

The laevorotatory form, levmetamfetamine (p.1564) is used as a nasal decongestant.

Preparations

USP 31: Methamphetamine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Cidrin; Escancil†; ***USA:*** Desoxyn.

Methcathinone ⊗

Ephedrone; Methylcathinone; Monomethylpropion. 2-(Methylamino)-1-phenyl-1-propan-1-one.

$C_{10}H_{13}NO = 163.2.$

CAS — 5650-44-2.

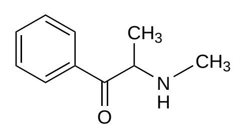

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methcathinone:
Bathtub speed; Cadillac express; Cat; Catt; Cosmos; Crank; Gagers; Gaggers; Go fast; Go-fast; Goob; Jee cocktail; Jeff; Khat; Mulk; Mulka; Qat; Slick superspeed; Sniff; Somali; Somali tea; Speed; Star; Stat; The C; Tweak; Tweek; Tweeker; Wild cat; Wonder star.

Profile

Methcathinone, a methyl derivative of cathinone (p.2152), produces CNS stimulant effects similar to those of the amfetamines (see Dexamfetamine, p.2153) and is subject to abuse.

◊ References.

1. Belhadj-Tahar H, Sadeg N. Methcathinone: a new postindustrial drug. *Forensic Sci Int* 2005; **153:** 99–101.

Methylenedioxymethamfetamine ⊗

MDMA; Methylenedioxymethamphetamine; 3,4-Methylenedioxymethamphetamine; Metilendioximetanfetamina. *N*,α-Dimethyl-1,3-benzodioxole-5-ethanamine.

$C_{11}H_{15}NO_2$ = 193.2.

CAS — 42542-10-9.

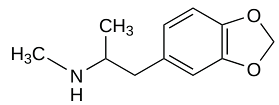

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methylenedioxymethamfetamine:

007s; 69s; Adam; Adam MTX; Anastasia; Apples; Baby slits; Bacalao; Batmans; B-bombs; Bean; Beans; Bens; Benzedrine; Bermuda triangles; Bibs; Bicho; Bickies; Bikkies; Biphetamine; Biscuits; Blue kisses; Blue lips; Blue nile; Booty juice; Bomber; Brownies; Burgers; Candies; Candy; Care bears; Cat in the hats; Charity; Chocolate chips; Chrystal methadrine; Clarity; Cloud nine; Clovers; Cowies; Cristal; Crowns; Dancing Shoes; Dead road; Debs; Decadence; Deccadence; Dennis the Menaces; Dex; Dexedrine; Diamonds; Diamond Whites; Disco biscuit; Disco biscuits; Doctor; Dollars; Dolls; Dolphins; Doobies; Dove; Doves; Drivers; E; EA1475; Eazy; Eazy E; E-ball; Ebeneezer; E-bomb; E-bombs; Eccies; Ecstacy; Ecstasy; Ecstasy Tablets; Eddie Bo; Egg Rolls; Egyptians; Ekies; Elaine; Elephants; Em; Empathy; Essence; Eve; Ex; Exiticity; Extasy; Fantasia; Fantasy; Fastin; Fizzle; Flipper; Flipping; Four leaf clover; Fuckstasy; Gaggler; Gary Abletts; Garys; Go; Googs; Green triangles; Greenies; Grey biscuits; Gum; Gurners; Gurns; GWM; Hamburger; Hamburgers; Happy drug; Happy pill; Herbal bliss; Hug drug; Hug-Drug; Huggers; Hydro; Hype; Iboga; Ice; Igloo; Illies; Jack and jills; Jellies; Jerry Garcias; Jiggas; Jills; Junnov; Khat; Kiks; Kleenex; Letter biscuits; Light meth; Lollies; Long lasting lollies; Louie Vuitton; Love-Bug; Love doctor; Love Doves; Love drug; Love drug of the '80s; Love drug of the '90s; Love Medicine; Love pill; Love potion #9; Lovers' special; Lover's speed; Lucky charmz; "M"; M25; Madman; Malcolm; Mandy; MAO; MDM; MDMA; Mercedes; Meth amps; Methedrine; Mini beans; Mitsibushis; Mitsies; Mitsu's; Mitsubishi; Mitsubishis; M&M; M&Ms; Mellow drug of America; Molly; Mollys; Monoamine oxidase; Morning shot; New Yorkers; Nineteen; Number 9; Orange bandits; Orbit; Pasti; Pillage; Pills; Pilules d'Amour; Pingers; Pink Calis; Pink panthers; Pink studs; Playboy bunnies; Playboys; Pollutants; Pressies; Rave energy; Red devils; Rhubarb & Custards; Rib; Ritual spirit; Road Runner; Roca; Roker's Barnet; Rolexes; Roll; Rolling; Rolls Royce; Running; Scooby snacks; Scum; Shabu; Skates; Slammin'; Slamming; Slits; Slows; Smartees; Smurfs; Speed for lovers; Spivias; Stars; Strawberry shortcake; Supermans; Swadger; Swans; Sweeties; Sweets; Tablets; Tabs; Tacha; Tachas; Tangos; Tens; The love drug; Thizz; Tom and Jerries; Triple crowns; Triple rolexes; Triple stacks; Tutus; Tweety Birds; Ultimate Xphoria; U.S.P.; Vitamin E; Vitamin X; Vowels; Wafers; Wee Boys; West Coast turnarounds; Wheels; Whiffledust; White diamonds; White dove; White doves; Whiz bombs; Wigits; Wingers; X; X-ing; X-Men; X-Men 2; X-Pills; XTC; Yips; Yokes; Yuppie psychedelic.

Profile

Methylenedioxymethamfetamine is a phenylethylamine compound structurally related to amfetamine and mescaline and is an analogue of tenamfetamine (p.2164). It is subject to abuse. Its toxicity is similar to that of dexamfetamine (see Abuse, below and under Dexamfetamine, p.2153) and may be treated similarly.

Abuse. Methylenedioxymethamfetamine may be ingested as tablets, capsules, or inhaled as a powder. It is often mixed with a combination of adulterants such as other amfetamines, caffeine, ephedrine, and pseudoephedrine.[1]

The toxicity associated with abuse of methylenedioxymethamfetamine has been the subject of a number of discussions.[2-7] Acute effects can be severe and symptoms have included cardiac arrhythmias, fulminant hyperthermia, convulsions, disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure; fatalities may occur. Repeated use may cause hepatic damage. Psychiatric effects reported include psychosis[8-10] and depression.[9-11] Damage to central serotonergic nerves has been implicated[8-12] and hence there is some concern regarding the long-term effects of methylenedioxymethamfetamine abuse.[13,14] Hyponatraemia, inappropriate antidiuretic hormone secretion, and cerebral oedema have also been reported;[15-20] the severity may be increased by excessive fluid intake that is frequently advocated to prevent dehydration and hyperthermia.[18-22] Urinary retention has also been reported.[23]

Concern has been expressed regarding abuse during *pregnancy*. Twelve congenital malformations, including 2 cases of congenital heart disease, have been noted among 78 liveborn infants whose mothers had taken methylenedioxymethamfetamine, often with other drugs of abuse, during their pregnancies.[24]

For reviews of the properties of other phenylethylamine compounds, see under Tenamfetamine, p.2164.

1. Smith KM, *et al.* Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health-Syst Pharm* 2002; **59:** 1067–76.
2. Henry JA. Ecstasy and the dance of death. *BMJ* 1992; **305:** 5–6.
3. Henry JA, *et al.* Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992; **340:** 384–7.
4. O'Connor B. Hazards associated with the recreational drug 'ecstasy'. *Br J Hosp Med* 1994; **52:** 507–14.
5. McCann UD, *et al.* Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'). *Drug Safety* 1996; **15:** 107–115.
6. Hall AP. Ecstasy and the anaesthetist. *Br J Anaesth* 1997; **79:** 697–8.
7. Schwartz RH, Miller NS. MDMA (ecstasy) and the rave: a review. *Pediatrics* 1997; **100:** 705–8.
8. McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). *BMJ* 1991; **302:** 697.
9. Winstock AR. Chronic paranoid psychosis after misuse of MDMA. *BMJ* 1991; **302**: 1150–1.
10. Schifano F. Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. *Lancet* 1991; **338:** 1335.
11. Benazzi F, Mazzoli M. Psychiatric illness associated with "ecstasy". *Lancet* 1991; **338:** 1520.
12. McCann UD, *et al.* Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352:** 1433–7.
13. Green AR, Goodwin GM. Ecstasy and neurodegeneration. *BMJ* 1996; **312:** 1493–4.
14. Bolla KI, *et al.* Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 1998; **51:** 1532–7.
15. Maxwell DL, *et al.* Hyponatraemia and catatonic stupor after taking "ecstasy". *BMJ* 1993; **307:** 1399.
16. Kessel B. Hyponatraemia after ingestion of "ecstasy". *BMJ* 1994; **308:** 414.
17. Satchell SC, Connaughton M. Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion. *Br J Hosp Med* 1994; **51:** 495.
18. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after ecstasy (3,4-MDMA). *Lancet* 1996; **347:** 1052.
19. Matthai SM, *et al.* Cerebral oedema after ingestion of MDMA (ecstasy) and unrestricted intake of water. *BMJ* 1996; **312:** 1359.
20. Parr MJA, *et al.* Hyponatraemia and death after ecstasy ingestion. *Med J Aust* 1997; **166:** 136–7.
21. Cook TM. Cerebral oedema after MDMA ('ecstasy') and unrestricted water intake. *BMJ* 1996; **313:** 689.
22. Henry JA, *et al.* Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 1998; **351:** 1784.
23. Bryden AA, *et al.* Urinary retention with misuse of 'ecstasy'. *BMJ* 1995; **310:** 504.
24. McElhatton PR, *et al.* Congenital anomalies after prenatal ecstasy exposure. *Lancet* 1999; **354:** 1441–2.

Interactions. A psychotic reaction has been reported in a patient who took methylenedioxymethamfetamine while receiving therapy with *citalopram*.[1]

A patient receiving *phenelzine* and lithium therapy experienced a serotonin syndrome (p.416) after ingesting methylenedioxymethamfetamine.[2] Symptoms included markedly increased muscle tension, tremulousness, abnormal posturing, limited pain response, tachycardia, hypertension, hyperthermia, increased white blood cell count, increased creatine phosphokinase concentration, respiratory acidosis, metabolic acidosis, delirium, and agitation. Within 15 minutes of methylenedioxymethamfetamine ingestion the patient was comatose; within 5 hours the patient was alert with a normal muscle tone. An interaction between phenelzine and methylenedioxymethamfetamine was suggested as the cause of the serotonin syndrome.

A fatal serotonergic reaction to methylenedioxymethamfetamine possibly due to an interaction with *ritonavir* has been described.[3] A prolonged and exaggerated effect from a small dose of methylenedioxymethamfetamine has been reported[4] in another patient also receiving ritonavir. Although this patient was also receiving saquinavir, the authors postulated that the mechanism may be ritonavir-induced inhibition of the cytochrome P450 isoenzyme CYP2D6.

1. Lauerma H, *et al.* Interaction of serotonin reuptake inhibitor and 3,4-methylenedioxymethamphetamine? *Biol Psychiatry* 1998; **43:** 923–8.
2. Kaskey GB. Possible interaction between an MAOI and "ecstasy". *Am J Psychiatry* 1992; **149:** 411–12.
3. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998; **352:** 1751–2.
4. Harrington RD, *et al.* Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and γ-hydroxybutyrate. *Arch Intern Med* 1999; **159:** 2221–4.

Methylphenidate Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metilfenidato; Methyl Phenidate Hydrochloride; Méthylphénidate, chlorhydrate de; Methylphenidati hydrochloridum; Metilfenidat Hidroklorür. Methyl α-phenyl-2-piperidylacetate hydrochloride.

Метилфенидата Гидрохлорид

$C_{14}H_{19}NO_2$,HCl = 269.8.

CAS — 113-45-1 (methylphenidate); 298-59-9 (methylphenidate hydrochloride).

ATC — N06BA04.

ATC Vet — QN06BA04.

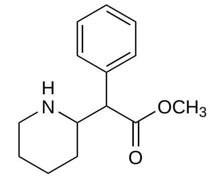

(methylphenidate)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of methylphenidate: Rities; Vitamin R; West coast.

Pharmacopoeias. In *Chin.*, *Swiss*, and *US.*

USP 31 (Methylphenidate Hydrochloride). A white, odourless, fine crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Solutions are acid to litmus.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153. Hypersensitivity reactions have been reported. Skin reactions have included exfoliative dermatitis and erythema multiforme. Purpura, thrombocytopenia, and leucopenia have occurred. Blood counts should be monitored periodically during prolonged therapy.

◊ References.

1. Ahmann PA, *et al.* Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993; **91:** 1101–6.
2. Efron D, *et al.* Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; **100:** 662–6.
3. Rappley MD. Safety issues in the use of methylphenidate: an American perspective. *Drug Safety* 1997; **17:** 143–8.
4. Klein-Schwartz W. Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 2002; **14:** 219–23.
5. Leonard BE, *et al.* Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol* 2004; **19:** 151–80.

Abuse. Reports of adverse effects after the abuse of methylphenidate by injecting solutions of crushed tablets.[1-3] Intravenous abuse of methylphenidate with pentazocine has also been reported.[4,5] In addition, there are also reports of intranasal methylphenidate abuse,[6-8] including fatalities.[8]

See also Effects on the Liver, below.

1. Wolf J, *et al.* Eosinophilic syndrome with methylphenidate abuse. *Ann Intern Med* 1978; **89:** 224–5.
2. Gunby P. Methylphenidate abuse produces retinopathy. *JAMA* 1979; **241:** 546.
3. Parran TV, Jasinski DR. Intravenous methylphenidate abuse: prototype for prescription drug abuse. *Arch Intern Med* 1991; **151:** 781–3.
4. Debooy VD, *et al.* Intravenous pentazocine and methylphenidate abuse during pregnancy: maternal lifestyle and infant outcome. *Am J Dis Child* 1993; **147:** 1062–5.
5. Carter HS, Watson WA. IV pentazocine/methylphenidate abuse—the clinical toxicity of another Ts and blues combination. *J Toxicol Clin Toxicol* 1994; **32:** 541–7.
6. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991; **30:** 773–5.
7. Garland EJ. Intranasal abuse of prescribed methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1998; **37:** 573–4.
8. Massello W, Carpenter DA. A fatality due to the intranasal abuse of methylphenidate (Ritalin). *J Forensic Sci* 1999; **44:** 220–1.

Breast feeding. No adverse effects were noted[1] in a 6-month-old breast-fed infant whose 26-year-old mother had been taking methylphenidate 40 mg twice daily for about 5 weeks. Despite the relatively high milk-to-plasma ratio of 2.7 the relative infant dose was low, at 0.2% of the maternal dose. Nonetheless the authors recommended caution when giving methylphenidate to breast-feeding mothers. Licensed product information also recommends that methylphenidate should be used with caution or avoided during breast feeding.

1. Hackett LP, *et al.* Methylphenidate and breast-feeding. *Ann Pharmacother* 2006; **40:** 1890–1.

Effects on the cardiovascular system. For mention of the adverse cardiovascular effects of stimulants, see under Dexamfetamine Sulfate, p.2153.

Effects on growth. Concern has been expressed about the effects of central stimulants such as methylphenidate on growth rate when used to treat hyperactivity in children. One study showed that methylphenidate produced decreases in weight percentiles after 1 year of therapy and progressive decrement in height percentiles that became significant after 2 years of use.[1] However, another suggested that moderate doses might have a lower risk for long-term height suppression than dexamfetamine.[2] There has also been a study which showed that, even when methylphenidate had an adverse effect on growth rate during active treatment, final height was not compromised and that a compensatory rebound of growth appeared to occur on stopping stimulant treatment.[3]

See also under Dexamfetamine Sulfate, p.2153.

1. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry* 1983; **40:** 317–21.

2. Greenhill LL, *et al.* Prolactin, growth hormone and growth responses in boys with attention deficit disorder and hyperactivity treated with methylphenidate. *J Am Acad Child Psychiatry* 1984; **23:** 58–67.
3. Klein RG, Mannuzza S. Hyperactive boys almost grown up III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; **45:** 1131–4.

Effects on the liver. Hepatotoxicity with raised liver enzyme values in a 67-year-old woman was associated with the use of methylphenidate hydrochloride 30 mg daily by mouth.[1] Methylphenidate-induced hepatocellular injury was reported in a 19-year-old woman who developed jaundice, fever, and malaise after intravenous abuse of methylphenidate hydrochloride tablets.[2]

1. Goodman CR. Hepatotoxicity due to methylphenidate hydrochloride. *N Y State J Med* 1972; **72:** 2339–40.
2. Mehta H, *et al.* Hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. *J Clin Gastroenterol* 1984; **6:** 149–51.

Effects on the skin. A fixed drug eruption of the scrotum has been reported in 2 children treated with methylphenidate for attention deficit disorder.[1]

1. Cohen HA, *et al.* Fixed drug eruption of the scrotum due to methylphenidate. *Ann Pharmacother* 1992; **26:** 1378–9.

Tourette's syndrome. For a discussion on whether central stimulants provoke Tourette's syndrome, see Dexamfetamine Sulfate, p.2153.

Interactions

As for Dexamfetamine Sulfate, p.2153.

Anticoagulants. For the effect of methylphenidate on *ethyl biscoumacetate*, see Central Stimulants under the Interactions of Warfarin, p.1430.

Antidepressants. For the effect of methylphenidate on *tricyclic antidepressants*, see under Amitriptyline, p.379.

Antiepileptics. Methylphenidate blood concentrations decreased, and symptoms of attention deficit hyperactivity disorder worsened, in a 13-year-old girl after starting therapy with *carbamazepine*.[1]

For the effect of methylphenidate on antiepileptics, see under Phenytoin, p.500.

1. Schaller JL, *et al.* Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* 1999; **38:** 112–13.

Pharmacokinetics

Methylphenidate is readily absorbed from the gastrointestinal tract. The presence of food in the stomach accelerates the rate of absorption but not the total amount absorbed. Peak plasma concentrations are reached about 2 hours after oral doses; methylphenidate undergoes extensive first-pass metabolism. Protein binding is low. It is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged methylphenidate. The major metabolite is ritalinic acid (2-phenyl-2-piperidyl acetic acid). The plasma elimination half-life is about 2 hours. Methylphenidate is distributed into breast milk.

◊ References.

1. Aoyama T, *et al.* Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44;** 79–84.
2. Aoyama T, *et al.* Pharmacokinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia. *Clin Pharmacol Ther* 1994; **55:** 270–6.
3. Shader RI, *et al.* Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999; **39:** 775–785.
4. Kimko HC, *et al.* Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999; **37:** 457–70.
5. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *J Clin Pharmacol* 2000; **40:** 379–88.
6. Teo SK, *et al.* A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects. *J Clin Pharmacol* 2004; **44:** 173–8.
7. Quinn D, *et al.* Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007; **47:** 760–6.

Uses and Administration

Methylphenidate hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions and uses similar to those of dexamfetamine (p.2154). It is used in the treatment of narcolepsy (p.2148) and as an adjunct to psychological, educational, and social measures in the treatment of hyperactivity disorders in children.

In the treatment of **narcolepsy** the usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In **hyperactivity disorders** in children aged 6 years and over, the usual initial dose is 5 mg once or twice daily by mouth, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses. Methylphenidate may be given before breakfast and lunch. A later dose may be considered if the effect wears off in the evening causing rebound hyperactivity.

Methylphenidate hydrochloride is also available as modified-release preparations for the treatment of hyperactivity disorders. Some modified-release preparations also contain immediate-release methylphenidate within the formulation. Doses of modified-release preparations may vary according to the brand chosen. Recommended doses for one brand of modified-release tablets (*Concerta*: *Janssen-Cilag, UK*; *McNeil, USA*) are as follows:

- children and adolescents aged 6 to 17 years and not currently taking conventional methylphenidate should be started on 18 mg once daily in the morning
- the dose may then be increased at weekly intervals to a maximum of 54 mg once daily; the USA permits a maximum of 72 mg once daily in those aged 13 to 17 years
- the dose in patients already taking conventional methylphenidate should be based on their current dose although the initial dose should not exceed 54 mg once daily

Transdermal patches delivering amounts of methylphenidate ranging from 1.1 to 3.3 mg/hour are available for once-daily application in the treatment of hyperactivity disorders in children aged 6 to 12 years. Patients should be started on the lowest strength patch regardless of any previous methylphenidate use; thereafter, doses should be individually titrated for each patient according to response and increased at weekly intervals if necessary to a maximum of 3.3 mg/hour (at week 4). Patches should be applied to the hip area 2 hours before an effect is needed and removed after a maximum of 9 hours later.

Methylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond, to assess the patient's condition. Treatment is not usually continued beyond puberty, however, in some patients drug therapy may be required into adulthood. In such cases doses are similar to those used in the treatment of narcolepsy.

A single isomer form of methylphenidate, dexmethylphenidate (p.2154) is also used for hyperactivity disorders.

◊ References.

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc* 2000; **75:** 711–21.

Depression. Stimulants are no longer recommended as sole treatment for depression (p.373), although they have been tried in augmenting the effect of standard antidepressants such as the SSRIs[1] in patients with refractory depressive disorders.

1. Stoll AL, *et al.* Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996; **57:** 72–6.

Disturbed behaviour. Disturbed behaviour can have a number of causes and is usually treated with an antipsychotic or benzodiazepine (see p.954). A review[1] of the published clinical trials between 1966 and June 2004 found that although methylphenidate was likely to improve memory, attention, concentration, and mental processing in patients with traumatic brain injury, its effect on behaviour remains to be determined; the most commonly used dosage was 300 micrograms/kg twice daily.

1. Siddall OM. Use of methylphenidate in traumatic brain injury. *Ann Pharmacother* 2005; **39:** 1309–13.

Hyperactivity. Methylphenidate is one of the main drugs used in hyperactivity, including attention deficit hyperactivity disorder (ADHD) (p.2148).

Small studies have indicated that different aspects of attention deficit disorders in children might respond to different doses of methylphenidate.[1-4] In addition to the morning and noon doses commonly used in hyperactivity disorders, studies[5,6] have shown improved clinical outcome with little adverse effect on sleep patterns if a third late afternoon dose is given.

Modified-release preparations with a slow onset of action have been developed to overcome the short duration of action of methylphenidate although they may be less effective than immediate-release preparations. A study,[7] using a regimen to simulate the prolonged steady plasma concentration profile obtained with the slow-onset, modified-release preparations, has suggested that unlike twice-daily treatment acute tolerance might develop with the use of modified-release preparations. However, a newer modified-release preparation has been reported to be as effective as an immediate-release preparation in short-term studies.[8,9] Transdermal patches containing methylphenidate released over 9 hours are available in the USA.[10]

UK guidelines for the use of methylphenidate in children and adolescents with ADHD are available.[11]

1. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science* 1977; **198:** 1274–6.
2. Tannock R, *et al.* Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. *Pediatrics* 1989; **84:** 648–57.
3. Sebrechts MM, *et al.* Components of attention, methylphenidate dosage, and blood levels in children with attention deficit disorder. *Pediatrics* 1986; **77:** 222–8.
4. Barkley RA, *et al.* Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991; **87:** 519–31.
5. Kent JD, *et al.* Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorders. *Pediatrics* 1995; **96:** 320–5.
6. Stein MA, *et al.* Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 1996; **98:** 748–56.
7. Swanson J, *et al.* Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999; **66:** 295–305.
8. Pelham WE, *et al.* Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Abstract: *Pediatrics* 2001; **107:** 1417. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/6/e105 (accessed 15/04/04)
9. Wolraich ML, *et al.* Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001; **108:** 883–92.
10. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. *Drugs* 2006; **66:** 1117–26.
11. NICE. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: review of Technology Appraisal 13 (Technology Appraisal 98, issued March 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA098guidance.pdf (accessed 11/08/08)

Preparations

USP 31: Methylphenidate Hydrochloride Extended-release Tablets; Methylphenidate Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Concerta; Methylin; Ritalina; Rubifen; ***Austral.:*** Attenta; Concerta; Lorentin†; Ritalin; ***Austria:*** Concerta; Ritalin; ***Belg.:*** Concerta; Rilatine; ***Braz.:*** Concerta; Ritalina; ***Canad.:*** Concerta; Riphenidate†; Ritalin; ***Chile:*** Aradix; Concerta; Elem†; Nebapul; Ritalin; Ritrocel; ***Cz.:*** Ritalin; ***Denm.:*** Equasym; Motiron; Ritalin; ***Fin.:*** Concerta; ***Fr.:*** Concerta; Ritaline; ***Ger.:*** Concerta; Equasym; Medikinet; Ritalin; ***Gr.:*** Concerta; Ritaline; ***Hong Kong:*** Concerta; Ritalin; ***Hung.:*** Ritalin; ***Indon.:*** Concerta; Ritalin; ***Irl.:*** Concerta; Equasym; Ritalin; ***Israel:*** Concerta; Metadate; Ritalin; ***Malaysia:*** Concerta; Ritalin; Rubifen; ***Mex.:*** Concerta; Ritalin; Tradea; ***Neth.:*** Concerta; Equasym; Ritalin; Rubifen†; Tifinidat; ***Norw.:*** Concerta; Equasym; Ritalin; ***NZ:*** Concerta; Ritalin; Rubifen; ***Philipp.:*** Concerta; ***Pol.:*** Concerta; ***Port.:*** Concerta; Ritalina; Rubifen; ***S.Afr.:*** Adaphen; Concerta; Ritalin; Ritaphen†; ***Singapore:*** Concerta; Ritalin; Rubifen; ***Spain:*** Concerta; Rubifen; ***Swed.:*** Concerta; Ritalin; ***Switz.:*** Concerta; Ritaline; ***Thai.:*** Concerta; Rubifen†; ***Turk.:*** Concerta; Ritalin; ***UK:*** Concerta; Equasym; Medikinet; Ritalin; Tranquilyn†; ***USA:*** Concerta; Daytrana; Metadate; Methylin; Ritalin; ***Venez.:*** Concerta; Ritalin.

Modafinil *(BAN, USAN, rINN)* ⊗

CEP-1538; CRL-40476; Modafinilo; Modafinilum. 2-[(Diphenylmethyl)sulfinyl]acetamide.

Модафинил

$C_{15}H_{15}NO_2S$ = 273.4.
CAS — 68693-11-8.
ATC — N06BA07.
ATC Vet — QN06BA07.

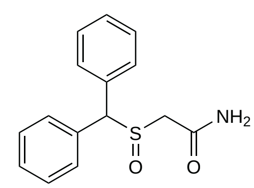

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Modafinil). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble or practically insoluble in water; sparingly soluble in methyl alcohol; slightly soluble in alcohol.

USP 31 (Modafinil). A white, odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

The most commonly reported adverse effect of modafinil, affecting about 21% of patients, is headache, which is usually mild or moderate, dose-dependent, and disappears within a few days. Other adverse effects may be a result of CNS stimulation and effects such as nervousness, insomnia, agitation, confusion, personality disorder, tremor, and anxiety have been noted. There may also be gastrointestinal disturbances, including nausea and abdominal pain, dry mouth, diarrhoea, dyspepsia, and constipation, dizziness, and anorexia. Cardiovascular effects such as hypertension, palpitations, and tachycardia have been reported.

Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, have been reported (see also Effects on the Skin, below). Benign pruritic rashes have also occurred and since it is not possible to predict which skin rashes will become serious, modafinil should be stopped at the first sign of rash unless it is clearly not drug-related. Other hypersensitivity reactions such as angioedema have also been reported rarely.

Psychiatric symptoms including psychosis, depression, hallucinations, suicidal ideation, and mania have been reported. Abnormal liver function tests including dose-related increases in alkaline phosphatase, and dyskinesia have been observed.

Modafinil is contra-indicated in patients with uncontrolled, moderate to severe hypertension or cardiac arrhythmias. It is not recommended in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, or other signs of mitral valve prolapse. Modafinil should be given with caution to those with a history of psychosis, depression, or mania.

As with other stimulants, there is the possibility of dependence with long-term use. Modafinil has been misused as a so-called 'lifestyle drug' to promote alertness and wakefulness in otherwise healthy subjects.

Effects on the skin. The FDA[1] reported that it had received 6 cases of severe cutaneous adverse effects associated with modafinil from its initial marketing in December 1998 to January 2007; of these, 5 required hospitalisation. The cutaneous effects, which included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, were reported in adults and children although use in patients under 16 years of age is unlicensed. The median time to onset was 17.5 days with a range of 5 days to 5 weeks.

1. Modafinil (marketed as Provigil): serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 5–7. Available at: http://www.fda.gov/cder/dsn/2007_fall/2007_fall.pdf (accessed 20/05/08)

Interactions

Modafinil is partially metabolised by the cytochrome P450 isoenzymes. In addition, it also has enzyme-inducing and -inhibiting activity. Use with other drugs that inhibit, induce, or act as a substrate to these isoenzymes such as oral contraceptives and antiepileptics may result in changes in plasma concentration of modafinil and/or the other drug.

Pharmacokinetics

Modafinil is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring after 2 to 4 hours. Plasma protein binding is about 60%, mainly to albumin. Modafinil is metabolised in the liver, partially by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5; two major metabolites have been identified: acid modafinil and modafinil sulfone, both of which are inactive. Excretion is mainly through the kidneys with less than 10% of the dose being eliminated unchanged. The elimination half-life after multiple doses is 15 hours.

◊ References.

1. Wong YN, *et al.* A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999; **39:** 30–40.
2. Wong YN, *et al.* Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol* 1999; **39:** 281–8.

Uses and Administration

Modafinil is a central stimulant chemically related to adrafinil (p.2149). It is used in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p.2148), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, modafinil is given orally in a dose of 200 to 400 mg daily, in two divided doses, in the morning and at midday, or as a single dose in the morning. For the treatment of shift-work sleep disorder, the daily dose is 200 mg taken as a single dose 1 hour before starting work. An initial dose of 100 mg daily should be used in the elderly and adjusted as necessary. For doses in hepatic and renal impairment, see below.

Modafinil is usually given as a racemic mixture but preparations containing only the *R*-isomer, armodafinil, are also available, see Armodafinil, p.2150.

Modafinil has also been investigated for the treatment of fatigue associated with multiple sclerosis and for the treatment of hyperactivity disorders.

◊ References.

1. Broughton RJ, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; **49:** 444–51.
2. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 1998; **43:** 88–97.
3. McClellan KJ, Spencer CM. Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. *CNS Drugs* 1998; **9:** 311–24.
4. Fry JM. Treatment modalities for narcolepsy. *Neurology* 1998; **50:** S43–S48.
5. Anonymous. Modafinil for narcolepsy. *Med Lett Drugs Ther* 1999; **41:** 30–1.
6. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; **54:** 1166–75.
7. Kingshott RN, *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; **163:** 918–23.
8. Czeisler CA, *et al.* The US Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005; **353:** 476–86. Correction. *ibid.*; 1078.
9. Gill M, *et al.* Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. *Acad Emerg Med* 2006; **13:** 158–65. Correction. *ibid.*; 477.
10. Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. *Expert Rev Neurother* 2006; **6:** 455–68.
11. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006; **67:** 554–66.
12. Lindsay SE, *et al.* Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother* 2006; **40:** 1829–33.

Administration in hepatic or renal impairment. The total oral dose of modafinil should be reduced to 100 to 200 mg daily in any patient with severe hepatic or renal impairment.

Preparations

USP 31: Modafinil Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Forcilin; Vigicer; ***Austral.:*** Modavigil; ***Austria:*** Modasomil; ***Belg.:*** Provigil; ***Canad.:*** Alertec; ***Chile:*** Mentix; Naxelan; Resotyl; ***Cz.:*** Vigil; ***Denm.:*** Modiodal; ***Fr.:*** Modiodal; ***Ger.:*** Vigil; ***Gr.:*** Modiodal; ***Irl.:*** Provigil; ***Israel:*** Provigil; ***Ital.:*** Provigil; ***Mex.:*** Modiodal; ***Neth.:*** Modiodal; ***Norw.:*** Modiodal; ***NZ:*** Modavigil; ***Pol.:*** Vigil; ***Port.:*** Modiodal; ***S.Afr.:*** Provigil; ***Spain:*** Modiodal; ***Swed.:*** Modiodal; ***Switz.:*** Modasomil; ***Turk.:*** Modiodal; ***UK:*** Provigil; ***USA:*** Provigil.

Nikethamide *(BAN, rINN)* ⊗

Cordiaminum; Nicetamid; Nicéthamide; Nicethamidum; Nicotinic Acid Diethylamide; Nicotinoyldiaethylamidum; Niketamid; Niketamidas; Niketamidi; Nikethamid; Nikethylamide; Niquetamida. *N,N*-Diethylnicotinamide; *N,N*-Diethylpyridine-3-carboxamide.

Никетамид

$C_{10}H_{14}N_2O$ = 178.2.
CAS — 59-26-7.
ATC — R07AB02.
ATC Vet — QR07AB02.

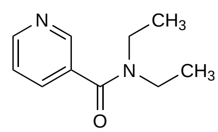

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Viet.*

Ph. Eur. 6.2 (Nikethamide). A colourless or slightly yellow oily liquid or crystalline mass. Miscible with water and with alcohol. A 25% solution in water has a pH of 6.0 to 7.8.

Profile

Nikethamide has actions similar to those of doxapram (p.2155). It was formerly used as a respiratory stimulant but has largely been abandoned because of toxicity. Nikethamide and its calcium thiocyanate salt have also been used in some countries as central stimulants and for hypotensive disorders.

Porphyria. Nikethamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

BP 2008: Nikethamide Injection.

Proprietary Preparations (details are given in Part 3)
Pol.: Cardiamidum.

Multi-ingredient: ***Fr.:*** Coramine Glucose; ***Ger.:*** Zellaforte N Plus†; ***Pol.:*** Cardiamid-Coffein; Glucardiamid; ***Switz.:*** Gly-Coramin.

Pemoline *(BAN, USAN, rINN)* ⊗

LA-956; NSC-25159; Pemoliini; Pemolin; Pemolina; Pémoline; Pemolinum; Phenoxazole; Phenylisohydantoin; Phenylpseudohydantoin. 2-Imino-5-phenyl-4-oxazolidinone.

Пемолин

$C_9H_8N_2O_2$ = 176.2.
CAS — 2152-34-3 (pemoline); 68942-31-4 (pemoline hydrochloride); 18968-99-5 (magnesium pemoline).
ATC — N06BA05.
ATC Vet — QN06BA05.

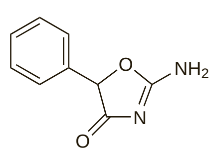

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153; however, the effects of over-stimulation and sympathomimetic activity are considered to be less with pemoline.

Reports of liver toxicity in patients taking pemoline (see Effects on the Liver, below) have led to its withdrawal in many countries including the UK and USA. Where available, it is contra-indicated in patients with liver disorders and there are stringent precautions to be observed with its use. Treatment should be initiated only in patients with normal baseline liver function tests and liver function should be monitored every 2 weeks. Pemoline should be stopped if serum alanine aminotransferase is increased to a clinically significant level or there is any increase greater than or equal to twice the upper limit of normal, or if any clinical signs or symptoms suggestive of liver failure develop. Pemoline should also be withdrawn from patients who have failed to show a substantial clinical response within 3 weeks of completing dose titration. There have also been rare or isolated reports of chorea, tics, mania, and neutropenia.

Abuse. Paranoid psychosis was observed in a 38-year-old man taking pemoline 75 to 225 mg daily.[1] His compulsive use of the drug, development of tolerance, depressive withdrawal syndrome, and inability to abstain indicated dependence and it was evident that the patient was addicted to pemoline.

Choreoathetosis and rhabdomyolysis developed in a patient following a marked increase in intake of pemoline.[2] Abnormal movements responded to diazepam.

1. Polchert SE, Morse RM. Pemoline abuse. *JAMA* 1985; **254:** 946–7.
2. Briscoe JG, *et al.* Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; **3:** 72–6.

Effects on growth. Results of a study in 24 hyperkinetic children suggested that growth suppression was a potential adverse effect of prolonged treatment with clinically effective doses of pemoline and that this effect might be dose-related.[1]

See also under Dexamfetamine Sulfate, p.2153.

1. Dickinson LC, *et al.* Impaired growth in hyperkinetic children receiving pemoline. *J Pediatr* 1979; **94:** 538–41.

Effects on the liver. Pemoline has been associated with hepatotoxicity.

Elevated concentrations of serum aspartate aminotransferase and serum alanine aminotransferase have been noted in 2% of children taking pemoline for hyperactivity; the effect was stated to be transient and reversible.[1]

However, more serious reactions have also occurred. Acute hepatitis[2] was associated with pemoline in a 10-year-old boy and the drug was believed to be the cause of fatal fulminant liver failure[3] in a 14-year-old boy and in 2 previously published cases. The UK CSM[4] subsequently became aware of 33 reports of serious hepatic reactions in the USA, including a total of 6 fatalities and the need for liver transplantation in 2 cases; this prompted the withdrawal of pemoline for the treatment of hyperactivity in the UK. Following further reports of liver failure resulting in transplantation or death, the FDA[5] similarly withdrew pemoline in the USA.

1. Anonymous. 'Hyperkinesis' can have many causes, symptoms. *JAMA* 1975; **232:** 1204–16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; **77:** 938.
3. Berkovitch M, *et al.* Pemoline-associated fulminant liver failure: testing the evidence for causation. *Clin Pharmacol Ther* 1995; **57:** 696–8.
4. CSM/MCA. Volital (pemoline) has been withdrawn. *Current Problems* 1997; **23:** 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 23/05/06)
5. FDA. Alert for healthcare professionals: pemoline tablets and chewable tablets (marketed as Cylert) (issued 24/10/05). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/pemolineHCP.pdf (accessed 24/04/06)

Effects on the prostate. Experience in one patient suggested that pemoline might adversely affect the prostate gland or interfere with tests for prostatic acid phosphatase used in the diagnosis of prostatic carcinoma.[1]

1. Lindau W, de Girolami E. Pemoline and the prostate. *Lancet* 1986; **i:** 738.

Interactions

Hypertensive crisis may possibly occur if pemoline is given with MAOIs. Reduced seizure threshold has been reported in epileptic patients taking pemoline and antiepileptics.

Pharmacokinetics

Pemoline is readily absorbed from the gastrointestinal tract. About 50% is bound to plasma proteins. It is metabolised in the liver and excreted in the urine as unchanged pemoline and metabolites.

◊ References.

1. Vermeulen NPE, *et al.* Pharmacokinetics of pemoline in plasma, saliva and urine following oral administration. *Br J Clin Pharmacol* 1979; **8:** 459–63.
2. Sallee F, *et al.* Oral pemoline kinetics in hyperactive children. *Clin Pharmacol Ther* 1985; **37:** 606–9.
3. Collier CP, *et al.* Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. *Clin Pharmacokinet* 1985; **10:** 269–78.

Uses and Administration

Pemoline is a central stimulant with actions similar to those of dexamfetamine (p.2154).

It has been used in the management of hyperactivity disorders in children (p.2148). In many countries pemoline was withdrawn from use after reports of serious hepatotoxicity.

Pemoline has been included in preparations also containing yohimbine hydrochloride and methyltestosterone that are claimed to combat failure of sexual desire and functioning in males and females; such preparations are not recommended.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tamilan†; ***Chile:*** Bimolin†; Ceractiv; Cylert; ***Ger.:*** Tradon†; ***Israel:*** Cylert; Nitan; ***USA:*** Cylert†; PemADD†; ***Venez.:*** Fenilona†.
Multi-ingredient: ***UK:*** Prowess.

Pentetrazol *(BAN, rINN)* ⊗

Corazol; Leptazol; Pentamethazol; 1,5-Pentamethylenetetrazole; Pentazol; Pentetratsoli; Pentétrazol; Pentetrazolum; Pentylenetetrazol. 6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine.

Пентетразол

$C_6H_{10}N_4$ = 138.2.
CAS — 54-95-5.
ATC — R07AB03.
ATC Vet — QR07AB03.

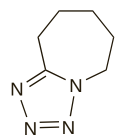

Pharmacopoeias. In *It.*

Profile

Pentetrazol is a central and respiratory stimulant similar to doxapram (p.2155). It has been used in respiratory depression and in multi-ingredient preparations intended for the treatment of respiratory-tract disorders including cough, cardiovascular disorders including hypotension, and for the treatment of pruritus. It has been given orally and by injection.

Porphyria. Pentetrazol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Braz.:*** Belacodid†; Revulsan†; Suprasten†; ***India:*** Cardiazol-Dicodid†; ***Ital.:*** Cardiazol-Paracodina; ***Port.:*** Broncodiazina.

Phendimetrazine Tartrate *(BANM, rINNM)* ⊗

Phendimetrazine Acid Tartrate; Phendimetrazine Bitartrate; Phendimétrazine, Tartrate de; Phendimetrazini Tartras; Tartrato de fendimetrazina. (+)-3,4-Dimethyl-2-phenylmorpholine hydrogen tartrate.

Фендиметразина Тартрат

$C_{12}H_{17}NO,C_4H_6O_6$ = 341.4.
CAS — 634-03-7 (phendimetrazine); 7635-51-0 (phendimetrazine hydrochloride); 50-58-8 (phendimetrazine tartrate).

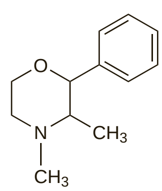

(phendimetrazine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phendimetrazine: Fringas; Prelo.

Pharmacopoeias. In *US.*

USP 31 (Phendimetrazine Tartrate). A white odourless crystalline powder. Freely soluble in water; sparingly soluble in warm alcohol; insoluble in acetone, in chloroform, in ether, and in benzene. pH of a 2.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153.

Pulmonary hypertension and valvular heart defects have been reported in patients receiving phendimetrazine with other anorectics; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride, p.2156. Phendimetrazine should not be used with other anorectics nor within a year of their use.

Interactions

Phendimetrazine is an indirect-acting sympathomimetic and may interact with other drugs similarly to dexamfetamine (p.2153).

Pharmacokinetics

Phendimetrazine tartrate is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as phenmetrazine and other metabolites.

Uses and Administration

Phendimetrazine tartrate is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2154). It has been used as an anorectic in the short-term treatment of obesity (p.2149), although stimulants are no longer recommended for this indication. The usual oral dose is 35 mg two or three times daily before food. An alternative dose is 105 mg once daily in the morning as a modified-release preparation.

Phendimetrazine hydrochloride has been used similarly.

Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

USP 31: Phendimetrazine Tartrate Capsules; Phendimetrazine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
S.Afr.: Obesan-X; Obex-LA; ***USA:*** Bontril; Melfiat; Prelu-2.

Phenmetrazine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de fenmetrazina; Oxazimédrine; Phenmétrazine, Chlorhydrate de; Phenmetrazini Hydrochloridum. (±)-*trans*-3-Methyl-2-phenylmorpholine hydrochloride.

Фенметразина Гидрохлорид

$C_{11}H_{15}NO,HCl$ = 213.7.
CAS — 134-49-6 (phenmetrazine); 1707-14-8 (phenmetrazine hydrochloride); 13931-75-4 (phenmetrazine teoclate).

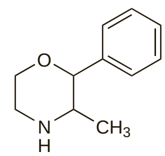

(phenmetrazine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of Phenmetrazine: Preludes.

Pharmacopoeias. In *US.*

USP 31 (Phenmetrazine Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 0.4 of water, 1 in 2 of alcohol, and 1 in 2 of chloroform. pH of a 2.5% solution in water is between 4.5 and 5.5. Store in airtight containers.

Profile

Phenmetrazine hydrochloride is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2153). It has been used as an anorectic in the treatment of obesity. Regulatory authorities in the EU have called for the withdrawal of all anorectics from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156). It has been subject to extensive abuse.

Abuse. For reference to a serious syndrome involving rhabdomyolysis after intravenous abuse of phenmetrazine, see Dexamfetamine Sulfate, p.2153.

Preparations

USP 31: Phenmetrazine Hydrochloride Tablets.

Phentermine *(BAN, USAN, rINN)* ⊗

Fentermiini; Fentermin; Fentermina; Phenterminum. α,α-Dimethylphenethylamine.

Фентермин

$C_{10}H_{15}N$ = 149.2.
CAS — 122-09-8.
ATC — A08AA01.
ATC Vet — QA08AA01.

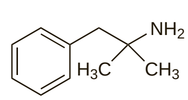

Phentermine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de fentermina; Phentermine, Chlorhydrate de; Phentermini Hydrochloridum.

Фентермина Гидрохлорид

$C_{10}H_{15}N,HCl$ = 185.7.
CAS — 1197-21-3.
ATC — A08AA01.
ATC Vet — QA08AA01.

Pharmacopoeias. In *US.*

USP 31 (Phentermine Hydrochloride). A white, odourless, hygroscopic, crystalline powder. Soluble in water and in the lower alcohols; slightly soluble in chloroform; insoluble in ether. pH of a 2% solution in water is between 5.0 and 6.0. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153. Urticaria may occur with use of phentermine.

Pulmonary hypertension has been reported in patients receiving phentermine and valvular heart defects in patients receiving the drug with other anorectics such as fenfluramine or dexfenfluramine; these adverse effects, with the relevant precautions to be observed, are discussed under Fenfluramine Hydrochloride (see Effects on the Cardiovascular System, p.2156).

Interactions

Phentermine is an indirect-acting sympathomimetic and may interact with other drugs, similarly to dexamfetamine (p.2153).

Pharmacokinetics

Phentermine is readily absorbed from the gastrointestinal tract and is excreted in the urine, partly unchanged and partly as metabolites.

Uses and Administration

Phentermine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2154). It has been given orally as the base or hydrochloride as an anorectic in the short-term treatment of moderate to severe obesity (p.2149), although stimulants are no longer recommended for this indication.

The usual dose of phentermine is 15 to 30 mg once daily before breakfast given as an ion-exchange resin complex that provides modified release. A suggested dose for phentermine hydrochloride is 8 mg three times daily before meals or 15 to 37.5 mg once daily in the morning. It should not be given for longer than a few weeks.

Regulatory authorities in the EU have called for the withdrawal of phentermine from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

USP 31: Phentermine Hydrochloride Capsules; Phentermine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Duromine; ***Canad.:*** Ionamin; ***Cz.:*** Adipex; ***Hong Kong:*** Duromine; Panbesy; Redusa; ***Israel:*** Razin; ***Malaysia:*** Adipex; Duromine; Ionamin†; ***Mex.:*** Acxion; Ifa Acxion; Ifa Reducing; Sinpet; Terfamex; ***NZ:*** Duromine; Umine†; ***Philipp.:*** Duromine; ***S.Afr.:*** Duromine; ***Singapore:*** Duromine; Ionamin†; Panbesy; Umine†; ***Switz.:*** Adipex; Ionamine†; ***Thai.:*** Duromine†; Panbesy; ***USA:*** Adipex-P; Ionamin; ***Venez.:*** Mirubal.

Pipradrol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipradrol; Pipradrol, Chlorhydrate de; Pipradroli Hydrochloridum. α-2-Piperidylbenzhydrol hydrochloride; α,α-Diphenyl-2-piperidinemethanol hydrochloride.

Пипрадрола Гидрохлорид

$C_{18}H_{21}NO,HCl$ = 303.8.
CAS — 467-60-7 (pipradrol); 71-78-3 (pipradrol hydrochloride).
ATC — N06BX15.
ATC Vet — QN06BX15.

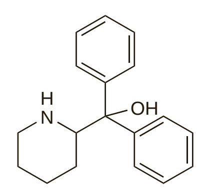

(pipradrol)

NOTE. The name pipradol hydrochloride has been used as a synonym for pipradrol hydrochloride.

Profile

Pipradrol hydrochloride has been given orally in tonic preparations as a CNS stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Alertonic†; ***Canad.:*** Alertonic; ***S.Afr.:*** Alertonic.

Prethcamide ⊗

G-5668; Pretcamida.

CAS — 8015-51-8.
ATC — R07AB06.
ATC Vet — QR07AB06.

Description. Prethcamide is a mixture of equal parts by weight of cropropamide and crotetamide.

Cropropamide (BAN, pINN) ⊗

Cropropamida; Cropropamidum; Kropropamid; Kropropamidi. *N,N*-Dimethyl-2-(*N*-propylcrotonamido)butyramide.

Кропропамид

$C_{13}H_{24}N_2O_2$ = 240.3.

CAS — 633-47-6.

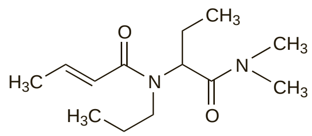

Crotetamide (BAN, rINN) ⊗

Crotetamida; Crotétamide; Crotetamidum; Crotethamide. 2-(*N*-Ethylcrotonamido)-*N,N*-dimethylbutyramide.

Кротетамид

$C_{12}H_{22}N_2O_2$ = 226.3.

CAS — 6168-76-9.

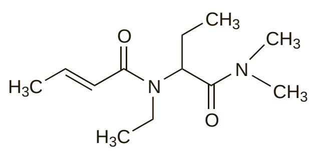

Profile

Prethcamide, a mixture of equal parts by weight of cropropamide and crotetamide, has actions similar to those of doxapram (p.2155) and has been used as a respiratory stimulant. Oral doses of 100 mg have been given three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Micoren.

Prolintane Hydrochloride (BANM, USAN, rINNM) ⊗

Hidrocloruro de prolintano; Prolintane, Chlorhydrate de; Prolintani Hydrochloridum; SP-732. 1-(α-Propylphenethyl)pyrrolidine hydrochloride.

Пролинтана Гидрохлорид

$C_{15}H_{23}N,HCl$ = 253.8.

CAS — 493-92-5 (prolintane); 1211-28-5 (prolintane hydrochloride).

ATC — N06BX14.

ATC Vet — QN06BX14.

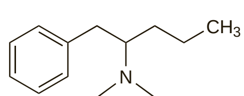

(prolintane)

Profile

Prolintane hydrochloride is a mild central stimulant and has properties similar to those of dexamfetamine (p.2153). It has been available mainly in tonic preparations that also contained vitamin supplements. It has also been used in narcolepsy.

Propylhexedrine (BAN, rINN) ⊗

Hexahydrodesoxyephedrine; Propilhexedrina; Propylhexed; Propylhexédrine; Propylhexedrinum. 2-Cyclohexyl-1-methylethyl-(methyl)amine; (±)-*N*-α-Dimethylcyclo-hexaneethylamine.

Пропилгекседрин

$C_{10}H_{21}N$ = 155.3.

CAS — 101-40-6; 3595-11-7 ((±)-propylhexedrine).

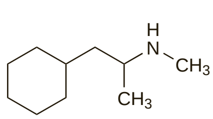

Pharmacopoeias. In *US.*

USP 31 (Propylhexedrine). A clear colourless liquid having a characteristic amine-like odour. It slowly volatilises at room temperature and absorbs carbon dioxide from the air. Very slightly soluble in water; soluble 1 in 0.4 of alcohol, 1 in 0.2 of chloroform, and 1 in 0.1 of ether. Its solutions are alkaline to litmus. Store in airtight containers.

Propylhexedrine Hydrochloride (BANM, rINNM) ⊗

Hidrocloruro de propilhexedrina; Propylhexédrine, Chlorhydrate de; Propylhexedrini Hydrochloridum.

Пропилгекседрина Гидрохлорид

$C_{10}H_{21}N,HCl$ = 191.7.

CAS — 1007-33-6; 6192-95-6 ((±)-propylhexedrine hydrochloride).

Adverse Effects, Treatment and Precautions

As for Dexamfetamine Sulfate, p.2153.

Nasal inhalation may cause transient burning, stinging, mucosal dryness, and sneezing. Prolonged use can cause rebound congestion, redness, swelling, and rhinitis. Systemic effects such as headache, hypertension, nervousness, and increased heart rate may occur.

Propylhexedrine is subject to abuse by mouth or intravenously; fatalities due to myocardial infarction, heart failure, or pulmonary hypertension have been reported. Psychosis may occur.

Abuse. References.

1. White L, DiMaio VJM. Intravenous propylhexedrine and sudden death. *N Engl J Med* 1977; **297:** 1071.
2. Anderson RJ, *et al.* Intravenous propylhexedrine (Benzedrex) abuse and sudden death. *Am J Med* 1979; **67:** 15–20.
3. Cameron J, *et al.* Possible association of pulmonary hypertension with an anorectic drug. *Med J Aust* 1984; **140:** 595–7.

Uses and Administration

Propylhexedrine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2154). It has been used as an inhalant for nasal decongestion (p.1548).

Propylhexedrine hydrochloride has been given orally as an anorectic in the treatment of obesity (p.2149) but stimulants are no longer recommended for this indication. The (–)-isomer, levopropylhexedrine hydrochloride, has been used similarly.

Preparations

USP 31: Propylhexedrine Inhalant.

Proprietary Preparations (details are given in Part 3)
USA: Benzedrex.
Multi-ingredient: ***S.Afr.:*** Reducealin†.

Sibutramine Hydrochloride (BANM, USAN, rINNM) ⊗

BTS-54524; Hidrocloruro de sibutramina; Sibutramin Hidroklorür; Sibutramine, Chlorhydrate de; Sibutramini Hydrochloridum. (±)-1-(*p*-Chlorophenyl)-α-isobutyl-*N,N*-dimethylcyclobutanemethylamine hydrochloride monohydrate.

Сибутрамина Гидрохлорид

$C_{17}H_{26}ClN,HCl,H_2O$ = 334.3.

CAS — 106650-56-0 (sibutramine); 84485-00-7 (anhydrous sibutramine hydrochloride); 125494-59-9 (sibutramine hydrochloride monohydrate).

ATC — A08AA10.

ATC Vet — QA08AA10.

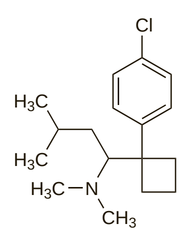

(sibutramine)

Adverse Effects

Commonly reported adverse effects of sibutramine are dry mouth, headache, insomnia, and constipation. Diarrhoea, back pain, increased appetite, dizziness, flu-like symptoms, and rhinitis have also occurred. Less frequently reported adverse effects include dyspepsia, nausea, dysmenorrhoea, increased sweating and thirst, oedema, paraesthesia, skin rashes, taste perversion, palpitations, vasodilatation, anxiety, nervousness, drowsiness, and depression. Abnormal bleeding including Henoch-Schönlein purpura and thrombocytopenia, acute interstitial nephritis, glomerulonephritis, emotional lability, seizures, and blurred vision have been reported rarely. Clinically significant increases in heart rate and blood pressure may occur. Sibutramine may decrease salivary flow and therefore increase the risk of dental caries, periodontal disease, or other oral disorders. It may also produce mydriasis. Reversible increases in liver enzymes have been reported.

Precautions

Sibutramine should be avoided in patients with a history of eating disorders such as anorexia nervosa and bulimia nervosa. It is also contra-indicated in patients with uncontrolled or poorly controlled hypertension and should be used with caution in patients with a history of, or with, well-controlled hypertension. Blood pressure and heart rate should be monitored (see below for details). In the event of sustained elevations, the dose should be reduced or treatment discontinued.

Sibutramine should not be used in patients with a history of cerebrovascular disease or cardiovascular disorders such as cardiac arrhythmias, heart failure, peripheral arterial occlusive disease, and coronary artery disease. It should be avoided in patients with severe hepatic or renal impairment; caution has been advised when using sibutramine in those with mild to moderate renal impairment. Sibutramine should also not be used in patients with bipolar disorder, Tourette's syndrome, hyperthyroidism, phaeochromocytoma, benign prostatic hyperplasia, or a history of drug or alcohol abuse. It should be used with caution, if at all, in patients with glaucoma. Sibutramine should also be used with caution in patients with a history of depression, seizures or gallstones (which may be precipitated or exacerbated by weight loss), or a family history of motor or verbal tics.

Any centrally-acting drug such as sibutramine may impair the ability to perform tasks requiring judgement or motor or cognitive skills; if affected, patients should not drive or operate machinery.

Bleeding disorders. Because other drugs that inhibit reuptake of serotonin have occasionally been associated with bleeding disorders and other effects on the blood (see under Fluoxetine, p.392) UK licensed product information for sibutramine recommends that it should be used with caution in patients predisposed to bleeding disorders and in those taking other drugs known to affect haemostasis or platelet function.

Cardiovascular monitoring. Sibutramine may cause clinically significant increases in blood pressure and heart rate and monitoring is recommended in the product information for all patients during treatment. In the first 3 months, blood pressure and heart rate should be checked every 2 weeks; this may be reduced to every month for the next 3 months, and at least every 3 months thereafter. Treatment should be stopped if resting heart rate increases by 10 beats/minute or more, or blood pressure by 10 mmHg or more, at two consecutive visits. In patients with previously well-controlled hypertension, treatment should be stopped if their blood pressure exceeds 145/90 mmHg at two consecutive visits.

Interactions

Sibutramine should not be given with, or within at least 2 weeks of stopping an MAOI; at least 2 weeks should elapse between discontinuation of sibutramine and starting therapy with an MAOI. There is a risk of the serotonin syndrome (p.416) developing if sibutramine is used with other serotonergic drugs such as SSRIs, sumatriptan, lithium, pethidine, fentanyl, dextromethorphan, and pentazocine. Caution is advised when sibutramine is given with other drugs that may increase heart rate or blood pressure such as ephedrine, phenylpropanolamine, and pseudoephedrine. It should not be used with other centrally acting anorectics. Alcohol should be avoided.

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole and erythromycin, may increase plasma concentrations of sibutramine. Conversely, inducers of this isoenzyme, such as rifampicin, phenytoin, carbamazepine, and phenobarbital, may reduce plasma concentrations of sibutramine.

Antibacterials. A study in 12 obese subjects indicated that addition of *erythromycin* to sibutramine therapy resulted in little significant alteration in sibutramine pharmacokinetics beyond a modest increase in maximum plasma concentration of one of the active metabolites.[1] A small increase in the QT interval was not considered clinically meaningful.

1. Hinson JL, *et al.* Steady-state interaction study of sibutramine (Meridia™) and erythromycin in uncomplicated obese subjects. *Pharm Res* 1996; **13** (suppl): S116.

Antifungals. A study in 12 obese subjects given sibutramine found that *ketoconazole* moderately increased steady-state plasma concentrations of sibutramine and its active metabolites.[1] There was a significant increase in heart rate but no clinically relevant change in the QT interval.

1. Hinson JL, *et al.* Steady-state interaction study of sibutramine (Meridia™) and ketoconazole in uncomplicated obese subjects. *Pharm Res* 1996; **13** (suppl): S116.

Pharmacokinetics

Sibutramine is well absorbed from the gastrointestinal tract; peak plasma concentrations appear after 1.2 hours (parent drug) and 3 to 4 hours (metabolites). It undergoes extensive first-pass hepatic metabolism, mediated mainly by the cytochrome P450 isoenzyme CYP3A4. Demethylation produces mono- and di-desmethylsibutramine (both of which are pharmacologically active) and is followed by hydroxylation and conjugation to inactive metabolites. Protein binding is 97%. Plasma-elimination half-life is 14 to 16 hours. Elimination is mainly in the urine as inactive metabolites, and partly in the faeces.

◊ References.

1. Hind ID, *et al.* Sibutramine pharmacokinetics in young and elderly healthy subjects. *Eur J Clin Pharmacol* 1999; **54:** 847–9.

Uses and Administration

Sibutramine, which is structurally related to amfetamine (p.2150), is a serotonin and noradrenaline reuptake inhibitor; it also inhibits dopamine reuptake but to a lesser extent. Sibutramine is used in the management of obesity (p.2149). It may also be used in overweight patients (body-mass index of 27 kg/m^2 or more) if other risk factors such as hypertension (but see Precautions, above), diabetes mellitus, or hyperlipidaemias are present.

Sibutramine hydrochloride is given orally in an initial daily dose of 10 mg, usually taken in the morning. Patients who cannot tolerate 10 mg daily may benefit from a dose of 5 mg daily. Treatment with sibutramine should be re-evaluated if weight loss is less than 2 kg in the first 4 weeks of therapy. At this stage, the dose may be increased to a maximum of 15 mg daily, taking into consideration effects on heart rate and blood pressure, or treatment may need to be stopped. It should be re-assessed again after a further 4 weeks at maximum dose, and stopped if weight loss is less than 2 kg. Treatment should also be stopped if:

- weight loss stabilises at less than 5% of the initial body-weight
- weight loss after 3 months is less than 5% of the initial body-weight
- weight gain of 3 kg or more occurs after previous weight loss

Treatment should not be given for longer than 1 year.

In patients with other risk factors (see Precautions, above), it is recommended that sibutramine is continued only if weight loss is associated with other clinical benefits.

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Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aderan; Downtrat; Ipomex; Raductil†; Sacietyl; Sertinal; Sibu-Estirol; Sibu-Tratobes; ***Austral.:*** Reductil; ***Austria:*** Meridia; Reductil; ***Belg.:*** Reductil; ***Braz.:*** Plenty; Reductil; Vazy; ***Canad.:*** Meridia; ***Chile:*** Adisar; Atenix; Ipogras; Medixil; Mesura; Milical; Mintagras; Noducil; Reductil; Reduten; Saton; ***Cz.:*** Lindaxa; Meridia; ***Denm.:*** Reductil; ***Fin.:*** Reductil; ***Fr.:*** Sibutral; ***Ger.:*** Reductil; ***Gr.:*** Reductil; ***Hong Kong:*** Reductil; ***Hung.:*** Reductil; ***India:*** Obestat; ***Indon.:*** Reductil; ***Irl.:*** Reductil; ***Israel:*** Reductil; ***Ital.:*** Ectiva; Reductil; Reduxade†; ***Malaysia:*** Reductil; ***Mex.:*** Ectiva; Ifa-Certez; Raductil; Serotramin; ***Neth.:*** Reductil; ***Norw.:*** Reductil; ***NZ:*** Reductil; ***Philipp.:*** Reductil; ***Pol.:*** Meridia; Zelixa; ***Port.:*** Reductil; Zelium; ***Rus.:*** Meridia (Меридиа); ***S.Afr.:*** Reductil; ***Singapore:*** Reductil; ***Spain:*** Reductil; ***Swed.:*** Reductil; ***Switz.:*** Reductil; ***Thai.:*** Reductil; ***Turk.:*** Reductil; ***UK:*** Reductil; ***USA:*** Meridia; ***Venez.:*** Milical; Reductil; Repentil; Vintix.

Multi-ingredient: *Mex.:* Redumed.

Tenamfetamine *(rINN)* ⊗

MDA; Methylenedioxyamphetamine; 3,4-Methylenedioxyamphetamine; SKF-5; Ténamfétamine; Tenamfetaminum; Tenanfetamina. α-Methyl-3,4-methylenedioxyphenethylamine.
Тенамфетамин
$C_{10}H_{13}NO_2$ = 179.2.
CAS — 4764-17-4; 51497-09-7.

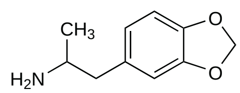

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of tenamfetamine:
EA1299; Eve; Love Drug; Love Pill; MDMA; Mellow Drug of America.

Profile

Tenamfetamine is a phenylethylamine compound, structurally related to amfetamine and mescaline, with hallucinogenic effects. It has been subject to abuse and dependence. A number of similar compounds are known because of their abuse and include:

- brolamfetamine (4-bromo-2,5-dimethoxyamfetamine; bromo-DMA; bromo-DOM; 2,5-dimethoxy-4-bromoamfetamine; DOB)
- 4-bromo-2,5-methoxyphenylethylamine (afterburner; 2-CB; MFT)
- 2,5-dimethoxy-4-metamfetamine (DOM; methyl-2,5-dimethoxyamfetamine; Serenity, Tranquillity and Peace; STP)
- *N*-ethyltenamfetamine (Eve; MDE; MDEA; 3,4-methylenedioxyethamfetamine)
- *N*-hydroxytenamfetamine (*N*-hydroxy MDA; 3,4-methylenedioxy-*N*-hydroxyamfetamine)
- methoxyamfetamine (Death; 4-methoxyamfetamine; *p*-methoxyamfetamine; PMA)
- methylenedioxymethamfetamine (Ecstasy) (see p.2159)
- 2,4,5-trimethoxyamfetamine (TMA; TMA-2)

In large doses the adverse effects of tenamfetamine and related compounds are similar to those of dexamfetamine and may be treated similarly (see p.2153). Fatalities have been associated with the abuse of some of these compounds.

◊ Reviews of the properties of some designer drugs, including phenylethylamine compounds.

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Thyroid and Antithyroid Drugs

The principal role of the thyroid gland is to regulate tissue metabolism through production of the **thyroid hormones** 3,5,3′,5′-tetra-iodo-L-thyronine (levothyroxine, L-thyroxine, thyroxine; T_4) and, in smaller amounts, 3,5,3′-tri-iodo-L-thyronine (liothyronine, L-tri-iodothyronine, tri-iodothyronine; T_3). In infants and children thyroid hormones are also necessary for the development of the CNS and for normal growth and bone maturation.

The production of thyroid hormones is dependent on an adequate supply of dietary iodine. Iodine is reduced to iodide in the gastrointestinal tract and is then readily absorbed and actively transported into the thyroid, where it undergoes oxidation, catalysed by thyroid peroxidase. Oxidised iodide is incorporated into the glycoprotein thyroglobulin to form L-mono-iodotyrosine (MIT) and L-di-iodotyrosine (DIT), which are inactive. A coupling reaction, also catalysed by thyroid peroxidase, yields the hormonally active iodothyronines, T_3 and T_4, joined by a peptide bond to thyroglobulin for storage in the follicular colloid. The release of proteolytic enzymes from lysosomes degrades the thyroglobulin into its constituent amino acids to release T_3 and T_4 into the circulation; iodide resulting from this reaction is recycled.

Whereas T_4 enters the circulation only by direct glandular secretion, most of the T_3 in the body is produced by the mono-deiodination of T_4 in the peripheral tissues. About 40% of secreted T_4 is converted to T_3 and about 40% is converted to inactive reverse tri-iodothyronine (reverse T_3; rT_3). The metabolic activity of T_3 is about 3 to 5 times that of T_4 and it has been suggested that T_3 is the active thyroid hormone with T_4 acting primarily as a prohormone.

Thyroid hormones are extensively protein bound in plasma, principally to thyroxine-binding globulin (TBG) but also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin.

Thyroid hormone homoeostasis is maintained by autoregulatory mechanisms within the gland, and by the hypothalamic-pituitary-thyroid axis. In response to falling plasma concentrations of unbound T_3 and T_4, the hypothalamus secretes thyrotropin releasing hormone (protirelin; TRH—see p.2175), which in turn stimulates the synthesis and release of thyroid stimulating hormone (thyrotropin; TSH—see p.2177) by the anterior pituitary gland. TSH acts on its receptor in the thyroid gland to increase production of T_3 and T_4, and also to release hormone stored in the gland. As thyroid hormone concentrations in blood increase, the secretion of TSH, and possibly TRH, will be suppressed. The term euthyroidism is used when the thyroid gland is functioning normally and there are normal amounts of thyroid hormone in the blood.

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Goitre and thyroid nodules

Goitre is the enlargement of the thyroid gland. The swelling may be focal (caused by a solitary thyroid nodule, adenoma, or cyst) or generalised, in which case it is usually diffuse at first, later becoming multinodular. Non-toxic goitres may be associated with hypothyroidism (see below) or euthyroidism. The management of toxic goitres is discussed under Hyperthyroidism, below.

Non-toxic goitres may be associated with intrinsic defects in hormone production, or extrinsic factors such as dietary-iodine deficiency in endemic goitre (see Iodine Deficiency Disorders, p.2170). Decreased secretion of thyroid hormone results in an excessive output of thyroid-stimulating hormone (TSH) from the pituitary. This stimulates thyroid-hormone production but also leads to hypertrophy and hyperplasia of the thyroid gland. If the response to TSH overcomes the deficiency in thyroid-hormone synthesis then the patient is goitrous and euthyroid but if the compensatory response to TSH is inadequate then goitre with hypothyroidism is observed. Other factors can also contribute, such as autoantibody-stimulated thyroid growth, and thyroid autonomy, in which the gland functions independently of TSH control.

The general aims in the management of thyroid masses are:

- the detection and treatment of malignancy
- the reduction of goitre or prevention of further enlargement, and the relief of obstructive symptoms
- the maintenance of a euthyroid state

A review[1] of clinical investigations for thyroid nodules found fine-needle aspiration biopsy to provide the most accurate information; US guidelines consider it an integral part of thyroid nodule evaluation.[2] Ultrasonography can also estimate the nodule size and goitre volume. It can differentiate between simple cysts, solid nodules, or mixed cystic and solid nodules, although it cannot reliably distinguish between benign and cancerous lesions. For the latter, fludeoxyglucose (^{18}F) may be used to evaluate glucose metabolism by positron-emission tomography, although this method is not as economical as fine-needle aspiration biopsy. Radionuclide scanning with iodine isotopes may be used to identify whether a nodule is functioning (these are nearly always benign). Nodule size cannot be measured accurately by radionuclide scanning.

In established **malignancy**, surgery, followed by levothyroxine replacement therapy, is the usual course (for further discussion of the treatment of thyroid cancer, see p.674).

The treatment of non-toxic **benign solitary nodules** is a matter of dispute. Many prefer simply to monitor patients with benign solitary nodules. Alternatively suppressive therapy with doses of levothyroxine (or, less often, liothyronine) sufficient to suppress TSH production and reduce the size of the nodule has been widely practised, but results conflict as to whether such therapy is effective.[3] A meta-analysis of 7 studies[4] suggested that although levothyroxine treatment produced some benefit, the number of patients who responded was quite small. Another meta-analysis[5] (which included 5 of the same studies and a later one) found an overall non-significant treatment response; the authors concluded that routine suppressive levothyroxine for single benign thyroid nodules could not be recommended, but that a subgroup of patients with small, solid nodules might benefit from therapy. US guidelines[2] consider that it should generally be avoided, but may be considered in patients from areas of iodine deficiency, young patients with small nodules, and in nodular goitres with no evidence of autonomous thyroid hormone production. There has been some concern about the possible risk of osteoporosis[6] with levothyroxine (see Effects on the Bones, p.2171). An alternative to levothyroxine is treatment with potassium iodide, although it is somewhat less effective,[7] and has adverse effects of its own.[6] Sclerotherapy by alcohol injection can produce substantial reductions,[2,8,9] but is painful and requires considerable skill.[1,2]

Levothyroxine suppression therapy is effective in patients with **diffuse** non-toxic goitre, and may be of benefit in some patients with **multinodular** disease. However, many patients with large multinodular goitres have autonomous thyroid hormone production, and in such patients levothyroxine is of no benefit and may cause overt hyperthyroidism. Radio-iodine (^{131}I) treatment appears to be more effective and better tolerated than levothyroxine,[10] and has been a useful alternative to surgery in selected cases of multinodular non-toxic goitre.[2,11]

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Hyperthyroidism

Hyperthyroidism is overactivity of the thyroid gland, with consequent excess secretion of hormones. The terms thyrotoxicosis and hyperthyroidism are used interchangeably, although some apply ‘thyrotoxicosis’ to the *effects* of excessive thyroid hormone. The most common causes of hyperthyroidism are Graves’ disease (diffuse toxic goitre) and hyperactivity arising from single or multiple thyroid nodules (toxic nodular goitre). Graves’ disease (or Basedow’s disease) is an auto-immune condition in which thyroid-stimulating antibodies bind to thyroid-stimulating hormone (TSH) receptors, mimicking the effect of prolonged TSH stimulation. Graves’ disease, which is more prevalent in females, frequently occurs with other diseases such as Addison’s disease, type 1 diabetes mellitus, and pernicious anaemia, and there may be a genetic predisposition. Iodine and its salts, or iodine-containing drugs such as amiodarone, can also be a cause of both hyperthyroidism and hypothyroidism.

The major clinical manifestations associated with clinical hyperthyroidism include goitre, nervousness, agitation, tremor, tachycardia or atrial fibrillation, weight loss (often despite increased appetite), emotional lability, muscle weakness, fatigue, heat intolerance and excessive perspiration, and increased bowel frequency. Exaggerated growth may occur in children. Females may occasionally experience amenorrhoea or oligomenorrhoea and males may develop gynaecomastia. Occasionally there is subcutaneous deposition of mucopolysaccharides around the shins, causing a non-pitting oedema (pretibial myxoedema).

A **diagnosis** of primary hyperthyroidism may be confirmed by demonstration of a low TSH value and a high concentration of free T_4 or T_3 in the circulation. Determination of TSH, which is low in hyperthyroidism due to negative feedback, allows differential diagnosis of hyperthyroidism from a TSH-secreting pituitary tumour.

Subclinical hyperthyroidism is characterised by normal thyroid hormone concentrations, decreased TSH concentrations, but no clinical symptoms. It has been reported to occur less frequently than subclinical hypothyroidism. Consensus on management has been lacking;[1-6] while treatment is not routinely recommended for mild subclinical hyperthyroidism, certain subgroups of patients, such as those at risk of atrial fibrillation or osteoporosis, may benefit from therapy.[7] Treatment may also be warranted in those with subclinical hyperthyroidism caused by toxic multinodular goitre or Graves’ disease in order to prevent progression to overt hyperthyroidism.[4]

There are three main forms of **treatment** for hyperthyroidism: drug therapy, use of radio-iodine, or surgery.

Drug therapy. The main **antithyroid drugs** are all thiourea derivatives that block the production of thyroid hormones through inhibition of thyroid peroxidase. Carbimazole (in the UK) or thiamazole (in the USA), or propylthiouracil, are the mainstays of treatment.[8] Antithyroid drugs do not block the release of stored thyroid hormones and it is only when the preformed hormones are depleted and concentrations of circulating hormones decline that clinical effects become apparent. An additional action of propylthiouracil is inhibition of the peripheral deiodination of thyroxine to tri-iodothyronine. The place of immunosuppression in the antithyroid activity of these drugs is subject to debate.

Many patients begin treatment with an antithyroid drug; they receive high doses initially until they become euthyroid, generally within 1 to 2 months. Once a response to the antithyroid drug has been obtained, patients with more severe or recurrent disease may require ablative treatment with either radio-iodine or surgery (see below), while those with mild to moderate disease may be best managed with lower maintenance doses of antithyroid drugs. These are either given indefinitely, or more usually for at least a year (often 18 months), followed by observation to see if remission is maintained in the absence of drug therapy.[2,8-14] Relapse at some stage after stopping therapy occurs in about 50 to 60% of cases, usually within 3 to 6 months after stopping the drugs, but is unpredictable.[8] Addition of levothyroxine to the maintenance dose of thiamazole has been reported to reduce the rate of relapse in patients with Graves' disease when therapy is subsequently withdrawn,[12,15] but later studies have not shown benefit.[14,16-19]

An alternative maintenance regimen is to add the thyroid hormone while maintaining the high initial doses of antithyroid drug. This '*blocking-replacement therapy*' has been suggested to help to prevent hypothyroidism which may be induced when antithyroid drugs are used alone. Because of the high doses of thioureas required and the insufficient placental transfer of levothyroxine,[20,21] the blocking-replacement regimen should not be used in pregnancy.

More rapid relief of the symptoms of hyperthyroidism can be achieved with beta blockers or iodide.[9,11] Beta blockers usually achieve a response within 48 hours, and are given as short-term adjuncts to antithyroid drugs to control severe sympathetic overactivity in patients such as those with thyroid storm (see below), but their use in heart failure associated with thyrotoxicosis is controversial because of the risk of cardiac deterioration.[22] The use of beta blockers in patients with mild to moderate hyperthyroidism is usually unnecessary.

Iodine and iodides are given with antithyroid drugs for 7 to 14 days as pre-operative preparation for patients who are to undergo thyroidectomy (but see also under Surgical Therapy, below); a combination of iodide and a beta blocker has also been used. Iodide has been used with antithyroid drugs, for control of thyroid storm. It is suggested that the antithyroid drugs should always be given first to prevent incorporation of iodide into new hormone stores.[9]

Other drugs tried in hyperthyroidism have included lithium, though its practical value is a matter of debate.[9] Potassium and sodium perchlorate have also been used; they increase responsiveness to conventional antithyroid drugs and may be useful in patients with iodine-induced hyperthyroidism.[23]

In those patients in whom drug therapy fails to achieve long-term remission, ablative therapy may be considered in the form of radio-iodine therapy or surgery.

Radio-iodine therapy with ^{131}I as oral ^{131}I-sodium iodide treats hyperthyroidism by destroying the functioning cells of the thyroid gland. It is increasingly used as initial therapy,[9,12,20,24,25] especially in the USA.[6,26] It is also useful for patients who have not responded to antithyroid drug therapy or who have relapsed after it.[2,10]

Pretreatment of patients with an antithyroid drug for 2 to 8 weeks before radio-iodine therapy has been advocated, to avoid the risk of precipitating thyroid storm. However, many no longer consider this to be necessary for all patients,[9,20,24] although it is generally agreed that the elderly or those with severe disease or increased risk of cardiac symptoms should receive some form of pretreatment.[6] In younger patients, a study has suggested that antithyroid pretreatment may exacerbate the risks when the drugs are withdrawn.[27] Such withdrawal, 2 to 4 days before radio-iodine is given, is standard practice to maximise the latter's effect, although some consider it unnecessary.[9] Meta-analysis has shown that use of antithyroid drugs in the week before or after radio-iodine therapy decreases its effectiveness, increasing the risk of treatment failure.[28] Although it has been considered that a poor response to radio-iodine was more likely with propylthiouracil than thiamazole,[8] this was not supported by meta-analysis.[28] An increased dose of radio-iodine has been advocated in pretreated patients.[24] Pretreatment or ancillary treatment with a beta blocker is a possible alternative to antithyroid drugs in patients receiving radio-iodine.[6,9,11,20,24]

The dose of radio-iodine needed to achieve euthyroidism is difficult to predict and there is little agreement on the most appropriate dosage schedule.[2,11,24] Radio-iodine therapy may take up to 10 weeks to achieve a clinical response, and cover with an antithyroid drug may be required during this period. Radio-iodine is not generally considered to increase the risk of malignancy,[9,24,29] or teratogenicity[20] but it is contra-indicated in pregnancy and while breast feeding.[6] The commonest unwanted effect of radio-iodine therapy is hypothyroidism and all patients require long-term follow-up and possible levothyroxine replacement therapy.[6] Iodide may be given after radio-iodine therapy to help the return of normal thyroid function.[9] Controversy exists as to whether radio-iodine therapy exacerbates Graves' ophthalmopathy[9,30,31] although it is considered to worsen disease in smokers.[20,25] Cohort studies have found increased mortality in those patients with hyperthyroidism treated with radio-iodine.[32,33] However, this risk was no longer evident once patients with overt hypothyroidism (induced by radio-iodine therapy) were given thyroxine replacement therapy. The authors considered these findings to strongly support a definitive treatment of hyperthyroidism with doses of radio-iodine sufficient to cause overt hypothyroidism, and the prompt treatment of subclinical hypothyroidism after radio-iodine therapy.[33]

Surgical treatment is usually reserved for patients with severe hyperthyroidism or for those with extreme thyroid enlargement or a single nodule. Euthyroidism is first established using antithyroid drugs and then iodide is given for 7 to 14 days before surgery to reduce the vasculature of the gland. Alternatively, a beta blocker and iodide may be used together for pre-operative preparation. However, a consensus view[1] suggested that pre-operative iodine probably has no beneficial effect. Levothyroxine replacement therapy may be required following surgical treatment.

Arterial embolisation. There are some patients who cannot, or choose not to, receive any of the three main forms of treatment for hyperthyroidism. Thyroid arterial embolisation has been used as an alternative with an outcome similar to that of subtotal thyroidectomy.[34]

If untreated or inadequately controlled, hyperthyroidism can complicate **pregnancy** and have adverse perinatal effects.[20,21,25,35] Hyperthyroidism is generally treated throughout pregnancy with an antithyroid drug, usually propylthiouracil[6,8,20,21,25,35] at the minimum dose needed to maintain a borderline euthyroid state. Occasionally, the antithyroid drug can be withdrawn in the third trimester.[8,20,25,26] Drug therapy during pregnancy may cause fetal or neonatal hypothyroidism, with or without goitre. This risk appears unrelated to the dose of the drug,[21,35] and the condition may mask neonatal hyperthyroidism[35] (see below).

Failure to control symptoms of hyperthyroidism with antithyroid drugs during pregnancy may indicate the need for surgery which is often delayed where possible until after the first trimester.[21,25,35,36] Iodide and radio-iodine are contra-indicated during pregnancy,[6,11,20,21,25,35,36] as is the blocking-replacement regimen.[20,21,26,35]

Neonatal hyperthyroidism may occur rarely due to transfer of thyroid-stimulating immunoglobulins across the placenta, and should be treated with antithyroid drugs, iodide, and appropriate therapy for cardiovascular complications.[37]

Thyroid storm (also known as thyroid crisis or thyrotoxic crisis) is an extreme accentuation of the hyperthyroid state and should be treated as a medical emergency. It is usually abrupt in onset and is often related to some precipitating factor such as inadequate preparation for thyroidectomy or radio-iodine therapy, or infection in previously unrecognised hyperthyroid subjects. The most common clinical manifestations are hyperpyrexia and extreme tachycardia; others may include arrhythmia, heart failure, shock, agitation, tremor, mania, delirium, stupor, coma, abdominal pain, diarrhoea, vomiting, jaundice, and hepatomegaly. Treatment consists of high-dose antithyroid drugs, gradually reduced as the condition improves, along with a beta blocker and iodide to control cardiovascular symptoms and prevent thyroid hormone release from the thyroid gland. Additional symptomatic treatment may also be required.

The clinical manifestations of **Graves' ophthalmopathy** may not occur with those of systemic hyperthyroidism, and it has been characterised as an independent manifestation of the immunological abnormality in Graves' disease.[38]

In Graves' ophthalmopathy, oedema and inflammation of the muscles around the eyes produces exophthalmos or proptosis and diplopia. On rare occasions patients may develop papilloedema and loss of vision. Treatment is generally unsatisfactory and signs of disease may persist indefinitely.[39] Opinions differ as to whether controlling associated hyperthyroidism improves ocular symptoms.[38] Reports that radio-iodine therapy may exacerbate Graves' ophthalmopathy are disputed,[6,9,20,24,30,31] but some prefer to avoid its use in active ocular disease.[1] Most patients with mild ocular involvement in hyperthyroidism require no specific therapy; dry eye should be managed appropriately (see p.2140). There is evidence indicating that glucocorticoids are effective in patients with Graves' ophthalmopathy, especially in patients with moderate and severe disease of recent onset. Glucocorticoids have a synergistic effect with orbital radiotherapy and the combination has been shown to be effective. If orbital radiotherapy is contra-indicated, ciclosporin with oral glucocorticoids is an effective alternative.[40] Surgical decompression may be required if patients do not respond to such therapy or cannot tolerate its adverse effects, or if vision is threatened by severe optic nerve compression.

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19. Rittmaster RS, *et al.* Effect of methimazole, with or without L-thyroxine, on remission rates in Graves' disease. *J Clin Endocrinol Metab* 1998; **83:** 814–18.
20. Weetman AP. Graves' disease. *N Engl J Med* 2000; **343:** 1236–48.
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22. Ko GTC, *et al.* Should β-blocking agents be used in thyrotoxic heart disease? *Med J Aust* 1995; **162:** 426–7.
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24. Kaplan MM, *et al.* Treatment of hyperthyroidism with radioactive iodine. *Endocrinol Metab Clin North Am* 1998; **27:** 205–23.
25. Woeber KA. Update on the management of hyperthyroidism and hypothyroidism. *Arch Intern Med* 2000; **160:** 1067–71.
26. Cooper DS. Hyperthyroidism. *Lancet* 2003; **362:** 459–68.
27. Burch HB, *et al.* Discontinuing antithyroid drug therapy before ablation with radioiodine in Graves disease. *Ann Intern Med* 1994; **121:** 553–9.
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31. Bartalena L, *et al.* Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998; **338:** 73–8.
32. Franklyn JA, *et al.* Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med* 1998; **338:** 712–18.
33. Franklyn JA, *et al.* Thyroid function and mortality in patients treated for hyperthyroidism. *JAMA* 2005; **294:** 71–80.
34. Xiao H, *et al.* Arterial embolization: a novel approach to thyroid ablative therapy for Graves' disease. *J Clin Endocrinol Metab* 2002; **87:** 3583–9.
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36. Masiukiewicz US, Burrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; **9:** 647–52.
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38. Char DH. Thyroid eye disease. *Br J Ophthalmol* 1996; **80:** 922–6.
39. Fleck BW, Toft AD. Graves' ophthalmopathy. *BMJ* 1990; **300:** 1352–3.
40. Hart RH, Perros P. Glucocorticoids in the medical management of Graves' ophthalmopathy. *Minerva Endocrinol* 2003; **28:** 223–31.

Hypothyroidism

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. It mainly affects women and is more prevalent in the middle-aged and elderly. The symptoms of hypothyroidism may be due to general deceleration of metabolism or to accumulation of mucopolysaccharide in the subcutaneous tissues and vocal cords. Common clinical manifestations include weakness, fatigue, lethargy, physical and mental slowness, and weight gain; puffy, nonpitted swelling of subcutaneous tissue often develops, particularly around the eyes. Menstrual disorders, hyperlipidaemia, and constipation can occur and goitre may develop despite associated cell destruction.

The term **myxoedema** is often reserved for severe or advanced hypothyroidism. In the most severely affected patients, progressive somnolence and torpor combine with cold intolerance and bradycardia to induce a state of coma often known as 'hypothyroid' or 'myxoedema coma' (see below).

In children, untreated hypothyroidism results in retardation of growth and mental development. Endemic cretinism is a result of maternal, and hence fetal, iodine deficiency and consequent lack of thyroid hormone production (see Iodine Deficiency Disorders, p.2170).

Hypothyroidism is usually primary, resulting from malfunction of the thyroid gland. In areas where iodine intake is sufficient the commonest cause of hypothyroidism is auto-immune lymphocytic thyroiditis of which there are two major variants. In **Hashimoto's thyroiditis** there is also goitre whereas in **idiopathic** or **primary myxoedema** (**atrophic thyroiditis**) there is no thyroid enlargement. Hypothyroidism can also be caused by either an excess or a deficiency of iodine. An excess may result from intake of iodine or its salts or iodine-containing drugs such as amiodarone. Drugs that decrease thyroid hormone synthesis such as lithium can also be a cause of hypothyroidism. In some patients hypothyroidism may be secondary to disorders of the hypothalamus or pituitary gland.

The **diagnosis** of hypothyroidism is essentially clinical but, given the non-specific nature of many of the symptoms, biochemical tests are performed for confirmation.[1-3] A raised thyroid stimulating hormone (TSH) value and a low free T_4 or T_3 concentration indicates primary hypothyroidism. Protirelin and thyrotrophin have also been used for the differential diagnosis of hypothyroidism.

Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms. Patients with subclinical hypothyroidism are at a greater risk of developing clinical hypothyroidism if they also have thyroid antibodies against thyroid peroxidase/microsomal antigen, although the best strategy for identifying those at risk is not yet known.[2]

Hypothyroidism is readily **treated** by lifelong replacement therapy with levothyroxine.[1,2,4-7] Although the thyroid gland produces both T_3 (liothyronine) and T_4 (thyroxine), T_3 is mainly produced by peripheral monodeiodination of circulating T_4 and it is therefore sufficient to give levothyroxine alone. There is no rationale for the use of combined preparations containing liothyronine and levothyroxine, or of dried thyroid hormone extracts, which may lead to elevated serum concentrations of T_3 and thyrotoxic symptoms. Liothyronine may, however, be used initially for its rapid onset of action in severe hypothyroid states such as myxoedema coma (see below). Initial checks should be made to ensure that thyroid replacement treatment is restoring deficiencies in thyroid hormone but not providing an excess. This is best done by monitoring hormone concentrations and the goal of replacement therapy is a normal TSH value, which is generally associated with a normal or slightly elevated T_4 value.[2,5]

In subclinical hypothyroidism, treatment with levothyroxine is controversial. It has been recommended[2-4,7,8] if antibodies to thyroid peroxidase are present, or if TSH levels are above 10 milliunits/litre. Some also recommend treatment if TSH levels are between 5 and 10 milliunits/litre and goitre or antibodies (or both) are evident.[7]

Although titres of antithyroid antibodies may fall during **pregnancy**, some patients may require progressive increases in levothyroxine dosage,[9,10] and therefore it has been recommended that thyroid function tests should be performed in each trimester;[1,2,4,11] some[7,12] currently advocate monitoring every 6 to 8 weeks.

The diagnosis of **congenital hypothyroidism** (neonatal hypothyroidism) is now most commonly made on the basis of screening programmes.[13] Early treatment with adequate doses of levothyroxine is required to minimise the effects of hypothyroidism on mental and physical development. It should be started as soon as possible after birth and should be reviewed regularly.[13,14] However, it is generally accepted that in those with more severe hypothyroidism at diagnosis some small degree of deficit and incoordination remains, although they should be mild enough to permit a normal life.[15]

Hypothyroid (myxoedema) coma is a medical emergency requiring prompt treatment usually with liothyronine given by intravenous injection because of its rapid action, although some centres use intravenous levothyroxine. Alternatively, the nasogastric route may be used. Other treatment includes intravenous hydrocortisone (because of the likelihood of adrenocortical insufficiency) and intravenous fluids (to maintain plasma-glucose and electrolyte concentrations). Respiratory function should be supported by assisted ventilation and oxygen. Hypothyroid coma carries a poor prognosis, with mortality around 50% even with treatment.

1. Singer PA, *et al.* Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA* 1995; **273:** 808–12. Also available at: http://www.thyroid.org/professionals/publications/documents/GuidelinesHyperHypo_1995.pdf (accessed 18/05/05)
2. Lindsay RS, Toft AD. Hypothyroidism. *Lancet* 1997; **349:** 413–17. Correction. *ibid.*; 1023.
3. Woeber KA. Update on the management of hyperthyroidism and hypothyroidism. *Arch Intern Med* 2000; **160:** 1067–71.
4. Vanderpump MPJ, *et al.* Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. *BMJ* 1996; **313:** 539–44.
5. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80.
6. Roberts CGP, Ladenson PW. Hypothyroidism. *Lancet* 2004; **363:** 793–803.
7. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; **8:** 457–69. Also available at: http://www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf (accessed 07/04/06)
8. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; **291:** 228–38.
9. Drake WM, Wood DF. Thyroid disease in pregnancy. *Postgrad Med J* 1998; **74:** 583–6.
10. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.
11. Girling JC. Thyroid disease in pregnancy. *Hosp Med* 2000; **61:** 834–40.
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13. LaFranchi S. Congenital hypothyroidism: etiologies, diagnosis, and management. *Thyroid* 1999; **9:** 735–40.
14. Hopwood NJ. Treatment of the infant with congenital hypothyroidism. *J Pediatr* 2002; **141:** 752–4.
15. Rovet JF. Congenital hypothyroidism: long term outcome. *Thyroid* 1999; **9:** 741–8.

Benzylthiouracil

Benciltiouracilo. 6-Benzyl-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; 6-Benzyl-2-mercaptopyrimidin-4-ol; 6-Benzyl-2-thiouracil.

$C_{11}H_{10}N_2OS = 218.3$.

CAS — 33086-27-0; 6336-50-1.

ATC — H03BA03.

ATC Vet — QH03BA03.

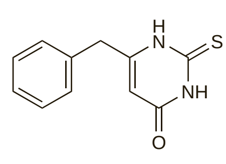

Profile

Benzylthiouracil is a thiourea antithyroid drug. It is given by mouth in the treatment of hyperthyroidism (p.2165) in an initial dose of 150 to 200 mg daily, reducing to a maintenance dose of 100 mg daily; it is given in divided doses, preferably with food.

Porphyria. Benzylthiouracil is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Basdene.

Carbimazole *(BAN, rINN)*

Carbimazol; Carbimazolum; Karbimatsoli; Karbimazol; Karbimazolas. Ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate.

Карбимазол

$C_7H_{10}N_2O_2S = 186.2$.

CAS — 22232-54-8.

ATC — H03BB01.

ATC Vet — QH03BB01.

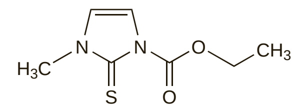

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Carbimazole). A white or yellowish-white crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone.

Adverse Effects and Precautions

Adverse effects from carbimazole and other thiourea antithyroid drugs occur most frequently during the first 8 weeks of treatment. The most common minor adverse effects are nausea and vomiting, gastric discomfort, headache, arthralgia, skin rashes, and pruritus. Hair loss has also been reported.

Bone-marrow depression may occur and mild leucopenia is common. Rarely, agranulocytosis can develop, and is the most serious adverse reaction associated with this class of drugs. Patients or their carers should be told how to recognise such toxicity and should be advised to seek immediate medical attention if mouth ulcers or sore throat, fever, bruising, malaise, or non-specific illness develop. Full blood counts should be performed, and treatment should be stopped immediately if there is any clinical or laboratory evidence of neutropenia. Aplastic anaemia or isolated thrombocytopenia have been reported rarely, as has hypoprothrombinaemia.

There have been several reports of liver damage, most commonly jaundice, in patients taking thiourea antithyroid drugs; the drug should be withdrawn if hepatic effects occur.

Other adverse effects sometimes observed with the thiourea antithyroid compounds include fever, a lupus-like syndrome, myopathy, vasculitis and nephritis, and taste disturbances. Creatine phosphokinase values should be measured if patients experience myalgia.

Excessive doses of antithyroid drugs may cause hypothyroidism and goitre. High doses in pregnancy may result in fetal hypothyroidism and goitre (see Pregnancy, below).

An immune mechanism has been implicated in many of these reactions and cross-sensitivity between the thiourea antithyroid drugs may occur.

Breast feeding. The safety of breast feeding during maternal treatment depends partly on how much drug is distributed into the breast milk. Thiourea antithyroid drugs may be used with care in breast-feeding mothers; neonatal development and thyroid function of the infant should be closely monitored and the lowest effective dose used.

Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily.[1-3] In a small study[4] of breast-feeding mothers taking doses of propylthiouracil as high as 750 mg daily for Graves' disease, no adverse effects were observed on the thyroid status of their infants.

Thiamazole enters breast milk freely, with plasma to milk ratios of almost one.[3,5] The infant's intake of thiamazole after maternal use of carbimazole (or thiamazole) might be greatly reduced by discarding the breast milk produced 2 to 4 hours after a dose,[6] since the highest concentration was found at this time. Two studies found no adverse effects on thyroid function,[7,8] thyroid hormone levels,[7] or physical and intellectual development, in breast-fed infants during up to 6 months[7] to 1 year[8] of maternal treatment with thiamazole. Maximum maternal daily doses of 10 mg of thiamazole,[3] 15 mg of carbimazole, and 150 mg of propylthiouracil[9] have been recommended, although thiamazole 20 to 30 mg has been given to thyrotoxic lactating women for the first month of a year of therapy with no observable adverse effects on the thyroid function of their breast-fed infants.[10] Despite stating that goitre has been associated with the use of carbimazole, the American Academy of Pediatrics considers the use of all three drugs to be compatible with breast feeding.[11]

1. Kampmann JP, *et al.* Propylthiouracil in human milk: revision of a dogma. *Lancet* 1980; **i:** 736–8.
2. Johansen K, *et al.* Excretion of methimazole in human milk. *Eur J Clin Pharmacol* 1982; **23:** 339–41.
3. Cooper DS. Antithyroid drugs: to breast-feed or not to breast-feed. *Am J Obstet Gynecol* 1987; **157:** 234–5.
4. Momotani N, *et al.* Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf)* 2000; **53:** 177–81.
5. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
6. Rylance GW, *et al.* Carbimazole and breastfeeding. *Lancet* 1987; **i:** 928.
7. Azizi F. Effect of methimazole treatment of maternal thyrotoxicosis on thyroid function in breast-feeding infants. *J Pediatr* 1996; **128:** 855–8.
8. Azizi F, *et al.* Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000; **85:** 3233–8.
9. Lamberg B-A, *et al.* Antithyroid treatment of maternal hyperthyroidism during lactation. *Clin Endocrinol (Oxf)* 1984; **21:** 81–7.
10. Azizi F, Hedayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. *J Endocrinol Invest* 2002; **25:** 493–6.
11. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)

Effects on the blood. While **leucopenia** is considered to be a common adverse effect of the thiourea antithyroid drugs, occurring in up to a quarter of patients, it is usually mild and improves as treatment continues.[1]

Agranulocytosis, a more serious hazard, is usually reported to affect 0.03% of patients in Europe,[2] who are mostly treated with carbimazole. However, the incidence has been reported to be higher (0.4%) in areas where thiamazole is used.[3,4] Fatalities have been reported.[1,2,4,5] Although a direct toxic effect had been suggested, the agranulocytosis associated with the thiourea drugs is generally considered to be immunologically mediated.[1,6] The onset of agranulocytosis is usually rapid and monitoring of the blood count is not always of predictive value;[3] routine monitoring is not indicated.[2] Agranulocytosis has occurred in patients receiving propylthiouracil for a second time who had no such complications in their first course of therapy.[7] There is limited evidence that agranulocytosis is more common at higher doses, and in older patients. However, this has not been proved conclusively.[1]

There have been some case reports of **aplastic anaemia** being produced by antithyroid drugs, but the excess risk associated with their use is considered to be very low[6,8] and complete recovery has been reported after withdrawal of the antithyroid drug. An immune mechanism has been implicated.

Carbimazole has produced **haemolytic anaemia**.[9] In this case the immune reaction was specific to carbimazole and could not be demonstrated with thiamazole.

On very rare occasions patients taking propylthiouracil have experienced a reduction in prothrombin values and bleeding.[10-12] In one patient bleeding was linked to propylthiouracil-induced **thrombocytopenia**.[13]

1. Bartalena L *et al.* Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety* 1996; **15:** 53–63.
2. Committee on Safety of Medicines/Medicines Control Agency. Reminder: agranulocytosis with antithyroid drugs. *Current Problems* 1999; **25:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
3. Tajiri J, *et al.* Antithyroid drug-induced agranulocytosis: the usefulness of routine white blood cell count monitoring. *Arch Intern Med* 1990; **150:** 621–4.
4. Anonymous. Elaboration: drug-induced agranulocytosis–monitoring antithyroid treatment. *Drug Ther Bull* 1997; **35:** 88.
5. Anonymous. Drug-induced agranulocytosis. *Drug Ther Bull* 1997; **35:** 49–52.
6. International Agranulocytosis and Aplastic Anaemia Study. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. *BMJ* 1988; **297:** 262–5.
7. Shiran A, *et al.* Propylthiouracil-induced agranulocytosis in four patients previously treated with the drug. *JAMA* 1991; **266:** 3129–30.
8. Bishara J. Methimazole-induced aplastic anemia. *Ann Pharmacother* 1996; **30:** 684.
9. Salama A, *et al.* Carbimazole-induced immune haemolytic anaemia: role of drug-red blood cell complexes for immunization. *Br J Haematol* 1988; **68:** 479–82.
10. D'Angelo G, Le Gresley LP. Severe hypoprothrombinaemia after propylthiouracil therapy. *Can Med Assoc J* 1959; **81:** 479–81.
11. Naeye RL, Terrien CM. Hemorrhagic state after therapy with propylthiouracil. *Am J Clin Pathol* 1960; **34:** 254–7.
12. Gotta AW, *et al.* Prolonged intraoperative bleeding caused by propylthiouracil-induced hypoprothrombinemia. *Anesthesiology* 1972; **37:** 562–3.
13. Ikeda S, Schweiss JF. Excessive blood loss during operation in the patient treated with propylthiouracil. *Can Anaesth Soc J* 1982; **29:** 477–80.

Effects on the ears. Earache, high-frequency hearing loss, and tinnitus in a patient with Graves' disease were attributed to hypersensitivity to carbimazole;[1] hearing loss, but not the tinnitus, resolved when carbimazole was replaced with propylthiouracil.

1. Hill D, *et al.* Hearing loss and tinnitus with carbimazole *BMJ* 1994; **309:** 929.

Effects on the kidneys. Glomerulonephritis associated with the development of antineutrophil cytoplasmic antibodies has been reported in patients receiving thiourea antithyroid drugs.[1-5]

1. Vogt BA, *et al.* Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment with propylthiouracil in children. *J Pediatr* 1994; **124:** 986–8.
2. D'Cruz D, *et al.* Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with anti-thyroid drug treatment. *Br J Rheumatol* 1995; **34:** 1090–1.
3. Yuasa S, *et al.* Antineutrophil cytoplasmic antibodies (ANCA)-associated crescentic glomerulonephritis and propylthiouracil therapy. *Nephron* 1996; **73:** 701–3.
4. Kudoh Y, *et al.* Propylthiouracil-induced rapidly progressive glomerulonephritis associated with antineutrophil cytoplasmic autoantibodies. *Clin Nephrol* 1997; **48:** 41–3.
5. Prasad GVR, *et al.* Propylthiouracil-induced diffuse proliferative lupus nephritis: review of immunological complications. *J Am Soc Nephrol* 1997; **8:** 1205–10.

Effects on the liver. Jaundice, usually cholestatic, has been reported with thiamazole and carbimazole.[1-5] An immune-mediated mechanism rather than a toxic reaction has been proposed. Hepatitis (sometimes progressing to cirrhosis[6]) and hepatic necrosis have been associated with propylthiouracil,[6-9] sometimes with fatal consequences.[7,8] However, in one study[10] almost 30% of patients being treated with propylthiouracil developed asymptomatic liver changes (increased alanine aminotransferase values). Dose reduction resulted in a return to normal values in 13 of the 15 patients affected.

Despite reports of liver damage, propylthiouracil has been investigated in the treatment of patients with alcoholic liver disease (see p.2175).

1. Becker CE, *et al.* Hepatitis from methimazole during adrenal steroid therapy for malignant exophthalmos. *JAMA* 1968; **206:** 1787–9.
2. Fischer MG, *et al.* Methimazole-induced jaundice. *JAMA* 1973; **223:** 1028–9.
3. Blom H, *et al.* A case of carbimazole-induced intrahepatic cholestasis. *Arch Intern Med* 1985; **145:** 1513–15.
4. Schmidt G, *et al.* Methimazole-associated cholestatic liver injury: case report and brief literature review. *Hepatogastroenterology* 1986; **33:** 244–6.
5. Arab DM, *et al.* Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1995; **80:** 1083–5.
6. Özenírler S, *et al.* Propylthiouracil-induced hepatic damage. *Ann Pharmacother* 1996; **30:** 960–3.
7. Hanson JS. Propylthiouracil and hepatitis. Two cases and a review of the literature. *Arch Intern Med* 1984; **144:** 994–6.
8. Limaye A, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987; **82:** 152–4.
9. Ichiki Y, *et al.* Propylthiouracil-induced severe hepatitis: a case report and review of the literature. *J Gastroenterol* 1998; **33:** 747–50.
10. Liaw Y-F, *et al.* Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. *Ann Intern Med* 1993; **118:** 424–8.

Effects on the lungs. Diffuse interstitial pneumonitis occurred in 2 patients given propylthiouracil[1] and a hypersensitivity reaction was suggested. Propylthiouracil was also implicated in 2 cases of alveolar haemorrhage associated with antineutrophil cytoplasmic antibody.[2,3]

1. Miyazono K, *et al.* Propylthiouracil-induced diffuse interstitial pneumonitis. *Arch Intern Med* 1984; **144:** 1764–5.
2. Ohtsuka M, *et al.* Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. *Eur Respir J* 1997; **10:** 1405–7.
3. Dhillon SS, *et al.* Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. *Chest* 1999; **116:** 1485–8.

Effects on the muscles. Myositis with pain, weakness, and increased creatine kinase concentrations has been reported with carbimazole.[1,2] This effect might be explained by 'tissue hypothyroidism', and might respond to dosage reduction.[3]

1. Page SR, Nussey SS. Myositis in association with carbimazole therapy. *Lancet* 1989; **i:** 964.
2. Pasquier E, *et al.* Biopsy-proven myositis with microvasculitis in association with carbimazole. *Lancet* 1991; **338:** 1082–3.
3. O'Malley B. Carbimazole-induced cramps. *Lancet* 1989; **i:** 1456.

Hypersensitivity. Many of the adverse effects associated with the thiourea antithyroid drugs appear to have an immune basis. These effects may be associated with polyarthritis[1] or hypersensitivity vasculitis.[2-7] The latter is sometimes severe and multisystemic, and fatalities have occurred.

Hypersensitivity reactions may also be associated with the development of antineutrophil cytoplasmic antibodies (ANCA), or sometimes with a lupus-like syndrome with or without the presence of antinuclear antibodies.[2,5]

Serum sickness with arthralgias and raised immunoglobulin M (IgM) concentrations has been reported with thiamazole,[8] and the production of antibodies to insulin, resulting in episodes of hypoglycaemia, has been associated with thiamazole[9] and carbimazole.[10]

The thiourea antithyroid drugs all contain a thioamide group and cross-sensitivity between them might be expected. In particular, complete cross-reactivity may be expected between thiamazole and carbimazole since the latter is converted *in vivo* to thiamazole, although one report[11] suggests this is not necessarily the case. Cross-sensitivity between propylthiouracil and carbimazole[12] or thiamazole[13] has been reported but the incidence and clinical importance is not clear. Although it has been suggested that carbimazole or thiamazole may be substituted for propylthiouracil in hypersensitive patients, it is safer to stop antithyroid drugs in such patients.[12]

1. Bajaj S, *et al.* Antithyroid arthritis syndrome. *J Rheumatol* 1998; **25:** 1235–9.
2. Kawachi Y, *et al.* ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. *Clin Exp Dermatol* 1995; **20:** 345–7.
3. Chastain MA, *et al.* Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. *J Am Acad Dermatol* 1999; **41:** 757–64.
4. Gunton JE, *et al.* Clinical case seminar: antithyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. *J Clin Endocrinol Metab* 1999; **84:** 13–16.
5. Mathieu E, *et al.* Systemic adverse effect of antithyroid drugs. *Clin Rheumatol* 1999; **18:** 66–8.
6. Dolman KM, *et al.* Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. *Lancet* 1993; **342:** 651–2.
7. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; **36:** 130–47.
8. Van Kuyk M, *et al.* Methimazole-induced serum sickness. *Acta Clin Belg* 1983; **38:** 68–9.
9. Hakamata M, *et al.* Insulin autoimmune syndrome after the third therapy with methimazole. *Intern Med* 1995; **34:** 410–12.
10. Burden AC, Rosenthal FD. Methimazole and insulin autoimmune syndrome. *Lancet* 1983; **ii:** 1311.
11. Kroll H, *et al.* Drug-dependent antibodies against the prodrug carbimazole do not react with the metabolite thiamazole. *Blood* 2001; **97:** 2186–7.
12. Smith A, *et al.* Cross sensitivity to antithyroid drugs. *BMJ* 1989; **298:** 1253.
13. De Weweire A, *et al.* Failure to control hyperthyroidism with a thionamide after potassium perchlorate withdrawal in a patient with amiodarone associated thyrotoxicosis. *J Endocrinol Invest* 1987; **10:** 529.

Pregnancy. Thiourea antithyroid drugs have been used successfully in pregnancy (see Hyperthyroidism, p.2165).

Thiamazole (the metabolite of carbimazole) has been the drug most frequently involved in the few reports of **congenital defects** following maternal use of such compounds. Several infants exposed to thiamazole *in utero* have been born with scalp defects (aplasia cutis congenita—a localised absence of skin at birth)[1,2] although hyperthyroidism itself may give rise to such defects.[3] Individual cases of other congenital defects associated with thiamazole have included choanal atresia (an upper respiratory-tract defect), oesophageal atresia, and tracheo-oesophageal fistula[3] but the incidence of congenital abnormalities is not increased compared with the general population.[4] Gastroschisis (an abdominal wall defect) has been reported in an infant after maternal exposure to carbimazole.[5] There have been some reports of neonates exposed to thiourea antithyroid drugs *in utero* displaying signs of **hypothyroidism** including goitre.[6,7]

1. Milham S. Scalp defects in infants of mothers treated for hyperthyroidism with methimazole or carbimazole during pregnancy. *Teratology* 1985; **32:** 321.
2. Vogt T, *et al.* Aplasia cutis congenita after exposure to methimazole: a causal relationship? *Br J Dermatol* 1995; **133:** 994–6.
3. Johnsson E, *et al.* Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 1997; **350:** 1520.
4. Wing DA, *et al.* A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994; **170:** 90–5.
5. Guignon A-M, *et al.* Carbimazole-related gastroschisis. *Ann Pharmacother* 2003; **37:** 829–31.
6. O'Doherty MJ, *et al.* Treating thyrotoxicosis in pregnant or potentially pregnant women. *BMJ* 1999; **318:** 5–6.
7. Masiukiewicz US, Barrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; **9:** 647–52.

Pharmacokinetics

The pharmacokinetics of carbimazole and thiamazole can be considered together since carbimazole is rapidly and completely metabolised to thiamazole in the body. The antithyroid activity of carbimazole is dependent upon this conversion to thiamazole.

Carbimazole and other thiourea antithyroid drugs are rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 2 hours after oral doses.

They are concentrated in the thyroid gland; since their duration of action is more closely related to the intrathyroidal drug concentration than their plasma half-life, prolonged antithyroid activity results from single daily doses. Thiamazole is not bound to plasma proteins.

Thiamazole has an elimination half-life from plasma of about 3 to 6 hours and is metabolised, probably by the liver, and excreted in the urine. Less than 12% of a dose of thiamazole may be excreted as unchanged drug. 3-Methyl-2-thiohydantoin has been identified as a metabolite of thiamazole. The elimination half-life may be increased in hepatic and renal impairment.

Thiamazole crosses the placenta and is distributed into breast milk.

◊ References to the pharmacokinetics of carbimazole and thiamazole.

1. Skellern GG, *et al.* The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol* 1980; **9:** 137–43.
2. Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet* 1981; **6:** 401–28.
3. Jansson R, *et al.* Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983; **57:** 129–32.
4. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
5. Jansson R, *et al.* Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985; **10:** 443–50.

Uses and Administration

Carbimazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165). It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Carbimazole is completely metabolised to thiamazole and it is this metabolite that is responsible for the antithyroid activity of carbimazole.

Carbimazole is given orally in a typical initial dosage of 15 to 40 mg daily, in divided doses; occasionally up to 60 mg daily may be required. Control of symptoms is usually achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to the smallest amount that will maintain the euthyroid state. Typical maintenance doses are 5 to 15 mg daily, which may be given as a single daily dose.

Treatment in children should be undertaken by a specialist. The *BNFC* recommends an initial dose of 250 micrograms/kg three times daily for neonates and children up to 12 years of age. Children aged 12 to 18 years may be given 10 mg three times daily initially. Doses are adjusted according to response; higher initial doses may be needed in thyrotoxic crisis.

Carbimazole is also given orally in a dose of 20 to 60 mg daily, with supplemental levothyroxine, as a *blocking-replacement regimen*.

Either form of maintenance treatment is usually continued for at least a year, and often for 18 months; up to 2 years of treatment may be required.

Preparations

BP 2008: Carbimazole Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Neo-Mercazole; ***Austria:*** Carbistad; ***Denm.:*** Neo-Mercazole; ***Fin.:*** Tyrazol; ***Fr.:*** Neo-Mercazole; ***Ger.:*** Car; Neo-Thyreostat†; ***Gr.:*** Thyrostat; ***Hong Kong:*** Cazole; ***India:*** Neo-Mercazole; ***Indon.:*** Neo-Mercazole; ***Irl.:*** Neo-Mercazole; ***Malaysia:*** Camazol†; ***Norw.:*** Neo-Mercazole; ***NZ:*** Neo-Mercazole; ***Philipp.:*** Neo-Mercazole; ***S.Afr.:*** Neo-Mercazole; ***Singapore:*** Camazol; Cazole†; ***Spain:*** Neo Tomizol; ***Switz.:*** Neo-Mercazole; ***UK:*** Neo-Mercazole.

Dibromotyrosine

Dibromotirosina. 3,5-Dibromo-L-tyrosine.

$C_9H_9Br_2NO_3$ = 339.0.
CAS — 300-38-9.
ATC — H03BX02.
ATC Vet — QH03BX02.

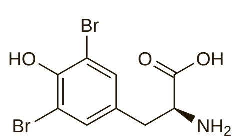

Profile

Dibromotyrosine is an antithyroid drug used in the treatment of hyperthyroidism (p.2165) in doses of 300 to 900 mg daily by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bromotiren.
Multi-ingredient: *Ital.:* Bromazolo.

Iodine

Iod; Iode; Iodium; Iodo; Iodum; Iyot; Jód; Jod; Jodas; Jodi; Jodum; Yodo.

I_2 = 253.80894.
CAS — 7553-56-2.
ATC — D08AG03.
ATC Vet — QD08AG03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Iodine). Greyish-violet, brittle plates or fine crystals, with a metallic sheen. It is slowly volatile at room temperature. Very slightly soluble in water; soluble in alcohol; slightly soluble in glycerol; very soluble in concentrated solutions of iodides.

USP 31 (Iodine). Heavy, greyish-black plates or granules with a metallic sheen and a characteristic odour. Soluble 1 in 3000 of water, 1 in 13 of alcohol, 1 in 4 of carbon disulfide, and 1 in 80 of glycerol; freely soluble in chloroform, in ether, and in carbon tetrachloride; soluble in solutions of iodides. Store in airtight containers.

Incompatibility. With acetone, iodine forms a pungent irritating compound.

Potassium Iodate

Iodato potásico; Potasu jodan.

KIO_3 = 214.0.
CAS — 7758-05-6.

Pharmacopoeias. In *Br., Chin.,* and *It.*

BP 2008 (Potassium Iodate). A white crystalline powder with a slight odour. Slowly soluble in water; insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 8.0.

Potassium Iodide

Iodeto de Potássio; Ioduro potásico; Jodid draselný; Kalii Iodetum; Kalii iodidum; Kalii Jodidum; Kalio jodidas; Kalium Iodatum; Kalium Jodatum; Kaliumjodid; Kálium-jodid; Kaliumjodidi; Pot. Iod.; Potassii Iodidum; Potassium (Iodure de); Potassium, iodure de; Potasu jodek; Potasyum Iyodür.

KI = 166.0.
CAS — 7681-11-0.
ATC — R05CA02; S01XA04; V03AB21.
ATC Vet — QR05CA02; QS01XA04; QV03AB21.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Potassium Iodide). A white or almost white powder or colourless crystals. Very soluble in water; soluble in alcohol; freely soluble in glycerol. Protect from light.

USP 31 (Potassium Iodide). Hexahedral crystals, either transparent and colourless or somewhat opaque and white, or a white, granular powder. It is slightly hygroscopic. Soluble 1 in 0.7 of water and 1 in 0.5 of boiling water, 1 in 22 of alcohol, and 1 in 2 of glycerol. Its solutions are neutral or alkaline to litmus.

Sodium Iodide

Iodeto de Sódio; Ioduro sódico; Jodid sodný; Natrii Iodetum; Natrii iodidum; Natrii Jodidum; Natrio jodidas; Natrium Iodatum; Natriumjodid; Nátrium-jodid; Natriumjodidi; Sod. Iod.; Sodii Iodidum; Sodium (Iodure de); Sodium, iodure de; Sodu jodek; Sodyum Iyodür.

NaI = 149.9.
CAS — 7681-82-5.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Sodium Iodide). Colourless crystals or white or almost white, crystalline powder. It is hygroscopic. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Sodium Iodide). Colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air and develops a brown tint upon decomposition. Soluble 1 in 0.6 of water, 1 in 2 of alcohol, and 1 in 1 of glycerol. Store in airtight containers.

Adverse Effects and Treatment

Iodine and iodides, whether applied topically or given systemically, can give rise to hypersensitivity reactions which may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.

Inhalation of iodine vapour is very irritating to mucous membranes.

Iodine and iodides have variable effects on the thyroid (see below) and can produce goitre and hypothyroidism as well as hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon). Goitre and hypothyroidism have also occurred in infants born to mothers who had taken iodides during pregnancy.

Prolonged use may lead to a range of adverse effects, often called 'iodism', some of which may again be due to hypersensitivity. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be acute rhinitis, coryza-like symptoms, and swelling and inflammation of the throat. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchitis may develop. Skin reactions include acneform or, more rarely, severe eruptions (iododerma). Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances, notably nausea, vomiting, and diarrhoea.

The symptoms of acute poisoning from ingestion of iodine are mainly due to its corrosive effects on the gastrointestinal tract; a disagreeable metallic taste, vomiting, abdominal pain, and bloody diarrhoea occur. Thirst and headache have been reported. Systemic toxicity may lead to shock, tachycardia, hypotension, fever, metabolic acidosis and renal impairment. Death may be due to circulatory failure, oedema of the epiglottis resulting in asphyxia, aspiration pneumonia, or pulmonary oedema. Oesophageal stricture may occur if the patient survives the acute stage.

Victims of acute poisoning have been given copious draughts of milk or starch mucilage; lavage should probably not be attempted, and certainly not unless the ingested iodine was in sufficiently dilute form not to produce gastrointestinal corrosion. Other possible oral treatments include activated charcoal or sodium thiosulfate solution (usually as a 1% solution) to reduce iodine to the less toxic iodides.

Effects on the thyroid. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (see also under Amiodarone, p.1212). Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.

The normal daily requirement ranges from 100 to 300 micrograms.[1,2] Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.[2] When progressively larger doses are given there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the Wolff-Chaikoff effect). This effect is usually seen with doses of more than about 2 mg daily, but is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goitre and **hypothyroidism**.[1,2]

Excess iodine may also induce **hyperthyroidism** (the Iod-Basedow or Jod-Basedow phenomenon). Iodine-induced hyperthyroidism has been associated with iodine prophylaxis programmes in developing countries.[3] The highest incidence of hyperthyroidism has been reported to occur 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.[4] Elderly subjects and those with nodular goitres have been found to be at greatest risk.

To overcome any adverse effects on thyroid function as a result of iodine prophylaxis during **pregnancy**, WHO has issued guidelines on the safe use of iodised oil during gestation.[5,6] There is some evidence that the use of iodine-containing antiseptics on pregnant women and neonates may cause disturbances in thyroid function.[7,8]

1. Arthur JR, Beckett GJ. Thyroid function. *Br Med Bull* 1999; **55:** 658–68.
2. WHO. Iodine. In *Trace elements in human nutrition and health.* Geneva: WHO, 1996: 49–71.
3. Delange F, *et al.* Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999; **9:** 545–56.
4. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)* 1983; **62:** 1–20.
5. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
6. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
7. Linder N *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
8. Weber G *et al.* Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F70–2.

Precautions

Caution is necessary if preparations containing iodine or iodides are taken for long periods, and such preparations should not be taken regularly during pregnancy except when iodine supplementation is required. Caution is also required when giving iodine or iodides to children. Patients over the age of 45 years or with nodular goitres are especially susceptible to hyperthyroidism when given iodine supplementation. Reduced doses should therefore be used and supplementation with iodised oil may not be appropriate.

Solutions of iodine applied to the skin should not be covered with occlusive dressings. The disinfectant activity of iodine is reduced by alkalis as well as by protein.

As iodine and iodides can affect the thyroid gland, their use may interfere with tests of thyroid function.

Breast feeding. Iodine is concentrated by the mammary gland into breast milk to ensure an adequate supply to the breast-fed infant. Since this is dependent on the maternal dietary intake,[1] WHO recommends a daily iodine intake of 200 micrograms for lactating women, see Iodine Deficiency Disorders, below.

The *BNFC* considers treatment with iodine or iodides to be a contra-indication to breast feeding. However, the American Academy of Pediatrics[2] considers that such treatment is usually compatible with breast feeding although it is noted that goitre or effects on thyroid function have been reported. Any risk is not confined to oral treatment: transient neonatal hypothyroidism has been reported in a breast-fed infant whose mother was treated with iodine tampons,[3] and for a report of increased milk-iodine concentrations associated with vaginal povidone-iodine see p.1659.

1. Semba RD, Delange F. Iodine in human milk: perspectives for infant health. *Nutr Rev* 2001; **59:** 269–78.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)
3. Casteels K, *et al.* Transient neonatal hypothyroidism during breastfeeding after post-natal maternal topical iodine treatment. *Eur J Pediatr* 2000; **159:** 716–17.

Interactions

The effects of iodine and iodides on the thyroid may be altered by other compounds including amiodarone and lithium.

Pharmacokinetics

Iodine is slightly absorbed when applied to the skin. When taken by mouth, iodine preparations (which are converted to iodide) and iodides are transported to, and concentrated in, the thyroid gland (see p.2165). Iodides not taken up by the thyroid are excreted mainly in the urine, with smaller amounts appearing in the faeces, saliva, and sweat. They cross the placenta and are distributed into breast milk.

Uses and Administration

Iodine is an essential trace element in the human diet, necessary for the formation of thyroid hormones (see p.2165), and consequently it is used in iodine deficiency and thyroid disorders. It also has antimicrobial activity.

For the prophylaxis and treatment of **iodine deficiency disorders** (below) it may be given as potassium or sodium iodide, iodised oil, or potassium iodate. Each g of potassium iodide represents about 6 mmol of potassium and of iodine. Each g of sodium iodide represents about 6.7 mmol of sodium and of iodine. Each g of potassium iodate represents about 4.7 mmol of potassium and of iodine.

In the pre-operative management of **hyperthyroidism** (p.2165) iodine and iodides are used with antithyroid drugs such as carbimazole, thiamazole, or propylthiouracil. Such use has been thought to render the thyroid firm and avoid the increased vascularity and friability (with increased risk of haemorrhage) that may result from the use of an antithyroid drug alone. However, there is little evidence of a beneficial effect.

Iodine may be given as a solution with potassium iodide (Aqueous Iodine Oral Solution BP 2008; Lugol's Solution or Strong Iodine Solution USP 31) which contains in each mL 130 mg of free and combined iodine; a dose of 0.1 to 0.3 mL in milk or water is given three times daily for 10 to 14 days. Alternatively, potassium iodide has been given in doses of up to 250 mg three times daily with food. Solutions of potassium iodide intended for oral use should be given well diluted to avoid gastric irritation. Potassium iodide may also be given 1 hour after an antithyroid drug as part of the management of thyroid storm; doses as high as 500 mg every 4 hours have been suggested. Sodium iodide has been given by intravenous injection as part of the management of thyroid storm.

Radioactive sodium iodide (see Iodine-131, p.2054) is also used for the treatment of hyperthyroidism, especially when medical treatment or compliance is problematic, in patients with cardiac disease, or in patients who relapse after thyroidectomy.

Potassium iodide has been tried in the treatment of benign **thyroid nodules** (p.2165).

Potassium iodide or potassium iodate are taken by mouth for **radiation protection** (below) to saturate the thyroid when uptake of radio-iodine by the gland is not desired.

Iodine has a powerful bactericidal action. It is also active against fungi, viruses, protozoa, cysts, and spores. Potassium iodide has been used in the treatment of fungal infections such as sporotrichosis (below). Iodine is used as an **antiseptic** and **disinfectant** generally as a 2% or 2.5% solution. Its activity is reduced in the presence of organic matter, though not to the same extent as with the other halogen disinfectants. If industrial methylated spirit is used for the solution, it should be free from acetone, with which iodine forms an irritant and lachrymatory compound. Iodine solutions may be applied to small wounds or abrasions as well as to unbroken skin, but an iodophore such as povidone-iodine (p.1659) may be preferred.

Iodine may also be used to sterilise drinking water; 5 drops of a 2% alcoholic solution added to about one litre (one US quart) of water is reported to kill amoebae and bacteria within 15 minutes. Water contaminated with *Giardia* requires 12 drops of a 2% alcoholic solution for each litre which may take one hour to achieve its effect. Tablets containing tetraglycine hydroperiodide (p.1663) may be preferred.

When iodine combines chemically it is decolorised and so-called colourless iodine preparations do not have the disinfectant properties of iodine.

Iodine stains the skin a deep reddish-brown; the stain can be readily removed by dilute solutions of alkalis or sodium thiosulfate. A dilute solution of iodine (Schiller's Iodine) may also be used as a **diagnostic** stain in colposcopy.

There have been numerous other uses of iodine and iodides. Iodides have long been used as ingredients of expectorant mixtures (see Cough, p.1547) but there has been concern over their safety because of their potential for thyroid suppression. A diatomic iodine formulation is under investigation for the treatment of fibrocystic breast disease. Iodinated organic compounds including iodised oil are used as X-ray contrast media (p.1474). Potassium iodide has been given in the treatment of Sweet's syndrome (acute febrile neutrophilic dermatosis). A mixture of iodine and sodium iodide is used as sclerotherapy for varicose veins (p.2347).

Fungal infections. Potassium iodide is used in the treatment of cutaneous sporotrichosis (p.522), although how it acts is unclear since antifungal activity was not found *in vitro* against *Sporothrix schenkii*.[1] It has also been shown to be effective in the treatment of phycomycosis caused by *Basidiobolus haptosporus*[2,3] but again the mode of action is unclear.[4] Potassium iodide is usually given orally in a gradually increasing dosage up to the limit of tolerance. The WHO recommended initial dose is 1 mL [1 g] of a saturated solution of potassium iodide (1 g/mL) given three times daily; treatment should be continued for at least 1 month after the disappearance or stabilisation of the lesions.

Potassium iodide and sodium iodide have been tried by local intracavitary instillation for the treatment of life-threatening haemoptysis from pulmonary aspergillomas.[5] Mechanical factors may have accounted for a beneficial effect rather than any antifungal action. Aspergillomas are usually managed conservatively or, in more severe disease, with antifungals or surgery (see p.517).

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Kelly S, *et al.* Subcutaneous phycomycosis in Sierra Leone. *Trans R Soc Trop Med Hyg* 1980; **74:** 396–7.
3. Kamalam A, Thambiah AS. Muscle invasion by Basidiobolus haptosporus. *Sabouraudia* 1984; **22:** 273–7.
4. Yangco BG, *et al.* In vitro susceptibilities of human and wild-type isolates of Basidiobolus and Conidiobolus species. *Antimicrob Agents Chemother* 1984; **25:** 413–16.
5. Rumbak M, *et al.* Topical treatment of life threatening haemoptysis from aspergillomas. *Thorax* 1996; **51:** 253–5.

Iodine deficiency disorders. Iodine is an essential trace element required for thyroid hormone production. In the UK the reference nutrient intake (RNI) for adults is 140 micrograms (1.1 micromoles) of iodine daily[1] and in the USA the recommended dietary allowance (RDA) is 150 micrograms daily.[2] A full explanation of the terms RNI and RDA can be found under Human Requirements of Vitamins, p.1925. In 1996, WHO[3] recommended the following daily iodine intakes:

- 50 micrograms up to 12 months of age
- 90 micrograms from 1 to 6 years
- 120 micrograms from 7 to 12 years
- 150 micrograms from 12 years of age
- 200 micrograms during pregnancy and lactation.

A subsequent document from the International Council for Control of Iodine Deficiency Disorders, UNICEF, and WHO recommended 90 micrograms daily for all infants and children up to 59 months of age and 120 micrograms from 6 to 12 years.[4]

When iodine requirements are not met, a range of disorders can develop. These iodine deficiency disorders include endemic goitre (enlargement of the thyroid), endemic cretinism (a syndrome characterised by deaf-mutism, intellectual deficit, spasticity, and sometimes hypothyroidism), impaired mental function in children and adults, and an increased incidence of still-births as well as perinatal and infant mortality.[3,5]

Iodine deficiency disorders can be prevented by iodine supplementation. The incidence of endemic goitre, endemic cretinism, and mental retardation can be reduced and some of the effects of established iodine deficiency ameliorated, with only modest risks.[6]

Although various methods of iodine supplementation, including iodination of sugar, water, and bread, as well as giving potassium iodide, have been investigated, the two methods generally used are iodination of culinary salt and the use of iodised oil.[3]

Salt may be iodinated by the addition of potassium iodide or potassium iodate. The concentration used in different countries varies over a wide range from 10 to about 80 ppm of elemental iodine.[4]

The chief alternative to supplementation with iodinated salt is *iodised oil*, usually by intramuscular injection; it is useful where salt consumption is unreliable or inadequate or where immediate action is necessary to correct severe iodine deficiency.[3] A commonly used type of iodised oil has been a poppyseed oil containing about 38% w/w or 480 mg/mL of iodine (see Iodised Oil, p.1482). Some countries have produced iodised oil based on alternatives such as peanut or rapeseed oil.[7,8] Single intramuscular doses can provide adequate protection from iodine deficiency for up to 3 years. WHO has recommended[9] that infants up to 1 year receive 190 mg iodine, as iodised oil (480 mg/mL iodine), by intramuscular injection; children and adults up to age 45 are given 380 mg. Subjects over the age of 45 years and those with nodular goitre are susceptible to hyperthyroidism when given iodine, and iodised oil may not be a suitable means of supplementation. If it is used, doses of 76 mg are given.[9]

Iodised oil may also be given orally once yearly. WHO recommends[9] that infants up to 1 year be given a single dose of 100 mg iodine, children from 1 to 5 years 200 mg, and those over 6 years 400 mg. The evidence suggests that oral iodised oil is as effective as intramuscular for preventing iodine deficiency disorders in children.[10] Adults are also given 400 mg, except during pregnancy, when a single dose of 200 mg is recommended.[9]

Iodine or iodides may suppress neonatal thyroid function and it is generally recommended that iodine compounds should be avoided during **pregnancy**. However, where it is essential to prevent neonatal goitre and cretinism, iodine supplementation should not be withheld from pregnant women.[11,12] Iodine supplementation has been found to be effective in preventing brain-damage in the fetus provided it is given to the mother in the first or second trimester;[11] treatment later in pregnancy was not effective in improving neurological status, although some developmental improvement was seen and hypothyroidism will be corrected. WHO has stated that in areas where iodine deficiency disorders are moderate to severe, iodised oil given either before or at any stage of gestation is beneficial.[9,12] A dose of 480 mg iodine intramuscularly each year, or 300 to 480 mg iodine by mouth each year, or 100 to 300 mg iodine by mouth every 6 months, is recommended for pregnant women and for at least one year postpartum. Similar intramuscular doses are recommended for non-pregnant fertile women with oral doses being 400 to 960 mg iodine every year, or 200 to 480 mg every 6 months.[9]

Indirect iodine supplementation, by addition of potassium iodate to the water used to irrigate crops, has been tried in areas of iodine deficiency where other methods had proved difficult to implement.[13]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the Committee on Medical Aspects of Food Policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
4. ICCIDD/UNICEF/WHO. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination*. Geneva: WHO, 2001. Also available at: http://www.who.int/nutrition/publications/en/idd_assessment_monitoring_eliminination.pdf (accessed 01/08/08)
5. WHO. Iodine status worldwide: WHO Global Database on Iodine Deficiency. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241592001.pdf (accessed 18/05/05)
6. Delange F, Lecomte P. Iodine supplementation: benefits outweigh risks. *Drug Safety* 2000; **22:** 89–95.
7. Ingenbleek Y, *et al.* Iodised rapeseed oil for eradication of severe endemic goitre. *Lancet* 1997; **350:** 1542–5.
8. Untoro J, *et al.* Efficacy of different types of iodised oil. *Lancet* 1998; **351:** 752–3.
9. WHO. *WHO model formulary*. Geneva: WHO, 2004.
10. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Available in The Cochrane Database of Systemic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/05/05).
11. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
12. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
13. Cao X-Y, *et al.* Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet* 1994; **344:** 107–10.

Radiation protection. Giving a radiologically stable form of iodine to saturate the thyroid gland confers thyroid protection from iodine radionuclides.[1,2] When thyroid protection from a *medical procedure* involving radio-iodine is needed 100 to 150 mg of iodide as potassium iodide may be given orally 24 hours before the procedure and daily for up to 10 days following it.

In the event of a *nuclear accident* authorities in the USA recommend[1,3] an oral dose of 130 mg of potassium iodide daily in adults (including pregnant and lactating women). Daily doses should be given until risk of exposure has passed and adjunctive measures have been implemented. Recommended daily doses of potassium iodide for children are:

- up to 1 month of age, 16 mg
- 1 month to 3 years, 32 mg
- 3 to 12 years (up to 18 years if body-weight is less than 70 kg), 65 mg

In the UK the oral dose recommended[4,5] is 100 mg of stable iodine (as 170 mg of potassium iodate) for adults (including pregnant women and women who are breast feeding) as soon as possible after exposure and before evacuation. Dosages for children are:

- 3 to 12 years, 50 mg of stable iodine (85 mg of potassium iodate)
- 1 month to 3 years, 25 mg of stable iodine (42.5 mg of potassium iodate)
- neonates, 12.5 mg of stable iodine (21.25 mg of potassium iodate) given as a single dose.

When evacuation is delayed, repeated daily doses may become necessary.

1. Halperin JA. Potassium iodide as a thyroid blocker— Three Mile Island today. *Drug Intell Clin Pharm* 1989; **23:** 422–7.
2. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Am J Med* 1993; **94:** 524–32.
3. FDA Center for Drug Evaluation and Research. Guidance: potassium iodide as a thyroid blocking agent in radiation emergencies (issued December 2001). Available at: http://www.fda.gov/cder/guidance/4825fnl.htm (accessed 18/05/05)
4. DoH. Practical guidance on planning for incidents involving radioactivity: potassium iodate (stable iodine) prophylaxis in the event of a nuclear accident. PL/CMO(93)1 (issued 15 February 1993).
5. National Radiological Protection Board. Stable iodine prophylaxis: recommendations of the 2nd UK Working Group on Stable Iodine Prophylaxis. *Doc NRPB* 2001; **12** (3): 1–30. Also available at: http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1194947336017 (accessed 01/08/08)

Preparations

BP 2008: Alcoholic Iodine Solution; Aqueous Iodine Oral Solution; Potassium Iodate Tablets; Sodium Iodide Injection;
BPC 1968: Compound Iodine Paint;
USP 31: Iodine Tincture; Iodine Topical Solution; Potassium Iodide Delayed-release Tablets; Potassium Iodide Oral Solution; Potassium Iodide Tablets; Strong Iodine Solution; Strong Iodine Tincture.

Proprietary Preparations (details are given in Part 3)
Austria: Jodid; Leukona-Jod-Bad†; ***Braz.:*** Elixir Americano†; Glitosslab; Iodeton; Iodetoss; Iodex; Iopotoss†; Minostoss†; Sifpol†; Xarope Neo; ***Canad.:*** Sclerodine; Thyro-Block†; ***Chile:*** Solucion De Lugol†; ***Cz.:*** Kalijev; ***Fin.:*** Jodix; ***Ger.:*** Jod beta; Jodetten; Jodgamma; Jodid; Leukona-Jod-Bad†; Mono-Jod; Strumex†; Thyprotect; Varigloban†; ***Hung.:*** Jod plus; Jodid; Jodomax; ***India:*** Collosol; ***Indon.:*** Yodsaben; ***Ital.:*** Chitodine; Goccemed; Sol-Jod†; ***Mex.:*** Yodolactina; ***Norw.:*** Jodosan; ***Philipp.:*** Jodid; Vitreolent; ***Pol.:*** Jodid; Jodox†; Vitreolent; ***Port.:*** Iodisis†; ***Rus.:*** Iodomarin (Йодомарин); Jodbalance (Йодбаланс); Jodid (Йодид); Microiodid (Микройодид); ***Spain:*** Yoduk; ***Thai.:*** Pose-Iodophore; ***Turk.:*** Tenturdiyot; ***UK:*** Bioiodine; ***USA:*** Geri-Dyne; Iodopen; Pima; SSKI; Thyro-Block; Thyro-Shield.

Multi-ingredient: ***Arg.:*** Antikatarata Plus; Iodotiazol†; Yodofrixon Salicilado†; ***Austral.:*** Asa Tones; Potassium Iodide and Stramonium Compound†; ***Austria:*** Jodthyrox; ***Belg.:*** Depuratif des Alpes; ***Braz.:*** ABC Solucao†; Antimicon†; Antiphlogistine†; Becantosse†; Bontoss†; Broncofisin†; Bronquidex; Brontoss; Dermicon; Dermol†; Dermycose†; Elixir 914†; Elixir de Marinheiro†; Endotussin; Expec; Expectobron†; Frenotossil†; Fungolab; Glycon; Glyteol Balsamico; Hebrin; Ikaflux; Iodepol†; Iodesin; Iodetal; Iodeto de Potassio Composto†; Iodeto de Potassio†; Iodeto de Potassium Composto†; Iodex com Salicilato de Metila; Iodopulmin†; Iol†; Iolin†; KI-Expectorante; Micotiazol; MM Expectorante; Pulmoforte†; Pulmonix†; Sedatux†; Spectolab; Teutoss†; Tossivitan†; Tussivit†; Tussol†; Xarope Iodo-Suma†; ***Canad.:*** Iode; ratio-Theo-Bronc; Vito Bronches†; ***Cz.:*** Aphlox†; Jodthyrox; Solutan†; ***Fr.:*** Folio; Nitrol; ***Ger.:*** Adelheid-Jodquelle, Tolzer; Eferox Jod; Jodthyrox; Krophan N†; L-Thyrox Jod; Thyreocomb N†; Thyronajod; ***Gr.:*** Iodocollyre; Tentil; Vitreolent; ***Hong Kong:*** Vitreolent; ***India:*** Catarest; Cato-Bell; ***Israel:*** Iodax; ***Ital.:*** Antiadiposo; Esoform Jod 20 and 50; Facovit; Fertomcidina-U; Jodo Calcio Vitaminico; Linfoiodine; Polijodurato; Rubjovit; ***Malaysia:*** Vitreolent†; ***Mex.:*** Calciyodina; Iodarsolo B12†; Iodex Clasico; ***Pol.:*** Jodthyrox; ***Port.:*** Prelus†; ***Rus.:*** Jodthyrox (Йодтирокс); Neo-Anusol (Нео-анузол); Solutan (Солутан); Thyreocomb (Тиреокомб); ***Singapore:*** Vitreolent†; ***Spain:*** Adiod; Audione; Callicida Rojo; Depurativo Richelet; Encialina†; Nitroina; ***Switz.:*** Perpector†; Radix; Variglobin†; Vitreolent; ***Turk.:*** Neo Sedeks; ***UK:*** Nasciodine; TCP; ***USA:*** Elixophyllin-KI; Iodex with Methyl Salicylate; KIE; ORA5; Pediacof; Pedituss Cough; Phylorinol; Quadrinal; ***Venez.:*** Fedratal†; Iodex con Salicilato de Metilo; Na-Iodina Compuesta†; Yodalmina†.

Levothyroxine Sodium *(BANM, rINN)*

Levothyroxin sodná sůl hydrát; Lévothyroxine sodique; Levothyroxinnatrium; Levothyroxinum natricum; Levothyroxinum Natricum Hydricum; Levotiroksin Sodyum; Levotiroksino natrio druska; Levotiroxina sódica; Levotiroxin-nátrium; Levotyroksiininatrium; Levotyroxinnatrium; Lewotyroksyna sodowa; 3,5,3′,5′-Tetraiodo-L-thyronine Sodium; Thyroxine Sodium; L-Thyroxine Sodium; Thyroxinum Natricum; Tirossina; Tiroxina Sodica. Sodium 4-*O*-(4-hydroxy-3,5-di-iodophenyl)-3,5-di-iodo-L-tyrosine hydrate.

Левотироксин Натрий

$C_{15}H_{10}I_4NNaO_4,xH_2O$ = 798.9 (anhydrous).

CAS — 51-48-9 (levothyroxine); 55-03-8 (anhydrous levothyroxine sodium); 25416-65-3 (levothyroxine sodium, hydrate); 8065-29-0 (liotrix).

ATC — H03AA01.

ATC Vet — QH03AA01.

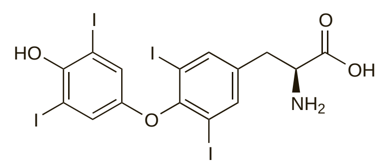

(levothyroxine)

NOTE. The abbreviation T_4 is often used for endogenous thyroxine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Int. includes the anhydrous form.

Ph. Eur. 6.2 (Levothyroxine Sodium). An almost white or slightly brownish-yellow powder or a fine, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Levothyroxine Sodium). The sodium salt of L-3,3′,5,5′-tetraiodothyronine. A light yellow to buff-coloured, odourless, hygroscopic, powder. It may assume a slight pink colour on exposure to light. Soluble 1 in 700 of water and 1 in 300 of alcohol; insoluble in acetone, in chloroform, and in ether; soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates. pH of a saturated solution in water is about 8.9. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

The adverse effects of levothyroxine are generally associated with excessive dosage and correspond to symptoms of hyperthyroidism. They may include tachycardia, palpitations, cardiac arrhythmias, increase in blood pressure, anginal pain, headache, restlessness, excitability, insomnia, tremors, muscle weakness and cramps, heat intolerance, sweating, flushing, fever, weight loss, menstrual irregularities, diarrhoea, and vomiting. These adverse reactions usually disappear after dosage reduction or temporary withdrawal of treatment. Thyroid storm has occasionally been reported after massive or chronic intoxication and convulsions, cardiac arrhythmias, heart failure, coma, and death have occurred.

In acute overdosage, activated charcoal may be used to reduce gastrointestinal absorption if ingestion of more than 10 mg by an adult, or 5 mg by a child, has occurred within 1 hour. Treatment is usually symptomatic and supportive; propranolol may be useful in controlling the symptoms of sympathetic overactivity. Levothyroxine overdosage requires an extended follow-up period as symptoms may be delayed for up to 6 days due to the gradual peripheral conversion of levothyroxine to tri-iodothyronine. US licensed product information has suggested that glucocorticoids may be given to inhibit this conversion.

Carcinogenicity. An association between the use of thyroid hormones and an increased risk of breast cancer in women has been proposed,[1] but a further analysis of the data did not confirm such an association,[2] and nor did later studies.[3-5]

1. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. *JAMA* 1976; **236:** 1124–7.
2. Mustacchi P, Greenspan F. Thyroid supplementation for hypothyroidism. An iatrogenic cause of breast cancer? *JAMA* 1977; **237:** 1446–7.
3. Wallace RB, *et al.* Thyroid hormone use in patients with breast cancer. Absence of an association. *JAMA* 1978; **239:** 958.
4. Shapiro S, *et al.* Use of thyroid supplements in relation to the risk of breast cancer. *JAMA* 1980; **244:** 1685–7.
5. Hoffman DA, *et al.* Breast cancer in hypothyroid women using thyroid supplements. *JAMA* 1984; **251:** 616–19.

Effects on the bones. Hyperthyroidism is a known risk factor for osteoporosis and theoretically thyroid hormone therapy may also be a risk factor. A review of over 3000 patients from 63 studies summarised the available evidence on the association of levothyroxine and bone mineral density.[1] It was stressed that current findings are complex and confusing and poor methodological quality makes comparison of results difficult. However, it was concluded that neither dose of levothyroxine nor duration of therapy had any relationship with bone mineral density: 31 studies showed no overall effect of levothyroxine, 23 studies provided partial negative and/or positive effects, while 9 showed overall negative effects. For postmenopausal women, particularly those with a history of hyperthyroidism, the review[1] recommended monitoring of thyroid hormone levels to avoid clinical hyperthyroidism, and screening for risk factors of osteoporosis; if warranted, bone densitometry, and appropriate management of any decline in bone mineral density, should be used.

1. Schneider R, Reiners C. The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature. *Exp Clin Endocrinol Diabetes* 2003; **111:** 455–70.

Effects on the muscles. A woman with previous normal thyroid function developed periodic paralysis affecting the limbs after abusing levothyroxine, 100 micrograms twice daily for 2 weeks, in order to lose weight.[1] The attack subsided after treatment with intravenous potassium and withdrawal of the levothyroxine.

1. Chen YC, *et al.* Thyrotoxic periodic paralysis in a patient abusing thyroxine for weight reduction. *Ren Fail* 2001; **23:** 139–42.

Effects on the nervous system. Two children aged 8 and 11 years developed pseudotumor cerebri (benign intracranial hypertension) shortly after starting levothyroxine for hypothyroidism.[1] There have been further reports on individual children[2,3] and infants.[4]

Partial complex status epilepticus, with confusion, agitation, and continuous myoclonic jerks in the left side of the face and left hand, was seen in a hypothyroid patient with Turner's syndrome who was receiving levothyroxine for myxoedema coma.[5] The condition responded to anticonvulsants; the patient subsequently remained seizure-free on a reduced dose of levothyroxine and concomitant phenytoin.

1. Van Dop C, *et al.* Pseudotumor cerebri associated with initiation of levothyroxine therapy for juvenile hypothyroidism. *N Engl J Med* 1983; **308:** 1076–80.
2. McVie R. Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 731.
3. Hymes LC, *et al.* Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 732.
4. Raghavan S, *et al.* Pseudotumor cerebri in an infant after -thyroxine therapy for transient neonatal hypothyroidism. *J Pediatr* 1997; **130:** 478–80.
5. Duarte J, *et al.* Thyroxine-induced partial complex status epilepticus. *Ann Pharmacother* 1993; **27:** 1139.

Hypersensitivity. A hypersensitivity reaction (fever, eosinophilia, and liver dysfunction) was reported[1] in a 63-year-old hypothyroid woman with Hashimoto's thyroiditis during treatment with liothyronine or levothyroxine. Symptoms disappeared when the drugs were stopped. After an interval of 4 months liothyronine was gradually reintroduced without adverse effect.

Urticaria and angioedema have been described in a patient who received thyroid and levothyroxine.[2] In a further case similar reactions were attributed to the presence of sunset yellow as colouring agent in the proprietary levothyroxine preparation.[3]

1. Shibata H, *et al.* Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. *Arch Intern Med* 1986; **146:** 1624–5.
2. Pandya AG, *et al.* Chronic urticaria associated with exogenous thyroid use. *Arch Dermatol* 1990; **126:** 1238–9.
3. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338:** 393.

Overdosage. In overdosage with thyroid drugs aggressive therapy is not normally justified in asymptomatic patients, although various regimens have been tried in large overdosage.

Massive overdoses of levothyroxine and liothyronine (up to 1000 times the normal dose over 2 to 12 days) have been described in small numbers of patients.[1-6] Symptoms of thyrotoxicosis can occur within the first 6 hours after ingestion of liothyronine but can be delayed for 2 to 5 days after levothyroxine, due to the time taken for metabolic conversion to liothyronine. Symptoms of thyrotoxicosis that have been reported include fever, arrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications, and coma.[1,2,5] Treatment of overdosage includes consideration of the use of activated charcoal and a beta blocker such as propranolol or metoprolol to treat tachyarrhythmia.[2,4,5] In most cases serious toxicity does not occur and patients recover with supportive therapy. Diuresis and haemodialysis do not enhance elimination because thyroid hormones are highly protein bound. It has also been concluded that plasmapheresis and haemoperfusion provide no significant clinical benefit.[4,6]

1. Kulig K, *et al.* Levothyroxine overdosage associated with seizures in a young child. *JAMA* 1985; **254:** 2109–10.
2. Binimelis J, *et al.* Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med* 1987; **13:** 33–8.
3. Golightly LK, *et al.* Clinical effects of accidental levothyroxine ingestion in children. *Am J Dis Child* 1987; **141:** 1025–7.
4. Henderson A, *et al.* Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. *Anaesth Intensive Care* 1994; **22:** 463–4.
5. Hack JB, *et al.* Severe symptoms following a massive intentional L-thyroxine ingestion. *Vet Hum Toxicol* 1999; **41:** 323–6.
6. Solá E, *et al.* Massive triiodothyronine intoxication: efficacy of hemoperfusion? *Thyroid* 2002; **7:** 637–40.

Precautions

Levothyroxine is contra-indicated in untreated hyperthyroidism. It has a narrow therapeutic index and should be used with extreme caution in patients with cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension; lower initial doses, smaller increments, and longer intervals between increases should be used as necessary. An ECG performed before starting treatment with levothyroxine may help to distinguish underlying myocardial ischaemia from changes induced by hypothyroidism. Levothyroxine should also be introduced very gradually in elderly patients and those with long-standing hypothyroidism to avoid any sudden increase in metabolic demands. It should not be given to patients with adrenal insufficiency without adequate corticosteroid cover otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis. Care is also required when levothyroxine is given to patients with diabetes mellitus or diabetes insipidus.

Tests of thyroid function are subject to alteration by a number of nonthyroidal clinical conditions and by a wide variety of drugs, some of which are mentioned under Interactions, below.

Abuse. For mention of abuse of levothyroxine by athletes for weight loss see Obesity, under Uses and Administration, below. For reference to periodic paralysis in a woman abusing levothyroxine as a slimming aid, see under Effects on the Muscles, above.

Adrenocortical insufficiency. Thyroid-hormone replacement without additional corticosteroids may precipitate acute adrenocortical insufficiency in patients with impaired adrenocortical function, including those with subclinical or unrecognised adrenocortical disease.[1] Prompt diagnosis and replacement of corticosteroids can prevent the development of a potentially fatal crisis. It has been pointed out that a raised concentration of thyroid-stimulating-hormone alone may not necessarily imply hypothyroidism in patients with chronic adrenocortical insufficiency.[2] Even confirmed hypothyroidism in these patients may not be permanent.

1. Fonseca V, *et al.* Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1185–6.
2. Davis J, Sheppard M. Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1595.

Anaemia. Four patients with iron deficiency anaemia and primary hypothyroidism developed palpitations and restlessness on treatment with levothyroxine sodium, and the drug had to be stopped. Upon correction of the anaemia with ferrous sulfate, all were able to tolerate levothyroxine therapy.[1] For a warning that ferrous sulfate reduces absorption of levothyroxine from the gastrointestinal tract, see Iron Salts under Interactions, below.

1. Shakir KMM, *et al.* Anemia: a cause of intolerance to thyroxine sodium. *Mayo Clin Proc* 2000; **75:** 189–92.

Breast feeding. Minimal amounts of thyroid hormones are distributed into breast milk.[1] Although levothyroxine in breast milk will be insufficient to treat any hypothyroidism in the suckling newborn, it has been suggested that it may mask detection of any hypothyroidism in such a neonate.[2] However, the *BNF* considers that the amounts involved are too small to affect tests for neonatal hypothyroidism. The American Academy of Pediatrics noted that no effects have been seen in breast-fed infants whose mothers were taking levothyroxine and as such considers its use to be usually compatible with breast feeding.[3]

1. Bennett PN, ed. *Drugs and human lactation.* Amsterdam: Elsevier, 1988.
2. Anonymous. Can a woman on thyroxine safely breast-feed her baby? *BMJ* 1977; **2:** 1589.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)

Cardiovascular disorders. There is a complex relationship between the heart and thyroid.[1] Cardiovascular abnormalities may be associated with hypothyroidism as well as with levothyroxine replacement therapy, hence the need for caution.

1. Gammage M, Franklyn J. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997; **77:** 189–90.

Myasthenia. Thyroid hormones may occasionally precipitate or exacerbate a pre-existing myasthenic syndrome.[1,2]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Pregnancy. Most authorities consider that thyroid hormones do not readily cross the placenta. Placental transfer has been reported,[1] but in amounts so limited that a mother with physiological concentrations of thyroxine and tri-iodothyronine would not provide normal thyroid hormone concentrations to a fetus with congenital hypothyroidism.[2-4]

Levothyroxine requirements increase in hypothyroid women during early pregnancy. A small study involving 20 pregnancies found that the dose requirement rose from the sixth to the sixteenth week of gestation before reaching a plateau; a mean dose increase of nearly 50% was eventually required in 17 cases.[5] The authors recommended that all hypothyroid women should have their levothyroxine dose increased by 30% as soon as pregnancy was confirmed, to avoid any risk of an initial period of hypothyroxinaemia before the first obstetric visit. Thereafter, dosage should be adjusted according to serum-thyrotropin concentrations.

1. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; **321:** 13–16.
2. Sack J, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549–50.
3. Bachrach LK, Burrow GN. Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549.
4. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1550.
5. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.

Interactions

Antiarrhythmics. *Amiodarone*[1] may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine with a rise in the concentration of inactive reverse tri-iodothyronine.

1. Hershman JM, *et al.* Thyroxine and triiodothyronine kinetics in cardiac patients taking amiodarone. *Acta Endocrinol (Copenh)* 1986; **111:** 193–9.

Antibacterials. Enzyme induction by *rifampicin*[1,2] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones.

Two patients with previously stable thyroid function while receiving levothyroxine were found to have developed hypothyroidism 3 to 4 weeks after starting oral treatment with *ciprofloxacin*.[3] In one patient increasing the dose of levothyroxine was ineffective and thyroid function only returned to normal after ciprofloxacin was withdrawn. In the other patient, giving the drugs 6 hours apart was sufficient to overcome the interaction.

1. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
2. Nolan SR, *et al.* Interaction between rifampin and levothyroxine. *South Med J* 1999; **92:** 529–31.
3. Cooper JG, *et al* Ciprofloxacin interacts with thyroid replacement therapy. *BMJ* 2005; **330:** 1002.

Anticoagulants. Thyroid hormones enhance the effects of *oral anticoagulants* (see under the interactions of Warfarin, p.1432). Patients on anticoagulant therapy therefore require careful monitoring when treatment with thyroid drugs is started or altered as the oral anticoagulant dose may need to be adjusted.

Antidepressants. Some drugs such as *lithium* act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.[1]

The effects of levothyroxine in hypothyroid patients may be decreased by use with *sertraline*, and the dose of levothyroxine may need to be increased.[2]

For the effects of thyroid hormones on *tricyclic antidepressants* see under Amitriptyline, p.381.

1. Ramsay I. Drugs and non-thyroid induced changes in thyroid function tests. *Postgrad Med J* 1985; **61:** 375–7.
2. McCowen KC, *et al.* Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* 1997; **337:** 1010–11.

Antidiabetics. As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any drug treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their *insulin* or *oral hypoglycaemic* requirements.[1]

1. Refetoff S. Thyroid hormone therapy. *Med Clin North Am* 1975; **59:** 1147–62.

Antiepileptics. Enzyme induction by drugs such as *carbamazepine*,[1,2] *phenytoin*,[2,3] or *barbiturates*[4] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these drugs are also given[5] and a decrease if the enzyme-inducing drug is withdrawn.[6] *Phenytoin*,[3] and *carbamazepine* may reduce protein binding by displacing the thyroid hormones from their plasma-binding sites. As thyroid hormones are highly protein bound, changes in binding might be expected to influence requirements in thyroid replacement therapy, but in practice there is little clinical evidence of any problems except with thyroid-function testing.

1. Connell JMC, *et al.* Changes in circulating thyroid hormones during short-term hepatic enzyme induction with carbamazepine. *Eur J Clin Pharmacol* 1984; **26:** 453–6.
2. Larkin JG, *et al.* Thyroid hormone concentrations in epileptic patients. *Eur J Clin Pharmacol* 1989; **36:** 213–6.
3. Franklyn JA, *et al.* Measurement of free thyroid hormones in patients on long-term phenytoin therapy. *Eur J Clin Pharmacol* 1984; **26:** 633–4.
4. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
5. Blackshear JL, *et al.* Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med* 1983; **99:** 341–2.
6. Hoffbrand BI. Barbiturate/thyroid-hormone interaction. *Lancet* 1979; **ii:** 903–4.

Antimalarials. Increased thyroid-stimulating hormone concentration has been noted after the use of *chloroquine* with *proguanil* for malaria prophylaxis in a patient stabilised on levothyroxine.[1] Induction of liver enzymes by chloroquine resulting in increased metabolism of levothyroxine was suggested as the mechanism.

1. Munera Y, *et al.* Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997; **314:** 1593.

Antineoplastics. Eight patients taking levothyroxine, subsequent to thyroidectomy, developed raised concentrations of thyroid-stimulating hormone (TSH) and clinical hypothyroidism when they were given *imatinib*. Increasing the levothyroxine dose reversed hypothyroidism in only 3 patients, but TSH concentrations returned to normal in all patients when imatinib was stopped. In contrast, these effects did not occur in 3 other patients with a normal functioning thyroid. The authors reasoned that imatinib might have stimulated the clearance of thyroxine and tri-iodothyronine by inducing uridine diphosphate glucuronosyltransferases, but evidence is needed to confirm this mechanism. They suggested that the dose of levothyroxine should be at least doubled, with close monitoring of thyroid function, before imatinib is given to patients with hypothyroidism.[1]

1. de Groot JWB, *et al.* Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther* 2005; **78:** 433–8.

Antivirals. There have been reports of interactions between HIV protease inhibitors and levothyroxine. An increased dose of levothyroxine was necessary with *ritonavir*[1] whereas a decreased dose was needed with *indinavir*.[2]

1. Tseng A, Fletcher D. Interaction between ritonavir and levothyroxine. *AIDS* 1998; **12:** 2235–6.
2. Lanzafame M, *et al.* Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002; **30:** 54–5.

Beta blockers. Studies have indicated that plasma concentrations of *propranolol* are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance[1-4] and hypothyroid patients receiving chronic propranolol therapy have had a reduction in plasma-propranolol concentrations when given levothyroxine treatment.[2]

Propranolol may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine and a rise in the concentration of inactive reverse tri-iodothyronine.[5,6]

1. Feely J, *et al.* Increased clearance of propranolol in thyrotoxicosis. *Ann Intern Med* 1981; **94:** 472–4.
2. Feely J, *et al.* Plasma propranolol steady state concentrations in thyroid disorders. *Eur J Clin Pharmacol* 1981; **19:** 329–33.

3. Aro A, *et al.* Pharmacokinetics of propranolol and sotalol in hyperthyroidism. *Eur J Clin Pharmacol* 1982; **21:** 373–7.
4. Hallengren B, *et al.* Influence of hyperthyroidism on the kinetics of methimazole, propranolol, metoprolol, and atenolol. *Eur J Clin Pharmacol* 1982; **21:** 379–84.
5. Chambers JB, *et al.* The effects of propranolol on thyroxine metabolism and triiodothyronines production in man. *J Clin Pharmacol* 1982; **22:** 110–16.
6. Wilkins MR, *et al.* Effect of propranolol on thyroid homeostasis of healthy volunteers. *Postgrad Med J* 1985; **61:** 391–4.

Cardiac glycosides. Serum-digoxin concentrations appear to be lower in hyperthyroidism and higher in hypothyroidism,[1] which may contribute in part to the observed insensitivity of hyperthyroid patients to *digoxin* therapy,[2] although other mechanisms have been proposed.[3]

1. Croxson MS, Ibbertson HK. Serum digoxin in patients with thyroid disease. *BMJ* 1975; **3:** 566–8.
2. Huffman DH, *et al.* Digoxin in hyperthyroidism. *Clin Pharmacol Ther* 1977; **22:** 533–8.
3. Lawrence JR, *et al.* Digoxin kinetics in patients with thyroid dysfunction. *Clin Pharmacol Ther* 1977; **22:** 7–13.

Gastrointestinal drugs. *Sucralfate* reduces absorption of levothyroxine from the gastrointestinal tract[1,2] as does *aluminium hydroxide*,[3] and *calcium carbonate*.[4,5]

1. Sherman SI, *et al.* Sucralfate causes malabsorption of L-thyroxine. *Am J Med* 1994; **96:** 531–5.
2. Campbell JA, *et al.* Sucralfate and the absorption of -thyroxine. *Ann Intern Med* 1994; **121:** 152.
3. Liel Y, *et al.* Nonspecific intestinal adsorption of levothyroxine by aluminium hydroxide. *Am J Med* 1994; **97:** 363–5.
4. Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy. *JAMA* 1998; **279:** 750.
5. Singh N, *et al.* Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; **283:** 2822–5.

General anaesthetics. Severe hypertension and tachycardia have been reported[1] when *ketamine* was used in patients taking levothyroxine.

1. Kaplan JA, Cooperman LH. Alarming reactions to ketamine in patients taking thyroid medication-treatment with propranolol. *Anesthesiology* 1971; **35:** 229–30.

Ion-exchange resins. *Colestyramine* significantly reduces the absorption of levothyroxine by binding with thyroid hormones in the gastrointestinal tract. The malabsorption of levothyroxine is minimised by allowing an interval of 4 to 5 hours to elapse between taking the two drugs.[1] A similar effect has been seen with *sodium polystyrene sulfonate*.[2]

1. Northcutt RC, *et al.* The influence of cholestyramine on thyroxine absorption. *JAMA* 1969; **208:** 1857–61.
2. McLean M, *et al.* Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993; **341:** 1286.

Iron salts. *Ferrous sulfate* reduces absorption of levothyroxine from the gastrointestinal tract.[1]

1. Campbell NRC, *et al.* Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992; **117:** 1010–13.

Lipid regulating drugs. Both decreased efficacy[1] and increased efficacy[2] of levothyroxine have been reported in individual patients given *lovastatin.* Increased thyroid stimulating hormone concentrations, requiring increased doses of levothyroxine, have been reported when *simvastatin* was begun.[3]

1. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1341–2.
2. Gormley GJ, Tobert JA. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1342.
3. Kisch E, Segall HS. Interaction between simvastatin and -thyroxine. *Ann Intern Med* 2005; **143:** 547.

NSAIDs. Falsely low concentrations of levothyroxine (T_4) or tri-iodothyronine (T_3) have been reported during treatment with some anti-inflammatory drugs. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.[1]

1. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Sex hormones. *Oestrogen* therapy increases serum concentrations of thyroxine-binding globulin, thus increasing the amount of bound thyroxine. Normal thyroid function stimulates thyroxine synthesis to compensate for this effect and maintain normal free-thyroxine serum concentrations. In hypothyroidism, however, patients treated with exogenous levothyroxine who receive oestrogens, as in oral contraceptives or HRT,[1] may require an increase in levothyroxine dose. In contrast, *androgens* reduce the concentration of the binding globulin, which has resulted in clinical hyperthyroidism when given to postmenopausal women maintained on levothyroxine replacement therapy.[2]

Increased levothyroxine requirements were noted in a 79-year-old woman when she took *raloxifene* at the same time as her levothyroxine; absorption studies indicated that the effect could be reversed by separating doses of the two drugs by about 12 hours.[3]

1. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001; **344:** 1743–9.
2. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. *Ann Intern Med* 1994; **121:** 247–51.
3. Siraj ES, *et al.* Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med* 2003; **163:** 1367–70.

Sympathomimetics. Thyroid drugs increase metabolic demands and should therefore be used with caution with other drugs known to influence cardiac function, such as the *sympathomimetics*, as they may enhance this effect. In addition, thyroid hormones may increase receptor sensitivity to catecholamines.

Pharmacokinetics

Levothyroxine is variably absorbed from the gastrointestinal tract after oral doses. Fasting increases absorption. Once in the circulation, levothyroxine is extensively protein bound, principally to thyroxine-binding globulin (TBG) but also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin. Levothyroxine has a plasma half-life of about 6 to 7 days in euthyroid subjects; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Levothyroxine is primarily metabolised in the liver and kidney to tri-iodothyronine (liothyronine) and, about 40%, to inactive reverse tri-iodothyronine (reverse T_3) both of which undergo further deiodination to inactive metabolites. Further metabolites result from the deamination and decarboxylation of levothyroxine to tetra-iodothyroacetic acid.

Levothyroxine undergoes enterohepatic recycling and excretion in the faeces.

The distribution of thyroid hormones into breast milk and across the placenta is discussed under Breast Feeding and Pregnancy (above).

Uses and Administration

Levothyroxine is a thyroid hormone (see p.2165 for a description of the endogenous hormones) used as replacement therapy in the treatment of hypothyroidism (p.2167). It is given in conditions such as diffuse non-toxic goitre (see Goitre and Thyroid Nodules, p.2165) and Hashimoto's thyroiditis (see Hypothyroidism, p.2167) to suppress the secretion of thyroid-stimulating hormone (TSH) and hence prevent or reverse enlargement of the thyroid gland. Levothyroxine is also used to suppress TSH production in the treatment of thyroid carcinoma (p.674) and as a diagnostic agent for the differential diagnosis of hyperthyroidism. It is given with antithyroid drugs in the blocking-replacement regimen for the management of hyperthyroidism (p.2165).

The peak therapeutic effect of regular oral levothyroxine may not be achieved for several weeks and there is a slow response to changes in dosage. Similarly, effects may persist for several weeks after withdrawal. Levothyroxine is given as the sodium salt in a single daily dose. Its absorption can be irregular and it is probably best taken on an empty stomach, usually before breakfast.

The dose of levothyroxine sodium for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

In hypothyroidism an initial adult oral dose of 50 to 100 micrograms of levothyroxine sodium daily may be increased by 25 to 50 micrograms at intervals of about 4 weeks until the thyroid deficiency is corrected and a maintenance dose is established. The adult maintenance dose is usually between 100 and 200 micrograms daily. In elderly patients, in those with cardiovascular disorders, or in those with severe hypothyroidism of long standing, treatment should be introduced more gradually: an initial dose of 12.5 to 50 micrograms daily increased by increments of 12.5 to 25 micrograms at intervals of about 4 weeks may be appropriate.

In children, individualisation of dosage and monitoring of treatment is especially important. In the UK, the *BNFC* recommends the following oral doses:

- neonates: 10 to 15 micrograms/kg once daily initially, adjusted in steps of 5 micrograms/kg every 2 weeks or as needed, to a usual dose of 20 to 50 micrograms daily
- children aged 1 month to 2 years: 5 to 10 micrograms/kg once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual dose of 25 to 100 micrograms daily
- children aged 2 to 12 years: 5 micrograms/kg once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual dose of 75 to 100 micrograms daily
- children aged 12 to 18 years: 50 to 100 micrograms once daily initially, adjusted in steps of 25 to 50 micrograms daily every 3 to 4 weeks until metabolism is normalised, to a usual dose of 100 to 200 micrograms daily

Doses are reduced by 50% in cardiac disease, and increased more slowly.

Levothyroxine sodium may be given by intravenous injection. It has also been given intramuscularly. In myxoedema (hypothyroid) coma doses of 200 to 500 micrograms by intravenous injection may be given initially. A further dose of 100 to 300 micrograms is given on the second day if no improvement is evident, and followed by daily supplements of about 100 to 200 micrograms until the patient is euthyroid and can tolerate oral doses.

Dextrothyroxine, the D-isomer of levothyroxine, has lipid regulating properties and has been used in the management of hypercholesterolaemia, but its use is severely limited by cardiotoxicity; it has only weak thyroid hormone activity.

◊ General references.

1. Mandel SJ, *et al.* Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* 1993; **119:** 492–502.
2. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80. Correction. *ibid.*; 1035.
3. Escobar-Morreale HF, *et al.* Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab* 2005; **90:** 4946–54.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of levothyroxine. Most studies and reports have come from the USA and results may have depended to some extent on the particular brands compared. Formulations may also have changed which makes comparison of results difficult. One study[1] concluded that 2 generic levothyroxine products were bioequivalent and interchangeable with 2 branded products.

In 2004 the FDA issued guidance on the bioequivalence of several levothyroxine products on the US market but this was heavily criticised in a joint statement by several American professional societies.[2] In response these societies recommended to physicians that patients should be maintained on the same brand of levothyroxine and if the brand were changed then the patient's serum TSH should be retested and the dosage of levothyroxine re-titrated as necessary.

1. Dong BJ, *et al.* Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997; **277:** 1205–13.
2. American Association of Clinical Endocrinologists, The Endocrine Society, and American Thyroid Association. Joint position statement on the use and interchangeability of thyroxine products. Available at: http://www.aace.com/pub/pdf/guidelines/AACE-TES-ATA-ThyroxineProducts.pdf (accessed 20/06/06) See also American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. Joint Statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid* 2004; **14:** 486.

Cardiomyopathies. Management of dilated cardiomyopathy (p.1163) usually involves conventional therapy for heart failure, but a small study has reported benefit from short-term use of levothyroxine.[1] Levothyroxine was well tolerated but thyroid-stimulating hormone levels were reduced, which might limit long-term therapy.

1. Moruzzi P, *et al.* Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996; **101:** 461–7.

Depression. While thyroid hormones may increase the activity of tricyclic antidepressants (see Thyroid Hormones, under Interactions of Amitriptyline, p.381), the benefits in the augmentation treatment of depression (p.373) are debatable. A meta-analysis[1] of 8 studies involving 292 patients with refractory depression treated with liothyronine in addition to tricyclic antidepressants indicated that such therapy was effective in a subgroup of cases but that the small number of patients studied made additional placebo-controlled data desirable.

In non-refractory depression a meta-analysis[2] also indicated a benefit when liothyronine was added to tricyclic antidepressants although it was acknowledged that many of the studies were old with methodological limitations. However, a controlled trial of liothyronine with paroxetine could not confirm any advantage of additive therapy.[3]

1. Aronson R, *et al.* Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996; **53:** 842–8.
2. Altshuler LL, *et al.* Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001; **158:** 1617–22.
3. Appelhof BC, *et al.* Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab* 2004; **89:** 6271–6.

Obesity. Thyroid drugs have been tried in the treatment of obesity (p.2149) in euthyroid patients, but they produce only temporary weight loss, mainly of lean body-mass, and can produce serious adverse effects, especially cardiac complications.[1] Hypothyroidism has also been reported[2] when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity. Levothyroxine appears to have been abused by some athletes to promote weight loss.[3]

1. Rivlin RS. Therapy of obesity with hormones. *N Engl J Med* 1975; **292:** 26–9.
2. Dornhorst A, *et al.* Possible iatrogenic hypothyroidism. *Lancet* 1981; **i:** 52.
3. MacAuley D. Drugs in sport. *BMJ* 1996; **313:** 211–15.

Urticaria. There is some suggestion that chronic urticaria (p.1584) may be associated with thyroid autoimmunity and that treatment with thyroid hormones may result in clinical remission.[1] In one study, a nine-year-old boy was successfully treated for chronic urticaria with levothyroxine therapy at doses of 50 to 100 micrograms daily.[2] The authors advised screening for thyroid function and anti-thyroid microsomal antibodies in cases of chronic urticaria as these patients may benefit from thyroid hormone therapy. A small investigative study concluded that treatment with levothyroxine sodium (in hypothyroid patients) or antithyroid drugs (in patients with Graves' disease) is of benefit in patients with severe chronic urticaria associated with thyroid autoimmunity.[3]

1. Rumbyrt JS, *et al.* Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96:** 901–5.
2. Dreyfus DH, *et al.* Steroid-resistant chronic urticaria associated with anti-thyroid microsomal antibodies in a nine-year-old boy. *J Pediatr* 1996; **128:** 576–8.
3. Gaig P, *et al.* Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity *J Investig Allergol Clin Immunol* 2000; **10:** 342–5.

Preparations

BP 2008: Levothyroxine Tablets;
USP 31: Levothyroxine Sodium Tablets; Liotrix Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Euthyrox; Juno†; T4; ***Austral.:*** Eutroxsig; Oroxine; ***Austria:*** Euthyrox; Neothyron; Thyrex; ***Belg.:*** Elthyrone; Euthyrox; Thyrax; ***Braz.:*** Euthyrox; Puran T4; Synthroid; Tetroid; Tiroidin; ***Canad.:*** Eltroxin; Euthyrox; Synthroid; ***Chile:*** Esaldox; Eutirox; ***Cz.:*** Eltroxin; Euthyrox; Letrox; Thyrax†; ***Denm.:*** Eltroxin; ***Fr.:*** Levothyrox; ***Ger.:*** Berlthyrox; Eferox; Euthyrox; L-Thyrox; Lixin; Thevier; ***Gr.:*** Levothroid; T-4; Thyro-4; Thyrohormone; ***Hong Kong:*** Eltroxin; ***Hung.:*** Euthyrox; Letrox; ***India:*** Eltroxin; ***Indon.:*** Euthyrox; Thyrax; ***Irl.:*** Eltroxin; ***Israel:*** Eltroxin; ***Ital.:*** Eutirox; Tiracrin; Tirosint; ***Jpn:*** Thyradin-S; ***Malaysia:*** Oroxine; ***Mex.:*** Abutiroi; Cynocuatro; Daltroid†; Eutirox; Sintrocid†; Tiroidine; ***Neth.:*** Eltroxin; Euthyrox; Thyrax; ***Norw.:*** Levaxin; ***NZ:*** Eltroxin; ***Philipp.:*** Eltroxin; Euthyrox; Thyrax; Thyrohex; ***Pol.:*** Eferox; Eltroxin; Euthyrox; Letrox; ***Port.:*** Eutirox; Letequatro; Letter; Thyrax; ***Rus.:*** Bagothyrox (Баготирокс); Euthyrox (Эутирокс); ***S.Afr.:*** Eltroxin; ***Singapore:*** Eltroxin; Euthyrox; Oroxine; ***Spain:*** Dexnon; Eutirox; Levothroid; ***Swed.:*** Euthyrox; Levaxin; ***Switz.:*** Eltroxine; Euthyrox; ***Thai.:*** Elthyro; Eltroxin; Euthyrox; Pondtroxin; Thyrosit; ***Turk.:*** Levotiron; Tefor; ***UK:*** Eltroxin; Evotrox; ***USA:*** Levothroid; Levoxyl; Novothyrox; Synthroid; Unithroid; ***Venez.:*** Euthyrox; Thyrax.

Multi-ingredient: ***Arg.:*** Eutroid; Levotrin; ***Austria:*** Combithyrex; Jodthyrox; Novothyral; Prothyrid; ***Belg.:*** Novothyral; ***Braz.:*** Tyroplus†; ***Chile:*** Novothyral; ***Cz.:*** Jodthyrox; Novothyral†; Thyreotom; ***Fr.:*** Euthyral; ***Ger.:*** Eferox Jod; Jodthyrox; L-Thyrox Jod; Novothyral; Prothyrid; Thyreocomb N†; Thyreotom†; Thyronajod; ***Gr.:*** Dithyron; ***Ital.:*** Dermocinetic; Somatoline; Tiroide Amsa; ***Mex.:*** Cynoplus; Novotiral; Proloid S†; ***Pol.:*** Jodthyrox; Novothyral; ***Rus.:*** Jodthyrox (Йодтирокс); Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.:*** Diotroxin; ***Switz.:*** Novothyral; ***Turk.:*** Bitiron; ***USA:*** Thyrolar.

Liothyronine Sodium *(BANM, rINNM)*

Liothyronin sodná sůl; Liothyronine sodique; Liothyroninum natricum; Liotironin Sodyum; Liotironina sódica; Liotironin-nátrium; Liotironino natrio druska; Liotyroniininatrium; Liotyronina sodowa; Liotyroninnatrium; Natrii Liothyroninum; Sodium Liothyronine; L-Tri-iodothyronine Sodium; 3,5,3′-Tri-iodo-L-thyronine Sodium; Tri-iodotironin Sodyum. Sodium 4-*O*-(4-hydroxy-3-iodophenyl)-3,5-di-iodo-L-tyrosine.

Натрий Лиотиронин

$C_{15}H_{11}I_3NNaO_4$ = 673.0.

CAS — 6893-02-3 (liothyronine); 55-06-1 (liothyronine sodium); 8065-29-0 (liotrix).

ATC — H03AA02.

ATC Vet — QH03AA02.

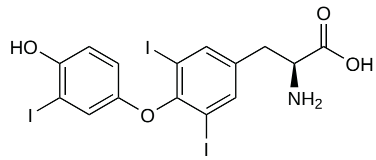

(liothyronine)

NOTE. The abbreviation T_3 is often used for endogenous tri-iodothyronine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Liothyronine Sodium). A white or almost white or slightly coloured powder. Practically insoluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Liothyronine Sodium). A light tan, odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Levothyroxine Sodium, p.2171.

Interactions

As for Levothyroxine Sodium, p.2172.

Pharmacokinetics

Liothyronine is readily and almost completely absorbed from the gastrointestinal tract. Once in the circulation, liothyronine binds principally to thyroxine-binding globulin (TBG), although less strongly than levothyroxine; some is also bound to thyroxine-binding pre-albumin (TBPA) or to albumin. Liothyronine has a plasma half-life in euthyroidism of about 1 to 2 days; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Liothyronine is metabolised by deiodination to inactive di-iodothyronine and mono-iodothyronine. Iodine released by deiodination is largely reused within the thyroid cells. Further metabolites result from deamination and decarboxylation to tiratricol (triac).

Uses and Administration

Liothyronine is a thyroid hormone (see p.2165). It is used in the treatment of hypothyroidism (p.2167), and is believed to be more active than levothyroxine (p.2173). The onset of action of liothyronine is rapid, developing within a few hours, and therefore it tends to be used in circumstances where this, and its short duration of action, are useful, particularly in hypothyroid (myxoedema) coma.

With regular dosing the peak therapeutic effect is usually achieved after 3 days; on withdrawal its effects may persist for 1 to 3 days.

The dose of liothyronine should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly. Although liothyronine is given as the sodium salt, doses can be expressed in terms of liothyronine sodium or liothyronine; the doses below are in terms of liothyronine sodium. Liothyronine sodium 10.3 micrograms is equivalent to about 10 micrograms of liothyronine. Liothyronine sodium 20 to 25 micrograms is generally considered to be equivalent in activity to about 100 micrograms of levothyroxine sodium.

In **hypothyroidism** a usual initial adult oral dose is 5 to 25 micrograms daily, increased gradually to a maintenance dose of 60 to 75 micrograms daily in 2 to 3 divided doses, although up to 100 micrograms daily may be required in some patients. In elderly patients, in those with cardiovascular disorders, or in those with severe long-standing hypothyroidism, treatment should be introduced with doses at the low end of the range, with smaller increments, and longer intervals between increases, as necessary.

In **myxoedema coma** liothyronine sodium may be given intravenously in a dose of 5 to 20 micrograms by slow intravenous injection, repeated as necessary, usually at intervals of 12 hours; the minimum interval between doses is 4 hours. An alternative regimen advocates an initial dose of 50 micrograms intravenously followed by further injections of 25 micrograms every 8 hours until improvement occurs; the dosage may then be reduced to 25 micrograms intravenously twice daily.

Liothyronine has also been given in the **diagnosis** of hyperthyroidism in adults. Failure to suppress the uptake of radio-iodine after several days of receiving liothyronine sodium suggests a diagnosis of hyperthyroidism.

Liothyronine hydrochloride has also been used.

Preparations

BP 2008: Liothyronine Tablets;
USP 31: Liothyronine Sodium Tablets; Liotrix Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Tertroxin; ***Braz.:*** Cynomel†; ***Canad.:*** Cytomel; ***Cz.:*** Tertroxin†; ***Fr.:*** Cynomel; ***Ger.:*** Thybon; Thyrotardin N; ***Gr.:*** Cynomel†; T-3; ***Ital.:*** Dispon†; Ti-Tre; ***Mex.:*** Cynomel; Liotrex; Triyotex; ***Neth.:*** Cytomel; ***NZ:*** Tertroxin; ***Port.:*** Neo-Tiroimade; ***S.Afr.:*** Tertroxin; ***Thai.:*** Tertroxin†; ***Turk.:*** Tiromel; ***UK:*** Tertroxin†; Triiodothyronine Injection; ***USA:*** Cytomel; Triostat; ***Venez.:*** Tertroxin†.

Multi-ingredient: ***Arg.:*** Eutroid; Levotrin; Tresite F; ***Austria:*** Combithyrex; Novothyral; Prothyrid; ***Belg.:*** Novothyral; ***Braz.:*** Tyroplus†; ***Chile:*** Novothyral; ***Cz.:*** Novothyral†; Thyreotom; ***Fr.:*** Euthyral; ***Ger.:*** NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Novothyral; Prothyrid; Thyreotom†; ***Gr.:*** Dithyron; ***Ital.:*** Tiroide Amsa; ***Mex.:*** Cynoplus; Novotiral; Proloid S†; Redotex; ***Pol.:*** Novothyral; ***Rus.:*** Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.:*** Diotroxin; ***Switz.:*** Novothyral; ***Turk.:*** Bitiron; ***USA:*** Thyrolar.

Potassium Perchlorate

Chloristan draselný; Kalii perchloras; Kalio perchloratas; Kaliumperkloraatti; Kaliumperklorat; Kálium-perklorát; Perclorato potásico; Potassium, perchlorate de.

$KClO_4$ = 138.5.

CAS — 7778-74-7.

ATC — H03BC01.

ATC Vet — QH03BC01.

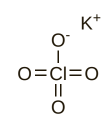

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Potassium Perchlorate). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; practically insoluble in alcohol.

USP 31 (Potassium Perchlorate). pH of a 0.1M solution in water is between 5.0 and 6.5.

Sodium Perchlorate

Perclorato sódico; Sodu nadchloran.

$NaClO_4$ = 122.4.

CAS — 7601-89-0 (anhydrous sodium perchlorate); 7791-07-3 (sodium perchlorate monohydrate).

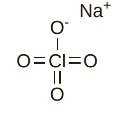

(anhydrous sodium perchlorate)

Handling. Potassium and sodium perchlorate have been used for the illicit preparation of explosives or fireworks; care is required with their supply. Great caution should be taken in handling perchlorates in solution or in the dry state as explosions may occur if brought into contact with organic or other readily oxidisable substances.

Adverse Effects

Fever and rashes have occurred after use of perchlorate. Some patients may experience nausea and vomiting. Potassium perchlorate seldom produces adverse effects when given as a single dose for diagnostic purposes. Prolonged use as an antithyroid drug has been associated with serious dose-related adverse effects. Aplastic anaemia (with some fatalities), agranulocytosis, leucopenia, pancytopenia, and the nephrotic syndrome have been reported. Excessive doses may cause hypothyroidism and goitre.

Effects on the blood. There have been reports of fatal aplastic anaemia[1,2] and of leucopenia and agranulocytosis[1] associated with the use of potassium perchlorate for the treatment of hyperthyroidism. A review[3] in 1998 noted that despite an increase in perchlorate use in recent years there did not appear to have been any further cases of aplastic anaemia since the 1960s.

1. Anonymous. Potassium perchlorate and aplastic anaemia. *BMJ* 1961; **i:** 1520–1.
2. Krevans JR, *et al.* Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. *JAMA* 1962; **181:** 182–4.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.

Uses and Administration

Potassium and sodium perchlorate reduce the uptake and concentration of iodide, pertechnetate, and other anions by the thyroid, choroid plexus, gastric mucosa, and salivary glands, probably by competitive inhibition of active transport mechanisms.

They are used **diagnostically** as adjuncts to pertechnetate (^{99m}Tc) to enhance visualisation of the brain, Meckel's diverticulum, or the placenta by reducing unwanted images of other organs. The usual oral dose of either potassium or sodium perchlorate is 200 to 400 mg given 30 to 60 minutes before the use of sodium pertechnetate (^{99m}Tc).

Potassium and sodium perchlorate are also used with sodium iodide (^{131}I) in the perchlorate discharge test of thyroid function. The release of radio-iodine from the gland following an oral dose of perchlorate indicates a defect in the binding of iodide by the thyroid and thus a defect in thyroid hormone synthesis. The test has also been used to investigate the action of antithyroid drugs.

Potassium and sodium perchlorate have been used in the treatment of **hyperthyroidism** (p.2165), but because of toxicity have been largely replaced by alternative treatments. However, perchlorates may be useful in patients with iodine-induced hyperthyroidism such as that associated with amiodarone therapy, by increasing responsiveness to conventional antithyroid drugs. A typical dose of potassium perchlorate in amiodarone-induced hyperthyroidism is 1 g daily.

◊ References.

1. Bartalena L, *et al.* Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab* 1996; **81:** 2930–3.
2. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.
3. Soldin OP, *et al.* Perchlorate clinical pharmacology and human health: a review. *Ther Drug Monit* 2001; **23:** 316–31.
4. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.

Preparations

USP 31: Potassium Perchlorate Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Irenat; ***Cz.:*** Irenat; ***Ger.:*** Irenat; ***Ital.:*** Pertiroid; ***Pol.:*** Irenat; ***USA:*** Perchloracap†.

Prolonium Iodide *(rINN)*

Ioduro de prolonio; Prolonii Iodidum; Prolonium, Iodure de. *NN*-(2-Hydroxytrimethylene)bis(trimethylammonium) di-iodide.

Пролония Йодид

$C_9H_{24}I_2N_2O = 430.1.$

CAS — 123-47-7.

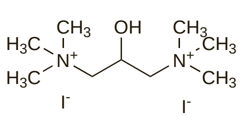

Pharmacopoeias. In *Chin.*

Profile

Prolonium iodide has been given by injection as a source of iodine (p.2169) as part of the treatment of thyroid storm and for the pre-operative management of hyperthyroidism.

Propylthiouracil *(BAN, rINN)*

Proiltiourasil; Propiltiouracil; Propiltiouracilas; Propiltiouracilo; Propylthiouracile; Propylthiouracilum; Propylthiouracil; Propylitiourasiili. 2,3-Dihydro-6-propyl-2-thioxopyrimidin-4(1*H*)-one; 2-Mercapto-6-propylpyrimidin-4-ol; 6-Propyl-2-thiouracil.

Пропилтиоурацил

$C_7H_{10}N_2OS = 170.2.$

CAS — 51-52-5.

ATC — H03BA02.

ATC Vet — QH03BA02.

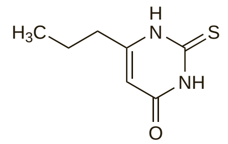

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Propylthiouracil). White or almost white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Propylthiouracil). A white, powdery, crystalline substance. It is starch-like in appearance and to the touch. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol; soluble in ammonium hydroxide and in alkali hydroxides. Protect from light.

Adverse Effects and Precautions

As for Carbimazole, p.2167, although cross-sensitivity to carbimazole does not necessarily occur.

Propylthiouracil has been associated with greater hepatotoxicity than other thiourea antithyroid drugs (such as carbimazole or thiamazole). Rarely hepatitis, hepatic necrosis, encephalopathy, and death have occurred; asymptomatic liver damage is more common (see Effects on the Liver, under Carbimazole, p.2168).

Propylthiouracil should be given with care, and in reduced doses, to patients with renal impairment.

Breast feeding. Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily, see Breast Feeding, under Carbimazole, p.2167.

Pharmacokinetics

Propylthiouracil is rapidly absorbed from the gastrointestinal tract with a 50 to 75% bioavailability and with peak plasma concentrations occurring about 2 hours after oral doses. It is concentrated in the thyroid gland; since its duration of action is more closely related to the intrathyroidal drug concentration than its plasma half-life, prolonged antithyroid activity results from single daily doses. Propylthiouracil is about 80% bound to plasma proteins.

Propylthiouracil has an elimination half-life of about 1 to 2 hours. It undergoes rapid first-pass metabolism in the liver, and is mainly excreted in the urine as the glucuronic acid conjugate, with less than 2% excreted as unchanged drug. The elimination half-life may be increased in renal or hepatic impairment.

Propylthiouracil crosses the placenta and is distributed into breast milk.

Uses and Administration

Propylthiouracil is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165); it also inhibits the peripheral deiodination of thyroxine to tri-iodothyronine. It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radioiodine therapy, and the treatment of thyroid storm.

Propylthiouracil is usually given orally. Initial doses range from 150 to 450 mg daily (the *BNF* recommends 200 to 400 mg daily), although in severe cases initial doses of 600 to 1200 mg daily have been used. It has often been given in divided daily doses but once daily dosage is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms is achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to a maintenance dose, usually 50 to 150 mg daily. Treatment is usually continued for 1 to 2 years. In the UK, the *BNFC* recommends the following initial doses by mouth for children:

- in neonates: 2.5 to 5 mg/kg twice daily
- in those aged 1 month to 1 year: 2.5 mg/kg three times daily
- in those aged 1 to 5 years: 25 mg three times daily
- in those aged 5 to 12 years: 50 mg three times daily
- in those aged 12 to 18 years: 100 mg three times daily

These doses are given until the patient is euthyroid and then adjusted as needed; higher doses may be required, especially in thyrotoxic crises.

Doses should be reduced in renal impairment (below). Doses may also need to be reduced in hepatic impairment.

Administration in renal impairment. The dosage of propylthiouracil should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 10 to 50 mL/minute, doses should be reduced by 25%
- CC less than 10 mL/minute, reduce doses by 50%

Alcoholic liver disease. Propylthiouracil has been said to reduce hyperoxic liver injury in hypermetabolic *animals* and despite reports of hepatotoxicity, including some fatalities, associated with propylthiouracil (see Effects on the Liver, under Carbimazole, p.2168), it has been investigated in the treatment of patients with alcoholic liver disease. A systematic review[1], however, concluded that there is no evidence to substantiate this use. Propylthiouracil was associated with adverse effects and it could not be shown to have any significant effects on mortality, liver related mortality, liver complications, and liver histology.

1. Rambaldi A, Gluud C. Propylthiouracil for alcoholic liver disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/08/08).

Psoriasis. Several reports have described benefit in patients with psoriasis (p.1583) given propylthiouracil. An oral dose of 300 mg daily for 8 to 12 weeks has been used and is said not to produce clinical hypothyroidism.[1]

1. Elias AN. Anti-thyroid thioureylenes in the treatment of psoriasis. *Med Hypotheses* 2004; **62:** 431–7.

Preparations

BP 2008: Propylthiouracil Tablets;
USP 31: Propylthiouracil Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Prothiucil; ***Braz.:*** Propil; Propilracil; ***Canad.:*** Propyl-Thyracil; ***Cz.:*** Propycil; ***Ger.:*** Propycil; Thyreostat II†; ***Gr.:*** Prothuril; ***Hong Kong:*** CP-PTU; ***Hung.:*** Propycil; ***Israel:*** Propylthiocil; ***Pol.:*** Thyrosan; ***Port.:*** Propycil; ***Swed.:*** Tiotil; ***Switz.:*** Propycil; ***Thai.:*** Propyl; Uracil; ***Turk.:*** Propycil.

Protirelin *(BAN, USAN, rINN)*

Abbott-38579; Lopremone; Protireliini; Protirelina; Protirelinas; Protiréline; Protirelinum; Synthetic TRH; Thyrotrophin-releasing Hormone; Thyrotropin-releasing Hormone; TRF; TRH. L-Pyroglutamyl-L-histidyl-L-prolinamide; 1-[*N*-(5-Oxo-L-prolyl)-L-histidyl]-L-prolinamide; Glu-His-Pro-NH_2.

Протирелин

$C_{16}H_{22}N_6O_4 = 362.4.$

CAS — 24305-27-9.

ATC — V04CJ02.

ATC Vet — QV04CJ02.

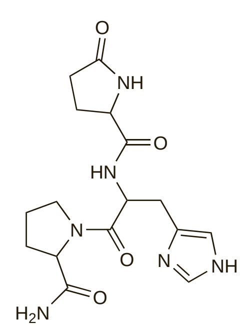

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*, which also includes the tartrate.

Ph. Eur. 6.2 (Protirelin). A synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, that stimulates the release and synthesis of thyrotrophin.

A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in methyl alcohol. Store at a temperature of 2° to 8°. Protect from light and moisture.

Adverse Effects

Protirelin given by intravenous injection may cause headache, nausea, a desire to micturate, flushing, dizziness, and a strange taste. These effects have been attributed to contraction of smooth muscles by the bolus injection. Hypertension and an increased pulse rate, or hypotension, have occasionally been reported as have a few cases of amaurosis and convulsions.

Amaurosis. Of 4 patients with pituitary tumours who developed severe headache after protirelin injection, one also developed amaurosis, apparently associated with pituitary apoplexy.[1] Visual acuity improved after surgery.

1. Drury PL, *et al*. Transient amaurosis and headache after thyrotropin releasing hormone. *Lancet* 1982; **i:** 218–19.

Effects on the cardiovascular system. Increased blood pressure has been reported in women given protirelin antenatally,[1,2] and the view has been expressed that although the magnitude of the change is unlikely to be clinically significant in normotensive women, much greater rises have been seen in pre-eclamptic women[2,3] and may be severe enough to increase the risk of cerebral haemorrhage.[2]

1. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 877–82.
2. Peek MJ, *et al*. Hypertensive effect of antenatal thyrotropin-releasing hormone in pre-eclampsia. *Lancet* 1995; **345:** 793. Correction. *ibid*.; 1124.
3. Tan ASA, *et al*. Is maternal thyrotropin releasing hormone administration safe in the pregnant women with preeclampsia? *Am J Perinatol* 1997; **14:** 5–6.

Effects on the CNS. Adverse effects reported after injection of 400 micrograms of protirelin included unconsciousness, hypotension, and convulsions.[1] In another patient with a history of convulsions, a 500-microgram injection induced epileptic seizures.[2]

1. Dolva LØ, *et al*. Side effects of thyrotrophin releasing hormone. *BMJ* 1983; **287:** 532.
2. Maeda K, Tanimoto K. Epileptic seizures induced by thyrotropin releasing hormone. *Lancet* 1981; **i:** 1058–9.

Effects on the respiratory system. Bronchospasm occurred in an asthmatic boy given protirelin intravenously.[1]

For a report that protirelin provoked bronchospasm in patients with motor neurone disease, see under Precautions, below.

1. McFadden RG, *et al*. TRH and bronchospasm. *Lancet* 1981; **ii:** 758–9.

Effect on sexual function. On questioning, 7 of 16 women reported a sensation of mild vaginal sexual arousal occurring 1 to 3 minutes after intravenous injection of protirelin.[1] Four women also had urinary sensations, and 3 described an urge to urinate with no sexual component.

1. Blum M, Pulini M. Vaginal sensations after injection of thyrotropin releasing hormone. *Lancet* 1980; **ii:** 43.

Pituitary apoplexy. Pituitary apoplexy has been reported after combined testing of anterior pituitary function in patients with a pituitary tumour.[1,2] Of the drugs given, protirelin was thought most likely to have an aetiological role. Pituitary apoplexy has also been reported after the use of protirelin alone.[3]

See also Amaurosis, above.

1. Chapman AJ, *et al*. Pituitary apoplexy after combined test of anterior pituitary function. *BMJ* 1985; **291:** 26.
2. Dökmetaş HS, *et al*. Pituitary apoplexy probably due to TRH and GnRH stimulation tests in a patient with acromegaly. *J Endocrinol Invest* 1999; **22:** 698–700.
3. Szabolcs I, *et al*. Apoplexy of a pituitary macroadenoma as a severe complication of preoperative thyrotropin-releasing hormone (TRH) testing. *Exp Clin Endocrinol Diabetes* 1997; **105:** 234–6.

Precautions

Protirelin should be given with care to patients with ischaemic heart disease, obstructive airways disease, or severe hypopituitarism. Giving protirelin while the patient is lying down may reduce the incidence of hypotension.

Eclampsia. For the suggestion that the hypertensive effects of protirelin increase the risk of cerebral haemorrhage in pre-eclamptic women, see Effects on the Cardiovascular System under Adverse Effects, above.

Motor neurone disease. In some patients with amyotrophic lateral sclerosis, intravenous injection of protirelin resulted in acute bronchospasm.[1] Five of 25 patients had falls in FEV_1 of more than 20%; in 2, a 15% decrease in arterial-oxygen pressure occurred. Patients with sclerosis and weakened respiratory muscles should be warned of this potential adverse effect.

1. Braun SR, *et al*. Pulmonary effects of thyrotropin-releasing hormone in amyotrophic lateral sclerosis. *Lancet* 1984; **ii** 529–30.

Interactions

◊ Drugs influencing the response to protirelin have been reviewed.[1] The secretion of thyrotrophin appears to be modulated by dopaminergic and noradrenergic pathways at both the hypothalamic and pituitary level. Dopamine and bromocriptine have depressed the response to protirelin; levodopa is a powerful depressant. Partial depression has been reported after the use of chlorpromazine, thioridazine, and phentolamine, all of which have alpha-receptor blocking properties. Beta-receptors do not appear to be involved in the thyrotrophin response to protirelin whereas the antiserotonin drug, cyproheptadine, has an inhibitory effect. Aspirin and corticosteroids with mainly glucocorticoid activity have also depressed the response. An enhanced response to protirelin has been seen after theophylline. Oestrogens may also increase the response in men but not usually in women; when combined with a progestogen a slightly depressed response has been reported.

Other drugs reported to depress the response to protirelin include lithium[2] and ranitidine.[3]

1. Lamberg B-A, Gordin A. Abnormalities of thyrotrophin secretion and clinical implications of the thyrotrophin releasing hormone stimulation test. *Ann Clin Res* 1978; **10:** 171–83.
2. Lauridsen UB, *et al*. Lithium and the pituitary-thyroid axis in normal subjects. *J Clin Endocrinol Metab* 1974; **39:** 383–5.
3. Tarditi E, *et al*. Impaired TSH response to TRH after intravenous ranitidine in man. *Experientia* 1983; **39:** 109–10.

Uses and Administration

Protirelin is a hypothalamic releasing hormone that stimulates the release of thyrotrophin (p.2177) from the anterior lobe of the pituitary. It also has prolactin-releasing activity. It may be obtained by synthesis.

Protirelin may be used in the assessment of the hypothalamic-pituitary-thyroid axis in the diagnosis of mild hyperthyroidism (p.2165) or hypothyroidism (p.2167), and ophthalmic Graves' disease, although in many cases immunoassays for thyroid-stimulating hormone are now preferred. The response to protirelin may be used for differentiating between primary and secondary hypothyroidism but care is required in interpreting the results of the test and it should not be used alone in establishing the diagnosis. Protirelin is given with gonadorelin (p.2107) in the assessment of anterior pituitary function.

Protirelin is given intravenously, usually in doses of 200 to 400 micrograms. A suggested intravenous dose in children is 1 microgram/kg for the assessment of thyroid function. The *BNFC* gives a dose of 7 micrograms/kg (to a maximum of 200 micrograms) for the diagnosis of hypopituitarism and hypothalamic disease.

Protirelin has been investigated in the treatment of neurological diseases, and in the prevention of neonatal respiratory distress syndrome, but results have been variable.

Protirelin tartrate has been given in the treatment of neurological disorders.

Lactation induction. Intranasal protirelin has been tried for stimulation of lactation (p.2003) but there is no suitable commercial preparation, and in any case mechanical stimulation is preferable to drug treatment.

Neonatal respiratory distress syndrome. The regulation of fetal lung development is under multihormonal control and thyroid hormones appear to stimulate pulmonary maturation. However, the thyroid hormones and thyrotrophin do not cross the placenta sufficiently for them to be given in premature labour where neonatal respiratory distress syndrome (p.1508) may develop; therapy with protirelin has therefore been investigated.[1]

Protirelin has been given with corticosteroids to the mother and some beneficial effects have been noted.[1] One study using protirelin 400 micrograms every 8 hours for 4 doses indicated that antenatal protirelin reduced the incidence of chronic lung disease when given with corticosteroids but did not affect the incidence of respiratory distress syndrome.[2] However, 2 large multicentre studies had found that addition of protirelin to corticosteroid treatment had no beneficial effects on outcome compared with corticosteroids only;[3,4] in fact, in the earlier of these studies,[3] respiratory distress syndrome and the need for ventilation were greater in the offspring of mothers given protirelin. Subsequent follow-up appeared to confirm the disadvantages of protirelin in this cohort;[5] however the unexpected conclusions of this study aroused some controversy.[6-8] The second study noted no difference in outcome in the 2 groups of infants.[4] A meta-analysis concluded[9] that prenatal treatment with protirelin was not beneficial, and that it was associated with more adverse effects than the use of corticosteroids alone.

1. de Zegher F, *et al*. Prenatal treatment with thyrotrophin releasing hormone to prevent neonatal respiratory distress. *Arch Dis Child* 1992; **67:** 450–4.
2. Ballard RA, *et al*. Respiratory disease in very-low-birthweight infants after prenatal thyrotropin-releasing hormone and glucocorticoid. *Lancet* 1992; **339:** 510–5.
3. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 877–82.
4. Ballard RA, *et al*. Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. *N Engl J Med* 1998; **338:** 493–8.
5. Crowther CA, *et al*. Australian collaborative trial of antenatal thyrotropin-releasing hormone: adverse effects at 12-month follow-up. *Pediatrics* 1997; **99:** 311–17.
6. Ballard RA, *et al*. Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 1572.
7. Moya FR, Maturana A. Thyrotropin-releasing hormone for prevention of neonatal respiratory disease. *Lancet* 1995; **345:** 1572–3.
8. McCormick MC. The credibility of the ACTOBAT follow-up study. *Pediatrics* 1997; **99:** 476–8.
9. Crowther CA, *et al*. Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 16/09/05).

Neurological disorders. Reports of the use of protirelin in various neurological disorders.

1. Bonuccelli U, *et al*. Oral thyrotropin-releasing hormone treatment in inherited ataxias. *Clin Neuropharmacol* 1988; **11:** 520–8.
2. Filla A, *et al*. Sperimentazione cronica del TRH per via intramuscolare nelle degenerazioni spino-cerebellari: studio in doppio cieco cross-over su 30 soggetti. *Riv Neurol* 1989; **59:** 83–8.
3. Mellow AM, *et al*. A peptide enhancement strategy in Alzheimer's disease: pilot study with TRH-physostigmine infusions. *Biol Psychiatry* 1993; **34:** 271–3.
4. Chemaly R, *et al*. Myélinolyse extra-pontine: traitement par T.R.H. *Rev Neurol (Paris)* 1998; **154:** 163–5.
5. Tzeng AC, *et al*. A study of thyrotropin-releasing hormone for the treatment of spinal muscular atrophy: a preliminary report. *Am J Phys Med Rehabil* 2000; **79:** 435–40.
6. Kubek MJ, Garg BP. Thyrotropin-releasing hormone in the treatment of intractable epilepsy. *Pediatr Neurol* 2002; **26:** 9–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: TRH; Trhelea; ***Austria:*** Antepan; Relefact TRH; Thyroliberin TRH†; ***Belg.:*** TRH; ***Braz.:*** TRH†; ***Canad.:*** Relefact TRH; ***Cz.:*** TRH†; ***Fr.:*** Stimu-TSH; ***Ger.:*** Antepan; Relefact TRH†; Thyroliberin; TRH; ***Gr.:*** Relefact†; TRH; ***Israel:*** Relefact TRH; TRH; ***Ital.:*** Irtonin†; Xantium†; ***Jpn:*** Hirtonin; ***Neth.:*** Relefact TRH; ***Spain:*** TRH Prem; ***Switz.:*** Relefact TRH†; ***Turk.:*** TRH.

Thiamazole *(BAN, rINN)*

Mercazolylum; Methimazole; Methylmercaptoimidazole; Metimazol; Thiamazol; Thiamazolum; Tiamatsoli; Tiamazol; Tiamazolas. 1-Methylimidazole-2-thiol.

Тиамазол

$C_4H_6N_2S$ = 114.2.

CAS — 60-56-0.

ATC — H03BB02.

ATC Vet — QH03BB02.

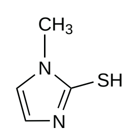

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Thiamazole). A white or pale brown, crystalline powder. Freely soluble in water and in dichloromethane; freely soluble or soluble in alcohol.

USP 31 (Methimazole). A white to pale buff crystalline powder having a faint characteristic odour. Soluble 1 in 5 of water, 1 in 5 of alcohol, 1 in 4.5 of chloroform, and 1 in 125 of ether. Its solutions are practically neutral to litmus. Protect from light.

Adverse Effects and Precautions

As for Carbimazole, p.2167.

Breast feeding. The use of thiamazole during breast feeding is discussed under Carbimazole, p.2167.

Pharmacokinetics

The pharmacokinetics of thiamazole can be considered with those of carbimazole (p.2168) since the latter is rapidly and completely metabolised to thiamazole in the body.

Uses and Administration

Thiamazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165). It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radio-iodine therapy, and the treatment of thyroid storm.

Thiamazole is given orally usually in an initial dosage of 15 to 60 mg daily. It is usually given in three divided doses but a single daily dose is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to a maintenance dose, usually 5 to 15 mg daily. Alternatively, the dose may be continued at the initial level with supplemental levothyroxine as a *blocking-replacement regimen*. Either form of maintenance treatment is usually continued for 1 to 2 years. The initial dose for children is 400 micrograms/kg daily in 3 divided doses; for maintenance this dose may be halved.

Thiamazole doses of 80 to 240 mg daily, usually in 3 or 4 divided doses, have been given intravenously in the management of thyroid storm.

Preparations

USP 31: Methimazole Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Danantizol; ***Austria:*** Favistan†; ***Belg.:*** Strumazol; ***Braz.:*** Tapazol; ***Canad.:*** Tapazole; ***Chile:*** Thyrozol; Tirozol 5/10†; ***Cz.:*** Favistan†; Thyrozol; ***Denm.:*** Thycapzol; ***Ger.:*** Favistan; Thyrozol; ***Gr.:*** Unimazole; ***Hung.:*** Metothyrin; ***Indon.:*** Thyrozol; ***Israel:*** Mercaptizol; ***Ital.:*** Tapazole; ***Mex.:*** Tapazol; Tizorol; ***Neth.:*** Strumazol; ***Philipp.:*** Strumazol; Tapazole; ***Pol.:*** Metizol; Thyrozol; ***Port.:*** Metibasol; ***Rus.:*** Mercazolil (Мерказолил); Thyrozol (Тирозол); ***Singapore:*** Thyrozol; ***Spain:*** Tirodril; ***Swed.:*** Thacapzol; ***Switz.:*** Tapazole†; ***Thai.:*** Tapazole; Timazol; ***Turk.:*** Thyromazol; ***USA:*** Northyx; Tapazole; ***Venez.:*** Tapazol.

Multi-ingredient: *Ital.:* Bromazolo.

Thyroglobulin *(USAN, rINN)*

Thyroglobuline; Thyroglobulinum; Tiroglobulina.

Тироглобулин

CAS — 9010-34-8.

Profile

Thyroglobulin is an extract obtained by the fractionation of porcine thyroid glands, that yields levothyroxine and liothyronine on hydrolysis. It has been used in the treatment of hypothyroidism, but such treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tiroide Vister.

Thyroid

Dry Thyroid; Getrocknete Schilddrüse; Glándula tiroides, extracto de; NSC-26492; Thyreoidin; Thyroid Extract; Thyroid Gland; Thyroidea; Thyroideum Siccum; Tiroide Secca.

ATC — H03AA05.
ATC Vet — QH03AA05.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 31 (Thyroid). It is the cleaned, dried, and powdered thyroid gland, previously deprived of connective tissue and fat, obtained from domesticated animals used for food by humans. On hydrolysis it yields not less than 90% and not more than 110% each of the labelled amounts of levothyroxine and liothyronine calculated on the dried basis. It is free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. It may contain a suitable diluent such as glucose, lactose, sodium chloride, starch, or sucrose. A yellowish to buff-coloured amorphous powder, having a slight, characteristic, meat-like odour. Store in airtight containers.

Profile

Thyroid has been used in the treatment of hypothyroidism, but treatment with mixtures of thyroid hormones or preparations of animal extracts is not recommended.

Preparations

USP 31: Thyroid Tablets.

Proprietary Preparations (details are given in Part 3)
Ital.: Cinetic; ***Mex.:*** Amet; ***Thai.:*** Thiroyd; ***USA:*** Nature Throid.

Multi-ingredient: *Braz.:* Emagrex†; Obesidex†; Obesifran†; ***India:*** Ebexid; ***Thai.:*** Metharmon-F.

Thyrotrophin *(BAN, rINN)*

Thyroid-stimulating Hormone; Thyrotrophic Hormone; Thyrotrophine; Thyrotrophinum; Thyrotropin; Thyrotropinum; Tirotrofina; TSH; Tyrotropiini; Tyrotropin.

Тиротропин

CAS — 9002-71-5.
ATC — H01AB01; V04CJ01.
ATC Vet — QH01AB01; QV04CJ01.

Description. Thyrotrophin is a glycoprotein from the anterior pituitary with a molecular weight in man of about 30 000.

Thyrotropin Alfa *(BAN, USAN, rINN)*

rhTSH; Thyrotropine Alfa; Thyrotropinum Alfa; Tirotropina alfa.

Тиротропин Альфа

CAS — 194100-83-9.
ATC — V04CJ01.
ATC Vet — QV04CJ01.

Units

0.037 units of human pituitary thyrotrophin for immunoassay and bioassay are contained in about 7.5 micrograms of thyrotrophin, with albumin 1 mg and lactose 5 mg, in one ampoule of the second International Reference Preparation (1983).

Adverse Effects

Infrequent adverse effects of thyrotrophin include nausea, vomiting, headache, a desire to micturate, and flushing. High doses may produce excessive thyroid stimulation, with angina, tachycardia or arrhythmias, dyspnoea, sweating, nervousness and irritability. Hypersensitivity reactions, including skin rash and urticaria, erythema and swelling at the injection site, and anaphylaxis have occurred, particularly on repeated use.

Precautions

Thyrotrophin should not be given to patients with recent myocardial infarction or uncorrected adrenocortical insufficiency, including adrenocortical insufficiency secondary to hypopituitarism. Care is also required in patients with cardiovascular disease.

Uses and Administration

Thyrotrophin is a glycoprotein that is secreted by the anterior lobe of the pituitary and has an alpha subunit essentially the same as that of the gonadotrophins. Its main actions are to increase iodine uptake by the thyroid and the formation and secretion of the thyroid hormones. It may produce hyperplasia of thyroid tissue. Thyrotrophin secretion is controlled by a hypothalamic releasing hormone (Protirelin, p.2175) and by circulating thyroid hormones; somatostatin (p.1809) inhibits the release of thyrotrophin.

Thyrotrophin has been used with radio-iodine in the diagnosis of hypothyroidism (p.2167) and to differentiate between primary and secondary hypothyroidism, but direct radio-immunoassay of circulating endogenous thyroid-stimulating hormone may be preferred. Thyrotrophin increases the uptake of radio-iodine by the thyroid and has been used as a diagnostic tool and as an adjunct in the treatment of certain types of thyroid cancer.

Thyrotropin alfa is a recombinant form of thyrotrophin used as an adjunctive diagnostic tool for serum-thyroglobulin testing, with or without radio-iodine imaging, in the follow-up of patients with thyroid cancer. It is also used to increase radio-iodine uptake for ablation of thyroid remnant tissue after thyroidectomy. The usual thyrotropin alfa regimen consists of 2 intramuscular doses of 900 micrograms given 24 hours apart. Radio-iodine is given 24 hours after the second dose of thyrotropin alfa for radio-iodine imaging or remnant ablation. Diagnostic scanning is performed 48 to 72 hours after the radio-iodine has been given, but post-therapy scanning may be delayed by additional days to allow background activity to decline. Samples for serum-thyroglobulin testing should be taken 72 hours after the second thyrotropin alfa dose.

Goitre and thyroid nodules. Thyrotropin alfa is under investigation[1-4] as an adjunct to increase thyroid uptake of radio-iodine (^{131}I) in the treatment of selected patients with nodular goitre (p.2165).

1. Nielsen VE, *et al.* The effects of recombinant human thyrotropin, in normal subjects and patients with goitre. *Clin Endocrinol (Oxf)* 2004; **61:** 655–63.
2. Duick DS, Baskin HJ. Significance of radioiodine uptake at 72 hours versus 24 hours after pretreatment with recombinant human thyrotropin for enhancement of radioiodine therapy in patients with symptomatic nontoxic or toxic multinodular goiter. *Endocr Pract* 2004; **10:** 253–60.
3. Nielsen VE, *et al.* Recombinant human thyrotropin markedly changes the I kinetics during I therapy of patients with nodular goiter: an evaluation by a randomized double-blinded trial. *J Clin Endocrinol Metab* 2005; **90:** 79–83.
4. Albino CC, *et al.* Recombinant human thyrotropin as adjuvant in the treatment of multinodular goiters with radioiodine. *J Clin Endocrinol Metab* 2005; **90:** 2775–80.

Malignant neoplasms of the thyroid. Patients with well-differentiated thyroid carcinoma (p.674) undergo surgery, with or without iodine-131 treatment. They then receive thyroid hormone therapy to suppress thyrotrophin (TSH), because most differentiated thyroid cancers express TSH receptors and grow in response to thyrotrophin stimulation. Monitoring for tumour recurrence in subsequent years requires interruption of thyroid hormone treatment so that thyrotrophin levels rise, and stimulate the uptake of a subsequent dose of iodine-131 by any residual or recurrent tumour. However, this results in hypothyroidism, with associated symptoms that may be severe in some patients.[1]

Studies[2,3] have examined the use of thyrotropin alfa as an alternative prelude to radio-iodine scanning, and found that it did stimulate radio-iodine uptake, although the sensitivity of scanning may depend on the technique used; thyrotropin alfa might be considered a suitable alternative to thyroid hormone withdrawal. In patients with CNS or spinal metastases, or who have substantial disease in the thyroid bed, thyrotropin alfa may cause tumour expansion with acute complications; it has been recommended[1] that prophylactic corticosteroid therapy should be considered in these cases.

Thyroid hormone withdrawal is also used in the treatment of differentiated thyroid cancer, to increase uptake of radio-iodine for thyroid remnant ablation and treatment of metastatic disease. The use of thyrotropin alfa as an alternative adjunct is under investigation.[4]

1. Basaria M, *et al.* The use of recombinant thyrotropin in the follow-up of patients with differentiated thyroid cancer. *Am J Med* 2002; **112:** 721–5.
2. Ladenson PW, *et al.* Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997; **337:** 888–96.
3. Haugen BR, *et al.* A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *J Clin Endocrinol Metab* 1999: **84:** 3877–85.
4. Robbins RJ, Robbins AK. Recombinant human thyrotropin and thyroid cancer management. *J Clin Endocrinol Metab* 2003; **88:** 1993–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Thyrogen; ***Belg.:*** Thyrogen; ***Braz.:*** Thyrogen†; ***Canad.:*** Thyrogen; ***Cz.:*** Thyrogen; ***Denm.:*** Thyrogen; ***Fin.:*** Thyrogen; ***Fr.:*** Thyrogen; ***Ger.:*** Thyrogen; ***Gr.:*** Thyrogen; ***Hung.:*** Thyrogen; ***Israel:*** Thyrogen; Thytropar†; ***Ital.:*** Thyrogen; ***Neth.:*** Thyrogen; ***Norw.:*** Thyrogen; ***Pol.:*** Thyrogen; ***Port.:*** Thyrogen; ***Singapore:*** Thyrogen; ***Spain:*** Thyrogen; ***Swed.:*** Thyrogen; ***UK:*** Thyrogen; ***USA:*** Thyrogen.

Tiratricol *(rINN)*

Tiratricolum; Tiratrikol; Tiratrikoli; Triac; Triiodothyroacetic Acid. [4-(4-Hydroxy-3-iodophenoxy)-3,5-di-iodophenyl]acetic acid.

Тиратрикол

$C_{14}H_9I_3O_4$ = 621.9.
CAS — 51-24-1.
ATC — D11AX08; H03AA04.
ATC Vet — QD11AX08; QH03AA04.

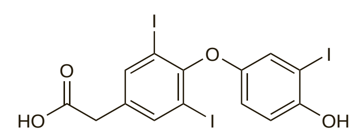

NOTE. Tri-ac has also been used as a name for proprietary preparations containing other drugs.

Profile

Tiratricol, a metabolite of tri-iodothyronine, is reported to be less active than the thyroid hormones but is given orally to suppress the secretion of thyroid-stimulating hormone.

Obesity. Abnormal thyroid function tests, severe diarrhoea, fatigue, lethargy, and profound weight loss have occurred in patients taking dietary supplements containing tiratricol.[1,2] The FDA has warned that tiratricol may cause heart attacks and strokes, and has advised consumers not to take these products.[3]

1. Anonymous. Triax : a harmful product sold on the internet. *WHO Drug Inf* 2000; **14:** 30.
2. Bauer BA, *et al.* Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. *Mayo Clin Proc* 2002; **77:** 587–90.
3. FDA. FDA warns against consuming dietary supplements containing tiratricol. FDA Talk Paper T00-64, 21 Nov 2000. Available at: http://www.fda.gov/bbs/topics/ANSWERS/ANS01057.html (accessed 18/05/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dimagrir Triac†; Nulobes; Triacana; ***Braz.:*** Redulip†; Triac†; Trimag†; ***Chile:*** Triacana†; ***Fr.:*** Teatrois; Triacana†.

Urological Drugs

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Cystitis, p.2178
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Prostatitis, p.2181
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Renal failure, p.2182
Sexually transmitted diseases, p.2182
Syndrome of inappropriate ADH secretion, p.2182
Urinary-tract infections, p.2182

This chapter includes a number of drugs used in the management of certain urological or urogenital conditions such as urinary incontinence, benign prostatic hyperplasia, and erectile dysfunction.

Other drugs used in these conditions may be found elsewhere in *Martindale*: they include the tricyclic antidepressants such as imipramine (p.400) and the serotonin and noradrenaline reuptake inhibitor duloxetine (p.389), which are in the chapter on Antidepressants (p.372); some alpha blockers such as doxazosin (p.1275), phentolamine (p.1370), and prazosin (p.1375), as well as, more generally, diuretics and drugs such as ACE inhibitors which may be used to alter urological function, all of which are to be found in the chapter on Cardiovascular Drugs (p.1152); and the various electrolytes (see p.1667).

For the treatment of urogenital infections, see under Choice of Antibacterial, p.162. For the management of urological and reproductive tract malignancies, see under Choice of Antineoplastic, p.643.

Benign prostatic hyperplasia

Benign enlargement of the prostate gland is common in men with increasing age: at least 50% of men aged over 60 years have histological evidence of hyperplasia. Men with an enlarged prostate may exhibit symptoms of lower urinary tract obstruction, such as acute or chronic urinary retention, or irritative symptoms such as frequency, urgency, nocturia, or occasionally urge incontinence, resulting from secondary bladder instability. Therapy is influenced by the severity of symptoms and their effect on the patient's quality of life. The three main options for management are watchful waiting (monitoring without active intervention), drug treatment, and surgery.[1-7]

Watchful waiting is suitable for men with mild to moderate symptoms that are not bothersome,[3] and for some men with moderate to severe symptoms who have not yet developed complications of benign prostatic hyperplasia such as renal impairment, urinary retention, or recurrent infection.[2] The patient is monitored and advised on lifestyle measures that may improve symptoms; these include decreasing fluid intake at specific times such as bedtime or when going out, reducing caffeine and alcohol intake in general, and bladder re-training techniques.

Drug treatment is essentially based on the use of alpha$_1$-adrenoceptor blockers and 5α-reductase inhibitors, and is begun once symptoms become bothersome.

- Alpha$_1$-adrenoceptor blockers (such as alfuzosin, doxazosin, prazosin, indoramin, tamsulosin, or terazosin) apparently act on the smooth muscle tone within the prostate and the bladder neck, and can produce symptomatic relief within weeks.[1,3] They are considered to have similar efficacy[1-3,8] and choice between them may be influenced by adverse effect profile and ease of use.[8]
- The 5α-reductase inhibitors (finasteride and dutasteride) reduce prostate volume, although this takes a number of months.[1,3,8] They reduce the risk of progression to urinary retention and prostatic surgery, and are given particularly to men with urinary symptoms and large prostates.[1-3,8] However, they are less effective for symptomatic improvement than alpha$_1$-adrenoceptor blockers.[2]
- Combined treatment using an alpha$_1$-adrenoceptor blocker and a 5α-reductase inhibitor may be more effective than monotherapy,[1,3] and is considered to be suitable for patients with symptoms associated with demonstrable prostatic enlargement who are at significant risk of progression.[2,8]

Other drug therapies exist but are largely unproven or unsuitable for general use. Gonadorelin analogues such as leuprorelin or nafarelin can produce a reduction in prostate size, but adverse effects make these drugs unsuitable for indefinite therapy. More recently, gonadorelin antagonists such as cetrorelix have been tried. The antifungal mepartricin has been reported to produce symptomatic improvement, possibly by binding to oestrogen in the intestinal lumen and lowering plasma-oestrogen concentrations. Injection of botulinum A toxin into the prostate gland, for the treatment of chronic urinary retention, has shown some promise in small studies. A number of plant extracts such as saw palmetto (*Serenoa repens*)[9] and *Pygeum africanum*[10] are also in use, and the phytosterol sitosterol, which is a constituent of these, is reported to be effective.[11]

Surgery is recommended for men with more severe symptoms that do not respond to drug therapy, or who have complications such as acute urinary retention, gross haematuria, renal failure, bladder calculi, or recurrent urinary-tract infection. The mainstay of treatment is transurethral resection of the prostate (TURP),[1-3] which is more effective than drug treatment but is associated with a risk of complications such as impotence (although this may not be attributable to the surgery in all cases) and bladder neck contracture.[2,3] Transurethral incision of the prostate may be used as an alternative for smaller prostates[1-3] and open prostatectomy may be indicated for removal of very large glands.[3] Various surgical alternatives to TURP use heat to destroy prostatic tissue surrounding the urethra.[1-3,12] These minimally invasive therapies include transurethral microwave thermotherapy, water-induced thermotherapy, radiofrequency transurethral needle ablation, interstitial laser treatment, and transrectal high-intensity focused ultrasound.

1. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; **361:** 1359–67. Correction. *ibid.*; **362:** 496.
2. American Urological Association Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: diagnosis and treatment recommendations. *J Urol (Baltimore)* 2003; **170:** 530–47. Also available at: http://www.auanet.org/guidelines/main_reports/bph_management/chapt_1_appendix.pdf (accessed 01/09/08)
3. Madersbacher S, *et al.* EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004; **46:** 547–54. Also available as: de la Rosette J, *et al.* European Association of Urology guidelines on benign prostatic hyperplasia (2004). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/BPH.pdf (accessed 02/09/08)
4. McNaughton-Collins M, Barry MJ. Managing patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Am J Med* 2005; **118:** 1331–9.
5. Patel AK, Chapple CR. Benign prostatic hyperplasia: treatment in primary care. *BMJ* 2006; **333:** 535–9.
6. Wilt TJ, N'Dow J. Benign prostatic hyperplasia: part 2 management. *BMJ* 2008; **336:** 206–10.
7. Gur S, *et al.* Guide to drug therapy for lower urinary tract symptoms in patients with benign prostatic obstruction: implications for sexual dysfunction. *Drugs* 2008; **68:** 209–29.
8. Speakman MJ, *et al.* Guideline for the primary care management of male lower urinary tract symptoms. *BJU Int* 2004; **93:** 985–90.
9. Wilt T, *et al.* Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 29/11/05).
10. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.
11. Wilt T, *et al.* Beta-sitosterols for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 29/11/05).
12. Larson TR. Rationale and assessment of minimally invasive approaches to benign prostatic hyperplasia therapy. *Urology* 2002; **59** (suppl 2A): 12–16.

Cystitis

Signs and symptoms of cystitis (inflammation of the bladder) include suprapubic pain, dysuria, frequency and urgency of urination, nocturia, and haematuria. It may have various causes but is usually associated with urinary-tract infections (see p.199). Non-infectious cystitis can occur as an adverse effect of some drugs such as NSAIDs (notably tiaprofenic acid).[1] Pelvic radiotherapy and some drugs used for cancer chemotherapy can also cause haemorrhagic cystitis (below). Other inflammatory non-infectious forms of cystitis include interstitial cystitis (see below) and rare conditions such as eosinophilic cystitis.[2]

1. Bramble FJ, Morley R. Drug-induced cystitis: the need for vigilance. *Br J Urol* 1997; **79:** 3–7.
2. Teegavarapu PS, *et al.* Eosinophilic cystitis and its management. *Int J Clin Pract* 2005; **59:** 356–60.

Haemorrhagic cystitis. Haemorrhagic cystitis results from damage to the bladder wall that causes diffuse bleeding from the endothelial lining; damage may range from minor telangiectatic bleeding to diffuse necrotic ulceration.[1] Signs and symptoms include haematuria, dysuria, urgency, and increased frequency of urination.

Haemorrhagic cystitis may be associated with various diseases, drug and radiation therapies, infections, and toxins. Associated diseases include carcinoma of the bladder, rheumatoid arthritis, and amyloidosis.[1] Drugs that are often associated with haemorrhagic cystitis are antineoplastics, particularly the oxazaphosphorine alkylating agents cyclophosphamide and ifosfamide[1,2] (see also Effects on the Bladder under Cyclophosphamide, p.702). Other drugs with which haemorrhagic cystitis has been reported include penicillins and NSAIDs.[2] Pelvic irradiation[3] for genito-urinary malignancies may cause acute symptoms that can occur up to 6 months after irradiation; some patients will develop chronic symptoms and in a small number the symptoms may become debilitating and refractory to conservative management. Viruses such as adenovirus, BK virus, and CMV can cause haemorrhagic cystitis, particularly in immunocompromised patients.[1] In some cases, bacterial or fungal infection, or parasitical infestation may be responsible.[2] Other causative agents have included toxins such as dyes, insecticides, and turpentine.[1]

Initial supportive **treatment** of haemorrhagic cystitis involves increasing fluid intake to hydrate the bladder and dilute the concentration of any toxic agent in the urine. Symptomatic relief with antispasmodics and analgesics may be indicated.[1] If haematuria does not improve or resolve, intravesical treatment may be considered. This usually begins with a continuous bladder irrigation of *sodium chloride 0.9%*, to remove existing clots.[1-3] For bleeding that persists or worsens, other treatments have been described, mostly in case reports or small series.[1-4] *Alum* irrigation has been used for its astringent properties, but its effect is rarely permanent. Adverse effects include suprapubic pain, fever, bladder spasm, and urinary retention or frequency; alum precipitation can block the catheter and aluminium toxicity may occur rarely. *Silver nitrate* instillation has a cauterising effect by coagulating proteins on the bladder mucosa, *phenol* causes a chemical cauterisation, and *formaldehyde* hydrolyses protein on the bladder wall, coagulating tissue and controlling bleeding in the mucosa and submucosa. However, the duration of effect of these cauterising agents is often short, they are contra-indicated in patients with ureteric reflux, and treatments are painful, necessitating anaesthesia. *Prostaglandins*, such as alprostadil, carboprost, and dinoprostone, have been instilled into the bladder for a cytoprotective effect, to stimulate platelet aggregation, and to cause local vasoconstriction.

There are also reports of successful systemic treatment in some cases that were refractory to intravesical therapy. *Conjugated oestrogens* have been given intravenously and orally.[1] The *antifibrinolytic drugs*, aminocaproic acid[1,2] and tranexamic acid[2] have been given intravenously and orally; aminocaproic acid has also been given intravesically. Oral *pentosan polysulfate sodium* has been used in radiation-induced haemorrhagic cystitis.[3] *Hyperbaric oxygen* therapy increases tissue oxygenation and has been used particularly in radiation-induced haemorrhagic cystitis to treat radionecrosis and tissue ischaemia.[3,4] Cryosurgery using *liquid nitrogen* has been used rarely.[1]

In cases that do not respond to drug treatment, *surgical* options include urinary diversion, internal iliac artery embolisation, unilateral hypogastric artery ligation, and if all else fails, cystectomy.[1-3] Hydrodistension, the application of pressure to the bladder wall by an inflated balloon, has also been used.[4] However, anaesthesia is required, its effect is short-lived, and it is associated with the risk of bladder perforation.[1,2,4]

Prophylaxis to reduce the risk of haemorrhagic cystitis associated with high-dose cyclophosphamide and ifosfamide includes intravenous hydration with diuresis, frequent voiding of the bladder or bladder catheterisation with sodium chloride 0.9% irrigation, and the use of *mesna* as a uroprotectant.[1,2] Improvements in radiotherapy techniques are reducing the risk of radiation-induced haemorrhagic cystitis.[3]

1. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; **17:** 696–706.
2. Traxer O, *et al.* Cystite hémorragique: étiologie et traitement. *Prog Urol* 2001; **11:** 591–601.
3. Crew JP, *et al.* Radiation-induced haemorrhagic cystitis. *Eur Urol* 2001; **40:** 111–23.
4. Choong SKS, *et al.* The management of intractable haematuria. *BJU Int* 2000; **86:** 951–9.

Interstitial cystitis. Interstitial cystitis is a chronic inflammatory condition of the bladder that mainly affects middle-aged women.[1-4] There are also rare reports of the condition occurring in children, usually girls.[5] Symptoms include perineal and pelvic pain (that is often relieved by voiding), urinary frequency, urgency, and nocturia. Interstitial cystitis is a disease of unknown aetiology and suggested possible causes have included abnormal bladder epithelial permeability, neurogenic abnormalities, autoimmune disorders, and allergic reactions with increased mast-cell activation.[1,2] It is considered to be incurable; attempts at management have included local and systemic drug therapy and surgery.

Non-drug therapies that may be tried include exercise, stress management, bladder training, and the avoidance of foods that patients have found to exacerbate symptoms, such as caffeine, artificial sweeteners, and acidic juices.[1,2,5] However, scientific data to support these strategies are lacking.[1,5]

Pentosan polysulfate sodium has been given orally to improve the protective glycosaminoglycan layer of the bladder, and has reduced symptoms in some patients. Benefits may take more than 3 months to become apparent.[1,2] Other oral treatments that have been used for symptom relief include amitriptyline and hydroxyzine;[1-3] cimetidine[3] and gabapentin[2] have also been tried. Intravesical instillation of dimethyl sulfoxide has been shown to improve symptoms of interstitial cystitis.[1-3] Heparin has also been given intravesically.[1,2] Cystoscopy under anaesthesia with bladder distension, a diagnostic procedure, has been reported to relieve symptoms by destruction of the mucosal nerve plexus and tension receptors in the bladder wall. Although some[1,3,5] support its use for diagnosis and treatment, others[2] suggest that it has limited efficacy. Surgery is reserved for intractable symptoms that have failed to respond to less drastic treatments.[1]

1. Selo-Ojeme DO, Onwude JL. Interstitial cystitis. *J Obstet Gynaecol* 2004; **24:** 216–25.
2. Kahn BS, *et al.* Management of patients with interstitial cystitis or chronic pelvic pain of bladder origin: a consensus report. *Curr Med Res Opin* 2005; **21:** 509–16.
3. Tincello DG, Walker ACH. Interstitial cystitis in the UK: results of a questionnaire survey of members of the Interstitial Cystitis Support Group. *Eur J Obstet Gynecol Reprod Biol* 2005; **118:** 91–5.
4. Theoharides TC. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs* 2007; **67:** 215–35.
5. Mattox TF. Interstitial cystitis in adolescents and children: a review. *J Pediatr Adolesc Gynecol* 2004; **17:** 7–11.

Diabetes insipidus

Diabetes insipidus deprives the kidney of its capacity to produce a concentrated urine, resulting in the passage of large volumes of dilute urine (polyuria) and excessive thirst (polydipsia). Patients generally have moderately raised serum-sodium concentrations but are prone to more severe hypernatraemia (p.1670) when fluid is restricted.

The syndrome of diabetes insipidus is caused either:

- by a deficiency in secretion of antidiuretic hormone (ADH; vasopressin) from the posterior pituitary gland (cranial, pituitary, or neurogenic diabetes insipidus)
- or by a failure in activity of secreted ADH on renal tubules (nephrogenic diabetes insipidus)

Cranial diabetes insipidus is most commonly idiopathic (although it is now increasingly suspected to have an autoimmune basis) or occurs following surgery or trauma when it may be temporary. More rarely, it results from neoplasms, infections, or infiltrations of the CNS, or forms part of the familial DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Nephrogenic diabetes insipidus may occur as a familial X-linked recessive disorder in male infants, but is more often secondary to hypercalcaemia, hypokalaemia, or drug therapy (including lithium salts, foscarnet, and demeclocycline).

The mainstay of **diagnosis** of diabetes insipidus is measurement of serum and urine osmolality, urine specific gravity, and serum-sodium concentration. If these are found to be normal a formal water deprivation test may be performed, with careful monitoring of urine volume, osmolality, and body-weight. The test should be stopped if more than 3 litres of urine is passed or 3% of total body-weight is lost, although this is in any case virtually diagnostic of diabetes insipidus. A dose of ADH in the form of desmopressin is then given to test renal responsiveness—prompt urine concentration is indicative of cranial diabetes insipidus, while failure indicates the nephrogenic form.

Cranial diabetes insipidus is usually **treated** by replacement therapy with ADH in the form of intranasal desmopressin, although tablets are now also available and may be preferred in children; desmopressin has greater antidiuretic efficacy and considerably less vasoconstrictor activity than lypressin or vasopressin itself.

Nephrogenic diabetes insipidus is by definition unresponsive to ADH therapy and water replacement tends to be the mainstay of treatment. Thiazide diuretics, notably hydrochlorothiazide, are given with some restriction of sodium intake to patients with nephrogenic diabetes insipidus; the resultant mild sodium depletion enhances proximal renal tubular sodium and water resorption. Giving them with amiloride has been reported to have an additive effect while also preventing hypokalaemia.

Other drugs have also been tried in the management of diabetes insipidus. Chlorpropamide stimulates ADH secretion and augments the activity of residual ADH in patients with partial cranial disease and as in nephrogenic disease the thiazides may be useful. Clofibrate and carbamazepine have also been found to promote ADH secretion in these patients. Indometacin and other prostaglandin synthetase inhibitors decrease urine volume in all types of the condition. Combination of indometacin with a thiazide and desmopressin has been investigated.

References.

1. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; **157:** 1293–1301.
2. Baylis PH, Cheetham T. Diabetes insipidus. *Arch Dis Child* 1998; **79:** 84–9.
3. Bendz H, Aurell M. Drug-induced diabetes insipidus. *Drug Safety* 1999; **21:** 449–56.
4. Cheetham T, Baylis PH. Diabetes insipidus in children: pathophysiology, diagnosis and management. *Pediatr Drugs* 2002; **4:** 785–96.
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Erectile dysfunction

Erectile dysfunction (impotence) signifies inability of a male to achieve satisfactory erection of the penis during sexual intercourse. Estimates of prevalence depend to some extent upon the definitions that are used, but the problem is thought to be not uncommon, particularly in older men. The causes of erectile dysfunction may be psychological, organic, or a combination of both. Psychological factors include stress, mental depression, and anxieties about sexual performance. Organic causes include androgen deficiency as a result of hypogonadism, neurological dysfunction (including central or peripheral lesions due to malignancy or trauma), peripheral vascular disorders, and penile abnormalities such as Peyronie's disease or microphallus. Sometimes organic dysfunction may be secondary to another disease, such as diabetes mellitus in which neurological and vascular damage lead to erectile dysfunction in over one-third of all patients. In addition, erectile dysfunction may be drug-induced.

Approaches to the management of erectile dysfunction depend to some extent upon the causative factors.

In those few patients in whom erectile dysfunction is secondary to androgen deficiency in hypogonadism, androgen replacement, preferably by the intramuscular injection or transdermal application of a suitable testosterone ester, may be of value. Androgen replacement therapy is inappropriate in patients with normal testosterone concentrations and may carry significant health risks. In patients with hypogonadism secondary to hyperprolactinaemia addition of bromocriptine is often effective in improving sexual function.

Psychotherapy or behavioural therapy alone may be adequate in patients in whom no organic cause is detected, but even when organic factors play a role psychosocial factors are also important and should be addressed by appropriate counselling.

When causes of erectile dysfunction are partly or primarily organic, the main options are:

- use of a vacuum pump to induce erection by negative pressure, followed by constriction of the base of the penis with a band to maintain tumescence
- oral or sublingual drugs
- injection of vasoactive substances into the corpora cavernosa
- transurethral dosage of vasoactive substances
- implantation of a penile prosthesis is generally reserved for patients in whom other therapy has failed or is refused, but it may also be a suitable first-line choice for some patients

Vascular surgery may have a limited application, in vasogenic dysfunction, but its role is not clearly defined and there are some doubts about its long-term effectiveness.

Oral therapy for erectile dysfunction has had a chequered history, and most of the drugs tried have proved little more effective than placebo. However, with the advent of sildenafil and other inhibitors of phosphodiesterase type-5, oral therapy is now established in erectile dysfunction. Data from randomised controlled studies have shown efficacy of sildenafil in erectile dysfunction compared with placebo, including in men with diabetes mellitus and spinal-cord injury; it has no effect on the penis in the absence of sexual stimulation. It is generally more effective in erectile dysfunction of psychogenic origin and in mild to moderate cases of organic origin. There has, however, been concern about cardiac-related deaths associated with the use of sildenafil, although causality has not been firmly established. Visual disturbances and sudden hearing loss have also been reported. Other phosphodiesterase type-5 inhibitors also used are tadalafil and vardenafil.

Yohimbine, an α_2-adrenoceptor antagonist, may have some benefit, although more in erectile dysfunction of psychological than organic origin. Oral phentolamine is available for the treatment of erectile dysfunction in some countries and has been reported to be of benefit. Trazodone, a serotonin antagonist and reuptake inhibitor used in the treatment of depression, may rarely cause priapism and has therefore been investigated for the treatment of erectile dysfunction. Beneficial effects have been reported either alone or with yohimbine. Oral L-arginine, the precursor of nitric oxide, has also shown some promise in studies.

Sublingual apomorphine, a dopaminergic (D_1 or D_2) agonist, has also shown efficacy, but nausea may be a problem.

Intracavernosal injection therapy is the most effective pharmacological method of treating erectile dysfunction and, until the advent of effective oral therapy, was the most widely used. Unfortunately, one major disadvantage of this method is the need for repeated self-injection of the penis, and studies suggest that the long-term drop-out rate is high. However, it is still a valuable option in men unresponsive to, or unable to take, oral therapy. The drugs most commonly used are alprostadil, papaverine, and phentolamine. Alprostadil is preferred because it is more effective than papaverine (with or without phentolamine), and is associated with a lower incidence of priapism and fibrosis. However, the erection is frequently painful. Papaverine, a non-specific phosphodiesterase inhibitor, has been used alone or with phentolamine, an α-adrenoceptor antagonist. Erectile dysfunction of neurogenic or psychogenic origin generally responds better to papaverine than dysfunction of vascular origin. However, long-term use of intracavernosal papaverine may result in fibrosis, and it has been suggested that it should not be used more than three times a week or on two successive days. Priapism may also be a problem. Triple therapy, involving the combination of alprostadil, papaverine, and phentolamine, has been reported to be effective and to have a relatively low incidence of adverse effects. Other drugs that have been used for intracavernosal therapy include aviptadil, a smooth muscle relaxant used with phentolamine, ketanserin used with alprostadil, and moxisylyte.

The **transurethral route** is a less invasive but also less effective option than intracavernosal therapy. A transurethral pellet of alprostadil is reported to be effective, although efficacy is inconsistent; common adverse effects include penile pain and urethral pain or burning. Transurethral alprostadil as a cream or gel has also shown promise.

A number of studies have also investigated **transcutaneous** therapy. Results from pilot studies investigating transcutaneous delivery of glyceryl trinitrate, papaverine, minoxidil, or alprostadil from creams, gels, or pastes have been variable. Topical treatment with a cream containing codergocrine mesilate, isosorbide dinitrate, and either aminophylline or testosterone has also been tried, with mixed results.

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Glomerular kidney disease

For a description of the various forms of glomerular kidney disease and their management, see p.1504.

Malignant neoplasms

Malignant neoplasms of the bladder are relatively common malignancies in the developed world; the management of bladder cancer is discussed on p.659. Prostate cancer is one of the most common malignancies in men and a leading cause of cancer death; its management is covered on p.671. For malignancies of the kidney see p.667.

Micturition disorders

Normal micturition (awareness of the need to void urine as a result of bladder filling, postponement of urination until convenient, and the ability to empty the bladder voluntarily) is controlled by the detrusor muscle of the bladder (smooth muscle innervated mainly by parasympathetic nerves) and the external sphincter (sympathetic innervation). During urination parasympathetic stimulation causes the detrusor muscle to contract while reduced sympathetic tone allows the external sphincter to relax. Micturition disorders can occur through local effects on the bladder or urethra or may result through disturbances of their nervous control. They include nocturnal enuresis, urinary incontinence, and urinary retention. The terms 'neurogenic bladder' and 'neuropathic bladder' are used loosely to describe any bladder dysfunction resulting from neurological disturbance.

Nocturnal enuresis. Involuntary discharge of urine during sleep, termed nocturnal enuresis (bed-wetting), is a normal occurrence in young children, but may persist in up to 5% by the age of 10 years. Nocturnal enuresis is defined as primary if there has never been a period of dryness for more than 6 months, and secondary if the child was dry for such a period before the onset of bed-wetting. Nonpharmacological approaches to treatment include bladder retention training, motivational therapy, and behaviour modification or conditioning therapy using moisture-sensitive alarms. Drug therapy may initially produce a more rapid response, but training and the use of alarms has generally appeared to be more effective and to have a lower relapse rate. Although preparations are available to treat children as young as 5 years of age the *BNFC* states that drug therapy is inappropriate for this age group, and that treatment is usually unnecessary for children under 7 years and in cases where the child and parents are not anxious about the bed-wetting; however, children over 10 years of age are usually considered to require prompt treatment. Drug therapy is probably most useful for intermittent use on special occasions such as sleeping away from home or when added to treatment in children who fail to respond to nonpharmacological methods alone. The long-term use of drugs for enuresis is controversial.

Use of oral *desmopressin* at night can be effective in the short-term control of nocturnal enuresis and many now consider it to be the drug of choice in terms of safety. However, it should not be given when enuresis is due to polydipsia as desmopressin may provoke water intoxication and convulsions due to hyponatraemia.

Tricyclic antidepressants have also been used and of these most experience has been with *imipramine.* Their mechanism of action in nocturnal enuresis is unclear. It may be partly the result of their antimuscarinic and antispasmodic actions.

Antimuscarinics such as *oxybutynin* reduce uninhibited bladder contractions, but although they may be of benefit in diurnal enuresis they are rarely of benefit in nocturnal enuresis alone.

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Urinary incontinence and retention. Urinary incontinence is defined as an involuntary loss of urine that is objectively demonstrable and a social or hygienic problem. Nocturnal enuresis in children is discussed above. Depending on the cause patients may have symptoms of urinary frequency, nocturia, urgency, dribbling, or dysuria. Classifications of incontinence vary but the main types include: stress incontinence, urge incontinence and overactive bladder, and overflow incontinence (a consequence of urinary retention). Patients may also have mixed types, for example combined stress and urge incontinence. The term functional incontinence is used when the patient's condition is due to impaired mobility or mental function. It is important to determine the type and, where possible, cause of urinary incontinence before attempting treatment. Urinary-tract infections, constipation, and benign prostatic hyperplasia may mimic or cause the symptoms of urinary incontinence and should be excluded.

Stress incontinence is the commonest form of incontinence in women. The patient usually has urethral sphincter incompetence and loss of urine is associated with increases in intra-abdominal pressure such as may occur on standing or coughing. Initial management should be conservative: first-line treatment is likely to be pelvic floor exercises; other treatments may include electrical stimulation or biofeedback, the use of devices such as vaginal cones, surgery, or drugs.

- Drug therapy has had only a secondary role in the treatment of stress incontinence although the serotonin and noradrenaline reuptake inhibitor *duloxetine* is now licensed in several countries to increase urethral tone in the treatment of moderate to severe stress urinary incontinence, and may be an alternative to surgical treatment. Alpha-adrenoceptor agonists such as *ephedrine, phenylpropanolamine*, and *pseudoephedrine* have been used to increase tone in the muscles of the urethra and at the base of the bladder; they may prevent incontinence in certain stress situations, but long-term experience has been mostly disappointing. *Oestrogens* used with an alpha-adrenoceptor agonist such as phenylpropanolamine appear to be effective and may be of use for postmenopausal women with mild stress incontinence; unfortunately, addition of a progestogen (necessary in women with an intact uterus) might exacerbate the incontinence. The value of oestrogens used without an alpha-adrenoceptor agonist is less clear. Intra-urethral injections of *collagen* or *polytef* appear to be effective, but there are concerns over migration and granuloma formation with polytef.

In **urge incontinence**, also known as unstable bladder or detrusor instability, contractions of the detrusor muscle occur without warning and overcome urethral sphincter resistance, despite any attempt the patient might make to prevent it. Urge incontinence is the most common form of incontinence in the elderly and is often refractory to treatment. The cause is usually unknown and these cases are referred to as being due to **idiopathic detrusor instability**. When there is overt neurological disease, such as upper motor neurone lesions in spinal cord injury or multiple sclerosis, the term **detrusor hyperreflexia** is used. **Overactive bladder syndrome** is defined as urgency (a compelling desire to urinate) with or without actual urge incontinence; patients usually exhibit urinary frequency and nocturia. Reduction of excessive fluid intake and avoidance of drinks containing alcohol or caffeine may control mild symptoms of urge incontinence or overactive bladder. Behavioural therapy may be helpful: bladder training for at least 6 weeks is a first-line option in women with urge or mixed incontinence. Women with mixed incontinence may also benefit from pelvic floor exercises. Other treatments that have been tried include hypnotherapy, acupuncture, and biofeedback.

- No drug treatment has been found to be universally effective. Drugs with antimuscarinic activity may inhibit unstable detrusor muscle contractions but the incidence of adverse effects can be high. As these drugs can increase bladder volume they should not be used in patients with urinary retention. The antimuscarinic *oxybutynin* also has direct smooth muscle relaxant properties and has been most widely used, but adverse effects are common. Transdermal or extended-release formulations may be considered in women who cannot tolerate conventional formulations of oxybutynin. *Tolterodine*, *trospium*, and *propiverine* are other alternatives. (In the UK, propiverine is suggested for overactive bladder but not for incontinence.) Selective M_3 antimuscarinics, *darifenacin* and *solifenacin*, may also be considered. They appear to be at least as effective as less selective antimuscarinics. The older antimuscarinics *flavoxate*, *propantheline*, and *emepronium* are not now recommended.

  Tricyclic antidepressants have also been used in urge incontinence because of their antimuscarinic activity but their main use has been in nocturnal enuresis and nocturia (see above). *Desmopressin* is also mainly used in nocturnal enuresis and nocturia. Evidence for *oestrogens* is inconclusive, but they may be useful as adjuncts in postmenopausal women with vaginal atrophy and symptoms of urgency, frequency, and nocturia. Injection of *botulinum A toxin* into the detrusor muscle may be effective in the treatment of detrusor hyperreflexia that is resistant to antimuscarinics. Sacral nerve stimulation, using an implantable device, may be an option in cases that are resistant to drug treatment. Surgery is reserved for intractable cases.

Urge incontinence can also be due to abnormalities in bladder sensation; the causes of **sensory urgency** are often unknown but may be due to conditions such as urinary-tract infections or interstitial cystitis. Bladder retraining techniques and antimuscarinic therapy have been suggested when no underlying disorder can be identified.

Patients with **overflow incontinence** suffer from a continuous or frequent dribbling of urine as a consequence of an overdistended bladder produced by **urinary retention**. It may result from some form of urethral blockage or may be associated with drug treatment or conditions that reduce detrusor contractions or interfere with relaxation of the urethra. Overflow incontinence is uncommon in women and most patients are elderly men with urethral blockage due to benign prostatic hyperplasia (p.2178). However, urinary retention may also occur postpartum or postoperatively. Treatment depends on the underlying condition. Catheterisation is used to relieve acute painful urinary retention or when no cause can be found. Surgical procedures or dilatation are often used to correct any mechanical outflow obstruction.

- Alpha-adrenoceptor blocking drugs such as *alfuzosin, doxazosin, indoramin, prazosin, tamsulosin,* and *terazosin* may be given to patients waiting for surgery or to those unfit for surgery. They decrease outflow resistance and improve bladder emptying. Patients with detrusor hypotonicity have been given parasympathomimetics such as *bethanechol, carbachol,* and *distigmine* to increase detrusor muscle contractions but there have been doubts about their efficacy. Use of parasympathomimetics for postoperative urinary retention has been superseded by catheterisation.

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Premature ejaculation

A universally accepted definition of premature ejaculation has not yet been established, but the American Urological Association has defined it as ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners.[1]

Management may include psychological, behavioural, and drug treatment.[1] Several antidepressants have been evaluated for a therapeutic effect in premature ejaculation,[1-3] based on their adverse effects of anorgasmia and delayed ejaculation. The SSRIs fluoxetine, paroxetine, and sertraline, and the tricyclic antidepressant clomipramine, have been used successfully. However, the optimal dosing regimen for these drugs has not been established, and they have been given either on a continuous daily basis or as single doses only before intercourse. Doses that have been effective in premature ejaculation have usually been lower than those recommended for the treatment of depression. A rapidly absorbed short-acting SSRI, dapoxetine, is under development specifically for on-demand treatment of premature ejaculation. Topical anaesthetics, such as lidocaine/prilocaine cream, have been applied to the penis to delay ejaculation.[1-3] Disadvantages of this therapy include loss of erection due to numbness associated with prolonged application, and numbness in the partner caused by residual topical anaesthetic.[1,3] Available commercial preparations intended for such use include benzocaine gels and lidocaine sprays. Sildenafil, a phosphodiesterase type-5 inhibitor used for erectile dysfunction, has also been tried with some success;[1] however, some consider that such drugs should only be used in patients with co-morbid erectile dysfunction.[3]

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Prostatitis

The term prostatitis is used to describe several clinical syndromes, including well-defined bacterial infections of the prostate gland, poorly-defined chronic pelvic pain, and asymptomatic inflammation of the prostate. Prostatitis is relatively common as a urological diagnosis, with about 30% of men having such symptoms at some time in their life.[1] The US National Institutes of Health classification system[1] for prostatitis consists of categories:

- I: acute bacterial prostatitis
- II: chronic bacterial prostatitis
- III: chronic prostatitis/chronic pelvic pain syndrome (subdivided into IIIA inflammatory and IIIB non-inflammatory)
- IV: asymptomatic inflammatory prostatitis

Acute bacterial prostatitis (category I) is most often due to Gram-negative pathogens, particularly *Escherichia coli* and other enterobacteriaceae. Symptoms include fever, chills, malaise and myalgia, with rectal, low back, or perineal pain. There is often bacteriuria with frequent and urgent dysuria. The prostate is enlarged, tender, and warm.[1,2] Chronic bacterial prostatitis (category II) is relatively rare, and may develop from acute bacterial prostatitis in some men. It is characterised by pelvic pain and recurrent urinary-tract infections. The prostate appears to be normal but in some cases is swollen or firm.[1] Bacterial prostatitis should be managed with appropriate antibacterial therapy[2-4] (see under Urinary-tract Infections, p.199).

Chronic prostatitis/chronic pelvic pain syndrome (category III), which has also been described as abacterial prostatitis, is the most common form of prostatitis. The aetiology and pathogenesis remain unclear, and suggestions have included infection with atypical organisms that cannot be detected by conventional techniques, intraprostatic reflux, or immunological processes.[1] Neurological[5] or psychological factors[1,5] may also play a role in some patients. Symptoms of chronic pelvic pain syndrome include pelvic, perineal, and genital pain, lower urinary-tract symptoms, sexual dysfunction, and general symptoms such as headache and fatigue.[1] In inflammatory chronic pelvic pain syndrome (category IIIA), leucocytes can be found in expressed prostatic secretion, in the urine after prostatic massage, and in semen; no leucocytes can be detected in non-inflammatory chronic pelvic pain syndrome (category IIIB; previously called prostatodynia).[1,5]

There are no universally effective treatments for chronic pelvic pain syndrome; treatment trials overall have been small and of poor quality.[2,4-6] Many clinicians favour initial management with antibacterials despite negative cultures, in order to treat occult atypical infection.[2] An oral fluoroquinolone is the antibacterial of choice (or a tetracycline for patients allergic to fluoroquinolones). Recommended duration of treatment varies, but courses are generally of 4 to 8 weeks, depending on response in the first few weeks.[2,3,5] However, there is no strong evidence to support this practice,[6] and although there are some studies to suggest that antibacterial treatment may be beneficial in inflammatory chronic pelvic pain syndrome, there is less evidence for the non-inflammatory form.[3] Other treatments that have been tried, with variable results, include[2,4-6] the 5α-reductase inhibitor finasteride, alpha blockers such as alfuzosin, terazosin, or tamsulosin, pentosan polysulfate sodium, mepartricin, pollen extract, quercetin, and NSAIDs. The role of allopurinol is controversial. Non-drug treatments that have shown some promise include transurethral or transrectal microwave thermotherapy[2,4-6] and sacral nerve stimulation.[5] Stress management therapy has also been tried.[2] Drugs used for symptomatic relief of neuropathic pain may include tricyclic antidepressants such as amitriptyline, or antiepileptics such as gabapentin. Anticholinergics such as oxybutynin or tolterodine may be used for urinary frequency.[5]

Asymptomatic inflammatory prostatitis (category IV) is often detected coincidentally during examination for other disorders.[1]

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Renal calculi

The solubility of calcium, oxalate, and phosphate in normal urine is maintained by a variety of inhibitors of crystallisation, both organic and inorganic. However, increases in the concentrations of crystalline substances in the urine, or decreases in the relative proportions of crystallisation inhibitors, may render individuals susceptible to urolithiasis, the formation of renal calculi (kidney stones). Renal calculi consist of crystalline components arranged around an organic matrix. They are typically formed in the calices or renal pelvis, and may become lodged in the ureter. Calcium-containing stones (usually calcium oxalate and calcium phosphate in variable proportions) account for the vast majority of occurrences although stones of other compositions including cystine, uric acid, or magnesium ammonium phosphate (also called struvite or infection stones), are occasionally seen.

The incidence and prevalence of renal calculi is increasing.[1,2] The lifetime risk of stone development varies between populations but is about 15% for white men and 6% for white women, with a lifetime recurrence rate of up to 50%.[3] Risk factors include obesity, low fluid intake, and a diet high in protein, refined carbohydrates, and salt.[1] Some conditions can promote calculi formation, including renal tubular acidosis, primary hyperparathyroidism, sarcoidosis, primary hyperoxaluria, inflammatory bowel disease, hyperuricaemic conditions, and cystic fibrosis.[4] Drug-induced calculi can be formed by crystallisation of poorly soluble drugs with a high urinary excretion, or by an effect on calcium oxalate or purine metabolism.[5]

Treatment. Most renal calculi are small, and stones that are less than 5 mm in diameter will usually pass spontaneously.[6-9] Patients may be asymptomatic or may pass small stones with relatively little discomfort, but passage of a larger stone down the ureter can be accompanied by excruciating pain (renal or ureteral colic) requiring analgesia (see Biliary and Renal Colic, p.5). If there is no obstruction, infection, or other complication, conservative treatment is favoured, with the patient being monitored radiographically over several weeks to see if the stone will pass of its own accord.[10] There is some interest in the possible use of drug treatment to ease the spontaneous passage of the stone. Small studies using a calcium-channel blocker (usually nifedipine) or an alpha$_1$-adrenoceptor blocker such as tamsulosin, sometimes with a corticosteroid such as deflazacort, have reported improvements in the rate of stone expulsion and expulsion time, and reductions in analgesic requirements, in patients with uncomplicated lower ureteral stones. A meta-analysis[11] of 9 such studies confirmed the apparent benefit of such treatment; patients had a 65% greater likelihood of spontaneous stone passage than those not given these drugs. Although a suitable randomised controlled study is required to confirm efficacy, such treatment may offer a viable alternative to lithotripsy or uteroscopy.[11] A literature review[12] suggested that daily doses of nifedipine 30 mg, doxazosin 4 mg, tamsulosin 400 micrograms, or terazosin 5 mg given for 28 to 45 days are effective in enhancing expulsion of ureteral stones that are less than 15 mm in diameter.

Where intervention is considered necessary for stone removal the choice of technique depends on the size, composition, and location of the stone. Extracorporeal shock wave lithotripsy is generally favoured, but other procedures such as ureteroscopy or percutaneous nephrolithotomy are used for more complex cases.[7,8,13] Antibacterials may be needed for infection (see Urinary-tract Infections, p.199).

Prevention. In the prevention of recurrence it is important to identify, and where possible correct, any underlying disease process or biochemical or anatomical abnormality. Certain general measures are also appropriate. Patients should drink at least 2 to 3 litres of fluid daily in order to maintain an adequate volume of urine.[1,3,7,14] In hot climates or working environments a higher volume of fluid should be taken.

In preventing the recurrence of *calcium stones*, a balanced diet that is low in protein and salt[1,3,10,15] and high in fibre[1,7] is generally advocated. In the past patients were advised to decrease their calcium intake, but studies have found an inverse relationship between dietary calcium intake and stone formation.[3,7,14,15] Also, because oxalate is bound by calcium in the gut, preventing its absorption, a low calcium intake can increase oxalate absorption and the risk of stone formation. Therefore, a normal level of dietary intake of calcium is now advised[1,3,7,15,16] (an exception to this is in patients with absorptive hypercalciuria type I, a rare condition of intestinal calcium hyperabsorption).[1] However, calcium supplements appear to increase the risk of stone formation and are generally avoided.[3,7,15] If they are used, they should be taken with meals to avoid hypercalciuria.[1,16] Excessive dietary oxalate intake should also be avoided;[3,7,10,15] foods containing large quantities of bioavailable oxalate include spinach, rhubarb, nuts, and cocoa.[15]

Where pharmacological therapy is indicated, choice of treatment depends on the underlying metabolic abnormality and stone composition. Alkaline citrate, usually given as potassium citrate, is commonly used to prevent the recurrence of calcium stones. It acts as a urinary alkaliniser and increases citrate excretion; citrate forms complexes with calcium to reduce urinary saturation of calcium salts and inhibits crystallisation.[2,7,14,16] Potassium citrate is the main treatment option in patients with hypocitraturia and renal tubular acidosis.[1,3,7] In hypercalciuria, a thiazide diuretic or indapamide can also be used to increase distal tubular calcium reabsorption;[1-3,6,7,10,14,17] potassium citrate can also prevent diuretic-induced hypokalaemia in these patients. In the prevention of calcium stones with hyperoxaluria, a restriction of oxalate-rich food and an adequate dietary calcium intake (or calcium supplements taken with meals) are advocated.[6,10,15,16] The use of magnesium has also been suggested[1] although it may be no better than placebo.[3,7] Some patients with primary hyperoxaluria may respond to high doses of pyridoxine.[1,3,7,10,16] In hyperuricosuria, reduced purine intake and allopurinol may be effective.[1,3,7,10]

Prevention of *uric acid stones* is based on adequate fluid intake, a low purine diet, and urinary alkalinisation with potassium citrate. Allopurinol may be used if there are high levels of urate.[1-3,6,7] Acetazolamide has been used short term.[6]

Struvite stones are caused by urease-producing bacteria. Antibacterials are used, and may be required long term, with urinary acidification using ammonium chloride[7] or methionine.[1,7] Dietary phosphate restriction may also be appropriate for patients with phosphate excretion of more than 35 mmol/day.[1] Acetohydroxamic acid, an inhibitor of bacterial urease, may be used as an adjunct in selected cases of severe infection,[7] but its use has been limited by adverse effects.[3,10]

Cystine stones are associated with cystinuria (p.1459) and are prevented by alkalinisation of the urine and a high fluid intake (3 to 4 litres daily).[2,3,6,7] Penicillamine may be used as a chelating agent.[3,6,10] Ascorbic acid, tiopronin,[1,7] and captopril[7] have also been suggested.

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4. Matlaga BR, Assimos DG. Urologic manifestations of nonurologic disease: urolithiasis. *Urol Clin North Am* 2003; **30:** 91–9.
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15. Baker MJ, Longyhore DS. Dietary calcium, calcium supplements, and the risk of calcium oxalate kidney stones. *Am J Health-Syst Pharm* 2006; **63:** 772–5.
16. Tiselius H-G. Epidemiology and medical management of stone disease. *BJU Int* 2003; **91:** 758–67.
17. Pearle MS, *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999; **13:** 679–85.

Renal colic

For the treatment of urological pain see Biliary and Renal Colic, p.5.

Renal failure

For discussions of acute and chronic renal failure and their management, see p.1672.

Sexually transmitted diseases

For discussion of sexually transmitted diseases and their treatment see p.191.

Syndrome of inappropriate ADH secretion

In some patients secretion of antidiuretic hormone (ADH; vasopressin) occurs despite hypotonicity of the extracellular fluid and normal or raised fluid volume, and such patients are said to have the syndrome of inappropriate ADH secretion (SIADH). With severe water excess, the resultant hyponatraemia may result in symptoms ranging from lassitude or headache to profound neurological symptoms such as confusion, convulsions, or coma. Some patients may experience inappropriate thirst as well as ADH secretion, thus exacerbating their condition. For a discussion of sodium homoeostasis and dilutional hyponatraemia, see p.1670.

Conditions that can precipitate SIADH include CNS disorders, infections such as encephalitis and meningitis, head trauma, porphyria, or pulmonary diseases such as tuberculosis and pneumonia. ADH may also be secreted ectopically from malignancies, most commonly from small-cell bronchial carcinoma. SIADH may also be drug-induced; drugs associated with the condition include carbamazepine, chlorpropamide, cytotoxic drugs such as cyclophosphamide and the vinca alkaloids, oxytocin, some antipsychotics, tricyclic antidepressants, and SSRIs.

Diagnosis of SIADH is initially prompted by the presence of hyponatraemia and corresponding plasma hypo-osmolality with or without neurological symptoms. Hypervolaemia, persistent excess sodium excretion, lack of oedema, and normality of both renal and adrenal function are confirmatory.

Mild water excess is frequently asymptomatic and may not require specific therapy, but patients with SIADH often have a more severe disorder and treatment is best aimed at the underlying cause. If such treatment is not possible or if symptoms persist, water restriction may be considered. However, fluid restriction is unpleasant, particularly for patients who retain inappropriate thirst, and may not be tolerable. In these patients demeclocycline may be given to antagonise the effect of ADH on the renal tubules. Lithium has been given as an alternative but has a high frequency of adverse effects, and phenytoin has been used occasionally to inhibit pituitary ADH secretion. Diuretics such as furosemide (used with oral sodium chloride) have also been tried in an attempt to optimise diuresis while retaining sodium. In patients with life-threatening severe acute water intoxication (see Hyponatraemia, p.1670), treatment initially involves cautious improvement of the profound hyponatraemia by intravenous infusion of hypertonic (usually 3%) or isotonic sodium chloride, often with furosemide or another loop diuretic to avoid volume expansion. Drugs that act directly in the renal tubules as vasopressin V_2 receptor antagonists are under investigation.

References.

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3. Miller M. Syndromes of excess antidiuretic hormone release. *Crit Care Clin* 2001; **17:** 11–23.
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Urinary-tract infections

The treatment of urinary-tract infections is discussed on p.199.

Acetildenafil

Hongdenafil. 5-{2-Ethoxy-5-[2-(4-ethylpiperazine-1-yl)-acetyl]-phenyl}-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one.

$C_{25}H_{34}N_6O_3$ = 466.6.

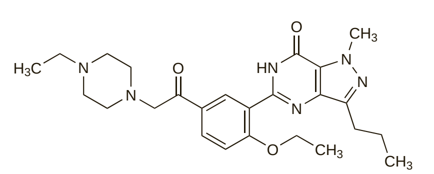

Profile

Acetildenafil is an analogue of sildenafil (p.2193) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction. Other analogues of sildenafil detected in similar products include homosildenafil and hydroxyhomosildenafil.

Alfuzosin Hydrochloride

(BANM, USAN, rINNM)

Alfutsosiinihydrokloridi; Alfuzosin Hidroklorür; Alfuzosine, chlorhydrate d'; Alfuzosin-hydrochlorid; Alfuzosinhydroklorid; Alfuzosini hydrochloridum; Alfuzosin-hidroklorid; Alfuzozino hidrochloridas; Hidrocloruro de alfuzosina; SL-77499-10; SL-77499 (alfuzosin). *N*-{3-[4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino]propyl}tetrahydro-2-furamide hydrochloride.

Альфузозина Гидрохлорид

$C_{19}H_{27}N_5O_4$,HCl = 425.9.

CAS — 81403-80-7 (alfuzosin); 81403-68-1 (alfuzosin hydrochloride).

ATC — G04CA01.

ATC Vet — QG04CA01.

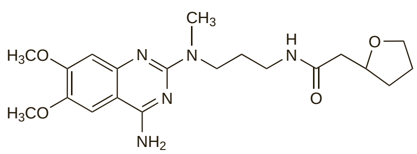

(alfuzosin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Alfuzosin Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375. Alfuzosin may be more selective for the urinary tract and vasodilator effects may be less frequent. It should be avoided in severe hepatic impairment, and doses may need to be reduced in mild to moderate hepatic impairment and in renal impairment (see below).

Incidence of adverse effects. In postmarketing surveillance involving 13 389 patients given alfuzosin 2.5 mg three times daily by mouth for benign prostatic hyperplasia, about 3.7% of patients failed to complete treatment because of adverse effects. These were mostly vasodilatory in nature (vertigo or dizziness, syncope or malaise, hypotension, and headache), and were more common in patients over 75 years of age and during the first week of treatment.[1]

1. Lukacs B, *et al.* Safety profile of 3 months' therapy with alfuzosin in 13,389 patients suffering from benign prostatic hypertrophy. *Eur Urol* 1996; **29:** 29–35.

Surgical procedures. Alpha blockers, including alfuzosin, have been associated with intraoperative floppy iris syndrome in cataract surgery patients. For further details, see under Tamsulosin, p.2197.

Interactions

As for Prazosin Hydrochloride, p.1376. Potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, itraconazole, and ritonavir, may increase blood concentrations of alfuzosin.

Pharmacokinetics

Alfuzosin is readily absorbed after oral doses and peak plasma concentrations generally occur 0.5 to 3 hours after a dose; bioavailability is about 64%. Absorption from modified-release preparations is improved if given with food. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to inactive metabolites that are excreted primarily in faeces via the bile. Only about 11% of a dose is excreted unchanged in the urine. Alfuzosin has a plasma elimination half-life of 3 to 5 hours. It is 90% bound to plasma proteins.

Uses and Administration

Alfuzosin is an $alpha_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376). It acts preferentially on receptors in the lower urinary tract and is therefore used in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction, including acute urinary retention.

Alfuzosin is given orally as the hydrochloride. Like other $alpha_1$-adrenoceptor blockers, it may cause collapse in some patients after the first dose, which should therefore be given just before bedtime to reduce the risk. Doses may need to be reduced in patients with hepatic or renal impairment (see below); the initial dose should also be reduced in the elderly.

In **benign prostatic hyperplasia,** the usual dose of alfuzosin hydrochloride is 2.5 mg three times daily, increased to 10 mg daily if necessary. In elderly patients, and those receiving treatment for hypertension, a lower initial dose of 2.5 mg twice daily should be considered. A modified-release preparation may also be given in a dose of 10 mg once daily after a meal.

In patients aged over 65 years catheterised for **acute urinary retention** associated with benign prostatic hyperplasia, a modified-release preparation may be given in a dose of 10 mg once daily after a meal for 3 to 4 days.

◊ Reviews.

1. Wilde MI, *et al.* Alfuzosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993; **45:** 410–29.
2. McKeage K, Plosker GL. Alfuzosin: a review of the therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. *Drugs* 2002; **62:** 633–53.
3. Lee M. Alfuzosin hydrochloride for the treatment of benign prostatic hyperplasia. *Am J Health-Syst Pharm* 2003; **60:** 1426–39. Correction. *ibid.* 2004; **61:** 437.
4. Weiner DM, Lowe FC. Alfuzosin for the management of benign prostate hyperplasia. *Expert Opin Pharmacother* 2003; **4:** 2057–63.
5. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother* 2004; **2:** 14–23.
6. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 2005; **66:** 780–8.
7. McVary KT. Alfuzosin for symptomatic benign prostatic hyperplasia: long-term experience. *J Urol (Baltimore)* 2006; **175:** 35–42.

Administration in hepatic or renal impairment. In patients with mild to moderate hepatic impairment the initial dose of alfuzosin hydrochloride should be 2.5 mg daily, increased to 2.5 mg twice daily according to response; modified-release preparations are not recommended.

In patients with renal impairment, 2.5 mg twice daily should be given initially, adjusted according to response. Although UK and US licensed product information advises caution with the use of modified-release preparations in severe renal impairment (creatinine clearance below 30 mL/minute), a study[1] in patients with varying degrees of renal impairment (including severe) suggested that no dose reduction was necessary.

1. Marbury TC, *et al.* Pharmacokinetics and safety of a single oral dose of once-daily alfuzosin, 10 mg, in male subjects with mild to severe renal impairment. *J Clin Pharmacol* 2002; **42:** 1311–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dalfaz; UroXatral; ***Austria:*** Urion†; Xatral; ***Belg.:*** Xatral; ***Braz.:*** Xatral; ***Canad.:*** Xatral; ***Chile:*** UroXatral; ***Cz.:*** Alfuzostad; Xatral; ***Denm.:*** Xatral; ***Fin.:*** Xatral; ***Fr.:*** Urion; Xatral; ***Ger.:*** Urion; UroXatral; ***Gr.:*** Alfuprost; Alfural; Alfuzin; Innosensitive; Spedamyl; Xatral; ***Hong Kong:*** Xatral; ***Hung.:*** Alfetim; Alfuzostad; ***India:*** Flotral; ***Indon.:*** Xatral; ***Irl.:*** Xatral; ***Israel:*** Xatral; ***Ital.:*** Mittoval; Xatral; ***Malaysia:*** Xatral; ***Mex.:*** Xatral; ***Neth.:*** Mittoval; Urion; UroXatral; Xatral; ***Norw.:*** Xatral; ***Philipp.:*** Xatral; ***Pol.:*** Alfuzostad; Dalfaz; ***Port.:*** Benestan; ***Rus.:*** Dalfaz (Дальфаз); ***S.Afr.:*** Xatral; ***Singapore:*** Xatral; ***Spain:*** Alfetim†; Benestan; Unibenestan; ***Swed.:*** Xatral; ***Switz.:*** Xatral; ***Thai.:*** Xatral; ***Turk.:*** Xatral; ***UK:*** Besavar; Xatral; ***USA:*** UroXatral; ***Venez.:*** Xatral.

Alprostadil *(BAN, USAN, rINN)*

Alprostadiili; Alprostadilis; Alprostadilum; Alprosztadil; PGE_1; Prostaglandin E_1; U-10136. (*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprost-13-enoic acid; 7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}heptanoic acid.

Алпростадил

$C_{20}H_{34}O_5$ = 354.5.

CAS — 745-65-3.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

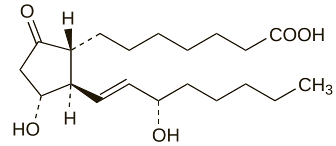

NOTE. In *Martindale* the term alprostadil is used for the exogenous substance and prostaglandin E_1 for the endogenous substance.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Alprostadil). A white or slightly yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in ethyl acetate.

USP 31 (Alprostadil). A white to off-white crystalline powder. M.p. about 110°. Soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in chloroform and in ether; slightly soluble in ethyl acetate. Store between 2° and 8° in airtight containers.

Alprostadil Alfadex *(BAN, rINNM)*

Alprostadilum Alfadexum; α-Cyclodextrin Alprostadil; PGE_1 α-CD; Prostaglandin E_1 α-Cyclodextrin Clathrate Compound.

Алпростадил Альфадекс

$C_{20}H_{34}O_5$,x[$C_{36}H_{60}O_{30}$].

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

The adverse effects reported most commonly in **infants** with congenital heart disease treated with alprostadil are apnoea, fever, flushing, hypotension, bradycardia, tachycardia, diarrhoea, and convulsions. Other adverse effects reported include oedema, cardiac arrest, hypokalaemia, disseminated intravascular coagulation, and cortical proliferation of the long bones. Weakening of the wall of the ductus arteriosus and pulmonary artery may occur on prolonged infusion. Alprostadil should be avoided in neonates with respiratory distress syndrome and should be used with caution in those with bleeding tendencies; blood pressure and respiratory status should be monitored during infusion.

Adverse effects reported in **adults** given alprostadil have included headache, flushing, hypotension, diarrhoea, and pain and inflammation at the infusion site.

After intracavernosal or intra-urethral alprostadil for the treatment of erectile dysfunction, the most frequently reported adverse effect is pain during erection. Local reactions including penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported. Priapism may occur (see below). Systemic effects are less common but hypotension and other adverse effects have been reported. Intracavernosal or intra-urethral use should be avoided in patients with complicating penile deformities or with sickle-cell disease, myeloma, leukaemias, or other conditions predisposing to prolonged erection.

In children. Reviews[1,2] of adverse effects associated with alprostadil in infants with congenital heart disease.

1. Lewis AB, *et al.* Side effects of therapy with prostaglandin E in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.
2. Lucron H, *et al.* Complications du traitement par prostaglandines E1 des cardiopathies congénitales en réanimation médicale pédiatrique. *Arch Mal Coeur Vaiss* 2005; **98:** 524–30.

Effects on the bones. Periosteal or cortical hyperostosis has been reported in infants given alprostadil for cyanotic congenital heart disease.[1-4] A retrospective review of 30 infants[2] treated with alprostadil revealed radiographic signs of periosteal reactions in 5. Changes could be detected after even short courses of therapy; 3 developed relatively mild periosteal changes in the ribs after infusions ranging from 9 to 205 hours and one had involvement of the left femur after infusion for 71 hours. Resolution of lesions had occurred in most bones 6 to 12 months later. In a further study,[5] radiological evidence of cortical hyperostosis was found in 53 of 86 infant heart transplant recipients who had received alprostadil infusion pre-operatively. Of 53 of the infants who had received alprostadil for less than 30 days, 21 were affected (2 severely). Correspondingly, of those treated for 30 to 60 days, 18 of 22 were affected (13 severely). All 14 infants treated for more than 60 days were affected (7 severely). Since the associated bone changes may persist for months after stopping alprostadil, caution should be exercised to avoid misdiagnosis.

1. Ueda K, *et al.* Cortical hyperostosis following long-term administration of prostaglandin E in infants with cyanotic congenital heart disease. *J Pediatr* 1980; **97:** 834–6.
2. Ringel RE, *et al.* Periosteal changes secondary to prostaglandin administration. *J Pediatr* 1983; **103:** 251–3.
3. Williams JL. Periosteal hyperostosis resulting from prostaglandin therapy. *Eur J Radiol* 1986; **6:** 231–2.
4. Kalloghlian AK, *et al.* Cortical hyperostosis simulating osteomyelitis after short-term prostaglandin E infusion. *Eur J Pediatr* 1996; **155:** 173–4.
5. Woo K, *et al.* Cortical hyperostosis: a complication of prolonged prostaglandin infusion in infants awaiting cardiac transplantation. *Pediatrics* 1994; **93:** 417–20.

Effects on the gastrointestinal tract. Hyperplasia of the gastric mucosa, resulting in gastric outlet obstruction, has been reported in several neonates receiving alprostadil infusion.[1-3] It was suggested that this effect was dose-dependent.[1] Regression of the obstruction usually occurred after cessation of therapy.

For a report of necrotising enterocolitis in infants receiving alprostadil for congenital heart disease, see Dinoprostone, p.2007.

1. Peled N, *et al.* Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992; **327:** 505–10.
2. Merkus PJFM, *et al.* Prostaglandin E1 and gastric outlet obstruction in infants. *Lancet* 1993; **342:** 747.
3. Kobayashi N, *et al.* Acute gastric outlet obstruction following the administration of prostaglandin: an additional case. *Pediatr Radiol* 1997; **27:** 57–9.

Effects on the metabolism. Severe hyperglycaemia with apparent ketoacidosis occurred during postoperative infusion of alprostadil in the infant of a diabetic mother.[1] The manufacturers had received reports of hyperglycaemia associated with alprostadil in 5 infants, one of whom had a diabetic mother. Hypoglycaemia has also been reported in a few infants.[2]

1. Cohen MH, Nihill MR. Postoperative ketotic hyperglycaemia during prostaglandin E infusion in infancy. *Pediatrics* 1983; **71:** 842–4.
2. Lewis AB, *et al.* Side effects of therapy with prostaglandin E in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.

Effects on the skin. A 63-year-old man with Peyronie's disease[1] developed toxic pustuloderma (acute generalised exanthematous pustulosis) 6 days after receiving a single intracavernosal injection of alprostadil to define the penile morphology. He was treated with antihistamines and topical corticosteroids and the condition resolved completely within a week.

1. Gallego I, *et al.* Toxic pustuloderma induced by intracavernous prostaglandin E . *Br J Dermatol* 1997; **136:** 975–6.

Priapism. If priapism (p.1333) occurs after the use of alprostadil for erectile dysfunction, its treatment should not be delayed more than 6 hours. Initial therapy is by penile aspiration. If aspiration is unsuccessful a sympathomimetic with action on alpha-adrenergic receptors is given by cautious intracavernosal injection, with continuous monitoring of blood pressure and pulse. Extreme caution is necessary in patients with coronary heart disease, hypertension, cerebral ischaemia, or if taking an antidepressant. Low doses and dilute solutions are recommended as follows:

- intracavernosal injection of phenylephrine 100 to 200 micrograms (0.5 to 1 mL of a 200 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 1 mg

alternatively

- intracavernosal injection of adrenaline 10 to 20 micrograms (0.5 to 1 mL of a 20 micrograms/mL solution) every 5 to 10 minutes; maximum total dose 100 micrograms

alternatively

- intracavernosal injection of metaraminol may be used, but it should be noted that fatal hypertensive crises have been reported; metaraminol 100 micrograms (5 mL of a 20 micrograms/mL solution) may be given by careful slow injection every 15 minutes; a maximum total dose of up to 1 mg has been suggested

If necessary the sympathomimetic injections can be followed by further penile aspiration. If sympathomimetics are unsuccessful, urgent surgical referral is required.

Pharmacokinetics

On infusion alprostadil is rapidly metabolised by oxidation during passage through the pulmonary circulation. It is excreted in the urine as metabolites within about 24 hours. Systemic absorption of alprostadil occurs after intracavernosal injection.

◊ References.

1. Cox JW, *et al.* Pulmonary extraction and pharmacokinetics of prostaglandin E during continuous intravenous infusion in patients with adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **137:** 5–12.
2. Cawello W, *et al.* Dose proportional pharmacokinetics of alprostadil (prostaglandin E) in healthy volunteers following intravenous infusion. *Br J Clin Pharmacol* 1995; **40:** 273–6.
3. Lea AP, *et al.* Intracavernous alprostadil: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in erectile dysfunction. *Drugs Aging* 1996; **8:** 56–74.

Uses and Administration

Alprostadil is a prostaglandin (p.2374) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostaglandin E_1. Alprostadil is used mainly in congenital heart disease and in erectile dysfunction (p.2179).

In the management of **erectile dysfunction**, alprostadil is given by intracavernosal injection; preparations may contain alprostadil or alprostadil alfadex, but the dose is expressed in terms of the base. Alprostadil may also be given as an intra-urethral application.

By *intracavernosal injection*, the initial dose should be low, for example 2.5 micrograms, and is increased incrementally until a suitable dose is established. Normally, the second dose should be 5 micrograms if some response to the first dose is observed, or 7.5 micrograms if there is no response; increments should then be of 5 to 10 micrograms until an effective dose is reached. The usual dose range is 5 to 20 micrograms and the maximum recommended dose is 60 micrograms. In cases of erectile dysfunction of neurogenic origin secondary to spinal cord injury an initial dose of 1.25 micrograms has been given, with a second dose of 2.5 micrograms, a third dose of 5 micrograms, and subsequent increments of 5 micrograms. While finding a suitable dose, the interval between doses should be at least 1 day if there has been a partial response. If there is no response however, the next, higher dose may be given within 1 hour. Once established, the optimal dose should be given not more than once daily and not more than three times per week.

Alprostadil may also be injected intracavernosally in the diagnosis of erectile dysfunction in doses ranging from 5 to 20 micrograms.

By *intra-urethral (transurethral) application*, the initial dose is 250 micrograms. The dose may be increased incrementally to 500 or 1000 micrograms or decreased to 125 micrograms according to response. The optimal dose should be given not more than twice daily or seven times per week. A dose of 500 micrograms may be used diagnostically.

Alprostadil is also available in some countries as a *topical* formulation for the treatment of erectile dysfunction. There is also ongoing investigation of the use of topical formulations for female sexual dysfunction.

Alprostadil is used to maintain the patency of the ductus arteriosus in neonates with **congenital heart disease** until surgery is possible. It is given by continuous intravenous infusion beginning with doses of 50 to 100 nanograms/kg per minute; doses should be reduced as soon as possible to the minimum necessary to maintain response. Lower starting doses may be effective in some patients. The dose can be increased to 400 nanograms/kg per minute but, in general, higher infusion rates do not improve effect. Alprostadil may also be given by continuous infusion through an umbilical artery catheter placed at the ductal opening.

Ergotamine poisoning. Alprostadil[1,2] is one of many drugs that have been used to treat the circulatory disturbances in ergotamine poisoning (p.620).

1. Levy JM, *et al.* Prostaglandin E for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7:** 28–30.
2. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus. *Dtsch Med Wochenschr* 1993; **118:** 1067–71.

Haemorrhagic cystitis. Bladder irrigation with alprostadil produced resolution of severe haemorrhagic cystitis in 5 of 6 children who had undergone bone marrow transplantation.[1] Alprostadil was given via a catheter and retained for 1 hour each day for at least 7 consecutive days.

1. Trigg ME, *et al.* Prostaglandin E bladder instillations to control severe hemorrhagic cystitis. *J Urol (Baltimore)* 1990; **143:** 92–4.

Hepatic disorders. Benefit has been reported in patients with *viral hepatitis* (p.851) given intravenous alprostadil alone or followed by oral dinoprostone or misoprostol.[1,2] Prostaglandins were studied because they had previously been shown to have a cytoprotective effect in experimentally induced hepatitis or in isolated hepatocytes, but the mechanism by which they exerted a beneficial effect was uncertain.

Combined intravenous therapy with glucagon, insulin, and alprostadil formulated in lipid microspheres has also been found effective in preventing *acute fulminant hepatic failure* after hepatic arterial infusion of antineoplastic chemotherapy.[3]

1. Sinclair SB, *et al.* Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E: a preliminary report. *J Clin Invest* 1989; **84:** 1063–9.
2. Flowers M, *et al.* Prostaglandin E in the treatment of recurrent hepatitis B infection after orthotopic liver transplantation. *Transplantation* 1994; **58:** 183–92.
3. Ikegami T, *et al.* Randomized control trial of lipo-prostaglandin E in patients with acute liver injury induced by Lipiodol-targeted chemotherapy. *Clin Pharmacol Ther* 1995; **57:** 582–9.

Organ and tissue transplantation. Alprostadil and other prostaglandin analogues have been investigated in regimens for the management of solid organ transplantation, with variable results. For reference to the use of alprostadil in intestinal grafts see p.1813.

References.

1. Merion RM. Prostaglandins in liver transplantation. *Adv Exp Med Biol* 1997; **433:** 13–18.
2. Iberer F, *et al.* Prostaglandins in heart transplantation. *Adv Exp Med Biol* 1997; **433:** 19–22.
3. Ray JG. Prostaglandin E1 analogs do not improve renal function among either transplant or nontransplant patients: no further trials required. *Transplantation* 1998; **66:** 476–83.

Peripheral vascular disease. Various prostaglandins, including alprostadil,[1-7] have been used in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome, but do not constitute mainline therapy.

1. Clifford PC, *et al.* Treatment of vasospastic disease with prostaglandin E . *BMJ* 1980; **281:** 1031–4.
2. Telles GS, *et al.* Prostaglandin E in severe lower limb ischaemia: a double-blind controlled trial. *Br J Surg* 1984; **71:** 506–8.
3. Mohrland JS, *et al.* A multiclinic, placebo-controlled, double-blind study of prostaglandin E in Raynaud's syndrome. *Ann Rheum Dis* 1985; **44:** 754–60.
4. Sethi GK, *et al.* Intravenous infusion of prostaglandin E (PGE) in management of limb ischemia. *Am Surg* 1986; **52:** 474–8.
5. Langevitz P, *et al.* Treatment of refractory ischemic skin ulcers in patients with Raynaud's phenomenon with PGE infusions. *J Rheumatol* 1989; **16:** 1433–5.
6. The ICAI Study Group. Prostanoids for chronic critical leg ischemia: a randomized, controlled, open-label trial with prostaglandin E . *Ann Intern Med* 1999; **130:** 412–21.
7. Bartolone S, *et al.* Efficacy evaluation of prostaglandin E1 against placebo in patients with progressive systemic sclerosis and significant Raynaud's phenomenon. *Minerva Cardioangiol* 1999; **47:** 137–43.

Preparations

USP 31: Alprostadil Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Cardiobron; Caverject†; Prolisina VR; Prostavasin; ***Austral.:*** Caverject; Muse†; Prostin VR; ***Austria:*** Alprostapint; Caverject; Minprog; Muse; Prostavasin; Virilan; ***Belg.:*** Caverject; Prostin VR; ***Braz.:*** Apilcav†; Aplicav; Caverject; Muse†; Prostavasin; ***Canad.:*** Caverject; Muse; Prostin VR; ***Chile:*** Caverject; Prostin Pediatrico; ***Cz.:*** Alprostan; Alprostapint; Caverject; Edex†; Karon; Muse; Prostavasin; Prostin VR†; ***Denm.:*** Caverject; Muse; Prostivas; ***Fin.:*** Caverject; Muse; Prostivas; ***Fr.:*** Caverject; Edex; Muse; Prostine VR; ***Ger.:*** Caverject; Minprog; Muse; Prostavasin; Viridal; ***Gr.:*** Caverject; Edex†; Prostin VR; ***Hong Kong:*** Befar; Caverject; Prostavasin; Prostin VR; ***Hung.:*** Alprostapint; Caverject; Prostavasin; Prostin VR; ***India:*** Prostin VR; ***Irl.:*** Caverject; Muse; Viridal; ***Israel:*** Alprostapint; Caverject; Muse†; Prostin VR; ***Ital.:*** Alprostar; Caverject; Prostavasin; Prostin VR; Viridal; ***Jpn:*** Liple; Palux; Prostandin; ***Malaysia:*** Caverject; Prostin VR; ***Mex.:*** Caverject; Muse†; ***Neth.:*** Caverject; Muse; Prostin VR; ***Norw.:*** Bondil; Caverject; Prostivas; ***NZ:*** Caverject; Muse†; Prostin VR; ***Pol.:*** Caverject; Prostavasin; Prostin VR; ***Port.:*** Caverject; Muse; Prostin VR; Vasoprost; ***Rus.:*** Alprostan (Алпростан); Caverject (Каверджект); Vasaprostan (Вазапростан); Vazaprostan (Вазапростан); ***S.Afr.:*** Caverject; Muse; Prostin VR; ***Singapore:*** Caverject; Eglandin†; ***Spain:*** Caverject; Sugiran; ***Swed.:*** Bondil; Caverject; Prostivas; ***Switz.:*** Caverject; Muse; Prostin VR; ***Thai.:*** Caverject†; Muse†; Prostin VR; ***UK:*** Caverject; Muse; Prostin VR; Viridal; ***USA:*** Caverject; Edex; Muse; Prostin VR; ***Venez.:*** Caverject.

Multi-ingredient: ***USA:*** Tri-Mix.

Aminotadalafil

6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-aminopyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione.

Аминотадалафил

$C_{21}H_{18}N_4O_4$ = 390.4.

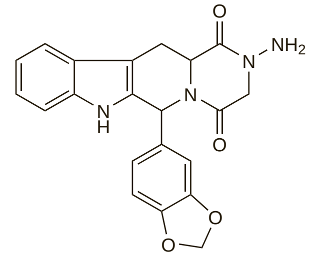

Profile

Aminotadalafil is an analogue of tadalafil (p.2196) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

Dapoxetine Hydrochloride *(USAN, rINNM)*

Dapoxétine, Chlorhydrate de; Dapoxetini Hydrochloridum; Hidrocloruro de dapoxetina; LY-210448 (dapoxetine). (+)-(*S*)-*N*, *N*-Dimethyl-alpha-[2-(l-naphthyloxy)ethyl]benzylamine hydrochloride.

Дапоксетина Гидрохлорид

$C_{21}H_{23}NO,HCl = 341.9.$

CAS — 119356-77-3 (dapoxetine); 129938-20-1 (dapoxetine hydrochloride).

Profile

Dapoxetine hydrochloride is a rapidly absorbed short-acting SSRI being investigated specifically for on-demand treatment of premature ejaculation (p.2181).

◊ References.

1. Pryor JL, *et al.* Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006; **368:** 929–37.
2. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006; **46:** 301–9.
3. Andersson KE, *et al.* Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. *BJU Int* 2006; **97:** 311–15.
4. Dresser MJ, *et al.* Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. *J Clin Pharmacol* 2006; **46:** 1023–9.

Darifenacin *(BAN, USAN, rINN)*

Darifenacina; Darifénacine; Darifenacinum; UK-88525. (*S*)-1-[2-(2,3-Dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide.

Дарифенацин

$C_{28}H_{30}N_2O_2 = 426.6.$

CAS — 133099-04-4.

ATC — G04BD10.

ATC Vet — QG04BD10.

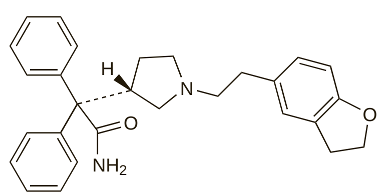

Darifenacin Hydrobromide *(BANM, USAN, rINNM)*

Darifénacine, Bromhydrate de; Darifenacini Hydrobromidum; Hidrobromuro de darifenacina; UK-88525-04. (*S*)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidnyl}-2,2-diphenylacetamide hydrobromide.

Дарифенацина Гидробромид

$C_{28}H_{30}N_2O_2,HBr = 507.5.$

CAS — 133099-07-7.

ATC — G04BD10.

ATC Vet — QG04BD10.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Darifenacin should be used with caution in patients also receiving inhibitors of cytochrome P450 isoenzymes (see Interactions and Uses and Administration, below). It should also be used with caution in hepatic impairment (see Administration in Hepatic Impairment, below).

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Exposure to darifenacin may be increased by drugs that inhibit the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Inducers of CYP3A4 may reduce plasma concentrations of darifenacin. Dosage adjustment for darifenacin may be necessary (see Uses and Administration, below). Darifenacin itself is also a moderate inhibitor of CYP2D6.

Pharmacokinetics

After an oral dose, darifenacin is subject to extensive first-pass metabolism and has a bioavailability of about 15 to 19%. It is about 98% bound to plasma proteins. Darifenacin is metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The pharmacokinetics of darifenacin at steady state are dose-dependent because of the saturation of CYP2D6 metabolism. Most of a dose is excreted as metabolites in the urine and faeces.

◊ References.

1. Kerbusch T, *et al.* Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability. *Br J Clin Pharmacol* 2003; **56:** 639–52.
2. Devineni D, *et al.* Pharmacokinetics of darifenacin, an M selective receptor antagonist: effects of renal or hepatic impairment. *Br J Clin Pharmacol* 2005; **59:** 632–3.
3. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* 2006; **45:** 325–50.

Uses and Administration

Darifenacin is a selective M_3 antimuscarinic with actions similar to those of atropine (p.1220); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder.

Darifenacin is used in the management of urinary frequency, urgency, and incontinence in detrusor instability (p.2180). It is given orally as the hydrobromide but doses are described in terms of the base: darifenacin hydrobromide 8.9 mg is equivalent to about 7.5 mg of darifenacin. The usual initial dose is the equivalent of darifenacin 7.5 mg once daily; after 2 weeks of treatment this may be increased to 15 mg once daily if necessary.

The starting dose of 7.5 mg should only be increased with caution in patients also receiving potent inhibitors of the cytochrome P450 isoenzyme CYP2D6, such as paroxetine and terbinafine. Darifenacin should be avoided, or a dose of 7.5 mg daily not exceeded, in patients also receiving potent inhibitors of CYP3A4, such as HIV-protease inhibitors, ketoconazole, and itraconazole. The dose of darifenacin should be increased with caution in the presence of moderate inhibitors of CYP3A4, such as macrolide antibacterials, fluconazole, and grapefruit juice.

Darifenacin should be used with caution in hepatic impairment, see below.

Darifenacin is being studied in irritable bowel syndrome.

◊ References.

1. Haab F, *et al.* Darifenacin, an M selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004; **45:** 420–9.
2. Chapple C, *et al.* A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005; **95:** 993–1001.
3. Foote J, *et al.* Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M selective receptor antagonist. *Eur Urol* 2005; **48:** 471–7.
4. Parsons M, *et al.* Darifenacin in the treatment of overactive bladder. *Int J Clin Pract* 2005; **59:** 831–8.

Administration in hepatic impairment. Licensed product information states that the dose of darifenacin should not exceed 7.5 mg once daily in patients with moderate hepatic impairment (Child-Pugh category B), and its use should be avoided in severe impairment (Child-Pugh category C).

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Emselex; ***Ger.:*** Emselex; ***Gr.:*** Emselex; ***Hung.:*** Emselex; ***Neth.:*** Emselex; ***S.Afr.:*** Enablex; ***Swed.:*** Emselex; ***UK:*** Emselex; ***USA:*** Enablex.

Desmopressin *(BAN, rINN)*

DDAVP; Desmopresina; Desmopresinas; Desmopressiini; Desmopressine; Desmopressinum; Dezmopresszin. 1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin; [1-Deamino,8-D-arginine]vasopressin.

Дезмопрессин

$C_{46}H_{64}N_{14}O_{12}S_2 = 1069.2.$

CAS — 16679-58-6.

ATC — H01BA02.

ATC Vet — QH01BA02.

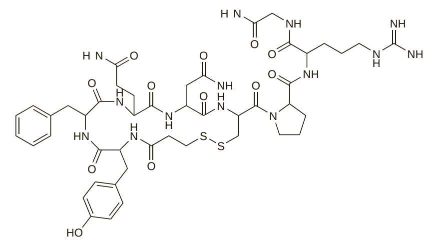

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Desmopressin). A synthetic cyclic nonapeptide, available as an acetate. A white or almost white, fluffy powder. Soluble in water, in alcohol, and in glacial acetic acid. Store in airtight containers at 2° to 8°. Protect from light.

Desmopressin Acetate *(BANM, USAN, rINNM)*

Acetato de desmopresina; Desmopresin Asetat; Desmopressine, Acétate de; Desmopressini Acetas.

Дезмопрессина Ацетат

$C_{46}H_{64}N_{14}O_{12}S_2,C_2H_4O_2,3H_2O = 1183.3.$

CAS — 62288-83-9 (anhydrous desmopressin acetate); 62357-86-2 (desmopressin acetate trihydrate).

ATC — H01BA02.

ATC Vet — QH01BA02.

Pharmacopoeias. In *US.*

USP 31 (Desmopressin Acetate). A white, fluffy powder. Soluble in water, in alcohol, and in acetic acid. Store in airtight containers at a temperature not exceeding 25°, but preferably between 2° and 8°. Protect from light.

Units

27 units of desmopressin are contained in about 27 micrograms of desmopressin (with 5 mg of human albumin and citric acid) in one ampoule of the first International Standard (1980).

Adverse Effects and Precautions

Adverse effects of desmopressin include headache, nausea, and mild abdominal cramps; there may be pain and swelling at the site of injection. With large intravenous doses hypotension, with tachycardia and facial flushing, may occur; some patients may experience an increase in blood pressure. Occasionally there may be cerebral or coronary thrombosis. Hypersensitivity reactions have also occurred. The antidiuretic action of desmopressin can produce water intoxication and hyponatraemia, occasionally leading to convulsions. The incidence of hyponatraemia may be higher with nasal formulations than with oral formulations. Nasal doses may cause local irritation, congestion, and epistaxis.

Precautions to be observed with desmopressin are similar to those for vasopressin (see p.2412). It should not be given to patients with type IIB von Willebrand's disease, in whom the release of clotting factors may lead to platelet aggregation and thrombocytopenia. When desmopressin is used diagnostically, or for the treatment of enuresis, the fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after use (see also Effects on Electrolytes, below).

Effects on the cardiovascular system. Facial flushing and warmth after intravenous desmopressin reflect a vasodilator action[1] or may be due to an opioid mechanism in the CNS.[2] A drop in diastolic blood pressure of about 14 mmHg and an increase in heart rate of 20 beats/minute are the rule during intravenous infusion of desmopressin in doses of 400 nanograms/kg or more.[1] The hypotensive effects of desmopressin were responsible for a serious reaction, involving cyanosis and dyspnoea, in a 21-month-old child with cyanotic heart disease.[3] Thrombosis (including myocardial infarction)[4-6] and cerebral infarction[7] have been associated rarely with the use of intravenous desmopressin. An analysis[8] of events in patients undergoing major surgery suggested, however, that co-existing conditions in elderly patients and the surgical procedures themselves were associated with a high risk of thrombosis, and that desmopressin did not increase the incidence of thrombotic events.

Licensed product information also warns of the possibility of an increase in blood pressure.

1. Brommer EJP, *et al.* Desmopressin and hypotension. *Ann Intern Med* 1985; **103:** 962.

2. Pigache RM. Facial flushing induced by vasopressin-like peptides lacking pressor activity. *J Clin Pharmacol* 1984; **17:** 369–71.
3. Israels SJ, Kobrinsky NL. Serious reaction to desmopressin in a child with cyanotic heart disease. *N Engl J Med* 1989; **320:** 1563–4.
4. Anonymous. Desmopressin and arterial thrombosis. *Lancet* 1989; **i:** 938–9.
5. Mannucci PM, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989; **ii:** 675–6.
6. Hartmann S, Reinhart W. Fatal complication of desmopressin. *Lancet* 1995; **345:** 1302–3. Correction. *ibid.;* 1648.
7. Grunwald Z, Sather SDC. Intraoperative cerebral infarction after desmopressin administration in infant with end-stage renal disease. *Lancet* 1995; **345:** 1364–5.
8. Mannucci PM, *et al.* Desmopressin, surgery and thrombosis. *Thromb Haemost* 1994; **71:** 154–5.

Effects on electrolytes. There have been a number of reports of seizures due to hyponatraemia and water intoxication after intranasal[1-8] or intravenous[9] desmopressin. The UK CSM noted in March 1996 that it had received reports of hyponatraemic convulsions in 21 children and 3 adults receiving desmopressin (which it somewhat inaccurately described as vasopressin).[10] It was recommended that when this drug was used to treat primary nocturnal enuresis the risks of hyponatraemia should be minimised by

- avoiding concomitant use of drugs, such as *tricyclic antidepressants*, that increase endogenous ADH secretion
- keeping to the recommended starting dose
- avoiding excessive fluid intake, including ingestion of water during swimming
- stopping treatment temporarily if vomiting or diarrhoea occurred, to allow recovery of normal fluid and electrolyte balance

Some have suggested that no more than 240 mL of fluid should be ingested on nights when desmopressin is given.[7] Others have suggested that serum-sodium concentrations be measured 24 to 48 hours, 1 week, and 1 month after starting treatment with desmopressin.[8] A systematic review[11] of the risk in older patients being treated for nocturia, which found the incidence of hyponatraemia to be about 8%, also recommended regular monitoring.

In April 2007, the MHRA requested that the indication for the treatment of primary nocturnal enuresis be removed from desmopressin nasal spray formulations in the UK. Compared with oral formulations, nasal forms were associated with most of the serious adverse effects reported in patients with primary nocturnal enuresis; these included hyponatraemia, water intoxication, and convulsions. Hyponatraemia was reported at a rate of about 15 cases per 100 000 years of patient exposure for nasal dosage forms, compared with 6 cases per 100 000 patient years for oral formulations; hyponatraemia was mainly associated with overdose, excessive fluid intake, or inappropriate use.[12] The FDA has issued similar warnings.[13]

1. Simmonds EJ, *et al.* Convulsions and coma after intranasal desmopressin in cystic fibrosis. *BMJ* 1988; **297:** 1614.
2. Salvatoni A, *et al.* Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. *J Pediatr* 1990; **116:** 835–6.
3. Davis RC, *et al.* Nocturnal enuresis. *Lancet* 1992; **340:** 1550.
4. Hamed M, *et al.* Hyponatraemic convulsion associated with desmopressin and imipramine treatment. *BMJ* 1993; **306:** 1169.
5. Hourihane J, Salisbury AJ. Use caution in prescribing desmopressin for nocturnal enuresis. *BMJ* 1993; **306:** 1545.
6. Robson WLM, Leung AKC. Hyponatraemia following desmopressin. *BMJ* 1993; **307:** 64–5.
7. Robson WLM, *et al.* Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr* 1996; **155:** 959–62.
8. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. *J Clin Pharmacol* 2001; **41:** 582–4.
9. Shepherd LL, *et al.* Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. *J Pediatr* 1989; **114:** 470–2.
10. Committee on Safety of Medicines/Medicines Control Agency. Hyponatraemic convulsions in patients with enuresis treated with vasopressin. *Current Problems* 1996; **22:** 4.
11. Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourol Urodyn* 2004; **23:** 302–5.
12. Medicines and Healthcare products Regulatory Agency. Desmopressin nasal spray: removal of the primary nocturnal enuresis (bedwetting) indication (issued 18th April 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2030795 (accessed 02/09/08)
13. FDA. Information for healthcare professionals: desmopressin acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) (issued 4th December 2007). Available at: http://www.fda.gov/ cder/drug/InfoSheets/HCP/desmopressinHCP.htm (accessed 11/06/08)

Effects on the eyes. Pseudotumor cerebri associated with desmopressin treatment has been reported in a patient.[1]

1. Neely DE, *et al.* Desmopressin (DDAVP)-induced pseudotumor cerebri. *J Pediatr* 2003; **143:** 808.

Effects on mental function. Paranoid psychosis occurred after desmopressin therapy in a patient with Alzheimer's dementia.[1]

1. Collins GB, *et al*. Paranoid psychosis after DDAVP therapy for Alzheimer's dementia. *Lancet* 1981; **ii:** 808.

Tolerance. In 3 uraemic patients desmopressin infusion produced an initial shortening of the bleeding time but after repeated infusions this response was reduced and there was even some increase in baseline bleeding times.[1] Two infusions of desmopressin 300 nanograms/kg in one day appear to induce a near maximum response; different treatment is required subsequently.

1. Canavese C, *et al*. Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1985; **i:** 867–8.

Interactions

As for Vasopressin, p.2412. See also Effects on Electrolytes, above. NSAIDs, such as ibuprofen (see Effects on Electrolytes under Ibuprofen, p.64) and indometacin, may enhance the antidiuretic effect of desmopressin.

Gastrointestinal drugs. In a study[1] in healthy subjects, *loperamide* caused a threefold increase in the gastrointestinal absorption of oral desmopressin, presumably by slowing gastrointestinal motility. In the same study, however, increased motility caused by *erythromycin* did not affect desmopressin absorption.

1. Callréus T, *et al.* Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* 1999; **55:** 305–9.

Pharmacokinetics

Desmopressin is absorbed from the nasal mucosa with a bioavailability of 10 to 20%. After oral doses it is largely destroyed in the gastrointestinal tract but sufficient is absorbed from high doses to produce therapeutic effects. When given intravenously desmopressin exhibits biphasic pharmacokinetics, with half-lives of about 8 minutes and 75 minutes for the 2 phases respectively.

◊ References.

1. Fjellestad-Paulsen A, *et al.* Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin Endocrinol (Oxf)* 1993; **38:** 177–82.
2. Lam KSL, *et al.* Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8- -arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996; **42:** 379–85.
3. Agersø H, *et al.* Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. *Br J Clin Pharmacol* 2004; **58:** 352–8.
4. Østerberg O, *et al.* Pharmacokinetics of desmopressin administrated [sic] as an oral lyophilisate dosage form in children with primary nocturnal enuresis and healthy adults. *J Clin Pharmacol* 2006; **46:** 1204–11.

Uses and Administration

Desmopressin is a synthetic analogue of vasopressin (p.2411). It has greater antidiuretic activity and a more prolonged action than vasopressin or lypressin. It also stimulates factor VIII and plasminogen activator activity in the blood, but has little pressor activity.

Desmopressin is used in the diagnosis and treatment of cranial diabetes insipidus, in the treatment of nocturnal enuresis, and in tests of renal function. It is also used in the management of mild or moderate haemophilia and type I von Willebrand's disease, and in tests of fibrinolytic response.

It is given as the acetate, orally, as a solution intranasally, and by injection. The intranasal dose is about ten times that required intravenously and the oral dose about ten times greater than the intranasal dose. Doses are usually expressed in terms of desmopressin acetate, but for some preparations they are given in terms of the base; 110.7 micrograms of desmopressin acetate is equivalent to about 100 micrograms of desmopressin.

In the control of **cranial diabetes insipidus**, desmopressin acetate is given orally in usual initial doses of 100 micrograms three times daily. Doses may be adjusted according to response, with maintenance doses usually between 100 and 200 micrograms three times daily though total doses of between 100 micrograms and 1200 micrograms daily have been used.

A sublingual lyophilisate preparation containing desmopressin acetate is also available in the UK, but doses are expressed in terms of the base. The initial dose is equivalent to 60 micrograms of desmopressin given sublingually three times daily. The dose may be adjusted, with usual maintenance doses between 60 and 120 micrograms three times daily, though total doses of up to 720 micrograms daily have been used.

Desmopressin acetate may also be used intranasally in usual doses of 10 to 40 micrograms daily as a single dose or in divided doses.

It may also be given subcutaneously, intramuscularly, or intravenously in a dose of 1 to 4 micrograms daily.

A single intranasal dose of 20 micrograms or 2 micrograms subcutaneously or intramuscularly has been given in the **diagnosis** of diabetes insipidus.

In the **testing of renal function**, desmopressin acetate has been given intranasally in single doses of 40 micrograms and subcutaneously or intramuscularly in doses of 2 micrograms.

In the management of **primary nocturnal enuresis**, desmopressin acetate is given in usual oral doses of 200 to 400 micrograms. The sublingual lyophilisate preparation may be given in a dose equivalent to desmopressin 120 micrograms at bedtime, increasing to 240 micrograms if needed. The need for continued treatment should be reassessed after 3 months by withdrawing desmopressin for at least 1 week. For the view that nasal preparations should not be used for primary nocturnal enuresis, see Effects on Electrolytes, under Adverse Effects, above. For the control of **nocturia** in multiple sclerosis desmopressin acetate 10 to 20 micrograms intranasally at bedtime is recommended (but see Urinary Incontinence, below).

Desmopressin acetate is given by intravenous infusion to boost concentrations of factor VIII before surgical procedures in patients with mild to moderate **haemophilia** or **type I von Willebrand's disease**. The usual dose is 300 or 400 nanograms/kg by slow intravenous infusion over 15 to 30 minutes just before surgery. It may be used similarly to treat spontaneous or trauma-induced bleeding episodes in these patients. It is also given intranasally in doses of 150 micrograms (in patients weighing less than 50 kg) or 300 micrograms; it should be given within 2 hours before surgery.

For **testing of fibrinolytic response** desmopressin acetate may be given by intravenous infusion in doses of 400 nanograms/kg over 20 minutes; a sample of venous blood is taken 20 minutes after completing the infusion and tested for fibrinolytic activity on fibrin plates. Alternatively, a dose of 300 micrograms may be given intranasally 60 minutes before collecting the blood sample.

For details of uses and doses in children, see below.

Administration in children. Although some desmopressin preparations are licensed in the UK and the USA for paediatric use, the indications are generally fewer than for adults and the age ranges are often not specified.

The *BNFC*, however, lists doses for both licensed and unlicensed indications, and the full range of *BNFC* doses, given according to age, is as follows:

Treatment of diabetes insipidus

orally

- neonate: initially 1 to 4 micrograms 2 or 3 times daily, adjusted according to response
- 1 month to 2 years: initially 10 micrograms 2 or 3 times daily, adjusted according to response (range 30 to 150 micrograms daily)
- 2 to 12 years: initially 50 micrograms 2 or 3 times daily, adjusted according to response (range 100 to 800 micrograms daily)
- 12 to 18 years: initially 100 micrograms 2 or 3 times daily, adjusted according to response (range 200 to 1200 micrograms daily)

sublingually

- 2 to 18 years: initially 60 micrograms 3 times daily, adjusted according to response (range 40 to 240 micrograms 3 times daily)

intranasally

- neonate: initially 100 to 500 nanograms, adjusted according to response (range 1.25 to 10 micrograms daily as a single dose or in 2 divided doses)
- 1 month to 2 years: initially 2.5 to 5 micrograms once or twice daily, adjusted according to response
- 2 to 12 years: initially 5 to 20 micrograms once or twice daily, adjusted according to response
- 12 to 18 years: initially 10 to 20 micrograms once or twice daily, adjusted according to response

subcutaneously or *intramuscularly*

- neonate: initially 100 nanograms once daily, adjusted according to response (use the intramuscular route only)

- 1 month to 12 years: initially 400 nanograms once daily, adjusted according to response
- 12 to 18 years: initially 1 to 4 micrograms once daily, adjusted according to response

Test for suspected diabetes insipidus

intranasally

- 1 month to 2 years: 5 to 10 micrograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 10 to 20 micrograms as a single dose
- 12 to 18 years: 20 micrograms as a single dose

subcutaneously or *intramuscularly*

- 1 month to 2 years: 400 nanograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 0.5 to 1 microgram as a single dose
- 12 to 18 years: 1 to 2 micrograms as a single dose

Testing of renal function

intranasally

- 1 month to 1 year: 10 micrograms
- 1 to 15 years: 20 micrograms
- 15 to 18 years: 40 micrograms

subcutaneously or *intramuscularly*

- 1 month to 1 year: 400 nanograms
- 1 to 18 years: 2 micrograms

Primary nocturnal enuresis

orally

- 5 to 18 years (but preferably over 7 years): 200 micrograms at bedtime, increased if necessary to 400 micrograms

sublingually

- 5 to 18 years (but preferably over 7 years): 120 micrograms at bedtime, increased if necessary to 240 micrograms

The need for continued treatment with either route should be reassessed after 3 months by withdrawing desmopressin for at least 1 week

Mild to moderate **haemophilia** or **von Willebrand's disease**

intravenously (infusion over 20 minutes) or *subcutaneously*

- 1 month to 18 years: 300 nanograms/kg as a single dose immediately before surgery or after trauma; the dose may be repeated at intervals of 12 hours if no tachycardia occurs

intranasally

- 1 to 18 years: 4 micrograms/kg as a single dose; for pre-operative use give 2 hours before the procedure

Testing of fibrinolytic response

intravenously (infusion over 20 minutes) or *subcutaneously*

- 2 to 18 years: 300 nanograms/kg as a single dose; blood is sampled after 20 minutes for fibrinolytic activity

Diabetes insipidus. Desmopressin is the usual treatment for cranial diabetes insipidus (p.2179).

Haemorrhagic disorders. Desmopressin is used in the management of patients with mild haemophilia A, carriers of haemophilia with low factor VIII concentrations, and patients with acquired haemophilia who have low titres of antibodies to factor VIII (see Haemophilias, p.1048). Desmopressin is also used in von Willebrand's disease (p.1051). The use of desmopressin results in a two- to sixfold increase in plasma concentrations of factor VIII and von Willebrand factor,[1] and patients must have measurable baseline concentrations of these factors in order to respond to desmopressin.[1,2] In general, a baseline factor VIII concentration of 0.1 to 0.15 units/mL is needed to achieve post-injection concentrations of about 0.3 to 0.5 units/mL, which are generally sufficient for minor bleeding or lesser procedures. Concentrations of at least 0.7 to 1 unit/mL must be achieved for major surgery.[1] Desmopressin can be given subcutaneously, but the peak levels of factor VIII are reached later than after intravenous use. Intranasal use is also effective and allows patients to treat bleeding episodes themselves, without delay, outside hospital.[1] The use of desmopressin as an alternative to blood products has been recommended whenever possible in the treatment of these disorders, as a precaution against blood-borne infection.[1]

Bleeding due to liver disease has been controlled by desmopressin,[3,4] as has that associated with uraemia[5-8] (but for a report of tolerance to the effects of repeated doses of desmopressin in uraemic patients, see under Adverse Effects and Precautions, above), and there are reports of bleeding being controlled in other disorders such as telangiectasia[9] and platelet storage deficiency.[10-12] See also Haemorrhagic Disorders in Vasopressin (p.2412), and Variceal Haemorrhage in Vasopressin (p.2413) and Terlipressin (p.2396).

Desmopressin has been tried in surgical procedures with conflicting results.[2] A meta-analysis, which mainly included trials in cardiac surgery, found no evidence that desmopressin reduces perioperative blood transfusion in patients who do not have congenital bleeding disorders.[13] A possible role for desmopressin has been proposed in the control of surgical bleeding in patients whose religious beliefs preclude the use of blood products.[14,15] It has also been reported to be effective in postoperative aspirin-related bleeding that was previously unresponsive to clotting factors.[16] However, studies of prophylactic desmopressin given to patients who had received aspirin in the 7 days before cardiac bypass surgery have produced conflicting results, with desmopressin either reducing blood loss[17] or having no effect.[18]

1. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost* 2003; **29:** 101–5.
2. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90:** 2515–21.
3. Burroughs AK, *et al.* Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1985; **291:** 1377–81.
4. Rak K, *et al.* Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1986; **292:** 138.
5. Mannucci PM, *et al.* Deamino-8- -arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; **308:** 8–12.
6. Shapiro MD, Kelleher SP. Intranasal deamino-8- -arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol* 1984; **4:** 260–1.
7. Viganò GL, *et al.* Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 1989; **31:** 32–5.
8. Jacquot C, *et al.* Addition of desmopressin to recombinant human erythropoietin in treatment of haemostatic defect of uraemia. *Lancet* 1988; **i:** 420.
9. Quitt M, *et al.* The effect of desmopressin on massive gastrointestinal bleeding in hereditary telangiectasia unresponsive to treatment with cryoprecipitate. *Arch Intern Med* 1990; **150:** 1744–6.
10. Nieuwenhuis HK, Sixma JJ. 1-Desamino-8- -arginine vasopressin (desmopressin) shortens the bleeding time in storage pool deficiency. *Ann Intern Med* 1988; **108:** 65–7.
11. Castaman G, Rodeghiero F. Consistency of responses to separate desmopressin infusions in patients with storage pool disease and isolated prolonged bleeding time. *Thromb Res* 1993; **69:** 407–12.
12. Zatik J, *et al.* Variable response of Hermansky-Pudlak syndrome to prophylactic administration of 1-desamino 8 -arginine in subsequent pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2002; **104:** 165–6.
13. Carless PA, *et al.* Desmopressin for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 15/09/05).
14. Martens PR. Desmopressin and Jehovah's witness. *Lancet* 1989; **i:** 1322.
15. Beholz S, *et al.* Use of desmopressin and erythropoietin in an anaemic Jehovah's Witness patient with severely impaired coagulation capacity undergoing stentless aortic valve replacement. *Perfusion* 2001; **16:** 485–9.
16. Chard RB, *et al.* Use of desmopressin in the management of aspirin-related and intractable haemorrhage after cardiopulmonary bypass. *Aust N Z J Surg* 1990; **60:** 125–8.
17. Sheridan DP, *et al.* Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Can J Surg* 1994; **37:** 33–6.
18. Pleym H, *et al.* Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesth Analg* 2004; **98:** 578–84.

Nocturnal enuresis. Desmopressin is one of the main drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of nocturnal enuresis in children (p.2180). Secretion of vasopressin during the night in normal individuals reduces urine output and it has been suggested that nocturnal enuresis in some children might be due to impaired nocturnal secretion of vasopressin. However, other possible mechanisms include bladder instability and reduced nightly functional bladder capacity, and it has been proposed that treatment should be based on a greater consideration of nocturnal enuresis as a multifactorial condition.[1]

The synthetic vasopressin analogue desmopressin is used for its presumed antidiuretic effect on the kidney,[2] although there is some evidence that it may act by some other mechanism, possibly having a central effect.[3,4] It has been shown that desmopressin given at night can be effective in the short-term control of nocturnal enuresis[2,5] and many now consider it to be the drug of choice in terms of safety. There is some evidence[6,7] that long-term use of desmopressin is also effective. However, a meta-analysis suggested that benefit might not be sustained once the drug was stopped.[8] It should not be given when enuresis is due to polydipsia as desmopressin may provoke water intoxication and convulsions due to hyponatraemia. For precautions to be observed when desmopressin is used to treat enuresis, and the view that nasal formulations should not be used for this indication, see Effects on Electrolytes, above.

1. Butler RJ, *et al.* Investigating the three systems approach to complex childhood nocturnal enuresis. *Scand J Urol Nephrol* 2004; **38:** 117–21.
2. Müller D, *et al.* Comparative tolerability of drug treatment for nocturnal enuresis in children. *Drug Safety* 2004; **27:** 717–27.
3. Jonat S, *et al.* Effect of DDAVP on nocturnal enuresis in a patient with nephrogenic diabetes insipidus. *Arch Dis Child* 1999; **81:** 57–9.
4. Müller D, *et al.* Desmopressin for nocturnal enuresis in nephrogenic diabetes insipidus. *Lancet* 2002; **359:** 495–7.
5. Moffat MEK, *et al.* Desmopressin acetate and nocturnal enuresis: how much do we know? *Pediatrics* 1993; **92:** 420–5.
6. Hjälmås K, *et al.* Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. *Br J Urol* 1998; **82:** 704–9.
7. Wolfish NM, *et al.* The Canadian Enuresis Study and Evaluation: short- and long-term safety and efficacy of an oral desmopressin preparation. *Scand J Urol Nephrol* 2003; **37:** 22–7.
8. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 15/09/05).

Orthostatic hypotension. The first drug tried in patients with orthostatic hypotension (p.1530) who cannot be managed by nonpharmacological methods is usually fludrocortisone, but desmopressin is sometimes useful in patients with central neurological abnormalities.[1]

1. Mathias CJ, *et al.* The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. *BMJ* 1986; **293:** 353–4.

Post-dural puncture headache. Desmopressin acetate has been given to adults in a dose of 4 micrograms subcutaneously or intramuscularly for the treatment or prophylaxis of headache due to lumbar puncture, repeated if necessary after 24 hours. However, results have generally been disappointing and many patients respond to conservative treatment (see p.1851).

References.

1. Durward WF, Harrington H. Headache after lumbar puncture. *Lancet* 1976; **ii:** 1403–4.
2. Widerlöv E, Lindström L. DDAVP and headache after lumbar puncture. *Lancet* 1979; **i:** 548.
3. Hansen PE, Hansen JH. DDAVP, a synthetic analogue of vasopressin, in prevention of headache after lumbar puncture and lumbar pneumoencephalography. *Acta Neurol Scand* 1979; **60:** 183–8.
4. Cowan JMA, *et al.* DDAVP in the prevention of headache after lumbar puncture. *BMJ* 1980; **280:** 224.

Renal colic. Intranasal desmopressin is being studied[1] in the management of the pain of acute renal colic (p.5).

1. Zabihi N, Teichman JMH. Dealing with the pain of renal colic. *Lancet* 2001; **358:** 437–8.

Urinary incontinence. Desmopressin given intranasally appeared to be effective in reducing voiding frequency/incontinence when studied in 26 patients with multiple sclerosis whose bladder dysfunction had previously been unresponsive to antimuscarinics;[1] similar results have been reported in other small studies in patients with multiple sclerosis.[2] However, a review of studies using desmopressin to treat nocturia in such patients cast doubt on the clinical relevance of the limited reductions achieved in voiding frequency.[3] Nevertheless, beneficial long-term use of desmopressin for nocturia has been described, with some patients also using it intermittently during the daytime to control symptoms for special occasions.[4] Oral desmopressin has been reported to have a favourable effect on measures such as the number of nocturnal voids and duration of sleep until the first nocturnal void in women[5] and men[6] with nocturia. Beneficial effects were maintained or improved in many responders who were treated for a further 10 or 12 months.[7] In the management of daytime urinary incontinence in women, an improvement in the incidence of periods without leakage during the 4 hours after an intranasal dose of desmopressin has been reported.[8]

For the usual treatment of incontinence, see Urinary Incontinence and Retention, p.2180.

1. Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* 1996; **94:** 31–4.
2. Cvetković RS, Plosker GL. Desmopressin: in adults with nocturia. *Drugs* 2005; **65:** 99–107.
3. Ferreira E, Letwin SR. Desmopressin for nocturia and enuresis associated with multiple sclerosis. *Ann Pharmacother* 1998; **32:** 114–16.
4. Tubridy N, *et al.* Long term use of desmopressin for urinary symptoms in multiple sclerosis. *Multiple Sclerosis* 1999; **5:** 416–17.
5. Lose G, *et al.* Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; **189:** 1106–13.
6. Mattiasson A, *et al.* Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002; **89:** 855–62.
7. Lose G, *et al.* Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol (Baltimore)* 2004; **172:** 1021–5.
8. Robinson D, *et al.* Antidiuresis: a new concept in managing female daytime urinary incontinence. *BJU Int* 2004; **93:** 996–1000.

Preparations

BP 2008: Desmopressin Injection; Desmopressin Intranasal Solution;
USP 31: Desmopressin Acetate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Emosint; Octostim; Presinex; ***Austral.:*** Minirin; Octostim; ***Austria:*** Minirin; Nocturin; Nocutil; Nordurine; Novidin; Octostim; ***Belg.:*** Minirin; ***Braz.:*** Octostim†; ***Canad.:*** DDAVP; Minirin; Octostim; ***Chile:*** DDAVP; Octostim; ***Cz.:*** Adiuretin†; Desmospray; Desmotabs; Minirin; Nocutil†; ***Denm.:*** Minirin; Octostim; ***Fin.:*** Minirin; Octostim; ***Fr.:*** Minirin; Minirinmelt; Octim; ***Ger.:*** Desmogalen; Minirin; Nocutil; Octostim; ***Gr.:*** DDAVP; Defirin; Desmoprol; Esmon; Minirin; ***Hong Kong:*** Minirin; Octostim; ***Hung.:*** Desmopress; Minirin; Nocutil; Octostim; ***India:*** D-Void; ***Irl.:*** DDAVP; Desmospray; Desmotabs; Nordurine; ***Israel:*** Adin; Minirin; Octostim; Presinex; ***Ital.:*** Emosint; Minirin/DDAVP; ***Malaysia:*** Minirin; ***Mex.:*** DDAVP†; Minirin; Nafiset; Octostim; ***Neth.:*** Adiuretin; Minrin; Minurin; Octostim; ***Norw.:*** Minirin; Octostim; ***NZ:*** Minirin; Octostim; ***Philipp.:*** Minirin; ***Pol.:*** Minirin; ***Port.:*** DDAVP; Desmospray; Minirin; ***Rus.:*** Emosint (Эмосинт); Minirin (Минирин); ***S.Afr.:*** DDAVP; ***Singapore:*** Minirin; Octostim†; ***Spain:*** Minurin; Nocturin; Octostim; Presinex; ***Swed.:*** Minirin; Octostim; ***Switz.:*** Minirin; Nocutil; Octostim; ***Thai.:*** Minirin; ***Turk.:*** Minirin; Octostim; ***UK:*** DDAVP; DesmoMelt; Desmospray; Desmotabs; Nocutil†; Octim; Presinex; ***USA:*** DDAVP; Minirin; Stimate.

Dutasteride *(BAN, USAN, rINN)* ⊗

Dutasterid; Dutasterida; Dutastéride; Dutasteridum; GG-745; GI-198745; GI-198745X. α,α,α,α′,α′,α′-Hexafluoro-3-oxo-4-aza-5α-androst-1-ene-17β-carboxy-2′,5′-xylidide; 3-Oxo-2′,5′-bis-(trifluoromethyl)-4-aza-5α-androst-1-ene-17β-carboxanilide.

Дутастерид

$C_{27}H_{30}F_6N_2O_2$ = 528.5.
CAS — 164656-23-9.
ATC — G04CB02.
ATC Vet — QG04CB02.

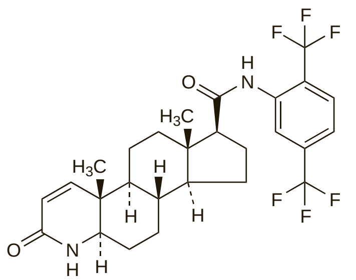

Adverse Effects and Precautions

As for Finasteride, p.2188.

Pharmacokinetics

Dutasteride is absorbed from the gastrointestinal tract, reaching a peak serum concentration in 1 to 3 hours, with a bioavailability of about 60%. It is highly bound to plasma proteins. Dutasteride is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and most of a dose is excreted as metabolites in the faeces. At steady state the elimination half-life is about 3 to 5 weeks.

Uses and Administration

Dutasteride, like finasteride (p.2189), is an inhibitor of 5α-reductase. Unlike finasteride, it is claimed to inhibit both the type-1 and type-2 isoforms of the enzyme. Dutasteride is used in the treatment of benign prostatic hyperplasia (p.2178); it may reduce the incidence of acute urinary retention and the need for surgery. Dutasteride is given in doses of 500 micrograms daily by mouth. Response may be delayed and treatment for 6 months may be required to assess whether benefit has been achieved.

Dutasteride is under investigation for the prevention of prostate cancer, and has been investigated in the treatment of alopecia.

◊ References.

1. Djavan B, *et al.* Dutasteride: a novel dual inhibitor of 5alpha-reductase for benign prostatic hyperplasia. *Expert Opin Pharmacother* 2005; **6:** 311–17. Correction. *ibid.*; 681.
2. Dolder CR. Dutasteride: a dual 5-α reductase inhibitor for the treatment of symptomatic benign prostatic hyperplasia. *Ann Pharmacother* 2006; **40:** 658–64.
3. Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. *Drugs* 2008; **68:** 463–85.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avodart; ***Austria:*** Avodart; Avolve; Zyfetor; ***Belg.:*** Avodart; ***Canad.:*** Avodart; ***Chile:*** Avodart; ***Cz.:*** Avodart; ***Denm.:*** Avodart; ***Fin.:*** Avodart; ***Fr.:*** Avodart; ***Ger.:*** Avodart; ***Gr.:*** Avodart; Duagen; ***India:*** Duprost; ***Indon.:*** Avodart; ***Irl.:*** Avodart; ***Israel:*** Avodart; ***Ital.:*** Avodart; ***Malaysia:*** Avodart; ***Mex.:*** Avodart; ***Neth.:*** Avodart; Duagen; ***Norw.:*** Avodart; ***Philipp.:*** Avodart; ***Pol.:*** Avodart; ***Port.:*** Avodart; Avolve; Duagen; ***Rus.:*** Avodart (Аводарт); ***S.Afr.:*** Avodart; ***Singapore:*** Avodart; ***Spain:*** Avidart; Duagen; ***Swed.:*** Avodart; ***Switz.:*** Avodart; ***Turk.:*** Avodart; ***UK:*** Avodart; ***USA:*** Avodart.

Emepronium Bromide *(BAN, rINN)*

Bromuro de emepronio; Emepronii Bromidum; Émépronium, Bromure d'; Emeproniumbromid; Emeproniumbromidi. Ethyldimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide.

Эмепрония Бромид

$C_{20}H_{28}BrN$ = 362.3.
CAS — 27892-33-7 (emepronium); 3614-30-0 (emepronium bromide).
ATC — G04BD01.
ATC Vet — QG04BD01.

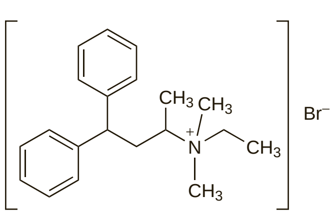

Emepronium Carrageenate *(BAN)*

Emepronio, carragenato de.
ATC — G04BD01.
ATC Vet — QG04BD01.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

To avoid oesophageal ulceration, tablets of emepronium bromide should always be swallowed with an adequate volume of water, and patients should always be in the sitting or standing position while, and for 10 to 15 minutes after, taking the tablets. Emepronium is contra-indicated in patients with symptoms or signs of oesophageal obstruction or with pre-existing oesophagitis.

Buccal and oesophageal ulceration. Tablet-induced oesophageal damage is a widely recognised problem and is related to direct mucosal injury by the medication. Emepronium bromide has been frequently implicated in this type of mucosal injury, although it rarely results in stricture formation.[1]

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics

Emepronium is incompletely absorbed from the gastrointestinal tract and is mainly excreted unchanged in the urine and faeces. It does not readily cross the blood-brain barrier at therapeutic doses.

Uses and Administration

Emepronium is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1220). It has been used orally as the bromide and the carrageenate in the treatment of urinary frequency and incontinence (p.2180); the bromide has also been given by subcutaneous or intramuscular injection.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that emepronium should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cetiprin†; ***Braz.:*** Cetiprin†; ***Denm.:*** Cetiprin†; ***Fin.:*** Cetiprin Novum†; ***Neth.:*** Cetiprin†; ***Norw.:*** Cetiprin†; ***Swed.:*** Cetiprin†.

Fesoterodine *(rINN)*

Fesoterodina; Fésotérodine; Fesoterodinum. 2-[(1*R*)-3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate.

Фезотеродин

$C_{26}H_{37}NO_3$ = 411.6.
CAS — 286930-02-7.
ATC — G04BD11.
ATC Vet — QG04BD11.

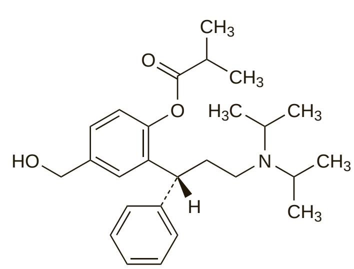

Fesoterodine Fumarate *(USAN, rINNM)*

Fésotérodine, Fumarate de; Fesoterodini Fumaras; Fumarato de fesoterodina; SPM-907; SPM-8272.

Фезотеродина Фумарат

$C_{26}H_{37}NO_3,C_4H_4O_4$ = 527.6.
CAS — 286930-03-8.

Profile

Fesoterodine is a selective M_3 antimuscarinic used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p.2180). It is given orally as the fumarate; the usual initial dose is 4 mg once daily, increased to a maximum of 8 mg once daily if necessary, according to response. Patients should be re-evaluated after 8 weeks of treatment. The dose of fesoterodine fumarate should not exceed 4 mg once daily in patients receiving potent CYP3A4 or CYP2D6 inhibitors. For doses in hepatic and renal impairment, see below.

Administration in hepatic impairment. UK licensed product information for fesoterodine fumarate states that patients with mild hepatic impairment should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed a dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with moderate impairment should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended. Fesoterodine fumarate is contra-indicated in those with severe impairment.

Administration in renal impairment. UK licensed product information for fesoterodine fumarate states that patients with mild (GFR 50 to 80 mL/minute) or moderate (GFR 30 to 50 mL/minute) renal impairment, should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed a dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with severe impairment (GFR less than 30 mL/minute) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Toviaz; ***Port.:*** Toviaz; ***UK:*** Toviaz.

Finasteride *(BAN, USAN, rINN)* ⊗

Finasterid; Finasterida; Finasteridas; Finastéride; Finasteridi; Finasteridum; Finaszterid; MK-906; MK-0906; YM-152. *N-tert*-Butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

Финастерид

$C_{23}H_{36}N_2O_2$ = 372.5.
CAS — 98319-26-7.
ATC — D11AX10; G04CB01.
ATC Vet — QD11AX10; QG04CB01.

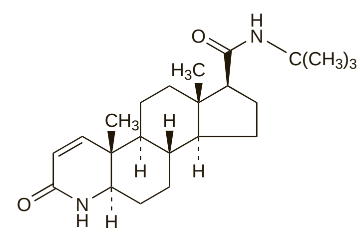

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Finasteride). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 31 (Finasteride). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Store in airtight containers.

Adverse Effects

The most commonly reported adverse effects of finasteride are decreased libido, erectile dysfunction, ejaculation disorders, and reduced volume of ejaculate.

Breast tenderness and enlargement (gynaecomastia) may occur, and there have been reports of hypersensitivity reactions such as swelling of the lips and face, pruritus, urticaria, and rashes. Testicular pain has also been reported.

Incidence of adverse effects. In a study using prescription event monitoring data,[1] the most commonly reported adverse effects of finasteride in 14 772 patients were impotence or ejaculatory failure (2.1% of patients), reduced libido (1%), and breast disorders such as gynaecomastia (0.4%). Adverse effects reported in a single patient each, and verified on rechallenge, were exfoliative dermatitis, perioral numbness, and swollen glands. Finasteride appeared to be associated with ataxia in 1 patient and wheeziness in another.

1. Wilton L, *et al.* The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14 772 patients. *Br J Urol* 1996; **78:** 379–84.

Effects on the breast. Gynaecomastia was the adverse effect of finasteride most frequently reported to the FDA between June 1992 and February 1995 (a total of 214 reports).[1] The onset after therapy ranged from 14 days to 2.5 years, and the condition could be unilateral or bilateral. Mastectomy was performed in 12 men. Of the 86 men for whom follow-up information was available, partial or complete remission of gynaecomastia occurred in 80%, and no change occurred in 20%. In 2 of the cases, primary intraductal breast carcinoma was subsequently found, although 1 probably had breast cancer before finasteride therapy. Continued surveillance of the relationship between finasteride and breast cancer is required.

1. Green L, *et al.* Gynecomastia and breast cancer during finasteride therapy. *N Engl J Med* 1996; **335:** 823.

Effects on mental function. Depression has been reported[1,2] in 20 patients given finasteride for the treatment of alopecia. In most cases the depression began about 3 to 4 months after starting finasteride, and resolved within a few weeks of stopping it. In 2 patients rechallenged with finasteride, depression recurred within 2 weeks of restarting the drug.[1]

1. Altomare G, Capella GL. Depression circumstantially related to the administration of finasteride for androgenetic alopecia. *J Dermatol* 2002; **29:** 665–9.
2. Health Canada. Finasteride: suspected association with depression. *Can Adverse React News* 2004; **14** (1): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 02/09/08)

Precautions

Finasteride should be used with caution in hepatic impairment. When used for benign prostatic hyperplasia, finasteride should be used with caution in men at risk of obstructive uropathy. Patients should be evaluated for prostatic carcinoma before and during therapy. Use of finasteride decreases concentrations of serum markers of prostate cancer such as prostate specific antigen (PSA) by up to 50% even when cancer is present, and reference values should be adjusted accordingly; the ratio of free to total PSA (percent free PSA) remains constant.

Studies in *animals* suggest finasteride could produce feminisation (hypospadia) of a male fetus if used in pregnant women; therefore, its use is contra-indicated in women who are or may become pregnant. In addition, it is recommended that women in this category should not handle crushed or broken finasteride tablets. Finasteride has been detected in semen, therefore use of a condom is recommended if the patient's sexual partner is, or may become, pregnant.

Pharmacokinetics

Finasteride is absorbed after oral doses, and peak plasma concentrations are achieved in 1 to 2 hours. The mean bioavailability has variously been reported as 63% and 80%. It is about 90% bound to plasma protein. Finasteride crosses the blood-brain barrier, and is distributed into semen. It is metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4, and excreted in urine and faeces as metabolites. The mean terminal half-life is about 6 hours in patients under 60 years of age but may be prolonged to about 8 hours in those 70 years of age or older.

◊ References.

1. Steiner JF. Clinical pharmacokinetics and pharmacodynamics of finasteride. *Clin Pharmacokinet* 1996; **30:** 16–27.

Uses and Administration

Finasteride is an azasteroid that inhibits the type-2 isoform of 5α-reductase, the enzyme responsible for conversion of testosterone to the more active dihydrotestosterone, and therefore has anti-androgenic properties. It is given orally in a dose of 5 mg daily in the management of benign prostatic hyperplasia to cause regression of the enlarged prostate and to improve symptoms; it may reduce the incidence of acute urinary retention and the need for surgery. Response may be delayed and treatment may be required for 6 months or more to assess whether benefit has been achieved.

In the treatment of male-pattern baldness (alopecia androgenetica) in men, finasteride is given orally in a dose of 1 mg daily. In general, use for 3 months or more is required before benefit is seen, and effects are reversed within 12 months of ceasing therapy.

Alopecia. In men with male-pattern baldness (alopecia—see p.1577), treatment with oral finasteride for 12 months resulted in an 11% increase in vertex hair count, which was maintained in those who continued therapy.[1] Extension of this study to 5 years found that long-term treatment with finasteride maintained beneficial effects, or at least slowed hair loss.[2] The use of oral finasteride for this purpose has been reviewed.[3-5] Some efficacy has also been found with topical finasteride.[6]

Although finasteride is contra-indicated in women who are or may become pregnant (see Precautions, above), it has been investigated in the treatment of male-pattern baldness in postmenopausal women. However, a 1-year placebo-controlled study[7] found no benefit from finasteride. There has been a report[8] of benefit from finasteride in 4 women with hair loss due to hyperandrogenism.

1. Kaufman KD, *et al.* Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998; **39:** 578–89.
2. The finasteride male pattern hair loss study group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol* 2002; **12:** 38–49.
3. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. *Drugs* 1999; **57:** 111–26.
4. Whiting DA. Advances in the treatment of male androgenetic alopecia: a brief review of finasteride studies. *Eur J Dermatol* 2001; **11:** 332–4.
5. Libecco JF, Bergfeld WF. Finasteride in the treatment of alopecia. *Expert Opin Pharmacother* 2004; **5:** 933–40.
6. Mazzerella F, *et al.* Topical finasteride in the treatment of androgenic alopecia. *J Dermatol Treat* 1997; **8:** 189–92.
7. Price VH, *et al.* Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *J Am Acad Dermatol* 2000; **43:** 768–76.
8. Shum KW, *et al.* Hair loss in women with hyperandrogenism: four cases responding to finasteride. *J Am Acad Dermatol* 2002; **47:** 733–9.

Benign prostatic hyperplasia. Finasteride[1] is used in the management of benign prostatic hyperplasia (p.2178). It produces moderate reductions in prostate volume, although this takes a number of months and is not always associated with much symptomatic improvement; therapy must be continued indefinitely for benefit to be maintained. A 4-year study found that finasteride reduced the probability of surgery and acute urinary retention in men with symptomatic benign prostate hyperplasia with prostatic enlargement.[2] Although the need for prostatectomy was reduced by 55% it was pointed out[3] that only 6% extra patients would benefit from treatment with finasteride. For every 100 men treated, 7 finasteride and 13 placebo recipients required surgery. A 2-year, open-label follow-up[4] of this study reported that the reductions in probability of surgery and acute urinary retention were maintained. It was also found that in patients who switched from placebo to finasteride, these measures decreased to become similar to those recorded in men already receiving finasteride. A comparative 12-month study[5] found the alpha blocker terazosin to be more effective than finasteride in relieving symptoms and improving peak urine flow rates; the combination of finasteride plus terazosin was no more effective than terazosin alone. Moreover, although finasteride reduced prostatic volume, it was no more effective than placebo, a finding that is at odds with previous placebo-controlled studies. It has been suggested that the smaller median prostate size in this study may explain the negative findings,[6] and that men with larger prostates do benefit from finasteride. Similar results were reported in a 12-month study using doxazosin.[7] Later results[8,9] from a large study showed that over a longer period of 4 or more years the combination of doxazosin and finasteride reduced the risk of clinical progression more than either drug alone. The combination of an alpha blocker and 5α-reductase inhibitor is therefore considered to be a suitable option for patients with urinary symptoms and demonstrable prostatic enlargement, and who are at significant risk of progression.

1. Wilde MI, Goa KL. Finasteride: an update of its use in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1999; **57:** 557–81.
2. McConnell JD, *et al.* The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostate hyperplasia. *N Engl J Med* 1998; **338:** 557–63.
3. Wasson JH. Finasteride to prevent morbidity from benign prostatic hyperplasia. *N Engl J Med* 1998; **338:** 612–13.
4. Roehrborn CG, *et al.* Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol (Baltimore)* 2004; **171:** 1194–8.
5. Lepor H, *et al.* The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996; **335:** 533–9.
6. Walsh PC. Treatment of benign prostatic hyperplasia. *N Engl J Med* 1996; **335:** 586–7.
7. Kirby RS, *et al.* Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003; **61:** 119–26.
8. McConnell JD, *et al.* The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; **349:** 2387–98.
9. Kaplan SA, *et al.* Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. *J Urol (Baltimore)* 2006; **175:** 217–20.

Hirsutism. Finasteride is reported to be effective for the treatment of hirsutism (p.2089) in women.[1-7] It should be noted that finasteride should not be used in women who are or may become pregnant (see Precautions, above).

1. Falsetti L, *et al.* Comparison of finasteride versus flutamide in the treatment of hirsutism. *Eur J Endocrinol* 1999; **141:** 361–7.
2. Moghetti P. *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85:** 89–94.
3. Müderris II, *et al.* A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. *Fertil Steril* 2000; **73:** 984–7.
4. Bayram F, *et al.* Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. *Eur J Endocrinol* 2002; **147:** 467–71.
5. Lumachi F, Rondinone R. Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertil Steril* 2003; **79:** 942–6.
6. Beigi A, *et al.* Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Int J Gynaecol Obstet* 2004; **87:** 29–33.
7. Tartagni M, *et al.* Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. *Fertil Steril* 2004; **82:** 752–5.

Malignant neoplasms of the prostate. Finasteride appears to have little effect in established prostate cancer,[1,2] but is under investigation for its prevention (p.671). The results of 1 small study[3] of its effects on the prostate found little evidence to support its use for prevention of malignancy in patients at high risk. In healthy men, a large controlled study, the Prostate Cancer Prevention Trial (PCPT),[4] found that 7 years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. The risk-benefit implications of these results have been debated, although some commentaries[5-7] suggest that preventive use would be justified, at least in selected patients. Further analysis[8] of the PCPT data found that finasteride had introduced a detection bias for both prostate cancer and for high-grade prostate cancer. Finasteride increased the sensitivity of prostate specific antigen (PSA) testing, implying that the PCPT primary findings of increased risk of high-grade tumours were due, at least in part, to improved detection. The reported 25% decrease in prostate cancer incidence was also likely to be an underestimate. The European Association of Urology has endorsed a recommendation that prostate cancer management guidelines be updated to reflect these findings.[9]

1. Presti JC, *et al.* Multicenter, randomized, double-blind placebo controlled study to investigate the effect of finasteride (MK-906) on stage D prostate cancer. *J Urol (Baltimore)* 1992; **148:** 1201–4.
2. Rittmaster RS. Finasteride. *N Engl J Med* 1994; **330:** 120–5.
3. Cote RJ, *et al.* The effect of finasteride on the prostate gland in men with elevated serum prostate-specific antigen levels. *Br J Cancer* 1998; **78:** 413–18.
4. Thompson IM, *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349:** 215–24.
5. Parnes HL, *et al.* Prevention of hormone-related cancers: prostate cancer. *J Clin Oncol* 2005; **23:** 368–77.
6. Unger JM, *et al.* Estimated impact of the Prostate Cancer Prevention Trial on population mortality. *Cancer* 2005; **103:** 1375–80.
7. Lotan Y, *et al.* Implications of the prostate cancer prevention trial: a decision analysis model of survival outcomes. *J Clin Oncol* 2005; **23:** 1911–20.
8. Thompson IM, *et al.* Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; **98:** 1128–33.
9. Teillac P, Abrahamsson P-A. The Prostate Cancer Prevention Trial and its implications for clinical practice: a european consensus. *Eur Urol Suppl* 2006; **5:** 640–6.

Preparations

BP 2008: Finasteride Tablets;
USP 31: Finasteride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Anatine†; Andropel; Avertex; Conef†; Daric; Eutiz†; Finasterin; Finprostat; Flutiamik; Folcres; HPB; Nasteril; Pelicrep†; Propecia; Proscar; Prosmin; Prostanil; Prostanovag; Prostene; Renacidin; Sutrico; Tealep; Tricofarma; Urofin; Urototal; Vetiprost; ***Austral.:*** Propecia; Proscar; ***Austria:*** Propecia; Proscar; ***Belg.:*** Proscar; ***Braz.:*** Alfasin; Capyla; Finalop; Finastec; Finastil; Flaxin; Nasterid; Nasterid A; Pracap; Prohair†; Pronasteron; Propecia; Proscar; Prostide; Reduscar†; ***Canad.:*** Propecia; Proscar; ***Chile:*** Apeplus†; Prohair; Proscar; Saniprostol; Vastus; ***Cz.:*** Androfin; Apo-Finas; Duromeran; Edufil; Finajelf; Finanorm; Finard; Finex; Finpros; Gefin; Ibition; Lekoprost; Mostrafin; Penester; Propecia; Proscar; Radicut; ***Denm.:*** Propecia; Proscar; ***Fin.:*** Gefina; Propecia; Proscar; ***Fr.:*** Chibro-Proscar; Propecia; ***Ger.:*** Propecia; Proscar; ***Gr.:*** Pervil; Poruxin; Propecia; Proscar; ***Hong Kong:*** Propecia; Proscar; ***Hung.:*** Finpros; Proscar; Prosterid; ***India:*** Fincar; Finpecia; Ultrafina†; ***Indon.:*** Finaxal; Finpro; Proscar; Prostacom; Reprostom; ***Irl.:*** Proscar; ***Israel:*** Pro-Cure; Propecia; ***Ital.:*** Finastid; Genaprost; Propecia; Proscar; Prostide; ***Malaysia:*** Propecia; Proscar; ***Mex.:*** Propeshia; Proscar; ***Neth.:*** Finaburg; Propecia; Proscar; ***Norw.:*** Proscar; ***NZ:*** Propecia; Proscar; ***Philipp.:*** Propecia; Proscar; ***Pol.:*** Ambulase; Finaride; Finaster; Lifin; Penester; Propecia; Proscar; Zasterid; ***Port.:*** Propecia; Proscar; Prostacide; Prostafin; Zidoril; Zylfina; ***Rus.:*** Finast (Финаст); Penester (Пенестер); Proscar (Проскар); Prosterid (Простерид); ***S.Afr.:*** Propecia; Proscar; ***Singapore:*** Propecia; Proscar; ***Spain:*** Eucoprost; Propecia; Proscar; ***Swed.:*** Propecia; Proscar; ***Switz.:*** Propecia; Proscar; ***Thai.:*** Firide; Harifin; Propecia; Proscar; ***Turk.:*** Dilaprost; Finarid; Propecia; Proscar; Prosterit; ***UK:*** Propecia; Proscar; ***USA:*** Propecia; Proscar; ***Venez.:*** Finast†; Nasterol; Propecia; Proscar; Prosdina†.

Multi-ingredient: ***Arg.:*** Tricoplus Conef†; ***India:*** Urimax F.

Flavoxate Hydrochloride

(BANM, USAN, rINNM)

DW-61; Flavoksat Hidroklorür; Flavoxate, chlorhydrate de; Flavoxati hydrochloridum; Hidrocloruro de flavoxato; NSC-114649; Rec-7-0040. 2-Piperidinoethyl 3-methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylate hydrochloride.

Флавоксата Гидрохлорид

$C_{24}H_{25}NO_4,HCl$ = 427.9.

CAS — 15301-69-6 (flavoxate); 3717-88-2 (flavoxate hydrochloride).

ATC — G04BD02.

ATC Vet — QG04BD02.

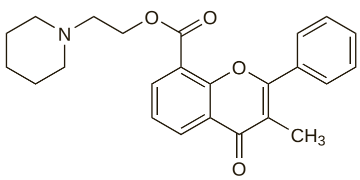

(flavoxate)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Flavoxate Hydrochloride). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Ocular effects, including increased intra-ocular pressure, are occasionally troublesome. Other adverse effects include sedation or fatigue, vertigo, and hypersensitivity reactions. Leucopenia or eosinophilia has been reported rarely.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics

Flavoxate is readily absorbed from the gastrointestinal tract and rapidly metabolised, about 50 to 60% of a dose being excreted in the urine within 24 hours as methyl flavone carboxylic acid.

Uses and Administration

Flavoxate hydrochloride is described as a smooth muscle relaxant but it also has antimuscarinic effects (see, p.1221); it is a tertiary amine. It is used for the symptomatic relief of pain, urinary frequency, and incontinence associated with inflammatory disorders of the urinary tract. It is also used for the relief of vesico-urethral spasms resulting from instrumentation or surgery. A usual dose is 200 mg orally three times daily.

Urinary incontinence. Flavoxate is indicated mainly in the treatment of urge incontinence (p.2180). Results of studies have sometimes been disappointing,[1,2] although adverse effects are said to be less marked than those seen with other antimuscarinics such as oxybutynin.[3] In the UK, guidelines issued by NICE suggest that flavoxate should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[4]

1. Chapple CR, *et al.* Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. *Br J Urol* 1990; **66:** 491–4.
2. Dahm TL, *et al.* Flavoxate treatment of micturition disorders accompanying benign prostatic hypertrophy: a double-blind placebo-controlled multicenter investigation. *Urol Int* 1995; **55:** 205–8.
3. Fehrmann-Zumpe P, *et al.* Using flavoxate as primary medication for patients suffering from urge symptomatology. *Int Urogynecol J* 1999; **10:** 91–5.
4. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

BP 2008: Flavoxate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bladuril; ***Austria:*** Urispas; ***Belg.:*** Urispas; ***Braz.:*** Genurin-S; ***Canad.:*** Urispas†; ***Chile:*** Bladuril; ***Cz.:*** Urispas†; ***Denm.:*** Urispadol; ***Fr.:*** Urispas; ***Ger.:*** Spasuret; ***Gr.:*** Verispasmin; ***Hong Kong:*** Genurin†; Urispas; ***India:*** Flavate; Urisol; Urispas; ***Indon.:*** Uroxal; ***Irl.:*** Urispas; ***Ital.:*** Genurin; ***Jpn:*** Bladderon; ***Malaysia:*** Uripax; Urispas; ***Mex.:*** Bladuril; ***Neth.:*** Urispas; Uronid; ***Port.:*** Urispas; ***S.Afr.:*** Urispas; ***Singapore:*** Cleanxate; Genurin†; Urispas; ***Spain:*** Uronid; ***Switz.:*** Urispas; ***Thai.:*** Flavo-Spa; Flavorin; Spasdic; Spasuri; U-Spa; Uroxate; Voxate; ***Turk.:*** Urispas; ***UK:*** Urispas; ***USA:*** Urispas; ***Venez.:*** Genurin.

Multi-ingredient: ***Arg.:*** Algio-Bladuril; ***Ital.:*** Cistalgan.

Imidafenacin *(rINN)*

Imidafenacina; Imidafénacine; Imidafenacinum; KRP-197; KRP-1979; Ono-8025. 4-(2-Methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide.

Имидафенацин

$C_{20}H_{21}N_3O$ = 319.4.

CAS — 170105-16-5.

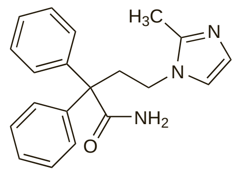

Profile

Imidafenacin is an antimuscarinic that is used in the treatment of urinary frequency, urgency, and incontinence (p.2180). It is given in an oral dose of 100 micrograms twice daily, after food.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Staybla; Uritos.

Naftopidil *(rINN)*

BM-15275; KT-611; Naftopidilum. (±)-4-(*o*-Methoxyphenyl)-α-[(1-naphthyloxy)methyl]-1-piperazineethanol.

Нафтопидил

$C_{24}H_{28}N_2O_3$ = 392.5.

CAS — 57149-07-2.

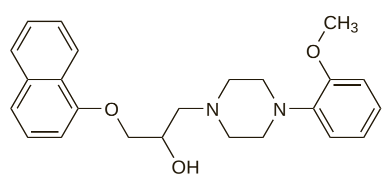

Profile

Naftopidil is a peripheral alpha$_1$-adrenoceptor blocker that is structurally related to urapidil (p.1419) and has similar general properties. It is used in benign prostatic hyperplasia to relieve symptoms of urinary obstruction.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Avishot; Flivas.

Oxendolone *(USAN, rINN)*

Oxendolona; Oxendolonum; TSAA-291. 16β-Ethyl-17β-hydroxyestr-4-en-3-one.

Оксендолон

$C_{20}H_{30}O_2$ = 302.5.

CAS — 33765-68-3.

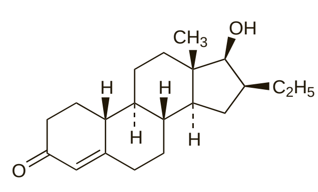

Profile

Oxendolone is an anti-androgen that has been used in the treatment of benign prostatic hyperplasia.

Oxybutynin *(BAN, USAN, rINN)*

Oxibutinina; Oxybutynine; Oxybutyninum. 4-Diethylaminobut-2-ynyl 2-cyclohexyl-2-phenylglycolate; 4-(Diethylamino)-2-butynyl α-phenylcyclohexaneglycolic acid ester.

Оксибутинин

$C_{22}H_{31}NO_3$ = 357.5.

CAS — 5633-20-5.

ATC — G04BD04.

ATC Vet — QG04BD04.

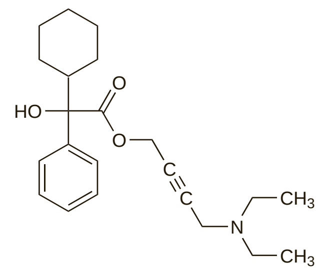

Oxybutynin Hydrochloride *(BANM, rINNM)*

5058; Hidrocloruro de oxibutinina; MJ-4309-1; Oksibütinin Hidroklorür; Oksibutinino hidrochloridas; Oksibutyniinihydrokloridi; Oksybutyniny chlorowodorek; Oxibutinin-hidroklorid; Oxibutyninhydroklorid; Oxybutynin Chloride *(USAN)*; Oxybutynin hydrochlorid; Oxybutynine, chlorhydrate d'; Oxybutynini hydrochloridum. 4-Diethylaminobut-2-ynyl α-cyclohexylmandelate hydrochloride; 4-(Diethylamino)but-2-ynyl (*RS*)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride.

Оксибутинина Гидрохлорид

$C_{22}H_{31}NO_3,HCl$ = 393.9.

CAS — 1508-65-2.

ATC — G04BD04.

ATC Vet — QG04BD04.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Oxybutynin Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; practically insoluble in cyclohexane. Protect from light.

USP 31 (Oxybutynin Chloride). A white, practically odourless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; very soluble in chloroform and in methyl alcohol; slightly soluble in ether; very slightly soluble in hexane.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Animal studies have shown reproductive toxicity with high doses of oxybutynin, hence the recommendation that it should be avoided during pregnancy; caution should also be observed during breast feeding.

Effects on body temperature. A 76-year-old man taking oxybutynin hydrochloride 5 mg three times daily suffered heatstroke on a day when the ambient temperature was about 37°. He had had a similar febrile episode the previous summer while taking oxybutynin.[1]

1. Adubofour KO, *et al.* Oxybutynin-induced heatstroke in an elderly patient. *Ann Pharmacother* 1996; **30:** 144–7.

Effects on the eyes. After 4 weeks of treatment, the adverse ocular effects of oxybutynin and tolterodine were evaluated in 24 and 28 women, respectively, being treated for urge incontinence.[1] The incidence of adverse effects reported by the patients was similar for the 2 drugs. A burning sensation in the eyes occurred in about half the women, but reports of a foreign-body sensation and dry eyes were less frequent. There was a reduction in accommodation amplitude although this was statistically significant only for oxybutynin, and pupillary diameter in dim light was only significantly larger for tolterodine. Tear film stability was found to be reduced for both drugs, but intra-ocular pressure was not significantly affected.

Acute angle-closure glaucoma has been reported in an elderly woman taking oxybutynin for urge incontinence.[2]

1. Altan-Yaycioglu R, *et al.* Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial. *Br J Clin Pharmacol* 2005; **59:** 588–92.
2. Sung VCT, Corridan PG. Acute-angle closure glaucoma as a side-effect of oxybutynin. *Br J Urol* 1998; **81:** 634–5.

Effects on the gastrointestinal tract. Reflux oesophagitis has been reported[1] in a 36-year-old woman with cerebral palsy and hiatus hernia who had taken oxybutynin for 5 years to prevent urinary incontinence. Symptoms of gastro-oesophageal reflux resolved when oxybutynin was stopped.

1. Lee M, Sharifi R. Oxybutynin-induced reflux esophagitis. *DICP Ann Pharmacother* 1990; **24:** 583–5.

Effects on mental function. Oxybutynin was associated with the development of acute confusional states in 4 patients with Parkinson's disease and some cognitive impairment.[1] A study[2] of healthy subjects, aged 65 years or older, also found oxybutynin to cause cognitive impairment.

1. Donnellan CA, *et al.* Oxybutynin and cognitive dysfunction. *BMJ* 1997; **315:** 1363–4.
2. Katz IR, *et al.* Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998; **46:** 8–13.

Night terrors. Night terrors have been reported in 5 patients taking oxybutynin.[1] Four of the patients were young children and the fifth was an elderly woman. Rechallenge was positive in 2 cases.

1. Valsecia ME, *et al.* New adverse effect of oxybutynin: "night terror". *Ann Pharmacother* 1998; **32:** 506.

Overdosage. A report[1] of a 34-year-old woman who ingested 100 mg of oxybutynin. The main symptoms were antimuscarinic effects and included drowsiness, hallucinations, dilatation of pupils, and urinary retention. Tachycardia resolved shortly after admission to hospital but ventricular ectopic beats and bigeminy persisted for over 24 hours. The patient recovered with symptomatic treatment.

1. Banerjee S, *et al.* Poisoning with oxybutynin. *Hum Exp Toxicol* 1991; **10:** 225–6.

Porphyria. Oxybutynin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Itraconazole. Use of itraconazole with oxybutynin resulted in moderate increases of serum concentrations of the latter.[1] However, concentrations of the active metabolite of oxybutynin, *N*-desethyloxybutynin, were virtually unchanged and the interaction was considered to be of minor clinical significance.

1. Lukkari E, *et al.* Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol* 1997; **52:** 403–6.

Pharmacokinetics

After oral doses of oxybutynin, peak plasma concentrations are reached within one hour. Oxybutynin is also absorbed after application to the skin. It is highly bound to plasma proteins. Oxybutynin undergoes extensive first-pass metabolism, particularly by the cytochrome P450 isoenzyme CYP3A4, and systemic oral bioavailability has been reported to be only 6%. *N*-desethyloxybutynin is an active metabolite. Oxybutynin and its metabolites are excreted in the urine and faeces, and an elimination half-life of 2 to 3 hours has been reported. Oxybutynin has been detected in breast milk. Evidence suggests that it may cross the blood-brain barrier.

◊ References.

1. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. *J Clin Pharmacol* 1999; **39:** 289–96.
2. Appell RA, *et al.* Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc* 2003; **78:** 696–702.
3. Reiz JL, *et al.* Pharmacokinetics and pharmacodynamics of once-daily controlled-release oxybutynin and immediate-release oxybutynin. *J Clin Pharmacol* 2007; **47:** 351–7.

Uses and Administration

Oxybutynin hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p.1220); it also has direct effects on smooth muscle. It is used for the management of urinary frequency, urgency, and incontinence in neurogenic bladder disorders and in idiopathic detrusor instability, and as an adjunct to nonpharmacological therapy for nocturnal enuresis.

Usual oral doses of oxybutynin hydrochloride are 5 mg two or three times daily, increased to 5 mg four times daily if required. In elderly patients lower doses of 2.5 or 3 mg twice daily initially, increased to 5 mg twice daily if necessary, may be adequate. Modified-release preparations of oxybutynin hydrochloride are also available. The initial dose is 5 mg once daily, increased by 5 mg at weekly intervals if necessary, up to a maximum of 20 or 30 mg daily, depending on the preparation. Oxybutynin is also given via a transdermal patch that supplies 3.9 mg of oxybutynin daily. The patch should be applied to intact skin on the abdomen, hip, or buttocks and replaced every 3 to 4 days; re-application to the same site should be avoided for 7 days.

In the UK, oxybutynin hydrochloride is licensed for neurogenic bladder disorders in children from the age of 5 years; in both the UK and the USA it is licensed from the age of 6 years as a modified-release formulation. The initial oral dose of conventional formulations is 2.5 or 3 mg twice daily, increased to 5 mg two or three times daily according to response; as a modified-release tablet the initial dose is 5 mg once daily, increased by 5-mg increments to a maximum daily dose of 15 or 20 mg, depending on the preparation, and according to response. Modified-release preparations are not recommended for children who are unable to swallow the tablet whole. The *BNFC* suggests that children aged 2 to 5 years may be given a dose of 1.25 to 2.5 mg as a conventional oral formulation 2 or 3 times daily. Children from the age of 2 years may also be given oxybutynin by intravesical instillation, in a dose of 5 mg (as the hydrochloride) in 30 mL of solution, 2 or 3 times daily.

Oxybutynin is also licensed in the treatment of nocturnal enuresis in children over 5 years, as the conventional formulations, in similar doses to those used for neurogenic bladder disorders; the last dose should usually be given before bedtime. However, the *BNFC* considers that drug therapy for nocturnal enuresis is usually not needed in children under 7 years of age.

Nocturnal enuresis. Antimuscarinics such as oxybutynin reduce uninhibited bladder contractions but, although they may be of use in diurnal enuresis, they are rarely of benefit in nocturnal enuresis (p.2180) alone. Oxybutynin did not appear to be effective in treating primary nocturnal enuresis in children with normal bladders.[1] However, children with low bladder capacity and detrusor instability may derive some benefit from oxybutynin.[2,3]

1. Lovering JS, *et al.* Oxybutynin efficacy in the treatment of primary enuresis. *Pediatrics* 1988; **82:** 104–6.
2. Koşar A, *et al.* Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna: a clinical and urodynamic study. *Scand J Urol Nephrol* 1999; **33:** 115–18.
3. Nevéus T. Oxybutynin, desmopressin and enuresis. *J Urol (Baltimore)* 2001; **166:** 2459–62.

Urinary incontinence. In addition to its antimuscarinic effect, oxybutynin has a direct antispasmodic effect which also contributes to reducing the number of uninhibited bladder contractions in urge incontinence (see p.2180). It is effective when given orally[1-4] or via a transdermal patch.[5-7] NICE considers conventional oral oxybutynin formulations to be the drug of first choice in women with overactive bladder syndrome or mixed incontinence if bladder training has been ineffective.[8] However, adverse effects may limit its use; if immediate-release oxybutynin is not well tolerated, a controlled-release or transdermal formulation may be considered as an alternative.[8]

Oxybutynin given orally can be useful in the management of neurogenic detrusor hyperreflexia in adults[9,10] and children.[11] Direct instillation of oxybutynin into the bladder has also been tried. In one study[12] that included patients aged 1 to 34 years, 21 out of 32 patients became totally continent using an intravesical dose of 300 micrograms/kg daily, given in 3 divided doses. A further 7 patients became continent with doses titrated up to a maximum of 900 micrograms/kg daily, but another 4 remained incontinent. Other reports[13,14] have used single or multiple doses of 5 mg, often prepared by dispersing a crushed 5-mg tablet in 30 mL of distilled water or sodium chloride 0.9%.

1. Riva D, Casolati E. Oxybutynin chloride in the treatment of female idiopathic bladder instability: results from double blind treatment. *Clin Exp Obstet Gynecol* 1984; **11:** 37–42.
2. Moore KH, *et al.* Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. *Br J Urol* 1990; **66:** 479–85.
3. Tapp AJS, *et al.* The treatment of detrusor instability in post-menopausal women with oxybutynin chloride: a double blind placebo controlled study. *Br J Obstet Gynaecol* 1990; **97:** 521–6.
4. Siddiqui MA, *et al.* Oxybutynin extended-release: a review of its use in the management of overactive bladder. *Drugs* 2004; **64:** 885–912.
5. Davila GW, *et al.* A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol (Baltimore)* 2001; **166:** 140–5.
6. Dmochowski RR, *et al.* Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol (Baltimore)* 2002; **168:** 580–6.
7. Dmochowski RR, *et al.* Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003; **62:** 237–42.
8. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)
9. O'Leary M, *et al.* Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; **26:** 159–62.
10. Bennett N, *et al.* Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol (Baltimore)* 2004; **171:** 749–51.
11. Franco I, *et al.* Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. *J Urol (Baltimore)* 2005; **173:** 221–5.
12. Haferkamp A, *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord* 2000; **38:** 250–4.
13. Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. *Spinal Cord* 1996; **34:** 284–7.
14. Lose G, Nørgaard JP. Intravesical oxybutynin for treating incontinence resulting from an overactive detrusor. *BJU Int* 2001; **87:** 767–73.

Preparations

BP 2008: Oxybutynin Tablets;
USP 31: Oxybutynin Chloride Extended-Release Tablets; Oxybutynin Chloride Syrup; Oxybutynin Chloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Continex†; Delak; Ditropan; Oxi-Q; Oxitina; Oxyurin; Retebem; Retemicon; Soxsup; Urequin; ***Austral.:*** Ditropan; Oxytrol; ***Austria:*** Cystrin; Detrusan; Ditropan; Lyrinel; ***Belg.:*** Ditropan; Driptane†; ***Braz.:*** Frenurin†; Incontinol; Retemic; ***Canad.:*** Ditropan; Nu-Oxybutyn; Oxybutyn†; Oxytrol; ***Chile:*** Odranal; Oxiburin†; Urazol; Uricont; ***Cz.:*** Cystrin†; Ditropan; Driptane†; Kentera; Uroxal; ***Denm.:*** Kentera; ***Fin.:*** Cystrin; Ditropan; Kentera; Oksibutin†; Spasmoxyl†; ***Fr.:*** Ditropan; Driptane; Zatur†; ***Ger.:*** Cystonorm†; Dridase; Lyrinel; Oxyb; Oxybase†; Oxybugamma; Oxybutin; Oxybuton; Oxymedin; Ryol; Spasyt; ***Gr.:*** Ditropan; Kentera; Lyrinel; Oxybase; ***Hong Kong:*** Ditropan†; ***Hung.:*** Ditropan; Uroxal; ***India:*** Oxyspas; ***Irl.:*** Cystrin; Ditropan; Kentera; Lyrinel XL; Renamel†; ***Israel:*** Novitropan; ***Ital.:*** Ditropan; ***Malaysia:*** Ditropan†; ***Mex.:*** Inprax; Lyrinel; Nefryl; Tavor; ***Neth.:*** Cystrin†; Dridase; Kentera; ***Norw.:*** Kentera; ***Philipp.:*** Driptane; ***Pol.:*** Cystrin; Ditropan; Driptane; Uroton; ***Port.:*** Ditropan; Kentera; Lyrinel; ***Rus.:*** Driptane (Дриптан); Novitropan (Новитропан)†; ***S.Afr.:*** Ditropan; Lenditro; Oxyspas†; Urihexal; ***Singapore:*** Ditropan†; Obutin; ***Spain:*** Ditropan; Dresplan; ***Swed.:*** Ditropan; Kentera; Oxybase†; ***Switz.:*** Ditropan; ***Thai.:*** Diutropan; ***Turk.:*** Uropan; ***UK:*** Cystrin; Ditropan; Kentera; Lyrinel XL; ***USA:*** Ditropan; Oxytrol; ***Venez.:*** Reteven.

Papaverine *(BAN)*

Papaveriini; Papaverin; Papaverina; Papaverinum. 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline.

$C_{20}H_{21}NO_4$ = 339.4.
CAS — 58-74-2.
ATC — A03AD01; G04BE02.
ATC Vet — QA03AD01; QG04BE02.

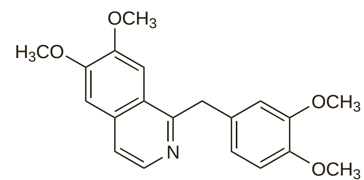

NOTE. Papaverine should not be confused with papaveretum (p.105).

Papaverine Hydrochloride *(BANM)*

Papaveriinihydrokloridi; Papaverina, hidrocloruro de; Papavérine, chlorhydrate de; Papaverin-hidroklorid; Papaverin-hydrochlorid; Papaverinhydroklorid; Papaverini hydrochloridum; Papaverinii Chloridum; Papaverinium Chloride; Papaverino hidrochloridas; Papaweryny chlorowodorek. 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride.

$C_{20}H_{21}NO_4,HCl$ = 375.8.
CAS — 63817-84-5 (papaverine cromesilate); 61-25-6 (papaverine hydrochloride); 39024-96-9 (papaverine monophosadenine); 2053-26-1 (anhydrous papaverine sulfate).
ATC — A03AD01; G04BE02.
ATC Vet — QA03AD01; QG04BE02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Papaverine Hydrochloride). White or almost white crystals or crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.0.

USP 31 (Papaverine Hydrochloride). Odourless white crystals or white, crystalline powder. Soluble 1 in 30 of water and 1 in 120 of alcohol; soluble in chloroform; practically insoluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

Adverse effects of oral papaverine include gastrointestinal disturbance, flushing of the face, headache, malaise, drowsiness, skin rash, sweating, orthostatic hypotension, and dizziness. Jaundice, eosinophilia, and signs of altered liver function may occur, sometimes due to hypersensitivity. In addition high parenteral doses can result in cardiac arrhythmias; intravenous or intramuscular doses should be given slowly. Thrombosis has been reported at the injection site.

Intracavernosal injection can cause dose-related priapism and local fibrosis has been reported after long-term therapy.

Papaverine should be given with caution to patients with reduced gastrointestinal motility. Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease, especially when papaverine is given parenterally. Intravenous dosage is contra-indicated in patients with complete AV block.

Glaucoma. There appeared to be no basis for the manufacturers' recommendation that papaverine should be used with caution in patients with glaucoma.[1] There was no obvious mechanism to support such a warning and only 1 report of an adverse reaction had been received by the FDA. The author had given papaverine intracavernosally to patients with glaucoma and had observed no deterioration.

1. Swartz DA, Todd MW. Intracavernous papaverine and glaucoma. *JAMA* 1990; **264:** 570.

Intracavernosal administration. Systemic adverse effects occurring after intracavernosal injection of papaverine are infrequent but include dizziness and syncope,[1,2] probably related to the hypotensive effects of papaverine; abnormal liver function test results have also occurred.[1-3]

The most serious acute adverse effect is priapism[1,2,4] and patients should be instructed to seek medical help if an erection lasts for more than 4 hours. Detumescence can be effected by aspiration of blood from the corpus or by local injection of an alpha-adrenergic agonist such as adrenaline, metaraminol, or phenylephrine (see Priapism under Alprostadil, p.2184). Other local effects include haematoma, infection, and, on long-term therapy, fibrosis and penile distortion.[1,2]

Dispensing errors have resulted in inadvertent injection of *papaveretum* with potentially fatal consequences.[2,5,6]

1. Krane RJ, *et al.* Impotence. *N Engl J Med* 1989; **321:** 1648–59.
2. Bénard F, Lue TF. Self-administration in the pharmacological treatment of impotence. *Drugs* 1990; **39:** 394–8.
3. Levine SB, *et al.* Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol (Baltimore)* 1989; **141:** 54–7.
4. Virag R. About pharmacologically induced prolonged erection. *Lancet* 1985; **i:** 519–20.
5. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.
6. Gregoire A. Self injection treatment for impotence. *BMJ* 1990; **300:** 537.

Interactions

Levodopa. For the effects of papaverine on levodopa, see p.808.

Pharmacokinetics

The biological half-life of papaverine given orally is reported to be between 1 and 2 hours, but there is wide interindividual variation. It is about 90% bound to plasma proteins.

Papaverine is mainly metabolised in the liver and excreted in the urine, almost entirely as glucuronide-conjugated phenolic metabolites.

The reports of infrequent systemic effects after intracavernosal injection of papaverine indicate that there is some distribution to the systemic circulation from the corpus cavernosus.

Uses and Administration

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to the other opium alkaloids. Papaverine has a direct relaxant effect on smooth muscle which is attributed in part to its ability to inhibit phosphodiesterase. It has been given in the management of cerebral, peripheral, and coronary vascular disorders; it is also given as an antispasmodic for gastrointestinal disorders and coughs. However, there is little evidence to justify its clinical use in these conditions.

Papaverine hydrochloride has been given orally in doses of up to 600 mg daily. Sustained-release preparations have been used. The codecarboxylase derivative, cromesilate, hydrobromide, monophosadenine, nicotinate, sulfate, and teprosilate have also been used. Papaverine hydrochloride has also been given in doses of 30 to 120 mg by intramuscular or slow intravenous injection, repeated every 3 hours as needed (but see Adverse Effects and Precautions, above).

Papaverine hydrochloride has been given by injection into the corpus cavernosum of the penis for the treatment of erectile dysfunction (p.2179). Doses have ranged from 2.5 to 60 mg, but must be initially titrated by the prescriber. Doses up to about 30 mg have been combined with phentolamine.

Preparations

BP 2008: Papaverine Injection;
USP 31: Papaverine Hydrochloride Injection; Papaverine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Mesotina; Ova†; ***Braz.:*** Dipaverina†; ***USA:*** Pavabid†; ***Venez.:*** Atrophena†; Atroveran; Papaveryl; Tropaverin†.

Multi-ingredient: ***Arg.:*** Antipasmol; Antispasmina; Gastranil†; Hepatodirectol; Saltos†; Trixol†; ***Austria:*** Androskat; Asthma 23 D; Myocardon; Ora-Gallin compositum; ***Braz.:*** Analgosedan†; Calmazin†; Codeverin†; Dipirol†; Ductoveran; Espasmalgon†; Espasmocron; Gaba†; Melpaz†; Monotrean; Monotrean B6; Nicopaverina B6†; Nicopaverina†; Pasmalgin†; Plenocedan†; Revulsan†; Sedalene; Sedalin; Spasmotropin; Vagostesyl; ***Chile:*** Belupan†; Buton; Dipatropin; Dolospam; Papatropin†; ***Cz.:*** Contraspan†; Spasmoveralgin Neo†; ***Fr.:*** Acticarbine; ***Hong Kong:*** Bromhexine Compound; Codolax; Codomex Orange†; Codomex Purple†; Codoplex; Enterocin Compound; Methor-Co; Metoplex; ***Hung.:*** Bilagit†; Meristin; Neo-Bilagit; Troparinum; ***India:*** Brovon; ***Indon.:*** Sanmag; Spaslic; Spasmal; Spasminal; ***Israel:*** Patropin; Spasmalgin; ***Ital.:*** Antispasmina Colica; Monotrean†; ***Mex.:*** Acilin; Ayoral†; Taliviform†; ***Neth.:*** Androskat; ***Pol.:*** Biospasmil; Fortestomachicae; Spasticol; Tolargin; ***Port.:*** Antispasmina Colica; Cosmaxil†; ***Spain:*** Sulmetin Papaver; Sulmetin Papaverina†; ***Swed.:*** Spasmofen; ***Switz.:*** Dolopyrine†; Spasmosol; ***UK:*** Brovon; ***USA:*** Tri-Mix; ***Venez.:*** Atrobel; Cloverin†; Neo-Atropan†; Tropifen†.

Propiverine Hydrochloride *(BANM, rINNM)*

BUP-4 (propiverine); Hidrocloruro de propiverina; Propiverin Hidroklorür; Propivérine, Chlorhydrate de; Propiverini Hydrochloridum. 1-Methyl-4-piperidyl diphenylpropoxyacetate hydrochloride.

Пропиверина Гидрохлорид
$C_{23}H_{29}NO_3,HCl = 403.9.$
CAS — 60569-19-9 (propiverine); 54556-98-8 (propiverine hydrochloride).
ATC — G04BD06.
ATC Vet — QG04BD06.

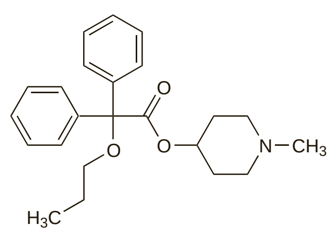

(propiverine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Hypotension and drowsiness may also occur with propiverine. Propiverine is contra-indicated in patients with moderate or severe hepatic impairment (but see below). Liver enzyme values should be monitored in patients receiving long-term therapy. Skeletal retardation has occurred in the offspring of *animals* given high doses of propiverine during pregnancy and therefore its use is not recommended during pregnancy.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Hypotension may occur in patients treated with propiverine and isoniazid. Drowsiness may be enhanced by drugs with CNS-depressant properties.

Pharmacokinetics

Propiverine is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved about 2.3 hours after oral doses. It undergoes extensive first-pass metabolism and the average absolute bioavailability is reported to be about 41%. Plasma concentrations of the principal metabolite, the *N*-oxide, greatly exceed those of the parent compound. Protein binding is about 90% for propiverine and 60% for the *N*-oxide metabolite. Propiverine and its metabolites are excreted in the urine, bile, and faeces. The elimination half-life is about 20 hours.

◊ References.

1. Haustein K-O, Hüller G. On the pharmacokinetics and metabolism of propiverine in man. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 81–90.

Uses and Administration

Propiverine hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1220). It is used for the management of urinary frequency, urgency, and incontinence (p.2180) in neurogenic bladder disorders and in idiopathic detrusor instability. Usual oral doses of propiverine hydrochloride are 15 mg two or three times daily, increased to 4 times daily if required. Some patients may respond to 15 mg once daily. A daily dose of 60 mg should not be exceeded. Propiverine hydrochloride can also be given as a modified-release preparation in a dose of 30 mg once daily.

Administration in hepatic impairment. Although UK licensed product information for propiverine does not recommend its use in patients with moderate or severe hepatic impairment some[1] suggest that on pharmacokinetic grounds it may be given to those with mild to moderate degrees of impairment at recommended doses without increasing the risk of adverse effects.

1. Siepmann M, *et al.* Pharmacokinetics and safety of propiverine in patients with fatty liver disease. *Eur J Clin Pharmacol* 1998; **54:** 767–71.

Urinary incontinence. Although propiverine is licensed in the UK for use in urinary frequency, urgency, and incontinence (see above), guidelines subsequently issued by NICE consider that although it should be an option for urinary frequency in women with overactive bladder syndrome, use in women with overt incontinence is not recommended.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mictonetten; Mictonorm; ***Ger.:*** Mictonetten; Mictonorm; ***Jpn:*** BUP-4; ***Port.:*** Detrunorm†; Mictonorm; ***S.Afr.:*** Detrunorm; ***Thai.:*** Mictonorm; ***UK:*** Detrunorm.

Pygeum Africanum

African Prune; Afrikankirsikkapuunkuori (pygeum africanum bark); Afrikinių slyvų žievė (pygeum africanum bark); Kůra slivoně africké (pygeum africanum bark); Pruni Africanae; Pruni africanae cortex (pygeum africanum bark); Prunier d'Afrique; Prunier d'Afrique, écorce de (pygeum africanum bark).
ATC — G04CX01.
ATC Vet — QG04CX01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Pygeum Africanum Bark; Pygeum Bark BP 2008). The whole or cut, dried bark of the stems and branches of *Prunus africana* (*Pygeum africanum*).

USP 31 (Pygeum). The bark of *Prunus africana* (*Pygeum africanum*) (Rosaceae). It contains not less than 9.0% of extractable matter.

Profile

An extract from the bark of the tree *Prunus africana* (*Pygeum africanum*) is used in the treatment of benign prostatic hyperplasia (p.2178). Like some other phytotherapies for this disorder, it appears to contain various sitosterols. A usual oral dosage is 100 mg daily.

Benign prostatic hyperplasia. Pygeum africanum appears to produce a modest benefit on urological symptoms and measures of urinary flow.

References.

1. Andro M-C, Riffaud J-P. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. *Curr Ther Res* 1995; **56:** 796–817.
2. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996; **78:** 325–36.
3. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.

Preparations

USP 31: Pygeum Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Tadenan; ***Braz.:*** Prostem; ***Cz.:*** Tadenan; ***Fr.:*** Tadenan; ***Gr.:*** Foudaril; Rotamat; Tadenan; ***Hung.:*** Tadenan†; ***Ital.:*** Pigenil; Tadenan; ***Mex.:*** Tadenom; ***Philipp.:*** Tadenan; ***Pol.:*** Poldanen; Tadenan; ***Port.:*** Tadenan†; ***Rus.:*** Tadenan (Таденан); Trianol (Трианол); ***Spain:*** Acubiron; Bidrolar; Pronitol; Tuzanil; ***Switz.:*** Tadenan; ***Thai.:*** Tadenan.

Multi-ingredient: ***Arg.:*** Catiz Plus; Normoprost Compuesto; Normoprost Plus; Ultracal; ***Austria:*** Prostatonin; ***Braz.:*** Prostem Plus; ***Canad.:*** Prostate Ease; Prostease; ***Cz.:*** Prostatonin†; ***Hong Kong:*** Prostease; ***Pol.:*** Neopoldanen; ***Port.:*** Neo Urgenin; ***Spain:*** Neo Urgenin; Prosturol; Tebetane Compuesto; ***Switz.:*** Prostatonin.

Saw Palmetto

American Dwarf Palm; *Brahea serrulata*; PA-109; Palmera de Florida; Sabal; Sabal, fruit de (saw palmetto fruit); *Sabal serrulata*; Sabalis Serrulatae; Sabalis serrulatae fructus (saw palmetto fruit); Sågpalmettofrukt (saw palmetto fruit); Sahapalmunhedelmä (saw palmetto fruit); *Serenoa repens*; *Serenoa serrulatum*; Serenový plod (saw palmetto fruit); Šliaužiančiųjų serenojų vaisiai (saw palmetto fruit).
ATC — G04CX02.
ATC Vet — QG04CX02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US. US* also includes the extract and the powdered form.

Ph. Eur. 6.2 (Saw Palmetto Fruit). The dried, ripe fruit of *Ser-*

enoa repens (*Sabal serrulata*). It contains not less than 11.0% of total fatty acids, calculated with reference to the dried drug. Protect from light.

USP 31 (Saw Palmetto). The partially dried, ripe fruit of *Serenoa repens* (Arecaceae). Store in airtight containers. Protect from light.

Profile

Saw palmetto is the dried fruit of the American dwarf palm tree, *Serenoa repens* (Arecaceae). It contains various steroidal compounds with anti-androgenic and oestrogenic activities, one of which is sitosterol (p.1373). Saw palmetto is used for the treatment of benign prostatic hyperplasia. Preparations of alcoholic or lipophilic extracts have typically been given in oral doses of 160 mg twice daily, or 320 mg once daily.

Adverse effects. ***EFFECTS ON THE LIVER.*** Cholestatic hepatitis occurred in a man who took a herbal preparation containing saw palmetto for 2 weeks to treat nocturia and hesitancy.[1]

1. Hamid S, *et al.* Protracted cholestatic hepatitis after the use of Prostata. *Ann Intern Med* 1997; **127:** 169–70.

Uses. ***BENIGN PROSTATIC HYPERPLASIA.*** A lipid hexane extract of saw palmetto has been shown to be generally superior to placebo,[1,2] and of similar efficacy to finasteride[3] in the treatment of benign prostatic hyperplasia (p.2178). A systematic review of randomised studies of various saw palmetto extracts concluded that they improve urological symptoms and flow measures.[4] However, a more recent double-blind study[5] concluded that treatment for one year was not superior to placebo for improving urinary symptoms and objective measures.

1. Champault G, *et al.* A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; **18:** 461.
2. Plosker GL, Brogden RN. Serenoa repens (Permixon): a review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging* 1996; **9:** 379–95.
3. Carraro J-C, *et al.* Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate* 1996; **29:** 231–40.
4. Wilt T, *et al.* Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 29/11/05).
5. Bent S, *et al.* Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; **354:** 557–66.

Preparations

USP 31: Saw Palmetto Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Beltrax Uno; Herbaccion Prostatico†; Permicaps; Permixon; Sereprostat†; ***Austral.:*** Bioglan Pro-Guard; Prosta†; ***Austria:*** Permixon; Prosta-Urgenin; ***Belg.:*** Prosta-Urgenin; Prostaserene; ***Braz.:*** Permixon†; Prostalium†; Prostat; Prostatal; Renopen; ***Chile:*** Prostafort; ***Cz.:*** Capistan; Prosta-Urgenin; Prostakan Mono; Prostamol Uno; Spalda Sabal; ***Fr.:*** Permixon; ***Ger.:*** Azuprostat Sabal†; Eviprostat-S; Hyperprost Uno; Normurol†; Planturol†; Prosta Urgenin Uno; Prostagutt mono; Prostagutt uno; Prostaplant†; Prostess; Remiprostan uno; Sabacur uno; Sabal; Sabal uno; Sabalvit; Sabonal Uno†; Sita; Steiprostat; Strogen; Talso; ***Gr.:*** Libeprosta; Urisedon†; ***Hung.:*** Prostakan†; Prostamol Uno; Saballo; Strogen Uno; ***Indon.:*** Lanaprost; Prostakur; ***Israel:*** Permixon; ***Ital.:*** Biosern†; Permixon; Prosteren; Rilaprost; Saba; Serpens; ***Mex.:*** Permixon; Prostasan; Prostex; Urogutt; ***Pol.:*** Bioprost; Fitoprost; Permixon; Prostamol Uno; Prostaplant; Sterko; ***Port.:*** Permixon; Prostiva†; Sereprosta; ***Rus.:*** Permixon (Пермиксон); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); ***Singapore:*** Permixon; ***Spain:*** Permixon; Sereprostat; ***Switz.:*** Permixon; Prosta-Urgenine; ProstaMed; Prostasan; SabCaps; ***Thai.:*** Permixon; Urogutt; ***UK:*** Prostasan; Sabalin; ***Venez.:*** Permixon†.

Multi-ingredient: ***Arg.:*** Anastim con RTH; Argeal; Catiz Plus; Keracnyl; Normoprost Plus; PR21; Sabal; Ultracal; ***Austral.:*** Bioglan Mens Super Soy/Clover; Extralife Flow-Care; Lifechange Mens Complex with Saw Palmetto†; Serenoa Complex†; Urapro†; Urgenin†; Urinase†; ***Austria:*** Prostagutt; Spasmo-Urgenin; Urgenin; ***Belg.:*** Urgenin; ***Canad.:*** Damiana-Sarsaparilla Formula†; Prostate Ease; Prostease; ProstGard†; ***Cz.:*** Prostakan Forte; ***Fr.:*** Argeal; Kelual DS; Keracnyl; Sabal; ***Ger.:*** Cefasabal; Granu Fink Prosta; Nephroselect M; Prostagutt forte; ***Hong Kong:*** Palmetto Plus†; Phyto-Ease; Prostease; Sawmetto Vivo-Livo†; Urgenin; ***Indon.:*** Instink; Maxirex; Menolia; Reximax; Soprost; ***Israel:*** Urgenin; ***Ital.:*** Biothymus M Urto; Pluvio; Prostaplant; ***Malaysia:*** Prostakan†; Total Man†; ***Mex.:*** Prosgutt; ***Pol.:*** Naturapia Prostata; Penigra; ***Port.:*** Efluvium Anti-caspa; Efluvium Anti-seborreico; Neo Urgenin; Spasmo-Urgenin†; ***Rus.:*** Prostagutt Forte (Простагут Форте); ***S.Afr.:*** Spasmo-Urgenin†; ***Singapore:*** Palmetto Plus; ***Spain:*** Neo Urgenin; Spasmo-Urgenin; Urgenin; ***Switz.:*** Granu Fink Prosta; Phytomed Prosta†; Prosta-Caps Chassot N; Prostagutt-F; ***Thai.:*** Spasmo-Urgenin; ***UK:*** Antiglan; Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Regina Royal Concorde; Strength; ***Venez.:*** Sabal.

Sildenafil Citrate *(BANM, USAN, rINNM)*

Citrato de sildenafilo; Sildénafil, citrate de; Sildenafil Sitrat; Sildenafili citras; UK-92480-10. 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one citrate; 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazone citrate.

Сильденафила Цитрат

$C_{22}H_{30}N_6O_4S,C_6H_8O_7 = 666.7.$

CAS — 139755-83-2 (sildenafil); 171599-83-0 (sildenafil citrate).

ATC — G04BE03.

ATC Vet — QG04BE03.

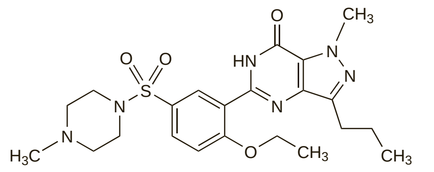

(sildenafil)

Stability. Sildenafil citrate tablets were ground to a powder and combined with a 1:1 mixture of methylcellulose 1% and simple syrup (USNF), or with a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (both *Paddock, USA*), to a nominal concentration of 2.5 mg/mL sildenafil citrate in each suspension.[1] Both suspensions were found to be chemically and physically stable for 91 days in plastic bottles, at both 4° and 25°.

1. Nahata MC, *et al.* Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. *Am J Health-Syst Pharm* 2006; **63:** 254–7.

Adverse Effects

Adverse effects most commonly reported with sildenafil are headache, flushing, and dyspepsia. Also common are visual disturbances such as blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, pain and redness of the eyes. Retinal haemorrhage has occurred, and non-arteritic anterior ischaemic optic neuropathy (NAION) causing permanent loss of vision has been reported rarely. Other common adverse effects include dizziness, insomnia, anxiety, vertigo, epistaxis, nasal congestion, pyrexia, and gastrointestinal disturbances such as diarrhoea and vomiting. Priapism can occur.

Other adverse effects include skin rashes, erythema, alopecia, limb and/or back pain, myalgia, facial oedema, fluid retention, paraesthesia, and urinary-tract infection. Dyspnoea, cough, rhinitis, sinusitis, bronchitis, and cellulitis can occur. Sudden decrease or loss of hearing has been reported. Other reported effects include anaemia, leucopenia, gynaecomastia, urinary frequency or incontinence, haematuria, and seizures.

Cerebrovascular haemorrhage and transient ischaemic attacks have occurred. There have also been reports of palpitations, syncope, hypertension, hypotension, and serious cardiovascular events including myocardial infarction, arrhythmias, tachycardia, unstable angina, and sudden cardiac death.

◊ Reviews.

1. Vitezic D. A risk-benefit assessment of sildenafil in the treatment of erectile dysfunction. *Drug Safety* 2001; **24:** 255–65.
2. Padma-nathan H, *et al.* A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; **60** (suppl 2): 67–90.

Convulsions. A report[1] of 2 patients who had a first tonic-clonic seizure shortly after taking sildenafil.

1. Gilad R, *et al.* Tonic-clonic seizures in patients taking sildenafil. *BMJ* 2002; **325:** 869.

Effects on the cardiovascular system. The effects of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) on the cardiovascular system,[1,2] and the potential risks of sexual activity in men with cardiovascular disease,[3] have been reviewed.

There has been considerable uncertainty about the potential cardiovascular risk associated with sildenafil treatment. Minor effects associated with vasodilatation, such as headache and flushing are relatively common, but in patients without pre-existing cardiovascular risk factors the risk of serious cardiovascular events associated with the drug appears to be low. However, there have been reports of myocardial infarction in patients who had no apparent risk factors,[4,5] and a consensus document issued by the American College of Cardiology and the American Heart Association (ACC/AHA) has pointed out that patients with erectile dysfunction are mostly over 45 years of age and are more likely to have risk factors predisposing them to cardiovascular disease.[6]

As of November 1998, 130 deaths in US patients taking sildenafil had been reported to the FDA; 3 of these were due to stroke and 77 to some other cardiovascular event.[7] The nature of the relationship between drug and event was considered unclear, but some of these patients were also receiving nitrates, a combination now contra-indicated because of the greatly increased risk of potentially life-threatening hypotension.[6] The Australian Adverse Drug Reactions Advisory Committee[8] stated in June 2002 that it had received 773 reports of adverse reactions associated with the use of sildenafil. There were 20 reports of myocardial infarction, including 4 fatalities; 9 of these 20 patients had pre-existing cardiovascular disease or diabetes or were considered to be at high risk of cardiovascular disease, and 1 patient was taking nitrates. Other cardiovascular effects reported included 26 reports of chest pain and 10 other fatalities (6 sudden unexplained deaths, 2 strokes, and 2 subarachnoid haemorrhages). However, it was pointed out that the timing of these adverse effects in relation to sildenafil ingestion was often not reported and that, since sildenafil is taken in the context of sexual activity and, in some cases, underlying coronary disease, the contribution of sildenafil to cardiac events was difficult to assess.

It is still uncertain whether patients with **pre-existing** cardiovascular disease are at increased risk when taking sildenafil without concomitant nitrates. The ACC/AHA consensus statement noted that the evidence was scanty and suggested that sildenafil could be used, but with caution, in patients with stable *coronary artery disease* provided that nitrates were not taken.[6] A later review[9] and studies using exercise testing[10,11] also concluded that sildenafil appeared to be well tolerated in most patients with chronic stable coronary artery disease. In men with mild to moderate chronic *heart failure*, small studies have found that sildenafil was well tolerated and effective for erectile dysfunction,[12-14] and improved measures of exercise capacity.[12] Analyses[15,16] of combined trial data have examined the effects of sildenafil in men stabilised on antihypertensive treatment (including diuretics, beta blockers, alpha blockers, ACE inhibitors, and calcium-channel blockers) compared with men who did not have *hypertension*. Similar results were found for both groups in terms of sildenafil's efficacy for erectile dysfunction.[16] Also, changes in blood pressure and heart rate after a dose of sildenafil,[15] and the incidence of treatment-related adverse effects that were potentially related to blood pressure decrease,[16] were not significantly different between the groups. Evidence to assess the risk in other cardiovascular disorders is less extensive, although a case report of a patient with hypertrophic *cardiomyopathy* who had cardiovascular adverse effects after a dose of sildenafil suggested that the drug may precipitate an unstable haemodynamic state in this condition.[17]

1. Brindis RG, Kloner RA. Sildenafil in patients with cardiovascular disease. *Am J Cardiol* 2003; **92** (suppl): 26M–36M.
2. Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation* 2004; **110:** 3149–55.
3. Kostis JB, *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005; **96:** 313–21.
4. Feenstra J, *et al.* Acute myocardial infarction associated with sildenafil. *Lancet* 1998; **352:** 957–8.
5. Kekilli M, *et al.* Acute myocardial infarction after sildenafil citrate ingestion. *Ann Pharmacother* 2005; **39:** 1362–4.
6. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. ACC/AHA Expert Consensus Document. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850. Also available at: http://circ.ahajournals.org/cgi/reprint/99/1/168.pdf (accessed 29/11/05)
7. FDA. Postmarketing safety of sildenafil citrate (Viagra): summary of reports of death in Viagra users received from marketing (late March) through mid-November 1998. Available at: http://www.fda.gov/cder/consumerinfo/viagra/safety3.htm (accessed 29/11/05)
8. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
9. Tran D, Howes LG. Cardiovascular safety of sildenafil. *Drug Safety* 2003; **26:** 453–60.
10. Arruda-Olson AM, *et al.* Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA* 2002; **287:** 719–25.
11. Fox KM, *et al.* Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. *Eur Heart J* 2003; **24:** 2206–12.
12. Bocchi EA, *et al.* Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction. *Circulation* 2002; **106:** 1097–1103.
13. Webster LJ, *et al.* Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med* 2004; **164:** 514–20.
14. Katz SD, *et al.* Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; **95:** 36–42.
15. Zusman RM, *et al.* Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* 2000; **18:** 1865–9.
16. Kloner RA, *et al.* Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* 2001; **14:** 70–3.
17. Stauffer J-C, *et al.* Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999; **341:** 700–701.

Effects on the ears. As of October 2007, the US FDA had received a total of 29 postmarketing reports of sudden hearing loss with phosphodiesterase type-5 inhibitors. The problem was sometimes accompanied by tinnitus, vertigo, or dizziness. In most of the cases, the hearing loss involved one ear, and it was either a partial or complete loss of hearing. In about one-third of cases, the loss was temporary. While a causal relationship could not be established, patients should be advised that hearing loss may be related to these drugs, and to seek medical attention if affected.[1]

1. FDA. FDA announces revisions to labels for Cialis, Levitra and Viagra: potential risk of sudden hearing loss with ED drugs to be displayed more prominently (issued 18th October 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html (accessed 18/01/08)

Effects on the eyes. The Australian Adverse Drug Reactions Advisory Committee[1] stated in June 2002 that it had received 65 reports of abnormal vision from a total of 773 adverse reactions associated with use of sildenafil reported over 3 years. A bluish tinge or haze to vision and some increased light sensitivity has been reported by patients taking sildenafil, with the percentage of reports increasing with increasing dose.[2] The visual symptoms usually peak 1 to 2 hours after ingestion and resolve about 3 to 4 hours later. The effects of a single dose of sildenafil 100 mg were studied in 5 healthy subjects.[3] Electroretinogram measurements showed significant changes that correlated well with plasma-sildenafil concentrations, peaking at 1 hour after administration and showing complete recovery at the 6-hour measurements. Inhibition of phosphodiesterase type-6 in rod photoreceptors is the most likely mechanism of sildenafil-associated retinal dysfunction. However, there is as yet no clear evidence of retinal toxic effects or whether repeated dosing with sildenafil causes prolonged or further retinal dysfunction.[2,3] Likewise, it remains to be determined whether recovery of function as plasma-sildenafil concentrations subside also occurs in older patients or those with retinal degenerative disorders such as retinitis pigmentosa.

Other visual disturbances reported in patients taking sildenafil have included temporary loss of vision and increased intra-ocular pressure.[4] A 69-year-old man who had permanent loss of vision in one eye a few hours after taking sildenafil 100 mg was found to have an occlusion in a retinal artery.[5] In another similar case of retinal artery occlusion[6] the patient also had uncontrolled hypertension; the authors suggested that embolisation by a pre-existing arteriosclerotic plaque of the carotid artery resulted from elevated blood pressure and cardiac workload during sexual activity, rather than as a direct adverse effect of sildenafil.

Several cases of persistent blurred vision and visual loss caused by nonarteritic anterior ischaemic optic neuropathy (NAION; vascular insufficiency and ischaemia at the optic nerve head) associated with sildenafil use have been reported.[7-10] Generally, visual defects developed in one eye only within 24 hours of sildenafil ingestion, although many of these men had taken doses of sildenafil on past occasions without adverse effect. A small number of cases have also been reported for tadalafil[10-13] and vardenafil.[10] However, many of these men had underlying anatomic or vascular risk factors for NAION, including low cup to disc ratio (crowded disc), age over 50, diabetes, hypertension, ischaemic heart disease, hyperlipidaemia, and smoking. As of May 2005 the FDA had concluded that it was not possible to determine whether NAION was directly related to the use of phosphodiesterase type-5 inhibitors, the patients' underlying vascular risk factors or anatomical defects, a combination of these factors, or other factors.[10]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
2. Marmor MF. Sildenafil (Viagra) and ophthalmology. *Arch Ophthalmol* 1999; **117:** 518–19.
3. Vobig MA, *et al.* Retinal side-effects of sildenafil. *Lancet* 1999; **353:** 375.
4. Committee on Safety of Medicines/Medicines Control Agency. Sildenafil (Viagra). *Current Problems* 1999; **25:** 16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 02/09/08)
5. Tripathi A, O'Donnell N. Branch retinal artery occlusion; another complication of sildenafil. *Br J Ophthalmol* 2000; **84:** 934–5.
6. Bertolucci A, *et al.* Hemi-retinal artery occlusion associated with sexual activity and sildenafil citrate (Viagra). *Acta Ophthalmol Scand* 2003; **81:** 198–200.
7. Boshier A, *et al.* A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; **40:** 422–3.
8. Pomeranz HD, *et al.* Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002; **109:** 584–7.
9. Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. *J Neuroophthalmol* 2005; **25:** 9–13.
10. FDA. Alert 07/2005: Sildenafil (marketed as Viagra). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/sildenafilHCP.pdf (accessed 28/07/05)
11. Peter NM, *et al.* Tadalafil-associated anterior ischaemic optic neuropathy. *Eye* 2005; **19:** 715–17.
12. Escaravage GK, *et al.* Tadalafil associated with anterior ischemic optic neuropathy. *Arch Ophthalmol* 2005; **123:** 399–400.
13. Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. *Arch Ophthalmol* 2005; **123:** 400–401.

Effects on mental function. There have been a few cases reported[1-3] of transient global amnesia after the use of sildenafil or tadalafil. Between January 1998 and February 2001, the FDA had received 35 reports of amnesia in which sildenafil was listed as the primary causal suspect.[4]

1. Gandolfo C, *et al.* Sildenafil and transient global amnesia. *Neurol Sci* 2003; **24:** 145–6.
2. Savitz SA, Caplan LR. Transient global amnesia after sildenafil (Viagra) use. *Neurology* 2002; **59:** 778.
3. Schiefer J, Sparing R. Transient global amnesia after intake of tadalafil, a PDE-5 inhibitor: a possible association? *Int J Impot Res* 2005; **17:** 383–4.
4. Milman HA, Arnold SB. Neurologic, psychological, and aggressive disturbances with sildenafil. *Ann Pharmacother* 2002; **36:** 1129–34.

Precautions

Caution is required in patients with hepatic or severe renal impairment, and dosage reduction of sildenafil may be necessary. Care is also needed in patients with anatomical deformation of the penis or haematological disorders that may predispose them to priapism. In the event of prolonged erection (for more than 4 hours), patients should seek medical assistance, as penile tissue damage and permanent loss of potency can occur. Patients are also advised to stop taking sildenafil and seek medical advice in cases of sudden visual or hearing loss. Sildenafil should not be given to those with loss of vision in one eye caused by non-arteritic anterior or ischaemic optic neuropathy (NAION), regardless of whether this was in connection with previous phosphodiesterase type-5 inhibitors or not. Patients who experience dizziness or visual disturbances should not drive or operate hazardous machinery.

The safety of sildenafil is uncertain in patients with severe hepatic impairment, bleeding disorders, active peptic ulceration, hypotension, hypertension, a recent history of stroke, myocardial infarction, or life-threatening arrhythmia, unstable angina, heart failure, or retinal disorders such as retinitis pigmentosa (a minority of whom have genetic disorders of retinal phosphodiesterases). Licensed product information advises that it should not be used in these groups.

Cardiovascular disease. For mention of a consensus statement on the use of sildenafil in patients with cardiovascular disease, see above.

Interactions

Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. Sildenafil may also enhance the hypotensive effect of nicorandil and use of the two drugs together should be avoided. Symptomatic hypotension may also occur when phosphodiesterase type-5 inhibitors are given with alpha blockers. Generally, the patient should be stabilised on alpha blocker therapy before the phosphodiesterase type-5 inhibitor is started at a low dose and adjusted according to response. Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as cimetidine, delavirdine, erythromycin, itraconazole, and ketoconazole, may reduce the clearance of phosphodiesterase type-5 inhibitors, necessitating a reduction in dosage. Plasma concentrations of phosphodiesterase type-5 inhibitors are significantly increased by HIV-protease inhibitors, and particularly so by ritonavir-boosted regimens. Such combinations should not be given unless absolutely essential. Grapefruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitors as it may increase their plasma concentrations. Inducers of CYP3A4, such as rifampicin, are likely to decrease plasma concentrations of phosphodiesterase type-5 inhibitors. Bosentan also reduces exposure to sildenafil.

Specific dosage recommendations have been made for the use of phosphodiesterase type-5 inhibitors with many of these drugs; see Uses and Administration under Sildenafil (below), Tadalafil (p.2196), and Vardenafil (p.2199).

Antivirals. Rises in sildenafil concentrations after use of *saquinavir* or *ritonavir* were consistent[1] with inhibition of metabolism mediated by the cytochrome P450 isoenzyme CYP3A4. The larger increases seen with ritonavir may be due to its additional inhibition of the isoenzyme CYP2C9. Fatal myocardial infarction has been reported[2] in a 47-year-old patient who took sildenafil 25 mg with ritonavir and saquinavir. In a study[3] of 6 HIV-positive men being treated with triple antiretroviral therapy that included *indinavir*, plasma concentrations of sildenafil were found to be significantly increased compared with historical controls.

1. Muirhead GJ, *et al.* Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Pharmacol* 2000; **50:** 99–107.
2. Hall MCS, Ahmad S. Interaction between sildenafil and HIV-1 combination therapy. *Lancet* 1999; **353:** 2071–2.
3. Merry C, *et al.* Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 1999; **13:** F101–F107.

Cardiovascular drugs. For the effects of sildenafil in men stabilised on *antihypertensives* in general, see Effects on the Cardiovascular System, above. For mention of a possible interaction between sildenafil and *verapamil*, see Immunosuppressants, below.

The plasma concentration of sildenafil was reduced by *bosentan* in a study[1] of 10 patients with pulmonary hypertension, probably by induction of the cytochrome P450 isoenzyme CYP3A4, which would increase the metabolism of sildenafil. The use of bosentan with sildenafil in pulmonary hypertension has been reported (see below) and this potential interaction should be taken into account.

1. Paul GA, *et al.* Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* 2005; **60:** 107–12.

Dihydrocodeine. The use of dihydrocodeine with sildenafil was associated with priapism in 2 men who had previously been treated successfully with sildenafil.[1] The first patient had two prolonged erections, lasting 4 and 5 hours, and the effect did not recur when the dihydrocodeine was stopped. The second patient had priapism on 3 occasions in the first week of dihydrocodeine treatment, but not in the subsequent 2 weeks despite continuing both drugs.

1. Goldmeier D, Lamba H. Prolonged erections produced by dihydrocodeine and sildenafil. *BMJ* 2002; **324:** 1555.

Food. *Grapefruit juice* has been shown to increase bioavailability but delay absorption of sildenafil in healthy subjects.[1]

1. Jetter A, *et al.* Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* 2002; **71:** 21–9.

Immunosuppressants. Studies in men with erectile dysfunction who were receiving *tacrolimus* after kidney transplantation found that sildenafil had no effect on tacrolimus pharmacokinetics.[1,2] However, the pharmacokinetic profile of sildenafil differed from that reported in healthy subjects; the maximal plasma concentration was higher, the area under the concentration-time curve was increased, and the elimination half-life was prolonged.[1] Reductions in blood pressure were also found when sildenafil was given, although this may have been due to an interaction with *verapamil*. The authors suggested that an initial dose of 25 mg sildenafil should be used, and that on the days of sildenafil use the doses of antihypertensive drugs may need to be adjusted according to blood pressure response.[1,2]

1. Christ B, *et al.* Interactions of sildenafil and tacrolimus in men with erectile dysfunction after kidney transplantation. *Urology* 2001; **58:** 589–93.
2. Christ B, *et al.* Investigation on interaction between tacrolimus and sildenafil in kidney-transplanted patients with erectile dysfunction. *Int J Clin Pharmacol Ther* 2004; **42:** 149–56.

Nitrates. Giving sildenafil 50 mg to patients receiving *isosorbide mononitrate*, or sublingual *glyceryl trinitrate* given 1 hour after sildenafil, resulted in substantially greater decreases in blood pressure than when the nitrate was given alone in 2 crossover studies in patients with angina.[1] Treatment-related adverse effects were reported in 8 of 16 patients who received sildenafil with isosorbide mononitrate and 3 of 15 who took sildenafil with glyceryl trinitrate. The authors confirmed that sildenafil should not be taken with nitrates.

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.

Pharmacokinetics

Sildenafil is rapidly absorbed after an oral dose, with a bioavailability of about 40%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when sildenafil is given with food.

Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 (the major route) and CYP2C9. The major metabolite, *N*-desmethylsildenafil (UK-103320) also has some activity. The terminal half-lives of sildenafil and the *N*-desmethyl metabolite are about 4 hours.

Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

◊ References.

1. Nichols DJ, *et al.* Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 5S–12S.
2. Muirhead GJ, *et al.* The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 21S–30S.
3. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.

Uses and Administration

Sildenafil is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension. It is given orally as the citrate although doses are expressed in terms of the base; 14 mg of sildenafil citrate is equivalent to about 10 mg of sildenafil.

In **erectile dysfunction** the usual dose is equivalent to sildenafil 50 mg about one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 100 mg, and sildenafil should not be taken more than once in 24 hours.

- An initial dose of 25 mg has been suggested in the USA for patients over 65 years of age, though such initial reductions are not considered necessary in the UK.
- An initial dose of no more than 25 mg daily is advised in patients taking sildenafil with inhibitors of cytochrome P450 isoenzyme CYP3A4; the dose should not exceed 25 mg every 48 hours if given with ritonavir-boosted HIV-protease inhibitors, although such a combination is best avoided entirely (see Interactions, above).
- In patients stabilised on alpha blocker therapy, an initial dose of sildenafil 25 mg should be considered.

To improve exercise ability in **pulmonary arterial hypertension**, sildenafil is given orally in a dose of 20 mg three times daily. The dose may need adjustment to account for drug interactions (see above) although licensed product information suggests that in these patients no adjustment is required when sildenafil is given with erythromycin or saquinavir. It also suggests that no adjustment is generally needed for pulmonary hypertension patients with renal or hepatic impairment, although patients with severe hepatic impairment (Child-Pugh category C) have not been studied. Although not licensed in the UK for children, the *BNFC* allows for a dose in neonates and children up to 18 years of age, of 250 to 500 micrograms/kg given orally every 4 to 8 hours, adjusted according to response up to a maximum of 2 mg/kg every 4 hours. Treatment should be withdrawn gradually in neonates.

For doses in hepatic and renal impairment, see below.

Administration in hepatic impairment. Sildenafil clearance is reduced in patients with hepatic impairment. Safety has not been established in patients with severe hepatic impairment (Child-Pugh class C) and its use is contra-indicated in these patients for this reason.

Licensed product information for patients with **erectile dysfunction** recommends an initial dose of 25 mg in patients with hepatic impairment.

Licensed product information for patients with **pulmonary arterial hypertension** states that initial dose adjustments are not needed for patients with mild or moderate hepatic impairment (Child-Pugh class A or B); in the UK, it is recommended that a reduction to 20 mg twice daily should be considered if therapy is not well tolerated.

Administration in renal impairment. Sildenafil clearance is reduced in patients with severe renal impairment.

Licensed product information for patients with **erectile dysfunction** recommends that in these patients, an initial dose of 25 mg should be considered. In the UK it is stated that the dose may be increased to 50 or 100 mg, if needed and tolerated.

Licensed product information for patients with **pulmonary arterial hypertension** states that no dose adjustments are required for patients with renal impairment, including those with severe renal impairment (creatinine clearance less than 30 mL/minute). However, in the UK, consideration of a reduction to 20 mg twice daily is suggested if therapy is not well tolerated.

Erectile dysfunction. Sildenafil, an inhibitor of phosphodiesterase type-5, is used as an oral therapy for erectile dysfunction (p.2179). It is effective in erectile dysfunction of psychogenic causes and organic causes such as diabetes mellitus, spinal-cord injury, and prostatectomy.

References.

1. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999; **57:** 967–89.
2. Montorsi F, *et al.* Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. *Urology* 1999; **53:** 1011–18.
3. Rendell MS, *et al.* Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. *JAMA* 1999; **281:** 421–6.
4. Kedia S, *et al.* Treatment of erectile dysfunction with sildenafil citrate (Viagra) after radiation therapy for prostate cancer. *Urology* 1999; **54:** 308–12.
5. Zippe CD, *et al.* Role of Viagra after radical prostatectomy. *Urology* 2000; **55:** 241–5.
6. Fink HA, *et al.* Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2002; **162:** 1349–60.
7. Fedele D, *et al.* Experience with sildenafil in diabetes. *Diabetes Nutr Metab* 2002; **15:** 49–52.
8. Derry F, *et al.* Efficacy and safety of sildenafil citrate (Viagra) in men with erectile dysfunction and spinal cord injury: a review. *Urology* 2002; **60** (suppl): 49–57.
9. Raina R, *et al.* Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. *Urology* 2003; **62:** 110–15.
10. Carson CC. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. *Curr Urol Rep* 2003; **4:** 488–96.
11. Setter SM, *et al.* Phosphodiesterase 5 inhibitors for erectile dysfunction. *Ann Pharmacother* 2005; **39:** 1286–95.
12. Shields KM, Hrometz SL. Use of sildenafil for female sexual dysfunction. *Ann Pharmacother* 2006; **40:** 931–4.

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p.1168) may respond to sildenafil. Small studies have shown some promising results.[1-3]

1. Ghofrani HA, *et al.* Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 2004; **141:** 169–77.
2. Richalet JP, *et al.* Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; **171:** 275–81.
3. Ricart A, *et al.* Effects of sildenafil on the human response to acute hypoxia and exercise. *High Alt Med Biol* 2005; **6:** 43–9.

Oesophageal motility disorders. Preliminary studies[1-3] have investigated the use of sildenafil in patients with oesophageal motility disorders (p.1702) such as achalasia or nutcracker oesophagus. Although some benefit has been reported, further studies are needed.

1. Bortolotti M, *et al.* Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. *Gastroenterology* 2000; **118:** 253–7.
2. Eherer AJ, *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 2002; **50:** 758–64.
3. Lee JI, *et al.* The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol Motil* 2003; **15:** 617–23.

Premature ejaculation. Early reports have suggested that sildenafil may be effective in the management of premature ejaculation (p.2181) and the rationale for such use has been reviewed.[1]

1. Abdel-Hamid IA. Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. *Drugs* 2004; **64:** 13–26.

Priapism. Sildenafil has been reported to be effective in the treatment of priapism in 3 patients with sickle-cell disease.[1] In 2 of these patients, sildenafil was also successful in preventing further episodes of priapism when it was taken at the onset of symptoms.

1. Bialecki ES. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med* 2002; **113:** 252.

Pulmonary hypertension. Oral sildenafil has produced beneficial responses in patients with pulmonary arterial hypertension (p.1179) and may have a role, particularly in patients who fail to respond to other therapies. It has been given either alone[1-7] or with other treatments such as inhaled nitric oxide,[6] inhaled iloprost,[1] intravenous epoprostenol,[8,9] or oral beraprost.[10] Sildenafil has also been added to bosentan therapy, with some benefit, in a small number of patients.[11] For a report on the pharmacokinetic interaction of these 2 drugs see Cardiovascular Drugs, above. The results of short-term and long-term studies of sildenafil have been reviewed.[12,13] In a study[14] using single doses of phosphodiesterase type-5 inhibitors, it was found that sildenafil and tadalafil had greater selectivity for the pulmonary circulation than vardenafil, and that arterial oxygenation was improved by sildenafil only. In a pivotal study,[7] sildenafil improved exercise capacity and haemodynamics in patients. Sildenafil was given at 20, 40, or 80 mg orally three times daily. While there was no evidence of a dose-response relationship in the primary end-point of exercise capacity, there was a linear trend in the response in haemodynamic measures. In an extension study, all patients were treated with 80 mg orally three times daily if tolerated. Some have questioned whether the licensed dose of 20 mg three times daily is sufficient,[15] especially if patients are given bosentan at the same time, leading the authors of the original study to suggest that this may be used as an initial dose, with an increase to 40 or 80 mg three times daily in order to achieve or maintain favourable effects.[16]

Sildenafil has also been studied for paediatric pulmonary hypertension. Some consider that it may have a role in persistent pulmonary hypertension in neonates,[17,18] as well as in those with pulmonary arterial hypertension associated with congenital heart disease, or secondary to lung disease, or in postoperative pulmonary hypertension and in neonates who are difficult to wean from inhaled nitric oxide.[18] However, further controlled studies are needed.[17,18] Nevertheless, although unlicensed in the UK, the *BNFC* suggests that sildenafil may be given orally to neonates and children for pulmonary hypertension after cardiac surgery, weaning from nitric oxide, idiopathic pulmonary arterial hypertension, and persistent pulmonary hypertension of the newborn (see above for details of doses).

Sildenafil has also been reported to be of benefit in high-altitude pulmonary hypertension.[19]

1. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
2. Ghofrani HA, *et al.* Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet* 2002; **360:** 895–900.
3. Watanabe H, *et al.* Sildenafil for primary and secondary pulmonary hypertension. *Clin Pharmacol Ther* 2002; **71:** 398–402.
4. Carroll WD, Dhillon R. Sildenafil as a treatment for pulmonary hypertension. *Arch Dis Child* 2003; **88:** 827–8.
5. Sastry BKS, *et al.* Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol* 2004; **43:** 1149–53.
6. Michelakis E, *et al.* Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation* 2002; **105:** 2398–2403.
7. Galiè N, *et al.* Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 2148–57.
8. Bhatia S, *et al.* Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003; **78:** 1207–13.
9. Stiebellehner L, *et al.* Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003; **123:** 1293–5.
10. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.
11. Hoeper MM, *et al.* Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; **24:** 1007–10.
12. Lee AJ, *et al.* Sildenafil for pulmonary hypertension. *Ann Pharmacother* 2005; **39:** 869–84.
13. Croom KF, Curran, MP. Sildenafil: a review of its use in pulmonary arterial hypertension. *Drugs* 2008; **68:** 383–97.
14. Ghofrani HA, *et al.* Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol* 2004; **44:** 1488–96.
15. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1091.
16. Galiè N, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1092–3.
17. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 18/01/08).
18. Leibovitch L, *et al.* Therapeutic applications of sildenafil citrate in the management of paediatric pulmonary hypertension. *Drugs* 2007; **67:** 57–73.
19. Aldashev AA, *et al.* Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax* 2005; **60:** 683–7.

Raynaud's syndrome. Sildenafil has been reported to be of benefit in Raynaud's phenomenon (see Vasospastic Arterial Disorders, p.1188) resistant to vasodilator therapy.[1]

1. Fries R, *et al.* Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112:** 2980–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Anaus; Bifort; Erectol; Expit; Falic; File; Firmel; Incresil; Juvigor; Lorbinafil; Lumix; Magnus; Maxdosa; Maximo; Nexofil; Nitro; Openvas; Permitil; Segurex; Sildefil; Tecnomax; Viagra; Vigor Plus; Vimax; Virilon; Viripotens; Vorst; ***Austral.:*** Revatio; Viagra; ***Austria:*** Viagra; ***Belg.:*** Viagra; ***Braz.:*** Revatio; Viagra; ***Canad.:*** Viagra; ***Chile:*** Alfin; Dirtop; Erosfil; Helpin; Lifter; Novalif; Ripol; Seler; Siafil; Viagra; Vimax; Zilfic; ***Cz.:*** Revatio; Viagra; ***Denm.:*** Viagra; ***Fin.:*** Viagra; ***Fr.:*** Revatio; Viagra; ***Ger.:*** Viagra; ***Gr.:*** Viagra; ***Hong Kong:*** Viagra; ***Hung.:*** Revatio; Viagra; ***India:*** Caverta; Fiagra†; Juan; Penegra; Silagra; Viagra; ***Indon.:*** Viagra; ***Irl.:*** Viagra; ***Israel:*** Viagra; ***Ital.:*** Viagra; ***Jpn:*** Viagra; ***Malaysia:*** Viagra; ***Mex.:*** Apodefil; Viagra; ***Neth.:*** Revatio; Viagra; ***Norw.:*** Viagra; ***NZ:*** Revatio; Viagra; ***Philipp.:*** Andros; Viagra; ***Pol.:*** Viagra; ***Port.:*** Revatio; Viagra; ***Rus.:*** Viagra (Виагра); ***S.Afr.:*** Viagra; ***Singapore:*** Viagra; ***Spain:*** Viagra; ***Swed.:*** Revatio; Viagra; ***Switz.:*** Viagra; ***Thai.:*** Viagra; ***Turk.:*** Sildegra; Viagra; Vigrande; ***UK:*** Revatio; Viagra; ***USA:*** Revatio; Viagra; ***Venez.:*** Duroval; Itaka; Viagra; Viasek; Viasil; Vigrasol; Viosex; Viridil.

Silodosin *(rINN)*

KMD-3213; Silodosina; Silodosine; Silodosinum. (−)-1-(3-Hydroxypropyl)-5-[(2*R*)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]-ethyl}amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide.

Сильодозин

$C_{25}H_{32}F_3N_3O_4$ = 495.5.
CAS — 160970-54-7.

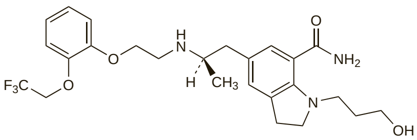

Profile

Silodosin is an $alpha_1$-adrenoceptor blocker (p.1153) that is reported to be selective for the $alpha_{1A}$-adrenoceptor subtype. It is used orally in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Urief.

Solifenacin Succinate *(BANM, USAN, rINNM)*

Solifénacine, Succinate de; Solifenacini Succinas; Succinato de solifenacina; YM-905; YM-67905. (3*R*)-1-Azabicyclo[2.2.2]oct-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate compound with butanedioic acid (1:1).

Солифенацина Сукцинат

$C_{23}H_{26}N_2O_2,C_4H_6O_4$ = 480.6.
CAS — 242478-37-1 (solifenacin); 242478-38-2 (solifenacin succinate).
ATC — G04BD08.
ATC Vet — QG04BD08.

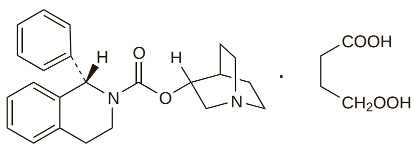

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Solifenacin succinate should be used with caution in patients also receiving inhibitors of the cytochrome P450 isoenzyme CYP3A4 (see Interactions and Uses and Administration, below). It should also be used with caution in hepatic and renal impairment.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Exposure to solifenacin succinate may be increased by drugs that inhibit the cytochrome P450 isoenzyme CYP3A4. Although there is a lack of data, licensed product information also warns of the potential for interaction between solifenacin succinate and substrates or inducers of CYP3A4. Dosage adjustment for solifenacin succinate may be necessary (see Uses and Administration, below).

Pharmacokinetics

After an oral dose, solifenacin succinate is absorbed from the gastrointestinal tract, with peak plasma concentrations reached after 3 to 8 hours and a bioavailability of about 90%. Solifenacin is about 98% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and has a terminal half-life of 45 to 68 hours. Solifenacin is excreted mainly as metabolites in urine and faeces.

◊ References.

1. Kuipers ME, *et al.* Solifenacin demonstrates high absolute bioavailability in healthy men. *Drugs R D* 2004; **5:** 73–81.
2. Smulders RA, *et al.* Pharmacokinetics and safety of solifenacin succinate in healthy young men. *J Clin Pharmacol* 2004; **44:** 1023–33.

Uses and Administration

Solifenacin succinate is a selective M_3 antimuscarinic with actions similar to those of atropine (p.1220). It is used in the treatment of urinary frequency, urgency, and incontinence in detrusor instability (p.2180). Usual doses of solifenacin succinate are 5 mg once daily by mouth, increased to 10 mg once daily if required. Maximum doses of 5 mg once daily are recommended in patients receiving drugs such as ketoconazole or ritonavir that are strong inhibitors of the cytochrome P450 isoenzyme CYP3A4. For doses in hepatic or renal impairment, see below.

◊ References.

1. Chapple CR, *et al.* Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; **93:** 303–10.
2. Cardozo L, *et al.* Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol (Baltimore)* 2004; **172:** 1919–24.
3. Haab F, *et al.* Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005; **47:** 376–84.
4. Chapple CR, *et al.* A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48:** 464–70.
5. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *Eur Urol* 2005; **48:** 483–7.
6. Payne CK. Solifenacin in overactive bladder syndrome. *Drugs* 2006; **66:** 175–90.

Administration in hepatic and renal impairment. Doses of 5 mg of solifenacin succinate once daily by mouth are recommended in patients with moderate hepatic impairment (Child-Pugh category B) or severe renal impairment (creatinine clearance less than 30 mL/minute). It should not be used in patients with severe hepatic impairment (Child-Pugh category C) or in those undergoing haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vesicare; ***Austral.:*** Vesicare; ***Belg.:*** Vesicare; ***Cz.:*** Vesicare; ***Denm.:*** Vesicare; ***Fin.:*** Vesicare; ***Fr.:*** Vesicare; ***Ger.:*** Vesikur; ***Gr.:*** Vesicare; ***Hung.:*** Vesicare; ***Indon.:*** Vesicare; ***Irl.:*** Vesitirim; ***Ital.:*** Vesiker; ***Jpn:*** Vesicare; ***Neth.:*** Flomin; Uriclin; Vesicare; ***Norw.:*** Vesicare; ***NZ:*** Vesicare; ***Pol.:*** Vesicare; ***Port.:*** Flomin; Uriclin; Vesicare; ***Rus.:*** Vesicare (Везикар); ***S.Afr.:*** Vesicare; ***Spain:*** Vesicare; ***Swed.:*** Vesicare; ***UK:*** Vesicare; ***USA:*** Vesicare.

Tadalafil *(BAN, USAN, rINN)*

GF-196960; IC-351; Tadalafiili; Tadalafilo; Tadalafilum. (6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)-phenyl]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione.

Тадалафил

$C_{22}H_{19}N_3O_4$ = 389.4.
CAS — 171596-29-5.
ATC — G04BE08.
ATC Vet — QG04BE08.

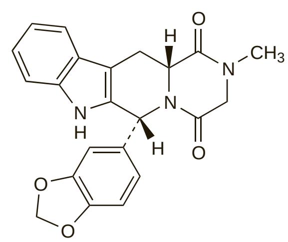

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of tadalafil:
Weekend Pill.

Adverse Effects and Precautions

As for Sildenafil, p.2193. Visual disturbances may occur less frequently with tadalafil than with sildenafil. Dosage reductions may be required in patients with hepatic or renal impairment.

◊ References.

1. Montorsi F, *et al.* Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004; **45:** 339–44.

Effects on the cardiovascular system. References.

1. Kloner RA, *et al.* Cardiovascular effects of tadalafil. *Am J Cardiol* 2003; **92:** 37M–46M.

Interactions

As for Sildenafil, p.2194.

Antifungals. Priapism occurred in a man who took two separate doses of tadalafil 10 mg, at least one month apart, during *itraconazole* treatment.[1] He was able to take sildenafil during itraconazole treatment without adverse effect. See also Uses and Administration, below, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.

1. Galatti L, *et al.* Interaction between tadalafil and itraconazole. *Ann Pharmacother* 2005; **39:** 200.

Nitrates. Phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. An interaction between tadalafil and sublingual *glyceryl trinitrate* was reported to occur when glyceryl trinitrate was given within 24 hours after tadalafil but was no longer detectable at 48 hours.[1] Licensed product information recommends that if nitrate treatment is needed in a life-threatening situation then it should only be given at least 48 hours after the last dose of tadalafil and under close medical supervision.

1. Kloner RA, *et al.* Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; **42:** 1855–60.

Pharmacokinetics

Tadalafil is well absorbed after an oral dose. Peak plasma concentrations are attained within 2 hours; the rate and extent of absorption are not affected by food.

Tadalafil is widely distributed into tissues and is about 94% bound to plasma proteins. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolite, the methylcatechol glucuronide, is inactive. The mean half-life of tadalafil is about 17.5 hours.

Tadalafil is excreted, mainly as metabolites, in the faeces (61% of the dose), and to a lesser extent the urine (36% of the dose). Clearance may be reduced in the elderly and in patients with renal impairment.

◊ References.

1. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.
2. Forgue ST, *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 280–8.
3. Forgue ST, *et al.* Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007; **63:** 24–35.

Uses and Administration

Tadalafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction (p.2179). Tadalafil is given orally in a usual dose of 10 mg at least 30 minutes before sexual intercourse and may be taken with or without food; the dose may be increased to 20 mg, or decreased to 5 mg, if necessary. Efficacy may persist for up to 36 hours after dosing. Tadalafil should not be taken more than once in 24 hours.

In the UK, for those who respond to tadalafil when taken as needed, and anticipate frequent use (defined as at least twice weekly), a regular daily regimen may be considered suitable. In these patients, the recommended dose is 5 mg once daily, taken at about the same time each day. The dose may be decreased to 2.5 mg once daily based on individual tolerability. In the USA, the recommended starting dose of tadalafil for daily use is 2.5 mg, taken at about the same time each day, which may then be increased to 5 mg, based on tolerability and efficacy. Dosage adjustments are not necessary in elderly patients; for recommendations in hepatic or renal impairment, see below.

Although the use of tadalafil with an alpha blocker is not recommended in the UK, the combination may be used in the USA; in patients stabilised on alpha blocker therapy a starting dose of tadalafil 5 mg may be used. In patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole or ritonavir-boosted HIV-protease inhibitors, the dose of tadalafil when used *as needed* should not exceed 10 mg once every 72 hours; when used on a *regular daily basis*, the dose should not exceed 2.5 mg.

◊ References.

1. Brock GB, *et al.* Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol (Baltimore)* 2002; **168:** 1332–6. Correction. *ibid.* 2005; **173:** 664. [dosage error in abstract]
2. Brock GB. Tadalafil: a new agent for erectile dysfunction. *Can J Urol* 2003; **10** (suppl 1): 17–22.
3. Bella AJ, Brock GB. Tadalafil in the treatment of erectile dysfunction. *Curr Urol Rep* 2003; **4:** 472–8.
4. Curran MP, Keating GM. Tadalafil. *Drugs* 2003; **63:** 2203–12. Correction. *ibid.*; 2703.
5. Meuleman EJ. Review of tadalafil in the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2003; **4:** 2049–56.
6. Padma-Nathan H. Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction. *Am J Cardiol* 2003; **92** (suppl 1): 19M–25M.
7. Carson CC, *et al.* The efficacy and safety of tadalafil: an update. *BJU Int* 2004; **93:** 1276–81.
8. Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. *Expert Opin Pharmacother* 2005; **6:** 75–84.

Administration in hepatic impairment. Exposure to tadalafil in patients with mild to moderate hepatic impairment is comparable to healthy subjects when a dose of 10 mg is used. Regular daily dosing has not been evaluated.

Licensed product information states the following:

- mild to moderate hepatic impairment (Child-Pugh Class A or B): the maximum dose is 10 mg; regular daily dosing has not been evaluated
- severe hepatic impairment (Child-Pugh Class C): insufficient data are available; in the UK, caution is advised, and in the USA use in this group is not recommended

Administration in renal impairment. The clearance of tadalafil is reduced in renal impairment.

In the UK, licensed product information recommends the following:

- mild to moderate renal impairment: no dose adjustment
- severe renal impairment: the maximum dose is 10 mg; regular daily dosing is not recommended in these patients

In the USA, the dose recommendations for tadalafil, when used *as needed*, in patients with renal impairment based on creatinine clearance (CC) are:

- mild (CC 51 to 80 mL/minute): no dose adjustment
- moderate (CC 31 to 50 mL/minute): an initial dose of 5 mg not more than once daily, with a maximum dose of 10 mg in 48 hours
- severe (CC less than 30 mL/minute or on haemodialysis): a maximum dose of 5 mg not more than once in every 72 hours

For patients taking tadalafil on a *regular daily basis*:

- mild (CC 51 to 80 mL/minute): no dose adjustment
- moderate (CC 31 to 50 mL/minute): no dose adjustment
- severe (CC less than 30 mL/minute or on haemodialysis): not recommended

High-altitude disorders. Hypoxic pulmonary hypertension associated with high altitude (p.1168) may respond to tadalafil. A small study[1] has shown some promising results in adults with a history of high-altitude pulmonary oedema.

1. Maggiorini M, *et al.* Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med* 2006; **145:** 497–506.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cialis; ***Austral.:*** Cialis; ***Austria:*** Cialis; ***Belg.:*** Cialis; ***Braz.:*** Cialis; ***Canad.:*** Cialis; ***Chile:*** Cialis; ***Cz.:*** Cialis; ***Denm.:*** Cialis; ***Fin.:*** Cialis; ***Fr.:*** Cialis; ***Ger.:*** Cialis; ***Gr.:*** Cialis; ***Hong Kong:*** Cialis; ***Hung.:*** Cialis; ***India:*** Forzest; Sialis†; Tadacip; Zydalis; ***Indon.:*** Cialis; ***Irl.:*** Cialis; ***Israel:*** Cialis; ***Ital.:*** Cialis; ***Malaysia:*** Cialis; ***Mex.:*** Cialis; ***Neth.:*** Cialis; ***Norw.:*** Cialis; ***NZ:*** Cialis; ***Philipp.:*** Cialis; ***Pol.:*** Cialis; ***Port.:*** Cialis; ***Rus.:*** Cialis (Сиалис); ***S.Afr.:*** Cialis; ***Singapore:*** Cialis; ***Spain:*** Cialis; ***Swed.:*** Cialis; ***Switz.:*** Cialis; ***Thai.:*** Cialis; ***UK:*** Cialis; ***USA:*** Cialis; ***Venez.:*** Cialis.

Tamsulosin Hydrochloride

(BANM, USAN, rINNM)

Amsulosin Hydrochloride; Hidrocloruro de tamsulosina; LY-253351; Tamsulosiinihydrokloridi; Tamsulosin Hidroklorür; Tamsulosine, chlorhydrate de; Tamsulosinhydroklorid; Tamsulosini hydrochloridum; YM-617; *R*-(−)-YM-12617; YM-12617-1. (−)-(*R*)-5-(2-{[2-(*o*-Ethoxyphenoxy)ethyl]amino}-propyl)-2-methoxybenzenesulfonamide hydrochloride.

Тамсулозина Гидрохлорид

$C_{20}H_{28}N_2O_5S,HCl = 445.0.$

CAS — 106133-20-4 (tamsulosin); 106463-17-6 (tamsulosin hydrochloride).

ATC — G04CA02.

ATC Vet — QG04CA02.

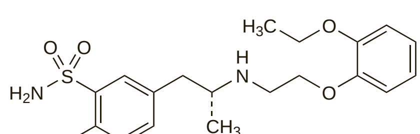

(tamsulosin)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Tamsulosin Hydrochloride). A white or almost white powder. Slightly soluble in water and anhydrous alcohol; freely soluble in formic acid.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375. Because tamsulosin is selective for α_1 receptors in the prostate the vasodilator effects may be less frequent. Tamsulosin may cause ejaculation abnormalities. It should be avoided in severe hepatic impairment.

Incidence of adverse effects. A study[1] using prescription event monitoring data for more than 12 000 patients treated with tamsulosin found that dizziness, headache, malaise, and hypotension were the adverse effects most commonly reported.

1. Mann RD, *et al.* The pharmacovigilance of tamsulosin: event data on 12 484 patients. *BJU Int* 2000; **85:** 446–50.

Surgical procedures. In 2005 the manufacturers[1,2] of tamsulosin warned that a syndrome of flaccidity of the iris, progressive miosis, and potential prolapse (intraoperative floppy iris syndrome; IFIS) had been reported in some patients undergoing cataract surgery who were receiving, or had received, alpha blockers. One group of workers[3] had reported that in one series of 741 patients undergoing cataract surgery, 15 of the 16 who developed IFIS had received tamsulosin. An earlier retrospective study of 511 similar patients by the same workers[3] had found IFIS in 10 of the 16 patients with a history of tamsulosin treatment but no cases in any of the other patients, including in 11 patients who had received other alpha blockers. The US manufacturer[2] stated that although most cases had occurred in patients who had been taking alpha blockers concurrently or up to 2 weeks before surgery the benefit of stopping such therapy before cataract surgery has not been established as a few cases had included patients who discontinued alpha blockers up to 9 months before surgery. The manufacturers of tamsulosin recommend that patients being considered for cataract surgery should be questioned to ascertain whether they are taking the drug.[1,2] A literature review[4] found that other alpha blockers, including alfuzosin, doxazosin, and terazosin, have also been associated with IFIS in this patient group; however, IFIS has been most strongly associated with the use of tamsulosin. In the UK, the MHRA[5] has required the inclusion of a warning in the labelling of all alpha blockers advising patients to inform their cataract surgeon about past and current use of these drugs.

1. Boehringer Ingelheim (Canada). Important safety information on intraoperative floppy iris syndrome (IFIS) (issued 14th October 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/flomax_hpc-cps-eng.pdf (accessed 02/09/08)
2. Boodee HW [Boehringer Ingelheim Pharmaceuticals, Inc (USA)]. Important drug information for physicians (issued November 2005) Available at: http://www.fda.gov/medwatch/safety/2005/Flomax_dearhcp_nov22_PI.pdf (accessed 01/12/05)
3. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg* 2005; **31:** 664–73.
4. Cantrell MA, *et al.* Intraoperative floppy iris syndrome associated with α -adrenergic receptor antagonists. *Ann Pharmacother* 2008; **42:** 558–63.
5. MHRA/CHM. α-1 adrenoceptor antagonists: intraoperative floppy iris syndrome. *Drug Safety Update* 2007: **1** (1): 4–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/ CON2031802 (accessed 17/06/08)

Interactions

As for Prazosin Hydrochloride, p.1376.

Pharmacokinetics

Tamsulosin is absorbed from the gastrointestinal tract and is almost completely bioavailable. The extent and rate of absorption are reduced by food. After oral doses of an immediate-release preparation, peak plasma concentrations occur after about 1 hour. Tamsulosin is about 99% bound to plasma proteins. It is metabolised slowly in the liver primarily by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4; it is excreted mainly in the urine as metabolites and some unchanged drug. The plasma elimination half-life has been reported to be between 4 and 5.5 hours.

Some of the pharmacokinetic values cited above may be altered when tamsulosin is given as a modified-release preparation, the form in which it is usually used; for instance, peak plasma concentrations occur about 6 hours after a dose and the apparent elimination half-life may be 10 to 15 hours.

Renal impairment. Plasma-tamsulosin concentrations were reported to be increased in patients with renal impairment when compared with subjects with normal renal function.[1,2] However, plasma concentrations of unbound, pharmacologically active drug were similar in both groups and it was suggested that the raised total plasma concentrations were due to an increase in plasma protein binding.

1. Koiso K, *et al.* Pharmacokinetics of tamsulosin hydrochloride in patients with renal impairment: effects of α -acid glycoprotein. *J Clin Pharmacol* 1996; **36:** 1029–38.
2. Wolzt M, *et al.* Pharmacokinetics of tamsulosin in subjects with normal and varying degrees of impaired renal function: an open-label single-dose and multiple-dose study. *Eur J Clin Pharmacol* 1998; **54:** 367–73.

Uses and Administration

Tamsulosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376); it is reported to be more selective for the alpha$_{1A}$-adrenoceptor subtype, which accounts for about 70% of the α_1 adrenoceptors in the prostate. It is used in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction.

In benign prostatic hyperplasia, tamsulosin hydrochloride is given orally in a modified-release formulation, in a dose of 400 micrograms once daily. Licensed US product information states that the dose may be increased after 2 to 4 weeks, if necessary, to 800 micrograms once daily.

◊ Reviews.

1. Wilde MI, McTavish D. Tamsulosin: a review of its pharmacological properties and therapeutic potential in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1996; **52:** 883–98.
2. Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann Pharmacother* 2000; **34:** 188–99.
3. Lyseng-Williamson KA, *et al.* Tamsulosin: an update of its role in the management of lower urinary tract symptoms. *Drugs* 2002; **62:** 135–67.
4. Wilt TJ, *et al.* Tamsulosin for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 29/11/05).

Antidepressant-induced genito-urinary disorders. Tamsulosin was used successfully[1] to treat urinary hesitancy observed in 6 male patients receiving reboxetine. Painful ejaculation associated with reboxetine was also treated successfully[2] in 2 men.

1. Demyttenaere K, *et al.* Tamsulosin as an effective treatment for reboxetine-associated urinary hesitancy. *Int Clin Psychopharmacol* 2001; **16:** 353–5.
2. Demyttenaere K, Huygens R. Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. *Eur Neuropsychopharmacol* 2002; **12:** 337–41.

Prostatitis. Alpha$_1$-adrenoceptor blockers are one of a number of classes of drugs that have been tried for symptomatic relief in men with chronic prostatitis (p.2181). In a 6-week multicentre, double-blind placebo-controlled study involving 58 men with moderate to severe chronic prostatitis/chronic pelvic pain syndrome, tamsulosin 400 micrograms daily produced greater symptomatic relief than placebo;[1] the effect was considered clinically significant for men with severe prostatitis. The benefit appeared to take several weeks to develop, and it was considered possible that longer exposure would produce additional benefit.

1. Nickel JC, *et al.* Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol (Baltimore)* 2004; **171:** 1594–7.

Renal calculi. In the conservative management of renal calculi (p.2181) there is increasing interest in the possible use of drug treatment to ease the spontaneous passage of the stone down the ureter. Alpha$_1$-adrenoceptor blockers can decrease smooth muscle spasm in the ureter, reducing obstruction and improving urine flow. In studies[1-5] of patients with uncomplicated lower ureteral stones, tamsulosin has been reported to improve the rate of stone expulsion and expulsion time, and to reduce analgesic requirements. Tamsulosin was generally given orally in a dose of 400 micrograms daily for up to 4 weeks. Comparison groups were treated with various other antispasmodics including benzodiazepines, phloroglucinol, and nifedipine; in most studies patients were also treated with antibacterial prophylaxis, deflazacort, and NSAIDs.

A review[6] found evidence suggesting that adjunctive tamsulosin is safe and effective in enhancing the clearance of renal stones with a larger diameter when used with extracorporeal shock wave lithotripsy. Although evidence regarding ureteral stone clearance is inconclusive, adjunctive tamsulosin has been reported to reduce painful episodes.

1. Červenàkov I, *et al.* Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker–tamsulosin. *Int Urol Nephrol* 2002; **34:** 25–9.
2. Dellabella M, *et al.* Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol (Baltimore)* 2003; **170:** 2202–5.
3. Porpiglia F, *et al.* Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol (Baltimore)* 2004; **172:** 568–71.
4. Yilmaz E, *et al.* The comparison and efficacy of 3 different α1-adrenergic blockers for distal ureteral stones. *J Urol (Baltimore)* 2005; **173:** 2010–12.
5. Dellabella M, *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol (Baltimore)* 2005; **174:** 167–72.
6. Losek RL, Mauro LS. Efficacy of tamsulosin with extracorporeal shock wave lithotripsy for passage of renal and ureteral calculi. *Ann Pharmacother* 2008; **42:** 692–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aclosan; Controlpros; Espontal; Lostam; Omnic; Reduprost; Secotex; Tamsuna; Tansiloprost; ***Austral.:*** Flomax; Flomaxtra; ***Austria:*** Alna; ***Belg.:*** Omic; ***Braz.:*** Contiflo; Omnic; Secotex; Tamsulon; ***Canad.:*** Flomax; ***Chile:*** Eupen; Gotely; Omnic; Prostall; Secotex; Sulix; Vi-Uril; ***Cz.:*** Apo-Tamis; Damurgin; Fokusin; Lannatam; Omnic; Solesmin; Taflosin; Tamipro; Tamsec; Tamurox; Tanyz; Urostad; ***Denm.:*** Omnic; ***Fin.:*** Expros; Omnic; Tamictor; Tamsumin; ***Fr.:*** Josir; Omix; ***Ger.:*** Alna; Omnic; ***Gr.:*** Omnic; Pradif; ***Hong Kong:*** Harnal; ***Hung.:*** Fokusin; Omnic; Provosal; Tamsol; Tamsudil; Tamsugen; Tanyz; Totalprost; Urostad; ***India:*** Urimax; ***Indon.:*** Harnal; ***Irl.:*** Omnex-

el; Omnic†; Omsil; Tamsu; ***Israel:*** Omnic; ***Ital.:*** Omnic; Pradif; ***Jpn:*** Harnal; ***Mex.:*** Asoflon; Secotex; ***Neth.:*** Mapelor; Omnic; ***Norw.:*** Omnic; ***NZ:*** Flomax; Flomaxtra; ***Philipp.:*** Harnal; ***Pol.:*** Bazetham; Fokusin; Omnic; Omsal; Prostamnic; Tamsudil; TamsuLek; Tanyz; Uprox; Urostad; ***Port.:*** Omnic; Pradif; ***Rus.:*** Fokusin (Фокусин); Hyperprost (Гиперпрост); Omnic (Омник); ***S.Afr.:*** Flomax; ***Spain:*** Omnic; Urolosin; ***Switz.:*** Omix; Pradif; ***Thai.:*** Harnal; ***Turk.:*** Flomax; ***UK:*** Bazetham; Contiflo; Flomax†; Flomaxtra; Stronazon; Tabphyn; ***USA:*** Flomax; ***Venez.:*** Secotex; Tamsulon.

Multi-ingredient: ***India:*** Urimax F.

Tolterodine Tartrate *(BANM, USAN, rINNM)*

Kabi-2234 (tolterodine); PNU-200583E; Tartrato de tolterodina; Tolterodin Tartrat; Tolterodine L-Tartrate; Toltérodine, Tartrate de; Tolterodini Tartras. (+)-(*R*)-2-{α-[2-(Diisopropylamino)ethyl]benzyl}-*p*-cresol tartrate.

Тольтеродина Тартрат

$C_{22}H_{31}NO,C_4H_6O_6$ = 475.6.

CAS — 124937-51-5 (tolterodine); 124937-52-6 (tolterodine tartrate).

ATC — G04BD07.

ATC Vet — QG04BD07.

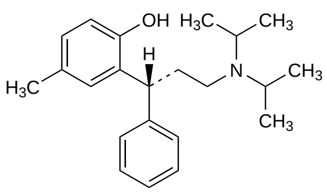

(tolterodine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. For a report of adverse ocular effects of tolterodine, see Effects on the Eyes under Oxybutynin, p.2190. Tolterodine should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that high doses may cause fetal toxicity and it is recommended that tolterodine should be avoided during pregnancy.

Prolongation of the QT interval has occurred in controlled studies using both therapeutic and higher doses of tolterodine, and although changes from baseline did not cross the threshold of concern, the clinical implications are unclear. Licensed product information therefore warns that tolterodine should be used with caution in patients with QT prolongation or relevant risk factors, such as electrolyte disturbances, bradycardia, pre-existing cardiac disease, or the concomitant use of other drugs known to prolong the QT interval. Patients with raised tolterodine concentrations because of drug interactions (see below) would also be at increased risk, particularly poor metabolisers (see Pharmacokinetics, below).

◊ References.

1. Layton D, *et al.* Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Safety* 2001; **24:** 703–13.
2. Garely AD, Burrows L. Benefit-risk assessment of tolterodine in the treatment of overactive bladder in adults. *Drug Safety* 2004; **27:** 1043–57.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

There is a risk of interactions between tolterodine and drugs that inhibit cytochrome P450 isoenzymes CYP2D6 (but see Antidepressants, below), or CYP3A4. For comment on dosage of tolterodine with potent CYP3A4 inhibitors (such as the macrolide antibacterials erythromycin or clarithromycin, or the azole antifungals ketoconazole, itraconazole, or miconazole), see Uses and Administration, below. Tolterodine can prolong the QT interval and should be used with caution in patients receiving other drugs known to have this effect, particularly class Ia and class III antiarrhythmics.

Anticholinesterases. For mention of an interaction between tolterodine and *donepezil* or *rivastigmine*, see Antimuscarinics, under Donepezil, p.365.

Anticoagulants. For reference to the effect of tolterodine on the activity of *warfarin*, see under Antimuscarinics, p.1429.

Antidepressants. The SSRI *fluoxetine* is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6 and use with tolterodine has resulted in more than a fourfold increase in the area under the serum concentration-time curve (AUC) of tolterodine, associated with an approximate 20% decrease in the AUC of its 5-hydroxymethyl metabolite.[1] However, since both are active these changes were thought likely to result in little clinical difference, and licensed product information does not recommend a dose adjustment when tolterodine is given with fluoxetine.

1. Brynne N, *et al.* Fluoxetine inhibits the metabolism of tolterodine—pharmacokinetic implications and proposed clinical relevance. *Br J Clin Pharmacol* 1999; **48:** 553–63.

Gastrointestinal drugs. In a study[1] in healthy subjects, a dose of *antacid* was found to speed up the release of tolterodine from a modified-release preparation, probably as a result of the increase in gastric pH. Plasma-tolterodine concentrations were increased, but the half-life and area under the plasma concentration-time curve were not significantly affected. *Omeprazole* was reported to have a similar effect in another study.[2] The possible clinical effect of this change in drug release is unclear.

1. Sathyan G, *et al.* Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and oxybutynin. *Clin Pharmacokinet* 2004; **43:** 1059–68.
2. Dmochowski R, *et al.* Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol* 2005; **45:** 961–8.

Pharmacokinetics

Peak plasma concentrations of tolterodine occur 1 to 3 hours after an oral dose. It is highly bound to plasma proteins. Tolterodine is mainly metabolised in the liver by the cytochrome P450 isoenzyme CYP2D6 to the active 5-hydroxymethyl derivative (DD-01); in a minority of poor metabolisers tolterodine is metabolised by CYP3A4 isoenzymes to its inactive *N*-dealkylated derivative. The absolute bioavailability of tolterodine is normally about 17%, and the half-life is 2 to 3 hours; these increase in poor metabolisers to an absolute bioavailability of 65% and a half-life of about 10 hours. However, the clinical use of tolterodine is not affected by these differences in metabolism because the exposure to unbound tolterodine in poor metabolisers is similar to the combined exposure to unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers. Tolterodine is excreted primarily in the urine with about 17% appearing in the faeces; less than 1% of a dose is excreted as unchanged drug.

◊ References.

1. Brynne N, *et al.* Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. *Int J Clin Pharmacol Ther* 1997; **35:** 287–95.
2. Brynne N, *et al.* Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. *Clin Pharmacol Ther* 1998; **63:** 529–39.

Uses and Administration

Tolterodine tartrate is a tertiary antimuscarinic with actions similar to those of atropine (p.1220); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder. Tolterodine is used in the management of urinary frequency, urgency, and incontinence in detrusor instability. Usual oral doses of tolterodine tartrate are 2 mg twice daily; modified-release preparations are given in a usual dose of 4 mg once daily. Doses of 1 mg twice daily (or 2 mg daily as a modified-release preparation) are recommended in patients experiencing troublesome adverse effects. The *BNFC* suggests that a dose of 1 mg daily, increased according to response to a maximum of 2 mg twice daily, may be used in children from 2 years of age. Licensed US product information advises that the dose of tolterodine should not exceed 2 mg daily in patients receiving potent CYP3A4 inhibitors; UK product information recommends against such combinations. See also below for doses in patients with hepatic or renal impairment.

Administration in hepatic or renal impairment. Oral doses of 1 mg of tolterodine tartrate twice daily (or 2 mg daily as a modified-release preparation) are recommended by UK and US licensed product information in patients with hepatic or severe renal impairment.

Urinary incontinence. Tolterodine is used as an alternative to oxybutynin in the treatment of urge incontinence (see p.2180). Tolterodine is said to have fewer adverse effects than oxybutynin, but these may be comparable to modified-release oxybutynin.

References.

1. Harvey M-A, *et al.* Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. *Am J Obstet Gynecol* 2001; **185:** 56–61.
2. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 97–102.
3. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin* 2002; **18:** 177–84.
4. Swift S, *et al.* A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14:** 50–4.
5. Diokno AC, *et al.* Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; **78:** 687–95.
6. Khullar V, *et al.* Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. *Urology* 2004; **64:** 269–74.
7. Sand PK, *et al.* A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15:** 243–8.
8. Nijman RJ, *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol (Baltimore)* 2005; **173:** 1334–9.
9. Rovner ES. Tolterodine for the treatment of overactive bladder: a review. *Expert Opin Pharmacother* 2005; **6:** 653–66.
10. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Breminal; Detrusitol; Toltem; Urginol; ***Austral.:*** Detrusitol; ***Austria:*** Detrusitol; Detsel; ***Belg.:*** Detrusitol; ***Braz.:*** Detrusitol; ***Canad.:*** Detrol; Unidet; ***Chile:*** Detrusitol; ***Cz.:*** Detrusitol; ***Denm.:*** Detrusitol; ***Fin.:*** Detrusitol; ***Fr.:*** Detrusitol; ***Ger.:*** Detrusitol; ***Gr.:*** Detrusitol; ***Hong Kong:*** Detrusitol; ***Hung.:*** Detrusitol; ***India:*** Detrusitol; Terol; ***Indon.:*** Detrusitol; ***Irl.:*** Detrusitol; ***Israel:*** Detrusitol; ***Ital.:*** Detrusitol; ***Malaysia:*** Detrusitol; ***Mex.:*** Detrusitol; ***Neth.:*** Detrusitol; Detsel†; ***Norw.:*** Detrusitol; ***NZ:*** Detrusitol; ***Pol.:*** Detrusitol; ***Port.:*** Detrusitol; ***Rus.:*** Detrusitol (Детрузитол); ***S.Afr.:*** Detrusitol; ***Singapore:*** Detrusitol; ***Spain:*** Detrusitol; Urotrol; ***Swed.:*** Detrusitol; ***Switz.:*** Detrusitol; ***Thai.:*** Detrusitol; ***Turk.:*** Detrusitol; ***UK:*** Detrusitol; ***USA:*** Detrol; ***Venez.:*** Detrusitol.

Trospium Chloride *(BAN, USAN, rINN)*

Cloruro de trospio; IP-631; Trospii chloridum; Trospio chloridas; Trospium, chlorure de; Trospium-chlorid; Trospiumklorid; Trospiumkloridi; Trospiyum Klorür. 3α-Benziloyloxynortropane-8-spiro-1′-pyrrolidinium chloride.

Троспия Хлорид

$C_{25}H_{30}ClNO_3$ = 428.0.

CAS — 10405-02-4.

ATC — G04BD09.

ATC Vet — QG04BD09.

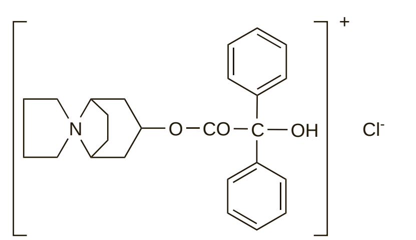

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Trospium Chloride). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Trospium should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that trospium crosses the placenta and is distributed into breast milk; licensed product information therefore recommends that caution should be observed during pregnancy and breast feeding.

Interactions
As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Pharmacokinetics
After oral doses of trospium chloride, peak plasma concentrations are reached at 4 to 6 hours. The bioavailability of trospium chloride is reduced by the simultaneous intake of food, especially with a high fat content. Plasma protein binding ranges from about 50% to about 80%. Trospium is excreted in the urine mainly by active renal tubular secretion as unchanged drug; about 10% appears as the spiroalcohol metabolite. The plasma half-life has been reported to be between 10 and 20 hours for the immediate-release preparation, and about 35 hours for the modified-release preparation. The mean half-life has been reported to be prolonged twofold in patients with severe renal impairment (creatinine clearance between 8 and 32 mL/minute). Trospium has been reported to cross the placenta and has been detected in the milk of *rats*.

◊ Reviews.

1. Doroshyenko O, *et al.* Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005; **44:** 701–20.

◊ For reference to the bioavailability of trospium chloride after intravesical instillation, see below.

Uses and Administration
Trospium chloride is a quaternary ammonium antimuscarinic with actions similar to those of atropine (p.1220). It is used for the management of urinary frequency, urgency, and incontinence in detrusor instability or detrusor hyperreflexia. It has also been used as an antispasmodic.

The immediate-release preparation is given orally in usual doses of 20 mg twice daily before meals on an empty stomach. Lower doses of 20 mg once daily may be warranted in patients aged 75 years and over. The need for continued treatment should be assessed at regular intervals of 3 to 6 months. A modified-release preparation is also available in some countries; the usual oral dose is 60 mg once daily in the morning, at least one hour before food. For use in patients with hepatic or renal impairment, see below.

Trospium chloride has also been given by slow intravenous injection. An inhaled formulation of trospium chloride for the treatment of chronic obstructive pulmonary disease is also being developed.

◊ References.

1. Walter P, *et al.* Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study. *Neurourol Urodyn* 1999; **18:** 447–53.
2. Frohlich G, *et al.* Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomized, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. *Int J Clin Pharmacol Ther* 2002; **40:** 295–303.
3. Halaska M, *et al.* Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003; **20:** 392–9.
4. Lopez Pereira P, *et al.* Trospium chloride for the treatment of detrusor instability in children. *J Urol (Baltimore)* 2003; **170:** 1978–81.
5. Zinner N, *et al.* Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol (Baltimore)* 2004; **171:** 2311–15.
6. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs* 2004; **64:** 2433–46.
7. Singh-Franco D, *et al.* Trospium chloride for the treatment of overactive bladder with urge incontinence. *Clin Ther* 2005; **27:** 511–30.
8. Rudy D, *et al.* Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; **67:** 275–80.
9. Menarini M, *et al.* TcP128-Study Group. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther* 2006; **44:** 623–32.
10. Staskin D, *et al.* Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol (Baltimore)* 2007; **178:** 978–83.

Administration in hepatic impairment. Licensed product information for trospium chloride states that maximum plasma concentrations and area under the concentration-time curve were increased in patients with mild (Child-Pugh score 5 to 6) or moderate (Child-Pugh score 7 to 12) hepatic impairment compared with healthy subjects. There is no information regarding the use of trospium chloride in patients with severe hepatic impairment. UK licensed product information advises caution in those with mild to moderate impairment, and advises against treatment in severe hepatic impairment. US licensed product information for both the immediate-release and the modified-release preparations advises caution in those with moderate to severe hepatic impairment. No specific dosage recommendations are given in either the UK or US product information.

Administration in renal impairment. Trospium chloride is mainly eliminated through active tubular secretion. Licensed product information states that increases in maximum plasma concentrations, area under the concentration-time curve, and half-life have been seen in patients with severe renal impairment given the immediate-release preparation; the pharmacokinetics of trospium chloride have not been studied in those with mild or moderate renal impairment.

UK licensed product information for the immediate-release preparation advises caution in those with mild to moderate renal impairment, while allowing for an oral dose of trospium chloride 20 mg once daily, or every alternate day, in those with severe renal impairment, defined as creatinine clearance (CC) of between 10 and 30 mL/minute per $1.73m^2$.

US licensed product information for the immediate-release preparation recommends a dose of 20 mg daily at bedtime for those with severe renal impairment (defined as CC less than 30 mL/minute). The modified-release preparation is not recommended for use in patients with severe renal impairment.

Preparations
Proprietary Preparations (details are given in Part 3)

Arg.: Spasmex; ***Austria:*** Inkontan; Rekont; Spasmolyt; ***Chile:*** Spasmex; ***Cz.:*** Spasmed; Spasmex; Uraplex; ***Denm.:*** Spasmo-Lyt; ***Fin.:*** Spasmo-Lyt; ***Fr.:*** Ceris; ***Ger.:*** Spasmex; Spasmo-Rhoival TC; Spasmo-Urgenin TC; Spasmolyt; Trospi; ***Gr.:*** Uraplex; ***Irl.:*** Regurin; ***Israel:*** Spasmex; ***Ital.:*** Uraplex; ***Port.:*** Spasmoplex; ***Rus.:*** Spasmex (Спазмекс); ***S.Afr.:*** Uricon; ***Spain:*** Uraplex; ***Switz.:*** Spasmo-Urgenine Neo; ***Thai.:*** Spasmo-Lyt; ***Turk.:*** Spasmex; ***UK:*** Regurin; ***USA:*** Sanctura.

Multi-ingredient: ***Arg.:*** Keptan Compuesto†; ***Austria:*** Spasmo-Urgenin; ***Port.:*** Spasmo-Urgenin†; ***S.Afr.:*** Spasmo-Urgenin†; ***Spain:*** Spasmo-Urgenin; ***Thai.:*** Spasmo-Urgenin.

Udenafil *(rINN)*

DA-8159; Udénafil; Udenafilo; Udenafilum. 3-(1-Methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-*N*-{2-[(2*RS*)-1-methylpyrrolidin-2-yl]ethyl}-4-propoxybenzenesulfonamide.

Уденафил

$C_{25}H_{36}N_6O_4S$ = 516.7.

CAS — 268203-93-6.

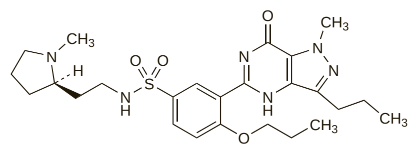

Profile
Udenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction.

Vardenafil *(rINN)*

Vardénafil; Vardenafilum. 1-{[3-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*]-*as*-triazin-2-yl)-4-ethoxyphenyl]sulfonyl}-4-ethylpiperazine.

Варденафил

$C_{23}H_{32}N_6O_4S$ = 488.6.

CAS — 224785-90-4.

ATC — G04BE09.

ATC Vet — QG04BE09.

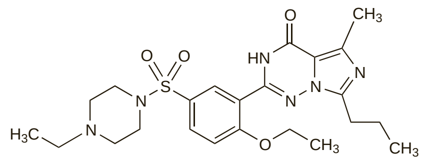

Vardenafil Dihydrochloride *(USAN, rINNM)*

Dihidrocloruro de vardenafil; Vardénafil, Dichlorhydrate de; Vardenafili Dihydrochloridum.

Варденафила Дигидрохлорид

$C_{23}H_{32}N_6O_4S,2HCl$ = 561.5.

CAS — 224789-15-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

Vardenafil Hydrochloride *(USAN, rINNM)*

Bay-38-9456; Hidrocloruro de vardenafil; Vardénafil, Chlorhydrate de; Vardenafil Monohydrochloride; Vardenafili Hydrochloridum.

Варденафила Гидрохлорид

$C_{23}H_{32}N_6O_4S,HCl$ = 525.1.

CAS — 224785-91-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

Adverse Effects and Precautions
As for Sildenafil, p.2193. Photosensitivity has also been reported. Vardenafil may prolong the QT interval and is best avoided in patients with relevant risk factors such as hypokalaemia, congenital QT prolongation, or the use of antiarrhythmics of class Ia or class III. Dosage reductions may be required in patients with hepatic or renal impairment.

Effects on the cardiovascular system. References.

1. Thadani U, *et al.* The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002; **40:** 2006–12.

Interactions
As for Sildenafil, p.2194. The use of vardenafil with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 (such as HIV-protease inhibitors, some azole antifungals, and macrolide antibacterials) is generally best avoided; if thought to be essential, dosage of vardenafil must be reduced and suggested doses are given below (p.2199). Use with ketoconazole and itraconazole is contra-indicated in men older than 75 years of age. An enhanced hypotensive effect may be seen if vardenafil is taken with nifedipine. Vardenafil may prolong the QT interval and its use with antiarrhythmics of class Ia or class III should be avoided.

Pharmacokinetics
Vardenafil is rapidly absorbed after an oral dose, with a bioavailability of about 15%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when vardenafil is given with a high-fat meal.

Vardenafil is widely distributed into tissues and is about 95% bound to plasma proteins. It is metabolised in the liver primarily by cytochrome P450 isoenzymes CYP3A4 (the major route) as well as CYP3A5 and CYP2C isoforms. The major metabolite produced by desethylation of vardenafil also has some activity. The terminal half-life is about 4 to 5 hours.

Vardenafil is excreted as metabolites mainly in the faeces (91 to 95%), and to a lesser extent in the urine (2 to 6%). Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

◊ References.

1. Rajagopalan P, *et al.* Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* 2003; **43:** 260–7.
2. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.

Uses and Administration
Vardenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction (p.2179). Vardenafil is given orally as the hydrochloride trihydrate although doses are expressed in terms of

the base; vardenafil hydrochloride trihydrate 11.85 mg is equivalent to about 10 mg of vardenafil.

The usual dose is 10 mg taken about 25 minutes to one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 20 mg, and vardenafil should not be taken more than once in 24 hours. The dose may be taken with or without food, but onset of activity may be delayed if taken with a high-fat meal.

- An initial dose of 5 mg is recommended in elderly patients, which may be increased to 10 mg and then to 20 mg if necessary.
- In patients stabilised on alpha blocker therapy, the dose of vardenafil should be no more than 5 mg daily and it should not be taken within 6 hours of the alpha blocker, although this interval may not be necessary with tamsulosin.
- A maximum daily dose of vardenafil 5 mg is advised in patients taking erythromycin (dose not specified in licensed product information), itraconazole (200 mg daily), or ketoconazole (200 mg daily). A daily dose of 2.5 mg is recommended for those taking clarithromycin (dose not specified in licensed product information), itraconazole (400 mg daily), or ketoconazole (400 mg daily).
- A maximum dose of vardenafil 2.5 mg every 24 hours is recommended in patients taking HIV-protease inhibitors. This dose should be reduced to 2.5 mg every 72 hours in those taking ritonavir-boosted regimens, although this combination may be best avoided (see also Interactions, above).

For doses in hepatic or renal impairment, see below.

◊ Reviews.

1. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003; **63:** 2673–2703.
2. Crowe SM, Streetman DS. Vardenafil treatment for erectile dysfunction. *Ann Pharmacother* 2004; **38:** 77–85.
3. Kendirci M, *et al.* Vardenafil: a novel type 5 phosphodiesterase inhibitor for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2004; **5:** 923–32.
4. Markou S, *et al.* Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. *Int J Impot Res* 2004; **16:** 470–8.
5. van Ahlen H, *et al.* The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study—results from 29 358 German patients. *J Int Med Res* 2005; **33:** 337–48.
6. Montorsi F, *et al.* Vardenafil for the treatment of erectile dysfunction: a critical review of the literature based on personal clinical experience. *Eur Urol* 2005; **47:** 612–21.

Administration in hepatic impairment. An initial dose of 5 mg of vardenafil is recommended by UK licensed product information in patients with mild to moderate hepatic impairment (Child-Pugh category A to B), which may be increased if necessary, according to response and tolerability. The maximum dose recommended in patients with moderate hepatic impairment is 10 mg. Vardenafil has not been evaluated in severe hepatic impairment (Child-Pugh category C).

Administration in renal impairment. In the UK, an initial dose of 5 mg of vardenafil is recommended by licensed product information in patients with a creatinine clearance of less than 30 mL/minute, which may be increased to 10 mg and then to 20 mg if necessary, according to response and tolerability. US licensing information does not consider adjustment to be necessary. The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Levitra; ***Austral.:*** Levitra; ***Austria:*** Levitra; ***Belg.:*** Levitra; ***Braz.:*** Levitra; Vivanza; ***Canad.:*** Levitra; ***Chile:*** Levitra; ***Cz.:*** Levitra; Vivanza; ***Denm.:*** Levitra; ***Fin.:*** Levitra; ***Fr.:*** Levitra; ***Ger.:*** Levitra; ***Gr.:*** Levitra; ***Hong Kong:*** Levitra; ***Hung.:*** Levitra; ***Indon.:*** Levitra; ***Irl.:*** Levitra; ***Israel:*** Levitra; ***Ital.:*** Levitra; Vivanza†; ***Malaysia:*** Levitra; ***Mex.:*** Levitra; ***Neth.:*** Levitra; Vivanza; ***Norw.:*** Levitra; ***NZ:*** Levitra; ***Philipp.:*** Levitra; ***Pol.:*** Levitra; ***Port.:*** Levitra; Vivanza; ***Rus.:*** Levitra (Левитра); ***S.Afr.:*** Levitra; ***Singapore:*** Levitra; ***Spain:*** Levitra; ***Swed.:*** Levitra; ***Switz.:*** Levitra; ***Thai.:*** Levitra; ***Turk.:*** Levitra; ***UK:*** Levitra; ***USA:*** Levitra; ***Venez.:*** Levitra.

Yohimbine Hydrochloride *(BAN)*

Aphrodine Hydrochloride; Chlorhydrate de Québrachine; Corynine Hydrochloride; Yohimbina, hidrocloruro de; Yohimbine, chlorhydrate de; Yohimbini hydrochloridum. Methyl 17α-hydroxy-yohimban-16α-carboxylate hydrochloride.

$C_{21}H_{26}N_2O_3$,HCl = 390.9.

CAS — 146-48-5 (yohimbine); 65-19-0 (yohimbine hydrochloride).

ATC — G04BE04.

ATC Vet — QG04BE04.

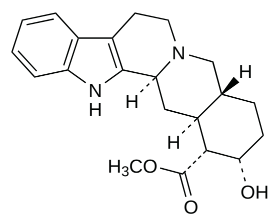

(yohimbine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Yohimbine Hydrochloride). A white or slightly yellowish, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Yohimbine Hydrochloride). A white to yellow powder. Slightly soluble in water and in alcohol; soluble in boiling water. Store in airtight containers.

Profile

Yohimbine is the principal alkaloid of the bark of the yohimbe tree, *Pausinystalia yohimbe* (*Corynanthe yohimbi*) (Rubiaceae); it is also found in *Rauwolfia serpentina.* It is an alpha$_2$-adrenoceptor blocker with a short duration of action. It has an antidiuretic effect and produces increases in heart rate and blood pressure. It has been reported to cause CNS effects including anxiety and manic reactions. It has been given orally in the treatment of erectile dysfunction (p.2179) and for its alleged aphrodisiac properties but convincing evidence of such an effect is lacking. It is contra-indicated in renal or hepatic disease.

Adverse effects. A warning about the potential adverse effects, including anxiety, manic reactions, bronchospasm, and a lupus-like syndrome, associated with yohimbine taken in health food products.[1] Interactions with tricyclic antidepressants and with phenothiazines might also occur.

1. De Smet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *BMJ* 1994; **309:** 958.

Uses. References to the use of yohimbine in erectile dysfunction.

1. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomised clinical trials. *J Urol (Baltimore)* 1998; **159:** 433–6.
2. Tam SW, *et al.* Yohimbine: a clinical review. *Pharmacol Ther* 2001; **91:** 215–43.
3. Lebret T, *et al.* Efficacy and safety of a novel combination of L-arginine glutamate and yohimbine hydrochloride: a new oral therapy for erectile dysfunction. *Eur Urol* 2002; **41:** 608–13.
4. Guay AT, *et al.* Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. *Int J Impot Res* 2002; **14:** 25–31.

Preparations

USP 31: Yohimbine Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Yohimex†; ***Austria:*** Yocon; ***Belg.:*** Yocoral; ***Braz.:*** Yomax; ***Canad.:*** Yocon; ***Chile:*** Yocon; ***Denm.:*** Virigen; ***Fr.:*** Yocoral; ***Ger.:*** Pluriviron mono†; Yocon; ***Port.:*** Zumba; ***Singapore:*** Urobine†; ***UK:*** Prowess Plain; ***USA:*** Aphrodyne; Yocon.

Multi-ingredient: ***Arg.:*** Ferona; Optimina Plus; ***Austria:*** Pasuma-Dragees; ***Braz.:*** Geravitine†; Libiplus; Testofran†; Tonaton; ***Fin.:*** Potentol†; ***Hong Kong:*** Wari-Procomil; ***Indon.:*** Sirec; ***Israel:*** Tesopalmed Forte cum Yohimbine; ***Thai.:*** Wari-Procomil†; ***UK:*** Prowess.

Vaccines Immunoglobulins and Antisera

The agents described in this section are immunological agents used for both active and passive immunisation.

Active immunisation is the exposure of the immune system to antigens in the form of micro-organisms or products of their activity in order to stimulate production of antibodies and acquired cell-mediated responses with a specific protective capacity. It may be a natural process after infection, or an artificial process induced by giving *vaccines*. It is inevitably a slow process dependent upon the rate at which the antibodies can be produced. Although the terms vaccination and immunisation are often used synonymously and interchangeably, *vaccination* simply refers to giving a vaccine whereas *immunisation* implies the development of protective levels of antibodies.

Passive immunisation, which results in immediate short-term protection, may be achieved by giving exogenous antibodies in the form of *antisera* (of animal origin) or *immunoglobulins*.

Antisera

Antisérums; Antisueros; Immunsera.

Антисыворотки

Description

Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunised animals by purification. The term antisera includes antitoxins, which are antibodies that combine with and neutralise specific toxins, and antivenins (antivenoms), which are antitoxins directed against the toxic principle of the venoms of poisonous animals such as certain snakes and arthropods.

Antisera are obtained from healthy animals immunised by injections of the appropriate toxins or toxoids, venins, or suspensions of micro-organisms or other antigens. The specific immunoglobulins may be obtained from the serum by fractional precipitation and enzyme treatment or by other chemical or physical means. A suitable antimicrobial preservative may be added, and is invariably added if the product is issued in multidose containers. The Ph. Eur. 6.2 directs that when antisera contain phenol, the concentration is not more than 0.25%. The antiserum is distributed aseptically into sterile containers, which are sealed so as to exclude micro-organisms. Alternatively they may be supplied as freeze-dried preparations for reconstitution immediately before use.

Adverse Effects and Precautions

Reactions are liable to occur after the injection of any serum of animal origin. Anaphylaxis (type I hypersensitivity reaction, p.561) may occur, with hypotension, dyspnoea, urticaria, and shock, which requires management as a medical emergency (see p.1205).

Serum sickness (type III hypersensitivity reaction, p.561) may also occur, frequently 7 to 10 days after the injection of serum of animal origin.

Before injecting serum, information should be obtained whenever possible as to whether the patient is subject to hypersensitivity disorders or has received serum injections before. Sensitivity testing should be performed before giving antisera. The patient must be kept under observation after giving a full dose of antisera. Adrenaline injection and resuscitation facilities should be available.

Uses and Administration

Antisera have the specific power of neutralising venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation. Most antisera in current use are antitoxins or antivenins. The use of antisera to induce passive immunity has declined; immunoglobulins are preferred. Although antisera are defined as being of animal origin (see above), the term antisera has been used in some countries to describe antitoxins of human origin (immunoglobulins).

Immunoglobulins

Immunglobuline; Inmunoglobulinas.

Иммуноглобулины

Description

Immunoglobulins are produced by B lymphocytes as part of the humoral response to foreign antigens. Immunoglobulins used in clinical practice are preparations containing antibodies, usually prepared from human plasma or serum, and mainly comprise IgG. Normal immunoglobulin, prepared from material from blood donors, contains several antibodies against infectious diseases prevalent in the general population, whereas specific immunoglobulins contain minimum specified levels of one antibody. Antibodies may also be prepared by genetic engineering techniques.

Adverse Effects

Local reactions with pain and tenderness at the site of intramuscular injection may follow the use of immunoglobulins. Hypersensitivity reactions, including, rarely, anaphylactic reactions, have also been reported; such reactions, though, are far less frequent than after the use of antisera of animal origin.

Some immunoglobulins are available as intravenous preparations. Systemic reactions with fever, chills, facial flushing, headache, and nausea may occur, particularly at high rates of infusion.

Precautions

Strenuous efforts are made to screen human donor material used in the preparation of immunoglobulins; the transmission of infections, including hepatitis B and HIV, which has been associated with the use of certain blood products (see p.1056), does not appear to be a problem with the immunoglobulins currently in use.

IgA, present in some immunoglobulin preparations, may give rise to the production of anti-IgA antibodies in patients with IgA deficiencies, with the consequent risk of anaphylactic reactions. For precautions in such patients, see Hypersensitivity under Adverse Effects and Precautions in Normal Immunoglobulins, p.2226.

Interactions

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response and a suitable interval should separate their use (see Vaccines, Interactions, p.2202).

Uses and Administration

Immunoglobulins are used for passive immunisation, thus conferring immediate protection against some infectious diseases. They are preferred to antisera of animal origin as the incidence of adverse reactions is lower.

It is generally important to follow the conferment of passive immunity, which is largely an emergency procedure, by the injection of suitable antigens to produce active immunity.

Vaccines

Vacunas.

Вакцины

Description

Vaccines are traditionally preparations of antigenic materials that are given with the objective of inducing in the recipient active immunity to specific infecting agents or toxins or antigens produced by them. They may contain living or killed micro-organisms, bacterial toxoids, or antigenic material from particular parts of the infecting organism, which may be derived from the organism or produced by recombinant DNA technology. Vaccines may be single-component vaccines or mixed combined vaccines. Vaccines against some non-infectious diseases are being developed.

Storage. All vaccines are sensitive to heat to differing extents, with oral poliomyelitis vaccines and measles vaccines the most heat-sensitive of the commonly used vaccines. Freeze-dried vaccines become much more heat-sensitive once reconstituted. The effect of heat on vaccines is generally irreversible loss of potency, but in some cases heat exposure may also cause the vaccine to become more reactogenic. The system used for storing and distributing vaccines at sufficiently low temperature is called the cold chain, and consists of a series of storage and transport links all designed to keep the vaccine at the correct temperature until it reaches the user. WHO recommends[1] that oral poliomyelitis vaccines be stored at −25 to −15° and that, in general, freeze-dried vaccines should be stored at 2 to 8°.

Some vaccines are also sensitive to excessive cold, notably hepatitis B vaccines and Haemophilus influenzae vaccines, and care should be taken not to store them at too low a temperature.[1]

In addition to temperature sensitivity, some vaccines are also sensitive to strong light, such as BCG vaccines, measles-containing vaccines, and rubella-containing vaccines. These are usually supplied in dark brown glass vials for protection, but further care should be taken to keep them covered.[1]

Further advice concerning vaccine storage is given in the references below.[2-6]

1. WHO. What are the correct conditions for storing EPI vaccines? Available at: http://www.who.int/vaccines-access/vacman/temperature/temperature.htm (accessed 26/09/05)
2. Galazka A, *et al.*: Global Programme for Vaccines and Immunization. *Thermostability of vaccines.* Geneva: WHO, 1998. Also available at: http://whqlibdoc.who.int/hq/1998/WHO_GPV_98.07.pdf (accessed 14/07/08)
3. Department of Vaccines and Other Biologicals. *Temperature monitors for vaccines and the cold chain.* Geneva: WHO, 1999. Also available at: http://www.who.int/vaccines-documents/DocsPDF/www9804.pdf (accessed 15/09/05)
4. CDC. Notice to readers: guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003; **52:** 1023–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5242.pdf (accessed 24/05/06)
5. Australian Government Department of Health and Ageing. National vaccine storage guidelines: strive for 5 (2005). Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/5B7381C34C511E54CA25719D00183397/06.00File/strive-4-five.pdf (accessed 14/07/08)
6. Public Health Agency of Canada. National vaccine storage and handling guidelines for immunization providers (2007). Available at: http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/index-eng.php (accessed 05/06/08)

Adverse Effects

Injection of a vaccine may be followed by a local reaction, possibly with inflammation and lymphangitis. An induration or sterile abscess may develop at the injection site. Fever, headache, and malaise may start a few hours after injection and last for 1 or 2 days. Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.

Further details, if appropriate, of adverse effects of vaccines may be found in the respective individual monographs.

Anaphylaxis. In a retrospective study[1] in the USA conducted to quantify the risk of anaphylaxis after vaccination of children and adolescents, only 5 cases potentially associated with vaccines were identified from more than 7.5 million doses given. Vaccines implicated were generally given in combination and included the following components: diphtheria and tetanus; diphtheria, tetanus, and pertussis; hepatitis B; Haemophilus influenzae; measles, mumps, and rubella; and oral poliomyelitis. One case followed measles, mumps, and rubella vaccine given alone. It was concluded that vaccine-associated anaphylaxis is a rare event.

1. Bohlke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112:** 815–20.

Long-term effects. The introduction of routine childhood vaccination has been accompanied by concerns over the safety and possible long term sequelae of some commonly used vaccines. Difficulties have arisen in distinguishing temporal and causal associations and in some cases the perceived dangers of vaccination have impeded uptake. Among the disorders that have been temporally (but generally not causally) associated with childhood vaccination are neurological disorders, sudden infant death syndrome, type 1 diabetes mellitus, and demyelinating disorders. Information on adverse effects associated with specific vaccines can be found under diphtheria, tetanus, and pertussis vaccines (p.2210), hepatitis B vaccines (p.2215), influenza vaccines (p.2218), measles, mumps, and rubella vaccines (p.2223), and pertussis vaccines (p.2230).

Additives or excipients have sometimes been alleged to be the cause of adverse reactions—see below for further details.

References.

1. Jefferson T. Vaccination and its adverse effects: real or perceived. *BMJ* 1998; **317:** 159–60.
2. Ball LK, *et al.* Risky business: challenges in vaccine risk communication. *Pediatrics* 1998; **101:** 453–8.
3. Hiltunen M, *et al.* Immunisation and type 1 diabetes mellitus: is there a link? *Drug Safety* 1999; **20:** 207–12.

4. Institute for Vaccine Safety Diabetes Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety workshop. *Pediatr Infect Dis J* 1999; **18:** 217–22.
5. Stratton K *et al. Immunization safety review: multiple immunizations and immune dysfunction*. Washington DC: National Academy Press, 2002. Also available at: http://www.nap.edu/catalog.php?record_id=10306 (accessed 14/07/08)
6. Offitt PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; **111:** 653–9.
7. Wraith DC, *et al.* Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; **362:** 1659–66.
8. Stratton K *et al. Immunization safety review: vaccinations and sudden unexpected death in infancy.* Washington DC: National Academy Press, 2003. Also available at: http://www.nap.edu/catalog.php?record_id=10649 (accessed 14/07/08)
9. CDC. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS) — United States, 1991–2001. *MMWR* 2003; **52** (SS-1): 1–24. Correction. *ibid.*; 113.
10. Hviid A, *et al.* Childhood vaccination and type 1 diabetes. *N Engl J Med* 2004; **350:** 1398–1404.
11. Koppen S, *et al.* No epidemiological evidence for infant vaccination to cause allergic disease. *Vaccine* 2004; **22:** 3375–85.
12. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005; **23:** 3876–86.

Effects of adjuvants. *Aluminium hydroxide* has been used frequently as an adsorbent in vaccines. A review[1] found significantly more erythema and induration with aluminium-containing vaccines than with plain ones. There was, however, no evidence of serious or long-lasting adverse effects that could be attributed to aluminium salts.

Thiomersal has been used as a preservative but because of alleged adverse effects is no longer used as widely as it once was (see Vaccines, under Thiomersal, p.1664 for further details). However, the comment has been made that in developing countries far more benefit will be seen from protecting children with current, inexpensive, domestically-manufactured thiomersal-containing vaccines, than by investing in thiomersal-free alternatives.[2]

1. Jefferson T, *et al* Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infect Dis* 2004: **4:** 84–90.
2. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28:** 89–101.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* Guillain-Barré syndrome (see p.2228) has occasionally been reported after vaccination, although causal relationships have been difficult to evaluate. Such reports have been made after diphtheria and tetanus vaccines (p.2210), haemophilus influenzae vaccines (p.2213), hepatitis A vaccines (p.2214), hepatitis B vaccines (p.2215), a swine influenza vaccine (p.2218), measles, mumps, and rubella vaccines (p.2223), meningococcal vaccines (p.2224), and oral poliomyelitis vaccines (p.2232), although only the association with swine influenza vaccine appears to have been accepted.

Precautions

Most persons can safely receive the majority of vaccines. In a few individuals vaccination is contra-indicated or should be deferred.

All vaccines are contra-indicated in those who have had a previous confirmed anaphylactic reaction to a previous dose of a vaccine containing the same antigens or a confirmed anaphylactic reaction to another component contained in the relevant vaccine (for example, neomycin, polymyxin B, or streptomycin which may be present in trace amounts).

Some vaccines are prepared in egg cultures and are contra-indicated in persons with a confirmed anaphylactic reaction to egg.

Live vaccines are contra-indicated in the following groups of immunosuppressed patients:

- severe primary immunodeficiency
- malignant disease being treated with either chemotherapy or radiotherapy and for at least 6 months after stopping such treatment
- solid organ transplant receiving immunosuppressive therapy
- bone marrow transplant and for at least 12 months after stopping immunosuppressive therapy (or longer if graft-versus-host disease develops)
- all patients receiving high-dose systemic corticosteroids until at least 3 months after stopping treatment; this includes children receiving prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg for at least 1 week or 1 mg/kg for 1 month and adults receiving a daily dose of 40 mg for more than 1 week.
- HIV positive patients with immunosuppression

Vaccination may be delayed in persons who are acutely unwell and in those with evolving neurological conditions (until stabilised). In pregnancy, vaccination should be delayed until after delivery; termination of pregnancy is not recommended if a vaccine is inadvertently given during pregnancy.

If any alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination otherwise inactivation of live vaccines may occur.

Immunocompromised patients. For a discussion of the use of vaccines in HIV-infected and otherwise immunocompromised patients, see under Uses, below.

Premature infants. In the UK, the Royal College of Paediatrics and Child Health[1] and the Department of Health[2] consider that all routine childhood immunisations should be scheduled on the basis of the child's actual date of birth with no allowance being made for prematurity. In the USA, the American Academy of Pediatrics offers similar advice.[3] It is acknowledged that more studies are required into immunisation in prematurity, particularly in infants receiving corticosteroids.[1] There is some evidence that a minority of premature infants may fail to respond adequately to Haemophilus influenzae vaccines and to hepatitis B immunisation.[1]

1. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/Publications/Publications-list-by-title (accessed 14/07/08)
2. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 26/04/06)
3. Pickering L, *et al.* eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006.

Interactions

The ability of vaccines to induce an immune response can be influenced by the recent use of other vaccines or immunoglobulins. Live vaccines should either be given simultaneously (but at different sites) or an interval of at least 3 weeks allowed between them. Live vaccines should normally be given at least 3 weeks before or at least 3 months after the use of immunoglobulin. However, travellers should receive appropriate vaccines regardless of these limitations if time is short.

Patients receiving immunosuppressant therapy, including antineoplastics or therapeutic doses of corticosteroids, may also display a reduced response to vaccines and deferral of immunisation is advised, see Precautions, above. For further details on immunisation in immunocompromised patients, see under Uses and Administration, below.

Any agent that is active against the bacterial or viral strain present in the vaccine may interfere with development of a protective immune response but treatment with antibacterials is not a contra-indication to immunisation.

Uses and Administration

Vaccines are used for active immunisation as a prophylactic measure against some infectious diseases. They provide partial or complete protection for months or years. For inactivated vaccines, a slight and rather slow antibody response of primarily immunoglobulin M (IgM) (the primary response) is produced after the first or second dose but, when a further dose is given after a suitable interval, a prompt antibody response follows and high concentrations of IgG occur in the blood (the secondary response). Though the antibody concentration may later fall, a further dose of vaccine promptly restores it. For most live vaccines only one dose is required, although 3 doses of live (oral) poliomyelitis vaccines are needed to achieve complete immunisation. Some inactivated vaccines contain an adjuvant such as aluminium hydroxide or aluminium phosphate to enhance the immune response.

Protection against several infectious diseases may be provided in early life by active immunisation and national schedules for childhood immunisation are regularly reviewed and updated. Schedules for routine immunisation of infants and children are generally designed to fit in with routine health checks and landmark events such as school starting and leaving ages. National immunisation schedules should be consulted for full details of local recommendations.

In the **UK**, the following schedule of vaccination and immunisation is recommended:

- at 2 months of age, the first dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine (p.2212), together with a first dose of pneumococcal conjugate vaccine (p.2231)
- at 3 months of age, a second dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, together with the first dose of meningococcal C conjugate vaccine (p.2224)
- at 4 months of age, a third dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, together with a second dose of meningococcal C conjugate vaccine and pneumococcal conjugate vaccine
- at 12 months of age, a fourth dose of *Haemophilus influenzae* vaccine (p.2213) and a third dose of a meningococcal C conjugate vaccine
- at about 13 months, measles, mumps, and rubella vaccine (p.2223) and a third dose of pneumococcal conjugate vaccine
- at 3 years 4 months to 5 years, a reinforcing dose of a combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine (p.2211) and a second dose of measles, mumps, and rubella vaccine
- at 12 to 13 years of age, human papillomavirus vaccine (p.2217) will be offered to all girls (starting in September 2008)
- before leaving school (age 13 to 18 years), a reinforcing dose of a low-dose diphtheria, tetanus, and poliomyelitis (inactivated) vaccine (p.2212).

The following schedule is recommended in the **USA**:

- at birth, the first dose of hepatitis B vaccine (p.2215)
- at age 1 to 2 months, a second dose of hepatitis B vaccine, not less than 1 month after the first
- at 2 months, a first dose of diphtheria, tetanus, and pertussis (acellular component) vaccine (p.2210), together with a *Haemophilus influenzae* vaccine (p.2213), a pneumococcal conjugate vaccine (p.2231), a poliomyelitis (inactivated) vaccine (p.2232) and a rotavirus vaccine (p.2236)
- at 4 months, a second dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, together with the second doses of a *Haemophilus influenzae* vaccine, pneumococcal conjugate vaccine, poliomyelitis (inactivated) vaccine, and rotavirus vaccine
- at 6 months, the third dose of *Haemophilus influenzae* vaccine if necessary (depending on the type of vaccine used), a third dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, a third dose of pneumococcal conjugate vaccine and a third dose of rotavirus vaccine
- at 6 to 18 months, the third doses of hepatitis B and poliomyelitis (inactivated) vaccines
- from 6 months to 18 years, annual influenza vaccine in high-risk patients, although influenza vaccine is also recommended in healthy infants aged 6 to 59 months
- from 12 months, 2 doses (at least 6 months apart) of a hepatitis A vaccine (p.2214)
- at 12 to 15 months, a reinforcing dose of *Haemophilus influenzae* vaccine, the first dose of measles, mumps, and rubella vaccine, the first dose of varicella-zoster vaccine (p.2242) and the fourth dose of pneumococcal conjugate vaccine
- at 15 to 18 months, the fourth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine
- at 2 to 18 years, pneumococcal polysaccharide vaccine (in addition to previously administered pneumococcal conjugate vaccine) in certain high-risk groups
- at 2 to 10 years, meningococcal C conjugate vaccine (p.2224) to children with terminal complement deficiencies or asplenia and other high-risk groups; meningococcal polysaccharide vaccine may alternatively be used
- at 4 to 6 years, the fifth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, the fourth dose of poliomyelitis (inactivated) vaccine, the second dose of measles, mumps, and rubella vaccine, and the second dose of varicella-zoster vaccine

- at age 11 to 12 years, a sixth dose of low-dose diphtheria, tetanus, and pertussis (acellular component) plus a meningococcal C conjugate vaccine in those not previously vaccinated (meningococcal polysaccharide vaccine may alternatively be used); the first dose of human papillomavirus vaccine (p.2217) may be given to girls, the second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose

Immunisation schedules for older children and adults are also produced, along with recommendations for vaccination of high-risk groups, including the immunocompromised and the elderly, and of travellers.

In addition to vaccines directed against bacteria and viruses, advances are being made in producing vaccines against fungi, protozoa, and helminths, and for non-infective diseases including cancer and auto-immune disorders.

Development of novel vaccine formulations and delivery methods is continuing, including transdermal and transmucosal systems. Genetic manipulation of foodstuffs is being investigated with the aim of producing edible vaccines.

Immunisation schedules. References to routine immunisation schedules in the UK[1] and USA.[2,3]

1. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" 2006 Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 26/04/06)
2. CDC. Child & Adolescent Immunization Schedules, United States, 2008. Available at: http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm (accessed 14/07/08)
3. CDC. Adult Immunization Schedule, United States, October 2007–September 2008. Available at: http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm (accessed 14/07/08)

EXPANDED PROGRAMME ON IMMUNIZATION. In 1974 the World Health Assembly adopted a resolution creating the Expanded Programme on Immunization (EPI), the aim of which was to provide immunisation against 6 target diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus, and tuberculosis) for all children throughout the world by 1990. More recently, EPI has added hepatitis B, yellow fever, and *Haemophilus influenzae* infection to the list of target diseases. Although the attention of WHO had been focussed mainly on the developing countries, it was emphasised that the programme was not created exclusively for these countries. Besides WHO, many other organisations, including UNICEF, were involved –more recently, much work has been carried out under the auspices of the Global Alliance for Vaccination and Immunisation (GAVI).

Although many cases of the target diseases and many deaths have been prevented, vaccine coverage, especially for measles and neonatal tetanus is still low. It is particularly important to immunise children as early in life as possible and not to withhold vaccines from those with minor illness or malnutrition. Vaccine uptake was around 70% in 1990 compared with less than 5% in 1974. By 2003, all 192 member states of WHO were routinely immunising against diphtheria, measles, pertussis, poliomyelitis, and tetanus before the age of 18 months. Also, 158 member states were routinely immunising against tuberculosis, but routine BCG vaccination has been discontinued in some countries, including the UK, due to low risk and prevalence of disease.

A schedule designed to provide protection at the earliest possible age consisted of: trivalent oral poliomyelitis vaccine together with BCG vaccine at birth; hepatitis B vaccine at birth, 6 weeks, and 14 weeks (where transmission at birth is likely), or at 6, 10, and 14 weeks (where transmission at birth is less likely); trivalent oral poliomyelitis vaccine together with diphtheria, tetanus, and pertussis vaccine and Haemophilus influenzae vaccine at 6, 10, and 14 weeks of age; and measles vaccine and yellow fever vaccine at 9 months of age. Tetanus vaccine is also given to all women of child-bearing age. Also included in the programme in parts of the Far East is Japanese encephalitis vaccine.

Some references to the EPI and global immunisation policy.

1. WHO Global Programme for Vaccines and Immunization: Expanded Programme on Immunization: Module 1: EPI target diseases. Geneva: WHO, 1998. Available at: http://www.who.int/vaccines-documents/DoxTrng/IIP-E/www9556-01.pdf (accessed 08/09/04)
2. WHO. Department of Vaccines and Biologicals: Module 2: EPI vaccines. Geneva: WHO, 2001. Available at: http://www.who.int/vaccines-documents/DoxTrng/IIP-E/www9556-02.pdf (accessed 08/09/04)
3. WHO. WHO vaccine-preventable diseases: monitoring system 2004 global summary. Geneva: WHO, 2004. Also available at: http://www.who.int/vaccines_documents/DocsPDF04/WHO_IVB_2004.pdf (accessed 30/09/05)

Immunisation of immunocompromised patients. Immunocompromised patients may require immunisation against opportunistic infections but immune response to vaccination may be impaired, and there is a risk of disseminated infection with live vaccines (see Precautions, above).

Recommendations for immunisation of HIV-positive individuals have varied, particularly with regard to live vaccines.

In the UK,[1] it is generally recommended that vaccines used for routine immunisation in childhood may be given to HIV-positive persons, providing they are not immunosuppressed, but that BCG and yellow fever vaccines should not be given at all. WHO and UNICEF recommend[2] that for asymptomatic HIV-positive persons routine immunisation should be carried out according to their usual Expanded Programme on Immunization (see above). In addition, an extra dose of measles vaccine should be given at 6 months of age with the standard dose given as soon after 9 months of age as possible.

Some detailed guidance on vaccination of immunocompromised children is provided by the Royal College of Paediatrics and Child Health in the UK[3] and by the Children's HIV Association of UK and Ireland.[4] Guidance on immunisation of HIV-infected adults is provided by the British HIV Association.[5]

1. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" 2006 Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 16/03/08)
2. WHO. *EPI vaccines in HIV-infected individuals* (5 October 2001). Available at: http://www.who.int/vaccines-diseases/diseases/HIV.shtml (accessed 07/09/04)
3. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/doc.aspx?id_Resource=1768 (accessed 15/07/08)
4. Riordan A. Children's HIV Association of UK and Ireland. Immunisation of HIV-infected children, May 2007. Available at: http://www.chiva.org.uk/protocols/immunisation.html (accessed 19/03/08)
5. Geretti AM, *et al.* British HIV Association Immunisation Subcommittee. Immunisation guidelines for HIV-infected adults, April 2006. Available at: http://www.bhiva.org/files/file1001634.pdf (accessed 19/03/08)

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO.[1] In 2008 the following information regarding certification of vaccination was given.

A *yellow fever* vaccination certificate is now the only one that may be required in international travel. The vaccine used must be approved by WHO and given at a designated centre. Vaccination is strongly recommended for travel outside the urban areas of countries in the yellow fever endemic zone even if these countries have not officially reported the disease and do not require evidence of vaccination on entry. Many countries require a certificate from travellers arriving from infected areas or from countries with infected areas, or who have been in transit through those areas. Some countries require a certificate from all entering travellers including those in transit; although there is no epidemiological justification for this requirement, and it is clearly in excess of the International Health Regulations (WHO recommendations for prevention of the international spread of diseases), travellers may find that it is strictly enforced, particularly for persons going to Asia from Africa or South America. The validity period of international certificates of vaccination against yellow fever is 10 years, beginning 10 days after vaccination.

No country or territory any longer requires a certificate of *cholera* immunisation as the introduction of cholera into any country cannot be prevented by cholera vaccination.

Now that *smallpox* has been eradicated, smallpox vaccination is no longer required by any country.

Apart from vaccinations required by countries for entry to their territory, other vaccinations are either recommended by WHO for general protection against certain diseases or advised in certain circumstances. A vaccination plan should be established, taking into account the traveller's destination, overall state of health and current immune status, the duration and type of travel, and the time available before travel.

Further information for international travellers is also often provided by national authorities including those in the UK[2] and USA.[3]

1. WHO. *International Travel and Health*. Geneva: WHO, 2008. Also available at: http://www.who.int/ith/en/ (accessed 16/03/08)
2. The National Travel Health Network and Centre. *Health Information for Overseas Travel*. Available at: http://www.nathnac.org/pro/yellowbook_revision.htm (accessed 30/04/06)
3. CDC. *Health Information for International Travel: The "Yellow Book" 2008*. Available at: http://wwwn.cdc.gov/travel/contentYellowBook.aspx (accessed 15/07/08)

Infection eradication. Eradication of infectious diseases has proved more difficult than was hoped, and smallpox is the only disease to have been recognised officially as having been eradicated so far. Eradication is defined as the extinction of the pathogen that causes the infectious disease in question, whereas in elimination the disease disappears but the causative agent remains. Of the target diseases of WHO's Expanded Programme on Immunization (see above), many of the factors necessary for elimination are present for each of the diseases, but some are not. *Measles* is so highly communicable a disease that a vaccine efficacy rate of about 95% is probably not high enough even to eliminate, much less eradicate, the disease. However, immunisation campaigns have produced substantial reductions of infection rate in some countries, although repeated vaccination may be necessary. *Pertussis* is also highly infectious and the vaccine is almost certainly not effective enough. *Tetanus* is not eradicable as the causative organism is ubiquitous. However, elimination of neonatal tetanus may be possible although it depends on protection of more than 80% of infants at birth. This depends not only on maternal vaccination but also on delivery practices. For *poliomyelitis*, countries that are efficient at giving vaccines have proved remarkably successful not only in practically eliminating the disease but also in virtually eradicating the organism. *Tuberculosis* is clearly not eradicable at present and *diphtheria* has many features that suggest it cannot be easily eradicated. Prospects for eradicating *congenital rubella syndrome* are more encouraging and the prospects for elimination or eradication of *mumps* are probably similar to those of rubella.

Other factors that may contribute to the failure of vaccination policies in eradicating disease include: concern, often unfounded, over the safety of vaccines and the perpetuation of invalid contra-indications, the use of inappropriate indicators for the effectiveness of vaccines, the suitability of different types of vaccine and of vaccination schedules, difficulties in vaccine supply, and social and behavioural pressures which reduce compliance with vaccination schedules.

Vaccine development. The WHO Initiative for Vaccine Research (IVR) supports and facilitates the development, clinical evaluation, and worldwide access to safe, effective, and affordable vaccines against infectious diseases of public health importance, especially in developing countries. The Global Vaccine Research Forum hosts an annual conference to discuss vaccine research and development issues, and to update research agendas. Information is frequently updated by WHO.[1,2].

1. WHO. State of the art of new vaccines: research and development (revised 2005). Available at: http://www.who.int/vaccine_research/documents/stateoftheart/ en/index.html (accessed 29/04/06)
2. WHO. New vaccines against infectious diseases: research and development status (April 2005, updated February 2006). Available at: http://www.who.int/vaccine_research/documents/en/Status_Table.pdf (accessed 29/04/06)

AIDS Vaccines

HIV Vaccines; Vacunas del SIDA.

Profile

Many prototype vaccines against AIDS have been or are being developed but the results of clinical studies have generally been disappointing.

◊ Despite the passage of more than two decades since the discovery of HIV, no effective vaccine has been found to either ameliorate the disease or to prevent infection.[1-10] Globally between 40 and 50 million people are infected with HIV, with the overwhelming majority of infections occurring in developing countries which in many cases lack the resources and infrastructure to acquire and deliver costly antiretroviral therapy. A safe, effective, easily administered, and inexpensive AIDS vaccine is therefore desperately required.

There are many reasons why no such vaccine has so far been developed. Firstly, natural infection with HIV does not result in protective immunity; rather, it establishes persistent and lifelong infection and viral clearance and development of resistance to re-infection never occur. This means that there is no model of protective immunity to emulate through vaccination. Various aspects of the biology of the virus have also presented thus far insurmountable problems in vaccine development. The complex structure of the HIV envelope glycoprotein is inherently resistant to antibody attack and the virus has the capacity to evolve quickly in order to evade any neutralising antibody responses mounted by the host. In addition, the selective infection, progressive destruction, and impaired regeneration of CD4+ T helper cells, and the enormous genetic diversity of HIV with its continually evolving geographical distribution and prevalence have proven problematical. Finally, the ability of HIV to evade immune surveillance enables it to establish a state of proviral latency in long-lived CD4+ cells thus providing a persistent, yet immunologically invisible, reservoir of virus infection.

Despite these problems, research has continued[1-9] into developing AIDS vaccines from two distinct perspectives, namely prophylactic vaccines aimed at preventing primary infection and therapeutic vaccines aimed at reducing the rate of disease progression in HIV-infected individuals. Subunit recombinant viral envelope proteins, notably gp120, have been investigated as both prophylactic and therapeutic vaccines, but phase III clinical studies have proved disappointing.[9] In one, involving a bivalent formulation of recombinant gp120 proteins from HIV subtype B, predominant in North America and Europe (AIDSVAX B/B) given to 5009 subjects most of whom were homosexual men, no effect on the rate of HIV infection was found. In a second study in Thailand using AIDSVAX B/E, a related vaccine consisting of recombinant gp120 proteins from HIV subtypes B and E predominant in South-East Asia, no protection against HIV infection was found among 2546 HIV-negative injection drug users. Despite these disappointing results, AIDSVAX B/E is being evaluated in a further study in Thailand as the booster component of a combination immunisation prime-boost regimen that includes an attenuated canarypox vector prime (ALVAC vCP1521). Concerns about the potential success of this trial have, however, been raised by a number of AIDS vaccine researchers and plans for a similar study in the USA have been cancelled due to poor immunogenicity exhibited by the combination during earlier investigations.[9]

While typical HIV neutralising antibody responses are only transiently effective within a given individual and generally not cross-reactive with other isolates, several monoclonal antibodies have been derived from B cells or molecular clones of immunoglobulin genes obtained from HIV-infected persons during the course of natural infection, and exhibit significant neutralisation activity against a wider array of HIV isolates. These monoclonal antibodies act by penetrating gp120 and other viral envelope proteins, thereby preventing CD4 attachment to the virus. Since they have activity against a broader range of isolates and may be produced in relatively large quantities by recombinant technology, passive delivery of a cocktail of monoclonal antibodies is being investigated in *animal* models as a means of prophylaxis.[9] The cost of this approach may, however, potentially prohibit its future use on a wide scale in humans.

Efforts at understanding why it is so difficult to configure immunogens from the HIV envelope that more effectively elicit neutralising antibody responses continue but, in addition, attention has turned to what is termed the cytotoxic T lymphocyte (CTL) hypothesis.[9] This proposes that vaccination of uninfected individuals will not prevent infection but will induce an anti-HIV CTL (CD8+) response. If subsequently infected with HIV these immunised persons would be better able to control viral replication and progress to AIDS much more slowly or perhaps not at all and potentially decrease viral transmission. The validity of this hypothesis is at present uncertain but it has been supported by the observation of low level, yet detectable, HIV-specific CD8+ T cell responses in certain cohorts of highly exposed but uninfected individuals.

Additionally, new vaccine strategies are becoming available which it is thought will probably be able to elicit HIV-specific CTL responses of sufficient magnitude to allow direct testing of the concept in humans. Numerous *animal* studies are underway to assess the safety and immunogenicity of a number of replication-defective recombinant viral vectors (modified vaccinia Ankara strain, vesicular stomatitis virus, Venezuelan equine encephalitis virus, adeno-associated virus, and adenovirus) and also bacterial, yeast, and plasmid DNA vectors, all of which are designed to elicit antiviral CD8+ T cell responses.[9] However, initial analyses from a large study of an adenovirus-based vaccine designed to boost T cell responses (the STEP trial) provoked alarm since results suggested that it did not decrease susceptibility to HIV infection and might have increased it in some cases.[11]

Recombinant plasmid DNA immunogens are also under investigation as potential AIDS vaccines because of their desirable safety profile and ability to express defined and discrete inserted HIV antigens. They are either used singly or as a priming immunogen in prime-boost regimens using different vaccine vectors for sequential immunisation. Initial results in preclinical *animal* studies were encouraging, but results have been disappointing in subsequent phase I human studies.[8]

Within the field of AIDS vaccine research, the decision to advance candidate vaccines from phase I or II to phase III efficacy studies is somewhat complex. At present there are no consistent criteria in place to provide guidance on such decisions and there is a need for a coordinated, objective, and rigorous process for prioritisation in order to facilitate vaccine development. To the same end, alternative designs for phase III studies are being considered, including the use of endpoints such as reduction of viral load or preservation of CD4+ T cell counts for assessing vaccine efficacy rather than prevention of infection as the single primary endpoint. These and other measures may facilitate licensure of vaccines which currently would not occur.

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6. Stevceva L, Strober W. Mucosal HIV vaccines: where are we now? *Curr HIV Res* 2004; **2:** 1–10.
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10. Duerr A, *et al.* HIV vaccines: new frontiers in vaccine development. *Clin Infect Dis* 2006; **43:** 500–11.
11. Sekaly R-P. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? *J Exp Med* 2008; **205:** 7–12.

Anthrax Vaccines

Vacunas del carbunco.

ATC — J07AC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates)); Vaccinum Anthracis Adsorbatum ab Colato Culturarum ad Usum Humanum. A preparation of *Bacillus anthracis* antigens precipitated by aluminium potassium sulphate. The antigens are prepared from a sterile culture filtrate produced by a non-encapsulated strain, either avirulent or attenuated, of *B. anthracis*. The main virulence components of *B. anthracis* are the polyglutamic acid capsule and 2 binary anthrax toxins, namely lethal toxin and oedema toxin, formed from the respective combination of protective antigen with either lethal factor or oedema factor. In addition, the vaccine is likely to contain many other *B. anthracis* antigens, including membrane proteins, secreted proteins, cytoplasmic proteins, peptidoglycans, nucleic acids, and carbohydrates. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

An anthrax vaccine that is an alum precipitate of the antigen found in the sterile filtrate of suitable cultures of the Sterne strain of *Bacillus anthracis* is available in the UK for human use. It is used for active immunisation against anthrax (p.163) and is recommended for persons working with potentially infected animals or animal products. It is given in 4 doses, each of 0.5 mL by intramuscular injection. The first 3 doses are separated by intervals of 3 weeks and the fourth dose follows after an interval of 6 months. In the USA, where an anthrax vaccine is also available, 6 doses, each of 0.5 mL, are given subcutaneously, the first 3 at intervals of 2 weeks and the last 3 at intervals of 6 months. Reinforcing doses of 0.5 mL are required each year.

◊ References.

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2. CDC. Use of anthrax vaccine in response to terrorism: supplemental recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2002; **51:** 1024–6.
3. Health Protection Agency. Guidelines for action in the event of a deliberate release: anthrax (April 2007). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 15/07/08)
4. Grabenstein JD. Countering anthrax: vaccines and immunoglobulins. *Clin Infect Dis* 2008; **46:** 129–36.

Preparations

Ph. Eur.: Anthrax Vaccine for Human Use (Adsorbed, Prepared from Culture Filtrates);
USP 31: Anthrax Vaccine Adsorbed.

Proprietary Preparations (details are given in Part 3)
USA: Biothrax.

Anti-D Immunoglobulins

Inmunoglobulinas anti-D.

ATC — J06BB01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Anti-D Immunoglobulin; Immunoglobulinum Humanum Anti-D; Anti-D (Rh_o) Immunoglobulin BP 2008). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is intended for intramuscular administration. It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies, such as anti-C, anti-E, anti-A, and anti-B. Normal immunoglobulin may be added. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored in an airtight container.

Ph. Eur. 6.2 (Human Anti-D Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Anti-D ad Usum Intravenosum; Anti-D Immunoglobulin for Intravenous Use BP 2008). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from D-negative donors who have been immunised against the D-antigen. It contains specific antibodies against the erythrocyte D-antigen and may also contain small quantities of other blood group antibodies. Human normal immunoglobulin for intravenous administration may be added. Storage requirements are similar to those for Human Anti-D Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25°.

USP 31 (Rh_o (D) Immune Globulin). A sterile solution of globulins derived from human plasma containing antibody to the erythrocyte factor Rh_o (D). It contains 10 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

In patients given anti-D immunoglobulin for idiopathic thrombocytopenic purpura (ITP) there have been rare reports of back pain, shaking chills, fever, and discoloured urine; such signs and symptoms may be associated with intravascular haemolysis. Serious and sometimes fatal complications of intravascular haemolysis including anaemia, acute renal insufficiency, or disseminated intravascular coagulation have been rarely reported. Most reported cases of haemolysis occurred within 4 hours of the dose.

For the treatment of ITP, anti-D immunoglobulin is contra-indicated in rhesus-negative or splenectomised patients. Patients with ITP who need a blood transfusion should be given rhesus-negative red blood cells so as not to exacerbate ongoing haemolysis. Those with low initial haemoglobin concentrations (less than 10 g/dL) should be given a reduced dosage of the immunoglobulin to minimise the risk of severe anaemia.

When given for prophylaxis of rhesus sensitisation, anti-D immunoglobulin should not be used in rhesus-positive individuals.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Anti-D immunoglobulin is used to prevent a rhesus-negative mother actively forming antibodies to fetal rhesus-positive red blood cells that may pass into the maternal circulation during childbirth, abortion, or certain other sensitising events. In subsequent rhesus-positive pregnancies these antibodies could produce haemolytic disease of the newborn (erythroblastosis foetalis). The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. Anti-D immunoglobulin is also used in the management of some blood disorders, primarily idiopathic thrombocytopenic purpura.

Anti-D immunoglobulin products are available either for intramuscular use only or for intramuscular or intravenous use. Doses differ for these products and the manufacturer's recommendation should be followed for commercial products.

In the UK, recommendations produced by expert groups relate to the use of a non-proprietary product produced by the National Blood Transfusion Service. They recommend that **postnatal prophylaxis** with anti-D immunoglobulin should always be given to rhesus-negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus-positive infants. It should be given as soon as possible after delivery but may give some protection even if treatment is delayed beyond 72 hours. A dose of 500 units (100 micrograms) by intramuscular injection will clear up to 4 mL of fetal red cells. An additional dose may be required depending on the amount of transplacental bleeding; for bleeds exceeding 4 mL an additional 125 units for each mL of red cells will be required.

For routine **antenatal prophylaxis**, two intramuscular doses of at least 500 units of anti-D immunoglobulin should be given at 28 and 34 weeks' gestation. Postnatal prophylaxis is still necessary.

There is also a risk of sensitisation during pregnancy from spontaneous, induced, or threatened abortion, amniocentesis, or external version. Any rhesus-negative woman at **risk of transplacental haemorrhage** during pregnancy and not known to be sensitised should be given an intramuscular dose of 250 units at up to 20 weeks' gestation and 500 units of anti-D immunoglobulin after 20 weeks' gestation.

Anti-D immunoglobulin is also given to rhesus-negative women of child-bearing potential after the inadvertent **transfusion of Rh-incompatible blood**, or after receiving blood components containing rhesus-positive red cells or organ donations from rhesus-positive donors. The dose is based on the amount of red blood cells transfused; an intramuscular dose up to 125 units/mL of transfused cells may be used.

In the USA, doses of anti-D immunoglobulin have traditionally been higher than in the UK; dosage recommendations are based on a standard dose that is capable of suppressing the immune response to 15 mL of incompatible red blood cells. One-sixth of this dose may be used up to 12 weeks of gestation for sensitising episodes.

For **idiopathic thrombocytopenic purpura**, a usual initial dose of 250 units/kg (50 micrograms/kg) of a licensed anti-D immunoglobulin product is given by intravenous injection; it may be given in two divided doses on separate days if desired. Maintenance doses usually range between 125 to 300 units/kg (25 to 60 micrograms/kg) depending on the clinical response. A reduced initial dose of 125 to 200 units/kg (25 to 40 micrograms/kg) is recommended in patients with pre-existing anaemia (haemoglobin below 10 g/dL).

Haemolytic disease of the newborn. Rhesus (Rh) incompatibility, in particular Rh(D) incompatibility, is a major cause of potentially severe haemolytic disease of the newborn, although other blood group antibodies may also cause the disease. The use of anti-D immunoglobulin to suppress the production of anti-D antibodies in a Rh(D)-negative mother in response to leakage of red blood cells across the placenta from a Rh(D)-positive fetus has produced a major reduction in the incidence of this disorder.

Prophylaxis. Postnatal prophylaxis of Rh(D)-negative mothers after the birth of a Rh(D)-positive infant is well established. In 1971, WHO[1] suggested a standard intramuscular dose of 200 to 300 micrograms but stated that a 100-microgram dose was likely to have a success rate only slightly inferior to that of a 200-microgram dose, thus allowing optimum use to be made of a limited resource. Clinical experience in the UK has confirmed the efficacy of the 100-microgram (500 units) intramuscular dose and this is the amount officially recommended in the UK in such situations.[2,3] Doses do, however, vary considerably in other countries: 200 to 300 micrograms (1000 to 1500 units) is given in the USA and in many European countries, and 125 micrograms (625 units) is used in Australia.

Despite the success of anti-D immunoglobulin prophylaxis, sensitisations have continued to occur. There are several possible reasons for this, the main one being immunisation during pregnancy where there has been no overt sensitising event. Postpartum doses may be omitted due to oversight or loss to follow-up. Assessment of the volume of any transplacental haemorrhage is essential to avoid inadequate dosing. Significantly large feto-maternal haemorrhage is likely to occur after traumatic deliveries including caesarean section, manual removal of the placenta, still-birth or intra-uterine death, abdominal trauma during the third trimester, delivery of twins, or unexplained hydrops fetalis.

The efficacy of postpartum prophylaxis is not in question but opinions differ on the need for prophylaxis during pregnancy. It is generally agreed that prophylaxis is necessary in all non-sensitised Rh(D)-negative women after therapeutic terminations at any stage of pregnancy, including medical termination utilising mifepristone, after ectopic pregnancy, spontaneous complete or incomplete miscarriage after 12 weeks' gestation, or threatened miscarriage after 12 weeks' gestation as evidenced by abnormal bleeding or abdominal pain. Recommendations have been made by the British Committee for Standards in Haematology for the management of these sensitising events.[3]

Prophylaxis should also be given to all non-sensitised Rh(D)-negative women after the following sensitising events during pregnancy: invasive prenatal diagnosis including amniocentesis, chorion villus sampling, or fetal blood sampling; other intra-uterine procedures such as insertion of shunts or embryo reduction; antepartum haemorrhage; external cephalic version of the fetus; closed abdominal injury; or intra-uterine death.[2,3] A dose of 50 micrograms (250 units) is recommended for prophylaxis after these events up to 20 weeks of pregnancy, and at least 100 micrograms (500 units) thereafter.

In the UK routine antenatal prophylaxis at 28 and 34 weeks' gestation is recommended for all Rh(D)-negative women[2-4] and should be given irrespective of whether anti-D prophylaxis had been given for other sensitising events during the same pregnancy or previous pregnancies.[3]

Treatment. In mild cases, the resultant hyperbilirubinaemia can be managed with phototherapy. In severe cases, exchange transfusions may be necessary and intra-uterine transfusions may be considered in pregnancies of less than about 34 weeks' gestation; beyond this, premature delivery is often preferable.[5] Some clinicians have reported treatment failures with intra-uterine transfusions but have found intravenous normal immunoglobulin 400 mg/kg daily for 5 days every 2 to 3 weeks to the mother to be effective. There are several case reports[6,7] of beneficial responses using similar doses, but no benefit was seen in 4 patients receiving 1000 mg/kg once a week.[8] This dose, however, appeared to reduce the severity of the disease in a patient with Kell sensitisation.[8] Reductions in bilirubin concentrations have been reported with intravenous normal immunoglobulin 500 mg/kg as a single dose in newborn infants,[9] and a systematic review[10] found that such treatment reduced the number of infants requiring exchange transfusion and the duration of hospital stay and phototherapy needed. Reports in small numbers of infants[11-15] suggest that epoetins may be of value in controlling anaemia which develops 2 to 8 weeks after birth.

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7. de la Cámara C, *et al.* High-dose intravenous immunoglobulin as the sole prenatal treatment for severe Rh immunization. *N Engl J Med* 1988; **318:** 519–20.
8. Chitkara U, *et al.* High-dose intravenous gamma globulin: does it have a role in the treatment of severe erythroblastosis fetalis? *Obstet Gynecol* 1990; **76:** 703–8.
9. Rübo J, *et al.* High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr* 1992; **121:** 93–7.
10. Gottstein R, Cooke RWI. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F6–F10.
11. Ohls RK, *et al.* Recombinant erythropoietin as treatment for the late hyporegenerative anemia of Rh hemolytic disease. *Pediatrics* 1992; **90:** 678–80.
12. Scaradavou A, *et al.* Suppression of erythropoiesis by intrauterine transfusions in hemolytic disease of the newborn: use of erythropoietin to treat the late anemia. *J Pediatr* 1993; **123:** 279–84.
13. Ovali F, *et al.* Management of late anemia in Rhesus hemolytic disease: use of recombinant human erythropoietin (a pilot study). *Pediatr Res* 1996; **39:** 831–4.
14. Zuppa AA, *et al.* Recombinant erythropoietin in the prevention of late anaemia in intrauterine transfused neonates with Rh-haemolytic disease. *Fetal Diagn Ther* 1999; **14:** 270–4.
15. Dhodapkar KM, Blei F. Treatment of hemolytic disease of the newborn caused by anti-Kell antibody with recombinant erythropoietin. *J Pediatr Hematol Oncol* 2001; **23:** 69–70.

Idiopathic thrombocytopenic purpura. Normal immunoglobulin is used for chronic idiopathic thrombocytopenic purpura (p.1505), and anti-D immunoglobulin has been found to have similar properties. The potential role of anti-D immunoglobulin in the treatment of idiopathic thrombocytopenic purpura has been discussed in several reviews.[1-3] In general, despite many studies showing the clinical efficacy and low toxicity of intravenous anti-D immunoglobulin, its precise role has not been defined for a number of reasons. Firstly, the optimal dose has not been established: doses used have ranged from 12.5 to 25 micrograms/kg daily, given for at least 2 days, in early studies to later more promising single doses of 50 to 75 micrograms/kg. Secondly, no study has shown anti-D immunoglobulin to be as effective as corticosteroid therapy for initial treatment. Furthermore, despite suggestions that anti-D immunoglobulin may be safer and easier to give than normal immunoglobulin, good comparative data is scanty. Clinical studies have, however, shown the safety and efficacy of intravenous anti-D immunoglobulin in Rh(D)-positive, non-splenectomised patients with idiopathic thrombocytopenic purpura.[1] A prospective, randomised clinical study[4] in Rh(D)-positive children with idiopathic thrombocytopenic purpura found that a single intravenous dose of 75 micrograms/kg raised the platelet count more rapidly than a single intravenous dose of 50 micrograms/kg, and was as effective as a single intravenous dose of 800 mg/kg of normal immunoglobulin.

1. Scaradavou A, Bussel JB. Clinical experience with anti-D in the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 1998; **35** (suppl 1): 52–7.
2. Sandler SG. Treating immune thrombocytopenic purpura and preventing Rh alloimmunization using intravenous rho (D) immune globulin. *Transfus Med Rev* 2001; **15:** 67–76.
3. Sandler SG. Intravenous Rh immune globulin for treating immune thrombocytopenic purpura. *Curr Opin Hematol* 2001; **8:** 417–20. Correction. *ibid.* 2002; **9:** 179.
4. Tarantino MD, *et al.* Single dose of anti-D immune globulin at 75μg/kg is as effective as intravenous immune globulin at rapidly raising the platelet count in newly diagnosed immune thrombocytopenic purpura in children. *J Pediatr* 2006; **148:** 489–94.

Preparations

Ph. Eur.: Human Anti-D Immunoglobulin; Human Anti-D Immunoglobulin for Intravenous Administration;
USP 31: Rh (D) Immune Globulin.

Proprietary Preparations (details are given in Part 3)

Arg.: BayRho-D†; Igantid; Immunorho; Kam Rho-D; Partoben; Partogamma; Rhesogamma; ***Austral.:*** WinRho; ***Austria:*** Partobulin; Rhesogam; ***Belg.:*** RhoGAM; ***Braz.:*** Matergam; Partogama†; WinRho†; ***Canad.:*** BayRho-D†; Hyperrho S/D; WinRho; ***Chile:*** BayRho-D†; Igamad; Immunorho; Rhesogamma P; ***Cz.:*** Igamad; Partobulin; Rhesonativ; Rhophylac; ***Denm.:*** Rhesogamma P; Rhophylac; ***Fin.:*** Rhophylac; ***Fr.:*** Rhophylac; ***Ger.:*** Partobulin; Rhesogam; Rhophylac; ***Gr.:*** Rhesogamma P; Rhophylac; WinRho; ***Hong Kong:*** BayRho-D; Partobulin; RhoGAM; WinRho; ***Hung.:*** Rhesonativ; RhoGAM; ***India:*** Matergam-P; ***Indon.:*** HyperRho S/D; ***Irl.:*** Rhesonativ†; ***Israel:*** BayRho-D; KamRho-D; Rhophylac; WinRho; ***Ital.:*** Haima-D†; Igamad; Immunorho; Parto-Gamma†; Partobulin; Rhophylac; ***Malaysia:*** Rhesonativ†; ***Mex.:*** BayRho-D†; Octaglob D; Probi-Rho D†; Rhesogamma P; Rhophylac; ***Neth.:*** RheDQuin; Rhophylac; ***Norw.:*** Rhesogamma†; Rhophylac; ***NZ:*** RhoGAM; WinRho; ***Philipp.:*** WinRho; ***Pol.:*** Gamma Anty D; Partobulin; ***Port.:*** Igantid†; Rhesonativ; Rhesuman†; Rhophylac; WinRho; ***Rus.:*** HyperRHO S/D (ГиперРОУ С/Д); ***S.Afr.:*** Rhesugam; ***Singapore:*** BayRho-D†; ***Spain:*** Gamma Anti D; Rhesogamma; Rhesuman†; ***Swed.:*** Rhesogamma†; Rhesonativ; Rhophylac; ***Switz.:*** Rhophylac; ***Thai.:*** Igamad; Rhesuman†; ***Turk.:*** BayRho-D; Partobulin; Rhesogamma P; Rhesuman; RhoGAM; ***UK:*** D-Gam; Partobulin; Rhophylac; WinRho; ***USA:*** HyperRho S/D; MICRhoGAM; RhoGAM; Rhophylac; WinRho; ***Venez.:*** RhoGAM†.

Argentine Haemorrhagic Fever Vaccines

Junin Haemorrhagic Fever Vaccines; Vacunas de la fiebre hemorrágica argentina.

Profile

A live attenuated vaccine is being investigated for active immunisation against Argentine haemorrhagic fever.

◊ References.

1. Maiztegui JI, *et al.* Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *J Infect Dis* 1998; **177:** 277–83.
2. Feuillade MR, Enría DA. Análisis de la utilidad de la vacuna Candid 1 en la prevención de la fiebre hemorrágica argentina en niños. *Rev Panam Salud Publica* 2005; **18:** 100–106.

BCG Vaccines

Bacillus Calmette-Guérin Vaccines; Vacunas BCG.

Вакцины БЦЖ

ATC — J07AN01; L03AX03.

Pharmacopoeias. Many pharmacopoeias, including *Br., Eur.* (see p.vii), and *US*, have monographs.

Ph. Eur. 6.2 (BCG Vaccine, Freeze-dried; Vaccinum Tuberculosis (BCG) Cryodesiccatum; Bacillus Calmette-Guérin Vaccine BP 2008). A freeze-dried preparation containing live bacteria obtained from a strain derived from the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity to protect against tuberculosis has been established. It may contain a stabiliser. The dried vaccine should be stored at 2° to 8° and be protected from direct sunlight.

The BP 2008 states that BCG may be used on the label.

The BP 2008 gives BCG Vaccine as an approved synonym.

BP 2008 (Percutaneous Bacillus Calmette-Guérin Vaccine). A suspension of living cells of an authentic strain of the bacillus of Calmette and Guérin with a higher viable bacterial count than Bacillus Calmette-Guérin Vaccine. It is supplied as a dried vaccine and is reconstituted immediately before use by the addition of a suitable sterile liquid. The dried vaccine should be stored at a temperature below −20° and be protected from light.

The BP 2008 states that Tub/Vac/BCG (Perc) may be used on the label.

The BP 2008 gives Percut. BCG Vaccine as an approved synonym.

USP 31 (BCG Vaccine). A dried living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*; it is grown from a strain that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It contains a suitable stabiliser and no antimicrobial agent. The dried vaccine should be stored in hermetically sealed containers at 2° to 8°. The reconstituted vaccine should be used immediately after preparation and any portion not used within 2 hours should be discarded.

Ph. Eur. 6.2 (BCG for Immunotherapy; BCG ad Immunocurationem). A freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) whose capacity for treatment has been established. It may contain a stabiliser. It is for intravesical use only. The product should be stored at 2° to 8° and be protected from direct sunlight.

USP 31 (BCG Live). A freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis*, var. BCG) for intravesical use only. It is reconstituted and further diluted aseptically with a sterile diluent before use. A reconstituted dose contains 1.0–19.2 × 10^8 colony-forming units (cfu). It does not contain a preservative.

BCG Live is sensitive to light and must be stored in a glass container, protected from direct light, and at 2° to 8°.

Adverse Effects and Treatment

As for vaccines in general, p.2201.

Serious adverse reactions to BCG vaccines used *for immunisation* against tuberculosis are rare, although the incidence may vary between strains. The normal therapeutic response involves induration and development of a lesion at the injection site, possibly with enlargement of local lymph nodes; this lesion may later ulcerate and heal over some months leaving a scar. In a few patients an exaggerated reaction, usually associated with overdose, inadvertent subcutaneous injection, or use in persons who are already tuberculin positive, may result in an abscess or discharging ulcer, or suppurative lymphadenitis. Nonspecific systemic reactions may include fever and headache. Generalised reactions, possibly due to hypersensitivity, have been reported with a few fatalities. Disseminated BCG infection may occur and has also led to fatalities, particularly in immunocompromised patients. Disseminated BCG complications such as osteitis have been reported with some BCG vaccines. Very rarely, a lupoid type of reaction has occurred, mostly after multiple revaccination.

Intravesical use of BCG in the treatment and prophylaxis of bladder cancer is associated with an inflammatory response; transient dysuria and urinary frequency, sometimes with fever or a flu-like syndrome, and haematuria, are common, especially with repeated treatment (as in maintenance therapy). Rarely bladder contracture and epididymo-orchitis have been reported. As with vaccination, disseminated BCG infection has occurred rarely and may potentially be fatal. Fever lasting more than 24 hours should be investigated, and antimycobacterial therapy given if necessary. Other reported adverse effects have included hypersensitivity reactions such as rashes and arthralgia, and ocular symptoms including uveitis, conjunctivitis, iritis, and keratitis.

◊ Reviews and studies of the adverse effects of BCG vaccines and their management.[1-6] An increased incidence of local effects has followed intradermal injection of high doses of BCG vaccines.[7,8] The incidence of adverse effects may vary between strains; an increase in incidence was reported in Ireland after withdrawal of a vaccine based on the Evans strain and its replacement with a vaccine containing the SSI strain of BCG.[9]

1. Lotte A, *et al.* Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 1988; **63:** 47–59.
2. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.
3. Grange JM. Complications of bacille Calmette-Guérin (BCG) vaccination and immunotherapy and their management. *Commun Dis Public Health* 1998; **1:** 84–8.
4. FitzGerald JM. Management of adverse reactions to bacille Calmette-Guerin vaccine. *Clin Infect Dis* 2000; **31** (suppl 3): S75–S76.
5. Turnbull FM, *et al.* National study of adverse reactions after vaccination with bacille Calmette-Guérin. *Clin Infect Dis* 2002; **34:** 447–53.
6. Bellet JS, Prose NS. Skin complications of bacillus Calmette-Guérin immunization. *Curr Opin Infect Dis* 2005; **18:** 97–100.
7. Miles MM, Shaw RJ. Effect of inadvertent intradermal administration of high dose percutaneous BCG vaccine. *BMJ* 1996; **312:** 1014.
8. Puliyel JM, *et al.* Adverse local reactions from accidental BCG overdose in infants. *BMJ* 1996; **313:** 528–9.
9. Bolger T, *et al.* Complications associated with the bacille Calmette-Guérin vaccination in Ireland. *Arch Dis Child* 2006; **91:** 594–7.

Effects on the bones and joints. The risk of osteitis after BCG vaccination varies from country to country and appears to be linked to the strain of bacillus used.[1]

Osteitis or arthritis has also been reported after intravesicular use of BCG (see below).

1. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bull WHO* 1990; **68:** 93–108.

Effects on the eyes. Follicular conjunctivitis occurred after accidental contamination of the eye with BCG vaccine.[1] The conjunctivitis responded to topical corticosteroid therapy, but a course of isoniazid was given as a precautionary measure.

For reference to uveitis after intravesical instillation see below.

1. Pollard AJ, George RH. Ocular contamination with BCG vaccine. *Arch Dis Child* 1994; **70:** 71.

Effects on the lymphatic system. Lymphadenitis associated with BCG vaccination has been reviewed.[1] It is the most common adverse effect of BCG vaccination and may develop 2 to 24 weeks after vaccination, with most cases occurring within 6 months. The incidence and severity depend on the dose, vaccine strain, the age at vaccination, and the immunological state of the patient. Suppurative BCG lymphadenitis in the form that develops in 30 to 80% of cases; neonates and immunodeficient patients are associated with an increased risk.

The treatment of BCG lymphadenitis remains controversial. Although antibacterials and antituberculous drugs such as isoniazid and rifampicin have been given, there is little evidence to support their use; the non-suppurative (simple) form regresses spontaneously without treatment while suppurating lymph nodes may be drained by needle aspiration and left to heal.

1. Goraya JS, Virdi VS. Bacille Calmette-Guerin lymphadenitis. *Postgrad Med J* 2002; **78:** 327–9.

Intravesicular administration. Intravesicular instillation of BCG can give rise to both localised and systemic adverse effects as a consequence of the immune stimulation required to eradicate cancer cells.[1-3] The most serious effects are due to disseminated infection and include severe sepsis with cardiorespiratory manifestations and a disseminated mycobacterial infection with granulomatous pneumonitis and hepatitis; prompt treatment with antimycobacterials is required.[1,4,5] Fatalities have occurred.[6,7] Other reports include severe haemophagocytic syndromes,[8] uveitis,[9,10] and arthritis and osteitis.[11,12] Epididymo-orchitis has also been reported up to 4 years after intravesicular BCG therapy.[13,14]

Initial findings of a study[15] involving 115 patients indicated that prophylactic use of ofloxacin, a fluoroquinolone with tuberculostatic activity, decreased the incidence of moderate to severe adverse effects associated with intravesical BCG without any significant decrease in recurrence-free survival at 12 months. Ofloxacin was given orally after each BCG instillation; a dose of 200 mg was given 6 hours after the first urination with a second dose about 10 to 12 hours later. Long-term study, however, was still needed to confirm these results.

1. Lamm DL. Efficacy and safety of bacille Calmette-Guérin immunotherapy in superficial bladder cancer. *Clin Infect Dis* 2000; **31:** S86–S90.
2. Rischmann P, *et al.* BCG intravesical instillations: recommendations for side-effects management. *Eur Urol* 2000; **37** (suppl 1): 33–6.
3. Huang TC. Management of complications of bacillus Calmette-Guerin immunotherapy in the treatment of bladder cancer. *Ann Pharmacother* 2000; **34:** 529–32.
4. Mooren FC, *et al.* Systemic granulomatous disease after intravesical BCG instillation. *BMJ* 2000; **320:** 219.
5. Gómez-Ferrer Lozano A, *et al.* Neumonitis granulomatosa por instilación endovesical de BCG. *Actas Urol Esp* 2006; **30:** 839–42.
6. Peyrière H, *et al.* Fatal systemic reaction after multiple doses of intravesical bacillus Calmette-Guérin for polyposis. *Ann Pharmacother* 2000; **34:** 1279–82.
7. Kamphuis JT, *et al.* BCG immunotherapy: be cautious of granulomas. Disseminated BCG infection and mycotic aneurysm as late complications of intravesical BCG instillations. *Neth J Med* 2001; **58:** 71–5.
8. Schleinitz N, *et al.* Severe hemophagocytic syndrome after intravesical BCG instillation. *Am J Med* 2002; **112:** 593–4.
9. Wertheim M, Astbury N. Bilateral uveitis after intravesical BCG immunotherapy for bladder carcinoma. *Br J Ophthalmol* 2002; **86:** 706.
10. Jacob M, *et al.* Pan-uvéite dans les suites d'instillations intravésicales de BCG (Bacille de Calmette et Guérin). *J Fr Ophtalmol* 2006; **29:** 552–5.
11. Morgan MB, Iseman MD. Mycobacterium bovis vertebral osteomyelitis as a complication of intravesical administration of Bacille Calmette-Guérin. *Am J Med* 1996; **100:** 372–3.
12. Tinazzi E, *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int* 2006; **26:** 481–8.
13. Menke JJ, Heins JR. Epididymo-orchitis following intravesical bacillus Calmette-Guérin therapy. *Ann Pharmacother* 2000; **34:** 479–82.
14. Falkensammer C, *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guérin therapy for superficial bladder carcinoma. *Urology* 2005; **65:** 175.
15. Colombel M, *et al.* The effect of ofloxacin on bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol (Baltimore)* 2006; **176:** 935–9.

Precautions

As for vaccines in general, p.2202.

BCG vaccines may be given with other live vaccines, but if they are not given at the same time it is preferable to allow an interval of 4 weeks between each although the period may be reduced to 10 days if absolutely necessary. However, routine primary immunisation in infants, including the use of live poliomyelitis vaccine, need not be delayed. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of lymphadenitis. BCG vaccination should be postponed in patients with fever or generalised skin infection. In patients with eczema, BCG vaccines should be given at a site free from lesions. Because of the possible risk of disseminated infections, BCG vaccines should not be given to immunocompromised patients including those with HIV infection. Infants born to HIV-positive mothers may be vaccinated once HIV infection has been ruled out; vaccination should be considered in infants of unknown status in areas of high tuberculosis prevalence if there are no signs suggestive of HIV infection. Vaccination is contra-indicated in patients taking antimycobacterial therapy, and those with a history of tuberculosis or a positive tuberculin skin test. Neonates in household contact with a known or suspected case of active tuberculosis should not be vaccinated.

The instillation of *intravesical* BCG should be postponed for 7 to 14 days after any trauma to the urinary tract including transurethral resection, biopsy, and trauma caused by catheterisation. Treatment should also be postponed in patients with acute febrile illness, urinary tract infection, or gross haematuria. Use is contra-indicated in patients with active tuberculosis, previous history of systemic reaction to BCG, or treatment with antimycobacterial therapy. As with vaccination, intravesical BCG should be avoided in immunocompromised patients, including those with HIV infection. Because BCG contains live mycobacteria that may be excreted in the urine, patients should be advised on the risk of contamination, and on appropriate infection control procedures to protect family and close contacts.

Immunocompromised patients. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients including those with symptomatic HIV infections and AIDS. An increased risk of disseminated BCG infection has been seen in infants and children with asymptomatic HIV infections,[1,2] leading to high mortality rates of about 80%. WHO Global Advisory Committee on Vaccine Safety therefore no longer recommends BCG vaccination of infants and children with known HIV infection (see Tuberculosis, HIV-infected Patients, below).

1. Hesseling AC, *et al.* Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006; **42:** 548–58.
2. Hesseling AC, *et al.* The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* 2007; **25:** 14–18.

Interactions

As for vaccines in general, p.2202.

Theophylline. For a report of increased theophylline half-life and serum concentrations after BCG vaccination, see under Theophylline Hydrate, p.1145.

Uses and Administration

BCG vaccines are used for active immunisation against tuberculosis. A form suitable for immunotherapy is also used locally in the treatment and prophylaxis of carcinoma *in-situ* of the bladder, and the prophylaxis of recurrent early stage bladder papillomas after resection.

For vaccination against **tuberculosis** different strategies may be adopted, depending on the prevalence of the disease in local populations, the prevalence of HIV co-infection, the potential for infant exposure to these diseases, and the existence of infrastructure to diagnose infection and follow-up vaccinated persons. WHO considers that BCG vaccination of adults is not normally recommended, although it may be considered for tuberculin-negative subjects in unavoidable and close contact with drug-resistant tuberculosis. In countries with a high prevalence of tuberculosis, infant immunisation with a single dose of BCG as soon as possible after birth is ideally to be recommended. However, these populations tend to have a high prevalence of HIV infection as well, and BCG vaccination is contra-indicated in HIV-infected subjects. Nonetheless, WHO considers that children without HIV infection will particularly benefit from vaccination in these circumstances, and recommends that immunisation should be carried out in:

- infants born to women of unknown HIV status
- infants without obvious signs of HIV infection born to women known to be HIV-infected
- infants known to be HIV-negative as a result of virological testing

It considers that immunisation should be avoided in infants known to be infected with HIV, or whose HIV status is unknown but who are born to HIV-infected mothers and have signs or symptoms suggestive of HIV infection.

In contrast, a country such as the UK has a relatively low prevalence of tuberculosis, and routine immunisation is no longer carried out. Instead, immunisation is targeted at groups considered to be at increased risk:

- all neonates and infants (0 to 12 months) living in areas where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- all neonates and infants with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated children aged 1 to 5 years with a parent or grandparent born in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population; such children aged from 6 to 16 years should also be vaccinated if they have been shown to be tuberculin-negative
- previously unvaccinated, tuberculin-negative contacts of persons suffering from active respiratory tuberculosis
- previously unvaccinated, tuberculin-negative immigrants under 16 years of age who were born in, or lived in for at least 3 months, a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population
- previously unvaccinated, tuberculin-negative persons under 16 years of age intending to stay or work with local people for more than 3 months in a country where the annual incidence of tuberculosis is greater than 40 cases per 100 000 of the population.
- vaccination should be *withheld* in all those known or suspected to be HIV-infected, regardless of clinical status. Where vaccination is indicated, as in infants born to HIV-positive mothers, it should only be given after two appropriately timed negative postnatal tests for HIV infection.

Vaccination is also recommended in the UK for previously unvaccinated, tuberculin-negative persons under 35 years of age in the following groups:

- health care workers or laboratory staff at high risk of infection
- veterinary and other staff who handle animals known to be susceptible to tuberculosis
- staff in any institution where the incidence of tuberculosis is high

In the USA, CDC advises still more selective use, with BCG vaccination restricted essentially to tuberculin-negative children or health workers who are continually exposed to individuals with untreated or drug-resistant tuberculosis.

BCG vaccine is given intradermally (intracutaneously) at the insertion of the deltoid muscle in a dose of 0.1 mL; infants under 12 months of age are given 0.05 mL.

Contacts of patients with active pulmonary tuberculosis may require chemoprophylaxis (see under Tuberculosis, p.196) despite previous vaccination. Neonates and children under 2 years of age should be given chemoprophylaxis and immunised, if appropriate, once the course is completed. An isoniazid-resistant form of the vaccine has been produced for use in patients who have received isoniazid, but its use is not recommended.

For use in immunotherapy of **bladder cancer** several regimens have been tried. A typical induction regimen consists of once-weekly intravesical instillation of a solution containing 1 to 16×10^8 colony forming units of BCG in about 50 mL of preservative-free saline 0.9%, for 6 consecutive weeks. Maintenance regimens vary widely from single doses or short courses (once a week for 3 weeks) at 3- to 6-monthly intervals, to instillation once a month; the period of suggested maintenance also varies from 6 months to 3 years. Some also favour a consolidation regimen of three further instillations, a week apart, carried out 6 weeks after completion of induction. Instillations should be retained in the bladder for 2 hours if possible, and then voided with the patient in a sitting position to minimise the risk of environmental contamination (see also Precautions, above).

Leprosy. BCG vaccination has been shown to protect recipients against leprosy and is considered to be one of the factors responsible for the decrease in the incidence of leprosy. A meta-analysis[1] of studies using BCG vaccine to prevent leprosy found that the average protective effect was 26% for the clinical studies and 61% for the observational (cohort or case-controlled) studies. Protection was better for multibacillary forms rather than paucibacillary forms of leprosy. Age at the time of vaccination was not a predictor of vaccine efficacy, but in the observational studies the protective effect was found to decrease with age. Clinical studies indicated that an additional dose of BCG was more effective than a single dose. For further details concerning the use of BCG vaccines in both the immunoprophylaxis and immunotherapy of leprosy, see Leprosy Vaccines, p.2220.

1. Setia MS, *et al.* The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006; **6:** 162–70.

Malignant neoplasms. Immunotherapy with BCG vaccines has been tried in various malignant disorders and is most successful when given locally. The possibility that BCG vaccination might protect children against malignancies has been discussed.[1]

1. Grange JM, Stanford JL. BCG vaccination and cancer. *Tubercle* 1990; **71:** 61–4.

BLADDER. Immunotherapy with adjuvant intravesical BCG is used in the management of bladder cancers and is the treatment of choice for carcinoma *in situ* (p.659). It does not have a direct toxic effect on tumour cells, but produces a cascade of immune reactions that is reported to reduce tumour recurrence and disease progression. A systematic review[1] indicated that intravesical BCG after transurethral resection (TUR) reduced recurrence of Ta and T1 bladder cancers compared with TUR alone. A systematic review[2] of intravesical therapy concluded that tumour recurrence was significantly reduced with BCG when compared with mitomycin C but only in patients at high risk of recurrence; there was no difference in terms of disease progression or survival. However, another meta-analysis[3] reported intravesical BCG to be better than mitomycin C in the prevention of tumour recurrences, particularly in those on BCG maintenance regime, irrespective of the risk of recurrence.

1. Shelley MD, *et al.* Intravesical bacillus Calmette-Guerin in Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 05/11/07).
2. Shelley MD, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 05/11/07).
3. Böhle A, *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol (Baltimore)* 2003; **169:** 90–5.

SKIN. Several studies have reported that BCG vaccine injected into intradermal metastases of melanoma can result in regression of the injected, and sometimes also the uninjected nodules. BCG therapy has been disappointing for visceral metastases. Many anecdotal reports and nonrandomised studies have shown benefit from BCG vaccine as adjuvant therapy, but these results have not been confirmed in large randomised, controlled studies.[1,2] More specific immunological interventions such as therapeutic vaccines are now becoming available for the treatment of melanomas (p.673).

1. Ho VC, Sober AJ. Therapy for cutaneous melanoma: an update. *J Am Acad Dermatol* 1990; **22:** 159–76.
2. Agarwala SS, *et al.* Mature results of a phase III randomized trial of bacillus Calmette-Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. *Cancer* 2004; **100:** 1692–8.

Tuberculosis. Studies from many parts of the world have evaluated the efficacy of BCG vaccine to protect against tuberculosis. Levels of protection have varied from 0 to over 80%.[1] Many explanations for such variability have been proposed: interaction with the immune response to other mycobacterial infections; antigenic, microbiological, or formulation differences between BCG vaccines; differences in the natural history of infection and disease; variations in host genetics or nutrition; or methodological differences between studies.[1,2] It has been noted that in general the efficacy of BCG vaccine in any region is proportional to its distance from the equator and this possibly reflects differences in exposure to environmental mycobacteria.[3] This could be the strongest influence on efficacy,[3] with the implication that BCG may be least effective in areas of the world where the risk of tuberculosis is greatest. BCG also appears to be more effective against systemic (miliary and meningitic tuberculosis) than against pulmonary tuberculosis. It is likely that BCG cannot produce complete protection against infection, and the development of new vaccines is ongoing.[4-6]

National policies of BCG vaccination vary widely. Some countries recommend routine vaccination; in others, such as the UK,[7] and USA[8] routine vaccination is no longer carried out and targeted immunisation aimed at infants and others at increased risk is performed (see Uses and Administration, above). Schedules throughout the world have varied from single vaccination at birth (as recommended by WHO),[9] to single vaccination at age 10 to 14, to repeated vaccination every few years (particularly in eastern Europe). These policy differences appear to be related as much to differences of opinion about the mechanism of action and effectiveness of vaccines as to local differences in the epidemiology of tuberculosis.[1] WHO considers BCG vaccination to be an adjunct to case detection and treatment in the control of tuberculosis,[9,10] and recommends that neither tuberculin skin testing nor repeat vaccination should be used.

1. Fine PEM, Rodrigues LC. Modern vaccines: mycobacterial diseases. *Lancet* 1990; **335:** 1016–20.
2. Fine PEM. BCG vaccination against tuberculosis and leprosy. *Br Med Bull* 1988; **44:** 691–703.
3. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; **346:** 1339–45. Correction. *ibid.*; **347:** 340.
4. von Reyn CF, Vuola JM. New vaccines for the prevention of tuberculosis. *Clin Infect Dis* 2002; **35:** 465–74.
5. Young DB, Stewart GR. Tuberculosis vaccines: *Br Med Bull* 2002; **62:** 73–86.
6. Orme IM. Tuberculosis vaccines: current progress. *Drugs* 2005; **65:** 2437–44.
7. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
8. CDC. TB elimination: BCG vaccine. (issued April 06). Available at: http://www.cdc.gov/tb/pubs/tbfactsheets/BCG.pdf (accessed 01/11/07)
9. Anonymous. WHO statement on BCG revaccination for the prevention of tuberculosis. *Bull WHO* 1995; **73:** 805–6.
10. WHO. BCG vaccine. *Wkly Epidem Rec* 2004; **79:** 27–38. Available at: http://www.who.int/entity/wer/2004/en/wer7904.pdf (accessed 01/11/07)

HIV-INFECTED PATIENTS. Like other live vaccines, BCG vaccine should not be given to immunocompromised patients, including patients with symptomatic HIV infection or AIDS. WHO[1] states that HIV prevalence is one of the factors that should be considered when determining local policies on BCG vaccination (see Uses and Administration, above), and recommends that infants with known or likely HIV infection should not be vaccinated because of the increased risk in this group (see under Precautions, above). In the UK and USA, BCG vaccination is also not recommended for HIV-positive patients.

1. WHO. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Wkly Epidem Rec* 2007; **82:** 193–6. Available at: http://www.who.int/wer/2007/wer8221.pdf (accessed 01/11/07)

Preparations

Ph. Eur.: BCG for Immunotherapy; Freeze-dried BCG Vaccine;
USP 31: BCG Live; BCG Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: ImmuCyst†; Pacis†; ***Austral.:*** ImmuCyst; OncoTICE; ***Austria:*** ImmuCyst; OncoTICE; ***Belg.:*** ImmuCyst; OncoTICE; ***Braz.:*** ImmuCyst†; Imunoest; ***Canad.:*** ImmuCyst; OncoTICE; Pacis†; ***Chile:*** ImmuCyst; ***Cz.:*** ImmuCyst; ***Denm.:*** OncoTICE; ***Fin.:*** OncoTICE; ***Fr.:*** ImmuCyst; Monovax†; ***Ger.:*** ImmuCyst; OncoTICE; ***Gr.:*** ImmuCyst; OncoTICE; ***Hong Kong:*** ImmuCyst; OncoTICE†; ***Hung.:*** ImmuCyst; ***Israel:*** ImmuCyst; Immune BCG Pasteur F; OncoTICE; ***Ital.:*** ImmuCyst; Imovax BCG†; OncoTICE; ***Malaysia:*** ImmuCyst; ***Mex.:*** Cultivo BCG; OncoTICE; ***Neth.:*** OncoTICE; ***Norw.:*** OncoTICE; ***NZ:*** ImmuCyst; OncoTICE; ***Philipp.:*** Glovax; ***Pol.:*** OncoTICE; Onko BCG; ***Port.:*** ImmuCyst; OncoTICE; ***Singapore:*** ImmuCyst; ***Spain:*** ImmuCyst; OncoTICE; Vejicur; ***Swed.:*** OncoTICE; ***Switz.:*** OncoTICE; ***Thai.:*** ImmuCyst; ***Turk.:*** ImmuCyst; OncoTICE; ***UK:*** ImmuCyst; OncoTICE; ***USA:*** Pacis†; TheraCys; Tice; ***Venez.:*** ImmuCyst†; OncoTICE.

Botulism Antitoxins

Antitoxinas botulínicas.

Ботулинические Антитоксины

ATC — J06AA04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Botulinum Antitoxin; Immunoserum Botulinicum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by type A, type B, type E, or any mixture of types A, B, and E, of *Clostridium botulinum*. It contains not less than 500 international units of each of type A and type B and not less than 50 units of type E per mL. It should be stored at 2° to 8° and not be allowed to freeze.

The BP 2008 states that Bot/Ser may be used on the label.

The BP 2008 states that when Mixed Botulinum Antitoxin or Botulinum Antitoxin is prescribed or demanded and the types to be present are not stated, Botulinum Antitoxin prepared from types A, B, and E shall be dispensed or supplied.

USP 31 (Botulism Antitoxin). A sterile solution of the refined and concentrated antitoxic antibodies, chiefly globulins, obtained from the blood of healthy horses that have been immunised against the toxins produced by type A and type B and/or E strains of *Clostridium botulinum*. It contains a suitable antimicrobial agent. It should be stored at 2° to 8° in single-use containers.

◊ NOTE. Some antitoxins used in the UK have not conformed to the requirements of the BP 2008 and Ph. Eur. 6.2 (having a higher phenol content than the pharmacopoeias allow), and thus have been referred to as **botulism antitoxin** rather than botulinum antitoxin.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Botulism antitoxins are used in the postexposure prophylaxis and treatment of botulism. Treatment should be given as early as possible in the course of the disease.

Since the type of botulism toxin is seldom known the polyvalent antitoxin is usually given. Sensitivity testing should always be performed before using the antitoxin.

In the UK, equine-derived trivalent antitoxins containing antitoxin types A, B, and E are used. One type contains not less than 500 units/mL of each of the 3 antitoxins. For the treatment of botulism, 20 mL of this antitoxin should be diluted to 100 mL with sodium chloride 0.9% and given by slow intravenous infusion over at least 30 minutes; another 10 mL may be given 2 to 4 hours later if necessary, and further doses at 12- to 24-hour intervals if indicated. Persons who have been exposed to the toxin and in whom symptoms have not developed should be given 20 mL intramuscularly as a prophylactic measure.

A second preparation used for treatment of botulism in the UK contains 750 units/mL of antitoxin type A, 500 units/mL of antitoxin type B, and 50 units/mL of antitoxin type E. Patients are given 250 mL by slow intravenous infusion, followed by a further 250 mL by continuous drip infusion. A further 250 mL may be given 4 to 6 hours later if necessary according to response. Patients with severe intoxication should be given an intralumbar injection of 20 mL, particularly if intravenous treatment has produced no improvement; this procedure may be repeated at 24-hour intervals if required..

In the USA, a human-derived intravenous botulism immunoglobulin (BIG-IV) is available for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. The recommended dose of 1 mL/kg (50 mg/kg), given as a single intravenous infusion, provides a protective level of neutralising antibodies for at least 6 months.

Botulism. Botulism[1-3] is caused by the exotoxin of *Clostridium botulinum*, a spore-forming, Gram-positive anaerobe which occurs in soil and mud. There are 3 naturally occurring forms of botulism; *food-borne botulism* caused by ingestion of contaminated foodstuffs, *wound botulism* due to the growth of toxin-releasing organisms in the wound, and *intestinal botulism* (including infant botulism and adult intestinal toxaemia) caused by intestinal colonisation and toxin production. Accidental or intentional exposure to botulinum toxin may result in inhalation botulism (from aerosolisation of botulinum toxin) or iatrogenic botulism (from injection of the toxin). Seven types of *C. botulinum* can be distinguished (types A to G), each producing a different exotoxin; human disease is usually caused by types A, B, and E. The toxin is heat labile, but the spores can survive temperatures of up to 120°.

All forms of botulism produce the same clinical syndrome. Symptoms arise as a result of the toxin blocking the release of acetylcholine at the neuromuscular junction and include symmetrical cranial nerve palsies and descending flaccid paralysis, orthostatic hypotension, dry mouth, and dilated pupils. Gastrointestinal symptoms occur with food-borne or intestinal colonisation botulism. Death is usually from respiratory arrest.

Treatment of botulism is with equine-derived antitoxins and intensive respiratory and supportive therapy. Antitoxins should be given as early as possible as only toxins that are not bound to nerve ending are neutralised; however, antitoxins may still be beneficial if treatment is delayed. Some patients may benefit from drugs, such as fampridine or guanidine, aimed at reversing the neuromuscular blockade.

Infant botulism is of increasing importance, especially in the USA where it is reported to be the most common form of botulism, with honey (see p.1948) reputed to be the most frequent source of infection. In contrast to food-borne botulism, in infant botulism low doses of toxin continue to be released into the gut for some time. Treatment is with intensive supportive care; equine botulism antitoxin used in adults is not generally used for infant botulism because of its serious adverse effects (including serum sickness and anaphylaxis), its short half-life, and the possibility of life-long sensitisation to equine proteins.[4] A human-derived intravenous botulism immunoglobulin (BIG-IV) is available in the USA for the treatment of patients under 1 year of age with infant botulism caused by toxin type A or B. Clinical studies[4] reported that treatment with BIG-IV within 7 days of hospital admission reduced the length of hospital stay and severity of illness in infant botulism type A or B; treatment given within 3 days was more effective than treatment given 4 to 7 days after admission.

1. Robinson RF, Nahata MC. Management of botulism. *Ann Pharmacother* 2003; **37:** 127–31.
2. Health Protection Agency. Guidelines for action in the event of a deliberate release: botulism (issued April 2007). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947315628 (accessed 15/07/08)
3. Sobel J. Botulism. *Clin Infect Dis* 2005; **41:** 1167–73.
4. Arnon SS, *et al.* Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med* 2006; **354:** 462–71.

Preparations

Ph. Eur.: Botulinum Antitoxin;
USP 31: Botulism Antitoxin.

Proprietary Preparations (details are given in Part 3)
USA: BabyBIG.

Multi-ingredient: ***Cz.:*** Bosea†.

Bovine Colostrum

Calostro bovino.

Profile

Bovine colostrum has been used similarly to antisera and human immunoglobulin preparations to provide passive immunity against infectious diseases. Hyperimmune bovine colostra have been prepared from cows previously immunised with specific antigens. In particular, these specific hyperimmune bovine colostra have been tried in cryptosporidiosis and in the prevention of rotavirus diarrhoea in infants. They may also have potential for use against *Helicobacter pylori*, *Shigella* spp., and measles.

◊ Reviews.

1. Kelly GS. Bovine colostrums: a review of clinical uses. *Altern Med Rev* 2003; **8:** 378–94. Correction. *ibid.* 2004; **9:** 69.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Travelan.

Multi-ingredient: ***Indon.:*** Stimox; Vistrum; ***Ital.:*** Colostrum; ***UK:*** BioXtra†.

Brucellosis Vaccines

Vacunas de la brucelosis.

ATC — J07AD01.

Profile

A brucellosis vaccine prepared from an antigenic extract of *Brucella abortus* has been used for active immunisation against brucellosis (p.165) in persons at high risk of contracting the disease.

Campylobacter Jejuni Vaccines

Vacunas contra el Campylobacter jejuni.

Profile

An oral vaccine is under development to provide active immunisation against *Campylobacter jejuni* infection.

Cholera Vaccines

Vacunas del cólera.

ATC — J07AE01; J07AE02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Cholera Vaccine; Vaccinum Cholerae). A sterile homogeneous suspension of a suitable killed strain or strains of *Vibrio cholerae*. It consists of a mixture of equal parts of vaccines prepared from smooth strains of 2 main serological types, Inaba and Ogawa of the classical biotype with or without the El Tor biotype. A single strain or several strains of each type may be included. All strains must contain, in addition to their type O antigens, the heat-stable O antigen common to the Inaba and Ogawa types. If more than one strain each of Inaba and Ogawa are used they may be selected to contain other O antigens. It contains not less than 8000 million *V. cholerae* per dose, which does not exceed 1 mL. It contains not more than 0.5% of phenol. It should be stored at 2° to 8° and protected from light.

The BP 2008 states that Cholera may be used on the label.

Ph. Eur. 6.2 (Cholera Vaccine, Freeze-dried; Vaccinum Cholerae Cryodesiccatum). Cholera vaccine that is freeze-dried and reconstituted immediately before use by the addition of a suitable sterile liquid. Phenol may not be used in the preparation of the dried vaccine. It should be stored at 2° to 8° and be protected from light.

Ph. Eur. 6.2 (Cholera Vaccine (Inactivated, Oral); Vaccinum Cholerae Perorale Inactivatum). A homogeneous suspension of inactivated suitable strains of *Vibrio cholerae* serogroup O1, representing serotypes and biotypes of epidemic strains. The vaccine may contain the B subunit of cholera toxin (CTB). Just prior to ingestion, one dose of vaccine suspension is mixed with a suitable buffer as stated on the label. Store at 2° to 8 °. Protect from light.

The BP 2008 states that Dried/Cholera may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Slight swelling, erythema, and tenderness occasionally occur at the injection site. Fever and malaise have been reported and general reactions, including anaphylaxis and hypersensitivity reactions, have occurred. Neurological and psychiatric reactions have occasionally occurred.

Gastrointestinal disturbances, headache, dizziness, and respiratory symptoms have followed use of oral cholera vaccine.

Interactions

As for vaccines in general, p.2202.

The oral cholera vaccine available in the UK is acid labile; consequently food should not be consumed for 1 hour before and after use.

Uses and Administration

Injectable inactivated whole-cell cholera vaccines have been used for active immunisation against cholera but are not considered to be very effective and the immunity conferred is short-lived. They have no role in the management of contacts of cases or in controlling the spread of infection.

Oral vaccines containing either live attenuated or inactivated strains are available in some countries and appear to be more effective than parenteral vaccines (see below). In the UK, an oral vaccine containing inactivated strains of *Vibrio cholerae* O1 and recombinant cholera toxin B subunit is available for use in adults and children aged over 2 years who are travelling to areas of risk. The vaccine is given as a suspension, in doses of 3 mL, mixed with sodium hydrogen carbonate solution. Adults and children aged over 6 years are given two doses, and children aged 2 to 6 years three doses, in each case at weekly intervals. Immunisation should be complete at least 1 week prior to potential exposure. Booster doses may be given after 2 years in adults and children over 6 years, or after 6 months in children aged 2 to 6 years, if continuous protection is required. Oral vaccines containing a live attenuated form of the *V. cholerae* strain CVD 103-HgR are available in some countries. They are effective against the O1 serogroup of cholera, but do not afford protection against the O139 serogroup. They may be given to adults and children aged over 2 years who are travelling to areas of risk and are given as a single-dose suspension in sodium hydrogen carbonate solution. Immunisation should be carried out at least 1 week before potential exposure. When necessary revaccination is recommended every 6 months.

The WHO International Health Regulations do not require cholera vaccination for travellers as the introduction of cholera into any country cannot be prevented by cholera vaccination. However, travellers may still be asked for evidence of immunisation at some borders.

Oral cholera vaccines. Since parenteral cholera vaccines are not considered to be very effective, providing at best 50% protection and confer immunity lasting only 3 to 6 months, attention has turned towards oral vaccines that stimulate intestinal immunity.[1] Both killed and live attenuated oral vaccines have been developed, and both types have been shown to be non-toxic and immunogenic.

Killed vaccines contain inactivated whole *Vibrio cholerae* O1 either alone or with B subunit component of cholera toxin. These vaccines typically produce a protective efficacy of about 60 to 70% and both modify established infections and prevent new ones. Although the vaccines are effective in areas where the El Tor biotype predominates, they are more effective against classical strains. Immunity particularly against El Tor may be less sustained in children under 5 years of age than in older children and adults. The main drawback is the need to give two or more doses at 1- to 2-week intervals to achieve a protective effect. The protective effect is rapidly established but diminishes over time and booster doses are necessary to maintain a high level of immunity.

A live attenuated vaccine is now available containing CVD 103-HgR in which the genes encoding the toxic A subunit are deleted by recombinant techniques.[2,3] This vaccine is effective 8 days after a single dose but less so against El Tor than against classical strains. It is not effective against *V. cholorae* O139.

Live oral vaccines effective against El Tor are now being developed,[4,5] and promising responses have also been reported with a live attenuated O139 vaccine.[6]

The efficacy and cost-effectiveness of oral vaccines to control cholera outbreaks in refugee populations is uncertain.

1. Ryan ET, Calderwood SB. Cholera vaccines. *Clin Infect Dis* 2000; **31:** 561–5.
2. Tacket CO, *et al.* Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with Vibrio cholerae O1 El tor inaba three months after vaccination. *Infect Immun* 1999; **67:** 6341–5.
3. Richie E, *et al.* Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. *Vaccine* 2000; **18:** 2399–2410.
4. Tacket CO, *et al.* Volunteer studies investigating the safety and efficacy of live El Tor Vibrio cholerae O1 vaccine strain CVD 111. *Am J Trop Med Hyg* 1997; **56:** 533–7.
5. Sack DA, *et al.* Evaluation of Peru-15, a new live oral vaccine for cholera, in volunteers. *J Infect Dis* 1997; **176:** 201–5.
6. Coster TS, *et al.* Safety, immunogenicity, and efficacy of live attenuated Vibrio cholerae O139 vaccine prototype. *Lancet* 1995; **345:** 949–52.

Preparations

Ph. Eur.: Cholera Vaccine; Cholera Vaccine (Inactivated, Oral); Freeze-dried Cholera Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Orochol; ***Austral.:*** Dukoral; Orochol†; ***Braz.:*** Vacina Oral Contra Colera e Diarrreia Causada Por ETEC; ***Canad.:*** Dukoral; Mutacol†; ***Cz.:*** Dukoral; ***Denm.:*** Dukoral; ***Fin.:*** Dukoral; ***Fr.:*** Dukoral; ***Hong Kong:*** Orochol†; ***Ital.:*** Dukoral; ***Malaysia:*** Dukoral; ***Neth.:*** Dukoral; ***Norw.:*** Dukoral; ***NZ:*** Dukoral; ***Philipp.:*** Dukoral; Orochol; ***Port.:*** Dukoral; ***S.Afr.:*** Dukoral; ***Singapore:*** Dukoral; ***Spain:*** Dukoral; ***Swed.:*** Dukoral; ***Switz.:*** Orochol; ***Thai.:*** Dukoral; ***Turk.:*** Dukoral; ***UK:*** Dukoral.

Contraceptive Vaccines

Vacunas anticonceptivas.

Profile

Various approaches to development of a contraceptive vaccine are under investigation. A synthetic contraceptive vaccine that stimulates the production of an antibody against human chorionic gonadotrophin has been studied in human trials.

◊ Reviews.

1. Delves PJ. The development of contraceptive vaccines. *Expert Opin Invest Drugs* 2002; **11:** 1225–37.
2. Aitken RJ. Immunocontraceptive vaccines for human use. *J Reprod Immunol* 2002; **57:** 273–87.
3. McLaughlin EA, *et al.* Contraceptive vaccines. *Expert Opin Biol Ther* 2003; **3:** 829–41.
4. Ferro VA, Mordini E. Peptide vaccines in immunocontraception. *Curr Opin Mol Ther* 2004; **6:** 83–9.

Crimean-Congo Haemorrhagic Fever Immunoglobulins

Inmunoglobulinas contra la fiebre hemorrágica de Congo-Crimea.

Profile

Preparations containing antibodies against Crimean-Congo haemorrhagic fever have been used for passive immunisation against the disease.

◊ References.

1. Vassilenko SM, *et al.* Specific intravenous immunoglobulin for Crimean-Congo haemorrhagic fever. *Lancet* 1990; **335:** 791–2.
2. Ergonul O. Treatment of Crimean-Congo hemorrhagic fever. *Antiviral Res* 2008; **78:** 125–31.

Crimean-Congo Haemorrhagic Fever Vaccines

Profile

An inactivated vaccine against Crimean-Congo haemorrhagic fever, derived from *mouse* brains, is used in parts of eastern Europe.

Cytomegalovirus Immunoglobulins

Inmunoglobulinas contra el citomegalovirus.

ATC — J06BB09.

Description. Cytomegalovirus immunoglobulins containing high levels of specific antibody against CMV have been prepared from human plasma.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Cytomegalovirus immunoglobulins are used for passive immunisation against CMV infection. They are used prophylactically, especially in patients undergoing certain transplant procedures. In transplants from CMV-seropositive donors into seronegative recipients, prophylactic use of cytomegalovirus immunoglobulin with ganciclovir should also be considered.

In the USA, a cytomegalovirus immunoglobulin G is available for use in recipients of heart, kidney, liver, lung, and pancreas transplants, and for CMV-seronegative recipients of these organs other than kidney from CMV-seropositive donors. The dosage schedule for kidney transplant recipients is 150 mg/kg by intravenous infusion within 72 hours of transplantation, then 100 mg/kg once every 2 weeks for 4 doses, then 50 mg/kg every 4 weeks for 2 doses. The rate of infusion should start at 15 mg/kg per hour increasing gradually to a maximum rate of 60 mg/kg per hour. For recipients of transplants other than kidney, the recommended dosage schedule is 150 mg/kg within 72 hours of transplantation and then once every 2 weeks for 4 further doses, then 100 mg/kg every 4 weeks for 2 doses. In the UK, cytomegalovirus immunoglobulin is available on a named patient basis for prophylaxis in patients receiving immunosuppressive treatment.

The name sevirumab is applied to a χ-chain human monoclonal cytomegalovirus immunoglobulin G1.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: CytoGam†; Megalotect; ***Austral.:*** CMV Immunoglobulin; ***Austria:*** Cytoglobin; Cytotect; ***Belg.:*** Ivegam-CMV; ***Chile:*** Cytotect; ***Cz.:*** Cytotect; ***Ger.:*** Cytoglobin; Cytotect; ***Gr.:*** Megalotect; ***Hong Kong:*** Cytotect; ***Hung.:*** Cytotect; ***Irl.:*** Megalotect†; ***Israel:*** Megalotect; ***Ital.:*** Cytotect; Imunoendocig†; Uman-Cig†; ***Neth.:*** Megalotect; ***Pol.:*** Cytotect; ***Port.:*** Megalotect; ***S.Afr.:*** Megalotect†; ***Singapore:*** Megalotect; ***Switz.:*** Cytotect; ***Thai.:*** Megalotect; ***Turk.:*** Cytotect; ***USA:*** CytoGam.

Cytomegalovirus Vaccines

Vacunas contra el citomegalovirus.

Profile

Several vaccines for active immunisation against CMV infection are under investigation, including some produced by recombinant technology. A live attenuated cytomegalovirus vaccine containing human CMV Towne strain has been investigated in humans since the late 1970s, particularly for the prevention of CMV infection in renal transplant recipients. However, there have been doubts over its safety.

◊ Several promising candidate vaccines against human CMV infection are under development, of which 5 have been or are being tested in humans.[1] Firstly, attenuated CMV (Towne strain) vaccine has been tried but found to be erratic in efficacy and loses segments of its genetic material; to overcome this a second, more robust, vaccine has been designed consisting of a chimera between the attenuated CMV and wild-type virus. The third vaccine developed, known as ALVAC, consists of a canarypox vector with either a glycoprotein B envelope or a core antigen from CMV pp65, a protein found to be recognised by CD8+ T lymphocytes during naturally acquired infection. Fourthly, a protein sub-unit vaccine consisting of a recombinant envelope glycoprotein has been found to be safe and to induce a neutralising antibody response. Finally, the fifth vaccine developed is a mixture of synthetic peptides incorporating a T helper epitope known as CD8+ cytotoxic T cell epitope and a lipid tail. Currently, the attenuated cytomegalovirus vaccine, the protein sub-unit vaccine, and the recombinant vector vaccine have been or are being tested in CMV-negative subjects, and the chimeric vaccine has been tested in CMV-positive patients as a precursor to testing in CMV-negative persons.[1]

Further vaccine candidates that have been proposed include DNA vaccines and a vaccine based on recombinant technology.[1] Some commentators[2] have suggested that reduction or prevention of cytomegalovirus disease may be a more realistic goal for a vaccine than prevention of infection.

1. Arvin AM, *et al.* Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004; **39:** 233–9.
2. Khanna R, Diamond DJ. Human cytomegalovirus vaccine: time to look for alternative options. *Trends Mol Med* 2006; **12:** 26–33.

Dengue Fever Vaccines

Vacunas del dengue.

Profile

Live attenuated vaccines under study for active immunisation against dengue fever contain dengue virus types 1, 2, 3, and 4 alone or in various combinations. WHO considers that protection against only one or two dengue viruses might actually increase the risk of more serious disease. The ultimate aim is to produce a vaccine active against all types of dengue virus.

Recombinant vaccines are also under investigation.

◊ References.

1. Velzing J, *et al.* Induction of protective immunity against dengue virus type 2: comparison of candidate live attenuated and recombinant vaccines. *Vaccine* 1999; **17:** 1312–30.
2. Kanesa-Thasan N, *et al.* Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine* 2001; **19:** 3179–88.
3. Rothman AL, *et al.* Induction of T lymphocyte responses to dengue virus by a candidate tetravalent live attenuated dengue virus vaccine. *Vaccine* 2001; **19:** 4694–99.
4. Sabchareon A, *et al.* Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. *Am J Trop Med Hyg* 2002; **66:** 264–72.
5. Sun W, *et al.* Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. *Am J Trop Med Hyg* 2003; **69** (suppl 6): 24–31.
6. Sabchareon A, *et al.* Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J* 2004; **23:** 99–109.
7. Monath TP. Dengue and yellow fever—challenges for the development and use of vaccines. *N Engl J Med* 2007; **357:** 2222–5.
8. Edelman R. Dengue vaccines approach the finish line. *Clin Infect Dis* 2007; **45** (suppl 1): S56–60.
9. Hatch S, *et al.* Dengue vaccine: opportunities and challenges. *IDrugs* 2008; **11:** 42–5.

Dental Caries Vaccines

Vacunas de la caries dental.

Profile

Dental caries vaccines consisting of purified proteins from *Streptococcus mutans* or *Str. sobrinus* are under investigation. Monoclonal antibodies are also being studied for local passive immunisation.

◊ Several *animal* studies of candidate vaccines for the prevention of dental caries have shown that immunisation with protein antigens from *Streptococcus mutans* or *Str. sobrinus* can induce salivary IgA antibodies which inhibit both sucrose-dependent or sucrose-independent accumulation of these organisms on tooth surfaces. It is thought that candidate vaccines for study in humans could be given by mucosal application since children are already naturally exposed to the antigens involved during the first years of life. Infection with *Str. mutans* normally occurs from the age of about 18 months and the intention is therefore to vaccinate 1-year-old children in order to intercept colonisation. However, progress towards a vaccine for active immunisation against dental caries requires further clinical evaluation. Passive administration of salivary antibodies to *Str. mutans* has also provided some protection in preclinical studies and small scale studies in humans.[1-4]

1. Koga T, *et al.* Immunization against dental caries. *Vaccine* 2002; **20:** 2027–44.
2. Smith DJ. Caries vaccines for the twenty-first century. *J Dent Educ* 2003; **67:** 1130–9.
3. Russell MW, *et al.* A caries vaccine? The state of the science of immunization against dental caries. *Caries Res* 2004; **38:** 230–5.
4. Smith DJ, Mattos-Graner RO. Secretory immunity following mutans streptococcal infection or immunization. *Curr Top Microbiol Immunol* 2008; **319:** 131–56.

Diphtheria Antitoxins

Antitoxinas diftéricas.

ATC — J06AA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria Antitoxin; Immunoserum Diphthericum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Corynebacterium diphtheriae*. It has a potency of not less than 1000 international units/mL when obtained from horse serum and not less than 500 international units/mL when obtained from other mammals. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Dip/Ser may be used on the label.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Diphtheria antitoxins neutralise the toxin produced by *Corynebacterium diphtheriae* locally at the site of infection and in the circulation.

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection. An antibacterial is usually given concomitantly (see p.168). Diphtheria antitoxin is generally not used for the prophylaxis of diphtheria because of the risk of provoking a hypersensitivity reaction. Contacts of a diphtheria case should be promptly investigated, given antibacterial prophylaxis and active immunisation with a suitable diphtheria-containing vaccine as appropriate (see below), and kept under observation.

A test dose of diluted diphtheria antitoxin should always be given intradermally to exclude hypersensitivity. In the UK, diphtheria antitoxin is given by intravenous infusion for the treatment of diphtheria of mild to moderate severity in the following recommended doses: for nasal diphtheria, 10 000 to 20 000 units; for tonsillar diphtheria, 15 000 to 25 000 units; for pharyngeal or laryngeal diphtheria, 20 000 to 40 000 units. In cases of combined disease, or when diagnosis is delayed, 40 000 to 60 000 units should be given, and, in severe disease, doses up to 100 000 units used. For most cutaneous infections, diphtheria antitoxin is insufficiently absorbed and is therefore not given; however, if the ulcer is sufficiently large (more than 2 cm^2) and especially if it is membranous, then 20 000 to 40 000 units may be given. Higher doses have been used in some countries.

Preparations

Ph. Eur.: Diphtheria Antitoxin.

Diphtheria Vaccines

Vacunas de la difteria.

ATC — J07AF01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed); Vaccinum Diphtheriae Adsorbatum). A preparation of diphtheria formol toxoid adsorbed on a mineral carrier. The formol toxoid is prepared from the toxin produced by the growth of *Corynebacterium diphtheriae*. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives, particularly those of the phenolic type. It contains not less than 30 international units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Ph. Eur. 6.2 (Diphtheria Vaccine (Adsorbed, Reduced Antigen Content); Vaccinum Diphtheriae, Antigeniis Minutum, Adsorbatum). It is an adsorbed diphtheria vaccine containing not less than 2 international units per dose.

The BP 2008 states that for a vaccine for use in the UK, the amount of toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents per dose.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Local reactions may occur but are generally not severe in young children; the frequency and severity of reactions is reported to be less in children under 2 years of age than in older children and adults. If diphtheria vaccines or vaccines containing a diphtheria component need to be given to children over the age of 10 years or to adults, vaccines with a reduced content of diphtheria toxoid and intended for adults and adolescents should be used. For further details see Uses and Administration, below.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Diphtheria vaccines are used for active immunisation against diphtheria. The non-adsorbed vaccine has poor immunogenic properties and its effects are enhanced if given as an adsorbed preparation. For primary immunisation combined diphtheria vaccines, usually diphtheria, tetanus, and pertussis vaccines (p.2210) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p.2212), are used. A single-component diphtheria vaccine has sometimes been used, for example in the event of contact with an infected patient or a carrier. For discussion of immunisation schedules, see under Vaccines, p.2202.

Individuals coming into contact with a case of diphtheria or carrier of a toxigenic strain, or those travelling to an endemic or epidemic area should receive a complete primary course or a reinforcing dose according to age and immunisation history; those not previously immunised should receive a primary course of immunisation, and those previously immunised should receive a single reinforcing dose of a diphtheria-containing vaccine. Contacts of a case of diphtheria or carrier of a toxigenic strain should in addition receive a prophylactic course of a suitable antibacterial (see p.168). Individuals at repeated risk of exposure to infection may be offered booster doses every 10 years.

Schick testing (p.2384) to ascertain immune status is no longer considered necessary before giving diphtheria vaccine to adults provided that a low dose is given; antibody testing is used to check immunity in those regularly exposed to diphtheria.

In some countries, booster doses of a diphtheria and tetanus vaccine are recommended every 10 years (see under Diphtheria and Tetanus Vaccines, p.2210).

Conjugation to diphtheria toxoid has been used to increase the immunogenicity of other vaccines (see Haemophilus Influenzae Vaccines, p.2213).

Preparations

Ph. Eur.: Diphtheria Vaccine (Adsorbed); Diphtheria Vaccine (Adsorbed, Reduced Antigen Content).

Proprietary Preparations (details are given in Part 3)
Cz.: Aldiana†; ***NZ:*** Di Anatoxal.

Diphtheria and Tetanus Vaccines

Vacunas de la difteria y el tétanos.

ATC — J07AM51.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed); Vaccinum Diphtheriae et Tetani Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid adsorbed on a mineral carrier. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid and not less than 40 international units of tetanus toxoid per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DT/Vac/Ads(Child) may be used on the label.

The BP 2008 gives Adsorbed Diphtheria-Tetanus Prophylactic as an approved synonym.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae et Tetani, Antigeni-o(-is) Minutum). It is diphtheria and tetanus vaccine (adsorbed) containing not less than 2 units of diphtheria toxoid and not less than 20 units of tetanus toxoid per dose.

The BP 2008 states that for a vaccine for use in the UK, the amount of diphtheria toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents of diphtheria toxoid per dose.

The BP 2008 states that dT may be used on the label.

USP 31 (Diphtheria and Tetanus Toxoids Adsorbed). A sterile suspension prepared by mixing suitable quantities of plain or adsorbed diphtheria toxoid and plain or adsorbed tetanus toxoid and, if plain toxoids are used, an aluminium adsorbing agent. The antigenicity or potency and the proportions of the toxoids are such as to provide an immunising dose of each toxoid in the labelled dose. It should be stored at 2° to 8° and not be allowed to freeze.

USP 31 (Tetanus and Diphtheria Toxoids Adsorbed for Adult Use). A sterile suspension prepared by mixing suitable quantities of adsorbed diphtheria toxoid and adsorbed tetanus toxoid using the same precipitating or adsorbing agent for both toxoids. The antigenicity or potency and the proportions of the toxoids are such as to provide, in the labelled dose, an immunising dose of adsorbed tetanus toxoid and one-tenth of the immunising dose of adsorbed diphtheria toxoid specified for children and not more than 2 Lf of diphtheria toxoid. It should be stored at 2° to 8° and not be allowed to freeze.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, above, and Tetanus Vaccines, p.2240. Diphtheria and tetanus vaccines are reported to produce fewer adverse effects than diphtheria, tetanus, and pertussis vaccines (see under Incidence of Adverse Effects, p.2210).

Dose-related effects. A high incidence of adverse effects was reported in teenagers inadvertently given a high-dose diphtheria and tetanus vaccine intended for use in infants.[1] Most reactions were classified as mild or moderately severe, but severe local or systemic reactions occurred in a third of those reporting reactions.

1. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996; **313:** 533–4.

Effects on the nervous system. Encephalopathy more commonly follows vaccination with diphtheria, tetanus, and pertussis vaccine than with diphtheria and tetanus vaccine (p.2210). Several cases of encephalopathy occurred in a small region in Italy in children after immunisation against diphtheria and tetanus,[1] although it was not possible to infer a causal relationship. A case of polyradiculoneuritis has been reported in a patient after the use of a diphtheria-tetanus vaccine and was considered most likely to have been due to the tetanus component.[2]

1. Greco D. Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy. *Bull WHO* 1985; **63:** 919–25.
2. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol* 1983; **40:** 56–7.

GUILLAIN-BARRÉ SYNDROME. Evidence mainly from case reports and uncontrolled studies favoured a causal relationship between vaccination with diphtheria and tetanus vaccines or single-antigen tetanus vaccines and Guillain-Barré syndrome. The data came primarily from immunocompromised patients.[1] However, a later analysis of active surveillance epidemiological studies of Guillain-Barré syndrome and tetanus vaccination history concluded that if an association exists, it must be extremely rare and not of public health significance.[2]

1. Stratton KR, *et al.* Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine. *JAMA* 1994; **271:** 1602–5.
2. Tuttle J, *et al.* The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997; **87:** 2045–8.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Combined adsorbed diphtheria and tetanus vaccines may be used for active immunisation, although vaccines used for primary immunisation usually combine diphtheria, tetanus, and pertussis, and sometimes also Haemophilus influenzae and poliomyelitis. Diphtheria and tetanus vaccines are used in some countries for reinforcing doses after primary immunisation; in the USA they are given to adults every 10 years. For discussion of immunisation schedules, see under Vaccines, p.2202.

The non-adsorbed combined diphtheria and tetanus vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Booster doses. In many countries, booster doses of combined diphtheria and tetanus vaccines are recommended every 10 years, and studies have been conducted to assess whether this is necessary. Since the incidence of clinical diphtheria in many countries in western Europe and North America approaches zero, it had been considered that there was no need for booster doses in adults, despite low antibody titres, so long as the policy of immunisation during infancy was maintained.[1,2] However, after a report[3] of an outbreak of clinical diphtheria in Sweden after a period of many years during which no indigenous cases of diphtheria had occurred and the disease was regarded as being eliminated from the country, the question of immunity in adults and the need for revaccination again arose. In the USA, it was considered[4] that re-immunisation every 10 years with a diphtheria and tetanus combined vaccine was mandatory and that this combined vaccine should be used whenever a tetanus vaccine was indicated as in treating emergency wounds. This policy is also adopted in the UK. Outbreaks of diphtheria in Russia and neighbouring countries[5] have prompted recommendations for booster doses in travellers to these countries.

1. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985; **i:** 1089–91.
2. Anonymous. Diphtheria and tetanus boosters. *Lancet* 1985; **i:** 1081–2.
3. Rappuoli R, *et al.* Molecular epidemiology of the 1984–1986 outbreak of diphtheria in Sweden. *N Engl J Med* 1988; **318:** 12–14.
4. Karzon DT, Edwards KM. Diphtheria outbreaks in immunized populations. *N Engl J Med* 1988; **318:** 41–3.
5. Anonymous. Diphtheria immunisation—advice from the Chief Medical Officer. *Commun Dis Rep* 1993; **3:** 27.

Preparations

Ph. Eur.: Diphtheria and Tetanus Vaccine (Adsorbed); Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content);
USP 31: Diphtheria and Tetanus Toxoids Adsorbed; Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.

Proprietary Preparations (details are given in Part 3)
Arg.: Diftavax†; DT Vax†; Imovax DT; Vacuna Doble; ***Austral.:*** ADT; CDT; ***Austria:*** DT-reduct; Td-pur; ***Belg.:*** Ditemer†; Tedivax; ***Braz.:*** Dif-Tet-All; DT Vax†; Refortrix†; ***Canad.:*** Td Adsorbed; ***Cz.:*** Alditeana†; ***Denm.:*** DiTe Booster; ***Fin.:*** DiTe Booster; ***Ger.:*** DT-Impfstoff†; Td-Impfstoff; Td-pur; Td-Rix; ***Gr.:*** Anatoxal Di Te Berna†; DT Vax; ***Hong Kong:*** DiTe Anatoxal†; ***India:*** DT-Vac; Dual Antigen; ***Irl.:*** Diftavax; ***Ital.:*** Anatoxal Adulti; Dif-Tet-All; Diftavax; Ditanrix; ***Malaysia:*** Di Te Anatoxal†; ***Norw.:*** DiTe Booster; ***NZ:*** ADT; CDT; DiTe Anatoxal; ***Philipp.:*** Di Te Anatoxal; ***Pol.:*** DT; ***S.Afr.:*** DT Vax; ***Singapore:*** Di Te Anatoxal†; ***Spain:*** Anatoxal Di Te†; Anatoxal Te Di; Diftavax; Ditanrix; TD; ***Swed.:*** DiTe Booster; ***Switz.:*** Anatoxal Di Te; Ditanrix; ***Thai.:*** Adsorbed DT Vaccine; Di Te Anatoxal†; Dif-Tet-All†; DT Vax†; ***Turk.:*** Di Te Anatoxal; ***UK:*** Diftavax†; ***USA:*** Decavac.

Diphtheria, Tetanus, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos y Haemophilus influenzae.

Profile

Combined adsorbed diphtheria, tetanus, and *Haemophilus influenzae* type b vaccines have been used in some countries for active immunisation of infants. For discussion of immunisation schedules see under Vaccines, p.2202. For concern over the antigenicity of *Haemophilus influenzae* type b vaccine in combined vaccines, see under Haemophilus Influenzae Vaccines, Interactions, p.2213.

Diphtheria, Tetanus, and Hepatitis B Vaccines

ATC — J07CA07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, and hepatitis B vaccines have been used in some countries for active immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Gr.: Primavax†.

Diphtheria, Tetanus, and Pertussis Vaccines

Vacunas de la difteria, el tétanos y la tos ferina.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid on a mineral carrier to which a suspension of killed *Bordetella pertussis* has been added. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid, not less than 40 international units if the test is performed in *guinea-pigs*, or 60 international units if the test is performed in *mice*, of tetanus toxoid, and not less than 4 international units of the pertussis component per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DTwP may be used on the label.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Sine Cellulis ex Elementis Praeparatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP2008 states that DTaP may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, p.2209, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

The incidence of local reactions and fever is reported to be lower with the current accelerated immunisation schedules than the formerly used schedules spreading primary immunisation over 6 months. Local reactions and pyrexia occur less commonly after acellular pertussis vaccines than whole-cell pertussis vaccines, especially in children older than 6 months.

In infants with a personal or close family history of seizures, precautions should be taken to avoid pyrexia. See under Pertussis Vaccines for further details of precautions and contra-indications in individuals with a history of neurological problems.

Incidence of adverse effects. The incidence of local reactions is lower with diphtheria and tetanus vaccines combined with an acellular pertussis component (acellular DTP) than with a whole-cell pertussis component, and is similar to that after diphtheria and tetanus (DT) vaccines. Such reactions are generally mild and self-limiting. Rarely, high fever, persistent or inconsolable crying (possibly as a reaction to pain), hypotonic-hyporesponsive collapse, or short-lived convulsions (frequently febrile convulsions) may occur, and have been reported after both DT and acellular DTP vaccines with equal frequency. These reactions do not appear to have any long-term consequences. Rare but serious acute neurological complications including encephalopathy and prolonged seizures have been reported after DTP vaccines and have been attributed to the whole-cell pertussis component (see Effects on the Nervous System, p.2230) but the association could be coincidental. Epidemiological studies have shown that such events are exceedingly rare and only occasionally followed by long-term neurological damage. Analysis of these studies has been difficult but authorities in the UK and USA concluded that the evidence was insufficient for a link.

A causal relationship between DTP vaccination and sudden infant death syndrome (SIDS) has not been established and any temporal relationship is likely to be due to chance.[1,2] There is evidence that the risk of SIDS is lower in infants who have been vaccinated.[3]

Immediate anaphylactic reactions have been reported and are regarded as a contra-indication to further use of DTP vaccine. However, the appearance of a rash is not generally regarded as a contra-indication to further doses.

For further details concerning the contra-indications and precautions to be observed for pertussis-containing vaccines, see p.2230.

1. Hoffman HJ, *et al.* Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors. *Pediatrics* 1987; **79:** 598–611.
2. Griffin MR, *et al.* Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med* 1988; **319:** 618–23.
3. Mitchell EA, *et al.* Immunisation and the sudden infant death syndrome. *Arch Dis Child* 1995; **73:** 498–501.

Interactions

As for vaccines in general, p.2202.

For a report of a diminished immune response to *Haemophilus influenzae* conjugated vaccine when mixed with diphtheria, tetanus, and acellular pertussis vaccine, see Haemophilus Influenzae Vaccines, p.2213.

Uses and Administration

Combined diphtheria, tetanus, and pertussis vaccines are used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p.2202.

Combined adsorbed vaccines may be given by deep subcutaneous or intramuscular injection (vaccines with acellular pertussis components are for intramuscular injection only) in usual doses of 0.5 mL. In the USA, a vaccine with an acellular pertussis component is used as part of the recommended schedule for primary immunisation. Three doses are given at intervals of 2 months (the first preferably at 2 months of age), a fourth dose at least 6 months after the third, and a fifth dose at school entry. Another dose of a vaccine specially formulated for use in adults and adolescents is given at 11 to 12 years of age.

Vaccines containing an acellular pertussis component are now preferred to those containing a whole-cell component (see Vaccine Development, p.2231). The non-adsorbed type of combined diphtheria, tetanus, and pertussis vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Preparations

Ph. Eur.: Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Arg.: Bustrix; Triacel; Vacuna Triple; ***Austral.:*** Boostrix; Infanrix; Tripacel; ***Austria:*** Boostrix; Infanrix; ***Belg.:*** Boostrix; Infanrix†; Triamer†; ***Braz.:*** DT-Coq/DTP†; Infanrix†; Pertacel†; Vacina Acel Ads Contra Dif, Tet e Coq; Vacina Comb. Contra Dif.-Tet.-Pert. Acel; Vacina Comb. Contra Dift.-Tet.-Coq.Acel; ***Canad.:*** Adacel; ***Cz.:*** Alditepera†; Boostrix; Infanrix; ***Denm.:*** Di-Te-Ki-Booster; ***Fin.:*** Boostrix; Di-Te-Kik†; Infanrix; ***Ger.:*** Boostrix; Covaxis; Infanrix; ***Gr.:*** Anatoxal Di Te Per†; DiTePer Anatoxal†; DT Coq†; Infanrix; ***Hong Kong:*** Adsorbed DT Coq†; Infanrix; Tripacel; Triple Antigen†; ***India:*** Triple Antigen; Tripvac; ***Indon.:*** Infanrix; Tripacel; ***Irl.:*** Infanrix†; ***Israel:*** Acelluvax DTP; Boostrix; DTCoq/DTP; Infanrix; ***Ital.:*** Boostrix; Infanrix; ***Malaysia:*** Boostrix; Infanrix; Tripacel†; ***Mex.:*** Boostrix; ***Neth.:*** Infanrix; ***Norw.:*** Boostrix; ***NZ:*** Boostrix; DiTePer Anatoxal; Infanrix; Tripacel; Triple Antigen; ***Philipp.:*** DPT, DT COQ; Infanrix; Tripacel; ***Pol.:*** DT Coq; DTaP; DTP; Infanrix DTPa; Tripacel; ***Port.:*** Boostrix; Infanrix; ***Rus.:*** Infanrix (Инфанрикс); ***S.Afr.:*** DTP-Merieux; Infanrix DTPa; ***Singapore:*** Boostrix; Infanrix; Tripacel; ***Spain:*** Anatoxal Di Te Per†; Boostrix; DTP-Merieux†; Infanrix; ***Swed.:*** Di-Te-Kik; Infanrix; ***Switz.:*** Boostrix; Infanrix DTPa†; ***Thai.:*** Boostrix; DTCoq/DTP; DTP Vaccine; Infanrix; Tripacel; ***Turk.:*** Acelluvax DTP; Di Te Per Anatoxal; Infanrix DTPa; Tripacel; ***UK:*** Infanrix†; Trivax-AD; ***USA:*** Adacel; Boostrix; Daptacel; Infanrix; Tripedia.

Diphtheria, Tetanus, Pertussis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y Haemophilus influenzae.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Diphtheria Vaccines, p.2209, Diphtheria, Tetanus, and Pertussis Vaccines, p.2210, Haemophilus Influenzae Vaccines, p.2213, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Combined adsorbed diphtheria, tetanus, whole-cell or acellular pertussis, and *Haemophilus influenzae* type b vaccines are available in some countries for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p.2202. Some combined vaccines are not licensed for use in primary immunisation regimens because of concerns over the response to the *Haemophilus influenzae* type b component (see under Interactions of Haemophilus Influenzae Vaccines, p.2213).

Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Haemophilus Type b Conjugate Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis, Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Arg.: Actacel; ***Austral.:*** Infanrix Hib; ***Belg.:*** Infanrix + Hib†; ***Braz.:*** Tetract-HIB†; Vacina Comb. Contra Dif.-Tet.-Pert. Acel e HIB; ***Chile:*** Actacel; Tetract-HIB; ***Cz.:*** Infanrix Hib; Tetract-HIB; ***Ger.:*** Infanrix + Hib†; ***Indon.:*** Infanrix Hib; Tetract-HIB; ***Israel:*** Infanrix Hib; Tetract-HIB; ***Malaysia:*** Infanrix Hib; Tetract-HIB†; ***NZ:*** Infanrix Hib; ***Philipp.:*** Tetract-HIB; ***Port.:*** Infanrix Hib; ***S.Afr.:*** Actacel; Combact-HIB; ***Singapore:*** Actacel; Infanrix Hib; Tetract-HIB; ***Spain:*** Infanrix Hib; Tetract-HIB†; ***Switz.:*** Infanrix DTPa-Hib†; ***Thai.:*** Actacel; Tetract-HIB; ***Turk.:*** Tetract-HIB; ***UK:*** Act-HIB DTP†; Infanrix Hib†; ***USA:*** TriHIBit; ***Venez.:*** Vacuna Tetract-HIB†.

Diphtheria, Tetanus, Pertussis, Haemophilus Influenzae, and Hepatitis B Vaccines

ATC — J07CA11.

Profile

Combined diphtheria, tetanus, pertussis, Haemophilus influenzae, and hepatitis B vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tritanrix HB-HIB; ***Cz.:*** Quintanrix; ***Mex.:*** Tritanrix HB + Hiberix; ***Neth.:*** Quintanrix; ***Port.:*** Quintanrix.

Multi-ingredient: ***NZ:*** Tritanrix HB + HIB.

Diphtheria, Tetanus, Pertussis, and Hepatitis B Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la hepatitis B.

ATC — J07CA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, pertussis, and hepatitis B vaccines are available in some countries for active immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Austral.: Infanrix HepB; ***Braz.:*** Vacina Comb. Contra Dif.-Tet.-Pert.Acel e Hepat.B; ***Cz.:*** Infanrix HepB†; Tritanrix HEPB; ***Fin.:*** Infanrix HepB†; ***Gr.:*** Infanrix HepB; Infanrix-Hep†; ***India:*** Tritanrix HB; ***Indon.:*** Tritanrix HB; ***Ital.:*** Infanrix HepB†; ***Malaysia:*** Tritanrix HB; ***Mex.:*** Tritanrix HB; ***Neth.:*** Tritanrix-HepB; ***NZ:*** Infanrix HepB; ***Philipp.:*** Tritanrix HB; ***S.Afr.:*** Infanrix HB†; Tritanrix HB; ***Spain:*** Infanrix HepB†; Tritanrix HB; ***Swed.:*** Infanrix HepB†; ***Thai.:*** Tritanrix HB; ***Turk.:*** Tritanrix HB; ***Venez.:*** Tritanrix HB†.

Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis, and Haemophilus Influenzae Vaccines

ATC — J07CA09.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum, Hepatitidis B (ADNr), Poliomyelitidis Inactivatum et Haemophili Stirpe b Coniugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, hepatitis B surface antigen, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product may be presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before or during use. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Profile

A combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Haemophilus influenzae vaccine is available in some countries for active immunisation.

◊ References.

1. Curran MP, Goa KL. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa). *Drugs* 2003; **63:** 673–82.

Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Arg.: Hexavac†; Infanrix Hexa; ***Austral.:*** Infanrix Hexa; ***Austria:*** Hexavac†; Infanrix Hexa; ***Belg.:*** Infanrix Hexa; ***Braz.:*** Hexavac†; Infanrix Hexa; Vacina Adsorvida Contra Dif, Tet, Coq Acel, Polio Inat Hepat B (Rec) e Hib Conj; Vacina Comb. Contra Dif.-Tet.-Pert. Acel Hepat.B r-DNA, Polio Inat e HIB; ***Chile:*** Hexavac; Infanrix Hexa; ***Cz.:*** Infanrix Hexa; ***Fin.:*** Infanrix Hexa; ***Fr.:*** Hexavac†; Infanrixhexa; ***Ger.:*** Hexavac†; Infanrix Hexa; ***Gr.:*** Hexavac†; Infanrix Hexa; Infanrix-HepB/Hl†; ***Hong Kong:*** Infanrix Hexa; ***Hung.:*** Hexavac; ***Ital.:*** Hexavac†; Infanrix Hexa; ***Malaysia:*** Infanrix Hexa; ***Mex.:*** Hexavac†; Infanrix Hexa; ***Neth.:*** Infanrix Hexa; ***NZ:*** Infanrix Hexa; ***Philipp.:*** Infanrix Hexa; ***Pol.:*** Hexavac†; Infanrix Hexa; ***Port.:*** Infanrix Hexa; ***Singapore:*** Infanrix Hexa; ***Spain:*** Hexavac†; Infanrix Hexa; ***Swed.:*** Hexavac†; Infanrix Hexa; ***Switz.:*** Hexavac; Infanrix Hexa; ***Thai.:*** Infanrix Hexa; ***Venez.:*** Infanrix Hexa.

Diphtheria, Tetanus, Pertussis, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos, la tos ferina y la poliomielitis.

ATC — J07CA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis et Poliomyelitidis Inactivatum Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared to vaccines generally used for primary vaccination; the amounts of tetanus toxoid and pertussis components may also be reduced. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Diphtheria Vaccines, p.2209, Diphtheria, Tetanus, and Pertussis Vaccines, p.2210, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p.2202.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose of 0.5 mL as a booster at pre-school age (3 years

4 months to 5 years). It is not suitable for primary immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed); Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content); Diphtheria, Tetanus, Pertussis and Poliomyelitis (Inactivated) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Austral.: Boostrix IPV; Infanrix IPV; Quadracel; ***Austria:*** Repevax; Tetravac; ***Belg.:*** Infanrix IPV; Tetracoq†; Tetravac; ***Braz.:*** Tetracoq†; Vacina Acel Ads Contra Dif, Tet, Coq e Polio Inat Comb C/Vac Conj Contra Hib; ***Canad.:*** Quadracel; ***Cz.:*** Infanrix Polio; ***Denm.:*** Di-Te-Ki-Pol; ***Fin.:*** Boostrix Polio; Di-Te-Ki-Pol†; Infanrix Polio; Tetravac; ***Fr.:*** Boostrixtetra; Infanrixtetra; Repevax; Tetravac; ***Ger.:*** Boostrix Polio; Quatro-Virelon†; Repevax; Tetravac†; ***Gr.:*** Boostrix Polio; Infanrix Tetra; Repevax; Tetracoq; Tetravac; ***Hung.:*** Tetraxim; ***Irl.:*** Tetravac; ***Israel:*** Tetracoq; ***Ital.:*** Tetravac; ***Malaysia:*** Infanrix IPV; Tetracoq†; Tetraxim; ***Mex.:*** Infanrix IPV; ***Neth.:*** Infanrix IPV; Triaxis; ***Norw.:*** Boostrix Polio; ***NZ:*** Boostrix IPV; Infanrix IPV; Quadracel; ***Philipp.:*** Tetracoq; Tetraxim; ***Pol.:*** DTaP-IPV; Tetracoq†; ***Port.:*** Boostrix Polio; Infanrix Tetra; Repevax; Tetravac; ***Swed.:*** Boostrix Polio; Di-Te-Ki-Pol†; Tetravac; ***Switz.:*** Boostrix Polio; Infanrix DTPa-IPV; Tetravac; ***Thai.:*** Tetracoq†; Tetraxin; ***Turk.:*** Tetracoq; ***UK:*** Infanrix IPV; Repevax; ***Venez.:*** Vacuna Adsorbida Tetravalente.

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos, la tos ferina, la poliomielitis y Haemophilus influenzae.
ATC — J07CA06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis Sine Cellulis ex Elementis Praeparatum Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
Ph. Eur. 6.2 (Diphtheria, Tetanus, Pertussis, Poliomyelitis (Inactivated) and Haemophilus type b Conjugate Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani, Pertussis, Poliomyelitidis Inactivatum et Haemophili Stirpe b Conjugatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, an inactivated suspension of *Bordetella pertussis*, suitable strains of human polioviruses type 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, polyribosylribitol phosphate derived from a suitable strain of *Haemophilus influenzae* type b and covalently bound to a carrier protein, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. The product is presented with the Haemophilus type b component in a separate container, the contents of which are mixed with the other components immediately before use. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Diphtheria Vaccines, p.2209, Diphtheria, Tetanus, and Pertussis Vaccines, p.2210, Haemophilus Influenzae Vaccines, p.2213, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

Premature neonates. In an observational study[1] of 78 very-low-birth-weight premature neonates given a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine before hospital discharge, increased incidences of apnoea, bradycardia, desaturation, or oxygen requirement occurred in 47% overall within 24 to 48 hours of vaccination. All neonates with increased events returned to baseline within 48 to 72 hours and there was no detrimental impact on clinical course. The authors considered that, although monitoring and appropriate intervention were required, delaying vaccination was not warranted, a view in line with UK and USA official recommendations (see p.2202).

1. Pfister RE, *et al.* Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. *J Pediatr* 2004; **145:** 58–66.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine is used for active immunisation of children. For discussion of immunisation schedules, see under Vaccines, p.2202.

In the UK it is used as part of the recommended schedule for primary immunisation. It is given by intramuscular injection in usual doses of 0.5 mL; three doses are given at intervals of one month, starting preferably at 2 months of age. Although it is not licensed for use after a child's fourth birthday, the national schedule considers it may be used up to the age of 10 years.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Pentaxim; Poliacel†; ***Austral.:*** Pediacel; Poliacel; ***Austria:*** Infanrix IPV + Hib; ***Belg.:*** Infanrix IPV + Hib†; ***Braz.:*** Infanrix IPV + Hib†; Pentact-HIB†; Poliacel†; Vacina Comb. Contra Dif.-Tet.-Pert. Acel, Polio Inat e HIB; ***Canad.:*** Pentacel; ***Chile:*** Pentact-HIB; ***Cz.:*** Infanrix IPV + Hib; ***Denm.:*** Di-Te-Ki-Pol/Act-Hib; ***Fin.:*** Infanrix Polio + Hib; Pentavac; ***Fr.:*** Infanrixquinta; Pentacoq†; Pentavac; ***Ger.:*** Infanrix IPV + Hib; Pentavac; ***Gr.:*** Infanrix IPV + Hib; Pentavac; ***Hong Kong:*** Infanrix IPV + Hib; Pentact-HIB; ***Hung.:*** Infanrix IPV + Hib; Pentaxim; ***Irl.:*** Infanrix IPV + Hib; Pentavac; ***Israel:*** Infanrix Polio IPV - Hib; Pentact-HIB; Poliacel-Act-Hib; ***Ital.:*** Cinquerix†; Pentavac; Quinivaxin†; ***Malaysia:*** Infanrix IPV + Hib; Pediacel; Pentaxim; ***Mex.:*** Infanrix IPV + Hib; Pediacel; ***Neth.:*** DKTP-Hib; Infanrix IPV + Hib; Pediacel; ***Norw.:*** Infanrix Polio + Hib; ***NZ:*** Infanrix IPV + Hib; ***Philipp.:*** Pentact-HIB; Pentaxim; ***Pol.:*** Infanrix IPV + Hib; Pentaxim; ***Port.:*** Infanrix IPV + Hib; Pediacel; ***S.Afr.:*** Pentact-HIB†; ***Singapore:*** Infanrix IPV + Hib; ***Spain:*** Pentavac; ***Swed.:*** Infanrix Polio + Hib; Pentavac; ***Switz.:*** Infanrix DTPa-IPV+Hib; Pentavac; ***Thai.:*** Infanrix IPV + Hib; Pediacel; Pentact-HIB†; Pentaxim; ***Turk.:*** Infanrix IPV-HIB; Pentact-HIB; Poliacel; ***UK:*** Infanrix IPV + Hib; Pediacel; ***Venez.:*** Infanrix IPV + Hib; Vacuna Adsorbida Pentavalente.

Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hepatitis B Vaccines

ATC — J07CA12.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Diphtheria Vaccines, p.2209, Diphtheria, Tetanus, and Pertussis Vaccines, p.2210, Hepatitis B Vaccines, p.2215, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

A combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and hepatitis B vaccine is available in some countries for active immunisation of children.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Infanrix Penta; ***Cz.:*** Infanrix Penta; ***Gr.:*** Infanrix Penta; ***Ital.:*** Infanrix Penta; ***Neth.:*** Infanrix Penta; ***NZ:*** Infanrix Penta; ***Port.:*** Infanrix Penta; ***USA:*** Pediarix.

Diphtheria, Tetanus, and Poliomyelitis Vaccines

Vacunas de la difteria, el tétanos y la poliomielitis.
ATC — J07CA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Diphtheria, Tetanus and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigens(s) Content); Vaccinum Diphtheriae, Tetani et Poliomyelitidis Inactivatum, Antigeni-o(-is) Minutum, Adsorbatum). A combined vaccine containing diphtheria formol toxoid, tetanus formol toxoid, suitable strains of human polioviruses types 1, 2, and 3 grown in suitable cell cultures and inactivated by a validated method, and a mineral adsorbent such as aluminium hydroxide or hydrated aluminium phosphate. The amount of diphtheria toxoid per single human dose is reduced compared to vaccines generally used for primary vaccination; the amount of tetanus toxoid may also be reduced. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Diphtheria Vaccines, p.2209, Diphtheria and Tetanus Vaccines, p.2210, and Tetanus Vaccines, p.2240.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

A combined diphtheria, tetanus, and poliomyelitis (inactivated) vaccine is used for active immunisation. For discussion of immunisation schedules see under Vaccines, p.2202.

In the UK it is used as part of the recommended schedule and is given by intramuscular injection in a single dose (usually 0.5 mL) as a booster at the ages of 13 to 18 years. It is not licensed for primary immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus, and Poliomyelitis (Inactivated) Vaccine (Adsorbed, Reduced Antigen(s) Content).

Proprietary Preparations (details are given in Part 3)
Austria: Revaxis; ***Belg.:*** Revaxis; ***Canad.:*** Td-Polio; ***Fr.:*** DT Polio; Revaxis; Vaccin DTP†; ***Ger.:*** Revaxis; Td-Virelon; ***Gr.:*** Revaxis; ***Hung.:*** Dultavax; ***Irl.:*** Revaxis; ***Ital.:*** Revaxis; ***Neth.:*** Revaxis; ***Port.:*** Revaxis; ***Switz.:*** Revaxis; Td-Virelon; ***UK:*** Revaxis.

Endotoxin Antibodies

Anticuerpos antiendotoxinas.

Profile

Antibodies against the endotoxin of Gram-negative bacteria have been tried as adjunctive therapy for the treatment and prevention of Gram-negative bacteraemia and shock.

Early preparations consisted of antisera prepared from the sera of donors immunised with *Escherichia coli* J5; these were superseded by human and murine IgM monoclonal antibodies. Nebacumab (HA-1A) is a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin. Lipid A in the circulation releases tumour necrosis factor and other cytokines from macrophages and endothelial cells which may ultimately culminate in physiological effects such as multiple organ failure. Despite early promising results of clinical studies the safety of nebacumab in patients without Gram-negative septicaemia was questioned and the product was withdrawn.

A murine monoclonal IgM antibody (edobacomab; E5) has also undergone clinical trials although results have been disappointing.

Epstein-Barr Virus Vaccines

Vacunas del virus de Epstein-Barr.

Profile

Several Epstein-Barr virus vaccines are under investigation for active immunisation against infectious mononucleosis and post-transplant lymphoproliferative disorders.

◊ Epstein-Barr virus is a herpesvirus that is ubiquitous in the adult population. It only causes clinical illness where primary infection occurs in adolescence or adulthood, when it prompts the symptoms of infectious mononucleosis in about 50% of cases. More than 90% of the world's population, however, carry the virus as a lifelong latent infection of B-lymphocytes and, as a result, Epstein-Barr virus can also be associated with malignancies including lymphoproliferative diseases, Burkitt's lymphoma, gastric carcinoma, oral hairy leucoplakia, nasopharyngeal carcinoma, and Hodgkin's disease.

Vaccines against Epstein-Barr virus infection are under investigation[1,2] and the main focus has been towards the development of a vaccine to prevent primary infection or to minimise its consequences, namely infectious mononucleosis and post-transplant lymphoproliferative disease, rather than towards the malignancies associated with the virus which occur in relatively fewer patients. Two main approaches have been adopted, the first of which seeks to exploit the major envelope glycoprotein of the virus, gp340, because of its ability to induce neutralising antibodies. This vaccine may prevent infectious mononucleosis by moderating the initial viral replication and spread during primary infection, thereby curtailing the cytotoxic T-lymphocyte response to lytic antigens that would otherwise invoke the immunological processes responsible for clinical symptoms. The second approach is based on the induction of cytotoxic T-cells specific to Epstein-Barr virus, thereby aiming to reduce the clinical symptoms of infectious mononucleosis rather than to prevent primary infection.

Potential future vaccines for malignancies associated with Epstein-Barr virus are likely to be therapeutic rather than preventative and to exploit the presence of the virus in tumour cells; alternatively they may be focussed on tumour antigens not encoded by Epstein-Barr virus.[1,2]

1. Moss DJ, *et al.* Candidate vaccines for Epstein-Barr virus. *BMJ* 1998; **317:** 423–4.
2. Macsween KF, Crawford DH. Epstein-Barr virus—recent advances. *Lancet Infect Dis* 2003; **3:** 131–40.

Escherichia Coli Vaccines

Vacunas de Escherichia coli.

Profile

Vaccines against enterotoxigenic strains of *Escherichia coli* are under investigation. Vaccine candidates include toxoids, inactivated whole bacteria, purified surface antigens, and live oral vaccines.

◊ Infectious diarrhoea remains a major source of morbidity and mortality in the world and a significant proportion is caused by pathogenic strains of *Escherichia coli* While it is considered feasible to develop effective vaccines against *E. coli*, at present there are no such vaccines available. Current approaches against enteropathogenic *E. coli* (EPEC) and enterohaemorrhagic *E. coli* (EHEC) have focussed on three main areas: the EPEC and EHEC proteins involved in colonisation of the intestine, the EHEC O157-specific side-chain of lipopolysaccharides, and the immunogenicity of Shiga toxin produced by the organism. While vaccination against EPEC has to be directed towards susceptible human populations, there are two possible approaches with regard to EHEC, namely vaccination of either humans or the animal reservoir, cattle. Studies of vaccine candidates are ongoing *in vitro*, in *animal* models, and in healthy subjects. For both pathogens, however, the development of vaccines would not in itself serve to eradicate the spread of infections and would need to be accompanied by public health campaigns to increase food hygiene and monitoring of water supplies and facilities.[1]

Enterotoxigenic *E. coli* (ETEC) is a major cause of travellers' diarrhoea. A phase II placebo-controlled study[2] found that a vaccine containing heat-labile enterotoxin from ETEC given as a skin patch (2 patches applied 2 to 3 weeks apart), reduced the risk of moderate to severe travellers' diarrhoea by 75% and severe diarrhoea by 84%. In vaccinated travellers who got diarrhoea, the illness was significantly shorter and milder.

Further references.[3-7]

1. Horne C, *et al*. Current progress in enteropathogenic and enterohemorrhagic Escherichia coli vaccines. *Expert Rev Vaccines* 2002; **1:** 483–93.
2. Frech SA, *et al.* Use of a patch containing heat-labile toxin from Escherichia coli against travellers' diarrhoea: a phase II, randomised, double-blind, placebo-controlled field trial. *Lancet* 2008; **371:** 2019–25.
3. Boedeker EC. Vaccines for enterotoxigenic Escherichia coli: current status. *Curr Opin Gastroenterol* 2005; **21:** 15–9.
4. Steffen R, *et al.* Vaccination against enterotoxigenic Escherichia coli, a cause of travelers' diarrhea. *J Travel Med* 2005; **12:** 102–7.
5. Walker RI, *et al.* Ad Hoc ETEC Technical Expert Committee. Analysis of strategies to successfully vaccinate infants in developing countries against enterotoxigenic E. coli (ETEC) disease. *Vaccine* 2007; **25:** 2545–66.
6. Goldwater PN. Treatment and prevention of enterohemorrhagic Escherichia coli infection and hemolytic uremic syndrome. *Expert Rev Anti Infect Ther* 2007; **5:** 653–63.
7. Serna A, Boedeker EC. Pathogenesis and treatment of Shiga toxin-producing Escherichia coli infections. *Curr Opin Gastroenterol* 2008; **24:** 38–47.

Gas-gangrene Antitoxins

Antitoxinas de la gangrena gaseosa.

ATC — J06AA05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Novyi); Immunoserum Gangraenicum (Clostridium Novyi)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium novyi*. It has a potency of not less than 3750 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Nov/Ser may be used on the label.

The BP 2008 gives Gas-gangrene Antitoxin (Oedematiens) as an approved synonym.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Perfringens); Immunoserum Gangraenicum (Clostridium Perfringens)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium perfringens*. It has a potency of not less than 1500 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Perf/Ser may be used on the label.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin (Septicum); Immunoserum Gangraenicum (Clostridium Septicum)). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the alpha toxin formed by *Clostridium septicum*. It has a potency of not less than 1500 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Sep/Ser may be used on the label.

Ph. Eur. 6.2 (Gas-gangrene Antitoxin, Mixed; Immunoserum Gangraenicum Mixtum). It is prepared by mixing Gas-gangrene Antitoxin (Novyi), Gas-gangrene Antitoxin (Perfringens), and Gas-gangrene Antitoxin (Septicum) in appropriate quantities. It has a potency of not less than 1000 international units/mL of Gas-gangrene Antitoxin (Novyi), not less than 1000 international units/mL of Gas-gangrene Antitoxin (Perfringens), and not less than 500 international units/mL of Gas-gangrene Antitoxin (Septicum). It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Gas/Ser may be used on the label.

Profile

Gas-gangrene antitoxins have been used for the treatment of gas gangrene and for prophylaxis in patients at risk after injury. They are now seldom used and have been superseded by antibacterials. Monovalent gas-gangrene antitoxins have been little used in practice owing to the difficulty of rapidly identifying the infecting organism.

Preparations

Ph. Eur.: Gas-gangrene Antitoxin (Novyi); Gas-gangrene Antitoxin (Perfringens); Gas-gangrene Antitoxin (Septicum); Mixed Gas-gangrene Antitoxin.

Proprietary Preparations (details are given in Part 3)

Cz.: Gasea†.

Gonococcal Vaccines

Gonorrhoea Vaccines; Vacunas de la gonorrea.

Profile

Several experimental gonococcal vaccines, produced usually from the surface antigens of *Neisseria gonorrhoeae*, have been investigated.

Haemophilus Influenzae Vaccines

Vacunas de Haemophilus influenzae.

ATC — J07AG01 (B, purified antig. conjugate).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Haemophilus type b Conjugate Vaccine; Vaccinum Haemophili Stirpe B Conjugatum). A liquid or freeze-dried preparation of a polysaccharide, polyribosylribitol phosphate (PRP), derived from a suitable strain of *Haemophilus influenzae* type b, covalently bound to a carrier protein. The carrier protein, when conjugated to PRP, is capable of inducing a T-cell-dependent B-cell immune response to the polysaccharide. Carrier proteins currently approved are diphtheria toxoid, tetanus toxoid, CRM 197 diphtheria protein, and meningococcal group B outer membrane protein (OMP). It should be stored at 2° to 8° and protected from light.

The BP 2008 states that Hib may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Erythema multiforme and transient cyanosis of the lower limbs have been reported rarely in children receiving haemophilus influenzae-containing vaccines.

Effects on the nervous system. Guillain-Barré syndrome has been reported[1] after vaccination with haemophilus influenzae conjugate vaccines in a small number of infants. In one report, onset of symptoms occurred within 1 week of vaccination of 3 infants with an haemophilus influenzae conjugate vaccine (diphtheria toxoid conjugate). However, a causal relationship has not yet been established.

1. D'Cruz OF, *et al.* Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with Haemophilus influenzae type b conjugate vaccine. *J Pediatr* 1989; **115:** 743–6.

Interactions

As for vaccines in general, p.2202.

Antineoplastics. Haemophilus influenzae infection occurred in a child who had received antineoplastic therapy despite having completed a primary course of immunisation before the neoplasia was diagnosed.[1] A subsequent booster dose produced an adequate antibody response. Antineoplastic therapy may have impaired the T-cell response to infection.

1. Jenkins DR, *et al.* Childhood neoplasia and Haemophilus influenzae type b vaccine failure. *Lancet* 1996; **348:** 131.

Diphtheria, tetanus, and pertussis vaccines. Some haemophilus influenzae conjugated vaccines may be mixed with diphtheria, tetanus, and pertussis vaccines before administration without adversely affecting the immunogenicity of the components[1,2] although there has also been a report of reduced immunogenicity.[3] Manufacturers may provide further information on compatibility.

1. Miller MA, *et al.* Safety and immunogenicity of PRP-T combined with DTP: excretion of capsular polysaccharide and antibody response in the immediate post-vaccination period. *Pediatrics* 1995; **95:** 522–7.
2. Mulholland EK, *et al.* The use of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine mixed with diphtheria-tetanus-pertussis vaccine in Gambian infants. *Vaccine* 1996; **14:** 905–9.
3. Eskola J, *et al.* Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of Haemophilus influenzae type b conjugated vaccine. *Lancet* 1996; **348:** 1688–92.

Uses and Administration

Haemophilus influenzae (Hib) vaccines are used for active immunisation against *Haemophilus influenzae* type b infections. Vaccines are prepared from the capsular polysaccharide of *H. influenzae* type b and immunogenicity, especially in young children, is improved by linking the polysaccharide to a protein carrier to form a conjugate vaccine.

Different proprietary vaccines may be conjugated to differing proteins but are generally regarded as interchangeable.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria Toxoid Conjugate) (PRP-D) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to diphtheria toxoid.

Haemophilus Influenzae Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (HbOC) consists of oligosaccharides derived from the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to a non-toxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae.*

Haemophilus Influenzae Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP or PRP-OMPC) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to an outer membrane protein complex of *Neisseria meningitidis* group B.

Haemophilus Influenzae Conjugate Vaccine (Tetanus Toxoid Conjugate) (PRP-T) consists of the purified capsular polysaccharide of *Haemophilus influenzae* type b covalently linked to tetanus toxoid.

For primary immunisation either combined vaccines or single-component Haemophilus influenzae vaccines may be used.

In the UK, a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine (p.2212) is used. Children over 1 year of age and under 10 years of age who have not been immunised against *Haemophilus influenza* or have not completed a primary vaccination course of diphtheria, tetanus, pertussis, or polio, should be given 3 doses of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine. Those who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio, should receive a single dose of a combined *Haemophilus influenzae* and meningococcal C conjugate vaccine. Routine use in children older than 10 years or adults is not recommended in the UK, but asplenic children (over 10 years of age) and adults who have not been previously immunised should receive two doses of combined *Haemophilus influenzae* and meningococcal C conjugate vaccine, two months apart.

In the USA, primary immunisation is also carried out in conjunction with diphtheria, tetanus, and pertussis vaccination. If a meningococcal protein conjugate vaccine is used, only 2 doses are given for the primary course. A reinforcing dose using any of the available vaccines is given at 12 to 15 months of age.

Where compatibility has been shown, Hib vaccines may be mixed immediately before use with diphtheria, tetanus, and pertussis vaccines (but see Interactions, above).

Preparations

Ph. Eur.: Haemophilus Type b Conjugate Vaccine.

Proprietary Preparations (details are given in Part 3)

Arg.: PedvaxHIB†; ***Austral.:*** Hiberix; HibTITER†; PedvaxHIB; ***Austria:*** Act-HIB; HibTITER; ***Belg.:*** Act-HIB; Hiberix†; HibTITER†; ***Braz.:*** Act-HIB†; Hiberix†; PedvaxHIB; Vacina Conj Com Proteina Tetanica Contra Haemophilus influenzae Tipo B; Vacina Conj Contra Haemophilus Influenzae Tipo B; ***Canad.:*** Act-HIB; PedvaxHIB; ***Chile:*** Act-HIB; ***Cz.:*** Act-HIB; Hiberix; HibTITER†; ***Denm.:*** Act-HIB; HibTITER†; ***Fin.:*** Hiberix†; HibTITER†; ***Fr.:*** Act-HIB; ***Ger.:*** Act-HIB†; HibTITER†; PedvaxHIB†; ***Gr.:*** Act-HIB; Hiberix; HibTITER†; ***Hong Kong:*** Act-HIB; Hiberix; PedvaxHIB; ***Hung.:*** Act-HIB; ***India:*** Hiberix; Vaxim HIB; ***Indon.:*** Act-HIB; Hiberix; PedvaxHIB; ***Irl.:*** Act-HIB; Hiberix; HibTITER†; ***Israel:*** Act-HIB; HibTITER†; PedvaxHIB†; ***Ital.:*** Act-HIB; Hiberix; HibTITER†; Vaxem Hib; ***Malaysia:*** Act-HIB†; Hiberix; PedvaxHIB†; ***Mex.:*** HibTITER†; PedvaxHIB; Vaxem Hib†; ***Neth.:*** Act-HIB; Hiberix; ***Norw.:*** Act-HIB; ***NZ:*** Hiberix; HibTITER†; ***Philipp.:*** Act-HIB; Hiberix; Vaxem Hib; ***Pol.:*** Act-HIB; Hiberix; HibTITER; PedvaxHIB; ***Port.:*** Hiberix; HibTITER†; ***Rus.:*** Hiberix (Хиберикс); ***S.Afr.:*** Act-HIB; Hiberix; ***Singapore:*** Act-HIB; Hiberix; PedvaxHIB†; ***Spain:*** Act-HIB; Hiberix; HibTITER; ***Swed.:*** Act-HIB; HibTITER†; ***Switz.:*** Hiberix; ***Thai.:*** Act-HIB; Hiberix; PedvaxHIB; Vaxem Hib; ***Turk.:*** Act-HIB; Hiberix; PedvaxHIB; ***UK:*** Act-HIB†; Hiberix; ***USA:*** Act-HIB; HibTITER; OmniHIB; PedvaxHIB; ProHIBiT†; ***Venez.:*** Act-HIB†; Hiberix.

Haemophilus Influenzae and Hepatitis B Vaccines

Vacunas de Haemophilus influenzae y la hepatitis B.

ATC — J07CA08.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Haemophilus influenzae type b (Hib) conjugate and hepatitis B vaccines are available in some countries for active immunisation as part of the primary immunisation of infants born to HBsAg-negative mothers. In the USA, an Haemophilus influenzae type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine is used. It is given in a schedule of 3 doses, 0.5 mL being given intramuscularly at 2 months, 4 months, and 12 to 15 months of age. Use in infants less than 6 weeks old is not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Comvax; ***Austria:*** Procomvax; ***Cz.:*** Procomvax; ***Ger.:*** Procomvax†; ***Gr.:*** Procomvax; ***Ital.:*** Procomvax; ***Mex.:*** Comvax; ***Neth.:*** Procomvax; ***NZ:*** Comvax; ***Pol.:*** Procomvax; ***Port.:*** Procomvax; ***USA:*** Comvax.

Haemophilus Influenzae and Meningococcal Vaccines

Profile

A combined Haemophilus influenza type b and meningococcal C conjugate vaccine is available for active immunisation in some countries; in the UK a single dose may be given to children between 1 and 10 years of age who have completed a primary vaccination course of diphtheria, tetanus, pertussis, and polio. Two doses given 2 months apart may be given to asplenic children (over 10 years of age) or adults who have not been previously immunised.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Menitorix.

Haemophilus Influenzae and Poliomyelitis Vaccines

ATC — J07CA04.

Profile

Combined haemophilus influenzae type b conjugate and inactivated poliomyelitis vaccines have been used in some countries for active immunisation of infants.

Preparations

Proprietary Preparations (details are given in Part 3)
Norw.: Act-HIB Polio†; ***Swed.:*** PolioHib†.

Haemorrhagic Fever with Renal Syndrome Vaccines

HFRS Vaccine; Vaccinum Haemorrhagia Febris cum Renis Sindronum; Vacunas de la fiebre renal epidémica.

Description. A fluid or freeze-dried preparation of a suitable hantavirus grown in the neural tissue of suckling rodents or in cell cultures and inactivated. The fluid vaccine should be stored at 2° to 8° and not allowed to freeze. The freeze-dried form should be stored below 10°.

Profile

Inactivated viral vaccines against haemorrhagic fever with renal syndrome have been investigated and are available in some countries, but there have been problems producing a sufficient and sustained immune response.

◊ References.

1. Sohn YM, *et al.* Primary humoral immune responses to formalin inactivated hemorrhagic fever with renal syndrome vaccine (Hantavax): consideration of active immunization in South Korea. *Yonsei Med J* 2001; **42:** 278–84.
2. Cho HW, *et al.* Review of an inactivated vaccine against hantaviruses. *Intervirology* 2002; **45:** 328–33.
3. Park K, *et al.* Protective effectiveness of hantavirus vaccine. *Emerg Infect Dis* 2004; **10:** 2218–20.

Helicobacter Pylori Vaccines

Vacunas de Helicobacter pylori.

Profile

Vaccines against *Helicobacter pylori* are being developed for prophylaxis of peptic ulcer disease and gastric cancer.

◊ Studies in *animals* have shown the feasibility of both prophylactic and therapeutic vaccination against *Helicobacter pylori* infection, but there have been few studies in humans. Encouraging results have been obtained with parenteral, multicomponent, aluminium hydroxide-based vaccines in terms of safety and immunogenicity. In contrast, preliminary results obtained with mucosally delivered single-component vaccines have been disappointing, partly due to the intrinsic difficulty in developing purified proteins that are sufficiently immunogenic following mucosal delivery. Studies are ongoing into the mechanisms by which the host's genetic make-up modifies the inflammatory and immunological response to *H. pylori*.[1-4]

1. Ruggiero P, *et al.* The quest for a vaccine against Helicobacter pylori: how to move from mouse to man? *Microbes Infect* 2003; **5:** 749–56.
2. Sutton P, Doidge C. Helicobacter pylori vaccines spiral into the new millennium. *Dig Liver Dis* 2003; **35:** 675–87.
3. Del Giudice G, Michetti P. Inflammation, immunity and vaccines for Helicobacter pylori. *Helicobacter* 2004; **9** (suppl 1): 23–8.
4. Agarwal K, Agarwal S. Helicobacter pylori vaccine: from past to future. *Mayo Clin Proc* 2008; **83:** 169–75.

Hepatitis A Immunoglobulins

Inmunoglobulinas contra la hepatitis A.

ATC — J06BB11.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Human Hepatitis A Immunoglobulin; Immunoglobulinum Humanum Hepatitidis A). A liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against the hepatitis A virus. Normal immunoglobulin may be added. It contains not less than 600 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container under vacuum or under an inert gas.

Profile

Immunoglobulins containing high levels of specific antibodies against hepatitis A have been used in some countries for passive immunisation against hepatitis A infection; in the UK, normal immunoglobulin is usually given.

Preparations

Ph. Eur.: Human Hepatitis A Immunoglobulin.

Proprietary Preparations (details are given in Part 3)
Port.: Globuman Hepatite A†.

Hepatitis A Vaccines

Vacunas de la hepatitis A.

ATC — J07BC02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Hepatitis A Vaccine (Inactivated, Adsorbed); Vaccinum Hepatitidis A Inactivatum Adsorbatum; Inactivated Hepatitis A Vaccine BP 2008). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures, inactivated by a validated method, and adsorbed on a mineral carrier. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that Hep A may be used on the label.

Ph. Eur. 6.2 (Hepatitis A Vaccine (Inactivated, Virosome); Vaccinum Hepatitidis A Inactivatum Virosomale). A liquid preparation of a suitable strain of hepatitis A virus grown in cell cultures and inactivated by a validated method. Virosomes composed of influenza proteins and phospholipids are used as adjuvants. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that HepA may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

◊ General references.

1. Niu MT, *et al.* Two-year review of hepatitis A vaccine safety: data from the Vaccine Adverse Event Reporting System (VAERS). *Clin Infect Dis* 1998; **26:** 1475–6.

Effects on the blood. WHO has received reports of 5 cases of thrombocytopenia, 3 with purpura, associated with hepatitis A vaccine.[1]

1. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.

Effects on the nervous system. Neurological symptoms resembling encephalitis have followed a third dose of hepatitis A vaccine.[1] Other serious neurological reactions reported in patients given inactivated hepatitis A vaccine include transverse myelitis, Guillain-Barré syndrome, and neuralgic amyotrophy.[2] Such reactions appear to be very rare, and, since other vaccines have often been given simultaneously, may not be directly attributable to hepatitis A vaccine.

1. Hughes PJ, *et al.* Probable post-hepatitis A vaccination encephalopathy. *Lancet* 1993; **342:** 302.
2. Committee on Safety of Medicines/Medicines Control Agency. Hepatitis A vaccination (Havrix). *Current Problems* 1994; **20:** 16.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Hepatitis A vaccines are used for active immunisation against hepatitis A infection.

In the UK, the use of an inactivated vaccine is recommended as an alternative to normal immunoglobulin for frequent travellers to areas of high or moderate hepatitis A endemicity or for those staying for more than 3 months in such areas; in some countries a hepatitis A immunoglobulin (p.2214) is available for those making shorter or less frequent journeys. Immunisation is also recommended in haemophiliacs, patients with chronic liver disease, and in those at risk of exposure to hepatitis A by virtue of their occupation, and should be considered in persons whose lifestyle is likely to place them at risk. The vaccine is given intramuscularly, except in haemophiliacs in whom it should be given by deep subcutaneous injection. In the UK, various vaccines are available and the dose (0.5 or 1 mL) depends on the product used and age of the patient. They may be prepared from several inactivated hepatitis A virus strains including CR326F, GBM, HM175, and RG-SB. The primary immunisation schedule for all vaccines consists of a single dose appropriate to the age of the patient and should be followed 6 to 12 months later by a booster dose. Immunity is provided for at least 10 years after these doses.

In the US, immunisation at 12 months of age (with a booster at least 6 months later) is recommended as part of the routine primary immunisation schedule. Post-exposure prophylaxis is recommended in persons who have not previously received a hepatitis A vaccine. Vaccination is also recommended for travellers to countries with intermediate to high hepatitis A endemicity.

◊ References.

1. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics* 2007; **120:** 189–99. http://pediatrics.aappublications.org/cgi/reprint/120/1/189.pdf (accessed 15/07/08)

Vaccine development. Commercially available hepatitis A vaccines are usually produced from inactivated hepatitis A virus strains propagated in cell culture, commonly of human diploid fibroblast cells. 'Virosome' hepatitis A vaccines consisting of inactivated hepatitis A virus epitopes formulated into liposomes are also becoming available. Live attenuated hepatitis A vaccines have also been developed, although an oral live vaccine does not appear to have yet been produced.

Preparations

Ph. Eur.: Hepatitis A Vaccine (Inactivated, Adsorbed); Hepatitis A Vaccine (Inactivated, Virosome).

Proprietary Preparations (details are given in Part 3)
Arg.: Avaxim; Epaxal; Havrix; VAQTA; Virohep-A; ***Austral.:*** Avaxim; Havrix; VAQTA; ***Austria:*** Havrix; VAQTA†; ***Belg.:*** Epaxal; Havrix; VAQTA†; ***Braz.:*** Avaxim†; Havrix†; Vacina Contra Hepatite A; VAQTA†; ***Canad.:*** Avaxim; Epaxal†; Havrix; VAQTA; ***Chile:*** Avaxim; Epaxal; Havrix; ***Cz.:*** Avaxim; Epaxal†; Havrix; VAQTA; ***Denm.:*** Epaxal; Havrix; ***Fin.:*** Epaxal; Havrix; VAQTA†; ***Fr.:*** Avaxim; Havrix; VAQTA†; ***Ger.:*** Epaxal†; Havpur; Havrix; VAQTA; ***Gr.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Hong Kong:*** Avaxim; Epaxal; Havrix; VAQTA; ***Hung.:*** Avaxim; Havrix; VAQTA; ***India:*** Havrix; ***Indon.:*** Avaxim; Havrix; VAQTA; ***Irl.:*** Avaxim; Havrix; VAQTA†; ***Israel:*** Avaxim; Epaxal; Havrix; VAQTA; ***Ital.:*** Avaxim; Epaxal; Havrix; Nothav†; VAQTA; ***Malaysia:*** Avaxim; Epaxal; Havrix; VAQTA†; ***Mex.:*** Avaxim; Havrix; VAQTA; ***Neth.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Norw.:*** Epaxal; Havrix; VAQTA†; ***NZ:*** Avaxim; Epaxal; Havrix; VAQTA; ***Philipp.:*** Avaxim; Epaxal; Havrix; ***Pol.:*** Avaxim; Havrix; VAQTA; ***Port.:*** Avaxim; Epaxal; Havrix; VAQTA; ***Rus.:*** Havrix (Хаврикс); VAQTA (ВАКТА); ***S.Afr.:*** Avaxim; Havrix; ***Singapore:*** Avaxim; Epaxal; Havrix; VAQTA; ***Spain:*** Avaxim; Epaxal; Havrix; VAQTA; ***Swed.:*** Avaxim; Epaxal; Havrix; VAQTA†; ***Switz.:*** Epaxal; Havrix; VAQTA†; ***Thai.:*** Avaxim; Havrix; VAQTA; ***Turk.:*** Avaxim; Epaxal; Havrix; VAQTA; ***UK:*** Avaxim; Epaxal; Havrix; VAQTA; ***USA:*** Havrix; VAQTA; ***Venez.:*** Epaxal†; Havrix.

Hepatitis B Immunoglobulins

Inmunoglobulinas contra la hepatitis B.

ATC — J06BB04.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Hepatitis B Immunoglobulin; Immunoglobulinum Humanum Hepatitidis B). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having specific antibodies against hepatitis B surface antigen. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

Ph. Eur. 6.2 (Human Hepatitis B Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Hepatitidis B ad Usum Intravenosum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface antigen. Human normal immunoglobulin for intravenous administration may be added. It contains not less than 50 international units/mL. Storage requirements are similar to those for Human Hepatitis B Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25°.

USP 31 (Hepatitis B Immune Globulin). A is a sterile solution consisting of globulins derived from the plasma of human donors who have high titres of antibodies against hepatitis B surface antigen. It contains 10 to 18% of protein, of which not less than 80% is monomeric immunoglobulin G. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Preparation strength. For a warning concerning possible lack of equivalence between different preparations of hepatitis B immunoglobulins, see under Uses and Administration, below.

Uses and Administration

Hepatitis B immunoglobulins are used for passive immunisation of persons exposed or possibly exposed to hepatitis B virus, including by sexual contact. They are not appropriate for treatment. Hepatitis B immunoglobulins should always be given in addition to active immunisation with hepatitis B vaccine in at-risk patients exposed to hepatitis B virus.

In the UK, a hepatitis B immunoglobulin containing 100 international units/mL is available for intramuscular use. The dose in adults and children over 10 years of age is a single dose of 500 international units by intramuscular injection given preferably within 48 hours of exposure and not more than 1 week after exposure. Children aged 5 to 9 years may be given 300 international units, and children under 5 years 200 international units. Hepatitis B immunoglobulin should also be given to newborn infants at risk whose mothers are persistent carriers of hepatitis B surface antigen or whose mothers are HBsAg-positive as a result of recent infection. The dose is 200 international units by intramuscular injection preferably at birth, and certainly within 24 hours of birth.

There is now a UK and European standard for a preparation for intravenous use containing not less than 50 international units/mL.

In the USA, a hepatitis B immunoglobulin containing 15 to 18% of protein is available for intramuscular use. The dose for adults is 0.06 mL/kg. A dose of 0.5 mL is given to infants perinatally exposed to hepatitis B; this appears to be a significantly lower dose than that used in the UK. A hepatitis B immunoglobulin is also available for the prevention of hepatitis B recurrence after liver transplantation in patients who are positive for hepatitis B surface antigen. It is given intravenously at a dose of 20 000 international units during surgery and then daily from day 1 to day 7 after transplant surgery, then every 2 weeks from week 2 to week 12, and then monthly from 4 months post-surgery.

Preparation strength. *The content of hepatitis B immunoglobulin may vary between countries and between manufacturers. Care should be taken in interpreting dosage recommendations which are not given in terms of international units.* Products available in the USA have their strength expressed with reference to an FDA standard but are considered to contain the equivalent of at least 200 international units/mL.

Monoclonal antibodies. The name tuvirumab is applied to a human hepatitis B monoclonal antibody. A murine monoclonal antibody has been tried in a few patients with primary antibody deficiency.[1]

1. Lever AML, *et al.* Monoclonal antibody to HBsAg for chronic hepatitis B virus infection with hypogammaglobulinaemia. *Lancet* 1990; **335:** 1529.

Organ and tissue transplantation. Studies[1-5] in patients positive for hepatitis B surface antigen undergoing liver transplantation (p.1815) suggest that long-term passive immunisation with hepatitis B immunoglobulin could reduce hepatitis B reinfection and improve survival in these patients.

1. Samuel D, *et al.* Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991; **337:** 813–15.
2. Nymann T, *et al.* Prevention of hepatitis B recurrence with indefinite hepatitis B immune globulin (HBIG) prophylaxis after liver transplantation. *Clin Transplant* 1996; **10:** 663–7.
3. McGory RW, *et al.* Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996; **61:** 1358–64.
4. Terrault NA, *et al.* Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; **24:** 1327–33.
5. Sanchez-Fueyo A, *et al.* Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; **31:** 496–501.

Postexposure prophylaxis. For discussion of the use of hepatitis B immunoglobulins in patients exposed to hepatitis B virus, see Postexposure Prophylaxis under Uses and Administration of Hepatitis B Vaccines, below.

Preparations

Ph. Eur.: Human Hepatitis B Immunoglobulin; Human Hepatitis B Immunoglobulin for Intravenous Administration;
USP 31: Hepatitis B Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Antib; Igantibe; ***Austria:*** Aunativ†; Hepatect; ***Belg.:*** Hepacaf; ***Canad.:*** BayHep B†; HyperHep B; ***Chile:*** Igantibe; ***Cz.:*** Aunativ†; Hepatect†; NeoHepatect; ***Denm.:*** Aunativ†; ***Fr.:*** Ivhebex; ***Ger.:*** Hepatect; ***Gr.:*** Aunativ; Ivhebex; ***Hong Kong:*** BayHep B; Hepatect†; Hepuman†; ***Hung.:*** Hepatect; ***Indon.:*** HyperHep B; ***Irl.:*** Hepatect; ***Israel:*** BayHep; Hepatect; Omri-Hep-B; ***Ital.:*** Haimabig†; Hepuman B†; Igantibe; ImmunoHBs; Neohepatect; Uman-Big†; Venbig; ***Jpn:*** Hebsbulin-IH; ***Malaysia:*** Hepabig; ***Neth.:*** Hepatect; HepBQuin; ***Norw.:*** Aunativ†; ***NZ:*** HyperHep B; ***Philipp.:*** BayHep B; Hepabig; ***Pol.:*** Gamma Anty HBs; Hepatect; ***Port.:*** Hepatect; Venbig; ***Rus.:*** Antihep (Антиген)†; ***S.Afr.:*** Hebagam IM; ***Singapore:*** BayHep B†; ***Spain:*** Gamma Antihepatitis B; Gammaglob Antihepatitis BP; Hepuman; ***Swed.:*** Aunativ; ***Switz.:*** Hepatect; Hepuman†; ***Turk.:*** BayHep B; Hepatect; Hepatitis B Ig-P; Hepuman; ***USA:*** HepaGam B; HyperHep B; Nabi-HB.

Hepatitis B Vaccines

Vacunas de la hepatitis B.
ATC — J07BC01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) have monographs.
Ph. Eur. 6.2 (Hepatitis B Vaccine (rDNA); Vaccinum Hepatitidis B (ADNr)). A preparation of hepatitis B surface antigen, that is obtained by recombinant DNA technology. It should be stored at a temperature of 2° to 8°, not be allowed to freeze, and be protected from light. Under these storage conditions it may be expected to retain its potency for 24 months.
The BP 2008 states that Hep B may be used on the label.

Adverse Effects

As for vaccines in general, p.2201.

In addition, abdominal pain and gastrointestinal disturbance, and musculoskeletal and joint pain and inflammation have been reported after hepatitis B vaccines. There may also be dizziness and sleep disturbance. Cardiovascular effects include occasional hypotension and, rarely, tachycardia. Other rare adverse effects include dysuria, visual disturbances, and earache.

◊ General references.

1. McMahon BJ, *et al.* Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; **92:** 254–6.
2. Anonymous. Adverse events after hepatitis B vaccination. *Can Med Assoc J* 1992; **147:** 1023–6.
3. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opin Drug Saf* 2003; **2:** 225–31.
4. Autret-Leca E, *et al.* Tolérance du vaccin contre l'hépatite B: exemple d'une complémentarité notification spontanée/études pharmacoépidémiologiques. *Presse Med* 2007; **36:** 563–4.

Effects on the blood. Rare cases of thrombocytopenia[1-4] and pancytopenia[5] associated with hepatitis B vaccination have been reported.

1. Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; **344:** 1293.
2. Meyboom RHB, *et al.* Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995; **345:** 1638.
3. Ronchi F, *et al.* Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child* 1998; **78:** 273–4.
4. Nuevo H, *et al.* Thrombocytopenic purpura after hepatitis B vaccine: case report and review of the literature. *Pediatr Infect Dis J* 2004; **23:** 183–4.
5. Viallard JF, *et al.* Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000; **110:** 230–3.

Effects on bones and joints. Reactive arthritis[1-3] and Reiter's syndrome[2] have been reported after hepatitis B vaccination. There have also been isolated reports of rheumatoid arthritis occurring after hepatitis B vaccination[3,4] and a suggestion that hepatitis B vaccination may trigger the onset of underlying SLE.[5] A number of reports of arthralgia have been received by the UK CSM and by the manufacturers of *Engerix B*.[2]

1. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
2. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; **309:** 94–5.
3. Gross K, *et al.* Arthritis after hepatitis B vaccination: report of three cases. *Scand J Rheumatol* 1995; **24:** 50–2.
4. Pope JE, *et al.* The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998; **25:** 1687–93.
5. Maillefert JF, *et al.* Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)* 1999; **38:** 978–83.

Effects on the eyes. There have been isolated case reports of acute posterior uveitis,[1] visual loss associated with eosinophilia,[2] acute posterior multifocal placoid pigment epitheliopathy,[3] central retinal vein occlusion,[4] and multiple evanescent white dot syndrome[5] after vaccination against hepatitis B.

For mention of optic neuritis in patients receiving hepatitis B vaccine, see under Effects on the Nervous System, below.

1. Fried M, *et al.* Uveitis after hepatitis B vaccination. *Lancet* 1987; **ii:** 631–2.
2. Brézin AP, *et al.* Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993; **342:** 563–4.
3. Brézin AP, *et al.* Acute posterior multifocal placoid pigment epitheliopathy after hepatitis B vaccine. *Arch Ophthalmol* 1995; **113:** 297–300.
4. Devin F, *et al.* Occlusion of central retinal vein after hepatitis B vaccination. *Lancet* 1996; **347:** 1626.
5. Baglivo E, *et al.* Multiple evanescent white dot syndrome after hepatitis B vaccine. *Am J Ophthalmol* 1996; **122:** 431–2.

Effects on the kidneys. There have been case reports of acute glomerulonephritis in patients after hepatitis B vaccine.[1,2]

1. Carmeli Y, Oren R. Hepatitis B vaccine side-effect. *Lancet* 1993; **341:** 250–1.
2. Pennesi M, *et al.* Glomerulonephritis after recombinant hepatitis B vaccine. *Pediatr Infect Dis J* 2002; **21:** 172–3.

Effects on the liver. There have been occasional reports of transient abnormalities in liver function associated with hepatitis B vaccine.[1-3] The appearance of autoantibodies has been reported in a patient,[2] and severe cytolysis consistent with an allergic mechanism in another.[3]

1. Rajendran V, Brooks AP. Symptomatic reaction to hepatitis B vaccine with abnormal liver function values. *BMJ* 1985; **290:** 1476.
2. Lilic D, Ghosh SK. Liver dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994; **344:** 1292–3.
3. Germanaud J, *et al.* A case of severe cytolysis after hepatitis B vaccination. *Am J Med* 1995; **98:** 595.

Effects on the nervous system. In the years 1982 to 1985 the Centers for Disease Control, the FDA, and the manufacturer of plasma-derived hepatitis B vaccine received 41 reports of adverse neurological effects.[1] It was estimated that about 850 000 persons had received the vaccine in this time. Neurological events were convulsions (5 cases), Bell's palsy (10), Guillain-Barré syndrome (9), lumbar radiculopathy (5), brachial plexus neuropathy (3), optic neuritis (5), and transverse myelitis (4). In some analyses Guillain-Barré syndrome was reported significantly more often than expected. However, no conclusive epidemiological association could be made between any neurological adverse effect and the vaccine.

In France, spontaneous reports of multiple sclerosis and central demyelinating disease in patients who had received hepatitis B vaccine led to the suspension by the French authorities of hepatitis B vaccination in schools in 1998. This decision was widely condemned by many authorities including WHO, the US National Multiple Sclerosis Society, and the Viral Hepatitis Prevention Board, and there was a fear that reduced confidence in the vaccine could have a profound effect on uptake. Arguments[2] against a link between hepatitis B vaccine and multiple sclerosis include the lack of correlation between the incidence of hepatitis B infection and demyelinating diseases, data from clinical studies including extensive postmarketing surveillance, and analysis of the French cases which concluded that the incidence of multiple sclerosis amongst vaccine recipients was not higher than would be expected in the population as a whole. A consultative group concluded[3] that, in the light of the evidence, the benefits of hepatitis B vaccination supported current WHO recommendations that all countries should have universal infant and/or adolescent hepatitis B immunisation programmes and that adults at increased risk of infection should also be immunised. More recent studies[4,5] have also indicated no association between hepatitis B vaccine and multiple sclerosis, although one study[6] did suggest a threefold increase in risk.

1. Shaw FE, *et al.* Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination: experience of the first three years. *Am J Epidemiol* 1988; **127:** 337–52.
2. Anonymous. Expanded Programme on Immunization (EPI): lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Wkly Epidem Rec* 1997; **72:** 149–52.
3. Halsey NA, *et al.* Hepatitis B vaccine and central nervous system demyelinating diseases. *Pediatr Infect Dis J* 1999; **18:** 23–4.
4. Ascherio A, *et al.* Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001; **344:** 327–32.
5. Mikaeloff Y, *et al.* Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007; **161:** 1176–82.
6. Hernán MA, *et al.* Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004; **63:** 838–42.

Effects on the skin. Skin reactions, which have been reported in a few individuals after hepatitis B vaccination, include erythema multiforme,[1,2] erythema nodosum,[3-5] lichen planus,[6-8] and vasculitis.[9,10]

1. Feldshon SD, Sampliner RE. Reaction to hepatitis B virus vaccine. *Ann Intern Med* 1984; **100:** 156–7.
2. Wakeel RA, White MI. Erythema multiforme associated with hepatitis B vaccine. *Br J Dermatol* 1992; **126:** 94–5.
3. Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. *Lancet* 1986; **ii:** 1042.
4. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; **321:** 1198–9.
5. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301:** 345.
6. Ciaccio M, Rebora A. Lichen planus following HBV vaccination: a coincidence? *Br J Dermatol* 1990; **122:** 424.
7. Ferrnado MF, *et al.* Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; **139:** 350.
8. Usman A, *et al.* Lichenoid eruption following hepatitis B vaccination: first North American case report. *Pediatr Dermatol* 2001; **18:** 123–6.
9. Cockwell P, *et al.* Vasculitis related to hepatitis B vaccine. *BMJ* 1990; **301:** 1281.
10. Le Helto C, *et al.* Suspected hepatitis B vaccination related vasculitis. *J Rheumatol* 1999; **26:** 191–4.

Hypersensitivity. There have been reports of hypersensitivity reactions after hepatitis B vaccination that have been attributed to components of the vaccines, including formaldehyde,[1] thiomersal,[2] and *Saccharomyces cerevisiae*.[3]

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patient. *Lancet* 1986; **ii:** 522–3.
2. Noel I, *et al.* Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991; **338:** 705.
3. Brightman CAJ, *et al.* Yeast-derived hepatitis B vaccine and yeast sensitivity. *Lancet* 1989; **i:** 903.

Precautions

As for vaccines in general, p.2202.

Reduced immune response. The immune response to hepatitis B vaccine is dependent on both host- and immunisation-related factors.[1] Host-related factors that appear to diminish the response include increasing age, increasing body-weight, smoking,[1,2] and male sex;[3] particular HLA haplotypes may also be associated with poor response.[4] Failure of hepatitis B immunisation in infants could be related to high perinatal maternal viraemia[5] rather than to inherent resistance to the vaccine.

Some studies have found a defective response in chronic alcoholics[6,7] whereas others have not;[8] the degree of liver impairment may be a significant factor. It has been suggested that an increased dose of hepatitis B vaccine may be appropriate in those with a history of alcoholism.[9] Active infection with *Schistosoma mansoni* also appears to decrease the response to hepatitis B vaccination.[10] A diminished response occurs in HIV-positive patients[11-13] and in patients on haemodialysis;[1] an increased dose of hepatitis B vaccine is recommended in these patients. In patients with haemophilia who are not HIV-positive[14] immunity is reported to wane rapidly after vaccination and frequent booster doses may be required. Biological response modifiers such as thymopentin[15] and interferon[16] have been used successfully in some patients on haemodialysis to overcome the immune deficit. Use of interleukin-2 has met with variable success. Granulocyte-macrophage colony-stimulating factor has also been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[17]

The immune response to hepatitis B vaccine is affected by the site of intramuscular injection. The deltoid region is recommended for adults and the anterolateral thigh for infants. A diminished response has been associated with injection into the gluteal region (buttock).[1]

A related problem is posed by subjects who become infected with hepatitis B despite mounting an adequate response to immunisation. In one study, evidence of viral replication was detected in 44 of 1590 hepatitis B vaccinees despite development of protective titres of antibody.[18] Acute hepatitis occurred in one patient. Although the infection may have been incubating at the time of vaccination, the virus isolated from the child with acute disease was an escape mutant with a different DNA sequence from that isolated from the mother.

1. Hollinger FB. Factors influencing the immune response to hepatitis b vaccine, booster dose guidelines, and vaccine protocol recommendations. *Am J Med* 1989; **87** (suppl 3A): 36S–40S.
2. Horowitz MM, *et al.* Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. *Ann Intern Med* 1988; **108:** 185–9.
3. Morris CA, *et al.* Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age. *Epidemiol Infect* 1989; **103:** 387–94.
4. Alper CA, *et al.* Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989; **321:** 708–12.
5. del Canho R, *et al.* Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol* 1994; **20:** 483–6.
6. Degos F, *et al.* Hepatitis B vaccination and alcoholic cirrhosis. *Lancet* 1983; **ii:** 1498.
7. Mendenhall C, *et al.* Hepatitis B vaccination: response of alcoholic with and without liver injury. *Dig Dis Sci* 1988; **33:** 263–9.
8. McMahon BJ, *et al.* Response to hepatitis B vaccine in Alaska Natives with chronic alcoholism compared with non-alcoholic control subjects. *Am J Med* 1990; **88:** 460–4.
9. Rosman AS, *et al.* Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997; **103:** 217–22.
10. Ghaffar YA, *et al.* Response to hepatitis B vaccine in infants born to mothers with schistosomiasis. *Lancet* 1989; **ii:** 272.
11. Carne CA, *et al.* Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine. *BMJ* 1987; **294:** 866–8.
12. Collier AC, *et al.* Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* 1988; **109:** 101–5.
13. Chan W, *et al.* Response to hepatitis B immunization in children with hemophilia: relationship to infection with human immunodeficiency virus type 1. *J Pediatr* 1990; **117:** 427–30.
14. Maris JM, *et al.* Loss of detectable antibody to hepatitis B surface antigen in immunized patients with hemophilia but without human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 269–71.
15. Donati D, Gastaldi L. Controlled trial of thymopentin in hemodialysis patients who fail to respond to hepatitis B vaccination. *Nephron* 1988; **50:** 133–6.
16. Quiroga JA, Carreño V. Interferon and hepatitis B vaccine in haemodialysis patients. *Lancet* 1989; **i:** 1264.
17. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.
18. Carman WF, *et al.* Vaccine-induced escape mutant of hepatitis B virus. *Lancet* 1990; **336:** 325–9.

Uses and Administration

Hepatitis B vaccines are used for active immunisation against hepatitis B infection. Two types of vaccine have been available, each containing hepatitis B surface antigen (HBsAg) adsorbed onto aluminium hydroxide or a similar adsorbent. The type of vaccine in which the surface antigen is produced in yeast cells using recombinant DNA techniques is now widely used and there has been considerable interest in further developments to improve immunogenicity. The second type of vaccine, in which the surface antigen is obtained from plasma after purification and inactivation processes is now not generally available.

WHO had recommended that national immunisation policies should include routine hepatitis B immunisation for the whole population by 1997 and this has been implemented in some countries including the USA (see Administration, below). The current recommendations in the UK are for immunisation of persons at high risk of contracting hepatitis B. High-risk groups include:

- health care personnel, laboratory workers, or any other personnel who have direct contact with patients or their body fluids or tissues
- staff and residents of accommodation for those with severe learning difficulties
- patients with chronic liver disease
- patients with chronic renal failure including those requiring haemodialysis
- haemophiliacs and those receiving regular blood transfusions or blood products
- close family contacts or sexual partners of cases or carriers of hepatitis B
- families adopting children from countries with a high prevalence of hepatitis B
- foster carers
- individuals who frequently change sexual partners
- parenteral drug abusers
- inmates of custodial institutions
- some travellers to areas where hepatitis B is endemic
- infants born to women who are persistent carriers of hepatitis B surface antigen or infants born to women who are HBsAg-positive as a result of recent infection

Hepatitis C carriers who are not immunised against hepatitis B should also receive immunisation.

A basic immunisation schedule consists of 3 doses of a hepatitis B vaccine, with the second and third doses 1 and 6 months, respectively, after the first. In the USA, some products may be given in an alternative 2-dose regimen to adolescents with doses given 4 to 6 months apart. Doses should be given intramuscularly, with the deltoid region being the preferred site in adults and older children and the anterolateral thigh the preferred site in neonates, infants, and younger children; the gluteal region (buttock) should not be used as efficacy may be reduced. The subcutaneous route should be used in patients with haemophilia. The dose of the recombinant vaccine depends on the product used. Typical doses for adults are 10 or 20 micrograms and for infants and children 5 or 10 micrograms. Products containing 40 micrograms are available for adult dialysis and predialysis patients who have a reduced immune response to the vaccine. However, *the dose of one recombinant preparation should not be seen as equivalent to the dose of another.*

For pre-exposure prophylaxis in high-risk groups and for postexposure prophylaxis an accelerated schedule should be used. It may also be used where more rapid immunisation, for instance with travellers, is required. This schedule involves giving the third dose 2 months after the initial dose with a further booster at 1 year. In exceptional circumstances in adults travelling to an endemic area who commence their vaccination course within a month of departure, an even more rapid schedule involving injections at 0, 7, and 21 days has been used; when this schedule is used, a booster dose is recommended after 1 year.

For newborn infants at risk combined active and passive immunisation against hepatitis B is recommended. The first dose of vaccine should preferably be given at birth, and certainly within 24 hours of birth. A single dose of hepatitis B immunoglobulin (200 international units) should be given at the same time into a different site. Additionally, in any patient in whom immediate protection is required, combined active and passive immunisation may be considered with a single dose of 500 international units of hepatitis B immunoglobulin being the dose for adults. See under Hepatitis B Immunoglobulins, p.2215, for children's doses.

◊ General references.

1. Buynak EB, *et al.* Vaccine against human hepatitis B. *JAMA* 1976; **235:** 2832–4.
2. Douglas RG. The heritage of hepatitis B vaccine. *JAMA* 1996; **276:** 1796–8.
3. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; **336:** 196–204.
4. Keating GM, Noble S. Recombinant hepatitis B vaccine (Engerix-B): a review of its immunogenicity and protective efficacy against hepatitis B. *Drugs* 2003; **63:** 1021–51.

Administration. The major public health burden of hepatitis B infection in the developing world is due to the consequences of chronic carriage of hepatitis B virus (hepatocellular carcinoma and chronic cirrhosis) rather than acute infection. WHO[1] considered that the most important means of controlling hepatitis B on a global scale and of reducing mortality from its sequelae was mass immunisation of infants. It stated that hepatitis B vaccine should be incorporated into the Expanded Programme on Immunization (EPI) and many countries have since done so. WHO later reiterated this aim[2] stating that hepatitis B vaccine should be integrated into national immunisation programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. WHO's aim was to reduce the incidence of new child carriers of hepatitis B by 80% by 2001. Results from Taiwan, where mass immunisation of infants has been in place since the mid-1980s have shown a marked decline in the number of child carriers under 10 years of age.[3,4] The incidence of hepatocellular carcinoma in children has also been reduced.[5,6]

Opinion has been divided in the UK regarding implementation of universal hepatitis B immunisation,[7-9] with some advising increased emphasis on alternative strategies already in place such as antenatal screening.[7,8]

The optimum vaccination strategy depends on the pattern of hepatitis B viral transmission in a particular country. In hyperendemic regions where most infections are acquired early in life, the vaccine should be given shortly after birth and hepatitis B immunisation integrated into the EPI. Immunisation of all infants should be considered for population groups with chronic hepatitis B virus carrier rates greater than 2% and should be a public health priority where carrier rates are greater than 10%. Countries with a lower carrier rate might opt to immunise all adolescents as an alternative to infant immunisation. Immunisation of individuals at high risk of infection should be continued in addition to routine vaccination schedules[2] and, if hepatitis B is not integrated into infant vaccination schedules, screening pregnant women for HBsAg and immunising the infants of HBsAg-positive mothers should continue.[1]

If use of hepatitis B vaccine is integrated into the EPI, 3 doses should be given intramuscularly, the first dose being given as soon as possible after birth with the first EPI immunisation. The exact timing of these doses will depend on the risk of transmission at birth and the EPI schedule in operation. In the USA, these recommendations have been implemented by immunisation of all infants and of children at any age between 2 and 18 years who have not previously received 3 doses of vaccine. The recommended schedule is for all infants to be given an initial dose of the monovalent hepatitis B vaccine soon after birth; then 2 further doses with the monovalent vaccine or 3 further doses with a combination vaccine containing hepatitis B. Infants of HBsAg-positive mothers should receive hepatitis B vaccine plus hepatitis B immunoglobulin within 12 hours of birth. Infants whose mother's HBsAg status is unknown should receive a hepatitis B vaccine within 12 hours of birth and the maternal blood should be checked at delivery and, if positive for HBsAg, the infant given hepatitis B immunoglobulin as soon as possible (no later than 1 week of age). The second dose is given at 1 to 2 months of age and the final dose at 6 months of age or later. Infants who receive a combination vaccine after the birth dose may be given an additional dose at 4 months of age. Alternatively, some products may be given in a two-dose regimen, with doses given 4 to 6 months apart.

1. WHO. Progress in the control of viral hepatitis: memorandum from a WHO meeting. *Bull WHO* 1988; **66:** 443–55.
2. Anonymous. Hepatitis B vaccine. *WHO Drug Inf* 1993; **7:** 130–1.
3. Chen H-L, *et al.* Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996; **276:** 906–8.
4. Hsu H-M, *et al.* Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. *J Infect Dis* 1999; **179:** 367–70.
5. Lee C-L, Ko Y-C. Hepatitis B vaccination and hepatocellular carcinoma in Taiwan. *Pediatrics* 1997; **99:** 351–3.
6. Chang M-H, *et al.* Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; **336:** 1855–9.
7. Mortimer PP, Miller E. Commentary: antenatal screening and targeting should be sufficient in some countries. *BMJ* 1997; **314:** 1036–7.
8. Dunn J, *et al.* Integration of hepatitis B vaccination into national immunisation programmes: alternative strategies must be considered before universal vaccination is adopted. *BMJ* 1997; **315:** 121–2.
9. Goldberg D, McMenamin J. The United Kingdom's hepatitis B immunisation strategy—where now? *Commun Dis Public Health* 1998; **1:** 79–83.

BOOSTER DOSES. There has been considerable interest in the duration of immunity conferred by hepatitis B vaccination and the possible need for booster doses.[1,2]

In the UK it is now recommended that individuals at continuing risk of infection should be offered a *single* booster dose of vaccine, *once only*, about 5 years after primary immunisation. Boosters are also recommended if contamination of eyes, mouth, or fresh cuts on skin with blood from a HBsAg-positive person occurs, unless they are known to have protective concentrations of antibody.

References.

1. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; **355:** 561–5.
2. Banatvala JE, Van Damme P. Hepatitis B vaccine—do we need boosters? *J Viral Hepatitis* 2003; **10:** 1–6.

Postexposure prophylaxis. A combination of passive immunisation with a hepatitis B immunoglobulin and active immunisation with a hepatitis B vaccine is generally recommended for postexposure prophylaxis against hepatitis B.

One group of patients who should be given postexposure prophylaxis are infants born to mothers who are persistent carriers of hepatitis B surface antigen (HBsAg). The risk is particularly high if the mother has detectable hepatitis B e antigen (HBeAg) or hepatitis B virus DNA or absence of detectable antibody to hepatitis Be antigen (anti-HBe). Postexposure prophylaxis is also recommended in the UK for persons accidentally inoculated, or who contaminate the eye or mouth or breaks to the skin with blood from a known HBsAg-positive person, as well as in sexual contacts (and sometimes close family contacts) of sufferers from acute hepatitis B and who are seen within a week of the onset of jaundice in the contact.

In the UK, the recommended schedule for postexposure prophylaxis is the first dose of vaccine given preferably within 48 hours of exposure and no later than one week after exposure, or, for neonates exposed to hepatitis B at birth, no later than 24 hours after birth, with a single dose of hepatitis B immunoglobulin given simultaneously at a separate site. The second and third doses of vaccine are given 1 and 2 months after the first dose, with a booster dose at 12 months. Health care workers who have been successfully immunised should be given a booster dose after subsequent contamination with blood from an infected person, unless they are known to have adequate antibody concentration.

Preparations

Ph. Eur.: Hepatitis B Vaccine (rDNA).

Proprietary Preparations (details are given in Part 3)
Arg.: AGB; Biovac HB; Engerix-B; H-B-Vax II†; HBVaxPro; Hepativax; Supervax; ***Austral.:*** Engerix-B; H-B-Vax II; ***Austria:*** Engerix-B; ***Belg.:*** Engerix-B; Fendrix; HBVaxPro; ***Braz.:*** Engerix-B†; Heberbiovac HB†; Recombivax HB†; Vacina Contra Hepatite B; ***Canad.:*** Engerix-B; Recombivax HB; ***Chile:*** Engerix-B; Heberbiovac HB; Hepavax-Gene; Recomvax B; ***Cz.:*** Engerix-B; Fendrix; H-B-Vax II†; HBVaxPro; ***Denm.:*** Engerix-B; H-B-Vax†; ***Fin.:*** Engerix-B; HBVaxPro; ***Fr.:*** Engerix-B; Fendrix; GenHevac B; HB-Vax-DNA†; HBVaxPro; ***Ger.:*** Engerix-B; Gen H-B-Vax†; HBVaxPro; ***Gr.:*** Engerix-B; Fendrix; HBVaxPro; Recombivax†; ***Hong Kong:*** Engerix-B; H-B-Vax II; HBVaxPro; Sci-B-Vac; ***Hung.:*** Engerix-B; HBVaxPro; ***India:*** Engerix-B; Enivac HB; Genevac-B; HB Vac; Shanvac-B; ***Indon.:*** Engerix-B; Euvax B; H-B-Vax II; Hepavax; ***Irl.:*** Engerix-B; H-B-Vax II†; HBVaxPro; ***Israel:*** Bio-Hep-B; Engerix-B; Recombinant H-B Vax II; ***Ital.:*** Engerix-B; HBVaxPro; Recombivax HB†; ***Malaysia:*** Engerix-B; Euvax B; H-B-Vax II†; HBVaxPro; Hepavax-Gene; ***Mex.:*** Engerix-B; H-B-Vax II; Heberbiovac HB; Probivac-B; ***Neth.:*** Engerix-B; Fendrix; HB-Vax-DNA; HBVaxPro; ***Norw.:*** Engerix-B; Fendrix; ***NZ:*** Engerix-B; H-B-Vax II; HBVaxPro; ***Philipp.:*** Engerix-B; Hepavax-Gene; Hepliv; Recomvax B; Shanvac-B; Temrevac-HB; ***Pol.:*** Engerix-B; Euvax B; HBVaxPro; Hepavax-Gene; ***Port.:*** Engerix-B; Recombivax HB†; ***Rus.:*** Biovac-B (Биовак-в); Engerix-B (Энджерикс В); H-B-Vax II (H-B-Вакс II); ***S.Afr.:*** Engerix-B; H-B-Vax II; Heberbiovac HB; Hepaccine-B; ***Singapore:*** Engerix-B; H-B-Vax II†; HBVaxPro; ***Spain:*** Engerix-B; HBVaxPro; Recombivax HB†; ***Swed.:*** Engerix-B; HBVaxPro; ***Switz.:*** Engerix-B; Gen H-B-Vax; HBVaxPro; Heprecomb; ***Thai.:*** Engerix-B; Euvax B; H-B-Vax II; HBVaxPro; Heberbiovac HB; Hepavax-Gene; ***Turk.:*** Engerix-B; Euvax B; GenHevac B; HBVaxPro; Hepavax-Gene; ***UK:*** Engerix-B; Fendrix; HBVaxPro; ***USA:*** Engerix-B; Recombivax HB; ***Venez.:*** Eberbiovac HB†; Engerix-B.

Hepatitis A and B Vaccines

Vacunas de las hepatitis A y B.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Hepatitidis A Inactivatum et Hepatitidis B (ADNr) Adsorbatum; Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine BP 2008). A suspension consisting of a suitable strain of hepatitis A virus, grown in cell cultures and inactivated by a validated method, and of hepatitis B surface antigen obtained by recombinant DNA technology; the antigens are adsorbed on a mineral carrier, such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that HepA/HepB may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Hepatitis A Vaccines, p.2214, and Hepatitis B Vaccines, p.2215.

Uses and Administration

Combined hepatitis A and B vaccines are used for active immunisation against hepatitis A and hepatitis B.

A hepatitis A and B vaccine (*Twinrix, GSK*) is available containing not less than 720 ELISA units of inactivated hepatitis A virus and not less than 20 micrograms of recombinant hepatitis B surface antigen (HBsAg) protein in 1 mL. For primary immunisation, three doses of 1 mL are given by intramuscular injection, with the second and third doses 1 and 6 months after the first. For children up to the age of 16 years a 0.5-mL dose is given.

Alternatively, in exceptional circumstances when travel is anticipated within one month or more after the first dose but when insufficient time is available for the standard course, adults may be given an accelerated schedule. In the UK, this consists of three doses at 0, 7 and 21 days. In the US the recommended schedule consists of doses at 0, 7, and 21 to 30 days plus a dose at 12 months.

Booster doses may be given as appropriate with the monovalent component vaccines since protection against hepatitis A and B declines at different rates, or a booster dose of the combined vaccine may be given after 5 years in adults or 4 years in children. A booster is recommended 1 year after the accelerated schedule.

In the UK a similar vaccine (*Ambirix, GSK*) is licensed for primary immunisation in a 2-dose schedule for children aged 1 to 15 years; the second dose is given between 6 and 12 months after the first.

◊ Reviews.

1. Murdoch DL, *et al*. Combined hepatitis A and B vaccines: a review of their immunogenicity and tolerability. *Drugs* 2003; **63:** 2625–49.
2. Van Damme P, Van Herck K. A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. *Expert Rev Vaccines* 2004; **3:** 249–67.
3. Zuckerman JN. Vaccination against hepatitis A and B: developments, deployment and delusions. *Curr Opin Infect Dis* 2006; **19:** 456–9.

Preparations

Ph. Eur.: Hepatitis A (Inactivated) and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Arg.: Twinrix; ***Austral.:*** Twinrix; ***Austria:*** Twinrix; ***Belg.:*** Twinrix; ***Braz.:*** Twinrix†; Vacina Comb. Contra Hepatite A e B; ***Canad.:*** Twinrix; ***Chile:*** Twinrix; ***Cz.:*** Ambirix; Twinrix; ***Denm.:*** Twinrix; ***Fin.:*** Twinrix; ***Fr.:*** Twinrix; ***Ger.:*** Twinrix; ***Gr.:*** Twinrix; ***Hong Kong:*** Twinrix; ***Hung.:*** Twinrix; ***Indon.:*** Twinrix; ***Irl.:*** Twinrix; ***Israel:*** Twinrix; ***Ital.:*** Twinrix; ***Malaysia:*** Twinrix; ***Mex.:*** Twinrix; ***Neth.:*** Ambirix; Twinrix; ***Norw.:*** Twinrix; ***NZ:*** Twinrix; ***Philipp.:*** Twinrix; ***Pol.:*** Twinrix; ***Port.:*** Ambirix; Twinrix; ***S.Afr.:*** Twinrix; ***Singapore:*** Twinrix; ***Spain:*** Twinrix; ***Swed.:*** Ambirix†; Twinrix; ***Switz.:*** Twinrix; ***Thai.:*** Twinrix; ***Turk.:*** Twinrix; ***UK:*** Ambirix; Ambrix; Twinrix; ***USA:*** Twinrix; ***Venez.:*** Twinrix.

Hepatitis A and Typhoid Vaccines

Vacunas de la hepatitis A y fiebre tifoidea.

ATC — J07CA10.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Uses and Administration

Combined hepatitis A and typhoid vaccines are used for active immunisation. They contain either inactivated HM175 or GBM hepatitis A virus strains together with the Vi capsular polysaccharide from *Salmonella typhi* Ty 2 strain. Adults and adolescents over 15 years of age may be given a dose of 1 mL by intramuscular injection, at least 2 weeks prior to risk of exposure to typhoid and hepatitis A. A booster dose may be given after 6 to 12 months to provide long-term protection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Vivaxim; ***Austria:*** Hepatyrix; ***Canad.:*** Vivaxim; ***Fr.:*** Tyavax; ***Ger.:*** Hepatyrix; ViATIM; ***Irl.:*** Hepatyrix; ViATIM; ***Israel:*** Hepatyrix; ***Malaysia:*** Vivaxim; ***Neth.:*** ViATIM; ***NZ:*** Hepatyrix; Vivaxim; ***Port.:*** ViATIM; ***UK:*** Hepatyrix; ViATIM.

Herpes Simplex Vaccines

Vacunas del herpes simple.

Profile

Several types of vaccines against herpes simplex virus types 1 and 2 have been developed. They have been tried both in oral and genital herpes infections. They are also being studied for the prevention of infection in sexual partners of patients with genital herpes.

◊ Herpes simplex virus types 1 and 2 are widespread in populations throughout the world. Herpes simplex virus type 2 causes lifelong infection with significant morbidity. Even with the availability of effective antiviral therapy, the increasing burden of herpes simplex virus infection makes it a suitable candidate for vaccine development. The incidence of neonatal herpes infections has also increased and this risk would also be addressed by development of appropriate vaccines. An additional benefit would be a reduced risk of acquiring HIV infection.

Vaccines for herpes simplex were first studied in the 1920s and many different types of vaccine have undergone evaluation. They have included auto-inoculation of live herpes simplex virus, whole inactivated vaccines, attenuated live virus vaccines, modified live virus subunit vaccines, cell culture-derived subunit vaccines, recombinant glycoprotein subunit vaccines, disabled infectious single cycle (DISC) vaccines, and nucleic acid (DNA) vaccines.[1,2]

Prophylactic vaccines against HSV-2 could be beneficial if they either shift the threshold of infection i.e. increase the titre of virus necessary to cause infection, or if they prevent clinical disease itself. An attenuated live virus vaccine based on modified HSV-1 has been tested in clinical studies but was poorly tolerated at the doses required to elicit an immune response. Prophylactic vaccines including subunit vaccines encoding virus glycoproteins and delivered with adjuvants have shown some benefits.[1,2]

To date, no randomised clinical studies have demonstrated useful benefit from therapeutic vaccines for HSV-1 or HSV-2. A therapeutic vaccine should prevent recurrences or at least minimise their severity or duration. Heat killed, whole virus vaccines from HSV-1 (Lupidon H) and HSV-2 (Lupidon G), and inactivated subunit vaccines have been studied but have generally produced disappointing results.[1,2] Recombinant glycoprotein vaccines have also been tested but again results have been disappointing.[1,2]

1. Morrison LA. Vaccines against genital herpes: progress and limitations. *Drugs* 2002; **62:** 1119–29.
2. Stanberry LR. Clinical trials of prophylactic and therapeutic herpes simplex virus vaccines. *Herpes* 2004; **11** (suppl 3): 161A–169A.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Lupidon G; Lupidon H.

Human Papillomavirus Vaccines

HPV Vaccines; Human Papilloma Virus Vaccines; Vacunas del virus del papiloma humano.

ATC — J07BM01.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Breast feeding. In mothers given the quadrivalent recombinant human papillomavirus vaccine or placebo during clinical studies, the rates of adverse reactions in the mother and in the breast-fed infant, as well as vaccine immunogenicity, were comparable in the 2 groups. Based on apparently the same data the UK licensed product information states that the vaccine can be given to breast-feeding women whereas the US information recommends caution.

Pregnancy. Although specific studies of the quadrivalent recombinant human papillomavirus vaccine in pregnant women have not been conducted, some women during clinical development did receive the vaccine in pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in those who received the vaccine and those who received placebo. It is, nevertheless, recommended that vaccination should be postponed until after completion of pregnancy.

Uses and Administration

A quadrivalent recombinant human papillomavirus (HPV) vaccine, prepared from purified virus-like particles of the capsid protein L1, is used to prevent genital warts, cervical cancer, and other pre-cancerous lesions caused by HPV types 6, 11, 16, and 18.

It is given in three doses of 0.5 mL intramuscularly. The first dose may be given at any time to girls and women between 9 and 26 years of age; the second dose is given 2 months later, and the third dose 6 months after the first dose.

A similar recombinant HPV vaccine, prepared from a mixture of L1 capsid proteins of HPV types 16 and 18 and containing an adjuvant AS04, is licensed in some countries for the prevention of cervical cancer and high grade cervical intraepithelial neoplasia (grades 2 and 3). It is given intramuscularly in 3 doses of 0.5 mL to girls and women between 10 and 25 years of age. The first dose may be given at any age in the approved range; the second dose is given 1 month later, and the third dose 6 months after the first dose.

Further vaccines are under investigation for the treatment or prophylaxis of genital warts and several malignant neoplasms.

◊ Reviews and studies.

1. Siddiqui MAA, Perry CM. Human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine (Gardasil). *Drugs* 2006; **66:** 1263–71.
2. Schmiedeskamp MR, Kockler DR. Human papillomavirus vaccines. *Ann Pharmacother* 2006; **40:** 1344–52.
3. Block SL, *et al*. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006; **118:** 2135–45. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/2135 (accessed 26/06/07)
4. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; **356:** 1915–27.
5. Garland SM, *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; **356:** 1928–43.
6. Joura EA, *et al*. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 2007; **369:** 1693–1702.
7. Cutts FT, *et al*. Human papillomavirus and HPV vaccines: a review. *Bull World Health Organ* 2007; **85:** 719–26.
8. Keam SJ, Harper DM. Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted, adsorbed) [Cervarix]. *Drugs* 2008; **68:** 359–72.

Vaccine development. There are more than 100 known human papillomavirus (HPV) genotypes; at least 13 of these can cause cervical cancer and are also associated with other anogenital cancers and cancers of the head and neck. Genotypes 16 and

18 cause about 70% of all cervical cancers, while genotypes 6 and 11 can cause genital warts. HPV is highly transmissible with risk of infection being highest soon after sexual activity begins. Asymptomatic and transient infection occurs in most people at some time in their life. However, the fact that more than 99% of cases of cervical cancer diagnosed are associated with the presence of sexually transmitted human papillomavirus DNA has prompted the possibility of vaccine development.

Viral recombinant proteins are being studied as antigenic components of both prophylactic and therapeutic vaccines.[1-8] Prophylactic vaccine candidates are based on the recombinant capsid proteins L1 and L2 which self-assemble into virus-like particles which induce antibodies that in turn neutralise the infecting virus. Therapeutic vaccines are based on the viral oncogenic proteins E6 and E7 and are designed to induce cell-mediated immune responses to eliminate infected cells. Prophylactic vaccines based on the recombinant capsid protein LI are licensed in several countries, while other prophylactic vaccines are in phase III and further therapeutic vaccine candidates are undergoing phase II evaluation. There is also some preliminary study being conducted into the possibility of a 'chimeric' vaccine combining both prophylactic and therapeutic components, but the immunogenicity and efficacy of such vaccines remains to be established.

For it to be claimed justifiably that a prophylactic vaccine prevents cervical cancer, it is necessary to demonstrate that such a vaccine not only prevents infection but also prevents cancer itself, or at least a defined precursor of disease. Since any placebo-controlled study defining established cancer as an end-point would clearly be unethical, an appropriate compromise is to use the appearance of high-grade dysplasia or pre-cancerous lesions as an end-point, this being regarded as a direct precursor to cervical cancer requiring treatment. However, true pre-cancerous lesions of this kind are relatively unusual in current practice and therefore phase III studies require tens of thousands of subjects in order to establish this efficacy.[3]

Guidance and technical information on HPV, HPV-related diseases, and HPV vaccines has been produced by WHO.[9] They consider HPV vaccines to be highly effective among females not exposed to HPV vaccine genotypes at the time of their first vaccination and that the target group for vaccination will probably be preadolescent girls (about 9 to 12 years of age). Guidelines for the use of HPV vaccine for the prevention of cervical cancer have been developed in the USA by the CDC,[10] the American Cancer Society[11] and the American Academy of Pediatrics.[12] These authorities recommend routine vaccination for all girls 11 to 12 years of age, although girls as young as 9 years of age may be vaccinated at the discretion of their doctor. Catch-up vaccinations may be given to older girls and young women who have not received or completed a vaccine course. In the UK the Joint Committee on Vaccination and Immunisation[13] recommends routine vaccination of all girls 12 to 13 years of age. Catch-up vaccination is recommended for girls under 18 years of age.

1. Galloway DA. Papillomavirus vaccines in clinical trials. *Lancet Infect Dis* 2003; **3:** 469–75.
2. Lehtinen M, Paavonen J. Effectiveness of preventive human papillomavirus vaccination. *Int J STD AIDS* 2003; **14:** 787–92.
3. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; **55:** 319–31.
4. Mandic A, Vujkov T. Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? *Ann Oncol* 2004; **15:** 197–200.
5. Roden RBS, *et al.* Vaccination to prevent and treat cervical cancer. *Hum Pathol* 2004; **35:** 971–82.
6. Lowndes CM, Gill ON. Cervical cancer, human papillomavirus, and vaccination. *BMJ* 2005; **331:** 915–16.
7. Harper DM, *et al.* Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; **364:** 1757–65.
8. Poland GA, *et al.* Immunogenicity and reactogenicity of a novel vaccine for human papillomavirus 16: a 2-year randomized controlled clinical trial. *Mayo Clin Proc* 2005; **80:** 601–10.
9. WHO. *Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals.* Geneva: WHO, 2007. Available at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf (accessed 26/06/07)
10. CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-2): 1–24. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5602.pdf (accessed 26/06/07)
11. Saslow D, *et al.* American Cancer Society guidelines for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; **57:** 7–28. Also available at: http://caonline.amcancersoc.org/cgi/reprint/57/1/7 (accessed 26/06/07)
12. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of human papillomavirus infection: provisional recommendations for immunization of girls and women with quadrivalent human papillomavirus vaccine. *Pediatrics* 2007; **120:** 666–8. http://pediatrics.aappublications.org/cgi/reprint/120/3/666.pdf (accessed 15/07/08)
13. Health Protection Report. HPV vaccination programme to begin in the UK in Autumn 2008 (issued 2 November, 2008). Available at: http://www.hpa.org.uk/hpr/archives/2007/news2007/news4407.htm (accessed 07/04/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gardasil; ***Austral.:*** Gardasil; ***Belg.:*** Gardasil; ***Cz.:*** Cervarix; Gardasil; Silgard; ***Fr.:*** Gardasil; ***Hung.:*** Silgard; ***Malaysia:*** Gardasil; ***NZ:*** Gardasil; ***Pol.:*** Silgard; ***Port.:*** Gardasil; Silgard; ***UK:*** Cervarix; Gardasil; ***USA:*** Gardasil.

Influenza Vaccines

Vacunas de la gripe.

Противогриппозные Вакцины

ATC — J07BB01; J07BB02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Influenza Vaccine (Whole Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Viris Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu may be used on the label.

The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Split Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Virorum Fragmentis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that the integrity of the virus particles has been disrupted without diminishing their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu may be used on the label.

The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum). A sterile suspension consisting predominantly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain is usually 15 micrograms per dose. It may contain an adjuvant. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu or Flu(adj) may be used on the label as appropriate.

The BP 2008 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum Virosomale). A sterile aqueous suspension consisting predominantly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties and reconstituted to virosomes with phospholipids and without reducing the antigenic properties of the antigens. The stated amount of haemagglutinin antigen for each strain is 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu may be used on the label.

Ph. Eur. 6.2 (Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Virisque Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu or Flu (adj) may be used on the label as appropriate.

Ph. Eur. 6.2 (Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Corticisque Antigeniis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Flu or Flu (adj) may be used on the label as appropriate.

USP 31 (Influenza Virus Vaccine). A sterile aqueous suspension of suitably inactivated influenza virus types A and B, either individually or combined, or virus subunits prepared from the extra-embryonic fluid of virus-infected chick embryos. Suitable strains of influenza virus are those designated by the US Government's Expert Committee on Influenza and recommended by the Surgeon General of the US Public Health Service. It may contain a suitable antimicrobial agent. It should be stored at 2° to 8° and not be allowed to freeze.

Nomenclature of strains. The strain designation for influenza virus types A, B, and C contains: a description of the antigenic specificity of the nucleoprotein antigen (types A, B, or C) (an internal antigen, the matrix antigen, has also been described); the host of origin (if not man, including, if appropriate, the inanimate source); the geographical origin; the strain number; and the year of isolation; e.g. A/lake water/Wisconsin/1/79. For type A viruses the antigenic description follows (in parentheses) including the antigenic character of the haemagglutinin (e.g. H1) and the antigenic character of the neuraminidase (e.g. N1). There is no provision for describing subtypes of B and C viruses. Recombination between viruses within a type is readily accomplished; the letter R should be added after the strain description to indicate the recombinant nature of the virus, e.g. A/Hong Kong/1/68(H3N2)R. In addition the strain of origin of the H and N antigens of antigenic hybrid recombinant A and B viruses should be given, e.g. A/BEL/42(H1)—Singapore/1/57(N2)R.[1]

1. Assaad FA, *et al.* Revision of the system of nomenclature for influenza viruses: a WHO Memorandum. *Bull WHO* 1980; **58:** 585–91.

Adverse Effects

As for vaccines in general, p.2201.

Local and systemic reactions may occur but are usually mild. Fever and malaise sometimes occur and severe febrile reactions have been reported particularly on giving whole-virion vaccine to children, although this type of vaccine is seldom used now. Flu-like symptoms may follow the use of intranasal vaccines.

Various neurological syndromes have been temporally associated with use of influenza vaccine, the most notable report being of the Guillain-Barré syndrome occurring after vaccination with inactivated swine influenza vaccine in 1976 (see below).

Effects on the eyes. For a discussion of bilateral eye redness, occurring as part of an oculorespiratory syndrome following influenza vaccination, see below.

Effects on the nervous system. ***BELL'S PALSY.*** Between October 2000 and April 2001, the Swiss Drug Monitoring Centre and the University of Zurich received 46 reports of Bell's palsy occurring in patients who had used an inactivated intranasal influenza vaccine (*Nasalflu*). The manufacturers suspended distribution of the vaccine and, after a subsequent study[1] suggested a strong association between the vaccine and the development of Bell's palsy, it was withdrawn from clinical use.

1. Mutsch M, *et al.* Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004; **350:** 896–903.

GUILLAIN-BARRÉ SYNDROME. In 1976 a limited outbreak of influenza in the USA caused by a virus closely resembling the swine influenza virus led to the use of a killed swine influenza virus vaccine.[1] After about 45 million doses of the vaccine had been given the vaccination programme ceased because there was some evidence of a temporal association between vaccination and the onset of a paralytic polyneuropathy of the Guillain-Barré type. An epidemiologic and clinical evaluation of these cases suggested a definite link between vaccination and the onset of the syndrome with extensive paralysis but no association with the onset of limited motor lesions.

Surveillance systems have since investigated any possible link with the development of Guillain-Barré syndrome. The Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence was inadequate to either accept or reject a causal relationship with non-swine influenza vaccines used after 1976. This review had inspected reports submitted from 1990 to 2003 to VAERS (Vaccine Adverse Events Reporting System in the USA) but considered that such case reports were uninformative with respect to causality, although they were useful for hypothesis generation. One suggestion made by workers monitoring the VAERS data[3] was the question as to whether *Campylobacter* infection could be involved. Influenza vaccines have traditionally been made in chicken eggs. *Campylobacter* is endemic in chickens and a known cause of Guillain-Barré syndrome.

1. Anonymous. Influenza and the Guillain-Barré syndrome. *Lancet* 1984; **ii:** 850–1.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog/10822 (accessed 15/07/08)
3. Haber P, *et al.* Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004; **292:** 2478–81.

MULTIPLE SCLEROSIS. Analysis[1] indicated that there was no association between the use in the USA during 1976 of influenza vaccines containing a swine virus component and the development of multiple sclerosis. Later analysis by the Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence favoured rejection of a causal relationship between influenza vaccines used in various years (including the swine vaccines of 1976) and relapse of multiple sclerosis but that the evidence was inadequate to either accept or reject a causal relationship with incident multiple sclerosis.

1. Kurland LT, *et al*. Swine flu vaccine and multiple sclerosis. *JAMA* 1984; **251:** 2672–5.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications*. Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog/10822 (accessed 15/07/08)

Effects on the respiratory tract. For a discussion of respiratory symptoms, occurring as part of an oculorespiratory syndrome following influenza vaccination, see below.

Henoch-Schönlein purpura. Influenza vaccination has been associated with both development[1] and exacerbation[2] of Henoch-Schönlein purpura.

1. Patel U, *et al*. Henoch-Schönlein purpura after influenza vaccination. *BMJ* 1988; **296:** 1800.
2. Damjanov I, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; **242:** 2555–6.

Oculorespiratory syndrome. During 2000 to 2001, an increased incidence of ocular and respiratory effects was reported in Canada in 960 patients, 96% of whom had received a specific split virion influenza vaccine (*Fluviral S/F*).[1] Symptoms included bilateral redness of the eyes and facial oedema with coughing, wheezing, tightness of the chest, breathing difficulty, or sore throat and were collectively termed oculorespiratory syndrome.[1,2] It was postulated that the syndrome might be due to numerous microaggregates of unsplit viruses present in the vaccine. A study[3] using an improved formulation of the vaccine found that oculorespiratory symptoms still occurred in 6.3% of recipients and that, since the improved formulation was otherwise minimally reactogenic, such symptoms might be associated with influenza vaccines in general. A subsequent study[4] of influenza vaccination among persons previously afflicted by oculorespiratory syndrome was halted early owing to a 33% rate of recurrence of symptoms within 24 hours. The authors concluded that previously afflicted patients should be warned of the risk of recurrence but that episodes of recurrence were usually mild and well tolerated.[4]

1. National Advisory Committee on Immunization. Supplementary statement for the 2001-2002 season: influenza vaccination of persons who experienced oculo-respiratory syndrome following previous influenza vaccination. *Can Commun Dis Rep* 2001; **27:** 1–7.
2. Boulianne N, *et al*. Clinical manifestations and incidence of oculo-respiratory syndrome following influenza vaccination—Quebec, 2000. *Can Commun Dis Rep* 2001; **27:** 85–90.
3. Scheifele DW, *et al*. Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis* 2003; **36:** 850–7.
4. Skowronski DM, *et al*. Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis* 2003; **37:** 1059–66.

Precautions

As for vaccines in general, p.2202.

Whole-virion influenza vaccine is not recommended for use in children because of the increased risk of febrile reactions. Split-virion and surface-antigen vaccines are, however, suitable for children and infants and are widely used in mass immunisation campaigns.

Influenza vaccines should not be given to individuals with a known hypersensitivity to egg products.

Vaccination should be postponed in patients with active infection or acute febrile illness.

Asthma. There have been reports of exacerbations of asthma after influenza vaccination,[1,2] but reviews[3,4] have concluded that evidence of a causal relationship is lacking and that any risk of exacerbation which might exist is outweighed by the risk of influenza itself. Chronic respiratory disease, including asthma, is an indication for influenza vaccination in both the UK and USA. A systematic review has supported the use of inactivated vaccines for patients with chronic obstructive pulmonary disease.[5] A further systematic review, however, has concluded that, while there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination), uncertainty remains about the degree of protection that vaccination affords against asthma exacerbations after influenza infection.[6]

1. Hassan WU, *et al*. Influenza vaccination in asthma. *Lancet* 1992; **339:** 194.
2. Nicholson KG, *et al*. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet* 1998; **351:** 326–31.
3. Watson JM, *et al*. Does influenza immunisation cause exacerbations of chronic airflow obstruction or asthma? *Thorax* 1997; **52:** 190–4.
4. Park CL, Frank A. Does influenza vaccination exacerbate asthma? *Drug Safety* 1998; **19:** 83–8.
5. Poole PJ, *et al*. Influenza vaccine for patients with chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 04/05/06).
6. Cates CJ, *et al*. Vaccines for preventing influenza in people with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Diagnostic tests. False-positive screening enzyme-linked immunosorbent assays (ELISAs) for antibodies to HIV-1, HTLV-1 and hepatitis C virus were reported in blood donors who had recently received influenza vaccine.[1] The reaction was attributed to cross-reactivity of the test kit in use at the time with non-specific IgM.

1. Anonymous. False-positive serologic tests for human T-cell lymphotropic virus type 1 among blood donors following influenza vaccination, 1992. *JAMA* 1993; **269:** 2076 and 2078.

Interactions

◊ For the effect of influenza vaccination on some other drugs see under Phenobarbital Sodium, p.494, Phenytoin Sodium, p.500, Theophylline Hydrate, p.1145, and Warfarin Sodium, p.1432.

Uses and Administration

Influenza vaccines are used for active immunisation against influenza.

Three types of the influenza virus occur, namely types A, B, and C, and the formulation and composition of influenza vaccines is constantly reviewed with changes made to accommodate the antigenic shifts and drifts of the influenza virus. Recommendations concerning the antigenic nature of influenza vaccines are made annually by WHO. Currently, influenza vaccines are mainly of the inactivated type and are available as split-virion vaccines or as various surface-antigen vaccines (including virosomal products); whole-virion vaccines are now seldom used. In the USA, a live attenuated influenza vaccine against influenza virus types A and B is available.

Influenza vaccination is recommended for persons considered to be at special risk, particularly the elderly, those with chronic heart disease, chronic respiratory disease including asthma (see above), chronic hepatic or renal disease, diabetes mellitus, and patients who are immunosuppressed. Vaccination is also recommended for residents, particularly elderly persons and children, in closed institutions. Medical personnel and other persons at risk from infection through contact with infected patients should also receive vaccination. Vaccination usually produces immunity after about 14 days, lasting for about 6 months to 1 year. Injections are therefore scheduled annually so that the period of maximum immunity coincides with the usual period of influenza infection. In the UK and USA, they are generally given between September and early November.

Influenza vaccines are given in the UK by deep subcutaneous injection or intramuscular injection. The preferred site for injection is the deltoid muscle in adults and older children and, in infants and young children, the anterolateral aspect of the thigh. The recommended dose is 0.5 mL for adults and children aged over 3 years. In children aged 6 months to 3 years, doses of 0.25 or 0.5 mL have been used. Children should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time.

The live attenuated influenza vaccine available in the USA is given intranasally, in a dose of 0.2 mL (0.1 mL in each nostril) in adults (up to 49 years of age) and children aged over 9 years and in children aged 2 to 8 years who have received it previously. Children aged 2 to 8 years who have not previously received the vaccine are given a repeat dose after at least 30 days.

Commercially available influenza vaccines are not effective against avian influenza virus H5N1; however, such a vaccine has been developed in the USA (see below).

◊ Reviews.

1. Jefferson TO, *et al*. Vaccines for preventing influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/06/08).
2. Jefferson T, *et al*. Vaccines for preventing influenza in healthy children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Administration. Haemagglutinin on the surface of the influenza virus allows the virus to attach to the host cells, and antibody against it is the main form of immunity to influenza. Antibody to neuraminidase on the virus surface and cell-mediated immunity may be important as well. Adults with previous exposure to the relevant subtype usually get a fourfold or greater increase in haemagglutinin antibody after vaccination with 20 to 30 micrograms of haemagglutinin [equivalent to about one 0.5-mL dose], but in some cases most of the new antibody is against the original strain rather than the variant in the vaccine. Children and unprimed adults need 2 injections of a much larger dose of haemagglutinin (60 micrograms or more) for an adequate antibody response. The level of antibody falls by about 75% over 8 months after split-virus vaccine and by 50% over 6 months after whole-virus vaccine. Because of this decrease in antibody level, and antigenic drift, immunisation against influenza is required each year. After 1 or 2 doses of killed vaccine, clinical infection rates are reduced by 60 to 80% in children and young adults. Vaccination reduces clinical infection by only about 30% in elderly patients in institutions, but serious illness and death are probably cut by about 70%. The effectiveness of vaccination has varied widely in different studies, probably because of differences in previous exposure to the influenza subtype, vaccine dose, interval between vaccination and challenge, and matching of vaccine and challenge antigens.

Avian influenza vaccine. Since 1997, infection of humans with avian influenza virus H5N1 has been reported and is associated with high mortality. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic. Candidate avian influenza vaccines have been investigated and *Sanofi Pasteur, USA* has developed a vaccine. Although the vaccine will not be commercially available, it has been licensed by the FDA and will be included in the National Stockpile in the USA for use in the event that the H5N1 virus develops the ability to become readily transmissible from human to human.[1]

1. FDA. FDA news: FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1 (issued 17th April, 2007). Available at: http://fda.gov/bbs/topics/NEWS/2007/NEW01611.html (accessed 06/07/07)

Preparations

Ph. Eur.: Inactivated Influenza Vaccine (Split Virion, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Influenza Vaccine (Whole Virion, Inactivated); Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures);
USP 31: Influenza Virus Vaccine.

Proprietary Preparations (details are given in Part 3)

Arg.: Agrippal; Berigripina†; Evagrip†; Fluad; Fluarix; Fluzone†; Imovax Gripe†; Inflexal; Influvac; Isiflu Zonale†; Istivac; Nilgrip; Vaxigrip; ***Austral.:*** Fluarix; Fluvax; Influvac; Vaxigrip; ***Austria:*** Addigrip; Batrevac; Begrivac; Fluad; Fluarix; Fluvaccinol; Inflexal; Influvac; Invivac; Sandovac; Vacciflu; Vaxigrip; ***Belg.:*** α-Rix; Addigrip†; Fluvirin†; Influvac S; Mutagrip†; Vaxigrip; ***Braz.:*** Agrippal; Fluarix†; Fluzone†; Vacina Contra Gripe; Vacina de Virus Inativado Contra Gripe; Vaxigrip†; ***Canad.:*** Fluviral; Fluzone†; Vaxigrip; ***Chile:*** Fluarix; Inflexal; Influvac; Vaxigrip; ***Cz.:*** Agrippal†; Begrivac; Daronrix; Fluad; Fluarix; Fluvirin†; Focetria; Inflexal; Influvac; Optaflu; Vaxigrip; ***Denm.:*** Fluarix; Influvac; Vaxigrip; ***Fin.:*** Begrivac; Fluarix; Flupar; Fluvirin†; Influvac; Vaxigrip; ***Fr.:*** Agrippal; Fluarix; Fluvirine†; Gripguard; Immugrip; Influvac; Mutagrip; Previgrip; Vaxigrip†; ***Ger.:*** Addigrip; Begrivac†; Fluad; Infectovac Flu; Inflexal; Inflsplit SSW; Influvac; Invivac; Mutagrip; ***Gr.:*** Addigrip; Agrippal; Evagrip; Fluarix; Influvac; Vaxigrip; ***Hong Kong:*** Agrippal; Fluad; Fluarix; Fluvax; Inflexal; Influvac; Vaxigrip; ***Hung.:*** Agrippal; Begrivac; Fluarix; Fluval; Influvac; Vaxigrip; ***Indon.:*** Vaxigrip; ***Irl.:*** Agrippal; Begrivac†; Fluarix; Fluvirin†; Influvac; ***Israel:*** Agrippal; Fluarix; Fluvirin; Influvac; Vaxigrip; ***Ital.:*** Adiugrip; Agrippal; Begrivac; Fluad; Fluarix; Focusvax†; Inflexal; Influpozzi; Influsplit†; Influvac S; Influvirus; Isiflu V; Isigrip Zonale; Mutagrip; Vaxigrip; ***Malaysia:*** Fluarix; Fluvax; Inflexal; Vaxigrip; ***Mex.:*** Agrippal; Fluarix; Fluzone; Influvac†; ***Neth.:*** Afluria; Agrippal; Batrevac; Fluarix; Fluvax; Fluvirin; Inflexal; Influject; Influvac; Invivac; Mutagrip; Vacciflu; Vaxigrip; ***Norw.:*** Begrivac; Fluarix; Fluvirin†; Influvac; Invivac; Vaxigrip; ***NZ:*** Begrivac†; Fluarix; Fluvax; Influvac; Vaxigrip; ***Philipp.:*** Agrippal; Fluad; Fluarix; Inflexal; Vaxigrip; ***Pol.:*** Begrivac; Fluarix; Inflexal; Influvac; Vaxigrip; ***Port.:*** Batrevac; Chiroflu; Fluad; Fluarix; Fluvirin; Focetria; Inflexal; Influvac; Istivac; Vaxigrip; ***Rus.:*** Fluarix (Флюарикс); Grippol (Гриппол); Influvac (Инфлювак); ***S.Afr.:*** Agrippal; Fluarix†; Fluvirin; Influvac; Mutagrip; Vaxigrip; Xflu†; ***Singapore:*** Agrippal; Fluad; Fluarix; Influvac; Vaxigrip; ***Spain:*** Chiroflu; Chiromas; Evagrip; Fluarix; Gripavac; Imuvac†; Influvac; Mutagrip; Prodigrip†; Vac Antigripal; Vacuna Antigripal; Vitagripe†; ***Swed.:*** Agrippal; Batrevac†; Begrivac; Fluad; Fluarix; Fluvirin†; Influvac; Vaxigrip; ***Switz.:*** Fluarix; Inflexal; Influvac; Mutagrip; Nasalflu†; ***Thai.:*** Agrippal; Fluad; Fluarix; Fluzone; Vaxigrip; ***Turk.:*** Agrippal; Fluarix; Inflexal; Vaxigrip; ***UK:*** Agrippal; Begrivac; Enzira; Fluarix; Fluvirin; Imuvac; Inflexal†; Influvac; Invivac; Mastaflu; Optaflu; Viroflu; ***USA:*** Afluria; Fluarix; FluLaval; FluMist; Fluvirin; Fluzone; ***Venez.:*** Fluarix; Imovax Gripe†; Isiflu; Vacuna Purificada.

Japanese Encephalitis Vaccines

Vacunas de la encefalitis japonesa.

ATC — J07BA02.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Hypersensitivity reactions including urticaria, angioedema, hypotension, and dyspnoea have been reported mainly in travellers from non-endemic areas. In May 2005 the Japanese government suspended routine vaccination with mouse brain-derived vaccine in response to a report of acute disseminated encephalomyelitis after vaccination; however, a causal link has not been established.

Persons with unstable neurological conditions, including convulsions in the past year, may be at higher risk of adverse events. It is suggested that vaccine should not be given to those who are recovering from acute disseminated encephalomyelitis or to those with Guillain-Barré syndrome, multiple sclerosis, or other demyelinating disorders.

◊ References.

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2. Ruff TA, *et al.* Adverse reactions to Japanese encephalitis vaccine. *Lancet* 1991; **338:** 881–2.
3. Plesner A-M, *et al.* Neurological complications and Japanese encephalitis vaccination. *Lancet* 1996; **348:** 202–3.
4. Nothdurft HD, *et al.* Adverse reactions to Japanese encephalitis vaccine in travellers. *J Infect* 1996; **32:** 119–22.
5. Jelinek T, Nothdurft HD. Japanese encephalitis vaccine in travellers: is wider use prudent? *Drug Safety* 1997; **16:** 153–6.
6. Berg SW, *et al.* Systemic reactions in US Marine Corps personnel who received Japanese encephalitis vaccine. *Clin Infect Dis* 1997; **24:** 265–6.
7. Liu ZL, *et al.* Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. *J Infect Dis* 1997; **176:** 1366–9.
8. Plesner AM. Allergic reactions to Japanese encephalitis vaccine. *Immunol Allergy Clin North Am* 2003; **23:** 665–97. Correction. *ibid.* 2004; **24:** 335.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Two types of inactivated Japanese encephalitis (JE) vaccine containing either the Nakayama or the Beijing-1 strain of the virus and grown in mouse-brain tissue are generally used for active immunisation against encephalitis due to JE virus. The Nakayama strain vaccine produced in Japan was widely available internationally, but production has been stopped. Another inactivated JE vaccine is made in China from the Beijing-3 strain of JE virus and grown in Syrian hamster kidney-cell cultures. This vaccine has been replaced in the Chinese vaccination programme by a live, attenuated JE virus (strain SA 14-14-2) vaccine that is also produced on primary hamster cells. JE vaccines are widely used in China, Japan and other parts of Asia where JE is endemic and may form part of the WHO Expanded Programme on Immunization. Vaccination is recommended for visitors to rural areas of South East Asia and the Far East where infection is endemic and where the visit is to be for more than one month; it is also recommended for shorter visits in individuals likely to be at exceptional risk.

In the UK adults and children over 3 years who are non-immune travellers are usually given 3 doses each of 1 mL of the inactivated mouse-brain vaccine subcutaneously at 0, 7 to 14, and 28 to 30 days; full immunity will take up to one month to develop. A two-dose schedule with doses given 7 to 14 days apart may provide short-term immunity but is less effective; in the USA, an abbreviated dosage schedule with doses at 0, 7, and 14 days is suggested if time is not available for the standard schedule. Children under 3 years of age may be given 3 doses of 0.5 mL; in the USA, the vaccine is not recommended for children under 1 year. Reinforcing doses may be needed but the interval at which they are given varies with the vaccine preparation.

In areas where JE is endemic, primary immunisation with inactivated vaccines has been given according to a different schedule. Although the ages and schedule of subsequent boosters varies in different countries, the same schedule is used for primary immunisation. The first dose is given at age 6 months to 3 years according to the country, but in all cases is followed by a second dose 1 to 4 weeks later and then a third after 1 year. Live attenuated Japanese encephalitis vaccines are also used, in single or 2-dose schedules (see below), in some countries in the Far East where disease is endemic.

◊ Inactivated Japanese encephalitis vaccines have been widely used in Asia for some years. In Japan, the incidence of the disease has decreased since the introduction of nationwide vaccination in the mid-1960s.

A live attenuated vaccine, SA14-14-2, is widely used in China and is replacing the use of inactivated vaccine. Studies[1,2] with the live attenuated vaccine showed that 2 doses given a year apart were 97% effective in an endemic region of rural China. Similar results were obtained when the interval between doses was reduced to 1 to 3 months. A further case-control study[3] in Nepal found that single-dose administration was more than 99% effective.

Other vaccines are under development including recombinant DNA and chimeric vaccines. Recombinant vaccines delivered using poxvirus vectors were also investigated but research appears to have been halted.[4,5]

1. Hennessy S, *et al.* Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. *Lancet* 1996; **347:** 1583–6.
2. Tsai TF, *et al.* Immunogenicity of live attenuated SA14-14-2 Japanese encephalitis vaccine—a comparison of 1- and 3-month immunization schedules. *J Infect Dis* 1998; **177:** 221–3.
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5. Schiøler KL, *et al.* Vaccines for preventing Japanese encephalitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 11/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: JE-Vax; ***Canad.:*** JE-Vax; ***Cz.:*** JE-Vax†; ***Thai.:*** JE-Vaccine; ***USA:*** JE-Vax.

Jellyfish Venom Antisera

Antisuero contra el veneno de la medusa; Jellyfish Antivenins; Jellyfish Antivenoms.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

An antiserum for use in the management of severe stings by the box jellyfish or sea wasp *Chironex fleckeri* is available in Australia. The preparation contains the specific antitoxic globulins that neutralise the venom of *Chironex fleckeri* and is prepared from the serum of sheep immunised with the venom of the box jellyfish.

Box jellyfish antivenom is usually given by the intravenous route in a dose of 20 000 units. Alternatively, 60 000 units may be injected intramuscularly.

Jellyfish stings. Many stings caused by the box jellyfish *Chironex fleckeri* are of little consequence and can be managed by simple first aid measures; however, some can be rapidly fatal so immediate assessment is vital.[1] Fragments of tentacle adhering to the skin should be inactivated by the application of vinegar or 3 to 10% acetic acid solution. Cardiopulmonary resuscitation may be necessary in severe cases. The antiserum can be effective if given quickly and in adequate dosage,[2,3] although use is mainly reserved for those with cardiorespiratory instability, severe pain refractory to opioid analgesics, or at risk of significant scarring.[1,3] Some experimental evidence suggested that verapamil might be useful for treatment of the cardiotoxic effects of the venom and allow more time for the antiserum to exert its action,[1,4] but is now considered to be contraindicated.[3] Some have suggested that the *Chironex fleckeri* antiserum may be effective for severe envenomation by related species.[3,5]

Irukandji syndrome consists of several hypercatecholaminergic symptoms (such as generalised pain, distress, hypertension, cardiomyopathy, and pulmonary oedema) arising from envenomation with the small box jellyfish *Carukia barnesi*.[1,6] Treatment is essentially symptomatic and supportive. The *Chironex fleckeri* antivenom is not effective.[3,5] Acetic acid may also be helpful for stings by related species (see p.2244).

1. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; **178:** 34–7.
2. Fenner PJ, *et al.* Successful use of chironex antivenom by members of the Queensland Ambulance Transport Brigade. *Med J Aust* 1989; **151:** 708–10.
3. Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. *Toxicon* 2006; **48:** 830–59.
4. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; **153:** 363.
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6. Macrokanis CJ, *et al.* Irukandji syndrome in northern Western Australia: an emerging health problem. *Med J Aust* 2004; **181:** 699–702.

Leishmaniasis Vaccines

Vacunas de la leishmaniasis.

Profile

Vaccines containing *Leishmania* spp. are under investigation in an attempt to prevent cutaneous leishmaniasis.

◊ The inoculation of an infective strain of a *Leishmania* sp. into the skin, a technique known as leishmanisation, has been used to protect against cutaneous leishmaniasis (p.824). Although the technique has been standardised it is not generally recommended since large, slow-healing lesions have occurred in some patients. There is currently no effective vaccine for any form of leishmaniasis. First-generation vaccines containing killed leishmanial promastigotes, with or without BCG as an adjuvant, have been developed and tested in humans. These have conferred some protection against cutaneous disease but it has waned relatively quickly in some cases. They have not been found to confer protection against visceral leishmaniasis. New studies are ongoing investigating the use of alum as an adjuvant. There is also further investigation into second-generation vaccines using different approaches such as the use of surface antigens (gp63 and lipophosphoglycan), promastigote antigen from *L. amazonensis*, enzyme receptor (LACK), Th1-driving adjuvant such as interleukin-12, oligodeoxynucleotides with leishmanial antigens, or recombinant leishmanial antigen (TSA, LmSTI-1), all of which have conferred some protection in *mice*. A glycoprotein-enriched *L. donovani* promastigote vaccine (*Leishmune*®) is available for prophylactic veterinary use in Brazil. DNA constructs encoding gp63 and LACK have also conferred protection against *L. major* in *mice*. A chimeric vaccine has also been developed combining three leishmanial antigens (LeIF, LmSTI-1, and TSA) in monophosphoryl lipid A adjuvant but had, at best, mixed results in trials in *dogs*. Attenuated vaccines prepared by gene deletion have shown promise in *mice*. The saliva of sandflies (the vector) seems to enhance infectivity, and vaccines against salivary or gut antigens of the insect have also been investigated.

References.

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2. Melby PC. Vaccination against cutaneous leishmaniasis: current status. *Am J Clin Dermatol* 2002; **3:** 557–70.
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5. WHO. State of the art of new vaccines: research & development. Information available at: http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html (accessed 24/03/06)
6. Palatnik-de-Sousa CB. Vaccines for leishmaniasis in the fore coming 25 years. *Vaccine* 2008; **26:** 1709–24.

Leprosy Vaccines

Vacunas de la lepra.

Profile

Vaccines against leprosy including those using *Mycobacterium leprae*, as well as other mycobacteria, are under investigation. A killed vaccine has been developed in India for use as an adjunct to standard multidrug therapy in the treatment of leprosy. Although studies of new vaccines are continuing, BCG vaccine (p.2207) also appears to be effective.

◊ Leprosy vaccines are being studied both to prevent infection with *M. leprae* (immunoprophylaxis) and to prevent disease in infected individuals (immunotherapeutic). Attempts to develop a vaccine against leprosy are based on the assumption that induction of a cell-mediated immune response to *Mycobacterium leprae* will lead to protection against the bacillus. Several vaccines have been studied and include BCG, BCG plus heat-killed *M. leprae*, heat-killed *Mycobacterium w*, and ICRC (Indian Cancer Research Centre) bacillus. The fortuitous finding that BCG vaccine, which is inexpensive and widely available, is effective against leprosy has important implications for leprosy control. Considerable **immunoprophylaxis** against leprosy is afforded by BCG vaccination (see p.2207), and a study in Malawi showed that repeated vaccination provided additional protection.[1] However, the addition of killed *M. leprae* did not produce any further improvement, confirming preliminary results of a study in Venezuela.[2] However, in a report of their sixth meeting,[3] the WHO Technical Advisory Group on the Elimination of Leprosy reported superior vaccine efficacy for BCG plus heat-killed *M. leprae* than with BCG alone in a prophylactic leprosy vaccine study in south India. The study was begun in 1991 and involved 171 400 subjects who received either BCG alone, BCG plus heat-killed *M. leprae*, *Mycobacterium w*, ICRC bacillus, or placebo. Three surveys of the results have since been conducted by way of follow-up; the preliminary findings of the latest of these surveys revealed that the overall efficacy rates for the vaccines were 22% for BCG alone, 67% for BCG plus heat-killed *M.leprae*, 41% for *Mycobacterium w*, and 51% for ICRC bacillus. Within these results, the findings specifically for efficacy in contacts of patients with leprosy were 11% for BCG alone, 88% for BCG plus heat-killed *M. leprae*, 87% for *Mycobacterium w*, and 11% for ICRC bacillus. Further studies are being conducted in Brazil regarding the use of BCG for booster doses in schoolchildren, and also for its use in household contacts.

Beneficial responses have been reported[4-10] from the **immunotherapeutic** use of *Mycobacterium w* vaccine with standard multidrug therapy (p.176) although a small increase in Type 1 lepra reactions has been observed.[9-11] A similar, and possibly identical, vaccine based on the ICRC bacillus has also been evaluated.[12,13] Immunotherapy with BCG and heat killed *M.leprae* has produced beneficial responses when given as an adjunct to chemotherapy.[14] WHO has suggested that the immunotherapeutic use of vaccines may ultimately prove to be more clinically relevant than the immunoprophylactic use,[12] and high compliance with immunotherapy appears to be attainable.[15]

1. Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996; **348:** 17–24.
2. Convit J, *et al.* Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results. *Lancet* 1992; **339:** 446–50.
3. WHO. Report on the sixth meeting of the WHO Technical Advisory Group on the Elimination of Leprosy: Geneva, February 2004. Available at: http://www.ops-oms.org/English/AD/DPC/CD/lep-TAG-6.pdf (accessed 01/04/08)
4. Zaheer SA, *et al.* Combined multidrug and Mycobacterium w vaccine therapy in patients with multibacillary leprosy. *J Infect Dis* 1993; **167:** 401–10.
5. Zaheer SA, *et al.* Immunotherapy with Mycobacterium w vaccine decreases the incidence and severity of type 2 (ENL) reactions. *Lepr Rev* 1993; **64:** 7–14.
6. Zaheer SA, *et al.* Addition of immunotherapy with Mycobacterium w vaccine to multi-drug therapy benefits multibacillary leprosy patients. *Vaccine* 1995; **13:** 1102–10.
7. Katoch K, *et al.* Treatment of bacilliferous BL/LL cases with combined chemotherapy and immunotherapy. *Int J Lepr* 1995; **63:** 202–12.
8. Talwar GP. An immunotherapeutic vaccine for multibacillary leprosy. *Int Rev Immunol* 1999; **18:** 229–49.
9. De Sarkar A, *et al.* Impact of combined Mycobacterium w vaccine and 1 year of MDT on multibacillary leprosy patients. *Int J Lepr Other Mycobact Dis* 2001; **69:** 187–94.
10. Kaur I, *et al.* Combined 12-month WHO/MDT MB regimen and Mycobacterium w vaccine in multibacillary leprosy: a follow-up of 136 patients. *Int J Lepr Other Mycobact Dis* 2002; **70:** 174–81.
11. Kar HK, *et al.* Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate for an antileprosy vaccine, Mycobacterium w. *Lepr Rev* 1993; **64:** 219–26.
12. Mangla B. Leprosy vaccine debate in India re-ignited. *Lancet* 1993; **342:** 233.
13. Jayaraman KS. Charges fly over rival leprosy vaccines. *Nature* 1994: **367:** 403.
14. Rada E, *et al.* A follow-up study of multibacillary Hansen's disease patients treated with multidrug therapy (MDT) or MDT + immunotherapy (IMT). *Int J Lepr* 1997; **65:** 320–7.

15. Walia R, *et al.* Field trials on the use of Mycobacterium w vaccine in conjunction with multidrug therapy in leprosy patients for immunotherapeutic and immunoprophylactic purposes. *Lepr Rev* 1993; **64:** 302–11.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Immuvac.

Leptospirosis Vaccines

Leptospira Vaccines; Vacunas de la leptospirosis.

Profile

Leptospirosis vaccines prepared from killed *Leptospira interrogans* are available in some countries. They are used for active immunisation against leptospirosis icterohaemorrhagica (spirochaetal jaundice; Weil's disease) in persons at high risk of contracting the disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Spirolept; ***Switz.:*** Spirolept.

Lyme Disease Vaccines

Vacunas de la enfermedad de Lyme.

Profile

Vaccines based on recombinant outer surface proteins of *Borrelia burgdorferi* were developed and used in some countries for active immunisation against Lyme disease in persons at risk of contracting the disease.

Lyme arthritis refractory to treatment with antibacterials has occurred rarely as an immune reaction to vaccine-derived outer surface proteins of *Borrelia burgdorferi*.

Malaria Vaccines

Vacunas del paludismo.

Profile

Malaria vaccines acting against the sporozoite, asexual, and sexual stages of the *Plasmodium falciparum* life cycle are under investigation, as well as multicomponent vaccines consisting of combined antigens from various stages.

Vaccine development. Chemoprophylaxis of malaria is becoming increasingly problematical (see p.594), resulting in the increased desirability of effective malaria vaccines, several of which have been, or are being, studied clinically. The various approaches to malaria vaccine development have been extensively reviewed.[1-15] Malaria vaccines can be categorised into 4 main groups:

- vaccines against pre-erythrocytic forms of the parasite, specifically the sporozoite and liver stages of infection. A sporozoite vaccine could prevent infection either via an antibody response to block invasion of liver cells or via a cell-mediated response to destroy infected liver cells by preventing release of parasites into the bloodstream. The most advanced of these vaccines are derived from the circumsporozoite antigen present on the sporozoite and the main vaccine candidate of this type is RTS,S/AS02A. This vaccine is comprised of the antigenic C-terminus of the circumsporozoite gene from *Plasmodium falciparum* fused to hepatitis B surface antigen and encouraging results in early studies in endemic African areas have been reported.[16] The US military is also investigating the possibility of DNA vaccines for malaria, including a liver-stage DNA candidate encoding the circumsporozoite (CS) protein of *P. falciparum*; however, this vaccine has so far failed to induce antigen-specific antibodies. A multiple-antigen version of this DNA vaccine, known as MuStDo5, encoding 5 different liver-stage antigens including CS is also under investigation. Some workers are investigating the prospect of priming with a DNA vaccine and boosting with recombinant antigen or viral vectors. There is also some development of vaccines that focus on the intracellular liver stage of the parasite, since some antigens expressed by sporozoites or merozoites can also be expressed by liver stage parasites
- vaccines against asexual erythrocytic stages, directed at the merozoite form of the parasite. These vaccines would be expected to reduce the severity and the duration of disease by decreasing the blood-parasite density; this effect correlates with reduced symptoms and risk of death. The most advanced asexual vaccine candidate is merozoite surface protein 1 (MSP-1), which forms part of a complex thought to be involved in erythrocyte invasion; antibodies to MSP-1 have been shown to block parasite entry to erythrocytes *in vitro*. Recombinant MSP-1 has also been shown to protect against lethal parasite challenge in *animal* studies. Several other merozoite surface proteins are also under development (MSP-2, 3, 4, 5, 8, and 9). A vaccine comprising MSP-1 and MSP-2 in combination with *P. falciparum* ring-infected erythrocyte (RESA) has recently shown a 62% reduction in parasite density in children in a study in Papua New Guinea. Two further promising asexual erythrocytic stage vaccine candidates are the apical membrane antigen-1 (AMA-1) and erythrocyte-binding antigen-175 (EBA-175)
- transmission-blocking vaccines to raise antibodies in humans against the gamete stage of the parasite present in the mosquito gut; these antibodies would then be taken up by the biting mosquito from in the blood and block further parasite development in the mosquito, thus rendering it non-infectious. Blocking transmission in this way could reduce infectivity of mosquitoes in that they would carry fewer parasites, and could extend the useful life of a pre-erythrocytic or erythrocytic vaccine by preventing transmission of antibody-resistant mutants. The most advanced candidate vaccines of this type contain the *P. falciparum* surface protein antigens Pfs-25 and Pfs-28 or the *P. vivax* homologues Pvs-25 and Pvs-28. Recombinant forms of these antigens are currently being investigated. Other similar sexual stage vaccines under development include Pfs-48/45 and Pfs-230
- vaccines against the toxins produced by the parasite that contribute to the disease itself. The glycosylphosphatidyl inositol (GPI) anchor, which binds several of the parasite's antigens to the erythrocyte membrane, has been shown to be highly toxic in *mouse* models, but has potential for disease attenuation if it can be detoxified and rendered safe.

A multi-antigen, multistage combination vaccine is thought to be the best approach to effective vaccination against malaria. One such vaccine, SPf66, a synthetic preparation of three antigens from the asexual phase of the parasite in the blood linked by a sporozoite antigen has been studied but little or no evidence for its protective efficacy has been found.[3] Another multicomponent vaccine, NYVAC-Pf7, using a recombinant vaccinia viral vector that expresses 7 proteins from different stages of malarial infection, has also been studied,[17] but results have been disappointing. A further multicomponent vaccine, CDC/NIIMALVAC-1 has provided encouraging preliminary results in *animals* and *in vitro*.[18]

1. Webster D, Hill AVS. Progress with new malaria vaccines. *Bull WHO* 2003; **81:** 902–9.
2. Moorthy VS, *et al.* Malaria vaccine developments. *Lancet* 2004; **363:** 150–6.
3. Graves P, Gelband H. Vaccines for preventing malaria (SPf66). Available in The Cochrane Library; Issue 2. Chichester: John Wiley; 2006.
4. WHO. State of the art of new vaccines: research & development. Information available at: http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html (accessed 24/03/06)
5. Graves P, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
6. Graves P, Gelband H. Vaccines for preventing malaria (blood-stage). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
7. Tetteh KK, Polley SD. Progress and challenges towards the development of malaria vaccines. *BioDrugs* 2007; **21:** 357–73.
8. Matuschewski K, Mueller AK. Vaccines against malaria - an update. *FEBS J* 2007; **274:** 4680–7.
9. Mikolajczak SA, *et al.* Preerythrocytic malaria vaccine development. *Curr Opin Infect Dis* 2007; **20:** 461–6. Correction. *ibid.*; 656.
10. Genton B, Reed ZH. Asexual blood-stage malaria vaccine development: facing the challenges. *Curr Opin Infect Dis* 2007; **20:** 467–75.
11. Saul A. Mosquito stage, transmission blocking vaccines for malaria. *Curr Opin Infect Dis* 2007; **20:** 476–81.
12. Sharma S, Pathak S. Malaria vaccine: a current perspective. *J Vector Borne Dis* 2008; **45:** 1–20.
13. Vekemans J, Ballou WR. Plasmodium falciparum malaria vaccines in development. *Expert Rev Vaccines* 2008; **7:** 223–40.
14. Pinzon-Charry A, Good MF. Malaria vaccines: the case for a whole-organism approach. *Expert Opin Biol Ther* 2008; **8:** 441–8.
15. Tyagi RK, *et al.* Various carrier system(s)-mediated genetic vaccination strategies against malaria. *Expert Rev Vaccines* 2008; **7:** 499–520.
16. Alonso PL, *et al.* Duration of protection with RTS,S/ASO2A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *Lancet* 2005; **366:** 2012–12.
17. Ockenhouse CF, *et al.* Phase I/IIa safety, immunogenicity, and efficacy trial of NYVAC-Pf7, a pox-vectored, multiantigen, multistage vaccine candidate for Plasmodium falciparum malaria. *J Infect Dis* 1998; **177:** 1664–73.
18. Shi YP, *et al.* Immunogenicity and in vitro protective efficacy of a recombinant multistage Plasmodium falciparum candidate vaccine. *Proc Natl Acad Sci U S A* 1999; **96:** 1615–20.

Measles Immunoglobulins

Inmunoglobulinas contra el sarampión.
ATC — J06BB14.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Human Measles Immunoglobulin; Immunoglobulinum Humanum Morbillicum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the measles virus. Normal immunoglobulin may be added. It contains not less than 50 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Measles immunoglobulins may be used for passive immunisation against measles. They have been used to prevent or modify measles in susceptible persons who have been exposed to infection; in the UK, normal immunoglobulin is usually given.

Preparations

Ph. Eur.: Human Measles Immunoglobulin.

Measles Vaccines

Vacunas del sarampión.
ATC — J07BD01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Measles Vaccine (Live); Vaccinum Morbillorum Vivum). A freeze-dried preparation of a suitable live attenuated strain of measles virus grown in cultures of chick-embryo cells or human diploid cells. It is prepared immediately before use by reconstitution from the dried vaccine. The virus concentration is not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Measles may be used on the label.

USP 31 (Measles Virus Vaccine Live). A bacterially sterile preparation of a suitable live strain of measles virus grown in cultures of chick-embryo cells. It contains not less than the equivalent of 1×10^3 $TCID_{50}$ in each immunising dose, and may contain suitable antimicrobial agents. It should be stored at 2° to 8° and be protected from light.

Adverse Effects

As for vaccines in general, p.2201.

Fever and skin rashes may occur after measles vaccines. The fever generally starts about 1 week after the injection, lasts for about 2 or 3 days, and has sometimes been accompanied by convulsions. More serious effects reported rarely include encephalitis and thrombocytopenia.

◊ Reviews.

1. Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Safety* 1998; **19:** 435–54.

Incidence of adverse effects. Some brief comments made by the Advisory Committee on Immunization Practices in the USA on adverse effects of standard measles vaccines.[1] An excellent safety record of measles vaccines has been indicated by the experience gained through the use of more than 240 million doses up to 1993. Fever with a temperature of 39.4° or more may develop in 5 to 15% of vaccinees beginning 5-12 days after vaccination and usually lasts several days. Transient rashes have been reported in about 5% of vaccinees. CNS disorders, including encephalitis and encephalopathy, have been reported with a frequency of less than one case per million doses given. The incidence of encephalitis or encephalopathy after vaccination is lower than the incidence rate of encephalitis of unknown origin suggesting that such events after vaccination may be only temporally related to, rather than due to, vaccination.

1. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; **45** (RR 12): 1–35.

Atypical measles. The atypical-measles syndrome has occurred in persons vaccinated against measles and later exposed to the natural infection. The syndrome has been characterised by high fever and atypical rash; abdominal pain has been common and pneumonia almost universal.[1] Although atypical measles has occurred particularly in patients given killed vaccine[1] (no longer used) it has been reported in recipients of live measles vaccines.[2,3]

Measles occurring in patients previously vaccinated with live measles vaccines may be mild and go unrecognised. However, secondary vaccine failure does not appear to be a major problem (see Immunisation Schedules under Uses, below).

1. Anonymous. The atypical-measles syndrome. *Lancet* 1979; **i:** 962–3.
2. Chatterji M, Mankad V. Failure of attenuated viral vaccine in prevention of atypical measles. *JAMA* 1977; **238:** 2635.
3. Henderson JAM, Hammond DI. Delayed diagnosis in atypical measles syndrome. *Can Med Assoc J* 1985; **133:** 211–13.

Effects on hearing. There have been individual case reports of sensorineural hearing loss after measles vaccination.[1,2] Similar reports have been made after vaccination with measles and rubella vaccines (p.2223) and measles, mumps, and rubella vaccines (p.2223).

1. Watson JG. Bilateral hearing loss in a 3-year-old girl following measles immunisation at the age of 15 months. *Int J Pediatr Otorhinolaryngol* 1990; **19:** 189–90.
2. Jayarajan V, Sedler PA. Hearing loss following measles vaccination. *J Infect* 1995; **30:** 184–5.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* No association was found between measles vaccination and Guillain-Barré syndrome in an analysis of 2296 cases.[1]

1. da Silveira CM, *et al.* Measles vaccination and Guillain-Barré syndrome. *Lancet* 1997; **349:** 14–16.

OPTIC NEURITIS. For a report of optic neuritis in 2 children after being given measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p.2223.

SUBACUTE SCLEROSING PANENCEPHALITIS. Subacute sclerosing panencephalitis (SSPE) is a rare complication of measles infection (p.860) and has been reported in children who have received measles vaccine but have no history of clinical disease. Nevertheless mass measles vaccination has been effective in reducing the incidence of SSPE in both developing and industrialised countries,[1,2] and the risks of remaining unimmunised are considered to be greater than those arising from immunisation.

1. Anonymous. SSPE in the developing world. *Lancet* 1990; **336:** 600.
2. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; **45** (RR 12): 1–35.

Effects on the skin. Stevens-Johnson syndrome was associated with measles vaccination in a 10-month-old infant.[1]

1. Hazir T, *et al.* Stevens-Johnson syndrome following measles vaccination. *J Pakistan Med Assoc* 1997; **47:** 264–5.

High-titre vaccines and mortality. After reports of excess mortality in children, especially among girls, who received high-titre Edmonston-Zagreb (EZ) measles vaccine,[1] WHO reversed its recommendation for the use of this vaccine in its Expanded Programme on Immunization in developing countries.[2,3] Subsequent study[4] of children who had received high-titre EZ vaccine showed adverse effects on the nutritional status in either sex, confirming a generally deleterious effect of the vaccine. Others, however, have argued that the problems associated with the use of EZ vaccine have been exaggerated.[5,6] A review[6] pointed out that excess mortality was not seen in all studies, and concluded that the problem was unlikely to be due to the vaccine itself.

1. Knudsen KM, *et al.* Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996; **25:** 665–73.
2. Anonymous. High-titre measles vaccines dropped. *Lancet* 1992; **340:** 232.
3. WHO. Expanded Programme on Immunization; safety of high-titre measles vaccines. *Wkly Epidem Rec* 1992; **67:** 357–61.
4. Garenne M. Effect of Edmonston-Zagreb high-titre vaccine on nutritional status. *Lancet* 1994; **344:** 261–2.
5. Bennett JV, *et al.* Edmonston-Zagreb measles vaccine: a good vaccine with an image problem. *Pediatrics* 1999; **104:** 1123–4.
6. Aaby P, *et al.* High-titer measles vaccination before 9 months of age and increased female mortality: do we have an explanation? *Semin Pediatr Infect Dis* 2003; **14:** 220–32.

Precautions

As for vaccines in general, p.2202.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response, but they have been given to younger infants when the risk of measles is particularly high (see Immunisation Schedules, under Uses, below, for further discussion).

Hypersensitivity. For discussion of precautions to be taken on giving measles vaccines to children allergic to egg, see Measles, Mumps, and Rubella Vaccines, p.2223.

Immunocompromised patients. For a discussion of the use of live vaccines in immunocompromised patients including those with HIV infection, see Precautions on p.2202.

As with other live vaccines, measles vaccine is generally not recommended for use in patients with impaired immunity, although combined measles, mumps, and rubella vaccine may be given to HIV-positive individuals unless they have severe immunosuppression or other contra-indications. WHO and UNICEF[1] recommend that children with suspected or confirmed HIV infection should receive a dose of measles vaccine at 6 months of age in addition to the scheduled dose at 9 months. Immunocompromised patients who come into contact with measles should be given normal immunoglobulin. Specific measles immunoglobulins (p.2221) have been used in some countries. Although measles vaccines have been given to immunocompromised patients without causing adverse effects[2] there have been some reports of severe reactions; disseminated measles infection was reported in a child with severe congenital immunodeficiency,[3] and fatal giant-cell pneumonitis was reported in an adult with AIDS.[4]

1. WHO. *EPI vaccines in HIV-infected individuals: 5 October 2001*. Available at: http://www.who.int/vaccines-diseases/diseases/HIV.shtml (accessed 22/06/04)
2. Krasinski K, Borkowsky W. Measles and measles immunity in children infected with human immunodeficiency virus. *JAMA* 1989; **261:** 2512–16.
3. Monafo WJ, *et al.* Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr* 1994; **124:** 273–6.
4. Angel JB, *et al.* Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med* 1998; **129:** 104–6.

Inflammatory bowel disease. Measles vaccination has been suggested as a possible factor in the development of inflammatory bowel disease.[1] However a case-control study involving 140 patients with inflammatory bowel disease provided no support for this hypothesis,[2] and measles virus has not been detected in biopsy specimens from patients with inflammatory bowel disease.[3] Later reviews[4-6] concluded that there is no evidence of any association between measles-containing vaccines and inflammatory bowel disease. A suggested link between measles vaccine-associated inflammatory bowel disease and autism is now refuted (see p.2223).

1. Thompson NP, *et al.* Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995; **345:** 1071–4.
2. Feeney M, *et al.* A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; **350:** 764–6.
3. Afzal MA, *et al.* Absence of measles-virus genome in inflammatory bowel disease. *Lancet* 1998; **351:** 646–7.
4. Davis RL, Bohlke K. Measles vaccination and inflammatory bowel disease: controversy laid to rest? *Drug Safety* 2001; **24:** 939–46.
5. Seagroatt V, Goldacre MJ. Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979-1998. *J Epidemiol Community Health* 2003; **57:** 883–7.
6. Demicheli V, *et al.* Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06).

Interactions

As for vaccines in general, p.2202

Vitamin A. Supplementation with vitamin A (see Deficiency States, p.1973) is now included as part of WHO's Expanded Programme on Immunization. There has been conflicting evidence of the effects of such supplementation on the response to measles vaccination. One study[1] reported a reduced immune response if vaccination occurs at 6 months (before the age at which measles vaccination is usually given in the EPI) while others[2,3] generally found no significant change in seroconversion or immune response in children vaccinated at 9 months (the age at which vaccination is generally started).

1. Semba RD, *et al.* Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 1995; **345:** 1330–2.
2. Benn CS, *et al.* Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, West Africa. *Lancet* 1997; **350:** 101–5.
3. Cherian T, *et al.* Effect of Vitamin A supplementation on the immune response to measles vaccination. *Vaccine* 2003; **23:** 2418–20.

Uses and Administration

Measles vaccines are used for active immunisation against measles. Measles strains currently used in vaccines are usually the more attenuated Enders' attenuated Edmonston strain or the Schwarz strain. A high-potency measles vaccine prepared from the Edmonston-Zagreb strain of measles virus was formerly used but was stopped because of evidence of increased mortality (see High-titre Vaccines and Mortality, under Adverse Effects, above).

For primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see below.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response. However, they have been given to infants at 6 to 9 months of age in developing countries and in the USA in certain circumstances (such as during measles outbreaks) (see also Immunisation Schedules, below).

Single-antigen measles vaccines have also been used for prophylaxis after exposure to measles provided they are given within 72 hours of contact.

Administration. Several alternative routes of administration of measles vaccines have been investigated in an attempt to overcome some of the disadvantages of subcutaneous or intramuscular injection.[1] Aerosol administration has produced good responses in children over 9 months of age, although this route was not so effective in younger children.[2,3] Aerosol administration could be potentially useful for mass immunisation campaigns, a suggestion confirmed in a randomised study.[4]

Oral vaccines against measles, produced in edible plants, are under investigation.[5,6]

Work is currently underway to develop oral and/or nasal vaccines that will be suitable in infants less than 9 months of age, a time when they are vulnerable due to waning maternal antibodies.

1. Cutts FT, *et al.* Alternative routes of measles immunization: a review. *Biologicals* 1997; **25:** 323–38.
2. Hiremath GS, Omer SB. A meta-analysis of studies comparing the respiratory route with the subcutaneous route of measles vaccine administration. *Hum Vaccin* 2005; **1:** 30–6.
3. Low N, *et al.* Immunogenicity and safety of aerosolized measles vaccine: systematic review and meta-analysis. *Vaccine* 2008; **26:** 383–98.
4. Dilraj A, *et al.* Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: a randomised trial. *Lancet* 2000; **355:** 798–803.
5. Webster DE, *et al.* Appetising solutions: an edible vaccine for measles. *Med J Aust* 2002; **176:** 434–7.
6. Muller CP, *et al.* Immunogenic measles antigens expressed in plants: role as an edible vaccine for adults. *Vaccine* 2003; **21:** 816–19. Correction. *ibid.*; 3093.

Immunisation schedules. In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. As a result of concern that measles vaccine would not elicit an appropriate immune response in young infants due to the persistence of maternal antibodies in circulation, vaccination has generally not been attempted in children under 12 months old. However, infants born to vaccinated mothers tend to have lower levels of maternal antibodies and are susceptible to measles infection at under 12 months of age; vaccination has been shown to be effective at 6 to 9 months of age in such children,[1-3] although antibody titres were lower in infants vaccinated at 6 months of age than in those vaccinated later.[1,4]

In the UK and USA, routine vaccination is given at between 12 and 15 months, with a second dose given at between 4 and 6 years (see the immunisation schedules summarised under Vaccines, p.2202). Similar schedules are used in other countries. There is evidence that these 2-dose strategies will produce high levels of immunity in the community. During an outbreak of measles, vaccination may be given as early as 6 months of age;[5] revaccination is recommended in any child who is vaccinated before their first birthday. Vaccine may be given to non-immune persons of any age considered to be at risk of infection even if their immune status is uncertain.

For discussion of immunisation schedules in the developing world, see under Expanded Programme on Immunization, below.

1. Johnson CE, *et al.* Measles vaccine immunogenicity in 6- versus 15-month-old infants born to mothers in the measles vaccine era. *Pediatrics* 1994; **93:** 939–44.
2. Carson MM, *et al.* Measles vaccination of infants in a well-vaccinated population. *Pediatr Infect Dis J* 1995; **14:** 17–22.
3. Markowitz LE, *et al.* Changing levels of measles antibody titers in women and children in the United States: impact on response to vaccination. *Pediatrics* 1996; **97:** 53–8.
4. Gans HA, *et al.* Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 1998; **280:** 527–32.
5. De Serres G, *et al.* Effectiveness of vaccination at 6 to 11 months of age during an outbreak of measles. *Pediatrics* 1996; **97:** 232–5.

EXPANDED PROGRAMME ON IMMUNIZATION. Measles remains a leading cause of death among young children, despite the availability of a safe and effective vaccine for the past 40 years. WHO estimated 454 000 people, the majority of them children, died from measles and measles complications in 2004.

In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. If given earlier, passively-acquired maternal antibodies against measles may interfere with development of protective immunity.

In the developing world, protection given by maternal antibodies is often rapidly lost and in hyperendemic areas, such as urban and peri-urban areas, clinical measles may occur in children as young as 5 to 6 months of age. Immunisation against measles is part of WHO's Expanded Programme on Immunization. The first dose of measles vaccine is given to children at the age of 9 months or shortly thereafter. A 'second opportunity' for immunisation is provided to all children (either through routine immunisation campaigns or by targeted supplementary activities depending on local need). This assures measles immunity in children who failed to receive a previous dose of measles vaccine, as well as in those who were vaccinated but failed to develop immunity following vaccination (about 10 to 15% of those children vaccinated at 9 months of age).

Immunisation for travellers. WHO recommends that all travellers from the age of 6 months who have not been immunised should be offered measles vaccine. Infants who are travelling to areas where measles is endemic and who receive the first dose of measles vaccine between the ages of 6 to 8 months should also receive the scheduled primary immunisation doses later.[1]

It is generally recommended that individuals with at least a moderate degree of immune deficiency should receive measles vaccine even when travelling to areas with a low risk of contracting the disease.[1]

1. WHO. *International travel and health* 2008 ed. Available at: http://www.who.int/ith/en/ (accessed 13/04/08)

Preparations

Ph. Eur.: Measles Vaccine (Live);
USP 31: Measles Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Lirugen†; ***Austral.:*** Rimevax; ***Braz.:*** Rouvax†; ***Cz.:*** Movivac; ***Denm.:*** Attenuvax†; ***Fr.:*** Rouvax; ***Ger.:*** Masern-Impfstoff Merieux; ***Gr.:*** Rouvax†; ***India:*** M-Vac; ***Israel:*** Rimevax†; Rouvax; ***Ital.:*** Morbilvax†; Rouvax†; ***Malaysia:*** Rimevax†; ***Mex.:*** Rimevax; ***Neth.:*** Attenuvax†; ***NZ:*** Rimevax; ***Philipp.:*** Rouvax; ***Pol.:*** Rouvax; ***S.Afr.:*** Diplovax; Morbilvax; Rimevax; Rouvax; ***Spain:*** Amunovax†; Rimevax; ***Switz.:*** Attenuvax; Moraten; Rimevax†; ***Thai.:*** Morbilvax†; Rouvax†; ***Turk.:*** Rouvax; ***USA:*** Attenuvax; ***Venez.:*** Imovax Sarampion†.

Measles and Mumps Vaccines

Vacunas del sarampión y la parotiditis.

ATC — J07BD51.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Measles Vaccines, p.2221, and Mumps Vaccines, p.2225.

Effects on the bones and joints. For a reference to arthritis occurring after measles and mumps vaccine, see under Adverse Effects and Precautions of Measles, Mumps, and Rubella Vaccines, p.2223.

Interactions

As for vaccines in general, p.2202.

See also under Measles Vaccines, p.2222.

Uses and Administration

Measles and mumps vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mopavac; ***Ger.:*** M-M Vax†.

Measles and Rubella Vaccines

Vacunas del sarampión y la rubéola.
ATC — J07BD53.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.
USP 31 (Measles and Rubella Virus Vaccine Live). Bacterially sterile preparation of suitable live strains of measles virus and live rubella virus. It may contain suitable antimicrobial agents. Each labelled dose provides an immunising dose of each component. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Measles Vaccines, p.2221, and Rubella Vaccines, p.2236.

Incidence of adverse effects. Eight million children aged between 5 and 16 years were immunised with a measles and rubella vaccine in 1994 in the UK. By October 1995 the UK CSM had received reports on 2735 suspected adverse reactions most of which were minor and self-limiting.[1] Serious suspected reactions were rare and generally the number of reported cases was consistent with the background frequency of the particular disorder.

1. Committee on Safety of Medicines/Medicines Control Agency. Adverse reactions to measles rubella vaccine. *Current Problems* 1995; **21:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015633&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)

Effects on hearing. Profound, irreversible sensorineural deafness was reported in a 27-year-old woman after administration of a measles and rubella vaccine.[1] Sensorineural deafness has also been reported after use of measles, mumps, and rubella vaccine (below), and monovalent measles vaccine (p.2221).

1. Hulbert TV, *et al.* Bilateral hearing loss after measles and rubella vaccination in an adult. *N Engl J Med* 1991; **325:** 134.

Effects on the nervous system. Optic neuritis was reported in 2 children given measles and rubella vaccine 2 to 3 weeks previously.[1]

1. Stevenson VL, *et al.* Optic neuritis following measles/rubella vaccination in two 13-year-old children. *Br J Ophthalmol* 1996; **80:** 1110–11.

Interactions

As for vaccines in general, p.2202.

See also under Measles Vaccines, p.2222.

Uses and Administration

Measles and rubella vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Preparations

USP 31: Measles and Rubella Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Braz.: Rudi-Rouvax†; ***Chile:*** MoRu-Viraten; ***Ital.:*** MoRu-Viraten†; ***Mex.:*** Moruviraten; ***Thai.:*** Rudi-Rouvax†.

Measles, Mumps, and Rubella Vaccines

Vacunas del sarampión, la parotiditis y la rubéola.
ATC — J07BD52.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.
Ph. Eur. 6.2 (Measles, Mumps and Rubella Vaccine (Live); Vaccinum Morbillorum, Parotitidis et Rubellae Vivum). A freeze-dried preparation containing suitable live attenuated strains of measles virus, mumps virus (*Paramyxovirus parotitidis*), and rubella virus. The vaccine is prepared immediately before use by reconstitution from the dried vaccine. It contains in each dose not less than 3.0 log $CCID_{50}$ of infective measles virus, not less than 3.7 log $CCID_{50}$ of infective mumps virus, and not less than 3.0 log $CCID_{50}$ of infective rubella virus. The dried vaccine should be stored at 2° to 8° and be protected from light.
The BP 2008 states that MMR may be used on the label.
USP 31 (Measles, Mumps, and Rubella Virus Vaccine Live). A bacterially sterile preparation of suitable live strains of measles virus, mumps virus, and rubella virus. It may contain suitable antimicrobial agents. Each labelled dose provides an immunising dose of each component. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Measles Vaccines, p.2221, Mumps Vaccines, p.2225, and Rubella Vaccines, p.2236.

Events due to the measles component usually occur 6 to 11 days after vaccination and those due to the mumps and rubella components after 2 to 3 weeks but may occur up to 6 weeks after vaccination.

Adverse effects tend to be less frequent after the second dose of vaccine than after the first dose.

Measles, mumps, and rubella vaccines should not be given to individuals with a confirmed anaphylactic reaction to any antibacterial such as neomycin or kanamycin, that may be used in the manufacturing process.

Recommendations on vaccination in persons with egg allergy are discussed under Hypersensitivity, below.

Incidence of adverse effects. A double-blind placebo-controlled crossover study[1] in 581 pairs of twins showed that the frequency of adverse effects from the use of measles, mumps and rubella (MMR) vaccine was between 0.5 and 4.0%, indicating that adverse reactions are much less common than was previously thought. A study in the USA[2] showed that children given the vaccine at age 4 to 6 years had fewer adverse effects than those given it at 10 to 12 years. A later study[3] based on family reported symptoms was unable to detect any vaccine-related adverse effects when the second dose of MMR vaccine was given at either 4 to 6 years or 10 to 12 years. Vaccine-related adverse effects after the first dose of MMR vaccine were reported in about 17% in those vaccinated between the age of 12 and 20 months.

A further study[4] that assessed the effect of almost 3 million doses of vaccines in 1.8 million individuals revealed that 173 potentially serious reactions were claimed to have been caused by vaccination. There were 77 neurologic, 73 allergic, and 22 miscellaneous reactions recorded, and 1 death reported. However, 45% of the reactions were probably caused by some other factor. It was therefore concluded that serious events caused by MMR vaccine are rare and are greatly outweighed by the risks of the natural diseases.

1. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine: a double-blind placebo-controlled trial in twins. *Lancet* 1986; **i:** 939–42.
2. Davis RL, *et al.* MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the vaccine safety datalink project. *Pediatrics* 1997; **100:** 767–71.
3. LeBaron CW, *et al.* Evaluation of potentially common adverse events associated with the first and second doses of measles-mumps-rubella vaccine. *Pediatrics* 2006; **118:** 1422–30.
4. Patja A, *et al.* Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J* 2000; **19:** 1127–34.

Effects on the blood. Thrombocytopenia occurs rarely in children receiving measles, mumps, and rubella vaccine and usually resolves spontaneously. The rubella component is considered to be the most likely cause. An increased incidence of thrombocytopenia after the second dose of the vaccine has been reported in children who developed thrombocytopenia after the first dose.[1] A study[2] by the UK Public Health Laboratory Service has suggested a link between measles, mumps, and rubella vaccine and the occurrence of idiopathic thrombocytopenic purpura, with an absolute risk of 1 in 22 300 of occurrence within 6 weeks of the first dose of the vaccine, and 2 out of every 3 cases attributable to it. Children with idiopathic thrombocytopenic purpura before receiving measles, mumps, and rubella vaccine experienced no vaccine-associated recurrences. A further study[3] of children aged 13 to 24 months and diagnosed with idiopathic thrombocytopenic purpura for the first time between January 1988 and December 1999 similarly found the attributable risk of developing it within 6 weeks of receiving the vaccine to be about 1 in 25 000. As a consequence of these findings, the UK CSM has recommended[4] that children developing idiopathic thrombocytopenic purpura within 6 weeks of vaccination with measles, mumps, and rubella vaccine, or any of its components, should have serological testing before their second dose is due; if this suggests that full immunity is not established, then a second dose should be given.

1. Vlacha V, *et al.* Recurrent thrombocytopenic purpura after repeated measles-mumps-rubella vaccination. *Pediatrics* 1996; **97:** 738–9.
2. Miller E, *et al.* Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001; **84:** 227–9.
3. Black C, *et al.* MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol* 2003; **55:** 107–11.
4. Committee on Safety of Medicines/Medicines Control Agency. MMR vaccine and idiopathic thrombocytopenic purpura. *Current Problems* 2001; **27:** 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 24/05/06)

Effects on the bones and joints. Arthralgia and arthritis occurring in patients given mumps, measles, and rubella vaccines have generally been attributed to the rubella component.[1] However, arthritis has been reported in an infant after vaccination with measles and mumps vaccine.[2]

1. Benjamin CM, *et al.* Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. *BMJ* 1992; **304:** 1075–8.
2. Nussinovitch M, *et al.* Arthritis after mumps and measles vaccination. *Arch Dis Child* 1995; **72:** 348–9.

Effects on hearing. Nine cases of sensorineural hearing loss after measles, mumps, and rubella vaccine were reported to the UK CSM between 1988 and 1993.[1] Of these, 3 cases were judged not to have been associated with the vaccine. In the remaining 6, the mumps virus component was considered to be the most likely cause of deafness if the vaccine was to blame, but the risk was considered to be small compared with the risks of natural infection. However, sensorineural deafness has also been reported after measles and rubella vaccine (see above) and monovalent measles vaccine (see p.2221).

1. Stewart BJA, Prabhu PU. Reports of sensorineural deafness after measles, mumps, and rubella immunisation. *Arch Dis Child* 1993; **69:** 153–4.

Effects on the nervous system. Although there have been case reports[1] linking Guillain-Barré syndrome with measles, mumps, and rubella vaccine, a retrospective study[2] that involved 189 patients with the syndrome and about 630 000 recipients of the vaccine could not find a causal association.

Prolonged tonic-clonic seizures were associated with prolonged hemiparesis in a 16-month-old girl 6 days after measles, mumps, and rubella vaccination.[3] There was evidence of transient encephalopathy. However, a causal relationship between measles-containing vaccines and encephalitis is generally considered to be unlikely. Other reported neurological effects after vaccination include gait disturbances,[4,5] and transverse myelitis.[6] However, a retrospective study[7] found no evidence for a causal association between vaccination and acute ataxia and the development of gait disturbances and suggested the original reports represented chance occurrence.

For discussion of meningitis and encephalitis occurring after measles, mumps, and rubella vaccination, see under Adverse Effects of Mumps Vaccines, p.2225.

1. Morris K, Rylance G. Guillain-Barré syndrome after measles, mumps, and rubella vaccine. *Lancet* 1994; **343:** 60.
2. Patja A, *et al.* Risk of Guillain-Barré syndrome after measles-mumps-rubella vaccination. *J Pediatr* 2001; **138:** 250–4.
3. Sackey AH, Broadhead RL. Hemiplegia after measles, mumps, and rubella vaccination. *BMJ* 1993; **306:** 1169.
4. Plesner A-M. Gait disturbances after measles, mumps, and rubella vaccine. *Lancet* 1995; **345:** 316.
5. Plesner AM, *et al.* Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. *Acta Paediatr* 2000; **89:** 58–63.
6. Joyce KA, Rees JE. Transverse myelitis after measles, mumps, and rubella vaccine. *BMJ* 1995; **311:** 422.
7. Miller E, *et al.* No evidence of an association between MMR vaccine and gait disturbance. *Arch Dis Child* 2005; **90:** 292–6.

Hypersensitivity. Since the measles and mumps components of measles, mumps, and rubella vaccines are grown in cell cultures of chick embryos the vaccine was formerly contra-indicated in individuals with a history of anaphylactic reactions to egg. In both the UK and USA, serious reactions to egg including anaphylaxis are no longer regarded as absolute contra-indications to vaccination although specialist advice should be obtained and vaccination performed only under controlled conditions. It is generally agreed that the vaccine can be given safely to children with less severe reactions to eggs.

A confirmed anaphylactic reaction to gelatin, kanamycin, or neomycin is a contra-indication to measles, mumps, and rubella vaccines.

Inflammatory bowel disease and autism. A controversial report[1] in 1998 linked measles, mumps, and rubella vaccination with the development of inflammatory bowel disease and behavioural abnormalities including autism. However, there is now overwhelming evidence from studies and analyses that the vaccine does not cause autism.[2-11] Similarly, the link between measles-containing vaccines and inflammatory bowel disease has not been substantiated (see under Precautions for Measles Vaccines, p.2222).

1. Wakefield AJ, *et al.* Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2. Peltola H, *et al.* No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet* 1998; **351:** 1327–8.
3. Roberts R. There is no causal link between MMR vaccine and autism. *BMJ* 1998; **316:** 1824.
4. Taylor B, *et al.* Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999; **353:** 2026–9.
5. Kaye JA, *et al.* Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001; **322:** 460–3. Correction. *ibid.*; 720.
6. Dales L, *et al.* Time trends in autism and in MMR immunization coverage in California. *JAMA* 2001; **285:** 1183–5.
7. Halsey NA, *et al.* Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the new challenges in childhood immunizations conference convened in Oak Brook, Illinois, June 12-13, 2000. Abstract: *Pediatrics* 2001; **107:** 1174. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/5/e84 (accessed 14/12/04)
8. Smeeth L, *et al.* MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004; **364:** 963–9.
9. Immunization Safety Review Committee. *Immunization safety review: vaccines and autism.* Washington DC: National Academy Press, 2004. Also available at: http://www.nap.edu/catalog/10997 (accessed 15/07/08)
10. Demicheli V, *et al.* Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06)
11. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 14/04/08)

Interactions

As for vaccines in general, p.2202.

See also under Measles Vaccines, p.2222.

Uses and Administration

Measles, mumps, and rubella vaccines are used for active immunisation against measles, mumps, and rubella. They are used for primary immunisation in children 12 months of age or older and to protect susceptible contacts during an outbreak of measles. For discussion of immunisation schedules, see under Vaccines, p.2202.

In the UK, it is recommended that all children receive two doses of 0.5 mL of a measles, mumps, and rubella vaccine by intramuscular injection (or subcutaneously if there is a bleeding disorder). These are usually given shortly after the first birthday and before school entry, but may be given at any age if routine vaccination has been omitted, allowing 3 months between doses. The combined vaccine may also be used for prophylaxis after exposure to measles provided it is given within 72 hours of contact. However, it is not considered to be effective for postexposure prophylaxis against either mumps or rubella. If the vaccine is given before 12 months of age, re-immunisation will be necessary starting at between 12 and 15 months with a further dose according to national schedules.

Similar schedules are used in the USA.

Preparations

Ph. Eur.: Measles, Mumps, and Rubella Vaccine (Live);
USP 31: Measles, Mumps, and Rubella Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: MMR II; Trimovax; Triviraten; ***Austral.:*** MMR II†; Priorix; ***Austria:*** Priorix; ***Belg.:*** MMR Vax; Priorix; ***Braz.:*** MMR II†; Priorix†; Trimovax†; Vacina Comb. Contra Sarampo, Caxumba e Rubeola; Vacina Contra Sarampo, Caxumba e Rubeola; Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola; ***Canad.:*** MMR II; Priorix; ***Cz.:*** MMR II; MMRVaxPro; Priorix; Trimovax†; Trivivac; ***Denm.:*** MMR; ***Fin.:*** MMR II; Priorix; ***Fr.:*** MMRVaxPro; Priorix; R.O.R.; ***Ger.:*** MMR Triplovax; MMR Vax; Priorix; ***Gr.:*** MMR II; MMRVaxPro; Priorix; ***Hong Kong:*** MMR II; Priorix; Trimovax; Triviraten†; ***Hung.:*** MMR II; ***India:*** Tresivac; ***Indon.:*** MMR II; Trimovax; ***Irl.:*** MMR II; Priorix; ***Israel:*** MMR II; Priorix; ***Ital.:*** MMR II; Morupar†; Priorix; ***Malaysia:*** MMR II; Priorix; Triviraten†; ***Mex.:*** MMR II; Morupar†; Priorix; ***Neth.:*** Priorix; ***Norw.:*** MMR II; Priorix; ***NZ:*** Priorix; Triviraten; ***Philipp.:*** Morupar†; Priorix; Trimovax; Triviraten; ***Pol.:*** MMR II; Priorix; Trimovax†; ***Port.:*** Priorix; ***Rus.:*** MMR II (MMP II); Priorix (Приорикс); ***S.Afr.:*** Morupar†; Priorix; Trimovax; ***Singapore:*** MMR II; Priorix; ***Spain:*** Priorix; Triviraten†; Vacuna Triple MSD; ***Swed.:*** MMR II; Priorix; ***Switz.:*** MMR II; Priorix; Triviraten; ***Thai.:*** MMR II; Morupar†; Priorix; Trimovax; Triviraten†; ***Turk.:*** MMR II; Priorix; Trimovax; Triviraten; ***UK:*** MMR II; Priorix; ***USA:*** MMR II; ***Venez.:*** Priorix; Trimovax†.

Multi-ingredient: *NZ:* MMR II.

Measles, Mumps, Rubella, and Varicella-Zoster Vaccines

ATC — J07BD54.

Profile

Measles, mumps, rubella, and varicella-zoster vaccines are used for active immunisation against measles, mumps, rubella and varicella (chickenpox).

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Priorix-Tetra; ProQuad; ***NZ:*** Priorix-Tetra; ***Port.:*** Priorix-Tetra; ProQuad; ***USA:*** ProQuad.

Meningococcal Vaccines

Vacunas de polisacáridos meningocócicos.
ATC — J07AH01; J07AH02; J07AH03; J07AH04; J07AH05; J07AH06; J07AH07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
Ph. Eur. 6.2 (Meningococcal Polysaccharide Vaccine; Vaccinum Meningitidis Cerebrospinalis). It consists of one or more purified capsular polysaccharides obtained from one or more suitable strains of *Neisseria meningitidis* group A, group C, group Y, and group W135; it may contain a single type of polysaccharide or any mixture of the types. It is prepared immediately before use by reconstitution from the stabilised freeze-dried vaccine with a suitable sterile liquid. The freeze-dried vaccine should be stored at 2° to 8° and be protected from light.
The BP 2008 states that Men plus the relevant antigen may be used on the label (for example MenAC).
Ph. Eur. 6.2 (Meningococcal Group C Conjugate Vaccine; Vaccinum Meningococcale Classis C Coniugatum). A liquid or freeze-dried preparation of purified capsular polysaccharide derived from a suitable strain of *Neisseria meningitidis* group C covalently linked to a carrier protein. The vaccine may contain an adjuvant. The freeze-dried vaccine should be stored at 2° to 8° and be protected from light.
The BP 2008 states that MenC(conj) may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Immunity to the unconjugated serogroup C polysaccharide in meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age.

Effects on the nervous system. From June 2005 to September 2006, 17 cases of Guillain-Barré syndrome were reported to the Vaccine Adverse Event Reporting System (VAERS) after use of a tetravalent (A, C, W135, and Y) meningococcal conjugate vaccine (Menactra). Whether the cases were caused by the vaccine or were coincidental was unknown.[1,2] The CDC recommends that persons with a history of Guillain-Barré syndrome should not be vaccinated with the tetravalent meningococcal conjugate vaccine.[2]

1. CDC. Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine - United States, June-July 2005. *MMWR* 2005; **54:** 1023–5.
2. CDC. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine— United States, June 2005-September 2006. *MMWR* 2006; **55:** 1120–4. Correction. *ibid.*; 1177.

Pregnancy and the neonate. A study[1] in 157 Asian women given a tetravalent polysaccharide vaccine in the third trimester of pregnancy found that immunisation was safe for both mothers and infants. Infants were provided with significantly increased levels of IgG for 2 to 3 months and of oral IgA for 6 months from breast feeding.

1. Shahid NS, *et al.* Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: a randomized, controlled evaluation. *Vaccine* 2002; **20:** 2404–9.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Meningococcal vaccines are used for active immunisation against *Neisseria meningitidis* infections, which include meningitis and septicaemia. They are preparations of purified polysaccharide antigens from *N. meningitidis* and may be monovalent, containing the antigen of only one serotype of *N. meningitidis* or polyvalent, containing antigens of two or more serotypes. Conjugation of the polysaccharide to a carrier such as diphtheria CRM_{197} protein or to tetanus toxoid protein increases the immunogenicity.

In the UK, primary immunisation is recommended during infancy whereas in the USA routine immunisation is recommended during adolescence or for those at increased risk for meningococcal disease from 2 to 10 years of age. In the UK, a conjugate meningococcal C vaccine is used and is generally given by intramuscular injection with the subcutaneous route reserved for patients with haemophilia or thrombocytopenia. Infants, starting at 2 months of age, are given 3 doses of 0.5 mL at monthly intervals. If primary immunisation is delayed until 5 months of age then 2 doses, one month apart, are sufficient; children over 1 year of age and adults should be given a single dose only. In the USA, routine immunisation with a single dose, given intramuscularly, of a conjugate tetravalent vaccine from groups A, C, Y, and W135 is performed at 11 to 18 years of age if not previously vaccinated. For discussion of immunisation schedules see under Vaccines, p.2202.

Asplenic persons or those who have terminal complement component deficiencies are at higher than normal risk of acquiring meningococcal infection and therefore they should be immunised. Either a conjugate meningococcal C vaccine or a tetravalent vaccine (A, C, Y, and W135, unconjugated or conjugated) may be used depending on availability.

Meningococcal vaccines are also indicated in persons travelling to countries where the risk of infection is high. They should receive a tetravalent meningococcal polysaccharide vaccine (either unconjugated or conjugated) rather than the group C conjugate vaccine, and should be immunised even if they have already received the latter. Vaccination is indicated particularly for visits of 1 month or more and for those backpacking or living or working with local residents. Vaccination is a visa requirement for Hajj pilgrims to Saudi Arabia.

Meningococcal vaccines may be given as an adjunct to chemoprophylaxis in contacts of persons with meningitis (see p.178).

A meningococcal group B vaccine has been developed in New Zealand and contains outer membrane vesicles from *N. meningitidis* group B strain NZ 98/254. It is given for primary immunisation against the New Zealand strain (P1.7-b,4* PorA protein) of group B meningococcal disease. Adults and children over 6 months old are given three doses of 0.5 mL at intervals of 6 weeks intramuscularly; infants less than 6 months old should be given 4 doses, at 6 weeks, 3 months, 5 months, and 10 months of age. Vaccines against other group B meningococci are under investigation (see below).

◊ Reviews.

1. Ruggeberg J, Heath PT. Safety and efficacy of meningococcal group C conjugate vaccines. *Expert Opin Drug Saf* 2003; **2:** 7–19.

Vaccine development. Despite the established use of vaccines against meningococcal groups A, C, W135, and Y, about 60 to 80% of meningococcal infections (p.179) in the UK and the USA are caused by *Neisseria meningitidis* of group B serotype. Unfortunately the purified group B polysaccharide is only poorly immunogenic, even after conjugation with proteins but several avenues of research are being followed in the development of an effective vaccine. These include vaccines based on other outer membrane proteins contained in outer membrane vesicles, in particular the most important outer membrane proteins, PorA, and on lipopolysaccharide derivatives. More recently, group B meningococcal vaccine based on PorA has been developed in New Zealand (see above) and is available for primary immunisation against the New Zealand strain specifically, and has resulted in a marked reduction in incidence in that country. Recombinant technology has been used in the Netherlands to develop both a monovalent PorA vaccine and a hexavalent vaccine containing 6 PorA proteins, including that of the New Zealand strain. Results obtained with the New Zealand PorA antigen in the hexavalent formulation have been poor, but it has been shown to stimulate a satisfactory immune response in infants or small children in the monovalent form. The successful sequencing of the meningococcal genome has allowed discovery of several new proteins and raised potential for the development of new candidate vaccines, including novel surface-located vaccine candidates which are currently in preclinical evaluation.

An intranasal meningococcal group B vaccine is also under development.

References.

1. Katial RK, *et al.* Immunogenicity and safety testing of a group B intranasal meningococcal native outer membrane vesicle vaccine. *Infect Immun* 2002; **70:** 702–7.
2. Jodar L, *et al.* Development of vaccines against meningococcal disease. *Lancet* 2002; **359:** 1499–1508.
3. Vermont CL, van den Dobbelsteen GP. Meningococcal serogroup B infections: a search for a broadly protective vaccine. *Expert Rev Vaccines* 2003; **2:** 673–81.
4. Broker M. Development of new vaccines against meningococcal disease. *Arzneimittelforschung* 2003; **53:** 805–13.
5. Zimmer SM, Stephens DS. Meningococcal conjugate vaccines. *Expert Opin Pharmacother* 2004; **5:** 855–63.
6. Zimmer SM, Stephens DS. Serogroup B meningococcal vaccines. *Curr Opin Investig Drugs* 2006; **7:** 733–9.
7. Holst J. Strategies for development of universal vaccines against meningococcal serogroup B disease: the most promising options and the challenges evaluating them. *Hum Vaccin* 2007; **3:** 290–4.
8. Kelly C, *et al.* A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. *Am J Epidemiol* 2007; **166:** 817–23.
9. McNicholas A, *et al.* Surveillance of vaccine breakthrough cases following MeNZB vaccination. *N Z Med J* 2008; **121:** 38–46.
10. van Alphen L, van den Dobbelsteen G. Meningococcal B vaccine development and evaluation of efficacy. *Hum Vaccin* 2008; **4:** 158–61.
11. WHO: Initiative for Vaccine Research (IVR). Neisseria meningitidis. Information available at: http://www.who.int/vaccine_research/diseases/soa_bacterial/en/index2.html (accessed 13/04/06)

Preparations

Ph. Eur.: Meningococcal Group C Conjugate Vaccine; Meningococcal Polysaccharide Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Antimeningococica A+C; Meningitec†; Menjugate; NeisVac-C; Va-Mengoc-BC; ***Austral.:*** Mencevax ACWY; Meningitec; Menjugate; Menomune; NeisVac-C; ***Austria:*** Mencevax ACWY; Meningitec; Menomune; NeisVac-C; ***Belg.:*** Mencevax ACWY; Meningitec; Meningovax A+C†; Menjugate; NeisVac-C; ***Braz.:*** Va-Mengoc-BC†; Vacina Meningococica A+C; Vacina Meningococica Conjugada Grupo C; ***Canad.:*** Meningitec; Menjugate; Menomune; NeisVac-C; ***Chile:*** Meningo A+C; ***Cz.:*** Menjugate; Menpovax A+C†; NeisVac-C; ***Denm.:*** Meningovax A+C; NeisVac-C; ***Fin.:*** Mencevax ACWY; Meningovax A+C; NeisVac-C; ***Fr.:*** Meningitec; Meninvact; Menjugate; Menomune; NeisVac; ***Ger.:*** Mencevax ACWY; Meningitec; Meningokokken-Impfstoff A + C; Menjugate; NeisVac-C; ***Gr.:*** Meningitec; Meninvact; Menjugate; Menomune; NeisVac-C; Vaccin Meningococcique; ***Hong Kong:*** Mencevax ACWY; Meningococcal A+C†; ***Hung.:*** Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Indon.:*** Mencevax ACWY; ***Irl.:*** Mengivac (A+C)†; Meningitec; Menjugate; ***Israel:*** Mencevax AC†; Mencevax ACWY; ***Ital.:*** Mencevax ACWY; Meningitec; Meninvact; Menjugate; Menomune; NeisVac-C; ***Malaysia:*** Mencevax ACWY; Menomune†; ***Neth.:*** Meningovax A+C; Meninvact; Menjugate; NeisVac-C; ***Norw.:*** Mencevax AC; Meningitec; Meningovax A+C; NeisVac-C; ***NZ:*** Mencevax ACWY; Meningitec; Menomune; MeNZB; ***Philipp.:*** Euro A & C; ***Pol.:*** NeisVac-C; ***Port.:*** Meningitec; Menjugate; NeisVac-C; ***Rus.:*** Mencevax ACWY (Менцевакс ACWY); ***S.Afr.:*** Imovax Meningo A & C; Mencevax; ***Singapore:*** Mencevax ACWY; Menomune; ***Spain:*** Mencevax AC; Meningitec; Meninvact†; Menjugate; NeisVac-C; Vacuna Antimeningococic A+C; ***Swed.:*** Meningitec†; Meningovax A+C; NeisVac-C; ***Switz.:*** Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; ***Thai.:*** Meningococcal A+C†; Menomune; ***Turk.:*** Imovax Meningo A+C; ***UK:*** ACWY Vax; Mengivac (A+C)†; Meningitec; Menjugate; NeisVac-C; ***USA:*** Menactra; Menomune; ***Venez.:*** Imovax Meningo A+C†; Mencevax ACWY†.

Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

◊ References.

1. Hellings N, *et al.* T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3:** 267–75.
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24:** 393–413.
3. Fontoura P, *et al.* Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24:** 415–46.
4. Correale J, *et al.* Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22:** 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Mumps Vaccines

Vacunas de la parotiditis.

ATC — J07BE01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Mumps may be used on the label.

USP 31 (Mumps Virus Vaccine Live). A bacterially sterile preparation of a suitable strain of mumps virus grown in cultures of chick-embryo cells. It contains not less than the equivalent of 5×10^3 $TCID_{50}$ in each immunising dose. It may contain suitable antimicrobial agents. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For a report of sensorineural hearing loss following measles, mumps, and rubella vaccination, see p.2223.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined measles, mumps, and rubella vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the observed background incidence for CNS dysfunction in the general population.

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; **ii:** 1015–16.
2. Maguire HC, *et al.* Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; **1** (review 6): R60–R61.
3. Miller E, *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; **341:** 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; **340:** 786. Correction. *ibid.*: 986.
5. McDonald JC, *et al.* Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; **8:** 751–5.
6. Forsey T, *et al.* Mumps vaccine and meningitis. *Lancet* 1992; **340:** 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; **340:** 722.
8. Čižman M, *et al.* Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; **8:** 302–8.
9. Tešović G, *et al.* Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; **341:** 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; **38:** 388–400.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

A vaccine prepared from the Jeryl Lynn (B level) strain of mumps virus is available in the USA, and may be given in a dose of 0.5 mL by subcutaneous injection although combined vaccines are usually preferred.

Preparations

Ph. Eur.: Mumps Vaccine (Live);
USP 31: Mumps Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Parotiditis†; ***Braz.:*** Imovax Mumps†; ***Canad.:*** Mumpsvax†; ***Cz.:*** Pavivac; ***Denm.:*** Mumpsvax†; ***Ger.:*** Mumpsvax†; ***Gr.:*** Mumpsvax†; ***Ital.:*** Vaxipar†; ***Spain:*** Vac Antiparotiditis†; ***Switz.:*** Mumpsvax; ***USA:*** Mumpsvax; ***Venez.:*** Imovax Parotiditis†.

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV_1 during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al.* The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; **21:** 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107:** 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; **149:** 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al.* A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; **83:** 853–7.
2. O'Brien ME, *et al.* SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; **15:** 906–14.
3. Stanford JL, *et al.* Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; **44:** 224–7.
4. Patel PM, *et al.* An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; **44:** 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced.

1. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; **39:** 51–8.
2. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; **26:** 233–41.
3. Dalbeth N, *et al.* A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; **63:** 718–22.

Tuberculosis. ***IMMUNISATION.*** References.

1. von Reyn CF, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; **27:** 1517–20.
2. Waddell RD, *et al.* Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; **30** (suppl 3): S309–S315.
3. Vuola JM, *et al.* Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; **17:** 2351–5.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Inmunoglobulinas inespecíficas.

ATC — J06BA01; J06BA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy, must not have been treated with substances of human pituitary origin, and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is added to the plasma used. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. Multidose, but not single dose, preparations contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 5.0 to 7.2. The liquid preparation should be stored, protected from light, in a sealed, colourless, glass container. The freeze-dried preparation should be stored, protected from light, in an airtight, colourless, glass container.

Ph. Eur. 6.2 (Human Normal Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Normale ad Usum Intravenosum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG); other proteins may be present and the total protein content is not less than 3%. It contains IgG antibodies of normal subjects; the standard does not apply to products intentionally prepared to contain fragments or chemically modified IgG. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. It does not contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 4.0 to 7.4. Storage requirements are similar to those for Human Normal Immunoglobulin, except that the freeze-dried preparation is stored in an airtight container at a temperature not exceeding 25°.

USP 31 (Immune Globulin). A sterile solution of globulins that contains many antibodies normally present in human adult blood. It is prepared from pooled material (approximately equal quantities of blood, plasma, serum, or placentas) from not fewer than 1000 donors. It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It is intended for intramuscular injection. It contains glycine as a stabiliser, and a suitable preservative. It contains antibodies against diphtheria, measles, and poliomyelitis. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201. Intravenous immunoglobulin preparations should be used with caution in patients with renal impairment. Immunoglobulin products containing sucrose may be associated with an increased risk of inducing acute renal failure (see Effects on the Kidneys, below).

Antibody titres for some common pathogens can vary widely not only between products from different manufacturers, but also from lot to lot. Formulations of intravenous immunoglobulins should therefore not be regarded as equivalent.

◊ Reviews.

1. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. *Drug Safety* 1999; **21:** 171–85.
2. Wittstock M, *et al.* Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003; **50:** 172–5.
3. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; **17:** 241–51.
4. Ameratunga R, *et al.* Increased risk of adverse events when changing intravenous immunoglobulin preparations. *Clin Exp Immunol* 2004; **136:** 111–13.
5. Singh-Grewal D, *et al.* A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child* 2006; **91:** 651–4.

Effects on the blood. Adverse effects on the blood have occasionally been reported after intravenous use of normal immunoglobulin to increase the platelet count in patients with idiopathic thrombocytopenic purpura and in the management of other auto-immune diseases. Reduced platelet adhesiveness with multiple subcutaneous haematomas occurred in one patient.[1] Thrombotic events have occurred after intravenous use,[2-4] particularly in elderly subjects (sometimes fatal) suggesting that a rising platelet count during normal immunoglobulin treatment may represent a risk in patients with severe atherosclerotic disease.[2] However, a review of 34 patients over 60 years of age treated with normal immunoglobulin could not confirm the association.[5]

Haemolytic reactions, including a case of haemolytic disease of the newborn, have sometimes been noted[6,7] and passive transfer of anti-A, anti-B, or anti-D antibodies or active immunisation by blood group substances from normal immunoglobulin preparations has been implicated. It has been suggested[7] that blood phenotyping be carried out before treatment with normal immunoglobulin is started.

Transient neutropenia has occurred after use of normal immunoglobulin in patients with thrombocytopenic purpura, but the clinical significance of this effect has been disputed.[8-10]

1. Ljung R, Nilsson IM. High-dose intravenous gammaglobulin: a cautionary note. *Lancet* 1985; **i:** 467.
2. Woodruff RK, *et al.* Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; **ii:** 217–18.
3. Go RS, Call TG. Deep venous thrombosis of the arm after intravenous immunoglobulin infusion: case report and literature review of intravenous immunoglobulin-related thrombotic complications. *Mayo Clin Proc* 2000; **75:** 83–5.
4. Marie I, *et al.* Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. *Br J Dermatol* 2006; **155:** 714–21.
5. Frame WD, Crawford RJ. Thrombotic events after intravenous immunoglobulin. *Lancet* 1986; **ii:** 468.
6. Potter M, *et al.* ABO alloimmunisation after intravenous immunoglobulin infusion. *Lancet* 1988; **i:** 932–3.
7. Nicholls MD, *et al.* Haemolysis induced by intravenously-administered immunoglobulin. *Med J Aust* 1989; **150:** 404–6.
8. Majer RV, Green PJ. Neutropenia caused by intravenous immunoglobulin. *BMJ* 1988; **296:** 1262.
9. Veys PA, *et al.* Neutropenia following intravenous immunoglobulin. *BMJ* 1988; **296:** 1800.
10. Ben-Chetrit E, Putterman C. Transient neutropenia induced by intravenous immune globulin. *N Engl J Med* 1992; **326:** 270–1.

Effects on the kidneys. There have been occasional case reports of renal failure or impairment associated with the use of intravenous normal immunoglobulin.[1,2] The incidence of renal failure appears to be greatest with immunoglobulin products containing sucrose.[1,3] The FDA in the USA had issued a warning alerting physicians to the potential risks of acute renal failure associated with intravenous use of normal immunoglobulin products, particularly those containing sucrose.[4]

1. Orbach H *et al.* Intravenous immunoglobulin and the kidney—a two-edged sword. *Semin Arthritis Rheum* 2004; **34:** 593–601.
2. Itkin YM, Trujillo TC. Intravenous immunoglobulin-associated acute renal failure: case series and literature review. *Pharmacotherapy* 2005; **25:** 886–92.
3. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; **93:** 901–4.
4. Food and Drug Administration. Important drug warning (issued 24 September 1999). Available at: http://www.fda.gov/Cber/ltr/igivrenal.pdf (accessed 31/05/06)

Effects on the nervous system. Aseptic meningitis has been reported after intravenous use of normal immunoglobulin.[1-5]

Migraine, associated with intravenous immunoglobulin therapy in a patient on 2 occasions, did not recur after prophylaxis with propranolol was started.[6]

Hemiplegia has been reported in a 4-year-old child given intravenous immunoglobulin for immune thrombocytopenic purpura.[7]

1. Kato E, *et al.* Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988; **259:** 3269–71.
2. Casteels-Van Daele M, *et al.* Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990; **323:** 614–15.
3. Sekul EA, *et al.* Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; **121:** 259–62.
4. Picton P, Chisholm M. Aseptic meningitis associated with high dose immunoglobulin: case report. *BMJ* 1997; **315:** 1203–4.
5. Boyce TG, Spearman P. Acute aseptic meningitis secondary to intravenous immunoglobulin in a patient with Kawasaki syndrome. *Pediatr Infect Dis J* 1998; **17:** 1054–6.
6. Constantinescu CS, *et al.* Recurrent migraine and intravenous immune globulin therapy. *N Engl J Med* 1993; **329:** 583–4.
7. Tsiouris J, Tsiouris N. Hemiplegia as a complication of treatment of childhood immune thrombocytopenic purpura with intravenously administered immunoglobulin. *J Pediatr* 1998; **133:** 717.

Effects on the skin. Diffuse alopecia has been reported[1] in 3 women within 1 to 4 weeks of treatment with intravenous normal immunoglobulin. There have been reports[2,3] of severe and extensive eczema in elderly patients up to 3 weeks after receiving normal immunoglobulin intravenously. There has also been a report of cutaneous vasculitic rash on the face of a woman receiving intravenous normal immunoglobulin.[4] Severe cutaneous vasculitis has been reported in a patient who received intravenous normal immunoglobulin for type II mixed cryoglobulinaemia.[5] An erythematous eruption occurred on the hands and feet of a patient 3 days after completing a 5-day treatment course of normal immunoglobulin for chronic inflammatory demyelinating polyneuropathy;[6] the lesions resolved 2 to 3 weeks after completion of therapy. A similar eruption had occurred following normal immunoglobulin therapy in 5 previous occasions.

For mention of a patient with AIDS who developed erythema characteristic of fifth disease following intravenous normal immunoglobulin, see Infection, below.

1. Chan-Lam D, *et al.* Alopecia after immunoglobulin infusion. *Lancet* 1987; **i:** 1436.
2. Barucha C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. *BMJ* 1987; **295:** 1141.
3. Whittam LR, *et al.* Eczematous reactions to human immune globulin. *Br J Dermatol* 1997; **137:** 481–2.
4. Howse M, *et al.* Facial vasculitic rash associated with intravenous immunoglobulin. *BMJ* 1998; **317:** 1291.
5. Yebra M, *et al.* Severe cutaneous vasculitis following intravenous infusion of gammaglobulin in a patient with type II mixed cryoglobulinemia. *Clin Exp Rheumatol* 2002; **20:** 225–7.
6. Mutasim DF, Sheth PB. An eruption secondary to intravenous immunoglobulin therapy. *Cutis* 2002 **69:** 35–6, 38.

Hypersensitivity. Hypersensitivity reactions may occasionally occur after intramuscular or intravenous use of normal immunoglobulins particularly in hypogammaglobulinaemic or agammaglobulinaemic patients. Both immediate and late[1] reactions have occurred.

The IgA content of normal immunoglobulins can result in the development of IgE and IgG anti-IgA antibodies in immunodeficient patients with IgA deficiency. It has been suggested by some[2] that the IgE anti-IgA antibodies are responsible for anaphylaxis although others have disagreed.[3] Two patients who had reactions to conventional normal immunoglobulin preparations tolerated preparations with a low content of IgA.[2] Some manufacturers of normal immunoglobulin preparations recommend that they should not be used in patients with selective IgA deficiencies who have known antibody against IgA.

The IgE content of some preparations has also been suggested as a cause of hypersensitivity reactions[4] although this has been disputed.[5] Complement-activating IgG aggregates may also be involved although the anticomplementary activity of the products does not appear to be related to the incidence of adverse effects.[5]

1. Hachimi-Idrissi S, *et al.* Type III allergic reaction after infusion of immunoglobulins. *Lancet* 1990; **336:** 55.
2. Burks AW, *et al.* Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. *N Engl J Med* 1986; **314:** 560–4.
3. Hammarström L, Smith CIE. Anaphylaxis after administration of gamma globulin for hypogammaglobulinemia. *N Engl J Med* 1986; **315:** 519.
4. Tovo P-A, *et al.* IgE content of commercial intravenous IgG preparations. *Lancet* 1984; **i:** 458.
5. Newland AC, *et al.* IgE in intravenous IgG. *Lancet* 1984; **i:** 1406–7.

Infection. An association between use of certain intravenous immunoglobulin preparations and hepatitis C infections led to changes in manufacturing procedures and withdrawal of the affected products from the market.[1-3]

In addition, there has been a report[4] of a patient with AIDS who developed fifth disease (erythema infectiosum) after intravenous normal immunoglobulin treatment for infection with parvovirus. Paradoxically, there has also been a report[5] of life-threatening parvovirus B19 infection, resulting in pure red-cell aplasia and aggravation of hepatitis and fulminant disease, from the use of normal immunoglobulin to treat a patient with existing hepatic dysfunction caused by coxsackie B4 virus infection.

1. Quinti I, *et al.* Intravenous gammaglobulin may still infect patients. *BMJ* 1994; **308:** 856.
2. Bader J-M. HCV and Gammagard in France. *Lancet* 1994; **343:** 1628. Corrections. *ibid.*; **344:** 201 and 206.
3. Anonymous. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. *JAMA* 1994; **272:** 424–5.
4. French AL, *et al.* Fifth disease after immunoglobulin administration in an AIDS patient with parvovirus-induced red cell aplasia. *Am J Med* 1996; **101:** 108–9.
5. Hayakawa F, *et al.* Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002; **118:** 1187–9.

Interactions

Normal immunoglobulin may interfere with the immune response to live viral vaccines. Such vaccines should therefore be given at least 3 weeks before, or 3 months after, normal immunoglobulin. This does not apply to yellow fever vaccine for immunoglobulins prepared in the UK, nor for booster doses of oral poliomyelitis vaccines. Where such an interval is impractical for immunisation preceding foreign travel it may have to be ignored.

Poliomyelitis vaccine. For a study indicating that normal immunoglobulin has no effect on the antibody response to oral poliomyelitis vaccine, see p.2233.

Uses and Administration

Normal immunoglobulin is available as two distinct preparations and formulations. One type of injection (Human Normal Immunoglobulin (Ph. Eur. 6.2) and Immune Globulin (USP 31)) generally containing 16% of protein is used for passive immunisation, and sometimes also for primary antibody deficiencies, and should only be given intramuscularly. The second type of preparation is formulated for intravenous use (Human Normal Immunoglobulin for Intravenous Administration (Ph. Eur. 6.2)) and is used in disorders such as primary antibody deficiencies and idiopathic thrombocytopenic purpura; solutions generally contain about 3 to 6% of protein, although some may contain up to 12%.

Doses of normal immunoglobulin often appear confusing, being expressed variously in terms of weight (protein or immunoglobulin G content) or in terms of volume to be given, and the two do not always appear to correspond. It should be remembered that there may be differences between intravenous preparations of normal immunoglobulin including differing IgA content and IgG subclass distribution.

Normal immunoglobulin, being derived from the pooled plasma of blood donors, contains antibodies to bacteria and viruses currently prevalent in the general population; in the UK, and also in some other countries, typical antibodies present include those against hepatitis A, measles, mumps, rubella, and varicella. Normal immunoglobulin therefore may be used to provide passive immunisation against such diseases.

Normal immunoglobulin may be used to control outbreaks of **hepatitis A**, the recommended intramuscular dose for close contacts being 250 mg in those under 10 years of age and 500 mg in older children and adults. It may also be used for prophylaxis against hepatitis A in immunocompromised patients if their response to hepatitis A vaccine is unlikely to be adequate.

Normal immunoglobulin may be used to prevent or possibly modify an attack of **measles** in children and adults at special risk (such as those who are immunocompromised) but should be given as soon as possible after contact with measles. In the UK recommended doses, given intramuscularly, for the prevention of an attack are 250 mg for those under 1 year of age, 500 mg for those aged 1 to 2 years, and 750 mg for those aged 3 years and over; to modify an attack, recommended doses are 100 mg for those under 1 year of age and 250 mg for older children.

Normal immunoglobulin does not prevent **rubella** infection and is not recommended for the protection of pregnant women exposed to rubella; it should only be considered where termination of pregnancy is unacceptable. The dose is 750 mg by intramuscular injection.

Normal immunoglobulin may be used in the management of patients with **primary antibody deficiencies** such as congenital agammaglobulinaemia, hypogammaglobulinaemia, or **immunocompromised patients** including those with immunodeficiency syndromes; the immunoglobulin is given to provide protection against infectious diseases that such patients may suffer. The intramuscular preparation has been used but the intravenous route is usually preferred as it is less painful for the doses required. Alternatively, the subcutaneous route may be used. For intravenous infusion the dose, expressed in terms of weight (protein or immunoglobulin G content), is usually 400 to 800 mg/kg initially, then 200 mg/kg every 3 weeks adjusted as necessary according to trough-immunoglobulin concentrations; the maintenance dose is usually 200 to 800 mg/kg per month. In patients with secondary immunodeficiency syndromes, doses of 200 to 400 mg/kg every 3 to 4 weeks have been recommended. Other dosage regimens have been used. Subcutaneous doses are 200 to 500 mg/kg as an initial loading dose (divided over several days), followed by maintenance doses at repeated intervals to achieve a cumulative monthly dose of 400 to 800 mg/kg. When infused intravenously, normal immunoglobulin should always be given very carefully and slowly with gradual increases in the rate of infusion.

For prophylaxis of infection after **bone marrow transplantation**, normal immunoglobulin is given intravenously in a dose of 500 mg/kg weekly, adjusted according to response.

Intravenous infusion of normal immunoglobulin is also used to raise the platelet count in patients with **idiopathic thrombocytopenic purpura**. Doses of 400 mg/kg are given daily for 2 to 5 consecutive days. Alternatively, a dose of 800 to 1000 mg/kg may be given on day 1 and repeated on day 3 if necessary. Further doses may be given as necessary.

For **Kawasaki disease**, normal immunoglobulin (used with aspirin) is given intravenously in a dose of 1.6 to 2 g/kg in divided doses over 2 to 5 days, or 2 g/kg given as a single dose. Similar doses of intravenous normal immunoglobulin have been tried in a range of disorders believed to have an auto-immune origin. The precise mode of action of normal immunoglobulin in such disorders is unknown.

For the treatment of **Guillain-Barré syndrome**, normal immunoglobulin is given intravenously in a dose of 400 mg/kg for 5 consecutive days, repeated every 4 weeks if required.

Administration. Oral dosage with normal immunoglobulins has been proposed to reduce the incidence and severity of gastrointestinal infections, particularly in patients with defective immune systems including neonates. Although the main immunoglobulin secreted into the gastrointestinal tract in subjects with a normal immune system is IgA, which is not present in large quantities in commercial normal immunoglobulins, beneficial responses, especially in viral infections, have been reported after oral use. Systematic reviews have not, however, supported routine use of oral immunoglobulin for the prevention or treatment of gastrointestinal infections.[1-3] Preparations of immunoglobulin A are available in some countries and have been tried, mainly in bacterial gastrointestinal infections.[4,5]

1. Mohan P, Haque K. Oral immunoglobulin for the prevention of rotavirus infection in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
2. Mohan P, Haque K. Oral immunoglobulin for the treatment of rotavirus diarrhoea in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
3. Foster J, Cole M. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/03/05).
4. Tjellström B, *et al.* Oral immunoglobulin A supplement in treatment of Clostridium difficile enteritis. *Lancet* 1993; **341:** 701–2.
5. Hammarström V, *et al.* Oral immunoglobulin treatment in Campylobacter jejuni enteritis. *Lancet* 1993; **341:** 1036.

Blood disorders. Intravenous normal immunoglobulins are used in the treatment of symptomatic severe acute and chronic idiopathic thrombocytopenic purpura (p.1505). Other blood disorders in which normal immunoglobulins have been tried include agranulocytosis[1] and haemolytic disease of the newborn (p.2204), haemolytic anaemias (p.1043), red cell aplasia caused by parvovirus B19 infections (see under Passive Immunisation, below), thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies p.1076), and thrombocytopenia with a variety of causes.[2-10]

1. Fasth A. Immunoglobulin for neonatal agranulocytosis. *Arch Dis Child* 1986; **61:** 86–7.
2. Hoffman DM, *et al.* Human immunodeficiency virus-associated thrombocytopenia. *DICP Ann Pharmacother* 1989; **23:** 157–160.
3. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; **111:** 946–7.
4. Howrie DL, *et al.* Use of iv immune globulin for treatment of phenytoin-induced thrombocytopenia. *Clin Pharm* 1989; **8:** 734–7.
5. Landonio G, *et al.* HIV-related severe thrombocytopenia in intravenous drug users: prevalence, response to therapy in a medium-term follow-up, and pathogenic evaluation. *AIDS* 1990; **4:** 29–34.
6. Goulder P, *et al.* Intravenous immunoglobulin in virus associated haemophagocytic syndrome. *Arch Dis Child* 1990; **65:** 1275–7.
7. Larner AJ, *et al.* Life threatening thrombocytopenia in sarcoidosis: response to vincristine, human immunoglobulin, and corticosteroids. *BMJ* 1990; **300:** 317–19.
8. Ray JB, *et al.* Intravenous immune globulin for the treatment of presumed quinidine-induced thrombocytopenia. *DICP Ann Pharmacother* 1990; **24:** 693–5.
9. Salzman MB, Smith EM. Phenytoin-induced thrombocytopenia treated with intravenous immune globulin. *J Pediatr Hematol Oncol* 1998; **20:** 152–3.
10. Majluf-Cruz A, *et al.* Usefulness of a low-dose intravenous immunoglobulin regimen for the treatment of thrombocytopenia associated with AIDS. *Am J Hematol* 1998; **59:** 127–32.

Bowel disorders. Intravenous normal immunoglobulin may be beneficial[1-3] in inducing remission of Crohn's disease and ulcerative colitis and in antibiotic-associated or pseudomembranous colitis associated with *Clostridium difficile* infection.[4,5]

1. Rohr G, *et al.* Treatment of Crohn's disease and ulcerative colitis with 7S-immunoglobulin. *Lancet* 1987; **i:** 170.
2. Knoflach P, *et al.* Crohn disease and intravenous immunoglobulin G. *Ann Intern Med* 1990; **112:** 385–6.
3. Körber J, *et al.* A case of Crohn's disease with increased CD8 T-cell activation and remission during therapy with intravenous immunoglobulins. *Scand J Gastroenterol* 1998; **33:** 1113–17.
4. Leung DYM, *et al.* Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. *J Pediatr* 1991; **118:** 633–7.
5. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother* 2004; **53:** 882–4.

Epilepsy. Normal immunoglobulins have sometimes been of benefit[1-3] in the treatment of children with intractable epilepsy, including Lennox-Gastaut syndrome or West's syndrome, but a review of the literature found that few well controlled studies had been conducted,[4] and a Canadian evidence-based guideline recommended against its use.[5] Although a positive trend in favour of intravenous immunoglobulin therapy for refractory epilepsy was noted in one double-blind controlled study[6] involving 61 patients, the results were not considered to be statistically significant.

1. Ariizumi M, *et al.* High dose gammaglobulin for intractable childhood epilepsy. *Lancet* 1983; **ii:** 162–3.
2. Sandstedt P, *et al.* Intravenous gammaglobulin for post-encephalitic epilepsy. *Lancet* 1984; **ii:** 1154–5.
3. van Engelen BGH, *et al.* High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome: an add-on study. *Eur J Pediatr* 1994; **153:** 762–9.
4. Duse M, *et al.* Intravenous immune globulin in the treatment of intractable childhood epilepsy. *Clin Exp Immunol* 1996; **104** (suppl 1): 71–6.
5. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.
6. van Rijckevorsel-Harmant K, *et al.* Treatment of refractory epilepsy with intravenous immunoglobulins: results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994; **24:** 162–6.

Hypogammaglobulinaemia. See under Primary Antibody Deficiency, below.

Immunocompromised patients. Immunodeficiency states may arise from primary disorders of the immune system, or, more commonly, they are secondary to immunosuppressive therapy, HIV infection, or haematological malignancies. Premature neonates may have deficits in their immune systems due to their immaturity; placental transfer of maternal antibodies usually occurs after about 32 weeks of gestation. Such patients and neonates may be deficient in gammaglobulins and they could potentially benefit from the use of normal immunoglobulins to address their increased susceptibility to infection. For information on the use of immunoglobulins in specific conditions, see the following sections and under Neonatal Infection, below.

BONE MARROW TRANSPLANTATION. Normal immunoglobulin is used in patients undergoing allogeneic bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811) with the aim of decreasing the incidence of bacterial and of symptomatic CMV infection, and that of graft-versus-host disease. Prophylaxis and treatment of CMV infection and prophylaxis of graft-versus-host disease are the indications with most clinical support, although there have been few prospective, randomised, controlled studies and these have had small or heterogeneous populations and varying end-points.[1] Overall survival[2] or overall incidence of CMV infection[2,3] has not decreased. A combination of normal immunoglobulin and ganciclovir appears to improve the outcome of CMV pneumonia subsequent to bone marrow transplantation.[4] However, no patients treated with normal immunoglobulin alone survived and ganciclovir monotherapy may be equally effective, thus casting some doubt on the effectiveness of normal immunoglobulin.[1] Cytomegalovirus immunoglobulins (p.2208) may be more appropriate for the specific prophylaxis and treatment of CMV infections.

Intravenous immunoglobulin therapy has been found to be ineffective in preventing infections in patients receiving autologous bone marrow transplants[5] and may have contributed to an increased incidence of fatal hepatic veno-occlusive disease.

Normal immunoglobulin has been associated with a reduced frequency of acute graft-versus-host disease,[2] possibly as a result of a direct immunomodulatory effect, but this has only been found in one study, and there are no studies showing efficacy of normal immunoglobulin in chronic graft-versus-host disease.[1] Furthermore, there is some suggestion that extended use of normal immunoglobulin for graft-versus-host disease prevention may impair recovery of humoral immunity.[1] Overall, the role of normal immunoglobulin for graft-versus-host disease has yet to be clearly defined.

1. Sokos DR, *et al.* Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002; **8:** 117–30.
2. Sullivan KM, *et al.* Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990; **323:** 705–12.
3. Winston DJ, *et al.* Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. *Ann Intern Med* 1987; **106:** 12–18.
4. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
5. Wolff SN, *et al.* High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy: a study of the American Bone Marrow Transplant Group. *Ann Intern Med* 1993; **118:** 937–42.

MALIGNANCIES. Hypogammaglobulinaemia and the effects of treatment may increase the susceptibility to infection of patients with *chronic lymphocytic leukaemia*.[1] In a study[2] of 81 patients with chronic lymphocytic leukaemia considered to be at an increased risk of infection, intravenous normal immunoglobulin 400 mg/kg given every 3 weeks for one year reduced the incidence of bacterial infection compared with saline placebo. The incidence of viral and fungal infections was not affected. A study in 34 patients[3] suggested that a dose of normal immunoglobulin 250 mg/kg per month was adequate for routine prophylaxis in most patients. Beneficial effects on infection rates have been reported in patients with *multiple myeloma* receiving normal immunoglobulins.[4]

1. Wierda WG. Immunologic monitoring in chronic lymphocytic leukaemia. *Curr Oncol Rep* 2003; **5:** 419–25.
2. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. *N Engl J Med* 1988; **319:** 902–7.
3. Chapel H, *et al.* Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994; **88:** 209–12.
4. Chapel HM, *et al.* Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. *Lancet* 1994; **343:** 1059–63.

PRIMARY ANTIBODY DEFICIENCY. There are 3 major forms of primary antibody deficiency: X-linked agammaglobulinaemia (XLA, Bruton's agammaglobulinaemia), common variable immunodeficiency (CVID) which includes IgG subclass and specific antibody deficiencies, and selective IgA deficiency. The disease is characterised by a wide range of infective complications as well as auto-immune disorders. Management is by replacement therapy with normal immunoglobulin accompanied by appropriate antimicrobial therapy for breakthrough infections.[1-4] Immunisation against infection is of no value and is contra-indicated for live viral vaccines.

Normal immunoglobulin was traditionally given by the intramuscular route. However, the maximum dose that could be reasonably given by this route was 25 mg/kg weekly, and it was therefore only satisfactory for patients with mild disease.[5] The introduction of intravenous preparations of normal immunoglobulin allowed high doses to be used in those with severe disease. This route should therefore be used for all patients with XLA and for patients with CVID who have more than mild disease.[1] The use of intravenous normal immunoglobulin in IgG subclass deficiency, with or without IgA deficiency, or in specific antibody deficiency is successful, though less well established. The dose and frequency of administration of intravenous normal immunoglobulin is variable and should be adjusted to prevent breakthrough infection. Most patients require 200 to 600 mg/kg every 2 or 3 weeks to maintain optimum protection.[5] In one study,[6] doses of between 260 and 1120 mg/kg every 3 weeks were necessary to maintain residual serum IgG concentrations above 500 mg/dL. These doses were found to be effective in reducing the incidence of severe acute bacterial infections and pulmonary insufficiency in children with XLA. Surgical procedures should be covered with additional normal immunoglobulin and appropriate prophylactic antibacterials. Home treatment with intravenous normal immunoglobulin has been used successfully in several countries in both adults and children.[5,7-10] Adverse reactions have been few and generally mild.[5,8,9] They are most likely to occur during the first infusion and during intercurrent illness, and may be precipitated by a high infusion rate.[10] Long-term treatment of children with antibody deficiencies with intravenous normal immunoglobulin has been shown to lead to normal growth and similar rates of infection to those found in non-immunodeficient children.[11]

Immunoglobulin replacement can alternatively be given by subcutaneous infusion as an alternative to intravenous therapy.[2,4,12,13] The intraventricular route has been of benefit in some patients with echovirus encephalitis.[5,14]

1. Carrock Sewell WA, *et al.* Therapeutic strategies in common variable immunodeficiency. *Drugs* 2003; **63:** 1359–71.
2. Schwartz SA. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am* 2000; **47:** 1355–69.
3. Empson M, *et al.* The assessment and management of primary antibody deficiency. *N Z Med J* 2004; **117:** U914.
4. Durandy A, *et al.* Immunoglobulin replacement therapy in primary antibody deficiency diseases—maximizing success. *Int Arch Allergy Immunol* 2005; **136:** 217–29.
5. Spickett GP, *et al.* Primary antibody deficiency in adults. *Lancet* 1991; **337:** 281–4.
6. Quartier P, *et al.* Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; **134:** 589–96.
7. Ochs HD, *et al.* Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. *Lancet* 1986; **i:** 610–11.
8. Ryan A, *et al.* Home intravenous immunoglobulin therapy for patients with primary hypogammaglobulinaemia. *Lancet* 1988; **ii:** 793.
9. Kobayashi RH, *et al.* Home self-administration of intravenous immunoglobulin therapy in children. *Pediatrics* 1990; **85:** 705–9.
10. Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. *BMJ* 1994; **308:** 581–5.
11. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93. *Arch Dis Child* 1996; **74:** 527–30.
12. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 2007; **21:** 105–16.
13. Helbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. *Br J Hosp Med* 2007; **68:** 206–10.
14. Erlendsson K, *et al.* Successful reversal of echovirus encephalitis in x-linked hypogammaglobulinemia by intraventricular administration of immunoglobulin. *N Engl J Med* 1985; **312:** 351–30.

Kawasaki disease. Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood, occurs mainly in children under 5 years of age. It is epidemic and endemic worldwide but is a particular problem in Japan. Kawasaki disease presents with high fever which persists for at least 5 days and may be followed by bilateral conjunctivitis, changes in the oropharyngeal mucosa, signs of vasculitis in the extremities, rash, and cervical lymphadenopathy. The major complications of Kawasaki disease are cardiac effects including coronary artery aneurysm, aortic or mitral incompetence, myocarditis, and pericarditis with effusion. The cause of the disease is unknown, although an infective aetiology has been suggested. Early diagnosis, expert cardiac assessment, and immediate treatment are essential for improved outcome.

Treatment aims to reduce inflammation, particularly in the coronary arterial wall and myocardium, and therefore prevent the development of cardiac complications. Long-term antiplatelet treatment is given as necessary to prevent coronary thrombosis.

Initial treatment is with aspirin and normal immunoglobulin.[1,2] Despite the anti-inflammatory and antiplatelet properties of aspirin it does not appear to lower the incidence of coronary abnormalities in Kawasaki disease when used alone; however, high-dose aspirin and normal immunoglobulin appear to possess an additive anti-inflammatory effect when used together and a decreased incidence of coronary-artery abnormalities has been found after such a combination as compared with aspirin alone. Treatment should begin if possible within 10, and preferably within 7, days of the onset of illness. Treatment before day 5 appears to offer no advantage in preventing cardiac sequelae than treating from days 5 to 7, but it may be associated with an increased need for re-treatment with normal immunoglobulin. Treatment should be given to children presenting after the tenth day of illness if they have either persistent unexplained fever or aneurysms with ongoing systemic inflammation.[2]

Normal immunoglobulin has been given by intravenous infusion in divided doses over 2 to 5 days, but high-dose administration as a single dose is now recommended; a meta-analysis[3] and a systematic review[4] have concluded that single-dose therapy is associated with a lower incidence of coronary abnormalities after 30 days than multiple-dose treatment. The optimum dosage and duration of treatment with aspirin is not yet established, but the usual practice is to use an anti-inflammatory regimen until the fever has settled and then to convert to an antithrombotic regimen. A few patients fail to respond to treatment with aspirin and normal immunoglobulin. A small study[5] suggested that re-treatment with normal immunoglobulin may be considered for those with persistent or recurring fever.

The use of corticosteroids remains controversial.[1] They have been given in some centres[6] but since the introduction of immunoglobulin therapy they have not been routinely used as there is a risk that they may exacerbate coronary artery aneurysms. Nevertheless, their use has received renewed attention; randomised studies comparing the adjunctive use of corticosteroids with standard therapy alone have suggested they may be of benefit.[7,8] Alternative suggested drugs for patients refractory to normal immunoglobulin include ulinastatin,[9] which has been used for adjunctive therapy in Japan, but its effectiveness remains currently unproven. Abciximab has been used to treat patients with large coronary aneurysms; in one study,[10] patients given abciximab in addition to standard therapy showed a greater regression in aneurysm diameter. Other treatments under investigation include infliximab[11] in patients unresponsive to initial normal immunoglobulin and the use of cyclophosphamide with corticosteroids in particularly refractory cases.[2]

Long-term management. Aspirin should be continued for 6 to 8 weeks after the onset of illness and then stopped if there are no coronary abnormalities.[1,2] Some practitioners use aspirin and dipyridamole as antithrombotic therapy although it is not known whether this provides benefit over aspirin alone. Dipyridamole may be used as an alternative antithrombotic agent for patients who cannot tolerate aspirin. Aspirin is usually continued for at least one year if coronary abnormalities are present and should be continued indefinitely if coronary aneurysms persist. Anticoagulation with warfarin or heparin in addition to aspirin may be necessary in some patients such as those with giant or multiple aneurysms.

1. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet* 2004; **364:** 533–44.
2. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114:** 1708–33. Correction. *ibid.* 2005; **115:** 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 25/05/06) Also published in *Circulation* 2004; **110:** 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
3. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; **96:** 1057–61.
4. Oates-Whitehead RM, *et al.* Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/03/05).
5. Sundel RP, *et al.* Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993; **123:** 657–9.
6. Shinohara M, *et al.* Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999; **135:** 465–9.
7. Sundel RP, *et al.* Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003; **142:** 611–16.
8. Okada Y, *et al.* Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003; **143:** 363–7.
9. Zaitsu M, *et al.* Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. *J Infect Dis* 2000; **181:** 1101–9.
10. Williams RV, *et al.* Does abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Abstract: *Pediatrics* 2002; **109:** 132. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/1/e4 (accessed 24/03/05)
11. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.

Kidney disorders. Treatment with normal immunoglobulin has been of benefit in some patients with haemolytic-uraemic syndrome and in those with lupus nephritis (see under Musculoskeletal and Nerve Disorders, below). For mention of the use of normal immunoglobulin in IgA nephropathy, see Glomerular Kidney Disease, p.1504.

Musculoskeletal and nerve disorders. High-dose intravenous normal immunoglobulin has been tried with some benefit in various disorders of the nerves, muscles, joints, and connective tissues which may have an auto-immune basis.[1] These include multiple sclerosis,[2-4] chronic inflammatory demyelinating polyneuropathy,[5,6] polymyositis and dermatomyositis,[7-12] myasthenia gravis,[13-17] stiff-man syndrome,[18-22] chronic systemic juvenile arthritis,[23-25] SLE[26] including lupus nephritis,[27] Guillain-Barré syndrome (see below), and motor neurone disease (see also below). Guidelines issued by an expert committee in Canada[28] included recommendations on the use and dose of normal immunoglobulin for acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis and polymyositis, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome and myasthenia gravis, multifocal motor neuropathy, multiple sclerosis, opsoclonus-myoclonus, neuropsychiatric disorders associated with streptococcal infections in children, short-term management of Rasmussen's encephalitis, and stiff man syndrome.

1. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; **291:** 2367–75.
2. Fazekas F, *et al.* Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; **349:** 589–93.
3. Hommes OR, *et al.* Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004; **364:** 1149–56.
4. Achiron A, *et al.* Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004; **61:** 1515–20.
5. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002; **59** (suppl 6): S13–S21.
6. Brannagan TH. Intravenous gammaglobulin (IVIg) for treatment of CIDP and related immune-mediated neuropathies. *Neurology* 2002; **59** (suppl 6): S33–S40.
7. Cherin P, *et al.* Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. *Am J Med* 1991; **91:** 162–8.
8. Lang BA, *et al.* Treatment of dermatomyositis with intravenous gammaglobulin. *Am J Med* 1991; **91:** 169–72.
9. Dalakas MC, *et al.* A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; **329:** 1993–2000.
10. Brownell AKW. Intravenous immune globulin for dermatomyositis. *N Engl J Med* 1994; **330:** 1392.
11. Collet E, *et al.* Juvenile dermatomyositis: treatment with intravenous gammaglobulin. *Br J Dermatol* 1994; **130:** 231–4.
12. Cherin P, *et al.* Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum* 2002; **46:** 467–74.
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14. Jongen JLM, *et al.* High-dose intravenous immunoglobulin therapy for myasthenia gravis. *J Neurol* 1998; **245:** 26–31.
15. Howard JF. Intravenous immunoglobulin for the treatment of acquired myasthenia gravis. *Neurology* 1998; **51** (suppl 5): S30–S36.
16. Selcen D, *et al.* High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. *Pediatr Neurol* 2000; **22:** 40–3.
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19. Amato AA, *et al.* Treatment of stiff-man syndrome with intravenous immunoglobulin. *Neurology* 1994; **44:** 1652–4.
20. Barker RA, Marsden CD. Successful treatment of stiff man syndrome with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1997; **62:** 426–7.
21. Khanlou H, Eiger G. Long-term remission of refractory stiff-man syndrome after treatment with intravenous immunoglobulin. *Mayo Clin Proc* 1999; **74:** 1231–2.
22. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; **345:** 1870–6.
23. Groothoff JW, van Leeuwen EF. High dose intravenous gammaglobulin in chronic systemic juvenile arthritis. *BMJ* 1988; **296:** 1362–3.
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25. Uziel Y, *et al.* Intravenous immunoglobulin therapy in systemic onset juvenile rheumatoid arthritis: a followup study. *J Rheumatol* 1996; **23:** 910–18.
26. Francioni C, *et al.* Long term IV Ig treatment in systemic lupus erythematosus. *Clin Exp Rheumatol* 1994; **12:** 163–8.
27. Lin C-Y, *et al.* Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin. *Nephron* 1989; **53:** 303–10.
28. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; **21** (suppl 1): S57–S107.

GUILLAIN-BARRÉ SYNDROME. Guillain-Barré syndrome[1] (acute idiopathic inflammatory polyneuropathy; acute idiopathic demyelinating neuropathy; acute infectious polyneuropathy) may follow an infection or, more rarely, immunisation, but very often no predisposing factor can be identified. An association with infection with *Campylobacter jejuni* has been suggested,[2] but the syndrome is also commonly associated with infection with CMV, Epstein-Barr virus, and *Mycoplasma pneumoniae*.[1] Reversible demyelination results in pain and progressive flaccid paralysis. An auto-immune aetiology seems likely. Severely affected patients require cardiovascular monitoring and respiratory support if respiratory muscles are affected or autonomic instability is present. Corticosteroids have been given but are generally considered to be of little value[3] (see Polyneuropathies, p.1511). Plasma exchange (see p.1076) is effective if given early,[4] but is not universally available and is not suitable for all patients. A systematic review[5] has concluded that use of normal immunoglobulins is at least as effective as plasma exchange, but that there is no advantage from combining the two forms of treatment. Deterioration has also been noted in some patients after immunoglobulin therapy,[6,7] although one study[8] found that the incidence of relapse was greater after plasma exchange than after normal immunoglobulin.

1. Kuwabara S. Guillain Barré syndrome: epidemiology, pathophysiology and management. *Drugs* 2004; **64:** 597–610.
2. Rees JH, *et al.* Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med* 1995; **333:** 1374–9.
3. Hughes RAC, van der Meché FGA. Corticosteroids for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 10/06/08).
4. Raphaël JC, *et al.* Plasma exchange for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 29/03/05).
5. Hughes RAC, *et al.* Intravenous immunoglobulin for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 10/09/08).
6. Irani DN, *et al.* Relapse in Guillain-Barré syndrome after treatment with human immune globulin. *Neurology* 1993; **43:** 872–5.
7. Castro LHM, Ropper AH. Human immune globulin infusion in Guillain-Barré syndrome: worsening during and after treatment. *Neurology* 1993; **43:** 1034–6.
8. Romano JG, *et al.* Relapses in the Guillain-Barré syndrome after treatment with intravenous immune globulin or plasma exchange. *Muscle Nerve* 1998; **21:** 1327–30.

MOTOR NEURONE DISEASE. Several studies and a systematic review have shown normal immunoglobulins to be of benefit in the treatment of multifocal motor neuropathy, a form of motor neurone disease (p.2380) associated with anti-GM_1 antibody formation.[1-7] In most patients, however, improvement has to be maintained with periodic infusion and some become less responsive to therapy over time, requiring higher doses. A retrospective study[8] of 10 patients with multifocal motor neuropathy treated with normal immunoglobulins showed that while the initial response could be maintained for several years, efficacy decreased during prolonged treatment even when doses were progressively adjusted. During the first few years of therapy, increased dosage restored the effectiveness of normal immunoglobulins, but was found to be less able to do so later in follow up.

1. Van den Berg LH, *et al.* Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; **59:** 248–52.
2. Meucci N, *et al.* Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1997; **63:** 765–9.
3. Van den Berg LH, *et al.* The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; **121:** 421–8.
4. Ellis CM, *et al.* Use of human intravenous immunoglobulin in lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999; **67:** 15–19.
5. Federico P, *et al.* Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; **55:** 1256–62.
6. Léger JM, *et al.* Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; **124:** 145–53.
7. van Schaik IN, *et al.* Intravenous immunoglobulin for multifocal motor neuropathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/02/06).
8. Terenghi F, *et al.* How long is IVIg effective in multifocal motor neuropathy? *Neurology* 2004; **62:** 666–8.

Neonatal disorders. ***HAEMOLYTIC DISEASE OF THE NEWBORN.*** For a discussion of haemolytic disease of the newborn and its management, including the use of intravenous immunoglobulin as an alternative to exchange transfusions in affected pregnancies, see p.2204.

NEONATAL INFECTION. Sepsis is a serious problem in premature infants despite appropriate antimicrobial therapy. Preterm infants are born with low serum-immunoglobulin concentrations which decrease over the next several weeks of life. There is also a deficiency of antibodies to specific organisms such as group B streptococci, *Staphylococcus epidermidis*, and *Escherichia coli*.

Some, but not all, studies suggest that prophylactic use of intravenous normal immunoglobulin in premature infants shortly after birth can decrease the incidence of septicaemia.[1] Aspects of the methodology of these studies have, however, been criticised[2] and a systematic review[3] concluded that prophylactic use of intravenous immunoglobulin for prevention of infection in preterm or low birth-weight neonates was of at best marginal benefit only, and of no benefit in preventing sepsis, and did not recommend routine use. Some benefit has been seen after use of intravenous immunoglobulin to treat infants with suspected sepsis[1] and it may improve the response to antibacterials,[4] although a further systematic review[5] found insufficient evidence to support routine use in infants with suspected, or subsequently proved, neonatal infection.

The optimum dosage of intravenous immunoglobulin is not established. A prophylactic dose of 500 mg/kg on admission repeated every 1 to 2 weeks has been suggested for units where infection is common in very low birth-weight infants.[1] Others have suggested adjusting the dose to maintain a specified serum-immunoglobulin concentration. Alternatively, normal immunoglobulin could be given only to infants with immunoglobulin concentrations below a certain level, or be reserved for immediate use in those who become ill with suspected sepsis.[1]

Normal immunoglobulin cannot protect against all types of infection. Normal immunoglobulin preparations from different manufacturers may have, for a specific pathogen, differing levels of specific antibody and differing levels of functional activity or there may be lot-to-lot variability in functional activity for normal immunoglobulin from a specific manufacturer. Such variability, resulting in low concentrations of functional antibodies in the 4 batches of immunoglobulins used in the National Institute of Child Health Study,[6] was held responsible for the lack of demonstrable effectiveness of immunoglobulins in that study, one of the largest to date.

1. Whitelaw A. Treatment of sepsis with IgG in very low birthweight infants. *Arch Dis Child* 1990; **65:** 347–8.
2. Noya FJD, Baker CJ. Intravenously administered immune globulin for premature infants: a time to wait. *J Pediatr* 1989; **115:** 969–71.
3. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
4. Christensen RD, *et al.* Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991; **118:** 606–14.
5. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
6. Fanaroff AA, *et al.* A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birthweight infants. *N Engl J Med* 1994; **330:** 1107–13.

Neuropsychiatric disorders. Benefit has been demonstrated from plasma exchange or intravenous immunoglobulin in children with exacerbations of obsessive-compulsive disorder or tic disorders including Tourette's syndrome associated with streptococcal infection.[1] These results suggested that these disorders may respond to immunomodulatory therapy in a subgroup of patients with paediatric auto-immune neuropsychiatric disorders associated with streptococcal infections (PANDAS), believed to be due to cross-reaction of antistreptococcal antibodies with neural tissue. In a double-blind, placebo-controlled study[2] of the use of normal immunoglobulins in 30 patients with tic disorders, despite initial improvement compared with placebo over 8 weeks no significant differences were found in the severity of obsessions and compulsions beyond this time.

1. Perlmutter SJ, *et al.* Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; **354:** 1153–8.
2. Hoekstra PJ, *et al.* Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry* 2004; **65:** 537–42.

Passive immunisation. ***CMV INFECTION.*** See Bone Marrow Transplantation, under Immunocompromised Patients, above.

HEPATITIS C. In a randomised, placebo-controlled study[1] in seronegative sexual partners of patients positive for antibody to hepatitis C, normal immunoglobulin given intramuscularly every 2 months was found to significantly reduce the incidence of subsequent seroconversion. One of 450 subjects who received normal immunoglobulin became seropositive during follow-up compared with 6 of 449 who had received placebo.

1. Piazza M, *et al.* Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin: a randomized controlled trial. *Arch Intern Med* 1997; **157:** 1537–44.

PARVOVIRUS B19 INFECTION. Persistent infection with human parvovirus B19 can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients. Normal immunoglobulins contain antibodies able to neutralise parvovirus B19 and have been used in various groups of infected patients.[1] Resolution of anaemia and clearance of parvovirus B19 from the circulation have been reported after use of normal immunoglobulin in a patient who had had red cell aplasia for 10 years.[2] Normal immunoglobulin was given by intravenous infusion in a dose of 400 mg/kg daily for 10 days and then periodically for several months. Successful treatment of anaemia due to parvovirus B19-induced red cell aplasia with plasmapheresis and intravenous immunoglobulin has been described in a liver transplant recipient.[3] Efficacy has also been found in recipients of other solid-organ transplants including heart, kidney, and lung.[1] Clearance of parvovirus B19 from the circulation has been reported in patients who also have AIDS, but the presence of concomitant opportunistic infections may prevent resolution of the anaemia.[4,5]

Normal immunoglobulin given to patients with parvovirus B19-associated chronic fatigue syndrome has also resulted in clearance of the virus from the circulation and resolution of symptoms.[6,7]

Beneficial responses to intravenous immunoglobulin have also been reported in a few patients with parvovirus B19 infections associated with vasculitic syndromes.[8,9]

1. Mouthon L, *et al.* Intravenous immunoglobulins in autoimmune- or parvovirus B19-mediated pure red-cell aplasia. *Autoimmun Rev* 2005; **4:** 264–9.
2. Kurtzman G, *et al.* Pure red-cell aplasia of 10 years' duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy. *N Engl J Med* 1989; **321:** 519–23.
3. Ramage JK, *et al.* Parvovirus B19-induced red cell aplasia treated with plasmapheresis and immunoglobulin. *Lancet* 1994; **343:** 667–8.
4. Frickhofen N, *et al.* Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990; **113:** 926–33.
5. Bowman CA, *et al.* Red cell aplasia associated with human parvovirus B19 and HIV infection: failure to respond clinically to intravenous immunoglobulin. *AIDS* 1990; **4:** 1038–9.
6. Kerr JR, *et al.* Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003; **36:** e100–e106. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/374666 (accessed 15/07/08)
7. McGhee SA, *et al.* Persistent parvovirus-associated chronic fatigue treated with high dose intravenous immunoglobulin. *Pediatr Infect Dis J* 2005; **24:** 272–4.
8. Finkel TH, *et al.* Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; **343:** 1255–8.
9. Viguier M, *et al.* Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. *N Engl J Med* 2001; **344:** 1481–2.

TOXIC SHOCK SYNDROME. For a discussion of toxic shock syndrome and its treatment, including reference to clinical improvement after administration of intravenous normal immunoglobulins, see p.196.

Pregnancy. Fetal loss has been attributed in some cases to the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin) in the mother. Successful pregnancy outcome has been reported after use of intravenous normal immunoglobulin during pregnancy to a few such women.[1]

1. Triolo G, *et al.* IVIG in APS pregnancy. *Lupus* 2004; **13:** 731–5.

Skin disorders. Normal immunoglobulins have been tried in a few patients with blistering skin diseases.[1-3] The usual treatment for pemphigus and pemphigoid is with systemic corticosteroids; normal immunoglobulins in high doses have produced generally transient improvement when used alone,[4] although corticosteroid-sparing effects have been reported.[5,6] There have been case reports of patients with severe epidermolysis bullosa acquisita responding to therapy with high-dose intravenous immunoglobulins.[7,8] Studies have been conducted into the use of high-dose normal immunoglobulin for the treatment of other blistering conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.[9] One retrospective analysis[10] of 48 consecutive cases of toxic epidermal necrolysis found a beneficial effect with survival in 42 patients. In contrast, a prospective open study[11] in 34 consecutive patients admitted to hospital with Stevens-Johnson syndrome or toxic epidermal necrolysis suggested that normal immunoglobulin might actually be associated with an increase in mortality. Further retrospective analyses, however, did find a reduction in mortality in 16 consecutive patients admitted with toxic epidermal necrolysis[12] and in 7 children with Stevens-Johnson syndrome.[13] Normal immunoglobulin has also produced benefit in patients with pyoderma gangrenosum.[14-17]

Clinical benefit was noted in 9 of 10 patients with auto-immune chronic urticaria who were given a 5-day course of intravenous immunoglobulins, 2 of whom had prolonged remission over 3 years of follow-up.[18] Benefit has also occurred after intravenous immunoglobulin therapy for atopic dermatitis[19] and psoriasis.[20]

1. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140:** 865–74.
2. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003; **139:** 1051–9.
3. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006; **6:** 557–78.
4. Godard W, *et al.* Bullous pemphigoid and intravenous gammaglobulin. *Ann Intern Med* 1985; **103:** 965.
5. Beckers RCY, *et al.* Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. *Br J Dermatol* 1995; **133:** 289–93.
6. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; **45:** 825–35.
7. Mohr C, *et al.* Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol* 1995; **132:** 824–6.
8. Gourgiotou K, *et al.* Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol* 2002; **16:** 77–80.
9. Mittmann N, *et al.* Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Am J Clin Dermatol* 2006; **7:** 359–68.
10. Prins C, *et al.* Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003; **139:** 26–32.
11. Bachot N, *et al.* Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; **139:** 33–6.
12. Trent JT, *et al.* Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. *Arch Dermatol* 2003; **139:** 39–43.
13. Metry DW, *et al.* Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003; **112:** 1430 6.
14. Dirschka T, *et al.* Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998; **39:** 789–90.
15. Hagman JH, *et al.* The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosum. *J Dermatol Treat* 2001; **12:** 19–22.
16. Dobson CM, *et al.* Superficial granulomatous pyoderma treated with intravenous immunoglobulin. *J Am Acad Dermatol* 2003; **48:** 456–60.
17. Cummins DL, *et al.* Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; **157:** 1235–9.
18. O'Donnell BF, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138:** 101–6.
19. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002; **27:** 3–7.
20. Gurmin V, *et al.* Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *Br J Dermatol* 2002; **147:** 554–7.

Preparations

Ph. Eur.: Human Normal Immunoglobulin; Human Normal Immunoglobulin for Intravenous Administration;
USP 31: Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Beriglobina; Citax F; Endobulin; Flebogamma; Gamimune†; Gammaglobulina; IgG; Isiven†; Pentaglobin; Sandoglobulina†; Seroglubin; ***Austral.:*** Intragam; Intraglobin†; Octagam; Sandoglobulin; ***Austria:*** Beriglobin; Endobulin; Gamma-Venin†; Gammabulin; Gammagard; Gammanorm; Intraglobin; Octagam; Pentaglobin; Sandoglobulin†; Subcuvia; Venimmun N; ***Belg.:*** Gammagard SD; Multigam; Octagam; Sandoglobuline; Subcuvia; Vivaglobin; ***Braz.:*** Armoglobulina; Beriglobina; Blauimuno†; Gama Venina; Gamimune†; Octagam†; Sandoglobulina†; Venimmuna; Vigam†; ***Canad.:*** Baygam†; Gamastan; Gamimune N†; Gammagard; Gamunex; Iveegam; ***Chile:*** Beriglobina P; Flebogamma; Gamimune N†; Ig Vena N; Octagam†; Sandoglobulina†; ***Cz.:*** Biaven†; Endobulin; Flebogamma; Gamimune N†; Gamma-Venin†; Gammagard; Gammanorm; Gamunex; Intraglobin F†; Kiovig; Octagam; Pentaglobin; Subcuvia; Venimmun N; Vivaglobin; ***Denm.:*** Beriglobin; Endobulin; Gammagard; Gammaglobulin†; Gammanorm; Gammonativ†; Octagam; Sandoglobulin; Subcuvia; ***Fin.:*** Endobulin; Gammagard; Gammaglobulin†; Gammanorm; Nanogam; Octagam; Subcuvia; Venogamma†; ***Fr.:*** Endobuline; Gammagard; Octagam; Subcuvia; Tegeline; Vivaglobin; ***Ger.:*** Beriglobin; Endobulin; Flebogamma; Gamma-Venin†; Gammagard; Gammanorm; Gammonativ†; Gamunex; Intraglobin†; Intratect; Octagam; Pentaglobin; Polyglobin; Sandoglobulin; Subcuvia; Venimmun†; Vivaglobin; ***Gr.:*** Flebogamma; Gamma-Venin P; Gammagard; Intraglobin F; Kiovig; Octagam; Pentaglobin; Sandoglobuline; Subcuvia; Vivaglobin; ***Hong Kong:*** Flebogam-

ma; Gammagard; Globuman†; Intraglobin F; Octagam; Pentaglobin; Venoglobulin-S†; ***Hung.:*** Gammagard; Gammanorm; Humaglobin; Intratect; Octagam; Pentaglobin; Vivaglobin; ***India:*** Gamafine; ***Indon.:*** Gamimune N; Gammaraas; ***Irl.:*** Intraglobin; ***Israel:*** Beriglobin P; Endobulin†; Flebogamma; Gammagard†; Intraglobin F; Omr-IgG; Sandoglobulin; Venoglobulin; Vigam; ***Ital.:*** Biaven; Endobulin; Flebogamma; Gamma-Venin P†; Gammagard; Globuman†; Haimaven†; Ig Gamma†; Ig Vena; Intraglobin; Isiven; Pentaglobin; Sandoglobulina; Uman-Gamma†; Venimmun†; ***Jpn:*** Venilon; Venoglobulin; ***Malaysia:*** Flebogamma; Gammagard†; Globuman†; Intraglobin F†; IV-Globulin; Pentaglobin†; Venoglobulin-S†; Vigam; ***Mex.:*** Beriglobina P; Gamma-Venin P; Gammagard†; Isiven†; Octagam; Pentaglobin; Sandoglobulina; Seroglubin†; Vigam; ***Neth.:*** Endobuline†; Flebogamma; Gammagard; Gammanorm; GammaQuin; Ivegam; Octagam; Subcuvia; Vivaglobin; ***Norw.:*** Gammaglobulin†; Gammanorm; Octagam; ***NZ:*** Intragam; Octagam; Sandoglobulin; ***Philipp.:*** Gamimune N; Gammagard; IV-Globulin S; ***Pol.:*** Endobulin; Gamma-Globulina; Gammagard; Intraglobin F; Intratect; Kiovig; Pentaglobin; Sandoglobulin; Subcuvia; Venimmun; ***Port.:*** Flebogamma; Gammagard; Gammanorm; Gamunex; Globuman†; Ig Vena; Octagam; Sandoglobulina; Subcuvia; Vivaglobin; ***Rus.:*** Gamimune N (Гамимун Н); Humaglobin (Хумаглобин)†; Immunovenin (Иммуновенин)†; Octagam (Октагам); ***S.Afr.:*** Beriglobin; Endobulin†; Intragam; Intraglobin F; Pentaglobin; Polygam; ***Singapore:*** Flebogamma; Gammagard†; Intraglobin F; Pentaglobin; Venoglobulin†; Vigam†; ***Spain:*** Beriglobina P; Endobulin; Flebogamma; Gammagard; Gammaglobulina; Globuman†; Octagamocta; ***Swed.:*** Beriglobin; Endobulin; Gammagard; Gammanorm; Gammonativ; Octagam; Polyglobin†; Subcuvia; Xepol; ***Switz.:*** Beriglobin; Endobulin; Gammagard; Globuman; Intraglobin F; Octagam; Pentaglobin; Redimune; ***Thai.:*** Flebogamma; Gammaraas; Globuman†; Ig Vena; Intraglobin; Octagam; Pentaglobin; Venoglobulin-S†; Vigam; ***Turk.:*** Biseko; Endobulin; Flebogamma; Gamimune N; Gammar; Globuman; IG Vena NIV; Intraglobin; Isiven; Octagam; Pentaglobin; Subcuvia; Tegeline; Vigam; ***UK:*** Flebogamma; Gammabulin†; Gammagard; Kiovig; Octagam; Sandoglobulin; Subcuvia; Subgam; Vigam; Vivaglobin; ***USA:*** Carimune; Flebogamma; Gamastan; Gamimune N†; Gammagard; Gammar-P†; Gamunex; Iveegam†; Octagam; Panglobulin†; Polygam; Privigen; Venoglobulin†; Vivaglobin; ***Venez.:*** Flebogamma; Sandoglobulina†; Venoglobulina†.

Multi-ingredient: ***Arg.:*** Biotaer Gamma†; Histaglobin; ***Austria:*** Histaglobin; ***Chile:*** Pentaglobin; ***Cz.:*** Histaglobin†; ***Ger.:*** Histadestal; ***India:*** Histaglobulin; ***Pol.:*** Histaglobulina; ***S.Afr.:*** Histaglobin.

Pertussis Immunoglobulins

Inmunoglobulinas contra la tos ferina.

ATC — J06BB13.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 31 (Pertussis Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with pertussis vaccine. It may contain glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Pertussis immunoglobulins have been used for passive immunisation against pertussis (whooping cough) and to prevent or modify pertussis in susceptible persons who have been exposed to infection.

Preparations

USP 31: Pertussis Immune Globulin.

Pertussis Vaccines

Vacunas de la tos ferina.

ATC — J07AJ01; J07AJ02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Pertussis Vaccine (Adsorbed); Vaccinum Pertussis Adsorbatum). A sterile suspension of inactivated whole cells of one or more strains of *Bordetella pertussis* in saline to which hydrated aluminium phosphate or aluminium hydroxide has been added. It may contain a suitable antimicrobial preservative. The estimated potency is not less than 4 units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that wP may be used on the label.

Ph. Eur. 6.2 (Pertussis Vaccine (Acellular, Component, Adsorbed); Vaccinum Pertussis sine Cellulis ex Elementis Praeparatum Adsorbatum). A preparation of individually prepared and purified antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It contains either a suitably prepared pertussis toxoid or a pertussis toxin-like protein free from toxic properties produced by expression of a genetically modified form of the corresponding gene. It may also contain filamentous haemagglutinin, pertactin, and other defined antigens such as fimbrial-2 and fimbrial-3 antigens. The final vaccine contains not more than 100 units of bacterial endotoxin per dose. It may contain a suitable antimicrobial preservative. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that aP may be used on the label.

Ph. Eur. 6.2 (Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Vaccinum Pertussis Sine Cellulis Copurificatum Adsorbatum). A preparation of antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that aP may be used on the label.

Adverse Effects

As for vaccines in general, p.2201.

Local reactions may occur at the site of injection of pertussis vaccines or pertussis-containing vaccines and use may be followed by fever and irritability. Local reactions and fever occur less frequently with the acellular vaccine than with whole-cell vaccine, especially in children over 6 months of age and adults. However, booster doses of acellular pertussis-containing vaccines are associated with an increased risk of injection site reactions.

Severe reactions which have been reported include persistent screaming and generalised collapse but these effects were generally associated with an earlier type of vaccine and the reactions are stated to be rarely observed with the currently available vaccines.

Rare neurological adverse reactions have included convulsions and encephalopathy. There has been much debate, however, on the causal role of pertussis vaccine in such reactions (see below for detailed discussion). It should be remembered that neurological complications occur more frequently as a consequence of pertussis infection than from vaccination.

Asthma. A higher incidence of asthma was reported in 243 children who had received whole-cell pertussis vaccine than in 203 children who had not.[1] However, follow-up of a large Swedish study[2] showed no difference in the incidence of wheezing or allergic reactions between children who had received diphtheria, tetanus, and whole-cell pertussis vaccines and those who had not. A later prospective study[3] also found no evidence that whole-cell pertussis vaccination increased the risk of wheezing illness in young children. Furthermore, no association was found between pertussis vaccination in infancy and development of asthma in children aged up to 7 years in a later study of the same group of children.[4]

1. Odent MR, *et al.* Pertussis vaccination and asthma: is there a link? *JAMA* 1994; **272:** 592–3.
2. Nilsson L, *et al.* Lack of association between pertussis vaccination and symptoms of asthma and allergy. *JAMA* 1996; **275:** 760.
3. Henderson J, *et al.* Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *BMJ* 1999; **318:** 1173–6.
4. Maitra A, *et al.* Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* 2004; **328:** 925–6.

Effects on the nervous system. There has been continuing debate over several decades concerning the perceived link between pertussis vaccination and brain damage. Anxiety among both the public and health care professionals in the UK in the mid-1970s over the safety of whole-cell pertussis vaccines led to a fall in the acceptance rates for infant vaccination and major epidemics of pertussis in 1977/79 and 1981/83. Since that time confidence has been restored and, with the introduction of acellular vaccines, the vast majority of infants now receive the vaccine before their second birthday. Comparison of whole-cell vaccines with acellular vaccines has since confirmed that the latter are associated with a greatly reduced incidence of serious neurological disorders.[1]

The consensus of opinion now seems to be that there is a temporal, but not necessarily causal, relationship between whole-cell pertussis vaccine and acute neurological illness that may occasionally lead to long-term dysfunction, and that risks of not immunising are greater than the potential risks associated with the vaccine.

The difficulty in ascertaining whether a causal relationship exists between whole-cell pertussis vaccine (usually given as diphtheria, tetanus, and pertussis (DTP) vaccine) and acute neurological reactions arises partly because primary vaccination is given at an age when neurological dysfunction with other causes is often first manifested. The observed temporal relationship may be entirely coincidental, may result from indirect factors such as pyrexia after vaccination, or may represent a direct effect of DTP vaccine. Much of the evidence is based on large epidemiological studies,[2-7] in particular the National Childhood Encephalopathy Study (NCES)[8] from the UK and its 10-year follow-up.[9] Serious acute neurological illnesses reported to the NCES[8] were found to be more common in infants immunised within 7 days (relative risk 2.4), and especially within 72 hours of onset, than in unimmunised children. For previously normal children, irrespective of outcome, the risk was estimated as 1 in 110 000 injections. In a subset of cases diagnosed as infantile spasms,[10] no link with vaccination was found overall, but there was a small excess of cases of infantile spasm in previously normal children who had received either DTP or diphtheria and tetanus vaccines during the previous 7 days (relative risk 2.0-2.5) followed by a corresponding deficit during the next 3 weeks. This suggested that vaccination may trigger the onset of spasms in a child with an underlying predisposition.

In 1991, the USA Institute of Medicine reviewed the available data, including the NCES results, and concluded that a causal relationship between the whole-cell pertussis component of DTP vaccine and acute encephalopathy probably existed, with an estimated excess risk of 0 to 10.5 per million vaccinations.[11] They concurred with the conclusion that a causal relationship between vaccination and infantile spasm was unlikely.

The NCES 10-year follow-up found that children who had had a serious acute neurological illness (excluding infantile spasms) had an increased risk of death or long-term dysfunction, but the risk was no greater in children given DTP vaccine in the 7 days before the original acute illness.[9] The National Vaccines Advisory Committee concluded that the results were insufficient to determine whether DTP vaccine influenced the development of chronic neurological dysfunction, and this conclusion has been accepted by both the Advisory Committee on Immunization Practices[12] and the American Academy of Pediatrics.[13]

1. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. *Brain Dev* 2004; **26:** 296–300.
2. Pollock TM, Morris J. A 7-year survey of disorders attributed to vaccination in North West Thames Region. *Lancet* 1983; **i:** 753–7.
3. Pollock TM, *et al.* Symptoms after primary immunisation with DTP and with DT vaccine. *Lancet* 1984; **ii:** 146–9.
4. Walker AM, *et al.* Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatrics* 1988; **81:** 345–9.
5. Shields WD, *et al.* Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr* 1988; **113:** 801–5.
6. Griffin MR, *et al.* Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *JAMA* 1990; **263:** 1641–5.
7. Gale JL, *et al.* Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine: a population-based case-control study. *JAMA* 1994; **271:** 37–41.
8. Miller DL, *et al.* Pertussis immunisation and serious acute neurological illness in children. *BMJ* 1981; **282:** 1595–9.
9. Miller D, *et al.* Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 1993; **307:** 1171–6.
10. Bellman MH, *et al.* Infantile spasms and pertussis immunisation. *Lancet* 1983; **i:** 1031–4.
11. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines: summary of a report of the Institute of Medicine. *JAMA* 1992; **267:** 392–6.
12. CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996; **45** (RR-12): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4512.pdf (accessed 25/05/06)
13. Committee on Infectious Disease, American Academy of Pediatrics. The relationship between pertussis vaccine and central nervous system sequelae: continuing assessment. *Pediatrics* 1996; **97:** 279–81.

Precautions

As for vaccines in general, p.2202. The precautions and contra-indications to the use of pertussis vaccines have sometimes been more stringent than is now considered necessary because of the controversy about their potential adverse effects, especially neurotoxicity (see under Adverse Effects, above). In the UK it is now recommended that immunisation should continue with acellular pertussis vaccine even when episodes of fever (irrespective of severity), hypotonic-hyporesponsive episodes, persistent crying or screaming, or severe local reactions (irrespective of extent) have occurred after a preceding dose. Children who have had a local or general reaction to a whole-cell pertussis vaccine should complete their immunisation with acellular pertussis vaccine.

Whether or not children with a personal or family history of convulsions or epilepsy or who have suffered cerebral damage in the neonatal period should receive pertussis vaccines appears to have been the most difficult question to resolve in the past. In the UK it is now considered that a family history of seizures is not a contra-indication to immunisation. When a child has a history of seizures associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal; advice on the prevention of fever should be given at the time of immunisation (see Fever and Hyperthermia, p.10 for comments on the prevention of fever after immunisation). Similarly when there is a history of seizures not associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal. If a seizure associated with fever occurs within 72 hours of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 24 hours. Immunisation should also be carried out in children with a history of cerebral damage in the neonatal period unless there is evidence of an evolving neurological abnormality. In children with a neurological problem that is still evolving it is recommended that immunisation should be deferred until the condition is stable. If a child develops encephalopathy or encephalitis within 7 days of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 7 days.

A personal or family history of hypersensitivity reactions is not generally considered to be a contra-indication to the use of pertussis vaccines, and neither are stable neurological conditions such as spina bifida, congenital brain abnormality, or perinatal hypoxic ischaemic encephalopathy.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Pertussis vaccines are used for active immunisation against pertussis (whooping cough) (p.185). Acellular pertussis vaccines have taken the place of whole-cell vaccines in several countries including the UK and the USA.

For primary immunisation combined pertussis vaccines, usually diphtheria, tetanus, and pertussis vaccines (p.2210) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p.2212) are used. For pre-school boosters diphtheria, tetanus, pertussis, and poliomyelitis vaccines (p.2211) are sometimes given. For discussion of immunisation schedules, see below.

Immunisation schedules. Pertussis is a common, highly infectious, respiratory disease, mainly affecting children, and for which there is no effective treatment. WHO estimates that 20 to 40 million cases of pertussis occur annually and that the disease is responsible for 200 000 to 400 000 deaths each year. The highest incidence of pertussis occurs in developing countries where immunisation is low.

Combined vaccines are now used in most countries but both the strength of the pertussis component and production methods vary, leading to vaccines of different potencies. The considerably higher cost of acellular over whole-cell pertussis vaccines means that the latter are still used widely in developing countries.

Depending upon the country, the age at which a child is given the first dose of a combined vaccine varies from 5 weeks to 6 months. (For summaries of immunisation schedules in the UK and USA, see under Vaccines, p.2202.) In countries with a high incidence of pertussis, WHO recommends that immunisation should start at 6 weeks of age and that the schedule involve 3 doses at monthly intervals followed by a booster dose at 18 months to 6 years of age. In the UK and USA, booster doses should be given after the end of the primary series of 3 injections before entry to school. Several reports have described the use of a 2-dose widely-spaced primary immunisation schedule and this would indeed simplify procedures in developing countries; however, the limitation of such a schedule is the long period of risk between doses without adequate protection and unless the interval can be shortened to 4 weeks, the wide use of such a schedule is not advisable in endemic areas.

Vaccine development. Dissatisfaction with whole-cell vaccines in the 1970s because of adverse reactions led to reduced uptake and a resurgence of pertussis in several countries. In Japan, research into less reactogenic pertussis vaccines resulted in the introduction of acellular vaccines for routine vaccination in the early 1980s. Acellular pertussis vaccines can contain a variety of pertussis components:

- pertussis toxin (PT; also formerly known as lymphocytosis-promoting factor, LPF)
- filamentous haemagglutinin (FHA)
- pertactin (PRN)
- fimbrial agglutinogens (FIM) 2 and 3

The acellular vaccines commonly used are a 3-component vaccine containing PT/FHA/PRN and a 5-component vaccine containing PT/FHA/PRN/FIM2/FIM3. The vaccine used in combination vaccines for primary immunisation in the UK is the 5-component vaccine. The 3-component vaccine does not provide the same level of protection against whooping cough in primary immunisation. Both 3-component and 5-component vaccines may be used in combination vaccines for pre-school boosting. The combination vaccine used for pre-school boosting that contains 5-component pertussis vaccine does not provide the recommended strength of diphtheria to be used for primary immunisation.

Acellular vaccines are now recommended in the UK and USA for both primary immunisation in infants and for the booster doses in young children before school entry. Whole-cell vaccines are still, however, widely used in other countries, particularly in the developing world.

Preparations

Ph. Eur.: Pertussis Vaccine (Acellular Component, Adsorbed); Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Pertussis Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)

Ger.: Pac Merieux†; ***Neth.:*** Acellulair.

Pigbel Vaccines

Vacunas de la enteritis necrotizante.

Profile

A vaccine against pigbel (necrotising enteritis), a disease occurring mainly in children in the highlands of Papua New Guinea, is used for active immunisation against the disease. The vaccine consists of an adsorbed *Clostridium perfringens* type C toxoid.

◊ An immunisation programme, in which pigbel vaccine was given to children at 2, 4, and 6 months of age and, initially, to older children, was introduced in Papua New Guinea in 1980.[1] A survey found a sustained overall fall in the incidence of severe pigbel in children coincident with the increased induced immunity. However, protection may be relatively short-lived and boosters may be necessary for full protection of young children.

1. Lawrence GW, *et al.* Impact of active immunisation against enteritis necroticans in Papua New Guinea. *Lancet* 1990; **336:** 1165–7.

Plague Vaccines

Vacunas de la peste.

ATC — J07AK01.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Plague vaccines have been used for active immunisation against plague in those occupationally exposed to the organism and in some field workers in infected areas. They may reduce morbidity and mortality in bubonic plague but their activity against pneumonic plague is unknown.

Pneumococcal Vaccines

Vacunas neumocócicas.

ATC — J07AL01; J07AL02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Pneumococcal Polysaccharide Vaccine; Vaccinum Pneumococcale Polysaccharidum). A mixture of purified polysaccharide capsular antigens from 23 differing serotypes of *Streptococcus pneumoniae*. Each 0.5-mL dose contains 25 micrograms of each of the 23 polysaccharide types. An antimicrobial preservative may be added. The vaccine has a pH of 4.5 to 7.4. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Pneumo may be used on the label.

Ph. Eur. 6.2 (Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Vaccinum Pneumococcale Polysaccharidicum Coniugatum Adsorbatum). A solution of purified immunochemically different capsular polysaccharides obtained from *Streptococcus pneumoniae* serotypes individually conjugated to a carrier protein. The vaccine may be adsorbed on a suitable adjuvant or adsorbant. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Pneumo(conj) may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201. Unless otherwise stated, the information below refers to the unconjugated polyvalent vaccine.

Revaccination of adults is not routinely recommended because of the increased incidence and severity of adverse reactions.

Pneumococcal vaccination is relatively ineffective in patients with multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, especially during treatment, and in chronic alcoholism. In patients with Hodgkin's disease the use of pneumococcal vaccines is not recommended in those who have received extensive chemotherapy or nodal irradiation. Pneumococcal vaccines should be given at least 2 weeks (and preferably 4 to 6 weeks) before starting immunosuppressive therapy or be delayed until at least 3 months after completion of therapy.

A satisfactory response to the unconjugated polyvalent pneumococcal vaccines is not obtained in children less than 2 years of age and therefore immunisation of this age group with this vaccine is not recommended. However, a pneumococcal conjugate vaccine is available that may be given to infants from 2 months of age.

Effects on the blood. Relapses have occurred on rare occasions in patients with stabilised idiopathic thrombocytopenic purpura at 2 to 14 days after vaccination against pneumococcal infections, lasting for up to 2 weeks. One such case was reported[1] following revaccination less than 2.5 years after an uneventful primary vaccination with pneumococcal vaccine.

1. Neil VS. Long term management after splenectomy: revaccination may cause relapse. *BMJ* 1994; **308:** 339.

Effects on the kidneys. Glomerulonephritis was described[1] in a splenectomised patient after use of pneumococcal vaccine. It was postulated that high antibody titres from a recent pneumococcal infection could have contributed. Minimal change nephrotic syndrome with mild interstitial nephritis following pneumococcal vaccination was suggested as the cause of oedema of the face and legs, visual disturbance suggestive of uveitis, and massive proteinuria in a 67-year-old woman who had been vaccinated about 4 months earlier.[2]

1. Tan SY, Cumming AD. Vaccine related glomerulonephritis. *BMJ* 1993; **306:** 248.
2. Kikuchi Y, *et al.* Minimal change nephrotic syndrome, lymphadenopathy and hyperimmunoglobulinemia after immunization with a pneumococcal vaccine. *Clin Nephrol* 2002; **58:** 68–72.

Effect of nutritional status. An impaired antibody response to pneumococcal vaccine was reported[1] in elderly patients with low serum concentrations of vitamin B_{12}.

1. Fata FT, *et al.* Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B12 levels. *Ann Intern Med* 1996; **124:** 299–304.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Of the many serotypes of *Streptococcus pneumoniae* the 23 from which antigens are obtained for the most commonly available pneumococcal vaccine are considered to cause up to 96% of pneumococcal disease.

Pneumococcal vaccines are used for active immunisation in those at increased risk from infection with the types of *Streptococcus pneumoniae* contained in the vaccine. Pneumococcal vaccines may be in the form of an unconjugated 23-valent polysaccharide vaccine (suitable only for patients over 2 years of age) or as a conjugate vaccine containing 7 serotypes (suitable for infants aged 2 months to 5 years).

In the UK, it is recommended that immunisation should be considered in all persons aged 65 and over; persons who have undergone splenectomy and those with splenic dysfunction, including that due to sickle-cell anaemia and coeliac disease; patients with immunodeficiency or immunosuppression due to disease or treatment, including HIV infection at all stages; persons with chronic cardiac, pulmonary, hepatic, or renal impairment, including nephrotic syndrome, or diabetes mellitus; persons with CSF shunts; children under 5 years old who have previously had invasive pneumococcal disease such as meningitis or septicaemia; and persons with cochlear implants.

An antibody response develops by the third week, and usually lasts about 5 years. The antibody response is less reliable and declines more rapidly in young children and persons with impaired immune function.

A single dose of 0.5 mL of the 23-valent vaccine, containing 25 micrograms of each of the 23 polysaccharide types, is given to at-risk adults and children over 5 years of age by intramuscular injection (or subcutaneously if there are bleeding disorders). The vaccine should be given at least 2 weeks (but preferably 4 to 6 weeks) before elective splenectomy, chemotherapy, or other immunosuppressive treatment. Revaccination is not generally recommended except, after 5 years, in patients likely to have rapidly declining antibody concentrations (for example, those with asplenia or splenic dysfunction and those with nephrotic syndrome).

The 7-valent pneumococcal conjugate vaccine is given by intramuscular injection. In the UK it is recommended that at-risk infants under 6 months should be given 3 single doses of 0.5 mL at intervals of 1 month, starting at 2 months of age, with a fourth dose given in the second year of life; those aged 6 to 11 months should receive 2 doses at least one month apart with a third dose given in the second year of life; and those aged 12 to 60 months should receive 2 doses at least two months apart. The 23-valent pneumococcal polysaccharide vaccine should also be given to the highest risk children (those with asplenia or splenic dysfunction and those with nephrotic syndrome) after their second birthday and at least 2 months after the final dose of conjugate vaccine.

In the USA, three doses of the 7-valent pneumococcal conjugate vaccine are recommended as part of the routine primary immunisation schedule at 2, 4, and 6 months of age. The 23-valent pneumococcal polysaccharide vaccine should be given to high-risk groups between the ages of 2 and 18 years in addition to previously administered 7-valent pneumococcal conjugate vaccine. The 23-valent vaccine is also used in at-risk adults similarly to that outlined for the UK above.

◊ Reviews.

1. Sheikh A, *et al.* Pneumococcal vaccine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 22/04/05).
2. Davies EG, *et al.* Pneumococcal vaccines for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/04/06).
3. Straetemans M, *et al.* Pneumococcal vaccines for preventing otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/04/05).
4. Bernatoniene J, Finn A. Advances in pneumococcal vaccines: advantages for infants and children. *Drugs* 2005; **65:** 229–55.
5. Moberley SA, *et al.* Vaccines for preventing pneumococcal infection in adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 10/06/08).

Preparations

Ph. Eur.: Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Pneumococcal Polysaccharide Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Pneumo†; Neumak†; Pneumo 23; Pneumovax 23; Prevenar; Prote-Neu; ***Austral.:*** Pneumovax 23; Prevenar; ***Austria:*** Pneumo 23; Pnu-Imune†; Prevenar; ***Belg.:*** Pneumo 23; Pneumovax 23†; Pneumune†; Prevenar; ***Braz.:*** Pneumo 23†; Pneumovax 23†; Vacina Pneumococica Conjugada 7-valate; Vacina Pneumococica Polivalente; Vacina Pneumococica Polivalente Pneumo 23; ***Canad.:*** Pneumo 23; Pneumovax 23; Prevnar; ***Chile:*** Pneumo 23; Prevenar; ***Cz.:*** Pneumo 23; Prevenar; ***Denm.:*** Pneumo Novum; Pneumovax; Prevenar; ***Fin.:*** Pneumovax; Prevenar; ***Fr.:*** Pneumo 23; Prevenar; ***Ger.:*** Pneumopur†; Pneumovax 23; Prevenar; ***Gr.:*** Pneumo 23; Pneumovax 23; Pnu-Imune 23†; Prevenar; ***Hong Kong:*** Pneumo 23; Pneumovax 23; Prevenar; ***Hung.:*** Pneumo 23; Pneumovax 23; Prevenar; ***Indon.:*** Pneumo 23; Prevenar; ***Irl.:*** Pneumovax II; Pnu-Imune†; Prevenar; ***Israel:*** Pneumo 23; Pneumovax 23; Prevnar; ***Ital.:*** Pneumo 23; Pneumopur†; Pneumovax; Pnu-Imune 23†; Prevenar; Streptopur; ***Malaysia:*** Pneumo 23; Pneumovax 23†; Prevenar; ***Mex.:*** Pnu-Imune 23†; Prevenar; Pulmovax; ***Neth.:*** Pneumo 23; Pneumovax 23; Prevenar; ***Norw.:*** Pneumovax; Pnu-Imune†; Prevenar; ***NZ:*** Pneumo 23; Pneumovax 23; Prevenar; ***Philipp.:*** Pneumo 23; Prevenar; ***Pol.:*** Pneumo 23; Pneumovax 23; Prevenar; ***Port.:*** Pneumo 23; Pneumovax 23; Pnu-Imune†; Prevenar; ***S.Afr.:*** Imovax Pneumo 23; Pneumovax 23; Prevenar; ***Singapore:*** Pneumo 23; Pneumovax 23; Prevenar; ***Spain:*** Pneumo 23; Pnu-Inmune†; Prevenar; ***Swed.:*** Pneumo 23; Pneumovax†; Pnu-Imune†; Prevenar; ***Switz.:*** Pneumovax 23; Pnu-Imune 23†; Prevenar; ***Thai.:*** Pneumo 23; Pneumovax 23†; Prevnar; ***Turk.:*** Pneumo 23; ***UK:*** Pneumovax II; Prevenar; ***USA:*** Pneumovax 23; Prevnar; ***Venez.:*** Imovax Neumo 23†; Prevenar.

Poliomyelitis Vaccines

Polio Vaccines; Poliovirus Vaccines; Vacunas de la poliomielitis.
ATC — J07BF01; J07BF02; J07BF03.

NOTE. Inactivated poliomyelitis vaccines are sometimes termed Salk Vaccine and live (oral) poliomyelitis vaccines are sometimes termed Sabin Vaccine.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Poliomyelitis Vaccine (Inactivated); Vaccinum Poliomyelitidis Inactivatum). A liquid preparation of suitable strains of poliomyelitis virus, types 1, 2, and 3, grown in suitable cell cultures and inactivated by a suitable method. Permitted antibacterials may be used in its production and it may contain preservatives. It should be stored at 2° to 8° and be protected from light.
The BP 2008 states that IPV may be used on the label.

Ph. Eur. 6.2 (Poliomyelitis Vaccine (Oral); Vaccinum Poliomyelitidis Perorale; Poliomyelitis Vaccine, Live (Oral) BP 2008). A liquid preparation of suitable live attenuated strains of poliomyelitis virus, types 1, 2, or 3, grown in suitable, approved cell cultures; it may contain any one of the 3 virus types or combinations of them. The trivalent vaccine is standardised for virus titre which is not less than 6.0 log $CCID_{50}$ for type 1, not less than 5.0 log $CCID_{50}$ for type 2, and not less than 5.5 log $CCID_{50}$ for type 3 per dose. Permitted antibacterials may be used in its production. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.
The BP 2008 states that OPV may be used on the label.

USP 31 (Poliovirus Vaccine Inactivated). A sterile aqueous suspension of poliomyelitis virus, types 1, 2, and 3, grown separately in cultures of monkey kidney tissue and inactivated. Suitable antimicrobial agents may be used during production. It should be stored at 2° to 8°.

Adverse Effects

As for vaccines in general, p.2201.

Vaccine-associated paralytic poliomyelitis has been reported rarely in recipients of oral poliomyelitis vaccines and in contacts of recipients (see below).

Carcinogenicity. Some poliomyelitis vaccines given in the 1950s and 1960s were found to be contaminated with Simian virus (SV40) from the monkey cell cultures used in the manufacturing process.[1] Once the contamination was realised, steps were taken to eliminate it from future vaccines. However, SV40 is believed to possess biological properties consistent with cancer-causing viruses and epidemiological studies have consequently been conducted to assess whether vaccine recipients have subsequently developed cancer. Although these studies did not find any increased cancer risk, a report by the USA Institute of Medicine in 2002 concluded that these studies were sufficiently flawed to preclude any conclusion being reached. Studies have also assessed the risk to offspring of women given these vaccines during pregnancy (see below). Vaccines now in use do not contain SV40 as they are not manufactured using monkey cell cultures.

1. Stratton K, *et al.*, eds., Institute of Medicine of the National Academies. SV40 contamination of polio vaccine and cancer. *Immunization Safety Review.* Washington D.C.: National Academies Press, 2003. Also available at: http://www.nap.edu/openbook.php?isbn=0309086108 (accessed 15/07/08)

Effects on the nervous system. There have been several case reports of the isolation of poliovaccine virus from the CSF after use of oral poliomyelitis vaccine. A 7-year-old girl who had previously been vaccinated with inactivated poliomyelitis vaccine in infancy received oral vaccine and developed prolonged headache, vomiting, and fever but no paralysis;[1] poliovirus was subsequently isolated from her CSF 34 days after she had received the oral vaccine, and it was concluded that her previous immunisations had been ineffective. In a further report,[2] poliovirus was isolated from the CSF of 2 infants with ventriculoperitoneal shunts who had developed aseptic meningitis without paralysis following oral poliomyelitis vaccination. A neurovirulent variant of Sabin type 2 oral poliomyelitis vaccine virus was detected in both the CSF and stools of an infant with transient hypogammaglobulinaemia who developed meningoencephalitis, retinitis, and irreversible hearing loss after oral poliomyelitis vaccination.[3] A 6-year-old girl given oral poliomyelitis vaccine at 1 and 2 years developed acute disseminated encephalomyelitis and a mutated form of poliovirus was isolated from her CSF;[4] it was thought that she had been infected with the mutated virus from extrafamilial contacts and that the cause of her condition may have been related to her HLA type.

1. Rantala H, *et al.* Poliovaccine virus in the cerebrospinal fluid after oral polio vaccination. *J Infect* 1989; **19:** 173–6.
2. Gutierrez K, Abzug MJ. Vaccine-associated poliovirus meningitis in children with ventriculoperitoneal shunts. *J Pediatr* 1990; **117:** 424–7.
3. Inaba H, *et al.* Polio vaccine virus-associated meningoencephalitis in an infant with transient hypogammaglobulinemia. *Scand J Infect Dis* 2001; **33:** 630–1.
4. Ozawa H, *et al.* Acute disseminated encephalomyelitis associated with poliomyelitis vaccine. *Pediatr Neurol* 2000; **23:** 177–9.

GUILLAIN-BARRÉ SYNDROME. A small cluster of cases of Guillain-Barré syndrome was seen[1] in children after a mass oral poliomyelitis vaccination campaign in Finland in 1985. An increased frequency of Guillain-Barré syndrome was also seen in adults. However, a direct link with poliovaccine virus infection could not be established and no link between Guillain-Barré syndrome and oral polio vaccine was found by a subsequent, epidemiological study in California.[2]

1. Uhari M, *et al.* Cluster of childhood Guillain-Barré cases after an oral poliovaccine campaign. *Lancet* 1989; **ii:** 440–1.
2. Rantala H, *et al.* Epidemiology of Guillain-Barré syndrome in children: relationship of oral polio vaccine administration to occurrence. *J Pediatr* 1994; **124:** 220–3.

VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS. Although generally considered safe and effective, in extremely rare cases the live attenuated virus in oral poliomyelitis vaccines can cause vaccine-associated paralytic poliomyelitis (VAPP) in either the vaccine recipient or in a close contact. There is no such risk associated with inactivated poliomyelitis vaccines. The incidence of VAPP is about 1 case in every 2.5 million doses of vaccine and may be increased in immunocompromised patients. A case control study[1] identified intramuscular injections given within 30 days of vaccination as a risk factor in the development of VAPP. This phenomenon, known as provocation paralysis or provocation poliomyelitis, has been described with the wild virus[2] and has been recognised as a factor in vaccine-associated paralysis in the UK and USA.[3] Paralytic poliomyelitis in contacts of vaccine recipients can be further reduced by ensuring that parents without evidence of previous immunisation receive the vaccine at the same time as their children. The benefits of oral poliomyelitis vaccination are considered to greatly outweigh the small risk involved, however, and many countries where the risk of wild virus-caused poliomyelitis has been reduced to zero are now considering combined immunisation schedules with both oral and inactivated poliomyelitis vaccines.

1. Strebel PM, *et al.* Intramuscular injections within 30 days of immunization with oral poliovirus vaccine—a risk factor for vaccine-associated paralytic poliomyelitis. *N Engl J Med* 1995; **332:** 500–6.
2. Anonymous. Provocation paralysis. *Lancet* 1992; **340:** 1005–6.
3. Wyatt HV. Vaccine-associated poliomyelitis. *Lancet* 1994; **343:** 610.

Precautions

As for vaccines in general, p.2202.

Poliomyelitis vaccine may contain trace amounts of antibacterials such as neomycin, polymyxin B, and streptomycin and should be used with caution in patients with severe hypersensitivity to these antibacterials.

Oral poliomyelitis vaccines should not be given to patients with diarrhoea or vomiting.

Because the vaccine virus of oral poliomyelitis vaccines is excreted in the faeces for up to 6 weeks, the contacts of recently vaccinated babies and infants should be advised of the need for strict personal hygiene, particularly hand washing after napkin changing, in order to reduce the possibility of infection in unimmunised contacts. Unimmunised adults can be immunised at the same time as their children.

Immunocompromised patients are at increased risk of developing vaccine-associated paralytic poliomyelitis. Oral poliomyelitis vaccines should not be given to immunocompromised patients or their household contacts and in these persons an inactivated vaccine should be used. Asymptomatic HIV-positive persons may receive oral poliomyelitis vaccines but faecal excretion of the vaccine virus may continue for longer than in uninfected individuals. For symptomatic HIV-positive persons the use of inactivated poliomyelitis vaccine may be considered.

Intramuscular injections given after the oral vaccine may also increase the risk of vaccine-associated paralytic poliomyelitis (see above).

Pregnancy. Live vaccines such as *oral poliomyelitis vaccines* are generally contra-indicated in pregnancy because of a theoretical risk to the fetus. Population-wide mass vaccination programmes become impossible, however, if pregnant mothers and women of child-bearing age are to be excluded.[1] In February 1985, mass vaccination with live oral poliomyelitis vaccine was started during a poliomyelitis outbreak in Finland.[1] Pregnant women were advised to take the vaccine. An analysis of all reported congenital malformations in the years 1982 to 1986 suggested that oral poliomyelitis vaccine had no harmful effects on fetal development as measured by overall prevalence of malformations or by the incidence of either CNS or orofacial defects. The results did not, however, exclude an effect measurable by other criteria of fetal development.

The incidence of spontaneous abortions was measured during a mass poliomyelitis vaccination campaign in Israel.[2] The number of spontaneous abortions did not differ between controls and women vaccinated during the first trimester of pregnancy; the percentage of spontaneous abortions in relation to live births was also similar. Microscopic examination of placentas from spontaneous abortions indicated no effect of oral poliomyelitis vaccine on the frequency or type of pathological changes. In addition, subsequent epidemiological study[3] found no increases in congenital malformations or in premature births during the period of and immediately following the vaccination campaign compared with those born before the campaign.

The Collaborative Perinatal Project (CPP) in the USA[4] followed up 50 897 pregnancies to examine risk factors for the development of malignancies in offspring born between 1959 and 1966. In 18 342 children whose mothers were vaccinated during pregnancy with *inactivated poliomyelitis vaccines*, there were 14 malignancies (7.6 per 10 000), while in 32 555 non-exposed children there were 10 malignancies (3.1 per 10 000). There were 7 tumours derived from neural tissue in the exposed children (3.8 per 10 000) and one in non-exposed children (0.3 per 10 000). Thus there was an excess of neural tumours but not of leukaemias or other malignancies in children exposed *in utero* to inactivated poliomyelitis vaccine. No malignancies occurred among the children born to 3056 women who received oral poliomyelitis vaccine. Serum samples collected from mothers on entry into the CPP and at delivery were subsequently analysed[5] for the presence of antibodies to Simian virus 40 (SV40). None of the serum samples from 8 mothers of infants with neural tumours had antibodies to SV40. Two of the 7 mothers of infants with leukaemia had SV40 antibodies, but only one had conversion during pregnancy. None of the samples from the 7 mothers of children with other types of cancer had antibodies. Three of 36 controls had antibodies, but in both the first and second samples. The association between administration of inactivated poliomyelitis vaccine to mothers and neural tumours in their offspring could not be attributed to contamination of vaccine with SV40. A later analysis[6] of 54 796 children enrolled in the CPP found an increased risk of neural tumours and of haematological malignancy in children whose mothers had received pre-1963 poliomyelitis vaccine, but concluded that this was unlikely to have been due to transmission of SV40.

1. Harjulehto T, *et al.* Congenital malformations and oral poliovirus vaccination during pregnancy. *Lancet* 1989; **i:** 771–2.
2. Ornoy A, *et al.* Spontaneous abortions following oral poliovirus vaccination in first trimester. *Lancet* 1990; **i:** 800.
3. Ornoy A, Ben Ishai P. Congenital anomalies after oral poliovirus vaccination during pregnancy. *Lancet* 1993; **341:** 1162.
4. Heinonen OP, *et al.* Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973; **2:** 229–35.
5. Rosa FW, *et al.* Absence of antibody response to simian virus 40 after inoculation with killed-poliovirus vaccine of mothers of offspring with neurologic tumors. *N Engl J Med* 1988; **318:** 1469.
6. Engels EA, *et al.* Poliovirus vaccination during pregnancy, maternal seroconversion to simian virus 40, and risk of childhood cancer. *Am J Epidemiol* 2004; **160:** 306–16.

Interactions

As for vaccines in general, p.2202.

Normal immunoglobulins. Although the use of live vaccines and immunoglobulins at the same time is generally not recommended, normal immunoglobulin had no effect on the antibody response to oral poliomyelitis vaccine when the 2 preparations were given together to 50 subjects.[1]

1. Green MS, *et al*. Response to trivalent oral poliovirus vaccine with and without immune serum globulin in young adults in Israel in 1988. *J Infect Dis* 1990; **162:** 971–4.

Uses and Administration

Poliomyelitis vaccines are used for active immunisation against poliomyelitis. For discussion of immunisation schedules, see under Vaccines, p.2202. Both live (oral) poliomyelitis vaccines and inactivated poliomyelitis vaccines are available. The oral vaccine stimulates the formation of antibodies both in the blood and in the mucosal tissues of the gastrointestinal tract.

In the UK, an inactivated poliomyelitis vaccine containing the 3 types of poliovirus (trivalent) is recommended for the primary immunisation of all age groups, given as a course of 3 doses at intervals of 4 weeks. It is given intramuscularly as a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine. For children who received primary immunisation during infancy, reinforcing doses are recommended at school entry (diphtheria, tetanus, pertussis, and poliomyelitis) and before leaving school (diphtheria, tetanus, and poliomyelitis). Further reinforcing doses are necessary only in adults exposed to infection including travellers to countries where poliomyelitis is epidemic or endemic and healthcare workers in contact with poliomyelitis cases. A single dose is given, repeated every 10 years if necessary.

In the USA, the recommended schedule consists of four doses of inactivated vaccine given at 2 months, 4 months, 6 to 18 months, and 4 to 6 years of age.

On the occurrence of a single case of paralytic poliomyelitis from wild virus, a single dose of the oral vaccine is recommended for all persons in the neighbourhood, regardless of whether they have previously been immunised. A primary course should be completed in previously unimmunised individuals.

Choice of vaccine. Two types of poliomyelitis vaccine are available: live attenuated oral poliomyelitis vaccine (OPV) and inactivated (killed) poliomyelitis vaccine (IPV) given by injection. Both vaccines are highly effective against all 3 types of poliovirus but there are advantages and disadvantages associated with their use.

The *advantages* of OPV are:

- it produces an immune response in both the blood and in the lining of the gut, thus preventing both spread of infection to the CNS and multiplication of the virus in the gastrointestinal tract and hence transmission via the stools and saliva
- it is given orally and is therefore easy to give without specialist training
- it is relatively inexpensive, an important consideration in developing countries in particular.

The *disadvantage* of OPV is:

- it causes very rare cases of vaccine-associated paralytic poliomyelitis (VAPP).

The *advantage* of IPV is:

- it is not a live vaccine and as such carries no risk of VAPP.

The *disadvantages* of IPV are:

- it confers very little immunity in the gastrointestinal tract, hence when an individual immunised with IPV is infected with wild poliovirus the virus can still multiply in the intestines and be shed in the stools, thus risking continued transmission
- trained health workers are required to give it by injection
- it costs far more than OPV.

Poliomyelitis has now been eradicated from most countries in the world (see below) and hence many, including the UK and the USA, consider it appropriate to use IPV exclusively for routine immunisation. However, the Global Polio Eradication Initiative will continue to use OPV where necessary until global eradication is achieved, at which time it has stated that the use of OPV should cease as soon as possible while population immunity against poliomyelitis and surveillance sensitivity for paralysis remain high, and be replaced by routine use of IPV.[1]

1. WHO. Framework for national policy makers in OPV-using countries: cessation of routine oral polio vaccine (OPV) use after global polio eradication. Geneva: WHO, 2005. Also available at: http://www.polioeradication.org/content/publications/OPVCessationFrameworkEnglish.pdf (accessed 12/10/05)

Eradication of infection. In 1988, WHO announced the goal of eradicating poliomyelitis by the year 2000. Other bodies joined the project which became known as the Global Polio Eradication Initiative.[1] Although the goal was not achieved in 2000, very considerable progress has been made. In 1988, wild poliovirus was endemic in 125 countries and more than 1000 children became paralysed every day. In 2005, only 4 countries still had endemic poliomyelitis. However, some countries are experiencing re-infection (11 by the end of August 2005) and in 2005, for the first time, case numbers were higher in these re-infected countries than in those where the disease is endemic. This illustrates the vulnerability of countries considered free of poliomyelitis when resultant low routine immunisation coverage puts children at risk. The global incidence of polio remained unchanged from 2005 to 2006.[2] A renewed goal was set of global polio eradication by the year 2008.

1. Global Polio Eradication Initiative. Information available at: http://www.polioeradication.org (accessed 25/04/06)
2. CDC. Progress towards interruption of wild poliovirus transmission—worldwide, January 2006–May 2007. *MMWR* 2007; **56:** 682–5. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5627a3.htm (accessed 15/04/08)

Preparations

Ph. Eur.: Poliomyelitis Vaccine (Inactivated); Poliomyelitis Vaccine (Oral); ***USP 31:*** Poliovirus Vaccine Inactivated.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Polio; Sabin; ***Austral.:*** Enpovax HDC†; Ipol; ***Belg.:*** Imovax Polio; Sabin†; ***Braz.:*** Imovax Polio†; IPV; Vacina Poliomielitica†; ***Cz.:*** Imovax Polio; IPV-Virelon; ***Fin.:*** Imovax Polio; ***Fr.:*** Imovax Polio; ***Ger.:*** IPV Merieux; IPV-Virelon; ***Gr.:*** Imovax Polio†; Poliorix; Vaccine Antipoliomyelitique/Merieux†; ***Hong Kong:*** Imovax Polio; ***Indon.:*** Imovax Polio; ***Israel:*** Imovax Polio; Polio Sabin; Polioral; ***Ital.:*** Imovax Polio; Polio Sabin†; Polioral†; Poliovax-IN; ***Malaysia:*** Polioral†; ***Mex.:*** Polio Sabin; Polioral; ***Norw.:*** Imovax Polio; ***NZ:*** Imovax Polio; Ipol; ***Philipp.:*** Polio Sabin; Polioral; Poliorix; ***Pol.:*** Imovax Polio; Polio Sabin; ***S.Afr.:*** OPV-Merieux; Polioral; ***Singapore:*** Imovax Polio†; ***Spain:*** Vac Antipolio Or†; Vac Polio Sabin; Vac Poliomielitica; ***Swed.:*** Imovax Polio; ***Switz.:*** Poliorix; ***Thai.:*** Polio Sabin; Polioral; ***Turk.:*** Buccapol; Polio Sabin; Poliorix; ***USA:*** Ipol; ***Venez.:*** Imovax Polio†; Vacuna Sabin†.

Pseudomonas Vaccines

Vacunas de pseudomonas.

Profile

A number of candidate *Pseudomonas aeruginosa* vaccines are under investigation for the prevention of pseudomonal infections in a variety of disease states.

◊ *Pseudomonas aeruginosa* is notably resistant to many antibacterials and there has consequently been considerable interest in developing an effective vaccine against it.[1-4] However, clinical results have tended to be disappointing, and together with improvements in antibacterial management have meant that no such vaccine is yet available for clinical use.

Early attempts in the 1960s at developing a vaccine focused on cell wall components (lipopolysaccharides). Multivalent lipopolysaccharide vaccines were tested in *animals* and in patients, including burns patients and patients with various forms of cancer and acute and chronic lung disease but, despite some positive results, these vaccines never gained clinical acceptance because of problems associated with the use of lipopolysaccharides. Vaccines designed at targeting the toxic exoproduct of *Ps. aeruginosa*, exotoxin A, produced mixed results at best; there has also been interest in exotoxin A toxoid in combination with other protective immunogens and in multicomponent and conjugate vaccines. There was brief interest in ribosomes and ribosomal RNA vaccines but these fell out of favour.

The discovery that motility was associated with *Ps. aeruginosa* virulence prompted research into the use of flagella as protective immunogens. The organism normally has two types of flagellum and a divalent vaccine has been tested, but with only modest benefit. There has also been some interest in development of vaccines against pili, bacterial appendages used for attachment.

Some investigators tried the use of high-molecular-weight polysaccharides as potential vaccine candidates but interest in this area has declined. Another defunct area of research is the use of pseudomonal alginate and mucoid exopolysaccharide; these were suggested for use in cystic fibrosis patients but did not progress beyond *animal* studies.

From the 1980s, there was considerable interest in the use of a variety of outer membrane proteins to develop a vaccine, partly because outer membrane proteins are exposed on the cell surface and at least one, protein F, is common to all serotypes. Encouraging results were obtained in *animal* models of infected burns and of chronic lung disease. Preliminary studies in healthy humans yielded large and sustained increases in antibody titres and found outer membrane proteins to be well tolerated. Multicomponent vaccines have been developed consisting of toxoids of known pseudomonal virulence factors such as proteases, elastases, and exotoxin A. Conjugate vaccines have been shown to be effective in *animal* models and to elicit a high antibody titre in cystic fibrosis patients.

In recent years, attention has also turned to the development of DNA vaccines, and to the use of some novel immunological approaches such as the use of pooled monoclonal antibodies directed against a variety of *Ps. aeruginosa* virulence antigens and of epitopes of pseudomonal elastase. In addition, research has shown that both active and passive immunisation with the purified type III translocation protein (PcrV) from *Ps. aeruginosa* is effective in *mouse* models of lung infection and burns, although results of combined active and passive immunisation in clinical studies were disappointing. Finally, there has been interest in obtaining immunological protection by presenting *Pseudomonas* antigens via mucous membranes, particularly in the gastrointestinal tract or intranasally.

1. Keogan MT, Johansen HK. Vaccines for preventing infection with Pseudomonas aeruginosa in people with cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 03/06/05).
2. Cachia PJ, Hodges RS. Synthetic peptide vaccine and antibody therapeutic development: prevention and treatment of Pseudomonas aeruginosa. *Biopolymers* 2003; **71:** 141–68.
3. Holder IA. Pseudomonas vaccination: a historical overview. *Vaccine* 2004; **22:** 831–9.
4. Döring G, Pier GB. Vaccines and immunotherapy against Pseudomonas aeruginosa. *Vaccine* 2008; **26:** 1011–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Psaeva†; ***Pol.:*** Pseudovac.

Q Fever Vaccines

Vacunas de la fiebre Q.

Profile

A Q fever vaccine consisting of a purified killed suspension of *Coxiella burnetii* is available in Australia. It is prepared from Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. A single 0.5-mL subcutaneous dose is given for active immunisation in individuals at high risk of Q fever. These include abattoir workers, veterinarians, farmers and others exposed to farm animals, and laboratory workers handling potentially infected tissue.

Before immunisation, patients should be tested for their serum antibody titre and a skin test performed; giving the vaccine to persons already sensitised to Q fever antigens may cause serious hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Q-Vax.

Rabies Antisera

Antisuero de la rabia.

ATC — J06AA06.

Profile

Rabies antisera have been used to provide passive immunisation against rabies but the use of rabies immunoglobulins (see below) is preferred.

Rabies Immunoglobulins

Inmunoglobulinas contra la rabia.

ATC — J06BB05.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Rabies Immunoglobulin; Immunoglobulinum Humanum Rabicum). A liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from donors immunised against rabies and contains specific antibodies that neutralise the rabies virus. Normal immunoglobulin may be added. It contains not less than 150 international units/mL. The liquid preparation should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

USP 31 (Rabies Immune Globulin). A sterile solution of globulins derived from plasma or serum from selected adult human donors who have been immunised with rabies vaccine and have developed high titres of rabies antibody. It contains 10 to 18% of protein of which not less than 80% is monomeric immunoglobulin G. It has a potency of 150 international units/mL. It contains glycine as a stabilising agent, and a suitable preservative. A solution diluted to contain 1% of protein has a pH of 6.4 to 7.2. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Uses and Administration

Rabies immunoglobulins are used for passive immunisation against rabies. They are combined with active immunisation by rabies vaccines (see below) in postexposure treatment for the prevention of rabies in previously unimmunised persons who have been bitten by rabid animals or animals suspected of being rabid. There are 2 types of immunoglobulin available: human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose of HRIG is 20 international units/kg; for ERIG products it is 40 international units/kg. The recommended dose should be infiltrated in and around the cleansed wound; if infiltration of the whole volume is not possible, any remaining immunoglobulin should be given intramuscularly (in the anterolateral thigh and not the gluteal region) at a different site to that at which the vaccine was given.

Preparations

Ph. Eur.: Human Rabies Immunoglobulin;
USP 31: Rabies Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Imogam Rabia; ***Austral.:*** Imogam; ***Austria:*** Berirab; ***Canad.:*** BayRab†; Hyperrab; Imogam; ***Cz.:*** Favirab; Imogam Rabies†; ***Fr.:*** Imogam Rage; ***Ger.:*** Berirab; Tollwutglobulin; ***Hong Kong:*** BayRab; Rabuman†; ***India:*** Berirab-P; Carig; ***Indon.:*** Imogam; ***Israel:*** BayRab; Berirab; Imogam

Rabies; ***Mex.:*** BayRab†; Berirab-P; Kamrab; ***Philipp.:*** BayRab; Berirab-P; Favirab; ***S.Afr.:*** Rabigam; ***Singapore:*** BayRab†; ***Spain:*** Imogam Rabia; ***Switz.:*** Berirab; Rabuman; ***Thai.:*** Favirab; Imogam Rabies; Rabuman†; ***Turk.:*** Imogam; ***USA:*** HyperRab; Imogam Rabies; ***Venez.:*** Imogan Rabia†.

Rabies Vaccines

Vacunas de la rabia.

ATC — J07BG01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Rabies Vaccine for Human Use Prepared in Cell Cultures; Vaccinum Rabiei ex Cellulis ad Usum Humanum; Rabies Vaccine BP 2008). A sterile freeze-dried suspension of inactivated rabies virus; a suitable strain is grown in an approved cell culture. The cell-culture medium may contain suitable antibacterials at the smallest effective concentration. The vaccine is prepared immediately before use by the addition of a suitable sterile liquid. The estimated potency is not less than 2.5 international units per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Rab may be used on the label.

USP 31 (Rabies Vaccine). A sterile preparation, in dried or liquid form, of inactivated rabies virus obtained from inoculated diploid cell cultures. It has a potency of not less than 2.5 international units per dose. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Patients receiving human diploid-cell or purified chick embryo-cell rabies vaccines may experience pain, erythema, and induration at the injection site. Systemic reactions including abdominal pain, diarrhoea, nausea and vomiting, headache, chills, dizziness, fever, malaise, convulsions, encephalitis, lymphadenopathy, arthralgia and myalgia, dyspnoea and wheezing, or rash may also occur. Reactions may become more severe with repeated doses. Hypersensitivity reactions including anaphylaxis occur more commonly with vaccines prepared from non-human sources than with human diploid-cell vaccine. However, these reactions have also been associated with the presence of β-propiolactone-altered human albumin in the human diploid-cell vaccine.

Neurological reactions (meningoencephalitis, meningoencephalomyelitis, mononeuritis multiplex, transverse myelitis, or ascending paralysis) have been associated with the use of animal nerve-tissue vaccines. WHO considers that nerve-tissue vaccines should no longer be used. There are only isolated reports of neurological reactions after use of human diploid-cell vaccines.

Patients known to be hypersensitive to a particular vaccine or its components should be given an alternative product if available, although there are no absolute contra-indications to postexposure treatment. Pre-exposure prophylaxis should be delayed in patients with febrile illness until fever has resolved.

Effects on the nervous system. Rabies vaccines were originally prepared from infected animal brain tissue. The incidence of neurological complications with these vaccines was about 1 in 1 600, with an overall mortality of 15%.[1] Neurological adverse effects were attributed to myelin basic proteins present in these vaccines.[1-4] Subsequently, a highly immunogenic rabies vaccine was produced from the relatively myelin-free nerve tissue of suckling mice. However, neuroparalytic complications were reported in about 1 in 8 000 persons treated.[1,5] Most of these complications were of a Guillain-Barré-type illness, and had a fatality rate of 20 to 50%.[1]

Neuroparalytic reactions occur less frequently (1 in 32 000 persons treated) with vaccines prepared from duck embryo tissue;[1,5] however, these vaccines are no longer manufactured.[5]

Cell-derived rabies vaccines have been developed with better safety profiles.[1,5,6]

Isolated cases of neuroparalytic reactions have been reported with human diploid-cell or chick embryo-cell vaccines, mostly manifesting as a Guillain-Barré-type illness.[1,7-10]

1. Bernard KW, *et al.* Neuroparalytic illness and human diploid cell rabies vaccine. *JAMA* 1982; **248:** 3136–8.
2. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
3. Kulkarni V, *et al.* Biphasic demyelination of the nervous system following anti-rabies vaccination. *Neurol India* 2004; **52:** 106–8.
4. Siddiqui A, *et al.* Guillain-Barre syndrome occurring after rabies vaccination. *J Pakistan Med Assoc* 2005; **55:** 87–8.
5. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
6. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2004. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
7. Knittel T, *et al.* Guillain-Barré syndrome and human diploid cell rabies vaccine. *Lancet* 1989; **i:** 1334–5.
8. Tornatore CS, Richert JR. CNS demyelination associated with diploid cell rabies vaccine. *Lancet* 1990; **335:** 1346–7.
9. Mortiere MD, Falcone AL. An acute neurologic syndrome temporally associated with postexposure treatment of rabies. *Pediatrics* 1997; **100:** 720–1.
10. Chakravarty A. Neurologic illness following post-exposure prophylaxis with purified chick embryo cell antirabies vaccine. *J Assoc Physicians India* 2001; **49:** 927–8.

Hypersensitivity. Systemic hypersensitivity reactions[1] have occurred in up to 6% of patients receiving booster immunisation with human diploid-cell rabies vaccine (HDCV), with onset after 2 to 21 days. Presenting features include generalised or pruritic rash or urticaria, angioedema, arthralgias, fever, nausea, and vomiting. These reactions have been linked to the presence of β-propiolactone-altered human albumin in HDCV. A lower risk of hypersensitivity reaction should exist with newer cell-derived vaccines that contain little or no human albumin, such as purified chick embryo cell rabies vaccines (PCECV) or purified Vero-cell rabies vaccines (PVRV). A review[2] noted that patients receiving booster immunisation with PCECV did not generally exhibit systemic hypersensitivity reactions. In a comparison study[3] involving 400 children, patients receiving a new chromatographically purified Vero-cell vaccine were found to have a lower incidence of systemic hypersensitivity (0.7%) than those in the HDCV group (1.2%) after booster immunisation.

1. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
2. Dreesen DW. A global review of rabies vaccines for human use. *Vaccine* 1997; **15** (suppl): S2–S6.
3. Sabchareon A, *et al.* A new Vero cell rabies vaccine: results of a comparative trial with human diploid cell rabies vaccine in children. *Clin Infect Dis* 1999; **29:** 141–9.

Spongiform encephalopathies. Possible transmission of Creutzfeldt-Jakob disease associated with sheep-brain rabies vaccine has been reported from India.[1] It was suggested that transmission of the abnormal prion protein from sheep with scrapie might be implicated.

1. Arya SC. Acquisition of spongiform encephalopathies in India through sheep-brain rabies vaccination. *Natl Med J India* 1992; **4:** 311–12.

Interactions

As for vaccines in general, p.2202.

Antimalarials. Studies have suggested that continuous antimalarial chemoprophylaxis with *chloroquine* during primary immunisation with human diploid-cell rabies vaccine, given intradermally for pre-exposure prophylaxis, may be associated with a poor antibody response.[1,2] WHO[3] recommends that people currently taking malaria prophylaxis or those unable to complete the 3-dose rabies pre-exposure regime before starting malaria prophylaxis should receive pre-exposure rabies vaccination by the intramuscular route instead.

1. Taylor DN, *et al*. Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* 1984; **i:** 1405.
2. Pappaioanou M, *et al.* Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med* 1986; **314:** 280–4.
3. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)

Uses and Administration

Rabies vaccines are used for active immunisation against rabies. They are used as part of postexposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Infection does not take place through unbroken skin but is possible through uninjured mucous membranes and has been reported after the inhalation of virus in the laboratory. Rabies vaccines are also used for pre-exposure prophylaxis against rabies in persons exposed to a high risk of being bitten by rabid or potentially rabid animals.

Schedules for prophylaxis and treatment of rabies are recommended by WHO (see Pre-exposure Immunisation, below) and many countries have immunisation schedules based on these.

In the UK, two types of rabies vaccine are available. The first type is prepared from inactivated Wistar rabies virus strain PM/WI38 1503-3M cultured on human diploid cells, and the second type is prepared from inactivated Flury LEP virus strain produced on purified chick embryo cells. Each contains not less than 2.5 international units/mL. The purified chick embryo-cell vaccine is given intramuscularly into the deltoid region in adults but into the anterolateral aspect of the thigh in children. The human diploid-cell vaccine is given intramuscularly into the deltoid region in both adults and children. Other cell culture-derived vaccines, such as Vero cell rabies vaccine, are available in other countries.

For **pre-exposure prophylaxis** against rabies, the recommended schedule in the UK is 3 doses, each of 1 mL, by intramuscular injection on days 0, 7, and 28; the third dose may in some instances be given on day 21 if there is insufficient time before travel. For persons at regular and continuous risk, a single reinforcing dose should be given 1 year after completion of the primary course with further doses at 3- to 5-year intervals. For those at intermittent risk, a booster dose should be given from 2 years after completion of the primary course.

For **postexposure treatment**, thorough cleansing of the wound with soap and water is imperative. The recommended schedule in the UK for unimmunised or incompletely immunised persons is 5 doses, each of 1 mL, by intramuscular injection on days 0, 3, 7, 14, and 30. In fully immunised persons two doses of vaccine should be given intramuscularly, one each on day 0 and day 3. Vaccination should be started as soon as possible after exposure, and may be stopped if it is proved that the patient was not at risk. In previously unimmunised patients at high risk, rabies immunoglobulin (see above) should also be given at the same time as the first dose of vaccine.

Rabies. Rabies is caused by infection with a rhabdovirus of the genus Lyssavirus. Rabies has a worldwide distribution, primarily in domesticated and wild dogs but also in bats and other warm-blooded animals, although some countries, including the UK, most of Australasia, and Antarctica are designated as rabies-free areas. Transmission of the rabies virus to humans is usually by the bite of an infected animal or contamination of broken skin by saliva. Infection is possible via intact mucous membranes and by aerosol transmission, but infection is unlikely after contamination of intact skin. Other body fluids such as urine and tears should be regarded as potentially infectious; rabies virus transmission has also been reported after organ transplantation from misdiagnosed donors.

Human rabies is almost always fatal once symptoms have appeared. The incubation period varies from 2 weeks to 6 years (average of 2 to 3 months) depending on the distance of the bite site from the brain and the amount of virus in the inoculum. There are 2 types of clinical presentations of rabies; encephalitic (furious) and paralytic (dumb). Encephalitic rabies presents with periods of hyperexcitability accompanied by severe agitation and bizarre behaviour alternating with periods of lucidity. Severe spasms of the larynx and pharynx may be provoked by attempts at swallowing (leading to hydrophobia) or by air blown at the face (aerophobia). Other symptoms include hypersalivation, fever, and convulsions. In the paralytic form, progressive flaccid paralysis develops in the bitten limb and ascends in a symmetrical or asymmetrical manner. Patients not dying through respiratory or cardiac arrest during the acute phase may develop any of a number of complications culminating in coma and death or (very rarely) recovery; only a few patients are documented as having survived after the onset of coma, and all had received either pre- or postexposure immunisation.

National control programmes involve epidemiological surveillance, mass canine immunisation campaigns, and dog population management. The development of oral animal vaccines delivered on baited food has met with considerable success in a number of areas and has become an essential tool for eliminating rabies in wild animals. Rigorously applied controls of international transfer of animals including certification of vaccination and quarantine for animals entering rabies-free areas are necessary to prevent re-introduction of rabies.

Although a number of treatments have been tried including antivirals, interferons, high doses of rabies immunoglobulin, and corticosteroids, none has shown evidence of effectiveness. Postexposure treatment after contact with a suspected or confirmed rabid animal may be effective in preventing death; it includes prompt and thorough cleansing of the contaminated site and the early use of rabies vaccine with or without rabies immunoglobulins. For a brief outline of postexposure treatment, see below.

Pre-exposure prophylaxis is recommended in persons at high risk of exposure, either due to their occupation or those travelling in enzootic areas. The main obstacle to mass pre-exposure vaccination appears to be the high cost of cell culture vaccines. See under Pre-exposure Immunisation (below) for outlines of recommended vaccination schedules.

CHOICE OF VACCINES. Many different rabies vaccines are available for human use. Some are derived from nerve tissue of animals, some from avian tissues (duck embryos), and some prepared in cell cultures. The first rabies vaccine was based on attenuated virus from desiccated nerve tissue. Later, inactivated nervous tissue-derived vaccines were prepared from rabid sheep, goat (Semple vaccines) or suckling mouse brains (Feunzalida Palacios vaccine). A complete postexposure treatment course of nerve-tissue vaccine consists of up to 23 injections and is associated with severe neurological reactions and a significant failure rate. WHO therefore strongly recommends that nerve-tissue vaccines should not be used, and that production should be stopped. Cell-derived rabies vaccines were subsequently developed; the human diploid cell rabies vaccine (HDCV) was introduced in 1967 and later less expensive purified chick embryo-cell vaccine (PCECV) and purified Vero-cell rabies vaccines (PVRV) entered use. There appears to be little difference in terms of safety and antigenicity between HDCV, PCECV, and PVRV in recommended regimens. The incidence of severe hypersensitivity reactions should, however, be lower with PVRV and PCECV than with HDCV since the purification process removes most human serum albumin in the cell-growth medium before virus inactivation (see Hypersensitivity, under Adverse Effects and Precautions, above). A purified duck-embryo vaccine (PDEV) provided similar efficacy and safety to vaccines produced from cell cultures, but is no longer manufactured.

There is little data concerning the efficacy of rabies vaccines. It appears that nerve-tissue vaccines afford limited protection after minor exposures to rabies virus, are less effective after head bites, and are of little use after very severe exposures. Failure rates for HDCV, PCECV, and PVRV (including cases with less than the recommended therapy) have been estimated as less than 1 in 80 000 treatments in the USA, Canada, and Europe, 1 in 12 000 to 20 000 in Thailand, and 1 in 30 000 in the remaining tropical countries. Reported failures of these vaccines are usually associated with severe lesions on or near the head and/or errors in treatment, such as deviation from recommendations, incorrect site of vaccine administration, or delay in treatment. WHO recommends a minimum potency of 2.5 international units per intramuscular dose for all cell-derived rabies vaccines.

The cost of cell-derived rabies vaccines is prohibitively high in the developing world. Although the adverse effects of nerve-tissue vaccines preclude their use for pre-exposure prophylaxis, they are still used in some countries for postexposure prophylaxis. WHO is anxious that nerve-tissue vaccines should be replaced with affordable cell-derived vaccines as soon as possible. In the meantime, cost-cutting regimens have been devised for use of cell-derived rabies vaccines by the intradermal route. Rapid immunisation is achieved by the use of several sites of injection; fewer injections are required than with traditional intramuscular regimens.

Pre-exposure immunisation. WHO[1,2] has developed guidelines as to who should receive pre-exposure vaccination with rabies vaccines. However, national policies may vary somewhat from that of WHO, depending on the local risk of contracting rabies and the vaccines available; it is generally recommended for use in persons at high risk of infection with rabies virus. Where available, the vaccines produced in cell culture or from purified embryonated eggs are preferred over the vaccines produced in animal tissues (see under Choice of Vaccine, above). WHO recommends[1,2] pre-exposure prophylaxis for persons regularly at high risk of exposure, such as certain laboratory workers, veterinarians, animal handlers, and wildlife officers, and those living in or travelling to areas where rabies is endemic (particularly in children under 15 years of age). The immunisation schedule should preferably consist of 3 injections of a rabies vaccine of potency at least 2.5 international units given on days 0, 7, and either day 21 or 28, but variation of a few days is unimportant. Vaccine should be given into the deltoid area of the arm or for young children into the anterolateral area of the thigh. Titres of virus-neutralising antibodies can be checked in serum samples collected 1 to 3 weeks after the last dose. Those who work with the live virus should have their antibody titres checked every 6 months and if the figure falls below 0.5 international units/mL they should receive a booster.[1,2] Other individuals at continuing risk should have their titres checked every 12 months and a booster given if the titre is below 0.5 international units/mL.[1]

WHO also suggests intradermal use of rabies vaccine in doses of 0.1 mL on days 0, 7, and either day 21 or 28 but intramuscular injection is preferable and is mandatory in those taking malaria prophylaxis.

In the UK,[3] the schedule for immunisation (see Uses and Administration, above) is similar to that recommended by WHO.

In the USA, immunisation with a human diploid cell vaccine, a vaccine adsorbed onto an aluminium salt, or a purified chick embryo cell vaccine is carried out similarly to the WHO schedule, with serum-antibody titres determined every 6 months to 2 years, depending upon the level of exposure, and booster doses given as necessary.[4]

1. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
2. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
3. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
4. CDC. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999; **48** (RR-1): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4801.pdf (accessed 25/05/06)

Postexposure treatment. WHO guidelines[1,2] emphasise the importance of prompt local treatment for all bite wounds and scratches that may be contaminated with rabies virus and that, depending on the category of animal contact, rabies vaccine on its own or with rabies immunoglobulin should be given. The combination of these measures immediately after exposure is considered to guarantee almost complete protection. Pregnancy and infancy are not contra-indications to postexposure vaccination. These measures should be instituted even in patients who present months after having been bitten.

First aid or local treatment consists of immediate thorough flushing and washing of the wound with water, or soap and water, or detergent followed by the application of alcohol 70% or tincture or aqueous solution of iodine. Medical care may then consist of the instillation of rabies immunoglobulin into the depth of the wound and infiltration around the wound. Ideally the wound should not be sutured, but if suturing is necessary then it is essential that it be preceded by rabies immunoglobulin as above. Antimicrobials and tetanus vaccine may also be given as necessary.

The use of rabies vaccine and of rabies immunoglobulin depends on the category of animal contact. WHO classifies the type of contact with a suspect or rabid animal into 3 categories:

- category I covers touching or feeding of animals and licks on intact skin
- category II covers nibbling of uncovered skin, minor scratches or abrasions without bleeding, and licks on broken skin
- category III covers single or multiple transdermal bites or scratches and contamination of mucous membranes with the animal's saliva

Generally no treatment is required for category I contact. Patients who have had category II contact should be given rabies vaccine but the course may be stopped if the contact has been with a cat or dog that remains healthy throughout an observation period of 10 days or if postmortem study of the contact animal shows it to be negative for rabies. Patients with category III contact should be given rabies vaccine preceded by rabies immunoglobulin infiltrated around the wound and instilled into it as described above.

There are 2 types of immunoglobulin available; human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose for HRIG is 20 international units/kg and for ERIG products is 40 international units/kg. As much as possible of the dose should be infiltrated into and around the wound, with the remainder being injected intramuscularly into a site remote from that where vaccine was given, such as the anterior thigh.

The potency of rabies vaccines should be at least 2.5 international units per single human dose. For intramuscular vaccination schedules one dose should be given on days 0, 3, 7, 14, and 28 into the deltoid region or, for small children, into the anterolateral area of the thigh. An abbreviated multisite intramuscular schedule (the 2-1-1 regimen) induces an early antibody response and may be particularly effective when postexposure treatment has not included a rabies immunoglobulin. This schedule consists of one dose given in the right arm and one in the left arm on day 0, and one dose intramuscularly into the deltoid region on days 7 and 21.

Intradermal vaccination reduces the volume of injection required and is therefore suited to situations where vaccine or money is in short supply. For intradermal vaccination one dose (0.1 mL) of purified chick embryo-cell or purified Vero-cell vaccine may be given at each of two sites, usually the left and right upper arm, on days 0, 3, 7, and 28. Alternatively, in emergency situations when no rabies immunoglobulin is available, either human diploid cell or purified chick embryo-cell rabies vaccine may be given intradermally in one dose at each of 8 sites on day 0, in one dose at 4 sites on day 7, and subsequently in one dose at one site on days 28 and 90.

For postexposure treatment of previously vaccinated patients, WHO recommends local treatment of wounds followed by rabies vaccine given on days 0 and 3, either as a standard intramuscular dose or as one intradermal dose per site. No rabies immunoglobulin should be given. Patients who previously received vaccines of unproven potency or who have failed to develop an acceptable rabies neutralising antibody titre should be given full treatment as for those previously unimmunised.

In the UK,[3] rabies immunoglobulin is given if the patient is previously unimmunised and at high risk. Vaccine is given on days 0, 3, 7, 14, and 30 (five doses) in unimmunised persons (although the UK licensed product information for human diploid cell vaccine also recommends a sixth dose on day 90); two doses, one each on day 0 and day 3 are given to previously fully immunised persons.

In the USA, a human diploid-cell vaccine, an adsorbed rabies vaccine, or a purified chick embryo cell vaccine may be used for postexposure treatment.[4] In previously unimmunised individuals, a 1-mL dose of vaccine is given intramuscularly on days 0, 3, 7, 14, and 28, with rabies immunoglobulin as in the WHO schedule. In previously immunised individuals, two doses of vaccine are given on days 0 and 3, and rabies immunoglobulin is not required.

1. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
2. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
3. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
4. CDC. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999; **48** (RR-1): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4801.pdf (accessed 25/05/06)

Preparations

Ph. Eur.: Rabies Vaccine for Human Use Prepared in Cell Cultures;
USP 31: Rabies Vaccine.

Proprietary Preparations (details are given in Part 3)

Arg.: Verorab; ***Austral.:*** Rabipur; ***Austria:*** Rabipur; ***Braz.:*** HDCV; Vacina Anti-Rabica Humana; Verorab†; ***Canad.:*** Imovax Rabies; RabAvert; ***Chile:*** Verorab; ***Cz.:*** Rabipur; Verorab; ***Denm.:*** Rabies-Imovax; ***Fin.:*** Rabies-Imovax; ***Fr.:*** Rabipur; ***Ger.:*** Rabipur; Rabivac†; Tollwut-Impfstoff (HDC); ***Hong Kong:*** Verorab; ***India:*** Rabipur; Rabivax; ***Indon.:*** Verorab; ***Israel:*** Rabipur; ***Ital.:*** Imovax Rabbia; Lyssavac N†; Rabipur; Rasilvax†; ***Malaysia:*** Verorab; ***Neth.:*** Rabipur; ***Norw.:*** Rabies-Imovax; ***Philipp.:*** Rabipur; Verorab; ***Pol.:*** Verorab; ***Port.:*** Rabipur; ***S.Afr.:*** Rabipor; Verorab; ***Spain:*** Vacuna Antirrabica; ***Swed.:*** Rabies-Imovax; ***Switz.:*** Lyssavac N†; ***Thai.:*** Lyssavac N; Rabipur; Verorab; ***Turk.:*** HDCV; Rabivac; ***UK:*** Rabipur; ***USA:*** Imovax Rabies; RabAvert; ***Venez.:*** Verorab.

Respiratory Syncytial Virus Immunoglobulins

Inmunoglobulinas contra el virus sincitial respiratorio.

Palivizumab *(BAN, rINN)*

Palivitsumabi; Palivizumabum. immunoglobulin G 1 (human-mouse monoclonal MEDI-493 γ1-chain antirespiratory syncytial virus protein F), disulfide with human-mouse monoclonal MEDI-493 κ-chain, dimer.

Паливизумаб

CAS — 188039-54-5.

ATC — J06BB16.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

There is some evidence that antibody responses to diphtheria, tetanus, pertussis, and Haemophilus influenzae vaccines may be reduced in infants also receiving respiratory syncytial virus immunoglobulins.

Uses and Administration

Respiratory syncytial virus immunoglobulin is available in some countries for the passive immunisation of infants against lower respiratory-tract infections caused by RSV. It is prepared from the pooled plasma of adults selected for high titres of antibodies that neutralise the virus. Each mL of respiratory syncytial virus immunoglobulin contains about 50 mg of protein.

In the USA, children under 2 years of age with chronic lung disease (bronchopulmonary dysplasia) or a history of premature birth may receive a prophylactic intravenous infusion once a month during the RSV season (typically November to April or early May). The drug is given in a dose of up to 750 mg/kg at an initial rate of 75 mg/kg per hour for 15 minutes, followed by 180 mg/kg per hour until the end of the infusion.

Palivizumab, a human monoclonal antibody to RSV, is available in some countries and is used intramuscularly for similar purposes, in a dose of 15 mg/kg monthly. Palivizumab is also recommended in children under 2 years of age with haemodynamically significant congenital heart disease. Children undergoing cardiac bypass should be given an extra dose of palivizumab as soon as they are stable after surgery; doses are subsequently resumed monthly thereafter.

◊ The American Academy of Pediatrics has issued revised indications for the use of palivizumab and respiratory syncytial virus immunoglobulin.[1] Palivizumab or respiratory syncytial virus immunoglobulin prophylaxis should be considered for infants younger than 2 years of age with chronic lung disease (bronchopulmonary dysplasia) who have required medical therapy for their condition within 6 months of the anticipated start of the RSV season. Infants born at 32 weeks' gestation or earlier may benefit from prophylaxis even if they do not have chronic lung disease. Although prophylaxis has been shown to reduce hospitalisation for infants born between 32 and 35 weeks' gestation, the cost for this large group of infants should be considered carefully. Palivizumab, may in addition be given to children under 2 years of age with haemodynamically significant congenital heart disease.

Both palivizumab and respiratory syncytial virus immunoglobulin have been shown to decrease the risk of severe RSV infection in high-risk infants and children. Palivizumab is preferred over respiratory syncytial virus immunoglobulin for most high-risk children because of its comparative ease of administration, safety, and efficacy. Monthly use of palivizumab during the RSV season results in a 45 to 55% reduction in hospitalisation. Although palivizumab is usually preferred, respiratory syncytial virus immunoglobulin may also decrease the incidence of other respiratory-tract infections in addition to those caused by RSV, and this may be of benefit for infants younger than 6 months who are not eligible for influenza immunisation and those with severe pulmonary disease who may be more prone to other respiratory-tract infections. Palivizumab has not been shown to affect the rate of hospitalisation for non-RSV infections or the incidence of otitis media.

1. Committee on Infectious Diseases and Committee on Fetus and Newborn, American Academy of Pediatrics. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003; **112:** 1442–6. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;112/6/1442.pdf (accessed 24/05/06)

The symbol † denotes a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Synagis; ***Austral.:*** Synagis; ***Belg.:*** Synagis; ***Braz.:*** Synagis; ***Canad.:*** Synagis; ***Chile:*** Synagis; ***Cz.:*** Synagis; ***Denm.:*** Synagis; ***Fin.:*** Synagis; ***Fr.:*** Synagis; ***Ger.:*** Synagis; ***Gr.:*** Synagis; ***Hong Kong:*** Synagis; ***Hung.:*** Synagis; ***Irl.:*** Synagis; ***Israel:*** Abbosynagis; ***Ital.:*** Synagis; ***Malaysia:*** Synagis; ***Mex.:*** Synagis; ***Neth.:*** Synagis; ***Norw.:*** Synagis; ***NZ:*** Synagis; ***Pol.:*** Synagis; ***Port.:*** Synagis; ***S.Afr.:*** Synagis; ***Singapore:*** Synagis†; ***Spain:*** Synagis; ***Swed.:*** Synagis; ***Switz.:*** Synagis; ***Turk.:*** Synagis; ***UK:*** Synagis; ***USA:*** RespiGam; Synagis; ***Venez.:*** Synagis.

Respiratory Syncytial Virus Vaccines

Vacunas del virus sincitial respiratorio.

Profile

Vaccines containing RSV protein subunit are being studied for active immunisation.

◊ Development of an effective and safe vaccine against RSV has been hampered by a number of factors.[1-3] The target population for a vaccine is mainly young infants who may not respond adequately to vaccination owing to the antigenic diversity of RSV, immunological immaturity, or the presence of maternal antibodies. In the early 1960s, a formalin inactivated respiratory syncytial virus vaccine known as FI-RSV (also sometimes called Lot 100) was tested in infants and children aged 2 months to 7 years but failed to protect against subsequent infection with wild-type virus; it also led to a catastrophically exaggerated clinical response to wild-type virus in infants who were naive to RSV before vaccination, resulting in hospitalisation for the majority of recipients and 2 fatalities. Since that time, a number of candidate vaccines have subsequently been developed including live attenuated virus and viral protein subunit vaccines.[1,2] Several of the live attenuated vaccine candidates have been investigated in humans but results have generally been disappointing. More recently, genetically engineered live attenuated vaccine candidates have been generated, and some are currently being investigated in clinical studies.[1,2]

Subunit vaccines are composed of the F and G glycoproteins from RSV since these are the glycoproteins that induce antibody responses.[1,2] They are most likely to be of use in older persons and in high-risk children and might also be used for maternal immunisation. A chimeric FG fusion protein vaccine was evaluated in phase I studies but is no longer in development.

1. Durbin AP, Karron RA. Progress in the development of respiratory syncytial virus and parainfluenza virus vaccines. *Clin Infect Dis* 2003; **37:** 1668–77.
2. Kneyber MCJ, Kimpen JLL. Advances in respiratory syncytial virus vaccine development. *Curr Opin Investig Drugs* 2004; **5:** 163–70.
3. Power UF. Respiratory syncytial virus (RSV) vaccines—two steps back for one leap forward. *J Clin Virol* 2008; **41:** 38–44.

Rift Valley Fever Vaccines

Vacunas de la fiebre del valle del Rift.

Profile

An inactivated rift valley fever vaccine has been developed for the active immunisation of persons at high risk of contracting the disease.

Rotavirus Vaccines

Vacunas de rotavirus.
ATC — J07BH01; J07BH02.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

The most common adverse effects reported in subjects receiving rotavirus vaccines (attenuated human strain or pentavalent reassortant rotavirus vaccine) are fever, fatigue, irritability, and gastrointestinal disturbances. Otitis media, nasopharyngitis, bronchospasm, and haematochezia (blood in the stools) have also been reported with the pentavalent vaccine. A few cases of Kawasaki disease have been reported with the pentavalent vaccine but no causal relationship has been established.

There has been much debate on the causal role of rotavirus vaccines for intussusception (see below); cases have been reported during post-marketing use.

The UK licensed product information for the attenuated human strain vaccine contraindicates the use of this vaccine in children with a history of intussusception or with congenital conditions of the gastrointestinal tract, while the US licensed product information for pentavalent vaccine advises that it be used with caution. Caution is also generally advised in those with gastrointestinal illnesses or growth retardation and use may be postponed in children suffering from diarrhoea or vomiting. Use of a rotavirus vaccine should be carefully considered before being given to infants with a close family contact who is immunocompromised; if given precautions should be taken to avoid transmission of any excreted vaccine virus.

Intussusception. A live oral tetravalent vaccine (RRV-TV) became available in the USA in August 1998 but was withdrawn from the market by the manufacturer in October 1999 after reports of intussusception (a condition when part of the intestine prolapses into the lumen of an adjacent part causing an obstruction). From September 1998 until July 1999, 15 patients with intussusception had been reported to the Vaccine Adverse Event Reporting System (VAERS), 12 of whom developed symptoms within a week of vaccination.[1] While this evidence was considered inconclusive, further studies were expected to clarify the risks associated with routine use of this vaccine. One such study,[2] in which 429 infants with intussusception were retrospectively analysed, found that 74 (17.2%) had received RRV-TV compared with 226 of 1763 controls (12.8%) and concluded that there was evidence of a causal relationship with the vaccine. Another retrospective study,[3] however, found that there was no evidence of an increase in hospital admissions due to intussusception during the period of RRV-TV availability and recommended that a large, randomised, double-blind vaccine trial be performed to determine the absolute risk. Further analysis of the incidence of intussusception associated with RRV-TV has prompted discussion as to whether the absolute risk might in fact be sufficiently low that withholding the vaccine results in greater mortality than would be caused by intussusception.[4] Reassessment of the data on RRV-TV and intussusception has suggested that the risk for intussusception was age-dependent; relative risk for intussusception following the first dose of RRV-TV increased with increasing age.[5,6] However, WHO Global Advisory Committee on Vaccine Safety found that there was insufficient evidence available to determine whether use of RRV-TV before 60 days of age was associated with a lower risk for intussusception but confirmed the association of a high risk of intussusception in infants immunised after day 60.[7] Such considerations have implications for the ongoing evaluation of other candidate live attenuated rotavirus vaccines in that, should cases of intussusception occur, a decision might be required as to what constitutes an acceptable rate.[4]

From February 2006 until February 2007, 35 patients with confirmed intussusception had been reported to VAERS following vaccination with the pentavalent reassortant vaccine; 17 of whom developed symptoms within 21 days of vaccination, including 11 that occurred within 7 days of vaccination. However, this number of cases is not higher than the age adjusted background rates for intussusception.[8]

1. CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR* 1999; **48:** 577–81.
2. Murphy TV, *et al.* Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001; **344:** 564–72. Correction. *ibid.*; 1564.
3. Simonsen L, *et al.* Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet* 2001; **358:** 1224–9.
4. Murphy BR, *et al.* Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. *J Infect Dis* 2003; **187:** 1301–8.
5. Rothman KJ, *et al.* Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. *J Infect Dis* 2006; **193:** 898.
6. Simonsen L, *et al.* More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis* 2005; **192** (suppl 1): S36–S43.
7. WHO. Global Advisory Committee on Vaccine Safety, 1–2 December 2005. *Wkly Epidem Rec* 2006; **81:** 15–19.
8. CDC. Postmarketing monitoring of intussusception after RotaTeq vaccination—United States, February 1, 2006–February 15, 2007. *MMWR* 2007; **56:** 218–22.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Several live oral rotavirus vaccines for use in the prevention of childhood diarrhoea have been developed and some are now licensed.

A live attenuated oral monovalent rotavirus vaccine (based on the human RIX4414 strain) is available in some countries. Two doses are given, the first at 6 weeks of age onwards and the subsequent dose at least 4 weeks later; the course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks. A live oral pentavalent reassortant rotavirus vaccine (based on human and bovine strains) is available in the USA. Three doses are given, the first at 6 to 12 weeks of age and the two subsequent doses at 4- to 10-week intervals; the third dose should not be given after 32 weeks of age.

A live oral tetravalent rotavirus vaccine (RRV-TV) was formerly available in the USA but was withdrawn by the manufacturer in October 1999 after reports of intussusception associated with its use.

◊ References.

1. Vesikari T, *et al.* Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; **354:** 23–33.
2. Ruiz-Palacios GM, *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; **354:** 11–22.
3. Buttery JP, Kirkwood C. Rotavirus vaccines in developed countries. *Curr Opin Infect Dis* 2007; **20:** 253–8.
4. Cunliffe N, Nakagomi O. Introduction of rotavirus vaccines in developing countries: remaining challenges. *Ann Trop Paediatr* 2007; **27:** 157–67.
5. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008; **21:** 198–208.

Vaccine development. Rotaviruses are an important cause of severe diarrhoea in both developed and developing countries (see Gastro-enteritis, p.850); rates of illness are similar in both and improvement in water quality and general hygiene does not have much effect on viral transmission. The disease infects almost all children before the age of 5 years but is most severe among children 3 to 35 months of age.[1,2] Human rotavirus diarrhoea is caused by group A, B, or C rotaviruses.[3] While an initial infection does not produce complete immunity, it does appear to be protective against further severe gastroenteritis. Vaccination therefore aims to produce a similar effect.[1,2] Development of a suitable vaccine has been made difficult by the diversity of rotaviruses.[3] Initial attempts at vaccine development used single bovine or rhesus monkey strains but these were associated with variable efficacy and adverse effects.[4-6]

To overcome these problems reassortant rotavirus (RRV) strains were constructed. These combined animal rotavirus strains with human rotavirus genes coding for serotype-specific antigens, enabling polyvalent vaccines to be produced against the major rotavirus serotypes causing disease. A number of such candidate vaccines are under development[7] and some are now licensed.[8] Guidelines have been developed in the USA for the use of rotavirus vaccine.[1,2]

1. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006; **55** (RR-12): 1–13. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5512.pdf (accessed 19/06/07)
2. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. *Pediatrics* 2007; **119:** 171–82. Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/1/171 (accessed 19/06/07)
3. Anonymous. Puzzling diversity of rotaviruses. *Lancet* 1990; **335:** 573–5.
4. Levine MM. Modern vaccines: enteric infections. *Lancet* 1990; **335:** 958–61.
5. Bernstein DI, *et al.* Evaluation of WC3 rotavirus vaccine and correlates of protection in healthy infants. *J Infect Dis* 1990; **162:** 1055–62.
6. Flores J, *et al.* Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants. *Lancet* 1987; **i:** 882–4.
7. Glass RI, *et al.* The future of rotavirus vaccines: a major setback leads to new opportunities. *Lancet* 2004; **363:** 1547–50.
8. Heaton PM, Ciarlet M. Vaccines: the pentavalent rotavirus vaccine: discovery to licensure and beyond. *Clin Infect Dis* 2007; **45:** 1618–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rotarix; RotaTeq; ***Austral.:*** Rotarix; RotaTeq; ***Belg.:*** Rotarix; ***Chile:*** Rotarix; ***Cz.:*** Rotarix; RotaTeq; ***Fr.:*** Rotarix; RotaTeq; ***Gr.:*** Rotarix; RotaTeq; ***Hung.:*** Rotarix; RotaTeq; ***Malaysia:*** Rotarix; RotaTeq; ***Mex.:*** Rotarix; ***NZ:*** Rotarix; RotaTeq; ***Philipp.:*** Rotarix; ***Pol.:*** Rotarix; RotaTeq; ***Port.:*** Rotarix; RotaTeq; ***Singapore:*** Rotarix; ***Thai.:*** Rotarix; ***UK:*** Rotarix; ***USA:*** Rotarix; RotaTeq; ***Venez.:*** Rotarix.

Rubella Immunoglobulins

Inmunoglobulinas contra la rubéola.
ATC — J06BB06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Human Rubella Immunoglobulin; Immunoglobulinum Humanum Rubellae). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the rubella virus. Normal immunoglobulin may be added. It contains not less than 4500 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Rubella immunoglobulins may be used for passive immunisation against rubella (German measles). They have been used to prevent or modify rubella in susceptible persons.

Preparations

Ph. Eur.: Human Rubella Immunoglobulin.

Rubella Vaccines

Vacunas de la rubéola.
ATC — J07BJ01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Rubella Vaccine (Live); Vaccinum Rubellae Vivum). A freeze-dried preparation of a suitable live attenuated strain of rubella virus grown in human diploid cell cultures. It is reconstituted immediately before use. The cell-culture medium may contain a permitted antibacterial at the smallest effective concentration, and a suitable stabiliser may be added to the bulk vaccine. The final vaccine contains not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Rubella may be used on the label.

USP 31 (Rubella Virus Vaccine Live). A bacterially sterile preparation of a suitable live strain of rubella virus grown in cultures of duck-embryo tissue or human tissue. It contains the equivalent of not less than 1×10^3 $TCID_{50}$ in each immunising dose. It should be stored at 2° to 8° and be protected from light.

Adverse Effects

As for vaccines in general, p.2201.

Generally, adverse effects have not been severe. Those occurring most commonly are skin rashes, pharyngitis, fever, and lymphadenopathy; arthralgia and arthritis may also occur. Thrombocytopenia (including idiopathic thrombocytopenic purpura) has been reported rarely.

Effects on bones and joints. Although acute arthralgia or arthritis occurs in up to 30% of women after rubella vaccination,[1] a retrospective analysis found no evidence of an increased risk of chronic arthropathies.[2]

1. Tingle AJ, *et al.* Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 1997; **349:** 1277–81.
2. Ray P, *et al.* Risk of chronic arthropathy among women after rubella vaccination. *JAMA* 1997; **278:** 551–6.

Effects on hearing. For a report of irreversible sensorineural deafness associated with use of measles and rubella vaccine, see p.2223.

Effects on the nervous system. For a report of optic neuritis in 2 children after use of measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p.2223.

Precautions

As for vaccines in general, p.2202.

Rubella vaccines should not be given during pregnancy. In the UK it is recommended that patients should be advised not to become pregnant within 1 month of vaccination. However, no case of congenital rubella syndrome has been reported after the inadvertent use of rubella vaccines shortly before or during pregnancy and there is no evidence that the vaccines are teratogenic. Inadvertent use of rubella vaccines during pregnancy should not therefore result in a recommendation to terminate the pregnancy. There is no risk to a pregnant woman from contact with recently vaccinated persons as the vaccine virus is not transmitted.

Rubella vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Vaccines may contain traces of neomycin and/or polymyxin and should therefore not be given to individuals with a history of anaphylaxis to these antibacterials.

Pregnancy. Since 1971 the US CDC has followed up women who received rubella vaccines within 3 months before or after conception.[1] Up to 1979 vaccines containing either the Cendehill or HPV-77 strains of rubella virus were available. None of the 290 infants born to the 538 women who had received these vaccines had defects indicative of congenital rubella syndrome; this included 94 live-born infants of women who were known to be susceptible to rubella before receiving the vaccine. In 1979 a rubella vaccine containing the Wistar RA 27/3 strain was introduced. None of 212 infants born live to 254 women known to be susceptible to rubella and who had received the RA 27/3 rubella vaccine from 1979 to 1988 had defects indicative of congenital rubella syndrome. These results are consistent with experiences in Germany[2] and the UK.[3,4] However, because of evidence that rubella vaccine viruses can cross the placenta and infect the fetus a theoretical risk to the fetus cannot be completely ruled out.[1] Thus in both the UK and USA pregnancy is considered a contraindication to rubella vaccination, and patients are also advised not to become pregnant within one month of vaccination. However, in neither country is termination of pregnancy recommended if the vaccine is inadvertently given during pregnancy.

1. Anonymous. Rubella vaccination during pregnancy—United States, 1971–1988. *JAMA* 1989; **261:** 3374–83.
2. Enders G. Rubella antibody titers in vaccinated and nonvaccinated women and results of vaccination during pregnancy. *Rev Infect Dis* 1985; **7** (suppl 1): S103–S107.
3. Sheppard S, *et al.* Rubella vaccination and pregnancy: preliminary report of a national survey. *BMJ* 1986; **292:** 727.
4. Tookey PA, *et al.* Rubella vaccination in pregnancy. *Commun Dis Rep* 1991; **1** (review 7): R86–R88.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Rubella vaccines are used for active immunisation against rubella (German measles). The symptoms of rubella infection are generally mild except in the early stages of pregnancy when it leads to fetal damage in most infants.

For primary immunisation combined measles, mumps, and rubella vaccine (p.2223) is usually given. For discussion of immunisation schedules, see under Vaccines, p.2202.

Women of child-bearing age should also be vaccinated with the combined vaccine if they are seronegative; women who are found to be seronegative during pregnancy should be vaccinated in the early postpartum period. Effective precautions against pregnancy must be observed for at least one month after vaccination. To avoid the risk of transmitting rubella to pregnant patients, all health service staff, both male and female, should be screened and those found to be seronegative should be vaccinated.

In the USA and in many other countries, a single-antigen rubella vaccine is available although combined vaccines are usually preferred.

Preparations

Ph. Eur.: Rubella Vaccine (Live);
USP 31: Rubella Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Rubeola†; Rudivax; ***Austral.:*** Ervevax; Meruvax II; ***Austria:*** Ervevax; Rubeaten; ***Braz.:*** Rudivax†; ***Cz.:*** Ervevax†; Rudivax†; ***Denm.:*** Meruvax†; ***Fr.:*** Rudivax; ***Ger.:*** Rubellovac†; ***Gr.:*** Vaccin Rubeole; ***Hong Kong:*** Rudivax†; ***India:*** R-Vac; ***Irl.:*** Ervevax†; ***Israel:*** Rudivax; ***Ital.:*** Ervevax†; Gunevax†; Rudivax†; ***Malaysia:*** Ervevax†; Gunevax†; ***Mex.:*** Ervevax; Gunevax†; ***NZ:*** Ervevax; ***Port.:*** Rubeaten†; Rudivax; ***Rus.:*** Ervevax (Эрвевакс); ***S.Afr.:*** Rudivax; ***Spain:*** Vac Antirrubeola†; ***Swed.:*** Meruvax†; ***Switz.:*** Ervevax†; Meruvax; Rubeaten; ***Thai.:*** Gunevax†; Rudivax†; ***UK:*** Almevax; ***USA:*** Meruvax II; ***Venez.:*** Imovax Rubeola†.

Rubella and Mumps Vaccines

Vacunas de la rubéola y la parotiditis.

ATC — J07BJ51.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

See also under Mumps Vaccines, p.2225, and Rubella Vaccines, above.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Rubella and mumps vaccines have been used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Biavax II.

Schistosomiasis Vaccines

Bilharzia Vaccines; Vacunas de la esquistosomiasis.

Profile

Vaccines against schistosomiasis are under development.

◊ Despite attempts since the 1960s, development of an effective vaccine against schistosomiasis has proved difficult.[1,2] The worms themselves are not thought to be responsible for the disease but the eggs elicit a powerful and damaging immune response when they are trapped in tissue.

As only the very young in endemic areas will not have been exposed to schistosomiasis a protective antigen for a candidate vaccine must be one that will attack the adult parasite without cross reacting with egg antigens thus increasing the risk of developing chronic disease in those already affected. Most antigen vaccine candidates tested to date have at best resulted in 50 to 60% protection in animal models although repeated immunisation with irradiated cercariae in *murine* models has resulted in almost 80% protection. Consequently it has been questioned whether sterilising immunity should be the aim. It might be more realistic to develop a vaccine which can reduce the overall worm burden and the fecundity of surviving worms, thus reducing the number of eggs released and deposited in the liver. This in turn would lead to lower rates of infection by reducing the numbers of miracidia available to infect snails. Such a vaccine would, however, only be effective in terms of infection and morbidity rates after a considerable period of time, probably more than 20 years. Alternatively, vaccine candidates that specifically attack particular stages of the parasite life cycle might be feasible. A number of potential vaccine candidate antigens have been identified although the only vaccine candidate to have progressed to phase I and II clinical studies is the glutathione-*S*-transferase antigen from *S. haematobium*, Sh28 GST, and these studies are currently ongoing. Use of antigens with recombinant cytokines in order to enhance immune response, or with the B subunit of cholera toxin in order to suppress harmful inflammatory responses, is also being investigated. There is also some suggestion that it might be possible to develop a multicomponent vaccine consisting of multiple antigens that will give protection against different stages in the parasite cycle.[1]

1. Lebens M, *et al.* Current status and future prospects for a vaccine against schistosomiasis. *Expert Rev Vaccines* 2004; **3:** 315–28.
2. McManus DP, Loukas A. Current status of vaccines for schistosomiasis. *Clin Microbiol Rev* 2008; **21:** 225–42.

Scorpion Venom Antisera

Antisuero contra el veneno de escorpión; Scorpion Antivenins; Scorpion Antivenoms.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

Some scorpion stings are dangerous and even fatal. The use of a scorpion venom antiserum suitable for the species of scorpion can prevent symptoms, provided that it is given with the least possible delay; other general supportive measures and symptomatic treatment are also needed. The effectiveness of scorpion venom antisera is disputed by some clinicians.

Scorpion stings. Scorpion stings are common throughout the tropics, but the most dangerous and potentially fatal species are found in India, North Africa and the Middle East, the southern states of North America and Mexico, Latin America and the Caribbean, and southern Africa. Local symptoms after scorpion stings include intense pain and swelling. Systemic symptoms result from excitation of nerve and muscle cells by the venom; the pattern of symptoms depends upon the species of scorpion. Symptoms such as hypersalivation, vomiting, and diarrhoea are generally followed by adrenergic features, with release of catecholamines producing hypertension, toxic myocarditis, arrhythmias, heart failure, and pulmonary oedema. The cardiotoxic effects are prominent features of stings in India, North Africa, and the Middle East. Neurotoxic effects such as fasciculations, spasms, and respiratory paralysis are seen with stings from North American species. Stings by the black scorpion of Trinidad may also produce pancreatitis.

Pain is treated with local infiltration or peripheral nerve block with local anaesthetics; opioid analgesics may be necessary, but are regarded as dangerous after stings by some North American species. An appropriate antiserum may be given as soon as possible after envenomation, although the effectiveness of some antisera has been questioned and in some countries they are no longer considered of benefit. Supportive treatment for cardiotoxic effects includes alpha blockers, calcium-channel blockers, and ACE inhibitors. The use of cardiac glycosides, beta blockers, and atropine is controversial. Phenobarbital has been suggested for neurotoxic effects.

References.

1. el Amin EO, *et al.* Scorpion sting: a management problem. *Ann Trop Paediatr* 1991; **11:** 143–8.
2. Bond GR. Antivenin administration for Centruroides scorpion sting: risks and benefits. *Ann Emerg Med* 1992; **21:** 788–91.
3. Warrell DA, Fenner PJ. Venomous bites and stings. *Br Med Bull* 1993; **49:** 423–39.
4. Müller GJ. Scorpionism in South Africa: a report of 42 serious scorpion envenomations. *S Afr Med J* 1993; **83:** 405–11.
5. Gateau T, *et al.* Response to specific centruroides sculpturatus antivenom in 151 cases of scorpion stings. *Clin Toxicol* 1994; **32:** 165–71.
6. Sofer S, *et al.* Scorpion envenomation and antivenom therapy. *J Pediatr* 1994; **124:** 973–8.
7. Karalliedde L. Animal toxins. *Br J Anaesth* 1995; **74:** 319–27.
8. Abroug F, *et al.* Serotherapy in scorpion envenomation: a randomised controlled trial. *Lancet* 1999; **354:** 906–9.
9. Isbister GK, *et al.* Scorpion stings in Australia: five definite stings and a review. *Intern Med J* 2004; **34:** 427–30.
10. Gazarian KG, *et al.* Immunology of scorpion toxins and perspectives for generation of anti-venom vaccines. *Vaccine* 2005; **23:** 3357–68.
11. Bencheikh RS, *et al.* Conduite à tenir devant une piqûre de scorpion au Maroc. *Ann Fr Anesth Reanim* 2008; **27:** 317–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Alacramyn.

Shigella Vaccines

Dysentery Vaccines; Shigellosis Vaccines; Vacunas contra Shigella.

Profile

Shigella vaccines have been under investigation since the 1960s but early prototypes were unsatisfactory. Live attenuated oral vaccines, parenteral conjugated vaccines, and intranasal vaccines are now also under development.

◊ Natural or experimental exposure to *Shigella* antigens has been shown to induce clinical immunity, and there has been some work towards developing an effective vaccine.[1,2] There have been 3 main approaches to vaccination under investigation.[1] Firstly, workers at the USA National Institutes of Health have developed a series of vaccines in which the O antigen of *S. sonnei*, *S. flexneri* 2a strain, or *S. dysenteriae* type 1 is conjugated to *Pseudomonas aeruginosa* recombinant exoprotein A. These vaccines are given intramuscularly and have elicited strong immune responses in adults and children tested, and some have reached phase III studies. A second approach has been to deliver *Shigella* lipopolysaccharide intranasally in proteasomes, which are purified outer membrane proteins that form a multimolecular vesicular complex around the antigen; these vaccines are being tested in phase I studies. The third approach is the use of live attenuated oral vaccines, attenuated by creating deletions in genes that govern vital metabolic processes within the organism or by mutating genes that encode specific virulence factors.

A major challenge in the development of a shigella vaccine is to provide protection against all of the numerous serotypes that appear epidemiologically important. Most experts agree that for a shigella vaccine to be totally effective globally it must protect against *S. dysenteriae* type 1, *S. sonnei*, and all 15 classical *S. flexneri* serotypes. However, it has been shown that a composite of 3 *S. flexneri* serotypes (2a, 3a, and 6) can provide cross protection against the remaining 12. Hence the ultimate plan is to develop a pentavalent vaccine comprising these 3 *S. flexneri* serotypes together with *S. sonnei* and *S. dysenteriae* type 1.[1] Shigella vaccines have been licensed for use in China.[2]

1. Kotloff KL. Progress in Shigella vaccine development. In: de Quadros CA, ed. *Vaccines: Preventing Disease and Protecting Health*. Washington D.C., 2004: 130–9.

2. Kweon MN. Shigellosis: the current status of vaccine development. *Curr Opin Infect Dis* 2008; **21:** 313–8.

Smallpox Vaccines

Vacunas de la viruela.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Smallpox Vaccine (Live)). A liquid or freeze-dried preparation of live vaccinia virus grown in the membranes of the chick embryo, in cell cultures, or in the skin of living animals. The cell culture medium may contain suitable antibacterials at the lowest effective concentration. Store at 2° to 8° and protect from light. The liquid vaccine should not be allowed to freeze.

USP 31 (Smallpox Vaccine). A suspension or solid containing a suitable strain of the living virus of vaccinia grown in the skin of bovine calves; it may contain a suitable preservative. The liquid vaccine should be stored below 0° and the dried vaccine at 2° to 8°.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Both first and second generation live smallpox vaccines have been associated with a high incidence of adverse effects. The most common adverse effects are injection site reactions, fatigue, fever, headache, malaise, myalgia, erythema, and generalised rash. Rarely there may be generalised vaccinial infection, or severe skin or CNS infection resulting in encephalitis, encephalomyelitis, encephalopathy, necrotising skin infection (progressive vaccinia, vaccinia necrosum), eczema vaccinatum, and erythema multiforme (including Stevens-Johnson syndrome). Fatalities have occurred, particularly from post-vaccination encephalitis and progressive vaccinia. Inadvertent contamination of other body sites (such as the face, mouth, nose, lips, and genitalia) from the site of vaccination also occurs frequently; autoinoculation of the eye (ocular vaccinia) may result in blindness. Benign and malignant lesions have also been reported at the vaccination site.

There have been reports of myocarditis or pericarditis or both, including some fatalities, associated with smallpox vaccination. Smallpox vaccination is not recommended for infants under 12 months of age, for persons with a history of eczema or other skin conditions, those who are immunocompromised, for pregnant women, or for women who breast feed. Household contacts of these groups should also not be vaccinated. Vaccination is best avoided in persons with known cardiac disease.

◊ References.

1. CDC. Smallpox vaccination and adverse reactions: guidance for clinicians. *MMWR* 2003; **52** (RR-04): 1–28. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5204.pdf (accessed 05/11/07)
2. CDC. Notice to readers: supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2003; **52** (RR-07): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5207.pdf (accessed 05/11/07)
3. Fulginiti VA, *et al.* Smallpox vaccination: a review, part II. Adverse events. *Clin Infect Dis* 2003; **37:** 251–71.
4. CDC. Update: adverse events following civilian smallpox vaccination—United States, 2003. *MMWR* 2004; **53:** 106–7. Correction. *ibid.*; 133. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5305a4.htm (accessed 06/11/07)
5. Sejvar JJ, *et al.* Neurologic adverse events associated with smallpox vaccination in the United States, 2002–2004. *JAMA* 2005; **294:** 2744–50. Corrections. *ibid.*; 3092 and **298:** 1864.
6. Casey CG, *et al.* Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. *MMWR* 2006; **55** (RR-1): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5501.pdf (accessed 05/11/07)

Uses and Administration

After the global eradication of smallpox in 1980, vaccination against smallpox (using first generation vaccinia virus vaccine) has been indicated for those considered to be at high risk such as laboratory workers handling certain orthopoxviruses, and key emergency, healthcare, and military personnel who may have to respond to a bioterrorist release of smallpox. A second generation smallpox vaccine has been licensed in the USA for inclusion to the National Stockpile for vaccination of those considered to be at high risk for smallpox infection. Persons at high risk and who have received primary vaccination against smallpox, should be re-vaccinated every 10 years. Vaccination is not recommended for persons working with highly attenuated strains of orthopoxviruses.

WHO considers that mass vaccination against smallpox is currently not appropriate, although individuals who may be at risk of exposure to smallpox or those with confirmed infection may be vaccinated.

Recombinant vaccinia viruses are being investigated as vectors of foreign antigens, for example in a candidate AIDS vaccine (p.2203).

Vaccine development. Smallpox[1] is an acute contagious and sometimes fatal disease caused by variola virus, a member of the Poxviridae family and of the orthopoxvirus genus. There is substantial cross-protection between poxviruses of the same genus; the very effective first generation smallpox vaccine used in the global vaccination programme was created from an orthopoxvirus, vaccinia. In 1980 WHO declared smallpox to have been globally eradicated.

There has since been concern that smallpox may be used as a terrorist weapon (although WHO considers this risk to be extremely low in most countries). Therefore, research into safer vaccines against smallpox has continued. First generation vaccine was produced from vaccinia strains grown on the skin of live animals or calf lymph. Despite purification processes, the vaccine contained some bacteria, animal proteins, and adventitious animal viruses, and produced a high incidence of adverse effects, some of which were extremely serious (see Adverse Effects and Precautions, above). Second generation vaccines are single clones of vaccinia isolated from the set of genetically related viruses that made up the first generation ones; they are grown in tissue culture (rather than on animal skin or calf lymph) and are free of bacteria and adventitious animal viruses. A second generation vaccine has been found to be effective and is licensed in the USA for inclusion to the National Stockpile. However, this vaccine still has a high incidence of adverse effects. Third generation vaccines are in the early stages of development. They are being developed from vaccinia strains attenuated by serial passage on non-human tissue or by genetic manipulation, and are expected to be safer than either first or second generation vaccines. Interest has also been shown in monoclonal variola antibodies for passive immunisation.[1,2]

Stocks of smallpox (variola) virus are being kept in a few secure laboratories in the USA and Russia. Since the eradication of smallpox, WHO maintains a stockpile of smallpox vaccine, and recommends vaccination for people with occupational exposure to fully potent orthopoxviruses, such as certain laboratory and healthcare workers. Because of concern that smallpox may be used for bioterrorism, WHO and several countries have increased the number of doses kept in stock.[1] Policies for the use of smallpox vaccine, including bioterrorism preparedness, have been developed in many countries such as the USA[3,4] and UK[5,6] with some countries recommending vaccination for key emergency and military personnel.

1. Moore ZS, *et al.* Smallpox. *Lancet* 2006; **367:** 425–35.
2. Metzger W, Mordmueller BG. Vaccines for preventing smallpox. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 14/09/07).
3. CDC. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *MMWR* 2001; **50** (RR-10): 1–25. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf (accessed 25/05/06)
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5. Health Protection Agency. Interim guidelines for action in the event of a deliberate release: smallpox (issued January 2008). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947373093 (accessed 15/07/08)
6. Department of Health. Guidelines for smallpox response and management in the post-eradication era (smallpox plan) (issued December 2003). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4070830 (accessed 15/07/08)

Preparations

Ph. Eur.: Smallpox Vaccine (Live);
USP 31: Smallpox Vaccine.

Proprietary Preparations (details are given in Part 3)
USA: ACAM2000; Dryvax.

Snake Venom Antisera

Antisuero contra el veneno de serpiente; Snake Antivenins; Snake Antivenoms.

ATC — J06AA03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Viper Venom Antiserum, European; Immunoserum Contra Venena Viperarum Europaearum). A preparation containing the specific antitoxic globulins that have the power of neutralising the venom of one or more species of viper (*Vipera ammodytes*, *V. aspis*, *V. berus*, or *V. ursinii*). The globulins are obtained by fractionation of the serum of animals that have been immunised against the venom or venoms. Each mL neutralises the venoms in not less than 100 mouse LD_{50} of *V. ammodytes*, 100 of *V. aspis*, 50 of *V. berus*, or 50 of *V. ursinii*. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that the only poisonous snake native to the British Isles is the adder or common viper, *Vipera berus*. In a geographical region where other species of snake (including elapids) are found, antisera able to neutralise the venoms of the species of snake indigenous to the region should be used. When the preparation is intended to neutralise the venom or venoms of one or more snakes other than vipers, the title Snake Venom Antiserum is used.

USP 31 (Antivenin (Crotalidae) Polyvalent). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against 4 species of pit vipers, *Crotalus atrox* (western diamondback), *Crotalus adamanteus*, *Crotalus durissus terrificus* (South American rattlesnake), and *Bothrops atrox* (South American fer de lance). One dose neutralises the venoms in not less than 180 mouse LD_{50} of *C. atrox*, 1320 of *C. durissus terrificus*, and 780 of *B. atrox*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

USP 31 (Antivenin (Micrurus Fulvius)). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against venom of *Micrurus fulvius* (eastern coral snake). One dose neutralises the venom in not less than 250 mouse LD_{50} of *M. fulvius*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Serum sickness is not uncommon and anaphylactic reactions may occur.

Anaphylaxis. Conjunctival or cutaneous hypersensitivity testing failed to predict early (anaphylactic) reactions to the antivenom given in a study of patients in Nigeria with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*) and in Thailand with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T. macrops*), the monocellate Thai cobra (*Naja kaouthia*), or the Malayan pit viper (*Calloselasma rhodostoma*). It was considered that conventional hypersensitivity testing has no predictive value for the occurrence of allergic reactions to antivenom and that it is not justifiable to delay treatment for 20 or 30 minutes to read the results of these tests. Although the rate at which antiserum can be given is more easily controlled by intravenous infusion, this method has serious practical disadvantages in the rural tropics where most cases of snake bite occur and an advantage of the intravenous push injection is that the person giving the antiserum must remain with the patient during the period when most severe anaphylactic reactions develop.

Pretreatment with low-dose subcutaneous adrenaline may reduce the incidence of anaphylaxis and other acute adverse reactions to the antiserum.[1] However, premedication with adrenaline, antihistamines, and corticosteroids, although widely practiced, is controversial. In one study,[2] prophylaxis with promethazine was ineffective in preventing anaphylaxis from antiserum against *Bothrops* envenomation.

1. Premawardhena AP, *et al.* Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ* 1999; **318:** 1041–3.
2. Fan HW, *et al.* Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; **318:** 1451–2.

Uses and Administration

Venomous snakes comprise the Viperidae (vipers), Elapidae (cobras, kraits, and mambas), and the Hydrophiidae (sea snakes).

The venom of snakes is a complex mixture chiefly of proteins, many of which have enzymatic activity, and may provoke local inflammatory reactions. The venom may have profound effects on tissue, blood vessels and other organs, blood cells, coagulation, and myotoxic or neurotoxic effects with sensory, motor, cardiac, renal, and respiratory involvement.

Snake venom antisera are the only specific treatment available for venomous snake bites, but can produce severe adverse reactions. They are generally only used if there are clear indications of systemic involvement, severe local involvement, or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. Adrenaline should be available in case of anaphylactic reactions to the antiserum; premedication with adrenaline, corticosteroids, and/or antihistamines is widely practiced but is regarded as controversial.

In Great Britain, the only indigenous poisonous snake is the adder, *Vipera berus*; its bite is rarely fatal but European Viper Venom Antiserum (or Zagreb antivenom) may sometimes be indicated as part of the overall treatment. The usual dose for adults and children is 10 mL by intravenous injection over 10 to 15 minutes or by intravenous infusion over 30 minutes after diluting in 5 mL/kg body-weight of sodium chloride 0.9%; the dose may be repeated after about 1 to 2 hours if symptoms of systemic envenoming persist.

In the USA, a polyvalent crotalidae antiserum against *Bothrops atrox*, *Crotalus adamanteus*, *C. atrox*, and *C. durissus terrificus*, and an antiserum against the North American coral snake, *Micrurus fulvius*, are available. In Australia, polyvalent antisera against the brown snake, death adder, taipan, and tiger snake, together with either the king brown snake or black snake, are available. A variety of polyvalent and monovalent antisera are also available as appropriate to the indigenous species of snakes in many other countries.

Snake bites. Most snake species are non-venomous and belong to the colubrid family although a few colubrids are technically venomous. The 3 families of venomous front-fanged snakes are the elapids, vipers, and sea snakes. Elapids include cobras, mambas, kraits, coral snakes, and the Australasian venomous land snakes. Vipers are subdivided into crotalids (pit vipers) and viperids. Viper bites are much more common than elapid bites, except in Australasia, where vipers do not occur naturally. Sea snake bites occur among fishermen of the Asian and western Pacific coastal areas. Although there are some notable exceptions, viper bites tend to cause vasculotoxicity, elapids cause neurotoxicity, and sea snakes cause myotoxicity.

Only a few snakes are known to be of medical importance. Of the vipers these include *Bothrops atrox* (Central and South America), *Bitis arietans* (Africa), *Echis carinatus* (Africa and Asia), *Vipera russelli* (Asia), and *Agkistrodon rhodostoma* (south-east Asia). In a few restricted areas of Africa and Asia, cobra bites are common; bites by mambas (Africa) and kraits (Asia) are rare. The carpet viper, *Echis pyramidum*, and saw-scaled viper, *Echis carinatus*, can justifiably be labelled the most dangerous snakes in the world and they cause more deaths and serious poisoning than any other snake.

Management of snake bite involves general supportive care and monitoring of vital functions but in a systemic snake-bite poisoning, specific snake venom antiserum is the most effective therapeutic agent available. If used correctly, it can reverse systemic poisoning when given hours or even days after the bite. It is highly desirable to wait for clear clinical evidence of systemic poisoning before giving an antiserum and therefore it should not be given routinely in all cases of snake bite. Monospecific antisera are more effective, and less likely to cause reactions, than polyvalent antisera. The dosage of antiserum to be used is dependent on the species of snake and the consequent potency of the requisite antiserum. The antiserum should be given intravenously diluted in isotonic saline, either by infusion or bolus injection (see under Adverse Effects and Precautions, above). First aid measures including incisions and suction to remove the venom and application of tourniquets are generally to be discouraged. In most cases, the bitten limb should be immobilised and the victim transferred to a medical facility, together with the snake if possible. For bites by elapids, when respiratory failure may occur before the patient reaches hospital, a tourniquet may be justified to delay the onset of neurotoxicity. Supportive treatment is necessary even in patients who have received an adequate dose of antiserum. Local pain may be treated with a suitable analgesic. Artificial respiration may be required in patients with symptoms of neurotoxicity. Anticholinesterases may be of benefit against the neurotoxic effects of some snake venoms and it has been recommended that an intravenous test dose of edrophonium preceded by atropine should be tried in patients with severe symptoms of neurotoxicity. For those patients who respond, treatment with neostigmine should be started but anticholinesterases are unlikely to affect outcome in patients who already require assisted respiration. Hypovolaemia should be corrected cautiously with parenteral fluids. Hypotension may be treated with subcutaneous adrenaline or, in patients bitten by Russell's viper, a response to dopamine has been noted. Patients with renal impairment may require dialysis if they do not respond to rehydration, diuretics, and dopamine. Broad spectrum antibacterials and a tetanus vaccine should be given as prophylactic measures. Surgical decompression and debridement of necrotic tissue may be necessary once normal haemostasis has been restored.

References.

1. Reid HA, Theakston RDG. The management of snake bite. *Bull WHO* 1983; **61:** 885–95.
2. Nelson BK. Snake envenomation: incidence, clinical presentation and management. *Med Toxicol* 1989; **4:** 17–31.
3. Warrell DA. Snake venoms in science and clinical medicine: 1. Russell's viper: biology, venom and treatment of bites. *Trans R Soc Trop Med Hyg* 1989; **83:** 732–40.
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12. Cheng AC, Currie BJ. Venomous snakebites worldwide with a focus on the Australia-Pacific region: current management and controversies. *J Intensive Care Med* 2004; **19:** 259–69.
13. Warrell DA. Treatment of bites by adders and exotic venomous snakes. *BMJ* 2005; **331:** 1244–7.
14. Currie BJ. Treatment of snakebite in Australia: the current evidence base and questions requiring collaborative multicentre prospective studies. *Toxicon* 2006; **48:** 941–56.
15. Gutiérrez JM, *et al.* Trends in snakebite envenomation therapy: scientific, technological and public health considerations. *Curr Pharm Des* 2007; **13:** 2935–50.
16. Prenzel F, *et al.* Kreuzotterbisse—Klinik, Diagnostik und Behandlung. *Dtsch Med Wochenschr* 2008; **133:** 1075–80.

Preparations

Ph. Eur.: European Viper Venom Antiserum;
USP 31: Antivenin (Crotalidae) Polyvalent; Antivenin (Micrurus Fulvius).

Proprietary Preparations (details are given in Part 3)
Arg.: Suero Antiofidico Polivalente; ***Austral.:*** Polyvalent Snake Antivenom; ***Fr.:*** Viperfav; ***Hong Kong:*** Tiger Snake; ***Mex.:*** Antivipmyn; Coralmyn; ***USA:*** CroFab.

Spider Venom Antisera

Antisuero contra el veneno de arañas; Spider Antivenins; Spider Antivenoms.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 31 (Antivenin (Latrodectus Mactans)). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against venom of black widow spiders (*Latrodectus mactans*). One dose neutralises the venom in not less than 6000 mouse LD_{50} of *L. mactans*. It contains thiomersal as preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

The use of a spider venom antiserum suitable for the species of spider can prevent symptoms, provided that it is done with the least possible delay; other general supportive measures and symptomatic treatment may also be needed.

An antiserum against the black widow spider (*Latrodectus mactans*) is available in the USA and Canada. The contents of a vial containing at least 6000 antivenin units is the usual dose for adults and children. In severe cases and in children under 12 years of age it is given by intravenous infusion in sodium chloride 0.9% over 15 minutes; in less severe cases, it may be given by intramuscular injection.

Antivenoms are also available against other *Latrodectus* species, including the Australian red-back spider (*L. hasselti*) and the South African button spiders. An antiserum against the funnel-web spider (*Atrax robustus*) is available in Australia.

Antivenoms have also been developed against *Loxosceles* spiders and against *Phoneutria* spiders, but there is little evidence of their effectiveness.

Spider bites. Although many species of spider are venomous, relatively few pose a danger to man. Two main clinical syndromes are recognised; necrotic araneism, produced mainly by members of the genus *Loxosceles* which includes the brown recluse spider *L. reclusa*, and neurotoxic araneism produced by members of the genera *Latrodectus* (including the black widow and red-back spiders), *Phoneutria* (South American banana spiders), and *Atrax* (funnel-web spiders).

Necrotic araneism presents as local pain and erythema at the site of the bite, commonly developing into a necrotic lesion with a black eschar that sloughs after a few weeks, sometimes leaving an ulcer that heals gradually. The area affected can be extensive. Rarely, systemic symptoms including intravascular coagulation, haemolytic anaemia, respiratory distress, and renal failure, occur and may be life-threatening. A number of therapies have been suggested, but conservative management is usually adequate with surgical repair of any persistent defects if necessary. Dapsone is reported to produce beneficial effects on healing. Treatment for systemic manifestations is supportive. Antisera are available in some countries.

Neurotoxic araneism may involve severe pain, headache, vomiting, tachycardia, hypertension, muscle spasms, and occasionally pulmonary oedema, and coma, depending upon the species. Antisera are available and reported to be more effective than those for necrotic araneism, but should be reserved for serious envenomation. Intravenous injection of calcium gluconate 10% has been suggested to relieve muscle spasm as an alternative to conventional muscle relaxants.

References.

1. Clark RF, *et al.* Clinical presentation and treatment of black widow spider envenomation: a review of 163 cases. *Ann Emerg Med* 1992; **21:** 782–7.
2. Isbister GK, *et al.* Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003; **41:** 291–300.
3. Nimorakiotakis B, Winkel KD. The funnel web and common spider bites. *Aust Fam Physician* 2004; **33:** 244–51.
4. Saucier JR. Arachnid envenomation. *Emerg Med Clin North Am* 2004; **22:** 405–22, ix.
5. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352:** 700–707.

Preparations

USP 31: Antivenin (Latrodectus Mactans).

Proprietary Preparations (details are given in Part 3)
Canad.: Antivenin (Latrodectus Mactans); ***Mex.:*** Aracmyn.

Staphylococcal Immunoglobulins

Profile

Staphylococcal immunoglobulins are under investigation for passive immunisation against infection with *Staphylococcus aureus*.

Staphylococcal Vaccines

Vacunas estafilocócicas.

Profile

Staphylococcal vaccines have been developed for the prophylaxis of staphylococcal infections.

◊ A vaccine containing *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A showed promise[1] in early studies in patients with end-stage renal disease who were receiving haemodialysis; however, later work failed to confirm benefit and its development was stopped.

1. Shinefield H, *et al.* Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. *N Engl J Med* 2002; **346:** 491–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Estafiloide; ***Cz.:*** Polystafana; Stafal; ***USA:*** SPL.

Stone Fish Venom Antisera

Antisuero contra el veneno del pez piedra estuarino; Stone Fish Antivenins; Stone Fish Antivenoms.

Adverse Effects and Precautions

As for antisera in general, p.2201.

Uses and Administration

An antiserum for use in the management of stings by the stone fish (*Synanceja trachynis*) is available in Australia. The antiserum is prepared from the serum of horses that have been immunised with the venom of the stone fish. Other symptomatic and supportive treatments are given in addition.

Stone fish venom antiserum may be given by intramuscular injection or, in more severe cases, by intravenous infusion. When given by intravenous infusion, it should be diluted 1 in 10 with an intravenous solution. The initial dose of stone fish antivenom given to both adults and children is dependent on the number of visible puncture sites: 1 to 2 puncture sites, 2000 units; 3 to 4 puncture sites, 4000 units; and 5 or more puncture sites, 6000 units. The initial dose may be repeated if necessary should symptoms persist.

◊ References.

1. Sutherland SK. Stone fish bite. *BMJ* 1990; **300:** 679–80.
2. Lehmann DF, Hardy JC. Stonefish envenomation. *N Engl J Med* 1993; **329:** 510–11.

Streptococcus Group B Vaccines

Vacunas contra estreptococos del grupo B.

Profile

Vaccines for active immunisation against group B streptococcal infections are being developed. Giving a vaccine to pregnant women to prevent neonatal infection has been proposed.

◊ References.

1. Baker CJ, Edwards MS. Group B streptococcal conjugate vaccines. *Arch Dis Child* 2003; **88:** 375–8.

Tetanus Antitoxins

Antitoxinas tetánicas.

ATC — J06AA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Tetanus Antitoxin for Human Use; Immunoserum Tetanicum ad Usum Humanum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Clostridium tetani*. It is obtained by fractionation from the serum of horses, or other mammals, that have been immunised against tetanus toxin. For prophylactic use, it has a potency of not less than 1000 international units/mL, and for therapeutic use not less than 3000 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that Tet/Ser may be used on the label.

Profile

Tetanus antitoxins neutralise the toxin produced by *Clostridium tetani* and have been used to provide temporary passive immunity against tetanus, but tetanus immunoglobulins (below) are preferred. A test dose of tetanus antitoxin should always be given to identify those who might suffer hypersensitivity reactions.

Whenever a non-immune patient is seen because of injury, a course of active immunisation should be instituted (see Tetanus Vaccines, p.2240).

Preparations

Ph. Eur.: Tetanus Antitoxin for Human Use.

Tetanus Immunoglobulins

Inmunoglobulinas contra el tétanos.

ATC — J06BB02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Tetanus Immunoglobulin; Immunoglobulinum Humanum Tetanicum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the toxin of *Clostridium tetani*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

USP 31 (Tetanus Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with tetanus vaccine. It contains not less than 50 units of tetanus antitoxin/mL. It contains 10 to 18% of protein of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable preservative. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Uses and Administration

Tetanus immunoglobulins are used for passive immunisation against tetanus.

The use of tetanus immunoglobulins is recommended in the UK and the USA as part of the management of tetanus-prone wounds in persons unimmunised or incompletely immunised against tetanus, in persons whose immunisation history is unknown, in persons who received the last dose of tetanus vaccine more than 10 years previously, and in patients with impaired immunity. Active immunisation with a tetanus vaccine (p.2240) should also be started simultaneously, and antibacterials and symptomatic therapy given as appropriate (see p.196 and p.1901). The usual dose of tetanus immunoglobulin is 250 units by intramuscular injection but, if more than 24 hours have elapsed since the wound was sustained, or if there is a risk of heavy contamination, or after burns, 500 units should be given irrespective of the immunisation history.

Tetanus immunoglobulin is also used in the treatment of tetanus, a recommended dose being 150 units/kg in total, given intramuscularly into multiple sites.

A preparation suitable for intravenous use is available in some countries. It is given for the treatment of tetanus in a dose of 5000 to 10 000 units by intravenous infusion.

Preparations

Ph. Eur.: Human Tetanus Immunoglobulin;
USP 31: Tetanus Immune Globulin.

Proprietary Preparations (details are given in Part 3)

Arg.: Gammatet; Igantet; IT SD-T; Tetabulin; ***Austria:*** Tetabulin; Tetagam; ***Belg.:*** Tetabuline; ***Braz.:*** Tetanobulin†; Tetanogamma; ***Canad.:*** BayTet†; Hypertet; ***Chile:*** Igantet; ***Cz.:*** Tetabulin; Tetaglobuline†; ***Fr.:*** Gamma-tetanos; ***Ger.:*** Tetagam N; Tetanobulin; ***Gr.:*** Tetagam-P; ***Hong Kong:*** BayTet; Tetabulin†; Tetuman†; ***Hung.:*** Tetig; ***India:*** Tetagam-P; ***Indon.:*** Tetagam P; ***Irl.:*** Tetabulin; ***Israel:*** BayTet; Tetaglobuline; ***Ital.:*** Gamma-Tet P; Ig Tetano†; Igantet; Immunotetan; Tetabulin; Tetagamma†; Tetanus-Gamma; Tetaven†; ***Malaysia:*** Igantet; Sero-Tet; Tetuman†; ***Mex.:*** BayTet†; Probi-Tet†; Tetanogamma; ***Neth.:*** TetaQuin; ***Philipp.:*** BayTet; Tetagam-P; Tetanea; ***Pol.:*** Tetabulin; ***Port.:*** Tetagam; Tetuman†; ***S.Afr.:*** Tetagam; ***Singapore:*** BayTet†; Igantet; ***Spain:*** Gamma Antitetanos; Tetagamma P; Tetuman†; ***Switz.:*** Tetagam; Tetuman; ***Thai.:*** Tetagam; Tetuman†; ***Turk.:*** Tetanea; Tetuman; ***UK:*** Liberim T†; Tetabulin†; ***USA:*** BayTet.

Tetanus Vaccines

Vacunas del tétanos.

ATC — J07AM01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Tetanus Vaccine (Adsorbed); Vaccinum Tetani Adsorbatum). It is prepared from tetanus formol toxoid adsorbed on a mineral carrier which may be hydrated aluminium phosphate or aluminium hydroxide. The resulting mixture is isotonic with blood. Suitable antimicrobial preservatives may be added. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type and these should not be added to the vaccine. It contains not less than 40 units per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Tet may be used on the label.

The BP 2008 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

BP 2008 (Tetanus Vaccine). It is prepared from tetanus toxin produced by the growth of *Clostridium tetani*. The toxin is converted to tetanus formol toxoid by treatment with formaldehyde solution. It contains suitable non-phenolic antimicrobial preservatives. It should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Tet/Vac/FT may be used on the label.

The BP 2008 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

USP 31 (Tetanus Toxoid). A sterile solution of the formaldehyde-treated products of growth of *Clostridium tetani*. It contains a non-phenolic preservative. It should be stored at 2° to 8° and not be allowed to freeze.

USP 31 (Tetanus Toxoid Adsorbed). A sterile preparation of plain tetanus toxoid precipitated or adsorbed by alum, aluminium hydroxide, or aluminium phosphate adjuvants. It should be stored at 2° to 8° and not be allowed to freeze.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Local reactions, usually after the use of adsorbed vaccines, and mild systemic reactions may occur. The incidence and severity of reactions increases with the number of doses given.

Anaphylaxis and neurological reactions have been reported rarely.

Although vaccination is usually postponed in patients suffering from an acute febrile illness, tetanus vaccine should be given to such patients in the presence of a tetanus-prone wound.

With the exception of the first booster dose of tetanus vaccine (which is usually given before school entry and about 3 years after the primary course), further boosters should not generally be given at intervals of less than 10 years because of an increased risk of severe local reactions.

Effects on the nervous system. Neuropathies have been reported rarely with tetanus vaccination. Optic neuritis and myelitis occurred[1] in an 11-year-old girl after a routine booster dose. Corticosteroids and immunoglobulin were given, and both vision and muscle power were restored after 11 months. Acute transverse myelitis was reported[2] in a 50-year-old man who received a tetanus vaccine and immunoglobulin after an injury. Neurological deficits were unchanged after 1 month despite use of corticosteroids. Other causes could not be ruled out in either case. Brachial neuritis that developed in 2 infants after immunisation with diphtheria, tetanus, and pertussis vaccine was attributed to the tetanus component.[3]

1. Topaloglu H, *et al.* Optic neuritis and myelitis after booster tetanus toxoid vaccination. *Lancet* 1992; **339:** 178–9.
2. Read SJ, *et al.* Acute transverse myelitis after tetanus toxoid vaccination. *Lancet* 1992; **339:** 1111–12.
3. Hamati-Haddad A, Fenichel GM. Brachial neuritis following routine childhood immunization for diphtheria, tetanus, and pertussis (DTP): report of two cases and review of the literature. *Pediatrics* 1997; **99:** 602–3.

GUILLAIN-BARRÉ SYNDROME. For a discussion on the relationship between tetanus-containing vaccines and Guillain-Barré syndrome, see Diphtheria and Tetanus Vaccines, p.2210.

Pregnancy. No connection has been found between use of tetanus vaccine during pregnancy and either congenital malformations[1] or spontaneous abortion.[2]

1. Silveira CM, *et al.* Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. *Bull WHO* 1995; **73:** 605–8.
2. Catindig N, *et al.* Tetanus toxoid and spontaneous abortions: is there epidemiological evidence of an association? *Lancet* 1996; **348:** 1098–9.

Interactions

As for vaccines in general, p.2202.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Uses and Administration

Tetanus vaccines are used for active immunisation against tetanus.

For primary immunisation combined tetanus vaccines, usually diphtheria, tetanus, and pertussis vaccines (p.2210) or diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccines (p.2212), are used. For discussion of immunisation schedules, see under Vaccines, p.2202. In adults requiring primary immunisation combined vaccines such as diphtheria and tetanus vaccines (p.2210) or diphtheria, tetanus, and poliomyelitis vaccines (p.2212) are used.

In children who complete the primary course in infancy, reinforcing doses are given at school entry and in adolescence using the recommended appropriate combined vaccines. In adults, a reinforcing dose is desirable 10 years later with a further dose after a further 10 years.

Tetanus vaccines should be part of wound management if primary immunisation is incomplete or boosters are not up-to-date. For tetanus-prone wounds, tetanus immunoglobulin (see above) may also be required. Tetanus vaccine and tetanus immunoglobulin may be given at the same time, but not at the same site. In the event of injury in non-immunised persons or if immunisation status is uncertain, the opportunity is usually taken to initiate a course of primary immunisation. Since this provides no immediate protection, prophylactic treatment with tetanus immunoglobulin is recommended for tetanus-prone wounds. Suitable antibacterial therapy may also be given (see p.196).

Neonatal tetanus. In 1989 WHO adopted a resolution to eliminate neonatal tetanus after estimates revealed that worldwide (but excluding China) it was the cause of 800 000 neonatal deaths each year, a figure representing about 50% of all such deaths in developing countries. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of the mother in late pregnancy. However, by mid-2000 there were 57 countries that had still not eliminated maternal and neonatal tetanus and WHO, UNICEF, and UNFPA agreed to set a target date of 2005 for elimination (defined as a rate of neonatal tetanus below 1 in 1000 live births at district level). However, by the end of 2007, 47 countries were still considered to have not achieved elimination.

Tetanus vaccine is given to all women of child-bearing age as part of WHO's Expanded Programme on Immunization. For pregnant women, 2 doses of vaccine should be given, the second dose at least 4 weeks after the first and at least 2 weeks before delivery; this may provide the newborn infant with about 80% protection against tetanus. For all women of child-bearing age, 3 doses of vaccine, with at least 4 weeks between the first two doses and 6 to 12 months between the second and third doses, provide 95 to 98% protection for at least 5 years. Fourth and fifth doses, each at least one year after the previous dose, prolong the immunity for 10 and 20 years respectively.

Reinforcing doses in adults. Although the current recommendation in the UK is that 5 doses of tetanus vaccine (as a 3-dose primary course in infancy and 2 reinforcing doses at pre-school and in adolescence) is sufficient to produce satisfactory long-term protection in most circumstances, there has been concern about immunity in the elderly, and in particular women. Routine primary immunisation against tetanus was introduced in the UK in 1961, so individuals born before that year would not have been immunised in infancy, and unless they had been in the armed forces, may never have received a full primary course. Unless there is a clear immunisation history immunity to tetanus may be difficult to assess. It is also recommended in the UK that travellers to areas where medical attention may not be accessible, and who had the last dose of vaccine more than 10 years previously, should receive a booster even if they have had 5 doses previously.

Studies in the USA,[1] Australia,[2] and Austria[3] have shown that at least half of healthy people over 50 years of age did not have adequate circulating tetanus antibodies. However, the level of circulating antibodies in the absence of an antigen challenge may not be an appropriate measure of the immune status. The low incidence of clinical tetanus in adults provides circumstantial evidence of an adequate inducible antibody response on exposure to tetanus despite a decline in antibody concentrations with increasing age.[4,5] Conversely, there have been reports of tetanus occurring despite high antibody concentrations.[6,7] There have been calls for the introduction of regular booster injections in adults,[3,7-9] as is standard practice in the USA or alternatively a single booster in late middle age[10,11] or giving a primary course to elderly persons who have never received one.[1]

1. Gergen PJ, *et al.* A population-based serologic survey of immunity to tetanus in the United States. *N Engl J Med* 1995; **332:** 761–6.
2. Heath TC, *et al.* Tetanus immunity in an older Australian population. *Med J Aust* 1996; **164:** 593–6.
3. Steger MM, *et al.* Vaccination against tetanus in the elderly: do recommended vaccination strategies give sufficient protection? *Lancet* 1996; **348:** 762.
4. Bowie C. Tetanus toxoid for adults—too much of a good thing. *Lancet* 1996; **348:** 1185–6.
5. Baily G. Are the elderly inadequately protected against tetanus? *Lancet* 1996; **348:** 1389–90.
6. Passen EL, Andersen BR. Clinical tetanus despite a 'protective' level of toxin-neutralising antibody. *JAMA* 1986; **255:** 1171–3.
7. Bowman C, *et al.* Tetanus toxoid for adults. *Lancet* 1996; **348:** 1664.
8. Rethy LA, Rethy L. Can tetanus boosting be rejected? *Lancet* 1997; **349:** 359–60.
9. Sehgal R. Tetanus toxoid for adults. *Lancet* 1997; **349:** 573.
10. Balestra DJ, Littenberg B. Tetanus immunization in adults. *JAMA* 1994; **272:** 1900.
11. Gardner P, LaForce FM. Protection against tetanus. *N Engl J Med* 1995; **333:** 599.

Preparations

Ph. Eur.: Tetanus Vaccine (Adsorbed);
USP 31: Tetanus Toxoid; Tetanus Toxoid Adsorbed.

Proprietary Preparations (details are given in Part 3)
Arg.: Tetanol; Tetavax; ***Austral.:*** Tet-Tox; ***Austria:*** Tetanol; ***Belg.:*** Tevax†; ***Braz.:*** Tetavax†; ***Chile:*** Tetavax; ***Cz.:*** Alteana; Tetavax; ***Ger.:*** Tetamun SSW†; Tetanol; ***Gr.:*** Anatoxal-TE-Berna†; ***Hong Kong:*** Te Anatoxal; Tetavax; ***Hung.:*** Tetanol; ***Ital.:*** Anatetall; Imovax Tetano; Tanrix†; Tetatox†; ***Malaysia:*** Te Anatoxal†; Tetavax†; TT Vaccine; ***Mex.:*** Tetamyn; Tetanol; Tetinox; ***Neth.:*** Tetavax†; ***Norw.:*** Tetavax; ***NZ:*** Te Anatoxal; Tet-Tox; ***Philipp.:*** Te Anatoxal; Tetavax; ***Port.:*** Anatoxal Te†; ***S.Afr.:*** Tetavax; ***Singapore:*** Te Anatoxal†; ***Spain:*** Anatoxal Te; ***Switz.:*** Anatoxal Te; ***Thai.:*** Anatetall†; Bio-TT; Te Anatoxal; Tetavax; TT Vaccine; ***Turk.:*** Anatetall; Tetavax; ***UK:*** Clostet†; ***USA:*** Te Anatoxal.

Tetanus and Influenza Vaccines

Vacunas del tétanos y la gripe.

Profile

Tetanus and influenza vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Tetagrip.

Tetanus and Poliomyelitis Vaccines

Vacunas del tétanos y la poliomielitis.

Profile

Tetanus and poliomyelitis (inactivated) vaccines have been used in some countries for active immunisation against tetanus and poliomyelitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: T. Polio†; Vaccin TP†.

Tick Venom Antisera

Antisuero contra el veneno de garrapata; Tick Antivenins; Tick Antivenoms.

Profile

An antiserum is available in Australia for treatment of the neurotoxic effects of envenomation by the tick *Ixodes holocyclus*. The antiserum is prepared from the serum of dogs that have been immunised with tick venom.

Tick venom antiserum is given by slow intravenous infusion.

Tick-borne Encephalitis Immunoglobulins

Inmunoglobulinas de la encefalitis transmitida por garrapatas.
ATC — J06BB12.

Profile

Preparations containing antibodies against tick-borne encephalitis are available in some countries for passive immunisation against the disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: FSME-Bulin†; ***Cz.:*** FSME-Bulin†; ***Ger.:*** FSME-Bulin†.

Tick-borne Encephalitis Vaccines

Vacunas de la encefalitis transmitida por garrapatas.
ATC — J07BA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Tick-borne Encephalitis Vaccine (Inactivated); Vaccinum Encephalitidis Ixodibus Advectae Inactivatum). A liquid preparation of a suitable strain of tick-borne encephalitis virus grown in cultures of chick-embryo cells or other suitable cell cultures and inactivated by a suitable method. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that Tic/enceph may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Effects on the nervous system. Severe progressive sensorimotor spastic paralysis occurred in a 54-year-old man after a second booster dose of tick-borne encephalitis vaccine.[1] Partial recovery was noted after about 6 months.

1. Bohus M, *et al.* Myelitis after immunisation against tick-borne encephalitis. *Lancet* 1993; **342:** 239–40.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

A vaccine is available in some countries for active immunisation against tick-borne viral encephalitis.

In the UK, vaccination against tick-borne encephalitis is recommended for those who anticipate prolonged exposure to the infective agent, for example persons visiting or working in the warm forested parts of Europe and Scandinavia. The vaccine is given by intramuscular injection in adult doses of 0.5 mL. The primary course consists of three doses, the second being given 4 to 12 weeks after the initial dose, and a third dose 5 to 12 months later. In children over 1 year of age and below 16 years of age, 3 doses of 0.25 mL of the junior formulation of the vaccine are given; the intervals between each dose are the same as for the adult schedule. To achieve rapid short-term protection in adults and children, the second dose may be given 2 weeks after the first dose. Booster doses for adults and children at continued risk should be given within 3 years of the last primary vaccination or booster dose.

Preparations

Ph. Eur.: Tick-borne Encephalitis Vaccine (Inactivated).

Proprietary Preparations (details are given in Part 3)
Austria: Encepur; FSME-Immun; ***Belg.:*** FSME-Immun; ***Canad.:*** FSME-Immun; ***Cz.:*** Encepur; FSME-Immun; ***Denm.:*** TicoVac; ***Fin.:*** Encepur; TicoVac; ***Fr.:*** TicoVac; ***Ger.:*** Encepur; FSME-Immun; ***Hung.:*** Encepur; FSME-Immun; ***Ital.:*** TicoVac; ***Norw.:*** TicoVac; ***Pol.:*** Encepur; FSME-Immun; ***Rus.:*** Encevir (Энцевир); ***Swed.:*** Encepur; FSME-Immun; ***Switz.:*** Encepur; FSME-Immun; ***UK:*** TicoVac.

Trichomoniasis Vaccines

Vacunas de la tricomoniasis.

Profile

A trichomoniasis vaccine containing inactivated *Lactobacillus* spp. is available in some countries for the prophylaxis of recurrent vaginal trichomoniasis. The vaccine is reported to stimulate production of antibodies against the aberrant coccoid forms of the lactobacilli associated with trichomoniasis and also, by cross-reaction, against the trichomonads themselves.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Gynatren.

Tularaemia Vaccines

Vacunas de la tularemia.

Profile

A tularaemia vaccine prepared from a live attenuated strain of *Francisella tularensis* has been used for active immunisation against tularaemia in persons at high risk of contracting the disease.

◊ References.

1. Titball R, Oyston P. A vaccine for tularaemia. *Expert Opin Biol Ther* 2003; **3:** 645–53.
2. Conlan JW. Vaccines against Francisella tularensis: past, present and future. *Expert Rev Vaccines* 2004; **3:** 307–14.

Typhoid Vaccines

Vacunas de la fiebre tifoidea.
ATC — J07AP01; J07AP02; J07AP03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Typhoid Vaccine; Vaccinum Febris Typhoidi). A sterile suspension of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone, formaldehyde, or phenol, or by phenol and heat. The vaccine should be stored at 2° to 8°, and be protected from light.

The BP 2008 states that Typhoid may be used on the label.

Ph. Eur. 6.2 (Typhoid Vaccine, Freeze-dried; Vaccinum Febris Typhoidi Cryodesiccatum). A freeze-dried preparation of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone or formaldehyde. Phenol may not be used in the preparation. The vaccine should be stored at 2° to 8°, and be protected from light. It is reconstituted by the addition of suitable sterile liquid and should be used within 8 hours.

The BP 2008 states that Typhoid may be used on the label.

Ph. Eur. 6.2 (Typhoid Vaccine (Live, Oral, Strain Ty 21a); Vaccinum Febris Typhoidis Vivum Perorale (Stirpe Ty 21a)). A freeze-dried preparation of live *S. typhi* strain Ty 21a grown in a suitable medium. It contains not less than 2×10^9 bacteria per dose. It should be stored at 2° to 8°, and be protected from light.

The BP 2008 states that Typhoid(live,oral) may be used on the label.

Ph. Eur. 6.2 (Typhoid Polysaccharide Vaccine; Vaccinum Febris Typhoidis Polysaccharidicum). A preparation of purified Vi capsular polysaccharide obtained from *S. typhi* Ty2 strain or some other suitable strain that has the capacity to produce Vi polysaccharide. It contains 25 micrograms of polysaccharide per dose. It should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Typhoid may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Oral live typhoid and parenteral polysaccharide vaccines have been associated with fewer adverse effects than parenteral killed typhoid vaccines and have replaced them in many countries.

Interactions

As for vaccines in general, p.2202.

Conflicting advice has been issued about the use of live oral typhoid vaccines with antibacterials or antimalarials (particularly mefloquine or proguanil). WHO has stated that all these drugs should be stopped from 3 days before until 3 days after receiving the Ty 21a live oral vaccine. The UK licensed product information advises a separation of 3 days for antibacterials, 12 hours for mefloquine, and 3 days for other antimalarials (but the fixed-dose combination of atovaquone and proguanil may be given with the vaccine). The US product information has indicated that mefloquine (and chloroquine) can be given with the vaccine but that proguanil should only be taken 10 days after the vaccine.

Uses and Administration

Typhoid vaccines are used for active immunisation against typhoid fever. As with many vaccines, the efficacy of typhoid vaccine is not complete and the importance of maintaining attention to hygiene should be emphasised to those travelling to endemic areas.

Typhoid vaccination is advised for laboratory workers handling specimens which may contain typhoid organisms and for persons travelling to areas where typhoid fever is endemic. In the UK, vaccination of contacts of a known typhoid carrier is not recommended; in the USA such persons are advised to receive the vaccine. Typhoid vaccine is not useful in controlling outbreaks of the disease in non-endemic areas.

In the UK, two vaccines are used: a capsular polysaccharide vaccine for parenteral use, and a live oral vaccine.

The capsular polysaccharide typhoid vaccine contains 25 micrograms of the Vi polysaccharide antigen per dose. A single dose of 0.5 mL is given by deep subcutaneous or intramuscular injection. Booster doses may be given every 3 years to those who remain at risk. The response in children under 18 months of age may be suboptimal, and the decision to vaccinate will be governed by the risk of exposure to infection.

The live oral typhoid vaccine contains an attenuated strain of *Salmonella typhi*, Ty 21a, and is given as enteric-coated capsules containing not less than 2×10^9 bacteria per dose. A primary immunisation schedule of one capsule every other day for 3 doses is given.

In the USA, the Vi capsular polysaccharide vaccine and the live oral Ty 21a vaccine are available. The capsular polysaccharide vaccine is given intramuscularly similarly to that in the UK, with a booster dose suggested every 2 years. For the oral vaccine, 4 doses on alternate days are recommended for both primary immunisation and boosters, which are given every 5 years if exposure continues.

In areas where typhoid is endemic WHO advises that immunisation should be considered as part of the routine schedules; either the Vi capsular polysaccharide vaccine or the Ty 21a live oral vaccine should be given to schoolchildren over the age of 2 years. Immunisation of the whole community should also be considered during an outbreak of typhoid; if this is not possible, persons aged 2 to 19 years should be the target group.

Immunisation for travellers. In most developed countries where typhoid is not endemic, the major use for typhoid vaccine is for non-immune travellers visiting endemic areas. The highest incidence of the disease is associated with travel to the Indian subcontinent and parts of tropical South America, although immunisation is also recommended for travellers to lower risk areas of Africa, Asia, and south-east Europe. By far the most important form of protection against gastrointestinal infection is strict attention to personal, food, and water hygiene, although in practice this advice is often difficult to follow.[1]

None of the vaccines used has been 100% effective in preventing disease. The effectiveness of the vaccines has generally been assessed in field trials in the populations of endemic areas. Such populations acquire a degree of natural immunity due to continued exposure and it may not be possible to equate protection rates in these populations to non-immune travellers. The live oral vaccine has been shown to confer a useful degree of immunity in field trials but the dose used may have been insufficient to protect non-immune individuals. The degree of immunity induced may be increased by the use of higher inocula or liquid preparations. In addition, compliance with dosing and storage requirements may further limit the effectiveness of this dosage form.

Large field studies have verified the effectiveness of the capsular polysaccharide vaccine but its efficacy has not been assessed in non-immune populations. However, it does have the advantage of being given as a single dose.

Whole-cell vaccines are generally no longer used because they are frequently associated with adverse effects.

1. WHO. *The diagnosis, treatment and prevention of typhoid fever.* Geneva: WHO, 2003. Also available at: http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf (accessed 20/02/06)

Preparations

Ph. Eur.: Freeze-dried Typhoid Vaccine; Typhoid Polysaccharide Vaccine; Typhoid Vaccine; Typhoid Vaccine (Live, Oral, Strain Ty 21a).

Proprietary Preparations (details are given in Part 3)
Arg.: Typhim Vi; Vivotif; ***Austral.:*** Typh-Vax; Typherix; Typhim Vi; Vivotif; ***Austria:*** Typherix; Typhim Vi; Vivotif; ***Belg.:*** Typherix; Typhim Vi; Vivotif; ***Canad.:*** Typherix; Typhim Vi; Vivotif; ***Chile:*** Typhim Vi; Vivotif; ***Cz.:*** Typherix; Typhim Vi; ***Denm.:*** Typhim Vi; Vivotif; ***Fin.:*** Typherix; Typhim Vi†; Vivotif; ***Fr.:*** Typherix; Typhim Vi; ***Ger.:*** Typherix; Typhim Vi; Typhoral L; Vivotif†; ***Gr.:*** Typherix; ***Hong Kong:*** Typhim Vi; Vivotif; ***Hung.:*** Typherix; Typhim Vi; ***India:*** Typhim Vi; Typhoral; Vactyph; ***Indon.:*** Typherix; Typhim Vi; Vivotif; ***Irl.:*** Typherix; Typhim Vi; Vivotif†; ***Israel:*** Typherix; Typhim Vi; ***Ital.:*** Typherix; Typhim Vi; Vivotif; ***Malaysia:*** Typherix; Typhim Vi; Typhovax†; Vivotif; ***Neth.:*** Typherix; Typhim Vi; Vivotif; ***Norw.:*** Typherix; Typhim Vi; Vivotif; ***NZ:*** Typh-Vax; Typherix; Typhim Vi; Vivotif; ***Philipp.:*** Typherix; Typhim Vi; Vivotif; ***Pol.:*** Typhim Vi; ***Port.:*** Vivotif†; ***S.Afr.:*** Typherix; Typhim Vi; Vivotif†; ***Singapore:*** Typherix; Typhim Vi; Vivotif; ***Spain:*** Typherix; Typhim Vi; Vivotif; ***Swed.:*** Typherix; Typhim Vi; Vivotif; ***Switz.:*** Vivotif; ***Thai.:*** Typhim Vi; Vivotif; ***Turk.:*** Typhim; ***UK:*** Typherix; Typhim Vi; Vivotif; ***USA:*** Typhim Vi; Vivotif; ***Venez.:*** Typhim Vi†.

Vaccinia Immunoglobulins

Inmunoglobulinas contra el virus de la vacuna.

ATC — J06BB07.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 31 (Vaccinia Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with vaccinia virus (smallpox vaccine). It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable antimicrobial agent. It should be stored at 2° to 8°.

Profile

Vaccinia immunoglobulins have been used intramuscularly for the treatment of clinical complications of smallpox vaccination. They are not effective for postviral encephalitis. A currently available intravenous vaccinia immunoglobulin is given in a usual dose of 100 mg/kg, increased to 200 to 500 mg/kg in the absence of a response.

◊ References.

1. Hopkins RJ, *et al.* Safety and pharmacokinetic evaluation of intravenous vaccinia immune globulin in healthy volunteers. *Clin Infect Dis* 2004; **39:** 759–66.
2. Hopkins RJ, Lane JM. Clinical efficacy of intramuscular vaccinia immune globulin: a literature review. *Clin Infect Dis* 2004; **39:** 819–26.

Preparations

USP 31: Vaccinia Immune Globulin.

Varicella-Zoster Immunoglobulins

Inmunoglobulinas contra el virus de la varicela zóster.

ATC — J06BB03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Varicella Immunoglobulin; Immunoglobulinum Humanum Varicellae). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against *Herpesvirus varicellae*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under inert gas.

Ph. Eur. 6.2 (Human Varicella Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Varicellae ad Usum Intravenosum). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having antibodies against human herpesvirus 3 (varicella-zoster virus 1). Human normal immunoglobulin for intravenous administration may be added. It contains not less than 25 international units/mL. Storage requirements are similar to those for Human Varicella Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25°.

USP 31 (Varicella-Zoster Immune Globulin). A sterile solution of globulins derived from the plasma of adult donors selected for high titres of varicella-zoster antibodies. It contains 15 to 18% of globulins, of which not less than 99% is immunoglobulin G with traces of immunoglobulin A and immunoglobulin M. It contains glycine as a stabilising agent and thiomersal as a preservative. It contains not less than 125 units of specific antibody in not more than 2.5 mL of solution. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Varicella-zoster immunoglobulins are used for passive immunisation against varicella (chickenpox) in susceptible persons considered to be at high risk of developing varicella-associated complications after exposure to varicella or herpes zoster (shingles).

In the UK, varicella-zoster immunoglobulins are recommended for individuals who are at high risk of severe varicella and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include immunosuppressed patients, neonates including those whose mothers develop chickenpox (but not herpes zoster) in the period 7 days before to 7 days after delivery, and pregnant women. Varicella-zoster immunoglobulin does not prevent infection when given after exposure but may modify the course of disease. Treatment with antivirals may be necessary in severe disease (see p.855).

The doses, given by deep intramuscular injection, of the varicella-zoster immunoglobulin available in the UK are: 250 mg for children up to 5 years of age; 500 mg for those aged 6 to 10 years; 750 mg for those aged 11 to 14 years; and 1 g for all those 15 years of age or older. A further dose is required if a second exposure occurs more than 3 weeks later. Varicella-zoster immunoglobulin should be given as soon as possible and not later than 10 days after exposure. Preparations of normal immunoglobulin for intravenous use may be used to provide an immediate source of antibody.

Preparations

Ph. Eur.: Human Varicella Immunoglobulin; Human Varicella Immunoglobulin for Intravenous Administration;
USP 31: Varicella-Zoster Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Varitect; ***Austria:*** Varitect; ***Canad.:*** VariZIG; ***Cz.:*** Varitect†; ***Ger.:*** Varicellon; Varitect; ***Gr.:*** Varitect; ***Hong Kong:*** Varitect; ***Irl.:*** Varitect; ***Israel:*** Varitect; ***Ital.:*** Uman-Vzig†; Varitect; ***Neth.:*** VariQuin; ***Pol.:*** Varitect; ***Port.:*** Varitect; ***S.Afr.:*** Vazigam; ***Singapore:*** Varitect; ***Switz.:*** Varitect; ***Thai.:*** Varitect; ***Turk.:*** Immunozig; Varitect.

Varicella-Zoster Vaccines

Vacunas de la varicela zóster.

Ветряночные Вакцины

ATC — J07BK01.

Pharmacopoeias. Many pharmacopoeias have monographs including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Varicella Vaccine (Live); Vaccinum Varicellae Vivum). A freeze-dried preparation of a suitable attenuated strain of *Herpesvirus varicellae* grown in cultures of human diploid cells. The culture medium may contain suitable antibiotics at the smallest effective concentration. It is prepared immediately before use by reconstitution from the dried vaccine; it may contain a stabiliser. The dried vaccine should be stored at 2° to 8°. Protect from light.

The BP 2008 states that Var(Live) may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Varicella vaccines are generally well tolerated. Rashes may occur at the injection site and generalised varicella-like rashes elsewhere have been reported. The vaccine strain of virus can become latent, which could result in late development of zoster infections, but the incidence of herpes zoster is lower after vaccination than in an unvaccinated population. Breakthrough cases of chickenpox have been reported after single- and 2-dose vaccination regimens, but were in most cases milder. The incidence of breakthrough varicella is markedly lower after the 2-dose regimen.

High potency varicella vaccines licensed for active immunisation against herpes zoster (shingles) should not be used for active immunisation against varicella (chickenpox). Persons with active untreated tuberculosis should not be vaccinated.

◊ General references.

1. Black S, *et al.* Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; **18:** 1041–6.

Pregnancy. Normally occurring varicella zoster infection may cause fetal harm, therefore as a precautionary measure, vaccination of pregnant women against varicella is generally contra-indicated; advice is also given to avoid pregnancy for 3 months after the last dose of vaccine. However, surveillance of women inadvertently vaccinated during pregnancy has not identified any increased risk, either in terms of congenital varicella or for congenital abnormalities.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Live attenuated varicella-zoster vaccines may be used for active immunisation against varicella (chickenpox) and herpes zoster (shingles).

In the UK, vaccination against varicella is recommended only for persons considered to be at high risk of contracting the infection or highly susceptible to any complications it might cause; such patients include susceptible healthcare workers, and healthy contacts of immunocompromised patients when continuing close contact is unavoidable. A single dose of 0.5 mL is given subcutaneously to children aged 12 months to 13 years. Those aged 13 years and older should receive two doses at an interval of 4 to 8 weeks.

In the USA, a 2-dose vaccination regimen is recommended as part of the primary immunisation schedule of infants and children (see under Vaccines, p.2202). The first dose of 0.5 mL is given subcutaneously to children aged 12 to 15 months and the second dose at 4 to 6 years of age. Routine vaccination is also recommended for persons over the age of 13 years without evidence of immunity; two doses are given at an interval of 4 to 8 weeks. Those who only received 1 dose should receive a second, catch-up dose.

In the USA, a high potency vaccine (containing a minimum of 19 400 plaque-forming units) against herpes zoster is recommended for persons 60 years of age and older. A single dose of 0.65 mL is given subcutaneously.

A combination vaccine of measles, mumps, rubella, and varicella (MMRV) is available in the USA for use in children aged 12 months to 12 years.

◊ Results of studies of varicella-zoster vaccines for active immunisation against chickenpox in healthy and leukaemic children have been largely favourable. Protective **efficacy** in healthy children appears to be over 90%. In healthy adolescents and adults, adding a second dose 4 or 8 weeks after the first increased seroconversion rates from about 70 to 80% to 97% or better.[1] A protective efficacy of about 85% has been reported in leukaemic children given one dose of varicella-zoster vaccine[2,3] and interruption of chemotherapy for vaccination does not appear necessary in terms of immunogenicity of the vaccine.[2,4]

The **duration of immunity** after a 1-dose regimen for active immunisation against chickenpox is also under debate; despite at least 70 to 90% effectiveness, some consider that a single dose does not provide sufficient herd immunity levels to prevent outbreaks, especially in school settings.[5,6] Initial studies show that the immunity induced by natural infection with wild type virus is superior to that induced by the vaccine. In one study,[3] antibodies were absent in about one-quarter of all vaccinees (both leukaemic children and healthy adults) 1 year after a second dose of vaccine, but were still present after up to 6 years in all those who had breakthrough varicella infection.

However, immunity to varicella-zoster is complex, depending not only on circulating antibody but also on cellular immunity and secretory antibody. Thus, although a person may become seronegative after vaccination, protection from varicella may remain, albeit partial.[2] Both humoral and cell mediated immunity have been shown to persist for up to 20 years after vaccination.[7] Leukaemic children observed up to 6 years after immunisation have continued to be well protected[2] and varicella in previously-vaccinated persons is usually mild.[5,6]

Surveillance data collected from 11 356 children in the USA between 1995 and 2004 found that annual rates of breakthrough varicella increased significantly with time. Children aged 8 to 12 years at the onset of disease who had been vaccinated 5 years or more previously were 2.6 times more likely to have moderate or severe breakthrough varicella than those vaccinated less than 5 years previously.[8] The efficacy of a 2-dose vaccination regimen (doses given 3 months apart) was assessed in 2216 children over a period of 9 to 10 years.[9] Children vaccinated with the 2-dose regimen were 3.3 times less likely to develop varicella more than 42 days after vaccination than those who had received a single dose. During the 10-year follow-up period most breakthrough cases occurred in years 2 to 5, for both treatment regimens. No breakthrough cases were reported in years 7 to 10 for those who received the 2-dose regimen, while 10 cases were reported for those who received the 1-dose regimen. Since June 2007 the US Advisory Committee on Immunization Practices (ACIP) has recommended that children between the ages of 4 and 6 years receive a second dose of varicella vaccine.[6]

Varicella-zoster vaccine may prevent or modify varicella if given within 3 days of exposure to the infection. It may be useful as an **adjunct** to varicella-zoster immunoglobulin. The treatment of varicella-zoster infections with antivirals is discussed on p.855.

One concern of varicella-zoster vaccination has been the possibility of an **increased risk of herpes zoster** (shingles) in immunised children. Although herpes zoster has been reported in vaccinated persons, a study involving 346 leukaemic children and 84 matched controls concluded that the incidence of herpes zoster following varicella-zoster vaccine was no greater than that following natural varicella infection.[10] The study did suggest that the risk of herpes zoster may be lowered by vaccination but this must be confirmed by long-term follow-up. Postmarketing surveys[11] of almost 90 000 vaccine recipients also showed a low incidence of herpes zoster. The vaccine strain of varicella-zoster virus is transmissible, particularly from vaccinees who develop a rash (see also Pregnancy under Adverse Effects, above). There is no evidence of reversion to virulence of the vaccine strain with secondary transmission.

Another concern is that vaccination of children could result in more severe infections in later life after immunity has waned. However, studies have shown that in general varicella is less severe in previously immunised than in non-immunised patients.[12,13]

The risk of zoster increases with age reflecting the waning of the specific cell-mediated immunity to the virus. Thus, the use of a high-potency varicella-zoster vaccine has been investigated in elderly subjects. In a randomised, double-blind, placebo-controlled study in over 38 000 subjects aged 60 or more the vaccine reduced the burden of illness due to herpes zoster by 61.1% and the incidence of herpes zoster and of postherpetic neuralgia by 51.3% and 66.5% respectively.[14] In the USA, high-potency varicella-zoster vaccine is recommended by the ACIP for all people 60 years of age and older, including those who have already had an episode of shingles.[15]

1. Kuter BJ, *et al.* Safety, tolerability, and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy adolescents and adults. *Vaccine* 1995; **13:** 967 72.
2. Gershon AA, *et al.* Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. *N Engl J Med* 1989; **320:** 892–7.
3. Gershon AA, *et al.* Live attenuated varicella vaccine: protection in healthy adults compared with leukemic children. *J Infect Dis* 1990; **161:** 661–6.
4. Arbeter AM, *et al.* Immunization of children with acute lymphoblastic leukemia with live attenuated varicella vaccine without complete suspension of chemotherapy. *Pediatrics* 1990; **85:** 338–44.
5. Lopez AS, *et al.* One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics* 2006; **117:** 2253–4. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/6/e1070 (accessed 06/07/07)
6. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-4): 1–40. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5604.pdf (accessed 06/07/07)
7. Asano Y, *et al.* Experience and reason: twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. *Pediatrics* 1994; **94:** 524–6.
8. Chaves SS, *et al.* Loss of vaccine-induced immunity to varicella over time. *N Engl J Med* 2007; **356:** 1121–9.
9. Kuter B, *et al.* Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J* 2004; **23:** 132–7.
10. Lawrence R, *et al.* The risk of zoster after varicella vaccination in children with leukemia. *N Engl J Med* 1988; **318:** 543–8.
11. Black S, *et al.* Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; **18:** 1041–6.
12. Watson BM, *et al.* Modified chickenpox in children immunized with the Oka/Merck varicella vaccine. *Pediatrics* 1993; **91:** 17–22.
13. Bernstein HH, *et al.* Clinical survey of natural varicella compared with breakthrough varicella after immunization with live attenuated Oka/Merck varicella vaccine. *Pediatrics* 1993; **92:** 833–7.
14. Oxman MN, *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; **352:** 2271–84.
15. CDC. CDC's Advisory Committee recommends "shingles" vaccination. Press release from the Advisory Committee on Immunization Practices (ACIP) (issued 26 October 2006). Available at: http://www.cdc.gov/od/oc/media/pressrel/r061026.htm (accessed 06/07/07)

Preparations

Ph. Eur.: Varicella Vaccine (Live).

Proprietary Preparations (details are given in Part 3)

Arg.: Varicela Biken; Varilrix; ***Austral.:*** Varilrix; Varivax; ***Austria:*** Varilrix; ***Belg.:*** Provarivax; Varilrix; ***Braz.:*** Vacina Contra A Varicela (Virus Atenuado); Vacina Contra Varicela; Varilrix†; Varivax†; ***Canad.:*** Varilrix; Varivax; ***Chile:*** Varicela Biken; Varilrix; ***Cz.:*** Varilrix; Zostavax; ***Denm.:*** Varilrix; ***Fin.:*** Varilrix; ***Fr.:*** Varilrix; Varivax; ***Ger.:*** Varilrix; Varivax; ***Gr.:*** Varilrix; Varivax; ***Hong Kong:*** Okavax; Varilrix; Varivax; ***Hung.:*** Varilrix; ***India:*** Varilrix; Varipox; ***Indon.:*** Okavax; Varilrix; ***Irl.:*** Varivax; ***Israel:*** Varilrix; ***Ital.:*** Varilrix; Varivax; ***Malaysia:*** Okavax; Varilrix; Varivax†; ***Mex.:*** Okavax; Varilrix; Varivax; ***Neth.:*** Provarivax; ***Norw.:*** Varilrix; ***NZ:*** Varilrix; Varivax; ***Philipp.:*** Okavax; V-Z Vax; Varilrix; ***Pol.:*** Varilrix; ***Port.:*** Varilrix; Varivax; Zostavax; ***S.Afr.:*** Varilrix; ***Singapore:*** Okavax; Varilrix; Varivax†; ***Spain:*** Varilrix; Varivax; ***Swed.:*** Varilrix; ***Switz.:*** Varilrix; Varivax; ***Thai.:*** Okavax; Varilrix; ***Turk.:*** Okavax; Varilrix; ***UK:*** Varilrix; Varivax; ***USA:*** Varivax; Zostavax; ***Venez.:*** Varilrix.

Yellow Fever Vaccines

Vacunas de la fiebre amarilla.

ATC — J07BL01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Yellow Fever Vaccine (Live); Vaccinum Febris Flavae Vivum). A freeze-dried preparation of the 17D strain of yellow fever virus grown in fertilised hen eggs. It is reconstituted immediately before use. It should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Yel(live) may be used on the label.

USP 31 (Yellow Fever Vaccine). A freeze-dried preparation of a selected attenuated strain of live yellow fever virus cultured in chick embryos. It is reconstituted, just prior to use, by the addition of sodium chloride containing no antimicrobial agent. It should be stored under nitrogen preferably below 0° but not above 5°.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Local and general reactions are not common after vaccination for yellow fever. Very rarely encephalitis has occurred, generally in infants under 9 months of age. Therefore, yellow fever vaccine is not usually given to infants under 9 months (but see Vaccine-associated Neurotropic Disease, below).

There is as yet limited data on the safety of yellow fever vaccine in HIV-positive individuals. In the UK, it is recommended that specialist advice should be sought regarding the use of yellow fever vaccine in such individuals. WHO advises that the vaccine should be given to HIV-positive individuals who are asymptomatic if the risk of infection is high.

Pregnancy. Although yellow fever vaccine has been given to women during pregnancy without producing adverse effects in the infants,[1] fetal infection has been reported.[2] US recommendations[3] therefore advise that the safety of yellow fever vaccination during pregnancy has not been established and the vaccine should only be given to pregnant women if travel to an endemic area is unavoidable and if an increased risk of exposure exists. Infants born to these women should be monitored closely for evidence of congenital infection or other adverse effects.

1. Nasidi A, *et al.* Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans R Soc Trop Med Hyg* 1993; **87:** 337–9.
2. Tsai TF, *et al.* Congenital yellow fever virus infection after immunization in pregnancy. *J Infect Dis* 1993; **168:** 1520–3.
3. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; **51** (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

Vaccine-associated neurotropic disease. Yellow fever vaccine has been associated with rare reports of encephalitis, now termed vaccine-associated neurotropic disease (YEL-AND). WHO has stated[1] that, since 1945, there have been at least 26 cases of proven or probable YEL-AND of which 16 occurred in infants aged less than 6 months. Of the 26 cases, 24 recovered without further complications and there were 2 fatalities.[1] Vaccine virus recovered from one of the fatalities, a 3-year-old child, revealed that mutation had occurred in the envelope gene of the virus, but it is not known whether similar mutations occurred in the other cases. The other fatality occurred in an immunocompromised adult with HIV infection. As a precaution against possible encephalitis, infants less than 9 months of age are not generally immunised, although it may be advisable to immunise at 6 to 8 months of age during epidemics.

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–59.

Vaccine-associated viscerotropic disease. Yellow fever vaccine has been associated with rare reports of multiple organ failure, now termed yellow fever vaccine-associated viscerotropic disease (YEL-AVD). WHO has stated[1] that, between 1996 and 2001, there were 7 recorded cases of YEL-AVD of which 2 occurred in Brazil,[2] 4 in the USA,[3] and one in Australia.[4] Six of these 7 cases were fatal. A further case, also leading to fatality, was reported to have occurred in Spain in 2004.[5] It has been suggested that the most likely explanation is an idiosyncratic host susceptibility to the 17D vaccine strain rather than a reversion of the vaccine strain to a wild-type strain.[5] There is also some evidence to suggest that the risk of YEL-AVD is greater in patients aged over 60 years.[6]

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–59.
2. Vasconcelos PFC, *et al.* Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. *Lancet* 2001; **358:** 91–7. Corrections. *ibid.*; 336. *ibid.*; 1018.
3. Chan RC, *et al.* Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. *Lancet* 2001; **358:** 121–2.
4. Martin M, *et al.* Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. *Lancet* 2001; **358:** 98–104.
5. Agencia Española del Medicamentos y Productos Sanitarios. A death associated with yellow fever vaccination reported in Spain. Available at: http://www.eurosurveillance.org/ew/2004/041104.asp (accessed 25/08/05)
6. Khromava AY, *et al.* Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005; **23:** 3265–63.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Yellow fever vaccines are used for active immunisation against yellow fever. Immunity is usually established within about 10 days of administration and persists for many years. Only one dose is required for immunisation and is given by deep subcutaneous injection; the dose (0.5 mL) is the volume containing at least 1000 mouse LD_{50} units.

In the UK, immunisation against yellow fever is recommended for laboratory workers handling infected material, for persons travelling through or living in areas of infection, and for travellers entering countries which require an International Certificate of Vaccination. The immunity produced may last for life although officially an International Certificate of Vaccination against yellow fever is valid only for 10 years starting 10 days after the primary immunisation and only if the vaccine used has been approved by WHO and given at a designated centre.

Vaccination under 9 months of age is not generally recommended (see Adverse Effects and Precautions, above).

◊ General references.

1. Barrett ADT. Yellow fever vaccines. *Biologicals* 1997; **25:** 17–25.

◊ Recommendations of the Advisory Committee on Immunization Practices for the prevention of yellow fever in the USA.[1]

1. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; **51** (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

Immunisation schedules. The 17D (Rockefeller) yellow fever vaccine is now the only yellow fever vaccine produced.[1,2] The quantity available in the world has been limited and its relatively short half-life does not permit the accumulation of large stocks. The demand for the vaccine is also somewhat irregular, being suddenly high during epidemics and low during inter-epidemic periods.

In Africa and in South America two different strategies for yellow fever immunisation have been followed.[1,2] Firstly, an emergency immunisation programme takes place once an outbreak has begun, in an attempt to limit the spread of infection by immunising all persons in the focus, regardless of their former immune status. One disadvantage is that immunity does not appear until 7 days after immunisation and deaths may be expected to occur in the interim period. Secondly, a routine mass immunisation programme for yellow fever is aimed at immunising in advance all populations considered to be at risk. Yellow fever vaccine is included in the WHO Expanded Programme on Immunization; there are obvious logistic advantages in giving it at the age of 9 months at the same time as measles vaccine. In rural areas of the endemic zone that are considered at high risk, the minimum age for routine immunisation may be lowered to 6 months (see Vaccine-associated Neurotropic Disease, above).

1. WHO. *Prevention and control of yellow fever in Africa*. Geneva: WHO, 1986.
2. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; **78:** 349–60.

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO. Information is provided concerning the countries in Africa and South America where yellow fever is endemic and also countries requiring a traveller to hold a valid vaccination certificate. For some further details, see p.2203.

Preparations

Ph. Eur.: Yellow Fever Vaccine (Live);
USP 31: Yellow Fever Vaccine.

Proprietary Preparations (details are given in Part 3)

Arg.: Stamaril; ***Austral.:*** Stamaril; ***Belg.:*** Stamaril; ***Canad.:*** YF-Vax; ***Chile:*** Stamaril; ***Cz.:*** Stamaril; ***Denm.:*** Stamaril; ***Fin.:*** Arilvax†; Stamaril; ***Fr.:*** Stamaril; ***Ger.:*** Stamaril; ***Irl.:*** Arilvax†; Stamaril; ***Israel:*** Arilvax; ***Ital.:*** Stamaril; ***Malaysia:*** Stamaril†; ***Neth.:*** Arilvax; Stamaril; ***Norw.:*** Stamaril; ***NZ:*** Stamaril; ***Pol.:*** Stamaril; ***Port.:*** Stamaril; ***S.Afr.:*** Arilvax; Stamaril; ***Singapore:*** Arilvax†; Stamaril; ***Swed.:*** Arilvax†; Stamaril; ***Switz.:*** Arilvax†; Stamaril; ***Turk.:*** Stamaril; ***UK:*** Arilvax; Stamaril; ***USA:*** YF-Vax; ***Venez.:*** Stamaril†.

Supplementary Drugs and Other Substances

This chapter includes some drugs not easily classified, herbal medicines, new drugs whose place in therapy is not yet clear, and drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

Abrus

Abrus Seed; Indian Liquorice; Jequirity Bean; Jumble Beads; Prayer Beads; Regaliz americano; Rosary Beans.

Profile

Abrus consists of the seeds of *Abrus precatorius* (Leguminosae), one of whose constituents is abrin. Abrin, which is closely related to ricin, is considered responsible for the toxic effects of the seeds. Children have died from eating one or more seeds. Toxicity may be less likely to occur if the seeds are swallowed whole, than if they are chewed, because of the hard seed coat. Toxic effects may occur within a few hours or may be delayed for several days after ingestion. Signs and symptoms of abrin poisoning are similar to those described for ricin, p.2379.

Abrus has been used as an oral contraceptive in herbal medicine.

Homoeopathy. Abrus has been used in homoeopathic medicines.

◊ References.

1. Aslam M, Shaw JMH. Abrus in Asian medicine. *Pharm J* 1998; **261:** 822–4.
2. Fernando C. Poisoning due to Abrus precatorius (jequirity bean). *Anaesthesia* 2001; **56:** 1178–80.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Enkasari; Ika Sariawan.

Absinthium

Absinthe; Absinthii herba; Ajenjo; Assenzio; Fehér ürömfű; Karčiųjų kiečių žolė; Losna; Mali, Koiruoho; Malört; Pelin; Pelyňková nať; Wermutkraut; Wormwood; Ziele piołunu.

CAS — 546-80-5 (α-thujone); 471-15-8 (β-thujone).

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of absinthium:
Green Fairy; Green Goddess; La Fée Verte.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Wormwood). The leaves or flowering tops, or a mixture of these dried, whole or cut organs of wormwood, *Artemisia absinthium*. It contains not less than 2 mL/kg of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Absinthium has been used as a bitter. It is also used in small quantities as a flavour in alcoholic beverages, although it is considered in some countries to be unsafe for use in foods, beverages, or drugs. Habitual use or large doses cause absinthism, which is characterised by restlessness, vomiting, vertigo, tremors, and convulsions. Thujone, related to camphor, is the major constituent of the essential oil derived from absinthium.

Homoeopathy. Absinthium has been used in homoeopathic medicines under the following names: Artemisia absinthium; Artemisia absinthium ex herba siccata; Absinth.

◊ References.

1. Weisbord SD, *et al.* Poison on line—acute renal failure caused by oil of wormwood purchased through the Internet. *N Engl J Med* 1997; **337:** 825–7.
2. Skyles AJ, Sweet BV. Wormwood. *Am J Health-Syst Pharm* 2004; **61:** 239–42.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Nat Pelynku Praveho.

Multi-ingredient: ***Austria:*** Abdomilon N; Eryval; Magentee St Severin; Mariazeller; Sigman-Haustropfen; Virgilocard; ***Braz.:*** Camomila; ***Cz.:*** Abdomilon†; Contraspan†; Eugastrin†; Original Schwedenbitter; Zaludecni Cajova Smes; ***Fr.:*** Tisane Hepatique de Hoerdt; ***Ger.:*** Abdomilon N; Amara-Pascoe; Amara-Tropfen; Anore X N†; Aristochol N†; Floradix Multipretten N; Gallemolan forte; Gallemolan G†; Gallexier; Gastralon N†; Gastritol; Gastrol S†; Hepaticum novo†; Leber-Galle-Tropfen 83†; Lomatol†; Majocarmin forte†; Majocarmin mite†; Marianon†; Nervosana†; Neurochol C†; Pascopankreat; Presselin Blahungs K 4 N†; Presselin Dyspeptikum†; rohasal†; Stomachysat N†; Stovalid N†; Stullmaton†; Unex Amarum†; ventriloges N; ***India:*** Toniazol†; ***Ital.:*** Assenzio (Specie Composta)†; Genziana (Specie Composta)†; ***Pol.:*** Artemisol; Krople Zoladkowe; ***Rus.:*** Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Amara; ***Switz.:*** Baume†; Kernosan Heidelberger Poudre; Phytomed Hepato†; Pommade au Baume.

Acedoben *(pINN)*

Acedobén; Acédobène; Acedobenum. *p*-Acetamidobenzoic acid.

Ацедобен

$C_9H_9NO_3$ = 179.2.

CAS — 556-08-1.

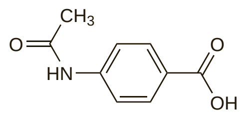

Profile

Acedoben is a component of inosine pranobex (p.884), and has been given orally as the potassium salt in the treatment of skin disorders. Acedoben and its sodium salt have been applied topically.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Amplidermis; Hongosan.

Aceglutamide *(rINN)*

Aceglutamida; Acéglutamide; Aceglutamidum. N^2-Acetyl-L-glutamine; 2-Acetylamino-L-glutaramic acid.

Ацеглутамид

$C_7H_{12}N_2O_4$ = 188.2.

CAS — 2490-97-3.

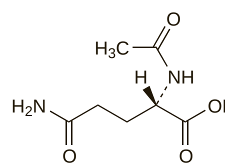

Profile

Aceglutamide has been given in an attempt to improve memory and concentration. Aceglutamide aluminium (p.1704) is used as an antacid.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Acutil Fosforo; Memovisus†; Tonoplus†.

Acemannan *(USAN, rINN)*

Acemanán; Acémannan; Acemannanum; Polymanoacetate.

Ацеманнан

CAS — 110042-95-0.

Profile

Acemannan is a highly acetylated, polydispersed, linear mannan obtained from the mucilage of *Aloe vera* (*A. barbadensis*). It has immunomodulating properties and is an ingredient of topical wound dressing products including those formulated for the oral mucosa.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Carrasyn; DiaB Gel; Oral Wound Rinse; RadiaGel; SaliCept; Ultrex.

Acetic Acid

Acide acétique; Ácido acético; Ácido etanóico; Acidum aceticum; Acto rūgštis; Asetik Asit; Ättiksyra; E260; Ecetsav; Eisessig (glacial acetic acid); Essigsäure; Etanoico; Ethanoic Acid; Etikkahappo; Kwas octowy; Kyselina octová.

$C_2H_4O_2$ = 60.05.

CAS — 64-19-7.

ATC — G01AD02; S02AA10.

ATC Vet — QG01AD02; QS02AA10.

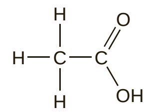

NOTE. The nomenclature of acetic acid often leads to confusion over whether concentrations are expressed as percentages of glacial acetic acid ($C_2H_4O_2$) or of a diluted form. In *Martindale*, the percentage figures given against acetic acid represent the amount of $C_2H_4O_2$.

Pharmacopoeias. Glacial acetic acid is included in *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.*

Solutions containing about 30 to 37% are included in *Br.* (33%), *Chin.* (36 to 37%), *Int., Jpn* (30 to 32%), and *Swiss* (30%). Also in *USNF* (36 to 37%).

Dilute acetic acid (6%) is included in *Br.* and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Acetic Acid, Glacial; Acidum Aceticum Glaciale). A crystalline mass or a clear colourless volatile liquid. F.p. not lower than 14.8°. Miscible with water, with alcohol, and with dichloromethane. Store in airtight containers.

BP 2008 (Acetic Acid (33 per cent)). It contains 32.5 to 33.5% w/w of $C_2H_4O_2$. It is a clear colourless liquid with a pungent odour. Miscible with water, with alcohol, and with glycerol.

BP 2008 (Acetic Acid (6 per cent)). It contains 5.7 to 6.3% w/w of $C_2H_4O_2$. It is prepared by diluting Acetic Acid (33 per cent).

USP 31 (Glacial Acetic Acid). A clear colourless liquid with a pungent characteristic odour. B.p. about 118°. Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 26 (Acetic Acid). It contains 36 to 37% w/v of $C_2H_4O_2$. It is a clear colourless liquid with a strong characteristic odour. Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 26 (Diluted Acetic Acid). It contains 5.7 to 6.3% w/v of $C_2H_4O_2$. It is prepared by diluting Acetic Acid. Store in airtight containers.

Adverse Effects and Treatment

Local or topical application of acetic acid preparations may produce stinging or burning. Ingestion of glacial acetic acid can produce similar adverse effects to those of hydrochloric acid (p.2322), which may be treated similarly.

Uses and Administration

Glacial acetic acid has been used as an escharotic. Diluted forms have been used as an antibacterial (it is reported to be effective against *Haemophilus* and *Pseudomonas* spp.), antifungal, and antiprotozoal in vaginal gels and douches, irrigations, topical preparations for the skin and nails, and in ear drops. Diluted forms have also been used as an expectorant, an astringent lotion, and as treatments for warts (p.1584), callosities, and for certain jellyfish stings (see below). Solutions have also been used to soften ear wax (p.1725) and in the treatment of otitis externa (p.182). Visual inspection of the uterine cervix with acetic acid (VIA) is being investigated as a screening method for cervical cancer, particularly where facilities for cytological methods may be limited.

A solution containing 4% w/v $C_2H_4O_2$ is known as artificial vinegar or non-brewed condiment. Vinegar is a product of fermentation.

Jellyfish sting. Vinegar or acetic acid 3 to 10% is applied to box jellyfish stings to inactivate any fragments of adherent tentacle[1,2] (see p.2220). Acetic acid solutions have been reported to be useful in stings by related species[3] although they may produce further discharge of venom in some jellyfish.[4]

1. Hartwick RJ, *et al*. Disarming the box jellyfish. *Med J Aust* 1980; **1:** 15–20.
2. Fenner PJ, Williamson JA. Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 1996; **165:** 658–61.
3. Fenner PJ, *et al*. "Morbakka", another cubomedusan. *Med J Aust* 1985; **143:** 550–5.
4. Fenner PJ, Fitzpatrick PF. Experiments with the nematocysts of Cyanea capillata. *Med J Aust* 1986; **145:** 174.

Wounds and burns. Infection of wounds (p.1585) and burns (p.1578) with *Pseudomonas aeruginosa* may delay healing. Acetic acid has been used, in concentrations of up to 5%, to eradicate these infections.[1]

1. Milner SM. Acetic acid to treat Pseudomonas aeruginosa in superficial wounds and burns. *Lancet* 1992; **340:** 61.

Preparations

BP 2008: Strong Ammonium Acetate Solution;
USP 31: Acetic Acid Irrigation; Acetic Acid Otic Solution; Hydrocortisone and Acetic Acid Otic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ecoshampoo†; Hexa-Defital Crema Enjuague; Otopreven; Pelo Libre Protectora; Pil-G Uso†; ***Austral.:*** Summers Eve Disposable; ***Chile:*** Soft Kilnits†; ***Fr.:*** Para Lentes; ***Gr.:*** Instaret; ***Irl.:*** Aci-Jel†; ***UK:*** Aci-Jel†; EarCalm; Meltus Baby; ***USA:*** Feminique; Massengill Disposable; Summers Eve Disposable; ***Venez.:*** Duvagin; Fem Ducha.

Multi-ingredient: ***Arg.:*** Aglio; Callicida; Detebencil Nit; Fuera Bicho; Hexa-Defital Plus; Microsona Otica; Uze Active; Yalu†; ***Austral.:*** Aci-Jel†; Aqua Ear; Ear Clear for Swimmer's Ear; ***Belg.:*** Aporil; ***Braz.:*** A Curitybina; Kalostop†; Lacto Vagin†; ***Canad.:*** SH-206; Viron Wart Lotion; VoSoL HC†; ***Chile:*** Summer's Eve Vinagre y Agua†; ***Cz.:*** Solcogyn†; ***Fr.:*** Nitrol; Ysol 206; ***Ger.:*** Gehwol Huhneraugen-Tinktur; Solco-Derman; ***Gr.:*** Otocort; ***Hong Kong:*** Baby Cough with Antihistamine; Solcoderm; ***India:*** Otek-AC†; Perfocyn; ***Irl.:*** Phytex; ***Ital.:*** Oleo Calcarea†; ***Malaysia:*** Solcoderm†; ***Neth.:*** Buckleys Kinderhoestsiroop; ***NZ:*** Aci-Jel†; Aqua Ear†; VoSoL; ***Pol.:*** Acifungin; Solcogyn; ***Rus.:*** Bubil (Бубил); Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Spain:*** Callicida Cor Pik; Callicida Rojo; Keranin; Nitroina; Quocin; ***Switz.:*** Coruzol†; Solcoderm; Solcogyn; Waruzol; ***Thai.:*** Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; ***Turk.:*** Dilan; Tuba;

UK: Ellimans; Goddards Embrocation; Phytex; Potters Gees Linctus; Sanderson's Throat Specific; ***USA:*** Acetasol; Acetasol HC; Acid Jelly; Auralgan; Borofair Otic; Burow's; Fem pH; Klout; Otic Domeboro; Star-Otic; Tridesilon†; VoSoL HC†; VoSoL†; ***Venez.:*** Gynovit; Kayivis; Saxacid.

Acetohydroxamic Acid *(USAN, rINN)*

N-Acetyl Hydroxyacetamide; Acide Acétohydroxamique; Ácido acetohidroxámico; Acidum Acetohydroxamicum; AHA.

Ацетогидроксамовая Кислота

$C_2H_5NO_2$ = 75.07.

CAS — 546-88-3.

ATC — G04BX03.

ATC Vet — QG04BX03.

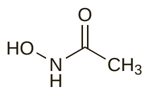

Pharmacopoeias. In *US*.

USP 31 (Acetohydroxamic Acid). White, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform. Store in airtight containers at a temperature between 8° and 15°.

Adverse Effects and Precautions

Phlebitis, thromboembolism, haemolytic anaemia, and iron-deficiency anaemia have occurred. Bone-marrow depression has been reported in *animal* studies. Other adverse effects include headache, gastrointestinal disturbances, alopecia, rash (particularly after ingestion of alcohol), trembling, and mental symptoms including anxiety and depression. Blood counts and renal function should be monitored regularly during treatment. Patients with acute renal failure should not be given acetohydroxamic acid.

Pregnancy. Studies in *animals* indicate that acetohydroxamic acid is teratogenic.

Interactions

Acetohydroxamic acid chelates iron given orally, resulting in reduced absorption of both. Ingestion with alcohol may precipitate skin rash.

Pharmacokinetics

Acetohydroxamic acid is rapidly absorbed from the gastrointestinal tract with peak serum concentrations being reached within 1 hour. The plasma half-life is reported to be up to 10 hours, but may be longer in patients with impaired renal function. Acetohydroxamic acid is partially metabolised to acetamide, which is inactive; up to about two-thirds of a dose may be excreted unchanged in the urine.

Uses and Administration

Acetohydroxamic acid acts by inhibiting bacterial urease, thus decreasing urinary ammonia concentration and alkalinity. It is used in the prophylaxis of struvite renal calculi (p.2181) and as an adjunct in the treatment of chronic urinary-tract infections (p.199).

Acetohydroxamic acid is given orally in a usual dose of 250 mg three or four times daily. The total dose should not exceed 1.5 g daily. Children have been given 10 mg/kg daily in 2 or 3 divided doses. Dosage should be adjusted in patients with renal impairment (see below).

Administration in renal impairment. Acetohydroxamic acid should not be given to patients with serum-creatinine concentrations in excess of about 220 micromoles/litre. If the concentration is between 160 and 220 micromoles/litre, the maximum daily dose should be 1 g and the dosing interval should be extended to every 12 hours.

Preparations

USP 31: Acetohydroxamic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Spain: Uronefrex; ***USA:*** Lithostat.

Acetylleucine *(rINN)*

Acetileucina; Acétylleucine; Acetylleucinum; RP-7542. *N*-Acetyl-DL-leucine.

Ацетиллейцин

$C_8H_{15}NO_3$ = 173.2.

CAS — 99-15-0.

ATC — N07CA04.

ATC Vet — QN07CA04.

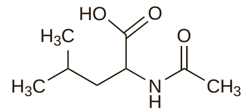

Profile

Acetylleucine has been used in the treatment of vertigo (p.565) in usual oral doses of up to 2 g daily, in divided doses, or 1 g daily by intravenous injection. Higher doses have occasionally been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Tanganil.

Acexamic Acid *(BAN, rINN)*

Acide Acexamique; Ácido acexámico; Acidum Acexamicum; CY-153; Epsilon Acetamidocaproic Acid. 6-Acetamidohexanoic acid.

Ацексамовая Кислота

$C_8H_{15}NO_3$ = 173.2.

CAS — 57-08-9 (acexamic acid); 70020-71-2 (zinc acexamate).

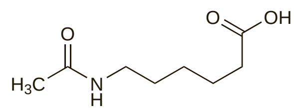

Pharmacopoeias. *Eur.* (see p.vii) includes Zinc Acexamate.

Profile

Acexamic acid is related structurally to the antifibrinolytic agent aminocaproic acid (p.1053). Acexamic acid, usually as the calcium or sodium salt, has been used topically or systemically to promote the healing of ulcers and various other skin lesions. Zinc acexamate has been given for peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Plastenan; Restaurene; ***Belg.:*** Plastenan; ***Fr.:*** Plastenan†; ***Mex.:*** Recoveron; ***Port.:*** Plastesol†; ***Spain:*** Copinal.

Multi-ingredient: ***Arg.:*** Bagoderm; Cicatrizol; Lisoderma; Plastenan con Neomicina; ***Fr.:*** Trofoseptine†; ***Mex.:*** Dermatolona; Recoveron N; Recoveron NC; ***Port.:*** Plastenan Neomicina†; ***Spain:*** Plaskine Neomicina; Unitul Complex†.

Achillea

Achillée millefeuille; Aquilea; Cickafarkfű; Kraujažolių žolė; Milfoil; Millefolii herba; Řebříčková nat'; Rölleka; Schafgarbe; Siankärsämö; Yarrow; Ziele krwawnika.

CAS — 8022-07-9 (yarrow root oil).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Yarrow). The whole or cut, dried flowering tops of yarrow, *Achillea millefolium*. It contains not less than 2 mL/kg of essential oil and not less than 0.02% of proazulenes, expressed as chamazulene ($C_{14}H_{16}$ = 184.3), both calculated with reference to the dried drug. Protect from light.

Profile

Achillea has been used in herbal medicine. It has been stated to have diaphoretic, anti-inflammatory, and other miscellaneous properties. It has been reported to cause contact dermatitis.

Yarrow root oil is used in aromatherapy.

Homoeopathy. Achillea has been used in homoeopathic medicines under the following names: Achillea millefolium; Millefolium; Achillea ex herba; Millef.

◊ References.

1. Phillipson JD, Anderson LA. Herbal remedies used in sedative and antirheumatic preparations: part 2. *Pharm J* 1984; **233:** 111–15.
2. Chandler RF. Yarrow. *Can Pharm J* 1989; **122:** 41–3.
3. Anonymous. Final report on the safety assessment of yarrow (Achillea millefolium) extract. *Int J Toxicol* 2001; **20** (suppl 2): 79–84.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Gallentee†; Nat Rebricku; Rebrickovy Caj, Rebrickova Nat; ***Mex.:*** Blancaler.

Multi-ingredient: ***Austral.:*** Diaco; Flavons; ***Austria:*** Abfuhrtee St Severin; Amersan; Gallen- und Lebertee St Severin; Mariazeller; Menodoron; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Amersan; Cajova Smes pri Redukcni Diete†; Cicaderma; Hemoral†; Hertz- und Kreislauftee†; Kamillan Plus†; Perospir†; Projimava; Species Urologicae Planta; Stomatosan†; Ungolen†; Zaludecni Cajova Smes; ***Fr.:*** Cicaderma; Gonaxine; Menoxine; Tisane Hepatique de Hoerdt; ***Ger.:*** Alasenn; Amara-Tropfen; Aristochol N†; Cheiranthol†; Floradix Multipretten N; Gallexier; Kamillan Plus†; Marianon†; Nervosana†; Sedovent; Stomachysat N†; Tonsilgon; ***Hung.:*** Hemorid; Noditran†; ***Ital.:*** Forticrin; Lozione Same Urto; Pik Gel; ***Pol.:*** Amarosal; Artecholin; Artecholwex; Cholavisol; Dyspepsin; Enterosol; Gastrobonisol; Hemorol; Liv 52; Nefrobonisol; Reumosol; Salviasept; Sanofil; ***Port.:*** Cicaderma; Fade Cream†; ***Rus.:*** Liv 52 (Лив 52); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Tonsilgon N (Тонзилгон Н); ***S.Afr.:*** Amara; Clairo; Menodoron; ***Spain:*** Jaquesor†; Menstrunat†; Natusor Circusil†; Natusor Gastrolen†; Natusor Jaquesan†; ***Switz.:*** Baume†; Gastrosan; Kernosan Heidelberger Poudre; Pommade au Baume; Tisane hepatique et biliaire; Tisane pour l'estomac; ***UK:*** Catarrheeze; Rheumatic Pain Remedy; Tabritis; Wellwoman.

Acid Alpha Glucosidase

Acid Maltase; α-Glucosidasa; Lysosomal α-glucosidase.

Alglucosidase Alfa *(USAN, rINN)*

Alglucosidasa alfa; Alglucosidasum Alfa; rhGAA.

Альглюкозидаза Альфа

CAS — 420784-05-0.

ATC — A16AB07.

ATC Vet — QA16AB07.

Profile

Alglucosidase alfa is a recombinant form of human acid alpha glucosidase given as enzyme replacement therapy for the treatment of the lysosomal storage disease Pompe disease (glycogen storage disease type II). This is a rare fatal autosomal recessive disorder caused by a deficiency of acid α-glucosidase, which cleaves α-1,4- and α-1,6-glucosidic linkages in lysosomal glycogen to liberate glucose. Glycogen accumulation results in progressive myopathy, especially of the skeletal muscles and heart.

Alglucosidase alfa is given intravenously using an infusion pump in doses of 20 mg/kg once every 2 weeks. The total volume of fluid, which is determined by the patient's body-weight, should be infused over about 4 hours. The infusion rate should be increased gradually: the initial rate should not exceed 1 mg/kg per hour; once the patient can tolerate this rate, it may be increased every 30 minutes by 2 mg/kg per hour with monitoring of vital signs before each increase; the maximum infusion rate is 7 mg/kg per hour.

Infusion reactions are common with alglucosidase alfa; symptoms may resolve on decreasing the infusion rate, temporarily stopping the infusion, and/or use of antihistamines and/or antipyretics, which may also be given as pre-treatment. Severe reactions may require stopping the infusion immediately. Serious hypersensitivity reactions, including anaphylactic shock, have also been reported during infusion of alglucosidase alfa.

◊ References.

1. Amalfitano A, *et al.* Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. *Genet Med* 2001; **3:** 132–8.
2. Van den Hout JM, *et al.* Enzyme therapy for Pompe disease with recombinant human alpha-glucosidase from rabbit milk. *J Inherit Metab Dis* 2001; **24:** 266–74.
3. Kishnani PS, Howell RR. Pompe disease in infants and children. *J Pediatr* 2004; **144** (suppl): S35–S43.
4. Hunley TE, *et al.* Nephrotic syndrome complicating alpha-glucosidase replacement therapy for Pompe disease. Abstract: *Pediatrics* 2004; **114:** 1080. Full version: http://www.pediatrics.org/cgi/content/full/114/4/e532 (accessed 17/01/06)
5. Kishnani PS, *et al.* Chinese hamster ovary cell-derived recombinant human acid α-glucosidase in infantile-onset Pompe disease. *J Pediatr* 2006; **149:** 89–97.
6. van der Beek NA, *et al.* Pompe disease (glycogen storage disease type II): clinical features and enzyme replacement therapy. *Acta Neurol Belg* 2006; **106:** 82–6.
7. Kishnani PS, *et al.* Recombinant human acid α-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007; **68:** 99–109.
8. Fukuda T, *et al.* Acid alpha-glucosidase deficiency (Pompe disease). *Curr Neurol Neurosci Rep* 2007; **7:** 71–7.
9. Rossi M, *et al.* Long-term enzyme replacement therapy for Pompe disease with recombinant human alpha-glucosidase derived from Chinese hamster ovary cells. *J Child Neurol* 2007; **22:** 565–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Myozyme; ***Fr.:*** Myozyme; ***Port.:*** Myozyme; ***UK:*** Myozyme; ***USA:*** Myozyme.

Multi-ingredient: ***Austral.:*** Digestaid; ***Canad.:*** Digesta.

Acid Fuchsine

Acid Magenta; Acid Roseine; Acid Rubine; CI Acid Violet 19; Colour Index No. 42685; Fucsina ácida.

Profile

Acid fuchsine is the disodium or diammonium salt of the trisulfonic acid of magenta. It is used as a microscopic stain and a pH indicator.

Acitazanolast (rINN)

Acitazanolastum; WP-871. 3′-(1*H*-tetrazol-5-yl)oxanilic acid.

Ацитазанопаст

$C_9H_7N_5O_3$ = 233.2.

CAS — 114607-46-4.

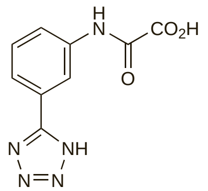

Profile

Acitazanolast is a leukotriene inhibitor used as the hydrate in a concentration of 0.1 or 0.3% in eye drops for the treatment of allergic conjunctivitis (p.564).

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Zepelin.

Aconite

Acetylbenzoylaconine (aconitine); Aconit.; Aconit napel; Aconite Root; Aconiti Tuber; Acónito; Aconitum napellus; Monkshood Root; Radix Aconiti; Wolfsbane Root. 8-Acetoxy-3,11,18-trihydroxy-16-ethyl-1,6,19-trimethoxy-4-methoxymethylaconitan-10-yl benzoate (aconitine).

$C_{34}H_{47}NO_{11}$ = 645.7 (aconitine).

CAS — 8063-12-5 (aconite); 302-27-2 (aconitine).

NOTE. Wolfsbane is also used as a common name for arnica flower (p.2260).

Description. Aconite consists of the dried tuberous root of *Aconitum napellus* agg. (Ranunculaceae). It contains a number of alkaloids, the main pharmacologically active one being aconitine.

Pharmacopoeias. In *Chin.*

Adverse Effects and Treatment

Aconite has variable effects on the heart leading to heart failure. It also affects the CNS.

Symptoms of aconite poisoning may appear within minutes or up to 2 hours after oral ingestion; in fatal poisoning death usually occurs within 12 hours, although with larger doses it may be instantaneous.

Initial symptoms (and an important diagnostic feature) are tingling sensations of the tongue, mouth, fingers, and toes followed by generalised paraesthesia. Other symptoms include nausea, vomiting, diarrhoea, muscle weakness, skeletal muscle paralysis, and difficult respiration; also sweats, chills and a feeling of intense cold may occur. Respiratory paralysis, hypotension, and cardiac arrhythmias may develop in severe cases.

Although the benefits of gastric decontamination are uncertain, gastric lavage may be tried in patients within one hour of life-threatening oral poisoning; activated charcoal may also be considered. Patients should be observed and monitored, and corrective and supportive treatment given as necessary. Arrhythmias are relatively resistant to treatment, although atropine has been tried for bradycardia.

Poisoning. Reports of poisoning with aconite.

1. Kelly SP. Aconite poisoning. *Med J Aust* 1990; **153:** 499.
2. Tai Y-T, *et al.* Cardiotoxicity after accidental herb-induced aconite poisoning. *Lancet* 1992; **340:** 1254–6.
3. Kolev ST, *et al.* Toxicity following accidental ingestion of Aconitum containing Chinese remedy. *Hum Exp Toxicol* 1996; **15:** 839–42.
4. Mak W, Lau CP. A woman with tetraparesis and missed beats. *Hosp Med* 2000; **61:** 438.
5. Imazio M, *et al.* Malignant ventricular arrhythmias due to Aconitum napellus seeds. *Circulation* 2000; **102:** 2907–8.
6. Chan TYK. Incidence of herb-induced aconitine poisoning in Hong Kong: impact of publicity measures to promote awareness among the herbalists and the public. *Drug Safety* 2002; **25:** 823–8.
7. Lowe L, *et al.* Herbal aconite tea and refractory ventricular tachycardia. *N Engl J Med* 2005; **353:**1532.

Uses and Administration

Aconite liniments have been used in the treatment of neuralgia, sciatica, and rheumatism. Sufficient aconitine may be absorbed through the skin to cause poisoning; liniments should never be applied to wounds or abraded surfaces. Aconite should not be used internally because of its low therapeutic index and variable potency; however it is reported to be a common ingredient in traditional Chinese remedies and is also an ingredient of some cough mixtures.

Homoeopathy. Aconite has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** No-Tos Adultos; ***Austria:*** Rheuma; ***Belg.:*** Colimax†; Eucalyptine Pholcodine Le Brun†; Saintbois; ***Braz.:*** Agrimel†; Expectomel; Gotas Nican†; Limao Bravo†; Melagriao; Pectal†; Xarope de Caraguata†; Xarope Peitoral de Ameixa Composto†; Xarope Sao Joao†; ***Chile:*** Gotas Nican†; ***Cz.:*** Homeovox; Pleumolysin; ***Ital.:*** Lactocol; ***Port.:*** Anti-Gripe†; Calmarum†; ***Spain:*** Encialina†.

Acridine Orange

Naranja de acridina. 3,6-Bis(dimethylamino)acridine.

$C_{17}H_{19}N_3$ = 265.4.

CAS — 494-38-2.

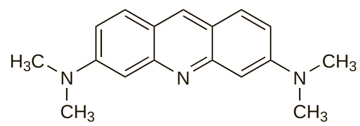

Profile

Acridine orange is a dye with antiseptic properties. It has been used as a diagnostic stain in microbiology.

For details of the antiseptic properties of acridine derivatives, see p.1624.

Diagnostic use. Acridine orange has been used for the diagnostic staining of malarial parasites.[1] For the quantitative buffy coat method, acridine orange is used to stain the parasites in a blood sample that is then centrifuged, and the area just below the buffy coat is examined under a fluorescence microscope. It has been described as easier and quicker to use than the standard examination of stained blood films. However, this method is not specific for diagnosis of malarial type, gives only a rough indication of infection intensity, and can give false-positive results. Acridine orange has also been tried for the staining of blood slides.[2-5]

1. Warhurst DC, Williams JE. ACP Broadsheet no 148, July 1996, Laboratory diagnosis of malaria. *J Clin Pathol* 1996; **49:** 533–8.
2. Gay F, *et al.* Direct acridine orange fluorescence examination of blood slides compared to current techniques for malaria diagnosis. *Trans R Soc Trop Med Hyg* 1996; **90:** 516–18.
3. Craig MH, Sharp BL. Comparative evaluation of four techniques for the diagnosis of Plasmodium falciparum infections. *Trans R Soc Trop Med Hyg* 1997; **91:** 279–82.
4. Tarimo DS, *et al.* Appraisal of the acridine orange method for rapid malaria diagnosis at three Tanzanian district hospitals. *East Afr Med J* 1998; **75:** 504–7.
5. Lema OE, *et al.* Comparison of five methods of malaria detection in the outpatient setting. *Am J Trop Med Hyg* 1999; **60:** 177–82.

Acrolein

Acraldehyde; Acrialdehído; Acroleína; Acrylaldehyde; Acrylic Aldehyde. Prop-2-enal.

C_3H_4O = 56.06.

CAS — 107-02-8.

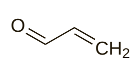

Profile

Acrolein is a volatile, highly flammable liquid at ordinary temperature and pressure. It has various industrial uses, but is also a toxic byproduct of combustion and may be present in exhaust gases, tobacco smoke, and smoke from fires. It is irritant to the skin and may cause skin burns. Ingestion of acrolein produces severe gastrointestinal distress. The vapour causes lachrymation and pulmonary irritation. Inhalation may cause pulmonary oedema and permanent lung damage.

Acrolein is a metabolite of cyclophosphamide (p.702) and may be responsible for the latter's bladder toxicity.

◊ References.

1. WHO. Acrolein. *IPCS Health and Safety Guide 67*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg067.htm (accessed 23/07/08)
2. WHO. Acrolein. *Environmental Health Criteria 127*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc127.htm (accessed 23/07/08)
3. Kehrer JP, Biswal SS. The molecular effects of acrolein. *Toxicol Sci* 2000; **57:** 6–15.

Acrylamide

Acrilamida; Akryloamid; Amida acrílica. Propenamide.

C_3H_5NO = 71.08.

CAS — 79-06-1.

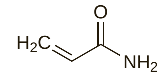

Profile

Acrylamide is highly toxic and irritant; it can be absorbed through unbroken skin. Symptoms of poisoning include burning and ulceration of the mouth and throat following ingestion. Excessive sweating is common and other symptoms may include numbness of limbs, paraesthesias, and muscle weakness. CNS effects such as somnolence, confusion, hallucinations, ataxia, tremors, dysarthria, and nystagmus may occur depending on the severity of exposure. Peripheral neuropathies may appear several weeks after severe acute exposure or as a result of chronic exposure. Gastric lavage may be tried in patients within one hour of ingestion; activated charcoal may also be considered. Contamination of eyes and skin should be irrigated and treated as for burns. Patients should be observed and monitored, and corrective and supportive treatment given as necessary.

Acrylamide has various industrial applications, including use as a plasticiser and a waterproof 'chemical grout'.

◊ References.

1. Kesson CM, *et al.* Acrylamide poisoning. *Postgrad Med J* 1977; **53:** 16–17.
2. WHO. Acrylamide *IPCS Health and Safety Guide 45*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg045.htm (accessed 31/03/06)

Food toxicity. Concerns have been expressed by the Swedish National Food Administration about the level of acrylamide they found in certain cooked foods, particularly those exposed to very high temperatures such as fried foods, and the potential carcinogenic risk. However, it has been acknowledged that, although the results have been replicated in other international laboratories, the total sample size is small and none of the methods being used have so far been validated.[1] One subsequent population-based study failed to find any excess risk or convincing trend of cancer of the bowel, bladder, or kidney in high consumers of foods with a high or moderate acrylamide content.[2] The joint FAO/WHO Expert Committee on Food Additives (JECFA)[3] reviewed data provided by 24 countries on acrylamide in food analysed between 2002 and 2004. Their recommendations were for re-evaluation of the effects of acrylamide on completion of studies of carcinogenicity and neurotoxicity, and that efforts to reduce the concentrations of acrylamide in food should continue.

1. Kapp C. WHO urges more research into acrylamide in food. *Lancet* 2002; **360:** 64.
2. Mucci LA, *et al.* Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. *Br J Cancer* 2003 **88:** 84–9.
3. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 18/07/08)

Actinoquinol Sodium (USAN, rINNM)

Actinoquinol sódico; Actinoquinol Sodique; Natrii Actinoquinolum; Sodium Etoquinol; Sodium Tequinol. Sodium 8-ethoxy-5-quinolinesulfonate.

Натрий Актинохинол

$C_{11}H_{10}NNaO_4S$ = 275.3.

CAS — 15301-40-3 (actinoquinol); 7246-07-3 (actinoquinol sodium).

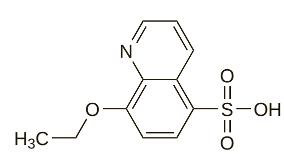

(actinoquinol)

Profile

Actinoquinol and actinoquinol sodium are ingredients of eye drop preparations intended to protect the eyes from the effects of light.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ultra Augenschutz.

Multi-ingredient: ***Fr.:*** Uvicol; ***Ger.:*** duraultra; ***Ital.:*** Fotofil.

Ademetionine *(rINN)*

Ademethionine; Ademetioniini; Adémétionin; Ademetionin; Ademetionina; Ademetioninum; *S*-Adenosyl-L-methionine; Methioninyl adenylate; SAMe. (*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulphonio]-5′-deoxyadenosine hydroxide, inner salt.

Адеметионин

$C_{15}H_{22}N_6O_5S$ = 398.4.
CAS — 29908-03-0; 485-80-3; 17176-17-9.
ATC — A16AA02.
ATC Vet — QA16AA02.

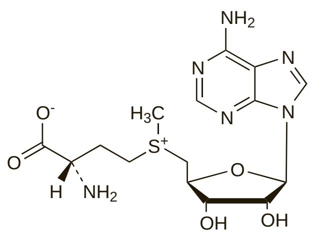

Profile

Ademetionine is a naturally occurring molecule found in virtually all body tissues and fluids. It acts as a methyl group donor in many transmethylation reactions and therefore is involved in the synthesis or metabolism of a wide range of compounds that maintain normal cell function. Ademetionine sulfate tosilate and ademetionine butanedisulfonate are stable forms of ademetionine that have been used for the treatment of depression (see below), liver disorders, and osteoarthritis.

◊ References.

1. Bottiglieri T, *et al.* The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. *Drugs* 1994; **48:** 137–52.
2. Chavez M. SAMe: S-adenosylmethionine. *Am J Health-Syst Pharm* 2000; **57:** 119–23.
3. Fetrow CW, Avila JR. Efficacy of the dietary supplement S-adenosyl-L-methionine. *Ann Pharmacother* 2001; **35:** 1414–25.
4. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): from the bench to the bedside—molecular basis of a pleiotrophic molecule. *Am J Clin Nutr* 2002; **76** (suppl): 1151S–1157S.
5. Gören JL, *et al.* Bioavailability and lack of toxicity of S-adenosyl-L-methionine (SAMe) in humans. *Pharmacotherapy* 2004; **24:** 1501–7.

Depression. Ademetionine has been given orally or parenterally in the management of depression (p.373). It appears to be of similar efficacy to the tricyclic antidepressants but evidence is limited to small, heterogeneous groups of patients studied over short periods of time; additionally many studies have involved parenteral rather than oral therapy.

References.

1. Bressa GM. S-Adenosyl-1-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994; **154** (suppl): 7–14.
2. Anonymous. SAMe for depression. *Med Lett Drugs Ther* 1999; **41:** 107–8.
3. Mischoulon D, Fava M. Role of *S*-adenosyl- -methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr* 2002; **76:** 1158S–1161S.
4. Papakostas GI, *et al.* S-Adenosyl-methionine in depression: a comprehensive review of the literature. *Curr Psychiatry Rep* 2003; **5:** 460–6.

Liver disorders. Some workers have found that ademetionine produced clinical improvement in patients with **intrahepatic cholestasis**,[1,2] including that associated with pregnancy.[3,4] Pruritus associated with the condition has also been relieved. Other studies,[5,6] however, have not found any benefit.

Ademetionine produced a good or excellent clinical response in patients with **hepatic steatosis**.[7] In a study[8] of patients with **alcoholic liver cirrhosis**, treated with ademetionine for 2 years, there was a trend towards reduced overall mortality or need for liver transplantation, but only in patients with less severe hepatic dysfunction. However, a systematic review[9] of 9 randomised placebo-controlled studies, which included the latter study could not find evidence to support or refute the claim that ademetionine has a beneficial effect in patients with alcoholic liver diseases, and larger high quality randomised placebo-controlled studies are needed.

1. Frezza M, *et al.* Oral S-adenosylmethionine in the symptomatic treatment of intrahepatic cholestasis: a double-blind, placebo-controlled study. *Gastroenterology* 1990; **99:** 211–15.
2. Almasio P, *et al.* Role of S-adenosyl- -methionine in the treatment of intrahepatic cholestasis. *Drugs* 1990; **40** (suppl 3): 111–23.
3. Bonfirraro G, *et al.* S-Adenosyl- -methionine (SAMe)-induced amelioration of intrahepatic cholestasis of pregnancy: results of an open study. *Drug Invest* 1990; **2:** 125–8.
4. Frezza M, *et al.* S-Adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy: results of a controlled clinical trial. *Hepatogastroenterology* 1990; **37** (suppl 2): 122–5.
5. Ribalta J, *et al.* S-Adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. *Hepatology* 1991; **13:** 1084–9.
6. Floreani A, *et al.* S-Adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol* 1996; **67:** 109–13.
7. Caballeria E, Moreno J. Therapeutic effects of S-adenosylmethionine (SAMe) in hepatic steatosis. *Acta Ther* 1990; **16:** 253–64.
8. Mato JM, *et al.* S-Adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 1999; **30:** 1081–9.
9. Rambaldi A, Gluud C. S-Adenosyl-L-methionine for alcoholic liver diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/04/08).

Osteoarthritis. Ademetionine has been reported to possess therapeutic efficacy in the treatment of osteoarthritis (p.11) and similar conditions, possibly due to an effect on cartilage metabolism and formation of anti-inflammatory mediators within the cell; it may also inhibit leukotrienes but does not appear markedly to interfere with prostaglandin synthesis.

References.

1. Domljan Z, *et al.* A double-blind trial of ademethionine vs naproxen in activated gonarthrosis. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 329–33.
2. Bradley JD, *et al.* A randomized, double blind, placebo controlled trial of intravenous loading with S-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J Rheumatol* 1994; **21:** 905–11.
3. Soeken KL, *et al.* Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. *J Fam Pract* 2002; **51:** 425–30.
4. Najm WI, *et al.* S-Adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. *BMC Musculoskelet Disord* 2004; **5:** 6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Transmetil†; Tunik; ***Austral.:*** MoodLift†; ***Cz.:*** Transmetil; ***Ger.:*** Gumbaral; ***Ital.:*** Donamet; Isimet†; Samyr; Transmetil; ***Mex.:*** Samyr; ***Rus.:*** Heptor (Гептор); Heptral (Гептрал); ***Spain:*** S Amet†.

Multi-ingredient: ***Arg.:*** Tunik B12.

Adenine

Adeniini; Adenin; Adenina; Adeninas; Adénine; Adeninum; Vitamin B_4; Vitamina B_4. 6-Aminopurine; 1,6-Dihydro-6-iminopurine.

Аденин

$C_5H_5N_5$ = 135.1.
CAS — 73-24-5.

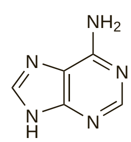

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Adenine). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 31 (Adenine). Odourless white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in boiling water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Profile

Adenine is a purine base and one of the components of adenosine nucleotides that form nucleic acids (p.2355). It is also a constituent of many coenzymes. It has been used to extend the storage life of whole blood (p.1056) and has also been given for the management of white blood cell disorders and alcoholism. Adenine hydrochloride has been used similarly.

Preparations

USP 31: Anticoagulant Citrate Phosphate Dextrose Adenine Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Leuco-4.

Multi-ingredient: ***Fr.:*** TTD-B -B ; ***Philipp.:*** Godex; ***Rus.:*** Lidevine (Лидевин); ***Spain:*** Hepadif.

Adenosine Phosphate *(BAN, USAN, rINN)*

Adenosine Monophosphate; Adenosine 5′-Monophosphate; Adénosine, Phosphate d'; Adenosine-5′-(dihydrogen phosphate); Adenosine-5′-phosphoric Acid; Adenosini Phosphas; 5′-Adenylic Acid; AMP; A-5MP; Fosfato de adenosina; Monophosadénine; Muscle Adenylic Acid; NSC-20264. 6-Amino-9-β-D-ribofuranosylpurine 5′-(dihydrogen phosphate).

Аденозина Фосфат

$C_{10}H_{14}N_5O_7P$ = 347.2.
CAS — 61-19-8.
ATC — C01EB10.
ATC Vet — QC01EB10.

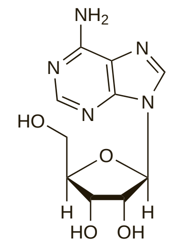

(adenosine)

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{12}N_5Na_2O_7P,xH_2O$).

Profile

Adenosine phosphate is an endogenous adenine nucleotide involved in many biological processes. Adenosine monophosphate (AMP) is a vasodilator and has been included in preparations for venous insufficiency, haemorrhoids, and varicose veins. It has also been used in pain and inflammation. Adenosine diphosphate and its disodium salt have also been used. AMP is also used in bronchial challenge tests to assess airway hyper-responsiveness in asthma and other respiratory disorders.

Unlike adenosine (p.1202) or adenosine triphosphate (below), adenosine phosphate is not used in supraventricular tachycardias.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Adenyl.

Multi-ingredient: ***Cz.:*** Laevadosin†; ***S.Afr.:*** Lipostabil†; ***Spain:*** Artri; Taurobetina†.

Adenosine Triphosphate

Adenosina, trifosfato de; Adenosine 5′-Triphosphate; 5′-Adenyldiphosphoric Acid; Adenylpyrophosphoric Acid; ATP; Trifosadenina; Triphosadénine. Adenosine 5′-(tetrahydrogen triphosphate).

Аденозинтрифосфат

$C_{10}H_{16}N_5O_{13}P_3$ = 507.2.
CAS — 56-65-5.
ATC — C01EB10.
ATC Vet — QC01EB10.

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{14}N_5Na_2O_{13}P_3$ = 551.1).

Profile

Adenosine triphosphate (ATP) is an endogenous adenine nucleotide with a fundamental role in cellular energy transformation; ATP is hydrolysed to adenosine diphosphate (ADP) releasing energy stored in phosphate bonds. In addition, extracellular ATP influences many biological processes.

ATP is a vasodilator that has been used in varied disorders. The sodium and disodium salts have been used in cerebral and peripheral vascular disorders and also for the treatment of supraventricular tachycardias, although adenosine (p.1202) is the form generally used as an antiarrhythmic. ATP has also been investigated for use in cachexia in patients with cancer.

◊ Reviews.

1. Agteresch HJ, *et al.* Adenosine triphosphate: established and potential clinical applications. *Drugs* 1999; **58:** 211–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Atepadene†; ***Fr.:*** Atepadene; Striadyne; ***Hong Kong:*** ATP-Daiichi; ***Jpn:*** Adetphos; ***Philipp.:*** Nutaphake; ***Rus.:*** Fosfobion (Фосфобион)†; ***Spain:*** Atepodin.

Multi-ingredient: ***Cz.:*** Laevadosin†; ***Indon.:*** Enerplus; Myoviton; Vitap; ***Spain:*** Refulgin.

Adiphenine *(rINN)*

Adifenina; Adiphénine; Adipheninum. 2-Diethylaminoethyl diphenylacetate.

Адифенин

$C_{20}H_{25}NO_2$ = 311.4.
CAS — 64-95-9.

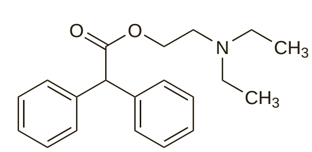

Adiphenine Hydrochloride *(USAN, rINNM)*

Adiphénine, Chlorhydrate d'; Adipheníni Hydrochloridum; Cloridrato de Adifenina; Hidrocloruro de adifenina; NSC-129224; Spasmolytine.

Адифенина Гидрохлорид

$C_{20}H_{25}NO_2,HCl$ = 347.9.

CAS — 50-42-0.

Profile

Adiphenine and adiphenine hydrochloride have been used as antispasmodics.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Braz.:* Analgosedan†; Dipirol†; Dorilen; Doriless; Lisador; Sedalene; Sedalin; ***Chile:*** Abalgin; Andil†; Immediat†; SAE; ***Switz.:*** Spasmo-Barbamin†; Spasmo-Barbamine compositum†; ***Turk.:*** Spasmo-Panalgine.

Adipic Acid

Acide adipique; Acidum adipicum; Adípico, ácido; Adipiinihappo; Adipinsäure; Adipinsav; Adipinsyra; Adipo rūgštis; Hexanedioic Acid; Kwas adypinowy; Kyselina adipová. 1,4-Butanedicarboxylic acid.

$C_6H_{10}O_4$ = 146.1.

CAS — 124-04-9.

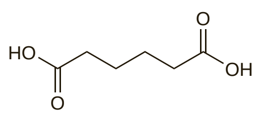

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Adipic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water; freely soluble in alcohol and in methyl alcohol; soluble in acetone.

USNF 26 (Adipic Acid). A white, crystalline powder. Slightly soluble in water; soluble in boiling water and in acetone; freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Profile

Adipic acid is an acidifier that is used in foods and has been included in preparations for the treatment of urinary-tract infections.

Adonis Vernalis

Adonide; Adonidis Vernalis Herba; Adonis; Adonis vernal; Adoniskraut; False Hellebore; Herba Adonidis; Vernal Pheasant's Eye; Ziele miłka wiosennego.

Pharmacopoeias. In *Ger.* and *Pol.*

Profile

Adonis vernalis, the dried aerial parts of *Adonis vernalis* (Ranunculaceae), contains cardiac glycosides which have actions similar to those of digoxin (p.1259).

Homoeopathy. Adonis vernalis has been used in homoeopathic medicines under the following names: Adonis v.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Braz.:* Calmazin†; Serenus; ***Ger.:*** Miroton; Miroton N†; Oxacant N†; Oxacant-forte N†; Oxacant-Khella N†.

Adrenalone *(USAN, pINN)* ⊗

Adrenalon; Adrenalona; Adrénalone; Adrenaloni; Adrenalonum. 3′,4′-Dihydroxy-2-(methylamino)acetophenone.

Адреналон

$C_9H_{11}NO_3$ = 181.2.

CAS — 99-45-6.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

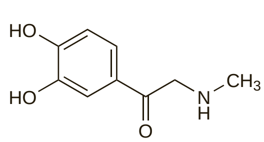

Adrenalone Hydrochloride *(pINNM)* ⊗

Adrénalone, Chlorhydrate d'; Adrenaloni Hydrochloridum; Adrenalonu chlorowodorek; Hidrocloruro de adrenalona.

Адреналона Гидрохлорид

$C_9H_{11}NO_3,HCl$ = 217.6.

CAS — 62-13-5.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

Profile

Adrenalone hydrochloride is used as a local haemostatic and vasoconstrictor. It has also been used with adrenaline in eye drops for glaucoma.

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Stryphnon†; ***Ger.:*** Stryphnasal†.

Multi-ingredient: *Ger.:* Links-Glaukosan†.

Aesculus

Aesculus hippocastanum; Castaño de indias; Hippocastani semen; Horse-chestnut; Marron d'Inde; Rosskastaniensamen.

CAS — 6805-41-0 (aescin); 11072-93-8 (β-aescin); 531-75-9 (anhydrous esculoside).

Pharmacopoeias. In *Fr., Ger., It.,* and *US.*

US also includes the powdered form and powdered extract.

Ger. also includes esculoside in the sesquihydrate form.

USP 31 (Horse Chestnut). The dried seeds of *Aesculus hippocastanum* (Hippocastanaceae), harvested in the autumn. It contains not less than 3.0% of triterpene glycosides, calculated on the dried basis as aescin. Protect from light and moisture.

Profile

The seeds (conkers) and other parts of the horse-chestnut, *Aesculus hippocastanum*, contain several active principles including esculoside (aesculin or esculin; 6-β-D-glucopyranosyloxy-7-hydroxycoumarin, $C_{15}H_{16}O_9$ = 340.3) and aescin (escin), which is a mixture of saponins.

Ingestion of aesculus may cause nausea, vomiting, diarrhoea, abdominal colic, delirium, and with large doses respiratory arrest.

Aescin and esculoside, the major active principles of aesculus, have been used in the prevention and treatment of various peripheral vascular disorders, including haemorrhoids (p.1697). They have been given by mouth, by intravenous injection (in the form of sodium aescinate), by rectal suppository, and applied topically. Aescin has also been given intravenously in the prevention and treatment of postoperative oedema. The maximum intravenous dose in adults for such conditions has been stated to be 20 mg daily; acute renal failure has been reported in patients given higher doses, sometimes with other nephrotoxic drugs.

Other derivatives such as sodium aescin polysulfate have also been used.

Homoeopathy. Aesculus has been used in homoeopathic medicines under the following names: Aesculus hippocastanum; Aesculus cortex; Aesculus hippocastanum ex cortice; Aesc. hip.

Esculoside has been used in homoeopathic medicines under the following names: Aesculinum; Aescul.

Adverse effects. EFFECTS ON THE KIDNEYS. A report of the incidence of acute renal failure in patients after cardiac surgery and implicating high-dose intravenous aescin therapy.[1] In 70 patients given a mean maximum daily dose of 340 micrograms/kg, no alteration of renal function was seen; in 16 receiving 360 micrograms/kg, mild renal impairment occurred; and in 40 given 510 micrograms/kg, acute renal failure developed.

1. Hellberg K, *et al.* Medikamentös bedingtes post-operatives Nierenversagen nach herzchirurgischen Eingriffen. *Thoraxchirurgie* 1975; **23:** 396–400.

EFFECTS ON THE RESPIRATORY TRACT. Bronchial asthma associated with aescin inhalation has been reported in a worker in the pharmaceutical industry.[1]

1. Muñoz X, *et al.* Occupational asthma related to aescin inhalation. *Ann Allergy Asthma Immunol* 2006; **96:** 494–6.

EFFECTS ON THE SKIN. Contact dermatitis[1] to aesculin and contact urticaria[2] to aescin have been reported after the use of topical preparations that contained these extracts. Both reactions were confirmed by positive skin tests.

1. Comaish JS, Kersey PJ. Contact dermatitis to extract of horse chestnut (esculin). *Contact Dermatitis* 1980; **6:** 150–1.
2. Escribano MM, *et al.* Contact urticaria due to aescin. *Contact Dermatitis* 1997; **37:** 233.

POISONING. There have been reports of poisoning in children from eating the seeds, or drinking infusions made from the leaves and twigs of horse-chestnut trees.[1] The toxic substance is considered to be esculoside. Symptoms of poisoning were muscle twitching, weakness, lack of coordination, dilated pupils, vomiting, diarrhoea, paralysis, and stupor.

1. Nagy M. Human poisoning from horse chestnuts. *JAMA* 1973; **226:** 213.

Uses. The use of aesculus has been reviewed;[1,2] although there is some evidence suggesting benefit in chronic venous insufficiency, more rigorous studies are needed.[2]

1. Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. *Pharmacol Res* 2001; **44:** 183–93.
2. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 31/03/06).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Grafic Retard; Herbaccion Venotonico; Nadem; Venastat; Venostasin; ***Austria:*** Aesculaforce; Provenen; Reparil; Venosin; Venostasin; ***Belg.:*** Reparil; Veinofytol; Venoplant; ***Braz.:*** Phytovein; Reparil; Varilise; Venafort; Venostasin†; Zarv; ***Chile:*** Venastat; ***Cz.:*** Reparil; Traumaril†; Venitan; Yellon; ***Fr.:*** Flogencyl; ***Ger.:*** Aescorin Forte; Aescorin N†; Aescusan; Aescuven; Concentrin; Essaven; Essaven Neu; Hamos-Tropfen-S†; Heweven Phyto; Hoevenol; Noricaven; Opino; opino N; Perivar Rosskaven†; Plissamur; Proveno N†; Reparil; Rexiluven S†; Sklerovenol N†; Vasoforte N†; Vasotonin†; Venalot novo†; Venen-Dragees†; Venen-Fluid; Venen-Tabletten; Venen-Tropfen N; Venentabs; veno-biomo; Venodura; Venoplant; Venopyronum; Venopyronum N†; Venostasin; ***Hong Kong:*** Reparil; ***Hung.:*** Venastat; ***Ital.:*** Curaven†; Edeven; Flebostasin; Reparil; ***Mex.:*** Alevarin; Venastat; Verisan†; ***Pol.:*** Aescuven; Esceven; Reparil; Sapoven; Venastat; Venitan; Venoplant; Venotonin; ***Port.:*** Varison; Venoparil†; ***Rus.:*** Venitan (Венитан); Venoplant (Веноплант); ***Spain:*** Flebostasin; Plantivenol; Provenen†; Varicid; ***Switz.:*** Aesculaforce; AesculaMed; Phlebostasin; Reparil†; Venavit N; Venostasin; ***Thai.:*** Reparil; ***Turk.:*** Reparil N; ***UK:*** Venaforce; ***Venez.:*** Vasoplant.

Multi-ingredient: *Arg.:* Escina Forte; Escina Omega; Esculeol P; Feparil†; Flaval; Grafic Forte; Ixana; Troxeven†; Tubarine; Venoful; Venostasin; VNS 45; ***Austral.:*** Bioglan Cirflo†; Bioglan Zellulean with Escin; Extralife Leg-Care; Herbal Capillary Care†; Proflo†; ***Austria:*** Amphodyn; Augentropfen Stulln; Dilaescol; Heparin Comp; Opino; Reparil; Urelium Neu; Venostasin compositum; ***Belg.:*** Mictasol-P; Rectovasol; Reparil; ***Braz.:*** Castanha de India Composta†; Digestron†; Hemorroidex†; Mirorroidin†; Novarrutina; Proctosan; Reparil; Supositorio Hamamelis Composto†; Traumed†; Varizol†; Venocur Triplex; Venofortan†; Venostasin†; ***Canad.:*** Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; ***Chile:*** Hemorrol†; Proctoplex; Repariven; Varicare†; ***Cz.:*** Anavenol; Evercil†; Heparin-Gel†; Ophthalmo-Evercil; Reparil-Gel N; ***Denm.:*** Proctosedyl; ***Fin.:*** Proctosedyl; ***Fr.:*** Aphloine P; Arterase; Climaxol; Creme Rap; Escinogel†; Evarose; Hemorrogel; Histo-Fluine P; Intrait de Marron d'Inde P; Mediflor Tisane Circulation du Sang No 12; Opo-Veinogene; Phlebogel; Phlebosedol†; Phytomelis; Preparation H; Reparil; Sedorrhoide; Veinophytum†; Veinostase; Veinotonyl; Vivene†; ***Ger.:*** Aescusan; Amphodyn†; Apoplectal N†; Augentropfen Stulln Mono; Cefasabal; Cycloven Forte N; Diu Venostasin; Essaven N†; Essaven ultra†; Essaven†; Fagorutin Rosskastanien-Balsam N; Hametum-N†; Hamos N†; Heparin Comp†; Heparin Kombi-Gel†; Heusin†; Intradermi; Lindigoa S†; opino N spezial†; PC 30 V; Posti N†; Reparil-Gel N; Revicain comp plus†; Revicain comp†; Salhumin Teilbad N†; Salus Venen Krauter Dragees N†; Solum Ol; Sportupac M; Trauma-cyl; Varicylum-S; Venacton†; Venen Krauter NT; Venen-Salbe N†; Venengel†; Veno-Kattwiga N†; Venoplant AHS†; Weleda Hamorrhoidalzapfchen; ***Gr.:*** Opino-jel; ***Hong Kong:*** Proctosedyl†; Proctosone†; Reparil; ***Hung.:*** Reparil N; ***India:*** Proctosedyl; ***Indon.:*** Lanaven; Lanaven Plus; Opino; ***Irl.:*** Proctosedyl; ***Ital.:*** Algorex; Altadrine; Angiovein; Bres†; Capill; Capill Venogel; Centella Complex; Centeril H; Dermocinetic; Dermoprolyn†; Edeven; Essaven; Flavion; Flebo-Si; Flebolider; Flodolor; Flogofort; Flogovis IdroGel; Hirudex†; Inflamase; Inflamase IdroGel; Levital Plus; Muscoril Trauma; Osmogel; Pik Gel; Proctonet†; Proctopure; Proctosedyl; Recto-Reparil; Reparil; RepaVen†; Sedalen Cort†; Sedilene Procto†; Signum; Snell Cell; Somatoline; Varicogel†; Venactive; Venalta; Venoplus†; Venoton; Venotrauma†; ***Malaysia:*** Proctosedyl; Proctosone†; ***Mex.:*** Almodin; ***Mon.:*** Fluon; ***Norw.:*** Proctosedyl; ***Philipp.:*** Proctosedyl; ***Pol.:*** Aesculan; Anavenol; Arcalen; Arnisol; Emorect; Escalar; Fitoven; Hemorol; Neo-Aesculan; Proctosone; Reparil N; Sapoven AT; Sapoven T; Savarix; Venacorn; Venescin; Venoforton; Venozel; ***Port.:*** Relmus Compositum†; Synchrocell; Venoparil; ***Rus.:*** Aescusan (Эскузан); Anavenol (Анавенол); ***S.Afr.:*** Essaven†; Proctosedyl; Reparil; Stibium Comp; ***Singapore:*** Erase; Proctosedyl; ***Spain:*** Caprofides Hemostatico; Contusin; Essavenon; Feparil; Hemodren Compuesto†; Roidhemo†; Ruscimel†; Urgenin; Venacol; ***Swed.:*** Proctosedyl†; ***Switz.:*** Augentonicum; Demoven N; Dolo-Veniten†; Flavovenyl; Flogecyl; Ipasin; Lapidar 4; Phlebostasin compositum†; Reparil; Strath Gouttes pour les veines; Suppositoires contre les hemorroides†; Veino-Gouttes-N†; Venoplant comp; Venoplant-N†; ***Thai.:*** Essaven; Proctosedyl; Reparil; Veno Gel; ***Turk.:*** Prepagel; ***Venez.:*** Gelsem.

Afelimomab *(rINN)*

Afélimomab; Afelimomabum; MAK-195F. Immunoglobulin G3, anti-(human tumor necrosis factor α) F(ab′)2 fragment (mouse monoclonal LU54107 γ3-chain), disulfide with mouse monoclonal LU54107 κ-chain, dimer.

Афелимомаб

CAS — 156227-98-4.

ATC — L04AB03.

ATC Vet — QL04AB03.

Profile

Afelimomab is a monoclonal tumour necrosis factor antibody that has been investigated for the treatment of sepsis.

◊ References.

1. Vincent JL. Afelimomab. *Int J Clin Pract* 2000; **54:** 190–3.
2. Reinhart K, *et al.* Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES study. *Crit Care Med* 2001; **29:** 765–9.
3. Gallagher J, *et al.* A multicenter, open-label, prospective, randomized, dose-ranging pharmacokinetic study of the anti-TNF-alpha antibody afelimomab in patients with sepsis syndrome. *Intensive Care Med.* 2001; **27:** 1169–78.
4. Panacek EA, *et al.* Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004; **32:** 2173–82.

Aflatoxins

Aflatoxinas.

CAS — 1162-65-8 (aflatoxin B_1); 7220-81-7 (aflatoxin B_2); 1165-39-5 (aflatoxin G_1); 7241-98-7 (aflatoxin G_2); 6795-23-9 (aflatoxin M_1); 6885-57-0 (aflatoxin M_2).

Profile

Aflatoxins are toxic metabolites produced by many strains of *Aspergillus flavus* and *A. parasiticus*, growing on many vegetable foods, notably maize and peanuts. A number of forms, including aflatoxins B_1, B_2, G_1, and G_2 have been identified. Aflatoxins M_1 and M_2 are metabolites produced by animals after ingestion of aflatoxins B_1 and B_2; they may be detected in cows' milk.

Aflatoxins can cause hepatitis and cirrhosis. They have been implicated in liver cancer, and may act as co-carcinogens with hepatitis B virus. Aflatoxin B_1 is reported to be one of the most potent carcinogens known in *animals*. It has been reported that aflatoxins have been developed in some countries as biological weapons.

◊ References.

1. Ross RK, *et al.* Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992; **339:** 943–6.
2. Jackson PE, Groopman JD. Aflatoxin and liver cancer. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13:** 545–55.
3. Peraica M, *et al.* Toxic effects of mycotoxins in humans. *Bull WHO* 1999; **77:** 754–66.
4. Pitt JI. Toxigenic fungi and mycotoxins. *Br Med Bull* 2000; **56:** 184–92.

Agnus Castus

Agni Casti; Agni casti fructus; Agnocasto; Chaste Tree Fruit; Chasteberry; Drmkový plod; Gattilier, fruit de; Keuschlamm; Mönchspfeffer; Monk's Pepper; Munkpeppar; Owoc niepokalanka zwyczajnego; Sauzgatillo; Siveydenpuunhedelmä; Zerolo.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Agnus Castus Fruit). The whole, ripe, dried fruit of *Vitex agnus castus*. It contains a minimum 0.08% of casticin calculated with reference to the dried drug. Protect from light.

USP 31 (Chaste Tree). The dried ripe fruits of *Vitex agnus-castus* (Verbenaceae). It contains not less than 0.05% of agnuside and not less than 0.08% of casticin, calculated on the dried basis.

Profile

Agnus castus is reported to affect the secretion of luteinising hormone, follicle stimulating hormone, and prolactin by the pituitary. Both inhibition and stimulation of prolactin secretion have been reported, and may be dose-dependent. Agnus castus is included in herbal preparations for the symptoms of premenstrual syndrome, including mastalgia; it has also been used for menstrual cycle irregularities or menopausal disorders, but should be avoided in patients receiving exogenous sex hormones, including oral contraceptives.

Homoeopathy. Agnus castus has been used in homoeopathic medicines under the following names: Vitex agnus-castus; Agn. cast.

◊ References.

1. Houghton P. Agnus castus. *Pharm J* 1994; **253:** 720–1.
2. Christie S, Walker AF. Vitex agnus-castus L.: (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. *Eur J Herbal Med* 1997; **3:** 29–45.
3. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; **322:** 134–7.
4. Chrubasik S, Roufogalis BD. Chaste tree fruit for female disorders. *Aust J Pharm* 2001; **82:** 156–7.

Adverse effects, precautions, and interactions. The adverse effects of agnus castus are reported to be mild and reversible, with acne, erythematous rash, headache, gastrointestinal disorders, menstrual disorders, nausea, and pruritus being the most frequently reported. Toxicity data for use of agnus castus during pregnancy and breast feeding are sparse, but in view of its pharmacological actions, use is not recommended. There is a theoretical possibility of drug interactions between agnus castus and dopamine antagonists.[1]

1. Daniele C, *et al.* Vitex agnus castus: a systematic review of adverse events. *Drug Safety* 2005; **28:** 319–32.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Premular; ***Austria:*** Agnofem; Agnucaston; Agnumens; ***Braz.:*** Lutene; Nalle; Regulatum†; Tenag; Vitenon; Vitex; ***Cz.:*** Agnucaston; Evana†; ***Ger.:*** Agno-Sabona†; Agnolyt; Agnucaston; Agnufemil†; Biofem; Castufemin; Cefanorm; Femicur N; Feminon A; Femisana mens; Gynocastus; Hevertogyn; Kytta-Femin†; Sarai; Strotan; Valverde Monchspfeffer bei Menstruationsbeschwerden†; ***Hung.:*** Agnucaston; Cefanorm; PreMens; ***Indon.:*** Agnu Gyne; Agnucaston; ***Mex.:*** Cicloplant; ***Philipp.:*** Ascof; ***Pol.:*** Agufem; Castagnus; ***Rus.:*** Agnucaston (Агнукастон)†; Cyclodynon (Циклодинон); ***Spain:*** Dismegyn; Femiplante; ***Switz.:*** Agnolyt; Emoton; Oprane; Prefemine; PreMens; ***Thai.:*** Agnucaston†; ***Turk.:*** Agnucaston; Biofem; ***UK:*** Herbal Premens; Premherb.

Multi-ingredient: *Austral.:* Dong Quai Complex; Feminine Herbal Complex; Lifesystem Herbal Formula 4 Women's Formula†; PMT Complex†; Women's Formula Herbal Formula 3†; ***Canad.:*** Natural HRT; ***Ger.:*** Femisana†; ***Hong Kong:*** Phytoestrin†; ***Indon.:*** Herbalacta; ***Singapore:*** Phytoestrin.

Agrimony

Agrimonia; Agrimoniae herba; Aigremoine; Dirvuolių žolė; Maarianverijuuri; Odermennigkraut; Párlófű; Řepíková nať; Småborre.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Agrimony). The dried flowering tops of *Agrimonia eupatoria* containing a minimum of 2.0% of tannins expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Agrimony, the aerial parts of *Agrimonia eupatoria* (Rosaceae) or more rarely *A. procera* (*A. odorata*; fragrant agrimony), has astringent and diuretic properties. It is used internally for diarrhoea, biliary and other gastrointestinal disorders, and urinary-tract disorders; it has also been used for inflammatory mouth and throat disorders. It has been used externally for wound healing and skin disorders.

Homoeopathy. Agrimony has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Nat Repiku Lekarskeho†; Repik Lekarsky†; Repikovy Caj, Repikova Nat†.

Multi-ingredient: *Austria:* Amersan; Gallen- und Lebertee St Severin; Novocholin; ***Cz.:*** Amersan; Cynarosan†; Eugastrin†; Hemoral†; Naturland Grosser Swedenbitter†; Nontusyl†; Species Cholagogae Planta; Stomaran; The Salvat; Ungolen†; Zlucnikova Cajova Smes; ***Fr.:*** Tisane Hepatique de Hoerdt; ***Ger.:*** Rhoival†; Stomasal Med†; ***Rus.:*** Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); ***Spain:*** Natusor Astringel†; Natusor Farinol†; ***UK:*** Piletabs.

Alfalfa

Lucerne; Purple medick.

Profile

Alfalfa is the plant *Medicago sativa* (Leguminosae) which is cultivated as an animal feedstuff. The seeds and sprouts of alfalfa contain canavanine (2-amino-4-(guanidinooxy)butyric acid), a toxic amino acid structurally related to arginine; content is reported to represent about 1.5% of the dry weight. A syndrome resembling SLE has been recorded in *monkeys* fed alfalfa.

Alfalfa is used in herbal preparations for a variety of disorders.

Homoeopathy. Alfalfa has been used in homoeopathic medicines under the following names: Alfa.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Austral.:* Irontona; Neo-Cleanse; Panax Complex†; Plantiodine Plus†; Vitatona; ***Chile:*** Calcio 520; Fucus Compuesto†; ***Fr.:*** Gonaxine; Gynosoja; Menoxine.

Alfaprostol *(BAN, USAN, rINN)*

Alfaprostolum; K-11941; Ro-22-9000. Methyl (*Z*)-7-{(1*R*,2*S*,3*R*,5*S*)-2-[(3*S*)-5-cyclohexyl-3-hydroxypent-1-ynyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

Альфапростол

$C_{24}H_{38}O_5$ = 406.6.

CAS — 74176-31-1.

ATC Vet — QG02AD94.

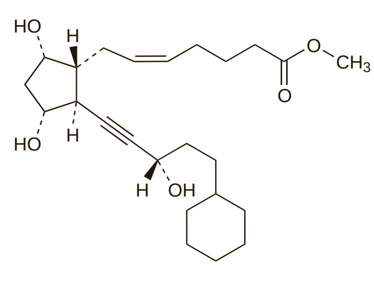

Profile

Alfaprostol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Alglucerase *(BAN, USAN, rINN)*

Alglucerasa; Alglucérase; Alglucerasum; Glucosylceramidase; Macrophage-targeted β-Glucocerebrosidase.

Альглюцераза

CAS — 143003-46-7.

ATC — A16AB01.

ATC Vet — QA16AB01.

Description. Alglucerase is a modified form of human placental β-glucocerebrosidase (ceramide glucosidase; β-D-glucosyl-*N*-acylsphingosine glucohydrolase). It is a monomeric glycoprotein of 497 amino acids with glycosylation making up about 6% of the molecule.

Imiglucerase *(BAN, USAN, rINN)*

Imiglucerasa; Imiglucérase; Imiglucerasum; Imiglukeraasi; Imiglukeras; Imigluseraz; Recombinant Macrophage-targeted β-Glucocerebrosidase; r-GCR.

Имиглюцераза

CAS — 154248-97-2.

ATC — A16AB02.

ATC Vet — QA16AB02.

Description. Imiglucerase is a recombinant human-derived β-glucocerebrosidase. It is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites

Adverse Effects and Precautions

Fever, chills, pruritus, flushing, and gastrointestinal symptoms, including cramps, diarrhoea, nausea, and vomiting have been reported after use of alglucerase or imiglucerase. Some of these may be hypersensitivity reactions; other hypersensitivity reactions, including urticaria and angioedema, respiratory symptoms, and hypotension have also occurred. Anaphylactoid reactions have occurred rarely with imiglucerase. Caution is required in patients who have exhibited signs of hypersensitivity; reduction of the rate of infusion, and pretreatment with antihistamines and/or corticosteroids may permit further treatment. Antibodies have developed in about 15% of patients receiving a glucocerebrosidase enzyme during the first year of therapy. Patients who develop antibodies are at increased risk of hypersensitivity reactions and periodic assessment for antibody formation is recommended.

Pain and irritation at the injection site may occur. Other adverse effects reported include fatigue, dizziness, headache, backache, peripheral oedema, mouth ulcers, and disturbances in sense of smell.

Alglucerase is prepared from human placentas and its infusion therefore carries a risk of transmission of infections although this is minimised by the manufacturing process. Chorionic gonadotrophin, a naturally occurring hormone in human placentas, has been detected in alglucerase. The presence of this hormone may produce early virilisation in young boys if sufficient is given, and has the potential to produce false positive results in pregnancy tests that rely on the detection of this hormone. Alglucerase should be used with caution, if at all, in patients with androgen-sensitive malignancies.

◊ References.

1. Starzyk K, *et al.* The long-term international safety experience of imiglucerase therapy for Gaucher disease. *Mol Genet Metab* 2007; **90:** 157–63.

Effects on the lungs. Pulmonary hypertension developed in 2 patients with Gaucher disease after starting treatment with alglucerase.[1] Neither patient had evidence of parenchymal lung infiltration with Gaucher cells.

1. Dawson A, *et al.* Pulmonary hypertension developing after alglucerase therapy in two patients with type 1 Gaucher disease complicated by the hepatopulmonary syndrome. *Ann Intern Med* 1996; **125:** 901–4.

Pharmacokinetics

After intravenous infusion, plasma enzymatic activities of alglucerase and imiglucerase decline rapidly from steady state, with an elimination half-life of between 3.6 and 10.4 minutes.

Uses and Administration

The enzyme β-glucocerebrosidase is given as imiglucerase (or occasionally alglucerase) for long-term enzyme replacement therapy to patients with symptomatic Gaucher disease (see below). The oligosaccharide chains of the enzyme are modified to terminate with mannose residues to ensure uptake into macrophages.

Imiglucerase is given by intravenous infusion over 1 to 2 hours for the treatment of type 1 or type 3 Gaucher disease. Alternatively, the dose may be infused at a rate not exceeding 1 unit/kg per minute. The dosage depends on the severity of symptoms, and initial doses can vary from 2.5 units/kg three times weekly to 60 units/kg once every two weeks. Further increases or decreases in doses are made according to individual response. Once the patient's condition is stabilised, monitoring and dosage adjustment up or down is carried out at usual intervals of 6 to 12 months. In the UK, the *BNFC* notes that higher doses of 120 units/kg infused over 1 to 2 hours are given once every 2 weeks for type 3 Gaucher disease.

Alglucerase has been given by intravenous infusion in similar doses with monitoring and dosage adjustment at intervals of 3 to 6 months in stabilised patients with type 1 Gaucher disease.

Gaucher disease. Gaucher disease[1-4] (glucocerebrosidosis) is a rare, autosomal recessive disorder, although it is the commonest lysosomal storage disorder. It is caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase (acid β-glucosidase, ceramide glucosidase, β-D-glucosyl-*N*-acylsphingosine glucohydrolase, or glucosylceramidase) which catalyses the hydrolysis of glucocerebroside, a lipid component of cell membranes, to glucose and ceramide. Deficiency of β-glucocerebrosidase results in accumulation of glucocerebroside in the lysosomes of reticuloendothelial cells, particularly macrophages.

Gaucher disease is **classified** into three main forms based on clinical signs and symptoms. Hepatosplenomegaly occurs in all forms. **Type 1 Gaucher disease** (chronic adult non-neuronopathic disease) accounts for 90% or more of cases and occurs especially in Ashkenazi Jews. More than half of all patients with type 1 disease are diagnosed before the age of 10 years.[5] The disease follows a chronic course of variable severity and onset, with hepatosplenomegaly and blood and bone disorders being the main features; there is no neurological involvement. In **type 2 Gaucher disease** (acute infantile neuronopathic disease), neurological involvement predominates. Patients show developmental delay by the age of 6 months, suffer seizures, pulmonary infections, and usually die in early childhood. **Type 3 Gaucher disease** is a subacute neuronopathic form and is slowly progressive.[4] There are 3 subtypes varying in severity and prognosis: in type 3a, there is slow progressive neurological deterioration with death usually occurring during childhood; in type 3b (Norrbotten disease) there is slow cognitive deterioration and patients may survive to adulthood; type 3c typically affects patients of Palestinian, Arab, or Japanese descent, with possible survival to the teenage years.

Treatment of Gaucher disease was previously limited to symptomatic management until the development of enzyme replacement therapy with β-glucocerebrosidase. Due to the rarity of Gaucher disease, early clinical studies were limited mainly to small case series of patients with type 1 disease. Use of alglucerase or imiglucerase has been shown to reverse hepatosplenomegaly and the haematological abnormalities;[6,7] effects may be seen within a few months, although in many the response is poor during the first 6 to 9 months and then improves rapidly.[2] Return to normal haemoglobin values within 6 to 12 months has been reported, as has reduction in liver size by 20 to 30% within 2 years and 30 to 40% by 5 years; a 50% reduction in spleen size also occurred.[8] Bone symptoms respond more slowly. Decreases in bone pain during the first year of treatment have been reported although there was no radiological improvement.[7] Existing bone manifestations are slow to respond or refractory to enzyme replacement therapy, but alendronate has been shown to be of benefit as adjunctive therapy for osteopenia in 36 adults with negative lumbar bone mineral density scores who had been receiving glucocerebrosidase for at least 2 years.[9] Normalised growth velocity has been reported in children[10] and radiographical assessments have shown improvements in bone density and mineralisation.[11] There is evidence that long-term enzyme replacement therapy for up to 5 years completely or partially ameliorates anaemia, thrombocytopenia, organomegaly, and bone pain in patients with type 1 Gaucher disease, as well as preventing further deterioration.[8] However, successful symptom control is dependent on the degree of damage that has already occurred, and early initiation of therapy is recommended for a more favourable prognosis. Enzyme replacement therapy in Gaucher disease is lifelong and relapses occur with prolonged interruptions to therapy.[5,12] Alglucerase has also been tried in rare cases of Gaucher disease affecting the heart[13] or the eye.[14] It is not yet known whether enzyme replacement therapy is able to prevent the development of symptoms in asymptomatic patients.

The efficacy of enzyme replacement therapy in managing neurological symptoms in patients with type 2 or type 3 disease[15] remains to be established. Most of the patients with type 3 Gaucher disease in a small study[16] did not deteriorate neurologically when treated with doses that reversed almost all the systemic manifestations. However, it was pointed out that the amount of enzyme that crosses the blood-brain barrier is unlikely to be significant, and other forms of treatment specifically for neuronopathic Gaucher disease need to be developed.

For those patients with type 1 Gaucher disease in whom enzyme replacement therapy may be unsuitable, miglustat may be used. It reduces the synthesis of glucocerebroside by inhibiting glucosyltransferase, one of the early enzymes in the sphingolipid biosynthetic pathway. However, the balance of benefits versus adverse affects with miglustat is less favourable than with imiglucerase, which remains the standard treatment where possible; the two drugs should not be used together.[17]

Possible future therapies under investigation for Gaucher disease include oral therapy with the pharmacological chaperone isofagomine, and gene therapy. Other modified forms of β-glucocerebrosidase are also under investigation to improve uptake into the affected macrophages.

1. NIH Technology Assessment Panel on Gaucher Disease. Gaucher disease: current issues in diagnosis and treatment. *JAMA* 1996; **275:** 548–53.
2. Morales LE. Gaucher's disease: a review. *Ann Pharmacother* 1996; **30:** 381–8.
3. Elstein D, *et al.* Gaucher's disease. *Lancet* 2001; **358:** 324–7.
4. Grabowski GA. Gaucher disease: lessons from a decade of therapy. *J Pediatr* 2004; **144** (suppl): S15–S19.
5. Charrow J, *et al.* Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. *J Pediatr* 2004; **144:** 112–20.
6. Grabowski GA, *et al.* Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. *Ann Intern Med* 1995; **122:** 33–9.
7. Pastores GM, *et al.* Enzyme therapy in Gaucher disease type 1: dosage efficacy and adverse effects in 33 patients treated for 6 to 24 months. *Blood* 1993; **82:** 408–16.
8. Weinreb NJ, *et al.* Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; **113:** 112–19.
9. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; **104:** 1253–7.
10. Kaplan P, *et al.* Acceleration of retarded growth in children with Gaucher disease after treatment with alglucerase. *J Pediatr* 1996; **129:** 149–53.
11. Rosenthal DI, *et al.* Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. *Pediatrics* 1995; **96:** 629–37.
12. Drelichman G, *et al.* Clinical consequences of interrupting enzyme replacement therapy in children with type 1 Gaucher disease. *J Pediatr* 2007; **151:** 197–201.
13. Spada M, *et al.* Cardiac response to enzyme-replacement therapy in Gaucher's disease. *N Engl J Med* 1998; **339:** 1165–6.
14. vom Dahl S, *et al.* Loss of vision in Gaucher's disease and its reversal by enzyme-replacement therapy. *N Engl J Med* 1998; **338:** 1471–2.
15. Bembi B, *et al.* Enzyme replacement treatment in type 1 and type 3 Gaucher's disease. *Lancet* 1994; **344:** 1679–82.
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Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cerezyme; ***Austria:*** Cerezyme; ***Belg.:*** Cerezyme; ***Canad.:*** Cerezyme; ***Cz.:*** Cerezyme; ***Denm.:*** Cerezyme; ***Fin.:*** Cerezyme; ***Ger.:*** Cerezyme; ***Gr.:*** Cerezyme; ***Hong Kong:*** Cerezyme; ***Israel:*** Ceredase†; Cerezyme; ***Ital.:*** Cerezyme; ***Jpn:*** Ceredase†; Cerezyme; ***Neth.:*** Cerezyme; ***Norw.:*** Cerezyme; ***NZ:*** Cerezyme; ***Pol.:*** Cerezyme; ***Port.:*** Cerezyme; ***S.Afr.:*** Cerezyme; ***Spain:*** Cerezyme; ***Swed.:*** Cerezyme; ***Switz.:*** Cerezyme; ***UK:*** Cerezyme; ***USA:*** Ceredase; Cerezyme.

Alibendol *(rINN)*

Alibendolum. 5-Allyl-*N*-(2-hydroxyethyl)-3-methoxysalicylamide.
Алибендол
$C_{13}H_{17}NO_4 = 251.3.$
CAS — 26750-81-2.

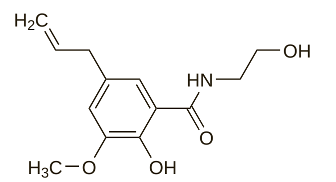

Profile

Alibendol is a choleretic used in the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cebera†.

Allergen Products

Alergenos; Allergeenivalmisteet; Allergenprodukter; Producta allergenica; Produits allergènes.

Adverse Effects and Treatment

Adverse effects to allergen products can range from mild local reactions to severe generalised reactions that may be fatal, especially reactions to bee and wasp venom. Hypersensitivity reactions may be immediate or delayed.

Adverse effects with **skin-prick testing** are uncommon, although swelling and irritation at the injection site, rhinitis, urticaria, wheezing, and chest tightness might occur, and rarely, anaphylactic shock.

Allergen immunotherapy injections may give rise to swelling, irritation, redness, and hardness at the injection site. Systemic reactions include itching eyes, sneezing, cough, wheezing, chest tightness, atopic eczema, urticaria, and oedema. Anaphylactic shock or severe delayed reactions may also occur. Commonly reported adverse effects with allergen preparations given sublingually include oral oedema, pruritus, and paraesthesia, throat irritation, sneezing, rhinitis, nasal congestion, itching of the eyes and ears, and headache; systemic reactions may occur if the dosage regimen is not adhered to.

Severe reactions to allergen products normally occur within 30 minutes and should be treated promptly with intramuscular adrenaline injection 1 in 1000. Full supportive measures should be implemented and treatment with antihistamines and corticosteroids may be required (for a discussion of the treatment of anaphylaxis and anaphylactic shock, see p.1205). Further allergen immunotherapy should be stopped or continued at reduced dosage depending on the severity of the reaction and in accordance with the licensed product information.

◊ Reviews.

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◊ In 1986 the UK CSM reported[1] that hyposensitising vaccines have the potential to induce severe bronchospasm and anaphylaxis, and that these reactions had caused 26 deaths in the UK since 1957. The majority of patients had no reaction to previous hyposensitising injections. In 1989 the FDA reported that since 1980, the American Academy of Allergy and Immunology and the FDA had received 14 reports of death after allergen immunotherapy, and 4 deaths after skin testing for allergies.[2] The most common clinical factor in these patients was a history of asthma.

In view of these and other reports, recommendations have been made to minimise the risks of systemic reactions.[3-6] Allergen immunotherapy should only be used for seasonal allergic rhinoconjunctivitis not responding to anti-allergic drugs, and for severe hypersensitivity to Hymenoptera stings. In the UK[4] such treatment has usually been avoided in patients with asthma (although asthma is not an absolute contra-indication to Hymenoptera allergen immunotherapy), but elsewhere[3,5,6] asthmatic patients whose asthma is stable and not severe may be treated. Hyposensitising agents should be used only where facilities for full cardiopulmonary resuscitation are immediately available. The recommended length of time after injection that patients should be kept under medical observation varies from 30 minutes[3] to 1 hour.[4] If the patient develops even mild symptoms of a general reaction, observation should be extended until they are completely resolved. The observation period should also be extended for patients at high risk of reactions.

Of 12 samples of *Aspergillus* extract used for allergen immunotherapy, 4 were found to contain aflatoxin (p.2249), one being highly mutagenic as determined by the Ames' test. The results suggested that careful screening of commercially available mould extracts was warranted.[7]

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Precautions

Patients should be observed for at least 30 to 60 minutes after administration of allergen products because of the risk of anaphylaxis (see also under Adverse Effects, above). Patients should avoid taking beta blockers since adrenaline may be ineffective if hypersensitivity reactions occur. Antiallergic medication taken concomitantly may mask the patient's reactivity.

Skin-prick testing should not be carried out in areas where there are skin lesions. Patients should be instructed not to rub or scratch the test site. Antiallergic medication should be stopped before allergen testing to prevent false negative reactions. Systemic or long-term topical use of potent corticosteroids may also mask skin reactivity.

Allergen immunotherapy should not be used in patients with serious immunological illness, cancer, disorders of amino acid metabolism, bleeding disorders, or hyperthyroidism. It should also be avoided during infections or febrile conditions, and administration of an allergen preparation delayed for 24 to 48 hours after recovery. Allergen immunotherapy should be avoided during pregnancy because of the risk to the fetus of any systemic reactions in the mother. Patients with asthma may be more susceptible to hypersensitivity reactions with allergen products and it is considered that allergen immunotherapy should be avoided or used with caution. Injection immunotherapy should be avoided in children under 6 years of age, and sublingual immunotherapy in children under 2 years. Sublingual immunotherapy is contra-indicated in patients with severe oral inflammatory conditions such as lichen planus with ulcerations, or severe mycosis. Sublingual immunotherapy should be stopped for 7 days in patients who have oral surgery, including dental extraction, to allow the wounds to heal.

Allergen immunotherapy should be avoided or used with caution in patients with cardiovascular or pulmonary insufficiency, or severe eczema. Rarely, patients may experience drowsiness with allergen immunotherapy preparations and, if affected, should avoid driving or operating machinery.

Allergen immunotherapy injections should only be given where facilities for full cardiopulmonary resuscitation are immediately available. Injections for immunotherapy should be given subcutaneously and not intravenously or intramuscularly. Patients should avoid strenuous exercise for at least 12 hours after injection immunotherapy, or 1 hour before and after sublingual immunotherapy. It is also recommended to avoid heavy meals and alcohol around the time of injection with some products. Severe anaphylactoid reactions have been reported in patients undergoing allergen immunotherapy who are also receiving ACE inhibitors (see Hypersensitivity, p.1195). Some manufacturers suggest that the reaction could be avoided by temporarily withholding ACE inhibitor therapy during each desensitisation. Allergen immunotherapy preparations and vaccines against infectious diseases should not be given within at least a week of each other or until all possible reactions to either vaccine have disappeared.

Interactions

For precautions to be observed in using allergen products in patients receiving ACE inhibitors, antiallergic drugs, beta blockers, or vaccines see Precautions, above.

Uses and Administration

Allergen products are used diagnostically in skin tests and provocation tests to confirm the cause of a suspected hypersensitivity reaction. They are also used for allergen immunotherapy in certain patients with hypersensitivity reactions, particularly to insect venoms such as bee or wasp venom, pollen (p.2370), house dust, and house-dust mite. Preparations for allergen immunotherapy are given by subcutaneous injection or sublingually. Other routes (such as oral, nasal, or bronchial) have also been tried.

Administration. Allergen vaccines used for allergen immunotherapy (see below) should be well characterised and standardised for total allergenic potency, biological activity, and shelf-life. Whenever possible, the same batch of allergen should be used during a course of treatment because of possible differences in potency between batches. Injections for allergen immunotherapy are given subcutaneously as aqueous extracts or combined with adjuvants to reduce adverse effects while retaining or enhancing immunogenicity. Such modified vaccines are slow-release formulations and therefore the interval between injections is increased. Vaccines can be physically modified by adsorption onto an inert carrier such as aluminium or calcium salts, or tyrosine, or chemically modified with glutaral, formaldehyde, or liposomes. Combinations of the two types of modified vaccine may also be used.

Dosage regimens for allergen immunotherapy are as recommended by the manufacturers and depend on the sensitivity of the patient. During the initial build-up phase, the dose of allergen vaccine is slowly increased (by increasing the concentration and/or the dose volume) until the maintenance dose is reached. However, the dose should be reduced after a systemic reaction, or stopped if the reaction is severe. Likewise, the dose might need to be reduced or not given at all to highly sensitised patients during periods of natural exposure to the allergen.

In *conventional* build-up schedules, injections of aqueous extracts are given once or twice weekly, with maintenance expected to be reached in 4 to 6 months. Depot preparations are given every 1 to 2 weeks. *Modified dosage schedules* have been used where maintenance needs to be achieved more quickly; such regimens may, however, be associated with an increased risk of adverse reactions, although this can be ameliorated by premedication with an antihistamine. Aqueous extracts should be used for modified schedules until the maintenance dose is reached. In *cluster schedules* several injections may be given on the same day, usually at 30-minute intervals, once or twice a week on non-consecutive days. Fewer total injections are used than with conventional schedules and maintenance therapy can be reached in as little as 4 weeks. There might be a slight increase in risk of systemic reactions. *Rush schedules* are more rapid than cluster schedules and several injections are given at specified intervals once daily on consecutive days allowing maintenance doses to be reached in a matter of days; naturally, this does increase the risk of systemic adverse effects and patients need to be monitored more closely and for longer than with conventional schedules. *Ultrarush schedules* are even faster and may be used to accelerate desensitisation to stinging insects in highly sensitive individuals. When the maintenance dose has been reached, the injection interval is progressively increased as necessary according to safety and efficacy. Injection intervals are typically 2 to 4 weeks for aeroallergens and 8 weeks for insect venom. The optimal duration of allergen immunotherapy is unknown, but a period of 3 to 5 years is usually recommended; the decision to discontinue therapy will depend on individual response. Some patients will remain desensitised after stopping allergen immunotherapy but others will relapse.

The sublingual route is also used for allergen immunotherapy, with the vaccine given daily either as a solution or as oral lyophilisate tablets. It is considered to be a good alternative to the subcutaneous route in terms of safety and efficacy, although problems of determining the optimal vaccine dose in relation to efficacy and duration of treatment still remains to be established. The oral, nasal, and bronchial routes have also been tried for allergen immunotherapy, although efficacy or safety has not always been demonstrated.

Modification of allergens is being investigated as an alternative way to increase safety and efficacy, and developments include recombinant proteins, peptides, plasmid DNA vaccines, and immunostimulatory sequences of DNA conjugated to specific allergens. Other immunomodulatory methods include use of allergen-specific antibodies or fragments, and humanised anti-IgE monoclonal antibodies (e.g. omalizumab, p.1128). Also, more efficient adjuvants such as monophosphoryl lipid A are being tried.

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Allergen immunotherapy. Allergic reactions are type I (immediate) hypersensitivity reactions mediated by IgE antibodies (see under Hypersensitivity, p.561) that are usually managed by anti-allergic medication or, where possible, allergen avoidance. For patients in whom these treatment methods are inadequate or unsuitable, allergen immunotherapy (desensitisation or hyposensitisation) may be tried. Specific allergen immunotherapy (SIT) is the administration of gradually increasing quantities of an allergen vaccine to a patient with diagnosed IgE-mediated allergy until a maintenance dose is reached that is effective in ameliorating symptoms associated with subsequent exposure to the allergen.[1-4] The mechanism of action is thought to be through T-helper (Th) cell switching by rectifying the balance between Th1 and Th2 lymphocytes and increasing the levels of protective IgG while decreasing the levels of IgE.[2,4-6] Long-lasting benefit is conferred, and the quality of life improved in patients for whom allergen avoidance is difficult or impossible. Patients must have demonstrable evidence of specific IgE antibodies before undergoing allergen immunotherapy (see Diagnostic Use below), and it is generally recommended that diagnosis of allergies and allergen immunotherapy should only be carried out in specialist centres. Subcutaneous injection immunotherapy (SCIT) is the traditional method of administration and has a long history of use. Sublingual immunotherapy (SLIT) is now also widely used, and other routes have been tried — see Administration, above. Reports of severe and sometimes fatal hypersensitivity reactions to injected allergen preparations prompted recommendations to reduce the risk of systemic reactions (see under Adverse Effects, above).

The use of allergen immunotherapy has been reviewed[4,7] and recommendations have been published.[2,3,8,9] The incidence and severity of allergic disease is increasing as a result of environmental changes, and allergies represent a major cause of illness in developed countries; in the UK for example, they are estimated to affect 1 in 3 people. Of particular concern is the rise in multi-system allergies.[4] Common sources of allergens include: pollen and fungal spores producing seasonal allergic rhinitis and conjunctivitis (hay fever); house dust, house-dust mites, and animal dander producing perennial allergic rhinitis; venom from bees, wasps, and stinging ants; latex rubber, flour, and other allergens giving rise to occupational rhinitis; drugs (e.g. penicillins, anaesthetics); and some foods (e.g. nuts, shellfish).[4] Allergic reactions are a common cause of childhood asthma and are also associated with atopic eczema.[4]

Not all allergies are suitable for treatment with specific allergen immunotherapy and recommendations made by the CSM[10] in the UK are that allergen immunotherapy should only be used for seasonal allergic rhinitis (hay fever) in patients not responsive to anti-allergic drugs, and for hypersensitivity to bee and wasp venoms; warnings against use in patients with asthma are also given (although allergen immunotherapy is used in some countries for the treatment of allergic asthma — see below). The UK CSM[10] also concludes that there is inadequate evidence of benefit from desensitisation to allergens such as house dust, house-dust mites, animal dander, and foods, and therefore does not recommend allergen immunotherapy in these cases.

Allergen immunotherapy is used in **children** and is thought to be more effective than in adults.[2] It has been suggested that its use in children with allergic rhinoconjunctivitis may also prevent the development of asthma.[3] Review of controlled studies and meta-analyses[11] confirmed that allergen injection immunotherapy is effective in allergic asthma in children, and early intervention may prevent progression to multiple allergen hypersensitivity. However, since adverse effects of allergen immunotherapy are more likely in asthmatics, it is contra-indicated in unstable asthma (see also below). Therapy is generally not recommended for children younger than 5 or 6 years of age[2,3,8] because it is less well tolerated, cooperation with a young child might be difficult,[3] and in this age group the differential diagnosis between allergic rhinitis and viral infection of the respiratory tract may not be clear.[2]

Allergen immunotherapy for seasonal **allergic rhinitis** and **conjunctivitis** triggered by pollen has generally been reserved for severely affected patients when anti-allergic drugs have failed.[2,3,8] A systematic review[5] of controlled studies concluded that there is a significant reduction in symptoms and use of medication in suitably selected patients who have not responded adequately to anti-allergic drugs, together with a known and relatively low risk of serious adverse effects with no long-term consequences. The sublingual route is a means of ameliorating the severe systemic reactions associated with injection immunotherapy. A systematic review[6] of studies using sublingual immunotherapy in patients with seasonal and perennial allergic rhinitis supported the promotion of this route because rhinitis symptoms and use of anti-allergic medication were reduced significantly in adults and no systemic adverse effects were reported. However, it was difficult to assess the magnitude of the effect and compare this route with injection immunotherapy. The treatment effect in children was not significant. However, a meta-analysis[12] of more controlled studies involving a greater total number of children concluded that sublingual immunotherapy was effective in children with allergic rhinitis.

There is some evidence that allergen immunotherapy for allergies such as rhinitis may prevent the development of **asthma**[3] and thus earlier use may be warranted.[13] A systematic review[14] of randomised controlled studies confirmed that allergen immunotherapy in asthmatic patients reduced the symptoms of asthma and the use of asthma medication, although it was not possible to quantify the benefits compared with other forms of therapy, and the possibility of severe or fatal anaphylaxis remains. Recommendations for the use of allergen immunotherapy in patients with asthma vary. Guidelines issued in the UK[10] in 1994 recommended that asthmatic patients should not be treated with allergen immunotherapy because they are more likely to develop severe adverse effects (although asthma is not considered a contra-indication to allergen immunotherapy for anaphylaxis caused by Hymenoptera spp.). Others,[3,9] including WHO,[2] consider that allergen immunotherapy for allergic rhinoconjunctivitis can be given to patients whose asthma is stable and not severe (FEV_1 is not less than 70% of predicted value),[2] when avoidance of allergens has not been sufficient or is not possible, and drug treatment has failed. Allergen immunotherapy should not be given to patients whose asthma can be controlled by antiasthmatic drugs and allergen avoidance.[15]

Allergen immunotherapy is indicated for patients with specific IgE antibodies who have experienced severe anaphylaxis after **insect stings**, particularly those of Hymenoptera (bees, wasps, and stinging ants).[2,3,8,16,17] Vaccines containing purified venom are available for most Hymenoptera spp. and have replaced whole body extract preparations, which were generally found to be ineffective. Venom immunotherapy is very effective in decreasing the risk of systemic reactions to venom in susceptible people.[17] Venom vaccines are not available for stinging ants but whole body extract vaccines may contain sufficient venom antigens to be effective.[2,3,17] Allergen immunotherapy for rhinoconjunctivitis and asthma due to house-dust mite or animal dander can be considered when the allergen is unavoidable.[2,3,9,14] A review[18] considering both injection and sublingual mite immunotherapy in adults and children with asthma and/or rhinitis confirms efficacy, although it is not possible to assess safety relative to other forms of allergen immunotherapy such as pollen vaccines. One multicentre, randomised, dose-response study[19] found that specific mite injection immunotherapy for 1 year improved eczema in patients with atopic dermatitis allergic to house-dust mite. Limited data indicate that allergen immunotherapy might be effective for atopic dermatitis associated with aeroallergen sensitivity.[3] However, more controlled studies are needed to confirm its place in treatment.[4]

Allergen immunotherapy for **drug hypersensitivity** may be warranted on the rare occasions when continued use is considered essential, possibly with penicillins or insulin.[8,20] In most cases the effect of desensitisation is temporary and if the medication is required again in the future, the process must be repeated.[21]

Allergen immunotherapy has also been tried in **other disorders** such as urticaria and food allergies, but there is insufficient evidence to support such use[3,4,8,10] and its use is not recommended. The traditional method of allergen immunotherapy in peanut allergy has an unacceptably high rate of systemic adverse reactions and other immunotherapeutic interventions are being sought.[22]

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Diagnostic use. Sensitivity testing can be used to confirm that suspected allergens are mainly responsible for the symptoms of a suspected hypersensitivity reaction. It is necessary before patients with allergies are managed either by allergen avoidance or treated with allergen immunotherapy (see above). However, sensitivity testing should not form the sole basis of the treatment of hypersensitivity reactions.

Type IV (delayed) hypersensitivity reactions such as contact dermatitis are normally diagnosed using patch tests. A number of standard techniques are available, but in general they all involve maintaining a standard amount of the test substance in contact with the skin for 48 to 72 hours. A positive response is shown by erythema, swelling, or vesiculation. The sensitivity of different parts of the body varies, and this should be accounted for in applying test substances and controls. The test results are normally read 30 to 60 minutes after removal of the patches to allow any pressure effects of the patches to subside. Patch testing with mixtures of allergens may be necessary to diagnose contact dermatitis in patients hypersensitive to multiple allergens.

Type I (immediate) hypersensitivity reactions such as allergic rhinitis, allergic asthma, and insect-sting hypersensitivity are tested using skin-prick or intradermal tests. Since the allergen is introduced through the skin in these tests, the risk of systemic reactions is greater than patch testing, and adrenaline injection should be kept available. The skin-prick test involves pricking the epidermis through a drop of allergen in solution, and comparing the result after 15 to 20 minutes with positive and negative controls. This test is inexpensive and the results available rapidly. The intradermal (intracutaneous) test is used if the skin-prick test result does not agree with a strong clinical suspicion, although now that potent allergen extracts are used for skin-prick tests, the intradermal test offers few advantages and has greater risk of systemic reactions. Skin testing is unreliable for evaluating hypersensitivity to drugs, except for penicillins and for certain macromolecules. Skin test titration, that is testing with a series of dilutions, has been used to determine a safe starting dose for allergen immunotherapy.

Provocation tests are designed to reproduce symptoms of hypersensitivity by controlled exposure to a suspected allergen. They are used when skin or laboratory tests are unavailable, or IgE is not involved in the mechanism. Provocation may be by the bronchial, oral, nasal, or ocular routes. Facilities for full cardiopulmonary resuscitation should be immediately available.

In-vitro methods for measuring antigen-specific IgE include immunoassays such as the enzyme-linked immunosorbent assay (ELISA), which has now replaced the radioallergosorbent test (RAST). These tests can be used in place of skin-prick tests but they are expensive and the results not available as quickly.

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Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Albay; Allpyral; ***Belg.:*** Alyostal; Pharmalgen; Pollinex†; ***Braz.:*** Nikkho Vac; ***Canad.:*** Pollinex-R; ***Cz.:*** Alutard SQ; Alyostal; APSI/AQ†; ASAD†; D-Al; Grazax; H-AL; Pangramin; Pollinex; Soluprick SQ; Staloral; ***Denm.:*** Alutard SQ; Aquagen SQ; Pharmalgen; Sensitiner; Soluprick SQ; True Test; ***Fr.:*** Albey; Alyostal; ASAD†; Diallertest; ***Ger.:*** ALK; Allergovit; Depot-Hal; Novo-Helisen; Oralvac; Phostal; Pollinex Quattro; Pollinose S†; Purethal; Reless; Staloral; TA Baume; TA Graser; TA MIX; Tol; Tyrosin TU; Venomenhal; Venomil; ***Hung.:*** Lais; Pangramin; Purethal; Venomenhal; ***Israel:*** True Test; ***Ital.:*** Phostal; Staloral; ***Mex.:*** True Test†; ***Neth.:*** Allergopharma; Allergovit; Alutard; Artu; Artuvac; Bencard Priktestoplossing; Depot-Hal; Immunovac†; Novo-Helisen; Oralgen; Pharmalgen; Pollinex; Purethal; Soluprick SQ; Sublivac B.E.S.T.†; ***Norw.:*** Alutard; ***NZ:*** Albay; Allpyral†; True Test; ***Pol.:*** Allergovit; Alutard SQ; Alyostal; Catalet; Novo-Helisen; Perosall; Pharmalgen; Phostal; Pollinex; Purethal; Staloral; Venomenhal; ***Port.:*** Grazax; Polagen†; Soluprick; Truetest; ***S.Afr.:*** Albay; Albey; Allpyral Pure Mite; Allpyral Special Grass; EH Retard†; Tol†; ***Swed.:*** Alutard SQ; Aquagen SQ; Soluprick SQ; ***Switz.:*** Alavac-S†; ALK; Allergovit; Alutard SQ; Alyostal; ASAD†; Novo-Helisen; Pharmalgen; Phostal; Polvac; Staloral; ***UK:*** Bencard Skin Testing Solutions; Grazax; Pharmalgen; Pollinex; ***USA:*** Albay; Allpyral; Center-Al; Pharmalgen; True Test; Venomil.

Multi-ingredient: ***Arg.:*** Summavac; ***Braz.:*** Alergoral; Aminovac; Multigen AL†; Multivac VR†; Rhinovac†; Urtivac; Vag Oral; ***Cz.:*** Apisarthron; Phostal; ***Fin.:*** Alutard SQ; Aquagen SQ; Soluprick SQ; ***Ger.:*** Alustal; BU Pangramin SLIT; Depigoid; Forapin E†; Slit One; Sublivac; ***Ital.:*** Alustal; ***Neth.:*** Trolab; Venomhal†; ***Rus.:*** Apisarthron (Апизартрон); ***Switz.:*** Alustal.

Almond Oil

Aceite de Almendra; Almendras dulces, aceite de; Amande, huile d'; Amygdalae oleum; Badem Yağı; Bitter Almond Oil; Expressed Almond Oil; Huile d'Amande; Mandelöl; Mandelolja; Mandlový olej; Mandulaolaj; Manteliöljy; Migdolų aliejus; Ol. Amygdal.; Olej migdałowy; Oleo de Amêndoas; Olio di Mandorla; Sweet Almond Oil.

CAS — 8007-69-0.

Pharmacopoeias. In *USNF.*
Eur (see p.vii) includes the virgin oil and a refined oil.
Fr. also specifies Huile de Noyaux, an oil obtained from various species of *Prunus.*

Ph. Eur. 6.2 (Almond Oil, Virgin; Amygdalae Oleum Virginale). A yellow, clear, liquid. It is the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* var. *amara* or *P. dulcis* var. *dulcis* or a mixture of both varieties. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 6.2 (Almond Oil, Refined; Amygdalae Oleum Raffinatum). The fatty oil obtained by refining and deodorisation of Almond Oil. It may contain a suitable antoxidant. A pale yellow, clear, transparent liquid. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

USNF 26 (Almond Oil). The refined fixed oil expressed from the kernels of varieties of *Prunus dulcis* [*Prunus amygdalus*] (Rosaceae). It may contain suitable antoxidants. A clear, colourless or pale straw-coloured, oily liquid with a bland taste. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in well-filled, airtight containers. Protect from light.

Profile

Almond oil, which consists mainly of glycerides of oleic acid with smaller amounts of linoleic and palmitic acid, has nutritive and demulcent properties. It is used as an emollient and to soften ear wax. It is also used as a vehicle in some injections.

Preparations

BP 2008: Almond Oil Ear Drops;
USP 31: Rose Water Ointment.

Proprietary Preparations (details are given in Part 3)
Braz.: Laderm; ***Mex.:*** Dermoskin†.

Multi-ingredient: ***Arg.:*** Caien; ***Austral.:*** Curash Babycare; Snor-Away†; ***Chile:*** Akerat; ***Cz.:*** Balmandol; ***Ger.:*** Excipial; ***Ital.:*** Baby Zanzara; Babysteril; Otosan Natural Ear Drops†; Proctonet†; Stilomagic†; ***Mex.:*** Caliderm; Liniderm; ***NZ:*** Am-O-Lin; Snorenz; ***Port.:*** Cuidaderma; Olidermil; ***Spain:*** Pasta Lassar Imba; ***Switz.:*** Antidry; Balmandol; Premandol; Viola; Woloderma†; ***Turk.:*** Balmandol; Metamorfoz; ***UK:*** Calendula Nappy Change Cream; Earex; Imuderm; Infaderm; Snor-Away.

Alpha Galactosidase A

α-D-Galactosidase; α-Galactosidase A; α-D-Galactoside Galactohydrolase.

Agalsidase Alfa *(BAN, USAN, rINN)*

Agalsidasa alfa; Agalsidasum Alfa.

Агальсидаза Альфа

CAS — 104138-64-9 (protein moiety).
ATC — A16AB03.
ATC Vet — QA16AB03.

Agalsidase Beta *(rINN)*

Agalsidasum Beta; Agalsidaz Beta; Alfasidasa β.

Агальсидаза Бета

CAS — 104138-64-9 (protein moiety).
ATC — A16AB04.
ATC Vet — QA16AB04.

Adverse Effects, Treatment, and Precautions

IgG antibodies to agalsidase alfa develop in some patients, and to agalsidase beta in the majority of patients. The presence of antibodies increases the risk of infusion reactions. Infusion reactions have been reported in about 14% of patients given agalsidase alfa, and in about 67% of patients treated with agalsidase beta. The frequency of the onset of these reactions decreases with continued use, with the majority of reports occurring during the first 2-4 months after the start of treatment, although onset after 1 year has also been reported. Symptoms generally start during, or within 1 hour of, infusion. The most common symptoms have included chills, dyspnoea, facial flushing, headache, nausea, fever, and fatigue. The infusion may be interrupted for about 5 to 10 minutes and restarted once symptoms have subsided. Pretreatment with oral antihistamines, paracetamol, ibuprofen, and/or corticosteroids 1 to 24 hours before infusion has been used to prevent subsequent reactions. Patients with compromised cardiac function should be monitored closely since they may be predisposed to a higher risk of severe complications arising from infusion reactions.

Interactions

Agalsidase alfa or beta should not be used with amiodarone, chloroquine, monobenzone, or gentamicin, which all have the potential to inhibit intracellular α-galactosidase activity.

Pharmacokinetics

The pharmacokinetic properties of agalsidase alfa appear to be unaffected by dose; the elimination half-life from blood following a single dose has been reported to be about 100 minutes. The pharmacokinetics of agalsidase beta indicate a saturated clearance; the elimination half-life following a single dose has been reported to range from 45 to 100 minutes.

◊ Most pharmacokinetic parameters of agalsidase alfa in children with Fabry disease were similar to those in adult patients after single and repeated doses, except for serum clearance, which was age dependent being significantly increased in children.[1] However, there was no difference in pharmacodynamics between the age groups.

1. Ries M, *et al.* Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J Clin Pharmacol* 2007; **47:** 1222–30.

Uses and Administration

Alpha galactosidase A is an endogenous enzyme that hydrolyses terminal α-D-galactose residues in oligosaccharides and galactolipids into more easily digestible mono- and disaccharides. A form derived from a fungal source is used to prevent intestinal gas.

Agalsidase alfa and beta are recombinant forms of alpha galactosidase A used for the long-term enzyme replacement therapy of Fabry disease (see below).

Agalsidase alfa is given by intravenous infusion in a dose of 200 micrograms/kg over 40 minutes, repeated every alternate week.

Agalsidase beta is given by intravenous infusion in a dose of 1 mg/kg at an initial rate of no more than 250 micrograms/minute; the rate of administration may be gradually increased (by 50 to 80 micrograms/minute in each subsequent infusion) once tolerance has been established. The dose should be repeated every alternate week.

Fabry disease. Fabry disease (Anderson-Fabry disease) is a rare X-linked recessive lysosomal storage disorder.[1-6] It predominantly affects males, although female carriers may sometimes have clinical manifestations.[4,5] It is characterised by a deficiency of the enzyme alpha galactosidase A resulting in the intracellular accumulation of globotriaosylceramide (Gb_3) and other glycosphingolipids, especially in vascular endothelium and smooth muscle. Symptoms include severe neuropathies, fevers, skin blemishes (angiokeratomas), corneal and lenticular opacities, and gastrointestinal disturbances. Cardiac, cerebrovascular, and renal deterioration is progressive placing patients at increased risk for early-onset myocardial infarction, stroke, and renal failure.

Symptomatic treatment was the only option until the development of enzyme replacement therapy with agalsidase alfa[7] and beta.[8] Results from controlled studies show this form of therapy to be effective in clearing deposits from the kidneys, heart, and skin[9-12] as well as improving peripheral neuropathy.[13] An open-label extension study[14] of agalsidase beta in the 58 patients formerly studied in a 20-week controlled phase III study[11] confirmed the continued safety and efficacy of enzyme replacement therapy after 30 months of treatment. Benefit continued in these patients followed up for a further 24 months,[15] and kidney biopsies in 8 of the patients confirmed complete clearance of globotriaosylceramide. The cardiac effects of Fabry disease have been reviewed,[16] and both agalsidase alfa and beta have been reported to improve left ventricular structure and function, although further studies are required. Although most studies have been in adults, enzyme replacement therapy has been shown to be safe in children over 6 years of age.[17] Expert opinion generally recommends that treatment is begun as soon as clinical signs and symptoms are observed.[5,18] Gene therapy[19] is also under investigation.

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6. Clarke JTR. Narrative review: Fabry disease. *Ann Intern Med* 2007; **146:** 425–33.
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8. Keating GM, Simpson D. Agalsidase beta: a review of its use in the management of Fabry disease. *Drugs* 2007; **67:** 435–55.
9. Moore DF, *et al.* Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001; **104:** 1506–12.
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12. Moore DF, *et al.* Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002; **33:** 525–31.
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17. Ries M, *et al.* Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006; **118:** 924–32.
18. Banikazemi M, *et al.* Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007; **146:** 77–86.
19. Siatskas C, Medin JA. Gene therapy for Fabry disease. *J Inherit Metab Dis* 2001; **24** (suppl 2): 25–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Replagal; ***Austria:*** Replagal; ***Belg.:*** Fabrazyme; Replagal; ***Canad.:*** Beano; Fabrazyme; Gaz Away; Replagal; ***Cz.:*** Fabrazyme; Replagal; ***Denm.:*** Fabrazyme; Replagal; ***Fin.:*** Fabrazyme; ***Fr.:*** Fabrazyme†; Replagal; ***Ger.:*** Fabrazyme; Replagal; ***Gr.:*** Fabrazyme; Replagal; ***Hung.:*** Fabrazyme; Replagal; ***Israel:*** Fabrazyme; Replagal; ***Ital.:*** Fabrazyme; Replagal; ***Jpn:*** Fabrazyme; ***Neth.:*** Fabrazyme; Replagal; ***Norw.:*** Fabrazyme; ***NZ:*** Fabrazyme; Replagal; ***Pol.:*** Fabrazyme; ***Port.:*** Fabrazyme; Replagal; ***Spain:*** Fabrazyme; Replagal; ***Swed.:*** Fabrazyme; ***Switz.:*** Fabrazyme; Replagal; ***UK:*** Beano; Fabrazyme; Replagal; ***USA:*** Beano; Fabrazyme.

Alpha$_1$-proteinase Inhibitor

Alpha$_1$ Antitrypsin; alpha-1-Antitrypsinum; Antitrypsine alpha-1; Inhibidor de la α_1- proteinasa.

ATC — B02AB02.

ATC Vet — QB02AB02.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human α-1-Proteinase Inhibitor). A plasma protein fraction containing mainly human α-1-proteinase inhibitor. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Other plasma proteins may be present. Freeze-dried products are hygroscopic, white or pale yellow or pale brown powders or friable solids; liquid products are clear or slightly opalescent, colourless or pale yellow or pale green or pale brown. pH of 6.5 to 7.8. Store in airtight and sterile containers at a temperature not exceeding 25°.

Adverse Effects and Precautions

Adverse effects of intravenous alpha$_1$-proteinase inhibitor include asthenia, chills, increase in cough, dizziness, dyspnoea, flu-like symptoms, headache, hypotension, pain at the injection site, paraesthesias, pharyngitis, pruritus, rashes, somnolence, and tachycardia. The infusion should be interrupted or the rate reduced if adverse effects occur and resumed at a more tolerable rate once the symptoms have subsided; the infusion should be stopped immediately in the event of anaphylactic or anaphylactoid reactions, and full supportive measures implemented. Preparations derived from pooled human plasma carry a risk of transmission of infection (see Blood, p.1056).

The drug is contra-indicated in patients with selective IgA deficiencies who have known antibody against IgA since they are at risk of severe reactions to IgA that may be present in the product.

Uses and Administration

Endogenous alpha$_1$-proteinase inhibitor is a serum glycoprotein synthesised in the liver that acts as an elastase inhibitor, primarily inhibiting neutrophil elastase. Alpha$_1$-proteinase inhibitor, prepared from pooled human plasma, is used as replacement therapy in patients with emphysema who have congenital alpha$_1$ antitrypsin deficiency (see below). It is given in a dose of 60 mg/kg once a week by intravenous infusion at a rate of about 0.08 mL/kg per minute (usually corresponding to a 15 to 30 minute infusion).

A recombinant form of alpha$_1$-proteinase inhibitor is under investigation for nebulised delivery in congenital alpha$_1$ antitrypsin deficiency and cystic fibrosis (see below).

Alpha$_1$-proteinase inhibitor has also been investigated for the prevention of bronchopulmonary dysplasia (p.1500) in preterm neonates.

Alpha$_1$ antitrypsin deficiency. Alpha$_1$ antitrypsin deficiency (alpha$_1$-proteinase inhibitor deficiency) is characterised by chronic obstructive pulmonary disease (COPD) and chronic liver disease associated with a lack of alpha$_1$-proteinase inhibitor.[1] This inhibitor is produced in the liver but exerts its main effects in the lungs as an inhibitor of neutrophil elastase, an enzyme released in response to inflammation. Congenital deficiency of the inhibitor thus leaves the lungs vulnerable to destruction by elastase, leading to the development of emphysema (see Chronic Obstructive Pulmonary Disease, p.1112), usually in the third or fourth decade of life. Hepatic manifestations of deficiency include hepatitis, cirrhosis, and hepatoma. Panniculitis and vasculitis may also occur less frequently in some phenotypes.[2,3]

Management of COPD associated with the deficiency involves avoidance of factors (mainly cigarette smoking) that cause pulmonary inflammation, and supportive treatment with bronchodilators and oxygen as appropriate. Augmentation therapy with alpha$_1$-proteinase inhibitor to raise serum concentrations above the protective threshold is also of benefit in some patients.[2,4] Intravenous infusion of the drug has been shown to correct the biochemical abnormality[5] and has been recommended in those patients with some deterioration of lung function.[2,6] In a short-term study[7] serum and secretion concentrations of alpha$_1$-proteinase inhibitor as well as markers of neutrophilic inflammation were monitored in 12 patients receiving augmentation therapy over 4 weeks. Results demonstrated a rise in serum levels of alpha$_1$-proteinase inhibitor to above the protective threshold, and reduction in elastase activity and levels of leukotriene B_4 levels (thought to be important in producing airway inflammation in alpha$_1$ antitrypsin deficiency). A small placebo-controlled study[8] found that the rate of decline of FEV_1 was not affected in patients treated for at least 3 years. Data[9] from a large registry of patients also suggested that, overall, treatment did not affect the rate of decline of FEV_1, but that it decreased mortality, although this may be influenced by other factors. Evaluation[6] of 2 of these studies[8,9] and one other concluded that replacement therapy might reduce the progression of disease in selected patients, but that further randomised placebo-controlled studies were required to provide conclusive evidence for overall clinical efficacy. The Canadian Thoracic Society[10] recommends that replacement therapy should be reserved for patients with an FEV_1 between 35 and 65% predicted who are no longer smoking and on optimal medical therapy but continuing to show a rapid decline in FEV_1. In a retrospective cohort study[11] in 96 patients followed up for a minimum of 12 months, results indicated that the rate of progression of pulmonary emphysema was reduced during the time that the patients received augmentation therapy, and patients with well-maintained lung function and a rapid decline in FEV_1 benefited most from therapy. These authors recommended early diagnosis to identify patients at risk and to start augmentation even if lung function is greater than 65% predicted.

Liver involvement does not respond to treatment with alpha$_1$-proteinase inhibitor and is managed symptomatically.[2]

Several new approaches to treatment of alpha$_1$ antitrypsin deficiency are under investigation:[2,3,12] plasma-derived and recombinant forms of alpha$_1$-proteinase inhibitor for inhalation; synthetic elastase inhibitors for oral use; synthetic chaperones to block intrahepatic polymerisation of the inhibitor and other methods to improve serum concentrations; retinoids; inhaled hyaluronic acid; and gene therapy.

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2. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; **168:** 818–900. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/alpha1.html (accessed 14/07/06)
3. Stoller JK, Aboussouan LS. α -Antitrypsin deficiency. *Lancet* 2005; **365:** 2225–36.
4. Juvelekian GS, Stoller JK. Augmentation therapy for α -antitrypsin deficiency. *Drugs* 2004; **64:** 1743–56.
5. Coakley RJ, *et al.* α1-Antitrypsin deficiency: biological answers to clinical questions. *Am J Med Sci* 2001; **321:** 33–41.
6. Abboud RT, *et al.* Alpha -antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J* 2001; **8:** 81–8.
7. Stockley RA, *et al.* The effect of augmentation therapy on bronchial inflammation in α1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2002; **165:** 1494–8.
8. Dirksen A, *et al.* A randomized clinical trial of α -antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; **160:** 1468–72.
9. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV decline in individuals with severe deficiency of α -antitrypsin. *Am J Respir Crit Care Med* 1998; **158:** 49–59.
10. O'Donnell DE, *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J* 2007; **14** (suppl B): 5B–32B.
11. Wencker M, *et al.* Longitudinal follow-up of patients with α -protease inhibitor deficiency before and during therapy with IV α -protease inhibitor. *Chest* 2001; **119:** 737–44.
12. Sandhaus RA. α -Antitrypsin deficiency 6: new and emerging treatments for α -antitrypsin deficiency. *Thorax* 2004; **59:** 904–9.

Cystic fibrosis. Some of the inflammatory damage that occurs in the lungs of patients with cystic fibrosis is thought to be caused by excessive amounts of elastase released locally. Alpha$_1$-proteinase inhibitor given by nebuliser is therefore under investigation[1-3] in patients with cystic fibrosis (p.166).

1. Martin SL, *et al.* Safety and efficacy of recombinant alpha -antitrypsin therapy in cystic fibrosis. *Pediatr Pulmonol* 2006; **41:** 177–83.
2. Cantin AM, *et al.* Prolastin aerosol therapy and sputum taurine in cystic fibrosis. *Clin Invest Med* 2006; **29:** 201–7.
3. Griese M, *et al.* α -Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *Eur Respir J* 2007; **29:** 240–50.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Prolastin; ***Canad.:*** Prolastin; ***Cz.:*** Trypsone; ***Fr.:*** Alfalastin; ***Ger.:*** Prolastin; ***Ital.:*** Prolastina; ***Port.:*** Prolastin; ***Spain:*** Prolastina; Trypsone; ***USA:*** Aralast; Prolastin; Zemaira.

Althaea

Altea; Alteablad (marshmallow leaf); Altearot (marshmallow root); Alteeanjuuri (marshmallow root); Alteeanlehti (marshmallow leaf); Alteia; Alth.; Althaea folium (marshmallow leaf); Althaeae radix (marshmallow root); Eibisch; Guimauve; Guimauve, feuille de (marshmallow leaf); Guimauve, racine de (marshmallow root); Korzeń prawoślazu (marshmallow root); Liść prawoślazu (marshmallow leaf); Malvavisco; Marshmallow; Orvosizilíz-gyökér (marshmallow root); Orvosizilíz-levél (marshmallow leaf); Proskurníkový kořen (marshmallow root); Proskurníkový list (marshmallow leaf); Svilarožių lapai (marshmallow leaf); Svilarožių šaknys (marshmallow root).

ATC — R05CA05.

ATC Vet — QR05CA05.

Pharmacopoeias. *Eur.* (see p.vii) includes the root and the leaf. *Fr.* also includes the flower.

Ph. Eur. 6.2 (Marshmallow Root; Althaeae Radix). The peeled or unpeeled, whole or cut, dried root of marshmallow, *Althaea officinalis*. Protect from light.

Ph. Eur. 6.2 (Marshmallow Leaf; Althaea Folium). The whole or cut dried leaf of *Althaea officinalis*. Protect from light.

Profile

Althaea is demulcent and emollient and has been used for irritation and inflammation of the mucous membranes of the mouth and pharynx, and relief of associated dry cough. It has also been used in traditional remedies for a variety of disorders including gastrointestinal disturbances.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Primadrill; ***Ger.:*** Phytohustil; ***Pol.:*** Althagem; Althamel; Rubital.

Multi-ingredient: ***Austral.:*** Althaea Complex; Cough Relief†; Garlic and Horseradish + C Complex; Hydrastis Complex†; ***Austria:*** Heumann's Bronchialtee; Paracodin; The Chambard-Tee; Tuscalman; ***Belg.:*** Sedemol; Sulfa-Sedemol; ***Braz.:*** Peitoral Angico Pelotense†; ***Canad.:*** Original Herb Cough Drops; Swiss Herb Cough Drops; ***Cz.:*** Detska Cajova Smes; Detsky Caj s Hermankem; Nontusyl†; Pruduškova; Pulmoran; Species Pectorales Planta; ***Fr.:*** Apilaxe†; Mediflor Tisane No 4 Diuretique; Pansoral Premieres Dents; ***Ger.:*** Em-eukal Husten- und Brusttee†; Heumann Bronchialtee Solubifix T; Junisana†; Tonsilgon; ***Indon.:*** Silex; ***Ital.:*** Altea (Specie Composta)†; Altuss; Gastrotuss; ***Malaysia:*** Horseradish Plus†; ***Pol.:*** Rubital Compositum; Syrop Prawoslazowy Zlozony; Tabulettae Laxantes; ***Rus.:*** Linkus (Линкас); Pansoral Teething (Пансорал Первые Зубы); Tonsilgon N (Тонзилгон Н); ***S.Afr.:*** Cough Elixir; ***Singapore:*** Pansoral Teething; ***Spain:*** Bronpul†; Llantusil†; Malvaliz†; Natusor Broncopul†; Natusor Farinol†; Natusor Gastrolen†; Natusor Malvasen†; Senalsor†; ***Switz.:*** Malveol; NeoDP†; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; Tisane Provencale No 1; Tuscalman; ***UK:*** Herb and Honey Cough Elixir; Herbheal Ointment; Modern Herbals Cold & Catarrh; Potter's Catarrh Pastilles; Sinotar; ***Venez.:*** Novacodin.

Alum

Alaun; Allume; Aluin; Alumbre; Alumen; Aluminium Kalium Sulfuricum; Aluminium Potassium Sulphate; Alumínium-káliumszulfát; Alun; Aluna; Alūnas; E522; Glinowo-potasowy siarczan; Glinu potasu siarczan; Kalii Aluminii Sulfas Dodecahydricus; Potash Alum; Potassium Alum; Síran draselno-hlinitý dodekahydrát. Potassium aluminium sulphate dodecahydrate.

$AlK(SO_4)_2,12H_2O = 474.4$.
CAS — 7784-24-9 (alum dodecahydrate); 10043-67-1 (anhydrous alum).
ATC — S01XA07.
ATC Vet — QS01XA07.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
US also includes dodecahydrated ammonia alum (Ammonium Alum). *Jpn* also includes dried alum.

Ph. Eur. 6.2 (Alum). Colourless, transparent, crystalline masses or a granular powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. A 10% solution in water has a pH of 3.0 to 3.5.

USP 31 (Potassium Alum). A white powder or large, colourless crystals or crystalline fragments. It is odourless. Soluble 1 in 7 of water and 1 in 0.3 of boiling water; insoluble in alcohol; freely but slowly soluble in glycerol. Its solutions are acid to litmus. Store in airtight containers.

Adverse Effects

Large doses of alum are irritant and may be corrosive; gum necrosis and gastrointestinal haemorrhage have occurred. Systemic absorption from bladder irrigation solutions can cause acute aluminium toxicity (see under Aluminium below) including encephalopathy.

◊ Acute encephalopathy has been reported[1,2] after bladder irrigation with alum solutions in the treatment of bladder haemorrhage. Anecdotal evidence would suggest that this practice should be avoided in patients with renal insufficiency.[1]

1. Phelps KR, *et al.* Encephalopathy after bladder irrigation with alum: case report and literature review. *Am J Med Sci* 1999; **318:** 181–5.
2. Nakamura H, *et al.* Acute encephalopathy due to aluminium toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; **40:** 296–300.

Uses and Administration

Alum precipitates proteins and is a powerful astringent. It is often included in preparations used as mouthwashes or gargles and in dermatological preparations.

Alum, either as a solid or as a solution, may be used as a haemostatic. Intravesical instillation of alum, typically as a 1% solution, has been used as a treatment for haemorrhagic cystitis (p.2178).

Alum is also used as a mordant in the dyeing industry.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Citramin†.

Multi-ingredient: ***Arg.:*** Bentophyto; ***Austria:*** EST; ***Braz.:*** Lucretin; ***Canad.:*** Fletchers Sore Mouth Medicine; ***Ger.:*** Retterspitz Ausserlich; Retterspitz Innerlich; ***India:*** Feel Chill; ***Ital.:*** Lavanda Sofar; ***Mex.:*** Forcremol; ***Neth.:*** Trachitol; ***NZ:*** Grans Remedy; ***Spain:*** Co Bucal; Lindemil; ***USA:*** BFI; Massengill; Mycinette; ***Venez.:*** Borogin.

Aluminium

Aluminio; Aluminum; E173; Glin.

Al = 26.9815386.
CAS — 7429-90-5.

Description. Aluminium is a malleable and ductile soft silvery-white metal, becoming coated with a thin layer of oxide.

Pharmacopoeias. *Br.* includes Aluminium Powder.

BP 2008 (Aluminium Powder). An odourless or almost odourless, silvery-grey powder. It consists mainly of metallic aluminium in very small flakes, usually with an appreciable quantity of aluminium oxide. It is lubricated with stearic acid to protect the metal from oxidation. Practically insoluble in water and in alcohol; it dissolves in dilute acids and in aqueous solutions of alkali hydroxides, with the evolution of hydrogen.

Handling. Aluminium powder has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Incompatibility. Incompatibilities have been reported between aluminium in injection equipment and metronidazole,[1,2] and between aluminium and various antineoplastics including cisplatin, daunorubicin, and doxorubicin.[3-6] The suitability of aluminium caps for sugar-containing liquids has also been questioned. Abrasion of the aluminium cap by sugar from *Ceporex Syrup* [cefalexin] has resulted in the formation of a black slime.[7]

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bohart RD, Ogawa G. An observation on the stability of cis-dichlorodiammineplatinum (II): a caution regarding its administration. *Cancer Treat Rep* 1979; **63:** 2117–18.
4. Gardiner WA. Possible incompatibility of doxorubicin hydrochloride with aluminum. *Am J Hosp Pharm* 1981; **38:** 1276.
5. Williamson MJ, *et al.* Doxorubicin hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1983; **40:** 214.
6. Ogawa GS, *et al.* Dispensing-pin problems. *Am J Hosp Pharm* 1985; **42:** 1042.
7. Tressler LJ. Medicine bottle caps. *Pharm J* 1985; **235:** 99.

Adverse Effects, Treatment, and Precautions

Aluminium toxicity is well recognised in patients with renal impairment. Patients undergoing dialysis have experienced encephalopathy, osteodystrophy, and anaemia associated with an aluminium salt taken as a phosphate binder or with aluminium present in the water supply. For this reason, aluminium-free phosphate binders are often used in dialysis patients and the concentration of aluminium in dialysis fluid has been limited to not more than 10 micrograms/litre (see Aluminium Overload under Dialysis Solutions, p.1671). Serum-aluminium concentrations should be monitored regularly in patients undergoing dialysis.

Aluminium toxicity has followed the use of parenteral fluids and infant feeds with a high concentration of aluminium.

Aluminium toxicity may be treated by removal of the aluminium with desferrioxamine (p.1441).

The adverse effects of aluminium salts and precautions to be observed are described under Aluminium Hydroxide, p.1706.

◊ A review of aluminium toxicity[1] lists possible sources of aluminium including water, antacids, phosphate-binding gels, total parenteral nutrition solutions, processed human serum albumin, fluids used in infants, and environmental pollution; cooking utensils and beverages such as tea have also been suggested as possible sources of aluminium. It has been suggested that over-the-counter preparations of antacids, which can contain significant amounts of aluminium, represent the most important quantitative source of aluminium exposure.[2] Toxicity tends to occur when the gastrointestinal barrier to aluminium absorption is circumvented, as in intravenous fluid use or dialysis, or if the excretion of aluminium is reduced, as in renal impairment. Infants, especially preterm infants, form a special risk group.[3-6]

Accidental deposition of 20 tonnes of aluminium sulfate in a reservoir in Cornwall, UK in 1988 led to contamination of a nearby town's water supply.[7] Symptoms reported included diarrhoea, mouth ulcers or blisters, malaise, joint symptoms (mainly deterioration of existing symptoms), and memory defects (usually beginning 2 to 3 months after the incident). Although some medical experts considered that no long-term toxic effects were to be expected,[7] aluminium deposits were found in the bones of 2 individuals 6 to 7 months later.[8] In a study[9] undertaken 3 years after the incident, 55 adults who claimed to have suffered cerebral damage performed poorly in psychomotor testing. The authors attributed this to aluminium exposure, but the study's design and conclusions have been criticised.[10-12] An inquiry by the UK DoH[13] does not anticipate that exposure to aluminium from this incident would have caused long-term health problems in people who were adults or toddlers at the time, although this possibility should be explored further in those who were bottle-fed infants (i.e. below one year of age) at that time. Further studies have also been recommended on the neuropsychological status and prevalence of joint problems in the population who consumed the contaminated water.

1. Monteagudo FSE, *et al.* Recent developments in aluminium toxicology. *Med Toxicol* 1989; **4:** 1–16.
2. Reinke CM, *et al.* Aluminium in over-the-counter drugs: risks outweigh benefits? *Drug Safety* 2003; **26:** 1011–25.
3. Bishop N, *et al.* Aluminium in infant formulas. *Lancet* 1989; **i:** 490.
4. Lawson M, *et al.* Aluminium and infant formulae. *Lancet* 1989; **i:** 614–15.
5. Anonymous. Aluminium content of parenteral drug products. *WHO Drug Inf* 1990; **4:** 70.
6. American Academy of Pediatrics Committee on Nutrition. Aluminum toxicity in infants and children. *Pediatrics* 1996; **97:** 413–16.
7. Anonymous. Camelford two years on. *Lancet* 1990; **336:** 366.
8. Eastwood JB, *et al.* Aluminium deposition in bone after contamination of drinking water supply. *Lancet* 1990; **336:** 462–4.
9. Altmann P, *et al.* Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 1999; **319:** 807–11.
10. David A. Cerebral dysfunction after water pollution incident in Camelford: results were biased by self selection of cases. *BMJ* 2000; **320:** 1337.
11. Esmonde TFG. Cerebral dysfunction after water pollution incident in Camelford: study has several methodological errors. *BMJ* 2000; **320:** 1337–8.
12. McMillan TM. Cerebral dysfunction after water pollution incident in Camelford: study may prolong the agony. *BMJ* 2000; **320:** 1338.
13. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Subgroup Report on the Lowermoor Water Pollution Incident. DoH (issued 26th January, 2005). Available at: http://www.advisorybodies.doh.gov.uk/cotnonfood/lsgreportjan05.pdf (accessed 04/04/08)

Burns. Thermal burns have been reported in patients undergoing magnetic resonance imaging (MRI) procedures when wearing transdermal medication patches containing aluminium in the backing material.[1] Aluminium is a conductive material and could induce a concentration of electrical currents sufficient to cause serious burns if placed in the MRI field; a similar phenomenon could also occur with external defibrillation.

1. Health Canada. Association of transdermal drug patches with thermal burns during magnetic resonance imaging procedures (issued 26th April 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/mri-irm_patch-timbre_nth-ah_e.pdf (accessed 03/04/08)

Effects on mental function. Encephalopathy with seizures has been associated with the use of aluminium-containing materials used for bone reconstruction.[1,2] In each case, reconstruction of areas of the skull resulted in high concentrations of aluminium in the CSF.

1. Renard JL, *et al.* Post-otoneurosurgery aluminium encephalopathy. *Lancet* 1994; **344:** 63–4.
2. Hantson P, *et al.* Encephalopathy with seizures after use of aluminium-containing bone cement. *Lancet* 1994; **344:** 1647.

ALZHEIMER'S DISEASE. The role of aluminium in the aetiology of Alzheimer's disease (see Dementia, p.362) is, at best, unclear.[1-4] Circumstantial evidence of a positive association arises from *animal* and *in-vitro* data, together with clinical observations that aluminium is present in senile plaques and neurofibrillary tangles occurring in Alzheimer's disease, that giving aluminium chelators to Alzheimer patients may slow the progression of the disease, and that the risk of brain changes is increased in people living in areas with a high aluminium content in the drinking water supply. Some of these findings have been criticised, disproved, or not confirmed by other workers. Listed below are some of the studies which point to an association between aluminium intake and Alzheimer's disease,[5-8] some criticisms,[9-13] and some negative findings.[14,15]

There does not appear to be a risk of aluminium accumulation from normal use of aluminium-containing antacids by patients with normal renal function; consequently use of these antacids by such patients should not be considered to put them at risk of Alzheimer's disease.[16,17]

1. Crapper McLachlan DR, *et al.* Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? *Can Med Assoc J* 1991; **145:** 793–804.
2. Anonymous. Is aluminium a dementing ion? *Lancet* 1992; **339:** 713–14.
3. Munoz DG. Is exposure to aluminium a risk factor for the development of Alzheimer disease?—No. *Arch Neurol* 1998; **55:** 737–9.
4. Forbes WF, Hill GB. Is exposure to aluminium a risk factor for the development of Alzheimer disease?—Yes. *Arch Neurol* 1998; **55:** 740–1.
5. Martyn CN, *et al.* Geographical relation between Alzheimer's disease and aluminium in drinking water. *Lancet* 1989; **i:** 59–62.
6. Crapper McLachlan DR, *et al.* Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 1991; **337:** 1304–8.
7. Good PF, *et al.* Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study. *Ann Neurol* 1992; **31:** 286–92.
8. Harrington CR, *et al.* Alzheimer's-disease-like changes in tau protein processing: association with aluminium accumulation in brains of renal dialysis patients. *Lancet* 1994; **343:** 993–7.
9. Ebrahim S. Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 267.
10. Schupf N, *et al.* Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 267.
11. Lindesay J. Aluminium and Alzheimer's disease. *Lancet* 1989; **i:** 268.
12. Birchall JD, Chappell JS. Aluminium, water chemistry, and Alzheimer's disease. *Lancet* 1989; **i:** 953.
13. Whalley LJ, *et al.* Aluminium and dementia. *Lancet* 1992; **339:** 1235–6.
14. Markesbery WR, *et al.* Instrumental neutron activation analysis of brain aluminum in Alzheimer's disease and aging. *Ann Neurol* 1981; **10:** 511–16.
15. Wettstein A, *et al.* Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. *Int Arch Occup Environ Health* 1991; **63:** 97–103.
16. Anonymous. Aluminium salts and Alzheimer's disease. *Pharm J* 1991; **246:** 809.
17. Flaten TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45:** 203–6.

Uses and Administration

Aluminium is used in packaging and in injection equipment. The foil is also used as a dressing and for insulation. Aluminium may also be employed as a colouring agent for some foodstuffs. Aluminium powder alone and in paste form with zinc oxide has been used as a dressing. Astringent aluminium salts are used as antiperspirants. Aluminium hydroxide (p.1706) is used as an antacid.

Aluminium oxide (p.1585) has been used as an abrasive agent.

Homoeopathy. Aluminium has been used in homoeopathic medicines under the following names: Aluminium metallicum; Al. met.

Preparations

BP 2008: Compound Aluminium Paste.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Effidrate†; ***Braz.:*** Belagin; ***Fr.:*** Supro; ***Mex.:*** Dicentril; Gavicid†; Ulgel.

Aluminium Acetate

Aluminio, acetato de; Aluminum Acetate.

$C_6H_9AlO_6$ = 204.1.

CAS — 139-12-8.

Profile

Aluminium acetate is prepared from aluminium sulfate and acetic acid.

Solutions containing aluminium acetate are astringent. Ear drops, which correspond to a solution of aluminium acetotartrate in that they are prepared from aluminium sulfate with the aid of acetic acid and tartaric acid, reduce oedema and inflammation of the ear in conditions such as otitis externa (p.182) by producing an acidic environment hostile to pathogenic bacteria; they are also hygroscopic. Solutions, usually prepared from glacial acetic acid and an aluminum subacetate topical solution (which is itself prepared from aluminium sulfate and acetic acid), have also been used in dermatology as astringent lotions for irritating skin conditions.

Various preparations containing aluminium acetate have been known as Burow's creams, emulsions, lotions, or solutions.

Aluminium acetotartrate and aluminium subacetate (basic aluminium acetate) are also used as topical astringents.

Preparations

BP 2008: Aluminium Acetate Ear Drops;
USP 31: Aluminum Subacetate Topical Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Buro-Sol; ***Ger.:*** Alsol; Alsol N†; Alsol†; Essigsaure Tonerde-Salbe; Essitol; ***Hung.:*** Alsol; ***Pol.:*** Altacet; Altix; ***Switz.:*** Euceta; ***USA:*** Bite Rx; Buro-Sol†; ***Venez.:*** Acid Mantle.

Multi-ingredient: ***Arg.:*** Aseptalum†; Epiprocto; ***Austral.:*** Xyloproct; ***Austria:*** Acetonal; Euceta mit Kamille; Methyment; Nasanal; ***Braz.:*** Xyloproct; ***Fin.:*** Xyloproct†; ***Fr.:*** Gel a l'Acetotartrate d'Alumine Defresne†; ***Ger.:*** Anisan†; ***Hong Kong:*** Haemoral; ***Indon.:*** Haemocaine; ***Irl.:*** Xyloproct; ***Israel:*** Proctozorin-N; ***Ital.:*** Betaderm; Micofoot; Oleo Calcarea†; Vegetallumina; ***Malaysia:*** Xyloproct; ***Mex.:*** Dermanol; Litiset; Xyloproct Plus; ***Norw.:*** Xyloproct; ***NZ:*** Xyloproct; ***Pol.:*** Kamagel; ***Port.:*** Proctonostrum†; ***Spain:*** Avril; ***Swed.:*** Xyloproct; ***Switz.:*** Anginesin†; Euceta avec camomille et arnica; Euceta Pic; Fortacet; Frigoplasma†; Fungex; Leucen; Mikutan N; Realderm; Topaceta; ***Turk.:*** Hemoralgine; ***UK:*** Xyloproct; ***USA:*** Borofair Otic; Burow's; Otic Domeboro; Star-Otic.

Aluminium Lactate

Aluminio, lactato de. Tris(lactato)aluminium.

$C_9H_{15}AlO_9$ = 294.2.

CAS — 537-02-0; 18917-91-4.

Profile

Aluminium lactate is used in the local treatment of various disorders of the mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Etiaxil; ***Ital.:*** Aluctyl.

Multi-ingredient: ***Israel:*** Aronal Forte; ***Ital.:*** Lacalut; ***Port.:*** Gartun; ***Switz.:*** Deaftol avec lidocaine.

Aluminium Sulfate

Aliuminio sulfatas; Alumiinisulfaatti; Aluminii sulfas; Aluminii Sulfas Hydricus; Aluminio, sulfato de; Aluminium, sulfate d'; Aluminium Sulfuricum; Aluminium Sulphate; Aluminium Trisulphate; Aluminiumsulfat; Alumínium-szulfát; Aluminum Sulfate; E520; Glinu siarczan; Síran hlinitý hydrát.

$Al_2(SO_4)_3,xH_2O$ = 342.2 (anhydrous).

CAS — 10043-01-3 (anhydrous aluminium sulfate); 17927-65-0 (aluminium sulfate hydrate).

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Aluminium Sulphate). Colourless lustrous crystals or crystalline masses. It contains 51 to 59% of $Al_2(SO_4)_3$. Soluble in cold water; freely soluble in hot water; practically insoluble in alcohol. Store in airtight containers.

USP 31 (Aluminum Sulfate). Contains 54 to 59% of $Al_2(SO_4)_3$. An odourless, white, crystalline powder, shining plates, or crystalline fragments. Soluble 1 in 1 of water; insoluble in alcohol. The pH of a 5% solution in water is not less than 2.9.

Profile

Aluminium sulfate has an action similar to that of alum (p.2254) but is more astringent. A 20% solution is used for the treatment of envenomation by certain insects and marine organisms. The aluminium may cause precipitation of the proteins contained within the venoms thus reducing local toxicity. Aluminium sulfate is also included in astringent preparations intended to soothe irritating skin conditions.

Aluminium sulfate is also used in the preparation of aluminium acetate solutions.

Adverse effects. Possible adverse effects or toxicity associated with aluminium, or aluminium salts such as aluminium sulfate, in the public water supply are discussed under Aluminium, p.2254.

Preparations

USP 31: Aluminum Subacetate Topical Solution; Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Stingose; ***Hong Kong:*** Stingose; ***NZ:*** Stingose; ***S.Afr.:*** Stingose†; ***UK:*** Stingose.

Multi-ingredient: ***Arg.:*** Gineseptina†; ***Ger.:*** Tannolil†; ***Hung.:*** Burofix†; ***Mex.:*** Domeboro; ***USA:*** Bluboro†; Boropak†; Domeboro; Ostiderm; Pedi-Boro Soak Paks.

Ambucetamide *(BAN, rINN)*

A-16; Ambucetamida; Ambucétamide; Ambucetamidum; Dibutamide. 2-Dibutylamino-2-(4-methoxyphenyl)acetamide.

Амбуцетамид

$C_{17}H_{28}N_2O_2$ = 292.4.

CAS — 519-88-0.

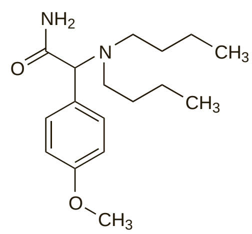

Profile

Ambucetamide is an antispasmodic and has been given for the relief of dysmenorrhoea. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Neth.:*** Femerital.

Ambutonium Bromide *(BAN)*

Ambutonii Bromidum; Ambutoniumbromid; Ambutoniumbromidi; BL-700B; R-100. (3-Carbamoyl-3,3-diphenylpropyl)ethyldimethylammonium bromide.

$C_{20}H_{27}BrN_2O$ = 391.3.

CAS — 14007-49-9 (ambutonium); 115-51-5 (ambutonium bromide).

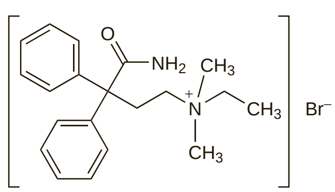

Profile

Ambutonium bromide is a quaternary ammonium antimuscarinic that has been used in gastrointestinal disorders with smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Port.:*** Sedioton†.

Amikhelline Hydrochloride *(rINNM)*

Amikhelline, Chlorhydrate d'; Amikhellini Hydrochloridum; Hidrocloruro de amikelina. 9-(2-Diethylaminoethoxy)-4-hydroxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one hydrochloride.

Амикеллина Гидрохлорид

$C_{18}H_{21}NO_5,HCl$ = 367.8.

CAS — 4439-67-2 (amikhelline); 40709-23-7 (amikhelline hydrochloride).

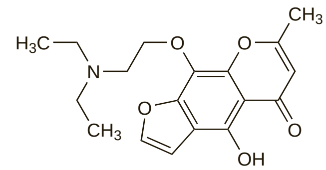

(amikhelline)

Profile

Amikhelline hydrochloride has been used as an antispasmodic.

Amilomer *(rINN)*

Amilomère; Amilómero; Amilomerum.

Амиломер

CAS — 42615-49-6.

Profile

Amilomer consists of microspheres produced by reaction of partially hydrolysed starch with epichlorohydrin, quickly degradable by amylase (with a half-life of less than 120 minutes); the name is followed by a hyphenated numerical code in which the number preceding the hyphen indicates the half-life in minutes and that following the hyphen indicates the mean diameter of the microspheres in μm.

Amilomer is used in transarterial chemoembolisation procedures in the management of hepatic malignancies.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Spherex.

Aminohippuric Acid

Acidum Aminohippuricum; *p*-Aminobenzoylglycine; *p*-Aminohippuric Acid; Aminohippurihappo; Aminohippursyra; Aminohipúrico, ácido; Kwas aminohipurowy; PAHA; Para-aminohippuric Acid. *N*-4-Aminobenzoylaminoacetic acid.

$C_9H_{10}N_2O_3$ = 194.2.

CAS — 61-78-9 (aminohippuric acid); 94-16-6 (sodium aminohippurate).

ATC — V04CH30.

ATC Vet — QV04CH30.

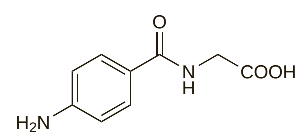

Pharmacopoeias. In *US.*

USP 31 (Aminohippuric Acid). A white crystalline powder which discolours on exposure to light. Soluble 1 in 45 of water, 1 in 50 of alcohol, and 1 in 5 of 3N hydrochloric acid; very slightly soluble in carbon tetrachloride, in chloroform, in ether, and in benzene; freely soluble in alkaline solutions with some decomposition, and in diluted hydrochloric acid. Store in airtight containers. Protect from light.

Adverse Effects

Sodium aminohippurate may cause nausea and vomiting, hypersensitivity reactions, vasomotor disturbances, flushing, tingling, cramps, and a feeling of warmth. Patients may develop an urge to urinate or defaecate after infusion.

Interactions

The estimation of sodium aminohippurate may be affected in patients taking procaine, sulfonamides, or thiazosulfone. Probenecid diminishes the excretion of aminohippuric acid. Clearance is also affected by penicillins, salicylates, and other drugs that compete for the same excretory pathways.

Uses and Administration

Aminohippuric acid is excreted mainly by proximal tubular secretion, with some glomerular filtration. It is given by intravenous infusion, as sodium aminohippurate (aminohippurate sodium; $C_9H_9N_2NaO_3$ = 216.2), for the estimation of effective renal plasma flow. Doses are aimed at producing a plasma concentration of 20 micrograms/mL; at these concentrations about 90% of aminohippurate is cleared from the renal bloodstream in a single circuit in patients with normal renal function. Sodium aminohippurate has also been used for the assessment of the renal tubular secretory mechanism. Doses for this purpose are infused slowly to achieve a plasma concentration of 400 to 600 micrograms/mL to saturate the tubular secretion. These tests are used mainly in research procedures.

Preparations

USP 31: Aminohippurate Sodium Injection.

Ammi Visnaga Fruit

Biznaga, fruto de la; Khella; Khellah; Picktooth Fruit; Visnaga.

Khellin *(rINN)*

Kelina; Khelline; Khellinum; Visammin. 4,9-Dimethoxy-7-methyl-5*H*-furo[3,2-*g*]chromen-5-one.

Келлин

$C_{14}H_{12}O_5$ = 260.2.

CAS — 82-02-0.

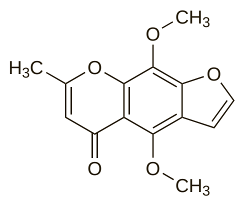

Visnadine *(BAN, rINN)*

Visnadina; Visnadinum. 10-Acetoxy-9,10-dihydro-8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[2,3-*f*]chromen-9-yl 2-methylbutyrate.

Виснадин

$C_{21}H_{24}O_7$ = 388.4.

CAS — 477-32-7.

ATC — C04AX24.

ATC Vet — QC04AX24.

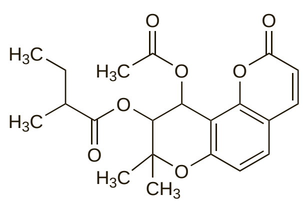

Profile

Ammi visnaga fruit is used in herbal preparations.

Khellin and visnadine are vasodilators obtained from *Ammi visnaga* fruit or by synthesis. Khellin also has a bronchodilatory action and has been used in angina pectoris and asthma. Khellin has also been tried in conjunction with UV light to treat vitiligo (see Pigmentation Disorders, p.1582). Visnadine has been used in coronary, cerebral, and peripheral vascular disorders.

Homoeopathy. Ammi visnaga has been used in homoeopathic medicines under the following names: Ammi vis.

◊ References.

1. Hofer A, *et al.* Long-term results in the treatment of vitiligo with oral khellin plus UVA. *Eur J Dermatol* 2001 **11:** 225–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Khellangan N†.

Multi-ingredient: ***Austria:*** Urelium Neu; ***Ger.:*** Cefadrin; Oxacant-Khella N†; Stenocrat†; ***Pol.:*** Kelicardina; Nefrol.

Ammonia

Amoníaco, solución diluida de; Amonowy wodorotlenek; Amonyak.

CAS — 7664-41-7.

NH_3

NOTE. The food additive number E527 is used for ammonium hydroxide. Solutions of ammonia in water have been referred to as ammonium hydroxide solutions. Strong solutions of ammonia have also been described by the synonyms Ammoniaca, Ammoniacum, Ammoniaque Officinale, and Liquor Ammoniae Fortis. Dilute solutions of ammonia have also been referred to as Ammonia Water, Ammonium Hydricum Solutum, Liquor Ammoniae, and Liquor Ammoniae Dilutus.

Pharmacopoeias. Strong ammonia solutions are included in *Chin.* (25 to 28%), *Eur.* (see p.vii) (25 to 30%), and *USNF* (27 to 31%). Dilute ammonia solutions are included in *Br.*, *Chin.*, *Ger.*, *Jpn*, and *Swiss* (all about 10%).

Ph. Eur. 6.2 (Ammonia Solution, Concentrated; Ammoniae Solutio Concentrata; Strong Ammonia Solution BP 2008). It contains between 25% and 30% (w/w) of ammonia, NH_3. A clear colourless liquid. Very caustic. Miscible with water and with alcohol. Store at a temperature not exceeding 20° in airtight containers.

BP 2008 (Dilute Ammonia Solution). It is prepared by diluting Strong Ammonia Solution with freshly boiled and cooled purified water. It contains 9.5 to 10.5% w/w of NH_3.

NOTE. The BP directs that when Ammonia Solution is prescribed or demanded, Dilute Ammonia Solution shall be dispensed or supplied.

USNF 26 (Strong Ammonia Solution). It contains between 27% and 31% (w/w) of NH_3. On exposure to air, it loses ammonia rapidly. A clear colourless liquid with an exceedingly pungent characteristic odour. Store at a temperature not exceeding 25° in airtight containers.

Handling. Strong ammonia solutions should be handled with great care because of the caustic nature of the solutions and the irritating properties of the vapour. Cool the container well before opening and avoid inhalation of the vapour.

Adverse Effects

Ingestion of strong solutions of ammonia causes severe pain in the mouth, throat, and gastrointestinal tract, as well as severe local oedema and salivation, with cough, vomiting, and shock. Burns to the oesophagus and stomach may result in perforation. Stricture formation, usually in the oesophagus, can occur weeks or months later. Ingestion may also cause oedema of the respiratory tract and pneumonitis, though this may not develop for a few hours.

Inhalation of ammonia vapour causes sneezing and coughing and in high concentration causes pulmonary oedema. Asphyxia has been reported after oedema or spasm of the glottis. Ammonia vapour is irritant to the eyes and causes weeping; there may be conjunctival swelling and temporary blindness.

Ammonia solution in contact with skin and eyes produces blistering and vesiculation; ammonia burns feel 'soapy' because of saponification of the tissues. Strong solutions on the conjunctiva cause a severe reaction with conjunctival oedema, corneal damage, and acute glaucoma. Late complications include angle-closure glaucoma, opaque corneal scars, atrophy of the iris, and formation of cataracts. Ammonia burns have resulted from treating insect bites and stings with the strong solution, and even with the dilute solution, especially if a dressing is subsequently applied.

◊ References.

1. Beare JDL, *et al.* Ammonia burns of the eye: an old weapon in new hands. *BMJ* 1988; **296:** 590.
2. WHO. Ammonia health and safety guide. *IPCS Health and Safety Guide 37*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg037.htm (accessed 04/04/06)
3. Payne MP, Delic JI. Ammonia. In: *Toxicity Review 24*. London: HMSO, 1991: 1–12.
4. Payne MP, *et al. Toxicology of substances in relation to major hazards: ammonia*. London: HMSO, 1991.
5. Leduc D, *et al.* Acute and long term respiratory damage following inhalation of ammonia. *Thorax* 1992; **47:** 755–7.
6. Michaels RA. Emergency planning and the acute toxic potency of inhaled ammonia. *Environ Health Perspect* 1999; **107:** 617–27.
7. Amshel CE, *et al.* Anhydrous ammonia burns case report and review of the literature. *Burns* 2000; **26:** 493–7.
8. Kerstein MD, *et al.* Acute management of exposure to liquid ammonia. *Mil Med* 2001; **166:** 913–14.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing ammonia-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p.1661.

Treatment of Adverse Effects

Ingestion of ammonia solutions should not be treated by lavage or emesis. Milk or water have been given as diluents, but small volumes should be used to reduce the risk of inducing emesis. Appropriate measures should be taken to alleviate pain, shock, and pulmonary oedema, and maintain an airway.

Contaminated skin and eyes should be flooded immediately with water and the washing continued for at least 15 minutes. Any affected clothing should be removed while flooding is being carried out.

Uses and Administration

Dilute solutions of ammonia have been used as reflex stimulants either as smelling salts or oral solutions. They have also been used as rubefacients and counter-irritants (see p.5) and to neutralise insect stings. Users should always be aware of the irritant properties of ammonia.

Hartshorn and Oil was sometimes used as a name for an ammonia liniment. Household ammonia and cloudy ammonia have been used as names for cleaning preparations of ammonia with oleic acid or soap respectively. A saturated solution containing about 35% w/w and known as '0.880 ammonia' has been used in many chemical and industrial applications.

Stings. Bathers who were stung by Portuguese men-of-war (*Physalia physalis*) were rapidly and effectively relieved of discomfort, paresis, irritation, and other symptoms by the application of aromatic ammonia spirit compresses.[1]

1. Frohman IG. Treatment of physalia stings. *JAMA* 1966; **197:** 733.

Preparations

BP 2008: Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment.

Proprietary Preparations (details are given in Part 3)
Canad.: After Bite; ***Israel:*** Afterbite; ***Spain:*** After Bite; Calmapica; ***Switz.:*** After Bite; ***UK:*** After Bite.

Multi-ingredient: ***Austral.:*** Senega and Ammonia; ***Austria:*** Rowalind; ***Canad.:*** Bronchex†; SJ Liniment; ***Chile:*** Rhus Opodeldoc; ***Cz.:*** Pain Expeller†; ***Hung.:*** Opodeldok†; ***Ital.:*** Baby Zanzara; Stilomagic†; ***S.Afr.:*** Enterodyne; ***Spain:*** Masagil; ***UK:*** Blistex Relief Cream; Goddards Embrocation; Mackenzies Smelling Salts; Pickles Smelling Salts; ***USA:*** Emergent-Ez.

Ammonium Citrate

Ammon. Cit.; Amonowy cytrynian; E380; Triammonium Citrate.

$C_6H_5O_7(NH_4)_3$ = 243.2.

CAS — 3458-72-8.

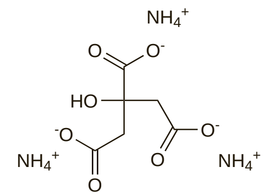

Profile

Ammonium citrate is used as a food additive and has been used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Ambrotos; Mucobrol.

Ammonium Phosphate ⊗

545 (ammonium polyphosphates); Amonowy wodorofosforan; Diammonium Hydrogen Phosphate; Dibasic Ammonium Phosphate; Fosfato de amonio. Diammonium hydrogen orthophosphate.

$(NH_4)_2HPO_4$ = 132.1.

CAS — 7783-28-0.

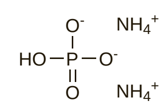

Pharmacopoeias. In *USNF.*

USNF 26 (Ammonium Phosphate). Colourless or white granules or powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 7.6 to 8.2. Store in airtight containers.

Profile

Ammonium phosphate was formerly used as a diuretic. It may be used as a buffering agent in pharmaceutical preparations.

Ammonium biphosphate (monobasic ammonium phosphate; $NH_4H_2PO_4$ = 115.0) has been used to acidify urine and as a phosphate supplement.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Phosphore Medifa; ***Pol.:*** Phosphor.

Amnion

Amnios.

Profile

Human extra-embryonic fetal membranes comprise an inner amniotic membrane, the amnion, and an outer membrane, the chorion. Amnion is used in ocular surgery for a range of conditions. Both amnion and combined membranes have been used as a dressing for raw wounds including chronic ulcers and burns.

Amylase

Amilasa; Amylaza; Diastase; Glucogenase; Ptyalin.

CAS — 9000-92-4 (amylase); 9000-85-5 (bacterial α-amylase); 9000-90-2 (porcine α-amylase, pancreatic); 9001-19-8 (taka-diastase);.

ATC — A09AA01.

ATC Vet — QA09AA01.

Pharmacopoeias. In *Fr.* and *Jpn.*

Adverse Effects

Hypersensitivity reactions have been reported.

Hypersensitivity. References to asthma developing after occupational exposure to amylases used in the flour milling[1-3] and detergent[4,5] manufacturing industries, and studies[6-8] to assess the likelihood of developing amylase hypersensitivity after ingesting wheat products including bread.

1. Smith TA, *et al.* Respiratory symptoms and wheat flour exposure: a study of flour millers. *Occup Med (Lond)* 2000; **50:** 25–9.
2. Cullinan P, *et al.* Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg* 2001; **45:** 97–103.
3. Quirce S, *et al.* Glucoamylase: another fungal enzyme associated with baker's asthma. *Ann Allergy Asthma Immunol* 2002; **89:** 197–202.
4. Hole AM, *et al.* Occupational asthma caused by bacillary amylase used in the detergent industry. *Occup Environ Med* 2000; **57:** 840–2.
5. Cullinan P, *et al.* An outbreak of asthma in a modern detergent factory. *Lancet* 2000; **356:** 1899–1900.
6. Cullinan P, *et al.* Clinical responses to ingested fungal alpha-amylase and hemicellulase in persons sensitized to Aspergillus fumigatus? *Allergy* 1997; **52:** 346–9.
7. Sander I, *et al.* Is fungal alpha-amylase in bread an allergen? *Clin Exp Allergy* 2000; **30:** 560–5.
8. Simonato B, *et al.* IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001; **31:** 1771–8.

Uses and Administration

The term amylase refers to an enzyme catalysing the hydrolysis of α-1,4-glucosidic linkages of polysaccharides such as starch, glycogen, or their degradation products. Amylases may be classified according to the manner in which the glucosidic bond is attacked. Endoamylases attack the α-1,4-glucosidic linkage at random. Alpha-amylases are the only types of endoamylases known and yield dextrins, oligosaccharides, and monosaccharides. The more common alpha-amylases include those isolated from human saliva, mammalian pancreas, *Bacillus subtilis*, *Aspergillus oryzae*, and barley malt. Exoamylases attack the α-1,4-glucosidic linkage only from the non-reducing outer polysaccharide chain ends. They include beta-amylases and glucoamylases (amyloglucosidases or gamma-amylases) and are of vegetable or microbial origin. Beta-amylases yield beta-limit dextrins and maltose, and glucoamylases yield glucose.

Amylase is used in the production of predigested starchy foods and for the conversion of starch to fermentable sugars in the baking, brewing, and fermentation industries.

Amylase from various sources has been used as an ingredient of preparations of mixed digestive enzymes, and has been given by mouth for its supposed activity in reducing respiratory-tract inflammation and local swelling and oedema. Pancreatic enzymes such as pancreatin (p.2360) and pancrelipase (p.2360) have amylase activity.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Orenzym; ***Fr.:*** Flaviastase; Maxilase; Megamylase; Ribamylase; ***Port.:*** Maxilase.

Multi-ingredient: ***Arg.:*** Docechol; Dom-Polienzim; Gastridin-E; Homocisteon Compuesto; Pakinase; Polienzim; Tridigestivo Soubeiran; ***Austral.:*** Enzyme; ***Austria:*** Wobenzym; ***Belg.:*** Digestomen; ***Braz.:*** Bromelin†; Enziprid†; Essen; Filogaster†; Pantopept†; Primeral; Thiomucase; ***Canad.:*** Digesta; ***Chile:*** Flapex E; ***Cz.:*** Wobenzym; ***Ger.:*** Enzym-Wied†; ***Hong Kong:*** Digezym; Enzyplex; Magesto; ***India:*** Aristozyme; Bestozyme; Catazyme-P; Digeplex; Digeplex-T; Dipep; Farizym; Lupizyme; Molzyme†; Neopeptine; Nutrozyme; Papytazyme; Sanzyme-DS; Unienzyme; Vitazyme; ***Indon.:*** Aludonna; Enzyplex; Excelase-E; Librozym; Librozym Plus; Vitazym; Xepazym; ***Ital.:*** Digestopan†; Essen Enzimatico†; ***Jpn:*** Cabagin; ***Malaysia:*** Biotase; Enzyplex; Pepfiz; ***Mex.:*** Ochozim; Wobenzym; Zimotris; ***Port.:*** Modulanzime; ***Rus.:*** Pepfiz (Пепфиз); Wobenzym (Вобэнзим); ***Singapore:*** Biotase; Enzyplex; Weisen-U†; ***Spain:*** Demusin; Digestomen Complex; Paidozim; ***Switz.:*** Zymoplex†; ***Thai.:*** Diasgest; Digestin; Endogest†; Enzyplex; Flatulence; Magesto; Mesto-Of; Papytazyme†; Pepfiz; Pepsitase; Polyenzyme-I; ***UK:*** Enzyme Digest; Enzyme Plus; ***USA:*** Enzyme; Ku-Zyme; Kutrase; Papaya Enzyme; ***Venez.:*** Festal Reformulado.

Anagrelide Hydrochloride *(BANM, USAN, rINNM)*

Anagrélide, Chlorhydrate d'; Anagrelidi Hydrochloridum; BL-4162a; BMY-26538-01; Hidrocloruro de anagrelida. 6,7-Dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3*H*)-one hydrochloride.

Анагрелида Гидрохлорид

$C_{10}H_7Cl_2N_3O,HCl = 292.5.$

CAS — 68475-42-3 (anagrelide); 58579-51-4 (anagrelide hydrochloride).

ATC — L01XX35.

ATC Vet — QL01XX35.

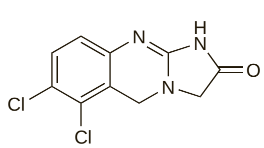

(anagrelide)

Adverse Effects

Adverse effects most commonly reported with anagrelide include headache, palpitations and tachycardia, fluid retention, diarrhoea, nausea, and abdominal pain; fatigue, dizziness, flatulence, vomiting, dyspnoea, skin rash, and anaemia have also occurred. Cardiovascular effects also include vasodilatation and positive inotropic effects; myocardial infarction, cardiomyopathy and heart failure have been reported. Anagrelide has been shown to be embryotoxic and fetotoxic in *animal* studies.

Effects on the heart. High-output heart failure occurred in a patient given anagrelide for essential thrombocytosis.[1] Clinical and haemodynamic adverse effects resolved almost immediately on stopping anagrelide.

1. Engel PJ, *et al.* High-output heart failure associated with anagrelide therapy for essential thrombocytosis. *Ann Intern Med* 2005; **143:** 311–13.

Effects on the lungs. Severe life-threatening hypersensitivity pneumonitis has been associated with anagrelide.[1]

1. Raghavan M, *et al.* Severe hypersensitivity pneumonitis associated with anagrelide. *Ann Pharmacother* 2003; **37:** 1228–31.

Erectile dysfunction. Erectile dysfunction associated with anagrelide therapy has been reported in a patient.[1]

1. Braester A, Laver B. Anagrelide-induced erectile dysfunction. *Ann Pharmacother* 2002; **36:** 1291.

Precautions

Anagrelide is mainly removed from the body by hepatic metabolism, and its use is contra-indicated in patients with severe hepatic impairment. In the UK it is additionally contra-indicated in those with moderate impairment, but in the USA its use is permitted in such patients at reduced doses (see below). Licensed drug information in the UK also contra-indicates its use in those with moderate to severe renal impairment (creatinine clearance less than 50 mL/minute).

Anagrelide should be used with caution in patients with cardiovascular disease. Cardiac function should be assessed in patients before and during treatment, and patients monitored for cardiovascular adverse effects during treatment. For precautions in patients taking anagrelide with aspirin, see Interactions, below.

Platelet counts should be monitored closely, especially at the start of treatment (see Uses and Administration, below). Haemoglobin, white blood cells, and hepatic and renal function should also be monitored until a maintenance dose is established.

Dizziness may affect the performance of skilled tasks such as driving.

Anagrelide should not be used during pregnancy.

Interactions

There is the theoretical possibility that inhibitors of the cytochrome P450 isoenzyme CYP1A2, including grapefruit juice, could reduce the clearance of anagrelide. Anagrelide itself demonstrates limited inhibitory activity towards CYP1A2. Anagrelide may exacerbate the effects of other phosphodiesterase inhibitors such as amrinone, cilostazol, enoximone, milrinone, and olprinone that also produce positive inotropic effects.

Potentiation of the effects of other drugs that modify platelet function when given with anagrelide is a theoretical possibility; although no clinically significant effects have been seen when given with aspirin, the UK manufacturer suggests that the risk-benefit potential should be assessed before using both drugs in patients with a platelet count above 1 500 000 cells/mm^3 and/or a history of haemorrhage.

Pharmacokinetics

Anagrelide is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 hour after an oral dose on an empty stomach, increasing to 3 hours in the presence of food, although this appears to have no clinically significant effect on bioavailability. It is extensively metabolised, primarily by the cytochrome P450 isoenzyme CYP1A2, and eliminated in the urine; less than 1% of a dose is excreted unchanged. The plasma half-life is about 1.3 hours.

Uses and Administration

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III that reduces platelet production and, at higher than therapeutic doses, inhibits platelet aggregation. It is used to treat primary (essential) thrombocythaemia (p.654) in patients intolerant of, or unresponsive to, other therapy, and also in thrombocythaemia secondary to other myeloproliferative disorders.

Anagrelide is given orally as the hydrochloride monohydrate ($C_{10}H_7Cl_2N_3O,HCl,H_2O = 310.6$) but doses are expressed in terms of the base; 1.2 mg of anagrelide hydrochloride monohydrate is equivalent to about 1 mg of anagrelide. The initial dose is the equivalent of anagrelide 1 mg daily in 2 divided doses. After at least a week, the dose is adjusted, by increasing the daily dose by not more than 500 micrograms in any one week, until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily. The dose should not exceed 10 mg daily or 2.5 mg as a single dose. In the USA, a higher initial dose of 2 mg daily, divided into 2 or 4 doses, is used; an initial daily dose of 500 micrograms is recommended in children. For doses to be used in patients with hepatic impairment, see below.

The effects of anagrelide therapy must be regularly monitored: platelet counts should be measured every 2 days during the first week of treatment and then at least weekly until the maintenance dose is reached.

◊ References.

1. Spencer CM, Brogden RN. Anagrelide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia. *Drugs* 1994; **47:** 809–22.
2. Chintagumpala MM, *et al.* Treatment of essential thrombocythemia with anagrelide. *J Pediatr* 1995; **127:** 495–8.
3. Petitt RM, *et al.* Anagrelide for control of thrombocythemia in polycythemia and other myeloproliferative disorders. *Semin Hematol* 1997; **34:** 51–4.
4. Oertel MD. Anagrelide, a selective thrombocytopenic agent. *Am J Health-Syst Pharm* 1998; **55:** 1979–86.
5. Lackner H, *et al.* Treatment of children with anagrelide for thrombocythemia. *J Pediatr Hematol Oncol* 1998; **20:** 469–73.
6. Bellucci S, *et al.* Studies of platelet volume, chemistry and function in patients with essential thrombocythaemia treated with anagrelide. *Br J Haematol* 1999; **104:** 886–92.
7. Pescatore SL, Lindley C. Anagrelide: a novel agent for the treatment of myeloproliferative disorders. *Expert Opin Pharmacother* 2000; **1:** 537–46.
8. Dingli D, Tefferi A. Anagrelide: an update on its mechanisms of action and therapeutic potential. *Expert Rev Anticancer Ther* 2004; **4:** 533–41.
9. Steurer M, *et al.* Anagrelide for thrombocytosis in myeloproliferative disorders: a prospective study to assess efficacy and adverse event profile. *Cancer* 2004; **101:** 2239–46.
10. Wagstaff AJ, Keating GM. Anagrelide: a review of its use in the management of essential thrombocythaemia. *Drugs* 2006; **66:** 111–31.

Administration in hepatic impairment. UK licensed drug information recommends that anagrelide should not be given to patients with moderate or severe hepatic impairment. In the USA, anagrelide therapy is not recommended in patients with severe hepatic impairment, although patients with moderate hepatic impairment have been given anagrelide in an initial daily dose of 500 micrograms, which should be maintained for a minimum of 1 week and with cardiovascular monitoring; the daily dose may then be increased cautiously as above.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Agrelid; ***Austral.:*** Agrylin; ***Austria:*** Thromboreductin; ***Belg.:*** Xagrid; ***Braz.:*** Agrylin†; ***Canad.:*** Agrylin; ***Cz.:*** Thromboreductin; Xagrid; ***Denm.:*** Xagrid; ***Fin.:*** Xagrid; ***Fr.:*** Xagrid; ***Ger.:*** Xagrid; ***Gr.:*** Agrylin†; Xagrid; ***Hong Kong:*** Agrylin; Thromboreductin; ***Hung.:*** Thromboreductin; ***Indon.:*** Agrylin; Thromboreductin; ***Irl.:*** Xagrid; ***Israel:*** Agrylin; ***Ital.:*** Xagrid; ***Malaysia:*** Thromboreductin; ***Neth.:*** Xagrid; ***Norw.:*** Xagrid; ***Philipp.:*** Agrylin; ***S.Afr.:*** Agrylin; ***Spain:*** Xagrid; ***Swed.:*** Xagrid; ***Switz.:*** Xagrid; ***UK:*** Xagrid; ***USA:*** Agrylin.

Anecortave *(rINN)*

AL-3789; Anecortava; Anécortave; Anecortave Acetate *(USAN)*; Anecortavum. 17,21-Dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate.

Анекортав

$C_{23}H_{30}O_5 = 386.5.$

CAS — 7753-60-8.

ATC — S01LA02.

ATC Vet — QS01LA02.

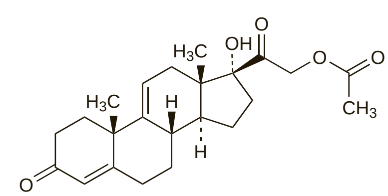

Profile

Anecortave is an angiostatic cortisene under investigation for the treatment of patients with neovascular (wet) age-related macular degeneration (p.785). It is similar in structure to cortisol acetate but without any glucocorticoid activity and is able to inhibit several steps of the neovascularisation process. It is given by posterior juxtascleral depot injection and is available in some countries for compassionate use on a named-patient basis.

◊ References.

1. Clark AF. Mechanism of action of the angiostatic cortisene anecortave acetate. *Surv Ophthalmol* 2007; **52** (suppl 1): S26–S34.
2. Regillo CD, *et al.* Clinical safety profile of posterior juxtascleral depot administration of anecortave acetate 15 mg suspension as primary therapy or adjunctive therapy with photodynamic therapy for treatment of wet age-related macular degeneration. *Surv Ophthalmol* 2007; **52** (suppl 1): S70–S78.
3. Russell SR, *et al.* Anecortave acetate for the treatment of exudative age-related macular degeneration—a review of clinical outcomes. *Surv Ophthalmol* 2007; **52** (suppl 1): S79–S90.
4. Geltzer A, *et al.* Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/04/08).

Anethole

Anethol; Anetol; *p*-Propenylanisole. (*E*)-1-Methoxy-4-(prop-1-enyl)benzene.

$C_{10}H_{12}O$ = 148.2.

CAS — 104-46-1; 4180-23-8 (E isomer).

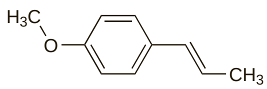

NOTE. Distinguish from Anethole Trithione (below).

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 26 (Anethole). Obtained from anise oil or other sources or prepared synthetically. At or above 23° anethole is a colourless or faintly yellow liquid with a sweet taste and the aromatic odour of aniseed. Very slightly soluble in water; soluble 1 in 2 by volume of alcohol; readily miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Anethole has similar properties to those of anise oil (below). It is also included in mixed terpene preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Rowatinex; ***Canad.:*** Beech Nut Cough Drops†; Bentasil Licorice with Echinacea†; Bentasil†; Bronco Asmol; ***Chile:*** Rowatinex; ***Cz.:*** Rowatinex; ***Ger.:*** Rowatinex; ***Hong Kong:*** Neo-Rowatinex; Rowatinex; ***Hung.:*** Rowatinex; ***Indon.:*** Listerine Coolmint; ***Irl.:*** Rowatinex; ***Israel:*** Rowatinex; ***Malaysia:*** Rowatinex; ***Philipp.:*** Listerine Coolmint; Rowatinex; ***Pol.:*** Rowatinex; ***Spain:*** Pulmofasa; Rowanefrin; Vicks Formula 44†; ***Switz.:*** GU Eau†; Neo-Angin sans sucre; Pectocalmine Junior N; ***Thai.:*** Rowatinex; ***Venez.:*** Rowatinex.

Anethole Trithione

Anethole Dithiolthione; Anetol tritiona; SKF-1717; Trithioparamethoxyphenylpropene. 5-(4-Methoxyphenyl)-3*H*-1,2-dithiole-3-thione.

$C_{10}H_8OS_3$ = 240.4.

CAS — 532-11-6.

ATC — A16AX02.

ATC Vet — QA16AX02.

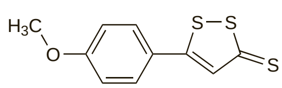

NOTE. Distinguish from Anethole (above).

Profile

Anethole trithione has been given orally in the management of dry mouth (p.2140) and as a choleretic. The usual daily dose is 75 mg, generally in 3 divided doses before meals; doses of up to 150 mg daily have sometimes been used. Anethole trithione may cause discoloration of the urine.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Sulfarlem; ***Canad.:*** Sialor; ***Fr.:*** Sulfarlem; ***Ger.:*** Mucinol†; ***India:*** Hepasulfol; ***Port.:*** Sufralem†; ***S.Afr.:*** Sulfarlem†; ***Spain:*** Sonicur; ***Switz.:*** Sulfarlem; ***Venez.:*** Sialor†.

Multi-ingredient: ***India:*** Hepasulfol-AA.

Angelica

Andělikový kořen; Angélica; Angelicae radix; Angelikarot; Angélique, racine d'; Angyalgyökér; Archangelica; Archangelicae Radix; Korzeń arcydzięgla; Šventagaršvių šaknys; Väinönputkenjuuri.

CAS — 8015-64-3 (angelica oils).

Pharmacopoeias. In *Eur.* (see p.vii).

Jpn has separate monographs for *Angelica acutiloba* (Japanese Angelica) and *A. dahurica*.

Chin. specifies *A. dahurica*, *A. dahurica* var. *formosana*, *A. pubescens*, and *A. sinensis*.

Ph. Eur. 6.2 (Angelica Root). The whole or cut, carefully dried rhizome and root of *Angelica archangelica* (*Archangelica officinalis*) containing a minimum of 0.2% v/w of essential oil, calculated with reference to the dried drug.

Profile

Angelica (*Angelica archangelica*) is widely used in herbal medicine. The root is used as a bitter to stimulate the appetite. Angelica also has diaphoretic and expectorant properties and has been used for circulatory and respiratory disorders.

Angelica oil is used in aromatherapy.

Angelica contains furanocoumarins and may cause photosensitivity reactions or interfere with anticoagulant therapy.

Other *Angelica* spp. that are used in herbal medicine include *A. acutiloba* (Japanese angelica), *A. dahurica*, *A. pubescens*, and *A. sinensis* (see Dong Quai, p.2258).

Angelica stems are candied for culinary use.

Homoeopathy. Angelica has been used in homoeopathic medicines under the following names: Archangelica; Angelica archangelica; Angelica archangelica var. archangelica.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Pascovegeton†.

Multi-ingredient: ***Arg.:*** Sigmafem; ***Austral.:*** Capsella Complex; Dong Quai Complex; Extralife Meno-Care; Feminine Herbal Complex; Infant Tonic†; Irontona; Lifesystem Herbal Formula 4 Women's Formula†; Medinat Esten†; Vitatona; Women's Formula Herbal Formula 3†; ***Austria:*** Abdomilon N; ***Canad.:*** Natural HRT; ***Cz.:*** Abdomilon†; Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; Iberogast; Klosterfrau Melisana; Original Schwedenbitter; Stomaran; Valofyt Neo; ***Fr.:*** Dystolise; Mediflor Tisane Digestive No 3; ***Ger.:*** Abdomilon N; Anore X N†; Carvomin†; Doppelherz Melissengeist†; Gastritol; Iberogast; Infi-tract†; Melissengeist; Schwedentrunk Elixier; Stovalid N†; ***Hong Kong:*** Phytoestrin†; ***Ital.:*** Florelax; ***Philipp.:*** Hemofer; Zilongjin; ***Pol.:*** Melis-Tonic; Melisal; Melisana Klosterfrau; Melissed; Nervosol; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Melissengeist; Spiritus Contra Tussim Drops; ***Singapore:*** Phytoestrin; ***Spain:*** Agua del Carmen; Himelan†; ***Switz.:*** Alcoolat de Melisse†; Gastrosan; Iberogast; Phytomed Gastro†; ***UK:*** Melissa Comp..

Aniseed

Anice; Anis; Anis, fruit d'; Anís, semilla de; Anis Verde; Anis Vert; Anise; Anise Fruit; Anisi fructus; Ánizstermés (fruit); Anyžių vaisiai (fruit); Anýzový plod (fruit); Owoc anyżu (fruit).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Aniseed; Anisi Fructus). The whole dried fruit of *Pimpinella anisum*, containing not less than 2% v/w of essential oil. It has an odour reminiscent of anethole. Protect from light.

Profile

Aniseed is carminative and mildly expectorant; it is used mainly as anise oil or as preparations of the oil. It may cause contact dermatitis, probably due to its anethole content.

Aniseed is the source of anise oil (below).

◊ References.

1. Chandler RF, Hawkes D. Aniseed—a spice, a flavor, a drug. *Can Pharm J* 1984; **117:** 28–9.
2. Fraj J, *et al.* Occupational asthma induced by aniseed. *Allergy* 1996; **51:** 337–9.
3. Garcia-Gonzalez JJ, *et al.* Occupational rhinoconjunctivitis and food allergy because of aniseed sensitization. *Ann Allergy Asthma Immunol* 2002; **88:** 518–22.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Neo-Cleanse; ***Austria:*** Asthmatee EF-EM-ES; Brady's-Magentropfen; Euka; Florissamin†; Nesthakchen; Species Carvi comp†; ***Braz.:*** Balsamo Branco; Camomila; ***Canad.:*** Herbal Laxative; ***Chile:*** Paltomiel; ***Cz.:*** Blahungstee N†; ***Fr.:*** Elixir Bonjean; Herbesan; Mediflor Tisane Digestive No 3; Mucinum a l'Extrait de Cascara; ***Ger.:*** Em-eukal Husten- und Brusttee†; Em-medical†; Floradix Multipretten N; Majocarmin-Tee; Ramend Krauter†; rohasal†; Stovalid N†; ***Hong Kong:*** Mucinum Cascara†; ***Israel:*** Jungborn; ***Ital.:*** Anice (Specie Composta)†; Cadifen; Cadimint; Dicalmir; Lassatina†; Tisana Kelemata; ***Pol.:*** Apinorm; ***Port.:*** Mucinum; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Clairo; Cough Elixir; ***Spain:*** Crislaxo; Digestovital†; Laxante Sanatorium; Laxomax†; ***Switz.:*** Kernosan Elixir; Kernosan Heidelberger Poudre; Tisane favorisant l'allaitement; ***UK:*** Herb and Honey Cough Elixir; Revitonil; ***Venez.:*** Neo-Atropan†.

Anise Oil

Anís, aceite esencial de; Anis, huile essentielle d'; Aniseed Oil; Anisi aetheroleum; Anisi Etheroleum; Anisolja; Anisöljy; Ánizsolaj; Anyžių eterinis aliejus; Anýzová silice; Esencia de Anís; Essence d'Anis; Olejek anyżowy; Oleum Anisi.

NOTE. The name anise oil is also applied to Star Anise Oil, p.2392.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Anise Oil; Anisi Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Pimpinella anisum*. It contains less than 1.5% linalol, 0.5 to 5.0% estragole, less than 1.2% α-terpineol, 0.1 to 0.4% *cis*-anethole, 87 to 94% *trans*-anethole, 0.1 to 1.4% anisaldehyde, and 0.3 to 2.0% pseudoisoeugenyl 2-methylbutyrate. A clear, colourless or pale yellow liquid. Relative density 0.980 to 0.990. F.p. 15° to 19°. Store in well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15°. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of anise oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Profile

Anise oil is carminative and mildly expectorant and is a common ingredient of cough preparations. It is also a flavour. Anise oil is used in aromatherapy.

It may cause contact dermatitis, probably due to its anethole content.

◊ For references to aniseed and anise oil, see Aniseed, above.

Preparations

BP 2008: Camphorated Opium Tincture; Compound Orange Spirit; Concentrated Anise Water; Concentrated Camphorated Opium Tincture;
USNF 26: Compound Orange Spirit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Cough Relief†; Digestive Aid; Gartech; ***Austria:*** Bradosol; Bronchostop; Expectal-Tropfen; Heumann's Bronchialtee; Kamillosan; Luuf-Hustentee; Neo-Angin; Nesthakchen; ***Braz.:*** Ovariuse-dan†; ***Canad.:*** Beech Nut Cough Drops†; ***Cz.:*** Biotussil; Bronchosan; Bronchostop†; Neo-Angin; Stopangin; ***Fr.:*** Paregorique; ***Ger.:*** Aspasmon N†; Bronchoforton; Em-eukal Husten- und Brusttee†; Em-medical†; Ephepect-Pastillen N; Floradix Multipretten N; Heumann Bronchialtee Solubifix T; Hevertopect N†; Kamillosan Mundspray; Leber-Galle-Tropfen 83†; Neo-Ballistol†; Pulmocordio mite SL†; Pulmotin; ratioGast†; Repha-Os; Salmiak†; Salviathymol N; Sinuforton; ***Hong Kong:*** Ephepect Blocker; ***India:*** Bestozyme; Kamillosan-N; Neopeptine; ***Indon.:*** Minyak Telon Cap Tiga Anak; OBH; Silex; ***Neth.:*** Bronchicum; ***Philipp.:*** Kamillosan M; ***Pol.:*** Carmolis; Herbolen D; Tobacoff; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; Stopangin (Стопангин); ***S.Afr.:*** Borsdruppels; Paragoriese-Elikser; Puma Cough Balsam; ***Spain:*** Carminativo Ibys†; Carminativo Juventus; H Tussan; Odontocromil c Sulfamida†; ***Switz.:*** Bronchofluid N†; Carmol; Carmol Plus†; Gem; Kamillosan; Makaphyt Gouttes antitussives; Neo-Bronchol; Odontal; Pastilles bronchiques S nouvelle formule; Pastilles pectorales Demo N; Penta; ***Thai.:*** Gas-Nep; Mesto-Of; ***UK:*** Hactos; Honey & Molasses; Lightning Cough Remedy; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Slippery Elm Stomach Tablets; Vegetable Cough Remover; Zubes; Zubes Blackcurrant.

Anisodamine

6-Hydroxy-hyoscyamine.

$C_{17}H_{23}NO_4$ = 305.4.

CAS — 55869-99-3.

Pharmacopoeias. *Chin.* has a monograph for Raceanisodamine and Anisodamine Hydrobromide.

Profile

Anisodamine is an alkaloid isolated from *Scopolia tangutica* (*Anisodus tanguticus*), a plant used as a traditional medicine in China. It is related to atropine and hyoscyamine and has similar antimuscarinic properties (p.1221). Anisodamine is given orally for its spasmolytic actions in the treatment of gastrointestinal spasm. It has also been tried in circulatory disorders, septic shock, and organophosphorus poisoning.

◊ References.

1. Poupko JM, *et al.* The pharmacological properties of anisodamine. *J Appl Toxicol* 2007; **27:** 116–21.
2. Fu XH, *et al.* Effect of intracoronary administration of anisodamine on slow reflow phenomenon following primary percutaneous coronary intervention in patients with acute myocardial infarction. *Chin Med J (Engl)* 2007; **120:** 1226–31.

Apis mellifera

Abeille domestique; Abeja de la Miel; The honey bee.

Медоносная Пчела Домашняя

Pharmacopoeias. *Eur.* (see p.vii) includes the live worker honey bee for homoeopathic preparations.

Ph. Eur. 6.2 (Honey Bee for Homoeopathic Preparations; Apis Mellifera ad Praeparationes Homoeopathicas). Live worker honey bee, *Apis mellifera*.

Profile

The honey bee is a source of purified honey (p.1948), royal jelly (p.2382), propolis (p.2373), and bee pollen (see Pollen and Pollen Extracts, p.2370).

Homoeopathy. Preparations of *Apis mellifera* have been used in homoeopathic medicines under the following names: Apis; Apis mellifica; Apis mel; Apis mell.

Arthritis. Bee venom has traditionally been used in the treatment of arthritis.[1,2] Studies *in vitro* have shown that bee venom has anti-inflammatory activity similar to that of cyclophosphamide. Melittin appears to be the active constituent, and seems to act by interfering with superoxide radical production from human leucocytes.[1]

1. Somerfield SD. Bee venom and arthritis: magic, myth or medicine? *N Z Med J* 1986; **99:** 281–3.
2. Caldwell JR. Venoms, copper and zinc in the treatment of arthritis. *Rheum Dis Clin North Am* 1999, **25:** 919–28.

Hypersensitivity. For reference to the use of whole body extracts or venom from Hymenoptera spp. for allergen immunotherapy in allergic subjects, see p.2251. For reference to hypersensitivity reactions to bee products see under Royal Jelly, p.2382.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Bolus Eucalypti Comp; ***Switz.:*** Forapin†.

Apricot

Pharmacopoeias. *Chin.* includes Bitter Apricot Seed, the kernel obtained from various species of *Prunus*. *Jpn* includes a monograph for Apricot Kernel.

Profile

The kernels of the apricot, *Prunus armeniaca* (*Armeniaca vulgaris*; *P. tiliifolia*) (Rosaceae), are used in Chinese medicine for disorders of the respiratory tract and for constipation.

Apricot is a source of persic oil (p.2365). Amygdalin, the major cyanogenic glycoside of apricot kernels, is the major constituent of laetrile (p.2330). Apricot kernels are also a source of pangamic acid (p.2362).

Apricot fruits are used as a food.

Aptiganel *(pINN)*

Aptiganelum. 1-(*m*-Ethylphenyl)-1-methyl-3-(1-naphthyl)guanidine.

Аптиганел

$C_{20}H_{21}N_3$ = 303.4.

CAS — 137159-92-3.

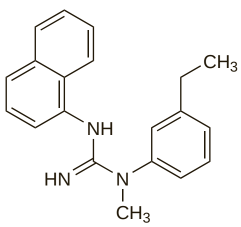

Aptiganel Hydrochloride *(USAN)*

CNS-1102.

$C_{20}H_{21}N_3$,HCl = 339.9.

CAS — 137160-11-3.

Profile

Aptiganel is a guanidine derivative that antagonises the effects of the excitatory amino-acid neurotransmitter glutamate at NMDA-receptors. It has been investigated for the prevention of ischaemic brain damage in patients with traumatic head injury or stroke.

◊ Following dose-ranging studies of aptiganel in healthy subjects[1] and in patients,[2] adverse effects reported[3] in patients with acute ischaemic stroke, at doses that had been neuroprotective in *animals*, included an increase in systolic blood pressure and an excess of CNS effects. A randomised controlled study[4] in patients with acute ischaemic stroke was suspended because of a lack of efficacy and a potential imbalance in mortality compared with placebo.

1. Muir KW, *et al*. Pharmacological effects of the non-competitive NMDA antagonist CNS 1102 in normal volunteers. *Br J Clin Pharmacol* 1994; **38:** 33–8.
2. Block GA, *et al*. Final results from a dose-escalating safety and tolerance study of the non-competitive NMDA antagonist CNS1102 in patients with acute cerebral ischaemia. *Stroke* 1995; **26:** 185.
3. Dyker AG, *et al*. Safety and tolerability study of aptiganel hydrochloride in patients with an acute ischemic stroke. *Stroke* 1999; **30:** 2038–42.
4. Albers GW, *et al*. Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. *JAMA* 2001; **286:** 2673–82.

Arachis Oil

Arachide, huile d', raffinée; Arachidis Oleum; Arachidis oleum raffinatum; Cacahuete, aceite de; Earth-nut Oil; Erdnussöl; Finomított földimogyoróolaj; Ground-nut Oil; Huile d'Arachide; Jordnötolja, raffinerad; Maapähkinäöljy, puhdistettu; Nut Oil; Ol. Arach.; Olej arachidowy oczyszczony; Óleo de Amendoim; Oleum Arachis; Peanut Oil; Podzemnicový olej čištěný; Refined Arachis Oil; Yerfıstığı Yağı; Žemės riešutų aliejus.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF*.

Eur. also includes hydrogenated arachis oil.

Ph. Eur. 6.2 (Arachis Oil, Refined; Arachis Oil BP 2008). The refined fatty oil obtained from the shelled seeds of *Arachis hypogaea*. A suitable antoxidant may be added. It is a clear, yellowish viscous liquid consisting of glycerides, chiefly of oleic and linoleic acids, with smaller amounts of other acids. It solidifies at about 2°. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

The BP 2008 gives Ground-nut Oil and Peanut Oil as approved synonyms.

Ph. Eur. 6.2 (Arachis Oil, Hydrogenated; Arachidis Oleum Hydrogenatum). Arachis oil that has been refined, bleached, hydrogenated, and deodorised. It is a white or faintly yellowish soft mass that melts to a clear pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65° to 70°). Protect from light.

USNF 26 (Peanut Oil). The fully-refined (alkali-refined, bleached, and deodorised at 230° to 260°) oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* (Leguminosae). It is a colourless or pale yellow, oily liquid with a bland taste; it may have a characteristic nutty odour. Very slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Profile

Emulsions containing arachis oil are used in nutrition. Arachis oil is given as an enema for softening impacted faeces. It is used in drops for softening ear wax (see under Docusates, p.1725) and in emollient creams. Arachis oil is given by mouth, usually with sorbitol, as a gallbladder evacuant prior to cholecystography.

Precautions. It has been suggested that the use during infancy of preparations containing arachis oil, including infant formulae and topical preparations, may be responsible for sensitisation to peanut, with a subsequent risk of hypersensitivity reactions.[1-3] The arachis oil used in such preparations is refined oil and it has been pointed out that such oil should not contain the proteins that produce allergic reactions in susceptible people.[4,5] In the USA, heating of arachis oil during preparation, to further reduce protein content, has been proposed.[6] Nonetheless, some consider that sufficient protein may be present in refined oil to cause sensitisation.[7] However, others have pointed out that to date, there are no reliable data about doses of topical arachis oil needed to induce sensitisation via the epidermal route and that the benefit of protecting skin barrier functions in atopic patients with products using refined arachis oil outweigh possible risks of sensitisation.[8] In the UK, the CSM considered that there was not enough evidence to conclude that medicinal products containing arachis oil could lead to sensitisation.[9] However, although they considered the risk of a reaction to be low, they recommended that patients known to be allergic to peanuts should not use medicines containing arachis oil (nor, because of the possibility of cross-sensitivity, should patients allergic to soya), and that such medicines should include an appropriate warning in the labelling.

1. de Montis G, *et al*. Sensitisation to peanut and vitamin D oily preparations. *Lancet* 1993; **341:** 1411.
2. Lever LR. Peanut and nut allergy: creams and ointments containing peanut oil may lead to sensitisation. *BMJ* 1996; **313:** 299.
3. Lack G, *et al*. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348:** 977–85.
4. Hourihane J O'B, *et al*. Randomised, double blind, crossover challenge study of allergenicity of peanut oil in subjects allergic to peanuts. *BMJ* 1997; **314:** 1084–8.
5. Committee on Toxicity of chemicals in Food, Consumer Products and the Environment. *Peanut allergy.* London: Department of Health, 1998.
6. Wilkin JK, *et al*. Peanut allergy. *N Engl J Med* 2003; **349:** 302.
7. Lack G, *et al*. Peanut allergy. *N Engl J Med* 2003; **349:** 302–3.
8. Ring J, Möhrenschlager M. Allergy to peanut oil — clinically relevant? *J Eur Acad Dermatol Venereol* 2007; **21:** 452–5.
9. Committee on Safety of Medicines/Medicines and Healthcare Regulatory Agency. Medicines containing peanut (arachis) oil. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Preparations

BP 2008: Arachis Oil Enema.

Proprietary Preparations (details are given in Part 3)

Austral.: Calogen; ***Chile:*** Oilatum; ***Denm.:*** Olie; ***Fin.:*** Calogen; ***Ger.:*** Olbad Cordes F; ***Indon.:*** Oilatum Cream; ***Irl.:*** Calogen; Fletcher's Arachis Oil; Oilatum Cream; ***Ital.:*** Calogen; ***Mex.:*** Dermo Bell; Nutrisil; Oilatum; ***NZ:*** Calogen; ***S.Afr.:*** Oilatum Cream; ***Singapore:*** Oilatum Cream; ***UK:*** Calogen; Fletchers Arachis Oil Retention Enema†.

Multi-ingredient: ***Austral.:*** Cerumol; Gold Cross Skin Basics Zinc Cream†; Medevac†; ***Austria:*** Balneum F; ***Chile:*** Tarytar†; ***Cz.:*** Balneum Hermal F; ***Ger.:*** Balneum F; Parfenac Basisbad†; ***Irl.:*** Cerumol; Hydromol†; ***Israel:*** Balneum F; Cerumol; ***Ital.:*** Balneum Hermal Forte; ***NZ:*** Medevac†; ***Pol.:*** Balneum Hermal F; ***S.Afr.:*** Cerumol; Haarlemensis; ***Singapore:*** Cerumol; ***Spain:*** Emolytar; ***Switz.:*** Balmed Hermal F; Balneum Hermal F†; ***UK:*** Cerumol; Earex; Hewletts; Nowax; Red Oil; Soothol.

Areca

Areca Nuts; Arecae Semen; Arekasame; Betel; Betel Nuts; Noix d'Arec.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of areca:

Daka; Gua; Maag; Mak; Marg; Pan parag; Pinang; Pugua; Puwak; Supai; Suparim.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Areca consists of the dried ripe seeds of *Areca catechu* (Palmae) containing the alkaloid arecoline.

Areca is used in Asian countries as a masticatory. It has sialogogue properties and is chewed for its mild intoxicant and euphoriant effects. The usual custom is to chew pieces of areca seed (areca nut; betel nut) wrapped with lime (calcium hydroxide) in the leaf of the betel pepper (betelvine) (*Piper betle*, which is unrelated to areca). This preparation is known as 'betel quid' (betel) or 'paan' (pan-masala), and produces a red juice when chewed, which stains the saliva, teeth and mucosa. Other ingredients that might be added include catechu gum, spices, or tobacco.

Arecoline and arecaidine (produced by the hydrolysis of arecoline when chewed with lime) have cholinergic activity, and adverse effects that may occur with initial or heavy use of areca include excessive salivation, sweating, lachrymation, urinary incontinence, or diarrhoea. An increased incidence of oral submucosal fibrosis, oral leucoplakia, and oral squamous cell carcinoma has been reported following habitual use.

Areca was formerly used in the treatment of tapeworm infection, and arecoline has been used in veterinary medicine as a purgative and taenifuge.

◊ Discussions of the health risks associated with the chewing of preparations containing areca nut by indigenous populations in Asia[1-3] and immigrant groups in the UK,[4] USA,[5] and New Zealand,[6] including acute effects.[2,3,5] See also Adverse Effects of Tobacco Products under Nicotine (p.2352) for reference to mixtures of areca and tobacco.

1. Mack TM. The new pan-Asian paan problem. *Lancet* 2001; **357:** 1638–9.
2. Deng JF, *et al*. Acute toxicities of betel nut: rare but probably overlooked events. *J Toxicol Clin Toxicol* 2001; **39:** 355–60.
3. Chu NS. Effects of Betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001; **8:** 229–36.
4. Warnakulasuriya S, *et al*. Areca nut use: an independent risk factor for oral cancer. *BMJ* 2002; **324:** 799–800.
5. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
6. Yoganathan P. Betel chewing creeps into the New World. *N Z Dent J* 2002; **98:** 40–5.

Carcinogenicity. Precancerous and cancerous conditions of the oral cavity have been attributed to the chewing of preparations containing areca (see above). In betel-chewer's mucosa, the oral mucosa is discoloured and there is desquamation or peeling of the oral epithelium from the traumatic effect of chewing and possibly a chemical action of the constituents. This condition may be a precursor of oral submucosal fibrosis, which is considered to be precancerous.[1] Oral leucoplakia is another precancerous condition that is reported. The role of areca in the development of these conditions and oral squamous cell carcinoma has been debated. The effects may be due to the arecaidine content of areca, the alkalinity of the lime, presence of tobacco, or a combination of these.[2,3] Results from a case-controlled study[4] point to an independent association between oral squamous cell carcinoma and chewing areca seeds in preparations without tobacco compared with non-users of areca. A review[5] of available evidence strongly supports this association.

1. Reichart PA, Philipsen HP. Betel chewer's mucosa—a review. *J Oral Pathol Med* 1998; **27:** 239–42.
2. Norton SA. Betel: consumption and consequences. *J Am Acad Dermatol* 1998; **38:** 81–8.
3. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
4. Merchant A, *et al*. Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer* 2000; **86:** 128–31.
5. Nair U, *et al*. Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; **19:** 251–62.

Effects on the lungs. Evidence suggesting that there is an association between betel-nut chewing and bronchoconstriction in asthmatic patients.[1,2]

1. Taylor RFH, *et al*. Betel-nut chewing and asthma. *Lancet* 1992; **339:** 1134–6.
2. Kiyingi KS. Betel nut chewing and asthma. *Lancet* 1992; **340:** 59–60.

Effects on the nervous system. Areca-nut (betel-nut) chewing is associated with habituation, addiction, and dependence,[1] and CNS symptoms of withdrawal have been described in 2 patients.[2] A case of neonatal withdrawal syndrome in an infant born to a chronic areca-nut user has also been reported.[3] Psychosis has also been reported.[1]

It has been suggested that the muscarinic action of areca alkaloids may have a beneficial effect on symptoms of schizophrenia, and a study of such patients in a Micronesian population provides some support for this idea.[4] However, severe extrapyramidal symptoms followed betel-nut chewing in 2 patients with chronic schizophrenia who were also receiving antipsychotic therapy.[5]

1. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.

2. Wiesner DM. Betel-nut withdrawal. *Med J Aust* 1987; **146:** 453.
3. López-Vilchez MA, *et al.* Areca-nut abuse and neonatal withdrawal syndrome. Abstract: *Pediatrics* 2006; **117:** 203. Full version: http://pediatrics.aappublications.org/cgi/content/full/117/1/e129 (accessed 10/04/08)
4. Sullivan RJ, *et al.* Effects of chewing betel nut (Areca catechu) on the symptoms of people with schizophrenia in Palau, Micronesia. *Br J Psychiatry* 2000; **177:** 174–8.
5. Deahl MP. Psychostimulant properties of betel nuts. *BMJ* 1987; **294:** 841.

Aristolochia

Serpentaria.

NOTE. *Aristolochia clematitis* has also been known as asarabacca (p.2261).

Pharmacopoeias. *Chin.* allows various species of *Aristolochia*.

Profile

Aristolochia spp. (birthworts) including *A. clematitis* and *A. ringens (A. brasiliensis)* have been used in herbal medicine.

Serpentary (serpentaria) is the dried rhizome and roots of *Aristolochia serpentaria* (Virginian snakeroot) and of *A. reticulata* (Texan snakeroot) (Aristolochiaceae). Snakeroot is also used as a common name to describe poisonous *Eupatorium* spp. Preparations of serpentary have been used as bitters. The active ingredient is aristolochic acid, which has been tried in a number of inflammatory disorders, mainly in folk medicine; the sodium salt of aristolochic acid has also been used. However, there is concern over such use since aristolochic acid has been reported to be carcinogenic and nephrotoxic.

Chinese medicine has employed various species of *Aristolochia* including *A. contorta*, *A. debilis* (but see under Adverse Effects, below), and *A. manshuriensis*. The terms Mu Tong and Fangji have been used for *Aristolochia* spp. in traditional medicine.

Adverse effects. Progressive interstitial fibrosis of the kidney related to a slimming regimen containing Chinese herbs had been reported in 70 patients in Belgium by 1993; 30 of these patients had terminal renal failure.[1] Renal failure has also been reported[2] in 2 patients in the UK after ingestion of Chinese herbal medicines that were later found to contain aristolochic acid, a known nephrotoxin;[3] one of these patients subsequently developed invasive urothelial carcinoma.[4] Inadvertent ingestion of aristolochic acid can originate as a result of the substitution of *Aristolochia* spp. (probably *A. manshuriensis*) for other innocuous herbal substances;[2,5] the Belgian cases were probably as a result of substitution of *A. fangchi* extracts for *Stephania tetrandra*.[1] As a result of these cases, the UK MCA issued a permanent ban on *Aristolochia* preparations in 1999. Similar bans have been made in several other countries;[3] in 2004, the Chinese regulatory authority also banned the use of *A. fangchi* and *A. debilis* in traditional medicine formulations. Examination of 39 patients in Belgium with nephropathy associated with *A. fangchi* ingestion had revealed 18 cases of urothelial carcinoma and evidence of mild to moderate dysplasia in 19 patients.[6] There had appeared to be a higher risk of carcinoma with total doses of *A. fangchi* in excess of 200 g.

Aristolochic acid has been proposed as the cause of endemic (Balkan) nephropathy,[7] which is confined to a very specific rural geographical distribution and first described in the 1950s. Data supporting this hypothesis included findings of DNA damage linked to aristolochic acid in kidney samples from affected patients, as well as renal failure in horses who had grazed in the local fields. *Aristolochia clematitis* is endemic to the region and has been found in fields cultivated for wheat grain. It is possible that the local population could be exposed to toxic amounts of aristolochic acid over time from bread made with grain contaminated with *A. clematitis* seeds.

1. Vanhaelen M, *et al.* Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; **343:** 174.
2. Lord GM, *et al.* Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; **354:** 481–2.
3. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. *Drug Safety* 2003; **26:** 33–48.
4. Lord GM, *et al.* Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001; **358:** 1515–6.
5. But PP, Ma S-c. Chinese-herb nephropathy. *Lancet* 1999; **354:** 1731–2.
6. Nortier JL, *et al.* Urothelial carcinoma associated with the use of a chinese herb (Aristolochia fangchi). *N Engl J Med* 2000; **342:** 1686–92.
7. Grollman AP, *et al.* Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 2007; **104:** 12129–34.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Euserpina Cellulite.

Multi-ingredient: *S.Afr.:* Borstol Cough Remedy.

Arnica

Árnica; Arnica, fleur d' (arnica flower); Arnicae Anthodium; Arnicae flos (arnica flower); Arnikablomma (arnica flower); Arnikinkukka (arnica flower); Arnikový květ (arnica flower); Arnikų žiedai (arnica flower); Hegyi árnika virág (arnica flower); Koszyczek arniki (arnica flower); Leopard's Bane; Mountain Tobacco; Wolf's Bane; Wolfsbane.

NOTE. Wolfsbane is also used as a common name for aconite (p.2246).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Arnica Flower; Arnica Flos). It consists of the whole or partially broken, dried flowerheads of *Arnica montana*. It contains not less than 0.4% w/w of total sesquiterpene lactones expressed as dihydrohelenalin tiglate, calculated with reference to the dried drug. It has an aromatic odour. Protect from light.

Profile

Arnica is generally used in the form of the flowerheads of *Arnica montana* (Compositae).

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Tincture of arnica may cause dermatitis when applied to the skin of sensitive persons.

Preparations of arnica flower and arnica root are used as astringents for topical application to unbroken skin in conditions such as sprains and bruises; such preparations are not considered suitable for internal use. Arnica flowers are the source of arnica oil, which has been used similarly.

Herbal preparations containing arnica are available for oral use.

Homoeopathy. Arnica has been used in homoeopathic medicines under the following names: Arnica montana; Arnica, Flos; Arnica montana e flore; Arnica montana ex herba; Arnica, Planta tota; Arnica montana ex planta tota; Arn. mont. Some homoeopathic preparations are available for oral use.

◊ References.

1. Leivers K. Unravelling the confusion around arnica's herbal and homoeopathic use. *Pharm J* 2005; **275:** 289–91.
2. Kouzi SA, Nuzum DS. Arnica for bruising and swelling. *Am J Health-Syst Pharm* 2007; **64:** 2434–43.

Preparations

Ph. Eur.: Arnica Tincture.

Proprietary Preparations (details are given in Part 3)
Arg.: Herbaccion Desinflamante†; ***Austral.:*** Sports Ice Bruising Relief; ***Belg.:*** Arnican; ***Chile:*** Arnikaderm; ***Fr.:*** Arnican; Pharmadose teinture d'arnica; ***Ger.:*** Arnikatinktur; Arthrosenex AR; Doc; Enelbin-Salbe; Hyzum N†; Vasotonin†; ***Mex.:*** Balsamo Nordin; Estimul; ***Port.:*** Arnigel; ***Singapore:*** SinEccH; ***UK:*** Arnicare; Atrogel.

Multi-ingredient: *Arg.:* Fluido; ***Austral.:*** Joint & Muscle Cream; Percutane; ***Austria:*** Arnicet; Asthmatee EF-EM-ES; Berggeist; Cional; Dynexan; Heparin Comp; Rheuma; Sportino Akut†; ***Belg.:*** Algi-Cool; Purigel Crisp; Purigel NF; ***Braz.:*** Dermol†; Traumed†; ***Chile:*** Lefkaflam; Matikomp; ***Cz.:*** Arnidol; Heparin-Gel†; ***Fr.:*** Arnicadol; Creme Rap; Decramp; Dermocica; Evarose; Lelong Contusions†; ***Ger.:*** Arnikamill†; Cefawell†; Combudoron; Dolo-cyl; Essaven Sport†; Gothaplast Rheumamed AC; Heparin Comp†; Heparin Kombi-Gel†; Heusin†; Lindofluid N; Retterspitz Ausserlich; Retterspitz Quick; Rhoival†; Sportino Akut; Stullmaton†; Trauma-cyl; Varicylum-S; Venengel†; Vitosal†; ***Hong Kong:*** New Patecs A; ***Ital.:*** Flebolider; Flodolor; Venalta; ***Malaysia:*** Arnica Comp†; ***Mex.:*** Reudol; ***Pol.:*** Arcalen; Arnisol; Dentosept; Dentosept A; Emorect; Escalar; Prostapol; Reumobonisol; Stomatosol; Uroprost; Venoforton; ***S.Afr.:*** Arnica Massage Oil; Combudoron; Dynexan; Lotio Pruni Comp cum Cupro; Muscle Rub; Wecesin; ***Spain:*** Amicon†; Encialina†; ***Switz.:*** Combudoron; Eubucal†; Euceta avec camomille et arnica; Fortacet; GU Eau†; Onguent aux herbes Keller; Perskindol Cool Arnica; Topaceta; Wecesin†; ***UK:*** Hansaplast Herbal Heat Plaster; Profelan; ***Venez.:*** Andantol Jalea; Biomicovo†; Gelsem.

Arsenic Trioxide *(USAN)*

Acidum Arsenicosum Anhydricum; Arseni Trioxydum; Arsenic; Arsenic Oxide; Arsénico, trióxido de; Arsenicum Album; Arsénieux, anhydride; Arsenii trioxidum; Arsenious Acid; Arsenous Oxide; White Arsenic. Diarsenic trioxide.

As_2O_3 = 197.8.
CAS — 1327-53-3 (arsenic trioxide); 7784-45-4 (arsenic triiodide).
ATC — L01XX27.
ATC Vet — QL01XX27.

Pharmacopoeias. In *Jpn.*
Eur. (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Arsenious Trioxide for Homoeopathic Preparations; Arsenii Trioxidum ad Praeparationes Homoeopathicae). A white or almost white powder. Practically insoluble to sparingly soluble in water; it dissolves in solutions of alkali hydroxides and carbonates.

Adverse Effects

The toxicity of arsenic compounds varies according to chemical composition, solubility, and valency. Inorganic arsenic compounds are much more toxic than organic compounds and elemental arsenic is the least toxic. Toxicity increases with increasing solubility, and trivalent (arsenite) compounds are more toxic than pentavalent (arsenate) compounds. Arsenic exerts its effects through a variety of pathophysiological mechanisms such as induction of oxidative stress and binding to sulphydryl groups in enzymes, and it has the potential to affect most of the major organ systems in the body; it also induces alteration in gene expression.

Acute poisoning. Estimates of lethal and toxic oral doses vary: the lethal dose of arsenic trioxide has been reported to be around 100 to 300 mg; a dose of 1 mg/kg of arsenic may be lethal in children; acute toxic doses of arsenic compounds have been reported to range from 1 mg to 10 g. Symptoms of acute poisoning occur within 30 minutes to several hours after ingestion and food delays the onset.

Early features of acute arsenic poisoning following ingestion involve the gastrointestinal tract with common symptoms of a metallic or garlic taste, a burning sensation in the mouth, dysphagia, abdominal pain, severe nausea, projectile vomiting, haemorrhagic gastritis, and profuse 'rice-water' diarrhoea leading to hypovolaemic shock; the breath may have an odour of garlic. In the absence of adequate treatment, death can occur within 24 hours of a severely toxic dose. Absorption of arsenic may produce multisystem toxicity days or weeks later, which could include cardiomyopathy, anaemia, leucopenia, skin disorders, acute respiratory distress syndrome, hepatitis, renal failure, encephalopathy, and peripheral polyneuropathy.

Arsenic compounds are irritant and corrosive when inhaled or in contact with the skin or eyes; acute systemic effects may occur after inhalation or skin contact.

Chronic poisoning. Arsenic is widely distributed in the environment: the smelting industry (non-ferrous metals) is a major industrial source of arsenic contamination in the soil, water, and air; mining residues and arsenical pesticides and wood preservatives also contribute to soil and water contamination. Seafood is a source of organic arsenic. Occupational exposure is a potential cause of chronic arsenic toxicity but in the general population, food and drinking water is usually the source of arsenic.

Chronic arsenic poisoning or occupational exposure typically produces varied skin disorders appearing over 1 to 10 years, particularly hyperkeratosis, especially affecting the palms and soles, and changes in skin pigmentation. Transverse white lines (Mee's lines) may appear in the nails several weeks after absorption. Gastrointestinal disturbances may occur, although are less likely with chronic exposure. Hypertension, cardiovascular disorders, and diabetes mellitus have been associated with chronic arsenic poisoning. Jaundice may occur as a result of hepatomegaly and portal hypertension may eventually develop. Encephalopathy and peripheral neuropathies may also occur. Arsenic is toxic to the bone marrow and produces a wide range of blood disorders including leucopenia and aplastic anaemia. Chronic exposure to arsenic has been associated with neoplasms of the skin, lungs, bladder, liver, and kidney. Chronic inhalation of arsenic salts may result in perforation of the nasal septum.

Adverse effects of therapeutic use. Reported adverse effects of arsenic trioxide therapy in patients with acute promyelocytic leukaemia (APL) include leucocytosis, neutropenia, raised liver enzyme values, gastrointestinal disturbances, fatigue, oedema, hyperglycaemia, hypokalaemia, dyspnoea, cough, skin rashes, pruritus, pyrexia, headaches, paraesthesia, and dizziness. Prolongation of the QT interval and other cardiac arrhythmias have occurred. The so-called 'leukocyte activation syndrome' ('APL differentiation syndrome') similar to one that develops with tretinoin therapy (see Retinoic Acid Syndrome, p.1618) has occurred in some patients. Sudden death has been reported in a few patients.

◊ References,[1-8] including discussion of epidemic toxicity due to arsenic-contaminated drinking water.[4,6-8]

1. Health and Safety Executive. Inorganic arsenic compounds. *Toxicity Review 16*. London: HMSO, 1986.
2. Shannon RL, Strayer DS. Arsenic-induced skin toxicity. *Hum Toxicol* 1989; **8:** 99–104.
3. Gebel T. Confounding variables in the environmental toxicology of arsenic. *Toxicology* 2000; **144:** 155–62.
4. WHO. Arsenic and arsenic compounds. *Environmental Health Criteria 224*. Geneva: WHO, 2001. Also available at: http://www.inchem.org/documents/ehc/ehc/ehc224.htm (accessed 11/04/08)
5. Borak J, Hosgood HD. Seafood arsenic: implications for human risk assessment. *Regul Toxicol Pharmacol* 2007; **47:** 204–12.
6. Flora SJ, *et al.* Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review. *J Environ Biol* 2007; **28** (2 suppl): 333–47.
7. Islam LN, *et al.* Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; **42:** 1807–14.
8. Guha Mazumder DN. Arsenic and non-malignant lung disease. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; **42:** 1859–67.

Adulteration. Arsenical compounds have reportedly been used to "cut" cocaine and symptoms of arsenic poisoning may occur in cocaine abusers.[1] Toxicity due to the presence of arsenic in various ethnic remedies has also been reported.[2-4]

1. Lombard J, *et al.* Arsenic intoxication in a cocaine abuser. *N Engl J Med* 1989; **320:** 869.
2. Kew J, *et al.* Arsenic and mercury intoxication due to Indian ethnic remedies. *BMJ* 1993; **306:** 506–7.
3. Ernst E, Thompson Coon J. Heavy metals in traditional Chinese medicines: a systematic review. *Clin Pharmacol Ther* 2001; **70:** 497–504.
4. Ernst E. Heavy metals in traditional Indian remedies. *Eur J Clin Pharmacol* 2002; **57:** 891–6.

Treatment of leukaemia. References[1-5] to and a review[6] of adverse effects in patients receiving arsenic trioxide for the treatment of acute promyelocytic leukaemia, including a report of sudden death occurring in 3 patients in a dose-finding study.[5]

1. Huang SY, *et al.* Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol* 1998; **103:** 1092–5.
2. Huang CH, *et al.* Complete atrioventricular block after arsenic trioxide treatment in an acute promyelocytic leukemic patient. *Pacing Clin Electrophysiol* 1999; **22:** 965–7.
3. Camacho LH, *et al.* Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol* 2000; **18:** 2620–5.
4. Ohnishi K, *et al.* Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med* 2000; **133:** 881–5.
5. Westervelt P, *et al.* Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood* 2001; **98:** 266–71.
6. Rust DM, Soignet SL. Risk/benefit profile of arsenic trioxide. *Oncologist* 2001; **6** (suppl 2): 29–32.

Treatment of Adverse Effects

Acute poisoning due to the ingestion of arsenic compounds should be treated by immediate gastric lavage if the patient presents within 1 hour and has not already vomited. Activated charcoal has been used to reduce absorption but is unlikely to be of benefit unless a significant amount of arsenic has been ingested. Intravenous replacement of fluids and electrolytes should be undertaken as necessary to correct dehydration and electrolyte imbalance; pressor agents may be required.

Chelation therapy should start immediately the cause of arsenic poisoning is suspected. The therapy of choice for acute poisoning is unithiol (p.1468) given intravenously in cases of gastrointestinal toxicity. Dimercaprol (p.1444) given intramuscularly is the second choice therapy if unithiol is unavailable. Oral therapy with unithiol or succimer (p.1466) should be substituted when gastrointestinal disturbances are no longer a problem. Oral penicillamine (p.1456) has also been used, including in conjunction with dimercaprol in severely ill patients, but its use in arsenic poisoning has been superseded by unithiol and succimer.

Patients suffering from chronic arsenic poisoning should be removed from the source of contamination as soon as possible. Initiation of oral chelation therapy with unithiol or succimer will depend on the patient's clinical condition and laboratory results of arsenic in urine, hair, and nails.

Chelation therapy should be continued until arsenic concentrations in urine have fallen to acceptable levels, although the therapeutic end-points of chelation therapy are poorly defined.

If renal failure occurs haemodialysis may be required.

Poisoning. The treatment of 3 patients who had ingested massive doses of arsenic has been described.[1,2] An adult survived after ingesting 54 g of arsenic trioxide:[1] in addition to standard supportive measures, attempts to remove the arsenic from his gastrointestinal tract included lavage, endoscopic removal, manual removal after gastrotomy, and cleansing enemas, plus chelation therapy. Of 2 siblings who ingested solubilised inorganic arsenic in a pesticide solution,[2] one child (aged 4 months) was estimated to have ingested 428 mg/kg arsenic and died despite aggressive attempts at removal of the arsenic, including chelation therapy, extracorporeal membrane oxygenation, exchange transfusion, and haemodialysis. The other child, aged 2 years, was estimated to have ingested 14.6 mg/kg arsenic, and survived following standard chelation therapy.

1. Dueñas-Laita A, *et al.* Acute arsenic poisoning. *Lancet* 2005; **365:** 1982.
2. Lai MW, *et al.* Acute arsenic poisoning in two siblings. *Pediatrics* 2005; **116:** 249–57.

Precautions

Patients receiving arsenic trioxide for acute promyelocytic leukaemia should have their ECG, blood sugar, electrolytes, blood count, and coagulation monitored at least twice weekly during induction and at least weekly during consolidation. More frequent monitoring may be needed in clinically unstable patients. Arsenic trioxide should be used with caution in renal impairment since renal excretion is the main route of elimination.

Pharmacokinetics

Water-soluble arsenic acids and their salts are more rapidly absorbed from the gastrointestinal tract than poorly soluble arsenicals such as arsenic trioxide. The absorption of arsenic trioxide is dependent upon the physical form of the compound and coarsely powdered material may be eliminated in the faeces before significant dissolution and absorption can occur. Soluble arsenic salts may also be absorbed following inhalation and through skin.

Once absorbed, arsenic is stored mainly in the liver, kidneys, heart, and lungs, with smaller amounts in the muscles and nervous tissue. About 2 weeks after ingestion, arsenic is deposited in the hair and nails and remains fixed to the keratin for years. It is also deposited in the bones and skin.

Although pentavalent arsenic is reduced to some degree *in vivo* to the more toxic trivalent form, trivalent arsenic is slowly and extensively oxidised to pentavalent arsenic. Both forms are methylated and excreted in the urine, mainly as dimethylarsinic acid, with smaller amounts appearing as monomethylarsonic acid and inorganic arsenic compounds. Although about 60% of a dose may be eliminated in the urine within 8 days, small amounts may continue to be excreted for several weeks after a single dose. Less significant amounts of arsenic are excreted in the faeces and sweat and via the lungs and skin. It is also distributed into breast milk and readily crosses the placenta.

Uses and Administration

Arsenic trioxide is used for induction of remission and consolidation in acute promyelocytic leukaemia (see below). It is given as an intravenous infusion over 1 to 2 hours to patients who are refractory to, or who have relapsed from, conventional therapy with retinoids and antineoplastics; if acute vasomotor reactions occur, the rate of infusion may be slowed and up to 4 hours may be taken. For induction, a dose of 150 micrograms/kg is given once daily until remission occurs; no more than 50 doses should be given (in the USA, the maximum number of induction doses allowed is 60). Treatment for consolidation must begin 3 to 4 weeks after completion of induction (or 3 to 6 weeks in the USA). The dose for consolidation is 150 micrograms/kg once daily given for 25 doses spread over a period of up to 5 weeks; the regimen suggested in the UK is to give the daily dose for 5 days each week followed by 2 days without dosing.

Arsenic trioxide is used in certain Asian herbal remedies. Arsenic anhydride has also been used.

Arsenic trioxide has been widely used as a constituent of weedkillers and sheepdips and as a rodenticide.

Arsenic trioxide and arsenic triiodide were formerly used internally as solutions or externally as ointments in the treatment of various skin diseases, but such use is generally no longer recommended. Externally, arsenic trioxide has a caustic action.

Homoeopathy. Arsenic trioxide has been used in homoeopathic medicines under the following names: Arsenious trioxide; Arsenici trioxidum; Arsenicum album; Acidum arsenicosum; Ars. alb.

Acute myeloid leukaemias. The use of arsenic trioxide in the management of patients with acute promyelocytic leukaemia (p.652) has been reviewed.[1-4] Remission was achieved in patients who had relapsed despite conventional therapy with retinoids and antineoplastics.[5,6] Arsenic trioxide is also being investigated for postremission therapy and in conjunction with transplantation.[4] Treatment was also successful in newly-diagnosed patients but severe liver toxicity occurred in some cases.[5]

For references to adverse effects occurring in patients receiving arsenic trioxide for acute promyelocytic leukaemia, see under Adverse Effects, above.

1. Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. *Oncologist* 2001; **6** (suppl 2): 11–6.
2. Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development Studies. *Oncologist* 2001; **6** (suppl 2): 22–8.
3. Slack JL, *et al.* Advances in the management of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide. *Oncologist* 2002; **7** (suppl 1): 1–13.
4. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol* 2005; **23:** 2396–2410.
5. Niu C, *et al.* Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999; **94:** 3315–24.
6. Soignet SL, *et al.* United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol* 2001; **19:** 3852–60.

Multiple myeloma. Arsenic trioxide is under investigation for the treatment of relapsed or refractory multiple myeloma (p.658).

References.

1. Munshi NC. Arsenic trioxide: an emerging therapy for multiple myeloma. *Oncologist* 2001; **6** (suppl 2): 17–21.
2. Munshi NC, *et al.* Clinical activity of arsenic trioxide for the treatment of multiple myeloma. *Leukemia* 2002; **16:** 1835–7.
3. Bahlis NJ, *et al.* Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res* 2002; **8:** 3658–68.
4. Berenson JR, Yeh HS. Arsenic compounds in the treatment of multiple myeloma: a new role for a historical remedy. *Clin Lymphoma Myeloma* 2006; **7:** 192–8.

Myelodysplastic syndromes. The use of arsenic trioxide for the treatment of myelodysplastic syndromes (p.654) is also under investigation.

References.

1. List A, *et al.* Opportunities for Trisenox (arsenic trioxide) in the treatment of myelodysplastic syndromes. *Leukemia* 2003; **17:** 1499–1507.
2. Vey N. Arsenic trioxide for the treatment of myelodysplastic syndromes. *Expert Opin Pharmacother* 2004; **5:** 613–21.
3. Schiller GJ, *et al.* Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. *J Clin Oncol* 2006; **24:** 2456–64.
4. Vey N, *et al.* Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. *J Clin Oncol* 2006; **24:** 2465–71.
5. Sekeres MA. New data with arsenic trioxide in leukemias and myelodysplastic syndromes. *Clin Lymphoma Myeloma* 2007; **8** (suppl 1): S7–S12.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Trisenox; ***Belg.:*** Trisenox; ***Cz.:*** Trisenox; ***Fr.:*** Trisenox; ***Gr.:*** Trisenox; ***Ital.:*** Trisenox; ***Jpn:*** Trisenox; ***Neth.:*** Trisenox; ***Spain:*** Trisenox; ***UK:*** Trisenox; ***USA:*** Trisenox.

Multi-ingredient: ***Ital.:*** Pasta Arsenicale.

Arsine

Arsenic Trihydride; Arsina; Hydrogen Arsenide.

AsH_3 = 77.95.

CAS — 7784-42-1.

Profile

Arsine is a heavy colourless gas with a garlic-like odour, which has no clinical uses but is an environmental or occupational hazard. It is highly toxic and causes severe haemolysis which may result in acute renal failure. It is potentially toxic below the odour threshold of 0.5 ppm and dangerously toxic after exposure to as little as 3 ppm; there may be a latent period of up to 24 hours following exposure before symptoms develop. Symptoms of arsine gas poisoning include generalised weakness, muscle cramps, thirst, headache, abdominal pain, nausea, vomiting, anorexia, jaundice, bronze skin coloration, haemolytic anaemia, haematuria, oliguria, and anuria. Pulmonary oedema, ECG abnormalities, and neurological disorders have also been reported. Treatment involves exchange transfusions and haemodialysis; dimercaprol and other chelating agents have been used but are of no value in the acute stage and do not prevent haemolysis.

◊ References.

1. Fowler BA, Weissberg JB. Arsine poisoning. *N Engl J Med* 1974; **291:** 1171–4.
2. Hesdorffer CS, *et al.* Arsine gas poisoning: the importance of exchange transfusions in severe cases. *Br J Ind Med* 1986; **43:** 353–5.
3. Rael LT, *et al.* The effects of sulfur, thiol, and thiol inhibitor compounds on arsine-induced toxicity in the human erythrocyte membrane. *Toxicol Sci* 2000; **55:** 468–77.

Asafetida

Asafétida; Asafoetida; Asant; Devil's Dung; Gum Asafetida.

Pharmacopoeias. In *Chin.*

Profile

Asafetida is an oleo-gum resin obtained from various species of *Ferula* (Umbelliferae). It has been used as a carminative and antispasmodic. It was also formerly used as an expectorant. It is used in cooking and is an ingredient of certain foods.

◊ References.

1. Kelly KJ, *et al.* Methemoglobinemia in an infant treated with the folk remedy glycerited asafoetida. *Pediatrics* 1984; **73:** 717–19.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Duiwelsdrekdruppels.

Multi-ingredient: ***India:*** Tummy Ease; ***S.Afr.:*** Entressdruppels HM; Stuidruppels; ***Thai.:*** Flatulence; ***UK:*** Daily Tension & Strain Relief.

Asarabacca

Ásaro europeo; Hazelwort; Rhizoma Asari; Wild Nard.

NOTE. Asarabacca has also been used as a common name for *Aristolochia clematitis* (see Aristolochia, p.2260).

Profile

Asarabacca is the dried rhizome, roots, and leaves of *Asarum europaeum* (Aristolochiaceae), which is an ingredient of snuffs. It is also an irritant emetic and has been used in rodent poisons. Asarabacca is an ingredient of preparations given for respiratory disorders.

Homoeopathy. Asarabacca has been used in homoeopathic medicines under the following names: Asarum; Asarum europaeum; Asar. eur.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Escarol†.

Asbestos

Amianto; Asbesto.

Profile

The name asbestos is applied to several naturally occurring and widely distributed fibrous mineral silicates of the serpentine and amphibole groups. They include amosite (brown asbestos), anthophyllite, chrysotile (white asbestos), and crocidolite (blue asbestos).

Asbestos has properties of heat resistance, insulation, and reinforcement and has been used extensively for heat or electrical insulation, fire protection, in friction materials, and in the construction industry in a wide variety of materials including cement, pipes, and tiles.

When inhaled, asbestos fibres can cause asbestosis (pulmonary fibrosis), lung cancer, and mesothelioma of the pleura and peritoneum. Mesothelioma has been reported in persons exposed to relatively small amounts of asbestos after an average latent period of 30 to 40 years. An association between occupational exposure and an increased incidence of gastrointestinal, laryngeal, and other cancers has also been reported. Some types of asbestos are more hazardous than others; crocidolite (a member of the amphibole group) is considered to be the most dangerous.

◊ References.

1. Landrigan PJ, *et al.* The hazards of chrysotile asbestos: a critical review. *Ind Health* 1999; **37:** 271–80.
2. Browne K, Gee JB. Asbestos exposure and laryngeal cancer. *Ann Occup Hyg* 2000; **44:** 239–50.
3. Bourdes V, *et al.* Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000; **16:** 411–7.
4. Bolton C, *et al.* Asbestos-related disease. *Hosp Med* 2002; **63:** 148–51.
5. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med* 2004; **170:** 691–715. Also available at: http://www.thoracic.org/sections/publications/statements/pages/eoh/asbestos.html (accessed 24/07/08)
6. Uibu T, *et al.* Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet* 2004; **363:** 1422–6.
7. Hessel PA, *et al.* Asbestos, asbestosis, and lung cancer: a critical assessment of the epidemiological evidence. *Thorax* 2005; **60:** 433–6.
8. O'Reilly KM, *et al.* Asbestos-related lung disease. *Am Fam Physician* 2007; **75:** 683–8.
9. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; **62** (suppl 2): ii1–ii19. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Malignant%20Mesothelioma/Guidelines/statement%20on%20malignant%20mesothelioma2007.pdf (accessed 24/07/08)

Ash

Askblad (ash leaf); Chinese Ash (*Fraxinus chinensis*); Common Ash; Esche; European Ash (*Fraxinus excelsior*); Fraxini folium (ash leaf); Frêne; Frêne, feuille de (ash leaf); Fresno; Jasanový list (ash leaf); Magas kőrisfa levél (ash leaf); Saarnenlehti (ash leaf); Uosių lapai (ash leaf).

Pharmacopoeias. *Chin.* includes Ash Bark (Cortex Fraxini, Qinpi). *Eur.* (see p.vii) includes Ash Leaf.

Ph. Eur. 6.2 (Ash Leaf; Fraxini Folium). The dried leaf of *Fraxinus excelsior* or *F. oxyphylla*. It contains a minimum of 2.5% of total hydroxycinnamic acid derivatives, expressed as chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated with reference to the dried drug. Protect from light.

Profile

The leaf of the European ash (*Fraxinus excelsior*) is included in herbal remedies for the treatment of rheumatic and joint disorders, urinary-tract disorders, and constipation. The leaf of *F. oxyphylla* is also used.

Ash bark has been used to reduce fever and as a tonic.

The bark of the Chinese ash, *F. chinensis* or related species is used in traditional Chinese medicine for disorders including acute dysentery and diarrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Phytodolor; ***Austria:*** Phytodolor; ***Cz.:*** Phytodolor; ***Fr.:*** Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane Contre la Constipation Passagere No 7; Mediflor Tisane No 4 Diuretique; Obeflorine; ***Ger.:*** Phytodolor; ***Spain:*** Natusor Artilane†.

Avena

Aven; Cultivated White Oats; Oatmeal; Oats.

Pharmacopoeias. *US* includes colloidal oatmeal.

USP 31 (Colloidal Oatmeal). The powder resulting from the grinding and further processing of whole oat grain. When dried at 120° for 4 hours it loses not more than 10% of its weight.

Profile

Avena is the grain of *Avena sativa* (Gramineae). It is used in herbal medicine and is reputed to have sedative activity.

A colloidal fraction extracted from avena is used in the preparation of emollient dermatological preparations.

Whether avenin, a protein present in oats, is harmful to patients with coeliac disease is controversial.

Homoeopathy. Avena has been used in homoeopathic medicines under the following names: Avena sativa; Avena e planta tota; Aven. sat.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dermopan; ***Austral.:*** DermaVeen Bath; DermaVeen Dry Skin; ***Canad.:*** Aveeno Preparations; Life Brand Soothing Bath Treatment; ***Fr.:*** Sensifluid; ***Hong Kong:*** DermaVeen; ***Israel:*** Nutrasoothe†; ***Ital.:*** Avalon; Aveeno Preparations; Emulave; Micaveen; ***NZ:*** DermaVeen; ***Port.:*** Aveeno Preparations; Emulave; ***Singapore:*** DermaVeen Bath; DermaVeen Dry Skin; DermaVeen Moisturising; DermaVeen Oatmeal Shampoo; DermaVeen Soap Free; ***Switz.:*** Avenaforce†; ***UK:*** Aveeno Preparations; ***USA:*** ActiBath.

Multi-ingredient: ***Arg.:*** Aveno; Cholesterol Reducing Plan†; Dermalibour; Epithelial†; Epitheliale A-Derma; Epitheliale AH; Exomega; Purasoft; Valeriana Oligoplex; ***Austral.:*** Avena Complex; Bioglan The Blue One; Calmo; DermaVeen Moisturising; DermaVeen Shower & Bath; Dong Quai Complex; Glycyrrhiza Complex†; Pacifenity†; Panax Complex†; ***Chile:*** Fucus Compuesto†; Homeofortin III†; ***Cz.:*** Valofyt Neo; ***Fr.:*** A-Derma Lait Solaire; Biocarde; Cytelium; Derm'Intim; Dermalibour; Epitheliale; Eryase; Exomega; Gonaxine; Menoxine; Septalibour†; ***Ger.:*** Requiesan; Vollmers praparierter gruner N; ***Hong Kong:*** Aderma Dermalibour†; Aderma Epitheliale†; Aderma Exomega†; Aderma Ultra High Protection†; ***Indon.:*** Menolia; ***Ital.:*** Acnaveen†; Altadrine; ***Mex.:*** Aveendix; Bonaven; Suavene; ***Pol.:*** Sedomix; ***Port.:*** D'Aveia†; Micaveen; ***S.Afr.:*** Avena Sativa Comp; ***Singapore:*** DermaVeen Acne†; DermaVeen Shower & Bath; ***Switz.:*** Mucilar Avena; The a l'avoine sauvage de Vollmer; ***UK:*** Avena Sativa Comp; Daily Overwork & Mental Fatigue Relief; Daily Tension & Strain Relief; ***USA:*** Aveeno Cleansing Bar; ***Venez.:*** Avensyl; Bonaven; Cytelium; Dagenol; Dermopan; Epitheliale AH; Fiberfull; Fibralax†.

Avocado

Aguacate; Ahuacate; Alligator Pear.

Авокадо; Аллигаторова Груша

Profile

Avocado, *Persea americana* (*P. persea*; *P. gratissima*) (Lauraceae), is included in herbal preparations mainly for respiratory-tract and hepatic disorders. Several parts of the plant, including the fruit and leaves, have been used for a variety of disorders.

The fruit is a dietary source of vitamin E, vitamin B_6, vitamin K, and iron.

Avocado oil is used topically as an emollient and as a neutral carrier for essential oils in aromatherapy. It may also be taken orally.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Piascledine.

Multi-ingredient: ***Arg.:*** Derrumal; ***Braz.:*** Abacateirol†; Lisian†; ***Chile:*** Codetol PM; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil; Paltomiel; Paltomiel Plus; Pulmosina; ***NZ:*** Mr Nits; ***Port.:*** Biureol.

Azadirachta

Margosa; Neem; Nim.

Profile

Azadirachta is the dried stem bark, root bark, and leaves of *Azadirachta indica* (*Melia azadirachta*) (Meliaceae), which has been used as a bitter. It is widely used in South Asia and has been reported to have insecticidal, antimalarial, and spermicidal properties. Azadirachta oil (neem oil, margosa oil) expressed from the seeds has also been used.

Adverse Effects. *EFFECTS ON THE SKIN.* Report of a patient who developed contact dermatitis of the face and ears 1 week after she started using neem oil for the treatment of alopecia areata.[1]

1. Reutemann P, Ehrlich A. Neem oil: an herbal therapy for alopecia causes dermatitis. *Dermatitis* 2008; **19:** E12–E15.

POISONING. Severe poisoning in Indian children given neem oil as a remedy for minor ailments.[1]

1. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome. *Lancet* 1981; **i:** 487–9.

Uses. *INSECT REPELLENT.* References.

1. Prakash A, *et al.* A preliminary field study on repellency of neem oil against Anopheles dirus (Diptera:Culicidae) in Assam. *J Commun Dis* 2000; **32**: 145–7.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Nimbola†; ***Malaysia:*** Moz-Away; ***UK:*** Nice 'n Clear.

Multi-ingredient: ***India:*** Flexi-muv; ***NZ:*** Mr Nits; ***UK:*** Dr Johnsons Nit & Lice; MozzyOff Cocktail.

Azapentacene Sulfonate Sodium

Disodium 5,12-dihydroquinoxalino[2,3-*b*]phenazine disulfonate.

$C_{18}H_{12}N_4O_6S_2,Na_2$ = 490.4.

CAS — 1790-56-3 (azapentacene disulfonic acid); 3863-80-7 (azapentacene disulfonate disodium).

Profile

Azapentacene sulfonate sodium has been used in the management of cataracts.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Quinax; ***Indon.:*** Pentacin; ***Mex.:*** Lutrax; ***Philipp.:*** Quinax; ***Pol.:*** Quinax; ***Rus.:*** Quinax (Квинакс); ***Singapore:*** Quinax; ***Thai.:*** Quinax.

Azintamide *(rINN)*

Azintamida; Azintamidum; Azinthiamide; ST-9067. 2-[(6-Chloro-3-pyridazinyl)thio]-*N*,*N*-diethylacetamide.

Азинтамид

$C_{10}H_{14}ClN_3OS$ = 259.8.

CAS — 1830-32-6.

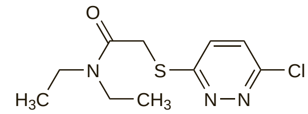

Profile

Azintamide has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Ora-Gallin purum; ***Port.:*** Colerin.

Multi-ingredient: ***Arg.:*** Biluen Enzimatico; ***Austria:*** Ora-Gallin; Ora-Gallin compositum; ***Port.:*** Colerin-F; ***Spain:*** Oragalin Espasmolitico.

Azovan Blue *(BAN)*

Azovanum Caeruleum; Azul de Evans; CI Direct Blue 53; Colour Index No. 23860; Evans Blue; T-1824. Tetrasodium 1,1′-diamino-8,8′-dihydroxy-7,7′-(2,2′-dimethylbiphenyl-4,4′-diylbisdiazo)di-(naphthalene-2,4-disulphonate); Tetrasodium 6,6′-[3,3′-dimethylbiphenyl-4,4′-diylbis(azo)]bis[4-amino-5-hydroxynaphthalene-1,3-disulphonate].

$C_{34}H_{24}N_6Na_4O_{14}S_4$ = 960.8.

CAS — 314-13-6.

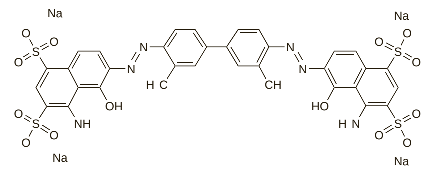

Profile

Azovan blue is a dye that has been given intravenously for the determination of blood volume; it is firmly bound to plasma proteins and is slow to leave the circulation. Some patients may experience staining of the skin.

Azulene

Atsuleeni; Azulen; Azuleno; Azulenum; Cyclopentacycloheptene.

$C_{10}H_8$ = 128.2.

CAS — 275-51-4.

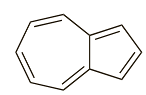

NOTE. The name 'Azulene' has also been used for a number of derivatives of azulene including azulene sodium sulfonate, chamazulene, guaiazulene, and sodium gualenate.

Profile

Azulene has been used in preparations for anorectal and skin disorders, and for oral hygiene. The sodium sulfonate salt has been used in preparations for mouth and throat disorders and for dyspepsia; sodium gualenate has also been used in gastrointestinal disorders.

Hypersensitivity. Allergic cheilitis occurred in a patient after long-term use of a toothpaste containing azulene.[1]

1. Balato N, *et al.* Allergic cheilitis to azulene. *Contact Dermatitis* 1985; **13:** 39–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Azunol†; ***Israel:*** Kamil Blue; ***Jpn:*** Azunol.

Multi-ingredient: ***Arg.:*** Domuderm; Ninderm; ***Austria:*** Emser Nasensalbe; ***Braz.:*** Eritrex A; Proctosan; ***Ger.:*** Emser Nasensalbe N†; ***Israel:*** Kamil Blue; ***Ital.:*** AZ 15.

Bactericidal Permeability Increasing Protein

Proteína bactericida incrementadora de la permeabilidad.

Opebacan *(BAN, USAN, rINN)*

Opébacan; Opebacán; Opebacanum; rBPI-21. 132-L-Alanine-1-193-bactericidal/permeability-increasing protein (human).

Опебакан

CAS — 206254-79-7.

Profile

Bactericidal permeability increasing protein is produced by human leucocytes and possesses both Gram-negative bactericidal and endotoxin-neutralising properties. It also inhibits angiogenesis. Several derivatives have been developed and are under investigation. Opebacan is a modified recombinant fragment of bactericidal permeability increasing protein that is under investigation for the treatment of Crohn's disease and meningococcal septicaemia. Other derivatives of bactericidal permeability increasing protein are under investigation for retinopathies and acne.

Bactericidal permeability increasing protein also possesses antifungal activity.

◊ References.

1. Giroir BP, *et al.* Preliminary evaluation of recombinant amino-terminal fragment of human bactericidal/permeability-increasing protein in children with severe meningococcal sepsis. *Lancet* 1997; **350:** 1439–43.
2. Levin M, *et al.* Recombinant bactericidal/permeability-increasing protein (rBPI) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. *Lancet* 2000; **356:** 961–7.
3. Levy O. A neutrophil-derived anti-infective molecule: bactericidal/permeability-increasing protein. *Antimicrob Agents Chemother* 2000; **44:** 2925–31.
4. van der Schaft DW, *et al.* The antiangiogenic properties of bactericidal/permeability-increasing protein (BPI). *Ann Med* 2002; **34:** 19–27.

Barium

Bario; Baryum.

Ba = 137.327.

CAS — 7440-39-3.

Description. Barium is a soft, highly reactive, silvery-white metal.

Adverse Effects and Treatment

All barium salts that are water- or acid-soluble are very toxic. The symptoms of barium poisoning arise from stimulation of all forms of muscle and include vomiting, excess salivation, colic, diarrhoea, slow or irregular pulse, hypertension, dysarthria, confusion, dizziness, paraesthesias, vertigo, muscle tremors, seizures, muscular paralysis, and respiratory or metabolic acidosis. Hypokalaemia is common. Renal impairment due to barium poisoning has been reported. Death from cardiac or respiratory failure may occur.

In acute poisoning, emptying the stomach by lavage is recommended if possible. Magnesium or sodium sulfate may be given to convert barium to insoluble barium sulfate. Hypokalaemia and metabolic acidosis should be corrected and ventilation assisted if necessary. Excretion may be increased by diuresis. Haemodialysis may be used in severe poisoning.

◊ Reports of barium intoxication.

1. Lewi Z, Bar-Khayim Y. Food poisoning from barium carbonate. *Lancet* 1964; **ii:** 342–3.
2. Diengott D, *et al.* Hypokalaemia in barium poisoning. *Lancet* 1964; **ii:** 343–4.
3. Gould DB, *et al.* Barium sulfide poisoning: some factors contributing to survival. *Arch Intern Med* 1973; **132:** 891–4.
4. Berning J. Hypokalaemia of barium poisoning. *Lancet* 1975; **i:** 110.
5. Wetherill SF, *et al.* Acute renal failure associated with barium chloride poisoning. *Ann Intern Med* 1981; **95:** 187–8.
6. Phelan DM, *et al.* Is hypokalaemia the cause of paralysis in barium poisoning? *BMJ* 1984; **289:** 882.
7. WHO. Barium. *Environmental Health Criteria 107.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc107.htm (accessed 24/07/08)
8. Sigue G, *et al.* From profound hypokalemia to life-threatening hyperkalemia: a case of barium sulfide poisoning. *Arch Intern Med* 2000; **160:** 548–51.
9. Wells JA, Wood KE. Acute barium poisoning treated with hemodialysis. *Am J Emerg Med* 2001; **19:** 175–7.
10. Jacobs IA, *et al.* Poisoning as a result of barium styphnate explosion. *Am J Ind Med* 2002; **41:** 285–8.
11. Bahlmann H, *et al.* Acute barium nitrate intoxication treated by hemodialysis. *Acta Anaesthesiol Scand* 2005; **49:** 110–12.

Uses and Administration

The soluble barium salts are not used in therapeutics but are widely used in industry. For the uses of barium chloride and barium hydroxide lime, see below. Barium sulfide has been used as a depilatory and barium carbonate was used as a rodenticide. The insoluble barium sulfate (p.1477) is used as a contrast medium.

Barium Chloride

Barii chloridum; Bario chloridas; Bariumklorid; Bariumkloridi; Baru chlorek; Baryum, chlorure de.

Бария Хлорид

Ba Cl_2 = 208.2.

CAS — 10361-37-2 (anhydrous barium chloride); 10326-27-9 (barium chloride dihydrate).

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Barium Chloride Dihydrate for Homoeopathic Preparations; Barii Chloridum Dihydricum ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble or practically insoluble in alcohol.

Profile

Barium chloride has several industrial uses including the manufacture of pigments and dyes, leather tanning, boiler detergents, water softeners, and aluminium refining.

Barium chloride is a soluble salt and therefore potentially toxic if ingested. Systemic toxicity arising from burns to skin from molten barium chloride has been reported. For the adverse effects and treatment of barium and barium salts, and reference to barium chloride poisoning, see under Barium, above.

Homoeopathy. Barium chloride has been used in homoeopathic medicines under the following names: Barium chloratum; Baryta muriatica; Bar. mur.

Barium Hydroxide Lime

Bario, cal con hidróxido de.

CAS — 17194-00-2 (anhydrous barium hydroxide); 12230-71-6 (barium hydroxide octahydrate).

Pharmacopoeias. In *US.*

USP 31 (Barium Hydroxide Lime). A mixture of barium hydroxide octahydrate and calcium hydroxide; it may also contain potassium hydroxide. White or greyish-white granules, or coloured with an indicator to show when absorptive power is exhausted. It absorbs not less than 19% of its weight of carbon dioxide. Store in airtight containers.

Profile

Barium hydroxide lime is used similarly to soda lime to absorb carbon dioxide in closed-circuit anaesthetic apparatus. Barium hydroxide lime contains a soluble form of barium and is toxic if swallowed. For the adverse effects and treatment of barium poisoning, see above.

Precautions. Excessive drying out of barium hydroxide lime in anaesthetic apparatus, which may occur if oxygen flow through the equipment is left on for prolonged periods, can lead to the production of carbon monoxide and the risk of inducing carboxyhaemoglobinaemia in patients undergoing anaesthesia using the apparatus.[1]

1. Committee on Safety of Medicines/Medicines Control Agency. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Basil

Albahaca; Basil Herb; Basilic; Basilici Herba; Basilienkraut; Sweet Basil.

Pharmacopoeias. In *Fr.*

Profile

The aerial parts of basil, *Ocimum basilicum* (Lamiaceae), are used in preparations for gastrointestinal disorders and as a diuretic. It is also used as a culinary herb.

Basil oil is an essential oil with antiseptic properties. It is used in perfumery and cosmetics and also in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Gastrol S†; Weleda-Rheumasalbe M; ***Ital.:*** Citrosystem; ***Rus.:*** Bronchitussin (Бронхитусен); Bronchocin (Бронхоцин).

Bay Oil

Laurel dulce, aceite esencial de; Myrcia Oil; Oleum Myrciae.

NOTE. Distinguish from Laurel Leaf Oil (Bay Leaf Oil) which is obtained from the leaves of *Laurus nobilis* (Lauraceae).

Profile

Bay oil is a yellow volatile oil that darkens rapidly on exposure to air and has a pleasant odour and spicy taste. It is obtained by distillation from the leaves of *Pimenta racemosa* (Myrtaceae) and probably other allied species. The principal use of bay oil is in the preparation of bay rum, which is used as a hair lotion and as an astringent application. Bay oils from both *P. racemosa* and *Laurus nobilis* are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Adiantine; Medicated Extract of Rosemary.

Bayberry

Árbol de la cera; Bayberry Bark; Candle Berry Bark; Myrica; Wax Myrtle Bark.

NOTE. Bayberry has also been used as a synonym for bog myrtle (see p.2267).

Profile

Bayberry, the root bark of *Myrica cerifera* (Myricaceae), is used in upper respiratory-tract disorders and as a gargle for sore throat. It has also been used in gastrointestinal disorders, to treat vaginal discharge, and topically on ulcers and sores.

Homoeopathy. Bayberry has been used in homoeopathic medicines under the following names: Myrica cerifera; Myri. cer.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** EP&C Essence; Peerless Composition Essence.

Bearberry

Bärentraubenblätter; Bearberry Leaves; Busserole; Busserole, feuille de; Gayuba; Liść mą; Medvědicový list; Medveszőlőlevél; Meškauogių lapai; Mjölonrisblad; Ptarmiganberry Leaves; Sianpuolukanlehti; Uvae ursi folium; Uva-Ursi.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Bearberry Leaf). The whole or cut dried leaves of the bearberry, *Arctostaphylos uva-ursi*. It contains not less than 7.0% of anhydrous arbutin, calculated with reference to the dried drug. Protect from light.

Profile

Bearberry has been reported to be a diuretic, bacteriostatic, and astringent and has been used in the treatment of urinary-tract disorders.

Homoeopathy. Bearberry has been used in homoeopathic medicines under the following names: Uva ursi; Uva ur.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Uromed; ***Cz.:*** List Medvedice Lecive†; Medvedice†; ***Ger.:*** Cystinol Akut; Uvalysat; ***Mex.:*** Uvavid†; ***Pol.:*** Uversan.

Multi-ingredient: ***Arg.:*** Ajolip; KLB6 Fruit Diet; Water Pill c Potasio†; ***Austral.:*** Althaea Complex; Bioglan Cranbiotic Super; Cranberry Complex; De Witts New Pills; Extralife Fluid-Care; Extralife PMS-Care; Extralife Uri-Care; Fluid Loss†; Herbal Diuretic Formula†; Medinat PMT-Eze†; Profluid†; Protemp†; Urinase†; Uva-Ursi Complex†; Uva-Ursi Plus†; ***Austria:*** Uropurat; ***Braz.:*** Composto Anticelulitico†; Emagrevit†; Lisian†; Pilulas De Witt's†; ***Canad.:*** Herbal Diuretic; ***Chile:*** Primacy Phyto +†; ***Cz.:*** Blasen- und Nierentee†; Species Urologicae Planta; Urcyston Planta; Urologicka Cajova Smes; ***Fr.:*** Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane No 4 Diuretique; Uromil; Urophytum†; ***Ger.:*** Arctuvan; Harntee STADA; Presselin Nieren-Blasen K 3†; Prostatin F†; ***Israel:*** Jungborn; ***Mex.:*** Noxivid; ***NZ:*** De Witts Pills†; ***Pol.:*** Nefrosept; Urofort; ***Port.:*** Asic†; Rilastil Dermo Solar; ***Rus.:*** Herbion Urological Drops (Гербион Урологические Капли); ***Spain:*** Genurat; Urisor†; ***Switz.:*** Demonatur Dragees pour les reins et la vessie; Dragees S pour les reins et la vessie; Strath Gouttes pour les reins et la vessie; Tisane pour les reins et la vessie; Urinex; ***UK:*** Antitis; Aqua Ban Herbal; Backache; Backache Relief; Cascade; De Witt's K & B Pills; Diuretabs; HealthAid Boldo-Plus; HRI Water Balance; Kas-Bah; Modern Herbals Water Retention; Prementaid; Sciargo; Tabritis; Uvacin; Watershed.

Belladonna

Belladon; Belladona; Belladone; Belladone, feuille de (belladonna leaf); Belladonnablad (belladonna leaf); Belladonnae folium (belladonna leaf); Belladonnanlehti (belladonna leaf); Deadly Nightshade; Liść pokrzyku (belladonna leaf); Nadragulyalevél (belladonna leaf); Rulíkový list (belladonna leaf); Šunvyšnių lapai (belladonna leaf); Tollkirschen.

ATC — A03BA04.

ATC Vet — QA03BA04.

Pharmacopoeias. *Eur.* (see p.vii) and *US* include a monograph for Belladonna Leaf. *Chin.* includes Belladonna Herb.

Eur. also includes Prepared Belladonna Leaf, Standardised Belladonna Leaf Tincture, and Standardised Belladonna Leaf Dry Extract.

Jpn includes only Belladonna Root.

Ph. Eur. 6.2 (Belladonna Leaf; Belladonnae Folium). It consists of the dried leaf, or dried leaf and flowering, and occasionally fruit-bearing, tops of *Atropa belladonna*. It contains not less than 0.30% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine together with smaller amounts of hyoscine. It has a slightly nauseous odour. Protect from light.

The BP 2008 directs that when Belladonna Herb, Belladonna Leaf, or Powdered Belladonna Herb is prescribed, Prepared Belladonna Herb shall be dispensed.

Ph. Eur. 6.2 (Belladonna, Prepared; Belladonnae Pulvis Normatus; Prepared Belladonna Herb BP 2008). It is belladonna leaf powder adjusted to an alkaloidal content of 0.28 to 0.32% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

USP 31 (Belladonna Leaf). It consists of the dried leaf and flowering or fruiting top of *Atropa belladonna* (Solanaceae). It yields not less than 0.35% of the alkaloids of belladonna leaf. When moistened, its odour is slight, somewhat tobacco-like. Avoid long exposure to direct sunlight. Protect powdered Belladonna Leaf from light.

Stability in mixtures. Atropine in belladonna preparations was unstable at alkaline pH and would quickly be degraded in mixtures with a pH above 7.[1] Such mixtures in the BPC 1973 included Aluminium Hydroxide and Belladonna Mixture, Cascara and Belladonna Mixture, and Magnesium Trisilicate and Belladonna Mixture.

1. *PSGB Lab Report P/71/9* 1971.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Belladonna has the actions of atropine (p.1219). Belladonna herb and its preparations have been used for their antimuscarinic actions in a wide range of conditions, including the relief of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm, but they are generally regarded as an outmoded form of treatment.

Belladonna liniments and plasters have been used as counter-irritants for the relief of pain but there is little evidence that they have a beneficial effect and adverse effects have occurred.

Homoeopathy. Belladonna has been used in homoeopathic medicines under the following names: Atropa bella-donna; Bell.

Preparations

Ph. Eur.: Belladonna Leaf Dry Extract, Standardised; Belladonna Leaf Tincture, Standardised;
USP 31: Belladonna Extract; Belladonna Extract Tablets; Belladonna Tincture.

Proprietary Preparations (details are given in Part 3)

Austral.: Atrobel†; ***Austria:*** Bellanorm; ***Chile:*** Felaxen†; ***Ger.:*** Belladonnysat Burger; Tremoforat†; ***Pol.:*** Bellapan; ***Venez.:*** Atroveran.

Multi-ingredient: ***Arg.:*** Antipasmol; Benitol; Cascara Sagrada Bouzen†; Cascara Sagrada Oligoplex; Dioxicolagol; Hepacur; Hepatodirectol; Opobyl; Passacanthine†; Trixol†; ***Austria:*** Asthma 23 D; Tampositorien mit Belladonna; ***Belg.:*** Colimax†; Eucalyptine Pholcodine Le Brun†; Gastrofilm†; Grains de Vals; Saintbois; ***Braz.:*** Acridin; Benzomel†; Bisuisan†; Broncol; Bronquidex; Brontoss; Calminex Atleta; Calminex H; Cessatosse†; Cystex; Dorveran†; Ductoveran; Etaverol†; Gastrobene; Gotas Nican†; Iodeto de Potassio†; Pilulas Ross; Regulador Xavier N-1†; Regulador Xavier N-2†; Revulsan†; Salicilato de Bismuto Composto†; Solvobil; Teutoss†; Tussifen†; Tussucalman†; Xarope de Caraguata†; Xarope Sao Joao†; ***Canad.:*** Bellergal; Cafergot-PB†; Rheumalan†; ***Chile:*** Bellergal Retardado†; Belupan†; Broncodeina; Cafergot-PB†; Ergobelan; Fenokomp 39; Fenolftaleina Compuesta†; Gotas Nican†; Gruben; Ramistos; ***Cz.:*** Bellaspon†; Capsicolle; Contraspan†; Homeovox; ***Denm.:*** Gynergen Comp; ***Fin.:*** Tannopon; ***Fr.:*** Gelumaline†; Humex†; Suppomaline; ***Ger.:*** Dalet Med Balsam†; ***Hung.:*** Artin†; Kefalgin; ***India:*** Emantid†; Migranil; Molzyme†; ***Indon.:*** Bellapheen; Spasmal; Spasminal; Stomadon; ***Israel:*** Laxative; Laxative Comp; ***Ital.:*** Antiemorroidali; Antispasmina Colica; Lassatina†; ***Jpn:*** Colgen Kowa Bien Soft Mini; ***Mex.:*** Chofabol; Parche Negro Belladona; Reudol; ***Pol.:*** Alax; Bellergot; Biospasmil; Cholitol; Hemorol; Kapsiplast; Spasticol; ***Port.:*** Anti-Gripe†; Antispasmina Colica; Anucet†; Balsamo Analgesico Sanitas; Migretil; Servetinal†; Vaporil; ***Rus.:*** Anusol (Анузол); Bethiol (Бетиол); Solutan (Солутан); ***S.Afr.:*** Bennetts Colic Mixture; Bolus Eucalypti Comp; Cafergot-PB†; ***Spain:*** Alofedina; Boldolaxin†; Broncovital†; Cafergot-PB†; Carminativo Juventus; Crislaxo; Digestovital†; Dolokey; Equidan†; Laxante Bescansa Aloico; Menabil Complex†; Sin Mareo x 4; Tanagel; ***Switz.:*** Bellagotin†; Bromocod N; Cafergot-PB; Demo Elixir pectoral N; Dragees S contre la toux†; Escotussin; Lysedil; Nican; Phol-Tux; Saintbois; ***Thai.:*** Belacid; Bellergal†; Benera; Delta Charcoal; Neuramizone; ***Turk.:*** Bellergal; ***UK:*** Opazimes; ***USA:*** B & O Supprettes No. 15A; B & O Supprettes No. 16A; Bel-Phen-Ergot S; Bellamine; Bellergal-S; Butibel; Cafatine-PB; Folergot-DF; Phenerbel-S; ***Venez.:*** Atrobel; Cloverin†; Codoformo†; Ervostal; Neo-Atropan†; Traveget.

Bendazol Hydrochloride *(rINNM)*

Bendazol, Chlorhydrate de; Bendazoli Hydrochloridum; Dibazol; Hidrocloruro de bendazol. 2-Benzylbenzimidazole hydrochloride.

Бендазола Гидрохлорид

$C_{14}H_{12}N_2$,HCl = 244.7.

CAS — 621-72-7 (bendazol); 1212-48-2 (bendazol hydrochloride).

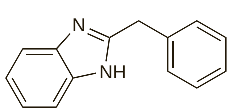

(bendazol)

Profile

Bendazol hydrochloride is used as an antispasmodic.

Bentiromide *(BAN, USAN, rINN)*

Bentiromid; Bentiromida; Bentiromidi; Bentiromidum; BTPABA; BT-PABA; E-2663; PFT; Ro-11-7891. 4-(N-Benzoyl-L-tyrosylamino)benzoic acid.

Бентиромид

$C_{23}H_{20}N_2O_5$ = 404.4.

CAS — 37106-97-1.

ATC — V04CK03.

ATC Vet — QV04CK03.

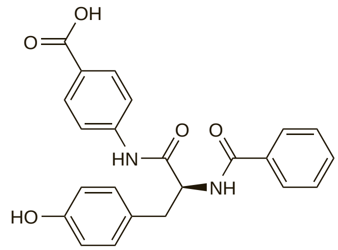

Profile

Bentiromide has been given orally as a noninvasive test of exocrine pancreatic function, the amount of *p*-aminobenzoic acid and its metabolites excreted in the urine being taken as a measure of the chymotrypsin-secreting activity of the pancreas. Headache and gastrointestinal disturbances have been reported in patients receiving bentiromide. The bentiromide test has given misleading results in patients with gastrointestinal, liver, or kidney disorders, or in patients receiving certain foods or drugs that are excreted as arylamines. Some of these drugs included benzocaine, chloramphenicol, lidocaine, paracetamol, procaine, procainamide, sulfonamides, and some diuretics.

◊ References.

1. Hoek FJ, *et al*. Improved specificity of the PABA test with p-aminosalicylic acid (PAS). *Gut* 1987; **28:** 468–73.
2. Puntis JWL, *et al*. Simplified oral pancreatic function test. *Arch Dis Child* 1988; **63:** 780–4.

Benzaldehyde

Benzaldehído; Benzaldehyd.

C_7H_6O = 106.1.

CAS — 100-52-7.

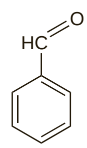

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2008 (Benzaldehyde). A clear colourless liquid with a characteristic odour of bitter almonds. Slightly soluble in water; miscible with alcohol and with ether. Store at a temperature not exceeding 15° in well-filled containers. Protect from light.

USNF 26 (Benzaldehyde). A colourless strongly refractive liquid with an odour resembling that of bitter almond oil and a burning aromatic taste. Slightly soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils. Store in well-filled, airtight containers. Protect from light.

Profile

Benzaldehyde is used as a flavour as an alternative to volatile bitter almond oil. It may cause contact dermatitis.

Preparations

USNF 26: Compound Benzaldehyde Elixir.

Benzyl Cinnamate

Benzylu cynamonian; Cinnamein. Phenylmethyl 3-phenyl-2-propenoate.

$C_{16}H_{14}O_2$ = 238.3.

CAS — 103-41-3.

Profile

Benzyl cinnamate is a constituent of various balsams and resins, including Peru balsam (p.2365), to which it has been used similarly. It is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Pulmex; Pulmex Baby; ***Braz.:*** Ozonyl; ***UK:*** Sudocrem.

Benzyl Isothiocyanate

Bencilo, isotiocinato de; Benzyl Mustard Oil; Benzylsenföl; Oleum Tropaeoli.

C_8H_7NS = 149.2.

CAS — 622-78-6.

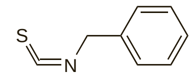

Pharmacopoeias. *Fr.* includes Capucine (*Tropaeolum majus*).

Profile

Benzyl isothiocyanate is an oil obtained from *Tropaeolum majus* (Capuchin cress; common nasturtium) (Tropaeolaceae) that has been given as an antibacterial.

Tropaeolum majus has been used in herbal medicine.

Homoeopathy. *Tropaeolum majus* has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Angocin Anti-Infekt N; Nephroselect M.

Benzyl Mandelate

Benzyl Phenylglycolate; Benzylin; Benzylis Mandelas; Benzylium Amygdalicum; Benzyl-DL-mandelate; Mandelsäurebenzylester.

Бензил Манделат

$C_{15}H_{14}O_3$ = 242.3.

CAS — 890-98-2.

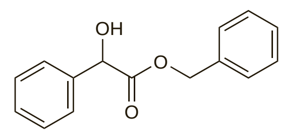

Profile

Benzyl mandelate has been used for its antispasmodic actions. It has also been included in preparations with analgesics in an attempt to increase the analgesic effect.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Spasmo Claim; Spasmocor; ***Ger.:*** Fohnetten N†; ***Switz.:*** Seranex sans codeine†; ***Turk.:*** Spalt.

Berberine

Berberina. 5,6-Dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium.

$C_{20}H_{18}NO_4$ = 336.4.

CAS — 2086-83-1 (berberine); 633-65-8 (berberine chloride); 633-66-9 (berberine sulfate).

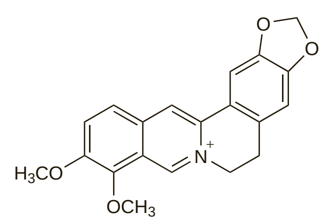

Pharmacopoeias. *Chin.* includes berberine chloride. *Jpn* includes berberine chloride hydrate and berberine tannate. *Viet.* includes berberine chloride dihydrate.

Profile

Berberine is a quaternary alkaloid present in hydrastis, in various species of *Berberis*, and in many other plants. It has been used as a bitter and as a flavour in food and alcoholic drinks. It possesses antimicrobial activity and has also been tried as various salts in a number of infections.

◊ References.

1. Khin-Maung-U, *et al*. Clinical trial of berberine in acute watery diarrhoea. *BMJ* 1985; **291**: 1601–5.
2. Rabbani GH, *et al*. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. *J Infect Dis* 1987; **155**: 979–84.
3. Vennerstrom JL, *et al*. Berberine derivatives as antileishmanial drugs. *Antimicrob Agents Chemother* 1990; **34**: 918–21.
4. Phillipson JD, Wright CW. Medicinal plants in tropical medicine: 1 Medicinal plants against protozoal diseases. *Trans R Soc Trop Med Hyg* 1991; **85**: 18–21.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Murine; ***Venez.:*** Irisol†.

Multi-ingredient: ***Braz.:*** Neo Quimica Colirio; Visazul; Visolon; ***Fr.:*** Sedacollyre; ***India:*** Emantid†.

Bergamot Oil

Bergamot Essence; Bergamota, aceite esencial de; Oleum Bergamottae.

Pharmacopoeias. In *Fr.* and *It.*

Profile

Bergamot oil is a greenish or brownish-yellow volatile oil with a characteristic fragrant odour and a bitter aromatic taste, obtained by expression from the fresh peel of fruit of *Citrus bergamia* (Rutaceae). Constituents include linalyl acetate and 5-methoxypsoralen (p.1607) and photosensitivity reactions have occurred following the topical use of preparations containing bergamot oil.

Bergamot oil is used in perfumery and as a flavour in Earl Grey tea. It has been included in some preparations for upper respiratory-tract disorders and hyperhidrosis. It is also used in aromatherapy.

◊ Muscle cramps have been reported[1] in a patient who drank up to 4 litres of 'Earl Grey' tea daily.

1. Finsterer J. Earl Grey tea intoxication. *Lancet* 2002; **359:** 1484.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Ephydrol; ***Ital.:*** Bergacid; ***Philipp.:*** Kamillosan M; ***Switz.:*** Perskindol Classic.

Betahistine *(BAN, rINN)*

Betahistiini; Betahistin; Betahistina; Bétahistine; Betahistinum. *N*-Methyl-2-(2-pyridyl)ethylamine.

Бетагистин

$C_8H_{12}N_2$ = 136.2.
CAS — 5638-76-6.
ATC — N07CA01.
ATC Vet — QN07CA01.

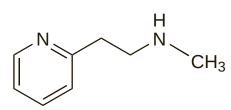

Betahistine Hydrochloride *(USAN, rINNM)*

Betahistiinidihydrokloridi; Betahistin Dihidroklorür; Betahistin-dihydrochlorid; Betahistindihydroklorid; Bétahistine, Chlorhydrate de; Bétahistine, dichlorhydrate de; Betahistine Dihydrochloride *(BANM)*; Betahistini dihydrochloridum; Betahistini Hydrochloridum; Betahistino dihidrochloridas; Hidrocloruro de betahistina; PT-9. *N*-Methyl-2-(2-pyridyl)ethylamine dihydrochloride.

Бетагистина Гидрохлорид

$C_8H_{12}N_2,2HCl$ = 209.1.
CAS — 5579-84-0.
ATC — N07CA01.
ATC Vet — QN07CA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Betahistine Dihydrochloride). A white to slightly yellow, very hygroscopic, powder. Very soluble in water; soluble in alcohol; practically insoluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

USP 31 (Betahistine Hydrochloride). A white to almost yellow, very hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in isopropyl alcohol. pH of a 10% solution in water is between 2.0 and 3.0.

Betahistine Mesilate *(BANM, rINNM)*

Betahistiinimesilaatti; Betahistin-dimesylát; Bétahistine, mésilate de; Betahistine Mesylate; Betahistini Dimesilas; Betahistini mesilas; Betahistinmesilat; Betahistino mesilatas; Betahisztin-mezilát; Mesilato de betahistina. *N*-Methyl-2-(2-pyridyl)ethylamine bismethanesulphonate.

Бетагистина Мезилат

$C_8H_{12}N_2,(CH_4O_3S)_2$ = 328.4.
CAS — 54856-23-4.
ATC — N07CA01.
ATC Vet — QN07CA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Betahistine Mesilate). A white or almost white, crystalline, very hygroscopic powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

Adverse Effects

Gastrointestinal disturbances, headache, skin rashes, and pruritus have been reported.

Precautions

Betahistine should not be given to patients with phaeochromocytoma. It should be given with care to patients with asthma, peptic ulcer disease, or a history of peptic ulcer disease.

Porphyria. Betahistine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Uses and Administration

Betahistine is an analogue of histamine and is claimed to improve the microcirculation of the labyrinth resulting in reduced endolymphatic pressure. It is used to reduce the symptoms of vertigo (p.565), tinnitus (p.1866), and hearing loss associated with Ménière's disease (p.564).

Betahistine is given orally as the hydrochloride or mesilate. The usual initial dose (of the hydrochloride) is 16 mg three times daily taken preferably with meals; maintenance doses are generally in the range of 24 to 48 mg daily. Betahistine mesilate is used in similar doses.

◊ Reviews

1. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. *CNS Drugs* 2001; **15:** 853–70.
2. James AL, Burton MJ. Betahistine for Ménière's disease or syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 30/05/06).

Preparations

BP 2008: Betahistine Dihydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Meniex; Microser; Ronistina; Travelmin; ***Austral.:*** Serc; ***Austria:*** Betaserc; ***Belg.:*** Betahistop; Betaserc; Docbetahi; ***Braz.:*** Betaserc; Labirin; ***Canad.:*** Serc; ***Chile:*** Microser; ***Cz.:*** Avertin; Betaserc; Microser; Polvertic; Zenostig; ***Denm.:*** Betaserc; ***Fin.:*** Betaserc; ***Fr.:*** Betaserc; Evolis†; Extovyl; Lectil; Serc; ***Ger.:*** Aequamen; Betavert; Melopat†; Vasomotal; ***Gr.:*** Antivom; Betaserc; Katabexin†; Ribrain; Riva; ***Hong Kong:*** Beta-Synto; Betaserc; Bymeniere; Meniero; Merislon; ***Hung.:*** Betagen; Betaserc; Elven; Microser; ***India:*** Betahist†; Vertin; ***Indon.:*** Betaserc; Merislon; Mertigo; Noverty; Vastigo; Vercure; Versilon; Vertex; ***Irl.:*** By-Vertin; Serc; Vertigon; ***Israel:*** Agiserc; Betistine; ***Ital.:*** Microser; Sincrover; Vertiserc; ***Jpn:*** Merislon; ***Malaysia:*** Alfinor; Betaserc; Merislon; ***Mex.:*** Serc; ***Neth.:*** Betaserc; ***NZ:*** Serc†; Vergo; ***Philipp.:*** Merislon; Serc; Vertilate; ***Pol.:*** Betaserc; Histimerck; Microser; ***Port.:*** Betaserc; ***Rus.:*** Betaserc (Бетасерк); Vestibo (Вестибо); ***S.Afr.:*** Serc; ***Singapore:*** Betaserc; Merislon; ***Spain:*** Fidium; Serc; ***Switz.:*** Betaserc; ***Thai.:*** Behistin; Betahist-B; Merislon; Merlin; Serc; ***Turk.:*** Betaserc; Vasoserc; ***UK:*** Serc; ***Venez.:*** Microser; Serc.

Betaine

Betaína; Glycine Betaine; Glycocoll Betaine; Lycine; Trimethylglycine. (Carboxymethyl)trimethylammonium hydroxide inner salt.

$C_5H_{11}NO_2$ = 117.1.
CAS — 107-43-7.
ATC — A16AA06.
ATC Vet — QA16AA06.

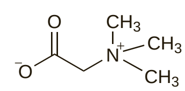

Betaine Hydrochloride

Betaiinihydrokloridi; Betaína, hidrocloruro de; Betainhydroklorid; Betaini Hydrochloridum; Trimethylglycine Hydrochloride. (Carboxymethyl)trimethylammonium hydroxide inner salt hydrochloride.

$C_5H_{11}NO_2,HCl$ = 153.6.
CAS — 590-46-5.
ATC — A09AB02.
ATC Vet — QA09AB02.

Pharmacopoeias. In *US.*

USP 31 (Betaine Hydrochloride). A white crystalline powder. Soluble in water and in alcohol; practically insoluble in chloroform and in ether. A 25% solution in water has a pH of 0.8 to 1.2.

Profile

Betaine is used as a methyl donor to remethylate homocysteine to methionine in the treatment of patients with homocystinuria (see Amino Acid Metabolic Disorders, p.1922). It is given orally in a usual dose of 3 g twice daily. Doses are adjusted according to plasma-homocysteine concentrations; up to 20 g daily has been required in some patients. In children under 3 years old, an initial dose of 100 mg/kg daily given in 2 divided doses may be used.

Severe cerebral oedema and hypermethioninaemia have been reported in a few patients, and it is recommended that plasma-methionine concentrations should be monitored at the start of betaine treatment and periodically thereafter. Patients being treated for cystathionine beta-synthase deficiency may pose particular problems because betaine may further raise their already elevated methionine concentrations increasing the risk of cerebral oedema.

Betaine has also been used as a variety of salts in preparations for liver and gastrointestinal disorders. The hydrochloride has been given as a source of hydrochloric acid in the treatment of hypochlorhydria.

Adverse effects. References.

1. Devlin AM, *et al.* Cerebral edema associated with betaine treatment in classical homocystinuria. *J Pediatr* 2004; **144:** 545–8.

Homocystinuria. References.

1. Smolin LA, *et al.* The use of betaine for the treatment of homocystinuria. *J Pediatr* 1981; **99:** 467–72.
2. Wilcken DEL, *et al.* Homocystinuria—the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983; **309:** 448–53.
3. Holme E, *et al.* Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency. *Arch Dis Child* 1989; **64:** 1061–4.
4. Anonymous. Betaine for homocystinuria. *Med Lett Drugs Ther* 1997; **39:** 12.

Liver disorders. Betaine has also been investigated for the treatment of nonalcoholic steatohepatitis.

References.

1. Miglio F, *et al.* Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis: a double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittelforschung* 2000; **50:** 722–7.
2. Abdelmalek MF, *et al.* Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *Am J Gastroenterol* 2001; **96:** 2711–7.

Pharmacokinetics. References.

1. Schwahn BC, *et al.* Pharmacokinetics of oral betaine in healthy subjects and patients with homocystinuria. *Br J Clin Pharmacol* 2003; **55:** 6–13.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Cystadane; ***Canad.:*** Cystadane; ***Cz.:*** Cystadane; ***Israel:*** Cystadan; ***Ital.:*** Somatyl; ***Port.:*** Cystadane; ***USA:*** Cystadane.

Multi-ingredient: ***Arg.:*** Eucos-L†; ***Austral.:*** Betaine Digestive Aid; Bioglan Digestive Zyme; Digestaid; ***Austria:*** CO Granulat; Oroacid; ***Belg.:*** Digestomen; ***Braz.:*** Aminotox†; Anekron; Betaliver†; Biohepax; Colachofra; Enterofigon; Epocler; Hepacitron†; Hepalin; Hepatobe†; Hepatox; Hormo Hepatico†; Metiocolin Composto; Necro B-6; Xantinon Complex; ***Cz.:*** Citrargine†; CO Granulat†; ***Fr.:*** Citrarginine†; Gastrobul†; Hepagrume; Nivabetol; Ornitaine; ***Ger.:*** CO Granulat†; Flacar; Unexym MD S; ***Gr.:*** Kloref; ***Hong Kong:*** Jetepar; ***Hung.:*** Betacid; Gastrobul†; ***Indon.:*** Naturica DFM; ***Israel:*** Betazim; ***Ital.:*** Citroepatina; Epabetina†; Ietepar†; ***Malaysia:*** Jetepar; ***Neth.:*** Gastrobul; ***Philipp.:*** Jetepar; ***S.Afr.:*** Kloref; ***Singapore:*** Jetepar; ***Switz.:*** Pepsi-Chlor†; ***UK:*** Enzyme Digest; Enzyme Plus; Kloref.

Bethanechol Chloride *(BAN)*

Betanecol, cloruro de; Betanekolikloridi; Betanekolklorid; Bethanecholi Chloridum; Carbamylmethylcholine Chloride. (2-Carbamoyloxypropyl)trimethylammonium chloride.

$C_7H_{17}ClN_2O_2$ = 196.7.
CAS — 674-38-4 (bethanechol); 590-63-6 (bethanechol chloride).
ATC — N07AB02.
ATC Vet — QN07AB02.

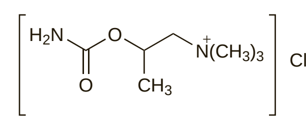

Pharmacopoeias. In *Jpn* and *US.*

USP 31 (Bethanechol Chloride). Colourless or white crystals, or white crystalline powder, usually having a slight, amine-like odour. It is hygroscopic and exhibits polymorphism. Freely soluble in water and in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 5.5 and 6.5. Store in airtight containers.

Stability. References to the stability of oral liquid preparations of bethanechol chloride prepared extemporaneously from tablets.

1. Schlatter JL, Saulnier J-L. Bethanechol chloride oral solutions: stability and use in infants. *Ann Pharmacother* 1997; **31:** 294–6.
2. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; **55:** 1804–9.

Sterilisation. The US manufacturers state that solutions of bethanechol chloride may be autoclaved at 120° for 20 minutes without discoloration or loss of potency.

Adverse Effects and Treatment

As described for choline esters under Acetylcholine Chloride, p.1877.

Precautions

As described for choline esters under Acetylcholine Chloride, p.1877.

Bethanechol should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse effects are liable to occur, calling for emergency use of atropine.

Autonomic neuropathy. Patients with autonomic neuropathy might be more susceptible to the adverse effects of bethanechol and they should be started on low-dosage regimens and observed closely for signs of toxicity.[1]

1. Caraco Y, *et al.* Bethanechol-induced cholinergic toxicity in diabetic neuropathy. *DICP Ann Pharmacother* 1990; **24:** 327–8.

Interactions

As for Neostigmine, p.632.

Pharmacokinetics

Bethanechol chloride is poorly absorbed from the gastrointestinal tract. It is not hydrolysed by cholinesterases. At standard doses bethanechol does not cross the blood-brain barrier.

Uses and Administration

Bethanechol chloride, a choline ester, is a quaternary ammonium parasympathomimetic that mainly exhibits the muscarinic actions of acetylcholine (p.1877). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine. Bethanechol chloride has little if any nicotinic activity and is used for its actions on the bladder and gastrointestinal tract. It has been used as an alternative to catheterisation in the treatment of urinary retention and has also been used for gastric atony and retention, abdominal distension following surgery, congenital megacolon, and gastro-oesophageal reflux disease.

Bethanechol chloride is given in usual doses of 5.15 mg subcutaneously or 10 to 50 mg orally, both up to 4 times daily, but dosage must be adjusted individually. Oral doses should be taken on an empty stomach. The effects usually occur within 5 to 15 minutes of a subcutaneous dose, or 30 to 90 minutes of an oral dose, and disappear within about 1 to 2 hours depending on the dose and route. However, large oral doses (300 to 400 mg) may produce effects for up to 6 hours. For a warning to avoid intravenous or intramuscular use, see under Precautions, above.

Decreased gastrointestinal motility. Parasympathomimetics such as bethanechol enhance gastric contractions and increase intestinal motility and form just one of many treatments that have been used in conditions associated with decreased gastrointestinal motility (p.1694).

Gastro-oesophageal reflux disease. Prokinetic drugs such as bethanechol have been tried in gastro-oesophageal reflux disease (p.1696).

References.

1. Thanick KD, *et al.* Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. *Ann Intern Med* 1980; **93:** 805–8.
2. Saco LS, *et al.* Double-blind controlled trial of bethanechol and antacid versus placebo and antacid in the treatment of erosive esophagitis. *Gastroenterology* 1982; **82:** 1369–73.
3. Thanick K, *et al.* Bethanechol or cimetidine in the treatment of symptomatic reflux esophagitis: a double-blind control study. *Arch Intern Med* 1982; **142:** 1479–81.
4. Strickland AD, Chang JHT. Results of treatment of gastroesophageal reflux with bethanechol. *J Pediatr* 1983; **103:** 311–15.

Stuttering. A double-blind placebo-controlled study[1] in 10 patients with stuttering (p.1001) on the whole failed to confirm an earlier report[2] of benefit using bethanechol although 2 patients who did respond elected to continue treatment after the study.

1. Kampman K, Brady JP. Bethanechol in the treatment of stuttering. *J Clin Psychopharmacol* 1993; **13:** 284–5.
2. Hays P. Bethanechol chloride in treatment of stuttering. *Lancet* 1987; **i:** 271.

Urinary incontinence and retention. Bethanechol is one of the parasympathomimetics that have been given to increase detrusor activity in patients with overflow incontinence, but there have been doubts about the effectiveness of such treatment (see p.2180). Bethanechol was also one of the parasympathomimetics used in the management of postoperative urinary retention but they have generally been superseded by catheterisation.

References.

1. Finkbeiner AE. Is bethanechol chloride clinically effective in promoting bladder emptying: a literature review. *J Urol (Baltimore)* 1985; **134:** 443–9.
2. Kemp B, *et al.* Prophylaxis and treatment of bladder dysfunction after Wertheim-Meigs operation: the positive effect of early postoperative detrusor stimulation using the cholinergic drug betanecholchloride. *Int Urogynecol J Pelvic Floor Dysfunct* 1997; **8:** 138–41.
3. Riedl CR, *et al.* Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. *J Urol (Baltimore)* 2000; **164:** 2108–11.

Preparations

USP 31: Bethanechol Chloride Injection; Bethanechol Chloride Oral Solution; Bethanechol Chloride Oral Suspension; Bethanechol Chloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Miotonachol; ***Austral.:*** Urocarb; ***Austria:*** Myocholine; ***Belg.:*** Myocholine; ***Braz.:*** Liberan; ***Canad.:*** Duvoid; Myotonachol†; ***Ger.:*** Myocholine; ***India:*** Urotone; Urotonine†; ***Israel:*** Urecholine†; ***Switz.:*** Myocholine; ***Thai.:*** Ucholine; Urecholine†; ***UK:*** Myotonine; ***USA:*** Myotonachol; Urecholine.

Bibrocathol *(rINN)*

Bibrocathin; Bibrocatholum; Bibrocatol; Bibrokatol; Bibrokatoli; Bismuth Tetrabrompyrocatechinate; Tetrabromopyrocatechol Bismuth. 4,5,6,7-Tetrabromo-2-hydroxy-1,3,2-benzodioxabismole.

Бибрократол

$C_6HBiBr_4O_3$ = 649.7.

CAS — 6915-57-7.

ATC — S01AX05.

ATC Vet — QS01AX05.

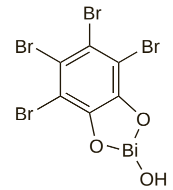

Profile

Bibrocathol is a bismuth-containing compound that has been applied topically in the treatment of eye disorders, wounds, and burns.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Noviform; Posiformin; ***Swed.:*** Noviform; ***Switz.:*** Noviform†.

Multi-ingredient: ***Ger.:*** Novifort†.

Bicyclol

4,4′-Dimethoxy-5,6,5′,6′-bis(methylene-dioxy)-2-hydroxymethyl-2′methoxycarbonyl biphenyl.

Бициклол

$C_{19}H_{18}O_9$ = 390.3.

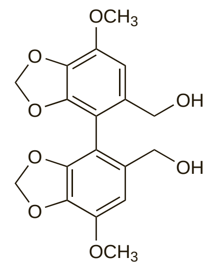

Profile

Bicyclol has been used as a hepatoprotectant in the management of hepatitis. It has been given orally in a dose of 25 or 50 mg three times daily for at least 6 months.

◊ References.

1. Liu Q, *et al.* A useful agent for chemoprevention of hepatocellular carcinoma? *Cancer Biol Ther* 2006; **5:** 1674–6.
2. Wu T, *et al.* Bicyclol for chronic hepatitis B. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/05/08).
3. Yang XY, *et al.* Bicyclol for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 01/05/08).

Bifendate

Dimethyl 7,7′-dimethoxy-(4,4′-bi-1,3-benzodioxole)-5,5′-dicarboxylate.

$C_{20}H_{18}O_{10}$ = 418.4.

CAS — 73536-69-3.

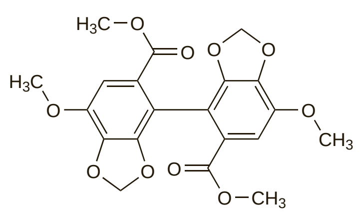

Pharmacopoeias. In *Chin.*

Profile

Bifendate is derived from schisandra (see p.2384). It is used in Chinese medicine for chronic hepatitis.

Bifendate has been reported to reduce blood concentrations of ciclosporin (see p.1826).

Bile Acids and Salts

Biliares, ácidos y sales.

CAS — 81-25-4 (cholic acid); 11006-55-6 (sodium tauroglycocholate); 361-09-1 (sodium cholate).

Pharmacopoeias. *Jpn* includes bear bile.

Profile

The principal primary bile acids, cholic acid and chenodeoxycholic acid (p.2280), are produced in the liver from cholesterol and are conjugated with glycine or taurine to give glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid, before being secreted into the bile where they are present as the sodium or potassium salts (bile salts). Secondary bile acids are formed in the colon by bacterial deconjugation and 7α-dehydroxylation of cholic acid and chenodeoxycholic acid, producing deoxycholic acid and lithocholic acid, respectively. Ursodeoxycholic acid (p.2408) is a minor bile acid in man although it is the principal bile acid in *bears*. Dehydrocholic acid (p.2292) is a semisynthetic bile acid.

The total body pool of bile salts is about 3 g, and most of the secreted bile salts are reabsorbed in a process of enterohepatic recycling, so that only a small fraction of this amount must be synthesised *de novo* each day.

Bile salts are strongly amphiphilic; with the aid of phospholipids they form micelles and emulsify cholesterol and other lipids in bile. Oral administration of chenodeoxycholic acid also reduces the synthesis of cholesterol in the liver, while ursodeoxycholic acid reduces biliary cholesterol secretion apparently by increasing conversion of cholesterol to other bile acids. The bile acids (but not the bile salts) also have a choleretic action, increasing the secretion of bile, when given by mouth.

Chenodeoxycholic acid and ursodeoxycholic acid are given by mouth in the management of cholesterol-rich gallstones (p.2409) in patients unsuited to, or unwilling to undergo, surgery. Ursodeoxycholic acid is also being studied in some liver disorders.

Preparations containing bile salts have been used to assist the emulsification of fats and absorption of fat-soluble vitamins in conditions in which there is a deficiency of bile in the gastrointestinal tract. Ox bile has also been used in the treatment of chronic constipation. Cholic acid is used for the treatment of inborn errors in primary bile synthesis.

Sodium cholate has been used for its spermicidal properties in barrier contraceptives.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Desicol; ***Ger.:*** Cholecysmon†; ***Mex.:*** Virulizin; ***Rus.:*** Festal (Фестал); ***S.Afr.:*** Bilron†; ***Venez.:*** Hepa-Desicol.

Multi-ingredient: ***Arg.:*** Bibol Leloup; Bil 13; Bilagol; Bilidren; Biliosan Compuesto†; Carbogasol Digestivo; Cascara Sagrada Bouzen†; Digesplen; Gastron Fuerte†; Hepatalgina; Nilflux; Opobyl; Pankreon Compuesto†; Veracolate; Zimerol; ***Austral.:*** Digestaid; Enzyme; Lexat†; ***Austria:*** Arca-Enzym; Buccalin; Combizym Compositum; Dragees Neunzehn†; Helopanzym; Intestinol; Silberne; ***Belg.:*** Buccaline; Grains de Vals; ***Braz.:*** B-Vesil; Dasc; Emagrex†; Figatil; Jurubileno†; Nutrizim†; ***Canad.:*** Bicholate; Herbalax†; Laxative†; Protectaid; ***Chile:*** Combizym Compositum; Combizym†; Flapex E; Hepabil; K.C.M.C; Katin; Onoton†; ***Cz.:*** Combizym Compositum; ***Fin.:*** Combizym Compositum; ***Fr.:*** Rectopanbiline; ***Ger.:*** Combizym Compositum†; ***Hong Kong:*** Bilsan; Buccaline†; Enzyplex; Hepatofalk; Protectaid; Topase†; ***Hung.:*** Combizym Compositum†; ***India:*** Digeplex-T; Dispeptal†; Farizym; Ipental†; Merckenzyme; Panolase†; Papytazyme; ***Indon.:*** Benozym; Berzymplex; Cotazym Forte; Enzymfort; Enzyplex; Eviprostat; Pankreon Comp; ***Israel:*** Encypalmed; ***Ital.:*** Solvobil; ***Malaysia:*** Enzyplex; ***Mex.:*** Dirfaben†; Dixiflen; Espaven Enzimatico; Ochozim; Onoton; Zimeton; ***NZ:*** Buccaline; ***Port.:*** Byl†; Caroid†; Combizym Compositum†; Fermetone Composto; ***Rus.:*** Ipental (Ипентал); ***Singapore:*** Enzyplex; ***Spain:*** Menabil Complex†; ***Swed.:*** Combizym Compositum; ***Switz.:*** Buccaline; Combizym Compositum; ***Thai.:*** Buccaline†; Combizym Compositum; Enzyplex; Papytazyme†; Veracolate; ***Turk.:*** Flaton; Intestinol; Multanzim; Pankrodigest; ***UK:*** Protectaid; ***USA:*** Digepepsin; ***Venez.:*** Combizym Forte; Nutizym Compositum; Pankreon Compositum; Stamyl.

Birch Leaf

Abedul, hojas de; Beržų lapai; Betulae folium; Birkenblätter; Björkblad; Bouleau; Bouleau, feuille de; Březový list; Koivunlehti; Liść brzozy; Nyírfalevél; Silver Birch Leaf.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Birch Leaf). The whole or fragmented dried leaves of *Betula pendula* and/or *B. pubescens* as well as hybrids of both species. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), with reference to the dried drug. Protect from light.

Profile

Birch leaf is used in herbal medicine, particularly for urinary-tract disorders. Birch leaf oil has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Urorenal†.

Multi-ingredient: ***Arg.:*** Sequals G; ***Austral.:*** Guaiacum Complex†; ***Austria:*** Blasentee St Severin; Heumann's Blasen- und Nierentee; Rheuma; Solubitrat; ***Cz.:*** Abfuhr-Heilkrautertee†; Blasen- und Nierentee†; Cajova Smes pri Redukcni Diete†; Fytokliman Planta; Nephrosal†; Reduktan; Senalax; Species Diureticae Planta†; Species Urologicae Planta; Stoffwechseltee N†; Urologicka Cajova Smes; ***Fr.:*** B.O.P.; Depuratum; Drainactil; Mediflor no 11 Draineur Renal et Digestif†; Mediflor Tisane Antirhumatismale No 2; ***Ger.:*** Antihypertonicum S; BioCyst; Canephron novo†; Cystinol N; Dr Wiemanns Rheumatonikum; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee; Harntee 400 N; Harntee STADA; Harntee-Steiner; Heumann Blasen- und Nierentee Solubitrat S†; Heumann Blasen- und Nierentee Solubitrat uro; Hevert-Blasen-Nieren-Tee N; Heweberberol-Tee; Nephro-Pasc†; Nephronorm med†; Nephropur tri†; Nephroselect M; Nephrubin-N†; Nierentee 2000†; Nieron Blasen- und Nieren-Tee VI†; Nieron-Tee N†; Presselin Nieren-Blasen K 3†; Renob Blasen- und Nierentee; Urodil phyto†; ***Ital.:*** Betulla (Specie Composta)†; Gramigna (Specie Composta)†; Lipaven; Listerine Fresh Citrus; Listerine Tartar Control; ***Pol.:*** Betasol; Diabetofort; Herbaton; Nefrobonisol; NeoFitolizyna; Urosept; ***Rus.:*** Herbion Urological

Drops (Гербион Урологические Капли); Sibectan (Сибектан); ***S.Afr.:*** Arnica Massage Oil; ***Spain:*** Diurinat; Genurat; Natusor Artilane†; Natusor High Blood Pressure†; Natusor Renal†; Renusor†; Tensiben†; ***Switz.:*** Dragees S pour les reins et la vessie; Nephrosolid; Phytomed Nephro†; Tisane Diuretique; Tisane pour le coeur et la circulation; Tisane pour les reins et la vessie; Urinex; ***UK:*** Massage Balm with Calendula.

Black Catechu

Cutch.

CAS — 8001-76-1.

NOTE. Distinguish from Catechu (p.2278).

Pharmacopoeias. In *Chin.*

Profile

Black catechu is an extract from *Acacia catechu* (Leguminosae) that is used as an astringent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Arowash.

Black Currant

Blackcurrant; Cassis; Grosella negra (casis); Rib. Nig.

Pharmacopoeias. *Br.* includes the fruit.
Fr. includes the leaf.

BP 2008 (Black Currant). The fresh ripe fruits of *Ribes nigrum* together with their pedicels and rachides. It has a strong, characteristic odour and a pleasantly acidic taste.

Profile

Black currant fruit is a source of vitamin C (p.1983). It is used to prepare black currant syrup, which is used as a nutritional supplement and as a flavour.

Black currant leaf is included in herbal preparations for urinary, musculoskeletal, and gastrointestinal disorders. Black currant is reported to contain bioflavonoids and is also included in preparations for vascular disorders. It has also been used as a diuretic in folk medicine.

Black currant seed oil (below) is used as a source of gamolenic acid (see p.2308).

Preparations

BP 2008: Black Currant Syrup.

Proprietary Preparations (details are given in Part 3)
Braz.: Tiliv.

Multi-ingredient: ***Austria:*** Amersan; ***Cz.:*** Amersan; ***Fr.:*** Arkophytum†; Drainactil; Hydracur; IgeE; Maxidraine†; Mediflor no 11 Draineur Renal et Digestif†; Mediflor Tisane Antirhumatismale No 2; Mincifit; Resource Rhubagil; Veinobiase; ***Ger.:*** Venobiase†; ***Ital.:*** Nepiros; Ribovir; ***Pol.:*** Melisal; Melissed; ***Spain:*** Exodren; Fitosvelt†.

Black Currant Seed Oil

Blackcurrant seed oil.

Profile

Black currant seed oil is derived from the seeds of *Ribes nigrum* (Grossulariaceae). It contains gamolenic acid (p.2308) and is used similarly to evening primrose oil (p.2302).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Proglan†.

Black Haw

American Sloe; Nanny Bush; Stag Bush.

Калина Сливолистная

Pharmacopoeias. In *Fr.*

Profile

The bark of black haw, *Viburnum prunifolium* (Adoxaceae) is claimed to have spasmolytic activity on uterine and other smooth muscle. It is included in herbal preparations for peripheral vascular disorders and menstrual disorders. The root bark is also used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Bromidrastina†; Gineburno†; ***Canad.:*** Thunas Tab for Menstrual Pain†; ***Fr.:*** Aphloine P; Climaxol; Jouvence de l'Abbe Soury; Phlebosedol†; ***Mex.:*** Reglosedyl†; ***Mon.:*** Fluon.

Black Nightshade

Hierba mora; Morelle Noire.

Profile

Black nightshade is the leaves and flowering tops of the black or garden nightshade, *Solanum nigrum* (Solanaceae). It contains solanine and its allied alkaloids. Black nightshade is distributed throughout most of the world as a weed of cultivation. It appears to have little medicinal value but was used in liniments, poultices, and decoctions for external application. Ingestion can cause typical antimuscarinic effects that may require treatment as described under Atropine, p.1220.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Pol.:*** Liv 52; ***Rus.:*** Dipana (Дипана); Liv 52 (Лив 52).

Blackthorn

Black Thorn; Épine noir; Prugnolo; Prundlier; Schlehe; Schwarzdorn; Sloe.

Тёрн; Терновник

Profile

The flowers of the blackthorn or sloe, *Prunus spinosa* (Rosaceae), are included in herbal preparations for constipation and urinary-tract disorders.

The fruit (sloes) are used for mild inflammation of oral and pharyngeal mucosa.

Prunus spinosa is used in homoeopathic medicine.

Culinary uses of sloes include preserves and as a flavour in alcoholic beverages.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Schlehen Elixir.

Multi-ingredient: ***Ger.:*** Nasenbalsam; Nasenbalsam fur Kinder; ***S.Afr.:*** Lotio Pruni Comp cum Cupro; ***Switz.:*** Wala Baume nasal; Wala Baume nasal doux.

Blue Cohosh

Caulófilo; Caulophyllum; Papoose Root; Squaw Root.

NOTE. Distinguish from Black Cohosh, which is Cimicifuga, p.2282.

Profile

Blue cohosh, the rhizome and roots of *Caulophyllum thalictroides* (Berberidaceae), has uterotonic and antirheumatic properties. It is used for menstrual and other gynaecological disorders.

Homoeopathy. Blue cohosh has been used in homoeopathic medicines under the following names: Caulophyllum; Caulophyllum thalictroides; Caulph.

Adverse effects. Acute myocardial infarction associated with profound congestive heart failure and shock has been reported in a newborn infant whose mother ingested blue cohosh to promote uterine contractions.[1]

1. Jones TK, Lawson BM. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr* 1998; **132:** 550–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Dyzco; Lifesystem Herbal Formula 4 Women's Formula†; Women's Formula Herbal Formula 3†.

Bog Myrtle

Sweet Gale.

NOTE. Bog myrtle has also been used as a common name for *Menyanthes trifoliata* (see Menyanthes, p.2340). Bayberry (see p.2263) has also been used as a synonym for bog myrtle.

Profile

The essential oil obtained from bog myrtle, *Myrica gale* (Myricaceae), has been used as an insect repellent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** MozzyOff Cocktail.

Boldo

Boldi folium; Boldo, feuille de; Boldo Folium; Boldo Leaves; Boldoblad; Boldólevél; Boldonlehti; Boldovníkový list; Kvapiųjų čilmedžių lapai; Liść boldo; Peumus.

CAS — 476-70-0 (boldine); 1398-22-7 (boldoglucin).

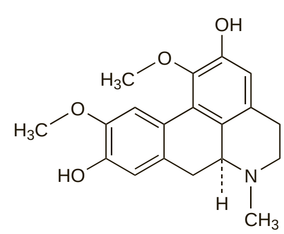

(boldine)

Pharmacopoeias. In *Eur.* (see p.vii), which also includes Boldo Leaf Dry Extract.
Fr. includes Boldine.

Ph. Eur. 6.2 (Boldo Leaf). The whole or fragmented dried leaf of *Peumus boldus*. It contains not more than 4% v/w of essential oil calculated with reference to the anhydrous drug. It contains not less than 0.1% of total alkaloids, expressed as boldine ($C_{19}H_{21}NO_4$ = 327.4), calculated with reference to the anhydrous drug. It has a characteristic odour especially when rubbed. Protect from light.

Profile

Boldo is employed in herbal medicine as a diuretic, for hepatobiliary disorders and for gastrointestinal disorders such as constipation. The alkaloid boldine is also used.

Homoeopathy. Boldo has been used in homoeopathic medicines under the following names: Peumus boldus.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Prinachol; ***Mex.:*** Bliz.

Multi-ingredient: ***Arg.:*** Bil 13; Biliosan Compuesto†; Boldina; Digenat; Dioxicolagol; Drenocol†; Hepacur; Hepatalgina; Hepatodirectol; Hepatotal Family†; Herbaccion Dig Fresh†; Herbaccion Digestivo†; Metiogen; Opobyl; Radicura; Trixol†; ***Austral.:*** Berberis Complex; Lexat†; ***Austria:*** St Bonifatius-Tee; ***Braz.:*** Alcafelol†; Alcaflor†; Bilifel†; Boldopeptan†; Boljuprima†; Colachofra; Dorveran†; Ductoveran; Emagrevit†; Eparema; Figatil; Gotas Digestivas; Hepatoregius†; Jurubileno†; Solvobil; ***Chile:*** Hepabil; Nature Complex Reduct-Te; Reduc-Te; Te Laxante; ***Cz.:*** The Salvat; ***Fr.:*** Bolcitol; Drainactil; Elixir Spark; Grains de Vals; Hepaclem; Hepax; Jecopeptol; Mediflor no 11 Draineur Renal et Digestif†; Mediflor Tisane Hepatique No 5; Mucinum a l'Extrait de Cascara; Opobyl; Oxyboldine; Petites Pilules Carters; Solution Stago Diluee; Tisane Hepatique de Hoerdt; Vegelax†; ***Ger.:*** Cynarzym N†; Gallemolan G†; Heumann Leber- und Gallentee Solu-Hepar S†; Heumann Verdauungstee Solu-Lipar; ***Hong Kong:*** Mucinum Cascara†; ***Ital.:*** Amaro Medicinale; Boldina He; Caramelle alle Erbe Digestive; Coladren; Colax; Confetti Lassativi CM; Critichol; Digelax†; Dis-Cinil Complex; Eparema; Eparema-Levul; Eupatol; Frangulina†; Hepatos; Hepatos B12; Magisbile†; Mepalax; Schias-Amaro Medicinale†; Solvobil; ***Mex.:*** Chofabol; Hepedren; Ifuchol; Peptochol†; ***Pol.:*** Boldaloin; Boldovera; ***Port.:*** Mucinum; ***Spain:*** Boldolaxin†; Menabil Complex†; Natusor Hepavesical†; Nico Hepatocyn; Odisor†; Opobyl; Resolutivo Regium; Solucion Schoum; ***Switz.:*** Boldocynara; Heparfelien; Stago N†; Tisane hepatique et biliaire; ***UK:*** Adios; Boldex; HealthAid Boldo-Plus; Weight Loss Aid; ***Venez.:*** Cynascool; Natrossil.

Boneset

Feverwort; Thoroughwort.

NOTE. Boneset has also been used as a common name for *Symphytum officinale* (see Comfrey, p.2286).

Profile

Boneset, the aerial parts of *Eupatorium perfoliatum* (Compositae), has diaphoretic and immunostimulant properties and has been used in the treatment of fever, influenza, the common cold, and other upper respiratory-tract disorders.

Homoeopathy. Boneset has been used in homoeopathic medicines under the following names: Eupatorium perfoliatum; Eup. perf.

◊ References.

1. Habtemariam S, Macpherson AM. Cytotoxicity and antibacterial activity of ethanol extract from leaves of a herbal drug, boneset (Eupatorium perfoliatum). *Phytother Res* 2000; **14:** 575–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Flavons; ***UK:*** Catarrh Mixture.

Borage

Borraja; Bourrache.

Pharmacopoeias. *Fr.* includes monographs for flowers and flowering tops.

Profile

The aerial parts of borage *Borago officinalis* (Boraginaceae), have been used in herbal medicine as a demulcent and emollient. However, it contains pyrrolizidine alkaloids that may be toxic and internal use is not recommended.

Borage seeds are the source of borage oil (below), which is used as a source of gamolenic acid.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Dexol.

Multi-ingredient: ***Chile:*** Celltech Gold; ***Ital.:*** Sclerovis H; ***Mex.:*** Aveendix; ***NZ:*** Mr Nits.

Borage Oil

Boraginis Oleum; Borago officinalis oleum; Borraja, aceite de; Bourrache, huile de; Brutnákový olej; Gurkörtolja; Purasruohoöljy; Starflower Oil; Vaistinių agurklių aliejus.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Borage (Starflower) Oil, Refined; Refined Borage Oil BP 2008). The fatty oil obtained from seeds of *Borago officinalis* by extraction and/or expression. It is then refined. A suitable antioxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.921. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers under an inert gas. Protect from light.

The BP 2008 gives Refined Starflower Oil as an approved synonym.

Profile

Borage oil is a source of essential fatty acids, principally gamolenic acid (p.2308). It is included in dietary supplements, often in combination with fish oils or other sources of omega-3 fatty acids (see p.1362).

Eczema. For the effects of borage oil on eczema, see under Gamolenic Acid, p.2308.

Rheumatoid arthritis. For the use of borage oil as a source of gamolenic acid for the management of rheumatoid arthritis, see under Gamolenic Acid, p.2309.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Tiliv L; ***Fr.:*** Gamatol†; Omegaline; ***Malaysia:*** Primolin GLA MAX†; ***Pol.:*** Biogal†; Neoglandyna; ***Switz.:*** Boracaps; ***UK:*** Floresse.

Multi-ingredient: ***Arg.:*** Ureadin Facial; ***Braz.:*** Borag; Gamaline-V; Livten Vit; ***Canad.:*** Primanol Borage Oil; ***Chile:*** Pruriced; Ureadin Facial; ***Fr.:*** Effadiane relipidantes; Elteans; Omegaline Solaire; Phytophanere; Phytosolaire; Pruriced; Topialyse; Topialyse Fluide; Topialyse Plus; ***Ital.:*** Topialyse; ***Pol.:*** Dehalid†; ***Port.:*** Antiestrias; Bioclin Sebo Care†; Hidratante VV; Nutraisdin; Rilastil Dermo Solar; Ureadin Facial; ***UK:*** Arheumacare.

Borax

Booraksi; Boraksas; Bórax; Disodium Tetraborate; Disodu tetraboran; E285; Natrii Tetraboras; Natrii Tetraboras Decahydricus; Natrium Boricum; Nátrium-tetraborát; Purified Borax; Sodium Biborate; Sodium Borate; Sodium Pyroborate; Sodium Tetraborate; Sodu tetraboran; Tetraboritan sodný dekahydrát.

$Na_2B_4O_7,10H_2O = 381.4.$

CAS — 1330-43-4 (anhydrous borax); 61028-24-8 (anhydrous borax); 1303-96-4 (borax decahydrate).

ATC — S01AX07.

ATC Vet — QS01AX07.

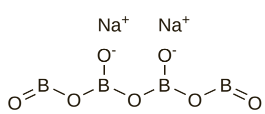

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Borax). Colourless crystals or crystalline masses, or white or almost white, crystalline powder. It effloresces. Soluble in water; very soluble in boiling water; freely soluble in glycerol. A 4% solution in water has a pH of 9.0 to 9.6.

The BP 2008 gives Sodium Borate and Sodium Tetraborate as official synonyms.

USNF 26 (Sodium Borate). Odourless transparent colourless crystals or white crystalline powder. Its solutions are alkaline to phenolphthalein. It effloresces in warm dry air. Soluble 1 in 16 of water, 1 in 1 of boiling water, and 1 in 1 of glycerol; insoluble in alcohol. Store in airtight containers.

Boric Acid

Acide borique; Ácido bórico; Acidum boricum; Boorihappo; Boracic Acid; Borato rūgštis; Borsäure; Bórsav; Borsyra; E284; Kwas borowy; Kyselina boritá; Orthoboric Acid; Sal Sedativa de Homberg.

$H_3BO_3 = 61.83.$

CAS — 10043-35-3.

ATC — S02AA03.

ATC Vet — QS02AA03.

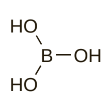

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Boric Acid). Colourless shiny plates greasy to the touch, or white or almost white crystals, or white or almost white crystalline powder. Soluble in water and in alcohol; freely soluble in boiling water and in glycerol (85%). A 3.3% solution in water has a pH of 3.8 to 4.8.

USNF 26 (Boric Acid). Odourless, colourless, somewhat pearly lustrous scales, or crystals, or white powder, slightly unctuous to the touch. Soluble 1 in 18 of water, 1 in 4 of boiling water, 1 in 18 of alcohol, 1 in 6 of boiling alcohol, and 1 in 4 of glycerol.

Stability. Boric acid volatilises in steam. It forms a complex with glycerol which is a stronger acid than boric acid.

Adverse Effects, Treatment, and Precautions

The main symptoms of acute boric acid poisoning are vomiting and diarrhoea, abdominal pain, an erythematous rash involving both skin and mucous membranes, followed by desquamation, and stimulation or depression of the CNS. There may be convulsions and hyperpyrexia. There may also be renal tubular damage. Abnormal liver function and jaundice have been reported rarely. Death, resulting from circulatory collapse and shock, may occur within several days.

The slow excretion of boric acid can lead to cumulative toxicity during repeated use. Symptoms of chronic intoxication include anorexia, gastrointestinal disturbances, debility, confusion, dermatitis, menstrual disorders, anaemia, convulsions, and alopecia.

Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid or after the application of boric acid powder to abraded skin.

In the UK the use of boric acid, borates, and tetraborates in cosmetics is controlled: the concentration is limited to 5% in talcs, to 0.1% in products for oral hygiene, and to 3% in other cosmetic products; tetraborates are limited to 18% in bath products. Such cosmetic products should not be used in children under 3 years of age; preparations used for oral hygiene should not be swallowed; and topical preparations containing greater than the equivalent of 1.5% of boric acid should not be applied to peeling or irritated skin.

Deaths have resulted from absorption after lavage of body cavities with solutions of boric acid, and this practice is no longer recommended.

Inhaled boric acid and borax are pulmonary irritants.

Treatment of poisoning is symptomatic. The stomach should be emptied if the patient presents within 1 hour of ingesting a large amount of boric acid; activated charcoal is not effective. Haemodialysis may be of value in severe cases.

◊ In Great Britain pharmacists have been advised not to sell boric acid as such for use as a dusting powder (see also above). Pharmacists have also been advised not to supply Borax Glycerin or Honey of Borax, even with an appropriate warning, because of the hazards associated with the use of these preparations in infants.

Pharmacokinetics

Boric acid is absorbed from the gastrointestinal tract, from damaged skin, from wounds, and from mucous membranes. It does not readily penetrate intact skin. About 50% of the amount absorbed is excreted in the urine within 24 hours and most of the remainder is excreted within 96 hours of ingestion.

Uses and Administration

Boric acid possesses weak bacteriostatic and fungistatic properties; it has generally been superseded by more effective and less toxic disinfectants. It is used as a pesticide against ants and cockroaches.

Boric acid is used, usually with borax, as a buffer and antimicrobial in eye drops, and was formerly used as a soluble lubricant in solution-tablets. It is also used as a preservative for urine samples. Boric acid and borax are not used internally.

In the UK, the use of boric acid in cosmetics and toiletries is restricted (see above).

Borax is used similarly to boric acid and has also been used externally as a mild astringent and as an emulsifier in creams. Preparations of borax in glycerol or in honey (Borax Glycerin; Honey of Borax) were formerly used as paints for the throat, tongue, and mouth, but should not be used because of the risk of toxicity.

Other salts of boric acid, including potassium and zinc salts, have been used.

Homoeopathy. Boric acid has been used in homoeopathic medicines under the following names: Acidum boricum; Acidum Boracicum; Ac. boric.

Borax has been used in homoeopathic medicines under the following names: Natrium tetraboracicum.

Antimicrobial activity. Evaluation of the antimicrobial activity of 1.22% borate buffer.[1]

1. Houlsby RD, *et al.* Antimicrobial activity of borate-buffered solutions. *Antimicrob Agents Chemother* 1986; **29:** 803–6.

Urine preservation. Boric acid in concentrations of about 2% may be a suitable preservative for urine samples in transit requiring bacteriological examination.[1,2] However, overnight storage of specimens preserved with boric acid may significantly alter culture results.[3]

1. Porter IA, Brodie J. Boric acid preservation of urine samples. *BMJ* 1969; **2:** 353–5.
2. Lum KT, Meers PD. Boric acid converts urine into an effective bacteriostatic transport medium. *J Infect* 1989; **18:** 51–8.
3. Gillespie T, *et al.* The effect of specimen processing delay on borate urine preservation. *J Clin Pathol* 1999; **52:** 95–8.

Vaginitis. Vaginal candidiasis (p.518) caused by *Candida glabrata* and other non-*albicans* species frequently responds to topical boric acid.[1,2] Satisfactory clinical and mycological responses to topical boric acid were reported in 2 patients with *Candida glabrata* vaginitis who had not responded to repeated courses of azole antifungals.[3] Treatment with boric acid effected clinical and mycological cure in 4 of 6 patients with refractory vaginitis caused by *C. krusei.*[4] Long-term boric acid treatment showed promise in the treatment and prevention of relapses of vulvovaginal candidiasis, but its efficacy ended when treatment was stopped.[5]

1. Sobel JD, Chaim W. Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997; **24:** 649–52.
2. Pappas PG, *et al.* Infectious Diseases Society of America. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; **38:** 161–89. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/380796 (accessed 24/07/08)
3. Redondo-Lopez V, *et al.* Torulopsis glabrata vaginitis: clinical aspects and susceptibility of antifungal agents. *Obstet Gynecol* 1990; **76:** 651–5.
4. Singh S, *et al.* Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. *Clin Infect Dis* 2002; **35:** 1066–70.
5. Guaschino S, *et al.* Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001; **184:** 598–602.

Preparations

BP 2008: Kaolin Poultice;
BPC 1973: Magenta Paint; Surgical Chlorinated Soda Solution;
USP 31: Rose Water Ointment.

Proprietary Preparations (details are given in Part 3)

Canad.: Eye Wash; ***Fr.:*** Dacryum; Hydralin; Optrex; ***Pol.:*** Aphtin; Borasol; Gemiderma; ***Turk.:*** Bibora; ***Venez.:*** Sax.

Multi-ingredient: ***Arg.:*** Anusol; Baby-Tex; Banoftal†; Bentophyto; Calcusan Bebe; Fungocop; Gineseptina†; Griseoplus; Hipoglos Cicatrizante; Hipoglos con Hidrocortisona; Histidanol†; Hyaluron; Irigal; Lagrimas de Santa Lucia†; Lemil; Parencias†; Perfungol†; Phylarm; Plusderm†; Prurisedan; Sebulex; ***Austral.:*** Gold Cross BOZ Ointment†; ***Austria:*** Coldophthal; Ophtaguttal; ***Belg.:*** Alcasol; Boradrine; Borostyrol; Ocal; Sedemol; Sulfa-Sedemol; ***Braz.:*** Adeglos†; Antiphlogistine†; Bluderm†; Cariderm†; Cloraseptic; Colpagex N; Dermosed†; Dinill; Gynax-N; Gyrol†; Higicler; Hipodermon; Lavolho†; Leucocida†; Lucretin; Malvona†; Oto-Biotic†; Oturga; Po Antisseptico; Polvilho Antisseptico†; Pomaderme; Senophile†; Talco Alivio†; Vagitrin-N; Visiplex; Visual†; ***Canad.:*** British Army Foot Powder†; Thunas Eye Drops†; ***Chile:*** Dexagin; Frescansol; Hipoglos; Homeoplasmina†; Perfungol; ***Cz.:*** Aphlox†; Herbadent; Ophtal; Ophthalmo-Septonex; Pityol; ***Fin.:*** Otiborin; ***Fr.:*** Borostyrol; Dacryoboraline; Dacryoserum; Dacudoses; Eau Precieuse; Homeoplasmine; Hydralin; Ophtaclair; Ophtalmine; Paps; Pate a l'Eau Roche-Posay†; Phylarm†; Sophtal; ***Ger.:*** Ensinger Schiller-Quelle Heilwasser†; ***Gr.:*** Oulogram; Septobore; Vaseline Borique; ***Hong Kong:*** Eye Glo Plus; Eye Glo Regular; Eye Wash; Gly Thymol; Hydralin; ***India:*** Andre; Feel Chill; New Eye Lotion; Proto-Boric; ***Indon.:*** Skintex; Verile; ***Irl.:*** Phytex; ***Israel:*** Gargol; ***Ital.:*** Aquasalina†; Bagno Oculare†; Bergacid; Boma; Fotofil; Fucsina Fenica; ***Mex.:*** Clarex; Forcremol; Hipoglos; Lav Ofteno; Lowila; Oftaboril; Tokolirio; ***Mon.:*** Boroclarine; ***Philipp.:*** Soothing Eye Wash; United Home Burn Ointment; ***Pol.:*** Acifungin; Afronis; Dentosept A; Gargarin; Hemorectal; Neo-Tormentil; Pigmentum Castellani; Tormentile Forte; Tormentiol; ***Rus.:*** Contraceptin T (Контрацептин Т); Lysoplac (Лизоплак); Osarbon (Осарбон); ***S.Afr.:*** Anugesic; Caloplast; Prep; Universal Eye Drops; Vagarsol; ***Singapore:*** Eye Mo†; New Daigaku†; ***Spain:*** Banoftal; Cloran Hemidex; Coliriocilina Adren Astr; Dermomycose Liquido; Fungusol; Lamnotyl†; Milrosina; Natusan; Oftalmol Ocular; Pomada Infantil Vera†; Topico Denticion Vera†; Vaselina Boricada; Zolina; ***Swed.:*** Antasten-Privin; ***Thai.:*** Eye Mo; Eye-Gene; Eye-Gene Soft; Mano; Opplin†; Opsil†; Optal; Optic; Quinradon-N; Visotone; ***Turk.:*** Antidot; Dermikolin; Undo-Talk; ***UK:*** Oxy Clean Facial Scrub; Phytex; ***USA:*** BFI; Castaderm; Collyrium for Fresh Eyes; Columbia Antiseptic Powder; Dri/Ear; Ear-Dry; Paladin; Phylorinol; RA Lotion; Saratoga; Seale's Lotion; Star-Otic; Trimo-San; ***Venez.:*** Ademina; Boramint†; Bori-Zinc†; Borocanfor; Borogin; Diodonato†; Hipoglos†; Micofeet; Polifix†; Sebaxyl.

Borneol

Baros Camphor; Bhimsaim Camphor; Borneo Camphor; Borneokampfer; Bornyl Alcohol; Camphol; Dryobalanops Camphor; Malayan Camphor; Sumatra Camphor. *endo*-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol.

Борнеол

$C_{10}H_{18}O = 154.2.$

CAS — 507-70-0.

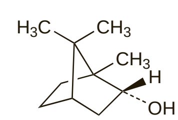

Pharmacopoeias. In *Chin* as synthetic borneol (Borneolum Syntheticum).

Profile

Borneol is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Rowachol; Rowatinex; ***Chile:*** Rowatinex; ***Cz.:*** Rowachol; Rowatinex; ***Fr.:*** Biolau; ***Ger.:*** Rowachol; Rowachol comp†; Rowachol-Digestiv; Rowatinex; ***Hong Kong:*** Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.:*** Rowachol; Rowatinex; ***Irl.:*** Rowachol; Rowatinex; ***Israel:*** Rowachol; Rowatinex; ***Malaysia:*** Rowachol; Rowatinex; ***Mex.:*** Cholex; ***Philipp.:*** Mentopas; Rowachol; Rowatinex; ***Pol.:*** Rowachol; Rowatinex; Terpichol; ***Singapore:*** New Daigaku†; ***Spain:*** Rowachol; Rowanefrin; ***Switz.:*** Rowachol; ***Thai.:*** Rowachol; Rowatinex; ***UK:*** Rowachol; ***Venez.:*** Rowachol; Rowatinex.

Bornyl Acetate *(USAN)*

Borneol Acetate; Bornilo, acetato de; Bornylu octan. 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate.

$C_{12}H_{20}O_2$ = 196.3.

CAS — 76-49-3.

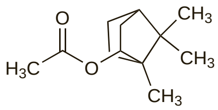

Profile

Bornyl acetate is a constituent of some essential oils. It has been used in aromatic preparations in the treatment of coughs, other respiratory-tract disorders, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Jabonacid; ***Chile:*** Expanden; ***Ger.:*** Lindofluid N.

Bromelains *(BAN, USAN, rINN)*

Bromelaiinit; Bromelaína; Bromelaina; Bromelainer; Bromelainy; Broméläïones; Bromelins; Plant Protease Concentrate.

Бромелаины

CAS — 9001-00-7.

ATC — B06AA11.

ATC Vet — QB06AA11.

Units

One Rorer unit of protease activity has been defined as that amount of enzyme which hydrolyses a standardised casein substrate at pH 7 and 25° so as to cause an increase in absorbance of 0.00001 per minute at 280 nm. FIP units are also defined in terms of rate of hydrolysis of bromelain activity of a casein preparation under standard conditions.

Activity has also been described in terms of milk-clotting units.

Adverse Effects

Bromelains may cause nausea, vomiting, and diarrhoea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.

Effects on the respiratory system. Bronchial asthma was experienced by 2 patients after exposure to bromelains.[1] Of 6 workers sensitised to papain, 5 showed positive skin tests to bromelains and 2 of them also showed immediate asthmatic reactions after bronchial challenge with bromelains.[2]

1. Galleguillos F, Rodriguez JC. Asthma caused by bromelin inhalation. *Clin Allergy* 1978; **8:** 21–4.
2. Baur X, Fruhmann G. Allergic reactions, including asthma, to the pineapple protease bromelain following occupational exposure. *Clin Allergy* 1979; **9:** 443–50.

Precautions

Bromelains should be given with care to patients with coagulation disorders or with severe hepatic or renal impairment.

Uses and Administration

Bromelains are a concentrate of proteolytic enzymes derived from the pineapple plant, *Ananas comosus* (*A. sativus*) (Bromeliaceae). They are used as an adjunct in the treatment of soft-tissue inflammation and oedema associated with trauma and surgery. Bromelains have also been given as an aid to digestion, and used in the treatment of partial deep dermal and full thickness burns.

◊ References.

1. Kane S, Goldberg MJ. Use of bromelain for mild ulcerative colitis. *Ann Intern Med* 2000; **132:** 680.
2. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci* 2001; **58:** 1234–45.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Ananase Forte; ***Fr.:*** Extranase; ***Ger.:*** dontisanin; Mucozym; Proteozym; Traumanase; ***Hong Kong:*** Internase; ***Ital.:*** Ananase; ***Port.:*** Ananase; ***Switz.:*** Traumanase; ***Venez.:*** Ananase.

Multi-ingredient: ***Arg.:*** Phlogenzym†; ***Austral.:*** Bio-Disc; Bioglan Discone†; Digestaid; Digestive Aid; Prost-1†; Prozyme†; ***Austria:*** Arca-Enzym; Phlogenzym; Rutozym; Traumazym; Wobenzym; ***Braz.:*** Bromelin†; Expectoral†; Monocetin; Nutrizim†; Plasil Enzimatico; Reumat†; Sintozima; ***Cz.:*** Phlogenzym; Wobenzym; ***Ger.:*** Enzym-Wied†; Mulsal N†; Phlogenzym; Wobenzym N; ***Hung.:*** Phlogenzym; ***India:*** Merckenzyme; ***Indon.:*** Benozym; Elsazym; ***Ital.:*** Algorex; Bres†; Flogofort; Flogovis IdroGel; Inflamase; Inflamase IdroGel; Signum; ***Jpn:*** Kimotab; ***Mex.:*** Phlogenzym; Plasil Enzimatico; Wobenzym; ***Port.:*** Bioregime SlimKit†; ***Rus.:*** Phlogenzym (Флогэнзим); Wobenzym (Вобэнзим); ***UK:*** BackOsamine; Enzyme Digest; ***Venez.:*** Enzima de Lechoza†; Nutizym Compositum; Phlogenzym; Wobenzym N.

Bromides

Bromuros.

ATC — N05CM11.

ATC Vet — QN05CM11.

Ammonium Bromide

Ammon. Brom.; Ammonii bromidum; Ammonium Bromatum; Ammonium, bromure d'; Ammoniumbromid; Ammónium-bromid; Ammoniumbromidi; Amonio bromidas; Amonowy bromek; Brometo de Amônio; Bromid amonný.

NH_4Br = 97.94.

CAS — 12124-97-9.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ammonium Bromide). A white or almost white, hygroscopic crystalline powder or colourless crystals. It becomes yellow when exposed to light or air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

Potassium Bromide

Brometo de Potássio; Bromid draselný; Bromure de Potassium; Kalii bromidum; Kalio bromidas; Kalium Bromatum; Kaliumbromid; Kálium-bromid; Kaliumbromidi; Pot. Brom.; Potassii Bromidum; Potassium, bromure de; Potasu bromek.

KBr = 119.0.

CAS — 7758-02-3.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Potassium Bromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

USP 31 (Potassium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

Sodium Bromide

Brometo de Sódio; Bromid sodný; Bromure de Sodium; Natrii bromidum; Natrio bromidas; Natrium Bromatum; Natriumbromid; Nátrium-bromid; Natriumbromidi; Sod. Brom.; Sodii Bromidum; Sodium, bromure de; Sodu bromek.

NaBr = 102.9.

CAS — 7647-15-6.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Sodium Bromide). A slightly hygroscopic, white or almost white, granular powder, or small, colourless, transparent, or opaque crystals. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 31 (Sodium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water; soluble in alcohol.

Adverse Effects and Precautions

During prolonged exposure bromide accumulation may occur giving rise to bromide intoxication or bromism. Symptoms include nausea and vomiting, anorexia, confusion, behavioural disturbances, slurred speech, memory impairment, drowsiness, irritability, ataxia, tremors, hallucinations, mania, delirium, psychoses, stupor, coma, and other manifestations of CNS depression. Skin rashes of various types may occur and toxic epidermal necrolysis has been reported. Death after acute poisoning appears to be rare as vomiting follows the ingestion of large doses.

There have been reports of neonatal bromide intoxication and growth defects associated with maternal bromide ingestion during pregnancy.

Breast feeding. The American Academy of Pediatrics[1] considers that intake of bromides is usually compatible with breast feeding, although rashes, weakness, and absence of crying have been reported in the infant following maternal intake. Exposure to bromides in photographic laboratories may also result in potential absorption and transfer into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://pediatrics.aappublications.org/cgi/content/full/108/3/776 (accessed 22/07/08)

Treatment of Adverse Effects

In acute poisoning, the stomach should be emptied (if emesis has not already occurred), and sodium chloride should be given by intravenous infusion. Glucose may also be used and furosemide may be given to aid diuresis.

In chronic poisoning, bromides are stopped and sodium chloride is given intravenously or orally with adequate amounts of fluid. Ammonium chloride has been given but is no longer recommended as it may precipitate metabolic acidosis. Diuretics are of value. In severe cases of bromide intoxication, or when the usual treatments cannot be used, haemodialysis may be of benefit.

Pharmacokinetics

Bromides are readily absorbed from the gastrointestinal tract. They displace chloride in extracellular body fluids and have a half-life in the body of about 12 days. They may be detected in the milk of nursing mothers and in the fetus.

Uses and Administration

Bromides depress the CNS. Calcium, potassium, and sodium bromide have been used as sedatives and anticonvulsants, but have generally been replaced by more effective, less toxic drugs. Ammonium and strontium bromide have been used similarly, as have bromoform and dilute hydrobromic acid. Bromides have also been used in multi-ingredient preparations for the treatment of coughs.

Homoeopathy. Hydrobromic acid and various bromides have been used in homoeopathic medicines under the following names:

- Hydrobromic acid: Hydr. ac.
- Ammonium bromide: Ammonium bromatum; Ammonium bromidum; Amm. brom.
- Arsenic bromide: Arsenicum bromatum; Ars. brom.
- Cadmium bromide: Cadmium bromatum; Cad. brom.
- Calcium bromide: Calcarea bromata; Calc. bro.
- Ferrous bromide: Ferrum bromatum; Fer. brom.
- Potassium bromide: Kalium bromatum; Kali bromatum; Kali. br.
- Sodium bromide: Natrum bromatum; Nat. brom.
- Radium bromide: Rad. br.
- Zinc bromide: Zincum bromatum; Zinc. br.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Dibro-Be Mono.

Multi-ingredient: ***Braz.:*** Alergitrat†; Bromidrastina†; Frenotosse; Gotas Nican†; Naquinto†; Xarope de Caraguata†; Xarope Peitoral de Ameixa Composto†; Xarope Sao Joao†; Xpe SPC†; ***Chile:*** Gotas Nican†; Gruben; Ramistos; ***Fr.:*** Galirene†; Sedatif Tiber; ***Indon.:*** Thymcal; ***Ital.:*** Fertomcidina-U; ***Pol.:*** Sal Ems Factitium; ***S.Afr.:*** Bronchicum†; ***Spain:*** Topico Denticion Vera†.

Bromine

Brom; Bromo; Bromum.

Br_2 = 159.808.

CAS — 7726-95-6.

Description. Bromine is a dark reddish-brown, heavy, mobile liquid that gives off intensely irritating brown fumes.

Adverse Effects

Bromine is intensely irritating and corrosive to eyes and mucous membranes; it may cause severe gastro-enteritis if swallowed. Contact with the skin can produce severe burns, and inhalation of the vapour causes violent irritation of the respiratory tract and pulmonary oedema.

Treatment of Adverse Effects

Milk or antacids should be given as soon as possible following ingestion of bromine. Gastric lavage is not recommended. If bromine vapour has been inhaled, oxygen should be administered and assisted ventilation may be necessary. The use of prophylactic corticosteroids for laryngeal and pulmonary oedema is controversial. Splashes on the skin and eyes should be immediately washed off; washing under running water should continue for at least 15 minutes.

Uses and Administration

Bromine is widely used in industry. It was formerly used, in the form of an adduct with a quaternary ammonium compound, in the treatment of plantar warts.

Bryonia

Bryony; Nueza.

Profile

Bryonia, the root of *Bryonia alba* or *B. dioica* (Cucurbitaceae), is an ingredient of preparations that have been used in respiratory-tract infections and inflammatory disorders. Toxic symptoms and fatalities have been reported after ingestion of the berries.

Homoeopathy. Bryonia has been used in homoeopathic medicines under the following names: Bryonia cretica; Bryonia e radice; Bry. cre.; Bryonia alba; Bry. alba.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Cough Relief†; Joint & Muscle Cream; ***Cz.:*** Homeovox; ***Fr.:*** Homeoplasmine; ***Mex.:*** Reudol.

Buchu

Barosma; Bucco; Buchú; Buchu Leaves; Diosma; Folia Bucco.

CAS — 68650-46-4 (buchu leaf oil).

Pharmacopoeias. In *Fr.*, which allows the dried leaves of *Agathosma betulina* (short or round buchu), *A. crenulata* (oval buchu), and *A. serratifolia* (long buchu).

Profile

Buchu, the dried leaves of 'short' or 'round' buchu, *Agathosma betulina* (*Barosma betulina*) (Rutaceae), is a weak diuretic and urinary antiseptic that has been used in multi-ingredient preparations for the treatment of urinary-tract disorders. Oval or long buchu, the leaves of *Agathosma crenulata* (*B. crenulata*), has also been used. The name long buchu is also applied to *A. serratifolia* (*B. serratifolia*). The leaves of *A. serratifolia* are also used medicinally.

Buchu leaf oil, usually from *A. betulina*, is occasionally promoted for use in aromatherapy, although it is rarely used in practice.

Homoeopathy. Buchu has been used in homoeopathic medicines under the following names: Barosma crenata; Bar. cren.; Barosma serratifolia; Bar. ser.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Water Pill c Potasio†; ***Austral.:*** Althaea Complex; Bioglan Cranbiotic Super; Cranberry Complex; De Witts New Pills; Extralife Uri-Care; Fluid Loss†; Medinat PMT-Eze†; PMS Support†; Serenoa Complex†; Urinase†; Uva-Ursi Complex†; ***Canad.:*** Herbal Diuretic; Herbal Laxative plus Yogurt; ***Cz.:*** Epilobin; ***Fr.:*** Urophytum†; ***NZ:*** De Witts Pills†; ***S.Afr.:*** Borstol Cough Remedy; Doans Backache Pills; Docrub; ***Switz.:*** Heparfelien; Urinex; ***UK:*** Antitis; Backache; Backache Relief; De Witt's K & B Pills; Diuretabs; HRI Water Balance; Kas-Bah; Skin Eruptions Mixture; Watershed.

Bucillamine *(rINN)*

Bucilamina; Bucillaminum; DE-019; SA-96; Tiobutarit. *N*-(2-Mercapto-2-methylpropionyl)-L-cysteine.

Буцилламин

$C_7H_{13}NO_3S_2$ = 223.3.
CAS — 65002-17-7.
ATC — M01CC02.
ATC Vet — QM01CC02.

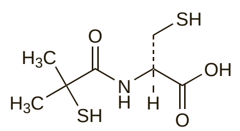

Pharmacopoeias. In *Jpn.*

Profile

Bucillamine is structurally related to penicillamine (p.1456) and is reported to be an immunomodulator that has been used in the treatment of rheumatoid arthritis.

Adverse effects. Bucillamine has been implicated in the development of skin,[1] kidney,[2,3] and lung disorders.[4]

1. Ogata K, *et al.* Drug-induced pemphigus foliaceus with features of pemphigus vulgaris. *Br J Dermatol* 2001; **144:** 421–2.
2. Nagahama K, *et al.* Bucillamine induces membranous glomerulonephritis. *Am J Kidney Dis* 2002; **39:** 706–12.
3. Hoshino J, *et al.* Outcome and treatment of bucillamine-induced nephropathy. *Nephron Clin Pract* 2006; **104:** c15–c19.
4. Saito Y, *et al.* A case of bucillamine-induced interstitial pneumonia with positive lymphocyte stimulation test for bucillamine using bronchoalveolar lavage lymphocytes. *Intern Med* 2007; **46:** 1739–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rimatil.

Buckwheat

Blé Noir; Boekweit; Boveteört (aerial parts); Buchweizen; Fagopyri Herba (aerial parts); Grano Turco; Grikių žolė (aerial parts); Pohanková nať (aerial parts); Sarrasin; Sarrasin Commun; Viljatatar (aerial parts); Ziele gryki.

Гречиха Обыкновенная

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Buckwheat Herb; Fagopyri Herba). The whole or cut aerial parts of *Fagopyrum esculentum*. It contains a minimum 4.0% of rutoside, calculated with reference to the dried drug. Protect from light.

Profile

The aerial parts of buckwheat, *Fagopyrum esculentum* (Polygonaceae), are included in herbal preparations for chronic venous insufficiency.

Buckwheat contains flavonoids and is a source of rutoside (see p.2305).

Homoeopathy. Buckwheat has been used in homoeopathic medicines under the following names: Fagopyrum; Fagopyrum esculentum Fago. esc.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Fagorutin Buchweizen.

Multi-ingredient: ***Fr.:*** Flebior; ***Ger.:*** Fagorutin Buchweizen; ***Pol.:*** Betasol; Fitoven.

Bucladesine Sodium *(rINNM)*

Bucladesina sódica; Bucladésine Sodique; DBcAMP (bucladesine); Dibutyryl Cyclic AMP Sodium; DT-5621 (bucladesine); Natrii Bucladesinum. *N*-(9-β-D-Ribofuranosyl-9*H*-purin-6-yl)butyramide cyclic 3′,5′-(hydrogen phosphate) 2′-butyrate sodium.

Натрий Букладезин

$C_{18}H_{24}N_5O_8PNa$ = 492.4.
CAS — 362-74-3 (bucladesine); 16980-89-5 (bucladesine sodium).
ATC — C01CE04.
ATC Vet — QC01CE04.

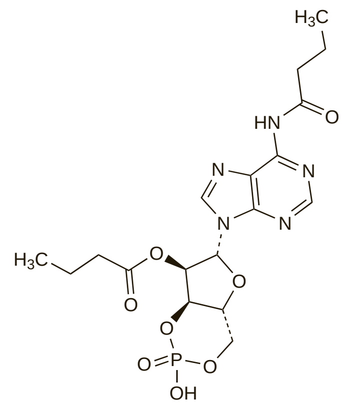

(bucladesine)

Profile

Bucladesine sodium has been reported to have cardiotonic properties when given intravenously. It has been applied topically for the treatment of bedsores.

Bufotenine

Bufotenin; Bufotenina; *NN*-Dimethylserotonin; 5-Hydroxy-*NN*-dimethyltryptamine; Mappine. 3-(2-Dimethylaminoethyl)indol-5-ol.

Буфотенин

$C_{12}H_{16}N_2O$ = 204.3.
CAS — 487-93-4.

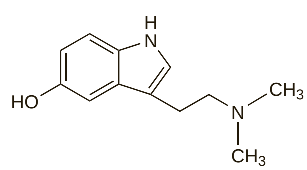

Profile

Bufotenine is an indole alkaloid obtained from the seeds and leaves of *Piptadenia peregrina*, from which the hallucinogenic snuff cohoba is prepared, and *P. macrocarpa* (Mimosaceae). It was first isolated from the skin glands of toads (*Bufo* spp.) and has also been isolated from species of *Amanita* (Agaricaceae). Bufotenine has serotonergic activity and is reported to have hallucinogenic properties. It has no therapeutic use.

Buphenine Hydrochloride *(BANM, rINNM)* ⊗

Buphénine, Chlorhydrate de; Buphenini Hydrochloridum; Hidrocloruro de bufenina; Nylidrin Hydrochloride; Nylidrinium Chloride. 1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)-propan-1-ol hydrochloride.

Буфенина Гидрохлорид

$C_{19}H_{25}NO_2,HCl$ = 335.9.
CAS — 447-41-6 (buphenine); 849-55-8 (buphenine hydrochloride).
ATC — C04AA02; G02CA02.
ATC Vet — QC04AA02; QG02CA02.

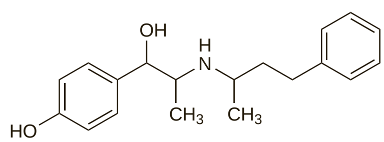

(buphenine)

Adverse Effects and Precautions

As for Sympathomimetics, p.1407; buphenine has mainly beta-agonist effects.

Uses and Administration

Buphenine produces peripheral vasodilatation through beta-adrenoceptor stimulation and a direct action on the arteries and arterioles of the skeletal muscles.

Buphenine has been used in the treatment of peripheral vascular and cerebrovascular disease. It has also been used in preparations for rhinitis and nasal congestion. Doses of buphenine hydrochloride in the range of 3 to 12 mg three or four times daily have been given orally.

An intravenous infusion of buphenine hydrochloride has been used to arrest premature labour. It has also been given orally as a prophylactic tocolytic agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Dilatol; ***Canad.:*** Arlidin; ***India:*** Arlidin; ***Mex.:*** Arlidin; Nilken; ***Switz.:*** Tocodrine†.

Multi-ingredient: ***Austria:*** Arbid; Dilaescol; Dilatol-Chinin; Opino; Tropoderm; ***Fr.:*** Ophtadil†; Phlebogel; ***Ger.:*** Apoplectal N†; opino N spezial†; ***Gr.:*** Opino-jel; ***Indon.:*** Opino; ***Mex.:*** Flumil; ***Switz.:*** Arbid; Visaline.

Burnet

Garden Burnet; Greater Burnet; Pimpinela mayor; Sanguisorba.

NOTE. Distinguish from Burnet Saxifrage (below).

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Sanguisorba Root). The whole or fragmented, dried underground parts of *Sanguisorba officinalis* without rootlets. The adventitious roots are about 5 to 25 cm long and up to 2 cm in diameter. They contain a minimum 5.0% of tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1) calculated with reference to the dried drug.

Profile

Burnet, the aerial parts and roots of *Sanguisorba officinalis* (*Poterium officinalis*) (Rosaceae), has antihaemorrhagic and astringent properties. It has been used internally to treat menorrhagia and gastrointestinal disorders and is also used topically for eczema, burns, and other skin disorders.

Burnet is also used as an animal fodder and salad vegetable, and as an ingredient in beer making.

Homoeopathy. Burnet has been used in homoeopathic medicines under the following names: Sanguisorba officinalis.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Swiss Herb Cough Drops; ***Cz.:*** Tormentan; ***Indon.:*** Ambeven.

Burnet Saxifrage

Bibernell; Boucage; Pimpinella.

NOTE. Distinguish from Burnet (above).

Profile

The root of burnet saxifrage, *Pimpinella saxifraga* (Apiaceae), or greater burnet saxifrage, *P. major* is included in herbal preparations for coughs and minor upper respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Expectosan Hierbas y Miel; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Bronchicum Elixir†; Bronchicum Hustensirup†; ***Ger.:*** Bronchicum Elixir N†; Majocarmin forte†; ***Neth.:*** Bronchicum; ***Pol.:*** Bronchicum Eliksir; ***S.Afr.:*** Bronchicough†; Bronchicum†; ***Spain:*** Himelan†; Natusor Aerofane†; Natusor Astringel†; Regamint†; ***Switz.:*** Kernosan Elixir; Kernosan Heidelberger Poudre; Makaphyt Gouttes antitussives.

Butcher's Broom

Box Holly; Dygiųjų pelžiedžių šakniastiebiai; Kłącze ruszczyka; Listnatcový kořen; Petit houx; Rautamyrtinjuurakko; Rusci Radix; Rusci rhizoma; Stickmyrtenrot.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Butcher's Broom; Rusci Rhizoma). The dried, whole or fragmented underground parts of *Ruscus aculeatus*. It contains a minimum of 1.0% of total sapogenins, expressed as ruscogenins (mixture of neoruscogenin ($C_{27}H_{40}O_4$ = 428.6) and ruscogenin), calculated with reference to the dried drug. Protect from light.

Profile

The dried rhizome and root of butcher's broom is used in herbal preparations for chronic venous insufficiency and haemorrhoids. It contains steroidal saponins including the sapogenin ruscogenin (see p.2382) which is used for similar purposes. The dose may be expressed in terms of total ruscogenins.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Venoserin; ***Ger.:*** Duoform Novo†; Fagorutin Ruscus; Phlebodril mono; Rhenus med†; Venelbin ruscus†; Venobiase mono†.

Multi-ingredient: ***Arg.:*** Celu-Atlas; CVP Flebo; Cyclo 3; Fiblast; Venart; Venidium; ***Austral.:*** Bioglan Cirflo†; Extralife Leg-Care; Proflo†; ***Austria:*** Phlebodril; ***Cz.:*** Cyclo 3 Fort; ***Fr.:*** Avene Antirougeurs; Bicirkan; Cirkan; Climaxol; Creme au Melilot Composee; Cyclo 3; Cyclo 3 Fort; Evarose; Veinobiase; Venyl†; ***Ger.:*** Phlebodril; Phlebodril N; Venobiase†; ***Gr.:*** Cyclo 3 Forte; ***Indon.:*** Venos; ***Ital.:*** Altadrine; Angiorex Complex; Capill Venogel; Dermoprolyn†; Flebolider; ***Mex.:*** Fabroven; ***Pol.:*** Cyclo 3 Fort; ***Port.:*** Creme Laser Hidrante; Cyclo 3; ***Rus.:*** Cyclo 3 (Цикло 3); Cyclo 3 Fort (Цикло-3 Форт); ***Singapore:*** Cyclo 3; Cyclo 3 Fort; ***Spain:*** Fabroven; Ruscimel†; Venofit; ***Switz.:*** Phlebodril; Phlebodril N; Veino-Gouttes-N†; ***Thai.:*** Cyclo 3 Fort.

Butinoline Phosphate *(rINNM)*

Butinoline, Phosphate de; Butinolini Phosphas; Fosfato de butinolina. 1,1-Diphenyl-4-pyrrolidino-1′-yl but-2-yn-1-ol phosphate.

Бутинолина Фосфат

$C_{20}H_{21}NO,H_3PO_4$ = 389.4.

CAS — 968-63-8 (butinoline); 54118-66-0 (butinoline phosphate).

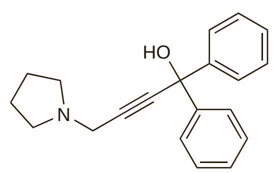

(butinoline)

Profile

Butinoline phosphate is used as an antispasmodic in preparations for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Spasmo-Solugastril; ***Ger.:*** Spasmo-Nervogastrol†; Spasmo-Solugastril†.

Butterbur

Profile

The leaves and roots of butterbur, *Petasites hybridus* (*P. officinalis*) (Asteraceae), have antispasmodic and anti-inflammatory properties and have been used in herbal preparations for a variety of disorders, including gastrointestinal and respiratory-tract disorders, and migraine.

◊ References.

1. Schapowal A. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *BMJ* 2002; **324:** 144–6.
2. Lee DK, *et al.* Butterbur, a herbal remedy, attenuates adenosine monophosphate induced nasal responsiveness in seasonal allergic rhinitis. *Clin Exp Allergy* 2003; **33:** 882–6.
3. Diener HC, *et al.* The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol* 2004; **51:** 89–97.
4. Jackson CM, *et al.* The effects of butterbur on the histamine and allergen cutaneous response. *Ann Allergy Asthma Immunol* 2004; **92:** 250–4.
5. Lipton RB, *et al.* Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004; **63:** 2240–4.
6. Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache* 2005; **45:** 196–203.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Petadolex; Petaforce V; ***Switz.:*** DoloMed†; Petadolor†; Pollivita; Tesalin.

Multi-ingredient: ***Switz.:*** Dragees aux figues avec du sene; Dragees pour la detente nerveuse; Relaxane; Valverde Constipation dragees; Valverde Detente dragees; Wala Pulmonium suc contre la toux.

Butyl Nitrite

Nitrito de butilo.

$C_4H_9NO_2$ = 103.1.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of butyl nitrite:

Bolt; Climax; Locker room; Poppers; Rush; Snappers; Video head cleaner.

Profile

Butyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p.1437).

Cadmium

Cadmio; Kadm; Kadmium.

Cd = 112.411.

CAS — 7440-43-9.

Cadmium Sulfate

Cadmii sulfas; Cadmium, sulfate de; Kadmiumsulfaatti; Kadmiumsulfat; Kadmu siarczan.

$CdSO_4$ = 208.5.

CAS — 10124-36-4.

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Cadmium Sulphate Hydrate for Homoeopathic Preparations; Cadmii Sulfas Hydricus ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Profile

Cadmium is used in a wide range of manufacturing processes and cadmium poisoning presents a recognised industrial hazard. Inhalation of cadmium fumes during welding procedures may not produce symptoms until 12 to 36 hours have passed and these symptoms include respiratory distress leading to pulmonary oedema; kidney toxicity is also a feature of acute cadmium poisoning. Ingestion of cadmium or its salts has the additional hazard of severe gastrointestinal effects. Cadmium has a long biological half-life and accumulates in body tissues, particularly the liver and kidneys. Chelation therapy is not generally recommended for cadmium poisoning, although sodium calcium edetate has been used after acute ingestion. However, chelators do not increase cadmium elimination in chronic poisoning and use of dimercaprol may increase cadmium toxicity and should be avoided. Chronic exposure to cadmium results in progressive renal impairment and other effects (see below).

Cadmium sulfide has been used topically in some countries for the treatment of skin and scalp conditions. Cadmium sulfate has been included in some preparations for the treatment of eye irritation.

Homoeopathy. Cadmium has been used in homoeopathic medicines under the following names: Cadmium metallicum; Cad. met.

Cadmium sulfate has been used in homoeopathic medicines under the following names: Cadmium sulfuricum; Cadmium sulphuricum; Cad. sul.

Cadmium sulphide has been used in homoeopathic medicines under the following names: Cadmium sulphuratum; Cad. sulph.

Adverse effects. The toxicity of cadmium has been reviewed.[1] Environmental or occupational exposure to cadmium has been associated with renal dysfunction,[2-5] although this may be reversible if exposure is reduced.[6] A reduction in bone density may also occur.[7] Fatalities due to industrial exposure or self-poisoning have also been reported.[8,9] No effect on testicular endocrine function was observed in 77 industrial workers exposed to cadmium.[3]

An increased incidence of cancer of the prostate has been reported in subjects exposed to high levels of cadmium but the evidence is not conclusive.[10] There may be an association between cadmium exposure and lung cancer, although observations on this type of cancer are difficult to interpret because of exposure to other hazards such as smoking.

1. Fielder RJ, Dale EA. Cadmium and its compounds. *Toxicity Review 7.* London: HMSO, 1983.
2. Buchet JP, *et al.* Renal effects of cadmium body burden of the general population. *Lancet* 1990; **336:** 699–702. Correction. *ibid.* 1991; **337:** 1554.
3. Mason HJ. Occupational cadmium exposure and testicular endocrine function. *Hum Exp Toxicol* 1990; **9:** 91–4.
4. Cai S, *et al.* Renal dysfunction from cadmium contamination of irrigation water: dose-response analysis in a Chinese population. *Bull WHO* 1998; **76:** 153–9.
5. Satarug S, *et al.* Safe levels of cadmium intake to prevent renal toxicity in human subjects. *Br J Nutr* 2000; **84:** 791–802.
6. Hotz P, *et al.* Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. *Lancet* 1999; **354:** 1508–13.
7. Staessen JA, *et al.* Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. *Lancet* 1999; **353:** 1140–44.
8. Taylor A, *et al.* Poisoning with cadmium fumes after smelting lead. *BMJ* 1984; **288:** 1270–1.
9. Buckler HM, *et al.* Self poisoning with oral cadmium chloride. *BMJ* 1986; **292:** 1559–60. Correction. *ibid.*; **293:** 236.
10. Bell GM. Carcinogenicity of cadmium and its compounds. *Toxicity Review 24.* London: HMSO, 1991.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Biocadmio.

Cajuput Oil

Cajeput Oil; Cajuput Essence; Cayeput, aceite esencial de; Oleum Cajuputi.

Profile

Cajuput oil is a volatile oil obtained by distillation from the fresh leaves and twigs of *Melaleuca cajuputi* (*M. leucadendron*) (Myrtaceae). It contains cineole. Cajuput oil has been applied externally as a stimulant and mild rubefacient in rheumatism. It is also used with other volatile agents in preparations for the relief of respiratory-tract disorders and nasal congestion. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Goanna Heat Cream; Methyl Salicylate Ointment Compound†; Tiger Balm Red; Tiger Balm White; ***Austria:*** Tiger Balsam Rot; ***Belg.:*** Olbas; ***Canad.:*** Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; Youngflex Massage 168; ***Cz.:*** Tiger Balm Rot†; ***Fr.:*** Phytolithe†; Vegebom; ***Ger.:*** Liniplant; Nasenbalsam; Olbas; Palatol†; ***Gr.:*** Tiger Balm; ***Hong Kong:*** Vida Salirub; ***India:*** Flexi-muv; ***Indon.:*** Balsam Sakti; Minyak Telon; Minyak Telon Cap Tiga Anak; ***Israel:*** Tiger Balm Red; Tiger Balm White; ***Ital.:*** Otosan Natural Ear Drops†; ***Philipp.:*** Begesic; ***Pol.:*** Argol Rheuma; Olbas; ***S.Afr.:*** Muscle Rub; ***Singapore:*** Begesic; ***Switz.:*** Frigoplasma†; Novital; Olbas; Wala Baume nasal; ***Thai.:*** Dexalin; Hot Ize; Olympic Balm†; ***UK:*** Bells Muscle Rub; Olbas; Olbas for Children; Soothol; Tiger Balm; Vadarex.

Calamus

Acore Vrai; Cálamo aromático; Calamus Rhizome; Kalmus; Sweet Flag Root.

CAS — 8015-79-0 (calamus oil).

Pharmacopoeias. In *Chin.* and *Swiss.*

Profile

Calamus, the dried rhizome of the sweet flag, *Acorus calamus* (Acoraceae), has been used as a bitter and carminative; it is also used as a source of calamus oil, which is employed in perfumery. The FDA in the USA has prohibited marketing calamus as a food or food additive; the oil (Jammu variety) is reported to be a carcinogen.

Homoeopathy. Calamus has been used in homoeopathic medicines under the following names: Calamus aromaticus; Acorus calamus.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Koren Puskvorce.

Multi-ingredient: ***Austria:*** Abdomilon N; ***Cz.:*** Abdomilon†; Dr Theiss Schwedenbitter; Eugastrin†; Original Schwedenbitter; Stomaran; ***Fr.:*** Jouvence de l'Abbe Soury; ***Ger.:*** Abdomilon N; Gastrol S†; Majocarmin mite†; Presselin Blahungs K 4 N†; Stomasal Med†; Stovalid N†; ventri-loges N; ***Israel:*** Rekiv; ***Ital.:*** Frerichs Maldifassi†; ***Pol.:*** Dentosept A; Gastro; Krople Zoladkowe; Seboren; ***Port.:*** Cholagutt†; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Switz.:*** Kernosan Elixir; Tisane pour l'estomac; Urinex; ***UK:*** Pegina.

Calcium Carbimide *(rINN)*

Calcii Carbimidum; Calcium Cyanamide; Carbimida cálcica; Carbimide Calcique; Cyanamide.

Кальция Карбимид

$CCaN_2$ = 80.1.

CAS — 156-62-7 (calcium carbimide); 8013-88-5 (citrated calcium carbimide).

ATC — N07BB02.

ATC Vet — QN07BB02; QV03AA02.

N≡—N=Ca

NOTE. The name cyanamide is also used to designate carbimide, which is used in veterinary medicine.

Adverse Effects and Precautions

Calcium carbimide may cause drowsiness, dizziness, fatigue, skin rash, tinnitus, depression, impotence, and urinary frequency. There may be a reversible increase in the white cell count. It should be used with caution in patients with asthma, coronary artery disease, or myocardial disease. Calcium carbimide causes a reaction in patients who have consumed alcohol similar to that seen with disulfiram (see p.2296).

Effects on the heart. Hypotension and tachycardia were reported during the carbimide-alcohol reaction.[1]

1. Peachey JE, *et al.* Cardiovascular changes during the calcium carbimide-ethanol interaction. *Clin Pharmacol Ther* 1981; **29:** 40–6.

Effects on the liver. Reports[1,2] of hepatic lesions in patients receiving calcium carbimide.

1. Vázquez JJ, Cervera S. Cyanamide-induced liver injury in alcoholics. *Lancet* 1980; **i:** 361–2.
2. Moreno A, *et al.* Structural hepatic changes associated with cyanamide treatment: cholangiolar proliferation, fibrosis and cirrhosis. *Liver* 1984; **4:** 15–21.

Uses and Administration

Calcium carbimide has actions and uses similar to those of disulfiram (p.2297). It is an aversive agent used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p.1626). It is given in a dose of up to 60 mg twice daily by mouth. Citrated calcium carbimide has been used similarly.

◊ References.

1. Peachey JE, *et al.* A comparative review of the pharmacological and toxicological properties of disulfiram and calcium carbimide. *J Clin Psychopharmacol* 1981; **1:** 21–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Colme; ***Rus.:*** Colme (Колме); ***Spain:*** Colme.

Calcium Dihydrogen Phosphate

Acid Calcium Phosphate; Calcium Dihydrogenphosphoricum; E341; Fosfato monocálcico; Monobasic Calcium Phosphate; Monocalcium Phosphate. Calcium tetrahydrogen diorthophosphate monohydrate.

$Ca(H_2PO_4)_2,H_2O = 252.1.$
CAS — 7758-23-8 (anhydrous calcium dihydrogen phosphate).

Pharmacopoeias. In *Jpn* and *Swiss*.

Profile

Calcium dihydrogen phosphate is used in fertilisers. It is also used as an antoxidant in baking powders and flours and as a source of calcium in some mineral supplement preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Phosphoneuros.

Calcium Dobesilate *(rINN)*

Calcii dobesilas; Calcium, dobésilate de; Calcium Doxybenzylate; CLS-2210; Dobesilan vápenatý; Dobésilate de Calcium; Dobesilato de calcio; 205E; Kalcio dobesilatas; Kalciumdobesilat; Kalcium-dobezilát; Kalsiumdobesilaatti; Kalsiyum Dobesilat. Calcium 2,5-dihydroxybenzenesulphonate.

Кальция Добезилат

$C_{12}H_{10}CaO_{10}S_2 = 418.4.$
CAS — 88-46-0 (dobesilic acid); 20123-80-2 (calcium dobesilate).
ATC — C05BX01.
ATC Vet — QC05BX01.

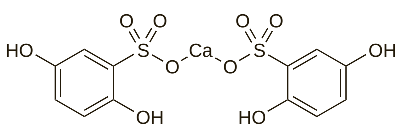

Pharmacopoeias. In *Eur.* (see p.vii) which specifies the monohydrate.

Ph. Eur. 6.2 (Calcium Dobesilate Monohydrate). A white or almost white hygroscopic powder. Very soluble in water; freely soluble in dehydrated alcohol; practically insoluble in dichloromethane; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Profile

Calcium dobesilate is claimed to reduce capillary permeability and has been used in various peripheral circulatory disorders including diabetic retinopathy and haemorrhoids (p.1697). Gastrointestinal disturbances have occurred with its use, and there are also reports of hypersensitivity reactions.

Calcium dobesilate is given orally in usual doses of 0.5 to 1.5 g daily in divided doses. It is also given rectally for haemorrhoids and is an ingredient of some preparations given for various skin disorders.

◊ Reviews.

1. Tejerina T, Ruiz E. Calcium dobesilate: pharmacology and future approaches. *Gen Pharmacol* 1998; **31:** 357–60.
2. Berthet P, *et al.* Calcium dobesilate: pharmacological profile related to its use in diabetic retinopathy. *Int J Clin Pract* 1999; **53:** 631–6.

Adverse effects. Agranulocytosis has been reported[1-3] in a few patients after treatment with calcium dobesilate, and in 2 cases recurred on rechallenge.[1,2] However, a later review[4] of the safety profile of calcium dobesilate concluded that the overall risk of adverse effects was low with the most prominent symptoms being fever, arthralgias, and gastrointestinal disturbances. Reports of agranulocytosis were rare and the authors concluded that there may have been methodological bias in previous assessments of risk.

1. Kulessa W, *et al.* Wiederholte Agranulozytose nach Einnahme von Calciumdobesilat. *Dtsch Med Wochenschr* 1992; **117:** 372–4.
2. Cladera Serra A, *et al.* Agranulocitosis inducida por dobesilato calcico. *Med Clin (Barc)* 1995; **105:** 558–9.
3. García Benayas E, *et al.* Calcium dobesilate-induced agranulocytosis. *Pharm World Sci* 1997; **19:** 251–2.
4. Allain H, *et al.* Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Safety* 2004; **27:** 649–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Doxium; Duflemina†; Eflevar; ***Austria:*** Doxium; Vasactin; ***Chile:*** Doxium; ***Cz.:*** Danium; Dobica; Doxium; ***Ger.:*** Dexium; Dobica; ***Gr.:*** Doxytrex; Nugatex; ***Hong Kong:*** Dobesifar†; Doxium; ***Hung.:*** Doxilek; Doxium; ***India:*** Dobilet; ***Ital.:*** Doxium; ***Malaysia:*** Doxium; ***Mex.:*** Doxium; ***Philipp.:*** Doxium; ***Pol.:*** Doxium; ***Port.:*** Doxi-Om; ***Rus.:*** Doxi-Hem (Докси-хем); ***S.Afr.:*** Doxium; ***Spain:*** Doxium; ***Switz.:*** Doxium; ***Turk.:*** Doxium; ***Venez.:*** Deoxical; Doxium.

Multi-ingredient: ***Arg.:*** Vasodual†; ***Cz.:*** Danium Compositum†; Dobexil; Dobexil Plus†; Doxiproct; Doxiproct Plus; Doxivenil†; ***Hung.:*** Doxiproct; Doxiproct Plus; Doxivenil; ***Ital.:*** Doxiproct; ***Mex.:*** Doxiproct Plus; Doxiproct†; ***Port.:*** Doxiproct; Doxiproct Plus; Doxivenil; ***Spain:*** Acnisdin; Acnisdin Retinoico; Proctium; ***Switz.:*** Doxiproct; Doxiproct Plus; Doxivenil; ***Venez.:*** Doxivenil.

Calcium Hopantenate *(rINNM)*

Calcii Hopantenas; Calcium Homopantothenate; Hopanténate de Calcium; Hopantenato cálcico. Calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethylbutyramido)butyrate hemihydrate.

Кальций Гопантенат

$Ca(C_{10}H_{18}NO_5)_2,\frac{1}{2}H_2O = 513.6.$
CAS — 18679-90-8 (hopantenic acid); 17097-76-6 (anhydrous calcium hopantenate); 1990-07-4 (calcium hopantenate hemihydrate).

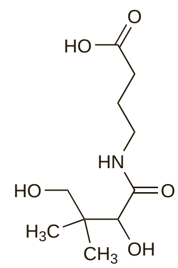

(hopantenic acid)

Profile

Calcium hopantenate is a homologue of pantothenic acid (p.1959) and has been tried in the treatment of various behavioural and extrapyramidal disorders. Its use is limited by severe metabolic adverse effects and fatalities have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Pantocalcin (Пантокальцин); Pantogam (Пантогам); Pantohamum (Пантогам)†.

Calcium Hydroxide

Calcii hydroxidum; Calcium Hydrate; Calcium, hydroxyde de; E526; Hidróxido cálcico; Hydroxid vápenatý; Kalcio hidroksidas; Kalcium-hidroxid; Kalciumhydroxid; Kalsiumhydroksidi; Slaked Lime; Wapnia wodorotlenek.

$Ca(OH)_2 = 74.09.$
CAS — 1305-62-0.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Calcium Hydroxide). A fine white or almost white powder. Practically insoluble in water.

USP 31 (Calcium Hydroxide). A white powder with a slightly bitter alkaline taste. Soluble 1 in 630 of water and 1 in 1300 of boiling water; insoluble in alcohol; soluble in glycerol and in syrup. Store in airtight containers.

Profile

Calcium hydroxide is a weak alkali. It is used in the form of Calcium Hydroxide Solution (lime water) in some skin lotions and oily preparations to form calcium soaps of fatty acids which produce water-in-oil emulsions.

Calcium hydroxide pastes are used in dentistry. A paste made from a mixture of calcium hydroxide and potassium hydroxide and known as Vienna paste was used as an escharotic. Soda lime (p.2388) is a mixture of calcium hydroxide and potassium hydroxide and/or sodium hydroxide. With sulfur, calcium hydroxide forms sulfurated lime solution (p.1614).

Homoeopathy. Calcium hydroxide has been used in homoeopathic medicines under the following names: Calcarea caustica; Cal. caus.

Adverse effects. A report of ocular alkali burns in children, leading to severe visual loss, caused by packets of calcium hydroxide ('Chuna') popularly consumed in India as an additive to chewing tobacco.[1]

For the use of sodium edetate in the treatment of calcium hydroxide burns of the eye, see p.1464.

1. Agarwal T, Vajpayee RB. A warning about the dangers of chuna packets. *Lancet* 2003; **361:** 2247.

Preparations

BP 2008: Calcium Hydroxide Solution;
USP 31: Calcium Hydroxide Topical Solution.

Proprietary Preparations (details are given in Part 3)
Ger.: Dermi-cyl; ***Mex.:*** Oleoderm.

Multi-ingredient: ***Cz.:*** Aviril H†; ***Mex.:*** Caliderm; Liniderm; Oleoderm Plus; ***Pol.:*** Acne Sulf; ***Spain:*** Cremsol; ***Switz.:*** Sansilla.

Calcium Oxide

Calcii Oxidum; Calcium Oxydatum; Calcium, oxyde de; Calx; Calx Usta; Chaux Vive; E529; Gebrannter Kalk; Lime; Oxid vápenatý; Óxido de calcio; Quicklime; Wapnia tlenek; Wapnia tlenek.

$CaO = 56.08.$
CAS — 1305-78-8.
ATC Vet — QP53AX18.

Pharmacopoeias. In *Jpn, Pol.,* and *US.*

USP 31 (Lime). Hard, odourless, white or greyish-white masses, granules, or powder. When it is moistened with water a reaction occurs, heat being evolved and calcium hydroxide formed. Slightly soluble in water; very slightly soluble in boiling water. Store in airtight containers.

Adverse Effects and Treatment

Calcium oxide may cause burns on contact with moist skin and mucous membranes; it is particularly irritant to the eyes. Washing or flooding of affected areas may need to be prolonged. Pneumonitis may follow inhalation.

◊ For the use of sodium edetate in the treatment of calcium oxide burns of the eye, see p.1464.

Uses and Administration

Calcium oxide has been used in various dermatological preparations. A paste made from a mixture of calcium oxide and sodium hydroxide and known as London paste was used as an escharotic.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Oleo Calcarea†.

Calcium Saccharate *(rINN)*

Calcii Saccharas; Calcium D-Saccharate; Sacarato cálcico; Sacarato de calcio; Saccharate de Calcium; Sucrate de Calcium. Calcium D-glucarate tetrahydrate.

Кальция Сахарат

$C_6H_8CaO_8,4H_2O = 320.3.$
CAS — 5793-88-4 (anhydrous calcium saccharate); 5793-89-5 (calcium saccharate tetrahydrate).

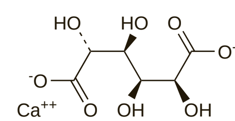

NOTE. The names calcium saccharate and calcium sucrate have also been used to describe saccharated lime.

Pharmacopoeias. In *US.*

USP 31 (Calcium Saccharate). A white, odourless, crystalline powder. Very slightly soluble in cold water and in alcohol; slightly soluble in boiling water; practically insoluble in chloroform and in ether; soluble in dilute mineral acids and in solutions of calcium gluconate.

Profile

Calcium saccharate is used as a stabilising agent in solutions of calcium gluconate for injection. Each g of calcium saccharate contains about 3.1 mmol of calcium. Calcium saccharate 8 g is equivalent to about 1 g of calcium.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Calcium Fresenius; ***Ger.:*** Calcium Fresenius†.

Multi-ingredient: ***Ger.:*** Calcium Braun; ***Switz.:*** C-Calcium; Glucocalcium.

Calcium Sulfate

Calcii sulfas; Calcium, sulfate de; Calcium Sulphate; E516; Gypsum (calcium sulfate dihydrate); Kalcio sulfatas; Kalciumsulfat; Kalcium-szulfát; Kalsiumsulfaatti; Síran vápenatý; Sulfato cálcico; Wapnia siarczan.

$CaSO_4 = 136.1.$
CAS — 7778-18-9 (anhydrous calcium sulfate); 10101-41-4 (calcium sulfate dihydrate).

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.,* and *Jpn* which specify the dihydrate. Also in *USNF* which specifies the dihydrate or the anhydrous material.

Ph. Eur. 6.2 (Calcium Sulphate Dihydrate). A white or almost white fine powder. Very slightly soluble in water; practically

insoluble in alcohol.
USNF 26 (Calcium Sulfate). It is anhydrous or contains two molecules of water of hydration. A white to slightly yellow-white odourless fine powder. Soluble 1 in 375 of water and 1 in 485 of boiling water; soluble in 3N hydrochloric acid.

Profile
Calcium sulfate dihydrate is used as an excipient for the preparation of tablets or capsules.

Homoeopathy. Calcium sulfate has been used in homoeopathic medicines under the following names: Calcium sulfuricum; Calcarea sulphurica; Cal. sul.

Preparations
Proprietary Preparations (details are given in Part 3)
Austral.: Celloids CS 36.

Dried Calcium Sulfate
Calcii Sulfas Hemihydricus; Calcined Gypsum; Calcium Sulfuricum ad Usum Chirurgicum; Calcium Sulphuricum Ustum; Dried Calcium Sulphate; Exsiccated Calcium Sulphate; Gebrannter Gips; Gêsso; Gypsum Siccatum; Plaster of Paris; Plâtre Cuit; Síran vápenatý hemihydrát; Sulfato cálcico anhidro; Sulphate of Lime; Yeso Blanco.

$CaSO_4, \frac{1}{2}H_2O$ = 145.1.
CAS — 10034-76-1 (calcium sulfate hemihydrate); 26499-65-0 (calcium sulfate hemihydrate).

Pharmacopoeias. In *Br., Chin., Ger., Jpn, Pol.,* and *Viet.*
BP 2008 (Dried Calcium Sulphate). A white or almost white, odourless or almost odourless hygroscopic powder. It may contain suitable setting accelerators or decelerators. Slightly soluble in water; more soluble in dilute mineral acids; practically insoluble in alcohol.
The BP gives Exsiccated Calcium Sulphate and Plaster of Paris as approved synonyms.

Profile
Dried calcium sulfate is used for the preparation of Plaster of Paris Bandage, which is used for the immobilisation of limbs and fractures. It is also employed for making dental casts and has been used as a bone graft substitute.

Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Biplatrix.

Calendula
Caléndula; Calendulae Anthodium; Calendulae flos; Gold-bloom; Kehäkukka; Körömvirág; Koszyczek nagietka; Marigold; Marybud; Medetkų žiedai; Měsíčkový květ; Pot Marigold; Ringblomma; Souci.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Calendula Flower). It consists of the whole or cut, dried, and fully opened flowers which have been detached from the receptacle of the cultivated, double-flowered varieties of *Calendula officinalis*. It contains not less than 0.4% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

Profile
Calendula has antiseptic, anti-inflammatory, and astringent properties. It is used in external preparations for minor skin disorders, and also internally for gastrointestinal and menstrual disorders. Calendula is also included in numerous herbal preparations to improve their appearance.
Calendula oil is also used.

Homoeopathy. Calendula has been used in homoeopathic medicines under the following names: Calendula officinalis; Calend.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Calendumed†; Dr Theiss Ringelblumen Salbe; Gallentee†; Mesickovy; ***Fr.:*** Calendulene; ***Mex.:*** Cicadin; ***Pol.:*** Calendulin; ***UK:*** Calendolon.

Multi-ingredient: ***Arg.:*** Acnetrol; Banoftal†; Brunavera; Bushi; Controlacne; Eurocolor Post Solar; Europrotec Post Solar†; Lavandula Oligoplex; Odontobiotic†; ***Austral.:*** Eczema Relief; Galium Complex†; Nappy Rash Relief Cream; Skin Healing Cream†; ***Austria:*** The Chambard-Tee; ***Braz.:*** Calendula Concreta†; Malvatricin Natural; ***Chile:*** Homeoplasmina†; Matikomp; ***Cz.:*** Abfuhr-Heilkrautertee†; Blahungstee N†; Blasen- und Nierentee†; Cicladerma; Epilobin; Hertz- und Kreislauftee†; Homeovox; ***Fr.:*** Alkagin; Cicaderma; Cicatridine; Dioptec; Eryange†; Hemorrogel; Homeoplasmine; ***Ger.:*** Befelka-Oel; bioplant-Kamillenfluid†; Cefawell†; Nephronorm med†; Unguentum lymphaticum; ***Hong Kong:*** Calmiderm; Pregnacare; ***Ital.:*** Alkagin; Allerlux; Babygella; Decon Ovuli; Lenirose†; Nevril; Proctopure; ***Malaysia:*** Arnica Comp†; Natberry Extra; ***Mex.:*** Sanicut; Suavene; Supranettes Naturalag; ***Philipp.:*** Lactaderm; ***Pol.:*** Arcalen; Azucalen; Dyspepsin; Escalar; Mucosit; Reumosol; Sanofil; ***Port.:*** Alkagin; Cicaderma; ***S.Afr.:*** Arnica Massage Oil; Heilsalbe; Oleum Rhinale Nasal Oil; Wecesin; ***Spain:*** Banoftal; Menstrunat†; ***Switz.:*** Gel a la consoude; Keppur; Kytta Gel†; Onguent aux herbes Keller; Urinex; Wala Echinacea; Wecesin†; Ziegella; ***UK:*** Calendula Nappy Change Cream; Eucanol; Massage Balm with Calendula; ***USA:*** Nasal-Ease; ***Venez.:*** Andantol Jalea; Biomicovo†; Flucirac; Gelsem; Linfoderm; Supranettes†.

Calumba
Calumba Root; Colombo.

Pharmacopoeias. In *Jpn.*

Profile
Calumba, the dried root of *Jateorhiza palmata* (*J. columba*) (Menispermaceae), has been used as a bitter and as a flavour.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Switz.:*** Padma-Lax; Padmed Laxan; ***UK:*** Appetiser Mixture; Pegina.

Camostat Mesilate *(pINNM)*
Camostat, Mésilate de; Camostat Mesylate; Camostati Mesilas; FOY-305; Mesilato de camostat. *N,N*-Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)phenylacetate methanesulphonate.
Камостата Мезилат
$C_{20}H_{22}N_4O_5,CH_4O_3S$ = 494.5.
CAS — 59721-28-7 (camostat); 59721-29-8 (camostat mesilate).
ATC — B02AB04.
ATC Vet — QB02AB04.

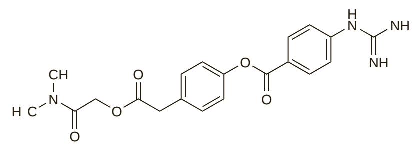

(camostat)

Pharmacopoeias. In *Jpn.*

Profile
Camostat mesilate is a proteolytic enzyme inhibitor that has been given orally for the treatment of postoperative reflux oesophagitis (p.1696) in a dose of 100 mg 3 times daily, and for remission of the acute symptoms of chronic pancreatitis (p.2361) in a dose of 200 mg 3 times daily.

Preparations
Proprietary Preparations (details are given in Part 3)
Jpn: Foipan.

Camphene
Kamfen. 2,2-Dimethyl-3-methylenebicyclo[2.2.1]heptane; .
Камфен
$C_{10}H_{16}$ = 136.2.
CAS — 79-92-5;.

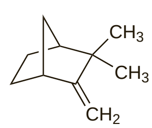

Profile
Camphene is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Rowachol; Rowatinex; ***Braz.:*** Quelodin†; ***Chile:*** Rowatinex; ***Cz.:*** Rowachol; Rowatinex; ***Ger.:*** Rowachol; Rowachol comp†; Rowachol-Digestiv; Rowatinex; ***Hong Kong:*** Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.:*** Rowachol; Rowatinex; ***Irl.:*** Rowachol; Rowatinex; ***Israel:*** Rowachol; Rowatinex; ***Malaysia:*** Rowachol; Rowatinex; ***Mex.:*** Cholex; ***Philipp.:*** Rowachol; Rowatinex; ***Pol.:*** Rowachol; Rowatinex; Terpichol; ***Spain:*** Rowachol; Rowanefrin; ***Switz.:*** Rowachol; ***Thai.:*** Rowachol; Rowatinex; ***UK:*** Rowachol; ***Venez.:*** Rowachol; Rowatinex.

Camphor
Alcanfor; 2-Camphanone; D-Camphor (natural); Camphora; Camphora D; Camphre; Camphre Droit (natural); Camphre du Japon (natural); Cânfora; D-Kafr; Kafr; Kamfer; Kamferi; Kámfor; Kamfora; Kamparas. Bornan-2-one; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one.
$C_{10}H_{16}O$ = 152.2.
CAS — 76-22-2 (± camphor); 21368-68-3 (± camphor); 464-49-3 (+ camphor); 464-48-2 (− camphor).
ATC — C01EB02.
ATC Vet — QC01EB02.

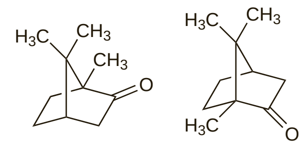

l-form d-form

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn, US,* and *Viet.*; some only describe natural camphor and some only synthetic camphor; *Eur.* and *Jpn* have separate monographs for natural and racemic or synthetic camphor.
Ph. Eur. 6.2 (Camphor, Racemic). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.
Ph. Eur. 6.2 (D-Camphor; Natural Camphor BP 2008). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.
USP 31 (Camphor). A ketone obtained from *Cinnamomum camphora* (Lauraceae) or produced synthetically. The natural product is dextrorotatory and the synthetic product is optically inactive.
Colourless or white crystals, granules, or crystalline masses, or colourless to white, translucent, tough masses with a penetrating characteristic odour. It slowly volatilises at ordinary temperatures.
Soluble 1 in 800 of water, 1 in 1 of alcohol, 1 in 0.5 of chloroform, and 1 in 1 of ether; freely soluble in carbon disulfide, in petroleum spirit, and in fixed and volatile oils. Store at a temperature not exceeding 40° in airtight containers.

Compounding. A liquid or soft mass is formed when camphor is triturated with cloral hydrate, menthol, phenol, and many other substances. Camphor is readily powdered by triturating with a few drops of alcohol, ether, or chloroform.

Adverse Effects
In addition to accidental ingestion of preparations containing camphor, poisoning has also occurred after giving camphorated oil (camphor liniment) to children in mistake for castor oil. The symptoms include nausea, vomiting, epigastric pain, headache, dizziness, oropharyngeal burning, delirium, muscle twitching, epileptiform convulsions, depression of the CNS, and coma. Breathing is difficult and the breath has a characteristic odour; anuria may occur. Death from respiratory failure or status epilepticus may occur; fatalities in children have been recorded from 1 g. There have been reports of instant collapse in infants following the local application of camphor to their nostrils.

Treatment of Adverse Effects
Supportive care, including anticonvulsant therapy, is the mainstay of treatment of camphor intoxication. Gastric lavage may be considered if the patient presents within 1 hour of ingestion; any convulsions must be controlled first. Activated charcoal may be given orally. Haemodialysis with a lipid dialysate or haemoperfusion have been tried but are of doubtful value.

Precautions
Camphor should not be applied to the nostrils of infants even in small quantities, as this may cause immediate collapse.

◊ The UK Committee on the Review of Medicines[1] recommended that camphor should not be included in products intended for the treatment of hepatic and biliary disorders, gallstones, colic, renal disorders, urinary-tract infections, or ureteral stones. The use of camphor parenterally or as irrigants was considered undesirable due to the associated safety hazard.

1. Anonymous. Camphorated oil: licensing authority takes action on camphor products. *Pharm J* 1984; **232:** 792.

Pharmacokinetics
Camphor is readily absorbed from all administration sites. It is hydroxylated in the liver to yield hydroxycamphor metabolites which are then conjugated with glucuronic acid and excreted in the urine. Camphor crosses the placenta.

◊ For reference to a study on the dermal absorption of camphor, menthol, and methyl salicylate, see Menthol, p.2340.

Uses and Administration
Applied externally, camphor acts as a rubefacient and mild analgesic (see p.5) and is used in liniments as a counter-irritant in fibrositis, neuralgia, and similar conditions. It is also an ingredient of many inhaled nasal decongestant preparations but it is of doubtful efficacy. The use of camphor liniment (camphorated oil) is discouraged because of its potential toxicity. It has been withdrawn from the market in both the UK and the USA. In the USA the concentration of camphor in preparations for external use may not exceed 11%.

Camphor oil is occasionally used in aromatherapy.

Taken internally camphor has irritant and carminative properties and has been used as a mild expectorant. It has also been used in mixed preparations for cardiovascular disorders.

Preparations

BP 2008: Camphorated Opium Tincture; Concentrated Camphor Water; Concentrated Camphorated Opium Tincture;
USP 31: Camphor Spirit; Camphorated Phenol Topical Gel; Flexible Collodion.

Proprietary Preparations (details are given in Part 3)
Canad.: Band-Aid Anti-Itch; ***Fr.:*** Camphrice Du Canada; ***Ger.:*** Camphoderm N; Caprisana†; Mulmicor; Pectocor N; Rheunervol N; Vaopin N; ***Pol.:*** Migrenol; ***Port.:*** Vicks Vaporub; ***Switz.:*** Nicobrevin N†; ***UK:*** Rohto Zi.
Multi-ingredient: numerous preparations are listed in Part 3.

Camylofin Hydrochloride *(rINNM)*

Acamylophenine Hydrochloride; Camylofin Dihydrochloride; Camylofine, Chlorhydrate de; Camylofini Hydrochloridum; Hidrocloruro de camilofina. Isopentyl 2-(2-diethylaminoethylamino)-2-phenylacetate dihydrochloride.

Камилофина Гидрохлорид

$C_{19}H_{32}N_2O_2,2HCl = 393.4.$
CAS — 54-30-8 (camylofin); 5892-41-1 (camylofin hydrochloride).
ATC — A03AA03.
ATC Vet — QA03AA03.

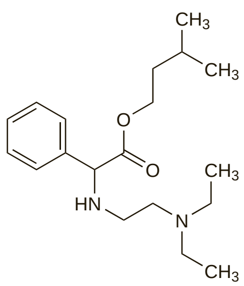

(camylofin)

Profile

Camylofin is used as an antispasmodic, usually in combination preparations. It is usually used as the hydrochloride; the noramidopyrine mesilate and the sodium salts have also been used.

Overdosage. Ingestion of large doses of camylofin by 2 infants produced symptoms similar to those of opioid intoxication.[1] Both infants responded to treatment with naloxone.

1. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; **ii:** 1246.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Anafortan.
Multi-ingredient: ***Arg.:*** Apasmo; ***Austria:*** Avamigran; ***Braz.:*** Espasmo Silidron; ***Fr.:*** Avafortan†; ***India:*** Anafortan.

Cannabidiol ⊗

CBD. (3*R*, 4*R*)-2-*p*-Mentha-1,8-dien-3-yl-5-pentylresorcinol.
$C_{21}H_{30}O_2 = 314.5.$
CAS — 13956-29-1.

Profile

Cannabidiol is a cannabinoid present in cannabis (p.2274) that is being used or under investigation for a number of potential therapeutic uses, including in combination with Δ^9-tetrahydrocannabinol (dronabinol, p.1728) in a buccal spray preparation (see under Cannabis, below).

◊ For references to the potential uses of cannabidiol, see under Cannabis, p.2275.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Canad.:*** Sativex.

Cannabis ⊗

Cáñamo Indiano; Cannab.; Cannabis Indica; Chanvre; Hanfkraut; Indian Hemp.
CAS — 8063-14-7.

Description. Cannabis consists of the dried flowering or fruiting tops of the pistillate plant of *Cannabis sativa* (Cannabinaceae). In the UK cannabis is defined by law as any part of any plant of the genus *Cannabis*. *Marihuana* usually refers to a mixture of the leaves and flowering tops. *Bhang*, *dagga*, *ganja*, *kif*, and *maconha* are commonly used in various countries to describe similar preparations. *Hashish* and *charas* are names often applied to the resin, although in some countries *hashish* is applied to any cannabis preparation.

A series of cannabinoids has been extracted from the plant, the most important being Δ^9-tetrahydrocannabinol (dronabinol), Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, cannabinol, and cannabidiol.

Cannabis and cannabis preparations have also been known by the following names, many of which are 'street names' (see p.vi) or slang names:

30s; 50; 420; 4.20; 4:20; 4/20; Abu-Sufian; Acapulco; Acapulco gold; Acapulco red; Ace; Afgani indica; Afghan; Afghan black; Afghanais; Afi; African; African black; African bush; Airplane; Ait makhlif; Ak-47; Al Green; Al Sharpton; Aliamba; Amsterdam; Anassa; Angola; Angolaise; Anhascha; Arathi; Arathi Highlands; Ashes; Assassin of Youth; Assyuni; Astro turf; Atshitshi; Aunt Mary; Baby; Baby belong; Baby bhang; Babysitter; Bad One; Bad seed; Bale; Bamba; Bambalacha; Bambia; Bammer; Bammies; Bammy; Bangi-Aku; Bango; Bangoo; Bangue; Banji; Bank Head Bud; Banzai Buds; Bar; Barbara Jean; Barn Man; Bash; BC bud; BC budd; BC Kindbud; Beaster; Beat N Sleep; Belyando spruce; Bergspinasie; Bhang; Bhangaku; Bheng; Biff; Bigfoot; Biggy; Birthday Cake; Black; Black bart; Black ganga; Black gold; Black gungi; Black gunion; Black Maria; Black mo; Black moat; Black powder; Black Russian; Blah; Blast; Blaze; Block; Blonde; Blonde hash; Blow; Blowhead; Blowing smoke; Blue de hue; Blue sage; Blue sky blond; Blueberry; Bo; Bob Hope; Bobby Brown; Bo-bo; Bobo bush; Bohd; Boi; Boléia; Bomb; Bombay Black; Bomb-dizzle; Bone; Boo; Boo boo bama; Boom; Bowgma-Chuff; Brass; Bread; Brick; Bristol Brown; Broccoli; Brown; Brown Frown; B-ster; Bubble gum; Bubonic Chronic; Bud; Buda; Buddha; Buddha grass; Buds; Buen; Bueno; Bullyon; Bunk; Burnie; Burrito; Bush; Butt; Butter; Butter flower; Buzzles; Cabbage; Cable; Caca; Caca de Chango; Cam red; Cam trip; Cambodian red; Can; Canadian black; Canamo; Canapa; Canappa; Cangonha; Canhama; Cann; Cannabis tea; Cannacoro; Can-Yac; Carmabis; Caroçuda; Cavite All Star; Cavite All Stars; CDs; Cereal; Cess; Cest; Chamom; Chara; Charas; Charge; Charris; Cheeba; Cheebong; Cheech and Chong; Cheeo; Cheese; Chemo; Chiba chiba; Chicago black; Chicago green; Chillums; Chippie; Chira; Chitari; Chocolate; Chocolate Thai; Choof; Chrin; Christmas bud; Christmas tree; Chro; Chron; Chron Chron; Chronic; Chucky; Chunky; Chur ganja; Churrus; Churus; Chus; Chutras; Chutsao; Citral; Citrol; Clone; Club; Cochornis; Coconut Rabbi; Colarado cocktail; Colas; Coli; Coliflor tostao; Collie Weed; Colombian; Colombo; Columbia; Columbian; Columbus black; Compresses; Cosa; Costo; Crazy weed; Creeper; Creeper Weed; Crippy; Crown Town Brown; Crying weed; Cryppie; Cryptonie; C.S.; Cubes; Culican; Cumming Air; Cung; Curro; Cush; D Nugs; Daboa; Dacha; Dagga; Dak; Dancouver; Dan K; Dank; Darakte-Bang; Dark; Dawamesk; Deaf; Dew; Diamba; Diambista; Diggidy; Diggity; Dimba; Ding; Dinkie dow; Dirijo; Dirt; Dirt grass; Ditch; Ditch weed; Ditchweed; Dizz; Djamba; Djoma; Do a joint; Doctor Kissinger's Crutch; DoggyNuggz; Doja; Dokka; Dolja; Domestic; Don jem; Don Juan; Dona Juana; Dona Juanita; Donajuanita; Doob; Doobee; Doobie; Dooko; Dope; Doradilla; Dormilona; Doshia; Double zero; Doug; Doug Funnie; Downtown brown; Dozer; Draf; Draf weed; Drag weed; Draw; Dread; Dro; Droski; Drottleneck; Dry high; Dubbe; Dube; Duby; Durban Poison; Durijo; Durog; Durong; Duros; Dustwallow Marsh; Ebenieghber; El Gallo; Electric Puha; Elephant; Elva; Endo; Erva do norte; Erva maligna; Esra; Esrar; Exotics; Fallbrook redhair; Faso; Feeling; Fêmea; Feng Shui inner tam-tam; Fine stuff; Finger; Finger lid; Fininha; Finote; Fir; Fire; Firebush; Firewood; Flack Juice; Flame; Flower; Flower tops; Fokkra; Food; Four twenty; Fraho; Frajo; Friend; Fruit; Fu; Fuma D'Angola; Fumo brabo; Fumo de caboclo; Funk; Funny stuff; Fur; Gage; Gandia; Ganga; Gange; Gangster; Ganj; Ganja; Ganjila; Garaouich; Garawiche; Garbage; Garoarsch; Gash; Gauche butt; Gauge; Gauge butt; Gauja; Gear; Gerp; Ghana; Ghanja; Giggle smoke; Giggle weed; Gnaoui; Goblet of jam; Gold; Gold star; Golden; Golden leaf; Gong; Gongo; Gonj; Good giggles; Good Goods; Good stuff; Goody-goody; Goof; Goof butt; Gorge; Gozah; Grahni Sherdool; Grain; Grand Pants; Gram; Grapefruit Hydro; Grass; Grass brownies; Grasshopper; Grata; Greefe; Green; Green buds; Green Candy; Green cheesy wham; Green Funk; Green Goblin; Green goddess; Green Jesus Love; Green paint; Green Penis; Greens; Greeter; Grefa; Grefer; Greta; Grey shields; Griefo; Griefs; Grifa; Griff; Griffa; Griffa-griffo; Griffo; Grim Creeper; Grimmy; Grolid; Guabza; Guaza; Gunga; Gungeon; Gungun; Gunja; Gunjah; Gunney; Gunney sack; Gunza; Gweeler; H; H caps; Hachiche; Haircut; Hairy Ogre; Hameni; Hamp; Hang Liu; Hanhich; Haouzi; Harm reducer; Harry Potter; Harsh; Has; Hascisc; Hash; Hash oil; Hashish; Hasis; Hasji's; Hasjisj; Haszysz; Hawaiian; Hawaiian Black; Hawiian homegrown hay; Hax; Haxixe; Hay; Haze; Headies; Heady Nugs; Heat; Heloua; Hemp; Hen-Nab; Herb; Herba; Herbals; Herbalz: High; High-Grade; Hippie Lettuce; Hocus; Hola-wola-shupidy-doo; Home Grown; Homegrown; Hooch; Hooda; Hooter; Huile; Humboltd Green; Hursini; Hydro; Hydrophonic; Hyge; Ice Cream; Igbo; Indian boy; Indian hay; Indian hemp; Indiana ditchweed; Indiana hay; Indica; Indische-hennepkruid; Indisk hampa; Indo; Indonesian bud; Indoor; Instaga; Instagu; Intianhamppu; Intsangu; Isangu; Ish; IZM; Jamaican gold; Jamaican red; Jamaican red hair; Jane; Janjah; Janjaweed; Jatiphaladya churna; Jay smoke; Jea; Jive; Jive stick; Johnson grass; Jolly green; Jonko; Joy smoke; Juan Valdez; Juana; Juanita; Juja; Kabak; Kaff; Kajees; Kalakit; Kali; Kamonga; Kanab; Kansas Grass; Karpura rasa; Kate bush; Kawaii electric; Kaya; KB; K.B.; Kee; Keif; Kentucky blue; Key; KGB; K.G.B.; Khanh-Chha; Khanje; Khayf; Khif-kiff; Ki; Kief; Kif; Kif Ktami; Kiff; Kill; Killer; Killer green bud; Killer weed; Kilroy; Kilter; Kind; Kind bud; Kind-Bud; Kine-Bud; King bud; Kinnab; Kitt; Kolto; Kona gold; Kraut; Krippies; Krippy; Kronic; Kryptonite; Kumba; Kush; Kushempeng; Kutchie; Kynd; Kynd-Bud; La-LaLa; Ladies; Lakbay diva; Lakbay viva; Lamb's bread; Lang; Laughing grass; Laughing weed; Leaf; Lebanese; Lebanese blonde; Lebanese gold; Leno; Leon Mcarthy; Leon Punders; LG; Liamba; Lianda; Light Green; Light stuff; Lima; Limbo; Lime green; Little green friends; Little smoke; L.L.; Llesca; Loaf; Lobo; Local weed; Loco; Loco Weed; Locoweed; Longbottom Leaf; Loose shank; Love nuggets; Love weed; Lows; Lubage; Lucas; Lumber; M; Macaroni; Machinery; Macon; Maconha; Maconia; Madi; Mafu; Maggie; Magic smoke; Magiyam; Majat; Makhlif; Malak; Malawi Cob; Malawi gold; Malawi grass; Malawian gold; Malva; Manhattan silver; Manitoba Hydro; Manzul; Marachuan; Maraguango; Marajuana; Marie Jeanne; Marie-Jane; Marie-Juana; Marigongo; Marihuana; Marijuana; Marimba; Mariquita; Marley; Maroc; Marocaine; Maruamba; Mary; Mary Ann; Mary Jane; Mary and Johnny; Mary Jonas; Mary Warner; Mary Weaver; Mary-Ann; Mary-Jane; Mary-Jonas; Matekwane; Maui wauie; Maui-wowie; May Ann; Mbanje; Meck; Meconha; Meg; Meggie; Merda; Merde; Mersh; Messorole; Method; Methtical; Mex; Mexican brown; Mexican green; Mexican locoweed; Mexican red; Mezz; Mid-Grade; Middies; Middys; Midies; Mids; Mighty mite; Mint; Misari; Mister Brownstone; M.J.; Mnoana; Mo; M.O.; Modams; Mohasky; Mohasty; Momea; Momeka; Monte; Mooca; Moocah; Mooster; Moota; Mooters; Mootie; Mootos; Mor a grifa; Moragrifa; Moroc; Mota; Motah; Mother; Moto; Mr. Piff; Mu; M.U.; Muggie; Muggle; Muggles; Mulatinha; Mull; Mundyadi vatika; Murphy; Musty Marty; Muta; Mutah; Mutha; Nail; Namba; Nederweed; Nederwiet; Neihe; Nigra; Nordle; Northern lights; N'rama; Ntsangu; Nug; Nugget; Nuggets; Nuggs; Nugglets; Nwonkaka; Oboy; O.J.; Old Toby; Oleo; Olja; Ooh-Wee; Orange Cat; Oregano; Out-Do; Owl; Ozone; Paca lolo; Pack; Pack a bowl; Pakaloco; Pakalolo; Paki black; Pakistani black; Panama cut; Panama gold; Panama red; Pappa C's funky space boots; Parsley; Passa; Pasta; Pasto; Pat; Pétard; Peinka; Penek; Penka; Philip Drummond; Philly blunts; Piff; Pin; Pine; Pito; Pizza; Platters; Plow; Pocket rocket; Pod; Poison; Poke; Poke Smot; Politics; Po-Pa; Porro; Pot; Potlikker; Potten bush; P.R.; Pretendica; Pretendo; Pretinha; Pretties; Pretty Ladies; Puff; Purp; Purple; Purple haze; Purple Urple; Purps; Quarter moon; Queen Ann's lace; Rafe; Rafi; Rafo; Ragweed; Railroad weed; Rainy day woman; Rangood; Rasta Plant; Rasta weed; RB; Red bud; Red cross; Red dirt; Red oil; Red seal; Redge; Reef; Reefer; Reggies; Reggiwegs; Regs; Regular; Relish; Resin; R.G.B.; Riamba; Righteous bush; Rip; RIP; Roacha; Rocky; Rongony; Root; Rope; Rora; Rosa Maria; Rose Maria; Rose Marie; Rose-Marie; Rough stuff; Rube; Rubia; Ruderalis; Rugs; Sabsi; Sadda; Salad; Salt and pepper; Santa Marta; Sasfras; Sativa; Schwag; Schwagg; Schwamp; Scissors; Scraps; Scrapes; Scrub; Seeds; Sen; Sense; Sensemilia; Sensi; Sess; Sezz; Shake; Sheeba; Sheebz; Shit; Shmagma; Shrimp; Shrubs; Shwig; Shwiggity Shwag; Shwag; Shwuggets; Siddhi; Siddi; Sighirma; Sins; Sinse; Sinsemilla; Sizzla; Skunk; Skunkweed; Sky; Smokage; Smoke; Smoke a bowl; Smoke Canada; Smoochywoochypoochy; Snop; Soap bar; Soles; Soñadora; Soruma; Soul Flower; Soussi; Speed boat; Splim; Square mackerel; Stack; Stank; Stank-a-dank; Stash; Stems; Stick; Sticks; Sticky; Sticky Black; Sticky brown; Sticky Icky; Sticky Icky Icky; Stink weed; Stinkweed; Stinky; Stoney weed; Stress; Striijj; Stuff; Subji; Sugar weed; Summitates cannabis; SupaDank; Super grass; Super pot; Supergrass; Suruma; Swag; Swamp Grass; Swazi Gold; SWED; Sweet Leaf; Sweet Lucy; T; Tablete; Tack; Tahgalim; Tai Alon; Taima; Takkouri; Takrouri; Tea; Tedrika; Teloeut; Tempel; Temple; Temple balls; Teriaki; Texas pot; Texas Red; Texas tea; Tex-mex; Thai Sticks; That Shit; THC; The Dank; The Peeping Jesus; The Pig Farmer's laptop; The Shit That Killed Elvis; The Wizard; Thirteen; Thumb; Thump! Thump! Thump!; Tia; Tical; Tijuana; Time; Time Machine's Glory; TJ; Tochi; Toke; Torch; Towels; Transkei; Trauma; Trees; Triple A; Tronadora; Trupence bag; Turtle; Tustin; Tweed; Tweeds; Twenty Twen Twen; Tweny Bag; Umya; Unotque; Urumogi; Utilities; Vipe; Viper's weed; Wacky Baccy; Wacky Backy; Wacky Tabacky; Wacky terbacky; Wacky tobaccky; Wacky weed; Wag; Wake and Bake; Wasch; Weasel feed; Wee; Weed; Weed tea; Weed tear; Wewe; Whack; Whackatabacky; Wheat; White Rhino; White Russian; White Widow; White-haired lady; Woo blunts; Woodle; Woof; Wooz; Wooze; X; Yaa; Yamba; Yandi; Yarndi; Yeah; Yeh; Yellow submarine; Yen pop; Yerba; Yerhia; Yesca; Yesco; Yeska; Ying; Yoda; Yoruba; Yum Yum; Zacate chino; Zacatecas purple; Zambi; Zani; Zerouali; Ziele konopi indyjskich; Zig Zag man; Zol; Zoot.

Pharmacopoeias. In *Chin.* and *Jpn.*

Dependence

Prolonged heavy use of cannabis may lead to tolerance and psychological dependence but the existence of physical dependence remains somewhat controversial. Reported withdrawal symptoms have included anorexia, agitation, apprehension, aggression, anxiety, insomnia, irritability, restlessness, fever, sweating, tremor, dysphoria, rhinorrhoea, headache, and nausea.

Symptoms of withdrawal have been reported in neonates born to mothers who used cannabis during pregnancy, and have included jitteriness and tremulousness, crying, and disturbances in sleep and response to light occurring up to 30 days after birth.

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Adverse Effects, Treatment, and Precautions

Cannabis is widely abused for its psychological effects and the most important psychoactive cannabinoid is Δ^9-tetrahydrocannabinol. The toxicity of cannabis is dose-related and when used recreationally depends to a large extent on the experience of the user and degree of tolerance. The effects may also be affected by CNS depressants taken at the same time.

The psychological effects produced by low doses of cannabis include calmness, euphoria, relaxation, drowsiness, a feeling of well-being, heightened sensory awareness, and alterations in perception of time, space, colour, or sound. Sedation may occur some time later after the initial effects. Anxiety or panic reactions may also occur at low doses.

As the level of intoxication increases, the user may experience feelings of depersonalisation, disorientation, decreased inhibition, altered mood, memory impairment, and difficulty in maintaining attention. Symptoms of heavy intoxication include incoordination, ataxia, skeletal muscle jerks, and slurred speech. Distrust, dysphoria, poor concentration, slowed reaction times, lethargy, and sedation may also occur. Fear, panic attacks in apprehensive patients, hallucinations, and transient paranoia or psychosis have also been reported.

Cannabis additionally affects several physiological body systems and symptoms of intoxication include tachycardia, palpitations, paroxysmal atrial fibrillation, and orthostatic hypotension; life-threatening ventricular tachycardia may occur after large doses. Decrease in intra-ocular pressure, conjunctival injection, cough, dry mouth, increased appetite, and reduced bowel motility have also been reported.

The toxicity of cannabis is increased with intravenous use. Gastrointestinal disturbances have been reported including nausea and vomiting, abdominal pain, and diarrhoea. Other symptoms include headache, rigors, fever, dyspnoea, cardiovascular irregularities, jaundice, shock, disseminated intravascular coagulation, renal impairment, and death.

Ingestion of cannabis by children is potentially fatal. Mydriasis, hypotonia, hyporeflexia, ataxia, hypothermia, tachycardia, respiratory depression, drowsiness, stupor, and coma have been reported.

Chronic use of cannabis has been reported to reduce resistance to infection, produce persistent neurotoxicity, and the carcinogens present in cannabis smoke potentially increase the risk of cancer. However, there is little conclusive evidence for the long-term effects of cannabis.

Cannabis has been presumed to affect driving because of slowed reaction times, effects on cognition, and perceptual alterations, although there is no conclusive evidence to this effect, and it has not been possible to correlate cannabis blood concentration with specific levels of impaired driving performance.

The risks of gastrointestinal decontamination following ingestion of cannabis may outweigh the benefits if the patient is drowsy or agitated. However, activated charcoal has been recommended within one hour of ingestion of a potentially toxic dose. Ipecacuanha given within 30 to 90 minutes of ingestion has been used as an alternative. Treatment of an overdose or acute toxicity following ingestion or inhalation of cannabis products is symptomatic and supportive. Adults often require little more than reassurance as clinical toxicity is rarely serious and recovery usually occurs spontaneously within several hours. Patients should be monitored for 6 hours after intravenous injection of cannabis products. Children should also be observed for 6 hours after ingestion. Agitated patients may require sedation with diazepam; lorazepam or midazolam have also been used. Haloperidol or ziprasidone are alternatives to benzodiazepines.

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Effects on the lungs. References.

1. Tashkin DR, *et al.* Respiratory and immunologic consequences of marijuana smoking. *J Clin Pharmacol* 2002; **42** (11 suppl): 71S–81S.
2. Aldington S, *et al.* Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 2007; **62:** 1058–63. Correction. *ibid.* 2008; **63:** 385.

Hyperthermia. Life-threatening hyperthermia was reported[1] in a 24-year-old man who went jogging after smoking cannabis.

1. Walter FG, *et al.* Marijuana and hyperthermia. *J Toxicol Clin Toxicol* 1996; **34:** 217–21.

Peripheral vascular disease. References.

1. Combemale P, *et al.* Cannabis arteritis. *Br J Dermatol* 2005; **152:** 166–9.

Pregnancy. Cannabis has effects on sperm and can alter reproductive hormonal systems. Infants born to mothers exposed to cannabis during pregnancy tend to have a lower birth-weight[1,2] and may suffer from increased excitation in the postnatal period.[3]

1. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; **320**: 762–8.
2. Frank DA, *et al.* Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *J Pediatr* 1990; **117:** 622–6.
3. Silverman S. Interaction of drug-abusing mother, fetus, types of drugs examined in numerous studies. *JAMA* 1989; **261**: 1689, 1693.

Interactions

Cannabis and alcohol have additive effects. The sedative effects of cannabis may be potentiated by other CNS depressants. Additive antimuscarinic effects, for example tachycardia, may occur with drugs such as tricyclic antidepressants. Cannabis induces microsomal enzymes and therefore interactions with a wide range of drugs that are metabolised by these enzymes might be expected (see, for example, Theophylline, p.1144).

Disulfiram. Limited evidence indicates that use of disulfiram with cannabis may produce a hypomanic state.[1]

1. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* 1983; **140:** 243–4.

Pharmacokinetics

Time to onset and duration of effects of cannabis vary with factors such as route of administration and the user's experience. The active principles of cannabis are readily absorbed from the lungs. Systemic bioavailability of Δ^9-tetrahydrocannabinol from smoked cannabis generally ranges between about 10 and 35%, with regular users achieving a higher efficiency. This produces an effect within minutes, reaches a peak in about 30 minutes, and lasts for about 3 to 4 hours. The pharmacokinetics of cannabis following injection are similar to smoking.

Δ^9-Tetrahydrocannabinol absorption may be slow and erratic from the gastrointestinal tract, and extensive first-pass liver metabolism reduces the systemic bioavailability to less than 20% with high interindividual variation. Effects peak in about 1 to 4 hours and last for up to 6 hours.

Δ^9-Tetrahydrocannabinol is lipophilic and becomes widely distributed in the body. Plasma protein binding is about 97 to 99%. Δ^9-Tetrahydrocannabinol is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP2C subfamily, primarily to the active 11-hydroxy derivative.

Within 72 hours of an oral dose, 10 to 15% is excreted in the urine mainly as conjugates and metabolites, and 35 to 50% in faeces mainly as unconjugated metabolites. About 80 to 90% of a dose is excreted within 5 days after ingestion. Duration of detectability of urinary metabolites varies greatly and can be several weeks for heavy chronic users.

Cannabis crosses the placenta and is distributed into breast milk.

◊ Review.

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42:** 327–60.

Uses and Administration

Cannabis contains about 60 cannabinoids of which the main active constituent is Δ^9-tetrahydrocannabinol. Two types of specific endogenous cannabinoid-binding receptors have been identified. CB_1 receptors are distributed throughout the CNS and some peripheral tissues and are involved in modulation of a number of neurotransmitters, which is thought to be responsible for the clinical effects of cannabinoids. CB_2 receptors are expressed mainly in immune cells and are thought to be involved in modulation of the immune system. Cannabinoid receptor agonists and antagonists have also been identified.

Therapeutic use. Cannabis was formerly used therapeutically as a sedative or narcotic. The cannabinoid Δ^9-tetrahydrocannabinol (dronabinol, p.1728) and a synthetic cannabinol (nabilone, p.1750) are used as antiemetics in patients receiving cancer chemotherapy. Dronabinol is also used to stimulate appetite in HIV patients with cachexia. Dronabinol and cannabidiol (p.2274), another cannabinoid, are used in combination in a buccal spray preparation (*Sativex*) as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults. This same preparation is also used as adjunctive analgesic treatment in adult patients with advanced cancer who have moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Cannabinoids are also being investigated for a number of other potential therapeutic uses, including relief of spasticity in multiple sclerosis, in spinal cord injury, and in various forms of pain, including diabetic neuropathy and other types of neuropathic pain, and pain associated with rheumatoid arthritis. Cannabis reduces intra-ocular pressure and it has been reported to be of benefit in glaucoma. Vaporisation is being investigated as a means of delivering therapeutic doses of cannabinoids.

Abuse. Cannabis is widely abused as a psychoactive agent and has a long history of such use. The amount of Δ^9-tetrahydrocannabinol in cannabis depends on its geographical source. Proportions also differ depending on the form used and have been reported as: 1 to 4% in the leaves and flowering tops, or even up to 15% in some varieties bred for a high yield of cannabinoids (so-called skunk); 5 to 12% in sinsemilla (obtained from unpollinated female plants); 3 to 6% in the dried resin (hashish); and 30 to 50% in hashish oil expressed from the pressed resin. The usual route of abuse is by smoking cigarettes containing the dried leaves and flowering parts of the plant or the more potent dried resin (hashish); inhalation using water pipes or vaporisers are alternative methods. Cannabis is also ingested in cakes or sweets. Less commonly, cannabis extract or hashish oil is injected intravenously.

◊ References to the potential medical uses of cannabis.

1. Robson P. Therapeutic aspects of cannabis and cannabinoids. *Br J Psychiatry* 2001; **178:** 107–15.
2. Mechoulam R, *et al.* Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol* 2002; **42** (11 suppl): 11S–19S.
3. Zajicek J, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362:** 1517–26.
4. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.
5. Berman JS, *et al.* Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; **112:** 299–306.
6. Guy GW, *et al. The Medicinal Uses of Cannabis and Cannabinoids*, London: The Pharmaceutical Press, 2004.
7. Fox P, *et al.* The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004; **62:** 1105–9.

8. Rog DJ, *et al.* Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; **65:** 812–19.
9. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother* 2006; **40:** 251–60.
10. Holdcroft A, *et al.* A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology* 2006; **104:** 1040–6.
11. Strasser F, *et al.* Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 2006; **24:** 3394–3400.
12. Abrams DI, *et al.* Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007; **68:** 515–21.
13. Abrams DI, *et al.* Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther* 2007; **82:** 572–8.
14. Seamon MJ, *et al.* Medical marijuana and the developing role of the pharmacist. *Am J Health-Syst Pharm* 2007; **64:** 1037–44.

Canola Oil

Cánola, aceite de.

CAS — 120962-03-0.

Profile

Canola oil is a form of rapeseed oil (p.2378) from strains selected for low erucic acid content. It is used as an edible oil and in pharmaceutical manufacturing and cosmetics.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***NZ:*** Mr Nits.

Cantharides

Blistering Beetle; Cantáridas; Cantharis; Insectes Coléoptères Hétéromères; Lytta; Méloides; Russian Flies; Spanish Fly.

Шпанские Мушки

Adverse Effects

The adverse effects of cantharides are those of its active component, cantharidin, below.

Uses and Administration

Cantharides is the dried beetle *Cantharis vesicatoria* (*Lytta vesicatoria*) (Meloidae) or other spp., containing not less than 0.6% of cantharidin, which is a protective exudate produced by the beetles. The properties of cantharides are those of its active principle, cantharidin (below).

Mylabris (Chinese blistering beetle; Chinese cantharides; Indian blistering beetle), the dried beetles of the species *Mylabrus sidae* (= *M. phalerata*), *M. cichorii*, and *M. pustulator*, has been used as a substitute for cantharides and as a source of cantharidin (see below) in the East.

Homoeopathy. Cantharides has been used in homoeopathic medicines under the following names: Cantharis; Lytta vesicatoria; Canthr.

Cantharidin

Cantaridina. Hexahydro-3aα,7aα-dimethyl-4β,7β-epoxyisobenzofuran-1,3-dione.

Кантаридин

$C_{10}H_{12}O_4$ = 196.2.

CAS — 56-25-7.

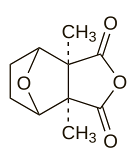

Adverse Effects and Treatment

The adverse effects of cantharidin, a protective exudate produced by blistering beetles (see under Cantharides above), are a result of its irritant and vesicant properties and may occur after exposure to preparations of cantharidin or to the beetle itself. Cantharidin produces blistering of mucous membranes. After ingestion of cantharidin there is burning pain in the throat and stomach, difficulty in swallowing, nausea, vomiting, haematemesis, abdominal pain, diarrhoea (sometimes bloody), tenesmus, renal pain, frequent micturition, dysuria, priapism, haematuria, proteinuria, renal failure, severe hypotension, and circulatory failure. Severe gastrointestinal disturbances can produce significant morbidity. Oral doses of cantharidin ranging from 10 to 80 mg have been lethal, although there have been reports of survival after doses up to 175 mg. Cantharidin is lipid soluble and oral bioavailability is increased in the presence of fatty substances.

Dermatological exposure may produce dermatitis, blisters, and ulceration, although symptoms may not appear until several hours later. Significant dermal exposure can give rise to systemic toxicity. Keratoconjunctivitis, iritis, and oedema may result from contact with the eyes or surrounding tissues.

Cantharidin has been abused as a sex stimulant.

Treatment of cantharidin poisoning is largely supportive. Emesis must be avoided following oral ingestion because of the severe irritant effect of cantharidin on mucous membranes. Activated charcoal has been tried, although it is not certain whether it binds to cantharidin.

Poisoning. References.

1. Hundt HKL, *et al.* Post-mortem serum concentration of cantharidin in a fatal case of cantharides poisoning. *Hum Exp Toxicol* 1990; **9:** 35–40.
2. Polettini A, *et al.* A fatal case of poisoning with cantharidin. *Forensic Sci Int* 1992; **56:** 37–43.
3. Karras DJ, *et al.* Poisoning from "Spanish fly" (cantharidin). *Am J Emerg Med* 1996; **14:** 478–83.
4. Tagwireyi D, *et al.* Cantharidin poisoning due to "Blister beetle" ingestion. *Toxicon* 2000; **38:** 1865–9.

Uses and Administration

Cantharidin is obtained from cantharides or mylabris (see under Cantharides, above). Cantharidin has vesicant activity and a solution of 0.7% in flexible collodion is applied for the removal of warts and molluscum contagiosum. Preparations of cantharides and cantharidin have also been used externally as rubefacients and counter-irritants. Owing to the intensely irritating nature of cantharidin it should not be taken internally. Also it should not be applied over large surfaces because of the risk of absorption.

Preparations of cantharides and cantharidin were formerly promoted for hair loss but their use in cosmetic products is now prohibited in the UK by law.

Molluscum contagiosum. References.

1. Silverberg NB, *et al.* Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol* 2000; **43:** 503–7.
2. Moed L, *et al.* Cantharidin revisited: a blistering defense of an ancient medicine. *Arch Dermatol* 2001; **137:** 1357–60.
3. Ross GL, Orchard DC. Combination topical treatment of molluscum contagiosum with cantharidin and imiquimod 5% in children: a case series of 16 patients. *Australas J Dermatol* 2004; **45:** 100–2.
4. Hanna D, *et al.* A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol* 2006; **23:** 574–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Canthacur; Cantharone.

Multi-ingredient: ***Canad.:*** Canthacur-PS; Cantharone Plus.

Capsicum

Capsic.; Capsici fructus; Chillies; Espanjanpippuri; Paprikový plod; Paprikų vaisiai; Piment de cayenne; Piment Rouge; Pimentão; Red Pepper; Spanischer Pfeffer; Spansk peppar.

NOTE. Ground cayenne pepper of commerce is normally a blend of varieties of capsicum. Paprika is from *Capsicum annuum* var. *longum*; it is milder than capsicum.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Eur. and *US* also include capsicum oleoresin (capsicin).

Ph. Eur. 6.2 (Capsicum). The dried ripe fruits of *Capsicum annuum* var. *minimum* and small-fruited varieties of *C. frutescens*. It contains a minimum of 0.4% of total capsaicinoids expressed as capsaicin, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Capsicum Oleoresin, Refined and Quantified). A red or brown mobile extract that contains 6.5 to 8.0% of capsaicinoids expressed as capsaicin. It is produced from the herbal drug and alcohol or methyl alcohol by an appropriate procedure.

USP 31 (Capsicum). The dried ripe fruits of *Capsicum frutescens*, known in commerce as African Chillies, or of *C. annuum* var. *connoides*, known in commerce as Tabasco Pepper, or *C. annuum* var. *longum*, known in commerce as Louisiana Long Pepper, or of a hybrid between the Honka variety of Japanese Capsicum and the Old Louisiana Sport Capsicum, known in commerce as Louisiana Sport Pepper.

USP 31 (Capsicum Oleoresin). An alcoholic extract of the dried ripe fruits of *Capsicum annum* var. *minimum* and small fruited varieties of *C. fruiscons* (Solanaceae). It contains not less than 8% of total capsaicins. It is a dark red oily liquid. Soluble in alcohol, in acetone, in chloroform, in ether, and in volatile oils; soluble with opalescence in fixed oils. Store in airtight containers.

Profile

Capsicum has a carminative action but it is mainly used externally, often in the form of capsicum oleoresin, as a counter-irritant (see Rubefacients and Topical Analgesia, p.5). It is also included in preparations for the management of cough and cold symptoms. However, preparations of capsicum and capsicum oleoresin can be very irritant. Capsaicin (p.32), the active ingredient of capsicum, is also used in topical preparations in the treatment of painful skin conditions.

Capsicum oleoresin is used in 'pepper sprays' for law enforcement and self defence.

Capsicum also has culinary uses.

Homoeopathy. Capsicum has been used in homoeopathic medicines under the following names: Capsicum annuum; Cap. a.

Effects on the gastrointestinal tract. The initial response to the ingestion of a hot pepper is a hot or burning sensation in the mouth, which is attributed to the binding of capsaicin to receptors in the oral cavity.[1] Casein-containing substances such as milk can reverse this burning sensation, apparently by displacing capsaicin, this being due to their lipophilicity.

Spicy meals have long been associated with gastrointestinal discomfort and ingestion of meals containing 1.5 g of red or black pepper has been shown to cause signs of gastric mucosal damage comparable with those caused by a 625-mg dose of aspirin.[2] However, other studies in *animals*[3] and humans[4,5] suggest that capsaicin may have a protective effect on gastric mucosa. Ingestion of about 30 g of jalapeño peppers (a capsicum fruit) caused no visible damage to the duodenal or gastric mucosa of 12 healthy subjects[6] and daily ingestion of meals containing a total of 3 g of chilli powder did not affect the clinical progress of patients with duodenal ulcers given antacids.[7]

1. Henkin R. Cooling the burn from hot peppers. *JAMA* 1991; **266:** 2766.
2. Myers BM, *et al.* Effect of red pepper and black pepper on the stomach. *Am J Gastroenterol* 1987; **82:** 211–14.
3. Holzer P. Peppers, capsaicin, and the gastric mucosa. *JAMA* 1989; **261:** 3244–5.
4. Kang JY, *et al.* Chili—protective factor against peptic ulcer? *Dig Dis Sci* 1995; **40:** 576–9.
5. Yeoh KG, *et al.* Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Dig Dis Sci* 1995; **40:** 580–3.
6. Graham DY, *et al.* Spicy food and the stomach: evaluation by videoendoscopy. *JAMA* 1988; **260:** 3473–5.
7. Kumar N, *et al.* Do chillies influence healing of duodenal ulcer? *BMJ* 1984; **288:** 1803–4.

Pepper sprays. References to the toxic effects of 'pepper sprays' containing capsicum oleoresin.

1. Zollman TM, *et al.* Clinical effects of oleoresin capsicum (pepper spray) on the human cornea and conjunctiva. *Ophthalmology* 2000; **107:** 2186–9.
2. Chan TC, *et al.* The effect of oleoresin capsicum "pepper" spray inhalation on respiratory function. *J Forensic Sci* 2002; **47:** 299–304.

Preparations

Ph. Eur.: Capsicum Tincture, Standardised.

Proprietary Preparations (details are given in Part 3)

Arg.: Redol†; ***Austria:*** ABC; ***Braz.:*** Hercap; ***Chile:*** Dolorub Capsico; Parche Leon Fortificante; ***Ger.:*** ABC Warme-Pflaster†; Capsamol; Dolenon†; Hansaplast ABC Warme-Pflaster†; Jucurba; Rheumamed; Thermo Burger; ***Israel:*** Dragon Plaster; ***Ital.:*** Cerotto Bertelli Arnikos; Dolpyc; Thermogene; ***Port.:*** Neodor; ***UK:*** Fiery Jack; ***USA:*** Salonpas Hot.

Multi-ingredient: ***Arg.:*** Bifena; Infrarub†; Sebulex; Veracolate; ***Austral.:*** APR Cream†; Bioglan Joint Mobility; Bioglan The Blue One; Euphrasia Complex; Euphrasia Compound; For Peripheral Circulation Herbal Plus Formula 5; Gingo A†; Goanna Heat Cream; Lifesystem Herbal Formula 6 For Peripheral Circulation†; Percutane; Radian-B†; Valerian†; ***Austria:*** Mentopin; Salhumin; Trauma-Salbe warmend; ***Belg.:*** Rado-Salil; Stilene; Thermocream; ***Braz.:*** Pilulas Ross; ***Canad.:*** Absorbine Arthritis; Cayenne Plus†; Rheumalan†; Rhumatisme; ***Fr.:*** Disalgyl†; Kamol†; Le Thermogene†; ***Ger.:*** Caye Rheuma-Balsam; Gothaplast Rheumamed AC; ***Hong Kong:*** LEAN Formula w/ Advantra†; ***India:*** Algipan; Flexi-muv; Inflazone; Relaxyl; ***Indon.:*** Osteor-C; Sloan's Liniment; ***Israel:*** Ment-O-Cap; Radian-B; Rublex Massage Cream; ***Ital.:*** Altadrine; Capso; Capsolin; Gelovis; Remy; Sloan; ***Malaysia:*** Dandelion Complex†; Total Man†; ***Mex.:*** Parche Negro Belladona; ***Neth.:*** Cremor capsici comp; Cremor Capsici compositus; Kruidvat Spierbalsem; ***Pol.:*** Kapsiplast; ***Port.:*** Caroid†; Medalginan; ***Rus.:*** Efcamon (Эфкамон); Espol (Эспол); ***S.Afr.:*** Brooklax Pills; Infrarub; Moultons Pain Paint; Muscle Rub; SB 3 Triple Action Pills; SB Shisalene; Sloan's Heat Rub; Sloan's Liniment Rub; Tandpyndruppels; ***Spain:*** Dolokey; Embrocacion Gras; Linimento Naion; Termosan; ***Switz.:*** Carmol Plus†; Massorax†; Midalgan; ***Thai.:*** Flatulence; Meloids; Veracolate; ***Turk.:*** Algo-Wax; Capsalgine; Capsi-Gel; Gelocaps; Mentolin; ***UK:*** Allens Dry Tickly Cough; Balmosa; Buttercup Syrup; Catarrh Mixture; Cremalgin; Fiery Jack; Hactos; Hansaplast Herbal Heat Plaster; Herbal Indigestion Naturtabs; Honey & Molasses; Indian Brandee; Indigestion and Flatulence; Indigestion Relief; Jamaican Sarsaparilla; Kilkof; Life Drops; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Radian-B; Ralgex; Rheumatic Pain Relief; Sanderson's Throat Specific; Vegetable Cough Remover; ***USA:*** Salonpas Gel Patch; Throat Discs; ***Venez.:*** Ehrlich Balsamo.

Caraway

Alcaravea; Alcaravia; Caraway Fruit; Caraway Seed; Carum; Carvi; Carvi fructus; Cumin des Prés; Fructus Carvi; Kmínový plod; Kmynų vaisiai; Köménytermés; Kumina; Kümmel; Kummin; Owoc kminku.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Caraway Fruit; Caraway BP 2008). The whole, dried fruits of *Carum carvi*. It contains not less than 3.0% v/w of essential oil, calculated with reference to the dried drug. It has an odour reminiscent of carvone. Protect from light.

The BP 2008 directs that when Powdered Caraway is prescribed or demanded, material containing not less than 2.5% v/w of essential oil shall be dispensed or supplied.

USNF 26 (Caraway). The dried, ripe fruit of *Carum carvi* (Apiaceae). Preserve against attack by insects.

Profile

Caraway is an aromatic carminative, and is used in gastrointestinal disorders and as a flavour. The seeds have culinary uses. It is the source of caraway oil (below).

Preparations

USNF 26: Compound Cardamom Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Mag Kottas Krauterexpress Abfuhrtee; Midro Tee; Montana; Nesthakchen; Species Carvi comp†; ***Braz.:*** Balsamo Branco; ***Cz.:*** Blahungstee N†; Iberogast; ***Ger.:*** Carminativum Hofmann; Carminativum-Hetterich; Carminativum-Pascoe†; Cholosom-Tee; Floradix Multipretten N; Gastrol S†; Gastrosecur†; Iberogast; Lomatol†; Majocarmin-Tee; Montana N; Pascoventral; Presselin Blahungs K 4 N†; Presselin Dyspeptikum†; Stovalid N†; ***Israel:*** Jungborn; Lido Tea; Midro-Tea; ***Ital.:*** Anice (Specie Composta)†; Cadifen; Cadimint; Camomilla (Specie Composta)†; Florelax; Midro; Relaxcol; Tarassaco (Specie Composta)†; ***Pol.:*** Apinorm; Laxantol; Melis-Tonic; Rhelax; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; ***Rus.:*** Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); Herbion Drops for the Stomach (Гербион Желудочные Капли); ***S.Afr.:*** Clairo; ***Spain:*** Natusor Aerofane†; ***Switz.:*** Kernosan Heidelberger Poudre; Phytomed Gastro†; Tisane favorisant l'allaitement.

Caraway Oil

Alcaravea, aceite esencial de; Carvi aetheroleum; Carvi Ethereoleum; Carvi, huile essentielle de; Kmínová silice; Kuminaöljy; Kümmelöl; Kumminolja; Olejek kminkowy; Oleum Cari; Oleum Carui; Oleum Carvi.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Caraway Oil). The oil obtained by steam distillation from the dry fruits of *Carum carvi*. A clear, colourless or yellow liquid. Relative density 0.904 to 0.920. Store in well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Caraway Oil). The volatile oil distilled from caraway. It contains not more than 50% v/v of carvone ($C_{10}H_{14}O$). Soluble 1 in 8 of alcohol (80%). Store in airtight containers. Protect from light.

Profile

Caraway oil is an aromatic carminative and is used in gastrointestinal disorders and as a flavour. It is also employed as caraway water for infant colic (see Gastrointestinal Spasm, p.1696).

Preparations

BP 2008: Aromatic Cardamom Tincture; Compound Cardamom Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Nesthakchen; Parodontax; Sabatif; Sigman-Haustropfen; Spasmo Claim; ***Cz.:*** Contraspan†; Naturident†; ***Ger.:*** Aspasmon N†; Enteroplant; Euflat I†; Floradix Multipretten N; Galloselect M†; Gastricard†; Gastrysat; Lomatol†; Majocarmin forte†; Neo-Ballistol†; Pascopankreat novo†; ratioGast†; ***Hung.:*** Enteroplant; ***India:*** Bestozyme; Catazyme-P; Neopeptine; Vitazyme; ***Ital.:*** Relaxcol; ***Mex.:*** Enterokan; ***Singapore:*** Enterokan†; ***Switz.:*** Flatulex; Huile Po-Ho A. Vogel; Parodontax†; ***Thai.:*** Gas-Nep; Gripe Mixture; ***UK:*** Atkinson & Barker's Gripe Mixture; Nurse Harvey's Gripe Mixture.

Carbon-13

Carbono 13.

CAS — 14762-74-4.

Profile

Carbon-13 is a naturally occurring, non-radioactive, stable isotope of carbon. It has been used to label organic compounds, such as urea (p.1620), for use in diagnostic tests, including breath tests for the diagnosis of *Helicobacter pylori* infection.

Preparations

USP 31: Urea C 13 for Oral Solution.

Proprietary Preparations (details are given in Part 3)

Cz.: Pylobactell; ***Denm.:*** Diabact; Helicobacter Test; ***Fr.:*** Heli-Kit; ***Gr.:*** Helicobacter; Pylobactel; ***Ital.:*** Breathquality-UBT; Citredici UBT Kit; Expirobacter; Helicokit; Pylobactell†; ***Mex.:*** Alitest†; ***Neth.:*** Helico State; Pylobactell-13C; UBTest; ***Port.:*** Helico-teste; Helicobacter Test; Ubit; ***Spain:*** Pylori Chek†; Tau Kit; Ubtest; ***Swed.:*** Diabact UBT; Helicobacter Test; ***Switz.:*** Helicobacter Test; Pylori 13†; ***UK:*** Diabact UBT; Pylobactell; ***USA:*** Meretek UBT.

Multi-ingredient: ***USA:*** Ez-HBT.

Cardamom

Cardamomi; Cardamomo, fruto del.

Pharmacopoeias. In *Br.* and *Jpn.* Also in *USNF.*

BP 2008 (Cardamom Fruit). The dried, nearly ripe fruit of *Elettaria cardamomum* var. *minuscula*. Only the seeds are used in making preparations of cardamom and they are used immediately after removal from the fruit. The seeds should not be stored after removal from the fruit. They have a strongly aromatic odour and taste and contain not less than 4% v/w of volatile oil.

USNF 26 (Cardamom Seed). The dried ripe seed of *Elettaria cardamomum* (Zingiberaceae), recently removed from the capsule. Preserve against attack by insects.

Profile

Preparations of cardamom are used as carminatives and as flavours. The seeds have culinary uses. Cardamom seeds are the source of cardamom oil (below).

Preparations

USNF 26: Compound Cardamom Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Peritone; Travelaide†; ***Austria:*** Mariazeller; ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schwedenbitter; Klosterfrau Melisana; ***Ger.:*** Gallexier; Montana N; Presselin Dyspeptikum†; Schwedentrunk Elixier; ***India:*** Carmicide; ***Pol.:*** Melisana Klosterfrau; ***Rus.:*** Suprima-Broncho (Суприма-бронхо); ***S.Afr.:*** Alma; Enterodyne; Helmontskruie; ***Spain:*** Digestovital†; ***Switz.:*** Stomacine; ***Thai.:*** Carmicide†; ***UK:*** Indian Brandee; Pegina.

Cardamom Oil

Cardamomo, aceite esencial de; Ol. Cardamom.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2008 (Cardamom Oil). A clear, colourless or pale yellow liquid, visibly free from water, with an odour of cardamom fruit. It is distilled from crushed cardamom fruit. At 20° it is soluble 1 in 6 of alcohol (70%). Store at a temperature not exceeding 25° in well-filled containers. Protect from light.

USNF 26 (Cardamom Oil). The volatile oil obtained from cardamom seed. Soluble 1 in 5 of alcohol (70%). Store in airtight containers. Protect from light.

Profile

Preparations of cardamom oil are used as carminatives and as flavours.

Preparations

BP 2008: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Compound Rhubarb Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***India:*** Catazyme-P; Digeplex; Vitazyme; ***Thai.:*** Gas-Nep.

Carglumic Acid *(rINN)*

Acide Carglumique; Ácido carglúmico; Acidum Carglumicum; Carglutamic Acid; Karglumik Asit. *N*-Carbamoyl-L-glutamic acid.

Карглумовая Кислота

$C_6H_{10}N_2O_5$ = 190.2.

CAS — 1188-38-1.

ATC — A16AA05.

ATC Vet — QA16AA05.

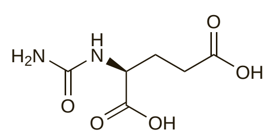

Profile

Carglumic acid is used for the treatment of hyperammonaemia in patients with *N*-acetylglutamate synthase deficiency. The initial daily dose ranges from 100 to 250 mg/kg, adjusted thereafter to maintain normal plasma levels of ammonia. Individual responsiveness to carglumic acid should be tested before starting long-term therapy; daily maintenance doses range from 10 to 100 mg/kg. The total daily dose should preferably be taken as 2 to 4 divided doses before food.

◊ References to the use of carglumic acid in the management of hyperammonaemia due to *N*-acetylglutamate synthase deficiency.

1. Bélanger-Quintana A, *et al.* Hyperammonaemia as a cause of psychosis in an adolescent. *Eur J Pediatr* 2003; **162:** 773–5.
2. Caldovic L, *et al.* Restoration of ureagenesis in N-acetylglutamate synthase deficiency by N-carbamylglutamate. *J Pediatr* 2004; **145:** 552–4.
3. Gebhardt B, *et al.* N-carbamylglutamate protects patients with decompensated propionic aciduria from hyperammonaemia. *J Inherit Metab Dis* 2005; **28:** 241–4.
4. Guffon N, *et al.* Neonatal hyperammonemia: the N-carbamoyl-L-glutamic acid test. *J Pediatr* 2005; **147:** 260–2.
5. Jones S, *et al.* N-Carbamylglutamate for neonatal hyperammonaemia in propionic acidaemia. *J Inherit Metab Dis* 2008. Available at: doi: 10.1007/s10545-008-0777-1

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Carbaglu; ***Cz.:*** Carbaglu; ***Denm.:*** Carbaglu; ***Fr.:*** Carbaglu; ***Ger.:*** Carbaglu; ***Ital.:*** Carbaglu; ***Neth.:*** Carbaglu; ***Pol.:*** Carbaglu; ***Port.:*** Carbaglu; ***Spain:*** Carbaglu; ***UK:*** Carbaglu.

Carnauba Wax

Brazil Wax; Caranda Wax; Carnauba, cire de; Cera carnauba; Cera Copeniciae; Cera de carnauba; E903; Karnauba pálmaviasz; Karnaubavaha; Karnaubavax; Karnaubo vaškas; Vosk karnaubský.

CAS — 8015-86-9.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera*. Pale yellow or yellow powder, flakes, or hard masses. It has a relative density of about 0.97. M.p. 80° to 88°. Practically insoluble in water and in alcohol; soluble on heating in ethyl acetate and in xylene. Protect from light.

USNF 26 (Carnauba Wax). It is obtained from the leaves of *Copernicia cerifera* (Palmae). A light brown to pale yellow, moderately coarse powder or flakes, possessing a characteristic bland odour, and free from rancidity. Sp. gr. about 0.99. M.p. 80° to 86°. Insoluble in water; slightly soluble in boiling alcohol; soluble in warm chloroform and in warm toluene; freely soluble in warm benzene.

Profile

Carnauba wax is used in pharmacy as a coating agent. Its use is also permitted in certain foods. Various types and grades are used industrially in the manufacture of polishes.

Caroverine *(pINN)*

Caroverina; Carovérine; Caroverinum. 1-[2-(Diethylamino)ethyl]-3-(*p*-methoxybenzyl)-2(1*H*)-quinoxalinone.

Кароверин

$C_{22}H_{27}N_3O_2$ = 365.5.

CAS — 23465-76-1.

ATC — A03AX11.

ATC Vet — QA03AX11.

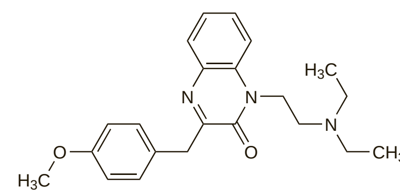

Profile

Caroverine is a smooth muscle relaxant with calcium-channel blocking and glutamate-antagonist properties. It is used as the base or the hydrochloride in conditions associated with painful smooth muscle spasm. Typical doses (expressed as the base) are 20 to 40 mg by mouth three or four times daily. It may also be given by slow intravenous or intramuscular injection in doses of 40 to 80 mg. Caroverine has also been given rectally. It is also used in cerebral circulatory disorders and in tinnitus.

◊ References.

1. Denk DM, *et al.* Caroverine in tinnitus treatment: a placebo-controlled blind study. *Acta Otolaryngol* 1997; **117:** 825–30.
2. Ehrenberger K. Clinical experience with caroverine in inner ear diseases. *Adv Otorhinolaryngol* 2002; **59:** 156–62.
3. Quint C, *et al.* The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol* 2002; **122:** 877–81.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Delirex; Spasmium; Tinnitin; ***Switz.:*** Calmaverine†.

Multi-ingredient: ***Austria:*** Spagall; Spasmium comp.

Cartilage and Cartilage Extracts

Profile

Preparations containing cartilage or cartilage extracts from various sources have been used in musculoskeletal and joint disorders and as nutritional supplements. A product derived from shark cartilage (AE-941, p.677) is under investigation as an antineoplastic.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Car-ti-buron; Cartilade†; Cartilago Vital; Cartimax; ***Austral.:*** Cartilag; ***Indon.:*** Fellafit; Sharko Inside.

Multi-ingredient: ***Arg.:*** Arrumalon†; Car-ti buron flex; Cartiflex; Collagen T2-Gag†; CT1000; Rep-Cartil; ***Braz.:*** Rumalon†; ***Chile:*** Cartilago Compuesto†; Cartilago T-500; Rumalon; ***Fr.:*** Oligo-Yang†; ***Hong Kong:*** Cervusen; ***Hung.:*** Rumalon†.

Carzenide *(rINN)*

Carcenida; Carzenida; Carzénide; Carzenidum. *p*-Sulphamoylbenzoic acid.

Карзенид

$C_7H_7NO_4S$ = 201.2.

CAS — 138-41-0.

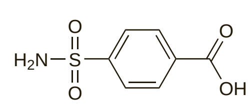

Profile
Carzenide is an antispasmodic that has been used in the treatment of dysmenorrhoea.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Saldeva†.

Oriental Cashew

Anacardier d'orient; Anacardium; Cashew-pähkinä; Indisk nöt; Marking Nut Tree; Markingnut Tree; Nanercz wschodni; Semecarpus anacardium.

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Oriental Cashew for Homoeopathic Preparations; Semecarpus Anacardium ad Praeparationes Homoeopathicas). The dried fruit of *Semecarpus anacardium* (*Anacardium orientale*). It contains a minimum 6.0% of total phenol derivatives expressed as eugenol.

Profile
Various parts of the oriental cashew, *Semecarpus anacardium* (Anacardiaceae), and their preparations are used in traditional Indian medicine. The oil contains bhilawanols, irritant substances reputed to have cytotoxic action.

Homoeopathy. The dried ripe fruit of oriental cashew is used in homoeopathic medicines under the following names: Anacardium; Semecarpus anacardium; Anacardium orientale; Anac. or.

Cassia Oil

Canela de la China, aceite de; Cannelier, huile essentielle de; Chinese Cinnamon Oil; Cinnamomi cassiae aetheroleum; Cinnamomi Cassiae Etheroleum; Kassiakaneliöljy; Kassiaolja; Kínai fahéjolaj; Kinini̧ cinamonų eterinis aliejus; Oleum Cassiae; Oleum Cinnamomi; Oleum Cinnamomi Cassiae; Silice skořicovníku čínského.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Chin. and *Jpn* also include cassia bark which may be known as cinnamon bark. In some countries cassia oil is known as cinnamon oil (p.2283).

Ph. Eur. 6.2 (Cassia Oil). The oil obtained by steam distillation of the leaves and young branches of *Cinnamomum cassia* (*C. aromaticum*). It contains 70 to 90% of cinnamaldehyde. A clear, mobile, yellow to reddish-brown liquid, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from light and heat.

Profile
Cassia oil has properties resembling those of cinnamon oil (p.2283) and is used similarly as a carminative and flavour. It has also been used in aromatherapy. Hypersensitivity to cinnamaldehyde, the main constituent of cassia oil, has been reported.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Tiger Balm Red; ***S.Afr.:*** Balsem Vita GEEL; Balsem Vita ROOI; Balsem Vita WIT; Moultons Pain Paint; Stuidruppels; ***UK:*** Dragon Balm.

Castor Oil

Aceite de Ricino; Hintyağı; Huile de Ricin; Ol. Ricin.; Oleum Ricini; Ricini Oleum; Ricini Oleum Virginale; Ricino, aceite de; Ricinolja (jungfruolja); Ricinový olej panenský; Ricinusolaj; Risiiniöljy, neitsytöljy; Rizinusöl.

ATC — A06AB05.
ATC Vet — QA06AB05.

NOTE. CASOIL is a code approved by the BP 2008 for use on single unit doses of eye drops containing castor oil where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Eur. also includes hydrogenated castor oil and refined castor oil. *USNF* includes hydrogenated castor oil.

Ph. Eur. 6.2 (Castor Oil, Virgin). The fatty oil obtained by cold expression from the seeds of *Ricinus communis*. Relative density about 0.958. It is a clear, almost colourless or slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled airtight containers. Protect from light.

Ph. Eur. 6.2 (Castor Oil, Hydrogenated; Ricini Oleum Hydrogenatum). The oil obtained by hydrogenation of castor oil. It consists mainly of the triglyceride of 12-hydroxystearic acid. Almost white to pale yellow fine powder, masses, or flakes. M.p. 83° to 88°. Practically insoluble in water and in petroleum spirit; very slightly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Store in well-filled containers.

Ph. Eur. 6.2 (Castor Oil, Refined). The fatty oil obtained by cold expression from the seeds of *Ricinus communis* and then refined. A suitable antoxidant may be added. Relative density about 0.958. It is a clear, almost colourless or slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled, airtight containers. Protect from light.

USP 31 (Castor Oil). The fixed oil obtained from the seed of *Ricinus communis* (Euphorbiaceae). It is a pale yellowish or almost colourless, transparent, viscid liquid. Has a faint, mild odour; is free from foreign and rancid odour; and has a bland, characteristic taste. Soluble in alcohol; miscible with dehydrated alcohol, with chloroform, with ether, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40°.

USNF 26 (Hydrogenated Castor Oil). Refined, bleached, hydrogenated, and deodorised castor oil, consisting mainly of the triglyceride of hydroxystearic acid. A white, crystalline wax. M.p. 85° to 88°. Insoluble in water and in most common organic solvents. Store in airtight containers at a temperature not exceeding 40°.

Adverse Effects and Precautions
Oral administration of castor oil, particularly in large doses, may produce nausea, vomiting, colic, and severe purgation. Castor oil should not be given when intestinal obstruction is present.

The seeds of *Ricinus communis* contain a toxic protein, ricin (p.2379). Allergic reactions have been reported in subjects handling the seeds.

Uses and Administration
Castor oil is used externally for its emollient effect. It has also been used topically to allay irritation due to foreign bodies in the eye. Castor oil may be employed as the solvent in some injections.

Hydrogenated castor oil is used as a stiffening agent. Polyoxyl castor oils (p.1918) are used as emulsifying and solubilising agents.

Castor oil has been used as a laxative, but such use is obsolete.

Preparations
BP 2008: Chloroxylenol Solution; Flexible Collodion; Zinc and Castor Oil Ointment;
USP 31: Aromatic Castor Oil; Castor Oil Capsules; Castor Oil Emulsion; Flexible Collodion.

Proprietary Preparations (details are given in Part 3)

Arg.: Capsulas Handel†; ***Braz.:*** Laxol; ***Canad.:*** Neoloid†; ***Ger.:*** Laxopol; ***Gr.:*** Kikelaio EF 3†; ***Israel:*** Laxopol; ***Mex.:*** Ricitel; ***Switz.:*** Herbapharm Rical†; Rical; ***Turk.:*** Ricilaks; Ricipan; ***USA:*** Emulsoil; Neoloid; Purge†.

Multi-ingredient: ***Arg.:*** Calculina†; ***Austral.:*** Seda-Rash†; ***Chile:*** Node DS; ***Cz.:*** Suspensio Visnevski cum Pice Liquida Herbacos; ***Mex.:*** Nutegen G†; ***Pol.:*** Salicylol; ***Spain:*** Otocerum; ***Switz.:*** Peru Stick; ***USA:*** Allanderm-T; Dermuspray; Dr Dermi-Heal; Granulderm; Granulex; GranuMed; Mammol; Proderm; Xenaderm.

Catalase

Caperase; Catalasa; Equilase; Optidase.

Profile
Catalase is an enzyme obtained from a wide variety of biological sources including animal liver (hepatocatalase) and certain bacteria and fungi. It is a protein composed of 4 polypeptide subunits, the precise composition of which varies according to the source, and has a molecular weight of about 240 000. Catalase has the ability to promote the decomposition of hydrogen peroxide to water and oxygen.

It has been applied to wounds and skin ulcers and has also been used in the treatment of eczema. It has sometimes been used with glucose oxidase (p.2313) in food preservation to break down hydrogen peroxide produced during oxidation of glucose, and is also included in preparations for contact lens care to neutralise hydrogen peroxide.

Catalase is a free-radical scavenger and has been investigated for its ability to limit reperfusion injury thought to be related to free-radical production. Combinations of catalase with superoxide dismutase have also been investigated.

◊ References.

1. Greenwald RA. Superoxide dismutase and catalase as therapeutic agents for human diseases: a critical review. *Free Radic Biol Med* 1990; **8:** 201–9.

Preparations
Proprietary Preparations (details are given in Part 3)

Ital.: Citrizan; ***Spain:*** Biocatalase†.

Multi-ingredient: ***Arg.:*** One Step†; Oxysept Comfort; Vitix; ***Canad.:*** UltraCare; ***Fr.:*** Pulvo 47 Neomycine†; Pulvo 47†; ***Ger.:*** Pulvo; Pulvo Neomycin; ***Gr.:*** Pulvo 47; ***Ital.:*** Citrizan Antibiotico; ***NZ:*** Omnicare 1 Step; ***Thai.:*** Pulvo 47; ***Turk.:*** Pulvo 47; ***USA:*** UltraCare.

Catechu

Gambier; Gambir; Pale Catechu.

CAS — 8001-48-7.

NOTE. Distinguish from Black Catechu (p.2267).

Pharmacopoeias. In *Jpn.* Also in *BP(Vet).*

Chin. and *Jpn* include Ramulus Uncariae cum Uncis, the thorn from various species of *Uncaria*.

BP(Vet) 2008 (Catechu). A dried aqueous extract of the leaves and young shoots of *Uncaria gambier* occurring as dull pale greyish-brown to dark reddish-brown cubes. Odourless or almost odourless.

Profile
Catechu is an astringent and has been given in preparations for the treatment of diarrhoea and other gastrointestinal disorders.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Chemists Own Diarrhoea Mixture†; Diarcalm; ***Fr.:*** Elixir Bonjean; ***Indon.:*** Entrodiar; ***Ital.:*** Flavion; ***S.Afr.:*** Enterodyne; SB Diarrhoea Mixture; Tandpyndruppels; ***UK:*** Chesty Cough Relief; Spanish Tummy Mixture.

CD4 Antibodies

Anti-CD4 Monoclonal Antibodies; Anticuerpos CD4; CD4mAb; Monoclonal CD4 Antibodies.

Антитела Против СД4-Клеток

Profile
Monoclonal antibodies raised against CD4 receptors are under investigation in the treatment of immunologically mediated disorders, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma, cutaneous T-cell lymphoma, psoriasis, and various other skin disorders, with the aim of decreasing and eliminating circulating helper T lymphocytes. They have also been tried in transplantation. CD4 antibodies investigated include: clenoliximab, keliximab, priliximab, and zanolimumab.

Red Cedar

Eastern Red Cedar.

NOTE. Distinguish cedar wood oil, obtained from species of *Juniperus virginiana*, and cedar leaf oil, obtained from *Thuja occidentalis* (see Thuja, p.2400).

Profile
Red cedar, *Juniperus virginiana* (Cupressaceae), is the source of cedarwood oil (cedar wood oil; red cedar oil). The oil is used in perfumery and is included in preparations for nasal congestion and various skin disorders. It is also used in aromatherapy. Atlantic cedarwood oil (Atlas cedarwood oil) from *Cedrus atlantica* (Pinaceae) and oils from the wood of other species of *Juniperus* and *Cedrus* are used similarly.

Cedarwood oil should be distinguished from cedar leaf oil, obtained from *Thuja occidentalis* (see Thuja, p.2400).

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Emser Nasensalbe; Wick Vaporub; ***Fr.:*** Vegebom; ***Ger.:*** Emser Nasensalbe N†; ***NZ:*** Vicks Vaporub; ***Port.:*** Betacade†; ***Swed.:*** Vicks Vaporub†; ***UK:*** No-Sor Vapour Rub.

Celery

Apio; Apium; Celery Fruit; Celery Seed.

CAS — 8015-90-5 (celery oil).

Profile
Celery consists of the dried ripe fruits of *Apium graveolens* (Umbelliferae). Other parts of the plant are also used. Celery is reported to have diuretic properties and has been included in herbal preparations for rheumatic disorders. Celery oil has also been used similarly. Allergic and photoallergic reactions have been reported.

Celery also has culinary uses. Celery seed oil is used in aromatherapy.

Homoeopathy. Celery has been used in homoeopathic medicines under the following names: Apium graveolens; Apium. gr.

◊ References.

1. Houghton P. Bearberry, dandelion and celery. *Pharm J* 1995; **255:** 272–3.

Insect repellent. A hexane extraction of celery seed has shown promise as a mosquito repellent.[1]

1. Tuetun B, *et al.* Repellent properties of celery, *Apium graveolens* L., compared with commercial repellents, against mosquitoes under laboratory and field conditions. *Trop Med Int Health* 2005; **10:** 1190–8.

Interactions. For a report of severe phototoxicity occurring in a patient who had consumed celery soup before undergoing PUVA therapy, see Interactions under Methoxsalen, p.1606.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Calmtabs†; ***Austral.:*** Arthriforte; Arthritic Pain Herbal Formula 1; Bioglan Arthri Plus; Boswellia Complex; Devils Claw Plus; Fluid Loss†; Guaiacum Complex†; Lifesystem Herbal Formula 1 Arthritic Aid†; ***Canad.:*** Herbal Diuretic; ***India:*** Flexi-muv; ***Malaysia:*** Celery Plus†; ***Philipp.:*** Ruflex; ***UK:*** Mixed Vegetable Tablets; Modern Herbals Rheumatic Pain; Rheumatic Pain; Rheumatic Pain Relief; Vegetex.

Cellaburate (rINN)

Celaburát; Celaburato; Celiuliozės acetatas-butiratas; Cellaburatum; Cellulosaacetatbutyrat; Cellulose Acetate Butanoate; Cellulose Acetate Butyrate; Cellulose, acétate butyrate de; Cellulosi acetas butyras; Cellulóz-acetát-butirát; Selluloosa-asetaattibutyraatti.

Целлабурат

CAS — 9004-36-8.

NOTE. Cabufocon A and Cabufocon B are both USAN for cellulose acetate butyrate.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cellulose Acetate Butyrate). A partly or completely *O*-acetylated and *O*-butyrated cellulose containing not less than 2.0% and not more than 30.0% of acetyl groups and not less than 16.0% and not more than 53.0% of butyryl groups, calculated with reference to the dried substance. A white, yellowish-white, or greyish-white, slightly hygroscopic, powder or granules. Practically insoluble in water and in alcohol; soluble in acetone, in formic acid, and in a mixture of equal volumes of methyl alcohol and dichloromethane. Store in airtight containers.

Profile

Cellaburate is a pharmaceutical excipient used in drug delivery systems. It has also been used in hydrophobic contact lens materials.

Cellobiose

Glucobiosa. 4-*O*-β-D-Glucopyranosyl-D-glucose.

$C_{12}H_{22}O_{11}$ = 342.3.

CAS — 528-50-7.

Profile

Cellobiose is an indigestible disaccharide that has been used to assess intestinal permeability. It has been used as an alternative to lactulose in the differential sugar absorption test (p.1739).

Cellulase (USAN)

Celulasa.

CAS — 9012-54-8.

Profile

Cellulase is a concentrate of cellulose-splitting (cellulolytic) enzymes derived from *Aspergillus niger* or other sources. It is used in food processing and has been given orally with other digestive enzymes for its supposed benefit in minor digestive disorders such as dyspepsia and flatulence. Hemicellulase has been given for similar purposes.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Pancrelase; ***Rus.:*** Festal (Фестал).

Multi-ingredient: ***Arg.:*** Arnol; Biletan Enzimatico; Biluen Enzimatico; Dom-Polienzim; Gastridin-E; Gastron Fuerte†; Pakinase; Pankreon Total; Polienzim; ***Austria:*** Arca-Enzym; Ora-Gallin; ***Belg.:*** Digestomen; ***Braz.:*** Dasc; Digecap-Zimatico; Digeplus; Essen; Sintozima; ***Canad.:*** Digesta; ***Chile:*** Onoton†; ***Hong Kong:*** Topase†; ***India:*** Dipep; Farizym; Ipental†; Panolase†; ***Indon.:*** Cotazym Forte; ***Ital.:*** Digestopan†; Essen Enzimatico†; ***Mex.:*** Dixiflen; Espaven Enzimatico; Ochozim; Onoton; ***Philipp.:*** Spasmo-Canulase; ***Port.:*** Colerin-F; Espasmo Canulase; Fermetone Composto; ***Rus.:*** Ipental (Ипентал); ***S.Afr.:*** Spasmo-Canulase; ***Spain:*** Paidozim; ***Switz.:*** Spasmo-Canulase; Zymoplex†; ***Thai.:*** Sanzyme-S†; ***Turk.:*** Flaton; ***USA:*** Enzyme; ***Venez.:*** Stamyl.

Centaury

Centáurea menor; Centaurée, petite; Centaurii herba; Centaurii Minoris Herba; Ezerjófű; Petite Centaurée; Rohtorantasappi; Širdažolių žolė; Tausendgüldenkraut; Tusengyllenört; Zeměžlučová nat'; Ziele centurii.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Centaury). The whole or fragmented dried flowering aerial parts of *Centaurium erythraea*. It has a bitter taste. Protect from light.

Profile

Centaury is used as a bitter, including for appetite loss and dyspepsia.

Hepatotoxicity. A report[1] of hepatotoxicity possibly associated with the use of *Copaltra*, a herbal preparation marketed as an adjunct in the treatment of diabetes mellitus and containing centaury and *Coutarea latiflora* (copalchi) (Rubiaceae). A further 5 cases had been reported to the French pharmacovigilance network.

1. Wurtz A-S, *et al.* Possible hepatotoxicity from Copaltra, an herbal medicine. *Ann Pharmacother* 2002; **36:** 941–2.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Nat Zemezluce†.

Multi-ingredient: ***Austria:*** China-Eisenwein; Eryval; Magentee St Severin; Mariazeller; ***Braz.:*** Camomila; ***Cz.:*** Naturland Grosser Swedenbitter†; Stomaran; ***Fr.:*** Diacure; Tisane Hepatique de Hoerdt; ***Ger.:*** Amara-Tropfen; Canephron; Leber-Galle-Tropfen 83†; Montana N; Stullmaton†; ***Ital.:*** Assenzio (Specie Composta)†; Centaurea (Specie Composta)†; Genziana (Specie Composta)†; ***Rus.:*** Canephron N (Канефрон Н); Herbion Drops for the Stomach (Гербион Желудочные Капли); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Amara; Clairo; ***Spain:*** Natusor Hepavesical†; Odisor†; ***Switz.:*** Gastrosan; Phytomed Gastro†; Tisane pour l'estomac.

Cereus

Cactus; Night-blooming Cereus.

Profile

Cereus, the flowers and stems of night-blooming cereus (*Selenicereus grandiflorus*; *Cactus grandiflorus*) (Cactaceae), is thought to have cardiac stimulant actions and has been used in various cardiovascular disorders. It has also been used as an anthelmintic and in the treatment of rheumatism.

Homoeopathy. Cereus has been used in homoeopathic medicines under the following names: Cactus; Selenicereus grandiflorus; Cactus grandiflorus.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Cardibisana†; Oxacant N†; Oxacant-forte N†; Oxacant-Khella N†.

Ceruletide (BAN, USAN, rINN)

Caerulein; Cerulein; Ceruletid; Ceruletida; Cérulétide; Ceruletidum; FI-6934; 883-S; Seruletidi.

Церулетид

$C_{58}H_{73}N_{13}O_{21}S_2$ = 1352.4.

CAS — 17650-98-5 (ceruletide); 71247-25-1 (ceruletide diethylamine).

ATC — V04CC04.

ATC Vet — QV04CC04.

NOTE. The name Ceruleinum has been applied to Indigo Carmine (p.2324).

Description. Ceruletide is a decapeptide amide originally isolated from the skin of the Australian frog, *Hyla caerulea*, and other amphibians. Ceruletide may exist as a salt with 1 to 3 moles of diethylamine (ceruletide diethylamine).

Adverse Effects

Ceruletide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Hypotensive reactions may also occur.

Uses and Administration

Ceruletide is structurally related to pancreozymin (p.2361) and has similar actions. When given parenterally it stimulates gallbladder contraction and relaxes the sphincter of Oddi; it also causes an increase in the secretion of pancreatic enzymes and stimulates intestinal muscle.

As ceruletide diethylamine it is used as an aid to diagnostic radiology and in the management of paralytic ileus. It is also used in tests of pancreatic exocrine function, sometimes with secretin (p.2384); these studies generally require duodenal intubation of the patient and examination of duodenal aspirate and are rarely performed.

For most radiographic procedures of the biliary and digestive tracts ceruletide diethylamine is given by intramuscular injection in a dose equivalent to 300 nanograms/kg of ceruletide. Doses equivalent to 1 to 2 nanograms/kg per minute are given by intravenous infusion in pancreatic function tests and in the treatment of paralytic ileus.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Takus.

Cevimeline Hydrochloride (USAN, rINNM)

AF-102; AF-102B; Céviméline, Chlorhydrate de; Cevimelini Hydrochloridum; FKS-508; Hidrocloruro de cevimelina; SND-5008; SNI-2011; SNK-508. (±)-*cis*-2-Methylspiro[1,3-oxathiolane-5,3′-quinuclidine] hydrochloride hemihydrate.

Цевимелина Гидрохлорид

$C_{10}H_{17}NOS,HCl,\frac{1}{2}H_2O$ = 244.8.

CAS — 107233-08-9 (cevimeline); 153504-70-2 (cevimeline hydrochloride).

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631.

Sweating is a common problem with cevimeline; patients who sweat excessively should be advised to drink extra fluids to avoid dehydration. The manufacturer recommends that cevimeline should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision may affect the performance of skilled tasks. In addition cevimeline should be given with care to those with renal calculi or with biliary-tract disorders. It should also be used with caution in patients deficient in the cytochrome P450 isoenzyme CYP2D6 who may be at a higher risk of adverse effects.

Interactions

As for Neostigmine, p.632.

Drugs which inhibit cytochrome P450 isoenzymes CYP2D6, CYP3A3, or CYP3A4 inhibit the metabolism of cevimeline.

Pharmacokinetics

After oral doses cevimeline is absorbed from the gastrointestinal tract; peak concentrations are reached in 1.5 to 2 hours. The rate and extent of absorption are decreased when given with food. Cevimeline is less than 20% bound to plasma proteins. It is metabolised in the liver by cytochrome P450 isoenzymes CYP2D6, CYP3A3, and CYP3A4. Cevimeline is primarily excreted in the urine, mainly as metabolites; about 0.5% of a dose is excreted in the faeces.

Uses and Administration

Cevimeline is a selective muscarinic M_1 agonist used to improve the symptoms of dry mouth (see p.2140) in patients with Sjögren's syndrome. It is given as the hydrochloride by mouth in doses of 30 mg 3 times daily.

Dementia. Muscarinic M_1 agonists such as cevimeline have proved unsuccessful in relieving the symptoms of Alzheimer's disease (see p.362).

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Evoxac.

Chamomile

Camomille romaine, fleur de (chamomile flower, Roman); Chamomillae romanae flos (chamomile flower, Roman); Heřmánkový květ (matricaria flower); Kamillavirágzat (matricaria flower); Kamomillankukka (matricaria flower); Kamomillankukka, roomalainen (chamomile flower, Roman); Kamomillblomma (matricaria flower); Kamomillblomma, romersk (chamomile flower, Roman); Koszyczek rumianku (matricaria flower); Květ heřmánku římského (chamomile flower, Roman); Manzanilla; Matricaire, fleur de (matricaria flower); Matricariae flos (matricaria flower); Ramunėlių žiedai (matricaria flower); Rómaikamillavirág (chamomile flower, Roman); Taurių̨jų didramunių žiedai (chamomile flower, Roman).

Description. The name Chamomile is used for the dried flowerheads from 2 species of *Compositae* having similar medicinal properties:

- Chamomile from *Anthemis nobilis* (*Chamaemelum nobile*) is known as Chamomile Flowers, Chamomillae Romanae Flos, Manzanilla Romana, or Roman Chamomile Flower.
- Chamomile from *Matricaria recutita* (*Chamomilla recutita*) is known as Camomile Allemande, Camomilla, Chamomilla, Chamomillae Anthodium, Flos Chamomillae, Flos Chamomillae Vulgaris, German Chamomile, Hungarian Chamomile, Kamillenblüten, Manzanilla Ordinaria, Matricaria Flower, or Matricariae Flos

Pharmacopoeias. *Eur.* (see p.vii) includes chamomile from *Anthemis nobilis* and *Matricaria recutita*. *US* includes chamomile from *Matricaria recutita*.
Eur. also includes Matricaria Oil.

Ph. Eur. 6.2 (Chamomile Flower, Roman; Chamomile Flowers BP 2008). The dried flowerheads obtained from the cultivated double variety of *Anthemis nobilis* (*Chamaemelum nobile*), containing not less than 0.7% v/w of essential oil, calculated with reference to the dried drug. It has a strong characteristic odour. Protect from light.

Ph. Eur. 6.2 (Matricaria Flower; Matricariae Flos; Matricaria Flowers BP 2008). The dried flowerheads obtained from *Matricaria recutita* (*Chamomilla recutita*), containing not less than 0.4% v/w of blue essential oil and 0.25% of apigenin-7-glucoside, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Matricaria Oil; Matricariae Aetheroleum). The blue essential oil obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *Matricaria recutita* (*Chamomilla recutita*). There are 2 types of matricaria oil which are characterised as rich in bisabolol oxides, or rich in levomenol. Store in a well-filled, airtight container at a temperature not exceeding 25°. Protect from light.

USP 31 (Chamomile). The dried flowerheads of *Matricaria recutita* (*Matricaria chamomilla*, *Matricaria chamomilla* var. *courrantiana, Chamomilla recutita*) (Asteraceae alt. Compositae). It contains not less than 0.4% of blue volatile oil, not less than 0.3% of apigenin-7-glucoside, and not less than 0.15% of bisabolane derivatives, calculated as levomenol. Protect from light.

Profile

Chamomile has been applied externally as a poultice in the early stages of inflammation, and preparations containing chamomile or extracts of chamomile (including the oil or a constituent, chamazulene), have been used for skin disorders, including the prevention and treatment of cracked nipples and nappy rash. Chamomile German oil and Chamomile Roman oil are used in aromatherapy. 'Chamomile tea' is a domestic remedy for indigestion and has also been reported to have hypnotic properties.

There have been reports of contact sensitivity and anaphylaxis.

Homoeopathy. Chamomile has been used in homoeopathic medicines under the following names: Chamomilla; Cham.

◊ Reviews.

1. Berry M. The chamomiles. *Pharm J* 1995; **254:** 191–3.

Hypersensitivity. References.

1. Van Ketel WG. Allergy to Matricaria chamomilla. *Contact Dermatitis* 1987; **16:** 50–1.
2. McGeorge BC, Steele MC. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis* 1991; **24:** 139–40.
3. Rodriguez-Serna M, *et al.* Allergic and systemic contact dermatitis from Matricaria chamomilla tea. *Contact Dermatitis* 1998; **39:** 192–3.
4. Jensen-Jarolim E, *et al.* Fatal outcome of anaphylaxis to camomile-containing enema during labor: a case study. *J Allergy Clin Immunol* 1998; **102:** 1041–2.
5. Giordano-Labadie F, *et al.* Allergic contact dermatitis from camomile used in phytotherapy. *Contact Dermatitis* 2000; **42:** 247.
6. Foti C, *et al.* Contact urticaria from Matricaria chamomilla. *Contact Dermatitis* 2000; **42:** 360–1.
7. de la Torre Morín F, *et al.* Clinical cross-reactivity between Artemisia vulgaris and Matricaria chamomilla (chamomile). *J Investig Allergol Clin Immunol* 2001; **11:** 118–22.
8. Paulsen E, *et al.* Cosmetics and herbal remedies with Compositae plant extracts — are they tolerated by Compositae-allergic patients? *Contact Dermatitis* 2008; **58:** 15–23.

Preparations

Ph. Eur.: Matricaria Liquid Extract.

Proprietary Preparations (details are given in Part 3)
Austria: Kamillosan; ***Belg.:*** Babygencal; Kamillosan; ***Braz.:*** Ad-Muc; Kamillosan; ***Chile:*** Kamillosan†; ***Cz.:*** APS Balneum†; Hermankovy; Kamillosan; Rumancek Pravy†; ***Fr.:*** Cefamig; ***Ger.:*** Azulon; Chamo S†; Eukamillat†; Galenat Kamill N†; Kamillan supra; Kamille N†; Kamille†; Kamillen-Bad N Ritsert; Kamillen†; Kamillenbad Intradermi; Kamillencreme N†; Kamillenextract†; Kamillin; Kamilloderm†; Kamillopur; Kamillosan; Markalakt†; Matmille; PC 30 N; Soledum med†; ***Hong Kong:*** Camoderm; ***India:*** Kamillosan; ***Indon.:*** Kamillosan; ***Irl.:*** Kamillosan; ***Ital.:*** Ceru Spray; Milla; ***Mex.:*** Balsamo Nordin; Kamillosan; ***NZ:*** Kamillosan†; ***Pol.:*** Azulan; Azuseptol; ***Port.:*** Kamilosan; ***Rus.:*** Romasulan (Ромазулан); ***S.Afr.:*** Ashton & Parsons Infants Powders; ***Singapore:*** Camoderm†; ***Switz.:*** Kamillen-Bad†; Kamillex; Kamillin Medipharm; Kamillofluid; Kamillosan; ***UK:*** Ashton & Parsons Infants Powders; Kamillosan; ***Venez.:*** Kamillen.

Multi-ingredient: numerous preparations are listed in Part 3.

Chaparral

Profile

Chaparral is derived from the creosote bush, *Larrea tridentata* (Zygophyllaceae). It has been included in various herbal preparations but such use has been associated with severe hepatotoxicity. Recommendations that products containing chaparral should not be consumed have been made in several countries.

Masoprocol (p.742) is an antineoplastic isolated from the creosote bush.

Hepatotoxicity. References.

1. Gordon DW, *et al.* Chaparral ingestion: the broadening spectrum of liver injury caused by herbal medications. *JAMA* 1995; **273:** 489–90.
2. Batchelor WB, *et al.* Chaparral-induced hepatic injury. *Am J Gastroenterol* 1995; **90:** 831–3.
3. Sheikh NM, *et al.* Chaparral-associated hepatotoxicity. *Arch Intern Med* 1997; **157:** 913–19.
4. Kauma H, *et al.* Toxic acute hepatitis and hepatic fibrosis after consumption of chaparral tablets. *Scand J Gastroenterol* 2004; **39:** 1168–71.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Proyeast†.

Chenodeoxycholic Acid *(BAN, rINN)*

Acide chénodésoxycholique; Ácido quenodeoxicólico; Acidum chenodeoxycholicum; CDCA; Chenic Acid; Chenodeoksicholio rūgštis; Chenodiol *(USAN)*; Kenodeoksikolik Asit; Kenodeoksikoolihappo; Kenodeoxicholsyra; Kenodezoxikólsav; Kyselina chenodeoxycholová. 3α,7α-Dihydroxy-5β-cholan-24-oic acid.

Хенодезоксихолевая Кислота

$C_{24}H_{40}O_4$ = 392.6.
CAS — 474-25-9.
ATC — A05AA01.
ATC Vet — QA05AA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Chenodeoxycholic Acid). A white or almost white powder. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

Adverse Effects and Precautions

As for Ursodeoxycholic Acid, p.2408. Diarrhoea may occur more frequently than with ursodeoxycholic acid. A transient rise in liver-function test values and hypercholesterolaemia (low-density lipoprotein) have been reported with chenodeoxycholic acid.

Chenodeoxycholic acid is embryotoxic in some *animals.*

Interactions

As for Ursodeoxycholic Acid, p.2408.

Pharmacokinetics

Chenodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes first-pass metabolism and enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile and, under the influence of intestinal bacteria, the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid. Some lithocholic acid is excreted directly in the faeces and the rest absorbed, mainly to be conjugated and sulfated by the liver before excretion in the faeces. Chenodeoxycholic acid also undergoes epimerisation to ursodeoxycholic acid.

◊ References.

1. Crosignani A, *et al.* Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet* 1996; **30:** 333–58.

Uses and Administration

Chenodeoxycholic acid is a naturally occurring bile acid (p.2266). When given orally it reduces hepatic synthesis of cholesterol and provides additional bile salts to the pool available for solubilisation of cholesterol and lipids. It has been used for the dissolution of cholesterol-rich gallstones (p.2409) in patients with a functioning gallbladder, in usual doses of about 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentrations seen overnight. Treatment may need to be given for up to 2 years, depending on the size of the stone. It should be continued for about 3 months after radiological disappearance of the stones. Chenodeoxycholic acid is also used in reduced doses with ursodeoxycholic acid.

Chenodeoxycholic acid has been used as a dietary supplement in neonates and children with inborn errors of bile acid synthesis: it has been used in the treatment of cerebrotendinous xanthomatosis; with cholesterol in the Smith-Lemli-Opitz syndrome; and with cholic acid for bile acid synthesis defects.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Chenofalk†; ***Belg.:*** Chenofalk†; ***Ger.:*** Chenofalk; ***Hong Kong:*** Chenofalk†; ***Hung.:*** Chenofalk†; ***Indon.:*** Chenofalk; ***Israel:*** Chenofalk; Soluston†; ***Mex.:*** Chenofalk†; Sulobil; ***Neth.:*** Chenofalk; ***Port.:*** Chebil†; Xebyl; ***Spain:*** Quenobilan; Quenocol†; ***Turk.:*** Chenofalk.

Multi-ingredient: ***Austria:*** Lithofalk†; ***Ger.:*** Lithofalk; Urso Mix†; ***Gr.:*** Lithiofalk†; ***Ital.:*** Bilenor.

Chloroacetophenone

ω-Chloroacetophenone; 1-Chloroacetophenone; Cloroacetofenona; CN; CN Gas; Phenacyl Chloride. 2-Chloroacetophenone.

C_8H_7ClO = 154.6.
CAS — 532-27-4.

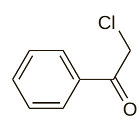

NOTE. The name mace is applied to solutions of chloroacetophenone.

Profile

Chloroacetophenone is a lachrymatory which is irritant to the skin and eyes. It has been used in a riot-control gas; it is described as a tear gas.

◊ References.

1. Hu H, *et al.* Tear gas—harassing agent or toxic chemical weapon? *JAMA* 1989; **262:** 660–3.
2. Treudler R, *et al.* Occupational contact dermatitis due to 2-chloracetophenone tear gas. *Br J Dermatol* 1999; **140:** 531–4.
3. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; **22:** 103–10.

Chloroplatinic Acid

Cloroplatínico, ácido; Kloroplatinasyra; Kwas chloroplatynowy. Hexachloroplatinic acid hexahydrate.

$H_2PtCl_6,6H_2O$ = 517.9.
CAS — 16941-12-1 (anhydrous chloroplatinic acid); 18497-13-7 (chloroplatinic acid hexahydrate).

Profile

Aqueous solutions of platinic chloride ($PtCl_4$ = 336.9) are used in corneal tattooing solutions.

Chondroitin Sulfate Sodium

Chondroitin 4-Sulfate (chondroitin sulfate A); Chondroitin Sulphate Sodium; Chondroïtine, sulfate sodique de; Chondroitini natrii sulfas; Chondroitin-sulfát sodná sůl; Chondroityny sodu siarczan; CSA (chondroitin sulfate A); Sodium Chondroitin Sulfate; Sodyum Kondroitin Sülfat.

$(C_{14}H_{19}NO_{14}SNa_2)_n$.
CAS — 9007-28-7 (chondroitin sulfate); 9082-07-9 (chondroitin sulfate sodium); 24967-93-9 (chondroitin sulfate A); 39455-18-0 (chondroitin sulfate A sodium); 25322-46-7 (chondroitin sulfate C); 12678-07-8 (chondroitin sulfate C sodium).
ATC — M01AX25.
ATC Vet — QM01AX25.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Chondroitin Sulphate Sodium). A natural copolymer based mainly on the two disaccharides obtained from cartilage of both terrestrial and marine origins. Depending on the animal species of origin, it shows different proportions of 4-sulfate and 6-sulfate groups. A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers. Protect from light.
USP 31 (Chondroitin Sulfate Sodium). The sodium salt of the sulfated linear glycosaminoglycan obtained from bovine, porcine, or avian cartilages of healthy and domestic animals used for food by humans. It consists mostly of the sodium salt of the sulfate ester of *N*-acetylchondrosamine (2-acetamido-2-deoxy-β-D-galactopyranose) and D-glucuronic acid copolymer. These hexoses are alternately linked β-1,4 and β-1,3 in the polymer. Chondrosamine moieties in the prevalent glycosaminoglycan are monosulfated primarily on position 4 and less so on position 6. Chondroitin sulfate sodium is extremely hygroscopic once dried. Store in airtight containers.

Profile

Chondroitin sulfate is an acid mucopolysaccharide that is a constituent of most cartilaginous tissues. It is used as the sodium salt, chondroitin sodium sulfate. It is given orally in reactive arthritides (see under Spondyloarthropathies, p.13), such as gonococcal arthritis, and is sometimes given with glucosamine (p.2313) for its supposed chondroprotective action in bone, joint, and connective tissue disorders. It is also used for its visco-elastic properties as an adjunct to ocular surgical procedures, including cataract extraction and intra-ocular lens implantation, and has been used for the relief of dry eye. A medium containing chondroitin sulfate A has been used to preserve corneas for transplantation. Chondroitin sulfate sodium has also been used as a means of replacing the glycosaminoglycan layer in the bladder in the treatment of interstitial cystitis (p.2179). Chondroitin sulfate A and C are components of the heparinoid danaparoid (p.1255).

Osteoarthritis. For references to the use of chondroitin in the treatment of osteoarthritis, including doubts about its value, see under Glucosamine, p.2313.

Preparations

USP 31: Chondroitin Sulfate Sodium Tablets; Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bioflogil; Condroitina†; Condrosulf†; Dunason; Liquiprin; Lubrictin; Norfisar†; Prof; Structum; ***Austria:*** Condrosulf; ***Belg.:*** Lacrypos; ***Braz.:*** Dunason; ***Canad.:*** Uracyst; ***Chile:*** Condro Sorb†; Condrosulf; ***Cz.:*** Condral; Condrosulf; ***Fr.:*** Chondrosulf; Lacrypos; Structum; ***Ger.:*** Uropol-S; ***Hung.:*** Condrosulf; ***Indon.:*** Viostin S; ***Malaysia:*** Chondril; ***Mex.:*** Condrosulf; Dunason; Maxus; Structum; ***Pol.:*** Condral; Recalcin; ***Port.:*** Condrosulf; Ossin; ***Rus.:*** Chondroitine-Akos (Хондроитин-Акос); Chondrolon (Хондролон)†; Structum (Структум); ***Spain:*** Condro San; Condrodin†; Condrosulf; ***Switz.:*** Condrosulf; Structum.

Multi-ingredient: ***Arg.:*** Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Cartiflex Forte; Ecosamina; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucotrin VL; Lacrimax; Maxus; Mecanyl Duo; Optilac; Sigmaflex; Vartalon Duo; Viscoat; ***Austral.:*** Duovisc; GenFlex 3; GenFlex Plus; Viscoat; ***Braz.:*** Artrolive; Condroflex; ***Canad.:*** Uracyst Test Kit; ***Chile:*** Artridol Duo; Condrosamina†; Dinaflex Duo; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex; ***Fr.:*** Viscoat; ***Ger.:*** Duovisc; Integra†; Viscoat; ***Hong Kong:*** Arthritil Plus; Duovisc†; Viscoat†; ***Hung.:*** Viscoat†; ***India:*** Cosantin†; Kondro; Osteocip; Osteoflex; ***Indon.:*** Aptivium Optimum Joint Formula; Artriox; Artritin; Bonic; Cartin Plus; Chondro-PA; Fitbon Plus; Flexor; Fripos; Joint Care; Jointfit; Maxitrin; Naturica Artro; Naturica Artro Plus; OA; OA Forte; OA Plus; Osamin; Oste; Ostela; Osteoflam; Osteokom; Osteokom Forte; Osteonic; Osteor; Osteor Plus; Osteor-C; Osvion Plus; Rheumatin; Rheumatin Forte; Triflexor; Triostee; Viopor; Viopor-M; Viostin Com; Viostin Com DS; Vosteon; ***Ital.:*** Cartago; Fitogenase; Joint Support; Reumilase SD; Viscoat; ***Malaysia:*** Duovisc; Viscoat; ***Mex.:*** Actiman; Artiflex; Vartalon Compositum; ***NZ:*** Viscoat; ***Philipp.:*** Flexxbon; Viscoat; ***Rus.:*** Artra (Артра); Chondroitine-Akos (Хондроитин-Акос); Chondroxide (Хондроксид); Theraflex (Терафлекс); ***S.Afr.:*** Duovisc; Viscoat; ***Singapore:*** Artril C; Duovisc; Flexeze†; Glutilage Plus; Seven Seas JointCare; Viscoat; ***Thai.:*** Duovisc; Viscoat; ***Turk.:*** Duovisc; Viscoat; ***UK:*** Flexeze; GlucOsamax; Joint Action; Jointace; ***USA:*** DisCoVisc; Viscoat; ***Venez.:*** Artrosamin; Viscoat†.

Chrome Alum

Chromium Potassium Sulfate; Chromium Potassium Sulphate; Cromo, alumbre de.

$KCr(SO_4)_2,12H_2O$ = 499.4.
CAS — 10141-00-1 (anhydrous chrome alum); 7788-99-0 (chromium potassium sulfate dodecahydrate).

Profile

Chrome alum is used in leather tanning, as a mordant in dyeing, and for hardening gelatin in photographic materials. It has been used as a sclerosant in medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Skleremo†; ***Braz.:*** Varikromo†; ***Fr.:*** Scleremo.

Chromium Trioxide

Anhídrido Crómico; Chromic Acid; Chromic Anhydride; Chromu(VI) tlenek; Cromo, tríóxido de.
CrO_3 = 99.99.
CAS — 1333-82-0.

Profile

Chromium trioxide and other chromium compounds are used in industry. Solutions of chromium trioxide are corrosive, acting by oxidation. Repeated contact with chromium and its salts may cause eczematous dermatitis, particularly in hypersensitive persons and can also cause deep perforating ulcers known as 'chrome holes'. If inhaled, chromic dusts cause rhinitis and painless ulcers which may perforate the nasal septum; inhalation may cause severe lung damage and inflammation of the eyes. There may also be involvement of the CNS and there is an increased risk of lung cancer. Hexavalent chromium compounds are more dangerous than di- or trivalent compounds.

Acute symptoms of poisoning from the ingestion of chromium salts include intense thirst, dizziness, abdominal pain with vomiting and diarrhoea, hepatic injury, anuria or oliguria, and peripheral vascular collapse. Kidney damage may lead to fatal uraemia.

Treatment is symptomatic and supportive. Protective measures should be taken when handling or working with chromium and its salts.

Chromium trioxide was formerly used as a caustic and astringent.

Chromium is an essential trace element as described on p.1934.

Adverse effects. General references[1-4] to chromium toxicity including reports of poisoning with ammonium dichromate,[5] chromium tripicolinate,[6] chromium trioxide,[7] potassium dichromate,[8-10] and sodium dichromate.[11]

1. WHO. Chromium. *Environmental Health Criteria 61.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/ehc/ehc/ehc61.htm (accessed 30/07/08)
2. Health and Safety Executive. The toxicity of chromium and inorganic chromium compounds. *Toxicity Review 21.* London: HMSO, 1989.
3. Barceloux DG. Chromium. *J Toxicol Clin Toxicol* 1999; **37:** 173–94.
4. Dayan AD, Paine AJ. Mechanisms of chromium toxicity, carcinogenicity and allergenicity: review of the literature from 1985 to 2000. *Hum Exp Toxicol* 2001; **20:** 439–51.
5. Meert KL, *et al.* Acute ammonium dichromate poisoning. *Ann Emerg Med* 1994; **24:** 748–50.
6. Cerulli J, *et al.* Chromium picolinate toxicity. *Ann Pharmacother* 1998; **32:** 428–31.
7. Matey P, *et al.* Chromic acid burns: early aggressive excision is the best method to prevent systemic toxicity. *J Burn Care Rehabil* 2000; **21:** 241–5.
8. Michie CA, *et al.* Poisoning with a traditional remedy containing potassium dichromate. *Hum Exp Toxicol* 1991; **10:** 129–31.
9. Stift A, *et al.* Liver transplantation for potassium dichromate poisoning. *N Engl J Med* 1998; **338:** 766–7.
10. Kolacinski Z, *et al.* Acute potassium dichromate poisoning: a toxicokinetic case study. *J Toxicol Clin Toxicol* 1999; **37:** 785–91.
11. Ellis EN, *et al.* Effects of hemodialysis and dimercaprol in acute dichromate poisoning. *J Toxicol Clin Toxicol* 1982; **19:** 249–58.

Handling. Chromium trioxide is a powerful oxidising agent and is liable to explode in contact with small quantities of alcohol, ether, glycerol, and other organic substances.

Chromocarb Diethylamine *(rINNM)*

Chromocarbe, Diéthylamine de; Chromocarbi Diethylaminum; Dietilamina de cromocarbo. The diethylamine salt of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid .
Хромокарба Диэтиламин
$C_{14}H_{17}O_4N$ = 263.3.
CAS — 4940-39-0 (chromocarb).

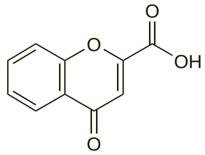

(chromocarb)

Profile

Chromocarb diethylamine is used to reduce capillary haemorrhage (including conjunctival haemorrhage) associated with various disorders, and for venous insufficiency. It is given by mouth in doses of 0.6 to 1.2 g daily in divided doses. It is also used as eye drops; 1 or 2 drops of a 10% solution have been instilled up to 6 times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Angioftal†; ***Fr.:*** Angiophtal†; Campel; ***Ital.:*** Fludarene; ***Port.:*** Fradilen; ***Spain:*** Activadone.

Chrysoidine Hydrochloride Citrate

Crisoidina, hidrocloruro del citrato de. 4-Phenylazobenzene-1,3-diamine hydrochloride citrate; Azobenzene-2,4-diamine hydrochloride citrate.
$C_{12}H_{12}N_4,HCl,C_6H_8O_7$ = 440.8.
CAS — 532-82-1 (chrysoidine hydrochloride); 5909-04-6 (chrysoidine hydrochloride citrate).

Profile

Chrysoidine hydrochloride citrate has been used as a dye but has been associated with tumours of the bladder.

Carcinogenicity. The development of tumours of the urinary bladder in anglers was possibly associated with the use of chrysoidine hydrochloride (chrysoidine Y; CI Basic Orange 2; Colour Index No. 11270) for colouring the maggots used as bait.[1-3]

1. Searle CE, Teale J. Chrysoidine-dyed bait: a possible carcinogenic hazard to anglers? *Lancet* 1982; **i:** 564.
2. Sole GM. Maggots dyed with chrysoidine: a possible risk to anglers. *BMJ* 1984; **289:** 1043–4.
3. Massey JA, *et al.* Maggots dyed with chrysoidine. *BMJ* 1984; **289:** 1451–2.

Chymopapain *(BAN, USAN, rINN)*

BAX-1526; Chymopapaïne; Chymopapainum; Kymopapaiini; Kymopapain; NSC-107079; Quimopapaína; Quimopapaina.
Химопапаин
CAS — 9001-09-6.
ATC — M09AB01.
ATC Vet — QM09AB01.

Description. Chymopapain is a proteolytic enzyme isolated from the latex of papaya (*Carica papaya*), differing from papain in electrophoretic mobility, solubility, and substrate specificity. Molecular weight about 27 000.

Units

One nanokatal (nKat) is defined as the amount of chymopapain which produces 1 nanomole of *p*-nitroaniline per second from DL-benzoylarginine-*p*-nitroanilide substrate at pH 6.4 and 37°.

In some countries CTE units have been used, defined as the amount of chymopapain that produces a hydrolysate from acid-denatured haemoglobin at pH 4.0 in one minute with an optical density at 275 nm equivalent to that of a tyrosine solution 0.0001%.

Adverse Effects

The most important adverse effect of chymopapain is anaphylaxis, which can occur in up to about 1% of patients. It has resulted in fatalities and restricts use to a single treatment session per patient. Typical symptoms include angioedema, hypotension, laryngeal oedema and bronchospasm, shock, and cardiac arrest. Allergic skin reactions may also occur. Other reported reactions include headache, nausea and vomiting, paralytic ileus, urinary retention, thrombophlebitis, paraesthesias, foot-drop, and discitis. Severe muscle spasm and an increase in back pain are common. Paraplegia, acute transverse myelitis, and intracerebral and subarachnoid haemorrhage have occurred.

Incidence of adverse effects. A 1984 postmarketing surveillance study on a US chymopapain preparation for intradiscal injection (*Chymodiactin*) involved data from 29 075 patients (representing about 50% of the total number of vials sold).[1] Anaphylactic reactions were confirmed in 194 patients (0.67%), 2 of whom died. The incidence was higher in women than in men. In 52 cases the reaction occurred after the test dose. Serious neurological reactions reported were: cerebral haemorrhage (6 cases, 3 fatal; autopsy revealed that they had underlying cerebrovascular abnormalities); paraplegia (11 cases, 5 of which may have been due to incorrect needle placement); transverse myelitis with paraplegia (2 cases, after 2 and 3 weeks, with subsequent recovery); and seizures (2 cases on injection and 1 several days after the procedure). Twenty-two patients had discitis with severe back pain and spasm. In 9 cases bacteria could be cultured, and 1 patient subsequently developed fatal *Staphylococcus aureus* meningitis.

Another review[2] of serious reactions associated with chymopapain between 1982 and 1991 (including data from the earlier postmarketing study) involved 121 reports among about 135 000 patients. They included fatal anaphylaxis (7), infections (24), haemorrhage (32), and neurological reactions (32).

Both reviews concluded that careful attention to proper patient selection and correct techniques of intradiscal needle placement are the most important factors in avoiding adverse effects with chymopapain.

1. Agre K, *et al.* Chymodiactin postmarketing surveillance: demographic and adverse experience data in 29075 patients. *Spine* 1984; **9:** 479–85.
2. Nordby EJ, *et al.* Safety of chemonucleolysis: adverse effects reported in the United States, 1982–1991. *Clin Orthop* 1993; **293:** 122–34.

Precautions

Chymopapain should not be used in those patients with a known sensitivity to papaya proteins or in patients with progressive paralysis, or tumours of the spinal cord, or lesions of the cauda equina. Severe spondylolisthesis is also a contra-indication. It should not be given to patients with heart failure, coronary artery disease, or respiratory failure who may be at increased risk if anaphylaxis occurs, nor to patients receiving beta blockers.

Care is required in administering chymopapain to ensure that the injection is into the disc and not intrathecal. However, discography is not recommended since the use of contrast media may exacerbate neurotoxicity and may inactivate the enzyme.

The risk of allergic reactions associated with chymopapain is so high that no patient should ever receive it more than once. Tests to identify those most at risk and pretreatment with antihistamines (H_1 and H_2) and corticosteroids may be used, but facilities for the emergency management of anaphylactic reactions should always be to hand when giving patients chymopapain. The risk of anaphylaxis is higher in women.

Injection of more than one disc is associated with an increased frequency of neurological reactions; therefore, such injection should only be carried out following confirmation of definite further disc involvement.

Uses and Administration

Chymopapain is used as an injection into the intervertebral disc in the treatment of sciatic pain and other symptoms secondary to herniation of intervertebral discs of the lumbar spine (chemonucleolysis).

Chymopapain injection should preferably be given under local, rather than general, anaesthesia. The dose for a single intervertebral disc is 2 to 4 nanokatals, with a maximum dose per patient of 8 nanokatals.

Chemonucleolysis. Dissolution of the disc by injection of chymopapain or other enzymes (chemonucleolysis) has been used as an effective alternative to surgery in patients with lumbar disc herniation (see Low Back Pain, p.7). However, concerns about its safety have led to a decline in its use, and discectomy is often preferred.

References.

1. Nordby EJ, *et al.* Chemonucleolysis. *Spine* 1996; **21:** 1102–5.
2. Brown MD. Update on chemonucleolysis. *Spine* 1996; **21** (24 suppl): 62S–68S.
3. Poynton AR, *et al.* Chymopapain chemonucleolysis: a review of 105 cases. *J R Coll Surg Edinb* 1998; **43:** 407–9.
4. Wittenberg RH, *et al.* Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; **26:** 1835–41.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Chymodiactin; ***Spain:*** Chymodiactin†.

Chymotrypsin *(BAN, rINN)*

Chimotripsinas; α-Chymotrypsin; Chymotrypsine; Chymotrypsinum; Kimotripszin; Kymotrypsiini; Kymotrypsin; Quimotripsina.
Химотрипсин
CAS — 9004-07-3.
ATC — B06AA04; S01KX01.
ATC Vet — QB06AA04; QS01KX01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Chymotrypsin). A proteolytic enzyme obtained by the activation of chymotrypsinogen extracted from the pancreas of beef. It contains not less than 5 microkatals in each mg. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 5.0. Solutions have a maximum stability at pH 3 and a maximum activity at about pH 8. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Chymotrypsin). A proteolytic enzyme crystallised from an extract of the pancreas gland of the ox, *Bos taurus* (Bovidae). It contains not less than 1000 USP units in each mg, calculated on the dried basis. A white to yellowish-white, crystalline or amorphous, odourless powder. An amount equivalent to 100 000 USP units is soluble in 10 mL of water and in 10 mL of sodium chloride 0.9%. Store in airtight containers at a temperature not exceeding 40°.

Units

Various methods have been used to assay the potency of chymotrypsin. Ph. Eur. 6.2 expresses activity in terms of microkatals while USP 31 expresses in terms of USP units. Other units that may be encountered are FIP units, Armour units, and Denver (or Wallace or Wampole) units.

Uses and Administration

Chymotrypsin is a proteolytic enzyme that has been used in ophthalmology for the dissection of the zonule of the lens, thus facilitating intracapsular cataract extraction and reducing trauma to the eye. For this purpose a solution of chymotrypsin in a sterile diluent such as sodium chloride 0.9% has been injected to irrigate the posterior chamber.

Chymotrypsin has also been given, usually by mouth or topically, for its supposed action in reducing soft-tissue inflammation and oedema associated with surgery or traumatic injuries, and in patients suffering from upper respiratory-tract disorders.

Hypersensitivity reactions have been reported.

Preparations

USP 31: Chymotrypsin for Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Alphacutanee†.

Multi-ingredient: ***Austria:*** Wobenzym; ***Braz.:*** Parenzyme; Parenzyme Ampicilina; Parenzyme Analgesico; Parenzyme Tetraciclina; Thiomucase; ***Cz.:*** Wobe-Mugos†; Wobenzym; ***Ger.:*** Enzym-Wied†; Wobe-Mugos E†; ***Gr.:*** Chymoral; ***India:*** Alfapsin; Orthal Forte; Soluzyme; ***Ital.:*** Essen Enzimatico†; ***Mex.:*** Ochozim; Quimotrip; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; ***Port.:*** Chimar; ***Rus.:*** Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Spain:*** Bristaciclina Dental; Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Quimodril; ***Venez.:*** Wobenzym N.

Ciliary Neurotrophic Factor

CNTF; Factor neurotrófico ciliar.

Цилиарный Нейротрофический Фактор

Profile

Ciliary neurotrophic factor (CNTF) is a nerve growth factor produced in neural tissues and released in response to injury. Recombinant CNTF has been investigated in motor neurone disease (p.2380), peripheral neuropathy, and obesity. CNTF is also under investigation for the treatment of retinitis pigmentosa and atrophic (dry) age-related macular degeneration as an intra-ocular polymer implant containing human retinal epithelial cells that have been genetically modified to secrete CNTF.

◊ References.

1. Miller RG, *et al.* A placebo-controlled trial of recombinant human ciliary neurotrophic (rhCNTF) factor in amyotrophic lateral sclerosis. *Ann Neurol* 1996; **39:** 256–60.
2. Ettinger MP, *et al.* Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA* 2003; **289:** 1826–32.
3. Sieving PA, *et al.* Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proc Natl Acad Sci U S A* 2006; **103:** 3896–901.

Cimicifuga

Actée à grappes; Black Cohosh; Black Snakeroot; Bugbane; Cimicífuga; Cimicifugae rhizoma; Cohosh negro.

NOTE. Distinguish from Blue Cohosh, p.2267.

Pharmacopoeias. *Chin.* includes the rhizome of *Cimicifuga heracleifolia*, *C. dahurica*, and *C. foetida*.
Jpn includes the rhizome of *C. simplex*, *C. heracleifolia*, *C. dahurica*, and *C. foetida*.
US includes the rhizome and roots of *C. racemosa*. *US* also includes the powdered form.
USP 31 (Black Cohosh). The dried rhizome and roots of *Actaea racemosa* (*Cimicifuga racemosa*). It contains not less than 0.4% triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$ = 660.8) with reference to the dried drug. Protect from light and moisture.

Profile

Cimicifuga, the roots of *Cimicifuga racemosa* (*Actaea racemosa*) (Ranunculaceae), is used for menopausal and gynaecological disorders and is included in preparations for coughs.

Homoeopathy. Cimicifuga has been used in homoeopathic medicines under the following names: Actaea racemosa; Actaea rac.; Cimicifuga racemosa; Cim. rac.

Adverse effects. A systematic review of the limited data available on adverse effects for cimicifuga concluded that adverse effects are generally mild and transient.[1] It has been reported that cimicifuga may cause dizziness, vertigo, headache, vomiting, and gastrointestinal irritation when taken in large doses.[2] From January 1998 to February 2005, Health Canada[3] had received 7 reports of adverse effects suspected of being associated with black cohosh, including dizziness, rash, pruritus, oedema, increased pulse, bradycardia, atrial fibrillation, changes in plasma-thyroid hormone concentration, vaginal bleeding, and convulsions. However, lack of data meant that causality could not be proved.

As of March 2006, the UK MHRA[2] had received 21 reports of **hepatotoxicity** associated with cimicifuga ingestion since 1998, which represented more than two-thirds of the total number of reports for any reaction related to cimicifuga. Likewise, there have been similar reports of hepatotoxicity in other countries including the USA, Germany, and Sweden.[2] Up to April 2006, 11 cases of liver impairment associated with cimicifuga had also been reported in Australia.[4] Adverse liver reactions reported worldwide have included abnormal liver function tests, jaundice, hepatitis, and liver failure.[2] In general, patients showed signs of recovery on stopping ingestion.[2] Some regulatory authorities consider that the available evidence supports a rare association between cimicifuga and risk of liver toxicity, even though the level of risk is difficult to determine.[2,5,6] They have recommended that warnings regarding potential adverse liver reactions should be added to product information and consumers are advised to stop taking cimicifuga if they develop symptoms of liver damage;[2,5-7] also, patients who have previously had liver or other serious health problems should consult their doctor before starting to take cimicifuga.[2,6]

1. Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003; **10:** 58–64.
2. Medicines and Healthcare Regulatory Agency. UK Public Assessment Report. Black Cohosh (issued 31st July 2006). Available at: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/CON2024279 (accessed 30/05/08)
3. Health Canada. Black cohosh: international reports of liver toxicity. *Can Adverse React News* 2005; **15** (3): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3_e.pdf (accessed 31/10/05)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Hepatotoxicity with black cohosh. *Aust Adverse Drug React Bull* 2006; **25:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0604.htm (accessed 25/05/06)
5. EMEA. EMEA Public statement on herbal medicinal products containing cimicifuga racemosae rhizoma (black cohosh, root) — serious hepatic reactions (issued 18th July 2006). Available at: http://www.emea.europa.eu/pdfs/human/hmpc/26925906en.pdf (accessed 01/11/07)
6. Australian Government Department of Health and Ageing: Therapeutic Goods Administration. Black cohosh (*Cimicifuga racemosa*): new labelling requirements and consumer information for medicines containing black cohosh (issued 29th May 2007). Available at: http://www.tga.gov.au/cm/0705blkcohosh.htm (accessed 01/11/07)
7. Health Canada. Health Canada is advising consumers about a possible link between black cohosh and liver damage (issued 18th August 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html (accessed 05/11/07)

Menopausal disorders. Cimicifuga is used in menopausal disorders, particularly for the relief of hot flushes[1-6] but several reviews and studies have concluded that there is little evidence of benefit.[2,3,5,6]

1. Pepping J. Black cohosh: Cimicifuga racemosa. *Am J Health-Syst Pharm* 1999; **56:** 1400–2.
2. Jacobson JS, *et al.* Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001; **19:** 2739–45.
3. Borrelli F, Ernst E. Cimicifuga racemosa: a systematic review of its clinical efficacy. *Eur J Clin Pharmacol* 2002; **58:** 235–41.
4. Uebelhack R, *et al.* Black cohosh and St. John's wort for climacteric complaints: a randomized trial. *Obstet Gynecol* 2006; **107:** 247–55.
5. Pockaj BA, *et al.* Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC . *J Clin Oncol* 2006; **24:** 2836–41.
6. Newton KM, *et al.* Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med* 2006; **145:** 869–79.

Preparations

USP 31: Black Cohosh Fluidextract; Black Cohosh Tablets; Powdered Black Cohosh Extract.

Proprietary Preparations (details are given in Part 3)
Arg.: Herbaccion Menopausia†; Menofem; ***Austria:*** Agnukliman; Jinda; Klimadynon; ***Braz.:*** Amenopam; Aplause; Clifemin; Mencirax; Menocalm; Menoliv†; Tensiane; ***Chile:*** Ginemaxim; Mensifem†; ***Cz.:*** Cimisan; Menofem; ***Fr.:*** Cimipax; ***Ger.:*** Cefakliman mono; Cimisan; Evalin†; Femi; Femikliman uno; Femilla N†; Feminon C; Femisana gyn; Indianische Frauenwurzel†; Jinda; Klimadynon; Kofemin; Natu-fem; Remifemin; Sinei; Solcosplen C; Valverde Traubensilberkerze†; ***Hong Kong:*** Klimadynon; ***Hung.:*** Cefakliman mono; Cimicin; Femitan; Klimadynon; Klimapur; Remifemin; ***Indon.:*** Klimadynon; Remifemin; ***Malaysia:*** Remifemin; ***Mex.:*** Avala; Clifenal; Mensifem; ***Philipp.:*** Remifemin; ***Pol.:*** Klimasol; Menofem; Remifemin; ***Rus.:*** Klimadynon (Климадинон); ***Singapore:*** Klimadynon; Remifemin; ***Spain:*** Avala; Remifemin; Ymea; ***Switz.:*** Cimifemine; Climavita; Femicine; Maxifem; ***Thai.:*** Remifemin; ***UK:*** Menoherb.

Multi-ingredient: ***Austral.:*** Cimicifuga Compound; Dong Quai Complex; Dyzco; Extralife Meno-Care; Extralife PMS-Care; Herbal PMS Formula†; Lifesystem Herbal Formula 4 Women's Formula†; Medinat Esten†; PMT Complex†; Proesten†; Soy Forte with Black Cohosh†; Women's Formula Herbal Formula 3†; ***Austria:*** Remifemin plus; ***Canad.:*** Natural HRT; Natural HRT Nightime; ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schwedenbitter; ***Ger.:*** Femisana†; Remifemin plus; ***Hong Kong:*** Phytoestrin†; ***Hung.:*** Remifemin Plus; ***Indon.:*** Anstrep; Femosa; Menose; Menoxa; Osteopor; Pectum; Voldilex; ***Ital.:*** Climil Complex; Climil-80; Hiperogyn; ***Malaysia:*** Gyno-Plus; ***Pol.:*** Klimax†; Naturapia Menopauza; ***S.Afr.:*** Bronchicough†; Bronchicum†; ***Singapore:*** Phytoestrin; ***UK:*** Gerard House Reumalex; Modern Herbals Rheumatic Pain; St Johnswort Compound; Vegetable Cough Remover; Vegetex; ***USA:*** Estrocare.

Cinametic Acid *(rINN)*

Acide Cinamétique; Ácido cinamético; Acidum Cinameticum.
4-(2-Hydroxyethoxy)-3-methoxycinnamic acid.

Цинаметовая Кислота

$C_{12}H_{14}O_5$ = 238.2.
CAS — 35703-32-3.

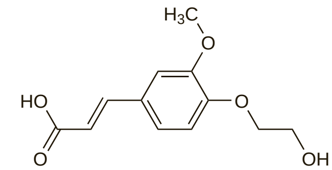

Profile

Cinametic acid has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Transoddi†.

Cinchona Bark

Chinae Cortex; Chinarinde; Chininmedžių žievė; Chinovníková kůra; Cinchona; Cinchonae cortex; Cinchonae Succirubrae Cortex; Jesuit's Bark; Kiinankuori; Kinabark; Peruvian Bark; Quina; Quina Vermelha; Quino, corteza del; Quinquina; Quinquina Rouge; Red Cinchona Bark; Vöröskínafa-kéreg.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cinchona Bark). The whole or cut, dried bark of *Cinchona pubescens* (*Cinchona succirubra*), of *C. calisaya*, of *C. ledgeriana*, or of its varieties or hybrids. It contains a minimum of 6.5% of total alkaloids, of which 30 to 60% are quinine-type alkaloids. It has an intensely bitter, somewhat astringent taste. Protect from light.

Profile

Cinchona contains a number of alkaloids, including two pairs of optical isomers: quinine (p.612) and quinidine, (p.1383) and cinchonine and cinchonidine. Cinchona alkaloids have long been used for their antimalarial activity either singly, as quinine or quinidine, or in mixtures, such as totaquine. Quinidine is also used for its antiarrhythmic properties.

Cinchona bark is used as a bitter and is also employed in herbal remedies.

Homoeopathy. Cinchona bark has been used in homoeopathic medicines under the following names: Cinchonae cortex; China; China pubescens; China rubra; Cinchora succirubra; China officinalis; Cinchona officinalis; Cinc. of.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Venustas Antiforfora†.

Multi-ingredient: ***Arg.:*** Bifena; ***Austria:*** Brady's-Magentropfen; China-Eisenwein; Ferrovin-Chinaeisenwein; Mariazeller; ***Braz.:*** Gastrogenol†; ***Fr.:*** Quinimax; Quintonine; ***Ger.:*** Amara-Pascoe; Cardibisana†; Gastrol S†; Hepaticum-Medice H†; Hicoton†; Majocarmin forte†; Majocarmin mite†; ***Ital.:*** Chinoidina†; ***Pol.:*** Melisana Klosterfrau; ***S.Afr.:*** Borstol Cough Remedy; Versterkdruppels; ***Switz.:*** Vin Tonique de Vial†.

Cineole

Cajuputol; Cineol; Cineolas; Cinéole; Cineolum; Cyneol; Eucaliptol; Eucalyptol *(USAN)*; Eucalyptolum; Sineoli. 1,8-Epoxy-*p*-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane.

$C_{10}H_{18}O$ = 154.2.
CAS — 470-82-6.

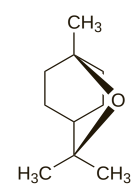

Description. Cineole is a colourless liquid, with an aromatic camphoraceous odour, obtained from eucalyptus oil, cajuput oil, and other oils.

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*
Ph. Eur. 6.2 (Cineole). A clear colourless liquid. It solidifies at about 0.5°. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.
USP 31 (Eucalyptol). It is obtained from eucalyptus oil and from other sources. Store in airtight containers.

Profile

Cineole has the actions and uses of eucalyptus oil (p.2301). It has been used in counter-irritant ointments and in dental products. It has also been used in nasal preparations, but oily solutions inhibit ciliary movement and may cause lipoid pneumonia. Preparations containing cineole with other volatile substances have been used in the treatment of renal and biliary calculi.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Soledum†; ***Ger.:*** Soledum; Soledum Balsam; ***Ital.:*** Fluirespir†.

Multi-ingredient: ***Arg.:*** Aseptobron; Aseptobron Ampicilina†; Aseptobron N; Atomo Desinflamante; Atomo Desinflamante Familiar; Atomo Desinflamante G; Bano Liquido con Eucalipto†; Bronco Etersan; Di-Neumobron; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; No-Tos Adultos; Otorinazol†; Refenax Caramelos Expectorantes; ***Austral.:*** Bosisto's Vaporising Ointment; Euky Bearub; Methyl Salicylate Ointment Compound†; Nasex; Spray-Tish Menthol; Tixylix Chest Rub†; Vasylox†; Vicks Sinex; ***Austria:*** Rhinospray Plus; Rowachol; Rowatinex; Wick Sinex; ***Belg.:*** Balsoclase Expectorans; Eucalyptine; Eucalyptine Le Brun†; Eucalyptine Pholcodine; Eucalyptine Pholcodine Le Brun†; Inhalene†; Inhalo Rhinathiol; Inopectol; Olbas; Pulmex; Pulmex Baby; ***Braz.:*** Algice; Angino-Rub; Baldin-CE†; Bromil; Broncopinol†; Canfomenol†; Eucaliptan†; Fluomint; Gargotan†; Gripanil†; Gripomatine†; Griponia†; Gripsay; Inhadrina†; Inhalante Yatropan; Killgrip†; Mentalol†; Ozonyl; Ozonyl Aquoso; Ozonyl Expectorante; Pastilhas Valda; Pectal†; Penetro; Quelodin†; Tabletes Valda†; Tetrapulmo; Transpulmin; Transpulmin Balsamo; Transpulmin†; Tripulmin Balsamico†; Tripulmin†; Valda†; Vick Pastilhas; ***Canad.:*** Alsirub†; Antiseptic Mouthwash; Arthriflex; Cal Mo Dol; Carboseptol†; Demo-Cineol; Listerine; Listerine Antiseptic Tartar Control; Mielocol; Mouthwash Antiseptic & Gargle†; Physio-Rub; Thermo Rub; Valda; ***Chile:*** Listerine; Oralfresh Citrus; Oralfresh Clasico; Rowatinex; ***Cz.:*** Biocalyptol S†; Rowachol; Rowatinex; ***Denm.:*** Otrivin Menthol; ***Fin.:*** Otrivin Menthol; ***Fr.:*** Biolau; Dinacode avec codeine†; Dinacode†; Essence Algerienne; Eucalyptine; Eucalyptine Le Brun; Hexapneumine; Listerine; Listerine protection dents et gencives; Neo-Codion†; Pectoderme†; Pholcones Bismuth; Pulmofluide Simple; Valda; Vegebom; ***Ger.:*** Eufimenth-Balsam N†; Rhinospray Plus; Rhinospray sensitiv; Rowachol; Rowachol comp†; Rowachol-Digestiv; Rowatinex; Transpulmin Balsam; ***Gr.:*** Cedovix; Faragel-Forte; ***Hong Kong:*** Biocalyptol†; Cool Mint Listerine; Listerine; Listerine Tartar Control; Listerine Teeth and Gum Defence; Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; Valda†; ***Hung.:*** Rhinospray Plus; Rowachol; Rowatinex; ***India:*** Dristan Nasal Drops; Endrine; Endrine Mild; Karvol Plus; Sinarest Vapocaps; ***Indon.:*** Dactylen; Listerine; Listerine Coolmint; ***Irl.:*** Rowachol; Rowatinex; Valda†; ***Israel:*** Gargol; Rowachol; Rowatinex; ***Ital.:*** Abiostil; Balsamico; Balta Intimo†; Calyptol; Lipobalsamo; Listerine Fresh Citrus; Listerine Tartar Control; Paidorinovit; Pastiglie Valda†; Pulmarin; Pumilene Vapo; Rinogutt Eucalipto-Fher; Rinovit; Transpulmina Gola; Transpulmina Tosse; Vicks Baby Balsam†; Vicks Sinex; ***Malaysia:*** Listerine†; Purporent†; Rowachol; Rowatinex; ***Mex.:*** Andociclina Balsamica†; Bronkitose Mielimon; Cholex; Eucalin†; Guayalin; Guayalin-Plus†; Iodex Cristal; Listerine; Numonyl†; ***Neth.:*** Balsoclase Compositum; Balsoclase-E; Otrivin Menthol; Rhinospray met menthol; ***NZ:*** Listerine; Listerine Tartar Control; Tixylix Chest Rub; Vicks Sinex; ***Philipp.:*** Kamillosan M; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar Control; Listerine Teeth & Gum Defense; Rhea Superscent Oil; Rowachol; Rowatinex; Transpulmin Balsam; ***Pol.:*** Rowachol; Rowatinex; Salviasept; Terpichol; ***Port.:*** Listerine†; Rectopulmo Adultos†; Rectopulmo Infantil†; Transpulmina; Valda†; ***Rus.:*** Nazol Advance (Назол Адванс); ***S.Afr.:*** Respisniffers; Woodwards Inhalant; ***Singapore:*** Listerine; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control; ***Spain:*** Balsamo Kneipp†; Broncovital†; Brota Rectal Balsamico; Caltoson Balsamico; Caramelos Agua del Carmen†; Diminex Antitusigeno; Doctomitil†; Dolmitin; Eucalyptospirine†; Eupnol; Mentobox; Pastillas Juanola†; Pastillas Pectoral Kely; Piorlis; Pulmofasa; Retarpen Balsamico†; Rinobanedif; Rowachol; Rowanefrin; Sinus Inhalaciones; Tifell†; Trophires†; Vitavox Pastillas†; ***Swed.:*** Otrivin Menthol; ***Switz.:*** Nasobol N; Neo-Bronchol; Onguent aux herbes Keller; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; Resorbane; Rowachol; Sedasept†; Sedotussin†; Transpulmin N; Vicks Sinex; ***Thai.:*** Dexalin; Hot Ize; Olympic Balm†; Rowachol; Rowatinex; Sore Mouth Gel; ***Turk.:*** Bugumentol; Bugusan; Buguseptil; Gelocaps; Mentimol; Mentolin; Mentoseptol; Otaci Oka Mentol; Otaci Salvia; Rinolar; Sulfarhin; ***UK:*** Dubam; Listerine Antiseptic Mouthwash; Lockets; Nostroline; Nowax; Rowachol; ***USA:*** Babee; BFI; Listerine; Pfeiffer's Cold Sore; Rid-a-Pain; Saratoga; Sting-Eze; ***Venez.:*** Derpinol†; Robitussin Caramelos†; Rowachol; Rowatinex; Transmin.

Cinnamedrine *(USAN, rINN)* ⊗

Cinamedrina; Cinnamédrine; Cinnamedrinum; *N*-Cinnamylephedrine. α-{1-[Methyl(3-phenyl-2-propenyl)amino]ethyl}benzenemethanol.

Циннамедрин

$C_{19}H_{23}NO = 281.4$.
CAS — 90-86-8.

Cinnamedrine Hydrochloride *(rINNM)* ⊗

Cinnamédrine, Chlorhydrate de; Cinnamedrini Hydrochloridum; *N*-Cinnamylephedrine Hydrochloride; Hidrocloruro de cinamedrina.

Циннамедрина Гидрохлорид

$C_{19}H_{23}NO,HCl = 317.9$.

Profile

Cinnamedrine hydrochloride is reported to have sympathomimetic actions resembling those of ephedrine. It was formerly used with analgesics in the symptomatic relief of dysmenorrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Chile:*** Tapal-2†.

Cinnamon

Canela; Canela do Ceilão; Cannelle dite de ceylan; Ceylon Cinnamon; Ceylonzimt; Cinamonų žievė; Cinnam.; Cinnamomi cortex; Cinnamon Bark; Fahéj; Kanel; Kaneli; Skořicovníková kůra; Zimt.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cinnamon). The dried bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* containing not less than 1.2% v/w of essential oil. It has a characteristic, aromatic odour. Protect from light.
The BP 2008 directs that when Powdered Cinnamon is prescribed or demanded, material containing not less than 1.0% v/w of essential oil shall be dispensed or supplied.

Profile

Cinnamon is carminative and slightly astringent and is included in some preparations for gastrointestinal disorders. It is also used as a flavour. It is a source of cinnamon oil (below).

Preparations

Ph. Eur.: Cinnamon Tincture;
USNF 26: Compound Cardamom Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Brady's-Magentropfen; China-Eisenwein; Mariazeller; Montana; ***Braz.:*** Balsamo Branco; Paratonico; ***Cz.:*** Blahungstee N†; Dr Theiss Rheuma Creme†; Dr Theiss Schwedenbitter; Klosterfrau Melisana; Magen- und Darmtee N†; Passedan; ***Fr.:*** Elixir Grez†; Quintonine; ***Ger.:*** Amara-Pascoe; Doppelherz Melissengeist†; Gastrosecur†; Majocarmin forte†; Melissengeist; Montana N; Schwedentrunk Elixier; Sedovent; ***India:*** Carmicide; ***Israel:*** Davilla; ***Ital.:*** Assenzio (Specie Composta)†; Biophase Shampoo; Dam; ***Jpn:*** The Guard Seichojo; ***Pol.:*** Reumpapai; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Himcolin (Химколин); ***S.Afr.:*** Melissengeist; Rooilavental; Spiritus Contra Tussim Drops; ***Spain:*** Agua del Carmen; Vigortonic; ***Switz.:*** Alcoolat de Melisse†; Baume†; Odontal; Tisane pour les problemes de prostate; ***Thai.:*** Carmicide†; Meloids; ***UK:*** Melissa Comp.; ***Venez.:*** Aftil.

Cinnamon Oil

Aetheroleum Cinnamomi Zeylanici; Canela, aceite esencial de; Cinnam. Oil; Esencia de Canela; Essence de Cannelle de Ceylan; Oleum Cinnamomi; Zimtöl.

Коричное Масло

CAS — 8015-91-6.

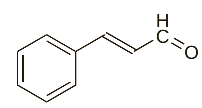

(cinnamaldehyde)

Pharmacopoeias. *Eur.* (see p.vii) includes oil from both the bark and the leaf of *Cinnamomum zeylanicum* (*C. verum*).
Cinnamon oil is also used as the name for cassia oil in some countries. For example, *Jpn* under the title Cinnamon Oil specifies oil from either *Cinnamomum cassia* or *Cinnamomum zeylanicum*.

Cinnamon Bark Oil

Cannelle dite de ceylan, huile essentielle de; Ceiloninių cinamonų žievės eterinis aliejus; Ceylon Cinnamon Bark Oil; Ceyloni fahéjfakéreg-olaj; Cinnamomi zeylanicii corticis aetheroleum; Cinnamomi Zeylanicii Corticus Aetheroleum; Kaneliöljy, Ceylonin; Kanelolja, ceylonesisk; Silice kůry skořicovníku cejlonského.

Коричное Масло Из Коры

Pharmacopoeias. In *Eur.* (see p.vii) and Jpn.
Ph. Eur. 6.2 (Cinnamon Bark Oil, Ceylon). The oil obtained by steam distillation of the bark of the shoots of *C. zeylanicum* (*C. verum*). It contains 55 to 75% of cinnamaldehyde and less than 7.5% of eugenol. A clear, mobile, light yellow liquid becoming reddish over time, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from light and heat.

Cinnamon Leaf Oil

Cannelier dit de ceylan (feuille de), huile essentielle de; Ceiloninių cinamonų lapų eterinis aliejus; Ceyloni fahéjfalevél-olaj; Cinnamomi zeylanici folii aetheroleum; Cinnamomi Zeylanici Folii Etheroleum; Kanelbladolja, ceylonesisk; Kanelinlehtiöljy, Ceylonin; Ol. Cinnam. Fol; Silice listu skořicovníku cejlonského.

Коричное Масло Из Листьев

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cinnamon Leaf Oil, Ceylon). The oil obtained by steam distillation of the leaves of *C. zeylanicum* (*C. verum*). It contains less than 3% of cinnamaldehyde, and 70 to 85% of eugenol. A clear, mobile, reddish brown to dark brown liquid, with a characteristic odour of eugenol. Store in well-filled airtight containers. Protect from light and heat.

Profile

Cinnamon bark oil has properties and uses similar to those of cinnamon (above). It is also included in preparations for musculoskeletal and joint disorders and for respiratory-tract disorders. There have been a number of reports of hypersensitivity to cinnamaldehyde and other constituents of cinnamon oil. Cinnamon leaf oil has also been used, although the amounts of eugenol and cinnamaldehyde are different from the bark oil. Cinnamon bark or leaf oil is also used in aromatherapy.

Preparations

BP 2008: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Concentrated Cinnamon Water; Tolu-flavour Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Gartech; ***Austria:*** Tiger Balsam Rot; ***Braz.:*** Ovariusedan†; ***Canad.:*** Tiger Balm Red; Tiger Balm Ultra; ***Chile:*** Agua del Carmen; Agua Melisa Carminativa; ***Cz.:*** Amol; Tiger Balm Rot†; ***Fr.:*** Aromasol; Gouttes aux Essences; Resistim; Stomargil; Tigridol; ***Ger.:*** Amol Heilkrautergeist N; esto-gast; Melissengeist; Salviathymol N; ***Gr.:*** Tiger Balm; ***Hong Kong:*** Magesto; ***Hung.:*** Fagifor†; ***India:*** Bestozyme; Catazyme-P; Digeplex; Sensur; Vitazyme; ***Indon.:*** Corsabalm; ***Israel:*** Karvol; ***Ital.:*** Relaxcol; Valda Propoli; ***NZ:*** Karvol; ***Pol.:*** Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; ***Rus.:*** Efcamon (Эфкамон); ***S.Afr.:*** Enterodyne; Karvol; ***Singapore:*** Karvol; ***Spain:*** Depurativo Richelet; ***Switz.:*** Baume de Chine Temple of Heaven blanc; Carmol; Pirom; Sansilla; Spagyrom; ***Thai.:*** Magesto; Mesto-Of; ***UK:*** Slippery Elm Stomach Tablets.

Citicoline *(pINN)*

CDP-Choline; Citicolina; Citicolinum; Citidoline; Cytidine Diphosphate Choline; Cytidine diphosphocholine; IP-302. Choline cytidine-5′-pyrophosphate.

Цитиколин

$C_{14}H_{26}N_4O_{11}P_2 = 488.3$.
CAS — 987-78-0.
ATC — N06BX06.
ATC Vet — QN06BX06.

Citicoline Sodium *(USAN, pINNM)*

Citicolina sódica; Citicoline Sodique; Natrii Citicolinum. Cytidine 5′-{sodium *P*′-[2-(trimethylammonio)-ethyl] hydrogen diphosphate}, inner salt.

Натрий Цитиколин

$C_{14}H_{25}N_4NaO_{11}P_2 = 510.3$.
CAS — 33818-15-4.

Pharmacopoeias. In *Chin.*

Profile

Citicoline is a derivative of choline and cytidine that is involved in the biosynthesis of lecithin. It is claimed to increase blood flow and oxygen consumption in the brain and has been given in the treatment of cerebrovascular disorders (including ischaemic stroke, p.1185), parkinsonism, and head injury. It is given by intravenous or intramuscular injection in doses of up to 1 g daily or orally in divided doses of 200 to 600 mg daily.

Citicoline sodium has also been used.

Cerebrovascular disorders. Citicoline has shown some short- to medium-term benefit for disturbances of memory and behaviour associated with cerebrovascular disorders.[1]

1. Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/05/06).

Strabismus. Experimental studies have shown that centrally-acting drugs such as citicoline may improve vision in patients with amblyopia (see Strabismus, p.1874). However, their role in clinical practice remains to be established.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2:** 91–100.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Complegel Novo; Neuriclor†; Nimo-Somazina; Reagin; Somazina; ***Austria:*** Startonyl; ***Braz.:*** Somazina; ***Chile:*** Somazina; ***Fr.:*** Rexort†; ***Indon.:*** Brainact; Bralin; Cibren; Lancolin; Neulin; Nicholin; Soholin; Takelin; ***Ital.:*** Brassel; Cebroton; Cidilin; Citifar†; Cition†; Difosfocin; Flussorex; Gerolin; Kemodyn†; Link†; Logan; Neurex; Neuroton; Nicholin; Nicolsint; Sinkron; Sintoclar; ***Jpn:*** Nicholin; ***Mex.:*** Onquevit; Somazina; ***Philipp.:*** Nicholin; Somazine; ***Port.:*** Hipercol; Somazina; Startonyl; Trausan; ***Spain:*** Numatol; Somazina; ***Thai.:*** Somazina; ***Venez.:*** Somazina.

Multi-ingredient: ***Arg.:*** Neuriclor Vascular†; Nimodilat Plus; Nimoreagin; Nivas Plus; Reagin Vascular.

Citiolone *(rINN)*

BO-714; Citiolona; Citiolonum. *N*-(Perhydro-2-oxo-3-thienyl)acetamide.

Цитиолон

$C_6H_9NO_2S = 159.2$.
CAS — 1195-16-0.
ATC — A05BA04.
ATC Vet — QA05BA04.

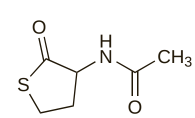

Profile

Citiolone has been used in the treatment of hepatic disorders and as a mucolytic. Hypersensitivity reactions have been reported.

◊ References.

1. de Barrio M, *et al.* Recurrent fixed drug eruption caused by citiolone. *J Investig Allergol Clin Immunol* 1997; **7:** 193–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Mucorex†.

Multi-ingredient: *Spain:* Hubergrip†.

Citral

Cytral. 3,7-Dimethyl-2,6-octadienal.

$C_{10}H_{16}O$ = 152.2.

CAS — 5392-40-5 (citral); 141-27-5 (geranial); 106-26-3 (neral).

Profile

Citral is a terpenoid constituent of lemon oil (p.2332), lemon grass oil (p.2333), melissa oil (p.2339), and many other essential oils; it exists as 2 isomers, *trans*-citral (geranial) and *cis*-citral (neral). It has been used in preparations for respiratory-tract, musculoskeletal, and other disorders. It is also used as a flavour and perfume.

Hypersensitivity. References.

1. Heydorn S, *et al.* Citral a fragrance allergen and irritant. *Contact Dermatitis* 2003; **49:** 32–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Fr.:* Bronchorectine au Citral; ***Switz.:*** Carmol Plus†.

Anhydrous Citric Acid

Acidum Citricum; Acidum citricum anhydricum; Cítrico anhidro, ácido; Citrinų rūgštis, bevandenė; Citrique (acide) anhydre; Citronensäure; Citronsyra, vattenfri; E330; Kyselina citronová; Sitruunahappo, vedetön; Vízmentes citromsav. 2-Hydroxypropane-1,2,3-tricarboxylic acid.

$C_6H_8O_7$ = 192.1.

CAS — 77-92-9.

ATC — A09AB04.

ATC Vet — QA09AB04.

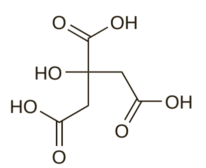

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Citric Acid, Anhydrous). Colourless crystals or granules or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol.

USP 31 (Anhydrous Citric Acid). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Citric Acid Monohydrate

Ácido del Limón; Acidum citricum monohydricum; Cítrico monohidrato, ácido; Citrinų rūgštis monohidratas; Citrique (acide) monohydraté; Citromsav-monohidrát; Citronsyramonohydrat; Hydrous Citric Acid; Kwas cytrynowy jednowodny; Kyselina citronová monohydrát; Sitruunahappomonohydraatti.

$C_6H_8O_7,H_2O$ = 210.1.

CAS — 5949-29-1.

ATC — A09AB04.

ATC Vet — QA09AB04.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Citric Acid Monohydrate). Efflorescent, colourless crystals or granules, or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 31 (Citric Acid Monohydrate). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. It is efflorescent in dry air. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Adverse Effects and Precautions

Citric acid ingested frequently or in large quantities may cause erosion of the teeth and have a local irritant action.

Interactions

Aluminium hydroxide. Intestinal absorption of aluminium ions may be enhanced by oral doses of citrates. Caution is needed in patients with chronic renal disease receiving aluminium hydroxide as a phosphate binder who are given a calcium supplement in the form of effervescent tablets that contain citric acid.[1]

1. Mees EJD, Başçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59:** 322.

Uses and Administration

Citric acid is used in effervescing mixtures; the monohydrate is used in the preparation of effervescent granules.

Citric acid monohydrate is used as a synergist to enhance the effectiveness of antoxidants.

Preparations containing citric acid are used in the management of dry mouth (p.2140) and to dissolve renal calculi, alkalinise the urine, and prevent encrustation of urinary catheters. Citric acid is an ingredient of citrated anticoagulant solutions. Citric acid has also been used in preparations for the treatment of coughs, gastrointestinal disturbances, and metabolic acidosis.

Preparations

BP 2008: Lemon Syrup; Paediatric Compound Tolu Linctus; Paediatric Simple Linctus; Potassium Citrate Mixture; Simple Linctus;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 31: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Sodium Citrate and Citric Acid Oral Solution; Tricitrates Oral Solution.

Proprietary Preparations (details are given in Part 3)
Gr.: Citrolithin; ***India:*** Revici; ***Mex.:*** Lipocinetic; ***Pol.:*** Citrolyt; ***S.Afr.:*** Crystacit; ***Venez.:*** Policitra.

Multi-ingredient: *Arg.:* Alikal; Alka-Seltzer Doble Accion; Sal de Fruta Eno; Uvasal; ***Austral.:*** Alka-Seltzer; Citralite; Citravescent; Durolax X-Pack†; Eno; Picolax†; Picoprep; Ural; Uricalm†; Uricosal†; ***Austria:*** Alka-Seltzer; Duplotrast Z; Helo-acid; Kalioral; ***Belg.:*** Alka-Seltzer; ***Braz.:*** Citrosodine†; Digestbem; Regulador Xavier N-2†; Sal de Andrews; Sal de Fruta Eno; Sonrisal; ***Canad.:*** Alka-Seltzer; Bromo Madelon; Dicitrate†; Pico-Salax; ***Chile:*** Disfruta; Fenokomp 39; Justegas†; Sal de Fruta Eno; Summer's Eve Hierbas†; Uroalquine; Yasta; ***Cz.:*** Alka-Seltzer; Blemaren N; Carbocit; E-Z-Gas†; Herbadent; ***Fin.:*** Alka-Seltzer; ***Fr.:*** Citrocholine; Doculyse; Elixir Grez†; Hepargitol; Ornitaine; Sebium AKN; Sphingogel†; ***Ger.:*** Alka-Seltzer; Barilux Brausetabletten†; Blemaren N; Citropepsin†; Lithurex S†; Pepzitrat; Retterspitz Ausserlich; Retterspitz Innerlich; Uronor†; ***Gr.:*** E-Z-Gas; Gastrovison†; ***Hong Kong:*** Alka-Seltzer; Eno†; ***Hung.:*** Alka-Seltzer; Blemaren N; E-Z-Gas; Magurlit†; ***India:*** Carmicide; Coscopin; Coscopin Plus; Dristan Expectorant; Urisoda; ***Indon.:*** Koffex for Children; Promethazine Ikapharmindo; ***Irl.:*** Andrews; Carbex†; Cymalon; Mictral†; ***Israel:*** E-Z-Gas II; Eno; Urikal; ***Ital.:*** Alka-Seltzer; Citroepatina; Duogas; Geffer; Lavanda Sofar; ***Malaysia:*** Alka-Seltzer; Citravescent†; Ezee; Picoprep; Potcit; Ural; ***Mex.:*** Kaposalt; Lipo Slim N†; Uroclasio NF; ***Neth.:*** Alka-Seltzer; Gastrogas; ***NZ:*** Alka-Seltzer; Lemsip Dry Cough†; Picoprep; Ural; ***Philipp.:*** Alka-Seltzer; ***Pol.:*** Citropepsin; ***Port.:*** Alka-Seltzer; Creme Laser Hidrante; Detoxergon; Eno; ***Rus.:*** Alka-Seltzer (Алка-Зельтцер); Blemaren (Блемарен); ***S.Afr.:*** Adco-Sodasol; Alkafizz; Betasoda†; Citro-Soda; Citrocit†; Effersol; Pneucid; Quatro-Soda†; Uri-Alk; Vicks Cough Syrup; ***Singapore:*** Alka-Seltzer; Dicitrate; Potcit; ***Spain:*** Alka-Seltzer; Justegas; Pastillas Antisep Garg L; Sal de Fruta Eno; Sales de Frutas P G; Uralyt Urato; ***Swed.:*** Alka-Seltzer; Renapur; ***Switz.:*** Alka-Seltzer; E-Z-Gas II; Pepsi-Chlor†; Siesta-1; ***Thai.:*** Alka-Seltzer; Carmicide†; ***Turk.:*** Alka-Seltzer; ***UK:*** Alka-Seltzer; Alka-Seltzer XS; Allens Junior Cough; Andrews; Carbex; Cymalon; Effercitrate; Eno; Hill's Balsam Chesty Cough for Children; Lemsip Cough & Cold Dry Cough; Potters Children's Cough Pastilles; Resolve; Uriflex G; Uriflex R; Uro-Tainer Solution R; Uro-Tainer Suby G; Zubes Blackcurrant; Zubes Honey & Lemon; ***USA:*** Alka-Seltzer; Alka-Seltzer Antacid; Alka-Seltzer with Aspirin; Bicitra; Bromo Seltzer Effervescent Granules; Cytra-2; Cytra-3; Cytra-K; Cytra-LC; Extra Strength Alka-Seltzer Effervescent Tablets; Gold Alka-Seltzer; Oracit; Original Alka-Seltzer Effervescent Tablets; Polycitra; Polycitra-K; Polycitra-LC; Renacidin; Sparkles; Zee-Seltzer; ***Venez.:*** Alka-Seltzer; Eno.

Citronella Oil

Citrinžolių eterinis aliejus; Citronela, aceite esencial de; Citronellae aetheroleum; Citronellae Etheroleum; Citronellaolaj; Citronellolja; Citronelová silice; Citronnelle, huile essentielle de; Oleum Citronellae; Sitronellaöljy.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Citronella Oil). The oil obtained by steam distillation from the fresh or partially dried aerial parts of *Cymbopogon winterianus*. It contains 30.0 to 45.0% citronellal, 9.0 to 15.0% citronellol, 2.0 to 4.0% citronellyl acetate, less than 2.0% geranial, 20.0 to 25.0% geraniol, 3.0 to 8.0% geranyl acetate, 1.0 to 5.0% limonene, and less than 2.0% neral. A pale yellow to brownish-yellow liquid with a very strong odour of citronellal. Store in well-filled containers. Protect from light.

Profile

Citronella oil is used as a perfume and insect repellent. It is also used in aromatherapy. Hypersensitivity has been reported.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aulo Gelio Repelente; Repelente Rep; ***Canad.:*** Buzz Away†; Druide Insect Repellent†; ***Ger.:*** Kneipp Beruhigungs-Bad spezial; Schupps Melissen Olbad†; ***Malaysia:*** Moz-Away; ***UK:*** Mozzie Patch; Natrapel.

Multi-ingredient: *Arg.:* Aulo Repelente De Piojos; Repelente Rep; ***Austral.:*** Apex Repel Natural; ***Austria:*** Valin Baldrian; ***Belg.:*** Mouskito Travel Stick; ***Canad.:*** Natrapel; ***Cz.:*** Amol; ***Fr.:*** Ysol 206; ***Ger.:*** esto-gast; Melissengeist; ***Indon.:*** Corsabalm; ***Ital.:*** Air Citronella†; Citrosystem; Mistick Verde; ***NZ:*** Apex Repel Natural; ***Pol.:*** Carmolis; ***S.Afr.:*** Melissengeist; No-Bite†; ***Switz.:*** Baume du Chalet; Novital; Saltrates†; Sansilla; ***UK:*** Snowfire; ***USA:*** Treo.

Clivers

Amor de hortelano; Cleavers; Galii Aparinis Herba; Galium; Goosegrass.

Profile

Clivers is the dried aerial parts of *Galium aparine* (Rubiaceae). It has been used in herbal medicine, mainly as a diuretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Austral.:* Dermaco; Galium Complex†; Herbal Cleanse†; Uva-Ursi Complex†; ***UK:*** Antitis; Aqua Ban Herbal; Athera; Backache; Cascade; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kas-Bah; Modern Herbals Menopause; Modern Herbals Water Retention; Psorasolv; Sciargo; Skin Cleansing; Tabritis; Water Naturtabs; Watershed.

Cloprostenol Sodium *(BANM, USAN, rINNM)*

Cloprostenol sódico; Cloprosténol sodique; Cloprostenoli natricum; ICI-80996; Natrii Cloprostenolum. Sodium (±)-(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(*E*)-(3*R*)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

Натрий Клопростенол

$C_{22}H_{28}ClNaO_6$ = 446.9.

CAS — 40665-92-7 (cloprostenol); 55028-72-3 (cloprostenol sodium).

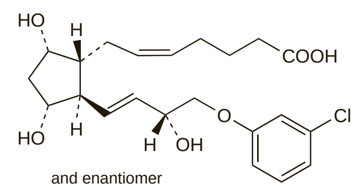

(cloprostenol)

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Cloprostenol Sodium). A white or almost white amorphous hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in acetone. Protect from light and moisture.

Profile

Cloprostenol is a synthetic analogue of dinoprost (prostaglandin F_2). The sodium salt is used as a luteolytic in veterinary medicine.

Clove

Caryoph.; Caryophylli flos; Caryophyllum; Clavo; Clou de girofle; Cloves; Cravinho; Cravo-da-Índia; Gewürznelke; Giroflier; Gvazdikėliai; Hřebíčkovcový květ; Kryddnejlika; Mausteneilikka; Szegfűszeg; Tropical Myrtle.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Clove). The whole flower buds of *Syzygium aromaticum* (*Eugenia caryophyllus*), containing not less than 15% v/w of volatile oil, dried until they become reddish-brown, and with a characteristic aromatic odour. Protect from light.

The BP 2008 directs that when Powdered Clove is prescribed or demanded, material containing not less than 12.0% v/w of essential oil shall be dispensed or supplied.

Profile

Clove is a carminative and is used as a flavour. It is the source of clove oil (below).

Clove and clove oil have been abused in the form of cigarettes.

Abuse. Smoking of cigarettes composed of a mixture of tobacco and cloves is a habit that originated in Indonesia and has spread to the USA. There have been reports of severe and sometimes fatal respiratory illness related to smoking clove cigarettes and there is also evidence from *animal* studies that clove cigarette smoke and eugenol (the principal constituent of clove oil) have harmful pulmonary effects. The Council on Scientific Affairs of the American Medical Association considers that in addition to the hazards associated with smoking tobacco, clove cigarettes may also produce severe lung injury in certain susceptible individuals and could also induce pulmonary aspiration in healthy individuals due to diminution of the gag reflex produced by the local anaesthetic action of eugenol.[1] The American Academy of Pediatrics has also alerted paediatricians in the USA to clove-cigarette smoking by young people and warned of the risks.[2]

1. American Medical Association Council on Scientific Affairs. Evaluation of the health hazard of clove cigarettes. *JAMA* 1988; **260:** 3641–4.
2. Committee on Substance Abuse. Hazards of clove cigarettes. *Pediatrics* 1991; **88:** 395–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Mariazeller; ***Braz.:*** Balsamo Branco; ***Cz.:*** Klosterfrau Melisana; Naturland Grosser Swedenbitter†; Stomatosan†; ***Ger.:*** Doppelherz Melissengeist†; Inconturina†; Melissengeist; ***Ital.:*** Biophase Shampoo; Promix†; Saugella Uomo; ***Port.:*** Midro†; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Clairo; Melissengeist; Spiritus Contra Tussim Drops; ***Switz.:*** Alcoolat de Melisse†; Odontal; Tisane pour les problemes de prostate; ***UK:*** Melissa Comp.; Revitonil.

Clove Oil

Caryophylli floris aetheroleum; Caryophylli Floris Etheroleum; Clavo, aceite esencial de; Clou de girofle, huile essentielle de; Esencia de Clavo; Essence de Girofle; Gvazdikėlių eterinis aliejus; Neilikkaöljy; Nejlikolja; Nelkenöl; Ol. Caryoph.; Oleum Caryophylli; Silice hřebíčkovcového květu; Szegfűszegolaj.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Clove Oil). A clear yellow liquid obtained by steam distillation from clove containing 75.0 to 88.0% of eugenol. It becomes brown on exposure to air. Miscible with dichloromethane, with toluene, and with fatty oils. Store in well-filled airtight containers. Protect from light and heat.

USNF 26 (Clove Oil). The volatile oil distilled with steam from clove. It contains not less than 85.0% of phenolic substances, chiefly eugenol. Soluble 1 in 2 of alcohol (70%). Store in well-filled airtight containers.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of clove oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Profile

Clove oil is a carminative that is sometimes used in the treatment of flatulent colic. It is also used as a flavour.

Applied externally clove oil is irritant but can produce local anaesthesia. It is used as a domestic remedy for toothache, a plug of cotton wool soaked in the oil being inserted in the cavity of the carious tooth; repeated application may damage the gingival tissues. Mixed with zinc oxide, it is used as a temporary anodyne dental filling, although eugenol (p.2301), one of its constituents, is often preferred. Clove oil is included as a counter-irritant in preparations for musculoskeletal and joint disorders. It is also used in aromatherapy.

Eugenol may cause hypersensitivity.

Adverse effects. Severe toxicity after ingestion of clove oil by young children has been reported.[1-4] Adverse effects included coma, acidosis, a generalised seizure, disordered blood clotting, and acute liver damage.

For reference to the harmful effects of smoking clove cigarettes, see under Clove, above.

1. Lane BW, *et al.* Clove oil ingestion in an infant. *Hum Exp Toxicol* 1991; **10:** 291–4.
2. Hartnoll G, *et al.* Near fatal ingestion of oil of cloves. *Arch Dis Child* 1993; **69:** 392–3.
3. Eisen JS, *et al.* N-acetylcysteine for the treatment of clove oil-induced fulminant hepatic failure. *J Toxicol Clin Toxicol* 2004; **42:** 89–92.
4. Janes SE, *et al.* Essential oil poisoning: N-acetylcysteine for eugenol-induced hepatic failure and analysis of a national database. *Eur J Pediatr* 2005; **164:** 520–2.

Preparations

BP 2008: Aromatic Cardamom Tincture.

Proprietary Preparations (details are given in Part 3)

S.Afr.: Naeltjie-Olie; ***UK:*** Dentogen; Soothake Toothache Gel.

Multi-ingredient: ***Austral.:*** Tiger Balm Red; Tiger Balm White; ***Austria:*** Parodontax; Tiger Balsam Rot; ***Braz.:*** Algidente†; Anestesiol†; Dentisan; ***Canad.:*** Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; ***Chile:*** Agua del Carmen; Agua Melisa Carminativa; Hustagil†; ***Cz.:*** Amol; Herbadent; Parodontal F5†; Stopangin; Tiger Balm Rot†; ***Fr.:*** Aromasol; Baume Aroma; Gouttes aux Essences; Nazinette du Docteur Gilbert; Tigridol; ***Ger.:*** Amol Heilkrautergeist N; China-Balsam†; esto-gast; Hustagil Erkaltungsbalsam†; Melissengeist; Nur 1 Tropfen medizinisches Mundwasser†; Repha-Os; Salviathymol N; ***Hong Kong:*** Magesto; ***India:*** Arowash; Sensur; ***Indon.:*** Balsam Sakti; Corsabalm; ***Israel:*** Tiger Balm Red; Tiger Balm White; ***Ital.:*** Dentosan Azione Intensiva; Dentosan Mese; Fialetta Odontalgica Dr Knapp; Ondroly-A†; ***NZ:*** Electric Blue Headlice; Toothache Drops†; ***Pol.:*** Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; Olbas; Salviasept; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; Efcamon (Эфкамон); ***S.Afr.:*** Alpha Toothache Essence; Balsem Vita GEEL; Balsem Vita ROOI; Balsem Vita WIT; Enterodyne; Helmontskruie; Moultons Pain Paint; Muscle Rub; Prep; Puma Balm; SB Toothache Drops; ***Spain:*** Dentol Topico; Otogen Calmante; ***Switz.:*** Baume de Chine Temple of Heaven blanc; Carmol; Carmol Plus†; Olbas; Osa gel dentaire aux plantes; Parodontax†; Sansilla; Spagyrom; ***Thai.:*** Magesto; Masaga; Mesto-Of; ***Turk.:*** Disinol; ***UK:*** Hactos; Nine Rubbing Oils; Olbas; Olbas for Children; Potters Sugar Free Cough Pastilles; Red Oil; Snowfire; Soothake Toothache Tincture; Teenstick; Tiger Balm; ***USA:*** Dentapaine; Numzit†; Toothache Gel; ***Venez.:*** One Drop Only†.

Red Clover

Cow Clover; Meadow Clover; Purple Clover; Trébol rojo; Trefoil.

Pharmacopoeias. In *US*, which also includes the powdered form and powdered extract.

USP 31 (Red Clover). The dried inflorescence of *Trifolium pratense* (Fabaceae). It contains not less than 0.5% of isoflavones, calculated on the dried basis as the sum of daidzein (p.2391), genistein (p.2391), formononetin, and biochanin A. Protect from light and moisture.

Profile

The flowerheads of red clover have been used in herbal medicine. The isoflavones present in red clover have been investigated, similarly to other phytoestrogens, for their potential endocrine effects.

Preparations

USP 31: Red Clover Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Promensil; Trinovin; ***Braz.:*** Climadil; Clinet; ***Indon.:*** Promeno; ***UK:*** Menoflavon.

Multi-ingredient: ***Austral.:*** Bioglan Mens Super Soy/Clover; Bioglan Soy Power Plus; Lifechange Menopause Formula†; Trifolium Complex†; ***Indon.:*** Femosa; Osteopor; ***Malaysia:*** Cleansa Plus†; ***Spain:*** Fitogyn.

Cnicus Benedictus

Blessed Thistle; Cardo Santo; Chardon Bénit; Holy Thistle; Kardobenediktenkraut.

Profile

Cnicus benedictus, the flowering tops of *Cnicus benedictus* (*Carbenia benedicta; Carduus benedictus*) (Compositae), has been used as a bitter.

Homoeopathy. Cnicus benedictus has been used in homoeopathic medicines under the following names: Carduus benedictus.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Mariazeller; ***Braz.:*** Digestron†; ***Cz.:*** Ungolen†; ***Ger.:*** Carvomin†; Cheiranthol†; Gallexier; Gastritol; ***Pol.:*** Artecholin; Artecholwex; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Essens Amara of Groen Amara; ***Switz.:*** Gastrosan; ***UK:*** Bio-Strath Artichoke Formula; Sure-Lax (Herbal).

Cobalt Chloride

Cloruro cobaltoso; Cobalto, cloruro de; Cobaltous Chloride; Kobaltu(II) chlorek.

$CoCl_2,6H_2O$ = 237.9.

CAS — 7646-79-9 (anhydrous cobalt chloride); 7791-13-1 (cobalt chloride hexahydrate).

Adverse Effects

Reactions to cobalt have included anorexia, nausea and vomiting, diarrhoea, precordial pain, cardiomyopathy, flushing of the face and extremities, skin rashes, tinnitus, temporary nerve deafness, renal injury, diffuse thyroid enlargement, and hypothyroidism. In large doses it may reduce the production of erythrocytes.

◊ References.

1. Kennedy A, *et al.* Fatal myocardial disease associated with industrial exposure to cobalt. *Lancet* 1981; **i:** 412–4.
2. Cugell DW, *et al.* The respiratory effects of cobalt. *Arch Intern Med* 1990; **150**: 177–83.
3. Evans P, *et al.* Cobalt and cobalt compounds. *Toxicity Review 29.* London: HMSO, 1993.

Uses and Administration

Cobalt chloride, when given to both normal and anaemic subjects, produces reticulocytosis and a rise in the erythrocyte count. This property suggested its use in the treatment of certain types of anaemia, but its general therapeutic use is, however, unjustified and not without danger.

In veterinary medicine, cobalt chloride has been given as a dietary supplement to ruminants.

Cobalt Oxide

Cobalto, óxido de; Tetraóxido de tricobalto; Tricobalt Tetroxide.

Co_3O_4 = 240.8.

CAS — 1308-06-1.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2008 (Cobalt Oxide). It consists of cobalt (II, III) oxide (tricobalt tetroxide) with a small proportion of cobalt (III) oxide (dicobalt trioxide). A black powder. Practically insoluble in water; dissolves in mineral acids and in solutions of alkali hydroxides.

Profile

Cobalt oxide is used in veterinary practice for the prevention of cobalt deficiency in ruminants. The chloride and sulfate have been used similarly. For the adverse effects of cobalt, see Cobalt Chloride, above.

Coccidioidin

Coccidioidina.

Pharmacopoeias. In *US.*

USP 31 (Coccidioidin). A sterile solution containing the antigens obtained from the byproducts of mycelial growth or from the spherules of the fungus *Coccidioides immitis*; it contains a suitable antimicrobial. A clear, practically colourless or amber-coloured liquid. Store at 2° to 8°. Any dilutions should be stored at 2° to 8° and used within 24 hours. The expiry date is not later than 3 years (mycelial product) or 18 months (spherule-derived product) after release from the manufacturer's cold storage.

Profile

Coccidioidin has been used as an aid to the diagnosis of coccidioidomycosis and, in conjunction with other antigens, to assess the status of cell-mediated immunity. A usual dose of 0.1 mL of a 1 in 100 dilution by intradermal (intracutaneous) injection has been used.

Preparations

USP 31: Coccidioidin.

Proprietary Preparations (details are given in Part 3)

USA: Spherulin.

Cocoyl Caprylocaprate

Coco-Caprylate/Caprate; Cocoyle, caprylocaprate de; Cocoylis caprylocapras; Cocoylis Octanodecanoas; Kokoilo kaprilokapratas; Kokoyl oktanodekanoát; Kokoylkaprylokaprat; Kokoyylikaprylokapraatti; Kókuszalkoholok kaprilátjai és kaprátjai.

CAS — 95912-86-0.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Cocoyl Caprylocaprate). A mixture of esters of saturated C_{12} to C_{18} alcohols with caprylic (octanoic) and capric (decanoic) acids obtained by the reaction of these acids with vegetable saturated fatty alcohols. Relative density about 0.86. Viscosity about 11 mPa s. A slightly yellowish liquid. Practically insoluble in water; miscible with alcohol and with liquid paraffin.

Profile

Cocoyl caprylocaprate is used as an emollient.

Coenzyme A

CoA; CoASH; Coenzima A. 5′-*O*-{3-Hydroxy-3-[2-(2-mercaptoethylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl}adenosine-3′-dihydrogenphosphate-5′-trihydrogendiphosphate.

$C_{21}H_{36}N_7O_{16}P_3S$ = 767.5.

CAS — 85-61-0.

Profile

Formed from adenosine triphosphate, cysteine, and pantothenic acid, coenzyme A is involved in the body in many physiological roles, including the formation of citrate, the oxidation of pyruvate, the oxidation and synthesis of fatty acids, the synthesis of triglycerides, cholesterol, and phospholipids, and the acetylation of amines, choline, and glucosamine. It has been given by injection in a variety of metabolic disorders.

Cogalactoisomerase Sodium

Cogalactoisomerasa sódica; UDPG; Uridine-5′-diphosphoglucose Sodium.

$C_{15}H_{22}N_2Na_2O_{17}P_2,3H_2O$ = 664.3.

CAS — 133-89-1 (cogalactoisomerase).

Profile

Cogalactoisomerase sodium has been used in various hepatic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Bivitox†; Epatoxil†; Liverasi†; Toxepasi†.

Colforsin *(USAN, rINN)*

Boforsin; Colforsina; Colforsine; Colforsinum; Forscolin; Forskolin; HL-362; L-75-1362B. (3*R*,4a*R*,5*S*,6*S*,6a*S*,10*S*,10a*R*,10b*S*)-Dodecahydro-5,6,10,10b-tetrahydroxy-3,4a,7,7,10a-pentamethyl-3-vinyl-1*H*-naphtho[2,1-*b*]pyran-1-one, 5-acetate.

Кольфорсин

$C_{22}H_{34}O_7$ = 410.5.

CAS — 66575-29-9.

Colforsin Daropate Hydrochloride *(rINNM)*

Colforsin Dapropate Hydrochloride; Colforsine, Chlorhydrate de Daropate de; Colforsini Daropatis Hydrochloridum; Hidrocloruro del daropato de colforsina; NKH-477.

Колфорсина Даропата Гидрохлорид

$C_{27}H_{43}NO_8,HCl = 546.1.$

CAS — 138605-00-2.

Profile

Colforsin is an adenylate cyclase stimulator derived from the plant *Plectranthus barbatus* (*Coleus forskohlii*) (Labiatae). It has been investigated for a number of conditions, including glaucoma and impotence. It is reported to have positive inotropic and bronchodilator effects. It has been used in the form of colforsin daropate hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Adehl.

Collagen

Colágeno.

ATC — B02BC07; G04BX11.

ATC Vet — QB02BC07; QG04BX11.

Pharmacopoeias. *US* includes Bovine Acellular Dermal Matrix.

USP 31 (Bovine Acellular Dermal Matrix). A remodelable collagen scaffold derived from fetal or neonatal bovine skin. It is presented as a flat white sheet that is cut to size and hydrated in sterile saline solution prior to implantation. It is utilised as a structural scaffold in orthopaedic, neurosurgical, urogynaecological, dermatological, plastic, and other reconstructive procedures. The source fetal or neonatal bovine skin is mechanically and chemically processed to isolate the dermis and remove cells and cellular components. To prevent the transmission of infectious disease, the manufacturing process is validated to inactivate viruses potentially present in the source material. To prevent the spread of transmissible spongiform encephalopathies, the source material is acquired from appropriate geographic locations. Store at 15° to 30°.

Profile

Collagen is a fibrous protein component of mammalian connective tissue making up almost one third of the total body protein.

Collagen, processed in a variety of ways, has been used in surgery as a haemostatic and as a repair and suture material. For cosmetic purposes it has been injected into the dermis to correct scars and other contour deformities of the skin. Collagen implants have been used to block tear outflow in the management of dry eye (p.2140).

Intraurethral administration of collagen has been used in the treatment of stress incontinence (p.2180). There has also been interest in the use of collagen by mouth to suppress the inflammatory process in rheumatoid arthritis (p.11), osteoarthritis (p.11), and scleroderma (p.1817).

Elastin, another component of connective tissue, is an ingredient, often with collagen, of various topical preparations promoted for skin disorders.

◊ References.

1. Herschorn S, *et al.* Early experience with intraurethral collagen injections for urinary incontinence. *J Urol (Baltimore)* 1992; **148:** 1797–1800.
2. Sieper J, *et al.* Oral type II collagen treatment in early rheumatoid arthritis: a double-blind, placebo-controlled, randomized trial. *Arthritis Rheum* 1996; **39:** 41–51.
3. Stanton SL, Monga AK. Incontinence in elderly women: is periurethral collagen an advance? *Br J Obstet Gynaecol* 1997; **104:** 154–7.
4. Anonymous. GAX collagen for genuine stress incontinence. *Drug Ther Bull* 1997; **35:** 86–7.
5. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum* 2000; **30:** 87–99.
6. Hamraoui K, *et al.* Efficacy and safety of percutaneous treatment of iatrogenic femoral artery pseudoaneurysm by biodegradable collagen injection. *J Am Coll Cardiol* 2002; **39:** 1297–1304.
7. Corcos J, *et al.* Multicenter randomized clinical trial comparing surgery and collagen injections for treatment of female stress urinary incontinence. *Urology* 2005; **65:** 898–904.
8. Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. *Curr Med Res Opin* 2006; **22:** 2221–32.
9. Poon CI, Zimmern PE. Is there a role for periurethral collagen injection in the management of urodynamically proven mixed urinary incontinence? *Urology* 2006; **67:** 725–9.
10. Sakamoto K, *et al.* Long-term subjective continence status and use of alternative treatments by women with stress urinary incontinence after collagen injection therapy. *World J Urol* 2007; **25:** 431–3.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Covadenyl; Eurohair; Hidroplus CL; Medic-S†; Membracel†; Proteita†; Skinderm CL; Zyplast†; ***Austral.:*** Ionil Rinse; Zyderm; Zyplast; ***Canad.:*** Dermatix Catrix†; ***Chile:*** Artrimax; ***Fr.:*** Pangen; ***Ger.:*** Catrix; Colloss; Hemocol; Matricur; Medifome; Pangen†; Porcoll†; Promogran†; Surgicoll†; Tachotop N†; TissuCone; TissuFleece; TissuFoil; Tutoplast Dura; Tutoplast Fascia lata; Zyderm†; Zyplast†; ***Gr.:*** Gelfix; ***Hong Kong:*** Avitene†; Zyderm†; Zyplast†; ***Ital.:*** Alfagen†; Condress; Idroskin; Neopelle†; Skinat; Stimtes†; ***Mex.:*** Fibroquel; ***Neth.:*** Willospon Forte†; ***NZ:*** Contigen; Ionil Rinse†; ***Port.:*** Catrix†; ***Singapore:*** Articolase†; CosmoDerm; CosmoPlast; Zyderm†; Zyplast†; ***UK:*** Catrix†; Contigen; ***USA:*** Avitene; Hemotene†.

Multi-ingredient: ***Arg.:*** Amenite E†; Amenite Plus†; Aristaloe; Aspergun†; Celuvital†; Colageno + C; Collagen T2-Gag†; E-devit; Estri-Atlas; Fibracol Plus; Galenic Restaurador Capilar; Hidroplus Nieve†; Hidrosam; Hidrosam T; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Medicreme; Puraloe Nutritivo; Rep-Cartil; Skinderm R; Totalos Plus; Turgent Colageno; ***Austral.:*** John Plunketts Protective Day Cream; John Plunketts Super Wrinkle Cream; ***Austria:*** TachoComb; ***Belg.:*** Duracoll; ***Chile:*** Acnoxyl Gel Humectante; ***Cz.:*** TachoComb†; ***Fr.:*** Collatamp G†; Promogran; Taido; ***Ger.:*** Collapat II; Integra†; Septocoll; TachoComb†; Targobone; ***Hong Kong:*** TachoComb; ***Hung.:*** TachoComb†; ***Indon.:*** Biolastin; Jointfit; Legreskin; OA Plus; ***Ital.:*** Artrodue; Biomineral 5-Alfa Shampoo; Emofix; Osteoclar; Promogran; Reumilase SD; Secril; Unidermo; ***Malaysia:*** Balance Elastin E†; ***Rus.:*** TachoComb (ТахоКомб); ***Singapore:*** Articolase (w/glucosamine); Seven Seas JointCare Max; ***Switz.:*** Gorgonium; ***Thai.:*** TachoComb†; ***UK:*** Collatamp EG; Jointace; JointCare Max; ***USA:*** PDP Liquid Protein; ***Venez.:*** Artrosamin.

Collagenase

Clostridiopeptidas; Clostridiopeptidase A; Clostridiopeptidasum A; Colagenasa; Klostridiopeptidaasi A.

CAS — 9001-12-1.

ATC Vet — QD03BA02.

Profile

Collagenase is a proteolytic enzyme derived from the fermentation of *Clostridium histolyticum* and has the ability to break down collagen. Preparations containing collagenase are used topically for the debridement of dermal ulcers and burns, and possibly other necrotic lesions, to facilitate granulation and epithelialisation. It has also been given by injection into the intervertebral disc for chemonucleolysis in the treatment of lumbar disc herniation (see low Back Pain, p.7). Collagenase is under investigation for use in Dupuytren's disease and Peyronie's disease.

Hypersensitivity reactions may occur. Local burning, erythema, and pain have been reported at the site of application. It has been suggested that debridement of infected wounds may increase the risk of bacteraemia and that patients should be watched for signs of systemic bacterial infection. The activity of collagenase may be reduced by antiseptics containing detergents, hexachlorophene, and heavy metal ions.

Collagenase potency is expressed in units based on the amount of enzyme required to degrade a standard preparation of undenatured collagen.

Chemonucleolysis. Collagenase has been studied as an alternative to chymopapain (p.2281) for chemonucleolysis because of the risk of anaphylaxis with the latter. Although early studies with collagenase reported benefit, there were also reports of back pain and muscle spasm.[1] Collagenase was not as effective as chymopapain in a comparative study,[2] and further study may be warranted before a firm recommendation can be made.

1. Brown MD. Update on chemonucleolysis. *Spine* 1996; **21** (24 suppl): 62S–68S.
2. Wittenberg RH, *et al.* Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; **26:** 1835–41.

Dupuytren's disease. Collagenase has been reported to be of benefit in the treatment of Dupuytren's contracture.[1]

1. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg (Am)* 2007; **32:** 767–74.

Peyronie's disease. Beneficial effects have been reported with intralesional collagenase in men with Peyronie's disease.[1-3]

1. Gelbard MK, *et al.* The use of collagenase in the treatment of Peyronie's disease. *J Urol (Baltimore)* 1985; **134:** 280–3.
2. Gelbard MK, *et al.* Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. *J Urol (Baltimore)* 1993; **149:** 56–8.
3. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med* 2008; **5:** 180–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Iruxol Mono; ***Braz.:*** Iruxol Mono; Kollagenase; ***Canad.:*** Santyl†; ***Gr.:*** Iruxol Mono; ***Hong Kong:*** Iruxol Mono; ***Ital.:*** Noruxol; ***Neth.:*** Novuxol; ***Port.:*** Ulcerase; ***Switz.:*** Iruxol Mono; ***Turk.:*** Novuxol; ***USA:*** Santyl; ***Venez.:*** Iruxol Simplex.

Multi-ingredient: ***Arg.:*** Iruxol; ***Braz.:*** Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; ***Cz.:*** Iruxol Mono; ***Fin.:*** Iruxol; Iruxol Mono; ***Ger.:*** Iruxol N†; ***Hung.:*** Iruxol Mono; ***Irl.:*** Iruxol Mono; ***Ital.:*** Iruxol; ***Malaysia:*** Iruxol Mono; ***Mex.:*** Ulcoderma; ***Rus.:*** Iruxol (Ируксол); ***S.Afr.:*** Iruxol Mono; ***Singapore:*** Iruxol Mono; ***Spain:*** Iruxol Mono; Iruxol Neo.

Colophony

Colofonia; Coloph.; Colophane; Colophonium; Kalafuna; Kanifolija; Kolofoni; Kolofónium; Kolofonium; Resin; Resina Pini; Resina Terebinthinae; Rosin.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Colophony). The residue remaining after distillation of the volatile oil from the oleoresin obtained from various species of *Pinus*. Translucent, pale yellow to brownish-yellow, angular, irregularly shaped, brittle, glassy pieces of different sizes the surfaces of which bear conchoidal markings. Do not reduce to a fine powder.

Profile

Colophony is an ingredient of some collodions and plaster-masses. It has been used as an ingredient of ointments and dressings for wounds and minor skin disorders. Skin sensitisation and allergic respiratory symptoms have been reported.

Hypersensitivity. Reviews.

1. Downs AM, Sansom JE. Colophony allergy: a review. *Contact Dermatitis* 1999; **41:** 305–10.

Preparations

BP 2008: Flexible Collodion.

Proprietary Preparations (details are given in Part 3)
Rus.: Biopin (Биопин)†.

Multi-ingredient: ***Austral.:*** Zam-Buk†; ***Austria:*** Ehrenhofer-Salbe; Vulpuran; ***Braz.:*** Basilicao†; ***Ital.:*** Fialetta Odontalgica Dr Knapp; ***Mex.:*** Parche Negro Belladona; ***Switz.:*** Leucen; ***UK:*** Dispello; Herbheal Ointment; Pickles Corn Caps.

Comfrey

Boneset; Comfrey Root; Consolidae Radix; Consuelda; Symphytum.

NOTE. Boneset is also a common name used for *Eupatorium perfoliatum* (see p.2267).

Pharmacopoeias. *Br.* includes Symphytum Officinale Root for Homoeopathic Preparations and Symphytum Officinale Root, Ethanol. decoctum for Homoeopathic Preparations.

BP 2008 (Symphytum Officinale Root for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

BP 2008 (Symphytum Officinale Root, Ethanol. decoctum for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

Profile

Comfrey consists of the dried root and rhizome of *Symphytum officinale* (Boraginaceae); the leaf has also been used. It contains about 0.7% of allantoin, large quantities of mucilage, and some tannin. It may also contain pyrrolizidine alkaloids.

Comfrey was formerly used as an application to wounds and ulcers to stimulate healing and was also given systemically for gastric ulceration. It has been applied topically in the treatment of inflammatory disorders. The healing action of comfrey has been attributed to the presence of allantoin (p.1588).

There are reports of hepatotoxicity attributed to pyrrolizidine alkaloids present in comfrey preparations and such preparations have been withdrawn or banned in a number of countries.

Homoeopathy. Comfrey has been used in homoeopathic medicines under the following names: Symphytum officinale; Symph. of.

◊ References.

1. Stickel F, Seitz HK. The efficacy and safety of comfrey. *Public Health Nutr* 2000; **3:** 501–8.
2. Grube B, *et al.* Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine* 2007; **14:** 2–10.
3. D'Anchise R, *et al.* Comfrey extract ointment in comparison to diclofenac gel in the treatment of acute unilateral ankle sprains (distortions). *Arzneimittelforschung* 2007; **57:** 712–16.

Adverse effects. Toxic pyrrolizidine alkaloids have been isolated from several species of comfrey plants including common comfrey (*Symphytum officinale*), prickly comfrey (*S. asperum*), and Russian comfrey (*S. uplandicum*). Ingestion of plants containing pyrrolizidine alkaloids is a common cause of hepatic veno-occlusive disease in developing countries[1] and pyrrolizidine alkaloid hepatotoxicity presumably due to comfrey has been reported in North America and Europe.[1,2] Pulmonary endothelial hyperplasia and carcinogenic activity have also been reported in *animals*.[1,2]

1. Ridker PM, McDermott WV. Comfrey herb tea and hepatic veno-occlusive disease. *Lancet* 1989; **i**: 657–8.
2. Bach N, *et al.* Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med* 1989; **87**: 97–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Traumaplant; ***Cz.:*** Traumaplant; ***Ger.:*** Kytta-Plasma f; Kytta-Salbe f; Traumaplant; ***Indon.:*** Mediflor; ***Switz.:*** Kytta Pommade; ***UK:*** Comfrelieve; ***Venez.:*** Traumaplant.

Multi-ingredient: ***Cz.:*** Dr Theiss Beinwell Salbe†; Stomatosan†; ***Ger.:*** Kytta-Balsam f; Rhus-Rheuma-Gel N; Syviman N†; ***Israel:*** Comfrey Plus; ***Switz.:*** Gel a la consoude; Keppur; Kytta Baume; Kytta Gel†.

Complement Blockers

Inhibidores del complemento.

Блокаторы Комплемента

Profile

Complement is a group of plasma and cellular proteins contributing to the innate immune system and is so called because it complements the microbicidal action of antibodies. The complement system is activated by the antigen-antibody complex followed by a cascade reaction of complement proteins culminating in microbial cell lysis. Complement also plays a part in many other physiological processes and regulatory mechanisms are in place to prevent inflammatory damage to host tissues through the inappropriate activation of complement. Hereditary or acquired abnormalities of the complement system are associated with a variety of disorders depending on which part of the system is affected, and include recurrent infections, partial lipodystrophy, hereditary angioedema, paroxysmal nocturnal haemoglobinuria, non-specific vasculitis, glomerulonephritis, cardiovascular disease, rheumatoid arthritis, sepsis, asthma, acute respiratory distress syndrome, psoriasis, SLE, bullous pemphigoid, discoid lupus, and graft survival after solid organ transplantation.

A number of substances are used or are under investigation for their ability to block activation of the complement system:

- complement C1 esterase inhibitor (p.2287) is given as replacement therapy in the treatment of hereditary angioedema
- eculizumab (p.2299) is a monoclonal antibody that targets the terminal C5 protein of complement and is given in the treatment of paroxysmal nocturnal haemoglobinuria
- pexelizumab (p.2366) is a similar substance under investigation in patients undergoing coronary artery revascularisation procedures
- mirococept (APT-070, SCR1-3) is a derivative of soluble complement receptor type 1 (SCR1) under investigation for the prevention of post transplantation graft dysfunction
- TP-10, a form of SCR1 has also been investigated for respiratory disorders
- myristoylated-peptidyl-recombinant human CD59 is under investigation for paroxysmal nocturnal haemoglobinuria

◊ References.

1. Bhole D, Stahl GL. Therapeutic potential of targeting the complement cascade in critical care medicine. *Crit Care Med* 2003; **31** (suppl): S97–S104.
2. Brook E, *et al*. Opportunities for new therapies based on the natural regulators of complement activation. *Ann N Y Acad Sci* 2005; **1056:** 176–88.

Complement C1 Esterase Inhibitor

Inhibidor de la C1 esterasa.

С1-Ингибитор Комплемента

ATC — B02AB03.

ATC Vet — QB02AB03.

Profile

Complement C1 esterase inhibitor is an endogenous complement blocker (p.2286) that plays a role in regulation of the complement system. It is prepared from human plasma and given as replacement therapy in hereditary angioedema (p.1081), in which there is a deficiency of natural complement C1-esterase inhibitor. It is given for both short-term prophylaxis and treatment of acute life-threatening attacks by slow intravenous injection or infusion in typical doses of 500 units or, in severe cases, 1000 units. The dose may be repeated if necessary after a few hours.

A recombinant human complement C1 esterase inhibitor (rh C1INH) is under investigation.

◊ Complement C1 esterase inhibitor may be effective in both the prevention and treatment of acute hereditary angioedema.[1] It has also been tried in the management of other conditions including sepsis (see Septicaemia, p.190) and capillary leak syndrome.[2] It is under investigation for the treatment of pancreatitis and for use in allogeneic lung transplantation, thermal injury, and shock.[2] It is also being studied as a means of limiting reperfusion injury in patients with acute myocardial infarction.[3]

1. Waytes AT, *et al*. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 1996; **334:** 1630–4.
2. Caliezi C, *et al*. C1-esterase inhibitor: an anti-inflammatory agent and its potential use in the treatment of diseases other than hereditary angioedema. *Pharmacol Rev* 2000; **52:** 91–112.
3. de Zwaan C, *et al*. Continuous 48-h C1-inhibitor treatment, following reperfusion therapy, in patients with acute myocardial infarction. *Eur Heart J* 2002; **23:** 1670–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Angioneurina†; Berinert P; ***Austria:*** Berinert; ***Cz.:*** Berinert; ***Fr.:*** Esterasine†; ***Ger.:*** Berinert; ***Hung.:*** Berinert P; ***Ital.:*** C1 Inattivatore Umano†; ***Neth.:*** Cetor; ***Switz.:*** Berinert.

Condurango

Condurango Bark; Condurango cortex; Condurango, écorce de; Eagle-vine Bark.

Pharmacopoeias. In *Jpn* and *Swiss.*

Profile

Condurango, the dried stem bark of *Marsdenia condurango* (*Gonolobus condurango*) (Asclepiadaceae), has been used as a bitter.

Homoeopathy. Condurango has been used in homoeopathic medicines under the following names: Marsdenia cundurango; Cond.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Sigman-Haustropfen; ***Braz.:*** Camomila; Estomafitino†; ***Ger.:*** Majocarmin forte†; Nervogastrol N†; Pankreaplex Neu†; Pascopankreat; Pascopankreat novo†; ***Pol.:*** Herbaton; ***Switz.:*** Elixir tonique N; Padma-Lax; Padmed Laxan; Stomacine.

Congo Red

CI Direct Red 28; Colour Index No. 22120; Czerwień Kongo; Rojo Congo; Rubrum Congoensis. Disodium 3,3′-[biphenyl-4,4′-diylbis(azo)]bis[4-aminonaphthalene-1-sulphonate].

$C_{32}H_{22}N_6Na_2O_6S_2$ = 696.7.

CAS — 573-58-0.

Profile

Congo red is used as a stain in the diagnosis of amyloidosis. It causes amyloid in tissue samples to fluoresce under polarised light.

Conivaptan Hydrochloride *(rINNM)* ⊗

CI-1025; Conivaptan, Chlorhydrate de; Conivaptán, hidrocloruro de; Conivaptani Hydrochloridum; YM-087 (conivaptan or conivaptan hydrochloride). 4″-[(4,5-Dihydro-2-methylimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]-2-biphenylcarboxanilide hydrochloride.

Кониваптана Гидрохлорид

$C_{32}H_{26}N_4O_2$,HCl = 535.0.

CAS — 210101-16-9 (conivaptan); 168626-94-6 (conivaptan hydrochloride).

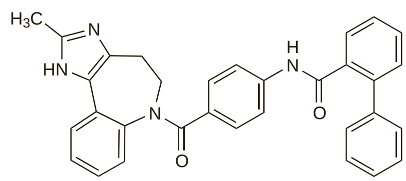

(conivaptan)

Adverse Effects and Precautions

The most common adverse effects of conivaptan are infusion site reactions such as erythema, pain, phlebitis, and swelling, which are usually mild but can be severe enough in some patients that infusion must be stopped. Other adverse effects include atrial fibrillation, gastrointestinal disturbances, pyrexia, thirst, electrolyte disturbances, headache, and hypertension or hypotension.

Conivaptan is contra-indicated in hypovolaemic hyponatraemia, and is not indicated for the treatment of patients with congestive heart failure. Rapid correction of serum-sodium concentrations with conivaptan could increase the risk of osmotic demyelination syndrome. Conivaptan should be used with caution in hepatic or renal impairment because systemic exposure can be increased.

Interactions

As a substrate of the cytochrome P450 isoenzyme CYP3A4, concentrations of conivaptan can be increased by CYP3A4 inhibitors. The use of conivaptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contra-indicated. Conivaptan itself is also a potent inhibitor of CYP3A4 and may increase the concentrations of other substrates of this isoenzyme, including amlodipine, midazolam, and simvastatin.

Conivaptan can reduce the clearance, and subsequently increase concentrations, of digoxin.

Pharmacokinetics

Conivaptan is metabolised by the cytochrome P450 isoenzyme CYP3A4, but inhibits its own metabolism. Using a regimen of intravenous loading dose followed by continuous infusion, concentrations of conivaptan initially decrease from the loading dose peak over about 12 hours, then gradually increase. After stopping the infusion, conivaptan has an elimination half-life of about 5 hours. Conivaptan is highly bound to plasma proteins.

Uses and Administration

Conivaptan hydrochloride is a vasopressin V_{1a} and V_2 receptor antagonist. In the management of hyponatraemia it acts mainly at V_2 receptors in the renal collecting ducts to increase the excretion of free water. It is used to treat euvolaemic and hypervolaemic hyponatraemia (p.1670), and is not indicated for congestive heart failure.

Conivaptan hydrochloride is given by intravenous infusion. To minimise infusion site irritation, it should be diluted in glucose 5% infusion (loading doses are given in 100 mL of fluid, the subsequent infusions in 250 mL) and given through a large vein; the infusion site should be changed every 24 hours. A loading dose of 20 mg is given over 30 minutes, followed by a continuous infusion of 20 mg over 24 hours. Treatment may be continued at a dose of 20 mg daily titrated to a maximum of 40 mg daily if required. The maximum duration of the infusion is 4 days. If a rapid rise in serum-sodium occurs (more than 12 mmol/litre in 24 hours) conivaptan should be stopped, and serum-sodium and neurological status should be carefully monitored because of the risk of osmotic demyelination syndrome. If hypovolaemia or hypotension develop, conivaptan should be stopped and volume status and vital signs should be monitored. Conivaptan may be resumed at a lower dose, if still indicated, when the rise in serum-sodium has stopped, if there is no evidence of adverse neurological effects and the patient is euvolaemic and no longer hypotensive.

◊ References.

1. Walter KA. Conivaptan: new treatment for hyponatremia. *Am J Health-Syst Pharm* 2007; **64:** 1385–95.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Vaprisol.

Convallaria

Convalaria; Convallariae Herba; Lily of the Valley; Maiblume; Maiglöckchenkraut; May Lily; Muguet; Ziele konwalii.

CAS — 3253-62-1 (convallatoxol); 13473-51-3 (convalloside); 13289-19-5 (convallatoxoloside); 508-75-8 (convallatoxin).

Pharmacopoeias. In *Ger.* and *Pol.* (from *C. majalis* or closely related species).

Profile

Convallaria consists of the dried flowers, herb, or the rhizomes and roots of lily of the valley, *Convallaria majalis* (Liliaceae). Several crystalline glycosides have been obtained from the plant including convallarin, convalloside, convallatoxoloside, and convallatoxin.

Convallaria contains cardiac glycosides and has actions on the heart similar to those of digoxin (p.1259). Convallaria is used in herbal medicine.

Homoeopathy. Convallaria has been used in homoeopathic medicines under the following names: Convallaria majalis; Conval. m.

◊ *Convallaria majalis* has been designated unsafe for inclusion in foods, beverages, or drugs by the FDA in the USA.[1]

1. Larkin T. *FDA Consumer* 1983; **17** (Oct.): 5.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Convacard†; Valdig-N Burger†; ***Pol.:*** Convafort.

Multi-ingredient: ***Arg.:*** Passacanthine†; ***Austria:*** Omega; ***Ger.:*** Cardibisana†; Convallocor-SL; Convastabil; Miroton; Miroton N†; Oxacant N†; Oxacant-forte N†; Oxacant-Khella N†; Viscorapas duo†; ***Pol.:*** Cardiol C; Kelicardina; Neocardina.

Copper Acetate

Cuivre, acétate de; Cupri acetas; Cupric Acetate; Kopparacetat; Kupariasetaatti; Miedzi(II) octan; Vario acetatas.

Ацетат Меди; Уксуснокислая Медь

$(C_2H_3O_2)_2Cu,H_2O$ = 199.6.

CAS — 142-71-2 (anhydrous).

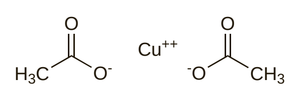

Pharmacopoeias. *Eur.* (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Copper Acetate Monohydrate for Homoeopathic Preparations; Cupri Acetas Monohydricus ad Praeparationes Homoeopathicas). Greenish-blue crystals or green powder. Soluble in water; slightly soluble or very slightly soluble in alcohol.

Profile

Copper acetate has been used in a variety of dermatological preparations. It is now more usually used complexed with a tripeptide in the form of prezatide copper acetate (p.1611). This acts as a source of ionic copper, which is needed by lysyl oxidase, a copper-dependent enzyme that has a crucial role in the crosslinking of collagen and elastin. For the nutritional and other uses of copper and its salts, see p.1936.

Homoeopathy. Copper acetate has been used in homoeopathic medicines under the following names: Cuprum aceticum; Cup. acet.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Verel; ***Mex.:*** Emplasto Monopolis.

Corbadrine (rINN) ⊗

Corbadrina; Corbadrinum; *l*-3,4-Dihydroxynorephedrine; Levonordefrin; *l*-Nordefrin. (−)-2-Amino-1-(3,4-dihydroxyphenyl)propan-1-ol.

Корбадрин

$C_9H_{13}NO_3$ = 183.2.

CAS — 829-74-3 (corbadrine); 6539-57-7 (nordefrin); 61-96-1 (nordefrin hydrochloride).

Pharmacopoeias. In *US.*

USP 31 (Levonordefrin). A white to buff-coloured, odourless, crystalline solid. Practically insoluble in water; slightly soluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in aqueous solutions of mineral acids.

Profile

Corbadrine is a sympathomimetic (p.1407) that has been added to local anaesthetic preparations in dentistry to diminish absorption and to localise the effect; a concentration of 1 in 20 000 has been used.

Preparations

USP 31: Mepivacaine Hydrochloride and Levonordefrin Injection; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection.

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Canad.:*** Polocaine†; ***USA:*** Carbocaine with Neo-Cobefrin; Isocaine; Polocaine.

Coriander

Coentro; Coriand.; Coriander Fruit; Coriander Seed; Coriandre; Coriandri fructus; Fruto del cilantro; Kalendrų vaisiai; Koriander; Koriandertermés; Koriandrový plod; Korianteri; Owoc kolendry.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Coriander). The dried cremocarp of *Coriandrum sativum*, containing not less than 0.3% v/w of essential oil, calculated with reference to the dried substance. Protect from light.

The BP 2008 directs that when Powdered Coriander is prescribed or demanded material containing not less than 0.2% v/w of essential oil shall be dispensed or supplied.

Profile

Coriander is the source of coriander oil (below). It is a carminative and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Salutaris; ***Austria:*** Brady's-Magentropfen; Mariazeller; Planta Lax; ***Braz.:*** Fitolax; Florlax; Fontolax; Frutalax†; Laxarine†; Laxtam; Naturetti; Sene Composta†; Tamaril; Tamarine; Tamarix†; ***Cz.:*** Abfuhr-Heilkrautertee†; Carminativum Babynos†; Hertz- und Kreislauftee†; ***Fr.:*** Mediflor Tisane Digestive No 3; ***Ger.:*** Carminativum Babynos†; Floradix Multipretten N; Gastrol S†; Presselin Dyspeptikum†; Ramend Krauter†; ***Ital.:*** Cadifen; Cadimint; Dicalmir; Tamarine; ***Mex.:*** Naturetti†; ***Pol.:*** Cholesol; Diges-Tonic; ***S.Afr.:*** Melissengeist; Spiritus Contra Tussim Drops; ***Spain:*** Agua del Carmen; Jarabe Manceau; Pruina; ***Switz.:*** Alcoolat de Melisse†; ***UK:*** Melissa Comp..

Coriander Oil

Cilantro, aceite esencial de; Coriandre, huile essentielle de; Coriandri aetheroleum; Coriandri Etheroleum; Kalendrų eterinis aliejus; Korianderolja; Koriandrová silice; Korianteriöljy; Ol. Coriand; Oleum Coriandri.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Coriander Oil). An essential oil obtained by steam distillation from the fruits of *Coriandrum sativum*. A clear colourless or pale yellow liquid, with the characteristic spicy odour. It contains not less than 65% and not more than 78% of linalol. Relative density 0.860 to 0.880. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Coriander Oil). The volatile oil obtained by steam distillation from coriander. Specific gravity 0.863 to 0.875. Soluble 1 in 3 of alcohol (70%). Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Coriander oil is aromatic and carminative and is used as a flavour.

Preparations

BP 2008: Compound Orange Spirit; Compound Rhubarb Tincture;
USNF 26: Compound Orange Spirit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Floradix Multipretten N; Gastricard†; Gastrysat; ***Ital.:*** Valda Propoli; ***Pol.:*** Argol Essenza Balsamica; Argol Grip; Argol Rheuma; ***Rus.:*** Espol (Эспол).

Corn Silk

Maíz, barba del; Stigma Maydis; Zea.

Pharmacopoeias. In *Fr.*

Profile

Corn silk, the stigma and style of maize (*Zea mays*) (Gramineae), has diuretic properties and is used for urinary-tract disorders including renal calculi.

Maize is widely used as a food and has also been used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Insadol; ***Switz.:*** Insadol; ***UK:*** Protat.

Multi-ingredient: ***Austral.:*** Althaea Complex; Urinase†; ***Pol.:*** Neopoldanen; ***Spain:*** Diurinat; Renusor†; ***UK:*** Elixir Damiana and Saw Palmetto.

Cottonseed Oil

Algodón, aceite de; Bomullsfröolja; Coton, huile de; Cotton Oil; Gossypii oleum; Gossypii Oleum Latin; Gyapotmagolaj; Ol. Gossyp. Sem.; Oléo de Algodoeiro; Oleum Gossypii Seminis; Puuvillansiemenöljy; Vilnamedžių aliejus.

CAS — 8001-29-4.

Pharmacopoeias. In *USNF*, which also includes hydrogenated cottonseed oil.

Eur. (see p.vii) includes only the hydrogenated oil.

Ph. Eur. 6.2 (Cottonseed Oil, Hydrogenated; Gossypii Oleum Hydrogenatum). Obtained by refining and hydrogenation of oil obtained from seeds of cultivated plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium*. It consists mainly of triglycerides of palmitic and stearic acids. It is a white or almost white mass or powder which melts to a clear pale yellow liquid when heated. M.p. 57° to 70°. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Protect from light.

USNF 26 (Cottonseed Oil). The refined fixed oil obtained from the seed of plants of various varieties of *Gossypium hirsutum* or of other species of *Gossypium* (Malvaceae). It is a pale yellow, oily liquid, odourless or nearly so. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, with ether, and with petroleum spirit. Store in airtight containers at a temperature not exceeding 40°. Protect from light. At temperatures below 10° particles of solid fat may separate from the oil and at about 0° to −5° the oil becomes a solid or nearly so.

USNF 26 (Hydrogenated Cottonseed Oil). It is obtained by hydrogenating Cottonseed Oil and consists mainly of triglycerides of palmitic and stearic acids. A white mass or powder that melts to a clear, pale yellow liquid when heated. M.p. 57° to 70°. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in toluene. Store in airtight containers. Protect from light.

Profile

Cottonseed oil is used as an oily vehicle.

An extract of cottonseed oil, gossypol (p.2316), has been tried as a contraceptive in males.

Couch-grass

Agropyron; Chiendent; Chiendent, rhizome de; Dogs Grass; Grama; Graminis rhizoma; Juolavehnänjuurakko; Kłącze perzu; Kvickrot; Pýrový oddenek; Quackgrass; Tarackbúza-gyökértörzs; Triticum; Twitch; Varpučių šakniastiebiai.

Пырей Ползучий

NOTE. Distinguish from Wheat, *Triticum aestivum* (see p.2415).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Couch Grass Rhizome). The whole or cut, washed and dried rhizome of *Agropyron repens* (*Elymus repens*); the adventitious roots are removed. Protect from light.

Profile

Couch-grass is a mild diuretic that has been used in herbal medicine in the treatment of urinary-tract disorders. It contains glucose, mannitol, inositol, and triticin (a carbohydrate resembling inulin). The Latin binomials *Elytrigia repens* and *Triticum repens* have also been applied to couch-grass.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Acorus.

Multi-ingredient: ***Austria:*** Abfuhrtee†; ***Fr.:*** Drainuryl; Herbesan; Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane No 4 Diuretique; Obeflorine; Tisane Hepatique de Hoerdt; ***Ger.:*** Hevert-Blasen-Nieren-Tee N; Presselin Stoffwechsel-Tee Hapeka 225 N†; Renob Blasen- und Nierentee; ***Ital.:*** Betulla (Specie Composta)†; Emmenoiasi; Gramigna (Specie Composta)†; Tisana Kelemata; ***Pol.:*** Dentosept; Diabetofort; Diabetosol; Laxantol; NeoFitolizyna; ***Spain:*** Diurinat; Renusor†; ***UK:*** Antitis; Kas-Bah.

Coumarin

1,2-Benzopyrone; 5,6-Benzo-α-pyrone; Cumarin; Cumarina; Kumaryna; Tonka Bean Camphor. 2*H*-1-Benzopyran-2-one.

$C_9H_6O_2$ = 146.1.

CAS — 91-64-5.

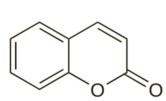

Pharmacopoeias. In *Ger.*

Profile

Coumarin is the odorous principle of Tonka seed (Tonka or Tonquin bean); it may be prepared synthetically. Coumarin has been given to reduce excess tissue protein and associated fluid in the treatment of lymphoedema (see below). It has also been used as a fixative in perfumery and as a flavour. It is reported to be an immunostimulant and has been tried in the treatment of malignant neoplasms.

Coumarin derivatives are used as anticoagulants; coumarin itself is not an active anticoagulant.

Effects on the liver. Coumarin has been classified as hepatotoxic based on studies in *animals* and effects ranging from elevated liver enzymes to serious organ damage has been reported in humans. Seventeen of 2173 patients enrolled in a study of coumarin developed elevated liver enzyme values;[1] the majority of patients were given 100 mg coumarin daily for 1 month followed by 50 mg daily for 2 years. However, none of the patients developed permanent liver damage and liver enzyme values returned to normal in 5 patients who continued taking coumarin. Results from 5 studies supported by the Lymphoedema Association of Australia, in which patients received 400 mg daily for a mean duration of 14.6 months, showed 2 cases of hepatotoxicity among 1106 patients.[2] In the period of 14 months up to May 1995, the Australian Drug Evaluation Committee received 10 reports of suspected adverse reactions to coumarin,[3] including 6 cases of jaundice in women who had taken 400 mg daily for 1 to 4 months. Periportal and lobular necrosis were found on biopsy in 1 case and another had a fatal outcome due to massive hepatic necrosis.

Reports of hepatotoxicity have led to the withdrawal of coumarin in a number of countries.

1. Cox D, *et al.* The rarity of liver toxicity in patients treated with coumarin (1,2-benzopyrone). *Hum Toxicol* 1989; **8:** 501–6.
2. Casley-Smith JR, Casley-Smith JR. Frequency of coumarin hepatotoxicity. *Med J Aust* 1995; **162:** 391.
3. Anonymous. Lodema and the liver. *Aust Adverse Drug React Bull* 1995; **14:** 11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/07/08)

Lymphoedema. Benzopyrones such as coumarin are reported to reduce excess protein in tissues with high-protein oedema, hence the use of coumarin in lymphoedema of various causes, including postmastectomy, and filarial lymphoedema and elephantiasis.[1-5] Evidence for its efficacy is, however, conflicting;[4-6] at best the action is slow and treatment may need to be given for 6 months to 2 years before any benefit is seen.

1. Jamal S, *et al.* The effects of 5,6 benzo-[a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India: preliminary results. *Ann Trop Med Parasitol* 1989; **83:** 287–90.
2. Turner CS. Congenital lymphoedema. *JAMA* 1990; **264:** 518.
3. Casley-Smith JR, *et al.* Treatment of lymphedema of the arms and legs with 5,6-benzo-[α]-pyrone. *N Engl J Med* 1993; **329:** 1158–63.
4. Casley-Smith JR, *et al.* Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-α-pyrone (coumarin). *BMJ* 1993; **307:** 1037–41.
5. Casley-Smith JR. Benzo-pyrones in the treatment of lymphoedema. *Int Angiol* 1999; **18:** 31–41.
6. Loprinzi CL, *et al.* Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 1999; **340:** 346–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Esberiven; ***Ger.:*** Venalot mono†; ***Ital.:*** Linfovenodren.

Multi-ingredient: ***Arg.:*** Esberiven; Microsuy; ***Braz.:*** Flebotrat†; Micotox†; Varicoss; Venalot; Venalot H; ***Ger.:*** Caye Rheuma-Balsam; Venalot; Venalot N†; ***Ital.:*** Flebolider; ***Mex.:*** Venalot.

Coutarea Latiflora

Copalchi.

NOTE. The name copalchi has also been applied to *Croton niveus* (Euphorbiaceae).

Profile

Coutarea latiflora is an ingredient of herbal remedies used in the management of diabetes mellitus. For a report of hepatotoxicity associated with a preparation containing *Coutarea latiflora* see Centaury, p.2279.

Adverse effects. Rhabdomyolysis and haemolysis occurred in a 58-year-old man 2 days after starting treatment with *Coutarea latiflora*.[1] The patient had a similar reaction 4 years earlier after taking the same product.

1. Roca B. Rhabdomyolysis and hemolysis after use of Coutarea latiflora. *Am J Med* 2003; **115:** 677.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Sucontral.

Cowberry

Alpine Cranberry; Arándano rojo; Liść brusznicy (leaf); Red Whortleberry; Vitis Idaeae Folium (leaf).

Pharmacopoeias. In *Pol.*

Profile

The leaves of the cowberry, *Vaccinium vitis-idaea* (Ericaceae), have astringent properties and have been used as a domestic remedy for diarrhoea.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Pol.:*** Diuronis.

CR Gas

EA-3547; Gas CR. Dibenz[*b*,*f*][1,4]oxazepine.

$C_{13}H_9NO = 195.2$.

CAS — 257-07-8.

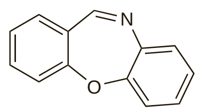

Profile

A riot-control gas with irritant and lachrymatory properties similar to those of CS gas (p.2290); it is described as a tear gas. CR gas is reported not to be hydrolysed by water and therefore to be suitable for use in water cannons.

◊ References.

1. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; **22:** 103–10.

Cranberry

Arándano.

Pharmacopoeias. *US* includes a liquid preparation.

USP 31 (Cranberry Liquid Preparation). The bright red juice derived from the fruits of *Vaccinium macrocarpon* or *V. oxycoccus* (Ericaceae). It contains no added substances and is for manufacturing purposes only. pH between 2.4 and 2.6. Store at 2° to 8°.

Profile

Cranberry consists of the fruit of *Vaccinium macrocarpon*, the American cranberry or *V. oxycoccus*, the European cranberry. Cranberry juice has been reported to reduce the incidence of urinary-tract infections.

Interactions. For a report of interactions between cranberry juice and *warfarin*, see p.1430.

Urinary-tract infections. Cranberries and cranberry juice have been used widely for many years for both the prevention and treatment of urinary-tract infections. A systematic review[1] of available data concluded that there was some evidence that cranberry juice for prevention may decrease the number of symptomatic urinary-tract infections in women over a 12 month period, particularly those with recurrent infections. However, evidence for efficacy in the elderly is inconclusive, and currently lacking in patients with neurogenic bladder. The authors recommended further controlled studies in all susceptible patient groups, and also into more acceptable dosage formulations. However, another such review[2] assessing the effectiveness of cranberry for treatment concluded that there was no good quality evidence to suggest that it is effective.

1. Jepson RG, Craig JC Cranberries for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/04/08).
2. Jepson RG, *et al.* Cranberries for treating urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 18/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Urosedac; ***Austral.:*** Uricleanse†; ***Canad.:*** Cran Max†; ***Fr.:*** Cys Control; Gyndelta; ***Ital.:*** Ivumir.

Multi-ingredient: ***Arg.:*** Uridon; ***Austral.:*** Bioglan Cranbiotic Super; Cranberry Complex; Extralife Uri-Care; ***Canad.:*** Cran-C†; Prostease; ***Hong Kong:*** Prostease; ***Pol.:*** Diabetosol; Urosept.

Crataegus

Aubépine; Aubépine, baie d' (hawthorn berries); Aubépine, feuille et fleur d' (hawthorn leaf and flowers); Biancospino; Crataegi folium cum flore (hawthorn leaf and flowers); Crataegi fructus (hawthorn berries); Crataegi Inflorescentia (hawthorn leaf and flowers); English Hawthorn; Galagonyatermés (hawthorn berries); Gudobelių vaisiai (hawthorn berries); Hagtornsbär (hawthorn berries); Haw; Hlohový plod (hawthorn berries); Kwiatostan głogu (hawthorn leaf and flowers); Orapihlajanmarja (hawthorn berries); Owoc głogu (hawthorn berries); Pilriteiro; Weissdorn; Whitethorn.

ATC — C01EB04.

ATC Vet — QC01EB04.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Hawthorn Berries; Crataegi Fructus). The dried false fruits of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or a mixture of these false fruits. They contain not less than 1% of procyanidins, calculated as cyanidin chloride ($C_{15}H_{11}ClO_6$ = 322.7) with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Hawthorn Leaf and Flower; Crataegi Folium cum Flore). The whole or cut, dried flower bearing branches of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or, more rarely, other European *Crataegus* species including *C. pentagyna*, *C. nigra*, and *C. azarolus*. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

USP 31 (Hawthorn Leaf with Flower). The dried tips of the flower-bearing branches up to 7 cm in length of *Crataegus monogyna* or *C. laevigata*, also known as *C. oxyacantha* (Rosaceae). It contains not less than 0.6% of *C*-glycosylated flavones, expressed as vitexin ($C_{21}H_{20}O_{10}$ = 432.4), and not less than 0.45% of *C*-glycosylated flavones, expressed as hyperoside, calculated with reference to the dried drug. Protect from light.

Profile

Crataegus contains flavonoid glycosides with cardiotonic properties similar to those of digoxin (p.1259). Crataegus is used in herbal medicine.

Homoeopathy. Crataegus has been used in homoeopathic medicines under the following names: Crataegus oxyacantha; Crat. oxy.

◊ Crataegus is used in herbal medicine for cardiovascular disorders.[1-4] A systematic review[4] of controlled studies concluded that it shows significant benefit compared with placebo as an adjunctive treatment for chronic heart failure. A review[3] of data currently available indicates that it is rarely associated with serious adverse affects, although the authors noted that problems may occur with its unsupervised use, especially if given with other drugs.

1. Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. *Am J Health-Syst Pharm* 2002; **59:** 417–22.
2. Chang Q, *et al.* Hawthorn. *J Clin Pharmacol* 2002; **42:** 605–12.
3. Daniele C, *et al.* Adverse-event profile of Crataegus spp.: a systematic review. *Drug Safety* 2006; **29:** 523–35.
4. Pittler MH, *et al.* Hawthorn extract for treating chronic heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/04/08).

Preparations

Ph. Eur.: Hawthorn Leaf and Flower Dry Extract.

Proprietary Preparations (details are given in Part 3)

Austria: Bericard; Crataegan; Crataegutt; ***Belg.:*** Aubeline; ***Braz.:*** Dekatin; ***Chile:*** Cratenox; ***Cz.:*** Caj z Hlohu; Cardiplant†; Hloh; Kneipp Pflanzen-Dragees Weissdorn†; ***Fr.:*** Aubeline; Cardiocalm; Spasmosedine†; ***Ger.:*** Adenylocrat†; Ardeycordal mono; Basticrat†; Born; Chronocard N; Cordapur Novo; Corocrat†; Craegium; Cratae-Loges; Crataegutt; Crataegysat; Crataepas†; Cratecor†; Dr Niedermaier Herztonikum; Esbericard novo; Faros; Koro-Nyhadin; Kytta-Cor; Lomacard†; Natucor; Orthangin novo; Oxacant-mono; Poikilocard Mono†; Protecor novo; Regulacor-POS; Senicor†; Steicorton†; Stenocrat mono; ***Hung.:*** Crataegutt†; ***Pol.:*** Cardiplant; Chronocard; Cratonic; ***Rus.:*** Doppelherz Cardiovital (Доппельгерц Кардиовитал); Novo-Passit (Ново-Пассит); ***Switz.:*** Cardiplant; Crataegisan; Crataegitan; Faros; Sedosan-N†; Vitacor.

Multi-ingredient: ***Arg.:*** Hepatodirectol; Passacanthine†; Sequals G; ***Austral.:*** Asa Tones; Bioglan Bioage Peripheral; Coleus Complex; Dan Shen Compound; For Peripheral Circulation Herbal Plus Formula 5; Gingo A†; Ginkgo Biloba Plus†; Ginkgo Complex†; Lifechange Circulation Aid†; Lifesystem Herbal Formula 6 For Peripheral Circulation†; Multi-Vitamin Day & Night†; ***Austria:*** Corodyn†; Omega; Rutiviscal; Virgilocard; Wechseltee St Severin; ***Belg.:*** Natudor; Sedinal; Seneuval; ***Braz.:*** Anevrase†; Calman; Calmazin†; Calmiplan; Floriny; Pasalix; Pasic; Passi Catha†; Passiflora Composta†; Passiflorine; Sedalin†; Serenus; Sominex; ***Chile:*** Armonyl; ***Cz.:*** Alvisan Neo; Fytokliman Planta; Hertz- und Kreislauftee†; Hypotonicka; Novo-Passit; Valofyt Neo; ***Fr.:*** Anxoral†; Biocarde; Euphytose; Germose†; Lenicalm†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Mediflor Tisane Circulation du Sang No 12; Natudor; Neuroflorine; Nicoprive; Nocvalene†; Okimus; Passiflorine; Passinevryl; Phytocalm†; Sedatif Tiber; Sedopal; Spasmine; Sympaneurol; Sympathyl; Sympavagol; Tranquital; Vagostabyl; ***Ger.:*** Antihypertonicum S; Ardeycordal N†; Asgoviscum N†; Biovital Aktiv†; Biovital Classic; Bomacorin; Cardibisana†; Cardio-Kreislauf-Longoral; Chlorophyl liquid "Schuh"†; Convallocor-SL; Convastabil; Cor-Select†; Fovysat†; Ginseng-Complex "Schuh"†; Herz-Starkung N†; Heusin†; Ilja Rogoff; JuViton†; Korodin; Lacoerdin Mg Plus†; Nephrisan P†; Nitro-Crataegutt†; Oxacant N†; Oxacant-forte N†; Oxacant-Khella N†; Oxacant-sedativ; Passin; Presselin Arterien K 5 P†; Protecor; Salus Herz-Schutz-Kapseln†; Saluscor Herz-Schutz; Septacord; Stenocrat†; Tornix; Viscorapas duo†; ***Hong Kong:*** Ginkgo Plus Vivo-Livo†; ***Hung.:*** Biovital†; ***Indon.:*** Procardio; ***Israel:*** Nerven-Dragees; Passiflora; ***Ital.:*** Anevrasi; Bianco Val†; Controller; Lenicalm; Noctis; Parvisedil; Passiflorine; Sedatol; Sedofit; Sedopuer F; Vagostabil; ***Malaysia:*** Circarol; ***Mex.:*** Ifupasil; ***Philipp.:*** Circulan; ***Pol.:*** Alliorut; Biovital N; Cardiactiv; Cardiobonisol; Cardiol C; Cardiotonic; Cravisol; Fitoven; Ginkgocard; Herbaton; Kelicardina; Melis-Tonic; Melisal; Melissed; Neocardina; Neospasmina; Neospasmol; Nerwobonisol; Nerwonal; Passibil; Passispasmin; Passispasmol; Perfocrat; Sedomix; Tabletki Tonizujace; Venoforton; ***Port.:*** Gabisedil†; Neurocardol†; ***Rus.:*** Doppelherz Vitalotonik (Доппельгерц Виталотоник); Herbion Drops for the Heart (Гербион Сердечные Капли); Passifit (Пассифит); ***Singapore:*** Noricaven†; ***Spain:*** Natusor High Blood Pressure†; Natusor Somnisedan†; Passiflorine; Sedasor†; Sedonat; Sonofit†; Tensiben†; ***Switz.:*** Arterosan Plus; Cardiaforce; Circulan; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Gouttes pour le coeur et les nerfs Concentrees†; Ipasin; Phytomed Cardio; Sirop Passi-Par†; Strath Gouttes pour le coeur; Tisane pour le coeur et la circulation; Triallin; Valverde Coeur; ***Venez.:*** Cratex†; Equaliv; Ervostal; Eufytose†; Pasidor; Pasifluidina; Passiflorum.

Creatine

N-(Aminoiminomethyl)-*N*-methylglycine.

$C_4H_9N_3O_2 = 131.1$.

CAS — 57-00-1 (creatine); 6020-87-7 (creatine monohydrate).

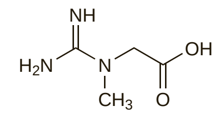

Creatine Phosphate

Creatina, fosfato de; Creatine Phosphoric Acid; Fosfocreatine; Phosphocreatine. *N*-[Imino(phosphonoamino)-methyl]-*N*-methylglycine.

$C_4H_{10}N_3O_5P = 211.1$.

CAS — 67-07-2 (creatine phosphate); 922-32-7 (creatine phosphate disodium).

ATC — C01EB06.

ATC Vet — QC01EB06.

Profile

Creatine is an endogenous substance found mainly in skeletal muscle of vertebrates. Creatine phosphate and its disodium salt have been tried in the treatment of cardiac disorders. Creatine phosphate has also been added to cardioplegic solutions. Creatine monohydrate has been tried in metabolic disorders and used as a dietary supplement. It is also under investigation for the treatment of Parkinson's disease, motor neurone disease (p.2380), Duchenne muscular dystrophy, and Huntington disease.

◊ References.

1. Pedone V, *et al.* An assessment of the activity of creatine phosphate (Neoton) on premature ventricular beats by continuous ECG monitoring in patients with coronary cardiac disease. *Clin Trials J* 1984; **21:** 91.
2. Ferraro S, *et al.* Acute and short-term efficacy of high doses of creatine phosphate in the treatment of cardiac failure. *Curr Ther Res* 1990; **47:** 917–23.
3. Mastoroberto P, *et al.* Creatine phosphate protection of the ischemic myocardium during cardiac surgery. *Curr Ther Res* 1992; **51:** 37–45.
4. Stöckler S, *et al.* Creatine replacement therapy in guanidinoacetate methyltransferase deficiency, a novel inborn error of metabolism. *Lancet* 1996; **348:** 789–90.
5. Mujika I, Padilla S. Creatine supplementation as an ergogenic aid for sports performance in highly trained athletes: a critical review. *Int J Sports Med* 1997; **18:** 491–6.
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7. Benzi G. Is there a rationale for the use of creatine either as nutritional supplementation or drug administration in humans participating in a sport? *Pharmacol Res* 2000; **41:** 255–64.
8. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol Rev* 2001; **53:** 161–76.
9. Mazzini L, *et al.* Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. *J Neurol Sci* 2001; **191:** 139–44.
10. Groeneveld JG, *et al.* A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol* 2003; **53:** 437–45.
11. Persky AM, *et al.* Pharmacokinetics of the dietary supplement creatine. *Clin Pharmacokinet* 2003; **42:** 557–74.
12. Shefner JM, *et al.* A clinical trial of creatine in ALS. *Neurology* 2004; **63:** 1656–61.
13. Ellis AC, Rosenfeld Jo. The role of creatine in the management of amyotrophic lateral sclerosis and other neurodegenerative disorders. *CNS Drugs* 2004; **18:** 967–80.
14. Tarnopolsky MA, *et al.* Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. *Neurology* 2004; **62:** 1771–7.
15. Pline KA, Smith CL. The effect of creatine intake on renal function. *Ann Pharmacother* 2005; **39:** 1093–6.
16. Hersch SM, *et al.* Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. *Neurology* 2006; **66:** 250–2.
17. Bender A, *et al.* Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. *Neurology* 2006; **67:** 1262–4.
18. Kley RA, *et al.* Creatine for treating muscle disorders. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Musashi Creatina†; ***Cz.:*** Neoton; ***Ital.:*** Creatile; Neoton†; ***Pol.:*** Neoton; ***Rus.:*** Neoton (Неотон).

Multi-ingredient: ***Ital.:*** Fortium.

Creatinine

Creatinina. 2-Amino-1-methyl-4-imidazolidinone.

$C_4H_7N_3O = 113.1$.

CAS — 60-27-5.

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 26 (Creatinine). White, odourless, crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether.

Profile

Creatinine is used as a bulking agent for freeze-drying.

Plasma concentrations or clearance of endogenous creatinine are used as an index of renal function.

Creatinolfosfate Sodium *(rINNM)*

Créatinolfosfate de Sodium; Creatinolfosfato sódico; Natrii Creatinolfosfatum. The sodium salt of 1-(2-hydroxyethyl)-1-methylguanidine *O*-phosphate .

Натрий Креатинолфосфат

$C_4H_{11}N_3NaO_4P$ = 219.1.
CAS — 6903-79-3 (creatinolfosfate).
ATC — C01EB05.
ATC Vet — QC01EB05.

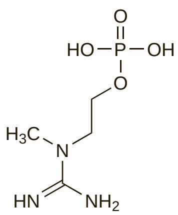

(creatinolfosfate)

Profile

Creatinolfosfate has been used as an adjuvant in the treatment of cardiac disorders.

Crotalaria

Profile

Crotalaria spp. have been used in herbal teas but liver damage has been reported after their ingestion, possibly due to their content of pyrrolizidine alkaloids.

CS Gas

CS Gazi; CS Spray; Gas CS.

$C_{10}H_5ClN_2$ = 188.6.
CAS — 2698-41-1.

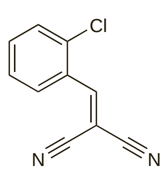

Profile

CS gas (more properly CS spray) is the name commonly given to a particulate dispersion of α-(*o*-chlorobenzylidene) malonitrile, used as a riot-control agent or 'tear gas'. Its toxic effects include irritation of the eyes and nose, with copious lachrymation and rhinorrhoea; blepharospasm; a burning sensation of the mouth and throat; tightness in the chest, with difficulty in breathing; coughing; an increase in salivation; and retching and vomiting. These effects usually disappear within 15 minutes after exposure ends. The effects of pre-existing disease of the respiratory tract may be exacerbated. Erythema and blistering of the skin may occur.

If symptoms persist, the patient should be removed to a well ventilated area. Treatment is symptomatic. Contaminated skin may be washed with soap and water, but only if symptoms persist since exposure to water may initially exacerbate symptoms. If contamination of the eyes has been severe they should be irrigated with physiological saline or water.

◊ References.

1. Hu H, *et al.* Tear gas—harassing agent or toxic chemical weapon? *JAMA* 1989; **262:** 660–3.
2. Yih J-P. CS gas injury to the eye. *BMJ* 1995; **311:** 276.
3. Gray PJ. Treating CS gas injuries to the eye: exposure at close range is particularly dangerous. *BMJ* 1995; **311:** 871.
4. Jones GRN. CS sprays: antidote and decontaminant. *Lancet* 1996; **347:** 968–9.
5. Anderson PJ, *et al.* Acute effects of the potent lacrimator o-chlorobenzylidene malonitrile (CS) tear gas. *Hum Exp Toxicol* 1996; **15:** 461–5.
6. Anonymous. "Safety" of chemical batons. *Lancet* 1998; **352:** 159.
7. Varma S, Holt PJ. Severe cutaneous reaction to CS gas. *Clin Exp Dermatol* 2001; **26:** 248–50.
8. Nathan R, *et al.* Long-term psychiatric morbidity in the aftermath of CS spray trauma. *Med Sci Law* 2003; **43:** 98–104.
9. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; **22:** 103–10.

Cubeb

Cubeb Berries; Cubeb Fruit; Cubeba; Java pepper; Tailed Pepper.

Profile

The unripe seeds of cubeb, *Piper cubeba* (Piperaceae), are the source of cubeb oil, which is used in perfumery and aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Naturland Grosser Swedenbitter†; ***Rus.:*** Doktor Mom (Доктор Мом); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера).

Cucurbita

Abóbora; Calabaza, semillas de; Kürbissamen; Melon Pumpkin Seeds; Pepo; Semence de Courge.

Pharmacopoeias. In *Ger.*

Profile

Cucurbita consists of the seeds of *Cucurbita pepo* (Cucurbitaceae) or related species. It was formerly used for the expulsion of tapeworms (*Taenia*).

It is an ingredient of several herbal preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Lefkur; ***Cz.:*** Turiplex†; ***Fr.:*** ViTiX; ***Ger.:*** Cysto-Urgenin; Granu Fink Kurbiskern; Nomon mono; Prosta Fink forte; Urgenin Cucurbitae oleum; Uvirgan mono; Vesiherb; ***Indon.:*** Inkurin; ***Pol.:*** Peponen; Pepосterol; Prostogal†; ***Rus.:*** Peponen (Пепонен); Tycveolum (Тыквеол).

Multi-ingredient: ***Arg.:*** Cellskinlab Phyto Spot; Clean-AC; Cleanance; ***Austral.:*** Lifechange Mens Complex with Saw Palmetto†; ***Canad.:*** Prostate Ease; Prostease; ProstGard†; ***Chile:*** Clean-AC; Cleanance; ***Fr.:*** Cleanance; Cleanance K; Phytolongbronze; ***Ger.:*** Granu Fink Kurbiskern N; Granu Fink Prosta; Prostamed; Uvirgan N†; ***Hong Kong:*** Prostease; Sawmetto Vivo-Livo†; ***Indon.:*** Soprost; ***Philipp.:*** Castoria; ***Pol.:*** Prostamer†; ***Port.:*** Bioclin Sebo Care†; Prostamed†; ***Rus.:*** Bioprost (Биопрост); ***Switz.:*** Granu Fink Prosta; Prosta-Caps Chassot N; ***UK:*** Ymea.

Cusparia

Angostura; Angostura Bark; Carony Bark; Cusparia Bark.

NOTE. 'Angostura Bitters' (*Dr. J.G.B. Siegert & Sons Ltd*) contains gentian and various aromatic ingredients but no cusparia; it is named after the town in which it was first made.

Profile

Cusparia, the bark of *Galipea officinalis* (Rutaceae), has been used as a bitter.

Cyanoacrylate Adhesives

Cianoacrilato, adhesivos de.

CAS — 1069-55-2 (bucrilate); 6606-65-1 (enbucrilate); 137-05-3 (mecrilate); 6701-17-3 (ocrilate);.

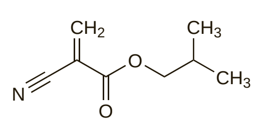

(bucrilate)

Profile

A number of cyanoacrylate compounds have been used as surgical tissue adhesives. They include:

- bucrilate (bucrylate; isobutyl 2-cyanoacrylate, $C_8H_{11}NO_2$ = 153.2)
- enbucrilate (butyl 2-cyanoacrylate, $C_8H_{11}NO_2$ = 153.2),
- mecrilate (mecrylate; methyl 2-cyanoacrylate, $C_5H_5NO_2$ = 111.1)
- ocrilate (ocrylate; octil 2-cyanoacrylate, $C_{12}H_{19}NO_2$ = 209.3).

Some cyanoacrylates are used for household purposes and as nail fixatives and others have been investigated as tubal occlusive agents for female sterilisation, for sclerotherapy in bleeding gastric varices (see under Monoethanolamine, p.2346), and for embolisation of intracranial vascular lesions. Cyanoacrylate adhesives have also been used to plug corneal perforations until donor tissue is available.

Adverse effects. Reports of inadvertent application of cyanoacrylate adhesives to the eyes,[1,2] mouth,[3] and ears.[4,5] Pulmonary embolisation of ocrilate has been reported[6] when it was used to obliterate gastric varices in a patient.

1. Lyons C, *et al.* Superglue inadvertently used as eyedrops. *BMJ* 1990; **300:** 328.
2. DeRespinis PA. Cyanoacrylate nail glue mistaken for eye drops. *JAMA* 1990; **263:** 2301.
3. Cousin GCS. Accidental application of cyanoacrylate to the mouth. *Br Dent J* 1990; **169:** 293–4.
4. O'Donnell JJ, *et al.* Cyanoacrylate adhesive mistaken for ear drops. *J Accid Emerg Med* 1997; **14:** 199.
5. Persaud R. A novel approach to the removal of superglue from the ear. *J Laryngol Otol* 2001; **115:** 901–2.
6. Rickman OB, *et al.* Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004; **79:** 1455–8.

Treatment of adverse effects. In the event of accidental adhesion of the skin the bonded surfaces may be separated after application of acetone, prolonged soaking in warm (not hot) soapy water, and/or mixtures of alcohol and water. Application of liquid paraffin may help in removal from the skin. If necessary, the surfaces may be peeled or rolled apart with the aid of a spatula; attempts should not be made to pull the surfaces directly apart. Acetone and alcohol should not be used near or in the eyes. Solvents such as nitromethane, toluene, or xylene may be used to aid skin detachment from solid objects. Solvents should be used with care and should not be introduced into the oropharynx. Eyelids stuck together or bonded to the eyeball should be washed thoroughly with saline or water at room temperature for 15 minutes and a gauze patch applied; the eye will open without further action in 1 to 4 days. Manipulative attempts to open the eyes should not be made. Although cyanoacrylate introduced into the eyes may cause double vision and lachrymation there is usually no residual damage. If lips are accidentally stuck together plenty of warm water should be applied and maximum wetting from saliva inside the mouth encouraged. Lips should be peeled or rolled apart and not pulled. Adhesive introduced into the mouth solidifies and adheres, but saliva will lift the adhesive in ⁄ to 2 days. Care should be taken to avoid choking.

Heat is evolved on solidification of cyanoacrylate and in rare cases may cause burns.

Uses. References to the use of cyanoacrylate adhesives,[1-10] including bucrilate,[1,2] enbucrilate,[3,4] and ocrilate.[5-9]

1. Kind R, *et al.* Bucrylate treatment of bleeding gastric varices: 12 years' experience. *Endoscopy* 2000; **32:** 512–9.
2. Shepler TR, Seiff SR. Use of isobutyl cyanoacrylate tissue adhesive to stabilize external eyelid weights in temporary treatment of facial palsies. *Ophthal Plast Reconstr Surg* 2001; **17:** 169–73.
3. Schonauer F, *et al.* Use of Indermil tissue adhesive for closure of superficial skin lacerations in children. *Minerva Chir* 2001; **56:** 427–9.
4. Sinha S, *et al.* A single blind, prospective, randomized trial comparing n-butyl 2-cyanoacrylate tissue adhesive (Indermil) and sutures for skin closure in hand surgery. *J Hand Surg (Br)* 2001; **26:** 264–5.
5. Kutcher MJ, *et al.* Evaluation of a bioadhesive device for the management of aphthous ulcers. *J Am Dent Assoc* 2001; **132:** 368–76.
6. Puri P. Tissue glue aided lid repositioning in temporary management of involutional entropion. *Eur J Ophthalmol* 2001; **11:** 211–4.
7. Bernard L, *et al.* A prospective comparison of octyl cyanoacrylate tissue adhesive (dermabond) and suture for the closure of excisional wounds in children and adolescents. *Arch Dermatol* 2001; **137:** 1177–80.
8. Mattick A, *et al.* A randomised, controlled trial comparing a tissue adhesive (2-octylcyanoacrylate) with adhesive strips (Steristrips) for paediatric laceration repair. *Emerg Med J* 2002; **19:** 405–7.
9. Magee WP, *et al.* Use of octyl-2-cyanoacrylate in cleft lip repair. *Ann Plast Surg* 2003; **50:** 1–5.
10. Singer AJ, *et al.* The cyanoacrylate topical skin adhesives. *Am J Emerg Med* 2008; **26:** 490–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dermabond; ***Fr.:*** Dermabond; ***UK:*** Dermabond; Histoacryl; Indermil; LiquiBand; SuperSkin.

Multi-ingredient: ***Ger.:*** Epiglu; ***Irl.:*** Epiglu; ***UK:*** Epiglu.

Cyclobutyrol Sodium *(rINNM)*

Ciclobutirol sódico; Cyclobutyrol Sodique; Natrii Cyclobutyrolum. Sodium 2-(1-hydroxycyclohexyl)butyrate.

Натрий Циклобутирол

$C_{10}H_{17}NaO_3$ = 208.2.
CAS — 512-16-3 (cyclobutyrol); 1130-23-0 (cyclobutyrol sodium).
ATC — A05AX03.
ATC Vet — QA05AX03.

Profile

Cyclobutyrol sodium is a choleretic that has been given by mouth. Cyclobutyrol betaine, cyclobutyrol calcium, and cyclobutyrol nicotinamide have been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Trommgallol; ***Spain:*** Menabil Complex†; Salcemetic†; Sugarbil.

Cyclodextrins

Ciclodextrinas.

Alfadex *(BAN, rINN)*

Alfadeksas; Alfadeksi; Alfadexum; Alpha Cyclodextrin; Alphacyclodextrin; α-Cyclodextrin; Cyclohexaamylose; Cyclomaltohexose. Cyclomaltohexaose.

Альфадекс

$C_{36}H_{60}O_{30}$ = 972.8.
CAS — 10016-20-3.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Alfadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.
USNF 26 (Alfadex). A white or almost white, amorphous or crystalline, powder. Freely soluble in water and in propylene glycol; practically insoluble in dehydrated alcohol and in dichloromethane. Store in airtight containers.

Betadex *(BAN, USAN, rINN)*

Beetadeksi; Betadeksas; Bétadex; Betadexum; β-Cyclodextrin; E459. Cyclo-α-(1→4)-D-heptaglucopyranoside.

Бетадекс

$C_{42}H_{70}O_{35}$ = 1135.
CAS — 7585-39-9.

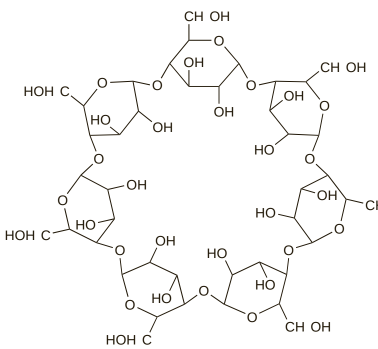

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Betadex). A white or almost white, amorphous or crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane; freely soluble in propylene glycol. Store in airtight containers.
USNF 26 (Betadex). A nonreducing cyclic compound composed of seven alpha-(1-4) linked D-glucopyranosyl units. It is a white, practically odourless, fine crystalline powder. Soluble 1 in 54 of water. Store in airtight containers.

Hydroxypropylbetadex

Hidroksipropilbetadeksas; Hydoxipropylbetadex; Hydroksipropyylibetadeksi; Hydroxypropylbétadex; Hydroxypropylbetadexum; 2-Hydroxypropyl-β-cyclodextrin.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Hydroxypropylbetadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.
USNF 26 (Hydroxypropyl Betadex). A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol.

Profile

Cyclodextrins, such as alfadex and betadex, are produced by the enzymatic degradation of starch and are used as carrier molecules for drug delivery systems. Hydroxypropylbetadex, a derivative of betadex, is also used.

◊ References.

1. Ridgway K. Drug release rates: cyclodextrin complexes. *Pharm J* 1990; **245:** 344–5.
2. Szejtli J. Cyclodextrins: properties and applications. *Drug Invest* 1990; **2** (suppl 4): 11–21.
3. El Shaboury MH. Physical properties and dissolution profiles of tablets directly compressed with β-cyclodextrin. *Int J Pharmaceutics* 1990; **63:** 95–100.
4. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. *Pharm Res* 1997; **14:** 556–67.
5. Loftsson T, Olafsson JH. Cyclodextrins: new drug delivery systems in dermatology. *Int J Dermatol* 1998; **37:** 241–6.
6. Redenti E, *et al.* Drug/cyclodextrin/hydroxy acid multicomponent systems: properties and pharmaceutical applications. *J Pharm Sci* 2000; **89:** 1–8.
7. Loftsson T, Masson M. Cyclodextrins in topical drug formulations: theory and practice. *Int J Pharm* 2001; **225:** 15–30.
8. Loftsson T, Stefansson E. Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye. *Acta Ophthalmol Scand* 2002; **80:** 144–50.
9. Dass CR. Cyclodextrins and oligonucleotide delivery to solid tumours. *J Drug Target* 2004; **12:** 1–9.
10. Kaur IP, *et al.* Role of cyclodextrins in ophthalmics. *Curr Drug Deliv* 2004; **1:** 351–60.
11. Challa R, *et al.* Cyclodextrins in drug delivery: an updated review. *AAPS PharmSciTech* 2005; **6:** E329–E357.

Cymene

Cimeno; *p*-Cymene; *p*-Cymol; p-Cymen. 4-Isopropyl-1-methylbenzene; 4-Isopropyltoluene.

$C_{10}H_{14}$ = 134.2.
CAS — 25155-15-1; 99-87-6 (p-cymene).

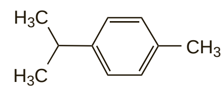

(p-cymene)

Profile

Cymene is used in perfumery. It has also been used as a topical local analgesic for the relief of pain in rheumatic conditions.

Cynara

Alcachofa; Alcachôfra; Artichaut; Artichaut, feuille d'; Artichoke Leaf; Artičokový list; Cynarae folium; Liść karczocha.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Artichoke Leaf). The whole or cut, dried leaf of *Cynara scolymus*. It contains a minimum 0.8% of chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated with reference to the dried drug. Protect from light.

Profile

Cynara, the leaf of the globe artichoke, *Cynara scolymus* (Compositae), is reputed to have diuretic and choleretic properties. It may also have some hypolipidaemic activity.

◊ References.

1. Joy JF, Haber SL. Clinical uses of artichoke leaf extract. *Am J Health-Syst Pharm* 2007; **64:** 1904–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Alcachofa Plus; Chofitol; Cynarex; ***Austria:*** Cynarix; Hepar-POS; ***Belg.:*** Cynarol; Hebucol; ***Braz.:*** Alcachofrax; Chophytol; ***Fr.:*** Chophytol; Gallexier†; Hepanephrol; ***Ger.:*** aar gamma N; Ardeycholan; Carminagal N†; Cefacynar; Cholagogum; Cyna Bilisan†; Cynacur; Cynalip duo†; Cynarix N†; Hepagallin N; Hepar SL; Hepar-POS; Heparstad†; Hewechol Artischockendragees; Lipei; Losapan†; Natu-Hepa; Naturreiner†; ratio-Hepar†; Valverde Artischocke†; ***Pol.:*** Cynacholin; Cynarex; Hepacynar; Liproxal; ***Port.:*** Hepanephrol†; ***Rus.:*** Chophytol (Хофитол); ***Switz.:*** Chophytol; Hepa-S; Natu-Hepa.

Multi-ingredient: ***Arg.:*** Arceligasol; Bagohepat; Bilidren; Biliosan Compuesto†; Boldina; Digenat; Dioxicolagol; HDG; Hepacur; Hepatalgina; Hepatodirectol; Herbaccion Dig Fresh†; Herbaccion Digestivo†; Lorbihepatic; Metiogen; Palatrobil; ***Austral.:*** Extralife Liva-Care; Lifesystem Herbal Formula 7 Liver Tonic†; Liver Tonic Herbal Formula 6†; Livstim†; Livton Complex†; ***Austria:*** Cynarix comp; ***Braz.:*** Alcafelol†; Alcaflor†; Chofranina; Colachofra; Composto Emagrecedor†; Digestron†; Emagrevit†; Figatil; Hecrosine B12†; Hepatoregius†; Jurubileno†; Lisotox; Olocynan†; Solvobil; ***Canad.:*** Milk Thistle; ***Cz.:*** Cynarosan†; ***Fr.:*** Actibil†; Benetransit; Canol; Elixir Spark; Hepaclem; Hepax; Vegelax†; ***Ger.:*** Bilicura Forte†; Carmol Magen-Galle-Darm; Cynarzym N†; Gallexier; Galloselect M†; Pascobilin novo†; ***Hong Kong:*** Hepatofalk; ***Indon.:*** Biocholes; ***Ital.:*** Cinarepa; Colax; Digelax†; Epagest†; Vadolax†; ***Malaysia:*** Dandelion Complex†; ***Mex.:*** Bagohepat; Chofabol; Hepedren; Ifuchol; ***Pol.:*** Cardiobonisol; Rapacholin AC; Rapacholin C; Sylicynar; ***Rus.:*** Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); ***Spain:*** Cynaro Bilina; Lipograsil; Menabil Complex†; Nico Hepatocyn; ***Switz.:*** Bilifuge; Boldocynara; Demonatur Gouttes pour le foie et la bile; Heparfelien; Phytomed Hepato†; Stago N†; Strath Gouttes pour le foie et la bile; Tisane hepatique et biliaire; ***UK:*** Bio-Strath Artichoke Formula; ***Venez.:*** Cynascool.

Cynarine *(rINN)*

Cinarina; Cynarin; Cynarinum; Cynaryna; 1,5-Dicaffeoylquinic Acid. 1-Carboxy-4,5-dihydroxy-1,3-cyclohexylene bis(3,4-dihydroxycinnamate).

Цинарин

$C_{25}H_{24}O_{12}$ = 516.5.
CAS — 1182-34-9; 1884-24-8.

Profile

Cynarine is an active ingredient of cynara (above). It has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** HDG; ***Austria:*** Trommgallol.

Cypress

Italian Cypress; Mediterranean Cypress.

Profile

Italian or Mediterranean cypress (*Cupressus sempervirens*, Cupressaceae) is included in preparations for peripheral vascular disorders.

It is the source of cypress oil. Cypress oil is used in preparations for the relief of cough and cold symptoms and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Arterase; Circulatonic; Mediflor Tisane Circulation du Sang No 12; Veinostase; ***Ital.:*** Colostrum; Venalta; ***Port.:*** Solubeol†; ***Spain:*** Natusor Circusil†; Proctosor†; Ruscimel†; Trophires†; Vapores Pyt; ***Switz.:*** Eucapinol; Makaphyt Baume†; Novital.

Cytidine

Cytosine Riboside. 4-Amino-1-β-D-ribofuranosyl-2-(1*H*)-pyrimidinone.

Цитидин

$C_9H_{13}N_3O_5$ = 243.2.
CAS — 65-46-3.

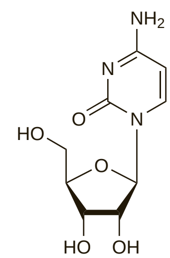

Profile

Cytidine is an endogenous cytosine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p.2355). Cytidine is used in preparations containing other nucleosides in the treatment of corneal damage. It has also been used in preparations for liver disorders, anaemias, and as a tonic. Disodium cytidine phosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; the triphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Nucleo CMP†; ***Belg.:*** Vitacic; ***Braz.:*** Nucleo CMP; ***Chile:*** Citoneuron; ***Cz.:*** Laevadosin†; ***Ger.:*** Keltican N; ***Hung.:*** Vitacic†; ***Ital.:*** Centrum; ***Mex.:*** Nucleo CMP; ***Mon.:*** Vitacic; ***Rus.:*** Vitacic (Витасик)†; ***Spain:*** Cefabol; Nucleo CMP.

Cytisine

Baptitoxine; Laburnine; Sophorine; Ulexine. 1,2,3,4,5,6-Hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one.

Цитизин

$C_{11}H_{14}N_2O$ = 190.2.
CAS — 485-35-8.

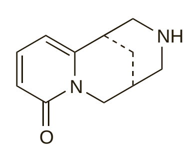

Profile

Cytisine is a highly toxic alkaloid found in laburnum (p.2329) and some other leguminous plants. It resembles nicotine (p.2352) in its actions and has been given orally as an aid to smoking cessation (p.2354). The dose is 1.5 mg 6 times daily for 3 days which is then gradually reduced over the next 3 weeks to 1.5 to 3 mg daily for the final 5 days of treatment. Treatment of adverse effects of cytisine is as described for Nicotine, p.2352.

A 0.15% solution of cytisine known as Cytitone has been used intravenously or intramuscularly in some countries as a respiratory stimulant.

◊ References.

1. Etter J-F. Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 2006; **166:** 1553–9.
2. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep* 2006; **58:** 777–98.

Preparations

Proprietary Preparations (details are given in Part 3)
Bulg.: Tabex (Табекс); ***Hung.:*** Tabex†; ***Pol.:*** Tabex; ***Rus.:*** Tabex (Табекс).

Cytochrome C

Citocromo C.

Pharmacopoeias. *Chin.* includes Cytochrome C Solution and preparations for injection.

Profile

Cytochrome C is a haemoprotein occurring in the body and involved in electron and hydrogen transport in biological oxidation processes. It has been given intravenously in various hypoxic conditions.

Cytochrome C is an ingredient of some eye drops used for the treatment of cataract but its actions, if any, are unclear.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Citophase; ***Jpn:*** Cytorest.

Multi-ingredient: ***Rus.:*** Oftan Catachrom (Офтан Катахром); ***Spain:*** Vitaphakol.

Cytokines

Citocinas; Citokinas; Citoquinas.

Цитокины

Profile

Cytokines are a group of endogenous soluble peptides produced by many different cell types in response to noxious stimuli. In contrast to peptide hormones, they tend to act locally. Cytokines affect expression of genes influencing changes at the cellular level and have a regulatory function, acting as growth factors in cellular differentiation and/or proliferation. Cytokines are also involved in host responses to disease such as infection or inflammation. Some cytokines induce inflammation whereas others have an anti-inflammatory action through inhibition of proinflammatory cytokines. Cytokines are classified by their biological activity rather than structure and most are pleiotropic (i.e. they are multifunctional). A large number of cytokines alter endothelial function affecting permeability and may also cause cellular damage or death. Some cytokines are involved in the pathophysiology of diseases, particularly immune, inflammatory, and infectious diseases; they may also be involved in the development of cardiovascular disease.

Cytokines that are used clinically include:

- granulocyte colony-stimulating factors such as filgrastim (p.1070)
- granulocyte-macrophage colony-stimulating factors such as molgramostim (p.1073)
- interferons (p.885)
- some interleukins (p.2325)
- oprelvekin (p.1074), a platelet growth factor
- palifermin (p.2359), a keratinocyte growth factor
- somatomedins (p.1807)
- thrombopoietin (p.1080)
- trafermin (p.1618), a fibroblast growth factor
- tumour necrosis factor (p.783)
- urogastrone (p.1778), an epidermal growth factor

Anticytokine-based therapy may involve suppressing the action of single or related cytokines by specific soluble cytokine receptors, antagonists to the cytokine receptor, or antibodies against the cytokine. Alternatively, the synthesis of several unrelated cytokines may be suppressed by a single therapeutic agent. Fusion toxins in which protein sequences from cytokines or natural growth factors are combined with a bacterial toxin have also been produced to target specific cytokines.

◊ References.

1. Xing Z, Wang J. Consideration of cytokines as therapeutics agents or targets. *Curr Pharm Des* 2000; **6:** 599–611.
2. Schooltink H, Rose-John S. Cytokines as therapeutic drugs. *J Interferon Cytokine Res* 2002; **22:** 505–16.
3. Andreakos ET, *et al.* Cytokines and anti-cytokine biologicals in autoimmunity: present and future. *Cytokine Growth Factor Rev* 2002; **13:** 299–313.
4. Stevceva L. Cytokines and their antagonists as therapeutic agents. *Curr Med Chem* 2002; **9:** 2201–7.
5. Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets* 2006; **7:** 675–81.
6. Villar CC, *et al.* Therapeutic modulation of cytokines in chronic infectious diseases. *Curr Pharm Des* 2006; **12:** 2329–48.
7. Feurino LW, *et al.* Current update of cytokines in pancreatic cancer: pathogenic mechanisms, clinical indication, and therapeutic values. *Cancer Invest* 2006; **24:** 696–703.

Damiana

Turnera.

Profile

Damiana is the dried leaves and stem of *Turnera diffusa* var. *aphrodisiaca* (Turneraceae) and possibly other species of *Turnera*.

Damiana is drunk as a tea, and is used in herbal medicine for a variety of indications. It has a reputation as an aphrodisiac, but there is no evidence for this.

Homoeopathy. Damiana has been used in homoeopathic medicines under the following names: Turnera diffusa.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Bioglan Mens Super Soy/Clover; Bioglan The Blue One; Medinat Esten†; Nevaton; ***Canad.:*** Damiana-Sarsaparilla Formula†; ***Indon.:*** Instink; Maxirex; Menolia; Neo Hormoviton; Tripote; Tristan; ***Ital.:*** Dam; Four-Ton; ***Malaysia:*** Total Man†; ***Pol.:*** Tripoten; ***Spain:*** Energysor†; ***UK:*** Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Regina Royal Concorde; Strength; Zotrim.

Dapiprazole Hydrochloride *(USAN, rINNM)*

AF-2139; Dapiprazole, Chlorhydrate de; Dapiprazoli Hydrochloridum; Hidrocloruro de dapiprazol. 5,6,7,8-Tetrahydro-3-[2-(4-*o*-tolyl-1-piperazinyl)ethyl]-*s*-triazolo[4,3-*a*]pyridine monohydrochloride.

Дапипразола Гидрохлорид

$C_{19}H_{27}N_5,HCl = 361.9.$

CAS — 72822-12-9 (dapiprazole); 72822-13-0 (dapiprazole hydrochloride).

ATC — S01EX02.

ATC Vet — QS01EX02.

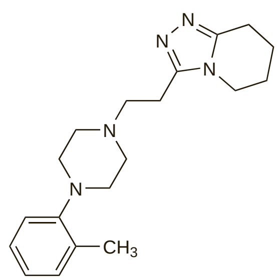

(dapiprazole)

Profile

Dapiprazole hydrochloride is an alpha blocker given as eye drops to reverse mydriasis; it is also used in some countries in the management of glaucoma.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Benglau; ***Gr.:*** Glamidolo; ***Israel:*** Glamidolo†; ***Ital.:*** Glamidolo; ***USA:*** Rev-Eyes.

Dehydrocholic Acid *(BAN, rINN)*

Acide Déhydrocholique; Ácido dehidrocólico; Acidum Dehydrocholicum; Chologon; Dehydrocholsyra; Dehydrokoolihappo; Triketocholanic Acid. 3,7,12-Trioxo-5β-cholan-24-oic acid.

Дегидрохолевая Кислота

$C_{24}H_{34}O_5 = 402.5.$

CAS — 81-23-2 (dehydrocholic acid); 145-41-5 (sodium dehydrocholate).

Pharmacopoeias. In *Chin., It., Jpn,* and *US.*

USP 31 (Dehydrocholic Acid). A white, fluffy, odourless powder. Practically insoluble in water; soluble 1 in 100 of alcohol, 1 in 135 of acetic acid at 15°, 1 in 130 of acetone at 15°, 1 in 35 of chloroform, 1 in 2200 of ether at 15°, 1 in 135 of ethyl acetate at 15°, and 1 in 960 of benzene at 15°; solutions in alcohol and in chloroform are usually slightly turbid; soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates.

Profile

Dehydrocholic acid is a semisynthetic bile acid (p.2266) that is given for its hydrocholeretic properties, increasing the volume and water content of the bile without appreciably altering the content of bile acids. It has been used to improve biliary drainage and has also been given for the temporary relief of constipation. The usual oral dose is 250 to 500 mg three times daily after meals.

Dehydrocholic acid is contra-indicated in significant cholelithiasis, complete mechanical biliary obstruction, and in severe hepatic impairment.

Preparations

USP 31: Dehydrocholic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Cholan-HMB; Decholin.

Multi-ingredient: ***Arg.:*** Arnol; Bagohepat; Bibol Leloup; Bil 13; Bil 13 Enzimatico; Bilagol; Carbogasol Digestivo; Digenorflat; Hepadigenor†; Hepatalgina; Lorbihepatic; Novodig†; Pakinase; Palatrobil; Pankreon Compuesto†; Pankreon Total; Zimerol; ***Braz.:*** B-Vesil; Digeplus; Digestron†; Essen; Filogaster†; Plasil Enzimatico; Sintozima; ***Hong Kong:*** Bilsan; ***Hung.:*** Neo-Bilagit; ***Mex.:*** Bagohepat; Plasil Enzimatico; ***Philipp.:*** Spasmo-Canulase; ***Pol.:*** Rapacholin C; Rapacholin Forte; ***Port.:*** Espasmo Canulase; ***S.Afr.:*** Spasmo-Canulase; ***Spain:*** Nulacin Fermentos; ***Switz.:*** Spasmo-Canulase.

Delmopinol Hydrochloride *(rINNM)*

Delmopinol, Chlorhydrate de; Delmopinoli Hydrochloridum; Hidrocloruro de delmopinol; M-1650. ±-3-(4-Propylheptyl)-4-morpholineethanol hydrochloride.

Дельмопинола Гидрохлорид

$C_{16}H_{33}NO_2,HCl = 307.9.$

CAS — 79874-76-3 (delmopinol); 98092-92-3 (delmopinol hydrochloride).

Profile

Delmopinol prevents the formation of dental plaque by coating the teeth and preventing adhesion of bacteria. It is used as the hydrochloride, as a mouth rinse in the treatment and prevention of gingivitis.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Decapinol.

Demelverine Hydrochloride *(rINNM)*

Démelvérine, Chlorhydrate de; Demelverini Hydrochloridum; Hidrocloruro de demelverina; Methphenaethamine Hydrochloride; *N*-Methyldiphenethylamine Hydrochloride. *N*-Methyl-*N*-(2-phenylethyl)-benzeneethanamine hydrochloride.

Демельверина Гидрохлорид

$C_{17}H_{21}N,HCl = 275.8.$

CAS — 13977-33-8 (demelverine); 18719-09-0 (demelverine hydrochloride).

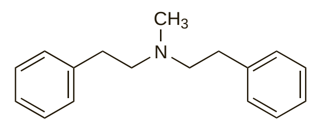

(demelverine)

Profile

Demelverine hydrochloride is an antispasmodic that has been used in the treatment of smooth muscle spasm.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Spasman†.

Denatonium Benzoate *(BAN, USAN, rINN)*

Benzoato de denatonio; Denatonii Benzoas; Dénatonium, Benzoate de; NSC-157658. Benzyldiethyl(2,6-xylylcarbamoylmethyl)ammonium benzoate monohydrate.

Денатония Бензоат

$C_{28}H_{34}N_2O_3,H_2O = 464.6.$

CAS — 3734-33-6 (anhydrous denatonium benzoate); 86398-53-0 (denatonium benzoate monohydrate).

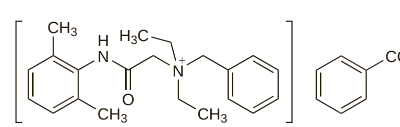

Pharmacopoeias. In *USNF.*

USNF 26 (Denatonium Benzoate). When dried at 105° for 2 hours, it contains one molecule of water of hydration or is anhydrous. Soluble 1 in 20 of water, 1 in 2.4 of alcohol, 1 in 2.9 of chloroform, and 1 in 5000 of ether; very soluble in methyl alcohol. pH of a 3% solution in water is between 6.5 and 7.5. Store in airtight containers.

Profile

Denatonium benzoate is used where an intensely bitter taste is required for medicinal or industrial purposes and as a partial denaturant for alcohol in toiletries. It is known commercially as Bitrex.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Skin Nail.

Deoxyribonucleic Acid

ADN; Animal Nucleic Acid; Desoxirribonucleico, ácido; Desoxypentose Nucleic Acid; Desoxyribonucleic Acid; Desoxyribose Nucleic Acid; DNA; Thymus Nucleic Acid.

ДНК; Дезоксирибонуклеиновая Кислота

Profile

Deoxyribonucleic acid (DNA) is a nucleic acid (p.2355) in which the pentose sugar moiety of the nucleotides is deoxyribose, the purine bases are adenine (p.2247) and guanine, and the pyrimidine bases are cytosine and thymine. Hydrogen bonds between complementary pairs of purine and pyrimidine bases link 2 polynucleotide strands, which are twisted to form a double helix with the bases on the inside of the structure and the sugar-phosphate backbone on the outside. Pairing of bases between complementary strands of DNA is always the same: adenine with thymine and cytosine with guanine. DNA is present in cell nuclei and its function is to carry the genetic material of cellular organisms and DNA viruses. It also provides the template for the production of ribonucleic acid (p.2379). For the role of DNA in gene therapy, see p.2310.

Proprietary preparations of DNA are marketed in some countries for a variety of debilitating and convalescent conditions; the sodium and magnesium salts of DNA have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: ADN; ***Ital.:*** Placentex; ***Rus.:*** Derinat (Деринат).

Multi-ingredient: ***Fr.:*** Adena C†; ***India:*** Placentrex.

Dextran Sulfate *(BANM, rINNM)*

Dextran, Sulfate de; Dextran Sulfate Sodium; Dextran Sulphate; Dextran Sulphate Sodium; Dextrani Sulfas; Sulfato de dextran.

Декстрана Сульфат

CAS — 9011-18-1.
ATC — B05AA05.
ATC Vet — QB05AA05.

Pharmacopoeias. In *Jpn.*

Profile

Dextran sulfate is the sodium salt of sulfuric acid esters of dextran. It has been used as an anticoagulant and as a lipid regulating drug, and has been investigated for its antiviral activity. Dextran sulfate potassium has also been used.

Interactions. As mentioned on p.1195 (under Hypersensitivity), anaphylactoid reactions have occurred in patients receiving ACE inhibitors during low-density lipoprotein apheresis using a dextran sulfate-cellulose column.[1,2] Withdrawal of the ACE inhibitor for 1 to 3 days before apheresis may prevent the reaction.[2]

1. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340:** 908–9.
2. Agishi T. Anion-blood contact reaction (ABC reaction) in patients treated by LDL apheresis with dextran sulfate-cellulose column while receiving ACE inhibitors. *JAMA* 1994; **271:** 195–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Diroseal; ***Austral.:*** VR†; ***Chile:*** Cicapost; Diroseal; Ureadin Rx DB; ***Cz.:*** Doxivenil†; ***Fr.:*** Avene Antirougeurs; Creme au Melilot Composee; Dextrarine Phenylbutazone; Diroseal; Prebutix; ***Ger.:*** Phlebodril N; ***Hung.:*** Doxivenil; ***Ital.:*** Stranoval; ***Port.:*** Cicapost; Doxivenil; ***Switz.:*** Doxivenil; ***Venez.:*** Doxivenil.

Dextrorphan *(BAN, pINN)*

Dextrorfano; Dextrorphane; Dextrorphanum. 17-Methyl-9α,-13α,14α-morphinan-3-ol.

Декстрорфан

$C_{17}H_{23}NO$ = 257.4.
CAS — 125-73-5.

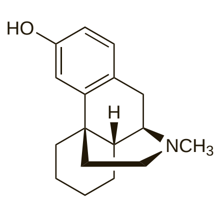

Dextrorphan Hydrochloride *(BANM, USAN, pINNM)*

Dextrorphane, Chlorhydrate de; Dextrorphani Hydrochloridum; Hidrocloruro de dextrorfano; Ro-01-6794/706.

Декстрорфана Гидрохлорид

$C_{17}H_{23}NO,HCl$ = 293.8.
CAS — 69376-27-8.

Profile

Dextrorphan, a metabolite of dextromethorphan (p.1555), is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It possesses some cough suppressant activity and has been investigated as a neuroprotective agent in the management of stroke.

◊ References.

1. Albers GW, *et al.* Safety, tolerability, and pharmacokinetics of the N-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. *Stroke* 1995; **26:** 254–8.

Dibutyl Sebacate

Sebacato de dibutilo.

$C_{18}H_{34}O_4$ = 314.5.
CAS — 109-43-3.

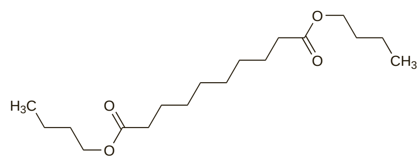

Pharmacopoeias. In *USNF.*

USNF 26 (Dibutyl Sebacate). It consists of esters of *n*-butyl alcohol and saturated dibasic acids, principally sebacic acid. A colourless, oily liquid of very mild odour. Practically insoluble in water and in glycerol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin; very slightly soluble in propylene glycol. Store in airtight containers.

Profile

Dibutyl sebacate is a plasticiser used in pharmaceutical formulation of tablets (including modified release), beads, and granules, and microcapsule preparations. It is also used as a food flavouring.

Dichlorodiethylsulfide

Dichlorodiethylsulphide; Gas mostaza; Iperita; Mustard Gas; Sulfur Mustard; Sulfuro de dicloroetileno; Yellow Cross Liquid; Yperite. Bis(2-chloroethyl)sulphide.

$C_4H_8Cl_2S$ = 159.1.
CAS — 505-60-2.

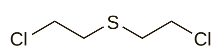

Profile

Dichlorodiethylsulfide was developed for use in chemical warfare and has even more severe vesicant and irritant properties than its nitrogen analogue, chlormethine (p.697). It was formerly used topically in the treatment of psoriasis.

◊ Reviews of the toxicology of dichlorodiethylsulfide,[1-4] and debate on the management of casualties injured by dichlorodiethylsulfide and other chemical warfare agents.[5-11] Most patients exposed to dichlorodiethylsulfide recover largely or completely and only a small proportion will have severe long-term eye or lung damage,[12,13] although death from respiratory, renal, and bone-marrow failure may occur.[11] A combination of 1% phenol and 1% menthol applied topically produced significant relief of pruritus compared with placebo in a randomised study of 80 war veterans with chronic skin lesions following exposure to dichlorodiethylsulfide.[14]

Eleven fishermen who accidentally retrieved corroded and leaking gas shells containing dichlorodiethylsulfide from underwater dumps, presented with very inflamed skin, especially in the axillary and genitofemoral regions, yellow blisters on the hands and legs, painful irritation of the eyes, and transient blindness. Two developed pulmonary oedema.[15] There was evidence of a mutagenic effect and in view of the increased risk of lung cancer in soldiers and workers exposed to the gas it is reasonable to assume that fishermen heavily exposed to dichlorodiethylsulfide also have an increased cancer risk.

1. Smith KJ, *et al.* Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. *J Am Acad Dermatol* 1995; **32:** 765–76.
2. Dacre JC, Goldman M. Toxicology and pharmacology of the chemical warfare agent sulfur mustard. *Pharmacol Rev* 1996; **48:** 289–326.
3. Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology* 2005; **214:** 198–209.
4. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. *Fundam Clin Pharmacol* 2005; **19:** 297–315.
5. Heyndrickx A, Heyndrickx B. Management of war gas injuries. *Lancet* 1990; **ii:** 1248–9.
6. Fouyn T, *et al.* Management of chemical warfare injuries. *Lancet* 1991; **337:** 121.
7. Willems JL, *et al.* Management of chemical warfare injuries. *Lancet* 1991; **337:** 121–2.
8. Maynard RL, *et al.* Management of chemical warfare injuries. *Lancet* 1991; **337:** 122.
9. Newman-Taylor AJ, Morris AJR. Experience with mustard gas casualties. *Lancet* 1991; **337:** 242.
10. Heyndrickx A. Chemical warfare injuries. *Lancet* 1991; **337:** 430.
11. Rees J, *et al.* Mustard gas casualties. *Lancet* 1991; **337:** 430.
12. Murray VSG, Volans GN. Management of injuries due to chemical weapons. *BMJ* 1991; **302:** 129–30.
13. Khateri S, *et al.* Incidence of lung, eye, and skin lesions as late complications in 34 000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003; **45:** 1136–43.
14. Panahi Y, *et al.* Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Med J* 2007; **48:** 392–5.
15. Wulf HC, *et al.* Sister chromatid exchanges in fishermen exposed to leaking mustard gas shells. *Lancet* 1985; **i:** 690–1.

Digitalin

Amorphous Digitalin; Digitalina; Digitalinum Purum Germanicum.

NOTE. Distinguish from Digitaline Cristallisée (digitoxin, p.1259) which is very much more potent.

Profile

Digitalin is a standardised mixture of glycosides from *Digitalis purpurea*. It has actions similar to those of digoxin (p.1259). Because of its ready solubility in water it was formerly used for the preparation of solutions for injection. It is also present in some ophthalmic preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Augentonikum N.

Multi-ingredient: ***Ital.:*** Digifar†.

Dihydroxydibutylether

Dihidroxidibutiléter; Hydroxybutyloxide. 4,4′-Oxybis(butan-2-ol).

$C_8H_{18}O_3$ = 162.2.
CAS — 821-33-0.

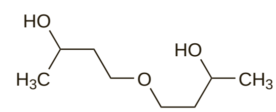

Profile

Dihydroxydibutylether is a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Diskin†.

Multi-ingredient: ***Arg.:*** Binvex; Cistoquine Plus†; ***Ital.:*** Dis-Cinil Complex.

Diisopropanolamine

Diisopropanolamina. 1,1′-Iminobis(propan-2-ol).

$C_6H_{15}NO_2$ = 133.2.
CAS — 110-97-4.

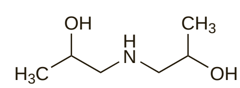

Pharmacopoeias. In *USNF.*

USNF 26 (Diisopropanolamine). A mixture of isopropanolamines, consisting largely of diisopropanolamine. Store in airtight containers. Protect from light.

Profile

Diisopropanolamine is an organic base that is used as a neutralising agent in cosmetics and toiletries.

Dill

Aneth; Anethum; Eneldo.

NOTE. Indian Dill is the dried ripe fruits of *Anethum sowa*.

Pharmacopoeias. *Fr.* includes dill fruit.

Profile

Dill (*Anethum graveolens*, Apiaceae) is a culinary herb and has also been used in herbal medicine. It is the source of dill oil (see below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Colax; ***Fr.:*** Calmosine†.

Dill Oil

Eneldo, aceite esencial de; European Dill Seed Oil; Oleum Anethi.

CAS — 8016-06-6.

Pharmacopoeias. In *Br.*

BP 2008 (Dill Oil). A clear colourless or pale yellow liquid, visibly free from water, obtained by distillation from the dried ripe fruits of *Anethum graveolens*. It darkens with age and has a characteristic odour of the crushed fruit. It contains 43 to 63% of carvone. At 20°, soluble 1 in 1 or more of alcohol (90%) and 1 in 10 or more of alcohol (80%). Store at a temperature not exceeding 25° in well-filled containers. Protect from light.

Profile

Dill oil, usually in the form of dill water, is used as an aromatic carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p.1696).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Chase Kolik Gripe Water; Woodwards Gripe Water; ***Fr.:*** Calmosine†; ***India:*** Bestozyme; Neopeptine; ***Israel:*** Dentinox; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water; ***Rus.:*** Solutan (Солутан); ***Singapore:*** Dentinox; ***Thai.:*** Baby Gripe; Bebidol†; Gripe Mixture; Woodwards Gripe Water; ***UK:*** Atkinson & Barker's Gripe Mixture; Neo Baby Gripe Mixture; Neo Gripe Mixture; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water.

Dimecrotic Acid *(rINN)*

Acide Dimécrotique; Ácido dimecrótico; Acidum Dimecroticum. 2,4-Dimethoxy-β-methylcinnamic acid.

Димекротовая Кислота

$C_{12}H_{14}O_4$ = 222.2.

CAS — 7706-67-4.

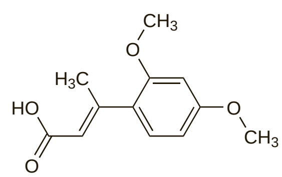

Profile

Dimecrotic acid has been used as the magnesium salt as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Hepadial; ***Port.:*** Hepadoddi; Hepaquifa; ***Spain:*** Fisiobil.

Dimethoxymethane

Dimetoximetano; Formal; Formaldehyde Dimethyl Acetal; Methylal.

$CH_2(OCH_3)_2$ = 76.09.

CAS — 109-87-5.

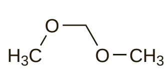

Profile

Dimethoxymethane has been used in perfumery. It has been included in preparations for topical analgesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** PR Freeze Spray.

Dimethyl Sulfone

Dimethyl Sulphone; Dimetylosulfon; $DMSO_2$; Methyl Sulphone; Methylsulfonylmethane; Methylsulphonylmethane; MSM; Sulfonylbismethane.

$C_2H_6O_2S$ = 94.13.

CAS — 67-71-0.

Pharmacopoeias. In *US.*

USP 31 (Methylsulfonylmethane). A white powder or flake crystal. Freely soluble in water, in alcohol, in acetone, and in methyl alcohol; sparingly soluble in ether.

Profile

Dimethyl sulfone is an oxidation product of dimethyl sulfoxide (p.2022) and has been used similarly as an organic solvent. It may be responsible for some of the pharmacological actions of dimethyl sulfoxide and has been tried in disorders including osteoarthritis, allergic rhinitis, and interstitial cystitis. It has also been used as a nutritional supplement.

◊ References.

1. Ely A, Lockwood B. What is the evidence for the safety and efficacy of dimethyl sulfoxide and methylsulfonylmethane in pain relief? *Pharm J* 2002; **269:** 685–7.
2. Anonymous. Methylsulfonylmethane (MSM). *Altern Med Rev* 2003; **8:** 438–41.
3. Brien S, *et al.* Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2008. Available at: doi: 10.1016/j.joca.2008.03.002

Preparations

USP 31: Glucosamine and Methylsulfonylmethane Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets; Methylsulfonylmethane Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Glucosamine Joint & Muscle Cream with MSM†; ***Indon.:*** Aptivium Optimum Joint Formula; Artriox; Artritin; Maxitrin; Naturica Artro Plus; OA Plus; Osteoflam; Osteokom; Osteokom Forte; Osteor Plus; Osvion Plus; Triflexor; Triostee; Viopor-M; ***Ital.:*** Neosulfur; Osteoclar; Reumafort; ***S.Afr.:*** ProFLEX 750; ***UK:*** GlucOsamax; NatraFlex; PainEaze.

p,α-Dimethylbenzyl Alcohol

Tolinol; *p*-Tolylmethylcarbinol; Tolynolum. 1-(*p*-Tolyl)ethanol.

$C_9H_{12}O$ = 136.2.

CAS — 536-50-5.

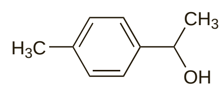

NOTE. The name tolynol has been applied to both *p*,α-dimethylbenzyl alcohol and mephenesin (p.1897).

Profile

p,α-Dimethylbenzyl alcohol has been used as a choleretic in the treatment of hepatic disorders and is an ingredient of preparations for gastrointestinal disorders. *p*,α-Dimethylbenzyl alcohol nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Apozema; Galle-Donau; Spagall; Spasmo Claim.

Dimethyltryptamine

N,N-Dimethyltryptamine; Dimetiltriptamina; DMT. 3-(2-Dimethylaminoethyl)indole.

$C_{12}H_{16}N_2$ = 188.3.

CAS — 61-50-7.

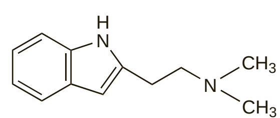

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dimethyltryptamine: 45 Minute Psychosis; 45 Minute Trip; AMT; Businessman's LSD; Businessman's special; Businessman's trip; DET; Disneyland; Disneyworld; Dmitri; DMT; Fantasia; Instant psychosis; Psychosis.

Profile

Dimethyltryptamine is an active principle obtained from the seeds and leaves of *Piptadenia peregrina* (Mimosaceae) from which the hallucinogenic snuff cohoba is prepared. It may also be obtained from other South American plants. It has been reported to be present in the tropical legume *Mucuna pruriens*.

Dimethyltryptamine produces hallucinogenic and sympathomimetic effects that are similar to those of lysergide (p.2335), but of shorter duration. It has no therapeutic use. Related synthetic hallucinogens subject to abuse include:

- diethyltryptamine (DET)
- dipropyltryptamine (DPT)
- 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT; Foxy; Foxy Methoxy; Methoxy Foxy)

◊ References.

1. Alatrash G, *et al.* Rhabdomyolysis after ingestion of "foxy," a hallucinogenic tryptamine derivative. *Mayo Clin Proc* 2006; **81:** 550–1.

Dimevamide *(rINN)*

Aminopentamide; Dimevamida; Dimévamide; Dimevamidum. α-[2-(Dimethylamino)propyl]-α-phenylbenzeneacetamide.

Димевамид

$C_{19}H_{24}N_2O$ = 296.4.

CAS — 60-46-8.

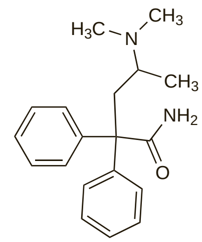

Dimevamide Sulfate *(rINNM)*

Aminopentamide Sulfate; Dimévamide, Sulfate de; Dimevamidi Sulfas; Sulfato de dimevamida.

Димевамида Сульфат

$C_{19}H_{24}N_2O,H_2SO_4$ = 394.5.

CAS — 35144-63-9 (xH_2SO_4).

Pharmacopoeias. In *US* for veterinary use only.

Profile

Dimevamide is a tertiary amine and has been used as an antimuscarinic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***S.Afr.:*** Kantrexil.

2,4-Dinitrochlorobenzene

2,4-Dinitroclorobenceno; DNCB. 1-Chloro-2,4-dinitrobenzene.

2,4-Динитрохлорбензол

$C_6H_3ClN_2O_4$ = 202.6.

CAS — 97-00-7.

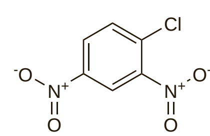

Profile

2,4-Dinitrochlorobenzene is a potent sensitiser that has been applied topically in the evaluation of delayed hypersensitivity. It has also been used as an immunostimulant in various conditions including some forms of cancer, and in the treatment of alopecia and warts. It has also been investigated in HIV infection and leprosy.

2,4-Dinitrochlorobenzene has been reported to be mutagenic *in vitro*.

◊ References.

1. Happle R. The potential hazards of dinitrochlorobenzene. *Arch Dermatol* 1985; **121:** 330–2.
2. Todd DJ. Topical treatment with dinitrochlorobenzene. *Lancet* 1995; **346:** 975.
3. Stricker RB, Goldberg B. Safety of topical dinitrochlorobenzene. *Lancet* 1995; **346:** 1293.
4. Strobbe LJ, *et al.* Topical dinitrochlorobenzene combined with systemic dacarbazine in the treatment of recurrent melanoma. *Melanoma Res* 1997; **7:** 507–12.
5. Yoshizawa Y, *et al.* Successful immunotherapy of chronic nodular prurigo with topical dinitrochlorobenzene. *Br J Dermatol* 1999; **141:** 387–9.
6. Yoshizawa Y, *et al.* Topical dinitrochlorobenzene therapy in the treatment of refractory atopic dermatitis: systemic immunotherapy. *J Am Acad Dermatol* 2000; **42:** 258–62.
7. Yoshizawa Y, *et al.* Systemic immunotherapy with topical dinitrochlorobenzene as additional treatment of alopecia areata. *Acta Derm Venereol* 2002; **82:** 136–8.
8. von Nida J, Quirk C. Successful treatment of in-transit melanoma metastases using topical 2-4 dinitrochlorobenzene. *Australas J Dermatol* 2003; **44:** 277–80.

Diolamine *(pINN)*

Diaethanolamin; Dietanoloamina; Diethanolamine; Diolamina; Diolaminum. Bis(2-hydroxyethyl)amine; 2,2′-Iminobisethanol.

Диоламин

$C_4H_{11}NO_2$ = 105.1.

CAS — 111-42-2.

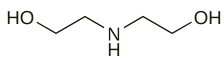

Pharmacopoeias. In *USNF.*

USNF 26 (Diethanolamine). It is a mixture of olamines, consisting largely of diolamine. White or clear, colourless crystals, deliquescing in moist air, or a colourless liquid. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; slightly soluble to insoluble in ether, in petroleum spirit, and in benzene. Store in airtight containers. Protect from light.

Profile

Diolamine is an organic base that is used as an emulsifier and dispersant.

It is used to solubilise fusidic acid and sulfafurazole by the formation of the diolamine salt. It has been used for the preparation of salts of iodinated organic acids used as contrast media. It may be irritating to the skin and mucous membranes.

Dioxins

Dioxinas.

NOTE. The name Dioxin has also been applied to dimethoxane.

Profile

The term 'dioxins' encompasses a large group of closely related chemicals known as polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). The most toxic is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

Dioxins are byproducts in the manufacture of commercial chemical products such as chlorinated phenols and polychlorinated biphenyls (PCBs), and can also be produced in smaller quantities by combustion processes and industrial waste. They first came to public attention during the Vietnam war, when they were found to be present in the herbicide Agent Orange used as a defoliant. They are incriminated as causing chloracne (a severe and persistent acne caused by chlorinated compounds). They are potent teratogens and carcinogens in *animals*. An increased incidence of cancer at different organs due to dioxins has been claimed but this has not been substantiated by clinical and follow-up studies. An effect on cell-mediated immunity has been observed.

Exposure should be limited to the lowest feasible concentration.

Adverse effects. The impact of dioxins in food and the environment has been reviewed.[1-4]

An excess of soft tissue sarcomas was found in workers exposed to chlorophenoxy herbicides including those contaminated with TCDD,[5] but cautious interpretation of these results was advised.[6] In Vietnam veterans the risk of non-Hodgkin's lymphoma was about 50% higher than control subjects, but was not related to exposure to Agent Orange, nor was there evidence for an increase in other cancers.[7] Exposure to TCDD was implicated in an increase in cancer mortality in chemical workers,[8,9] but confounding factors such as smoking may have been present.[9,10] Other studies[11,12] have not shown an association between dioxin exposure and an increase in the incidence of human cancer, and epidemiological studies after occupational or accidental exposures have found no clear persistent systemic effects, except for chloracne, and no clear association with carcinogenesis or reproductive disorders.[1,2] Decreased plasma immunoglobulin G concentrations were measured in people after exposure to TCDD 20 years earlier as a result of accidental environmental contamination in Seveso, Italy.[13] A statistically significant increase in the incidence of breast cancer related to serum levels of TCDD was observed in a cohort of 981 women who ranged in age from infancy to 40 years in 1976 at the time of the Seveso accident.[14] The authors pointed out that this cohort is relatively young and continued follow-up would clarify any possible pathogenic role of TCDD.

In the USA, the National Academy of Sciences' Institute of Medicine is reported to have carried out an evaluation of publications on herbicide exposure, largely in industrial and agricultural workers.[15] They concluded that exposure to herbicides or dioxin was associated with soft-tissue sarcomas, Hodgkin's disease, non-Hodgkin lymphoma, chloracne, and porphyria cutanea tarda, and that there was limited evidence of an association with respiratory and prostate cancers and multiple myeloma. An update to the report has also suggested a link between Agent Orange exposure and spina bifida in veterans' offspring.[16] There is some evidence that exposure of men to TCDD is associated with a decreased male to female sex ratio in their offspring.[17] Results from studies[18-20] suggest that prenatal exposure to PCBs has an effect on mental and motor development in early childhood, although this may be counteracted by an advantageous home environment. However, virtually no adverse effects in relation to postnatal exposure to PCBs present in breast milk were demonstrated.[20]

1. Food Standards Agency UK. Dioxins and PCBs in the UK diet: 1997 Total Diet Study (Number 04/00) (issued September 2000). Available at: http://www.food.gov.uk/science/surveillance/fsis2000/4diox (accessed 24/07/08)
2. DEFRA. Dioxins and dioxin-like PCBs in the UK environment (issued October 2002). Available at: http://www.scotland.gov.uk/Resource/Doc/1052/0002248.pdf (accessed 24/07/08)
3. WHO. Dioxins and their effects on human health (issued November 2007). Available at: http://www.who.int/mediacentre/factsheets/fs225/en/print.html (accessed 24/07/08)
4. FAO. Dioxins in the food chain: prevention and control of contamination (issued April 2008). Available at: http://www.fao.org/ag/agn/agns/files/Dioxin_fact%20sheet.pdf (accessed 24/07/08)
5. Saracci R, *et al.* Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; **338**: 1027–32.
6. Peto R. Occupational exposure to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; **338**: 1392.
7. Suskind R. The association of selected cancers with service in the US military in Vietnam. *Arch Intern Med* 1990; **150**: 2449–50.
8. Manz A, *et al.* Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 1991; **338**: 959–64.
9. Fingerhut MA, *et al.* Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991; **324**: 212–18.
10. Triebig G. Is dioxin carcinogenic? *Lancet* 1991; **338:** 1592.
11. Coggon O, *et al.* Mortality and incidence of cancer at four factories making phenoxy herbicides. *Br J Ind Med* 1991; **48:** 173–8.
12. Green LM. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. *Br J Ind Med* 1991; **48:** 234–8.
13. Baccarelli A, *et al.* Immunologic effects of dioxin: new results from Seveso and comparison with other studies. *Environ Health Perspect* 2002; **110:** 1169–73.
14. Warner M, *et al.* Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* 2002; **110:** 625–8.
15. McCarthy M. Agent Orange. *Lancet* 1993; **342:** 362.
16. Stephenson J. New IOM report links Agent Orange Exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; **275:** 1066–7.
17. Mocarelli P, *et al.* Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000; **355:** 1858–63.
18. Walkowiak J, *et al.* Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet* 2001; **358:** 1602–7.
19. Vreugdenhil HJ, *et al.* Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. *J Pediatr* 2002; **140:** 48–56.
20. Jacobson JL, Jacobson SW. Association of prenatal exposure to an environmental contaminant with intellectual function in childhood. *J Toxicol Clin Toxicol* 2002; **40:** 467–75.

Diphemanil Metilsulfate *(BAN, rINN)*

Diphemanil Methylsulfate; Diphemanil Methylsulphate; Diphémanil, Métilsulfate de; Diphemanili Metilsulfas; Diphenmethanil Methylsulphate; Metilsulfato de difemanilo; Vagophemanil Methylsulphate. 4-Benzhydrylidene-1,1-dimethylpiperidinium methylsulphate.

Дифеманила Метилсульфат

$C_{20}H_{24}N,CH_3SO_4$ = 389.5.

CAS — 62-97-5.

ATC — A03AB15.

ATC Vet — QA03AB15.

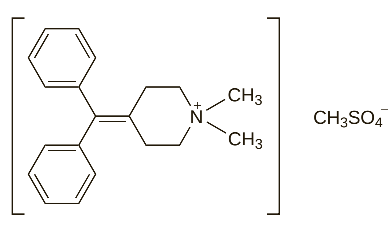

Profile

Diphemanil metilsulfate is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It is used topically as a 2% cream or powder to treat hyperhidrosis (p.1580).

Diphemanil metilsulfate, given orally, has been used for the treatment of symptomatic bradycardia in infants.

◊ References.

1. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in healthy subjects. *Eur J Clin Pharmacol* 1992; **42:** 689–91.
2. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in infants. *Eur J Clin Pharmacol* 1993; **45:** 89–91.
3. Pariente-Khayat A, *et al.* Pharmacokinetics of diphemanil methylsulphate in neonates and in premature infants. *Eur J Clin Pharmacol* 1996; **50:** 429–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Prantal; ***Chile:*** Nivelon†; ***Ital.:*** Prantal†; ***NZ:*** Prantal.

Diphenyl

Difenilo; E230; Phenylbenzene. Biphenyl.

$C_{12}H_{10}$ = 154.2.

CAS — 92-52-4.

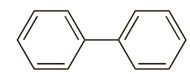

Profile

Diphenyl is fungistatic against a limited number of moulds and has been employed for impregnating the material used for wrapping citrus fruits.

Adverse effects. Workers exposed to high concentrations of diphenyl (up to 128 mg/m^3) developed toxic symptoms that included irritation of the throat and eyes, headache, nausea, diffuse abdominal pain, numbness, aching of limbs, and general fatigue.[1] One of the workers, who also had somnolence, icterus, ascites, and oedema of the legs, died; at autopsy, the liver showed necrosis. Chronic hepatitis was reported in a woman exposed over a 25-year period to diphenyl in the paper used to pack citrus fruit.[2]

1. Häkkinen I, *et al.* Diphenyl poisoning in fruit paper production. *Arch Environ Health* 1973; **26:** 70–4.
2. Carella G, Bettolo PM. Reversible hepatotoxic effects of diphenyl: report of a case and a review of the literature. *J Occup Med* 1994; **36:** 575–6.

Dipivefrine *(BAN, rINN)* ⊗

Dipivalyl Epinephrine; Dipivefriini; Dipivefrin *(USAN)*; Dipivefrina; Dipivéfrine; Dipivefrinum; DPE.

Дипивефрин

$C_{19}H_{29}NO_5$ = 351.4.

CAS — 52365-63-6.

ATC — S01EA02.

ATC Vet — QS01EA02.

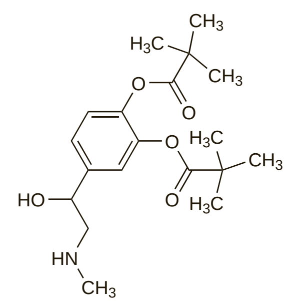

Dipivefrine Hydrochloride *(BANM, rINNM)* ⊗

Dipivalyl Adrenaline Hydrochloride; Dipivalyl Epinephrine Hydrochloride; Dipivefriinihydrokloridi; Dipivefrin Hydrochloride; Dipivéfrine, chlorhydrate de; Dipivefrin-hydrochlorid; Dipivefrin-hydroklorid; Dipivefrini hydrochloridum; Dipivefrino hidrochloridas; Dipiwefryny chlorowodorek; Hidrocloruro de dipivefrina. (*RS*)-4-[1-Hydroxy-2-(methylamino)ethyl]-*o*-phenylene dipivalate hydrochloride.

Дипивефрина Гидрохлорид

$C_{19}H_{29}NO_5,HCl$ = 387.9.

CAS — 64019-93-8.

ATC — S01EA02.

ATC Vet — QS01EA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Dipivefrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane; very soluble in methyl alcohol.

USP 31 (Dipivefrin Hydrochloride). White, crystalline powder or small crystals, having a faint odour. Very soluble in water. Store in airtight containers.

Profile

Dipivefrine is an ester and prodrug of adrenaline (p.1203). A 0.1% solution of the hydrochloride is used topically as eye drops to reduce intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (p.1873).

◊ References.

1. Parrow KA, *et al.* Is it worthwhile to add dipivefrin HCl 0.1% to topical β -, β -blocker therapy? *Ophthalmology* 1989; **96:** 1338–41.

2. Drake MV, *et al.* Levobunolol compared to dipivefrin in African American patients with open angle glaucoma. *J Ocul Pharmacol* 1993; **9:** 91–5. Correction. *ibid.*; 385.
3. Albracht DC, *et al.* A double-masked comparison of betaxolol and dipivefrin for the treatment of increased intraocular pressure. *Am J Ophthalmol* 1993; **116:** 307–13.
4. Widengard I, *et al.* Effects of latanoprost and dipivefrin, alone or combined, on intraocular pressure and on blood-aqueous barrier permeability. *Br J Ophthalmol* 1998; **82:** 404–6.

Preparations

BP 2008: Dipivefrine Eye Drops;
USP 31: Dipivefrin Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Propine†; ***Austral.:*** Dipoquin; Propine; ***Austria:*** Glaucothil†; ***Belg.:*** Propine; ***Braz.:*** Propine; ***Canad.:*** Propine†; ***Cz.:*** d Epifrin†; Oftanex†; ***Denm.:*** Oftapinex†; Propine; ***Fin.:*** Oftapinex†; Propine; ***Fr.:*** Propine; ***Ger.:*** d Epifrin; Glaucothil; ***Gr.:*** Diopine†; Glaucodose; Prodren†; Thilodrin; ***Hong Kong:*** Propine; ***Irl.:*** Propine; ***Israel:*** Difrin; ***Ital.:*** Propine; ***Jpn:*** Pivalephrine; ***Malaysia:*** Propine†; ***Mex.:*** Diopine†; ***Neth.:*** Diopine; ***Norw.:*** Oftapinex†; Propine; ***NZ:*** Dipoquin†; Propine; ***Port.:*** Propine†; ***S.Afr.:*** Propine†; ***Singapore:*** Propine†; ***Spain:*** Diopine; Glaudrops†; ***Swed.:*** Oftapinex†; Propine; ***Switz.:*** Diopine†; ***Thai.:*** Propine†; ***UK:*** Propine; ***USA:*** AkPro; Propine.

Multi-ingredient: ***Austria:*** Thiloadren; Thilodigon†; ***Canad.:*** Probeta†; ***Ger.:*** Thiloadren N; Thilodigon; ***Gr.:*** Ryvina†; Thilocombin†.

Disodium Guanylate

Disodium Guanosine-5′-monophosphate; E627; Guanilato disódico; Sodium 5′-Guanylate. Guanosine 5′-(disodium phosphate).

Гуанилат Натрия Двузамещенный

$C_{10}H_{12}N_5Na_2O_8P,xH_2O$ = 407.2 (anhydrous).

CAS — 5550-12-9 (anhydrous disodium guanylate).

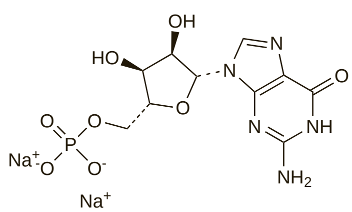

Profile

Disodium guanylate is used in preparations containing other nucleosides in the treatment of corneal damage. Disodium guanylate has been used as a flavour enhancer in foods. The term sodium 5′-ribonucleotide (disodium 5′-ribonucleotide) has been used to refer to a mixture of disodium guanylate with disodium inosinate (see below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Vitacic; ***Cz.:*** Laevadosin†; ***Hung.:*** Vitacic†; ***Mon.:*** Vitacic; ***Rus.:*** Vitacic (Витасик)†.

Disodium Inosinate

Disodium Inosine-5′-monophosphate; E631; Inosinato disódico; Sodium 5′-Inosinate. Inosine 5′-(disodium phosphate).

$C_{10}H_{11}N_4Na_2O_8P,xH_2O$ = 392.2 (anhydrous).

CAS — 4691-65-0 (anhydrous disodium inosinate).

Profile

Disodium inosinate has been used as a flavour enhancer in foods. It has also been given by mouth and been applied topically in the treatment of visual disturbance. The term sodium 5′-ribonucleotide has been used to refer to a mixture of disodium inosinate with disodium guanylate (above).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lumiclar; Opacout; ***Fr.:*** Catacol; Correctol; ***Ger.:*** Antikataraktikum N.

Multi-ingredient: ***Arg.:*** Antikatarata†.

Disodium Uridine Monophosphate

Disodium UMP. 5′-Uridylic acid, disodium salt; disodium 5′ uridylate.

Уридин Монофосфат Динатрия

$C_9H_{11}N_2O_9PNa_2$ = 368.1.

CAS — 3387-36-8.

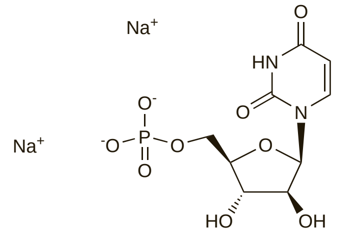

Profile

Uridine monophosphate is an endogenous uracil nucleotide involved in many biological processes. Disodium uridine monophosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; disodium uridine diphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Laevadosin†; ***Ger.:*** Keltican N; ***Spain:*** Nucleo CMP.

Disulfiram *(BAN, rINN)*

Dissulfiramo; Disulfiraami; Disulfiramas; Disulfirame; Disulfiramum; Diszulfirám; Éthyldithiourame; TTD. Tetraethylthiuram disulphide; Bis(diethylthiocarbamoyl) disulfide.

Дисульфирам

$C_{10}H_{20}N_2S_4$ = 296.5.

CAS — 97-77-8.

ATC — N07BB01; P03AA04.

ATC Vet — QN07BB01; QV03AA01.

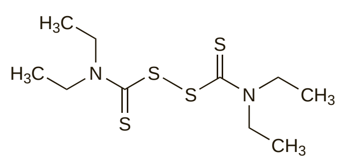

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Disulfiram). A white or almost white, crystalline powder. M.p. 70° to 73°. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Disulfiram). A white to off-white, odourless crystalline powder. M.p. 69° to 72°. Very slightly soluble in water; soluble 1 in 30 of alcohol and 1 in 15 of ether; soluble in acetone, in carbon disulfide, and in chloroform. Store in airtight containers. Protect from light.

Stability. Studies[1,2] on the stability of disulfiram preparations.

1. Gupta VD. Stability of aqueous suspensions of disulfiram. *Am J Hosp Pharm* 1981; **38:** 363–4.
2. Philips M, *et al.* Stability of an injectable disulfiram formulation sterilized by gamma irradiation. *Am J Hosp Pharm* 1985; **42:** 343–5.

Adverse Effects and Treatment

Drowsiness and fatigue are common during initial treatment with disulfiram. Other adverse effects reported include a garlic-like or metallic aftertaste, gastrointestinal upsets, body odour, bad breath, headache, impotence, and allergic dermatitis. Peripheral and optic neuropathies, psychotic reactions, and hepatotoxicity may occur.

Disulfiram-alcohol reaction. The use of disulfiram in the management of alcoholism is based on the extremely unpleasant, but generally self-limiting, systemic effects which occur when a patient receiving the drug ingests alcohol. These effects begin with flushing of the face and, as vasodilatation spreads, throbbing in the head and neck and a pulsating headache may develop. Respiratory difficulties, nausea, copious vomiting, sweating, thirst, chest pain, tachycardia, palpitations, marked hypotension, giddiness, weakness, blurred vision, and confusion may follow. The intensity and duration of symptoms is very variable and even small quantities of alcohol may result in alarming reactions. In addition to the above effects, severe reactions have included respiratory depression, cardiovascular collapse, cardiac arrhythmias, myocardial infarction, acute heart failure, unconsciousness, convulsions, and sudden death.

Severe reactions require intensive supportive therapy; oxygen and intravenous fluids may be necessary. Potassium concentrations should be monitored. Giving intravenous ascorbic acid, ephedrine sulfate, or antihistamines has been suggested.

◊ Reviews.

1. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety* 1999; **20:** 427–35.

Effects on the blood. There were isolated reports of blood dyscrasias associated with disulfiram in the 1960s. US licensed product information recommends that blood counts should be performed during treatment.

Effects on the liver. A review of 18 cases of hepatitis in patients receiving disulfiram.[1] Symptoms have appeared between 10 days and 6 months after starting disulfiram, and clinical improvement has been seen within 2 weeks of stopping the drug, although liver enzyme values may not return to normal for several months. Fatal hepatic coma had been reported in 7 patients. The clinical picture of disulfiram-induced hepatitis is consistent with a hypersensitivity reaction. Another review[2] evaluated 82 cases of liver injury thought to be due to disulfiram and reported to the Swedish Adverse Drug Reactions Advisory Committee between 1966 and 2002. All but one of the cases were of hepatocellular liver damage, and 4 patients died and 4 underwent liver transplantation. Although there was some evidence that hypersensitivity played a role, it might not be the only mechanism of disulfiram-induced liver disease.

1. Mason NA. Disulfiram-induced hepatitis: case report and review of the literature. *DICP Ann Pharmacother* 1989; **23:** 872–4.
2. Björnsson E, *et al.* Clinical characteristics and prognostic markers in disulfiram-induced liver injury. *J Hepatol* 2006; **44:** 791–7.

Effects on the nervous system. *ENCEPHALOPATHY.* A 2% incidence of reversible toxic encephalopathy has been reported in patients receiving disulfiram.[1] Onset varies from days to months following the start of therapy and early signs include impaired concentration, memory deficits, anxiety, depression, and somnolence. Confusion and disorientation follow, often accompanied by paranoid delusions and sometimes hallucinations. Other symptoms may include ataxia, loss of fine motor coordination, slurred speech, and intention tremor. The encephalopathy usually resolves within 3 days to 2 weeks of stopping disulfiram, although symptoms may persist for 6 weeks. There are conflicting opinions on whether this psychosis is a toxic reaction to disulfiram or a response to abstinence from alcohol, but the authors suspected that most cases represent a toxic encephalopathy. However, psychosis without any suggestion of encephalopathy has been reported.[2]

1. Hotson JR, Langston JW. Disulfiram-induced encephalopathy. *Arch Neurol* 1976; **33:** 141–2.
2. Rossiter SK. Psychosis with disulfiram prescribed under probation order. *BMJ* 1992; **305:** 763.

PERIPHERAL NEUROPATHY. Reports of peripheral neuropathy associated with disulfiram and reference to previously reported cases.[1,2] Onset of neuropathy varied from days to months after starting disulfiram treatment and could develop with doses of 250 or 500 mg daily. The most common symptom reported was pins and needles, but numbness, pain/burning, and weakness were frequently described; usually both muscle weakness and sensory loss were noted. Optic atrophy has also been described. Although there might be some improvement immediately after disulfiram withdrawal, the neurological deficit only improved slowly and symptoms might persist for as long as 2 years.[1]

1. Watson CP, *et al.* Disulfiram neuropathy. *Can Med Assoc J* 1980; **123:** 123–6.
2. Frisoni GB, Di Monda V. Disulfiram neuropathy: a review (1971-1988) and report of a case. *Alcohol Alcohol* 1989; **24:** 429–37.

Effects on the respiratory tract. Bronchospasm and hypertension were observed in an asthmatic patient taking disulfiram after an alcohol challenge test.[1]

1. Zapata E, Orwin A. Severe hypertension and bronchospasm during disulfiram-ethanol test reaction. *BMJ* 1992; **305:** 870.

Effects on the skin. Orange-coloured palms and soles, provoking an initial diagnosis of jaundice, developed in a 55-year-old man who had been taking disulfiram for about 2 months.[1] It was postulated that the discoloration was due to accumulation of carotenes in the skin as a result of inhibition of vitamin A metabolism by disulfiram. The discoloration disappeared soon after disulfiram was stopped.

1. Santonastaso M, *et al.* Yellow palms with disulfiram. *Lancet* 1997; **350:** 266.

Overdosage. There has been a report of a 6-year-old boy who experienced disulfiram intoxication after receiving disulfiram 250 mg four times daily to a total of 13 doses but who later recovered.[1] Of 6 previous reports one child died and 3 had moderate or severe brain damage. The syndrome of disulfiram intoxication in children is distinct from the disulfiram-alcohol interaction or acute disulfiram intoxication in adults. It is characterised by lethargy or somnolence, weakness, hypotonia, and vomiting, beginning about 12 hours after ingestion and progressing to stupor or coma. Dehydration, moderate tachycardia, and marked tachypnoea occur frequently, muscle tone is greatly decreased, and deep-tendon reflexes may be weak or absent.

Severe neurological damage has also been reported[2] in a 5-year-old girl after acute disulfiram intoxication which was initially diagnosed as diabetic ketoacidosis.

1. Benitz WE, Tatro DS. Disulfiram intoxication in a child. *J Pediatr* 1984; **105:** 487–9.
2. Mahajan P, *et al.* Basal ganglion infarction in a child with disulfiram poisoning. *Pediatrics* 1997; **99:** 605–8.

Precautions

Disulfiram is contra-indicated in the presence of cardiovascular disease or psychosis or severe personality disorders, and should not be given to patients known to be hypersensitive to it or to other thiuram compounds, such as those used in rubber vulcanisation or pesticides. It should be used with caution in the presence of diabetes mellitus, epilepsy, impaired hepatic or renal function, respiratory disorders, cerebral damage, or hypothyroidism. Caution is also advised when giving disulfiram to those who are addicted to other drugs in addition to alcohol. It is probably best avoided in pregnancy.

Disulfiram should not be given until at least 24 hours after the last ingestion of alcohol. Patients beginning therapy should be fully aware of the disulfiram-alcohol reaction and should be warned to avoid alcohol in any form, including alcohol-containing medicines and alcohol-based topical preparations. Reactions to alcohol may occur as long as 2 weeks after the cessation of disulfiram.

The US manufacturers have recommended that regular blood counts and liver function tests should be performed during long-term therapy.

Pregnancy. A report of 2 infants with severe limb-reduction anomalies whose mothers had taken disulfiram during pregnancy.[1] Only 2 similar cases had previously been reported.

1. Nora AH, *et al.* Limb-reduction anomalies in infants born to disulfiram-treated alcoholic mothers. *Lancet* 1977; **ii:** 664.

Interactions

Disulfiram inhibits hepatic enzymes and may interfere with the metabolism of other drugs taken at the same time. It enhances the effects of phenytoin and coumarin anticoagulants and their dosage may need to be reduced. It also inhibits the metabolism and excretion of rifampicin. Toxic reactions have occurred when disulfiram was given with isoniazid or metronidazole. Disulfiram may inhibit the metabolism of paraldehyde leading to an accumulation of acetaldehyde and these drugs should not be used together.

◊ In a study[1] to evaluate the effects of disulfiram on cytochrome P450 isoenzymes, the results suggested that disulfiram-mediated inhibition is mainly selective for CYP2E1 after both acute and chronic dosage.

1. Frye RF, Branch RA. Effect of chronic disulfiram administration on the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and N-acetyltransferase in healthy human subjects. *Br J Clin Pharmacol* 2002; **53:** 155–62.

Analgesics. The potential of disulfiram to impair drug metabolism was shown[1] when it was found to prolong the plasma half-life of *phenazone*, probably by inhibiting the hepatic microsomal mixed function oxidases. It was also suggested[1] that disulfiram alters catecholamine metabolism since urinary excretion of vanilmandelic acid was significantly reduced and that of homovanillic acid was increased.

1. Vesell ES, *et al.* Impairment of drug metabolism by disulfiram in man. *Clin Pharmacol Ther* 1971; **12:** 785–92.

Antidepressants. It has been reported[1] that *amitriptyline* appeared to enhance the disulfiram-alcohol reaction. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *tricyclic antidepressants* or those inhibiting the same enzymes as disulfiram, such as *MAOIs*.[2]

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Antiprotozoals. For reference to toxicity associated with *metronidazole* given to alcoholic patients who were also receiving disulfiram, see Alcohol, under Interactions of Metronidazole, p.838.

Antipsychotics. It has been suggested[1] that phenothiazine antiemetics such as *chlorpromazine* might increase hypotension because of their α-adrenoceptor blocking activity and should therefore be contra-indicated in patients taking disulfiram. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *phenothiazines*.[2]

1. Kwentus J, Major LF. Disulfiram in the treatment of alcoholism: a review. *J Stud Alcohol* 1979; **40:** 428–46.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Benzodiazepines. *Diazepam* was reported[1] to reduce the intensity of the disulfiram-alcohol reaction.

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.

Cannabis. For a suggestion that a combination of disulfiram and *cannabis* may produce a hypomanic state, see p.2275.

Cardiovascular drugs. Clinically serious pharmacodynamic interactions might be anticipated during the disulfiram-alcohol reaction in patients taking other drugs that impair blood pressure regulation, such as *alpha blockers*, *beta blockers*, or *vasodilators*.[1]

1. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Macrolides. Fatal toxic epidermal necrolysis and fulminant hepatitis have been reported[1] after starting *clarithromycin* treatment in a patient who was receiving disulfiram.

1. Masiá M, *et al.* Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. *Arch Intern Med* 2002; **162:** 474–6.

Pharmacokinetics

Disulfiram is absorbed variably from the gastrointestinal tract and is rapidly reduced to diethyldithiocarbamate (ditiocarb, p.1445), principally by the glutathione reductase system in the erythrocytes; reduction may also occur in the liver. Diethyldithiocarbamate is metabolised in the liver to its glucuronide and methyl ester and to diethylamine, carbon disulfide, and sulfate ions. Metabolites are excreted primarily in the urine; carbon disulfide is exhaled in the breath.

◊ There was marked intersubject variability in plasma concentrations of disulfiram and its metabolites in a study of 15 male alcoholics given single 250-mg doses of disulfiram by mouth and repeated dosing with 250 mg daily for 12 days.[1] Variability might result from the marked lipid solubility of disulfiram, differences in plasma protein binding, or enterohepatic cycling. Average times to reach peak plasma concentrations after single or repeated doses were 8 to 10 hours for disulfiram, diethyldithiocarbamate, diethyldithiocarbamate-methyl ester, and diethylamine, and for carbon disulfide in breath; peak plasma concentrations of carbon disulfide occurred after 5 to 6 hours. Plasma concentrations of disulfiram were negligible within 48 hours of a dose, although concentrations of some metabolites were still raised. In urine, 1.7 and 8.3% of a disulfiram dose was eliminated as diethyldithiocarbamate-glucuronide in the 24 hours after a single and repeated dose respectively, while diethylamine accounted for 1.6 and 5.7%, respectively. In the 24 hours after a single and repeated dose 22.4 and 31.3%, respectively, was eliminated as carbon disulfide in the breath.

1. Faiman MD, *et al.* Elimination kinetics of disulfiram in alcoholics after single and repeated doses. *Clin Pharmacol Ther* 1984; **36:** 520–6.

Uses and Administration

Disulfiram is used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p.1626). Disulfiram is not a cure and the treatment is likely to be of little value unless it is undertaken with the willing cooperation of the patient and is used with supportive psychotherapy.

Disulfiram inhibits aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde, a metabolite of alcohol. The resulting accumulation of acetaldehyde in the blood is widely believed to be responsible for many of the unpleasant symptoms of the disulfiram-alcohol reaction which occur when alcohol is taken, even in small quantities, after disulfiram (see Adverse Effects and Treatment, above). Symptoms can arise within 10 minutes of the ingestion of alcohol and last from half an hour in mild cases to several hours in severe cases. It is advisable to carry out the initial treatment in hospital or in a specialised unit where the patient can be kept under close supervision.

Disulfiram is given by mouth. In the UK, the dose is 800 mg, taken as a single dose, on the first day of treatment, reduced by 200 mg daily to a maintenance dose which is usually 100 to 200 mg daily. In the USA, where doses above 500 mg daily are not recommended, an initial dose of 500 mg daily for 1 to 2 weeks is given, followed by a maintenance dose of 250 mg daily or within the range of 125 to 500 mg daily. Treatment should be reviewed after no longer than 6 months. Maintenance therapy with disulfiram may need to be continued for months or years, until the patient is fully recovered socially and a basis for permanent self-control has been established.

A test dose of alcohol has been given under close supervision when the patient is receiving maintenance doses of disulfiram, in order to demonstrate the nature of the disulfiram-alcohol reaction. However, these challenge tests are not routinely recommended, and should not in any case be used in patients over 50 years of age. Many authorities consider that an explicit description of the reaction is sufficient.

Disulfiram implants have been used in an attempt to overcome problems of patient compliance but have been largely abandoned due to lack of clinical efficacy.

Alcoholism. References.

1. Wright C, Moore RD. Disulfiram treatment of alcoholism. *Am J Med* 1990; **88:** 647–55.
2. Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction* 1997; **92:** 381–95.
3. O'Shea B. Disulfiram revisited. *Hosp Med* 2000; **61:** 849–51.
4. Brewer C, *et al.* Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs* 2000; **14:** 329–341.
5. Suh JJ, *et al.* The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; **26:** 290–302.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; disulfiram is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (see Cocaine Withdrawal Syndrome, p.1860).

References.

1. Carroll KM, *et al.* Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004; **61:** 264–72.

Preparations

BP 2008: Disulfiram Tablets;
USP 31: Disulfiram Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Abstensyl; Vandisul†; ***Austral.:*** Antabuse; ***Austria:*** Antabus; ***Belg.:*** Antabuse; ***Braz.:*** Antietanol; Sarcoton; ***Chile:*** Antabus; Tolerane; ***Cz.:*** Antabus; ***Denm.:*** Antabus; ***Fin.:*** Antabus; ***Fr.:*** Esperal; ***Ger.:*** Antabus; ***Hung.:*** Antaethyl; ***India:*** Esperal; ***Irl.:*** Antabuse; ***Israel:*** Antabuse†; ***Ital.:*** Antabuse; Etiltox; ***Mex.:*** Etabus; ***Neth.:*** Antabus; Refusal; ***Norw.:*** Antabus; ***NZ:*** Antabuse; ***Pol.:*** Anticol; ***Port.:*** Tetradin; ***Rus.:*** Esperal (Эспераль); ***S.Afr.:*** Antabuse; ***Spain:*** Antabus; ***Swed.:*** Antabus; ***Switz.:*** Antabus; ***Thai.:*** Antabuse†; Difiram; ***Turk.:*** Antabus; ***UK:*** Antabuse; ***USA:*** Antabuse.

Multi-ingredient: ***Fr.:*** TTD-B -B ; ***Rus.:*** Lidevine (Лидевин); ***Swed.:*** Tenutex.

Dizocilpine Maleate *(USAN, rINNM)*

Dizocilpine, Maléate de; Dizocilpini Maleas; Maleato de dizocilpina; MK-801. (+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine maleate.

Дизоцилпина Малеат

$C_{16}H_{15}N,C_4H_4O_4 = 337.4.$

CAS — 77086-21-6 (dizocilpine); 77086-22-7 (dizocilpine maleate).

Profile

Dizocilpine is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It has been investigated for its antiepileptic properties as well as for a potential role in various other neurological disorders including the prevention of damage due to cerebral ischaemia.

◊ Dizocilpine has good anticonvulsant activity but as it causes alarming psychotropic effects it was abandoned as a possible therapy for epilepsy.[1] Interest in its use as a possible therapy for stroke continued.

1. Richens A. New antiepileptic drugs. *Br J Hosp Med* 1990; **44:** 241.

Dolomite

Profile

Dolomite is a naturally occurring mineral composed of calcium and magnesium carbonate. It has been used as a nutritional supplement but may contain lead and other toxic metals and is not generally recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Frutin; ***USA:*** Dolomite.

Multi-ingredient: ***Austral.:*** Prosteo†.

Dong Quai

Angelica Sinensis; Chinese Angelica; Dang Gui; Dang Qui; Danggui.

Pharmacopoeias. In *Chin.*, which specifies the root.
Br. includes separate monographs for Angelica Sinensis Root for use in Traditional Herbal Medicine, and Processed Angelica Sinensis Root for use in Traditional Herbal Medicinal Product.
BP 2008 (Angelica Sinensis Root for use in THM). The dried whole root of *Angelica sinensis* (*A. polymorpha* var. *sinensis*). It contains not less than 0.1% of *Z*-ligustilide ($C_{12}H_{14}O_2$ = 190.2), calculated with reference to the dried material. Protect from moisture.
BP 2008 (Processed Angelica Sinensis Root for use in THMP). The smoked, sliced, and dried root of Angelica Sinensis Root for use in THM. It contains not less than 0.1% of *Z*-ligustilide, calculated with reference to the dried material. Protect from moisture.

Profile

Dong quai is the dried root of Chinese angelica, *Angelica sinensis* (*A. polymorpha* var. *sinensis*) (Apiaceae). It is used in traditional Chinese medicine in the treatment of menstrual and menopausal disorders, respiratory disorders, and herpes zoster infections.

Other *Angelica* spp. employed in herbal medicine are described on p.2258.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Capsella Complex; Dong Quai Complex; Extralife Meno-Care; Feminine Herbal Complex; ***Canad.:*** Natural HRT; ***Hong Kong:*** Phytoestrin†; ***Singapore:*** Phytoestrin.

Drosera

Droséra; Droserae herba; Herba Rorellae; Rorela; Ros Solis; Rossolis; Sonnentau; Sundew.

Profile

Drosera consists of the air-dried entire plant *Drosera rotundifolia* (Droseraceae) and other *Drosera* spp. Preparations of drosera have been used for its reputed value in respiratory disorders.

Homoeopathy. Drosera has been used in homoeopathic medicines under the following names: Drosera rotundifolia; Dros rot.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Makatussin Saft Drosera†; Makatussin Tropfen Drosera†.

Multi-ingredient: ***Austral.:*** Asa Tones; ***Austria:*** Pilka; Pilka Forte; ***Belg.:*** Saintbois; ***Chile:*** Fitotos; Gotas Nican†; Notosil†; Pectoral Pasteur; Pulmagol; Ramistos; Sedotus†; ***Cz.:*** Bronchicum Pflanzlicher Hustenstiller†; Stodal; Tussilen; ***Fr.:*** Pastilles Monleon; Tussidoron; ***Ger.:*** Bronchicum Pflanzlicher†; Drosithym-N; Lomal†; Makatussin Tropfen forte†; Tussiflorin Hustenstiller†; ***Indon.:*** Silex; ***Israel:*** Pilka; ***Mex.:*** Citos; Fen-y-Tos; ***Port.:*** Broncodiazina; Pilka F†; ***S.Afr.:*** Cough Elixir; ***Spain:*** Broncovital†; Pazbronquial; Pilka; ***Switz.:*** Bromocod N; Bronchofluid N†; Demo Elixir pectoral N; DemoTussil; Dragees S contre la toux†; Drosinula†; Escotussin; Famel; Gouttes contre la toux "S"; Makaphyt Gouttes antitussives; Makaphyt Sirop; Nican; Pastilles bronchiques S nouvelle formule; Pastilles pectorales Demo N; Pilka†; Sirop pectoral contre la toux S; Sirop S contre la toux et la bronchite; Thymodrosin N†; Tussanil Compositum†; ***Venez.:*** Codebromil; Dromil Sauco; Pi-Fedrin.

Drotaverine *(rINN)*

Drotaverina; Drotavérine; Drotaverinum. 1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline.

Дротаверин

$C_{24}H_{31}NO_4$ = 397.5.

CAS — 14009-24-6 (drotaverine); 985-12-6 (drotaverine hydrochloride).

ATC — A03AD02.

ATC Vet — QA03AD02.

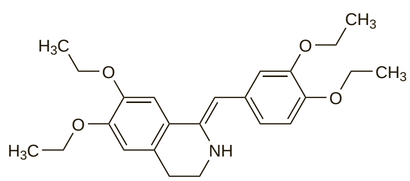

Pharmacopoeias. *Pol.* includes Drotaverine Hydrochloride.

Profile

Drotaverine is used as an antispasmodic in the management of biliary-tract, urinary-tract, and gastrointestinal spasm, in usual oral doses of 120 to 240 mg daily in divided doses. It has also been given by intramuscular or intravenous injection.

◊ References.

1. Bolaji OO, *et al.* Pharmacokinetics and bioavailability of drotaverine in humans. *Eur J Drug Metab Pharmacokinet* 1996; **21:** 217–21.
2. Romics I, *et al.* The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int* 2003; **92:** 92–6.
3. Singh KC, *et al.* Drotaverine hydrochloride for augmentation of labor. *Int J Gynaecol Obstet* 2004; **84:** 17–22.

Porphyria. Drotaverine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Proconfial†; ***Cz.:*** No-Spa; ***Hung.:*** No-Spa; ***India:*** Drotin; Drovera†; DVN; ***Malaysia:*** No-Spa; ***Philipp.:*** No-Spa; ***Pol.:*** Galospa; No-Spa; ***Rus.:*** Bезра (Беспа); No-Spa (Но-Шпа); Spacovin (Спаковин); Spasmol (Спазмол); Spazoverin (Спазоверин); ***Thai.:*** D-Tarine†; Deolin; No-Spa; Spablock; Spacovin; Sparax; Sparta; Toverine.

Multi-ingredient: ***Cz.:*** Quarelin†; ***Hung.:*** Algoflex-M; Algopyrin Complex; No-Spalgin; Paniverin; Quarelin; ***Rus.:*** No-Spalgin (Но-Шпалгин).

Dulcamara

Bittersüss; Bittersweet; Douce-Amère; Dulcamarae Caulis; Woody Nightshade.

Profile

Dulcamara consists of the dried stems and branches of *Solanum dulcamara* (Solanaceae). It was formerly a popular remedy for chronic rheumatism and skin eruptions and was given as an infusion.

All parts of the plant are poisonous due to the presence of solanaceous alkaloids. The berries have caused poisoning in children. Adverse effects are treated as described under Atropine, p.1220.

Homoeopathy. Dulcamara has been used in homoeopathic medicines under the following names: Solanum dulcamara; Dulc.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Cefabene; Solapsor†.

Multi-ingredient: ***Austria:*** Dermatodoron; ***Ger.:*** Dermatodoron; ***S.Afr.:*** Cough Elixir; Dermatodoron.

Ebselen *(rINN)*

DR-3305; Ebsélène; Ebseleno; Ebselenum; PZ-51. 2-Phenyl-1,2-benzisoselenazolin-3-one.

Эбселен

$C_{13}H_9NOSe$ = 274.2.

CAS — 60940-34-3.

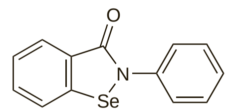

Profile

Ebselen has antoxidant activity and inhibits lipid peroxidation. It has been investigated as a neuroprotectant in stroke.

◊ References.

1. Yamaguchi T, *et al.* Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. *Stroke* 1998; **29:** 12–17.
2. Saito I, *et al.* Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1998; **42:** 269–78.

Echinacea

Black Sampson; Blyškiųjų ežiuolių šaknys (pale coneflower root); Brauneria; Coneflower; Echinacea angustifolia, racine d' (narrow-leaved coneflower root); Echinacea pallida, racine d' (pale coneflower root); Echinacea purpurea, parties aériennes fleuries d' (purple coneflower herb); Echinacea purpurea, racine d' (purple coneflower root); Echinaceae angustifoliae radix (narrow-leaved coneflower root); Echinaceae pallidae radix (pale coneflower root); Echinaceae purpureae herba (purple coneflower herb); Echinaceae purpureae radix (purple coneflower root); Equinácea; Kaitapäivänhatunjuuri (narrow-leaved coneflower root); Kořen třapatky bledé (pale coneflower root); Kořen třapatky úzkolisté (narrow-leaved coneflower root); Läkerudbeckiarot (pale coneflower root); Liten läkerudbeckiarot (narrow-leaved coneflower root); Rohtopäivänhatunjuuri (pale coneflower root); Rudbeckia; Siauralapių ežiuolių šaknys (narrow-leaved coneflower root); Sonnenhutkraut.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Narrow-Leaved Coneflower Root; Echinaceae Angustifoliae Radix). The dried, whole, or cut underground parts of *Echinacea angustifolia*. It contains a minimum 0.5% of echinacoside ($C_{35}H_{46}O_{20}$ = 786.7), calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 6.2 (Pale Coneflower Root; Echinaceae Pallidae Radix). The dried, whole, or cut underground parts of *Echinacea pallida*. It contains a minimum 0.2% of echinacoside calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 6.2 (Purple Coneflower Herb; Echinaceae Purpureae Herba). The dried, whole or cut flowering aerial parts of *Echinacea purpurea*. It contains a minimum of 0.1% of the sum of caftaric acid ($C_{13}H_{12}O_9$ = 312.2) and cichoric acid ($C_{22}H_{18}O_{12}$ = 474.4). Store uncomminuted.

Ph. Eur. 6.2 (Purple Coneflower Root; Echinaceae Purpureae Radix). The dried, whole or cut underground parts of *Echinacea purpurea*. It contains a minimum of 0.5% of the sum of caftaric acid ($C_{13}H_{12}O_9$ = 312.2) and cichoric acid ($C_{22}H_{18}O_{12}$ = 474.4). Store uncomminuted.

USP 31 (Echinacea Angustifolia). It consists of the dried rhizome and roots of *Echinacea angustifolia* (Asteraceae), harvested in the autumn after 1 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 31 (Echinacea Pallida). It consists of the dried rhizome and roots of *Echinacea pallida* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 31 (Echinacea Purpurea Root). It consists of the dried rhizome and roots of *Echinacea purpurea* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 31 (Echinacea Purpurea Aerial Parts). The aerial parts of *Echinacea purpurea* (Asteraceae) harvested during the flowering stage. It contains not less than 1.0% of chicoric acid, and not less than 0.01% of dodecatetraenoic acid isobutylamides ($C_{16}H_{25}NO$), calculated on the dried basis. Store in airtight containers. Protect from light.

Profile

Echinacea, the dried, whole, or cut underground parts of *Echinacea angustifolia* (*Brauneria angustifolia*), *E. pallida* (*B. pallida*), or *E. purpurea*, or the aerial parts of *E. purpurea*, is reported to have immunostimulant properties. It is used in herbal preparations for the prophylaxis of bacterial and viral infections.

Homoeopathy. Echinacea has been used in homoeopathic medicines under the following names: Echinacea purpurea; Echinacea purpurea ex planta tota; Echinacea purpurea, Planta tota; Echinacea angustifolia; Echin. an.

Adverse effects. The most common adverse effects reported on short-term use of echinacea were gastrointestinal and skin-related; these were generally transient and reversible.[1] Hypersensitivity reactions including anaphylaxis have been reported.[1-4]

1. Huntley AL, *et al.* The safety of herbal medicinal products derived from Echinacea species. *Drug Safety* 2005; **28:** 387–400.
2. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002; **88:** 42–51.
3. Health Canada. Natural health products and adverse reactions. *Can Adverse React News* 2004; **14** (1): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1_e.pdf (accessed 11/08/05)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Adverse reactions to complementary medicines. *Aust Adverse Drug React Bull* 2005; **24:** 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0502.htm (accessed 11/08/05)

Pharmacokinetics. The pharmacokinetics of alkamides extracted from *Echinacea angustifolia* roots have been studied[1] in human subjects. Fast absorption of some alkamides was shown after oral use; highly lipophilic alkamides could not be detected in plasma.

1. Woelkart K, *et al.* Bioavailability and pharmacokinetics of alkamides from the roots of Echinacea angustifolia in humans. *J Clin Pharmacol* 2005; **45:** 683–9.

Use in respiratory disorders. Echinacea is widely used in herbal preparations to treat upper respiratory-tract infections such as the common cold. Studies[1-3] have produced conflicting results, but systematic reviews suggest that most have methodological flaws[4] rendering evidence of efficacy unconvincing.[4,5] A meta-analysis[6] of 14 randomised controlled studies suggested that echinacea does have a benefit in decreasing the incidence and duration of the common cold, although it was acknowledged that larger prospective studies controlling for several variables (e.g. species) are needed before it can be routinely recommended. Comparative evaluation of specific preparations is also difficult because of varying composition. Evaluation of the effect of 3 extracts of *Echinacea angustifolia* root, each produced by a different extraction method and with defined phytochemical profiles, demonstrated no clinically significant effects by any of them on experimental rhinovirus infection or ensuing illness compared with placebo.[7] Alkamides, polysaccharides, and caffeic acid derivatives, which have been proposed as the active components of echinacea preparations, were present in varying amounts in the extracts.

1. Turner RB, *et al.* Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob Agents Chemother* 2000; **44:** 1708–9.
2. Barrett BP, *et al.* Treatment of the common cold with unrefined echinacea: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; **137:** 939–46.
3. Taylor JA, *et al.* Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. *JAMA* 2003; **290:** 2824–30.
4. Caruso TJ, Gwaltney JM. Treatment of the common cold with echinacea. *Clin Infect Dis* 2005; **40:** 807–10.
5. Linde K, *et al.* Echinacea for preventing and treating the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 31/07/08).
6. Shah SA, *et al.* Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *Lancet Infect Dis* 2007; **7:** 473–80.
7. Turner RB,*et al.* An evaluation of Echinacea angustifolia in experimental rhinovirus infections. *N Engl J Med* 2005; **353:** 341–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Echinacin; ***Austria:*** Echinacin; Echinaforce; Sanvita Immun; ***Belg.:*** Echinacin; ***Braz.:*** Enax; Equinacea†; Imunnal; Imunocel†; Imunogreen; ***Canad.:*** Citranacea†; Triple Blend Echinacea; ***Cz.:*** Echinacin; Immunal; ***Ger.:*** aar vir; Cefatox†; Echan; Echifit†; Echiherb†; Echinacin; Echinaforce; Echinapur; Echinatur; Episcorit; Esberitox mono; Lymphozil; Pascotox forte-Injektopas†; Pascotox mono†; Pascotox Purpurea; Resistan mono; Resplant†; toxi-loges; Wiedimmun†; ***Gr.:*** Echinacin; ***Hung.:*** Echinacin; ***Ital.:*** EuMunil; ***Mex.:*** Inmune Booster†; Regripax; ***Pol.:*** Echinapur; Echinerba; Immunal; Lymphozil; Purex; ***Rus.:*** Immunal (Иммунал); Immunorm (Иммунорм); ***Spain:*** Echinacin; Ekian; Revitonil; ***Switz.:*** Echinacin; Echinaforce; Echina-Med; Echiplant†; ***UK:*** Benylin Active Response†; Echinacea; Echinaforce; Phytocold; Skin Clear; ***Venez.:*** Flucaps.

Multi-ingredient: ***Arg.:*** Parodontax Fluor; SX-22; ***Austral.:*** Andrographis Complex; Andrographis Compound; Astragalus Complex; Broncafect; Cats Claw Complex; Cold and Flu Relief†; Cough Relief†; Diaco; Digest; Echinacea 4000; Echinacea ACE + Zinc; Echinacea Complex; Echinacea Lozenge; Euphrasia Complex; Flavons; Galium Complex†; Gartech; Herbal Cleanse†; Herbal Cold & Flu Relief†; Lifesystem Herbal Plus Formula 8 Echinacea†; Logicin Natural Lozenges†; Odourless Garlic†; Proyeast†; Sambucus Complex†; Urgenin†; Urinase†; ***Austria:*** Esberitox; Parodontax; Spasmo-Urgenin; Urgenin; ***Belg.:*** Medica Junior; Urgenin; ***Braz.:*** Infantoss†; Malvatricin Natural; Malvatricin Natural Organic; Malvatricin Natural Soft; Parodontax; ***Canad.:*** Bentasil Licorice with Echinacea†; Benylin First Defense†; Echinacea Goldenseal Formula†; ***Chile:*** Citro-C; Paltomiel Plus; ***Ger.:*** Ermsech†; Esberitox N; Hewenephron duo†; ***Hong Kong:*** Urgenin; ***Indon.:*** Biofos; Curmunos; Ekinase; Flavin; Hepasil; Hepatin; Imboost; Imboost Force; Imudator; Norflam; Primunox; Proimbus; Proza; Stamino; Star-Muno; Stimox; Tribost; ***Israel:*** Parodontax†; Urgenin; ***Ital.:*** Bodyguard; Dermilia Flebozin; Golatux; Immumil Plus; Immumil†; Immun-up; Influ-Zinc; Nepiros; Probigol; Promix 3†; Promix†; Ribovir; Sclerovis H; ***Malaysia:*** Echinacea Plus†; Esberitox N; Total Man†; ***Mex.:*** Gripaleta†; ***NZ:*** Lice Blaster; Strepsils Echinacea Defence; ***Pol.:*** Cardiobonisol; Echinasal; Esberitox N; Immunofort; Pectobonisol; Plantifort; Reumaherb; ***Port.:*** Neo Urgenin; Spasmo-Urgenin†; Vitace; ***Rus.:*** Prostanorm (Простанорм); ***S.Afr.:*** Spasmo-Urgenin†; Wecesin; ***Singapore:*** Noricaven†; Proza; ***Spain:*** Neo Urgenin; Spasmo-Urgenin; Urgenin; ***Switz.:*** Demonatur Capsules contre les refroidissements; Demonatur Dragees pour les reins et la vessie; Drosana Resiston avec vitamine C; Esberitop; Gel a la consoude; Kytta Gel†; Parodontax F†; Parodontax†; Phytomed Prosta†; Prosta-Caps Chassot N; Spagymun; Spagyrom; Wala Echinacea; Wecesin†; ***Thai.:*** Spasmo-Urgenin; ***UK:*** Antifect; Echinacea; Goodypops; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Modern Herbals Cold & Catarrh; Revitonil; Sinotar.

Eculizumab *(USAN, rINN)*

Éculizumab; Eculizumabum; h5G1.1. Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer.

Экулизумаб

CAS — 219685-50-4.
ATC — L04AA25.
ATC Vet — QL04AA25.

Profile

Eculizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p.2286) by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia (p.1043). Eculizumab is given by intravenous infusion over 25 to 45 minutes in a dose of 600 mg every 7 days for the first 4 weeks, followed by 900 mg 7 days later, and then 900 mg every 14 days thereafter. The infusion should be diluted to 5 mg/mL in sodium chloride 0.45% or 0.9%, glucose 5%, or Ringer's injection. The infusion rate may be decreased in the event of infusion reactions but the total infusion time should not exceed 2 hours; the infusion may be stopped in severe reactions. Patients should be monitored for at least one hour after the infusion for signs of infusion reactions. Patients who stop treatment altogether are at increased risk for serious haemolysis and should be monitored for 8 weeks.

Use of eculizumab increases susceptibility to meningococcal infections and patients who are not up to date with their meningococcal vaccinations should be vaccinated at least 2 weeks before receiving the first dose of eculizumab and receive booster vaccinations according to current guidelines. Patients should be monitored during treatment for early signs of meningococcal infections and treated as required. Susceptibility to other infections may also increase and eculizumab should be used with caution in patients with systemic infection. Other adverse effects that have been reported with eculizumab include headache, nasopharyngitis, back pain, and nausea.

◊ References.

1. Hillmen P, *et al.* The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006; **355:** 1233–43.
2. Hillmen P, *et al.* Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2007; **110:** 4123–8.
3. Schubert J, *et al.* Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 2008; **142:** 263–72.
4. Charneski L, Patel PN. Eculizumab in paroxysmal nocturnal haemoglobinuria. *Drugs* 2008; **68:** 1341–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Soliris; ***Fr.:*** Soliris; ***Port.:*** Soliris; ***UK:*** Soliris; ***USA:*** Soliris.

Eledoisin *(rINN)*

ELD-950; Eledoisina; Élédoïsine; Eledoisinum. 5-Oxo-Pro-Pro-Ser-Lys-Asp-Ala-Phe-Ile-Gly-Leu-Met-NH_2.

Элeдоизин

$C_{54}H_{85}N_{13}O_{15}S$ = 1188.4.
CAS — 69-25-0 (eledoisin); 10129-92-7 (eledoisin trifluoroacetate).

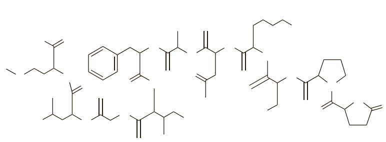

Profile

Eledoisin is a peptide extracted from the posterior salivary glands of certain small octopuses (*Eledone* spp., Mollusca), or obtained by synthesis. Its actions resemble those of substance P; it is a potent vasodilator and increases capillary permeability. It has been given as the trifluoroacetate in eye drops to stimulate lachrymal secretion in Sjögren's syndrome and other dry eye conditions.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Eloisin.

Eniluracil *(BAN, USAN, rINN)*

776C85; Eniluracilo; Eniluracilum. 5-Ethynyluracil.

Энилурацил

$C_6H_4N_2O_2$ = 136.1.
CAS — 59989-18-3.

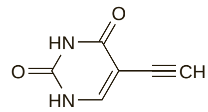

Profile

Eniluracil inactivates the enzyme dihydropyrimidine dehydrogenase, which plays an important role in the metabolism of the antineoplastic fluorouracil (p.723). Eniluracil increases the bioavailability of fluorouracil, particularly when the latter is given by mouth. It is being investigated as an adjunct to fluorouracil therapy in the treatment of colorectal, breast, and pancreatic cancer. However, the optimal dose and regimen remains to be determined.

Entsufon Sodium *(USAN, rINNM)*

Entsufón sódico; Entsufon Sodique; Natrii Entsufonum. Sodium 2-{2-[2-(*p*-1,3,3-tetramethylbutylphenoxy)ethoxy]ethoxy}ethanesulfonate.

Натрий Энтсуфон

$C_{20}H_{33}NaO_6S$ = 424.5.
CAS — 55837-16-6 (entsufon); 2917-94-4 (entsufon sodium).

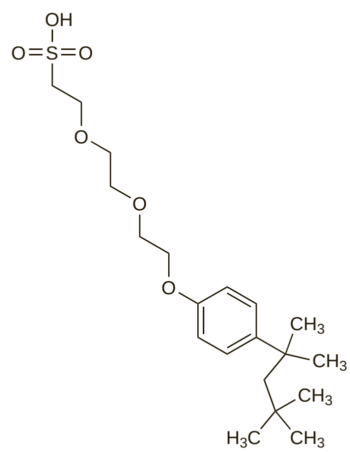

(entsufon)

Profile

Entsufon sodium is a detergent used as a soap substitute for cleansing the skin.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Canad.:*** pHisoHex; ***USA:*** pHisoHex.

Epostane *(BAN, USAN, rINN)*

Épostane; Epostano; Epostanum; Win-32729. 4α,5α-Epoxy-3,17β-dihydroxy-4β,17α-dimethyl-5α-androst-2-ene-2-carbonitrile.

Эпостан

$C_{22}H_{31}NO_3$ = 357.5.
CAS — 80471-63-2.

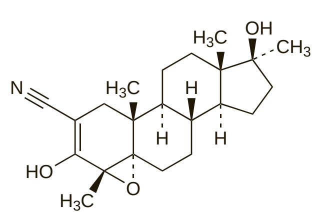

Profile

Epostane has antiprogestogenic activity and has been investigated for use with prostaglandins in the termination of pregnancy, and as a uterine stimulant for the induction of labour.

Eprodisate Disodium *(USAN, rINNM)*

Éprodisate Disodique; Eprodisato disódico; Eprodisatum Dinatricum; NC-503. Disodium propane-1,3-disulfonate.

Динатрий Эпродисат

$C_3H_6Na_2O_6S_2$ = 248.2.
CAS — 36589-58-9.

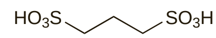

(eprodisate)

Profile

Eprodisate disodium is a glycosaminoglycan mimetic under investigation for the prevention of amyloid fibril formation and deposition in the treatment of AA amyloidosis.

◊ References.

1. Dember LM, *et al.* Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; **356:** 2349–60.

Equisetum

Åkerfräken; Asiūklių žolė; Cola de Caballo; Equiseti herba; Equiseto; Herba Equiseti; Horsetail; Peltokorte; Prêle; Prêle, tige de; Přesličková nať; Schachtelhalmkraut; Ziele skrzypu.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Equisetum Stem; Horsetail BP 2008). The whole or cut, dried sterile aerial parts of *Equisetum arvense*. It contains a minimum of 0.3% of total flavonoids expressed as isoquercitroside ($C_{21}H_{20}O_{12}$ = 464.4), calculated with reference to the dried drug.

Profile

Equisetum is an ingredient of herbal preparations that have been used in the treatment of genito-urinary and respiratory disorders. Similar preparations have been used in the treatment of cardiovascular disorders, rheumatic disorders, liver disorders, constipation, and as a tonic.

The related species *Equisetum hiemale* is used in China for the treatment of eye disorders.

Homoeopathy. Equisetum has been used in homoeopathic medicines under the following names: Equisetum arvense.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Bioglan Silica-Vite; ***Cz.:*** Nat Preslicky†; Preslicka; Preslickova; ***Fr.:*** Siliprele; ***Ger.:*** Lomaren; Nieron E; Prodiuret†; Pulvhydrops Mono†; Redaxa fit; Zinnkraut-Tropfen†; ***Ital.:*** Bioequiseto; Osteosil†.

Multi-ingredient: ***Arg.:*** Arceligasol; Centella Queen Complex; Centellase Gel; Silueta Plus; ***Austral.:*** Cal Alkyline; Extralife Fluid-Care; Medinat Esten†; Serenoa Complex†; Silicic Complex†; ***Austria:*** Blasentee St Severin; Entschlackender Abfuhrtee EF-EM-ES; Nierentee St Severin; Pneumopan; St Bonifatius-Tee; Uropurat; ***Chile:*** Nature Complex Reduct-Te; Reduc-Te; ***Cz.:*** Alvisan Neo; Antirevmaticky Caj; Blasen- und Nierentee†; Nephrosal†; Senalax; Species Diureticae Planta†; Stoffwechseltee N†; Urcyston Planta; ***Fr.:*** Arterase; Obeflorine; ***Ger.:*** Equisil N; Eviprostat N; Harntee STADA; Hevert-Blasen-Nieren-Tee N; nephro-loges; Nephroselect M; Nieron-Tee N†; Presselin Nieren-Blasen K 3†; Presselin Stoffwechsel-Tee Hapeka 225 N†; Solidagoren N; Solum Ol; Tonsilgon; ***Indon.:*** Eviprostat; ***Ital.:*** Osteosil Calcium; Pik Gel; ***Jpn:*** Eviprostat; ***Pol.:*** Betasol; Cholesol; Nefrobonisol; NeoFitolizyna; Reumosol; Sanofil; ***Rus.:*** Herbion Urological Drops (Гербион Урологические Капли); Tonsilgon N (Тонзилгон Н); ***Singapore:*** Eviprostat; ***Spain:*** Diurette; Diurinat; Natusor Artilane†; Natusor Harpagosinol†; Natusor Infenol†; Natusor Renal†; Resolutivo Regium; ***Switz.:*** Nephrosolid; Tisane Diuretique; Urinex; ***UK:*** Antiglan; Antitis; Aqualette; Kas-Bah; ***Venez.:*** Demerung; Rheu-Tarx 1.

Etaden

Ethaden. 2-[(6-Amino-1*H*-purin-8-yl)amino]ethanol.

$C_7H_{10}N_6O$ = 194.2.
CAS — 66813-29-4.

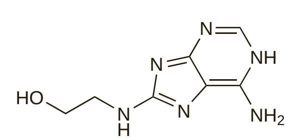

Profile

Etaden is used in the form of eye drops to stimulate epithelial regrowth.

Ethanethiol

Ethyl Mercaptan Thioethyl Alcohol; Ethylmercaptan; l-Ethanethiol.

Этантиол; Этил Меркаптан

C_2H_6S = 62.13.
CAS — 75-08-1.

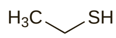

Profile

Mercaptans such as ethanethiol have an extremely disagreeable odour that is detectable by humans at very low concentrations and therefore they are added as a safety measure to odourless gases such as natural gas. Inhalation of high concentrations of ethanethiol can cause dizziness, headache, nausea, vomiting, and unconsciousness.

Ethaverine Hydrochloride *(rINNM)*

Éthavérine, Chlorhydrate d'; Ethaverini Hydrochloridum; Hidrocloruro de etaverina. 6,7-Diethoxy-1-(3,4-diethoxybenzyl)isoquinoline hydrochloride.

Этаверина Гидрохлорид

$C_{24}H_{29}NO_4,HCl$ = 432.0.
CAS — 486-47-5 (ethaverine); 985-13-7 (ethaverine hydrochloride).

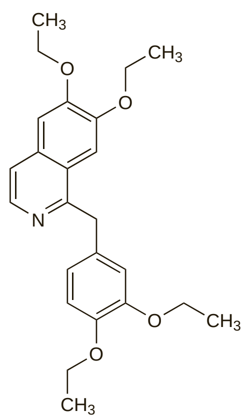

(ethaverine)

Profile

Ethaverine is the tetraethoxy analogue of papaverine (p.2191) and has been used as the hydrochloride as an antispasmodic in respiratory-tract, biliary, gastrointestinal, and genito-urinary disorders. It has also been used in migraine, vascular disorders and as an antiarrhythmic.

Ethaverine sulfamate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Asthma Efeum; Gastripan; Oddispasmol; ***Braz.:*** Eufermen†; ***Thai.:*** Elzym†.

Ethyl Cinnamate

Cinamato de etilo. Ethyl (*E*)-3-phenylprop-2-enoate.

$C_{11}H_{12}O_2$ = 176.2.
CAS — 103-36-6.

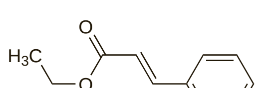

Pharmacopoeias. In *Br.*

BP 2008 (Ethyl Cinnamate). A clear, colourless or almost colourless liquid with a fruity, balsamic odour. Practically insoluble in water; miscible with most organic solvents.

Profile

Ethyl cinnamate is used as a flavour and perfume; it is an ingredient of Tolu-flavour Solution (BP 2008).

Preparations

BP 2008: Tolu-flavour Solution.

Ethyl Lactate

Etilo, lactato de.

Этиллактат

$C_5H_{10}O_3$ = 118.1.
CAS — 97-64-3.

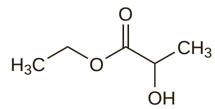

Profile

Ethyl lactate has been applied topically in the treatment of acne vulgaris. It is reported to lower the pH within the skin thereby exerting a bactericidal effect.

Ethyl lactate is also used in the flavouring of foods.

Ethyl Nitrite

Nitrous Acid Ethyl Ester; Nitrous Ether.

Этилнитрит

$C_2H_5NO_2$ = 75.07.
CAS — 109-95-5.

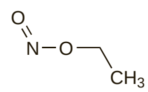

NOTE. Do not confuse with *O*-nitrosoethanol, a substance that has been referred to in the literature as 'ethyl nitrite gas'.

Profile

Ethyl nitrite has vasodilator effects similar to other volatile nitrites (see Amyl Nitrite, p.1437). Alcoholic solutions of ethyl nitrite (Ethyl Nitrite Spirit; Nitrous Ether Spirit; Sweet Nitre Spirit; Sp. Aether. Nitros.) have been used as a diaphoretic in the treatment of colds and fevers.

◊ Methaemoglobinaemia occurred in 2 infants given a folk remedy containing ethyl nitrite. Despite treatment with methylthionium chloride 1 infant died.[1]

1. Chilcote RR, *et al.* Sudden death in an infant from methemoglobinemia after administration of "sweet spirits of nitre". *Pediatrics* 1977; **59:** 280–2.

Preparations

Proprietary Preparations (details are given in Part 3)

S.Afr.: Witdulsies.

Ethyl Oleate

Aethylis Oleas; Éthyle, oléate d'; Ethylis oleas; Ethyl-oleát; Etiloleát; Etiloleatas; Etyloleat; Etyylioleaatti; Oleato de etilo.

$C_{20}H_{38}O_2$ = 310.5.
CAS — 111-62-6.

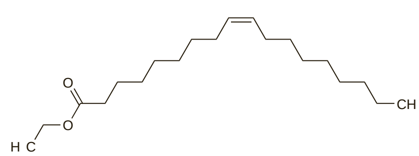

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Ethyl Oleate). A clear, pale yellow or colourless liquid. It consists of the ethyl esters of fatty acids, mainly oleic acid. It may contain a suitable antioxidant. Practically insoluble in water; miscible with alcohol, with dichloromethane, and with petroleum spirit (40° to 60°). Protect from light.

USNF 26 (Ethyl Oleate). It consists of esters of ethyl alcohol and high-molecular-weight fatty acids, principally oleic acid. A mobile, practically colourless liquid. Insoluble in water; miscible with alcohol, with vegetable oils, with liquid paraffin, and with most organic solvents. Store in airtight containers. Protect from light.

Incompatibility. Ethyl oleate dissolves some types of rubber and causes others to swell.

Profile

Ethyl oleate is used as an oily vehicle.

Ethyl Vanillin

Etilvanilina. 3-Ethoxy-4-hydroxybenzaldehyde.

$C_9H_{10}O_3$ = 166.2.
CAS — 121-32-4.

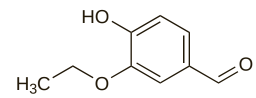

Pharmacopoeias. In *USNF.*

USNF 26 (Ethyl Vanillin). Fine, white or slightly yellowish crystals with a vanilla-like odour. M.p. is between 76° and 78°. Soluble 1 in 100 of water at 50° and 1 in 2 of alcohol; freely soluble in chloroform, in ether, and in solutions of alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile

Ethyl vanillin is used as a flavour and in perfumery to impart the odour and taste of vanilla.

Ethylene Glycol

Ethylene Alcohol; Etilen Glikol; Etilenglicol; Glikol etylenowy; Glycol. Ethane-1,2-diol.

$C_2H_6O_2$ = 62.07.
CAS — 107-21-1.

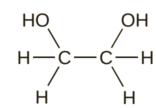

Adverse Effects

Toxic effects arising from ingestion of ethylene glycol result from its major metabolites: aldehydes, glycolate, lactate, and oxalate. Clinical features may be divided into three stages depending on the time elapsed since ingestion. In the first 12 hours, the patient may show signs of drunkenness and experience nausea and vomiting. Convulsions and neurological defects may occur. From 12 to 24 hours, there may be tachycardia, mild hypertension, pulmonary oedema, and heart failure. Between 24 and 72 hours, patients with severe ethylene glycol poisoning may experience flank pain and renal involvement with associated decreased plasma concentrations of calcium and bicarbonate, metabolic acidosis, deposition of oxalate in tissues and kidney tubules, proteinuria, oxaluria, haematuria, and renal failure. There may be respiratory failure, cardiovascular collapse, and sometimes coma and death. The fatal dose is reported to be about 100 mL.

Skin irritation and penetration have been reported after topical application.

Diethylene glycol produces similar toxicity, except that there is no conversion to oxalate and there is greater nephrotoxicity. Poisoning has followed adulteration of medicinal products with diethylene glycol.

◊ References.

1. Anonymous. Some wine to break the ice. *Lancet* 1985; **ii:** 254.
2. Vale JA, Buckley BM. Metabolic acidosis in diethylene glycol poisoning. *Lancet* 1985; **ii:** 394.
3. Buckley BM, Vale JA. Poisoning by alcohols and ethylene glycol. *Prescribers' J* 1986; **26:** 110–15.
4. Hanif M, *et al.* Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *BMJ* 1995; **311:** 88–91.
5. Lewis LD, *et al.* Delayed sequelae after acute overdoses or poisonings: cranial neuropathy related to ethylene glycol ingestion. *Clin Pharmacol Ther* 1997; **61:** 692–9.
6. O'Brien KL, *et al.* Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. *JAMA* 1998; **279:** 1175–80.
7. Singh J, *et al.* Diethylene glycol poisoning in Gurgaon, India, 1998. *Bull WHO* 2001; **79:** 88–95.
8. Hasbani MJ, *et al.* Encephalopathy and peripheral neuropathy following diethylene glycol ingestion. *Neurology* 2005; **64:** 1273–5.

Treatment of Adverse Effects

The stomach should be emptied by lavage if ingestion of ethylene glycol was within the preceding hour. Severe metabolic acidosis should be corrected. Hypocalcaemia may require correction with calcium gluconate in severe cases, although this is not usually done routinely because it may increase the formation of calcium oxalate crystals. Haemodialysis may be of value. Alcohol may be given by mouth or intravenously as it is a competitor of the metabolism of ethylene glycol. Alternatively fomepizole (p.1446), an alcohol-dehydrogenase inhibitor, may be used for the treatment of ethylene glycol poisoning.

◊ References.

1. Harry P, *et al.* Ethylene glycol poisoning in a child treated with 4-methylpyrazole. *Pediatrics* 1998; **102:** E31.

2. Barceloux DG, *et al.* American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *Clin Toxicol* 1999; **37:** 537–60.
3. Brent J, *et al.* Fomepizole for the treatment of ethylene glycol poisoning. *N Engl J Med* 1999; **340:** 832–8.
4. Borron SW, *et al.* Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet* 1999; **354:** 831.
5. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; **106:** 1489–91.
6. Brent J. Current management of ethylene glycol poisoning. *Drugs* 2001; **61:** 979–88.
7. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; **36:** 1085–9.

Pharmacokinetics

Ethylene glycol is absorbed from the gastrointestinal tract and is metabolised, chiefly in the liver, by alcohol dehydrogenase. Its breakdown products account for its toxicity and include aldehydes, glycolate, lactate, and oxalate.

◊ References.

1. Sivilotti ML, *et al.* Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. *Ann Emerg Med* 2000; **36:** 114–25.

Uses

Ethylene glycol is commonly encountered in antifreeze solutions and has been used illicitly to sweeten some wines. Diethylene glycol has been used similarly.

Ethylenediamine

Edamine *(USAN, pINN)*; Edamina; Édamine; Edaminum; Ethylendiamin; Ethylendiaminum; Éthylènediamine; Ethylenediaminum; Etilén-diamin; Etilendiaminas; Etyleenidiamiini; Etylendiamin; Etylenodiamina.

Эдамин

$C_2H_8N_2$ = 60.10.

CAS — 107-15-3 (anhydrous ethylenediamine); 6780-13-8 (ethylenediamine monohydrate).

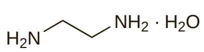

(ethylenediamine hydrate)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ethylenediamine). A clear, colourless or slightly yellow, hygroscopic liquid. On exposure to air, white fumes are evolved. On heating it evaporates completely. Miscible with water and with alcohol. Store in airtight containers. Protect from light.

USP 31 (Ethylenediamine). A clear, colourless or only slightly yellow liquid having an ammonia-like odour. It is strongly alkaline and may readily absorb carbon dioxide from the air to form a non-volatile carbonate. Miscible with water and with alcohol. Store in well-filled, airtight, glass containers.

Adverse Effects

Ethylenediamine is irritant to the skin and to mucous membranes. Severe exfoliative dermatitis has been reported after systemic use of preparations containing ethylenediamine. Hypersensitivity reactions are common. Concentrated solutions cause skin burns. Headache, dizziness, shortness of breath, nausea, and vomiting have also been reported after exposure to fumes. Ethylenediamine splashed onto the skin or eyes should be removed by flooding with water for a prolonged period.

Hypersensitivity. A review of allergy to ethylenediamine and aminophylline.[1]

1. Anonymous. Allergy to aminophylline. *Lancet* 1984; **ii :** 1192–3.

Precautions

Skin reactions may occur in patients given aminophylline after they have become sensitised to ethylenediamine. Cross-sensitivity with edetic acid and with some antihistamines has been reported.

Cross-sensitivity. It was reported that some topical corticosteroid creams, including *Tri-Adcortyl* in the UK,[1] and *Kenacomb*, *Halcicomb*, and *Viaderm* in Canada,[2] contained ethylenediamine and could cause unexpected cross-sensitivity reactions with piperazine[1] or aminophylline.[2]

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; **287:** 463–4.
2. Hogan DJ. Excipients in topical corticosteroid preparations in Canada. *Can Med Assoc J* 1989; **141:** 1032.

Uses and Administration

Ethylenediamine or ethylenediamine hydrate forms a stable mixture with theophylline to produce aminophylline or aminophylline hydrate. Ethylenediamine is widely used in the chemical and pharmaceutical industries and as an ingredient of some topical creams.

Etiproston Trometamol *(rINNM)*

Etiprostón trometamol; Etiproston Tromethamine; Étiprostone Trométamol; Etiprostonum Trometamolum. Trometamol salt of (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-2-[2-(phenoxymethyl)-1,3-dioxolan-2-yl]vinyl]cyclopentyl]-5-heptenoic acid.

Этипростон Трометамол

$C_{24}H_{32}O_7,C_4H_{11}NO_3$ = 553.6.

CAS — 59619-81-7 (etiproston).

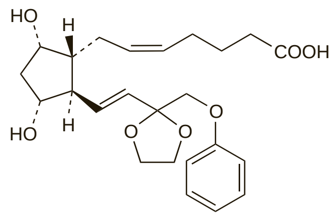

(etiproston)

Profile

Etiproston trometamol is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as a luteolytic in veterinary medicine.

Eucalyptus Leaf

Blahovičníkový list; Eucalypti folium; Eucalyptus, feuille d'; Eucalyptusblätter; Eukaliptų lapai; Eukaliptuszlevél; Eukalyptuksenlehti; Eukalyptusblad.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. (Eucalyptus Leaf). It consists of the whole or cut dried leaves of older branches of *Eucalyptus globulus*. The whole drug contains not less than 2% v/w of essential oil and the cut drug not less than 1.5% v/w of essential oil, both calculated with reference to the anhydrous drug. It has an aromatic odour of cineole. Protect from light.

Profile

Eucalyptus leaf has been used in oral preparations for coughs and associated respiratory-tract disorders. It is also used as a flavour. It is a source of eucalyptus oil (see below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Pre Calent; ***Austria:*** Euka; ***Braz.:*** Broncol; Tussifen†; ***Canad.:*** Beech Nut Cough Drops†; ***Chile:*** Codetol PM; Paltomiel; Paltomiel Plus; Pulmosina; ***Fr.:*** Balsofumine; Balsofumine Mentholee; ***Ger.:*** Em-medical†; Hevertopect N†; ***Israel:*** Gingisan; ***Ital.:*** Altuss; Fosfoguaiacol; ***NZ:*** Otrivine Menthol; ***Rus.:*** Insti (Инсти); ***S.Afr.:*** Bolus Eucalypti Comp; ***Spain:*** Bronpul†; Diabesor†; Llantusil†; Natusor Broncopul†; Natusor Gripotul†; Pastillas Antisep Garg M; Vapores Pyt; ***UK:*** Calrub; Collins Elixir Decongesant Pasilles; No-Sor Nose Balm; PainEaze; Revitonil; Sinose; Sudarub; ***Venez.:*** Gamasol†; Mixagel†.

Eucalyptus Oil

Blahovičníková silice; Esencia de Eucalipto; Essence d'Eucalyptus Rectifiée; Eucalipto, aceite esencial de; Eucalypti aetheroleum; Eucalypti Etheroleum; Eucalyptus, huile essentielle d'; Eukaliptų eterinis aliejus; Eukaliptuszolaj; Eukalyptusolja; Eukalyptusöljy; Ökaliptüs Yağı; Olejek eukaliptusowy; Oleum Eucalypti.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Eucalyptus Oil). A colourless or pale yellow liquid with a characteristic aromatic camphoraceous odour and a pungent camphoraceous taste. It is obtained by steam distillation and rectification from the fresh leaves or terminal branches of various species of *Eucalyptus* rich in cineole. The species mainly used are *E. globulus*, *E. polybractea*, and *E. smithii*. It contains not less than 70% w/w of cineole. Relative density 0.906 to 0.927. Soluble 1 in 5 of alcohol (70%). Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Adverse Effects and Precautions

The symptoms of poisoning with eucalyptus oil include gastrointestinal symptoms such as epigastric burning, nausea and vomiting, and CNS depression, including coma. Cyanosis, ataxia, miosis, pulmonary damage, delirium, and convulsions may occur. Deaths have been reported.

Oily solutions of eucalyptus oil were formerly used in nasal preparations, but this use is now considered unsuitable as the vehicle inhibits ciliary movements and may cause lipoid pneumonia.

◊ References.

1. Patel S, Wiggins J. Eucalyptus oil poisoning. *Arch Dis Child* 1980; **55:** 405.
2. Spoerke DG, *et al.* Eucalyptus oil: 14 cases of exposure. *Vet Hum Toxicol* 1989; **31:** 166–8.
3. Webb NJA, Pitt WR. Eucalyptus oil poisoning in childhood: 41 cases in south-east Queensland. *J Paediatr Child Health* 1993; **29:** 368–71.
4. Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Med J Aust* 1995; **163:** 177–80.
5. Anpalahan M, Le Couteur DG. Deliberate self-poisoning with eucalyptus oil in an elderly woman. *Aust N Z J Med* 1998; **28:** 58.
6. Darben T, *et al.* Topical eucalyptus oil poisoning. *Australas J Dermatol* 1998; **39:** 265–7.

Uses and Administration

Eucalyptus oil has been taken orally for catarrh and coughs and is an ingredient of many preparations. It has been used as an inhalation often in combination with other volatile substances. Eucalyptus oil has also been applied as a rubefacient and is used as a flavour. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Bosisto's Eucalyptus Spray; ***Ger.:*** Aspecton Eukaps; Broncho-Truw Erkaltungsbalsam; Eucotol†; Exeu; Gelodurat†; Pinimenthol Erkaltungsbad fur Kinder; Pinimenthol Erkaltungskapseln†; Pulmotin Inhalat; Schnupfen Kapseln; Tussidermil N; ***Pol.:*** Migrenol; ***Port.:*** Vicks Vaporub; ***Switz.:*** Nicobrevin N†.

Multi-ingredient: numerous preparations are listed in Part 3.

Eugenol

4-Allylguaiacol; Eugen.; Eugenic Acid; Eugénol; Eugenoli; Eugenolis; Eugenolum. 4-Allyl-2-methoxyphenol.

$C_{10}H_{12}O_2$ = 164.2.

CAS — 97-53-0.

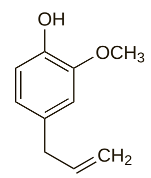

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*

Ph. Eur. 6.2 (Eugenol). A colourless or pale yellow liquid with a strong odour of clove. Practically insoluble in water and in glycerol; freely soluble in alcohol (70%); miscible with alcohol, with glacial acetic acid, with dichloromethane, and with fatty oils. Eugenol darkens in colour on exposure to air. Store in well-filled containers. Protect from light.

USP 31 (Eugenol). It is obtained from clove oil or from other sources. A colourless or pale yellow liquid having a strongly aromatic odour of clove. Upon exposure to air, it darkens and thickens. Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers. Protect from light.

Profile

Eugenol is a constituent of clove oil (p.2285) and some other essential oils. It is used in dentistry, often mixed with zinc oxide, as a temporary anodyne dental filling, and is an ingredient in oral hygiene preparations. Eugenol has been used as a flavour.

Eugenol is an irritant and sensitiser and can produce local anaesthesia. It is reported to inhibit prostaglandin synthesis.

For the pulmonary effects of eugenol inhalation from clove cigarettes, see Abuse, under Clove, p.2284.

◊ References.

1. Sarrami N, *et al.* Adverse reactions associated with the use of eugenol in dentistry. *Br Dent J* 2002; **193:** 257–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Analgesico Dental; ***USA:*** Red Cross Toothache.

Multi-ingredient: ***Arg.:*** Sicadentol Plus†; ***Austria:*** Ledermix; ***Belg.:*** Dentophar; Olbas; ***Braz.:*** Passaja†; Relampago†; Um Instante†; ***Chile:*** Astrijesan; Listermint Con Fluor; ***Cz.:*** Alvogyl; Parodontal F5†; ***Denm.:*** Ledermix†; ***Fr.:*** Alodont; Pectoderme†; ***Ger.:*** Ledermix; ***Gr.:*** Counterpain; ***Hong Kong:*** Begesic; Counterpain; Flanil; ***Indon.:*** Counterpain; Counterpain-PXM; Lafalos; Molakrim; Nufasic; Painkila; Remakrim; Stop X; Zeropain; ***Israel:*** Dentin; ***Ital.:*** Creosoto Composto; Eugenol-Guaiacolo Composto; Odongi; Odontalgiche (Dentali)†; ***Malaysia:*** Flanil; ***Philipp.:*** Begesic; Counterpain; ***S.Afr.:*** Counterpain; ***Singapore:*** Antipain; Begesic; Counterpain; Flanil; ***Spain:*** Alvogil; Piorlis; Tangenol†; Tifell†; ***Switz.:*** Alodont†; Alvogyl; Benzocaine PD; Ledermix; ***Thai.:*** Begesic†; Centropain; Counterpain; Counterpain Plus; Filup; Flanil; Heat Cream; Hot Ize; Masabalm; Muscalax; Neotica†; Nox-Pain; Olympic Balm†; Painza; Reduxpain; Sancago; Stopain; X-Pain; ***UK:*** Ledermix; ***Venez.:*** Flemicaine.

Euphorbia

Euforbia; Pill-bearing Spurge; Snake Weed.

Pharmacopoeias. *Chin.* includes monographs for *Euphorbia humifusa* or *E. maculata* herb and *E. pekinensis* root.

Profile

Euphorbia, the aerial parts of *Euphorbia hirta* (*E. pilulifera*, *Chamaesyce hirta*) (Euphorbiaceae), has sedative and expectorant properties and is used in the treatment of asthma and other respiratory-tract disorders. It has also been used for intestinal amoebiasis.

Other *Euphorbia* spp. are used for a variety of disorders. The seeds and latex of *E. lathyrus* (caper spurge) have been used as a purgative but are too toxic for general use. Many species have been used as arrow poisons.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Thankgod.

Multi-ingredient: ***Austral.:*** Asa Tones; Euphorbia Complex; Procold†; Sambucus Complex†; ***Belg.:*** Toularynx; ***Canad.:*** Sirop Cocillana Codeine; Sirop Cocillana Compose; ***Hong Kong:*** Cocillana Christo; Cocillana Compound; Mefedra-N†; ***UK:*** Antibron.

Euphrasia

Augentrost; Eufrasia; Euphraise; Eyebright.

Profile

Euphrasia, the aerial parts of various *Euphrasia* spp. including *E. rostkoviana* and *E. officinalis* (Scrophulariaceae), has been used topically for blepharitis, conjunctivitis, and other eye disorders. However, such use is not generally recommended. Euphrasia has also been used for nasal catarrh and sinusitis, and to prevent snoring.

Homoeopathy. Euphrasia has been used in homoeopathic medicines under the following names: Euphrasia officinalis; Euphrasia ex planta tota; Euph. of.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Snore Calm.

Multi-ingredient: ***Austral.:*** Bilberry Plus; Euphrasia Complex; Euphrasia Compound; Eye Health Herbal Plus Formula 4; Lifesystem Herbal Plus Formula 5 Eye Relief†; Sambucus Complex†; ***Ger.:*** Herba-Vision Augenbad; ***Ital.:*** Altacura Ipragocce; Eulux; Iridil; ***Malaysia:*** Eyebright Plus†; ***Switz.:*** Collypan; Oculosan; Tendro; ***UK:*** Se-Power; Vital Eyes.

Evening Primrose

King's Cureall; Onagre.

Profile

Evening primrose, the aerial parts of *Oenothera biennis* (Onagraceae) and related species of *Oenothera*, is reported to have sedative and astringent properties. It has been used in herbal preparations for respiratory and gastrointestinal disorders.

Evening primrose seed is the source of evening primrose oil (below), which is a source of essential fatty acids.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Sclerovis H.

Evening Primrose Oil

Helokkiöljy; Nakvišų aliejus; Nattljusolja; Oenotherae oleum; Olej wiesiołkowy; Olej wiesiołkowy bezpośredniego tłoczenia (virgin evening primrose oil); Onagra, aceite de; Onagre, huile d'; Pupalkový olej.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Evening Primrose Oil, Refined; Oenotherae Oleum Raffinatum). The fatty oil obtained from the seeds of *Oenothera biennis* or *O. lamarkiana* by extraction and/or expression, and then refined. A suitable antoxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.923. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40° to 60°). Store in well-filled, airtight containers under an inert gas. Protect from light.

Adverse Effects and Precautions

See Gamolenic Acid, p.2308.

Effects on the nervous system. Temporal lobe epilepsy was diagnosed after treatment with evening primrose oil in 3 patients who had previously been diagnosed as schizophrenic.[1] Tonic-clonic (grand mal) seizures occurred in 2 additional schizophrenic patients during treatment with evening primrose oil.[2] All of these patients had received or were taking phenothiazine antipsychotics.

1. Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. *Prostaglandins Med* 1981; **6:** 375–9.
2. Holman CP, Bell AFJ. A trial of evening primrose oil in the treatment of chronic schizophrenia. *J Orthomol Psychiatry* 1983; **12:** 302–4.

Uses and Administration

Evening primrose oil is a source of linoleic and gamolenic acid which are essential fatty acids of the omega-6 series that act as prostaglandin precursors (see p.2308). Evening primrose oil has been given orally for the symptomatic relief of atopic eczema in usual doses of up to 3 grams twice daily; it is also used topically as a cream for the relief of dry or inflamed skin. Evening primrose oil has also been given orally for mastalgia. Evening primrose oil has been studied in a variety of other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome. Mixtures of essential fatty acids (including EF-4, EF-12, and EF-27) derived from evening primrose oil and other oils have also been investigated in various disorders, including diabetic neuropathy, restenosis after angioplasty, and skin damage after radiotherapy.

◊ General references.

1. Kleijnen J. Evening primrose oil. *BMJ* 1994; **309:** 824–5.

Eczema. For the use of evening primrose oil as a source of essential fatty acids for the management of eczema, see under Gamolenic Acid, p.2308.

Mastalgia. For the use of evening primrose oil as a source of gamolenic acid for the management of mastalgia, see p.2308.

Menopausal disorders. Although there are anecdotal reports of benefit, a controlled study[1] found that evening primrose oil was no more effective than placebo for managing menopausal vasomotor symptoms (p.2077).

1. Chenoy R, *et al.* Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994; **308:** 501–3.

Multiple sclerosis. For the use of evening primrose oil in the management of multiple sclerosis, see under Gamolenic Acid, p.2308.

Premenstrual syndrome. For conflicting results from the use of evening primrose oil in premenstrual syndrome see under Gamolenic Acid, p.2308.

Rheumatoid arthritis. For the use of evening primrose oil as a source of gamolenic acid for the management of rheumatoid arthritis, see p.2309.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Efamol†; ***Austral.:*** Bioglan Primrose Micelle; Naudicelle†; ***Canad.:*** Efamol†; Primanol†; ***Cz.:*** Efamast†; Epogam†; ***Fr.:*** Bioleine; Bionagre; Bionagrol; Osmonagre; ***Ger.:*** Epogam; Gammacur; Linola gamma; Neobonsen; Unigamol†; ***India:*** Simrose; ***Irl.:*** Epogam†; Naudicelle; ***Malaysia:*** Primolin†; ***NZ:*** Efamol; ***Philipp.:*** Eveprim; ***Pol.:*** Linoeparol; Oeparol; ***S.Afr.:*** Primolin; ***Switz.:*** Biennol; Efamol; Epogam; ***UK:*** Efamol; Evening Gold; Evoprim; Linola Gamma; ***Venez.:*** Eve 500.

Multi-ingredient: ***Austral.:*** Bioglan Arthri Plus; Bioglan Ginger-Vite Forte; Bioglan Primrose-E; Bioglan Zellulean with Escin; Efalex†; Efamarine†; For Women Multi Plus EPO; Maxepa & EPO†; Medinat PMT-Eze†; Naudicelle Marine†; PMS Support†; ***Canad.:*** Efalex†; Glucosamine Joint & Muscle Cream with MSM†; Primanol Borage Oil; ***Fr.:*** Bi-Osteo; Bionagrol Plus; Dioptec; GLA; Phytosolaire; Regederm; ***Hong Kong:*** Mumomega; Pregnacare; ***Indon.:*** Epocaldi; ***Malaysia:*** Prim E; VitaEPA Plus†; ***Mex.:*** Rodan; ***NZ:*** Efacal†; Efalex; Efamarine; Efamax; Mr Nits; ***Pol.:*** Alliogal†; Tran z Olejem Wiesiolkowym†; ***Port.:*** Atopic†; ***S.Afr.:*** CalmolinADD; Femolin PMS; ***Singapore:*** Vita Natal; VitaEPA Plus; ***UK:*** Efalex; Efamarine; Efamol PMP; PMT Formula; ***USA:*** Eucerin Itch-Relief.

Febuprol *(rINN)*

Fébuprol; Febuproll; Febuprolum. 1-Butoxy-3-phenoxy-2-propanol.

Фебупрол

$C_{13}H_{20}O_3$ = 224.3.
CAS — 3102-00-9.

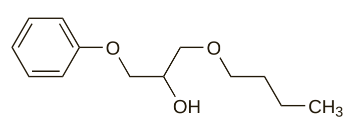

Profile

Febuprol is a choleretic used in the treatment of biliary-tract disorders in an oral dose of 100 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Valbil; ***Port.:*** Valbil.

Felypressin *(BAN, USAN, rINN)*

Felipresina; Felipresinas; Felipressin; Felypresin; Felypressiini; Félypressine; Felypressinum; Phelypressine; PLV2. [2-Phenylalanine,8-lysine]vasopressin; Cys-Phe-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2.

Фелипрессин

$C_{46}H_{65}N_{13}O_{11}S_2$ = 1040.2.
CAS — 56-59-7.

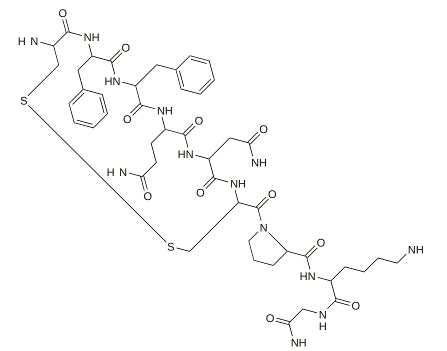

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Felypressin). A synthetic nonapeptide available as an acetate. A white or almost white powder or flakes. Freely soluble in water; practically insoluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Profile

Felypressin is a synthetic analogue of vasopressin (p.2411) with similar actions. Its antidiuretic effects are less than those of vasopressin. It is used as a vasoconstrictor in local anaesthetic injections for dental use when sympathomimetics should be avoided. It is also an ingredient of preparations that have been used in the treatment of pain and inflammation of the mouth.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Austral.:*** Citanest Dental; ***Braz.:*** Citanest; Citocaina; ***Denm.:*** Citanest Octapressin; ***Fin.:*** Citanest Octapressin; ***Ger.:*** Xylonest; ***Ital.:*** Citanest con Octapressin; ***Mex.:*** Citanest Octapresin†; Pristesin F; ***Neth.:*** Citanest Octapressine; ***Norw.:*** Citanest Octapressin; ***NZ:*** Citanest with Octapressin†; ***Spain:*** Citanest Octapressin; ***Swed.:*** Citanest Octapressin; ***Switz.:*** Citanest Octapressin; ***Turk.:*** Citanest Octapressin; ***UK:*** Citanest with Octapressin.

Fenchone

Fenchon. 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one.

Фенхон

$C_{10}H_{16}O$; = 152.2.
CAS — 4695-62-9 ((+)-fenchone); 7787-20-4 ((−)-fenchone); 1195-79-5 ((±)-fenchone).

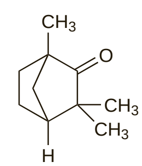

Profile

Fenchone is a constituent of several essential oils. It has been used in preparations in the treatment of biliary and urinary-tract disorders. It is reported to have counter-irritant properties. Fenchone is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Rowatinex; ***Chile:*** Rowatinex; ***Cz.:*** Rowatinex; ***Ger.:*** Rowatinex; ***Hong Kong:*** Neo-Rowatinex; Rowatinex; ***Hung.:*** Rowatinex; ***Irl.:*** Rowatinex; ***Israel:*** Rowatinex; ***Malaysia:*** Rowatinex; ***Philipp.:*** Rowatinex; ***Pol.:*** Rowatinex; ***Spain:*** Rowanefrin; ***Thai.:*** Rowatinex; ***Venez.:*** Rowatinex.

Fencibutirol *(USAN, rINN)*

Fencibutirolum; Mg-4833. 2-(1-Hydroxy-4-phenylcyclohexyl)butyric acid.

Фенцибутирол

$C_{16}H_{22}O_3$ = 262.3.
CAS — 5977-10-6.

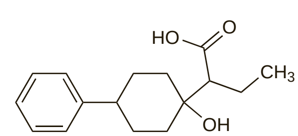

Profile

Fencibutirol is a choleretic that has been used in the treatment of constipation and biliary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Magisbile†.

Fenipentol *(rINN)*

Fénipentol; Fenipentolum. 1-Phenylpentan-1-ol; α-Butylbenzyl alcohol.

Фенипентол

$C_{11}H_{16}O$ = 164.2.

CAS — 583-03-9.

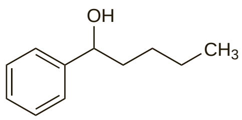

Profile

Fenipentol is a choleretic that has been given orally for the treatment of hepatic and biliary-tract disorders in doses of 100 to 200 mg three times daily. The hemisuccinate and sodium hemisuccinate have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Febichol; ***Ger.:*** Febichol; ***Ital.:*** Pentabil†.

Multi-ingredient: ***Chile:*** Digezin†; ***Ital.:*** Critichol; ***Spain:*** Menabil Complex†; ***Venez.:*** Cholipin.

Fennel

Édesköménytermés (bitter fennel); Fänkål, bitter (bitter fennel); Fänkål, söt (sweet fennel); Fenchel; Fenkoli, karvas (bitter fennel); Fenkoli, makea (sweet fennel); Fennel Fruit; Fennel Seed; Fenouil; Fenouil Amer; Fenouil amer, fruit de (bitter fennel); Fenouil doux, fruit de (sweet fennel); Foeniculi amari fructus (bitter fennel); Foeniculi dulcis fructus (sweet fennel); Foeniculum; Fruto de Hinojo; Funcho; Hinojo; Kartieji pankolių vaisiai (bitter fennel); Kerti édesköménytermés (sweet fennel); Owoc kopru włoskiego (bitter fennel); Plod fenyklu obecného pravého (bitter fennel); Plod fenyklu obecného sladkého (sweet fennel); Saldieji pankolių vaisiai (sweet fennel).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Fennel, Bitter; Foeniculi Amari Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains not less than 4.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 60.0% of anethole and not less than 15.0% of fenchone. Bitter fennel is greenish-brown, brown, or green. Protect from light and moisture.

Ph. Eur. 6.2 (Fennel, Sweet; Foeniculi Dulcis Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *dulce*. It contains not less than 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 80.0% of anethole. Sweet fennel is pale green or pale yellowish-brown. Protect from light and moisture.

Profile

Fennel is the source of fennel oil (below). It is used as a flavour and carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p.1696). It is also used in herbal remedies for respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Fenyklovy Caj; Gallentee†; ***Rus.:*** Plantex (Плантекс).

Multi-ingredient: ***Arg.:*** Arceligasol; ***Austral.:*** Bupleurum Compound; Crampeze Stomach Cramps; Digestive Aid; ***Austria:*** Brady's-Magentropfen; Euka; Illings Bozner Maycur-Tee†; Laxalpin; Mag Kottas Krauterexpress Abfuhrtee; Mag Kottas May-Cur-Tee; Nesthakchen; Planta Lax; Species Carvi comp†; ***Canad.:*** Herbal Laxative; Herbal Laxative plus Yogurt; Thunas Laxative†; ***Chile:*** Instalax; Reduc-Te; ***Cz.:*** Blahungstee N†; Bronchialtee N†; Cajova Smes pri Nachlazeni; Carminativum Babynos†; Detska Cajova Smes; Detsky Caj s Hermankem; Diabetan; Erkaltungstee†; Nervova Cajova Smes; Projimava; Pulmoran; Reduktan; Species Pectorales Planta; Stoffwechseltee N†; Stomaran; Ungolen†; Zaludecni Cajova Smes; ***Fr.:*** Benetransit; Bolcitol; Mediflor Tisane Contre la Constipation Passagere No 7; Mediflor Tisane Digestive No 3; Mediflor Tisane No 4 Diuretique; ***Ger.:*** Carminativum Babynos†; Carminativum-Hetterich; Em-eukal Husten- und Brusttee†; Em-medical†; Floradix Multipretten N; Gallexier; Gastricholan-L; Gastrol S†; Kneipp Husten- und Bronchial-Tee; Leber-Galle-Tropfen 83†; Lomatol†; Majocarmin-Tee; Pascopankreat novo†; Presselin Blahungs K 4 N†; Presselin Dyspeptikum†; Presselin Stoffwechsel-Tee Hapeka 225 N†; Ramend Krauter†; Stovalid N†; ***Israel:*** Jungborn; ***Ital.:*** Actenacol; Altea (Specie Composta)†; Anice (Specie Composta)†; Cadifen; Cadimint; Colimil; Dicalmir; Epagest†; Evamilk; Relaxcol; Senna-Specie Composta†; Timo (Specie Composta)†; ***Jpn:*** The Guard Seichojo; ***Malaysia:*** Eyebright Plus†; ***Pol.:*** Amarosal; Diges-Tonic; Rhelax; Salviasept; Sirupus Pini Compositus; Sirupus Tussipini; Sirupus Tussipini D; ***Rus.:*** Insti (Инсти); ***Spain:*** Crislaxo; Himelan†; Natusor Aerofane†; Natusor Malvasen†; Senalsor†; ***Switz.:*** Kernosan Elixir; Kernosan Heidelberger Poudre; Tisane favorisant l'allaitement; Tisane laxative; Tisane pectorale et antitussive; Tisane pour nourissons et enfants; ***UK:*** Cleansing Herbs; Herbal Indigestion Naturtabs; Indigestion and Flatulence; Lion Cleansing Herbs; Lustys Herbalene; Out-of-Sorts; Revitonil; Senokot Dual Relief; Sure-Lax (Herbal).

Fennel Oil

Aetheroleum Foeniculi; Bitterfänkålsolja (bitter-fennel fruit oil); Esencia de Hinojo; Essência de Funcho; Fenouil amer (fruit de), huile essentielle de (bitter-fennel fruit oil); Foeniculi amari fructus aetheroleum (bitter-fennel fruit oil); Hinojo, aceite esencial; Karčiųjų pankolių vaisių eterinis aliejus (bitter-fennel fruit oil); Karvasfenkoliöljy (bitter-fennel fruit oil); Olejek kopru włoskiego (bitter-fennel fruit oil); Oleum Foeniculi; Rezene Yağı; Silice fenyklu hořkého (bitter-fennel fruit oil).

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Bitter-Fennel Fruit Oil; Foeniculi Amari Fructus Aetheroleum). The essential oil obtained by steam distillation from the ripe fruits of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains 12.0 to 25.0% fenchone and 55.0 to 75.0% anethole. A clear, colourless or pale yellow liquid with a characteristic odour. Store in well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Fennel Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Foeniculum vulgare* (Apiaceae). Congealing temperature not lower than 3°. Soluble 1 in 1 of alcohol (90%). If solid matter has separated, carefully warm the oil until it is completely liquefied, and mix before using. Store in airtight containers.

Profile

Fennel oil is used as an aromatic flavour and carminative (but see the comment under Fennel, above); the German expert committee for herbal drugs and preparations (Commission E) considers that the use of fennel oil in infants and toddlers is contra-indicated. It is also used in herbal remedies for respiratory-tract disorders and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Babyfen; ***Ger.:*** Stern Biene Fenchelsirup†; ***Rus.:*** Plantex (Плантекс).

Multi-ingredient: ***Austria:*** Eucarbon; Luuf-Hustentee; Nesthakchen; Sabatif; Spasmo Claim; ***Canad.:*** Chase Kolik Gripe Water Alcohol-Free; ***Chile:*** Calmatol; ***Cz.:*** Biotussil; Bronchosan; Contraspan†; Herbadent; Naturident†; Ophthalmo-Septonex; Solutan†; ***Ger.:*** Cystium-wern†; Em-eukal Husten- und Brusttee†; Ephepect-Pastillen N; Euflat I†; Floradix Multipretten N; Gastricard†; Gastrysat; Hevertopect N†; Majocarmin forte†; Nierentee 2000†; Pulmocordio mite SL†; ratioGast†; Salviathymol N; ***Hong Kong:*** Magesto; ***Indon.:*** Minyak Telon; ***Israel:*** Novicarbon; ***Ital.:*** Relaxcol; ***Malaysia:*** Eucarbon†; ***Pol.:*** Woodwards Gripe Water; ***S.Afr.:*** Borsdruppels; Oleum Salviae Comp; ***Switz.:*** Flatulex; Huile Po-Ho A. Vogel; Laxasan; ***Thai.:*** Gas-Nep; Magesto; ***Turk.:*** Eucarbon.

Fenoverine *(rINN)*

Fenoverina; Fénovérine; Fenoverinum. 10-[(4-Piperonyl-1-piperazinyl)acetyl]phenothiazine.

Феноверин

$C_{26}H_{25}N_3O_3S$ = 459.6.

CAS — 37561-27-6.

ATC — A03AX05.

ATC Vet — QA03AX05.

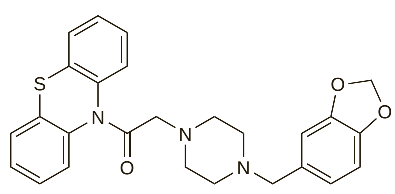

Profile

Fenoverine has been used as an antispasmodic but has been withdrawn in some countries after reports of rhabdomyolysis.

Adverse effects. Reports of rhabdomyolysis associated with fenoverine,[1-3] including a fatality.[1] A genetic predisposition has been suggested.[2]

1. Chariot P, *et al.* Fenoverine-induced rhabdomyolysis. *Hum Exp Toxicol* 1995; **14:** 654–6.
2. Jouglard J, *et al.* Research into individual predisposition to develop acute rhabdomyolysis attributed to fenoverine. *Hum Exp Toxicol* 1996; **15:** 815–20.
3. Chen CW, Chang MH. Rhabdomyolysis induced by fenoverine: a case report and literature review. *Acta Neurol Taiwan* 2005; **14:** 143–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Mex.: Spasmopriv; ***Singapore:*** Spasmopriv; ***Thai.:*** Spasmopriv; Tavidan†.

Fenpipramide *(BAN, rINN)*

Fenpipramid; Fenpipramida; Fenpipramidi; Fenpipramidum. 2,2-Diphenyl-4-piperidinobutyramide.

Фенпипрамид

$C_{21}H_{26}N_2O$ = 322.4.

CAS — 77-01-0.

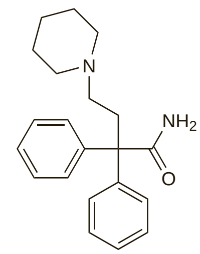

Fenpipramide Hydrochloride *(BANM, rINNM)*

Fenpipramide, Chlorhydrate de; Fenpipramidi Hydrochloridum; Hidrocloruro de fenpipramida.

Фенпипрамида Гидрохлорид

$C_{21}H_{26}N_2O,HCl$ = 358.9.

CAS — 14007-53-5.

Fenpiverinium Bromide *(rINN)*

Bromuro de fenpiverinio; Fenpipramide Methobromide; Fenpipramide Methylbromide; Fenpiverinii Bromidum; Fenpivérinium, Bromure de. 1-(3-Carbamoyl-3,3-diphenylpropyl)-1-methylpiperidinium bromide; 2,2-Diphenyl-4-piperidinobutyramide methyl bromide.

Фенпиверииния Бромид

$C_{22}H_{29}BrN_2O$ = 417.4.

CAS — 125-60-0.

ATC — A03AB21.

ATC Vet — QA03AB21.

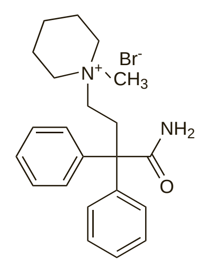

Profile

Fenpipramide (as the hydrochloride) and its methobromide, fenpiverinium bromide have been used as antispasmodics. Fenpipramide hydrochloride is also used for its antimuscarinic actions in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Algifen; Analgin; Spasmopan; ***Pol.:*** Spasmalgon; ***Rus.:*** Baralgetas (Баралгетас)†; Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); ***S.Afr.:*** Baralgan†; ***Thai.:*** Kanegan; ***Venez.:*** Flemibar.

Fenugreek

Bockhornsfrö; Bockshornsame; Faenum-Graecum; Fenogreco; Fenugrec; Görögszénamag; Greek hay; Ožragių sėklos; Sarviapilansiemen; Semen Foenugraeci; Semen Trigonellae; Semeno pískavice řeckého sena; Trigonella Foenugraeci Semen; Trigonellae foenugraeci semen.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fenugreek). The dried ripe seeds of *Trigonella foenum-graecum*. It has a strong characteristic odour. Protect from light.

Profile

Fenugreek has been used as an appetite stimulant and as an ingredient in preparations for respiratory disorders. It also has emollient properties.

Adverse effects. Loss of consciousness occurred in a 5-week-old infant after ingestion of a herbal tea containing fenugreek.[1] On recovery the infant and his urine had an aroma characteristic of that found in 'maple syrup urine disease', an inborn condition involving defective metabolism of branched-chain amino acids.

Further investigation revealed that the infant did not have the disease; the aroma was due to the presence of sotolone in the fenugreek seeds used to prepare the tea.

1. Sewell AC, *et al.* False diagnosis of maple syrup urine disease owing to ingestion of herbal tea. *N Engl J Med* 1999; **341:** 769.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Fenugrene; Sthenorex†.

Multi-ingredient: ***Austral.:*** Bilberry Plus; Garlic and Horseradish + C Complex; Panax Complex†; ***Fr.:*** Phytheol; ***India:*** Happy'tizer; ***Indon.:*** Provigor; ***Malaysia:*** Horseradish Plus†.

Ferric Chloride

Chlorid železitý hexahydrát; Chlorure Ferrique; Ferr. Perchlor.; Ferri chloridum hexahydricum; Férrico, cloruro; Ferrikloridhexahydrat; Ferrikloridiheksahydraatti; Ferrique (chlorure) hexahydraté; Ferrum Sesquichloratum; Geležies(III) chloridas heksahidratas; Iron Perchloride; Iron Sesquichloride; Iron Trichloride; Vas(III)-klorid-hexahidrát; Żelaza(III) chlorek.

$FeCl_3,6H_2O$ = 270.3.

CAS — 7705-08-0 (anhydrous ferric chloride); 10025-77-1 (ferric chloride hexahydrate).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ferric Chloride Hexahydrate). A very hygroscopic, crystalline mass or orange-yellow to brownish-yellow crystals. Very soluble in water and in alcohol; freely soluble in glycerol. Store in airtight containers. Protect from light.

Profile

Ferric chloride has the general properties of iron salts (p.1949) but is exceptionally astringent. It has been used mainly by local application for its styptic and astringent properties. Local application of ferric chloride or other iron salts may cause permanent discoloration of the skin.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Cotone Emostatico; ***Rus.:*** Hemofer (Гемофер); ***S.Afr.:*** Staaldruppels.

Multi-ingredient: ***Belg.:*** Ouate Hemostatique; ***UK:*** Glykola.

Fibronectins

Fibronectina.

Фибронектины

Profile

Fibronectins are high molecular weight endogenous adhesive glycoproteins found in plasma and in the extracellular matrix. Plasma fibronectin was originally known as cold-insoluble globulin. Fibronectins are principally involved in cellular attachment and migration in normal physiological processes as well as in various malignant diseases. They have an important role in the function of the extracellular matrix, and in morphogenesis and tissue remodelling. They also play a part in aggregation of platelets, and are used in combinations with other blood products in wound-sealant preparations. Manipulation of the activity of fibronectins (for example with fibronectin inhibitors or fibronectin fragments) is being investigated in the treatment of connective tissue diseases, malignancies, and wound healing. Fibronectin itself has potential use as a research tool for the study of cell adhesion and migration processes.

◊ References.

1. Kaspar M, *et al.* Fibronectin as target for tumor therapy. *Int J Cancer* 2006; **118:** 1331–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Canad.:*** Tisseel; ***Cz.:*** Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Tissucol; ***Ger.:*** Quixil; Tissucol Duo S; Tissucol-Kit; ***Hong Kong:*** Tisseel; ***Hung.:*** Tissucol-Kit; ***Israel:*** Tisseel; ***Ital.:*** Quixil; ***Mex.:*** Tissucol†; ***Neth.:*** Quixil; Tissucol; Tissucol Duo; ***Spain:*** Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Tissucol; Tissucol Duo S; ***UK:*** Tisseel.

Fingolimod *(rINN)*

Fingolimodum; FTY-720 (fingolimod hydrochloride). 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol.

Финголимод

$C_{19}H_{33}NO_2$ = 307.5.

CAS — 162359-55-9 (fingolimod); 162359-56-0 (fingolimod hydrochloride).

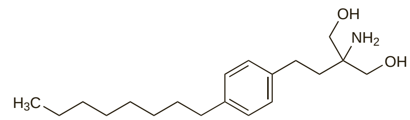

NOTE. Fingolimod hydrochloride is *USAN*.

Profile

Fingolimod is an immunomodulator under investigation for multiple sclerosis and prophylaxis of acute rejection in kidney transplantation. Fingolimod is a prodrug, which after phosphorylation, acts as a sphingosine-1-phosphate receptor agonist that binds to the surface of lymphocytes and redirects them from the bloodstream and graft sites to the lymph nodes.

◊ References.

1. Kappos L, *et al.* Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* 2006; **355:** 1124–40.

Flavonoid Compounds

Bioflavonoids; Flavonoides; Vitamin P Substances.

Benzquercin *(rINN)*

Benzquercina; Benzquercine; Benzquercinum. 3,3′,4′,5,7-Pentakis(benzyloxy)flavone.

Бензкверцин

$C_{50}H_{40}O_7$ = 752.8.

CAS — 13157-90-9.

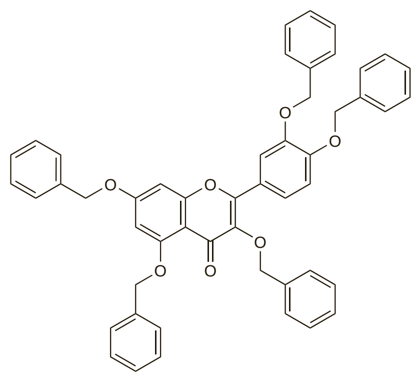

Diosmin *(BAN, rINN)*

Barosmin; Buchu Resin; Diosmetin 7-Rutinoside; Diosmiini; Diosmina; Diosminas; Diosmine; Diosminum; Diozmin. 3′,5,7-Trihydroxy-4′-methoxyflavone 7-[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside].

Диосмин

$C_{28}H_{32}O_{15}$ = 608.5.

CAS — 520-27-4.

ATC — C05CA03.

ATC Vet — QC05CA03.

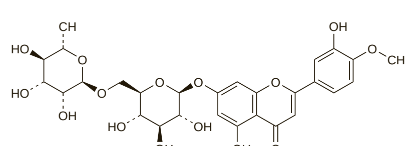

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Diosmin). A greyish-yellow or light yellow hygroscopic powder. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

Ethoxazorutoside *(rINN)*

Aethoxazorutin; Aethoxazorutoside; Ethoxazorutin; Éthoxazorutoside; Ethoxazorutosidum; Etoxazorutósido; Oxarutinum. 2-Morpholinoethylrutin.

Этоксазорутозид

$C_{33}H_{41}NO_{17}$ = 723.7.

CAS — 30851-76-4.

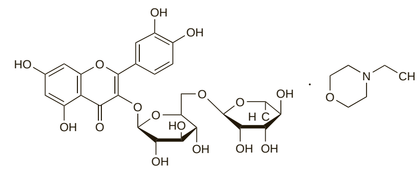

Flavodate Sodium *(rINNM)*

Flavodate de Sodium; Flavodate Disodium; Flavodato sódico; Natrii Flavodas. Disodium (4-oxo-2-phenyl-4*H*-chromene-5,7-diyldioxy)diacetate.

Натрий Флаводовая

$C_{19}H_{12}Na_2O_8$ = 414.3.

CAS — 37470-13-6 (flavodic acid); 13358-62-8 (flavodate disodium).

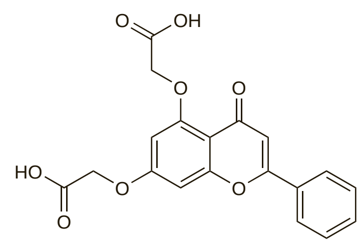

(flavodic acid)

Hesperidin

Hesperidiini; Hesperidina; Hesperidinum; Hesperydyna. 5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl rutinoside.

Гесперидин

$C_{28}H_{34}O_{15}$ = 610.6.

CAS — 520-26-3 (hesperidin); 24292-52-2 (hesperidin methyl chalcone).

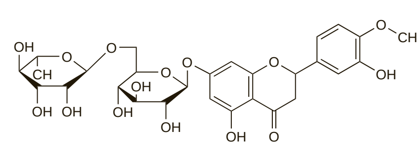

Description. Hesperidin is a flavonoid isolated from the rind of certain citrus fruits.

Leucocianidol *(rINN)*

Leucocianidolum; Leucocyanidin; Leucocyanidol. 2-(3,4-Dihydroxyphenyl)chroman-3,4,5,7-tetrol.

Лейкоцианидол

$C_{15}H_{14}O_7$ = 306.3.

CAS — 480-17-1.

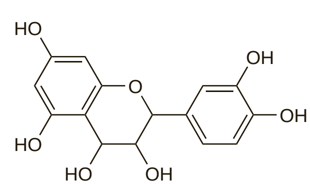

Monoxerutin *(rINN)*

Monohydroxyethylrutosides; Monokserutiini; Monoxerutina; Monoxérutine; Monoxerutinum. 7-(β-Hydroxyethyl)rutoside.

Моноксерутин

$C_{29}H_{34}O_{17}$ = 654.6.
CAS — 23869-24-1.
ATC — C05CA02.
ATC Vet — QC05CA02.

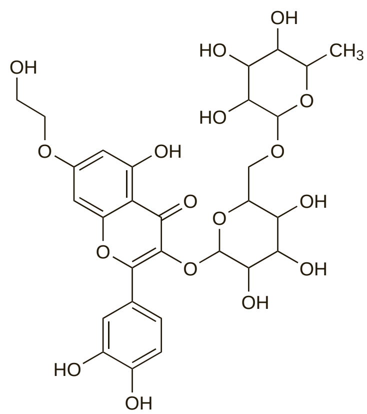

Oxerutins *(BAN)*

Hydroxyethylrutosides; Oxerutinas.

Оксерутины

Description. Oxerutins consist of a mixture of 5 different *O*-(β-hydroxyethyl)rutosides, not less than 45% of which is troxerutin (trihydroxyethylrutoside, below), but which also includes monohydroxyethylrutoside, dihydroxyethylrutoside, and tetrahydroxyethylrutoside.

Quercetin

3,3′,4′,5,7-Pentahydroxyflavone; Quercetina. 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one.

Кверцетин

$C_{15}H_{10}O_7$ = 302.2.
CAS — 117-39-5.

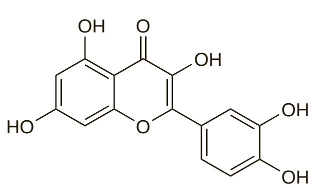

Rutoside *(BAN, rINN)*

Rutin; Rutosid; Rutoside trihydraté; Rutosidi; Rutosiditrihydraatti; Rutósido; Rutosidtrihydrat; Rutosidum; Rutosidum trihydricum; Rutozidas trihidratas; Rutozid-trihidrát; Rutozyd; Rutyna. 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4-oxo-4*H*-chromen-3-yl rutinoside trihydrate; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl 6-*O*-(α-L-rhamnosyl)-β-D-glucoside.

Рутозид

$C_{27}H_{30}O_{16},3H_2O$ = 664.6.
CAS — 153-18-4 (anhydrous rutoside).
ATC — C05CA01.
ATC Vet — QC05CA01.

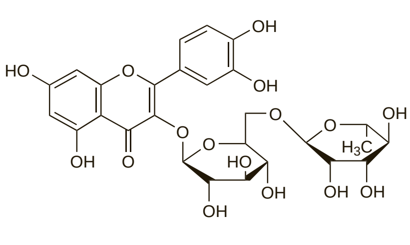

Description. Rutoside is a flavonoid obtained from buckwheat, *Fagopyrum esculentum* (Polygonaceae), or from other sources which include the flower buds of the Japanese pagoda-tree, *Sophora japonica*, and the leaves of several species of *Eucalyptus*.

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.*

Ph. Eur. 6.2 (Rutoside Trihydrate). A yellow or greenish-yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane; soluble in methyl alcohol. It dissolves in solutions of alkali hydroxides. Protect from light.

Troxerutin *(BAN, rINN)*

THR; Trihydroxyethylrutoside; Trioxyethylrutin; Trokserutiini; Trokserutyna; Troxerutina; Troxérutine; Troxerutinum. 3′,4′,7-Tris[*O*-(2-hydroxyethyl)]rutin; 5-Hydroxy-7-(2-hydroxyethoxy)-2-[3,4-bis(2-hydroxyethoxy)phenyl]-4-oxo-4*H*-chromen-3-yl rutinoside.

Троксерутин

$C_{33}H_{42}O_{19}$ = 742.7.
CAS — 7085-55-4.
ATC — C05CA04.
ATC Vet — QC05CA04.

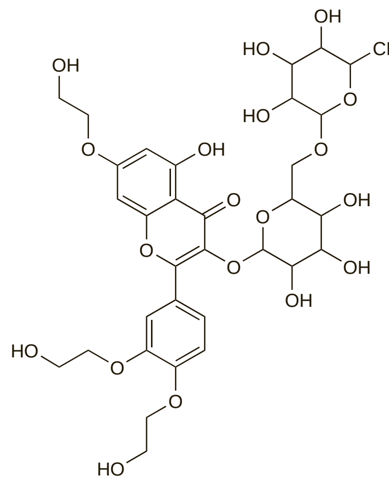

Description. Troxerutin is the principal component of oxerutins, above.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Troxerutin). A yellowish-green, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flavonoids are naturally occurring antoxidants that are widely distributed in plants. Preparations containing natural or semisynthetic flavonoids are thought to improve capillary function by reducing abnormal leakage. They have been given to relieve capillary impairment and venous insufficiency of the lower limbs, and for haemorrhoids.

It has been suggested that flavonoids present in some foods, such as fruit, vegetables, tea, and red wine may protect against the development of atherosclerosis (p.1159).

◊ References.

1. Knekt P, *et al.* Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ* 1996; **312:** 478–81.
2. Hertog MGL, *et al.* Antioxidant flavonols and coronary heart disease risk. *Lancet* 1997; **349:** 699.
3. Youdim KA, *et al.* Dietary flavonoids as potential neuroprotectants. *Biol Chem* 2002; **383:** 503–19.
4. Lopez-Lazaro M. Flavonoids as anticancer agents: structure-activity relationship study. *Curr Med Chem Anti-Canc Agents* 2002; **2:** 691–714.
5. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003; **63:** 71–100.
6. Alonso-Coello P, *et al.* Meta-analysis of flavonoids for the treatment of haemorrhoids. *Br J Surg* 2006; **93:** 909–20.
7. Cermak R. Effect of dietary flavonoids on pathways involved in drug metabolism. *Expert Opin Drug Metab Toxicol* 2008; **4:** 17–35.

Interactions. For a report of quercetin increasing the bioavailability and concentration of ciclosporin, see p.1828.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Flebon; Flebotropin; Flerox†; Jatamansin†; Rutilina; Terbenol; Venoruton; Venosmil; ***Austral.:*** Paroven; ***Austria:*** Venoruton; ***Belg.:*** Docrutosi; Veinamitol; Ven-Detrex; Venoruton; ***Braz.:*** Daflon; Flavonid; Venoruton; ***Chile:*** Flebopex; Insuven; Venoruton; ***Cz.:*** Cilkanol; Venoruton; ***Denm.:*** Venoruton; ***Fr.:*** Daflon; Diamoril†; Dio; Diosmil†; Diovenor; Endium; Flavan; Flebosmil; Intercyton; Mediveine; Preparation H Veinotonic; Relvene; Rheoflux; Titanoral; Veinamitol; Veineva; Venirene; ***Ger.:*** Drisi-Ven†; Posorutin; Rutinion; Tovene; Troxeven; Vastribil†; Veno SL; Venoruton; Venotrulan Trox; ***Gr.:*** Radiavit; Rioven†; Venoruton; ***Hong Kong:*** Venoruton†; ***Hung.:*** Veinamitol†; Venoruton; ***India:*** Venusmin; ***Indon.:*** Ardium; Venaron; ***Israel:*** Veinamitol†; Venoruton; Vridol†; ***Ital.:*** Alven; Arvenum; Diosven; Doven; Pericel; Venolen; Venoruton; Venosmine; ***Mex.:*** Sies; Teboven; ***Neth.:*** Venoruton; ***NZ:*** Paroven; ***Philipp.:*** Varemoid; Venoruton; ***Pol.:*** Otrex; Phlebodia; Posorutin; Rutinoven; Rutoven; Troxeratio; Venolan; Venoruton; Venotrex; ***Port.:*** Arvenum; Hepacalmina; Muralion; Venex; Veno V; Venoruton; Venosmil; Veroven; ***Rus.:*** Phlebodia (Флебодиа); Troxevazin (Троксевазин); Venoruton (Венорутон); ***S.Afr.:*** Paroven; ***Spain:*** Esberiven; Pentovena†; Venolep; Venoruton; Venosmil; ***Switz.:*** Hemerven; Neorutin†; Pur-Rutin; Venoruton; Venutabs; ***Thai.:*** Flavon; Heteroid; Venoruton; ***Turk.:*** Daflon; Venoruton; ***UK:*** Paroven; ***USA:*** Citro-Flav; Limbrel; ***Venez.:*** Diovenor; Flavol; Hyflon; Verutil.

Multi-ingredient: ***Arg.:*** Accesum; Ajomast Circulatorio†; CVP B1 B6 B12†; CVP Duo; CVP Flebo; CVP Forte; Cyclo 3; Daflon; Dipemina; Diroseal; Epiteliol-C; Esberiven; Escina Forte; Escina Omega; Esculeol P; Exail; Fiblast; Flebitol; Flebotropin†; GB 100; HDG; Kacerutin; Microsuy; Mimixin; Phlogenzym†; Terbenol Duo; Troxeven†; Tubarine; Ulcevarin†; Varisedan; Vefluxan†; Venart; Venidium; Veraldid; Vitamina C-Complex; VNS 45; ***Austral.:*** B-Complex Threshold; Beta A-C; Bio C; Bio-C Complex; Bioglan Cirflo†; Bioglan Mega C; Bioglan Super Cal C; Bioglan The Blue One; Bioglan Zellulean with Escin; Bioglan Zn-A-C; C Supa + Bioflavonoids†; Cold & Flu Tablets Non Drowsy; Devils Claw Plus; Extralife Leg-Care; Eye Health Herbal Plus Formula 4; Flavonoid Complex; Flavons; For Peripheral Circulation Herbal Plus Formula 5; Gentle C with Bioflavonoids†; Lifesystem Herbal Formula 6 For Peripheral Circulation†; Lifesystem Herbal Plus Formula 5 Eye Relief†; Macro C†; Proflo†; Rubus Complex†; Super Cal-C Bio; Sustained Release C; ***Austria:*** Calcipot C; Cebion plus Rutin; Daflon; Helopyrin; Iroviton Multivitamin; Phlebodril; Phlogenzym; Ruticalzon; Rutiscorbin†; Rutiviscal; Rutozym; Sklerovitol; Tetesept; Traumazym; Trimedil; Venotop; Vit-C-Lutsch; Waldheim Influvidon; Wobenzym; ***Belg.:*** Daflon; Mictasol-P; ***Braz.:*** Castanha de India Composta†; Dactil OB; Daflon 500; Diosmin; Flebotrat†; Gingilone; Gripen; Hemodotti; Hemorroidex†; Manolio†; Mirorroidin†; Novarrutina; Panvitrop; Trimedal; Varicoss; Varizol†; Venaflon; Venalot; Venocur Triplex; Venovaz; ***Canad.:*** Ultra Quercitin; ***Chile:*** Daflon 500; Dipemina; Diroseal; Duo-CVP; Hemoplex†; Phyto Corrective Gel; Primacy Phyto +†; Venartel; Vesnidan; ***Cz.:*** Anavenol; Ascorutin; Cyclo 3 Fort; Detralex; Ginkor Fort; Phlogenzym; Wobenzym; ***Denm.:*** Capiven; ***Fr.:*** Avene Antirougeurs; Bicirkan; Cemaflavone; Cirkan; Cyclo 3 Fort; Diroseal; Esberiven Fort; Gel a l'Acetotartrate d'Alumine Defresne†; Ginkor; Ginkor Fort; Ophtadil†; Rheobral; Vascocitrol; Veliten; Venyl†; Vivene†; ***Ger.:*** Antihypertonicum S; Calcium-Rutinion†; Cycloven Forte N; Emocrat forte†; Enzym-Wied†; Essaven N†; Essaven ultra†; Eukalisan N; Fagorutin Buchweizen; Fagorutin Rosskastanien-Balsam N; Intradermi; Lindigoa S†; Movicard; Perivar†; Phlebodril; Phlogenzym; Posti N†; Ruticalzon VC†; Tornix; Vaso-E-Bion; Venalot; Venalot N†; Veno-Tebonin N†; Vitosal†; Wobenzym N; ***Gr.:*** Abanifan; Antican; Bioflevin; Cidoston; Cyclo 3 Forte; Daflon; Diosper; Dispedrol; Flavon†; Flevion; Flevostol; Gamophen; Mecaton; Noxarel; Oflazet; Pelethrocin; Roxydral; Smudal; Venosman†; ***Hong Kong:*** Daflon; Ginkor Fort; Hemo Rid; Poly C†; Quali-Flon; ***Hung.:*** Detralex; Ginkor Fort; Phlogenzym; Rutascorbin; ***India:*** Cadisper C; CKP; CVP; Gynae-CVP; Kalpastic; Styptocid; Styptocip†; ***Indon.:*** Ambeven Plus; Ciflon; Papaven; Vedium; ***Israel:*** Opti-safe; ***Ital.:*** Angioton; Capill Venogel; Daflon 500; Dermoangiopan†; Digifar†; Diosmina Complex; Emortrofine; Facosmina; Flebil Plus; Flebo-Si; Flebofort; Flebolider; Fleboside; Ginkoftal; Levital Plus; Neomyrt Plus; Pulsalux; RepaVen†; Rutisan CE†; Traumal†; Varicofit; Venactive†; Venodin; Venoton; Voltatrauma; ***Malaysia:*** Daflon 500; Ginkor Fort; Hemorid; Nat-C; ***Mex.:*** Cal-Rutina; Daflon; Elatec; Fabroven; Flavit; Phlogenzym; Variton; Venalot; Wobenzym; ***NZ:*** Botanica Hayfever; ***Philipp.:*** Daflon; ***Pol.:*** Alliorut; Anavenol; Ascorutical; Biovision; Cerutin; Cyclo 3 Fort; Detralex; Kelicardina; Pelethrocin; Rutinacea; Rutinoscorbin; Rutinoscorbin Plus; Rutokal C; Rutovit C; Sapoven AT; Sapoven T; Scorbolamid; Troxescorbin; Venacorn; Venescin; ***Port.:*** Actilam; Cegripe; Cyclo 3; Daflon; Rimanal; Rutinice Fortissimo; ***Rus.:*** Anavenol (Анавенол); Antigrippin-ANVI (Антигриппин-АНВИ); Ascorutical (Аскорутикаль); Cyclo 3 Fort (Цикло-3 Форт); Detralex (Детралекс); Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); Indovasin (Индовазин); Phlogenzym (Флогэнзим); Prophylactin C (Профилактин С); Venolife (Венолайф); Wobenzym (Вобэнзим); ***S.Afr.:*** Essaven†; ***Singapore:*** Cyclo 3 Fort; Daflon 500; Diosper; Poly C; ***Spain:*** Caprofides Hemostatico; Daflon 500; Epistaxol; Fabroven; Flebeside†; Gingilone; Nasopomada; ***Switz.:*** Biovital Ginseng; Daflon 500; Demoven N; Flavovenyl; Lapidar 4; Phlebodril N; Video-Net†; ***Thai.:*** Biocalron; Cyclo 3 Fort; Daflon; Dafomin; Essaven; Ginkor Fort; Heroid; Nat-C Medicrafts; Siduol; ***USA:*** Amino-Opti-C; C Factors "1000" Plus; Cholinoid; Citrus-flav C; Ester-C Plus; Ester-C Plus Multi-Mineral; Flavons; Lipoflavonoid; Pan C; Peridin-C; Proflavanol; Pycnogenol Plus; Span C; ***Venez.:*** Daflon; Disolina; Dremo-K†; Phlogenzym; Wobenzym N.

Flopropione *(rINN)*

Flopropiona; Flopropionum; Fluropropiofenone; Phloropropiophenone; RP-13907. 2′,4′,6′-Trihydroxypropiophenone.

Флопропион

$C_9H_{10}O_4$ = 182.2.
CAS — 2295-58-1.

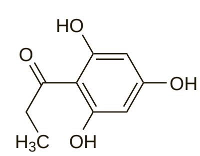

Pharmacopoeias. In *Jpn.*

Profile

Flopropione is an antispasmodic that has been given orally in doses of 40 to 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Cospanon.

Fluorescein *(BAN)*

Fluoresceína; Fluoresceina; Fluorescéine; Fluoresceinum. 3′,6′-Dihydroxyspiro[isobenzofuran-1(3*H*),9′(9*H*)xanthen]-3-one.

Флуоресцеин

$C_{20}H_{12}O_5$ = 332.3.
CAS — 2321-07-5.
ATC — S01JA01.
ATC Vet — QS01JA01.

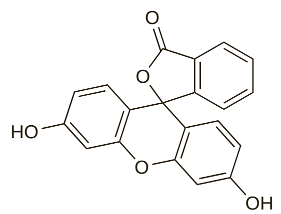

Pharmacopoeias. In *Eur* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluorescein). An orange-red, fine powder. Practically insoluble in water; soluble in hot alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Fluorescein). A yellowish-red to red, odourless powder. Insoluble in water; soluble in dilute alkali hydroxides. Store in airtight containers.

Fluorescein Dilaurate *(BANM)*

Fluoresceína, dilaurato de.

Флуоресцеина Дилаурат

$C_{44}H_{56}O_7$ = 696.9.
CAS — 7308-90-9.
ATC — S01JA01.
ATC Vet — QS01JA01.

Fluorescein Sodium *(BANM)*

CI Acid Yellow 73; Colour Index No. 45350; D & C Yellow No. 8; Fluorescein Natrium; Fluorescein sodná sůl; Fluoresceína sódica; Fluorescéine sodique; Fluoresceinnatrium; Fluoresceino natrio druska; Fluoresceinum natricum; Fluoreseiininatrium; Fluoresein Sodyum; Fluoreszcein-nátrium; Obiturin; Resorcinolphthalein Sodium; Sodium Fluorescein; Soluble Fluorescein; Uranin. Disodium fluorescein.

Флуоресцин Натрий

$C_{20}H_{10}Na_2O_5$ = 376.3.
CAS — 518-47-8.
ATC — S01JA01.
ATC Vet — QS01JA01.

NOTE. FLN is a code approved by the BP 2008 for use on single unit doses of eye drops containing fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information. LIDFLN is a similar code approved for eye drops containing lidocaine hydrochloride and fluorescein sodium, and PROXFLN a code for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn,* and *US.*

Ph. Eur. 6.2 (Fluorescein Sodium). An orange-red, fine hygroscopic powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane and in hexane. A 2% solution in water has a pH of 7.0 to 9.0. Store in airtight containers. Protect from light.

USP 31 (Fluorescein Sodium). An orange-red, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Adverse Effects and Precautions

The intravenous injection of fluorescein sodium may produce nausea and vomiting. Extravasation is painful. Hypersensitivity reactions range from urticaria to occasional instances of severe anaphylaxis. Cardiac arrests and fatalities have occurred rarely. Concern that impurities or a defect in manufacturing processes might be responsible for the serious reactions led to a review of the BP specification in the early 1980s and a reduction in the permitted level of impurities. Facilities for resuscitation should be available whenever fluorescein sodium is used intravenously.

The skin and urine may be coloured yellow but this is transient. Fluorescein sodium can stain skin, clothing, and soft contact lenses on contact. Intra-ocular fluorescein can produce transient blurring of vision.

Oral fluorescein dilaurate should not be given to patients with acute necrotising pancreatitis. Sulfasalazine may interfere with estimations of fluorescein in the fluorescein dilaurate test.

◊ Two large studies have examined the incidence of adverse reactions after intravenous fluorescein angiography. An international survey[1] collected information concerning 594 687 angiographic procedures; the incidence of serious reactions was 1 in 18 020, and that of fatal reactions, 1 in 49 557. Reactions included anaphylactic shock, cardiac arrest, myocardial infarction, and shock with hypotension or respiratory distress. A US survey of 221 781 fluorescein angiograms[2] reported frequency rates of 1 in 63 for a moderate reaction (urticaria, syncope, thrombophlebitis, pyrexia, tissue necrosis, or nerve palsy) and 1 in 1900 for severe reactions (respiratory or cardiac events or tonic-clonic seizures); there was one death.

Individual reports of adverse reactions to intravenous fluorescein sodium include pancreatitis,[3] painful crises in patients with sickle-cell disease,[4] psoriasiform drug eruption,[5] and photoallergy[6] and phototoxicity.[7]

1. Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluoresceinique. *J Fr Ophtalmol* 1983; **6:** 495–506.
2. Yannuzzi LA, *et al.* Fluorescein angiography complication survey. *Ophthalmology* 1986; **93:** 611–17.
3. Morgan LH, Martin JM. Acute pancreatitis after fluorescein. *BMJ* 1983; **287:** 1596.
4. Acheson R, Serjeant G. Painful crises in sickle cell disease after fluorescein angiography. *Lancet* 1985; **i:** 1222.
5. Mayama M, *et al.* Psoriasiform drug eruption induced by fluorescein sodium used for fluorescein angiography. *Br J Dermatol* 1999; **140:** 982–4.
6. Hochsattel R, *et al.* Photoallergic reaction to fluorescein. *Contact Dermatitis* 1990; **22:** 42–4.
7. Kearns GL, *et al.* Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985; **107:** 796–8.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of fluorescein by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Uses and Administration

Fluorescein sodium stains damaged cornea and ocular fluids and is applied to the eye for the detection of corneal lesions and foreign bodies, as an aid to the fitting of hard contact lenses, and in various other diagnostic ophthalmic procedures. It is applied as a 1 or 2% solution as eye drops or as sterile papers impregnated with fluorescein sodium. It may also be given with a local anaesthetic, typically as a 0.25% solution with lidocaine hydrochloride, oxybuprocaine hydrochloride, or proxymetacaine hydrochloride.

Fluorescein sodium may be given by rapid intravenous injection, usually as a solution equivalent to fluorescein 10 or 25%, for retinal angiography. The usual dose is the equivalent of 500 mg of fluorescein. A dose of 7.5 mg/kg has been suggested for children. The oral route has also been tried for angiography. Other uses of intravenous fluorescein sodium have included the differentiation of healthy from diseased or damaged tissue and visualisation of the biliary tract.

Fluorescein dilaurate is given by mouth for the assessment of exocrine pancreatic function (see below). Pancreatic enzymes hydrolyse the ester and the amount of free fluorescein excreted in the urine can therefore be taken as a measure of pancreatic activity. A dose of 348.5 mg of fluorescein dilaurate, equivalent to 0.5 mmol of fluorescein, is given with a standard meal, and urine collected for the next 10 hours. The manufacturers give instructions concerning the type and amount of liquid and food which may be taken during this period. A control dose of 188.14 mg of fluorescein sodium, also equivalent to 0.5 mmol of fluorescein, is given on the next day under the same conditions.

Pancreatic function test. Studies of the fluorescein dilaurate test have considered it to be a useful noninvasive screening test for the exclusion of pancreatic exocrine failure in outpatients, particularly those presenting with steatorrhoea.[1-3] The need for tests such as the pancreozymin-secretin test, which requires duodenal intubation, may thus be avoided. However, low specificity (a relatively high rate of false-positive responses) has been reported with the fluorescein dilaurate test in some patient populations,[2,4] and the need for careful patient instruction in performance of the test has been emphasised.[3] In order to avoid the prolonged collection of urine necessary in the standard test, serum concentrations of fluorescein may be measured several hours after taking the test substance.[5]

The test has been used successfully in children,[6] particularly when the doses of fluorescein dilaurate and fluorescein sodium are reduced and fluid intake modified,[7] although the manufacturers recommend that the commercially available test is not used for this age group. In children, a simplified, single-day test using dual markers, fluorescein dilaurate and mannitol, has been investigated with encouraging results.[8] The fluorescein dilaurate test was found to be more sensitive than the faecal elastase 1 test for the diagnosis of mild-to-moderate exocrine pancreatic insufficiency in a study involving 40 patients.[9]

1. Barry RE, *et al.* Fluorescein dilaurate—tubeless test for pancreatic exocrine failure. *Lancet* 1982; **ii:** 742–4.
2. Boyd EJS, *et al.* Prospective comparison of the fluorescein-dilaurate test with the secretin-cholecystokinin test for pancreatic exocrine function. *J Clin Pathol* 1982; **35:** 1240–3.
3. Gould SR, *et al.* Evaluation of a tubeless pancreatic function test in patients with steatorrhoea in a district general hospital. *J R Soc Med* 1988; **81:** 270–3.
4. Braganza JM. Fluorescein dilaurate test. *Lancet* 1982; **ii:** 927–8.
5. Dimagno EP. A perspective on the use of tubeless pancreatic function tests in diagnosis. *Gut* 1998; **43:** 2–3.
6. Cumming JGR, *et al.* Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test. *Arch Dis Child* 1986; **61:** 573–5.
7. Dalzell AM, Heaf DP. Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis. *Arch Dis Child* 1990; **65:** 788–9.
8. Green MR, *et al.* Dual marker one day pancreolauryl test. *Arch Dis Child* 1993; **68:** 649–52.
9. Leodolter A, *et al.* Comparison of two tubeless function tests in the assessment of mild-to-moderate exocrine pancreatic insufficiency. *Eur J Gastroenterol Hepatol* 2000; **12:** 1335–8.

Pediculosis. Infestation of the eye lashes or brows with pubic lice (p.2034) has been successfully treated with a single application of a 20% solution of fluorescein.[1]

1. Mathew M, *et al.* A new treatment of pthiriasis palpebrarum. *Ann Ophthalmol* 1982; **14:** 439–41.

Retinal angiography. Fluorescein is usually given intravenously for retinal angiography, but a study in 20 healthy subjects concluded that an oral dose of fluorescein sodium 25 mg/kg could produce good quality retinal angiograms in the majority of subjects.[1] This study used specially prepared 500-mg capsules of fluorescein sodium; the authors commented that previous oral studies had used the liquid preparation intended for intravenous use. Only mild reactions, possibly due to hypersensitivity, appear to have been reported with oral fluorescein.

1. Watson AP, Rosen ES. Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules. *Br J Ophthalmol* 1990; **74:** 458–61.

Preparations

BP 2008: Fluorescein Eye Drops; Fluorescein Injection;
USP 31: Fluorescein Injection; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Fluorescein Sodium Ophthalmic Strips.

Proprietary Preparations (details are given in Part 3)

Arg.: Angiofluor†; Fluorescite; RFG-Kit†; ***Austral.:*** Disclo-Plaque; Fluorescite; Fluorets; Ful-Glo†; ***Canad.:*** Diofluor; Fluorescite; Fluorets†; ***Cz.:*** Fluorescite; ***Hong Kong:*** Fluorescite†; Fluorets; ***India:*** Fluore Stain Strips; ***Irl.:*** Fluorets; ***Ital.:*** Fluoralfa; ***Malaysia:*** Fluorescite; Fluorets; ***Mex.:*** Optifluor; ***NZ:*** Fluorescite; Fluorets; ***Pol.:*** Fluorescite; ***Port.:*** Fluorescite; ***S.Afr.:*** Fluorescite; Fluorets; ***Singapore:*** Fluorescite; Fluorets; ***Thai.:*** Fluorescite; ***Turk.:*** Fluorescite; ***UK:*** Fluorets; ***USA:*** Ak-Fluor; Fluor-I-Strip; Fluorescite; Fluorets; Ful-Glo; Funduscein; Ophthifluor.

Multi-ingredient: ***Austral.:*** Fluress; ***Austria:*** Flurekain; Pancreolauryl-Test; ***Canad.:*** Fluoracaine†; ***Cz.:*** Thilorbin†; ***Fin.:*** Oftan Flurekain; ***Ger.:*** Pancreolauryl-Test N†; Thilorbin; ***NZ:*** Fluress†; ***Port.:*** Fluotest; ***Spain:*** Fluotest; Pancreolauryl; ***Swed.:*** Fluress; ***USA:*** Flu-Oxinate†; Fluoracaine; Fluorocaine; Fluorox; Flurate; Fluress; Flurox; Healon Yellow.

Formic Acid

Ácido amínico; Ácido formílico; Acidum Formicum; Ameisensäure; Aminic Acid; E236; E238 (calcium formate); E237 (sodium formate); Fórmico, ácido; Kwas mrówkowy.

CH_2O_2 = 46.03.
CAS — 64-18-6.
ATC Vet — QP53AG01.

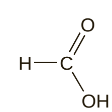

Pharmacopoeias. In *Pol.*

Profile

Formic acid resembles acetic acid in its properties (see p.2244) but is more irritating and pungent. The acid and its sodium and calcium salts are used as preservatives in food. Solutions containing about 60% formic acid have been marketed for the removal of lime scale from kettles. Formic acid has also been used for the removal of tattoos. It is an ingredient of some external preparations promoted for the relief of musculoskeletal and joint disorders, and has been used with benzyl alcohol to aid the removal of nits.

◊ In a report of 3 patients who swallowed descaling agents containing 40 or 55% formic acid, the major complications included local corrosive effects, metabolic acidosis, derangement of blood-clotting mechanisms, and acute onset of respiratory and renal failure.[1] All 3 patients died between 5 and 14 days after admission to hospital. A further report of 53 cases of formic acid ingestion included 15 fatalities.[2]

1. Naik RB, *et al*. Ingestion of formic acid-containing agents — report of three fatal cases. *Postgrad Med J* 1980; **56:** 451–6.
2. Rajan N, *et al.* Formic acid poisoning with suicidal intent: a report of 53 cases. *Postgrad Med J* 1985; **61:** 35–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Acimont; Berggeist; ***Ital.:*** Rubjovit; ***Switz.:*** Fortalis.

Fosfocreatinine *(rINN)*

Fosfocreatinina; Fosfocréatinine; Fosfocreatininum; Phosphocreatinine. (1-Methyl-4-oxo-2-imidazolidinylidene)phosphoramidic acid.

Фосфокреатинин

$C_4H_8N_3O_4P$ = 193.1.

CAS — 5786-71-0 (fosfocreatinine); 19604-05-8 (fosfocreatinine sodium).

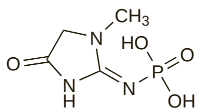

Profile

Fosfocreatinine or fosfocreatinine sodium has been used in muscle disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Sustenium.

Fosfructose Trisodium *(USAN, rINNM)*

CPC-111; Fosfructosa trisódica; Fosfructose Trisodique; Fosfructosum; Sodium Fructose-1,6-diphosphate. D-Fructose 1,6-bis(dihydrogen phosphate) trisodium octahydrate.

Тринатрий Фосфруктоза

$C_6H_{11}Na_3O_{12}P_2,8H_2O$ = 550.2.

CAS — 488-69-7 (fosfructose); 6055-82-9 (fosfructose calcium); 38099-82-0 (fosfructose trisodium); 81028-91-3 (fosfructose trisodium octahydrate);.

ATC — C01EB07.

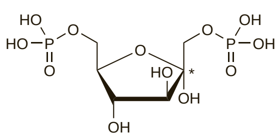

and epimer at C*

(fosfructose)

Profile

Fosfructose is a metabolic intermediate. It is used as the trisodium salt as a source of phosphate in deficiency states and in total parenteral nutrition, and has also been used to protect against ischaemic tissue damage. Fosfructose calcium has also been promoted for a variety of disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Esafosfina; ***Ital.:*** Esafosfina; FDP; Frut†; ***Thai.:*** Esafosfina.

Multi-ingredient: ***Hong Kong:*** Esafosfina Glutammica; ***Ital.:*** Esaglut†.

Frankincense

Olibanum; Ru Xiang.

Ладан

CAS — 8016-36-2 (frankincense oil).

NOTE. Distinguish from Indian Frankincense, below.

Profile

Frankincense is the aromatic gum resin of *Boswellia sacra* (*B. carteri*) (Burseraceae) or other species of *Boswellia*. It is used in incense and as a fumigant.

Frankincense (ru xiang) is also used in Chinese medicine. Frankincense oil is used in aromatherapy.

Indian Frankincense

Encens indien; Indian Olibanum; Olibanum indicum; Salai Guggal.

NOTE. Indian frankincense is obtained from *Boswellia serrata* and should be distinguished from Frankincense (above) obtained from other species of *Boswellia*.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Indian Frankincense). Air-dried gum-resin exudate, obtained by incision in the stem or branches of *Boswellia serrata*. It contains a minimum of 1.0% of 11-keto-β-boswellic acid ($C_{30}H_{46}O_4$ = 470.7) and a minimum of 1.0% of acetyl-11-keto-β-boswellic acid ($C_{32}H_{48}O_5$ = 512.7) calculated with reference to the dried drug.

Profile

Indian frankincense is the gum resin of *Boswellia serrata* (*B. glabra*) (Burseraceae). It has anti-inflammatory activity and is included in herbal preparations for musculoskeletal and joint disorders. It is also under investigation for use in inflammatory bowel disease and asthma. Boswellic acids extracted from the gum resin of *B. serrata* have also been tried for their anti-inflammatory actions in similar disorders.

◊ References.

1. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997; **2:** 37–43.
2. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res* 1998; **3:** 511–14.
3. Gupta I, *et al.* Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001; **67:** 391–5.
4. Kimmatkar N, *et al.* Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. *Phytomedicine* 2003; **10:** 3–7.
5. Ammon HPT. Boswellic acids in chronic inflammatory diseases. *Planta Med* 2006; **72:** 1100–16.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Glucobefol; ***Austral.:*** Bioglan Joint Mobility; Boswellia Complex; Boswellia Compound; ***Ital.:*** Actires; Fitogenase; Reumafort; Revios; ***Malaysia:*** Rumalaya; ***Singapore:*** Artrex†; ***UK:*** NatraFlex; PainEaze.

Fucoidan

Fucoidin; Fucoidine; Nemacystus Mucilage.

Фукоидан

CAS — 9072-19-9.

Profile

Fucoidan is a sulfated polysaccharide, based mainly on L-fucose, that is extracted from brown seaweed. It is reported to have anticoagulant, antithrombotic, and antineoplastic activity and has been promoted for a wide-range of disorders and as a food supplement.

◊ References.

1. Mourão PA. Use of sulfated fucans as anticoagulant and antithrombotic agents: future perspectives. *Curr Pharm Des* 2004; **10:** 967–81.

Nomenclature. Fucans are a class of sulfated polysaccharides first isolated from marine algae. Their nomenclature can be somewhat varied and confusing. The original polysaccharide isolated from algae was termed fucoidin and this was later changed to fucoidan. These polysaccharides have also been found in marine invertebrates and improved analytical and separation techniques have allowed different types of sulfated polysaccharides to be identified. It has been suggested that the term sulfated fucan should be defined as a polysaccharide based mainly on sulfated L-fucoses, with less than 10% other monosaccharides.[1] This term has been applied to the sulfated fucans of marine invertebrates, whereas the term fucoidan has been used for fucans extracted from algae. Some define fucoidan as a sulfated polysaccharide of L-fucose and D-galactose extracted from brown seaweed although others have used this term for sulfated polysaccharide complexes having a content of L-fucose of only 60% or less. Other terms that have been coined for these compounds include fucansulfate and fucan sulfate.

1. Berteau O, Mulloy B. Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 2003; **13:** 29R–40R.

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Mozuku.

Fumitory

Erdrauchkraut; Fumaria; Fumariae herba; Fumeterre; Zemědýmová nat'; Ziele dymnicy.

Дымовая Трава; Дымянка Лекарственная

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Fumitory). The whole or fragmented, dried aerial parts of *Fumaria officinalis* harvested in full bloom. It contains a minimum of 0.40% of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5$ = 353.4). Protect from light.

Profile

Fumitory comprises the dried or fresh flowering plant *Fumaria officinalis* (Papaveraceae) and is used in herbal medicine. It is an ingredient of preparations used mainly for gastrointestinal and biliary-tract disorders.

Homoeopathy. Fumitory has been used in homoeopathic medicines under the following names: Fumaria officinalis.

Irritable bowel syndrome. Neither fumitory nor Javanese turmeric (p.2406) was effective in a study[1] in patients with irritable bowel syndrome.

1. Brinkhaus B, *et al.* Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. *Scand J Gastroenterol* 2005; **40:** 936–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Bilobene; Oddibil; ***Braz.:*** Oddibil; ***Fr.:*** Oddibil; ***Ger.:*** Bilobene; Bomagall mono†; Oddibil†; ***Hung.:*** Bilobene; ***Pol.:*** Amphochol.

Multi-ingredient: ***Austria:*** Hepabene; Oddispasmol; ***Cz.:*** Hepabene†; ***Fr.:*** Actibil†; Bolcitol; Depuratif Parnel; Depuratum; Schoum; ***Hung.:*** Hepabene; ***Ital.:*** Soluzione Schoum; ***Pol.:*** Boldovera; ***Rus.:*** Hepabene (Гепабене); ***Spain:*** Natusor Hepavesical†; Odisor†; Solucion Schoum; ***UK:*** Echinacea; Skin Cleansing.

Gabexate Mesilate *(rINNM)*

Gabexate, Mésilate de; Gabexate Mesylate; Gabexati Mesilas; Mesilato de gabexato. Ethyl 4-(6-guanidinohexanoyloxy)benzoate methanesulphonate.

Габексата Мезилат

$C_{16}H_{23}N_3O_4,CH_4SO_3$ = 417.5.

CAS — 39492-01-8 (gabexate); 56974-61-9 (gabexate mesilate).

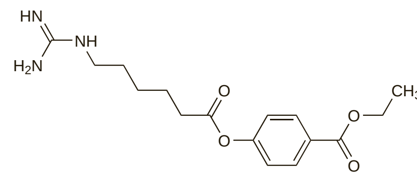

(gabexate)

Pharmacopoeias. In *Jpn.*

Profile

Gabexate mesilate is a proteolytic enzyme inhibitor that has been used for the treatment of pancreatitis (p.2361) in an initial dose of 100 to 300 mg daily given by intravenous infusion. The dose may be reduced, or a further 100 to 300 mg given on the same day, according to response. It has also been used for disseminated intravascular coagulation (p.1048) in a dose of 20 to 39 mg/kg given as a continuous intravenous infusion over 24 hours. Hypersensitivity reactions including anaphylaxis have occurred.

◊ References.

1. Messori A, *et al.* Effectiveness of gabexate mesilate in acute pancreatitis: a metaanalysis. *Dig Dis Sci* 1995; **40:** 734–8.
2. Cavallini G, *et al.* Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N Engl J Med* 1996; **335:** 919–23.
3. Matsukawa Y, *et al.* Anaphylaxis induced by gabexate mesylate. *BMJ* 1998; **317:** 1563.
4. Ranucci M, *et al.* Gabexate mesilate and antithrombin III for intraoperative anticoagulation in heparin pretreated patients. *Perfusion* 1999; **14:** 357–62.
5. Matsukawa Y, *et al.* Fatal cases of gabexate mesilate-induced anaphylaxis. *Int J Clin Pharmacol Res* 2002; **22:** 81–3.
6. Masci E, *et al.* Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; **98:** 2182–6.
7. Andriulli A, *et al.* Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. *Clin Gastroenterol Hepatol* 2004; **2:** 713–18.
8. Hsu JT, *et al.* Efficacy of gabexate mesilate on disseminated intravascular coagulation as a complication of infection developing after abdominal surgery. *J Formos Med Assoc* 2004; **103:** 678–84.
9. Rudin D, *et al.* Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. *J Gastroenterol Hepatol* 2007; **22:** 977–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Foy; ***Jpn:*** Foy.

Gall

Agallas de roble; Aleppo Galls; Blue Galls; Duběnka; Galla; Galläpfel; Galls; Noix de Galle; Nutgall.

Чернильный Орешек

Pharmacopoeias. In *Chin.*

Profile

Gall is the excrescences on the twigs of *Quercus infectoria* (Fagaceae), resulting from the stimulus given to the tissues of the young twigs by the development of the larvae of the gall-wasp, *Adleria gallae-tinctoriae* (*Cynips gallae-tinctoriae*) (Cynipidae). It contains about 50 to 70% of gallotannic acid.

Gall is an astringent and has been used in ointments and suppositories for the treatment of haemorrhoids. It is a source of tannic acid (p.2394).

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Litiax.

Galsulfase *(BAN, USAN, rINN)*

BM-102; Galsulfasa; Galsulfasum; recombinant human arylsulfatase B; rhASB. *N*-Acetylgalactosamine 4-sulfatase.

Гальсульфас

CAS — 552858-79-4.
ATC — A16AB08.
ATC Vet — QA16AB08.

Profile

Galsulfase is recombinant human *N*-acetylgalactosamine 4-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis VI (see below). Galsulfase is given by intravenous infusion in a dose of 1 mg/kg once a week. Infusion reactions are common and patients should be pre-treated with antihistamines with or without antipyretics. Galsulfase should be reconstituted to a final volume of 250 mL in sodium chloride 0.9% and given using an infusion pump. The initial infusion rate should be 6 mL/hour for the first hour, which may then be increased to 80 mL/hour if well tolerated. The total infusion time should be at least 4 hours to minimise the risk of infusion reactions, but may be extended to up to 20 hours, or interrupted, if necessary, in the event of infusion reactions. Patients weighing 20 kg and under may be susceptible to fluid overload and a smaller infusion volume of 100 mL should be considered, in which case, the infusion rate should be decreased accordingly so that the total infusion time is not less than 4 hours.

Adverse effects. References.

1. Kim KH, *et al.* Successful management of difficult infusion-associated reactions in a young patient with mucopolysaccharidosis type VI receiving recombinant human arylsulfatase B (galsulfase [Naglazyme]). Abstract: *Pediatrics* 2008; **121:** 609. Full version: http://pediatrics.aappublications.org/cgi/content/full/121/3/e714 (accessed 01/05/08)

Mucopolysaccharidosis VI. Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) is a rare progressive disorder characterised by inherited deficiency of the enzyme *N*-acetylgalactosamine 4-sulfatase, which is necessary to catalyse the hydrolysis of the sulfate moiety of the glycosaminoglycan, dermatan sulfate. This results in accumulation of dermatan sulfate in the lysosomes producing widespread irreversible cellular and tissue damage, and organ dysfunction. There is a rapidly advancing form of the disease that presents in the first year of life characterised by short stature, skeletal and joint deformities, dysmorphic facial features, upper airway obstruction requiring tracheostomy, and recurrent ear infections. There is also a more slowly advancing form that progresses over many decades. Both forms result in significant morbidity and functional problems with a reduced lifespan.[1]

Treatment is supportive and symptomatic involving many body systems; physical and occupational therapy is also necessary.[1] Haematopoietic stem-cell transplantation to supply the deficient enzyme is of benefit to some patients, although it is associated with significant morbidity and mortality.[1] Enzyme replacement therapy with galsulfase has been reported to confer benefit with an acceptable safety profile.[1,2]

1. Giugliani R, *et al.* Management guidelines for mucopolysaccharidosis VI. *Pediatrics* 2007; **120:** 405–18.
2. Harmatz P, *et al.* Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human *N*-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr* 2006; **148:** 533–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Naglazyme; ***Fr.:*** Naglazyme; ***Port.:*** Naglazyme; ***USA:*** Naglazyme.

Gamma-aminobutyric Acid

Ácido gamma-aminobutírico; Acidum Aminobutyricum Gamma; γ-Aminobutírico, ácido; Aminobutyric Acid; GABA; Gamma-aminosmörsyra; Gamma-aminovoihappo; Piperidic Acid. 4-Aminobutyric acid.

Гамма-аминобутировая Кислота

$C_4H_9NO_2$ = 103.1.
CAS — 56-12-2.
ATC — N03AG03.
ATC Vet — QN03AG03.

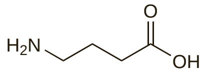

Profile

Gamma-aminobutyric acid is a principal inhibitory neurotransmitter in the CNS. It has been claimed to be of value in cerebral disorders and to have an antihypertensive effect.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Gammar; ***Hong Kong:*** Gammalon; ***Port.:*** Mielomade†; ***Thai.:*** Bainto; Gammalon.

Multi-ingredient: ***Arg.:*** Butineuron; Cadencial Plus; ***Braz.:*** Complevit; Gaba†; Gabax; Id Sedin†; ***Chile:*** Actebral; Gamalate B6; ***Spain:*** Cefabol; Gamalate B6.

Gamolenic Acid *(BAN, rINN)*

Acide Gamolénique; Ácido gamolénico; Acidum Gamolenicum; GLA; γ-Linolenic Acid. (*Z,Z,Z*)-Octadeca-6,9,12-trienoic acid.

Гамоленовая Кислота

$C_{18}H_{30}O_2$ = 278.4.
CAS — 506-26-3.
ATC — D11AX02.
ATC Vet — QD11AX02.

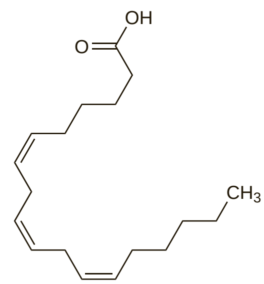

Linoleic Acid

Kwas linolowy; Linoleico, ácido; Linolic Acid; Linolsäure. (*Z,Z*)-Octadeca-9,12-dienoic acid.

Линолевая Кислота

$C_{18}H_{32}O_2$ = 280.4.
CAS — 60-33-3.

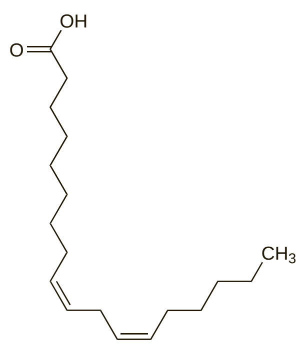

Adverse Effects and Precautions

Gamolenic and linoleic acids from evening primrose oil, and presumably other sources, can produce minor gastrointestinal disturbances and headache. They can precipitate symptoms of undiagnosed temporal lobe epilepsy, and should be used with caution in patients with a history of epilepsy or those taking epileptogenic drugs, in particular phenothiazines. Hypersensitivity reactions may also occur.

Uses and Administration

Gamolenic and linoleic acid are essential fatty acids of the omega-6 series that act as prostaglandin precursors. Endogenous gamolenic acid is derived from linoleic acid, which is present in many vegetable oils and is an essential constituent of the diet. The most widely-used source of these acids is evening primrose oil (see p.2302). Gamolenic and linoleic acids have been used in skin disorders and mastalgia, and have been investigated in other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome.

Preparations containing essential fatty acids (formerly known collectively as vitamin F), including arachidonic acid, linoleic acid, linolenic acid (α-linolenic acid, p.1362), oleic acid, and their derivatives, have been used similarly. Conjugated linoleic acid (CLA), a mixture of isomers in which *cis*-9,*trans*-11-octadecadienoic acid and *trans*-10,*cis*-12-octadecadienoic acid predominate, has also been used.

Products containing gamolenic-acid rich plant oils are promoted in many countries as dietary supplements, often in combination with fish oils or other sources of omega-3 fatty acids (see p.1362).

A derivative of gamolenic acid, lithium gamolenate, has been investigated in pancreatic cancer.

Eczema. Atopic eczema (p.1579) may be due to a defect in essential fatty acid metabolism[1,2] and some beneficial symptomatic effects have been reported with evening primrose oil.[1,3] Meta-analysis of 9 studies involving 311 patients[4] has reported improvement in disease symptoms, especially itching, but a subsequent study in 123 patients found no therapeutic effect of evening primrose oil, alone or with fish oil.[5] Although the design and interpretation of this study has been criticised by the manufacturers of evening primrose oil,[6] the authors consider such criticism invalid,[7] and point out that an earlier large study yielded similar results.[8] No difference was found between placebo and evening primrose oil in a further study[9] in children with eczema, and there was also no effect on asthma symptoms in those patients suffering from both disorders. Studies[10,11] of borage oil (another source of gamolenic acid) also found no overall efficacy in adults or children with atopic eczema, although one study noted a suggestion of benefit in a subgroup of patients.[10] In a study[12] of a group of formula-fed infants with a high maternal familial risk of developing atopic eczema, borage oil supplementation did not prevent the expression of atopy, although it showed a tendency to alleviate the severity of the condition later in infancy.

Benefit has been reported in infants with seborrhoeic dermatitis from local application of borage oil.[13]

1. Wright S. Essential fatty acids and the skin. *Br J Dermatol* 1991; **125:** 503–15.
2. Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. *Am J Clin Nutr* 2000; **71** (suppl): 367S–372S.
3. Rustin MHA. Dermatology. *Postgrad Med J* 1990; **66:** 894–905.
4. Morse PF, *et al.* Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema: relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989; **121:** 75–90.
5. Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **341:** 1557–60. Correction. *ibid.*; **342:** 564.
6. Shield MJ, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **342:** 377.
7. Berth-Jones J, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; **342:** 377–8. Correction. *ibid.*; 752.
8. Bamford JTM, *et al.* Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1985; **13:** 959–65.
9. Hederos C-A, Berg A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. *Arch Dis Child* 1996; **75:** 494–7.
10. Henz BM, *et al.* Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999; **140:** 685–8.
11. Takwale A, *et al.* Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003; **327:**1385–7.
12. van Gool CJ, *et al.* γ-Linolenic acid supplementation for prophylaxis of atopic dermatitis—a randomized controlled trial in infants at high familial risk. *Am J Clin Nutr* 2003; **77:** 943–51.
13. Tollesson A, Frithz A. Borage oil, an effective new treatment for infantile seborrhoeic dermatitis. *Br J Dermatol* 1993; **129:** 95.

Mastalgia. Gamolenic acid (usually given in the form of evening primrose oil) has fewer adverse effects than drugs such as danazol or bromocriptine and has been preferred for mastalgia (p.2092), especially in patients with less severe symptoms or those who require prolonged or repeated treatment. However, there is no clear evidence of efficacy.

Multiple sclerosis. There is some evidence that modifying the intake of dietary fats and supplementing the diet with omega-6 polyunsaturated fatty acids, such as linoleic acid, could influence the clinical course of multiple sclerosis (p.892) and many patients practise dietary modification, including taking evening primrose oil. One study[1] has shown a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil), and another[2] has reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[3] of the relationship between dietary interventions (including linoleic acid supplements) and MS concluded that there was insufficient evidence to determine their benefits or risks.

1. Millar JHD, *et al.* Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; **1:** 765–8.
2. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; **336:** 37–9.
3. Farinotti M, *et al.* Dietary interventions for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Premenstrual syndrome. Progressive improvement in premenstrual syndrome (p.2099) was reported over 5 cycles in an open pilot study in 19 patients receiving evening primrose oil.[1] However, subsequent results have not shown any benefit.[2-4] Evening primrose oil has been considered for cyclical mastalgia (see above).

1. Larsson B, *et al.* Evening primrose oil in the treatment of premenstrual syndrome: a pilot study. *Curr Ther Res* 1989; **46:** 58–63.
2. Khoo SK, *et al.* Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990; **153:** 189–92.
3. Collins A, *et al.* Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol* 1993; **81:** 93–8.
4. Budeiri DJ, *et al.* Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996; **17:** 60–8.

Rheumatoid arthritis. Patients with rheumatoid arthritis (p.11) taking NSAIDs have shown subjective improvement after 12 months of treatment with evening primrose oil, with or without fish oil, when compared with placebo.[1] A clinically important reduction in signs and symptoms of disease activity has also been seen in patients treated with gamolenic acid in the form of borage oil.[2] During treatment with evening primrose oil patients with rheumatoid arthritis have increased plasma concentrations of gamolenic, dihomo-gamma-linolenic, and arachidonic acids, and decreased plasma concentrations of oleic and eicosapentaenoic acids and apolipoprotein B.[3] The increase in plasma-arachidonic acid and decrease in eicosapentaenoic acid might be unfavourable in such patients, since arachidonic acid is the precursor of inflammatory prostaglandins and eicosapentaenoic acid may have an anti-inflammatory role. However, a systematic review[4] of these and other studies concluded that there does appear to be some potential benefit for the use of gamolenic acid in rheumatoid arthritis, although optimum dosage and duration of treatment remains to be established.

1. Belch JJF, *et al.* Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988; **47:** 96–104.
2. Leventhal LJ, *et al.* Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993; **119:** 867–73.
3. Jäntti J, *et al.* Evening primrose oil in rheumatoid arthritis: changes in serum lipids and fatty acids. *Ann Rheum Dis* 1989; **48:** 124–7.
4. Little CV, Parsons T. Herbal therapy for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 23/05/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Vitamin F; ***Ger.:*** Cefafloria†; Linola-Fett 2000†; Sanyrene; ***Ital.:*** Ictage 6†; Normogam†; Triene; Vitef; ***Pol.:*** Dermovit F; Linola; Linomag; ***UK:*** Super GLA.

Multi-ingredient: ***Arg.:*** Exomega; KW; Quelodin F; ***Austria:*** Cehasol; Mamellin; Sulgan 99; ***Braz.:*** Glavit; Oleo de Primula; Primoris; ***Canad.:*** Bionagre plus E; ***Chile:*** Ureadin Pediatrics; ***Cz.:*** Linola; Linola-Fett; ***Fr.:*** Exomega; ***Ger.:*** Hydro Cordes; Linola; Linola-Fett; Lipo Cordes; Unguentacid; ***Hong Kong:*** Aderma Exomega†; Eye Q; Welsan Lipocream; ***Hung.:*** Linola; Linola-Fett N†; ***Ital.:*** Derman-Oil; Dermana Crema; Dermana Pasta; Efagel; Granoleina†; Neuralfa; Osteolip; Pasta Dicofarm; Secril; Tiofort; Topialyse; Trofinerv Antiox; ***Mex.:*** Nutrem; ***NZ:*** Efamast; ***Port.:*** Geriso; Zolium†; ***S.Afr.:*** Efamol G†; ***Spain:*** Amplidermis; Doctofril Antiinflamat; Mahiou†; Nutracel; Vitamina F99 Topica; Wobenzimal†; ***Switz.:*** Keroderm†; Linola; Linola gras; Linola mi-gras; Linoladiol†; Sulgan N; Vitafissan N; Vitamine F99†.

Gangliosides

Gangliósidos.

Ганглиозиды

Profile

Gangliosides are endogenous substances present in mammalian cell membranes, especially in the cortex of the brain. They are glycosphingolipids composed of a hydrophilic oligosaccharide chain, characterised by sialic acid residues, attached to a lipophilic moiety. The four major gangliosides found in the mammalian brain are referred to as G_{M1}, G_{D1a}, G_{D1b}, and G_{T1b}.

Experimental studies have reported that gangliosides may have a neuroprotective effect on the CNS and peripheral nervous system. Preparations of gangliosides from bovine brain have been given for peripheral neuropathies and cerebrovascular disorders and their role in spinal cord injury has also been investigated. The modified ganglioside siagoside has been studied in patients with Parkinson's disease.

Concern was expressed about the development of Guillain-Barré syndrome and other motor neurone disorders in some patients, and it was suggested that gangliosides were contra-indicated in Guillain-Barré syndrome and all auto-immune disorders. Subsequently these concerns over safety and doubts about efficacy led to the withdrawal of ganglioside preparations in many countries.

◊ References.

1. Geisler FH, *et al.* Recovery of motor function after spinal-cord injury—a randomized, placebo-controlled trial with GM-1 ganglioside. *N Engl J Med* 1991; **324:** 1829–38.
2. Raschetti R, *et al.* Guillain-Barré syndrome and ganglioside therapy in Italy. *Lancet* 1992; **340:** 60.
3. Figueras A, *et al.* Bovine gangliosides and acute motor polyneuropathy. *BMJ* 1992; **305:** 1330–1.
4. Roberts JW, *et al.* Iatrogenic hyperlipidaemia with GM-1 ganglioside. *Lancet* 1993; **342:** 115.
5. Landi G, *et al.* Guillain-Barré syndrome after exogenous gangliosides in Italy. *BMJ* 1993; **307:** 1463–4.
6. Nobile-Orazio E, *et al.* Gangliosides: their role in clinical neurology. *Drugs* 1994; **47:** 576–85.
7. Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 23/05/06).
8. Fredman P, *et al.* Gangliosides as therapeutic targets for cancer. *BioDrugs* 2003; **17:** 155–67.
9. Govoni V, *et al.* Is there a decrease in Guillain-Barré syndrome incidence after bovine ganglioside withdrawal in Italy? A population-based study in the Local Health District of Ferrara, Italy. *J Neurol Sci* 2003; **216:** 99–103.
10. Chinnock P, Roberts I. Gangliosides for acute spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/05/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Sinaxial; Sygen.

Garcinia Cambogia

Brindleberry; Malabar Tamarind.

CAS — 90045-23-1 (Garcinia cambogia extract).

Profile

Extracts of Garcinia cambogia (*Garcinia gummi-gutta*, Clusiaceae) are a source of hydroxycitric acid and are included in preparations for the treatment of obesity.

Several species of *Garcinia* are used in traditional medicine, as a food source, and as a source of the pigment gamboge.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Citrimax†; ***Mex.:*** Terocaps.

Multi-ingredient: ***Arg.:*** Garcinia Cambogia Compuesta; Garcinol Max; Mermelax; Metabolic; Reductase; Redudiet; Silueta Plus; Top Life Diet†; ***Austral.:*** Bioglan 3B Beer Belly Buster; Citri Slim+Trim; Pro-Shape†; ***Canad.:*** Biotrim†; ***Indon.:*** Betaslim; Combes; Vitaslim; ***Ital.:*** Altadrine; Snell Cell; ***Mex.:*** Slim-D; ***Port.:*** Fit Form 3†; ***Singapore:*** Chitosano; Colenon.

Garlic

Aglio; Ail; Ail, poudre d' (garlic powder); Ajo; Allii sativi bulbi pulvis (garlic powder); Allium; Allium Sativum; Česnakų milteliai (garlic powder); Cibule česneku setého práškovaná (garlic powder); Fokhagymapor (garlic powder); Knoblauch; Valkosipuli; Vitlök.

Чеснок

CAS — 8008-99-9 (garlic extract).

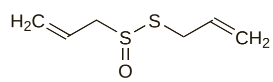

allicin

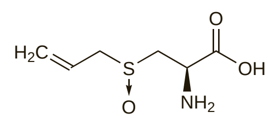

alliin

Pharmacopoeias. In *US*, which also includes Garlic Fluidextract, Powdered Garlic, and Powdered Garlic Extract. *Eur.* (see p.vii) includes Garlic Powder.

Eur. also includes Garlic for Homoeopathic Preparations.

Ph. Eur. 6.2 (Garlic Powder). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65°, and powdered. It contains not less than 0.45% of allicin, calculated with reference to the dried drug. It is a light yellowish powder. Protect from light.

Ph. Eur. 6.2 (Garlic for Homoeopathic Preparations). The fresh bulb of *Allium sativum*. Store in airtight containers. Protect from light.

USP 31 (Garlic). The fresh or dried compound bulbs of *Allium sativum* (Liliaceae). It contains not less than 0.5% of alliin and not less than 0.2% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8° to 15°. Protect from light.

USP 31 (Powdered Garlic). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65°, and powdered. It contains not less than 0.3% of alliin and not less than 0.1% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8° to 15°. Protect from light.

Adverse Effects

◊ Reports of burns or skin lesions after topical application of garlic to children,[1,2] and to adults,[3,4] including self-inflicted injury.[5]

1. Garty B-Z. Garlic burns. *Pediatrics* 1993; **91:** 658–9.
2. Canduela V, *et al.* Garlic: always good for the health? *Br J Dermatol* 1995; **132:** 161–2.
3. Farrell AM, Staughton RCD. Garlic burns mimicking herpes zoster. *Lancet* 1996; **347:** 1195.
4. Eming SA, *et al.* Severe toxic contact dermatitis caused by garlic. *Br J Dermatol* 1999; **141:** 391–2.
5. Lachter J, *et al.* Garlic: a way out of work. *Mil Med* 2003; **168:** 499–500.

Uses and Administration

The constituents of garlic include alliin, allicin, diallyl disulfide, and ajoene. It has traditionally been reported to have expectorant, diaphoretic, disinfectant, and diuretic properties. More recently, it has been investigated for antimicrobial, antihypertensive, lipid-lowering, fibrinolytic, antiplatelet, and cancer protective effects. Garlic oil has also been used.

Homoeopathy. Garlic has been used in homoeopathic medicines under the following names: Allium sativum; All. sat.

◊ References.

1. Kleijnen J, *et al.* Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; **28:** 535–44.
2. Mansell P, Reckless JPD. Garlic. *BMJ* 1991; **303:** 379–80.
3. McElnay JC, Po ALW. Garlic. *Pharm J* 1991; **246:** 324–6.
4. Kiesewetter H, *et al.* Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *Eur J Clin Pharmacol* 1993; **45:** 333–6.
5. Deshpande RG, *et al.* Inhibition of Mycobacterium avium complex isolates from AIDS patients by garlic (Allium sativum). *J Antimicrob Chemother* 1993; **32:** 623–6.
6. Dorant E, *et al.* Garlic and its significance for the prevention of cancer in humans: a critical review. *Br J Cancer* 1993; **67:** 424–9.
7. Ackermann RT, *et al.* Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 2001; **161:** 813–24.
8. Tattelman E. Health effects of garlic. *Am Fam Physician* 2005; **72:** 103–6.
9. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. *J Nutr* 2006; **136** (suppl): 736S–740S.

Hyperlipidaemia. Garlic has been widely promoted for use in the treatment of hyperlipidaemia (p.1169). Several early placebo-controlled trials[1,2] and meta-analyses[3,4] showed that garlic significantly decreased total serum-cholesterol concentrations. However, more recent data suggest that the effect is at best modest[5] or that there is no significant difference[6-9] when compared with placebo.

1. Jain AK, *et al.* Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med* 1993; **94:** 632–5.
2. Kenzelmann R, Kade F. Limitation of the deterioration of lipid parameters by a standardized garlic-ginkgo combination product: a multicenter placebo-controlled double-blind study. *Arzneimittelforschung* 1993; **43:** 978–81.
3. Warshafsky S, *et al.* Effect of garlic on total serum cholesterol: a meta-analysis. *Ann Intern Med* 1993; **119:** 599–605.
4. Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Physicians Lond* 1994; **28:** 39–45.
5. Stevinson C, *et al.* Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. *Ann Intern Med* 2000; **133:** 420–9.
6. Neil HAW, *et al.* Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and a meta-analysis. *J R Coll Physicians Lond* 1996; **30:** 329–34.
7. Berthold HK, *et al.* Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *JAMA* 1998; **279:** 1900–2.
8. Isaacsohn JL, *et al.* Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med* 1998; **158:** 1189–94.
9. Gardner CD, *et al.* Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. *Arch Intern Med* 2007; **167:** 346–53.

Preparations

USP 31: Garlic Delayed-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ajomast; Alliocaps; Kyolic Super Formula†; ***Austral.:*** Garlix; Macro Garlic†; ***Austria:*** Kwai; ***Canad.:*** Kwai†; Kyolic†; ***Cz.:*** Kwai†; ***Ger.:*** Alliosan†; beni-cur†; Carisano†; Ilja Rogoff Forte†; Kwai; Ravalgen†; Sapec; Strongus†; Vitagutt Knoblauch†; ***Ital.:*** Kwai; ***Malaysia:*** Kyolic; ***Pol.:*** Aliovital; Alitol; Geriacaps; ***Port.:*** Alho Rogoff†; ***Switz.:*** A Vogel Capsules a l'ail†; Kwai†; ***UK:*** Garlimega; Kwai; Kyolic; ***Venez.:*** Kwai†.

Multi-ingredient: ***Arg.:*** Aglio; Ajo 1000 + C; Ajo Forte; Ajolip; Ajomast Circulatorio†; Exail; Varisedan; ***Austral.:*** Garlic Allium Complex; Garlic and Horseradish + C Complex; Garlic, Horseradish, A & C Capsules†; Gartech; Herbal Cold & Flu Relief†; Lifesystem Herbal Formula 7 Liver Tonic†; Liver Tonic Herbal Formula 6†; Odourless Garlic; Procold†; Proesten†; Protol†; Proyeast†; Silybum Complex†; ***Austria:*** Rutiviscal; ***Canad.:*** Kyolic 101; Kyolic 102; Kyolic 103†; Kyolic 104†; Kyolic 106†; ***Fr.:*** Arterase; ***Ger.:*** Asgoviscum N†; Ilja Rogoff; Lipidavit; Presselin Arterien K 5 P†; ***Hong Kong:*** Ginkgo Plus Vivo-Livo†; ***Indon.:*** Garlic-Plus; Resvica; Sotens; ***Ital.:*** Angiovein; ***Malaysia:*** Circarol; Echinacea Plus†; Horseradish Plus†; Total Man†; ***Mex.:*** Supravital; ***Philipp.:*** Circulan; Nutrotal; ***Pol.:*** Alliofil; Alliogal†; Alliorut; Cepasmel; Cepastil; Doppelherz Vital Kapseln; ***Switz.:*** Allium Plus; Arterosan Plus; Keli-med; Triallin; ***UK:*** Antifect; Clogar; Fishogar; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Liqufruta Garlic Cough Medicine.

Gavestinel *(BAN, USAN, rINN)*

Gavestinelum; GV-150526X. 4,6-Dichloro-3-[(*E*)-2-(phenylcarbamoyl)vinyl]indole-2-carboxylic acid.

Гавестинел

$C_{18}H_{12}Cl_2N_2O_3$ = 375.2.

CAS — 153436-22-7.

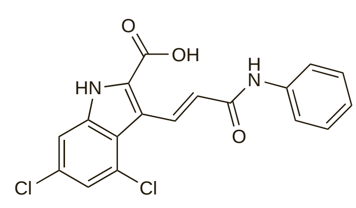

Profile

Gavestinel is a glycine antagonist that has been investigated as a neuroprotectant in stroke.

The symbol † denotes a preparation no longer actively marketed

Stroke. Gavestinel has been tried for its supposed neuroprotective properties in acute stroke, but two major multicentre, randomised controlled studies have failed to show any benefit over placebo in acute ischaemic stroke.[1,2] Analysis of the data from these two studies in patients with primary intracerebral haemorrhage found no benefit of gavestinel in this subgroup either.[3]

1. Lees KR, *et al.* Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. *Lancet* 2000; **355:** 1949–54.
2. Sacco RL, *et al.* Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. *JAMA* 2001; **285:** 1719–28.
3. Haley EC, *et al.* Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. *Stroke* 2005; **36:** 1006–10.

Gelsemium

Gelsemium Root; Jessamine; Yellow Jasmine Root.

Корень Желтого Жасмина

CAS — 509-15-9 (gelsemine).

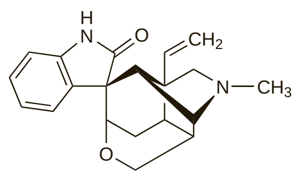

(gelsemine)

Profile

Gelsemium consists of the dried rhizome and roots of *Gelsemium sempervirens* (Loganiaceae). It contains toxic indole alkaloids including gelsemine ($C_{20}H_{22}N_2O_2$ = 322.4). It depresses the CNS and has been used mainly in neuralgic conditions, particularly trigeminal neuralgia and migraine.

Homoeopathy. Gelsemium has been used in homoeopathic medicines under the following names: Gelsemium sempervirens; Gels.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Coquelusedal; Coquelusedal Paracetamol.

Gene Therapy

Terapéutica génica.

Генотерапия

Profile

Gene therapy is a product of the increasing knowledge of genetic function and the availability of methods to examine and manipulate the genome. Exogenous genetic material, which may be synthetic or recombinant nucleic acids (p.2355), is introduced into somatic cells (transfection) in such a way that the cells are able to express the products of the new genes. It may be used for therapeutic, prophylactic, or diagnostic purposes. Gene therapy should be distinguished from the use of products derived from organisms (usually micro-organisms) whose genome has been manipulated by similar recombinant DNA technology, for example the use of recombinant cytokines, monoclonal antibodies, or antisense products.

Gene therapy is under investigation in three main areas:

- the replacement of abnormal or defective genes in patients with inherited disease
- the alteration of the characteristics of cells to change their relative susceptibility to other therapies (for example by making haematopoietic stem cells more resistant to the adverse effects of antineoplastics, or by making tumour cells selectively express an enzyme that converts an otherwise non-toxic prodrug into a cytotoxic agent)
- for localised production of a biologically active substance that cannot be given directly or would have unacceptable effects if used systemically.

To date, all gene therapy in humans has been of differentiated somatic cells. Alteration of the human genome in a manner transmissible to offspring, either by treating the germ cells or the early embryo, is considered at present to pose insuperable ethical problems.

Various methods for delivery of genetic material have been investigated, none of which is yet completely satisfactory. These include biological vectors (e.g. viruses or plasmids) or stem cells that have been genetically modified, oncolytic viruses, nucleic acids, either naked plasmids or carried by delivery vehicles, and genetic vaccines. Antisense techniques to modify, correct, or silence aberrant genes are also being developed, as is RNA interference. Xenotransplantation of animal cells may also be an option. Removal of donor cells from the patient followed by *ex vivo* transfer of the new gene (by physical or viral methods) and return of the modified cells may be feasible for modifying haematopoietic stem cells. However, for most tissues, methods of *in vivo* transfer are required. Modified viruses rendered incapable of replicating have been widely studied as vectors for gene therapy. Retroviruses have the advantage that the DNA they carry is integrated into the host genome, resulting in permanent expression of the gene, but there has been some concern that they may disrupt existing genetic material with possibly oncogenic effect; in addition, their small size limits the size of gene that they can carry, and they are largely ineffective in infecting non-dividing cells. Adenoviruses are more stable and can infect non-dividing as well as dividing cells, but their genetic freight is not integrated into the chromosome and transmitted to the cell's progeny, and the gene products are therefore only expressed transiently; they are also highly immunogenic which limits repeated use. Some other viral types, including herpes simplex viruses, adeno-associated viruses, and lentiviruses, are also under investigation. Viruses with tropisms for a particular tissue may be useful in producing localised effects.

Chemical or physical methods for DNA delivery have been extensively investigated. Such methods include direct injection of DNA, the use of DNA complexes bound to a ligand which can be taken up by cells, formulation of DNA in liposomes which can fuse with cell membranes and allow the DNA to enter the cell, and more exotic methods such as 'gene guns', in which DNA-coated gold particles are fired into the cells. Although gene expression can be achieved after use of such methods, it is again transient because the new genetic material is not integrated with that of the host, and physical methods are currently less efficient and more limited in scope than viral ones.

Numerous clinical studies are being carried out. The first successful therapy was for severe combined immunodeficiency, a single-gene disorder due to deficiency of the enzyme adenosine deaminase. Transfection of the gene for this enzyme into the patient's T-cells *ex vivo* and re-infusion of the modified T-cells has been shown to produce substantial clinical improvement, although therapy must be repeated periodically because of the limited lifespan of the lymphocytes.

Studies in patients with cystic fibrosis have also shown some success, and a number of other single-gene disorders, including alpha$_1$ antitrypsin deficiency, familial hypercholesterolaemia, Gaucher disease, the haemoglobinopathies and haemophilias, and Duchenne muscular dystrophy are being studied or have been proposed as possible candidates.

Gene therapy is also under investigation in various acquired diseases, particularly in the management of various types of cancer. Strategies being studied include modification of tumour cells either to increase their immunogenicity or to render them selectively sensitive to antineoplastics, and transfection of tumour cells with tumour suppressor genes. Other disorders being studied clinically include HIV infection, rheumatoid arthritis, Parkinson's disease and atherosclerosis.

◊ Some reviews and references concerning gene therapy are listed below. See also under the discussions of individual diseases for comments on gene therapy in the context of their conventional treatment.

1. Hu WS, Pathak VK. Design of retroviral vectors and helper cells for gene therapy. *Pharmacol Rev* 2000; **52:** 493–511.
2. WHO. Gene transfer medicinal products. *WHO Drug Inf* 2002; **16:** 275–82.
3. Tomanin R, Scarpa M. Why do we need new gene therapy viral vectors? Characteristics, limitations and future perspectives of viral vector transduction. *Curr Gene Ther* 2004; **4:** 357–72.
4. Department of Health. Recommendations of the GTAC/CSM working party on retroviruses. Internet Document: May 2005. Available at: http://www.advisorybodies.doh.gov.uk/genetics/gtac/FinalrecommendationsJune2005.pdf (accessed 11/02/08)
5. Basu J, Willard HF. Artificial and engineered chromosomes: non-integrating vectors for gene therapy. *Trends Mol Med* 2005; **11:** 251–8.
6. Barzon L, *et al.* Versatility of gene therapy vectors through viruses. *Expert Opin Biol Ther* 2005; **5:** 639–62.
7. Sinn PL, *et al.* Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors—design, biosafety, and production. *Gene Ther* 2005; **12:** 1089–98.
8. Wierdl M, Potter PM. Update on gene therapy approaches for cancer. *Curr Hematol Rep* 2005; **4:** 294–9.
9. Hart SL. Lipid carriers for gene therapy. *Curr Drug Deliv* 2005; **2:** 423–8.
10. Kaplan JM. Adenovirus-based cancer gene therapy. *Curr Gene Ther* 2005; **5:** 595–605.
11. Ohlfest JR, *et al.* Nonviral vectors for cancer gene therapy: prospects for integrating vectors and combination therapies. *Curr Gene Ther* 2005; **5:** 629–41.
12. Dobson J. Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther* 2006; **13:** 283–7.
13. Pelletier R, *et al.* RNA based gene therapy for dominantly inherited diseases. *Curr Gene Ther* 2006; **6:** 131–46.
14. Park F, Gow KW. Gene therapy: future or flop. *Pediatr Clin North Am* 2006 **Aug:** 621–38.
15. Lavigne MD, Gorecki DC. Emerging vectors and targeting methods for nonviral gene therapy. *Expert Opin Emerg Drugs* 2006; **11:** 541–57.
16. Chan S, Harris J. The ethics of gene therapy. *Curr Opin Mol Ther* 2006; **8:** 377–83.
17. Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: are we there yet? *J Clin Invest* 2007; **117:** 1456–65.

Gentian

Bitter Root; Enzianwurzel; Genciana; Gencijonų šaknys; Gentian Root; Gentiana; Gentianae radix; Gentianarot; Gentiane; Gentiane, racine de; Genziana; Hořcový kořen; Katkeronjuuri; Korzeń goryczki; Raiz de Genciana; Tárnicsgyökér.

Горький Корень

Pharmacopoeias. In *Eur.* (see p.vii), and *Jpn.*

Jpn includes Japanese Gentian, from *G. scabra* and other species.

Chin. also specifies *G. scabra* and other species.

Ph. Eur. 6.2 (Gentian Root; Gentian BP 2008). The dried, fragmented underground organs of *Gentiana lutea* yielding not less than 33% of water-soluble extractive. It has a characteristic odour. Protect from light.

Profile

Gentian is used as a bitter. An alcoholic infusion of gentian, bitter-orange peel, and lemon peel has been used as an ingredient in a number of bitter mixtures.

Homoeopathy. Gentian has been used in homoeopathic medicines under the following names: Gentiana lutea; Gent. lut.

Preparations

BP 2008: Acid Gentian Mixture; Alkaline Gentian Mixture; Compound Gentian Infusion; Concentrated Compound Gentian Infusion;
Ph. Eur.: Gentian Tincture.

Proprietary Preparations (details are given in Part 3)
Ger.: Digestivum-Hetterich S†; Enziagil Magenplus†; Sern-SL.

Multi-ingredient: ***Austral.:*** Calmo; Digest; Digestaid; Digestive Aid; Extralife Sleep-Care; Pacifenity†; Relaxaplex†; Sinulin†; ***Austria:*** Abdomilon N; Brady's-Magentropfen; China-Eisenwein; Mariazeller; Montana; Sigman-Haustropfen; Sinupret; Solvopret; ***Braz.:*** Camomila; Digestar†; Estomafitino†; Gotas Digestivas; Xarope Iodo-Suma†; ***Canad.:*** Herbal Laxative; Herbal Laxative plus Yogurt; ***Cz.:*** Abdomilon†; Biotussil; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; Klosterfrau Melisana; Naturland Grosser Swedenbitter†; Original Schwedenbitter; Sinupret; ***Fr.:*** Elixir Grez†; Quintonine; ***Ger.:*** Abdomilon N; Amara-Pascoe; Amara-Tropfen; Anore X N†; Gallexier; Gastralon N†; Gastrol S†; Gastrosecur†; Hepaticum-Medice H†; Infi-tract†; Leber-Galle-Tropfen 83†; Majocarmin forte†; Majocarmin mite†; Montana N; Schwedentrunk Elixier; Sedovent; Sinupret; Stovalid N†; Unex Amarum†; ventri-loges N; ***Hong Kong:*** Sinupret; ***Hung.:*** Sinupret; ***Indon.:*** Sinupret; ***Ital.:*** Amaro Medicinale; Assenzio (Specie Composta)†; Caramelle alle Erbe Digestive; Centaurea (Specie Composta)†; Chinoidina†; Frerichs Maldifassi†; Genziana (Specie Composta)†; ***Mex.:*** Bisolsinus; ***Philipp.:*** Sinupret; ***Pol.:*** Dyspepsin; Kalms; Melisana Klosterfrau; Sinupret; ***Rus.:*** Herbion Drops for the Stomach (Гербион Желудочные Капли); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sinupret (Синупрет); ***S.Afr.:*** Amara; Enzian Anaemodoron Drops; Helmontskruie; Lewensessens; Versterkdruppels; Wonderkroonessens; ***Singapore:*** Sinupret; ***Spain:*** Depurativo Richelet; ***Switz.:*** Demonatur Gouttes pour le foie et la bile; Gastrosan; Padma-Lax; Padmed Laxan; Sinupret; Strath Gouttes pour l'estomac; ***Thai.:*** Pepsitase; Sinupret; ***UK:*** Acidosis; Appetiser Mixture; Indigestion Mixture; Kalms; Quiet Tyme; Scullcap & Gentian Tablets; Stomach Mixture.

Gentisic Acid Ethanolamide

Etanolamida del ácido gentísico. 2,5-Dihydroxybenzoic acid ethanolamide.

$C_9H_{11}NO_4$ = 197.2.

CAS — 61969-53-7.

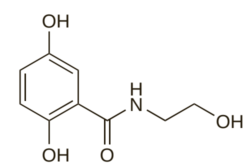

Profile

Gentisic acid ethanolamide has been used as a complexing agent in the manufacture of pharmaceutical preparations.

Geraniol

Lemonol. (*E*)-3,7-Dimethyl-2,6-octadien-1-ol; .

Гераниол

$C_{10}H_{18}O$ = 154.2.

CAS — 106-24-1.

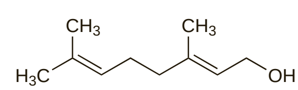

Profile

Geraniol is a constituent of several essential oils and is used in insect repellent preparations. It was formerly used as an anthelmintic. Geraniol is also used as a flavour and in perfumery. Contact dermatitis has been reported.

◊ References.

1. Yamamoto A, *et al.* Contact urticaria from geraniol. *Contact Dermatitis* 2002; **46:** 52.

2. Murphy LA, White IR. Contact dermatitis from geraniol in washing-up liquid. *Contact Dermatitis* 2003; **49:** 52.
3. Tamagawa-Mineoka R, *et al.* Allergic contact cheilitis due to geraniol in food. *Contact Dermatitis* 2007; **56:** 242–3.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Cholestin.

Multi-ingredient: ***Canad.:*** Natrapel; ***Fr.:*** Biolau; Moustidose.

Geranium Oil

Aetheroleum Pelargonii; Geranii Etheroleum; Geranio, aceite esencial de; Geraniová silice; Oleum Geranii; Pelargonium Oil; Rose Geranium Oil.

Гераниевое Масло

Profile

Geranium oil is a volatile oil obtained by distillation from the aerial parts of various species and hybrid forms of *Pelargonium* (Geraniaceae). It contains geraniol (p.2310). It is used to perfume various preparations and has been included in insect repellent preparations. It is also used in aromatherapy.

Adverse effects. Allergic reactions have been reported[1] with herbal preparations containing extracts of *Pelargonium sidoides* and *P. reniforme* used for respiratory-tract infections.

1. de Boer HJ, *et al.* Allergic reactions to medicines derived from Pelargonium species. *Drug Safety* 2007; **30:** 677–80.

Postherpetic neuralgia. A study[1] involving 30 patients has indicated that topically applied geranium oil is of benefit in the management of the pain of postherpetic neuralgia. Pain relief was obtained within a few minutes but further study is required to determine the duration of effect beyond 1 hour. Adverse effects were considered to be minor and included burning in the eye, skin rash, and lightheadedness.

1. Greenway FL, *et al.* Temporary relief of postherpetic neuralgia pain with topical geranium oil. *Am J Med* 2003; **115:** 586–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Kaloba; Umckan; ***Ger.:*** Umckaloabo; ***Ital.:*** Entom Nature; ***Mex.:*** Umckaloabo; ***Rus.:*** Umckalor (Умкалор); ***UK:*** Kaloba; ***Venez.:*** Kaloba.

Multi-ingredient: ***Fr.:*** Acarcid†; Sedermyl Actifroid; ***Ger.:*** Rosatum Heilsalbe; ***Ital.:*** Air Citronella†; Dentosan Azione Intensiva; Dentosan Mese; Mistick Verde; Otosan Natural Ear Drops†; ***NZ:*** Mr Nits; ***UK:*** Medicated Extract of Rosemary; Nostroline; Teenstick.

Germanium

Germanio.

Ge = 72.64.

CAS — 7440-56-4.

Profile

Germanium compounds have been used in dietary supplements promoted for conditions including cancer, chronic fatigue syndrome, and immunodeficiency disorders. However, germanium compounds can produce severe renal damage and their use should be discouraged.

Germanium has also been used in dental alloys and has various industrial uses.

Effects on the kidneys. In the UK the DOH has recommended that germanium should not be taken as a dietary supplement because of a significant incidence of renal toxicity. There have been a number of reports of severe renal damage, including fatalities, resulting from germanium ingestion.

References.

1. Okada K, *et al.* Renal failure caused by long-term use of a germanium preparation as an elixir. *Clin Nephrol* 1989; **31:** 219–24.
2. van der Spoel JI, *et al.* Dangers of dietary germanium supplements. *Lancet* 1990; **336:** 117. Correction. *ibid.* 1991; **337:** 864.
3. Schauss AG. Nephrotoxicity in humans by the ultratrace element germanium. *Ren Fail* 1991; **13:** 1–4.
4. Hess B, *et al.* Tubulointerstitial nephropathy persisting 20 months after discontinuation of chronic intake of germanium lactate citrate. *Am J Kidney Dis* 1993; **21:** 548–52.
5. Tao SH, Bolger PM. Hazard assessment of germanium supplements. *Regul Toxicol Pharmacol* 1997; **25:** 211–19.
6. Swennen B, *et al.* Epidemiological survey of workers exposed to inorganic germanium compounds. *Occup Environ Med* 2000; **57:** 242–8.

Ginkgo Biloba

Árbol de los cuarenta escudos; EGB-761; Fossil Tree; GBE-761; Ginkgo, feuille de (ginkgo leaf); Ginkgo folium (ginkgo leaf); Ginkgoblad (ginkgo leaf); Ginkmedžių lapai (ginkgo leaf); Jinanový list (ginkgo leaf); Kew Tree; Maidenhair Tree; Neidonhiuspuunlehti (ginkgo leaf); Páfrányfenyőlevél (ginkgo leaf); *Salisburia adiantifolia.*

Гинкго Билоба

ATC — N06DX02.

ATC Vet — QN06DX02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US. Eur.* (see p.vii) also includes Ginkgo Dry Extract, Refined and Quantified. *US* includes a powdered extract.

Ph. Eur. 6.2 (Ginkgo Leaf). The whole or fragmented dried leaf of *Ginkgo biloba* containing not less than 0.5% of flavonoids, calculated as flavone glycosides with reference to the dried drug. The leaf is greyish or yellowish-green or yellowish-brown.

USP 31 (Ginkgo). The dried leaf of *Ginkgo biloba* (Ginkgoaceae) containing not less than 0.5% of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7, and not less than 0.1% of terpene lactones, both on the dried basis. The leaf is khaki green to greenish-brown. Protect from light and moisture.

Adverse Effects

Adverse effects include headaches, dizziness, palpitations, gastrointestinal disturbances, bleeding disorders, and skin hypersensitivity reactions.

Poisoning. Reports[1,2] of convulsions induced by ingestion of large amounts of ginkgo seeds. Convulsions were thought to be due to the presence of 4-metoxypyridoxine, a competitive antagonist of pyridoxine; giving suitable quantities of a vitamin-B_6 source may be of benefit in preventing such convulsions.[2]

1. Miwa H, *et al.* Generalized convulsions after consuming a large amount of gingko nuts. *Epilepsia* 2001; **42:** 280–1.
2. Kajiyama Y, *et al.* Ginkgo seed poisoning. *Pediatrics* 2002; **109:** 325–7.

Interactions

It has been suggested that ginkgo biloba should be used with caution in patients receiving anticoagulants or drugs that affect platelet aggregation. For reference to a possible interaction with *warfarin*, see p.1431.

Uses and Administration

An extract from the leaves of *Ginkgo biloba* has been used in cerebrovascular and peripheral vascular disorders. It is also being investigated in Alzheimer's disease, multi-infarct dementia, and in tinnitus. *Ginkgo biloba* is a source of ginkgolides (below).

Homoeopathy. Ginkgo biloba has been used in homoeopathic medicines under the following names: Ginkgo.

Cerebrovascular disorders. A systematic review[1] of 10 randomised or quasi-randomised studies concluded that the routine use of ginkgo biloba extracts to promote recovery after ischaemic stroke was not supported by any convincing evidence, and that larger better quality studies were required.

1. Zeng X, *et al.* Ginkgo biloba for acute ischaemic stroke. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/05/06).

Dementia. Ginkgo biloba extracts have been tried in the treatment of dementia including Alzheimer's disease (p.362). Meta-analyses[1-3] have found the extracts to be more effective than placebo in some cases but results are inconsistent and unconvincing[3] and the authors of all analyses commented that further investigation is needed to establish any clinical value. A subsequent study found no evidence of benefit.[4] Another study assessing whether ginkgo biloba can prevent cognitive decline in very elderly people with normal memory function found positive effects only after adjustment for noncompliance.[5] In this study[5] a greater number of cases of stroke or transient ischaemic attacks was noted in those given ginkgo biloba but further study is required to confirm any link to use of ginkgo.

1. Oken BS, *et al.* The efficacy of ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 1998; **55:** 1409–15.
2. Ernst E, Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 1999; **17:** 301–8.
3. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 02/05/08).
4. McCarney R, *et al.* Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry* 2008. Available at: doi: 10.1002/gps.2055
5. Dodge HH, *et al.* A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 2008; **70:** 1809–17.

Peripheral vascular disorders. Ginkgo biloba extracts have been tried in the treatment of peripheral vascular disorders (p.1178). A meta-analysis[1] found the extracts to be more effective than placebo in the symptomatic treatment of intermittent claudication, although the authors considered the size of the effect to be modest and of uncertain clinical relevance.

1. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000; **108:** 276–81.

Tinnitus. Ginkgo biloba extracts have been tried in the treatment of tinnitus (p.1866). A systematic review[1] of 5 randomised controlled studies cautiously concluded that these results were favourable, although a later systematic review[2] failed to show benefit.

1. Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clin Otolaryngol* 1999; **24:** 164–7.
2. Hilton M, Stuart E. Ginkgo biloba for tinnitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/05/06).

Preparations

USP 31: Ginkgo Capsules; Ginkgo Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Clarvix; Herbaccion Cerebral†; Kalter; Tanakan; ***Austral.:*** Proginkgo†; Tavonin†; ***Austria:*** Cerebokan; Ceremin; Gingohexal; Gingol; Tebofortan; Tebonin; ***Belg.:*** Memfit; Tanakan; Tavonin; ***Braz.:*** Binko†; Bioflavin; Clibium†; Dinaton; Equitam; Gibilon; Ginbiloba; Gincobem; Gincolin; Ginkoba; Ginkobil†; Ginkofarma†; Ginkogreen; Ginkolab; Ginkomed; Ginkoplus; Gyncobem; Kiadon†; Kirsan; Mensana†; Oxian; Tanakan; Tebonin; ***Chile:*** Kiadon; Memokit; Ment Vital†; Nokatar; Rokan; Tebokan†; ***Cz.:*** Gingio; Gingium†; Tanakan; Tebokan; ***Fr.:*** Ginkogink; Tanakan; Tramisal; ***Ger.:*** Alz†; Duogink; Gincuran†; Gingiloba; Gingium; Gingobeta; Gingopret; Ginkobil; Ginkodilat; Ginkokan†; Ginkopur; Isoginkgo; Kaveri; Rokan; Tebonin; ***Gr.:*** Tanacain; Tebokan; ***Hong Kong:*** Ebamin; Ginkolin; Tanakan; ***Hung.:*** Bilobil; Gingium; Ginkgold; Tanakan; Tebofortan; Tebonin†; ***Indon.:*** Brenax; Gingkan; Ginkgoforce; Ginkona; Lanaginkola; ***Ital.:*** Ginkoba; Novel Ginkgo†; ***Malaysia:*** Appeton Memocap†; Giloba; Gincare; Ginkocer†; Tanakan; ***Mex.:*** Bilogink†; Kolob†; Nemoril; Tanakan†; Tebonin; Vasodil; ***Neth.:*** Tavonin; ***Philipp.:*** Ginkocer; Tebokan; ***Pol.:*** Bilobil; Geriacaps; Ginkgomax; Ginkofar; Herbabiloba; Memoplant; Tanakan; ***Port.:*** Abolibe; Biloban; Gincoben; Ginkoftal†; Vasactife; ***Rus.:*** Bilobil (Билобил); Ginos (Гинос); Memoplant (Мемоплант); Tanakan (Танакан); ***Singapore:*** Gincare; Ginexin-F†; Ginkapran; Ginkosen; Gitako; Neuroxin; Tanakan; Tebonin; ***Spain:*** Fitokey Ginkgo; Normocir†; Tanakene; ***Switz.:*** Demonatur Ginkgo; Geriaforce; Gingosol; Oxivel†; Symfona; Tanakene; Tebofortin†; Tebokan; Valverde Vitalite dragees†; ***Thai.:*** Tanakan; ***Turk.:*** Gingobil; Tanakan; ***UK:*** Ginkovital; ***USA:*** BioGinkgo; ***Venez.:*** Kiadon; Neukob; Tanakan; Tebokan; Varginko.

Multi-ingredient: ***Arg.:*** Centellase de Centella Queen; Flebitol; Garcinol Max†; GB 100; Ginkgo Biloba Forte; Ginkgo Biloba Memo Diates; Ginkgo Forte; Herbaccion Celfin; Herbaccion Memory; Neuroton; SCV 300; Snell Patch; Snell Progress; Top Life Memory†; Venoful; VNS 45; ***Austral.:*** Bilberry Plus Eye Health; Bioglan Vision-Eze; Bioglan Zellulean with Escin; Clements Tonic; Extralife Extra-Brite; Extralife Eye-Care; Extralife Leg-Care; Eye Health Herbal Plus Formula 4; For Peripheral Circulation Herbal Plus Formula 5; Gingo A†; Ginkgo Biloba Plus†; Ginkgo Complex†; Ginkgo Plus Herbal Plus Formula 10†; Herbal Arthritis Formula†; Herbal Capillary Care†; Lifechange Circulation Aid†; Lifechange Multi Plus Antioxidant†; Lifesystem Herbal Formula 6 For Peripheral Circulation†; Lifesystem Herbal Plus Formula 11 Ginkgo†; Lifesystem Herbal Plus Formula 5 Eye Relief†; Prophthal†; Vig; ***Braz.:*** Composto Anticelulitico†; Derm'attive Solaire†; Traumed†; ***Canad.:*** Ginkoba†; ***Chile:*** Celltech Gold; Gincosan; Gingo-Ther†; Mentania; Sebium AKN; ***Cz.:*** Gincosan; Ginkor Fort; ***Fr.:*** Ginkor; Ginkor Fort; Photoderm Flush†; Sebium AKN; ***Ger.:*** Perivar†; Veno-Tebonin N†; ***Hong Kong:*** Flavo-C; Ginkgo Plus Vivo-Livo†; Ginkgo-PS†; Ginkor Fort; ***Hung.:*** Ginkor Fort; ***Indon.:*** Cereton; Ginokan; Hemaviton Brain Nutrient; Proseval; ***Ital.:*** Angioton; Angiovein; Forticrin; Ginkoba Active; Ginkoftal; Ginkoret; Memoactive†; Memorandum; Neuralta Migren; Pik Gel; Pollingel con Ginkgo Biloba†; Pulsalux; Varicofit; Vasobrain; Vasobrain Plus; Vasopt; Venalta; Vertiginkgo; ***Malaysia:*** Cerestar†; Circarol; Ginkor Fort; Total Man†; ***Mex.:*** Maxibiloba; ***Philipp.:*** Circulan; Nutrotal; ***Pol.:*** Bioginko; Cardiobonisol; Ginkgocard; Intelektan; Passibil; Venoforton; ***Rus.:*** Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); ***Singapore:*** Ginkgo-PS; Memoloba†; ***Switz.:*** Allium Plus; Arterosan Plus; Capsules-vital; Gincosan; Triallin; ***Thai.:*** Ginkor Fort; ***UK:*** ProBrain; ***USA:*** Aphrofem; Cavigen; Dorofen; Gentaplex; ***Venez.:*** Sebium AKN; Sengobil.

Ginkgolides

Ginkgólidos.

Гинкголиды

CAS — 15291-75-5 (ginkgolide A); 15291-77-7 (ginkgolide B); 15291-76-6 (ginkgolide C).

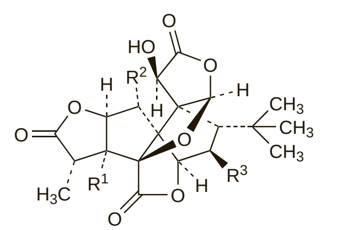

	R^1	R^2	R^3
ginkgolide A	OH	H	H
ginkgolide B	OH	OH	H
ginkgolide C	OH	OH	OH

(ginkgolide A)

Description. Ginkgolides A, B, and C (BN-52020, BN-52021, and BN-52022 respectively) are isolated from *Ginkgo biloba* (Ginkgoaceae) (see above).

Profile

Ginkgolides are terpenoid molecules isolated from *Ginkgo biloba* (above), with platelet-activating factor (PAF) antagonist properties. They have been investigated as BN-52063, a mixture of ginkgolides A (BN-52020), B (BN-52021), and C (BN-52022), for asthma and other inflammatory and allergic disorders, and also in immune disorders such as endotoxic shock and graft rejection; ginkgolide B, which has the most potent PAF antagonist properties, has been tried alone in similar conditions.

Other ginkgolides, including ginkgolide M (BN-52023) and ginkgolide J (BN-52024), have also been identified.

◊ References.

1. Braquet P. The ginkgolides: potent platelet-activating factor antagonists isolated from Ginkgo biloba L: chemistry, pharmacology and clinical applications. *Drugs Of The Future* 1987; **12:** 643–99.
2. Chung KF, *et al.* Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man. *Lancet* 1987; **i:** 248–51.

3. Roberts NM, *et al.* Effect of a PAF antagonist, BN52063, on PAF-induced bronchoconstriction in normal subjects. *Br J Clin Pharmacol* 1988; **26:** 65–72.
4. Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet* 1992; **340:** 1136–9.
5. Houghton P. Ginkgo. *Pharm J* 1994; **253:** 122–3.
6. Brochet B, *et al.* The Ginkgolide Study Group in Multiple Sclerosis. Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; **58:** 360–2.
7. Maclennan KM, *et al.* The CNS effects of Ginkgo biloba extracts and ginkgolide B. *Prog Neurobiol* 2002; **67:** 235–57.

Preparations

Proprietary Preparations (details are given in Part 3)
Turk.: Bilokan; Seremaks; Tebokan.

Ginseng

Ginseng radix; Ginzenggyökér; Jintsam; Ninjin; Panax; Pannag; Renshen; Schinsent; Všehojový kořen; Ženšenių šaknys.

Description. Ginseng is the dried root of *Panax ginseng* (*P. schinseng*) (Araliaceae). Other varieties of ginseng include *Panax quinquefolius* (American Ginseng) and *P. pseudoginseng*. The root commonly known as Siberian or Russian ginseng belongs to the same family, Araliaceae, but is an entirely different plant, *Eleutherococcus senticosus* (see Siberian Ginseng, p.2386). Brazilian ginseng is reported to be derived from another unrelated plant, *Pfaffia paniculata*.
Ginseng contains complex mixtures of saponins termed ginsenosides or panaxosides. At least 13 saponins have been isolated from extracts of *P. ginseng* roots.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn*. Also in *US* (as Asian Ginseng and American Ginseng). *US* includes additionally powdered forms of these two varieties of ginseng.
Jpn also includes Red Ginseng, the dried root of *P. ginseng* which has been steamed.
Chin. and *Jpn* also include Rhizoma Panacis Japonica from *Panax japonicus*. *Eur.* (see p.vii) also includes Notoginseng Root from *P. notoginseng*. *Chin.* also includes Radix Notoginseng from *P. notoginseng*, and Rhizoma Panacis Majoris from *P. japonicus* var. *major* and *P. japonicus* var. *bipinnatifidus*.
Ph. Eur. 6.2 (Ginseng). The whole or cut dried root of *Panax ginseng*. It contains not less than 0.4% of combined ginsenosides, Rg1 ($C_{42}H_{72}O_{14},2H_2O = 837.0$) and Rb1 ($C_{54}H_{92}O_{23},3H_2O = 1163.3$), calculated with reference to the dried drug. Protect from light.
USP 31 (Asian Ginseng). The dried roots of *Panax ginseng* (Araliaceae). It contains not less than 0.2% of ginsenoside Rg_1 and not less than 0.1% of ginsenoside Rb_1, both calculated on the dried basis. Store in a dry place at a temperature of 8° to 15°.
USP 31 (American Ginseng). The dried roots of *Panax quinquefolius* (Araliaceae). It contains not less than 4.0% of total ginsenosides, calculated on the dried basis. Store in airtight containers. Protect from light and heat.

Adverse Effects

◊ A 2-year study[1] of ginseng in 133 subjects who had used commercial preparations including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum, and candies reported that the majority of preparations were taken orally, but a few subjects had experimented with intranasal or parenteral routes, and topical preparations had also been used. The stimulant effects of ginseng were confirmed but there was also a high incidence of adverse effects including 47 cases of morning diarrhoea, 33 of skin eruptions, 26 of sleeplessness, 25 of nervousness, 22 of hypertension, 18 of euphoria, and 14 of oedema. The 'ginseng abuse syndrome' defined as hypertension together with nervousness, sleeplessness, skin eruptions, and morning diarrhoea was experienced by 14 subjects who took ginseng orally in an average daily dose of 3 g. Abrupt withdrawal precipitated hypotension, weakness, and tremor in 1 user. About 50% of the subjects had stopped the use of ginseng within the 2 years. Oestrogenic effects have also been reported from the use of ginseng,[2-4] and a case of Stevens-Johnson syndrome has also occurred.[5]
A systematic review[6] of some of these and other studies and case reports concluded that single-ingredient preparations of ginseng were well tolerated when data from clinical studies were examined. Adverse effects were generally mild and reversible, the most common being headache, sleep disturbances, and gastrointestinal disorders. It was more difficult to determine causality from the evidence given in isolated case reports; likewise, interpretation of data involving combination products was difficult.

1. Siegel RK. Ginseng abuse syndrome: problems with the panacea. *JAMA* 1979; **241:** 1614–15.
2. Palmer BV, *et al.* Gin Seng and mastalgia. *BMJ* 1978; **1:** 1284.
3. Punnonen R, Lukola A. Oestrogen-like effect of ginseng. *BMJ* 1980; **281:** 1110.
4. Greenspan EM. Ginseng and vaginal bleeding. *JAMA* 1983; **249:** 2018.
5. Dega H, *et al.* Ginseng as a cause for Stevens-Johnson syndrome? *Lancet* 1996; **347:** 1344.
6. Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Safety* 2002; **25:** 323–44.

Interactions

◊ For reports of interactions between *phenelzine* and ginseng, see p.419. For details of an interaction between *warfarin* and ginseng, see p.1431. For a suggestion that ginseng may interfere with *digoxin* assays, see p.1260.

Uses and Administration

Ginseng is reported to enhance the natural resistance and recuperative power of the body and to reduce fatigue. It is available commercially as roots, powdered roots, tablets, capsules, teas, oils, or extracts.

Preparations

USNF 26: American Ginseng Capsules;
USP 31: American Ginseng Tablets; Asian Ginseng Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ginsana; Herbaccion Bioenergizante; Juvitan†; Transformal†; Vitagenol†; ***Austral.:*** Herbal Stress Relief†; ***Austria:*** Ginsana; ***Belg.:*** Ginsana†; ***Braz.:*** Enerseng; Fortilan; Ginsana; Ginsex; ***Canad.:*** Ginsana†; ***Cz.:*** Ginsana; ***Fr.:*** Gerimax Tonique; Ginsana†; ***Ger.:*** Ardey-aktiv; Coriosta Vitaltonikum N†; Ginsana; Hevert-Aktivon Mono†; IL HWA; Orgaplasma; ***Ital.:*** Fon Wan Ginsenergy; Gi-Sen†; Ginsana; ***Malaysia:*** Ginsana; ***Mex.:*** Gincaps†; Raigin†; Rutying; Sanjin Royal Jelly; ***Pol.:*** Ginsana; Ginsenol; Panaxan; ***Port.:*** Ginsana; ***Rus.:*** Gerimax Ginseng (Геримакс Женьшень); Ginsana (Гинсана); ***Singapore:*** Ginsana; ***Spain:*** Bio Star; Ginsana†; ***Switz.:*** Ginsana; Ginsavita†; KintaVital; ***Thai.:*** Ginsana; Ginsroy; ***UK:*** Korseng; Red Kooga.

Multi-ingredient: ***Arg.:*** Dynamisan; Energy Plus; Galenic Restaurador Capilar; Ginseng Bioplus Diates; Herbaccion Ginseng Y Magnesio; Holomagnesio Vital; Inteligen Ginseng†; Neuroton; Optimina Plus; Top Life Memory†; Total Magnesiano con Ginseng; Total Magnesiano con Vitaminas y Minerales; Vifortol; ***Austral.:*** Bioglan Ginsynergy; Clements Tonic; Extralife Extra-Brite; Ginkgo Biloba Plus†; Ginkgo Complex†; Glycyrrhiza Complex†; Infant Tonic†; Irontona; Nervatona Focus; Panax Complex†; Vig; Vitatona; ***Austria:*** Gerimax Plus; ProAktiv; ***Braz.:*** Gerin; Poliseng; ***Canad.:*** Damiana-Sarsaparilla Formula†; Energy Plus†; Ginkoba†; ***Chile:*** Gincosan; Mentania; Nectaday; ***Cz.:*** Gincosan; ***Fr.:*** Gintonal†; Nostress; Notabac; Thalgo Tonic; Tonactil†; ***Ger.:*** Cardibisana†; Doppelherz Ginseng Aktiv†; Ginseng-Complex "Schuh"†; Peking Ginseng Royal Jelly N; ***Hong Kong:*** Cervusen; GinsengSure†; Sanjukei Panax Ginseng; ***Indon.:*** Armovit; Cerebrovit Active; Ginokan; Hemaviton Brain Nutrient; Hemaviton Energy Drink; Hemaviton Jreng; Instink; Maxirex; Menolia; Neo Hormoviton; Neo Hormoviton Greng; Procur Plus; Proseval; Provital; Provital Plus; Ratax; Sirec; Tripid; Tristan; ***Ital.:*** Alvear con Ginseng; Apergan; Bioton; Fon Wan Ginsenergy; Forticrin; Fosfarsile Forte; Four-Ton; Ginsana Ton; Neoplus; Ottovis; Pollingel Ginseng†; ***Jpn:*** Eki Cabe; ***Malaysia:*** 30 Plus; Adult Citrex Multivitamin + Ginseng + Omega 3; Cerestar†; Ginsomin; Imuvit; Total Man†; ***Philipp.:*** BSI Medicated Spray; Ginsomin; Homtamin-G Plus; Immuvit; K-A Plus; Korgivit-E; Nutrotal; ***Pol.:*** Bioginko; Doppelherz Vital Kapseln; Ginjal; Intelektan; ***Rus.:*** Doppelherz Ginseng Aktiv (Доппельгерц Женьшень Актив); Doppelherz Vitalotonik (Доппельгерц Виталотоник); ***S.Afr.:*** Activex 40 Plus; ***Singapore:*** Gin-Vita; Immuvital; ***Spain:*** Energysor†; Esforza†; Redseng Polivit; Ton Was; Vigortonic; ***Switz.:*** Biovital Ginseng; Burgerstein TopVital; Geri; Gincosan; Imuvit; Supradyn Vital 50+; Triallin; Vigoran†; ***Thai.:*** Imugins; Imuvit; Multilim RG; Revitan; ***UK:*** Red Kooga Co-Q-10 and Ginseng; Regina Royal Concorde; ***Venez.:*** Hivit; Pharmorat; Sengobil; Vigoran.

Glatiramer Acetate *(BAN, USAN)*

COP-1; Copolymer 1; Glatirameeriasetaatti; Glatiramer, acetato de; Glatiramer Asetat; Glatirameracetat; Glatirameri Acetas. L-Glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate.

Глатирамер Ацетат

CAS — 28704-27-0 (glatiramer); 147245-92-9 (glatiramer acetate).

ATC — L03AX13.

ATC Vet — QL03AX13.

Adverse Effects and Precautions

Immediate post-injection reactions are common with glatiramer acetate and include chest pain, palpitations or tachycardia, dyspnoea, throat constriction, urticaria, flushing (vasodilatation), and anxiety. These reactions are generally short-lived and resolve spontaneously. They have generally occurred only some months after treatment with glatiramer was started. Other common adverse effects include asthenia, nausea, constipation, diarrhoea, rash, sweating, arthralgia, hypertonia, and dizziness. Convulsions and anaphylactoid reactions have been reported rarely. Antibodies to the drug develop with chronic therapy but are of unknown clinical significance. Pain, erythema, inflammation, mass, pruritus, and induration may occur at the injection site; localised lipoatrophy and, rarely, skin necrosis has also been reported.

Glatiramer acetate should be given with caution to patients with pre-existing cardiac disorders; such patients should be followed up regularly during treatment.

◊ References.

1. Ziemssen T, *et al.* Risk-benefit assessment of glatiramer acetate in multiple sclerosis. *Drug Safety* 2001; **24:** 979–90.

Anaphylaxis. A systemic anaphylactic reaction to glatiramer acetate developed in a patient who showed a strong immunoglobulin response including specific immunoglobulin E.[1]

1. Rauschka H, *et al.* Severe anaphylactic reaction to glatiramer acetate with specific IgE. *Neurology* 2005; **64:** 1481–2.

Effects on the skin. Localised lipoatrophy at the injection site developed in 6 patients receiving glatiramer acetate.[1] Examination of 76 patients over a 6-month period in one centre[2] revealed evidence of lipoatrophy in at least one injection site in 34 patients; of these, 5 cases were severe. Prevalence of lipoatrophy was much higher than expected, and in some cases, it occurred only a few months after treatment started.[2]
Erythema nodosum confirmed by biopsy has been reported in one patient;[3] spontaneous resolution occurred without stopping treatment.

1. Drago F, *et al.* Localized lipoatrophy after glatiramer acetate injection in patients with remitting-relapsing multiple sclerosis. *Arch Dermatol* 1999; **135:** 1277–8.
2. Edgar CM, *et al.* Lipoatrophy in patients with multiple sclerosis on glatiramer acetate. *Can J Neurol Sci* 2004; **31:** 58–63.
3. Thouvenot E, *et al.* Erythema nodosum and glatiramer acetate treatment in relapsing-remitting multiple sclerosis. *Multiple Sclerosis* 2007; **13:** 941–4.

Interactions

UK licensed product information reports that an increased incidence of injection-site reactions to glatiramer acetate has been seen in patients also given corticosteroids.

Pharmacokinetics

A substantial fraction of a subcutaneous dose of glatiramer is believed to be hydrolysed locally. Some of the injected dose is also presumed to enter the lymphatic system, either intact or partially hydrolysed.

Uses and Administration

Glatiramer acetate, a random polymer of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, is a polypeptide that has some structural resemblance to myelin basic protein, and is used to reduce the frequency of relapses in the management of relapsing-remitting multiple sclerosis (p.892). It is given by subcutaneous injection in a dose of 20 mg daily. It should not be given by the intravenous or intramuscular route. An oral formulation has been investigated with disappointing results.

Multiple sclerosis. Reviews[1,2] and a meta-analysis[3] of controlled studies of glatiramer acetate in the treatment of multiple sclerosis concluded that it is of benefit, although one systematic review[4] questions this and failed to find evidence to support its routine use. The mechanism of glatiramer acetate has also been reviewed.[5]

1. Simpson D, *et al.* Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis. *CNS Drugs* 2002; **16:** 825–50.
2. Ruggieri M, *et al.* Glatiramer acetate in multiple sclerosis: a review. *CNS Drug Rev* 2007; **13:** 178–91.
3. Boneschi FM, *et al.* Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. *Multiple Sclerosis* 2003; **9:** 349–55.
4. Munari L, *et al.* Therapy with glatiramer acetate for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/01/08).
5. Schrempf W, Ziemssen T. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Autoimmun Rev* 2007; **6:** 469–75.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Copaxone; ***Austral.:*** Copaxone; ***Austria:*** Copaxone; ***Belg.:*** Copaxone; ***Braz.:*** Copaxone; ***Canad.:*** Copaxone; ***Cz.:*** Copaxone; ***Denm.:*** Copaxone; ***Fin.:*** Copaxone; ***Fr.:*** Copaxone; ***Ger.:*** Copaxone; ***Gr.:*** Copaxone; ***Hung.:*** Copaxone; ***Irl.:*** Copaxone; ***Israel:*** Copaxone; ***Ital.:*** Copaxone; ***Mex.:*** Copaxone; ***Neth.:*** Copaxone; ***Norw.:*** Copaxone; ***NZ:*** Copaxone; ***Pol.:*** Copaxone; ***Port.:*** Copaxone; ***Rus.:*** Copaxone (Копаксон); ***Spain:*** Copaxone; ***Swed.:*** Copaxone; ***Switz.:*** Copaxone; ***Turk.:*** Copaxone; ***UK:*** Copaxone; ***USA:*** Copaxone.

Glicofosfopeptical

AM-3; Fosfoglicopeptical; Glycophosphopeptical; Immunoferon.

Иммуноферон

CAS — 87139-86-4.

Profile

Glicofosfopeptical is a polysaccharide-protein complex that is reported to possess immunostimulant properties. It has been given orally in doses of 1 g every eight hours.

◊ References.

1. Alvarez-Mon M, *et al.* Treatment with the immunomodulator AM3 improves the health-related quality of life of patients with COPD. *Chest* 2005; **127:** 1212–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Inmunol; ***Port.:*** Imunoferon; ***Spain:*** Inmunoferon.

Glucomannan

E425; Glucomanano; Harina de Konjac; Konjac Flour; Konjac Mannan.

Profile

Glucomannan, a powdered extract from the tubers of *Amorphophallus konjac*, has been promoted as an anorectic. It has been claimed to reduce the appetite by absorbing liquid in the gastrointestinal tract. It is also used in the treatment of constipation and hyperlipidaemia. Glucomannan has been investigated as a dietary adjunct in the management of diabetes mellitus.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if it is swallowed dry. Therefore, it should always be taken with sufficient fluid and should not be taken immediately before going to bed. It should be avoided in patients who have difficulty swallowing.

◊ References.

1. Henry DA, *et al.* Glucomannan and risk of oesophageal obstruction. *BMJ* 1986; **292:** 591–2.
2. Renard E, *et al.* Noninsulin-dependent diabetes and glucose intolerance: effect of glucomannan fibre on blood glucose and serum insulin. *Sem Hop Paris* 1991; **67:** 153–7.
3. Vuksan V, *et al.* Beneficial effects of viscous dietary fiber from konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. *Diabetes Care* 2000; **23:** 9–14.
4. Staiano A, *et al.* Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. *J Pediatr* 2000; **136:** 41–5.
5. Loening-Baucke V, *et al.* Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Abstract: *Pediatrics* 2004; **113:** 259. Full version: http://pediatrics.org/cgi/content/full/113/3/e259 (accessed 23/05/06)
6. Keithley J, Swanson B. Glucomannan and obesity: a critical review. *Altern Ther Health Med* 2005; **11:** 30–4.
7. Vanderbeek PB, *et al.* Esophageal obstruction from a hygroscopic pharmacobezoar containing glucomannan. *Clin Toxicol* 2007; **45:** 80–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Modekal†; ***Chile:*** Redicres Rapido†; ***Fr.:*** Muraligne†; ***Ger.:*** bioNorm mit Konjak†; ***India:*** Dietmann; ***Ital.:*** Dicoplus; Dietoman; NormaLine; ***Mex.:*** Dietoman; Esbeltex; Naturalfit†; ***Port.:*** Bioregime†; Florilax†.

Multi-ingredient: ***Arg.:*** KLB6 Fruit Diet; ***Chile:*** Delgadol Fibra; ***Fr.:*** Filigel; ***Ital.:*** Agioslim; Ecamannan; Glucoman; Lactomannan; ***Port.:*** Bioregime Fort†; Bioregime SlimKit†; Excess†.

Gluconic Acid

Dextronic Acid; E574; Glycogenic Acid; Maltonic Acid; Pentahydroxycaproic Acid. D-Gluconic acid.

Глюконовая Кислота

$C_6H_{12}O_7$ = 196.2.

CAS — 526-95-4.

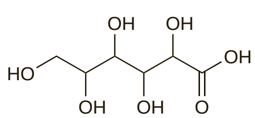

Gluconolactone

E575; Glucono delta-lactone; Glucono-delta-lactone; 1,5-Gluconolactone; D-Glucono-1,5-lactone. D-Gluconic acid δ-lactone.

Глюконолактон

$C_6H_{10}O_6$ = 178.1.

CAS — 90-80-2.

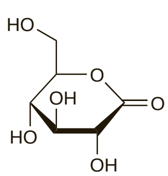

Pharmacopoeias. In *US.*

USP 31 (Gluconolactone). A fine, white, practically odourless, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Profile

Gluconolactone is hydrolysed to gluconic acid, a polyhydroxy acid. It has similar properties to the alpha hydroxy acids glycolic acid (p.1598) and mandelic acid (p.296) and has been used in skin disorders and for urinary catheter care. Gluconolactone and gluconic acid are also used as food additives.

◊ References.

1. Grimes PE, *et al.* The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* 2004; **73** (suppl 2): 3–13.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Neostrata.

Multi-ingredient: ***Arg.:*** Neoceuticals Crema Despigmentante de Dia†; Neoceuticals Gel de Limpieza Facial; Neostrata; ***Austral.:*** Neostrata; ***Canad.:*** Neostrata; ***Chile:*** Neostrata; ***Fr.:*** Ruboderm Plus; ***UK:*** Uriflex R; Uro-Tainer Solution R; ***USA:*** Renacidin.

Glucosamine *(USAN, rINN)*

Chitosamine; Glucosamina; Glucosaminum; NSC-758. 2-Amino-2-deoxy-β-D-glucopyranose.

Глюкозамин

$C_6H_{13}NO_5$ = 179.2.

CAS — 3416-24-8.

ATC — M01AX05.

ATC Vet — QM01AX05.

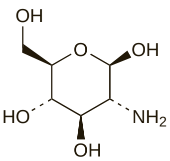

Glucosamine Hydrochloride *(rINNM)*

Chitosamine Hydrochloride; Glucosamine, Chlorhydrate de; Glucosamini Hydrochloridum; Glukozaminy chlorowodorek; Hidrocloruro de glucosamina.

Глюкозамина Гидрохлорид

$C_6H_{13}NO_5,HCl$ = 215.6.

CAS — 66-84-2.

Pharmacopoeias. In *US.*

USP 31 (Glucosamine Hydrochloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Potassium Chloride

$(C_6H_{14}NO_5)_2SO_4,2KCl$ = 605.5.

Pharmacopoeias. In *US.*

USP 31 (Glucosamine Sulfate Potassium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Sodium Chloride

$(C_6H_{14}NO_5)_2SO_4,2NaCl$ = 573.3.

Pharmacopoeias. In *US.*

USP 31 (Glucosamine Sulfate Sodium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Profile

Glucosamine is a natural substance found in chitin, mucoproteins, and mucopolysaccharides. It is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue in the body; glucosamine is also present in tendons and ligaments. Glucosamine must be synthesised by the body but the ability to do this declines with age. Glucosamine and its salts have therefore been advocated in the treatment of rheumatic disorders including osteoarthritis. Glucosamine may be isolated from chitin or prepared synthetically; glucosamine sulfate and hydriodide, have also been used.

Effects on glucose metabolism. Glucosamine has a role in glucose metabolism, increasing insulin resistance in skeletal muscle,[1,2] which has raised concerns about its safety profile in diabetic patients.[3] However, alteration of glycaemic homoeostasis was not found in a 3-year randomised controlled study in patients without diabetes.[4] A review[5] of the literature found limited data on diabetic patients taking glucosamine supplements, and recommended close monitoring of blood glucose levels in this group until more data are available.

1. Adams ME. Hype about glucosamine. *Lancet* 1999; **354:** 353–4.
2. Chan NN, *et al.* Drug-related hyperglycemia. *JAMA* 2002; **287:** 714–15.
3. Chan NN, *et al.* Glucosamine sulphate and osteoarthritis. *Lancet* 2001; **357:** 1618–9.
4. Reginster JY, *et al.* Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; **357:** 251–6.
5. Stumpf JL, Lin SW. Effect of glucosamine on glucose control. *Ann Pharmacother* 2006; **40:** 694–8.

Osteoarthritis. Glucosamine and its salts are widely available as licensed products or so-called 'health supplements' used for the management of osteoarthritis (p.11); they may be combined with other substances supposed to be of benefit, including chondroitin (p.2280), vitamins, and various herbs. Meta-analyses[1,2] of randomised placebo-controlled studies concluded that while there was some evidence for efficacy of glucosamine and chondroitin in the treatment of osteoarthritis, methodological flaws and publication bias had led to exaggeration of its potential benefit,[1] and that further studies are needed to fully characterise their disease-modifying properties.[2] A systematic review[3] of the use of glucosamine for osteoarthritis that included later controlled studies concluded that glucosamine is as safe as placebo but there was little evidence of improvement in pain or function. A further randomised controlled study[4] in 222 patients with hip osteoarthritis found no benefit after treatment with glucosamine for 2 years compared with placebo, and a meta-analysis[5] of controlled studies of chondroitin for osteoarthritis of the knee or hip concluded that chondroitin had minimal or no benefit. Further research is needed to confirm whether there are differences in efficacy between glucosamine salts, preparations, or routes, and when used with other agents (e.g. chondroitin) or in different patient subgroups.[3] A large multicentre double-blind study[6] in 1583 patients with symptomatic knee osteoarthritis to compare glucosamine and chondroitin, either alone or in combination, found no clear evidence of benefit in pain reduction compared with placebo or celecoxib, although there was a tendency to more positive results in a subset of patients with moderate to severe knee pain.

1. McAlindon TE, *et al.* Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000; **283:** 1469–75.
2. Richy F, *et al.* Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003; **163:** 1514–22.
3. Towheed TE, *et al.* Glucosamine therapy for treating osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/05/08).
4. Rozendaal RM, *et al.* Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008; **148:** 268–77.
5. Reichenbach S, *et al.* Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007; **146:** 580–90.
6. Clegg DO, *et al.* Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; **354:** 795–808.

Skin reactions. The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] has received 51 reports of allergic skin reactions with glucosamine, including erythematous rash, angioedema, urticaria, rash, and pruritus. It was noted that some preparations contain glucosamine sourced from seafood and therefore people with an allergy to shellfish may be at greater risk for hypersensitivity reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Skin reactions with glucosamine. *Aust Adverse Drug React Bull* 2005; **24:** 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0512.pdf (accessed 14/05/08)

Preparations

USP 31: Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine and Methylsulfonylmethane Tablets; Glucosamine Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Adaxil; Artrilase; Asoglutan; Baliartrin; Belmalen Plus; Findol; Gluco Arrumalon; Glucocartiflex; Mecanyl; Ostatac; Pertinar; Vartalon Complemento; Vartalon K; ***Austral.:*** GenFlex; ***Braz.:*** Dinaflex; Glucoreumin; Injeflex; ***Chile:*** Artridol; Bioflex; Dinaflex; Reufin; Viartril†; ***Cz.:*** Dona; Flexove; Gool; Mediflex; Voltadyn; ***Denm.:*** Ledamin; Ledflex†; ***Fin.:*** Arthryl; G-Lenk; Glucadol; Movere; ***Fr.:*** Oscart; ***Ger.:*** Dona 200-S; ***Gr.:*** Anarthril; Donarot; Glucosamil; Glusamon; Nerita; Recosine; Viartril; ***Hong Kong:*** Arthritil; Cartril-S; Chitaq; Doctor's Choice for Joints; Donna; F-Vial; MarinEx; Viartril S; Vidatril; Vitoport; Vocarxil; ***Hung.:*** Dona; Gool; ***Indon.:*** Jointfit Cream; Mediflex; Reflexor; ***Irl.:*** Arthrimel; Dona; ***Ital.:*** Dona; Viartril S†; ***Malaysia:*** Artronil; Cartril-S; Cosamine; Donna; Procosa; Viartril S; ***Mex.:*** Artriman; Faximin; Vartalon; Viartril†; ***Neth.:*** Cartimin; Glucadol; ***Norw.:*** Gluxine; Movere; ***Philipp.:*** Viartril S; ***Pol.:*** Arthryl; ***Port.:*** Arthramina; Glucomed; Glucosine; Glufan; Viartril S; ***Singapore:*** ArthriCare; Artril; Artronil; Gluco-S†; Glutilage; Kudona†; Viartril S; Vital; ***Spain:*** Cartisorb; Ceremir; Coderol; Glufan; Hespercorbin; Obifax†; Xicil; ***Swed.:*** Artrox; Glucomed; Glucosine; ***Thai.:*** Artronil; Athril; Flexsa; Gluco-S; Glucosa; Glusa; Glusamine; Viartril S; ***UK:*** Alateris; Flexeze; Joint-e-Licious; ***Venez.:*** Vartalon; Viartril S.

Multi-ingredient: ***Arg.:*** Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Car-ti buron flex; Cartiflex Forte; Ecosamina; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucobefol; Glucotrin VL; Mecanyl Duo; Nectar G; Sigmaflex; Vartalon Duo; ***Austral.:*** Bioglan Joint Mobility; GenFlex 3; GenFlex Plus; OsteoEze Bone & Joint Care; ***Braz.:*** Artrolive; Condroflex; ***Canad.:*** Glucosamine Joint & Muscle Cream with MSM†; ***Chile:*** Artridol Duo; Condrosamina†; Dinaflex Duo; Eniflex†; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex; ***Hong Kong:*** Arthritil Plus; Procosamine†; ***India:*** Cosantin†; Kondro; Osteocip; Osteoflex; ***Indon.:*** Aptivium Optimum Joint Formula; Artriox; Artritin; Bonic; Cartin Plus; Chondro-PA; Fitbon; Fitbon Plus; Flexor; Fripos; Joint Care; Jointfit; Maxitrin; Naturica Artro; Naturica Artro Plus; OA; OA Forte; OA Plus; Osamin; Oste; Ostela; Osteoflam; Osteokom; Osteokom Forte; Osteonic; Osteor; Osteor Plus; Osteor-C; Osvion Plus; Rheumatin; Rheumatin Forte; Triflexor; Triostee; Viopor; Viopor-M; Viostin Com; Viostin Com DS; Vosteon; ***Ital.:*** Cartago; Fitogenase; Joint Support; Osteoclar; Reumilase SD; ***Mex.:*** Actiman; Artiflex; Vartalon Compositum; ***Philipp.:*** Flexxbon; Ruflex; ***Port.:*** Synchrocell; Synchrorose; Synchrovit; ***Rus.:*** Artra (Артра); Theraflex (Терафлекс); ***S.Afr.:*** ProFLEX; ProFLEX 750; ***Singapore:*** Arthro-Flex; Articolase (w/glucosamine); Artril C; Cartipro; Flexeze†; Glucocal; Glutilage Plus; Seven Seas JointCare; Seven Seas JointCare Max; ***UK:*** Arheumacare; BackOsamine; Flexeze; GlucOsamax; Healtheries Musseltone & Glucosamine; Joint Action; Jointace; Joint-Care Max; ***USA:*** Dorofen; ***Venez.:*** Artrosamin; Flexurat.

Glucose Oxidase

Corylophyline; β-D-Glucopyranose aerodehydrogenase; Glucosa oxidasa; Microcide; Notatin; P-FAD.

CAS — 9001-37-0.

Profile

Glucose oxidase is an enzyme obtained from certain fungi, which catalyses the oxidation of glucose to gluconic acid, with the concomitant production of hydrogen peroxide. It is used for its preservative properties as an additive in certain foods, sometimes with catalase (p.2278). It is also used in fertility tests and tests of diabetic control. It has been used as an ingredient of toothpastes for its supposed benefits in the prophylaxis of dental caries.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Bromelin†; Expectoral†; ***Singapore:*** Biotene; ***UK:*** Biotene Dry Mouth; Biotene Oralbalance; ***USA:*** Biotene with Calcium.

Glucose Tests

Glucosa, pruebas de.

Profile

Several tests are available so that patients with diabetes mellitus (p.431) can monitor their disease. Tests can be employed to detect the presence of glucose in the urine and some of the preparations are used to detect several substances in the urine. These tests are easy to carry out but are not considered reliable enough for insulin-dependent patients who should ideally check their blood-glucose concentrations using one of the available blood tests. Diabetic clinics often measure the degree of haemoglobin glycosylation as an indicator of mean blood-glucose control over a period of weeks or months.

Urine tests generally use either the copper-reduction method or the glucose-oxidase method and both produce a colour change in the presence of glucose. Blood tests generally use the glucose-oxidase method; they may be read visually or by means of a meter. A meter gives the more precise reading. Patients should be properly trained in the use of these tests and in the interpretation of the results; they should be aware that concomitant drug therapy might affect the result.

Precautions. Preparations that contain, or are metabolised to, maltose (p.1956), galactose (p.1481), or xylose (p.2416) may interfere with the results from glucose tests based on dehydrogenase pyrroloquinolinequinone (GDH-PQQ) monitoring systems as these are non-specific for glucose. Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/cber/safety/maltose110405.htm (accessed 01/07/08)

Preparations

USP 31: Glucose Enzymatic Test Strip.

Proprietary Preparations (details are given in Part 3)

Arg.: Accu-Chek; Accutrend Glucosa; Ascensia; Betachek; Dextrostix; Diabur-Test 5000†; Diastix; Elite; Glucostix; Glucotide†; Glucotrend†; Glukotest†; Haemo-Glukotest 20-800†; One Touch; Precision Plus; Prestige†; Sure Step; ***Austral.:*** Accu-Chek; Accutrend Glucose; Advantage†; Ascensia; Betachek†; BM-Test BG; BM-Test Glycemie 20-800; Clinistix; Clinitest; Diabur-Test 5000; Diascreen Glucose†; Diastix; Esprit; ExacTech†; Glucoflex-R†; Glucometer†; Glucostix; Medi-Test Glucose; MediSense SofTact†; Omnitest†; Optium†; Precision Plus†; Tes-Tape†; ***Braz.:*** Accu-Chek; Accutrend; Glico-Fita; Haemo-Glukotest; ***Canad.:*** Accu-Chek†; Accutrend GC†; Advantage; Ascensia Elite; Chemstrip uG; Clinistix; Clinitest; Diastix; One Touch; Sof-Tact; ***Chile:*** Accu-Chek; Accutrend Glucosa; Ascencia; Glukotest†; ***Fr.:*** Accu-Chek; Ascensia; BM-Test Glycemie†; Clinistix; Clinitest†; Euroflash; Glucomen; Glucotide†; Glucotrend†; Medisense; One Touch; ***India:*** Diastix; ***Irl.:*** Accu-Chek; BM-Accutest; BM-Test 1-44†; Clinistix; Clinitest; Combina Glucose; Diabur-Test 5000; Diastix; Freestyle; Glucomen; Glucometer Elite; Glucostix; Glucotide; Hypoguard†; Medisense†; One Touch; PocketScan; ***Ital.:*** Accu-Chek; Accutrend Glucose†; Ascensia; Clinistix; Clinitest; Diabur-Test 5000; Diastix; Euroflash; EZ Smart; Freestyle Papillon; Glucocard; Glucofilm†; Glucometer†; Glucosan†; Glucostix†; Glucotrend†; Glukurtest†; Haemoglukotest 20-800†; One Touch; Uni-Check; ***Mex.:*** Accu-Chek; Accutrend Glucose; Clinitest; Dextrostix; Diabur-Test 5000; Diastix; Gluco-Cinta†; Glucostix†; Glucotide†; Haemo-Glukotest 20-800; ***NZ:*** Accu-Chek Advantage; Accutrend Glucose†; BM-Test 1-44†; Clinistix; Clinitest; Diabur-5000; Diastix; Glucocard†; Glucometer Elite†; Glucometer Esprit†; Glucostix†; Precision Plus†; ***Port.:*** Clinistix; Elite†; Euroflash†; Glucocard; Glucodisk; Glucostix; Glucotouch†; One Touch; ***UK:*** Ascensia Glucodisc; BM-Accutest; BM-Test 1-44; Breeze 2; Clinistix; Clinitest; Diabur-Test 5000; Diastix; ExacTech; Freestyle; Glucomen; Glucostix†; Glucotide†; Hypoguard Supreme Plus; Medi-Test Glucose; Medi-Test Glycaemie C†; Medisense; Optium Plus; ***USA:*** Accu-Chek Advantage; Chemstrip bG; Chemstrip uG; Choice DM; Clinistix; Clinitest; Diascan; Diastix; First Choice; Glucofilm; Glucostix; One Touch.

Glucuronic Acid

D-Glucuronic acid.

$C_6H_{10}O_7$ = 194.1.

CAS — 576-37-4 (D,L-glucuronic acid); 6556-12-3 (D-glucuronic acid); 3789-97-7 (glucuronamide); 3574-23-0 (D-glucuronamide); 61914-43-0 (D-glucuronamide); 63-29-6 (glucurolactone); 32449-92-6 (glucurolactone); 14984-34-0 (sodium glucuronate).

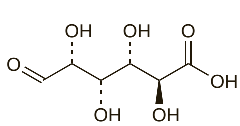

(D-glucuronic acid)

Profile

Glucuronic acid is one of the components of hyaluronic acid (p.2320) and also has an important role in the metabolism of many endogenous substances, drugs, and toxins. It has been used topically as a potential precursor of hyaluronic acid, and has also been used as a nutritional supplement. Glucuronamide, glucurolactone (glucuronic acid lactone), diolamine glucuronate, and other glucuronates have also been used as supplements.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Guronsan†.

Multi-ingredient: ***Belg.:*** Guronsan; ***Chile:*** Neostrata†; ***Fr.:*** Detoxalgine†; Guronsan; ***Hong Kong:*** Jetepar; ***Ital.:*** Ietepar†; ***Malaysia:*** Jetepar; ***Philipp.:*** Jetepar; ***Port.:*** Guronsan; Synchrocell; Synchrovit; ***Singapore:*** Jetepar; ***Spain:*** Guronsan.

Gluten

Profile

Gluten is a mixture of 2 proteins, gliadin and glutenin, and is present in wheat flour and to a lesser extent in barley and rye. Gliadin is a prolamine, one of the 2 chief groups of plant proteins, and glutenin belongs to the other main group termed glutelins.

Gluten is of medicinal and pharmaceutical interest in that patients with coeliac disease (p.1922) are sensitive to the protein fraction of gluten contained in the normal diet. Treatment consists of the use of gluten-free diets; gluten-free foods are available.

A gluten-free diet may also be beneficial in patients with dermatitis herpetiformis (p.1578).

Glycerol *(rINN)*

E422; Glicerin; Glicerol; Glicerolis; Gliserin; Gliserol; Glisin; Glycerin; Glycerine; Glycérol; Glycerolum; Glyseroli. Propane-1,2,3-triol.

Глицерол

$C_3H_8O_3$ = 92.09.

CAS — 56-81-5.

ATC — A06AG04; A06AX01.

ATC Vet — QA06AG04; QA06AX01; QA16QA03.

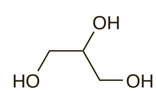

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Eur. and *Int.* also include Glycerol (85 per cent).

Ph. Eur. 6.2 (Glycerol). A clear, colourless or almost colourless, very hygroscopic, syrupy liquid, unctuous to the touch. Miscible with water and with alcohol; slightly soluble in acetone; practically insoluble in fixed oils and in essential oils. Store in airtight containers.

USP 31 (Glycerin). A clear, colourless, hygroscopic, syrupy liquid. Has not more than a slight characteristic odour, which is neither harsh nor disagreeable. Miscible with water and with alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Its solutions are neutral to litmus. Store in airtight containers.

Incompatibility. Strong oxidising agents form explosive mixtures with glycerol. Black discoloration has been reported with glycerol and bismuth subnitrate or zinc oxide when exposed to light.

Adverse Effects and Precautions

The adverse effects of glycerol are primarily due to its dehydrating action.

When taken orally glycerol may cause headache, nausea, and vomiting; diarrhoea, thirst, dizziness, and mental confusion may occur less frequently. Cardiac arrhythmias have been reported.

Glycerol increases plasma osmolality resulting in the withdrawal of water from the extravascular spaces. The consequent expansion of extracellular fluid, especially if sudden, can lead to circulatory overload, pulmonary oedema, and heart failure; glycerol must therefore be used with caution in patients at risk, such as those with hypervolaemia, cardiac failure, or renal disease. Severe dehydration can occur and glycerol should be used cautiously in dehydrated patients. Patients with diabetes mellitus may additionally develop hyperglycaemia and glycosuria after metabolism of glycerol. Nonketotic hyperosmolar hyperglycaemic coma is rare, but fatalities have been reported.

Haemolysis, haemoglobinuria, and acute renal failure have also been associated with glycerol when given intravenously (see Raised Intracranial Pressure, below).

Glycerol can cause irritation when given topically or rectally. A local anaesthetic may be used before application of glycerol to the cornea to reduce the likelihood of a painful response.

For incompatibilities with glycerol, including the risk of explosive mixtures, see above.

Effects on the cardiovascular system. A 73-year-old man, free of cardiac complaints but who had previously had an acute myocardial infarction, developed severe pulmonary oedema after use of glycerol orally for elevated intra-ocular pressure.[1] The necessity for detailed cardiac evaluation before the use of oral glycerol was emphasised.

1. Almog Y, *et al.* Pulmonary edema as a complication of oral glycerol administration. *Ann Ophthalmol* 1986; **18:** 38–9.

Effects on the ears. A 56-year-old man given 100 mL of glycerol and 100 mL of sodium chloride 0.9% as part of a test for Ménière's disease developed temporary hearing loss in the non-involved ear. Two previous reports of deterioration in hearing associated with the glycerol test were reviewed by the author.[1]

1. Mattox DE, Goode RL. Temporary loss of hearing after a glycerin test. *Arch Otolaryngol* 1978; **104:** 359–61.

Effects on the eyes. Caution in applying glycerol to the cornea has been recommended. Studies in *animals*[1] and in man[2] have indicated that the topical application of glycerol to the eye can damage the endothelial cells of the cornea.

1. Sherrard ES. The corneal endothelium in vivo: its response to mild trauma. *Exp Eye Res* 1976; **22:** 347–57.
2. Goldberg MH, *et al.* The effects of topically applied glycerin on the human corneal endothelium. *Cornea* 1982; **1:** 39–44.

Hyperosmolar nonketotic coma. Hyperosmolar nonketotic coma has been associated with the oral use of glycerol[1] and deaths have occurred.[2] The most susceptible patients are maturity-onset elderly diabetics with acute or chronic disease predisposing to fluid deprivation, and in these patients oral glycerol may be best avoided.[1] If glycerol is used in patients with predisposing conditions, adequate measures should be taken to recognise the development of hyperosmolar nonketotic hyperglycaemia and prevent dehydration.[1,2]

1. Oakley DE, Ellis PP. Glycerol and hyperosmolar nonketotic coma. *Am J Ophthalmol* 1976; **81:** 469–72.
2. Sears ES. Nonketotic hyperosmolar hyperglycemia during glycerol therapy for cerebral edema. *Neurology* 1976; **26:** 89–94.

Pharmacokinetics

Glycerol is readily absorbed from the gastrointestinal tract and undergoes extensive metabolism, mainly in the liver; it may be used in the synthesis of lipids, metabolised to glucose or glycogen, or oxidised to carbon dioxide and water. It may also be excreted in the urine unchanged.

◊ References.

1. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; **29:** 782–7.
2. Heinemeyer G. Clinical pharmacokinetic considerations in the treatment of increased intracranial pressure. *Clin Pharmacokinet* 1987; **13:** 1–25.

Uses and Administration

Glycerol is an osmotic dehydrating agent with hygroscopic and lubricating properties. When given orally or parenterally, glycerol increases the plasma osmolality, resulting in the movement of water by osmosis from the extravascular spaces into the plasma.

Glycerol is given by mouth for the short-term reduction of vitreous volume and intra-ocular pressure before and after ophthalmic surgery, and as an adjunct in the management of acute glaucoma (p.1873). Its onset of action is rapid, with a maximal reduction in intra-ocular pressure occurring about 1 to 1⁄ hours after a dose; the duration of action is about 5 hours. The usual initial dose of glycerol is 1 to 1.8 g/kg given as a 50% solution. There can be problems of palatability when glycerol solutions are given orally; chilling or flavouring the solutions may help.

Glycerol may be applied topically to reduce corneal oedema, but as the effect is only transient its use is largely limited to an adjunct in eye examination and diagnosis. Glycerol eye drops can be painful on instillation and use of a local anaesthetic beforehand has been recommended.

Glycerol has also been given orally or intravenously to reduce intracranial pressure (see below).

Glycerol may be used rectally as suppositories or a solution in single doses to promote faecal evacuation in the management of constipation (p.1693). It usually acts within 15 to 30 minutes. Glycerol is commonly classified as an osmotic laxative but may act additionally or alternatively through its local irritant effects; it may also have lubricating and faecal softening actions.

Glycerol is used as a demulcent in cough preparations (p.1547).

Glycerol has many applications in pharmaceutical formulation; these include its use as a vehicle and solvent, as a sweetening agent, as a preservative in some liquid medications, as a plasticiser in tablet film-coating, and as a tonicity adjuster. It is often included in topical preparations such as eye drops, creams, and lotions as a lubricant and also for its moisturising properties since, when absorbed, its hygroscopic action can enhance moisture retention. Ear drops for the removal of ear wax often contain glycerol as a lubricating and softening agent.

Glycerol is also used as a cryoprotectant in cryopreservation.

Diagnosis of Ménière's disease. Glycerol has been used[1] in the diagnosis of Ménière's disease (p.564) to distinguish potentially reversible cochlear dysfunction from the relatively irreversible pathology of advanced disease, or to predict the results of endolymphatic sac surgery. Glycerol is given by mouth to reduce the endolymphatic fluid volume and pressure and any transient improvement in hearing is measured. However, the adverse effects of glycerol such as headache, nausea, and vomiting can be a problem and the test has been reported to have low sensitivity and to give false-positive results. See also under Effects on the Ears, above.

1. Skalabrin TA, Mangham CA. Analysis of the glycerin test for Meniere's disease. *Otolaryngol Head Neck Surg* 1987; **96:** 282–8.

Raised intracranial pressure. Glycerol has been given intravenously or by mouth for its osmotic diuretic effect to reduce cerebral oedema and hence decrease the intracranial pressure (p.1181). It is also reported to be able to increase blood flow to areas of brain ischaemia. It has been used in a variety of clinical conditions[1] including cerebral infarction or stroke,[2] Reye's syndrome,[3] and meningitis.[4,5] It has been postulated[5] that glycerol's beneficial action in preventing the neurological sequelae in bacterial meningitis is due to its effects in increasing cerebral plasma osmolality, which reduces cerebral oedema and enhances cerebral circulation by reducing the excretion of cerebrospinal fluid, and that this may be more important than the decrease in intracranial pressure induced by osmotic diuresis. Glycerol has been reported to be ineffective in hepatic coma.[6] Some patients have had serious adverse effects including haemolysis, haemoglobinuria, and renal failure.[7,8]

1. Frank MSB, *et al.* Glycerol: a review of its pharmacology, pharmacokinetics, adverse reactions, and clinical use. *Pharmacotherapy* 1981; **1:** 147–60.
2. Righetti E, *et al.* Glycerol for acute stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/05/06).
3. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; **29:** 782–7.
4. Kilpi T, *et al.* Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J* 1995; **14:** 270–8.
5. Peltola H, *et al.* Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2007; **45:** 1277–86.
6. Record CO, *et al.* Glycerol therapy for cerebral oedema complicating fulminant hepatic failure. *BMJ* 1975; **ii:** 540.
7. Hägnevik K, *et al.* Glycerol-induced haemolysis with haemoglobinuria and acute renal failure: report of three cases. *Lancet* 1974; **i:** 75–7.
8. Welch KMA, *et al.* Glycerol-induced haemolysis. *Lancet* 1974; **i:** 416–17.

Trigeminal neuralgia. Selective destruction of pain-bearing nerves is reserved for patients who do not respond to conventional drug therapy for trigeminal neuralgia (p.9). This may be achieved by the instillation of glycerol among the trigeminal rootlets (percutaneous retrogasserian glycerol rhizolysis).[1-5] The efficacy and safety of this procedure have been debated,[1,4] but some centres report good long-term results in the majority of patients.[5] It has been suggested that variations in viscosity and osmolality may influence results.[2]

1. Sweet WH. The treatment of trigeminal neuralgia (tic douloureux). *N Engl J Med* 1986; **315:** 174–7.
2. Waltz TA, Copeland BR. Treatment of trigeminal neuralgia. *N Engl J Med* 1987; **316:** 693.
3. Young RF. Glycerol rhizolysis for treatment of trigeminal neuralgia. *J Neurosurg* 1988; **69:** 39–45.
4. Burchiel KJ. Percutaneous retrogasserian glycerol rhizolysis in the management of trigeminal neuralgia. *J Neurosurg* 1988; **69:** 361–6.
5. Jho H-D, Lunsford LD. Percutaneous retrogasserian glycerol rhizotomy: current technique and results. *Neurosurg Clin N Am* 1997; **8:** 63–74.

Preparations

BP 2008: Glycerol Eye Drops; Glycerol Suppositories; Phenol and Glycerol Injection;
USP 31: Calamine Topical Suspension; Glycerin Ophthalmic Solution; Glycerin Oral Solution; Glycerin Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Refenax Lagrimas; Vixorfit; ***Austral.:*** Bausch & Lomb Computer Eye Drops; ***Braz.:*** Glicel†; ***Chile:*** Fleet Babylax; ***Fr.:*** Bebegel; ***Ger.:*** Glycerosteril; Glycilax; Milax; Nene-Lax; Otodolor Soft; ***Gr.:*** Glicerolo microclismi†; Glycare; Microclismata; ***Hong Kong:*** Computer Eye Drops; Fleet Babylax; Glyceol; Wet Stuff; ***Irl.:*** Babylax; ***Israel:*** Minilax†; ***Ital.:*** Verolax; Zetalax; ***Jpn:*** Glyceol; ***Malaysia:*** Egozite Protective Baby Lotion; Fleet Babylax; ZenCare; ***Mex.:*** Estrin; Fleet Adulto; Fleet Infantil; Fleet Pedialax; Micronovag; Neutrobar; PC; Supositorios Senosiain; ***Philipp.:*** Babylax; Computer Eye Drops; Novas; United Home Glydolax; ***Port.:*** Bebegel; Dolorecto; Glycelax; Microcel; Rectiole; Verolax; ***S.Afr.:*** Regard; ***Singapore:*** Acnederm Wash; Fleet Babylax†; ***Spain:*** Adulax; Comosup; Gely; Glicerotens; Paidolax; Supo Gliz; Verolax; Vitrosups; ***Swed.:*** Miniderm; ***Switz.:*** Bulboid; Practomil; ***Thai.:*** Glyceol; Glycerosteril†; ***UAE:*** Laxolyne; ***UK:*** Benylin Tickly Coughs; Boots Cough Syrup 3 Months Plus; CalCough Tickly; Neutrogena Norwegian Formula Dermatological Cream; Nirolex Dry Cough; Senokot Direct Relief; Tixylix Baby Syrup; ***USA:*** Colace Infant/Child; Computer Eye Drops†; Eye-Lube-A; Fleet Babylax; Listermint Arctic Mint Mouthwash; Osmoglyn; Sani-Supp; ***Venez.:*** Fleet Babylax.

Multi-ingredient: ***Arg.:*** Irix Lagrimas; Keracnyl; Micronema; Sincerum Dry; Skleremo†; Ureadin Facial; Visine Lagrimas; ***Austral.:*** Aci-Jel†; Anusol; Auralgan; Egopsoryl TA; Hamilton Body Lotion†; Hamilton Cleansing Lotion†; Hamilton Dry Skin; Magnoplasm; SM-33; Soothe'n Heal; Visine True Tears†; ***Austria:*** Lacrisic; ***Belg.:*** Aloplastine; Laxavit; ***Braz.:*** Bluderm†; Dermamina; Effidrate†; Estomafitino†; Pasta d'Agua†; Trisorb; Varikromo†; ***Canad.:*** Agarol Plain; Auralgan; Bronchex†; Epi-Lyt; Lubriderm Advanced Moisture†; Moisture Drops†; Rhinedrine Moisturizing†; Swim-Ear†; Tears Naturale Forte; Tucks; ***Chile:*** Acnoxyl Jabon Liquido; Agarol; Cicapost; Nasivin; Ureadin Rx DB; Ureadin Rx RD; ***Denm.:*** Analka; Glyoktyl; Pectyl; ***Fr.:*** Aloplastine; Charlieu Topicrem; Derm'Intim; Dexeryl; Eryange†; Ictyane; Ictyane HD; Kertyol-S; Pharmatex; PSO; Rectopanbiline; Saugella; Scleremo; Septiane; Taido; ***Ger.:*** GeloBacin; Lacrisic; Lubrikano; Norgalax Miniklistier; Zinksalbe; ***Hong Kong:*** Acnederm; Acnederm Wash; Aderma Dermalibour†; Aderma Exomega†; Apaisac; Baby Cough with Antihistamine; Ego Skin Cream; Egopsoryl TA; Gly Thymol; Moisture Eyes; Tears Naturale Forte; Visine for Contacts; ***India:*** Neotomic; Otogesic; ***Indon.:*** Isotic Tearin; Laxadine; ***Irl.:*** Micolette; ***Israel:*** Dryears; Kamil Blue; Microlet; Taro Gel; ***Ital.:*** Dropyal; Evasen Dischetti; Evasen Liquido; Glicerolax; Microclismi Marco Viti; Microclismi Sella; Naturalass; Novilax; Rinogutt Atlantic; Salviette H; Solecin; ***Malaysia:*** Ego Skin Cream; Lorasil Feminine Hygeine†; ***Mex.:*** Maxibiloba; Moisture Eyes; Nasalub; Nutegen G†; Nutrasorb; ***NZ:*** Aci-Jel†; Auralgan; Ego Skin Cream; Karicare Breast and Body Cream†; Karicare Ointment†; Lemsip Dry Cough†; Rosken Skin Repair; Silic; ***Philipp.:*** Lactaderm; Moisture Eyes; pHCare; Visine Refresh; ***Pol.:*** Rektiolax; Unibasis; ***Port.:*** Antiacneicos Niacex†; Cicapost; Dagragel; Hidratante VG; Lubrificante Anestesico; Multi-Mam Compressas†; Nutraisdin; Ureadin Facial; Ureadin Maos; ***S.Afr.:*** Auralyt; Caloplast; Moisture Drops†; ***Singapore:*** Acnederm; Ego Skin Cream; Egozite Protective Baby Lotion†; Topicrem; Tropex; ***Switz.:*** Lacrycon; Neo-Decongestine; Realderm; ***Thai.:*** Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; ***Turk.:*** Gleitgelen; Kalmosan; Kansilak; Libalaks; Sabalax; ***UK:*** Allens Junior Cough; Asonor; Beehive Balsam; Earex Plus; Honey & Molasses; Imuderm; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets; Lockets Medicated Linctus; Meltus Honey & Lemon; Micolette; Relaxit; Swim-Ear; ***USA:*** Allergen; Astroglide; Auralgan; Cetaklenz; Clearasil Antibacterial; Collyrium Fresh†; Entertainer's Secret; Epi-Lyt; Formulation R; Hemorid For Women; Maxilube; Moisture Drops; N'ice; Numzit†; Preparation H; Refresh Dry Eye Therapy; Summers Eve Anti-Itch; Surgel; Swim-Ear; Therevac Plus; Therevac SB; Trimo-San; Tucks; Visine Pure Tears; Visine Tears; ***Venez.:*** Audocaina†.

Glycerophosphoric Acid

Glicerofosfórico, ácido; Glycerylphosphoric Acid; Monoglycerylphosphoric Acid.

$C_3H_9O_6P = 172.1.$

CAS — 27082-31-1; 57-03-4 (α-glycerophosphoric acid); 17181-54-3 (β-glycerophosphoric acid); 5746-57-6 (L-α-glycerophosphoric acid); 1509-81-5 (DL-α-glycerophosphoric acid).

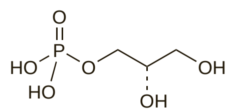

(L-α-glycerophosphoric acid)

Sodium Glycerophosphate

Glycerofosforečnan sodný; Natrii glycerophosphas; Natrio glicerofosfatas; Natrium Glycerophosphoricum; Nátriumglicerofoszfát; Natriumglycerofosfat; Natriumglyserofosfaatti hydratoitu; Sodium, glycérophosphate de; Sodium Glycerylphosphate.

$C_3H_7Na_2O_6P,xH_2O = 216.0$ (anhydrous).

CAS — 1555-56-2 (anhydrous α-sodium glycerophosphate); 819-83-0 (β-sodium glycerophosphate, anhydrous).

ATC — B05XA14.

ATC Vet — QB05XA14.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sodium Glycerophosphate, Hydrated). A white or almost white, crystalline powder or crystals. Freely soluble in water; practically insoluble in alcohol and in acetate.

Profile

Glycerophosphoric acid and various glycerophosphates have been used in tonics. They were once considered as a suitable means of providing phosphorus. Calcium and magnesium glycerophosphates (see p.1676 and p.1679, respectively) may be considered as a source of calcium or magnesium.

◊ Reference to the use of sodium glycerophosphate as a source of phosphorus in infant parenteral nutrition.[1]

1. Costello I, *et al.* Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. *Arch Dis Child* 1995; **73:** F44–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Glycophos; ***Fin.:*** Glycophos; ***Gr.:*** Glycophos; ***Hong Kong:*** Glycophos; ***Malaysia:*** Glycophos; ***Neth.:*** Glycophos; ***NZ:*** Glycophos; ***Pol.:*** Glycophos; ***Port.:*** Glycophos; ***Swed.:*** Glycophos; ***Switz.:*** Glycophos; ***UK:*** Glycophos.

Multi-ingredient: ***Arg.:*** Antikatarata†; ***Fr.:*** Biotone†; Ionyl; Phosphore Medifa; Verrulyse-Methionine; ***Israel:*** Babyzim; ***Ital.:*** Calciofix; Glicero-Valerovit; Neuroftal†; Neurol.

Glyceryl Palmitostearate

Glicerol, palmitoestearato de. A mixture of mono-, di-, and triglycerides of C_{16} and C_{18} fatty acids.

CAS — 8067-32-1.

Profile

Glyceryl palmitostearate is used in pharmaceutical manufacturing as a diluent and lubricant for tablets and capsules.

Glycopyrronium Bromide *(BAN, rINN)*

AHR-504; Bromuro de glicopirronio; Glikopironyum Bromür; Glycopyrrolate *(USAN)*; Glycopyrronii bromidum; Glycopyrronium, bromure de; Glykopyrroniumbromid; Glykopyrronium-bromidi. 3-(α-Cyclopentylmandeloyloxy)-1,1-dimethylpyrrolidinium bromide.

Гликопиррония Бромид

$C_{19}H_{28}BrNO_3 = 398.3.$

CAS — 596-51-0.

ATC — A03AB02.

ATC Vet — QA03AB02.

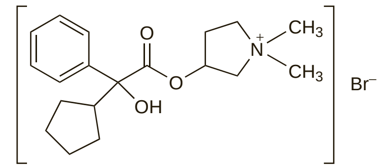

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Glycopyrrolate). A white, odourless, crystalline powder. Soluble 1 in 4.2 of water, 1 in 30 of alcohol, 1 in 260 of chloroform, and 1 in 35 000 of ether. Store in airtight containers.

Incompatibility. Glycopyrronium bromide is incompatible with alkalis.

Stability. Investigation of the compatibility of glycopyrronium bromide with infusion solutions and additives showed that the stability of glycopyrronium bromide is questionable above a pH of 6, owing to ester hydrolysis.[1]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; **36:** 508–10. Correction. *ibid.*; 745.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Renal impairment. A comparison[1] of the pharmacokinetics of intravenous glycopyrronium in 11 uraemic and 7 control patients indicated that the renal elimination of glycopyrronium is considerably prolonged in patients with uraemia. The mean amount of a dose excreted in the urine within 3 hours of a dose was 0.7% in the uraemic patients and 50% in the control patients; 24-hour excretion was 7% and 65%, respectively. The authors concluded that repeated or large doses of glycopyrronium should be avoided or perhaps the drug should not be used in patients with uraemia.

1. Kirvelä M, *et al.* Pharmacokinetics of glycopyrronium in uraemic patients. *Br J Anaesth* 1993; **71:** 437–9.

Interactions

As for Atropine Sulfate, p.1220.

Pharmacokinetics

Glycopyrronium bromide is poorly absorbed from the gastrointestinal tract; about 10 to 25% is absorbed after an oral dose. Glycopyrronium bromide penetrates the blood-brain barrier only poorly. Glycopyrronium is excreted in bile and urine.

◊ References.

1. Kaltiala E, *et al.* The fate of intravenous [H]glycopyrrolate in man. *J Pharm Pharmacol* 1974; **26:** 352–4.
2. Ali-melkkilä TM, *et al.* Pharmacokinetics of IM glycopyrronium. *Br J Anaesth* 1990; **64:** 667–9.
3. Rautakorpi P, *et al.* Pharmacokinetics of glycopyrrolate in children. *J Clin Anesth* 1994; **6:** 217–20.

Uses and Administration

Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). After intramuscular doses, onset of effects is within 15 to 30 minutes; vagal blocking effects last for 2 to 3 hours and antisialagogue effects persist for up to 7 hours. After intravenous doses, onset of actions occurs within 1 minute.

Glycopyrronium bromide is used similarly to atropine in anaesthetic practice. It has also been used in the iontophoretic treatment of hyperhidrosis and as an adjunct in the treatment of peptic ulcer disease. It is also under investigation for the treatment of chronic moderate to severe drooling in children.

See under headings below for details of dosage in specific indications.

Anaesthesia. Glycopyrronium bromide is given as a premedicant before general anaesthesia (see under Atropine, p.1221) to diminish the risk of vagal inhibition of the heart and to reduce salivary and bronchial secretions. It is given in doses of 200 to 400 micrograms intravenously or intramuscularly before the induction of anaesthesia; alternatively, it may be given in a dose of 4 to 5 micrograms/kg to a maximum of 400 micrograms. If necessary, similar or lower doses may be given intravenously during the operation and repeated if required. A suggested dosage for premedication in neonates is 5 micrograms/kg given intravenously or intramuscularly; doses in children aged 1 month and over are 4 to 8 micrograms/kg up to a maximum of 200 micrograms.

Glycopyrronium bromide is given before or with anticholinesterases to counteract their muscarinic effects when they are used to reverse the effects of competitive muscle relaxants (see Neostigmine, p.632). The dose is glycopyrronium bromide 200 micrograms intravenously per 1 mg of neostigmine (or per 5 mg of pyridostigmine); alternatively, it may be given in a dose of 10 to 15 micrograms/kg intravenously with neostigmine 50 micrograms/kg. A suggested dosage for neonates and children is 10 micrograms/kg intravenously with neostigmine 50 micrograms/kg. Glycopyrronium bromide can be given mixed in the same syringe with the anticholinesterase, and it has been suggested that greater cardiovascular stability results from use in this way.

Gastrointestinal disorders. Antimuscarinics, including glycopyrronium bromide, have a limited role as antispasmodics (see p.1692), and have been used as adjuncts in the treatment of peptic ulcer disease (see p.1702).

As an adjunct in the treatment of peptic ulcer disease the usual initial dose of glycopyrronium bromide has been 3 to 6 mg daily by mouth in divided doses adjusted according to response to a maximum of 8 mg daily; a maintenance dose of 1 mg twice daily is often adequate. Doses of 100 to 200 micrograms have been given by intramuscular or intravenous injection.

Hyperhidrosis. Adverse effects generally preclude oral use of antimuscarinics for the management of hyperhidrosis (p.1580), but glycopyrronium, has been applied topically as an alternative to aluminium salts.

In studies involving 22 patients with the Frey syndrome (localised flushing and sweating on eating) glycopyrronium bromide as 1 and 2% cream or roll-on solution gave good control of symptoms;[1] patients tended to prefer the roll-on lotion as it was easier to apply. Topical hyoscine as 0.25, 1, or 3% solution or cream also gave control of sweating, but was associated with a much higher incidence of adverse effects. Patients with diabetic gustatory sweating have also noted a reduction in the frequency and severity of episodes after applying glycopyrronium 0.5% cream.[2]

Glycopyrronium bromide has also been used as a 0.05% solution in the iontophoretic treatment of hyperhidrosis.

1. Hays LL, *et al.* The Frey syndrome: a simple, effective treatment. *Otolaryngol Head Neck Surg* 1982; **90:** 419–25.
2. Shaw JE, *et al.* A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997; **40:** 299–301.

Palliative care. Glycopyrronium bromide is used in palliative care as an alternative to hyoscine to reduce excessive respiratory secretions. A dose of 200 micrograms may be given subcutaneously or intramuscularly every 4 hours. Alternatively, a dose of 0.6 to 1.2 mg may be given by continuous subcutaneous infusion over 24 hours.

Respiratory-tract disorders. Antimuscarinics have potent bronchodilatory activity and some, such as ipratropium (p.1124), may be used in the management of reversible airways obstruction. Glycopyrronium has been studied, although it is not one of the preferred drugs.

References.

1. Schroeckenstein DC, *et al.* Twelve-hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988; **82:** 115–19.
2. Gilman MJ, *et al.* Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990; **98:** 1095–8.
3. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1995; **25:** 470–3.

Preparations

USP 31: Glycopyrrolate Injection; Glycopyrrolate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Acpan; ***Austral.:*** Robinul; ***Austria:*** Robinul; ***Belg.:*** Robinul; ***Denm.:*** Robinul; ***Fin.:*** Robinul; ***Ger.:*** Robinul; ***Hong Kong:*** Robinul†; ***Norw.:*** Robinul; ***NZ:*** Robinul; ***S.Afr.:*** Robinul; ***Swed.:*** Robinul; ***UK:*** Robinul; ***USA:*** Robinul.

Multi-ingredient: ***Fin.:*** Gastrodyn comp.

Used as an adjunct in: ***Belg.:*** Robinul-Neostigmine; ***Denm.:*** Robinul-Neostigmine; ***Fin.:*** Glycostigmin; Robinul-Neostigmin; ***Norw.:*** Robinul-Neostigmin; ***Swed.:*** Robinul-Neostigmin; ***Switz.:*** Robinul-Neostigmine; ***UK:*** Robinul-Neostigmine.

Glycyrrhizic Acid

Glycyrrhizin; Glycyrrhizinic Acid.

$C_{42}H_{62}O_{16}$ = 822.9.

CAS — 1405-86-3.

Ammonium Glycyrrhizate

Ammonii glycyrrhizas; Ammonium, glycyrrhizate d'; Ammonium Glycyrrhizinate; Ammónium-glicirrizát; Ammoniumglycyrrhizat; Ammoniumglykyrritsaatti; Amonio glicirizatas; Amonium-glycyrrhizát; Glycyrram; Monoammonium Glycyrrhizinate.

$C_{42}H_{65}NO_{16}$ = 840.0.

CAS — 53956-04-0.

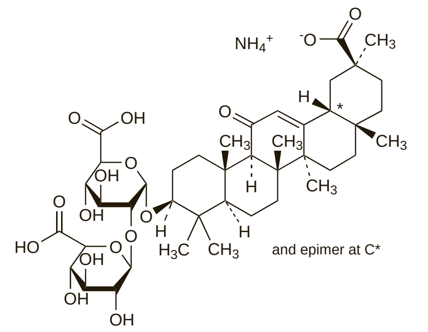

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Ammonium Glycyrrhizate). A white or yellowish-white, hygroscopic powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. Store in airtight containers.

Dipotassium Glycyrrhizate

Potassium Glycyrrhizinate.

$C_{42}H_{60}K_2O_{16}$ = 899.1.

CAS — 68039-19-0 (potassium glycyrrhizate); 42294-03-1 (monopotassium glycyrrhizate); 68797-35-3 (dipotassium glycyrrhizate);.

Profile

Glycyrrhizic acid is a constituent of liquorice (p.1740). The mild anti-inflammatory and mineralocorticoid properties of liquorice have been attributed to the presence of glycyrrhizic acid and its metabolite glycyrrhetinic acid (Enoxolone, p.50).

Glycyrrhizic acid and its ammonium and potassium salts have been used in products promoted for the relief of coughs, viral infections, and gastrointestinal, liver, and skin disorders. Ammonium glycyrrhizate has also been used as a sweetener, flavour enhancer, and as an emulsifying and gel-forming agent in foodstuffs and cosmetics.

Other derivatives of glycyrrhizic acid discussed elsewhere include metoclopramide glycyrrhizinate (p.1749) and enoxolone (p.50).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Epigen; ***Indon.:*** Neo-Minophagen C; ***Jpn:*** Neo-Minophagen C; ***Mex.:*** Epigen; ***Rus.:*** Epigen (Эпиген).

Multi-ingredient: ***Austria:*** Enicul; ***Fr.:*** Keracnyl stop bouton; Topialyse Fluide; Topialyse Plus; ***Ital.:*** Biothymus DS; ***Jpn:*** Colgen Kowa Bien Soft Mini; ***Mex.:*** Bexident Pediatrics†; ***Port.:*** Alkagin; Bexident.

GMDP

Glucosaminylmuramyl Dipeptide. *N*-acetylglucosaminyl-β1-4-*N*-acetylmuramyl-alanyl-D-isoglutamine.

ГМДП

$C_{25}H_{43}N_5O_{15}$ = 653.6.

CAS — 97590-38-0.

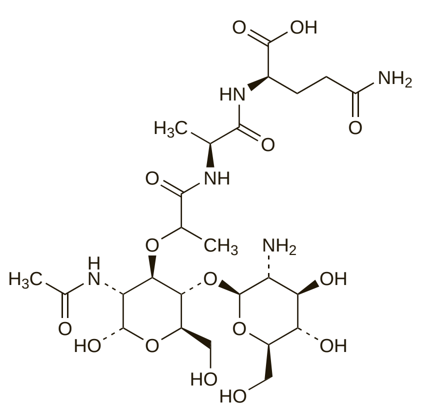

Profile

GMDP, a component of bacterial cell walls, is reported to have immunomodulator properties and is used in a wide range of diseases stated to be associated with secondary immunodeficiency.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Licopid (Ликопид).

Gold

Aurum; E175; Or; Oro.

Au = 196.966569.

CAS — 7440-57-5.

Profile

Gold is a bright-yellow, malleable, and ductile metal; the finely divided powder may be black, ruby, or purple. The main use of metallic gold in health care is now in dentistry. Gold may also be used as a colouring agent for some foodstuffs. In the treatment of rheumatoid arthritis, gold is used in the form of compounds such as auranofin (p.25), aurothioglucose (p.26), and sodium aurothiomalate (p.122). The radionuclide gold-198 is described in the chapter on radiopharmaceuticals (p.2053). There have been rare reports of hypersensitivity reactions to metallic gold.

Homoeopathy. Gold has been used in homoeopathic medicines under the following names: Aurum; Aurum met.; Aurum metallicum; Aur. met.

◊ References.

1. Merchant B. Gold, the noble metal and the paradoxes of its toxicology. *Biologicals* 1998; **26:** 49–59.
2. Ehrlich A, Belsito DV. Allergic contact dermatitis to gold. *Cutis* 2000; **65:** 323–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Cefassin†.

Gossypol

Gosipol. 2,2′-Bis(1,6,7-trihydroxy-3-methyl-5-isopropylnaphthalene-8-carboxaldehyde).

$C_{30}H_{30}O_8$ = 518.6.

CAS — 303-45-7.

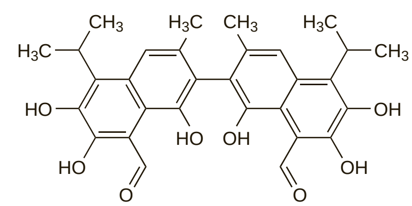

Profile

Gossypol is a pigment extracted from cottonseed oil (p.2288). It possesses antispermatogenic activity and has been studied, especially in China, as a male contraceptive. It has also been investigated for its antineoplastic, antiprotozoal, antiviral, and spermicidal activity and has been studied in women in the treatment of gynaecological disorders.

Adverse effects have included fatigue, changes in appetite, gastrointestinal effects, burning sensation of the face and hands, some loss of libido, and persistent oligospermia. Hypokalaemia has occurred.

◊ The pharmacology and therapeutic potential of gossypol have been reviewed.[1] Although controlled studies[2,3] have shown gossypol to be an effective male contraceptive, WHO concluded[4] that gossypol would not be acceptable as a male antifertility drug because of the occurrence of adverse effects such as hypokalaemia and irreversible testicular damage resulting in azoospermia or severe oligozoospermia.

1. Wu D. An overview of the clinical pharmacology and therapeutic potential of gossypol as a male contraceptive agent and in gynaecological disease. *Drugs* 1989; **38:** 333–41.
2. Coutinho EM, *et al.* Antispermatogenic action of gossypol in men. *Fertil Steril* 1984; **42:** 424–30.
3. Liu G, *et al.* Clinical trial of gossypol as a male contraceptive drug part I: efficacy study. *Fertil Steril* 1987; **48:** 459–61.
4. Waites GMH, *et al.* Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. *Int J Androl* 1998; **21:** 8–12.

Grape

Grapevine; Rebe; Vigne Rouge; Weinstock.

NOTE. Distinguish from grape bark, Cocillana, p.1554.

Pharmacopoeias. *Fr.* includes Red Vine Extract (Extrait de Vigne Rouge (Sec)), prepared from the leaves.

Profile

The seeds and the leaves of the grape, *Vitis vinifera* (Vitaceae), are used in herbal medicine. The dried fruit (raisins) have laxative and demulcent properties.

Many parts of the plant including the fruit skin, seeds, and leaves are used. Both dietary sources and various extracts are promoted for their antioxidant properties in venous insufficiency and capillary impairment, and it has been suggested that they may protect against atherosclerosis.

A standardised red vine leaf extract (AS-195) has been given for the management of chronic venous insufficiency.

Grape seed and grape seed extracts have been included in preparations for peripheral vascular disorders and venous insufficiency and for prophylaxis of cardiovascular disorders. Extracts of grape seed proanthocyanidins, including IH636, are being investigated for a range of other disorders in which antioxidant and free-radical scavenging activity is thought to be beneficial, including cancer prevention, hepatic disorders, radiation-induced fibrosis, cataracts, and macular degeneration, although there is currently little evidence of effectiveness.

Resveratrol, a compound present in grapes, (see p.2378) is also promoted as an antoxidant.

Grape seed oil is included in topical preparations.

The fresh and dried fruits of the grape and the leaves are used as foodstuffs.

◊ Review.

1. Bombardelli E, Morazzoni P. Vitis vinifera L. *Fitoterapia* 1995; **66:** 291–317.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Viticalm; ***Austria:*** Antistax; Pedopur; ***Braz.:*** Celox; Radifree; Vinera; Vitium†; ***Chile:*** Endotelon; Juvenit†; Uvanox; ***Cz.:*** Antistax; Endotelon†; ***Fr.:*** Endotelon; ***Ger.:*** Antistax; ***Hung.:*** Endotelon; ***Ital.:*** Antistax; ***Pol.:*** Endotelon; ***Spain:*** Antistax; ***Switz.:*** Antistax; ***UK:*** Antistax.

Multi-ingredient: ***Austral.:*** Anthogenol; Antioxidant Forte Tablets; Bioglan Pygno-Vite; Bioglan Zellulean with Escin; Lifechange Multi Plus Antioxidant†; Pykno†; Vitanox; ***Austria:*** Hepatodoron; ***Canad.:*** Glucosamine Joint & Muscle Cream with MSM†; ***Chile:*** Celltech Gold; ***Fr.:*** A-Flam; D'Contract; Detoxell; Ditavene; Flebior; Jouvence de l'Abbe Soury†; Mediflor Tisane Circulation du Sang No 12; Ophtalmine; Opo-Veinogene; Phlebosedol†; Veinophytum†; ***Ger.:*** Hepatodoron; ***Hong Kong:*** Proflavanol†; ***Indon.:*** Lanaven Plus; Lycoq; Resvica; ***Ital.:*** Angiovein; Capill; Mirtilux; Neosulfur; Venalta; ***Malaysia:*** Proflavanol; ***Mex.:*** Proflavanol; ***S.Afr.:*** Hepatodoron; ***Singapore:*** Proflavanol; ***Switz.:*** Kawaform†; ***UK:*** Atopiclair; Xclair; ***USA:*** Atopiclair; Pycnogenol Plus.

Gravel Root

Joe Pye Weed; Queen of the Meadow; Raíz de eupatorio.

Profile

Gravel root is the root of *Eupatorium purpureum* (Compositae) and has diuretic, antilithic, and antirheumatic properties. It is used for renal and urinary calculus and other urinary-tract disorders, and has also been used for gout and rheumatism.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Backache.

Greater Celandine

Celidonia; Chélidoine; Chelidonii herba; Chelidonium; Keltamo; Schöllkraut; Skelört; Tetterwort; Ugniažolių žolė; Vérehulló fecskefű; Vlašťovičníková nať; Ziele glistnika.

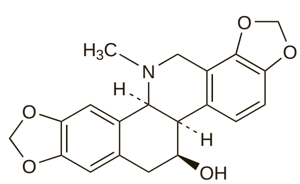

(+)-form

(chelidonine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Greater Celandine). The dried, whole, or cut aerial parts of *Chelidonium majus* collected during flowering. It contains a minimum of 0.6% of total alkaloids expressed as chelidonine ($C_{20}H_{19}NO_5$ = 353.4), calculated with reference to the dried drug.

Profile

Greater celandine has sedative and spasmolytic properties and the aerial parts are used for liver, biliary, and gastrointestinal disorders, and have also been used for respiratory-tract disorders. The latex has been used externally for warts and other skin conditions.

It has been reported to cause hepatotoxicity.

Homoeopathy. Greater celandine has been used in homoeopathic medicines under the following names: Chelidonium; Chelidonium majus; Chelidonium, Flos; Chelidonium majus e floribus; Che. maj.

Effects on the liver. References.

1. Benninger J, *et al.* Acute hepatitis induced by greater celandine (Chelidonium majus). *Gastroenterology* 1999; **117:** 1234–7.
2. Stickel F, *et al.* Acute hepatitis induced by Greater Celandine (Chelidonium majus). *Scand J Gastroenterol* 2003; **38:** 565–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Aristochol CC†; Cholarist; Cholspasmin Phyto†; Gallopas†; Paverysat forte N; ***Switz.:*** Virulex.

Multi-ingredient: ***Arg.:*** Quelodin F; ***Austral.:*** Berberis Complex; Extralife Liva-Care; Lexat†; Livstim†; Livton Complex†; ***Austria:*** Choleodoron; ***Belg.:*** Aporil; ***Braz.:*** Quelodin†; ***Cz.:*** Iberogast; ***Fr.:*** Nitrol; ***Ger.:*** Aristochol N†; Aristochol†; Chol-Kugeletten Neu; Cholagogum F†; Cholagogum N†; Cholagutt-N†; Cholhepan N; Cholosom Phyto N; Cholosom SL†; Cynarzym N†; Femisana†; Gallemolan forte; Gallemolan G†; Galloselect M†; Hepaticum-Medice H†; Horvilan N; Iberogast; Infi-tract†; Marianon†; Nervogastrol N†; Neurochol C†; Opobyl-phyto†; Presselin Hepaticum P†; Schwohepan S†; spasmo gallo sanol†; ***Hong Kong:*** Hepatofalk; Hepatofalk Planta; ***Indon.:*** Lanagogum; ***Pol.:*** Artecholin; Artecholwex; Chelicur; Cholavisol; Cholitol; Enterosol; Neoazarina; Sirupus Pini Compositus; Sirupus Tussipini; Sirupus Tussipini D; ***Port.:*** Cholagutt†; ***S.Afr.:*** Choleodoron; ***Singapore:*** Hepatofalk Planta; ***Spain:*** Menstrunat†; Natusor Hepavesical†; Nitroina; ***Switz.:*** Choleodoron†; Demonatur Gouttes pour le foie et la bile; Iberogast; Stago N†; ***Venez.:*** Demerung.

Green-lipped Mussel

Extracto de mejillón de labios verdes.

Зеленого Губчатого Моллюска

Profile

An extract from the green-lipped mussel *Perna canaliculus* (Mytilidae), stated to contain omega-3 polyunsaturated fatty acids, amino acids, fats, carbohydrates, and minerals, has been promoted for the treatment of rheumatic disorders including rheumatoid arthritis (p.11). It has also been tried in asthma.

Rheumatic disorders. Reviews of the investigation of green-lipped mussel in the treatment of arthritis have not revealed conclusive evidence of its usefulness.[1,2]

1. Li Wan Po A, Maguire T. Green-lipped mussel. *Pharm J* 1990; **244:** 640–1.
2. Cobb CS, Ernst E. Systematic review of a marine nutriceutical supplement in clinical trials for arthritis: the effectiveness of the New Zealand green-lipped mussel *Perna canaliculus*. *Clin Rheumatol* 2006; **25:** 275–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Lyprinol; ***UK:*** Healtheries Musseltone; Lyprinol; Mobilyzer; Oceantone; Seatone; Supplex.

Multi-ingredient: ***Austral.:*** Prost-1†; ***Ital.:*** Osteoclar; ***UK:*** Healtheries Musseltone & Glucosamine.

Griffonia Simplicifolia

Profile

The leaf, stem, and twigs of *Griffonia simplicifolia* (Fabaceae) have been used for a variety of disorders in its native West Africa. It is included in herbal and nutritional supplements. It is a source of lectins and has insecticidal properties.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Prosatietil†; Tryptonat; ***Ital.:*** Brioplus; Calmason; Climil Complex.

Grindelia

Gum Plant; Gumweed; Tar Weed.

Pharmacopoeias. In *Fr.* which allows *Grindelia camporum*, *G. humilis*, *G. robusta*, and *G. squarrosa*.

Profile

Various *Grindelia* spp. (Asteraceae) have been included in herbal preparations used for respiratory-tract disorders.

Homoeopathy. Grindelia has been used in homoeopathic medicines under the following names: Grindelia robusta; Grind. ro.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Expectosan Hierbas y Miel; ***Austral.:*** Asa Tones; Euphorbia Complex; ***Austria:*** Paracodin; ***Braz.:*** Calmatoss†; Gotas Nican†; Infantoss†; Limao Bravo†; Pectal†; Xarope de Caraguata†; Xarope Peitoral de Ameixa Composto†; Xpe SPC†; ***Canad.:*** Herbal Cold Relief†; ***Chile:*** Gotas Nican†; Ramistos; ***Cz.:*** Bronchicum Elixir†; Bronchicum Hustensirup†; ***Fr.:*** Coquelusedal; Coquelusedal Paracetamol; Dinacode†; Ephydion; Germose†; Neo-Codion; Vegetoserum; ***Ger.:*** Asthma 6-N†; Bronchicum Elixir N†; ***Indon.:*** Pectum; ***Ital.:*** Broncosedina; Tussanyl; ***Neth.:*** Bronchicum; ***Pol.:*** Bronchicum Eliksir; Echinasal; ***Rus.:*** Bronchicum (Бронхикум); Bronchicum Husten (Бронхикум Сироп от Кашля); Neo-Codion (Нео-Кодион); Neo-Codion Babies (Нео-Кодион Для Младенцев); ***S.Afr.:*** Bronchicough†; Bronchicum†; ***Spain:*** Pazbronquial; ***Switz.:*** Famel; Neo-Codion N; Nican; ***Venez.:*** Novacodin.

Ground Ivy

Ale-hoof; Gundelrebe; Gundermann; Hiedra terrestre; Lierre Terrestre.

Pharmacopoeias. In *Chin.* and *Fr.*

Profile

Ground ivy, the aerial parts of *Glechoma hederacea* (*Nepeta hederacea*) (Labiatae) has been used for respiratory-tract and gastrointestinal disorders.

Homoeopathy. Ground ivy has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Gerard House Water Relief Tablets; Water Naturtabs.

Guaiacum Resin

Guaiac; Guaiacum; Guajakharz; Gwajakowa żywica; Resina de guayaco.

CAS — 9000-29-7.

Profile

Guaiacum resin is obtained from guaiacum wood (lignum vitae; *Guaiacum officinale* or *G. sanctum*) (Zygophyllaceae) and has been used in the treatment of rheumatism. It is used in herbal medicine.

Guaiacum resin is used in the detection of occult blood in the faeces. The accuracy of the guaiacum test has been questioned and some drugs may interfere with the result.

Homoeopathy. Guaiacum resin has been used in homoeopathic medicines under the following names: Guaiacum; Guajacum; Guaic.

◊ References.

1. Ko CW, *et al.* Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003; **115:** 111–14.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Boswellia Compound; Guaiacum Complex†; ***Switz.:*** Pommade au Baume; ***UK:*** Gerard House Reumalex; Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain Remedy.

Guaiazulene

Gayazulen; Guayazuleno; Gwajazulen. 1,4-Dimethyl-7-isopropylazulene.

$C_{15}H_{18}$ = 198.3.

CAS — 489-84-9.

ATC — S01XA01.

ATC Vet — QS01XA01.

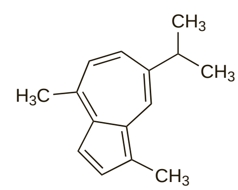

Profile

Guaiazulene has been reported to have anti-allergic, anti-inflammatory, antipyretic, and antiseptic properties.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Azulon; ***Austria:*** Azulen; Azulenal; Garmastan; ***Cz.:*** Garmastan†; Ophthalmo-Azulen; ***Fr.:*** Azulene†; ***Hung.:*** Azulenol; ***Turk.:*** Garmastan.

Multi-ingredient: ***Arg.:*** Sodorant; ***Austria:*** Piniment; Spasmo Claim; Tampositorien mit Belladonna; Thrombocid; ***Cz.:*** Dermazulen; Ophthalmo-Septonex; Pinosol; Pityol; Vitazulen†; ***Fr.:*** Cicatryl; Pepsane; ***Ger.:*** Azupanthenol†; Thrombocid; ***Hong Kong:*** Thrombocid; ***Israel:*** Aronal Forte; ***Ital.:*** Collyria†; ***Mex.:*** Pepsane; ***Pol.:*** Pinosol; ***Port.:*** Thrombocid; ***Rus.:*** Pinosol (Пиносол); ***Spain:*** Predni Azuleno; ***Switz.:*** Bain extra-doux dermatologique; Thrombocid.

Guanidine Hydrochloride

Carbamidine Hydrochloride; Guanidina, hidrocloruro de; Guanidyny chlorowodorek; Iminourea Hydrochloride.

CH_5N_3,HCl = 95.53.

CAS — 113-00-8 (guanidine); 50-01-1 (guanidine hydrochloride).

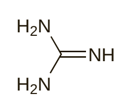

(guanidine)

Profile

Guanidine hydrochloride enhances the release of acetylcholine from nerve terminals. It has been given by mouth to reverse neuromuscular blockade in patients with botulism (p.2207), but its efficacy has not been established. Guanidine hydrochloride has also been tried in Eaton-Lambert myasthenic syndrome (p.629)

and other neurological disorders, but its use has been associated with bone-marrow suppression in some patients.

◊ References.

1. Kaplan JE, *et al.* Botulism, type A, and treatment with guanidine. *Ann Neurol* 1979; **6:** 69–71.
2. Critchley EMR, *et al.* Outbreak of botulism in North West England and Wales. *Lancet* 1989; **ii:** 849–53.
3. Neal KR, Dunbar EM. Improvement in bulbar weakness with guanoxan in type B botulism. *Lancet* 1990; **335:** 1286–7.
4. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; **20:** 1146–52.

Guanosine

Guanine Riboside; NSC-19994; Vernine. 2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6(1*H*)-one.

Гуанозин

$C_{10}H_{13}N_5O_5$ = 283.2.

CAS — 118-00-3.

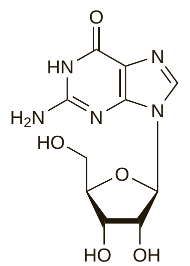

Profile

Guanosine is an endogenous guanine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p.2355). Guanosine is included in preparations for peripheral and cerebral vascular disorders and myopathies; guanosine monophosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Laevadosin†; ***Spain:*** Nutracel.

Gutta Percha

Gummi Plasticum; Gutapercha; Gutt. Perch.

Pharmacopoeias. In *US.*

USP 31 (Gutta Percha). The coagulated, dried, purified latex of the trees of the genera *Palaquium* and *Payena* and most commonly *Palaquium gutta* (Sapotaceae). It occurs in lumps or blocks of variable size; externally brown or greyish-brown to greyish-white in colour; internally reddish-yellow or reddish-grey and having a laminated or fibrous appearance. It is flexible but only slightly elastic. Has a slight, characteristic odour. Insoluble in water; partly soluble in carbon disulfide, in turpentine oil, and in benzene; about 90% soluble in chloroform. Store under water. Protect from light.

Profile

Gutta percha has been used in various dressings. In dentistry, gutta percha has been used as a filling material and as the basis of compounds for taking dental impressions.

Haematoporphyrin

Hematoporfirina.

$C_{34}H_{38}N_4O_6$ = 598.7.

CAS — 14459-29-1.

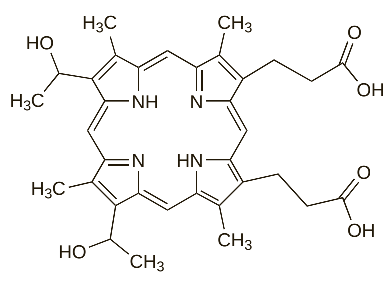

Profile

Haematoporphyrin is a red pigment, free from iron, obtained from haematin. It is an ingredient of preparations promoted as tonics, particularly for the elderly, and has been used in the treatment of depression. Derivatives of haematoporphyrin are used as photosensitisers in the photodynamic therapy of malignant neoplasms (see Porfimer Sodium, p.764).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** KH3; ***Chile:*** Actebral; KH3-Vit†; KH3†; ***Ger.:*** KH3†; Revicain comp plus†; ***Hong Kong:*** KH3; ***Ital.:*** Porfirin 12; Tonogen; Vit-Porphyrin†; ***NZ:*** KH3; ***Thai.:*** KH3.

Hamamelis

Amamelide; Csodamogyorólevél (hamamelis leaf); Hamamelidis; Hamamelidis folium (hamamelis leaf); Hamameliksenlehti (hamamelis leaf); Hamamélis de virginie; Hamamélis, feuille d' (hamamelis leaf); Hamamelisblad (hamamelis leaf); Hamamelių lapai (hamamelis leaf); Trollhassel; Vilínový list (hamamelis leaf); Virginsk Troldnød; Witch Hazel; Zauberhasel; Zaubernuss.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Hamamelis Leaf). The whole or cut dried leaves of *Hamamelis virginiana* containing not less than 3% tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1), calculated with reference to the dried drug. Protect from light.

USP 31 (Witch Hazel). A clear, colourless distillate prepared from recently cut and partially dried dormant twigs of *Hamamelis virginiana*. pH between 3.0 and 5.0. Store in airtight containers at a temperature not exceeding 40°.

Profile

Hamamelis has astringent properties and contains gallic acid, a bitter principle, and a trace of volatile oil. It is used in preparations for the symptomatic relief of haemorrhoids (p.1697). Hamamelis water is used as a cooling application and has been applied as a haemostatic.

Hamamelis is used in herbal preparations for a variety of disorders.

Homoeopathy. Hamamelis has been used in homoeopathic medicines under the following names: Hamamelis virginiana; Hamamelis, Folium; Hamamelis virginiana e foliis; Hamamelis virginiana ex cortice summitatibusque; Hamamelis virginica; Ham. virg.

Preparations

USP 31: Witch Hazel.

Proprietary Preparations (details are given in Part 3)

Austral.: Optrex Original; Witch Doctor†; ***Austria:*** Hametum; Sperti Praparation H†; ***Canad.:*** Optrex; ***Chile:*** Similia†; Sperti Preparacion H Clear Gel†; ***Fr.:*** Optrex; ***Ger.:*** Aescorin N†; Fiamelis†; Haemo Duoform†; Hamasana†; Hametum; Posterine; Tampositorien H†; Venoplant top†; ***Ital.:*** Acqua Virginiana; Derminiol; Optrex; ***Malaysia:*** Optrex; ***Mex.:*** Tia Puppy; ***NZ:*** Optrex; ***Pol.:*** Phloderm; ***Port.:*** Optrex; ***Singapore:*** Optrex; ***Spain:*** Derminiol; Hametol; Hemo Derminiol; Optrex; ***Switz.:*** Mavena Anal-Gen; Optrex; ***Thai.:*** Optrex; ***Turk.:*** Hametan; ***UK:*** Optrex; Preparation H Clear Gel; Witch Doctor; Witch Sunsore; ***USA:*** A-E-R; Fleet Medicated Pads†; Neutrogena Drying.

Multi-ingredient: ***Arg.:*** Banoftal†; Clematis III Oligoplex†; Domuderm; Ecnagel; Esculeol P; Lavandula Oligoplex; Manzan; Venoful; VNS 45; ***Austral.:*** Anusol; Bioglan Cirflo†; Gentlees; Hemocane; Optrex; Proflo†; ***Austria:*** Arnicet; Inotyol; Mirfulan; Sulgan 99; Tampositorien mit Belladonna; ***Belg.:*** Hemorhinol; Purigel Crisp; Rectovasol; ***Braz.:*** Bromidrastina†; Hemodotti; Hemorroidex†; Higicler; Malvatricin Natural Organic; Manolio†; Mirorroidin†; Proctosan; Supositorio Hamamelis Composto†; Varizol†; Visionom; ***Canad.:*** Onrectal; Penaten; Preparation H Cooling Gel; Tucks; ***Chile:*** Hemorrol†; Proctoplex; Varicare†; ***Cz.:*** Aviril H†; Sagittaproct†; ***Fr.:*** Aphloine P; Climaxol; Ekseme; Evarose; HEC; Histo-Fluine P; Inotyol†; Jouvence de l'Abbe Soury; Keracnyl eau nettoyante; Keracnyl stop bouton; Mediflor Tisane Circulation du Sang No 12; Ophtalmine; Pastilles Monleon; Phlebosedol†; Phytomelis; Purif-Ac Gel; Veinostase; ***Ger.:*** Aescusan; Anisan†; Chlorophyllin Salbe "Schuh"†; Eulatin NN; Hametum-N†; Heusin†; Leukona-Wundsalbe†; Mirfulan; Sanaderm†; Trauma-cyl; Varicylum-S; Venacton†; Weleda Hamorrhoidalzapfchen; ***Hong Kong:*** Eye Glo Plus; ***Indon.:*** Oculosan; ***Israel:*** Aforinol; Derma Care; Inotyol; ***Ital.:*** Altacura Ipragocce; Centella Complex; Centeril H; Decon Ovuli; Dermilia Flebozin; Dermitina; Dermoprolyn†; Eulux; Ginoxil Ecoschiuma; Hamamilla†; Herbe†; Inotyol†; Intim; Iridil; Lycia Luminique; Nevril; Proctonet†; Proctopure; Sacnel; Salviette H; Sedalen Cort†; Sedilene Procto†; Steril Zeta; Stilomagic†; Varicogel†; Venactive; Venalta; Venoplus†; Venotrauma†; ***Mex.:*** Almodin; Prespir; Supranettes Naturalag; ***Mon.:*** Fluon; ***NZ:*** Lacto Calamine†; Optrex Red-Eye Relief; ***Port.:*** Hemofissural; ***S.Afr.:*** Lacto Calamine†; Lotio Pruni Comp cum Cupro; Stibium Comp; ***Singapore:*** HEC†; Stop-Itch Plus; ***Spain:*** Banoftal; Hemodren Compuesto†; Lamnotyl†; Ojosbel; Roidhemo†; Ruscimel†; Solucion Schoum; Venofit; ***Switz.:*** Anal-Gen†; Collypan; Euproctol N; Frigoplasma†; Haemocortin; Haemolan; HEC; Mavena Proctal-Gen; Oculosan; Optrex compresses; Pommade Nasale Radix†; Riccovitan†; Suppositoires contre les hemorroides†; Tendro; ***Thai.:*** Opplin†; ***UK:*** Adiantine; Eye Dew; Heemex; Lacto Calamine; Modern Herbals Pile; Optrex Red Eyes; Swarm; Tea Tree & Witch Hazel Cream; Varicose Ointment; Vital Eyes; ***USA:*** Clearasil Double Clear; Preparation H Cooling Gel; Tucks; ***Venez.:*** Biomicovo†; Camolyn; Camolyn Plus; Flucirac; Supranettes†.

Harmaline

Harmalina. 3,4-Dihydroharmine.

$C_{13}H_{14}N_2O$ = 214.3.

CAS — 304-21-2.

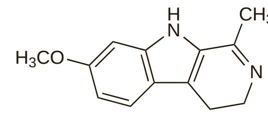

Description. Harmaline is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae).

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of harmaline or preparations containing harmaline:

Caapi; Huasca; Purga, la; Vine; Yage.

Harmine

Harmina; 7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole.

Хармин

$C_{13}H_{12}N_2O$ = 212.2.

CAS — 442-51-3.

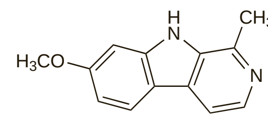

Description. Harmine is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae), also known as syrian rue.

Harmine is identical with an alkaloid known as banisterine or telepathine obtained from *Banisteriopsis caapi* (Malpighiaceae).

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of harmine or preparations containing harmine:

Rue.

Profile

Harmine and harmaline are the main active principles of a hallucinogenic drink, known in South American regions as 'ayahuasca', 'caapi', or 'yagé', that is made from closely related plants of the family Malpighiaceae. They have no therapeutic use.

Helonias

Blazing Star; Chamaelirium; False Unicorn; Starwort.

Profile

Helonias is the root of *Chamaelirium luteum* (*Helonias dioica*) (Liliaceae). It is used in herbal medicine particularly for gynaecological disorders.

Homoeopathy. Helonias has been used in homoeopathic medicines under the following names: Chamaelirium luteum; Helonias dioica; Helon.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Capsella Complex; Nervatona Calm; Nervatona Focus; ***UK:*** Period Pain Relief.

Henna

Henna Leaf; Henné; Lawsonia.

Profile

Henna is the dried leaves of *Lawsonia inermis* (*L. alba*) (Lythraceae), containing lawsone (p.2331). Powdered henna is used for dyeing the hair, skin, and nails.

Adverse effects. Allergic skin reactions to henna used to dye the skin have been reported.[1] Such reactions were usually due to additives used to shorten the application time of the dye and allergic reactions to 'plain' henna were rare. Similar reactions have been reported[2-10] after henna tattoos on the skin. The adulterant, which is added to natural henna to darken it ('black henna'), was identified[2,5] as paraphenylenediamine (p.2363). There have been reports of the paraphenylenediamine adulterant producing permanent skin pigment changes[7,10] and also cross-sensitisation to paraphenylenediamine-containing hair dyes[7-10] and textile dyes;[10] there is also the possibility of sensitisation to other allergens such as natural rubber latex.[10]

The suggestion that henna may cause neonatal hyperbilirubinaemia is discussed under Lawsone, p.2331.

1. Lestringant GG, *et al.* Cutaneous reactions to henna and associated additives. *Br J Dermatol* 1999; **141:** 598–600.
2. Brancaccio RR, *et al.* Identification and quantification of *para*-phenylenediamine in a temporary black henna tattoo. *Am J Contact Dermat* 2002; **13:** 15–8.
3. Marcoux D, *et al.* Sensitization to para-phenylenediamine from a streetside temporary tattoo. *Pediatr Dermatol* 2002; **19:** 498–502.

4. Neri I, *et al.* Childhood allergic contact dermatitis from henna tattoo. *Pediatr Dermatol* 2002; **19:** 503–5.
5. Bowling JC, Groves R. An unexpected tattoo. *Lancet* 2002; **359:** 649.
6. Leggiadro RJ, *et al.* Temporary tattoo dermatitis. *J Pediatr* 2003; **142:** 586.
7. Matulich J, Sullivan J. A temporary henna tattoo causing hair and clothing dye allergy. *Contact Dermatitis* 2005; **53:** 33–6.
8. Sosted H, *et al.* Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; **54:** 87–91.
9. Redlick F, DeKoven J. Allergic contact dermatitis to paraphenylendiamine in hair dye after sensitization from black henna tattoos: a report of 6 cases. *CMAJ* 2007; **176:** 445–6.
10. Sonnen G. Type IV hypersensitivity reaction to a temporary tattoo. *Proc (Bayl Univ Med Cent)* 2007; **20:** 36–8.

Heptaminol Hydrochloride *(BANM, rINNM)* ⊗

Heptaminol, Chlorhydrate d'; Heptaminol, chlorhydrate de; Heptaminol hydrochlorid; Heptaminol-hidroklorid; Heptaminolhydroklorid; Heptaminoli hydrochloridum; Heptaminolihydrokloridi; Heptaminolio hidrochloridas; Hidrocloruro de heptaminol; RP-2831. 6-Amino-2-methylheptan-2-ol hydrochloride.

Гептаминола Гидрохлорид

$C_8H_{19}NO,HCl = 181.7.$

CAS — 372-66-7 (heptaminol); 543-15-7 (heptaminol hydrochloride).

ATC — C01DX08.

ATC Vet — QC01DX08.

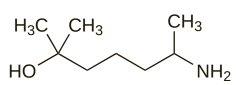

(heptaminol)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Heptaminol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Profile

Heptaminol hydrochloride is a cardiac stimulant and vasodilator and has been given in the treatment of cardiovascular disorders. Heptaminol and heptaminol adenosine phosphate have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Ampecyclal; Hept-A-Myl; ***Indon.:*** Hept-a-myl; ***Ital.:*** Coreptil†.

Multi-ingredient: ***Arg.:*** Flebitol; ***Cz.:*** Ginkor Fort; ***Fr.:*** Debrumyl; Ginkor Fort; ***Ger.:*** Normotin-R†; Perivar†; Veno-Tebonin N†; ***Hong Kong:*** Ginkor Fort; ***Hung.:*** Ginkor Fort; ***Malaysia:*** Ginkor Fort; ***Port.:*** Debrumyl; Forticol; ***Rus.:*** Ginkor Fort (Гинкор Форт); ***Spain:*** Denubil; Largatrex†; ***Thai.:*** Ginkor Fort.

Herniaria

Bruchkraut; Herba Herniariae; Herniary; Rupturewort; Rupturewort.

Profile

Herniaria consists of the dried leaves and flowering tops of various species of rupture-wort, chiefly *Herniaria glabra* and *H. hirsuta* (Caryophyllaceae). It has astringent and diuretic properties and has been given in urinary-tract disorders.

Homoeopathy. Herniaria has been used in homoeopathic medicines under the following names: Herniaria glabra; Hern. gla.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Blasentee St Severin; Uropurat; ***Cz.:*** Urologicka Cajova Smes.

Hexylene Glycol

Hexilenglicol. 2-Methyl-2,4-pentanediol.

$C_6H_{14}O_2 = 118.2.$

CAS — 107-41-5.

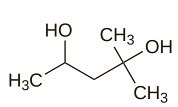

Pharmacopoeias. In *USNF.*

USNF 26 (Hexylene Glycol). A clear, colourless, viscous liquid. Absorbs moisture when exposed to moist air. Miscible with water and with many organic solvents including alcohol, acetone, chloroform, ether, and hexanes. Store in airtight containers.

Profile

Hexylene glycol has properties similar to those of propylene glycol (p.2374). It is used as a pharmaceutical aid.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Bodi Kleen.

Hibiscus

Guinea Sorrel; Hibisci Flos (flowers); Hibisci Sabdariffae Flos (flowers); Hibiscusblüten (flowers); Jamaica Sorrel; Jamaikinių hibiskų žiedai (flowers); Karkadé; Květ ibišku sudánského (flowers); Oseille de Guinée; Red Sorrel; Rosella; Rosellenkukka (flowers) ; Rosellhibiskusblomma (flowers); Rozella (flowers).

Гибискус Сабдарифа; Кислица Ямайская

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Roselle; Hibisci Sabdariffae Flos). The whole or cut dried calyces and epicalyces of *Hibiscus sabdariffa* collected during fruiting.

Profile

Hibiscus is a large genus of flowering plants in the Malvaceae family. The flowers of roselle, *Hibiscus sabdariffa*, are included in herbal preparations for loss of appetite and a range of disorders of the upper respiratory and gastrointestinal tracts.

Culinary uses of *H. sabdariffa* include hibiscus tea, a refreshing caffeine-free beverage made from the flowers.

Homoeopathy. *Hibiscus sabdariffa* has been used in homoeopathic medicines under the following names: Sabdariffa.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Calmophytum; Hydracur.

Histamine

Histamiini; Histamin; Histamina; Histaminum. 2-(Imidazol-4-yl)ethylamine.

$C_5H_9N_3 = 111.1.$

CAS — 51-45-6.

ATC — V04CG03.

ATC Vet — QV04CG03.

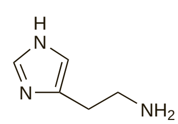

Histamine Hydrochloride

Histamiinidihydrokloridi; Histamina, hidrocloruro de; Histamindihydrochlorid; Histamindihydroklorid; Histamine, dichlorhydrate d'; Histamine Dihydrochloride *(USAN)*; Histamini dihydrochloridum; Histamino dihidrochloridas; Histaminy dichlorowodorek; Hisztamin-dihidroklorid.

$C_5H_9N_3,2HCl = 184.1.$

CAS — 56-92-8.

ATC — L03AX14; V04CG03.

ATC Vet — QL03AX14; QV04CG03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Histamine Dihydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.85 to 3.60. Protect from light.

Histamine Phosphate

Histamiinifosfaatti; Histamin difosfát monohydrát; Histamina, fosfato de; Histamine Acid Phosphate; Histamine Diphosphate; Histamine, phosphate d'; Histaminfosfat; Histamini Diphosphas Monohydricus; Histamini phosphas; Histamino fosfatas; Histaminy fosforan; Hisztamin-foszfát.

$C_5H_9N_3,2H_3PO_4,H_2O = 325.2.$

CAS — 51-74-1 (anhydrous histamine phosphate).

ATC — V04CG03.

ATC Vet — QV04CG03.

Pharmacopoeias. In *Eur.* (see p.vii). *Chin.* and *US* specify the anhydrous substance.

Ph. Eur. 6.2 (Histamine Phosphate). Colourless, long prismatic crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.75 to 3.95. Protect from light.

USP 31 (Histamine Phosphate). Anhydrous histamine phosphate occurs as colourless, odourless, long prismatic crystals. Is stable in air but is affected by light. Soluble 1 in 4 of water. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. A study concluded that solutions of histamine phosphate could be sterilised by heating in an autoclave with little degradation.[1] Autoclaved solutions could be stored for a minimum of 4 months.

1. McDonald C, *et al.* Stability of solutions of histamine acid phosphate after sterilization by heating in an autoclave. *J Clin Pharm Ther* 1990; **15:** 41–4.

Adverse Effects and Treatment

Injection of histamine salts can produce adverse effects including headache, flushing of the skin, general vasodilatation with a fall in blood pressure, tachycardia, bronchial constriction and dyspnoea, visual disturbances, vomiting, diarrhoea, and other gastrointestinal effects. These reactions can be severe; excessive dosage can produce collapse and shock, and may be fatal. Reactions may occur at the injection site.

Some of these effects may be relieved by an antihistamine, but adrenaline may be required and should always be available.

Precautions

Histamine salts should be used with care in patients with asthma or other hypersensitivity disorders, in elderly patients, and in patients with cardiovascular disorders.

Pharmacokinetics

Histamine salts exert a rapid, though transient, effect when given parenterally. Histamine is rapidly metabolised by methylation and oxidation; the metabolites are excreted in the urine.

◊ References.

1. Middleton M, *et al.* Pharmacokinetics of histamine dihydrochloride in healthy volunteers and cancer patients: implications for combined immunotherapy with interleukin-2. *J Clin Pharmacol* 2002; **42:** 774–81.

Uses and Administration

Histamine causes stimulation of smooth muscle, especially of the bronchioles, and lowers blood pressure by dilating the arterioles and capillaries. It also stimulates exocrine gland secretion, especially the gastric glands.

Intradermal injection of histamine produces the characteristic 'triple response' of erythema, flare, and wheal. This is utilised as a control response in skin testing for hypersensitivity. Also, since it is mediated in part by axon reflexes, it has been used to test the integrity of sensory nerves, for example in leprosy.

Inhalation of histamine causes bronchoconstriction and is used as a test of bronchial reactivity.

Histamine has also been given subcutaneously to identify the causes of achlorhydria and intravenously in the diagnosis of phaeochromocytoma, but safer tests are generally preferred.

Histamine is included in some combination topical preparations for musculoskeletal disorders.

Histamine hydrochloride is under investigation as an adjunct in the management of acute myeloid leukaemia and malignant melanoma. It has also been tried as an adjunct to interferons and other drugs in the management of hepatitis C.

Preparations

USP 31: Histamine Phosphate Injection.

Proprietary Preparations (details are given in Part 3)

Mex.: Destamin; ***Port.:*** Soluprick; ***Venez.:*** Histalgan Balsamo†.

Multi-ingredient: ***Arg.:*** Histaglobin; Infrarub†; ***Austria:*** Histaglobin; ***Canad.:*** Midalgan†; ***Cz.:*** Histaglobin†; ***Fr.:*** Algipan; ***Ger.:*** Histadestal; ***India:*** Algipan; Histaglobulin; ***Neth.:*** Cremor capsici comp; Cremor Capsici compositus; Kruidvat Spierbalsem; ***Pol.:*** Histaglobulina; ***Port.:*** Midalgan†; ***S.Afr.:*** Histaglobin; Infrarub; ***Switz.:*** Midalgan; Radalgin.

Histoplasmin

Histoplasmina.

Pharmacopoeias. In *US.*

USP 31 (Histoplasmin). A clear, colourless, sterile solution containing standardised culture filtrates of *Histoplasma capsulatum* grown on liquid synthetic medium. It may contain a suitable antimicrobial. Store at 2° to 8°. The expiry date is not later than 2 years after release from the manufacturer's cold storage.

Profile

Histoplasmin, in an intradermal (intracutaneous) dose of 0.1 mL of a 1 in 100 dilution, may be used as an aid to the diagnosis of histoplasmosis. However, the diagnostic value of the test has been questioned and it may interfere with serological tests for histoplasmosis.

Histoplasmin has also been used, in conjunction with other antigens, to assess cell-mediated immunity.

Preparations

USP 31: Histoplasmin.

Proprietary Preparations (details are given in Part 3)

USA: Histolyn-CYL.

Homocysteine Thiolactone Hydrochloride

3-Aminodihydro-2(3*H*)-thiophenone hydrochloride.

$C_4H_8ClNOS = 153.6$.

CAS — 10593-85-8 (homocysteine thiolactone); 3622-59-1 (homocysteine thiolactone hydrochloride).

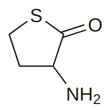

(homocysteine thiolactone)

Profile

Homocysteine thiolactone has been used in preparations for the treatment of liver disorders. Its hydrochloride salt has been used as a mucolytic. Homocysteine thiolactone is a metabolite of homocysteine and has been implicated in the pathogenesis of some cardiovascular diseases (see p.1941).

◊ References.

1. Chwatko G, Jakubowski H. Urinary excretion of homocysteine-thiolactone in humans. *Clin Chem* 2005; **51:** 408–15.
2. Jakubowski H. The molecular basis of homocysteine thiolactone-mediated vascular disease. *Clin Chem Lab Med* 2007; **45:** 1704–16.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Filogaster†.

Horseradish

Armoracia; Meerrettich; Rábano rusticano; Raifort.

Profile

Horseradish, the root of *Cochlearia armoracia* (*Armoracia rusticana*; *Nasturtium armoracia*; *Radicula armoracia*) (Cruciferae), has diuretic and antiseptic properties and stimulates the digestion. It is used in gastrointestinal, respiratory-tract, and urinary-tract disorders, and has also been used externally.

Horseradish is widely used as a food flavouring and condiment.

Homoeopathy. Horseradish has been used in homoeopathic medicines under the following names: Cochlearia armoracia; Coch. ar.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Garlic and Horseradish + C Complex; Garlic, Horseradish, A & C Capsules†; Procold†; ***Braz.:*** Infantoss†; ***Ger.:*** Angocin Anti-Infekt N; ***Malaysia:*** Horseradish Plus†; ***Switz.:*** Kernosan Elixir; Pectosan N†; Sanogencive; ***UK:*** Mixed Vegetable Tablets.

Hyaluronic Acid *(BAN)*

Hialurónico, ácido. (1→3)-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-*O*-β-D-glucopyranosiduronan.

CAS — 9004-61-9.

ATC — D03AX05; M09AX01; S01KA01.

ATC Vet — QD03AX05; QM09AX01; QS01KA01.

NOTE. The term Hyaluronan is used to cover both hyaluronic acid and sodium hyaluronate.

Sodium Hyaluronate *(BANM)*

Hialuronato sódico; Hyaluronate Sodium *(USAN)*; Natrii hyaluronas; Natrio hialuronatas; Nátrium-hialuronát; Natriumhyaluronaatti; Natriumhyaluronat; Natrium-hyaluronát; Sodium, hyaluronate de; Sodyum Hiyalüronat.

CAS — 9067-32-7.

ATC — D03AX05; M09AX01; S01KA01.

ATC Vet — QD03AX05; QM09AX01; QS01KA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sodium Hyaluronate). The sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units. It is extracted from cocks' combs or obtained by fermentation from streptococci (Lancefield Groups A and C). A white or almost white, very hygroscopic powder or a fibrous aggregate. Sparingly soluble to soluble in water; practically insoluble in dehydrated alcohol and in acetone. A 0.5% solution in water has a pH of 5.0 to 8.5. Store in airtight containers. Protect from light and humidity.

Adverse Effects

There have been reports of a transient rise in intra-ocular pressure when sodium hyaluronate was given into the eye. When injected into the knee, pain and inflammation may occur at the injection site. There have also been occasional reports of hypersensitivity, including, rarely, anaphylaxis.

Effects on the eyes. Crystalline deposits on intra-ocular lenses have been reported in patients after use of a high viscosity sodium hyaluronate preparation during cataract surgery.[1]

1. Jensen MK, *et al.* Crystallization on intraocular lens surfaces associated with the use of Healon GV. *Arch Ophthalmol* 1994; **112:** 1037–42.

Effects on the skin. A cutaneous granulomatous reaction has been reported in a woman 5 weeks after treatment with synthetic hyaluronic acid for cosmetic use as a dermal filler.[1] All cutaneous lesions resolved spontaneously within 3 months without scarring.

1. Ghislanzoni M, *et al.* Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br J Dermatol* 2006; **154:** 755–8.

Inflammatory reaction. Severe peritoneal inflammation has been reported[1] after use of a sodium hyaluronate-based bioresorbable membrane to prevent postoperative adhesion formation.

1. Klingler PJ, *et al.*. Seprafilm -induced peritoneal inflammation: a previously unknown complication: report of a case. *Dis Colon Rectum* 1999; **42:** 1639–43.

Uses and Administration

Hyaluronic acid is widely distributed in body tissues and intracellular fluids, including the aqueous and vitreous humour, and synovial fluid; it is a component of the ground substance or tissue cement surrounding cells.

A viscous solution of sodium hyaluronate is used during surgical procedures on the eye, for example for cataract extraction. Introduction of the solution into the anterior or posterior chamber via a fine cannula or needle allows tissues to be separated during surgery and protects them from trauma. Sodium hyaluronate eye drops 0.1% are also used for the relief of dry eye and as a contact lens lubricant.

Sodium hyaluronate is given by intra-articular injection in the treatment of osteoarthritis of the knee. Doses vary according to the preparation used, but are of the order of 20 to 25 mg once weekly for 5 weeks or up to 30 mg once weekly for 3 or 4 weeks; it is generally recommended that the treatment course for any individual joint should not be repeated within 6 months. Sodium hyaluronate is also used during arthroscopic procedures to flush out irrigating solutions and act as a temporary substitute for synovial fluid.

Hyaluronic acid is applied topically to promote wound healing. Zinc hyaluronate has also been used. A film containing sodium hyaluronate and carmellose is used to prevent surgical adhesion. Sodium hyaluronate has also been used in the management of lesions of the oral mucosa.

Hylans, which are polymers derived from hyaluronic acid, are used similarly for osteoarthritis and wound care.

Sodium hyaluronate instilled intravesically has been used as a temporary replacement of the glycosaminoglycan layer in the bladder for the symptomatic treatment of interstitial cystitis.

Topical formulations of diclofenac in hyaluronic acid (CT-1101, AT-2101) are used in the treatment of actinic keratoses (but distinguish from an oral formulation of isofagomine tartrate (p.2327) under investigation for use in Gaucher disease that also carries the code AT-2101).

Hyaluronic acid has been used as a dermal filler for the correction of moderate to severe facial wrinkles and folds (see Photoageing, p.1581).

◊ Reviews.

1. Goa KL, Benfield P. Hyaluronic acid: a review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994; **47:** 536–66.
2. Adams ME, *et al.* A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Safety* 2000; **23:** 115–30.

Actinic keratoses. For references to the use of diclofenac in a hyaluronic acid gel in the treatment of actinic keratoses, see p.46.

Dry eye. The usual management of dry eye (p.2140) is with artificial tears. Sodium hyaluronate has also been reported to be of some benefit. Alleviation of symptoms[1-3] and an increase in tear film stability[1,2] has been shown after topical application of sodium hyaluronate solution (0.1 or 0.2%) compared with saline-based placebo solutions. However, another study[4] failed to show any advantage over placebo, although it has been suggested[4,5] that sodium hyaluronate might play a role in maintaining a healthy corneal epithelium.

1. Mengher LS, *et al.* Effect of sodium hyaluronate (0.1%) on break-up time (NIBUT) in patients with dry eyes. *Br J Ophthalmol* 1986; **70:** 442–7.
2. Sand BB, *et al.* Sodium hyaluronate in the treatment of keratoconjunctivitis sicca: a double masked clinical trial. *Acta Ophthalmol (Copenh)* 1989; **67:** 181–3.
3. Condon PI, *et al.* Double blind, randomised, placebo controlled, crossover, multicentre study to determine the efficacy of a 0.1% (w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. *Br J Ophthalmol* 1999; **83:** 1121–4.
4. Shimmura S, *et al.* Sodium hyaluronate eyedrops in the treatment of dry eyes. *Br J Ophthalmol* 1995; **79:** 1007–11.
5. Aragona P, *et al.* Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br J Ophthalmol* 2002; **86:** 181–4.

Osteoarthritis. In osteoarthritis, the size and concentration of hyaluronic acid molecules naturally present in synovial fluid is reduced. Thus, one approach in the management of osteoarthritis (p.11) of the knee is viscosupplementation of the synovial fluid by the intra-articular injection of hyaluronic acid or its derivatives. Such injections may reduce pain over 1 to 6 months but may be associated with a short-term increase in knee inflammation; there is some suggestion that any benefit is longer lasting than with intra-articular corticosteroids. Some studies suggest that viscosupplementation may be an effective option for patients who are unable to take oral NSAIDs or have regular intra-articular corticosteroids, and who are unsuitable candidates for joint replacement surgery, although there appears to be considerable variability in clinical response between products, as well as in the variables being assessed and length of treatment.

References.

1. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. *J Rheumatol* 1998; **25:** 2203–12. Correction. *ibid.* 1999; **26:** 1216.
2. Anonymous. Hyaluronan or hylans for knee osteoarthritis? *Drug Ther Bull* 1999; **37:** 71–2.
3. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; **38:** 602–7.
4. Wobig M, *et al.* The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther* 1999; **21:** 1549–62.
5. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med* 2002; **162:** 245–7.
6. Lo GH, *et al.* Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; **290:** 3115–21.
7. Bellamy N, *et al.* Viscosupplementation for the treatment of osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/05/06).

Wound healing. Hyaluronic acid has been used to aid wound healing,[1,2] the overall management of which is discussed on p.1585.

1. Soldati D, *et al.* Mucosal wound healing after nasal surgery: a controlled clinical trial on the efficacy of hyaluronic acid containing cream. *Drugs Exp Clin Res* 1999; **25:** 253–61.
2. Harris PA, *et al.* Use of hyaluronic acid and cultured autologous keratinocytes and fibroblasts in extensive burns. *Lancet* 1999; **353:** 35–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aquify; Artflex; Dropstar; Gengigel; Hialudorf; Hyalart†; Hyasol; Iuronicoderm; Lacripharma†; Maxiostenil; Miniostenil; Provisc; Synvisc; ***Austral.:*** AMO Vitrax; Fermathron†; Healon; Ophthalin; Provisc; Synvisc; Vismed†; ***Austria:*** Artzal; Connettivina; Etamucin; Hyalgan; ***Belg.:*** Gengigel; Healon†; Hyalgan; ***Braz.:*** Healon; Hyaludermin; Polireumin; Suprahyal; Synvisc; ***Canad.:*** Biolon†; Cystistat; Eyestil†; Healon†; Hyalgan; Hyalofill†; NeoVisc; Orthovisc; Suplasyn; Synvisc; ***Chile:*** Biolon; Eucerin Emulsion; Healon; Hyalgan; Lagricel Ofteno; Suprahyal; Synvisc; Toptear; ***Cz.:*** Curasan†; Healon†; Hyalgan; ***Denm.:*** Artz; Hyalgan; ***Fin.:*** Artzal; Healon†; Hyalgan; ***Fr.:*** Adant; Arthrum H; Effidia; Hyabak; Hyal-Drop; Hyalgan; Hyalofemme; Hyalofill; Hyalugel; Hylo-COMOD; Hyluprotect; Ialuset; Ostenil; Provisc; Sinovial; Suplasyn; Synvisc; Vismed†; ***Ger.:*** Arthrease†; Biolan; Biolon; Dispasan; Endogel; Fermathron; Gelbag; Go-On; Healon†; Hy-GAG; Hya-ject; Hya-Ophtal†; Hyal-System†; Hyalart; Hyalubrix; Hylaform†; Hylan; Hylo-COMOD; Hylo-Vision; Hysan; Laservis; Orthovisc; Ostenil; Oxyal; Provisc; Suplasyn; Synvisc; TwinVisc; Viscoseal; Visiol; Vislube; Vismed; VisThesia; Xidan EDO; ***Gr.:*** Hyalart; ***Hong Kong:*** Connettivina; Go-On; Healon; Hialid; Hyalgan; Hyruan; Provisc†; Vismed; ***Hung.:*** Curiosin; Healon†; Hyalgan; Ial†; Ophthalin†; Provisc†; ***India:*** Halonix; Lghyal; Synvisc; Visial; ***Indon.:*** Adant; Durolane; Hialid; Hyalgan; Osflex; Suplasyn; ***Irl.:*** Hyalgan; Ophthalin†; Provisc†; Suplasyn; ***Israel:*** Adant; Arthrease; Biolon; Curavisc; Eyecon; Healon; Hylo-COMOD; Hysan; Ophthalin; Orthovisc; Suplasyn; Synvisc†; ***Ital.:*** Artz; Connettivina; Dropstar; Durolane; Go-On; Hy-Drop; Hyabak; Hyalart; Hyalgan; Hyalistil; Hylo-COMOD; Hyluprotect; Ial; Ialect†; Ialum; Ialurex; Irilens; Ocustil†; Ophtalin; Oxyal; Provisc; Synocrom; Synvisc; Vismed; ***Jpn:*** Hyalein; Suvenyl; ***Malaysia:*** Curiosin; Gengigel; Go-On; Healon†; Hyal; Hyalgan; Hyruan; Laservis†; Provisc; Sinovial; Synvisc; Viscoseal; Visiol; Vislube; Vismed; ***Mex.:*** Biolon; Hyasol; Lagricel; Suprahyal; Synvisc; Zonaker; ***Mon.:*** Oxyal; ***NZ:*** AMO Vitrax†; Healon; Hylaform; Ophthalin; Provisc; Synvisc; ***Philipp.:*** Hialid; Provisc; ***Pol.:*** Hyalgan; Synvisc; ***Port.:*** Artz; Gengigel†; Hyalart; Hyalofill†; Hylo-COMOD†; ***Rus.:*** Curiosin (Куриозин); Healon (Хеалон)†; Hylo-COMOD (Хило-КОМОД); ***S.Afr.:*** AMO Vitrax; Biolon; Biolone; Healon; Provisc; ***Singapore:*** AMO Vitrax†; Healon†; Hialid; Hyalgan; Hylaform; Provisc; Restylane†; Suplasyn; Synvisc; ***Spain:*** Hyalart; Hyalgan; ***Swed.:*** Artzal; Hyalgan; Synvisc; ***Switz.:*** Fermavisc; Healon†; Hyal-Drop; HycoSan5; Hylo-COMOD; Hysan; Ial; Ialugen; Laservis; Ostenil; Rhinogen; Sinovial; Suplasyn; Synvisc; Viscoseal; Visiol; Vislube; Vismed; ***Thai.:*** Adant; Connettivina†; Healon†; Hialid; Hyalgan; Hyruan; Ial; Ophthalin; Provisc; Synvisc; ***Turk.:*** Adant; Amvisc; Biolon; Healon; Hyalgan; Ial; Ophtalin Plus; Ostenil; Provisc; Synvisc; ***UK:*** Arthrease; Cystistat; Euflexxa; Fermathron; Gengigel; Healonid†; Hyabak; Hyalgan; Hyalofill; Hycosan; Ophthalin; Optrex Contact Lens Friendly Eye Drops; Orthovisc; Ostenil; Supartz†; Suplasyn; Synocrom; Synvisc; Viscoseal; ***USA:*** AMO Vitrax; Amvisc; Bionect; Coease; Euflexxa; Healon; Hyalgan; Hylaform; Hylira; Juvederm; Orthovisc; Perlane; Restylane; Shellgel; Supartz; Synvisc; ***Venez.:*** Healon†; Hyalgan; Lagricel Ofteno; Provisc†; Suprahyal; Synvisc; Toptear.

Multi-ingredient: ***Arg.:*** Blink Contacts; Cellskinlab Hydragel B5; Cremisona†; Culuflex H; Epiteliale AH; Estri-Atlas; Hyalcrom; Hyalcrom NF; Hyanac†; Hydratone†; Ingebrax; Iuronico Biotic; Lacrimax; Maxilac; Maxus; Muvar; Panoxi; Timed 0.5; Viscoat; Vita-C Derms's; Yusin Tears II; ***Austral.:*** Blink Contacts; Duovisc; Viscoat; ***Belg.:*** Physiologica; ***Chile:*** Hydrating B5 Gel; Ureadin Rx RD; ***Cz.:*** Curiosin†; Ialugen Plus; ***Fr.:*** Cicaplast; Cicatridine; Hyalogran; Hyarhinol; Ialuset Plus; Mucogyne; Saugella; Tonimer; Viscoat; ***Ger.:*** Duovisc; Hylo-Care; Viscoat; ***Hong Kong:*** Duovisc†; Viscoat†; ***Hung.:*** Ialugen Plus; Viscoat†; ***Israel:*** Aphtagone; Aptha-X; Gelclair†; ***Ital.:*** Altergen; Connettivina Plus; Dropyal; Idroskin C; Migel; Osmogel; Sirmiogel†; Trofo 5; Viscoat; ***Malaysia:*** Duovisc; Viscoat; ***Mex.:*** Cetopic; Emolin Neo; Grimal; Hyalcrom NF; Hyalox; ***Mon.:*** Monasens; ***NZ:*** Viscoat; ***Philipp.:*** Viscoat; ***Port.:*** Synchrorose; Synchrovit; ***Rus.:*** Hylozar-COMOD

(Хилозар-КОМОД); ***S.Afr.:*** Duovisc; Viscoat; ***Singapore:*** Duovisc; Viscoat; ***Switz.:*** Alphastria; Ialugen Plus; Lacrycon; ***Thai.:*** Duovisc; Viscoat; ***Turk.:*** Duovisc; Viscoat; ***UK:*** Atopiclair; Gelclair; Seprafilm; Xclair; Zuidex; ***USA:*** Atopiclair; Deflux; DisCoVisc; Gelclair; Healon Yellow; RadiaPlex Rx; Seprafilm; Viscoat; Zacare Kit; ***Venez.:*** Cepin; Epitheliale AH; Viscoat†.

Hyaluronidase *(BAN, rINN)*

Hialuronidasa; Hialuronidáz; Hialuronidazė; Hiyalüronidaz; Hyaluronidaasi; Hyaluronidas; Hyaluronidasa; Hyaluronidasum.

Гиалуронидаза

CAS — 9001-54-1.
ATC — B06AA03.
ATC Vet — QB06AA03.

NOTE. The name kinetin (p.1603) has also been used as a proprietary name for hyaluronidase.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). *US* includes as an injectable form.

Ph. Eur. 6.2 (Hyaluronidase). An enzyme capable of hydrolysing mucopolysaccharides of the hyaluronic acid type. It is prepared from the testes of mammals by a method that has been shown to reduce contamination by known infectious agents to acceptable limits; a suitable stabilising agent may be added to the purified preparation. A white or yellowish-white, amorphous powder; it contains not less than 300 international units of hyaluronidase activity per mg, calculated with reference to the dried substance. Soluble in water; practically insoluble in alcohol and in acetone. A 0.3% solution in water has a pH of 4.5 to 7.5. Store at 2° to 8° in airtight containers.

Units

The international and USP units are equivalent. One international or USP unit is equivalent to one turbidity-reducing unit or about 3.3 viscosity-reducing units.

Adverse Effects and Precautions

Sensitivity to hyaluronidase occasionally occurs. Because of the danger of spreading infection, the enzyme generally should not be injected into or around an infected area. It has been suggested that the presence of malignancy may similarly be a contra-indication to the use of hyaluronidase. It should not be given by intravenous injection nor should it be used for anaesthetic procedures in cases of unexplained premature labour. Hyaluronidase should not be applied directly to the cornea. It should not be used to reduce the swelling of bites or stings.

Uses and Administration

Hyaluronidase is an enzyme that reversibly depolymerises hyaluronic acid (above), a component of the ground substance or tissue cement surrounding cells, thereby temporarily reducing its viscosity and rendering the tissues more readily permeable to injected fluids.

Hyaluronidase is used to increase the speed of absorption and reduce discomfort due to subcutaneous or intramuscular injection of fluids, to promote resorption of excess fluids and extravasated blood in the tissues, and to increase the effectiveness of local anaesthesia.

In the UK, the usual dose as an adjunct to subcutaneous or intramuscular injection is 1500 units, added directly to the injection. To aid the dispersal of extravasated fluids or blood, the same dose is given in 1 mL of Water for Injections or 0.9% sodium chloride into the affected area. Lower doses of hyaluronidase are used in some countries; in the USA, the usual dose is 150 units.

In hypodermoclysis, hyaluronidase is used to aid the subcutaneous administration of relatively large volumes of fluids, especially in infants and young children, where intravenous injection is difficult. Care should be taken in the treatment of children and the elderly to control the speed and total volume given and to avoid overhydration. Hyaluronidase may be added to the injection fluid or may be injected into the site before the fluid is given. In the UK, 1500 units of hyaluronidase is generally given with each 500 to 1000 mL of fluid for subcutaneous use, but in the USA, 150 units of hyaluronidase is considered adequate for each litre of hypodermoclysis solution.

The diffusion of local anaesthetics is accelerated by the addition of 1500 units (in the USA, 150 units) of hyaluronidase to the anaesthetic solution. It has also been used in ophthalmology as an aid to local anaesthesia at recommended doses of 15 units/mL of local anaesthetic solution. Hyaluronidase has also been used for the treatment of vitreous haemorrhage and diabetic retinopathy.

To improve the resorption of radiopaque agents in subcutaneous urography, hyaluronidase is injected subcutaneously in a dose of 75 units over each scapula followed by injection of the contrast medium at the same site.

Recombinant human hyaluronidase is used for the preparation of oocytes during IVF.

Hyalosidase (GL enzyme) is a highly purified form of hyaluronidase that has been studied.

◊ General references.

1. Watson D. Hyaluronidase. *Br J Anaesth* 1993; **71:** 422–5.

Ophthalmic surgery. In a study[1] involving 150 consecutive patients undergoing surgery for senile cataract, retrobulbar anaesthesia with lidocaine 2% solution plus adrenaline 1:100 000 and hyaluronidase 15 units/mL produced successful anaesthesia in 69 of 75 cases (92%), which was significantly better than 42 of 75 treated with lidocaine plus adrenaline alone. Although poor results have been reported from hyaluronidase and a local anaesthetic without adrenaline to restrict local anaesthetic absorption, the use of the enzyme and adrenaline was recommended as an aid to achieving complete ocular akinesia and anaesthesia in cataract surgery. Hyaluronidase has also been used with a mixture of bupivacaine and lidocaine for peribulbar anaesthesia, but results have been conflicting. In a study[2] in 50 patients, addition of hyaluronidase 25 units/mL of local anaesthetic mixture had no significant effect on time to satisfactory anaesthesia. However, in a second study[3] involving 200 patients, addition of hyaluronidase 50 or 300 units/mL improved the quality of the peribulbar block and, in the case of the higher concentration, also increased the speed of onset.

1. Thomson I. Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract. *Br J Ophthalmol* 1988; **72:** 700–2.
2. Prosser DP, *et al.* Re-evaluation of hyaluronidase in peribulbar anaesthesia. *Br J Ophthalmol* 1996; **80:** 827–30.
3. Dempsey GA, *et al.* Hyaluronidase and peribulbar block. *Br J Anaesth* 1997; **78:** 671–4.

Preparations

BP 2008: Hyaluronidase Injection;
USP 31: Hyaluronidase for Injection; Hyaluronidase Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Unidasa; ***Austral.:*** Hyalase; ***Braz.:*** Hyalozima; ***Chile:*** Wydase†; ***Cz.:*** Hyasa†; Hylase; ***Ger.:*** Hylase; ***Gr.:*** Hyalase; ***Hung.:*** Hyase†; ***India:*** Hynidase; ***Israel:*** Hyalase; ***Ital.:*** Jaluran†; ***Neth.:*** Hyason; ***NZ:*** Hyalase; ***S.Afr.:*** Hyalase; ***Turk.:*** Orthovisc; ***UK:*** Hyalase; ***USA:*** Amphadase; Hydase; Hylenex; Vitrase; Wydase†.

Multi-ingredient: ***Arg.:*** Nilflux; ***Austria:*** Lemuval; ***Braz.:*** Oto Xilodase; Postec; Xilodase; ***Ital.:*** Lido-Hyal; ***Pol.:*** Helason; ***Spain:*** Lasonil†; Oto Difusor†; ***Switz.:*** Lido-Hyal.

Hydrangea

Hidrangea; Seven Barks; Smooth Hydrangea; Wild Hydrangea.

Profile

Hydrangea, the root of *Hydrangea arborescens* (Hydrangeaceae), has diuretic and litholytic properties and is used for genitourinary disorders including renal and urinary calculi.

Homoeopathy. Hydrangea has been used in homoeopathic medicines under the following names: Hydrangea arborescens; Hydrang.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Antiglan; Backache.

Hydrastine Hydrochloride

Hidrastina, hidrocloruro de; Hydrastyny chlorowodorek. 6,7-Dimethoxy-3-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one hydrochloride.

$C_{21}H_{21}NO_6,HCl = 419.9.$

CAS — 118-08-1 (hydrastine); 5936-28-7 (hydrastine hydrochloride).

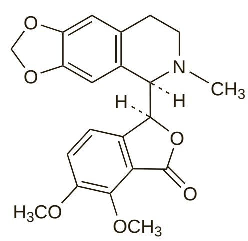

(hydrastine)

Profile

Hydrastine hydrochloride, the hydrochloride of an alkaloid obtained from *Hydrastis canadensis* (Ranunculaceae) (see Hydrastis, below), has been reputed to cause uterine contractions and arrest uterine haemorrhage but it is of doubtful value. It was also formerly used in gastrointestinal disorders. Toxic doses are reported to cause strychnine-like convulsions and relaxation of the gut.

Hydrastinine Hydrochloride

Idrastinina Cloruro. 5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-ol hydrochloride.

$C_{11}H_{11}NO_2,HCl = 225.7.$

CAS — 6592-85-4 (hydrastinine); 4884-68-8 (hydrastinine hydrochloride).

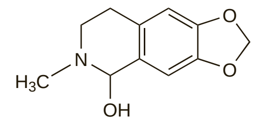

(hydrastinine)

Profile

Hydrastinine is a derivative of the alkaloid hydrastine (p.2321) and has been used similarly. It has vasoconstrictor properties and has been used as the hydrochloride as an ingredient of topical preparations for minor eye disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Dacrin; Haemanal.

Hydrastis

Golden Seal; Goldenseal; Hidraste; Hidrastis; Hydrast.; Hydrastidis Radix; Hydrastis rhizoma; Hydrastisjuuri; Hydrastisrot; Idraste; Kanadinių auksašaknių šakniastiebiai; Vodilkový kořen; Yellow Root.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Goldenseal Rhizome; Goldenseal Root BP 2008). The whole or cut, dried rhizome and root of *Hydrastis canadensis* containing not less than 2.5% of hydrastine and not less than 3.0% of berberine, calculated on the dried basis. Protect from light.

USP 31 (Goldenseal). The dried roots and rhizomes of *Hydrastis canadensis* (Ranunculaceae), containing not less than 2.0% of hydrastine and not less than 2.5% of berberine, calculated on the dried basis. Store in airtight containers. Protect from light, moisture, and heat.

Profile

Hydrastis was formerly used to arrest excessive uterine haemorrhage. It is included in some herbal preparations for gastrointestinal disorders and peripheral vascular disorders. The pharmacological activity of hydrastis is attributed primarily to 2 of its constituent alkaloids, berberine (p.2264) and hydrastine (above).

Homoeopathy. Hydrastis has been used in homoeopathic medicines under the following names: Hydrastis canadensis; Hydr. can.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Gingivitol N.

Multi-ingredient: ***Austral.:*** Bilberry Plus; Euphrasia Complex; Herbal Cleanse†; Hydrastis Complex†; Sambucus Complex†; Urapro†; Urinase†; ***Braz.:*** Bromidrastina†; ***Canad.:*** Echinacea Goldenseal Formula†; ***Fr.:*** Climaxol; ***Spain:*** Proctosor†; Solucion Schoum; ***Turk.:*** Ma-Ka-Ta; ***UK:*** Digestive; HRI Golden Seal Digestive; Wind & Dyspepsia Relief.

Hydrazine Sulfate

Hidrazina, sulfato de; Hydrazine Sulphate; Hydrazyny siarczan.

$H_6N_2O_4S = 130.1.$

CAS — 302-01-2 (hydrazine); 10034-93-2 (hydrazine sulfate).

$H_2N{-}NH_2$

(hydrazine)

Profile

Hydrazine sulfate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinic chloride for corneal tattooing. It has been tried, but with little if any benefit, in the management of cancer-related anorexia and cachexia.

Adverse effects and treatment. References to adverse effects resulting from exposure to hydrazine.[1-5] Pyridoxine has been used in the management of hydrazine intoxication.[6-8]

1. Albert DM, Puliafito CA. Choroidal melanoma: possible exposure to industrial toxins. *N Engl J Med* 1977; **296:** 634–5.
2. Durant PJ, Harris RA. Hydrazine and lupus. *N Engl J Med* 1980; **303:** 584–5.
3. WHO. Hydrazine. *Environmental Health Criteria 68.* Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc68.htm (accessed 24/07/08)
4. WHO. Hydrazine health and safety guide. *IPCS Health and Safety Guide 56.* Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg056.htm (accessed 24/07/08)
5. Hainer MI, *et al.* Fatal hepatorenal failure associated with hydrazine sulfate. *Ann Intern Med* 2000; **133:** 877–80.
6. Kirklin JK, *et al.* Treatment of hydrazine-induced coma with pyridoxine. *N Engl J Med* 1976; **294:** 938–9.

7. Harati Y, Niakan E. Hydrazine toxicity, pyridoxine therapy, and peripheral neuropathy. *Ann Intern Med* 1986; **104:** 728–9.
8. Nagappan R, Riddell T. Pyridoxine therapy in a patient with severe hydrazine sulfate toxicity. *Crit Care Med* 2000; **28:** 2116–18.

Anorexia and cachexia. References[1-3] to the use of hydrazine sulfate in patients with anorexia or cachexia associated with cancer.

1. Tayek JA, *et al*. Effect of hydrazine sulphate on whole-body protein breakdown measured by C-lysine metabolism in lung cancer patients. *Lancet* 1987; **ii:** 241–4.
2. Loprinzi CL, *et al*. Cancer-associated anorexia and cachexia: implications for drug therapy. *Drugs* 1992; **43:** 499–506.
3. Kaegi E. Unconventional therapies for cancer: hydrazine sulfate. *Can Med Assoc J* 1998; **158:** 1327–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Sehydrin (Сегидрин).

Hydrochloric Acid

Acide chlorhydrique; Acidum Hydrochloricum; Acidum hydrochloridum; Clorhídrico, ácido; E507; Kloorivetyhappo; Kwas solny; Kyselina chlorovodíková; Saltsyra; Salzsäure; Sósav; Suolahappo; Vandenilio chlorido rūgštis; Vetykloridihappo.

HCl = 36.46.
CAS — 7647-01-0.
ATC — A09AB03; B05XA13.
ATC Vet — QA09AB03; QB05XA13.

NOTE. The impure acid of commerce is known as Spirits of Salt and as Muriatic Acid.

Pharmacopoeias. *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *Swiss*, and *Viet.* include various concentrations. Also in *USNF.*

Ph. Eur. 6.2 (Hydrochloric Acid, Concentrated; Acidum Hydrochloridum Concentratum; Hydrochloric Acid BP 2008). It contains 35.0 to 39.0% w/w of HCl. A clear, colourless, fuming liquid. Miscible with water. Store below 30° in stoppered containers of glass or other inert material.

Ph. Eur. 6.2 (Hydrochloric Acid, Dilute; Acidum Hydrochloridum Dilutum). It contains 9.5 to 10.5% w/w of HCl prepared by mixing hydrochloric acid 274 g with water 726 g.

USNF 26 (Hydrochloric Acid). It contains 36.5 to 38.0% w/w of HCl. A colourless, fuming liquid having a pungent odour. It ceases to fume when it is diluted with 2 volumes of water. Store in airtight containers.

USNF 26 (Diluted Hydrochloric Acid). It contains 9.5 to 10.5% w/v of HCl and may be prepared by mixing hydrochloric acid 226 mL with sufficient water to make 1000 mL. A colourless, odourless liquid. Store in airtight containers.

Adverse Effects

Hydrochloric acid is highly irritant and corrosive and ingestion has proved fatal. The corrosive effect causes chemical burns and severe pain. There may be violent vomiting, haematemesis, and circulatory collapse; acids can also produce intravascular coagulation and haemolysis. Ulceration may lead to perforation and patients can suffer strictures and pyloric stenosis. Asphyxiation may result from laryngeal oedema. Inhalation of acid fumes or aspiration of ingested acids may cause pneumonitis.

◊ References.

1. WHO. Chlorine and hydrogen chloride. *Environmental Health Criteria 21*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc21.htm (accessed 16/06/04)
2. Munoz Munoz E, *et al*. Massive necrosis of the gastrointestinal tract after ingestion of hydrochloric acid. *Eur J Surg* 2001; **167:** 195–8.

Treatment of Adverse Effects

Treatment of ingestion is mainly symptomatic. Gastric lavage and activated charcoal are not generally appropriate and emetics must *not* be used. Small amounts of water or milk may be given to dilute the acid but larger volumes may increase the risk of emesis and hence of further damage. Neutralising agents are not recommended because of the possibility of heat being produced during exothermic reactions, which may increase the injury further. Opioid analgesia may be required for pain. Endoscopy should be performed and surgical intervention may be necessary. There is little evidence to support the value of corticosteroids in preventing stricture formation.

Acid burns of the skin should be flooded immediately with water and the washing should be copious and prolonged. Any affected clothing should be removed while flooding is being carried out. For burns in the eye, the lids should be kept open and the eye flushed with a steady stream of water at room temperature or sodium chloride 0.9%. A few drops of a local anaesthetic solution will relieve lid spasm and facilitate irrigation.

Uses and Administration

Hydrochloric acid has been used as an escharotic. It has been used in the diluted form for the treatment of achlorhydria and other gastrointestinal disorders. It has also been given intravenously in the management of metabolic alkalosis (p.1667). An acid perfusion test using hydrochloric acid has been used in the diagnosis of oesophageal disorders. When taken orally, it should be sipped through a straw to protect the teeth.

Homoeopathy. Hydrochloric acid has been used in homoeopathic medicines under the following names: Acidum hydrochloricum; Muriaticum acidum; Hydrochloridum acidum; Chlorhydricum acidum; Acidum muriaticum; Ac. mur.

Diagnosis and testing. References and comments on the use of an acid perfusion test in the diagnosis of oesophageal disorders,[1-5] such as gastro-oesophageal reflux disease (p.1696) and oesophageal motility disorders (p.1702). The test involves intra-oesophageal perfusion of 0.1M hydrochloric acid; subsequent development of pain indicates an acid-sensitive oesophagus. This test has also been used in the differential diagnosis of angina.[2]

1. Sladen GE, *et al*. Oesophagoscopy, biopsy, and acid perfusion test in diagnosis of "reflux oesophagitis". *BMJ* 1975; **1:** 71–6.
2. Anonymous. Angina and oesophageal disease. *Lancet* 1986; **i:** 191–2.
3. Hewson EG, *et al.* Acid perfusion test: does it have a role in the assessment of non cardiac chest pain? *Gut* 1989; **30:** 305–10.
4. de Caestecker JS, Heading RC. Acid perfusion in the assessment of non-cardiac chest pain. *Gut* 1989; **30:** 1795–7.
5. Howard PJ, *et al.* Acid perfusion is a good screening test for symptomatic oesophageal reflux. *Gut* 1989; **30:** A1445.

Pregnancy. Heartburn during pregnancy may be due to reflux of alkaline duodenal contents. A dilute solution of hydrochloric acid (pH 2) taken after meals and at bedtime produced improvements in heartburn in pregnant women.[1]

1. Anonymous. Heartburn in pregnancy. *Drug Ther Bull* 1990; **28:** 11–12.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Mixtura Pepsini.
Multi-ingredient: *Ital.:* Gastro-Pepsin; ***S.Afr.:*** Sentinel Ulcer Mixture.

Hydrofluoric Acid

Fluohydric Acid; Fluorhídrico, ácido; Fluoric Acid; Kwas fluorowodorowy.

HF = 20.01.
CAS — 7664-39-3.

Description. Hydrofluoric acid is a solution of hydrogen fluoride in water. Various strengths are used. It attacks glass strongly.

Adverse Effects

As for Hydrochloric Acid, above. Although the corrosive effects of hydrofluoric acid tend to predominate, absorption may produce systemic fluoride poisoning as described under Sodium Fluoride, p.1962.

The pain from contact with weak solutions may be delayed, so that the patient is not aware of being burnt until some hours later, when the area begins to smart; intense pain then sets in and this may persist for several days. Destruction of tissue proceeds under the toughened coagulated skin, so that the ulcers extend deeply, heal slowly, and leave a scar.

The fumes of hydrofluoric acid are highly irritant.

Treatment of Adverse Effects

The initial treatment of poisoning after oral exposure to hydrofluoric acid is similar to that described for hydrochloric acid, see above. Calcium gluconate should also be given intravenously to correct known or suspected hypocalcaemia. Burns in the eye are also managed as for hydrochloric acid, although irrigation of the eye may be continued with calcium gluconate solution 2% after initial flood with water or sodium chloride 0.9%.

In the event of skin burns with hydrofluoric acid, contaminated clothing or articles should be removed and the skin washed with copious cold water. A calcium gluconate gel is sometimes used and it may be necessary to infiltrate the affected areas with calcium gluconate intradermally or subcutaneously. Regional intravenous infusion of calcium gluconate may be necessary in severe burns of the forearm, hand, or fingers; if ineffective, intra-arterial infusion for burns of the fingers may be considered. Hydrofluoric acid passes through finger- and toe-nails without causing any apparent damage; nails will therefore have to be removed or perforated to be able to treat the underlying tissues. Other first-aid measures reported to be effective include prolonged soaks in iced solutions of benzalkonium chloride; iced water has sometimes been used as has iced magnesium sulfate solution. Local anaesthesia may be needed. Burn eschars should be excised and necrotic tissue debrided. Absorption may lead to systemic fluoride toxicity and the need for intravenous calcium gluconate to manage hypocalcaemic symptoms.

◊ References to the treatment of hydrofluoric acid burns.

1. Browne TD. The treatment of hydrofluoric acid burns. *J Soc Occup Med* 1974; **24:** 80–9.
2. MacKinnon MA. Hydrofluoric acid burns. *Dermatol Clin* 1988; **6:** 67–74.
3. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5**; 79–85.
4. Kirkpatrick JJR, *et al.* Hydrofluoric acid burns: a review. *Burns* 1995; **21:** 483–93.
5. Sanz-Gallen P, *et al.* Hypocalcaemia and hypomagnesaemia due to hydrofluoric acid. *Occup Med (Lond)* 2001; **51:** 294–5.
6. Martin HCO, Muller MJ. Hydrofluoric acid burns from a household rust remover. *Med J Aust* 2002; **176:** 296.
7. Foster KN, *et al.* Hydrofluoric acid burn resulting from ignition of gas from a compressed air duster. *J Burn Care Rehabil* 2003; **24:** 234–8.

Uses

Hydrofluoric acid is used in industry. Its main use has been for the production of fluorocarbons for use as refrigerants and propellants. It has also been used as an ingredient of preparations for glass etching and rust removal.

Homoeopathy. Hydrofluoric acid has been used in homoeopathic medicines under the following names: Fluoricum acidum; Acidum hydrofluoricum; Ac. fluor.

Hydroquinine Hydrobromide

Dihydrochinin Hydrobromide; Dihydroquinine Hydrobromide; Hidroquinina, hidrobromuro de; Hydrochinin Hydrobromide; Methylhydrocupreine Hydrobromide. 8α,9*R*-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrobromide.

$C_{20}H_{26}N_2O_2,HBr$ = 407.3.
CAS — 522-66-7 (hydroquinine).
ATC — M09AA01.
ATC Vet — QM09AA01.

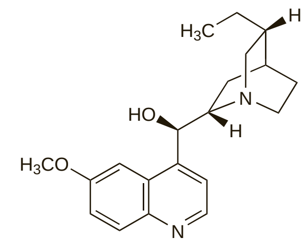

(hydroquinine)

NOTE. Do not confuse with Hydroquinone (p.1598).

Profile

Hydroquinine is a derivative of quinine (p.612) used similarly in the treatment of nocturnal muscle cramps. It is given as the hydrobromide in an oral dose of 200 mg with the evening meal and a further 100 mg at bedtime for 14 days.

Muscle spasm. Quinine and its derivatives such as hydroquinine have traditionally been used for the prevention of nocturnal cramps (p.1887) but there has been concern over their efficacy and potential for adverse effects, especially in the elderly.

References.

1. Jansen PHP, *et al.* Randomised controlled trial of hydroquinine in muscle cramps. *Lancet* 1997; **349:** 528–32.
2. van Kan HJM, *et al.* Hydroquinine pharmacokinetics after oral administration in adult patients with muscle cramps. *Eur J Clin Pharmacol* 2000; **56:** 263–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Neth.: Inhibin.

Hydroxyamfetamine Hydrobromide

(BANM, rINNM) ⊗

Bromhidrato de Hidroxianfetamina; Hidrobromuro de hidroxianfetamina; Hydroxyamfétamine, Bromhydrate d'; Hydroxyamfetamini Hydrobromidum; Hydroxyamphetamine Hydrobromide; *p*-Hydroxyamphetamine Hydrobromide; Oxamphetamine Hydrobromide. (±)-4-(2-Aminopropyl)phenol hydrobromide.

Гидроксиамфетамина Гидробромид

$C_9H_{13}NO,HBr$ = 232.1.
CAS — 103-86-6 (hydroxyamfetamine); 1518-86-1 ((±)-hydroxyamfetamine); 306-21-8 (hydroxyamfetamine hydrobromide); 140-36-3 ((±)-hydroxyamfetamine hydrobromide).

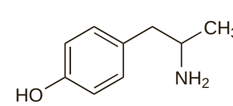

(hydroxyamfetamine)

Pharmacopoeias. In *US.*

USP 31 (Hydroxyamphetamine Hydrobromide). A white, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water are slightly acid to litmus, having a pH of about 5. Protect from light.

Profile

Hydroxyamfetamine hydrobromide is a sympathomimetic with an action similar to that of ephedrine (p.1559), but it has little or no stimulant effect on the CNS. It was formerly used as a vasopressor and in the management of some cardiac disorders.

In ophthalmology, hydroxyamfetamine hydrobromide has been used in a 1% solution as a mydriatic and in the diagnosis of Horner's syndrome.

Preparations

USP 31: Hydroxyamphetamine Hydrobromide Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Cz.: Pedrolon†; ***USA:*** Paredrine†.

Multi-ingredient: ***USA:*** Paremyd.

Hydroxyapatite *(BAN)*

542 (edible bone phosphate); Durapatite *(USAN)*; Hidroxiapatito; Hydroxylapatite; Win-40350. Decacalcium dihydroxide hexakis(orthophosphate).

$3Ca_3(PO_4)_2,Ca(OH)_2$ =1004.6;
$Ca_5(OH)(PO_4)_3$ =502.3.
CAS — 1306-06-5.

Profile

Hydroxyapatite is a natural mineral with composition similar to that of the mineral in bone. Hydroxyapatite for therapeutic purposes is prepared from bovine bone and contains, in addition to calcium and phosphate, trace elements, fluoride and other ions, proteins, and glycosaminoglycans. It is given orally to patients requiring both calcium and phosphorus supplementation. Hydroxyapatite with tricalcium phosphate has been used in bone grafts.

Hydroxyapatite derived from marine coral has been used in the construction of orbital implants for use after surgical removal of the eye. A synthetic calcium hydroxyapatite (CaHA) is used for the correction of facial lipoatrophy in patients with HIV infection and as a cosmetic filler for moderate to severe facial wrinkles and folds.

Adverse effects. Reference to problems associated with the use of coral-derived orbital implants[1] and synthetic calcium hydroxyapatite.[2]

1. Shields CL, *et al.* Problems with the hydroxyapatite orbital implant: experience with 250 consecutive cases. *Br J Ophthalmol* 1994; **78:** 702–6.
2. Sankar V, McGuff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J Am Dent Assoc* 2007; **138:** 1093–96.

Uses. A mixture of calcium phosphates with calcium carbonate could be combined to form a paste which could be injected into acute fractures;[1] under physiological conditions the paste hardened within minutes, due to the formation of dahllite, a carbonated apatite, and held the bones in place as it was progressively replaced by living bone.

1. Constantz BR, *et al.* Skeletal repair by in situ formation of the mineral phase of bone. *Science* 1995; **267:** 1796–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ossopan; Osteogenon; ***Braz.:*** Ossopan; ***Cz.:*** Osteogenon; ***Fr.:*** Ossopan; ***Ger.:*** Calcibon; Endobon; Ossopan†; ***Hung.:*** Osteogenon; ***India:*** Ossopan; ***Indon.:*** Ossopan; Ossoral; ***Irl.:*** Ossopan; ***Ital.:*** Apagen; ***Mex.:*** Ossopan; ***Pol.:*** Ossopan; Osteogenon; ***Port.:*** Ossopan; ***Rus.:*** Osteogenon (Остеогенон); ***Singapore:*** Ossopan†; ***Spain:*** Ossopan; Osteopor; ***Switz.:*** Ossopan; ***Thai.:*** Ossopan; ***UK:*** Ossopan†; Osteo Support; ***USA:*** Radiesse.

Multi-ingredient: ***Arg.:*** Totalos Plus; ***Ger.:*** Collapat II; ***Malaysia:*** Supa Biocal Vitahealth†.

Hydroxymethylnicotinamide

Hidroximetilnicotinamida; *N*-Hydroxymethylnicotinamide; Nicotinylmethylamide; Nicotinylmethylamidum; Nikotynylometyloamid. *N*-Hydroxymethylpyridine-3-carboxamide.

$C_7H_8N_2O_2$ = 152.2.
CAS — 3569-99-1.
ATC — A05AB01.
ATC Vet — QA05AB01.

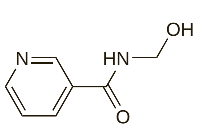

Pharmacopoeias. In *Pol.*

Profile

Hydroxymethylnicotinamide is a cholagogue and has been used in the treatment of various disorders of the gallbladder.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Bilamide.

Hydroxyquinoline Sulfate

Chinosolum; Hidroxiquinolina, sulfato de; Hydroxyquinoline Sulphate; Oksikinoliinisulfaatti; Oxichinolini Sulfas; Oxikinolinsulfat; Oxine Sulphate; Oxyquinol; Oxyquinoline Sulfate *(USAN)*; Sulfate d'Orthoxyquinoléine. Quinolin-8-ol sulphate; 8-Quinolinol sulphate.

$(C_9H_7NO)_2,H_2SO_4$ = 388.4.
CAS — 148-24-3 (hydroxyquinoline); 134-31-6 (hydroxyquinoline sulfate).
ATC — A01AB07; D08AH03; G01AC30; R02AA14.
ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

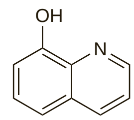

(hydroxyquinoline)

Pharmacopoeias. In *Fr.* and *Swiss.* Also in *USNF.*

USNF 26 (Oxyquinoline Sulfate). A yellow powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether; freely soluble in methyl alcohol.

Potassium Hydroxyquinoline Sulfate

Oxiquinol potásico; Oxyquinol Potassium; Potassii Hydroxyquinolini Sulphas; Potassium Hydroxyquinoline Sulphate; Potassium Oxyquinoline Sulphate.

CAS — 14534-95-3.
ATC — A01AB07; D08AH03; G01AC30; R02AA14.
ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

Pharmacopoeias. In *Br., Fr.,* and *Ger.*

BP 2008 (Potassium Hydroxyquinoline Sulphate). An equimolecular mixture of potassium sulfate and quinolin-8-ol sulfate monohydrate. It contains 50.6 to 52.6% of quinolin-8-ol and 29.5 to 32.5% of potassium sulfate, calculated with reference to the anhydrous substance. A pale yellow, odourless or almost odourless, microcrystalline powder. Freely soluble in water; insoluble in ether. On extraction with hot dehydrated alcohol a residue of potassium sulfate and a solution of quinolin-8-ol sulfate are obtained.

Profile

Hydroxyquinoline sulfate and potassium hydroxyquinoline sulfate have antibacterial, antifungal, and deodorant properties, and have been used similarly in the topical treatment of skin, oropharyngeal, and vaginal disorders. Potassium hydroxyquinoline sulfate is often used with benzoyl peroxide.

Derivatives of hydroxyquinoline including the salicylate, benzoate, borate, hydrofluoride, iodochloride, silicofluoride, and sodium hydroxyquinoline sulfate have been used similarly.

Preparations

BP 2008: Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream.

Proprietary Preparations (details are given in Part 3)
Ger.: Leioderm; ***Ital.:*** Aftir Shampoo; ***Neth.:*** Superol.

Multi-ingredient: ***Arg.:*** Curisept†; ***Austral.:*** Aci-Jel†; ***Belg.:*** Aseptosyl†; ***Braz.:*** Andolba; Cerumin; Colpolase; Lacto Vagin†; Leucocida†; Malvatricin Ginecologico; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Pan-Emecort†; Senol†; ***Chile:*** Diproquin; ***Cz.:*** Aviril H†; ***Fr.:*** Chromargon; Dermacide; Nestosyl; ***Ger.:*** Chinosol; Leioderm P; ***Hung.:*** Germicid†; ***Irl.:*** Quinocort†; Quinoderm; Valderma†; ***Ital.:*** Disinfene; Ustiosan; Viderm†; ***NZ:*** Aci-Jel†; ***Philipp.:*** Auralgan; ***Port.:*** Apyrol†; Queimax; ***Rus.:*** Contraceptin T (Контрацептин Т); ***S.Afr.:*** Cuticura†; Oto-Phen Forte; Quinoderm; Universal Earache Drops; ***Switz.:*** Benzocaine PD; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; ***UK:*** Quinoderm; Valderma; ***USA:*** Acid Jelly; Auroguard Otic; Fem pH; Medicone Derma†; Oxzal; Stypto-Caine; Trimo-San; Triv; ***Venez.:*** Borogin; Fluquinol†.

Hymecromone *(BAN, USAN, rINN)*

Himecromona; Himekromon; Himekromonas; Hymechromon; Hymécromone; Hymecromonum; Hymekromon; Hymekromoni; Imecromone; LM-94. 7-Hydroxy-4-methylcoumarin.

Гимекромон

$C_{10}H_8O_3$ = 176.2.
CAS — 90-33-5.
ATC — A05AX02.
ATC Vet — QA05AX02.

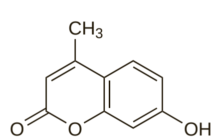

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Hymecromone). An almost white crystalline powder. Very slightly soluble in water; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol. It dissolves in dilute solutions of ammonia. Protect from light.

Profile

Hymecromone is a choleretic and biliary antispasmodic. It has been given orally in doses of 400 mg three times daily at mealtimes. It has also been given as the sodium salt by slow intravenous injection as an adjunct to diagnostic procedures. Diarrhoea may occasionally occur.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cholonerton; Unichol; ***Belg.:*** Cantabiline; ***Cz.:*** Cholestil; Isochol; ***Fr.:*** Cantabiline; ***Ger.:*** Chol-Spasmoletten; Cholspasmin; Gallo Merz Spasmo†; ***Gr.:*** Cholirene; ***Ital.:*** Cantabilin; ***Pol.:*** Cholestil; ***Rus.:*** Odeston (Одестон); ***Spain:*** Bilicanta†; ***Turk.:*** Cantabiline.

Hyoscyamus

Banotu; Beleño; Bilsenkraut; Bolmört; Giusquiamo; Henbane; Hullukaali; Hyoscy.; Hyoscyami; Hyoscyami folium (hyoscyamus leaf); Jusquiame; Jusquiame Noire; Jusquiame noire, feuille de (hyoscyamus leaf); Meimendro.

Pharmacopoeias. *Chin.* specifies only the seeds.

Eur. (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Hyoscyamus for Homoeopathic Preparations; Hyoscyamus Niger ad Praeparationes Homoeopathicas). The whole, fresh flowering plant of *Hyoscyamus niger.* Protect from light.

Profile

Hyoscyamus contains the alkaloid hyoscyamine with varying amounts of hyoscine and has peripheral and central effects similar to those of atropine (p.1219); its preparations have been used mainly for the relief of visceral spasm. The fresh whole flowering plant (*Hyoscyamus niger*) as well as the dried leaves have been used in herbal and medicine.

Homoeopathy. Hyoscyamus has been used in homoeopathic medicines under the following names: Hyoscyamus leaf; Hyoscyamus niger; Hyos. nig.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Kelosoft; ***Switz.:*** Kelosoft; ***Venez.:*** Atroveran.

Multi-ingredient: ***Arg.:*** Hepacur; Trixol†; ***Braz.:*** Dorveran†; Ductoveran; Espasmalgon†; MM Expectorante; Sedatux†; ***Denm.:*** Zink-Calmitol†; ***Fr.:*** Laccoderme a l'huile de cade; ***Ger.:*** Unguentum lymphaticum; ***Switz.:*** Cardiodoron†; Dragees S contre la toux†; Gouttes contre la toux "S"; Kelimed; Sirop pectoral contre la toux S; Sirop S contre la toux et la bronchite; ***UK:*** Onopordon Comp B; ***Venez.:*** Atrobel; Cloverin†; Cratex†; Linfoderm; Neo-Atropan†; Tropifen†.

Hypoglycin A

Hipoglicina A. L-2-Amino-3-(2-methylenecyclopropyl)propionic acid.

$C_7H_{11}NO_2$ = 141.2.
CAS — 156-56-9.

Profile

Hypoglycin A is a toxic substance present in the arillus of unripe ackee (akee), the fruit of *Blighia sapida* (Sapindaceae). It is responsible for Jamaican vomiting sickness, with symptoms of acute and severe vomiting, hypoglycaemia, muscular weakness, CNS depression, convulsions, and coma, frequently fatal. Glycine has been suggested for the management of hypoglycin A toxicity.

Hypophosphorous Acid

Acidum Hypophosphorosum; Hipofosforoso, ácido; Phosphinic Acid.

H_3PO_2 = 66.0.
CAS — 6303-21-5; 14332-09-3.

Pharmacopoeias. In *USNF.*

USNF 26 (Hypophosphorous Acid). It contains 30 to 32% of H_3PO_2. A colourless or slightly yellow, odourless liquid. Store in airtight containers.

Profile

Hypophosphorous acid is used as an antoxidant. Hypophosphates were used in tonics; like the glycerophosphates they are not a suitable source of phosphorus.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Dispello.

Hyssop

Herba Hyssopi; Hysope; Hyssop Wort; Ysop.

Pharmacopoeias. In *Fr.*

Profile

Hyssop is the fresh or dried aerial parts of *Hyssopus officinalis* (Lamiaceae). The herb and its preparations are included in herbal preparations mainly for disorders of the gastrointestinal and upper respiratory tracts.

It is the source of hyssop oil which is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Yzop Lekarsky†.

Multi-ingredient: ***Arg.:*** Arceligasol; ***Austria:*** The Chambard-Tee; ***Fr.:*** Item Lentes; Mediflor Tisane Circulation du Sang No 12; Mediflor Tisane Digestive No 3; ***Ital.:*** Tisana Kelemata; ***Pol.:*** Pectosol; ***Port.:*** Solubeol†; ***Rus.:*** Linkus (Линкас); Linkus Lor (Линкас Лор); ***Spain:*** Agua del Carmen; Natusor Asmaten†; ***Switz.:*** Saintbois; ***UK:*** Catarrh Mixture; Tickly Cough & Sore Throat Relief; Vegetable Cough Remover.

Ibogaine

Ibogaina; NIH-10567. 12-Methoxyibogamine.

$C_{20}H_{26}N_2O$ = 310.4.
CAS — 83-74-9.

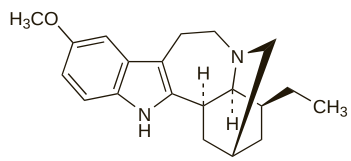

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of ibogaine or preparations containing ibogaine:
Iboga.

Profile

Ibogaine is a hallucinogenic indole alkaloid extracted from the West African shrub *Tabernanthe iboga* (Apocynaceae). It has been investigated as an aid to withdrawal from drug addiction.

◊ References.

1. Popik P, *et al.* 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol Rev* 1995; **47:** 235–53.
2. Alper KR, *et al.* Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999; **8:** 234–42.
3. Pace CJ, *et al.* Novel iboga alkaloid congeners block nicotinic receptors and reduce drug self-administration. *Eur J Pharmacol* 2004; **492:** 159–67.
4. Hittner JB, *et al.* Combating substance abuse with ibogaine: pre- and posttreatment recommendations and an example of successive model fitting analyses. *J Psychoactive Drugs* 2004; **36:** 191–9.

Icatibant Acetate *(USAN, rINNM)*

Hoe-140 (icatibant, icatibant acetate); Icatibant, Acétate d'; Icatibanti Acetas; Icatibanto; JE-049 (icatibant). (*R*)-Arginyl-(*S*)-arginyl-(*S*)-prolyl-(2*S*,4*R*)-(4-hydroxyprolyl)glycyl-(*S*)-[3-(2-thienyl)-alanyl]-(*S*)-seryl-(*R*)-[(1,2,3,4-tetrahydro-3-isoquinolyl)-carbonyl]-(2*S*,3a*S*,7a*S*)-[(hexahydro-2-indolinyl)-carbonyl]-(*S*)-arginine acetate.

Икатибанта Ацетат

$C_{59}H_{89}N_{19}O_{13}S,xC_2H_4O_2$.
CAS — 130308-48-4 (icatibant); 138614-30-9 (icatibant acetate).

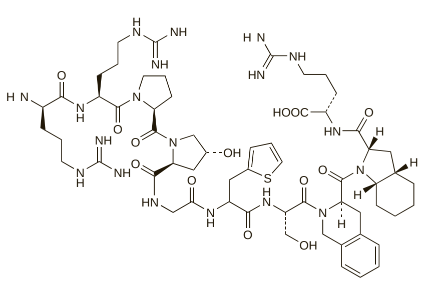

Profile

Icatibant acetate is a selective bradykinin B_2 antagonist under investigation for hereditary angioedema.

Iceland Moss

Islandinių kerpenų gniužulas; Isländisches Moos; Islandslav; Islanninjäkälä; Izlandi zuzmó; Lichen d'Islande; Lichen islandicus; Lišejník islandský; Porost islandzki.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Iceland Moss; Lichen Islandicus). The whole or cut dried thallus of *Cetraria islandica*. Protect from light.

Profile

Iceland moss, *Cetraria islandica* (Parmeliaceae), is a lichen with demulcent and mild antimicrobial activity. It is included in herbal medicines for dry cough, and irritation or inflammation of the oral and pharyngeal mucosa. It is also used as a bitter to stimulate the appetite.

Iceland moss has been used as a foodstuff and a flavouring agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Isla-Mint†; Isla-Moos†; ***Hong Kong:*** Isla-Mint†; Isla-Moos†; ***Singapore:*** Isla-Mint Herbal†.

Multi-ingredient: ***Austral.:*** Cough Relief†; ***Braz.:*** Peitoral Angico Pelotense†; ***Ital.:*** Altea (Specie Composta)†; Balta Intimo†; Kevis; Sclerovis H; ***Pol.:*** Pectosol; ***Port.:*** Bioclin Sebo Care†; ***Switz.:*** Kernosan Elixir; Tisane pectorale et antitussive; ***UK:*** Herb and Honey Cough Elixir.

Idanpramine

Idampramina. 5,5-Bis(4-methoxyphenyl)-3-[2-(1-piperidinyl)-ethyl]-2,4-imidazolidinedione.

Иданпрамин

$C_{24}H_{29}N_3O_4$ = 423.5 112 25466-44-8.
ATC — A03AX06.
ATC Vet — QA03AX06.

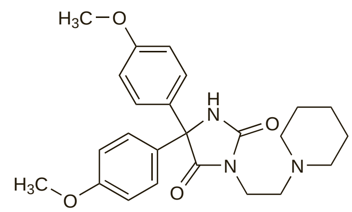

Idanpramine Hydrochloride

Иданпрамина Гидрохлорид

$C_{24}H_{29}N_3O_4$,HCl = 460.0.
CAS — 25466-21-1.
ATC — A03AX06.
ATC Vet — QA03AX06.

Idanpramine Sulfate

Idampramina Sulfato.

Иданпрамина Сульфат

ATC — A03AX06.
ATC Vet — QA03AX06.

Profile

Idanpramine is an antimuscarinic that has been used as the hydrochloride and sulfate salts in the relief of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Gastroidam.

Idursulfase *(BAN, USAN, rINN)*

Iduronate-2-sulfatase; Idursulfasa; Idursulfasum; Idusulfase. α-L-Iduronate sulfate sulfatase.

Идусульфас

CAS — 50936-59-9.
ATC — A16AB09.
ATC Vet — QA16AB09.

Profile

Idursulfase is recombinant human iduronate-2-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder that results in the accumulation of glycosaminoglycans in cells with consequent progressive damage. Idursulfase is given by intravenous infusion in a dose of 500 micrograms/kg once a week. Infusion reactions are common and treatment with antihistamines with or without corticosteroids, or a reduction in infusion rate may be necessary. Stopping the infusion should be considered in severe reactions. Anaphylactoid reactions have been reported, in some cases up to 24 hours after the infusion.

Idursulfase should be diluted in 100 mL of sodium chloride 0.9% and infused over 1 to 3 hours. The initial infusion rate should be 8 mL/hour for the first 15 minutes, which may then be increased by 8 mL/hour every 15 minutes if well tolerated, up to a maximum rate of 100 mL/hour. If the infusion rate is decreased because of infusion reactions, the infusion time should not exceed 8 hours because of lack of preservative in the product.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Elaprase; ***Port.:*** Elaprase; ***UK:*** Elaprase; ***USA:*** Elaprase.

Indigo Carmine

Blue X; Ceruleinum; CI Food Blue 1; Colour Index No. 73015; Disodium Indigotin-5,5′-disulphonate; E132; FD & C Blue No. 2; Indicarminum; Indigo Karmin; Indigotina; Indigotindisulfonate Sodium; Indigotine; Indygokarmin; Sodium Indigotindisulphonate. Disodium 3,3′-dioxo-2,2′-bi-indolinylidene-5,5′-disulphonate.

$C_{16}H_8N_2Na_2O_8S_2$ = 466.4.
CAS — 483-20-5 (indigotin-5,5′-disulphonic acid); 860-22-0 (indigo carmine).
ATC — V04CH02.
ATC Vet — QV04CH02.

NOTE. The name Cerulein has been applied to Ceruletide (p.2279).

Pharmacopoeias. In *It.*, *Jpn*, and *US.*

USP 31 (Indigotindisulfonate Sodium). A dusky, purplish-blue powder, or blue granules having a coppery lustre. Soluble 1 in 100 of water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Its solutions have a blue or bluish-purple colour. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions

Indigo carmine may cause nausea, vomiting, hypertension, and bradycardia, and occasionally, hypersensitivity reactions such as skin rash, pruritus, and bronchoconstriction. Skin discoloration may occur after large parenteral doses.

Hypersensitivity. Cardiac arrest after a dose of indigo carmine 80 mg intravenously resulted in the deaths of 2 elderly patients.[1] Both had a history of asthmatic bronchitis. A life-threatening anaphylactoid reaction associated with indigo carmine use has also been reported, although the authors commented that such events are rare.[2]

1. Voiry AM, *et al.* Deux accidents mortels lors d'une injection peropératoire de carmin d'indigo. *Ann Med Nancy* 1976; **15:** 413–19.
2. Gousse AE, *et al.* Life-threatening anaphylactoid reaction associated with indigo carmine intravenous injection. *Urology* 2000; **56:** 508.

Uses and Administration

On intravenous injection indigo carmine is rapidly excreted, principally by the kidneys. It has been used in a test of renal function, but has largely been replaced by agents that give more precise results. It is used as a marker dye, particularly in urological procedures, when it is given in a usual dose of 40 mg, preferably by intravenous injection but sometimes intramuscularly. It has also been used as a marker dye in amniocentesis.

Indigo carmine has been used as a blue dye in medicinal preparations but it is relatively unstable. It has also been investigated as a dye-spray in the detection of colorectal adenomas. It is used as a food colour.

Preparations

USP 31: Indigotindisulfonate Sodium Injection.

Indocyanine Green

Verde de indocianina. Sodium 2-{7-[1,1-dimethyl-3-(4-sulphobutyl)benz[e]indolin-2-ylidene]hepta-1,3,5-trienyl}-1,1-dimethyl-1*H*-benz[e]indolio-3-(butyl-4-sulphonate).

$C_{43}H_{47}N_2NaO_6S_2$ = 775.0.
CAS — 3599-32-4.

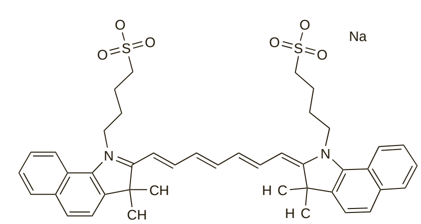

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Indocyanine Green). An olive-brown, dark green, blue-green, dark blue, or black powder. Is odourless or has a slight odour. It contains not more than 5.0% of sodium iodide, calculated on the dried basis. Soluble in water and in methyl alcohol; practically insoluble in most other organic solvents. Its solutions are deep emerald-green in colour. pH of a 0.5% solution in water is about 6. Its aqueous solutions are stable for about 8 hours. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

Indocyanine green is reported to be well tolerated. Anaphylaxis and urticaria have been reported. Solutions contain a small amount of sodium iodide and should be used with caution in patients hypersensitive to iodine. Clearance of indocyanine green may be altered by drugs that interfere with liver function.

◊ References.

1. Jackson TL. Indocyanine green accused. *Br J Ophthalmol* 2005; **89:** 395–6.
2. Cheng SN, *et al.* Ocular toxicity of intravitreal indocyanine green. *J Ocul Pharmacol Ther* 2005; **21:** 85–93.

Hypersensitivity. A report of anaphylactoid reactions to indocyanine green in 3 patients.[1] The authors commented that of 20 reactions that had been reported 9 involved anaphylactoid shock (with 2 subsequent deaths) and 11 involved hypotension or bronchospasm; they suggested that such reactions were dose-dependent and had a non-immune mechanism.

1. Speich R, *et al.* Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med* 1988; **109:** 345–6.

Pharmacokinetics

After intravenous injection indocyanine green is rapidly bound to plasma protein. It is taken up by the liver and is rapidly excreted unchanged into the bile.

Uses and Administration

Indocyanine green is an indicator dye used for assessing cardiac output and liver function, and for examining the choroidal vasculature in ophthalmic angiography. It is also used to assess blood flow and haemodynamics in various organs including the liver.

The usual dose for cardiac assessment is 5 mg injected rapidly via a cardiac catheter. A suggested dose for children is 2.5 mg, and for infants 1.25 mg. Several doses need to be given to obtain a number of dilution curves. However, the total dose should not exceed 2 mg/kg.

The usual dose of indocyanine green for testing liver function is 500 micrograms/kg given intravenously.

Diagnostic use. Indocyanine green has been used to assess blood flow to various organs and in other haemodynamic studies. However, some methods of determination of indocyanine green clearance as a measure of liver blood flow have been questioned on the grounds that extraction of the dye by the liver is not complete as is often assumed.[1] Interindividual variability in indocyanine clearance may introduce further error.[2]

There have been reports of the use of indocyanine green to assess cerebral blood flow in children during cardiopulmonary bypass[3] and to measure plasma volume in neonates.[4] In ophthalmology, indocyanine green angiography is used to visualise the choroidal circulation,[5,6] and as a stain during surgical repair of macular holes.[7,8]

1. Skak C, Keiding S. Methodological problems in the use of indocyanine green to estimate hepatic blood flow and ICG clearance in man. *Liver* 1987; **7:** 155–62.
2. Bauer LA, *et al.* Variability of indocyanine green pharmacokinetics in healthy adults. *Clin Pharm* 1989; **8:** 54–5.
3. Roberts I, *et al.* Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1993; **342:** 1425.
4. Anthony MY, *et al.* Measurement of plasma volume in neonates. *Arch Dis Child* 1992; **67:** 36–40.
5. Owens SL. Indocyanine green angiography. *Br J Ophthalmol* 1996; **80:** 263–6.
6. Dzurinko VL, *et al.* Intravenous and indocyanine green angiography. *Optometry* 2004; **75:** 743–55.
7. Rodrigues EB, *et al.* Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. *Ophthalmologica* 2005; **219:** 251–62.
8. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89:** 420–4.

Preparations

USP 31: Indocyanine Green for Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Infracyanine; ***Ger.:*** ICG-Pulsion; ***Gr.:*** ICG-Pulsion; ***Israel:*** IC Green; ICG-Pulsion; ***Neth.:*** ICG-Pulsion; ***USA:*** Cardio-Green†; IC Green.

Inhibin

Inhibina.

Ингибин

CAS — 57285-09-3.

NOTE. The name inhibin has also been used as a proprietary name for hydroquinine hydrobromide (p.2322).

Profile

Inhibin is a dimeric glycoprotein secreted by the testes and ovaries that suppresses secretion of follicle-stimulating hormone by the pituitary. As a member of the transforming growth factor-β family, it is also involved in mediation and regulation of many other physiological processes. Its two isoforms inhibin A and inhibin B have been widely investigated for their potential as markers of male infertility, ovarian cancer, and placental function. It has also been studied as a prognostic indicator of ovarian function in women undergoing assisted reproduction.

◊ References.

1. Kumanov P, *et al.* Significance of inhibin in reproductive pathophysiology and current clinical applications. *Reprod Biomed Online* 2005; **10:** 786–812.

Inosine *(rINN)*

Hypoxanthine Riboside; Inosina; Inosinum. 6,9-Dihydro-9-β-D-ribofuranosyl-1*H*-purin-6-one.

Инозин

$C_{10}H_{12}N_4O_5$ = 268.2.
CAS — 58-63-9.
ATC — D06BB05; G01AX02; S01XA10.
ATC Vet — QD06BB05; QG01AX02; QS01XA10.

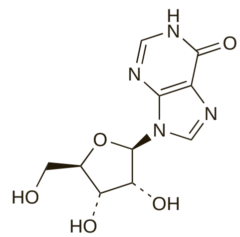

Pharmacopoeias. In *Chin.*

Profile

Inosine has been used in the treatment of anaemias and cardiovascular, liver, and skin disorders and has been used as a tonic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Laevadosin†; ***Ital.:*** Neo-Eparbiol†; ***Spain:*** Nutracel; Rubrocortin†.

Inositol

i-Inositol; *meso*-Inositol; Inositoli; Inositolum; *myo*-Inositolum; mio-Inozytol; myo-Inositol; myo-Inositoli; myo-Inositolum. *myo*-Inositol.

$C_6H_{12}O_6$ = 180.2.
CAS — 87-89-8.
ATC — A11HA07.
ATC Vet — QA11HA07.

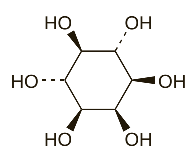

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (*myo*-Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in alcohol.

USNF 26 (Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Inositol, an isomer of glucose, has traditionally been considered to be a vitamin B substance although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. Sources of inositol include whole-grain cereals, fruits, and plants, in which it occurs as the hexaphosphate, fytic acid. It also occurs in both vegetables and meats in other forms. The usual daily intake of inositol from the diet is about 1 g. It is an ingredient of numerous vitamin preparations and dietary supplements, and of preparations promoted for a wide variety of disorders.

Inositol appears to be involved physiologically in lipid metabolism and has been tried, with little evidence of efficacy, in disorders associated with fat transport and metabolism. It has been investigated in the treatment of depression and anxiety, in diabetic neuropathy, and in neonatal respiratory distress syndrome and retinopathy of prematurity.

Neonatal respiratory distress syndrome. Inositol supplementation has been tried in premature infants with respiratory distress syndrome (p.1508). A meta-analysis[1] found that infants given inositol had improved survival and lower rates of bronchopulmonary dysplasia and retinopathy of prematurity than those given placebo.

1. Howlett A, Ohlsson A. Inositol for respiratory distress syndrome in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 19/04/06).

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Inositech.

Multi-ingredient: ***Arg.:*** Bifena; ***Austral.:*** Hair and Skin Formula†; Liv-Detox†; ***Austria:*** Aslavital; Lemazol; ***Braz.:*** Hecrosine B12†; Hepatogenol†; Hormo Hepatico†; Metiocolin B12; Xantinon Complex; ***Canad.:*** Amino-Cerv; ***Chile:*** Hepabil; ***Cz.:*** Lipovitan†; ***Fr.:*** Hepagrume; ***Ger.:*** Lipovitan†; ***Hong Kong:*** Bilsan; Lipochol; ***India:*** Alcrin-M; Delphicol; ***Indon.:*** Naturica DFM; ***Ital.:*** Digelax†; Hepatos B12; Porfirin 12; Stimolfit; ***S.Afr.:*** Hepavite; Prohep; ***Spain:*** Complidermol†; Dertrase; Policolinosil; Tri Hachemina; ***Thai.:*** Lipochol; Liporon; ***UK:*** Lipotropic Factors; ***USA:*** Amino-Cerv.

Interleukins

Интерлейкины

Profile

Interleukins are cytokines (p.2292) that are thought to target leukocytes. As with other cytokines, interleukins are involved in the regulation of normal immune and inflammatory responses and have both proinflammatory and anti-inflammatory actions. Interleukins used clinically include interleukin-1 (p.2325), interleukin-2 (p.735), and aldesleukin (recombinant interleukin-2) (p.735). Interleukins under investigation include interleukin-3 (p.1073), ilodecakin (recombinant interleukin-10) (p.2326), and edodekin alfa (recombinant interleukin-12) (p.2326).

Interleukins have also been implicated in the pathogenesis of some diseases, and inhibitors of interleukins or their receptors may therefore be of therapeutic value.

Antagonists acting against interleukin receptors used clinically include anakinra (recombinant interleukin-1 receptor antagonist) (p.19), basiliximab (p.1821), and daclizumab (p.1833), which are all interleukin-2 receptor antibodies, and tocilizumab (recombinant interleukin-6 receptor antibody) (p.2326) Inolimomab (p.1835) is an interleukin-2 receptor antibody under investigation.

Antibodies targeting interleukins have been developed and those under investigation include mepolizumab (recombinant interleukin-5 antibody) (p.743) and elsilimomab (recombinant interleukin-6 antibody) (p.2326).

Interleukin fusion toxins are produced by combining interleukin protein sequences with a bacterial toxin (e.g. diphtheria or pseudomonas) with the aim of inhibiting specific interleukin activity. Those under investigation include interleukin-2 fusion toxins (p.2326), interleukin-4 fusion toxins, and cintredekin besudotox, an interleukin-13 fusion toxin.

Soluble interleukin receptors may have therapeutic value and are also being tried therapeutically: rilonacept (p.2379) is an interleukin-1 blocker used in the treatment of a group of rare inherited auto-inflammatory disorders; interleukin-4 receptor is also being investigated.

Inhibitors of cysteine protease IL-1β converting enzyme (ICE) have been investigated as a means of reducing secretion of interleukin-1β (p.2325).

Interleukin-1

Catabolin; Endogenous Pyrogen; Haematopoietin-1; IL-1; Interleucina 1; Leucocyte Endogenous Mediator; Lymphocyte Activating Factor.

Интерлейкин-1

Profile

Interleukin-1 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced in blood and a variety of tissues by mononuclear phagocytes involved in the complex regulation of immune responses. It enhances the immune response and has proinflammatory and pyrogenic properties. There are two distinct forms, interleukin-1α and interleukin-1β.

Interleukin-1 may also be produced by recombinant DNA technology, and human recombinant interleukin-1β has been used as an adjunct to cancer chemotherapy or radiotherapy for its haematopoietic activity. It has also been investigated for its immunotropic effects in purulent infections of the lung and ear, although it has no intrinsic antibacterial activity. Adverse effects of interleukin-1 include fever, chills, flu-like symptoms, hypotension, and pain, swelling, and erythema at the site of subcutaneous injection.

Interleukin-1 is also implicated in the pathogenesis of some diseases, particularly auto-immune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Betaleukin.

Interleukin-1 Receptor Antagonists

Antagonista del Receptor de la Interleucina 1; IL-1ra; IL-1i; Interleukin-1 Inhibitors.

Profile

Endogenous antagonists to interleukin-1 receptor block the actions of interleukin-1 (p.2325) and recombinant forms have been investigated in inflammatory and immune-modulated disorders.

Anakinra (p.19) is a human recombinant interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis.

Interleukin-2 Fusion Toxins

Toxinas de fusión de interleucina 2.

Profile

Interleukin-2 fusion toxin is produced by replacing the receptor binding domain of diphtheria toxin with sequences from interleukin-2, thus producing specific cytotoxicity in cells expressing the interleukin-2 receptor. The interleukin-2 fusion toxin denileukin diftitox (p.710) is used in the treatment of cutaneous T-cell lymphoma. The related compound DAB_{486} interleukin-2 has also been investigated in a variety of disorders.

Interleukin-6

B-cell Stimulatory Factor-2; BSF-2; Hepatocyte-Stimulating Factor; Hybridoma Growth Factor; IFN-β_2; IL-6; Interferon-β2.

Интерлейкин-6

Profile

Interleukin-6 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by many cell types and induces differentiation of B-lymphocytes and activation of T-cells. It has proinflammatory and pyrogenic properties and is involved in the regulation of immune responses and inflammation. Interleukin-6 has also been implicated in haematopoiesis.

Atexakin alfa is human recombinant interleukin-6 under investigation.

Since overproduction of interleukin-6 plays a crucial role in the pathogenesis of chronic inflammatory diseases, interleukin-6 antibodies (p.2326) and interleukin-6 receptor antagonists (p.2326) are being investigated or used as therapeutic agents.

Interleukin-6 Antibodies

IL-6 Antibody.

Elsilimomab *(rINN)*

Elsilimomabum. Immunoglobulin G1, anti-(human interleukin 6) (mouse monoclonal B-E8 heavy chain), disulfide with mouse monoclonal B-E8 κ-chain, dimer.

Эльсилимомаб

CAS — 468715-71-1.

Profile

Monoclonal antibodies to interleukin-6 (p.2326) are under investigation for the treatment of disorders including post-transplant lymphoproliferative disorders and renal cell carcinoma.

Elsilimomab is an interleukin-6 monoclonal antibody under investigation.

Interleukin-6 Receptor Antagonists

Tocilizumab *(USAN, rINN)*

Atlizumab; MRA; R-1569; Tocilizumabum. Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer.

Тоцилизумаб

CAS — 375823-41-9.

Profile

Antagonists to the interleukin-6 receptor block the actions of interleukin-6 (p.2326) and are under investigation for rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Crohn's disease, and haemolytic anaemia.

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder. It is also used for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.

◊ References.

1. Nishimoto N, *et al.* Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000; **95:** 56–61.
2. Ito H, *et al.* A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126:** 989–96.
3. Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005; **28:** 221–30.
4. Yokota S, *et al.* Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis. *Clin Rev Allergy Immunol* 2005; **28:** 231–8.
5. Lipsky PE. Interleukin-6 and rheumatic diseases. *Arthritis Res Ther* 2006; **8** (suppl 2): S4. Available at: http://arthritis-research.com/content/8/S2/S4 (accessed 11/02/08)
6. Maini RN, *et al.* Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; **54:** 2817–29.
7. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 2006; **42:** 559–76.
8. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; **2:** 619–26. Correction. *ibid.*; 691.
9. Kanda J, *et al.* Reversible cardiomyopathy associated with multicentric Castleman disease: successful treatment with tocilizumab, an anti-interleukin 6 receptor antibody. *Int J Hematol* 2007; **85:** 207–11.
10. Matsuyama M, *et al.* Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Intern Med* 2007; **46:** 771–4.
11. Smolen JS, *et al.* OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; **371:** 987–97.
12. Yokota S, *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; **371:** 998–1006.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Actemra.

Interleukin-10

CSIF; Cytokine synthesis inhibitory factor; IL-10.

Интерлейкин-10

CAS — 130068-27-8.

Ilodecakin *(USAN, rINN)*

Ilodecakina; Ilodécakine; Ilodecakinum; Interleukin-10 (human clone pH15C); rhIL-10; Sch-52000.

Илодекакин

CAS — 149824-15-7.

Profile

Interleukin-10 is one of a number of polypeptides known collectively as interleukins (p.2325). It regulates the differentiation and proliferation of several immune cells including T-cells and B-cells. It is postulated that it has immunostimulant as well as immunosuppressive properties; it also has anti-inflammatory actions. Interleukin-10 is under investigation for inflammatory bowel disease, malignant neoplasms, skin disorders including psoriasis and reduction of scarring, rheumatoid arthritis, hepatitis C, and organ transplantation.

Ilodecakin is a recombinant form of interleukin-10 under investigation.

◊ References.

1. Asadullah K, *et al.* Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; **55:** 241–69.
2. Braat H, *et al.* Interleukin-10-based therapy for inflammatory bowel disease. *Expert Opin Biol Ther* 2003; **3:** 725–31.
3. Weiss E, *et al.* The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. *J Am Acad Dermatol* 2004; **50:** 657–75.
4. Asadullah K, *et al.* Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; **3:** 185–92.
5. Vicari AP, Trinchieri G. Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol Rev* 2004; **202:** 223–36.
6. Mocellin S, *et al.* Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol* 2005; **78:** 1043–51.
7. Mege JL, *et al.* The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006; **6:** 557–69.

Interleukin-12

IL-12.

Интерлейкин-12

Edodekin Alfa *(USAN, rINN)*

Edodekina alfa; Édodékine Alfa; Edodekinum Alfa; Ro-24-7472/000.

Эдодекин Альфа

CAS — 187348-17-0.

Description. A recombinant human interleukin-12.

Profile

Interleukin-12 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by macrophages and dendritic cells and enhances cellular immunity through induction of the activity of interferon-γ and cytotoxic T-lymphocytes. It has been investigated for the treatment of severe infections such as mycobacterial infections; it is worthy of note that children with a rare inherited susceptibility to fatal mycobacterial infections exhibit mutations in the interleukin-12 gene. Interleukin-12 is also under study for the treatment of various cancers, including as adenovirus-mediated gene therapy.

Edodekin alfa is human recombinant interleukin-12 under investigation for the treatment of renal cell carcinoma.

◊ References.

1. Mazzolini G, *et al.* Gene therapy of cancer with interleukin-12. *Curr Pharm Des* 2003; **9:** 1981–91.
2. Kikuchi T, *et al.* Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. *J Immunother* 2004; **27:** 452–9.
3. Trudeau C, *et al.* A single administration of recombinant human interleukin-12 is associated with increased expression levels of interferon-gamma and signal transducer and activator of transcription in healthy subjects. *J Clin Pharmacol* 2005; **45:** 649–58.
4. Sangro B, *et al.* Gene therapy of cancer based on interleukin 12. *Curr Gene Ther* 2005; **5:** 573–81.
5. Little RF, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 2006; **107:** 4650–7.

Intrinsic Factor

Antianemic Factor; Castle's Intrinsic Factor; Gastric Intrinsic Factor.

Внутренне Присущий Фактор

CAS — 9008-12-2.

Profile

Intrinsic factor, a glycoprotein secreted by the parietal glands in the stomach, is required for absorption of vitamin B_{12} in the small intestine. Deficiency in intrinsic factor leads to vitamin B_{12} deficiency disorders and pernicious anaemia.

Intrinsic factor is given orally with cyanocobalamin in the Schilling test in the differential diagnosis of pernicious anaemia (see p.1981). It is also included in some oral preparations containing cyanocobalamin, presumably as an aid to absorption.

◊ Difficulty in obtaining intrinsic factor and/or radio-labelled cyanocobalamin for the original Schilling test prompted studies using a recombinant human intrinsic factor in a new vitamin B_{12} absorption test. Initial results with this recombinant form were promising.[1]

1. Hvas A-M, *et al.* The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency. *Haematologica* 2006; **91:** 805–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Hemofer†; ***Indon.:*** Biosanbe; ***Philipp.:*** TriHEMIC; ***USA:*** Anemagen†; Chromagen; Contrin; Ferotrinsic; Fetrin; Livitrinsic-f; Pronemia Hematinic; TriHEMIC; Trinsicon.

Inulin *(BAN)*

Alant Starch; Inulina.

CAS — 9005-80-5.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Inulin). A polysaccharide obtained from the tubers of *Dahlia variabilis*, *Helianthus tuberosus*, and other genera of the family Compositae. It is a white, odourless or almost odourless, hygroscopic, amorphous, granular powder. Slightly soluble in cold water, but freely soluble in hot water; slightly soluble in organic solvents.

USP 31 (Inulin). A polysaccharide which, on hydrolysis, yields mainly fructose. A white, friable, chalk-like, amorphous, odourless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Pharmacokinetics

Inulin is rapidly removed from the circulation after intravenous doses but is not metabolised. A trace may be found in the bile and may cross the placenta, but it is mainly eliminated in the urine by glomerular filtration without secretion or reabsorption in the renal tubule.

Uses and Administration

Inulin is used intravenously as a diagnostic agent to measure the glomerular filtration rate. Although an accurate test, it is complex to perform and is generally reserved for research purposes. Crystals of inulin may be deposited on storage of the injection; they should be dissolved by heating for not more than 15 minutes before use and the injection cooled to a suitable temperature before use.

Polyfructosan, an inulin analogue of lower average molecular weight, has been used similarly.

Preparations

BP 2008: Inulin Injection;
USP 31: Inulin in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Inutest; ***Cz.:*** Inutest†.

Multi-ingredient: ***Chile:*** Reduc-Te; Reducform-F; ***Fr.:*** Actyfilus; Effadiane relipidantes; ***Ital.:*** Enterolactis; Lactolas; Naturalass; Snell'it.

Iris Versicolor

Blue Flag; Iris Virginica.

Profile

The rhizomes of *Iris versicolor* (Iridaceae) are used in herbal preparations for skin and gastrointestinal disorders.

Homoeopathy. Iris versicolor has been used in homoeopathic medicines under the following names: Iris; Iris ver.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Catarrh Mixture; HRI Clear Complexion; Skin Eruptions Mixture.

Isobutyl Nitrite

$C_4H_9NO_2$ = 103.1.
CAS — 542-56-3.

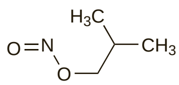

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of isobutyl nitrite:
Aroma of men; Bolt; Bullet; Climax; Hardware; Krypt tonight; Locker room; Poppers; Quicksilver; Rush; Rush Snappers; Snappers; Thrust; White out; Whiteout.

Profile

Isobutyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p.1437).

Isofagomine

AT-2101 (tartrate). (3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine.

$C_6H_{13}NO_3$ = 147.2.
CAS — 169105-89-9 (isofagomine); 161302-93-8 (isofagomine hydrochloride).

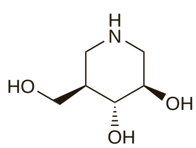

NOTE. The code AT-2101 has also been applied to a topical formulation of diclofenac in hyaluronic acid used in the treatment of actinic keratoses.

Profile

Isofagomine is an iminosugar under investigation as the tartrate for oral therapy of Gaucher disease (p.2249). It is a pharmacological chaperone that stabilises the variant lysosomal glucocerebrosidase facilitating its folding and transport from the endoplasmic reticulum into lysosomes, thereby increasing the pool of active endogenous enzyme.

Isometheptene Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isometepteno; Isométheptène, Chlorhydrate d'; Isometheptení Hydrochloridum. 1,5,*N*-Trimethylhex-4-enylamine hydrochloride; 1,5-Dimethylhex-4-enyl(methyl)amine hydrochloride.

Изометептена Гидрохлорид

$C_9H_{19}N,HCl$ = 177.7.
CAS — 503-01-5 (isometheptene); 6168-86-1 (isometheptene hydrochloride).
ATC — A03AX10.
ATC Vet — QA03AX10.

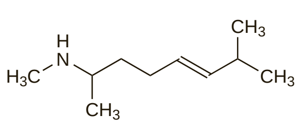

(isometheptene)

Isometheptene Mucate *(BANM, rINNM)* ⊗

Isométheptène, Mucate d'; Isometheptení Mucas; Mucato de isometepteno. Isometheptene galactarate.

Изометептена Мукат

$(C_9H_{19}N)_2,C_6H_{10}O_8$ = 492.6.
CAS — 7492-31-1.
ATC — A03AX10.
ATC Vet — QA03AX10.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Isometheptene Mucate). A white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 5.4 to 6.6. Store in airtight containers. Protect from light.

USP 31 (Isometheptene Mucate). A white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 6.0 and 7.5.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407.

Porphyria. Isometheptene mucate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Sympathomimetics, p.1407. Isometheptene has been reported to produce severe hypertensive reactions in patients receiving MAOIs.

Bromocriptine. For a report of hypertension and life-threatening complications after use of isometheptene and *bromocriptine*, see under Sympathomimetics, p.800.

Uses and Administration

Isometheptene is an indirect-acting sympathomimetic (p.1408). It is included for its vasoconstrictor effect, usually as the mucate, in some analgesic combination products used to treat acute migraine attacks (p.616). Typical oral doses of isometheptene mucate in migraine are 130 mg at the beginning of an attack, with 65 mg hourly thereafter as necessary, up to a total maximum dose of 325 mg in a 12-hour period.

Isometheptene hydrochloride has also been used in the management of migraine and smooth muscle spasm; it has been given orally, as well as by intramuscular, or occasionally subcutaneous, or slow intravenous, injection. The mucate has also been used in the management of muscle spasms.

Preparations

USP 31: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Proprietary Preparations (details are given in Part 3)
Turk.: Octinum.

Multi-ingredient: ***Braz.:*** Cefaldina; Doralgina; Doridina; Dorsedin; Migranette; Neomigran†; Neosaldina; Neuralgina; Sedalgina; Sedol; Tensaldin; ***Hong Kong:*** Midrid†; ***UK:*** Midrid; ***USA:*** Duradrin†; Midrin; MigraTen; Migratine†.

Isospaglumic Acid *(rINN)*

Acide Isospaglumique; Ácido isospaglúmico; Acidum Isospaglumicum; NAAGA. *N*-(*N*-Acetyl-L-α-aspartyl)-L-glutamic acid.

Изоспаглумовая Кислота

$C_{11}H_{16}N_2O_8$ = 304.3.
CAS — 3106-85-2.

Spaglumic Acid *(rINN)*

Acide Spaglumique; Ácido espaglúmico; Acidum Spaglumicum. *N*-(*N*-Acetyl-L-β-aspartyl)-L-glutamic acid.

Спаглумовая Кислота

CAS — 4910-46-7.
ATC — R01AC05; S01GX03.
ATC Vet — QR01AC05; QS01GX03.

Profile

N-Acetyl-L-aspartylglutamate is a mast cell stabiliser and has been used as the sodium or magnesium salts of spaglumic or isospaglumic acids in eye drops for allergic eye conditions and in nasal solutions for allergic rhinitis.

N-Acetyl-L-aspartylglutamate also has a role as a neurotransmitter and has been investigated in CNS disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Naabak; ***Austria:*** Rhinaaxia; ***Braz.:*** Naabak; Naaxia; ***Chile:*** Alerbak; Naaxia; ***Cz.:*** Naaxia†; ***Fr.:*** Naabak; Naaxia; Naaxiafree; Rhinaaxia; ***Gr.:*** Rhinaaxia†; ***Hong Kong:*** Naaxia; ***Hung.:*** Naaxia; Rhinaaxia†; ***Ital.:*** Naaxia; Rhinaaxia; ***Philipp.:*** Naaxia; ***Port.:*** Naabak; Naaxia†; ***Singapore:*** Naabak; ***Spain:*** Naaxia; ***Switz.:*** Rhinaaxia†; ***Turk.:*** Naaxia; ***Venez.:*** Naabak.

Multi-ingredient: ***Gr.:*** Naaxia; ***S.Afr.:*** Naaxia†; ***Switz.:*** Naaxia.

Isoxsuprine Hydrochloride *(BANM, rINNM)*

Caa-40; Hidrocloruro de isoxsuprina; Isoksupriinihydrokloridi; Isoxsuprin hydrochlorid; Isoxsuprine, chlorhydrate d'; Isoxsuprinhydroklorid; Isoxsuprini hydrochloridum; Izoksuprino hidrochloridas; Izoxszuprin-hidroklorid; Phenoxyisopropylnorsuprifen. 1-(4-Hydroxyphenyl)-2-(1-methyl-2-phenoxyethylamino)propan-1-ol hydrochloride.

Изоксуприна Гидрохлорид

$C_{18}H_{23}NO_3,HCl$ = 337.8.
CAS — 395-28-8 (isoxsuprine); 579-56-6 (isoxsuprine hydrochloride).
ATC — C04AA01.
ATC Vet — QC04AA01.

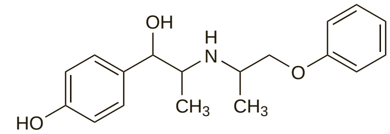

(isoxsuprine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Isoxsuprine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Isoxsuprine Hydrochloride). A white, odourless, crystalline powder. Soluble 1 in 500 of water, 1 in 100 of alcohol and of 0.1N sodium hydroxide solution, and 1 in 2500 of 0.1N hydrochloric acid; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 6.0. Store in airtight containers.

Adverse Effects

Isoxsuprine may cause transient flushing, hypotension, tachycardia, rashes, and gastrointestinal disturbances. Maternal pulmonary oedema and fetal tachycardia have been reported after intravenous use in premature labour.

Pulmonary oedema. Pulmonary oedema has been reported in mothers given isoxsuprine for premature labour.[1,2]

1. Nagey DA, Crenshaw MC. Pulmonary complications of isoxsuprine therapy in the gravida. *Obstet Gynecol* 1982; **59** (suppl): 38S–42S.
2. Nimrod C, *et al.* Pulmonary edema associated with isoxsuprine therapy. *Am J Obstet Gynecol* 1984; **148:** 625–9.

Precautions

Isoxsuprine is contra-indicated after recent arterial haemorrhage. It should not be given immediately post partum, nor should it be used for premature labour if there is infection.

In women being treated for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p.1132, apply.

Pregnancy. Ileus was found to be more common in the offspring of mothers who received isoxsuprine than in matched controls.[1] The incidence of respiratory distress syndrome also rose as the isoxsuprine concentration in cord blood exceeded 10 nanograms/mL; likewise the incidence of hypocalcaemia and hypotension rose progressively with increasing concentrations. The cord concentrations correlated inversely with the drug-free interval before delivery and it was suggested that with frequent assessment of uterine response it should be possible to avoid delivering infants at a time when they have high plasma-isoxsuprine concentrations.[1]

In another study[2] of the association between ruptured membranes, beta-adrenergic therapy, and respiratory distress syndrome, it was found that both therapy with isoxsuprine and premature rupture of membranes were individually associated with a lowered incidence of respiratory distress syndrome, but when present together they resulted in an increased risk of respiratory distress syndrome. It was suggested that therapy with beta-adrenergic drugs including isoxsuprine should be restricted to patients with intact membranes.[1]

1. Brazy JE, *et al.* Isoxsuprine in the perinatal period II: relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. *J Pediatr* 1981; **98:** 146–51.
2. Curet LB, *et al.* Association between ruptured membranes, tocolytic therapy, and respiratory distress syndrome. *Am J Obstet Gynecol* 1984; **148:** 263–8.

Pharmacokinetics

Isoxsuprine hydrochloride is well absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 1 hour after an oral dose. A plasma half-life of about 1.5 hours has been reported. Isoxsuprine is excreted in the urine mainly as conjugates.

Uses and Administration

Isoxsuprine is a vasodilator that also stimulates beta-adrenergic receptors. It causes direct relaxation of vascular and uterine smooth muscle and its vasodilating action is greater on the arteries supplying skeletal muscles than on those supplying skin. Isoxsuprine also produces positive inotropic and chronotropic effects.

Isoxsuprine hydrochloride has been used to arrest premature labour (p.2003), but drugs with a more selective action are now preferred. It has also been given in the treatment of cerebral and peripheral vascular disease.

For use as a vasodilator, isoxsuprine hydrochloride is given by mouth in doses of 10 to 20 mg 3 or 4 times daily.

To arrest premature labour, isoxsuprine hydrochloride is given initially by intravenous infusion in doses of 200 to 500 micrograms/minute, adjusted according to the patient's response, until control is achieved. It is now common practice to give beta agonists by syringe pump when using them to delay premature labour. Maternal blood pressure and hydration, and maternal and fetal heart rates should be monitored during the infusion. Once labour has been arrested intramuscular injections of 10 mg are given every 3 to 8 hours for several days. Prophylaxis may be continued by mouth with 30 to 90 mg daily in divided doses.

The resinate has also been used similarly.

Preparations

USP 31: Isoxsuprine Hydrochloride Injection; Isoxsuprine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Duvadilan; Fadaespasmol†; Isodilan; Isotenk; Samaruc; Uterine; ***Austria:*** Xuprin; ***Braz.:*** Inibina; ***Gr.:*** Duvadilan†; ***India:*** Duvadilan; ***Indon.:*** Duvadilan; Hystolan; ***Israel:*** Vasolan†; ***Ital.:*** Vasosuprina Ilfi; ***Mex.:*** Vadosilan; ***Philipp.:*** Duvadilan; Isoxilan; ***Port.:*** Dilum; ***Thai.:*** Duvadilan†; ***USA:*** Vasodilan; Voxsuprine; ***Venez.:*** Duvadilan.

Ivy

Břečťanový list (ivy leaf); Efeu; Gebenių lapai (ivy leaf); Hederae folium (ivy leaf); Herba Hederae Helicis; Lierre, feuille de (ivy leaf); Lierre Grimpant; Muratinlehti (ivy leaf); Murgröneblad (ivy leaf).

Pharmacopoeias. *Eur.* (see p.vii) includes the leaf and also a form for homoeopathic preparations.

Ph. Eur. 6.2 (Ivy Leaf; Hederae Folium). The whole or cut, dried leaves of *Hedera helix*, collected in the spring. It contains a minimum of 3% of hederacoside C ($C_{59}H_{96}O_{26}$ = 1221.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 6.2 (Hedera Helix for Homoeopathic Preparations; Hedera Helix ad Praeparationes Homoeopathicas). The fresh, young, fully developed but not yet lignified branch of *Hedera helix*, harvested immediately before or at the beginning of flowering. Protect from light.

Profile

The dried leaves of ivy, *Hedera helix* (Araliaceae), contain saponins, and extracts are reported to have expectorant and spasmolytic actions. Ivy leaf is used for catarrh and chronic inflammation of the respiratory tract. It has also been applied externally.

Fresh ivy leaves can cause allergic contact dermatitis.

Homoeopathy. Ivy has been used in homoeopathic medicines under the following names: Hedera helix; Hed. hel.

◊ Reviews.

1. Hofmann D, *et al.* Efficacy of dry extract of ivy leaves in children with bronchial asthma—a review of randomized controlled trials. *Phytomedicine* 2003; **10:** 213–220.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Athos; Cedric; ***Austria:*** Prospan; Sedo-Efeu; ***Braz.:*** Abrilar; ***Chile:*** Aeromed; Hedilar; ***Cz.:*** Hedelix; Helixir; Prospan; ***Fr.:*** Activox Lierre; Prospan; ***Ger.:*** Bronchilon; Bronchoforton; Bronchostad Hustenloser; Cefapulmon mono†; Efeu; Gallith; Hedelix; Prospan; Sedotussin Efeu; Sinuc; Tuma; ***Gr.:*** Prospan; ***Ital.:*** Vertuss; ***Malaysia:*** Prospan; ***Mex.:*** Panoto-S; ***Pol.:*** Bronchopect; Hedelix; Hederasal; Hederoin; Helical; Prospan; ***Singapore:*** Prospan; ***Spain:*** Arkotux; ***Switz.:*** Comprimes contre la toux†; DemoPectol Junior; Prospan; Pumonal eco natura; ***Venez.:*** Prospan.

Multi-ingredient: ***Arg.:*** Celu-Atlas; Expectosan Hierbas y Miel; Garcinol Max†; Nio Marine; Snell Patch; Varisedan Gel; ***Austral.:*** Asa Tones; ***Austria:*** Bronchipret; ***Fr.:*** Bronchipret; Muc-Sabona†; Naranopect P; Tussiflorin forte†; ***Hung.:*** Bronchipret; ***Indon.:*** Bronchipret; ***Ital.:*** Dermoprolyn†; Flebolider; Golatux; Hederix; ***Pol.:*** ApiHelix; Hedelicum; PiniHelix; ***Rus.:*** Bronchipret (Бронхипрет); Insti (Инсти); ***Spain:*** H Tussan; ***Switz.:*** Bronchofluid N†; Bronchosan Nouvelle formule†; Demo Elixir pectoral N; DemoPectol; Dragees S contre la toux†; Drosinula†; Foral†; Hederix; Kernosan Elixir; Liberol Dragees contre la toux†; Liberol Sirop contre la toux†; Pastilles pectorales Demo N; ***Thai.:*** Solvopret.

Jamaica Dogwood

Fish Poison Bark; Piscidia.

Profile

Jamaica dogwood, the root bark of *Piscidia erythrina* (*P. piscipula*; *Ichthyomethia piscipula*) (Leguminosae), has analgesic, antispasmodic, and sedative properties. It is mainly used for insomnia due to neuralgia or nervous tension. The bark and twigs of Jamaica dogwood have been used as a fish poison.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Jouvence de l'Abbe Soury; Schoum; ***Ital.:*** Sedatol; Soluzione Schoum; ***Spain:*** Solucion Schoum; ***UK:*** Anased; HRI Calm Life; Nodoff; Slumber; ***Venez.:*** Femendol.

Java Tea

Arbatinių inkstažolių lapai; Jaavalainen tee, Intialainen munuaisteе; Jávai vesetealevél; Javate; Orthosiphon; Orthosiphonblätter; Orthosiphonis folium; Ortosifón; Trubkovcový list.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Java Tea). The fragmented, dried leaves and tops of stems of *Orthosiphon stamineus* (*O. aristatus*; *O. spicatus*). Protect from light.

Profile

Java tea is used in herbal medicine mainly for the treatment of urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Urosiphon; ***Ger.:*** Ardeynephron; Carito mono; Diurevit Mono; Nephronorm med; Orthosiphonblatter Indischer Nierentee; Repha Orphon.

Multi-ingredient: ***Austria:*** Solubitrat; ***Fr.:*** Dellova†; Promincil†; Tealine†; ***Ger.:*** Aqualibra; BioCyst; Canephron novo†; Dr. Scheffler Bergischer Kräutertee Blasen- und Nierentee; Harntee 400 N; Harntee STADA; Harntee-Steiner; Heumann Blasen- und Nierentee Solubitrat S†; Hevert-Blasen-Nieren-Tee N; Heweberberol-Tee; Nephro-Pasc†; Nephronorm med†; Nephropur tri†; Nephrubin-N†; Nierentee 2000†; Nieron Blasen- und Nieren-Tee VI†; Presselin Arterien K 5 P†; Presselin Nieren-Blasen K 3†; Urodil phyto†; ***Indon.:*** Renax; ***Ital.:*** Lipaven; ***Pol.:*** Ginjal; ***Spain:*** Lepisor†; Urisor†; ***Switz.:*** Bilifuge; Demonatur Dragees pour les reins et la vessie; Phytomed Nephro†; Prosta-Caps Chassot N; Tisane pour les reins et la vessie.

Jin Bu Huan

Profile

Jin bu huan is a traditional Chinese remedy used as a sedative and analgesic and variously stated to contain *Lycopodium serratum* or *Polygala chinensis*. Adverse effects including CNS depression and acute hepatotoxicity have been attributed to its alkaloidal content of L-tetrahydropalmatine.

Adverse effects. Acute hepatitis has been reported in 7 previously healthy patients after taking jin bu huan; symptoms occurred again in 2 after re-use.[1] It was noted that the content of plant material did not seem to correspond to the labelled species. Hepatitis and extreme fatigue have also been reported in 3 adults after taking jin bu huan for periods ranging from 6 days to 6 months.[2]

Accidental ingestion of jin bu huan by 3 children[2] produced profound lethargy and muscle weakness. Two of the children also developed respiratory depression and bradycardia.

1. Woolf GM, *et al.* Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med* 1994; **121:** 729–35.
2. Horowitz RS, *et al.* The clinical spectrum of jin bu huan toxicity. *Arch Intern Med* 1996; **156:** 899–903.

Juniper

Baccae Juniperi; Boróka tobozbogyó; Enbär; Enebro; Genièvre; Iuniperi pseudo-fructus; Jalovcový plod; Juniper Berry; Juniper Fruit; Juniperi Fructus; Juniperi Galbulus; Juniperi Pseudo-fructus; Kadagių vaisiai; Katajanmarja; Szyszkojagoda jałowca; Wacholderbeeren; Zimbro.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Juniper). The dried ripe cone berry of *Juniperus communis*. It contains not less than 1% v/w of essential oil, calculated with reference to the anhydrous drug. It has a strongly aromatic odour, especially if crushed. Protect from light.

Profile

Juniper is the source of juniper oil (below). It has carminative, diuretic, antiseptic, and anti-inflammatory properties. It is used in herbal medicine and as a flavour in gin.

Homoeopathy. Juniper has been used in homoeopathic medicines under the following names: Juniperus communis; Juniperus communis sicc.; Juniperus communis e fructibus siccatis; Junip. c.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Plod Jalovce†.

Multi-ingredient: ***Arg.:*** Water Pill c Potasio†; ***Austral.:*** Arthritic Pain Herbal Formula 1; Lifesystem Herbal Formula 1 Arthritic Aid†; Profluid†; Protemp†; ***Austria:*** Mariazeller; St Bonifatius-Tee; ***Braz.:*** Pilulas De Witt's†; ***Canad.:*** Herbal Diuretic; Herbal Laxative plus Yogurt; ***Cz.:*** Abfuhr-Heilkrautertee†; ***Fr.:*** Depuratum; Mediflor Tisane Antirhumatismale No 2; ***Ger.:*** Amara-Tropfen; Gastrol S†; Junisana†; Presselin Stoffwechsel-Tee Hapeka 225 N†; ***Ital.:*** Broncosedina; ***Pol.:*** Cholesol; ***S.Afr.:*** Amara; ***Switz.:*** Heparfelien; Kernosan Heidelberger Poudre; Phytomed Nephro†; Tisane pour les reins et la vessie; ***UK:*** Backache; Watershed.

Juniper Oil

Borókaolaj; Enbärsolja; Enebro, aceite esencial de; Essence de Genièvre; Genièvre, huile essentielle de; Iuniperi aetheroleum; Jalovcová silice; Juniper Berry Oil; Juniperi Aetheroleum; Juniperi Etheroleum; Kadagių vaisių eterinis aliejus; Katajanmarjaöljy; Oleum Juniperi; Wacholderöl.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Juniper Oil). The essential oil obtained by steam distillation from the ripe, non-fermented berry cones of *Juniperus communis*. A suitable antoxidant may be added. A mobile, colourless to yellowish liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Juniper oil has been used as a carminative and as an ingredient of herbal remedies for urinary-tract disorders and muscle and joint pain. It is also used in aromatherapy. Prolonged use may cause gastrointestinal irritation and there may be a risk of renal damage from high doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Caprisana†; Leukona-Stoffwechsel-Bad†; Roleca Wacholder.

Multi-ingredient: ***Austral.:*** Medinat PMT-Eze†; ***Austria:*** Berggeist; ***Belg.:*** Olbas; ***Braz.:*** Solvobil; ***Ger.:*** Dolo-cyl; Kneipp Rheumabad; Nierentee 2000†; Nieroxin N†; Olbas; ***Ital.:*** Flodolor; Otosan Natural Ear Drops†; ***Pol.:*** Analgol; Olbas; Pinimentol; Pulmonil; ***S.Afr.:*** Oleum Salviae Comp; ***Spain:*** Emolytar; Polytar; ***Switz.:*** Bain antirhumatismal†; Frixo-Dragon Vert†; Huile Po-Ho A. Vogel; Liberol Baby N; Olbas; Pinimenthol Baby†; Spagyrom; Ziegella; ***UK:*** Diuretabs; HealthAid Boldo-Plus; Olbas; Olbas for Children; Sciargo; St Johnswort Compound; Watershed.

Kallidinogenase *(BAN, rINN)*

Callicrein; Kalidinogenasa; Kalléone; Kallidinogenaasi; Kallidinogenas; Kallidinogénase; Kallidinogenasum; Kallikrein.

Каллидиногеназа

CAS — 9001-01-8.
ATC — C04AF01.
ATC Vet — QC04AF01.

Pharmacopoeias. In *Jpn.*

Profile

Kallidinogenase is an enzyme isolated from the pancreas and urine of mammals. It converts kininogen into the kinin, kallidin. Kallidinogenase has been used in male infertility (p.2080) since the kallikrein-kinin system has a physiological role in the male genital tract. It also has vasodilating properties and has been used in the treatment of peripheral vascular disease (p.1178).

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Padutin.

Kava

Kava-Kava.

CAS — 500-64-1 (kawain); 495-85-2 (methysticin); 500-62-9 (yangonin).

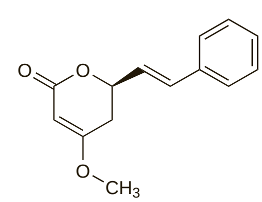

(kawain)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of kava:
'ava; 'awa; Grog; Kawa; Lewena; Sakau; Waka; Wati; Yaqona.

Profile

Kava is the rhizome of *Piper methysticum* (Piperaceae), a shrub indigenous to islands of the South Pacific. It contains pyrones including kawain, methysticin, and yangonin. Kava has been used in the South Pacific to produce an intoxicating beverage used for recreational purposes and during convalescence. It is reported to have sedative, skeletal muscle relaxant, and anaesthetic properties. It is given in some anxiety- and stress-related disorders. It was formerly used as an antiseptic and diuretic in inflammatory conditions of the genito-urinary tract in the form of a liquid extract. Kawain has also been used for nervous disorders and as a tonic.

A characteristic rash resembling that of pellagra occurs in some heavy consumers of kava. Extrapyramidal effects and cases of hepatitis have been reported. Preparations of kava for internal use have been withdrawn in the UK and some other western countries on account of its potential for serious hepatotoxic effects.

Homoeopathy. Kava has been used in homoeopathic medicines under the following names: Piper methysticum; Piper. m.

◊ References.

1. Anonymous. Kava. *Lancet* 1988; **ii:** 258–9.
2. Anonymous. Tonga trouble. *Pharm J* 1990; **245:** 288.
3. Ruze P. Kava-induced dermopathy: a niacin deficiency? *Lancet* 1990; **335:** 1442–5.
4. Schelosky L, *et al.* Kava and dopamine antagonism. *J Neurol Neurosurg Psychiatry* 1995; **58:** 639–40.
5. Spillane PK, *et al.* Neurological manifestations of kava intoxication. *Med J Aust* 1997; **167:** 172–3.
6. Pepping J. Kava: piper methysticum. *Am J Health-Syst Pharm* 1999; **56:** 957–60.
7. Anonymous. Kava extract linked to hepatitis. *WHO Drug Inf* 2000; **14:** 98.
8. Escher M, *et al.* Hepatitis associated with kava, a herbal remedy for anxiety. *BMJ* 2001; **322:** 139.
9. Anonymous. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland, 1999-2002. *MMWR* 2002; **51:** 1065–7. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm (accessed 15/07/04)
10. Stickel F, *et al.* Hepatitis induced by Kava (Piper methysticum rhizoma). *J Hepatol* 2003; **39:** 62–7.
11. Clouatre DL. Kava kava: examining new reports of toxicity. *Toxicol Lett* 2004; **150:** 85–96.
12. Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (Piper methysticum Forst. f.). *J Ethnopharmacol* 2004; **93:** 153–60.
13. Perez J, Holmes JF. Altered mental status and ataxia secondary to acute Kava ingestion. *J Emerg Med* 2005; **28:** 49–51.
14. Ulbricht C, *et al.* Safety review of kava (Piper methysticum) by the Natural Standard Research Collaboration. *Expert Opin Drug Saf* 2005; **4:** 779–94.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Ansiopax†; Calmiton†; Calmonex; Farmakava†; Kavakan; Kavalac†; Kavamed; Kavasedon; Laitan; Natuzilium†; ***Chile:*** Laikan 100†; ***Cz.:*** Antares†; Kavasedon†; Leikan†; ***Ger.:*** Aigin†; Ardeydystin†; Eukavan†; Kasabona†; Kava-Phyton†; Kavain Harras N†; Kavasedon†; Kavosporal forte†; Laitan†; Maoni†; Nervonocton N†; Neuronika†; ***Mex.:*** Laiken; ***Switz.:*** Kavasedon†; ***Venez.:*** Kavasedon†.

Multi-ingredient: ***Ger.:*** Bilicura Forte†; Hewepsychon duo†; Hyposedon N†; Kavosporal comp†; Somnuvis S†; ***Ital.:*** Controller; ***Switz.:*** Kawaform†; Yakona N†.

Keracyanin *(rINN)*

Cyaninoside; Keracianina; Kéracyanine; Keracyaninum. 3-[6-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-3′,4′,5,7-tetrahydroxyflavylium chloride.

Керацианин

$C_{27}H_{31}ClO_{15}$ = 631.0.
CAS — 18719-76-1.

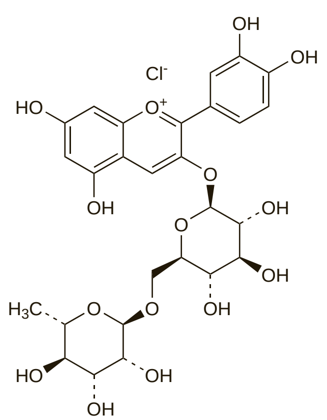

Profile

Keracyanin is claimed to improve visual function in poor light conditions and has been given orally in vision disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Meralop†; ***Spain:*** Meralop†.

Keratinase

Queratinasa.
CAS — 9025-41-6.

Profile

Keratinase is a proteolytic enzyme that has been obtained from cultures of *Streptomyces fradiae*. It can digest keratin, which is resistant to most proteolytic enzymes, in the presence of trace amounts of metal ions. It is used in the commercial separation of hair from animal hides, and has been tried as a depilatory; it has also been included in some topical antibacterial ointments, presumably to aid penetration of the active substances.

Kinkeliba

Combreti Folium; Kinkéliba.

Pharmacopoeias. In *Fr.*

Profile

Kinkeliba is the dried leaves of *Combretum micranthum* (*C. altum*; *C. raimbaultii*) (Combretaceae), a shrub indigenous to West Africa. It has been used as an ingredient of herbal remedies given for the treatment of biliary, liver, and gastrointestinal disorders. Other species of *Combretum* are also used.

Homoeopathy. Kinkeliba has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Hepaclem; Hepax; Jecopeptol; Mediflor Tisane Hepatique No 5; Romarene; Solution Stago Diluee; ***Mon.:*** Romarinex; ***Switz.:*** Bilifuge.

Klebsiella Pneumoniae Glycoprotein

Glucoproteína de Klebsiella pneumoniae; RU-41740.

Profile

Klebsiella pneumoniae glycoprotein is an immunostimulant that has been used in the management of respiratory-tract infections, wounds, and burns.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Biostim; ***Cz.:*** Biostim; ***Fr.:*** Biostim†; ***Ital.:*** Acintor; Biostim; ***Mex.:*** Biostim; ***Port.:*** Biostim†.

Knotgrass

Knotweed; Nat' rdesna ptačího; Pihatatar; Polygoni avicularis herba; Renouée des oiseaux; Takažolių žolė; Trampgräs; Vogelknöterichkraut; Ziele rdestu ptasiego.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Knotgrass; Polygoni Avicularis Herba). It consists of the whole or cut, dried aerial parts of *Polygonum aviculare*. It contains not less than 0.3% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

Profile

Knotgrass, *Polygonum aviculare* (*P. heterophyllum*) (Polygonaceae), is included in herbal preparations for mild catarrh and associated upper respiratory-tract disorders.

Homoeopathy. Knotgrass has been used in homoeopathic medicines under the following names: Polygonum aviculare.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Pulmoran; Species Urologicae Planta; ***Pol.:*** Cholesol; Reumosol.

Krebiozen

Crebiocén.

Кребиозен

CAS — 9008-19-9.

Profile

Krebiozen is the name of a preparation that was formerly promoted as a 'cancer cure' in the USA, but totally discredited by the FDA. It was stated to be obtained from the blood of horses previously injected with an extract of *Actinomyces bovis*.

Kveim Antigen

Antígeno de Kveim.

Profile

Kveim antigen is a fine suspension in physiological saline of sarcoid tissue prepared from spleens taken from patients with active sarcoidosis. It is used as an intradermal injection in the Kveim (Kveim-Siltzbach) test for the diagnosis of sarcoidosis (p.1512).

◊ References.

1. James DG, Williams WJ. Kveim-Siltzbach test revisited. *Sarcoidosis* 1991; **8:** 6–9.

◊ The safety of the Kveim test has been questioned, particularly with reference to the risk of transmission of sarcoidosis, and of hepatitis B, HIV, and Creutzfeldt-Jakob disease.[1] However, the procedure to identify acceptable sarcoid spleens and the method of preparation were considered sufficient to reduce the risk of transmission of infections[2] and of Creutzfeldt-Jakob disease.[3]

1. Wigly RD. Moratorium on Kveim tests. *Lancet* 1993; **341:** 1284.
2. du Bois RM, *et al.* Moratorium on Kveim tests. *Lancet* 1993; **342:** 173.
3. de Silva RN, Will RG. Moratorium on Kveim tests. *Lancet* 1993; **342:** 173.

Laburnum

Golden Chain; Golden Rain; Lluvia de oro.

Profile

All parts of laburnum, *Laburnum anagyroides* (*L. vulgare*; *Cytisus laburnum*) (Leguminosae), are toxic. The toxic principle is cytisine (p.2291) which has actions similar to nicotine.

Lactic Acid

Acide lactique; Acidum lacticum; E270; E326 (potassium lactate); Kwas mlekowy; Kyselina mléčná; Láctico, ácido; Laktik Asit; Maitohappo; Milchsäure; Mjölksyra; Pieno rūgštis; Tejsav. 2-Hydroxypropionic acid; 2-Hydroxypropanoic acid.

$C_3H_6O_3$ = 90.08.
CAS — 50-21-5; 79-33-4 ((+)-lactic acid); 10326-41-7 ((−)-lactic acid); 598-82-3 ((±)-lactic acid).
ATC — G01AD01.
ATC Vet — QG01AD01; QP53AG02.

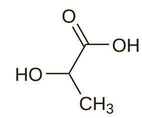

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.
Eur. (see p.vii) includes monographs for the racemate and the (*S*)-enantiomer.

Ph. Eur. 6.2 (Lactic Acid). A mixture of lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It is usually the racemate (*RS*-lactic acid), and contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

Ph. Eur. 6.2 ((*S*)-Lactic Acid). A mixture of (*S*)-lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$, of which not less than 95% is the (*S*)-enantiomer. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

USP 31 (Lactic Acid). A mixture of lactic acid and lactic acid lactate equivalent to a total of 88 to 92% w/w of $C_3H_6O_3$. It is obtained by the lactic fermentation of sugars or is prepared synthetically. Lactic acid obtained by fermentation of sugars is laevorotatory, while that prepared synthetically is racemic.

A colourless or yellowish, hygroscopic, practically odourless, syrupy liquid. When it is concentrated by boiling, lactic acid lactate is formed. Miscible with water, with alcohol, and with ether; insoluble in chloroform. Store in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322, although in the concentrations used it is less corrosive.

Neonates. There was evidence that neonates had difficulty in metabolising *R*-(−)-lactic acid and this isomer and the racemate should not be used in foods for infants less than 3 months old.[1]

1. FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications: seventeenth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 539* 1974.

Uses and Administration

Lactic acid has actions similar to those of acetic acid (p.2244) and has been used similarly in the treatment of infective skin and vaginal disorders. It has been used in the preparation of lactate injections and infusions to provide a source of bicarbonate for the treatment of metabolic acidosis (for the problems of using lactate in metabolic acidosis, see p.1667). It is also applied topically in the treatment of warts (p.1584), often with salicylic acid, and in emollient creams. Other uses include the treatment of severe aphthous stomatitis in terminally ill, immunocompromised patients.

Lactic acid has also been used as a food preservative and as an ingredient of cosmetics.

Preparations

BP 2008: Lactic Acid Pessaries;
USP 31: Compound Clioquinol Topical Powder.

Proprietary Preparations (details are given in Part 3)
Arg.: Celucrem†; ***Austria:*** Espritin; Warzin; ***Belg.:*** Lacta-Gynecogel; ***Braz.:*** Verrux; ***Canad.:*** Dermalac; Lubriderm AHA†; Penederm†; ***Chile:*** Eucerin; ***Fr.:*** Ictyoderm†; Lactacyd Femina; ***Ger.:*** Lactisan; Lactisol; RMS†; ***Irl.:*** Relact; ***Ital.:*** Saugella Intilac; Unigyn; ***Malaysia:*** Avecyde†; ***Mex.:*** Acid-Lac; Avecyde; Eucerin Piel con Tendencia Acneica†; Lactibon; ***NZ:*** BK†; ***Philipp.:*** Lactacyd VG; ***Pol.:*** Keratolysin; ***Port.:*** Atopic†; ***Singapore:*** Avecyde†; ***Spain:*** Keratisdin; ***Swed.:*** Calmuril; ***Switz.:*** Vagoclyss; ***USA:*** Lactinol; Lactrex; ***Venez.:*** Dermalact; Jabolac†; Lactibon.

Multi-ingredient: ***Arg.:*** Acilac; Akerat; Callicida; Caminol†; Cellskinlab C + AHA; Coltix†; Controlacne; Dermocridin; Duofilm; Hidrolac; Keracnyl; Lacticare; Muvar; Nutrafilm; Opoenterol†; Oxidermos; Pasem; Ureadin Facial; Verruclean; Verrutopic; ***Austral.:*** Aussie Tan Skin Moisturiser; Calmurid; Cornkil†; Dermadrate; Dermatech Wart Treatment; Duofilm; ***Austria:*** Calmurid; Calmurid HC; Duofilm; Helo-acid; Hylak; Hylak Forte; Lavagin; ***Belg.:*** Aporil; Calmurid†; ***Braz.:*** Calope†; Calotrat†; Colpolase;

Dermacyd; Dermafree; Duofilm; Kalostop†; Lacticare; Lacto Vagin†; Salic; ***Canad.:*** Duofilm; Duoplant; Epi-Lyt; P & S; Penederm†; Viron Wart Lotion; ***Chile:*** Akerat; Cuidado Intimo; Duofilm; Eucerin Piel Grasa; Lactacyd; Lacticare†; Node DS; Primacy C+AHA†; Ureadin 30; ***Cz.:*** Acne Lotio†; Duofilm; ***Denm.:*** Verucid; ***Fin.:*** Calmuril; Wicnelact; ***Fr.:*** Akerat; Cleanance K; Contragel Vert; Correcteur Anti-Taches; Duofilm; Geliofil; Keracnyl; Kerafilm; Lactacyd Derma; Lactacyd Femina; Lacticare; Pedi-Relax Anti-callosites†; Propy-Lacticare; Saugella; Sebium AKN; Topic 10; Verrufilm; Verrupan; ***Ger.:*** Akaderm N; Calmurid†; Clabin; Collomack†; Duofilm; Gehwol Huhneraugen Pflaster†; Sagrosept†; Solco-Derman; Vagisan; W-Tropfen; Warzen-Alldahin†; ***Gr.:*** Duofilm; ***Hong Kong:*** Collomack; Dermadrate; Dermatech Wart Treatment; Duofilm; Eubos Feminin; Lactacyd; Lacticare†; Solcoderm; Verrufilm; ***Hung.:*** Duofilm; ***India:*** Cotaryl; Lacgel; ***Indon.:*** Exfoliac; Lactacyd; Lacticare; ***Irl.:*** Calmurid; Calmurid HC; Cuplex; Duofilm; Lacticare; Salactol; Salatac; ***Israel:*** Babyzim; Calmurid; Calmurid HC†; Salatac; U-Lactin Foot Cream; U-Lactin Forte; ***Ital.:*** Bruciaporri; Decon Lavanda; Duofilm; Eudermico†; Gastro-Pepsin; Geliofil; Geroderm Zolfo†; Ginil; Ipso Urea; Kerafilmver; Lactacyd Derma; Lactacyd Intimo; Lactocol; Saugella Salviettine; Sensigel; Sensiquell; Triacid; Unidermo; Verel; Verunec; ***Malaysia:*** Collomack†; Duofilm; Lactacyd; Lacticare; Lorasil Feminine Hygeine†; Solcoderm†; ***Mex.:*** Duofilm; Kinor; Lacticare; Rug-Derm; Urader Lactato; ***Neth.:*** Calmurid; Calmurid HC; Duofilm; ***Norw.:*** Verucid; ***NZ:*** Calmurid†; Dermadrate; Duofilm; ***Philipp.:*** Duofilm; Intima; Lactacyd; Lacticare; ***Pol.:*** ABE-Plyn; Acerin; Brodacid; Duofilm; Masc na Odciski; ***Port.:*** Atopic†; Bioclin Sebo Care; Calicida Indiano; Calmurid; Creme Laser Hidrante; Despigmentante; Duofilm†; Halitol†; Lactacyd†; Lecia†; Pansebase; Pansebase Composto; Secpel; Secpel Composto; Ureadin Maos; Verrucare; ***Rus.:*** Solcoderm (Солкодерм); ***S.Afr.:*** Duofilm; Kroko; Lacticare; ***Singapore:*** Collomack†; Dermadrate; Dermatech Wart Treatment; Duofilm; Lactacyd; Lacticare; U-Lactin; ***Spain:*** Antiverrugas; Callicida Cor Pik; Callix; Euzymina Lisina I; Ginejuvent; Keranin; Roidhemo†; Unguento Callicida Naion; Verufil; ***Switz.:*** Calmurid; Calmurid HC†; Clabin; Coruzol†; Duofilm; Solcoderm; Va-t'en; Vin Tonique de Vial†; Waruzol; Warz-ab Extor; ***Thai.:*** Collomack†; Duofilm; Lactacyd; Lacticare; ***Turk.:*** Duoderm; ***UK:*** Bazuka; Calmurid; Calmurid HC; Cuplex; Duofilm; Lacticare†; Salactol; Salatac; ***USA:*** AmLactin AP; Epi-Lyt; Lacticare; Lactinol-E; SLT†; ***Venez.:*** Akerat; Collomack; Duofilm†; Kayivis.

Lactobionic Acid

Acide Lactobionique; Acidum lactobionicum; Kwas laktobionowy; Kyselina laktobionová; Laktobionihappo; Laktobiono rūgštis; Laktobionsyra.

CAS — 96-82-2 (4-O-β-D-galactopyranosylD-gluconic acid).

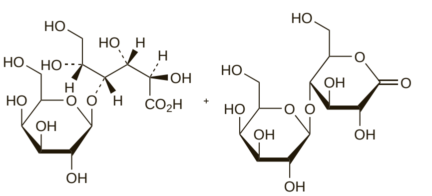

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lactobionic Acid). A mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid ($C_{12}H_{22}O_{12}$ = 358.3) and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone ($C_{12}H_{20}O_{11}$ = 340.3). A white or almost white powder. Freely soluble in water; slightly soluble in anhydrous ethanol, methyl alcohol, and glacial acetic acid.

Profile

Lactobionic acid is used to form water-soluble salts of drugs such as calcium and the macrolide antibacterials clarithromycin and erythromycin. It is present, in the form of potassium lactobionate, in preservation fluids such as UW (University of Wisconsin) solution for organ transplantation; the lactobionate anion acts as an impermeant and provides an osmotic force to oppose cellular oedema in the stored organ. Lactobionic acid has similar properties to gluconic acid (p.2313) and is being tried in skin care products.

Lactoferrin

Lactotransferrin; rhLF (talactoferrin alfa).

CAS — 308240-58-6 (talactoferrin alfa).

Profile

Lactoferrin is an iron-binding protein found in milk, saliva, and other exocrine secretions. It has antimicrobial actions and has been used in preparations for the management of dry mouth (p.2140) and other mouth disorders.

Lactoferrin and other whey proteins have also been used as nutritional supplements. Recombinant forms of lactoferrin such as talactoferrin alfa are under investigation.

◊ Reviews.

1. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004; **9:** 136–56.
2. Valenti P, *et al.* Lactoferrin functions: current status and perspectives. *J Clin Gastroenterol* 2004; **38** (suppl 2): S127–S129.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Immune Boost; ImmunoDefence; ***Ital.:*** Endvir Simplex.

Multi-ingredient: ***Indon.:*** Laktobion; ***Ital.:*** Liverton; Nepiros; Rivuclin; ***Singapore:*** Biotene; ***UK:*** Biotene Dry Mouth; BioXtra†; ***USA:*** Biotene with Calcium.

Lactoperoxidase

CAS — 9003-99-0.

Profile

Lactoperoxidase is a peroxidase enzyme that is present in milk and saliva. It reacts with hydrogen peroxide and thiocyanate to produce an antibacterial effect and has been used in preparations for the management of dry mouth (p.2140) and other mouth disorders. It has also been used for its preservative action in cosmetics and skin-care products.

In the lactoperoxidase system for milk preservation, sodium thiocyanate and sodium percarbonate (a source of hydrogen peroxide) are added to fresh bovine milk to activate the lactoperoxidase it contains.

◊ Reviews.

1. Kussendrager KD, van Hooijdonk AC. Lactoperoxidase: physico-chemical properties, occurrence, mechanism of action and applications. *Br J Nutr* 2000; **84** (suppl 1): S19–S25.
2. Tenovuo J. Clinical applications of antimicrobial host proteins lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. *Oral Dis* 2002; **8:** 23–9.
3. Lönnerdal B. Nutritional and physiologic significance of human milk proteins. *Am J Clin Nutr* 2003; **77** (suppl): 1537S–1543S.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Singapore:*** Biotene; ***UK:*** Biotene Dry Mouth; Biotene Oralbalance; BioXtra†; ***USA:*** Biotene with Calcium.

Laetrile

CAS — 1332-94-1 (laetrile); 29883-15-6 (amygdalin).

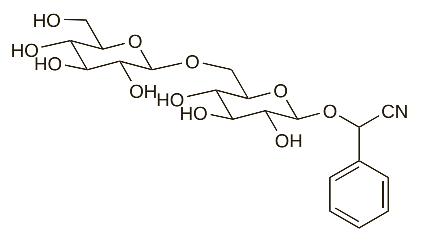

(amygdalin)

Profile

Laetrile is the term used for a product consisting chiefly of amygdalin, which is the major cyanogenic glycoside of apricot kernels. Amygdalin is *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosyl-β-D-glucopyranoside ($C_{20}H_{27}NO_{11}$ = 457.4). Laetrile is also used as a term for *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosiduronic acid ($C_{14}H_{15}NO_7$ = 309.3).

Laetrile was claimed to be preferentially hydrolysed in cancer cells by β-glucosidases to benzaldehyde and hydrogen cyanide, which killed the cell, but amygdalin does not appear to be absorbed from the gastrointestinal tract, and both normal and malignant cells contain only traces of β-glucosidases. Laetrile has also been claimed to be 'vitamin B_{17}', the deficiency of which is said to result in cancer; there is no evidence for this view and laetrile is of no known value in human nutrition.

There have been several reports of cyanide poisoning and other adverse reactions associated with the use of laetrile, especially when taken orally.

◊ A systematic review[1] concluded that data from controlled studies do not support the claims of efficacy for laetrile in cancer patients. Further references[2-4] to laetrile, including case reports[3,4] of toxic effects.

1. Milazzo S, *et al.* Laetrile treatment for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 17/07/08).
2. Chandler RF, *et al.* Controversial laetrile. *Pharm J* 1984; **232:** 330–2.
3. Bromley J, *et al.* Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. *Ann Pharmacother* 2005; **39:** 1566–9.
4. O'Brien B, *et al.* Severe cyanide toxicity from 'vitamin supplements'. *Eur J Emerg Med* 2005; **12:** 257–8.

Laminaria

Stipites Laminariae; Styli Laminariae; Thallus Eckloniae; Thallus Laminariae.

Pharmacopoeias. In *Chin.*

Profile

Laminaria is the dried stalks of the seaweeds *Laminaria japonica*, *L. digitata*, and possibly other species of *Laminaria*. The stalks swell in water to about 6 times their volume and have been used surgically to dilate cavities and to dilate the cervix in labour or abortion induction.

An extract of various species of *Laminaria* has been used as a dietary supplement (see Seaweeds, Kelps, and Wracks, p.2384).

Adverse effects. Anaphylaxis[1-3] and toxic shock syndrome[4] have been reported after the insertion of laminaria for cervical dilatation.

1. Nguyen MT, Hoffman DR. Anaphylaxis to laminaria. *J Allergy Clin Immunol* 1995; **95:** 138–9.
2. Cole DS, Bruck LR. Anaphylaxis after laminaria insertion. *Obstet Gynecol* 2000; **95:** 1025.
3. Chanda M, *et al.* Hypersensitivity reactions following laminaria placement. *Contraception* 2000; **62:** 105–6.
4. Sutkin G, *et al.* Toxic shock syndrome after laminaria insertion. *Obstet Gynecol* 2001; **98:** 959–61.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Okovidit (Оковидит).

Multi-ingredient: ***Fr.:*** Marinol; ***Spain:*** Fucusor†.

Lappa

Bardana; Bardanae Radix; Bardane (Grande); Burdock; Burdock Root; Lappa Root.

Pharmacopoeias. In *Fr.*

Chin. and *Jpn* include the fruits.

Profile

Lappa is the dried root of the great burdock, *Arctium lappa* (*A. majus*), and other species of *Arctium* (Compositae). It was formerly used in the form of a decoction as a diuretic and diaphoretic but there is little evidence of its efficacy. Herbal preparations containing lappa have been used in the treatment of skin, musculoskeletal, and gastrointestinal disorders. The leaves and fruits of *Arctium* spp. have also been used.

Homoeopathy. Lappa has been used in homoeopathic medicines under the following names: Lappa major; Lap. maj.

Preparations

Proprietary Preparations (details are given in Part 3)

Mex.: Saforelle†; ***Port.:*** Saforelle; ***Venez.:*** Saforelle.

Multi-ingredient: ***Austral.:*** Acne Oral Spray†; Dermaco; Herbal Cleanse†; Percutane; Trifolium Complex†; ***Canad.:*** Herbal Laxative; Natural HRT; ***Cz.:*** Diabetan; ***Fr.:*** Arbum; Depuratif Parnel; Fitacnol†; Zeniac LP†; Zeniac†; ***Ital.:*** Allerlux; ***Malaysia:*** Celery Plus†; Cleansa Plus†; Dandelion Complex†; ***Pol.:*** Betasol; Immunofort; Seboren; ***S.Afr.:*** Lotio Pruni Comp cum Cupro; ***Spain:*** Diabesor†; ***UK:*** Aqua Ban Herbal; Backache; Cascade; Catarrh Mixture; GB Tablets; Gerard House Skin; Gerard House Water Relief Tablets; HRI Clear Complexion; Modern Herbals Water Retention; Rheumatic Pain Remedy; Skin Cleansing; Skin Eruptions Mixture; Tabritis; Water Naturtabs.

Laronidase (USAN, rINN)

Alpha-L-iduronidase; Alronidase; Laronidasa; Laronidasum; Laronidaz. 8-L-Histidine-α-L-iduronidase (human).

Ларонидаз

CAS — 210589-09-6.
ATC — A16AB05.
ATC Vet — QA16AB05.

Adverse Effects, Treatment, and Precautions

Anaphylactic and other infusion reactions, sometimes delayed in onset, have been reported in patients given laronidase and facilities for resuscitation should be available whenever laronidase is used. Common symptoms include flushing, fever, headache, and rash; bronchospasm has also been reported. Other adverse effects commonly reported include abdominal pain, arthralgia, back pain, nausea, vomiting, diarrhoea, cough, dyspnoea, urticaria, angioedema, pruritus, chills, paraesthesia, dizziness, tachycardia, increased blood pressure, and decreased oxygen saturation. Patients with existing respiratory disease may be at risk of more severe reactions. Antihistamines and/or antipyretics (e.g. paracetamol or ibuprofen) may relieve symptoms. A reduction in the rate of infusion to half the rate at which the reaction occurred should also be considered for mild or moderate reactions; for severe reactions, the infusion should be stopped until symptoms have subsided, and then restarted at one-half to one-quarter the rate at which the reaction occurred. Adrenaline should be used with caution because there is a greater incidence of coronary artery disease in patients with mucopolysaccharidosis I. Pre-treatment with antihistamines and/or antipyretics about 60 minutes before infusion is recommended to prevent reactions. IgG antibodies to laronidase are expected to develop within 3 months of starting treatment in the majority of patients, although the effect of this on safety and efficacy is not clear. However, such patients may be at increased risk of hypersensitivity reactions and should be treated with caution. Injection site reactions have also been reported.

Interactions

Licensed product information for laronidase recommends that it should not be given with chloroquine or procaine because of the potential risk of interference with the intracellular uptake of the enzyme.

Uses and Administration

Laronidase is recombinant human α-L-iduronidase and is used as enzyme replacement therapy for the treatment of the non-neurological manifestations of mucopolysaccharidosis I (see below). It is given by intravenous infusion in a dose of 100 units/kg each week. The initial infusion rate should be 2 units/kg per hour, increased every 15 minutes during the first hour, as tolerated, to a maximum of 43 units/kg per hour such that the infusion is completed in about 3 to 4 hours (but see also under Adverse Effects, Treatment, and Precautions, above). In some countries, the dose is expressed as mg/kg: 100 units is equivalent to about 580 micrograms of laronidase.

Mucopolysaccharidosis I. Mucopolysaccharidosis I is a progressive disorder characterised by deficiency of the enzyme α-L-iduronidase, which is necessary to catalyse the hydrolysis of terminal α-L-iduronic residues of the glycosaminoglycans, dermatan sulfate and heparan sulfate. This results in their accumulation in tissues, with many clinical manifestations including hepatomegaly, skeletal abnormalities, pulmonary disease, eye disease, and progressive deterioration of the CNS. Mucopolysaccharidosis I has traditionally been classified into three main forms based on clinical symptoms and severity: Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome. Hurler syndrome is the most severe form with a life expectancy of less than 10 years. However, there is a degree of overlap between the syndromes and they are indistinguishable by routine enzyme or urine tests.

Treatment was previously limited to symptomatic management but other options to halt disease progression are now available. Haematopoietic stem-cell transplantation using bone marrow or umbilical cord blood is of benefit in systemic disease and can prevent (but not usually reverse) CNS deterioration. However, substantial adverse effects limit its use to patients with severe disease. Enzyme replacement therapy with laronidase has been reported to confer benefit on the systemic manifestations of the disease, but since it does not cross the blood-brain barrier in appreciable amounts, beneficial effect on CNS symptoms is again predicted to be unlikely. However, the improvements conferred by enzyme replacement therapy might make haematopoietic stem-cell transplantation easier to tolerate.

References.

1. Kakkis ED, *et al.* Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med* 2001; **344:** 182–8.
2. Wraith JE. Enzyme replacement therapy in mucopolysaccharidosis type I: progress and emerging difficulties. *J Inherit Metab Dis* 2001; **24:** 245–50.
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4. Kakavanos R, *et al.* Immune tolerance after long-term enzyme-replacement therapy among patients who have mucopolysaccharidosis I. *Lancet* 2003; **361:** 1608–13.
5. Muenzer J, Fisher A. Advances in the treatment of mucopolysaccharidosis type I. *N Engl J Med* 2004; **350:** 1932–4.
6. Staba SL, *et al.* Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med* 2004; **350:** 1960–9.
7. Wraith JE, *et al.* Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α-L-iduronidase (laronidase). *J Pediatr* 2004; **144:** 581–8.
8. Grewal SS, *et al.* Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. *Genet Med* 2005: **7:** 143–6.
9. Miebach E. Enzyme replacement therapy in mucopolysaccharidosis type I. *Acta Paediatr Suppl* 2005; **94** (suppl 447): 58–60.
10. Wraith JE, *et al.* Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human α- -iduronidase (laronidase). Abstract: *Pediatrics* 2007; **120:** 158. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/1/e37 (accessed 07/02/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Aldurazyme; ***Canad.:*** Aldurazyme; ***Cz.:*** Aldurazyme; ***Denm.:*** Aldurazyme; ***Fin.:*** Aldurazyme; ***Fr.:*** Aldurazyme; ***Ger.:*** Aldurazyme; ***Israel:*** Aldurazyme; ***Ital.:*** Aldurazyme; ***Neth.:*** Aldurazyme; ***Norw.:*** Aldurazyme; ***NZ:*** Aldurazyme; ***Pol.:*** Aldurazyme; ***Spain:*** Aldurazyme; ***Swed.:*** Aldurazyme; ***UK:*** Aldurazyme; ***USA:*** Aldurazyme.

Lavender

English Lavender; Kwiat lawendy (lavender flower); Lavande, fleur de (lavender flower); Lavande Vrai; Lavandulae flos (lavender flower); Lavendelblomma (lavender flower); Lavendelblüten; Laventelinkukka (lavender flower); Levandų žiedai (lavender flower); Levandulový květ (lavender flower); Levendulavirág (lavender flower).

Pharmacopoeias. *Eur.* (see p.vii) includes lavender flower.
Ph. Eur. 6.2 (Lavender Flower; Lavandulae flos). It consists of the dried flower of *Lavandula angustifolia* (*L. officinalis*). It contains not less than 1.3% v/w of essential oil, calculated with reference to the anhydrous drug. Protect from light.

Profile

Lavender flower is used as a sedative. It has also been used as a cholagogue. It is an ingredient of herbal remedies used for a variety of disorders.

Lavender flowers are the source of lavender oil (below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Lavandula Oligoplex; ***Austral.:*** Cimicifuga Compound; ***Austria:*** Euka; Mentopin; ***Braz.:*** Balsamo Branco; Traumac; ***Cz.:*** Melaton†; Schlaf-Nerventee N†; Valofyt Neo; ***Fr.:*** Mediflor Tisane Digestive No 3; ***Ger.:*** Presselin Dyspeptikum†; ***NZ:*** Botanica Hayfever; ***Pol.:*** Lumewal; Nervinolum; Nervosol; Reumobonisol; ***Port.:*** Cholagutt†; Erpecalm; ***S.Afr.:*** Krampdruppels; ***Spain:*** Linimento Naion; ***Switz.:*** Tisane relaxante N†; ***UK:*** Vital Eyes.

Lavender Oil

English Lavender Oil (from *L. intermedia*); Esencia de Alhucema; Esencia de Espliego; Essência de Alfazema; Foreign Lavender Oil (from *L. officinalis*); Huile Essentielle de Lavande; Lavanda, aceite esencial de; Lavande, huile essentielle de; Lavandulae aetheroleum; Lavandulae Etheroleum; Lavanta Yağı; Lavendelöl; Lavendelolja; Lavender Flower Oil; Laventeliöljy; Levandų eterinis aliejus; Levandulová silice; Olejek lawendowy; Oleum Lavandulae.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Lavender Oil). An essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* (*L. officinalis*). A colourless or pale yellow clear liquid with a characteristic odour. Relative density 0.878 to 0.892. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Lavender oil has been used as a carminative and as a flavour. It is sometimes applied externally as an insect repellent. Its chief use is in perfumery and it is occasionally used in ointments and other pharmaceutical preparations to cover disagreeable odours. It has been suggested that lavender oil may have sedative properties after inhalation. It is also used in aromatherapy.

Lavender oil has been reported to produce nausea, vomiting, headache, and chills when inhaled or absorbed through the skin. It may cause contact allergy and phototoxicity.

Adverse effects. There have been reports of contact dermatitis associated with lavender oil in a shampoo,[1] and facial dermatitis after application of the oil to pillows for its sedative properties.[2]

1. Brandão FM. Occupational allergy to lavender oil. *Contact Dermatitis* 1986; **15:** 249–50.
2. Coulson IH, Khan ASA. Facial 'pillow' dermatitis due to lavender oil allergy. *Contact Dermatitis* 1999; **41:** 111.

Insomnia. Ambient exposure to lavender oil produced similar sleep patterns to conventional sedatives in 4 elderly patients.[1]

1. Hardy M, *et al.* Replacement of drug treatment for insomnia by ambient odour. *Lancet* 1995; **346:** 701.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Lawenol.

Multi-ingredient: ***Austral.:*** Apex Repel Natural; Neutralice; ***Austria:*** Berggeist; Rowalind; ***Belg.:*** Mouskito Travel Milk; ***Braz.:*** Aliviol; Analgen†; Benegel; Gelflex; Gelol†; Gelonevral†; Inhalante Yatropan; Mentalol†; Mialgex†; Nevrol; Salimetin†; ***Cz.:*** Amol; Ondrejova Mast; Tiger Ol†; ***Fr.:*** Aromasol; Balsofumine; Balsofumine Mentholee; Ephydrol; Gouttes aux Essences; Maghora; Moustidose; Moustidose Bebe-Nourrisson; Paps; Pectoderme†; Perubore; Poudre du Marcheur; Resistim; ***Ger.:*** Amol Heilkrautergeist N; Dolo-cyl; Leber-Galle-Tropfen 83†; Solum Ol; ***Hong Kong:*** Calmiderm; ***Hung.:*** Opodeldok†; ***Israel:*** Headache Pads; ***Ital.:*** Citrosystem; Controller; Mistick Verde; Venalta; Vicks Baby Balsam†; ***NZ:*** Apex Repel Natural; Electric Blue Headlice; Vicks Baby Balsam; ***Pol.:*** Amol; Aromatol; Carmolis; ***Port.:*** Solubeol†; Vaporil; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; Espol (Эспол); ***S.Afr.:*** Arnica Massage Oil; Entressdruppels HM; Rooilavental; ***Spain:*** Dolokey; Termosan; ***Switz.:*** Baume du Chalet; Carmol; Dolo-Arthrosenex sine Heparino†; Hygiodermil; Liberol Bain†; Massorax†; Muco-Sana†; Nasobol†; Oculosan; Perskindol Classic; Perubare†; Pommade Nasale Radix†; Pulmex; Saltrates†; Spagyrom; Ziegella; ***Turk.:*** Algo-Wax; ***UK:*** Arnica Massage Balm; Eucanol; Larch Resin comp.; Massage Balm with Calendula; Migrastick; ***USA:*** Nasal Jelly; ***Venez.:*** Friccion Aromatica.

Lawsone

Lawsonia. 2-Hydroxy-1,4-naphthoquinone.
$C_{10}H_6O_3$ = 174.2.
CAS — 83-72-7.

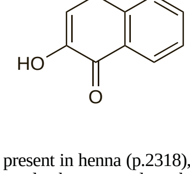

Profile

Lawsone is a dye present in henna (p.2318), the leaves of *Lawsonia* spp., and may also be prepared synthetically. It has been used with dihydroxyacetone in sunscreen preparations. There appears to be no evidence that it has any sunscreening properties when used alone.

Adverse effects. Observation that lawsone causes oxidative damage to red blood cells *in vitro* supported a suggestion that percutaneous absorption of henna could contribute to unexplained neonatal hyperbilirubinaemia in countries where the ceremonial use of henna is widespread.[1]

1. Zinkham WH, Oski FA. Henna: a potential cause of oxidative hemolysis and neonatal hyperbilirubinemia. *Pediatrics* 1996; **97:** 707–9.

Lead

Blei; Plomb; Plomo; Plumbum.
Pb = 207.2.
CAS — 7439-92-1.

Description. Lead is a grey, malleable and ductile metal.

Adverse Effects

Lead poisoning (plumbism) may be due to inorganic or organic lead and may be acute or, more often, chronic. It has followed exposure to a wide range of compounds and objects from which lead may be absorbed following ingestion or inhalation. Some of those that have been incriminated include paint, pottery glazes, crystal glassware, domestic water supplies, petrol, poteen, cosmetics (particularly home-made or traditional forms such as kohl or surma), herbal or folk remedies, including traditional Chinese medicines, newsprint, and retained bullets. Children are often the victims of accidental poisoning and may be vulnerable to chronic exposure to lead from environmental pollution.

Acute effects of lead poisoning include metallic taste, abdominal pain, diarrhoea, vomiting, hypotension, muscle weakness and cramps, fatigue, abnormal liver function tests, and acute interstitial nephritis. Encephalopathy may occur and is more common in children. Symptoms of chronic poisoning with inorganic lead include anorexia, abdominal pain, constipation, anaemia, headache, fatigue, irritability, peripheral neuropathy, and encephalopathy with convulsions and coma. There may be kidney damage and impairment of mental function. Children with elevated lead concentrations may be asymptomatic apart from intellectual deficits and behavioural disorders.

Organic lead poisoning produces mainly CNS symptoms; there can be gastrointestinal and cardiovascular effects, and renal and hepatic damage.

◊ General references to lead exposure, adverse effects, screening, and management,[1-15] and case reports of specific sources of lead exposure.[16-21]

1. WHO. Recommended health-based limits in occupational exposure to heavy metals: report of a WHO study group. *WHO Tech Rep Ser 647* 1980. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_647.pdf (accessed 08/07/08)
2. WHO. Lead—environmental aspects. *Environmental Health Criteria 85*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc85.htm (accessed 08/07/08)
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5. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; **116:** 1036–46.
6. Kordas K, *et al.* Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *J Pediatr* 2005; **147:** 632–9.
7. Stewart WF, *et al.* Past adult lead exposure is linked to neurodegeneration measured by brain MRI. *Neurology* 2006; **66:** 1476–84.
8. Zimmermann MB, *et al.* Iron fortification reduces blood lead levels in children in Bangalore, India. *Pediatrics* 2006; **117:** 2014–21.
9. Téllez-Rojo MM, *et al.* Longitudinal associations between blood lead concentrations lower than 10 μg/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 2006; **118:** e323–e330. Available at: http://pediatrics.aappublications.org/cgi/content/full/118/2/e323 (accessed 08/07/08)
10. Yuan W, *et al.* The impact of early childhood lead exposure on brain organization: a functional magnetic resonance imaging study of language function. *Pediatrics* 2006; **118:** 971–7.
11. Menke A, *et al.* Blood lead below 0.48 μmol/L (10 μg/dL) and mortality among US adults. *Circulation* 2006; **114:** 1388–94.
12. Rischitelli G, *et al.* Screening for elevated lead levels in childhood and pregnancy: an updated summary of evidence for the US Preventive Services Task Force. *Pediatrics* 2006; **118:** e1867–e1895. Available at: http://pediatrics.aappublications.org/cgi/content/full/118/6/e1867 (accessed 08/07/08)
13. Gracia RC, Snodgrass WR. Lead toxicity and chelation therapy. *Am J Health-Syst Pharm* 2007; **64:** 45–53.
14. Chen A, *et al.* Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? *Pediatrics* 2007; **119:** e650–e658. Available at: http://pediatrics.aappublications.org/cgi/content/full/119/3/e650 (accessed 08/07/08)
15. CDC Advisory Committee on Childhood Lead Poisoning Prevention. Interpreting and managing blood lead levels <10 μg/dL in children and reducing childhood exposures to lead: recommendations of CDC's Advisory Committee on Childhood Lead Poisoning Prevention. *MMWR* 2007; **56 (RR-8)**: 1–16. Correction. *ibid.*; **56 (47)**: 1241. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5608a1.htm (accessed 05/08/08)
16. Powell ST, *et al.* Succimer therapy for congenital lead poisoning from maternal petrol sniffing. *Med J Aust* 2006; **184:** 84–5.
17. Coon T, *et al.* Lead toxicity in a 14-year-old female with retained bullet fragments. *Pediatrics* 2006; **117:** 227–30.

18. Frith D, *et al.* Lead poisoning—a differential diagnosis for abdominal pain. *Lancet* 2005; **366:** 2146.
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20. Guillard O, *et al.* A case of acute lead poisoning in a 2-year-old child. *Br J Clin Pharmacol* 2006; **62:** 246–7.
21. Berkowitz S, Tarrago R. Acute brain herniation from lead toxicity. *Pediatrics* 2006; **118:** 2548–51.

Treatment of Adverse Effects

The main aim in the management of both acute and chronic lead poisoning is to control the symptoms and reduce the concentration of lead in the body. Patients should be removed from the source of exposure and iron and calcium deficiencies corrected.

Treatment of acute symptomatic poisoning entails supportive therapy including intravenous fluids. Renal and hepatic function should also be monitored and convulsions controlled with a benzodiazepine. Encephalopathy, which is rare in adults but more common in children, requires urgent treatment.

Acute ingestion of lead or its salts should be treated if appropriate by activated charcoal or gastric lavage if within 1 hour of ingestion of a potentially life-threatening dose. Emesis is not recommended for organic lead compounds.

In severe cases of inorganic or organic lead poisoning, chelation therapy may be required to facilitate removal of lead from the body. A lead mobilisation test that measures urinary excretion of lead after a standard dose of sodium calcium edetate (p.1462) has been widely used as a means of assessing the need for therapy. However, because of difficulties in administering the test and uncertainties in interpreting results, some authorities have recommended blood-lead concentrations as a guide to treatment. The lead mobilisation test in addition to measurement of blood-lead concentrations may be useful in determining the necessity for chelation therapy in children (see below). Blood-lead concentrations should be obtained before starting chelation therapy, and then again after the first course since mobilisation of stored lead from body tissues may cause blood-lead concentrations to rebound after an initial drop; a second course of chelator may then be required. Raised blood-lead concentrations despite chelation therapy could also indicate continued exposure.

Chelation therapy is not indicated for children with a blood-lead concentration less than 25 micrograms per 100 mL. Children with a blood-lead concentration of 25 to 44 micrograms per 100 mL and a positive sodium calcium edetate mobilisation test should be considered for treatment with oral succimer (p.1466); alternative chelators are oral penicillamine (p.1456), and in the USA but not UK, dimercaprol (p.1444). For blood-lead concentrations of 45 to 70 micrograms per 100 mL, oral succimer should be given, followed by a second course if necessary. If encephalopathy is present or blood-lead concentrations are over 70 micrograms per 100 mL, parenteral sodium calcium edetate should be given with monitoring of renal and hepatic function, followed by a second course of chelator if necessary. In the USA, dimercaprol is given with sodium calcium edetate and 4 hours before the first dose; While dimercaprol has been used in the UK, it is not currently recommended as first-line treatment for lead poisoning.

It is considered that asymptomatic adults do not generally require chelation therapy. Symptomatic adults without encephalopathy may be treated with succimer; alternatives are unithiol, penicillamine or sodium calcium edetate. Adults with severe toxicity or encephalopathy should be treated with parenteral sodium calcium edetate followed by a second course if necessary. As with children (see above), dimercaprol is given with sodium calcium edetate in the USA but not in the UK.

Lead foreign bodies may need to be removed surgically or endoscopically to prevent further exposure. Long-term management of chronic lead poisoning involves eliminating environmental lead exposure. Chelation therapy is not a substitute for environmental controls in those suffering occupational exposure.

◊ Results from one study[1] indicated that succimer did not improve scores on tests of cognition, behaviour, or neuropsychological function despite lowering blood levels of lead in children who had initial levels of less than 45 micrograms per 100 mL. The authors suggested that, since succimer is as effective a chelator as any other currently available, chelation therapy in general may not be beneficial in children with these blood-lead levels.

1. Rogan WJ, *et al.* The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; **344:** 1421–6.

Lead in the Environment

Many countries have taken action to reduce lead exposure from environmental sources, including food, paint, and petrol, by limiting or banning altogether the use of lead compounds in such sources. Such measures have been of value in reducing childhood exposure to lead. Screening of all children to detect those at risk of chronic lead poisoning and developmental deficit has been advocated, but selective screening in areas perceived as high risk may be more appropriate in countries where the overall level of lead contamination is low.

Pharmacokinetics

Lead is absorbed from the gastrointestinal tract. It is also absorbed by the lungs from dust particles or fumes.

Inorganic lead is not absorbed through intact skin, but organic lead compounds may be absorbed rapidly.

Lead is distributed in the soft tissues, with higher concentrations in the liver and kidneys. In the blood it is associated with the erythrocytes. Over a period of time lead accumulates in the body and is deposited in calcified bone, hair, and teeth. Lead crosses the placental barrier. It is excreted in the faeces, urine, and sweat, and also appears in breast milk.

Uses and Administration

Lead compounds were formerly used as astringents, but the medicinal use of preparations containing lead is no longer recommended. The lead salts or compounds that have been used have included lead acetate and lead subacetate (for lead lotion, still known sometimes as lotio plumbi), lead carbonate, lead monoxide, and lead oleate (for lead plaster-mass).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Vulpuran; ***Mex.:*** Emplasto Monopolis.

Lecithin

E322; E442 (ammonium phosphatides); Lécithine; Lecithinum; Lecitina; Lesitinler.

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 26 (Lecithin). A complex mixture of acetone-insoluble phosphatides, which consists chiefly of phosphatidyl choline, phosphatidyl olamine, phosphatidyl serine, and phosphatidyl inositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. It contains not less than 50% of acetone-insoluble matter.

The consistency of both natural grades and refined grades of lecithin may vary from plastic to fluid, depending upon the content of free fatty acid and oil, and upon the presence or absence of other diluents. Its colour varies from light yellow to brown, depending on the source, on crop variations, and on whether it is bleached or unbleached.

It is odourless or has a characteristic, slight nutlike odour. It is partially soluble in water, but readily hydrates to form emulsions. The oil-free phosphatides are soluble in fatty acids, but are practically insoluble in fixed oils. When all phosphatide fractions are present, lecithin is partially soluble in alcohol and practically insoluble in acetone.

Profile

Lecithin is an emulsifying and stabilising agent used in both the pharmaceutical and the food industries.

Lecithin has also been used as a source of choline in the treatment of dementia (p.362) but with little evidence of clinical benefit. Phosphatidyl serine (p.2367) has been used similarly. Other constituents of lecithin such as phosphatidyl olamine and phosphatidyl inositol may be found in natural pulmonary surfactants (p.2375).

Lecithin is also an ingredient of preparations promoted as tonics and dietary supplements in an enormous range of disorders.

◊ References.

1. Higgins JPT, Flicker L. Lecithin for dementia and cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 14/02/06).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Herbaccion Lecitina; Reducin; ***Austral.:*** Buerlecithin; ***Austria:*** Buerlecithin Compact; Dermo WAS; ***Cz.:*** Buerlecithin†; Essentiale N†; ***Ger.:*** Buerlecithin; ***India:*** Essentiale-L; ***Indon.:*** Neurochol; ***Mex.:*** Leciderm; ***Pol.:*** Lecitan; ***Port.:*** Pansebase Solido†; ***Switz.:*** Buerlecithin Compact†; ***Venez.:*** Lecivar.

Multi-ingredient: ***Arg.:*** Ayton; Cholesterol Reducing Plan†; Herbaccion Memory; KLB6 Fruit Diet; No-Gras; Prueboi†; Sojasterol†; Top Life Diet†; ***Austral.:*** Berberis Complex; Bioglan Zellulean with Escin; Extralife Arthri-Care; Extralife Extra-Brite; Extralife Liva-Care; ML 20†; Plantiodine Plus†; ***Austria:*** Bilatin; Buerlecithin; Lecikur; ***Canad.:*** Complex 15†; Kyolic 104†; ***Chile:*** Cartilago T-500; ***Cz.:*** Vita Buerlecithin†; ***Fr.:*** Cholegerol†; ***Ger.:*** Hicoton†; Lipidavit; Tears Again; Vita Buerlecithin†; ***Hong Kong:*** Apaisac; Ginkgo-PS†; Wari-Procomil; ***India:*** Livage; ***Indon.:*** BIO-EPL; Cholesvit; Curson; Epatin; Hepachol; Lanagogum; Lanaven Plus; Lesichol; Nutriflam; Verona; ***Ital.:*** Nutrigel†; Ottovis; Solecin; Tricortin; ***Malaysia:*** Livguard; ***Mex.:*** Lecifar-K†; ***Philipp.:*** Korgivit-E; Liverine; Memori Plus; Memory DD; ***Pol.:*** Lecigal†; Lecytyna E; ***Port.:*** Pansebase; Pansebase Composto; Secpel; Secpel Composto; ***Singapore:*** Ginkgo-PS; ***Switz.:*** Biovital Ginseng; Vita Buerlecithin; ***Thai.:*** Wari-Procomil†; ***UK:*** Kelp Plus 3; S.P.H.P.; ***USA:*** KLB6; ***Venez.:*** Lecivar Plus.

Leishmanin

Leishmanina.

Profile

Leishmanin is a suspension of *Leishmania* promastigotes used in an intradermal test to indicate previous exposure to leishmanial antigens. Its chief use is in epidemiological studies of leishmaniasis (p.824). The leishmanin skin test has also been known as the Montenegro test.

Lemon

Pharmacopoeias. *Br.* includes dried lemon peel and *Swiss* includes fresh lemon peel.

BP 2008 (Dried Lemon Peel). The dried outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus limon*. It contains not less than 2.5% v/w of volatile oil.

Profile

Lemon, *Citrus limon* (*Citrus limonum*) (Rutaceae), is an ingredient of herbal remedies used for gastrointestinal disorders and as tonics. The juice is traditionally included in preparations for colds and coughs. Lemon is a source of bioflavonoids used to improve capillary function (see Flavonoid Compounds, p.2304). The peel is the source of lemon oil (p.2332). Citrus fruits are a source of vitamin C (p.1983).

Photosensitivity is associated with citrus oils.

Preparations

BP 2008: Concentrated Compound Gentian Infusion;
USNF 26: Lemon Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Gencydo; ***Braz.:*** Balsamo Branco; ***Ger.:*** Doppelherz Melissengeist†; Gencydo; ***Ital.:*** Altadrine; ***Port.:*** Erpecalm; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); ***Switz.:*** Gencydo.

Lemon Oil

Aetheroleum Citri; Citri Etheroleum; Citrinų eterinis aliejus; Citromolaj; Citron, huile essentielle de; Citronenöl; Citronolja; Citronová silice; Esencia de Cidra; Essence de Citron; Essência de Limão; Limón, aceite esencial de; Limonis aetheroleum; Ol. Limon.; Olejek cytrynowy; Oleum Citri; Oleum Limonis; Sitruunaöljy.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Lemon Oil). The essential oil obtained by suitable mechanical means without the aid of heat from the fresh peel of *Citrus limon*. It contains a maximum of 0.5% β-caryophyllene, 0.5 to 2.3% geranial, 0.1 to 0.8% geranyl acetate, 56.0 to 78.0% limonene, 0.3 to 1.5% neral, 0.2 to 0.9% neryl acetate, 7.0 to 17.0% β-pinene, 1.0 to 3.0% sabinene, 6.0 to 12.0% γ-terpinene, and a maximum of 0.6% α-terpineol.

A clear mobile pale yellow to greenish-yellow liquid with a characteristic odour. It may become cloudy at low temperatures. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light. Where applicable the label should state that the contents are Italian-type lemon oil.

USNF 26 (Lemon Oil). The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus × limon* (Rutaceae), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral, is not less than 2.2% and not more than 3.8% for California-type lemon oil, and not less than 3.0% and not more than 5.5% for Italian-type lemon oil. Store in well-filled airtight containers.

Profile

Lemon oil is chiefly used in perfumery and as a flavour. It is used in the preparation of terpeneless lemon oil (below). It has also been used with other volatile agents in rubefacient preparations and preparations for respiratory-tract disorders. Both lemon oil and lemon petitgrain oils (prepared from the leaves and twigs) are used in aromatherapy.

Photosensitivity reactions and contact dermatitis have been reported.

Preparations

BP 2008: Aromatic Ammonia Spirit;
USNF 26: Compound Orange Spirit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Genuine Australian Eucalyptus Drops†; ***Austria:*** Spasmo Claim; ***Canad.:*** SH-206; ***Chile:*** Agua del Carmen; Agua Melisa Carminativa; ***Cz.:*** Amol; Coldastop; ***Fr.:*** Ephydrol; Poudre du Marcheur; ***Ger.:*** Amol Heilkrautergeist N; Babix-Wundsalbe N†; GeloSitin; Melissengeist; ***Indon.:*** OBH; ***Israel:*** Garonsept; ***Ital.:*** Esoklin; Valda Timo e Limone; Venalta; ***NZ:*** Electric Blue Headlice; Lemsip Dry Cough†; ***Pol.:*** Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; ***Rus.:*** Carmolis (Кармолис)†; ***S.Afr.:*** Balsem Vita GEEL; Balsem Vita ROOI; Spiritus Contra Tussim Drops; ***Switz.:*** Alcoolat de Melisse†; Carmol; Neo-Angin au miel et citron; Perskindol Classic; Pirom; Sansilla; Sibrovita; ***UK:*** Melissa Comp.; ***USA:*** Mexsana.

Terpeneless Lemon Oil

Limón exento de terpeno, aceite esencial de; Oleum Limonis Deterpenatum.

Pharmacopoeias. In *Br.*

BP 2008 (Terpeneless Lemon Oil). A clear colourless or pale yellow liquid, visibly free from water, with the characteristic odour and taste of lemon, prepared by concentrating lemon oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 40% w/w of aldehydes calculated as citral. Soluble 1 in 1 of alcohol (80%). Store in well-filled containers at a temperature not exceeding 25°. Protect from light.

Profile

Terpeneless lemon oil is used as a flavour. It has the advantages of being stronger in taste and odour and more readily soluble than the natural oil and is used in the preparation of lemon spirit and lemon syrup.

Photosensitivity is associated with citrus oils.

Preparations

BP 2008: Compound Orange Spirit; Lemon Spirit; Lemon Syrup.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Lemsip Cough & Cold Dry Cough; Meltus Honey & Lemon.

Lemon Grass Oil

Essência de Capim-Limão; Indian Melissa Oil; Indian Verbena Oil; Lemongrass, aceite de; Lemongrass Oil; Oleum Graminis Citrati.

Profile

Lemon grass oil is the volatile oil obtained by distillation from *Cymbopogon flexuosus* or *C. citratus* (Gramineae). It contains citral (p.2284) and citronellal.

Lemon grass oil was formerly given as a carminative. It has been used in perfumery and as a flavour. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Apex Repel Natural; ***NZ:*** Apex Repel Natural; ***Switz.:*** Carmol; Carmol Plus†.

Lemon Verbena

Herba Lippiae Citriodorae; Herba Verbenae Odoratae; Hierba luisa; Verbenae citriodoratae folium (lemon verbena leaf); Verveine Odorante; Verveine odorante, feuille de (lemon verbena leaf).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lemon Verdana Leaf). The whole or fragmented, dried leaves of *Aloysia citriodora* (*A. triphylla*, *Verbena triphylla*, *Lippia citriodora*). It contains a minimum of 2.5% acteoside ($C_{29}H_{36}O_{15}$ = 624.6) expressed as ferulic acid and not less than 0.3% v/w essential oil for the whole drug and 0.2% v/w essential oil for the fragmented drug, all calculated with reference to the dried drug. After grinding it has a characteristic odour reminiscent of lemon.

Profile

Lemon verbena, the flowering tops or leaves of *Lippia citriodora* (*Aloysia triphylla*; *Verbena triphylla*) (Verbenaceae), has antispasmodic and sedative actions and has been used for gastrointestinal disorders and as a tonic. It is most commonly used as an ingredient of herbal teas.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Agua del Carmen.

Lentinan

LC-33; Lentinano.

Лентинан

CAS — 37339-90-5.
ATC — L03AX01.
ATC Vet — QL03AX01.

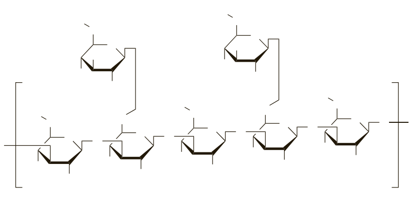

Profile

Lentinan is a β-1,3-D-glucan extracted from the shiitake mushroom *Lentinus edodes* (*Lentinula edodes*). It appears to act as an immunostimulant and has been tried in the treatment of malignant neoplasms and in HIV infection.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Better Cholesterol.

Lepromin

Lepromina.

Profile

Lepromin is a suspension of killed *Mycobacterium leprae* prepared from the skin of heavily infected patients suffering from lepromatous leprosy (lepromin H) or from armadillo tissue infected with *M. leprae* (lepromin A). It is used in an intradermal skin test for the classification of leprosy (p.176) and the assessment of immune responsiveness to *M. leprae.* The test is not diagnostic for leprosy.

◊ The original lepromin (of Mitsuda and Hayashi), a suspension of the whole autoclaved homogenised lepromа including some tissue elements, is sometimes called integral lepromin, whereas purified bacillary suspensions are sometimes called bacillary lepromins.[1] Leprolins are the soluble proteins of the bacilli with or without proteins of the lepra, not coagulated by heating, and do not elicit the early reaction. The Dharmendra antigen is neither a lepromin nor a leprolin and is used especially for testing the early reactions; it gives only a weak late reaction. Purified protein derivatives of *Mycobacterium leprae*, such as leprosin A,[2] have also been developed.

1. Abe M, *et al*. Immunological problems in leprosy research. *Lepr Rev* 1974; **45:** 244–72.
2. Stanford JL. Skin testing with mycobacterial reagents in leprosy. *Tubercle* 1984; **65:** 63–74.

Leptin

Leptina; OB protein.

Лептин

Profile

Leptin, an endogenous peptide hormone produced mainly by white adipocytes in adipose tissue, is involved in the long-term maintenance of body-weight through regulation of food intake and energy expenditure. Leptin has a negative feedback effect on hypothalamic control of neurotransmitters involved in the control of appetite: thus, an increase in adipose tissue mass results in an increase in leptin concentrations that in turn suppresses expression of appetite stimulatory peptides and *vice versa*. Mutations of either the leptin receptor or the *ob* gene that encodes the leptin protein result in failure of leptin's control over appetite producing forms of morbid early-onset obesity. However, it is not clear that common obesity (p.2149) is associated with similar genetic mutations or, as also postulated, is associated with functional leptin resistance caused by sustained high leptin concentrations.

Leptin is produced in other tissues, and studies have suggested additional functions and properties including modulation of neuroendocrine, immune, and reproductive processes. The potential role of leptin in a variety of disease states including syndromes of insulin resistance, auto-immune diseases, and cardiovascular disorders is also being studied.

Replacement therapy with recombinant leptin is under investigation in the management of obesity as well as some other disorders including generalised lipodystrophy and hypothalamic amenorrhoea secondary to energy deficits or low body-weight.

◊ References.

1. Hukshorn CJ, *et al.* Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men. *J Clin Endocrinol Metab* 2000; **85:** 4003–4009.
2. Oral EA, *et al.* Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002; **346:** 570–8.
3. Proietto J, Thorburn AW. The therapeutic potential of leptin. *Expert Opin Invest Drugs* 2003; **12:** 373–8.
4. Veniant MM, LeBel CP. Leptin: from animals to humans. *Curr Pharm Des* 2003; **9:** 811–8.
5. Cochran E, *et al.* Efficacy of recombinant methionyl human leptin therapy for the extreme insulin resistance of the Rabson-Mendenhall syndrome. *J Clin Endocrinol Metab* 2004; **89:** 1548–54.
6. Javor ED, *et al.* Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. *J Clin Endocrinol Metab* 2004; **89:** 3199–3207.
7. Ebihara K, *et al.* Long-term leptin-replacement therapy for lipoatrophic diabetes. *N Engl J Med* 2004; **351:** 615–6.
8. Welt CK, *et al.* Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 2004; **351:** 987–97.
9. Bell-Anderson KS, Bryson JM. Leptin as a potential treatment for obesity: progress to date. *Treat Endocrinol* 2004; **3:** 11–18.
10. Chan JL, Mantzoros CS. Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa. *Lancet* 2005; **366:** 74–85.
11. Zelissen PM, *et al.* Effect of three treatment schedules of recombinant methionyl human leptin on body weight in obese adults: a randomized, placebo-controlled trial. *Diabetes Obes Metab* 2005; **7:** 755–61.
12. Brennan AM, Mantzoros CS. Drug insight: the role of leptin in human physiology and pathophysiology — emerging clinical applications. *Nat Clin Pract Endocrinol Metab* 2006; **2:** 318–27.
13. Ebihara K, *et al.* Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007; **92:** 532–41.
14. Chan JL, *et al.* Pharmacokinetics of recombinant methionyl human leptin after subcutaneous administration: variation of concentration-dependent parameters according to assay. *J Clin Endocrinol Metab* 2007; **92:** 2307–11.

Lerdelimumab *(rINN)*

Lérdelimumab; Lerdelimumabum. Immunoglobulin G4, anti-(human transforming growth factor β2) (human monoclonal CAT-152 γ4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer.

Лерделимумаб

CAS — 285985-06-0.

Profile

Lerdelimumab is a human monoclonal antibody specific for transforming growth factor β2 that has been investigated for the prevention of excessive postoperative scarring after glaucoma surgery.

Levomenol *(rINN)*

(−)-α-Bisabolol; Lévoménol; Levomenolum; Lewomenol. (−)-6-Methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol.

Левоменол

$C_{15}H_{26}O$ = 222.4.
CAS — 23089-26-1.

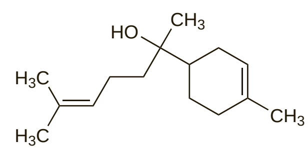

Profile

Levomenol is a sesquiterpene isolated from the volatile oil of chamomile (p.2279). It has been tried as a transepidermal penetration enhancer and is present in many emollient preparations.

◊ References.

1. Kadir R, Barry BW. α-Bisabolol, a possible safe penetration enhancer for dermal and transdermal therapeutics. *Int J Pharmaceutics* 1991; **70:** 87–94.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Confortel†; Keracnyl; ***Austria:*** Sensicutan; ***Belg.:*** Purigel Crisp; ***Chile:*** Cuidado Intimo; Eucerin Piel Grasa; Queratopil; Ruboril; Suavigel; ***Cz.:*** Fyterol†; Sensicutan; ***Fr.:*** Alpha 5 DS†; Apaisance†; Clean-AC; Dermophil Indien†; Epiphane†; Keracnyl; Keracnyl eau nettoyante; Seborheane; Squaphane E; Tefirax; ***Ger.:*** Mirfulan Spray N; Sensicutan; ***Hong Kong:*** Kamillosan†; ***Ital.:*** Biothymus DS; Broxo al Fluoro; Decon Lavanda; Intim; Pitiren; Saugella Poligyn 7; Tial-Z; ***Mex.:*** Aveendix; ***Port.:*** Hidratante VV; Lactonico†; ***Switz.:*** Antidry; Dermophil Indien; Tenderdol; ***Thai.:*** Kamillosan†; ***UK:*** Xclair; ***Venez.:*** Kamillosan.

Lexipafant *(BAN, USAN, rINN)*

BB-882; DO-6; Lexipafantum. Ethyl *N*-methyl-*N*-[α-(2-methylimidazo[4,5-*c*]pyridin-1-yl)tosyl]-L-leucinate.

Лексипафант

$C_{23}H_{30}N_4O_4S$ = 458.6.
CAS — 139133-26-9.

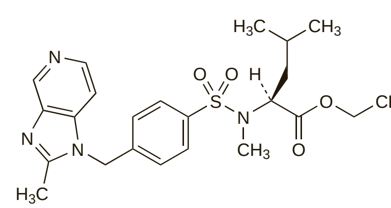

Profile

Lexipafant is a platelet-activating factor antagonist that is being investigated in the prevention of neurological and renal complications after cardiac surgery. It has also been studied for possible applications in asthma, sepsis, and pancreatitis.

Linseed

Flaxseed; Leinsamen; Lenmag; Lin; Lin, graine de; Linaza; Linfrö; Linho; Lini semen; Lini Semina; Linum; Lněné semeno; Nasienie lnu; Pellavansiemen; Sėmenys; Semilla de Lino.

ATC — A06AC05.
ATC Vet — QA06AC05.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Linseed). The dried ripe seeds of *Linum usitatissimum.* Protect from light.

Profile

Preparations of linseed have been administered for their demulcent and laxative actions. Crushed linseed has been used as a poultice. Linseed is the source of linseed oil, below. Linseed has also been tried as a dietary supplement to improve postmenopausal symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Aloelax; Instalax; ***Ger.:*** Duoventrin; Pascomag†; ***Pol.:*** Laxantol; ***Singapore:*** Tofupill†; ***Switz.:*** Linoforce; LinoMed; ***UK:*** Salinum.

Linseed Oil

Aceite de Linaza; Flaxseed Oil; Huile de Lin; Leinöl; Lenolaj; Lin, huile de; Linaza, aceite de; Lini oleum; Linolja; Lněný olej; Oleum Lini; Pellavaöljy; Sėmenų aliejus.

ATC — A06AC05.
ATC Vet — QA06AC05.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Linseed Oil, Virgin). The oil obtained by cold expression from ripe seeds of *Linum usitatissimum*. A suitable antoxidant may be added. A clear, yellow or brownish-yellow liquid. It turns dark and gradually thickens on exposure to air. When cooled, it becomes a soft mass at about –20°. Relative density about 0.931. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in airtight containers. Protect from light.

Profile

Linseed oil is used in veterinary medicine as a purgative for horses and cattle. In man, linseed oil is included in topical preparations for a variety of skin disorders. It has been tried as a vegetable source of omega-3 fatty acids (p.1362).

Boiled linseed oil ('boiled oil') is linseed oil heated with litharge, manganese resinate, or other driers, to a temperature of about 150° so that metallic salts of the fatty acids are formed and cause the oil to dry more rapidly. It must not be used for medicinal purposes.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Linna-Oil; ***Mex.:*** Omelina.

Multi-ingredient: ***Austria:*** Dermowund; ***Canad.:*** Prostate Ease; ***India:*** Buta-Proxyvon; Duoflam Gel; Nicip Super; Nimulid Nugel; ***Rus.:*** Dicloran Plus (Диклоран Плюс); ***Switz.:*** Epithelial†; Malvedrin; ***UK:*** Nine Rubbing Oils.

Lithium Benzoate ⊗

Litio, benzoato de.

$C_7H_5LiO_2$ = 128.1.
CAS — 553-54-8.

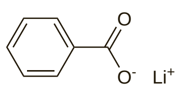

Profile

Lithium benzoate has been used as a diuretic and urinary disinfectant. Its use cannot be recommended because of the pharmacological effect of the lithium ion (p.401). Each g contains 7.8 mmol of lithium.

Lixivaptan *(USAN, rINN)* ⊗

Lixivaptán; Lixivaptanum; VPA-985; WAY-VPA-985. 3′-Chloro-5-fluoro-4′-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-*o*-toluanilide.

Ликсиваптан

$C_{27}H_{21}ClFN_3O_2$ = 473.9.
CAS — 168079-32-1.

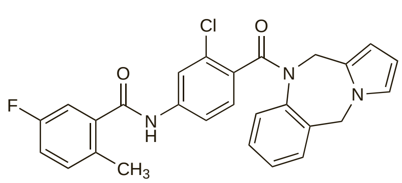

Profile

Lixivaptan is a selective vasopressin V_2-receptor antagonist under investigation for the treatment of hyponatraemia in patients with heart failure.

◊ References.

1. Abraham WT, *et al.* Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol* 2006; **47:** 1615–21.

Lobenzarit Sodium *(USAN, rINNM)*

CCA; Lobenzarit sódico; Lobenzarit Sodique; Natrii Lobenzaritum. 4-Chloro-2,2′-iminodibenzoate disodium.

Натрий Лобензарит

$C_{14}H_8ClNNa_2O_4$ = 335.7.
CAS — 63329-53-3 (lobenzarit); 64808-48-6 (lobenzarit sodium).

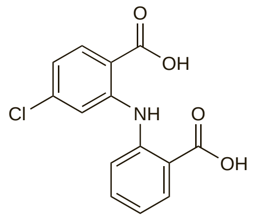

(lobenzarit)

Profile

Lobenzarit sodium has been used as an immunomodulator in rheumatoid arthritis.

Lodoxamide *(BAN, rINN)*

Lodoksamidi; Lodoxamid; Lodoxamida; Lodoxamidum; U-42585. *N,N′*-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid.

Лодоксамид

$C_{11}H_6ClN_3O_6$ = 311.6.
CAS — 53882-12-5.
ATC — S01GX05.
ATC Vet — QS01GX05.

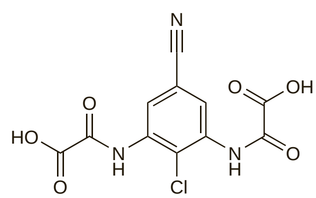

Lodoxamide Ethyl *(BANM, USAN, rINNM)*

Ethylum Lodoxamidum; Lodoxamida etilo; Lodoxamide Ethyle; U-42718. Diethyl *N,N′*-(2-Chloro-5-cyano-*m*-phenylene)dioxamate.

Этил Лодоксамид

$C_{15}H_{14}ClN_3O_6$ = 367.7.
CAS — 53882-13-6.

Lodoxamide Trometamol *(BANM, rINNM)*

Lodoksamid Trometamin; Lodoxamida trometamol; Lodoxamide Trométamol; Lodoxamide Tromethamine *(USAN)*; Lodoxamidum Trometamolum; U-42585E. *N,N′*-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid compound with trometamol.

Лодоксамид Трометамол

$C_{11}H_6ClN_3O_6,2C_4H_{11}NO_3$ = 553.9.
CAS — 63610-09-3.
ATC — S01GX05.
ATC Vet — QS01GX05.

Adverse Effects

Lodoxamide eye drops may cause local irritation. Reported effects include burning or stinging, and itching. Flushing and dizziness have also been reported.

Uses and Administration

Lodoxamide has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1136). Lodoxamide trometamol is used in eye drops for allergic conjunctivitis (p.564), particularly vernal keratoconjunctivitis; a concentration equivalent to 0.1% of lodoxamide is used, 1 or 2 drops usually being instilled into the eye four times daily.

Lodoxamide has also been studied for its prophylactic effect in the treatment of asthma, but has not proved to be of benefit; it has usually been given orally as the ethyl ester or by inhalation as the trometamol salt.

Conjunctivitis. Lodoxamide is an effective treatment for vernal keratoconjunctivitis.[1,2] There is some evidence that it may be more effective than sodium cromoglicate for this purpose (see p.1138).

1. Anonymous. Lodoxamide for vernal keratoconjunctivitis. *Med Lett Drugs Ther* 1994; **36:** 26.
2. Lee S, Allard TRFK. Lodoxamide in vernal keratoconjunctivitis. *Ann Pharmacother* 1996; **30:** 535–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Alomide; ***Austral.:*** Lomide; ***Austria:*** Alomide†; ***Belg.:*** Alomide; ***Braz.:*** Alomide; ***Canad.:*** Alomide; ***Chile:*** Alomide; ***Cz.:*** Alomide; ***Denm.:*** Alomide; ***Fin.:*** Alomide; ***Fr.:*** Almide; ***Ger.:*** Alomide; ***Gr.:*** Alomide; Thilomide; ***Hong Kong:*** Alomide; ***Hung.:*** Alomide; ***Indon.:*** Alomide; ***Irl.:*** Alomide; ***Israel:*** Alomide; ***Ital.:*** Alomide; ***Malaysia:*** Alomide; ***Mex.:*** Alomide; ***Norw.:*** Alomide; ***NZ:*** Lomide; ***Philipp.:*** Alconmide; ***Pol.:*** Alomide; ***Port.:*** Alomide; ***Rus.:*** Alomide (Аломид); ***S.Afr.:*** Alomide; ***Singapore:*** Alomide; ***Spain:*** Alomide; ***Switz.:*** Alomide†; ***Thai.:*** Alomide; ***Turk.:*** Alomide; Thilomide; ***UK:*** Alomide; ***USA:*** Alomide; ***Venez.:*** Alomide.

Lomifylline *(rINN)*

Lomifilina; Lomifyllinum. 7-(5-Oxohexyl)theophylline.

Ломифиллин

$C_{13}H_{18}N_4O_3$ = 278.3.
CAS — 10226-54-7.

Profile

Lomifylline is a theophylline derivative that has been used in preparations for cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Cervilane; Micerfin; ***Braz.:*** Norogil; ***Chile:*** Cervilane; ***Mex.:*** Cervilan; ***Port.:*** Cervilane†.

Loosestrife

Fackelblomster; Kyprejová nať; Lythri herba; Purple Loosestrife; Rantakukka; Raudoklių žolė; Réti fűzényfű; Salicaire.

NOTE. Do not confuse with yellow willowherb, *Lysimachia vulgaris* which is also known as loosestrife.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Loosestrife; Lythri Herba). The dried flowering tops, whole or cut, of *Lythrum salicaria*. It contains not less than 5.0 % of tannins, expressed as pyrogallol and calculated with reference to the dried drug. Protect from light.

Profile

Purple loosestrife, *Lythrum salicaria* (Lythraceae), is used in herbal medicine for the treatment of diarrhoea. It is also used for its astringent and antimicrobial properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Salicairine.

Multi-ingredient: ***Fr.:*** Saugella; ***Ital.:*** Gynegella P†; ***Spain:*** Natusor Astringel†.

Lorenzo's Oil

Lorenzo, aceite de.

Glyceryl Trierucate

Trierucin. 1,2,3-Propanetriol tri(13-docosenoate).

$C_{69}H_{128}O_6$ = 1053.8.
CAS — 2752-99-0.

Glyceryl Trioleate

Triolein. 1,2,3-Propanetriol tri(9-octandecenoate).

$C_{57}H_{104}O_6$ = 885.4.
CAS — 122-32-7.

Profile

Lorenzo's oil is a liquid containing glyceryl trierucate (a source of erucic acid) and glyceryl trioleate (a source of oleic acid), in the ratio 1 part to 4 parts respectively. It has been used with dietary modification for the treatment of adrenoleucodystrophy, a genetic disorder characterised by demyelination, adrenal cortical insufficiency, and accumulation of saturated 'very-long-chain fatty acids'.

Adrenoleucodystrophy. Adrenoleucodystrophy is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids results in diffuse and multifocal demyelination of the nervous system and adrenocortical insufficiency. The most common form usually affects children and is characterised primarily by cerebral demyelination; it is usually fatal within a few years. In the adult variant, called adrenomyeloneuropathy, demyelination of the spinal cord and peripheral neuropathy progress slowly over many years.[1,2]

There appears to be no effective treatment for adrenoleucodystrophy or its variants. A high dietary intake of long-chain monounsaturated fatty acids, as provided by the mixture Lorenzo's oil (glyceryl trierucate with glyceryl trioleate), has been tried, the idea being to monopolise the specific enzyme involved in the conversion of long-chain fatty acids to very-long-chain fatty acids. Although dietary therapy with Lorenzo's oil has reduced plasma concentrations of saturated very-long-chain fatty acids, there is no evidence that this improves or delays progression of adrenoleucodystrophy or adrenomyeloneuropathy.[3-6] However, it has been suggested that these disorders may not respond to correction of the biochemical abnormality once neurological damage has occurred.[5] The effectiveness of treatment before the appearance of neurological symptoms is currently being studied with some encouraging results.[7] There is some evidence to suggest that the childhood form may have an immunological component, but results using immunosuppressants or immunoglobulins have been reported to be disappointing.[5] Bone marrow transplants may improve symptoms but should only be tried in those with mild cerebral involvement.[1] Lovastatin can also reduce plasma concentrations of very-long-chain fatty acids.[8]

1. van Geel BM, *et al.* X linked adrenoleukodystrophy: clinical presentation, diagnosis, and therapy. *J Neurol Neurosurg Psychiatry* 1997; **63:** 4–14.
2. Moser HW, *et al.* Adrenoleukodystrophy: new approaches to a neurodegenerative disease. *JAMA* 2005; **294:** 3131–4.
3. Aubourg P, *et al.* A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med* 1993; **329:** 745–52.
4. Kaplan PW, *et al.* Visual evoked potentials in adrenoleukodystrophy: a trial with glycerol trioleate and Lorenzo oil. *Ann Neurol* 1993; **34:** 169–74.
5. Rizzo WB. Lorenzo's oil—hope and disappointment. *N Engl J Med* 1993; **329:** 801–2.
6. van geel BM, *et al.* Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". *J Neurol Neurosurg Psychiatry* 1999; **67:** 290–9.
7. Moser HW, *et al.* Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. *Arch Neurol* 2005; **62:** 1073–80.
8. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Adverse effects. Thrombocytopenia has been reported in patients receiving Lorenzo's oil, although patients are often asymptomatic.[1] It is possible that giant platelets which retain most of their function are produced and that these are not counted by automatic counting procedures giving a false impression of thrombocytopenia.[2]

Lymphocytopenia with an increased incidence of infection has also been reported in few patients.[3]

1. Zinkham WH, *et al.* Lorenzo's oil and thrombocytopenia in patients with adrenoleukodystrophy. *N Engl J Med* 1993; **328:** 1126–7.
2. Stöckler S, *et al.* Giant platelets in erucic acid therapy for adrenoleukodystrophy. *Lancet* 1993; **341:** 1414–15.
3. Unkrig CJ, *et al.* Lorenzo's oil and lymphocytopenia. *N Engl J Med* 1994; **330:** 577.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: GTO Oil.

Lovage Root

Gelsvių šaknys; Korzeń lubczyka; Lestyángyökér; Levistici radix; Levístico; Libečkový kořen; Libstickerot; Liebstöckelwurzel; Liperinjuuri; Livèche (racine de); Livèche, racine de.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Lovage Root). The whole or cut, dried rhizome and root of *Levisticum officinale*. The whole drug contains not less than 0.4% v/w of essential oil and the cut drug not less than 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Lovage root is used in herbal medicine for gastrointestinal and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Ehrenhofer-Salbe; ***Cz.:*** Zaludecni Cajova Smes; ***Ger.:*** Canephron; Nephroselect M; Presselin Nieren-Blasen K 3†; ***Rus.:*** Canephron N (Канефрон Н); ***Switz.:*** Tisane pour les reins et la vessie.

Luprostiol *(BAN, rINN)*

Luprostioli; Luprostiolum. (±)-(*Z*)-7-{(1*S*,2*R*,3*R*,5*S*)-2-[(2*S*)-3-(3-Chlorophenoxy)-2-hydroxypropylthio]-3,5-dihydroxycyclopentyl}hept-5-enoic acid.

Лупростиол

$C_{21}H_{29}ClO_6S$ = 445.0.
CAS — 67110-79-6.
ATC Vet — QG02AD91.

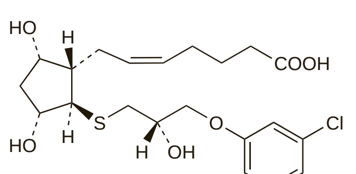

and enantiomer

Profile

Luprostiol is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as a luteolytic in veterinary medicine.

Lupulus

Apynių spurgai; Chmelová šištice; Hop Strobile; Hopfenzapfen; Hops; Houblon; Houblon, cône de; Humalankukka; Humlekotte; Humulus; Komlótoboz; Lupuli flos; Lupuli Strobulus; Lúpulo; Strobili Lupuli; Szyszka chmielu.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Hop Strobile). The dried, generally whole, female inflorescences (strobiles) of the hop plant *Humulus lupulus*. It has a characteristic aromatic odour. Protect from light.

Profile

Lupulus has been used as a bitter, and supplies the characteristic flavour of beers. It is used in herbal and folk medicine as a sedative.

Homoeopathy. Lupulus has been used in homoeopathic medicines under the following names: Humulus lupulus; Lupulinum; Humulus lupulus e glandulis; Lupul.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Lactidorm†; ***Rus.:*** Novo-Passit (Ново-Пассит); ***Switz.:*** Klosterfrau Nervenruh Dragees.

Multi-ingredient: ***Arg.:*** Calmtabs†; ***Austral.:*** Extralife Sleep-Care; Humulus Compound; Natural Deep Sleep; Pacifenity†; Passiflora Complex†; Passionflower Plus; Prosed-X†; ReDormin; Relaxaplex†; ***Austria:*** Baldracin; Baldrian AMA; Hova; Montana; Nervenruh; Nerventee St Severin; Sedadom; Wechseltee St Severin; ***Braz.:*** Remilev; ***Canad.:*** Herbal Nerve; Herbal Sleep Well†; Relax and Sleep; ***Chile:*** Valupass; ***Cz.:*** Baldracin; Detsky Caj s Hermankem; Fytokliman Planta; Hova; Klosterfrau Beruhigungs Forte†; Novo-Passit; Sanason; Schlaf-Nerventee N†; Species Nervinae Planta; Valofyt Neo; Visinal†; ***Fr.:*** Nostress; Notabac; ***Ger.:*** Alluna Nacht; Ardeysedon; Avedorm duo; Baldrian-Dispert Nacht; Baldriparan N Stark†; Biosedon†; Boxocalm; Cefasedativ†; Dormeasan; Dormoverlan; Gutnacht†; Hicoton†; Ilja Rogoff; JuDorm†; Kneipp Gute Nacht; Kytta-Sedativum; Leukona-Beruhigungsbad†; Lomasleep†; Luvased; Moradorm S; Nervendragees†; Nervenkapseln; Nervinfant N†; Nervoregin forte†; Nervoregin phyto; Pascosedon; Phytogran†; Presselin Nerven K 1 N†; Schlaf- und Nerventee; Seda-Plantina†; Sedacur; Sedaselect D; Sedasyx†; Selon; Sensinerv forte†; Somnuvis S†; Stomasal Med†; Valdispert comp†; Valeriana mild†; Valverde Baldrian Hopfen bei Einschlafstorungen und zur Beruhigung†; Vivinox Day; ***Hung.:*** Hova; ReDormin; Sedacur; ***Israel:*** Nerven-Dragees; ***Ital.:*** Calmason; Emmenoiasi; Melissa (Specie Composta)†; Valeriana (Specie Composta)†; ***Mex.:*** Ivel; Nervinetas; ***Pol.:*** Calmina; Hova; Kalms; Klimax†; Lekosen; Lumewal; Nervendragees; Nervinolum; Nervomix; Nervosol; Nerwobonisol; Passispasmin; Passispasmol; Sedomix; Tabletki Uspokajajace; Vallup; Valused; ***Rus.:*** Doppelherz Vitalotonik (Доппельгерц Виталотоник); Passifit (Пассифит); Sanason (Санасон); ***S.Afr.:*** Avena Sativa Comp; ***Switz.:*** Baldriparan; Dicalm†; Dormeasan; Dragees pour le coeur et les nerfs; Dragees pour le sommeil; Dragees sedatives Dr Welti; Hova; Hyperiforce comp; Nervinetten; Phytomed Nervo†; Phytomed Somni†; ReDormin; Relaxo; Soporin; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Valverde Coeur; Valverde Sommeil; Zeller Sommeil; ***UK:*** Anased; Avena Sativa Comp; Gerard House Serenity; Gerard House Somnus; HRI Calm Life; HRI Night; Kalms; Kalms Sleep; Natrasleep; Newrelax; Nodoff; Nytol Herbal; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B ; Slumber; Sominex Herbal; Stressless; Unwind Herbal Nytol; Valerina Night-Time; Ymea; ***Venez.:*** Insocaps; Lupassin; Nervinetas.

Lycopene

E160(d).
CAS — 502-65-8.

Pharmacopoeias. In *US* which also includes Tomato Extract Containing Lycopene.
USP 31 (Lycopene). A mixture of geometrical isomers of lycopene. Store in airtight containers under an inert gas at a temperature of 8° to 15°. Protect from light.

Profile

Lycopene is a carotenoid responsible for the red colour of tomatoes and some other fruits including rose fruit (p.2381). It is used as a colouring agent and antioxidant. Much interest has been expressed in the antioxidant properties of lycopene for the potential prevention of diseases such as cardiovascular disease and some cancers, particularly of the prostate gland. Lycopene is also an ingredient of some skin preparations.

◊ References.

1. Everson KM, McQueen CE. Lycopene for prevention and treatment of prostate cancer. *Am J Health-Syst Pharm* 2004; **61:** 1562–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Licopenox.

Multi-ingredient: ***Arg.:*** Natubrown; ***Braz.:*** Licovit; ***Fr.:*** Phytolongbronze; Phytosolaire; ***Hong Kong:*** Palmetto Plus†; ***India:*** Lycored; ***Indon.:*** Legres; Legreskin; Lycoq; Optimax; Stacare; ***Philipp.:*** Nutrotal; ***Singapore:*** Palmetto Plus.

Lysergide *(BAN, rINN)*

Lisergida; Lisérgido; LSD; LSD-25; Lysergic Acid Diethylamide; Lysergidum. (+)-*NN*-Diethyl-D-lysergamide; (6a*R*,9*R*)-*NN*-Diethyl-4,6,6a,7,8,9-hexahydro-7-methylindolo[4,3-*fg*]quinoline-9-carboxamide.

Лизергид

$C_{20}H_{25}N_3O$ = 323.4.
CAS — 50-37-3.

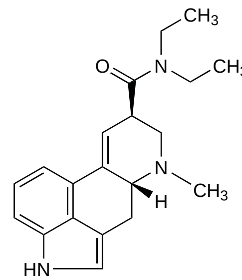

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of lysergide:
25; 25s; 100s; A; Acid; Acid tabs; Acido; Aeon flux; Alice; Alphabet; Angel tears; Angry paper; Animal; Barrels; Bart Simpson; Battery acid; Beast; Beavis & Butthead; Bells; Bevis & Butthead; Big D; Big daddy; Bird head; Birdhead; Black acid; Black star; Black sunshine; Black tabs; Blackbird; Blaze; Blotter; Blotter acid; Blotter cube; Blotters; Blue acid; Blue barrels; Blue chairs; Blue cheers; Blue fly; Blue heaven; Blue heavens; Blue microdot; Blue mist; Blue moons; Blue star; Blue tabs; Blue vials; Boomers; Brown bombers; Brown dots; Buvard; California sunshine; Cap; Caps; Casper the ghost; Caviar; Cheap basing; Cheers; Chief; Chinese dragons; Cid-drip the entertainer; Chocolate chips; Church; Cid; Class; Coffee; Colors; Comic book; Conductor; Contact lens; Crackers; Crystal; Crystal tea; Cube; Cupcakes; D; Deeda; Dental floss; Diablo; Dinosaurs; Domes; Dose; Doses; Dosure; Dots; Double dome; Dragon; DSL; El Cid; Electric Kool Aid; Ellis Day; Elvis; Eye Candy; Felix; Felix the Cat; Fields; Flash; Flashers; Flat blues; Flats; Flying triangle; Frogs; Fry; Gel; Gel caps; Gelatine squares; Geltab; Ghost; God's flesh; Golden dragon; Golf balls; Goofy's; Gooney birds; Grape parfait; Green double domes; Green single dome; Green single domes; Green wedge; Grey shields; Groovy lemon; Hats; Hawaiian sunshine; Hawk; Haze; Head light; Head lights; Headlights; Heaven; Heavenly; Heavenly blue; Illusions; Infinity; Instant zen; Jesus Christ acid; Kaliedescope; Keys to the kingdom; L; LAD; Lake Shore Drive; Laogor; Lason daga; Lason sa daga; Lavender; LBJ; Leary's; Lenos; Lens; Lids; Lime acid; Little smoke; Live, Spit and Die; Logor; Loony Toons; LSD; LSD-25; Lucy; Lucy in the sky with diamonds; Magic Tickets; Mellow yellow; Mickey's; Microdot; Microdots; Midnight Quinn; Mighty Quinn; Mikes; Mind blow; Mind detergent; Mist; Mister Natural; Monstre rouge; Monstre vert; Monterey Purple; Moons; Mother of God; Newspapers; One way; Oneway; Optical illusions; Orange ba; Orange barrels; Orange cubes; Orange haze; Orange micro; Orange sunshine; Orange wedges; Owsley; Owsley's acid; Owsley's blue dot; Ozzie's stuff; Pane; Paper; Paper acid; Peace; Peace tablets; Peaks; Pearly gates; Pellets; Pepa; Phoenix; Pills; Pink blotters; Pink panther; Pink robots; Pink wedge; Pink wedges; Pink witche; Pink witches; Pizza; Potato; Pure love; Purple barrels; Purple dome; Purple dots; Purple flats; Purple gel tabs; Purple haze; Purple hearts; Purple mikes; Purple ozoline; Purple wedge; Pyramid; Pyramids; Rain Drops; Rainbow; Recycle; Red lips; Rips; Royal blues; Roz-rox; Russian sickles; Sacrament; Sandoz; Serenity; Sheets; Shields; Sherman; Sid; Smears; Smiley; Snowmen; South parks; Specks; Square dancing tickets; Squirrel; Stamp; Stanley's stuff; Star; Strawberries; Strawberry; Strawberry fields; Sugar; Sugar cubes; Sugar lumps; Sunrise; Sunshine; Sunshine Acid; Superman; Syd; T; Tab; Tabs; Tail lights; Teddy bears; The Ghost; The Hawk; Ticket; Tickets; Ticket to ride; Timothy Leary; Timothy Leary Ticket; Trip; Trippers; Trips; Twenty-five; Uncle Sid; Uncle Sidney; Valley dolls; Vodka acid; Volcano 5; Vulcoes; Wafer; Waffles; Watercolors; Wedding bells; Wedge; Wedges; White dust; White lightning; White Owsley's; Window glass; Window pane; Woodstock; Yellow; Yellow dimples; Yellow sunshine; Yellows; Ying Yang; Zen; Zig Zag man.

Profile

Lysergide was formerly used therapeutically but is now encountered as a drug of abuse for its hallucinogenic and psychedelic properties.

There is considerable variation in individual reaction to lysergide. Disorders of visual perception are among the first and most constant reactions to lysergide. Subjects may be hypersensitive to sound. Extreme alterations of mood, depression, distortion of body image, depersonalisation, disorders of thought and time sense, and synaesthesia may be experienced. Anxiety, often amounting to panic, may occur (a 'bad trip'). Duration of effects may last for up to 12 hours after ingestion, although hallucinations can sometimes last up to 48 hours and psychoses for up to 4 days. The effects of lysergide may recur months after ingestion of lysergide; the recurrence or 'flashback' may be spontaneous or induced by alcohol, other drugs, stress, or fatigue.

The subjective effects of lysergide may be preceded or accompanied by somatic effects that are mainly sympathomimetic in nature and include mydriasis, tremor, hyperreflexia, hyperthermia, piloerection, muscle weakness, and ataxia. There may be nausea and vomiting and increased heart rate and blood pressure. Derangement of blood clotting mechanisms has been described. In addition, respiratory arrest, convulsions, and coma may result from overdoses. There is no evidence of fatal reactions to lysergide in man, although accidental deaths, suicides, and homicides have occurred during lysergide intoxication.

Tolerance develops to the behavioural effects of lysergide after several days and may be lost over a similar period. There is cross-tolerance between lysergide, mescaline, and psilocybine and psilocin, but not to amfetamine or to cannabis.

Physical dependence on lysergide does not seem to occur.

Mace Oil

Macis, aceite de.

NOTE. Mace has also been used as a name for solutions of chloroacetophenone (p.2280), a tear gas.

Profile

Mace oil is a volatile oil obtained by distillation from mace, the arillus of the seed of *Myristica fragrans* (Myristicaceae).

Nutmeg (p.2355) is the dried kernel of the seed of *M. fragrans.*

Mace is used as a flavour and carminative similarly to nutmeg. It has also been used with herbal substances and other volatile agents in preparations for musculoskeletal and respiratory-tract disorders. As with nutmeg, large doses of mace may cause epileptiform convulsions and hallucinations.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** China-Eisenwein; ***Cz.:*** Dr Theiss Schwedenbitter; Original Schwedenbitter; ***Rus.:*** Himcolin (Химколин).

Macrogols

Macrogola; Macrogoles; Macrogoller; Makrogoler; Makrogoliai; Makrogolit; Makrogolok; Makrogoly; PEGs; Polietilen Glikoller; Polyethylene Glycols; Polyoxyethylene Glycols.

$CH_2(OH)(CH_2OCH_2)_mCH_2OH$. Alternatively some authorities use the general formula $H(OCH_2CH_2)_nOH$ when the number assigned to n for a specified macrogol is 1 more than that of m in the first formula.

CAS — 25322-68-3 (macrogols); 37361-15-2 (macrogol 300).

ATC — A06AD15.

ATC Vet — QA06AD15.

Nomenclature. Macrogol is *BAN* and *rINN*. The name is followed by a figure which corresponds approximately to its average molecular weight.

Pharmacopoeias. Macrogols of various molecular weights are included in many pharmacopoeias.

Eur. (see p.vii) has a general monograph describing macrogol 300, 400, 600, 1000, 1500, 3000, 3350, 4000, 6000, 8000, 20 000, and 35 000. *USNF* has a general monograph describing Polyethylene Glycol which requires that it be labelled with the average nominal molecular weight as part of the official title.

Ph. Eur. 6.2 (Macrogols). Mixtures of polymers with the general formula $H(OCH_2CH_2)_nOH$, where n represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

Macrogol 300, 400, and 600 are clear, viscous, colourless or almost colourless, hygroscopic liquids. Miscible with water; very soluble in alcohol, in acetone, and in dichloromethane.

Macrogol 1000 is a white or almost white, hygroscopic solid with a waxy or paraffin-like appearance. Very soluble in water; freely soluble in alcohol and in dichloromethane.

Macrogol 1500 is a white or almost white solid with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; freely soluble in alcohol.

Macrogol 3000 and 3350 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; very slightly soluble in alcohol.

Macrogol 4000, 6000, and 8000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; practically insoluble in alcohol.

Macrogol 20 000 and 35 000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water; practically insoluble in alcohol; soluble in dichloromethane.

All macrogols are practically insoluble in fatty oils and in mineral oils. All macrogols should be stored in airtight containers.

USNF 26 (Polyethylene Glycol). Addition polymers of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which n represents the average number of oxyethylene groups. They may contain a suitable antioxidant. Each macrogol is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight increases, the water solubility, hygroscopicity, and solubility in organic solvents decrease, while the viscosity increases.

Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids, having a slight, characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material having a consistency similar to beeswax, or as creamy-white flakes, beads, or powders. Liquid grades are miscible with water; solid grades are freely soluble in water; all grades are soluble in alcohol, in acetone, in chloroform, in ethoxyethanol, in ethyl acetate, and in toluene; all grades are insoluble in ether and in hexane. The pH of a 5% solution of a macrogol in water is between 4.5 and 7.5.

Store in airtight containers.

Incompatibility. Macrogols can demonstrate oxidising activity leading to incompatibilities. The activity of bacitracin or benzylpenicillin may be reduced in a macrogol base. Some plastics are softened by macrogols.

Adverse Effects and Precautions

Macrogols appear to have relatively low toxicity, although any toxicity appears to be greatest with the macrogols of low molecular weight. They may cause stinging when used topically, especially on mucous membranes, and have been associated with hypersensitivity reactions such as urticaria. Hyperosmolality, metabolic acidosis, and renal failure have been reported after topical application of macrogols to burn patients. Topical preparations with a macrogol base should therefore be used with caution in patients with renal impairment and/or large areas of raw surfaces, burns, or open wounds.

Patients undergoing bowel cleansing with mixtures of macrogols (3350 or 4000) and electrolytes commonly experience local gastrointestinal discomfort, bloating, and nausea. Abdominal cramps, vomiting, and anal irritation may also occur and there have been rare reports of possible hypersensitivity reactions. These colonic lavage solutions are contra-indicated in gastrointestinal obstruction or perforation, ileus, gastric retention, peptic ulcer disease, and toxic megacolon; caution is advisable in patients with ulcerative colitis. Since aspiration may be a problem, they should be used with caution in patients with an impaired gag reflex, reflux oesophagitis, or diminished levels of consciousness. They should be given with caution to diabetic patients. Drugs taken within one hour of starting colonic lavage with an oral macrogol and electrolyte mixture may be flushed from the gastrointestinal tract unabsorbed.

Effects on fluid and electrolyte homoeostasis. A syndrome of elevated total serum calcium (with a concomitant decrease in ionised calcium), hyperosmolality, metabolic acidosis, and renal failure has been observed in *animals*[1] and in burn patients[2] after the topical application of preparations with a macrogol base. The FDA has recommended that topical preparations containing macrogols should be used with caution in burn patients with known or suspected renal impairment, as macrogols absorbed through denuded skin and not excreted normally by a compromised kidney could lead to symptoms of progressive renal impairment.[3]

The use of macrogol and electrolyte solutions for bowel preparation has also been associated with sodium and water retention, resulting in exacerbation of heart failure in a patient with diabetic gastroparesis,[4] and with the development of pulmonary oedema possibly due to aspiration in a child without cardiac or renal disease.[5]

1. Herold DA, *et al.* Toxicity of topical polyethylene glycol. *Toxicol Appl Pharmacol* 1982; **65:** 329–35.
2. Bruns DE, *et al.* Polyethylene glycol intoxication in burn patients. *Burns* 1982; **9:** 49–52.
3. Anonymous. Topical PEG in burn ointments. *FDA Drug Bull* 1982; **12:** 25–6.
4. Granberry MC, *et al.* Exacerbation of congestive heart failure after administration of polyethylene glycol-electrolyte lavage solution. *Ann Pharmacother* 1995; **29:** 1232–5.
5. Paap CM, Ehrlich R. Acute pulmonary edema after polyethylene glycol intestinal lavage in a child. *Ann Pharmacother* 1993; **27:** 1044–7.

Effects on the kidneys. Macrogol 400, which was present in a lorazepam injection, could have contributed to renal damage suggestive of acute tubular necrosis in a patient who received large doses (averaging lorazepam 95 mg daily) for 43 days.[1] The cumulative dose of macrogol 400 during this period was about 220 mL.

1. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; **29:** 1110–14.

Hypersensitivity. Hypersensitivity to macrogols is uncommon but both immediate urticarial reactions and delayed allergic contact dermatitis have been reported following the topical application of preparations with a macrogol vehicle or base.[1] An anaphylactic reaction has been associated with the ingestion of macrogols in a multivitamin tablet.[2] The manufacturers of preparations containing macrogols and electrolytes for bowel cleansing have reported isolated instances of skin reactions and rhinorrhoea.

1. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978; **4:** 135–8.
2. Kwee YN, Dolovich J. Anaphylaxis to polyethylene glycol (PEG) in a multivitamin tablet. *J Allergy Clin Immunol* 1982; **69:** 138.

Overdosage. Ingestion of 2 litres of a colonic lavage solution containing macrogol 400 instead of macrogol 4000 resulted in a patient developing severe metabolic acidosis due to systemic absorption of the macrogol and rapidly becoming comatose.[1] The patient was successfully treated with intravenous bicarbonate and dialysis.

1. Bélaïche J, *et al.* Coma acidosique après préparation colique par du polyèthylène glycol. *Gastroenterol Clin Biol* 1983; **7:** 426–7.

Pharmacokinetics

Liquid macrogols may be absorbed when taken by mouth but macrogols of high molecular weight, such as macrogol 3350, are not significantly absorbed from the gastrointestinal tract. There is evidence of absorption of macrogols when applied to damaged skin. Macrogols entering the systemic circulation are predominantly excreted unchanged in the urine; low-molecular-weight macrogols may be partly metabolised.

◊ References.

1. DiPiro JT, *et al.* Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. *Clin Pharm* 1986; **5:** 153–5.

Uses and Administration

Macrogols are relatively stable, non-toxic compounds which have a range of properties depending on their molecular weight. They are widely used in pharmaceutical manufacturing as water-soluble bases for topical preparations and suppositories, as solvents and vehicles, and as solubilising agents, tablet binders, plasticisers in film coating, and tablet lubricants. They have also been reported to have antibacterial properties. Macrogols of high molecular weight such as macrogol 4000 have been used as inert markers in studies on intestinal absorption and excretion.

A mixture of macrogol 3350 or 4000 with electrolytes is used for **bowel preparation** before colonoscopy, radiological procedures, or surgery. These preparations have been formulated so that the osmotic activity of the macrogol and concentrations of the electrolytes result in a minimum net effect on the fluid and electrolyte balance. Reconstituted aqueous solutions of different preparations contain about 59 g or 100 g or 105 g of the macrogol per litre. The method of administration depends on the preparation. Adults are given 200 to 300 mL of the reconstituted aqueous solution, which they have to swallow rapidly, and this is repeated every 10 to 15 minutes until the rectal effluent is clear, or until a total of 3 to 4 litres of the solution has been consumed. Alternatively, 2 litres of reconstituted solution is taken in the evening preceding the clinical procedure, or divided as 1 litre in the evening and 1 litre in the early morning of the day of the procedure. A dose for children is 25 mL/kg per hour. Bowel evacuation usually begins about 1 hour after starting dosage and is complete in about 4 hours. Patients should fast for at least 2 or 3 hours before drinking the solution. Additional flavouring ingredients, sugar, or other sweeteners should not be added to the solution. If distension or pain occur, dosage should be temporarily stopped or the interval between drinks extended. For use by nasogastric tube, a rate of 20 to 30 mL per minute has been used.

Similar preparations are used in patients 12 years of age and over for the treatment of **chronic constipation** in a usual dose of 125 mL of a solution containing 105 g of the macrogol per litre, up to three times daily. The maximum course is 2 weeks, which may be repeated if necessary. For children with chronic constipation, the usual initial daily dose for those aged 2 to 6 years is 62.5 mL, and for those aged 7 to 11 years, 125 mL. Thereafter, the dose should be increased or decreased as necessary to produce regular soft stools; the usual maximum dose is 250 mL daily.

In the management of **faecal impaction**, 8 doses of 125 mL of solution should be consumed within 6 hours for a maximum of 3 days. Patients with impaired cardiovascular function should take no more than 2 doses in any one hour. Children aged 5 to 11 years may be treated for faecal impaction in an escalating dose until disimpaction occurs up to a maximum of 7 days; the total daily dose should be divided and consumed within a 12-hour period. Four doses of 62.5 mL of solution are given initially on the first day, increasing steadily to a maximum of 12 doses daily on days 5 to 7. Doses for prevention of recurrence of faecal impaction in children are as for children's doses for chronic constipation (see above). The *BNFC* recommends that children aged 1 to 5 years with faecal impaction may be given two doses of 62.5 mL of solution on the first day, then four doses daily for 2 days, then 6 doses daily for 2 days, and finally 8 doses daily on days 6 and 7.

Conjugation of drugs and therapeutic proteins with macrogols (**pegylation**) has been tried in an attempt to improve their pharmacokinetic profiles and to reduce their adverse effects. Pegylation may also reduce the immunogenicity of therapeutic proteins. Examples of pegylated proteins include pegademase (p.2364), pegaspargase (p.682), and peginterferon alfa (p.888).

Drug delivery systems. References to the use of macrogols in delivery systems for drugs and proteins.

1. Reddy KR. Controlled-release, pegylation, liposomal formulations: new mechanisms in the delivery of injectable drugs. *Ann Pharmacother* 2000; **34:** 915–23.
2. Harris JM, *et al.* Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* 2001; **40:** 539–51.

Phenol poisoning. Washing with liquid macrogols has been recommended in the emergency treatment of skin contamination with phenol, see p.1656.

Preparations

USP 31: PEG 3350 and Electrolytes for Oral Solution.

Proprietary Preparations (details are given in Part 3)

Austria: DrinkaLax; MixaLax; ***Belg.:*** Forlax; ***Cz.:*** Forlax; ***Fr.:*** Forlax; ***Ger.:*** Forlax; Glandomed; Laxofalk; ***Gr.:*** Tanilas; Transorbin†; ***Hong Kong:*** Forlax; ***Hung.:*** Forlax; ***Israel:*** Peglax; ***Ital.:*** Onlipeg; Paxabel; Pergidal; ***Malaysia:*** Forlax; ***Mex.:*** Contumax; ***Neth.:*** Forlax; ***Pol.:*** Forlax; Prolaxatan; ***Port.:*** Forlax; Philenterol; Transipeg; ***Rus.:*** Forlax (Форлакс); Polyoxidin (Полиоксидин); ***Singapore:*** Forlax; ***Swed.:*** Forlax; ***Thai.:*** Forlax; ***Turk.:*** Transipeg; ***UK:*** Idrolax†; ***USA:*** GlycoLax; MiraLax.

Multi-ingredient: ***Arg.:*** Adital; Barex; Irix Lagrimas; Systane; Transipeg; Visine Lagrimas; Visine Plus; ***Austral.:*** Colonic Lavage Powder†; Colonlytely; Colonprep†; Glycoprep; Glycoprep-C; Movicol; Prep Kit-C; Visine Advanced Relief; Visine Revive†; Visine True Tears†; ***Austria:*** Klean-Prep; Movicol; Transipeg; ***Belg.:*** Colofort; Colopeg; Delpeg; Endofalk; Endopeg; Klean-Prep; Movicol; Precosol†; Transipeg; ***Braz.:*** Muvinlax; NuLytely; ***Canad.:*** CoLyte; GoLytely; Klean-Prep; Peglyte; Rhinaris; Salinol†; Secaris; Systane; Visine Advance Triple Action; Visine Cool; ***Chile:*** Systane; ***Cz.:*** Fortrans; Movicol; ***Denm.:*** Klean-Prep†; Ledermix†; Movicol; ***Fin.:*** Colonsoft; Colonsteril; Klean-Prep; Movicol; ***Fr.:*** Colopeg; Fortrans; Klean-Prep; Movicol; Moviprep; SST; Systane; Transipeg; ***Ger.:*** Colonorm N†; Delcoprep; Endofalk; Isomol; Klean-Prep; Movicol; Oralav; ***Gr.:*** Fortrans; Izetafin; Klean-Prep; ***Hong Kong:*** Clinac OC; Hypotears; Klean-Prep; Movicol; Systane; Visine Moisturizing; ***Indon.:*** Laxarec; Microlax; Visine Extra; ***Irl.:*** Klean-Prep; Movicol; ***Israel:*** Meroken New; ***Ital.:*** Hypotears; Isocolan; Klean-Prep; Macro-P; Movicol; Selg; Selg-Esse; Systane; ***Malaysia:*** Fortrans; Hypotears; Systane; ***Mex.:*** NuLytely; Systane; Visine Extra; ***Neth.:*** Colofort; Eleprep; Endofalk; Klean-Prep; Movicolon; Transipeg; ***Norw.:*** Klean-Prep; Laxabon; Movicol; ***NZ:*** Glycoprep†; Klean-Prep; Movicol; Visine Advanced Relief; ***Philipp.:*** Moisturizing All Clear; Systane; Visine Refresh; ***Pol.:*** Fortrans; ***Port.:*** Endofalk; Fortrans; Klean-Prep; Movicol; Pecol; ***Rus.:*** Fortrans (Фортранс); Transipeg (Транзипег); ***S.Afr.:*** GoLytely; Klean-Prep; Movicol; ***Singapore:*** Fortrans; Klean-Prep; Movicol; Systane; ***Spain:*** Casenglicol; Evacuante; Klean-Prep; Movicol; Omesal; ***Swed.:*** Klean-Prep†; Laxabon; Movicol; ***Switz.:*** Colo-Sol; Colyt; Fordtran; Gleitmittel†; Hypotears; Isocolan; Klean-prep; Movicol; Transipeg; ***Thai.:*** Niflec; Systane; Unison Enema; ***Turk.:*** Movicol; ***UK:*** Hypotears†; Klean-Prep; Laxido; Movicol; Moviprep; SST; ***USA:*** Advanced Relief Visine; Aquasite†; CoLyte; GoLytely; HalfLytely; Hypotears; MoviPrep; Nu-Tears II; NuLytely; Numoisyn; OCL; Tetrasine Extra†; TriLyte; Visine Moisturizing†; Visine Pure Tears; Visine Tears; ***Venez.:*** Lic Polvo†; Systane.

Magnesium Glutamate Hydrobromide

Glutamato magnésico, hidrobromuro de; Magnesium α-Aminoglutarate Hydrobromide; Magnesium Bromoglutamate.

$(C_5H_8NO_4)_2Mg,HBr = 397.5.$

Profile

Magnesium glutamate hydrobromide has been used as a sedative and hypnotic in the treatment of insomnia, neuroses, and behavioural disorders. The use of bromides is generally deprecated (see p.2269).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Gamalate B6; ***Spain:*** Cefabol; Gamalate B6; Psicosoma Solucion.

Maleic Acid

Acide maléique; Acidum maleicum; (*Z*)-Butenedioic Acid; Kwas maleinowy; Kyselina maleinová; Maleico, ácido; Maleiinihappo; Maleino rūgštis; Maleinsav; Maleinsyra; Toxilic Acid. *cis*-Butenedioic acid.

$C_2H_2(CO_2H)_2 = 116.1.$

CAS — 110-16-7.

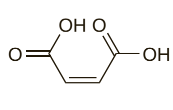

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Maleic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of less than 2. Store in glass containers. Protect from light.

USNF 26 (Maleic Acid). A white crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in ether. Store in airtight glass containers. Protect from light.

Profile

Maleic acid is used in the preparation of Ergometrine Injection (BP 2008) and Ergometrine and Oxytocin Injection (BP 2008).

Malic Acid

Acide Malique; Acidum malicum; Acidum Malicum Racemicum; Äppelsyra; Apple Acid; E296; Hydroxysuccinic Acid; Kyselina jablečná racemická; Málico, ácido; Obuolių rūgštis; Omenahappo. (2*RS*)-2-Hydroxybutanedioic acid.

$C_4H_6O_5 = 134.1.$

CAS — 6915-15-7 (malic acid); 636-61-3 ((+)-malic acid); 97-67-6 ((−)-malic acid); 617-48-1 ((±)-malic acid).

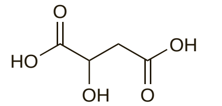

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ger. also includes the *S*-form ((−)-malic acid).

Ph. Eur. 6.2 (Malic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol, sparingly soluble in acetone.

USNF 26 (Malic Acid). A white or practically white, crystalline powder or granules. Very soluble in water; freely soluble in alcohol.

Profile

Malic acid is used in pharmaceutical formulations as an acidifier, flavour, and as an alternative to citric acid in effervescent powders. It is used with butylated hydroxytoluene as an antioxidant in vegetable oils. It is used topically with benzoic acid and salicylic acid for desloughing of ulcers, burns, and wounds, and systemically with arginine (p.1928) in preparations for the treatment of liver disorders. Pastilles containing malic acid are also used in the management of dry mouth (p.2140).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Acerbine; Leberinfusion; Rocmaline; ***Chile:*** Secand; ***Fin.:*** Xerodent; ***Fr.:*** Rocmaline; Sphingogel†; Squaphane; SST; ***Hung.:*** Rocmalat†; ***Ital.:*** Keraflex; ***Neth.:*** Sterofundin M; ***Norw.:*** Xerodent; ***S.Afr.:*** Aserbine; ***Spain:*** Acerbiol; ***Swed.:*** Xerodent; ***Switz.:*** Acerbine†; ***UK:*** Aserbine†; Hydrotab; Salivix; SST; ***USA:*** Numoisyn; ***Venez.:*** Lecivar Plus.

Mallow

Erdei mályvavirág (mallow flower); Květ slézu lesního (mallow flower); Liść ślazu (mallow leaf); Malvablomma (mallow flower); Malvae folium (mallow leaf); Malvae sylvestris flos (mallow flower); Malvenblätter (mallow leaf); Malvenblüten (mallow flower); Mauve des Bois (*Malva silvestris*); Mauve, feuille de (mallow leaf); Mauve, fleur de (mallow flower); Metsämalvankukka (mallow flower); Miškinių dedešvų žiedai (mallow flower).

Pharmacopoeias. *Eur.* (see p.vii) includes the dried flowers. *Swiss* includes Mallow Leaf (Malvae Folium) which may be *Malva sylvestris* or *M. neglecta*.

Ph. Eur. 6.2 (Mallow Flower; Malvae sylvestris flos). The whole or fragmented dried flower of *Malva sylvestris* or its cultivated varieties. Protect from light.

Profile

Mallow flower and leaf act as demulcents and are ingredients of herbal remedies for coughs and cold symptoms. Mallow flower is used to enhance the colour of herbal teas and other foodstuffs. Mallow is also included in herbal remedies for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Mictasol; ***Cz.:*** Slezovy Kvet; ***Switz.:*** Malvedrin.

Multi-ingredient: ***Arg.:*** Acnetrol; KW; Mictasol Azul; Prurigel; ***Austral.:*** Neo-Cleanse; ***Austria:*** Midro Tee; ***Belg.:*** Mictasol-P; Mictasol†; ***Braz.:*** Malvatricin Natural Soft; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvodon; Mictasol com Sulfa†; Peitoral Angico Pelotense†; ***Canad.:*** Original Herb Cough Drops; Swiss Herb Cough Drops; ***Cz.:*** Erkaltungstee†; Magen- und Darmtee N†; ***Fr.:*** Alkagin; Erygine; Mediflor Tisane Hepatique No 5; Mictasol; Mucogyne; ***Israel:*** Midro-Tea; ***Ital.:*** Alkagin; Dentaton; Glicerolax; Iridil; Microclismi Marco Viti; Microclismi Sella; Mictasol Bleu†; Mictasone; Neoderma 47; Nevril; Ninfagin; Piodermina; Proctonet†; ***Port.:*** Alkagin; Midro†; ***Rus.:*** Herbion Plantain Syrup (Гербион Сироп Подорожника); ***Switz.:*** Malvedrin; Malveol.

Malotilate *(USAN, rINN)*

Malotilato; Malotilatum; NKK-105. Diisopropyl 1,3-dithiole-$\Delta^{2,}$ -malonate.

Малотилат

$C_{12}H_{16}O_4S_2 = 288.4.$

CAS — 59937-28-9.

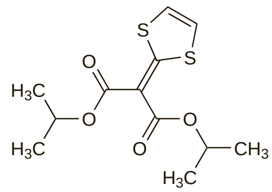

Profile

Malotilate has been investigated for its reported protective effects on liver function in patients with chronic hepatic disease.

◊ References.

1. A European Multicentre Study Group. The results of a randomized double blind controlled trial evaluating malotilate in primary biliary cirrhosis. *J Hepatol* 1993; **17:** 227–35.

Mammalian Tissue Extracts

Mamíferos, extractos tisulares.

Экстракты из Млекопитающей Ткани

Profile

Many medicinal preparations with definite pharmacological activity and valid clinical uses are of mammalian origin and are described under their appropriate monographs—for example, calcitonin, corticotropin, hydrocortisone (cortisol), some enzymes, heparin, insulin, parathyroid hormone, pituitary hormones, some sex hormones, and thyroid.

Other preparations of animal origin have been promoted for various disorders. Evidence of pharmacological activity is generally lacking and such preparations are often of doubtful benefit.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bros†; Raw Prostate†; Sigmatrofic; Solcoseryl; ***Austria:*** Actovegin; Ambotonin; Apoderm; Cerebrolysin; Cerebrotonin; Enzynorm; Medoenzym; Solcoseryl; ***Braz.:*** Acrosin†; Sukepar†; ***Chile:*** Renacenz; ***Cz.:*** Solcoseryl; ***Fr.:*** Eurobiol; ***Ger.:*** Actihaemyl; Actovegin; Cerebrolysin; Chrysocor†; NeyFegan (Revitorgan-Dilutionen Nr 26)†; NeyFegan-Solubile†; NeyPsorin (Revitorgan-Dilutionen Nr 5)†; Solcosplen†; Voltil†; ***Hong Kong:*** Actovegin; Cerebrolysin; Leviden; Solcoseryl; ***Hung.:*** Actovegin; Raveron†; Sirepar†; ***India:*** Placentrex; ***Indon.:*** Solcoseryl; ***Ital.:*** Cellulin Retinale; Liposom; ***Jpn:*** Solcoseryl; ***Malaysia:*** Solcoseryl; ***Mex.:*** Reposton; ***Neth.:*** Solcoseryl†; ***Philipp.:*** Solcoseryl; ***Pol.:*** Solcoseryl; ***Rus.:*** Actovegin (Актовегин); Cerebrolysin (Церебролизин); Cortexin (Кортексин); Prostacor (Простакор)†; Prostatilen (Простатилен); Retinalamin (Ретиналамин); Sirepar (Сирепар); Solcoseryl (Солкосерил); Vitaprost (Витапрост); ***S.Afr.:*** Enzynorm†; ***Singapore:*** Solcoseryl; ***Spain:*** Solcoseryl; ***Switz.:*** Solcoseryl; ***Thai.:*** Actovegin†; Cerebrolysin; Hepavit; Sirepar; Solcoseryl; ***USA:*** Kutapressin†.

Multi-ingredient: ***Arg.:*** ITE B12 Forte; Melagel; Pat-Chobet; Solcoseryl Dental†; ***Austria:*** Bilatin; Intestinol; Solcoseryl Dental; Wobe-Mugos; ***Belg.:*** Grains de Vals; ***Braz.:*** Boldopeptan†; Digestron†; Extrato Hepatico Composto; Extrato Hepatico Vitaminado†; Fol Sang; Hecrosine B12†; Hematiase B12; Hemofer†; Hormo Hepatico†; Lisan†; Lisotox; Olohepat†; Panvitrop; Xantina B12†; Xantinon B12; ***Canad.:*** ratio-Heracline; ***Cz.:*** Cerebrolysin; ***Ger.:*** Enzym-Harongan; Enzynorm f; Factor AF2; Geriaplasma†; Hevert-Enzym Comp; Lomazell forte N†; NeyTumorin (Revitorgan-Lingual Nr 66)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; poliomyelan†; Ribo-Wied†; Solcoseryl Dental; tactu-nerval†; ***Hong Kong:*** Solcoseryl Dental; ***Hung.:*** Dipankrin; Neogranormon; ***India:*** Hepatoglobine; Iberol; Livogen†; Plastules; ***Indon.:*** Bioplacenton; Centabio; LaktaFit; Moloco + B12; Solcoseryl Dental; ***Ital.:*** Biotrefon Plus; Gastro-Pepsin; ***Malaysia:*** Solcoseryl Dental; ***Mex.:*** Cholal Modificado; ***NZ:*** Movelat†; ***Philipp.:*** Godex; Solcoseryl Dental; ***Port.:*** Cerebrolysine; ***Rus.:*** Solcoseryl Dental (Солкосерил Дентальная); ***S.Afr.:*** Prohep; ***Singapore:*** Solcoseryl Dental; ***Spain:*** Hepacomplet B12 Triple†; Hepadif; Policolinosil; Rubrocortin†; ***Switz.:*** Solcoseryl Dentaire; Zymoplex†; ***Thai.:*** Solcoseryl Dental; Trinsicon†; ***UK:*** Hematinic; S.P.H.P.; ***USA:*** Feocyte; FeoGen; Geritonic; I-L-X.

Manuka

New Zealand Tea Tree.

Profile

The oil of manuka (*Leptospermum scoparium*) is used for its antimicrobial properties as an alternative to melaleuca oil (p.2338). It is also used in aromatherapy. Manuka honey has also been used as a wound dressing (p.1948).

◊ References.

1. Cooper RA, *et al.* The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. *J Appl Microbiol* 2002; **93:** 857–63.
2. Cooper RA, *et al.* The efficacy of honey in inhibiting strains of Pseudomonas aeruginosa from infected burns. *J Burn Care Rehabil* 2002; **23:** 366–70.
3. English HK, *et al.* The effects of manuka honey on plaque and gingivitis: a pilot study. *J Int Acad Periodontol* 2004; **6:** 63–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Antiac; Sinose.

Marjoram

Majoranae Herba; Marjolaine; Sweet Marjoram; Ziele majeranku.

NOTE. Distinguish from wild marjoram (see Oregano, p.2357).

Pharmacopoeias. In *Pol.*

Profile

The dried leaves and flowers of marjoram, *Origanum majorana* (*Majorana hortensis*) (Lamiaceae), and the essential oil obtained from them have antibacterial properties. They are used, either separately or in combination, in herbal remedies for a variety of disorders. Marjoram is also used as a culinary herb.

Marjoram oil is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Menodoron; ***Fr.:*** Dystolise; ***Neth.:*** Luuf Verkoudheidsbalsem (voor babies); ***Pol.:*** Salviasept; ***S.Afr.:*** Menodoron; ***Spain:*** Natusor Sinulan†.

Mastic

Almáciga; Mastiche; Mastiksi; Mastix; Pistacijų mastika.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Mastic). The dried resinous exudate obtained from stems and branches of *Pistacia lentiscus* var. *latifolius*. It contains a minimum of 1% v/w of essential oil, calculated with reference to the anhydrous drug. It should not be powdered.

Profile

Solutions of mastic in alcohol, chloroform, or ether have been used, applied on cotton wool, as temporary fillings for carious teeth. Compound Mastic Paint (BP 1980) was formerly used as a protective covering for wounds and to hold gauze in position.

Mastic gum has been used in the management of peptic ulcer disease.

Peptic ulcer disease. Mastic may be effective in the treatment of peptic ulcer disease possibly due to an antibacterial action on *Helicobacter pylori*.[1] However, one small clinical study found no benefit.[2]

1. Huwez FU, *et al.* Mastic gum kills Helicobacter pylori. *N Engl J Med* 1998; **339:** 1946. Correction. *ibid.*: **340:** 576 [dose].
2. Bebb JR, *et al.* Mastic gum has no effect on Helicobacter pylori load in vivo. *J Antimicrob Chemother* 2003; **52:** 522–3.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Mastika.

Meadowsweet

Älgört; Filipendulae ulmariae herba; Mesiangervo; Nať tužebníku jilmového; Pelkinių vingiorykščių žolė; Queen of the Meadows; Reina de los prados; Reine des Prés; Reine des prés, sommité fleurie de; Spiraeae Herba; Ulmaria.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Meadowsweet). The whole or cut, dried flowering tops of *Filipendula ulmaria* (*Spiraea ulmaria*). It contains a minimum of 0.1% v/w of steam-volatile substances (dried drug). It has an aromatic odour of methyl salicylate after crushing.

Profile

Meadowsweet is used in herbal medicine as a diuretic and in gastrointestinal and rheumatic disorders.

Homoeopathy. Meadowsweet has been used in homoeopathic medicines under the following names: Filipendula ulmaria; Spiraea ulmaria; Spiraea ulmaria ex herba; Filip. ul.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Antirevmaticky Caj; ***Fr.:*** Drainuryl; Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane No 4 Diuretique; Polypirine; ***Ital.:*** Flodolor; Neuralta Migren; Pik Gel; Sambuco (Specie Composta)†; Tiglio (Specie Composta)†; ***Mex.:*** Rodan; ***Pol.:*** Reumaherb; ***Spain:*** Dolosul†; Natusor Harpagosinol†; Natusor Renal†; ***Switz.:*** Urinex; ***UK:*** Acidosis; Indigestion Mixture; ***USA:*** Amerigel.

Meclofenoxate Hydrochloride *(BANM, rINNM)* ⊗

Centrophenoxine Hydrochloride; Clofenoxine Hydrochloride; Clophenoxate Hydrochloride; Deanol 4-Chlorophenoxyacetate Hydrochloride; Hidrocloruro de meclofenoxato; Meclofenoxane Hydrochloride; Méclofénoxate, Chlorhydrate de; Meclofenoxati Hydrochloridum. 2-Dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride.

Меклофеноксата Гидрохлорид

$C_{12}H_{16}ClNO_3,HCl = 294.2.$

CAS — 51-68-3 (meclofenoxate); 3685-84-5 (meclofenoxate hydrochloride).

ATC — N06BX01.

ATC Vet — QN06BX01.

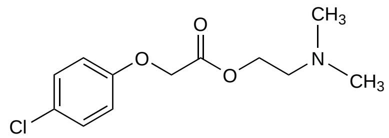

(meclofenoxate)

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Meclofenoxate hydrochloride has been claimed to aid cellular metabolism in the presence of diminished oxygen concentrations. It has been given mainly for mental changes in the elderly, or after strokes or head injury.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Lucidril; ***Ger.:*** Cerutil†; Helfergin†; ***Hung.:*** Helfergin†.

Meglumine *(BAN, rINN)*

Meglumiini; Meglumin; Meglumina; Megluminas; Méglumine; Megluminum. *N*-Methylglucamine; 1-Methylamino-1-deoxy-D-glucitol.

Меглюмин

$C_7H_{17}NO_5 = 195.2.$

CAS — 6284-40-8.

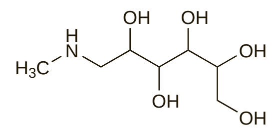

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Meglumine). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane.

USP 31 (Meglumine). White to faintly yellowish-white, odourless crystals or powder. Freely soluble in water; sparingly soluble in alcohol.

Profile

Meglumine is an organic base used for the preparation of salts of organic acids including many used as contrast media.

Melaleuca Oil

Australian Tea Tree Oil; Melaleuca, aceite de; Mélaleuca, huile essentielle de; Melaleucae aetheroleum; Melaleucae Etheroleum; Mirtenių eterinis aliejus; Oleum Melaleucae; Silice kajeputu střídavolistého; Tea Tree Oil; Teepuuöljy; Teträdolja.

CAS — 68647-73-4; 8022-72-8.

NOTE. Though the synonym Ti-tree Oil has been used for melaleuca oil (e.g. in BPC 1949), the name Ti-tree is also applied to species of *Cordyline* (Liliaceae) indigenous to New Zealand.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tea Tree Oil). The essential oil obtained by steam distillation from the foliage and terminal branchlets of *Melaleuca alternifolia*, *M. linariifolia*, *M. dissitiflora*, and/or other species of *Melaleuca*. It contains less than 7.0% aromadendrene, less than 15% cineole, 0.5 to 12.0% *p*-cymene, 0.5 to 4.0% limonene, 1.0 to 6.0% α-pinene, less than 3.5% sabinene, 5.0 to 13.0% α-terpinene, 10.0 to 28.0% γ-terpinene, minimum of 30% terpinen-4-ol, 1.5 to 8.0% α-terpineol, and 1.5 to 5.0% terpinolene.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Melaleuca oil has bactericidal and fungicidal properties and is used topically for various skin disorders. It is also used in aromatherapy.

◊ References.

1. Carson CF, *et al.* Efficacy and safety of tea tree oil as a topical antimicrobial agent. *J Hosp Infect* 1998; **40:** 175–8.
2. Allen P. Tea tree oil: the science behind the antimicrobial hype. *Lancet* 2001; **358:** 1245.
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4. Hammer KA, *et al.* In vitro activity of Melaleuca alternifolia (tea tree) oil against dermatophytes and other filamentous fungi. *J Antimicrob Chemother* 2002; **50:** 195–9.
5. Satchell AC, *et al.* Treatment of dandruff with 5% tea tree oil shampoo. *J Am Acad Dermatol* 2002; **47:** 852–5.
6. Koh KJ, *et al.* Tea tree oil reduces histamine-induced skin inflammation. *Br J Dermatol* 2002; **147:** 1212–7.
7. Mozelsio NB, *et al.* Immediate systemic hypersensitivity reaction associated with topical application of Australian tea tree oil. *Allergy Asthma Proc* 2003; **24:** 73–5.
8. Perrett CM, *et al.* Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; **28:** 167–70.
9. Hammer KA, *et al.* Antifungal effects of Melaleuca alternifolia (tea tree) oil and its components on Candida albicans, Candida glabrata and Saccharomyces cerevisiae. *J Antimicrob Chemother* 2004; **53:** 1081–5.
10. Hammer KA, *et al.* A review of the toxicity of Melaleuca alternifolia (tea tree) oil. *Food Chem Toxicol* 2006; **44:** 616–25.
11. Carson CF, *et al.* Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev* 2006; **19:** 50–62.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Clean Skin Anti Acne; Rapaid Antiseptic†; Rapaid Itch Relief; ***Chile:*** Acnoxyl Gel Cuidado Intensivo†; Acnoxyl Gel De Limpieza†; Acnoxyl Stick Corrector†; Sebolic; ***Fr.:*** Myleuca; ***Israel:*** Burnshield; ***Malaysia:*** MOOV; ***Singapore:*** Rapaid†; ***UK:*** Burnshield Gel; Melavir.

Multi-ingredient: ***Arg.:*** Aveno; ***Austral.:*** Apex Repel Natural; APR Cream†; Clean Skin Face Wash; Curaderm†; Neutralice; Rapaid Rash-Relief; SP Cream†; VR†; ***Chile:*** Acnoxyl Abrasivo; Acnoxyl Gel Humectante; Acnoxyl Jabon Liquido; Acnoxyl Jabon†; Acnoxyl Locion Tonica; Acnoxyl Shampoo Cabello Graso†; ***Fr.:*** Cicatridine; Dermocica; Mycogel; Phytosquame; Squaphane P; ***Hong Kong:*** Mycogel; ***Ital.:*** Proctopure; ***Malaysia:*** T3 Acne; ***NZ:*** Apex Repel Natural; Electric Blue Headlice; Lice Blaster; ***Singapore:*** Burnaid; Rapaid†; T3; Tinasolve†; ***Thai.:*** Fungicon; Gynecon-T; ***UK:*** Dr Johnsons Nit & Lice; Sinose; Skin Clear; Tea Tree & Witch Hazel Cream; Teenstick.

Melanocyte-stimulating Hormone

B Hormone; Chromatophore Hormone; Intermedin; Intermedina; Melanotropin; MSH; Pigment Hormone.

CAS — 9002-79-3.

Profile

Melanocyte-stimulating hormone is a polypeptide isolated from the pars intermedia of the pituitary of fish and amphibia which causes dispersal of melanin granules in the skin of fish and amphibia and allows adaptation to the environment.

In adult humans, the pituitary gland lacks a distinct intermediate lobe, and the pituitary is not thought to secrete melanocyte-stimulating hormone (MSH) directly. However, the precursor molecule, pro-opiomelanocortin, is cleaved in the pituitary into corticotropin (p.1523), the glycoprotein β-lipotrophin (β-LPH), and an amino-terminal peptide. Subsequent processing in other tissues, such as the brain and gastrointestinal tract, may yield three forms of MSH, α-MSH (via corticotropin cleavage), β-MSH, and γ-MSH. The presence and function of these melanocyte-stimulating hormones in man are uncertain. A receptor analogous to that in amphibians is apparently lacking in humans; effects on skin pigmentation emanating from the pituitary are primarily mediated by corticotropin.

Release of melanocyte-stimulating hormone is inhibited in *animals* by melanostatin; there is also evidence for a hypothalamic releasing factor (MRF).

Melanocyte-stimulating hormone is under investigation, as α-MSH, in the prevention and treatment of ischaemic intrinsic acute renal failure. A synthetic analogue of α-MSH (4-L-norleucine-7-D-phenylalanine-α-MSH; melanotan-I) is under investigation as a stimulant of melatonin production for the prevention of sunburn.

Melanostatin

Intermedin-inhibiting Factor; Melanocyte-stimulating-hormone-release-inhibiting Factor; Melanostatina; Melanotropin Release-inhibiting Factor; MIF. Pro-Leu-Gly-NH_2.

CAS — 9083-38-9.

Profile

Melanostatin is a tripeptide, obtained from the hypothalamus, that inhibits the release of melanocyte-stimulating hormone (see above) in *animals*. However, there is little evidence of its activity in man. It has been tried in the treatment of depression and parkinsonism but with little benefit.

Melatonin

N-Acetyl-5-methoxytryptamine; Melatoniini; Melatonina; Melatoninum. *N*-[2-(5-Methoxyindol-3-yl)ethyl]acetamide.

$C_{13}H_{16}N_2O_2 = 232.3.$

CAS — 73-31-4.

ATC — N05CH01.

ATC Vet — QN05CH01.

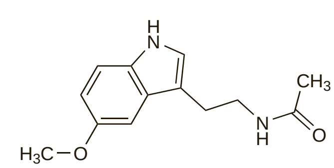

Profile

Melatonin is a hormone produced in the pineal gland from the amino acid tryptophan. Results mainly from *animal* studies indicate that melatonin increases the concentration of aminobutyric acid and serotonin in the midbrain and hypothalamus and enhances the activity of pyridoxal-kinase, an enzyme involved in the synthesis of aminobutyric acid, dopamine, and serotonin. Melatonin is involved in the inhibition of gonadal development and in the control of oestrus. It is also involved in protective changes in skin coloration. There appears to be a diurnal rhythm of melatonin secretion; it is secreted during hours of darkness and may affect sleep pattern. Because of its possible role in influencing circadian rhythm, melatonin has been tried in the alleviation of jet lag and other disorders resulting from delay of sleep. Doses of 2 mg given orally before bedtime are used in the short-term management of insomnia in patients aged 55 or over. Melatonin has also been studied in various depressive disorders including seasonal affective disorder, and in large doses for its contraceptive activity.

A number of melatonin analogues are being developed.

Adverse effects. An increase in seizure activity was noted in 4 of 6 children with severe neurological deficits during treatment with melatonin for sleep disorders.[1] Seizure activity returned to baseline values when melatonin was stopped and recurred on rechallenge.

1. Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998; **351:** 1254.

Uses. Melatonin has been tried in a number of disorders[1] including, in large doses, as an adjunct to conventional chemotherapy for malignant neoplasms[2,3] and, with norethisterone, as a contraceptive.[4] It is possible that contraceptive use of melatonin may be associated with a reduced risk of breast cancer.[5] For mention of response to melatonin in 2 patients with sarcoidosis, see p.1512. Preliminary studies have also suggested that melatonin may be beneficial in hyperlipidaemias,[6] cluster headaches,[7] tinnitus,[8] alopecia in women,[9] and irritable bowel syndrome associated with sleep disturbances.[10] Repeated bedtime doses may also play a part in reducing nocturnal blood pressure in patients with essential hypertension.[11] Claims for its value as an anti-ageing treatment and for use in conditions such as Alzheimer's disease and AIDS are unfounded.[2,12] The effects of long-term use of melatonin have yet to be assessed.

1. Wetterberg L. Melatonin and clinical application. *Reprod Nutr Dev* 1999; **39:** 367–82.
2. Pepping J. Melatonin. *Am J Health-Syst Pharm* 1999; **56:** 2520–7.
3. Lissoni P, *et al.* Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer* 1999; **35:** 1688–92.
4. Short RV. Melatonin. *BMJ* 1993; **307:** 952–3.
5. Cohen M, *et al.* Hypotheses: melatonin/steroid combination contraceptives will prevent breast cancer. *Breast Cancer Res Treat* 1995; **33:** 257–64.
6. Pittalis S, *et al.* Effect of a chronic therapy with the pineal hormone melatonin on cholesterol levels in idiopathic hypercholesterolemic patients. *Recenti Prog Med* 1997; **88:** 401–2.
7. Leone M, *et al.* Melatonin versus placebo in the prophylaxis of cluster headache; a double-blind pilot study with parallel groups. *Cephalalgia* 1996; **16:** 494–6.
8. Rosenberg SI, *et al.* Effect of melatonin on tinnitus. *Laryngoscope* 1998; **108:** 305–10.
9. Fischer TW, *et al.* Melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia: results of a pilot randomized controlled trial. *Br J Dermatol* 2004; **150:** 341–5.
10. Song GH, *et al.* Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 1402–7.
11. Scheer FAJL, *et al.* Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004; **43:** 192–7.
12. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997; **336:** 186–95.

INSOMNIA. Although melatonin is considered[1-6] to be potentially useful in the management of various forms of insomnia (p.957), especially those associated with circadian rhythm disturbances, there is little evidence of efficacy from large studies and its long-term safety remains to be established. A meta-analysis[7] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency in secondary sleep disorders or those accompanying sleep restriction such as jet lag and shift work. In healthy subjects melatonin has been reported[8,9] to reduce the time to onset of sleep and to increase the time spent asleep. Whether this is due to adjustment of the 'body clock' or any hypnotic action of melatonin is unclear. Measurement of nocturnal urinary excretion of the major metabolite, 6-sulfatoxymelatonin, demonstrated that low nocturnal melatonin production is associated with insomnia in patients over 55 years of age, and might identify those more likely to respond to treatment with melatonin.[10] Improved quality of sleep has been reported in elderly patients treated with melatonin for insomnia,[11] and it might be of use in delayed sleep phase syndrome[12] and insomnia in shift workers and totally blind people, although some[13,14] have found no beneficial effects of melatonin in night shift workers or emergency medicine employees. There has also been a report[15] of a patient with somnolence associated with melatonin deficiency after pinealectomy who responded to treatment with melatonin. A preliminary report[16] has suggested that use of melatonin may enable benzodiazepine therapy for insomnia to be stopped without impairing the quality of sleep. However, melatonin might adversely affect sleep patterns in some circumstances.[17]

1. Haimov I, Lavie P. Potential of melatonin replacement therapy in older patients with sleep disorders. *Drugs Aging* 1995; **7:** 75–8.
2. Brown GM. Melatonin in psychiatric and sleep disorders: therapeutic implications. *CNS Drugs* 1995; **3:** 209–26.
3. Anonymous. Melatonin. *Med Lett Drugs Ther* 1995; **37:** 111–12.
4. Arendt J. Melatonin. *BMJ* 1996; **312:** 1242–3.
5. Lamberg L. Melatonin potentially useful but safety, efficacy remain uncertain. *JAMA* 1996; **276:** 1011–14.
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7. Buscemi N, *et al.* Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; **332:** 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385 (accessed 25/07/08)
8. Zhdanova IV, *et al.* Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther* 1995; **57:** 552–8.
9. Attenburrow MEJ, *et al.* Low dose melatonin improves sleep in middle-aged subjects. *Psychopharmacology (Berl)* 1996; **126:** 179–81.
10. Leger D, *et al.* Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *Am J Med* 2004; **116:** 91–5.
11. Garfinkel D, *et al.* Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995; **346:** 541–4.
12. Nagtegaal JE, *et al.* Effects of melatonin on the quality of life in patients with delayed sleep phase syndrome. *J Psychosom Res* 2000; **48:** 45–50.
13. Wright SW, *et al.* Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. *Ann Emerg Med* 1998; **32:** 334–40.
14. Jockovich M, *et al.* Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts. *Acad Emerg Med* 2000; **7:** 955–8.
15. Lehmann ED, *et al.* Somnolence associated with melatonin deficiency after pinealectomy. *Lancet* 1996; **347:** 323.
16. Garfinkel D, *et al.* Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999; **159:** 2456–60.
17. Middleton BA, *et al.* Melatonin and fragmented sleep patterns. *Lancet* 1996; **348:** 551–2.

JET LAG. Melatonin has been reported to alleviate jet lag following long flights.[1-4] The most appropriate dosing schedule has yet to be determined but will depend on both the direction of travel and the distance travelled. A systematic review[5] concluded that melatonin was effective in preventing or reducing jet lag in those travelling across 5 or more time zones, particularly in an easterly direction, and especially if jet lag had been experienced previously; travellers crossing 2 to 4 time zones might also derive benefit. However, a meta-analysis[6] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency accompanying jet lag.

1. Waterhouse J, *et al.* Jet-lag. *Lancet* 1997; **350:** 1611–16.
2. Arendt J. Jet-lag. *Lancet* 1998; **351:** 293–4.
3. Arendt J. Jet-lag and shift work: (2) therapeutic use of melatonin. *J R Soc Med* 1999; **92:** 402–5.
4. Waterhouse J, *et al.* Jet lag: trends and coping strategies. *Lancet* 2007; **369:** 1117–29.
5. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 28/04/05).
6. Buscemi N, *et al.* Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; **332:** 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385 (accessed 25/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Armonil Noche; Buenas Noches; Melatol; Nochix†; Repentil†; ***Chile:*** Novel†; ***Hong Kong:*** Melapure†; ***Hung.:*** Bio-Melatonin; ***India:*** Meloset; ***Mex.:*** Benedorm; Cronocaps; Revenox†; ***Port.:*** Circadin; ***Rus.:*** Melaxen (Мелаксен); ***UK:*** Circadin; ***USA:*** Transzone.

Multi-ingredient: ***Arg.:*** Plenovit Melatonina; ***India:*** Eternex; Stresnil; ***USA:*** Bevitamel; Melagesic PM.

Melilot

Barkūno žolė; Gelber Steinklee; Komonicová nať; Mélilot; Meliloti herba; Rohtomesikkä; Sötväppling; Sweet Clover; Yellow Melilot; Yellow Sweet Clover; Ziele nostrzyka.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Melilot; Meliloti Herba). The whole or cut, dried aerial parts of *Melilotus officinalis*. It contains a minimum of 0.3% coumarin, calculated with reference to the dried drug. Protect from light.

Profile

Melilot is used internally in herbal preparations for chronic venous insufficiency. It contains coumarin (see p.2288) and its derivatives and the dose may be expressed in terms of coumarin. The German expert committee for herbal drugs and preparations (Commission E) also allows the addition or substitution of *M. altissimus* (tall melilot), tall yellow sweet clover.

Melilotus officinalis is also used externally.

Homoeopathy. Melilot has been used in homoeopathic medicines under the following names: Melilotus officinalis; Mel. off.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Vecasten; ***Ger.:*** Meli Rephastasan.

Multi-ingredient: ***Arg.:*** Snell Patch; Snell Progress; ***Austral.:*** Bioglan Zellulean with Escin; ***Chile:*** Celltech Gold; ***Fr.:*** Antinerveux Lesourd; Creme au Melilot Composee; Cyclo 3; Ditavene; Esberiven; Esberiven Fort; Evarose; Sedopal; ***Ger.:*** Phlebodril N; Salus Venen Krauter Dragees N†; Venen Krauter NT; ***Ital.:*** Capill Venogel; Dermilia Flebozin; Diosmina Complex; Facosmina; Flebo-Si; Flebofort; Levital Plus; Lipaven; Pulsalux; RepaVen†; Venodin; Venoton; ***Rus.:*** Cyclo 3 (Цикло 3); ***Singapore:*** Cyclo 3; ***Spain:*** Fabroven; Venofit; ***Switz.:*** Phlebodril; Veino-Gouttes-N†.

Melissa

Citromfűlevél; Lemon Balm; Liść melisy; Meduňkový list; Melisa; Meliss; Melissae folium; Mélisse, feuille de; Melissenblatt; Melisų lapai; Sitruunamelissanlehti.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Melissa Leaf). The dried leaf of *Melissa officinalis*. It contains not less than 4% of total hydroxycinnamic derivatives expressed as rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3), calculated with reference to the dried drug. It has an odour reminiscent of lemon. Protect from light.

Profile

Melissa has been used as a carminative and sedative. It is an ingredient of herbal remedies used for a variety of disorders. It is also reported to have virustatic activity. The chief constituent of melissa is citral (p.2284). Hypersensitivity reactions to melissa have been reported.

Melissa is the source of melissa oil (see below).

Homoeopathy. Melissa has been used in homoeopathic medicines under the following names: Melissa officinalis.

◊ References.

1. Ballard CG, *et al.* Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with melissa. *J Clin Psychiatry* 2002; **63:** 553–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Balm-Mint†; Lomaherpan; ***Belg.:*** Dormiplant; ***Chile:*** Citromel; ***Cz.:*** Lakinal†; Lomaherpan†; Medovka Lekarska†; Medunkovy, Medunkova; ***Ger.:*** Gastrovegetalin; Lomaherpan; Me-Sabona; Sedinfant†; ***Rus.:*** Novo-Passit (Ново-Пассит); ***Switz.:*** Valverde Boutons de fievre creme.

Multi-ingredient: ***Arg.:*** Dr Calm†; Erbonda Noche†; Nervocalm; Sedante Arceli†; Valeriana Oligoplex; Valeriana Relax Diates; ***Austral.:*** Natural Deep Sleep; ***Austria:*** Abdomilon N; Baldracin; Euvekan; Mariazeller; Passedan; Passelyt; Sedogelat; Songha; Species nervinae; The Chambard-Tee; Wechseltee St Severin; ***Belg.:*** Minhavez; Songha; ***Braz.:*** Anevrase†; Balsamo Branco; Calmapax; Camomila; Elixir de Passiflora†; Passaneuro; Passilex†; Sonhare; ***Canad.:*** Herbal Sleep Well†; Natural HRT Nightime; ***Chile:*** Melipass; Recalm; ***Cz.:*** Abdomilon†; Alvisan Neo; Baldracin; Blahungstee N†; Eugastrin†; Euvekan; Fytokliman Planta; Hertz- und Kreislauftee†; Hypotonicka; Iberogast; Klosterfrau Melisana; Melaton†; Nervova Cajova Smes; Nontusyl†; Novo-Passit; Passedan; Persen; Schlaf-Nerventee N†; Senalax; Songha Night†; Species Nervinae Planta; Valofyt Neo; ***Fr.:*** Biocarde; Dystolise; Elixir Bonjean; Mediflor Tisane Calmante Troubles du Sommeil No 14; Mediflor Tisane Circulation du Sang No 12; Vagostabyl; ***Ger.:*** Abdomilon N; Baldriparan N Stark†; Doppelherz Melissengeist†; Dormarist†; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee; Euvegal; Euvegal Entspannungs- und Einschlafdragees†; Euvegal Entspannungs- und Einschlaftropfen; Gastrol S†; Gutnacht†; Heumann Beruhigungstee Tenerval; Iberogast; JuDorm†; Jukunda Melissen-Krautergeist N†; Lindofluid N; Me-Sabona plus†; Melissengeist; Nervosana†; Oxacant N†; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival novo; Presselin Blahungs K 4 N†; Pronervon Phyto; RubieSed†; Schlaf- und Nerventee; Seda-Plantina†; Sedacur; Sedariston plus; Sedasyx†; Sedinfant N†; Stullmaton†; ***Hung.:*** Euvekan; Sedacur; ***Israel:*** Songha Night; ***Ital.:*** Actenacol; Calmason; Colimil; Dormiplant; Emmenoiasi; Melissa (Specie Composta)†; Sedatol; Tisana Kelemata; Vagostabil; Valeriana (Specie Composta)†; ***Malaysia:*** Circarol; ***Mex.:*** Nordimenty; Plantival; ***NZ:*** Botanica Hayfever; Mr Nits; ***Philipp.:*** Circulan; ***Pol.:*** Amarosal; Aromatol; Calmina; Carmolis; Cravisol; Dormiplant; Klimax†; Lumewal; Melisal; Melisana Klosterfrau; Melissed; Nervinolum; Nervomix; Nervosol; Nerwobonisol; Perfocrat; Persen; Psychotonisol; Relana; Sedomix; ***Port.:*** Erpecalm; Songha†; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Persen (Персен); ***S.Afr.:*** Melissengeist; Spiritus Contra Tussim Drops; ***Spain:*** Agua del Carmen; Caramelos Agua del Carmen†; Dormiplant; Himelan†; Jaquesor†; Melival; Mesatil†; Natusor Aerofane†; Natusor Jaquesan†; Nervikan; Relana; Resolutivo Regium; Solucion Schoum; ***Switz.:*** Alcoolat de Melisse†; Arterosan Plus; Baldriparan; Baldrisedon plus†; Cardiaforce; Carmol; Dormiplant; Dragees pour la detente nerveuse; Gastrosan; Hyperiforce comp; Iberogast; Phytomed Nervo†; Relaxane; Relaxo; Songha Night; Soporin; Tisane calmante pour les enfants; Tisane favorisant l'allaitement; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs; Tisane pour nourissons et enfants; Tisane relaxante N†; Valverde Detente dragees; Valviska; ***UK:*** Melissa Comp.; Valerina Day Time; Valerina Night-Time; ***Venez.:*** Euvekan; Sedival.

Melissa Oil

Balm Oil; Esencia de Melisa; Lemon Balm Oil.

CAS — 8014-71-9.

Profile

Melissa oil is the essential oil obtained from melissa (*Melissa officinalis*), above. It is used in preparations with other essential oils in a variety of disorders. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Opino; ***Chile:*** Agua del Carmen; Agua Melisa Carminativa; ***Cz.:*** Thrombocid; ***Fr.:*** Stomargil; ***Ger.:*** Amol Heilkrautergeist N; Cor-Select†; Thrombocid; ***Gr.:*** Opino-jel; ***Indon.:*** Opino; ***Ital.:*** Dentosan Azione Intensiva; Dentosan Mese; Neuralta Migren; ***Pol.:*** Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; ***Port.:*** Thrombocid; ***Switz.:*** Anal-Gen†; Thrombocid.

Menbutone *(BAN, rINN)*

Menbuton; Menbutona; Menbutoni; Menbutonum; SC-1749 (menbutone sodium). 4-(4-Methoxy-1-naphthyl)-4-oxobutyric acid.

Менбутон

$C_{15}H_{14}O_4$ = 258.3.
CAS — 3562-99-0.
ATC Vet — QA05AX90.

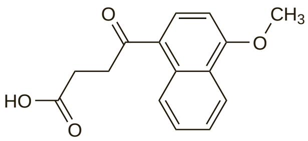

Profile

Menbutone is used as a choleretic to stimulate gastrointestinal function in veterinary medicine.

Menthol

Hexahydrothymol; Mentholum; Mentol; Mentoli; Mentolis. *p*-Menthan-3-ol; 2-Isopropyl-5-methylcyclohexanol.

$C_{10}H_{20}O$ = 156.3.
CAS — 1490-04-6 (menthol); 15356-60-2 ((+)-menthol); 2216-51-5 ((−)-menthol); 89-78-1((±)-menthol).

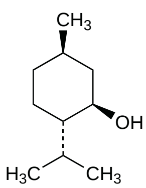

Description. Menthol is either the laevo-isomer, levomenthol (*BAN*, *rINN*), or a racemic mixture, racementhol (*BAN*, *rINN*). The laevo-isomer may be obtained from the volatile oils of various species of *Mentha* (Labiatae) or it may be prepared synthetically.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet. Eur.* and *Jpn* have separate monographs for laevo-menthol (levomenthol) and racemic menthol (racementhol).

Ph. Eur. 6.2 (Levomenthol). It occurs as colourless, acicular or prismatic shiny crystals. M.p. about 43°. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

Ph. Eur. 6.2 (Menthol, Racemic; Racementhol BP 2008). It occurs as colourless, acicular or prismatic shiny crystals or as a free-flowing or agglomerated crystalline powder. M.p. about 34°. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

USP 31 (Menthol). An alcohol obtained from diverse mint oils or prepared synthetically. It may be laevorotatory (*l*-menthol), from natural or synthetic sources, or racemic (*dl*-menthol). It occurs as colourless, hexagonal crystals, usually needle-like, or in fused masses, or crystalline powder. Has a pleasant, peppermint-like odour. M.p. of *l*-menthol 41° to 44°. Slightly soluble in water; very soluble in alcohol, in chloroform, in ether, and in petroleum spirit; freely soluble in glacial acetic acid, in fixed and volatile oils, and in liquid paraffin. Store in airtight containers preferably at a temperature of 15° to 30°.

Compounding. A liquid or soft mass is formed when menthol is triturated with camphor, cloral hydrate, phenol, and many other substances.

Methods of preparing menthol 1% w/w in aqueous cream BP and the stability of the resultant product have been discussed.[1]

1. Cable C. The preparation of menthol (1 per cent w/w) in aqueous cream BP. *Pharm J* 2005; **274:** 469.

Adverse Effects, Treatment, and Precautions

Menthol may give rise to hypersensitivity reactions including contact dermatitis. Ingestion of significant quantities of menthol is reported to cause symptoms similar to those seen after ingestion of camphor (p.2273), including severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma; they may be managed similarly. There have been reports (below) of apnoea and instant collapse in infants after the local application of menthol to their nostrils.

Administration to infants. Instillation of decongestant preparations containing menthol directly into the nostrils of infants and young children has resulted in acute respiratory distress with cyanosis[1] and respiratory arrest,[2] and must be avoided. In one case,[1] nasal application was associated with concurrent chemical conjunctivitis.

1. Wyllie JP, Alexander FW. Nasal instillation of 'Olbas Oil' in an infant. *Arch Dis Child* 1994; **70:** 357–8.
2. Blake KD. Dangers of common cold treatments in children. *Lancet* 1993; **341:** 640.

Effects on the nervous system. Ataxia, confusion, euphoria, nystagmus, and diplopia developed in a 13-year-old boy following the inhalation of 5 mL of Olbas oil instead of the recommended few drops.[1] It was considered probable that the menthol in the preparation was responsible for the symptoms; the amount of menthol inhaled was approximately 200 mg.

1. O'Mullane NM, *et al*. Adverse CNS effects of menthol-containing Olbas oil. *Lancet* 1982; **i:** 1121.

Pharmacokinetics

After absorption, menthol is excreted in the urine and bile as a glucuronide.

Absorption. The systemic absorption of camphor, menthol, and methyl salicylate from dermal patches containing all three ingredients has been studied.[1] The absolute bioavailability of these compounds could not be determined from this study, but there did not appear to be any substantial systemic accumulation even after unrealistically high exposure for prolonged periods.

1. Martin D, *et al*. Dermal absorption of camphor, menthol, and methyl salicylate in humans. *J Clin Pharmacol*. 2004; **44:** 1151–7.

Uses and Administration

Menthol is chiefly used to relieve symptoms of bronchitis, sinusitis, and similar conditions. For this purpose it may be used as an inhalation, usually with benzoin or eucalyptus oil, as pastilles, or as an ointment with camphor and eucalyptus oil for application to the chest or nostrils (but see Adverse Effects above). However, as mentioned under the section on the management of cough (p.1547), the use of menthol in inhalations is unlikely to provide any additional benefit.

When applied to the skin menthol dilates the blood vessels, causing a sensation of coldness followed by an analgesic effect. It relieves itching and is used in creams, lotions, or ointments in pruritus and urticaria. It has also been applied to the forehead, presumably as a counter-irritant, for the relief of headache.

In small doses by mouth menthol has a carminative action.

Action. It has been suggested that the apparent benefits of menthol in nasal congestion may be due to an effect on calcium channels of sensory nerves.[1] This mechanism has also been implicated in its muscle relaxant action on the gastrointestinal tract when used as peppermint oil (p.1761).

1. Anonymous. How does menthol work? *Pharm J* 1993; **251:** 480.

Preparations

BP 2008: Levomenthol Cream; Menthol and Benzoin Inhalation;
USP 31: Benzocaine and Menthol Topical Aerosol; Menthol Lozenges; Tetracaine and Menthol Ointment.

Proprietary Preparations (details are given in Part 3)
Arg.: Flex-All; Rati Salil Ice; Robitussin Caramelos†; ***Austral.:*** Dencorub Arthritis Ice; Ice Gel; Vicks Throat Drops†; Vicks Vapodrops with Butter and Menthol; ***Braz.:*** Analgen†; ***Canad.:*** Absorbine Jr; Absorbine Jr Roll-on Ice; Absorbine Power Gel; Antiphlogistine Rub A-535 Ice; Bengay Ice†; Bentasil†; Certified Ice; Cough Drops; Cough Lozenges; Deep Cold; Fisherman's Friend; Flex-All; Ice Gel Therapy; Ice Gel†; Meggezones†; Physiomenthol; Polar Ice; Soothing Ice Rub; Vicks Throat Drops; ***Chile:*** Friorub; Hielorub; Mentholatum Patch; ***Ger.:*** Klosterfrau Franzbranntwein Menthol; Nifint†; ***Hong Kong:*** Counterpain; ***India:*** Dolocide Plus; ***Indon.:*** Counterpain Cool; ***Malaysia:*** Menzza Ice; ***Mex.:*** Friocal†; ***NZ:*** Vicks Throat Drops; Vicks Vapodrops; ***Pol.:*** Deep Relief†; Migrenol; ***Port.:*** Vicks Vaporub; ***Singapore:*** Celatrac; Counterpain Cool; ***Spain:*** Prulit; ***Switz.:*** Perskindol Cool; ***Thai.:*** Centropain; Counterpain Cool; Painza Cool; Stopain; ***UK:*** Arjun; Deep Freeze Cold Gel; Dermacool; Happinose; Ice Cool Stress & Tension Relief; Meggezones; Quool; Vicks Vaposyrup for Tickly Coughs; ***USA:*** Absorbine Jr; Ben-Gay Patch; Ben-Gay Vanishing; Cepacol Sore Throat Post Nasal Drip; Extra Strength Vicks Cough Drops; Halls-Plus Maximum Strength; Icy Hot Back Pain Relief; Icy Hot Pop & Peel; Icy Hot Pro-Therapy; Kof-Eze; Mineral Freez Gel; N'ice; N'ice 'n Clear; Salonpas Aqua Patch; Sportscreme Ice; Therapeutic Mineral Ice; Therapy Ice; Vicks Cough Drops; Wonder Ice; ***Venez.:*** Dencorub Ice; Inquifric†.

Multi-ingredient: numerous preparations are listed in Part 3.

Menthone

(±)-menthone; (*dl*)-menthone; Menton. (2*R*,5*S*)-*rel*-5-Methyl-2-(1-methylethyl)cyclohexanone; .

Ментон

$C_{10}H_{18}O$ = 154.2.
CAS — 3391-87-5 ((+)-menthone); 14073-97-3 ((−)-menthone); 89-80-5 ((±)-menthone); 1196-31-2 ((+)-isomenthone); 491-07-6 ((±)-isomenthone);.

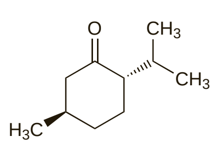

((−)-menthone)

Profile

Menthone is a constituent of several essential oils. Of the 4 possible stereoisomers of menthone, (−)-menthone (*l*-menthone) is the most abundant in nature. Menthone is reported to be a cholagogue and has been used in preparations for biliary-tract and liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Rowachol; ***Braz.:*** Quelodin†; ***Cz.:*** Rowachol; ***Ger.:*** Rowachol; Rowachol comp†; Rowachol-Digestiv; ***Hong Kong:*** Neo-Rowachol; Rowachol; ***Hung.:*** Rowachol; ***Irl.:*** Rowachol; ***Israel:*** Rowachol; ***Malaysia:*** Rowachol; ***Mex.:*** Cholex; ***Philipp.:*** Rowachol; ***Pol.:*** Rowachol; Terpichol; ***Switz.:*** Rowachol; ***Thai.:*** Rowachol; ***UK:*** Rowachol; ***Venez.:*** Rowachol.

Menyanthes

Bitterklee; Bogbean; Buckbean; Folia Trifoli Fibrini; Liść bobrka (bogbean leaf); Marsh Trefoil; Ményanthe; Menyanthidis Folium (bogbean leaf); Menyanthidis trifoliatae folium; Raatteenlehti (bogbean leaf); Trébol de agua; Trèfle d'Eau; Trifolii Fibrini Folium (bogbean leaf); Trilapių pupalaiškių lapai (bogbean leaf); Vachtový list (bogbean leaf); Vattenklöverblad (bogbean leaf); Vidrafűlevél (bogbean leaf).

NOTE. Bog myrtle (see p.2267) has also been used as a common name for *Menyanthes trifoliata*.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Bogbean Leaf). The dried, entire or fragmented leaf of *Menyanthes trifoliata*. It has a very bitter and persistent taste.

Profile

Menyanthes has been used as a bitter. It is used in herbal medicine for rheumatic, gastrointestinal, and biliary-tract disorders. It is also used in folk medicine.

Homoeopathy. Menyanthes has been used in homoeopathic medicines under the following names: Menyanthes trifoliata; Menyan. t.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: List Vachty Trojliste†.

Multi-ingredient: ***Austria:*** Mariazeller; ***Cz.:*** Naturland Grosser Swedenbitter†; ***Fr.:*** Tisane Hepatique de Hoerdt; ***Ger.:*** Gallexier; ***Pol.:*** Krople Zoladkowe; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***UK:*** Modern Herbals Rheumatic Pain; Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain Remedy; Vegetex.

Mercaptamine *(BAN, rINN)*

Cysteamine *(USAN)*; L-1573; MEA; Mercamine; Mercaptamina; Mercaptaminum; Merkaptamiini; Merkaptamin. 2-Aminoethanethiol.

Меркаптамин

C_2H_7NS = 77.15.
CAS — 60-23-1.
ATC — A16AA04.
ATC Vet — QA16AA04.

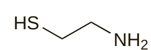

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine (p.744) and mercaptamine (formerly cysteamine) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Mercaptamine Bitartrate *(BANM, rINNM)*

Bitartrato de mercaptamina; Cysteamine Bitartrate; Mercaptamine, Bitartrate de; Mercaptamini Bitartras.

Меркаптамина Битартрат

$C_2H_7NS,C_4H_6O_6$ = 227.2.
CAS — 27761-19-9.
ATC — A16AA04.
ATC Vet — QA16AA04.

Mercaptamine Hydrochloride *(BANM, rINNM)*

CI-9148; Cysteamine Hydrochloride *(USAN)*; Hidrocloruro de mercaptamina; Mercaptamine, Chlorhydrate de; Mercaptamini Hydrochloridum.

Меркаптамина Гидрохлорид

C_2H_7NS,HCl = 113.6.
CAS — 156-57-0.
ATC — A16AA04.
ATC Vet — QA16AA04.

Adverse Effects and Precautions

Mercaptamine can be unpalatable and may cause breath and body odour. It may cause gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain, and occasionally, gastrointestinal ulceration. Other adverse effects may include drowsiness, lethargy, headache, rashes, fever, and encephalopathy. Mercaptamine may cause increases in liver enzyme values, and there have been some reports of nephrotic syndrome. Nervousness and, sometimes, hallucinations, have also been reported.

Intolerance. Three patients with nephropathic cystinosis developed fever, maculopapular eruption, leucopenia, or headache within 2 weeks of starting mercaptamine at doses of 53, 67, and 75 mg/kg daily by mouth, respectively.[1] These adverse effects resolved within 48 hours of drug withdrawal and all 3 patients were able to tolerate mercaptamine when restarted at a dose of 10 mg/kg daily, slowly increased to therapeutic levels over 2 to 3 months. Higher doses of mercaptamine had been associated with lethargy and seizures.

1. Schneider JA, *et al*. Cysteamine therapy in nephropathic cystinosis. *N Engl J Med* 1981; **304:** 1172.

Pharmacokinetics

◊ Results of a pharmacokinetic-pharmacodynamic study[1] in paediatric patients with nephropathic cystinosis showed that although mercaptamine is rapidly cleared from plasma, dosing every 6 hours was sufficient to maintain the content of cystine in the white blood cells below the target value (see below).

1. Belldina EB, *et al.* Steady-state pharmacokinetics and pharmacodynamics of cysteamine bitartrate in paediatric nephropathic cystinosis patients. *Br J Clin Pharmacol* 2003; **56:** 520–5.

Uses and Administration

Mercaptamine reduces intracellular cystine levels and is given orally as the bitartrate in the treatment of cystinosis (see below); it has also been given as the hydrochloride. Doses are expressed in terms of the base; 2.94 g of the bitartrate or 1.47 g of the hydrochloride are each equivalent to 1 g of mercaptamine. Mercaptamine bitartrate is given in an initial dose that is one-sixth to one-quarter of the expected maintenance dose, and is then increased gradually over 4 to 6 weeks. The usual maintenance dose in adults weighing over 50 kg is 2 g daily in 4 divided doses with or after food. Children up to 12 years of age are given 1.3 g/m^2 (approximately 50 mg/kg) daily in 4 divided doses. Doses are given in conjunction with monitoring of leucocyte-cystine levels which should be kept below 1 nanomol of hemicystine per mg of protein.

Phosphocysteamine, a phosphorothioester of mercaptamine, has been said to be more palatable, and is used similarly.

Mercaptamine facilitates glutathione synthesis and was formerly used intravenously in the treatment of severe paracetamol poisoning to prevent hepatic damage, but other forms of treatment are now preferred (see p.108).

Cystinosis. Mercaptamine and phosphocysteamine (which appears to be rapidly hydrolysed to mercaptamine after ingestion) have been reported to be of benefit in children with cystinosis, a rare autosomal recessive metabolic disorder characterised by the intracellular accumulation of cystine. Cystinosis is marked by growth retardation, rickets, Fanconi syndrome, and renal failure; acute episodes of acidosis and dehydration may develop, and there may be photophobia associated with deposition of cystine in the eye.[1] Use of mercaptamine, which results in a reduction in the concentrations of cystine in leucocytes, has been shown to be effective in controlling many of the symptoms,[2-5] especially if begun early, although it has not been clear from contradictory results[4,6] how much benefit would be seen on renal function. Excellent clinical outcomes were reported[7] on long-term follow-up of 2 siblings with severe nephropathic cystinosis, reinforcing the need for early and diligent treatment in order to avoid progressive renal disease. Compliance may be a problem, because of the taste and odour of mercaptamine, and the more palatable prodrug phosphocysteamine has been developed as an alternative;[8,9] more palatable formulations of mercaptamine are also being investigated. Mercaptamine eye drops are reportedly of benefit in reversing or preventing deposition of corneal cystine crystals.[10] A strength of 0.11% has been used. Renal transplantation may be necessary if renal failure develops.

1. Gahl WA, *et al.* Cystinosis. *N Engl J Med* 2002; **347:** 111–21.
2. Yudkoff M, *et al.* Effects of cysteamine therapy in nephropathic cystinosis. *N Engl J Med* 1981; **304:** 141–5.
3. Gahl WA, *et al.* Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987; **316:** 971–7.
4. Reznik VM, *et al.* Treatment of cystinosis with cysteamine from early infancy. *J Pediatr* 1991; **119:** 491–3.
5. Gahl WA, *et al.* Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* 2007; **147:** 242–50.
6. Markello TC, *et al.* Improved renal function in children with cystinosis treated with cysteamine. *N Engl J Med* 1993; **328:** 1157–62.
7. Kleta R, *et al.* Long-term follow-up of well-treated nephropathic cystinosis patients. *J Pediatr* 2004; **145:** 555–60.
8. Gahl WA, *et al.* Cystinosis: progress in a prototypic disease. *Ann Intern Med* 1988; **109:** 557–69.
9. van't Hoff WG, *et al.* Effects of oral phosphocysteamine and rectal cysteamine in cystinosis. *Arch Dis Child* 1991; **66:** 1434–7.
10. Kaiser-Kupfer MI, *et al.* A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990; **108;** 689–93.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cystagon; ***Belg.:*** Cystagon; ***Cz.:*** Cystagon; ***Denm.:*** Cystagon; ***Fin.:*** Cystagon; ***Fr.:*** Cystagon; ***Ger.:*** Cystagon; ***Ital.:*** Cystagon; ***Neth.:*** Cystagon; ***Pol.:*** Cystagon; ***Port.:*** Cystagon; ***Spain:*** Cystagon; ***Swed.:*** Cystagon; ***UK:*** Cystagon.

Mercuric Chloride

Bicloruro de Mercurio; Chlorid rtuťnatý; Cloreto Mercúrico; Corrosive Sublimate; Gyvsidabrio dichloridas; Higany(II)-klorid; Hydrarg. Perchlor.; Hydrargyri dichloridum; Hydrargyri Perchloridum; Hydrargyrum Bichloratum; Kvicksilverdiklorid; Mercuric Chlor.; Mercúrico, cloruro; Mercurique (Chlorure); Mercurique, chlorure; Mercury Bichloride; Mercury Perchloride; Merkuridikloridi; Quecksilberchlorid; Rtęci(II) chlorek.

$HgCl_2$ = 271.5.
CAS — 7487-94-7.
ATC — D08AK03.
ATC Vet — QD08AK03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Mercuric Chloride). A white or almost white, crystalline powder, or colourless or white or almost white crystals or heavy crystalline masses. Soluble in water and in glycerol; freely soluble in alcohol. Protect from light.

Profile

The use of mercuric chloride as an antibacterial substance is limited by its toxicity, its precipitating action on proteins, its irritant action on raw surfaces, its corrosive action on metals, and by the fact that its activity is greatly reduced in the presence of excreta or body fluids.

Details of the adverse effects of inorganic mercury compounds are provided under Mercury, below.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Pantenil.

Yellow Mercuric Oxide

Gelbes Quecksilberoxyd; Hydrargyri Oxidum Flavum; Hydrargyri Oxydum Flavum; Mercúrico amarillo, óxido; Mercurique (Oxyde) Jaune; Oxido Amarillo de Mercurio; Yellow Precipitate.

HgO = 216.6.
CAS — 21908-53-2.

Pharmacopoeias. In *Fr.* and *It.*

Profile

Yellow mercuric oxide has been used in eye ointments for the local treatment of minor infections including the eradication of pubic lice from the eyelashes. Absorption can occur and produce the adverse effects of inorganic mercury (see Mercury, below).

Pediculosis. Yellow mercuric oxide 1% eye ointment was considered to be a safe and effective treatment in pediculosis (p.2034) of the eyelashes caused by pubic lice (pthiriasis palpebrarum).[1]

1. Ashkenazi I, *et al.* Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum. *Br J Ophthalmol* 1991; **75:** 356–8.

Porphyria. Mercuric oxide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Golden Eye Ointment†; ***Fr.:*** Pommade Maurice.
Multi-ingredient: ***Hung.:*** Dermaforine†; ***India:*** Bell Diono Resolvent; Bell Resolvent.

Mercurous Chloride

Calomel; Calomelanos; Cloreto Mercuroso; Hydrarg. Subchlor.; Hydrargyri Subchloridum; Hydrargyrosi Chloridum; Hydrargyrum Chloratum (Mite); Mercureux (Chlorure); Mercurioso, cloruro; Mercurius Dulcis; Mercury Monochloride; Mercury Subchloride; Mild Mercurous Chloride; Protocloruro de Mercurio; Quecksilberchlorür.

$HgCl$ = 236.0; Hg_2Cl_2 = 472.1.
CAS — 7546-30-7 (HgCl); 10112-91-1 (Hg_2Cl_2).

NOTE. Precipitated Mercurous Chloride (Hydrargyri Subchloridum Praecipitatum), is a white amorphous powder, for which the synonym 'White Precipitate' (Praecipitatum Album) has been used. White Precipitate has also been used as a name for Ammoniated Mercury.

Pharmacopoeias. In *Chin.* as Hg_2Cl_2.

Profile

Mercurous chloride was formerly given as a laxative and was applied topically as an antibacterial. It was one of the mercury compounds employed in the management of syphilis in the pre-antibiotic era.

The mercurous form of mercury does not possess the corrosive properties of the mercuric form and is not absorbed to any great extent. However, the mercurous form can be converted to the mercuric, with consequent toxicity as described under Mercury (see below).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Hung.:*** Dermaforine†.

Mercury

Hydrarg.; Hydrargyrum; Hydrargyrum Depuratum; Mercure; Mercurio; Quecksilber; Quicksilver; Rtęć.

Hg = 200.59.
CAS — 7439-97-6.
ATC — D08AK05.

Description. Mercury is a shining, silvery white, very mobile liquid, easily divisible into globules, which readily volatilises on heating.

Adverse Effects

Poisoning with liquid mercury or inorganic mercury salts has arisen from sources such as batteries, cosmetics, dental materials, medical equipment, and jewellery manufacture. Barometers, sphygmomanometers, and thermometers are still sources of liquid mercury. Trace amounts of organic and inorganic mercury may also be ingested in the diet.

The effects of **acute** exposure depend on the nature of the compound.

- *Elemental (liquid) mercury* if ingested is poorly absorbed and, unless there is aspiration or pre-existing gastrointestinal disorders, is not considered to be a severe toxicological hazard. The greatest dangers from elemental mercury arise from the inhalation of mercury vapour, which can cause gastrointestinal effects including nausea, vomiting, and diarrhoea; more importantly it is toxic to the respiratory system and this effect can be fatal. Some CNS involvement has also been reported. Adverse effects have also been reported after accidental or intentional parenteral dosage.
- *Inorganic salts* such as mercuric chloride are corrosive when ingested causing severe nausea, vomiting, pain, bloody diarrhoea, and necrosis. The kidney is also involved and tubular necrosis may develop. Mercurous salts are considered to be less hazardous, but the mercurous form can be converted to the mercuric.
- *Organic mercurial compounds* produce similar toxic effects to inorganic compounds, but they have a more selective action on the CNS that has proved difficult to treat. The degree of toxicity varies; those used as preservatives or disinfectants are less toxic than the ethyl or methyl compounds that are not used pharmaceutically or clinically. Methylmercury is notorious for its toxicity; there have been cases of fetal neurotoxicity during outbreaks of methylmercury poisoning.

Chronic mercury poisoning may result from inhalation of mercury vapour, skin contact with mercury or mercury compounds, or ingestion of mercury salts over prolonged periods. It is characterised by many symptoms including tremor, motor and sensory disturbances, mental deterioration, gastrointestinal symptoms, dermatitis, kidney damage, salivation, and gingivitis. A blue line may be present on the gums. There is little difference between acute and chronic poisoning with organic mercurials.

The syndrome of *acrodynia* (pink disease), with symptoms of sweat, rash, erythema of the extremities, photophobia, wasting, weakness, hypertension, tachycardia, and diminished reflexes, occurred in children given mercury in teething powders or in ointments or dusting powders. Such preparations have long since been withdrawn from use. However, the syndrome is still a feature of mercury poisoning from other sources.

Hypersensitivity to mercury and mercurial compounds has been reported.

Mercurialentis has been reported in patients treated with eye drops containing an organomercurial preservative.

Chronic exposure. Acute *occupational exposure* to mercury vapour in 53 men resulted in an initial phase described as metal fume fever, an intermediate phase of severe symptoms with CNS, gastrointestinal, respiratory, and urological involvement, and a late phase with persistent CNS symptoms, dysuria, and pain on ejaculation.[1,2] Although persistent hyperchloraemia was noted in the 11 patients with the highest mercury levels, renal impairment tended to be temporary.[2]

Long-term follow-up of a patient who had an intravenous *injection* of mercury 12 years previously also revealed no persistent renal impairment,[3] despite the presence of mercury microemboli in lungs, kidneys, liver, and subcutaneous tissues and high concentrations in the urine. At this time, the patient had residual reductions in respiratory function, polyneuropathy, and marked asthenozoospermia. Spermatozoal abnormalities may also have contributed to his wife's miscarriage. Mercury deposits mimicking gallbladder cancer were found in the gallbladder of a patient 35 years after he had injected himself with elemental mercury.[4]

Fetal neurotoxicity after *maternal exposure* to methylmercury is well recognised, and there has been widespread concern about the effect of maternal diets on the developing fetus because of mercury concentrations in freshwater and marine organisms. Results from a study in the Faroe Islands showed an association between delays in neurological development in children and maternal consumption of pilot whale meat.[5] Follow-up studies of this population when they reached 14 years of age suggest that the neurotoxic effects of methylmercury might compromise brain development into the teenage years,[6] as well as affecting autonomic regulation of heart function.[7] However, data from a study conducted in a fish-consuming population in the Seychelles failed to find a similar connection.[8]

There has been considerable concern over the systemic absorption of mercury from *dental amalgam*, which typically contains between 40 and 70% of mercury. However, the quantity absorbed from amalgam fillings is reported to be relatively small[9,10] and current evidence suggests that the use of dental amalgam for tooth restoration is both safe and effective.[11-14] The main risks appear to be occupational exposure of dental staff and environmental pollution. Some patients with hypersensitivity to mercury (manifest most commonly as local lichenoid reactions) may benefit from removal of amalgam fillings.[15-17]

Ethylmercury is contained in *thiomersal*, which is used as a preservative in some vaccines for infants and children, thus representing a potential source of mercury exposure. The safety of these vaccines has been a matter of considerable debate worldwide for many years although it is now usually accepted that there is no evidence of neurotoxicity. However, some countries have phased out vaccines containing thiomersal in favour of alternative preservatives. For further details and references, see Thiomersal p.1664.

The symptoms of *acrodynia* have been mistaken for those of phaeochromocytoma.[18-21]

1. Bluhm RE, *et al.* Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992; **11:** 201–10.
2. Bluhm RE, *et al.* Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part II: hyperchloraemia and genitourinary symptoms. *Hum Exp Toxicol* 1992; **11:** 211–15.
3. dell'Omo M, *et al.* Long-term toxicity of intravenous mercury injection. *Lancet* 1996; **348:** 64.
4. Zippel D, *et al.* Quicksilver cholecystitis. *Ann Intern Med* 2006; **144:** 941.
5. Grandjean P, *et al.* Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* 1997; **19:** 417–28.
6. Murata K, *et al.* Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr* 2004; **144:** 177–83.
7. Grandjean P, *et al.* Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. *J Pediatr* 2004; **144:** 169–76.
8. Myers GJ, *et al.* Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet* 2003; **361:** 1686–92.
9. Eley BM. The future of dental amalgam: a review of the literature. Part 3: mercury exposure from amalgam restorations in dental patients. *Br Dent J* 1997; **182:** 333–8.
10. Eley BM. The future of dental amalgam: a review of the literature. Part 4: mercury exposure hazards and risk assessment. *Br Dent J* 1997; **182:** 373–81.
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13. Bellinger DC, *et al.* Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. *JAMA* 2006; **295:** 1775–83.
14. DeRouen TA, *et al.* Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. *JAMA* 2006; **295:** 1784–92.
15. Ibbotson SH, *et al.* The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions. *Br J Dermatol* 1996; **134:** 420–3.
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17. Laeijendecker R, *et al.* Oral lichen planus and allergy to dental amalgam restorations. *Arch Dermatol* 2004; **140:** 1434–8.
18. Henningsson C, *et al.* Acute mercury poisoning (acrodynia) mimicking pheochromocytoma in an adolescent. *J Pediatr* 1993; **122:** 252–3.
19. Velzeboer SCJM, *et al.* A hypertensive toddler. *Lancet* 1997; **349:** 1810.
20. Wößmann W, *et al.* Mercury intoxication presenting with hypertension and tachycardia. *Arch Dis Child* 1999; **80:** 556–7.
21. Torres AD, *et al.* Mercury intoxication and arterial hypertension: report of two patients and review of the literature. Abstract: *Pediatrics* 2000; **105:** 627. Full version: http://pediatrics.aappublications.org/cgi/reprint/105/3/e34.pdf (accessed 14/07/06)

Effects on the kidneys. The kidneys are one of the primary sites for the accumulation of mercury in the body. All forms of mercury (liquid mercury, inorganic mercury, and organic mercury) may be toxic to the kidney although the inorganic forms are the most nephrotoxic.[1]

1. Zalups RK. Molecular interactions with mercury in the kidney. *Pharmacol Rev* 2000; **52:** 113–43.

Hypersensitivity. Systemic contact dermatitis in a patient apparently sensitised by red, mercury-based tattoo pigments, developed when he ate raw swordfish and alfonsino, both renowned for high mercury levels.[1]

1. Tsuruta D, *et al.* A red tattoo and a swordfish supper. *Lancet* 2004; **364:** 730.

Treatment of Adverse Effects

The treatment of **acute** mercury toxicity depends on the form of mercury, the route of exposure, and the dose. Supportive measures may be needed with all types of toxicity. Ingestion of elemental mercury seldom requires active treatment since it is poorly absorbed by this route, although inhalation or aspiration of elemental mercury vapour is a potentially serious problem. Poisoning due to organic mercury is difficult to treat and supportive measures are the mainstay of treatment. Acute exposure to mercury by injection requires mainly supportive therapy, although excision of the affected area has been recommended after subcutaneous or intramuscular injection. Mercurials on the skin should be removed by copious washing with soap and water; for contamination in the eye, irrigation with water at room-temperature for at least 15 minutes should be performed.

Acute oral poisoning due to inorganic mercury salts should be treated if appropriate by activated charcoal or gastric lavage to reduce absorption if within 1 hour of ingestion of a potentially life-threatening dose. Decontamination is not usually necessary after ingestion of small amounts such as elemental mercury from a thermometer. Some inorganic mercury compounds may be corrosive to the gastrointestinal tract when ingested, which can make gastrointestinal decontamination problematic; induction of emesis is not recommended. Gastric decontamination may be tried for organic mercury compounds, although the benefits are uncertain.

In severe cases of toxicity with all forms of mercury poisoning, chelation therapy may be required to facilitate the removal of mercury from the body. Unithiol (p.1468) is the chelating agent of choice in the UK and should be considered in symptomatic patients with a blood-mercury concentration of 100 micrograms/litre, and in asymptomatic patients with a blood-mercury concentration of 200 micrograms/litre. Other chelating agents that may be used are succimer (p.1466), dimercaprol (p.1444), and penicillamine (p.1456). The treatment of choice may vary in other countries depending on local policies and availability of the above chelating agents. Penicillamine may be associated with more adverse effects than other chelating agents and should be reserved for use when others are unavailable or not tolerated. Dimercaprol should be avoided in poisoning with metallic mercury or methylmercury because it may exacerbate neurological effects through redistribution of mercury to the brain from other sites.

Some centres start haemodialysis early in the course of treatment; others wait until renal failure develops. Giving a thiol resin complex to prevent the reabsorption of mercury from the bile has also been tried.

The management of **chronic** toxicity is generally symptomatic although chelation therapy has been used in some patients if the blood-mercury concentration is raised or the patient is symptomatic.

◊ References.

1. Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Exp Toxicol* 1990; **9:** 137–41.
2. Ferguson L, Cantilena LR. Enhanced mercury clearance during hemodialysis with chelating agents. *Clin Pharmacol Ther* 1991; **49:** 131.
3. Florentine MJ, Sanfilippo DJ. Elemental mercury poisoning. *Clin Pharm* 1991; **10:** 213–21.
4. Bluhm RE, *et al.* Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992; **11:** 201–10.
5. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13:** 11–16.
6. Houeto P, *et al.* Elemental mercury vapour toxicity: treatment and levels in plasma and urine. *Hum Exp Toxicol* 1994; **13:** 848–52.
7. Aaseth J, *et al.* Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate: a review. *Analyst* 1995; **120:** 853–4.
8. Isik S, *et al.* Subcutaneous metallic mercury injection: early, massive excision. *Ann Plast Surg* 1997; **38:** 645–8.
9. Baum CR. Treatment of mercury intoxication. *Curr Opin Pediatr* 1999; **11:** 265–8.
10. Satar S, *et al.* Intoxication with 100 grams of mercury: a case report and importance of supportive therapy. *Eur J Emerg Med* 2001; **8:** 245–8.
11. Risher JF, Amler SN. Mercury exposure: evaluation and intervention — the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning. *Neurotoxicology* 2005; **26:** 691–9.

Pharmacokinetics

There is little absorption of elemental mercury from globules in the gastrointestinal tract. The main hazard of elemental mercury is from absorption after inhalation of mercury vapour; this mercury is widely distributed before being oxidised to the mercuric form. Concentrations can be detected in the brain.

Soluble inorganic mercuric salts are absorbed from the gastrointestinal tract and can also be absorbed through the skin. The mercury is distributed throughout the soft tissues with high concentrations in the kidneys; it is mainly excreted in the urine and faeces with an elimination half-life of about 60 days, although it may take years to eliminate mercury from the brain; elimination from other tissues can take several months.

Organic alkyl mercury compounds are more readily absorbed from both the gastrointestinal and the respiratory tracts. They are widely distributed and can produce high concentrations in the brain. Alkyl mercury compounds are excreted in urine and in the faeces with extensive enterohepatic recycling. The biological half-life varies but is longer than that of inorganic mercury.

Organic mercury, and to some extent inorganic mercury, diffuse across the placenta and are distributed into breast milk.

Uses and Administration

The hazards associated with mercury generally outweigh any therapeutic benefit and its clinical use has largely been abandoned. The use of mercurial diuretics such as mersalyl (p.1333) has generally been superseded by other diuretics. Ointments containing mercurials, such as ammoniated mercury (p.1604) have also generally been replaced by less toxic preparations. Mercurials were formerly used as spermicides.

Some ionisable inorganic mercury salts and certain organic compounds of mercury have been used as disinfectants, and some mercury salts are effective parasiticides and fungicides. Organic mercurials such as phenylmercuric acetate, borate, and nitrate are also used as preservatives (p.1657). Mercury is a component of dental amalgams.

Other mercury salts that have been used for their antibacterial activity include mercuric chloride, yellow mercuric oxide, and mercurous chloride (above).

Homoeopathy. Mercury and some mercury compounds have been used in homoeopathic medicines under the following names:

- Mercury: Hydrargyrum metallicum; Mercurius vivus; Merc. viv.
- Mercuric cyanide: Hydrargyrum bicyanatum; Mercurius cyanatus
- Mercuric iodide: Mercurius iodatus flavus; Merc. i. f.
- Red mercuric iodide: Hydrargyrum biiodatum; Mercurius bijodatus; Mercurius iodatus ruber; Merc. i. r.
- Mercuric nitrate: Hydrargyrum nitricum oxydulatum; Mercurius nitricus oxydulatus; Mercurius nitricus; Merc. nit.
- Red mercuric sulfide: Hydrargyrum sulfuratum rubrum; Cinnabaris; Cinbar.
- Ammoniated mercuric nitrate: Mercurius solubilis; Mere. sol.
- Potassium mercuric iodide: Mercurius et kali iodatus; Merc. ki.

See also Ammoniated Mercury (p.1604), Mercuric Chloride (above), and Mercurous Chloride (above).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lagrimas de Santa Lucia†.

Multi-ingredient: ***Austria:*** Coldophthal; ***Belg.:*** Ocal; ***Spain:*** Oftalmol Ocular.

Mescaline

Mescalina; Mescalinum; Meskaliini; Meskalin. 3,4,5-Trimethoxyphenethylamine.

$C_{11}H_{17}NO_3$ = 211.3.
CAS — 54-04-6.

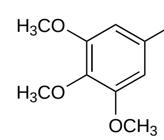

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for mescaline or peyote:
Bad seed; Beans; Big chief; Black button; Blue caps; Britton; Buttons; Cactus; Cactus buttons; Cactus head; Chief; Crystal; Dusty; Full moon; Green button; Half moon; Hikori; Hikula; Hikuli; Hyatari; Indians; M; Mesc; Mesca; Mescal; Mescalito; Mescap; Mescy; Mese; Mess; Mezc; Moon; Musk; Nubs; P; Peyote; Peyotl; Pixie sticks; San Pedro; Seni; Shaman; Topi; Tops.

Profile

Mescaline is an alkaloid obtained from the cactus *Lophophora williamsii* (*Anhalonium williamsii*, *A. lewinii*) (Cactaceae), which grows in the northern regions of Mexico. The cactus is known in those areas by the Aztec name 'peyote' or 'peyotl' and dried slices of the cactus are called 'mescal buttons'.

Mescaline produces hallucinogenic and sympathomimetic effects similar to those produced by lysergide (see p.2335), but it is less potent. Its effects last for up to 12 hours. It has no therapeutic use. Both Mexican and North American Indians have used peyote in religious ceremonies on account of its hallucinogenic activity.

Botulism. Peyote consumed during a ceremonial ritual was believed to have caused botulism in three men.[1] The sample was found to contain type B botulinum toxin when assayed.

1. Hashimoto H, *et al.* Botulism from peyote. *N Engl J Med* 1998; **339:** 203–4.

Mesoglycan Sodium

Mesoglicano sódico.

Profile

Mesoglycan sodium is a mucopolysaccharide complex (glycosaminoglycan) extracted from calf aorta, containing mainly suleparoid (heparan sulfate) (p.1406) and dermatan sulfate (p.1256). It has been claimed to have antithrombotic, antiplatelet, and antihyperlipidaemic properties.

◊ References.

1. Forconi S, *et al.* A randomized, ASA-controlled trial of mesoglycan in secondary prevention after cerebral ischemic events. *Cerebrovasc Dis* 1995; **5:** 334–41.

2. Laurora G, *et al.* Controllo della progressione dell'arteriosclerosi in soggetti ad alto rischio trattati con mesoglicano: misurazione dell'intima-media. *Minerva Cardioangiol* 1998; **46:** 41–7.
3. Arosio E, *et al.* A placebo-controlled, double-blind study of mesoglycan in the treatment of chronic venous ulcers. *Eur J Vasc Endovasc Surg* 2001; **22:** 365–72.
4. Nenci GG, *et al.* Treatment of intermittent claudication with mesoglycan—a placebo-controlled, double-blind study. *Thromb Haemost* 2001; **86:** 1181–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Perclar†; Prisma; ***Port.:*** Prisma.

Metamfepramone Hydrochloride *(rINNM)* ⊗

Dimepropion Hydrochloride *(BANM)*; Hidrocloruro de metanfepramona; Métamfépramone, Chlorhydrate de; Metamfepramoni Hydrochloridum; Metamfepyramone Hydrochloride. 2-Dimethylaminopropiophenone hydrochloride.

Метамфепрамона Гидрохлорид

$C_{11}H_{15}NO,HCl$ = 213.7.
CAS — 15351-09-4 (metamfepramone); 10105-90-5 (metamfepramone hydrochloride).

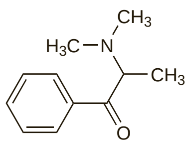

(metamfepramone)

Profile

Metamfepramone, the dimethyl analogue of diethylpropion (p.2154), is a sympathomimetic that has been used as the hydrochloride in the treatment of hypotension and in preparations for the symptomatic relief of the common cold. It was formerly used as an anorectic agent.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ger.:* Tempil N.

Metergoline *(BAN, rINN)*

FI-6337; MCE; Metergoliini; Metergolin; Metergolina; Métergoline; Metergolinum; Methergoline. Benzyl (8*S*,10*S*)-(1,6-dimethylergolin-8-ylmethyl)carbamate.

Метэрголин

$C_{25}H_{29}N_3O_2$ = 403.5.
CAS — 17692-51-2.
ATC — G02CB05.
ATC Vet — QG02CB05.

Profile

Metergoline, an ergot derivative, is a dopamine agonist with actions and uses similar to those of bromocriptine (p.798). It is also a serotonin antagonist. Metergoline has been used similarly to bromocriptine in disorders associated with hyperprolactinaemia in usual oral doses of 12 mg daily in divided doses; up to 24 mg daily has been given in hyperprolactinaemic men. It has also been used orally to inhibit lactation, for the treatment of gastrointestinal disorders, and for the prophylaxis of migraine and other vascular headaches.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p.2079). Metergoline has been tried in patients intolerant of bromocriptine.[1] In this report metergoline lowered plasma-prolactin concentrations, although not to normal, in 3 men and 8 women with hyperprolactinaemia. Galactorrhoea was abolished and/or a regular menstrual cycle established in 5 of the women. Prolactin concentrations and symptoms were unchanged in 3 further women with normoprolactinaemic galactorrhoea.

1. Casson IF, *et al.* Intolerance of bromocriptine: is metergoline a satisfactory alternative? *BMJ* 1985; **290:** 1783–4.

Migraine. Although metergoline has been used in some countries for the prophylaxis of migraine (p.616) it is not usually considered to be the drug of choice or even one of the main alternatives.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Liserdol; ***Hong Kong:*** Liserdol†; ***Ital.:*** Liserdol; ***Singapore:*** Liserdol†; ***Switz.:*** Liserdol†.

Metesculetol Sodium *(rINNM)*

Metesculetol sódico; Métesculétol Sodique; Natrii Metesculetolum. [(7-Hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-6-yl)-oxy]acetate sodium.

Натрий Метэскулетол

$C_{12}H_9NaO_6$ = 272.2.
CAS — 52814-39-8 (metesculetol); 53285-61-3 (metesculetol sodium).

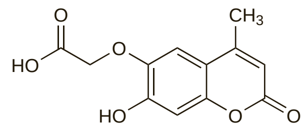

(metesculetol)

Profile

Metesculetol is included in preparations for peripheral vascular disorders and haemorrhoids. Metescufylline is a compound of metesculetol and etamiphylline (p.1120) that has been given by mouth for its reputed vasoprotectant effect.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Chile:* Parogencyl Bi-Actif; Vitis Encias Colutorio; Vitis Encias Pasta; ***Fr.:*** Intrait de Marron d'Inde P; Parogencyl gencives fragilisees†; Parogencyl prevention gencives; Parogencyl sensibilite gencives; Veinotonyl; ***Hong Kong:*** Pyodontyl; ***Ital.:*** Parogencyl; Parogencyl Gengive Delicate; ***Mon.:*** Fluon.

Methacholine Chloride *(BAN, rINN)*

Acetyl-β-methylcholine Chloride; Amechol Chloride; Cloruro de metacolina; Méthacholine, Chlorure de; Methacholini Chloridum; Methacholinium Chloratum. (2-Acetoxypropyl)trimethylammonium chloride.

Метахолиния Хлорид

$C_8H_{18}ClNO_2$ = 195.7.
CAS — 55-92-5 (methacholine); 62-51-1 (methacholine chloride).

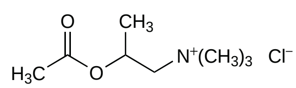

Pharmacopoeias. In *Fr., Swiss,* and *US.*

USP 31 (Methacholine Chloride). Colourless or white crystals, or a white crystalline powder. It is odourless or has a slight odour, and is very hygroscopic. Soluble 1 in 1.2 of water, 1 in 1.7 of alcohol, and 1 in 2.1 of chloroform. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects and Treatment

As for Acetylcholine Chloride, p.1877. Severe adverse cholinergic effects have followed the oral and parenteral use of methacholine and these routes are no longer used.

Precautions

As for Neostigmine, p.632.

Methacholine has the potential to produce severe bronchoconstriction and it should not be used for inhalation challenge tests in patients with clinically apparent asthma, wheezing, or poor pulmonary function.

Methacholine should not be given orally or parenterally.

Interactions

As for Neostigmine, p.632. Methacholine is slowly hydrolysed by acetylcholinesterase, and its effects are markedly enhanced if used after anticholinesterases.

Uses and Administration

Methacholine is a quaternary ammonium parasympathomimetic with the muscarinic actions of acetylcholine (p.1877). It is hydrolysed by acetylcholinesterase at a considerably slower rate than acetylcholine and is more resistant to hydrolysis by non-specific cholinesterases so that its actions are more prolonged.

Inhalation of nebulised solutions of methacholine chloride are used to provoke bronchoconstriction in the diagnosis of bronchial airway hypersensitivity (but see Precautions, above).

Methacholine chloride has been used in eye drops as a miotic for diagnostic purposes.

◊ References.

1. Crapo RO, *et al.* Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000; **161:** 309–29. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/161/1/309 (accessed 30/05/08)
2. Swartz E, Lang D. When should a methacholine challenge be ordered for a patient with suspected asthma? *Cleve Clin J Med* 2008; **75:** 37–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Provocholine; ***Ger.:*** Provokit; ***USA:*** Mecholyl; Provocholine.
Multi-ingredient: *Braz.:* Frixodon†.

Methiosulfonium Chloride

Methylmethionine Sulfonium Chloride; Metiosulfonio, cloruro de; Vitamin U. (3-Amino-3-carboxypropyl)dimethylsulphonium chloride.

$C_6H_{14}ClNO_2S$ = 199.7.
CAS — 1115-84-0.
ATC — A02BX04.
ATC Vet — QA02BX04.

Profile

Methiosulfonium chloride has been used for its reputed protective effect on the liver and gastrointestinal mucosa.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Hong Kong:* Rudd-U†; ***Jpn:*** Cabagin; Cabe 2; The Guard Seichojo; ***Singapore:*** Weisen-U†.

Methyl Fluorosulfate

Fluorosulfato, metilo de; Magic Methyl; Methyl Fluorosulphate; Methyl Fluorosulphonate.

CH_3FO_3S = 114.1.
CAS — 421-20-5.

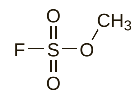

Profile

Methyl fluorosulfate has been used as a laboratory methylating agent. Pulmonary oedema has occurred after inhalation, and concern has been expressed concerning possible carcinogenicity.

Methylenedioxycinnamic Acid

3,4-Methylenedioxycinnamic acid.

$C_{10}H_8O_4$ = 192.2.
CAS — 2373-80-0.

Profile

Methylenedioxycinnamic acid and its potassium salt have been used in preparations for the treatment of liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vacuobil.
Multi-ingredient: *Arg.:* Vacuobil Plus.

Methylhydroxyquinoline Metilsulfate

Methylhydroxyquinoline Methylsulphate; Metilhidroxiquinolina, metilsulfato de. 1-Methyl-8-hydroxyquinolinium methyl sulphate.

$C_{10}H_{10}NO,CH_3O_4S$ = 271.3.

Profile

Methylhydroxyquinoline metilsulfate has been used topically to treat eye irritation.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Uvestat; ***Fr.:*** Uveline†.

Methylmethacrylate

Metacrilato de metilo; Méthacrylate de méthyle; Methylis methacrylas. Methyl 2-methylacrylate; Methyl 2-methylpropenoate.

$C_5H_8O_2$ = 100.1.
CAS — 80-62-6.

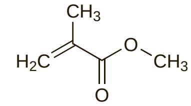

Adverse Effects and Precautions

Occupational exposure to methylmethacrylate monomer vapour during preparation of the bone cement may irritate the respiratory tract, eyes, and skin. Cases of occupational asthma have been reported. Contact dermatitis, dizziness, nausea and vomiting may also occur. Methylmethacrylate monomer may be harmful to the liver.

Methylmethacrylate monomer acts as a peripheral vasodilator and has caused hypotension and, rarely, cardiac arrest and death when absorbed during the use of polymethylmethacrylate (PMMA) as a bone cement during orthopaedic surgery. Other adverse effects associated with the use of polymethylmethacrylate as a bone cement include thrombophlebitis, pulmonary embolism, haemorrhage, haematoma, short-term irregularities in cardiac conduction, cerebrovascular accident, compression of the spinal cord and/or nerve roots, and new fractures in adjacent non-augmented vertebrae. Recommendations when using PMMA include monitoring with high quality imaging systems to detect leakage, and close monitoring of blood pressure during and immediately after the procedure.

Effects on the nervous system. Sensory polyneuropathy has been reported in a dental technician after occupational exposure to methylmethacrylate monomer.[1]

1. Sadoh DR, *et al.* Occupational exposure to methyl methacrylate monomer induces generalised neuropathy in a dental technician. *Br Dent J* 1999; **186:** 380–1.

Uses and Administration

Methylmethacrylate forms the basis of acrylic bone cements used in orthopaedic surgery. A liquid consisting chiefly of methylmethacrylate monomer with a polymerisation initiator is mixed with a powder consisting of polymethylmethacrylate (PMMA) or a methylmethacrylate ester copolymer. The reaction is exothermic. Barium sulfate or zirconium dioxide may be added as a contrast medium. Polymethylmethacrylate beads containing gentamicin have been implanted for the prophylaxis and treatment of bone infections and some soft-tissue infections. Bone cements containing antibacterials such as gentamicin or erythromycin are also available.

Polymethylmethacrylate has also been used as a material for intra-ocular lenses, for denture bases, as a cement for dental prostheses, and in composite resins for dental restoration.

A number of polymers based on methacrylic acid are used in pharmaceutical technology mainly as film coating agents and binders.

Ph. Eur. 6.2 includes:

- Ammonio Methacrylate Copolymer (Type A) (a copolymer of acrylic and methacrylic acid esters)
- Ammonio Methacrylate Copolymer (Type B) (a copolymer of acrylic and methacrylic acid esters)
- Basic Butylated Methacrylate Copolymer
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:2)
- Polyacrylate Dispersion 30 per cent (a dispersion of an ethyl-acrylate-methyl methacrylate copolymer in water)

USNF 26 includes:

- Methacrylic Acid Copolymer (a copolymer of methacrylic acid and an acrylic or methacrylic ester)
- Amino Methacrylate Copolymer
- Ammonio Methacrylate Copolymer
- Ammonio Methacrylate Copolymer Dispersion
- Ethyl Acrylate and Methyl Methacrylate Copolymer

Bone disorders. Polymethylmethacrylate bone cements may be injected percutaneously into vertebral fractures or lesions to relieve pain and stabilise the damaged vertebra.[1-6] The technique has been used in the treatment of metastatic bone lesions and myeloma (p.660 and p.658) as well as for vertebral compression fractures due to osteoporosis (p.1084). Complications[5,7-9] are uncommon but may include both local and systemic effects (including pulmonary embolism) due to leakage of the cement and sudden drop in blood pressure, probably due to the monomer.

1. Barr JD, *et al.* Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine* 2000; **25:** 923–8.
2. Lingar L. Percutaneous polymethacrylate vertebroplasty. *Radiol Technol* 2004; **76:** 109–13.
3. Burton AW, *et al.* Vertebroplasty and kyphoplasty: a comprehensive review. *Neurosurg Focus* 2005; **18:** e1. Available at: http://www.medscape.com/viewarticle/501670 (accessed 15/02/06)
4. Suresh SP, Whitehouse RW. Vertebroplasty and kyphoplasty. *J Br Menopause Soc* 2005; **11:** 28–32.
5. Guglielmi G, *et al.* Percutaneous vertebroplasty: indications, contraindications, technique, and complications. *Acta Radiol* 2005; **46:** 256–68.
6. Hochmuth K, *et al.* Percutaneous vertebroplasty in the therapy of osteoporotic vertebral compression fractures: a critical review. *Eur Radiol* 2006; **16:** 998–1004.
7. Laredo JD, Hamze B. Complications of percutaneous vertebroplasty and their prevention. *Semin Ultrasound CT MR* 2005; **26:** 65–80.
8. Barragan-Campos HM, *et al.* Percutaneous vertebroplasty for spinal metastases: complications. *Radiology* 2006; **238:** 354–62.
9. Health Canada. Complications associated with the use of bone cements in vertebroplasty and kyphoplasty procedures (issued 30th May, 2007). Available at: http://www.hc-sc.gc.ca/ dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bone_cement-ciment_acrylique_nth-aah_2_e.pdf (accessed 30/5/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Palacos E†; Palacos R; **Ger.:** CMW; flint; Palacos R; Palamed; Smart-Set HV; **Port.:** Septopal; **Singapore:** Palacos R†; **Thai.:** Palacos R; **UK:** Palacos R.

Multi-ingredient: Arg.: Septopal†; **Austral.:** Palacos E with Garamycin; Palacos R with Garamycin; Septopal; **Austria:** Septopal; **Belg.:** Palacos LV avec Gentamicine†; Palacos R avec Gentamicine†; Septopal; **Braz.:** Septopal; **Chile:** Palacos E con Gentamicina; Palacos R con Gentamicina; Perlas De PMMA con Gentamicina; **Cz.:** Septopal†; **Denm.:** Septopal; **Fin.:** Palacos R cum Gentamicin†; Septopal; **Fr.:** Palacos LV avec Gentamicine; Palacos R avec Gentamicine; **Ger.:** CMW mit Gentamicin; Copal; Epiglu; Palamed G; Refobacin-Palacos R; Septopal; SmartSet GHV; **Gr.:** Palacos R with Gentamycin†; Septopal†; **Hong Kong:** Septopal; **Hung.:** Plastubol†; Septopal; **India:** Septopal; **Irl.:** Epiglu; **Malaysia:** Septopal†; **Neth.:** Septopal; **Norw.:** Septopal; **NZ:** Antibiotic Simplex; CMW Gentamicin; Palacos with Garamycin; Vacu-Mix Plus with CMW gentamicin; **Philipp.:** Septopal; **S.Afr.:** Palacos R with Garamycin; Septopal; **Singapore:** Refobacin Bone Cement R; Refobacin-Palacos R†; Septopal†; **Swed.:** Septopal†; **Switz.:** Septopal; **Thai.:** Refobacin-Palacos R; Septopal; **UK:** Epiglu; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal.

Metochalcone *(rINN)*

CB-1314; Methochalcone; Metocalcona; Métochalcone; Metochalconum; Trimethoxychalcone. 2′,4,4′-Trimethoxychalcone.

Метохалкон

$C_{18}H_{18}O_4$ = 298.3.

CAS — 18493-30-6.

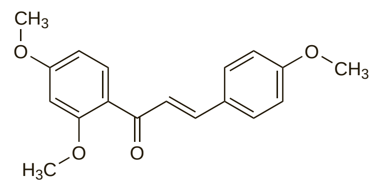

Profile

Metochalcone has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: Spain: Neocolan.

Metocinium Iodide *(pINN)*

Ioduro de metocinio; Metocinii Iodidum; Métocinium, Iodure de. (2-Hydroxyethyl)trimethylammonium iodide benzilate.

Метоциния Йодид

$C_{19}H_{24}INO_3$ = 441.3.

CAS — 2424-71-7.

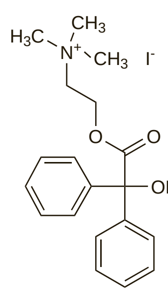

Profile

Metocinium iodide is used as an antispasmodic.

Metyrapone *(BAN, USAN, rINN)*

Metirapon; Metirapona; Metyrapon; Métyrapone; Metyraponi; Metyraponum; Su-4885 (metyrapone tartrate). 2-Methyl-1,2-di(3-pyridyl)propan-1-one.

Метирапон

$C_{14}H_{14}N_2O$ = 226.3.

CAS — 54-36-4.

ATC — V04CD01.

ATC Vet — QV04CD01.

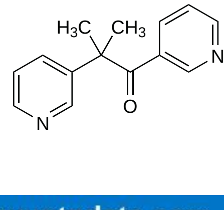

Pharmacopoeias. In *Br., Jpn,* and *US.*

BP 2008 (Metyrapone). A white to light amber crystalline powder with a characteristic odour. M.p. 50° to 53°. Sparingly soluble in water; freely soluble in alcohol and in chloroform; it dissolves in dilute mineral acids. Protect from light.

USP 31 (Metyrapone). A white to light amber, fine, crystalline powder, having a characteristic odour. It darkens on exposure to light. Sparingly soluble in water; soluble in chloroform and in methyl alcohol; forms water-soluble salts with acids. Store in airtight containers. Protect from heat and light.

Adverse Effects

Metyrapone may give rise to nausea and vomiting, abdominal pain, headache, sedation, dizziness, hypotension, and hypersensitivity rashes. Hypoadrenalism, hirsutism, and bone marrow depression may occur rarely. Long-term use of metyrapone can cause hypertension.

Alopecia. Reports of alopecia[1,2] associated with administration of metyrapone for Cushing's syndrome.

1. Harris PL. Alopecia associated with long-term metyrapone use. *Clin Pharm* 1986; **5:** 66–8.
2. Harries-Jones R, Overstall P. Metyrapone-induced alopecia. *Postgrad Med J* 1990; **66:** 584.

Precautions

Metyrapone should be used with extreme caution, if at all, in patients with gross hypopituitarism or with reduced adrenal secretory activity because of the risk of precipitating acute adrenal failure. Thyroid dysfunction or liver cirrhosis may alter the response to metyrapone.

Dizziness and sedation may affect the performance of skilled tasks such as driving.

Porphyria. Metyrapone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Phenytoin is reported to increase the metabolism of metyrapone; doubling the dose of metyrapone may counteract the interaction. However, as many other drugs may interfere with steroid assessment, medication is best avoided where possible during the metyrapone test. Drugs reported to interfere with the metyrapone test include antidepressants such as amitriptyline, antithyroid drugs, antipsychotics such as chlorpromazine, barbiturates, corticosteroids, cyproheptadine, and hormones that affect the hypothalamic-pituitary axis such as oestrogens and progestogens.

Pharmacokinetics

Metyrapone is rapidly absorbed from the gastrointestinal tract. It is metabolised by rapid reduction to metyrapol and excreted in the urine as glucuronide conjugates of metyrapone and metyrapol.

Uses and Administration

Metyrapone inhibits the enzyme 11β-hydroxylase responsible for the synthesis of the glucocorticoids cortisone and hydrocortisone (cortisol) as well as aldosterone from their precursors. The consequent fall in the plasma concentrations of circulating glucocorticoids stimulates the anterior pituitary gland to produce more corticotropin. This, in turn, stimulates the production of more 11-deoxycortisol and other precursors which are metabolised in the liver and excreted in the urine where they can be measured. Metyrapone is therefore used as a test of the feedback hypothalamic-pituitary mechanism in the diagnosis of Cushing's syndrome, although the dexamethasone suppression test (p.1527) may be preferred.

After demonstration of the responsiveness of the adrenal cortex, metyrapone is given orally, usually in a dose of 750 mg every 4 hours for 6 doses. Taking doses with milk or after a meal may minimise the gastrointestinal adverse effects of metyrapone. A suggested oral dose for children is 15 mg/kg, with a minimum dose of 250 mg, every 4 hours for 6 doses. In patients with a normally functioning pituitary gland excretion of 17-hydroxycorticosteroids is increased two- to fourfold and that of 17-ketosteroids about twofold.

Metyrapone is also used in the management of Cushing's syndrome (below) when doses may range from 250 mg to 6 g daily.

Since metyrapone inhibits the synthesis of aldosterone it has been used to treat some cases of resistant oedema; it is given with a glucocorticoid to suppress the normal corticotropin response to low plasma concentrations of glucocorticoids. The suggested usual dosage of metyrapone in resistant oedema is 3 g daily in divided doses.

Metyrapone tartrate has also been used.

Cushing's syndrome. Cushing's syndrome is the result of a chronic excess of glucocorticoids.[1,2] It may be independent of the secretion of adrenocorticotrophic hormone (ACTH; corticotropin), either due to an adrenal tumour secreting cortisol, or to exogenous corticosteroids, or it may be ACTH-dependent, such as Cushing's disease proper, which is caused by excessive ACTH secretion from a pituitary adenoma; other ACTH-dependent forms may be due to pituitary hyperplasia, or an ectopic ACTH-secreting tumour elsewhere—usually bronchus or lung cancer. About two-thirds of all cases are due to Cushing's disease, which is 8 times more common in women than men.

Symptoms may develop insidiously over several years and include obesity, particularly of the trunk, rounding of the face, atrophy of the skin leading to striae, poor wound healing, muscle weakness, osteoporosis, hypertension, diabetes mellitus, and depression and other psychological disturbances. Hypokalaemia is rare in Cushing's disease but common in other forms of the syndrome. Women may have hirsutism due to adrenal androgen secretion, and both sexes may develop hypogonadism and loss of libido.

Diagnosis of Cushing's syndrome can be problematic because no test is wholly reliable.[1,3-6] Where there is suspicion, options for initial screening include measurement of urinary cortisol, late-night salivary cortisol, midnight plasma-cortisol, and overnight low-dose dexamethasone suppression testing. A dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism. Once a diagnosis of Cushing's syndrome has been made, plasma-ACTH measurements are used to distinguish between ACTH-dependent and ACTH-independent forms. High-dose dexamethasone suppression testing and corticorelin stimulation testing have been used to differentiate between pituitary and ectopic ACTH-dependent Cushing's syndrome, but they both have disadvantages and their usefulness has been debated. For further discussion of dexamethasone suppression testing, see p.1527, and for corticorelin stimulation testing, see p.1523. Imaging techniques and sampling of central (petrosal) venous blood are additional procedures that may be used for localising tumours.

Appropriate **treatment** depends on accurate identification of the cause of the syndrome.[1] The usual treatment in Cushing's disease is transsphenoidal resection of the tumour, which when carried out by an experienced surgeon produces a successful response in the majority of patients. Pituitary radiotherapy is slower than surgery to take effect, produces a lower remission rate, and is more likely to produce hypopituitarism. It is therefore usually used as second-line therapy when initial surgery has not been curative and a second operation is considered unsuitable. If pituitary surgery or radiotherapy fails, bilateral adrenalectomy may be considered (although this has some risks including that of Nelson's syndrome due to hyperactivity of residual pituitary tumour). Patients who undergo such surgery require glucocorticoid and mineralocorticoid replacement therapy for life. Surgery is also the treatment of choice for a resectable adrenal tumour or ectopic ACTH-secreting tumour; even where there is metastasis it may be useful in moderating symptoms.

A number of drugs have been used in patients with Cushing's disease, but their role appears to be mainly adjuvant.[1,7] Drugs acting at the hypothalamic-pituitary level, aimed at reducing ACTH secretion, do not seem to be of much value; there have been occasional reports of benefit with bromocriptine, cyproheptadine, and sodium valproate. Drugs that inhibit steroid synthesis in the adrenal gland are more effective, and include mitotane, metyrapone, and ketoconazole. These may be used to control severe complications quickly, prepare patients for surgery, or provide cover while radiotherapy takes effect. Mifepristone acts as a glucocorticoid receptor antagonist, and has been used successfully in a few patients with Cushing's syndrome. Etomidate can be useful for acute control of hypercortisolaemia if the oral route is not available.

In patients with the ectopic ACTH syndrome in whom surgery is unsuitable or ineffective, chemotherapy aimed at the primary tumour is the treatment of choice but is likely to be only palliative. Inhibitors of steroid synthesis can be used to control symptoms, and somatostatin analogues such as octreotide may decrease ACTH secretion by ectopic tumours that have somatostatin receptors.[1]

Surgery is the preferred treatment for an adrenal tumour but, although this is usually curative for adrenal adenoma, it is less successful for adrenal carcinoma.[1]

In patients who are successfully treated for Cushing's syndrome adrenocortical replacement therapy (see p.1498) is usually required until the hypothalamic-pituitary-adrenal axis recovers normal function, a process which may take many months.

1. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.
2. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.
3. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138:** 980–91.
4. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88:** 5593–5602.
5. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab* 2006; **91:** 3746–53.
6. Nieman LK, *et al.* The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93:** 1526–40. Also available at: http://www.endo-society.org/guidelines/final/upload/Cushings_Guideline.pdf (accessed 06/08/08)
7. Nieman LK. Medical therapy of Cushing's disease. *Pituitary* 2002; **5:** 77–82.

Preparations

BP 2008: Metyrapone Capsules;
USP 31: Metyrapone Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Metopirone; ***Cz.:*** Metopirone†; ***Fr.:*** Metopirone; ***Gr.:*** Metopirone; ***Irl.:*** Metopiron; ***Israel:*** Metopirone; ***Neth.:*** Metopiron; ***NZ:*** Metopirone; ***Swed.:*** Metopiron; ***Switz.:*** Metopirone; ***UK:*** Metopirone; ***USA:*** Metopirone.

Miglustat *(BAN, USAN, rINN)*

Butyldeoxynojirimycin; *n*-Butyl-deoxynojirimycin; Miglustaatti; Miglustatum; OGT-918; OXAIDS; SC-48334. 1,5-(Butylimino)-1,5-dideoxy-D-glucitol; (2*R*,3*R*,4*R*,5*S*)-1-Butyl-2-(hydroxymethyl)piperidine-3,4,5-triol.

Миглустат

$C_{10}H_{21}NO_4$ = 219.3.
CAS — 72599-27-0.
ATC — A16AX06.
ATC Vet — QA16AX06.

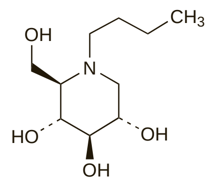

Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances, weight loss, tremor, dizziness, headache, cramps, and visual disturbances are frequent in patients receiving miglustat, and some patients may experience paraesthesias, peripheral neuropathy, or thrombocytopenia. Studies in *animals* have indicated an effect on spermatogenesis; male patients should not attempt conception during, or for 3 months after stopping, treatment. Care is required in renal impairment.

Pharmacokinetics

Miglustat is rapidly absorbed after oral doses with maximum plasma concentrations reached in about 2 hours. It is mainly excreted in the urine with some also excreted in the faeces; the average elimination half-life is 6 to 7 hours.

Food. The average peak plasma concentration was reduced by 37% when miglustat was taken with food by 24 healthy subjects. However, there was no clinically significant effect on the extent of absorption (area under the curve was decreased by 14%).[1] Licensed product information states that miglustat may be taken with or without food.

1. van Giersbergen PLM, Dingemanse J. Influence of food intake on the pharmacokinetics of miglustat, an inhibitor of glucosylceramide synthase. *J Clin Pharmacol* 2007; **47:** 1277–82.

Uses and Administration

Miglustat is an inhibitor of the enzyme glucosylceramide synthase, responsible for the first step in the synthesis of glucosylceramide and most other glycolipids. It is used to help prevent the accumulation of glucosylceramide in patients with mild to moderate type 1 Gaucher disease (p.2249) who cannot be treated with enzyme replacement therapy. The initial dose is 100 mg orally 3 times daily; reduction to 100 mg once or twice daily may be necessary in some patients because of diarrhoea. For details of reduced doses in patients with renal impairment, see below. Miglustat has also been used for the treatment of Niemann-Pick disease, type C.

◊ References.

1. McCormack PL, Goa KL. Miglustat. *Drugs* 2003; **63:** 2427–34.
2. Weinreb NJ, *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80:** 223–9.
3. Giraldo P, *et al.* Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica* 2006; **91:** 703–6.
4. Elstein D, *et al.* Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood* 2007; **110:** 2296–2301.
5. Patterson MC, *et al.* Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007; **6:** 765–72.

Administration in renal impairment. The initial dose of miglustat should be reduced in renal impairment according to the patient's creatinine clearance (CC):

- CC 50 to 70 mL/minute per 1.73 m^2: 100 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Zavesca; ***Canad.:*** Zavesca; ***Cz.:*** Zavesca; ***Denm.:*** Zavesca; ***Fin.:*** Zavesca; ***Fr.:*** Zavesca; ***Ger.:*** Zavesca; ***Gr.:*** Zavesca; ***Hung.:*** Zavesca; ***Israel:*** Zavesca; ***Ital.:*** Zavesca; ***Neth.:*** Zavesca; ***Norw.:*** Zavesca; ***Port.:*** Zavesca; ***Spain:*** Zavesca; ***Swed.:*** Zavesca; ***Switz.:*** Zavesca; ***UK:*** Zavesca; ***USA:*** Zavesca.

Dementholised Mint Oil

Csökkentett mentoltartalmú mezei mentaolaj (partly dementholised mint oil); Menta, aceite esencial desmentolado de; Mentha arvensis, huile essentielle partiellement démentholée de (mint oil, partly dementholised); Menthae arvensis aetheroleum partim mentholum depletum (mint oil, partly dementholised).
CAS — 68917-18-0 (cornmint oil).

Pharmacopoeias. In *Eur.* (see p.vii).
Mentha oil is in *Jpn.*

Ph. Eur. 6.2 (Mint Oil, Partly Dementholised; Menthae Arvensis Aetheroleum Partim Mentholum Depletum; Dementholised Mint Oil BP 2008). The essential oil obtained by steam distillation from the fresh, flowering aerial parts, recently gathered from *Mentha canadensis* (*M. arvensis* var. *glabrata*; *M. arvensis* var. *piperascens*) followed by partial separation of menthol by crystallisation. A colourless or pale yellow to greenish-yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Dementholised mint oil is used as a flavour. *Mentha arvensis* is used in herbal medicine as a febrifuge and for rheumatic disorders. Cornmint oil, obtained from *M. arvensis*, is used in aromatherapy as an adulterant or substitute for peppermint oil. Peppermint oil (p.1761) and spearmint oil (p.2391) are used as carminatives and flavours.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Japanol; JHP Rodler; Retterspitz Muskel- und Nervenol; ***Pol.:*** Migrenol; ***Switz.:*** Carmol; Minthi JHP Huile.

Multi-ingredient: ***Austral.:*** Tiger Balm White; ***Austria:*** Parodontax; ***Chile:*** Astrijesan; Calmatol; ***Ger.:*** Dreierlei; Trachiform†; ***Israel:*** Tiger Balm Red; Tiger Balm White; ***Ital.:*** Broncosedina; Listerine Fresh Citrus; Listerine Tartar Control; Venalta; ***Malaysia:*** Eucarbon†; ***Pol.:*** Argol Essenza Balsamica; Milocardin; Mucosit; Rapacholin C; Rapacholin Forte; Rhin-Bac; Salviasept; ***Switz.:*** GU Eau†; Huile analgesique "Temple of Heaven" contre les maux de tete†; Malveol; Neo-Angin au miel et citron; Neo-Angin sans sucre; Novital; Odontal; Onguent nasal Ruedi; Osa gel dentaire aux plantes; Parodontax F†; Parodontax†; Pastilles pectorales Demo N; Pommade nasale de Nager; Pommade nasale de Ruedi; Pommade Nasale Radix†; Radix; Tyrothricin; Unathene; Unatol; ***Turk.:*** Sandolin; ***UK:*** Olbas; Olbas for Children; Sinose.

Miracle Fruit

Fruta milagrosa.

Profile

Miracle fruit is the fruit of *Synsepalum dulcificum* (*Richardella dulcifica*) (Sapotaceae). It contains a glycoprotein 'miraculin' with no apparent taste of its own but which is able to make sour substances taste sweet and to improve the flavour of foods. Its activity is reduced by heating.

Mistletoe

European Mistletoe; Gui; Mistelkraut; Muérdago; Tallo de Muérdago; Visci Caulis; Visci herba; Viscum; Viscum Album.

Pharmacopoeias. In *Ger.*

Profile

Mistletoe is the dried, evergreen, dioecious semi-parasite, *Viscum album* (Loranthaceae), which grows on the branches of deciduous trees, chiefly apple, poplar, and plum. It occurs as a mixture of broken stems and leaves and occasional fruits. Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders although its activity when taken orally is questionable. It has also been used in nervous disorders.

Mistletoe contains lectins with cytotoxic and immunomodulatory actions *in vitro* and preparations have been given by injection in a number of neoplastic diseases.

Ingestion of the berries and other parts has been reported to cause nausea, vomiting, diarrhoea, and bradycardia.

Homoeopathy. Mistletoe has been used in homoeopathic medicines under the following names: Viscum album; Vis. alb.

◊ A review of mistletoe.[1] There are about 1300 species of mistletoe representing 36 genera of the Loranthaceae, and what is called the "common mistletoe" varies from country to country: in Europe the term describes *Viscum album* while in the USA it describes *Phoradendron flavescens*. The toxicity of aqueous extracts of mistletoe has been found to depend upon the nature of the host plant. Three classes of cytotoxic compounds are present in the leaves and stems of *V. album* although the berries are generally considered to be the most toxic part of the plant. These are alkaloids, viscotoxins, and lectins. The viscotoxins have been shown to cause hypotension, bradycardia, arterial vasoconstriction, and a negative inotropic effect, and may act as acetylcholine agonists. The lectins show toxic effects in *animals* similar to those seen with ricin.

1. Anderson LA, Phillipson JD. Mistletoe—the magic herb. *Pharm J* 1982; **229:** 437–9.

Adverse effects. There have been reports of hepatitis after the ingestion of herbal remedies containing mistletoe.[1,2] Severe delayed hypersensitivity has been reported[3] in a patient given intravenous chemotherapy for breast cancer concurrently with subcutaneous injections of a mistletoe extract. It was thought that mistletoe had stimulated the reaction to methotrexate and gemcitabine.

1. Harvey J, Colin-Jones DG. Mistletoe hepatitis. *BMJ* 1981; **282:** 186–7.

2. Weeks GR, Proper JS. Herbal medicines—gaps in our knowledge. *Aust J Hosp Pharm* 1989; **19:** 155–7.
3. Shaw HS, *et al.* Delayed-type hypersensitivity reaction with Iscador M given in combination with cytotoxic chemotherapy. *J Clin Oncol* 2004; **22:** 4432–4.

Malignant neoplasms. Reviews[1-3] of the use of mistletoe for the treatment of malignant neoplasms revealed that studies have been of variable quality, and have produced conflicting results; it has been suggested that the more rigorous studies do not show benefit.[3] A systematic review[4] of 21 randomised controlled studies found major methodological flaws in most of the studies and concluded that there was insufficient evidence to provide guidelines for the use of mistletoe extracts in oncology.

1. Mansky PJ. Mistletoe and cancer: controversies and perspectives. *Semin Oncol* 2002; **29:** 589–94.
2. Kienle GS, *et al.* Mistletoe in cancer—a systematic review on controlled clinical trials. *Eur J Med Res* 2003; **8:** 109–19.
3. Ernst E, *et al.* Mistletoe for cancer? A systematic review of randomised clinical trials. *Int J Cancer* 2003; **107:** 262–7.
4. Horneber MA, *et al.* Mistletoe therapy in oncology. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 03/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Eurixor; Helixor; Iscador; Isorel; ***Cz.:*** Nat Jmeli; ***Ger.:*** Abnobaviscum; Cefalektin; Eurixor; Helixor; Iscador; Lektinol; Mistel Curarina; Mistel-Krautertabletten; Mistelol-Kapseln†; Misteltropfen Hofmanns; Misteltropfen†; Salus Mistel-Tropfen; Viscysat; ***Switz.:*** Iscador.

Multi-ingredient: ***Austral.:*** Calmo; Pacifenity†; ***Austria:*** Rutiviscal; Wechseltee St Severin; ***Cz.:*** Alvisan Neo; Hypotonicka; ***Fr.:*** Mediflor Tisane Circulation du Sang No 12; ***Ger.:*** Antihypertonicum S; Asgoviscum N†; Heusin†; Hypercircin; Ilja Rogoff; Presselin Arterien K 5 P†; Syviman N†; Viscophyll†; ***Pol.:*** Cravisol; Venoforton; ***Rus.:*** Herbion Drops for the Heart (Гербион Сердечные Капли).

Mitratapide *(USAN, rINN)*

Mitratapid; Mitratapida; Mitratapidum; R-103757. 2-[(2*R*)-Butan-2-yl]-4-(4-{4-[4-({(2*S*,4*R*)-2-(4-chlorophenyl)-2-[(4-methyl-4*H*-1,2,4-triazol-3-ylsulfanyl)methyl]-1,3-dioxolan-4-yl}methoxy)-phenyl]piperazin-1-yl}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

Митратапид

$C_{36}H_{41}ClN_8O_4S = 717.3.$
CAS — 179602-65-4.
ATC Vet — QA08AB90.

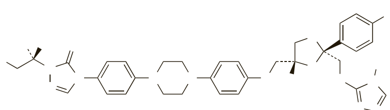

Profile

Mitratapide is an inhibitor of the microsomal triglyceride transfer protein. It is used in veterinary medicine as an aid to management of obesity in *dogs*.

Monoctanoin *(BAN, USAN)*

Monoctanoína; Monooctanoin; Mono-octanoin.
CAS — 26402-26-6 (glyceryl mono-octanoate).

Description. Monoctanoin is a semisynthetic mixture of glycerol esters, containing 80 to 85% of glyceryl mono-octanoate ($C_{11}H_{22}O_4$ = 218.3), 10 to 15% of glyceryl mono-decanoate ($C_{13}H_{26}O_4$ = 246.3) and glyceryl di-octanoate ($C_{19}H_{36}O_5$ = 344.5), and a maximum of 2.5% of free glycerol ($C_3H_8O_3$ = 92.09).

Profile

Monoctanoin given by continuous perfusion through a catheter inserted directly into the common bile duct has been used to dissolve cholesterol gallstones (p.2409) retained after cholecystectomy.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Moctanin†.

Monoethanolamine

2-Hydroxyethylamine; 2-Aminoethanol.
$C_2H_7NO = 61.08.$
CAS — 141-43-5.

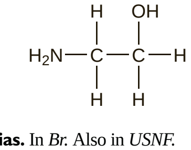

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2008 (Ethanolamine). A clear, colourless, or pale yellow liquid with a slight odour. It is alkaline to litmus. Miscible with water and with alcohol; slightly soluble in ether.

USNF 26 (Monoethanolamine). A clear, colourless, moderately viscous liquid having a distinctly ammoniacal odour. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; immiscible with ether, with petroleum spirit, and with fixed oils, although it dissolves many essential oils. Store in airtight containers. Protect from light.

Monoethanolamine Oleate *(rINN)*

Ethanolamine Oleate *(USAN)*; Monoéthanolamine, Oléate de; Monoethanolamini Oleas; Oleato de monoetanolamina. 2-Hydroxyethylamine compound with oleic acid; 2-Aminoethanol compound with oleic acid.

Моноэтаноламина Олеат

$C_2H_7NO,C_{18}H_{34}O_2 = 343.5.$
CAS — 2272-11-9.
ATC — C05BB01.
ATC Vet — QC05BB01.

Adverse Effects and Precautions

Monoethanolamine oleate is irritant to skin and mucous membranes. Local injection may cause sloughing, ulceration, and, in severe cases, necrosis. Pain may occur at the site of injection. Patients receiving treatment for oesophageal varices may develop pleural effusion or infiltration. Hypersensitivity reactions have been reported.

Sclerotherapy should not be used to treat varicose veins of the legs in patients unable to walk, with obese legs, with thrombosis or a tendency to thrombosis, or with acute phlebitis, marked arterial, cardiac, or renal disease, local or systemic infections, or uncontrolled metabolic disorders such as diabetes mellitus. Monoethanolamine oleate should not be used in patients taking oral contraceptives.

Effects on the kidneys. Acute renal failure, which cleared spontaneously within 3 weeks, occurred in 2 obese women given sclerosing injections of 15 to 20 mL of a solution containing monoethanolamine oleate 5% and benzyl alcohol 2%.[1]

1. Maling TJB, Cretney MJ. Ethanolamine oleate and acute renal failure. *N Z Med J* 1975; **82:** 269–70.

Uses and Administration

Monoethanolamine oleate is used as a sclerosant in the treatment of varicose veins and oesophageal varices. For sclerotherapy of varicose veins, 2 to 5 mL of a 5% solution of monoethanolamine oleate is injected slowly into empty isolated sections of vein, divided between 3 or 4 sites. Injection into full veins is also possible. For sclerotherapy of oesophageal varices, the dose is 1.5 to 5 mL of a 5% solution per varix to a maximum total dose of 20 mL per treatment session. Treatment may be given in the initial management of bleeding varices, then repeated at intervals until the varices are occluded.

Variceal haemorrhage. Portal hypertension may occur in many conditions that affect the liver, and leads to the development of collateral channels linking the portal and systemic circulations. Enlargement of such blood vessels beneath the oesophageal and gastric mucosa produces varices which have about a 30% risk of rupture and bleeding. Oesophageal varices are more often a cause of haemorrhage than gastric varices. Capillaries and veins in the gastric mucosa may also become swollen, a condition known as portal hypertensive gastropathy, and clinically important bleeding may occur in severe cases.

Variceal haemorrhage is usually severe, with mortality as high as 50% for the initial episode; the recurrence rate may be as high as 100% in patients who survive without treatment. Bleeding may stop spontaneously, but in those who continue to bleed, control of haemorrhage is difficult and patients should be referred to a centre with appropriate specialist facilities. Treatment to stabilise the patient may be necessary before they can be safely transferred.

Acute management. Initial treatment is supportive and requires measures to prevent aspiration and maintain a clear airway, and volume replacement with colloid and blood. Emergency endoscopy should be performed to establish the site of haemorrhage and exclude non-variceal sources of bleeding. The choice of treatment depends on the site of haemorrhage.[1-9] ***Endoscopic methods*** have been favoured for initial management. Injection sclerotherapy or banding ligation are used for bleeding oesophageal varices but the optimum management of bleeding gastric varices remains to be defined; the value of injection sclerotherapy varies with their location. Intravariceal injection of bovine or human thrombin, or cyanoacrylate tissue adhesives, has been used in gastric varices. Where the source of haemorrhage is non-variceal and due to gastropathy, portal decompressive surgery is effective, although it is associated with a high incidence of encephalopathy in cirrhotic patients. Small studies have shown propranolol to be effective in arresting haemorrhage.[10]

Injection sclerotherapy for variceal haemorrhage may be performed during the emergency endoscopy procedure. Intravariceal injection, paravariceal injection, or a combination of the two have been used. The most widely used sclerosants are monoethanolamine oleate and sodium tetradecyl sulfate for intravariceal injection and lauromacrogol 400 for paravariceal injection. Sclerotherapy controls bleeding in up to 95% of cases. Ulceration and stricture formation occur frequently following injection sclerotherapy.

An alternative technique is ***endoscopic banding ligation***, where elastic bands are placed around the varices. The tissue subsequently necroses to leave a superficial ulcer. This technique is more successful than injection sclerotherapy, but may be more difficult to perform if active bleeding is occurring. Procedures may be repeated if bleeding continues or restarts.

Where endoscopy is unavailable, drug therapy or balloon tamponade may be used until the patient can be transferred to a specialist centre. These techniques may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy[11] or endoscopy.[12]

Drug therapy is aimed at controlling portal venous pressure, although it is ineffective in massive haemorrhage and its effects cease once the drug is stopped. Two meta-analyses[11,13] have examined data from studies comparing drug therapy with endoscopic methods for the treatment of acute variceal bleeding. Sclerotherapy did not appear to be superior to vasoactive drugs as the first single treatment, and was associated with more frequent adverse effects.[11] Adjunctive drug therapy improved the efficacy of endoscopic therapy (injection sclerotherapy or band ligation) compared with endoscopic methods alone, although overall mortality was not affected; severe adverse effects were similar in both groups.[13]

Drugs used include vasopressin and its analogue terlipressin and, more recently, somatostatin and its analogue octreotide. Vasopressin controls haemorrhage in about 50% of patients. It is given by continuous intravenous infusion, together with glyceryl trinitrate, which counteracts the adverse cardiac effects of vasopressin, while potentiating its reduction of portal pressure. Terlipressin has the advantage of a longer therapeutic action, enabling bolus doses to be given. A comparison[14] of terlipressin and sclerotherapy found them to be equally effective for the control of acute variceal bleeding. A systematic review[15] of studies comparing terlipressin with placebo, or other drugs or interventions, also gave favourable results. However, somatostatin,[2] and particularly octreotide,[2,16,17] which may be given by bolus injection, are now generally preferred as they are thought to have similar efficacy to vasopressin but fewer adverse effects. A meta-analysis[18] of studies comparing somatostatin or its analogues octreotide and vapreotide with either placebo or no drug treatment suggested a small benefit in controlling bleeding; however, no mortality benefit has yet been shown. Clinical studies with recombinant factor VIIa to control acute variceal bleeding have produced beneficial results.[12]

Balloon tamponade controls bleeding by direct pressure on the varices. Although it is a very effective means of controlling haemorrhage, there is a high incidence of rebleeding once pressure is removed and the incidence of complications is high. It is useful in cases of massive haemorrhage when drug therapy is ineffective and sclerotherapy is difficult.

Surgery, such as the formation of a shunt or oesophageal transection, may be necessary if the above measures fail to control the bleeding. However, such techniques have been associated with high mortality in some series. Formation of a transjugular intrahepatic portal-systemic shunt (TIPS) is now generally preferred.[4] It may be particularly useful in candidates for liver transplantation. Limited data suggest that the shunt may remain patent in the majority of patients for at least 3 years.[19]

Short-term ***antibacterial prophylaxis*** has been proposed[20] for cirrhotic patients with gastrointestinal bleeding, including variceal bleeding, because reduced rates of infection and improved short-term survival have been reported in a few studies, although there is no benefit on overall mortality.[21]

Long-term management. Once the acute bleeding has been controlled measures are needed to prevent rebleeding. Endoscopic therapy is widely used, with injection sclerotherapy or banding ligation being repeated until the varices are obliterated. Banding ligation is now the treatment of choice; it eradicates varices in fewer treatment sessions than injection sclerotherapy and reduces the risk of ulceration and stricture formation.[22,23] Sucralfate has been given following sclerotherapy as it may reduce the frequency of stricture formation and reduce bleeding from treatment-related ulcers. It seems to have no influence on ulcer healing following banding ligation.[24] Some practitioners carry out regular endoscopic checks and repeat sclerotherapy or banding ligation when varices reappear, although this approach is no more effective in terms of improving survival than giving treatment once bleeding occurs. Drug therapy is an alternative to endoscopic methods.[25] Beta blockers (mainly propranolol) reduce the incidence of recurrent variceal bleeding and may improve survival.[23,26,27] A combination of nadolol with isosorbide mononitrate has been reported to reduce the risk of rebleeding more than repeated sclerotherapy, although there was no significant effect on mortality.[28] Drug therapy has also been used as an adjunct to endoscopic methods to control rebleeding in the period before variceal obliteration has occurred, or for long-term management following endoscopic therapy. However, studies comparing endoscopic band ligation with combination drug therapy have produced variable results.[29] Long-term octreotide therapy following sclerotherapy has also been investigated and may reduce recurrent variceal bleeding.[30] Several studies[31-33] have compared TIPS with endoscopic treatment, but no clear benefit has been demonstrated and there may be an increased risk of encephalopathy with the use of shunts. Surgery, including liver transplantation, should be considered in patients with recurrent life-threatening haemorrhage. Propranolol may also have a role in patients with portal hypertensive gastropathy. In a controlled study, propranolol reduced the incidence of recurrent bleeding from portal hypertensive gastropathy in patients with cirrhosis.[34]

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed, but should probably be given to patients with cirrhosis and varices thought to be at high risk of bleeding. A reliable system that will identify those at high risk of haemorrhage has yet to be devised. The NIEC (North Italian Endoscopic Club) system is probably the best so far,[35,36] and is based on size of the varices, presence of red wale marks on the varices, and Child-Pugh class; amendments to improve the traditional index have been suggested.[36] Sclerotherapy had been considered as a method of prophylaxis, but its value has not been clearly established. Studies show that beta blockers decrease the incidence of a first bleed[27,37] and are probably the treatment of choice if prophylaxis is to be given. Banding ligation may be a suitable alternative for patients who are unable to take beta blockers.[38] Others consider banding ligation to be the standard therapy for prophylaxis.[9] A meta-analysis[39] of 9 randomised controlled studies concluded that variceal banding ligation was superior to beta blockers in preventing a first variceal bleed, whereas a systematic review[40] of 16 randomised controlled studies found both treatments to be effective and suggested that the estimated effect of banding ligation in some studies may be biased and was associated with shorter duration of follow-up.

It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought, and isosorbide mononitrate[9,41,42] (as adjunctive therapy with a beta blocker) and clonidine[43] have been investigated for the prophylaxis of a first bleed and prevention of recurrent haemorrhage in patients with portal hypertension.

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Varicose veins. Varicose veins are tortuous, protruding veins in the legs, that occur when weak vein walls and valve incompetence result in venous reflux and dilatation. Symptoms associated with varicose veins include heaviness, tension, aching, and itching of the legs. Complications include oedema, thrombophlebitis, deep venous thrombosis, lipodermatosclerosis, and venous ulceration. Risk factors for varicose veins include increasing age, pregnancy, and occupations that involve prolonged standing.[1]

The management of varicose veins has been reviewed.[1-3] Conservative management using compression hosiery may be effective for relief of symptoms in some patients but longer-term compliance is poor.[3] Surgery or sclerotherapy are other treatment options, depending on the veins affected. Surgical treatment, which is the gold standard for treatment of more severe varicose veins, may involve ligation of the affected vein, stripping of the affected stem vein, or avulsions of the varicosities.[3] In sclerotherapy, which may be the treatment of choice for thread veins,[2] a sclerosant is injected into the affected vein where it irritates and damages the lining of the vein causing local thrombosis, fibrosis, and stenosis. Detergent sclerosants include monoethanolamine oleate, sodium tetradecyl sulfate, lauromacrogol 400, and sodium morrhuate; osmotic sclerosants include hypertonic sodium chloride solutions, and hypertonic mixtures of sodium chloride and glucose; caustic sclerosants include chromated glycerol, and a mixture of iodine and sodium iodide. Graduated compression dressings are usually applied after sclerotherapy to minimise the time taken for the surrounding tissue to absorb the damaged segment of vein. Compression may also help to reduce complications of sclerotherapy including hyperpigmentation, oedema, aching, thrombophlebitis, and deep venous thrombosis. A systematic review[4] of randomised controlled trials of injection sclerotherapy failed to determine its place in the overall management of varicose veins, since the type of sclerosant, formulation, local pressure dressing, or degree and length of compression do not appear to have a significant effect on efficacy. However, the evidence supports its current place in practice, which is in the treatment of recurrent varicose veins following surgery, and thread veins. In another systematic review,[5] the use of surgery or sclerotherapy for the management of primary varicose veins was compared. There was a tendency for better early outcomes with sclerotherapy whereas surgery produced more long-term benefits. However, there was insufficient evidence to recommend the use of one form of treatment over the other, and the extent of the varicose veins ultimately governs the choice.

New methods of treatment being tried include foam sclerotherapy, in which a detergent-like sclerosant is mixed with air to create a foam,[2] ambulatory phlebectomy, endovenous laser therapy, and radiofrequency ablation.[3,6]

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Preparations

BP 2008: Ethanolamine Oleate Injection.

Proprietary Preparations (details are given in Part 3)
Braz.: Ethamolin; ***Jpn:*** Oldamin; ***USA:*** Ethamolin.

Monosodium Glutamate

Chinese Seasoning; E621; Glutamato monosódico; MSG; Natrii Glutamas; Sodium Glutamate. Sodium hydrogen L-(+)-2-aminoglutarate monohydrate.

$C_5H_8NNaO_4,H_2O = 187.1.$

CAS — 142-47-2 (anhydrous monosodium glutamate).

Pharmacopoeias. In *Chin.* Also in *USNF.*

USNF 26 (Monosodium Glutamate). White, practically odourless, free-flowing crystals or crystalline powder. It may have either a slightly sweet or slightly salty taste. Freely soluble in water; sparingly soluble in alcohol. pH of a 5% solution in water is between 6.7 and 7.2. Store in airtight containers.

Profile

Monosodium glutamate is widely used as a flavour enhancer and imparts a meaty flavour.

In susceptible individuals, ingestion of foods containing monosodium glutamate may cause MSG symptom complex, a condition characterised by burning sensations, or numbness, in the back of the neck and arms, tingling or warmth or weakness in the face, back and neck, facial pressure, chest pain, headache, nausea, drowsiness or weakness. In patients with asthma, who may be predisposed to develop this condition, bronchospasm may occur. The symptoms tend to occur within an hour of eating 3 g or more of monosodium glutamate on an empty stomach.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Chile:*** Glutacyl Vitaminado; ***Thai.:*** Hemo-Cyto-Serum.

Motherwort

Agripalma; Agripaume, herbe de; Hjärtstilla; Leonuri cardiacae herba; Leonuri Herba; Leonurus; Motherwort Herb; Nukula; Srdečníková nat'; Sukatžolių žolė.

Pharmacopoeias. In *Eur.* (see p.vii). *Chin.* includes the fruit.

Ph. Eur. 6.2 (Motherwort). The whole or cut, dried, flowering aerial parts of *Leonurus cardiaca.* It contains not less than 0.2% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

Profile

Motherwort is given in herbal medicine for nervous and cardiac disorders; it is also used in products promoted for mild hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Pacifenity†; Valerian†; ***Austria:*** Thyreogutt; ***Canad.:*** Thunas Tab for Menstrual Pain†; ***Fr.:*** Biocarde; ***Ger.:*** Biovital Aktiv†; Biovital Classic; Mutellon; Oxacant N†; Oxacant-sedativ; ***Hung.:*** Biovital†; ***Pol.:*** Biovital N; Klimax†; Lumewal; Nervinolum; Nerwobonisol; ***Switz.:*** Tisane pour le coeur et la circulation; ***UK:*** Menopause Relief; Modern Herbals Stress; Period Pain Relief; Prementaid; Quiet Life; SuNerven; Wellwoman.

Moxaverine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxaverina; Meteverine Hydrochloride; Moxavérine, Chlorhydrate de; Moxaverini Hydrochloridum. 1-Benzyl-3-ethyl-6,7-dimethoxyisoquinoline hydrochloride.

Моксаверина Гидрохлорид

$C_{20}H_{21}NO_2,HCl = 343.8.$

CAS — 10539-19-2 (moxaverine); 1163-37-7 (moxaverine hydrochloride).

ATC — A03AD30.

ATC Vet — QA03AD30.

Profile

Moxaverine hydrochloride has a similar structure to papaverine (p.2191) and has been given by mouth and injection as an antispasmodic and in vascular disorders. The base is also used as an antispasmodic.

Doses of moxaverine hydrochloride of up to 300 mg three times daily by mouth have been suggested for the treatment of vasospastic disorders; it has also been given by intravenous infusion.

Much lower doses have been recommended for the treatment of gastrointestinal and biliary-tract spasm.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Certonal†; Kollateral.

Multi-ingredient: ***Austria:*** Hedonin.

Mozavaptan *(rINN)* ⊗

Manavaptan; Mozavaptán; Mozavaptanum; OPC-31260. *N*-(4-{[(5*RS*)-5-(Dimethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylbenzamide.

Мозаваптан

$C_{27}H_{29}N_3O_2$ = 427.5.
CAS — 137975-06-5.

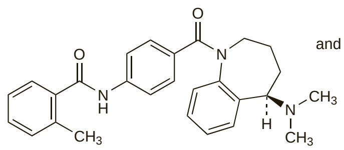

and enantiomer

Profile

Mozavaptan is a selective vasopressin V_2-receptor antagonist used for the treatment of hyponatraemia in cancer-related syndrome of inappropriate antidiuretic hormone secretion.

Mulungu

Profile

The bark of the mulungu tree, *Erythrina verna* (*E. mulungu*) Fabaceae, has traditionally been used in South America as a sedative and as a hypotensive.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Anevrase†; Calmapax; Elixir de Passiflora†; Passaneuro; Passicalm†; Passiflora Composta†; Passilex†; Sedalin†; Xarope Sao Joao†.

Mumps Skin Test Antigen

Parotiditis, prueba cutánea contra el antígeno de la.

Pharmacopoeias. In *US.*

USP 31 (Mumps Skin Test Antigen). A sterile suspension of formaldehyde-inactivated mumps virus prepared from the extra-embryonic fluid of virus-infected chick embryos, concentrated and purified by differential centrifugation, and diluted with isotonic sodium chloride solution. It contains a preservative and glycine as a stabilising agent. Each mL contains not less than 20 complement-fixing units. It should be stored at 2° to 8°. The expiry date is not later than 18 months after date of manufacture or of release from manufacturer's cold storage.

Profile

Recovery from mumps produces skin hypersensitivity to mumps virus. Mumps skin test antigen, has been used with other antigens to assess the status of cell-mediated immunity. A positive reaction may indicate previous infection with mumps virus but it is not considered to be very reliable. It should not be given to patients hypersensitive to egg protein.

Preparations

USP 31: Mumps Skin Test Antigen.

Proprietary Preparations (details are given in Part 3)
USA: MSTA†.

Muramidase Hydrochloride

N-Acetylmuramide Glycanohydrolase Hydrochloride; E1105 (muramidase); Globulin G_1 Hydrochloride; Lysozyme Hydrochloride; Muramidasa, hidrocloruro de.

CAS — 9001-63-2 (muramidase); 9066-59-5 (muramidase hydrochloride).
ATC — D06BB07; J05AX02.
ATC Vet — QD06BB07; QJ05AX02.

Pharmacopoeias. In *Jpn.*

Profile

Muramidase is a mucopolysaccharidase normally present in saliva and other tissues and secretions. It is active against Gram-positive bacteria, possibly by transforming the insoluble polysaccharides of the cell wall to soluble mucopeptides. It is also thought to be active against some viruses and some Gram-negative bacteria.

Muramidase has been given, usually as the hydrochloride, to patients with herpes zoster and other painful viral infections, and for mouth and respiratory-tract disorders. It has been used with antibacterials in an attempt to enhance their activity. Sensitivity reactions have been reported.

Adverse effects. A report[1] of a toxic epidermal necrolysis-type drug eruption in a patient who took an oral cold preparation containing muramidase chloride, which was considered to be the probable cause. The patient's condition improved after intravenous corticosteroid therapy.

1. Kobayashi M, *et al.* A case of toxic epidermal necrolysis-type drug eruption induced by oral lysozyme chloride. *J Dermatol* 2000; **27:** 401–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Murazyme; ***Braz.:*** Murazyme†; ***Hong Kong:*** CP-Lyso; Eurozyme; Flemizyme; Jemizym†; Leftose; Lysosmin; Neuzym; ***Ital.:*** Immunozima†; ***Jpn:*** Leftose; Neuzym; ***Malaysia:*** Leftose†; Neuzym; Noflux; ***Singapore:*** Leftose; Lyzyme; Neuflo; Neuzyme; ***Thai.:*** Leftose.

Multi-ingredient: ***Arg.:*** Bim†; Gammanova†; ***Braz.:*** Colpistar; Tricomax; Trinotrex†; ***Cz.:*** Larypront†; ***Fr.:*** Cantalene; Glossithiase; Hexalyse; Lyso-6; Lysopaine; ***Ger.:*** Frubienzym; ***Gr.:*** Lyso-6; Lysopaine; Sopain-Plus; ***Hong Kong:*** Hexalyse; Quadezyme; ***Ital.:*** Narlisim; ***Port.:*** Narizima; ***Rus.:*** Hexalyse (Гексализ); Lysobact (Лизобакт); ***Singapore:*** Biotene; ***Spain:*** Egarone†; Espectral†; Lizipaina; Normo Nar†; Pulmotropic; Rino Dexa; Trofalgon; ***Switz.:*** Arbid-top; Gem; Lyso-6†; Lysopaine; Mebucasol f; Sangerol; ***Thai.:*** Siduol; ***UK:*** Biotene Dry Mouth; BioXtra†; ***USA:*** Biotene with Calcium.

Poisonous Mushrooms or Toadstools

Champignons vénéneux; Giftpilze; Setas venenosas.

CAS — 23109-05-9 (α-amanitin); 21150-22-1 (β-amanitin); 21150-23-2 (γ-amanitin); 58919-61-2 (coprine); 16568-02-8 (gyromitrin); 2552-55-8 (ibotenic acid); 60-34-4 (methylhydrazine); 300-54-9 (muscarine); 2763-96-4 (muscimol); 37338-80-0 (orellanine); 17466-45-4 (phalloidin); 28227-92-1 (phalloin); 39412-56-1 (phallolysin).

Classification

This monograph describes poisonous mushrooms often known as toadstools, their toxins, toxic effects, and the treatment of those effects. Their only use is in homoeopathic medicine (see below). *Amanita muscaria* and *Psilocybe* spp. are abused for their psychoactive properties (see also Psilocin, p.2375).

Mushrooms can be classified into 8 groups according to their principal toxins and toxic effects:

- *Group I.* Most deaths due to mushroom poisoning follow the ingestion of mushrooms containing cyclopeptides and among these mushrooms *Amanita phalloides* ('death cap') has been reported to be responsible for 90% of all mushroom fatalities. The cyclopeptides are a group of heat-stable cyclic polypeptides with molecular weights ranging from 800 to 1100 and include the amatoxins (α-, β-, γ-amanitin) and phallotoxins (phalloidin, phaloin, phallolysin). Other mushrooms containing cyclopeptides include *A. verna* ('deadly agaric', 'fool's mushroom'), *A. virosa*, ('destroying angel') and *A. bisporigera* ('white destroying angel'), and *Galerina autumnalis*, *G. marginata*, and *G. venenata*.
- *Group II.* Although *A. muscaria* ('fly agaric') and *A. pantherina* ('panther cap', 'false blusher') may contain small amounts of muscarine, the antimuscarinic effects of the hallucinogenic agent muscimol and the insecticidal agent ibotenic acid usually predominate.
- *Group III.* Many species of *Gyromitra* contain toxins known as gyromitrins that decompose to release methylhydrazine (monomethylhydrazine; MMH) an inhibitor of the coenzyme pyridoxal phosphate.
- *Group IV.* Mushrooms whose principal toxin is muscarine include many of the *Clitocybe* and *Inocybe* spp. *A. muscaria* and *A. pantherina* (see above) may also contain small amounts.
- *Group V. Coprinus atramentarius* ('ink cap') contains the compound coprine, one of whose metabolites is an inhibitor of acetaldehyde dehydrogenase and it may therefore produce 'disulfiram-like' symptoms after drinking alcohol.
- *Group VI.* Mushrooms that may contain the hallucinogenic indoles psilocin and psilocybin include species of *Psilocybe*, *Panaeolus*, *Gymnopilus*, *Stropharia*, and *Conocybe*.
- *Group VII.* Many mushrooms that only act as gastrointestinal irritants and do not produce systemic effects are included in this group.
- *Group VIII.* A further group has sometimes been used to classify some species of *Cortinarius* that contain a renal toxin thought by some to be orellanine, but whose exact nature remains to be determined.

Adverse Effects

The clinical course of poisoning due to mushrooms is related to their principal toxins:

- *Group I.* Initial symptoms may occur 6 to 24 hours after ingestion of mushrooms containing cyclopeptides, and usually consist of gastrointestinal effects such as abdominal pain, nausea, severe vomiting, and profuse diarrhoea similar to that in cholera. The patient may then appear to recover and be symptom-free for 2 to 3 days, although liver-enzyme values may be increasing. After this phase, the more serious toxic effects of the amatoxins become apparent and there are signs of hepatic, renal, cardiac, and CNS toxicity. Symptoms include jaundice, oliguria, anuria, hypoglycaemia, coagulopathies, circulatory collapse, convulsions, and coma. The mortality rate is high in this third phase, with death usually being due to hepatic failure following hepatic necrosis. Up to 90% of untreated patients may die, though the rate can be as low as 15 to 30% after treatment.
- *Group II.* The adverse effects of mushrooms containing ibotenic acid and muscimol usually occur within 2 hours of ingestion. Symptoms may include ataxia, euphoria, delirium, and hallucinations associated with other antimuscarinic effects. Fatalities are rare.
- *Group III.* Patients who have ingested mushrooms containing gyromitrins usually develop symptoms of poisoning within 6 to 24 hours. These consist initially of nausea, vomiting, abdominal pain, and muscle cramps, headache, dizziness and fatigue. Delirium, convulsions, coma, methaemoglobinaemia and haemolysis may also occur. Occasionally jaundice and hepatic necrosis lead to hepatic failure and death. Up to 40% of patients die.
- *Group IV.* Symptoms typical of 'cholinergic crisis' (see Adverse Effects of Neostigmine, p.631) may appear about 30 minutes to 2 hours after ingestion of mushrooms containing muscarine. These include bradycardia, bronchospasm, salivation, perspiration, lachrymation, rhinorrhoea, involuntary urination and defaecation, and diarrhoea. Miosis, hypotension, and cardiac arrhythmias may also occur. Rarely death may follow due to cardiac arrest or respiratory-tract obstruction.
- *Group V.* Since one of the metabolites of coprine is an acetaldehyde dehydrogenase inhibitor, drinking alcohol, even up to several days after ingestion of mushrooms containing this compound, will produce symptoms similar to those of the 'disulfiram-alcohol' interaction (see Disulfiram, Adverse Effects, p.2296). Fatalities are rare.
- *Group VI.* The adverse effects of ingestion of mushrooms containing psilocin and psilocybine are similar to those described under lysergide (p.2335). Symptoms usually occur within about 30 minutes to 2 hours. Fatalities are rare.
- *Group VII.* Generally no treatment is required for adverse gastrointestinal effects seen with this group of mushrooms.
- *Group VIII.* There may be a delay of as long as 14 to 20 days before symptoms of poisoning due to *Cortinarius* appear. Patients will develop an intense thirst. Other symptoms usually include nausea, vomiting, diarrhoea, and anorexia. Muscle aching and spasms and a feeling of coldness may also occur. In severe cases renal failure may lead to death. It has been reported that up to 15% of patients die.

Pregnancy. α-Amanitine does not appear to cross the placental barrier, even during the acute phase of intoxication.[1]

1. Belliardo F, *et al.* Amatoxins do not cross the placental barrier. *Lancet* 1983; **i:** 1381.

Treatment of Adverse Effects

As there are no specific antidotes for the majority of cases of mushroom poisoning and which species is involved is often unknown, treatment consists primarily of symptomatic and supportive measures. The stomach may be emptied by gastric lavage if the patient has not already vomited spontaneously. However, if presentation is delayed (because of the slow onset of symptoms seen with some types of mushrooms) measures to empty the stomach are unlikely to be productive. Activated charcoal may be of use in binding toxins in the gastrointestinal tract and preventing absorption. Determining the interval between ingestion and the onset of symptoms often helps to identify the type of mushrooms ingested. If possible specimens of the mushrooms or a sample of the stomach contents should be sent to an expert mycologist for identification. Particular attention should be paid to intravenous replacement of fluids and electrolytes especially if vomiting and diarrhoea are severe. If the ingestion of hepatotoxic or nephrotoxic mushrooms is suspected liver and renal function should be monitored.

Since some mushrooms contain a wide range of toxins and patients may have ingested more than one species, specific therapy should only be instituted following positive identification.

- *Group I.* There is little clinical evidence to support the efficacy of specific agents or treatments for the management of cyclopeptide poisoning. Drugs such as benzylpenicillin, silymarin or silibinin have been given to try to protect the liver against the hepatotoxic effects of the amatoxins. Exchange transfusions, haemodialysis, or charcoal haemoperfusion have been tried to facilitate amatoxin removal. The removal of bile via a duodenal tube left *in situ* has been suggested to reduce enterohepatic circulation of amatoxins. Forced diuresis has also been advocated. Liver transplantation may be required for progressive hepatic failure. A radio-immunoassay for the detection of amatoxins is available in some countries to confirm a diagnosis of cyclopeptide poisoning.

- *Group II.* Specific treatment is usually only required if symptoms are severe. Physostigmine has been used to treat antimuscarinic symptoms. As mushrooms containing ibotenic acid and muscimol may also contain small amounts of muscarine, atropine may be required to control muscarinic symptoms.
- *Group III.* Pyridoxine hydrochloride has been given as an intravenous infusion as specific therapy to overcome the inhibition of pyridoxal phosphate by methylhydrazine, but the use of large doses of pyridoxine might itself produce adverse neurological effects. Methylthioninium chloride may be required if methaemoglobinaemia is severe.
- *Group IV.* Atropine sulfate may be required to control the symptoms of muscarine poisoning but it should only be used if definite muscarinic symptoms are present.
- *Group V.* There is no specific treatment for the 'disulfiram-alcohol' reaction except for the maintenance of blood pressure.
- *Group VI.* If symptoms are severe some patients may require sedation with diazepam.

◊ General reviews.

1. Köppel C. Clinical symptomatology and management of mushroom poisoning. *Toxicon* 1993; **31:** 1513–40.

Amanita phalloides. The use of specific antidotes in the treatment of poisoning due to *Amanita phalloides* remains controversial. Acetylcysteine, benzylpenicillin, sulfamethoxazole, thioctic acid, cytochrome C, ascorbic acid, insulin, growth hormone, silymarin or silibinin, and corticosteroids have all been used or suggested. Evidence to support most of these is lacking;[1,2] there is limited evidence to support the use of silibinin and acetylcysteine, but benzylpenicillin, although widely used, does not have proven efficacy.[1] In patients who develop fulminant liver failure the definitive treatment is liver transplantation.[1,2]

1. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40:** 715–57.
2. Berger KJ, Guss DA. Mycotoxins revisited: part I. *J Emerg Med* 2005; **28:** 53–62.

Uses

Homoeopathy. Several types of poisonous mushrooms have been used in homoeopathic medicines under the following names:

- *Amanita phalloides*: Agaricus phalloides; Agaricus bulbosus
- *Russula emetica*: Agaricus emeticus: Agar. e.
- *Amanita muscaria*: Agaricus muscarius; Agar. m.
- *Coprinus stercorarius* (*Stropharia stercoraria*): Agaricus stercorarius; Aga. ster.

Musk

Almíscar; Almizcle; Deer Musk; Mosc.; Moschus.

CAS — 541-91-3 (muskone).

Pharmacopoeias. In *Chin.*

Profile

Musk is the dried secretions from the preputial follicles of the musk deer, *Moschus moschiferus* or some other spp. of *Moschus* (Cervidae). It is used as a fragrance and fixative in perfumery. The main source of musk's fragrance is muskone (muscone).

A series of nitrated tertiary butyl toluenes or xylenes, or related compounds, are used as artificial musks. Musk ambrette, a synthetic nitromusk compound used in perfumery and as a food flavour, has been reported to cause contact dermatitis and photosensitivity.

Homoeopathy. Musk has been used in homoeopathic medicines under the following names: Moschus; Mosc.

◊ References.

1. Schmeiser HH, *et al.* Evaluation of health risks caused by musk ketone. *Int J Hyg Environ Health* 2001; **203:** 293–9.

Black Mustard

Graine de Moutarde Noire; Mostarda Preta; Mostaza negra; Moutarde Jonciforme; Schwarzer Senfsame; Semen Sinapis; Semilla de Mostaza; Sinapis Nigra.

Description. Black mustard is the dried ripe seeds of *Brassica nigra* (*B. sinapioides*) (Cruciferae).

Pharmacopoeias. In *Swiss* which allows *B. nigra*, *B. juncea*, and other species.

White Mustard

Mostaza blanca; Sinapis Alba.

Description. White mustard is the dried ripe seeds of *Brassica alba* (Cruciferae).

Pharmacopoeias. *Chin.* allows *B. alba* or *B. juncea*.

Volatile Mustard Oil

Allylsenföl; Essence of Mustard; Mostaza, aceite esencial de; Oleum Sinapis Volatile.

Allyl Isothiocyanate *(USAN)*

Isothiocyanato-l-propene.

$C_4H_5NS = 99.15$.

CAS — 57-06-7.

Pharmacopoeias. *Fr.* and *US*

USP 31 (Allyl Isothiocyanate). A colourless to pale yellow, very refractive, liquid with a pungent, irritating odour and an acrid taste. Slightly soluble in water; miscible with alcohol, with carbon disulfide, and with ether. Store in airtight containers.

Profile

Black and white mustard seeds have been used as emetics, in counter-irritant and rubefacient preparations, and as condiments. Volatile mustard oil, prepared from black mustard seeds, is largely composed of allyl isothiocyanate. It is an extremely powerful irritant that has been used as a counter-irritant and rubefacient. Expressed mustard oil contains a smaller proportion of volatile oil and has been used as a less powerful counter-irritant.

Adverse effects. A report of 2 cases of IgE-mediated anaphylaxis to mustard condiment.[1]

1. Vidal C, *et al.* Anaphylaxis to mustard. *Postgrad Med J* 1991; **67:** 404.

Handling. Allyl isothiocyanate is a potent lachrymator, with a pungent irritating odour. Care should be taken to protect the eyes, to prevent inhalation of fumes, and to avoid tasting.

Preparations

Proprietary Preparations (details are given in Part 3)
Mon.: Autoplasme Vaillant; Sinapisme Rigollot.

Multi-ingredient: *Braz.:* Aliviol; Analgen†; Benegel; Gelflex; Gelol†; Gelonevral†; Mialgex†; Mostardina†; Nevrol; ***Canad.:*** Rheumalan†; ***Cz.:*** Apisarthron; Rheumosin†; ***Ger.:*** Cor-Select†; ***Pol.:*** Reumobonisol; ***Rus.:*** Apisarthron (Апизартрон); Efcamon (Эфкамон); ***Spain:*** Dolokey; ***Switz.:*** Knobel Huile N; ***UK:*** Nine Rubbing Oils; Radian-B Red Oils; Red Oil; ***USA:*** Dermolin; Methalgen†; Musterole Extra.

Myristyl Alcohol

Alcohol miristilo; Alkohol mirystylowy; NSC-8549; 1-Tetradecanol.

$C_{14}H_{30}O = 214.4$.

CAS — 112-72-1.

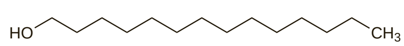

Pharmacopoeias. In *USNF.*

USNF 26 (Myristyl Alcohol). M.p. 36° to 42°.

Profile

Myristyl alcohol is used as an oleaginous vehicle. Contact dermatitis has been associated with its use.

Myrrh

Gum Myrrh; Gummiresina Myrrha; Mira; Mirhami; Mirra; Mirrha; Myrhovníková klejopryskyřice; Myrra; Myrrha; Myrrhe.

Мирра

CAS — 9000-45-7 (myrrh); 8016-37-3 (myrrh oil).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Myrrh). A gum-resin, hardened in air, obtained from the stem and branches of *Commiphora molmol* and/or other species of *Commiphora*. Protect from light.

USP 31 (Myrrh). The oleo-gum resin obtained from the stems and branches of *Commiphora molmol* and other related species of *Commiphora* (Burseraceae) other than *C. mukul*. Store in airtight containers in a dry place.

Profile

The principal source of myrrh is *Commiphora myrrha* (*C. molmol*) (Burseraceae). Myrrh is astringent to mucous membranes; the tincture is used in mouthwashes and gargles for inflammatory disorders of the mouth and pharynx. It has also been used as a carminative. Myrrh has been tried in the treatment of schistosomiasis and fascioliasis.

Myrrh oil is used in aromatherapy.

Contact dermatitis has been reported.

Helminth infections. Myrrh was of benefit in a small study[1] of 7 patients with fascioliasis and in another study[2] of 204 patients with schistosomiasis. However, it showed low cure rates in the treatment of schistosomiasis when compared with praziquantel.[3,4]

1. Massoud A, *et al.* Preliminary study of therapeutic efficacy of a new fasciolicidal drug derived from Commiphora molmol (myrrh). *Am J Trop Med Hyg* 2001; **65:** 96–9.
2. Sheir Z, *et al.* A safe, effective, herbal antischistosomal therapy derived from myrrh. *Am J Trop Med Hyg* 2001; **65:** 700–4.
3. Botros S, *et al.* Efficacy of mirazid in comparison with praziquantel in Egyptian Schistosoma mansoni-infected school children and households. *Am J Trop Med Hyg* 2005; **72:** 119–23.
4. Barakat R, *et al.* Efficacy of myrrh in the treatment of human schistosomiasis mansoni. *Am J Trop Med Hyg* 2005; **73:** 365–7.

Preparations

Ph. Eur.: Myrrh Tincture;
USP 31: Myrrh Topical Solution.

Proprietary Preparations (details are given in Part 3)
Ger.: Inspirol P; ***Rus.:*** Myrtoplex (Миртоплекс).

Multi-ingredient: *Arg.:* Parodontax Fluor; ***Austral.:*** Eczema Relief; ***Austria:*** Brady's-Magentropfen; Dentinox; Paradenton; Parodontax; ***Braz.:*** Paratonico; Parodontax; ***Canad.:*** Lotion pour Feux Sauvages†; ***Chile:*** Astrijesan; ***Cz.:*** Dr Theiss Rheuma Creme†; Dr Theiss Schweden Krauter; Dr Theiss Schwedenbitter; Original Schwedenbitter; ***Denm.:*** Dolodent; ***Ger.:*** Ad-Muc†; Infi-tract†; Mint-Lysoform; Myrrhinil-Intest; Ratanhia comp; Repha-Os; ***Hong Kong:*** Ad-Muc; ***Israel:*** Parodontax†; ***Ital.:*** Gengivario†; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Helmontskruie; Lewensessens; ***Spain:*** Buco Regis; ***Switz.:*** Baume†; Eubucal†; GU Eau†; Parodontax F†; Parodontax†; Pommade au Baume; Sanogencive; ***UK:*** Herbal Indigestion Naturtabs; HRI Golden Seal Digestive; Indigestion and Flatulence; Vocalzone; Wind & Dyspepsia Relief; ***Venez.:*** One Drop Spray†.

Myrtillus

Baccae Myrtilli; Bilberry; Blåbär (bilberry fruit); Blaeberry; Borůvkový plod; Fekete áfonya termés (bilberry fruit); Heidelbeere; Huckleberry; Hurtleberry; Mėlynių uogos, džiovintos (bilberry fruit); Mirtilo; Mustikka (bilberry fruit); Myrtille, fruit de (bilberry fruit); Myrtilli Fructus; Myrtilli fructus (bilberry fruit); Whortleberry.

Pharmacopoeias. In *Eur.* (see p.vii). *US* includes Powdered Bilberry Extract.

Ph. Eur. 6.2 (Bilberry Fruit, Dried; Dried Bilberry BP 2008; Bilberry Fruit, Fresh; Fresh Bilberry BP 2008). The ripe fruit of *Vaccinium myrtillus*. It has a sweet and slightly astringent taste. The dried fruit contains a minimum of 1.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. The fresh or frozen fruit contains a minimum of 0.30% of anthocyanins, expressed as cyanidin-3-glucoside chloride (chrysanthemin, $C_{21}H_{21}ClO_{11} = 484.8$), calculated with reference to the dried drug. The frozen fruit should be stored at or below –18°.

Profile

Myrtillus has diuretic and astringent properties. It has been used for ophthalmic and circulatory disorders and for diarrhoea.

Homoeopathy. Myrtillus has been used in homoeopathic medicines under the following names: Vaccinium myrtillus; Vac. myrt.

Preparations

Ph. Eur.: Fresh Bilberry Fruit Dry Extract, Refined and Standardised.

Proprietary Preparations (details are given in Part 3)
Arg.: Mirtilene Forte†; ***Austral.:*** Herbal Eye Care Formula†; ***Braz.:*** Miralis; ***Ger.:*** Difrarel; ***Indon.:*** Lanavision; ***Ital.:*** Alcodin; Angiorex†; Mirtilene Forte; Retinol†; Tegens; ***Malaysia:*** Natberry; ***Pol.:*** Bilberin; Fibs; ***Port.:*** Difrarel; Tegens; Varison†; ***Rus.:*** Mirtilene Forte (Миртилене Форте); ***Switz.:*** Myrtaven.

Multi-ingredient: *Austral.:* Bilberry Plus; Bilberry Plus Eye Health; Bioglan Pygno-Vite; Bioglan Vision-Eze; Extralife Eye-Care; Extralife Leg-Care; Herbal PMS Formula†; Prophthal†; Pykno†; St Mary's Thistle Plus; ***Austria:*** Amersan; ***Braz.:*** Antomiopic†; ***Chile:*** Gingo-Ther†; ***Cz.:*** Amersan; Diabetan; Diabeticka Cajova Smes-Megadiabetin; Tormentan; Urcyston Planta; ***Fr.:*** Diacure; Difrarel; Difrarel E; Flebior; Klorane Shampooing Antipelliculaire; Stomargil; ***Ger.:*** Salus Augenschutz-Kapseln NA†; ***Hung.:*** Difrarel E; ***Indon.:*** Berry Vision; Bioretin; Eyevit; Lanavision; Lanavision Plus; Lutevision; Lutevision Extra; Matase; Matovit; Matovit Fifty; Nuvision; Oculex; Opibright; Optha-LL; Optimax; Visivit; Vita-Vision; Vitop; ***Israel:*** Opti-safe; ***Ital.:*** Alvear con Ginseng; Angiorex Complex; Angioton; Api Baby; Bebimix; Biolactine; Capill; Dermilia Flebozin; Evamilk; Flebo-Si; Flebofort; Levital Plus; Lipaven; Memovisus†; Mirtilene; Mirtilux; Neomyrt Plus; Nerex; Pik Gel; Promix 3†; Retinovit; Rivuclin; Tussol; Ultravisin; Varicofit; ***Malaysia:*** Natberry Extra; Natberry Plus; ***Neth.:*** Difrarel; ***Pol.:*** Biovision; Pelogel; Reumosol; ***Rus.:*** Strix (Стрикс); ***Spain:*** Antomiopic†; Mirtilus; ***UK:*** Se-Power.

Myrtle

Arrayán; Mirto; Myrte.

CAS — 8008-46-6 (myrtle oil); 8002-55-9 (myrtol).

NOTE. Distinguish from Myrtillus, p.2349, from *Vaccinium myrtillus.*

Profile

Myrtle (*Myrtus communis*, Myrtaceae) has been included in herbal preparations for cough.

Myrtle oil is obtained from the leaves and twigs. Myrtle oil is included in preparations for disorders of the upper respiratory tract and is used in aromatherapy.

The term myrtol has been used to describe an extract of myrtle, standardised on its content of α-pinene, *d*-limonene, and cineole. It is used for respiratory-tract disorders.

◊ References.

1. Matthys H, *et al.* Efficacy and tolerability of myrtol standardized in acute bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. *Arzneimittelforschung* 2000; **50:** 700–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gelomyrtol; ***Ger.:*** Gelomyrtol; ***Gr.:*** Gelomyrtol; ***Hong Kong:*** Gelomyrtol; ***Neth.:*** Gelodurat; ***Thai.:*** Gelomyrtol.

Multi-ingredient: ***Austria:*** Tetra-Gelomyrtol; ***Braz.:*** Broncopinol†; ***Fr.:*** Acarcid†; Nazinette du Docteur Gilbert; Pectoderme†; ***Ger.:*** Tetra-Gelomyrtol; ***Spain:*** Trophires†.

Nadide *(BAN, USAN, rINN)*

Codehydrogenase I; Coenzyme I; Co-I; Diphosphopyridine Nucleotide; DPN; NAD; Nadida; Nadidum; Nicotinamide Adenine Dinucleotide; NSC-20272. 1-(3-Carbamoylpyridinio)-β-D-ribofuranoside 5-(adenosine-5′-pyrophosphate).

Надид

$C_{21}H_{27}N_7O_{14}P_2$ = 663.4.

CAS — 53-84-9.

Profile

Nadide is a naturally occurring coenzyme claimed to be of value in the treatment of alcohol and opioid addiction. The reduced form of nadide, NADH, has been used in the management of chronic fatigue syndrome.

Parkinsonism. The reduced form of nadide, NADH (β-NADH; reduced DPN) and its phosphate derivative (NADPH) have been given in the management of Parkinson's disease in an attempt to enhance endogenous dopamine synthesis by stimulating the enzyme tyrosine hydroxylase. Although some beneficial effects have been reported in several case series, a placebo-controlled study failed to find any evidence of efficacy and the routine use of NADH has not been recommended.[1]

1. Swerdlow RH. Is NADH effective in the treatment of Parkinson's disease? *Drugs Aging* 1998; **13:** 263–8.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: DPN; ***Spain:*** Nad.

Nafamostat Mesilate *(rINNM)*

FUT-175; Mesilato de nafamostat; Nafamostat, Mésilate de; Nafamostat Mesylate *(USAN)*; Nafamostati Mesilas. 6-Amidino-2-naphthyl *p*-guanidinobenzoate dimethanesulfonate.

Нафамостата Мезилат

$C_{21}H_{25}N_5O_8S_2$ = 539.6.

CAS — 81525-10-2 (nafamostat); 82956-11-4 (nafamostat mesilate).

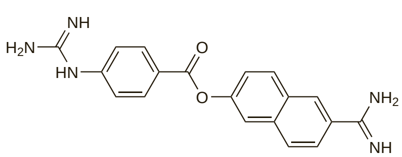

(nafamostat)

Profile

Like aprotinin (p.1055) nafamostat is a proteolytic enzyme inhibitor. The mesilate is used in the treatment of acute pancreatitis and disseminated intravascular coagulation, and as an anticoagulant in haemodialysis.

Hyperkalaemia has been reported.

◊ References.

1. Yanamoto H, *et al.* Therapeutic trial of cerebral vasospasm with the serine protease inhibitor, FUT-175, administered in the acute stage after subarachnoid hemorrhage. *Neurosurgery* 1992; **30:** 358–63.
2. Akizawa T, *et al.* Nafamostat mesilate: a regional anticoagulant for haemodialysis in patients at high risk for bleeding. *Nephron* 1993; **64:** 376–81.
3. Miyata T, *et al.* Effectiveness of nafamostat mesilate on glomerulonephritis in immune-complex diseases. *Lancet* 1993; **341:** 1353.
4. Murase M, *et al.* Nafamostat mesilate reduces blood loss during open heart surgery. *Circulation* 1993; **88:** 432–6.
5. Kitagawa H, *et al.* Hyperkalaemia due to nafamostat mesylate. *N Engl J Med* 1995; **332:** 687.
6. Yamazato M, *et al.* Severe abdominal pain associated with allergic reaction to nafamostat mesilate in a chronic hemodialysis patient. *Intern Med* 2002; **41:** 864–6.
7. Kaminishi Y, *et al.* Effects of nafamostat mesilate and minimal-dose aprotinin on blood-foreign surface interactions in cardiopulmonary bypass. *Ann Thorac Surg* 2004; **77:** 644–50.
8. Ota T, *et al.* Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage. *Interact Cardiovasc Thorac Surg* 2007; **6:** 270–3.

Naphthylacetic Acid

Naftilacético, ácido; 1-Naphthaleneacetic Acid; 1-Naphthylacetic Acid.

$C_{12}H_{10}O_2$ = 186.2.

CAS — 86-87-3.

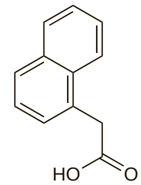

Profile

Naphthylacetic acid has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Galle-Donau; Spagall; ***Switz.:*** Bilipax†.

Natalizumab *(rINN)*

Natalizumabum. Immunoglobulin G 4 (human-mouse monoclonal AN100226 4-chain antihuman integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer.

Натализумаб

CAS — 189261-10-7.

ATC — L04AA23.

ATC Vet — QL04AA23.

Adverse Effects and Precautions

Natalizumab commonly causes infusion-related reactions including headache, dizziness, fatigue, urticaria, pruritus, rash, fever, rigors, nausea, hypotension, flushing, dyspnoea, and chest pain. Serious hypersensitivity reactions such as anaphylaxis can also occur. These reactions are usually associated with antibodies to natalizumab. The presence of these antibodies results in reduced serum concentrations and efficacy of natalizumab. The risk of infection is increased and there have been a few cases of progressive multifocal leukoencephalopathy (PML) reported; all patients should be monitored and if signs or symptoms of PML appear treatment should be withheld pending investigation. Clinically significant hepatotoxicity has also been reported with natalizumab and treatment should be stopped if there is evidence of jaundice or other significant liver injury.

Natalizumab is contra-indicated in patients who have previously had PML. It is also contra-indicated in patients with, or at risk for, opportunistic infections, and in those with malignancies.

Antibody formation. The incidence and clinical effects of antibody formation to natalizumab therapy in patients with relapsing multiple sclerosis were studied in the AFFIRM and SENTINEL studies.[1] Of 625 patients treated with natalizumab in the AFFIRM study 20 (3%) were transiently positive for antibodies to natalizumab and 37 (6%) were persistently positive. Equivalent figures for 585 natalizumab-treated patients in the SENTINEL study were 32 (5%) and 38 (6%) respectively. Overall the presence of antibodies was generally correlated with reduced serum concentrations of natalizumab and a poorer treatment response, efficacy being restored in those patients who became antibody-negative during therapy. Antibody-positive patients also had a higher incidence of infusion-related adverse effects, including hypersensitivity reactions (17 of the 37 persistently positive patients in the AFFIRM study). It is recommended that patients with suboptimal response to natalizumab or persistent infusion-related adverse effects should be considered for antibody testing. UK licensed product information warns that therapy should not be restarted in patients who remain positive for antibodies 6 weeks after interrupting an initial short exposure to natalizumab.

1. Calabresi PA, *et al.* The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; **69:** 1391–1403.

Hypersensitivity. A review[1] of the data for patients who had hypersensitivity reactions in the AFFIRM study[2], which included 627 patients in the natalizumab treatment group, found that there was a low incidence (<1%) of serious reactions described as anaphylactoid or anaphylactic. All patients with hypersensitivity reactions responded promptly to discontinuation of the infusion and standard pharmacotherapy as necessary (adrenaline, oxygen, and antihistamines with or without corticosteroids); all recovered fully about 1 to 2 hours after the end of the infusion. UK licensed product information warns that patients should be counselled on the importance of uninterrupted dosing, particularly in the early months of treatment; the risk for hypersensitivity reactions is greatest with early infusions and in patients who, after an initial short exposure to natalizumab, are re-exposed after a treatment-free period of 3 or more months.

1. Phillips JT, *et al.* Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology* 2006; **67:** 1717–18. Correction. *ibid.* 2007; **68:** 473.
2. Polman CH, *et al.* AFFIRM investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.

Infections. Three cases of progressive multifocal leukoencephalopathy (an opportunistic infection of the brain caused by JC virus, a human polyomavirus) have been described in patients given natalizumab.[1-3] One patient[1] died after receiving natalizumab with azathioprine for Crohn's disease. The other patients[2,3] were given natalizumab with interferon beta for multiple sclerosis; one of these[2] also died. After these reports, the use of natalizumab has been restricted (see Uses and Administration, below). A subsequent retrospective evaluation[4] of more than 3000 patients who had received natalizumab found no further cases. However, 2 further cases have subsequently been reported[5] in patients taking natalizumab as monotherapy for 14 months and 17 months; one of the patients had previously taken immunosuppressants.

1. Van Assche G, *et al.* Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353:** 362–8.
2. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; **353:** 369–74.
3. Langer-Gould A, *et al.* Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; **353:** 375–81.
4. Yousry TA, *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; **354:** 924–33.
5. FDA. Alert for healthcare professionals: natalizumab injection for intravenous use (marketed as Tysabri) (issued 25/08/08). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/natalizumab2008HCP.htm (accessed 26/08/08)

Melanoma. Long-standing naevi in two women developed into melanoma shortly after starting natalizumab treatment for multiple sclerosis.[1]

1. Mullen JT, *et al.* Melanoma complicating treatment with natalizumab for multiple sclerosis. *N Engl J Med* 2008; **358:** 647–8.

Interactions

Use with antineoplastics, immunosuppressants, or immunomodulators may further increase the risk of opportunistic infections including progressive multifocal leukoencephalopathy associated with natalizumab. Concurrent treatment with interferon beta or glatiramer acetate is contra-indicated.

Uses and Administration

Natalizumab is a murine monoclonal antibody raised against human α4 integrin that is used as monotherapy to prevent relapses and delay progression of disability in patients with highly active relapsing-remitting multiple sclerosis. It is also used for inducing and maintaining response and remission in moderate to severe Crohn's disease (see Inflammatory Bowel Disease, p.1697). However, because of an increased risk of progressive multifocal leukoencephalopathy (PML) its availability is restricted, and use is limited to patients who have had an inadequate response to, or are unable to tolerate, other therapies. A baseline magnetic resonance imaging scan must be done before natalizumab is started in order to differentiate newly developed lesions from pre-existing lesions. Patients should be evaluated for signs and symptoms of PML at 3 and 6 months after the first dose, then every 6 months thereafter. Natalizumab must be discontinued at the first sign of PML or other opportunistic infection developing; treatment may resume if this diagnosis is excluded, but should be permanently discontinued if confirmed.

Patients who were previously taking interferon beta or glatiramer acetate may switch directly to natalizumab provided there are no treatment-related adverse effects such as neutropenia; blood counts must return to normal before starting natalizumab. Patients who have been receiving immunosuppressants such as azathioprine and cyclophosphamide must not start natalizumab until it has been confirmed that they are no longer immunocompromised. Likewise, the pharmacodynamic effects of natalizumab remain for about 12 weeks after stopping treatment, and therefore a wash-out period may be appropriate on stopping natalizumab before giving immunosuppressive drugs.

Natalizumab 300 mg is given by intravenous infusion once every 4 weeks. The dose is diluted in 100 mL of sodium chloride 0.9% and given over about 1 hour. The patient should be observed during the infusion and for a further hour after it is complete; the infusion should be stopped if a hypersensitivity reaction occurs and treatment with natalizumab permanently discontinued. Treatment should also be discontinued if there is evidence of persistent raised antibodies to natalizumab since these reduce efficacy and increase the risk of hypersensitivity reactions. Continuation of therapy in multiple sclerosis patients who have shown no benefit after 6 months should be reconsidered. In the treatment of Crohn's disease, natalizumab should be stopped if patients have not obtained therapeutic benefit after 12 weeks of induction therapy or when patients are unable to discontinue chronic concomitant corticosteroid use within 6 months of starting natalizumab.

Natalizumab has also been investigated for the treatment of ulcerative colitis.

◊ References.

1. Sweet BV. Natalizumab update. *Am J Health-Syst Pharm* 2007; **64:** 705–16.

Inflammatory bowel disease. The efficacy and safety of natalizumab in the treatment of *Crohn's disease* have been reviewed, including proposed mechanisms for the role of α4 integrins in the immunopathogenesis of inflammatory bowel disease (p.1697).[1,2] A systematic review[3] of controlled studies of the use of natalizumab in the treatment of Crohn's disease concluded that it is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease, particularly those with active inflammation or chronically active disease despite use of conventional treatment. However, this benefit must be weighed against the risks of developing progressive multifocal leukoencephalopathy.

Natalizumab is also under investigation for *ulcerative colitis*.[4]

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Lanzarotto F, *et al.* Novel treatment options for inflammatory bowel disease: targeting α 4 integrin. *Drugs* 2006; **66:** 1179–89.
3. MacDonald JK, McDonald JWD. Natalizumab for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Feagan BG, *et al.* Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. *N Engl J Med* 2005; **352:** 2499–2507.

Multiple sclerosis. The efficacy and safety of natalizumab in the treatment of multiple sclerosis (p.892) have been reviewed, including proposed mechanisms for the role of α4 integrins in its immunopathogenesis.[1-3] Randomised controlled studies[4-7] showed beneficial results in suppressing inflammatory lesions and reducing the frequency of relapse. Subsequent review[8] of the data from the AFFIRM trial[5] and the SENTINEL study[6] demonstrated reduction of visual loss. In the SENTINEL study,[6] natalizumab was given with interferon beta, a combination that may have contributed to the development of progressive multifocal leukoencephalopathy in 2 of the study patients, one of whom died (see Infections, above). As a consequence, natalizumab is currently licensed only as monotherapy.

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; **39:** 1833–43.
2. Rice GPA, *et al.* Anti-α4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology* 2005; **64:** 1336–42.
3. Ransohoff RM. Natalizumab for multiple sclerosis. *N Engl J Med* 2007; **356:** 2622–9.
4. Miller DH, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; **348:** 15–23.
5. Polman CH, *et al.* AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.
6. Rudick RA, *et al.* SENTINEL investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 911–23.
7. Miller DH, *et al.* AFFIRM Investigators. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68:** 1390–1401.
8. Balcer LJ, *et al.* AFFIRM and SENTINEL investigators. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007; **68:** 1299–1304.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Tysabri; ***Cz.:*** Tysabri; ***Gr.:*** Tysabri; ***Port.:*** Tysabri; ***UK:*** Tysabri; ***USA:*** Tysabri.

Neroli Oil

Aurantii amari floris aetheroleum; Aurantii Amari Floris Aetheroleum (bitter-orange flower oil); Aurantii Amari Floris Etheroleum; Azahar, aceite esencial de; Bitter-Orange Flower Oil; Esencia de Azahar; Essência de Flor de Laranjeira; Karčiavaisių citrinmedžių žiedų eterinis aliejus (bitter-orange flower oil); Keserű narancs virág olaj (bitter-orange flower oil); Neroli aetheroleum; Néroli, huile essentielle de; Neroliolja; Nerolióljy; Olejek z kwiatu pomarańczy gorzkiej; Oleum Neroli; Orange Flower Oil; Orange-flower Oil; Silice květů hořkého pomeranče.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Neroli Oil). A clear, pale yellow or dark yellow liquid with a characteristic odour obtained by steam distillation from the fresh flowers of *Citrus aurantium* subsp. *aurantium* (*C. aurantium* subsp. *amara*). Relative density 0.863 to 0.880. Store in well-filled airtight containers at a temperature below 25°. Protect from light.

Profile

Neroli oil is used as a flavour and in perfumery. It is also used in aromatherapy. Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Agua Melisa Carminativa; ***Cz.:*** Stopangin; ***Ital.:*** Controller; ***Rus.:*** Stopangin (Стопангин); ***Switz.:*** Hygiodermil; Kemeol; Oculosan.

Nerve Agents

Gases nerviosos.

Sarin

GB; Sarín. Isopropyl methylphosphonofluoridate.

$C_4H_{10}FO_2P$ = 140.1.

CAS — 107-44-8.

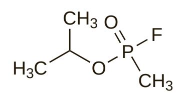

Soman

GD; Somán. Pinacolyl methylphosphonofluoridate.

$C_7H_{16}FO_2P$ = 182.2.

CAS — 96-64-0.

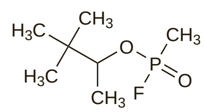

Tabun

GA; Tabún. Ethyl *N*-dimethylphosphoramidocyanidate.

$C_5H_{11}N_2O_2P$ = 162.1.

CAS — 77-81-6.

VX

Methylphosphonothioic acid S-{2-[bis(1-methylethyl)amino]ethyl} *O*-ethyl ester.

$C_{11}H_{26}NO_2PS$ = 267.4.

CAS — 50782-69-9.

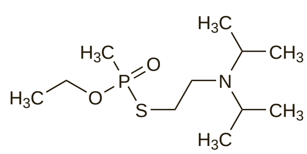

Profile

The nerve agents, sarin, soman, tabun, and VX (also referred to as 'nerve gases') used in chemical warfare are extremely potent inhibitors of cholinesterase. The effects of poisoning due to these agents, and their treatment, are similar to those for organophosphorus insecticides (p.2047) but as the nerve agents have a much greater intrinsic toxicity the symptoms of poisoning are more severe. Pyridostigmine has been given prophylactically to personnel at risk from exposure to nerve agents (see p.634).

◊ References.

1. Ministry of Defence. *Medical manual of defence against chemical agents.* London: HMSO, 1987. (JSP312)
2. World MJ. Toxic gas trauma. *Lancet* 1995; **346:** 260–1.
3. Nozaki H, *et al.* A case of VX poisoning and the difference from sarin. *Lancet* 1995; **346:** 698–9.
4. Okumura T, *et al.* Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996; **28:** 129–35.
5. Suzuki J, *et al.* Eighteen cases exposed to sarin in Matsumoto, Japan. *Intern Med* 1997; **36:** 466–70.
6. Holstege CP, *et al.* Chemical warfare: nerve agent poisoning. *Crit Care Clin* 1997; **13:** 923–42.
7. United States Army. *Medical Management of Chemical Casualties Handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense; 1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/RedHandbook/001TitlePage.htm (accessed 24/07/08)
8. Weinbroum AA, *et al.* Anaesthesia and critical care considerations in nerve agent warfare trauma casualties. *Resuscitation* 2000; **47:** 113–23.
9. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–3.
10. Janowsky DS. Central anticholinergics to treat nerve-agent poisoning. *Lancet* 2002; **359:** 265–6.
11. Anonymous. Nerve agents. *J R Army Med Corps* 2002; **148:** 344–57.
12. Lee EC. Clinical manifestations of sarin nerve gas exposure. *JAMA* 2003; **290:** 659–62.
13. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
14. Newmark J. The birth of nerve agent warfare: lessons from Syed Abbas Foroutan. *Neurology* 2004; **62:** 1590–6.

Neutral Red

CI Basic Red 5; Colour Index No. 50040; Neutral Red Chloride; Nuclear Fast Red; Rojo neutro; Toluylene Red. 3-Amino-7-dimethylamino-2-methylphenazine hydrochloride.

$C_{15}H_{16}N_4,HCl$ = 288.8.

CAS — 553-24-2.

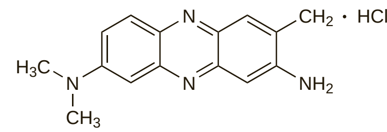

Profile

Neutral red is used as an indicator for alkalinity and for preparing neutral-red paper. It is also used as a stain in microscopy.

It is a photoactive dye that has been tried in photodynamic therapy of recurrent herpes simplex infections, but with limited success.

Niaouli Oil

Essence de Niaouli; Gomenol.

Pharmacopoeias. In *It.*

Profile

Niaouli oil is a volatile oil, obtained by distillation from the fresh leaves of *Melaleuca viridiflora* or *Melaleuca quinquenervia* (Myrtaceae). It contains cineole and has similar actions to eucalyptus oil (p.2301). It is an ingredient of many preparations. Typical indications include respiratory tract congestion. Cajuput oil (p.2271) and melaleuca oil (p.2338) are also prepared from *Melaleuca* spp.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Gomenol; Gomenoleo; Huile Gomenolee.

Multi-ingredient: ***Arg.:*** Aseptobron; Aseptobron Ampicilina†; Di-Neumobron; Medex Rub; No-Tos Adultos; Otorinazol†; Refenax Caramelos Expectorantes; ***Braz.:*** Algice; Baldin-CE†; Canfomenol†; Gripanil†; Griponia†; Gripsay; Killgrip†; Mentalol†; Ozonyl; Ozonyl Aquoso; Ozonyl Expectorante; Tetrapulmo; ***Canad.:*** Balminil Suppositories; ***Fr.:*** Balsolene; Biogaze†; Dinacode†; Hexaquine; Terpone; Vaseline Gomenolee; ***Ger.:*** Palatol†; ***Ital.:*** Paidorinovit; Rinantipiol†; Rinobalsamiche†; Rinofomentil†; Rinopaidolo; Rinovit; ***Pol.:*** Argol Grip; ***Port.:*** Rectopulmo Adultos†; Rectopulmo Infantil†; ***Spain:*** Broncovital†; Brota Rectal Balsamico; Pastillas Pectoral Kely; Rinobanedif; Vapores Pyt; Vitavox Pastillas†; ***Switz.:*** Liberol Bain†; Pulmex; Resorbane; ***Turk.:*** Buguseptil; Rinolar.

Nicaraven *(rINN)*

Nicaravén; Nicaravenum. (±)-*N*,*N*′-Propylenebis[nicotinamide].

Никаравен

$C_{15}H_{16}N_4O_2$ = 284.3.

CAS — 79455-30-4.

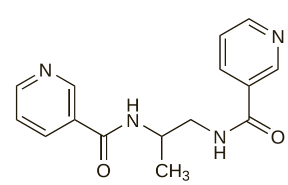

Profile

Nicaraven is under investigation as a cerebral vasodilator.

◊ References.

1. Jain KK. Nicaraven for the treatment of cerebral vasospasm in subarachnoid haemorrhage. *Expert Opin Invest Drugs* 2000; **9:** 859–70.

Nicergoline *(BAN, USAN, rINN)*

FI-6714; Nicergolin; Nicergolina; Nicergolinas; Nicergolinum; Nisergoliini; Nisergolin. 10α-Methoxy-1,6-dimethylergolin-8β-ylmethyl 5-bromonicotinate.

Ницерголин

$C_{24}H_{26}BrN_3O_3$ = 484.4.
CAS — 27848-84-6.
ATC — C04AE02.
ATC Vet — QC04AE02.

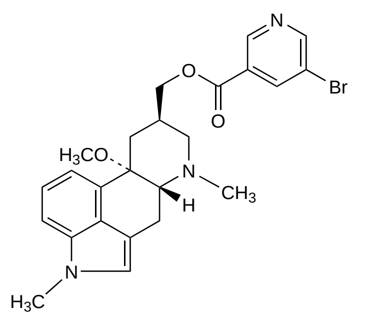

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Nicergoline). A fine to granular white or yellowish powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane.

Adverse Effects and Precautions

Adverse effects that may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral doses, hypotension.

Incidence of adverse effects. Adverse effects occurred in 25 of 359 patients with cerebrovascular insufficiency treated with nicergoline for 1 month;[1] the drug had to be withdrawn in 11. The reactions included 6 cases of hot flushes, 8 of general malaise, 2 of agitation, 3 of hyperacidity, 1 of nausea, 3 of diarrhoea, and 2 of dizziness and somnolence.

1. Dauverchain J. Bedeutung von Nicergolin bei der symptomatischen Behandlung des arteriellen Hochdrucks und der chronischen, zerebro-vaskulären Insuffizienz. *Arzneimittelforschung* 1979; **29:** 1308–10.

Porphyria. Nicergoline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems, although there is conflicting evidence of porphyrinogenicity.

Interactions

For a study indicating that nicergoline enhances the cardiac depressant action of propranolol, see Ergot Derivatives, in Interactions of Beta Blockers, p.1229.

Uses and Administration

Nicergoline is an ergot derivative. It has been used similarly to codergocrine mesilate (p.364) to treat symptoms of mental deterioration associated with cerebrovascular insufficiency (see Dementia, p.362) and has also been used in peripheral vascular disease (p.1178). Nicergoline has been given in doses of up to 60 mg daily by mouth in divided doses, and by intramuscular injection in doses of 2 to 4 mg twice daily; 4 to 8 mg daily has been given by intravenous infusion. Nicergoline tartrate has been used in parenteral dosage forms.

◊ References.

1. Ronchi F, *et al.* Symptomatic treatment of benign prostatic obstruction with nicergoline: a placebo controlled clinical study and urodynamic evaluation. *Urol Res* 1982; **10:** 131–4.
2. Bousquet J, *et al.* Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol* 1989; **83:** 825–8.
3. Saletu B, *et al.* Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)* 1995; **117:** 385–95.
4. Herrmann WM, *et al.* A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. *Dementia Geriatr Cogn Disord* 1997; **8:** 9–17.
5. Fioravanti M, Flicker L. Nicergoline for dementia and other age associated forms of cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/04/05).
6. Felisati G, *et al.* Nicergoline in the treatment of dizziness in elderly patients: a review. *Arch Gerontol Geriatr Suppl* 2004; 163–70.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cergodun; Nicergolent†; Sermion; ***Austria:*** Ergotop; Nicergin; Sermion; ***Braz.:*** Sermion; ***Chile:*** Sermion; ***Cz.:*** Ergotop; Nilogrin†; Sermion; ***Fr.:*** Sermion; ***Ger.:*** Circo-Maren†; Ergobel; Nicergobeta; Nicerium; Sermion†; ***Gr.:*** Albotyl†; Sermion; ***Hong Kong:*** Cergodun; Qualigoline; Sermion; ***Hung.:*** Ergotop; Sermion; ***Indon.:*** Serolin; ***Ital.:*** Cebran; Nicer†; Sermion; ***Jpn:*** Sermion; ***Mex.:*** Sermion; ***Philipp.:*** Sermion; ***Pol.:*** Adavin; Circulat; Nicerin; Nilogrin; Sermion; ***Port.:*** Erg XXI†; Sermion; ***Rus.:*** Nilogrin (Нилогрин); Sermion (Сермион); ***Spain:*** Fisifax†; Sermion; Varson; ***Switz.:*** Sermion; ***Thai.:*** Sermion; ***Turk.:*** Sermion; ***Venez.:*** Sermion.

Multi-ingredient: ***Arg.:*** Angiolit†; Sibelium Plus.

Nicotine

Nicotina; Nicotinum; Nikotiini; Nikotin; Nikotinas. (*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine.

$C_{10}H_{14}N_2$ = 162.2.
CAS — 54-11-5.
ATC — N07BA01.
ATC Vet — QN07BA01; QP53AX13.

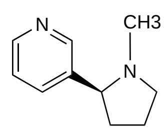

Description. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Nicotine). A colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water; miscible with dehydrated alcohol. Store under nitrogen in airtight containers. Protect from light.

USP 31 (Nicotine). It should be stored under nitrogen at a temperature below 25°. Protect from light and moisture.

Nicotine Polacrilex *(USAN)*

CAS — 96055-45-7.
ATC — N07BA01.
ATC Vet — QN07BA01.

Pharmacopoeias. In *US.*

USP 31 (Nicotine Polacrilex). A weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. Store in airtight containers.

Nicotine Resinate

Nicotine, résinate de; Nicotini resinas; Nicotinresinat; Nikotiiniresinaatti; Nikotino rezinatas; Nikotin-resinát; Nikotin-rezinát.

ATC — N07BA01.
ATC Vet — QN07BA01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nicotine Resinate). A complex of nicotine with a weak cationic exchange resin. It may contain glycerol. A white or slightly yellowish powder. Practically insoluble in water. Store in airtight containers. Protect from light.

Nicotine Tartrate

Nicotine Bitartrate *(USAN).*

$C_{10}H_{14}N_2,2C_4H_6O_6,2H_2O$ = 498.4.
CAS — 65-31-6 (anhydrous nicotine tartrate).
ATC — N07BA01.
ATC Vet — QN07BA01.

Dependence and Withdrawal

Nicotine dependence is most commonly associated with cigarette smoking. It is characterised by a strong desire to continue taking the agent, a physical and psychological need for it, and a characteristic abstinence syndrome on withdrawal. Common symptoms seen on nicotine withdrawal include irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain, and insomnia. The management of smoking cessation is discussed under Uses and Administration, below.

Mild withdrawal symptoms have been reported from nicotine replacement preparations used to aid smoking cessation.

◊ References.

1. Hatsukami D, *et al.* Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993; **111:** 449–56.
2. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med* 1994; **331:** 123–5.
3. Keenan RM, *et al.* Pharmacodynamic effects of cotinine in abstinent cigarette smokers. *Clin Pharmacol Ther* 1994; **55:** 581–90.
4. Slade J, *et al.* Nicotine and addiction: the Brown and Williamson documents. *JAMA* 1995; **274:** 225–33.
5. Kessler DA. Nicotine addiction in young people. *N Engl J Med* 1995; **333:** 186–9.
6. Doll R, Crofton J, eds. Tobacco and health. *Br Med Bull* 1996; **52:** 1–223.
7. Benowitz NL. Nicotine addiction. *Prim Care* 1999; **26:** 611–31.
8. Colby SM, *et al.* Are adolescent smokers dependent on nicotine? A review of the evidence. *Drug Alcohol Depend* 2000; **59** (suppl 1): S83–S95.
9. Royal College of Physicians. *Nicotine addiction in Britain: a report of the Tobacco Advisory Group of the Royal College of Physicians.* London: Royal College of Physicians, 2000. Also available at: http://www.rcplondon.ac.uk/pubs/books/nicotine/index.htm (accessed 30/07/08)
10. West R, *et al.* A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)* 2000; **149:** 198–202.

Adverse Effects and Treatment

Nicotine is a highly toxic substance and in acute poisoning death may occur within 1 hour due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Typical symptoms include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

Nicotine is rapidly absorbed through the skin or by inhalation as well as by ingestion, and nicotine poisoning may occur due to careless handling when it is used as a horticultural insecticide.

Prompt treatment of nicotine poisoning is essential. If contact was with the skin, contaminated clothing should be removed and the skin washed thoroughly with cold water without rubbing. If the patient has swallowed nicotine, gastric lavage and activated charcoal may be beneficial. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Apart from effects such as dizziness, headache, and gastrointestinal disturbances mentioned above, adverse effects associated with *nicotine replacement preparations* have also included cold and flu-like symptoms, palpitations, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety, irritability, somnolence, and dysmenorrhoea. Allergic reactions have been reported. Adverse effects associated with specific preparations include skin reactions with transdermal patches; nasal irritation, epistaxis, lachrymation, and sensations in the ear with the nasal spray; throat irritation with the spray, inhalator, sublingual tablets, lozenges, or chewing gum; aphthous ulceration with the inhalator, sublingual tablets, lozenges, or chewing gum; increased salivation and sometimes swelling of the tongue with chewing gum; cough, rhinitis, stomatitis, sinusitis, and dry mouth with the inhalator; and unpleasant taste with the sublingual tablets or lozenges. Excessive swallowing of nicotine released from oral replacement preparations may cause hiccups in the first few days of treatment.

◊ References.

1. Greenland S, *et al.* A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998; **18:** 297–308.
2. Gourlay SG, *et al.* Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Safety* 1999; **20:** 545–55.

Adverse effects of tobacco products. Chronic use of tobacco is linked to a variety of diseases. By the mid-1960s, epidemiological data established tobacco smoking as a cause of lung cancer (p.668). Smoking is also associated with cancers of the larynx, mouth, cervix, bladder, pancreas, oesophagus, stomach, and kidneys, and with leukaemia.[1] Smoking is a risk factor in cardiovascular, respiratory, and peripheral and cerebral vascular diseases.[1-3] Smoking also increases the risk of developing peptic ulcer disease and may affect other gastrointestinal disorders.[2] There is also evidence that smoking tobacco products increases the risk of developing age-related macular degeneration,[4] type 2 diabetes mellitus,[5] and adenomatous polyps.[6]

Maternal smoking in pregnancy is associated with low birth-weight infants and increased risk of abortion, still-birth, and neonatal death (see also Pregnancy under Precautions, below).

Passive smoking refers to inhalation of secondhand tobacco smoke or environmental tobacco smoke. Risks to health from passive exposure are lower than those from active smoking. However, studies have established passive smoking as a cause of lung cancer;[7] passive smoking is also associated with increased risk of heart disease[8] and chronic respiratory disease.[9,10] Smokeless tobacco products also carry risks to health, for example the association of cancers of the head and neck (see p.666) with the use of mixtures of tobacco and areca (p.2259) and probably snuff or chewing tobacco.[11,12]

1. Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
2. Ashton H. Adverse effects of nicotine. *Adverse Drug React Bull* 1991; **149**: 560–3.
3. Teo KK, *et al.* INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368:** 647–58.
4. Tan JSL, *et al.* Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol* 2007; **125:** 1089–95.
5. Willi C, *et al.* Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007; **298:** 2654–64.
6. Botteri E, *et al.* Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008; **134:** 388–95.
7. Lam TH. Passive smoking in perspective. *Med Toxicol Adverse Drug Exp* 1989; **4:** 153–62.

8. Steenland K. Passive smoking and the risk of heart disease. *JAMA* 1992; **267**: 94–9.
9. Law MR, Hackshaw AK. Environmental tobacco smoke. *Br Med Bull* 1996; **52:** 22–34.
10. DiFranza JR, Lew RA. Mortality and morbidity in children associated with the use of tobacco products by other people. *Pediatrics* 1996; **97:** 560–8.
11. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93:** 511–15.
12. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003; **58:** 435–43.

Effects on carbohydrate metabolism. Hyperinsulinaemia and insulin resistance have been associated with long-term use of nicotine gum.[1] Smoking tobacco products may increase the risk of developing type 2 diabetes mellitus (see above).

1. Eliasson B, *et al.* Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation* 1996; **94:** 878–81.

Effects on the cardiovascular system. As mentioned above, nicotine from tobacco products is associated with increased risk of cardiovascular disease. It would not be surprising, therefore, if nicotine replacement preparations were also associated with cardiovascular adverse effects, and there are anecdotal reports of cardiovascular events, including myocardial infarction,[1,2] stroke,[3,4] and cerebral haematoma,[5] associated with use of such products. However, a case-control study in the general population,[6] and both cohort studies[7] and short-term placebo-controlled trials[8,9] in patients with cardiovascular disease have failed to show any increased cardiovascular risk associated with transdermal nicotine.

1. Warner JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994; **120:** 695.
2. Arnaot MR. Nicotine patches may not be safe. *BMJ* 1995; **310:** 663–4.
3. Pierce JR. Stroke following application of a nicotine patch. *Ann Pharmacother* 1994; **28:** 402.
4. Ang R, *et al.* Nicotine replacement therapy and ischaemic stroke. *Hosp Med* 2005; **66:** 366–7.
5. Riche G, *et al.* Intracerebral haematoma after application of nicotine patch. *Lancet* 1995; **346:** 777–8.
6. Kimmel SE, *et al.* Risk of acute first myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol* 2001; **37:** 1297–1302.
7. Meine TJ, *et al.* Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol* 2005; **95:** 976–8.
8. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994; **154:** 989–95.
9. Joseph AM, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; **335:** 1792–8.

Vasculitis. Vasculitis occurring in 2 patients was associated with transdermal nicotine patches.[1]

1. van der Klauw MM, *et al.* Vasculitis attributed to the nicotine patch (Nicotinell). *Br J Dermatol* 1996; **134:** 361–4.

Precautions

Nicotine preparations should not be used in patients who have experienced recent cerebrovascular accident. They should be used with caution in patients with cardiovascular disease. Use should preferably be avoided completely in severe cardiovascular disease, including during the immediate postmyocardial infarction period, and in patients with severe arrhythmias or unstable angina pectoris, although use under medical supervision may be considered if the patient is otherwise unable to stop smoking. They should be used with caution in those with peripheral vascular disease, in endocrine disorders including phaeochromocytoma, hyperthyroidism, and diabetes mellitus, in peptic ulcer disease, or renal or hepatic impairment. They should also be used with caution, and avoided if possible, during pregnancy or breast feeding (see below).

Skin patches should not be used on broken skin.

Breast feeding. The American Academy of Pediatrics[1] notes that there have been reports of decreased milk production in breast-feeding mothers who smoke, and of decreased weight gain in the infant. There is, however, controversy regarding the effects of nicotine on infant size at 1 year of age. Although nicotine and its metabolite cotinine have been shown to be distributed into breast milk there are hundreds of compounds in tobacco smoke; nicotine is not necessarily the only component that might be detrimental to the breast-fed infant. Nicotine is present in breast milk in concentrations between 1.5 to 3 times the maternal plasma concentration, but there is no evidence documenting whether this amount of nicotine presents a health risk to the infant. Indeed, one study reported that the incidence of acute respiratory illness in infants whose mothers smoked was decreased in those who were breast fed when compared with those infants who were bottle fed.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/07/04)

Exercise. Physical exercise increased mean peak plasma concentrations of nicotine in 8 healthy subjects treated with a transdermal nicotine patch.[1] The effect was thought to be most likely due to increased skin perfusion resulting in increased uptake.

1. Klemsdal TO, *et al.* Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. *Br J Clin Pharmacol* 1995; **39:** 677–9.

Myasthenia gravis. A patient with myasthenia gravis noted worsening of his symptoms after application of transdermal nicotine patches, the effects being most severe about 1 hour after application, and resolving within 3 hours once the patch was removed.[1] Previous heavy smoking had not produced similar adverse effects, despite the fact that blood-nicotine concentrations are typically higher just after finishing a cigarette than when using the patch.[2]

1. Moreau T, *et al.* Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 548–9.
2. Pethica D. Nicotine-sensitive myasthenia gravis. *Lancet* 1994; **344:** 961.

Pregnancy. Cigarette smoking during pregnancy is associated with an increased risk of low birth-weight, spontaneous abortion, and perinatal mortality.[1] There is also some evidence of a possible association between smoking during pregnancy and the sudden infant death syndrome (SIDS).[2] In addition to nicotine, cigarette smoke contains many other chemicals, which are also fetal toxins, including carbon monoxide and lead.[3] Although smoking poses a far greater risk than pure nicotine, nicotine replacement therapy (NRT) is not without potential risks and should be reserved for mothers unable to quit with behavioural therapy alone.[3] It has been suggested that where NRT is required, the intermittent delivery formulations such as nicotine gum or inhalator, which expose the fetus to a lower total dose of nicotine, are preferable to continuous use formulations such as patches.[3]

1. British Medical Association. *Smoking and reproductive life: the impact of smoking on sexual, reproductive and child health.* London: British Medical Association, 2004. Available at: http://www.bma.org.uk/ap.nsf/AttachmentsByTitle/PDFsmokingreproductivelife/06.00file/Smoking.pdf (accessed 06/08/08)
2. Wisborg K, *et al.* A prospective study of smoking during pregnancy and SIDS. *Arch Dis Child* 2000; **83:** 203–6. Corrections. *ibid.* 2001; **84:** 93 and 187.
3. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; **24:** 277–322.

Interactions

Tobacco smoking induces hepatic metabolic enzymes and the pharmacokinetics of many drugs are altered. Drugs such as methoxsalen which inhibit the cytochrome P450 isoenzyme CYP2A6 may decrease the metabolism of nicotine, resulting in increased plasma concentrations.

◊ References.

1. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.
2. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.
3. Sellers EM, *et al.* Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clin Pharmacol Ther* 2000; **68:** 35–43.

Nicotinic acid. As described on p.1958, a possible interaction between nicotinic acid and nicotine from a transdermal patch has been reported.

Pharmacokinetics

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first-pass metabolism. Nicotine is widely distributed; it crosses the blood-brain barrier and the placenta and is found in breast milk. The elimination half-life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotinine and nicotine-*N*-oxide. Nicotine and its metabolites are excreted in the urine.

◊ References.

1. Gorsline J, *et al.* Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm (nicotine transdermal system). *J Clin Pharmacol* 1993; **33:** 161–8.
2. Gupta SK, *et al.* Bioavailability and absorption kinetics of nicotine following application of a transdermal system. *Br J Clin Pharmacol* 1993; **36:** 221–7.
3. Schneider NG, *et al.* Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 1996; **31:** 65–80.
4. Benowitz NL, *et al.* Sources of variability in nicotine and cotinine levels with the use of nicotine nasal spray, transdermal nicotine and cigarette smoking. *Br J Clin Pharmacol* 1997; **43:** 259–67.
5. Zins BJ, *et al.* Pharmacokinetics of nicotine tartrate after single-dose liquid enema, oral, and intravenous administration. *J Clin Pharmacol* 1997; **37:** 426–36.
6. Schneider NG, *et al.* The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001; **40:** 661–84.

Uses and Administration

The main physiological action of nicotine is paralysis of all autonomic ganglia, preceded by stimulation. Centrally, small doses cause respiratory stimulation, while larger doses produce convulsions and arrest of respiration. The effects on skeletal muscle are similar to those on ganglia.

Nicotine chewing gum, transdermal patches, lozenges, sublingual tablets, nasal spray, or inhalator are used as aids for smoking cessation (below) and many such products are also used to reduce the amount smoked. For smoking *cessation*, treatment is usually continued for up to 3 months, then gradually withdrawn. For smoking *reduction*, it may be continued for up to 6 months, and an attempt to quit then made. If use is to be continued beyond 9 months, additional advice from a healthcare professional should be sought.

- *Chewing gum* is available in strengths of 2 mg and 4 mg; the nicotine may be present in the gum in the form of a complex with methacrylic acid polymer (nicotine polacrilex). Individuals who smoke 20 cigarettes or less per day should start with the 2-mg strength gum chewed slowly over about 30 minutes when the urge to smoke occurs. Those who smoke over 20 cigarettes a day or require more than 15 pieces daily of the 2-mg gum should receive the 4-mg strength. Not more than 15 pieces should be used per day.
- *Sublingual tablets* containing the equivalent of 2 mg of nicotine as a β-cyclodextrin complex may be used: the recommended dose is 1 or 2 tablets sublingually every hour, increased to a maximum of 40 tablets daily if necessary.
- *Lozenges* containing 1 or 2 mg of nicotine (as the polacrilex or as the tartrate) are available. The initial dose is 1 lozenge every 1 to 2 hours increased to a maximum daily dose of 30 of the 1-mg lozenges or 15 of the 2-mg lozenges.
- Adhesive *transdermal patches* are designed to be worn for 16 or 24 hours and are available in different strengths that deliver from 5 to 21 mg during the recommended wearing time. One patch should be applied daily, on waking, to a dry, non-hairy area of skin on the hip, trunk, or upper arm, usually beginning with the highest strength or with a dose determined by the previous daily consumption of cigarettes. A different site of application should be used each day with several days elapsing before the patch is applied to the same area of skin.
- A suggested initial dosage for a *nasal spray* containing 500 micrograms per spray is one spray administered into each nostril up to twice hourly as required up to a maximum of 80 sprays daily for the first 8 weeks and reduced gradually thereafter. Treatment for more than 3 months is not recommended.
- Nicotine *inhalator cartridges* contain nicotine 10 mg for use in an appropriate inhaler mouthpiece. The initial dose is 6 to 16 cartridges daily for up to 12 weeks and is reduced gradually over a further 4 to 12 weeks.

Nicotine has been used as a horticultural insecticide.

Alzheimer's disease. The use of nicotine as a cholinergic agonist is one of a number of methods being studied[1] to overcome brain cholinergic deficits in patients with Alzheimer's disease (see Dementia, p.362). Preliminary studies[2,3] using nicotine patches have been of limited duration and were inconclusive. Transdermal nicotine has been used for the control of behavioural symptoms such as agitation in a small number of patients with Alzheimer's disease.[4] A systematic review[5] was unable to present any conclusions on the efficacy and safety of nicotine in Alzheimer's disease because of a lack of adequate randomised controlled studies.

1. Baldinger SL, Schroeder DJ. Nicotine therapy in patients with Alzheimer's disease. *Ann Pharmacother* 1995; **29:** 314–15.
2. Wilson AL, *et al.* Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 1995; **51:** 509–14.
3. Snaedal J, *et al.* The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. *Dementia* 1996; **7:** 47–52.
4. Rosin RA, *et al.* Transdermal nicotine for agitation in dementia. *Am J Geriatr Psychiatry* 2001; **9:** 443–4.
5. López-Arrieta JLA, Sanz FJ. Nicotine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 28/04/05).

Blepharospasm. Nicotine nasal spray was reported to be of benefit in a patient with blepharospasm (p.1891) refractory to botulinum A toxin.[1] However, a subsequent study in 4 patients with blepharospasm reported no improvement with the use of nicotine nasal spray.[2]

1. Dursun SM, *et al.* Treatment of blepharospasm with nicotine nasal spray. *Lancet* 1996; **348:** 60.
2. Dressler D, *et al.* Nicotine nasal spray is not reliable treatment for blepharospasm: results of a pilot study. *Mov Disord* 1998; **13:** 190.

Extrapyramidal disorders. Nicotine transdermal patches have been reported to produce beneficial effects[1] in schizophrenic patients with antipsychotic-induced akathisia (p.971). Because of an apparent inverse association between smoking and Parkinson's disease (p.791), transdermal nicotine patches have been investigated in the treatment of parkinsonian symptoms, but with little evidence of overall benefit.[2,3]

1. Anfang MK, Pope HG. Treatment of neuroleptic-induced akathisia with nicotine patches. *Psychopharmacology (Berl)* 1997; **134:** 153–6.
2. Vieregge A, *et al.* Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* 2001; **57:** 1032–5.
3. Lemay S, *et al.* Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 31–9.

Skin disorders. There have been anecdotal reports of nicotine producing beneficial effects in various skin disorders, including pyoderma gangrenosum,[1] and dermatitis due to fluorouracil therapy.[2]

1. Kanekura T, *et al.* Nicotine for pyoderma gangrenosum. *Lancet* 1995; **345:** 1058.
2. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; **120:** 813.

Smoking cessation. Smoking is the single most important cause of preventable illness and premature death in the UK and USA; it is estimated that around 1 in 5 deaths are due to smoking-related illnesses. The financial burden of smoking-related diseases on healthcare providers is also substantial. Many governments have undertaken initiatives to promote smoking cessation for which there is substantial evidence of a decline in the risk of disease[1] and death.[2] As the abstinence period increases, the reduced risk of disease in former smokers may even approach, although rarely does it ever equal, that of people who have never smoked.[1].

Nicotine dependence and the development of a characteristic withdrawal syndrome (see Dependence and Withdrawal, above) make stopping smoking very difficult. Many individuals relapse when trying to give up or need several attempts before successfully stopping. Both nonpharmacological and pharmacological treatments can improve the abstinence rate and are most effective when the two approaches are combined.[3-12]

Nonpharmacological methods include counselling, training in coping skills, and support groups; although the abstinence rate increases with the intensity of the support, even brief advice is effective in encouraging cessation.

The first-line pharmacological intervention is *nicotine replacement therapy* (NRT) which is an effective treatment for reducing the cravings associated with stopping smoking. NRT is available in numerous formulations: chewing gum, transdermal patches, inhalators, nasal sprays, sublingual tablets, and lozenges. A systematic review[10] of NRT found abstinence was more than doubled when compared with controls, regardless of the intensity of any additional nonpharmacological support.

Choice of formulation is based on patient preference, tolerance, and previous treatments, if any. The transdermal patch is easiest to use and compliance is greatest with this route but local effects may be troublesome. The gum has an unpleasant taste initially and some find the chewing action difficult. The sublingual tablet may be useful for those who have difficulty chewing the gum. The nasal spray has a fast onset of action but may cause local irritation. The inhalator has the advantage of simulating cigarette smoking but may cause local irritation of the mouth and throat. The lozenge has the advantage that it can be sucked discreetly. Patients who are unable to tolerate one type of NRT may benefit from a course of an alternative NRT preparation.

Combination therapy with different types of NRT (patches with either the nasal spray, inhalator, or chewing gum) has also been tried as a means of increasing efficacy.

NRT for smoking cessation is usually continued for about 3 months before being withdrawn. Although the manufacturers advise gradual withdrawal, others[6,8] have found that this offers no advantage and recommend abrupt withdrawal. NRT for smoking reduction is typically continued for longer periods. NRT has also been used long-term and may be of particular benefit in those patients who feel they would relapse if NRT was stopped or in those who have persistent withdrawal symptoms.

There has been concern over the use of NRT in patients with cardiovascular disease (see Effects on the Cardiovascular System, above) but clinical experience and studies have shown that NRT can be used with caution in these patients. The use of NRT in those who have suffered a recent myocardial infarction or those with severe arrhythmias or unstable angina is, however, contra-indicated as such patients have not been adequately studied.

A number of other drugs have also been used to achieve abstinence from smoking.[13-15] *Bupropion* is effective and recommended by some as a first-line alternative to NRT; its action is said to be independent of its antidepressant activity. Bupropion in combination with NRT has been used successfully. Evidence to support the use of most other antidepressants is lacking,[16] but *nortriptyline* appears to be effective and is used as a second-line drug. A study[17] found, however, that there was no advantage in combining nortriptyline with NRT. *Clonidine* is also effective but adverse effects limit its usefulness.[15] Preliminary investigations suggest that *selegiline* and *mecamylamine* may be effective.[13,15] The cannabinoid-1 receptor antagonist *rimonabant* has produced promising results in early studies,[13,14] although a systematic review[18] of 3 randomised controlled studies found the evidence to be inconclusive. A systematic review[19] of studies on the use of the oral nicotine receptor partial agonists *varenicline* and *cytisine* concluded that both drugs have a potential place in smoking cessation. Varenicline compared favourably with placebo and bupropion in helping smokers to quit, but its efficacy in preventing relapse still remains to be fully established. Like bupropion, varenicline is recommended by some as a first-line alternative to NRT. Cytisine is widely used in central and eastern Europe but the current evidence for efficacy is limited and better designed studies are required to test earlier findings. There is little or no evidence to support the efficacy of other treatments such as *silver acetate*, *lobeline*, or *anxiolytics* such as *buspirone*, and their use is not recommended. A *vaccine* for the prevention of smoking relapse is under investigation.[13,14]

1. Dresler CM, *et al.* Reversal of risk upon quitting smoking. *Lancet* 2006; **368:** 348–9.
2. Vollset SE, *et al.* Smoking and deaths between 40 and 70 years of age in women and men. *Ann Intern Med* 2006; **144:** 381–9.
3. American Society of Health-System Pharmacists. ASHP therapeutic position statement on smoking cessation. *Am J Health-Syst Pharm* 1999; **56:** 460–4.
4. Anonymous. Nicotine replacement to aid smoking cessation. *Drug Ther Bull* 1999; **37:** 52–4.
5. West R, *et al.* Smoking cessation guidelines for health professionals: an update. *Thorax* 2000; **55:** 987–99.
6. Royal College of Physicians. *Nicotine addiction in Britain: a report of the Tobacco Advisory Group of the Royal College of Physicians.* London: Royal College of Physicians, 2000. Also available at: http://www.rcplondon.ac.uk/pubs/books/nicotine/index.htm (accessed 02/07/04)
7. Fiore MC, *et al.* A clinical practice guideline for treating tobacco use and dependence: a US public health service report. *JAMA* 2000; **283:** 3244–54.
8. Simpson D. Smoking cessation. In: *Doctors and tobacco: medicine's big challenge.* London: Tobacco Control Resource Centre, British Medical Association, 2000. Also available at: http://www.bma.org.uk/tcrc.nsf/4723e4b3bbc9362e802566e300360f8e/d51b23fb23791f22802568ab00668cf1/06.00FILE/D&T_EN.pdf (accessed 14/07/06)
9. Covey LS, *et al.* Advances in non-nicotine pharmacotherapy for smoking cessation. *Drugs* 2000; **59:** 17–31.
10. Stead LF, *et al.* Nicotine replacement therapy for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/07/08).
11. Nides M. Update on pharmacologic options for smoking cessation treatment. *Am J Med* 2008; **121** (suppl 1): S20–S31.
12. Ranney L, *et al.* Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med* 2006; **145:** 845–56.
13. Foulds J, *et al.* Developments in pharmacotherapy for tobacco dependence: past, present and future. *Drug Alcohol Rev* 2006; **25:** 59–71.
14. Garwood CL, Potts LA. Emerging pharmacotherapies for smoking cessation. *Am J Health-Syst Pharm* 2007; **64:** 1693–8. Correction. *ibid.*; 1995.
15. Buchhalter AR, *et al.* Novel pharmacological approaches for treating tobacco dependence and withdrawal: current status. *Drugs* 2008; **68:** 1067–88.
16. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 09/07/08).
17. Aveyard P, *et al.* Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial. *BMJ* 2008; **336:** 1223–7.
18. Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/07/08).
19. Cahill K, *et al.* Nicotine receptor partial agonists for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 28/06/07).

Spasticity. There have been anecdotal reports[1] of beneficial responses to nicotine in spastic dystonia.

1. Vaughan CJ, *et al.* Treatment of spastic dystonia with transdermal nicotine. *Lancet* 1997; **350:** 565.

Tics. Tourette's syndrome (see Tics, p.954) is characterised by motor and vocal tics and behavioural disturbances. Nicotine[1-5] has been reported to be of benefit when used alone or with the more usual treatment of haloperidol in patients with Tourette's syndrome whose symptoms were not satisfactorily controlled with haloperidol alone. It is hoped that the use of transdermal nicotine patches will avoid the reported problems of compliance associated with the taste and gastrointestinal effects of nicotine gum.

1. McConville BJ, *et al.* The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency to Tourette's disorder. *Biol Psychiatry* 1992; **31:** 832–40.
2. Silver AA, Sanberg PR. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet* 1993; **342:** 182.
3. Dursun SM, *et al.* Longlasting improvement of Tourette's syndrome with transdermal nicotine. *Lancet* 1994; **344:** 1577.
4. Sanberg PR, *et al.* Nicotine for the treatment of Tourette's syndrome. *Pharmacol Ther* 1997; **74:** 21–5.
5. Silver AA, *et al.* Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. *J Clin Psychiatry* 2001; **62:** 707–14.

Ulcerative colitis. Investigation of the use of nicotine in ulcerative colitis (see Inflammatory Bowel Disease, p.1697) has been prompted by the observation that this condition is rare in smokers.[1] A systematic review[2] found that transdermal nicotine was more effective than placebo in producing remission in patients with active ulcerative colitis, but appeared to be no more effective than standard therapy with a corticosteroid or aminosalicylate, and was associated with more adverse effects. It appears to be ineffective in maintaining disease remission.[3] Any role is likely to be limited to patients who do not respond to standard therapy and who can tolerate the adverse effects.[2] Local delivery to the colon, in the form of enemas[4-6] and oral modified-release capsules,[7] is under investigation as a means of reducing the adverse effects of nicotine.

1. Guslandi M. Nicotine treatment for ulcerative colitis. *Br J Clin Pharmacol* 1999; **48:** 481–4.
2. McGrath J, *et al.* Transdermal nicotine for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/03/06).
3. Thomas GAO, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995; **332:** 988–92.
4. Sandborn WJ, *et al.* Nicotine tartrate liquid enemas for mildly to moderately active left-sided ulcerative colitis unresponsive to first-line therapy: a pilot study. *Aliment Pharmacol Ther* 1997; **11:** 663–71.
5. Ingram JR, *et al.* Nicotine enemas for treatment of ulcerative colitis: a study of the pharmacokinetics and adverse events associated with three doses of nicotine. *Aliment Pharmacol Ther* 2004; **20:** 859–65.
6. Ingram JR, *et al.* A randomized trial of nicotine enemas for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2005; **3:** 1107–14.
7. Green JT, *et al.* An oral formulation of nicotine for release and absorption in the colon: its development and pharmacokinetics. *Br J Clin Pharmacol* 1999; **48:** 485–93.

Preparations

USP 31: Nicotine Polacrilex Gum; Nicotine Transdermal System.

Proprietary Preparations (details are given in Part 3)

Arg.: Nicorette; Nicotinell TTS; ***Austral.:*** Nicabate; Nicorette; Nicotinell; QuitX; ***Austria:*** Nicorette; Nicotinell; Nicotrol; ***Belg.:*** Nicorette; Nicotinell; NiQuitin; ***Braz.:*** Nicorette; Nicotinell TTS; NiQuitin; ***Canad.:*** Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep; ***Chile:*** Nicorette; Nicotinell; ***Cz.:*** Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Denm.:*** Nicorette; Nicotinell; NiQuitin†; ***Fin.:*** Nicorette; Nicotinell; ***Fr.:*** Nicogum; Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***Ger.:*** Nicorette; Nicotinell; nikofrenon; NiQuitin; ***Gr.:*** Nicopass; Nicorette; Nicotinell; ***Hong Kong:*** Nicorette; Nicotinell; ***Hung.:*** Nicopass; Nicorette; Nicotinell; NiQuitin; ***India:*** Nicotinell TTS†; ***Irl.:*** Nicorette; Nicotinell; NiQuitin; ***Israel:*** Nicorette; Nicotinell; NiQuitin; ***Ital.:*** Nicorette; Nicotinell; NiQuitin; ***Malaysia:*** Nicorette; Nicotinell; ***Mex.:*** Nicorette; Nicotinell TTS†; NiQuitin; ***Neth.:*** Nicorette; Nicotinell; NiQuitin; ***Norw.:*** Nicorette; Nicotinell; ***NZ:*** Habitrol; Nicabate; Nicorette; Nicotinell; Nicotrol; ***Pol.:*** Nicorette; Nicotinell; NiQuitin; ***Port.:*** Nicopass; Nicopatch; Nicorette; Nicotinell TTS; NiQuitin; ***Rus.:*** Nicorette (Никоретте); ***S.Afr.:*** Nicorette; Quit; ***Singapore:*** Nicorette; Nicotinell; ***Spain:*** Nicomax; Nicorette; Nicotinell; Nicotrol†; NiQuitin; ***Swed.:*** Nicorette; Nicotinell; Nikotugg; NiQuitin; ***Switz.:*** Nicorette; Nicotinell; ***Thai.:*** Nicorette; Nicotinell; ***Turk.:*** Nicotinell; ***UK:*** Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; ***USA:*** Commit; Habitrol; Nicoderm; Nicorette; Nicotrol; Prostep; ***Venez.:*** Nicorette†.

Nitisinone *(USAN, rINN)*

Nitisinonum; NTBC; SC-0735. 2-(α,α,α-Trifluoro-2-nitro-*p*-toluoyl)-1,3-cyclohexanedione.

Нитизинон

$C_{14}H_{10}F_3NO_5$ = 329.2.
CAS — 104206-65-7.
ATC — A16AX04.
ATC Vet — QA16AX04.

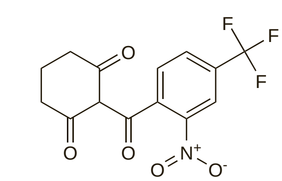

Profile

Nitisinone is a 4-hydroxyphenylpyruvate dioxygenase inhibitor used in the management of hereditary tyrosinaemia type 1; dietary restriction of tyrosine and phenylalanine is also necessary. An initial daily dose of 1 mg/kg given orally is recommended; daily dosage should be given in 2 divided doses, which may be unequally split. Monitoring of urine succinylacetone and plasma alpha-fetoprotein, as well as liver function tests, must be carried out. If necessary, the daily dose may be increased to 1.5 mg/kg after one month; the maximum daily dose is 2 mg/kg. If satisfactory results are obtained from biochemical testing, doses should only be increased in line with body-weight gain.

Adverse effects have included granulocytopenia, leucopenia, and thrombocytopenia; regular monitoring of platelet and white cell counts is recommended. Eye disorders may occur due to increases in plasma tyrosine; they include conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain. Slit-lamp examination of the eyes is recommended before starting treatment; patients developing visual disturbances during treatment should be referred to an ophthalmologist immediately, and further dietary restrictions implemented if plasma tyrosine is too high. Although it is not known if nitisinone is excreted into human milk, breast feeding is contra-indicated because of the potential effects on a suckling child.

Nitisinone is under investigation for the treatment of alkaptonuria, another hereditary metabolic disorder.

◊ References.

1. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inherit Metab Dis* 1998; **21:** 507–17.
2. Phornphutkul C, *et al.* Natural history of alkaptonuria. *N Engl J Med* 2002; **347:** 2111–21.

3. Gissen P, *et al.* Ophthalmic follow-up of patients with tyrosinaemia type I on NTBC. *J Inherit Metab Dis* 2003; **26:** 13–16.
4. Joshi SN, Venugopalan P. Experience with NTBC therapy in hereditary tyrosinaemia type I: an alternative to liver transplantation. *Ann Trop Paediatr* 2004; **24:** 259–65.
5. Suwannarat P, *et al.* Use of nitisinone in patients with alkaptonuria. *Metabolism* 2005; **54:** 719–28.
6. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* 2006; **66:** 743–50.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Orfadin; ***Cz.:*** Orfadin; ***Denm.:*** Orfadin; ***Fin.:*** Orfadin; ***Fr.:*** Orfadin; ***Ger.:*** Orfadin; ***Neth.:*** Orfadin; ***Port.:*** Orfadin; ***Spain:*** Orfadin; ***Swed.:*** Orfadin; ***USA:*** Orfadin.

Nitric Acid

Acide nitrique; Acidum nitricum; Acidum Nitricum 70%; Aqua Fortis; Azotic Acid; Kwas azotowy; Kyselina dusičná 70%; Nit. Acid; Nitrato rūgštis; Nítrico, ácido; Salétromsav; Salpetersäure; Salpetersyra; Typpihappo.

HNO_3 = 63.01.

CAS — 7697-37-2.

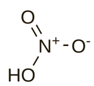

Pharmacopoeias. In *Eur.* (see p.vii) (68 to 70%). Also in *USNF* (69 to 71%).

Ph. Eur. 6.2 (Nitric Acid). A clear, colourless to almost colourless liquid. Miscible with water. It contains 68.0 to 70.0% w/w of HNO_3. Protect from light.

USNF 26 (Nitric Acid). A highly corrosive fuming liquid, having a characteristic, highly irritating odour. It contains 69.0 to 71.0% w/w of HNO_3. Store in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322.

There may be methaemoglobinaemia. Nitric acid stains the skin yellow.

Effects on the respiratory system. Respiratory failure due to pulmonary oedema occurred in a 56-year-old man after inhaling nitric acid which he had used as a metal cleaner.[1] The man died despite extensive ventilatory support.

1. Bur A, *et al.* Fatal pulmonary edema after nitric acid inhalation. *Resuscitation* 1997; **35:** 33–6.

Uses and Administration

Nitric acid has a powerful corrosive action and has been used to remove warts (p.1584), but it should be applied with caution, and less corrosive substances are available. It has also been used for the removal of tattoos.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Solcogyn†; ***Ger.:*** Solco-Derman; ***Hong Kong:*** Solcoderm; ***Malaysia:*** Solcoderm†; ***Pol.:*** Solcogyn; ***Rus.:*** Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Switz.:*** Solcoderm; Solcogyn.

Nitrobenzene

Aceite de mirbana; Nitrobenceno; Nitrobenzen; Nitrobenzol; Oil of Mirbane.

$C_6H_5NO_2$ = 123.1.

CAS — 98-95-3.

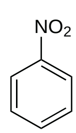

Adverse Effects

Nitrobenzene is highly toxic and the ingestion of 1 g may be fatal. Poisoning may occur from absorption through the skin, by inhalation, or by ingestion. Toxic effects are usually delayed for several hours and may include nausea, prostration, burning headache, methaemoglobinaemia with cyanosis, haemolytic anaemia, vomiting (with characteristic odour), convulsions, and coma, ending in death after a few hours.

Treatment of Adverse Effects

Although the benefit of gastric decontamination following ingestion of nitrobenzene is uncertain, gastric lavage or activated charcoal may be considered if given within 1 hour of ingestion. Methaemoglobinaemia may be treated with methylthioninium chloride. Oxygen should be given if cyanosis is severe.

If the skin or eyes are splashed with nitrobenzene, contaminated clothing should be removed immediately and the affected areas washed thoroughly with water at room temperature for at least 15 minutes.

Uses

Nitrobenzene is used in the manufacture of aniline, as a preservative in polishes, and in perfumery and soaps.

Nix-0699

Hemoxin; Nicosan; Niprisan.

Profile

Nix-0699 is an extract of the leaf of *Sorghum bicolor* (sorghum), the stem of *Pterocarpus osun* (camwood), the seed of *Piper guineense* (Ashanti or Benin pepper), and the flower of *Syzygium aromaticum*; *Eugenia caryophyllus* (clove). It is being investigated in the treatment of sickle-cell disease.

◊ Reviews.

1. Cordeiro NJV, Oniyangi O. Phytomedicines (medicines derived from plants) for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 19/08/08).

Nucleic Acid

Acide Zymonucléique; Acidum Nucleicum; Nucleico, ácido; Nucleinic Acid.

Нуклеиновая Кислота

Profile

Nucleic acids, which are present in all cellular organisms and viruses, are composed of high molecular weight polynucleotides. A nucleotide is a phosphate ester of a nucleoside, which is made up of either a purine or pyrimidine nitrogenous base attached to a pentose sugar by an *N*-glycosidic linkage. Diester phosphate linkages between the sugar moieties produce a polynucleotide strand. Nucleic acids are of two types: deoxyribonucleic acid (DNA) (p.2293) and ribonucleic acid (RNA) (p.2379). Synthetic or recombinant nucleic acids are used in gene therapy (p.2310).

Since the administration of nucleic acid gives rise to a marked temporary leucocytosis (usually preceded by a short period of leucopenia) it was formerly given in the treatment of a variety of bacterial infections in the hope of enhancing the natural defence mechanisms. Its therapeutic value, however, has never been established.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Nulip.

Nutmeg

Muscade; Myristica; Noz Moscada; Nuez moscada; Nux Moschata.

Description. Nutmeg consists of the dried kernels of the seeds of *Myristica fragrans* (Myristicaceae), containing not less than 5% v/w of volatile oil; the powdered drug contains not less than 4% v/w. Mace (see Mace Oil, p.2336) is the dried arillus of the seed of *M. fragrans*.

Pharmacopoeias. In *Chin.*

Adverse Effects

Nutmeg, taken in large doses, may cause nausea and vomiting, flushing, dry mouth, tachycardia, stimulation of the CNS possibly with epileptiform convulsions, miosis or occasionally mydriasis, euphoria, and hallucinations. Myristicin and elimicin are thought to be the constituents responsible for the psychotic effects of nutmeg, possibly because of metabolism to amfetamine-like compounds.

◊ Some references to the adverse effects of nutmeg.

1. Panayotopoulos DJ, Chisholm DD. Hallucinogenic effect of nutmeg. *BMJ* 1970; **1:** 754.
2. Venables GS, *et al.* Nutmeg poisoning. *BMJ* 1976; **1:** 96.
3. Dietz WH, Stuart MJ. Nutmeg and prostaglandins. *N Engl J Med* 1976; **294:** 503.
4. Faguet RA, Rowland KF. "Spice cabinet" intoxication. *Am J Psychiatry* 1978; **135:** 860–1.
5. Abernethy MK, Becker LB. Acute nutmeg intoxication. *Am J Emerg Med* 1992; **10:** 429–30.
6. Brenner N, *et al.* Chronic nutmeg psychosis. *J R Soc Med* 1993; **86:** 179–80.
7. Quin GI, *et al.* Nutmeg intoxication. *J Accid Emerg Med* 1998; **15:** 287–8.
8. Sangalli BC, Chiang W. Toxicology of nutmeg abuse. *J Toxicol Clin Toxicol* 2000; **38:** 671–8.
9. Stein U, *et al.* Nutmeg (myristicin) poisoning—report on a fatal case and a series of cases recorded by a poison information centre. *Forensic Sci Int* 2001; **118:** 87–90.

Uses and Administration

Nutmeg is the source of nutmeg oil (below). It is aromatic and carminative and is used as a flavour. Nutmeg has been reported to inhibit prostaglandin synthesis.

Homoeopathy. Nutmeg has been used in homoeopathic medicines under the following names: Myristica fragrans; Nux moschata; Nux. mos.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Mariazeller; ***Braz.:*** Paratonico; ***Cz.:*** Dr Theiss Schwedenbitter; Klosterfrau Melisana; Naturland Grosser Swedenbitter†; Original Schwedenbitter; ***Ger.:*** Doppelherz Melissengeist†; Melissengeist; ***Pol.:*** Melisana Klosterfrau; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Fitovit (Фитовит); Himcolin (Химколин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Entressdruppels HM; Melissengeist; Rooilavental; Spiritus Contra Tussim Drops; ***Spain:*** Agua del Carmen; ***Switz.:*** Alcoolat de Melisse†; ***UK:*** Melissa Comp..

Nutmeg Oil

Átherisches Muskatöl; Esencia de Nuez Moscada; Essence de Muscade; Essência de Moscada; Muškátovníková silice; Muskatų eterinis aliejus; Muskotolja; Muskottiöljy; Myristica Oil; Myristicae Etheroleum; Myristicae fragrantis aetheroleum; Noix muscade, huile essentielle de; Nuez moscada, aceite esencial de; Oleum Myristicae; Szerecsendióolaj.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Nutmeg Oil). The oil obtained by steam distillation of the dried and crushed kernels of *Myristica fragrans*. A colourless to pale yellow liquid with a spicy odour. Store in well-filled, airtight containers. Protect from light and heat.

Profile

Nutmeg oil is aromatic and carminative and is used as a flavour. Nutmeg oil and expressed nutmeg oil, a solid fat, are rubefacient. Nutmeg oil is also used in aromatherapy.

Preparations

BP 2008: Aromatic Ammonia Spirit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Vicks Vaporub; ***Austria:*** Emser Nasensalbe; Expectal-Balsam; Pe-Ce; Wick Vaporub; ***Belg.:*** Vicks Vaporub; ***Braz.:*** Vick Vaporub; ***Canad.:*** Vaporizing Ointment; ***Chile:*** Agua Melisa Carminativa; ***Fr.:*** Vegebom; Vicks Vaporub; ***Ger.:*** Emser Nasensalbe N†; esto-gast; ***NZ:*** Vicks Vaporub; ***Pol.:*** Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Wick Vaporub; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; Doktor Mom (Доктор Мом); ***S.Afr.:*** Balsem Vita GEEL; Balsem Vita ROOI; Balsem Vita WIT; Enterodyne; Stuidruppels; Vicks Vaporub; ***Swed.:*** Vicks Vaporub†; ***Switz.:*** Carmol; Carmol Plus†; Eucapinol; Frixo-Dragon Vert†; Vicks Vaporub N; ***Thai.:*** Tiffyrub†; ***Turk.:*** Vicks Vaporub; ***UK:*** Dragon Balm; No-Sor Vapour Rub; Nowax; ***USA:*** Vicks Vaporub.

Nux Vomica

Brechnuss; Noce Vomica; Noix Vomique; Nuez vómica; Strychni Semen.

CAS — 357-57-3 (anhydrous brucine).

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Nux vomica consists of the dried ripe seeds of *Strychnos nux-vomica* (Loganiaceae). It has the actions of strychnine (see p.2393). As well as containing strychnine, nux vomica contains brucine which has similar properties.

Nux vomica is used in herbal medicine for a wide variety of disorders including those of digestion or debility.

Homoeopathy. Nux vomica has been used in homoeopathic medicines under the following names: Nux vom.; Strychnos nux-vomica.

The dried ripe seeds of *Strychnos ignatii* have been used in homoeopathic medicines under the following names: Iamara; Ignatia; Ignatia amara; Ign..

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Cessagripe†.

Multi-ingredient: ***Braz.:*** Estomafitino†; Gotas Digestivas; Kola Fosfatada Soel†; ***Chile:*** Fenokomp 39; Fenolftaleina Compuesta†; Homeofortin III†; ***Ital.:*** Lassatina†; ***Mex.:*** Bigenol; ***Philipp.:*** BSI Medicated Spray; ***Rus.:*** Tentex (Тентекс); ***Spain:*** Alofedina; ***Switz.:*** Padma-Lax; Padmed Laxan; ***Thai.:*** Flatulence.

Oak Bark

Ąžuolų žievė; Chêne, écorce de; Common Oak; Corteza de roble; Dubová kůra; Durmast Oak; Écorce de Chêne; Eichenrinde; Ekbark; Kora dębowa; Quercus; Quercus cortex; Tammenkuori; Tölgyfakéreg.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oak Bark). The cut and dried bark from the fresh young branches of *Quercus robur*, *Q. petraea*, and *Q. pubescens*. It contains a minimum of 3.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Oak bark contains quercitannic acid. It has astringent properties and is used in some herbal preparations. It was formerly used for haemorrhoids and as a gargle.

Homoeopathy. Oak bark has been used in homoeopathic medicines under the following names: Quercus.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dubova Kura; ***Ger.:*** Traxaton; ***Hong Kong:*** Urocalun; ***Jpn:*** Urocalun; ***Pol.:*** Quecor; ***Singapore:*** Urocalun; ***USA:*** Amerigel.

Multi-ingredient: ***Austria:*** Menodoron; ***Cz.:*** Hemoral†; ***Fr.:*** Delabarre Bio-adhesif; ***Ger.:*** Tonsilgon; ***Pol.:*** Arnisol; Dentosept; Dentosept A; Enterosol; Mucosit; Sanofil; Stomatosol; ***Rus.:*** Tonsilgon N (Тонзилгон Н); ***S.Afr.:*** Menodoron; ***Spain:*** Natusor Astringel†; ***Switz.:*** Kemosan Elixir; ***UK:*** Peerless Composition Essence; ***USA:*** Amerigel.

Octamylamine *(rINN)*

Octamilamina; Octamylaminum; Octisamyl hydrochloride (octamylamine hydrochloride). *N*-Isopentyl-1,5-dimethylhexylamine.

Октамиламин

$C_{13}H_{29}N = 199.4.$
CAS — 502-59-0 (octamylamine); 5964-56-7 (octamylamine hydrochloride).

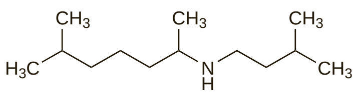

Profile

Octamylamine is a smooth muscle relaxant that has been used as an antispasmodic. The hydrochloride and mucate salts have been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Octinum-D†.

Octanoic Acid *(USAN, rINN)*

Acide caprylique; Acide Octanoïque; Ácido octanoico; Acidum caprylicum; Acidum Octanoicum; Caprylic Acid; Kaprilo rūgštis; Kaprilsav; Kaprylsyra; Kapryylihappo; Kwas kaprylowy; Kyselina oktanová.

Октановая Кислота

$CH_3.(CH_2)_6.CO_2H = 144.2.$
CAS — 124-07-2.

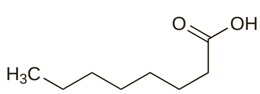

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Caprylic Acid; Octanoic Acid BP 2008). A clear, colourless or slightly yellowish, oily liquid. Very slightly soluble in water; very soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides.

Sodium Octanoate

Natrii caprylas; Natrii Octanoas; Natrio kaprilatas; Nátrium-kaprilát; Natriumkaprylaatti; Natriumkaprylat; Natrium-oktanoát; Octanoato sódico; Sodium Caprylate; Sodium, caprylate de.

$C_8H_{15}NaO_2 = 166.2.$
CAS — 1984-06-1.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Sodium Caprylate). A white or almost white, crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

USNF 26 (Sodium Caprylate). A white crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

Profile

Octanoic acid and its salts have antifungal activity.

Sodium octanoate is used to stabilise albumin solution against the effects of heat. Octanoic acid labelled with carbon-13 has been used in a breath test to measure gastric emptying.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Caprilate.

Olaquindox *(BAN, rINN)*

Bay-Va-9391; Olaquindoxum. 2-(2-Hydroxyethylcarbamoyl)-3-methylquinoxaline 1,4-dioxide.

Олахиндокс

$C_{12}H_{13}N_3O_4 = 263.2.$
CAS — 23696-28-8.
ATC Vet — QJ01MQ01.

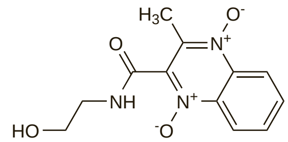

Profile

Olaquindox is an antibacterial added to animal feedstuffs as a growth promotor. Photoallergic reactions in animal handlers have been reported on exposure to olaquindox.

Oleander

Adelfa; Baladre; Common Oleander; Espirradeira; Laurier Rose; Oleanderblätter; Oleandri Folium; Rose Bay.

Profile

The dried leaves of the oleander shrub, *Nerium oleander* (Apocynaceae), contain cardioactive glycosides, including oleandrin. They have been used in the treatment of heart disorders. The flowers and bark have been used similarly. Toxicity, similar to that seen with digoxin, may occur after ingestion of any part of the plant; fatalities have been reported. Yellow oleander (*Thevetia peruviana*) also contains cardiac glycosides and exhibits similar toxicity to oleander.

Homoeopathy. Oleander has been used in homoeopathic medicines under the following names: Nerium oleander; Oleand.

Treatment of adverse effects. References to the treatment of oleander poisoning or yellow oleander poisoning.

1. Shumaik GM, *et al.* Oleander poisoning: treatment with digoxin-specific Fab antibody fragments. *Ann Emerg Med* 1988; **17:** 732–5.
2. Safadi R, *et al.* Beneficial effect of digoxin-specific Fab antibody fragments in oleander intoxication. *Arch Intern Med* 1995; **155:** 2121–5.
3. Eddleston M, *et al.* Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. *Lancet* 2000; **355:** 967–72.
4. Fonseka MM, *et al.* Yellow oleander poisoning in Sri Lanka: outcome in a secondary care hospital. *Hum Exp Toxicol* 2002; **21:** 293–5.
5. de Silva HA, *et al.* Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; **361:** 1935–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Miroton.

Olive

Oleae folium (olive leaf); Olivier, feuille d' (olive leaf).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Olive Leaf; Oleae Folium). The dried leaf of *Olea europaea*. It contains a minimum of 5.0% of oleuropein ($C_{25}H_{32}O_{13}$ = 540.5), calculated on the dried basis. Protect from light.

Profile

The fresh or dried leaf of the olive, *Olea europaea* (Oleaceae), is used in herbal medicine for its antihypertensive and diuretic actions.

Olive fruit is the source of Olive Oil, p.2356.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Olivevital; ***Fr.:*** Oliviase†; ***Ger.:*** Olivysat.

Multi-ingredient: ***Austral.:*** Bioglan Bioage Peripheral; ***Fr.:*** B.O.P.; ***Ger.:*** Antihypertonicum S; Hypercircin.

Olive Oil

Aceite de oliva; Alyvuogių aliejus; Azeite; Huile d'Olive; Olej z oliwek; Oliiviöljy; Olivae oleum; Olivaolaj; Olive, huile d'; Olivenöl; Olivolja; Olivový olej.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

Eur. (see p.vii) includes monographs for virgin olive oil and refined olive oil.

Ph. Eur. 6.2 (Olive Oil, Virgin; Olivae Oleum Virginale). The fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea*. It is a clear, yellow or greenish-yellow, transparent liquid with a characteristic odour. When cooled it begins to become cloudy at 10° and becomes a butter-like mass at 0°. Practically insoluble in alcohol; miscible with petroleum spirit (50° to 70°). Store in well-filled containers at a temperature not exceeding 25°. Protect from light.

Ph. Eur. 6.2 (Olive Oil, Refined; Olivae Oleum Raffinatum). The fatty oil obtained by refining of crude olive oil. A suitable antioxidant may be added. It is a clear, colourless, or greenish-yellow, transparent liquid. When cooled it begins to become cloudy at 10° and becomes a butter-like mass at about 0°. Practically insoluble in alcohol; miscible with petroleum spirit (50° to 70°). Store in well-filled containers at a temperature not exceeding 25°. Protect from light. Store under an inert gas if intended for use in the manufacture of parenteral dosage forms.

USNF 26 (Olive Oil). The fixed oil obtained from the ripe fruits of *Olea europaea* (Oleaceae). It may contain suitable antioxidants. It is a pale yellow, or light greenish-yellow, oily liquid, having a slight characteristic odour. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store in airtight containers at a temperature not exceeding 40°.

Profile

When taken internally, olive oil is nutrient, demulcent, and mildly laxative. It may also be given rectally (100 to 500 mL warmed to about 32°) to soften impacted faeces (p.1693).

Externally, olive oil is emollient and soothing to inflamed surfaces, and is used to soften the skin and crusts in eczema (p.1579) and psoriasis (p.1583), and as a lubricant for massage. It is used to soften ear wax (p.1725).

Olive oil is used in the preparation of liniments, ointments, plasters, and soaps; it is also used as a vehicle for oily suspensions for injection.

Epidemiological evidence points to the cardiovascular benefits of olive oil in the diet. Olive leaf (p.2356) is used in herbal medicine.

Preparations

BP 2008: Olive Oil Ear Drops.

Proprietary Preparations (details are given in Part 3)
Mex.: Oleomed†.

Multi-ingredient: ***Arg.:*** Calculina†; Clinoleic; ***Austral.:*** Gold Cross BOZ Ointment†; Snor-Away†; ***Austria:*** Clinoleic; OliClinomel; SMOFlipid; ***Braz.:*** Quelodin†; ***Cz.:*** Clinoleic; OliClinomel; SMOFlipid; ***Denm.:*** Clinoleic; OliClinomel; SMOFlipid; ***Fin.:*** Clinoleic; OliClinomel; ***Fr.:*** Clinoleic; Maghora; OliClinomel; ***Ger.:*** Clinoleic; OliClinomel; SMOFlipid; ***Gr.:*** Clinoleic; OliClinomel; SMOFlipid; ***Hung.:*** OliClinomel; SMOFlipid; ***Israel:*** Clinoleic; ***Ital.:*** Acumel; Clinoleic; OliClinomel; ***Mex.:*** Clinoleic†; ***Neth.:*** Clinoleic; OliClinomel; SMOFlipid; ***Norw.:*** SMOFlipid; ***NZ:*** Snorenz; ***Pol.:*** Clinoleic; SMOFlipid; ***Port.:*** Clinoleic; OliClinomel; ***Rus.:*** Olimetin (Олиметин)†; ***Spain:*** Aceite Acalorico; Clinoleic; Natusor High Blood Pressure†; OliClinomel; Tensiben†; ***Swed.:*** Clinoleic; OliClinomel; SMOFlipid; ***Switz.:*** Clinoleic; OliClinomel; ***Thai.:*** OliClinomel; ***UK:*** Clinoleic; OliClinomel; SMOFlipid; Snor-Away.

Ololiuqui

CAS — 2889-26-1 (isoergine); 478-94-4 (ergine); 2390-99-0 (chanoclavine); 548-43-6 (elymoclavine); 602-85-7 (lysergol).

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for 'morning glory' seeds:
Flying saucers; Glories; Heavenly blue; Pearly gates; Tlitlilzin; Yaxce'lil.

Profile

Ololiuqui consists of the seeds of *Rivea corymbosa* or *Ipomoea tricolor* (*I. violacea*) both convolvulaceous plants similar to the garden plant 'morning glory', *Ipomoea purpurea*. The brown seeds of *R. corymbosa* are known as 'badoh' and the black seeds of *I. tricolor* as 'badoh negro'.

Ololiuqui has hallucinogenic properties and is considered to be sacred by some Mexican Indians. Alkaloidal fractions contain at least 5 closely related individual components, namely D-isolysergic acid amide (isoergine), D-lysergic acid amide (ergine), chanoclavine, elymoclavine, and lysergol.

The name 'ololiuqui' has been erroneously applied to seeds of *Datura meteloides* (Solanaceae).

Onion

Cebolla; Cipolla; Oignon; Zwiebel.

Profile

Onion is the bulb of *Allium cepa* (Liliaceae). It has been reported to reduce platelet aggregation, lower serum cholesterol, and to enhance fibrinolysis. It has been used in preparations for the treatment of urinary-tract disorders and in topical preparations for scars and contractures.

Homoeopathy. Onion has been used in homoeopathic medicines under the following names: Cepa; Allium cepa; All. cepa.

Cardiovascular disease. A review of controlled studies purporting to show beneficial effects of garlic and/or onion on cardiovascular risk factors found those studies to have severe methodological failings.[1]

1. Kleijnen J, *et al.* Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; **28:** 535–44.

Stings. An onion bulb was used to treat the wound caused by a blue-spotted stingray (*Dasyatis kuhlii*).[1] Pain relief occurred within 30 minutes.

1. Whiting SD, Guinea ML. Treating stingray wounds with onions. *Med J Aust* 1998; **168:** 584.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Mederma; ***Chile:*** Mederma†; ***Israel:*** Mederma; ***Malaysia:*** Mederma; ***Pol.:*** Alcep; ***Singapore:*** Mederma; ***USA:*** Mederma.

Multi-ingredient: ***Arg.:*** Contractubex; ***Austral.:*** Garlic Allium Complex; ***Austria:*** Contractubex; ***Braz.:*** Contractubex; ***Cz.:*** Contractubex; ***Ger.:*** Contractubex; ***Hong Kong:*** Contractubex; ***Hung.:*** Contractubex; ***India:*** Contractubex; ***Indon.:*** Mederma; ***Ital.:*** Skarflex; ***Malaysia:*** Palmer's Cocoa Butter Formula Scar Serum; ***Philipp.:*** Contractubex; ***Pol.:*** Alcepalan; Cepan; Cepasmel; Cepastil; Contractubex; ***Rus.:*** Contractubex (Контрактубекс); ***Singapore:*** Erase; ***Switz.:*** Contractubex.

Ononis

Arrête-Boeuf; Bugrane, racine de; Busktörnerot; Dirvenių šaknys; Gatuña; Hauhechelwurzel; Jehlicový kořen; Ononidis radix; Piikkiorakonjuuri; Racine de Bugrane; Radix Ononidis; Restharrow Root; Spiny Restharrow; Tövisesiglice-gyökér.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Restharrow Root). The whole or cut, dried root of *Ononis spinosa*.

Profile

Onon is has diuretic activity. It has been used in herbal preparations for the treatment of oedema, urinary-tract disorders, rheumatic disorders, and constipation.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Krauter Hustensaft; Nierentee St Severin; Uropurat; ***Cz.:*** Nephrosal†; Species Diureticae Planta†; Species Urologicae Planta; Stoffwechseltee N†; Urologicka Cajova Smes; ***Fr.:*** Depuratum; Schoum; ***Ger.:*** Alasenn; Aqualibra; Hevert-Blasen-Nieren-Tee N; Heweberberol-Tee; nephro-loges; Nephronorm med†; Nephroselect M; Nephrubin-N†; Nieron Blasen- und Nieren-Tee VI†; Nieron-Tee N†; Presselin Nieren-Blasen K 3†; Renob Blasen- und Nierentee; Uvirgan N†; ***Ital.:*** Gramigna (Specie Composta)†; Soluzione Schoum; ***Pol.:*** Betasol; Diuronis; ***Rus.:*** Herbion Urological Drops (Гербион Урологические Капли); ***Switz.:*** Demonatur Dragees pour les reins et la vessie; Nephrosolid; Phytomed Nephro†; Prosta-Caps Chassot N.

Bitter Orange

Aurantii amari flos (bitter-orange flower); Aurantii Amari Pericarpium (bitter orange fruit); Bigaradier; Karčiavaisių citrinmedžių žiedai (bitter-orange flower); Keserű narancs virág (bitter-orange flower); Květ hořkého pomeranče (bitter-orange flower); Naranja Amarga; Naranja amarga, corteza de; Oranger amer, fleur d' (bitter-orange flower); Owocnia pomarańczy gorzkiej (bitter orange fruit); Pomeransblomma (bitter-orange flower); Pomeranssinkukka (bitter-orange flower); Pomeranze; Seville Orange.

Апельсин; Померанец

Pharmacopoeias. *Eur.* includes the dried peel and flowers. *Jpn* includes the peel.

Ph. Eur. 6.2 (Bitter-orange Epicarp and Mesocarp; Aurantii amari epicarpium et mesocarpium; Dried Bitter-orange Peel BP 2008). The dried epicarp and mesocarp of the ripe fruit of *Citrus aurantium*, partly freed from the white spongy tissue of the mesocarp and endocarp, containing a minimum of 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. It has an aromatic odour and a spicy bitter taste.

Ph. Eur. 6.2 (Bitter-orange Flower; Aurantii amari flos). The whole, dried, unopened flower of *C. aurantium* subsp. *aurantium* containing a minimum of 8.0% of total flavonoids, expressed as naringin ($C_{27}H_{32}O_{14}$ = 580.5), calculated with reference to the dried drug.

Profile

The dried peel of the bitter orange, *Citrus aurantium* subsp. *aurantium* (*Citrus aurantium* subsp. *amara*) (Rutaceae) is used as a flavour and for its bitter and carminative properties. An essential oil is prepared from fresh bitter-orange peel (bitter-orange oil) and is similar to sweet orange oil (p.2357). Both bitter-orange oil and petitgrain bigarade oil (prepared from the leaves and twigs) are used in aromatherapy.

The flowers are an ingredient of herbal remedies used for nervous and sleep disorders. Bitter-orange flower is the source of Neroli Oil (p.2351).

The whole dried immature fruit is used similarly to the dried peel. In Chinese medicine, the dried immature fruits are known as zhi shi and zhi qiao.

Photosensitivity is associated with citrus oils.

Action and use. *Citrus aurantium* was one of the most frequently used herbal remedies in Puerto Rico.[1] Indications included sleep disorders, gastrointestinal disorders, respiratory ailments, and raised blood pressure.

The volatile oil of dried bitter-orange peel has shown antifungal activity.[2]

Bitter-orange extract has been added to herbal weight loss remedies as it contains the sympathomimetic synephrine (a name that has been used for both phenylephrine and oxedrine), which is claimed to increase metabolism and promote thermogenesis, although efficacy is not proven. Variant angina[3] and ischaemic colitis[4] have been reported in patients taking dietary supplements containing bitter orange, and reports of serious cardiovascular adverse effects possibly associated with the synephrine content of bitter orange present in such preparations have been received in Canada.[5,6] Raised systolic and diastolic blood pressure and heart rate were seen after ingestion of a proprietary bitter orange preparation in one small randomised placebo-controlled crossover study.[7] However, in a similar study[8] comparing a single-ingredient bitter orange preparation with a combination preparation, adverse haemodynamic effects appeared to be related to the additional presence of other possible stimulants such as caffeine, rather than directly proportional to the dose of bitter orange alone.

1. Hernández L, *et al.* Use of medicinal plants by ambulatory patients in Puerto Rico. *Am J Hosp Pharm* 1984; **41:** 2060–4.
2. Ramadan W, *et al.* Oil of bitter orange: new topical antifungal agent. *Int J Dermatol* 1996; **35:** 448–9.
3. Gange CA, *et al.* Variant angina associated with bitter orange in a dietary supplement. *Mayo Clin Proc* 2006; **81:** 545–8.
4. Sultan S, *et al.* Ischemic colitis associated with use of a bitter orange-containing dietary weight-loss supplement. *Mayo Clin Proc* 2006; **81:** 1630–1.
5. Health Canada. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *Can Adverse React News* 2004; **14** (4): 3–4. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 06/08/08)
6. Health Canada. Bitter orange or synephrine: update on cardiovascular adverse reactions. *Can Adverse React News* 2007; **17** (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 06/08/08)
7. Bui LT, *et al.* Blood pressure and heart rate effects following a single dose of bitter orange. *Ann Pharmacother* 2006; **40:** 53–7.
8. Haller CA, *et al.* Hemodynamic effects of ephedra-free weight-loss supplements in humans. *Am J Med* 2005; **118:** 998–1003.

Preparations

BP 2008: Concentrated Compound Gentian Infusion; Concentrated Orange Peel Infusion; Orange Peel Infusion; Orange Syrup;
Ph. Eur.: Bitter-Orange-Epicarp and Mesocarp Tincture.

Proprietary Preparations (details are given in Part 3)
Ger.: Carvomin Magentropfen mit Pomeranze†.

Multi-ingredient: ***Arg.:*** Calmtabs†; Hepatodirectol; ***Austria:*** China-Eisenwein; Eicebaer; Ferrovin-Chinaeisenwein; Mariazeller; Montana; Sigman-Haustropfen; St Bonifatius-Tee; Tussimont; ***Canad.:*** Biotrim†; ***Cz.:*** Klosterfrau Melisana; Naturland Grosser Swedenbitter†; Pleumolysin; Schlaf-Nerventee N†; ***Fr.:*** Calmophytum; Elixir Bonjean; Elixir Grez†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Quintonine; Vegetoserum; ***Ger.:*** Carminativum-Hetterich; Doppelherz Melissengeist†; Gallexier; Gastrosecur†; Montana N; Sedovent; ***Hong Kong:*** LEAN Formula w/ Advantra†; ***India:*** Toniazol†; ***Indon.:*** Jesscool; ***Israel:*** Passiflora; ***Ital.:*** Assenzio (Specie Composta)†; Gastro-Pepsin; Genziana (Specie Composta)†; Valeriana (Specie Composta)†; ***Pol.:*** Herbaton; Krople Zoladkowe; ***Rus.:*** Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Versterkdruppels; ***Singapore:*** Chitosano; ***Spain:*** Euzymina Lisina I; Euzymina Lisina II; Jaquesor†; Natusor Jaquesan†; Sedonat; ***Switz.:*** Pastilles pectorales Demo N; Phytomed Nervo†; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; ***UK:*** Vital Eyes.

Sweet Orange

Naranja.

Pharmacopoeias. *Chin.* includes both the dried immature fruit of *Citrus aurantium* and its cultivated varieties and the dried young fruit of *C. aurantium*. *Swiss* includes the ripe fresh fruit of *Citrus sinensis*.

Profile

Sweet orange, *Citrus sinensis* (*Citrus aurantium* var. *dulcis*) (Rutaceae), is an ingredient of herbal remedies used for nervous and sleep disorders. The peel is the source of sweet orange oil (below). Citrus fruits are a source of vitamin C (p.1983).

Photosensitivity is associated with citrus oils.

Preparations

USNF 26: Orange Syrup; Sweet Orange Peel Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Expectal-Tropfen; Magentee St Severin; Mariazeller; ***Cz.:*** Passedan; ***Ger.:*** Majocarmin forte†; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера).

Sweet Orange Oil

Apelsininių citrinmedžių vaisių žievelių eterinis aliejus; Apelsinolja; Appelsiininkuoriöljy; Arancia Dolce Essenza; Aurantii dulcis aetheroleum; Aurantii Dulcis Pericarpii Etheroleum; Essence of Orange; Essence of Portugal; Essência de Laranja; Naranja, aceite esencial de; Orange douce, huile essentielle d'; Orange Oil; Silice oplodí sladkého pomeranče.

NOTE. The oil from the flowers of *Citrus aurantium* var. *amara* is known as neroli oil or orange flower oil (p.2351).

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*. Also in *USNF.*

Ph. Eur. 6.2 (Sweet Orange Oil). An essential oil obtained without heating, by suitable mechanical treatment from the fresh peel of the fruit of *Citrus sinensis* (*Citrus aurantium* var. *dulcis*). A suitable antoxidant may be added. It contains 0.4 to 0.6% α-pinene, 0.02 to 0.3% β-pinene, 0.2 to 1.1% sabinene, 1.7 to 2.5% β-myrcene, 92.0 to 97.0% limonene, 0.1 to 0.4% octanal, 0.1 to 0.4% decanal, 0.2 to 0.7% linalol, 0.02 to 0.10% neral, 0.02 to 0.5% valencene, and 0.03 to 0.02% geranial.

A clear, pale yellow to orange, mobile liquid, which may become cloudy when chilled. It has a characteristic odour of fresh orange peel. Relative density 0.842 to 0.850. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Orange Oil). The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Rutaceae), containing not less than 1.2% w/v and not more than 2.5% w/v of aldehydes, calculated as decanal ($C_{10}H_{20}O$ = 156.3). It may be California-type or Florida-type orange oil. Store in well-filled airtight containers.

Profile

Sweet orange oil is used as a flavour, in perfumery, and in aromatherapy. It is used in the preparation of terpeneless orange oil. Photosensitivity reactions have been reported with citrus oils.

Preparations

USNF 26: Compound Orange Spirit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Coldastop; ***Ger.:*** GeloSitin; ***Hong Kong:*** Magesto; ***Switz.:*** Perskindol Classic; Pinimenthol†; Sansilla; Sibrovita; ***Thai.:*** Magesto.

Terpeneless Orange Oil

Naranja sin terpeno, aceite esencial de; Oleum Aurantii Deterpenatum.

Pharmacopoeias. In *Br.*

BP 2008 (Terpeneless Orange Oil). A clear yellow or orange-yellow liquid, visibly free from water, with the odour and taste of orange, prepared by concentrating orange oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 18% w/w of aldehydes calculated as decanal ($C_{10}H_{20}O$ = 156.3). Soluble 1 in 1 of alcohol (90%). Store in well-filled containers at a temperature not exceeding 25°. Protect from light.

Profile

Terpeneless orange oil consists chiefly of the free alcohols (+)-linalol and (+)-terpineol. It is used as a flavour. It is stronger in flavour and more readily soluble than the natural oil. Photosensitivity is associated with citrus oils.

Preparations

BP 2008: Compound Orange Spirit.

Orazamide *(rINN)*

AICA Orotate; Orazamida; Orazamidum; Oroxamide. 5-Aminoimidazole-4-carboxamide orotate dihydrate.

Оразамид

$C_9H_{10}N_6O_5,2H_2O$ = 318.2.

CAS — 2574-78-9 (anhydrous orazamide); 60104-30-5 (orazamide dihydrate).

Profile

Orazamide has been given orally in the treatment of liver disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Aicamin.

Multi-ingredient: ***Port.:*** Oraica†.

Orchis Mascula

Early Purple Orchid.

Ятрышник Мужской

Profile

Orchis mascula, which is alleged to have aphrodisiac properties, has been used in herbal preparations for male sexual disorders.

Salep, a flour made from the dried ground tubers of *Orchis mascula* and various other species of orchid, contains a nutritious mucilage called bassorin; ice-cream made from salep is a great delicacy in Turkey.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Rus.:*** Speman (Спеман); Speman Forte (Спеман Форте); Tentex (Тентекс).

Oregano

Dost; Origan; Origani herba; Origani Vulgaris Herba; Wild Marjoram.

CAS — 8007-11-2 (origanum oil).

NOTE. Distinguish from Marjoram, p.2337

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Oregano). The dried leaves and flowers, separated from the stems, of *Origanum onites* or *O. vulgare* subsp. *hirtum*, or a mixture of both species. It contains a minimum of 2.5% v/w of essential oil, which contains a minimum of 60% of carvacrol and thymol, calculated with reference to the anhydrous drug. Protect from light.

Profile

The aerial parts of oregano, *Origanum onites* (Lamiaceae), or *O. vulgare* or its subspecies, are used as a culinary herb and in herbal preparations.

There is some confusion over the naming of origanum oils. Oil from *O. vulgare* has been used medicinally. Origanum Oil is the oil obtained from *Coridothymus capitatus* (*Thymus capitatus*) but oils from other related species may also be referred to as origanum oils, and Oil of Origanum was also given as a synonym for Thyme Oil in BPC 1949. Preparations listed in *Martindale* as containing origanum oil may contain an oil from any of these related species.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Gartech; ***Austria:*** Asthmatee EF-EM-ES; Baby Luuf; ***Cz.:*** Bronchosan; Fytokliman Planta; Melaton†; ***Pol.:*** Herbolen; Herbolen D; ***Spain:*** Pazbronquial; ***Switz.:*** Demonatur Capsules contre les refroidissements.

Orlistat *(BAN, USAN, rINN)*

Orlipastat; Orlistaatti; Orlistatum; Ro-18-0647; Ro-18-0647/002; Tetrahydrolipstatin. *N*-Formyl-L-leucine, ester with (3*S*,4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]-2-oxetanone; (*S*)-1-[(2*S*,3*S*)-3-Hexyl-4-oxo-oxetan-2-ylmethyl]dodecyl *N*-formyl-L-leucinate.

Орлистат

$C_{29}H_{53}NO_5$ = 495.7.
CAS — 96829-58-2.
ATC — A08AB01.
ATC Vet — QA08AB01.

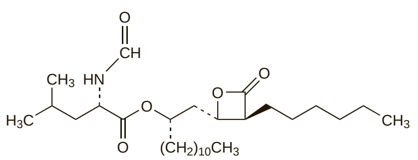

Adverse Effects

Gastrointestinal disturbances, including faecal urgency and incontinence, flatulence, and fatty stools or discharge, are the most frequently reported adverse effects during treatment with orlistat. They may be minimised by limiting the amount of fat in the diet. Other reported effects have included headache, anxiety, fatigue, and menstrual irregularities. There have been concerns about an increased risk of breast cancer in patients taking orlistat but the manufacturers consider that there is no evidence of a causal link.

Effects on the cardiovascular system. A report of hypertension associated with orlistat therapy.[1] Blood pressure decreased on stopping orlistat and increased again on rechallenge. The authors noted that 13 cases of hypertension associated with orlistat had been reported to the manufacturers.

1. Persson M, *et al.* Orlistat associated with hypertension. *BMJ* 2000; **321:** 87.

Effects on the skin. Lichenoid drug eruption affecting the vulva, feet, and axillae has been reported in a woman during orlistat treatment.[1] Symptoms resolved on stopping orlistat with only the vulval lesions requiring topical treatment with mometasone furoate 0.1%.

1. Sergeant A, *et al.* Lichenoid eruption associated with orlistat. *Br J Dermatol* 2006; **154:** 1020–21.

Precautions

Orlistat should not be given to patients with chronic malabsorption syndrome or cholestasis and should be given with caution to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis. Adjustments to dosage of hypoglycaemics may be necessary in patients with type II diabetes because of improved metabolic control after weight loss in these patients. Supplements of fat-soluble vitamins may be necessary during long-term therapy, but they should be taken at least 2 hours before or after an orlistat dose or at bedtime. Hormonal contraceptive failure may occur in the event of severe diarrhoea with orlistat, and patients are advised to use an additional contraceptive method.

Interactions

Orlistat may reduce the absorption of fat-soluble vitamins. Licensed product information recommends that it not be taken with acarbose. In patients taking warfarin, international normalised ratio should be monitored during treatment with orlistat. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported in transplant recipients given orlistat (see p.1826). Orlistat may also reduce the absorption of propafenone. For the possibility of hormonal contraceptive failure with orlistat see Precautions, above.

Pharmacokinetics

Orlistat is minimally absorbed after oral doses.

Uses and Administration

Orlistat is a gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat. It is used together with dietary modification in the management of obesity (p.2149), i.e. in patients with a BMI of 30 kg/m^2 or greater. It may also be used in overweight patients with a BMI of 27 kg/m^2 or more if there are associated risk factors. Orlistat is given in a usual dose of 120 mg orally three times daily, immediately before, during, or up to 1 hour after meals. If a meal is missed or contains no fat, the dose should be omitted. Orlistat therapy should be stopped if the patient does not lose at least 5% of their body-weight during the first 12 weeks of therapy.

◊ References.

1. NICE. Guidance on the use of orlistat for the treatment of obesity in adults (issued March 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/orlistatguidance.pdf (accessed 06/08/08)
2. Lucas KH, Kaplan-Machlis B. Orlistat—a novel weight loss therapy. *Ann Pharmacother* 2001; **35:** 314–28.
3. Keating GM, Jarvis B. Orlistat: in the prevention and treatment of type 2 diabetes mellitus. *Drugs* 2001; **61:** 2107–21.
4. Snider LJ, Malone M. Orlistat use in type 2 diabetes. *Ann Pharmacother* 2002; **36:** 1210–18.
5. Torgerson JS, *et al.* XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27:** 155–61.
6. Guy-Grand B, *et al.* Effects of orlistat on obesity-related diseases—a six-month randomized trial. *Diabetes Obes Metab* 2004; **6:** 375–83.
7. Chanoine J-P, *et al.* Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005; **293:** 2873–83. Correction. *ibid.*; **294:** 1491.
8. Henness S, Perry CM. Orlistat: a review of its use in the management of obesity. *Drugs* 2006; **66:** 1625–56.
9. Filippatos TD, *et al.* Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Safety* 2008; **31:** 53–65.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Crisplus; Fingras; Xenical; Xeniplus; Xinplex; ***Austral.:*** Xenical; ***Austria:*** Xenical; ***Belg.:*** Xenical; ***Braz.:*** Xenical; ***Canad.:*** Xenical; ***Chile:*** Viplena; Xenical; ***Cz.:*** Xenical; ***Denm.:*** Xenical; ***Fin.:*** Xenical; ***Fr.:*** Xenical; ***Ger.:*** Xenical; ***Gr.:*** Xenical; ***Hong Kong:*** Xenical; ***Hung.:*** Xenical; ***Indon.:*** Xenical; ***Irl.:*** Xenical; ***Israel:*** Xenical; ***Ital.:*** Xenical; ***Malaysia:*** Xenical; ***Mex.:*** Redustat; Xenical; ***Neth.:*** Xenical; ***Norw.:*** Xenical; ***NZ:*** Xenical; ***Philipp.:*** Xenical; ***Pol.:*** Xenical; ***Port.:*** Xenical; ***S.Afr.:*** Xenical; ***Singapore:*** Xenical; ***Spain:*** Xenical; ***Swed.:*** Xenical; ***Switz.:*** Xenical; ***Thai.:*** Xenical; ***Turk.:*** Xenical; ***UK:*** Xenical; ***USA:*** Alli; Xenical; ***Venez.:*** Xenical.

Ornipressin *(rINN)*

Ornipresina; Ornipressine; Ornipressinum. [8-Ornithine]-vasopressin.

Орнипрессин

$C_{45}H_{63}N_{13}O_{12}S_2$ = 1042.2.
CAS — 3397-23-7.
ATC — H01BA05.
ATC Vet — QH01BA05.

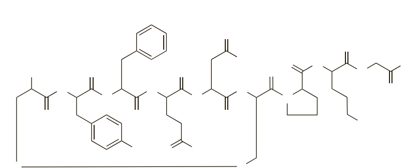

Profile

Ornipressin is a synthetic derivative of vasopressin (p.2411) with similar actions. It is reported to be a strong vasoconstrictor with only weak antidiuretic properties and is used to reduce bleeding during surgery. A solution containing up to 5 units in 20 to 60 mL of sodium chloride 0.9% is infiltrated into the area involved. Ornipressin is also used for bleeding oesophageal varices (under Monoethanolamine, p.2346) in a dose of 20 units diluted in 100 mL of sodium chloride 0.9% given as a continuous intravenous infusion over 48 hours.

◊ References.

1. Kam PC, Tay TM. The pharmacology of ornipressin (POR-8): a local vasoconstrictor used in surgery. *Eur J Anaesthesiol* 1998; **15:** 133–9.
2. De Kock M, *et al.* Ornipressin (Por 8): an efficient alternative to counteract hypotension during combined general/epidural anesthesia. *Anesth Analg* 2000; **90:** 1301–7.

Adverse effects. Acute pulmonary oedema occurred in a patient after infiltration of ornipressin (12 units in 40 mL isotonic saline) as a local vasoconstrictor during surgery.[1] It was suggested that no more than 100 milliunits/kg should be given in this manner.

1. Borgeat A, *et al.* Acute pulmonary oedema following administration of ornithine-8-vasopressin. *Br J Anaesth* 1990; **65:** 548–51.

Hepatorenal syndrome. Ornipressin has been found to be of benefit[1-4] in the hepatorenal syndrome, a form of renal insufficiency associated with cirrhosis of the liver, and thought to be due to severe renal vasoconstriction secondary to systemic arterial vasodilatation. However, caution in its use has been urged[2] because of the risk of ischaemic complications.

1. Lenz K, *et al.* Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis: effects on renal hemodynamics and atrial natriuretic factor. *Gastroenterology* 1991; **101:** 1060–7.
2. Guevara M, *et al.* Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998; **27:** 35–41.
3. Gülberg V, *et al.* Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology* 1999; **30:** 870–5.
4. Restuccia T, *et al.* Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome: a case-control study. *J Hepatol* 2004; **40:** 140–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: POR 8; ***Austria:*** POR 8; ***NZ:*** POR 8; ***S.Afr.:*** POR 8.

Orotic Acid *(BAN, pINN)*

Acide Orotique; Ácido orótico; Acidum Oroticum; Animal Galactose Factor; Orootihappo; Orotsyra; Uracil-6-carboxylic Acid; Vitamin B_{13}; Vitamina B_{13}; Whey Factor. 1,2,3,6-Tetrahydro-2,6-dioxopyrimidine-4-carboxylic acid.

Оротовая Кислота

$C_5H_4N_2O_4$ = 156.1.
CAS — 65-86-1 (anhydrous orotic acid); 50887-69-9 (orotic acid monohydrate).

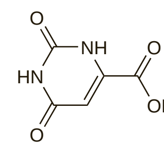

Profile

Orotic acid, an intermediate in the biosynthesis of pyrimidine nucleotides, occurs naturally in the body and is also found in milk. Orotic acid and its calcium, carnitine, choline, lithium, lysine, and potassium salts have been used in liver disorders. Some of these salts, as well as chromium, cyproheptadine, deanol, magnesium, and zinc orotates have been given as tonics or dietary supplements.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Magnerot; Zinkorotat-POS; ***Ger.:*** magnerot Classic; Magnesorot; Power Orot; Zinkorot; ***Hung.:*** Magnerot; ***Rus.:*** Magnerot (Магнерот).

Multi-ingredient: ***Arg.:*** Bil 13; Zimerol; ***Austral.:*** Bioglan Bioage Peripheral; Mag-Oro; Magnesium Plus†; Potasi; ***Austria:*** Lemazol; ***Hong Kong:*** Hepatofalk; Lipochol; Tres Orix Forte; ***Mex.:*** Lipovitasi-Or; ***Philipp.:*** Godex; ***Port.:*** Oraica†; ***S.Afr.:*** Hepabionta; ***Spain:*** Hepadif; Hepato Fardi†; Tres Orix Forte†; ***Switz.:*** Kawaform†; Magnesium Complexe; Vigoran†; ***Thai.:*** Lipochol; ***UK:*** Sugar Bloc.

Orthodichlorobenzene

Ortodiclorobenceno. 1,2-Dichlorobenzene.

$C_6H_4Cl_2$ = 147.0.
CAS — 95-50-1.

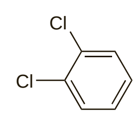

Profile

Orthodichlorobenzene has been used as an ingredient of solutions for dissolving ear wax. It has also been used as a wood and furniture preservative. Orthodichlorobenzene is an irritant volatile liquid; lens opacities have occurred.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Cerumol; ***Switz.:*** Cerumenol.

Oryzanol

Gamma Oryzanol; Orizanol; γ-Oryzanol; γ-OZ. Triacontanyl 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate.

$C_{40}H_{58}O_4$ = 602.9.
CAS — 11042-64-1.

Profile

Oryzanol is a substance extracted from rice bran oil and rice embryo bud oil. It has been given orally in the treatment of hyperlipidaemias. It has also been used for its supposed effects on autonomic and endocrine function.

◊ References.

1. Cicero AF, Gaddi A. Rice bran oil and gamma-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. *Phytother Res* 2001; **15:** 277–89.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Cosmodex Depigmenten†; ***Ital.:*** Anasterol; Lenirose†; Mavipiu†; ***Jpn:*** Q & P; Sin Q & P Gold; ***Singapore:*** Gin-Vita.

Osalmid *(rINN)*

L-1718; Osalmida; Osalmide; Osalmidum; Oxaphenamide. 4′-Hydroxysalicylanilide.

Осальмид

$C_{13}H_{11}NO_3$ = 229.2.

CAS — 526-18-1.

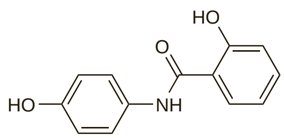

Profile

Osalmid has been used as a choleretic.

Otilonium Bromide *(BAN, rINN)*

Bromuro de otilonio; Octylonium Bromide; Otilonii Bromidum; Otilonium, Bromure d'; SP-63. Diethylmethyl{2-[4-(2-octyloxybenzamido)benzoyloxy]ethyl}ammonium bromide.

Отилония Бромид

$C_{29}H_{43}BrN_2O_4$ = 563.6.

CAS — 26095-59-0.

ATC — A03AB06.

ATC Vet — QA03AB06.

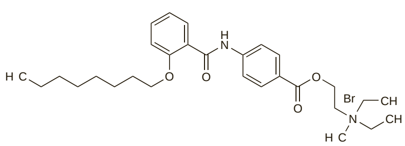

Profile

Otilonium bromide is used in the symptomatic treatment of gastrointestinal disorders associated with smooth muscle spasms in oral doses up to 120 mg daily. It has also been given rectally and by nebuliser.

◊ References.

1. Battaglia G, *et al.* Otilonium bromide in irritable bowel syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol Ther* 1998; **12:** 1003–10.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pasminox; Spasmoctyl; ***Belg.:*** Spasmomen; ***Braz.:*** Lonium; ***Cz.:*** Spasmomen; ***Gr.:*** Doralin; ***Hong Kong:*** Spasmomen; ***Hung.:*** Spasmomen; ***Indon.:*** Spasmomen; ***Ital.:*** Spasen; Spasmomen; ***Port.:*** Spasmomen; ***Spain:*** Spasmoctyl.

Multi-ingredient: ***Arg.:*** Pasminox Somatico; ***Ital.:*** Spasen Somatico; Spasmomen Somatico.

Oxaceprol *(rINN)*

Acetylhydroxyproline; C061; Oxacéprol; Oxaceprolum. (−)-1-Acetyl-4-hydroxy-L-proline.

Оксацепрол

$C_7H_{11}NO_4$ = 173.2.

CAS — 33996-33-7.

ATC — D11AX09; M01AX24.

ATC Vet — QD11AX09; QM01AX24.

Profile

Oxaceprol is reported to affect connective tissue metabolism and has been used in dermatology, to promote wound healing, and in rheumatic disorders. Adverse effects have included gastric pain, nausea, diarrhoea, dizziness, headache, and skin rashes.

◊ References.

1. Bauer HW, *et al.* Oxaceprol is as effective as diclofenac in the therapy of osteoarthritis of the knee and hip. *Clin Rheumatol* 1999; **18:** 4–9.
2. Herrmann G, *et al.* Oxaceprol is a well-tolerated therapy for osteoarthritis with efficacy equivalent to diclofenac. *Clin Rheumatol* 2000; **19:** 99–104.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Joint†; ***Fr.:*** Jonctum; ***Ger.:*** AHP 200; ***Spain:*** Tejuntivo.

Multi-ingredient: ***Spain:*** Robervital.

Oxalic Acid

Kwas szczawiowy; Oxálico, ácido.

$HO_2C.CO_2H,2H_2O$ = 126.1.

CAS — 144-62-7 (anhydrous oxalic acid); 6153-56-6 (oxalic acid dihydrate).

ATC Vet — QP53AG03.

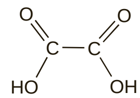

Adverse Effects

On ingestion, severe gastroenteritis is produced by the corrosive action of oxalic acid and its soluble salts on the gastrointestinal tract. Burning of the mouth, throat, and oesophagus with ulceration may also occur. Hypoxia may occur in the presence of laryngeal oedema, and shock and hypotension may arise in severe cases. Oxalates can chelate body calcium following systemic absorption, and may produce symptoms of hypocalcaemia such as tetany, convulsions, and, in some cases, ventricular fibrillation. Oxalate crystals may be deposited in the blood vessels, brain, heart, liver, and lungs; deposition in the renal tubules leads to acute renal failure. The mean fatal dose of oxalates has been reported to be about 15 to 30 g, although death has occurred with much lower doses. Death may occur within a few hours of ingestion.

◊ Fatalities have resulted from intravenous administration of sodium oxalate[1] or ingestion of oxalic acid.[2]

Crystals of calcium oxalate present in the sap of daffodils[3] or *Agave tequilana* plants[4] have been reported to contribute to the rash experienced by workers coming into contact with these plants.

1. Dvořáčková I. Tödliche Vergiftung nach intravenöser Verabreichung von Natriumoxalat. *Arch Toxikol* 1966; **22:** 63–7.
2. Farré M, *et al.* Fatal oxalic acid poisoning from sorrel soup. *Lancet* 1989; **ii:** 1524.
3. Julian CG, Bowers PW. The nature and distribution of daffodil pickers' rash. *Contact Dermatitis* 1997; **37:** 259–62.
4. Salinas ML, *et al.* Irritant contact dermatitis caused by needle-like calcium oxalate crystals, raphides, in Agave tequilana among workers in tequila distilleries and agave plantations. *Contact Dermatitis* 2001; **44:** 94–6.

Treatment of Adverse Effects

After ingestion of oxalic acid, a dilute solution of any soluble calcium salt should be given to precipitate the oxalate; alternatively milk may be given. Oral activated charcoal has also been suggested if ingestion has occurred within 1 hour. Gastric lavage is contra-indicated by some centres given the corrosive nature of oxalic acid. Calcium gluconate 10% should be given intravenously to prevent tetany. Acute renal failure should be anticipated in surviving patients and calls for careful fluid management. Haemodialysis or peritoneal dialysis have also been suggested for the removal of oxalate in primary oxalosis in an attempt to prevent acute renal failure and correct hypocalcaemia.

Uses

Oxalic acid has varied industrial uses and has been used in escharotic preparations. Oxalic acid salts have been given orally and the urinary excretion of oxalate used as a screening test for lipid malabsorption.

Diagnostic use. References.

1. Rampton DS, *et al.* Screening for steatorrhoea with an oxalate loading test. *BMJ* 1984; **288:** 1419. Correction. *ibid.*; 1728.
2. Sangaletti O, *et al.* Urinary oxalate recovery after oral oxalic acid load: an alternative method to the quantitative determination of stool fat for the diagnosis of lipid malabsorption. *J Int Med Res* 1989; **17:** 526–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Solcogyn†; ***Ger.:*** Solco-Derman; ***Hong Kong:*** Solcoderm; ***Malaysia:*** Solcoderm†; ***Pol.:*** Solcogyn; ***Rus.:*** Solcoderm (Солкодерм); Solcovagin (Солковагин); ***Switz.:*** Solcoderm; Solcogyn.

Ozagrel *(rINN)*

OKY-046 (ozagrel hydrochloride); Ozagrelum. (*E*)-*p*-(Imidazol-1-ylmethyl)cinnamic acid.

Озагрел

$C_{13}H_{12}N_2O_2$ = 228.2.

CAS — 82571-53-7.

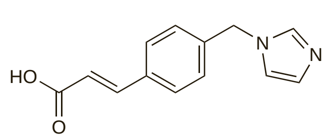

Profile

Ozagrel is a thromboxane synthetase inhibitor that has been given orally as the hydrochloride for the treatment of asthma in doses of 200 mg twice daily. It has also been given as the sodium salt by intravenous infusion for the treatment of cerebrovascular disorders in a dose of 80 mg.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Cataclot; Domenan; Xanbon.

Palifermin *(USAN, rINN)*

AMJ-9701; Palifermina; Palifermine; Paliferminum; rHu-KGF. 24-163 Fibroblast growth factor 7 (human).

Палифермин

CAS — 162394-19-6; 178254-26-7.

ATC — V03AF08.

ATC Vet — QV03AF08.

Adverse Effects

Adverse reactions reported with palifermin therapy have included rash, erythema, oedema, pruritus, perioral dysaesthesia, tongue discoloration and thickening, and altered taste. Fever, and gastrointestinal and respiratory disturbances have also been reported. The safety and efficacy of palifermin in patients given treatment for non-haematological neoplasms has not been established; stimulation and growth of tumour cell lines have been found in *animal* and *in-vitro* models of non-haematopoietic human tumours.

Pharmacokinetics

The pharmacokinetics of palifermin were approximately dose-linear after a single intravenous dose in healthy subjects given larger than usual doses. The terminal elimination half-life is about 4.5 hours.

◊ References.

1. Zia-Amirhosseini P, *et al.* Pharmacokinetics, pharmacodynamics, and safety assessment of palifermin (rHuKGF) in healthy volunteers. *Clin Pharmacol Ther* 2006; **79:** 558–69.
2. Gillespie B, *et al.* Effect of renal function on the pharmacokinetics of palifermin. *J Clin Pharmacol* 2006; **46:** 1460–8.

Uses and Administration

Palifermin is a human recombinant keratinocyte growth factor (KGF) used to reduce the incidence and duration of severe oral mucositis (p.640) in patients with haematological neoplasms who receive myelotoxic chemotherapy, with or without radiotherapy, followed by haematopoietic stem cell transplantation. The recommended course of palifermin is 6 doses of 60 micrograms/kg, by intravenous bolus injection. A dose is given on each of 3 consecutive days before, and 3 consecutive days after, myelotoxic therapy. Palifermin should not be given during, or for 24 hours before or after, myelotoxic therapy. Thus, the third pre-chemotherapy dose of palifermin should be given 24 to 48 hours before myelotoxic therapy, and the first post-chemotherapy dose of palifermin should be given after, but on the same day as, the haematopoietic stem cell infusion, and at least 4 days after the third pre-myelotoxic dose.

Mucositis. Palifermin is a human recombinant keratinocyte growth factor (KGF) that binds to KGF receptors and repairs damaged epithelium by stimulating the proliferation, differentiation, and migration of epithelial cells.[1,2] Controlled studies have shown it to be effective in reducing the severity and duration of oral mucositis (p.640) in patients receiving myelotoxic therapy for haematological neoplasms and requiring haematopoietic stem cell support.[3,4] It has also shown benefit compared with placebo in reducing the incidence of oral mucositis and diarrhoea in patients receiving fluorouracil and leucovorin for metastatic colorectal cancer.[5]

1. Siddiqui MAA, Wellington K. Palifermin: in myelotoxic therapy-induced oral mucositis. *Drugs* 2005; **65:** 2139–46.
2. McDonnell AM, Lenz KL. Palifermin: role in the prevention of chemotherapy- and radiation-induced mucositis. *Ann Pharmacother* 2007; **41:** 86–94.
3. Spielberger R, *et al.* Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; **351:** 2590–8.
4. Stiff PJ, *et al.* Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *J Clin Oncol* 2006; **24:** 5186–93.
5. Rosen LS, *et al.* Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *J Clin Oncol* 2006; **24:** 5194–5200.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Kepivance; ***Cz.:*** Kepivance; ***Fin.:*** Kepivance; ***Fr.:*** Kepivance; ***Gr.:*** Kepivance; ***Hung.:*** Kepivance; ***Irl.:*** Kepivance; ***Neth.:*** Kepivance; ***Pol.:*** Kepivance; ***Port.:*** Kepivance; ***Swed.:*** Kepivance; ***UK:*** Kepivance; ***USA:*** Kepivance.

Palmarosa

Profile

Palmarosa (*Cymbopogon martini*, Poaceae) is a source of palmarosa oil (Indian geranium oil, Turkish geranium oil). Palmarosa oil is used in perfumery and in aromatherapy.

Palmidrol *(rINN)*

Palmidrolum. *N*-(2-Hydroxyethyl)palmitamide.

Пальмидрол

$C_{18}H_{37}NO_2$ = 299.5.

CAS — 544-31-0.

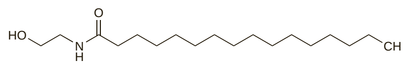

Profile

Palmidrol is a naturally occurring lipid compound that may be isolated from soybean lecithin, egg-yolk, or peanut meal. It has been used as an immunostimulant. It is given orally in doses of 1 g two or three times daily for the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Palmitan†.

Pancreatic Enzymes

Pancreatin *(BAN)*

Haimajauhe (pancreas powder); Kasos milteliai (pancreas powder); Pancréas, poudre de (pancreas powder); Pancreatina; Pancreatinum; Pancreatis pulvis (pancreas powder); Pankreaspulver (pancreas powder); Pankreatiini; Pankreatin; Pankreáz-por (pancreas powder).

CAS — 8049-47-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US* as pancreatin or another pancreatic exocrine extract or both.

Ph. Eur. 6.2 (Pancreas Powder; Pancreatis Pulvis; Pancreatic Extract BP 2008). It is prepared from the fresh or frozen pancreases of mammals. It contains various enzymes having proteolytic, lipolytic, and amylolytic activities. Each mg of pancreas powder contains not less than 1 Ph. Eur. unit of total proteolytic activity, not less than 15 Ph. Eur. units of lipolytic activity, and not less than 12 Ph. Eur. units of amylolytic activity. A slightly brown, amorphous powder. Partly soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP 2008 (Pancreatin). A preparation of mammalian pancreas containing enzymes having protease, lipase, and amylase activity. Each mg of pancreatin contains not less than 1.4 FIP units of free protease activity, not less than 20 FIP units of lipase activity, and not less than 24 FIP units of amylase activity. It may contain sodium chloride. A white or buff amorphous powder, free from unpleasant odour. Soluble or partly soluble in water forming a slightly turbid solution; practically insoluble in alcohol and in ether. Store at a temperature not exceeding 15°.

USP 31 (Pancreatin). A substance containing enzymes, principally amylase, lipase, and protease, obtained from the pancreas of the hog or of the ox. It is a cream-coloured, amorphous powder, having a faint, characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancreatin contains, in each mg, not less than 25 USP units of amylase activity, not less than 2 USP units of lipase activity, and not less than 25 USP units of protease activity. Pancreatin of a higher digestive power may be labelled as a whole-number multiple of the 3 minimum activities, or may be diluted with lactose, or with sucrose containing not more than 3.25% of starch, or with pancreatin of lower digestive power. Store in airtight containers at a temperature not exceeding 30°.

Pancrelipase *(USAN)*

Pancrelipasa.

CAS — 53608-75-6.

Pharmacopoeias. In *US.*

USP 31 (Pancrelipase). A substance containing enzymes, principally lipase, with amylase and protease, obtained from the pancreas of the hog. It is a cream-coloured, amorphous powder having a faint characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action. Pancrelipase contains, in each mg, not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity. Store in airtight containers preferably at a temperature not exceeding 25°.

Units

The Ph. Eur. and USP units of protease activity depend upon the rate of hydrolysis of casein, those of lipase activity depend upon the rate of hydrolysis of olive oil, and those of amylase activity depend upon the rate of hydrolysis of starch. Because of differences in the assay conditions, the Ph. Eur. and USP units are not readily comparable.

FIP units of protease, lipase, and amylase activity are approximately equivalent to Ph. Eur. units.

Adverse Effects and Precautions

Pancreatic enzyme supplements commonly cause gastrointestinal adverse effects such as abdominal discomfort and nausea and vomiting. They may also cause buccal and perianal irritation, particularly in infants. Colonic strictures (fibrosing colonopathy) have occurred, mainly in children with cystic fibrosis receiving high doses of pancreatin preparations; the use of high doses in patients with cystic fibrosis should preferably be avoided (see Effects on the Gastrointestinal Tract, below). Adequate hydration should be maintained at all times in patients receiving higher strength preparations.

Hypersensitivity reactions have been reported; these may be sneezing, lachrymation, or skin rashes. Hyperuricaemia or hyperuricosuria have occurred with high doses. There have been occasional reports of the contamination of pancreatin preparations with *Salmonella* spp.

Effects on folic acid. Pancreatic extract significantly inhibited folate absorption in healthy subjects and in pancreatic insufficient patients.[1] Testing *in vitro* showed that pancreatic extract formed insoluble complexes with folate. It was suggested[1] that patients being treated for pancreatic insufficiency should be monitored for folate status or given folic acid supplementation, particularly if pancreatic enzymes and bicarbonate (or cimetidine) were being used together in the treatment regimen.

1. Russell RM, *et al.* Impairment of folic acid absorption by oral pancreatic extracts. *Dig Dis Sci* 1980; **25:** 369–73.

Effects on the gastrointestinal tract. *FIBROSING COLONOPATHY.* After the introduction of high-strength pancreatic enzyme preparations, there were a number of reports[1-6] of colonic strictures in children with cystic fibrosis who received these formulations, and the problem, now dubbed fibrosing colonopathy, was reviewed.[7,8] Fibrosing colonopathy has also been reported[9] in an adult who was not thought to have cystic fibrosis, but who had been taking high doses of pancreatic enzyme supplements, including 2 with methylacrylic acid copolymer (MAC) coatings, for 5 years after surgical removal of the pancreas.

The pathogenesis and aetiology of this condition still remain unclear. Dose-related thickening of the colon wall has been described,[10] and an inflammatory or immune-mediated mechanism has been suggested.[11,12] It has also been suggested that the type of preparation used may have a role. An analysis[13] of cases of fibrosing colonopathy occurring in the UK between 1984 and 1994 demonstrated that there was a dose-related association between the high-strength preparations and this adverse effect although there was some criticism and debate surrounding the methodology of this particular analysis.[14-16] A subsequent case-control study[17] of patients in the US presenting between 1990 and 1994 concluded that there was a strong association between high daily doses of pancreatic enzymes, in any form, and the development of fibrosing colonopathy; no significant differences were observed between the various high- and low-strength preparations used. Re-analysis[18] of the UK data found a highly statistically significant association with the intake of preparations using MAC for enteric coating, but no evidence that a high intake of lipase in the absence of MAC was a risk factor for the disease. However, at least one case has been reported with a preparation that did not contain this material.[19]

As a result of these problems, high-strength preparations were withdrawn in the USA, while in the UK, the CSM recommended[20] that unless special reasons exist, patients with cystic fibrosis should not use high-strength pancreatin preparations, and that all patients treated with these products should be monitored carefully for gastrointestinal obstruction. The CSM later elaborated on these recommendations:[21] they advised that *Nutrizym 22, Pancrease HL,* and *Panzytrat 25 000* [now discontinued in the UK] should not be used in children with cystic fibrosis who were aged 15 years or less; that the total daily dose of pancreatic enzyme supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg; and that patients on any pancreatin preparation should be reviewed to exclude colonic damage if new abdominal symptoms or a change in symptoms occurred. Other risk factors identified were male sex, more severe cystic fibrosis, and the concomitant use of laxatives.[21] The US Cystic Fibrosis Foundation has made recommendations for the management of patients who do not respond adequately to moderate doses of pancreatic enzymes,[22] and similar recommendations have been made in the UK.[23]

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3. Campbell CA, *et al.* High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis. *Lancet* 1994; **343:** 109–110.
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6. Pettei MJ, *et al.* Pancolonic disease in cystic fibrosis and high-dose pancreatic enzyme therapy. *J Pediatr* 1994; **125:** 587–9.
7. Taylor CJ. Colonic strictures in cystic fibrosis. *Lancet* 1994; **343:** 615–16. Correction. *ibid.*; 1108.
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9. Bansi DS, *et al.* Fibrosing colonopathy in an adult owing to over use of pancreatic enzyme supplements. *Gut* 2000; **46:** 283–5.
10. MacSweeney EJ, *et al.* Relationship of thickening of colon wall to pancreatic-enzyme treatment in cystic fibrosis. *Lancet* 1995; **345:** 752–6.
11. Croft NM, *et al.* Gut inflammation in children with cystic fibrosis on high-dose enzyme supplements. *Lancet* 1995; **346:** 1265–7.
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21. Committee on Safety of Medicines/Medicines Control Agency. Fibrosing colonopathy associated with pancreatic enzymes. *Current Problems* 1995; **21:** 11. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023217 (accessed 06/08/08)
22. Borowitz DS, *et al.* Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995; **127:** 681–4.
23. Littlewood JM. Fibrosing colonopathy in cystic fibrosis: commentary, implications of the Committee on Safety of Medicines 10 000 IU lipase/kg/day recommendation for use of pancreatic enzymes in cystic fibrosis. *Arch Dis Child* 1996; **74:** 466–8.

MOUTH ULCERATION. In 3 children taking preparations of pancreatic extracts (*Pancrex V powder, Pancrex V Forte*), severe mouth ulceration and angular stomatitis, causing dysphagia, loss of weight, and pyrexia, were attributed to digestion of the mucous membrane due to retention of the preparations in the mouth before swallowing.[1]

1. Darby CW. Pancreatic extracts. *BMJ* 1970; **2:** 299–300.

Hypersensitivity. A successful desensitisation regimen has been described[1] for a child with cystic fibrosis who vomited within 1 to 2 hours after ingestion of pancreatic enzymes, suggestive of a type I hypersensitivity reaction.

1. Chamarthy LM, *et al.* Desensitization to pancreatic enzyme intolerance in a child with cystic fibrosis. Abstract: *Pediatrics* 1998; **102:** 134–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/102/1/e13.pdf (accessed 14/07/06)

Uses and Administration

Pancreatic enzymes (as pancreatin or pancrelipase) hydrolyse fats to glycerol and fatty acids, break down protein into peptides, proteoses and derived substances, and convert starch into dextrins and sugars. They are given by mouth in conditions of pancreatic exocrine deficiency such as pancreatitis and cystic fibrosis. They are available in the form of powder, capsules containing powder or enteric-coated granules (which may be opened before use and the contents sprinkled on soft food), enteric-coated tablets, or granules. If pancreatic enzymes are mixed with liquids or food the resulting mixture should not be allowed to stand for more than 1 hour before use. Histamine H_2-receptor antagonists, such as cimetidine or ranitidine, have been given an hour before a dose in an attempt to lessen destruction of the pancreatic enzymes by gastric acid, or proton pump inhibitors such as omeprazole may be used; alternatively, antacids may be given with the dose.

The dose of pancreatic enzymes is adjusted according to the needs of the individual patient and will also depend on the dosage form. In the UK, proprietary preparations generally provide about 5 000 to 10 000 units of lipase activity per dose-unit and usual doses, given with each meal, range from about 5 000 to 56 000 units of lipase activity (with varying proportions of protease and amylase activity, depending on the preparation). In the USA, doses providing up to 40 000 USP units of lipase activity may be given with each meal. So-called high-strength or high-potency preparations are available for those receiving high doses, and typically contain about 20 000 to 40 000 units of lipase activity per dose unit, but their use has been associated with the development of fibrosing colonopathy in children with cystic fibrosis (see Effects on the Gastrointestinal Tract, above). Such preparations are consequently not recommended for children in the UK and authorities there consider the total daily dose of pancreatic supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg.

Purified lipase preparations have also been used. A recombinant human bile-salt stimulated lipase is under investigation for the treatment of fat malabsorption in patients with exocrine pancreatic insufficiency and cystic fibrosis.

Pancreatin is also used to remove protein deposits from the surface of soft contact lenses (p.1622).

Cystic fibrosis. Patients with cystic fibrosis (p.166) suffer from pancreatic insufficiency and consequent malabsorption. Pancreatin or pancrelipase may therefore play a role in the management of the disorder, being taken before or with each meal or snack.

Generic substitution. Three patients with cystic fibrosis whose gastrointestinal symptoms had been well controlled with pancrelipase developed symptoms after substitution of generic pancrelipase for their previous brand.[1] The generic product had a different lipase content and was almost inactive at stomach pH *in vitro*, apparently because of a defective enteric coating. Different brands of pancrelipase may not be therapeutically equivalent and should not be routinely substituted.

1. Hendeles L, *et al.* Treatment failure after substitution of generic pancrelipase capsules: correlation with in vitro lipase activity. *JAMA* 1990; **263:** 2459–61.

Pancreatitis. Pancreatitis is an inflammatory process affecting the pancreas. Acute pancreatitis comprises necrosis of pancreatic tissue occurring in an otherwise healthy gland, whereas chronic pancreatitis is the manifestation of pathological processes resulting in inflammation and progressive fibrosis of pancreatic tissue. Acute disease may be superimposed on a background of chronic pancreatitis.

Acute pancreatitis is frequently associated with either biliary-tract disorders (such as gallstones or cholecystitis) or the intake of large amounts of alcohol, or less frequently with abdominal surgery, pancreatic trauma, hyperparathyroidism, hyperlipidaemia, infection, or the adverse effects of drugs. Endoscopic retrograde cholangiopancreatography (ERCP) is followed by acute pancreatitis in anywhere between 3 and 40% of patients,[1] although it may also be used successfully to treat acute pancreatitis associated with gallstones.[2]

Symptoms of acute pancreatitis include pain, which ranges from mild to extremely severe and which typically persists for several days, nausea and vomiting, ileus, and hypovolaemic shock. In severe disease, pulmonary, renal, and hepatic failure, encephalopathy, and death may ensue. A mortality rate of about 10% has been reported.

The management of acute disease is essentially supportive.[1,3-8] Adequate analgesia for pain is important (see Pancreatic Pain, p.9); in mild cases, analgesia, adequate hydration, and temporary interruption of oral intake of food to 'rest' the pancreas may be adequate. In more severe disease enteral or parenteral nutrition may be needed,[1,7] although some[5,6,8] advocate enteral over parenteral nutrition because of potential complications with the latter. Since most patients suffer from hypoxaemia it has been recommended that they should receive additional humidified oxygen by mask, with mechanical ventilation if blood gases indicate the development of severe pulmonary failure. Shock should be managed with blood or plasma, and electrolyte solutions, while insulin may be required for disturbances of glucose homoeostasis.

The value of other interventions is mostly doubtful. As an extension of the concept of 'pancreatic rest', inhibitors of pancreatic secretion including somatostatin or octreotide have been tried but without significant effect, while protease inhibitors such as aprotinin or gabexate mesilate have also proven disappointing,[3] perhaps because activation of pancreatic proteases (thought to play a significant role in pathogenesis) has already taken place by the time therapy is begun.[3] A meta-analysis[9] of studies using aprotinin or gabexate mesilate suggested that these might reduce mortality in moderate to severe acute pancreatitis. However, this conclusion has been criticised[10] based on weaknesses in the original studies and the criteria used for severity grading. Gabexate and somatostatin may have roles in the prevention of acute pancreatitis after ERCP,[11] but it remains difficult to identify which patients should be offered prophylaxis, since not all will develop the condition.[1,3] Furthermore, it has been suggested[12] that with improved techniques, the use of prolonged infusions of pharmacological prophylaxis against severe pancreatitis after ERCP may no longer be justified. Preliminary studies of the platelet-activating factor antagonist lexipafant for treatment of pancreatitis were initially promising but were not supported by subsequent larger studies.[4]

Although prophylactic antibacterials are often given, there has been some uncertainty about their value (see p.183). In a review[13] of the treatment of acute necrotising pancreatitis, it was pointed out that early studies that failed to show any benefit of prophylactic antibacterials had also included patients with interstitial oedematous acute pancreatitis. The authors emphasised that the prevention of infection is critical in acute necrotising pancreatitis, since the development of infected necrosis substantially increases mortality, and concluded that use of antibacterials is the mainstay of management in such patients. Some[6] do not recommend antibacterial prophylaxis in patients with necrotising pancreatitis; for others,[8] accepted treatment is to start intravenous imipenem or meropenem for 14 days when infection is suspected but to stop it rapidly if not confirmed, although this view was challenged.[14] A systematic review[15] found that antibacterial prophylaxis appeared to be associated with significantly decreased mortality in patients with pancreatic necrosis but there was no significant reduction in the rates of infected pancreatic necrosis. It is also possible that beta lactams might be preferable to quinolone plus imidazole regimens, although no firm conclusions could be drawn because of small sample size. Further better designed studies are needed to support antibacterial prophylaxis and, should these prove beneficial, to compare beta lactams with quinolones directly.

The role of surgery continues to be somewhat controversial; it is accepted for complications or when a potential surgical emergency exists.[1,3,5-8] Surgery to remove the gallbladder is usually delayed in severe episodes of acute, gallstone-related pancreatitis to allow resolution of the inflammatory process and improvement in the patient's nutritional state.[1] Early ERCP to clear an obstructed bile duct may reduce complications in patients with predicted severe pancreatitis, but does not reduce mortality.[2]

Chronic pancreatitis is frequently associated with high alcohol-intake although a tropical form,[1] associated with malnutrition, also exists, and some cases are idiopathic[16] or auto-immune.[17] Symptoms include recurrent episodes of pain (often less excruciating and of shorter duration than in acute pancreatitis) which normally become less severe and frequent over the years with the inexorable progression of fibrosis. Loss of exocrine tissue eventually leads in many patients to pancreatic exocrine insufficiency, with maldigestion and steatorrhoea, and in some to diabetes mellitus due to islet cell loss. Other symptoms may include cholestatic jaundice, fatty degeneration of the liver, stenosis of the bile duct, and hepatic cirrhosis (although this may also be due to alcohol intake). It has been estimated that more than 50% of patients die within 20 years of diagnosis, with those who continue to drink alcohol being at greatest risk. In some patients, chronic pancreatitis is a premalignant disorder.[1]

Adequate analgesia with opioids is essential (see Pancreatic Pain, p.9). Nerve blocks of the coeliac plexus with phenol or alcohol have generally proved disappointing, although coeliac plexus blocks using corticosteroids and local anaesthetic may be effective.[1] However, response to nerve ablation procedures is often limited and of short duration.[16] Patients should be advised to abstain from alcohol, which can exacerbate the frequency and severity of painful episodes.[1] A low-fat diet is also recommended, or for patients who cannot tolerate oral intake, parenteral or enteral nutrition.[16] Steatorrhoea requires replacement of pancreatic enzymes with preparations of pancreatin or pancrelipase. Because the enzymes are inactivated by gastric acid they may be taken after inhibitors of acid secretion[1] or with a sodium-containing antacid such as sodium bicarbonate (magnesium-, calcium-, and possibly aluminium-containing antacids may further interfere with fat absorption). Alternatively, enteric-coated enzyme preparations may be used.[16] In some patients with mild disease pancreatic enzyme replacement may also improve pain, although for this purpose only non-enteric coated preparations are effective.[16] Supplements of fat-soluble vitamins are not normally necessary, but may be given intravenously if required. Diabetes should be managed appropriately once steatorrhoea is under control.

Surgery, up to and including total pancreatectomy, has an important role in the relief of intractable pain, and may also be necessary for the management of complications.[1,16] Endoscopic decompression using contrast media containing prednisolone and ulinastatin has been reported to produce beneficial responses.[18] Anecdotal results suggest that some patients with pancreatic pseudocysts, which usually require surgical drainage, may respond to octreotide.[19]

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Preparations

BP 2008: Gastro-resistant Pancreatin Tablets; Pancreatin Granules;
USP 31: Pancreatin Tablets; Pancrelipase Capsules; Pancrelipase Delayed-release Capsules; Pancrelipase Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Creon; Pancrecura†; Pankreozym; Prolipase; ***Austral.:*** Bioglan Panazyme; Cotazym S Forte; Creon; Opti-Free Enzymatic†; Opti-Plus†; Pancrease; Panzytrat; Polyzym†; ***Austria:*** Kreon; Pancrin; Pankreon forte; Panzynorm; ***Belg.:*** Creon; Pancrease†; ***Braz.:*** Cotazym; Creon; Opti-Free Enzimatica†; Opti-Free Supraclens; Pancrease; Panzytrat; Polyzym; ***Canad.:*** Cotazym; Creon; Opti-Zyme†; Pancrease; Ultrase; Viokase; ***Chile:*** Creon; ***Cz.:*** Gastrix; Kreon; Pancreolan; Pangrol; Panzynorm; Panzytrat; ***Denm.:*** Creon; Pancrease; Pankreon†; ***Fin.:*** Creon; Pancrease; Pankreon†; ***Fr.:*** Creon; Licrease†; Polyzym†; ***Ger.:*** Bilipeptal Mono; Carzodelan†; Cholspasminase N; Cotazym; Euflat-E†; Fermento duodenal; Hevertozym†; Kreon; Lipazym; Meteophyt forte†; Mezym F; Nutrizym N†; Ozym; Pangrol; Pankreatan; Pankreon; Panpeptal N; Panpur; Panzynorm forte-N; Panzytrat; Tryptoferm†; Unexym mono; ***Gr.:*** Creon; Pancrease; Panzytrat; ***Hong Kong:*** Creon; ***Hung.:*** Kreon; Mezym Forte; Neo-Panpur; Pangrol; Panzytrat; ***India:*** Biopank†; Festal N; Panstal N; Panzynorm-N; ***Irl.:*** Creon; Nutrizym; Pancrease†; Pancrex†; ***Israel:*** Creon; Pancrease; ***Ital.:*** Creon; Enzipan; Krebsilasi†; Luitase†; Pancrease; Pancrex; ***Malaysia:*** Creon; ***Mex.:*** Creon; Kenyna; Opti-Free; Opti-Free Supra Clens; Pancrease; Selecto†; Trepetan; ***Neth.:*** Cotazym-S†; Creon; Pancrease; Pancrease HL; Panzytrat; ***Norw.:*** Creon; Pancrease; Pankreon†; ***NZ:*** Cotazym; Creon; Pancrease; Pancrex; Panzytrat; ***Philipp.:*** Creon; ***Pol.:*** Kreon; Lipancrea; Neo-Pancreatinum; Panzytrat; ***Port.:*** Kreon; ***Rus.:*** Enzystal (Энзистал); Festal (Фестал); Kreon (Креон); Mezym Forte (Мезим Форте); Mikrazym (Микразим); Normoenzym Forte (Нормоэнзим Форте); Panzynorm (Панзинорм); Panzytrat (Панцитрат)†; Penzital (Пензитал); ***S.Afr.:*** Creon; Pankrease; Polyzym; Viokase; ***Singapore:*** Creon; Norzyme; ***Spain:*** Kreon; Pancrease; Papine; ***Swed.:*** Creon; Pancrease; Pankreon†; ***Switz.:*** Creon; Panzytrat; Prolipase†; ***Thai.:*** Creon; ***Turk.:*** Festal N; Kreon; ***UK:*** Clen-Zym; Creon; Nutrizym; Pancrease HL; Pancrease†; Pancrex; ***USA:*** Creon; Dygase; Enzymatic Cleaner; Ku-Zyme HP; Lapase; Lipram; Opti-Zyme; Palcaps; PAN-2400; Pancrease; Pancrecarb; Panocaps; Ultrase; Viokase; Vision Care Enzymatic Cleaner; ***Venez.:*** Orozim; Pancrease†; Pankreon.

Multi-ingredient: ***Arg.:*** Arnol; Bibol Leloup; Bil 13 Enzimatico; Biletan Enzimatico; Biluen Enzimatico; Carbogasol Digestivo; Digenorflat; Digesplen; Dom-Polienzim; Facilgest†; Faradil Enzimatico; Gastridin-E; Gastrimet Enzimatico†; Gastron Fuerte†; Hepadigenor†; Homocisteon Compuesto; Moperidona Enzimatica; Mosar Enzimatico; Novodig†; Pakinase; Pankreoflat; Pankreoflat Sedante†; Pankreon Compuesto†; Pankreon Total; Polienzim; Praxis; Pulsar Enzimatico†; Tridigestivo Soubeiran; ***Austral.:*** Digestaid; Enzyme; Lexat†; Prozyme†; ***Austria:*** Arca-Enzym; Combizym; Combizym Compositum; Enzyflat†; Gingivan; Helopanflat; Helopanzym; Intestinol; Ora-Gallin; Pankreoflat; Paspertase; Rennie Digestif; Wobenzym; ***Belg.:*** Digestomen; ***Braz.:*** Azime†; Combizym Composto†; Dasc; Digecap-Zimatico; Digeplus; Elozima†; Enziprid†; Essen; Filogaster†; Hepatoregius†; Nutrizim†; Pankreoflat; Peptopancreasi; Plasil Enzimatico; Primeral; Sintozima; ***Canad.:*** Digesta; ***Chile:*** Combizym Compositum; Digenil; Flapex E; Hepabil; Neopankreoflat; Nutrizima; Onoton†; ***Cz.:*** Combizym Compositum; Digestif Rennie; Wobenzym; ***Fin.:*** Combizym; Combizym Compositum; ***Ger.:*** Arbuz†; Chol-Arbuz NF; Combizym Compositum†; Combizym†; Enzym-Lefax; Enzym-Wied†; Meteozym; Pankreoflat; Pascopankreat; Paspertase†; Unexym MD S; Ventracid N; Wobenzym N; ***Hong Kong:*** Combizym; Digezym; Pankreoflat†; Topase†; ***Hung.:*** Combizym Compositum†; Combizym†; Digestif Rennie; Dipankrin; Pankreoflat; ***India:*** Biohep†; Digeplex-T; Dipep; Dispeptal†; Farizym; Hepa-Merz; Ipental†; Merckenzyme; Pankreoflat; Panolase†; Papytazyme; ***Indon.:*** Benozym; Berzymplex; Cotazym Forte; Elsazym; Enzymfort; Excelase-E; Librozym; Librozym Plus; Nutriflam; Pankreoflat; Pankreon Comp; Pankreon for Children; Primperan Compositum; Tripanzym; Vitazym; Xepazym; ***Israel:*** Encypalmed; Pankreoflat; ***Ital.:*** Combizym†; Digestopan†; Ede 6†; Essen Enzimatico†; Eudigestio†; Pancreoflat†; Pancresil†; Pepto-Pancreasi†; ***Malaysia:*** Biotase; ***Mex.:*** Difarben; Dirfaben†; Dixiflen; Espaven Enzimatico; Ochozim; Onoton; Pankreoflat; Plasil Enzimatico; Selecto-D†; Wobenzym; Zimeton; Zimotris; ***Neth.:*** Combizym; ***Norw.:*** Combizym; ***NZ:*** Combizym†; ***Philipp.:*** Pankreoflat; Spasmo-Canulase; ***Pol.:*** Combizym; Hepa-Merz; ***Port.:*** Colerin-F; Combizym; Combizym Compositum†; Espasmo Canulase; Fermetone Composto; Helopanflat; Pankreoflat; ***Rus.:*** Ipental (Ипентал); Pankreoflat (Панкреофлат); Wobenzym (Вобэнзим); ***S.Afr.:*** Pankreoflat; Spasmo-Canulase; ***Singapore:*** Biotase; ***Spain:*** Digestomen Complex; Nulacin Fermentos; Pankreoflat; Wobenzimal†; ***Swed.:*** Combizym; Combizym Compositum; ***Switz.:*** Combizym; Combizym Compositum; Fermento duodenal†; Helopanflat†; Spasmo-Canulase; ***Thai.:*** Combizym; Combizym Compositum; Enzymet; Gaszym; Papytazyme†; Pepsitase; Polyenzyme-I; Polyenzyme-N; Proctase-P; Sanzyme-S†; ***Turk.:*** Flaton; Hazmolin; Intestinol; Multanzim; Pankreoflat; Pankrodigest; ***UK:*** Enzyme Digest; Enzyme Plus; ***USA:*** Digepepsin; Hi-Vegi-Lip; Pangestyme; ***Venez.:*** Combizym Forte; Nutizym Compositum; Pankreon Compositum; Pankreosil; Stamyl; Wobenzym N.

Pancreozymin *(BAN)*

CCK-PZ; Pancreocimina; Pankreotsymiini; Pankreozymin.

ATC — V04CK02.

ATC Vet — QV04CK02.

NOTE. The endogenous hormone is known as cholecystokinin (CCK).

Units

The potency of pancreozymin may be expressed as Crick-Harper-Raper units based on the pancreatic secretion in *cats* or as Ivy *dog* units based on the increase in gallbladder pressure. One Ivy dog unit is considered to be approximately equivalent to 1 Crick-Harper-Raper unit.

Profile

Pancreozymin is a polypeptide hormone prepared from the duodenal mucosa of *pigs*. When given by intravenous injection it causes an increase in the secretion of pancreatic enzymes and stimulates gallbladder contraction.

Pancreozymin has been used, usually with secretin, as a test for exocrine pancreatic function and in the diagnosis of biliary-tract disorders; these tests generally involved duodenal intubation of the patient and examination of duodenal aspirate. Pancreozymin has also been used as an adjunct to cholecystography. Vasomotor reactions, abdominal discomfort, and hypersensitivity have been reported.

Biliary-tract disorders. It was concluded that cholecystokinin provocation testing was ineffective in predicting which patients with acalculous biliary pain would receive symptomatic relief from cholecystectomy in a study involving 58 patients.[1]

1. Smythe A, *et al*. A requiem for the cholecystokinin provocation test? *Gut* 1998; **43:** 571–4.

Pangamic Acid

Pangámico, ácido.

Profile

The name pangamic acid has been applied variously to gluconic acid 6-[bis(diisopropylamino)acetate] ($C_{20}H_{40}N_2O_8$ = 436.5), gluconic acid, 6-ester with N,N-dimethylglycine ($C_{10}H_{19}NO_8$ = 281.3), gluconic acid, 6-ester with N,N-diisopropylglycine ($C_{14}H_{27}NO_8$ = 337.4), and a substance or mixture of substances isolated from apricot kernels and rice bran. It has also been known as 'vitamin B_{15}' although there is no evidence that pangamic acid is a vitamin. Preparations containing the vasoactive substance di-isopropylammonium dichloroacetate (p.1265) have sometimes been described as pangamic acid or 'vitamin B_{15}'. There is much uncertainty about the identity of products sold in health food stores as 'vitamin B_{15}', pangamic acid, or sodium or calcium pangamate and different brands have been reported to have completely different compositions.

Claims for the activity of pangamic acid as a promotor of tissue oxygenation and its alleged value in numerous disorders have not been substantiated.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: B15†; ***Ger.:*** Oyo†; ***Port.:*** Desfatigan; Pulsor.

Multi-ingredient: ***Mex.:*** B1-12-15; ***Spain:*** Policolinosil.

Panthenol *(BAN, USAN, rINN)*

Pantenol; Panthénol; *dl*-Panthenol; Panthenolum; (±)-Pantothenyl Alcohol.

Пантенол

$C_9H_{19}NO_4$ = 205.3.
CAS — 16485-10-2.

Pharmacopoeias. In *US.*

USP 31 (Panthenol). A racemic mixture of the dextrorotatory and laevorotatory isomers of panthenol. A white to creamy white, crystalline powder with a slight, characteristic odour. Freely soluble in water, in alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Dexpanthenol *(BAN, USAN, rINN)*

Dekspantenoli; Dekspantenolis; Dexpantenol; Dexpanthénol; Dexpanthenolum; Dextro-Pantothenyl Alcohol; Pantothenol; Provitamin B_5. (*R*)-2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutyramide.

Декспантенол

$C_9H_{19}NO_4$ = 205.3.
CAS — 81-13-0.
ATC — A11HA30; D03AX03; S01XA12.
ATC Vet — QA11HA30; QD03AX03; QS01XA12.

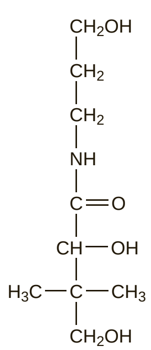

Pharmacopoeias. In *Eur.* (see p.vii), *US*, and *Viet.*

Ph. Eur. 6.2 (Dexpanthenol). A colourless or slightly yellowish, hygroscopic, viscous liquid, or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH not greater than 10.5. Store in airtight containers.

USP 31 (Dexpanthenol). A clear, viscous, somewhat hygroscopic liquid, having a slight characteristic odour. Some crystallisation may occur on standing. Freely soluble in water, in alcohol, in methyl alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Adverse Effects and Precautions

There have been a few reports of allergic reactions possibly associated with dexpanthenol. Dexpanthenol is contra-indicated in haemophiliacs and in patients with ileus due to mechanical obstruction.

Uses and Administration

Dexpanthenol is the alcoholic analogue of D-pantothenic acid (p.1959). It has been given intramuscularly in doses of 250 to 500 mg to prevent or control gastrointestinal atony but its value has not been established. It has also been given by slow intravenous infusion.

Dexpanthenol and the racemate panthenol have been used topically in strengths of 2 or 5% for the treatment of various minor skin disorders. They are also included in some vitamin preparations.

◊ References.

1. Kehrl W, Sonnemann U. Verbesserung der Wundheilung nach Nasenoperationen durch kombinierte Anwendung von Xylometazolin und Dexpanthenol. *Laryngorhinootologie* 2000; **79:** 151–4.
2. Gehring W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration: results of a human in vivo study. *Arzneimittelforschung* 2000; **50:** 659–63.
3. Ebner F, *et al*. Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol* 2002; **3:** 427–33.
4. Biro K, *et al*. Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. *Contact Dermatitis* 2003; **49:** 80–4.
5. Rockmann H, *et al*. Anaphylaxis after dexpanthenol exposure by multivitamin tablets. *Clin Exp Dermatol* 2005; **30:** 714–16.

Preparations

USP 31: Dexpanthenol Preparation.

Proprietary Preparations (details are given in Part 3)
Arg.: Nutraisdin†; Recugel; ***Austria:*** Bepanthen; Corneregel; Pantothen; ***Braz.:*** Bepantol; Uvless; ***Chile:*** Bepantol; ***Cz.:*** Bepanthen; Panthenol; ***Fin.:*** Bepanthen; ***Fr.:*** Bepanthen; Bepanthene; Pan-Sun; ***Ger.:*** Bepanthen; Corneregel; Marolderm; NasenSpray Panthenol; Nasic-cur; Otriven mit Dexpanthenol; Pan Rhinol; Pan-Ophtal; Panthenol; Panthogenat†; Pelina; Rhinoclir†; Siozwo Sana; Ucee D†; Urupan†; Wund- und Heilsalbe N†; Wund- und Heilcreme N; ***Gr.:*** Corneregel; ***Hung.:*** Bepanthen; Corneregel; Panthenol; ***Indon.:*** Bepanthen; Pasquam; ***Israel:*** Bepanthen; Neocutan; ***Ital.:*** Bepanten; ***Mex.:*** Bepanthen; Corneregel; ***NZ:*** Bepanthen; ***Philipp.:*** Corneregel; ***Pol.:*** Bepanthen; Corneregel; Dermopanten; ***Port.:*** Bepanthene; ***Rus.:*** Bepanthen (Бепантен); Corneregel (Корнерегель); Panthenol (Пантенол); Panthoderm (Пантодерм); ***S.Afr.:*** Bepanthen; Bepantol†; ***Singapore:*** Bepanthen; ***Spain:*** Bepanthene; ***Switz.:*** Bepanthene; ***Turk.:*** Bepanthene; Bepantol; Pantenol; ***UAE:*** Dexipan; ***UK:*** Bepanthen; ***USA:*** Ilopan; Panthoderm; ***Venez.:*** Beducen†.

Multi-ingredient: ***Arg.:*** Dermocridin; Dermvien†; Heduline; Hydratone†; Lociherp Liposomas Vitaminado; Mucobase; Nutraisdin†; Sebulex; Talowin; ***Austral.:*** Macro Natural Vitamin E Cream; Sebirinse; Superfade; ***Austria:*** Beneuran Vit B-Komplex†; Bepanthen; Bepanthen Plus; Colda; Coldistan; Dolobene; Keratosis; Keratosis forte; Oleovit; Panto Liquid; Siccaprotect; Sigman-Haustropfen; Venobene; ***Belg.:*** Algi-Cool; Purigel NF; ***Braz.:*** Capel; Dolobene; Naridrin; Nariflux; Nazobio†; Varizol†; ***Canad.:*** Selsun with Provitamin B†; ***Chile:*** Acnoxyl Shampoo Cabello Graso†; Cicapost; Eucerin Piel Grasa; Panthoderm-A; Pomada Vitaminica; Queratopil; Ureadin Rx DB; Ureadin Rx RD; Vitis Encias Colutorio; Vitis Encias Pasta; ***Cz.:*** Bepanthen Plus; Brand- und Wundgel†; Dolobene; Lipovitan†; Panlid; Siccaprotect; ***Fin.:*** Oftan A-Pant; Pantyson; Wicaran; Wicarba; Wicnevit; ***Fr.:*** Alkagin; Mela'aura; Parogencyl gencives fragilisees†; Tonimer; ***Ger.:*** Bepanthen Antiseptische; Brand- und Wund-Gel Eu Rho†; Dispatenol; Dolobene; Essaven Tri-Complex†; GeloBacin; Hermalind†; Hewekzem novo N; Hydro Cordes; Hylo-Care; Lipo Cordes; Lipovitan†; Mar Plus†; Nasic; PC 30 V; Remederm; Saseem; Siccaprotect; ***Gr.:*** Aquasol A†; Novaquasol-A; ***Hong Kong:*** Dolobene; Mar Plus; Pregnacare; Sebirinse; ***Hung.:*** Alksebor; Aurobin; Bepanthen Plus; Dolobene; Phlogosam; Vipsogal†; ***India:*** Optineuron; Sioneuron; Vitneurin; ***Indon.:*** Romilar; Skintex; ***Israel:*** Bepanthen Plus; Kamil Blue; Neocutan Silver; Panthisone; Pedisol; ***Ital.:*** Alfa Acid; Emazian B12†; Emoantitossina†; Gastrotuss; Keto Z; Lenirose†; Parogencyl; Rinopanteina; ***Malaysia:*** Mar Plus; ***Mex.:*** Bexident Pediatrics†; Cetopic; Emolin Neo; Nutrem; Salilex; ***Neth.:*** Prunacolon; Prunasine; ***NZ:*** Sebirinse; ***Philipp.:*** pHCare; Remederm; Sebo Fluid; ***Pol.:*** Acodin; Alantan-Plus; Bepanthen Plus; Dolobene; ***Port.:*** Bepanthene; Bepanthene Plus; Bexident; Carmitol; Cicapost; Efluvium Anti-seborreico; Lactigriet; Nutraisdin; Ureadin 10 Plus; ***Rus.:*** Aurobin (Ауробин); Bepanthen Plus (Бепантен Плюс); Dolobene (Долобене); Hepatrombin (Гепатромбин); Hylozar-COMOD (Хилозар-КОМОД); Venolife (Венолайф); ***S.Afr.:*** Broncol†; ***Switz.:*** Alphastria; Bepanthene Plus; Carbamide + VAS; Carbamide Creme; Cortimycine; Demostan N; Dermacalm-d; Dolobene; Galamila; Gorgonium; Hepathrombine†; Lenidermt†; Lyman; Nose Fresh au D-panthenol; Osa Gel de dentition; Parapic; Pelsano; Pigmanorm; Remexal; Siccalix; Siccaprotect; Sportium; Sportusal; Sportusal Spray sine heparino; Stilex; Tendro; Turexan Capilla; Turexan Lotion; Unathene; Unatol; Venucreme; Venugel; Wulnasin; ***Thai.:*** Mar Plus; Romilar; ***Turk.:*** Bepanthene Plus; Pantenol Plus; Siccaprotect; Stilex; ***UK:*** Oilatum Scalp Intensive; Uvistat Eye Drops; Vipsogal; ***Venez.:*** Cepin; Diadex; Pantonic; Vitenol†.

Papain

Papaína; Papaina; Papayotin.
CAS — 9001-73-4.

Pharmacopoeias. In *US.*

USP 31 (Papain). A purified proteolytic substance derived from *Carica papaya* (Caricaceae). It contains not less than 6000 USP units per mg. A white to light tan, amorphous powder. Soluble in water, the solution being colourless to light yellow and more or less opalescent; practically insoluble in alcohol, in chloroform, and in ether. pH of a 2% solution in water is between 4.8 and 6.2. Store in airtight containers at a temperature of 8° to 15°. Protect from light.

Units

USP 31 defines the USP unit of papain activity as the activity that releases the equivalent of 1 microgram of tyrosine from a specified casein substrate under the conditions of the assay, using the enzyme concentration that liberates 40 micrograms of tyrosine per mL of test solution.

One FIP unit of papain is defined as the enzyme activity which under specified conditions hydrolyses 1 micromol of *N*-benzoyl-L-arginine ethyl ester per minute.

The Warner-Chilcott unit, based on the quantity of enzyme required to clot 2.64 microlitre of milk substrate in 2 minutes at 40°, under specified conditions, has also been used for papain.

Adverse Effects

Hypersensitivity reactions have occurred.

Effects on the eyes. Ocular and periorbital angioedema occurring within 4 hours of use of a contact lens cleansing solution containing papain has been reported.[1]

1. Bernstein DI, *et al*. Local ocular anaphylaxis to papain enzyme contained in a contact lens cleansing solution. *J Allergy Clin Immunol* 1984; **74:** 258–60.

Oesophageal perforation. Extensive destruction of the oesophageal wall, with perforation, resulted from the use of a papain suspension given to treat an obstruction caused by impacted meat.[1] The patient had been given 1.2 g of papain over a 12-hour period. Ten days after a thoracotomy, the descending thoracic aorta ruptured, and she died from haemorrhage.

1. Holsinger JW, *et al*. Esophageal perforation following meat impaction and papain ingestion. *JAMA* 1968; **204:** 734–5.

Uses and Administration

Papain consists chiefly of a mixture of papain and chymopapain, proteolytic enzymes that hydrolyse polypeptides, amides, and esters, especially at bonds involving basic amino acids, or leucine or glycine, yielding peptides of lower molecular weight. It is used with urea as a topical debriding agent. It is also used for the removal of protein deposits from the surface of soft contact lenses (p.1622).

Preparations of papain, alone or combined with antibacterial agents and/or other substances, have been taken orally for their supposed anti-inflammatory properties, and it has also been used as an ingredient of various mixtures claimed to aid digestion.

Papain is widely used as a meat tenderiser and in the clarification of beverages.

Malignant neoplasms. Papain has been included in proteolytic enzyme preparations used in oncology to reduce the adverse effects of chemotherapy and radiotherapy. Although the number of clinical studies on which to judge efficacy is limited, a review[1] of such studies suggested that systemic enzyme therapy might be beneficial. Clinical studies have used a preparation containing papain, trypsin, and chymotrypsin in a weight ratio of 5:2:2, and the beneficial effect seems to be based on its anti-inflammatory potential.

1. Leipner J, Saller R. Systemic enzyme therapy in oncology: effect and mode of action. *Drugs* 2000; **59:** 769–80.

Preparations

USP 31: Papain Tablets for Topical Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Tromasin†; ***Austral.:*** Hydrocare Enzymatic Protein Remover†; Stop Itch; ***Canad.:*** Solarcaine Stop Itch; Stop Itch†; ***Chile:*** Papenzima; ***Ger.:*** Vermizym†; ***Hong Kong:*** Eurolase; ***Malaysia:*** Beazyme; ***NZ:*** Stop Itch; ***USA:*** Allergan Enzymatic; ProFree.

Multi-ingredient: ***Arg.:*** Butimerin; Docechol; Homocisteon Compuesto; Opoenterol†; Pankreon Total; Solustres; Tromasin con Aspirina†; Vulnofilin Compuesto†; ***Austral.:*** Betaine Digestive Aid; Bio-Disc; Bioglan Discone†; Digestaid; Digestive Aid; Enzyme; Prost-1†; Prozyme†; ***Austria:*** Rennie Digestif; Wobe-Mugos; Wobenzym; ***Belg.:*** Digestomen; ***Braz.:*** Filogaster†; ***Cz.:*** Digestif Rennie; Wobe-Mugos†; Wobenzym; ***Ger.:*** Arbuz†; Enzym-Wied†; Mulsal N†; Wobe-Mugos E†; Wobenzym N; ***Gr.:*** Lysopaine; Sopain-Plus; ***Hong Kong:*** Digezym; ***Hung.:*** Digestif Rennie; ***India:*** Bestozyme; Catazyme-P; Dipep; Molzyme†; Neopeptine; Nutrozyme; Papytazyme; Unienzyme; ***Indon.:*** Papaven; ***Ital.:*** Digestopan†; ***Malaysia:*** Pepfiz; ***Mex.:*** Dermobion†; Digenor Plus; Wobe-Mugos; Wobenzym; ***Pol.:*** Carident; ***Port.:*** Caroid†; ***Rus.:*** Pepfiz (Пепфиз); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Singapore:*** Stop-Itch Plus; ***Spain:*** Digestomen Complex; Lizipaina; ***Switz.:*** Lysopaine; ***Thai.:*** Papytazyme†; Pepfiz; Pepsitase; Polyenzyme-I; ***UK:*** Enzyme Digest; Herbal Indigestion Naturtabs; Indigestion and Flatulence; ***USA:*** Accuzyme; AllanEnzyme; AllanfillEnzyme; Ethezyme; Gladase; Gladase-C; Kovia; Panafil; Panafil-White; Pap-Urea; Papaya Enzyme; Ziox; ***Venez.:*** Enzima de Lechoza†; Wobenzym N.

Paradichlorobenzene

Dichlorbenzol; Paradiclorobenceno. 1,4-Dichlorobenzene.
$C_6H_4Cl_2$ = 147.0.
CAS — 106-46-7.

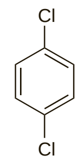

Profile

Paradichlorobenzene has general properties similar to those of orthodichlorobenzene (see p.2358) but is considered to be less toxic. It is present in several preparations intended for the removal of ear wax (see p.1725). It has been used as a furniture preservative and in mothballs and lavatory deodorant blocks. Abuse of preparations containing paradichlorobenzene has been reported.

Abuse. Neurocutaneous symptoms have been reported[1] in 2 18-year-old twin girls after abuse of mothballs by inhaling the fumes, and in one twin, also chewing the mothballs. Once they stopped, both sisters recovered completely within 3 to 6 months depending on their previous level of abuse.

1. Feuillet L, *et al.* Twin girls with neurocutaneous symptoms caused by mothball intoxication. *N Engl J Med* 2006; **355:** 423–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Cerumol; ***Canad.:*** Cerumol; ***India:*** Clearwax; Waxolve; ***Irl.:*** Cerumol; ***Israel:*** Cerumol; ***Malaysia:*** Cerumol; ***Port.:*** Otoceril; ***S.Afr.:*** Cerumol; ***Singapore:*** Cerumol; ***Switz.:*** Cerumenol; ***UK:*** Cerumol.

Paraphenylenediamine

Parafenilendiamina. *p*-Phenylenediamine; 1,4-Benzenediamine.
$C_6H_4(NH_2)_2$ = 108.1.
CAS — 106-50-3.

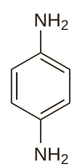

NOTE. Commonly known in the hairdressing trade as *'para'*. 'PPD' is an abbreviation sometimes used for paraphenylenediamine, which should not be confused with tuberculin purified protein derivative (see Tuberculins, p.2405), which is also referred to by the same abbreviation.

Profile

Paraphenylenediamine is widely used in permanent hair colour preparations. However it is a potent contact allergen and EU legislation restricts its concentration in the finished product to a maximum of 6% calculated as free base. Both type I and type II reactions occur and symptoms usually present as dermatitis on the face or hands. More severe reactions can lead to angioedema; anaphylaxis has also been reported. Systemic symptoms similar to those after ingestion (see below) may also occur following absorption through intact skin. For references to hypersensitivity after skin tattoos with henna that was adulterated with paraphenylenediamine, see p.2318.

Application of tints to the eyelashes or eyebrows may produce blepharoconjunctivitis, eye oedema, and eye pain, with progression to facial oedema and dermatitis, lachrymation, photophobia, uveitis, and keratitis in severe cases. Corneal necrosis has led to blindness. In some countries, use of paraphenylenediamine in eyelash or eyebrow tints is not permitted.

Early symptoms after ingestion of paraphenylenediamine are vomiting and abdominal pain. Severe oedema of the face and oropharynx can lead to life-threatening obstruction of the airways. Other symptoms may include hypotension or hypertension, tachycardia, hepatotoxicity, renal failure, metabolic acidosis, methaemoglobinaemia, rhabdomyolysis, tremor, convulsions, and coma; multisystem failure may be fatal.

Some studies have linked hair dyes with mutagenicity and carcinogenicity, although such findings have often been refuted. In Europe, EU legislation carefully controls which substances may be safely used in hair dye products.

Paraphenylenediamine is also used in the textile and photographic industries.

Adverse effects. References.

1. Ashraf W, *et al.* Systemic paraphenylenediamine (PPD) poisoning: a case report and review. *Hum Exp Toxicol* 1994; **13:** 167–70.
2. Lifshits M, *et al.* Fatal paraphenylenediamine (hair dye) intoxication in a child resembling Ludwig's angina. *J Toxicol Clin Toxicol* 1993; **31:** 653–6.
3. Anuradha S, *et al.* Acute renal failure following para-phenylenediamine (PPD) poisoning: a case report and review. *Ren Fail* 2004; **26:** 329–32.
4. Kallel H, *et al.* Clinical manifestations of systemic paraphenylene diamine intoxication. *J Nephrol* 2005; **18:** 308–11.
5. Sosted H, *et al.* Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; **54:** 87–91.
6. Brahmi N, *et al.* Acute myocarditis and myocardial infarction induced by paraphenylenediamine poisoning. Interest of angiocoronarography. *Int J Cardiol* 2006; **113:** E93–E95.
7. Teixeira M, *et al.* Contact allergy to para-phenylenediamine in a permanent eyelash dye. *Contact Dermatitis* 2006; **55:** 92–4.
8. Patel S, *et al.* Patch test frequency to *p*-phenylenediamine: follow up over the last 6 years. *Contact Dermatitis* 2007; **56:** 35–7.

Paratoluenediamine

Paratoluendiamina. 2-Methyl-1,4-phenylenediamine.
$C_7H_{10}N_2$ = 122.2.
CAS — 95-70-5.

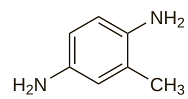

Profile

Paratoluenediamine is used in hair colour preparations.

Like paraphenylenediamine, above, paratoluenediamine may be associated with sensitivity reactions.

Parsley

Perejil; Persil; Persil, racine de (parsley root); Petersilie; Petroselini radix (parsley root); Petroselinum; Petrželový kořen (parsley root).

Profile

Parsley (*Petroselinum crispum*, Umbelliferae) is used in herbal medicine, where it is mainly given as a diuretic. It is also used as a culinary herb and flavouring.

Parsley oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Odo-fre.

Multi-ingredient: ***Arg.:*** Alofresh†; Water Pill c Potasio†; ***Austral.:*** Extralife Fluid-Care; Medinat PMT-Eze†; Odourless Garlic; Uva-Ursi Plus†; ***Canad.:*** Herbal Diuretic; Herbal Throat†; ***Cz.:*** Species Diureticae Planta†; Species Urologicae Planta; Urologicka Cajova Smes; ***Fr.:*** Oropur; ***Ger.:*** Asparagus-P; nephro-loges; ***Malaysia:*** Total Man†; ***Rus.:*** Herbion Urological Drops (Гербион Урологические Капли); ***UK:*** Athera; Fre-bre; Mixed Vegetable Tablets; Modern Herbals Menopause.

Parsley Piert

Alchémille des Champs; Alquimila arvense; Aphanes; Gewöhnlicher Acker-Frauenmantel.

Profile

Parsley piert, the aerial parts of *Aphanes arvensis* (*Alchemilla arvensis*) (Rosaceae) has astringent, diuretic, and demulcent properties. It is used for urinary-tract disorders, including renal and urinary calculi.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Kontryhelova Nat.

Multi-ingredient: ***Austral.:*** Profluid†; Protemp†; ***Canad.:*** Swiss Herb Cough Drops; ***Cz.:*** Fytokliman Planta; Gynastan†; ***Fr.:*** Gonaxine; ***UK:*** Backache Relief; Diuretabs; HRI Water Balance; Watershed.

Passion Flower

Golgotavirág hajtásvég; Grenadille; Kärsimyskukka; May-pop; Mučenková nať; Pasiflora; Pasiflorų žolė; Pasionari; Passiflora; Passiflorae herba; Passiflore; Passionsblomma.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Passion Flower). The fragmented or cut, dried aerial parts of *Passiflora incarnata*; it may also contain flowers and/or fruits. It contains not less than 1.5% of total flavonoids expressed as vitexin ($C_{21}H_{20}O_{10}$ = 432.4), calculated with reference to the dried drug. Protect from light.

Profile

Passion flower is reputed to have antispasmodic and sedative properties and has been used as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture.

Homoeopathy. Passion flower has been used in homoeopathic medicines under the following names: Passiflora incarnata; Passi. in.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sedante Noche; ***Austria:*** Passiflorin; ***Belg.:*** Sedanxio; ***Ger.:*** Hoggar Balance; Kytta-Sedativum fur den Tag; Passidon; Passiflora Curarina; ***Pol.:*** Passiflor; ***Rus.:*** Novo-Passit (Ново-Пассит); ***Switz.:*** Passelyt; Plantival Mono†; ***Turk.:*** Alora; ***UK:*** Modern Herbals Sleep Aid; Natracalm; Naturest; Nodoff; Phytocalm; ***Venez.:*** Floral Pas.

Multi-ingredient: ***Arg.:*** Armonil; Calmtabs†; Herbaccion Sedante†; Insomnal†; Nervocalm; No-Nerviol†; Passacanthine†; SDN 200; Sedanat; Sedante Arceli†; Sedante Dia; Serenil; Sigmasedan; Top Life Relax†; Yerba Diet; ***Austral.:*** Calm; Calmo; Euphorbia Complex; Executive B; Extralife Sleep-Care; Goodnight Formula†; Herbal Anxiety Formula†; Humulus Compound; Lifesystem Herbal Plus Formula 2 Valerian†; Multi-Vitamin Day & Night†; Natural Deep Sleep; Nervatona Calm; Nervatona Focus; Pacifenity†; Passiflora Complex†; Passionflower Plus; Proesten†; Prosed-X†; Relaxaplex†; Valerian Plus Herbal Plus Formula 12†; ***Austria:*** Nervenruh; Passedan; Passelyt; Sedogelat; Wechseltee St Severin; ***Belg.:*** Sedinal; Seneuval; ***Braz.:*** A Saude da Mulher; Anevrase†; Benzomel†; Bronquiogem; Calman; Calmapax; Calmazin†; Calmiplan; Composto Emagrecedor†; Elixir de Passiflora†; Emagrevit†; Floriny; Gotas Nican†; Pasalix; Pasic; Passaneuro; Passi Catha†; Passicalm†; Passiflora Composta†; Passiflorine; Passilex†; Sedalin†; Serenus; Sominex; Vagostesyl; ***Canad.:*** Herbal Sleep Well†; Natural HRT Nightime; Relax and Sleep; ***Chile:*** Armonyl; Recalm; ***Cz.:*** Bio-Strath†; Novo-Passit; Passedan; Visinal†; ***Fr.:*** Anxoral†; Biocarde; Euphytose; Mediflor Tisane Calmante Troubles du Sommeil No 14; Natudor; Neuroflorine; Nocvalene†; Panxeol; Passiflorine; Passinevryl; Phytocalm†; Sedatif Tiber; Sympaneurol; Sympavagol; ***Ger.:*** Biosedon†; Dormo-Sern†; Dormoverlan; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee; Gutnacht†; Habstal-Nerv N†; Hyposedon N†; Kytta-Sedativum; Moradorm S; Nervendragees†; Nervinfant N†; Nervoregin forte†; Nervoregin phyto; Neurapas; Passin; Phytonoctu; Presselin Nerven K 1 N†; Pronervon Phyto; RubieSed†; Seda-Plantina†; Sedinfant N†; Somnuvis S†; Tornix; Valeriana mild†; Vivinox Day; ***Hong Kong:*** Epizon†; ***Indon.:*** Slip-iZZZ; ***Israel:*** Calmanervin; Nerven-Dragees; Passiflora; Passiflora Compound; ***Ital.:*** Actenacol; Anevrasi; Biocalm; Calmason; Controller; Dormil; Fitosonno; Noctis; Parvisedil; Passiflorine; Reve; Sedatol; Sedofit; Sedopuer F; Val-Plus†; ***Malaysia:*** Cleansa Plus†; ***Mex.:*** Ifupasil; Pasinordin; ***Pol.:*** Nervendragees; Nerwonal; Passibil; Passispasmin; Passispasmol; Psychotonisol; Valused; ***Port.:*** Gabisedil†; Neurocardol†; Valesono†; ***S.Afr.:*** Avena Sativa Comp; Biral; ***Spain:*** Passiflorine; Sedasor†; Sedonat; Sonofit†; Valdispert Complex; ***Switz.:*** Circulan; Dicalm†; Dragees antirhumatismales; Dragees pour la detente nerveuse; Dragees pour le coeur et les nerfs; Gouttes pour le coeur et les nerfs Concentrees†; Phytomed Cardio; Phytomed Nervo†; Phytomed Somni†; Relaxane; Relaxo; Sirop Passi-Par†; Soporin; Strath Gouttes pour le coeur; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane antirhumatismale; Tisane calmante pour les enfants; Tisane relaxante N†; Valverde Coeur; Valverde Detente dragees; ***UK:*** Anased; Avena Sativa Comp; Bio-Strath Valerian Formula; Daily Tension & Strain Relief; Gerard House Serenity; Herbal Pain Relief; HRI Night; Kalms Sleep; Modern Herbals Stress; Niteherb Plus; Nodoff; Nytol Herbal; PMT Formula; Quiet Life; Quiet Nite; Quiet Tyme; Relax B ; Slumber; Sominex Herbal; SuNerven; ***Venez.:*** Cratex†; Equaliv; Eufytose†; Lupassin; Pasidor; Pasifluidina; Passiflorum; Rendetil; Sedival.

Patchouli

Profile

Patchouli (*Pogostemon cablin*, Lamiaceae) is the source of patchouli oil, which is distilled from the dried leaves and young shoots. Patchouli oil is used in aromatherapy.

In traditional Chinese medicine the dried aerial part is known as Guang Huo Xiang.

Homoeopathy. Patchouli oil has been used in homoeopathic medicines.

Patent Blue V

Acid Blue 3; Azul Patente V; CI Food Blue 5; Colour Index No. 42051; E131. Calcium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclohexa-2,5-dienylidene)-5-hydroxytoluene-2,4-disulphonate.
$(C_{27}H_{31}N_2O_7S_2)_2Ca$ = 1159.4.
CAS — 3536-49-0.

NOTE. The name Patent Blue V is also used as a synonym for Sulphan Blue (CI No. 42045) (see p.2394).

Pharmacopoeias. In *Fr.*

Adverse Effects and Precautions

Hypersensitivity reactions may occur immediately or a few minutes after injection of patent blue V; on rare occasions they may be severe and include shock, dyspnoea, laryngeal spasm, and oedema. Nausea, hypotension, and tremor have been reported.

Giving a small dose to test for hypersensitivity has been suggested.

Hypersensitivity. An urticarial rash occurred in a 5-year-old girl after use of tablets containing patent blue V to disclose the presence of dental plaque.[1] Severe anaphylactic reactions, including shock, have been reported.[2-5]

1. Chadwick BL, *et al.* Allergic reaction to the food dye patent blue. *Br Dent J* 1990; **168:** 386–7.
2. Woltsche-Kahr I, *et al.* Anaphylactic shock following peritumoral injection of patent blue in sentinel lymph node biopsy procedure. *Eur J Surg Oncol* 2000; **26:** 313–14.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Patent blue V and anaphylaxis. *Aust Adverse Drug React Bull* 2002; **21:** 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.htm (accessed 02/07/04)
4. Wöhrl S, *et al.* Near-fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004; **150:** 1037–8.
5. Dewachter P, *et al.* Anaphylactic reaction to patent blue V after sentinel lymph node biopsy. *Acta Anaesthesiol Scand* 2006; **50:** 245–7.

Uses and Administration

Patent blue V is injected subcutaneously to colour the lymph vessels so that they can be injected with a contrast medium. A dose of 0.25 mL of the 2.5% solution diluted with an equal volume of sodium chloride 0.9% or lidocaine hydrochloride 1% injected subcutaneously in each interdigital web space has been used. Additional injections at different sites may be required when the lower limbs are to be examined. A bluish skin colour may develop after injection but usually disappears after 24 to 48 hours.

Patent blue V is used as a food colour.

Malignant neoplasms of the breast. Intradermal injection of patent blue V at the site of a primary breast tumour has been used to identify the associated lymph nodes,[1] but concern has been expressed regarding possible long-term staining of the skin.[2]

1. Borgstein PJ, *et al.* Intradermal blue dye to identify sentinel lymph-node in breast cancer. *Lancet* 1997; **349:** 1668–9.
2. Giuliano AE. Intradermal blue dye to identify sentinel lymph node in breast cancer. *Lancet* 1997; **350:** 958.

Pegademase *(rINN)*

PEG-ADA; Pegademasa; Pégadémase; Pegademasum; PEG-Adenosine Deaminase.

Пэгадемаза

ATC — L03AX04.
ATC Vet — QL03AX04.

NOTE. Pegademase Bovine is *USAN*.

Profile

Pegademase is a conjugate of adenosine deaminase, an endogenous enzyme that converts adenosine to inosine, with a macrogol (polyethylene glycol). Pegademase bovine is used in the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase, in patients who are not suitable for bone marrow transplantation or in whom the transplantation has failed. It is given by intramuscular injection once every 7 days, in an initial dose of 10 units/kg; increments of 5 units/kg are then given weekly up to a usual weekly maintenance dose of 20 units/kg. A single dose of 30 units/kg should not be exceeded. Pegademase should be given with caution to patients with thrombocytopenia and avoided if the latter is severe.

◊ References.

1. Hershfield MS, *et al.* Treatment of adenosine deaminase deficiency with polyethylene glycol-modified adenosine deaminase. *N Engl J Med* 1987; **316:** 589–96.
2. Anonymous. Pegademase. *Med Lett Drugs Ther* 1990; **32:** 87–8.
3. Lee CR, *et al.* Pegademase bovine: replacement therapy for severe combined immunodeficiency disease. *DICP Ann Pharmacother* 1991; **25:** 1092–5.
4. Shovlin CL, *et al.* Adult presentation of adenosine deaminase deficiency. *Lancet* 1993; **341:** 1471.
5. Hershfield MS. Adenosine deaminase deficiency: clinical expression, molecular basis, and therapy. *Semin Hematol* 1998; **35:** 291–8.
6. Husain M, *et al.* Burkitt's lymphoma in a patient with adenosine deaminase deficiency-severe combined immunodeficiency treated with polyethylene glycol-adenosine deaminase. *J Pediatr* 2007; **151:** 93–5.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Adagen.

Pegaptanib Sodium *(BANM, USAN, rINNM)*

EYE-001; Natrii Pegaptanibum; NX-1838; Pegaptanib Octasodium; Pegaptanib sodico; Pégaptanib Sodique.

Натрий Пегаптаниб

CAS — 222716-86-1.
ATC — S01LA03.
ATC Vet — QS01LA03.

Adverse Effects and Precautions

Endophthalmitis has been reported in patients given pegaptanib sodium and patients should be monitored for signs of infections for a week after the procedure. Retinal haemorrhage, retinal detachment, iatrogenic traumatic cataract, and raised intra-ocular pressure have also been reported. Immediate or delayed intravitreous haemorrhage may occur after injection. Common but less serious ocular adverse effects include eye pain, irritation, inflammation, blurred vision, visual disturbances, corneal oedema, punctate keratitis, and vitreous floaters.

Non-ocular adverse effects that have been reported include headache, rhinorrhoea, bronchitis, diarrhoea, dizziness, nausea, and urinary-tract infections.

Hypersensitivity reactions, including anaphylaxis or anaphylactoid reactions, and angioedema have been reported rarely within several hours of a dose.

Pegaptanib is contra-indicated in patients with active or suspected ocular or periocular infections.

◊ Data from two concurrent international multicentre prospective randomised controlled studies[1] were analysed to assess the safety of pegaptanib after 2 years of treatment for neovascular (wet) age-related macular degeneration. The most common ocular adverse effects were attributed to the injection procedure and were transient and mild to moderate in intensity. Failure to follow the injection preparation protocol accounted for most cases of endophthalmitis. The incidence of adverse effects associated with systemic inhibition of vascular endothelial growth factor or severe ocular inflammation, cataract progression, or glaucoma was not higher in the pegaptanib-treated patients compared with patients receiving sham injections. Overall, the safety profile of pegaptanib was favourable in these studies.

1. D'Amico DJ, *et al.* VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006; **113:** 992–1001.

Uses and Administration

Pegaptanib is a pegylated modified oligonucleotide (aptamer) given as the sodium salt in the treatment of neovascular (wet) age-related macular degeneration. It is given by intravitreal injection into the affected eye in a dose of 300 micrograms once every 6 weeks. Stopping or withholding treatment should be considered if there has been no demonstrable benefit after 2 consecutive injections (i.e. at the 12-week visit).

Pegaptanib is also under investigation as an adjunct in the management of diabetic retinopathy.

Age-related macular degeneration. Pegaptanib is a pegylated modified oligonucleotide (aptamer) used in the treatment of age-related macular degeneration (AMD) (p.785). It binds to and inhibits vascular endothelial growth factor (VEGF), which is a stimulant of angiogenesis thought to play a role in the neovascularisation and retinal changes associated with AMD. Pegaptanib is a selective antagonist of VEGF.[1,2]

Positive outcomes have been reported from two concurrent international multicentre prospective randomised controlled studies.[3] Vision loss was prevented and mean visual acuity improved in patients given 6-weekly injections of 300 micrograms, 1 mg, or 3 mg for 48 weeks compared with patients receiving sham injections. No dose-response relationship was found. In order to assess the effects of long-term therapy, patients who had been given pegaptanib in the first part of the study were then randomised at week 54 to receive either pegaptanib for a further 48 weeks or stop treatment, and patients who had been given sham injections were similarly re-randomised.[4] Results showed that patients given pegaptanib for a second year continued to derive additional benefit. A systematic review[5] of 5 randomised controlled studies found that pegaptanib was effective in reducing the risk of loss of visual acuity.

1. Siddiqui MAA, Keating GM. Pegaptanib: in exudative age-related macular degeneration. *Drugs* 2005; **65:** 1571–7.
2. Chapman JA, Beckey C. Pegaptanib: a novel approach to ocular neovascularization. *Ann Pharmacother* 2006; **40:** 1322–6.
3. Gragoudas ES, *et al.* Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351:** 2805–16.
4. Chakravarthy U, *et al.*. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113:** 1508–21.
5. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Macugen; ***Canad.:*** Macugen; ***Cz.:*** Macugen; ***Fr.:*** Macugen; ***Gr.:*** Macugen; ***Pol.:*** Macugen; ***Port.:*** Macugen; ***Singapore:*** Macugen; ***UK:*** Macugen; ***USA:*** Macugen.

Penicilloyl-polylysine

Benzylpenicilloyl-polylysine; Peniciloil polilisina; PO-PLL; PPL.

CAS — 53608-77-8.

Description. Penicilloyl-polylysine is a polypeptide compound formed by the interaction of a penicillanic acid and polylysine of an average degree of polymerisation of 20 lysine residues per molecule.

Pharmacopoeias. *US* includes a concentrated form.

USP 31 (Benzylpenicilloyl Polylysine Concentrate). It has a molar concentration of benzylpenicilloyl moiety of not less than 0.0125 M and not more than 0.020 M. It contains one or more suitable buffers. It is not intended for direct administration. pH of the concentrate is between 6.5 and 8.5. Store in airtight containers.

Adverse Effects and Precautions

Severe hypersensitivity reactions have occasionally been reported after use of penicilloyl-polylysine; a scratch test is recommended before intradermal use.

Uses and Administration

Penicilloyl-polylysine is used to detect penicillin hypersensitivity. It is generally indicated only for adults with a history of penicillin hypersensitivity. After a preliminary scratch test it may then be given by intradermal injection. The development, usually within 5 to 15 minutes, of a wheal, erythema, and pruritus is generally judged a positive reaction. The incidence of penicillin hypersensitivity is stated to be less than 5% in patients showing a negative reaction. Penicilloyl-polylysine does not detect those liable to suffer late reactions or reactions due to minor antigen determinants; these reactions require other tests. False-positive reactions to penicilloyl-polylysine also occur.

Preparations

USP 31: Benzylpenicilloyl Polylysine Injection.

Proprietary Preparations (details are given in Part 3)
USA: Pre-Pen†.

Pentagastrin *(BAN, USAN, rINN)*

AY-6608; ICI-50123; Pentagastriini; Pentagastrina; Pentagastrine; Pentagastrinum. *tert*-Butyloxycarbonyl-[β-Ala[13]]gastrin-(13-17)-pentapeptide amide; Boc-β-Ala-Trp-Met-Asp-Phe—NH_2.

Пентагастрин

$C_{37}H_{49}N_7O_9S$ = 767.9.
CAS — 5534-95-2.
ATC — V04CG04.
ATC Vet — QV04CG04.

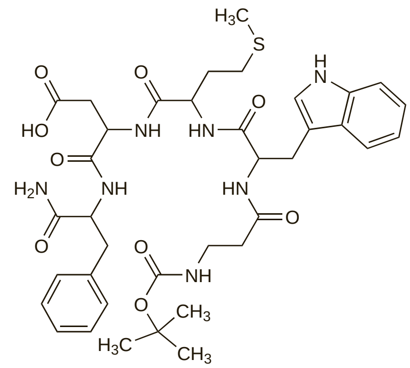

Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Pentagastrin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dimethylformamide and in 5M ammonia. Protect from light.

Adverse Effects

Pentagastrin may cause gastrointestinal effects including nausea and abdominal cramps. Cardiovascular effects including flushing of the skin, tachycardia, and hypotension have occasionally been reported. There may be headache, drowsiness, dizziness, and altered sensations in the extremities. Hypersensitivity reactions are rare.

Precautions

Pentagastrin should be given with care to patients with acute peptic ulceration or with active pancreatic, hepatic, or biliary-tract disease.

Uses and Administration

Pentagastrin is a synthetic pentapeptide that is not active when given by mouth but when given parenterally has effects similar to those of natural gastrin. Since it stimulates the secretion of gastric acid, pepsin, and intrinsic factor, it is used as a diagnostic agent to test the secretory action of the stomach. It has been used to diagnose disorders associated with increased or decreased gastric acid secretion and in the evaluation of gastric acid secretion following vagotomy or gastric resection. The usual dose is 6 micrograms/kg by subcutaneous or intramuscular injection. By intravenous infusion the dose is 600 nanograms/kg per hour, in sodium chloride 0.9%.

Pentagastrin stimulates the secretion of pancreatic enzymes and thus has been used as a test for pancreatic function. It has also been tried in the diagnosis of medullary carcinoma of the thyroid.

Preparations

BP 2008: Pentagastrin Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Peptavlon.

Black Pepper

Pepper; Pimenta; Piper.

CAS — 8006-82-4 (black pepper oil).

Pharmacopoeias. In *Chin.*, which describes both black and white pepper.

Profile

Black pepper is the dried unripe fruit of *Piper nigrum* (Piperaceae). It is used as a culinary spice and is included in some herbal remedies.

Pepper oil, obtained from black pepper, is used in aromatherapy.

White pepper is the ripe fruit with the outer part of the pericarp removed. It too is used as a culinary spice.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Cz.:* Klosterfrau Melisana; ***India:*** Happy'tizer; Tummy Ease; ***Philipp.:*** Bo-D-Fense; ***Pol.:*** Melisana Klosterfrau; ***Rus.:*** Maraslavin (Мараславин); Tentex (Тентекс).

Pepsin

Pepsiini; Pepsiinijauhe; Pepsin práškový; Pepsin, pulver; Pepsina; Pepsine; Pepsini Pulvis; Pepsino milteliai; Pepsinum; Pepszin-por.

CAS — 9001-75-6.

ATC — A09AA03.

ATC Vet — QA09AA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Viet.* In *Jpn* as Saccharated Pepsin.

Ph. Eur. 6.2 (Pepsin Powder; Pepsin BP 2008). It is prepared from the gastric mucosa of pigs, cattle, or sheep. It contains gastric proteinases active in acid medium (pH 1 to 5). It has an activity of not less than 0.5 Ph. Eur. units/mg, calculated with reference to the dried substance. A hygroscopic, white or slightly yellow, crystalline or amorphous powder. Soluble in water; practically insoluble in alcohol. A solution in water may be slightly opalescent with a weak acidic reaction. Store at 2° to 8° in airtight containers. Protect from light.

Uses and Administration

Pepsin contains proteolytic enzymes secreted by the stomach, which control the degradation of proteins into proteoses and peptones. It hydrolyses polypeptides including those with bonds adjacent to aromatic or dicarboxylic L-amino-acid residues.

Pepsin has been given with dilute hydrochloric acid, or with substances such as glutamic acid hydrochloride, or betaine hydrochloride, as an adjunct in the treatment of gastric hypochlorhydria, or to treat deficiencies of digestive enzyme secretion. It has also been given for its supposed benefit as an ingredient of mixtures for dyspepsia and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Fermentol; ***Ger.:*** Hettral N†; ***Pol.:*** Mixtura Pepsini.

Multi-ingredient: *Arg.:* Docechol; Gastridin-E; Opoenterol†; Tridigestivo Soubeiran; ***Austral.:*** Betaine Digestive Aid; Bioglan Digestive Zyme; Digestaid; Enzyme; Prozyme†; ***Austria:*** Helo-acid; Helopanzym; Oroacid; ***Belg.:*** Digestomen; ***Braz.:*** Digeplus; Essen; Filogaster†; Hepatoregius†; Pantopept†; Peptopancreasi; Primeral; ***Chile:*** Flapex E; ***Ger.:*** Citropepsin†; Pepzitrat; ***Hung.:*** Betacid; ***India:*** Aristozyme; Digeplex; Digeplex-T; Dipep; Lupizyme; Nutrozyme; Papytazyme; ***Indon.:*** Librozym; Librozym Plus; ***Israel:*** Babyzim; Betazim; ***Ital.:*** Digestopan†; Essen Enzimatico†; Eudigestio†; Gastro-Pepsin; Pepto-Pancreasi†; ***Mex.:*** Ochozim; Zimotris; ***Philipp.:*** Spasmo-Canulase; ***Pol.:*** Citropepsin; ***Port.:*** Espasmo Canulase; Modulanzime; ***S.Afr.:*** Sentinel Ulcer Mixture; Spasmo-Canulase; ***Spain:*** Digestomen Complex; Euzymina Lisina I; Euzymina Lisina II; Troforex Pepsico; ***Switz.:*** Pepsi-Chlor†; Spasmo-Canulase; Stomacine; ***Thai.:*** Papytazyme†; Pepsitase; ***UK:*** Enzyme Plus; ***USA:*** Digepepsin.

Perflubron *(USAN, rINN)* ⊗

Perflubrón; Perflubronum; Perfluorooctylbromide; PFOB. 1-Bromoheptadecafluorooctane.

Перфлуброн

C_8BrF_{17} = 499.0.

CAS — 423-55-2.

ATC — V08CX01.

ATC Vet — QV08CX01.

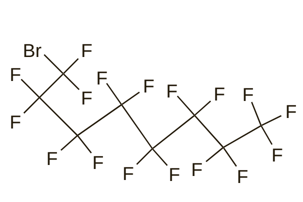

Pharmacopoeias. In *US.*

USP 31 (Perflubron). A clear, colourless, practically odourless liquid. Store in airtight containers. Protect from light.

Profile

Perfluorocarbons can absorb, transport, and release oxygen and carbon dioxide. Perflubron is a perfluorocarbon tried as an alternative to red blood cell preparations to improve gaseous transport, in particular oxygen supply, to the tissues. It may also be instilled directly to the lungs for use in partial liquid ventilation as an adjunct to mechanical ventilation in patients with respiratory failure.

Perflubron is being studied for use as an intravenous contrast medium in computed tomography and ultrasound. It has also been given orally to enhance delineation of the bowel during magnetic resonance imaging.

Other perfluorocarbons have also been used. A mixture of perfluamine (perfluorotripropylamine) and perflunafene (p.2365) has been used to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Perfluorocarbons such as perflunafene and perfluorooctane (p.2365) have been used in eye surgery.

Blood substitutes. References to the use of perflubron and other perfluorocarbons as oxygen carriers.

1. Garrelts JC. Fluosol: an oxygen-delivery fluid for use in percutaneous transluminal coronary angioplasty. *DICP Ann Pharmacother* 1990; **24:** 1105–12.
2. Ravis WR, *et al.* Perfluorochemical erythrocyte substitutes: disposition and effects on drug distribution and elimination. *Drug Metab Rev* 1991; **23:** 375–411.
3. Urbaniak SJ. Artificial blood. *BMJ* 1991; **303:** 1348–50.
4. Jones JA. Red blood cell substitutes: current status. *Br J Anaesth* 1995; **74:** 697–703.
5. Remy B, *et al.* Red blood cell substitutes: fluorocarbon emulsions and haemoglobin solutions. *Br Med Bull* 1999; **55:** 277–98.
6. Lowe KC. Perfluorinated blood substitutes and artificial oxygen carriers. *Blood Rev* 1999; **13:** 171–84.
7. Prowse CV. Alternatives to standard blood transfusion: availability and promise. *Transfus Med* 1999; **9:** 287–99.
8. Matsumoto S, Kuroda Y. Perfluorocarbon for organ preservation before transplantation. *Transplantation* 2002; **74:** 1804–9.
9. Jahr JS, *et al.* Blood substitutes and oxygen therapeutics: an overview and current status. *Am J Ther* 2002; **9:** 437–43.
10. Kim HW, Greenburg AG. Artificial oxygen carriers as red blood cell substitutes: a selected review and current status. *Artif Organs* 2004; **28:** 813–28.
11. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11:** 4099–4114.
12. Riess JG. Perfluorocarbon-based oxygen delivery. *Artif Cells Blood Substit Immobil Biotechnol* 2006; **34:** 567–80.

Respiratory distress syndrome. References to the use of perfluorocarbons, including perflubron, for partial liquid ventilation in neonatal respiratory distress syndrome (p.1508) and acute respiratory distress syndrome (p.1498).

1. Hirschl RB, *et al.* Liquid ventilation in adults, children, and full-term neonates. *Lancet* 1995; **346:** 1201–2.
2. Leach CL, *et al.* Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 1996; **335:** 761–7.
3. Hirschl RB, *et al.* Initial experience with partial liquid ventilation in adult patients with acute respiratory distress syndrome. *JAMA* 1996; **275:** 383–9.
4. Wolfson MR, Shaffer TH. Liquid assisted ventilation update. *Eur J Pediatr* 1999; **158:** S27–S31.
5. Davies M. Liquid ventilation. *J Paediatr Child Health* 1999; **35:** 434–7.
6. Weis CM, Fox WW. Current status of liquid ventilation. *Curr Opin Pediatr* 1999; **11:** 126–32.
7. Kacmarek RM. Liquid ventilation. *Respir Care Clin N Am* 2002; **8:** 187–209.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/04/05).

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Imagent GI; LiquiVent.

Perflunafene *(BAN, rINN)* ⊗

Perflunafène; Perflunafeno; Perflunafenum; Perfluorodecahydronaphthalene; Perfluorodecalin; Perfluorodekalin.

Перфлунафен

$C_{10}F_{18}$ = 462.1.

CAS — 306-94-5.

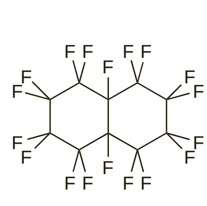

Profile

Perflunafene is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injection of perflunafene is used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment. Perflunafene and perfluamine have been used together for their oxygen-carrying properties in blood substitute preparations and to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Preparations

Proprietary Preparations (details are given in Part 3)

Israel: Adato-Deca†; ***Neth.:*** Eftiar Decalin; ***Turk.:*** DK-Line.

Perfluorooctane

Octadecafluorooctane; Perfluoro-*n*-octane; Perfluoro-octa.

C_8F_{18} = 438.1.

CAS — 307-34-6.

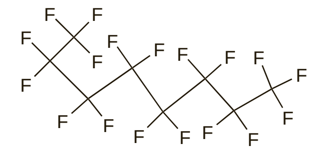

Profile

Perfluorooctane is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injection of perfluorooctane is used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment.

◊ References.

1. Scott IU, *et al.* Outcomes of surgery for retinal detachment associated with proliferative vitreoretinopathy using perfluoro-n-octane: a multicenter study. *Am J Ophthalmol*. 2003; **136;** 454–63.

Preparations

Proprietary Preparations (details are given in Part 3)

Israel: Adato-Octa†; ***Neth.:*** Eftiar Octane; ***USA:*** Perfluoron.

Persic Oil

Melocotón, aceite de; Oleum Persicorum; Peach or.

Pharmacopoeias. *Chin.* and *Jpn* include Peach Kernel (Persicae Semen) and also Apricot Kernel (Armeniacae Semen).

Profile

Persic oil is the fixed oil expressed from the kernels of varieties of *Prunus persica* (peach) or *P. armeniaca* (apricot) (Rosaceae). It closely resembles almond oil (p.2252) in its general characteristics and is used as an oily vehicle.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Fr.:* Item Lentes.

Peru Balsam

Bals. Peruv.; Bálsamo del Perú; Balsamum peruvianum; Baume du Pérou; Baume du San Salvador; Peru balzamas; Peruánský balzám; Perubalsam; Perui balzsm; Perunpalsami; Peruvian Balsam.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Peru Balsam). The balsam obtained from the scorched and wounded trunk of *Myroxylon balsamum* var. *pereirae*. It contains not less than 45.0% w/w and not more than 70.0% w/w of esters, mainly benzyl benzoate and benzyl cinnamate.

A dark brown, viscous liquid which is not sticky, is non-drying, and does not form threads. It is transparent and yellowish-brown when viewed in a thin layer. Practically insoluble in water, freely soluble in dehydrated alcohol; not miscible with fatty oils except for castor oil. Protect from light.

Profile

Peru balsam has a very mild antiseptic action by virtue of its content of cinnamic and benzoic acids. Diluted with an equal part of castor oil, it has been used as an application to bedsores and chronic ulcers; it has also been used in topical preparations for the treatment of superficial skin lesions and pruritus. It is an ingredient of some rectal preparations used for the symptomatic relief of haemorrhoids (see p.1697).

Peru balsam is an ingredient of some preparations used in the treatment of respiratory congestion. It is also used in aromatherapy.

Skin sensitisation has been reported.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Tulle Gras Lumiere†; ***Pol.:*** Balsolan.

Multi-ingredient: *Arg.:* Anusol; Anusol Duo S; Anusol-A; ***Austral.:*** Anusol; Ayrton's Chilblain; ***Austria:*** Mamellin; Pudan-Lebertran-Zinksalbe; Pulmex; Rombay; Vulpuran; ***Belg.:*** Perubore; Rectovasol; ***Braz.:*** Anusol-HC; Balmex; Calminex H; Claudemor; ***Chile:*** Pulmex†; ***Cz.:*** Pulmex Baby†; Pulmex†; ***Fr.:*** Agathol; Anaxeryl; Balsofumine; Balsofumine Mentholee; Brulex; Dermophil Indien†; Oxyperol; Perubore; Pommade Lelong†; ***Ger.:*** Anusol†; Nasenbalsam; Nasenbalsam fur Kinder; Peru-Lenicet†; ***Hong Kong:*** Anusol; Anusol-HC†; Haemoral; ***Indon.:*** Sapona; ***Irl.:*** Anugesic-HC; Anusol; Anusol-HC; ***Israel:*** Anusol†; Hemo; Pulmex; ***Ital.:*** Anusol; Fomentil; ***Malaysia:*** Anucare; Anusol; ***NZ:*** Anusol; ***Pol.:*** Aromagel; Depulol; Hemorectal; Pulmex Baby; Rectosec; ***Port.:*** Claudemor†; ***Rus.:*** Pulmex (Пульмекс); Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); ***S.Afr.:*** Anugesic; Heilsalbe; Ung Vernleigh; ***Singapore:*** Anusol; ***Spain:*** Antigrietun; Balsamo Kneipp†; Cicatral; Grietalgen; Linitul; Vapores Pyt; Vitamina F99 Topica; ***Switz.:*** Demo pommade contre les refroidissements†; Dermophil Indien; Euproctol N; Haemocortin; Haemolan; HEC; Leucen; Nasobol†; Peru Stick; Perubare†; Pinimenthol Baby†; Pommade au Baume; Pulmex; Pulmex Baby; Rapura; Wala Baume nasal; Wala Baume nasal doux; ***Thai.:*** Anusol; ***UK:*** Anugesic-HC; Anusol; Anusol-HC, Plus HC; Dragon Balm; ***USA:*** Allanderm-T; Anumed; Anumed HC; Balmex Baby; Dermuspray; Dr Dermi-Heal; Flanders Buttocks; Granulderm; Granulex; GranuMed; Hemril; Mammol; Proderm; Saratoga; Xenaderm; ***Venez.:*** Claudemor†.

Pexelizumab *(BAN, USAN, rINN)*

h5G1.1 scFv; h5G1.1 scFv (CDR); Pexélizumab; Pexelizumabum. Immunoglobulin, anti-(human complement C5α-chain)(human-mouse monoclonal 5G1.1-SC chain).

Пекселизумаб

CAS — 219685-93-5.

Profile

Pexelizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p.2286) by inhibiting terminal complement activation at the C5 protein. It is under investigation for treatment of patients undergoing coronary artery reperfusion and revascularisation procedures.

◊ References.

1. Mahaffey KW, *et al.* Effect of pexelizumab on mortality in patients with acute myocardial infarction or undergoing coronary artery bypass surgery: a systematic overview. *Am Heart J* 2006; **152:** 291–6.
2. Armstrong PW, *et al.* APEX AMI Investigators. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2007; **297:** 43–51.

Phencyclidine Hydrochloride *(BANM, USAN, rINNM)*

CI-395; CN-25253-2; GP-121; Hidrocloruro de fenciclidina; NSC-40902; PCP; Phencyclidine, Chlorhydrate de; Phencyclidini Hydrochloridum. 1-(1-Phenylcyclohexyl)piperidine hydrochloride.

Фенциклидина Гидрохлорид

$C_{17}H_{25}N,HCl$ = 279.8.

CAS — 77-10-1 (phencyclidine); 956-90-1 (phencyclidine hydrochloride).

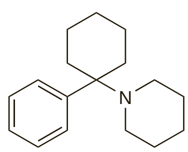

(phencyclidine)

NOTE. The name PCP has also been used as a synonym for pentachlorophenol.

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of phencyclidine:

Ace; AD; Aliamba; Amoeba; Amoebae; Amp; Angel; Angel dust; Angel hair; Angel mist; Angel poke; Animal trank; Animal tranq; Animal tranquilizer; Aurora borealis; Bad pizza; Belladonna; Black dust; Black whack; Blotter acid; Blud madman; Blue madman; Boat; Bohd; Bush; Busy bee; Butt naked; Buzy bee; Cadillac; Cannabinol; Christal; Cigarrode cristal; CJ; Cliffhanger; Cliqum; Columbo; Cozmo's; Crazy coke; Crazy Eddie; Cristal; Crystal; Crystal joint; Crystal T; Crystal TAC; Cycline; Cyclona; Cyclone; Cyclones; Cystal T; D; Detroit pink; Devil's dust; Dipper; Dips; Dirge; Disembalming Fluid; DMT; Do it Jack; DOA; Drink; Drinks; Dummy dust; Dust; Dust joint; Dust of angels; Dusted parsley; Elephant; Elephant trank; Elephant tranquilizer; Embalming fluid; Energizer; Engelenspul; Erth; Fake STP; Fake THC; Fake X; Flakes; Formaldehyde; Fresh; Fry; Fuel; Good; Goon; Goon crystal; Goon dust; Gorilla biscuits; Gorilla pills; Gorilla tab; Green; Green double domes; Green leaves; Green tea; Green tear; Half track; Happy sticks; HCP; Heaven & Hell; Heaven and Hell; Herms; High; Hinkley; Hog; Horse tracks; Horse tranquilizer; Ice; Ill; Illies; Illy momo; Jet fuel; Juice; K; Kaps; K-blast; Killer; Killer joints; Killer weed; KJ; Koller joints; Kools; Kools sherms; Krystal; Krystal joint; Krystal joints; KW; LBJ; Leak; Leakie; Leaky; Leaky bolla; Leaky leak; Lemon 714; Lenos; Lethal weapon; Little ones; Live ones; Log; Love boat; Loveboat; Lovely; Mad dog; Mad man; Madman; Magic; Magic dust; Mean green; Mesk; Mint leaf; Mint weed; Missile; Mist; Monkey dust; Monkey gland; Monkey tranquilizer; More; New acid; New magic; Niebla; Oil; OPP; O.P.P.; Orange crystal; Ozone; P; Parsley; Paz; PCP; PCPA; Peace; PeaCe Pill; Peace pill; Peace pills; Peace weed; Peep; Peter Pan; Pig killer; Pit; Pits; Po-de-anjo; Polvo; Polvo de angel; Polvo de estralos; Polvo de estrellas; Puffy; Purple rain; Red devil; Red devils; Rocket fuel; Rocketfuel; Rupture; Scaffle; Scuffle; Serenity Tranquility Peace; Sernyl; Sernylan; Shabu; Sheets; Sherm; Sherm sticks; Sherman Hemsley; Shermans; Sherms; Skuffle; Smoking; Snorts; Soma; Space rock; Speed boat; Spores; Star dust; Stardust; Stick; STP; Sugar; Super; Super grass; Super joint; Super kools; Super weed; Supergrass; Surfer; Synthetic cocaine; Synthetic THT; T; TAC; Tac et tic; Taking a cruise; T-buzz; Tea; THC; Tic; Tic tac; Tick; Tic-tac; TicTac; Tish; Titch; Trank; Tranq; Tranquilizer (cat, horse, elephant); TT 1; TT 2; TT 3; Venom; Vredestro; Wack; Water; Wave; Weed; Wet; Wet daddies; Wetdaddy; Whack; White horizon; White powder; Wobble weed; Wolf; Woolies; Wooly blunts; Worm; Yellow fever; Zombie; Zombie weed; Zoom; Zoot.

Adverse Effects, Treatment, and Precautions

Phencyclidine can induce a psychosis clinically indistinguishable from schizophrenia. Adverse effects reported include bizarre and violent behaviour, hallucinations, euphoria, agitation, catatonic rigidity, disorientation, incoordination, nystagmus, hypersalivation, vomiting, convulsions, numbness, hypertension, tachycardia, rhabdomyolysis leading to renal failure, acidosis, and, occasionally, malignant hyperthermia. Severe intoxication may result in respiratory depression, coma, and death.

In cases of phencyclidine overdose, activated charcoal should preferably be given within 1 hour of ingestion; multiple doses may be of benefit since phencyclidine is actively secreted into the gastrointestinal tract. Treatment of the adverse effects of phencyclidine is symptomatic; if agitated the patient should be kept quiet in a darkened room, and diazepam given if necessary. Butyrophenone antipsychotics such as haloperidol have been used for severe behavioural problems and psychoses, although they are associated with adverse effects and some suggest that they should generally be avoided. Phenothiazines may lower the seizure threshold and should also be avoided. Hyperthermia should be treated. Renal excretion should be promoted by hydration and use of diuretics if necessary. Acidification of the urine is no longer recommended since acidosis may be exacerbated and renal failure precipitated.

Breast feeding. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by a breast-feeding mother, phencyclidine has caused hallucinogenic effects in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/07/04)

Uses and Administration

Phencyclidine is related chemically to ketamine (see p.1787) and is a potent analgesic and anaesthetic. It was formerly given intravenously to produce an amnesic trance-like state, with analgesia, but severe adverse effects, especially postoperative psychoses, precluded its use. It was formerly used in veterinary medicine as an immobilising agent. Phencyclidine is widely abused in some countries for its hallucinogenic effects and has been taken orally, sniffed, injected, or smoked.

Numerous analogues of phencyclidine have been similarly abused and include:

- PHP (rolicyclidine; 1-(1-phenylcyclohexyl)pyrrolidine)
- PCC (1-piperidinocyclohexanecarbonitrile)
- PCE (*N*-ethyl-1-phenylcyclohexylamine)
- TCP (1-[1-(2-thienyl)cyclohexyl]piperidine)

Phenolsulfonphthalein

Czerwień fenolowa; Fenolisulfoniftaleiini; Fenolsulfonftaleina; Fenolsulfonftalein; Fenolsulfonftaleína; Fenolsulfonftaleinas; Fenolszulfonftalein; Phenol Red; Phénolsulfonephtaléine; Phenolsulfonphthaleinum; Phenolsulphonphthalein *(BAN)*; PSP. 4,4′-(3*H*-2,1-Benzoxathiol-3-ylidene)diphenol *S,S*-dioxide.

$C_{19}H_{14}O_5S$ = 354.4.

CAS — 143-74-8.

ATC — V04CH03.

ATC Vet — QV04CH03.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Phenolsulfonphthalein; Phenolsulphonphthalein BP 2008). A bright to dark red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

USNF 26 (Phenolsulfonphthalein). A bright-red to dark-red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

Profile

Phenolsulfonphthalein has been used as a test of renal function by estimating the rate of urinary excretion after intravenous administration. It has also been given intramuscularly.

Alkaline urine is coloured red to violet.

Phenolsulfonphthalein has also been used as a drug ingestion indicator, a marker in drug absorption studies, and in a test of residual urine.

Hypersensitivity reactions to phenolsulfonphthalein may occasionally occur.

Phenylpropanol

Ethyl Phenyl Carbinol; Fenilpropanol; α-Hydroxypropylbenzene; SH-261. 1-Phenylpropan-1-ol; α-Ethylbenzyl alcohol.

$C_9H_{12}O$ = 136.2.

CAS — 93-54-9.

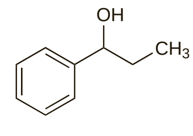

Pharmacopoeias. In *Chin.*

Profile

Phenylpropanol is a choleretic used for the treatment of biliary-tract and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Hedonin; ***Braz.:*** Quelodin†.

Phloroglucinol *(BAN)*

Floroglucinol; Floroglucynol; Floroglusinoli; Phloroglucin; Phloroglucinolum. Benzene-1,3,5-triol.

$C_6H_6O_3$ = 126.1.

CAS — 108-73-6.

ATC — A03AX12.

ATC Vet — QA03AX12.

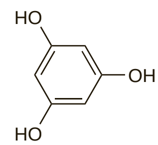

Pharmacopoeias. In *Eur.* (see p.vii), which also includes the dihydrate.

Ph. Eur. 6.2 (Phloroglucinol, Anhydrous; Phloroglucinolum Anhydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Ph. Eur. 6.2 (Phloroglucinol Dihydrate; Phloroglucinolum Dihydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Profile

Phloroglucinol is used as an antispasmodic sometimes in combination with trimethylphloroglucinol. It has been given by mouth, intravenous or intramuscular injection, and rectally.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pasmovit; ***Fr.:*** Spasfon-Lyoc; Spassirex; ***Ital.:*** Spasmex; ***Mex.:*** Panclasa.

Multi-ingredient: ***Arg.:*** Nero; ***Belg.:*** Spasfon; ***Fr.:*** Meteoxane; Spasfon; ***Gr.:*** Spasfon; ***Ital.:*** Spasmex; ***Mex.:*** Klonaza; Morelax; Panclasa.

Phosgene

Carbonic Dichloride; Carbonyl Chloride; Chloroformyl Chloride; Fosgen; Fosgeno.

$COCl_2$ = 98.92.

CAS — 75-44-5.

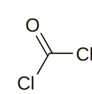

Adverse Effects

Poisoning may occur from industrial use or from the generation of phosgene from chlorinated compounds such as dichloromethane, chloroform, or carbon tetrachloride in the presence of heat. Symptoms of poisoning, which may be delayed for up to 24 (rarely 72) hours, include burning of the eyes and throat, cough, dyspnoea, cyanosis, and pulmonary congestion and oedema. Death may result from anoxia. Exposure to 50 ppm may be rapidly fatal. Massive exposure may cause intravascular haemolysis, thrombus formation, and immediate death. Exertional dyspnoea may persist for months after exposure to high concentrations.

Treatment of Adverse Effects

After inhalation of phosgene or absorption from the skin, treatment consists of complete rest and inhalation of oxygen. The mouth, eyes, nose, and skin should be irrigated with copious amounts of water. Oral or parenteral corticosteroids have been used for bronchospasm but the role of inhaled corticosteroids is considered to be controversial. Antibacterials may reduce respiratory infections. Further treatment is symptomatic.

Uses and Administration

Phosgene is used in the chemical industry. It has been used as a war gas.

◊ References.

1. Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med* 2001; **43:** 110–9.

Phosphatidyl Choline

Fosfatidilcolina; Phosphatidylcholine.

Profile

Phosphatidyl choline is a phospholipid and a constituent of lecithin (p.2332). Phosphatidyl choline is an ingredient of preparations that have been promoted for liver disorders, peripheral vascular disorders, hyperlipidaemias, and fat emboli. Some injection preparations of phosphatidyl choline have been promoted for use in cosmetic surgery to remove subcutaneous fat deposits, but this use is not licensed in the UK.

Ulcerative colitis. Phosphatidyl choline is a component of mucus and plays a key role in mucosal defence. Since a disturbed mucosal barrier is believed to be a factor in the pathogenesis of ulcerative colitis, exogenous phosphatidyl choline has been investigated to improve the protective effects of colonic mucus. Controlled-release oral phosphatidyl choline was beneficial compared with placebo in patients with ulcerative colitis in 2 small short-term studies.[1,2]

1. Stremmel W, *et al.* Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. *Gut* 2005; **54:** 966–71.
2. Stremmel W, *et al.* Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. *Ann Intern Med* 2007; **147:** 603–10.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Essentiale†; Lipostabil†; ***Singapore:*** Hepakur; ***USA:*** PhosChol.

Multi-ingredient: ***Arg.:*** Ikx Gel Reductor; ***Austral.:*** Tyroseng†; ***Ger.:*** Repithel; ***India:*** Livage; ***Indon.:*** Liposerin; ***Ital.:*** Essaven; Zeroac; ***Singapore:*** Memoloba†.

Phosphatidyl Serine

Fosfatidilserina; Phosphatidylserine.

Profile

Phosphatidyl serine is a phospholipid that has been tried in the treatment of organic psychiatric syndromes and investigated as a cognition adjuvant. Phosphatidyl serine is a constituent of lecithin (p.2332).

Phosphoserine, which lacks the lipid and glycerol groups of phosphatidyl serine, has been used similarly; both (+)-L-phosphoserine (dexfosfoserine) and the racemic form (DL-phosphoserine) have been used. Phosphoserine has sometimes been used as a synonym for phosphatidyl serine.

◊ References.

1. Pepping J. Phosphatidylserine. *Am J Health-Syst Pharm* 1999; **56:** 2038, 2043–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Bros; ***UK:*** Cognito.

Multi-ingredient: ***Ger.:*** Vitasprint B †; ***India:*** Livage; ***Indon.:*** Liposerin; ***Ital.:*** Acutil Fosforo; Briogen†; Fosfo Plus; Glutamin Fosforo; Memovisus†; Memovit B12; NeoBros; NeoBros 10; NeoBros C; Vitasprint Complex†; Vitasprint†; ***Spain:*** Agudil; Nucleserina; ***Switz.:*** Vitasprint Complex.

Phosphoric Acid

Acide phosphorique; Acido Fosfórico; Acidum phosphoricum; Concentrated Phosphoric Acid; E338; Fosfato rūgštis; Fosfórico, ácido; Fosforihappo; Fosforsyra; Foszforsav; Kwas fosforowy; Kyselina fosforečná; Orthophosphoric Acid; Phosph. Acid; Phosphorsäure.

H_3PO_4 = 98.00.
CAS — 7664-38-2.

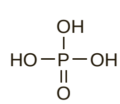

Pharmacopoeias. *Eur.* (see p.vii) includes various concentrations. Also in *USNF.*

Ph. Eur. 6.2 (Phosphoric Acid, Concentrated; Phosphoric Acid BP 2008). It contains 84 to 90% w/w of H_3PO_4. A clear, colourless, corrosive, syrupy liquid. When stored at a low temperature it may solidify, forming a mass of colourless crystals which do not melt until the temperature reaches 28°. Miscible with water and with alcohol. Store in glass containers.

Ph. Eur. 6.2 (Phosphoric Acid, Dilute). It contains 9.5 to 10.5% w/w H_3PO_4 and is prepared by mixing phosphoric acid 115 g with water 885 g.

USNF 26 (Phosphoric Acid). It contains 85 to 88% w/w of H_3PO_4. A colourless, odourless liquid of syrupy consistency. Miscible with water and with alcohol. Store in airtight containers.

USNF 26 (Diluted Phosphoric Acid). It contains 9.5 to 10.5% w/v H_3PO_4 and may be prepared by mixing phosphoric acid 69 mL with purified water to 1000 mL. A clear, colourless, odourless liquid. Store in airtight containers.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing phosphoric acid-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p.1661.

Uses and Administration

Phosphoric acid has industrial uses. Dilute phosphoric acid has been used well diluted in preparations intended for the management of nausea and vomiting (p.1700); it has also been included in preparations for vaginal infections. Phosphoric acid is used in dentistry to etch tooth enamel.

Homoeopathy. Phosphoric acid has been used in homoeopathic medicines under the following names: Acidum phosphoricum; Phosphoricum acidum; Ac. phos.

Preparations

USP 31: Sodium Fluoride and Phosphoric Acid Gel.

Proprietary Preparations (details are given in Part 3)
Fr.: Phosoforme†.

Multi-ingredient: ***Arg.:*** Plus & White†; ***Austral.:*** Emetrol†; ***Braz.:*** Paratonico; ***Chile:*** Homeofortin III†; ***Fr.:*** Actiphos†; Biotone†; Ionyl; Marinol; Phosphoneuros; ***Gr.:*** Enter-Out; Kathargon; Mineralin; Phospho-Laxat; Phosphoclean; Trifalac; ***Israel:*** Peptical; ***S.Afr.:*** Emetrol; Emex; ***Spain:*** Oximen; ***Thai.:*** Quinradon-N; ***USA:*** Emetrol; Formula EM; Nausetrol.

Phosphorus

Fósforo; Fósforo amarillo; Fósforo blanco; Phosphor; Phosphore; White Phosphorus; Yellow Phosphorus.

P = 30.973762.
CAS — 7723-14-0.

Handling. Phosphorus has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Stability and storage. Phosphorus is unstable in air and should be stored under water.

Adverse Effects

Acute poisoning by yellow (white) phosphorus, a general protoplasmic poison, occurs in three distinct stages. The first stage represents local gastrointestinal irritation with intense thirst, pain, nausea, vomiting, and diarrhoea. The vomitus and stool may smell of garlic and are luminescent. Shock, delirium, convulsions, coma, and death may occur. In patients who survive, a second, asymptomatic stage may be present lasting for up to several days or even weeks. The third stage represents systemic toxicity characterised by hepatic and renal damage, cardiovascular collapse, and CNS involvement including confusion, convulsions, and coma. Death may occur during either the first or third stages.

The fatal dose is about 1 mg/kg.

Symptoms of chronic poisoning are associated with defective tissue repair, including necrosis of the mandible ('phossy jaw').

Externally, phosphorus causes severe burns to the skin. Phosphorus is absorbed after skin contamination and systemic symptoms may occur.

Treatment of Adverse Effects

Gastric lavage may be considered after ingestion of elemental yellow (white) phosphorus, although the risks versus potential benefits must be considered in order to prevent spontaneous combustion. Activated charcoal may be used, although there is no clear evidence of benefit. Induction of emesis is contra-indicated. Potassium permanganate solution 1 in 5000 has been instilled into the stomach in an attempt to convert elemental phosphorus to an oxide, but there is no sound clinical reason to recommend this.

Further treatment is symptomatic and supportive and may include fluid and electrolyte replacement, and management of convulsions and renal and hepatic dysfunctions.

Contaminated areas on skin should be immersed in water or irrigated with copious amounts of warm water. Solutions containing copper sulfate have also been suggested for dermal irrigation to convert elemental phosphorus to copper phosphate, although concerns have been raised due to its potential to cause lethal haemolysis through inhibition of G6PD. Eyes contaminated with phosphorus should be irrigated with copious amounts of tepid water for at least 15 minutes. Exposed areas should be covered with wet dressings or compresses to prevent spontaneous combustion. It is essential that all particles of unoxidised phosphorus are removed from the skin. Lipid or oil-based topical preparations may increase the absorption of phosphorus through the skin and should not be used.

Uses and Administration

Elemental phosphorus is no longer used in medicine. Inorganic phosphates are given in deficiency states and bone diseases (see Uses and Administration of Sodium Phosphate, p.1683). Phosphorus has been used in the manufacture of rat and cockroach poisons.

Homoeopathy. Phosphorus has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Sigmaflex; ***Singapore:*** Lacto Calcium†.

Physalis

Alkékenge; Alkekengi; Alquequenje; Amour en cage; Bladder Cherry; Blasenkirsche; Chinese Lantern; Coqueret; Ground Cherry; Judenkirsche; Lampionblume; Strawberry Tomato; Winter Cherry.

Pharmacopoeias. In *Chin.*

Profile

The berries of *Physalis alkekengi* (Solanaceae) are reputed to have diuretic properties.

Cape gooseberry is the edible fruit of *P. peruviana.*

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Hyric.

Picibanil

OK-432.

Пицибанил
CAS — 39325-01-4.

Profile

Picibanil is a lyophilised preparation of a low-virulence strain of *Streptococcus pyogenes* inactivated by heating with benzylpenicillin; it is reported to act as an immunomodulator. It has been given by injection in the treatment of malignant neoplasms.

◊ References.

1. Luzzatto C, *et al.* Sclerosing treatment of lymphangiomas with OK-432. *Arch Dis Child* 2000; **82:** 316–18.
2. Sakamoto J, *et al.* Meta-analysis of adjuvant immunochemotherapy using OK-432 in patients with resected non-small-cell lung cancer. *J Immunother* 2001; **24:** 250–6.
3. Laranne J, *et al.* OK-432 (Picibanil) therapy for lymphangiomas in children. *Eur Arch Otorhinolaryngol* 2002; **259:** 274–8.
4. Sakamoto J, *et al.* Efficacy of adjuvant immunochemotherapy with OK-432 for patients with curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials. *J Immunother* 2002; **25:** 405–12.
5. Giguere CM, *et al.* Treatment of lymphangiomas with OK-432 (Picibanil) sclerotherapy: a prospective multi-institutional trial. *Arch Otolaryngol Head Neck Surg* 2002; **128:** 1137–44.
6. Watanabe M, *et al.* Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur. *Int J Clin Oncol* 2004; **9:** 98–106.
7. Sato Y, *et al.* A randomized controlled study of immunochemotherapy with OK-432 after curative surgery for gastric cancer. *J Immunother* 2004; 394–7.
8. Taniguchi T, *et al.* Clinical results of OK-432 injection therapy for ganglions. *J Dermatol* 2005; **32:** 262–5.
9. Kasahara K, *et al.* Randomized phase II trial of OK-432 in patients with malignant pleural effusion due to non-small cell lung cancer. *Anticancer Res* 2006; **26:** 1495–9.
10. Knipping S, *et al.* Sclerotherapy of cervical cysts with Picibanil (OK-432). *Eur Arch Otorhinolaryngol* 2007; **264:** 423–7.
11. Nygaard U, *et al.* New treatment of early fetal chylothorax. *Obstet Gynecol* 2007; **109:** 1088–92.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Picibanil.

Pidotimod *(rINN)*

Pidotimodum. (*R*)-3-[(*S*)-5-Oxoprolyl]-4-thiazolidinecarboxylic acid.

Пидотимод
$C_9H_{12}N_2O_4S$ = 244.3.
CAS — 121808-62-6.
ATC — L03AX05.
ATC Vet — QL03AX05.

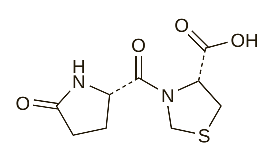

Profile

Pidotimod is an immunostimulant used in patients with cell-mediated immunodepression during respiratory- and urinary-tract infections. It is given orally in usual doses of 800 mg twice daily.

The symbol † denotes a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Polimod; ***Ital.:*** Onaka; Pigitil; Polimod; ***Mex.:*** Adimod.

Pilewort

Celidonia menor; Ficaire; Ficaria Ranunculoides; Ficaria Verna; Lesser Celandine.

Pharmacopoeias. In *Fr.*

Profile

Pilewort, the aerial parts of *Ranunculus ficaria* (Ranunculaceae), has astringent and demulcent properties and is used topically for the treatment of haemorrhoids.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Confortel†; ***Cz.:*** Avenoc; ***Fr.:*** Apaisance; Hemorrogel; ***UK:*** Piletabs.

Pinaverium Bromide *(rINN)*

Bromuro de pinaverio; Pinaverii Bromidum; Pinavérium, Bromure de; Pinaveriumbromid; Pinaveriumbromidi; Pinaveryum Bromür. 4-(6-Bromoveratryl)-4-{2-[2-(6,6-dimethyl-2-norpinyl)ethoxy]ethyl}morpholinium bromide.

Пинаверия Бромид

$C_{26}H_{41}Br_2NO_4$ = 591.4.
CAS — 59995-65-2 (pinaverium); 53251-94-8 (pinaverium bromide).
ATC — A03AX04.
ATC Vet — QA03AX04.

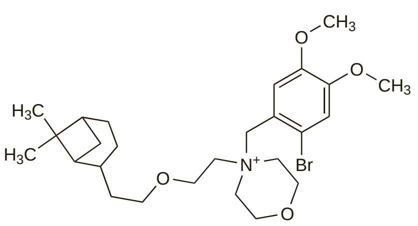

(pinaverium)

Profile

Pinaverium bromide is a calcium-channel blocker with some antimuscarinic-like effects. It is used for the relief of gastrointestinal spasm in usual doses of 50 mg orally three times daily at mealtimes.

Effects on the gastrointestinal tract. Two patients had heartburn and dysphagia after taking pinaverium bromide orally between meals; endoscopy revealed acute oesophageal ulceration, which healed on stopping treatment.[1] The manufacturer's recommendation to take pinaverium bromide during meals was emphasised.

1. André J-M, *et al.* Ulcères oesophagiens après prise de bromure de pinaverium. *Acta Endosc* 1980; **10:** 289–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dicetel; ***Austria:*** Dicetel; ***Belg.:*** Dicetel; ***Braz.:*** Dicetel; ***Canad.:*** Dicetel; ***Chile:*** Eldicet; Laudil†; ***Cz.:*** Dicetel; ***Fr.:*** Dicetel; ***Gr.:*** Dicetel; ***Hung.:*** Dicetel; ***India:*** Eldicet; ***Ital.:*** Dicetel; ***Mex.:*** Dicetel; Zerpyco; ***Philipp.:*** Eldicet; ***Port.:*** Dicetel; ***Rus.:*** Dicetel (Дицетел); ***Spain:*** Eldicet; ***Switz.:*** Dicetel; ***Thai.:*** Dicetel; ***Turk.:*** Dicetel; ***Venez.:*** Dicetel.

Maritime Pine

Cluster Pine; Strandkiefer.
CAS — 174882-69-0 (pycnogenol).

Pharmacopoeias. In *USNF.*

USNF 26 (Maritime Pine). It consists of the bark of stems of *Pinus pinaster* (*Pinus maritima*) (Pinaceae). It contains not less than 8.0% and not more than 12.0% of procyanidins, calculated on the dried basis and is intended to be used in the preparation of extracts only and is not for direct human consumption. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from moisture.

Profile

The bark of the maritime pine, *Pinus pinaster* (*P. maritima*) (Pinaceae) is a source of flavonoid compounds (p.2304). A mixture of procyanidins extracted from the bark is known as pycnogenol, although the term pycnogenols has also been applied to procyanidin flavonoids in general. Preparations of such bark extracts are promoted for their antioxidant action.

Maritime pine is a source of pine needle oil (see Pine Oil, p.2368). Pine needle oil from maritime pine (Pinus pinaster oil) is included in preparations for minor respiratory-tract disorders and in topical preparations for the relief of musculoskeletal, joint, and soft-tissue disorders. Turpentine oil (p.2406) is distilled from the oleoresin.

Preparations

USP 31: Maritime Pine Extract.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Aseptobron; ***Ital.:*** Algorex; Flebil Plus; Flogofort; Signum; ***Philipp.:*** Pynocare 40 Actisome; ***UK:*** Zinopin; ***USA:*** Pycnogenol Plus.

Scots Pine

Pin Sylvestre; Pinus Sylvestris; Scotch pine.

Pharmacopoeias. In *Fr.*

Profile

The sprouts of the Scots pine, *Pinus sylvestris* (Pinaceae), are used in herbal medicine for the treatment of catarrh and in topical preparations for mild muscular pain.

Scots pine is a source of pine sylvestris oil, (see p.2368) and pine needle oil (see Pine Oil, p.2368).

Pine Oil

Profile

Pine oil from unspecified species of pine is included in preparations for the relief of coughs and cold symptoms and in topical preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Oils from fresh needles, tips, and boughs of *Pinus nigra*, *P. mugo* var. pumilio, *P. pinaster* (Maritime Pine, p.2368), and *P. sylvestris* (Scots Pine, p.2368) are all described as pine needle oil.

Specific pine oils include Pine Silvestris Oil (p.2368), Pumilio Pine Oil (p.2376), and Pinus pinaster oil.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Bayagel; Inhalador Medex; Medex Rub; Novobroncol†; Pre Calent; ***Austral.:*** Solyptol†; Tixylix Chest Rub†; ***Belg.:*** Inopectol; ***Braz.:*** Peitoral Martel†; ***Chile:*** Balsamo Leon†; Hansaplast Descongestionante; Hustagil†; Mentholatum Inhalador; Menthose; ***Cz.:*** Dr Theiss Eucalyptus Erkaltungs-Balsam†; Pinosol; ***Fr.:*** Aromasol; Dinacode†; Febrectol; Maghora; Poudre du Marcheur; ***Ger.:*** Babiforton†; Bronchialbalsam†; Bronchoforton Kinderbalsam; Emser Nasensalbe N†; Nasentropfen-ratiopharm†; Pinimenthol Erkaltungsinhalat; Pinimenthol Erkaltungssalbe; Pinimenthol Liquidum; Pinimenthol Nasensalbe†; Pinimenthol S†; stas Erkaltungssalbe mild†; stas Erkaltungssalbe†; Tetesept Badekonzentrat Erkaltungs Bad N†; Tetesept Erkaltungs Balsam N mentholfrei; Transpulmin Baby; Transpulmin Kinderbalsam S; Tussamag Erkaltungsbalsam N†; ***Indon.:*** Sloan's Liniment; ***Israel:*** Ment-O-Cap; ***Ital.:*** Calyptol; Ozopulmin; Ozopulmin G; Pulmarin; Sloan; Vicks Inalante; ***Mex.:*** Balsamo Ifusa; ***NZ:*** Karvol; Tixylix Chest Rub; ***Philipp.:*** Kamillosan M; ***Pol.:*** Analgol; Analgolan; Eukaliptiss; Herbolen; Herbolen D; Inhalol; Pinimentol; Pinosol; Pulmonil; Reumatik; Reumosol; Rhin-Bac; ***Port.:*** Freimax†; Lesil; ***Rus.:*** Carmolis Fluid (Кармолис Жидкость)†; Pinosol (Пиносол); Tussamag Balsam (Туссамаг Бальзам от Простуды); ***S.Afr.:*** Karvol; Respisniffers; Woodwards Inhalant; ***Singapore:*** Karvol; ***Switz.:*** Carmol; Demo pommade contre les refroidissements†; Makaphyt Baume†; Novital; Perskindol Classic; Pinimenthol Baby†; Pinimenthol-N†; Pinimenthol†; Pulmex; Wolo Bain antirefroidissement; Wolo Medicinal bain antirhumatismal; Ziegella; ***UK:*** Dragon Balm; Pickles Smelling Salts; ***Venez.:*** Derpinol†; Reugel.

Pine Silvestris Oil

Borovicová silice; Fir-wool Oil; Kiefernnadelöl; Olejek sosny zwyczajnej; Oleum Pini Silvestris; Pin sylvestre, huile essentielle de; Pini silvestris aetheroleum; Pini Silvestris Etheroleum; Pini Sylvestris Aetheroleum; Scotch Pine Needle Oil; Scots Pine Needle Oil; Sylvestris Pine Oil.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Pine Sylvestris Oil). An essential oil obtained by steam distillation of the fresh leaves and branches of *Pinus sylvestris*. A suitable antioxidant may be added. A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.855 to 0.875. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Pine silvestris oil is obtained from the needles and tips of Scots Pine (p.2368). It is used for catarrh and related disorders of the respiratory tract, often with other volatile substances. It is applied externally for rheumatic disorders and is used in aromatherapy.

P. sylvestris is a source of pine needle oil (see Pine Oil, p.2368).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Bronco Etersan; ***Austral.:*** Karvol†; ***Austria:*** Bronchoforton†; Colda; Emser Nasensalbe; Erkaltungsbalsam; Luuf Balsam; Piniment; ***Cz.:*** Mucoplant Eukalyptovy; Pinosol; ***Fr.:*** Bronchorectine au Citral; Nazinette du Docteur Gilbert; ***Ger.:*** Aerosol Spitzner N†; Bronchicum Balsam mit Eukalyptusol†; Eucabal-Balsam S†; Hustagil Erkaltungsbalsam†; Melrosum Medizinalbad†; Olynth Erkaltungsbalsam†; Phardol Rheuma†; Piniol Erkaltungsbalsam†; Sanopinwern; Tumarol Kinderbalsam; ***Irl.:*** Karvol; ***Israel:*** Karvol; ***Ital.:*** Abiostil; ***Neth.:*** Luuf Verkoudheidsbalsem; ***Pol.:*** Sirupus Pini Compositus; Sirupus Tussipini; Sirupus Tussipini D; ***Port.:*** Solubeol†; ***Rus.:*** Eucabal-S (Эвкабал С); ***S.Afr.:*** Oleum Salviae Comp; ***Spain:*** Balsamo Kneipp†; Genurat; Mitiderma†; Pulmofasa; Sinus Inhalaciones; Vapores Pyt; ***Switz.:*** Frixo-Dragon Vert†; Marament-N; ***UK:*** Karvol; Potter's Catarrh Pastilles; Proctor's Pinelyptus.

Pinene

2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (α-pinene); 6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptane (β-pinene).

$C_{10}H_{16}$ = 136.2.
CAS — 80-56-8 (α-pinene); 127-91-3 (β-pinene).

Profile

Pinene is a terpene constituent of turpentine oil (p.2406) and many other essential oils and has been used in preparations for biliary-tract, urinary-tract, and other disorders. It exists as 2 isomers, α-pinene and β-pinene (nopinene, norpinene, terbenthene, terebenthene).

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Anastim con RTH; ***Austria:*** Rowachol; Rowatinex; ***Braz.:*** Quelodin†; ***Chile:*** Rowatinex; ***Cz.:*** Rowachol; Rowatinex; ***Fr.:*** Pectoderme†; ***Ger.:*** Lindofluid N; Rowachol; Rowachol comp†; Rowachol-Digestiv; Rowatinex; ***Hong Kong:*** Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.:*** Rowachol; Rowatinex; ***Irl.:*** Rowachol; Rowatinex; ***Israel:*** Rowachol; Rowatinex; ***Malaysia:*** Rowachol; Rowatinex; ***Mex.:*** Cholex; ***Philipp.:*** Rowachol; Rowatinex; ***Pol.:*** Rowachol; Rowatinex; Terpichol; ***Spain:*** Rowachol; Rowanefrin; ***Switz.:*** Rowachol; ***Thai.:*** Rowachol; Rowatinex; ***UK:*** Rowachol; ***Venez.:*** Rowachol; Rowatinex.

Pipoxolan *(BAN, pINN)*

Pipoxolán; Pipoxolanum. 5,5-Diphenyl-2-(2-piperidinoethyl)-1,3-dioxolan-4-one.

Пипоксолан

$C_{22}H_{25}NO_3$ = 351.4.
CAS — 23744-24-3.

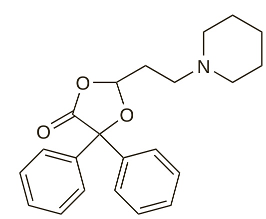

Pipoxolan Hydrochloride *(BANM, USAN, pINNM)*

Hidrocloruro de pipoxolán; Pipoxolan, Chlorhydrate de; Pipoxolani Hydrochloridum.

Пипоксолана Гидрохлорид

$C_{22}H_{25}NO_3,HCl$ = 387.9.
CAS — 18174-58-8.

Profile

Pipoxolan has been used as the base and the hydrochloride as a smooth muscle relaxant.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Rowapraxin†; ***Hong Kong:*** Rowapraxin†; ***Malaysia:*** Rowapraxin†.
Multi-ingredient: ***Irl.:*** Migranat.

Pirenoxine Sodium *(rINNM)*

Catalin Sodium; Natrii Pirenoxinum; Pirenoxina sódica; Pirénoxine Sodique; Pirfenoxone Sodium. Sodium 1-hydroxy-5-oxo-5*H*-pyrido[3,2-*a*]phenoxazine-3-carboxylate.

Натрий Пиреноксин

$C_{16}H_7N_2NaO_5$ = 330.2.
CAS — 1043-21-6 (pirenoxine); 51410-30-1 (pirenoxine sodium).
ATC Vet — QS01XA91.

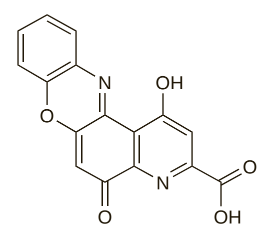

(pirenoxine)

Pharmacopoeias. *Jpn* includes Pirenoxine.

Profile
Pirenoxine sodium is used in the treatment of cataracts, usually as 0.005% eye drops.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Catalin†; ***Braz.:*** Clarvisol; ***Ger.:*** Clarvisor†; ***Gr.:*** Catalin; ***Hong Kong:*** Catalin; Kary Uni; ***India:*** Catalin; ***Indon.:*** Catalin; Kary Uni; ***Ital.:*** Clarvisan; Pirfalin; ***Jpn:*** Catalin; ***Malaysia:*** Catalin†; ***Mex.:*** Clarvisan†; ***Philipp.:*** Catalin; Kary Uni; ***Pol.:*** Catalin; ***Port.:*** Clarvisan; ***Singapore:*** Catalin; Kary Uni; ***Spain:*** Clarvisan; ***Thai.:*** Catalin; Kary Uni.

Pirfenidone *(USAN, rINN)*
AMR-69; Pirfenidona; Pirfénidone; Pirfenidonum. 5-Methyl-1-phenyl-2(1*H*)-pyridone.

Пирфенидон

$C_{12}H_{11}NO = 185.2.$
CAS — 53179-13-8.

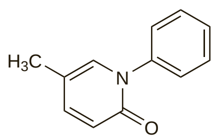

Profile
Pirfenidone is an antifibrotic drug under investigation in disorders such as idiopathic pulmonary fibrosis, multiple sclerosis, and familial adenomatous polyposis.

◊ References.

1. Nicod LP. Pirfenidone in idiopathic pulmonary fibrosis. *Lancet* 1999; **354:** 268–9.
2. Walker JE, Margolin SB. Pirfenidone for chronic progressive multiple sclerosis. *Multiple Sclerosis* 2001; **7:** 305–12.
3. Nagai S, *et al.* Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. *Intern Med* 2002; **41:** 1118–23.
4. Bowen JD, *et al.* Open-label study of pirfenidone in patients with progressive forms of multiple sclerosis. *Multiple Sclerosis* 2003; **9:** 280–3.
5. Lindor NM, *et al.* Desmoid tumors in familial adenomatous polyposis: a pilot project evaluating efficacy of treatment with pirfenidone. *Am J Gastroenterol* 2003;**98:** 1868–74.
6. Azuma A, *et al.* Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; **171:** 1040–7.
7. Walker JE, *et al.* A double-blind, randomized, controlled study of oral pirfenidone for treatment of secondary progressive multiple sclerosis. *Multiple Sclerosis* 2005; **11:** 149–58.
8. Babovic-Vuksanovic D, *et al.* Phase II trial of pirfenidone in adults with neurofibromatosis type 1. *Neurology* 2006; **67:** 1860–2.
9. Shi S, *et al.* Single- and multiple-dose pharmacokinetics of pirfenidone, an antifibrotic agent, in healthy Chinese volunteers. *J Clin Pharmacol* 2007; **47:** 1268–76.

Pirglutargine
Arginina, piroglutamato de; Arginine Pidolate; Arginine Pyroglutamate. L-Arginine DL-pyroglutamate.

$C_{11}H_{21}N_5O_5 = 303.3.$
CAS — 64855-91-0.

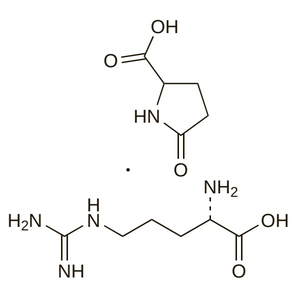

Profile
Pirglutargine has been used for its reputed cerebral stimulant effect.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Adiuvant†.

Multi-ingredient: *Port.:* Detoxergon.

Piridoxilate *(BAN, rINN)*
Piridoxilato; Piridoxilatum; Pyridoxine α_5-Hemiacetal Glyoxylate; Pyridoxylate. The reciprocal salt of 2-(5-hydroxy-4-hydroxymethyl-6-methyl-3-pyridylmethoxy)glycolic acid with 2-[4,5-bis(hydroxymethyl)-2-methyl-3-pyridyloxy]glycolic acid (1:1).

Пиридоксилат

$C_{10}H_{13}NO_6,C_{10}H_{13}NO_6 = 486.4.$
CAS — 24340-35-0.

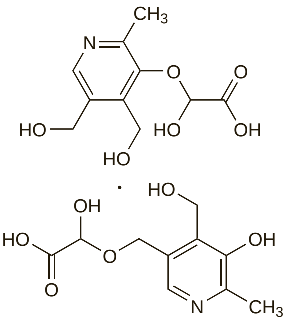

Profile
Piridoxilate was formerly used in the treatment of various circulatory disorders. It has been associated with the development of kidney stones and renal impairment.

Pirisudanol Maleate *(rINNM)*
Dimaleato de pirisudanol; Pirisudanol, Maléate de; Pirisudanoli Maleas; Pyrisuccideanol Maleate. 2-Dimethylaminoethyl 5-hydroxy-4-hydroxymethyl-6-methyl-3-pyridylmethyl succinate maleate.

Пирисуданола Малеат

$C_{16}H_{24}N_2O_6,(C_4H_4O_4)_2 = 572.5.$
CAS — 33605-94-6 (pirisudanol); 53659-00-0 (pirisudanol maleate).
ATC — N06BX08.
ATC Vet — QN06BX08.

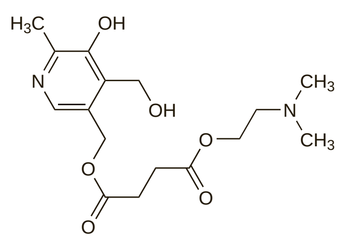

(pirisudanol)

Profile
Pirisudanol is the succinic acid ester of pyridoxine and of deanol. It has been given as the maleate in the management of impaired mental function in doses of up to 1.2 g daily.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Mentium†; ***Port.:*** Pridana; ***Spain:*** Mentis.

Pitofenone Hydrochloride *(rINNM)*
Hidrocloruro de pitofenona; Pitofénone, Chlorhydrate de; Pitofenoni Hydrochloridum. Methyl 2-[4-(2-piperidinoethoxy)benzoyl]benzoate hydrochloride.

Питофенона Гидрохлорид

$C_{22}H_{25}NO_4,HCl = 403.9.$
CAS — 54063-52-4 (pitofenone); 1248-42-6 (pitofenone hydrochloride).

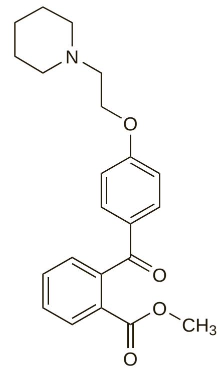

(pitofenone)

Profile
Pitofenone hydrochloride has been used as an antispasmodic.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Cz.:* Algifen; Algifen Neo; Analgin; Spasmopan; ***Fin.:*** Litalgin; ***Pol.:*** Spasmalgon; ***Rus.:*** Baralgetas (Баралгетас)†; Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); ***S.Afr.:*** Baralgan†; ***Thai.:*** Kanegan; ***Venez.:*** Flemibar.

Powdered Pituitary (Posterior Lobe)
Hipófisis pulverizada (neurohipófisis); Hypophysis Cerebri Pars Posterior; Hypophysis Sicca; Ipofisi Posteriore; Pituitarium Posterius Pulveratum; Pituitary; Posterior Pituitary.

NOTE. Pituitary Extract (Posterior) is *BAN*.

Pharmacopoeias. In *Chin.*

Profile
Powdered pituitary (posterior lobe) is a preparation from the posterior lobes of mammalian pituitary bodies. It has oxytocic, pressor, antidiuretic, and hyperglycaemic actions and has generally been replaced by compounds or preparations with more specific actions such as oxytocin (p.2015) and desmopressin (p.2185).

It has been included as an ingredient of a number of preparations of combined tissue extracts promoted as tonics or for a variety of non-endocrine disorders. Hypersensitivity reactions, including anaphylaxis, have occasionally been reported.

Plantain
Llantén; Plantain grand.

Pharmacopoeias. *Chin.* and *Jpn.* include the herb and seeds from *Plantago asiatica*. *Chin* also permits *P. depressa*.

Profile
The seeds and leaves of the common or greater plantain (*Plantago major*) are reported to possess diuretic and antihaemorrhagic properties. They are used in herbal preparations.

The Asian plantain (*P. asiatica*) and the depressed plantain (*P. depressa*) are also used in herbal medicine.

The ribwort plantain (*P. lanceolata*) is described on p.2379.

Homoeopathy. Plantain has been used in homoeopathic medicines under the following names: Plantago; Plantago major; Plant. m.

Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Fr.:* Biopause solution intime; Ephydrol; ***Indon.:*** Hyric; Renax; ***Port.:*** Erpecalm; ***Switz.:*** Kernosan Elixir; Pastilles pectorales Demo N; Pectoral N; Tisane pectorale et antitussive; Tisane pectorale pour les enfants.

Plastics
Plásticos.

Pharmacopoeias. Many pharmacopoeias include standards for plastic containers and closures.

Adverse Effects
Plastic materials used in medicine and pharmacy may give rise to adverse effects, either by direct contact of the plastic with tissues or by indirect contact (for example, when a solution stored in a plastic container, such as a disposable syringe, is injected). Adverse effects may also arise among workers through handling the materials or by inhaling fumes during manufacture.

Pure polymeric plastics appear to be of low toxicity, though carcinogenic effects have been produced by some on prolonged implantation. However, some monomers are toxic, as may be substances added during manufacture to impart specific physical properties. These additives include plasticisers added to reduce brittleness, ultraviolet-ray absorbers to prevent degradation by light, and antoxidants and lubricants which are sometimes needed for satisfactory processing. Monomer residues or additives can leach out from the finished plastic materials and have been the main causes of adverse effects. These may include haemolysis of blood cells, thrombosis, hypersensitivity reactions, precancerous changes, and local tissue necrosis. Silicone particles have been shed from dialysis tubing resulting in hypersplenism, pancytopenia, and occasionally in the production of a granulomatous hepatitis.

See also under Vinyl Chloride, p.2414, Methylmethacrylate, p.2343, and Polytef, below.

Pleurisy Root

Asclepia tuberosa; Butterfly Weed.

Profile

The root of *Asclepias tuberosa* (Asclepiadaceae) has traditionally been used for pleurisy and other respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Broncafect; Verbascum Complex†; ***UK:*** Antibron; Chest Mixture; Horehound and Aniseed Cough Mixture; Vegetable Cough Remover.

Pokeroot

Fitolaca; Poke Root.

Pharmacopoeias. In *Chin.*

Profile

Pokeroot, the root of *Phytolacca decandra* (*P. americana*) (Phytolaccaceae) has emetic, purgative, anti-inflammatory, and anti-infective actions. It has been used for rheumatic and arthritic disorders, and for respiratory-tract infections, but is highly toxic in large doses and is not generally recommended. It has also been used externally for skin disorders.

The related species, *P. dodecandra*, is the source of the molluscicide endod (p.2042).

Homoeopathy. Pokeroot has been used in homoeopathic medicines under the following names: Phytolacca; Phytolacca americana; Phytolacca americana e baccis; Phytolacca e baccis; Phyto.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Homeoplasmina†; ***Fr.:*** Homeoplasmine; ***UK:*** Psorasolv.

Polacrilin Potassium *(USAN, rINNM)*

Kalii Polacrilinum; Polacrilina potásica; Polacriline Potassique; Polacrilinum Kalii.

Калия Полакрилин

CAS — 54182-62-6 (polacrilin); 50602-21-6 (polacrilin).

Pharmacopoeias. In *USNF.*

USNF 26 (Polacrilin Potassium). The potassium salt of a unifunctional low-cross-linked carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene. A white to off-white, free-flowing powder. Has a faint odour or is odourless. Insoluble in water and in most liquids.

Profile

Polacrilin potassium is used as a tablet and capsule disintegrant.

Poliglusam *(USAN, rINN)*

Chitosan; Poliglusamum.

Полиглузам

CAS — 9012-76-4.

Poliglusam Hydrochloride *(rINNM)*

Chitosan Hydrochloride; Chitosane, chlorhydrate de; Chitosanhydrochlorid; Chitosani hydrochloridum; Chitozano hidrochloridas; Hidrocloruro de poliglusam; Kitosaanihydrokloridi; Kitosanhydroklorid; Kitozán-hidroklorid; Poliglusam, Chlorhydrate de; Poliglusami Hydrochloridum.

Полиглузама Гидрохлорид

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Chitosan Hydrochloride). The chloride salt of an unbranched binary heteropolysaccharide consisting of the two units *N*-acetyl-D-glucosamine and D-glucosamine, obtained by partial deacetylation of chitin, normally leading to a degree of deacetylation of 70.0 to 95.0%. Chitin is extracted from the shells of shrimp and crab. A white or almost white fine powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Profile

Poliglusam is a polysaccharide composed of polymers of glucosamine and *N*-acetylglucosamine produced by partial deacetylation of chitin. It is manufactured commercially by chemical treatment of crustacean shells. Poliglusam is under investigation as a pharmaceutical excipient for formulations including oral dosage forms and gene carrier systems. It has been used as a dietary supplement in preparations for obesity and hypercholesterolaemia.

◊ References.

1. Ylitalo R, *et al.* Cholesterol-lowering properties and safety of chitosan. *Arzneimittelforschung* 2002; **52:** 1–7.
2. Jull AB, *et al.* Chitosan for overweight or obesity. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 07/08/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Chito-Lafarmen; ***Braz.:*** Lipenan†; Magrix; ***UK:*** Bio Slim Silueta; Formoline L112.

Multi-ingredient: ***Arg.:*** Exo'Fat†; Redualgas; ***Braz.:*** Control; ***Indon.:*** Betaslim; Combes; Kitoles; Vitaslim; ***Malaysia:*** Chitosan C†; ***Port.:*** Lipoabsorver†; Lipoforte†; Redusan Plus†; ***Singapore:*** Chitosano; Colenon.

Pollen and Pollen Extracts

Profile

Preparations containing pollen and pollen extracts from various sources have been used as nutritional supplements and in preparations for urological disorders. They are also used for allergen immunotherapy (p.2251).

◊ In common with other products derived from bees, products containing bee pollen may cause serious adverse reactions. Many plant pollens may contribute to bee pollen, including common allergens such as ragweed pollen. For reference to hypersensitivity reactions with bee products, including bee pollen, see under Royal Jelly, p.2382.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cernilton; Polenat; ***Austria:*** Prostaflor; ***Belg.:*** Pollinex†; ***Canad.:*** Pollinex-R; ***Cz.:*** Grazax; Pollinex; ***Fr.:*** Pollergon; Prostal; Sodilen; Sthenorex†; ***Ger.:*** Cernilton; Depot-Hal; Pollinex Quattro; Pollinose S†; Purethal; TA Baume; TA Graser; TA MIX; ***Hung.:*** Pollstimol; ***Jpn:*** Cernilton; ***Neth.:*** Allergopharma; Allergovit; Pollinex; Purethal; ***Norw.:*** Alutard; ***Pol.:*** Allergovit; Catalet; Perosall; Pollinex; ***Port.:*** Grazax; ***S.Afr.:*** Allpyral Special Grass; ***Switz.:*** Adenoprostal†; ALK; Polvac; Prostaflor; Staloral; ***UK:*** Grazax; Pollinex.

Multi-ingredient: ***Arg.:*** Optimina Plus; PR21; ***Braz.:*** Multigen AL†; ***Fr.:*** Pollen Royal†; Propargile; ***Ger.:*** Pollstimol; Sublivac; ***Ital.:*** Api Baby; Apistress; Bio-200; Biotrefon Plus; Longevital; Neoplus; Ottovis; Pollingel; Pollingel con Ginkgo Biloba†; Pollingel Ginseng†; ***Philipp.:*** Jamieson Total Energy; Korgivit-E; ***UK:*** Regina Royal Five.

Poly A.poly U

Poli (A). poli (U); Polyadenylic-polyuridylic Acid.

Поли(А).поли(У)

$(C_{10}H_{14}N_5O_7P)x.(C_9H_{13}N_2O_9P)x.$

CAS — 24936-38-7.

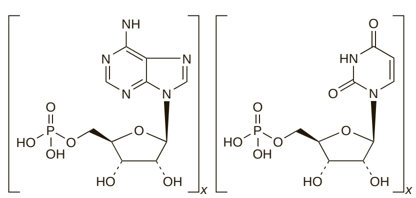

adenylic acid (adenosine phosphate) uridylic acid (uridine phosphate)

Profile

Poly A.poly U is a double-stranded polyribonucleotide comprising polyadenylic and polyuridylic acids, and is believed to be an immunostimulant. It has been studied as an adjuvant in the management of operable solid tumours and in the management of hepatitis B. A complex of potassium polyriboadenylate-potassium polyribouridylate is used in the treatment of viral eye infections.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Poludan (Полудан).

Poly I.poly C

Poli (I). poli (C); Polyinosinic-polycytidylic Acid.

Поли(И).поли(Ц)

$(C_{10}H_{13}N_4O_8P)x.(C_9H_{14}N_3O_8P)x.$

CAS — 24939-03-5.

ATC — L03AX07.

ATC Vet — QL03AX07.

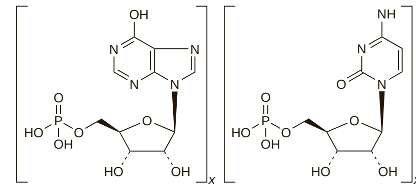

inosinic acid (inosine monophosphate) cytidylic acid (cytidine monophosphate)

Profile

Poly I.poly C is a synthetic double-stranded polyribonucleotide complex of equimolar concentrations of polyinosinic and polycytidylic acids, described as a mismatched double-strand RNA.

Poly I.poly C and the complex of poly I.poly C stabilised with poly-L-lysine in carmellose [poly(ICLC)] have been found to induce the production of interferon and have been investigated in the treatment of malignant neoplasms and viral infections. In the form of poly I.poly C12U (p.902) it has been investigated for the treatment of AIDS, SARS, avian influenza, chronic fatigue syndrome, renal cell carcinoma, and invasive metastatic melanoma; poly(ICLC) has been investigated for the treatment of primary brain tumours.

Polysaccharide-K

Polisacárido-K; PSK; PS-K.

Полисахарид-К

Profile

Polysaccharide-K is a protein-bound polysaccharide isolated from a fungus, *Coriolus versicolor.* It is claimed to have immunostimulant and antineoplastic properties.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Krestin.

Polytef *(USAN)*

Politef *(pINN)*; Politefo; Politefum; PTFE. Poly(tetrafluoroethylene).

Политеф

$(C_2F_4)_n$.

CAS — 9002-84-0.

Profile

Polytef has numerous industrial applications. As 'Teflon' it is used on 'non-stick' cooking utensils.

A paste of polytef has been used for a variety of purposes including the treatment of aphonia, for replacement grafts in vascular surgery, and in the correction of some forms of urinary incontinence (p.2180). The main concern with these procedures is migration of polytef particles. It has also been applied to the skin as a barrier paste with perfluoroalkylpolyether to reduce exposure to chemical warfare agents.

Adverse effects. Brain injury in a child was possibly associated with migration of polytef particles from a periureteral injection performed 1 year earlier.[1] Three cases of polytef adenopathy and one case of giant granuloma have been reported[2] in children who had previously undergone subureteral polytef injection for the treatment of vesicoureteral reflux.

1. Borgatti R, *et al.* Brain injury in a healthy child one year after periureteral injection of Teflon. *Pediatrics* 1996; **98:** 290–1.
2. Aragona F, *et al.* Polytetrafluoroethylene giant granuloma and adenopathy: long-term complications following subureteral polytetrafluoroethylene injection for the treatment of vesicoureteral reflux in children. *J Urol (Baltimore)* 1997; **158:** 1539–42.

Uses. References.

1. Polley JW, *et al.* The use of Teflon in orbital floor reconstruction following blunt facial trauma: a 20-year experience. *Plast Reconstr Surg* 1987; **79:** 39–43.
2. Puri P. Endoscopic correction of primary vesicoureteric reflux by subureteric injection of polytetrafluoroethylene. *Lancet* 1990; **335:** 1320–2.
3. Maskell R, *et al.* Correction of vesicoureteric reflux by endoscopic injection. *Lancet* 1991; **338:** 1460–1.
4. Anonymous. Use of Teflon preparations for urinary incontinence and vesicoureteral reflux. *JAMA* 1993; **269:** 2975–80.
5. Duckett JRA. The use of periurethral injectables in the treatment of genuine stress incontinence. *Br J Obstet Gynaecol* 1998; **105:** 390–6.
6. Su TH, *et al.* Injection therapy for stress incontinence in women. *Int Urogynecol J* 1999; **10:** 200–6.

7. Chaffange P, *et al.* Traitement endoscopique du réflux vésico-rénal chez l'enfant: résultats à court et à long terme des injections de polytétrafluoroéthylene (Téflon). *Prog Urol* 2001; **11:** 546–51.
8. Meschia M, *et al.* Injection therapy for the treatment of stress urinary incontinence in women. *Gynecol Obstet Invest* 2002; **54:** 67–72.
9. Huber TS, *et al.* Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. *J Vasc Surg* 2003; **38:** 1005–11.
10. Klinkert P, *et al.* Saphenous vein versus PTFE for above-knee femoropopliteal bypass: a review of the literature. *Eur J Vasc Endovasc Surg* 2004; **27:** 357–62.

Poplar Buds

Álamo, brotes de; Balm of Gilead Buds.

Pharmacopoeias. *Pol.* includes the leaves from *Populus nigra*.

Profile

The buds of various species of *Populus*, including *P. nigra*, *P. candicans*, *P. gileadensis*, and *P. tacamahacca* (*P. balsamifera*), have been used for the analgesic effect of their salicin content, as well as in preparations for a variety of other disorders. They also contain volatile oil, resin, and other substances. The resin from poplar buds is one of the major sources of propolis (p.2373).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Phytodolor; Valerian†; ***Austria:*** Phytodolor; Prostagutt; ***Braz.:*** Eviprostat†; ***Canad.:*** Bronchial Cough; Mielocol; Wampole Bronchial Cough Syrup†; ***Cz.:*** Homeovox; Phytodolor; ***Ger.:*** Eviprostat N; Phytodolor; Prostamed; ***Indon.:*** Eviprostat; ***Jpn:*** Eviprostat; ***Port.:*** Prostamed†; ***Singapore:*** Eviprostat; ***Switz.:*** Phytomed Prosta†; ***UK:*** Balm of Gilead; Gerard House Reumalex; Peerless Composition Essence; Tabritis.

Poppy-seed Oil

Adormidera, aceite de semilla de; Huile d'Oeillette; Maw Oil; Oleum Papaveris; Oleum Papaveris Seminis.

Profile

Poppy-seed oil is the fixed oil expressed from the ripe seeds of the opium poppy, *Papaver somniferum* (Papaveraceae). It is used as a substitute for olive oil for culinary and pharmaceutical purposes. It is also used in the preparation of Iodised Oil Fluid Injection (BP 2008). Commercial grades are used in making soaps, paints, and varnishes.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Switz.:*** GU Eau†; Olbas.

Potassium Aminobenzoate

Aminobenzoate Potassium; Aminobenzoato potásico. Potassium 4-aminobenzoate.

$C_7H_6KNO_2$ = 175.2.
CAS — 138-84-1.

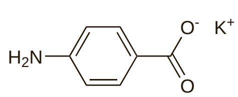

Pharmacopoeias. In *US.*

USP 31 (Aminobenzoate Potassium). A white crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 7, while a 5% solution has a pH of 8.0 to 9.0.

Adverse Effects and Precautions

Anorexia, nausea, fever, and skin rash have been reported.

Potassium aminobenzoate should be given with caution to patients with renal impairment. Licensed product information recommends that treatment should be interrupted during periods of fasting, anorexia, or low food intake, to avoid the possible development of hypoglycaemia.

Interactions

Potassium aminobenzoate can inactivate sulfonamides.

Uses and Administration

Potassium aminobenzoate has been used in the treatment of various disorders associated with excessive fibrosis, such as scleroderma (p.1817) and Peyronie's disease, in usual doses of 12 g daily by mouth in 4 to 6 divided doses.

Peyronie's disease. Variable results have been reported with potassium aminobenzoate in the treatment of Peyronie's disease,[1-3] but evidence from well controlled trials is lacking. It has been suggested that a successful response is more likely if treatment is started in the acute stage.[2]

1. Gingell JC, Desai KM. Peyronie's disease. *BMJ* 1988; **298:** 1489–90.
2. Mohanty KC, Strachan RG. Peyronie's disease. *BMJ* 1989; **298:** 254.
3. Carson CC. Potassium para-aminobenzoate for the treatment of Peyronie's disease: is it effective? *Tech Urol* 1997; **3:** 135–9.

Preparations

USP 31: Aminobenzoate Potassium Capsules; Aminobenzoate Potassium for Oral Solution; Aminobenzoate Potassium Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Potaba; ***Canad.:*** Potaba; ***Ger.:*** Potaba; ***Gr.:*** Potaba; ***UK:*** Potaba; ***USA:*** Potaba.

Potassium Borotartrate

Borotartrato potásico; Potassium Sodium Borotartrate; Soluble Cream of Tartar.
CAS — 12001-68-2.

Profile

Potassium borotartrate is reported to have similar properties to those of bromides (p.2269). It has been used in nervous disorders and has been used in photography as a retarder for alkaline developers. Chronic boron poisoning (see under Boric Acid, p.2268) has been reported following the use of potassium borotartrate internally.

Potassium Bromate

924; Bromato potásico; Potasu bromian.
$KBrO_3$ = 167.0.
CAS — 7758-01-2.

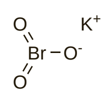

Adverse Effects

Nausea, vomiting, severe abdominal pains, diarrhoea, and lethargy are common after ingestion of potassium bromate. Acute renal failure arising from tubular necrosis usually presents with oliguria or anuria within 1 to 3 days of significant ingestion, and is the most frequent cause of death. Ototoxicity may present as tinnitus or hearing loss within hours of ingestion, and can progress to sensorineural deafness in some patients. Ototoxicity and nephrotoxicity may be irreversible.

Potassium bromate poisoning can also produce hypotension, myocarditis, hepatitis, and encephalopathy characterised by agitation, delirium, convulsions, and coma. Microangiopathic anaemia has also been reported.

Potassium bromate is carcinogenic in *animals.*

Acute toxicity. Reports of bromate poisoning.

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; **7:** 66–70.
2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; **114:** 891–4.
3. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion of potassium bromate; use of a 2 to 5% solution of sodium bicarbonate has been suggested to reduce bromate absorption and prevent hydrobromic acid production. Activated charcoal has also been recommended as an adsorbent. Attention to the patient's fluid, acid–base, and electrolyte status is important, particularly in the presence of acute renal failure. An intravenous infusion of 100 to 500 mL of a 1% sodium thiosulfate solution has sometimes been given. Oxygen may be indicated. The prompt use of haemodialysis or peritoneal dialysis has been suggested.

Thiosulfate. Although the use of intravenous sodium thiosulfate is an accepted practice in the treatment of bromate poisoning, convincing evidence that it reduces bromate to bromide is lacking.[1,2] Oral sodium thiosulfate solutions have also been used but are no longer recommended because hydrogen sulfide, itself a powerful irritant and toxic agent, may be evolved in the presence of hydrochloric acid.[2]

1. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 570–2.
2. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.

Uses

Potassium bromate is an oxidising agent. It has no therapeutic uses but it has been widely used as the 'neutraliser' of thioglycollate hair-waving lotions. It has been used in the preparation of barley malt for beer. It has also been used as a flour-maturing agent but such use is no longer considered appropriate and is prohibited in some countries.

Food additive. Potassium bromate is a genotoxic carcinogen and should not be present in foods when consumed. Its use for the treatment of flour for bread-making is not appropriate.[1]

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 859* 1995. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_859.pdf (accessed 18/07/08)

Potassium Chlorate

Clorato potásico; Kalium Chloricum; Potassii Chloras; Potasu chloran.
$KClO_3$ = 122.5.
CAS — 3811-04-9.

Handling and storage. Potassium chlorate is unstable and, in contact with organic or readily oxidisable substances such as charcoal, phosphorus, or sulfur it is liable to explode especially if heated or subjected to friction or percussion. It should not be allowed to come into contact with matches or surfaces containing phosphorus compounds. Reasonable steps should be taken before supplying potassium chlorate to ensure that it will not be used for the illicit preparation of explosives or fireworks.

Profile

Potassium chlorate has been used as an astringent, usually as a mouthwash or gargle. Concentrated solutions are irritant.

Acute poisoning from ingestion requires prompt symptomatic treatment. Symptoms include nausea, vomiting, diarrhoea, abdominal pain, haemolytic anaemia, haemorrhage, methaemoglobinaemia, hyperkalaemia, and renal failure. There may be liver damage and central effects with convulsions and coma.

Gastric lavage should be considered within 1 hour of ingestion of potassium chlorate; activated charcoal is also recommended by some. If methaemoglobinaemia is severe, patients may require exchange transfusion with whole blood. Several authorities consider that methylthioninium chloride should be given intravenously if methaemoglobinaemia is greater than 30%, although some have advised against such use for fear of converting chlorate to the more toxic hypochlorite.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Fletchers Sore Mouth Medicine; ***Spain:*** Edifaringen; Faringenilo; Solurrinol.

Potassium Hydroxide

Ätzkali; Caustic Potash; E525; Hidróxido potásico; Hydroxid draselný; Kalii hydroxidum; Kalii Hydroxydum; Kalio hidroksidas; Kalium Hydroxydatum; Kálium-hidroxid; Kaliumhydroksidi; Kaliumhydroxid; Potash Lye; Potassium, hydroxyde de; Potasu wodorotlenek.
KOH = 56.11.
CAS — 1310-58-3.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Potassium Hydroxide). White or almost white, crystalline, hard masses, supplied as sticks, pellets, or irregularly shaped pieces; it is deliquescent in air, hygroscopic, and absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. Store in airtight, nonmetallic containers.

USNF 26 (Potassium Hydroxide). It contains not less than 85% of total alkali, calculated as KOH, including not more than 3.5% of K_2CO_3. White or practically white, fused masses, or small pellets, or flakes, or sticks, or other forms. It is hard and brittle and shows a crystalline fracture. Exposed to air, it rapidly absorbs carbon dioxide and moisture, and deliquesces. Soluble 1 in 1 of water, 1 in 3 of alcohol, and 1 in 2.5 of glycerol; very soluble in boiling alcohol. Store in airtight containers.

Adverse Effects and Treatment

As for Sodium Hydroxide, p.2390.

Uses and Administration

Potassium hydroxide is a powerful caustic that has been used to remove warts. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of potassium hydroxide and calcium hydroxide was known as Vienna paste. Potassium hydroxide is used to adjust the pH of solutions in pharmaceutical formulations.

Preparations

BP 2008: Chloroxylenol Solution; Potassium Hydroxide Solution.

Proprietary Preparations (details are given in Part 3)
Spain: Cerumenol.

Multi-ingredient: ***Austria:*** Leberinfusion; ***Ger.:*** Acarex†; Glutarsin E†; Kalium-Magnesium-Asparaginat†; Sekudrill†; ***Ital.:*** Sekudrill.

Potassium Metaphosphate

E452 (potassium polyphosphates); Polifosfato potásico; Potassium Kurrol's Salt; Potassium Polymetaphosphate.

$(KPO_3)_x$.

CAS — 7790-53-6.

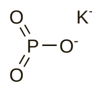

Pharmacopoeias. In *USNF.*

USNF 26 (Potassium Metaphosphate). A straight-chain polyphosphate, having a high degree of polymerisation. It contains the equivalent of 59 to 61% of P_2O_5. A white, odourless powder. Insoluble in water; soluble in dilute solutions of sodium salts.

Profile

Potassium metaphosphate is used as a buffer.

Pramiverine Hydrochloride *(BANM, rINNM)*

EMD-9806 (pramiverine); Hidrocloruro de pramiverina; HSP-2986 (pramiverine); Pramivérine, Chlorhydrate de; Pramiverini Hydrochloridum. *N*-Isopropyl-4,4-diphenylcyclohexylamine hydrochloride.

Прамиверина Гидрохлорид

$C_{21}H_{27}N,HCl = 329.9$.

CAS — 14334-40-8 (pramiverine); 14334-41-9 (pramiverine hydrochloride).

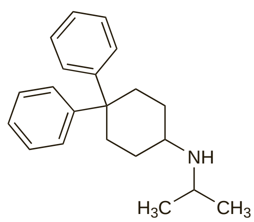

(pramiverine)

Profile

Pramiverine hydrochloride has been used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Systabon; ***Venez.:*** Sistalcin.

Multi-ingredient: *Chile:* Sistalgina†; ***Venez.:*** Sistalcin Compositum.

Pregnancy and Fertility Tests

Pruebas de embarazo y de fertilidad.

Profile

There are a number of kits available for simple pregnancy and fertility testing. A common method of detecting pregnancy is to use specific antibodies to measure the increase in chorionic gonadotrophin in the urine. The period of ovulation can be detected by measuring luteinising hormone excretion in similar ways.

These tests can give false results. Those carrying out the tests should be aware of this and of problems such as contaminated specimens, drug therapy, or other factors that could affect the result.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: After 10†; Ahora Test†; B-Quick; Biofem Test; Evanol; Evaplan; Evatest; Gestatest†; Gravitest†; Mater Test; Nueve Lunas; Ovutest†; PG/53; Si o No†; Simple HCG; Tea Test; Very-Test†; ***Austral.:*** Answer†; Clearblue One Step†; Clearplan One Step†; Clearview HCG; Clinitek HCG†; Crystal Clear†; Discover Onestep; Discover Onestep Ovulation Prediction; Dotest†; Fortel†; Nimbus†; Ovuplan; Pregnosis; ***Braz.:*** Clearblue Easy; Detect Baby; Fertility Day; My Check†; Predictor; ***Canad.:*** Answer Now†; Clearblue; Clearplan; Confirm; Fact Plus; First Response; Simplicity†; ***Chile:*** Clear Blue; Clearplan†; Test Pack Plus†; ***Fr.:*** Babycheck-Plus; BB Test; Bluetest†; Clearblue test d'ovulation; Clearblue test de grossesse; Elle-Test; Emotion; G.Test†; Indicatest†; Predictor; Primastick; Primatime; Revelatest; ***Irl.:*** Omega 1-step; Testpack hCG-Urine; Today Ovulation Test; Uni-Gold hCG; ***Israel:*** Clearblue; Gravindex†; Predictor; Pregnosticon; Prepurex†; ***Ital.:*** Amuelle; Clearblue; Clearplan; Conferma 3 Plus; Confidelle Progress; Diagnosis; Gravitest Crual; Illa; Predictor; ***Jpn:*** Gonavislide; ***Mex.:*** Fertility Day; Intimide†; Pre-Baby; ***NZ:*** Cards HCG-Urine†; Clearblue; Clearplan; Crystal Clear; Discover One Step; LH Predict†; MDS Quick; ***Switz.:*** Clearblue; Clearplan; ***UK:*** Auratek hCG†; Calista; Check-Mate; Clearblue; Clearview HCG; Concept; Discover; Early Bird; Fertell; First Response; Neo-Planotest†; Ovuquick; Predictor; Pregnospia Duoclon†; Quick N Easy; Reveal; Test Pack Plus; ***USA:*** Advance; Answer; Clearblue Easy; Clearblue Easy Ovulation; Clearplan Easy†; Clearview HCG; Conceive Ovulation Predictor†; Conceive Pregnancy; ept Stick Test; Fact Plus; First Response; Fortel; Nimbus; OvuGen†; Ovukit†; Ovuquick†; Pregnosis; QTest; QTest Ovulation†; QuickVue; RapidVue; TestPack Plus hCG-Urine; UCG-Slide; Unistep hCG; ***Venez.:*** Clear Blue Easy†; Clear Plus Easy†.

Prenylamine *(BAN, USAN, rINN)*

B-436; Hoechst-12512; Prenilamina; Prenylamin; Prénylamine; Prenylaminum; Prenyyliamiini. 2-Benzhydrylethyl(α-methylphenethyl)amine.

Прениламин

$C_{24}H_{27}N = 329.5$.

CAS — 390-64-7.

ATC — C01DX02.

ATC Vet — QC01DX02.

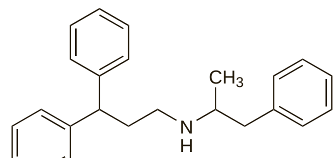

Prenylamine Lactate *(BANM, rINNM)*

Lactato de prenilamina; Prénylamine, Lactate de; Prenylamini Lactas; Prenylaminii Lactas.

Прениламина Лактат

$C_{24}H_{27}N,C_3H_6O_3 = 419.6$.

CAS — 69-43-2.

ATC — C01DX02.

ATC Vet — QC01DX02.

Profile

Prenylamine depletes myocardial catecholamine stores and has some calcium-channel blocking activity. It was formerly used in the treatment of angina pectoris but has been superseded by less toxic drugs. Use of prenylamine has been associated with the development of ventricular arrhythmias and ECG abnormalities. Tremor and extrapyramidal symptoms have also occurred.

Porphyria. Prenylamine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Primula Root

Gullviverot; Kankalingyökér; Kevätesikonjuuri; Primelwurzel; Primevère, racine de; Prímula; Primulae radix; Prvosenkový kořen; Racine de Primevère; Raktažolių šaknys; Schlüsselblumenwurzel.

Pharmacopoeias. *Eur.* (see p.vii) includes Primula root.

Ph. Eur. 6.2 (Primula Root; Primulae Radix). Consists of the whole or cut, dried rhizome and root of *Primula veris* [cowslip] or *P. elatior* [oxlip]. It has a bitter taste. Protect from light.

Profile

Primula root has expectorant properties and is used for cough and other respiratory-tract disorders.

Cowslip, the flowers, leaves, and roots of *Primula veris* (*P. officinalis*) (Primulaceae), is widely used in herbal medicine. The flowers have sedative properties and are used for insomnia, hyperactivity, and anxiety disorders. The flowers and leaves have also been used similarly to primula root.

Oxlip flowers and root (*P. elatior*) and primrose root (*P. vulgaris*) have also been used.

Homoeopathy. Cowslip has been used in homoeopathic medicines under the following names: Primula veris.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *Arg.:* Expectosan Hierbas y Miel; ***Austria:*** Bronchithym; Cardiodoron; Heumann's Bronchialtee; Krauter Hustensaft; Sinupret; Solvopret; Thymoval; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Biotussil; Bronchialtee N†; Bronchicum Elixir†; Bronchicum Hustensirup†; Bronchicum Sekret-Loser†; Bronchipret; Sinupret; ***Ger.:*** Bronchicum Elixir N†; Bronchicum Elixir Plus†; Bronchicum Elixir S; Bronchicum Sekret-Loser†; Bronchicum Thymian†; Bronchipret; Brust- und Hustentee; Cardiodoron; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N; Equisil N; Expectysat N; Harzer Hustenloser†; Heumann Bronchialtee Solubifix T; JuViton†; Kinder Em-eukal Hustensaft†; Kneipp Husten- und Bronchial-Tee; Phytobronchin; Sinuforton; Sinupret; Tussiflorin forte†; Tussiflorin Hustensaft†; Tussiflorin Hustentropfen†; TUSS-infant N†; ***Hong Kong:*** Pectoral†; Sinupret; ***Hung.:*** Bronchipret; Sinupret; ***Indon.:*** Bronchipret; Silex; Sinupret; ***Mex.:*** Bisolsinus; ***Neth.:*** Bronchicum; ***Philipp.:*** Bronchipret; Sinupret; ***Pol.:*** Bronchicum Eliksir; Bronchosol; Herbapect; Sinupret; ***Rus.:*** Bronchicum (Бронхикум); Bronchicum Husten (Бронхикум Сироп от Кашля); Bronchipret TP (Бронхипрет ТП); Sinupret (Синупрет); ***S.Afr.:*** Bronchicough†; Bronchicum†; Cardiodoron; ***Singapore:*** Sinupret; ***Switz.:*** Cardiodoron†; DemoPectol; Kernosan Elixir; Pectoral N; Perpector†; Sinupret; Sirop pectoral contre la toux S; Sirop S contre la toux et la bronchite; Strath Gouttes contre la toux; Strath Gouttes pour les veines; Strath Gouttes Rhumatisme; Tisane pectorale pour les enfants; ***Thai.:*** Sinupret; Solvopret TP; ***UK:*** Bio-Strath Willow Formula; Onopordon Comp B.

Proadifen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de proadifeno; NSC-39690; Proadifène, Chlorhydrate de; Proadifeni Hydrochloridum; Propyladiphenine Hydrochloride; RP-5171; SKF-525-A. 2-Diethylaminoethyl 2,2-diphenylvalerate hydrochloride.

Проадифена Гидрохлорид

$C_{23}H_{31}NO_2,HCl = 390.0$.

CAS — 302-33-0 (proadifen); 62-68-0 (proadifen hydrochloride).

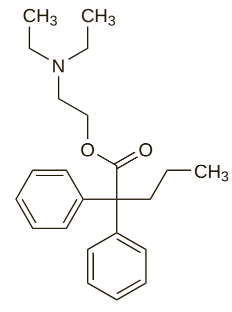

(proadifen)

Profile

Proadifen has been found to enhance the effects of many drugs, possibly by inhibiting metabolism.

Probiotics

Probiotics are defined as live micro-organisms used as food supplements to improve the health of the host when given in adequate amounts.

Lactic-acid-producing Organisms

Láctico, organismos productores de ácido.

МолочноКислые Бактерии

ATC Vet — QA07FA01.

Profile

Lactic-acid-producing organisms were first introduced as potential therapeutic agents with the idea of acidifying the intestinal contents and thus preventing the growth of putrefactive organisms. *Lactobacillus bulgaricus* (*Lactobacillus delbrueckii* subsp. *bulgaricus*), which occurs in naturally soured milk, was the organism originally used but it can be difficult to obtain growth of this organism in the intestines. Natural yogurt is a common source of lactic-acid-producing organisms.

It is now thought that the gastrointestinal tract may play a wider part in host defences and consequently there is increasing interest in the use of live non-pathogenic microbial cultures to optimise the enteric microbiota, including in neonates. These are referred to as probiotics and are generally commensal lactic-acid producing bacteria, although some yeasts are also used. Organisms currently being used in probiotic preparations include *Lactobacillus* spp. and *Bifidobacterium* spp. Other organisms that may be used are *Enterococcus* and *Streptococcus* spp., and the yeast *Saccharomyces boulardii*.

Probiotics are promoted to restore or maintain a healthy microbial flora, and are widely available as yogurts or other fermented milk products, as well as oral dosage forms such as tablets, capsules, and powders. They are being investigated in the management of several gastrointestinal disorders including diarrhoea and inflammatory bowel disorders. Probiotics are also being investigated in vaginal disorders and allergic disorders such as atopic eczema.

A vaccine produced from strains of lactobacillus found in women with trichomoniasis has been used in the prophylaxis of recurrent trichomoniasis (see p.2241).

Adverse effects. Metabolic acidosis has occurred after use of tablets containing *Lactobacillus acidophilus*.[1] Cases of infection associated with the use of lactic-acid-producing organisms seem to be very rare,[2] although fungaemia associated with the use of *Saccharomyces boulardii*,[3] and sepsis associated with *Lactobacillus* spp.[4] have been reported. Reviews[5,6] on the safety of probiotics concluded that their overall safety record is good. However, the authors recommend caution in certain patient groups such as the elderly and premature or immunocompromised neonates because of occasional reports of sepsis that have rarely occurred in previously healthy patients.[5] Use of enterococci and streptococci as probiotics give a theoretical cause for concern since these genera include pathogenic bacteria.[5] Properties of probiotics are specific to species and strain and therefore reports on safety for one probiotic cannot be generalised to others.[5]

1. Oh MS, *et al.* -Lactic acidosis in a man with short-bowel syndrome. *N Engl J Med* 1979; **301:** 249–52.
2. Borriello SP, *et al.* Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003; **36:** 775–80.

3. Piarroux R, *et al.* Are live saccharomyces yeasts harmful to patients? *Lancet* 1999; **353:** 1851–2.
4. Land MH, *et al.* Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005; **115:** 178–81.
5. Boyle RJ, *et al.* Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; **83:** 1256–64.
6. Hammerman C, *et al.* Safety of probiotics: comparison of two popular strains. *BMJ* 2006; **333:** 1006–8.

Composition and viability. Some preparations of probiotics have been found to contain smaller quantities or different species of organisms to those specified on the label.[1] An FAO/WHO working group[2] published some guidelines that should be followed in order to claim that a food has a probiotic effect. These include the genus, species, and strain of the organisms in the preparation to be stated on the product label using currently recognised systematic nomenclature, and a statement of the minimum number of viable organisms remaining at the end of the product shelf-life.

1. Hamilton-Miller JMT, *et al.* "Probiotic" remedies are not what they seem. *BMJ* 1996; **312:** 55–6.
2. FAO/WHO. *Guidelines for the evaluation of probiotics in food.* London Ontario, Canada: Food and Agriculture Organization of the United Nations, 2002. Also available at: http:// www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed 11/02/08)

Uses. ***ALLERGIC DISORDERS.*** Oral ingestion of probiotic bacteria may play a role in the development of the adaptive immune system[1] and there has been some interest in their use in the management of allergic disorders such as atopic eczema.[2-5] However, reviews[6,7] of studies in allergic disorders have concluded that although there appears to be a reasonable theoretical basis for expecting benefit with probiotics, there are insufficient data to support their inclusion in routine treatment regimens for atopic eczema, perennial allergic rhinitis, or asthma.

1. Rinne M, *et al.* Effect of probiotics and breastfeeding on the *Bifidobacterium* and *Lactobacillus/Enterococcus* microbiota and humoral immune responses. *J Pediatr* 2005; **147:** 186–91.
2. Kalliomäki M, *et al.* Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; **361:** 1869–71.
3. Rosenfeldt V, *et al.* Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; **145:** 612–16.
4. Weston S, *et al.* Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; **90:** 892–7.
5. Fölster-Holst R, *et al.* Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155:** 1256–61.
6. Anonymous. Probiotics for atopic diseases. *Drug Ther Bull* 2005; **43:** 6–8.
7. Prescott SL, Björkstén B. Probiotics for the prevention or treatment of allergic diseases. *J Allergy Clin Immunol* 2007; **120:** 255–62.

GASTROINTESTINAL DISORDERS. Oral probiotics are under investigation for several gastrointestinal disorders and although they appear to be of benefit in some conditions, further study is required to confirm these findings. It is probable that efficacy depends on the species and strain of the organism as well as on the condition being treated.[1,2]

Conclusions from a systematic review[3] suggest that probiotics might be a useful adjunct to oral rehydration therapy in the treatment of acute infectious *diarrhoea* in adults and children. A meta-analysis[4] of studies of *Lactobacillus* therapy in children reached a similar conclusion. However, it was not possible to draw up definitive treatment guidelines because of a lack of standardisation in probiotic regimens, patient groups, or definition of acute diarrhoea between the available studies.[3,4] Meta-analyses[5,6] and a systematic review[7] of studies investigating the use of probiotics in the prevention of antibiotic-associated diarrhoea in adults[5] and children[5-7] also suggest a beneficial effect, although again, further clinical confirmation is required before they can be routinely recommended.[5-7] A review[8] of studies that looked specifically at treatment or prevention of *Clostridium difficile*-associated diarrhoea with the probiotics *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* concluded that while these specific probiotics might be useful in patients at risk of recurrent *C. difficile* infection, the potential risks of bacteraemia or fungaemia in this particular patient group might outweigh any benefit.

Probiotics have been investigated to correct aberrant intestinal microflora associated with chronic *inflammatory bowel disease* and reviews of such studies suggest some benefit in the prevention and treatment of ulcerative colitis[9-11] and maintenance of remission in pouchitis,[10-12] although the data are not so clear for Crohn's disease.[10,13] Larger controlled clinical studies, again with standardised probiotic preparations and treatment regimens, are necessary to establish the place of probiotics in the management of inflammatory bowel disease.[9-13] Probiotics do not appear to improve abdominal pain in patients with *irritable bowel syndrome* but they may reduce bloating.[14]

Probiotics given to preterm neonates of very low birth-weight reduced the incidence and severity of *necrotising enterocolitis* in 2 randomised controlled studies.[15,16] A systematic review[17] of these and other controlled studies reached the same conclusion, although the authors called for confirmation of these results by a larger study to strengthen the case for routine use of probiotics in preterm neonates.

Probiotics have also been tried in constipation[18] and infantile colic.[19]

1. Anonymous. Probiotics for gastrointestinal disorders. *Drug Ther Bull* 2004; **42:** 85–8.
2. Limdi JK, *et al.* Do probiotics have a therapeutic role in gastroenterology? *World J Gastroenterol* 2006; **12:** 5447–57.
3. Allen SJ, *et al.* Probiotics for treating infectious diarrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 11/02/08).
4. Van Niel CW, *et al. Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; **109:** 678–84.
5. D'Souza AL, *et al.* Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; **324:** 1361–6.
6. Szajewska H, *et al.* Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *J Pediatr* 2006; **149:** 367–72.
7. Johnston BC, *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 11/02/08).
8. Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. *Ann Pharmacother* 2007; **41:** 1212–21.
9. Bai A-P, Ouyang Q. Probiotics and inflammatory bowel diseases. *Postgrad Med J* 2006; **82:** 376–82.
10. Ewaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 2006; **12:** 5941–50.
11. Chapman TM, *et al.* VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. *Drugs* 2006; **66:** 1371–87.
12. Sandborn W, *et al.* Pharmacotherapy for induction and maintenance of remission in pouchitis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 11/02/08).
13. Rolfe VE, *et al.* Probiotics for maintenance of remission in Crohn's disease. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 11/02/08).
14. Bausserman M, Michail S. The use of *Lactobacillus* GG in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr* 2005; **147:** 197–201.
15. Bin-Nun A, *et al.* Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; **147:** 192–6.
16. Lin H-C, *et al.* Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; **115:** 1–4.
17. Deshpande G, *et al.* Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. *Lancet* 2007; **369:** 1614–20.
18. Banaszkiewicz A, Szajewska H. Ineffectiveness of *Lactobacillus* GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr* 2005; **146:** 364–9.
19. Savino F, *et al. Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007; **119:** e124-e30. Available at: http:// pediatrics.aappublications.org/cgi/reprint/119/1/e124 (accessed 11/02/08)

UROGENITAL INFECTIONS. Probiotic preparations given orally or intravaginally are under investigation for the prevention or treatment of vaginal infections. Reviews of studies in vulvovaginal candidiasis[1] and bacterial vaginosis[2] concluded that while there was some indication of benefit, larger controlled studies are required to confirm efficacy and the place of probiotics in therapy. A systematic review[3] confirmed that probiotics may be of benefit in the prevention and treatment of bacterial vaginosis in pregnancy but due to insufficient data it was not possible to assess the effect that this might have in preventing preterm labour. A review[4] of studies investigating probiotics for the prevention of urinary-tract infections in women has suggested some benefit.

1. Falagas ME, *et al.* Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. *J Antimicrob Chemother* 2006; **58:** 266–72.
2. Falagas ME, *et al.* Probiotics for the treatment of women with bacterial vaginosis. *Clin Microbiol Infect* 2007; **13:** 657–64.
3. Othman M, *et al.* Probiotics for preventing preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Falagas ME, *et al.* Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs* 2006; **66:** 1253–61.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acidofilofago; Flevic; Floratil; Lactinex; Tropivag; ***Austral.:*** Bioglan Acidophilus; Bioglan Superdophilus; Forbiotic; ProTract; ***Austria:*** Antibiophilus; Bioflorin; Lactofit; Reflor; Symbioflor Enterococcus; Yomogi; ***Belg.:*** Enterol; Lacteol; ***Braz.:*** Flomicin; Floratil; Floren; Florent; Lactipan; Leiba; Repoflor; ***Canad.:*** Bacid; Lacidofil; ***Chile:*** Bio-Flora; Biolactus; Econormotil; Gastrofloral; Lacteol Forte†; Lactil; Perenteryl; Perocur†; ***Cz.:*** Enterol; Santax S†; Solco-Trichovac†; ***Denm.:*** Paraghurt; Precosa; ***Fin.:*** Lactophilus; Precosa; ***Fr.:*** Bacilor; Bioprotus; Diarlac†; Gynophilus; Lacteol; Lyo-Bifidus; Ultra-Levure; Ultraderme†; ***Ger.:*** Acidophilus†; Hylak N; Hylak Plus; Infectodiarrstop GG†; Lacteol; Lyseen; Omnisept†; Paidoflor; Perenterol; Symbioflor 1; Vagiflor; ***Gr.:*** Ultra-Levure; ***Hong Kong:*** Bioflor; Lacteol; Reuteri; ***Hung.:*** Enterol; Gynevac; Symbioflor 1; ***India:*** Cefocef-LB; Myconip; Sporlac; ***Indon.:*** Lacbon; Rillus; ***Ital.:*** Bioflorin; Calagin; Codex; Dicoflor; Ecoflorina; Ferlactis†; Inulac; Lab/A†; Lacteol; Lactonorm; Ramno-Flor†; Regolact Plus; Reuflor; ***Mex.:*** Floratil; Lacteol Fort; Lactipan; Lactocil; Lactovita; Liolactil; Neoflor; Sinuberase; ***NZ:*** Blis K12 Throat Guard; ***Philipp.:*** Infloran; ***Pol.:*** Enterol; Lactovaginal; Lakcid†; ***Port.:*** Antibiophilus; Enterol†; Lacteol; UL 250†; ***Rus.:*** Enterol (Энтерол); Gastropharm (Гастрофарм); IRS 19 (ИРС 19); ***S.Afr.:*** Actiflora; Inteflora; ***Singapore:*** DiarrStope; Lacteol; Protexin; Reutefene; ***Spain:*** Casenfilus; Lacteol; Lactofilus; Ultra-Levura; ***Swed.:*** Precosa; ***Switz.:*** Bioflorin; Fiormil†; Florosan; Lacteol†; Lactoferment; Perenterol; SolcoTrichovac Lyophilisat; Ultra-Levure; Ventrux†; ***Thai.:*** Lacbon†; Lacteol†; ***Turk.:*** Reflor; ***UK:*** Bio Acidophilus; Biodophilus; Gum PerioBalance; Infacol Probiotic; ***USA:*** Acidophilus; Bacid; Florastor; Intestinex; Kala; Lactinex; Lacto-Key; MoreDophilus; Pro-Bionate; Superdophilus; ***Venez.:*** Florcidin; Florestor; Lacteol; Lactobacilos; Liolactil; Proflor.

Multi-ingredient: ***Arg.:*** Bioflora; Biol Preo; Factor Bioenterico; Faelac†; Nilflux; Totalflora; Tropivag Plus; ***Austral.:*** Acidophilus Bifidus; Acidophilus Plus; Cyto-Bifidus; ***Austria:*** Gynoflor; Hylak; Hylak Forte; Infloran; Omniflora; Prosymbioflor†; Trevis; ***Belg.:*** Carbolactanose; Gynoflor; ***Canad.:*** Fermalac Vaginal; ***Chile:*** Bion 3; ***Cz.:*** Fermalac Vaginal; Gynoflor; Hylak Forte; Imudon; IRS 19†; Lacidofil; Solco-Urovac†; ***Fr.:*** Actyfilus; Biolactyl; Biotravel; Ergyphilus; Estrofort; Florgynal; Imgalt; Imudon†; IRS 19†; Maxi-Flore; Ophidus; Probionat; Triphidus; Trophigil; Ultrabiotique; ***Ger.:*** Antiprurit†; Gynoflor; InfectoDiarrstop LGG; IRS 19; Omniflora N; Perison; Pro-Symbioflor; StroVac; ***Hong Kong:*** Infloran; Lacspan; Protexin Balance; Protexin Balance+; Protexin Restore; Protexin Vitality; Shin-Biofermin S; ***Hung.:*** Gynoflor; Trevis; ***India:*** ABClox; Ampilox-LB; Amplus; Ampoxin-LB; Bicidal Plus; Bifilac; Biomoxil-LB; Campicillin Plus; Cefix LB; Cephadex LB; Clax; Imox-Clo LB; Lactisyn; LMX; Megaclox LB; Novaclox LB; Novamox LB; Nutrolin-B; Symbiotik; Symoxyl-LB; Vitazyme; Vizylac; ***Indon.:*** Dialac; Gastro-Ad; Lacidofil; Lacto-B; Laktobion; Protexin; Synbio; ***Ital.:*** Al-Flor†; Altaflora Probiotici; Bifilact; Bio Fibralax Bi-Attivo; Bio Flora; Biolactine; Colifagina; Decon Lavanda; Ecofermenti; Endolac; Enterolactis; Enteroseven; Fermenturto-Lio; Floragermina 6; Florbiox†; Florelax; Floren; Floridral; Florvis GG; Gastroenterol; Genefilus F19; Giflorex; Ginil; Infloran; Infloran Bio; Kiri; Lactipan; Lactisporin; Lactivis; Lactogermine; Lactolife; Liozim; Liverton; Neo Lactoflorene; Neogyn; Nepiros; Ninfagin; Psyllogel Fermenti; Ramno Fix; Ramnoflor Plus; Rivuclin; Triacid; Vaxitiol; Yovis; Yovita; ***Jpn:*** The Guard Seichojo; ***Malaysia:*** Hexbio; ***Mex.:*** Neo-Panlacticos; Neo-Panlacticos Plus; Pro-T-Flor; ***Pol.:*** IRS 19; Lacidofil; Trilac; ***Port.:*** Coli-Fagina S; Gynoflor; Infloran†; ***Rus.:*** Acipol (Аципол); Bifiform (Бифиформ); Hylak Forte (Хилак Форте); Imudon (Имудон); Linex (Линекс); SolcoTrichovac (Солкотриховак); ***S.Afr.:*** Culturelle; Culturelle VC; ***Spain:*** Infloran; ***Switz.:*** Gynoflor; Infloran; Ribolac; SolcoTrichovac; ***Thai.:*** Infloran; ***Turk.:*** Gynoflor; ***UK:*** Acidophilus Plus; Beneflora; Culture Care; Fibre Dophilus; Natudophilus; Vinalac; ***USA:*** Acidophilus with Bifidus; Floranex; Pamine FQ Kit; SynBiotics-3; VSL#3; ***Venez.:*** Glutapak-R.

Promelase *(pINN)*

Promelasa; Promélase; Promelasum; Seaprose S.

Промелаза

CAS — 9074-07-1.

Profile

Promelase is an alkaline protease derived from *Aspergillus melleus*. It has been taken by mouth in doses of 30 to 90 mg daily for its supposed benefit in oedema and inflammation associated with trauma, infection, and surgical procedures.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Altan; Flaminase; Mezen†; ***Port.:*** Onoprose†; ***Thai.:*** Korynase†.

Pronase

Profile

Pronase is a mixture of proteinases obtained from *Streptomyces griseus*.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Empynase.

Propolis

Bee Glue; Propóleo; Própolis.

Прополис

Profile

Propolis is a resinous substance collected by bees, primarily, at least in temperate climates, from poplar buds (see also p.2371) and to a lesser extent from conifers. It is mixed with wax by bees and used in the construction and maintenance of their hives. Propolis is composed of resins, balsams, essential and aromatic oils, and pollen, although the exact proportions of each varies from region to region, bee species, and local flora, therefore making standardisation of propolis for medicinal use difficult. Propolis has been reported to have anti-inflammatory and antimicrobial properties. It has been used as a nutritional supplement and in preparations for coughs, mouth disorders, and skin disorders. It has been used as an ointment for the relief of symptoms of herpes labialis. Propolis has also been used in cosmetics and varnishes.

Hypersensitivity reactions have been reported.

◊ For reference to hypersensitivity reactions with bee products, including propolis, see under Royal Jelly, p.2382.

Further references to propolis are given below.

1. Grange JM, Davey RW. Antibacterial properties of propolis (bee glue). *J R Soc Med* 1990; **83:** 159–60.
2. Krol W, *et al.* Synergistic effect of ethanolic extract of propolis and antibiotics on the growth of Staphylococcus aureus. *Arzneimittelforschung* 1993; **43:** 607–9.
3. Volpert R, Elstner EF. Interactions of different extracts of propolis with leukocytes and leukocytic enzymes. *Arzneimittelforschung* 1996; **46:** 47–51.
4. Murray MC, *et al.* A study to investigate the effect of a propolis-containing mouthrinse on the inhibition of de novo plaque formation. *J Clin Periodontol* 1997; **24:** 796–8.

The symbol † denotes a preparation no longer actively marketed

5. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem Toxicol* 1998; **36:** 347–63.
6. Lieberman HD, *et al.* Allergic contact dermatitis to propolis in a violin maker. *J Am Acad Dermatol* 2002; **46** (suppl): S30–S31.
7. Giusti F, *et al.* Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis* 2004; **51:** 255–8.
8. Walgrave SE, *et al.* Allergic contact dermatitis from propolis. *Dermatitis* 2005; **16:** 209–15.
9. Majiene D, *et al.* Antifungal and antibacterial activity of propolis. *Curr Nutr Food Sci* 2007; **3:** 304–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Propoleos; ***Austral.:*** Helastop†; ***Chile:*** Propolkit; ***Ger.:*** Propolisept-Salbe; ***Ital.:*** Golapiol; Oral Spray; Pro-30C†; Pro-Gola; Propociclina; Propolcream; ***Pol.:*** Apizel; Propolan; Propolisan; Propolisol; ***USA:*** Probax.

Multi-ingredient: ***Braz.:*** Calmatoss†; Infantoss†; Malvatricin Natural Organic; Proplax†; ***Fr.:*** Pollen Royal†; Propargile; ***Ital.:*** Actires; Altuss; Apistress; Biogreen; Bodyguard; Fosfarsile Forte; Golapiol C; Immumil Plus; Immumil†; Keratolip; Neo-Stomygen; Nepiros; Otosan Natural Ear Drops†; Probigol; Promix 3†; Promix†; Propast; Propomill†; Valda Propoli; ***Switz.:*** Osa gel dentaire aux plantes; ***UK:*** Sinose.

Propylene Glycol

E1520; Glicol Propilênico; Glikol propylenowy; Propilenglicol; Propilénglikol; Propilenglikolis; Propilenoglicol; Propyleeniglykoli; Propylèneglycol; Propylenglycolum; Propylenglykol. (±)-Propane-1,2-diol.

$C_3H_8O_2 = 76.09$.

CAS — 57-55-6 ((±)-propylene glycol); 4254-16-4 ((±)-propylene glycol); 4254-14-2 ((−)-propylene glycol); 4254-15-3 ((+)-propylene glycol).

ATC Vet — QA16QA01.

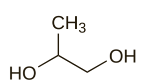

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Propylene Glycol). A clear, colourless, viscous, hygroscopic liquid. Miscible with water and with alcohol. Store in airtight containers.

USP 31 (Propylene Glycol). A clear, colourless, practically odourless, viscous liquid. It absorbs moisture when exposed to moist air. Miscible with water, with acetone, and with chloroform; soluble in ether; will dissolve in many essential oils but is immiscible with fixed oils. Store in airtight containers.

Adverse Effects and Precautions

Systemic toxicity of propylene glycol is considered to be low after oral doses unless large quantities have been ingested, or when preparations containing propylene glycol are given to neonates or to patients in renal failure. Systemic toxicity is manifested most commonly by CNS depression, especially in neonates and children. Other reported adverse effects include hepatic or renal impairment, intravascular haemolysis, seizures, coma, arrhythmias, and cardiorespiratory arrest. Hyperosmolality has occurred, particularly in small infants and in patients with renal impairment; lactic acidosis may also be a greater problem in the latter group.

After topical use, propylene glycol may produce some local irritation, particularly if applied under occlusive dressings or to mucous membranes; toxicity may occur on application to burns. Hypersensitivity reactions have also been reported. Local sensitivity has been reported after use of ear drops with a propylene glycol vehicle. Injections of preparations containing high concentrations of propylene glycol may produce pain or irritation.

Lactic acidosis. Lactic acidosis developed in a patient with normal renal function given a high-dose continuous lorazepam infusion for which propylene glycol was the principal diluent.[1] Despite temporary resolution of symptoms when the infusion was stopped and bicarbonate given, the patient eventually died. A prospective observational pilot study[2] found propylene glycol to be a common cause of metabolic disturbances in intensive care patients receiving intravenous benzodiazepines, and the authors recommended close monitoring of all such patients.

1. Neale BW, *et al.* Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother* 2005; **39:** 1732–6.
2. Wilson KC, *et al.* Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines: a case series and prospective, observational pilot study. *Chest* 2005; **128:** 1674–81.

Interactions

Anticoagulants. Propylene glycol has been reported to decrease the effect of *heparin*.[1]

1. Col J, *et al.* Propylene glycol-induced heparin resistance during nitroglycerin infusion. *Am Heart J* 1985; **110:** 171–3.

Pharmacokinetics

Propylene glycol is rapidly absorbed from the gastrointestinal tract. There is evidence of topical absorption when applied to damaged skin.

It is extensively metabolised in the liver primarily by oxidation to lactic and pyruvic acid and is also excreted in the urine unchanged.

◊ References.

1. Yu DK, *et al.* Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. *J Pharm Sci* 1985; **74:** 876–9.
2. Speth PAJ, *et al.* Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. *Ther Drug Monit* 1987; **9:** 255–8.

Uses and Administration

Propylene glycol is widely used in pharmaceutical manufacturing as a solvent and vehicle, especially for drugs unstable or insoluble in water. It may also be used as a stabiliser in vitamin preparations, as a plasticiser, and as a preservative. Propylene glycol is used extensively in foods and cosmetics.

Propylene glycol has humectant properties and is used similarly to glycerol in topical moisturising preparations.

Propylene glycol is used in veterinary medicine as a glucose precursor.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Advanced Eye Relief.

Multi-ingredient: ***Arg.:*** Systane; ***Austral.:*** Dermatech Liquid; ***Austria:*** Acerbine; ***Canad.:*** Episec; Gyne-Moistrin†; Rhinaris; Rhinedrine Moisturizing†; Salinol†; Secaris; Systane; ***Chile:*** Systane; ***Fr.:*** Intrasite; Propy-Lacticare; Systane; ***Ger.:*** Sekudrill†; ***Hong Kong:*** Moisture Eyes; Systane; ***Israel:*** Pedisol†; Taro Gel; ***Ital.:*** Dopo Pik; Sekudrill; Systane; ***Malaysia:*** Systane; ***Mex.:*** Moisture Eyes; Systane; ***Philipp.:*** Moisture Eyes; Systane; ***S.Afr.:*** Aserbine; ***Singapore:*** Systane; ***Spain:*** Acerbiol; ***Switz.:*** Acerbine†; ***Thai.:*** Systane; ***UK:*** Aserbine†; ***USA:*** Astroglide; Biotene with Calcium; Surgel; Zonite; ***Venez.:*** Systane.

Prostaglandins

Profile

The prostaglandins, along with thromboxanes and leukotrienes, are all derived from 20-carbon polyunsaturated fatty acids and are collectively termed *eicosanoids*. In man, the most common precursor is arachidonic acid (eicosatetraenoic acid) whereas eicosapentaenoic acid is a predominant precursor in fish and marine animals.

Arachidonic acid is released from cell-membrane phospholipids by the enzyme phospholipase A_2 and is then rapidly metabolised by several enzymes, the major ones being cyclo-oxygenase (prostaglandin synthetase) and lipoxygenase (see Figure 1, below). The prostaglandins, thromboxanes, and prostacyclin (sometimes collectively termed *prostanoids*) all contain ring structures and are products of arachidonic acid oxidation by cyclo-oxygenase, an enzyme with 2 isoforms (COX-1 or COX-2) widely distributed in cell membranes.

The leukotrienes are products of the lipoxygenase pathway; arachidonic acid is metabolised by lipoxygenases to hydroperoxyeicosatetraenoic acids, which are then further metabolised to leukotrienes.

The initial step in the cyclo-oxygenase pathway is the formation of cyclic endoperoxide prostaglandin G_2 (PGG_2) which is then reduced to the endoperoxide prostaglandin H_2 (PGH_2). Prostaglandin H_2 is then converted to the primary prostaglandins prostaglandin D_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$, to thromboxane A_2 (TXA_2) via the enzyme thromboxane synthetase, or to prostacyclin (PGI_2) via the enzyme prostacyclin synthetase. These products are further metabolised and rapidly inactivated in the body.

The secondary prostaglandins, prostaglandin A_2 (PGA_2), prostaglandin B_2 (PGB_2), and prostaglandin C_2 (PGC_2) are derived from prostaglandin E_2, but are formed during extraction and probably do not occur biologically.

The prostaglandins are all derivatives of the carbon skeleton 7-(2-octilcyclopentyl)heptanoic acid (also known as prostanoic acid). All natural prostaglandins have a double bond at position 1,2 and a hydroxyl group at position 3 of the octil side-chain. Depending on the substitutions on the cyclopentane ring, the main series of prostaglandins are distinguished by the letters A, B, C, D, E, and F; the members of each series are further subdivided by subscript numbers which indicate the degree of unsaturation in the side-chains—hence, those derived from eicosatrienoic acid (dihomo-γ-linolenic acid) have the subscript 1, those derived from arachidonic acid have the subscript 2, and those derived from eicosapentaenoic acid have the subscript 3. In man, only prostaglandins of the '2' series appear to be of physiological importance. Thromboxane A_2 has an oxane rather than a cyclopentane ring; it is chemically unstable and breaks down to thromboxane B_2. Prostacyclin has a double-ring structure and breaks down to 6-keto-prostaglandin $F_{1\alpha}$.

Endogenous prostaglandins are autacoids; they can be formed by virtually all tissues and cells in response to a variety of stimuli, have a wide range of **actions**, and are involved in the regulation of virtually all biological functions. Prostaglandins appear to act through various receptor-mediated mechanisms. Some of their effects are mediated within cells by activation or inhibition of adenylate cyclase and the regulation of cyclic adenosine monophosphate production. At one time prostaglandin E_2 and prostaglandin $F_{2\alpha}$ were thought to be of paramount importance, but with the discovery of thromboxane A_2, prostacyclin, and the leukotrienes it was realised that these primary prostaglandins belong to a large family of physiologically active eicosanoids. Thromboxane A_2 induces platelet aggregation and constricts arterial smooth muscle whereas prostacyclin causes vasodilatation and prevents platelet aggregation; the balance between these opposing actions has an important role in the regulation of intravascular platelet aggregation and thrombus formation. The leukotrienes are important mediators of inflammation.

The pharmacological properties of prostaglandins are wide-ranging and include contraction or relaxation of smooth muscle in the blood vessels, bronchi, uterus, and gastrointestinal tract; inhibition of gastric acid secretion; and effects on platelet aggregation, the endocrine system, and metabolic processes.

Individual prostaglandins vary greatly in their activities and potencies; their actions also depend on the animal species, on the tissues in which they are acting, and on the concentration present, and entirely opposite actions may be elicited with very small structural changes in the molecule.

The diverse **clinical applications** of prostaglandins reflect their wide-ranging physiological and pharmacological properties. Synthetic analogues have been developed with the aim of obtain-

Figure 1. Prostaglandin biosynthesis.

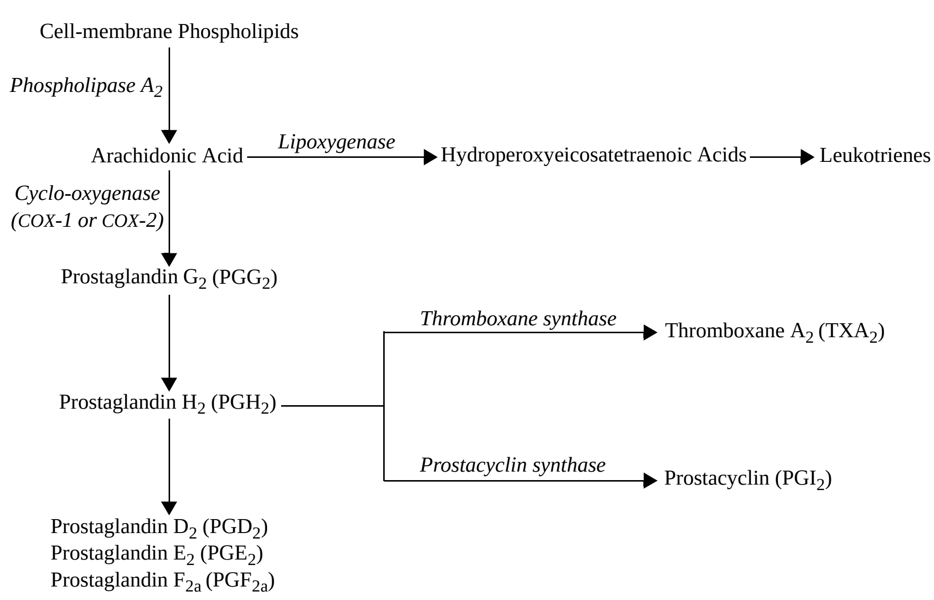

ing compounds that are more stable, have a longer duration of action, and a more specific effect. Applications include:

- softening and dilating the cervix and for uterine stimulation, e.g. dinoprost (prostaglandin F_{2}) (p.2006) and its analogue carboprost (p.2006); dinoprostone (prostaglandin E_2) (p.2007) and its analogue sulprostone (p.2018); and gemeprost (p.2010) and misoprostol (p.2013), analogues of prostaglandin E_1
- vasodilators and inhibitors of platelet aggregation, e.g. alprostadil (prostaglandin E_1) (p.2183) and its analogue limaprost (p.1325); and epoprostenol (prostacyclin) (p.1279) and its analogue iloprost (p.1313)
- inhibition of gastric acid secretion and protection of the gastrointestinal mucosa, e.g. misoprostol (p.2013)
- glaucoma treatment, e.g. bimatoprost (p.1878), latanoprost (p.1882), travoprost (p.1886), and unoprostone (p.1886)
- as luteolytics (causing regression of the corpus luteum in the ovary) in veterinary medicine, e.g. synthetic analogues of prostaglandin F_{2} .

◊ References.

1. Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. *N Engl J Med* 1979; **300:** 1142–7.
2. Higgs GA, Vane JR. Inhibition of cyclo-oxygenase and lipoxygenase. *Br Med Bull* 1983; **39:** 265–70.
3. Halushka PV, *et al.* Thromboxane, prostaglandin and leukotriene receptors. *Annu Rev Pharmacol Toxicol* 1989; **29:** 213–39.
4. Smith WL, *et al.* Prostaglandin and thromboxane biosynthesis. *Pharmacol Ther* 1991; **49:** 153–79.
5. O'Neill C. The biochemistry of prostaglandins: a primer. *Aust N Z J Obstet Gynaecol* 1994; **34:** 332–7.
6. Wu KK. Molecular regulation and augmentation of prostacyclin biosynthesis. *Agents Actions Suppl* 1995; **45:** 11–17.

Protoporphyrin IX Disodium

Protoporfirina IX disódica; Protoporphyrin Disodium. Disodium 7,12-diethenyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoate.

$C_{34}H_{32}N_4Na_2O_4$ = 606.6.

CAS — 50865-01-5 (protoporphyrin IX disodium); 553-12-8 (protoporphyrin IX).

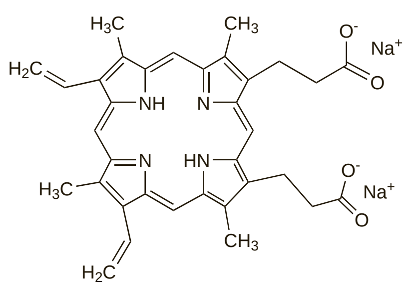

Profile

Protoporphyrin IX disodium has been given by mouth for the treatment of impaired hepatic function associated with gallstones and cholecystitis.

Proxazole Citrate *(USAN, rINNM)*

AF-634; Citrato de proxazol; Propaxoline Citrate; Proxazole, Citrate de; Proxazoli Citras; PZ-17105. *NN*-Diethyl-3-(1-phenylpropyl)-1,2,4-oxadiazole-5-ethanamine citrate.

Проксазола Цитрат

$C_{17}H_{25}N_3O,C_6H_8O_7$ = 479.5.

CAS — 5696-09-3 (proxazole); 132-35-4 (proxazole citrate).

ATC — A03AX07.

ATC Vet — QA03AX07.

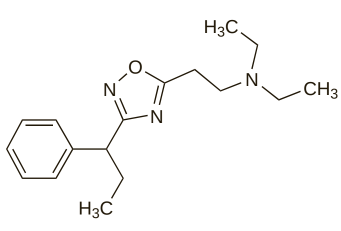

(proxazole)

Profile

Proxazole citrate has been used as an antispasmodic and in vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Toness†.

Prozapine Hydrochloride *(rINNM)*

Hexadiphane Hydrochloride; Hidrocloruro de prozapina; Prozapine, Chlorhydrate de; Prozapini Hydrochloridum. 1-(3,3-Diphenylpropyl)cyclohexamethyleneimine hydrochloride.

Прозапина Гидрохлорид

$C_{21}H_{27}N,HCl$ = 329.9.

CAS — 3426-08-2 (prozapine); 13657-24-4 (prozapine hydrochloride).

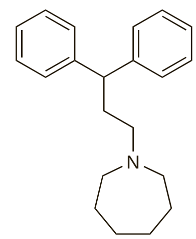

(prozapine)

Profile

Prozapine hydrochloride is an antispasmodic that has been given orally with sorbitol in biliary and gastrointestinal disorders.

Psilocin

4-Hydroxy-*NN*-dimethyltryptamine; Psilocina; Psilocyn. 3-(2-Dimethylaminoethyl)indol-4-ol.

$C_{12}H_{16}N_2O$ = 204.3.

CAS — 520-53-6.

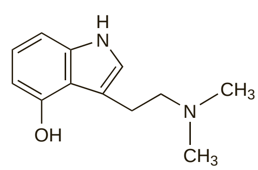

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of psilocin or mushrooms containing psilocin:

1UP's; Abhort; Aborts; Alice; Benzies; Blue Rimmers; Boom-Dads; Boomers; Caps; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; God's flesh; Goombas; Gus; Jesus; Lalkas; Liberty caps; Little smoke; Magic mushroom; Magic Mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushrooms; Musk; Pizza Toppings; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Toads; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Psilocybine *(BAN, rINN)*

CY-39; 4-Phosphoryloxy-*NN*-dimethyltryptamine; Psilocibina; Psilocybin; Psilocybinum; Psilosybiini. 3-(2-Dimethylaminoethyl)indol-4-yl dihydrogen phosphate.

Псилоцибин

$C_{12}H_{17}N_2O_4P$ = 284.2.

CAS — 520-52-5.

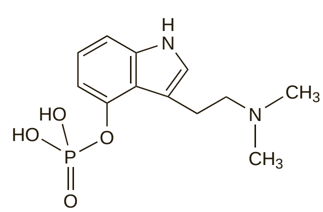

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of psilocybine or mushrooms containing psilocybine:

1 UP's; Alice; Benzies; Blue caps; Blue Rimmers; Boom-Dads; Boomers; Booms; Buttons; Caps; Champ; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; Funguys; God's flesh; Goombas; Gus; Hombrecitos; Jesus; Lalkas; Las mujercitas; Little smoke; Magic mushroom; Magic mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushroom soup; Mushroom tea; Mushrooms; Musk; Philosopher's Stones; Pizza toppings; Rooms; Sacre mushroom; Sacred mushroom; Sacred mushrooms; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Teonanactl; Toads; Truffles; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Profile

Psilocin and psilocybine are indole alkaloids obtained from the sacred Mexican mushroom (teonanácatl), *Psilocybe mexicana* (Agaricaceae).

In the UK, psilocybine is present in the indigenous mushroom *Psilocybe semilanceata* (magic mushroom; liberty cap). Psilocybine is also present in other species of mushrooms including *Stropharia cubensis* and *Conocybe* spp.

Psilocybine has hallucinogenic and sympathomimetic properties similar to those of lysergide (p.2335). It is less potent than lysergide and its hallucinogenic effects last for up to 6 hours. There is evidence to suggest that psilocybine is converted to the active form psilocin in the body. It has no therapeutic use.

Pulegium Oil

Pennyroyal Oil; Poleo, aceite esencial de.

Profile

Pulegium oil is a volatile oil distilled from pennyroyal herb, *Mentha pulegium* (Labiatae), containing pulegone ($C_{10}H_{16}O$ = 152.2). It was formerly used as an emmenagogue. Severe toxic effects have followed its use as an abortifacient with convulsions, hepatotoxicity, and death. It is reported to have insect repellent activity.

Adverse effects. Severe hepatotoxicity accompanied by seizures occurred in 2 infants each of whom had received herbal teas containing pulegium oil.[1] In one of the infants multiple organ failure developed, and fulminant hepatic failure with hepatocellular necrosis and cerebral oedema proved fatal. A further 4 cases of toxicity associated with ingestion of pulegium oil have been reported;[2] three of the cases were adult patients who had ingested either herbal teas to induce menses (2 cases) or a herbal extract as an abortifacient (1 fatality), and the fourth was a 22-month old child who had ingested the oil.

1. Bakerink JA, *et al.* Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. *Pediatrics* 1996; **98:** 944–7.
2. Anderson IB, *et al.* Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. *Ann Intern Med* 1996; **124:** 726–34.

Pulmonary Surfactants

Tensioactivos pulmonares.

Description. Pulmonary surfactants are mixtures consisting mainly of phospholipids and surfactant proteins that are used to replace deficient endogenous lung surfactants. A number of preparations have been studied including:

- natural human surfactant obtained from amniotic fluid or biosynthetic material
- natural animal-derived surfactants, which are bovine or porcine lung extracts that may be modified by the addition of synthetic surfactants, as in the case of beractant, or unmodified, as in the case of bovactant and calfactant
- synthetic or semisynthetic preparations, which may contain the phospholipid colfosceril palmitate, a major constituent of natural lung surfactants, in combination with other substances that aid spreading and absorption such as the synthetic peptide sinapultide.

Beractant *(BAN, USAN)*

A-60386X.

CAS — 108778-82-1.

Description. Beractant is a modified bovine lung extract containing mostly phospholipids, modified by the addition of colfosceril palmitate, palmitic acid, and tripalmitin.

The term Surfactant TA has been applied to a modified bovine lung surfactant.

Bovactant *(BAN)*

SF-R11.

Description. Bovactant is an extract of bovine lung containing about 92% of phospholipids, 3.2% of cholesterol, 0.6% of surfactant-associated hydrophobic proteins, and 0.4% of free fatty acid.

Calfactant *(BAN, USAN)*

CAS — 183325-78-2.

Description. Calfactant is an unmodified calf lung extract that includes mostly phospholipids and hydrophobic surfactant-specific proteins (SP-B and SP-C).

The symbol † denotes a preparation no longer actively marketed

Colfosceril Palmitate *(BAN, USAN, rINN)*

Colfoscéril, Palmitate de; Colfoscerili Palmitas; Dipalmitoylphosphatidylcholine; DPPC; Palmitato de colfoscerilo; 129Y83. 1,2-Dipalmitoyl-*sn*-glycero(3)phosphocholine.

Кольфосцерила Пальмитат

$C_{40}H_{80}NO_8P$ = 734.0.
CAS — 63-89-8.
ATC — R07AA01.
ATC Vet — QR07AA01.

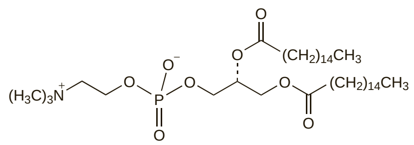

Description. Colfosceril palmitate is a phospholipid which forms an important constituent of natural and many synthetic pulmonary surfactant compounds.

Lucinactant *(USAN)*

ATI-02; KL_4-surfactant.

Description. Lucinactant is a mixture of sinapultide, colfosceril palmitate, sodium palmitoyloleaylphosphatidyl glycerol, and palmitic acid.

Poractant Alfa *(BAN)*

CAS — 129069-19-8.

Description. Poractant alfa is an extract of porcine lung containing not less than 90% of phospholipids, about 1% of hydrophobic proteins (SP-B and SP-C), and about 9% of other lipids.

Pumactant *(BAN)*

Artificial Lung Expanding Compound.

Description. Pumactant is a mixture of colfosceril palmitate and phosphatidyl glycerol (2-oleoyl-1-palmitoyl-*sn*-glycero(3)phospho(1)-*sn*-glycerol) in the proportion 7:3.

Sinapultide *(USAN, rINN)*

ATI-01; Sinapultida; Sinapultidum.

Синапультид

CAS — 138531-07-4.

Description. Sinapultide is a synthetic peptide that mimics the actions of human surfactant protein B, an important constituent of natural pulmonary surfactant compounds.

Adverse Effects and Precautions

Surfactant therapy may be associated with an increased risk of pulmonary haemorrhage, especially in more premature infants. Therapy should only be given where there are adequate facilities for ventilation and monitoring. Rapid chest expansion and improvement of oxygenation may follow successful treatment, and peak ventilatory pressure and inspired oxygen concentration may need to be reduced promptly to avoid the risk of pneumothorax and hyperoxaemia. A transient decrease in brain electrical activity has been reported in neonates given surfactant but its significance is unknown. Transient bradycardia has also been reported. Giving surfactant has occasionally been associated with obstruction of the endotracheal tube by mucus.

◊ While surfactant therapy is clearly associated with an increased risk of pulmonary haemorrhage,[1-4] meta-analysis suggests that the risk is small compared with the benefits.[1] However, neonates who do develop moderate or severe pulmonary haemorrhage after surfactant therapy are at increased risk of death or short-term morbidity.[5] Haemodynamic changes associated with surfactant therapy or consequent pulmonary haemorrhage may also predispose premature infants to intracranial (periventricular) haemorrhage.[5,6] Early preventive use of surfactant in very low birthweight infants may be associated with a poorer neurodevelopmental outcome,[7] although a long-term follow-up study[8] of premature infants born in the surfactant era concluded that these children had similar neurodevelopmental outcomes to such children born before the introduction of surfactant therapy. Decreased brain electrical activity has been reported after surfactant treatment.[9]

The rate of instillation of surfactant may be significant: one study,[10] in which the apparatus was adapted so that mechanical ventilation could continue while giving surfactant, found that rapid instillation over a 5-minute period provoked a transient increase in cerebral blood flow velocity associated with an increase in carbon dioxide tension, compared with slow instillation over 15 minutes. Although the authors acknowledged that such changes were likely to be related to several factors, particularly the type of surfactant, they recommended that, until further data were available, instillation should take place slowly, over at least 15 to 20 minutes.

1. Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a metaanalysis. *J Pediatr* 1993; **123:** 603–10.
2. Majeed-Saidan MA, *et al.* Pulmonary haemorrhage in low-birthweight babies. *Lancet* 1993; **341:** 120.
3. Rogers D. Pulmonary haemorrhage, surfactant, and low-birthweight babies. *Lancet* 1993; **341:** 698.
4. Pappin A, *et al.* Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. *J Pediatr* 1994; **124:** 621–6.
5. Pandit PB, *et al.* Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F40–F44.
6. Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. *Pediatrics* 1993; **92:** 775–86.
7. Vaucher YE, *et al.* Outcome at twelve months of adjusted age in very low birth weight infants with lung immaturity: a randomized placebo-controlled trial of human surfactant. *J Pediatr* 1993; **122:** 126–32.
8. D'Angio CT, *et al.* Longitudinal, 15-year follow-up of children born at less than 29 weeks' gestation after introduction of surfactant therapy into a region: neurologic, cognitive, and educational outcomes. *Pediatrics* 2002; **110:** 1094–1102.
9. Hellström-Westas L, *et al.* Cerebroelectrical depression following surfactant treatment in preterm neonates. *Pediatrics* 1992; **89:** 643–7.
10. Saliba E, *et al.* Instillation rate effects of Exosurf on cerebral and cardiovascular haemodynamics in preterm neonates. *Arch Dis Child* 1994; **71:** F174–8.

Uses and Administration

Pulmonary surfactants are compounds with surface active properties similar to those natural substances in the lung that help to maintain the patency of the airways by reducing the surface tension of pulmonary fluids. Exogenous pulmonary surfactants are used in the treatment of neonatal respiratory distress syndrome (p.1508) in premature infants, and may also be given for prevention in infants considered to be at risk of developing the syndrome. Doses vary, but most pulmonary surfactants are given in recommended doses of 100 to 200 mg phospholipids per kg birth-weight; a suggested dose for colfosceril palmitate is 67.5 mg/kg. For the treatment of overt neonatal respiratory distress syndrome, the initial dose is given as soon as possible after diagnosis, while for prevention it is given as soon as possible after birth. It is given as a suspension via an endotracheal tube to intubated neonates receiving mechanical ventilation. Manufacturers may recommend regimens with or without disconnection from the ventilator. Repeat doses may be given if necessary, although the number of doses and the dosage interval varies.

Pulmonary surfactants have also been tried in bronchopulmonary dysplasia in premature infants, meconium aspiration syndrome in newborn infants, and acute respiratory distress syndrome in adults. A similar compound lusupultide is also under investigation for aspiration pneumonitis.

Acute respiratory distress syndrome. Pulmonary surfactants have been investigated for acute respiratory distress syndrome (p.1498). In adults, they have been given by intrabronchial instillation[1] or nebulisation[2-4] but results have been largely disappointing. Sequential bronchopulmonary segmental lavage with a synthetic surfactant has also been tried[5] and appeared to be well tolerated. Endotracheal poractant alfa moderately improved oxygenation in some children with severe acute respiratory distress syndrome secondary to pulmonary or systemic disease.[6]

1. Haslam PL, *et al.* Surfactant replacement therapy in late-stage adult respiratory distress syndrome. *Lancet* 1994; **343:** 1009–11.
2. do Campo JL, *et al.* Natural surfactant aerosolisation in adult respiratory distress syndrome. *Lancet* 1994; **344:** 413–14.
3. Weg JG, *et al.* Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress syndrome. *JAMA* 1994; **272:** 1433–8.
4. Anzueto A, *et al.* Aerosolized surfactant in adults with sepsis-induced respiratory distress syndrome. *N Engl J Med* 1996; **334:** 1417–21.
5. Wiswell TE, *et al.* Bronchopulmonary segmental lavage with Surfaxin (KL -Surfactant) for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **160:** 1188–95.
6. López-Herce J, *et al.* Surfactant treatment for acute respiratory distress syndrome. *Arch Dis Child* 1999; **80:** 248–52.

Drowning. Reference to the use of colfosceril palmitate in the management of a 9-year-old rescued after near drowning.[1]

1. McBrien M, *et al.* Artificial surfactant in the treatment of near drowning. *Lancet* 1993; **342:** 1485–6.

Meconium aspiration syndrome. Meconium aspiration syndrome produces respiratory distress in infants born at term or later and is a consequence of disturbances of the pulmonary surfactant system. Bolus doses of exogenous pulmonary surfactant are of benefit in some ventilated infants, although lung lavage with dilute surfactant is also under investigation.[1] Results from a pilot study[2] of beractant as a tracheobronchial lavage fluid for the treatment of infants with severe meconium aspiration syndrome were promising, and a small comparative trial[3] found that bronchoalveolar lavage with diluted beractant, with or without intravenous dexamethasone, significantly improved oxygenation in neonates when compared with standard therapy. Systematic review[4] of 4 randomised controlled trials evaluating the effect of pulmonary surfactants also found encouraging results, although comparison with other established treatments for meconium aspiration syndrome remains to be done.

1. Dargaville PA, Mills JF. Surfactant therapy for meconium aspiration syndrome: current status. *Drugs* 2005; **65:** 2569–91.
2. Lam BCC, Yeung CY. Surfactant lavage for meconium aspiration syndrome: a pilot study. *Pediatrics* 1999; **103:** 1014–18.
3. Salvia-Roigés MD, *et al.* Efficacy of three treatment schedules in severe meconium aspiration syndrome. *Acta Paediatr* 2004; **93:** 60–5.
4. El Shahed AI, *et al.* Surfactant for meconium aspiration syndrome in full term/near term infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 13/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Baby Fact B; Exosurf†; Natsurf†; Surfactante B; Survanta; ***Austral.:*** Curosurf; Exosurf; Survanta; ***Austria:*** Alveofact†; Curosurf; Exosurf; Survanta; ***Belg.:*** Alvofact†; Curosurf; Survanta; ***Braz.:*** Alveofact; Curosurf; Exosurf†; Survanta; ***Canad.:*** BLES; Exosurf†; Survanta; ***Chile:*** Exosurf†; Survanta; ***Cz.:*** Alveofact†; Curosurf; Exosurf†; Survanta; ***Denm.:*** Curosurf; ***Fin.:*** Curosurf; ***Fr.:*** Curosurf; Survanta; ***Ger.:*** Alveofact; Curosurf; Survanta; ***Gr.:*** Alvofact; Curosurf; Exosurf†; Survanta; ***Hong Kong:*** Exosurf†; Survanta; ***Hung.:*** Curosurf; Survanta; ***Indon.:*** Survanta; ***Irl.:*** Curosurf; Exosurf†; ***Israel:*** Curosurf; Exosurf†; Infasurf; ***Ital.:*** Curosurf; Exosurf†; ***Jpn:*** Surfacten; ***Malaysia:*** Survanta; ***Mex.:*** Exosurf; Survanta; ***Neth.:*** Alvofact†; Curosurf; Exosurf†; Survanta; ***Norw.:*** Curosurf; Survanta-Vent; ***NZ:*** Curosurf; Survanta; ***Philipp.:*** Survanta; ***Pol.:*** Alveofact; Curosurf; Survanta; ***Port.:*** Curosurf; ***Rus.:*** Curosurf (Куросурф); ***S.Afr.:*** Curosurf; Survanta; ***Singapore:*** Survanta; ***Spain:*** Curosurf; Survanta; ***Swed.:*** Curosurf; Survanta-Vent†; ***Switz.:*** Curosurf; Survanta; ***Thai.:*** Curosurf; Survanta; ***UK:*** Curosurf; Survanta; ***USA:*** Curosurf; Exosurf†; Infasurf; Survanta; ***Venez.:*** Survanta.

Pulsatilla

Anémone pulsatille; Meadow Anemone; Pasque Flower.
CAS — 62887-80-3.

Profile

Pulsatilla is the whole flowering plant of *Pulsatilla vulgaris* (*Anemone pulsatilla*) or *Pulsatilla pratensis* (Ranunculaceae). It has been used in herbal preparations for the treatment of conditions including nervous disorders, circulatory disorders, and gynaecological disorders and benign prostatic hyperplasia.

Homoeopathy. Pulsatilla has been used in homoeopathic medicines under the following names: Pulsatilla pratensis; Pulsatilla vulgaris; Pulsatilla nigricans; Puls.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Yeast-X†.

Multi-ingredient: ***Austral.:*** Bioglan Cirflo†; Calmo; Lifesystem Herbal Formula 4 Women's Formula†; Proflo†; Women's Formula Herbal Formula 3†; ***Braz.:*** Eviprostat†; ***Cz.:*** Cicaderma; ***Fr.:*** Cicaderma; Hepatoum; Histo-Fluine P; ***Ger.:*** Eviprostat N; ***Indon.:*** Eviprostat; ***Jpn:*** Eviprostat; ***Port.:*** Cicaderma; ***S.Afr.:*** Cough Elixir; ***Singapore:*** Eviprostat; ***UK:*** Anased; Menopause Relief; Period Pain Relief; Prementaid.

Pumilio Pine Oil

Dwarf Pine Needle Oil; Dwarf Pine Oil; Essence de Pin de Montagne; Latschenöl; Oleum Pini Pumilionis; Olio di Mugo; Pin de montagne, huile essentielle de; Pini pumilionis aetheroleum; Pino mugo, aceite esencial de.
CAS — 8016-46-4.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dwarf Pine Oil). An essential oil obtained by steam distillation of the fresh leaves and twigs of *Pinus mugo*. A suitable antioxidant may be added. Relative density 0.857 to 0.868. A clear, colourless or pale yellow liquid. Store in inert, well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Pumilio pine oil is a volatile oil obtained by distillation from the fresh leaves of *Pinus mugo* var. *pumilio* (Pinaceae). It has been inhaled with steam, sometimes with other essential oils, to relieve cough and nasal congestion and has been applied externally as a rubefacient. It has also been used as a perfume.

P. mugo is a source of pine needle oil (see Pine Oil, p.2368).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Biosal Arthritis; Biosal†; Goanna Heat Cream; Goanna Salve; Karvol†; Menalation†; Vicks Inhaler; ***Austria:*** Berggeist; Bronchostop; Colda; Emser Nasensalbe; Erkaltungsbalsam; Expectal-Balsam; Leukona-Rheuma-Bad; Luuf Balsam; Mentopin; Nasanal; Opino; Piniment; ***Cz.:*** Thrombocid; Transpulmin; ***Ger.:*** Aerosol Spitzner N†; Dolo-cyl; Em-eukal†; Emser Nasensalbe N†; Euflux; Franzbranntwein; Hevertopect N†; Klosterfrau Franzbranntwein Latschenkiefer; Nasentropfen-ratiopharm†; Ner-fluid S; polio-elan; Rosarthron†; Thrombocid; ***Gr.:*** Opino-jel; ***Irl.:*** Karvol; ***Israel:*** Karvol; Mentholatum Balm; ***Ital.:*** Altuss; Antipulmina†; Broncosedina; Pinedrin†; Pumilene Vapo; ***Malaysia:*** Purporent†; ***Neth.:*** Luuf Verkoudheidsbalsem; ***NZ:*** Vicks Inhaler; ***Port.:*** Thrombocid; ***Switz.:*** Eau-de-vie de France avec huile de pin nain du Tirol†; Eucapinol; Liberol Baby N; Liberol Bain†; Liberol N; Makaphyt Baume†; Pinimenthol†; Piniol Pommade Speciale†; Thrombocid; ***UK:*** Allens Pine & Honey; Karvol; Mentholatum Rub; Original Cabdrivers Expectorant; Potter's Catarrh Pastilles.

Punarnava

Punarnaba.

Profile

Punarnava is the fresh or dried plant *Boerhaavia diffusa* (*B. repens*) (Nyctaginaceae), containing an alkaloid, punarnavine. It has been used as a diuretic and for liver disorders, usually in the form of a liquid extract.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Dipana (Дипана).

Pyricarbate *(rINN)*

Piricarbato; Pyricarbatum; Pyridinolcarbamate. 2,6-Pyridinediyldimethylene bis(methylcarbamate).

Пирикарбат

$C_{11}H_{15}N_3O_4$ = 253.3.
CAS — 1882-26-4.

Profile

Pyricarbate has been given by mouth in the treatment of atherosclerosis and other vascular disorders, hyperlipidaemias, and thromboembolic disorders. Adverse effects have included gastrointestinal disturbances and liver damage.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Cicloven; ***Port.:*** Anginin†.

Quassia

Bitter Wood; Cuasia; Leño de Cuasia; Quassia Wood; Quassiae Lignum; Quassiaholz.

CAS — 76-78-8 (quassin); 76-77-7 (neoquassin).
ATC — P03AX04.
ATC Vet — QP53AX03.

Profile

Quassia is the dried stem wood of Jamaica quassia, *Picrasma excelsa* (*Aeschrion excelsa; Picraena excelsa*) (Simaroubaceae), or of Surinam quassia, *Quassia amara* (Simaroubaceae). It has been used as a bitter. It was formerly given as an enema for the expulsion of threadworms and was applied for pediculosis. It may also be used as a flavour in food, drinks, and confectionery. Extracts of quassia or preparations containing its triterpenoid bitter principle quassin are used to denature alcohol.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Cuassicum Prevent 2 en 1; Picutex.

Multi-ingredient: ***Arg.:*** Aulo Repelente De Piojos; Cuassicum; Fuera Bicho; Uze Active; Yalu†; ***Braz.:*** Camomila; ***Fr.:*** Quintonine; Skin Nail; ***Ital.:*** Dekar 2; ***S.Afr.:*** Essens Amara of Groen Amara; Versterkdruppels; ***Switz.:*** Stomacine; ***UK:*** Sanderson's Throat Specific.

Quebracho

Quebracho Blanco; White Quebracho.

Квебрахо Белое

NOTE. Do not confuse with trees belonging to the genus *Schinopsis* that may also be referred to as quebracho.

Profile

The bark of white quebracho, *Aspidosperma quebracho-blanco* (Apocynaceae) is used in herbal medicine for the treatment of respiratory disorders. It has also been used to reduce fever, as an antihypertensive, and as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Afrodor; Bronchicum Elixir†; Bronchicum Tropfen†; ***Ger.:*** Afrodor; Bronchicum Elixir N†; Bronchicum Tropfen N†; ***Hung.:*** Afrodor†; ***Pol.:*** Bronchicum Eliksir; Bronchicum†; ***Rus.:*** Afrodor (Афродор); Bronchicum (Бронхикум); ***S.Afr.:*** Bronchicough†; Bronchicum†; ***Spain:*** Broncovital†.

Quinagolide Hydrochloride *(BANM, rINNM)*

CV-205-502 (quinagolide); Hidrocloruro de quinagolida; Quinagolide, Chlorhydrate de; Quinagolidi Hydrochloridum; SD2-CV-205-502 (quinagolide). (±)-*N*,*N*-Diethyl-*N*′-[(3*R**,4a*R**,10a*S**)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[*g*]quinolin-3-yl]sulfamide hydrochloride.

Хинаголида Гидрохлорид

$C_{20}H_{33}N_3O_3S,HCl$ = 432.0.
CAS — 87056-78-8 (quinagolide); 94424-50-7 (quinagolide hydrochloride).
ATC — G02CB04.
ATC Vet — QG02CB04.

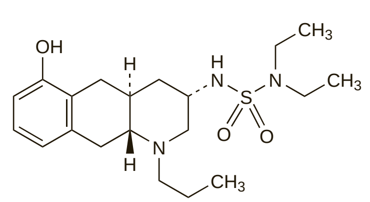

(quinagolide)

Adverse Effects and Precautions

As for Bromocriptine, p.798, although it is not an ergot derivative and does not seem to be associated with fibrotic reactions or vasoconstriction. Licensed product information contra-indicates the use of quinagolide in patients with hepatic or renal impairment; however, this is based on a lack of data in such patients.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including quinagolide, see Effects on Mental Function, under Adverse Effects of Levodopa, p.805.

Interactions

As for Bromocriptine, p.800.

Pharmacokinetics

Quinagolide is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism to the *N*-desethyl analogue which is biologically active and the *N*,*N*-didesethyl analogue. Roughly equal amounts of a dose appear in the urine and the faeces; it is excreted in the urine as sulfate or glucuronide conjugates of quinagolide and its metabolites and in the faeces as the unconjugated forms. Protein binding has been reported to be about 90%. The elimination half-life of quinagolide at steady state is about 17 hours.

Uses and Administration

Quinagolide is a non-ergot dopamine D_2-agonist that has actions and uses similar to those of bromocriptine (p.800). It is used in the treatment of disorders associated with hyperprolactinaemia.

Quinagolide is given as the hydrochloride, but doses are described in terms of the base; 27.3 micrograms of quinagolide hydrochloride is equivalent to about 25 micrograms of quinagolide. The initial dose, given once daily with food at bedtime, is 25 micrograms daily for 3 days. Doses are increased thereafter at 3-day intervals in steps of 25 micrograms until the optimal response is achieved, which is usually within the range of 75 to 150 micrograms daily. If doses greater than 300 micrograms daily are required, the daily dosage may be increased in steps of 75 to 150 micrograms at intervals of not less than 4 weeks.

Quinagolide has also been investigated in the treatment of acromegaly and lactation inhibition.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p.1798). Bromocriptine has been the main dopamine agonist used, but quinagolide has been tried and results of an open study[1] in which quinagolide was given to 17 patients with acromegaly suggest that quinagolide has a more prolonged effect on suppression of growth hormone secretion than bromocriptine. However, it was ineffective in bromocriptine-resistant patients. In another study involving 34 patients, quinagolide was more effective than either cabergoline or a depot preparation of bromocriptine in normalising circulating growth hormone and insulin-like growth factor.[2]

1. Chiodini PG, *et al.* CV 205-502 in acromegaly. *Acta Endocrinol (Copenh)* 1993; **128:** 389–93.
2. Colao A, *et al.* Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 1997; **82:** 518–23.

Hyperprolactinaemia and prolactinomas. Dopamine agonists such as quinagolide are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (see p.2079).

References.

1. Rohmer V, *et al.* Efficacy of quinagolide in resistance to dopamine agonists: results of a multicenter study. *Ann Endocrinol (Paris)* 2000; **61:** 411–17.
2. Schultz PN, *et al.* Quinagolide in the management of prolactinoma. *Pituitary* 2000; **3:** 239–49.
3. Barlier A, Jaquet P. Quinagolide—a valuable treatment option for hyperprolactinaemia. *Eur J Endocrinol* 2006; **154:** 187–95.

Lactation inhibition. A small preliminary study[1] has suggested that quinagolide is of similar efficacy to bromocriptine for prevention of puerperal lactation. However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation (see p.2003).

1. van der Heijden PFM, *et al*. Lactation inhibition by the dopamine agonist CV 205-502. *Br J Obstet Gynaecol* 1991; **98:** 270–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Norprolac; ***Canad.:*** Norprolac; ***Cz.:*** Norprolac; ***Fin.:*** Norprolac; ***Fr.:*** Norprolac; ***Ger.:*** Norprolac; ***Gr.:*** Norprolac; ***Hong Kong:*** Norprolac†; ***Hung.:*** Norprolac; ***Israel:*** Norprolac; ***Mex.:*** Norprolac; ***Neth.:*** Norprolac; ***Norw.:*** Norprolac; ***Pol.:*** Norprolac; ***Port.:*** Norprolac; ***Rus.:*** Norprolac (Норпролак); ***S.Afr.:*** Norprolac; ***Spain:*** Norprolac; Prodelion; ***Swed.:*** Norprolac; ***Switz.:*** Norprolac; ***UK:*** Norprolac.

Quinine and Urea Hydrochloride

Carbamidated Quinine Dihydrochloride; Chininum Dihydrochloricum Carbamidatum; Quinina y urea, hidrocloruro de; Urea-Quinine.

$C_{20}H_{24}N_2O_2,CH_4N_2O,2HCl,5H_2O$ = 547.5.
CAS — 549-52-0 (anhydrous quinine and urea hydrochloride).

Profile

Quinine and urea hydrochloride has been used for the treatment of haemorrhoidal bleeding and anal fissure. It was formerly used as a local anaesthetic and for the therapeutic actions of quinine.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Kinurea H.

Quinine Ascorbate *(USAN)*

Quinina, ascorbato de; Quinine Biascorbate.

$C_{20}H_{24}N_2O_2,2C_6H_8O_6$ = 676.7.
CAS — 146-40-7.

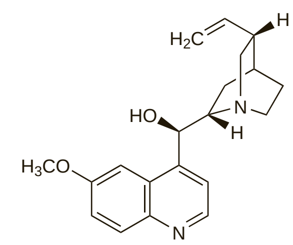

(quinine)

Profile

Quinine ascorbate is a compound (2 : 1) of ascorbic acid with quinine. It has been used as an ingredient of preparations promoted as smoking deterrents.

Ramatroban *(BAN, rINN)*

BAY-U-3405; EN-137774; Ramatrobán; Ramatrobanum. (*R*)-3-[3-(4-Fluorophenylsulphonylamino)-1,2,3,4-tetrahydrocarbazol-9-yl]propionic acid.

Раматробан

$C_{21}H_{21}FN_2O_4S$ = 416.5.
CAS — 116649-85-5.

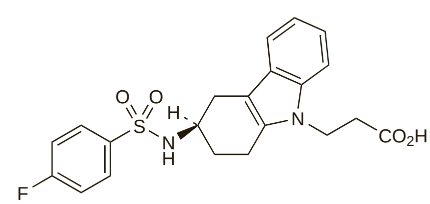

Profile

Ramatroban is a thromboxane A_2 inhibitor that has been used for the treatment of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Baynas.

Ranibizumab *(BAN, USAN, rINN)*

Ranibizumabum; rhuFab V2. Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFAB V2 γ1-chain), disulfide with human-mouse monoclonal rhuFAB V2 κ-chain.

Ранибицумаб

CAS — 347396-82-1.
ATC — S01LA04.
ATC Vet — QS01LA04.

Adverse Effects and Precautions

Intra-ocular inflammation and raised intra-ocular pressure may occur with ranibizumab. Adverse effects relating to the injection procedure include endophthalmitis, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Patients should be monitored for signs of infections for a week after the procedure. Common but less serious ocular adverse effects include red eye, eye pain, vitreous floaters, eye irritation, increased lachrymation, and the sensation of a foreign body in the eye.

Non-ocular adverse effects that have been reported include headache, nausea, arthralgia, back pain, bronchitis, anaemia, and hypertension. Arterial thromboembolic events are a theoretical possibility with vascular endothelial growth factor inhibitors.

Ranibizumab is contra-indicated in patients with active or suspected ocular or periocular infections, or active severe intra-ocular inflammation.

Stroke. The manufacturers of ranibizumab have reported that interim analysis of results from an ongoing study have revealed a higher incidence of stroke in a group of patients given doses of 500 micrograms compared with a group receiving 300 micrograms. Patients with a history of stroke appeared to be at greater risk.

Uses and Administration

Ranibizumab is a recombinant humanised monoclonal antibody used in the treatment of neovascular (wet) age-related macular degeneration. It is given by intravitreal injection into the affected eye in doses of 500 micrograms once a month initially for 3 to 4 months. In the UK, after the first 3 months, maintenance treatment is based on regular assessment of visual acuity, with ranibizumab being given if the patient had a loss of greater than 5 letters in visual acuity; the interval between consecutive doses should be at least one month. In the USA, if monthly administration is not feasible after the first four injections, treatment may be given once every 3 months, although this is not as effective as monthly doses.

Age-related macular degeneration. Ranibizumab is a recombinant humanised monoclonal antibody fragment related to bevacizumab (p.684) used in the treatment of (wet) age-related macular degeneration (AMD) (p.785). It binds to and inhibits vascular endothelial growth factor A (VEGF-A), which is a stimulant of angiogenesis thought to play a role in the neovascularisation and retinal changes associated with AMD. Ranibizumab inhibits all active forms of VEGF-A.[1]

Positive outcomes have been reported from two international multicentre randomised controlled phase III studies.[2,3] Vision loss was prevented and mean visual acuity improved in patients given either monthly injections of 300 micrograms or 500 micrograms for 2 years compared with patients receiving sham injections.[2] Ranibizumab given in the same doses was also shown to be superior to photodynamic therapy with verteporfin at 1 year in the second study.[3]

A review[4] of interim results of other ongoing phase III studies of ranibizumab for AMD suggests that reducing the dosing interval to once every 3 months is less satisfactory than monthly injections, although tailoring the treatment to morphological parameters was as effective at 1 year as giving a fixed dosage regimen. However, ranibizumab in combination with photodynamic therapy does not necessarily result in better visual acuity outcomes and may even be worse than ranibizumab alone. A systematic review[5] of 5 randomised controlled studies found that ranibizumab was effective in reducing the risk of loss of visual acuity, and also improved visual acuity in a significant proportion of eyes.

1. Blick SKA, *et al.* Ranibizumab. *Drugs* 2007; **67:** 1199–1206.
2. Rosenfeld PJ, *et al.* for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1419–31.
3. Brown DM, *et al.* for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355:** 1432–44.
4. Rosenfeld PJ, *et al.* Ranibizumab: phase III clinical trial results. *Ophthalmol Clin North Am* 2006; **19:** 361–72.
5. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Lucentis; ***Cz.:*** Lucentis; ***Fr.:*** Lucentis; ***Gr.:*** Lucentis; ***Indon.:*** Lucentis; ***Malaysia:*** Lucentis; ***Port.:*** Lucentis; ***UK:*** Lucentis; ***USA:*** Lucentis.

Rapeseed Oil

Colza, aceite de; Colza, huile de; Colza Oil; Olej rzepakowy; Oleum Rapae; Rapae oleum; Rape Oil; Rapsolja; Rapsų aliejus; Repceolaj; Řepkový olej; Rypsiöljy.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. USNF* includes fully hydrogenated rapeseed oil and superglycerinated fully hydrogenated rapeseed oil.

Ph. Eur. 6.2 (Rapeseed Oil, Refined). The fatty oil obtained from the seeds of *Brassica napus* and *Brassica campestris* by mechanical expression or extraction and then refined. A suitable antioxidant may be added. It contains not more than 2% of erucic acid. A clear light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Protect from light.

USNF 26 (Fully Hydrogenated Rapeseed Oil). A mixture of triglycerides in which the fatty acid composition is a mixture of saturated fatty acids. It is obtained by refining and hydrogenating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white, waxy solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 26 (Superglycerinated Fully Hydrogenated Rapeseed Oil). A mixture of mono-, di-, and triglycerides, with triglycerides as a minor component. It is obtained by refining, hydrogenating, and glycerinating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Rapeseed oil has been used in liniments in place of olive oil. It is used in some countries as an edible oil but the erucic acid ($C_{22}H_{42}O_2$ = 338.6) content of the oil has been implicated in muscle damage. The erucic acid content of oils and fats intended for human consumption and of foodstuffs containing oil or fat is subject to legal control. Contaminated rapeseed oil was the cause of the toxic oil syndrome that affected thousands of Spanish citizens in early 1981. Rapeseed oil is also used in industrial manufacturing.

There has been some debate whether the frequency of allergic respiratory symptoms in sensitive individuals is increased in areas in which oilseed rape is cultivated.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Gr.:* Fissan-Pate†.

Raspberry Leaf

Frambuesa, hoja de; Rubi Idaei Folium.

Profile

Raspberry leaf consists of the dried leaflets of *Rubus idaeus* (Rosaceae). It contains a principle, readily extracted with hot water, which relaxes the smooth muscle of the uterus and intestine of some *animals.*

Raspberry 'tea' has been a traditional remedy for painful and profuse menstruation and for use before and during labour. The infusion has also been used as an astringent gargle.

◊ References.

1. Simpson M, *et al.* Raspberry leaf in pregnancy: its safety and efficacy in labor. *J Midwifery Womens Health* 2001; **46:** 51–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Austral.:* Rubus Complex†; ***Cz.:*** Detsky Caj s Hermankem; Diabetan; Hertz- und Kreislauftee†; Hypotonicka; Species Cholagogae Planta.

Relaxin

Relaxina.
CAS — 9002-69-1.

Profile

Relaxin is a polypeptide hormone that has been extracted from the corpus luteum of the ovaries of pregnant sows, although a human recombinant form is also now available. It is reported to be related structurally to insulin and has a molecular weight of about 6000.

Relaxin is secreted by the human corpus luteum during pregnancy and is thought to interact with other reproductive hormones. It acts on connective tissue, including collagen, and causes relaxation of the pubic symphysis and softening of the uterine cervix. In many *animal* species relaxin appears to play a major part in cervical ripening before parturition; significant species difference is shown. It has been studied for cervical ripening in humans. Recombinant human relaxin has also been investigated in infertility, cardiovascular disorders, and scleroderma (p.1817).

◊ References.

1. Seibold JR, *et al.* Safety and pharmacokinetics of recombinant human relaxin in systemic sclerosis. *J Rheumatol* 1998; **25:** 302–7.
2. Seibold JR, *et al.* Recombinant human relaxin in the treatment of scleroderma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **132:** 871–9.
3. Kelly AJ, *et al.* Relaxin for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. John Wiley; Chichester; 2001 (accessed 28/04/06).

Resveratrol

NSC-327430; 3,4′,5-Stilbenetriol; 3,4′,5-Trihydroxystilbene. (E)-5-[2-(4-Hydroxyphenyl)ethenyl]-1,3-benzenediol.
$C_{14}H_{12}O_3$ = 228.2.
CAS — 501-36-0.

Profile

Resveratrol is a phytoalexin present in a range of plant sources including species of *Arachis*, *Pinus*, *Polygonum*, *Veratrum*, and *Vitis*. It is thought to be one of the compounds responsible for the cardioprotective action of wine (see Grape, p.2316, and Flavonoid Compounds, p.2304).

Resveratrol used in commercial preparations is often derived from the root of Japanese knotweed, *Fallopia japonica* (*Polygonum cuspidatum*; *Reynoutria japonica*) (Polygonaceae) often as the racemate although the *trans*-isomer is also promoted.

Resveratrol is promoted as an antioxidant for the prevention of atherosclerosis. It also has mixed agonist/antagonist activity at oestrogen receptors and some anti-inflammatory and antiproliferative activity, and is under investigation in the prevention and treatment of malignancy.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Resvelife†.

Rhamnose

Ramnosa; Ramnoza; L-Rhamnose. 6-Deoxy-L-mannose.
$C_6H_{12}O_5$ = 164.2.
CAS — 3615-41-6.

Profile

Rhamnose is a monosaccharide used to assess intestinal permeability.

For reference to the use of rhamnose in the differential sugar absorption test, see Diagnosis and Testing under Lactulose, p.1739.

◊ References.

1. van Nieuwenhoven MA, *et al.* The sensitivity of the lactulose/rhamnose gut permeability test. *Eur J Clin Invest* 1999; **29:** 160–5.
2. Haase AM, *et al.* Dual sugar permeability testing in diarrheal disease. *J Pediatr* 2000; **136:** 232–7.
3. van Nieuwenhoven MA, *et al.* Effects of pre- and post-absorptive factors on the lactulose/rhamnose gut permeability test. *Clin Sci* 2000; **98:** 349–53.

Rhatany Root

Krameria; Krameria Root; Ratanhia, racine de; Ratanhiae radix; Ratanhiagyökér; Ratanhový kořen; Ratania, raíz de; Ratanianjuuri; Rataniarot; Ratanijų šaknys.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Rhatany Root). The dried, usually fragmented, underground organs of *Krameria triandra*. It contains not less than 5% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. It is known as Peruvian rhatany. Protect from light.

Profile

Rhatany root has astringent properties and is used in herbal preparations for a variety of disorders, including oropharyngeal inflammation.

Homoeopathy. Rhatany root has been used in homoeopathic medicines under the following names: Ratanhia; Krameria triandra; Ratanhiae radix; Ratania peruviana; Ratan.

Preparations

Ph. Eur.: Rhatany Tincture.

Proprietary Preparations (details are given in Part 3)
Ger.: ratioSept.
Multi-ingredient: *Arg.:* Esculeol P; Parodontax Fluor; ***Austria:*** Parodontax; ***Braz.:*** Malvatricin Natural Organic; Parodontax; ***Chile:*** Hemorrol†; ***Fr.:*** Delabarre Bio-adhesif; ***Ger.:*** Ratanhia comp; Repha-Os; ***Israel:*** Parodontax†; ***Ital.:*** Gengivario†; ***Spain:*** Encialina†; ***Switz.:*** Eubucal†; GU Eau†; Parodontax F†; Parodontax†; Sanogencive.

Rhus

Sumach Berries; Zumaque.

Pharmacopoeias. *Br.* includes Toxicodendron Quercifolium for Homoeopathic Preparations.

BP 2008 (Toxicodendron Quercifolium for Homoeopathic Preparations). Fresh, young, not yet lignified shoots, with leaves, of *Toxicodendron quercifolium*. The shoots contain a yellowish-white milky sap that is a strong cutaneous irritant and darkens the skin. Contact with the skin and mucous membranes is to be avoided.

Profile

Rhus consists of the dried fruits of the smooth or Pennsylvanian sumach, *Rhus glabra* (Anacardiaceae). It has astringent and reputed diuretic properties. *R. aromatica* has been used similarly to *R. glabra*.

Poison ivy (*R. radicans*) and poison oak (*R. toxicodendron*), species growing in the USA, contain irritant poisons, such as urushiol, that produce severe contact dermatitis. Extracts of poison ivy and poison oak have been used for the prophylaxis of poison ivy dermatitis but their effectiveness has not been proved. The spice sumac is prepared from the berries of *R. coriaria.*

Homoeopathy. Some *Rhus* spp. are used in homoeopathic medicine. Poison oak has been used in homoeopathic medicines under the following names: Toxicodendron quercifolium; Rhus toxicodendron; Rhus. tox.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Austral.:* Joint & Muscle Cream; ***Chile:*** Rhus Opodeldoc; ***Ger.:*** Hicoton†; Rhus-Rheuma-Gel N.

Ribonuclease

Ribonucleasa; RNase.
CAS — 9001-99-4.

Profile

Ribonuclease is an enzyme present in most mammalian tissue, and it is involved in the catalytic cleavage of ribonucleic acid. It has been applied, alone or with other drugs, for its supposed anti-inflammatory properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Cro 50.

Multi-ingredient: ***Braz.:*** Bromelin†; Expectoral†; ***Fr.:*** Ribatran; ***Mex.:*** Ofzim; Ridasa.

Ribonucleic Acid

ARN; Plant Nucleic Acid; Ribonucleico, ácido; Ribose Nucleic Acid; RNA; Yeast Nucleic Acid.

Рибонуклеиновая Кислота

Profile

Ribonucleic acid (RNA) is a nucleic acid (p.2355) in which the pentose sugar moiety of the nucleotides is ribose, the purine bases are adenine (p.2247) and guanine, and the pyrimidine bases are cytosine and uracil (p.2407). RNA exists as a single polynucleotide strand that replicates using DNA as a template during which process the pairing of bases between the complementary strands of RNA and DNA is always the same: adenine with uracil and cytosine with guanine. RNA is present in cell nuclei and cytoplasm and is directly involved in protein synthesis; it also plays a part in encoding genetic information. RNA also carries the genetic material of RNA viruses. Gene suppression by RNA interference (RNAi), using specific double-stranded ribonucleic acid sequences, is under investigation. For the role of RNA as a tool in gene therapy, see p.2310.

Proprietary preparations containing RNA are marketed in some countries for a variety of asthenic and convalescent conditions. RNA has also been tried in the treatment of mental retardation and to improve memory in senile dementia. It may also have a role in enteral feeds under some circumstances.

Immune RNA (extracted from the spleens and lymph nodes of immunised animals) has been tried in the immunotherapy of hepatitis and cancer.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: AU 4 Regeneresen; Osteochondrin S; Regeneresen; RN13 Regeneresen.

Multi-ingredient: ***India:*** Placentrex; ***Spain:*** Dertrase; Nucleserina; Policolinosil.

Ribwort Plantain

Heinäratamonlehti; Jitrocelový list; Liść babki lancetowatej; Plantaginis Folium; Plantaginis Lanceolatae; Plantaginis lanceolatae folium; Plantain Herb; Plantain lancéolé; Siauralapių gysločių lapai; Spitzwegerich; Spitzwegerichkraut; Svartkämparblad.

Pharmacopoeias. *Eur.* (see p.vii) includes the leaf.

Ph. Eur. 6.2 (Ribwort Plantain; Plantaginis Lanceolatae Folium). The whole or fragmented, dried leaf and scape of *Plantago lanceolata*. It contains not less than 1.5% of total *ortho*-dihydroxycinnamic acid derivatives expressed as acteoside ($C_{29}H_{36}O_{15}$ = 624.6) with reference to the dried drug. Protect from light.

Profile

Ribwort plantain is an ingredient in herbal remedies used for catarrh and inflammation of the upper respiratory tract.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Jitrocel v Nalevovych†; Jitrocelovy; ***Fr.:*** Sensivision au plantain; ***Ger.:*** Broncho-Sern; Proguval†; Tetesept Husten Saft; Tetesept Husten Tropfen; ***Pol.:*** Lancetan; Lanceticum; Plantagen.

Multi-ingredient: ***Austria:*** Brust- und Hustentee St Severin; Grippetee St Severin; Pneumopan; Scottopect; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Biotussil; Bronchialtee N†; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Dr Theiss Spitzwegerich Hustensaft†; Mucoplant Jitrocelovy; Naturident†; Prudušková; Pulmoran; Species Pectorales Planta; Thymomel; ***Ger.:*** Bronchicum Elixir Plus†; Equisil N; Eucabal†; Kneipp Husten- und Bronchial-Tee; ***Hong Kong:*** Pectoral†; ***Ital.:*** Altea (Specie Composta)†; Timo (Specie Composta)†; ***Pol.:*** Babicum; Echinasal; Flegatussin; Gwajatussin; Pectobonisol; Plantifort; Saponarex; ***Rus.:*** Eucabal (Эвкабал); Herbion Plantain Syrup (Гербион Сироп Подорожника); Stoptussin-Fito (Стоптуссин-фито); ***Spain:*** Llantusil†; Natusor Farinol†; Natusor Gastrolen†; Natusor Infenol†; ***Switz.:*** Bronchofluid N†; Gouttes contre la toux "S"; Neo-DP†; Nican; Pastilles bronchiques S nouvelle formule; Thymodrosin N†; Wala Pulmonium suc contre la toux.

Ricin

Ricino.
CAS — 9009-86-3.

NOTE. The title ricin is used for the castor seed in *Chin.* and *Fr.*

Profile

Ricin is a lectin present in castor seeds, the seeds of *Ricinus communis* (Euphorbiaceae). It is extremely toxic when given parenterally and the fatal dose by injection has been reported to be around 1 microgram/kg. The toxicity of orally ingested beans depends on how thoroughly they are chewed since the hard seed coat prevents absorption. Ingestion of as few as 3 castor seeds by a child and 4 by an adult may be fatal. Ricin may also be absorbed through abraded skin. It has potential use in aerosol form as an agent of chemical warfare. Toxic effects may be delayed for several days after exposure by any route. Early symptoms include severe gastrointestinal irritation, haemorrhage, vomiting, and diarrhoea, which may result in circulatory collapse. Abnormal liver function tests and pulmonary oedema have been reported. Ophthalmological disturbances ranging from irritation and conjunctivitis to optic nerve damage may occur; miosis and mydriasis have also been reported. Proteinuria, haematuria, and renal impairment may develop and serum creatinine levels may be raised. In severe cases haemolysis of the red blood cells with subsequent acute renal failure may occur. Fatalities due to multi-organ failure have occurred. If the patient presents within 1 hour of ingestion any seeds may be removed by gastric lavage and activated charcoal given. Treatment thereafter is symptomatic.

After expression of the oil from castor seeds (see p.2278), the ricin remaining in the seed cake or 'pomace' is destroyed by steam treatment. The detoxified pomace is used as a fertiliser.

Ricin conjugated with monoclonal or polyclonal antibodies is being studied in the treatment of cancers; zolimomab aritox is an example of such a conjugate. Some of these conjugates have been investigated for various malignancies, particularly leukaemias and lymphomas.

Toxicity. A report of ricin toxicity after partial chewing and ingestion of 10 to 15 castor oil seeds,[1] and reviews[2-4] of ricin toxicity, including its potential as an agent of chemical warfare.

1. Aplin PJ, Eliseo T. Ingestion of castor oil plant seeds. *Med J Aust* 1997; **167:** 260–1.
2. Bradberry SM, *et al.* Ricin poisoning. *Toxicol Rev* 2003; **22:** 65–70.
3. Lord MJ, *et al.* Ricin: mechanisms of cytotoxicity. *Toxicol Rev* 2003; **22:** 53–64.
4. Audi J, *et al.* Ricin poisoning: a comprehensive review. *JAMA* 2005; **294:** 2342–51.

Uses. References to the use of ricin conjugates with monoclonal antibodies in the treatment of cancer.

1. Byers VS, *et al.* Phase I study of monoclonal antibody-ricin A chain immunotoxin XomaZyme-791 in patients with metastatic colon cancer. *Cancer Res* 1989; **49:** 6153–60.
2. Oratz R, *et al.* Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (XMMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: results of a phase II trial. *J Biol Response Mod* 1990; **9:** 345–54.
3. Anonymous. Application considered for immunotoxin in treatment of graft-vs-host disease. *JAMA* 1991; **265:** 2041–2.
4. Amlot PL, *et al.* A phase I study of an anti-CD22-deglycosylated ricin A chain immunotoxin in the treatment of B-cell lymphomas resistant to conventional therapy. *Blood* 1993; **82:** 2624–33.
5. Senderowicz AM, *et al.* Complete sustained response of a refractory, post-transplantation, large B-cell lymphoma to an anti-CD22 immunotoxin. *Ann Intern Med* 1997; **126:** 882–5.
6. Multani PS, *et al.* Phase II clinical trial of bolus infusion anti-B4 blocked ricin immunoconjugate in patients with relapsed B-cell non-Hodgkin's lymphoma. *Clin Cancer Res* 1998; **4:** 2599–2604.
7. Dinndorf P, *et al.* Phase I trial of anti-B4-blocked ricin in pediatric patients with leukemia and lymphoma. *J Immunother* 2001; **24:** 511–16.
8. Schnell R, *et al.* Clinical evaluation of ricin A-chain immunotoxins in patients with Hodgkin's lymphoma. *Ann Oncol* 2003; **14:** 729–36.
9. Tsimberidou AM, *et al.* Anti-B4 blocked ricin post chemotherapy in patients with chronic lymphocytic leukemia—long-term follow-up of a monoclonal antibody-based approach to residual disease. *Leuk Lymphoma* 2003; **44:** 1719–25.

Ricinoleic Acid

Kwas rycynolowy; Ricinoleico, ácido.
CAS — 141-22-0.

Profile

Ricinoleic acid is a mixture of fatty acids obtained by the hydrolysis of castor oil. It is an ingredient of some proprietary vaginal jellies used to maintain or restore normal vaginal acidity.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Aci-Jel†; ***Israel:*** Glovan; ***NZ:*** Aci-Jel†; ***USA:*** Acid Jelly.

Rilonacept *(USAN, rINN)*

IL-1 Trap; Interleukin-1 Receptor; Interleukin-1 Trap; Rilonaceptum.

Рилонацепт
CAS — 501081-76-1.

Profile

Rilonacept is an interleukin-1 blocker used in the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckel-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders. Rilonacept is a soluble decoy interleukin-1 receptor that binds interleukin-1_{beta} (p.2325) and blocks its actions at cell surfaces.

Rilonacept is given by subcutaneous injection. The solution, when prepared according to the manufacturer's directions, contains 160 mg per 2 mL and this is the maximum amount that should be given as a single injection or at a single site; if a larger dose is required (as at loading) two separate injections should be given on the same day at two different sites.

The loading dose is 320 mg (as two separate injections). A single injection of 160 mg is then given once weekly. The loading dose for children aged 12 to 17 years is 4.4 mg/kg up to a maximum of 320 mg (given as one or two injections depending on the dose). A single injection of 2.2 mg/kg up to a maximum of 160 mg is then given once weekly.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Arcalyst.

Riluzole *(BAN, USAN, rINN)*

PK-26124; Rilutsoli; Riluzol; Riluzolum; RP-54274. 2-Amino-6-(trifluoromethoxy) benzothiazole; 6-Trifluoromethoxy-1,3-benzothiazol-2-ylamine.

Рилузол
$C_8H_5F_3N_2OS$ = 234.2.
CAS — 1744-22-5.
ATC — N07XX02.
ATC Vet — QN07XX02.

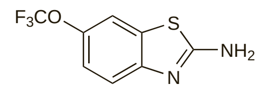

Adverse Effects and Treatment

Adverse effects associated most commonly with riluzole are asthenia, nausea, elevations in liver enzyme values, headache, and abdominal pain. Other gastrointestinal effects may include diarrhoea or constipation, anorexia, and vomiting. There may be tachycardia, dizziness, vertigo, or somnolence. Circumoral paraesthesia has been reported and decreased lung function and rhinitis may occur. Anaphylactoid reactions, angioedema, pancreatitis, and neutropenia have all been reported rarely.

Effects on the blood. Severe neutropenia has been reported[1] in a 71-year old patient with amyotrophic lateral sclerosis receiving standard doses of riluzole. The neutrophil count returned to normal on cessation of riluzole.

See also under Overdosage, below.

1. Weber G, Bitterman H. Riluzole-induced neutropenia. *Neurology* 2004; **62:** 1648.

Effects on the kidneys. A 44-year-old patient developed renal tubular impairment 3 months after starting riluzole for amyotrophic lateral sclerosis.[1] Tubular function recovered 1 month after stopping riluzole.

1. Poloni TE, *et al.* Renal tubular impairment during riluzole therapy. *Neurology* 1999; **52:** 670.

Effects on the liver. Icteric toxic hepatitis, with jaundice and elevated liver enzyme values, has been reported[1] in an elderly woman receiving riluzole for amyotrophic lateral sclerosis (ALS). Acute hepatitis developed in 2 patients several weeks after starting therapy with riluzole for ALS.[2] Liver histology showed hepatocellular damage with inflammatory infiltration and microvesicular steatosis without fibrosis. Hepatotoxicity was reversed in all these cases when riluzole was stopped.

1. Castells LI, *et al.* Icteric toxic hepatitis associated with riluzole. *Lancet* 1998; **351:** 648.
2. Remy A-J, *et al.* Acute hepatitis after riluzole administration. *J Hepatol* 1999; **30:** 527–30.

Effects on the pancreas. Riluzole was cited[1] as the most likely cause of severe pancreatitis that developed in a 77-year-old woman 6 months after starting therapy for sporadic amyotrophic lateral sclerosis; pancreatic symptoms improved when riluzole was stopped.

1. Drory VE, *et al.* Riluzole-induced pancreatitis. *Neurology* 1999; **52:** 892–3.

Hypersensitivity. A severe life-threatening systemic inflammatory reaction occurred in a patient 2 weeks after starting treatment with riluzole for amyotrophic lateral sclerosis.[1] Symptoms resolved spontaneously on stopping riluzole.

1. Sorenson EJ. An acute, life-threatening, hypersensitivity reaction to riluzole. *Neurology* 2006; **67:** 2260–1.

Overdosage. Severe neutropenia developed in a 63-year-old woman receiving riluzole for amyotrophic lateral sclerosis 10 days after inadvertent dose increase to 200 mg daily (twice the standard recommended dose).[1]

Methaemoglobinaemia has been reported[2] in a 43-year-old patient with amyotrophic lateral sclerosis after intentional overdose with 2.8 g of riluzole. The patient was treated with gastric lavage followed by activated charcoal; intravenous methylthioninium chloride successfully reversed the methaemoglobinaemia. However, the patient died of respiratory failure related to her underlying disease 7 days after the overdose.

An amnesic syndrome that persisted for over a year developed in a woman 4 days after ingestion of 3 g of riluzole.[3]

1. North WA, *et al.* Reversible granulocytopenia in association with riluzole therapy. *Ann Pharmacother* 2000; **34:** 322–4.

2. Viallon A, *et al.* Methemoglobinemia due to riluzole. *N Engl J Med* 2000; **343:** 665–6.
3. Haaxma CA, *et al.* Delayed amnesic syndrome after riluzole autointoxication in Huntington disease. *Neurology* 2006; **66:** 1123–4.

Precautions

Riluzole is contra-indicated in patients with hepatic disease or markedly raised liver enzyme values. Liver function tests should be performed before and throughout treatment with riluzole. In the UK, riluzole is not recommended in patients with renal impairment although US licensed product information states that the pharmacokinetics are not significantly different in renal impairment. Caution should be exercised in those with a history of liver disorders. Patients or their carers should be told how to recognise signs of neutropenia and should be advised to seek immediate medical attention if symptoms such as fever develop; white blood cell counts should be determined in febrile illness and riluzole stopped if neutropenia occurs. Riluzole may cause dizziness or vertigo and patients should be warned not to drive or operate machinery if these symptoms occur.

Riluzole has been reported to impair fertility in *animals*.

Pharmacokinetics

Riluzole is rapidly absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring in 1 to 1⁄ hours. The rate and extent of absorption are decreased when riluzole is given with a high-fat meal. Riluzole is widely distributed throughout the body and is about 97% bound to plasma proteins. It crosses the blood-brain barrier. Riluzole is extensively metabolised to several metabolites in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and subsequent glucuronidation. Riluzole is excreted mainly in the urine, mainly as glucuronides, with an elimination half-life of about 9 to 15 hours. About 2% is excreted unchanged in the urine. Small amounts are excreted in faeces. There is some evidence that clearance of riluzole is reduced in Japanese patients.

◊ References.

1. Le Liboux A, *et al.* Single- and multiple-dose pharmacokinetics of riluzole in white subjects. *J Clin Pharmacol* 1997; **37:** 820–7.
2. Le Liboux A, *et al.* A comparison of the pharmacokinetics and tolerability of riluzole after repeat dose administration in healthy elderly and young volunteers. *J Clin Pharmacol* 1999; **39:** 480–6.
3. Groeneveld GJ, *et al.* Riluzole serum concentrations in patients with ALS: associations with side effects and symptoms. *Neurology* 2003; **61:** 1141–3.
4. van Kan HJ, *et al.* Association between CYP1A2 activity and riluzole clearance in patients with amyotrophic lateral sclerosis. *Br J Clin Pharmacol* 2005; **59:** 310–13.

Uses and Administration

Riluzole is a glutamate antagonist used in the management of amyotrophic lateral sclerosis, a form of motor neurone disease. Riluzole is indicated to slow progression of early disease but efficacy has not been demonstrated in its late stages. The precise mechanism of action is unknown but it may inhibit presynaptic glutamate release and interfere with its postsynaptic effects. The usual adult dose of riluzole is 50 mg twice daily by mouth on an empty stomach.

Motor neurone disease. Motor neurone disease (motoneuron disease) represents a group of fatal progressive degenerative disorders that affect upper and/or lower motor neurones in the brain and spinal cord. The most common form of motor neurone disease is amyotrophic lateral sclerosis (known in the USA as Lou Gehrig's disease), which involves both upper and lower motor neurones. It produces muscular atrophy and weakness and symptoms of progressive bulbar palsy such as slowness of movement and speech disturbances. Most patients die within 2 to 5 years of disease onset, usually from respiratory failure. There is no completely effective treatment and management remains largely supportive with appropriate symptomatic management of spasticity (p.1887), pain (p.8), and sialorrhoea. Tricyclic antidepressants are widely used for their multiple beneficial effects. Occupational and speech therapy also play a crucial role in maximising function. Pathological crying or laughing (pseudobulbar affect) may occur in as many as 50% of patients and has been treated with amitriptyline or fluvoxamine. Dysphagia may eventually compromise food and fluid intake necessitating enteral nutrition as an alternative or supplemental route for oral nutrition. Respiratory support will ultimately be necessary, initially with non-invasive ventilation but progressing eventually to tracheostomy.

Although the pathogenesis of motor neurone disease is still uncertain, it is thought that accumulation of the excitatory neurotransmitter glutamate in the CNS may be involved. Clinical studies have shown riluzole, a glutamate antagonist, to be modestly effective in prolonging survival by an average of 3 months and delaying the time to use of tracheostomy. However, there is still insufficient data to be able to assess which patients would derive greatest benefit. Additionally, questions have been raised about the clinical usefulness of riluzole in terms of cost-benefit, and there are concerns about adverse effects, notably hepatotoxicity.

Also under study for the treatment of motor neurone disease are somatomedins, in particular mecasermin (insulin-like growth factor I). Neurotrophic factors have been investigated including brain-derived neurotrophic factor (BDNF) and recombinant ciliary neurotrophic factor (CNTF), but results have been generally inconclusive. Glial-cell-derived neurotrophic factor (GDNF) and xaliproden are under investigation.

There has been some interest in the antiepileptic drug gabapentin, which may inhibit glutamate formation in the CNS from branched-chain amino acids. Lamotrigine and topiramate have also been tried but with disappointing results. ONO-2506 is an enantiomeric homologue of valproate that is also under investigation. Dextromethorphan has been studied in amyotrophic lateral sclerosis. Minocycline has demonstrated neuroprotective effects in *animal* studies and is therefore also being studied in this condition; ceftriaxone is also under investigation. Immunoglobulins have been tried in some forms of motor neurone disease such as multifocal motor neuropathy.

Antioxidants, including vitamins C and E, are commonly used by patients in the belief that one mechanism for neuronal death is free radical accumulation resulting from oxidative stress. However, despite substantial literature on the subject and widespread use of antioxidants, significant evidence to support their benefit in motor neurone disease is lacking. Creatine supplements have been tried in a bid to preserve motor function and motor neurones, although benefit has not been shown in controlled studies.

A small percentage of patients with familial amyotrophic lateral sclerosis has been shown to have a mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase but there has been no consensus as to whether patients with this mutation should be given superoxide dismutase supplements.

References.

1. Ludolph AC, Riepe MW. Do the benefits of currently available treatments justify early diagnosis and treatment of amyotrophic lateral sclerosis? — Arguments against. *Neurology* 1999; **53** (suppl 5): S46–S49.
2. Cashman NR. Do the benefits of currently available treatments justify early diagnosis and announcement? — Arguments for. *Neurology* 1999; **53** (suppl 5): S50–S52.
3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344:** 1688–1700.
4. Dib M. Amyotrophic lateral sclerosis: progress and prospects for treatment. *Drugs* 2003; **63:** 289–310.
5. Leigh PN, *et al.* The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003; **74** (suppl 4): iv32–iv47.
6. Ashworth NL, *et al.*. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 28/04/06).
7. Choudry RB, Cudkowicz ME. Clinical trials in amyotrophic lateral sclerosis: the tenuous past and the promising future. *J Clin Pharmacol* 2005; **45:** 1334–44.
8. Traynor BJ, *et al.* Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67:** 20–7.
9. Miller RG, *et al.* Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
10. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
11. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet* 2007; **369:** 2031–41.
12. Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: prepare for the worst and hope for the best. *JAMA* 2007; **298:** 207–16.
13. McDermott CJ, Shaw PJ. Diagnosis and management of motor neurone disease. *BMJ* 2008; **336:** 658–62.
14. Corcia P, Meininger V. Management of amyotrophic lateral sclerosis. *Drugs* 2008; **68:** 1037–48.

Movement disorders. Beneficial results have been obtained with riluzole in small studies of patients with Huntington's chorea.[1,2] Riluzole has been tried in a small number of patients with early Parkinson's disease but no evidence of benefit was observed.[3] It has also been tried in levodopa-induced dyskinesias in advanced Parkinson's disease with conflicting reports of benefit[4] or no benefit.[5]

1. Rosas HD, *et al.* Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999; **14:** 326–30.
2. Huntington Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. *Neurology* 2003; **61:** 1551–6.
3. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8:** 271–6.
4. Merims D, *et al.* Riluzole for levodopa-induced dyskinesias in advanced Parkinson's disease. *Lancet* 1999; **353:** 1764–5.
5. Braz CA, *et al.* Effect of riluzole on dyskinesia and duration of the ON state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* 2004; **27:** 25–9.

Psychiatric disorders. Glutamate is implicated in the aetiology of various psychiatric disorders and consequently riluzole has been suggested as a potential treatment in view of its glutamate-modulating properties.

References.

1. Zarate CA, *et al.* An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 2004; **161:** 171–4.
2. Sanacora G, *et al.* Riluzole augmentation for treatment-resistant depression. *Am J Psychiatry* 2004; **161:** 2132.
3. Zarate CA, *et al.* An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry* 2005; **57:** 430–2.
4. Coric V, *et al.* Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry* 2005; **58:** 424–8.
5. Coric V, *et al.* Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with trichotillomania. *J Clin Psychiatry* 2007; **68:** 170–1.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rilasat; Rilutek; ***Austral.:*** Rilutek; ***Austria:*** Rilutek; ***Belg.:*** Rilutek; ***Braz.:*** Rilutek; ***Canad.:*** Rilutek; ***Chile:*** Rilutek; ***Cz.:*** Rilutek; ***Denm.:*** Rilutek; ***Fin.:*** Rilutek; ***Fr.:*** Rilutek; ***Ger.:*** Rilutek; ***Gr.:*** Rilutek; ***Hong Kong:*** Rilutek; ***Hung.:*** Rilutek; ***Irl.:*** Rilutek; ***Israel:*** Rilutek; ***Ital.:*** Rilutek; ***Jpn:*** Rilutek; ***Mex.:*** Rilutek; ***Neth.:*** Rilutek; ***Norw.:*** Rilutek; ***NZ:*** Rilutek; ***Pol.:*** Rilutek; ***Port.:*** Rilutek; ***S.Afr.:*** Rilutek; ***Singapore:*** Rilutek; ***Spain:*** Rilutek; ***Swed.:*** Rilutek; ***Switz.:*** Rilutek; ***Thai.:*** Rilutek; ***Turk.:*** Rilutek; ***UK:*** Rilutek; ***USA:*** Rilutek; ***Venez.:*** Rilutek.

Rimonabant *(USAN, rINN)*

Rimocaban; Rimonabantum; SR-141716. 5-(*p*-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide.

Римонабант

$C_{22}H_{21}Cl_3N_4O$ = 463.8.

CAS — 168273-06-1 (rimonabant); 158681-13-1 (rimonabant hydrochloride).

ATC — A08AX01.

ATC Vet — QA08AX01.

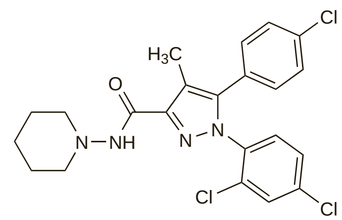

Profile

Rimonabant is a selective cannabinoid type-1 receptor antagonist used as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), and also for overweight patients (BMI > 27 kg/m^2) who have associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. It is given orally in doses of 20 mg daily before breakfast. However, following concern about psychiatric reactions marketing of rimonabant was suspended in Europe in October 2008.

Nausea, anxiety, and dizziness occur commonly with rimonabant. Depressive symptoms have also occurred and rimonabant should not be given to patients with major depression or to those being treated with antidepressants; it is also not recommended in patients with other uncontrolled serious psychiatric disorders. Since rimonabant is metabolised by the liver, caution is advised in patients with moderate hepatic impairment. Licensed product information does not recommend its use in patients with severe hepatic or renal impairment because of lack of data in these patient groups. Plasma concentrations of rimonabant are increased when given with ketoconazole; other CYP3A4 inhibitors might have the same effect.

Rimonabant is also being investigated as an aid for smoking cessation.

◊ The action and potential uses of rimonabant have been reviewed.[1-5] Rimonabant is a selective cannabinoid type-1 receptor antagonist that reduces the overactivity of the endocannabinoid (endogenous cannabinoid) system. Studies of rimonabant *in vitro* and in *animals* have shown that it inhibits the proliferation and maturation of adipocytes, improves lipid and glucose metabolism, and regulates food intake and energy balance.[1,3,4]

Four large multicentre randomised controlled studies have been carried out to examine the effects of rimonabant in obesity (RIO) in conjunction with a mildly hypocalorific diet (deficit of about 600 kcal/day),[6-9] and all studies showed that rimonabant was of benefit when given at a dose of 20 mg daily. A significant decrease in body-weight and waist circumference was reported from the RIO-Europe study[6] over 1 year, although results from the RIO-North America study[7] conducted over 2 years were more modest; both studies also showed improvement in cardiovascular risk factors. The RIO-Lipids study[8] examined the effects of rimonabant over 1 year in overweight or obese patients with untreated dyslipidaemias and noted improvement in several metabolic risk factors as well as weight loss. Similar results including improvement in plasma-glucose concentrations (as indicated by glycosylated haemoglobin measurements) were obtained in overweight or obese patients with type 2 diabetes mellitus given rimonabant over 1 year in the RIO-Diabetes study.[9] Meta-analysis[10] and systematic review[11] of the 4 studies in the RIO-programme agreed that rimonabant produced statistically greater weight loss than placebo, although some problems with methodology were noted. Since no follow-up data were reported, no conclusion could be reached about weight regain.[10] Of particular concern was the increase in incidence of psychiatric adverse effects such as depression and anxiety in the treatment group.[10]

Rimonabant is also being studied as an aid to smoking cessation but a systematic review[12] of randomised controlled studies concluded that although rimonabant 20 mg daily may be of benefit in stopping smoking, the evidence in maintaining abstinence is inconclusive.

1. Boyd ST, Fremming BA. Rimonabant—a selective CB1 antagonist. *Ann Pharmacother* 2005; **39:** 684–90.
2. Gelfand EV, Cannon CP. Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol* 2006; **47:** 1919–26.
3. Henness S, *et al.* Rimonabant. *Drugs* 2006; **66:** 2109–19.
4. Patel PN, Pathak R. Rimonabant: a novel selective cannabinoid-1 receptor antagonist for treatment of obesity. *Am J Health-Syst Pharm* 2007; **64:** 481–9.
5. Xie S, *et al.* The endocannabinoid system and rimonabant: a new drug with a novel mechanism of action involving cannabinoid CB receptor antagonism — or inverse agonism — as potential obesity treatment and other therapeutic use. *J Clin Pharm Ther* 2007; **32:** 209–31.
6. Van Gaal LF, *et al.* Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; **365:** 1389–97. Correction. *ibid.* **366:** 370.
7. Pi-Sunyer FX, *et al.* Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006; **295:** 761–75.
8. Després J-P, *et al.* Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; **353:** 2121–34.
9. Scheen AJ, *et al.* RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006; **368:** 1660–72.
10. Christensen R, *et al.* Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370:** 1706–13.
11. Curioni C, André C. Rimonabant for overweight or obesity. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 14/02/08).
12. Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/02/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acomplia; Resibant; ***Cz.:*** Acomplia†; Zimulti; ***Fr.:*** Acomplia†; ***Gr.:*** Acomplia† ***Port.:*** Zimulti; ***UK:*** Acomplia†.

Rociverine *(rINN)*

LG-30158; Rociverina; Rocivérine; Rociverinum. 2-Diethylamino-1-methylethyl *cis*-1-hydroxy(bicyclohexyl)-2-carboxylate.

Роциверин

$C_{20}H_{37}NO_3$ = 339.5.
CAS — 53716-44-2.
ATC — A03AA06.
ATC Vet — QA03AA06.

Profile

Rociverine is an antispasmodic that has been given orally in doses of 30 to 40 mg or rectally in doses of 50 to 75 mg daily. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Rilaten.

Rose Bengal Sodium

CI Acid Red 94; Colour Index No. 45440; Rosa de bengala sódico; Rose Bengal; Sodium Rose Bengal. The disodium salt of 4,5,6,7-tetrachloro-2′,4′,5′,7′-tetraiodofluorescein .

$C_{20}H_2Cl_4I_4Na_2O_5$ = 1017.6.
CAS — 11121-48-5 (rose bengal); 632-69-9 (rose bengal disodium).
ATC — S01JA02.
ATC Vet — QS01JA02.

NOTE. The name Rose Bengale has been applied to the substance described in this monograph as well as to dichlorotetraiodofluorescein (CI Acid Red 93; Ext. D & C Reds Nos. 5 and 6; Colour Index No. 45435), a compound used as its disodium or dipotassium salt as a colouring agent.

ROS is a code approved by the BP 2008 for use on single unit doses of eye drops containing rose bengal sodium where the individual container may be too small to bear all the appropriate labelling information.

Profile

Rose bengal sodium stains devitalised conjunctival and corneal epithelial cells as well as mucus and is used as an aid in the diagnosis of dry eye. It is used to detect or assess ocular damage resulting from Sjögren's syndrome or from ill-fitting contact lenses, and for keratitis, squamous cell carcinomas, and detection of foreign bodies. Rose bengal sodium is applied as 1% eye drops or as sterile papers impregnated with the dye.

Instillation of this dye may be painful, especially in dry eyes. Rose bengal sodium can stain exposed skin, clothing, and soft contact lenses. Rose bengal sodium should not be used before taking swabs as it possesses some antiviral activity.

Rose bengal sodium is taken up by the liver and excreted in the bile; the iodine-131-labelled compound (p.2054) has been used as a diagnostic aid in the determination of hepato-biliary function.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Ak-Rose; ***USA:*** Rosets.

Rose Fruit

Brier Fruit; Csipkerózsa áltermés; Cynorrhodon; Cynosbati Fructus; Cynosbati Pseudofructus; Dog Rose Fruits; Églantier; Erškėčių vaisiai; Escaramujo; Hips; Hypanthium Rosae; Nypon; Rosae Fructus; Rosae pseudo-fructus; Rose Hips; Ruusunmarja; Šípek.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*.

Ph. Eur. 6.2 (Dog Rose). The rose hips made up by the receptacle and the remains of the dried sepals of *Rosa canina*, *R. pendulina*, and other *Rosa* spp., with the achenes removed. It contains not less than 0.3% of ascorbic acid, calculated with reference to the dried drug. Protect from light.

Profile

The fruits of various *Rosa* species, in particular the dog rose, *R. canina*, are used as a source of vitamin C (p.1983). Rose fruit is included in herbal preparations for constipation and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: LitoZin.

Multi-ingredient: ***Arg.:*** Vitamina C-Complex; ***Austral.:*** Bio C; Bioglan Mega C; Bioglan Super Cal C; C Supa + Bioflavonoids†; Flavons; Glycyrrhiza Complex†; Plantiodine Plus†; Sustained Release C; ***Austria:*** Amersan; ***Chile:*** Calcio 520; Natursel-C; Reduc-Te; Romox-ARL; ***Cz.:*** Amersan; Bronchicum Hustensirup†; Prudušková; Stoffwechseltee N†; ***Ger.:*** Nephronorm med†; ***Ital.:*** Angiorex Complex; Golapiol C; Longevital; Nepiros; Sambuco (Specie Composta)†; ***Malaysia:*** Nat-C; ***Philipp.:*** Delrosa; ***Pol.:*** Cholesol; Diabetofort; Diges-Tonic; Echinasal; Sedomix; Tiliros; ***Rus.:*** Bronchicum Husten (Бронхикум Сироп от Кашля); ***Switz.:*** A Vogel Capsules polyvitaminees†; Tisane contre les refroidissements; ***Thai.:*** Nat-C Medicrafts; ***UK:*** GlucOsamax; Top C; ***USA:*** Amino-Opti-C; C Factors "1000" Plus; Ester-C Plus; Ester-C Plus Multi-Mineral; ***Venez.:*** Ro-C-Var.

Rose Oil

Attar of Rose; Esencia de Rosa; Oleum Rosae; Otto of Rose; Rosa, aceite esencial de.

Pharmacopoeias. In *USNF.*

USNF 26 (Rose Oil). A volatile oil distilled with steam from the fresh flowers of *Rosa gallica*, *R. damascena*, *R. alba*, *R. centifolia*, and varieties of these species (Rosaceae). It is a colourless or yellow liquid, having the characteristic odour of rose. At 25° it is a viscous liquid. On gradual cooling, it changes to a translucent, crystalline mass, easily liquefied by warming. Miscible with an equal volume of chloroform. Store in well-filled airtight containers.

Profile

Rose oil is largely employed in perfumery and toilet preparations and has been used as a flavour. It is also used in aromatherapy. It contains citronellol. Hypersensitivity reactions have been reported.

Preparations

USNF 26: Stronger Rose Water;
USP 31: Rose Water Ointment.

Proprietary Preparations (details are given in Part 3)
Hung.: Naksol†.

Multi-ingredient: ***Arg.:*** Estri-Atlas; ***Chile:*** Cicapost; ***Ger.:*** Rosatum Heilsalbe; ***Port.:*** Cicapost.

Rosemary

Romarin; Romarin (rosemary leaf); Roris Marini; Rosmariininlehti (rosemary leaf); Rosmarin; Rosmarinblad (rosemary leaf); Rosmarini folium (rosemary leaf); Rozmaringlevél (rosemary leaf); Rozmarinų lapai (rosemary leaf); Rozmarýnový list (rosemary leaf).

Pharmacopoeias. *Eur.* (see p.vii) includes the dried leaf.

Ph. Eur. 6.2 (Rosemary Leaf; Rosmarini Folium). The whole, dried leaf of *Rosmarinus officinalis*. It contains not less than 1.2% v/w of essential oil and not less than 3% of total hydroxycinnamic derivatives, expressed as rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3) both with reference to the anhydrous drug.

Profile

Rosemary (*Rosmarinus officinalis*, Lamiaceae) has rubefacient and mild analgesic activity when applied topically, and is included in external preparations for rheumatic and circulatory disorders. It is also reported to have carminative, spasmolytic, and diuretic effects and is included in herbal preparations for gastrointestinal, cardiovascular, and urinary-tract disorders.

Rosemary is a source of rosemary oil (below).

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Alrinte.

Multi-ingredient: ***Arg.:*** Acnetrol; Sequals G; ***Austral.:*** Avena Complex; Garlic Allium Complex; Vitanox; ***Austria:*** Euka; ***Chile:*** Rhus Opodeldoc; Romox-ARL; ***Cz.:*** Hertz- und Kreislauftee†; Naturland Grosser Swedenbitter†; ***Fr.:*** Depuratum; Hepax; Mediflor Tisane Contre la Constipation Passagere No 7; Mediflor Tisane Digestive No 3; Mediflor Tisane Hepatique No 5; Romarene; ***Ger.:*** Canephron; JuViton†; Melissengeist; Seda-Plantina†; ***Mon.:*** Romarinex; ***Pol.:*** Cardiactiv; ***Rus.:*** Canephron N (Канефрон Н); ***Spain:*** Linimento Naion; Mesatil†; Natusor Hepavesical†; Natusor Low Blood Pressure†; Natusor Sinulan†; Resolutivo Regium; ***Switz.:*** Phytomed Cardio; ***Venez.:*** Flocadep.

Rosemary Oil

Esencia de Romero; Essence de Romarin; Essência de Alecrim; Oleum Roris Marini; Oleum Rosmarini; Romarin, huile essentielle de; Romero, aceite esencial de; Rosmariiniöljy; Rosmarini aetheroleum; Rosmarini Etheroleum; Rosmarinöl; Rosmarinolja; Rozmaringolaj; Rozmarinų eterinis aliejus; Rozmarýnová silice.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Rosemary Oil). The essential oil obtained by steam distillation from the flowering aerial parts of *Rosmarinus officinalis*. It is available as Spanish type rosemary oil and Moroccan and Tunisian type rosemary oil. Spanish type rosemary oil contains 2.0 to 4.5% borneol, 0.5 to 2.5% bornyl acetate, 8.0 to 12.0% camphene, 13.0 to 21.0% camphor, 16.0 to 25.0% cineole, 1.0 to 2.2% *p*-cymene, 2.5 to 5.0% limonene, 1.5 to 5.0% β-myrcene, 18 to 26% α-pinene, 2.0 to 6.0% β-pinene, 1.0 to 3.5% α-terpineol, and 0.7 to 2.5% verbenone. Moroccan and Tunisian type rosemary oil contains 1.5 to 5.0% borneol, 0.1 to 1.5% bornyl acetate, 2.5 to 6.0% camphene, 5.0 to 15.0% camphor, 38.0 to 55.0% cineole, 0.8 to 2.5% *p*-cymene, 1.5 to 4.0% limonene, 1.0 to 2.0% β-myrcene, 9.0 to 14.0% α-pinene, 4.0 to 9.0% β-pinene, 1.0 to 2.6% α-terpineol, and a maximum of 0.4% verbenone.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Rosemary oil is carminative and mildly irritant. It is used in perfumery and as a flavour and has been employed in hair lotions, inhalations, and liniments. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Caprisana†; Rosapinol.

Multi-ingredient: ***Arg.:*** Bano Liquido con Eucalipto†; ***Austral.:*** Bacopa Complex; Bosisto's Vaporising Ointment; Euky Bearub; Tixylix Chest Rub†; ***Austria:*** Berggeist; Carl Baders Divinal; Criniton; Opino; Pulmex; Rheuma; Rowalind; Salhumin; ***Belg.:*** Perubore; Pulmex; Pulmex Baby; ***Braz.:*** Aliviol; Analgen†; Benegel; Gelflex; Gelol†; Gelonevral†; Mialgex†; Nevrol; ***Chile:*** Agua del Carmen; Agua Melisa Carminativa; Lefkaflam; Pulmex†; ***Cz.:*** Pulmex Baby†; Pulmex†; Thrombocid; ***Fr.:*** Aromasol; Dinacode†; Item Lentes; Maghora; Perubore; ***Ger.:*** Arthrodeformat P†; Arthrodynat P†; Cor-Vel; Criniton†; Dolo-cyl; Hingfong-Essenz Hofmanns; Leukona-Kreislauf-Bad†; Leukona-Rheumasalbe†; polio-elan; Retterspitz Ausserlich; Retterspitz Quick; Rheuma Bad; Rosarthron†; Tetesept Badekonzentrat Rheuma Bad†; Thrombocid; Top-Sabona†; Vaxicum NA†; Weleda-Rheumasalbe M; ***Gr.:*** Opino-jel; ***Indon.:*** Opino; ***Ital.:*** Calyptol; Cinarepa; Neuralta Migren; Valda Propoli; Vicks Baby Balsam†; ***Malaysia:*** Purporent†; ***NZ:*** Electric Blue Headlice; Tixylix Chest Rub; Vicks Baby Balsam; ***Pol.:*** Argol Rheuma; Aromagel; Depulol; Pulmex Baby; ***Port.:*** Thrombocid; ***Rus.:*** Carmolis Fluid (Кармолис Жидкость)†; Pulmex (Пульмекс); Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); ***S.Afr.:*** Arnica Massage Oil; Balsem Vita GEEL; Balsem Vita ROOI; Entressdruppels HM; Oleum Salviae Comp; Rooilavental; Stuidruppels; ***Spain:*** Beta Romero; Dolokey; Linimento Klari†; Masagil; Tonimax; ***Switz.:*** Carmol; Carmol Plus†; Frigoplasma†; Frixo-Dragon Vert†; Liberol Bain†; Nasobol N; Novital; Perskindol Classic; Perubare†; Pulmex; Pulmex Baby; Spagyrom; Thrombocid; Wolo Medicinal bain antirhumatismal; Ziegella; ***UK:*** Adiantine; Arnica Massage Balm; Medicated Extract of Rosemary; Soothol.

Roxarsone *(BAN, USAN, rINN)*

NSC-2101; Roxarsona; Roxarsonum. 4-Hydroxy-3-nitrophenylarsonic acid.

Роксарсон

$C_6H_6AsNO_6$ = 263.0.
CAS — 121-19-7.

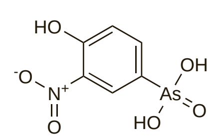

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Roxarsone). A pale yellow, crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in dehydrated alcohol, in acetic acid, in acetone, in methyl alcohol, and in alkalis; insoluble in ether and in ethyl acetate; sparingly soluble in dilute mineral acids. It puffs up and deflagrates on heating.

Profile

Roxarsone has been used as a growth promotor in animal feeds.

Royal Jelly

Apilak; Jalea real; Queen Bee Jelly.

Маточное Молочко

CAS — 8031-67-2.

Profile

Royal jelly is a milky-white viscid secretion from the salivary glands of the worker honey bee, *Apis mellifera* (Apidae); it is essential for the development of queen bees. Royal jelly has been used as a nutritional supplement, but of the many and diverse claims made for its therapeutic value, none has been substantiated.

Royal jelly is also included in some cosmetic preparations for its supposed beneficial effect on skin tissue.

Hypersensitivity reactions have been reported.

Hypersensitivity. There were 14 reports of suspected adverse effects (10 considered serious) involving bee products such as royal jelly, propolis (p.2373), and bee pollen (p.2370) reported to the Canadian health authorities (Health Canada) between January 1998 and October 2004.[1] Anaphylactoid reactions[2] and acute severe exacerbations of asthma[3-6] (one fatal[4]) have occurred in atopic individuals who took royal jelly.

1. Health Canada. Products derived from bees: serious adverse reactions. *Can Adverse React News* 2005; **15** (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2-eng.pdf (accessed 08/08/08)
2. Takahama H, Shimazu T. Food-induced anaphylaxis caused by ingestion of royal jelly. *J Dermatol* 2006; **33:** 424–6.
3. Thien FCK, *et al.* Royal jelly-induced asthma. *Med J Aust* 1993; **159:** 639.
4. Bullock RJ, *et al.* Fatal royal jelly-induced asthma. *Med J Aust* 1994; **160:** 44.
5. Peacock S, *et al.* Respiratory distress and royal jelly. *BMJ* 1995; **311:** 1472.
6. Thien FCK, *et al.* Asthma and anaphylaxis induced by royal jelly. *Clin Exp Allergy* 1996; **26:** 216–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Apiserum; ***Ital.:*** Alvear; Biogel; Biovital; Clinvit; Gelamel†; Novel Jelly†; Pa-Real; Ritmogel; Roburvit; Telergon II; ***Rus.:*** Apilac (Апилак); ***UK:*** Biobees; Regina Royal One Hundred; Rojema.

Multi-ingredient: ***Fr.:*** Gintonal†; Pollen Royal†; ***Ger.:*** Peking Royal Jelly N†; ***Indon.:*** Hemaviton Energy Drink; Hemaviton Jreng; Neo Hormoviton; Neo Hormoviton Greng; ***Ital.:*** Alvear con Ginseng; Apergan; Api Baby; Apiserum con Telergon 1; Apistress; Bebimix; Bio-200; Bioton; Biotrefon Plus; Eurogel; Fon Wan Ginsenergy; Fosfarsile Forte; Fosfarsile Junior; Four-Ton; Granvit; Longevital; Neoplus; Nerex; Nutrigel†; Ottovis; Pollingel; Provitamin A-E; Ribovir; Royal E; ***Mex.:*** Supravital; ***Philipp.:*** Jamieson Total Energy; ***Thai.:*** Multilim RG; ***UK:*** Regina Royal Concorde; Regina Royal Five.

Rubber

Caoutchouc; Caucho; India-Rubber.

Profile

Rubber consists of the prepared latex of *Hevea brasiliensis* and other species of *Hevea* (Euphorbiaceae). It is used as a component of many medical devices such as catheters, syringes, enema tips, ostomy bags, balloons, and surgical gloves. Hypersensitivity reactions have occurred after direct contact of skin and mucous membranes with rubber components of such products and also after indirect contact with preparations stored in or given by them; deaths have been reported. Reactions have been attributed either to protein components of the rubber or to additives such as preservatives or vulcanisation accelerators. For references to glove starch powder as a possible risk factor in the development of rubber latex allergy, see Glove Powder under Adverse Effects of Starch, p.1968. Cross-sensitivity between rubber proteins and those of certain fruits, including bananas and chestnuts, has been reported.

◊ References.

1. Landwehr LP, Boguniewicz M. Current perspectives on latex allergy. *J Pediatr* 1996; **128:** 305–12.
2. Senst BL, Johnson RA. Latex allergy. *Am J Health-Syst Pharm* 1997; **54:** 1071–5.
3. Woods JA, *et al.* Natural rubber latex allergy: spectrum, diagnostic approach, and therapy. *J Emerg Med* 1997; **15:** 71–85.
4. Zaidi Z, *et al.* Latex allergy: a life-threatening complication. *Hosp Med* 1998; **59:** 505–7.
5. Smith CC. Risk of latex allergy from medication vial closures. *Ann Pharmacother* 1999; **33:** 373–4.
6. Wakelin SH, White IR. Natural rubber latex allergy. *Clin Exp Dermatol* 1999; **24:** 245–8.
7. Bowyer RVStL. Latex allergy: how to identify it and the people at risk. *J Clin Nurs* 1999; **8:** 144–9.
8. Levy DA, Leynadier F. Latex allergy: review of recent advances. *Curr Allergy Rep* 2001; **1:** 32–8.
9. Hamann CP, *et al.* Management of dental patients with allergies to natural rubber latex. *Gen Dent* 2002; **50:** 526–36.
10. Bernstein DI. Management of natural rubber latex allergy. *J Allergy Clin Immunol* 2002; **110** (suppl 2): S111–S116.
11. Nieto A, *et al.* Efficacy of latex avoidance for primary prevention of latex sensitization in children with spina bifida. *J Pediatr* 2002; **140:** 370–2.
12. Hourihane JO'B, *et al.* Impact of repeated surgical procedures on the incidence and prevalence of latex allergy: a prospective study of 1263 children. *J Pediatr* 2002; **140:** 479–82.
13. Cullinan P, *et al.*. British Society of Allergy and Clinical Immunology. Latex allergy: a position paper of the British Society of Allergy and Clinical Immunology. *Clin Exp Allergy* 2003; **33:** 1484–99.
14. LaMontagne AD, *et al.* Primary prevention of latex related sensitisation and occupational asthma: a systematic review. *Occup Environ Med* 2006; **63:** 359–64.
15. Nettis E, *et al.* Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. *Br J Dermatol* 2007; **156:** 674–81.

Rubidium Iodide

Rubidio, ioduro de.

RbI = 212.4.

CAS — 7790-29-6.

Profile

Rubidium iodide has the actions of iodine and the iodides (see p.2169). It is an ingredient of several proprietary ophthalmic preparations promoted for the treatment of eye disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Facovit; Jodo Calcio Vitaminico; Polijodurato; Rubjovit.

Rue Oil

Oleum Rutae; Ruda, aceite esencial de.

Profile

Rue oil is a volatile oil obtained from rue, *Ruta graveolens* (Rutaceae). Rue oil and infusions of rue were formerly used as antispasmodics and emmenagogues and are reported to have abortifacient properties. Rue is a photosensitiser and the oil is a powerful local irritant.

Homoeopathy. Rue has been used in homoeopathic medicines under the following names: Ruta; Ruta gra. Ruta grav. Ruta graveolens.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Aulo Repelente De Piojos; ***Austral.:*** Joint & Muscle Cream; ***Singapore:*** Noricaven†.

Ruscogenin

Ruscogenina; Ruskojenin. (25*R*)-Spirost-5-ene-1β,3β-diol.

$C_{27}H_{42}O_4$ = 430.6.

CAS — 472-11-7.

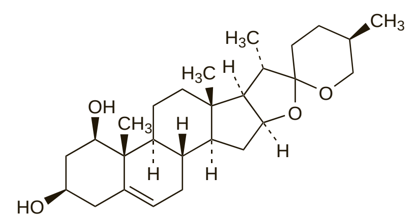

Profile

Ruscogenin is a sapogenin obtained from butcher's broom, *Ruscus aculeatus* (Liliaceae). It has been applied in the local treatment of haemorrhoids as rectal ointment or suppositories. It has also been tried in peripheral vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Flebodolor; Flebopom†; ***Spain:*** Ruscorectal†.

Multi-ingredient: ***Arg.:*** Miopropan Proctologico; Procto Venart; ***Fr.:*** Proctolog; ***Gr.:*** Ibuproct; ***Ital.:*** Ruscoroid; ***Pol.:*** Ruskorex; ***Port.:*** Proctolog; ***Singapore:*** Proctolog; ***Spain:*** Abrasone Rectal; Hemodren Compuesto†; Neo Analsona; Proctolog; Ruscus; Venacol; ***Turk.:*** Proctolog.

Sacrosidase *(USAN)*

Sacrosidasa.

CAS — 85897-35-4.

ATC — A16AB06.

ATC Vet — QA16AB06.

Profile

Sacrosidase is a therapeutic enzyme used for sucrase replacement therapy in congenital sucrase-isomaltase deficiency. It is given with each meal or snack in usual doses of 8 500 international units for patients up to 15 kg, or 17 000 international units for patients over 15 kg.

◊ References.

1. Treem WR, *et al.* Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999; **28:** 137–42.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Sucraid.

Sage

Feuilles de Sauge; Hármaslevelű zsálya levél (sage leaf, three-lobed); Krūminių šalavijų lapai (sage leaf, three-lobed); Liść szałwii (sage leaf); List šalvěje lékařské (sage leaf); List šalvěje trojlaločné (sage leaf, three-lobed); Orvosizsálya-levél (sage leaf); Salbeiblätter; Salvia; Salviablad (sage leaf); Salviablad, treflikat (sage leaf, three-lobed); Salviae Folium (sage leaf); Salviae Officinalis Folium (sage leaf); Salviae trilobae folium (sage leaf, three-lobed); Salvianlehti, kolmiliuskainen (sage leaf, three-lobed); Salvianlehti (sage leaf); Sauge officinale, feuille de (sage leaf); Sauge trilobée, feuille de (sage leaf, three-lobed); Vaistinių šalavijų lapai (sage leaf).

Pharmacopoeias. In *Eur.* (see p.vii), which also includes three-lobed sage.

Ph. Eur. 6.2 (Sage Leaf (Salvia officinalis); Salviae Officinalis Folium). The whole or cut dried leaves of *Salvia officinalis*. The whole drug contains not less than 1.5% v/w and the cut drug not less than 1.0% v/w of essential oil, both calculated with reference to the anhydrous drug. Sage leaf oil is rich in thujone. Protect from light.

Ph. Eur. 6.2 (Sage Leaf, Three-lobed; Salviae Trilobae Folium). The whole or cut, dried leaves of *Salvia fructicosa* (*S. triloba*). The whole drug contains not less than 1.8% v/w of essential oil, and the cut drug not less than 1.2% v/w of essential oil, both calculated with reference to the anhydrous drug. It has a spicy odour when ground, similar to eucalyptus oil. Protect from light.

Profile

Sage has carminative, antispasmodic, antiseptic, and astringent properties and is used as a flavour. It is used in preparations for a wide variety of purposes, including respiratory-tract disorders, gastrointestinal disorders, and in mouthwashes and gargles for disorders of the mouth and throat. Three-lobed sage leaf (Greek sage) is also used; it is sometimes found as an adulterant of sage.

Sage is the source of sage oil (see below).

Homoeopathy. Sage has been used in homoeopathic medicines under the following names: Salvia officinalis; Salvia officinalis e foliis siccatis; Sal. off.

Preparations

Ph. Eur.: Sage Tincture.

Proprietary Preparations (details are given in Part 3)
Austria: Salvysat; ***Cz.:*** Aperisan†; Caj ze Salveje; Florsalmin; Nat Salveje Lekarske; Salvej Lekarske List; Salvejova Nat; ***Ger.:*** Aperisan; Fichtensirup N†; Salbei Curarina; Salvysat; Sweatosan N; Viru-Salvysat†; ***Ital.:*** Saugella Dermoliquido; ***Pol.:*** Aperisan.

Multi-ingredient: ***Arg.:*** Acnetrol; Parodontax Fluor; Sedante Arceli†; Sigmafem; Sigmafen Free; Tereonsit†; ***Austral.:*** Feminine Herbal Complex; ***Austria:*** Cional; Dynexan; Mentopin; Paradenton; ***Canad.:*** Original Herb Cough Drops; ***Chile:*** Eclicean; ***Cz.:*** Diabetan; Diabeticka Cajova Smes-Megadiabetin; Pulmoran; Stomatosan†; Tormentan; ***Fr.:*** Bolcitol; Gonaxine; Menoxine; Saugella; Tisane Hepatique de Hoerdt; ***Ger.:*** Amara-Tropfen; Helago-Pflege-Oel†; Leber-Galle-Tropfen 83†; Melissengeist; Mycatox†; Parodontal; Presselin Blahungs K 4 N†; Presselin Dyspeptikum†; Vitosal†; ***Israel:*** Baby Paste + Chamomile; Kamilotract; ***Ital.:*** Donalg; Saugella Attiva; Saugella Dermolatte; Saugella Fitothym; Saugella Salviettine; Saugella Solido ph 3.5; ***Pol.:*** Dentosept; Dentosept A; Enterosol; Herbogastrin; Mucosit; Salumin; Salviasept; Sanofil; Tymsal; ***S.Afr.:*** Amara; Dynexan; ***Spain:*** Diabesor†; Menstrunat†; Natusor Farinol†; Natusor Low Blood Pressure†; ***Switz.:*** Anginesin†; Strath Gouttes pour les muqueuses; Tisane pectorale et antitussive; Wala Echinacea; ***Venez.:*** One Drop Spray†.

Sage Oil

Kvapiųjų šalavijų eterinis aliejus (clary sage oil); Muskatellsalviaöljy (clary sage oil); Muskatellsalviaolja (clary sage oil); Salviae sclareae aetheroleum (clary sage oil); Salviae Sclareae Etheroleum (clary sage oil); Sauge sclarée, huile essentielle de (clary sage oil); Silice šalvěje muškátové (clary sage oil).

CAS — 8016-63-5 (clary sage oil).

NOTE. The oil of three-lobed sage leaf (see above), which is sometimes found as an adulterant, has a lower thujone content than oil from *Salvia officinalis*

Pharmacopoeias. In *Swiss. Eur.* (see p.vii) includes Clary Sage Oil from *Salvia sclarea.*

Profile

Sage oil is used similarly to sage (see above). Sage oil and clary sage oil are also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Node G; ***Ger.:*** Fichtensirup N†.

Multi-ingredient: ***Austria:*** Colda; Coldistan; Parodontax; Piniment; ***Cz.:*** Parodontal F5†; ***Fr.:*** Item Lentes; ***Ger.:*** Pernionin N†; Salviathymol N; Trauma-cyl; Varicylum-S; ***Israel:*** Parodontax†; ***Ital.:*** Venalta; ***Philipp.:*** Kamillosan M; Transpulmin Balsam; ***Pol.:*** Carmolis; Salviasept; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; ***S.Afr.:*** Oleum Salviae Comp; ***Switz.:*** Bismorectal; Carmol; Carmol Plus†; Frixo-Dragon Vert†; Osa gel dentaire aux plantes; Parodontax F†; Parodontax†; Pinimenthol Baby†; Radix†; Ziegella.

Salicyl Alcohol *(USAN)*

Salicain; Saligenin; Saligenol. 2-Hydroxybenzyl alcohol.

Салициловый Спирт

$C_7H_8O_2$ = 124.1.

CAS — 90-01-7.

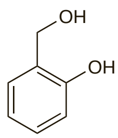

NOTE. The name salicain has also been used as a proprietary name for hydroxytetracaine.

Profile

Salicyl alcohol is reported to have local anaesthetic and analgesic properties and has been used in various topical preparations. It is present in the bark of some trees and has been associated with contact sensitivity; it is also a metabolite of salicin (salicyl alcohol glucoside—see Salix, p.121).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Ephydrol.

Salverine Hydrochloride *(rINNM)*

Hidrocloruro de salverina; M-811 (salverine); Salvérine, Chlorhydrate de; Salverini Hydrochloridum. 2-[2-(Diethylamino)ethoxy]-benzanilide hydrochloride.

Сальверина Гидрохлорид

$C_{19}H_{24}N_2O_2$,HCl = 348.9.

CAS — 6376-26-7 (salverine).

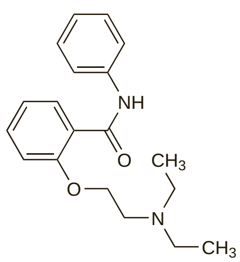

(salverine)

Profile

Salverine hydrochloride has been used as an antispasmodic in combination preparations for the treatment of biliary-tract disorders, respiratory-tract disorders, and pain.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Cynarix comp; Montamed; Novipec.

Salvia Divinorum

Diviner's Sage; Divining Sage; Hierba de María; *Salvia divinorum*; ska María Pastora.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of Salvia divinorum:

Big Sal; La Pastora; LSD Lite; Maria Pastora; Sally D; Salvia; Ska; The Shepherdess.

Profile

Salvia divinorum has been traditionally used in Mexican Indian culture to induce hallucinations and is now a substance of abuse.

◊ References.

1. Prisinzano TE. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*. *Life Sci* 2005; **78:** 527–31.
2. Singh S. Adolescent salvia substance abuse. *Addiction* 2007; **102:** 823–4.

Sambucus

Bodzavirág; Elder Flower; Fläderblomma; Fleurs de Sureau; Holunderblüten; Juoduogių šeivamedžių žiedai; Květ bezu černého; Kwiat bzu czarnego; Mustaseljankukka; Sabugueiro; Sambuc.; Sambuci flos; Sambuci Nigrae Flos; Saúco; Sureau, fleur de.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Elder Flower). The dried flowers of *Sambucus nigra*. It contains not less than 0.8% of flavonoids, calculated as isoquercitroside with reference to the dried drug. Protect from light.

Profile

Sambucus has astringent, diaphoretic, and anticatarrhal properties and is used in herbal preparations for a variety of disorders, particularly respiratory-tract disorders. Elder-flower water has been used as a vehicle for eye and skin lotions. Elder-flower ointment has been used as a basis for pomades and cosmetic ointments.

Homoeopathy. Sambucus has been used in homoeopathic medicines under the following names: Sambucus nigra; Samb. nig.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Caj z Kvetu Bezu Cerneho; Kvet Bazy Ciernej†; ***Rus.:*** Novo-Passit (Ново-Пассит).

Multi-ingredient: ***Austral.:*** Diaco; Sambucus Complex†; ***Austria:*** Entschlackender Abfuhrtee EF-EM-ES; Grippetee St Severin; Krauter Hustensaft; Laxalpin; Sinupret; Solvopret; Tuscalman; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Biotussil; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Erkaltungstee†; Novo-Passit; Perospir†; Pulmoran; Reduktan; Sinupret; Species Urologicae Planta; Urcyston Planta; ***Ger.:*** Sinupret; ***Hong Kong:*** Sinupret; ***Hung.:*** Sinupret; ***Indon.:*** Imboost Force; Sinupret; StarMuno; ***Ital.:*** Sambuco (Specie Composta)†; Tiglio (Specie Composta)†; ***Mex.:*** Bisolsinus; Bronkitose Mielimon; ***Philipp.:*** Sinupret; ***Pol.:*** Betasol; Pyrosal; Sinupret; Termasil; ***Rus.:*** Sinupret (Синупрет); ***Singapore:*** Sinupret; ***Spain:*** Natusor Gripotul†; Natusor Sinulan†; ***Switz.:*** Sinupret; Tisane contre les refroidissements; ***Thai.:*** Sinupret; ***UK:*** Cleansing Herbs; EP&C Essence; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Herb and Honey Cough Elixir; Life Drops; Lion Cleansing Herbs; Lustys Herbalene; Modern Herbals Cold & Catarrh; Sinotar; Tabritis; ***Venez.:*** Dromil Sauco.

Sandalwood

East Indian Sandalwood; White Sandalwood.

Pharmacopoeias. In *Chin.*

Profile

The wood of white sandalwood, *Santalum album* (Santalaceae), has antibacterial and antispasmodic activity and is used in herbal medicine as an adjunct in the treatment of infections of the lower urinary tract. Sandalwood and its preparations contain essential oil.

Sandalwood oil is used in aromatherapy and in perfumery.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Brady's-Magentropfen.

Sanguinaria

Bloodroot; Red Puccoon; Sanguinaria canadensis; Sanguinaris canadensis.

Profile

Sanguinaria consists of the dried rhizome of *Sanguinaria canadensis* (Papaveraceae). Sanguinarine, an alkaloid extracted from sanguinaria, has been used as an antiplaque agent in toothpaste and mouthwash preparations. Sanguinaria was formerly used as an expectorant but fell into disuse because of its toxicity. Sanguinaria has also been classified by the FDA as a herb that is unsafe for use in foods, beverages, or drugs.

Homoeopathy. Sanguinaria has been used in homoeopathic medicines under the following names: Sanguinaria canadensis; Sang. ca.

Sanguinarium nitrate has been used in homoeopathic medicines under the following names: Sanguinarinum Nitricum; Sang. nit.

◊ Reviews.

1. Karlowsky JA. Bloodroot: Sanguinaria canadensis L. *Can Pharm J* 1991; **124:** 260, 262–3, 267.
2. Grenby TH. The use of sanguinarine in mouthwashes and toothpaste compared with some other antimicrobial agents. *Br Dent J* 1995; **178:** 254–8.
3. Tenenbaum H, *et al.* Effectiveness of a sanguinarine regimen after scaling and root planing. *J Periodontol* 1999; **70:** 307–11.

Malignant neoplasms of the skin. Self-treatment of basal cell carcinoma on the nasal tip by a 51-year-old man using a topical caustic preparation containing *Sanguinaria canadensis* has been reported.[1] Although a similar caustic paste was originally used in the 1930s as part of Mohs' micrographic surgery (MMS) for some types of skin cancer, the MMS technique in use today is more refined, and self-administration of caustic pastes containing sanguinaria for skin lesions is not recommended.

1. Affleck AG, Varma S. A case of do-it-yourself Mohs' surgery using bloodroot obtained from the internet. *Br J Dermatol* 2007; **157:** 1078–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Clematis III Oligoplex†; ***Austral.:*** Lexat†; ***Canad.:*** Bronchial Cough; Mielocol; Viadent†; Wampole Bronchial Cough Syrup†; ***Ital.:*** Dentosan Carie & Alito†; Eudent con Glysan†.

Sapropterin Hydrochloride *(rINNM)*

Dapropterin Hydrochloride; Hidrocloruro de sapropterina; Sapropterin Dihydrochloride *(USAN)*; Saproptérine, Chlorhydrate de; Sapropterini Hydrochloridum; SUN-0588 (sapropterin or sapropterin hydrochloride); T-1401; (6*R*)-5,6,7,8-Tetrahydrobiopterin Hydrochloride. (−)-(6*R*)-2-Amino-6-[(1*R*,2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(3*H*)-pteridinone dihydrochloride.

Сапроптерина Гидрохлорид

$C_9H_{15}N_5O_3$,2HCl = 314.2.

CAS — 62989-33-7 (sapropterin); 69056-38-8 (sapropterin hydrochloride).

ATC — A16AX07.

ATC Vet — QA16AX07.

Profile

Sapropterin, the active form of tetrahydrobiopterin, is used as the hydrochloride for the diagnosis and treatment of variant forms of phenylketonuria (hyperphenylalaninaemia, p.1922) associated with tetrahydrobiopterin (BH_4) deficiency. It is given by mouth in daily doses of 1 to 20 mg/kg, in 2 or more divided doses. It has also been tried for the correction of hyperphenylalaninaemia seen in patients receiving treatment for leukaemia and which has been suggested as a possible cause of neurological symptoms.

◊ References.

1. Ueda S, *et al.* Tetrahydrobiopterin restores endothelial function in long-term smokers. *J Am Coll Cardiol* 2000; **35:** 71–5.
2. Thony B, *et al.* Tetrahydrobiopterin biosynthesis, regeneration and functions. *Biochem J* 2000; **347:** 1–16.
3. Muntau AC, *et al.* Tetrahydrobiopterin as an alternative treatment for mild phenylketonuria. *N Engl J Med* 2002; **347:** 2122–32.
4. Okano Y, *et al.* In vivo studies of phenylalanine hydroxylase by phenylalanine breath test: diagnosis of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *Pediatr Res* 2004; **56:** 714–19.
5. Pérez-Dueñas B, *et al.* Tetrahydrobiopterin responsiveness in patients with phenylketonuria. *Clin Biochem* 2004; **37:** 1083–90.
6. Opladen T, *et al.* Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria. *Eur J Pediatr* 2005; **164:** 395–6.
7. Fiege B, Blau N. Assessment of tetrahydrobiopterin (BH) responsiveness in phenylketonuria. *J Pediatr* 2007; **150:** 627–30.
8. Levy HL, *et al.* Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *Lancet* 2007; **370:** 504–10.
9. Cosentino F, *et al.* Chronic treatment with tetrahydrobiopterin reverses endothelial dysfunction and oxidative stress in hypercholesterolaemia. *Heart* 2008; **94:** 487–92.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Biopten; ***USA:*** Kuvan.

Sarsaparilla

Salsaparilha; Salsepareille; Sarsa; Sarsaparilla Root; Smilacis Rhizoma; Zarzaparrilla.

Pharmacopoeias. In *Chin.* and *Jpn.* which specify *Smilax glabra.*

Profile

Sarsaparilla is the dried root of various species of *Smilax* (Liliaceae). It has been used, usually in the form of a decoction or extract, as a vehicle and flavour for medicaments. It is also an ingredient of herbal preparations.

Homoeopathy. Sarsaparilla has been used in homoeopathic medicines under the following names: Smilax; Sarsap.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Urinefrol†; ***Austral.:*** Dermaco; Herbal Cleanse†; Proesten†; ***Braz.:*** Elixir de Inhame†; Elixir de Marinheiro†; ***Canad.:*** Damiana-Sarsaparilla Formula†; ***Ger.:*** Pankreaplex Neu†; ***Indon.:*** Instink; Provigor; ***Ital.:*** Tisana Kelemata; ***Malaysia:*** Cleansa Plus†; Total Man†; ***UK:*** Gerard House Reumalex; HRI Clear Complexion; Jamaican Sarsaparilla; Skin Eruptions Mixture; ***Venez.:*** Flocadep.

Sassafras Oil

Oleum Sassafras; Sasafrás, aceite esencial de.

Profile

Sassafras oil is a volatile oil distilled from the root or root bark of *Sassafras albidum* (Lauraceae), or from the wood of certain species of *Ocotea* (Lauraceae). It contains safrole.

Sassafras oil has rubefacient properties and was formerly used as a pediculicide. Neither sassafras nor the oil should be taken internally; the use of herb teas of sassafras may lead to a large dose of safrole. The use of safrole in foods has been banned because of carcinogenic and hepatotoxic risks. The use of safrole in toilet preparations is also controlled.

Poisoning. A 47-year-old woman experienced 'shakiness', vomiting, anxiety, tachycardia, and raised blood pressure after ingestion of a potentially fatal dose of sassafras oil (5 mL). She was given activated charcoal and symptomatic management.[1]

1. Grande GA, Dannewitz SR. Symptomatic sassafras oil ingestion. *Vet Hum Toxicol* 1987; **29:** 447.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Inhalador Medex; ***Austral.:*** Urinase†; Zam-Buk†; ***Cz.:*** Stopangin; ***Fr.:*** Vegebom; ***Indon.:*** Thymcal; ***Rus.:*** Stopangin (Стопангин); ***S.Afr.:*** Moultons Pain Paint; Zam-Buk†; ***Spain:*** Linimento Klari†.

Satavaptan *(rINN)* ⊗

Satavaptán; Satavaptanum; SR-121463 (satavaptan); SR-121463B (satavaptan phosphate). *N-tert*-Butyl-4-({cis-5′-ethoxy-4-[2-(morpholin-4-yl)ethoxy]-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1:3′-indole]-1′-yl}sulfonyl)-3-methoxybenzamide.

Сатаваптан

$C_{33}H_{45}N_3O_8S$ = 643.8.
CAS — 185913-78-4 (satavaptan); 308145-17-7 (satavaptan phosphate).

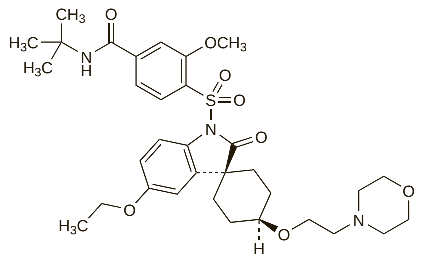

Profile

Satavaptan is a selective vasopressin V_2-receptor antagonist under investigation for the treatment of hyponatraemia in the syndrome of inappropriate antidiuretic hormone secretion.

◊ References.

1. Soupart A, *et al.* Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V -receptor antagonist. *Clin J Am Soc Nephrol* 2006; **1:** 1154–60.

Saxitoxin

Saxitoxina.
CAS — 35523-89-8.

Profile

Saxitoxin is a neurotoxin associated with paralytic shellfish poisoning. It is an endotoxin produced by species of dinoflagellate plankton present in infected molluscs.

◊ References.

1. Halstead BW, Schantz EJ. *Paralytic shellfish poisoning.* Geneva: WHO, 1984.
2. WHO. Aquatic (marine and freshwater) biotoxins. *Environmental Health Criteria 37*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc37.htm (accessed 24/07/08)
3. Hartigan-Go K, Bateman DN. Redtide in the Philippines. *Hum Exp Toxicol* 1994; **13:** 824–30.
4. Gessner BD, *et al.* Hypertension and identification of toxin in human urine and serum following a cluster of mussel-associated paralytic shellfish poisoning outbreaks. *Toxicon* 1997; **35:** 711–22.
5. de Carvalho M, *et al.* Paralytic shellfish poisoning: clinical and electrophysiological observations. *J Neurol* 1998; **245:** 551–4.
6. Lehane L. Paralytic shellfish poisoning: a potential public health problem. *Med J Aust* 2001; **175:** 29–31.
7. Garcia C, *et al.* Paralytic shellfish poisoning: post-mortem analysis of tissue and body fluid samples from human victims in the Patagonia fjords. *Toxicon* 2004; **43:** 149–58.
8. Llewellyn LE. Saxitoxin, a toxic marine natural product that targets a multitude of receptors. *Nat Prod Rep* 2006; **23:** 200–22.

Schick Test

Prueba de Schick.

Pharmacopoeias. *Br.* include standards for Schick test toxin and control.

BP 2008 (Schick Test Toxin). It is prepared from a toxigenic strain of *Corynebacterium diphtheriae*. It contains a suitable antimicrobial preservative. Store at 2° to 8°.

BP 2008 (Schick Control). It is Schick Test Toxin that has been heated at a temperature not lower than 70° and not higher than 85° for not less than 5 minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is to be used. Store at 2° to 8°.

Profile

Intradermal injection of Schick test toxin has been used for the diagnosis of susceptibility to diphtheria and, more importantly, to detect patients who might experience an adverse reaction to diphtheria vaccines. Children up to the age of about 8 to 10 years rarely suffer from such reactions and therefore the Schick test is not usually performed in this age group. In older children and adults a Schick test was formerly used before the use of standard diphtheria vaccines. However, diphtheria vaccines for use in adults and adolescents (p.2209) are now formulated with lesser amounts of toxoid so Schick testing is unnecessary.

Schisandra

Schizandra.

Pharmacopoeias. *Chin.* includes the dried ripe fruit of *Schisandra chinensis* (Fructus Schisandrae Chinensis) and *S. sphenanthera* (Fructus Schisandra Sphenanthera)

Profile

The dried ripe fruit of *Schisandra chinensis* or *S. sphenanthera*, sometimes referred to as schizandrae fructus, are known in Chinese medicine as wuweizi and nanwuweizi respectively. Schisandra is used in a variety of disorders and contains lignans claimed to have protective effects on the liver. The oil is also used.

The derivative bifendate has been reported to interact with ciclosporin (see p.1826). SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin, has been reported to increase maximum blood concentrations of tacrolimus (see p.1845).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Bacopa Complex; ***Indon.:*** Curliv; Curliv Plus; Hepa-Q; Hepacell; Hepamax; ***Pol.:*** Penigra; ***Rus.:*** Carmolis (Кармолис)†.

Scoparium

Broom Tops; Genêt; Genêt à Balai; Planta Genista; Retama negra; Scoparii Cacumina.

Pharmacopoeias. In *Fr.*

Profile

Scoparium is the dried tops of broom, *Sarothamnus scoparius* (*Cytisus scoparius*) (Leguminosae). It is a mild diuretic, haemostatic, and vasoconstrictor and has been given as a decoction or alcoholic extract. It has oxytocic properties and should be avoided in pregnancy. It contains sparteine (p.2391).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Repowine mono†; Spartiol.

Multi-ingredient: ***Fr.:*** Creme Rap; ***Ger.:*** Oxacant N†; Venacton†; ***Pol.:*** Fitoven.

Sea Buckthorn

Argousier; Sallowthorn; Sea-buckthorn.

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p.1732) and from Buckthorn (p.1713).

Profile

Sea buckthorn (*Hippophae rhamnoides*, Eleagnaceae) is the source of sea buckthorn oil, below.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Hippophan†.

Sea Buckthorn Oil

Profile

Sea buckthorn oil is extracted from the seeds and berries of sea buckthorn (above) and has been taken orally for skin and mucous membrane disorders and as a tonic. It has also been investigated in liver fibrosis.

Preparations

Proprietary Preparations (details are given in Part 3)
UK: Omega 7.

Seaweeds, Kelps, and Wracks

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Kelp; Fucus vel Ascophyllum). The fragmented dried thallus of *Fucus vesiculosus* or *F. serratus* or *Ascophyllum nodosum*. It contains not less than 0.03% and not more than 0.2% of total iodine, calculated with reference to the dried drug. It has a salty and mucilaginous taste, and an unpleasant marine odour. Protect from light.

The Ph. Eur. title was formerly Bladderwrack and the BP 2008 gives Bladderwrack and Fucus as approved synonyms.

Profile

Dried seaweeds of various species are ingredients of a number of herbal preparations.

The terms kelps and wracks have been used indiscriminately for each other and other brown seaweeds. For example, Kelp (Ph. Eur. 6.2) refers to a preparation of various species of wrack and was formerly titled Bladderwrack.

Bladder wrack (*Fucus vesiculosus*), toothed wrack (*F. serratus*), or knotted wrack (*Ascophyllum nodosum*) are included in preparations given for various disorders including obesity, constipation, and iodine deficiency.

Kelps refer properly to species of *Laminaria* and *Macrocystis*. They are present as an ingredient of several dietary supplements and herbal preparations, including for use in obesity; they have also been used as a source of iodine. Laminaria stalks (p.2330) are used for dilation of cavities or the cervix.

Fucoidan (p.2307) is a sulfated polysaccharide extracted from brown seaweeds.

Homoeopathy. *F. vesiculosus* has been used in homoeopathic medicines under the following names: Fucus v.

Adverse effects and precautions. Kelp can concentrate various heavy metals; auto-immune thrombocytopenic purpura and disordered erythropoiesis in a patient who had been taking kelp tablets for 6 weeks was attributed to the arsenic content of the preparation.[1]

Clinical hyperthyroidism has also been reported in patients taking kelp-containing preparations as part of a slimming regimen[2] or a dietary supplement.[3]

The FDA has advised that preparations containing compounds such as kelp, which may be taken orally in bulk laxatives or weight-control preparations, should be taken with a full glass of water or, if the patient has difficulty in swallowing, they should be avoided. Such compounds swell into masses that may obstruct the oesophagus if not taken with sufficient water.

1. Pye KG, *et al.* Severe dyserythropoiesis and autoimmune thrombocytopenia associated with ingestion of kelp supplements. *Lancet* 1992; **339:** 1540.
2. de Smet PA, *et al.* Hyperthyreoidie tijdens het gebruik van kelp tabletten. *Ned Tijdschr Geneeskd* 1990; **134:** 1058–9.
3. Eliason BC. Transient hyperthyroidism in a patient taking dietary supplements containing kelp. *J Am Board Fam Pract* 1998; **11:** 478–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Sual; ***Braz.:*** Redufat; ***Fr.:*** Dictyolone; Dyctiol†; ***UK:*** Adios Max; Phytoslim.

Multi-ingredient: ***Arg.:*** Arceligasol; Celu-Atlas; Centellase de Centella Queen; Centellase Gel; Herbaccion Celfin; Herbaccion Diet; KLB6 Fruit Diet; Nio Marine; Redualgas; Silueta Plus; Varisedan Gel; Yerba Diet; ***Austral.:*** Bioglan Zellulean with Escin; Gartech; Plantiodine Plus†; PMT Complex†; ***Braz.:*** Composto Anticelulitico†; Composto Emagrecedor†; Emagrevit†; Emagrex†; Obesidex†; Obesifran†; ***Canad.:*** Damiana-Sarsaparilla Formula†; Kelp B Cider Vinegar; ***Chile:*** Celltech Gold; Fucus Compuesto†; ***Cz.:*** Cajova Smes pri Redukcni Diete†; Reduktan; ***Fr.:*** Algoceanic†; Dellova†; Dragees Fuca; Duo Reparation; Marinol; Maxidraine†; Obeflorine; Promincil†; Tonimer; ***Ger.:*** Krophan N†; Viscophyll†; ***Indon.:*** Naturica DFM; ***Ital.:*** Fave di Fuca; Neoform†; Skarflex; ***Mex.:*** Lecifar-K†; ***Pol.:*** Herbaton; ***S.Afr.:*** Activex 40 Plus; ***Spain:*** Fucusor†; Lipograsil; ***UK:*** Adios; Boldex; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kelp Plus 3; Water Naturtabs; Weight Loss Aid; ***USA:*** KLB6; ***Venez.:*** Demerung; Fugras; Lecivar Plus.

Secretin *(BAN, USAN, rINN)*

Secretina; Sécrétine; Secretinum; Sekretiini; Sekretin.

Секретин

CAS — 17034-35-4 (porcine); 108153-74-8 (human).
ATC — V04CK01.
ATC Vet — QV04CK01.

Units

The potency of secretin may be expressed as Crick-Harper-Raper (CHR) units based on the pancreatic secretion in *cats* or as clinical units, the value of which was amended in the 1960s. One clinical unit is considered to be approximately equivalent to 4 CHR units. One clinical unit is equivalent to 200 nanograms of a purified synthetic preparation of secretin.

Adverse Effects

Hypersensitivity reactions may occasionally occur. Diarrhoea has occurred in patients given high doses by intravenous infusion.

Precautions

The secretin test should be avoided in patients with acute pancreatitis. Patients should receive an intravenous test dose because of the risk of hypersensitivity reactions.

Uses and Administration

Secretin is a polypeptide hormone involved in the regulation of gastric function. It may be prepared from the duodenal mucosa of *pigs*; synthetic human and porcine versions are also available. On intravenous injection it causes an increase in the secretion by the pancreas of water and bicarbonate into the duodenum.

Secretin is used as a diagnostic agent in various disorders of the pancreas. Patients should be given an initial intravenous test dose of 1 clinical unit (200 nanograms); if no hypersensitivity reaction is noted after 1 minute, the diagnostic dose may be given.

Secretin is used alone, or with pancreozymin (p.2361) or other cholecystokinetic agents such as ceruletide (p.2279) or sincalide (p.2388), as a test for exocrine pancreatic function. The test usually involves duodenal intubation of the patient and examination of duodenal aspirate. The diagnostic dose of secretin used has varied but common doses have been 1 clinical unit/kg (200 nanograms/kg) given by slow intravenous injection.

Patients with the Zollinger-Ellison syndrome (p.1704) show an increase in gastrin when given secretin; this is in contrast to a small change or no effect in subjects without the disorder. The usual dose of secretin for the diagnosis of Zollinger-Ellison syndrome is 2 clinical units/kg (400 nanograms/kg) by slow intravenous injection. Serum-gastrin concentrations are measured for up to 30 minutes following the diagnostic dose.

Secretin is also used in a dose of 1 clinical unit/kg (200 nanograms/kg) by slow intravenous injection as an aid in the identification of the pancreatic ducts in patients undergoing endoscopic retrograde cholangiopancreatography.

Autism. There have been anecdotal reports of improvement in behaviour in autistic children given porcine secretin. However, a double-blind placebo-controlled study[1] involving 60 children with autism or pervasive developmental disorder noted no benefit over 4 weeks after a single infusion of 400 nanograms/kg of synthetic human secretin. A randomised, placebo-controlled study[2] in 64 children with autism has similarly found no evidence of efficacy from 2 repeated doses of porcine secretin. Further controlled studies have likewise failed to demonstrate efficacy.[3,4]

1. Sandler AD, *et al.* Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. *N Engl J Med* 1999; **341:** 1801–6.
2. Roberts W, *et al.* Repeated doses of porcine secretin in the treatment of autism: a randomized, placebo-controlled trial. Abstract: *Pediatrics* 2001; **107:** e71. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/5/e71 (accessed 08/07/04)
3. Levy SE, *et al.* Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin. *Arch Dis Child* 2003; **88:** 731–6.
4. Coplan J, *et al.* Children with autistic spectrum disorders. II: parents are unable to distinguish secretin from placebo under double-blind conditions. *Arch Dis Child* 2003; **88:** 737–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Secrelux; ***USA:*** ChiRhoStim; SecreFlo.

Selfotel *(USAN, rINN)*

CGS-19755; Selfotelum. *cis*-4-(Phosphonomethyl)pipecolic acid.

Сельфотел

$C_7H_{14}NO_5P$ = 223.2.
CAS — 110347-85-8.

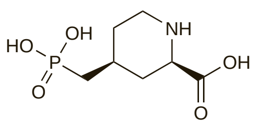

Profile

Selfotel is an *N*-methyl-D-aspartate (NMDA) antagonist that has been investigated for use in ischaemic stroke and head trauma.

◊ References.

1. Davis SM, *et al.* Termination of acute stroke studies involving selfotel treatment. *Lancet* 1997; **349:** 32.
2. Yenari MA, *et al.* Dose escalation safety and tolerance study of the competitive NMDA antagonist selfotel (CGS 19755) in neurosurgery patients. *Clin Neuropharmacol* 1998; **21:** 28–34.
3. Stewart L, *et al.* First observations of the safety and tolerability of a competitive antagonist to the glutamate NMDA receptor (CGS 19755) in patients with severe head injury. *J Neurotrauma* 1999; **16:** 843–50.
4. Morris GF, *et al.* The Selfotel Investigators. Failure of the competitive N-methyl-D-aspartate antagonist selfotel (CGS 19755) in the treatment of severe head injury: results of two phase III clinical trials. *J Neurosurg* 1999; **91:** 737–43.
5. Davis SM, *et al.* Selfotel in acute ischemic stroke: possible neurotoxic effects of an NMDA antagonist. *Stroke* 2000; **31:** 347–54.

Senecio

Крестовник Золотистый (*Senecio aureus*); Крестовник Якова (*Senecio jacobaea*)

Profile

The ragwort, *Senecio jacobaea*, and, in the USA, the golden ragwort (golden senecio; liferoot; squaw weed), *S. aureus* (Compositae), have been used in the form of extracts as emmenagogues but are of doubtful value. Ragwort, in the form of a decoction or ointment, has also been applied externally to aid wound healing and in the treatment of peripheral vascular disorders.

Many species of the genus *Senecio*, which includes the ragworts and groundsels, are poisonous. They have been found to contain pyrrolizidine alkaloids, which produce hepatic necrosis. The ragwort, *S. jacobaea*, which is abundant throughout the British Isles, is poisonous to livestock when eaten in quantity. Poisoning has also been reported in humans after ingestion of herbal teas containing pyrrolizidine alkaloids. In the UK, the sale, supply, or importation of unlicensed medicinal products containing *Senecio* spp. for internal use is prohibited.

Homoeopathy. Golden ragwort has been used in homoeopathic medicines under the following names: Senecio aur.; Senecio aureus; Sen. aur..

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Canad.:* Thunas Tab for Menstrual Pain†.

Senicapoc *(USAN, rINN)*

17043; ICA-17043; Sénicapoc; Senicapocum. 2,2-bis (4-Fluorophenyl)-2-phenylacetamide.

Сеникапок

$C_{20}H_{15}F_2NO$ = 323.3.
CAS — 289656-45-7.

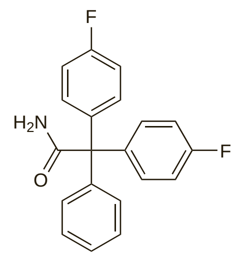

Profile

Senicapoc is an inhibitor of the Gardos calcium-activated potassium channel. It has been investigated to prevent the dehydration of red cells in sickle-cell anaemia.

Senlizumab *(BAN)*

Bay-10-3356; Bay-w-3356; CDP-571.

Сенлизумаб

CAS — 336128-48-4.

Profile

Senlizumab is a humanised monoclonal antibody to tumour necrosis factor. It has been investigated in the treatment of Crohn's disease, ulcerative colitis, and rheumatoid arthritis.

◊ References.

1. Rankin EC, *et al.* The therapeutic effects of an engineered human anti-tumour necrosis factor alpha antibody (CDP571) in rheumatoid arthritis. *Br J Rheumatol* 1995; **34:** 334–42.
2. Evans RC, *et al.* Treatment of ulcerative colitis with an engineered human anti-TNF alpha antibody CDP571. *Aliment Pharmacol Ther* 1997; **11:** 1031–5.
3. Stack WA, *et al.* Randomised controlled trial of CDP571 antibody to tumour necrosis factor-α in Crohn's disease. *Lancet* 1997; **349:** 521–4.
4. Anonymous. CDP 571: anti-TNF monoclonal antibody, BAY 103356, BAY W 3356, Humicade. *Drugs R D* 2003; **4:** 174–8.
5. Sandborn WJ, *et al.* CDP571, a humanised monoclonal antibody to tumour necrosis factor α, for moderate to severe Crohn's disease: a randomised, double blind, placebo controlled trial. *Gut* 2004; **53:** 1485–93.
6. Mamula P, *et al.* CDP571, a humanized anti-tumor necrosis factor-alpha monoclonal antibody in pediatric Crohn's disease. *Inflamm Bowel Dis* 2004; **10:** 723–30.
7. Feagan BG, *et al.* A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, in patients with corticosteroid-dependent Crohn's disease. *Aliment Pharmacol Ther* 2005; **21:** 373–84.
8. Feagan BG, *et al.* CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; **23:** 617–28.

Sepia

Profile

Sepia is the dried inky secretion of the cuttle fish.

Homoeopathy. Sepia has been used in homoeopathic medicines under the following names: Sepia officinalis.

Serotonin

Enteramina; Enteramine; 5-Hidroxitriptamina; 5-HT; 5-Hydroxytryptamine; Serotonina. 3-(2-Aminoethyl)-1*H*-indol-5-ol.

Серотонин

$C_{10}H_{12}N_2O$ = 176.2.
CAS — 50-67-9.

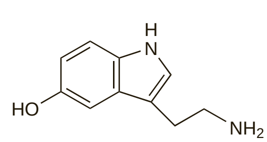

Profile

Serotonin, which is synthesised in the body from the essential amino acid tryptophan, is found in the brain, blood platelets, and throughout the gastrointestinal tract. It acts as a biochemical mediator and its roles include involvement in CNS neurotransmission, haemostasis, vascular spasm, and gastrointestinal motility. Abnormalities within the serotonin system are associated with a variety of disorders and many drugs have been developed to manipulate serotonin concentrations.

Serotonin itself may be of value in the treatment of posthypoxic myoclonus (p.470). Concentrations of endogenous serotonin may be increased through synthesis and serotonin precursors have been given for the treatment of depression (see Oxitriptan, p.414 and Tryptophan, p.427).

Some antidepressants increase serotonin concentrations by inhibiting the metabolism of monoamine oxidase type A, the enzyme that deaminates serotonin. Examples include the older non-selective irreversible inhibitors of monoamine oxidase types A and B (MAOIs) such as phenelzine (p.415), and the newer selective reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (p.411).

Drugs that inhibit the neuronal reuptake of serotonin after release (and thus potentiate its action) are also used in the treatment of depression. They include tricyclic antidepressants such as amitriptyline (p.376), the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (p.391), and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine (p.427). Some SSRIs and SNRIs are also used in the management of anxiety disorders, and SSRIs have been tried in the management of premature ejaculation. Sibutramine (p.2163) is an SNRI used in the management of obesity.

Serotonin receptors, a major site of drug action, are classified by structure and function into seven families: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 with each family having further subtypes. Consequently, drugs acting on serotonin receptors exhibit widely differing chemical structures and diverse pharmacological activities depending on which receptor subtype they act on and whether they act as agonists or antagonists. Serotonin receptor activity is complex and it is possible for the same disorder to be treated by both serotonin agonists or antagonists. For example, serotonin antagonists used in the treatment of migraine include the older ergot-derived compounds such as methysergide (p.623) and metergoline (p.2343) whereas the newer triptans such as sumatriptan (p.625) are selective 5-HT_1 agonists. Buspirone (p.965) is a 5-HT_{1A} partial agonist used in the treatment of anxiety disorders. Cisapride (p.1720) is a 5-HT_4 agonist used for gastrointestinal disorders. 5-HT_{2C} agonists are under investigation for obesity.

Many different drugs act as serotonin antagonists. They include sedating antihistamines such as carbinoxamine (p.570), cyproheptadine (p.575), methdilazine (p.585), and promethazine (p.588) used for allergic conditions. Some antiserotonergic antihistamines such as cyproheptadine, oxetorone (p.624), and pizotifen (p.624) are also used in the management of migraine. Antagonists specific for the $5\text{-HT}_{2A/2C}$ receptor include the antihypertensive ketanserin (p.1320), the antipsychotic risperidone (p.1024), and the antidepressant trazodone (p.424). The antipsychotic clozapine (p.981) also has antiserotonergic activity at the $5\text{-HT}_{2A/2C}$ receptor in addition to its other properties. Ondansetron (p.1756) is a 5-HT_3 antagonist used for chemotherapy-induced emesis and postoperative nausea and vomiting.

Drugs with other mechanisms of action involving serotonin systems include fenclonine, an inhibitor of serotonin synthesis that has been used in the treatment of carcinoid syndrome. Reserpine (p.1387) depletes serotonin stores in the brain, heart, and many other organs and has been used in hypertension and psychoses. Fenfluramine (p.2156) and its isomer dexfenfluramine (p.2154) appear to stimulate the release of serotonin and selectively inhibit its reuptake resulting in increased CNS serotonin concentrations; both were formerly used in the treatment of obesity.

Some hallucinogenic drugs of abuse such as bufotenine (p.2270) and lysergide (p.2335) have serotonergic properties.

Serotonin also occurs in stinging nettles (*Urtica dioica*) (p.2409), bananas, and other fruit, and in the stings of wasps and scorpions.

◊ References.

1. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. *Br J Anaesth* 1994; **73:** 395–407.
2. Hoyer D, *et al.* International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994; **46:** 157–203.

Serrapeptase *(rINN)*

Serrapeptasa; Serrapeptasum; Serrapeptidase; Serratia Extracellular Proteinase; Serratiopeptidase.

Серрапептаза

CAS — 37312-62-2; 95077-02-4.

Pharmacopoeias. In *Jpn.*

Profile

Serrapeptase is a proteolytic enzyme derived from *Serratia* spp. It has been taken orally for its supposed action in relieving inflammation and oedema associated with conditions such as trauma, infection, respiratory-tract congestion, or chronic venous insufficiency, in usual doses of 5 to 10 mg (10 000 to 20 000 units) up to three times daily.

◊ References.

1. Tachibana M, *et al*. A multi-centre, double-blind study of serrapeptase versus placebo in post-antrotomy buccal swelling. *Pharmatherapeutica* 1984; **3:** 526–30.
2. Paparella P, *et al*. Serratia peptidase and acute phase protein behavior following vaginal hysterectomy: results of a randomized double-blind, placebo-controlled trial. *Curr Ther Res* 1989; **45:** 664–76.
3. Shimizu H, *et al*. A case of serratiopeptidase-induced subepidermal bullous dermatosis. *Br J Dermatol* 1999; **141:** 1139–40.
4. Nakamura S, *et al*. Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease. *Respirology* 2003; **8:** 316–20.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Danzen; ***Chile:*** Damizen; ***Fr.:*** Dazen; ***Ger.:*** Aniflazym; ***Gr.:*** Brasan; Enziflur†; Eze†; Lergan†; Verolin†; ***Hong Kong:*** Danzen; Unizen; ***India:*** Bidanzen; Cipzen; Flanzen; Infladase; Kineto; Seraim; Serato-M; ***Ital.:*** Danzen; ***Jpn:*** Dasen; ***Malaysia:*** Danzen; Unizen; ***Mex.:*** Danzen; ***Port.:*** Aniflazime; ***Singapore:*** Danzen; Korzen†; Serrazyme; Sinsia; Unizen†; ***Thai.:*** Dailat; Danzen; Danzyme; Denzo; Medizyme†; Podase†; Rodase; Seramed; Serradase; Serrano; Serrao; Serrapep; Serrason; Serrin; Sumidin; Unizen.

Multi-ingredient: ***India:*** Cipzen D; Cipzen N; Diser; Flanzen-D; Nimulid SP; Serato-M Forte†; ***Indon.:*** Dansera; Flavin; Nutriflam.

Sesame Oil

Aceite de Ajonjolí; Benne Oil; Gingelly Oil; Oleum Sesami; Refined Sesame Oil; Seesamiöljy; Sésame, huile de; Sesami oleum; Sésamo, aceite de; Sesamolja; Sezamový olej; Sezamų aliejus; Szezámolaj; Teel Oil.

CAS — 8008-74-0.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Sesame Oil, Refined; Sesami Oleum Raffinatum). The fatty oil obtained from the ripe seeds of *Sesamum indicum* by expression or extraction and subsequent refining. It may contain a suitable antioxidant. It is a clear, light yellow, almost colourless liquid. It solidifies to a soft mass at about –4°. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers. Protect from light. Refined sesame oil for use in the manufacture of parenteral dosage forms should be stored under an inert gas in airtight containers.

USNF 26 (Sesame Oil). The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* (Pedaliaceae). It may contain suitable antioxidants. A pale yellow, practically odourless, oily liquid. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, with ether, and with petroleum spirit. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Profile

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been seen.

Adverse effects. References to hypersensitivity reactions[1-7] associated with sesame, and subcutaneous nodules[8] after injection of the oil.

1. Kanny G, *et al*. Sesame seed and sesame seed oil contain masked allergens of growing importance. *Allergy* 1996; **51:** 952–7.
2. Stern A, Wuthrich B. Non-IgE-mediated anaphylaxis to sesame. *Allergy* 1998; **53:** 325–6.
3. Pecquet C, *et al*. Immediate hypersensitivity to sesame in foods and cosmetics. *Contact Dermatitis* 1998; **39:** 313.
4. Asero R, *et al*. A case of sesame seed-induced anaphylaxis. *Allergy* 1999; **54:** 526–7.
5. Dalal I, *et al*. The pattern of sesame sensitivity among infants and children. *Pediatr Allergy Immunol* 2003; **14:** 312–16.
6. Agne PS, *et al*. Sesame seed allergy in children. *Allerg Immunol (Paris)* 2004; **36:** 300–305.
7. Gangur V, *et al*. Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol* 2005; **95:** 4–11.
8. Darsow U, *et al*. Subcutaneous oleomas induced by self-injection of sesame seed oil for muscle augmentation. *J Am Acad Dermatol* 2000; **42:** 292–4.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Rhinaris Nozoil; ***UK:*** Noseeze.

Multi-ingredient: ***Austral.:*** Snor-Away†; ***Ger.:*** GeloSitin; ***NZ:*** Snorenz; ***UK:*** Goodnight StopSnore; Snor-Away.

Shark-liver Oil

Profile

Shark-liver oil is the fixed oil extracted from the liver of various species of shark and is used in preparations for anorectal disorders. It has been used as a source of vitamin A.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Sperti Preparacion H†; ***Fr.:*** Alkocean†; ***Pol.:*** Ecomer; Ekogal†; Selamer; ***Rus.:*** Relief Advance (Релиф Адванс); ***UK:*** Immutone; ***Venez.:*** Sperti†; Vitaburon†.

Multi-ingredient: ***Arg.:*** Sperti Plus Preparacion H; ***Austral.:*** Preparation H†; ***Austria:*** Sperti Praparation H; ***Canad.:*** Preparation H; ***Chile:*** Sperti Preparation H; ***Cz.:*** Preparation H; ***Ger.:*** Sperti Praparation H†; ***Gr.:*** Preparation H; ***Hong Kong:*** Preparation H; ***India:*** Medithane; ***Irl.:*** Preparation H; ***Israel:*** Preparation H; ***Ital.:*** Preparazione H; ***Malaysia:*** Palmer's Cocoa Butter Formula Scar Serum; ***Mex.:*** Preparation H; ***Neth.:*** Sperti Preparation H; ***Pol.:*** Preparation H†; Prostamer†; ***Port.:*** Sperti Preparacao H; ***Rus.:*** Preparation H (Препарейшн Эйч); Relief (Релиф); Relief Ultra (Релиф Ультра); ***S.Afr.:*** Preparation H; ***Singapore:*** Preparation H; ***Spain:*** Preparacion H; ***Switz.:*** Sperti Preparation H; ***Thai.:*** Preparation H; ***UK:*** Preparation H; ***USA:*** Hem-Prep; Medicone†; Preparation H; Rectacaine; Rectagene Medicated Balm; Wyanoids Relief Factor; ***Venez.:*** Bargonil.

Shellac

E904; Goma laca; Gomme Laque; Gommes laques; Lacca; Lacca in Tabulis; Schellack; Šelak; Šelakas; Sellak; Shellack; Shellakka.

CAS — 9000-59-3.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Jpn includes Purified Shellac and White Shellac (Bleached).

Ph. Eur. 6.2 (Shellac). It is obtained by purification of the resinous secretion of the female insect *Kerria lacca* (Kerr) Lindinger (*Laccifer lacca* Kerr). There are 4 types of shellac depending on the nature of the treatment of crude secretion (seedlac): Wax-containing Shellac; Bleached Shellac; Dewaxed Shellac; and Bleached, Dewaxed Shellac.

Brownish-orange or yellow, shining, translucent, hard or brittle more or less thin flakes (Wax-containing Shellac; Dewaxed Shellac), or a creamy-white or brownish-yellow powder (Bleached Shellac; Bleached, Dewaxed Shellac).

Practically insoluble in water. With dehydrated alcohol it gives a more or less opalescent solution (Wax-containing Shellac; Bleached Shellac) or a clear solution (Dewaxed Shellac; Bleached, Dewaxed Shellac). When warmed, it is sparingly soluble or soluble in alkaline solutions. Protect from light. Store Bleached Shellac and Bleached, Dewaxed Shellac at a temperature not exceeding 15°.

USNF 26 (Shellac). It is obtained by purification of lac, the resinous secretion of the insect *Laccifer lacca kerr* (Coccidae). There are 4 varieties: Orange Shellac, Dewaxed Orange Shellac, Regular Bleached (White) Shellac, and Refined Bleached Shellac. Orange Shellac occurs as thin, hard, brittle, transparent, pale lemon-yellow to brownish-orange flakes, having little or no odour. Bleached Shellac occurs as opaque, amorphous, cream to yellow granules or coarse powder, having little or no odour.

Insoluble in water; very slowly soluble in alcohol, 85 to 95% (w/w); soluble in ether, 13 to 15%, in petroleum spirit, 2 to 6%, in benzene, 10 to 20%, and in aqueous solutions of ethanolamines, alkalis, and borax; sparingly soluble in turpentine oil. Store preferably at a temperature not exceeding 8°.

Profile

Shellac is used as an enteric coating for pills and tablets, but disintegration time has been reported to increase markedly on storage.

Preparations

USNF 26: Pharmaceutical Glaze.

Shepherd's Purse

Bolsa de pastor; Bourse à pasteur; Capsella; Herba Bursae Pastoris; Shepherds Burse Herb.

Pharmacopoeias. In *Fr.*

Profile

Shepherd's purse, the aerial parts of *Capsella bursa-pastoris* (*Thlaspi bursa-pastoris*) (Cruciferae) has antihaemorrhagic and astringent properties. It is used to prevent or arrest bleeding, and has been specifically used for menorrhagia. It is also used for urinary-tract disorders and diarrhoea.

Homoeopathy. Shepherd's purse has been used in homoeopathic medicines under the following names: Capsella bursapastoris; Thlaspi bursa pastoris; Capsella; Thal. b. p.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Styptysat.

Multi-ingredient: ***Austral.:*** Capsella Complex; ***Austria:*** Menodoron; ***Fr.:*** Histo-Fluine P; ***Ger.:*** Rhoival†; ***Pol.:*** Klimax†; Prostapol; Uroprost; ***S.Afr.:*** Menodoron; ***Spain:*** Proctosor†; ***UK:*** Antitis; Sciargo.

Siam Benzoin

Benjoin du Laos; Benjuí de Siam; Bensoe, Siam; Bentsoe, Siam; Benzoe tonkinensis; Benzoino derva; Benzoová pryskyřice siamská.

CAS — 9000-72-0.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii). Also in some pharmacopoeias under the title benzoin and should not be confused with Sumatra benzoin. *Jpn* and *US* allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 6.2 (Benzoin, Siam). The resin obtained by incising the trunk of *Styrax tonkinensis*. It has a characteristic odour of vanillin and contains 45.0 to 55.0% of total acids, calculated as benzoic acid, and with reference to the dried drug. Protect from light.

USP 31 (Benzoin). A balsamic resin from *Styrax tonkinensis*, or other species of the *Anthostyrax* section of the genus *Styrax* (Styracaceae). It yields not less than 90% of alcohol-soluble extractive. It occurs as pebble-like tears of variable size and shape, compressed, yellowish-brown to rusty brown externally, milky white on fracture, separate or very slightly agglutinated, hard and brittle at ordinary temperatures but softened by heat. It has an agreeable, balsamic, vanilla-like odour.

Profile

Siam benzoin has been used similarly to Sumatra benzoin (p.2394). It has also been used as a preservative and was formerly used in the preparation of benzoinated lard.

Preparations of Sumatra and Siam benzoins are used in aromatherapy.

Preparations

USP 31: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Dermol†; ***Fr.:*** Balsolene; Borostyrol; Homeoplasmine; Inotyol†; ***Israel:*** Inotyol; ***Ital.:*** Ondroly-A†; ***Switz.:*** Borostyrol N†.

Siberian Ginseng

Ciwujia; Eleuterokokový kořen (eleutherococcus); Eleuterokokų šaknys (eleutherococcus); Eleuthero; Eleutherococci radix (eleutherococcus); Éleuthérocoque (eleutherococcus); Korzeń eleuterokoka (eleutherococcus); Rysk rot (eleutherococcus); Tajgagyökér (eleutherococcus); Venäjänjuuri (eleutherococcus).

NOTE. The name Russian Ginseng has been applied to *Eleutherococcus senticosus*.

The name Ginseng usually refers to *Panax ginseng* and related species (see p.2312).

Some material supplied as Siberian ginseng may be *Periploca sepium* (Asclepiadaceae), a plant unrelated to *Eleutherococcus senticosus*, due to the similarity of the Chinese names for these plants.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Eleutherococcus; Eleutherococci Radix). The dried, whole or cut underground organs of *Eleutherococcus senticosus*. It contains not less than 0.08% for the sum of eleutheroside B and eleutheroside E.

USP 31 (Eleuthero). The dried rhizome with roots of *Eleutherococus senticosus* (Araliaceae) (*Acanthopanax senticosus*) (Araliaceae). It contains not less than 0.08% of the sum of eleutheroside B and eleutheroside E, calculated on the dried basis. Protect from light.

Profile

Siberian ginseng is reported to enhance natural resistance and to improve performance under stress. It is used similarly to ginseng (*Panax ginseng*) (see p.2312) although the constituents of the two herbs are different. It is also used in traditional Chinese medicine.

◊ Reviews.

1. Davydov M, Krikorian AD. Eleutherococcus sentiosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* 2000; **72:** 345–93.

Adverse effects. Thalamic infarction occurred in a 26-year-old man who had taken oral high-energy dietary supplements containing Siberian ginseng daily for about a year during a vigorous training programme for a marathon.[1] He had taken about 1.5 to 2 g of Siberian ginseng daily; small amounts of caffeine were also contained in the preparations. In the absence of other aetiological factors, it was proposed that prolonged daily use of Siberian ginseng in combination with caffeine and vigorous exercise was responsible for the stroke.

1. Polenakovik S. Dietary supplements and stroke. *Mayo Clin Proc* 2005; **80:** 1240–1.

Interactions. For a report of raised serum-digoxin concentrations in a patient taking *digoxin* and Siberian ginseng, see Interference with Digoxin Assays, p.1260.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Benylin Energy Boosting†; ***Cz.:*** Eleutherosan†; ***Ger.:*** Eleu; Eleu-Kokk; Eleu-Twardypharm†; Eleutheroforce; Eleutherokokk†; Konstitutin; Lebensenergie-Kapseln†; Lomavital; Vital-Kapseln†; ***Pol.:*** Immunostim; Syberian; ***Spain:*** Fitokey Eleuterococo; ***UK:*** Elagen.

Multi-ingredient: ***Arg.:*** Sigmafem; ***Austral.:*** Astragalus Complex; Bacopa Complex; Bioglan Ginsynergy; Gingo A†; Ginkgo Biloba Plus†; Medinat Esten†; Tyroseng†; ***Chile:*** Gingo-Ther†; ***Indon.:*** Reximax; Tripote; ***Ital.:*** Fon Wan Eleuthero†; ***Philipp.:*** Immuvit; Jamieson Total Energy; ***Pol.:*** Tripoten; ***Spain:*** Energysor†; Esforza†; Natusor Low Blood Pressure†; Tonimax.

Sigetin

Sygethin. Dipotassium *meso*-3,4-Bis(*p*-sulfophenyl)hexane.

Сигетин

$C_{18}H_{20}O_6S_2K_2$ = 474.7.

CAS — 13517-49-2.

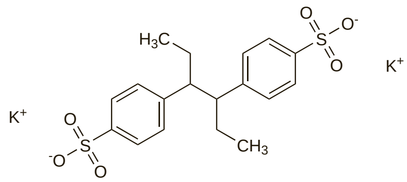

Profile

Sigetin is an analogue of hexestrol (p.2109) but is reported to have no oestrogenic activity. It is used in the management of menopausal symptoms in a usual oral daily dose of 100 to 200 mg.

Sigetin is also reported to enhance the action of oxytocin and to improve placental blood flow and has been given intravenously or intramuscularly in the active management of labour and for threatened intra-uterine fetal asphyxia.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Sagenit (Сагенит).

Silver

Argent; Argentum; E174; Plata; Silber.

Ag = 107.8682.

CAS — 7440-22-4.

ATC — D08AL30.

ATC Vet — QD08AL30.

Profile

Silver is a pure white, malleable and ductile metal. It possesses antibacterial properties and is used topically either as the metal or as silver salts. It is not absorbed to any great extent and the main problem associated with the metal is argyria, a grey discoloration of the tissues. Silver is also present as the core in some copper-wound plastic intra-uterine contraceptive devices. Silver is used as a colouring agent for some types of confectionery.

Salts or compounds of silver that have been used therapeutically include silver acetate (p.2387), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (p.2387), silver-nylon polymers, silver protein (p.2387), and sulfadiazine silver (p.337).

Homoeopathy. Silver has been used in homoeopathic medicines under the following names: Argentum metallicum; Arg. met.

Silver chloride has been used in homoeopathic medicines under the following names: Argentum muriaticum; Arg. mur.

Silver cyanide has been used in homoeopathic compounds under the following names: Argentum cynatum; Arg. cy.

Silver iodide has been used in homoeopathic medicines under the following names: Argentum iodatum; Arg. iod.

Argyria. Argyria (generalised argyrosis), characterised by a slate, blue-grey discoloration of the skin, sclera, mucosal surfaces, and nails, developed in a patient who had used vasoconstrictor nasal drops containing silver protein for 4 years. The colour changes were most obvious in skin exposed to the sun. Argyria is irreversible and withdrawal of the nasal drops and use of other measures such as use of sun block and chemical peeling had little effect in this patient.[1]

1. Tomi NS, *et al.* A silver man. *Lancet* 2004; **363:** 532.

Catheter care. The benefits of silver coated or impregnated catheters in preventing or reducing urinary-tract infection are uncertain, and studies have provided conflicting evidence. Some[1] consider that the benefits are statistically insignificant. However, a meta-analysis[2] involving 8 studies with a total of 2355 patients concluded, despite some concerns about the quality and heterogeneity of the studies, that there was a benefit, but that silver alloy coated catheters were significantly more effective in preventing urinary-tract infections than were those coated with silver oxide.

1. Reiche T, *et al.* A prospective, controlled, randomized study of the effect of a slow-release silver device on the frequency of urinary tract infection in newly catheterized patients. *BJU Int* 2000; **85:** 54–9.
2. Saint S, *et al.* The efficacy of silver alloy-coated urinary catheters in preventing urinary tract infection: a meta-analysis. *Am J Med* 1998; **105:** 236–41.

Wound healing. Silver is incorporated into topical dressings for wound care although a systematic review[1] of 3 randomised controlled studies found insufficient evidence to support the use of silver-containing dressings or other formulations for the treatment of infected or contaminated wounds. Bacterial resistance to silver can occur, but this risk can be minimised by choosing dressings that release high levels of silver ions and have a rapid bactericidal action.[2]

The mechanism of bactericidal action of silver in dressings is that silver atoms are oxidised and slowly released as positively charged silver cations when in contact with fluid. The silver ions bind to and disrupt bacterial cell walls as well as binding to bacterial enzymes and DNA. A nanocrystalline silver coating to the dressing increases the surface area of exposure and facilitates release of silver ions. Silver can also be incorporated as complex silver molecules in various different topical formulations that regulate the speed of delivery.[1] Proposed mechanisms of silver resistance have been plasmid acquisition and gene mutation.[2]

1. Vermeulen H, *et al.* Topical silver for treating infected wounds. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/06/08).
2. Chopra I. The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern? *J Antimicrob Chemother* 2007; **59:** 587–90.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Ultradina†; ***Fr.:*** Micropur†; ***Ger.:*** Contreet; ***Ital.:*** Acticoat; Katomed; ***UK:*** Avance; Contreet.

Multi-ingredient: ***Arg.:*** Efodil†; Nova-T; ***Canad.:*** Nova-T; ***Chile:*** Nova-T†; ***Fr.:*** Actisorb Ag ; Aquacel Ag; Biatain Argent; Micropur Forte DCCNa; Nova-T; Oligorhine; Release Ag; ***Ger.:*** Actisorb Silver†; Nova-T; ***Hong Kong:*** Nova-T; ***Indon.:*** Nova-T; ***Irl.:*** Actisorb Silver; ***Israel:*** Neocutan Silver; Nova-T; ***Ital.:*** Actisorb Plus; Agipiu†; Aquacel Ag; Katoxyn; Nova-T; Silvercel; Silverdres; Vulnopur; ***Malaysia:*** Nova-T; ***Mex.:*** Nova-T; ***Neth.:*** Nova-T†; ***NZ:*** Nova-T; ***S.Afr.:*** Nova-T; ***Singapore:*** Nova-T; ***Spain:*** Argentocromo†; ***Switz.:*** Argent†; Gyrosan†; Nova-T; ***Thai.:*** Nova-T†; ***Turk.:*** Nova-T; ***UK:*** Actisorb Silver; Nova-T; ***Venez.:*** Nova-T.

Silver Acetate

Argenti Acetas; Plata, acetato de.

$C_2H_3AgO_2$ = 166.9.

CAS — 563-63-3.

Profile

Silver acetate has been used similarly to silver nitrate as an antiseptic. It has also been used in antismoking preparations.

Smoking cessation. References.

1. Lancaster T, Stead LF. Silver acetate for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 12/04/06).

Silver Nitrate

Argent, nitrate d'; Argenti nitras; Dusičnan stříbrný; Ezüst-nitrát; Gümüş Nitrat; Hopeanitraatti; Nitrato de Plata; Nitrato de Prata; Plata, nitrato de; Sidabro nitratas; Silvernitrat; Srebra azotan.

$AgNO_3$ = 169.9.

CAS — 7761-88-8.

ATC — D08AL01.

ATC Vet — QD08AL01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Silver Nitrate). A white or almost white, crystalline powder or transparent colourless crystals. Very soluble in water; soluble in alcohol. Store in nonmetallic containers. Protect from light.

USP 31 (Silver Nitrate). Colourless or white crystals. On exposure to light in the presence of organic matter, it becomes grey or greyish-black. Soluble 1 in 0.4 of water, 1 in 0.1 of boiling water, 1 in 30 of alcohol, and 1 in 6.5 of boiling alcohol; slightly soluble in ether. Its solutions in water have a pH of about 5.5. Store in airtight containers. Protect from light.

Incompatibility. Silver nitrate is incompatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.[1]

1. *PSGB Lab Report P/80/6* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, abdominal pain, diarrhoea, vomiting, coma, and convulsions.

Short-term mild conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria (see Silver, above), which though difficult to treat is mainly a cosmetic hazard.

Although silver nitrate is not readily absorbed, absorption of nitrite after reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Effects on the eyes. Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibacterials and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; **231:** 245.

Uses and Administration

Silver nitrate possesses antiseptic properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.180). However, as it can cause irritation, other drugs are often used.

In stick form it has been used as a caustic to destroy warts (p.1584) and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical antiseptics and astringents in other conditions. Instillation of silver nitrate solution has been investigated for pleurodesis in the management of malignant effusions.

Silver nitrate has been used in cosmetics to dye eyebrows and eye lashes.

Homoeopathy. Silver nitrate has been used in homoeopathic medicines under the following names: Argent. Nit.; Argenti nitras; Argentum nitricum; Arg. nit.

◊ References.

1. van Hasselt P, Gudde H. Randomized controlled trial on the treatment of otitis externa with one per cent silver nitrate gel. *J Laryngol Otol* 2004; **118:** 93–6.
2. Dalela D, *et al.* Silver nitrate sclerotherapy for 'clinically significant' chyluria: a prospective evaluation of duration of therapy. *Urol Int* 2004; **72:** 335–40.
3. da Silveira Paschoalini M, *et al.* Prospective randomized trial of silver nitrate vs talc slurry in pleurodesis for symptomatic malignant pleural effusions. *Chest* 2005; **128:** 684–9.
4. Alidaee MR, *et al.* Silver nitrate cautery in aphthous stomatitis: a randomized controlled trial. *Br J Dermatol* 2005; **153:** 521–5.

Preparations

BP 2008: Sterile Silver Nitrate Solution;
USP 31: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations (details are given in Part 3)

Denm.: Helvedstensstifter†; Lapis; ***Ger.:*** Mova Nitrat; ***Pol.:*** Mova Nitrat; ***Port.:*** Argenpal†; ***Spain:*** Argenpal.

Multi-ingredient: ***Austral.:*** Super Banish†; ***Spain:*** Argentofenol†; ***UK:*** Avoca.

Silver Protein

Albumosesilber; Argent, protéinate d'; Argentoproteinum; Argentum proteicum; Argentum Proteinicum; Hopeaproteiini; Plata, proteína de; Protargolum; Proteinato de Plata; Proteinato de Prata; Silverprotein; Srebra proteinicum; Strong Protargin; Strong Protein Silver; Strong Silver Protein.

CAS — 9007-35-6 (colloidal silver); 9015-51-4 (silver protein).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinicum; Mild Protargin; Mild Silver Proteinate; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Prata.

Pharmacopoeias. In *It.*, *Jpn*, and *Viet.*

Eur. (see p.vii) includes Silver, Colloidal, for External Use.

Ph. Eur. 6.2 (Silver, Colloidal, for External Use; Argentum Colloidale ad Usum Externum). It is colloidal metallic silver, containing protein. It contains 70.0 to 80.0% of Ag, calculated with reference to the dried substance. Green or bluish-black, metallic, hygroscopic, shiny flakes or powder. Freely soluble or soluble in water; practically insoluble in alcohol and in dichloromethane. Store in airtight containers.

Profile

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver, which is also a preparation of silver in combination with protein, has also been used topically for its antibacterial activity.

Homoeopathy. Silver protein has been used in homoeopathic medicines under the following names: Argentum colloidale.

Adverse effects. Irreversible neurotoxicity associated with the daily ingestion of a home-made colloidal silver drink for 4 months developed in an elderly patient.[1] He presented with myoclonic status epilepticus, then entered into a prolonged coma, and eventually died of pneumonia some months later. On admission, high levels of silver were found in the plasma, erythrocytes, and CSF, and at autopsy there was evidence of selective silver accumulation in the brain. As of October 2007, four reports of silver toxicity in patients ingesting home-made products, likewise prepared using a colloidal silver generator, had also been received by the Australian Adverse Drug Reactions Advisory Committee (ADRAC);[2] one patient also applied it topically after shaving. All patients had high plasma-silver concentrations and

The symbol † denotes a preparation no longer actively marketed

developed skin discoloration; some also had systemic symptoms including hepatotoxicity, cardiomyopathy, amnesia, and incoherent speech.

For argyria after prolonged use of nasal drops containing silver protein see under Silver, above.

1. Mirsattari SM, *et al.* Myoclonic status epilepticus following repeated oral ingestion of colloidal silver. *Neurology* 2004; **62:** 1408–10.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Dangers associated with chronic ingestion of colloidal silver. *Aust Adverse Drug React Bull* 2007; **26:** 19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.pdf (accessed 24/06/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Argirol; ***Fr.:*** Stillargol; ***Ger.:*** Rhinoguttae Argenti diacetylotannici proteinici; Rhinoguttae pro Infantibus N.

Multi-ingredient: ***Austria:*** Coldargan; ***Belg.:*** Argyrophedrine; ***Ger.:*** Gastrarctin N; ***Hung.:*** Coldargan; ***Ital.:*** Argirofedrina†; Argisone; Argotone; Arscolloid; Bio-Arscolloid; Corti-Arscolloid; Rinantipiol†; Rinofomentil†; ***Port.:*** Naso-Calma†.

Sincalide *(BAN, USAN, rINN)*

CCK-OP; Sincalida; Sincalidum; Sinkalid; Sinkalidi; SQ-19844. De-1-(5-oxo-L-proline)-de-2-L-glutamine-5-methionine-caerulein.

Синкалид

$C_{49}H_{62}N_{10}O_{16}S_3$ = 1143.3.
CAS — 25126-32-3.
ATC — V04CC03.
ATC Vet — QV04CC03.

Pharmacopoeias. *US* includes Sincalide for Injection.

Adverse Effects

Sincalide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Dizziness, nausea, and flushing may also occur.

Uses and Administration

Sincalide is the synthetic C-terminal octapeptide of cholecystokinin (see pancreozymin, p.2361) and when given by intravenous injection it stimulates gallbladder contraction; it also stimulates intestinal muscle.

Sincalide is used for testing gallbladder function and as an adjunct to cholecystography. It is usually given in doses of 20 nanograms/kg by intravenous injection over 30 to 60 seconds. It is also used as a diagnostic agent, often with secretin (p.2384), for testing the functional capacity of the pancreas; this test generally requires duodenal intubation of the patient and examination of duodenal aspirate. A suggested procedure is to give a 1-hour intravenous infusion of secretin, and 30 minutes after starting this infusion, to start a separate infusion of sincalide 20 nanograms/kg over a 30-minute period. A dose of 40 nanograms/kg may be given to accelerate the transit time of a barium meal through the small bowel; it should be given after the barium meal has passed the proximal jejunum.

Preparations

USP 31: Sincalide for Injection.

Proprietary Preparations (details are given in Part 3)
Canad.: Kinevac†; ***USA:*** Kinevac.

Sivelestat *(USAN, rINN)*

EI-546; LY-544349; ONO-5046; Sivélestat; Sivelestatum. *o*-(*p*-Hydroxybenzenesulfonamido)hippuric acid pivalate.

Сивелестат

$C_{20}H_{22}N_2O_7S$ = 434.5.
CAS — 127373-66-4.

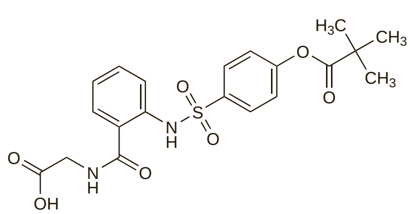

Sivelestat Sodium *(USAN, rINNM)*

Natrii Sivelestatum; Sivelestat sódico; Sivélestat Sodique.

Натрий Сивелестат

$C_{20}H_{21}N_2NaO_7S,4H_2O$ = 528.5.
CAS — 201677-61-4.

Profile

Sivelestat is an elastase inhibitor that primarily inhibits neutrophil elastase. It is given by intravenous infusion as the sodium salt in the treatment of acute lung injury associated with systemic inflammatory response syndrome. However, a large study in patients with acute lung injury did not find it of benefit.

◊ References.

1. Zeiher BG, *et al.* Neutrophil elastase and acute lung injury: prospects for sivelestat and other neutrophil elastase inhibitors as therapeutics. *Crit Care Med* 2002; **30** (suppl): S281–S287.
2. Zeiher BG, *et al.* Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. *Crit Care Med* 2004; **32:** 1695–1702.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Elaspol.

Skullcap

Escutelaria; Scullcap; Scutellaria.

Pharmacopoeias. *Chin.* includes Herba Scutellariae Barbatae (Barbated Skullcap Herb; *Scutellaria barbata*) and Radix Scutellariae (Baical Skullcap Root; *S. baicalensis*). *Jpn* includes Scutellaria Root (*S. baicalensis*).

Profile

Skullcap, the aerial parts of *Scutellaria lateriflora* (Labiatae) and other *Scutellaria* spp., has sedative and antispasmodic properties. It is used as a nerve tonic, and for insomnia and menstrual disorders.

Baical skullcap (*S. baicalensis*) is used in Chinese herbal medicine.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Baikadent.

Multi-ingredient: ***Austral.:*** Albizia Complex; Andrographis Compound; Calmo; Euphrasia Compound; Feminine Herbal Complex; Goodnight Formula†; Nevaton; Pacifenity†; Passiflora Complex†; Passionflower Plus; Relaxaplex†; Valerian†; ***Canad.:*** Herbal Nerve; ***UK:*** Herbal Indigestion Naturtabs; HRI Calm Life; Newrelax; Nodoff; Quiet Days; Quiet Tyme; Scullcap & Gentian Tablets; St Johnswort Compound; Stressless; Vegetable Cough Remover; Wellwoman.

Skunk Cabbage

Col apestosa; Skunkweed.

Profile

Skunk cabbage, the root and rhizome of *Symplocarpus foetidus* (*Dracontium foetidum*) (Araceae), has expectorant properties and is used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Horehound and Aniseed Cough Mixture; Vegetable Cough Remover.

Slippery Elm

Elm Bark; Olmo resbaladizo; Slippery Elm Bark; Ulmus.

Pharmacopoeias. In *US.*
USP 31 (Elm). The dried inner bark of *Ulmus rubra* (*U. fulva*) (Ulmaceae). Store in a dry place at a temperature of 8° to 15°.

Profile

Slippery elm contains a considerable amount of mucilage and has been used as a demulcent.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Bioglan Psylli-Mucil Plus; Cal Alkyline; Digestive Aid; Herbal Cleanse†; PC Regulax†; Travelaide†; ***Canad.:*** Herbal Throat†; ***UK:*** Modern Herbals Pile; Pileabs; Slippery Elm Stomach Tablets.

Soapwort

Bouncing Bet; Fuller's Herb; Red Soapwort; Saponaire.

NOTE. Distinguish from White Soapwort, *Gypsophila paniculata* (Caryophyllaceae)

Pharmacopoeias. In *Fr.*

Profile

The root of red soapwort, *Saponaria officinalis* (Caryophyllaceae), contains saponins and is included in herbal preparations for catarrh and other respiratory-tract disorders and for skin disorders. It has been used as a foaming agent. The aerial parts of the herb have also been used.

Homoeopathy. Soapwort has been used in homoeopathic medicines under the following names: Saponaria; Saponaria officinalis.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Aspectonetten N†.

Multi-ingredient: ***Cz.:*** Bronchicum Tropfen†; Pleumolysin; Tussilen; ***Fr.:*** Depuratif Parnel; ***Ger.:*** Bronchicum Tropfen N†; Em-medical†; ***Pol.:*** Bronchicum†; Pectosol; Reumosol; Saponarex; ***Port.:*** Erpecalm.

Soda Lime

Cal sodada; Calcaria absorbens; Calcaria Compositio; Calx Sodica; Chaux Sodée.

CAS — 8006-28-8.

Pharmacopoeias. In *Br.* Also in *USNF.*
BP 2008 (Soda Lime). A mixture of sodium hydroxide, or sodium hydroxide and potassium hydroxide, with calcium hydroxide. White or greyish-white granules, or it may be coloured with an indicator to show when its absorptive capacity is exhausted. It absorbs about 20% of its weight of carbon dioxide. Partially soluble in water; almost completely soluble in 1M acetic acid. A suspension in water is strongly alkaline to litmus.
USNF 26 (Soda Lime). A mixture of calcium hydroxide and sodium or potassium hydroxide or both. It may contain an indicator that is inert and that changes colour when the soda lime can no longer absorb carbon dioxide. White or greyish-white granules. May have a colour if an indicator is added.

Incompatibility. Soda lime is incompatible with trichloroethylene.

Profile

Soda lime is used to absorb carbon dioxide, for instance in closed-circuit anaesthetic apparatus, and in the determination of the basal metabolic rate. Limits are specified for particle size, and particles should be free from dust.

Soda lime must not be used with trichloroethylene, since this is decomposed by warm alkali to produce a toxic end product that gives rise to lesions of the nervous system.

Soda lime is irritating and corrosive to skin, mucous membranes, and eyes.

Sodium Aminobenzoate

Aminobenzoate Sodium. Sodium 4-aminobenzoate.

$C_7H_6NNaO_2$ = 159.1.

Pharmacopoeias. In *US.*
USP 31 (Aminobenzoate Sodium). pH of a 5% solution in water is between 8.0 and 9.0.

Profile

Sodium aminobenzoate has been used in analgesic preparations.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ital.:*** Fotofil; Neo-Ustiol; ***Spain:*** Tri Hachemina.

Sodium Arsenate

Arseniato de sodio; Natrium Arsenicicum; Sodium Arseniate.

$Na_2HAsO_4,7H_2O$ = 312.0.
CAS — 7778-43-0 (anhydrous sodium arsenate); 10048-95-0 (sodium arsenate heptahydrate).

Profile

Sodium arsenate was formerly used in the treatment of chronic skin diseases, in parasitic diseases of the blood, and in some forms of anaemia. It has the adverse effects of Arsenic Trioxide, p.2260.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Mex.:*** Iodarsolo B12†.

Sodium Camsilate

Sodium Camphorsulphonate. Sodium (+)-camphor-10-sulfonate.

$C_{10}H_{15}NaO_4S$ = 254.3.
CAS — 21791-94-6; 34850-66-3.

Pharmacopoeias. In *Viet.*

Profile

Sodium camsilate has been used as a respiratory and cardiac stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Eucalyptine Pholcodine Le Brun†; Kamfeine†; Tux†; ***Braz.:*** Algice; Baldin-CE†; Broncopinol†; Cafalena†; Gripanil†; Gripomatine†; Griponia†; Gripsay; Killgrip†; Ozonyl Aquoso; Ozonyl Expectorante; Pulmorien†; Tetrapulmo; Tripulmin†; ***Chile:*** Gruben.

Sodium Carbonate Anhydrous

Carbonato de sodio anhidro; Cenizas de Soda; E500; Exsiccated Sodium Carbonate; Natrii Carbonas; Natrii carbonas anhydricus; Natrio karbonatas, bevandenis; Natrium Carbonicum Calcinatum; Natrium Carbonicum Siccatum; Natriumkarbonaatti, vedetön; Natriumkarbonat, vattenfritt; Sodium (carbonate de) anhydre; Uhličitan sodný; Uhličitan sodný bezvodý; Vízmentes nátrium-karbonát.

Na_2CO_3 = 106.0.
CAS — 497-19-8.

NOTE. Soda ash is a synonym for the technical grade of sodium carbonate anhydrous.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn. USNF* allows the anhydrous substance or the monohydrate.
Ph. Eur. 6.2 (Sodium Carbonate, Anhydrous). A white or almost white, slightly granular, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.
USNF 26 (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Sodium Carbonate Decahydrate

Carbonato de sodio decahidratado; Cristales de Sosa; E500; Natrii Carbonas; Natrii carbonas decahydricus; Natrio karbonatas dekahidratas; Natrium Carbonicum Crystallisatum; Natriumkarbonaattidekahydraatti; Nátrium-karbonát-dekahidrát; Natriumkarbonatdekahydrat; Sodium (carbonate de) décahydraté; Uhličitan sodný dekahydrát.

$Na_2CO_3,10H_2O$ = 286.1.
CAS — 6132-02-1.

NOTE. Washing soda is a synonym for the technical grade of sodium carbonate decahydrate.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Sodium Carbonate Decahydrate). Colourless, efflorescent, transparent crystals or a white or almost white crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

Sodium Carbonate Monohydrate

Carbonato de sodio monohidratado; E500; Natrii carbonas monohydricus; Natrio karbonatas monohidratas; Natriumkarbonaattimonohydraatti; Nátrium-karbonát-monohidrát; Natriumkarbonatmonohydrat; Sodium (carbonate de) monohydraté; Sodu węglan jednowodny; Uhličitan sodný monohydrát.

Na_2CO_3,H_2O = 124.0.
CAS — 5968-11-6.

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* allows the anhydrous substance or the monohydrate.
Ph. Eur. 6.2 (Sodium Carbonate Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.
USNF 26 (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. When exposed to dry air above 50°, it effloresces and at 100° it becomes anhydrous. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Profile

Sodium carbonate is used in antacid preparations. Anhydrous sodium carbonate and the monohydrate are also used as reagents. The decahydrate has been used in alkaline baths. Sodium carbonate in its anhydrous or hydrated form is also used as a water softener.

Sodium carbonate may be irritating or mildly corrosive to skin, mucous membranes, and eyes.

Preparations

BPC 1973: Surgical Chlorinated Soda Solution;
USP 31: Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Alikal; Otocalmia Biotic; Otocerol; Otoclean Gotas Oticas; Sal de Fruta Eno; Sincerum; Uvasal; Yasta; ***Austral.:*** Eno; ***Braz.:*** Digestbem; Sal de Fruta Eno; Sonrisal; ***Fr.:*** Bactident; Hydralin; ***Hong Kong:*** Eno†; Hydralin; ***Irl.:*** Cymalon; ***Israel:*** Eno; Urikal; ***Ital.:*** Gastrotuss; ***Port.:*** Eno; Gastropensan; ***Spain:*** Sal de Fruta Eno; Tanasid†; ***Switz.:*** Saltrates Rodell†; ***UK:*** Cymalon; Eno; Resolve; ***Venez.:*** Eno.

Sodium Chlorate

Clorato de potasio; Natrium Chloricum; Sodii Chloras.

$NaClO_3$ = 106.4.
CAS — 7775-09-9.

Profile

Sodium chlorate closely resembles potassium chlorate (p.2371) in its properties and has been used as an astringent. Its main use is as a weedkiller and it is therefore a common household chemical. Poor storage conditions can lead to explosions.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Co Bucal.

Sodium Dichloroacetate *(USAN)*

CPC-211; DCA; Dicloroacetato de sodio.

$C_2HCl_2NaO_2$ = 150.9.
CAS — 2156-56-1 (sodium dichloroacetate); 79-43-6 (dichloroacetic acid).

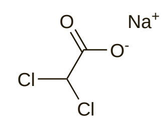

Profile

Dichloroacetic acid activates pyruvate dehydrogenase, a mitochondrial enzyme that catalyses metabolism of pyruvate and lactate, and it inhibits glycolysis. It also stimulates myocardial contractility. Sodium dichloroacetate has been used for the treatment of congenital lactic acidosis, lactic acidosis in patients with severe malaria, homozygous familial hypercholesterolaemia, and for severe brain injury. It is also under investigation for stroke.

Adverse effects. Adverse effects reported with sodium dichloroacetate have mainly involved the central and peripheral nervous systems.[1] Anxiolytic or sedative effects are common. Reversible polyneuropathy has been reported after chronic use, as has asymptomatic elevation of serum transaminases. Reduced urate clearance and elevated serum urate levels have been reported in patients with type 2 diabetes mellitus. See also under Use in Metabolic Acidosis, below for reference to early termination of a study due to development of peripheral neuropathy.

1. Stacpoole PW, *et al.* Pharmacokinetics, metabolism, and toxicology of dichloroacetate. *Drug Metab Rev* 1998; **30:** 499–539.

Pharmacokinetics. References.

1. Henderson GN, *et al.* Pharmacokinetics of dichloroacetate in adult patients with lactic acidosis. *J Clin Pharmacol* 1997; **37:** 416–25.
2. Shangraw RE, Fisher DM. Pharmacokinetics and pharmacodynamics of dichloroacetate in patients with cirrhosis. *Clin Pharmacol Ther* 1999 **66:** 380–90.

Use in metabolic acidosis. In a study[1] in 29 patients with lactic acidosis (p.1667), sodium dichloroacetate 50 mg/kg given by intravenous infusion over 30 minutes, followed by a second dose 2 hours after beginning the first infusion, produced a metabolic response in 23 patients with a short-term increase in survival. However, a subsequent study[2] found that, while dichloroacetate infusion did reduce blood-lactate concentrations, it did not alter haemodynamics or survival in patients with severe lactic acidosis. A review[3] of these and other controlled studies in the treatment of acquired and congenital lactic acidosis concluded that the maximum lactate-lowering effect is dose-dependent but independent of time after dosing. Whether lowering lactate levels contributes to reducing morbidity and mortality in hyperlactataemia remains controversial, although data from recent studies suggest that treatment in mild cases may reduce the risk of death. A review[4] of the treatment of children with dichloroacetate for congenital lactic acidosis hypothesised that it might improve quality of life by reducing the frequency of acid–base decompensations, improving neurological function, and stimulating linear growth. A randomised controlled study[5] of dichloroacetate for the treatment of congenital lactic acidosis in 43 patients ranging in age from 3 months to 18 years found that dichloroacetate for 6 months was well tolerated and reduced blood-lactate response to a carbohydrate challenge but had no effect on basal-lactate concentrations nor did it improve neurologic or other measures of clinical outcome. In another randomised controlled study[6] of the effects of dichloroacetate in the treatment of the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), 13 of 15 patients given the study medication developed peripheral neuropathy, displaying either clinical signs and symptoms or electrophysiological evidence. The study was therefore stopped early, and on this basis, the authors concluded that dichloroacetate could not be recommended for the treatment of MELAS.

In a randomised, double-blind, placebo-controlled study[7] in 124 West African children with severe *Plasmodium falciparum* malaria, a single intravenous infusion of sodium dichloroacetate in a dose of 50 mg/kg given at the same time as quinine increased the rate and magnitude of fall in blood-lactate levels without compromising the plasma kinetics of quinine.

In the UK, the *BNFC* includes the following doses for neonates and children with pyruvate dehydrogenase defects: 12.5 mg/kg 4 times daily by mouth, adjusted according to response up to 200 mg/kg daily.

Sodium dichloroacetate has also been studied[8] in patients with traumatic brain injury for its lactate-lowering effect in cerebrospinal fluid.

1. Stacpoole PW, *et al.* Dichloroacetate in the treatment of lactic acidosis. *Ann Intern Med* 1988; **108**: 58–63.
2. Stacpoole PW, *et al.* A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. *N Engl J Med* 1992; **327:** 1564–9.
3. Stacpoole PW, *et al.* Efficacy of dichloroacetate as a lactate-lowering drug. *J Clin Pharmacol* 2003; **43:** 683–91.
4. Stacpoole PW, *et al.* Treatment of congenital lactic acidosis with dichloroacetate. *Arch Dis Child* 1997; **77:** 535–41.
5. Stacpoole PW, *et al.* Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. *Pediatrics* 2006; **117:** 1519–31.
6. Kaufmann P, *et al.* Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology* 2006; **66:** 324–30.
7. Agbenyega T, *et al.* Population kinetics, efficacy, and safety of dichloroacetate for lactic acidosis due to severe malaria in children. *J Clin Pharmacol* 2003; **43:** 386–96.
8. Williams PJ, Dichloroacetate: population pharmacokinetics with a pharmacodynamic sequential link model. *J Clin Pharmacol* 2001; **41:** 259–67.

Sodium Dithionite

Ditionito de sodio; Natrii Dithionis; Sodium Hydrosulfite; Sodium Hydrosulphite; Sodium Sulphoxylate; Sodu ditionian; Sodu podsiarczyn.

$Na_2S_2O_4$ = 174.1.
CAS — 7775-14-6.

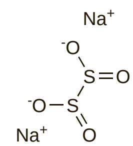

NOTE. The name sodium hydrosulfite is also applied to $NaHSO_2$ = 88.06.

Pharmacopoeias. In *Pol.*

Profile

Sodium dithionite is used as a reducing agent. It may be used in the form of a simple urine test in the detection of paraquat poisoning. A 0.25% solution has been used to remove phenazopyridine stains from fabric. It is irritant to the skin.

Sodium Gluconate

E576; Gluconato de sodio. Monosodium D-gluconate.

$C_6H_{11}NaO_7$ = 218.1.
CAS — 527-07-1.

Pharmacopoeias. In *US.*

Profile

Sodium gluconate is a food additive.

Gluconates act as acceptors of hydrogen ions produced by metabolic processes and are an indirect source of bicarbonate ions.

Sodium Humate

CAS — 1415-93-6 (humic acids); 68131-04-4 (sodium humates).

Profile

Humic acids are mixtures of complex macromolecules derived from the decomposition of organic material and are found in soils and peats. They have been used topically, usually as sodium humate, for musculoskeletal and joint disorders. They also have industrial applications.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Leukona-Sulfomoor-Bad F†; Rheumasan Moor-Bad S†.

Multi-ingredient: ***Austria:*** Humal; Leukona-Sulfomoor-Bad†; Salhumin; ***Ger.:*** Salhumin Rheuma-Bad; Salhumin Sitzbad N†; Salhumin Teilbad N†.

Sodium Hydroxide

Ätznatron; Caustic Soda; E524; Hidróxido de sodio; Hydroxid sodný; Natrii hydroxidum; Natrio hidroksidas; Natrium Hydricum; Natrium Hydroxydatum; Nátrium-hidroxid; Natriumhydroksidi; Natriumhydroxid; Soda Lye; Sodium, hydroxyde de; Sodu wodorotlenek; Sosa cáustica.

NaOH = 40.00.
CAS — 1310-73-2.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Sodium Hydroxide). White or almost white, crystalline masses supplied as pellets, sticks, or slabs. It is deliquescent and readily absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. A 0.01% solution in water has a pH of not less than 11.0. Store in airtight, nonmetallic containers.
USNF 26 (Sodium Hydroxide). White or practically white fused masses, small pellets, flakes, sticks, or other forms. It is hard and

brittle and shows a crystalline fracture. When exposed to air it rapidly absorbs moisture and carbon dioxide. Soluble 1 in 1 of water; freely soluble in alcohol. Store in airtight containers.

Adverse Effects

Sodium hydroxide is strongly alkaline and corrosive, and rapidly destroys organic tissues.

The ingestion of caustic alkalis causes immediate burning pain in the mouth, throat, substernal region, and epigastrium, and the lining membranes become swollen and detached. There is dysphagia, hypersalivation, vomiting with the vomitus becoming blood-stained, diarrhoea, and shock. In severe cases, abdominal pain, asphyxia due to oedema of the glottis, circulatory failure, oesophageal or gastric perforation, peritonitis, or pneumonia may occur. Stricture of the oesophagus can develop weeks or months later.

Caustic alkalis on contact with the skin can produce full thickness burns leading to extensive damage. Alkali burns to the eyes cause conjunctival oedema and corneal destruction; damage may be irreversible.

Treatment of Adverse Effects

Ingestion should not be treated by lavage or emesis. Dilution with water or milk is generally considered controversial for management of corrosive ingestion. However, early dilution therapy of alkalis may reduce oesophageal injury; large volumes of fluid should be avoided. Neutralisation of alkalis is contra-indicated. The airway should be maintained and shock and pain alleviated.

In cases of skin contamination, clothing should be removed immediately and the skin flooded with copious amounts of water for at least 15 minutes. Excision or skin grafting of burnt areas may be necessary in severe cases. Contaminated eyes should be irrigated thoroughly with water or 0.9% sodium chloride until the conjunctival sac pH is normal, which may require irrigation for up to an hour.

Uses and Administration

Sodium hydroxide is a powerful caustic. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of sodium hydroxide and calcium oxide was known as London paste. Sodium hydroxide is also used for adjusting the pH of solutions.

Disinfection. For reference to the possible use of sodium hydroxide for the disinfection of material contaminated by the agent causing Creutzfeldt-Jakob disease, see p.1622.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Leberinfusion; Sulfo-Schwefelbad; ***Ger.:*** Glutarsin E†; ***Switz.:*** Saltrates†.

Sodium Iodoheparinate

Iodoheparinate Sodium; Iodoheparinato de sodio.

ATC — S01XA09.
ATC Vet — QS01XA09.

Profile

Sodium iodoheparinate is a derivative of heparin (p.1301) that has been used topically for the treatment of corneal burns and ulceration.

Sodium Methylarsinate

Metilarsinato de sodio; Natrium Methylarsonicum; Sodium Metharsinite. Disodium monomethylarsonate hexahydrate.

$CH_3AsNa_2O_3,6H_2O$ = 292.0.
CAS — 5967-62-4.

Profile

Sodium methylarsinate is an organic arsenic compound with adverse effects similar to those of arsenic trioxide (p.2260). It was formerly included in some vitamin and mineral preparations. It has also been used as a herbicide.

Sodium Morrhuate *(rINN)*

Morrhuate de Sodium; Morrhuate Sodium; Morruato de sodio; Natrii Morrhuas; Natriummorruaatti; Natriummorruat.

Натрия Морруат

CAS — 8031-09-2.

Pharmacopoeias. *Chin.* and *US* include the injection.

Profile

Sodium morrhuate consists of the sodium salts of the fatty acids of cod-liver oil. It is a sclerosant that has been used in the treatment of varicose veins (p.2347). Usual doses are 50 to 100 mg for small or medium veins or 150 to 250 mg for large veins given as a 5% solution by intravenous injection.

Preparations

USP 31: Morrhuate Sodium Injection.

Proprietary Preparations (details are given in Part 3)
USA: Scleromate.

Sodium Phenylacetate *(USAN)*

Fenilacetato de sodio.

$C_8H_7NaO_2$ = 158.1.
CAS — 114-70-5.

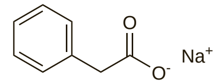

Profile

Sodium phenylacetate is used as adjunctive treatment for acute hyperammonaemia and associated encephalopathy in patients with enzymatic deficiencies in the urea cycle (p.1929). It is given with sodium benzoate (p.1630) as a combined preparation for intravenous infusion in which 1 mL contains 100 mg of each component. The preparation is diluted in sterile glucose injection 10% at ≥25 mL/kg before infusion. Other similar therapies (e.g. oral sodium phenylbutyrate, see below) should be stopped before starting the infusion. A loading dose is infused over 90 to 120 minutes followed by an equivalent maintenance dose infused over 24 hours. Doses of sodium phenylacetate (together with the same amount of sodium benzoate) are 250 mg/kg for patients weighing 20 kg or less, and 5.5 g/m^2 for those over 20 kg. Maintenance infusions are continued until plasma ammonia concentrations are normal or oral nutrition and therapy can be tolerated. Sodium phenylacetate has also been given by mouth.

◊ References.

1. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S1–S5.
2. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S30–S39.
3. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl 1): S46–S55. Correction. *ibid.* 2002; **140:** 490.
4. MacArthur RB, *et al.* Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers. *Mol Genet Metab* 2004; **81** (suppl 1): S67–S73.
5. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356:** 2282–92.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Ammonul; Ucephan.

Sodium Phenylbutyrate *(BAN, USAN)*

Fenilbutirato de sodio; Natrii phenylbutyras; Natriumfenylbutyrat; Natriumfenyylibutyraatti; Sodium, phénylbutyrate de; Sodyum Fenilbutirat. Sodium 4-Phenylbutyrate.

$C_{10}H_{11}NaO_2$ = 186.2.
CAS — 1716-12-7.
ATC — A16AX03.
ATC Vet — QA16AX03.

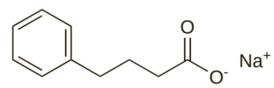

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Sodium Phenylbutyrate). A white or yellowish-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5.

Profile

Sodium phenylbutyrate is a prodrug for sodium phenylacetate (see above) and is used as adjunctive treatment of hyperammonaemia in patients with urea cycle disorders (p.1929). It is given orally in equally divided doses with meals. The total daily dose for patients weighing under 20 kg is 450 to 600 mg/kg, and for those weighing over 20 kg, 9.9 to 13.0 g/m^2.

Sodium phenylbutyrate is also under investigation for the treatment of some sickle-cell disorders (p.1044) and for use as a potential differentiation-inducing agent in malignant glioma and acute myeloid leukaemia. Sodium phenylbutyrate is also under investigation for spinal muscular atrophy, which is caused by homozygous absence of the SMN1 gene, after reports that it significantly increased SMN transcript expression in both fibroblast cultures and leucocytes from these patients.

◊ References.

1. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl 1): S46–S55. Correction. *ibid.* 2002; **140:** 490.
2. Mercuri E, *et al.* Randomized, double-blind, placebo-controlled trial of phenylbutyrate in spinal muscular atrophy. *Neurology* 2007; **68:** 51–5.
3. Caruthers RL, Johnson CE. Stability of extemporaneously prepared sodium phenylbutyrate oral suspensions. *Am J Health-Syst Pharm* 2007; **64:** 1513–15.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Ammonaps; ***Fr.:*** Ammonaps†; ***Ger.:*** Ammonaps†; ***Ital.:*** Ammonaps; ***Neth.:*** Ammonaps; ***Pol.:*** Ammonaps; ***Port.:*** Ammonaps; ***Spain:*** Ammonaps; ***UK:*** Ammonaps; ***USA:*** Buphenyl.

Sodium Polymetaphosphate

E452 (sodium polyphosphates); Polimetafosfato de sodio.

CAS — 50813-16-6.

NOTE. Although Sodium hexametaphosphate has been used as a synonym for the polymetaphosphate, the latter also exists in much higher degrees of polymerisation.

Profile

Sodium polymetaphosphate has been used as a 5% dusting powder in hyperhidrosis and bromhidrosis, and as a prophylactic against athlete's foot.

Sodium polymetaphosphate combines with calcium and magnesium ions to form complex soluble compounds and is used as a water softener.

Sodium Pyrophosphate *(USAN)*

Sodu pirofosforan; Tetrasodium Pyrophosphate; TSPP.

$Na_4P_2O_7$ = 265.9.
CAS — 7722-88-5.

Profile

Sodium pyrophosphate acts as a calcium chelator and is used in products for dental care to reduce tartar formation. It is also used as a food additive, and as a water softener in detergents and for industrial applications. Potassium pyrophosphate (tetrapotassium pyrophosphate) and sodium acid pyrophosphate (disodium pyrophosphate) are used similarly.

Sodium pyrophosphate is also used in kits for the preparation of technetium-99m pyrophosphate.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Esmedent Dientes Sens Blanq + Ctrol Sarro; Fluordent PX; Odol Control Sarro†; ***Braz.:*** Malvatricin Antiplaca; ***Chile:*** FKD; ***Ital.:*** AZ Tartar Control; ***USA:*** Plax.

Sodium Pyruvate

Piruvato de sodio. Sodium α-ketopropionate; sodium 2-oxopropanoate.

$C_3H_4NaO_3$ = 111.1.
CAS — 127-17-3 (pyruvic acid); 113-24-6 (sodium pyruvate).

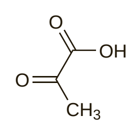

(pyruvic acid)

Profile

Sodium pyruvate has been given intravenously in the diagnosis of disorders of pyruvate metabolism.

◊ Relative serum concentrations of lactate and pyruvate after a 10-minute intravenous infusion of sodium pyruvate 500 mg/kg have been used as an aid to the diagnosis of disorders of pyruvate metabolism.[1] Death shortly after pyruvate loading in a 9-year-old child with restrictive cardiomyopathy suggests that the test should not be performed when cardiac function is decreased.[2]

1. Dijkstra U, *et al.* Friedreich's ataxia: intravenous pyruvate load to demonstrate a defect in pyruvate metabolism. *Neurology* 1984; **34:** 1493–7.
2. Matthys D, *et al.* Fatal outcome of pyruvate loading test in child with restrictive cardiomyopathy. *Lancet* 1991; **338:** 1020–1.

Sodium Silicate

Silicato de sodio; Soluble Glass; Water Glass.

CAS — 1344-09-8.

Profile

Concentrated aqueous solutions of sodium silicate are commercially available and have many industrial uses. The solutions vary in composition, viscosity, and density; the greater the ratio of Na_2O to SiO_2 the more tacky and alkaline the solution.

Sodium Succinate

E363 (succinic acid); Succinato de sodio.

$C_4H_4Na_2O_4,6H_2O = 270.1.$

CAS — 150-90-3 (anhydrous sodium succinate); 6106-21-4 (sodium succinate hexahydrate).

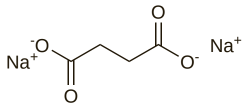

Profile

Sodium succinate is an ingredient of topical preparations tried for the treatment of cataract. It is also used as a food additive.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Cristopal†; ***Spain:*** Vitaphakol.

Solidago

Aranyvesszűfű (solidaginis herba); Echtes Goldrutenkraut (*S. virgaurea*); European Goldenrod (*S. virgaurea*); Golden Rod; Goldrutenkraut (*S. gigantea* or *S. canadensis*); Gullris, europeisk (solidaginis virgaureae herba); Gullris (solidaginis herba); Herba Virgaureae (*S. virgaurea*); Kultapiisku, eurooppalainen (solidaginis virgaureae herba); Kultapiisku (solidaginis herba); Nat' zlatobýlu obecného (solidaginis virgaureae herba); Paprastųjų rykštenių žolė (solidaginis virgaureae herba); Rykštenių žolė (solidaginis herba); Solidage; Solidage verge d'or (*S. virgaurea*); Solidaginis Herba (*S. gigantea* or *S. canadensis*); Solidaginis virgaureae herba (*S. virgaurea*); Solidago Virga Aurea (*S. virgaurea*); Verge d'or; Ziele nawłoci (*S. virgaurea*); Ziele nawłoci pospolitej (*S. virgaurea*); Zlatobýlová nat' (solidaginis herba).

NOTE. The name Aaron's Rod has been applied to a number of plants including *Solidago* spp., *Verbascum* spp., and *Sempervivum tectorum.*

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Goldenrod, European; Solidaginis virgaureae herba). The whole or cut dried, flowering aerial parts of *Solidago virgaurea*. It contains not less than 0.5% and not more than 1.5% flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12} = 464.4$) with reference to the dried drug.

Ph. Eur. 6.2 (Goldenrod; Solidaginis herba). The whole or cut dried, flowering aerial parts of *Solidago gigantea* or *S. canadensis*. It contains not less than 2.5% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12} = 464.4$) with reference to the dried drug.

Profile

Solidago virgaurea (Asteraceae) has diuretic and anti-inflammatory activity. It is mainly used in inflammatory disorders of the bladder and kidneys and for the treatment of renal stones. It is also included in herbal preparations used for a variety of disorders.

S. gigantea (Early golden-rod) and *S. canadensis* were once considered to be adulterants of *S. virgaurea* but are now recognised as having similar activity.

Homoeopathy. Solidago has been used in homoeopathic medicines under the following names: Solidago virgaurea; Sol. vir.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Zlatobylova Nat; ***Ger.:*** Calcufel Aqua†; Canephron S; Cystinol Long; Cystium Solidago; Cysto Fink Mono†; Granu Fink Durchspulungs†; Kalkurenal Goldrute; Nephrisol mono; Nephrolith mono†; Nieral; Solidagoren mono; Stromic; Urol; Uroplant†.

Multi-ingredient: ***Austral.:*** Bioglan Cranbiotic Super; Euphrasia Complex; Euphrasia Compound; Extralife Fluid-Care; Phytodolor; ***Austria:*** Heumann's Blasen- und Nierentee; Phytodolor; Solubitrat; Urelium Neu; ***Cz.:*** Antirevmaticky Caj; Epilobin; Phytodolor; Stoffwechseltee N†; Urcyston Planta; ***Fr.:*** Solution Stago Diluee; ***Ger.:*** Aqualibra; BioCyst; Canephron novo†; Cefasabal; Cystinol N; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee; Harntee 400 N; Harntee STADA; Harntee-Steiner; Heumann Blasen- und Nierentee Solubitrat S†; Heumann Blasen- und Nierentee Solubitrat uro; Heweberberol-Tee; Hewenephron duo†; Inconturina†; nephro-loges; Nephro-Pasc†; Nephronorm med†; Nephropur tri†; Nephroselect M; Nephrubin-N†; Nieron Blasen- und Nieren-Tee VI†; Nieron S†; Nieroxin N†; Phytodolor; Presselin Nieren-Blasen K 3†; Prostamed; Renob Blasen- und Nierentee; Rhoival†; Solidagoren N; Urodil phyto†; ***Ital.:*** Flavion; Gramigna (Specie Composta)†; ***Pol.:*** Diuronis; Fitoven; Nefrobonisol; Nefrol; Nefrosept; NeoFitolizyna; Prostapol; Reumacor; Urofort; Uromix; Uroprost; ***Port.:*** Prostamed†; ***Rus.:*** Prostanorm (Простанорм); ***Spain:*** Natusor Artilane†; Natusor Renal†; Renusor†; ***Switz.:*** Demonatur Dragees pour les reins et la vessie; Dragees S pour les reins et la vessie; Gem; Nephrosolid; Phytomed Nephro†; Phytomed Prosta†; Urinex.

Sorrel

Acedera Común; Azeda-Brava; Garden Sorrel; Herba Rumicis Acetosae; Oseille; Sorrel Dock; Sour Dock; Vinagrera; Wiesensauerampfer.

NOTE. The name sour dock has also been used for yellow dock (p.2416).

Profile

Sorrel (*Rumex acetosa*, Polygonaceae) has been used for respiratory-tract disorders. It is also used as a culinary herb.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Sinupret; Solvopret; ***Cz.:*** Sinupret; ***Ger.:*** Sinupret; ***Hong Kong:*** Sinupret; ***Hung.:*** Sinupret; ***Indon.:*** Sinupret; ***Mex.:*** Bisolsinus; ***Philipp.:*** Sinupret; ***Pol.:*** Sinupret; ***Rus.:*** Sinupret (Синупрет); ***Singapore:*** Sinupret; ***Switz.:*** Sinupret; ***Thai.:*** Sinupret.

Soya Isoflavones

Daidzein

4′,7-Dihydroxyisoflavone; 7-Hydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.

$C_{15}H_{10}O_4 = 254.2.$

CAS — 486-66-8.

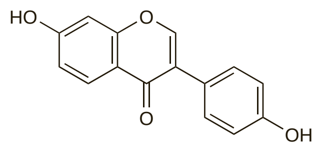

Genistein

CI-75610; Genisteol; Prunetol. 4′,5,7-Trihydroxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.

$C_{15}H_{10}O_5 = 270.2.$

CAS — 446-72-0.

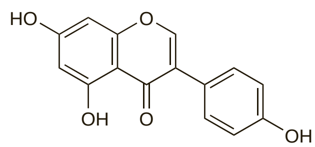

Profile

Genistein and daidzein are soya isoflavones. Genistein, a tyrosine kinase inhibitor, is a phytoestrogen that has been tried for the relief of menopausal symptoms. It is also being investigated for its beneficial effect on blood lipids and for its proposed tumour-suppressing activity. Daidzein has been investigated similarly. Daidzein, mainly in the form of its glycoside daidzin, is a component of some herbal medicines traditionally used in the management of alcohol abuse.

Effects on the endocrine system. For a suggestion that isoflavones in soya-based formulas may exert biological effects, see p.1966.

Hyperlipidaemias. For a discussion of possible beneficial effects of soya isoflavones on blood lipids, see p.1967.

Menopausal disorders. Soya isoflavones have been investigated for their oestrogen-modulating effects, see p.1967.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Sojadiol; Sojar Men; Tanvimil Isoflavonas; ***Braz.:*** Buona; Flavonil; Isoflavine; Menop; Soy 50; Soyfemme; ***Fr.:*** Flavonex; Inoclim; ***Hong Kong:*** Phyto Soya; Phyto-Care; ***Indon.:*** Calvonin; Promensil; ***Ital.:*** Soymen Gel; ***Mex.:*** Pausicaps†; ***Port.:*** Isogyn†; ***S.Afr.:*** Phytopause; ***Singapore:*** Isovon; ***Venez.:*** Climasoy.

Multi-ingredient: ***Arg.:*** Isaflavon; Sigmafen Free; Snella; Sojar Plus-Calcio; Sojasterol†; ***Canad.:*** Natural HRT; ***Fr.:*** Anacaps; Effia; Estrofort; Gynalpha Plus; ***Hong Kong:*** Caltrate + Soy; Palmetto Plus†; Phyto-Ease; Phytoestrin†; ***Indon.:*** Cal-95; Calosbon; Femosa; Hi-Bone; Isofem; ***Ital.:*** Apogeo; Climil Gel; Evestrel; Fitogenase; Rinnova; ***Port.:*** Afron†; Femnet†; ***S.Afr.:*** Phytopause BSF; ***Singapore:*** Caltrate + Soy; Palmetto Plus; Phytoestrin; ***UK:*** Aria; SoyPlus; ***USA:*** Better Cholesterol; Fosteum; ***Venez.:*** Calcibon D Soya.

Sparteine Sulfate *(USAN, rINNM)*

Spart. Sulph.; Spartéine, Sulfate de; Sparteine Sulphate; (−)-Sparteine Sulphate; *l*-Sparteine Sulphate; Sparteini Sulfas; Sparteinum Sulfuricum; Sulfato de esparteína. Dodecahydro-7,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*e*][1,5]diazocine sulphate pentahydrate.

Спартеина Сульфат

$C_{15}H_{26}N_2,H_2SO_4,5H_2O = 422.5.$

CAS — 90-39-1 (sparteine); 299-39-8 (anhydrous sparteine sulfate); 6160-12-9 (sparteine sulfate pentahydrate).

ATC — C01BA04.

ATC Vet — QC01BA04.

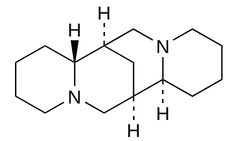

(sparteine)

Pharmacopoeias. In *Fr.* and *Viet.*

Profile

Sparteine sulfate is a salt of the dibasic alkaloid, sparteine, which is obtained from scoparium (p.2384). Sparteine sulfate has been reported to lessen the irritability and conductivity of cardiac muscle and has been used in the treatment of cardiac arrhythmias. Small doses stimulate and large doses paralyse the autonomic ganglia. Peripherally, it has a fairly strong curare-like action, arresting respiration by paralysing the phrenic endings.

The metabolic oxidation of sparteine exhibits genetic polymorphism and this property has been exploited in *in-vitro* screening tests to identify other drugs that may be subject to similar genetic variations in their metabolism.

Precautions. Sparteine present in a herbal slimming preparation might cause adverse effects in slow metabolisers if excessive doses were ingested; pregnant women might be particularly at risk.[1]

1. Galloway JH, *et al.* Potentially hazardous compound in a herbal slimming remedy. *Lancet* 1992; **340:** 179.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Belacodid†.

Spearmint

Menta; Mentha Viridis; Menthae Crispae Folium; Mint.

Profile

Spearmint consists of the dried leaves and flowering tops of common spearmint, *Mentha spicata* (*M. viridis*) or of scotch spearmint (*M. cardiaca*) (Labiatae). Spearmint is the source of spearmint oil (below). It has carminative properties and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Giamebil†.

Multi-ingredient: ***Chile:*** Te Laxante; ***Cz.:*** Hertz- und Kreislauftee†; ***Fr.:*** Mediflor Tisane Digestive No 3; ***Switz.:*** Gel a la consoude; Tisane antirhumatismale; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs.

Spearmint Oil

Huile Essentielle de Menthe Crépue; Menta, aceite esencial de; Oleum Menthae Crispae; Oleum Menthae Viridis.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Spearmint Oil). It is obtained by distillation from fresh flowering plants of *Mentha spicata* or *Mentha × cardiaca*. A clear colourless, pale yellow or greenish-yellow liquid when freshly distilled, visibly free from water and with the odour of spearmint. It becomes darker and viscous on keeping. It contains not less than 55% w/w of carvone. Soluble 1 in 1 of alcohol (80%) at 20°; the solution may become cloudy when diluted. Store at a temperature not exceeding 25° in well-filled containers. Protect from light.

Profile

Spearmint oil has similar properties to peppermint oil (p.1761) and is used as a carminative and as a flavour. It is also used in aromatherapy.

Allergy. Allergic contact cheilitis in a patient has been attributed to the spearmint oil present in tooth paste.[1]

1. Skrebova N, *et al.* Allergic contact cheilitis from spearmint oil. *Contact Dermatitis* 1998; **39:** 35.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Euka; ***Chile:*** Polvos Alcalinos; ***Cz.:*** Parodontal F5†; ***Indon.:*** Listerine Coolmint; ***Ital.:*** Dentosan Azione Intensiva; Dentosan Mese; ***Philipp.:*** Listerine Coolmint; ***Switz.:*** Alvogyl; ***UK:*** Fre-bre; Profelan.

Spike Lavender

Lavande aspic.

Profile

Spike lavender, *Lavandula latifolia* (Lamiaceae), is used similarly to lavender (p.2331) as a sedative and for biliary disorders. It is the source of spike lavender oil (below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Cholagutt-N†; ***Spain:*** Natusor Somnisedan†; Sedasor†.

Spike Lavender Oil

Alhucema, aceite esencial de; Huile Essentielle d'Aspic; Ol. Lavand. Spic.; Oleum Lavandulae Spicatae; Spicae Aetheroleum; Spike Oil.

Pharmacopoeias. In *Fr.*

Profile

Spike lavender oil is the volatile oil from *Lavandula latifolia* (Labiatae). It resembles lavender oil (p.2331) in its properties and is mainly used in perfumery. It is also used in aromatherapy. Hypersensitivity reactions may occur.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Tavipec; ***Ger.:*** Bronchobest†; ***Thai.:*** Tavipec.

Multi-ingredient: ***Austria:*** Novipec; Tussamag; ***Rus.:*** Carmolis (Кармолис)†; ***S.Afr.:*** Balsem Vita GEEL; Balsem Vita ROOI; Balsem Vita WIT; Stuidruppels; ***Switz.:*** Baume du Chalet; Fortalis.

Spirulina

Espirulina.

Спирулина

Profile

Spirulina is a species of blue-green algae that has been promoted as an anorectic, but there is no convincing evidence that it is safe or effective for this indication.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Phycocyane†; ***India:*** Fitness; ***Indon.:*** Spirumate; ***UK:*** Biolina.

Multi-ingredient: ***Arg.:*** No-Gras; ***Austral.:*** Cal Alkyline; Rubus Complex†; ***Chile:*** Natur-Zin; Natursel-C; Reducform-F; ***Fr.:*** Thalgo Tonic; ***India:*** Vitexid; ***Malaysia:*** Eyebright Plus†.

Star Anise

Anís Estrellado; Anis Étoilé; Anisi stellati fructus; Anisum Badium; Anisum Stellatum; Badiana; Badiane; Badiane de Chine; Badyáníkový plod; Chinese Star Anise; Csillagánizs; Owoc anyżu gwiaździstego; Star Anise Fruit; Sternanis; Stjärnanis; Tähtianis; Žvaigždanyžių vaisiai.

NOTE. Distinguish from Japanese star anise.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Star Anise; Anisi Stellati Fructus). The dried composite fruit of *Illicium verum*, containing not less than 7% v/w of essential oil with reference to the anhydrous drug and a minimum 86.0% of *trans*-anethole in the essential oil. Protect from light.

Profile

The fruit of star anise, *Illicium verum* (Illiciaceae), is used as an expectorant for catarrh and as a gastrointestinal antispasmodic. It is used with thyme (p.2401) in herbal preparations for colds and upper respiratory-tract disorders. It is also used as a culinary spice.

Star anise is the source of star anise oil (below). It is also the source of shikimic acid, which is used in the production of the anti-influenza drug oseltamivir (p.900).

Adulteration of star anise with Japanese star anise (shikimi fruits; *I. anisatum*) has been responsible for a number of cases of neurotoxicity (see below). Import restrictions have been implemented in the EU. The problem is further complicated because the name *I. anisatum* has been applied to *I. verum*.

Adverse effects. Neurotoxicity has been associated with the use of star anise infusions in infants.[1-3] The toxicity is attributed to adulteration or contamination of Chinese star anise (*Illicium verum*) with Japanese star anise (*I. anisatum*) which contains toxic sesquiterpene lactones such as anisatin.

1. Garzo Fernandez C, *et al.* Casos de enfermedad de sintomatología neurológica asociados al consumo de anís estrellado empleado como carminativo. *An Esp Pediatr* 2002; **57:** 290–4.
2. Minodier P, *et al.* Intoxication aiguë par la badiane chez Le nourrisson. *Arch Pediatr* 2003; **10:** 619–21.
3. Ize-Ludlow D, *et al.* Neurotoxicities in infants seen with the consumption of star anise tea. Abstract: *Pediatrics* 2004; **114:** 1330. Full version: http://pediatrics.aappublications.org/cgi/content/full/114/5/e653 (accessed 04/05/06)

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Dorveran†; Ductoveran; Elixir 914†; ***Cz.:*** Naturland Grosser Swedenbitter†; ***Ital.:*** Relaxcol; ***Spain:*** Digestovital†; ***Switz.:*** Tisane laxative; Tisane pectorale et antitussive; ***Venez.:*** Atrobel; Cloverin†; Ervossil.

Star Anise Oil

Anisi stellati aetheroleum; Anisi Stellati Etheroleum; Badiane, huile essentielle de; Badyáníková silice; Oleum Badianae; Stjärnanisolja; Tähtianisöljy; Žvaigždanyžių eterinis aliejus.

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes star anise oil under the title Anise Oil.

Ph. Eur. 6.2 (Star Anise Oil; Anisi Stellati Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Illicium verum*. It contains 0.2 to 2.5% linalol, 0.5 to 6.0% estragole, less than 0.3% α-terpineol, 0.1 to 0.5% *cis*-anethole, 86 to 93% *trans*-anethole, 0.1 to 0.5% anisaldehyde, and 0.1 to 3.0% foeniculin. A clear, colourless or pale yellow liquid. Relative density 0.979 to 0.985. F.p. 15° to 19°. Store in well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

USNF 26 (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15°. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Profile

Star anise oil is included in preparations for the treatment of coughs and cold symptoms. It is used in the pharmaceutical and food industries as an alternative to anise oil (see p.2258). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Eupatal†; Makatussin Tropfen; ***Switz.:*** Foral†; Liberol Baby N; Odontal; ***Turk.:*** Sandolin.

Stearic Acid

Acide stéarique; Acido Esteárico; Acidum stearicum; Esteárico, ácido; Kwas stearowy; Kwas stearynowy; Kyselina stearová; Octadecanoic Acid; Steariinihappo; Stearino rūgštis; Stearinsäure; Stearinsyra; Sztearinsav.

CAS — 57-11-4 (stearic acid); 57-10-3 (palmitic acid).

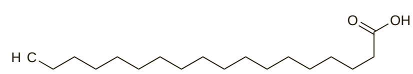

NOTE. Stearic acid is sometimes incorrectly called 'stearine' in commerce.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.* Also in *USNF.*

USNF also includes a purified form.

Ph. Eur. 6.2 (Stearic Acid). It is obtained from fat or oils from a vegetable or animal source and is a mixture consisting mainly of stearic acid ($C_{18}H_{36}O_2$ = 284.5) and palmitic acid ($C_{16}H_{32}O_2$ = 256.4). Stearic Acid 50 contains 40 to 60% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 70 contains 60 to 80% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 90%. Stearic Acid 95 contains a minimum of 90% stearic acid, the sum of the contents of stearic and palmitic acids being a minimum 96%. White or almost white, waxy, flaky crystals, white or almost white, hard masses, or a white or yellowish-white powder. Practically insoluble in water; soluble in alcohol and in petroleum spirit (50° to 70°).

USNF 26 (Stearic Acid). A mixture of stearic acid and palmitic acid, the content of stearic acid being not less than 40%, and the sum of the two not less than 90%. Congealing point not lower than 54°. Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder, with a slight odour, suggesting tallow. Practically insoluble in water; soluble 1 in 20 of alcohol, 1 in 2 of chloroform, and 1 in 3 of ether.

USNF 26 (Purified Stearic Acid). It contains not less than 90% stearic acid and not less than 96% of stearic and palmitic acids. Congealing point 66° to 69°.

Profile

Stearic acid is used as a lubricant in making tablets and capsules. It is also used as an emulsifying and solubilising agent. Various stearates are also used as pharmaceutical aids (see Nonionic Surfactants, p.1914, and Soaps and other Anionic Surfactants, p.2138).

Stone Root

Collinsonia; Collinsonia del Canadá; Hardhack; Heal-all; Knob Root.

Profile

Stone root, the root and rhizome of *Collinsonia canadensis* (Labiatae), has diuretic and litholytic properties and is used in the treatment of renal and urinary calculi. It is also used as an astringent for gastrointestinal disorders. It has also been included in herbal preparations for haemorrhoids.

Homoeopathy. Stone root has been used in homoeopathic medicines under the following names: Collinsonia canadensis; Collin. c.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Piletabs.

Storax

Balsamum Styrax Liquidus; Estoraque; Estoraque Líquido; Liquid Storax; Styrax.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Storax). The balsam obtained from the trunk of *Liquidambar orientalis* (Levant storax) or *L. styraciflua* (American storax) (Hamamelidaceae). It is a semiliquid greyish to greyish-brown, sticky, opaque mass depositing on standing a heavy dark brown layer (Levant storax), or semisolid, sometimes a solid mass, softened by gently heating (American storax). It is transparent in thin layers, has a characteristic odour, and is more dense than water.

Insoluble in water; soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, in carbon disulfide, and in ether, some insoluble residue usually remaining.

Profile

Storax has actions similar to those of Peru balsam (p.2365). Purified storax or prepared storax was formerly applied as an ointment in the treatment of parasitic skin diseases. Storax has a mild antiseptic action and is an ingredient of some preparations for upper respiratory-tract disorders and for application to skin and mucous membranes. Skin sensitisation has been reported.

Preparations

BP 2008: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
USP 31: Compound Benzoin Tincture.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Phytolithe†; ***NZ:*** Frador; ***S.Afr.:*** Turulington Tincture; ***UK:*** Frador.

Stramonium

Datura; Durmanový list (stramonium leaf); Durnaropių lapai (stramonium leaf); Estramonio; Hulluruohonlehti (stramonium leaf); Inferno; Jamestown Weed; Jimson Weed; Maszlaglevél (stramonium leaf); Stechapfel; Stramoine; Stramoine, feuille de (stramonium leaf); Stramonii folium (stramonium leaf); Stramoniumblad (stramonium leaf); Thornapple.

ATC Vet — QR03BB03.

NOTE. The terms Datura, Datura Herb, and Datura Leaf have been applied to preparations of various species of the genus Datura including *Datura metel*.

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of stramonium:
Devil's weed; Loco weed.

Pharmacopoeias. *Eur.* (see p.vii) includes a monograph for Stramonium Leaf and Prepared Stramonium.

Ph. Eur. 6.2 (Stramonium Leaf; Stramonii Folium). It consists of the dried leaf or the dried leaf, flowering tops and occasionally fruit-bearing tops of *Datura stramonium* and its varieties. It contains not less than 0.25% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine with varying proportions of hyoscine. It has an unpleasant odour. Protect from light and moisture.

The BP 2008 directs that when stramonium leaf or powdered stramonium leaf is prescribed, prepared stramonium shall be dispensed.

Ph. Eur. 6.2 (Stramonium, Prepared; Stramonii Pulvis Normatus). It is stramonium leaf powder adjusted to contain 0.23 to 0.27% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Abuse. Some reports[1-5] of poisoning after abuse of *Datura stramonium* or its preparations.

1. Gowdy JM. Stramonium intoxication: review of symptomatology in 212 cases. *JAMA* 1972; **221:** 585–7.
2. Shervette RE, *et al.* Jimson "Loco" weed abuse in adolescents. *Pediatrics* 1979; **63:** 520–3.
3. Anonymous. Jimson weed poisoning—Texas, New York, and California, 1994. *MMWR* 1995; **44:** 41–4.
4. Salen P, *et al.* Effect of physostigmine and gastric lavage in a Datura stramonium-induced anticholinergic poisoning epidemic. *Am J Emerg Med* 2003; **21:** 316–17.
5. Boumba VA, *et al.* Fatal poisoning from ingestion of Datura stramonium seeds. *Vet Hum Toxicol* 2004; **46:** 81–2.

Effects on the eyes. Anisocoria (unequal dilatation of the pupils) developed after accidental entry of a piece of jimson weed *(Datura stramonium)* into a patient's eye while gardening.[1]

1. Savitt DL, *et al.* Anisocoria from Jimsonweed. *JAMA* 1986; **255:** 1439–40.

Uses and Administration

Stramonium has the actions of atropine (p.1219). It has been given with other drugs in oral and rectal dosage forms for respiratory-tract disorders. It has also been smoked in cigarettes or burnt in powders and the fumes inhaled but the irritation produced by the fumes may aggravate bronchitis.

Homoeopathy. Stramonium has been used in homoeopathic medicines under the following names: Datura stramonium; Stram.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Potassium Iodide and Stramonium Compound†; ***Braz.:*** Asmatiron†; Expectol†; Teutoss†.

Streptodornase *(BAN, rINN)*

Estreptodornasa; Streptococcal Deoxyribonuclease; Streptodornaasi; Streptodornas; Streptodornasum.

Стрептодорназа

CAS — 37340-82-2.

Profile

Streptodornase is an enzyme obtained from cultures of various strains of *Streptococcus haemolyticus*. It catalyses the depolymerisation of polymerised deoxyribonucleoproteins. It liquefies the viscous nucleoprotein of dead cells; it has no effect on living cells. It is used with streptokinase in the topical treatment of lesions, wounds, and other conditions that require the removal of clots or purulent matter; the combination may also be used to dissolve clots in the bladder or in urinary catheters.

It has also been given orally with streptokinase and sometimes with antibacterials, for its supposed benefit in reducing oedema and inflammation associated with trauma and infection.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Varidasa†; ***Austral.:*** Varidase†; ***Austria:*** Varidase; ***Denm.:*** Varidase; ***Fin.:*** Varidase; ***Ger.:*** Varidase; ***Irl.:*** Varidase†; ***Ital.:*** Varidase†; ***Mex.:*** Varidasa; ***Norw.:*** Varidase; ***Pol.:*** Distreptaza; ***Port.:*** Varidasa†; ***Spain:*** Ernodasa; Varidasa; ***Swed.:*** Varidase; ***UK:*** Varidase†.

Strontium Chloride

Estroncio, cloruro de; Stronsiyum Klorür; Strontii Chloridum; Strontiumklorid; Strontiumkloridi.

$SrCl_2,6H_2O$ = 266.6.

CAS — 10476-85-4 (anhydrous strontium chloride).

Profile

Strontium chloride is used as a 10% toothpaste for the relief of dental hypersensitivity. Strontium acetate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Sensodyne Original; ***Austria:*** Sensodyne med; ***Braz.:*** Sensodyne Formula Original; ***Canad.:*** Sensodyne; ***Chile:*** Dentoxil; ***Switz.:*** Sensodent†; ***Turk.:*** Sensodyne Mint; ***UK:*** Sensodyne Original; ***USA:*** Sensodyne-SC; ***Venez.:*** Sencia; Tekdent†.

Multi-ingredient: ***Arg.:*** Esme Topico; ***Canad.:*** Reversa UV; ***Ital.:*** Pitiren; ***Singapore:*** 2Sensitive†.

Strychnine ⊗

Estricnina; Strychnina. Strychnidin-10-one.

$C_{21}H_{22}N_2O_2$ = 334.4.

CAS — 57-24-9.

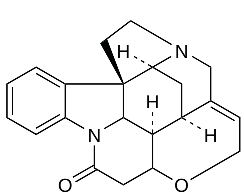

Description. Strychnine is an alkaloid obtained from the seeds of nux vomica (p.2355) and other species of *Strychnos.*

Strychnine Hydrochloride ⊗

Estricnina, hidrocloruro de; Strych. Hydrochlor.; Strychninae Hydrochloridum.

$C_{21}H_{22}N_2O_2,HCl,2H_2O$ = 406.9.

CAS — 1421-86-9 (anhydrous strychnine hydrochloride); 6101-04-8 (strychnine hydrochloride dihydrate).

Strychnine Nitrate ⊗

Azotato de Estricnina; Estricnina, nitrato de; Nitrato de Estricnina; Strychninae Nitras; Strychnini Nitras; Strychninum Nitricum; Strykniininitraatti; Strykninnitrat.

$C_{21}H_{22}N_2O_2,HNO_3$ = 397.4.

CAS — 66-32-0.

Pharmacopoeias. In *Chin.*

Strychnine Sulfate ⊗

Estricnina, sulfato de; Strychninae Sulphas; Strychnine Sulphate; Strychninum Sulfuricum; Sulfato de Estricnina.

$(C_{21}H_{22}N_2O_2)_2,H_2SO_4,5H_2O$ = 857.0.

CAS — 60-41-3 (anhydrous strychnine sulfate); 60491-10-3 (strychnine sulfate pentahydrate).

Pharmacopoeias. In *Fr.* and *Viet.*

Adverse Effects

The symptoms of strychnine poisoning are mainly those arising from stimulation of the CNS. Early signs occurring within 15 to 30 minutes of ingestion include tremors, slight twitching, and stiffness of the face and limbs. Painful convulsions develop and may be triggered by minor sensory stimuli; since consciousness is not impaired patients may be extremely distressed. All forms of sensation are heightened. The body becomes arched backwards in hyperextension with the head retracted, arms and legs extended, fists clenched, and the feet turned inward. The jaw is rigidly clamped and contraction of the facial muscles produces a characteristic grinning expression known as 'risus sardonicus'. The convulsions may recur repeatedly and are interspersed with periods of relaxation. If not treated adequately, few patients survive more than 5 episodes of convulsions, death usually occurring due to respiratory and cardiac arrest. Fatalities in adults have occurred with doses as little as 16 mg.

Secondary effects arising from the severe spasms include lactic acidosis, rhabdomyolysis, renal failure, hyperthermia, hyperkalaemia, and dehydration.

Poisoning. References.

1. O'Callaghan WG, *et al.* Unusual strychnine poisoning and its treatment: report of eight cases. *BMJ* 1982; **285:** 478.
2. Blain PG, *et al.* Strychnine poisoning: abnormal eye movements. *J Toxicol Clin Toxicol* 1982; **19:** 215–17.
3. Boyd RE, *et al.* Strychnine poisoning: recovery from profound lactic acidosis, hyperthermia, and rhabdomyolysis. *Am J Med* 1983; **74:** 507–12.
4. Burn DJ, *et al.* Strychnine poisoning as an unusual cause of convulsions. *Postgrad Med J* 1989; **65:** 563–4.
5. Yamarick W, *et al.* Strychnine poisoning in an adolescent. *J Toxicol Clin Toxicol* 1992; **30:** 141–8.
6. Heiser JM, *et al.* Massive strychnine intoxication: serial blood levels in a fatal case. *J Toxicol Clin Toxicol* 1992; **30:** 269–83.
7. Nishiyama T, Nagase M. Strychnine poisoning: natural course of a nonfatal case. *Am J Emerg Med* 1995; **13:** 172–3.
8. Katz J, *et al.* Strychnine poisoning from a Cambodian traditional remedy. *Am J Emerg Med* 1996; **14:** 475–7.
9. Hernandez AF, *et al.* Acute chemical pancreatitis associated with nonfatal strychnine poisoning. *J Toxicol Clin Toxicol* 1998; **36:** 67–71.
10. Greene R, Meatherall R. Dermal exposure to strychnine. *J Anal Toxicol* 2001; **25:** 344–7.
11. Wood D, *et al.* Case report: survival after deliberate strychnine self-poisoning, with toxicokinetic data. *Crit Care* 2002; **6:** 456–9.
12. Scheffold N, *et al.* Strychninvergiftung. *Dtsch Med Wochenschr* 2004; **129:** 2236–8.
13. Shadnia S, *et al.* A case of acute strychnine poisoning. *Vet Hum Toxicol* 2004; **46:** 76–9.

Treatment of Adverse Effects

The main aim of therapy in strychnine poisoning is the prompt prevention or control of convulsions and asphyxia. Activated charcoal should be given if the patient presents within 1 hour of ingestion. Convulsions should be controlled or prevented by diazepam or lorazepam. Intubation and assisted respiration may be required. Should benzodiazepines fail then phenytoin or phenobarbital may be tried. All unnecessary external stimuli should be avoided and if possible the patient should be kept at rest in a quiet darkened room. Patients should be monitored for any secondary effects such as metabolic acidosis so that appropriate symptomatic treatment can be given.

Uses and Administration

Strychnine competes with glycine, which is an inhibitory neurotransmitter; it thus exerts a central stimulant effect by blocking an inhibitory activity.

Strychnine was formerly used as a bitter and analeptic but is now mainly used under strict control as a rodenticide. It has also been used as a mole poison, although this use is banned in some countries including the UK. Strychnine has been used in multi-ingredient preparations for the treatment of ophthalmic and urinary-tract disorders. It has also been tried in the treatment of nonketotic hyperglycinaemia.

Nonketotic hyperglycinaemia. Nonketotic hyperglycinaemia (also known as glycine encephalopathy) is an inborn defect in the enzyme system responsible for the metabolism of glycine. It is characterised by raised concentrations of glycine in plasma, CSF, and urine. Symptoms of glycine accumulation include respiratory distress, muscular hypotonia, seizures, vomiting, and extreme lethargy. Mental retardation and early infant death are common.

Sodium benzoate can reduce plasma-glycine concentrations to near normal[1] but is relatively ineffective in reducing CSF levels or in preventing mental retardation.[2] Strychnine, a glycine antagonist, has been of some benefit in counteracting its CNS effects.[3-5] However, even treatment with both drugs may be ineffective in severe cases[6] and may ultimately have little effect on the course of the disease.[7] Glycine is reported to stimulate *N*-methyl-D-aspartate (NMDA) receptors in the CNS and the combination of strychnine and ketamine (an NMDA receptor antagonist) was of some benefit in a newborn infant with severe non-ketotic hyperglycinaemia.[8] Addition of low-dose dextromethorphan (an NMDA receptor antagonist) to treatment with sodium benzoate, arginine, carnitine, diazepam, and phenobarbital in an infant with nonketotic hyperglycinaemia[9] was associated with resolution of nystagmus and improvement in eye contact and interactive behaviour, without altering serum- or CSF-glycine concentrations. Dextromethorphan with sodium benzoate alone may also be helpful, although the combination is not uniformly effective.[10] Treatment with sodium benzoate and dextromethorphan was beneficial in a 6-month-old child with mild atypical nonketotic hyperglycinaemia,[11] although it was later shown that it was sodium benzoate that had the greatest effect on EEG and behavioural changes. A partial response to low-protein diet and sodium benzoate occurred in a patient with late-onset nonketotic hyperglycinaemia; there was a more dramatic response when imipramine was added to therapy.[12]

1. Van Hove JLK,*et al.* Benzoate treatment and the glycine index in nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2005; **28:** 651–63.
2. Krieger I, *et al.* Cerebrospinal fluid glycine in nonketotic hyperglycinemia: effect of treatment with sodium benzoate and a ventricular shunt. *Metabolism* 1977; **26:** 517–24.
3. Ch'ien LT, *et al.* Glycine encephalopathy. *N Engl J Med* 1978; **298:** 687.
4. Gitzelmann R, *et al.* Strychnine for the treatment of nonketotic hyperglycinaemia. *N Engl J Med* 1978; **298:** 1424.
5. Arneson D, *et al.* Strychnine therapy in nonketotic hyperglycinemia. *Pediatrics* 1979; **63:** 369–73.
6. Sankaran K, *et al.* Glycine encephalopathy in a neonate. *Clin Pediatr (Phila)* 1982; **21:** 636–7.
7. MacDermot KD, *et al.* Attempts at use of strychnine sulfate in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1980; **65:** 61–4.
8. Tegtmeyer-Metzdorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.
9. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97:** 924–6.
10. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132:** 709–13.
11. Neuberger JM, *et al.* Effect of sodium benzoate in the treatment of atypical nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2000; **23:** 22–6.
12. Wiltshire EJ, *et al.* Treatment of late-onset nonketotic hyperglycinaemia: effectiveness of imipramine and benzoate. *J Inherit Metab Dis* 2000; **23:** 15–21.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Vigofortal; ***Hung.:*** Artin†; ***Israel:*** Tesopalmed Forte cum Yohimbine; ***Ital.:*** Neuroftal†; ***Pol.:*** Cardiamid-Coffein; ***Port.:*** Hipersex†; ***Thai.:*** Hemo-Cyto-Serum.

Suanzaorentang

Ziziphus Soup.

Profile

Suanzaorentang is a traditional Chinese remedy for anxiety and insomnia. It contains five herbs: suanzaoren (*Zizyphus spinosus*, Rhamnaceae), fuling (*Poria cocos*, Polyporaceae), gancao (*Glycyrrhiza uralensis*, Leguminosae), zhimu (*Anemarrhena asphodeloides*, Liliaceae), and chuanxiong (*Ligusticum chuanxiong*, Umbelliferae).

Subtilisin A

Subtilisin Carlsberg; Subtilopeptidase A.

Субтилизин А

CAS — 9014-01-1 (subtilisin).

Profile

Subtilisins are a class of serine proteases isolated initially from *Bacillus subtilis* but which are also excreted by other *Bacillus* species. They are widely used in the manufacture of enzymatic detergents. Hypersensitivity reactions have been reported.

Subtilisin A, which is obtained from *Bacillus licheniformis*, is used as an enzymatic cleanser for contact lenses.

◊ References.

1. Lemiere C, *et al.* Isolated late asthmatic reaction after exposure to a high-molecular-weight occupational agent, subtilisin. *Chest* 1996; **110:** 823–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ultrazyme; ***Austral.:*** Complete Protein Remover; Ultrazyme; ***Braz.:*** Fizziclean†; Ultrazyme†; ***Canad.:*** Complete Protein Remover†; Efferzyme†; Ultrazyme; Unizyme; ***NZ:*** Ultrazyme; ***USA:*** Renu Enzymatic Cleaner; Soft Mate Enzyme Plus Cleaner; Ultrazyme.

Multi-ingredient: ***Canad.:*** Comfortcare Dual Action†.

Sucrose Octa-acetate

Sacarosa, octaacetato de; Sucrose Octaacetate.
$C_{28}H_{38}O_{19}$ = 678.6.
CAS — 126-14-7.

Pharmacopoeias. In *USNF.*

USNF 26 (Sucrose Octaacetate). A white, practically odourless, hygroscopic powder. M.p. not lower than 78°. Soluble 1 in 1100 of water, 1 in 11 of alcohol, 1 in 0.3 of acetone, 1 in 0.5 of toluene, and 1 in 0.6 of benzene; very soluble in chloroform and in methyl alcohol; soluble in ether. Store in airtight containers.

Profile

Sucrose octa-acetate has been used as an alcohol denaturant. It is also incorporated into preparations intended to deter nail biting.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Morde X.

Sulfobromophthalein Sodium

Bromsulfophthalein Sodium; Bromsulphthalein Sodium; BSP; SBP; Sodium Sulfobromophthalein; Sulfobromoftaleína sódica; Sulphobromophthalein Sodium *(BANM)*. Disodium 4,5,6,7-tetrabromophenolphthalein-3′,3″-disulphonate; Disodium 5,5′-(4,5,6,7-tetrabromophthalidylidene)bis(2-hydroxybenzenesulphonate).
$C_{20}H_8Br_4Na_2O_{10}S_2$ = 838.0.
CAS — 297-83-6 (sulfobromophthalein); 71-67-0 (sulfobromophthalein sodium).
ATC — V04CE02.
ATC Vet — QV04CE02.

Pharmacopoeias. In *Chin., It.,* and *Jpn.*

Profile

In patients with normal hepatic function sulfobromophthalein sodium is rapidly extracted, conjugated, and excreted in bile. It was formerly used intravenously as a diagnostic agent for testing the functional capacity of the liver but may cause severe hypersensitivity reactions.

Sulfuric Acid

Acid. Sulph.; Acid. Sulph. Dil.; Acide sulfurique; Acidum sulfuricum; E513; Kénsav; Kwas siarkowy; Kyselina sírová; Oil of Vitriol; Rikkihappo; Sulfato rūgštis; Sulfúrico, ácido; Sulphuric Acid; Svavelsyra; Verdünnte Schwefelsäure (dilute sulfuric acid).
H_2SO_4 = 98.08.
CAS — 7664-93-9.

NOTE. Concentrated oil of vitriol of commerce, 'COV', contains about 95 to 98% w/w, and brown oil of vitriol, 'BOV', contains 75 to 85% w/w of H_2SO_4.
Nordhausen or fuming sulfuric acid, 'Oleum', is sulfuric acid containing SO_3.
Battery or accumulator acid is sulfuric acid diluted with distilled water to a specific gravity of 1.2 to 1.26.

Pharmacopoeias. *Br.* and *Eur.* (see p.vii) include various concentrations. Also in *USNF.*

BP 2008 (Dilute Sulphuric Acid). It contains 9.5 to 10.5% w/w of H_2SO_4 and is prepared by adding 104 g of sulfuric acid to 896 g of water, with constant stirring and cooling.

Ph. Eur. 6.2 (Sulphuric Acid). It contains 95.0 to 100.5% w/w of H_2SO_4. A colourless, very hygroscopic, oily liquid. Miscible with water and with alcohol producing intense heat. Store in airtight containers.

USNF 26 (Sulfuric Acid). It contains 95.0 to 98.0% w/w of H_2SO_4. A clear, colourless, oily liquid. Is very caustic and corrosive. Miscible with water and with alcohol with the generation of much heat. Store in airtight containers.

Dilution. When sulfuric acid is mixed with other liquids, it should always be added slowly, with constant stirring, to the diluent.

Adverse Effects and Treatment

As for Hydrochloric Acid, p.2322.

Uses and Administration

Sulfuric acid has various industrial uses. Dilute sulfuric acid has been used as an astringent in diarrhoea and it has occasionally been prescribed in mixtures with vegetable bitters to stimulate appetite.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Debacterol.

Sulphan Blue *(BAN)*

Azul sulfán; Błękit sulfanowy; Blue VRS; Isosulfan Blue *(USAN)*; P-1888; P-4125; Sulfan Blue. Sodium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclo-hexa-2,5-dienylidene)toluene-2,5-disulfonate.
$C_{27}H_{31}N_2NaO_6S_2$ = 566.7.
CAS — 68238-36-8 (2,5-disulfonate isomer); 129-17-9 (2,4-disulfonate isomer).

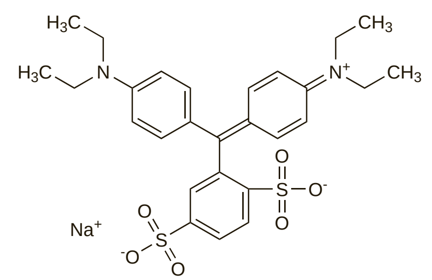

(2,5-disulfonate isomer)

NOTE. Sulphan blue was formerly described in *BPC 1954* as the 2,4-disulfonate isomer and the following synonyms have been applied to this 2,4-isomer: Acid Blue 1; Alphazurine 2G; Colour Index No. 42045; Patent Blue V; Sulphanum Caeruleum. The name Patent Blue V, however, is mainly used for CI No. 42051 (p.2363).

Profile

Intravenous doses of sulphan blue produce staining of the skin and have been used as a direct visual test of the state of the circulation in healthy and damaged tissues, particularly in assessing tissue viability in burns and soft-tissue trauma. It has also been used subcutaneously in lymphangiography to outline the lymph vessels.

Hypersensitivity reactions including anaphylaxis and attacks of asthma have been reported with sulphan blue. It has also been reported to interfere with blood tests for protein and iron.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Lymphazurin; ***USA:*** Lymphazurin.

Sumatra Benzoin

Benjoim; Benjoin; Benjoin de sumatra; Benjuí, bálsamo de; Benzoë; Benzoe sumatranus; Benzoin; Benzoina; Gum Benjamin; Gum Benzoin; Styrax tonkinensis et Styrax benzoin.
CAS — 9000-05-9.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
US allows both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 6.2 (Sumatra Benzoin). A resin obtained by incising the trunk of *Styrax benzoin*. It contains 25 to 50% of total acids, calculated as benzoic acid (dried drug).
Creamy white, rounded to ovoid tears, which may be embedded in a dull, greyish-brown or reddish-brown matrix. It is hard and brittle and the fractured surface is dull and uneven.

USP 31 (Benzoin). A balsamic resin from *Styrax paralleloneurus* or *S. benzoin* (Styracaceae). It yields not less than 75% of alcohol-soluble extractive. It occurs as blocks or lumps of variable size made up of tears, compacted together, with a reddish-brown, reddish-grey, or greyish-brown resinous mass. The tears are externally yellowish or rusty brown, milky white on fresh fracture, hard and brittle at ordinary temperatures but softened by heat. It has an aromatic and balsamic odour. When heated it does not emit a pinaceous odour. When digested with boiling water, the odour suggests cinnamates or storax.

Profile

Sumatra benzoin is an ingredient of inhalations which are used in the treatment of catarrh of the upper respiratory tract. Sumatra benzoin is also used in topical preparations for its antiseptic and protective properties. Skin sensitisation has been reported.

Preparations of Sumatra and Siam benzoins are used in aromatherapy.

Preparations

BP 2008: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
Ph. Eur.: Benzoin Tincture, Sumatra;
USP 31: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Nappy-Mate†; ***Belg.:*** Borostyrol; ***Braz.:*** Inhadrina†; Inhalante Yatropan; Micoz†; ***Canad.:*** Cold Sore Lotion; Lotion pour Feux Sauvages†; ***Fr.:*** Balsofumine; Balsofumine Mentholee; ***Ger.:*** Nur 1 Tropfen medizinisches Mundwasser†; ***Israel:*** Kank-A; ***Ital.:*** Citrosil Nubesan; Fomentil; ***NZ:*** Cold Sore; ***Port.:*** Vaporil; ***S.Afr.:*** Turulington Tincture; ***Switz.:*** Baume†; Pommade au Baume; ***Turk.:*** Buguseptil; Rinolar; ***UK:*** Allens Dry Tickly Cough; Frador; Kilkof; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Snowfire; Throaties Pastilles; ***USA:*** Pfeiffer's Cold Sore; ***Venez.:*** Aftil; Podoben†.

Summer Savory

Bohnenkraut; Sarriette; Savory.

Profile

Summer savory (*Satureja hortensis*, Lamiaceae) is included in herbal preparations and is used as a culinary herb.

It is the source of savory oil which is included in herbal preparations, mainly for the relief of cold symptoms. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Gartech; ***Fr.:*** Resistim; ***Spain:*** Natusor Astringel†; Natusor Low Blood Pressure†; Tonimax; ***Switz.:*** Demonatur Capsules contre les refroidissements; Spagyrom.

Surgibone *(USAN)*

Profile

Surgibone is sterile, specially processed mature bovine bone, that has been used for grafting procedures in orthopaedic and reconstructive surgery.

Taltirelin *(rINN)*

TA-0910; Taltirelina; Taltiréline; Taltirelinum. (−)-*N*-{[(*S*)-Hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl]carbonyl}-L-histidyl-L-prolinamide.
Тальтирелин
$C_{17}H_{23}N_7O_5$ = 405.4.
CAS — 103300-74-9.

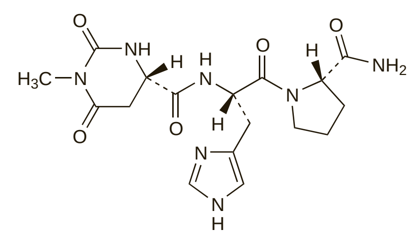

Profile

Taltirelin is an analogue of protirelin (p.2175) and is claimed to have beneficial effects on CNS function. It is used in the treatment of spinocerebellar degeneration.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Ceredist.

Tannic Acid

Acide tannique; Acidum Tannicum; Gallotannic Acid; Garvsyra; Gerbstoff; Kwas taninowy; Tánico, ácido; Tanin; Tanina; Taninas; Tann. Acid; Tanniini (Parkkihappo); Tannin; Tanninum.
CAS — 1401-55-4.

NOTE. In pharmaceutical literature, the name digallic acid is frequently confused with tannic acid.
Commercial grades of tannic acid may contain gallic acid and being less soluble are not suitable for medicinal use.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Tannic Acid). A mixture of esters of glucose with gallic acid and 3-galloylgallic acid. A yellowish-white or slightly brown amorphous light powder or shiny plates. Very soluble in water; freely soluble in alcohol, in acetone, and in glycerol (85%); practically insoluble in dichloromethane. Protect from light.

USP 31 (Tannic Acid). A tannin usually obtained from nutgalls (see Gall, p.2307), the excrescences produced on the young twigs of *Quercus infectoria* and allied species of *Quercus*, from the seed pods of tara (*Caesalpinia spinosa*), or from the nutgalls or leaves of sumac (any of genus *Rhus*).
Amorphous powder, glistening scales, or spongy masses, varying in colour from yellowish-white to light brown. Is odourless or has a faint, characteristic odour. Very soluble in water, in alcohol, and in acetone; freely soluble in diluted alcohol; slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ether, in petroleum spirit, and in benzene; soluble 1 in about 1 of warm glycerol. Store in airtight containers. Protect from light.

Profile

Tannic acid has been used as an astringent for the mucous membranes of the mouth and throat, and in suppositories for the treatment of haemorrhoids. It is an ingredient in a number of dermatological preparations.

Former uses of tannic acid include application to burns, addition to barium sulfate enemas to improve the quality of radiological pictures of the colon, and as an ingredient of 'Universal Antidote'. However, tannic acid has been associated with liver toxicity, sometimes fatal.

Tattoo removal. Although tannic acid may be used by plastic surgeons and dermatologists to produce a controlled partial-thickness burn in tattoo removal[1] it has been pointed out that in unskilled or amateur hands this procedure has resulted in full thickness burns requiring skin grafting to obtain satisfactory healing.[2]

1. Mercer NSG, Davies DM. Tattoos. *BMJ* 1991; **303:** 380.
2. Scott M, Ridings P. Tattoos. *BMJ* 1991; **303:** 720.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Tannosynt; ***Spain:*** Tanagel Papeles.

Multi-ingredient: ***Austral.:*** SM-33; ***Austria:*** Haemanal; Paradenton; ***Belg.:*** Hemorhinol; ***Braz.:*** Lacto Vagin†; ***Canad.:*** Tanac; ***Fr.:*** Allerbiocid S†; Eau Precieuse; HEC; ***Ger.:*** Bioget†; Tannolil†; ***Gr.:*** Oulogram; ***Irl.:*** Phytex; ***Israel:*** Rectozorin; ***Ital.:*** Blefarolin; Neo Emocicatrol; ***Philipp.:*** Zilactin; ***Pol.:*** Acifungin; Salumin; ***Rus.:*** Contraceptin T (Контрацептин Т); Neo-Anusol (Нео-анузол); ***Singapore:*** HEC†; ***Spain:*** Antihemorroidal; Depurativo Richelet; Dextricea; Sabanotropico; Tanagel; Tangenol†; ***Switz.:*** HEC; Tanno-Hermal; ***UK:*** Colsor; Phytex; TCP; ***USA:*** Dermasept Antifungal; Orasept; Outgro; Tanac; Tanac Dual Core.

Tansy

Atanasia; Barbotine; Hierba lombriguera; Rainfarn; Tanaceto; Tanaisie.

Profile

Tansy, the flowering tops of *Tanacetum vulgare* (*Chrysanthemum vulgare*) (Compositae), has been used as an anthelmintic and to stimulate menstruation. The oil is highly toxic and use of tansy is generally not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Calmo; ***Pol.:*** Artemisol.

Taraxacum

Dandelion Root; Diente de León; Korzeń mniszka (root); Löwenzahnwurzel; Pissenlit; Taraxaci Herba; Taraxaci Radix (root); Taraxacum officinalis; Taraxacum Root; Ziele mniszka.

Pharmacopoeias. In *Pol.*

Chin. specifies Taraxacum Herb from other species of *Taraxacum.*

Profile

Taraxacum is the fresh or dried root of the common dandelion, *Taraxacum officinale* (Compositae). It has been used as a bitter, as a diuretic, and as a mild laxative.

Homoeopathy. Taraxacum has been used in homoeopathic medicines under the following names: Taraxacum officinale; Tarax.

◊ References.

1. Houghton P. Bearberry, dandelion and celery. *Pharm J* 1995; **255:** 272–3.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Gallentee†; ***Ger.:*** Carvicum†; Taraleon†; ***Pol.:*** Talion.

Multi-ingredient: ***Arg.:*** Quelodin F; ***Austral.:*** Berberis Complex; Bioglan Cranbiotic Super; Colax; Digest; Extralife Fluid-Care; Extralife Liva-Care; Feminine Herbal Complex; Fluid Loss†; Glycoplex†; Herbal Cleanse†; Herbal Diuretic Formula†; Lifesystem Herbal Formula 7 Liver Tonic†; Liver Tonic Herbal Formula 6†; Livstim†; Livton Complex†; Profluid†; Silybum Complex†; St Mary's Thistle Plus; Trifolium Complex†; Uva-Ursi Complex†; Uva-Ursi Plus†; ***Austria:*** Gallen- und Lebertee St Severin; Magentee St Severin; Montana; Urelium Neu; ***Canad.:*** Milk Thistle Extract Formula†; ***Cz.:*** Cynarosan†; Diabetan; Diabeticka Cajova Smes-Megadiabetin; Original Schwedenbitter; The Salvat; Ungolen†; ***Fr.:*** Detoxell; Diacure; Drainuryl; Hydracur; Maxidraine†; Romarene; ***Ger.:*** Alasenn; Amara-Tropfen; Aristochol N†; Carmol Magen-Galle-Darm; Cholosom SL†; Cholosom-Tee; Gallemolan forte; Gallemolan G†; Gallexier; Galloselect M†; Neurochol C†; Nieron S†; Nieron-Tee N†; Pascobilin novo†; Presselin Hepaticum P†; Tonsilgon; ***Hong Kong:*** Hepatofalk; ***Indon.:*** Naturica DFM; ***Ital.:*** Centaurea (Specie Composta)†; Cinarepa; Tarassaco (Specie Composta)†; Varicofit; ***Malaysia:*** Dandelion Complex†; ***Pol.:*** Artecholin; Artecholwex; Cholavisol; Cholesol; Cholitol; Diabetosol; Dyspepsin; Gastrobonisol; Nefrobonisol; Nefrol; Tabletki Przeciw Niestrawnosci; ***Rus.:*** Tonsilgon N (Тонзилгон Н); ***S.Afr.:*** Amara; ***Spain:*** Diurette; ***Switz.:*** Boldocynara; Demonatur Gouttes pour le foie et la bile; Gastrosan; Heparfelien; Phytomed Hepato†; Phytomed Nephro†; Strath Gouttes pour les reins et la vessie; Tisane hepatique et biliaire; ***UK:*** Adios; Aqualette; Backache; Boldex; HealthAid Boldo-Plus; Herbulax; HRI Water Balance; Natravene; Natural Herb Tablets; Out-of-Sorts; Rheumatic Pain; Senokot Dual Relief; Stomach Mixture; Uvacin; Weight Loss Aid; Wind & Dyspepsia Relief; ***Venez.:*** Celyth's; Flocadep; Rheu-Tarx I.

Tartaric Acid

Acide tartrique; Acidum tartaricum; Borkősav; E334; E353 (metatartaric acid); Kwas winowy; Kyselina vinná; Tart. Acid; Tartárico, ácido; Tartarik Asit; Tartrique (Acide); Viinihappo; Vinsyra; Vyno rūgštis; Weinsäure. (+)-L-Tartaric acid; (2*R*,3*R*)-2,3-Dihydroxybutane-1,4-dioic acid.

$C_4H_6O_6$ = 150.1.
CAS — 87-69-4; 526-83-0.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.* Also in *USNF.*
Ph. Eur. 6.2 (Tartaric Acid). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol.
USNF 26 (Tartaric Acid). Colourless or translucent crystals or a white, fine to granular, crystalline powder. Is odourless. Soluble 1 in 0.8 of water, 1 in 0.5 of boiling water, 1 in 3 of alcohol, 1 in 250 of ether, and 1 in 1.7 of methyl alcohol.

Adverse Effects

Strong solutions of tartaric acid are mildly irritant and if ingested undiluted may cause violent vomiting and diarrhoea, abdominal pain, and thirst. Cardiovascular collapse or acute renal failure may follow.

Pharmacokinetics

Tartaric acid is absorbed from the gastrointestinal tract but up to 80% of an ingested dose is probably destroyed by micro-organisms in the lumen of the intestine before absorption occurs. Absorbed tartaric acid is excreted unchanged in the urine.

Uses and Administration

Tartaric acid is used in the preparation of effervescent powders, granules, and tablets, as an ingredient of cooling drinks, and as a saline purgative. If not neutralised, it must be taken well diluted. Tartaric acid or metatartaric acid are used in wine-making as deacidifying agents to assist in the removal of excess malic acid by forming an insoluble double salt with calcium carbonate.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Citralite; Citravescent; Dexsal; Salvital; Ural; Uricalm†; ***Austria:*** Duplotrast Weinsaure; Helo-acid; Lactolavol; ***Belg.:*** Zoru†; ***Canad.:*** E-Z-Gas II†; ***Chile:*** Frunalia; Frutasal Knop; Uroknop; ***Fr.:*** Dermacide; Zeniac LP Fort†; ***Ger.:*** Retterspitz Ausserlich; Retterspitz Innerlich; ***India:*** Urisoda; ***Ital.:*** Antimicotica Solforata; Geffer; Magnesia Effervescente Sella; ***Malaysia:*** Citravescent†; Ezee; Ural; ***NZ:*** Ural; ***Port.:*** Safrux; Thiospot; ***S.Afr.:*** Adco-Sodasol; Alkafizz; Citro-Soda; Quatro-Soda†; Uri-Alk; ***Spain:*** Citinoides; Hectonona; Salcedol; Sales de Frutas P G; Sales Fruta Mag Viviar; Salmagne; ***Switz.:*** Siesta-1; ***Turk.:*** Enhos; Purgyl; ***UK:*** Jaaps Health Salt; ***USA:*** Baros.

Taurine *(rINN)*

Taurina; Taurinum. 2-Aminoethanesulphonic acid.

Таурин

$C_2H_7NO_3S$ = 125.1.
CAS — 107-35-7.

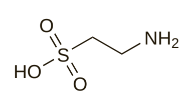

Pharmacopoeias. In *Chin.*, *Jpn*, and *US.*
USP 31 (Taurine). White crystals or crystalline powder. Soluble in water.

Profile

Taurine is an amino acid known to be involved in bile acid conjugation as well as other physiological functions. It has been included in preparations for parenteral nutrition of low-birth-weight infants and in infant formulas but its role as an essential nutrient has not been established.

Taurine is included in some preparations for cardiovascular and metabolic disorders.

◊ References.

1. Redmond HP, *et al.* Immunonutrition: the role of taurine. *Nutrition* 1998; **14:** 599–604.
2. Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: experimental and clinical studies. *Amino Acids* 2002; **23:** 381–93.
3. Bidri M, Choay P. La taurine : un aminoacide particulier aux fonctions multiples. *Ann Pharm Fr* 2003; **61:** 385–91.
4. Kingston R, *et al.* The therapeutic role of taurine in ischaemia-reperfusion injury. *Curr Pharm Des* 2004; **10:** 2401–10.
5. Franconi F, *et al.* Taurine supplementation and diabetes mellitus. *Curr Opin Clin Nutr Metab Care* 2006; **9:** 32–6.
6. Verner A, *et al.* Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: O-Due; ***Philipp.:*** Taurex; ***Rus.:*** Dibicor (Дибикор); Taufone (Тауфон)†.

Multi-ingredient: ***Indon.:*** Biofos; ***Ital.:*** Novostatin; ***Port.:*** Detoxergon; ***Spain:*** Taurobetina†.

Terlipressin *(BAN, USAN, rINN)*

Terlipresina; Terlipressine; Terlipressinum; Triglycyl-lysine-vasopressin. *N*-[*N*-(*N*-Glycylglycyl)glycyl]lypressin; Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (4→9) disulphide.

Терлипрессин

$C_{52}H_{74}N_{16}O_{15}S_2$ = 1227.4.
CAS — 14636-12-5.
ATC — H01BA04.
ATC Vet — QH01BA04.

Terlipressin Acetate *(BANM, rINNM)*

Acetato de terlipresina; Terlipresin Asetat; Terlipressiiniasetaatti; Terlipressin Diacetate; Terlipressinacetat; Terlipressine, Acétate de; Terlipressini Acetas.

Терлипрессина Ацетат

$C_{52}H_{74}N_{16}O_{15}S_2,2C_2H_4O_2,5H_2O$ = 1437.6.
ATC — H01BA04.
ATC Vet — QH01BA04.

Adverse Effects, Treatment, and Precautions

As for Vasopressin, p.2412.

The pressor and antidiuretic effects of terlipressin are reported to be less marked than those of vasopressin.

Effects on electrolytes. A report of hypokalaemia in a patient receiving terlipressin.[1]

1. Stéphan F, Paillard F. Terlipressin-exacerbated hypokalaemia. *Lancet* 1998; **351:** 1249–50.

Effects on the skin. Ischaemic skin necrosis developed in 3 patients several days after starting terlipressin treatment.[1] Skin lesions developed on the abdomen and lower limbs, which are not typical areas for ischaemia related to vasoconstrictors, and the authors concluded that obesity and venous insufficiency in these patients put them at particular risk.

1. Donnellan F, *et al.* Ischaemic complications of Glypressin in liver disease: a case series. *Br J Clin Pharmacol* 2007; **64:** 550–2.

Uses and Administration

Terlipressin is an inactive prodrug which is slowly converted in the body to lypressin, and has the general physiological actions of vasopressin (p.2412).

Terlipressin acetate is used to control bleeding oesophageal varices and is given by intravenous injection in doses of 2 mg, followed by 1 or 2 mg every 4 to 6 hours if necessary, until bleeding is controlled, for up to 72 hours.

Terlipressin is under investigation in the treatment of hepatorenal syndrome and shock.

Hepatorenal syndrome. Terlipressin has been found to be of benefit in the hepatorenal syndrome, a form of renal impairment associated with cirrhosis of the liver. A retrospective study[1] found that doses of about 3 mg/day for a mean of 11 days appeared to improve renal function in 58 of 91 patients; it may also have improved survival. Further prospective studies have also reported beneficial effects on renal function; these used doses of terlipressin 1 mg every 4 hours for 7 to 15 days,[2] and 1 mg every 12 hours for up to 15 days.[3] Meta-analysis[4] of 11 studies confirmed the efficacy of terlipressin in hepatorenal syndrome although a significant number of patients who responded to treatment relapsed after it was stopped. A systematic review[5] of 3 small randomised controlled studies of terlipressin suggested that it may reduce mortality and improve renal function in patients with hepatorenal syndrome, although the evidence was not sufficiently reliable to make recommendations for clinical practice.

1. Moreau R, *et al.* Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology* 2002; **122:** 923–30.
2. Alessandria C, *et al.* Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002; **14:** 1363–8.
3. Solanki P, *et al.* Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol* 2003; **18:** 152–6.
4. Fabrizi F, *et al.* Meta-analysis: terlipressin therapy for the hepatorenal syndrome. *Aliment Pharmacol Ther* 2006; **24:** 935–44.
5. Gluud LL, *et al.* Terlipressin for hepatorenal syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 25/06/08).

Shock. Terlipressin has vasopressor effects and has been tried[1,2] in the management of septic shock (p.1183). In a group of 8 patients who could not be adequately managed with conventional vasopressor therapy, an intravenous bolus of terlipressin 1 to 2 mg produced a progressive increase in mean arterial pressure over 10 to 20 minutes that was sustained for at least 5 hours, allowing reduction or cessation of noradrenaline.[3] Similar beneficial results have also been reported by others.[4,5] The use of a continuous infusion of terlipressin (500 micrograms/hour for 6 hours followed by half this dose for a further 12 hours) has been described in one case and appeared to be effective.[6] There is also a report[7] of 4 children treated with bolus doses of 20 micrograms/kg every 4 hours for up to 72 hours.

1. Delmas A, *et al.* Clinical review: vasopressin and terlipressin in septic shock patients. *Crit Care* 2005; **9:** 212–22.
2. Pesaturo AB, *et al.* Terlipressin: vasopressin analog and novel drug for septic shock. *Ann Pharmacother* 2006; **40:** 2170–7.
3. O'Brien A, *et al.* Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; **359:** 1209–10.

4. Morelli A, *et al.* Effects of terlipressin on systemic and regional haemodynamics in catecholamine-treated hyperkinetic septic shock. *Intensive Care Med* 2004; **30:** 597–604.
5. Leone M, *et al.* Terlipressin in catecholamine-resistant septic shock patients. *Shock* 2004; **22:** 314–19.
6. Jolley DH, *et al.* Terlipressin infusion in catecholamine-resistant shock. *Anaesth Intensive Care* 2003; **31:** 560–4.
7. Rodríguez-Núñez A, *et al.* Terlipressin for catecholamine-resistant septic shock in children. *Intensive Care Med* 2004; **30:** 477–80.

Variceal haemorrhage. Systematic review has indicated[1] that terlipressin is effective in the management of acute oesophageal variceal haemorrhage (see under Monoethanolamine, p.2346), and reduces the relative risk of mortality by about one-third. Differences in effectiveness from other therapies could not be conclusively shown. Comparison of a regimen of terlipressin given by intravenous bolus injection, plus glyceryl trinitrate given sublingually, with balloon tamponade in variceal bleeding has suggested similar efficacy.[2] However, tamponade was successful in all patients that were previously unresponsive to terlipressin plus glyceryl trinitrate whereas this drug combination failed in all patients previously unresponsive to tamponade. A comparison of terlipressin and endoscopic injection sclerotherapy found them to be equally effective for the control of acute variceal bleeding.[3]

1. Ioannou G, *et al.* Terlipressin for acute esophageal variceal hemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
2. Fort E, *et al.* A randomized trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute variceal hemorrhage. *Hepatology* 1990; **11:** 678–81.
3. Escorsell À, *et al.* Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology* 2000; **32:** 471–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Glycylpressin; ***Austria:*** Glycylpressin; Haemopressin; ***Belg.:*** Glypressin; ***Braz.:*** Glypressin†; ***Cz.:*** Glypressin; Remestyp; ***Denm.:*** Glypressin; ***Fin.:*** Glypressin; ***Fr.:*** Glypressine; ***Ger.:*** Glycylpressin; Haemopressin; ***Gr.:*** Glypressin; ***Hong Kong:*** Glypressin; ***Hung.:*** Glypressin; ***Irl.:*** Glypressin; ***Ital.:*** Glipressina; ***Malaysia:*** Glypressin; ***Mex.:*** Glyverase; ***Neth.:*** Glypressin; ***Pol.:*** Remestyp; ***Rus.:*** Remestyp (Реместип)†; ***Singapore:*** Glypressin; ***Spain:*** Glypressin; ***Switz.:*** Glypressine; ***Thai.:*** Glypressin; ***Turk.:*** Glypressin; ***UK:*** Glypressin.

Terpineol

$C_{10}H_{18}O$ = 154.2.
CAS — 8000-41-7 (terpineol); 98-55-5 (α-terpineol).

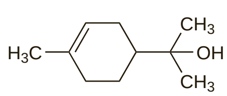

Pharmacopoeias. In *Br.*

BP 2008 (Terpineol). A mixture of structural isomers in which α-terpineol predominates. It is a colourless, slightly viscous liquid which may deposit crystals; it has a pleasant characteristic odour. Very slightly soluble in water; freely soluble in alcohol (70%); soluble in ether.

Profile

Terpineol has disinfectant and solvent properties. It is used with other volatile agents in preparations for respiratory-tract disorders.

Preparations

BP 2008: Chloroxylenol Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Aseptobron; Aseptobron Ampicilina†; Atomo Desinflamante; Atomo Desinflamante Familiar; Atomo Desinflamante G; Bronco Etersan; Di-Neumobron; ***Austral.:*** Karvol†; Tixylix Chest Rub†; ***Braz.:*** Bromil; Eucaliptan†; Mentalol†; Penetro; Tabletes Valda†; Valda†; ***Cz.:*** Coldastop; ***Fr.:*** Nazinette du Docteur Gilbert; Pectoderme†; Valda; ***Hong Kong:*** Valda†; ***India:*** Dettol Obstetric; Easi Breathe; Fairgenol†; Karvol Plus; Sinarest Vapocaps; ***Irl.:*** Karvol; Valda†; ***Israel:*** Gargol; Karvol; Rexitol; ***Ital.:*** Calyptol; Rikospray; Skab 2; ***NZ:*** Tixylix Chest Rub; ***Port.:*** Valda†; ***S.Afr.:*** AF; Karvol; ***Singapore:*** Karvol; ***Spain:*** Caltoson Balsamico; Eupnol; Pastillas Juanola†; ***Switz.:*** Perskindol Classic; Sedotussin†; ***UK:*** Chymol; Jacksons Mentholated Balm; Karvol; Nowax; Waxwane†.

Tesmilifene Hydrochloride *(USAN, rINNM)*

BMS-217380-01; BMY-33419; DPPE; Hidrocloruro de tesmilifeno; Tesmilifène, Chlorhydrate de; Tesmilifeni Hydrochloridum. 2-[(α-Phenyl-*p*-tolyl)oxy]triethylamine hydrochloride; *N,N*-Diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine hydrochloride.

Тезмилифена Гидрохлорид

$C_{19}H_{25}NO,HCl$ = 319.9.
CAS — 98774-23-3 (tesmilifene); 92981-78-7 (tesmilifene hydrochloride).

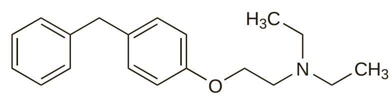

(tesmilifene)

Profile

Tesmilifene hydrochloride is an intracellular histamine antagonist that appears to augment the antineoplastic activity of drugs such as the anthracyclines and taxanes. It is under investigation for the treatment of various cancers, including hormone-refractory cancer of the prostate and gastric and hepatic cancers.

◊ References.

1. Reyno L, *et al.* Phase III study of N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA19. *J Clin Oncol* 2004; **22:** 269–76.
2. Raghavan D, *et al.* Phase II trial of tesmilifene plus mitoxantrone and prednisone for hormone refractory prostate cancer: high subjective and objective response in patients with symptomatic metastases. *J Urol (Baltimore)* 2005; **174:** 1808–13.

Tetrabenazine *(BAN, rINN)*

Ro-1-9569; Tetrabenatsiini; Tetrabenazin; Tetrabenazina; Tétrabénazine; Tetrabenazinum. 1,3,4,6,7,11b-Hexahydro-3-isobutyl-9,10-dimethoxybenzo-[*a*]quinolizin-2-one.

Тетрабеназин

$C_{19}H_{27}NO_3$ = 317.4.
CAS — 58-46-8.
ATC — N07XX06.
ATC Vet — QN07XX06.

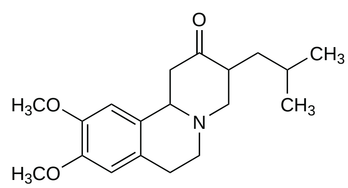

Adverse Effects

Drowsiness is the most frequent adverse effect of tetrabenazine. Orthostatic hypotension, symptoms of extrapyramidal dysfunction, gastrointestinal disturbances, and depression may also occur. Neuroleptic malignant syndrome and parkinsonism have been reported rarely. Overdosage has produced sedation, sweating, hypotension, and hypothermia.

Effects on mental function. Depression is well documented as an adverse effect of tetrabenazine, and occurs in about 15% of patients; it has been reported to respond to reboxetine.[1] Florid psychiatric symptoms such as panic attacks and obsessive-compulsive symptoms may be precipitated or exacerbated by tetrabenazine.[2]

1. Schreiber W, *et al.* Reversal of tetrabenazine induced depression by selective noradrenaline (norepinephrine) reuptake inhibition. *J Neurol Neurosurg Psychiatry* 1999; **67:** 550.
2. Bruneau MA, *et al.* Catastrophic reactions induced by tetrabenazine. *Can J Psychiatry* 2002; **47:** 683.

Extrapyramidal disorders. Dysphagia and choking were associated with tetrabenazine in the treatment of Huntington's chorea.[1] Fatal pneumonia, probably as a consequence of aspiration, had also been reported.

1. Snaith RP, Warren H de B. Treatment of Huntington's chorea with tetrabenazine. *Lancet* 1974; **i:** 413–14.

Overdosage. A patient who swallowed about 1 g (40 tablets) of tetrabenazine became drowsy 2 hours later and marked sweating occurred.[1] Her state of consciousness improved after 24 hours and she talked rationally and gained full control of micturition after 72 hours.

1. Kidd DW, McLellan DL. Self-poisoning with tetrabenazine. *Br J Clin Pract* 1972; **26:** 179–80.

Precautions

Tetrabenazine may exacerbate the symptoms of parkinsonism. It may cause drowsiness; affected patients should not drive or operate machinery.

Interactions

Tetrabenazine has been reported to block the action of reserpine. It may also diminish the effects of levodopa and exacerbate the symptoms of parkinsonism. Use of tetrabenazine immediately after a course of an MAOI may lead to confusion, restlessness, and disorientation; tetrabenazine should not be given with, or within 14 days of stopping, such therapy.

Pharmacokinetics

Absorption of tetrabenazine is poor and erratic after oral doses. It appears to be extensively metabolised by first-pass metabolism. Its major metabolite, hydroxytetrabenazine, which is formed by reduction, is reported to be as active as the parent compound. It is excreted in the urine mainly in the form of metabolites.

Uses and Administration

Tetrabenazine is used in the management of movement disorders including chorea (p.953), ballism (p.953), dystonias (p.809), tardive dyskinesia (see under Extrapyramidal Disorders, p.971), and similar symptoms of CNS dysfunction.

For the treatment of chorea, ballism, and other organic CNS movement disorders, a starting oral dose of 25 mg three times daily has been recommended; the *BNF* considers a dose of 12.5 mg twice daily (or 12.5 mg daily in the elderly) more appropriate initially, which is less likely to cause excessive sedation. The dose may be gradually increased by 25 mg daily every 3 or 4 days according to response up to a maximum of 200 mg daily. If the patient does not respond within 7 days of receiving the maximum dose further treatment with tetrabenazine is unlikely to be of benefit.

For moderate to severe tardive dyskinesia, a dose of 12.5 mg daily is recommended initially, subsequently titrated according to response.

Extrapyramidal disorders. In a long-term study[1] of the use of tetrabenazine in 400 patients with movement disorders, the best responses seemed to be in tardive dyskinesia, tardive dystonia, and Huntington's disease but benefit was also obtained in some patients with idiopathic dystonia, segmental myoclonus, and Tourette's syndrome. Others have commented that in severe dystonia unresponsive to other drugs a combination of tetrabenazine with trihexyphenidyl and pimozide is sometimes effective.[2] Tetrabenazine significantly reduced chorea in ambulatory patients with Huntington's disease in a small 12-week randomised placebo-controlled study.[3] It was well tolerated, although there was a significant increase in reports of drowsiness and insomnia, which generally resolved with adjustment of doses.

1. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997; **48:** 358–62.
2. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; **66:** 366–72.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Nitoman; ***Denm.:*** Nitoman; ***Fr.:*** Xenazine; ***India:*** Revocon; ***Irl.:*** Nitoman; ***Israel:*** Xenazine; ***NZ:*** Xenazine; ***Port.:*** Nitoman; Revocon; ***UK:*** Xenazine.

Tetrachlorodecaoxide

TCDO; Tetrachlorodecaoxygen Anion Complex; Tetraclorodecaóxido; WF-10.

Cl_4O_{10} = 301.8.
CAS — 92047-76-2.

Profile

Tetrachlorodecaoxide is a water-soluble anion complex containing oxygen in a chlorite matrix. Active oxygen is only released in the presence of biological material. It has been applied as a solution for the stimulation of wound healing.

Wounds. Tetrachlorodecaoxide was reported to promote wound healing compared with saline in a double-blind study of 271 patients,[1] but a smaller study failed to show any benefit over glycerol.[2]

1. Hinz J, *et al.* Rationale for and results from a randomised, double-blind trial of tetrachlorodecaoxygen anion complex in wound healing. *Lancet* 1986; **i:** 825–8.
2. Hughes LE, *et al.* Failure of tetrachlorodecaoxygen anion complex to assist wound healing. *Lancet* 1989; **ii:** 1271.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Oxilium; ***Indon.:*** Oxoferin; ***Port.:*** Oxoferin; ***Switz.:*** Oxilium†; ***Thai.:*** Immunokine; Oxoferin; ***Venez.:*** Oxoferin.

Tetramethylammonium Iodide

Tetrametilamonio, ioduro de.

$C_4H_{12}IN$ = 201.0.
CAS — 75-58-1.

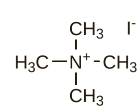

Profile

Tetramethylammonium iodide is a quaternary ammonium compound that has been used for the emergency disinfection of drinking water. It has also been employed for its ganglion-blocking properties.

Thalidomide *(BAN, USAN, rINN)*

E-217; K-17; NSC-66847; Talidomid; Talidomida; Talidomidi; Thalidomidum. 2-Phthalimidoglutarimide.

Талидомид

$C_{13}H_{10}N_2O_4$ = 258.2.
CAS — 50-35-1.
ATC — L04AX02.
ATC Vet — QL04AX02.

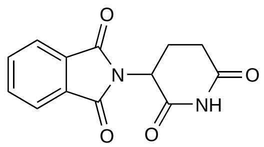

Pharmacopoeias. In *US*.

USP 31 (Thalidomide). A white to off-white powder. Sparingly soluble in water, in dehydrated alcohol, in acetone, in butyl acetate, in ethyl acetate, in glacial acetic acid, and in methyl alcohol; practically insoluble in chloroform, in ether, and in benzene; very soluble in dimethylformamide, in dioxan, and in pyridine. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Thalidomide was withdrawn from use as a hypnotic in the early 1960s after it was discovered that it produced teratogenic effects when given in early pregnancy. These effects, which could develop after a single dose, involved mainly malformations of the limbs and defects of the ears, eyes, and internal organs. Death at or shortly after birth was also common. Further abnormalities and problems, including effects on the CNS, developed in later life.

Thalidomide was reintroduced in 1998 for use as an immunomodulator but because of its severe teratogenic effects, it should not be used in women of child-bearing potential, or if such use is absolutely essential then stringent contraceptive measures must be used, including the simultaneous use of 2 reliable forms of contraception for at least 4 weeks before, during, and for 4 weeks after, thalidomide therapy. A pregnancy test must be carried out no longer than 24 hours before starting thalidomide treatment, and regular tests carried out during treatment. If pregnancy occurs during thalidomide therapy the drug must be stopped immediately and the patient given appropriate evaluation and counselling. As thalidomide is present in semen, male patients receiving thalidomide should use barrier methods of contraception even after successful vasectomy if their partner is of child-bearing potential. Patients should not donate blood or sperm during thalidomide therapy.

The other major adverse effect of thalidomide is peripheral neuropathy, which can be severe and irreversible.

Venous thromboembolism has been reported in a significant number of patients receiving thalidomide for multiple myeloma, particularly in those also receiving chemotherapeutic drugs, including dexamethasone.

Other common adverse effects include constipation, dizziness, and orthostatic hypotension. Drowsiness or somnolence occur frequently and, if affected, patients should not drive or operate machinery. Hypersensitivity reactions have occurred. An erythematous macular rash may develop, usually 2 to 10 days after initiation of therapy. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported, and therefore thalidomide should be stopped if skin rash develops and only restarted after appropriate clinical evaluation. Thalidomide therapy should not be resumed if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Bradycardia, neutropenia, and an increase in the viral load in HIV-infected patients have also been reported; thalidomide therapy should not be started in neutropenic patients.

Although human data for breast feeding while taking thalidomide are lacking, licensed product information recommends that it should be avoided in view of the potential for serious adverse effects in the infant.

◊ Reviews.

1. Günzler V. Thalidomide in human immunodeficiency virus (HIV) patients: a review of safety considerations. *Drug Safety* 1992; **7:** 116–34.
2. Clark TE, *et al.* Thalomid (thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
3. Grover JK, *et al.* The adverse effects of thalidomide in relapsed and refractory patients of multiple myeloma. *Ann Oncol* 2002; **13:** 1636–40.
4. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. *J Support Oncol* 2003; **1:** 194–205.
5. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. *Am J Med* 2004; **117:** 508–15.
6. Uhl K, *et al.* Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Safety* 2006; **29:** 321–9.

The symbol † denotes a preparation no longer actively marketed

Effects on the blood. Thrombocytopenia has been reported in patients given thalidomide for multiple myeloma.[1,2]

1. Duyvendak M, *et al.* Thalidomide-associated thrombocytopenia. *Ann Pharmacother* 2005; **39:** 1936–9.
2. Prasad HK, *et al.* Isolated thrombocytopenia induced by thalidomide in a patient with multiple myeloma: case report and review of literature. *Am J Hematol* 2007; **82:** 855–7.

Effects on the cardiovascular system. Use of thalidomide in patients with malignant neoplastic disease has been associated with an increased risk of deep-vein thrombosis. There were 27 spontaneous reports of thromboembolic events in the first 18 months of thalidomide returning to the US market in July 1998; 26 of these were in patients with malignancies.[1] A review[2] of thromboembolic events associated with thalidomide identified 67 such reports from a total of 2075 adverse events reported to the FDA between October 1998 and June 2001; a further 29 cases were identified from clinical study data. Deep-vein thrombosis occurred in 48 of these patients, pulmonary embolism in 25, and 23 developed both. The most common primary diagnoses among these patients were multiple myeloma and renal cell carcinoma. However, it should be noted that patients with cancer are known to be at increased risk of venous thromboembolism and some chemotherapeutic regimens may further increase this risk. The contribution of thalidomide to the development of venous thromboembolism remains to be fully evaluated in controlled studies. Further reviews[3,4] of reports of venous thromboembolism associated with thalidomide concluded that the incidence of venous thromboembolism in patients with multiple myeloma is higher when thalidomide is given with chemotherapeutic drugs such as dexamethasone, melphalan, or doxorubicin.

Studies suggest that prophylactic use of a low-molecular-weight heparin (enoxaparin),[5] aspirin,[6] or warfarin[7] may reduce the incidence of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapeutic drugs.

Bradycardia has been associated with thalidomide therapy in some patients, although symptoms may be managed by a reduction in dose.[8,9] See also under Effects on the Endocrine System, below.

1. Clark TE, *et al.* Thalomid (thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
2. Bennett CL, *et al.* Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med* 2002; **113:** 603–6.
3. Bennett CL, *et al.* Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 2006; **296:** 2558–60.
4. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1549–51.
5. Zangari M, *et al.* Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br J Haematol* 2004; **126:** 715–21.
6. Baz R, *et al.* The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1568–74.
7. Ikhlaque N, *et al.* Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol* 2006; **81:** 420–2.
8. Coutsouvelis J, Corallo CE. Thalidomide-induced bradycardia and its management. *Med J Aust* 2004; **180:** 366–7.
9. Fahdi IE, *et al.* Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol* 2004; **93:**1052–5.

Effects on the endocrine system. Amenorrhoea has been reported[1,2] in women taking thalidomide for severe dermatological conditions; menses resumed 2 to 3 months after stopping thalidomide.[2]

Hypothyroidism has been associated with thalidomide use in patients with multiple myeloma,[3,4] and it was suggested[3] that some adverse effects of thalidomide, such as bradycardia and constipation, may be manifestations of hypothyroidism.

Severe hyperglycaemia has been reported[5] in a 70-year-old man 4 weeks after starting thalidomide for multiple myeloma. Plasma-glucose concentrations returned to normal after treatment with insulin and an oral antidiabetic and he continued with thalidomide therapy.

1. Passeron T, *et al.* Thalidomide-induced amenorrhoea: two cases. *Br J Dermatol* 2001; **144:** 1292–3.
2. Francès C, *et al.* Transient secondary amenorrhea in women treated by thalidomide. *Eur J Dermatol* 2002; **12:** 63–5.
3. Badros AZ, *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am J Med* 2002; **112:** 412–13.
4. de Savary N, *et al.* Severe hypothyroidism after thalidomide treatment. *J R Soc Med* 2004; **97:** 443.
5. Pathak RD, *et al.* Thalidomide-associated hyperglycemia and diabetes: case report and review of literature. *Diabetes Care* 2003; **26:** 1322–3.

Effects on the gastrointestinal tract. Bowel perforation requiring surgery has been reported[1] in 3 patients taking thalidomide for malignant neoplasms. A fourth case of acute abdominal pain and suspected bowel perforation is also described but the patient died of a cardiac arrest before surgery.

1. McClay H, Cervi P. Thalidomide and bowel perforation: four cases in one hospital. *Br J Haematol* 2008; **140:** 360–1.

Effects on the liver. Hepatitis has been reported[1] in a 58-year-old woman taking thalidomide for end-stage plasma cell leukaemia. In another report of hepatotoxicity,[2] a 76-year-old woman with multiple myeloma being treated with thalidomide and dexamethasone developed jaundice and acute increases in liver enzymes, which returned to normal when thalidomide was stopped. Fatal fulminant hepatic failure with encephalopathy that appeared to be associated with thalidomide developed in a 64-year-old woman being treated for multiple myeloma.[3]

1. Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am J Hematol* 2001; **66:** 300–2.
2. Hanje AJ, *et al.* Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 2006; **26:** 1018–22.
3. Hamadani M, *et al.* Thalidomide-induced fulminant hepatic failure. *Mayo Clin Proc* 2007; **82:** 638.

Effects on the lungs. Interstitial pneumonitis has been reported in a patient taking thalidomide for multiple myeloma.[1] There have also been reports of dyspnoea in women taking thalidomide for ovarian cancer; resolution of symptoms occurred on drug withdrawal and some patients were able to continue therapy when reintroduced at a reduced dose.[2]

1. Onozawa M, *et al.* Thalidomide-induced interstitial pneumonitis. *J Clin Oncol* 2005; **23:** 2425–6.
2. Gordinier ME, Dizon DS. Dyspnea during thalidomide treatment for advanced ovarian cancer. *Ann Pharmacother* 2005; **39:** 962–5.

Effects on mental function. Symptoms of dementia appeared in a patient who had been taking thalidomide for about 2 months for the treatment of multiple myeloma.[1] Dementia later resolved completely within 48 hours of stopping thalidomide.

1. Morgan AE, *et al.* Reversible dementia due to thalidomide therapy for multiple myeloma. *N Engl J Med* 2003; **348:** 1821–2.

Effects on the nervous system. Peripheral neuropathy is a major adverse effect of thalidomide therapy, although the underlying mechanisms, risk factors, and optimum management are still not clear.[1] One prospective study[2] in patients with cutaneous or systemic lupus erythematosus concluded that the cumulative dose of thalidomide had no effect on the incidence of peripheral neuropathy, whereas results from a retrospective study[3] in patients with SLE or multiple myeloma showed that the risk of developing neurotoxicity as well as severity of symptoms did correlate with cumulative dose. However, the latter study[3] examined a range of doses and found that this correlation was most significant at cumulative doses over 20 g but either absent or equivocal at lower doses, which might explain the discrepancies in results between studies using different doses. Two further studies[4,5] in patients with multiple myeloma concluded that neurotoxicity was associated with duration of treatment of greater than 6 to 12 months rather than dose-intensity or total cumulative dose. Conversely, another study,[6] also in multiple myeloma patients, found electrophysiologic evidence of peripheral neuropathy in two-thirds of patients as early as 4 months from the start of treatment, and in all of them by 7 months; many patients also had clinical symptoms.

Central neurotoxicity has also been reported[7] in a patient who developed encephalopathy after receiving thalidomide monotherapy for multiple myeloma over 21 months.

1. Apfel SC, Zochodne DW. Thalidomide neuropathy: too much or too long? *Neurology* 2004; **62:** 2158–9.
2. Briani C, *et al.* Thalidomide neurotoxicity: prospective study in patients with lupus erythematosus. *Neurology* 2004; **62:** 2288–90.
3. Cavaletti G, *et al.* Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. *Neurology* 2004; **62:** 2291–3.
4. Tosi P, *et al.* Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol* 2005; **74:** 212–16.
5. Mileshkin L, *et al.* Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 2006; **24:** 4507–14.
6. Plasmati R, *et al.* Neuropathy in multiple myeloma treated with thalidomide: a prospective study. *Neurology* 2007; **69:** 573–81.
7. Sohlbach K, *et al.* Encephalopathy in a patient after long-term treatment with thalidomide. *J Clin Oncol* 2006; **24:** 4942–4.

Effects on sexual function. Dose-related sexual dysfunction, including loss of libido, loss of penile rigidity, and premature ejaculation, was associated with thalidomide use in 2 male patients.[1] Erectile dysfunction has been reported[2] in 6 patients within 4 weeks of starting thalidomide therapy.

1. Pouaha J, *et al.* Thalidomide and sexual dysfunction in men. *Br J Dermatol* 2002; **146:** 1112–13.
2. Murphy PT, O'Donnell JR. Thalidomide induced impotence in male hematology patients: a common but ignored complication? *Haematologica* 2007; **92:** 1440.

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a 62-year-old woman about 5 weeks after starting thalidomide for the treatment of a glioblastoma. Although she was taking several other drugs, including dexamethasone, thalidomide was considered responsible since its use had the closest temporal relationship to the adverse effect. Toxic epidermal necrolysis has also been reported[2] in a 64-year-old patient 24 days after starting thalidomide and dexamethasone for myeloma. It was suggested that there might be an adverse interaction between thalidomide and dexamethasone. Thalidomide had previously been studied[3] for the *treatment* of toxic epidermal necrolysis, but the study was prematurely terminated because of significantly higher mortality in the thalidomide group; the causes of death were those usually attributed to the disease itself. Thalidomide had been chosen as an investigative drug because it is a potent inhibitor of TNF-α, which has been implicated in the pathogenesis of this condition. However, the authors noted that there was a tendency for plasma concentrations of TNF-α to increase after treatment with thalidomide compared with the placebo group, and postulated that thalidomide might paradoxically enhance TNF-α production in these patients.

Exacerbation of psoriasis by thalidomide, reported, in 2 patients might also have been due to an increase in TNF-α production.[4,5]

In an open-label study in 87 patients with multiple myeloma[6] comparing thalidomide given as monotherapy or given with dexamethasone, minor to moderate skin eruptions were noted in about 45% of patients in each group, and included morbilliform, seborrhoeic, maculopapular, and non-specific dermatitis. Three patients receiving thalidomide and dexamethasone developed severe skin reactions (exfoliative erythroderma, erythema multiforme, or toxic epidermal necrolysis) that required treatment to be stopped.

1. Horowitz SB, Stirling AL. Thalidomide-induced toxic epidermal necrolysis. *Pharmacotherapy* 1999; **19:** 1177–80.
2. Rajkumar SV, *et al.* Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000; **343:** 972–3.
3. Wolkenstein P, *et al.* Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352:** 1586–9.
4. Dobson CM, Parslew RA. Exacerbation of psoriasis by thalidomide in Behçet's syndrome. *Br J Dermatol* 2003; **149:** 432–3.
5. Varma K, Finlay AY. Exacerbation of psoriasis by thalidomide in a patient with erythema multiforme. *Br J Dermatol* 2006; **154:** 789–90.
6. Hall VC, *et al.* Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48:** 548–52.

Migraine. Migraine attacks were associated with thalidomide use in a 36-year-old man.[1]

1. García-Albea E, *et al.* Jaqueca típica y talidomida. *Med Clin (Barc)* 1993; **100:** 557.

Mutagenicity. Reports of the birth of 3 malformed infants to parents who had themselves been exposed to thalidomide *in utero*[1,2] provoked fears that thalidomide may be a mutagen. However, the limb malformations seen in the infants were not typical of mutagenesis[3] and the teratogenic effect of thalidomide was likely to be associated with interference with angiogenesis in the fetus rather than mutation.[4] Review[5] of the evidence up to 1998 concluded that there was no scientific basis for the hypothesis that thalidomide is a mutagen and birth defects appeared to be no more common in children born to thalidomide-affected parents than in the population as a whole. Further support for the counter-argument came in 2002 from a Swedish retrospective study in which malformations or functional anomalies consistent with thalidomide embryopathy were not found in 64 children born to 34 parents with thalidomide embryopathy.[6]

1. McBride WG. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1635–6.
2. Tenconi R, *et al.* Amniotic band sequence in child of thalidomide victim. *BMJ* 1994; **309:** 1442.
3. Read AP. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1636.
4. D'Amato RJ, *et al.* Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; **91:** 4082–5.
5. Smithells D. Does thalidomide cause second generation birth defects? *Drug Safety* 1998; **19:** 339–41.
6. Strömland K, *et al.* Offspring of male and female parents with thalidomide embryopathy: birth defects and functional anomalies. *Teratology* 2002; **66:** 115–21.

Interactions

The sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine has been reported to be enhanced by thalidomide. Use with other drugs that have the potential to cause peripheral neuropathy should be undertaken cautiously.

Antineoplastics. There may be an increased risk of deep-vein thrombosis from the use of thalidomide with *doxorubicin* (see p.714). See also Effects on the Cardiovascular System, above.

For the effect of thalidomide on the metabolism of *irinotecan*, see under Interactions of Irinotecan, p.738.

Corticosteroids. For reference to a possible interaction between thalidomide and *dexamethasone*, see under Effects on the Skin, above.

Hormonal contraceptives. Thalidomide does *not* alter the metabolism of ethinylestradiol and norethisterone,[1,2] and so the efficacy of oral contraceptives should not be affected by thalidomide therapy. Nevertheless, 2 reliable forms of contraception should always be used simultaneously when taking thalidomide (see Adverse Effects and Precautions, above), bearing in mind that the reliability of hormonal contraceptives may be compromised by drugs other than thalidomide (see p.2067).

1. Trapnell CB, *et al.* Thalidomide does not alter the pharmacokinetics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 1998; **64:** 597–602.
2. Scheffler MR, *et al.* Thalidomide does not alter estrogen-progesterone hormone single-dose pharmacokinetics. *Clin Pharmacol Ther* 1999; **65:** 483–90.

Interferons. Neurological toxicity was reported[1] in 4 of 13 patients in a phase II study of thalidomide and interferon alfa-2a used together in the treatment of renal cell carcinoma. It was suggested that the membrane-destabilising properties of both drugs could have produced such serious toxicity since it exceeded that expected from either drug alone. A fifth patient experienced a Stevens-Johnson reaction that was also attributed to the combination. The study was halted as a result of these serious adverse effects.

Severe bone marrow depression has been reported[2] in a patient given thalidomide with peginterferon alfa-2b that was also attributed to the combined effect of the 2 drugs.

1. Nathan PD, *et al.* Unexpected toxicity of combination thalidomide and interferon alfa-2a treatment in metastatic renal cell carcinoma. *J Clin Oncol* 2002; **20:** 1429–30.
2. Gómez-Rangel JD, *et al.* Pegylated-interferon induced severe bone marrow hypoplasia in a patient with multiple myeloma receiving thalidomide. *Am J Hematol* 2003; **74:** 290–1.

Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract; peak plasma concentrations are reached within about 3 to 6 hours of an oral dose. It crosses the placenta and is distributed into the semen. The exact metabolic route and fate of thalidomide is unknown, although it appears to undergo non-enzymatic hydrolysis in plasma. The elimination half-life is about 5 to 7 hours.

◊ References.

1. Aweeka F, *et al.* Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. *J Clin Pharmacol* 2001; **41:** 1091–7.
2. Wohl DA, *et al.* Safety, tolerability, and pharmacokinetic effects of thalidomide in patients infected with human immunodeficiency virus: AIDS Clinical Trials Group 267. *J Infect Dis* 2002; **185:** 1359–63.
3. Teo SK, *et al.* Clinical pharmacokinetics of thalidomide. *Clin Pharmacokinet* 2004; **43:** 311–27.
4. Kamikawa R, *et al.* The pharmacokinetics of low-dose thalidomide in Japanese patients with refractory multiple myeloma. *Biol Pharm Bull* 2006; **29:** 2331–4.

Uses and Administration

Thalidomide has immunomodulating activity. It should always be given under appropriately supervised and controlled conditions because of the teratogenic risks and other potential adverse effects (see Adverse Effects and Precautions, above).

Thalidomide is used for the treatment of acute cutaneous manifestations of moderate to severe type 2 (erythema nodosum leprosum) lepra reactions (see Leprosy, p.176), but should not be given as monotherapy if moderate to severe neuritis is present; in such cases, corticosteroid therapy should also be given and continued until neuritis improves. Thalidomide may also be used for maintenance therapy for prevention and suppression of the cutaneous manifestations of recurrent type 2 lepra reactions. It is of no value in type 1 lepra reactions. It may be given orally in usual initial doses of 100 to 300 mg once daily. In severe cases up to 400 mg daily may be given. The dose should be reduced gradually by 50 mg every 2 to 4 weeks once a satisfactory response has been achieved. An alternative regimen is to start treatment with 100 mg once daily, and if symptoms are not controlled, increase the dose by increments of 100 mg at weekly intervals up to a maximum of 400 mg once daily.

Thalidomide is also used in the treatment of multiple myeloma (p.658) refractory to standard therapies. It is given orally in an initial dose of 200 mg once daily and, according to patient tolerance, the dose may be increased by 100 mg at weekly intervals up to a maximum dose of 800 mg daily. Thalidomide may be used with melphalan (p.742) and prednisone (p.1542) in patients with newly diagnosed multiple myeloma who are over 65 years of age or in those ineligible for high dose chemotherapy; thalidomide is given in a dose of 200 mg daily for a maximum of 12 cycles of 6 weeks each. Thalidomide may also be used with dexamethasone (p.1526) in the treatment of patients with newly diagnosed multiple myeloma: thalidomide 200 mg is given once daily; dexamethasone 40 mg is given orally on days 1 to 4, 9 to 12, and 17 to 20 in 28-day cycles.

Thalidomide should preferably be given at bedtime and at least 1 hour after the evening meal.

Thalidomide has been used in several other conditions whose aetiology may involve the immune system, such as treatment and prevention of graft-versus-host disease, treatment and prevention of recurrent aphthous stomatitis in severely and terminally immunocompromised patients, treatment of the clinical manifestations of both tuberculous and non-tuberculous mycobacterial infection, treatment of myelodysplastic syndrome and treatment of HIV-associated wasting syndrome, Kaposi's sarcoma, and Crohn's disease. It has also been used in the treatment of primary brain malignancies. Thalidomide is being investigated in some other malignancies.

◊ Guidelines on the clinical use of thalidomide.

1. Powell RJ, Gardner-Medwin JMM. Guideline for the clinical use and dispensing of thalidomide. *Postgrad Med J* 1994; **70:** 901–4.
2. Lary JM, *et al.* The return of thalidomide: can birth defects be prevented? *Drug Safety* 1999; **21:** 161–9.
3. Zeldis JB, *et al.* S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther* 1999; **21:** 319–30. Further information available at: http://www.thalomid.com/steps_program.aspx (accessed 27/05/08)
4. Chave TA, *et al.* All-Wales Dermatology Audit Committee. Thalidomide usage in Wales: the need to follow guidelines. *Br J Dermatol* 2001; **144:** 310–15.

Action. The mechanism of action of thalidomide is not completely understood, although investigations have shown that it has anti-inflammatory and immunomodulating effects, including inhibition of the synthesis of tumour necrosis factor (TNF)-α. However, this inhibition is incomplete and selective, and increased plasma-TNF-α concentrations have been seen in some patient groups. Other immunomodulatory and anti-inflammatory properties include inhibition of leucocyte chemotaxis into the site of inflammation and reduction of phagocytosis by polymorphonuclear leucocytes. Thalidomide also appears to modulate interleukins, although results of investigations into its effect on specific interleukins and interferon gamma have so far been equivocal. Effects on CD4+ cells and variable effects on other mediators of intercellular reactions have also been implicated. Thalidomide also inhibits angiogenesis, which may have implications in solid tumours and other diseases.

General references to the mechanism of action and uses of thalidomide.[1-8]

1. Schuler U, Ehninger G. Thalidomide: rationale for renewed use in immunological disorders. *Drug Safety* 1995; **12:** 364–9.
2. Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med* 2000; **108:** 487–95.
3. Peuckmann V, *et al.* Potential novel uses of thalidomide: focus on palliative care. *Drugs* 2000; **60:** 273–92.
4. Franks ME, *et al.* Thalidomide. *Lancet* 2004; **363:** 1802–11.
5. Rajkumar SV. Thalidomide: tragic past and promising future. *Mayo Clin Proc* 2004; **79:** 899–903.
6. Joglekar S, Levin M. The promise of thalidomide: evolving indications. *Drugs Today* 2004; **40:** 197–204.
7. Bessmertny O, Pham T. Thalidomide use in pediatric patients. *Ann Pharmacother* 2002; **36:** 521–5.
8. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 2005; **7:** E14–E19.

Behçet's syndrome. Thalidomide was effective for the treatment of oral and genital ulceration and follicular lesions in a randomised, double-blind, placebo-controlled study[1] in 96 male patients with Behçet's syndrome (p.1499). It was also noted that the development of new oral and genital ulcers was prevented, although relapses may occur on cessation of therapy. Thalidomide has also been reported[2,3] to be of benefit for severe oral and genital ulceration in children with Behçet's syndrome unresponsive to other treatments. Thalidomide also improved symptoms in a woman with Behçet's syndrome who had recurrent perforating intestinal ulcers.[4]

1. Hamuryudan V, *et al.* Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128:** 443–50.
2. Shek LP-C, *et al.* Thalidomide responsiveness in an infant with Behçet's syndrome. *Pediatrics* 1999; **103:** 1295–7.
3. Kari JA, *et al.* Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology (Oxford)* 2001; **40:** 933–8.
4. Sayarlioglu M, *et al.* Treatment of recurrent perforating intestinal ulcers with thalidomide in Behçet's disease. *Ann Pharmacother* 2004; **38:** 808–11.

Cachexia. For the use of thalidomide in HIV-associated wasting, see HIV-associated Complications, below, and in cancer-related cachexia, see Malignant Neoplasms, below.

Graft-versus-host disease. A review[1] of studies investigating the use of thalidomide in chronic graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p.1811) concluded that although thalidomide appeared to be of benefit in some patients unresponsive to other treatments, doses greater than 200 mg daily are poorly tolerated in most patients. Giving thalidomide as prophylaxis led to poor survival, possibly through interfering with development of tolerance. Thalidomide was not of benefit when given as treatment for newly diagnosed disease.

1. Flowers MED, Martin PJ. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma* 2003; **44:** 1141–6.

HIV-associated complications. It has been proposed that thalidomide's inhibitory activity against TNF-α may explain its anti-HIV effect. However, there are conflicting reports as both decreased and increased TNF-α levels, as well as unchanged levels, have been seen in HIV-patients.[1] Nevertheless, thalidomide has shown some promise as a therapeutic agent for some AIDS-related diseases. It is an effective treatment for severe ulceration of the mouth (p.1700), oropharynx, and oesophagus in patients with HIV-infection.[2-5] Thalidomide has also been tried with some success in HIV-infected patients with prurigo nodularis,[6] alopecia areata[7] (p.1577), and hypertrophic genital herpes[8] (p.854). It has also proved to be of benefit in HIV-associated wasting[9] (p.858), and has shown promise in high doses for the treatment of AIDS-related Kaposi's sarcoma[10] (p.675). However, of concern is the finding that modest increases in plasma HIV RNA levels have been seen in some patients, which correlated with increases in TNF-α levels.[2,4]

1. Ravot E, *et al.* New uses for old drugs in HIV infection: the role of hydroxyurea, cyclosporin and thalidomide. *Drugs* 1999; **58:** 953–63.
2. Jacobson JM, *et al.* Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med* 1997; **336:** 1487–93.
3. Ramirez-Amador VA, *et al.* Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis* 1999; **28:** 892–4.
4. Jacobson JM, *et al.* Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. *J Infect Dis* 1999; **180:** 61–7.
5. Shetty K. Thalidomide in the management of recurrent aphthous ulcerations in patients who are HIV-positive: a review and case reports. *Spec Care Dentist* 2005; **25:** 236–41.
6. Maurer T, *et al.* Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140:** 845–9.

7. Baranda L, *et al.* Severe and unresponsive HIV-associated alopecia areata successfully treated with thalidomide. *Acta Derm Venereol* 2005; **85:** 277–8.
8. Holmes A, *et al.* Thalidomide therapy for the treatment of hypertrophic herpes simplex virus-related genitalis in HIV-infected individuals. *Clin Infect Dis* 2007; **44:** e96–e99. Available at: http://www.journals.uchicago.edu/doi/abs/10.1086/517513 (accessed 18/01/08)
9. Reyes-Terán G, *et al.* Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled trial. *AIDS* 1996; **10:** 1501–7.
10. Little RF, *et al.* Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18:** 2593–2602.

Inflammatory bowel disease. Small open-label studies[1-3] have shown efficacy of thalidomide in patients with refractory Crohn's disease (see under Inflammatory Bowel Disease, p.1697). In many of those patients already receiving corticosteroids the dosage could be reduced and in some corticosteroids could be stopped completely. Reduction of TNF-α and interleukin-12 by thalidomide may be responsible for its clinical effects in Crohn's disease.[4] Thalidomide has also been reported[5] to be of benefit in children and young adults with intractable inflammatory bowel disease (both Crohn's disease and ulcerative colitis).

1. Ehrenpreis ED, *et al.* Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117:** 1271–7.
2. Vasiliauskas EA, *et al.* An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117:** 1278–87.
3. Bariol C, *et al.* Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17:** 135–9.
4. Bauditz J, *et al.* Thalidomide reduces tumour necrosis factor α and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50:** 196–200.
5. Lazzerini M, *et al.* Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther* 2007; **25:** 419–27.

Kaposi's sarcoma. See under HIV-associated complications, above and under Malignant Neoplasms, below.

Lupus erythematosus. Thalidomide has been found to be of benefit in lupus erythematosus, including chronic discoid lupus erythematosus,[1,2] lupus erythematosus profundus,[3,4] SLE[5] (p.1513), and cutaneous lupus erythematosus.[6-11] The beneficial effect of thalidomide on cutaneous lupus erythematosus may be partly mediated through protection against UV-induced inflammation.[11]

1. Knop J, *et al.* Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108:** 461–6.
2. Brocard A, *et al.* Lupus érythémateux chronique: traitement par thalidomide. *Ann Dermatol Venereol* 2005; **132:** 853–6.
3. Burrows NP, *et al.* Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125:** 62–7.
4. Wienert S, *et al.* Facetten des Lupus erythematodes: Pannikulitis mit gutem Ansprechen auf Thalidomid. *J Dtsch Dermatol Ges* 2008; **6** 214–16.
5. Bessis D, *et al.* Thalidomide for systemic lupus erythematosus. *Lancet* 1992; **339:** 549–50.
6. Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol* 1993; **11:** 487–93.
7. Stevens RJ, *et al.* Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in sixteen consecutive patients. *Br J Rheumatol* 1997; **36:** 353–9.
8. Duong DJ, *et al.* American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol* 1999; **135:** 1079–87.
9. Pelle MT, Werth VP. Thalidomide in cutaneous lupus erythematosus. *Am J Clin Dermatol* 2003; **4:** 379–87.
10. Cuadrado MJ, *et al.* Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med* 2005; **118:** 246–50.
11. Cummins DL, Gaspari AA. Photoprotection by thalidomide in patients with chronic cutaneous and systemic lupus erythematosus: discordant effects on minimal erythema dose and sunburn cell formation. *Br J Dermatol* 2004; **151:** 458–64.

Malignant neoplasms. Thalidomide has shown benefit in the treatment of patients with relapsed advanced multiple myeloma[1-4] (p.658) and also in patients with newly diagnosed disease;[4-8] the response improves when given with dexamethasone. Thalidomide also improved response when added to the regimen of pegylated liposomal doxorubicin, vincristine, and decreased frequency dexamethasone in patients with relapsed-refractory or newly diagnosed multiple myeloma,[9] and when added to melphalan and prednisone in newly-diagnosed elderly patients.[10,11] Thalidomide has also been investigated as maintenance treatment after intensive chemotherapy supported with haematopoietic stem-cell transplantation in patients with newly diagnosed disease;[12,13] thalidomide improved the response rate and event-free survival in both studies, although no improvement in overall survival was seen in one.[12] Thalidomide has also been tried in the treatment of several non-plasma cell malignancies with variable results.[14] It has shown promise in patients with recurrent high-grade gliomas[15] (p.660) and is under investigation for non-AIDS-related Kaposi's sarcoma[16,17] (p.675), metastatic melanoma[18] (p.673), myelofibrosis with myeloid metaplasia,[19-21] and androgen-independent prostate cancer[22,23] (p.671). Thalidomide has shown some benefit in the treatment of cancer-related cachexia (p.2115) in patients with pancreatic cancer.[24]

1. Singhal S, *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341:** 1565–71.
2. Rajkumar SV, *et al.* Thalidomide in the treatment of relapsed multiple myeloma. *Mayo Clin Proc* 2000; **75:** 897–901.
3. Kumar S, *et al.* Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. *Mayo Clin Proc* 2003; **78:** 34–9.
4. Palumbo A, *et al.* Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; **111:** 3968–77.
5. Rajkumar SV, *et al.* Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002; **20:** 4319–23.
6. Weber D, *et al.* Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 2003; **21:** 16–19.
7. Rajkumar SV, *et al.* Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006; **24:** 431–6.
8. Rajkumar SV, *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol* 2008; **26:** 2171–7.
9. Hussein MA, *et al.* Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. *Mayo Clin Proc* 2006; **81:** 889–95.
10. Palumbo A, *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367:** 825–31.
11. Facon T, *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 2007; **370:** 1209–18.
12. Barlogie B, *et al.* Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **354:** 1021–30.
13. Attal M, *et al.* Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108:** 3289–94.
14. Kumar S, *et al.* Thalidomid: current role in the treatment of non-plasma cell malignancies. *J Clin Oncol* 2004; **22:** 2477–88. Correction. *ibid.*; 2973. [title]
15. Fine HA, *et al.* Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18:** 708–15.
16. Ben M'barek L, *et al.* A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. *Dermatology* 2007; **215:** 202–5.
17. Rubegni P, *et al.* Thalidomide in the treatment of Kaposi's sarcoma. *Dermatology* 2007; **215:** 240–4.
18. Danson S, *et al.* Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003; **21:** 2551–7.
19. Mesa RA, *et al.* Durable responses to thalidomide-based drug therapy for myelofibrosis with myeloid metaplasia. *Mayo Clin Proc* 2004; **79:** 883–9.
20. Marchetti M, *et al.* Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol* 2004; **22:** 424–31.
21. Thomas DA, *et al.* Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 2006; **106:** 1974–84.
22. Figg WD. The 2005 Leon I. Goldberg Young Investigator Award Lecture: Development of thalidomide as an angiogenesis inhibitor for the treatment of androgen-independent prostate cancer. *Clin Pharmacol Ther* 2006; **79:** 1–8.
23. Cox MC, *et al.* The use of thalidomide in androgen-independent prostate cancer. *Urol Oncol* 2006; **24:** 246–9.
24. Gordon JN,*et al.* Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54:** 540–5.

Mouth ulceration. See under Behçet's syndrome, above and under HIV-associated complications, above.

Oesophageal ulceration. Thalidomide has been shown to be of benefit in the treatment of idiopathic oesophageal ulcers in patients with AIDS (see under HIV-associated complications, above). Thalidomide has also been reported to have healed an oesophageal ulcer refractory to other treatments in an immunocompetent patient,[1] and in an immunocompromised patient after liver transplant.[2]

1. Ollivier S, *et al.* Idiopathic giant oesophageal ulcer in an immunocompetent patient: the efficacy of thalidomide treatment. *Gut* 1999; **45:** 463–4.
2. Atiq M, *et al.* Successful treatment with thalidomide in a liver transplant recipient with giant esophageal ulcers. *Liver Transpl* 2006; **12:** 987–8.

Rheumatic disorders. Beneficial responses to thalidomide have been reported in the treatment of refractory rheumatoid arthritis[1] and adult-onset Still's disease.[2] Thalidomide also improved symptoms in 2 children with systemic onset juvenile rheumatoid arthritis, in whom other therapy, including etanercept, had been ineffective.[3] Efficacy was also shown in a further 11 children with refractory disease who were able to reduce their use of prednisone.[4]

1. Gutiérrez-Rodríguez O, *et al.* Treatment of refractory rheumatoid arthritis—the thalidomide experience. *J Rheumatol* 1989; **16:** 158–63.
2. Stambe C, Wicks IP. TNFα and response of treatment-resistant adult-onset Still's disease to thalidomide. *Lancet* 1998; **352:** 544–5.
3. Lehman TJA, *et al.* Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. *J Pediatr* 2002; **140:** 125–7.
4. Lehman TJ, *et al.* Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study. *J Pediatr* 2004; **145:** 856–7.

Sarcoidosis. Case reports[1-5] of thalidomide in the treatment of sarcoidosis suggest that it might be of benefit.

1. Carlesimo M, *et al.* Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995; **32:** 866–9.
2. Baughman RP, *et al.* Thalidomide for chronic sarcoidosis. *Chest* 2002; **122:** 227–32.
3. Walter MC, *et al.* Successful treatment of muscle sarcoidosis with thalidomide. *Acta Myol* 2003; **22:** 22–5.
4. Nguyen YT, *et al.* Treatment of cutaneous sarcoidosis with thalidomide. *J Am Acad Dermatol* 2004; **50:** 235–41.
5. Hammond ER, *et al.* Thalidomide for acute treatment of neurosarcoidosis. *Spinal Cord* 2007; **45:** 802–3.

Skin disorders. Thalidomide has shown efficacy in several severe dermatological disorders refractory to conventional therapies.[1,2] A review[3] of studies of thalidomide in the treatment of severe type 2 (erythema nodosum leprosum) lepra reactions concluded that it is an effective alternative to corticosteroid therapy. It has also been investigated in other severe skin disorders and beneficial responses have been reported in erythema multiforme[4,5] (p.1580), pruritus associated with uraemia,[6] Langerhans-cell histiocytosis[7] (p.650), epidermolysis bullosa and its variants,[8-10] prurigo nodularis,[11,12] pyoderma gangrenosum[13,14] (p.1583), and Schnitzler's syndrome.[15]

1. Wu JJ, *et al.* Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153:** 254–73.
2. Faver IR, *et al.* Thalidomide for dermatology: a review of clinical uses and adverse effects. *Int J Dermatol* 2005; **44:** 61–7.
3. Walker SL, *et al.* The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 2007; **78:** 197–215.
4. Bahmer FA, *et al.* Thalidomide treatment of recurrent erythema multiforme. *Acta Derm Venereol (Stockh)* 1982; **62:** 449–50.
5. Moisson YF, *et al.* Thalidomide for recurrent erythema multiforme. *Br J Dermatol* 1992; **126:** 92–3.
6. Silva SRB, *et al.* Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994; **67:** 270–3.
7. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48:** 44–9.
8. Goulden V, *et al.* Linear prurigo simulating dermatitis artefacta in dominant dystrophic epidermolysis bullosa. *Br J Dermatol* 1993; **129:** 443–6.
9. Ozanic Bulic S, *et al.* Thalidomide in the management of epidermolysis bullosa pruriginosa. *Br J Dermatol* 2005; **152:** 1332–4.
10. Strauss RM, *et al.* A child with laryngo-onychocutaneous syndrome partially responsive to treatment with thalidomide. *Br J Dermatol* 2006; **155:** 1283–6.
11. Ferrándiz C, *et al.* Sequential combined therapy with thalidomide and narrow-band (TL01) UVB in the treatment of prurigo nodularis. *Dermatology* 1997; **195:** 359–61.
12. Lan C-CE, *et al.* Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide. *J Dermatol* 2007; **34:** 237–42.
13. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. *Mayo Clin Proc* 2000; **75:** 842–4.
14. Koca E, *et al.* Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum. *Neth J Med* 2006; **64:** 422–4.
15. Worm M, Kolde G. Schnitzler's syndrome: successful treatment of two patients using thalidomide. *Br J Dermatol* 2003; **148:** 601–2.

Preparations

USP 31: Thalidomide Capsules.

Proprietary Preparations (details are given in Part 3)
India: Thalix; ***Mex.:*** Inmunoprin; Talizer; ***USA:*** Thalomid.

Thallium Acetate

Talio, acetato de; Thallous Acetate.

$C_2H_3O_2Tl = 263.4$.

CAS — 7440-28-0 (thallium); 563-68-8 (thallium acetate); 7446-18-6 (thallium sulfate).

Adverse Effects

Thallium salts are toxic when inhaled, ingested, or absorbed through the skin. Symptoms of poisoning may appear within 12 to 24 hours of a single toxic dose and include severe abdominal pain, nausea and vomiting, diarrhoea, gastrointestinal haemorrhage, salivation, metallic taste, paralytic ileus, pancreatic damage, and in severe cases cardiovascular collapse, tremors, delirium, convulsions, paralysis, and coma, leading to death in 1 to 2 days. However, the acute reaction may subside, to be followed within about 10 days by the development of neurological effects including paraesthesia, myalgia, myopathy, motor neuropathy, and visual disturbances due to optic neuropathy, psychosis, delirium, convulsions, and other signs of encephalopathy, tachycardia, hypertension, skin eruptions, and hepatorenal injury. Recovery from neurological damage is slow and may be incomplete. Alopecia occurs within 15 to 20 days; stomatitis may also develop. Death may result from respiratory failure; patients are also predisposed for several weeks to cardiac arrhythmias and sudden death. Fatalities have occurred after ingestion of 1 g or less in adults, although the UK Poisons Information Service consider the usual lethal dose by ingestion to be in the range 3 to 10 g in adults.

Smaller repeated doses are also toxic, with symptoms appearing over several weeks. Constipation is a common feature of less severe poisoning.

Poisoning. References.

1. Moeschlin S. Thallium poisoning. *Clin Toxicol* 1980; **17:** 133–46.
2. Heyl T, Barlow RJ. Thallium poisoning: a dermatological perspective. *Br J Dermatol* 1989; **121:** 787–92.
3. Luckit J, *et al.* Thrombocytopenia associated with thallium poisoning. *Hum Exp Toxicol* 1990; **9:** 47–8.
4. Moore D, *et al.* Thallium poisoning. *BMJ* 1993; **306:** 1527–9.
5. Tabandeh H, Thompson GM. Visual function in thallium toxicity. *BMJ* 1993; **307:** 324.
6. Questel F, *et al.* Thallium-contaminated heroin. *Ann Intern Med* 1996; **124:** 616.
7. Tromme I, *et al.* Skin signs in the diagnosis of thallium poisoning. *Br J Dermatol* 1998; **138:** 321–5.
8. Hoffman RS. Thallium poisoning during pregnancy: a case report and comprehensive literature review. *J Toxicol Clin Toxicol* 2000; **38:** 767–75.
9. Misra UK, *et al.* Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J* 2003; **79:** 103–5.
10. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
11. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.
12. Kuo H-C, *et al.* Acute painful neuropathy in thallium poisoning. *Neurology* 2005; **65:** 302–4.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion. Intensive supportive therapy is necessary.

Attempts have been made to increase the faecal and urinary excretion of thallium. A suspension of activated charcoal has been given to reduce intestinal absorption and enteric recycling. Prussian blue (p.1461) given orally as a drink or via a nasogastric tube is also used routinely. A purgative such as mannitol may be required with either activated charcoal or Prussian blue as constipation is common in severe thallium toxicity. Giving potassium chloride by mouth may mobilise thallium from the tissues but is hazardous, especially if given during the early stage as signs of poisoning may be aggravated. Traditional chelation therapy is not generally recommended for thallium poisoning.

Haemoperfusion, haemodialysis, or peritoneal dialysis have been reported to be effective in eliminating absorbed thallium, although clinical benefit is doubtful.

Uses and Administration

Thallium acetate was formerly used by mouth for depilation in ringworm and as an ingredient of depilatory creams but both systemic and local treatments have caused deaths, and it is no longer used for such purposes. It has also been used as a rodenticide and insecticide; thallium sulfate has been used similarly. The use of thallium salts is strictly regulated in many countries. However, use in industry could still constitute a hazard. Cases of malicious poisoning still occur occasionally.

Theobroma

Cacao or Cocoa Powder; Chocolate; Teobroma; Theobrom.

Pharmacopoeias. In *USNF.*

USNF 26 (Chocolate). A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* (Sterculiaceae).

Profile

Theobroma is used as a flavoured basis for tablets and lozenges. Theobroma oil (p.2033) is used as a basis for suppositories.

Breast feeding. The American Academy of Pediatrics[1] states that irritability or increased bowel activity have been reported in infants whose mothers ate excessive amounts of chocolate (16 ounces (about 450 g) or more daily).

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.* 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/07/04)

Preparations

USNF 26: Chocolate Syrup.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Asthmatee EF-EM-ES.

Theodrenaline Hydrochloride *(BANM, rINNM)* ⊗

H-8352; Hidrocloruro de teodrenalina; Noradrenaline Theophylline Hydrochloride; Théodrénaline, Chlorhydrate de; Theodrenalini Hydrochloridum. 7-[2-(3,4,β-Trihydroxyphenethylamino)ethyl]theophylline hydrochloride.

Теодреналина Гидрохлорид

$C_{17}H_{21}N_5O_5,HCl = 411.8.$

CAS — 13460-98-5 (theodrenaline); 2572-61-4 (theodrenaline hydrochloride).

ATC — C01CA23.

ATC Vet — QC01CA23.

Profile

Theodrenaline is mainly used as the hydrochloride in preparations with cafedrine promoted for the treatment of hypotension.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Akrinor; ***Fr.:*** Praxinor; ***Ger.:*** Akrinor†; ***S.Afr.:*** Akrinor; ***Spain:*** Bifort†.

Thioctic Acid

Acide thioctique; Acidum thiocticum; Alpha Lipoic Acid; Kwas tioktynowy; Kyselina thioktová; Lipoic Acid; α-Liponic Acid; Tióctico, ácido. 5-(1,2-Dithiolan-3-yl)valeric acid.

$C_8H_{14}O_2S_2 = 206.3.$

CAS — 62-46-4.

ATC — A16AX01.

ATC Vet — QA16AX01.

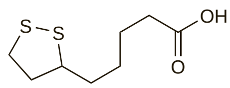

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Thioctic Acid). A yellow, crystalline powder. M.p. about 61°. Very slightly soluble in water; very soluble in dimethylformamide; freely soluble in methyl alcohol. Protect from light.

USP 31 (Alpha Lipoic Acid). M.p. 60.0° to 62.0°.

Profile

Thioctic acid is used for its antoxidant effects in the treatment of diabetic neuropathy. It has been tried in the treatment of liver dysfunction and in subacute necrotising encephalopathy. Beneficial results have been claimed in amanitin poisoning after ingestion of the mushroom *Amanita phalloides*, but such use is controversial (see under Poisonous Mushrooms or Toadstools, p.2349). Ethylenediamine thioctate, sodium thioctate, thioctic acid amide (thioctamide), and trometamol thioctate have been used similarly.

Diabetic neuropathy. References[1-5] to the benefits of thioctic acid in diabetic neuropathy.

1. Ziegler D, *et al.* Effects of treatment with the antioxidant α-lipoic acid on cardiac autonomic neuropathy in NIDDM patients: a 4-month randomized controlled multicenter trial (DEKAN study). *Diabetes Care* 1997; **20:** 369–73.
2. Ziegler D, *et al.* Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III study). *Diabetes Care* 1999; **22:** 1296–1301.
3. Ametov AS, *et al.* The sensory symptoms of diabetic polyneuropathy are improved with α-lipoic acid: the SYDNEY trial. *Diabetes Care* 2003; **26:** 770–6. Correction. *ibid.*; 2227.
4. Ziegler D, *et al.* Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis. *Diabet Med* 2004; **21:** 114–21.
5. Ziegler D, *et al.* Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care* 2006; **29:** 2365–70.

Pharmacokinetics. References.

1. Teichert J, *et al.* Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage renal disease. *J Clin Pharmacol* 2005; **45:** 313–28.

Preparations

USP 31: Alpha Lipoic Acid Capsules; Alpha Lipoic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Biletan; Ciagen; Neurotioct; Neutracol; Sigmus; Tioctan; ***Austria:*** Thioctacid; Tioctan; ***Cz.:*** Alpha-Lipon†; Thioctacid; Thiogamma; ***Ger.:*** Alpha-Lipogamma; Alpha-Lipon; alpha-Vibolex; Alphaflam; Azulipont†; Biomo-lipon; duralipon; espa-lipon†; Fenint†; Juthiac†; Neurium; Pleomix-Alpha†; Thioctacid; Thiogamma; Tromlipon; Verla-Lipon; Vitatrans; ***Hung.:*** Thioctacid; Thiogamma; ***Indon.:*** Alanox; Mecola Forte; ***Ital.:*** Tiobec Crema; ***Jpn:*** Tioctan†; ***Mex.:*** Thioctacid; ***Pol.:*** Neurex; Thiogamma; ***Rus.:*** Berlithion (Берлитион); Espa-Lipon (Эспа-липон); Thioctacid (Тиоктацид); Thiogamma (Тиогамма); ***Thai.:*** Lipoicin†.

Multi-ingredient: ***Arg.:*** Biletan Enzimatico; Carbogasol Digestivo; Co-Tioctan; Nervomax TB12; ***Canad.:*** Biotrim†; ***Hong Kong:*** Lipochol; ***India:*** Alcrin-M; ***Indon.:*** Alicron; Aptivium Liver Support; Mecola; Reliv; ***Ital.:*** Alfa Lip; Angiovein; Byodinoral; Depatox; Lipoacid Combi; Neuralfa; Neuroptic; Osteolip; Tiobec; Tiofort; ***Philipp.:*** Illumina; ***Port.:*** Lipoacid; Lipoacid Combi†; ***Spain:*** Policolinosil; ***Thai.:*** Lipochol.

Thiomucase

C-84-04; Chondroitinsulphatase; Tiomucasa.

Profile

Thiomucase is a mucopolysaccharidase with general properties similar to those of hyaluronidase, p.2321, but which also depolymerises chondroitin sulfate. It has been given to assist the diffusion of local anaesthetic injections.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Thiocase.

Multi-ingredient: ***Braz.:*** Thiomucase.

Thiotriazoline

Tiotriazolin. Morpholine 5-methyl-1,2,4-triazoline-5-thioacetate.

Тиотриазолин

Profile

Thiotriazoline is reported to have anti-ischaemic, membrane stabilising, and antoxidant actions. It is used as a hepatoprotectant in various liver disorders and as a protectant in cardiovascular and cerebrovascular disorders. It is also used locally as an anti-inflammatory for wounds and lesions of the skin and mucous membranes and for vaginal or rectal inflammation.

Thiram *(USAN, rINN)*

NSC-1771; SQ-1489; Thirame; Thiramum; Tiram; Tiramo; TMT; TMTD. Tetramethylthiuram disulphide.

Тирам

$C_6H_{12}N_2S_4 = 240.4.$

CAS — 137-26-8.

ATC — P03AA05.

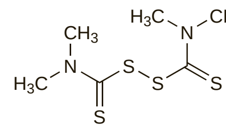

Profile

Thiram, the methyl analogue of disulfiram (p.2296), has antibacterial and antifungal activity. It has been applied topically as an aerosol in the treatment of wounds and other skin disorders. It has been used as a fungicide in agriculture, and in industry as a rubber accelerator. Occupational exposure to thiram may cause irritation of mucous membranes and skin.

Thorium Dioxide

Thorium Oxide; Torio, dióxido de.

$ThO_2 = 264.0.$

CAS — 1314-20-1.

Profile

Colloidal solutions of thorium dioxide were formerly used as X-ray contrast media for examination of the liver and spleen, for arteriography, and occasionally for outlining the cerebral ventricles. Its elimination is very slow and incomplete. It accumulates in the reticuloendothelial system, especially in the liver and spleen. As it is radioactive (half-life: 1.41×10^{10} years), this accumulation is dangerous and there is strong evidence that the ensuing prolonged exposure to its radiation is a contributing factor in the development of malignant diseases and blood disorders often 20 to 30 years after its use.

Thuja

Tuya; White Cedar.

Profile

Thuja consists of the fresh leaves and twigs of *Thuja occidentalis* (Cupressaceae). It is included in some topical preparations for warts and in herbal antiseptic preparations. It is also used in herbal preparations for respiratory-tract disorders.

The oil distilled from the leaves and twigs is known as thuja oil or cedar leaf oil. It has been included in preparations for inhalation for the relief of respiratory-tract symptoms and for external use but is generally considered to be too toxic for internal use. Cedar leaf oil should be distinguished from cedar wood oil, obtained from *Juniperus virginiana* (see Red Cedar, p.2278).

Homoeopathy. Thuja has been used in homoeopathic medicines under the following names: Thuja occidentalis.

Preparations

Proprietary Preparations (details are given in Part 3)

Chile: Thujaderm.

Multi-ingredient: ***Austral.:*** Vicks Vaporub; ***Austria:*** Colda; Esberitox; Pe-Ce; ***Belg.:*** Aporil; Vicks Vaporub; ***Braz.:*** Calope†; Mentalol†; Vick Vaporub; ***Fr.:*** Item Alphacade; Item Alphazole; Item Lentes; Nitrol; Verrupan; Vicks Vaporub; ***Ger.:*** Esberitox N; ***Malaysia:*** Esberitox N; ***Pol.:*** Esberitox N; ***Port.:*** Alpha Cade; Alphacedre; Alphazole†; ***S.Afr.:*** Vicks Vaporub; ***Spain:*** Nitroina; ***Switz.:*** Esberitop; Vicks Vaporub N; ***Turk.:*** Kataljin; Vicks Vaporub; ***USA:*** Vicks Vaporub.

Thymalfasin *(USAN, rINN)*

Thymalfasine; Thymalfasinum; Thymosin α1; Timalfasina.

Тимальфазин

CAS — 62304-98-7; 69521-94-4.

Profile

Thymalfasin is a thymus hormone (p.2401) found in thymosin fraction 5 (a crude thymus gland extract) but now produced by synthesis. Thymalfasin is used alone or with interferon as an immunomodulator for the treatment of chronic hepatitis B, and with interferon for hepatitis C (p.851). It is given by subcutaneous injection in a dose of 1.6 mg twice weekly for up to 12 months. The dose in patients who weigh less than 40 kg is 40 micrograms/kg. Thymalfasin is also used to enhance the effectiveness of influenza vaccines in immunocompromised or elderly patients and of influenza and hepatitis B vaccines in chronic haemodialysis patients.

Thymalfasin is under investigation for a number of other diseases, including hepatitis D, hepatocellular carcinoma, non-small cell lung cancer, melanoma, and HIV infection and AIDS.

◊ References.

1. Garaci E, *et al.* Sequential chemoimmunotherapy for advanced non-small cell lung cancer using cisplatin, etoposide, thymosin-α1 and interferon-α2a. *Eur J Cancer* 1995; **31A:** 2403–5.
2. Rasi G, *et al.* Combination thymosin α and lymphoblastoid interferon treatment in chronic hepatitis C. *Gut* 1996; **39:** 679–83.
3. Zavaglia C, *et al.* A pilot study of thymosin-α1 therapy for chronic hepatitis D. *J Clin Gastroenterol* 1996; **23:** 162–3.
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5. Sherman KE, *et al.* Combination therapy with thymosin α1 and interferon for the treatment of chronic hepatitis C infection: a randomized, placebo-controlled double-blind trial. *Hepatology* 1998; **27:** 1128–35.
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7. Rasi G, *et al.* Combined treatment with thymosin-α1 and low dose interferon-α after dacarbazine in advanced melanoma. *Melanoma Res* 2000; **10:** 189–92.
8. Ancell CD, *et al.* Thymosin alpha-1. *Am J Health-Syst Pharm* 2001; **58:** 879–85.
9. Andreone P, *et al.* Thymosin-alpha 1 plus interferon-alpha for naive patients with chronic hepatitis C: results of a randomized controlled pilot trial. *J Viral Hepatitis* 2004; **11:** 69–73.
10. Sjogren MH. Thymalfasin: an immune system enhancer for the treatment of liver disease. *J Gastroenterol Hepatol* 2004; **19:** S69–S72.
11. Rustgi V. Combination therapy of thymalfasin (thymosin-alpha 1) and peginterferon alfa-2a in patients with chronic hepatitis C virus infection who are non-responders to standard treatment. *J Gastroenterol Hepatol* 2004; **19:** S76–S78.
12. Iino S, *et al.* The efficacy and safety of thymosin alpha-1 in Japanese patients with chronic hepatitis B; results from a randomized clinical trial. *J Viral Hepatitis* 2005; **12:** 300–306.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zadaxin; ***Hong Kong:*** Zadaxin; ***Indon.:*** Zadaxin; ***Ital.:*** Zadaxin; ***Malaysia:*** Zadaxin; ***Mex.:*** Zadaxin; ***Philipp.:*** Zadaxin; ***Singapore:*** Zadaxin; ***Thai.:*** Zadaxin†.

Thyme

Common Thyme; French Thyme; Garden Thyme; Kakukkfű; Rubbed Thyme; Thym; Thymi herba; Thymian; Timjami; Timjan; Timo; Tomillo; Tymiánová nať; Vaistinių čiobrelių žolė; Ziele tymianku.

NOTE. Distinguish from Wild Thyme, p.2415.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Thyme). The whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris*, or *T. zygis*, or a mixture of both species. It contains not less than 12 mL/kg of essential oil, of which a minimum of 40% is thymol and carvacrol, both calculated with reference to the anhydrous drug. It has a strong aromatic odour reminiscent of thymol.

Profile

Thyme is the source of thyme oil (below). It has carminative, antiseptic, antitussive, and expectorant properties and is used chiefly in preparations for respiratory-tract disorders and as a flavour.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Scottopect; ***Chile:*** Hustagil†; ***Cz.:*** Bronchicum Husten-Pastillen†; ***Ger.:*** Anastil†; Aspecton; Biotuss; Bronchicum Pastillen†; Bronchipret; Expectal N†; Fichtensirup N†; Gelobronchial; Hustagil Thymian-Hustensaft; Hustagil Thymiantropfen; Husties†; Isephca S; Makatussin Saft†; Melrosum Hustensirup; Menthymin mono†; Mirfusot†; Nimopect; Pertussin; Sanopinwern; Soledum Hustensaft; Soledum Hustentropfen; Tetesept Erkaltungs; Thymipin N; Thymiverlan; Tussamag Hustenlosung; Tussamag Hustensaft N; Tussiflorin Thymian; ***Israel:*** Thymi Syrup; ***Pol.:*** Bronchicum N; Bronchicum T; ***Rus.:*** Bronchicum Husten (Бронхикум Пастилки от Кашля); Tussamag (Туссамаг); ***Switz.:*** Thymusin N.

Multi-ingredient: ***Arg.:*** Cellskinlab Phyto Spot; Expectosan Hierbas y Miel; ***Austral.:*** Broncafect; Bronchilin†; Cough Relief†; Euphorbia Complex; ***Austria:*** Bronchipret; Bronchithym; Bronchostop; Brust- und Hustentee St Severin; Codelum; Eicebaer; Expectal-Tropfen; Krauter Hustensaft; Luuf-Hustentee; Paracodin; Pilka; Pilka Forte; Pneumopan; Pneumopect; Scottopect; Thymoval; Tussamag; Tussimont; ***Belg.:*** Colimax†; Thymoseptine; ***Canad.:*** Herbal Throat†; Original Herb Cough Drops; Swiss Herb Cough Drops; ***Chile:*** Phyto Corrective Gel; Phyto Spot; Primacy Phyto +†; Rhus Opodeldoc; ***Cz.:*** Biotussil; Bronchialtee N†; Bronchicum Elixir†; Bronchicum Hustensirup†; Bronchicum Sekret-Loser†; Bronchicum Tropfen†; Bronchipret; Bronchostop†; Erkaltungstee†; Nontusyl†; Perospir†; Pleumolysin; Pulmoran; Stomatosan†; Thymomel; Urcyston Planta; ***Fin.:*** Katapekt; ***Fr.:*** Depuratum; Germose†; Saugella; Tussidoron; ***Ger.:*** Bronchicum; Bronchicum Elixir N†; Bronchicum Elixir Plus†; Bronchicum Elixir S; Bronchicum Pflanzlicher†; Bronchicum Sekret-Loser†; Bronchicum Thymian†; Bronchicum Tropfen N†; Bronchipret; Bronchosyx N†; Brust- und Hustentee; Cefadrin; Cito-Guakalin†; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N; Em-medical†; Ephepect-Pastillen N; Equisil N; Eucabal†; Eupatal†; Expectysat N; Harzer Hustenloser†; Hevertopect N†; Junisana†; Kinder Em-eukal Hustensaft†; Kneipp Husten- und Bronchial-Tee; Lomal†; Makatussin Tropfen; Melissengeist; Muc-Sabona†; Original Schneckensirup†; Phytobronchin; Pulmocordio mite SL†; Pulmotin†; Sinuforton; Thymipin N†; Tussiflorin forte†; Tussiflorin Hustenstiller†; TUSSinfant N†; ***Hong Kong:*** Pectoral†; ***Hung.:*** Bronchipret; ***Indon.:*** Bronchipret; Codipront cum Expectorant; Jesscool; Pectum; Silex; Thymcal; ***Israel:*** Pilka; ***Ital.:*** Altea (Specie Composta)†; Broncosed; Broncosedina; Immumil Plus; Immumil†; Pinedrin†; Piodermina; Saugella Attiva; Saugella Fitothym; Saugella Poligyn 7; Sebacnol†; Timo (Specie Composta)†; Tussol; ***Neth.:*** Balsoclase Compositum; Bronchicum; ***Philipp.:*** Bronchipret; ***Pol.:*** ApiHelix; Bobodent; Bronchicum Eliksir; Bronchicum†; Bronchosol; Dentosept; Dentosept A; Echinasal; Enterosol; Hedelicum; Herbapect; Mucosit; Neoazarina; Pectobonisol; Pectosol; PiniHelix; Salviasept; Saponarex; Tussipect; Tymsal; ***Port.:*** Calmarum†; ***Rus.:*** Bronchicum (Бронхикум); Bronchicum Husten (Бронхикум Сироп от Кашля); Bronchipret (Бронхипрет); Bronchipret TP (Бронхипрет ТП); Codelac Phyto (Коделак Фито); Eucabal (Эвкабал); Maraslavin (Мараславин); Passifit (Пассифит); Stoptussin-Fito (Стоптуссин-фито); ***S.Afr.:*** Bronchicough†; Bronchicum†; Cough Elixir; ***Spain:*** Natusor Asmaten†; Natusor Farinol†; Natusor Gripotul†; Natusor Infenol†; Natusor Renal†; Natusor Sinulan†; Pilka; Wobenzimal†; ***Switz.:*** Bronchofluid N†; Bronchosan Nouvelle formule†; Codipront cum Expectorans†; DemoPectol; Dinacode N†; Expectoran Codein†; Expectoran†; Liberol Dragees contre la toux†; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives; Makaphyt Sirop; Neo-DP†; Nican; Pectoral N; Pilka†; Strath Gouttes contre la toux; Thymodrosin N†; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; ***Thai.:*** Solvopret; Solvopret TP; ***UK:*** Herb and Honey Cough Elixir; ***Venez.:*** Codebromil; Mixagel†; T-Samag.

Thyme Oil

Esencia de Tomillo; Essência de Tomilho; Kakukkfűolaj; Kekik Yağı; Ol. Thym.; Olejek tymiankowy; Oleum Thymi; Thym, huile essentielle de; Thymi aetheroleum; Thymi Etheroleum; Timjamiöljy; Timjanolja; Tomillo, aceite esencial de; Tymiánová silice; Vaistinių čiobrelių eterinis aliejus.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Thyme Oil). The essential oil obtained by steam distillation from the fresh flowering aerial parts of *Thymus vulgaris*, *T. zygis*, or a mixture of both species. A clear, yellow or very dark reddish-brown, mobile liquid with a characteristic aromatic, spicy odour, reminiscent of thymol. Miscible with dehydrated alcohol and with petroleum spirit. It contains between 36 and 55% of thymol. Store in well-filled, airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Thyme oil is used similarly to thyme (above). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Bronchicum Medizinal-Bad†; Fichtensirup N†; Penaten; Thymian Erkaltungs-Bad.

Multi-ingredient: ***Arg.:*** Cuassicum; ***Austral.:*** Efalex†; Tixylix Chest Rub†; Zam-Buk†; ***Austria:*** Bronchostop; Expectal-Balsam; Heumann's Bronchialtee; Luuf-Hustentee; Scottopect; ***Belg.:*** Perubore; ***Canad.:*** Efalex†; ***Chile:*** Hustagil†; ***Cz.:*** Tussilen; ***Fr.:*** Acarcid†; Balsofumine; Balsofumine Mentholee; Biogaze†; Gouttes aux Essences; Nazinette du Docteur Gilbert; Perubore; ***Ger.:*** Antitussivum Burger N†; Aspecton-Balsam†; Emeukal†; Heumann Bronchialtee Solubifix T; Hustagil Erkaltungsbalsam†; Medizinisches Erkaltungs Bad; Melrosum Medizinalbad†; Nasulind; Pulmotin; Retterspitz Innerlich; Tetesept Badekonzentrat Erkaltungs Bad N†; Tetesept Bademedizin Erkaltungs Intensiv Bad N†; ***Gr.:*** Snufflebabe†; ***Ital.:*** Altuss; Calyptol; Esoklin; Fomentil; Valda Timo e Limone; Vegetallumina; ***NZ:*** Efalex; Tixylix Chest Rub; ***Pol.:*** Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Carmolis; Inhalol; Salviasept; ***Port.:*** Erpecalm; Vaporil; ***Rus.:*** Carmolis (Кармолис)†; Carmolis Fluid (Кармолис Жидкость)†; ***S.Afr.:*** Balsem Vita GEEL; Balsem Vita ROOI; Balsem Vita WIT; Oleum Rhinale Nasal Oil; Zam-Buk†; ***Spain:*** H Tussan; Termosan; ***Switz.:*** Carmol; Carmol Plus†; Demo pommade contre les refroidissements†; Demonatur Capsules contre les refroidissements; Dolo-Arthrosenex sine Heparino†; Eucapinol; Frigoplasma†; Frixo-Dragon Vert†; Liberol Bain†; Liberol N; Makaphyt Baume†; Nasobol N; Perubare†; Pinimenthol Baby†; Pulmex; Sedasept†; Spagyrom; Wolo Bain antirefroidissement; ***Thai.:*** St Luke's Oil; ***Turk.:*** Algo-Wax; Mentoseptol; ***UK:*** Efalex; Nine Rubbing Oils; Snowfire; Snufflebabe; ***USA:*** Maximum Strength Flexall 454; Unguentine.

Thymidine

NSC-21548; Thymine 2-Desoxyriboside; Timidina; Tymidyna. 1-(2-Deoxy-β-D-ribofuranosyl)-5-methyluracil; 1-(2-Deoxy-β-D-ribofuranosyl)-1,2,3,4-tetrahydro-5-methylpyrimidine-2,4-dione.

Тимидин

$C_{10}H_{14}N_2O_5$ = 242.2.

CAS — 50-89-5.

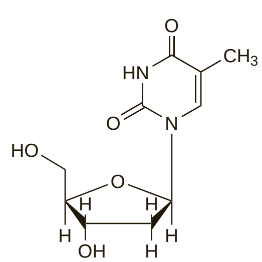

Profile

Thymidine is an endogenous thymine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p.2355). It was formerly given by intravenous infusion to modulate the toxicity of methotrexate but is not considered to be a substitute for calcium folinate; it may also have an antineoplastic action of its own.

Thymidine is given topically with other nucleosides in preparations for the treatment of corneal damage.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Vitacic; ***Hung.:*** Vitacic†; ***Mon.:*** Vitacic; ***Rus.:*** Vitacic (Витасик)†.

Thymus Hormones

Timo, hormonas del.

CAS — 69558-55-0 (thymopentin); 60529-76-2 (thymopoietin); 63340-72-7 (thymic humoral factor).

Profile

The thymus gland controls the development of T-lymphocytes and thereby plays a central role in cell-mediated immunity and the regulation of immune responses. Several polypeptides characterised in the thymus or serum are able to induce lymphocyte differentiation *in vitro* and *in vivo*. They include: thymosin fraction 5, a crude thymus gland extract; thymalfasin (p.2400); thymosin beta 4; thymic humoral factor (THF), isolated from crude thymic extract dialysate; nonathymulin (thymulin, serum thymic factor, Facteur Thymique Serique, FTS), a synthetic nonapeptide; thymomodulin, a partially purified extract from calf thymus; thymogene A, extracted from calf thymus; thymopoietin, a polypeptide of known amino acid sequence; thymopentin (thymopoietin pentapeptide, TP-5), a fragment of thymopoietin with 5 amino acids; and thymostimulin (TP-1), extracted from calf thymus.

Various preparations, including crude extracts from calf thymus gland, thymomodulin, thymopentin, and thymostimulin have been tried as immunomodulators in numerous conditions including rheumatoid arthritis, diabetes mellitus, immunodeficiency disorders, skin disorders, malignant neoplasms, and some infections.

◊ References.

1. Huff T, *et al.* β-Thymosins, small acidic peptides with multiple functions. *Int J Biochem Cell Biol* 2001; **33:** 205–20.
2. Hannappel E, Huff T. The thymosins—prothymosin alpha, parathymosin, and beta-thymosins: structure and function. *Vitam Horm* 2003; **66:** 257–96.
3. Goldstein AL, Badamchian M. Thymosins: chemistry and biological properties in health and disease. *Expert Opin Biol Ther* 2004; **4:** 559–73.
4. Chen C, *et al.* Roles of thymosins in cancers and other organ systems. *World J Surg* 2005; **29:** 264–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Leucotrofina; ***Austral.:*** Thymunes; ***Braz.:*** Leucogen; ***Cz.:*** TP-1†; ***Ger.:*** Thym-Uvocal; Thymo-Glandurretten†; Thymoject; Thymophysin; Thymowied†; ***Ital.:*** Sintomodulina.

Multi-ingredient: ***Austria:*** Wobe-Mugos; ***Cz.:*** Wobe-Mugos†.

Tiaprost Trometamol *(BANM, rINNM)*

Tiaprost Trométamol; Tiaprostum Trometamolum. Trometamol salt of (±)-(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*RS*)-3-hydroxy-4-(3-thienyloxy)but-1-enyl]cyclopentyl}hept-5-enoic acid.

Тиапрост Трометамол

$C_{20}H_{28}O_6S,C_4H_{11}NO_3$ = 517.6.

CAS — 71116-82-0 (tiaprost).

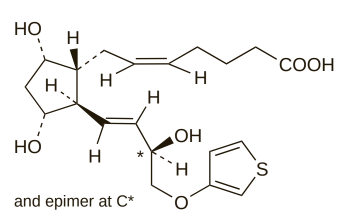

(tiaprost)

Profile

Tiaprost trometamol is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as a luteolytic in veterinary medicine.

Tibezonium Iodide *(rINN)*

Ioduro de tibezonio; Rec-15/0691; Tibezonii Iodidum; Tibézonium, Iodure de. Diethylmethyl{2-[4-(4-phenylthiophenyl)-3*H*-1,5-benzodiazepin-2-ylthio]ethyl}ammonium iodide.

Тибезония Йодид

$C_{28}H_{32}IN_3S_2$ = 601.6.

CAS — 54663-47-7.

ATC — A01AB15.

ATC Vet — QA01AB15.

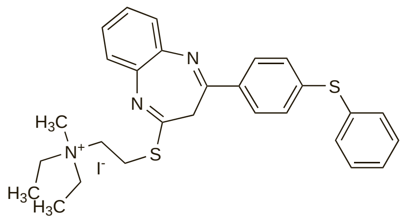

Profile

Tibezonium iodide has been used in the treatment of infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)

Gr.: Riposon; ***Ital.:*** Antoral; ***Mex.:*** Maxoral; ***Port.:*** Maxius.

Tilactase *(rINN)*

β-Galactosidase; β-D-Galactosidase; β-D-Galactoside Galactohydrolase; Lactase; Tilactasa; Tilactasum.

Тилактаза

CAS — 9031-11-2.

ATC — A09AA04.

ATC Vet — QA09AA04.

Pharmacopoeias. In *Jpn* (from *Aspergillus oryzae* or *Penicillium multicolor*) and *US* (from *Aspergillus oryzae*).

USP 31 (Lactase). A hydrolytic enzyme derived from *Aspergillus oryzae*. Each g contains not less than 30 000 USP units. Store in airtight containers at room temperature.

Profile

Tilactase hydrolyses lactose into glucose and galactose. It has been added to milk and milk products, or taken by mouth with a meal containing dairy products, in order to prevent the symptoms of lactose intolerance (p.1954) in persons deficient in the endogenous enzyme.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lac-Tas; ***Austral.:*** Lact-Easy†; Lactaid†; ***Canad.:*** Dairyaid; Lactaid; Lactrase†; Prolactase; ***Irl.:*** Colief; ***Ital.:*** Lacdigest; Silact; ***Jpn:*** Galantase†; ***Malaysia:*** Lactaide†; ***Port.:*** Lisolac; ***Switz.:*** Lacdigest; ***UK:*** Colief; ***USA:*** Dairy Ease; Lactaid; Lactrase; SureLac; ***Venez.:*** Lectozim†.

Multi-ingredient: *Canad.:* Digesta.

Tilarginine *(rINN)*

BW-546C88; 546C88; L-NMMA; Targinina; Targinine *(BAN)*; Targininum; Tilarginina; Tilargininum. *N*-Methyl-L-arginine.

Таргинин

$C_7H_{16}N_4O_2$ = 188.2.

CAS — 17035-90-4.

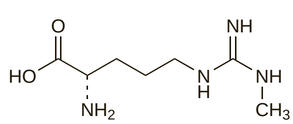

Profile

Tilarginine is a nitric oxide synthase inhibitor under investigation in the treatment of cardiogenic shock, although results have been disappointing. It has also been tried in septic shock but appears to have been associated with increased mortality. It has also been investigated in migraine.

◊ References.

1. Lassen LH, *et al.* The effect of nitric oxide synthase inhibition on histamine induced headache and arterial dilatation in migraineurs. *Cephalalgia* 2003; **23:** 877–86.
2. Bakker J, *et al.* Administration of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; **32:** 1–12.
3. Watson D, *et al.* Cardiovascular effects of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) in patients with septic shock: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; **32:** 13–20.
4. Lopez A, *et al.* Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; **32:** 21–30.
5. Alexander JH, *et al.* TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 2007; **297:** 1657–66.

Tilia

Hársfavirág; Kwiatostan lipy; Lehmuksenkukka; Liepų žiedai; Lime Flower; Lindblomma; Linden; Lipový květ; Tiliae flos; Tilleul; Tilleul, fleur de; Tilo.

Pharmacopoeias. *Eur.* (see p.vii) includes the flowers.
Fr. also includes the bark.

Ph. Eur. 6.2 (Lime Flower). The whole dried inflorescences of *Tilia cordata*, *Tilia platyphyllos*, *Tilia × vulgaris* (=[*Tilia × europaea*]), or a mixture of these species. It has a faint aromatic odour. Protect from light.

Profile

Tilia is mildly astringent and is reputed to have antispasmodic and diaphoretic properties. Lime-flower 'tea' is a traditional domestic remedy.

Various species of tilia are used in herbal preparations for a variety of disorders.

Homoeopathy. Tilia has been used in homoeopathic medicines under the following names: Tilia europaea; Til. euro.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Vibtil; ***Cz.:*** Kvet Lipy†; Lipovy; ***Pol.:*** Lipomal.

Multi-ingredient: *Arg.:* Armonil; Dr Calm†; Herbaccion Sedante†; Incaico Serenidad; Insomnal†; Nervocalm; No-Nerviol†; Sedanat; Sedante Arceli†; Sedante Dia; Serenil; Top Life Relax†; ***Austral.:*** Diaco; ***Austria:*** Grippetee St Severin; St Bonifatius-Tee; ***Belg.:*** Natudor; ***Canad.:*** Herbal Sleep Well†; ***Chile:*** Calmatol; Nature Complex Reduct-Te; Recalm; Reduc-Te; ***Cz.:*** Cajova Smes pri Nachlazeni; Nontusyl†; Průdušková; ***Fr.:*** Alkagin; Apaisance; Calmophytum; Lenicalm†; Mediflor Tisane Antirhumatismale No 2; Mediflor Tisane Calmante Troubles du Sommeil No 14; Vigilia; ***Ger.:*** Nervosana†; ***Israel:*** Jungborn; ***Ital.:*** Alkagin; Lenicalm; Sambuco (Specie Composta)†; Sebacnol†; Sedofit; Tiglio (Specie Composta)†; Tussol; Videorelax†; ***Pol.:*** Fitoven; Melisal; Melissed; Pectobonisol; Pyrosal; Termasil; Tiliros; ***Port.:*** Alkagin; ***Spain:*** Agua del Carmen; Jaquesor†; Mesatil†; Natusor Gripotul†; Natusor Jaquesan†; Natusor Sinulan†; Natusor Somnisedan†; ***Switz.:*** Tisane contre les refroidissements; Tisane pour nourissons et enfants; ***UK:*** Menopause Relief; Wellwoman.

Timonacic *(rINN)*

ATC; NSC-25855; Thioproline; Timonácico; Timonacicum. Thiazolidine-4-carboxylic acid.

Тимонацик

$C_4H_7NO_2S$ = 133.2.

CAS — 444-27-9.

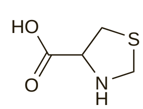

NOTE. The name ATC has also been used for a combination of paracetamol and trichloroethanol (4-acetamidophenyl 2,2,2-trichloroethyl carbonate).

Profile

Timonacic is used as an adjuvant in the treatment of acute and chronic hepatic disorders.

Timonacic methyl hydrochloride (carbolidine hydrochloride) has been used as a mucolytic.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Muvial†; ***Pol.:*** Hepacom; Heparegen; ***Switz.:*** Heparegen†.

Tin

Cyna; Estaño; Étain; Stannum; Zinn.

Sn = 118.71.

CAS — 7440-31-5.

Profile

Tin is a silver-white, lustrous, malleable, ductile metal. Owing to their low solubility, tin and tin oxide are very poorly absorbed from the gastrointestinal tract and have low toxicity. Chronic inhalation causes a benign form of pneumoconiosis.

Organic compounds of tin are highly toxic and may cause liver and kidney damage as well as severe neurological damage associated with oedema of the white matter of the brain. Treatment has been symptomatic. Contamination of the skin with organic tin compounds can cause severe burning; suitable precautions should be taken to prevent absorption of organic tin compounds through the skin.

Tin and tin oxide have been given in the treatment of boils, but there is little evidence of effectiveness; they were also formerly used in some countries for the treatment of tapeworm. Organic tin compounds, especially tributyltin oxide (TBTO), are used as molluscicides.

Tin in food. Excess amounts of inorganic tin in food tend to arise from tin-coated cans, especially unlacquered ones, and may produce gastric irritation. Concentrations as low as 150 mg/kg in canned beverages and 250 mg/kg in other canned foods have produced adverse effects in certain individuals, but some foods containing up to 700 mg/kg have not produced any detectable effects. Consumers should be advised not to store foods in opened tinplated cans.[1]

A recommended acceptable daily intake for chronic exposure to tin has been suggested as a provisional tolerable weekly intake of 14 mg/kg, although it was subsequently noted that this value may have been derived from intakes associated with acute effects, and it was concluded that the toxicokinetics and effects of inorganic tin after long-term exposure to dietary doses at concentrations that did not elicit acute effects should be re-assessed.[1] It was also concluded that it was inappropriate to establish an acute reference dose for inorganic tin, since development of gastric irritation depends on the concentration and nature of tin in the food product rather than on the dose ingested on a body-weight basis.[1] In the EU regulations limit the maximum amount of tin in foods sold in member states to wet weights of 200 mg/kg in canned foods other than beverages, 100 mg/kg in canned beverages including fruit and vegetable juices, and 50 mg/kg in various canned foods for infants.[2]

1. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 22/07/08)
2. The Commission of the European Communities. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Off J EU* 2006; **49:** L364/5–24. Also available at: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_364/ l_36420061220en00050024.pdf (accessed 22/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)

S.Afr.: Metinox.

Tin-protoporphyrin

Protoporfirina-Estaño; (Sn)-protoporphyrin.

Profile

Tin-protoporphyrin and the related compound tin-mesoporphyrin are metalloporphyrins which inhibit haem oxygenase, an enzyme involved in the breakdown of haem to bile pigments. They have been investigated as inhibitors of bilirubin production in hyperbilirubinaemia of various causes, and have been tried in porphyria (p.1448).

◊ References.

1. Valaes T, *et al.* Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. Abstract: *Pediatrics* 1998; **101:** 915. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/5/e1 (accessed 09/07/04)
2. Martinez JC, *et al.* Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics* 1999; **103:** 1–5.
3. Kappas A, *et al.* A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. *Pediatrics* 2001; **108:** 25–30.
4. Kappas A, *et al.* Sn-mesoporphyrin interdiction of severe hyperbilirubinemia in Jehovah's Witness newborns as an alternative to exchange transfusion. *Pediatrics* 2001; **108:** 1374–7.
5. Kappas A. A method for interdicting the development of severe jaundice in newborns by inhibiting the production of bilirubin. *Pediatrics* 2004; **113:** 119–23.
6. Drummond GS, Kappas A. Chemoprevention of severe neonatal hyperbilirubinemia. *Semin Perinatol* 2004; **28:** 365–8.
7. Dennery PA. Metalloporphyrins for the treatment of neonatal jaundice. *Curr Opin Pediatr* 2005; **17:** 167–9.

Tiropramide Hydrochloride *(rINNM)*

Hidrocloruro de tiropramida; Tiropramide, Chlorhydrate de; Tiropramidi Hydrochloridum. DL-α-Benzamido-*p*-[2-(diethylamino)ethoxy]-*N*,*N*-dipropylhydrocinnamamide hydrochloride.

Тиропрамида Гидрохлорид

$C_{28}H_{41}N_3O_3$,HCl = 504.1.

CAS — 55837-29-1 (tiropramide); 57227-16-4 (tiropramide hydrochloride).

ATC — A03AC05.

ATC Vet — QA03AC05.

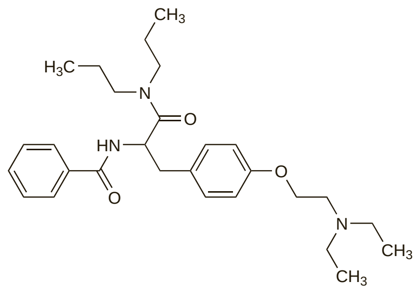

(tiropramide)

Profile

Tiropramide hydrochloride is used as an antispasmodic. Doses of 100 mg 2 or 3 times daily or 200 mg twice daily have been given by mouth. It has also been given rectally and parenterally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Alfospas; Maiorad; ***Port.:*** Maiorad; ***Thai.:*** Maiorad.

Titanium

Titan; Titane; Titanio; Tytan.

Ti = 47.867.

CAS — 7440-32-6.

Profile

Titanium has been used in the repair of skull damage and for implantation in dental surgery.

◊ References.

1. Brown D. All you wanted to know about titanium, but were afraid to ask. *Br Dent J* 1997; **182:** 393–4.
2. Williams D. The golden anniversary of titanium biomaterials. *Med Device Technol* 2001; **12:** 8–11.

Tolonium Chloride *(rINN)*

CI Basic Blue 17; Cloruro de tolonio; Colour Index No. 52040; Tolonii Chloridum; Tolonium, Chlorure de; Toluidine Blue O. 3-Amino-7-dimethylamino-2-methylphenazathionium chloride.

Толония Хлорид

$C_{15}H_{16}ClN_3S$ = 305.8.

CAS — 92-31-9.

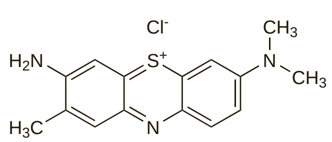

NOTE. Distinguish from Toluidine Blue, Colour Index No. 63340.

Profile

Tolonium chloride is a thiazine dye chemically related to methylthioninium chloride (p.1450). It has been used to stain oral and gastric neoplasms and was given intravenously to stain the parathyroid glands. Other uses have included the treatment of menstrual disorders and methaemoglobinaemia.

Tolonium chloride should be avoided in patients with G6PD deficiency as haemolysis may occur.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Toluidinblau; ***Ger.:*** Toluidinblau; ***Gr.:*** OraTest; ***Neth.:*** OraTest; ***NZ:*** Orascreen; ***Port.:*** OraTest.

Tolvaptan *(USAN, rINN)* ⊗

OPC-41061; Tolvaptán; Tolvaptanum. (±)-4′-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-*o*-tolu-*m*-toluidide.

Толваптан

$C_{26}H_{25}ClN_2O_3$ = 448.9.

CAS — 150683-30-0.

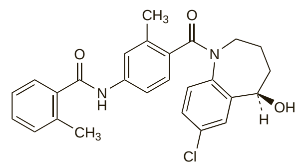

and enantiomer

Profile

Tolvaptan is a selective vasopressin V_2-receptor antagonist under investigation for the treatment of hyponatraemia, including that in heart failure.

◊ References.

1. Schrier RW, *et al.* SALT Investigators. Tolvaptan, a selective oral vasopressin V -receptor antagonist, for hyponatremia. *N Engl J Med* 2006; **355:** 2099–2112.
2. Konstam MA, *et al.* Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA* 2007; **297:** 1319–31.
3. Gheorghiade M, *et al.* Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials. *JAMA* 2007; **297:** 1332–43.
4. Udelson JE, *et al.* Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. *J Am Coll Cardiol* 2007; **49:** 2151–9.
5. Shoaf SE, *et al.* Pharmacokinetics, pharmacodynamics, and safety of tolvaptan, a nonpeptide AVP antagonist, during ascending single-dose studies in healthy subjects. *J Clin Pharmacol* 2007; **47:** 1498–1507.

Tonzonium Bromide *(rINN)*

Bromuro de tonzonio; NC-1264; NSC-5648; Thonzonium Bromide *(USAN)*; Tonzonii Bromidum; Tonzonium, Bromure de. Hexadecyl[2-(*N*-*p*-methoxybenzyl-*N*-pyrimidin-2-ylamino)ethyl]dimethylammonium bromide.

Тонзония Бромид

$C_{32}H_{55}BrN_4O$ = 591.7.

CAS — 553-08-2.

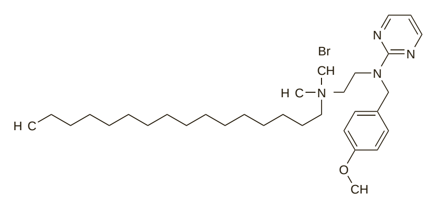

Profile

Tonzonium bromide is a cationic surfactant. As an additive in ear drops and aerosol sprays it has been claimed to promote tissue contact by dispersion and penetration of cellular debris and exudate.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *USA:* Coly-Mycin S Otic; Cortisporin-TC.

Tormentil

Blodrot; Consolda Vermelha; Erect Cinquefoil; Miškinių sidabražolių šakniastiebiai; Nátržníkový oddenek; Rätvänänjuurakko; Tormentilla; Tormentillae rhizoma; Tormentille; Vérontófűgyökértörzs.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tormentil). The whole or cut, dried rhizome, freed from the roots, of *Potentilla erecta* (*P. tormentilla*). It contains not less than 7% of tannins expressed as pyrogallol, calculated with reference to the dried drug. Protect from light.

Profile

Tormentil has astringent properties and is used in herbal preparations for diarrhoea and other indications. Gastrointestinal irritation and vomiting have occasionally occurred.

◊ References.

1. Subbotina MD, *et al.* Effect of oral administration of tormentil root extract (Potentilla tormentilla) on rotavirus diarrhea in children: a randomized, double blind, controlled trial. *Pediatr Infect Dis J* 2003; **22:** 706–11.

Preparations

Ph. Eur.: Tormentil Tincture.

Proprietary Preparations (details are given in Part 3)
Ger.: Blutwurz; ratioGast†.

Multi-ingredient: *Cz.:* Dr Theiss Schwedenbitter; Original Schwedenbitter; Stomatosan†; Tormentan; ***Ger.:*** Repha-Os; ***Pol.:*** Hemorol; Neo-Tormentil; Stomatosol; Tobacoff; Tormentile Forte; Tormentiol; ***Rus.:*** Linkus (Линкас); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Switz.:*** Baume†; Pommade au Baume.

Transfer Factor

Transferencia, factor de.

Трансферный Фактор

Profile

Transfer factor is a peptide constituent of dialysable leucocyte extracts prepared from the leucocytes of a sensitised donor, that can passively transfer cell-mediated immunity to a non-sensitised recipient.

Transfer factor has been suggested for use in infections due to bacteria, fungi, and viruses, inflammatory disorders, skin disorders such as eczema, nervous system disorders, immunodeficiency diseases, and malignancies, although the response when it has been tried in some of these conditions has not always been satisfactory.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Imunor.

Transforming Growth Factor Antibodies

Антитела к Трансформирующему Фактору Роста

Profile

A human monoclonal antibody specific for transforming growth factor β1 is under investigation for the treatment of systemic sclerosis.

Lerdelimumab (p.2333) is a human monoclonal antibody specific for transforming growth factor β2.

Trepibutone *(rINN)*

AA-149; Trepibutona; Trépibutone; Trepibutonum; Trepionate. 3-(2,4,5-Triethoxybenzoyl)propionic acid.

Трепибутон

$C_{16}H_{22}O_6$ = 310.3.

CAS — 41826-92-0.

ATC — A03AX09.

ATC Vet — QA03AX09.

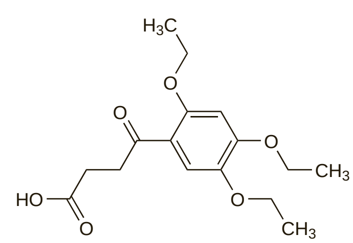

Pharmacopoeias. In *Jpn.*

Profile

Trepibutone has been reported to have spasmolytic and choleretic activity and is used in biliary-tract disorders and pancreatitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Choliatron.

Tribenoside *(BAN, USAN, rINN)*

21401-Ba; Ba-21401; Tribenosid; Tribénoside; Tribenosidi; Tribenósido; Tribenosidum; Tribenozid; Tribenozidas. Ethyl 3,5,6-tri-*O*-benzyl-D-glucofuranoside.

Трибенозид

$C_{29}H_{34}O_6$ = 478.6.

CAS — 10310-32-4.

ATC — C05AX05; C05CX01.

ATC Vet — QC05AX05; QC05CX01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tribenoside). A yellowish to pale yellow, clear, viscous liquid. Practically insoluble in water; very soluble in acetone, in dichloromethane, and in methyl alcohol. Store under nitrogen in airtight containers.

Profile

Tribenoside has been used in inflammatory and varicose disorders of the veins, including haemorrhoids (p.1697). It has been given orally in usual doses of 800 mg daily. It has also been given rectally and topically.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Glyvenol; ***Braz.:*** Glyvenol; ***Cz.:*** Glyvenol; ***Gr.:*** Glyvenol†; ***Mex.:*** Glyvenol; ***Philipp.:*** Glyvenol; ***Rus.:*** Glyvenol (Гливенол); ***Venez.:*** Glyvenol; Veglysin†.

Multi-ingredient: ***Arg.:*** Procto-Glyvenol; ***Braz.:*** Procto-Glyvenol; ***Chile:*** Euproct†; Procto-Glyvenol; Proctogel; ***Cz.:*** Procto-Glyvenol; ***Gr.:*** Procto-Glyvenol†; ***Israel:*** Procto-Glyvenol; ***Mex.:*** Procto-Glyvenol; ***Philipp.:*** Procto-Glyvenol; ***Pol.:*** Procto-Glyvenol; Venozel; ***Port.:*** Procto-Glyvenol; ***Rus.:*** Procto-Glyvenol (Прокто-Гливенол); ***Switz.:*** Procto-Glyvenol; ***Turk.:*** Procto-Glyvenol; ***UAE:*** Haemoproct; ***Venez.:*** Bargonil; Procto-Glyvenol.

Tribulus Terrestris

Caltrp.; Gokhru; Jili; Puncture Vine; Puncturevine; Tribulus.

Pharmacopoeias. In *Chin.*, which specifies the dried ripe fruit.

Profile

The fruit, flowers, and root of *Tribulus terrestris* (Zygophyllaceae) are used in herbal medicine for many different purposes, including the treatment of urinary stones and other urinary disorders, for digestive disorders, for male sexual disorders, and as a diuretic and an aphrodisiac.

The fruit is also used in Ayurvedic and traditional Chinese medicine.

It is included in a number of dietary supplements and tonics, and has been taken by athletes for its reported anabolic effects.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Androsten; ***Indon.:*** Tribestan; ***Rus.:*** Tribestan (Трибестан).

Multi-ingredient: ***Austral.:*** Bioglan The Blue One; ***Indon.:*** Bioretin; Instink; Maxirex; Reximax; Sirec; Tristan; ***Malaysia:*** Rumalaya; ***Rus.:*** Fitovit (Фитовит); Speman (Спеман); Speman Forte (Спеман Форте); Verona (Верона).

Tributyl Acetylcitrate

Tributilo acetilcitratas; Tributylacetylcitrat; Tributyl-acetylcitrát; Tributyle, acétylcitrate de; Tributylis acetylcitras; Tributyyliasetyylisitraatti. Tributyl 2-(acetyloxy)propane-1,2,3-tricarboxylate.

$C_{20}H_{34}O_8$ = 402.5.
CAS — 77-90-7.

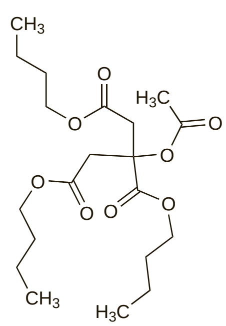

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Tributyl Acetylcitrate). A clear oily liquid. Immiscible with water; miscible with alcohol and with dichloromethane.
USNF 26 (Acetyltributyl Citrate). A clear, practically colourless, oily liquid. Insoluble in water; freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene. Store in airtight containers.

Profile

Tributyl acetylcitrate is a plasticiser and flavour used in pharmaceutical manufacturing and in the food industry.

Triethyl Citrate

E1505; Triethyl citrát; Triéthyle, citrate de; Triethyli Citras; Triethylis citras; Trietil-citrát; Trietilo citratas; Trietilo, citrato de; Trietylcitrat; Trietyylisitraatti. 2-Hydroxy-1,2,3-propanetricarboxylic acid triethyl ester.

$C_{12}H_{20}O_7$ = 276.3.
CAS — 77-93-0.

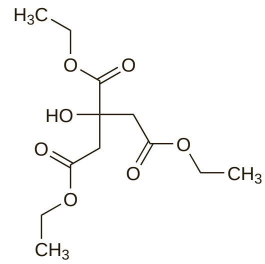

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*
Ph. Eur. 6.2 (Triethyl Citrate). A clear, viscous, colourless or almost colourless, hygroscopic liquid. Soluble in water; miscible with alcohol; slightly soluble in fatty oils. Store in airtight containers.
USNF 26 (Triethyl Citrate). A practically colourless oily liquid. Soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Profile

Triethyl citrate is a plasticiser used in pharmaceutical manufacturing and in the food and cosmetics industries.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Chile:*** Uriage Desodorante Tri-Actif; ***Fr.:*** Spirial.

Trilostane *(BAN, USAN, pINN)*

Trilostaani; Trilostan; Trilostano; Trilostanum; Win-24540. 4α,5α-Epoxy-17β-hydroxy-3-oxoandrostane-2α-carbonitrile.

Трилостан

$C_{20}H_{27}NO_3$ = 329.4.
CAS — 13647-35-3.
ATC — H02CA01.
ATC Vet — QH02CA01.

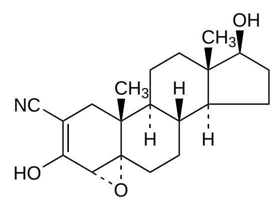

Adverse Effects

Adverse effects associated with trilostane have included flushing, nausea, vomiting, diarrhoea, rhinorrhoea, and tingling and swelling of the mouth. Skin rashes may occur and, rarely, granulocytopenia in immunocompromised patients.

Precautions

Trilostane is contra-indicated in pregnancy and should be used with caution in patients with renal or hepatic impairment. Circulating corticosteroids and blood electrolytes should be monitored. In some patients, supplementation with corticosteroids may be necessary.

Interactions

Trilostane may interfere with the activity of oral contraceptives. Hyperkalaemia may occur if trilostane is given with potassium-sparing diuretics or aldosterone antagonists.

Uses and Administration

Trilostane is an adrenocortical suppressant that inhibits the enzyme system essential for the production of glucocorticoids and mineralocorticoids. It is used for the treatment of adrenal cortical hyperfunction such as Cushing's syndrome and primary hyperaldosteronism. It is also used in postmenopausal breast cancer that has relapsed after oestrogen antagonist therapy.

The usual daily dose in adrenal cortical hyperfunction is 240 mg orally in divided doses for at least 3 days and then adjusted, according to response, within the range of 120 to 480 mg daily. Doses of 960 mg daily have been given.

In postmenopausal breast cancer an initial daily dose of 240 mg is given in divided doses, with glucocorticoid replacement therapy. This is increased in steps of 240 mg every 3 days up to a maintenance dose of 960 mg daily; this may be reduced to 720 mg daily if adverse effects are intolerable.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Desopan; ***UK:*** Modrenal.

Trimebutine Maleate *(BANM, rINNM)*

Maleato de trimebutina; Trimebutin Maleat; Trimébutine, maléate de; Trimebutini maleas. 2-Dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoate hydrogen maleate.

Тримебутина Малеат

$C_{22}H_{29}NO_5,C_4H_4O_4$ = 503.5.
CAS — 39133-31-8 (trimebutine); 34140-59-5 (trimebutine maleate).
ATC — A03AA05.
ATC Vet — QA03AA05.

Pharmacopoeias. In *Jpn.*

Profile

Trimebutine maleate has been used as an antispasmodic in gastrointestinal disorders in oral doses of up to 600 mg daily in divided doses. It has also been given by injection and rectally. Trimebutine base has also been used.

Irritable bowel syndrome. Trimebutine has been reported[1-3] to be effective in the treatment of irritable bowel syndrome (p.1699) although a considerable placebo response has been seen.[1] Its action is thought to be mediated both via gastrointestinal opioid receptors and modulation of the release of gastrointestinal peptides.[4]

1. Ghidini O, *et al.* Single drug treatment for irritable colon: rociverine versus trimebutine maleate. *Curr Ther Res* 1986; **39:** 541–8.
2. Schaffstein W, *et al.* Comparative safety and efficacy of trimebutine versus mebeverine in the treatment of irritable bowel syndrome. *Curr Ther Res* 1990; **47:** 136–45.
3. Kountouras J, *et al.* Efficacy of trimebutine therapy in patients with gastroesophageal reflux disease and irritable bowel syndrome. *Hepatogastroenterology* 2002; **49:** 193–7.
4. Delvaux M, Wingate D. Trimebutine: mechanism of action, effects on gastrointestinal function and clinical results. *J Int Med Res* 1997; **25:** 225–46.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Biorgan; Colixane; Debridat; Eumotil; Fenatrop; Miopropan; Plidex T; Tributina; ***Austria:*** Debridat; ***Braz.:*** Debridat†; Digedrat; ***Canad.:*** Modulon; ***Chile:*** Debridat; Dolpic Forte; Trim; ***Fr.:*** Debridat; Modulon; Transacalm; ***Gr.:*** Garapepsin; Ibutin; Trienter; ***Hong Kong:*** Cerekinon; ***Hung.:*** Debridat†; ***Ital.:*** Debridat; Digerent; Trimedat†; ***Jpn:*** Cerekinon; ***Malaysia:*** Cerekinon; Trima; ***Mex.:*** Cineprac; Debridat; Espabion; Farbutin; Kriskon; Libertrim; Muttifen; Prescol; Scitin; ***Pol.:*** Debridat; Tribux; ***Port.:*** Debridat; ***Singapore:*** Cerekinon; Debridat; ***Spain:*** Polibutin; ***Switz.:*** Debridat; ***Thai.:*** Cerekinon; ***Turk.:*** Debridat; Tribudat; ***Venez.:*** Bumetin; Colypan; Debridat†.

Multi-ingredient: ***Arg.:*** Biorgan B; Colixane B; Debridat B; Eumotil-T; Fenatrop-A; Miopropan Proctologico; Miopropan-T; ***Fr.:*** Proctolog; ***Gr.:*** Ibuproct; ***Ital.:*** Debrum; ***Mex.:*** Libertrim SDP; ***Port.:*** Proctolog; ***Singapore:*** Proctolog; ***Spain:*** Proctolog; ***Turk.:*** Proctolog.

Trinitrophenol

Carbazotic Acid; Kwas pikrynowy; Picric Acid; Picrinic Acid; Trinitrofenol. 2,4,6-Trinitrophenol.

$C_6H_3N_3O_7$ = 229.1.
CAS — 88-89-1.

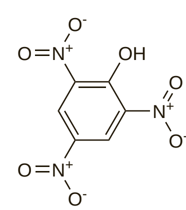

Pharmacopoeias. In *Fr.*

Storage and hazards. Trinitrophenol burns readily and explodes when heated rapidly or when subjected to percussion.

For safety in handling, trinitrophenol is usually supplied mixed with not less than half its weight of water. It should be stored in a cool place. It must not be stored in glass-stoppered bottles.

Trinitrophenol combines with metals to form salts, some of which are very explosive.

Profile

Trinitrophenol has disinfectant properties and was formerly used in the treatment of burns. It is now chiefly used in manufacturing and as a laboratory reagent.

Dermatitis, skin eruptions, severe itching, and yellow staining of the skin may occur after contact with trinitrophenol. Systemic toxicity may follow ingestion or absorption through the skin or lungs; symptoms may include vomiting, pain, and diarrhoea, progressing to haemolysis, hepatitis, anuria, convulsions, unconsciousness, and death. The metabolic rate is increased, causing pyrexia.

Homoeopathy. Trinitrophenol has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Chile:*** Agua Sulfatada Picrica; ***Spain:*** Oftalmol Ocular.

Trolamine *(pINN)*

Trietanoloamina; Triethanolamine; Trolamiini; Trolamin; Trolamina; Trolaminas; Trolaminum.

Троламин

CAS — 102-71-6.

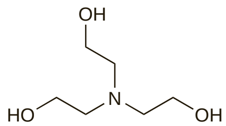

Description. Trolamine is a variable mixture of bases containing mainly 2,2′,2″-nitrilotriethanol (trolamine $(CH_2OH.CH_2)_3N$), together with 2,2′-iminobisethanol (diolamine) and smaller amounts of 2-aminoethanol (monoethanolamine).

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Trolamine; Triethanolamine BP 2008). A clear, viscous, colourless or slightly yellow, very hygroscopic liquid. Miscible with water and with alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 26 (Trolamine). A mixture of alkanolamines consisting largely of trolamine containing some diolamine and monoethanolamine. A colourless to pale yellow, viscous, hygroscopic liquid having a slight ammoniacal odour. Miscible with water and with alcohol; soluble in chloroform. Store in airtight containers. Protect from light.

Adverse Effects

Trolamine salts may be irritating to the skin and mucous membranes. Contact dermatitis has been reported after the use of ear drops containing trolamine polypeptide oleate-condensate.

Carcinogenicity. Because of concern about the possible production of carcinogenic nitrosamines in the stomach, the Swiss authorities restricted the use of trolamine to preparations for external use.[1]

1. Anonymous. Trolamine: concerns regarding potential carcinogenicity. *WHO Drug Inf* 1991; **5:** 9.

Uses and Administration

Trolamine is used with fatty acids such as stearic and oleic acids as an emulsifier and as an alkalinising agent. It has also been used to reduce dithranol-induced staining of the skin.

Ear drops containing trolamine polypeptide oleate-condensate 10% are used for the removal of impacted ear wax (p.1725).

Trolamine salicylate (p.132) has also been used.

Radiotherapy. An emulsion of trolamine has been widely used in the treatment and prevention of radiation-induced dermatitis in patients undergoing radiotherapy. However, several studies have suggested that it is of little or no benefit.[1-3]

1. Fisher J, *et al.* Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys* 2000; **48:** 1307–10.
2. Szumacher E, *et al.* Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys* 2001; **51:** 81–6.
3. Elliott EA, *et al.* Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *J Clin Oncol* 2006; **24:** 2092–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Biafine; Orla-Wax†; Solucer; ***Austral.:*** Neutrogena; ***Belg.:*** Xerumenex; ***Canad.:*** Cerumenex; ***Chile:*** Biafine; ***Fr.:*** Biafine; Lamiderm; ***Ger.:*** Cerumenex N; ***Hong Kong:*** Biafine; ***Israel:*** Biafine; ***Malaysia:*** Biafine†; ***Mex.:*** Orlawax; ***S.Afr.:*** Cerumenex†; ***Singapore:*** Biafine†; ***Switz.:*** Biafine; Cerumenex; ***USA:*** Biafine; Cerumenex†; ***Venez.:*** Biafine.

Multi-ingredient: ***Arg.:*** Eucos-L†; Onixol†; Tereonsit†; ***Braz.:*** Cerumin; Paraqueimol; ***Canad.:*** Soropon; ***Ital.:*** Dopo Pik; ***USA:*** Maxilube.

Trometamol *(BAN, rINN)* ⊗

NSC-6365; THAM; Trihydroxymethylaminomethane; TRIS; Tris(hydroksymetylo)aminometan; Tris(hydroxymethyl)aminomethane; Trométamol; Trometamoli; Trometamolis; Trometamolum; Tromethamine *(USAN)*. 2-Amino-2-(hydroxymethyl)propane-1,3-diol.

Трометамол

$C_4H_{11}NO_3$ = 121.1.

CAS — 77-86-1.

ATC — B05BB03; B05XX02.

ATC Vet — QB05BB03; QB05XX02.

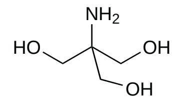

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Trometamol). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ethyl acetate. A 5% solution in water has a pH of 10.0 to 11.5.

USP 31 (Tromethamine). A white, crystalline powder having a slight characteristic odour. Soluble 1 in 1.8 of water and 1 in 45.5 of alcohol; freely soluble in low-molecular-weight aliphatic alcohols; practically insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 5% solution in water is between 10.0 and 11.5. Store in airtight containers.

Incompatibilities. There is evidence to suggest that fluorouracil degrades to cardiotoxic compounds in formulations buffered with trometamol.[1]

1. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Adverse Effects and Precautions

Great care must be taken to avoid extravasation at the injection site as solutions may cause tissue damage. Local irritation, venospasm and phlebitis have occurred.

Respiratory depression can occur and mechanical ventilation may be required. Hypoglycaemia may also occur. Trometamol is contra-indicated in anuria and uraemia, and should be used cautiously in patients with renal impairment as hyperkalaemia has been reported in such patients. Trometamol is not recommended for use in patients with respiratory acidosis alone. If it is used in patients with respiratory acidosis accompanying metabolic acidosis, ventilation should be maintained mechanically. Trometamol is contra-indicated in chronic respiratory acidosis.

Blood concentrations of bicarbonate, glucose, and electrolytes, partial pressure of carbon dioxide, and blood pH should be monitored during infusion of trometamol.

Uses and Administration

Trometamol is an organic amine proton acceptor used as an alkalinising agent in the treatment of metabolic acidosis (p.1667). It also acts as a weak osmotic diuretic. Trometamol is mainly used during cardiac bypass surgery and during cardiac arrest. It may also be used to reduce the acidity of citrated blood for use in bypass surgery.

The dose used should be the minimum required to increase the pH of the blood to within normal limits and is based on the bodyweight and the base deficit. Trometamol is given by slow intravenous infusion as a 0.3M solution; it should not be given for longer than a day except in life-threatening emergencies.

Trometamol citrate is given by mouth for the management of urinary calculi and acidosis. Trometamol acefyllinate has also been used for acidosis.

◊ References.

1. Nahas GG, *et al.* Guidelines for the treatment of acidaemia with THAM. *Drugs* 1998; **55:** 191–224.

Preparations

USP 31: Tromethamine for Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Tham; ***Austria:*** Tris; ***Ger.:*** Tham; Tris; ***Ital.:*** Thamesol; ***Swed.:*** Addex-THAM.

Multi-ingredient: ***Arg.:*** Solocalm Plus; ***Austral.:*** Blink-N-Clean; ***Fr.:*** Alcaphor; ***Norw.:*** Tribonat; ***Swed.:*** Theranyl†; Tribonat; ***Switz.:*** Saltrates†.

Trypan Blue

CI Direct Blue 14; Colour Index No. 23850; Trypanum Caeruleum. Tetrasodium 3,3′-[(3,3′-dimethylbiphenyl-4,4′-diyl)bisazo]-bis[5-amino-4-hydroxynaphthalene-2,7-disulphonate].

$C_{34}H_{24}N_6Na_4O_{14}S_4$ = 960.8.

CAS — 72-57-1.

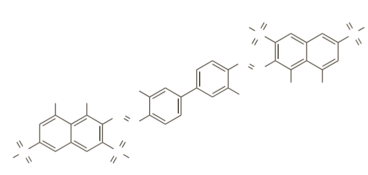

Profile

Trypan blue solutions are used as stains in microscopy and for visualisation of various tissues as an aid to ophthalmic surgery.

◊ References.

1. Werner L, *et al.* Permanent blue discoloration of a hydrogel intraocular lens by intraoperative trypan blue. *J Cataract Refract Surg* 2002; **28:** 1279–86.
2. Haritoglou C, *et al.* Functional outcome after trypan blue-assisted vitrectomy for macular pucker: a prospective, randomized, comparative trial. *Am J Ophthalmol* 2004; **138:** 1–5.
3. Gouws P, *et al.* Cystoid macular oedema with trypan blue use. *Br J Ophthalmol* 2004; **88:** 1348–9.
4. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89:** 420–4.
5. Healey PR, Crowston JG. Trypan blue identifies antimetabolite treatment area in trabeculectomy. *Br J Ophthalmol* 2005; **89:** 1152–6.
6. Roos JC, Kerr Muir MG. Use of trypan blue for penetrating keratoplasty. *J Cataract Refract Surg* 2005; **31:** 1867–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Oftalblu; ***Neth.:*** MembraneBlue; VisionBlue; ***USA:*** VisionBlue.

Multi-ingredient: ***Fr.:*** Parkipan†.

Trypsin *(BAN)*

Thrypsinum; Tripsina; Tripsinas; Tripszin; Trypsiini; Trypsine; Trypsinum; Trypsyna.

CAS — 9002-07-7.

ATC — B06AA07; D03BA01.

ATC Vet — QB06AA07; QD03BA01.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Trypsin). A proteolytic enzyme obtained by the activation of trypsinogen extracted from mammalian pancreas. It has an activity of not less than 0.5 microkatals/mg, calculated with reference to the dried substance. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 6.0. Solutions have a maximum stability at pH 3 and a maximum activity at pH 8. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Crystallized Trypsin). A proteolytic enzyme crystallised from an extract of the pancreas of healthy bovine or porcine animals, or both. It contains not less than 2500 USP units in each mg, calculated on the dried basis. A white to yellowish-white, odourless, crystalline or amorphous powder. Store in airtight containers at temperature not exceeding 40°.

Profile

Trypsin is a proteolytic enzyme that has been applied for the debridement of wounds. It has also been taken by mouth, usually with chymotrypsin (p.2281), and sometimes with antibacterial or other drugs, for its supposed benefit in relieving oedema and inflammation associated with infection or trauma. Trypsin solutions have been inhaled for the liquefaction of viscous sputum, and trypsin is also an ingredient of mixtures intended to relieve various gastrointestinal disorders. Trypsin has been used in oncology in a combination preparation with chymotrypsin and papain (see under Uses and Administration of Papain, p.2362).

Hypersensitivity reactions may occasionally occur.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Phlogenzym†; ***Austria:*** Leukase; Leukase-Kegel; Phlogenzym; Rutozym; Traumazym; Wobenzym; ***Braz.:*** Parenzyme; Parenzyme Ampicilina; Parenzyme Analgesico; Parenzyme Tetraciclina; ***Cz.:*** Phlogenzym; Wobe-Mugos†; Wobenzym; ***Fr.:*** Ribatran; ***Ger.:*** Enzym-Wied†; Mulsal N†; Phlogenzym; Wobe-Mugos E†; Wobenzym N†; ***Gr.:*** Chymoral; ***Hung.:*** Phlogenzym; Trypsin†; ***India:*** Alfapsin; Orthal Forte; Soluzyme; ***Ital.:*** Essen Enzimatico†; ***Jpn:*** Kimotab; ***Mex.:*** Ochozim; Phlogenzym; Quimotrip; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; ***Port.:*** Anginova; Chimar; ***Rus.:*** Phlogenzym (Флогэнзим); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); ***Spain:*** Bristaciclina Dental; Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Kanapomada; Naso Pekamin; Oxidermiol Enzima†; Quimodril; ***USA:*** Allanderm-T; Dermuspray; Granulderm; Granulex; GranuMed; Xenaderm; ***Venez.:*** Phlogenzym; Wobenzym N.

Tuberculins

Tuberculinas.

ATC — V04CF01.

ATC Vet — QV04CF01.

NOTE. 'PPD' is an abbreviation sometimes used for tuberculin purified protein derivative which should not be confused with para-phenylenediamine (p.2363), which is also referred to by the same abbreviation.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Tuberculin for Human Use, Old). It consists of a filtrate, concentrated by heating, containing the soluble products of the culture and lysis of one or more strains of *Mycobacterium tuberculosis* and/or *M. bovis*. It contains a suitable preservative that does not give rise to false-positive reactions. In concentrated form, it is a transparent, viscous, yellow or brown liquid. Protect from light.

Ph. Eur. 6.2 (Tuberculin Purified Protein Derivative for Human Use). A preparation obtained by precipitation from the heated products of the culture and lysis of *Mycobacterium tuberculosis* and/or *M. bovis.* It contains a suitable preservative that does not give rise to false-positive reactions. It is a colourless or pale yellow liquid; the diluted preparation may be a freeze-dried powder which upon dissolution gives a colourless or pale yellow liquid. Protect from light.

USP 31 (Tuberculin). A sterile solution derived from the concentrated, soluble products of growth of the tubercle bacillus (*Mycobacterium tuberculosis* or *M. bovis*) prepared in a special medium. It is provided either as Old Tuberculin, a culture filtrate adjusted to the standard potency by the addition of glycerol and isotonic sodium chloride solution, or as Purified Protein Derivative (PPD), a further purified protein fraction. Store at 2° to 8°.

Adverse Effects

Pain and pruritus may occur at the injection site, occasionally with vesiculation, ulceration, or necrosis in highly sensitive persons. Granuloma has been reported.

Nausea, headache, dizziness, malaise, rash, urticaria, oedema, and pyrexia have been reported occasionally; immediate systemic hypersensitivity, including anaphylaxis, has been reported rarely. There have also been rare reports of lymphangitis.

Hypersensitivity. There are rare reports[1-4] of severe anaphylactic or anaphylactoid reactions, occasionally fatal,[1] to tuberculin.

1. DiMaio VJM, Froede RC. Allergic reactions to the tine test. *JAMA* 1975; **233:** 769.
2. Spiteri MA, *et al.* Life threatening reaction to tuberculin testing. *BMJ* 1986; **293:** 243–4.
3. Wright DN, *et al.* Systemic and local allergic reactions to the tine test purified protein derivative. *JAMA* 1989; **262:** 2999–3000.
4. Sanofi Pasteur, Canada. Risk of serious allergic reactions following TUBERSOL [Tuberculin Purified Protein Derivative (Mantoux)] administration (issued 19th May 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tubersol_hpc-cps-eng.pdf (accessed 08/08/08)

Lymphangitis. Lymphangitis has been reported on 5 occasions after the Mantoux test and on 7 occasions after the Heaf test.[1] However, it was noted that a tuberculin test may have been inappropriate in some of these patients, particularly older subjects and those with evidence of healed tuberculous lesions.[2]

1. Morrison JB. Lymphangitis after tuberculin tests. *BMJ* 1984; **289:** 413.
2. Festenstein F. Lymphangitis after tuberculin tests. *BMJ* 1984; **289:** 625–6.

Precautions

Tuberculin should be given with caution to patients who have, or are suspected of having, active tuberculosis; although severe local reactions may occur in patients with active tuberculosis, sensitivity may be diminished if it is particularly severe. Sensitivity to tuberculin may also be diminished in the following conditions: viral or severe bacterial infection including HIV infection and infectious mononucleosis; neoplastic disease particularly lymphoma; sarcoidosis; corticosteroid or immunosuppressive therapy; recent use of live virus vaccines; ultraviolet light treatment; chronic renal failure; dehydration; and malnutrition.

Tuberculins may be adsorbed onto the surface of syringes and should therefore be given immediately.

Uses and Administration

Tuberculin skin tests are used to detect tuberculoprotein hypersensitivity when BCG vaccination is being considered or as an aid to diagnosis of tuberculosis. A person showing a specific sensitivity to tuberculin is considered to have been infected with the tubercle bacillus, though the infection may be inactive. Tuberculin for sensitivity testing is given by intradermal injection as in the Mantoux test. Multiple-puncture devices such as the Heaf test or tine tests have also been used, although they are no longer available in the UK.

In the UK, it is recommended that tuberculin testing should always be performed when BCG vaccination is being considered, and the **Mantoux** test is recommended. For a routine Mantoux test, a diluted solution of tuberculin purified protein derivative (PPD) is given by intradermal injection and the reaction, which is graded by the degree of induration, read 48 to 72 hours later. A retest with a stronger solution of PPD may be considered if the results of the initial test are unclear. Different commercial preparations vary in labelling format and potency, and doses and interpretation of results cannot therefore be extrapolated from one preparation to another.

Individuals with no or minimal reactions who have not previously been given BCG vaccines may be offered BCG vaccination. Patients with a positive reaction are considered to be hypersensitive to tuberculoprotein and should not be vaccinated. Investigation for the presence of active tuberculosis is generally only indicated for patients showing a strongly positive reaction to a tuberculin skin test. However, there are many factors that should be considered when interpreting the results; in addition to those listed under Precautions (see above), there are the effects of previous BCG vaccination, repeated tuberculin testing, and age. In some areas, a positive reaction may be a result of cross-sensitivity of the test to non-tuberculous mycobacteria (see below).

For the **Heaf** test, a solution of PPD is applied to the forearm using a multiple-puncture gun (Heaf gun), and the reaction evaluated about a week later.

The term **tine** test is generally used for disposable multiple-puncture devices coated with dried old tuberculin or PPD. However, some consider tine tests to be unreliable.

In some other countries, the population tested, the procedures used, and grading of reactions may differ slightly from that outlined above.

Tuberculins have also been used, in conjunction with other antigens, for anergy testing to assess the status of cell-mediated immunity.

Latent tuberculosis. Full eradication of tuberculosis from developed countries requires identification of latent as well as active cases.[1] Tuberculin testing has been in use for over 100 years and, while still considered a useful diagnostic agent for tuberculosis, the problems of false-positive reactions or reduced sensitivity to the test are well recognised.[1] Use of the test to identify latent disease has evolved with experience.[2] Previous BCG vaccination is one factor that significantly increases the likelihood of a false-positive reaction to tuberculin testing, which makes the diagnosis of latent tuberculosis particularly difficult.[3] Interpretation of the skin test should therefore be made by considering the induration size in the context of the individual clinical profile, including other risk factors for infection.[2,3] Three different approaches to assess the annual risk of tuberculous infection using tuberculin testing gave different results in a study of schoolchildren who had been given BCG vaccinations early in life.[4] This led the authors to conclude that the effect of previous BCG vaccination on tuberculin reactivity may be more complex than assumed, and that the tuberculin test is a poor indicator of latent infection. It has been suggested[2] that it is not necessary for low-risk persons in the general population of the USA to receive routine tuberculin testing for tuberculosis; high-risk groups of adults and children for whom screening might be warranted have been defined, and consensus recommendations made. An opinion has also been ventured[5] that tuberculin testing before BCG vaccination is not necessary in children in the UK.

1. Lee E, Holzman RS. Evolution and current use of the tuberculin test. *Clin Infect Dis* 2002; **34:** 365–70.
2. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. 1999. Available at: http://www.thoracic.org/sections/publications/statements/pages/mtpi/latenttb1-27.html (accessed 14/07/06)
3. Wang L, *et al.* A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax* 2002; **57:** 804–9. Correction: *ibid.* 2003; **58:** 188.
4. Leung CC, *et al.* Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. *Thorax* 2005; **60:** 124–9.
5. Bothamley GH, *et al.* Tuberculin testing before BCG vaccination. *BMJ* 2003; **327:** 243–4.

Malignant disease. Benefit has been reported[1] in 2 patients with adult T-cell leukaemia/lymphoma predominantly involving the skin after local treatment with tuberculin purified protein derivative.

1. Kanekura T, *et al.* Purified protein derivative treatment for skin lesions of adult T-cell leukaemia/lymphoma. *Br J Dermatol* 1999; **140:** 767–8.

Non-tuberculous mycobacterial infection. The tuberculin skin test is not specific for *Mycobacterium tuberculosis*, but can also represent a cross-reaction caused by antigens on other non-tuberculous mycobacteria. Re-examination[1] of results from children with non-tuberculous mycobacterial infection concluded that the avian Mantoux test (avian tuberculin purified protein derivative (PPD) prepared from *M. avium*) was more sensitive than the human Mantoux test (tuberculin PPD prepared from *M. tuberculosis*) in the detection of non-tuberculous mycobacteria in regions with a low incidence of tuberculosis, and may be a useful aid to differential diagnosis in areas where tuberculosis is prevalent.

1. Daley AJ, Isaacs D. Differential avian and human tuberculin skin testing in non-tuberculous mycobacterial infection. *Arch Dis Child* 1999; **80:** 377–9.

Preparations

Ph. Eur.: Old Tuberculin for Human Use; Tuberculin Purified Protein Derivative for Human Use;
USP 31: Tuberculin.

Proprietary Preparations (details are given in Part 3)
Austria: Monotest; ***Belg.:*** Monovacc-Test†; ***Canad.:*** Tubersol; ***Fr.:*** Monotest†; Tubertest; ***Ger.:*** Tubergen-Test†; ***Gr.:*** Imotest Tuberculin; ***Ital.:*** Biocine Test PPD; Monotest†; ***NZ:*** Monotest†; Tubersol; ***S.Afr.:*** Biocine Test; Japan Freeze-Dried Tuberculin; Monotest†; ***Spain:*** Tubersol PPD†; ***Swed.:*** Monotest†; ***USA:*** Aplisol; Tubersol; ***Venez.:*** Imotest Tuberculina†.

Multi-ingredient: ***Austral.:*** Multitest CMI; ***Austria:*** Multitest; ***Cz.:*** Imunoskintest†; ***Ger.:*** Multitest†; ***Israel:*** Multitest CMI; ***NZ:*** Multitest CMI†; ***S.Afr.:*** Multitest CMI†.

Tucaresol *(BAN, rINN)* ⊗

BW-589C; 589C; 589C80; Tucarésol; Tucaresolum. α-(2-Formyl-3-hydroxyphenoxy)-*p*-toluic acid.

Тукарезол

$C_{15}H_{12}O_5$ = 272.3.

CAS — 84290-27-7.

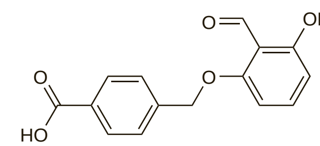

Profile

Tucaresol is reported to interact with haemoglobin to increase oxygen affinity. It has been investigated as an oral drug for the treatment of sickle-cell disease (p.1044). Tucaresol is also reported to have immunostimulant properties and is under investigation in HIV infection and hepatitis B. Hypersensitivity reactions have occurred.

◊ References.

1. Rolan PE, *et al.* The pharmacokinetics, tolerability and pharmacodynamics of tucaresol (589C80; 4[2-formyl-3-hydroxyphenoxymethyl]benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects. *Br J Clin Pharmacol* 1993; **35:** 419–25.
2. Arya R, *et al.* Tucaresol increases oxygen affinity and reduces haemolysis in subjects with sickle cell anaemia. *Br J Haematol* 1996; **93:** 817–21.
3. Peck RW, *et al.* Effect of food and gender on the pharmacokinetics of tucaresol in healthy volunteers. *Br J Clin Pharmacol* 1998; **46:** 83–6.
4. Gori A, *et al.* Immunomodulation induced by tucaresol in HIV infection: results of a 16 week pilot Phase I/II trial. *Antivir Ther* 2004; **9:** 603–14.

Javanese Turmeric

Curcuma Zanthorrhiza; Curcumae Javanicae; Curcumae xanthorrhizae rhizoma; Geltonšaknių ciberžolių šakniastiebiai; Gurkmeja, javanesisk; Jaavan kurkuma; Jávai-kurkuma gyökértörzs; Oddenek kurkumy žlutokořenné; Temoe lawacq; Temoe Lawak; Témoé-lawaq.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Turmeric, Javanese). It consists of the dried rhizome, cut in slices, of *Curcuma xanthorrhiza*. It contains not less than 5% v/w of essential oil and not less than 1% of dicinnamoyl methane derivatives expressed as curcumin, both calculated with reference to the anhydrous drug. It has an aromatic odour. Protect from light.

Profile

Javanese turmeric is an ingredient of preparations indicated for biliary and gastrointestinal disorders. It is a close relative of the spice turmeric (p.1473), which has been used similarly.

Irritable bowel syndrome. For reference to the ineffectiveness of Javanese turmeric in patients with irritable bowel syndrome see under Fumitory, p.2307.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Gallentee†; ***Ger.:*** Bilagit Mono†; Curcu-Truw; Curcumen; Infi-tract; Pankreaplex mono.

Multi-ingredient: ***Austria:*** Choleodoron; ***Fr.:*** Hepaclem; ***Ger.:*** Bilisan Duo; Cholosom SL†; Cholosom-Tee; Divalol W†; Enzym-Harongan; Gallexier; Hepaticum novo†; Infi-tract†; ***Hong Kong:*** Hepatofalk; ***Indon.:*** Curliv; Curliv Plus; Curson; Gramuno; Hepa-Q; Hepacell; Hepatofalk Planta; Hepimun; Librozym; Norflam; Verona; ***S.Afr.:*** Choleodoron; ***Singapore:*** Hepatofalk Planta; ***Switz.:*** Choleodoron†.

Turpentine Oil

Aetheroleum Terebinthinae; Esencia de Trementina; Essence de Térébenthine; Oleum Terebinthinae; Oleum Terebinthinae Depuratum; Rectified Turpentine Oil; Spirits of Turpentine; Térébenthine, huile essentielle de; Terebentin Yağı; Terebinthini aetheroleum; Terebintin Esansı; Trementina, aceite esencial de.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Turpentine Oil, Pinus Pinaster Type; Terebinthini Aetheroleum ab Pinum Pinastrum). An essential oil obtained by steam distillation, followed by rectification at a temperature below 180°, from the oleoresin obtained by tapping *Pinus pinaster*. A suitable antioxidant may be added. It contains 70.0 to 85.0% α-pinene, 0.5 to 1.5% camphene, 11.0 to 20.0% β-pinene, maximum 1% car-3-ene, 0.4 to 1.5% β-myrcene, 1.0 to 7.0% limonene, 0.2 to 2.5% longifolene, 0.1 to 3.0% β-caryophyllene, and maximum 1.0% caryophyllene oxide.

A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.856 to 0.872. Store in well-filled airtight containers at a temperature not exceeding 25°. Protect from light.

Adverse Effects

In poisoning with turpentine oil there may be local burning and gastrointestinal upset, coughing and choking, pulmonary oedema, excitement, coma, fever, tachycardia, liver damage, haematuria, and albuminuria. Fatalities have occurred.

The application to the skin of liniments containing turpentine oil may cause irritation and absorption of large amounts may cause some of the effects listed above. Hypersensitivity reactions and local irritation have been reported.

Uses and Administration

Turpentine oil is widely used as a solvent. It is applied topically as a rubefacient. It is an ingredient of many preparations used in respiratory-tract disorders, but is now judged to be neither safe nor effective.

Preparations

BP 2008: White Liniment.

Proprietary Preparations (details are given in Part 3)

Fr.: Ozothine; ***Ger.:*** Caprisana†; ***Port.:*** Vicks Vaporub.

Multi-ingredient: ***Arg.:*** Atomo Desinflamante C; Bronco Etersan; Fluido; Notoxin; Otocalmia; Rati Salil Crema; ***Austral.:*** Goanna Heat Cream; Goanna Salve; Vicks Vaporub; ***Austria:*** Acimont; Baby Luuf; Bronchostop; Carl Baders Divinal; Emser Nasensalbe; Ilon Abszess; Kinder Luuf; Leukona-Rheuma-Bad; Luuf Balsam; Pe-Ce; Piniment; Rubriment; Salhumin; Scottopect; Trauma-Salbe warmend; Tussamag; Vulpuran; Wick Vaporub; ***Belg.:*** Algis-Spray; Reflexspray; Vicks Vaporub; ***Braz.:*** A Curitybina; Aliviol; Analgen†; Angino-Rub; Benegel; Frixopel; Gelflex; Gelofrix; Gelol†; Gelonevral†; Massageol; Mentalol†; Mialgex†; Nevrol; Oleo Eletrico†; Salimetin†; Traumac; Traumagel; Vick Vaporub; ***Canad.:*** Cal Mo Dol; Cerumol; ***Chile:*** Balsamo Leon†; Calorub Nueva Formula; Hansaplast Descongestionante; Mentobalsam; ***Cz.:*** Ilon Abszess; Viprosal B†; ***Fin.:*** Vicks Vaporub; ***Fr.:*** Dinacode†; Lumbalgine; Ozothine; Ozothine a la Diprophylline; Vicks Vaporub; ***Ger.:*** Em-eukal†; Emser Nasensalbe N†; Erkaltungsbalsam-ratiopharm E Salbe†; Hevertopect; Hevertopect N†; Ilon Abszess; Leukona-Rheuma-Bad N†; Leukona-Rheumasalbe†; Ozothin†; tactu-mobil; Tetesept Badekonzentrat Erkaltungs Bad N†; Trauma-Salbe Rodler 302 N†; Wick Vaporub; ***Gr.:*** Deep Heat; Faragel-Forte; ***India:*** Clearwax; Flexi-muv; Waxolve; ***Indon.:*** Opino; Sloan's Liniment; ***Israel:*** Deep Heat Rub; Ment-O-Cap; ***Ital.:*** Capsolin; Vicks Vaporub; ***Malaysia:*** Thermorub; ***Neth.:*** Luuf Verkoudheidsbalsem; Luuf Verkoudheidsbalsem (voor babies); Luuf Verkoudheidsbalsem (voor Kinderen); Vicks Vaporub; ***NZ:*** Vicks Vaporub; ***Pol.:*** Analgol; Analgolan; Capsigel N; Deep Heat; Derhotill; Dip Hot; Herbolen; Inhalol; Neo-Capsiderm; Pulmonil; Reumatik; Rub-Arom; Wick Vaporub; ***Port.:*** Balsamo Analgesico Basi; Balsamo Analgesico Labesfal; Calicida Indiano; Freimax†; Lauromentol†; ***Rus.:*** Capsicam (Капсикам); Carmolis Fluid (Кармолис Жидкость)†; Doktor Mom (Доктор Мом); Olimetin (Олиметин)†; Suprima-Plus (Суприма-Плюс); Viprosal B (Випросал В); ***S.Afr.:*** Balsem Sulphuris; Deep Heat Rub; Haarlemensis; Puma Balm; Respisniffers; Sloan's Liniment Rub; Vicks Vaporub; Woodwards Inhalant; ***Spain:*** Dologex†; Embrocacion Gras; Linimento Klari†; Masagil; Otocerum; Reflex; Termosan; ***Swed.:*** Vicks Vaporub†; ***Switz.:*** Alginex†; Baume du Chalet; Carmol; Cerumenol; Eucapinol; Frixo-Dragon Vert†; Knobel Huile N; Makaphyt Baume†; Massorax†; Pinimenthol†; PO-HO bleu; Pommade au Baume; Vicks Vaporub N; ***Thai.:*** Stopain; Tiffyrub†; ***Turk.:*** Algo-Wax; Bugumentol; Buguseptil; Capsalgine; Gelocaps; Kataljin; Vicks Vaporub; ***UK:*** Deep Heat Rub; Dragon Balm; Ellimans; Goddards Embrocation; Gonne Balm; Modern Herbals Muscular Pain; Nasciodine; Nine Rubbing Oils; Vicks Vaporub; Waxwane†; ***USA:*** Vicks Vaporub; ***Venez.:*** Friccion Aromatica.

Tyramine Hydrochloride ⊗

Tiramina, hidrocloruro de; *p*-Tyramine Hydrochloride; Tyrosamine Hydrochloride. 4-Hydroxyphenethylamine hydrochloride; 4-(2-Aminoethyl)phenol hydrochloride.

$C_8H_{11}NO,HCl$ = 173.6.

CAS — 51-67-2 (tyramine); 60-19-5 (tyramine hydrochloride).

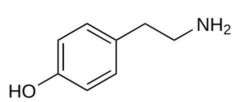

(tyramine)

Profile

Tyramine hydrochloride is a sympathomimetic with indirect effects on adrenergic receptors. It has been given orally or by injection in the tyramine pressor test for the investigation of monoamine oxidase inhibitory activity or amine uptake blocking activity. It has also been used in studies of physiological and disease states, and in the diagnosis of migraine and phaeochromocytoma.

The hazards of taking foods rich in tyramine while under treatment with MAOIs are described in the chapter on Antidepressants (see Phenelzine, p.417).

◊ The bioavailability of tyramine given by mouth is significantly reduced by the presence of food, which could have implications when used in tyramine pressor tests.[1]

1. VanDenBerg CM, *et al.* Tyramine pharmacokinetics and reduced bioavailability with food. *J Clin Pharmacol* 2003; **43:** 604–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ger.:*** Mydrial-Atropin†.

Ubidecarenone *(BAN, rINN)*

Coenzyme Q10; Ubidecarenona; Ubidécarénone; Ubidecarenonum; Ubidekarenon; Ubidekarenonas; Ubidekarenoni; Ubiquinone-10. 2-Deca(3-methylbut-2-enylene)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.

Убидекаренон

$C_{59}H_{90}O_4$ = 863.3.
CAS — 303-98-0.
ATC — C01EB09.
ATC Vet — QC01EB09.

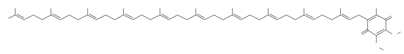

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Ubidecarenone). A yellow or orange crystalline powder. It gradually decomposes and darkens on exposure to light. M.p. about 48°. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in acetone. Store in airtight containers. Protect from light.

USP 31 (Ubidecarenone). A yellow to orange, crystalline powder. M.p. about 48°. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in ether. Protect from light.

Profile

Ubidecarenone is a naturally occurring coenzyme involved in electron transport in the mitochondria. It is claimed to be a free radical scavenger and to have antoxidant and membrane stabilising properties. It has been given by mouth as an adjunct in cardiovascular disorders, including mild or moderate heart failure. It has also been tried in other conditions associated with coenzyme deficiency, and is promoted as a dietary supplement. Ubidecarenone is under investigation for the management of cancer, Huntington's chorea (p.953) and parkinsonism.

◊ For discussion of the use of ubidecarenone in statin-induced muscle disorders, see Effects on Skeletal Muscle, under Simvastatin, p.1391.

◊ References.

1. Greenberg S, Frishman WH. Co-enzyme Q : a new drug for cardiovascular disease. *J Clin Pharmacol* 1990; **30:** 596–608.
2. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; **344:** 1372–3.
3. Garcia Silva MT, *et al.* Improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1994; **343:** 1039.
4. Gattermann N, *et al.* No improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1995; **345:** 1121–2.
5. Nagao T, *et al.* Treatment of warfarin-induced hair loss with ubidecarenone. *Lancet* 1995; **346:** 1104–5.
6. Pepping J. Coenzyme Q . *Am J Health-Syst Pharm* 1999; **56:** 519–21.
7. Khatta M, *et al.* The effect of coenzyme Q in patients with congestive heart failure. *Ann Intern Med* 2000; **132:** 636–40.
8. Tran MT, *et al.* Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy* 2001; **21:** 797–806.
9. Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001; **57:** 397–404.
10. Rahman S, *et al.* Neonatal presentation of coenzyme Q10 deficiency. *J Pediatr* 2001; **139:** 456–8.
11. Roffe L, *et al.* Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review. *J Clin Oncol* 2004; **22:** 4418–24.
12. Sándor PS, *et al.* Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005; **64:** 713–15.
13. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q during statin therapy. *Ann Pharmacother* 2006; **40:** 290–4.
14. The NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q and GPI-1485 in early Parkinson disease. *Neurology* 2007; **68:** 20–8.
15. Rosenfeldt FL, *et al.* Coenzyme Q in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens* 2007; **21:** 297–306.

Preparations

USP 31: Ubidecarenone Capsules; Ubidecarenone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: QX 100; ***Braz.:*** Coex†; Vinocard Q10; ***Canad.:*** Co-Q-10†; ***Fr.:*** Bio-Quinon Q10 Super†; Q10; ***Hong Kong:*** CoQuinone†; Eiquinon; ***Hung.:*** Myoqinon; ***Indon.:*** Co-En Q; Ubi-Q; ***Ital.:*** Coedieci†; Decafar; Decorenone; Iuvacor; Miodene†; Miotyn†; Mitocor†; Oropigma Gel; Tricoxen; Ubicardio†; Ubicor; Ubidenone; Ubidex; Ubimaior; Ubiten†; Ubivis; ***Jpn:*** Neuquinon; ***Malaysia:*** Alerten; Bio-Quinone; Neuquinon; ***Philipp.:*** Adlife; Alerten; Neuquinon; ***Pol.:*** Envit Q ; Vita Care Q ; ***Port.:*** Q 10; Ubenzima; Ubicondrial†; ***Singapore:*** CoQuinone; Ubi-Q; ***Thai.:*** Bio-Quinone; Decaquinon; ***UK:*** Co-Q-10†; ***USA:*** Co-Q-10†; CoQuinone.

Multi-ingredient: ***Arg.:*** QX 10; ***Canad.:*** Mega AO; ***Indon.:*** Car-Q; Co-Q-10; Corsel; Lycoq; RG-Q; ***Ital.:*** Agedin Plus; Coqun; Ener-E†; Visu Q10; ***Philipp.:*** Immuvit; Nutrotal; ***UK:*** Red Kooga Co-Q-10 and Ginseng.

Ulinastatin *(rINN)*

Ulinastatina; Ulinastatine; Ulinastatinum; Urinastatin.

Улинастатин

CAS — 80449-31-6; 80449-32-7.

Pharmacopoeias. In *Jpn.*

Profile

Ulinastatin is a glycoprotein proteolytic enzyme inhibitor isolated from human urine. It has been given by slow intravenous injection or by intravenous infusion in acute pancreatitis (p.2361) and in acute circulatory insufficiency.

◊ References.

1. Ohwada M, *et al.* New endoscopic treatment for chronic pancreatitis, using contrast media containing ulinastatin and prednisolone. *J Gastroenterol* 1997; **32:** 216–21.
2. Sugita T, *et al.* Effect of a human urinary protease inhibitor (Ulinastatin) on respiratory function in pediatric patients undergoing cardiopulmonary bypass. *J Cardiovasc Surg* 2002; **43:** 437–40.
3. Tsujino T, *et al.* Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005; **3:** 376–83.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Miraclid.

Uracil *(USAN)*

BMS-205603-01; Sq-6201; Sq-7726; Sq-8493. 2,4(1*H*,3*H*)-pyrimidinedione.

Урацил

$C_4H_4N_2O_2$ = 112.1.
CAS — 66-22-8.

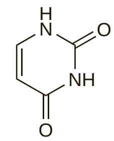

Profile

Uracil is a pyrimidine base and one of the components of uridine nucleotides that form ribonucleic acid (p.2379). It inhibits dihydropyrimidine dehydrogenase and reduces the metabolism of fluorouracil; it is given orally with tegafur (p.776), an oral fluorouracil prodrug, to increase the bioavailability of fluorouracil.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: UFT; ***Thai.:*** UFUR.

Multi-ingredient: ***Arg.:*** Asofurtal; UFT; ***Austria:*** UFT; ***Belg.:*** UFT; ***Braz.:*** UFT; ***Denm.:*** Uftoral; ***Fr.:*** UFT; ***Ger.:*** UFT; ***Gr.:*** UFT; ***Hong Kong:*** UFT; ***Hung.:*** UFT; ***Israel:*** UFT†; ***Ital.:*** UFT; ***Jpn:*** UFT; ***Malaysia:*** UFT; ***Mex.:*** UFT; ***Neth.:*** UFT; ***Norw.:*** UFT; ***NZ:*** Orzel†; ***Philipp.:*** Tefudex; UFT; ***Port.:*** UFT; ***Rus.:*** UFT (УФТ); ***S.Afr.:*** UFT; ***Singapore:*** UFT; ***Spain:*** UFT; ***Swed.:*** UFT; ***Thai.:*** UFT; ***Turk.:*** UFT; ***UK:*** Uftoral.

Urazamide

5-Aminoimidazole-4-carboxamide ureidosuccinate.

$C_9H_{14}N_6O_6$ = 302.2.

Profile

Urazamide has been given orally in the treatment of hepatic disorders. It has also been given by intramuscular and intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Carbaica†.

Uridine

Uracil Riboside; Uridina; Urydyna. 1-β-D-Ribofuranosyluracil; 1-β-D-Ribofuranosylpyrimidine-2,4(1*H*,3*H*)-dione.

Уридин

$C_9H_{12}N_2O_6$ = 244.2.
CAS — 58-96-8.

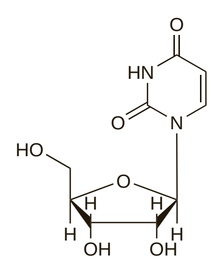

Profile

Uridine is an endogenous uracil nucleoside involved in many biological processes; it is one of the components of nucleic acids (p.2355). Uridine is used in preparations containing other nucleosides in the treatment of corneal damage. It has been included in preparations for peripheral and cerebral vascular disorders and myopathies; it has also been used for liver disorders, anaemias, and as a tonic. Uridine has been tried in patients with hereditary orotic aciduria.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Vitacic; ***Cz.:*** Laevadosin†; ***Hung.:*** Vitacic†; ***Ital.:*** Centrum; ***Mon.:*** Vitacic; ***Rus.:*** Vitacic (Витасик)†.

Uridine Triphosphate

Ins-316; Trifosfato de uridina; Uridina trifosfato; Uridine Triphosphoric Acid; UTP. Uridine 5′-(tetrahydrogen triphosphate).

Уридин Трифосфат

$C_9H_{15}N_2O_{15}P_3$ = 484.1.
CAS — 63-39-8.

Profile

Uridine triphosphate is an endogenous uracil nucleotide involved in many biological processes. It has been claimed to be of value in muscular atrophy and muscular weakness, and has been included in preparations for neuralgia, neuritis, and muscular disorders; the disodium and trisodium salts have also been used.

◊ Uridine triphosphate has been reported to have beneficial effects on mucociliary clearance in chronic respiratory disease such as cystic fibrosis, asthma, and chronic bronchitis, although it may not be suitable for such therapy because it is rapidly degraded by enzymatic activity within sputum and by airway epithelial cells.[1,2] It may, however, have a role as a method of producing deep-lung sputum specimens for cytological evaluation and is being investigated as an aid to the diagnosis of for example, lung cancer[1,2] or airway inflammation in asthma.[3]

1. Bennett WD, *et al.* Effect of aerosolized uridine 5'-triphosphate on mucociliary clearance in mild chronic bronchitis. *Am J Respir Crit Care Med* 2001; **164:** 302–6.
2. Johnson FL, *et al.* Improved sputum expectoration following a single dose of INS316 in patients with chronic bronchitis. *Chest* 2002; **122:** 2021–9.
3. Tamaoki J, *et al.* Validity and safety of sputum induction by inhaled uridine 5′-triphosphate. *Am J Respir Crit Care Med* 2001; **164:** 378–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Uteplex; ***Ital.:*** Miocuril†.

Multi-ingredient: ***Arg.:*** Nucleo CMP†; ***Braz.:*** Nucleo CMP; ***Chile:*** Citoneuron; ***Ital.:*** Fosfoutipi Vitaminico†; ***Mex.:*** Nucleo CMP; ***Spain:*** Cefabol; Nucleo CMP; Taurobetina†.

Ursodeoxycholic Acid *(BAN, rINN)*

Acide Ursodéoxycholique; Acide ursodésoxycholique; Ácido ursodeoxicólico; Acidum ursodeoxycholicum; Kyselina ursodeoxycholová; UDCA; Ursodeoksicholio rūgštis; Ursodeoksikolik Asit; Ursodeoksikoolihappo; Ursodeoxicholsyra; Ursodesoxycholic Acid; Ursodiol *(USAN)*; Urzodezoxikólsav. 3α,7β-Dihydroxy-5β-cholan-24-oic acid.

Урсодезоксихолевая Кислота

$C_{24}H_{40}O_4$ = 392.6.
CAS — 128-13-2.
ATC — A05AA02.
ATC Vet — QA05AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Ursodeoxycholic Acid). A white or almost white powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol; slightly soluble in acetone.

USP 31 (Ursodiol). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether. Store in airtight containers.

Stability. References.

1. Mallett MS, *et al.* Stability of ursodiol 25 mg/mL in an extemporaneously prepared oral liquid. *Am J Health-Syst Pharm* 1997; **54:** 1401–4.
2. Johnson CE, Streetman DD. Stability of oral suspensions of ursodiol made from tablets. *Am J Health-Syst Pharm* 2002; **59:** 361–3.

Adverse Effects and Precautions

Ursodeoxycholic acid may cause nausea, vomiting, and other gastrointestinal disturbances; diarrhoea is reported to occur less frequently than with chenodeoxycholic acid. Increased liver enzyme values are also less likely. Pruritus may occur. Treatment with ursodeoxycholic acid may cause more calcification of cholesterol stones than chenodeoxycholic acid.

Ursodeoxycholic acid should not be given to patients with intestinal and hepatic disorders that interfere with entero-hepatic circulation of bile salts (but see Chronic Liver Disease below). It is ineffective for the dissolution of calcified and pigment gallstones and is of no value in patients without a patent and functioning gallbladder. Licensed product information recommends that its use should be avoided in pregnancy.

◊ References.

1. Hempfling W, *et al.* Systematic review: ursodeoxycholic acid—adverse effects and drug interactions. *Aliment Pharmacol Ther* 2003; **18:** 963–72.

Interactions

Ursodeoxycholic acid should not be used with drugs that increase bile cholesterol such as oestrogenic hormones and cholesterol-lowering drugs such as clofibrate. Use with bile-acid binding drugs including antacids, charcoal, and colestyramine should be avoided since this may reduce the effectiveness of therapy with ursodeoxycholic acid.

For references to the possible effects of ursodeoxycholic acid on ciclosporin, see p.1828.

Pharmacokinetics

Ursodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile. Under the influence of intestinal bacteria the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid, some of which is excreted directly in the faeces and the rest absorbed and mainly conjugated and sulfated by the liver before excretion in the faeces. However, in comparison with chenodeoxycholic acid, less ursodeoxycholic acid undergoes such bacterial degradation.

◊ References.

1. Crosignani A, *et al.* Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet* 1996; **30:** 333–58.

Uses and Administration

Ursodeoxycholic acid is a naturally occurring bile acid (see p.2266) present in small quantities in human bile. Ursodeoxycholic acid suppresses the synthesis and secretion of cholesterol by the liver and inhibits intestinal absorption of cholesterol. It is used for the dissolution of cholesterol-rich **gallstones** in patients with functioning gallbladders (see below). The licensed dose is 6 to 12 mg/kg daily as a single bedtime dose or in 2 or 3 divided doses; obese patients may require up to 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentration seen overnight. The time required for dissolution of gallstones is likely to be between 6 and 24 months depending on stone size and composition. Treatment should be continued for 3 to 4 months after radiological disappearance of the stones. A dose of 300 mg twice daily has been suggested for the *prevention* of gallstones in patients undergoing rapid weight loss. Ursodeoxycholic acid has also been given in reduced doses in combination with chenodeoxycholic acid (p.2280).

Ursodeoxycholic acid is also used in **primary biliary cirrhosis**. The usual dose is 10 to 15 mg/kg daily in 2 to 4 divided doses.

Ursodeoxycholic acid has been tried in the treatment of primary sclerosing cholangitis.

The more hydrophilic derivative, tauroursodeoxycholic acid, has also been used.

Chronic liver disease. The use of ursodeoxycholic acid in chronic liver diseases has been summarised.[1-5] There have been differing opinions of its value in primary biliary cirrhosis (below). Response has been reported in obstetric cholestasis of pregnancy,[6-10] primary sclerosing cholangitis,[11] chronic active hepatitis,[12] and viral hepatitis.[13,14] Although ursodeoxycholic acid is widely used in the treatment of obstetric cholestasis, data on its safety and efficacy in this indication are lacking, and its possible role therefore remains unclear until further larger studies have been done.[15] See also Adverse Effects and Precautions, above. Ursodeoxycholic acid appears to be of benefit in liver disease associated with cystic fibrosis[16-18] and in the UK the *BNFC* recommends a dose of 10 to 15 mg/kg twice daily in children and adolescents with this condition; alternatively the total daily dose may be given in 3 divided doses. Ursodeoxycholic acid had initially shown some promise in the treatment of nonalcoholic steatohepatitis,[19] but a randomised, controlled study[20] failed to confirm this. There has also been some interest in the use of ursodeoxycholic acid to treat refractory graft-versus-host disease of the liver in transplant patients,[21] and possibly as an adjuvant to immunosuppressant therapy[22-24] after orthotopic liver transplantation (p.1815). It may also be of benefit in the prevention of hepatic complications following allogeneic bone marrow transplantation (p.1811).[25,26] Ursodeoxycholic acid has shortened the clinical course of parenteral nutrition-associated cholestasis in very-low-birth-weight infants,[27] and the *BNFC* recommends a dose of 10 mg/kg three times daily for this purpose. Benefit has also been reported[28] in parenteral-nutrition associated cholestasis in children and adults, although the optimal timing and duration of therapy remains to be evaluated. Ursodeoxycholic acid has also been associated with a lower incidence of colonic dysplasia in patients with ulcerative colitis and primary sclerosing cholangitis.[29,30] For sclerosing cholangitis in children and adolescents, the *BNFC* recommends a dose of 5 to 10 mg/kg 2 or 3 times daily up to a maximum of 15 mg/kg 3 times daily depending on response. In children with biliary atresia, ursodeoxycholic acid may be used to treat associated cholestasis. The *BNFC* suggests a dose of 5 mg/kg three times daily in neonates and children up to 2 years of age, the dose and frequency adjusted according to response up to a maximum of 10 mg/kg three times daily.

1. de Caestecker JS, *et al.* Ursodeoxycholic acid in chronic liver disease. *Gut* 1991; **32:** 1061–5.
2. Rubin RA, *et al.* Ursodiol for hepatobiliary disorders. *Ann Intern Med* 1994; **121:** 207–18.
3. Kowdley KV. Ursodeoxycholic acid therapy in hepatobiliary disease. *Am J Med* 2000; **108:** 481–6.
4. Trauner M, Graziadei IW. Review article: mechanisms of action and therapeutic applications of ursodeoxycholic acid in chronic liver diseases. *Aliment Pharmacol Ther* 1999; **13:** 979–95.
5. Lazaridis KN, *et al.* Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *J Hepatol* 2001; **35:** 134–46.
6. Palma J, *et al.* Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol* 1997; **27:** 1022–8.
7. Roncaglia N, *et al.* A randomised controlled trial of ursodeoxycholic acid and S-adenosyl-l-methionine in the treatment of gestational cholestasis. *Br J Obstet Gynaecol* 2004; **111:** 17–21.
8. Kondrackiene J, *et al.* Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology* 2005; **129:** 894–901.
9. Glantz A, *et al.* Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology* 2005; **42:** 1399–1405.
10. Zapata R, *et al.* Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: a 12-year experience. *Liver Int* 2005; **25:** 548–54.
11. Lindor KD, *et al.* Ursodiol for primary sclerosing cholangitis. *N Engl J Med* 1997; **336:** 691–5.
12. Rolandi E, *et al.* Effects of ursodeoxycholic acid (UDCA) on serum liver damage indices in patients with chronic active hepatitis: a double-blind controlled study. *Eur J Clin Pharmacol* 1991; **40:** 473–6.
13. Puoti C, *et al.* Ursodeoxycholic acid and chronic hepatitis C infection. *Lancet* 1993; **341:** 1413–14.
14. Angelico M, *et al.* Recombinant interferon-α and ursodeoxycholic acid versus interferon-α alone in the treatment of chronic hepatitis C: a randomized clinical trial with long-term follow-up. *Am J Gastroenterol* 1995: **90:** 263–9.
15. Royal College of Obstetricians and Gynaecologists. Obstetric Cholestasis. RCOG Guideline No. 43 (issued January 2006). Available at: http://www.rcog.org.uk/resources/Public/pdf/obstetric_cholestasis43.pdf (accessed 01/07/08)
16. Colombo C, *et al.* Effects of ursodeoxycholic acid therapy for liver disease associated with cystic fibrosis. *J Pediatr* 1990; **117:** 482–9.
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30. Pardi DS, *et al.* Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology* 2003; **124:** 889–93.

PRIMARY BILIARY CIRRHOSIS. Primary biliary cirrhosis (PBC) is a chronic liver disease of unknown aetiology that develops due to progressive destruction of small and intermediate bile ducts within the liver, subsequently evolving to fibrosis and cirrhosis. Over 90% of patients are female, usually aged between 40 and 60 years. The disease is thought to be auto-immune in nature. Most patients develop antimitochondrial antibodies that may be evident even before disease is clinically apparent.[1,2] Genetic factors and hormonal stimulation may play a role in precipitating PBC.[1,2] Infectious agents such as *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*)[2] or retroviruses[3] may be involved in the pathogenesis.

Clinical manifestations include pruritus, fatigue, jaundice, hepatomegaly, and hypercholesterolaemia leading to xanthoma formation. In late disease portal hypertension, bleeding oesophageal varices and liver failure may develop. Impaired calcium and vitamin D absorption may result in osteomalacia or osteoporosis, and fat-soluble vitamin deficiencies may occur. There may be accumulation of copper in the liver.[4] Other disorders including rheumatoid arthritis, scleroderma, thyroiditis, and Sjögren's syndrome may be associated with PBC.[1,5]

The disease is slowly progressive, with a mean survival of 8 years for symptomatic patients, and 16 years for asymptomatic individuals.[1,6] Despite its presumed auto-immune aetiology, few immunosuppressive drugs have shown any benefit,[5,7] although newer drugs such as mycophenolate mofetil, sirolimus, and tacrolimus have yet to be fully evaluated.[7]

The best-studied treatment for PBC is ursodeoxycholic acid, which is thought to replace toxic endogenous bile acids, stimulate bile acid secretion, and exert local immunosuppressive and cytoprotective effects.[1,4,5,7-9] The value of ursodeoxycholic acid is controversial: its reported therapeutic benefits in terms of delaying disease progression and the need for liver transplantation[5,10] have not been confirmed by meta-analysis or systematic review.[11,12] Both of these were, however, criticised[13,14] on the grounds that most of the studies included had follow-up periods of only 2 years. In consequence, some do not recommend its use,[12,15] but others still believe it to be the treatment of choice.[1,7,13,14,16] Its advocates consider that it appears to be efficacious for about 10 years and improves long-term survival by delaying the progression of hepatic fibrosis, development of oesophageal varices, and the need for liver transplantation. However, it is not effective in the presence of extensive fibrosis or cirrhosis in advanced disease.[13,14,16]

Both penicillamine and azathioprine have been used in PBC, but trials have failed to show any benefit from treatment[5-7] and their use has declined. A systematic review[17] identified a significant increase in the occurrence of adverse effects with penicillamine and concluded that its use could not be supported for patients with PBC. Corticosteroids, colchicine, ciclosporin, and chlorambucil have also been tried, but toxicity has restricted their use.[5,7] They may be of benefit[2,4,6,7] when used with ursodeoxycholic acid, although some guidelines[5] do not recommend their use. A systematic review[18] of studies with methotrexate concluded that it tended to increase mortality or the need for liver transplantation and should not therefore be used in patients with PBC outside clinical trials. Budesonide[7] and bezafibrate[1,7] have also been tried.

Symptomatic treatment includes the use of bile acid sequestrants, such as colestyramine, to treat both pruritus and hypercholesterolaemia. Ursodeoxycholic acid may also improve pruritus in up to 40% of patients, and rifampicin, phenobarbital, and opioid antagonists are used as second-line therapies.[1,4,5,8] Vitamin D and calcium supplementation will prevent osteomalacia; supplementation with vitamins A, E, and K may also be necessary.[1,4,5,8] Liver transplantation is recommended for liver failure, although PBC can recur in the allograft.[5,13,14,16]

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15. Anonymous. Ursodeoxycholic acid for primary biliary cirrhosis. *Drug Ther Bull* 1999; **37:** 30–2.
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Gallstones. Gallstones (cholelithiasis) occur when mechanisms for the solubilisation of cholesterol or bilirubin fail or are overcome. They may be divided into those formed of pure cholesterol, which are usually solitary; pigment stones, largely made up of bilirubin or its derivatives; and mixed stones of cholesterol, bile pigment, and calcium salts, which form the great majority of cases seen in the West.

Gallstones are generally more common in women than in men. The prevalence also increases with age and obesity, although rapid weight loss as a result of dieting or surgery is associated with an increased risk.

As many as two-thirds of patients with gallstones are asymptomatic. Symptoms usually relate to the site of the stone although biliary colic is often present regardless of whether the stone is in the gallbladder or biliary tract. If the stone blocks the exit from the gallbladder, inflammation and bacterial infection may follow (acute cholecystitis), sometimes leading to perforation and subsequent peritonitis. Less commonly, obstruction of the common bile duct by gallstones (choledocholithiasis) may lead to cholestasis and jaundice; infection of the bile ducts and septicaemia may follow. Pancreatitis may also be associated with gallstone disease, and there may be an increased risk of developing malignant neoplasms of the gallbladder.

Treatment. Asymptomatic gallstones discovered during other investigations should not be treated, and even mildly symptomatic patients may be managed with analgesics and subsequent observation. Potent analgesics such as morphine may be needed in more severe cases (see Biliary and Renal Colic, p.5). In symptomatic patients the preferred treatment for gallstones is surgical removal of the gallbladder; laparoscopic cholecystectomy causes less postoperative morbidity than open surgery, and has largely replaced other methods of treatment.

In patients unsuited to, or unwilling to undergo, surgery for gallbladder stones, drug therapy, alone or with lithotripsy, may be considered.

Exogenous bile acids have been tried in an attempt to dissolve the cholesterol component of gallstones. Ursodeoxycholic acid is more effective and is associated with fewer adverse effects than chenodeoxycholic acid. Combination therapy has also been tried but this is no more effective than ursodeoxycholic acid alone. Dissolution of gallstones is slow but can be achieved in about one-third of cases with the best results seen with small stones. However, about half of all successfully treated patients will develop further gallstones within 10 years. Studies of prophylactic bile acid therapy have mostly yielded disappointing results, although such therapy may be of benefit in patients on very-low-calorie diets, after surgery for weight loss, and in those receiving treatment with octreotide.

Somewhat larger stones may respond to extracorporeal shock-wave lithotripsy, or fluoroscopically guided laser lithotripsy, which may be more effective. Oral bile acids should then be given to dissolve the stone fragments.

Another method that has been used is the direct instillation of a solvent (usually methyl *tert*-butyl ether) into the gallbladder, which dissolves stones within a matter of hours, and is effective against almost all cholesterol-based stones regardless of size and number. Care is required to avoid overflow of the solvent into the common bile duct or the duodenum, where it can cause inflammation. Other solvents, such as ethyl propionate have been investigated as potentially less toxic alternatives, and edetic acid has been suggested as a possible solvent for non-cholesterol gallstones. As with all non-surgical methods, recurrence is likely.

Patients with **stones in the common bile duct** or **acute cholecystitis** require prompt therapy because of the risk of serious complications; endoscopic sphincterotomy and physical retrieval of the stones with a basket or balloon appears to be the preferred treatment, with open surgery as an alternative. A biliary stent to allow bile flow around the stone has been used as a temporary measure in patients with stones too large to remove by endoscopic sphincterotomy. Lithotripsy or infusion of a solvent such as monoctanoin or methyl *tert*-butyl ether are possible alternatives in patients unfit for surgery.

In patients who develop cholecystitis or cholangitis antibacterial therapy may be required (see Biliary-tract Infections, p.164).

References.

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2. Ransohoff DF, Gracie WA. Treatment of gallstones. *Ann Intern Med* 1993; **119:** 606–19.
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8. Jakobs R, *et al.* Fluoroscopically guided laser lithotripsy versus extracorporeal shock wave lithotripsy for retained bile duct stones: a prospective randomised study. *Gut* 1997; **40:** 678–82.
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12. Bellows CF, *et al.* Management of gallstones. *Am Fam Physician* 2005; **72:** 637–42.
13. Portincasa P, *et al.* Cholesterol gallstone disease. *Lancet* 2006; **368:** 230–9.
14. Caddy GR, Tham TCK. Symptoms, diagnosis and endoscopic management of common bile duct stones. *Best Pract Res Clin Gastroenterol* 2006; **20:** 1085–1101.

Preparations

BP 2008: Ursodeoxycholic Acid Capsules; Ursodeoxycholic Acid Tablets; ***USP 31:*** Ursodiol Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Dexo; Solutrat; UDCA; Ursidesox; Ursomax; Urzac; ***Austral.:*** Ursofalk; ***Austria:*** Ursofalk; ***Belg.:*** Ursochol; Ursofalk; ***Braz.:*** Ursacol; ***Canad.:*** Urso; ***Chile:*** Solvobil; Ursofalk; ***Cz.:*** Ursochol; Ursofalk; Ursosan; ***Fin.:*** Adursal; ***Fr.:*** Delursan; Ursolvan; ***Ger.:*** Cholit-Ursan; Cholofalk; UDC; Urso†; Ursochol; Ursofalk; ***Gr.:*** Ursofalk; ***Hong Kong:*** Ursofalk; Ursosan; ***Hung.:*** Ursofalk; ***India:*** Udiliv; ***Indon.:*** Estazor; Pramur; Urdafalk; Urdahex; ***Irl.:*** Ursofalk; ***Israel:*** Ursofalk; Ursolit; ***Ital.:*** Benursil†; Biliepar; Coledos†; Desocol; Desoxil; Deursil; Dissolursil; Epasol†; Fraurs; Galmax†; Lentorsil†; Litoff; Litursol; Tauro; Tudcabil†; Urdes; Ursacol; Ursilon; Ursobil; Ursodamor; Ursodexil†; Ursodiol; Ursofalk†; Ursoflor; Ursolac†; Ursolisin; Ursoproge†; ***Jpn:*** Urso; Ursosan†; ***Malaysia:*** Ursofalk; ***Mex.:*** Ursofalk; ***Neth.:*** Ursochol; Ursofalk; ***Norw.:*** Ursofalk; ***NZ:*** Actigall; Ursofalk; ***Philipp.:*** Ursofalk; ***Pol.:*** Proursan; Ursocam; Ursofalk; Ursopol; ***Port.:*** Destolit; Ursofalk; ***Rus.:*** Ursosan (Урсосан); ***S.Afr.:*** Ursotan†; ***Singapore:*** Ursofalk; ***Spain:*** Ursobilane; Ursochol; ***Swed.:*** Ursofalk; ***Switz.:*** De-ursil; Ursochol; Ursofalk; ***Thai.:*** Udihep; Ursofalk; Ursolin; ***Turk.:*** Ursofalk; ***UK:*** Destolit; Urdox; Ursofalk; Ursogal; ***USA:*** Actigall; Urso.

Multi-ingredient: ***Austria:*** Lithofalk†; ***Ger.:*** Lithofalk; Urso Mix†; ***Gr.:*** Lithiofalk†; ***Ital.:*** Bilenor; ***Jpn:*** Cabe 2; Eki Cabe.

Urtica

Brännässleblad (nettle leaf); Brennessel; Dilgėlių lapai (nettle leaf); Kopřivový list (nettle leaf); Liść pokrzywy (nettle leaf); Nokkosenlehti (nettle leaf); Ortie; Ortie dioïque; Ortie, feuille d' (nettle leaf); Ortiga; Pokrzywa zwyczajna; Stinging Nettle; Urtica dioica; Urticae folium (nettle leaf).

Pharmacopoeias. In *Ger.* and *US* (both specify the root and rhizome of *Urtica dioica*).
Eur. (see p.vii) includes the leaf of *Urtica* spp. and also a form of *Urtica dioica* for homoeopathic preparations.
Br. includes a form of *Urtica urens* for homeopathic preparations.

Ph. Eur. 6.2 (Nettle Leaf; Urticae Folium). The whole or cut dried leaves of *Urtica dioica*, *Urtica urens*, or a mixture of the 2 species. It contains a minimum of 0.3% for the sum of caffeoylmalic acid and chlorogenic acid expressed as chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated on the dried basis.

Ph. Eur. 6.2 (Common Stinging Nettle for Homoeopathic Preparations). The whole, fresh, flowering plant of *Urtica dioica*. Protect from light.

BP 2008 (Urtica Urens Herb for Homeopathic Preparations). Fresh leaves and flowers of *Urtica urens*. The plant produces an itchy, burning sensation.

USP 31 (Stinging Nettle). The dried roots and rhizomes of *Urtica dioica* (Urticaceae), and may contain *Urtica urens*, known in commerce as dwarf nettle, as a minor component. It contains not less than 0.8% of total amino acids, not less than 0.05% of sitosterol, and not less than 0.003% scopoletin ($C_{10}H_8O_4$ = 192.2), calculated on the dried basis. Store in airtight containers. Protect from light.

Profile

Urtica (*Urtica dioica*) has been used in herbal medicine, mainly for urinary-tract and rheumatic disorders. *Urtica urens* has been used similarly.

Homoeopathy. Urtica has been used in homoeopathic medicines under the following names: Common stinging nettle; Urtica dioica; Urtica urens; Urt. u.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Uro-POS; ***Braz.:*** Imuno Max; ***Cz.:*** Koprivovy Caj, Koprivova Nat; Zihlava†; ***Ger.:*** Arthrodynat N†; Asendra†; Azuprostat Urtica†; Bazoton; Flexal Brennessel; Hox Alpha; Natu-lind; Natu-prosta; Pro-Sabona Uno†; Prosta-Truw; Prostaforton; Prostagalen; Prostaherb N; Prostamed Urtica; Prostaneurin†; Prostata; Prostawern; Rheuma-Hek; Rheuma-Kapseln; Rheuma-Stada†; Serless†; Uro-POS; Urol pros; Urticaprostat uno†; Urtipret†; Urtivit; utk; ***Pol.:*** Prostaherb N; Urtix; ***Switz.:*** Valverde Prostate capsules.

Multi-ingredient: ***Austral.:*** Cough Relief†; Extralife Flow-Care; Haemo-Red Formula; Infant Tonic†; Irontona; Urapro†; Vitatona; ***Austria:*** Anaemodoron; Berggeist; Florissamin†; Florissamol†; Menodoron; Mentopin; Prostagutt; Prostatonin; Species Carvi comp†; ***Braz.:*** Prostem Plus; ***Canad.:*** Allercept†; Ultra Quercitin; ***Cz.:*** Abfuhr-Heilkrautertee†; Diabeticka Cajova Smes-Megadiabetin; Nephrosal†; Perospir†; Prostakan Forte; Prostatonin†; Pulmoran; Species Urologicae Planta; Stoffwechseltee N†; ***Fr.:*** Fitacnol†; ***Ger.:*** Combudoron; Presselin Nieren-Blasen K 3†; Prostagutt forte; Prostatin F†; Uvirgan N†; Vollmers praparierter gruner N; Winar†; ***Hong Kong:*** Calmiderm; ***Ital.:*** Biothymus DS; Pluvio; Prostaplant; Sebacnol†; Shamday Antiforfora†; ***Malaysia:*** Cleansa Plus†; Prostakan†; ***Mex.:*** Prosgutt; ***Pol.:*** Alliofil; Herbaton; Immunofort; Naturapia Prostata; Nefrobonisol; Seboren; Urofort; ***Rus.:*** Herbion Urtica (Гербион Уртика); Prostagutt Forte (Простагут Форте); ***S.Afr.:*** Combudoron; Enzian Anaemodoron Drops; Menodoron; ***Spain:*** Natusor Artilane†; ***Switz.:*** Combudoron; Prostagutt-F; Prostatonin; The a l'avoine sauvage de Vollmer; Tisane Diuretique; Tisane pour les problemes de prostate; ***UK:*** Sinose.

Usnea Barbata

Barba de capuchino.
CAS — 125-46-2 (usnic acid).

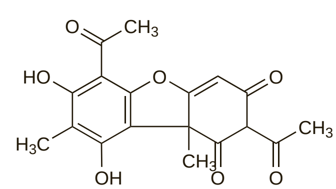

(usnic acid)

Profile

Usnea barbata is a lichen. It contains usnic acid, which is reported to have antimicrobial activity. *Usnea barbata* extract, usnic acid, and copper usnate have been used in topical preparations.

Adverse effects. Two patients developed severe hepatotoxicity believed to be associated with usnic acid contained in a multi-ingredient herbal preparation promoted for weight loss; one patient required emergency liver transplantation.[1]

1. Sanchez W, *et al.* Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. *Mayo Clin Proc* 2006; **81:** 541–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Dr Grandel Granobil†; Tetesept Hals-activ; ***Ital.:*** Vidermina; Zeta N.

Multi-ingredient: ***Indon.:*** Scabicid; ***Ital.:*** Foot Zeta; Micofoot; Steril Zeta.

Valepotriates

Valepotriatos.

Acevaltrate *(rINN)*

Acévaltrate; Acevaltrato; Acevaltratum. 4-Acetoxymethyl-(1 or 6)-3-(acetoxy-3-methylbutyryloxy)-1,6,7,7a-tetrahydro-(6 or 1)-isovaleryloxycyclopenta[*c*]pyran-7-spiro-2′-oxiran.

Ацевалтрат

$C_{24}H_{32}O_{10}$ = 480.5.
CAS — 25161-41-5.

Didrovaltrate *(rINN)*

Didrovaltrato; Didrovaltratum. 6-Acetoxy-1,4a,5,6,7,7a-hexahydro-1-isovaleryloxy-4-isovaleryloxymethylcyclopenta[*c*]pyran-7-spiro-2′-oxiran.

Дидровальтрат

$C_{22}H_{32}O_8$ = 424.5.
CAS — 18296-45-2.

Valtrate *(pINN)*

Valtrato; Valtratum. 4-Acetoxymethyl-1,6-di-isovaleryloxy-1,6,7,7a-tetrahydrocyclopenta[*c*]pyran-7-spiro-2′-oxiran.

Вальтрат

$C_{22}H_{30}O_8$ = 422.5.
CAS — 18296-44-1.

Profile

Valepotriates are epoxy-iridoid esters, isolated from valerian (see below). They include acevaltrate, didrovaltrate, and valtrate. On prolonged storage and drying they are hydrolysed to yield isovaleric acid.

A mixture stated to contain acevaltrate, didrovaltrate, and valtrate has been used as a sedative and as an anxiolytic. Concern has been expressed over the potential toxicity of valepotriates which have been reported to have cytotoxic properties *in vitro*.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Valmane; ***Gr.:*** Valmane.

Multi-ingredient: ***Arg.:*** SDN 200.

Valerian

Baldrianwurzel; Korzeń kozłka; Kozlíkový kořen; Macskagyökér; Valer; Valeriaananjuuri; Valerian Rhizome; Valerian Root; Valeriana; Valerianae radix; Valerianarot; Valériane, racine de; Valerijonų šaknys.

CAS — 8057-49-6 (valerian extract).
ATC — N05CM09.
ATC Vet — QN05CM09.

Pharmacopoeias. In *Eur.* (see p.vii) and *US. Eur.* also includes valerian dry hydroalcoholic extract and tincture. *US.* includes the powdered form.

Jpn has Japanese Valerian from *V. fauriei*.

Ph. Eur. 6.2 (Valerian Root; Valerian BP 2008). The yellowish-grey to pale brownish-grey whole underground parts of *Valeriana officinalis*, including the rhizome surrounded by the roots and stolons, or by fragments of these parts. It contains not less than 0.4% v/w of essential oil for the whole drug and not less then 0.3% v/w for the cut drug, both calculated with reference to the dried drug. Protect from light.

USP 31 (Valerian). The subterranean parts of *Valeriana officinalis* (Valerianaceae), including the rhizome, roots, and stolons. It contains not less than 0.5% of volatile oil and not less than 0.05% of valerenic acid, calculated on the dried basis. Store in airtight containers. Protect from light.

Profile

Valerian has sedative properties and is used as an extract, infusion, or tincture, or occasionally as the dried root, in preparations for anxiety states. It has also been used as a carminative. Valerian oil is used in aromatherapy. The odour of valerian may be removed from the skin and from hard surfaces with sodium bicarbonate.

◊ References.

1. Houghton P. Valerian. *Pharm J* 1994; **253:** 95–6.
2. Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol* 1999; **51:** 505–12.
3. Plushner SL. Valerian: valeriana officinalis. *Am J Health-Syst Pharm* 2000; **57:** 328–35.
4. Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. *Sleep Med* 2000; **1:** 91–9.
5. Bent S, *et al.* Valerian for sleep: a systematic review and meta-analysis. *Am J Med* 2006; **119:** 1005–12.

Adverse effects. Liver damage[1] was reported in 4 patients who took herbal stress remedies that contained valerian. Cardiac complications and delirium in a 58-year-old man may have been caused by the withdrawal of prolonged therapy with a valerian root extract preparation.[2]

1. MacGregor FB, *et al.* Hepatotoxicity of herbal remedies. *BMJ* 1989; **299:** 1156–7.
2. Garges HP, *et al.* Cardiac complications and delirium associated with valerian root withdrawal. *JAMA* 1998; **280:** 1566–7.

Preparations

Ph. Eur.: Valerian Dry Hydroalcoholic Extract; Valerian Tincture;
USP 31: Valerian Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Nervisatis; Sedante Nativa†; ***Austral.:*** Herbal Sleep Formula†; ***Austria:*** Baldrinetten†; ***Belg.:*** Dormiplant; Relaxine; Valdispert†; Valerial; ***Braz.:*** Noctaval; Recalm; Sonoripan; Traminer; Valdorm; Valeriane; Valerimed; Valerin; Valerix; Valezen; Valmane; ***Canad.:*** Nytol Natural Source; Sleep-Eze V Natural; Unisom Natural Source†; ***Chile:*** Sominex; ***Cz.:*** Koren Kozliku Lekarskeho†; Kozlik; Valdispert†; ***Fin.:*** Valrian; ***Ger.:*** Baldorm; Baldriparan Stark†; Baldrivit; Baldurat; Cefaluna†; Cefan; Dolestan; Euvegal Balance; Kytta-Sedativum; Luvased mono; Phytodorma†; Recvalysat†; Sedonium; Sporal mono; Valdispert; ***Hong Kong:*** Cirku Sed†; ***Israel:*** Relaxine; Valeton; ***Ital.:*** Ticalma; Val-Uno†; ***Mex.:*** Neolaikan; ***Neth.:*** Dormiplant; Sedonium; Valdispert; ***Pol.:*** Cirkused; Relana Forte; Valerin; ***Port.:*** Valdispert; Valditas; ***Rus.:*** Novo-Passit (Ново-Пассит); ***S.Afr.:*** Calmettes; ***Spain:*** Ansiokey; Cirkused†; Coenrelax; Tauval†; Valdispert; Valeriana Orto; Valsedan; ***Swed.:*** Baldrian-Dispert; Neurol; Valerecen; ***Switz.:*** Baldriparan pour la nuit; Baldrisedon†; Natu-Seda; Plantival Mono†; ReDormin; Sedasol eco natura; Sedonium; Sirop pour le sommeil†; Valdispert; Valverde Sommeil†; ***UK:*** Niteherb; Phytorelax; Sedonium; ***Venez.:*** Floral Pas.

Multi-ingredient: ***Arg.:*** Armonil; Calmtabs†; Dioxicolagol; Erbonda Noche†; Herbaccion Sedante†; Incaico Serenidad; Insomnal†; Nervocalm; SDN 200; Sedanat; Sedante Arceli†; Sedante Dia; Serenil; Sigmasedan; Top Life Relax†; Trixol†; Valeriana Diates; Valeriana Oligoplex; Valeriana Relax Diates; ***Austral.:*** Calmo; Coleus Complex; Dan Shen Compound; Executive B; Extralife Sleep-Care; Goodnight Formula†; Humulus Compound; Lifesystem Herbal Plus Formula 2 Valerian†; Macro Anti-Stress†; Multi-Vitamin Day & Night†; Natural Deep Sleep; Pacifenity†; Passiflora Complex†; Passionflower Plus; Prosed-X†; ReDormin; Relaxaplex†; Valerian Plus Herbal Plus Formula 12†; Valerian†; ***Austria:*** Baldracin; Baldrian AMA; Eryval; Euvekan; Hova; Nervenruh; Nerventee St Severin; Sedadom; Sedogelat; Songha; Species nervinae; Thymoval; Valin Baldrian; Wechseltee St Severin; ***Belg.:*** Natudor; Seneuval; Songha; ***Braz.:*** Anevrase†; Passicalm†; Remilev; Sominex; Sonhare; ***Canad.:*** Herbal Nerve; Herbal Sleep Well†; Relax and Sleep; ***Chile:*** Armonyl; Recalm; Valupass; ***Cz.:*** Baldracin; Bio-Strath†; Contraspan†; Dr Theiss Rheuma Creme†; Dr Theiss Schwedenbitter; Euvekan; Hertz- und Kreislauftee†; Hova; Klosterfrau Beruhigungs Forte†; Nervova Cajova Smes; Novo-Passit; Persen; Sanason; Schlaf-Nerventee N†; Songha Night†; Species Nervinae Planta; Valofyt Neo; Visinal†; ***Fr.:*** Anxoral†; Biocarde; Euphytose; Mediflor Tisane Calmante Troubles du Sommeil No 14; Mediflor Tisane Circulation du Sang No 12; Neuroflorine; Palpipax†; Passinevryl; Phytocalm†; Spasmine; Sympaneurol; Tranquital; ***Ger.:*** Alluna Nacht; Ardeysedon; Avedorm duo; Baldrian-Dispert Nacht; Baldriparan N Stark†; Biosedon†; Boxocalm; Cefasedativ†; Cor-Select†; Dormarist†; Dormeasan; Dormo-Sern†; Dormoverlan; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee; Dreierlei; Euvegal; Euvegal Entspannungs- und Einschlafdragees†; Euvegal Entspannungs- und Einschlaftropfen; Gutnacht†; Habstal-Nerv N†; Heumann Beruhigungstee Tenerval; Hingfong-Essenz Hofmanns; Hyperesa; JuDorm†; Kavosporal comp†; Kneipp Gute Nacht; Kytta-Sedativum; Leukona-Beruhigungsbad†; Lomasleep†; Luvased; Majocarmin mite†; Moradorm S; Mutellon; Nervendragees†; Nervenkapseln; Nervoregin forte†; Nervoregin phyto; Nervosana†; Neurapas; Nitrangin compositum†; Oxacant N†; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival novo; Presselin Nerven K 1 N†; Pronervon Phyto; Psychotonin-sed; Rhoival†; RubieSed†; Schlaf- und Nerventee; Schwedentrunk Elixier; Seda-Plantina†; Sedacur; Sedariston Konzentrat; Sedariston plus; Sedaselect D; Sedasyx†; Sedinfant N†; Selon; Sensinerv forte†; Somnuvis S†; Tornix; Valdispert comp†; Valeriana comp novum; Valeriana forte N†; Valeriana mild†; Valverde Baldrian Hopfen bei Einschlafstorungen und zur Beruhigung†; Vivinox Day; ***Hong Kong:*** Epizon†; ***Hung.:*** Euvekan; Hova; ReDormin; Sedacur; ***India:*** Well-Beeing†; ***Indon.:*** Slip-iZZZ; ***Israel:*** Calmanervin; Nerven-Dragees; Passiflora; Passiflora Compound; Songha Night; ***Ital.:*** Anevrasi; Bianco Val†; Biocalm; Calmason; Camomilla (Specie Composta)†; Dormiplant; Fitosonno; Florelax; Glicero-Valerovit; Melissa (Specie Composta)†; Noctis; Parvisedil; Reve; Sedatol; Sedopuer F; Val-Plus†; Valeriana (Specie Composta)†; ***Mex.:*** Ivel; Nervinetas; Pasinordin; Plantival; ***Pol.:*** Calmina; Cardiol C; Cardiotonic; Cholitol; Dormiplant; Fortestomachicae; Guttae Stomachicae; Hova; Kalms; Krople Zoladkowe; Lekosen; Lumewal; Neocardina; Neospasmina; Neospasmol; Nervendragees; Nervomix; Nervosol; Nerwobonisol; Passispasmin; Passispasmol; Persen; Prostapol; Relana; Sedomix; Tabletki Uspokajajace; Uroprost; Vallup; Valused; ***Port.:*** Antispasmina Colica; Gabisedil†; Neurocardol†; Songha†; Valesono†; ***Rus.:*** Doppelherz Vitalotonik (Доппельгерц Виталотоник); Herbion Drops for the Heart (Гербион Сердечные Капли); Insti (Инсти); Passifit (Пассифит); Persen (Персен); Sanason (Санасон); ***S.Afr.:*** Avena Sativa Comp; Biral; Entressdruppels HM; Helmontskruie; Krampdruppels; Restin; Stuidruppels; Wonderkroonessens; ***Spain:*** Dormiplant; Melival; Natusor Somnisedan†; Nervikan; Relana; Sedasor†; Sedonat; Valdispert Complex; ***Switz.:*** Baldriparan; Baldrisedon plus†; Dicalm†; Dormeasan; Dormiplant; Dragees pour la detente nerveuse; Dragees pour le coeur et les nerfs; Dragees pour le sommeil; Dragees sedatives Dr Welti; Hova; Nervinetten; Perpector†; Phytomed Somni†; ReDormin; Relaxane; Relaxo; Songha Night; Soporin; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Tisane relaxante N†; Valverde Coeur; Valverde Detente dragees; Valverde Sommeil; Valviska; Zeller Sommeil; ***UK:*** Avena Sativa Comp; Bio-Strath Valerian Formula; Daily Tension & Strain Relief; Digestive; Gerard House Serenity; Gerard House Somnus; Herbal Indigestion Naturtabs; Herbal Pain Relief; HRI Calm Life; HRI Golden Seal Digestive; HRI Night; Indigestion and Flatulence; Kalms; Kalms Sleep; Laxative Tablets; Menopause Relief; Modern Herbals Stress; Natrasleep; Natural Herb Tablets; Newrelax; Niteherb Plus; Nodoff; Nytol Herbal; Period Pain Relief; PMT Formula; Prementaid; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B ; Scullcap & Gentian Tablets; Sominex Herbal; Stressless; SuNerven; Sure-Lax (Herbal); Tranquil; Unwind Herbal Nytol; Valerina Day Time; Valerina Night-Time; Vegetable Cough Remover; Wellwoman; Wind & Dyspepsia Relief; ***Venez.:*** Cratex†; Equaliv; Eufytose†; Euvekan; Femendol; Insocaps; Lupassin; Nervinetas; Pasidor; Pasifluidina; Rendetil; Sedival.

Valspodar *(BAN, USAN, rINN)*

PSC-833; SDZ-PSC-833; Valspodarum. Cyclo{[(2*S*,4*R*,6*E*)-4-methyl-2-(methylamino)-3-oxo-6-octenoyl]-L-valyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl}.

Вальсподар

$C_{63}H_{111}N_{11}O_{12}$ = 1214.6.
CAS — 121584-18-7.

Profile

Valspodar is an analogue of ciclosporin (p.1822). It inhibits P-glycoprotein, which is associated with multidrug resistance. Valspodar is being investigated in various neoplasms to restore sensitivity of resistant tumour cells to anticancer drugs, but results have been disappointing.

Valspodar inhibits the cytochrome P450 isoenzyme CYP3A4, and may reduce the metabolism and clearance of other drugs.

◊ References.

1. Advani, R, *et al.* Treatment of poor prognosis AML patients using PSC833 (valspodar) plus mitoxantrone, etoposide, and cytarabine (PSC-MEC). *Adv Exp Med Biol* 1999; **457:** 47–56.
2. Sparreboom A, Nooter K. Does P-glycoprotein play a role in anticancer drug pharmacokinetics? *Drug Resist Updat* 2000; **3:** 357–63.
3. Kang MH, *et al.* The P-glycoprotein antagonist PSC 833 increases the plasma concentrations of 6α-hydroxypaclitaxel, a major metabolite of paclitaxel. *Clin Cancer Res* 2001; **7:** 1610–17.
4. Fracasso PM, *et al.* Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2001; **19:** 2975–82.
5. Baekelandt M, *et al.* Phase I/II trial of the multidrug-resistance modulator valspodar combined with cisplatin and doxorubicin in refractory ovarian cancer. *J Clin Oncol* 2001; **19:** 2983–93.
6. Baer MR, *et al.* Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: Cancer and Leukemia Group B Study 9720. *Blood* 2002; **100:** 1224–32.
7. Ma MK, *et al.* Pharmacokinetic study of infusional valspodar. *J Clin Pharmacol* 2002; **42:** 412–18.
8. Greenberg PL, *et al.* Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-risk myelodysplastic syndrome: a phase III trial (E2995). *J Clin Oncol* 2004; **22:** 1078–86. Correction. *ibid.*; 2747.
9. van der Holt B, *et al.* The value of the MDR1 reversal agent PSC-833 in addition to daunorubicin and cytarabine in the treatment of elderly patients with previously untreated acute myeloid leukemia (AML), in relation to MDR1 status at diagnosis. *Blood* 2005; **106:** 2646–54.
10. Friedenberg WR, *et al.* Phase III study of PSC-833 (valspodar) in combination with vincristine, doxorubicin, and dexamethasone (valspodar/VAD) versus VAD alone in patients with recurring or refractory multiple myeloma (E1A95): a trial of the Eastern Cooperative Oncology Group. *Cancer* 2006; **106:** 830–8.

Vanilla

Baunilha; Vainilla; Vanilla Beans; Vanilla Pods.

Pharmacopoeias. In *USNF.*

USNF 26 (Vanilla). The cured, full-grown, unripe fruit of *Vanilla planifolia*, often known in commerce as Mexican, Bourbon, or Madagascar vanilla, or of *V. tahitensis*, known in commerce as Tahitian vanilla (Orchidaceae). Vanilla that has become brittle should not be used. Store in airtight containers at a temperature not exceeding 8°.

Profile

Vanilla is used as a flavour and in perfumery. However, the odour and flavour of vanilla are not entirely due to vanillin (see below) but depend on the presence of other aromatic substances. Preparations of vanilla have been used in aromatherapy.

Preparations

USNF 26: Vanilla Tincture.

Vanillin

Vainillina; Vaniliini; Vanilin; Vanilinas; Vanillic Aldehyde; Vanilline; Vanillinum; Wanilina. 4-Hydroxy-3-methoxybenzaldehyde.

$C_8H_8O_3$ = 152.1.
CAS — 121-33-5.

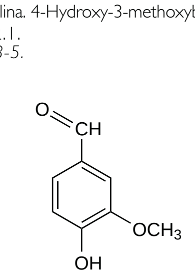

Pharmacopoeias. In *Eur.* (see p.vii) and *Viet.* Also in *USNF.*

Ph. Eur. 6.2 (Vanillin). White or slightly yellowish crystalline needles or powder. M.p. 81° to 84°. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Vanillin). Fine, white to slightly yellow crystals, usually needle-like, having an odour and taste suggestive of vanilla.

M.p. 81° to 83°. Soluble 1 in 100 of water at 25°, 1 in 20 of water at 80°, 1 in 20 of glycerol; freely soluble in alcohol, in chloroform, in ether, and in solutions of fixed alkali hydroxides. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Profile
Vanillin is used as a flavour and in perfumery.

Preparations
BP 2008: Tolu-flavour Solution.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Pulmex; Pulmex Baby; ***Turk.:*** Musilaks.

Varenicline *(BAN, rINN)*

Vareniclina; Varénicline; Vareniclinum. 7,8,9,10-Tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline.

Варениклин

$C_{13}H_{13}N_3$ = 211.3.
CAS — 249296-44-4.
ATC — N07BA03.
ATC Vet — QN07BA03.

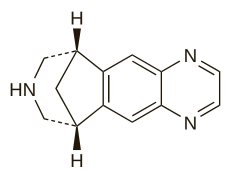

Varenicline Tartrate *(BANM, USAN, rINNM)*

CP-526555-18; Tartrato de vareniclina; Varénicline, Tartrate de; Vareniclini Tartras.

Варениклина Тартрат

$C_{13}H_{13}N_3,C_4H_6O_6$ = 361.3.
CAS — 375815-87-5.
ATC — N07BA03.
ATC Vet — QN07BA03.

Adverse Effects and Precautions
The most common adverse effect of varenicline is nausea; other adverse effects also commonly reported are headache, dizziness, somnolence, fatigue, sleep disturbances, increased appetite, and gastrointestinal disturbances including vomiting, constipation, and flatulence. There have been reports of neuropsychiatric symptoms as well as exacerbation of pre-existing psychiatric illness in patients who have taken varenicline. Patients should be monitored for such symptoms, including suicidal ideation or behaviour, agitation, depression, or other changes in behaviour.

Dizziness and somnolence may affect the performance of skilled tasks such as driving.

Pharmacokinetics
Varenicline is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 3 to 4 hours; bioavailability is high. Steady state concentrations are reached within 4 days of multiple oral dosing. Metabolism is minimal and about 92% of a dose is excreted unchanged in the urine; the elimination half-life is about 24 hours.

◊ References.

1. Faessel HM, *et al.* Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *J Clin Pharmacol* 2006; **46:** 991–8.
2. Burstein AH, *et al.* Pharmacokinetics, safety, and tolerability after single and multiple oral doses of varenicline in elderly smokers. *J Clin Pharmacol* 2006; **46:** 1234–40.
3. Burstein AH, *et al.* Pharmacokinetics, safety, and tolerability after single and multiple oral doses of varenicline in elderly smokers. *J Clin Pharmacol* 2006; **46:** 1234–40.
4. Faessel HM, *et al.* Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. *J Clin Pharmacol* 2006; **46:** 1439–48.

Uses and Administration
Varenicline is a selective nicotinic receptor partial agonist that is used as an aid for smoking cessation.

Varenicline is given orally as the tartrate with doses expressed in terms of the equivalent amount of varenicline; 1.71 mg of varenicline tartrate is equivalent to about 1 mg of varenicline. An initial dose equivalent to 500 micrograms varenicline is given once daily for the first 3 days, increasing to 500 micrograms twice daily for the next 4 days. The dose from the eighth day for the remainder of the course is 1 mg twice daily. The dose may be reduced to 500 micrograms twice daily if adverse effects are intolerable. Patients are advised to set a date to stop smoking and start varenicline 1 to 2 weeks before. Treatment is normally given for 12 weeks; in patients who successfully stop smoking, a further 12 weeks of treatment has been recommended to reduce the risk of relapse. For doses in renal impairment, see below.

◊ Reviews.

1. Zierler-Brown SL, Kyle JA. Oral varenicline for smoking cessation. *Ann Pharmacother* 2007; **41:** 95–9.
2. Potts LA, Garwood CL. Varenicline: the newest agent for smoking cessation. *Am J Health-Syst Pharm* 2007; **64:** 1381–4.
3. Hays JT, *et al.* Efficacy and safety of varenicline for smoking cessation. *Am J Med* 2008; **121** (suppl 1): S32–S42.
4. Anonymous. Varenicline for smoking cessation. *Drug Ther Bull* 2008; **46:** 33–6.

Administration in renal impairment. In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) licensed product information recommends a starting dose of 500 micrograms daily increased if necessary after 3 days to a maximum dose of 500 micrograms twice daily (in the USA) or 1 mg once daily (in the UK). In patients with end-stage renal disease undergoing haemodialysis, a maximum dose of 500 micrograms once daily may be given provided that this is well tolerated. No dosage adjustment is considered to be needed in patients with lesser degrees of impairment.

Smoking cessation. Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist that is used as an aid for smoking cessation (p.2354). Results from 2 randomised controlled studies[1,2] show greater efficacy than placebo as well as favourable results compared with bupropion, a standard treatment for smoking cessation. However, these studies also showed that nausea was reported in almost 30% of participants in the varenicline group; abnormal dreams were also a problem. A further 12 weeks of treatment with varenicline improved abstinence at 24 weeks in patients who stopped smoking in the first 12 weeks of treatment; after stopping all treatment, the reduced relapse rate was maintained in this group up to 28 weeks later (i.e. 1 year from the start of treatment).[3]

1. Gonzales D, *et al.* Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 47–55.
2. Jorenby DE, *et al.* Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 56–63. Correction. *ibid.*; 1355.
3. Tonstad S, *et al.* Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006; **296:** 64–71.

Preparations
Proprietary Preparations (details are given in Part 3)

Austral.: Champix; ***Braz.:*** Champix; ***Cz.:*** Champix; ***Fr.:*** Champix; ***Gr.:*** Champix; ***Hung.:*** Champix; ***NZ:*** Champix; ***Port.:*** Champix; ***UK:*** Champix; ***USA:*** Chantix.

Vascular Endothelial Growth Factor

Сосудистого Эндотелиального Фактора Роста; Фактор Роста Эндотелия Сосудов

Profile
Vascular endothelial growth factor is a family of structurally related proteins involved in angiogenesis and vasculogenesis. VEGF-A, the first member of the family to be discovered and still often referred to as simply VEGF, is thought to provide most of the angiogenic effect of this family. Other members described to date include: VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.

A gene therapy product supplying the gene for vascular endothelial growth factor D via an adenoviral vector is under investigation for the prevention of stenosis in synthetic grafts used in haemodialysis.

Vasoactive Intestinal Peptide

Péptido vasoactivo intestinal; PIV; Vasoactive Intestinal Polypeptide; VIP.

Вазоактивный Пептид Кишечника

CAS — 37221-79-7.

His–Ser–Asp–Ala–Val–Phe–Thr–Asp–Asn–Tyr–Thr–Arg–Leu–Arg
Asn–Leu–Ile–Ser–Asn–Leu–Tyr–Lys–Lys–Val–Ala–Met–Gln–Lys

Aviptadil *(BAN, rINN)*

Aviptadilum; Vasoactive Intestinal Octacosapeptide (Swine).

Авиптадил

$C_{147}H_{238}N_{44}O_{42}S$ = 3325.8.
CAS — 40077-57-4.

Profile
Vasoactive intestinal peptide acts as a hormone and neurotransmitter in various parts of the body; it is a potent relaxant of smooth muscle and has vasodilator and bronchodilator properties as well as stimulating the gastrointestinal tract to increased secretion. It is available as a synthetic analogue, aviptadil. It has been tried in the management of acute oesophageal food impaction, and for the treatment of acute respiratory distress syndrome, pulmonary arterial hypertension, acute lung injury, and chronic thromboembolic pulmonary hypertension. Aviptadil has been tried as a combination product with phentolamine for erectile dysfunction (p.2179).

◊ Vasoactive intestinal peptide has potential therapeutic applications in immunological disorders since it appears to inhibit inflammatory responses; it modulates the function of inflammatory cells via specific receptors affecting both innate and adaptive immunity.[1] It also appears to have endogenous neuroprotective properties within the CNS, possibly through influencing the expression and secretion of glial-cell derived neuroprotective factors. Consequently, it may have therapeutic potential in neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and stroke.[2]

1. Delgado M, *et al.* The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev* 2004; **56:** 249–90.
2. Dejda A, *et al.* Neuroprotective potential of three neuropeptides PACAP, VIP and PHI. *Pharmacol Rep* 2005; **57:** 307–20.

Preparations
Proprietary Preparations (details are given in Part 3)

NZ: Invicorp.

Vasopressin *(rINNM)*

ADH; Antidiuretic Hormone; Beta-Hypophamine; Vasopresina; Vasopressiini; Vasopressine; Vasopressinum; Vazopresin.

Вазопрессин

CAS — 11000-17-2 (vasopressin injection).
ATC — H01BA01.
ATC Vet — QH01BA01.

NOTE. Vasopressin Injection is *rINN*.

Pharmacopoeias. In *US*, which includes both argipressin and lypressin in this title.

An injection is included in *Jpn*.

USP 31 (Vasopressin). A polypeptide hormone having the properties of causing the contraction of vascular and other smooth muscles, and of antidiuresis. It is prepared by synthesis or obtained from the posterior lobe of the pituitary of healthy, domestic animals used for food by humans. Its vasopressor activity is not less than 300 USP units/mg. Store in airtight containers at 2° to 8°.

Argipressin *(BAN, rINN)*

[8-Arginine]vasopressin; Argipresina; Argipressine; Argipressinum; AVP. Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2 cyclic (1→6) disulphide.

Аргипрессин

$C_{46}H_{65}N_{15}O_{12}S_2$ = 1084.2.
CAS — 113-79-1.
ATC — H01BA06.
ATC Vet — QH01BA06.

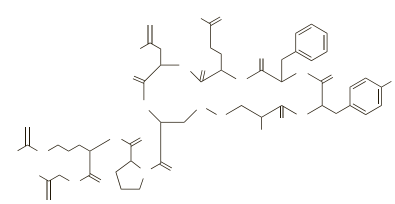

Description. Argipressin is a form of vasopressin obtained from most mammals including man but excluding pig. It is usually prepared synthetically. Lypressin (see below) is vasopressin from pig.

Argipressin Tannate *(BANM, USAN, rINNM)*

8-L-Arginine-vasopressin Tannate; Argipressine, Tannate d'; Argipressini Tannatum; CI-107; Tanato de argipresina. Tannins compound with argipressin.

Аргипрессина Таннат

ATC — H01BA06.
ATC Vet — QH01BA06.

Units
8.2 units of argipressin for bioassay are contained in approximately 20 micrograms of synthetic peptide acetate (with human albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Lypressin *(BAN, USAN, rINN)*

L-8; Lipresina; Lipressina; Lipresszin; LVP; Lypressiini; Lypressine; Lypressinum. [8-Lysine]vasopressin; Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (1→6) disulphide.

Липрессин

$C_{46}H_{65}N_{13}O_{12}S_2$ = 1056.2.
CAS — 50-57-7.
ATC — H01BA03.
ATC Vet — QH01BA03.

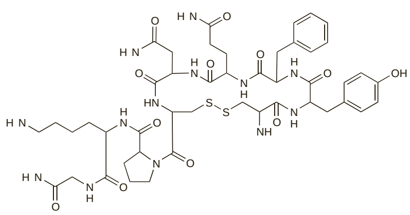

Description. Lypressin is the form of vasopressin present in the posterior pituitary of pigs.

Pharmacopoeias. *US* includes Lypressin Nasal Solution.

Incompatibility. Vasopressin was shown to be physically compatible (when injected at the Y-site in an intravenous tubing set) when tested in intravenous fluids with other drugs commonly used in cardiac arrest.[1] However, tests of vasopressin with drugs commonly used in septic shock showed physical incompatibility with phenytoin (when mixed in infusion bags).[2] Precipitation has also been reported[3] with vasopressin and furosemide together in intravenous fluids (tested at the Y-site).

1. Feddema S, *et al.* Physical compatibility of vasopressin with medications commonly used in cardiac arrest. *Am J Health-Syst Pharm* 2003; **60:** 1271–2.
2. Barker B, *et al.* Visual compatibility of vasopressin with other injectable drugs. *Am J Health-Syst Pharm* 2005; **62:** 1969, 1975–6.
3. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; **63:** 906–8.

Units

7.7 units of lypressin are contained in about 23.4 micrograms of synthetic peptide (with albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Adverse Effects

Large parenteral doses of vasopressin may give rise to marked pallor, pounding headache, vertigo, sweating, tremor, nausea, vomiting, diarrhoea, eructation, cramp, and a desire to defaecate; some of these effects may also occur after large intranasal doses of lypressin. In women, vasopressin may cause uterine cramps of a menstrual character. Hyponatraemia with water retention and signs of water intoxication can occur.

Hypersensitivity reactions have occurred and include urticaria and bronchoconstriction. Anaphylactic shock and cardiac arrest have been reported.

Vasopressin may constrict coronary arteries. Chest pain, myocardial ischaemia, and infarction have occurred following injection, and fatalities have been reported. Other cardiovascular effects include occasional reports of arrhythmias and bradycardia, as well as hypertension. Peripheral vasoconstriction has resulted in gangrene, and thrombosis as well as local irritation at the injection site may occur.

Nasal congestion, irritation, and ulceration have been reported occasionally after intranasal use, usually as lypressin; systemic effects at usual intranasal doses are mostly reported to be mild.

Effects on the heart. Arrhythmias, including ventricular tachycardia and fibrillation,[1] torsade de pointes,[2-4] and asystole[5] are among the adverse effects of vasopressin. Paradoxical bradycardia and hypotension have also been reported.[6]

1. Kelly KJ, *et al*. Vasopressin provocation of ventricular dysrhythmia. *Ann Intern Med* 1980; **92:** 205–6.
2. Eden E, *et al.* Ventricular arrhythmia induced by vasopressin: torsade de pointes related to vasopressin-induced bradycardia. *Mt Sinai J Med* 1983; **50:** 49–51.
3. Stein LB, *et al.* Fatal torsade de pointes occurring in a patient receiving intravenous vasopressin and nitroglycerin. *J Clin Gastroenterol* 1992; **15:** 171–4.
4. Faigel DO, *et al.* Torsade de pointes complicating the treatment of bleeding esophageal varices: association with neuroleptics, vasopressin, and electrolyte imbalance. *Am J Gastroenterol* 1995; **90:** 822–4.
5. Fitz JD. Vasopressin induction of ventricular ectopy. *Arch Intern Med* 1982; **142:** 644.
6. Kraft W, *et al.* Paradoxical hypotension and bradycardia after intravenous arginine vasopressin. *J Clin Pharmacol* 1998; **38:** 283–6.

Ischaemia. Reports of ischaemia and infarction associated with vasopressin.[1-10]

1. Greenwald RA, *et al*. Local gangrene: a complication of peripheral Pitressin therapy for bleeding esophageal varices. *Gastroenterology* 1978; **74:** 744–6.
2. Colombani P. Upper extremity gangrene secondary to superior mesenteric artery infusion of vasopressin. *Dig Dis Sci* 1982; **27:** 367–9.
3. Lambert M, *et al.* Reversible ischemic colitis after intravenous vasopressin therapy. *JAMA* 1982; **247:** 666–7.
4. Anderson JR, Johnston GW. Development of cutaneous gangrene during continuous peripheral infusion of vasopressin. *BMJ* 1983; **287:** 1657–8.
5. Reddy KR, *et al.* Bilateral nipple necrosis after intravenous vasopressin therapy. *Arch Intern Med* 1984; **144:** 835–6.
6. Brearly S, *et al.* A lethal complication of peripheral vein vasopressin infusion. *Hepatogastroenterology* 1985; **32:** 224–5.
7. Sweren BS, Bohlman ME. Gastric and splenic infarction: a complication of intraarterial vasopressin infusion. *Cardiovasc Intervent Radiol* 1989; **12:** 207–9.
8. Maceyko RF, *et al.* Vasopressin-associated cutaneous infarcts, alopecia, and neuropathy. *J Am Acad Dermatol* 1994; **31:** 111–13.
9. Lin RY, *et al.* Vasopressin-induced amber-like skin necrosis. *Dermatology* 1997; **195:** 271–3.
10. Dunser MW, *et al.* Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003; **31:** 1394–8.

Treatment of Adverse Effects

The antidiuretic effects on water retention and sodium imbalance may be treated by water restriction and a temporary withdrawal of vasopressin. Severe cases may require osmotic diuresis alone or with furosemide.

Extravasation. Localised intravenous and intra-arterial guanethidine was used in the treatment of a patient with extravasation of vasopressin.[1] The intra-arterial use of guanethidine was considered to have helped to avoid necrotic changes.

1. Crocker MC. Intravascular guanethidine in the treatment of extravasated vasopressin. *N Engl J Med* 1981; **304:** 1430.

Precautions

Vasopressin should not be used in patients with chronic nephritis with nitrogen retention. It should be avoided or given only with extreme care, and in small doses, to patients with vascular disease, especially of the coronary arteries.

It should be given with care to patients with conditions which might be aggravated by water retention including asthma, epilepsy, migraine, and heart failure. Fluid intake should be adjusted to avoid hyponatraemia and water intoxication. Care is also required in hypertension or other conditions that may be exacerbated by a rise in blood pressure. Nasal absorption of vasopressin may be impaired in patients with rhinitis.

Abuse. Vasopressin or its analogues have been abused as so-called 'smart drugs' for their supposed effect on memory recall and cognition.

Resistance. Antibodies to vasopressin were detected in 6 of 28 patients being treated for diabetes insipidus, all of whom had a decrease in antidiuretic effect with previously effective argipressin or lypressin therapy;[1] desmopressin and chlorpropamide remained effective in these patients. There have been reports of patients with diabetes insipidus of pregnancy unresponsive to argipressin but responsive to desmopressin.[2] This was probably due to excessive placental production of vasopressinase, an enzyme which degrades argipressin.

1. Vokes TJ, *et al.* Antibodies to vasopressin in patients with diabetes insipidus: implications for diagnosis and therapy. *Ann Intern Med* 1988; **108:** 190–5.
2. Shah SV, Thakur V. Vasopressinase and diabetes insipidus of pregnancy. *Ann Intern Med* 1988; **109:** 435–6.

Interactions

The antidiuretic effects of vasopressins might be expected to be enhanced in some patients receiving chlorpropamide, clofibrate, carbamazepine, fludrocortisone, urea, or tricyclic antidepressants. Lithium, heparin, demeclocycline, noradrenaline, and alcohol may decrease the antidiuretic effect. Ganglion-blocking drugs may increase sensitivity to the pressor effects of vasopressins.

Cimetidine. A report of severe bradycardia and heart block leading to asystole in a patient given combined vasopressin and cimetidine therapy.[1]

1. Nikolic G, Singh JB. Cimetidine, vasopressin and chronotropic incompetence. *Med J Aust* 1982; **2:** 435–6.

Uses and Administration

Vasopressin is secreted by the hypothalamus and stored in the posterior lobe of the pituitary gland. It may be prepared from the gland of mammals or by synthesis. Vasopressin has a direct antidiuretic action on the kidney, increasing tubular reabsorption of water. It also constricts peripheral blood vessels and causes contraction of the smooth muscle of the intestine, gallbladder, and urinary bladder. It has practically no oxytocic activity.

Vasopressin, which is usually given parenterally or intranasally in the synthetic forms of argipressin or lypressin, is used in the treatment of cranial diabetes insipidus due to a deficiency in antidiuretic hormone. It is ineffective in nephrogenic diabetes insipidus. Argipressin has also been used in the prevention and treatment of postoperative abdominal distension, and was formerly given to remove gas in abdominal visualisation procedures. Argipressin or lypressin are used in the treatment of bleeding oesophageal varices. Argipressin may have a role in cardiopulmonary resuscitation and shock due to vasodilatation.

In the treatment of cranial diabetes insipidus to control polyuria, argipressin may be given subcutaneously or intramuscularly; the dose in the UK is 5 to 20 units every 4 hours. In the USA, 5 to 10 units given 2 or 3 times daily or more has been used. Alternatively, argipressin or lypressin has been given as a nasal spray; dosage should be individually adjusted as required. A long-acting oily suspension of vasopressin tannate was formerly used by intramuscular injection in diabetes insipidus.

In the initial control of variceal bleeding argipressin is given in an initial dose of 20 units in 100 mL of glucose 5% infused intravenously over 15 minutes. Lypressin has also been given for bleeding oesophageal varices. Doses for children are given under Administration in Children, below.

Vasopressin has also been used as a vasoconstrictor in local anaesthetic injections.

Administration. Results[1] suggesting that although intravenous argipressin produced much higher plasma concentrations than intranasal, the latter evoked a greater CNS response.

1. Pietrowsky R, *et al.* Brain potential changes after intranasal vs intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. *Biol Psychiatry* 1996; **39:** 332–40.

Administration in children. Although not licensed in the UK for use in children, the *BNFC* includes a dose for adjunctive treatment of acute massive haemorrhage of the gastrointestinal tract or oesophageal varices in patients aged from 1 month to 18 years. An initial dose of 0.3 units/kg (up to 20 units) is given intravenously over 20 to 30 minutes, followed by a continuous infusion of 0.3 units/kg per hour adjusted according to response to a maximum of 1 unit/kg per hour. If the bleeding stops the infusion is continued at the same dose for 12 hours, then gradually withdrawn over 24 to 48 hours; the maximum duration of treatment should be 72 hours.

Vasopressin given by continuous intravenous infusion in an average dose of 9 milliunits/kg per hour was safe and effective in 5 children who had diabetes insipidus as a manifestation of severe brain injury.[1] A dose of 1.5 to 3 milliunits/kg per hour has also been used safely for postoperative diabetes insipidus in 2 children aged 3 years and under.[2] Similar initial doses of argipressin were used in 3 comatose children with cranial diabetes insipidus,[3] while a published algorithm for the management of acute cranial diabetes insipidus has recommended an initial dose of vasopressin of 0.25 to 1 milliunits/kg per hour, subsequently titrated to achieve an appropriate output and specific gravity of urine, and a serum sodium value of between 140 and 145 mmol/litre.[4]

1. Ralston C, Butt W. Continuous vasopressin replacement in diabetes insipidus. *Arch Dis Child* 1990; **65:** 896–7.
2. McDonald JA, *et al.* Treatment of the young child with postoperative central diabetes insipidus. *Am J Dis Child* 1989; **143:** 201–4.
3. Lee Y-J, *et al.* Continuous infusion of vasopressin in comatose children with neurogenic diabetes insipidus. *J Pediatr Endocrinol Metab* 1995; **8:** 257–62.
4. Lugo N, *et al.* Diagnosis and management algorithm of acute onset of central diabetes insipidus in critically ill children. *J Pediatr Endocrinol Metab* 1997; **10:** 633–9.

Advanced cardiac life support. Vasopressin (as argipressin) may be used as an alternative to adrenaline in cardiopulmonary resuscitation (see p.1156). In a preliminary study argipressin 40 units by intravenous injection appeared to be of value in the treatment of cardiac arrest due to ventricular fibrillation.[1] Spontaneous circulation returned in 16 of 20 patients so treated; 14 were successfully resuscitated on arrival in hospital and 8 survived to be discharged. In comparison, of 20 patients treated with 1 mg of adrenaline intravenously only 7 were resuscitated and 3 survived till discharge. However, a larger study[2] found no difference between vasopressin and adrenaline in the rates of survival to hospital admission for patients with ventricular fibrillation or pulseless electrical activity, although vasopressin was associated with a higher rate of hospital admission and discharge among patients with asystole. It also found that two doses of vasopressin followed by a single dose of adrenaline resulted in a better survival rate than three doses of adrenaline. Another large study[3] of patients who experienced cardiac arrest while in hospital and were treated with either vasopressin 40 units or adrenaline 1 mg, found no difference in survival to discharge from hospital. A systematic review[4] of 5 trials, including these 3, found no clear advantage for the use of vasopressin over adrenaline in the treatment of cardiac arrest.

1. Lindner KH, *et al.* Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997; **349:** 535–7.
2. Wenzel V, *et al.* A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; **350:** 105–13.
3. Stiell IG, *et al.* Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; **358:** 105–9.
4. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med* 2005; **165:** 17–24.

Diabetes insipidus. For a discussion of diabetes insipidus and its management, including reference to the use of vasopressin analogues (particularly desmopressin), see p.2179.

Haemorrhagic disorders. There are reports of vasopressin being used in the management of various haemorrhagic disorders including blood loss in abortion and caesarean section[1,2] and haemoptysis.[3,4] Infusion of vasopressin into the superior or inferior mesenteric artery has been used in the management of lower gastrointestinal bleeding, but modern embolisation techniques may be associated with fewer complications.[5] For the use of vasopressin in upper gastrointestinal variceal haemorrhage, see below.

1. Schulz KF, *et al.* Vasopressin reduces blood loss from second-trimester dilatation and evacuation abortion. *Lancet* 1985; **ii:** 353–6.
2. Lurie S, *et al.* Subendometrial vasopressin to control intractable placental bleeding. *Lancet* 1997; **349:** 698.
3. Noseworthy TW, Anderson BJ. Massive hemoptysis. *Can Med Assoc J* 1986; **135:** 1097–9.
4. Bilton D, *et al.* Life threatening haemoptysis in cystic fibrosis: an alternative therapeutic approach. *Thorax* 1990; **45:** 975–6. Correction. *ibid.* 1991; **46:** 274.
5. Darcy M. Treatment of lower gastrointestinal bleeding: vasopressin infusion versus embolization. *J Vasc Interv Radiol* 2003; **14:** 535–43.

Nocturnal enuresis. For references to the use of the vasopressin analogue, desmopressin, in nocturnal enuresis, see p.2187.

Shock. Argipressin has been reported to have beneficial vasopressor effects in the management of shock (p.1183) due to vasodilatation. It has been given by continuous intravenous infusion at a dose of about 2 to 6 units/hour as supplemental therapy in patients who could not be adequately managed with conventional vasopressor therapy.[1,2] In a retrospective study[3] vasopressin given with or without catecholamines for haemodynamic support of shock did not increase the incidence of venous thromboembolism compared with catecholamines given alone. Further reports[4,5] of the benefit of vasopressin in septic shock suggest that it may be of value in reducing doses of catecholamine vasopressors.

1. Dünser MW, *et al.* Management of vasodilatory shock: defining the role of arginine vasopressin. *Drugs* 2003; **63:** 237–56.
2. Dünser MW, *et al.* Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003; **107:** 2313–19.
3. Doepker BA, *et al.* Thromboembolic events during continuous vasopressin infusions: a retrospective evaluation. *Ann Pharmacother* 2007; **41:** 1383–9.
4. Obritsch MD, *et al.* Effects of continuous vasopressin infusion in patients with septic shock. *Ann Pharmacother* 2004; **38:** 1117–22.
5. Szumita PM, *et al.* Vasopressin for vasopressor-dependent septic shock. *Am J Health-Syst Pharm* 2005; **62:** 1931–6.

Variceal haemorrhage. Vasopressin has been widely used to control bleeding from oesophageal varices, as discussed under Monoethanolamine, on p.2346. However, terlipressin, and more recently octreotide, have been found to have some advantages over vasopressin, including bolus dosage and fewer adverse effects, and octreotide is increasingly preferred for this purpose. Glyceryl trinitrate has been given with the aim of counteracting the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure.[1-4]

1. Stump DL, Hardin TC. The use of vasopressin in the treatment of upper gastrointestinal haemorrhage. *Drugs* 1990; **39:** 38–53.
2. Williams SGJ, Westaby D. Management of variceal haemorrhage. *BMJ* 1994; **308:** 1213–17.
3. Sung JJY. Non-surgical treatment of variceal haemorrhage. *Br J Hosp Med* 1997; **57:** 162–6.
4. McCormack G, McCormack PA. A practical guide to the management of oesophageal varices. *Drugs* 1999; **57:** 327–35.

Preparations

USP 31: Lypressin Nasal Solution; Vasopressin Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Pitressin; ***Canad.:*** Pressyn; ***Ger.:*** Pitressin†; ***Gr.:*** Pitressin†; ***Irl.:*** Pitressin; ***NZ:*** Pitressin; ***UK:*** Pitressin; ***USA:*** Pitressin.

Used as an adjunct in: ***Thai.:*** Neo-Lidocaton†.

Vegetable Fatty Oils

Kasvirasvaöljyt; Olea Herbaria; Oljor, feta, vegetabiliska.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Vegetable Fatty Oils). Vegetable fatty oils are mainly solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids such as waxes, free fatty acids, partial glycerides, or unsaponifiable matters. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. The following are defined:

- *virgin oil*: the oil obtained from raw materials of special quality by mechanical procedures such as cold expression or centrifugation.
- *refined oil*: the oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining (followed by bleaching and deodorisation) or physical refining.
- *hydrogenated oil*: an oil obtained by expression and/or solvent extraction, and subsequently, either alkali refining or physical refining, then possible bleaching, followed by drying, hydrogenation, and subsequently bleaching and deodorisation.

Only phosphoric acid and alkali refined oils may be used in the preparation of parenteral dosage forms.

Hydrogenated Vegetable Oil

Aceite vegetal hidrogenado.

Pharmacopoeias. In *Br. Jpn* allows under the title Hydrogenated Oil a product from fish, other animals or vegetables. Also in *USNF.*
BP 2008 (Hydrogenated Vegetable Oil). A mixture of triglycerides of fatty acids of vegetable origin. An almost white, fine powder at room temperature and a pale yellow, oily liquid above its m.p. of 57° to 70°. Practically insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store at a temperature of 8° to 25°.
USNF 26 (Hydrogenated Vegetable Oil). Type 1 Hydrogenated Vegetable Oil occurs as a fine, white powder, beads, or small flakes; m.p. 57° to 85°. Type 2 Hydrogenated Vegetable Oil occurs as a plastic (semi-solid) or flakes, having a softer consistency than Type 1; m.p. 20° to 50°.
Insoluble in water; soluble in chloroform, in hot isopropyl alcohol, and in petroleum spirit. Store in airtight containers at a temperature of 8° to 15°.

Profile

Vegetable fatty oils are generally solid or liquid triglycerides of fatty acids that may contain small amounts of other lipids. They are obtained from the seeds or fruits of plants by expression and/or solvent extraction, and may then be refined or hydrogenated with the addition of a suitable antoxidant if necessary. They are fixed oils (expressed oils) and do not evaporate on warming as opposed to essential oils (ethereal oils, volatile oils), which evaporate readily and are usually obtained from their aromatic plant source by distillation. Some fixed vegetable oils are used to modify the consistency of ointments and for their emollient properties. They have also been used as vehicles for fat-soluble substances such as vitamins.

Hydrogenated vegetable oil is refined, bleached, hydrogenated, and deodorised vegetable oil stearins consisting mainly of the triglycerides of stearic and palmitic acids. It is used as a tablet lubricant and as an ointment or suppository basis.

Preparations

Proprietary Preparations (details are given in Part 3)
Spain: Blodex†.

Veratrine

Veratriini; Veratrin; Veratrina; Veratrinum.

CAS — 8051-02-3 (veratrine mixture); 71-62-5 (veratrine amorphous); 62-59-9 (veratrine crystallised, cevadine).

Description. Veratrine is a mixture of alkaloids from the dried ripe seeds of *Schoenocaulon officinale* (Liliaceae) (sabadilla). Veratrine should be distinguished from protoveratrines obtained from veratrum.

Adverse Effects, Treatment, and Precautions

Veratrine resembles aconite (p.2246) in its action on the peripheral nerve endings and poisoning should be treated similarly. It is an intense local irritant and has a powerful direct stimulating action on all muscle tissues. It has a violent irritant action on mucous membranes, even in minute doses, and must be handled with great care. When ingested it causes violent vomiting, purging, an intense burning sensation in the mouth and throat, and general muscular weakness.

Uses and Administration

Veratrine should not be used internally. It was formerly applied externally for its analgesic properties and as a parasiticide, especially for head lice, but even when used in this way there is danger of systemic poisoning from absorption.

Green Veratrum

American Hellebore; American Veratrum; Eléboro verde; Green Hellebore; Green Hellebore Rhizome; Veratro Verde; Veratrum Viride.

CAS — 8002-39-9.
ATC — C02KA01.
ATC Vet — QC02KA01.

Description. Green veratrum consists of the dried rhizome and roots of *Veratrum viride* (Liliaceae) from which are derived the alkaloidal mixtures alkavervir and cryptenamine.

White Veratrum

Eléboro blanco; European Hellebore; Veratrum Album; White Hellebore; White Hellebore Rhizome.

ATC — C02KA01.
ATC Vet — QC02KA01.

Description. White veratrum consists of the dried rhizome and roots of *Veratrum album* (Liliaceae) from which are derived the alkaloids protoveratrine A and B.

Adverse Effects

Veratrum alkaloids may cause nausea and vomiting at conventional therapeutic doses. Other adverse effects include epigastric and substernal burning, sweating, mental confusion, bradycardia or cardiac arrhythmias, dizziness, and hiccup. Profound hypotension and respiratory depression can occur at high doses.

Sneezing powder. Various symptoms of intoxication occurred in 7 patients due to the use of a sneezing powder containing white veratrum alkaloids.[1]

1. Fogh A, *et al.* Veratrum alkaloids in sneezing-powder: a potential danger. *J Toxicol Clin Toxicol* 1983; **20:** 175–9.

Treatment of Adverse Effects

After oral ingestion of veratrum alkaloids the stomach should be emptied by aspiration and lavage; activated charcoal may be considered within 1 hour of ingestion. Excessive hypotension with bradycardia or cardiac arrhythmias can be treated with atropine. The patient should be placed in a supine position with the feet raised.

Uses and Administration

White and green veratrum contain a number of pharmacologically active alkaloids that produce centrally mediated peripheral vasodilatation and bradycardia. They have been used in the treatment of hypertension but are generally considered to produce an unacceptably high incidence of adverse effects and have largely been replaced by less toxic antihypertensives.

Both green and white veratrum have also been used as insecticides.

Homoeopathy. White Veratrum has been used in homoeopathic medicines under the following names: Veratrum album; Ver. alb.

Verbascum

Aaron's Rod (*Verbascum thapsus*); Bouillon Blanc; Bouillon blanc, fleur de (mullein flower); Diviznový květ (mullein flower); Great Mullein (*Verbascum thapsus*); Kungsljusblomma (mullein flower); Mullein; Ökörfarkkoró virág (mullein flower); Orange Mullein (*Verbascum phlomoides*); Tūbių žiedai (mullein flower); Ukontulikukankukka (mullein flower); Verbasci flos (mullein flower); Wollblumen.

NOTE. The name Aaron's Rod has been applied to a number of plants including *V. densiflorum*, *Solidago* spp., and *Sempervivum tectorum.*

Pharmacopoeias. *Eur.* (see p.vii) includes the dried flowers.
Ph. Eur. 6.2 (Mullein Flower; Verbasci flos). The dried flowers, reduced to the corolla and the androecium, of *Verbascum thapsus*, *V. densiflorum*, and *V. phlomoides*. Store in airtight containers.

Profile

Verbascum flower is an ingredient of herbal remedies for cough and cold symptoms. The dried leaves and stems have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Eres N†; ***Pol.:*** Noverban.

Multi-ingredient: ***Austral.:*** Procold†; Verbascum Complex†; ***Austria:*** Brust- und Hustentee St Severin; ***Cz.:*** Naturland Grosser Swedenbitter†; Species Pectorales Planta; ***Fr.:*** Detoxell; ***Ger.:*** Equisil N; Hevertopect N†; ***Mex.:*** Bronkitose Mielimon; ***Pol.:*** Flegatussin; Gwajatussin; Termasil; ***Rus.:*** Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***Spain:*** Bronpul†; Natusor Broncopul†.

Verbenone

Werbenon. 2-Pinen-4-one; 4,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-one.

$C_{10}H_{14}O = 150.2.$
CAS — 80-57-9 (verbenone); 18309-32-5 (d-verbenone); 1196-01-6 (l-verbenone).
ATC Vet — QR05CA11 (L-verbenone).

Profile

Verbenone is a terpene found in lemon-verbena oil, rosemary oil (p.2381) and some other essential oils. It has been used, sometimes with pine oil, for respiratory disorders.

Verbenone has also been used as an insect repellent in forestry.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Ozopulmin; Ozopulmin G.

Multi-ingredient: ***Ital.:*** Ozopulmin; Ozopulmin G.

Vervain

Herba Columbariae; Herba Verbenae; Shop Vervain Wort; Verbena; Verveine Officinale.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Verbena Herb). The whole or fragmented, dried aerial parts of *Verbena officinalis* collected during flowering. It contains a minimum of 15% of verbenalin ($C_{17}H_{24}O_{10}$ = 388.4) calculated with reference to the dried drug.

Profile

Vervain, the aerial parts of *Verbena officinalis* (Verbenaceae), has been used for a wide range of disorders. It is a bitter and has been used for digestive disorders. It also has sedative properties and has been used for anxiety disorders and as a tonic during convalescence from chronic illness.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Avena Complex; Calmo; Nevaton; ***Austria:*** Sinupret; ***Cz.:*** Sinupret; Stomatosan†; ***Fr.:*** Calmophytum; Vigilia; ***Ger.:*** Sinupret; ***Hong Kong:*** Sinupret; ***Hung.:*** Sinupret; ***Indon.:*** Sinupret; ***Ital.:*** Neoderma 47; ***Mex.:*** Bisolsinus; ***Philipp.:*** Sinupret; ***Pol.:*** Sinupret; ***Rus.:*** Sinupret (Синупрет); ***Singapore:*** Sinupret; ***Switz.:*** Sinupret; Tisane pour nourissons et enfants; ***Thai.:*** Sinupret; ***UK:*** Athera; HRI Night; Kalms Sleep; Modern Herbals Menopause; Modern Herbals Stress; Newrelax; Period Pain Relief; Prementaid; Scullcap & Gentian Tablets; Stressless; SuNerven.

Vetrabutine Hydrochloride *(BANM, rINNM)*

Dimophebumine Hydrochloride; Hidrocloruro de vetrabutina; Sp-281; Vétrabutine, Chlorhydrate de; Vetrabutini Hydrochloridum. *N,N*-Dimethyl-α-(3-phenylpropyl)veratrylamine hydrochloride.

Ветрабутина Гидрохлорид

$C_{20}H_{27}NO_2,HCl$ = 349.9.

CAS — 3735-45-3 (vetrabutine); 5974-09-4 (vetrabutine hydrochloride).

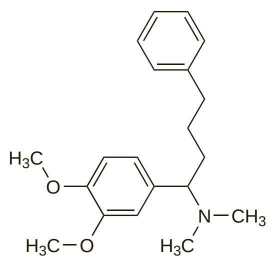

(vetrabutine)

Profile

Vetrabutine hydrochloride is used as a uterine relaxant in veterinary medicine.

Vinburnine *(rINN)*

CH-846; (−)-Eburnamonine; 3α,16α-Eburnamonine; Vinburnina; Vinburninum; Vincamone. (3α,16α)-Eburnamenin-14(15*H*)-one.

Винбурнин

$C_{19}H_{22}N_2O$ = 294.4.

CAS — 4880-88-0.

ATC — C04AX17.

ATC Vet — QC04AX17.

Profile

Vinburnine is an alkaloid related to vincamine (below) and has been used in conditions associated with cerebral circulatory insufficiency.

Vinburnine phosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Cervoxan; ***Ital.:*** Eburnal†; Tensiplex†; ***Port.:*** Cervoxan; ***Spain:*** Cervoxan.

Vincamine *(BAN, rINN)*

Vincamina; Vincaminum. Methyl (3α,16α)-14,15-dihydro-14β-hydroxyeburnamenine-14-carboxylate.

Винкамин

$C_{21}H_{26}N_2O_3$ = 354.4.

CAS — 1617-90-9.

ATC — C04AX07.

ATC Vet — QC04AX07.

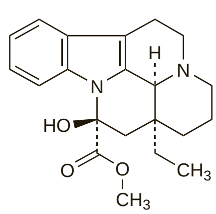

Pharmacopoeias. In *Fr.*

Profile

Vincamine is an alkaloid obtained from *Vinca minor* (Apocynaceae). It is claimed to increase cerebral circulation and utilisation of oxygen and has been used in a variety of cerebral disorders. Vincamine may have adverse effects on the cardiovascular system and care should be taken in patients with hypertension or cardiac dysfunction.

Vincamine salts including vincamine hydrochloride, oxoglurate, teprosilate, and hydrogen tartrate have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cincuental†; Vinkhum; ***Austria:*** Cetal†; ***Belg.:*** Cerebroxine; ***Fr.:*** Vinca†; ***Ger.:*** Ophdilvas N†; ***Hong Kong:*** Aethroma†; ***Ital.:*** Vasonett†; Vinca-Ri†; Vinca-Treis; Vincadar†; Vraap†; ***Mex.:*** Vincapan; ***Port.:*** Arteriovinca; Cervinca; Vincagil†; ***Spain:*** Arteriovinca†; Domeni†; Tefavinca; Vadicate†; Vincacen; Vincaminol; ***Switz.:*** Cetal†; Oxygeron.

Multi-ingredient: ***Arg.:*** Ribex; ***Fr.:*** Rheobral; ***Port.:*** Anacervix; Centracetam†; Stimilfar†; ***Spain:*** Anacervix; Devincal; ***Venez.:*** Devincal†.

Vinpocetine *(USAN, rINN)*

AY-27255; Ethyl Apovincaminate; Ethyl Apovincaminoate; RGH-4405; Vinpocetin; Vinpocetina; Vinpocétine; Vinpocetinum; Vinposetiini. Ethyl (3α,16α)-eburnamenine-14-carboxylate.

Винпоцетин

$C_{22}H_{26}N_2O_2$ = 350.5.

CAS — 42971-09-5.

ATC — N06BX18.

ATC Vet — QN06BX18.

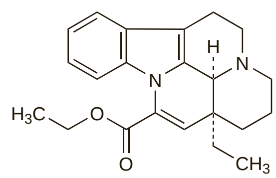

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Vinpocetine). A white or slightly yellow, crystalline powder. Practically insoluble in water; soluble in dichloromethane; slightly soluble in anhydrous alcohol.

Profile

Vinpocetine is a derivative of vincamine (above) that has been given orally in cerebrovascular disorders and dementia. Good evidence to support its use in cognitive impairment is lacking.

◊ References.

1. Grandt R, *et al.* Vinpocetine pharmacokinetics in elderly subjects. *Arzneimittelforschung* 1989; **39:** 1599–1602.
2. Blaha L, *et al.* Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome. *Hum Psychopharmacol Clin Exp* 1989; **4:** 103–11.
3. Bereczki D, Fekete I. A systematic review of vinpocetine therapy in acute ischaemic stroke. *Eur J Clin Pharmacol* 1999; **55:** 349–52.
4. Szatmari SZ, Whitehouse PJ. Vinpocetine for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 31/03/06).
5. Kemény V, *et al.* Acute and chronic effects of vinpocetine on cerebral hemodynamics and neuropsychological performance in multi-infarct patients. *J Clin Pharmacol* 2005; **45:** 1048–54.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cavinton†; ***Braz.:*** Vicog; ***Cz.:*** Cavinton; Vicebrol; ***Ger.:*** Cavinton†; ***Hung.:*** Cavinton; ***Pol.:*** Cavinton; Vicebrol; Vinpoton; ***Port.:*** Cavinton; Ultra-Vinca; Vipocem; ***Rus.:*** Cavinton (Кавинтон); Telectol (Телектол); ***Singapore:*** Cavinton; ***Thai.:*** Cavinton; Vinpocen.

Multi-ingredient: ***Rus.:*** Vinpotropile (Винпотропил).

Vinyl Chloride

Cloruro de vinilo; VCM; Vinilo, cloruro de; Vinyl Chloride Monomer; Winylu chlorek. Chloroethylene.

C_2H_3Cl = 62.50.

CAS — 75-01-4.

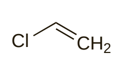

Profile

Vinyl chloride is used in the manufacture of polyvinyl chloride (PVC) and other vinyl polymers. Occupational exposure to vinyl chloride in polymerisation plants has been associated with acro-osteolysis, especially in the terminal phalanges of the fingers, a condition resembling Raynaud's phenomenon, and sclerodermatous skin changes. Liver damage and hepatic angiosarcoma, splenomegaly, thrombocytopenia, impaired respiratory function, and chromosomal abnormalities have also occurred.

◊ References.

1. Infante PF, *et al.* Genetic risks of vinyl chloride. *Lancet* 1976; **i:** 734–5.
2. Black CM, *et al.* Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. *Lancet* 1983; **i:** 53–5.
3. Piratsu R, *et al.* La mortalità dei produttori di cloruro di vinile in Italia. *Med Lav* 1991; **82:** 388–423.
4. Riordan SM, *et al.* Vinyl chloride related hepatic angiosarcoma in a polyvinyl chloride autoclave cleaner in Australia. *Med J Aust* 1991; **155:** 125–8.
5. Mur JM, *et al.* Spontaneous abortion and exposure to vinyl chloride. *Lancet* 1992; **339:** 127–8.
6. McLaughlin JK, Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. *J Epidemiol Biostat* 1999; **4:** 253–75.

Water

Agua; Aqua; Aqua Communis; Aqua Fontana; Aqua Potabilis; Eau Potable; Vatten; Vesi; Víz; Wasser; Woda.

H_2O = 18.02.

CAS — 7732-18-5.

Purified Water

Agua purificada; Aqua purificata; Eau purifiée; Išgrynintas vanduo; Puhdistettu vesi; Tisztított víz; Vatten, renat; Voda čištěná; Woda oczyszczona.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Eur. also includes Highly Purified Water. *US* also includes Sterile Purified Water.

Some pharmacopoeias only include distilled water or have additional monographs for demineralised water or distilled water.

Ph. Eur. 6.2 (Water, Purified; Aqua Purificata). It is water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised. It is prepared from suitable potable water either by distillation, by ion exchange, by reverse osmosis, or by any other suitable method. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Submonographs cover Purified Water in Bulk and Purified Water in Containers.

Ph. Eur. 6.2 (Water, Highly Purified; Aqua Valde Purificata). It is water intended for the preparation of medicinal products where water of high biological quality is needed, except where Water for Injections is required.

USP 31 (Purified Water). It is prepared from potable water by a suitable process.

Preparation. ***DEIONISATION.*** By passing potable water through columns of anionic and cationic ion-exchange resins, ionisable substances can be removed, producing a water of high specific resistance. Colloidal and non-ionisable impurities such as pyrogens may not be removed by this process.

DISTILLATION. In this process water is separated as vapour from non-volatile impurities and is subsequently condensed. In practice, non-volatile impurities may be carried into the distillate by entrainment unless a suitable baffle is fitted to the still.

Water for Injections

Agua para inyecciones; Aq. pro Inj.; Aqua ad iniectabilia; Aqua ad Injectionem; Aqua Injectabilis; Aqua Pro Iniectione; Aqua pro Injectione; Aqua pro Injectionibus; Eau pour préparations injectables; Injekcinis vanduo; Injektionesteisiin käytettävä vesi; Vatten för injektionsvätskor; Víz parenterális célra; Voda na injekci; Wasser für Injektionszwecke; Water for Injection; Woda do wstrzykiwań.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

US also includes Sterile Water for Injection, Sterile Water for Inhalation, Sterile Water for Irrigation, and Bacteriostatic Water for Injection.

Ph. Eur. 6.2 (Water for Injections). It is water for the preparation of medicines for parenteral administration when water is used as the vehicle, and for dissolving or diluting substances or preparations for parenteral administration. It is prepared by distillation of potable water or purified water from a neutral glass, quartz, or suitable metal still fitted with an effective device for preventing the entrainment of droplets; the first portion of the distillate is discarded and the remainder collected. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Sub-monographs cover Water for Injections in Bulk and Sterilised Water for Injections.

USP 31 (Water for Injection). It is purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and micro-organisms. When used for the preparation of parenteral solutions it should be sterilised first or the final preparation should be sterilised after preparation. Sterile Water for Injection, Inhalation, or Irrigation and Bacteriostatic Water for Injection are the subjects of separate monographs.

Profile

There are international standards for the quality of water intended for human consumption. Toxic substances such as arsenic, barium, cadmium, chromium, copper, cyanide, lead, and selenium may constitute a danger to health if present in drinking water in excess of the recommended concentrations. Water-borne infections are also a hazard.

Fluoride is regarded as an essential constituent of drinking water but may endanger health if present in excess—see Sodium Fluoride, p.1962. Ingestion of water containing large quantities of nitrates may cause methaemoglobinaemia in infants; many countries have standards for nitrates in water.

The use of tap water containing metal ions (such as aluminium, copper, and lead), fluoride, or tosylchloramide sodium, for dialysis may be hazardous.

Hard water contains soluble calcium and magnesium salts, which form scale and sludge in boilers, water pipes, and autoclaves; they also cause the precipitation of soap and prevent its lathering. Temporary hardness in water is due to the presence of bicarbonates which are converted to insoluble carbonates on heating. Permanent hardness is due to dissolved chlorides, nitrates, and sulfates, which do not form a precipitate on heating. The presence or absence of such salts can play a part in cardiovascular health.

Without further purification, potable water may be unsuitable for certain pharmaceutical purposes. In such instances, purified water should always be used. Most pharmacopoeias include monographs on various preparations of water, such as water suitable for injections. Potable water should not be used when such preparations of water are specified.

Excessive ingestion of water can lead to water intoxication with disturbances of the electrolyte balance.

◊ References.

1. Manz F, *et al.* The most essential nutrient: defining the adequate intake of water. *J Pediatr* 2002; **141:** 587–92.

Preparations

Proprietary Preparations (details are given in Part 3)
Fin.: Aquasteril; ***Hung.:*** Humaqua; Rins-Aqua; ***Port.:*** Estericlean†; ***UK:*** Aquasol; Uriflex W; ***USA:*** Fleet Bagenema.

Wheat

Blé; Froment; Frumento; Grano; Trigo; Weizen.

Пшеница Мягкая

NOTE. Distinguish from Triticum, a synonym for Couch-grass (see p.2288).

Profile

Wheat (*Triticum* spp., Poaceae) is a grass cultivated worldwide as a cereal crop. Common wheat (*Triticum aestivum*, (*T. vulgare*)) is the source of wheat germ and wheat-germ oil (below). Malted grain of wheat is used in the preparation of malt extract (p.1955). Wheat is also used as a source of bran (p.1712) and starch (p.1968).

Wheat germ and wheat-germ oil are used in preparations for lesions of the skin and mucous membranes and as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Dermocrem; Vagitrene; ***Canad.:*** Dermatix Fitocream; ***Ger.:*** Vulnostimulin; ***Ital.:*** Fitostimoline; Step 2; ***Turk.:*** Fito; ***Venez.:*** Derain; Gynoderain.

Multi-ingredient: ***Arg.:*** Amenite Plus†; Cicatul; Microlift; ***Fr.:*** Phytolongbronze; ***Ital.:*** Decon Ovuli; Fitostimoline; Sclerovis H; Solecin; ***Mex.:*** Fitoestimulina; Italdermol; ***Port.:*** Fitocreme; ***UK:*** S.P.H.P..

Wheat-germ Oil

Búzacsíraolaj; Germes de blé, huile de; Kviečių gemalų aliejus; Oleum Tritici Germinis; Pšeničný olej; Tritici aestivi oleum; Tritici Oleum; Vehnänalkioöljy; Vetegroddolja.

Масло Пшеничных Зародышей

CAS — 8006-95-9.

Pharmacopoeias. *Eur.* (see p.vii) includes Wheat-germ Oil, Refined, and Wheat-germ Oil, Virgin.

Ph. Eur. 6.2 (Wheat-germ Oil, Refined; Tritici Aestivi Oleum Raffinatum). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or by other suitable mechanical means and/or by extraction. It is then refined. A suitable antoxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40° to 60°. Relative density about 0.925. Store in an airtight container. Protect from light.

Ph. Eur. 6.2 (Wheat-germ Oil, Virgin; Tritici Aestivi Oleum Virginale). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or other suitable mechanical means. A clear, light yellow or golden-yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40° to 60°. Relative density about 0.925. Store in an airtight container. Protect from light.

Profile

Wheat-germ oil is a rich source of vitamin E (p.1992). It is included in dietary supplements and in preparations for lesions of the skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Braz.:*** Gamaline-V; ***Fr.:*** Bio-Selenium; Phytophanere; ***Indon.:*** Eviprostat; ***Ital.:*** Babigoz Crema Protettiva; Babysteril; Ottovis; ***Jpn:*** Eviprostat; ***Singapore:*** Eviprostat; ***Switz.:*** Sanhelios Capsules a la vitamine A†; ***UK:*** No-Sor Nose Balm.

Wild Carrot

Dauci Herba; Daucus; Queen Anne's Lace; Zanahoria silvestre.

NOTE. The name Queen Anne's lace has also been used for cow parsley (*Anthriscus sylvestris*), another umbellifer.

Pharmacopoeias. In *Chin.*

Profile

The fruits of the wild carrot, *Daucus carota* (Umbelliferae) have been used as a diuretic and anthelmintic, and are included in herbal preparations for various indications. Other parts of the plant have been used in folk medicine. Carrot seed oil is used in aromatherapy. The root of the cultivated form, *D. carota* subsp. *sativus*, is a culinary item and a source of carotenoids in the diet.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Hepatalgina; Metiogen; Palatrobil; ***Chile:*** Natur-Zin; Natursel-C; ***Ital.:*** Evamilk; ***Malaysia:*** Eyebright Plus†; ***UK:*** Sciargo; Watershed.

Wild Cherry Bark

Corteza de cerezo silvestre; Prunus Serotina; Virginian Prune; Virginian Prune Bark; Wild Black Cherry Bark; Wild Cherry.

Profile

Wild cherry bark is the dried bark of the wild or black cherry, *Prunus serotina* (Rosaceae), known in commerce as Thin Natural Wild Cherry Bark, containing not less than 10% of water-soluble extractive. It has a slight odour and an astringent, aromatic, bitter taste, recalling that of bitter almonds. It contains (+)-mandelonitrile glucoside (prunasin) and an enzyme system, which interact in the presence of water yielding benzaldehyde, hydrocyanic acid, and glucose.

Wild cherry bark, in the form of the syrup, has been used in the treatment of cough but it has little therapeutic value. It has also been used as a flavour.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Bronchial Cough; Mielocol; Rophelin†; Wampole Bronchial Cough Syrup†; ***Venez.:*** Cerylana.

Wild Lettuce

Herba Lactucae Virosae; Laitue Vireuse; Lechuga silvestre.

Profile

The wild lettuce, *Lactuca virosa* (Compositae), has been given in herbal medicine as a sedative and antitussive. The dried latex extract (lactucarium; lettuce opium) is also used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Sirop Cocillana Codeine; Sirop Cocillana Compose; ***S.Afr.:*** Choats Extract of Lettuce Cough Mixture; ***UK:*** Anased; Antibron; Gerard House Somnus; HRI Night; Kalms Sleep; Quiet Life; Quiet Nite; Slumber; Unwind Herbal Nytol; ***Venez.:*** Cerylana.

Wild Pansy

European Field Pansy (*Viola arvensis*); European Wild Pansy (*Viola arvensis* or *V. tricolor*); Field Pansy (*Viola arvensis* or *V. tricolor*); Heart's Ease; Heartsease (*Viola tricolor*); Johnny-jump-up (*Viola tricolor*); Keto-orvokki; Love-in-idleness (*Viola tricolor*); Pansy (*Viola tricolor*); Pensée sauvage; Viol; Violae herba; Violae Tricoloris Herba (viola tricolor); Ziele fiołka trójbarwnego (viola tricolor).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Wild Pansy (Flowering Aerial Parts); Viola Herba cum Flore). The dried flowering aerial parts of *Viola arvensis* and/or *V. tricolor*. It contains a minimum of 1.5% of flavonoids, expressed as violanthin ($C_{27}H_{30}O_{14}$ = 578.5), calculated with reference to the dried drug. Protect from light.

Profile

Wild pansy, *Viola tricolor* or *V. arvensis* (Violaceae) is used in herbal medicine in topical preparations for minor skin disorders, in particular for seborrhoeic skin diseases. Wild pansy is also included in oral preparations for gastrointestinal and respiratory-tract disorders.

Homoeopathy. Wild Pansy has been used in homoeopathic medicines under the following names: Viola tricolor.

Adverse effects. Haemolysis was reported in a 9-month-old infant with G6PD deficiency given an extract of wild pansy orally.[1]

1. Behmanesh Y, Abdollahi M. Haemolysis after consumption of Viola tricolor. *WHO Drug Inf* 2002; **16:** 15–16.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Bioglan Bioage Peripheral; ***Cz.:*** Antirevmaticky Caj; Bronchialtee N†; ***Fr.:*** Depuratif Parnel; Evacrine; Fitacnol†; ***Ital.:*** Neoderma 47; ***Switz.:*** Antidry; Viola; ***UK:*** Gerard House Skin.

Wild Thyme

Backtimjan; Kangasajuruoho; Mateřídoušková nat' (Nat' mateřídoušky); Mother of Thyme; Paprastųjų čiobrelių žolė; Quendel; Serpolet; Serpylli herba.

NOTE. Distinguish from Thyme, p.2401.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Wild Thyme; Serpylli Herba). The whole or cut, dried, flowering aerial parts of *Thymus serpyllum* containing a minimum of 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Wild thyme (*Thymus serpyllum*, Lamiaceae) is included in herbal medicines for disorders of the upper respiratory tract. Its actions are similar to, but weaker than, those of thyme (p.2401). Commercially, *T. pulegioides* and *T. praecox* subsp. *arcticus* are also offered as *T. serpyllum.*

Wild thyme oil is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Gartech; ***Austria:*** Scottopect; ***Belg.:*** Colimax†; Thymoseptine; ***Cz.:*** Bronchialtee N†; Detsky Caj s Hermankem; Prudušková; Thymomel; ***Fr.:*** Aromasol; Bronchorectine au Citral; Dinacode avec codeine†; Dinacode†; Nazinette du Docteur Gilbert; ***Indon.:*** Silex; ***Ital.:*** Stenobronchial; Tussamag; Tussamag Complex; ***Port.:*** Pilka F†; ***Rus.:*** Stoptussin-Fito (Стоптуссин-фито); ***Spain:*** Llantusil†; ***Switz.:*** Frixo-Dragon Vert†; Nasobol†; Pectosan N†; Tisane contre les refroidissements.

Xanthine-containing Beverages

Xantina, bebidas con.

Adverse Effects

The adverse effects of xanthine-containing beverages are largely due to their caffeine (p.1116), theophylline (p.1140), and theobromine (p.1140) content. Common adverse effects are sleeplessness, anxiety, tremor, palpitations, and withdrawal headache.

Breast feeding. For references to the effects of caffeinated beverages in breast feeding, see under Caffeine, p.1117.

Effects on the heart. A meta-analysis of published studies found no evidence of an association between coffee consumption and the development of coronary heart disease,[1] and a large cohort study in men followed up for 14 years and women for up to 20 years also found no evidence of a link.[2] Expert opinion in the UK[3] has been that the evidence that caffeine or coffee consumption contributes to coronary heart disease development is inconsistent. Coffee prepared by boiling, as is the practice in Scandinavia for example, does raise serum cholesterol concentrations due to the presence of the diterpenes cafestol and kahweol, and coffee made in a cafetière (French press) has a similar effect, but filtered coffee does not, as the hypercholesterolaemic fraction does not pass a paper filter.[4] A case-control study has suggested a relationship between consumption of boiled, but not filtered, coffee and incidence of a first non-fatal myocardial infarction.[5] Others have raised concern that the potential pressor effect of caffeine itself may be a cardiovascular risk factor,[6] but as mentioned above there is little evidence for this. A large prospective cohort study[7] found no association between dietary caffeine and risk of atrial fibrillation or flutter.

Tea drinking has not been associated with increased cardiovascular risk[3]—indeed, its polyphenol content has been suggested to have beneficial antioxidant effects.[8,9]

1. Myers MG, Basinski A. Coffee and coronary heart disease. *Arch Intern Med* 1992; **152:** 1767–72.
2. Lopez-Garcia E, *et al.* Coffee consumption and coronary heart disease in men and women: a prospective cohort study. *Circulation* 2006; **113:** 2045–53.
3. Department of Health. Nutritional aspects of cardiovascular disease. Report of the cardiovascular review group committee on medical aspects of food policy. Report on health and social subjects no. 46. London: HMSO, 1994.
4. Urgert R, *et al.* Comparison of effect of cafetière and filtered coffee on serum concentrations of liver aminotransferases and lipids: six month randomised controlled trial. *BMJ* 1996; **313:** 1362–6.
5. Hammar N, *et al.* Association of boiled and filtered coffee with incidence of first nonfatal myocardial infarction: the SHEEP and the VHEEP study. *J Intern Med* 2003; **253:** 653–9.
6. James JE. Is habitual caffeine use a preventable cardiovascular risk factor? *Lancet* 1997; **349:** 279–81.

7. Frost L, Vestergaard P. Caffeine and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005; **81:** 578–82.
8. Luo M, *et al.* Inhibition of LDL oxidation by green tea extract. *Lancet* 1997; **349:** 360–1.
9. Geleijnse JM, *et al.* Tea flavonoids may protect against atherosclerosis: the Rotterdam study. *Arch Intern Med* 1999; **159:** 2170–4.

Effects on the muscles. Severe myositis in an elderly man who drank around 14 litres of tea daily was attributed to hypokalaemia produced by the xanthine content of the beverage.[1] The patient improved after intravenous potassium replacement and subsequently remained well with a reduction in tea intake.

1. Trewby PN, *et al.* Teapot myositis. *Lancet* 1998; **351:** 1248.

Malignant neoplasms. A review of available data did not suggest a clinically significant association between the regular use of coffee and the development of cancer of the lower urinary tract in men or women.[1]

1. Viscoli CM, *et al.* Bladder cancer and coffee drinking: a summary of case-control research. *Lancet* 1993; **341:** 1432–7.

Interactions

The possibility of synergistic effects in patients receiving xanthines who consume large amounts of xanthine-containing beverages should be borne in mind.

Antipsychotics. Xanthine-containing beverages have been reported to precipitate some antipsychotic drugs from solution *in vitro*, but do not appear to alter antipsychotic concentrations *in vivo*. For references, see p.975.

Uses and Administration

Xanthine-containing beverages including chocolate, coffee, cocoa, cola, maté, and tea are widely consumed and have a mild stimulant effect on the CNS. The primary xanthine constituent is caffeine (p.1116) but other xanthine derivatives such as theobromine (p.1140) and theophylline (p.1140) may also be present; cocoa and chocolate contain significant amounts of theobromine.

Coffee is the kernel of the dried ripe seeds of *Coffea arabica*, *C. liberica*, *C. canephora* (robusta coffee), and other species of *Coffea* (Rubiaceae), roasted until it acquires a deep brown colour and a pleasant characteristic aroma. It contains about 1 to 2% of caffeine. Coffee has been used in the form of an infusion or decoction as a stimulant and as a flavour in some pharmaceutical preparations. A decoction is used as a beverage containing up to about 100 mg of caffeine per 100 mL. Preparations of instant coffee may contain up to 40% less caffeine while decaffeinated preparations may contain only up to about 3 mg per 100 mL.

Kola (cola, cola seeds, kola nuts) is the dried cotyledons of *Cola nitida* and *C. acuminata* (Sterculiaceae), containing up to about 2.5% of caffeine and traces of theobromine. Kola is used in the preparation of cola drinks which may contain up to 20 mg of caffeine per 100 mL.

Maté (Paraguay Tea) is the dried leaves of *Ilex paraguensis* (Aquifoliaceae), containing 0.2 to 2% of caffeine and traces of theobromine. Maté is less astringent than tea and is extensively used as a beverage in South America.

Tea (thea, chá, thé, tee) is the prepared young leaves and leaf-buds of *Camellia sinensis* (=*C. thea*) (Theaceae). It contains 1 to 5% of caffeine, up to 24% of tannin, and small amounts of theobromine and theophylline. Tea is used in an infusion as a beverage containing up to about 60 mg of caffeine per 100 mL.

Guarana consists of the crushed seeds of *Paullinia cupana* var *sorbilis* (Sapindaceae). Caffeine appears to be its major active ingredient which was once termed guaranine. Herbal preparations include a beverage or liquid extract and may contain 5% caffeine.

Homoeopathy. Coffee has been used in homoeopathic medicines under the following names: Coffea arabica; Coffea; Coffea cruda; Coff. cr.

Kola has been used in homoeopathic medicines under the following names: Cola.

Maté has been used in homoeopathic medicines under the following names: Ilex paraguayensis; Ile. para.

Guarana has been used in homoeopathic medicines.

Diabetes mellitus. Regular coffee consumption has been reported[1-6] to reduce the risk of developing type 2 diabetes mellitus, although it is not clear whether this effect is due to caffeine or some other constituent in coffee.

1. Salazar-Martinez E, *et al.* Coffee consumption and risk for type 2 diabetes mellitus. *Ann Intern Med* 2004; **140:** 1–8.
2. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA* 2005; **294:** 97–104.
3. van Dam RM, *et al.* Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. *Diabetes Care* 2006; **29:** 398–403.
4. Iso H, *et al.* The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. *Ann Intern Med* 2006; **144:** 554–62.
5. Pereira MA, *et al.* Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28 812 postmenopausal women. *Arch Intern Med* 2006; **166:** 1311–16.
6. Smith B, *et al.* Does coffee consumption reduce the risk of type 2 diabetes in individuals with impaired glucose? *Diabetes Care* 2006; **29:** 2385–90.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Radite; ***Braz.:*** Guarafort; ***Fr.:*** Camiline; ***Ger.:*** Carbo Konigsfeld; ***Ital.:*** Categ; ***UK:*** Yariba; ***USA:*** Tegreen.

Multi-ingredient: ***Arg.:*** Centella Incaico; Energy Plus; Ginkgo Biloba Memo Diates; Guarana Diates; Ikx Gel Reductor; Yerba Diet; ***Austral.:*** Avena Complex; Bioglan 3B Beer Belly Buster; Infant Tonic†; Irontona; Vig; Vig Recovery†; Vig†; Vitanox; Vitatona; ***Braz.:*** Astenol†; Derm'attive 10†; Gastrogenol†; Kola Fosfatada Soel†; ***Canad.:*** Biotrim†; Energy Plus†; ***Cz.:*** Abfuhr-Heilkrautertee†; ***Fr.:*** Biotone†; Drainuryl; Filigel; Maxidraine†; Mincifit; Promincil†; Quintonine; Tealine†; Tonactil†; Uromil; YSE; ***Ger.:*** Cardibisana†; Myrrhinil-Intest; Nieroxin N†; Ramend Krauter†; ***Hong Kong:*** LEAN Formula w/ Advantra†; Wari-Procomil; ***Indon.:*** F-Slim; Lycoq; ***Irl.:*** Biofreeze; ***Ital.:*** Altadrine; Biomineral 5-Alfa Shampoo; Calmason; Chinoidina†; Dam; Four-Ton; Ginkoba Active; Memorandum; Snell Cell; ***Mex.:*** Noxivid; ***Philipp.:*** Fitrum; Jamieson Total Energy; Memory DD; Nutrafit; ***Pol.:*** Cardiol C; Penigra; Tobacoff; ***Port.:*** Lipoforte†; ***Rus.:*** Insti (Инсти); ***Spain:*** Exodren; Fitosvelt†; Rimagrip; Vigortonic; ***Thai.:*** Wari-Procomil†; ***UK:*** Biofreeze; Chlorophyll; Cleansing Herbs; Daily Fatigue Relief; Damiana and Kola Tablets; Glykola; Labiton†; Lion Cleansing Herbs; S.P.H.P.; Strength; Zotrim; ***Venez.:*** Demerung; Eufytose†.

Xanthopterin

2-Amino-4,6-dihydroxypteridine.

$C_6H_5N_5O_2 = 179.1.$

CAS — 119-44-8.

Profile

Xanthopterin is a natural pigment that has been used in the management of eye disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Ital.:*** Xantervit; Xantervit Antibiotico; Xantervit Epa-rina.

Xylazine *(BAN, rINN)*

Ksylatsiini; Xilazina; Xylazin; Xylazinum. *N*-(5,6-Dihydro-4*H*-1,3-thiazin-2-yl)-2,6-xylidine.

Ксилазин

$C_{12}H_{16}N_2S = 220.3.$

CAS — 7361-61-7.

ATC Vet — QN05CM92.

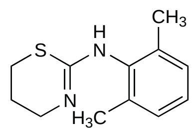

Pharmacopoeias. In *US.*

USP 31 (Xylazine). Colourless to white crystals. Sparingly soluble in acetone, in chloroform, and in dilute acid; insoluble in dilute alkali. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Xylazine Hydrochloride *(BANM, USAN, rINNM)*

Bay-Va-1470; Hidrocloruro de xilazina; Ksylatsiinihydrokloridi; Xilazin-hidroklorid; Xylazine, chlorhydrate de; Xylazin-hydrochlorid; Xylazinhydroklorid; Xylazini hydrochloridum.

Ксилазина Гидрохлорид

$C_{12}H_{16}N_2S, HCl = 256.8.$

CAS — 23076-35-9.

Pharmacopoeias. In *US.*

Eur. (see p.vii) includes for veterinary use only.

Ph. Eur. 6.2 (Xylazine Hydrochloride for Veterinary Use; Xylazine Hydrochloride BP(Vet) 2008). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in dichloromethane; very soluble in methyl alcohol. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 31 (Xylazine Hydrochloride). Colourless to white crystals. Sparingly soluble in acetone, in methyl alcohol, and in dilute acid; insoluble in dilute alkali. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Profile

Xylazine is a sedative, analgesic, and muscle relaxant used in veterinary medicine. The hydrochloride is used similarly. Abuse has been reported.

Adverse effects. Reports[1-5] of toxicity and abuse associated with xylazine. Bradycardia, hypotension, and coma were associated with the self-administration of 200 mg of xylazine. Treatment was supportive.[1]

1. Samanta A, *et al.* Accidental self administration of xylazine in a veterinary nurse. *Postgrad Med J* 1990; **66:** 244–5.
2. Mittleman RE, *et al.* Xylazine toxicity—literature review and report of two cases. *J Forensic Sci* 1998; **43:** 400–2.
3. Hoffmann U, *et al.* Severe intoxication with the veterinary tranquilizer xylazine in humans. *J Anal Toxicol* 2001; **25:** 245–9.
4. Capraro AJ, *et al.* Severe intoxication from xylazine inhalation. *Pediatr Emerg Care* 2001; **17:** 447–8.
5. Elejalde JI, *et al.* Drug abuse with inhalated xylazine. *Eur J Emerg Med* 2003; **10:** 252–3.

Xylose

Ksilozė; Ksyloosi; Ksyloza; Wood Sugar; Xilosa; Xilóz; Xylos; Xylosa; D-Xylose; Xylosum. α-D-Xylopyranose.

$C_5H_{10}O_5 = 150.1.$

CAS — 58-86-6; 6763-34-4.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Xylose). A white or almost white crystalline powder or colourless needles. Freely soluble in water; soluble in hot alcohol.

USP 31 (Xylose). Odourless, colourless needles or white crystalline powder. Very soluble in water; slightly soluble in alcohol. Store in airtight containers at a temperature of 15° to 30°.

Profile

Xylose has been used for the investigation of absorption from the gastrointestinal tract. In the absence of malabsorption, about 35% of a 5-g oral dose and about 25% of a 25-g oral dose are reported to be excreted in the urine within 5 hours. It has been given by mouth, usually in a dose of either 5 or 25 g, with up to 700 mL of water. The amount recovered in the urine is estimated and used to assess any malabsorption. Adjustment may have to be made for renal impairment. Xylose may cause some gastrointestinal discomfort with large doses. Other drugs may affect the absorption of xylose and interfere with the xylose test.

The test has been adapted to use blood-xylose concentrations.

◊ References.

1. Craig RM, Ehrenpreis ED. D-xylose testing. *J Clin Gastroenterol* 1999; **29:** 143–50.

Precautions. Preparations that contain, or are metabolised to, xylose may interfere with the results from glucose tests (p.2314). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/cber/safety/maltose110405.htm (accessed 01/07/08)

Yellow Dock

Curly Dock; Lengua de vaca; Sour Dock.

NOTE. The name sour dock has also been used for sorrel (p.2391).

Profile

Yellow dock, the root of *Rumex crispus* (Polygonaceae) has laxative and choleretic properties. It is used for constipation, jaundice, and chronic skin disorders.

Homoeopathy. Yellow Dock has been used in homoeopathic medicines under the following names: Rumex; Rumex crispus; Rumex c.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Colax; Dermaco; Haemo-Red Formula; Herbal Cleanse†; Trifolium Complex†; ***Canad.:*** Herborex; ***UK:*** Skin Eruptions Mixture.

Ylang Ylang

Cananga; Ylang-ylang.

Profile

The flowers of ylang ylang (*Cananga odorata*, Annonoceae) are the source of ylang ylang oil. Ylang ylang oil is used in perfumery, as a flavouring agent, and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Teenstick.

Yucca

Yuca.

Profile

Various species of *Yucca* (Liliaceae), including Mohave yucca (*Y. schidigera*; *Y. mohavensis*), the Joshua tree (*Y. brevifolia*; *Y. arborescens*), and bear grass (*Y. filamentosa*) have been used in herbal medicine and as foods.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Prost-1†; ***Braz.:*** Bronquiogem.

Zanthoxylum Fruit

Prickly Ash Berries; Zanthoxylum, fruto de.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Zanthoxylum fruit is the pericarp of the ripe fruit of *Zanthoxylum piperitum* (*Xanthoxylum piperitum*) (Rutaceae) or other species of *Zanthoxylum*. It contains about 3.3% v/w of essential oil.

Zanthoxylum (BPC 1934) (Toothache Bark; Xanthoxylum) is the dried bark of the northern prickly ash, *Z. americanum*, or the southern prickly ash, *Z. clavaherculis*. Both varieties contain a complex mixture of components, including benzophenanthridine alkaloids; northern prickly ash also contains coumarins.

Zanthoxylum fruit has carminative properties and has been used for rheumatic disorders. Zanthoxylum bark has been used similarly, but there is some concern about the potential toxicity of the benzophenanthridine alkaloids which it contains, and some authorities consider that it should not be recommended.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** For Peripheral Circulation Herbal Plus Formula 5; Lifesystem Herbal Formula 6 For Peripheral Circulation†; Uva-Ursi Plus†; ***Fr.:*** Node K; Phytheol; ***UK:*** Daily Overwork & Mental Fatigue Relief; Peerless Composition Essence; Tabritis.

Zein

Zeína.

CAS — 9010-66-6 (zeins).

Pharmacopoeias. In *Chin.* Also in *USNF.*

USNF 26 (Zein). A prolamine derived from corn, *Zea mays* (Gramineae). A white to yellow powder. Insoluble in water and in acetone; readily soluble in acetone-water mixtures between the limits of 60% and 80% of acetone by volume; soluble in aqueous alcohols, in ethoxyethanol; in glycols, in furfuryl alcohol, in tetrahydrofurfuryl alcohol, and in aqueous alkaline solutions of pH 11.5 and above; insoluble in all anhydrous alcohols except methyl alcohol. Store in airtight containers.

Profile

Zein is used as a tablet binder and coating agent for pharmaceutical preparations and foodstuffs. It has been used as a substitute for shellac.

Zilpaterol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de zilpaterol; RU-42173 (base or hydrochloride); Zilpatérol, Chlorhydrate de; Zilpateroli Hydrochloridum. (±)-*trans*-4,5,6,7-Tetrahydro-7-hydroxy-6-(isopropylamino)imidazo-[4,5,1-*jk*][1]benzazepin-2(1*H*)-one hydrochloride.

Зилпатерола Гидрохлорид

$C_{14}H_{19}N_3O_2,HCl = 297.8.$

CAS — 117827-79-9 (zilpaterol); 119520-05-7 (zilpaterol); 119520-06-8 (zilpaterol hydrochloride);.

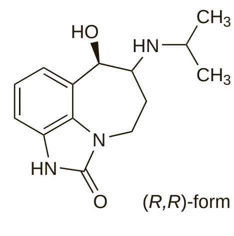

(zilpaterol)

Profile

Zilpaterol hydrochloride is a beta$_2$-agonist. It is employed in the USA and some other countries as an animal-feed additive to promote weight gain but such use is not permitted in the EU. It has anabolic properties and may be subject to abuse in sport.

Zinc Ricinoleate

Рицинолеат Цинка

$(C_{18}H_{33}O_3)_2Zn = 660.3.$

CAS — 13040-19-2.

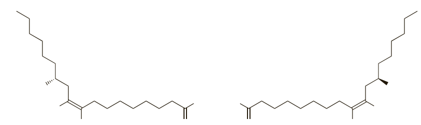

Profile

Zinc ricinoleate is used in preparations to combat body odour including underarm, colostomy, and ileostomy deodorant products. It is also used as a deodoriser in laundry products.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Antio.

Multi-ingredient: ***Austral.:*** Banish II.

Zirconium

Circonio; Zirconio; Zirkonium.

Zr = 91.224.

CAS — 7440-67-7 (zirconium); 1314-23-4 (zirconium dioxide); 60676-90-6 (zirconium lactate); 7699-43-6 (zirconium oxychloride);.

Profile

Zirconium and its compounds e.g. zirconium dioxide, zirconium lactate, and zirconium oxychloride, have been used in deodorant preparations; the dioxide is also used in dentistry. There have been reports of hypersensitivity reactions with granulomas. Zirconium dioxide has also been used as a contrast medium.

Adverse effects. A report[1] of pulmonary fibrosis associated with inhalation of a polishing agent containing mainly zirconium dioxide with quartz.

1. Bartter T, *et al.* Zirconium compound-induced pulmonary fibrosis. *Arch Intern Med* 1991; **151:** 1197–1201.

Volume 2

Preparations

This section of Martindale contains brief details of proprietary preparations available in a number of countries and includes those supplied on prescription as well as those sold directly to the public. They are provided to help the reader identify preparations and to suggest their uses. Inclusion is not an endorsement of the activity of any ingredient nor of the preparation's indications.

For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, the United Arab Emirates, UK, USA, and Venezuela. We have also included some proprietary preparations from Japan. Generally each entry consists of: the proprietary name; manufacturer or source of supply and country; ingredients usually listed by the manufacturer as being active; and a guide to the manufacturer's indications. Where possible, entries from different countries but with the same name and active ingredients have been amalgamated for clarity. We have tried to highlight instances where preparations are available with the same name, but significantly different ingredients.

An entry may cover a range of dosage forms and strengths. Dosage forms are only specified when different forms have the same proprietary name but different active ingredients. Specifying all dosage forms and the quantity of each active ingredient would have vastly increased the number of entries. Furthermore, this section is not intended as a guide to prescribing; where a preparation is to be supplied the dose should be appropriate for that preparation and that particular patient, and authoritative local sources should be consulted.

The ingredients have usually been translated into English. Almost all the ingredients listed are described in the monographs in Volume 1, and readers are directed to an appropriate monograph by the page number provided after the ingredient.

We have tried to include preparations that were available in the last few years since they may still be in circulation and their names may still be referred to in the literature and in practice. Such preparations that have been withdrawn from the market or are no longer being actively marketed may be identified by the symbol †. Readers should be aware that since this section was prepared other preparations are likely to have been withdrawn or introduced; also ingredients may change, as may indications.

The manufacturer's full name and address can be found in the Directory of Manufacturers.

Each preparation title is also listed in the General Index. Where thought helpful, preparation titles have also been listed at the end of the relevant monograph. However, it should be noted that the absence of such a list at the end of a monograph is no indication as to the availability of a substance as many drugs are marketed as generic or unbranded preparations.

2-4-2 *Medipharma, Hong Kong†.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Keratinisation disorders; psoriasis.

50:50 *BCM, UK.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry skin.

123 *Frisian Flag, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement.

222 *Johnson & Johnson, Canad.*
Aspirin (p.20·3); caffeine citrate (p.1116·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

282 *Lioh, Canad.†.*
Aspirin (p.20·3); caffeine citrate (p.1116·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

292 *Lioh, Canad.†.*
Aspirin (p.20·3); caffeine citrate (p.1116·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

456 *Frisian Flag, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement.

642 *Lioh, Canad.†.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

A-200 *Shalpharm, Israel†.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

A 313
Pharmadeveloppement, Fr.
Capsules: Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Pharmadeveloppement, Fr.
Ointment: Vitamin A (p.1971·2).
Dermatitis.

A Acido *Dominguez, Arg.*
Tretinoin (p.1618·1).

A Curitybina
Note.This name is used for preparations of different composition.
Uniao Quimica, Braz.
Paste: Salicylic acid (p.1612·2).
Keratinisation disorders.

Uniao Quimica, Braz.
Topical liquid: Salicylic acid (p.1612·2); glacial acetic acid (p.2244·2); turpentine oil (p.2406·3).
Keratinisation disorders.

A & D *Swiss Herbal, Canad.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).

A D & Calcium *Rolmex, Canad.*
Vitamin A; vitamin D; calcium phosphate (p.1922·1).

A and D Medicated *Schering-Plough, USA.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); vitamin A (p.1971·2); vitamin D (p.1986·1).
Nappy rash.

A & D Ointment
Note.This name is used for preparations of different composition.
National Care, Canad.†.
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Minor skin disorders.

Schering-Plough, Canad.
Wool fat (p.2033·2); yellow soft paraffin (p.2031·3).

A + E Thilo *Alcon, Ger.†.*
Vitamin A acetate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

A Grin *Grin, Mex.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

3A Ofteno *Volta, Chile; Sophia, Mex.; Elmor, Venez.*
Diclofenac sodium (p.44·3).
Cystoid macular oedema; inhibition of miosis during surgery; pain and inflammation associated with eye surgery.

A Saude da Mulher *EMS, Braz.*
Sodium salicylate (p.124·2); plumeria lancifolia; passion flower (p.2363·2).
Dysmenorrhoea.

A Vogel Capsules a l'ail *Bioforce, Switz.†.*
Garlic (p.2309·2).
Cerebrovascular disease.

A Vogel Capsules polyvitaminees *Bioforce, Switz.†.*
Halibut-liver oil (p.1948·1); rose fruit (p.2381·2); acerola; dried yeast (p.1998·3); safflower oil (p.1960·3).
Tonic.

A to Z *Hall, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

AAA
Note.This name is used for preparations of different composition.
Roche Consumer, S.Afr.†.
Benzocaine (p.1854·1); cetalkonium chloride (p.1634·1).
Mouth and throat disorders.

Manx, UK.
Benzocaine (p.1854·1).
Sore throat.

Aacidexam *Organon, Belg.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Aacifemine *Organon, Belg.*
Estriol (p.2101·1).
Oestrogen deficiency.

aar brain N *aar, Ger.†.*
St John's wort (p.422·3).
Depression.

aar gamma N *aar, Ger.*
Cynara (p.2291·2).
Dyspepsia.

aar os *aar, Ger.*
Putamen ovi.
Bone and teeth disorders; calcium deficiency.

aar vir *aar, Ger.*
Echinacea pallida (p.2298·1).
Influenza.

Aarane *Aventis, Switz.†.*
⊗ Sodium cromoglicate (p.1136·3); reproterol hydrochloride (p.1131·1).
Obstructive airways disease.

Aarane N *Aventis, Ger.*
⊗ Sodium cromoglicate (p.1136·3); reproterol hydrochloride (p.1131·1).
Obstructive airways disease.

AAS *Sanofi-Aventis, Braz.; GSK Consumer, Port.; Sanofi-Aventis, Spain.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Aasedatil *Vitapan, Braz.†.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

AB *Saval, Chile.*
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

AB Antitusivo *Saval, Chile.*
Chlorhexidine hydrochloride (p.1635·3); noscapine (p.1566·2).
Coughs.

AB FE *Camps, Spain†.*
Aspirin (p.20·3); caffeine (p.1116·3); phenazone (p.116·1).
Fever; pain.

3200 AB (Low Phe/Tyr) *BMS, Cz.†.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Abacateirol *Regius, Braz.†.*
Avocado (p.2262·2); sodium salicylate (p.124·2); methenamine (p.298·3); theophylline (p.1140·1).
Kidney disorders.

Abacin *Benedetti, Ital.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Abacten *Andromaco, Chile.*
Azithromycin (p.207·1).
Bacterial infections.

Abacus *Pharmaland, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions; pruritus; tension.

Abaglin *Teva Tuteur, Arg.*
Gabapentin (p.482·3).
Epilepsy; postherpetic neuralgia.

Abajos *Nufarindo, Indon.*
Paracetamol (p.108·1); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis.

Abaktal *Lek, Cz.; Lek, Hung.; Lek, Pol.; Lek, Rus.; Lek, Thai.†.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Abalgin
Note.This name is used for preparations of different composition.
Nycomed, Denm.; Leiras, Fin.
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Laboratorios Chile, Chile.
Oral drops: Adiphenine (p.2247·3); phenobarbital (p.492·2).
Muscle spasm; pain.

Laboratorios Chile, Chile.
Suppositories: Propyphenazone (p.119·3); adiphenine (p.2247·3).
Muscle spasm; pain.

Abamune *Cipla, India.*
Abacavir sulfate (p.861·3).
HIV infection.

Abanifan *Biospray, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Abanta
Note.This name is used for preparations of different composition.
Columbia, Arg.
Ointment: Zinc oxide (p.1621·2); allantoin (p.1588·1); cod-liver oil (p.1935·2).
Skin disorders.

Columbia, Arg.
Skin cleanser: Vitamin E (p.1992·2); aloe vera (p.1588·2).
Soap substitute.

Abatem *Wermar, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Abaxon *Roemmers, Venez.*
Alprazolam (p.960·1).
Anxiety.

Abba
Note. This name is used for preparations of different composition.
Medichrom, Gr.
Ketoconazole (p.539·1).
Fungal scalp infections.

Fidia, Ital.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Abbocalcijex *Abbott, Gr.*
Calcitriol (p.1986·2).
Renal osteodystrophy; vitamin D deficiency.

Abbocillin-V *Sigma, Austral.*
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Abbocillin-VK *Sigma, Austral.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Abbocurium *Abbott, Pol.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Abboderm *Abbott, Chile†.*
⊗ Erythromycin (p.269·2); alcohol (p.1625·2).
Acne.

Abbodop *Abbott, Denm.; Electra-Box, Fin.; Abbott, Norw.; Electra-Box, Swed.*
Dopamine hydrochloride (p.1273·2).
Heart failure; oliguria; shock.

Abbofol *Abbott, Pol.*
Propofol (p.1791·1).
General anaesthesia; sedation in intensive care patients.

Abbokinase *Abbott, Austria; Abbott, Israel; Abbott, Swed.†; ImaRx, USA.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Abbolipid *Abbott, Ger.†.*
Safflower oil (p.1960·3); soya oil (p.1965·3).
Lipid infusion for parenteral nutrition.

Abboplegisol *Hospira, Spain.*
Electrolyte infusion (p.1667·1).
Adjunct to open-heart surgery.

Abbosynagis *Abbott, Israel.*
Palivizumab (p.2235·3).
Respiratory syncytial virus infections.

Abbotic *Abbott, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Abboticin
Abbott, Denm.
Erythromycin ethyl succinate (p.269·3), erythromycin lactobionate (p.270·1), or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Fin.; Abbott, Norw.
Erythromycin ethyl succinate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial infections.

Abbott, Swed.
Erythromycin (p.269·2), erythromycin ethyl succinate (p.269·3), or erythromycin lactobionate (p.270·1).
Bacterial infections.

Abboticine *Abbott, Fr.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Abbottracurium *Abbott, Braz.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Abbottselsun *Abbott, Spain.*
Selenium sulfide (p.1613·1).
Scalp disorders.

Abbovir *Abbott, Pol.*
Aciclovir sodium (p.862·3).
Herpesvirus infections.

ABC
Note. This name is used for preparations of different composition.
Beiersdorf, Austria.
Capsicum (p.2276·2).
Muscle and joint pain.

Offenbach, Mex.
Multivitamin and mineral preparation (p.1922·1).

ABC Hydrogel-Warmepflaster *Beiersdorf, Austria.*
Nonivamide (p.96·2).
Muscle pain.

ABC Solucao *Hertz, Braz.†.*
Benzoic acid (p.1630·2); iodine (p.2169·2); potassium iodide (p.2169·2).
Fungal skin infections.

ABC Warme-Pflaster *Beiersdorf, Ger.†.*
Cayenne pepper (p.2276·2).
Musculoskeletal and joint disorders.

ABC Warme-Pflaster Sensitive *Beiersdorf, Ger.†.*
Nonivamide (p.96·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ABC Warme-Salbe *Beiersdorf, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Formerly contained diethylamine salicylate, benzyl nicotinate, and nonivamide.
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

ABC to Z *Nature's Bounty, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

ABCDin *Ferrosan, Denm.†.*
Multivitamin preparation (p.1922·1).

ABClox *Centaur, India.*
Amoxicillin (p.202·2); cloxacillin (p.256·1); lactic-acid-producing organisms (p.2372·3).
Bacterial infections.

Abdec *Pfizer, Indon.*
Vitamin preparation (p.1922·1).

Abdelyn *Coronet, Indon.*
Vitamins A, B, and D; lysine hydrochloride (p.1922·1).
Vitamin supplement.

Abdiflam *Tunggal Idaman, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Abdimox *Tunggal Idaman, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Abdine Cold Relief *Bell, UK.*
Paracetamol (p.108·1).
Cold and influenza symptoms.

Abdomilon *Cesra, Cz.†.*
Calamus (p.2271·3); rhubarb (p.1768·3); gentian (p.2310·3); frangula bark (p.1732·2); melissa (p.2339·3); angelica (p.2258·1); absinthium (p.2244·1).
Gastrointestinal disorders.

Abdomilon N *Caesaro, Austria; Cesra, Ger.*
Absinthium (p.2244·1); angelica (p.2258·1); calamus (p.2271·3); gentian (p.2310·3); melissa (p.2339·3).
Dyspepsia; gastrointestinal disorders.

Abdominol *Medea, Spain.*
Atropine methobromide (p.1219·2); caffeine (p.1116·3); propyphenazone (p.119·3).
Pain due to smooth muscle spasm.

Abdoscan *Nycomed Amersham, UK†.*
Ferristene (p.1478·1).
Contrast medium for magnetic resonance imaging.

Abduce *Pharmanik (Φαρμανικ), Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Abecidin A C D *Pasteur, Chile.*
Vitamin A palmitate; ergocalciferol; vitamin C (p.1922·1).
Vitamin supplement.

Abefen *Pisa, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Abelcet *Bioprofarma, Arg.; Orphan, Austral.; Liposome Company, Austria; Wyeth, Belg.; Bago, Braz.; Enzon, Canad.; Cephalon, Cz.; Elan, Denm.; Zeneus, Fin.; Zeneus, Fr.; Zeneus, Ger.; Wyeth, Gr.; Asia Pacific, Hong Kong; Zeneus, Hong Kong; Zeneus, Hung.; Zeneus, Irl.; Elan, Ital.; Medeus, Malaysia†; St Ives, NZ; Zeneus, Neth.; Elan, Norw.; Cephalon, Port.; Elan, Singapore; Pacific Biosciences, Singapore; Zeneus, Spain; Meda, Swed.†; Elan, Switz.†; Onko, Turk.; Cephalon, UK; Enzon, USA.*
Amphotericin B phospholipid complex (p.523·2) (p.523·2).
Fungal infections; leishmaniasis.

Abenol *Pendopharm, Canad.*
Paracetamol (p.108·1).
Fever; pain.

Abentel *Atlantic, Thai.*
Albendazole (p.139·2).
Worm infections.

ABE-Plyn *Inco Veritas, Pol.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Corns.

Aberela *Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
Tretinoin (p.1618·1).
Acne; photoageing of the skin.

Aberten *Menarini, Gr.*
Theophylline (p.1140·1).
Asthma; neonatal apnoea and bradycardia; obstructive airways disease.

Abesira *Clariana, Spain†.*
Vitamin B substances and amino acids (p.1922·1).
Anaemias; metabolic disorders; tonic.

Abflex *Xeragen, S.Afr.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain with tension.

Abfuhr-Heilkrautertee *Abtswinder, Cz.†.*
Senna (p.1769·2); frangula bark (p.1732·2); urtica (p.2409·3); maté (p.2416·1); juniper (p.2328·2); coriander (p.2288·1); birch leaf (p.2266·3); centaurea cyanus; calendula (p.2273·1).
Digestive disorders; slimming aid.

Abfuhrtee *Sanochemia, Austria†.*
Couch-grass (p.2288·2); chamomile (p.2279·3); centaurea cyanus; frangula bark (p.1732·2); rhubarb (p.1768·3); senna (p.1769·2).
Constipation.

Abfuhrtee N *Bad Heilbrunner, Ger.*
Senna (p.1769·2).
Constipation.

Abfuhrtee St Severin *Smetana, Austria.*
Achillea (p.2245·2); peppermint leaf (p.1761·2); senna (p.1769·2).
Constipation.

Abiclav *Lindopharm, Ger.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Abidec *Pfizer Consumer, Irl.; Teofarma, Ital.; Chefaro, UK.*
Multivitamin preparation (p.1922·1).

Abilify *BMS, Austral.; BMS, Belg.; BMS, Braz.; BMS, Chile; BMS, Cz.; Otsuka, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; Otsuka, Hong Kong; Otsuka, Hung.; Otsuka, Indon.; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, NZ; Otsuka, Neth.; Otsuka, Norw.; Otsuka, Philipp.; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; Thai Otsuka, Thai.; BMS, UK; Otsuka, UK; BMS, USA; Otsuka, USA; BMS, Venez.*
Aripiprazole (p.962·3).
Adjunct in depression; bipolar disorder; mania; schizophrenia.

Abine *Dosa, Arg.*
Gemcitabine (p.728·1).
Malignant neoplasms.

Abinol *Recalcine, Chile.*
Lorazepam (p.1004·1).
Anxiety; childhood behaviour disorders; insomnia; premedication.

Abiocef *IBI, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Abiolex *Andromaco, Chile.*
Amoxicillin (p.202·2).
Bacterial infections.

Abiostil *Deca, Ital.*
Neomycin sulfate (p.305·1); cineole (p.2282·3); pine silvestris oil (p.2368·2); camphor (p.2273·2); menthol (p.2340·1).
Nasopharyngeal infections.

Abiotyl *Biocrom, Arg.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Abiplatin *Teva, Israel; Teva, S.Afr.; Abic-Teva, Thai.*
Cisplatin (p.698·2).
Malignant neoplasms.

Abitaxel *Teva, Rus.†.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Abitren *Abic, Israel.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal colic.

Abitrexate *Teva, Israel; Teva, S.Afr.; Abic-Teva, Thai.*
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Abitrol *Intermed, Gr.*
⊗ Bisoprolol (p.1234·2).
Hypertension.

Abixa *Lundbeck, Philipp.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

ABKI *Quimica y Farmacia, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ablok *Biolab Sanus, Braz.*
⊗ Atenolol (p.1217·3).
Hypertension.

Ablok Plus *Biolab Sanus, Braz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Formerly contained atenolol and hydrochlorothiazide.
Hypertension.

Abloom *Duncan, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Abluent *Tolmann, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with excessive mucus.

Abnobaviscum *Abnoba, Ger.*
Mistletoe (p.2345·3).
Malignant neoplasms.

Abodine *Abbott, Indon.*
Povidone-iodine (p.1659·2).
Antiseptic.

Abolibe *Sidefarma, Port.*
Ginkgo biloba (p.2311·1).
Mental function disorders; vascular disorders.

Abopur *Norton Healthcare, Denm.*
Allopurinol (p.552·2).
Gout; renal calculi.

Abovis *Taisho, Jpn.*
Aclatonium napadisilate (p.1704·2).
Abdominal distension; nausea; reduced appetite; vomiting.

Abralux *Valuge, Arg.*
Polyethylene granules (p.1585·3).
Abrasive skin wash.

Abrasone *Seid, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); framycetin sulfate (p.279·1).
Infected skin disorders.

Abrasone Rectal *Seid, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); hexetidine (p.1647·1); ruscogenin (p.2382·2).
Anorectal disorders.

Abrax *CTI, Israel.*
Dicosanol.
Herpes labialis.

Abraxane *Abraxis, USA.*
Paclitaxel albumin-bound particles (p.759·1).
Breast cancer.

Abreva *GSK Consumer, Canad.; SmithKline Beecham Consumer, USA.*
Docosanol (p.872·2).
Herpes labialis.

Abrilar
Note. This name is used for preparations of different composition.
Roemmers, Arg.†.
⊗ Salmeterol xinafoate (p.1135·1).
Asthma.

Farmoquimica, Braz.
Ivy (p.2328·1).
Respiratory-tract disorders with increased mucus.

Pharma Investi, Chile.
Alfa-hederina.
Coughs; respiratory-tract congestion.

Abrixone *Eurodrug, Mex.*
Metadoxine (p.1978·2).
Alcohol withdrawal; liver disorders.

Abrobion *Medicus, Gr.*
Ambroxol (p.1550·3).

Abroflor *VSM, Neth.*
Homoeopathic preparation.

Abrol *Rekah, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Abrolen *Alet, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Abrolet *Rekah, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Absenor *Orion, Cz.; Orion, Fin.; Orion, Swed.*
Sodium valproate (p.508·2).
Epilepsy; mania.

Absint *Medochemie, Hong Kong†.*
Flunitrazepam (p.996·2).
Insomnia.

Absolue *Lancome, Canad.*
SPF 15: Avobenzone (p.1589·3); octisalate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

Absorbase *Carolina, USA.*
Vehicle for topical preparations.

Absorber HFV *Arteva, Ger.†.*
Dimeticone (p.1770·2).
Reduction of gastrointestinal gas.

Absorbine Analgesic *Young, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Absorbine Antifungal Foot Powder *Young, USA†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Absorbine Arthritis *Young, Canad.*
Menthol (p.2340·1); capsicum (p.2276·2).

Absorbine Athletes Foot Care *Young, USA.*
Tolnaftate (p.548·3); menthol (p.2340·1).
Fungal infections.

Absorbine Jr *Young, Canad.; Young, USA.*
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Absorbine Jr Antifungal *Young, Canad.*
Tolnaftate (p.548·3).
Tinea pedis.

Absorbine Jr Roll-on Ice *Young, Canad.*
Menthol (p.2340·1).

Absorbine Junior Patch *Young, Canad.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1).

Absorbine Power Gel *Young, Canad.*
Menthol (p.2340·1).

Absorlent *Esteve, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Absorlent Plus *Esteve, Spain.*
Patch A, estradiol (p.2097·2); patch B, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Absten S *Medley, Braz.*
⊗ Mazindol (p.2157·3).
Obesity.

Abstensyl *Sintesina, Arg.*
Disulfiram (p.2296·2).
Alcoholism.

Abtrim *Ashbourne, UK†.*
Clotrimazole (p.530·1).
Fungal skin infections; vaginal candidiasis.

Abufene *Bouchara-Recordati, Fr.; Bouchara, Singapore.*
Beta-alanine (p.1928·1).
Menopausal disorders.

Abuglib *Pharmacos Abug, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Abutiroi *Pharmacos Abug, Mex.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Abutol *Schwarz, Pol.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

Abvitos *Gache, Venez.*
Vitamins A, C, and D (p.1922·1).
Vitamin A, C, and D deficiency.

AC & C *Pendopharm, Canad.; Vita Health, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

AC Lan *Lanpharm, Arg.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

AC Vascular *Biotenk, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders.

Aca *Atlantic, Malaysia; Atlantic, Thai.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Acabel *Grunenthal, Arg.†; Grunenthal, Chile†; Altana, Port.; Andromaco, Spain; Grunenthal, Venez.*
Lornoxicam (p.77·3).
Inflammation; musculoskeletal and joint disorders; pain.

Acacin *Ivax, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Acadione *Sanofi-Aventis, Fr.*
Tiopronin (p.1467·1).
Cystinuric lithiasis; rheumatoid arthritis.

A-Calcid *Biomedica-Chemica, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Acalix *Roemmers, Arg.; Vargas, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Acalka *Gross, Braz.†; Silesia, Chile; Patriot, Philipp.; Ferrer, Port.; Robert, Spain; Ferrer, Thai.*
Potassium citrate (p.1673·2).
Alkalinisation of urine; renal calculi.

ACAM2000 *Acambis, USA.*
A smallpox vaccine (p.2238·1).
Active immunisation.

Acamed *Medifive, Thai.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Acamol *Volta, Chile; Teva, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Acamol Compuesto *Volta, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).

Acamol Tsinun Day *Teva, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Acamol Tsinun Night *Teva, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Acamoli *Teva, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Acamoli Cold *Teva, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Acanol *Sanofi Synthelabo, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Acantex
Roche, Arg.
Ceftriaxone (p.238·1).
Bacterial infections.

Roche, Chile.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Acarbay *Cipla, India.*
Acarbose (p.436·2).
Diabetes mellitus.

Acarbixin *Sons, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Acarcid *Pierre Fabre Sante, Fr.†.*
Acetamide; crotamiton (p.1593·2); benzalkonium chloride (p.1629·1); thyme oil (p.2401·2); geranium oil (p.2311·1); myrtle oil (p.2349·3).
Elimination of house dust mites.

Acard *Polfa Warszawa, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Acardi *Boehringer Ingelheim, Jpn.*
Pimobendan (p.1371·3).
Heart failure.

Acardust *Raymos, Arg.†; Pharmygiene, Fr.; Scot, Israel.*
Esdepallethrine (p.2042·3); piperonyl butoxide (p.2049·1).
Acaricide; eradication of house dust mite.

Acarex *Allergopharma, Ger.†.*
Potassium hydroxide (p.2371·3); methyl alcohol (p.2024·3).
Test for detection of house dust mite excretae.

Acaril *Allergopharma, Ger.†.*
Benzyl benzoate (p.2036·1).
Elimination of house dust mites.

Acarilbial *Bial, Port.*
Benzyl benzoate (p.2036·1).
Scabies.

Acarosan *Allergopharma, Ger.†.*
Benzyl benzoate (p.2036·1).
Elimination of house-dust mites.

Acarsan *Biosintetica, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Acasmul *Pharma Investi, Chile.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; ischaemic heart disease.

Acatar
Note. This name is used for preparations of different composition.
SMB, Belg.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

US Pharmacia, Pol.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

ACB
Pacific, NZ.
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

Merck, Singapore†; Pacific, Singapore†.
⊗ Acebutolol (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

Ac-Butamol *Acemed, Hung.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

ACC
Hexal, Arg.†; Hexal, Austria; Sandoz, Hung.; Sandoz, Mex.; Hexal, Rus.; Hexal, S.Afr.; Ecosol, Switz.
Acetylcysteine (p.1548·2).
Paracetamol overdosage; respiratory-tract congestion.

Hexal, Cz.; Hexal, Ger.; Hexal, Pol.
Acetylcysteine (p.1548·2) or acetylcysteine sodium (p.1548·2).
Paracetamol overdosage; respiratory-tract congestion.

Accesum *Roux-Ocefa, Arg.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Accolate *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Mex.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Thai.†; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Zafirlukast (p.1150·2).
Asthma.

Accoleit *AstraZeneca, Ital.*
Zafirlukast (p.1150·2).
Asthma.

Accomin *Wyeth Consumer, Austral.*
Vitamin B substances with lysine and iron (p.1922·1).

Accu-Chek *Roche, Arg.; Roche Diagnostics, Austral.; Roche, Braz.; Roche Diagnostics, Canad.†; Roche, Chile; Roche Diagnostics, Fr.; Roche Diagnostics, Irl.; Roche Diagnostics, Ital.; Roche Diagnostics, Mex.*
Test for glucose in blood (p.2314·1).

Accu-Chek Advantage *Roche Diagnostics, NZ; Boehringer Mannheim, USA.*
Test for glucose in blood (p.2314·1).

Accuhist *Pediamed, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).

Accuhist LA *Pediamed, USA†.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).

Accuhist DM Pediatric
Note. This name is used for preparations of different composition.
Pediamed, USA†.
Oral drops: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Pediamed, USA.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Accuhist PDX
Note. This name is used for preparations of different composition.
Pediamed, USA.
Oral drops: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Pediamed, USA.
Syrup: Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Accuneb *Dey, USA.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma.

Accupaque *Amersham, Austria; Amersham, Ger.; Amersham, Switz.*
Iohexol (p.1483·1).
Contrast medium for radiography and computerised tomography.

AccuPeel *ICN, Hong Kong†; ICN, Singapore†.*
Trichloroacetic acid (p.1620·1).
Dyschromia; facial wrinkles.

Accupep *Sherwood, USA.*
Preparation for enteral nutrition (p.1922·1).
Gastrointestinal disorders.

Accupril *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia†; Pfizer, NZ; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore†; Pfizer, Thai.; Parke, Davis, USA; Pfizer, Venez.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Accuprin *Pfizer, Ital.*
Quinapril hydrochloride (p.1382·2) or quinaprilat (p.1382·3).
Heart failure; hypertension.

Accupro
Pfizer, Austria.
Quinapril hydrochloride (p.1382·2) or quinaprilat (p.1382·3).
Heart failure; hypertension.

Godecke, Cz.; Pfizer, Denm.; Pfizer, Fin.; Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Irl.; Godecke, Pol.; Parke, Davis, Pol.; Goedecke, Rus.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK.
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Accupro Comp *Pfizer, Fin.; Pfizer, Swed.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Accupron *Pfizer, Gr.*
Quinapril (p.1382·3).
Heart failure; hypertension; myocardial infarction.

Accuran *Alvia (Αλβια), Gr.*
Isotretinoin (p.1599·2).
Acne.

Accurbron *Marion Merrell Dow, USA.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

Accure *Alphapharm, Austral.*
Isotretinoin (p.1599·2).
Acne.

Accuretic *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, NZ; Pfizer, S.Afr.; Pfizer, Switz.; Pfizer, UK; Parke, Davis, USA; Pfizer, Venez.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Accusol *Baxter, Cz.; Baxter, Port.*
Calcium chloride; magnesium chloride; sodium chloride; sodium bicarbonate; with or without potassium chloride and glucose (p.1670·3).
Haemodiafiltration; haemodialysis; haemodialysis and haemofiltration solution; haemofiltration.

Accutane *Roche, Canad.; Roche, USA.*
Isotretinoin (p.1599·2).
Acne.

Accutest Fecal *Marco, Austral.†.*
Test for haemoglobin in faeces.

Accutest Multi-Drug *Marco, Austral.†.*
Test for amfetamine, benzoylecgonine, methamfetamine, morphine, or THC in urine.

Accutin *Durascan, Denm.*
Isotretinoin (p.1599·2).
Acne.

Accutrend *Roche, Braz.*
Tests for cholesterol, triglycerides or glucose (p.2314·1) in blood.

Accutrend Cholesterol *Roche Diagnostics, Ital.; Roche Diagnostics, Mex.; Roche Diagnostics, UK.*
Test for cholesterol in blood.

Accutrend Colesterol *Roche, Arg.; Roche, Chile.*
Test for cholesterol in blood.

Accutrend GC *Roche Diagnostics, Canad.†.*
Test for glucose and cholesterol in blood (p.2314·1).

Accutrend GCT *Roche, Chile.*
Tests for cholesterol (Accutrend Colesterol), glucose (Accutrend Glucosa), or triglycerides (Accutrend Trigliceridos) in blood.

Accutrend Glucosa *Roche, Arg.; Roche, Chile.*
Test for glucose in blood (p.2314·1).

Accutrend Glucose *Roche Diagnostics, Austral.; Roche Diagnostics, Ital.†; Roche Diagnostics, Mex.; Roche Diagnostics, NZ†.*
Test for glucose in blood (p.2314·1).

Accutrend Triglicerides *Roche, Chile.*
Test for triglycerides in blood.

Accuvit *Ache, Braz.*
Multivitamin preparation (p.1922·1).

Accuzide *Pfizer, Austria; Parke, Davis, Cz.; Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Hung.; Pfizer, Philipp.; Parke, Davis, Pol.; Pfizer, Turk.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Accuzyme *Healthpoint, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).
Debridement of necrotic tissue.

ACD *Gobbi, Arg.*
Vitamin A; vitamin C; vitamin D (p.1922·1).

Ac-De *Lemery, Mex.*
Dactinomycin (p.707·2).
Malignant neoplasms.

ACE plus Selenyum *Kocak, Turk.*
Vitamins A, C, and E plus selenium (p.1922·1).

Acea *Ferndale, UK.*
Metronidazole (p.837·1).
Rosacea.

Acebitor *Unison, Philipp.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Aceclo *Aristo, India.*
Aceclofenac (p.14·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Aceclofar *Julphar, UAE.*
Aceclofenac (p.14·3).
Musculoskeletal and joint disorders; pain.

Aceclonac *Verisfield, Gr.*
Aceclofenac (p.14·3).
Inflammation.

Acecol *Daiichi Sankyo, Jpn.*
Temocapril hydrochloride (p.1409·3).
Hypertension.

Acecomb *AstraZeneca, Austria.*
⊗ Hydrochlorothiazide (p.1307·3); lisinopril (p.1325·2).
Hypertension.

Acecor *SPA, Cz.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Acecovyl *Alpharma, Mex.*
Vitamin A palmitate; colecalciferol; ascorbic acid (p.1922·1).
Vitamin A, C, and D deficiency.

Acecromol *Wolff, Ger.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Acedicon *Boehringer Ingelheim, Belg.*
Thebacon hydrochloride (p.1574·2).
Formerly known as Acedicone.
Coughs.

Acediur
Note. This name is used for preparations of different composition.
Menarini, Ital.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Sigma-Tau, Spain.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Acef *KG, Ital.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Aceflan *Uniao Quimica, Braz.†.*
Aceclofenac (p.14·3).
Inflammation; pain.

ACE-Hemmer *RAN, Ger.; Ratiopharm, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

ACE-Hemmer comp *Ratiopharm, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Aceite Acalorico *Ordesa, Spain.*
Olive oil (p.2356·2); betacarotene (p.1930·3); liquid paraffin (p.2030·3).
Constipation; obesity.

Aceite Esmeralda Moone *Gordon, Arg.*
Camphor (p.2273·2); methyl salicylate (p.85·3); phenol (p.1656·1).
Musculoskeletal and joint disorders.

Aceite Geve Concentrado *Teofarma, Spain.*
Cod-liver oil (p.1935·2).
Deficiency of vitamins A and D.

Acekapton *Strallhofer, Austria.*
Aspirin (p.20·3).
Fever; pain.

Acelisino comp *Lannacher, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acellulair *GSK, Neth.*
An acellular pertussis vaccine (p.2230·1).
Active immunisation.

Acelluvax DTP *Chiron, Israel; Berk, Turk.*
A diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation; active immunisation of infants and young children.

Acelopram *Ferakon, Gr.*
Citalopram (p.385·3).
Depression.

Acemedrox *Bunker, Braz.*
Medroxyprogesterone acetate (p.2113·1).
Progestogenic.

Acemetadoc *Docpharm, Ger.*
Acemetacin (p.15·1).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders.

Acemin *AstraZeneca, Austria.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acemix *Bioprogress, Ital.*
Acemetacin (p.15·1).
Musculoskeletal and joint disorders.

Acemuc *Betapharm, Ger.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Acemucol *Streuli, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with excess or viscous mucus.

Acemuk *Hexal, Arg.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with increased or viscous mucus.

Acemuk Biotic *Investi, Arg.*
Amoxicillin trihydrate (p.202·2); acetylcysteine (p.1548·2).
Respiratory-tract infections.

Acemycin *Elpen (Ελπεν), Gr.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Acenil *Tocogino, Mex.*
⊗ Fluocinolone (p.1531·3); nystatin (p.543·2); metronidazole (p.837·1).
Vaginal infections.

Acenol *Galena, Pol.*
Paracetamol (p.108·1).
Fever; pain.

Acenorm *Alphapharm, Austral.; Azupharma, Ger.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acenor-M *BMS, Indon.*
Fosinopril sodium (p.1291·3).
Hypertension.

Acenorm HCT *Azupharma, Ger.†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acenotromb *Prieto, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Acenox *Pasteur, Chile.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Acenterine *Christiaens, Belg.*
Aspirin (p.20·3).
Fever; pain.

Aceomel *PannonPharma, Hung.; Clonmel, Irl.*
Captopril (p.1239·2).
Heart failure; hypertension.

Aceon *Solvay, USA.*
Perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; hypertension.

Aceoto *Zambon, Spain.*
Ciprofloxacin (p.243·3).
Otitis externa.

Aceoto Plus *Zambon, Spain.*
⊗ Ciprofloxacin hydrochloride (p.243·3); fluocinolone acetonide (p.1531·3).
Otitis externa.

Acephen *G & W, USA.*
Paracetamol (p.108·1).
Pain.

Acephlogont *Azupharma, Ger.†.*
Acemetacin (p.15·1).
Gout; inflammation, musculoskeletal, joint, and soft-tissue disorders.

Aceplus
Note. This name is used for preparations of different composition.
BMS, Austria.
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

BMS, Ital.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acepramin *PannonPharma, Hung.*
Aminocaproic acid (p.1053·2).
Fibrinolysis.

Acepran *Andromaco, Chile.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Acepress *Bernofarm, Indon.; BMS, Ital.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acepril
Note. This name is used for preparations of different composition.
United Nordic, Denm.†; Duopharma, Hong Kong; Duopharma, Malaysia.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Teva, Hung.; Spirig, Switz.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

BMS, UK.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acepril PlusZ *PharmaConsult, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Aceprilex *Pliva, Ital.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Aceprin *Hovid, Malaysia.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Aceptin *Metro, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acequide *Recordati, Ital.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acequin *Recordati, Ital.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acer *Ratiopharm, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Aceratun *Delta, Braz.*
Urea hydrogen peroxide (p.1666·2).
Cleansing of external ear.

Acerbine
Note. This name is used for preparations of different composition.
Montavit, Austria.
Benzoic acid (p.1630·2); malic acid (p.2337·1); propylene glycol (p.2374·1); propylene glycol malate (p.2374·1); salicylic acid (p.1612·2).
Bruises; burns; sunburn; ulcers; wounds.

Interdelta, Switz.†.
Ointment: Benzoic acid (p.1630·2); malic acid (p.2337·1); salicylic acid (p.1612·2); propylene glycol (p.2374·1); propylene glycol malate (p.2374·1); hexachlorophene (p.1646·1).
Burns; wounds.

Interdelta, Switz.†.
topical gel; Topical solution: Benzoic acid (p.1630·2); malic acid (p.2337·1); salicylic acid (p.1612·2); propylene glycol (p.2374·1); propylene glycol malate (p.2374·1).
Burns; wounds.

Acerbiol *Vitafarma, Spain.*
Benzyl alcohol (p.1631·3); benzoic acid (p.1630·2); malic acid (p.2337·1); propylene glycol malate (p.2374·1); propylene glycol (p.2374·1); salicylic acid (p.1612·2).
Burns; skin ulcers; wounds.

Acerbon *AstraZeneca, Ger.; Promed, Ger.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acercomp *AstraZeneca, Fin.†; AstraZeneca, Ger.; Promed, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acerdil *Recalcine, Chile.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Acerdil-D *Recalcine, Chile.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Aceren *Nycomed, Denm.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Aceril *Dexcel, Israel.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acerilin *Ilsan, Turk.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acerin *Scan-Anida, Pol.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Calluses; corns.

Acerpes *Investi, Arg.; Riemser, Ger.; Ecosol, Switz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acertil *Servier, Hong Kong.*
Perindopril (p.1368·2).
Heart failure; hypertension.

Acertol *Lacer, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Aces *Carlson, USA.*
Betacarotene; calcium ascorbate; *d*-alpha tocoferol; selenomethionine (p.1922·1).
Nutritional supplement.

Acesal *Altana, Ger.; Geymonat, Ital.†.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Acesan *Sun-Farm, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Acesial *Adamed, Cz.*
Ramipril (p.1385·3).
Diabetic nephropathy; hypertension; myocardial infarction.

Acesistem *Sigma-Tau, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Acespargin *Filofarm, Pol.*
Potassium N-acetylhydroaspartate.
Potassium deficiency.

Acestrol *Almirall, Port.*
Megestrol acetate (p.2114·3).
Breast cancer; cachexia associated with malignant neoplasms; endometrial cancer; prostatic cancer.

Acet *Pharmascience, Canad.; Pharmascience, Malaysia†; Euro-Med, Philipp.; Pharmascience, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Acet-2, Acet-3 *Pharmascience, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Acet Codeine *Pharmascience, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Aceta *Century, USA.*
Paracetamol (p.108·1).
Fever; pain.

Aceta with Codeine *Century, USA.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Acetabs *Krewel, Ger.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Acetacol *PP Lab, Thai.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever; nasal congestion.

Aceta-Diazol *Grin, Mex.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma; oedema.

Acetadol *Medi-Rx, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Acetadote *Cumberland, USA.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning.

Acetafen *Rayere, Mex.; Infinity, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Aceta-Gesic *Rugby, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Acetalgine *Streuli, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Acetalis *Proula, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Acetamil *Ducto, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Acetaminophen with Codeine *Pharmascience, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Coughs; fever; pain.

Acetamol *Abiogen, Ital.*
Paracetamol (p.108·1).
Fever; pain.

Acetan *Kwizda, Austria.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Aceta-P *PP Lab, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Acetapyrin-C *PP Lab, Thai.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever.

Acetar
Note. This name is used for preparations of different composition.
Labesfal, Port.
Piracetam (p.368·2).
Cerebrovascular disorders; chronic alcoholism; mental function impairment; Raynaud's syndrome.

Thai Otsuka, Thai.
Electrolyte infusion with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Acetasil *Silom, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Acetasol *Actavis, USA.*
Acetic acid (p.2244·2); propylene glycol acetate (p.1919·3); benzethonium chloride (p.1630·1).
Ear infection.

Acetasol HC *Actavis, USA.*
⊗ Hydrocortisone (p.1535·2); acetic acid (p.2244·2); propylene glycol diacetate (p.1919·3); benzethonium chloride (p.1630·1).
Ear infection.

Acetazone Forte *Rougier, Canad.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Pain; skeletal muscle spasm.

Acetazone Forte C8 *Rougier, Canad.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain; skeletal muscle spasm.

Acetec *Biolab, Malaysia.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Aceten *Wockhardt, India; Wockhardt, Rus.; Biotech, S.Afr.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Acetensa *Fahrenheit, Indon.*
Losartan potassium (p.1326·1).
Hypertension.

Acetensil *Andromaco, Cz.†; Librapharm, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Acetensil Plus *Librapharm, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Acetest *Bayer, Canad.†; Bayer Diagnostics, Fr.†; Bayer Diagnostics, Irl.; Bayer Diagnostics, Mex.; Bayer Diagnostics, UK; Bayer, USA.*
Test for ketones in urine.
In the UK these are described in the Drug Tariff as Nitroprusside Reagent Tablets (Rothera's Tablets).

Aceticil *Cazi, Braz.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Acetif *Novag, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Acetil-A *Precimex, Mex.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolic disorders.

Acetin
Note. This name is used for preparations of different composition.
IQFA, Mex.
Aspirin (p.20·3).
Fever; inflammation; pain.

LBS, Thai.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Acetoben *Ronava, Venez.*
Ammonium acetate (p.1551·2); ammonium carbonate (p.1551·3); sodium benzoate (p.1630·2); camacho; polygala (p.1572·3).
Cough.

Acetocaustin *Temmler, Ger.*
Monochloroacetic acid (p.1608·1).
Verrucas.

Acetocaustine *Viatris, Switz.*
Monochloroacetic acid (p.1608·1).
Warts.

Acetofen *Medley, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Acetoflux *EMS, Braz.*
Medroxyprogesterone acetate (p.2113·1).
Progestogenic.

Acetolit *Mertens, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Acetolyt *Medicopharm, Austria; Combustin, Ger.*
Calcium-sodium-hydrogencitrate.
Acidosis; metabolic acidosis.

Acetonal *Brady, Austria.*
Aluminium acetotartrate (p.2255·1); trichlorisobutyl salicylate.
Anorectal disorders.

Acetopt *Sigma, Austral.; Healthcare Logistics, NZ; Sigma, Philipp.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Acetosal *Rekah, Israel.*
Aspirin (p.20·3).
Influenza symptoms; pain; rheumatic disorders.

Acetoxyl *Valeo, Canad.*
Benzoyl peroxide (p.1590·2).
Acne.

Acetuber *Teofarma, Spain.*
Cocarboxylase (p.1975·2); dimenhydrinate (p.576·2); glucose (p.1945·3); pyridoxine (p.1979·1); potassium chloride (p.1684·3).
Formerly contained cocarboxylase, dimenhydrinate, glucose, pyridoxine, potassium chloride, and dibasic sodium phosphate.
Acetonaemia; vomiting in pregnancy.

Acetylcodone *UCB, Belg.*
Acetyldihydrocodeine hydrochloride (p.1550·3).
Coughs.

Acetylin *BMS, Ger.†.*
Aspirin (p.20·3).
Fever; pain.

Acetyst *Ritsert, Ger.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Aceval *Valmor, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Acevit *Pediapharm, Chile.*
Vitamin A palmitate; ergocalciferol; ascorbic acid (p.1922·1).
Vitamin supplement.

Acevor *Help, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Acezide *BMS, UK.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-zidocapt.
Hypertension.

AC-FA *Pharmasant, Thai.*
Ketoconazole (p.539·1).
Fungal skin infections.

Ac-Fast *Hormona, Mex.*
Paracetamol (p.108·1).
Pain.

Acfol *Cazi, Braz.†; ITF, Port.; Italfarmaco, Spain.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Acheflan *Ache, Braz.*
Cordia verbenacea oil.
Inflammatory disorders.

Aches & Pains *Homeocan, Canad.*
Homoeopathic preparation.

Achillea Comp *Weleda, S.Afr.*
Homoeopathic preparation.

Achromide *Adcock Ingram, S.Afr.*
Merbromin (p.1652·1); acriflavinium chloride (p.1625·1); sulfanilamide (p.343·1); zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Burns; ulcers; wounds.

Achromycin
Sigma, Austral.†; Wyeth Lederle, Austria†; Riemser, Ger.; Wyeth, India; Wyeth-Ayerst, Thai.†.
Tetracycline hydrochloride (p.347·2).
Amoebiasis; bacterial infections; intestinal amoebiasis.

Achromycin V *Sigma, Austral.†; Lederle, USA†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Aciban *Be-Tabs, S.Afr.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Acic
Hexal, Austria; Rowex, Irl.
Aciclovir (p.862·3).
Herpes labialis.

Hexal, Ger.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Aciclin *Fidia, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclo *Ahimsa, Arg.; Basics, Ger.; CT, Ger.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclobene *Ratiopharm, Austria.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Aciclobeta *Betapharm, Ger.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclodan *Pharmacodane, Denm.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclomed *Ethimed, Belg.; Cimed, Braz.*
Aciclovir (p.862·3).
Herpesvirus skin infections.

Aciclophar *Teva, Belg.*
Aciclovir (p.862·3).
Herpesvirus skin infections.

Aciclor *Hertz, Braz.†; Megat, Venez.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclosina *Cipan, Port.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclostad *Stada, Austria; Stada, Ger.; Stada, Rus.†; VP, Spain.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclotex *Sertex, Arg.*
Aciclovir (p.862·3).
Herpes simplex infections of the face and lips.

Aciclotyrol *Tyrol, Austria†.*
Aciclovir (p.862·3).
Herpes simplex skin infections.

Aciclovan *HB, Braz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aciclovax *Labesfal, Port.*
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Aciclovivax *Ivax, Fr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acic-Ophtal *Winzer, Ger.*
Aciclovir (p.862·3).
Herpes simplex eye infections.

Acicvir *Pacific, NZ†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acid A Vit *Pierre Fabre, Neth.*
Tretinoin (p.1618·1).
Acne.

Acid Control *Novopharm, Canad.; Stanley, Canad.*
Famotidine (p.1730·1).

Acid Halt *Wampole, Canad.*
Famotidine (p.1730·1).

Acid Jelly *Hope, USA.*
Hydroxyquinoline sulfate (p.2323·1); ricinoleic acid (p.2379·2); acetic acid (p.2244·2).
Maintenance of vaginal acidity.

Acid Mantle
Note.This name is used for preparations of different composition.
Darier, Mex.
Emollient.
Skin irritation.

Bayer, Venez.
Aluminium acetate (p.2255·1).

Acid Reducer *Genpharm, Canad.; Pharmascience, Canad.; Vita Health, Canad.*
Ranitidine hydrochloride (p.1766·1).

Acidan *Ace, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Acidanon *Zentiva, Cz.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Acide acetylsalicylique comp. "Radix" *Streuli, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); codeine hydrochloride (p.37·2); lidocaine hydrochloride (p.1862·3).
Fever; pain.

Aciderm *Sanval, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Acidex
Note.This name is used for preparations of different composition.
Ivax, Arg.
Ranitidine hydrochloride (p.1766·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Stada, Austria.
Cimetidine (p.1716·2).
Gastro-oesophageal reflux.

Pinewood, Irl.; Pinewood, UK.
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Flatulence; gastro-oesophageal reflux; heartburn.

Acidigen *Human, Cz.†; Human, Hung.†.*
Ammonium chloride (p.1551·3); sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Gastric hyperacidity; metabolic alkalosis.

Acidin *East India Pharma, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastritis; gastrointestinal hyperacidity; peptic ulcer.

Acidine *Upha, Malaysia†.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Acidion *Inibsa, Spain†.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2); magnesium carbonate (p.1743·1); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity; peptic ulcer.

Acidix *Solfran, Mex.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Acid-Lac *Remexa, Mex.*
Lactic acid (p.2329·3).
Maintenance of normal skin pH.

Acidofilofago *Roux-Ocefa, Arg.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; enterocolitis.

Acidophilus *Novartis Consumer, Ger.†; Mason, USA; Nature's Bounty, USA.*
Lactobacillus acidophilus (p.2372·3).
Dietary supplement; gastrointestinal disorders.

Acidophilus Bifidus *Blackmores, Austral.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium animalis.*
Maintenance of normal gastrointestinal flora.

Acidophilus with Bifidus *Mason, USA; Nature's Bounty, USA.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus bifidus.*
Dietary supplement.

Acidophilus Plus
Note.This name is used for preparations of different composition.
GNLD, Austral.
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium bifidum* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Lactobacillus casei* (p.2372·3); *Streptococcus thermophilus* (p.2372·3).
Digestive disorders.

Quest, UK.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus casei* (p.2372·3).
Maintenance of normal gastrointestinal flora.

Acidosis
Note.This name is used for preparations of different composition.
Potter's, UK.
Oral liquid: Meadowsweet (p.2338·1); compound gentian infusion (p.2310·3); euonymus (p.1730·1).
Dyspepsia; flatulence; heartburn.

Potter's, UK.
Tablets: Meadowsweet (p.2338·1); vegetable charcoal (p.1435·3); rhubarb (p.1768·3).
Dyspepsia; gastric hyperacidity; heartburn.

Acidovert *Klein, Ger.†.*
Calcium citrate (p.1675·3); magnesium citrate (p.1743·2).
Acid–base regulation; metabolic acidosis.

Acidrine *Teofarma, Fr.; Cheplapharm, Ger.†; Solvay, Indon.; Teofarma, Ital.*
Aluminium glycinate (p.1706·2); galactane sulfate; myrtecaine laurilsulfate (p.1867·2).
Gastro-oesophageal pain; gastrointestinal disorders.

Acidum phosphoricum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Acidum picrinicum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Acidumphos-Gastreu *Reckeweg, Ger.†.*
Homoeopathic preparation.
Formerly known as Diabetes-Gastreu S R40.

Acid-X *BDI, USA.*
Paracetamol (p.108·1); calcium carbonate (p.1714·1).
Gastrointestinal disorders.

Acifar *Ifars, Indon.*
Aciclovir (p.862·3).
Herpes simplex skin and mucous membrane infections.

Acifein *Herbacos, Cz.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Aciflux
Note.This name is used for preparations of different composition.
Andromaco, Chile†.
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastric hyperacidity.

GSK, Neth.
Cimetidine (p.1716·2); alginic acid (p.2140·3).
Gastro-oesophageal reflux.

Acifol
Note.This name is used for preparations of different composition.
Dominguez, Arg.
Folic acid (p.1940·1).
Folic acid supplement.

Fustery, Mex.†.
⊗ Propranolol (p.1381·1).

Acifol-B12 *Dominguez, Arg.*
Folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Folic acid and vitamin B deficiency.

Acifolik *Hasco-Lek, Pol.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Acifugan *Jaba, Port.†; Lacer, Spain†.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Acifungin *Unia, Pol.*
Boric acid (p.2268·1); methyl salicylate (p.85·3); salicylic acid (p.1612·2); gallic acid; acetic acid (p.2244·2); tannic acid (p.2394·3).
Fungal skin, scalp, and nail infections.

Acifur *Ivax, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acigon *Nicholas Piramal, India†.*
Alginic acid (p.2140·3) or sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux.

Acihexal *Hexal, Austral.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Aci-Jel
Note.This name is used for preparations of different composition.
Janssen-Cilag, Austral.†; Janssen-Cilag, NZ†.
Acetic acid (p.2244·2); hydroxyquinoline sulfate (p.2323·1); ricinoleic acid (p.2379·2); glycerol (p.2314·2).
Maintenance of vaginal acidity.

Janssen-Cilag, Irl.†; Janssen-Cilag, UK†.
Acetic acid (p.2244·2).
Vaginal infections.

Acilac
Note.This name is used for preparations of different composition.
Euroderm, Arg.
⊗ Lactic acid (p.2329·3); vitamin E (p.1992·2); urea (p.1620·2).
Formerly contained alpha hydroxyacid, vitamin E, and urea.
Dry skin.

Technilab, Canad.†.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Acilax *Jean-Marie, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acilene *UCB, Spain†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); aluminium hydroxide-magnesium carbonate co-dried precipitate (p.1707·2).
Gastric hyperacidity; peptic ulcer.

Acilin *Berman, Mex.*
Charcoal (p.1435·2); iodochloride; papaverine (p.2191·3).
Gastrointestinal astringent.

Acilmed *Bajamed, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Aciloc
Note.This name is used for preparations of different composition.
Orion, Denm.
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cadila Pharma, India; Cadila, Philipp.; Cadila, Rus.; Cadila, Thai.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; pancreatic insufficiency; peptic ulcer; short bowel syndrome; Zollinger-Ellison syndrome.

Aciloc RD *Cadila, India.*
Ranitidine hydrochloride (p.1766·1); domperidone (p.1726·2).

Acimax *Alphapharm, Austral.*
Omeprazole magnesium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acimed
Note. A similar name is used for preparations of different composition (see below).
Sanitas, Arg.
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aci-Med
Note. A similar name is used for preparations of different composition (see above).
Triomed, S.Afr.
Cimetidine (p.1716·2).
Dyspepsia; gastric hyperacidity; heartburn.

Acimethin *Madaus, Austria; Gry, Ger.; Vifor, Switz.*
Methionine (p.1450·1).
Adjunct in antibiotic therapy; paracetamol overdosage; renal calculi; urinary-tract disorders.

Acimol *Pfleger, Ger.*
Methionine (p.1450·1).
Adjunct in antibacterial therapy; renal calculi; urine acidification.

Acimont *Pharmonta, Austria.*
⊗ Formic acid (p.2306·3); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Musculoskeletal, joint, and soft-tissue disorders.

Acimox *Diba, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Acimox AC *Diba, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Acimox-Ex *Diba, Mex.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Acinat *Natufarma, Arg.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dietary supplement; gastric hyperacidity.

Acinic *Adelco, Gr.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Acinil *Hexal, Denm.; Hexal, Swed.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Acintor *Lepetit, Ital.*
Klebsiella pneumoniae glycoprotein (p.2329·2).
Respiratory-tract infections.

Acipem *Caber, Ital.†.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Acipen *Astellas, Neth.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Acipen-V *Astellas, Neth.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Aciphen *Wagner, Hung.*
Diethylamine salicylate (p.47·2).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Aciphex *Eisai, Spain; Eisai, USA.*
Rabeprazole sodium (p.1765·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acipol *Lekko, Rus.*
Lactobacillus acidophilus (p.2372·3); kefir.
Regulation of intestinal flora.

Acirufan *Laetitia, Ger.*
Homoeopathic preparation.

Acitab
Note. A similar name is used for preparations of different composition

(see below).
Mavi, Mex.
Aspirin (p.20·3).
Fever; pain.

Acitab DT
Note. A similar name is used for preparations of different composition (see above).
Cipla-Medpro, S.Afr.
Aciclovir (p.862·3).
Herpesvirus infections.

Acitak Trinity, UK†.
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aci-Tip Investi, Arg.; Pharma Investi, Chile†.
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux.

Acitop Cipla-Medpro, S.Afr.
Aciclovir (p.862·3).
Herpes labialis.

Acitral Interbat, Indon.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; hiatus hernia; peptic ulcer.

Acitrom Sarabhai Piramal, India.
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Acival Geminis, Arg.
Nimodipine (p.1357·2).
Cerebrovascular disorders.

Aciveral Bunker, Braz.
Aciclovir (p.862·3).

Acivir
Pharmacodane, Denm.; Cipla, India; Cipla, Israel; Spirig, Switz.
Aciclovir (p.862·3).
Herpes simplex infections.

DeltaSelect, Ger.
Aciclovir sodium (p.862·3).
Herpes simplex infections.

Acivirax Cifarma, Braz.
Aciclovir (p.862·3).
Herpesvirus infections.

Acix
Note.This name is used for preparations of different composition.
Zentiva, Cz.
Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Hexal, Pol.
Aciclovir (p.862·3).
Herpesvirus infections.

Acks BPL, India.
Ibuprofen (p.64·2); mephenesin (p.1897·2); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Aclam Lapi, Indon.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Aclarex Pfizer, Gr.
Celecoxib (p.34·2).
Inflammation.

Aclaro JSJ, USA.
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Aclasta Novartis, Arg.; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Novartis, Norw.; Novartis, Spain; Novartis, Swed.; Novartis, UK.
Zoledronic acid (p.1106·1).
Hypercalcaemia of malignancy; metastatic bone disease; osteoporosis; Paget's disease of bone.

Aclav Columbia, Arg.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Aclene Cipla, India.
Adapalene (p.1587·1).
Acne.

Aclimafel AF, Mex.
Veralipride (p.1035·2).
Menopausal disorders.

Aclin Alphapharm, Austral.; Alphapharm, Hong Kong; Alphapharm, Malaysia†; Merck, Malaysia†.
Sulindac (p.126·3).
Gout; musculoskeletal and joint disorders; pain with inflammation.

Aclinda Azupharma, Ger.†.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Aclophen Nutripharm, USA.
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Aclor Aspen, Austral.
Cefaclor (p.217·2).
Bacterial infections.

Acloral Liomont, Mex.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Aclorisan Dovalle, Braz.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Aclosan Gobbi, Arg.
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Aclosone Schering-Plough, Neth.
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Aclotan Piam, Ital.†.
Dermatan sulfate sodium (p.1256·3).
Thrombosis prophylaxis.

Aclotin Valeant, Hung.; ICN, Pol.
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders; thrombosis prophylaxis.

Aclotine Lab Francais du Fractionnement, Fr.
Antithrombin (human) (p.1054·1).
Thromboembolic disorders.

Aclovate PharmaDerm, USA.
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Aclovir Ratiopharm, Fin.
Aciclovir (p.862·3).
Herpes simplex infections; varicella-zoster infections.

Aclovirax Marching, Hong Kong.
Aciclovir (p.862·3).
Herpesvirus infections.

ACM 20 ACM, Fr.
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Acnacyl Rosken, Hong Kong†; Pfizer Consumer, Singapore†.
Benzoyl peroxide (p.1590·2).
Acne.

Acnaid
Note.This name is used for preparations of different composition.
Stiefel, Mex.
Soap substitute.
Acne.

Stiefel, Chile†.
Cream: Sulfur (p.1614·1); resorcinol (p.1612·1); chloroxylenol (p.1640·2).
Acne.

Stiefel, Chile.
Soap: Sulphonated rice bran oil; sulfonated mustard oil; liquid paraffin (p.2030·3).
Acne.

Acnase
Note.This name is used for preparations of different composition.
Zurita, Braz.
Cream: Benzoyl peroxide (p.1590·2); sulfur (p.1614·1).
Acne.

Zurita, Braz.
Topical gel: Benzoyl peroxide (p.1590·2).
Acne.

Acnaveen Johnson & Johnson, Ital.†.
Avena (p.2262·1); salicylic acid (p.1612·2).
Acne; seborrhoea.

Acne Homeocan, Canad.†.
Homoeopathic preparation.

Acne Clear
Note.This name is used for preparations of different composition.
ICM, Singapore.
Sulfur (p.1614·1); zinc oxide (p.1621·2); resorcinol (p.1612·1); calamine (p.1591·2).
Acne.

Altaire, USA.
Benzoyl peroxide (p.1590·2).
Acne.

Acne Cream Widmer, Cz.†.
Salicylic acid (p.1612·2); colloidal sulfur (p.1614·1); triclosan (p.1665·2); silica (p.2146·2).
Acne.

Acne Creme Widmer, Switz.
Salicylic acid (p.1612·2); colloidal sulfur (p.1614·1); colloidal silicon dioxide (p.2146·3); triclosan (p.1665·2).
Acne.

Acne Creme Plus Widmer, Switz.
Benzoyl peroxide (p.1590·2); miconazole nitrate (p.541·3).
Acne.

Acne Derm
Note. A similar name is used for preparations of different composition (see Acnederm, below).
Fischer, Israel.
Benzoyl peroxide (p.1590·2).
Acne.

Acne Feldin Galenium, Indon.
Sulfur (p.1614·1).
Acne.

Acne Gel Widmer, Switz.
⊗ Colloidal sulfur (p.1614·1); pyridoxine hydrochloride (p.1978·2); triclosan (p.1665·2); urea (p.1620·2).
Acne.

Acne Hermal Olvos, Gr.
Erythromycin (p.269·2).
Acne.

Acne Lotio Widmer, Cz.†.
Salicylic acid (p.1612·2); lactic acid (p.2329·3); triclosan (p.1665·2); zinc sulfate (p.1999·2); magnesium sulfate (p.1679·3).
Acne.

Acne Lotion
Note. A similar name is used for preparations of different composition (see below).
Widmer, Switz.
Salicylic acid (p.1612·2); triclosan (p.1665·2); zinc sulfate (p.1999·2); magnesium sulfate (p.1679·3).
Acne.

Acne Lotion 10
Note. A similar name is used for preparations of different composition (see above).
C & M, USA.
Sulfur (p.1614·1).
Acne.

Acne Mask Neutrogena, Israel†.
Benzoyl peroxide (p.1590·2).
Acne.

Acne Oral Spray Brauer, Austral.†.
Lappa (p.2330·3); artemisia abrotanum; bellis perennis; fumaria; hepar sulf; juglans reg.; kali brom.; nat. mur.; rhus ven.; saponaria; selenium; sulfur; sulfur iod.; viola tric.
Acne.

Acne & Pimple Gel Curacel, Austral.†.
Sulfur (p.1614·1); allantoin (p.1588·1); zinc oxide (p.1621·2); resorcinol (p.1612·1); *dl*-alpha tocoferil acetate; vitamin A palmitate; eicosapentaenoic acid.
Acne.

Acne Plus Widmer, Austria; Widmer, Ger.; Widmer, Philipp.
Miconazole nitrate (p.541·3); benzoyl peroxide (p.1590·2).
Acne.

Acne Solutions Clinique, Canad.
Salicylic acid (p.1612·2).
Acne.

Acne Sulf RiC, Pol.
Sulfur (p.1614·1); camphor (p.2273·2); lime water (p.2272·2).
Acne; rosacea; seborrhoea.

Acne-Aid
Note.This name is used for preparations of different composition.
Stiefel, Arg.; Stiefel, Austral.; Stiefel, Canad.; Stiefel, Israel; Stiefel, Mex.†; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Thai.
Soap.
Acne; cleansing of oily skin.

Stiefel, Hong Kong; Stiefel, Singapore.
Bar: Soap.
Acne.

Stiefel, Malaysia.
Bar; liquid cleanser: Skin cleanser.
Acne.

Stiefel, Hong Kong; Stiefel, Malaysia; Stiefel, Singapore.
Cream: Sulfur (p.1614·1); resorcinol (p.1612·1); chloroxylenol (p.1640·2).
Acne.

Stiefel, Hong Kong.
Topical liquid: Liquid skin cleanser.
Acne.

Acnecare Widmer, Neth.
Benzoyl peroxide (p.1590·2); miconazole nitrate (p.541·3).
Acne.

Acnecide Galderma, Irl.; Galderma, UK.
Benzoyl peroxide (p.1590·2).
Acne.

Acneclear
Note.This name is used for preparations of different composition.
Christo, Hong Kong.
Benzoyl peroxide (p.1590·2).
Acne.

Janpharm, S.Afr.
Cleansing bar: Triclosan (p.1665·2).
Acne.

Janssen-Cilag, S.Afr.
Cream: Miconazole nitrate (p.541·3); benzoyl peroxide (p.1590·2).
Acne.

Acneclin Valeant, Arg.
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Acnecolor Spirig, Switz.
Clotrimazole (p.530·1).
Acne.

Acnecure Taxandria, Neth.†.
Miconazole nitrate (p.541·3); benzoyl peroxide (p.1590·2).
Acne.

Acne-Derm
Note. A similar name is used for preparations of different composition (see Acne Derm, above).
Unia, Pol.
Azelaic acid (p.1589·3).
Acne.

Acnederm
Note.This name is used for preparations of different composition.
Ego, Singapore.
Azelaic acid (p.1589·3); phenoxyethanol (p.1657·1); glycerol (p.2314·2).
Formerly contained sulfur, ichthammol, undecylenic alkanolamide, and zinc oxide.
Acne.

Ego, Malaysia†.
Sulfur (p.1614·1); ichthammol (p.1599·1); undecenoic acid monoethanolamide (p.549·3); zinc oxide (p.1621·2).
Acne.

Ego, Hong Kong.
Lotion: Azelaic acid (p.1589·3); glycerol (p.2314·2).
Acne.

Ego, NZ.
Lotion: Azelaic acid (p.1589·3); phenoxyethanol (p.1657·1).
Acne.

Ego, Hong Kong.
Ointment: Sulfur (p.1614·1); ichthammol (p.1599·1); undecylenic alkanolamide (p.549·3); zinc oxide (p.1621·2).
Acne.

Ego, NZ†.
Ointment: Sulfur (p.1614·1); ammoniumsulfobitol (p.1599·1); undecylenic alkanolamide (p.549·3); zinc oxide (p.1621·2); alcloxa (p.1587·2).
Acne.

Acnederm Foaming Wash Ego, Austral.; Ego, Malaysia; Ego, NZ.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3); phenoxyethanol (p.1657·1).
Acne.

Acnederm Lotion Ego, Malaysia.
Azelaic acid (p.1589·3); phenoxyethanol (p.1657·1).
Acne.

Acnederm Medicated Ego, Austral.
Azelaic acid (p.1589·3); phenoxyethanol (p.1657·1).
Acne.

Acnederm Wash
Note.This name is used for preparations of different composition.
Ego, Hong Kong.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3); glycerol (p.2314·2).
Formerly contained cetrimide, chlorhexidine gluconate, and phenoxyethanol.
Acne.

Ego, NZ†.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3); propylene phenoxyethanol.
Acne.

Ego, Singapore.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3); phenoxyethanol (p.1657·1); glycerol (p.2314·2).
Formerly contained cetrimide only.
Acne.

Acnefuge Spirig, Switz.†.
Benzoyl peroxide (p.1590·2).
Acne.

Acnelyse Abdi, Turk.
Tretinoin (p.1618·1).
Acne.

Acne-Med Heliopharma, Hung.†.
Benzoyl peroxide (p.1590·2).
Acne.

Acne-Med Wolff Simplex Medika, Switz.†.
Hexachlorophene (p.1646·1).
Acne.

Acnemin Vinas, Spain.
Isotretinoin (p.1599·2).
Acne.

Acneout Ingens, Arg.
Tretinoin (p.1618·1); erythromycin (p.269·2).
Acne.

Acnepas Atlas, Arg.
Benzoyl peroxide (p.1590·2).
Acne.

Acnepas E Atlas, Arg.
Benzoyl peroxide (p.1590·2); erythromycin (p.269·2).
Acne.

Acneplus Widmer, Belg.
Benzoyl peroxide (p.1590·2); miconazole nitrate (p.541·3).
Acne.

Acneryne Galderma, Belg.
Erythromycin (p.269·2).
Acne.

Acnesan
Note.This name is used for preparations of different composition.
Fortbenton, Arg.
Benzoyl peroxide (p.1590·2).
Acne.

Novogaleno, Ital.†.
Sulfur (p.1614·1); zinc sulfate (p.1999·2); glycolic acid (p.1598·1); enoxolone (p.50·1).
Seborrhoea.

Acnesoap Stiefel, Braz.
Soap substitute.
Acne.

Acnesol Systopic, India.
Erythromycin (p.269·2).
Acne.

Acnestop Euroderm, Arg.
Clindamycin phosphate (p.251·2).
Acne.

Acnetane Adcock Ingram, S.Afr.
Isotretinoin (p.1599·2).
Acne.

Acnetrex Mega Lifesciences, Philipp.
Isotretinoin (p.1599·2).
Acne.

Acnetrim Trima, Israel.
Erythromycin (p.269·2).
Acne.

Acnetrol
Note.This name is used for preparations of different composition.
Lagos, Arg.
Lotion: Mallow (p.2337·2); calendula (p.2273·1); rosemary (p.2381·2); enebro (p.1616·1).
Skin disorders.

Lagos, Arg.
Topical gel: Chamomile (p.2279·3); trepadora; sage (p.2382·3); rosemary (p.2381·2).
Skin disorders.

Acnex
Note.This name is used for preparations of different composition.
Dermtek, Canad.†.
Salicylic acid (p.1612·2).
Acne.

Rafa, Israel†.
Hexachlorophene (p.1646·1); tyrothricin (p.358·2); resorcinol (p.1612·1); sulfur (p.1614·1); zinc oxide (p.1621·2).
Acne; dermatitis; eczema.

Konsuma, Venez.
Benzoyl peroxide (p.1590·2).
Acne.

Acnexyl *Pharmasant, Thai.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Acnezaic *Pfizer Consumer, Ital.†.*
Azelaic acid (p.1589·3).
Acne.

Acniben *Isdin, Arg.*
A soap substitute and moisturiser.
Acne.

Acniben Rx Hidratante *Isdin, Chile.*
Emmollient and barrier preparation.
Acne.

Acniben Rx Limpiadora *Isdin, Chile.*
Soap substitute.
Acne.

Acnidazil *Italchimici, Ital.; Janssen-Cilag, Neth.†; Janssen-Cilag, S.Afr.*
Miconazole nitrate (p.541·3); benzoyl peroxide (p.1590·2).
Acne.

Acnil
Note.This name is used for preparations of different composition.
Cristalia, Braz.
Isotretinoin (p.1599·2).
Acne.

IQFA, Mex.
Tretinoin (p.1618·1).
Acne.

Medipha r, Venez.
Gel; liquid soap; lotion: Salicylic acid (p.1612·2).
Acne.

Medipharr, Venez.†.
Soap: Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne.

Acnisal *Alliance, Irl.; Alliance, UK.*
Salicylic acid (p.1612·2).
Acne.

Acnisdin *Isdin, Spain.*
Sulfur (p.1614·1); calcium dobesilate (p.2272·1); resorcinol (p.1612·1).
Acne.

Acnisdin Retinoico *Isdin, Spain.*
Calcium dobesilate (p.2272·1); tretinoin (p.1618·1).
Acne; psoriasis.

Acno *Baker Cummins, USA.*
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne.

Acno Cleanser *Baker Cummins, USA.*
Skin cleanser.

Acnocin *Sandoz, UK.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.

Acnogen *Genepharm, Gr.*
Isotretinoin (p.1599·2).
Acne.

Acnoil Free *Dermoteca, Port.*
Magnesium silicate (p.2144·3); aluminium silicate (p.1707·3).
Acne.

Acnomel
Note.This name is used for preparations of different composition.
Key, Arg.†.
Resorcinol (p.1612·1); sulfur (p.1614·1).
Acne.

Numark, USA.
Resorcinol (p.1612·1); sulfur (p.1614·1); titanium dioxide (p.1617·3).
Acne.

Acnotex *C & M, USA.*
Sulfur (p.1614·1); salicylic acid (p.1612·2); methylbenzethonium chloride (p.1653·1).
Acne.

Acnotin *Bago, Chile; Medicap, Hong Kong; Mega Lifesciences, Malaysia; Mega Lifesciences, Singapore; Mega Lifesciences, Thai.*
Isotretinoin (p.1599·2).
Acne.

A-Cnotren *Pharmathen, Gr.*
Isotretinoin (p.1599·2).

A1cNOW *Metrika, USA.*
Test for glycosylated haemoglobin in blood.

Acnoxin *Andromaco, Arg.*
Salicylic acid (p.1612·2); resorcinol monoacetate (p.1612·1); chloramphenicol (p.239·3).
Acne.

Acnoxyl Abrasivo *Mepro, Chile.*
Essential fatty acids; melaleuca oil (p.2338·2).
Acne.

Acnoxyl Gel Cuidado Intensivo *Mepro, Chile†.*
Melaleuca oil (p.2338·2).
Acne.

Acnoxyl Gel Humectante *Koni-Cofarm, Chile.*
Melaleuca oil (p.2338·2); collagen (p.2286·1).
Acne.

Acnoxyl Gel De Limpieza *Mepro, Chile†.*
Melaleuca oil (p.2338·2).
Acne.

Acnoxyl Jabon *Koni-Cofarm, Chile†.*
Palmitic acid; oleic acid (p.2030·1); docosahexaenoic acid (p.1362·1); liquid paraffin (p.2030·3); melaleuca oil (p.2338·2).
Acne.

Acnoxyl Jabon Liquido *Mepro, Chile.*
Melaleuca oil (p.2338·2); alfa hydroxy acids; glycerol (p.2314·2).
Acne.

Acnoxyl Locion Tonica *Koni-Cofarm, Chile.*
⊗ Melaleuca oil (p.2338·2); alfa hydroxy acids; alcohol (p.1625·2); menthol (p.2340·1).
Acne.

Acnoxyl Shampoo Cabello Graso *Mepro, Chile†.*
Melaleuca oil (p.2338·2); dexpanthenol (p.2362·1); menthol (p.2340·1).
Seborrhoeic dermatitis.

Acnoxyl Stick Corrector *Mepro, Chile†.*
Melaleuca oil (p.2338·2).
Acne.

ACNU *Baxter Oncology, Ger.; Viatris, Neth.†; Asta Medica, Switz.†.*
Nimustine hydrochloride (p.756·3).
Malignant neoplasms.

Acobelin *Globo, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Acocontin *Modi-Mundipharma, India.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Acodin
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Pol.
Syrup: Dextromethorphan hydrobromide (p.1555·2); dexpanthenol (p.2362·1).
Cough.

Sanofi-Aventis, Pol.
Tablets: Dextromethorphan hydrobromide (p.1555·2).
Cough.

Acodon *Nakorn, Thai.†.*
Dipyrone (p.49·2).
Fever; pain.

Acoflam *Goldshield, UK†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Acoin *Combustin, Ger.*
Tetracaine hydrochloride (p.1871·3); lauromacrogol 400 (p.1916·1).
Local anaesthesia.

Acolyt *Modi-Mundipharma, India.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Acomir con hierro *Medipharm, Chile.*
Ferrous sulfate (p.1939·3); vitamin A palmitate; ergocalciferol; ascorbic acid (p.1922·1).
Iron and vitamin deficiency.

Acomplia *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Cz.†; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Gr.†; Sanofi-Aventis, UK†.*
Rimonabant (p.2380·3).
Obesity.

Acon
Note.This name is used for preparations of different composition.
Aventis, Mex.
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Roemmers, Venez.
Pyritinol (p.369·2).
Mental function disorders.

Acondicionador Labial *Rider, Chile†.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Aconex *Agepha, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2).
Conjunctivitis.

Aconit Schmerzol *Wala, Ger.*
Homoeopathic preparation.

Aconitum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Aconitum Nicotiana comp *Weleda, Ger.*
Homoeopathic preparation.

Aconitum-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

Acordin *Mepha, Switz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

Acorus *Zeppenfeldt, Ger.*
Couch-grass (p.2288·2).
Urinary-tract disorders.

Acorvio Plus *Ferndale, UK.*
⊗ Miconazole nitrate (p.541·3); fluprednidene acetate (p.1533·1).
Skin disorders with fungal infection.

Acotoss *Neckerman, Braz.†.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Coughs and cold symptoms.

Acotral *Phoenix, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Acovil *Sanofi-Aventis, Spain.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure following myocardial infarction; hypertension; myocardial infarction prevention.

Acpan *Gray, Arg.*
Glycopyrronium bromide (p.2315·3).

Ac-Pulmin *Vomelin, Hung.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Acpulsif *Dexa, Indon.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Acqta *Rayere, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Acqua di Sirmione *Terme Sirmione, Ital.†.*
Sulfurous thermal water (p.1614·1).
Catarrh; cold symptoms; rhinitis; sinusitis.

Acqua Virginiana *Kelemata, Ital.*
Hamamelis (p.2318·2).
Skin irritation.

Acquin *Arrow, Austral.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acran *Sanbe, Indon.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Acrea *Aulo Gelio, Arg.*
Arginine (p.1928·2); menthol (p.2340·1); jojoba oil.
Vaginal lubricant.

Acrel *Vita, Spain.*
Risedronate sodium (p.1103·3).
Osteoporosis; Paget's disease of bone.

Acrexon *Shin Poong, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Acridilole *Akrikhin, Rus.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Acridin *Legrand, Braz.*
Acriflavinium chloride (p.1625·1); methenamine (p.298·3); methylthioninium chloride (p.1450·3); belladonna (p.2263·3).
Urinary-tract infections.

Acriflex *Thornton & Ross, UK.*
Chlorhexidine gluconate (p.1635·3).
Burns; scalds; wounds.

Acrilans *Akrikhin, Rus.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Acromax
Note.This name is used for preparations of different composition.
Agepha, Austria.
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Climax, Braz.†.
Adenosine; methionine; betaine; choline; pyridoxine; cyanocobalamin; sorbitol (p.1922·1).
Digestive disorders; liver disorders.

Acromicina *Wyeth, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Acrosin *Climax, Braz.†.*
Liver extract (p.2337·3).
Liver disorders.

Acroxil *Sons, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Acroxil-C *Sons, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Acrylarm *Poen, Arg.; Roemmers, Venez.*
Carbomer 940 (p.2141·3).
Dry eyes.

Acsacea *Chemomedica, Austria.*
Metronidazole (p.837·1).
Rosacea.

Ac-Sal *Isdin, Chile.*
Salicylic acid (p.1612·2); triclosan (p.1665·2); aloe vera (p.1588·2).
Acne.

ACT
Note. A similar name is used for preparations of different composition (see below).
Johnson & Johnson Medical, USA.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

ACT-3
Note. A similar name is used for preparations of different composition (see above).
Whitehall Consumer, Austral.; Wyeth Consumer, NZ.
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Acta *Jean-Marie, Hong Kong.*
Tretinoin (p.1618·1).
Acne.

Actacel *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Actacode *Sigma, Austral.*
Codeine phosphate (p.37·2).
Coughs.

Actagen *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Actagen-C Cough *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Actal
Note.This name is used for preparations of different composition.
Valeant, Hong Kong; ICN, Malaysia; Valeant, Singapore; ICN, Thai.
Alexitol sodium (p.1704·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Combiphar, Indon.; Valeant, Indon.
Aluminium hydroxide (p.1706·2).
Dyspepsia; gastric hyperacidity; gastritis; peptic ulcer.

Merck Consumer, UK.
Alexitol sodium (p.1704·2).
Dyspepsia; gastric hyperacidity.

Actal Plus
Note.This name is used for preparations of different composition.
Valeant, Hong Kong; Combiphar, Indon.; Valeant, Indon.; Valeant, Singapore.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

ICN, Malaysia.
Alexitol sodium (p.1704·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Actalipid *Actavis, Rus.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Actan *Saval, Chile.*
Fluoxetine (p.397·3).
Depression; obsessive-compulsive disorder.

Actapront *Purissimus, Arg.*
Isothipendyl hydrochloride (p.582·1).
Pruritus.

Actapulgite *Ipsen, Belg.; Beaufour, Fr.; Beaufour, Switz.*
Attapulgite (p.1709·1).
Diarrhoea; gastrointestinal disorders; meteorism.

Actastav *Actavis, Rus.*
Stavudine (p.907·1).
HIV infection.

Actasulid *Actavis, Rus.*
Nimesulide (p.95·3).

Actebral
Note.This name is used for preparations of different composition.
Menarini, Belg.†.
⊗ Cyprodenate (p.2152·3).
Cerebral disorders.

Recalcine, Chile.
Dedietilaminoetil-p-aminobenzoato hydrochloride; gamma-aminobutyric acid (p.2308·1); haematoporphyrin hydrochloride (p.2318·1).
Mental function impairment.

Actemra *Chugai, Jpn.*
Tocilizumab (p.2326·1).
Castleman's disease.

Actenacol *Dicofarm, Ital.*
Fennel (p.2302·3); passion flower (p.2363·2); melissa (p.2339·3).
Gastrointestinal disorders.

Acthar *Aventis, Irl.†; Questcor, USA.*
⊗ Corticotropin (p.1523·3).
Corticosteroid release stimulant; diagnostic testing of adrenocortical function.

Acthelea *Elea, Arg.*
⊗ Corticotropin (p.1523·3).
Corticosteroid release stimulant; diagnostic testing of adrenocortical function.

Act-HIB *Pasteur Merieux, Austria; Sanofi Pasteur, Belg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Aventis Pasteur, Cz.; Sanofi Pasteur, Denm.; Aventis Pasteur, Fr.; Aventis Pasteur, Ger.†; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Pasteur Merieux, Israel; Sanofi Pasteur, Ital.; Aventis Pasteur, Malaysia†; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Aventis Pasteur, Philipp.; Sanofi Pasteur, Pol.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.; Aventis Pasteur, UK†; Sanofi Pasteur, USA; Zuoz, Venez.†.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p.2213·2).
Active immunisation.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Act-HIB DTP *Aventis Pasteur, UK†.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Act-HIB Polio *Aventis Pasteur, Norw.†.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) and an injectable inactivated poliomyelitis vaccine (types I, II and III) (p.2214·1).
Active immunisation.

Acthrel *Ferring, USA.*
⊗ Corticorelin triflutate (p.1523·2).
Determination of ACTH production in Cushing's syndrome.

Acti 5 *Pierre Fabre Sante, Fr.*
⊗ Deanol pidolate (p.2152·3); sodium ascorbate (p.1984·1); magnesium aminobenzoate.
Tonic.

Acti-B$_{12}$ *Sandoz, Canad.*
Hydroxocobalamin (p.1980·3); amino acids (p.1922·1).
Anaemia.

ActiBath *Jergens, USA.*
Avena (p.2262·1).
Dry skin; pruritus.

Actibil *Arkomedika, Fr.†.*
Cynara (p.2291·2); fumitory (p.2307·2).
Gastrointestinal and urinary-tract disorders.

ActiCal Plus *Usana, Canad.†.*
A vitamin D and mineral preparation (p.1922·1).

Acticalcin *TRB, Braz.*
Calcitonin (salmon) (p.1093·1).
Bone pain due to malignancy; hypercalcaemia; osteoporosis; Paget's disease of bone; sympathetic pain syndromes.

Acticarbine *Elerte, Fr.*
Papaverine hydrochloride (p.2191·3); activated charcoal (p.1435·2).
Gastrointestinal disorders.

Actichlor *Adams, Hong Kong.*
Troclosene sodium (p.1665·3).
Disinfection of surfaces and equipment.

Acticillin *British Dispensary, Thai.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Acticin *Alpharma, USA; Penederm, USA.*
Permethrin (p.2048·2).
Scabies.

Acticoat *Smith & Nephew, Ital.*
Silver (p.2387·1).
Medicated dressing for infected wounds.

Acticort *Baker Cummins, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Acticrom *Euro-Pharma, Ital.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; keratoconjunctivitis.

Actidem *GSK, Turk.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Respiratory-tract congestion.

Actidil *Warner-Lambert, Ital.†.*
Triprolidine hydrochloride (p.592·3).
Skin irritation.

Actidose with Sorbitol *Paddock, USA.*
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Emergency treatment of poisoning.

Actidose-Aqua *Cambridge, UK; Paddock, USA.*
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Actidox *Saninter, Port.*
Doxycycline (p.267·1).
Bacterial infections.

Actidue *Pfizer Consumer, Ital.*
White tablets (daytime), paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); blue tablets (night-time) paracetamol; diphenhydramine hydrochloride (p.577·2).
Daytime tablets formerly contained paracetamol and phenylpropanolamine hydrochloride.
Cold and influenza symptoms.

Actifed
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; GSK, Belg.; Pfizer Consumer, Canad.; GSK, Hong Kong; GSK, Indon.; Pfizer Consumer, Irl.; GSK, Israel†; Pfizer Consumer, Ital.; GSK, Malaysia; Pfizer Consumer, Mex.; Johnson & Johnson, NZ; Janssen-Cilag, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Thai.; GSK, Turk.; Wellcome, USA; GSK, Venez.†.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold and influenza symptoms; otitis media; respiratory-tract congestion.

Pfizer Sante, Fr.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms; upper respiratory-tract congestion.

GSK, India†.
Triprolidine hydrochloride (p.592·3); phenylpropanolamine (p.1569·2).
Respiratory-tract congestion.

GSK, Pol.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Actifed Allergy *Wellcome, USA.*
White daytime caplets, pseudoephedrine (p.1571·2); blue night time caplets, pseudoephedrine; diphenhydramine hydrochloride (p.577·2).

Actifed CC Chesty *Pfizer Consumer, Austral.; Pfizer, NZ†.*
Guaifenesin (p.1561·3).
Cough; coughs and cold symptoms.

Actifed CC Dry *Johnson & Johnson, Austral.; Pfizer, NZ†.*
Pholcodine (p.1570·2).
Cough; coughs.

Actifed CC Junior *Pfizer Consumer, Austral.*
Dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract disorders.

Actifed Chesty
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer, NZ†.
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; cold symptoms; respiratory-tract congestion.

Pfizer Consumer, Irl.†.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; upper respiratory-tract congestion.

Actifed Cold & Allergy *Warner-Lambert, USA.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Actifed Cold & Fever *GSK, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly known as Actigesic.
Cold and influenza symptoms.

Actifed Cold & Sinus *Warner-Lambert, USA.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms.

Actifed Composto *Pfizer Consumer, Ital.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; respiratory-tract congestion.

Actifed Compound
Note. This name is used for preparations of different composition.
GSK, Hong Kong; GSK, Israel†; GSK, Singapore; GSK, Thai.†.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Cough; cold symptoms; upper respiratory-tract congestion.

Pfizer Consumer, Irl.†.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; upper respiratory-tract congestion.

Actifed DM
Note. This name is used for preparations of different composition.
GSK, Hong Kong†; GSK, Indon.; GSK, Israel†; GSK, Malaysia; Pfizer Consumer, Mex.; GSK, Singapore; GSK, Thai.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Allergic rhinitis; coughs; cold symptoms; nasal congestion.

GSK, India†.
Triprolidine hydrochloride (p.592·3); phenylpropanolamine (p.1569·2); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract congestion.

Actifed Dry *Pfizer Consumer, Austral.; Pfizer, NZ†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; upper respiratory-tract disorders.

Actifed Dry Cough Regular *GSK, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Formerly known as Actifed Co.
Coughs.

Actifed Dry Cough Sugar Free *GSK, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Actifed DM.
Coughs.

Actifed Expectorant
Note. This name is used for preparations of different composition.
Pfizer Sante, Fr.†.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

GSK, Indon.; GSK, Israel†; GSK, Malaysia; GSK, Singapore.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Allergic rhinitis; cold symptoms; cough; upper respiratory-tract congestion.

Actifed jour et nuit *Pfizer Sante, Fr.*
White tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); blue tablets, paracetamol; diphenhydramine hydrochloride (p.577·2).
The white tablets replaced yellow tablets which contained paracetamol and phenylpropanolamine hydrochloride.
Cold symptoms.

Actifed Nasale *Pfizer Consumer, Ital.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Actifed New *GSK, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Actifed PE *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p.1568·1).

Actifed Plus
Note. This name is used for preparations of different composition.
Pfizer Consumer, Canad.; Wellcome, USA.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms; sinusitis.

GSK, India†.
Triprolidine hydrochloride (p.592·3); phenylpropanolamine (p.1569·2); paracetamol (p.108·1).
Respiratory-tract congestion associated with pain or fever.

Actifed Sinus Daytime *Wellcome, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Actifed Sinus Nighttime *Wellcome, USA.*
Pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Actifed Toux Seche *Pfizer Sante, Fr.†.*
Triprolidine hydrochloride (p.592·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Actifed Wet Cough Non Drowsy *GSK, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Actifedduo *Pfizer Sante, Fr.*
Cetirizine (p.571·1); pseudoephedrine (p.1571·2).
Allergic rhinitis.

Actifedrin
Note. This name is used for preparations of different composition.
Farmoquimica, Braz.; GSK, Chile.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; nasal congestion; rhinitis.

Investi, Arg.
Lozenges: Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders.

Investi, Arg.
Syrup; tablets: Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Actifedrin Antitusivo *GSK, Chile.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Upper respiratory-tract disorders.

Actifedrin Nasal *Investi, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Actifen *Gebro, Austria.*
Dexibuprofen (p.39·2).
Fever; inflammation; pain.

Actiferrine *Mepha, Switz.*
Ferrous sulfate (p.1939·3).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Actiferrine-F Nouvelle formule *Mepha, Switz.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron and folate deficiency; iron-deficiency anaemia.

Actiferro *Lampugnani, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Iron-deficiency disorders.

Actiflora *Brovar, S.Afr.*
Lactobacillus acidophilus (p.2372·3).
Restoration of a normal gastrointestinal flora.

Actiflu *Cipla, India.*
Triprolidine hydrochloride (p.592·3); phenylpropanolamine (p.1569·2).

Actiflu Plus *Cipla, India.*
Triprolidine hydrochloride (p.592·3); phenylpropanolamine (p.1569·2); paracetamol (p.108·1).

Actifluor *Altana, Ital.†.*
Sodium fluoride (p.1962·2); stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Actigall *Novartis, NZ; Watson, USA.*
Ursodeoxycholic acid (p.2408·1).
Gallstones; primary biliary cirrhosis; primary sclerosing cholangitis.

Actigeron *Bago, Chile.*
Acetylcarnitine hydrochloride (p.1932·2).
Dementia.

Actigesic *GSK, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms; nasopharyngitis; sinusitis.

Actigrip *Pfizer Consumer, Ital.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Influenza symptoms; respiratory-tract congestion.

Actihaemyl *Stulln, Ger.; Valeant, Ger.*
Protein-free bovine blood extract (p.2337·3).
Eye disorders; wounds.

Actihist *Hovid, Malaysia.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms; rhinitis.

Actihist Expectorant *Hovid, Malaysia.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Actihist-Co *Hovid, Hong Kong†; Hovid, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Actil *Masa, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Actilam *Sofex, Port.*
⊗ Hesperidin (p.2304·3); deanol acetamidobenzoate (p.2152·3); magnesium glycerophosphate (p.1679·2).
Mental function disorders; vascular disorders.

Actilax
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Medic, Denm.
Sodium picosulfate (p.1771·1).
Constipation.

Actilis *Laphi, Fr.*
Barrier cream.

Actilyse *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; German Remedies, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Venez.*
Alteplase (p.1207·2).
Ischaemic stroke; myocardial infarction; peripheral arterial thromboembolism; pulmonary embolism.

Actimag *Vita, Ital.†; Iquinosa, Spain.*
Magnesium pidolate (p.1679·3).
Magnesium depletion.

Actiman *Biofarma, Mex.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); ascorbic acid (p.1983·3); manganese sulfate (p.1956·2).
Osteoarthritis.

Actimax *Sandoz, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Actiment *Tecnonat, Arg.*
Nutritional supplement (p.1922·1).

Actimmune *Genentech, USA.*
Interferon gamma-1b (p.893·3).
Infections in chronic granulomatous disease; osteopetrosis.

Actimol *Pharmed, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Rheumatoid arthritis.

Actimoxi *Clariana, Spain†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Actin *The Forty-Two, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Actinac *Peckforton, UK.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2); nicoboxil (p.95·1); allantoin (p.1588·1); precipitated sulfur (p.1614·1).
Acne.

Actine
Note. This name is used for preparations of different composition.
Darrow, Braz.
Liquid soap: Salicylic acid (p.1612·2); aloe vera (p.1588·2).
Acne; seborrhoea.

Darrow, Braz.
Soap: Salicylic acid (p.1612·2); sulfur (p.1614·1); aloe vera (p.1588·2).
Acne; seborrhoea.

Actinerval *Bago, Arg.*
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Actinium *Armstrong, Mex.*
Oxcarbazepine (p.490·3).
Epilepsy; neuropathic pain.

Actinoma *Orva, Turk.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Actinic keratosis; musculoskeletal and joint pain.

Action *Sante Naturelle, Canad.*
Ascorbic acid (p.1983·3).

Action Chewable *Bayer Consumer, Austral.*
Chlorphenamine maleate (p.571·3); phenylephrine tartrate (p.1568·1).
Cold symptoms; hay fever.

Action Cold & Flu *Bayer Consumer, Austral.*
Chlorphenamine maleate (p.571·3); phenylephrine acid tartrate (p.1568·1); aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Actiphos *Teofarma, Fr.†.*
Phosphoric acid salts (p.2367·1).
Tonic.

Actiplex *Umeda, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Actipol *Diafarm, Rus.†.*
Aminobenzoic acid (p.1589·1).
Viral eye infections.

Actipram *Laboratorios Chile, Chile.*
Citalopram hydrobromide (p.385·3).
Depression.

Actiprofen *GSK Consumer, Austral.; Sanofi Synthelabo, Braz.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Actiq *Orphan, Austral.; Cephalon, Denm.; Orphan, Fin.; Cephalon, Fr.; Cephalon, Ger.; Gerolymatos, Gr.; Cephalon, Irl.; Dompe, Ital.; Cephalon, Neth.; Cephalon, Norw.; Ferrer, Spain; Swedish Orphan, Swed.; Cephalon, Switz.; Cephalon, UK; Cephalon, USA.*
⊗ Fentanyl citrate (p.55·3).
Pain.

Actiquim *Quimica y Farmacia, Mex.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Actira *Bayer, Austria; Baycare, Ital.; Bayer, Neth.†; Bayer, Spain.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Actirelax *Northia, Arg.*
Suxamethonium (p.1912·1).
Depolarising neuromuscular blocker.

Actires *Dicofarm, Ital.*
Propolis (p.2373·3); boswellia (p.2307·1).
Respiratory-tract disorders.

Actisac *Polipharm, Thai.†.*
Fluoxetine (p.397·3).
Depression.

Actisens *Altana, Ital.†.*
⊗ Sodium fluoride (p.1962·2); potassium nitrate (p.1658·3).
Gum hypersensitivity.

Actiser-T *Silesia, Chile.*
⊗ Testosterone (p.2129·3).
Hypogonadism.

Actisite *Willvonseder, Austria; Solco, Ital.†; Dentaid, Spain; Solco, Switz.†; Alza, USA†.*
Tetracycline hydrochloride (p.347·2).
Bacterial mouth infections.

Actiskenan *BMS, Fr.*
⊗ Morphine sulfate (p.86·3).
Pain.

Actison *Buxton, Arg.*
Amantadine hydrochloride (p.792·3).
Parkinsonism.

Actisorb Ag+ *Johnson & Johnson Medical, Fr.*
Activated charcoal (p.1435·2); silver (p.2387·1).
Formerly known as Actisorb Plus.
Infected wounds.

Actisorb Plus *Johnson & Johnson, Ital.*
Activated charcoal (p.1435·2); silver (p.2387·1).
Infected or malodorous wounds.

Actisorb Silver *Johnson & Johnson, Ger.†; Johnson & Johnson, Irl.; Johnson & Johnson Medical, UK.*
Activated charcoal (p.1435·2); silver (p.2387·1).
Previously known as Actisorb Plus.
Infected or malodorous wounds; ulcers.

Actisoufre *Grimberg, Fr.*
Sodium sulfate (p.1771·3); dried yeast (p.1998·3).
Rhinitis; upper respiratory-tract inflammation.

Actithiol *Almirall, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Actithiol Antihist *Almirall, Spain.*
Carbocisteine (p.1553·2); promethazine hydrochloride (p.588·2).
Respiratory-tract disorders.

Actitonic *Amido, Fr.†.*
Amino-acid and mineral preparation (p.1922·1).
Tonic.

Actitrin *Hasco-Lek, Pol.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold and influenza symptoms; cough.

Activacin *Kyowa, Jpn.*
Alteplase (p.1207·2).
Myocardial infarction.

Activadone *Thea, Spain.*
Chromocarb diethylamine (p.2281·1).
Adjunct in eye surgery; conjunctival capillary fragility.

Activarol *Carlo Erba OTC, Ital.†; Azevedos, Port.†.*
Haematoporphyrin hydrochloride; glycine; cyanocobalamin; calcium gluconate (p.1922·1).
Tonic.

Activase *Roche, Canad.; Genentech, USA.*
Alteplase (p.1207·2).
Maintenance of central venous catheter patency; myocardial infarction; pulmonary embolism; stroke.

Activator *Andromaco, Chile†.*
Magnesium oxide (p.1744·1); pyridoxine hydrochloride (p.1978·2).
Magnesium deficiency disorders.

Active C *Roche-Posay, Braz.; Roche-Posay, Singapore.*
Ascorbic acid (p.1983·3).
Skin ageing; wrinkles.

Active Calcium *Usana, Singapore.*
Calcium; magnesium; colecalciferol; silicon (p.1922·1).
Dietary supplement.

Active Calcium Plus *Usana, Canad.*
Calcium; colecalciferol; magnesium; silicon (p.1922·1).
Dietary supplement.

Active Dry Lotion *Norwood, Canad.†.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Activella *Novo Nordisk, USA.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Activelle *Novo Nordisk, Arg.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.†; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Isdin, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Hormone replacement therapy; menopausal disorders; osteoporosis.

Activent *More, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm.

Activex 40 Plus *Propan, S.Afr.*
Ginseng (p.2312·1); muira-puama; vitamins (p.1922·1); minerals; kelp (p.2384·2); lysine hydrochloride.
Tonic.

Activir *GSK, Austria; GSK, Fr.; GSK, S.Afr.*
Aciclovir (p.862·3).
Herpes labialis.

Activital Forte *Welti, Switz.*
Arginine aspartate (p.1928·2); magnesium aspartate (p.1679·1).
Activital formerly contained arginine aspartate, calcium gluconate, and magnesium gluconate.
Tonic.

Activon *Drossapharm, Switz.†.*
Etofenamate (p.53·1).
Soft-tissue disorders.

Activon Extra *Goodwill, Hung.*
Etofenamate (p.53·1).
Musculoskeletal, joint, and soft-tissue disorders.

Activox *Arkopharma, Fr.*
Erysimum; chamomile (p.2279·3).
Mouth and throat disorders.

Activox Lierre *Arkopharma, Fr.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Actizid *Overseas, India†.*
Pyrazinamide (p.320·2).
Tuberculosis.

Actocortina *Altana, Spain.*
⊗ Hydrocortisone sodium phosphate (p.1535·3).
Corticosteroid.

Actokit *Procter & Gamble, Neth.*
Blue tablets, calcium carbonate (p.1714·1); orange tablets, risedronate sodium (p.1103·3).
Osteoporosis.

Actomite *Ceuta, UK.*
Bioallethrin (p.2036·2).
Elimination of house dust mite.

Actonel *Aventis, Arg.; Sanofi-Aventis, Austral.; Aventis, Austria; Procter & Gamble, Belg.; Sanofi-Aventis, Braz.; Procter & Gamble, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Procter & Gamble, Fr.; Aventis, Ger.; Procter & Gamble, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Aventis, Irl.; Procter & Gamble, Irl.; Aventis, Israel; Procter & Gamble, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Procter & Gamble, Neth.; Aventis, Philipp.; Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Procter & Gamble, UK; Procter & Gamble, USA; Sanofi-Aventis, Venez.*
Risedronate sodium (p.1103·3).
Osteoporosis; Paget's disease of bone.

Actonel with Calcium *Procter & Gamble, USA.*
4 Tablets, risedronate sodium (p.1103·3); 24 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Actonel Combi
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Austral.; Procter & Gamble, Irl.; Sanofi-Aventis, Irl.
7 Tablets, risedronate sodium (p.1103·3); 21 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Procter & Gamble, UK.
Tablets, risedronate sodium (p.1103·3); effervescent granules, calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Actonel Trio *Sanofi-Aventis, Hung.*
4 Tablets, risedronate sodium (p.1103·3) (Actonel); 60 tablets, colecalciferol (p.1986·2); calcium carbonate (p.1714·1) (Calcichew-D).
Osteoporosis.

Actonelcombi *Procter & Gamble, Fr.*
Tablets, risedronate sodium (p.1103·3); effervescent granules, calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Actonorm
Note. This name is used for preparations of different composition.
Wallace Mfg Chem., UK.
Oral gel: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence.

Wallace Mfg Chem., UK.
Oral powder: Magnesium carbonate (p.1743·1); aluminium hydroxide (p.1706·2); atropine sulfate (p.1219·3); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2); peppermint oil (p.1761·2).
Dyspepsia; flatulence; gastric hyperacidity.

Actophlem *Adcock Ingram, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1); diphenylpyraline hydrochloride (p.578·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Actoplus Met *Takeda, USA.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Actopril *Ergha, Irl.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Actorin *Hua, Thai.*
Aspirin (p.20·3).
Pain.

Actos *Abbott, Arg.; Lilly, Austral.; Takeda, Austria; Lilly, Belg.; Abbott, Braz.; Lilly, Canad.; Abbott, Chile†; Takeda, Cz.; Takeda, Denm.; Lilly, Fin.; Takeda, Fr.; Takeda, Ger.; Lilly, Gr.; Takeda, Hong Kong; Takeda, Indon.; Takeda, Ital.; Takeda, Jpn; Takeda, Malaysia; Lilly, NZ; Takeda, Neth.; Takeda, Norw.; Takeda, Philipp.; Takeda, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Spain; Lilly, Swed.; Takeda, Switz.; Takeda, Thai.; Takeda, UK; Lilly, USA; Takeda, USA; Abbott, Venez.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Actosolv *Aventis, Austria; Eumedica, Belg.; Aventis, Ital.†.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Actospect *Adcock Ingram, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Actovegin *Nycomed, Austria; Nycomed, Ger.; Nycomed, Hong Kong; Nycomed, Hung.; Nycomed, Rus.; Nycomed, Thai.†.*
Protein-free bovine blood extract (p.2337·3).
Burns; cerebral and peripheral vascular disorders; cerebral metabolic disorders; eye disorders; radiation-induced lesions; scalds; ulcers; wounds.

Actparin *Bergamo, Braz.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Actraphane *Novo Nordisk, Cz.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin (human) 70% (p.443·2).
Diabetes mellitus.

Actraphane 10, 20, 30, 40, 50 *Novo Nordisk, Ger.; Novo Nordisk, Ital.; Novo Nordisk, Neth.*
⊗ Mixtures of insulin injection (human) 10%, 20%, 30%, 40% and 50% and isophane insulin injection (human) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Formerly known as Actraphane HM 10/90, 20/80, 30/70, 40/60, and 50/50.
Diabetes mellitus.

Actraphane HM *Novo Nordisk, Gr.†; Novo Nordisk, S.Afr.*
⊗ Mixtures of insulin injection (human, recombinant) and isophane insulin (human, recombinant) in varying proportions (p.443·2).
Diabetes mellitus.

Actrapid *Novo Nordisk, Austral.; Pentafarma, Chile†; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hung.; Abbott, India; Novo Nordisk, Irl.; Novo Nordisk, Ital.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, UK.*
⊗ Neutral insulin injection (human, pyr, monocomponent) (p.443·2).
Formerly known as Human Actrapid.
Diabetes mellitus.

Actrapid HM *Novo Nordisk, Arg.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Chile; Novo Nordisk, Hong Kong; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Malaysia; Novo Nordisk, Philipp.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Switz.; Novo Nordisk, Thai.*
⊗ Neutral insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Actrapid MC *Novo Nordisk, Arg.†; Novo Nordisk, Braz.†; Novo Nordisk, Hong Kong†; Novo Nordisk, Rus.; Novo Nordisk, Switz.*
⊗ Neutral insulin injection (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Actron
Note. This name is used for preparations of different composition.
Bayer Consumer, Arg.; Bayer, Chile; Bayer, Mex.
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Bayer, Fr.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Bayer, Spain†.
Paracetamol (p.108·1).
Fever; pain.

Actron Compuesto *Bayer, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Actual *Bago, Arg.*
Famotidine (p.1730·1); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Actualene *Carlo Erba OTC, Ital.*
Cabergoline (p.802·1).
Hyperprolactinaemia; lactation suppression; prolactinoma.

Actuss *Sigma, Austral.†.*
Pholcodine (p.1570·2).
Coughs.

Actyfilus *Codifra, Fr.*
Capsules (transparent), *Lactobacillus lactis* (p.2372·3); *Lactobacillus paracasei*; Lacidophilus NCFM; *Lactobacillus casei* (p.2372·3); *Bifidobacterium longum* (p.2372·3); capsules (cream), inulin (p.2326·3).
Digestive disorders.

Actymine *Codifra, Fr.*
Vitamins; minerals; vegetable oils; fish oil (p.1922·1).
Dry skin; sun-induced skin damage.

Actypral *Codifra, Fr.*
Bioflavonoids; vitamins; minerals; lycopene (p.1922·1).
Skin ageing.

Acuaderm *Bajer, Arg.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); aloe vera (p.1588·2).
Pruritus.

Acuafil *Sophia, Mex.†.*
Wool fat (p.2033·2); liquid paraffin (p.2030·3).
Dry eyes.

Acuafil Ofteno *Sophia, Mex.; Elmor, Venez.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Acuatim *Otsuka, Indon.; Otsuka, Jpn.*
Nadifloxacin (p.303·2).
Acne.

Acubiron *Bohm, Spain.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Acubisina *Intra, Venez.†.*
Acubigenina.

Acucil *Apotex, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Acuco *Apotex, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Acudex *Polfa Kutno, Pol.*
Dextranomer (p.1593·3).
Ulcers; wounds.

Acudor *Ferring, Port.*
Etodolac (p.52·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

ACU-dyne *Acme, USA.*
Povidone-iodine (p.1659·2).
Skin disinfection; vaginal disorders.

Acu-Erylate S *Apotex, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Acuflam *Unison, Philipp.*
Diclofenac potassium (p.44·3).
Actinic keratoses; fever; gout; musculoskeletal and joint disorders; pain.

Acuflex *Acupharm, S.Afr.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Acuflu P *Apotex, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Acugel *Acupharm, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Acugesic *Duopharma, Hong Kong; Duopharma, Malaysia.*
Tramadol hydrochloride (p.130·3).
Pain.

Acugest *Acupharm, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Acugest Co *Acupharm, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Acugest DM *Apotex, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Acugest Expect *Acupharm, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Acuilfem *Gezzi, Arg.*
Ibuprofen (p.64·2).
Pain.

Acuilix *Pfizer, Fr.*
⊗ Hydrochlorothiazide (p.1307·3); quinapril hydrochloride (p.1382·2).
Hypertension.

Acuitel *Pfizer, Fr.; Pfizer, Turk.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acular *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Ital.; Allergan, Malaysia; Allergan, NZ; Allergan, Neth.; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Gervasi, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA; Allergan, Venez.†.*
Ketorolac trometamol (p.74·2).
Allergic eye disorders; cystoid macular oedema; inflammation, pain, and photophobia following ocular surgery.

Aculare *Allergan, Belg.*
Ketorolac trometamol (p.74·2).
Ocular inflammation following cataract surgery.

Acularen *Allergan, Mex.*
Ketorolac trometamol (p.74·2).
Allergic conjunctivitis; postoperative ocular inflammation.

Aculoid *Apotex, S.Afr.*
Cyclizine hydrochloride (p.574·2).
Nausea; vestibular disorders; vomiting.

Acumel *Baxter, Ital.*
Lipid (from olive oil (p.2356·2) and soya oil (p.1965·3)), amino-acid, and glucose infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Acumerck *Generics, Hung.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acumet *Acupharm, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Acunaso *Apotex, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Acuode *Recalcine, Chile.*
Colecalciferol (p.1986·2).
Hypoparathyroidism; osteomalacia; rickets; tetanus; vitamin D deficiency.

Acuolens *Alcon Cusi, Spain.*
Hypromellose (p.2144·2).
Dry eyes.

Acu-Oxytet *Apotex, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Acupan *3M, Belg.; Biocodex, Fr.; 3M, Irl.; 3M, NZ; 3M, Switz.†; 3M, UK.*
Nefopam hydrochloride (p.94·2).
Pain.

Acuphlem *Acupharm, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excess mucus.

Acupillin *Apotex, S.Afr.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Acuprel *Parke, Davis, Spain.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acupril *Pfizer, Mex.; Pfizer, Neth.; Pfizer, Port.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Acura *Nordic Drugs, Norw.; Nordic, Swed.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Acurate *Apotex, S.Afr.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain with tension.

Acurenal *ICN, Pol.*
Quinapril (p.1382·3).
Heart failure; hypertension.

Acuretic *Pfizer, Port.; Binesa, Spain.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Acurmil *Lisapharma, Ital.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Acusprain *Apotex, S.Afr.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Acustat *Transpen, UK.*
Skin patch.
Musculoskeletal, joint, and soft-tissue injury.

Acustop *Apotex, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Acustop Cataplasma *Sang-A, Malaysia; Sang-A, Singapore†.*
Flurbiprofen (p.61·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

AcuTect *Diatide, USA.*
Technetium-99m apcitide (p.2055·3).
Scintigraphic imaging of acute venous thrombosis.

Acuten *Farma, Venez.*
Paracetamol (p.108·1); codeine (p.37·2).
Fever; pain.

Acutil *Body Spring, Ital.*
Multivitamin preparation (p.1922·1).

Acutil Fosforo *Angelini, Ital.*
Aceglutamide (p.2244·2) or glutamine (p.1947·2); -asparagine (p.1929·3); -phosphoserine (p.2367·1); pyridoxine (p.1979·1) or pyridoxine hydrochloride (p.1978·2).
Tonic.

Acutret *Ipca, India†.*
Isotretinoin (p.1599·2).
Acne.

Acutussive *Acupharm, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Acuzide *Pfizer, Neth.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

ACV *Greater Pharma, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections of skin and mucous membranes.

ACWY Vax *GSK, UK.*
A meningococcal vaccine (groups A, C, W , and Y) (p.2224·1).
Active immunisation.

Acxen *Loren, Mex.†.*
Paracetamol (p.108·1); naproxen (p.92·3).
Inflammation; pain.

Acxion *IFA, Mex.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

ACY *Ecobi, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acyclostad *Stada, Cz.; Berner, Fin.†; Stada, Hung.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acyclo-V *Alphapharm, Austral.; CTI, Israel.*
Aciclovir (p.862·3).
Herpesvirus infections; HIV infection.

Acyclox *Amat, Austria.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acydona *Pliva, Spain.*
Povidone-iodine (p.1659·2).
Disinfection of burns, skin, and wounds.

Acyflox *Pliva, Spain.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Acyhex *Hexal, Philipp.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acyl *Biofarma, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acylcoffin *Slovakofarma, Cz.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Acylene *UCB, Spain†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastrointestinal hyperacidity.

Acylete *Kireen, Malaysia.*
Aciclovir (p.862·3).
Herpesvirus infections.

Acylpyrin *Herbacos, Cz.*
Aspirin (p.20·3).
Fever; pain.

Acylpyrin + C *Herbacos, Cz.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Acyprin *Collins, Mex.*
Allopurinol (p.552·2).
Hyperuricaemia.

Acypront *Mack, Malaysia†.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Acyrax *Orion, Fin.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Acyvir *APT, Hong Kong; Glaxo Allen, Ital.; Pharmasant, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aczebri *Shin Poong, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Aczone *QLT, Canad.; QLT, USA.*
Dapsone (p.261·2).
Acne.

AD Mycin *Boryung, Thai.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

AD Pabyrn *LPB, Ital.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2).
Vitamin A and D deficiency.

A-D Plex *Kalbe, Indon.*
Vitamins A, B, and D (p.1922·1).
Nutritional supplement.

AD Shock *Mertens, Arg.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1).
Hypocalcaemia; hypoparathyroidism; osteoarthritis; osteomalacia; renal osteodystrophy; rickets; tetanus.

ADA *Estedi, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion; sinus congestion.

Adacai *Schering-Plough, Chile; Schering-Plough, Venez.*
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Hypercholesterolaemia.

Adacel *Sanofi Pasteur, Canad.; Aventis Pasteur, USA.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Adaderm *Vargas, Venez.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Skin disorders.

Adafen *Akdeniz, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Adaferin *Lavipharm, Gr.; Galderma, India; Galderma, Israel; Galderma, Mex.*
Adapalene (p.1587·1).
Acne.

Adagen *Enzon, USA.*
Pegademase bovine (p.2364·1).
Adenosine deaminase deficiency.

Adalat *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer, Jpn; Bayer, Malaysia; Bayer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Norw.; Bayer, Philipp.; Bayer, Pol.; Centrofarma, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, USA; Schering, USA; Bayer, Venez.*
Nifedipine (p.1350·1).
Angina pectoris; coronary spasm; hypertension; Raynaud's syndrome.

Adalate *Bayer, Fr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Adalex *HB, Braz.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Adalgen *Andromaco, Chile†.*
Paracetamol (p.108·1); chlormezanone (p.968·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Adalgur *Teofarma, Spain.*
Paracetamol (p.108·1); thiocolchicoside (p.1898·2).
Pain; skeletal muscle spasm.

Adalgur N *Angelini, Port.*
Paracetamol (p.108·1); thiocolchicoside (p.1898·2).
Musculoskeletal and joint pain.

Adalken *Kendrick, Mex.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; Wilson's disease.

Adamin *Leti, Venez.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Adamin-G *Scientific Hospital Supplies, Irl.*
Glutamine (p.1947·2).
Nutritional supplement.

Adamon
Note. This name is used for preparations of different composition.
Kampel Martian, Arg.†; Viatris, Austria; Meda, Hung.; Viatris, Ital.
Tramadol hydrochloride (p.130·3).
Pain.

Transfarma, Thai.†.
Ciclonium bromide (p.1716·2).
Dysmenorrhoea; gastro-intestinal, biliary, and urinary-tract spasm.

Adana *Sandoz, Arg.*
Irbesartan (p.1316·1).
Hypertension.

Adana Plus *Sandoz, Arg.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Adancor *Lipha Sante, Fr.*
Nicorandil (p.1349·1).
Angina pectoris.

Adant *Daiichi Sankyo, Fr.; Meiji, Indon.; Tedec Meiji, Israel; Meiji, Thai.; Er-Kim, Turk.*
Sodium hyaluronate (p.2320·1).
Joint disorders; osteoarthritis.

Adapettes
Note. This name is used for preparations of different composition.
Alcon, Mex.
Disodium edetate (p.1463·3); sorbic acid (p.1662·2) (p.1622·2).
Wetting solution for contact lenses.

Alcon, USA.
Range of solutions for contact lenses (p.1622·2).

Adaphen *Triomed, S.Afr.*
⊗ Methylphenidate (p.2160·1) or methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Adapne *Cinetic, Arg.*
Adapalene (p.1587·1).
Acne.

Adaptic *Johnson & Johnson, Ital.*
White soft paraffin (p.2031·2).
Burns; wounds.

Adaptoplast *Vican, Gr.*
Salicylic acid (p.1612·2).
Calluses.

Adartrel
GSK, Cz.; GSK, Switz.
Ropinirole hydrochloride (p.816·1).
Restless legs syndrome.

GSK, Fr.; GSK, Gr.; GSK, UK.
Ropinirole (p.816·2).
Restless legs syndrome.

Adasept
Note. This name is used for preparations of different composition.
Odan, Canad.
Cleanser: Triclosan (p.1665·2).
Skin cleanser.

Odan, Canad.
Topical gel: Triclosan (p.1665·2); salicylic acid (p.1612·2); sodium thiosulfate (p.1466·1).
Acne.

Adaspor *IMS, Ital.*
Adazone; peracetic acid (p.1655·2).
Instrument disinfection.

Adato-Cel *Chiron, Israel†.*
Hypromellose (p.2144·2) in sodium chloride.
Aid in eye surgery and gonioscopy.

Adato-Deca *Chiron, Israel†.*
⊗ Perflunafene (p.2365·2).
Aid in eye surgery.

Adato-Octa *Chiron, Israel†.*
Perfluorooctane (p.2365·3).
Ophthalmic tamponade.

Adato-Sil Ol *Chiron, Israel†.*
Dimethicone (p.2032·1).
Aid in eye surgery.

Adavin *Lek, Pol.*
Nicergoline (p.2352·1).
Migraine and vascular headache; pulmonary hypertension; vascular disorders.

Adavite *Hudson, USA.*
A range of vitamin preparations (p.1922·1).

Adax *Saval, Chile.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic attacks.

Adaxil *Altana, Arg.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

A-D-C *Mertens, Arg.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1); ascorbic acid (p.1983·3).
Vitamin A, D, and C supplement.

ADC Fluor *Mertens, Arg.*
Vitamin A; vitamin D; vitamin C (p.1922·1) sodium fluoride (p.1962·2).
Nutritional supplement.

Adcal *ProStrakan, UK.*
Calcium carbonate (p.1714·1).
Calcium supplement; hyperphosphataemia; osteoporosis.

Adcal-D_3 *ProStrakan, UK.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Adco-Amoclav *Ranbaxy, S.Afr.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Adco-Bisocor *Adcock Ingram, S.Afr.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Adco-Ciprin *Ranbaxy, S.Afr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Adco-Clofelam *Adcock Ingram, S.Afr.*
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Adco-Dermed *Adcock Ingram, S.Afr.*
Ketoconazole (p.539·1).
Pityriasis versicolor; seborrhoeic dermatitis.

Adco-Dol *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); doxylamine succinate (p.578·2).
Fever; pain.

Adco-Flupain *Adcock Ingram, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Adco-Indogel *Adcock Ingram, S.Afr.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Adco-Kiddipayne *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Adco-Linctopent *Adcock Ingram, S.Afr.*
⊗ Bromhexine hydrochloride (p.1552·2); orciprenaline sulfate (p.1129·1).
Coughs.

Adco-Liquilax *Adcock Ingram, S.Afr.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Adco-Loten *Adcock Ingram, S.Afr.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Adcomag Trisil *Adco, S.Afr.*
Magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Flatulence; gastric hyperacidity.

Adco-Payne *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and tension.

Adco-Phenobarbitone Vitalet *Adcock Ingram, S.Afr.*
Phenobarbital (p.492·2); vitamin B substances (p.1922·1).
Epilepsy; insomnia; sedative.

Adco-Retic *Adcock Ingram, S.Afr.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Adco-Roznal *Adcock Ingram, S.Afr.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Adcortyl *BMS, Irl.; BMS, Israel†; BMS, UK.*
⊗ Triamcinolone acetonide (p.1544·3).
Inflammatory disorders; musculoskeletal, joint, and peri-articular disorders; skin disorders.

Adcortyl in Orabase *BMS, Irl.; BMS, UK.*
⊗ Triamcinolone acetonide (p.1544·3).
Inflammatory disorders of the mouth.

Adco-Sinal Co *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1); codeine phosphate (p.37·2).
Cold and influenza symptoms.

Adco-Sodasol *Adcock Ingram, S.Afr.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); anhydrous citric acid (p.2284·1); tartaric acid (p.2395·2).
Gastric hyperacidity; urinary alkalinisation.

Adco-Sporozole *Adcock Ingram, S.Afr.*
Itraconazole (p.536·3).
Fungal infections.

Adco-Sufedrin *Adcock Ingram, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Adco-Talomil *Adcock Ingram, S.Afr.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Adco-Tussend *Adcock Ingram, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Adco-Wormex *Adcock Ingram, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Add Ins *SHS, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

Addamel *Fresenius Kabi, Rus.; Fresenius Kabi, Spain.*
Electrolyte (p.1667·1) and trace element preparation (p.1922·1).
Parenteral nutrition.

Addamel N *Fresenius Kabi, Cz.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Pharmacia Upjohn, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Baxter, NZ†; Fresenius Kabi, NZ†; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.*
Electrolyte (p.1667·1); and trace element preparation (p.1922·1).
Parenteral nutrition.

Addel N *Baxter, Ger.*
Electrolyte (p.1667·1) and trace element (p.1922·1) preparation.
Parenteral nutrition.

Addera *Novartis, Fin.*
Nutritional supplement (p.1922·1).

Adderall *Shire Biochem, Canad.; Shire Richwood, USA.*
⊗ Dexamfetamine sulfate (p.2153·1); dexamfetamine saccharate (p.2154·1); amfetamine sulfate (p.2150·2); amfetamine aspartate (p.2150·2).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Addex *Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
A range of electrolyte preparations (p.1667·1).

Addex-THAM *Fresenius Kabi, Swed.*
⊗ Trometamol (p.2405·1).
Acute metabolic acidosis; acute respiratory acidosis.

Addigrip *Aventis Pasteur, Austria; Aventis Pasteur, Belg.†; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Addi-K *Leo, Hong Kong†; Leo, Singapore†; Leo, Thai.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Addiphos *Fresenius Kabi, Denm.; Pharmacia, Irl.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, UK.*
Electrolyte preparation (p.1667·1).
Hypophosphataemia; parenteral nutrition.

Additiva *Scheffler, Cz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Additiva Calcium *Natur Produkt, Pol.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Additiva Ferrum *Natur Produkt, Pol.*
Ferrous gluconate (p.1939·1); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Additiva Magnesium *Natur Produkt, Pol.*
Magnesium carbonate (p.1743·1).
Magnesium deficiency.

Additrace *Pharmacia, Irl.; Fresenius Kabi, UK.*
Trace-element preparation (p.1922·1).
Parenteral nutrition.

Addivit *Medice, Ger.*
Vitamin preparation (p.1922·1).

Addivita *Scheffler, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Addlife *Pascual, Philipp.*
Ubidecarenone (p.2407·2).
Dietary supplement.

Addos *Arrow, Austral.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

ADE 2 (Adedois) *Prodotti, Braz.*
Vitamin A acetate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Adebit *Chinoin, Cz.†; Zentiva, Hung.*
Buformin hydrochloride (p.438·3).
Diabetes mellitus.

Adecal
Note. This name is used for preparations of different composition.
Teuto, Braz.
Vitamin A acetate (p.1973·1); colecalciferol (p.1986·2).
Bio-Kem, Turk.
Vitamin A; vitamin D; calcium gluconate; calcium phosphate (p.1922·1).

Adecaps *Pharmaselect, Austria.*
Cod-liver oil (p.1935·2).
Vitamin A and D deficiency.

Adeconce *Lafedar, Arg.*
Vitamins A, C, and D (p.1922·1).

Adecur
Tecnofarma, Chile; Nolver, Venez.
Terazosin (p.1410·3).
Benign prostatic hyperplasia; hypertension.
Asofarma, Mex.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Adecut *Takeda, Jpn.*
Delapril hydrochloride (p.1256·2).
Hypertension.

Adederme *EMS, Braz.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); zinc oxide (p.1621·2).
Skin disorders.

Adefin *Alphapharm, Austral.; Pacific, NZ.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Adeflor M *Upjohn, USA†.*
Multivitamin and mineral preparation with fluoride (p.1962·2) and iron (p.1922·1).
Dental caries prophylaxis; dietary supplement.

Adeforte *Gross, Braz.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); tocoferil acetate (p.1992·3).
Vitamin supplement.

Adeglos *Ortoquimica, Braz.†.*
Zinc oxide (p.1621·2); boric acid (p.2268·1); dogfish-liver oil.
Skin disorders.

Adehl *Kayaku, Jpn.*
Colforsin daropate hydrochloride (p.2285·3).

Adekals *Offenbach, Mex.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Adekin *Desitin, Ger.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Adekon *Concordia, Mex.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Adekon C *Concordia, Mex.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1); ascorbic acid (p.1983·3).
Vitamin A, D, and C deficiency.

Adeks *Axcan, Canad.; Scandipharm, USA.*
Multivitamin preparation with zinc (p.1922·1).

Adel
Note. This name is used for preparations of different composition.
Senosiain, Mex.
Clarithromycin (p.248·2).
Bacterial infections.
Ponce, Venez.†.
Vitamin A; vitamin D; boric acid; zinc oxide; talc.
Barrier preparation.

Adelcort *Adelco, Gr.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Ad-Element *Darrow, Braz.*
Trace-element preparation (p.1922·1).
Parenteral nutrition.

Adelfan-Esidrex *Novartis, Braz.†; Novartis, Spain†.*
⊗ Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Adelheid-Jodquelle, Tolzer *Jodquellen, Ger.*
Sodium iodide (p.2169·2); potassium; sodium; ammonium; calcium; magnesium; iron; chloride; sodium bromide; bicarbonate.
Iodine-deficiency disorders.

Adelone *Cooper (Κοπερ), Gr.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Adeloren *Loren, Mex.†.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).

Adelphan *Novartis, Turk.*
Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3).
Hypertension.

Adelphane *Novartis, India.*
Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3).
Hypertension.

Adelphane-Esidrex *Novartis, Hong Kong; Novartis, India; Novartis, Rus.*
⊗ Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Adelphan-Esidrex *Novartis, Switz.; Novartis, Turk.*
⊗ Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Adelphan-Esidrix *Novartis, Ger.†.*
⊗ Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ademina *Etifar, Venez.*
Vitamin A (p.1971·2); vitamin D (p.1992·2); zinc oxide (p.1621·2); boric acid (p.2268·1).
Skin disorders.

Adena C *Innotech, Fr.†.*
Pink tablets, deoxyribonucleic acid (p.2292·3); white tablets, ascorbic acid (p.1983·3).
Tonic.

Adenamin *Farmamust, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Adenar *Proula, Venez.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Vitamin deficiency.

Adenas *Eagle, Austral.†.*
Vitamins; minerals; ginseng; eleutherococcus senticosis root (p.1922·1).
Tonic.

Adenil *Lamsa, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Adenobeta *Salus, Ital.†.*
Cocarboxylase chloride (p.1976·3); cyanocobalamin (p.1980·2).
Neuritis.

Adenocard *Libbs, Braz.; Astellas, Canad.; Fujisawa, USA.*
Adenosine (p.1202·1).
Diagnosis of arrhythmias; paroxysmal supraventricular tachycardia.

Adenocor *Sanofi Synthelabo, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi Winthrop, Israel; Sanofi-Aventis, Malaysia; Sanofi-Aventis, NZ; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi-Aventis, Pol.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, UK; Sanofi Synthelabo, Venez.†.*
Adenosine (p.1202·1).
Acute intermittent porphyria; diagnosis of arrhythmias; paroxysmal supraventricular tachycardia.

Adenoject *Sun, India.*
Adenosine (p.1202·1).
Coronary vasodilator in diagnostic procedures; paroxysmal supraventricular tachycardia.

Adenoplex *EG, Ital.*
Cocarboxylase (p.1975·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuritis.

Adenoprostal *IBSA, Switz.†.*
Pollen extract (p.2370·2).
Micturition disorders associated with benign prostatic hyperplasia.

Adenosan *Farmanic, Gr.*
Ketoconazole (p.539·1).
Fungal skin infections.

Adenoscan *Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Austria; Sanofi Synthelabo, Cz.†; Sanofi Synthelabo, Fin.†; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Ital.; Asubio, Jpn; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Spain; Sanofi Synthelabo, UK; Fujisawa, USA.*
Adenosine (p.1202·1).
Coronary vasodilator during radionuclide myocardial perfusion imaging.

Adenovit *NCSN, Ital.†.*
Cyanocobalamin (p.1980·2); cocarboxylase hydrochloride (p.1976·3); pyridoxine hydrochloride (p.1978·2).
Neuropathies.

Adenyl *Aerocid, Fr.*
Adenosine phosphate (p.2247·2).
Haemorrhoids; venous insufficiency.

Adenylocrat *Godecke, Ger.†.*
Crataegus (p.2289·1).
Cardiac disorders.

Adepal *Wyeth, Fr.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Adepiron *Adeka, Turk.*
Dipyrone (p.49·2).
Fever; pain.

A-Depress-Therapy *AG Therapy, Gr.*
Citalopram (p.385·3).
Depression.

Adepril
Note. This name is used for preparations of different composition.
Teofarma, Ital.
Amitriptyline hydrochloride (p.376·1).
Depression.
Carbel, Mex.†.
Carbamazepine (p.471·3).
Depression.

Adepsique *Psicofarma, Mex.*
Amitriptyline hydrochloride (p.376·1); diazepam (p.986·3); perphenazine (p.1017·1).
Insomnia; mixed anxiety depressive states.

Adepssir *Ferrer, Philipp.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Adept *Shire, UK.*
Icodextrin (p.1937·2).
Prevention of surgical adhesions.

Aderan *Roemmers, Arg.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Aderm *Sigma, Austral.†.*
Aqueous Cream BP.

Aderma Dermalibour *Bio-Merieux, Hong Kong†; Pierre Fabre, Hong Kong†.*
Avena (p.2262·1); zinc oxide (p.1621·2); zinc sulfate (p.1999·2); copper sulfate (p.1935·3); glycerol (p.2314·2).
Dry skin; eczema; nappy rash.

Aderma Epitheliale *Bio-Merieux, Hong Kong†; Pierre Fabre, Hong Kong†.*
Avena (p.2262·1); vitamin A (p.1971·2); vitamin E (p.1992·2).
Skin abrasions; sunburn; wounds.

Aderma Exomega *Bio-Merieux, Hong Kong†; Pierre Fabre, Hong Kong†.*
Avena (p.2262·1); omega 6 fatty acids (p.2308·2); glycerol (p.2314·2).
Eczema.

A-Derma Lait Solaire *Ducray, Fr.*
SPF 25: Avena (p.2262·1); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

A-Derma Pain Salicylique *Ducray, Fr.†.*
Salicylic acid (p.1612·2).
Skin disorders.

Aderma Ultra High Protection *Bio-Merieux, Hong Kong†; Pierre Fabre, Hong Kong†.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); avena (p.2262·1).
Sunscreen.

Adermicina *Medical, Arg.*
Neomycin sulfate (p.305·1); vitamin A (p.1971·2); ergocalciferol (p.1987·1); zinc oxide (p.1621·2); benzocaine (p.1854·1).
Burns; skin disorders; wounds.

Adermicina A *Medical, Arg.*
Vitamin A (p.1971·2); zinc oxide (p.1621·2); benzocaine (p.1854·1).
Burns; skin disorders; wounds.

Adermicina A Mama *Medical, Arg.*
Vitamin A palmitate (p.1973·1).
Stretch marks.

Adermina *Koni-Cofarm, Chile.*
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Aderogil D3 *Sanofi-Aventis, Braz.*
Colecalciferol (p.1986·2); vitamin A acetate (p.1973·1).
Vitamin deficiencies.

Aderogyl *Millet-Franklin, Arg.; Aventis, Mex.†.*
Vitamin A palmitate; ergocalciferol; acetomenaphthone (p.1922·1).
Vitamin A, D, and K supplement.

Aderosol *Medical, Arg.*
Ergocalciferol (p.1987·1).
Vitamin D supplement.

Aderplus spezial Dr Hagedorn *Naturarzneimittel, Ger.*
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Adesera *Cipla, India.*
Adefovir dipivoxil (p.865·1).
Chronic hepatitis B.

Adesipress-TTS *Boehringer Ingelheim, Ital.†.*
Clonidine (p.1247·1).
Hypertension.

Adesitrin *Pharmacia, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Adetphos *Kowa, Jpn.*
Adenosine triphosphate, disodium salt (p.2247·3).
Heart failure; vertigo.

Adevitan G *Kener, Mex.*
Vitamins A, C, and D (p.1922·1).

Adex *Dexxon, Israel.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Adexone *Rekah, Israel.*
⊗ Dexamethasone (p.1526·1); salicylic acid (p.1612·2).
Skin disorders.

Adexor *Egis, Cz.; EGIS, Hung.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; vestibular disorders.

Adezan *Adelco, Gr.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Adezio *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Adfer *Fahrenheit, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate (p.1922·1); folic acid (p.1940·1); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Adiamil *Mediderm, Chile.*
Adapalene (p.1587·1).
Acne.

Adiantine *Potter's, UK.*
Hamamelis (p.2318·2); rosemary oil (p.2381·3); bay oil (p.2263·2).
Scalp disorders.

Adiaril *ABC, Fr.*
Glucose; sucrose; potassium gluconate; sodium citrate; sodium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Adiatin *Novag, Mex.*
Famotidine (p.1730·1).
Peptic ulcer.

Adiazine *Bouchara-Recordati, Fr.†; IFET (ΙΦΕΤ), Gr.*
Sulfadiazine (p.336·2).
Bacterial infections; nocardiosis; toxoplasmosis.

Adibal *Diba, Mex.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Adicanil *Pharmathen, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Adiclair *Ardeypharm, Ger.*
Nystatin (p.543·2).
Fungal infections.

Adiecal *Francia, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Adifen
Note. This name is used for preparations of different composition.
Adipharm (Αδηφαρμ), Gr.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Raza, Malaysia†.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Adiff *Ipca, India.*
Adapalene (p.1587·1).
Acne.

Adilox *David, India.*
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Adimet *Ratiopharm, Cz.; Ratiopharm, Hung.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Adimod *Armstrong, Mex.*
Pidotimod (p.2367·3).
Immunostimulant.

Adin *Ferring, Israel.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis.

Adine *Laboratorios Chile, Chile.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Hypotension.

Adinol *Teva, Israel.*
Zinc oxide (p.1621·2); Burrow's solution; wool alcohols (p.2033·2); silicon dioxide (p.2146·2).
Barrier preparation; eczema; nappy rash; skin irritation.

Adiod *Teofarma, Spain.*
Colecalciferol (p.1986·2); vitamin A (p.1971·2); iodine (p.2169·2).
Deficiency of vitamins A and D.

Adios *Diomed, UK.*
Bladderwrack (*Fucus* spp.) (p.2384·2); boldo (p.2267·2); butternut; taraxacum (p.2395·1).
Obesity.

Adios Max *Diomed, UK.*
Bladderwrack (*Fucus* spp.) (p.2384·2).
Obesity.

Adipex
Gerot, Cz.
⊗ Phentermine resinate (p.2162·3).
Obesity.

Gerot, Malaysia; Gerot, Switz.
⊗ Phentermine (as an ion-exchange resin complex) (p.2162·2).
Obesity.

Adipex-P *Gate, USA.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Adipine *Trinity, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Adipodiet *Frandiet, Fr.*
Nutritional supplement (p.1922·1).

Adiporell *Sanorell, Ger.*
Homoeopathic preparation.

Adiporetic *Frandiet, Fr.†.*
Nutritional supplement (p.1922·1).

Adiprost *Adipharm (Αδηφαρμ), Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Adipur *Medika, Switz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Adiro *Bayer, Arg.†; Bayer, Mex.†; Bayer, Spain.*
Aspirin (p.20·3).
Fever; inflammation; musculoskeletal and joint disorders; pain; thromboembolism prophylaxis.

Adisar *Pharma Investi, Chile.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Adistan *Chinoin, Mex.†.*
Astemizole (p.567·2).

Adisterolo *Abiogen, Ital.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Vitamin A and D deficiency.

Adital *Gobbi, Arg.*
Macrogol (p.2336·1); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Adiugrip *Sanofi Pasteur, Ital.*
An influenza vaccine (p.2218·2).
Active immunisation.

Adiuretin
Ferring, Cz.†.
Desmopressin (p.2185·2) or desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; polyuria; test of renal concentrating capacity.

Ferring, Neth.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; polydipsia; polyuria.

Adiuvan *Lazar, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Adiuvant *Manetti Roberts, Ital.†.*
Pirglutargine (p.2369·1).
Mental function disorders.

Adivit *Tripharma, Rus.*
Vitamin preparation (p.1922·1).

Adivon *Ederka, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Adizem *Napp, Irl.; Rafa, Israel; Napp, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Adjuvin *Lannacher, Cz.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorders; panic disorder; post-traumatic stress disorder; social phobia.

Adlynx *Aldril, Philipp.*
Lincomycin hydrochloride (p.293·2).
Staphylococcal infections.

Admiral *SJA, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Admon *Esteve, Spain.*
Nimodipine (p.1357·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Ad-Muc
Note. This name is used for preparations of different composition.
Biolab Sanus, Braz.
Chamomile (p.2279·3).

Merz Consumer, Ger.†; Merz, Hong Kong.
Chamomile (p.2279·3); myrrh (p.2349·2).
Inflammation of gums and oral mucosa; inflammatory disorders of the mouth and gums; skin ulcers.

ADN
Note. This name is used for preparations of different composition.
Braun, Arg.; Braun, Chile†.
Preparation for enteral nutrition with or without fibre (p.1922·1).

Sigma, Arg.
Deoxyribonucleic acid (p.2292·3).
Tonic.

ADN Nutricomp *Behrens, Venez.*
A range of preparations for enteral nutrition (p.1922·1).

Adnemic *Nakornpatana, Thai.†.*
Multivitamin and mineral preparation with ferrous fumarate (p.1938·3) (p.1922·1).
Iron-deficiency anaemia; vitamin deficiency.

Adnemic F *Nakornpatana, Thai.†.*
Multivitamin and mineral preparation with ferrous fumarate (p.1938·3) and folic acid (p.1940·1) (p.1922·1).
Iron-deficiency anaemia; vitamin deficiency.

Adnexba *Sevapharma, Cz.†.*
Staphylococcus aureus; streptococci; enterococci; *Escherichia coli*; *Neisseria gonorrhoeae*.
Adnexitis.

Ado C *Kwizda, Austria.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Adocomp *TAD, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Adocor *TAD, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Adofen *Ferrer, Spain.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Adol
Note. A similar name is used for preparations of different composition (see Adoll, below).
Julphar, UAE.
Paracetamol (p.108·1).
Fever; pain.

Adol Allergy Sinus *Julphar, UAE.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Hay fever; sinusitis; upper respiratory-tract disorders.

Adol Cold *Julphar, UAE.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Adol Compound *Julphar, UAE.*
Salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

Adol Extra *Julphar, UAE.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Adol PM *Julphar, UAE.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold symptoms; insomnia.

Adol Sinus *Julphar, UAE.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; sinus headache.

Adolan *Abic, Israel.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome; pain.

Adolcas *Casasco, Arg.*
Monofluoride phosphate; calcium carbonate (p.1714·1).
Osteoporosis.

Adolen *Konsuma, Venez.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Adoless *Farmoquimica, Braz.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Adoll
Note. A similar name is used for preparations of different composition (see Adol, above).
HPP, Hong Kong.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Adolonta *Grunenthal, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Adolor *Obolenskoe, Rus.*
Ketorolac trometamol (p.74·2).
Pain.

Adolorin *Kwizda, Austria.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Adolorin ASS/Vit C *Kwizda, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Adolphs Salt Substitute *Adolphs, USA.*
Sodium-free dietary salt substitute (p.1922·1).

Adolquir *Kin, Spain.*
Dexketoprofen trometamol (p.73·1).
Pain.

Adona
Note. This name is used for preparations of different composition.
Silesia, Chile.
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; inflammation; pain.

Tanabe, Hong Kong; Tanabe, Indon.; SIT, Ital.; Tanabe, Jpn.
Carbazochrome sodium sulfonate (p.1058·2).
Haemorrhagic disorders.

Adop-Tar *ICN, Arg.†.*
⊗ Fluocinolone acetonide (p.1531·3); salicylic acid (p.1612·2); coal tar (p.1616·2).
Psoriasis.

Adoquick Vit C *Kwizda, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Adormix *Sanofi-Aventis, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Adovia *Pharmacypria, Gr.*
Risperidone (p.1024·2).
Psychoses.

Adoxa
Note. This name is used for preparations of different composition.
S Med, Austria.
Doxazosin mesilate (p.1275·1).
Hypertension.

Doak, USA.
Doxycycline (p.267·1).
Bacterial infections.

Adprex *Hebron, Braz.†.*
St John's wort (p.422·3).
Depression.

Adprin-B *Pfeiffer, USA.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1), magnesium carbonate (p.1743·1), and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Adratan *Elpen (Ελπεν), Gr.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Adrebloc *Beta, Arg.†.*
Amlodipine (p.1214·2); benazepril hydrochloride (p.1223·2).
Hypertension.

Adrecort *Allen, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Adreject *ALK, Spain.*
⊗ Adrenaline (p.1203·2).
Anaphylaxis.

Adrekar *Sanofi Synthelabo, Austria; Sanofi Synthelabo, Ger.*
Adenosine (p.1202·1).
Arrhythmias.

Adrena *Human, Philipp.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Adrenam *NAM, Ger.†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Adrenin *Oboi, Philipp.*
⊗ Adrenaline hydrochloride (p.1203·3).
Adjunct in infiltration anaesthesia; haemorrhage; shock; urticaria.

Adrenol *Fabra, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Adrenoplasma *Climax, Braz.†.*
Carbazochrome (p.1058·2).
Haemorrhage.

Adrenor *Samarth, India.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Adjunct in cardiac arrest; hypotension.

Adrenotone *Merck, S.Afr.*
⊗ Adrenaline (p.1203·2).
Bronchospasm; cardiac arrest; hypersensitivity reactions.

Adrenoxil *Climax, Braz.†; CPH, Port.*
Carbazochrome (p.1058·2).
Haemorrhage; haemorrhagic disorders.

Adrenoxyl *Sanofi Synthelabo, Ger.†.*
Carbazochrome (p.1058·2).
Haemorrhage.

Adreson *Organon, Belg.†; Organon, Neth.†.*
⊗ Cortisone acetate (p.1524·2).
Corticosteroid.

AdreView *GE Healthcare, Neth.*
Iodine-123 iobenguane (p.2054·2).
Detection of malignant neoplasms.

Adrexan *Mayoly-Spindler, Fr.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Cardiovascular disorders.

Adriacin *Kyowa, Jpn.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Adriaderm *Terapeutico, Ital.*
Barrier preparation.

Adrianol *Actavis, Rus.*
⊗ Phenylephrine hydrochloride (p.1568·1); tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Adriblastin *Pfizer, Austria; Pharmacia, Ger.; Pfizer, Switz.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Adriblastina *Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hung.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Philipp.; Pharmacia, Pol.; Pharmacia,*

Port.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Carlo Erba, Turk.; Deva, Turk.; Pfizer, Venez.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Adriblastine *Pfizer, Fr.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Adrigyl *Bouchara-Recordati, Fr.†.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Adrim
Dabur, India†; Dabur, Philipp.; Dabur, Thai.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Biogalenic, Venez.
Doxorubicin (p.712·2).
Malignant neoplasms.

Adrimedac *Medac, Ger.; Medac, Pol.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Adrinex *Medical, Port.†.*
⊗ Adrenaline (p.1203·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Adrocil *Oftalder, Port.†.*
Trifluridine (p.910·3).
Viral eye infections.

Adrome *Landson, Indon.*
Carbazochrome sodium sulfonate (p.1058·2).
Haemorrhage.

Adronat *Alphapharm, Austral.; Neopharmed, Ital.; Tecnifar, Port.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Adrovance *MSD, Cz.; Beaufour, Fr.; Vianex (Βιανεξ), Gr.*
Alendronate sodium (p.1088·1); colecalciferol (p.1986·2).
Osteoporosis.

Adroxef *Laboratorios Chile, Chile.*
Cefadroxil (p.218·1).
Bacterial infections.

Adroyd *Pfizer, India.*
⊗ Oxymetholone (p.2123·3).
Aplastic anaemia.

Adrucil *Pharmacia, Canad.†; Gensia, USA.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Adrusen *SIFI, Ital.; SIFI, Singapore†.*
Lycopene; vitamins; minerals (p.1922·1).

Ad-Sorb *Key, Austral.*
Activated charcoal (p.1435·2).
Flatulence.

Adsorbed DT Coq *Aventis Pasteur, Hong Kong†.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Adsorbed DT Vaccine *Bio Farma, Thai.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Adsorbocarpine *Alcon, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Adsorbonac *Alcon, Ger.; Alcon, Ital.; Alcon, Singapore†; Alcon, USA.*
Sodium chloride (p.1686·1).
Corneal oedema; eye irritation.

ADT
Note. This name is used for preparations of different composition.
CSL, Austral.; CSL, NZ.
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Generis, Port.
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

AD-Til *Nycomed, Braz.*
Colecalciferol (p.1986·2); vitamin A acetate (p.1973·1).
Vitamin deficiencies.

Aduar *Vannier, Arg.*
Mebendazole (p.148·3); tinidazole (p.848·3).

Aducin *Nettopharma, Denm.†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Adulax *Casen Fleet, Spain.*
Glycerol (p.2314·2).
Constipation.

Adulfen Codeine *Boots Healthcare, Belg.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Pain.

Adulfen Lysine *Boots Healthcare, Belg.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Adult Chesty Cough *Numark, UK.*
Diphenhydramine (p.577·1).
Coughs.

Adult Chesty Cough Non Drowsy *Numark, UK.*
Guaifenesin (p.1561·3).
Coughs.

Adult Citrex *Pharmaniaga, Malaysia.*
Vitamin preparations with zinc (p.1999·1) (p.1922·1).
Dietary supplement.

Adult Citrex Cal-Mag-D3 *Pharmaniaga, Malaysia.*
Calcium (p.1675·2); colecalciferol (p.1986·2); magnesium (p.1678·3).
Vitamin D and mineral supplement.

Adult Citrex Multivitamin + Ginseng + Omega 3 *Pharmaniaga, Malaysia.*
Vitamin preparation with ginseng (p.2312·1) and omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Adult Dry Cough *Numark, UK.*
Dextromethorphan (p.1555·2).
Coughs.

Adult Meltus for Chesty Coughs & Catarrh *SSL, UK.*
Guaifenesin (p.1561·3); cetylpyridinium chloride (p.1635·1); honey (p.1948·2).
Catarrh; coughs.

Adumbran *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Spain†.*
Oxazepam (p.1014·2).
Anxiety; sleep disorders.

Adurix *Nycomed, Denm.*
⊗ Clopamide (p.1250·1).
Diabetes insipidus; oedema.

Adursal *Leiras, Fin.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; chronic active hepatitis; gallstones.

Advabase *Intendis, Ital.*
Emollient.

Advagraf *Astellas, Cz.; Astellas, Fr.; Astellas, UK.*
Tacrolimus (p.1843·1).
Transplant rejection.

Advair *GSK, Canad.; GSK, USA.*
⊗ Fluticasone propionate (p.1533·2); salmeterol xinafoate (p.1135·1).
Asthma; obstructive airways disease.

Advance
Note. This name is used for preparations of different composition.
Avon, Canad.†.
Pyrithione zinc (p.1611·2).
Dandruff.

Advanced Care, USA.
Pregnancy test (p.2372·1).

Advance Formance *Abbott, Mex.*
Preparation for enteral nutrition (p.1922·1).

Advanced Eye Relief *Bausch & Lomb, USA.*
Propylene glycol (p.2374·1).
Dry eyes.

Advanced Formula Di-Gel *Schering-Plough, USA.*
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1); simeticone (p.1770·2).
Hyperacidity.

Advanced Formula Zenate *Solvay, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Formerly called Zenate.
Nutritional supplement in pregnancy and lactation.

Advanced Relief Visine *Pfizer Consumer, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3); povidone (p.2146·1); dextran 70 (p.1059·3).
Dry eyes; eye irritation.

Advanced-RF Natal Care *Ethex, USA.*
Vitamin and mineral preparation (p.1922·1).

Advantage *Roche Diagnostics, Austral.†; Roche Diagnostics, Canad.*
Test for glucose in blood (p.2314·1).

Advantage 24 *Wellspring, Canad.†; Lake, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Advantan *Schering, Arg.; CSL, Austral.; Schering, Austria; Schering, Belg.; Intendis, Braz.; Intendis, Cz.; Schering, Fin.; Intendis, Ger.; Schering, Gr.; Schering, Hong Kong; Schering, Indon.; Intendis, Ital.; Intendis, Mex.; CSL, NZ; Schering, Philipp.; Intendis, Pol.; Intendis, Port.; Intendis, Rus.; Schering, S.Afr.; Schering, Switz.; Schering, Turk.; Schering, Venez.*
⊗ Methylprednisolone aceponate (p.1539·1).
Skin and scalp disorders.

Advate *Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Ital.; Baxter, Jpn; Baxter, NZ; Baxter, Neth.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.*
Octocog alfa (p.1067·2).
Haemorrhagic disorders.

Advel *Hexal, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Adventan *Intendis, Spain.*
⊗ Methylprednisolone aceponate (p.1539·1).
Skin disorders.

Advera *Abbott, Arg.†; Abbott, Austral.†; Abbott, Braz.; Abbott, Cz.†; Ross, Israel; Abbott, Mex.; Ross, USA.*
Preparation for enteral nutrition in patients with HIV infection or AIDS (p.1922·1).
Nutritional supplement in HIV infection.

Adversuten *AWD, Ger.†.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Advicor *Abbott, USA.*
Nicotinic acid (p.1957·3); lovastatin (p.1328·2).
Hypercholesterolaemia.

Advil *Wyeth Consumer, Austral.; Wyeth Lederle, Austria; Wyeth Consumer, Braz.; Wyeth Consumer, Canad.; Wyeth Consumer, Chile†; Wyeth, Cz.; Wyeth Sante, Fr.; Wyeth, Gr.; Wyeth Consumer, Hong Kong; Wyeth, Hung.; Wyeth Consumer, Irl.; Wyeth, Israel; Wyeth Consumer, Mex.; Wyeth Consumer, Neth.; Wyeth, Philipp.; SA Druggists Self Med, S.Afr.; Wyeth, Spain; Wyeth, Turk.; Wyeth Consumer, UK; Whitehall, USA; Wyeth-Ayerst, USA; Wyeth, Venez.*
Ibuprofen (p.64·2).
Fever; inflammation; osteoarthritis; pain; peri-articular and soft-tissue disorders; rheumatoid arthritis.

Advil Allergy Sinus *Wyeth Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); ibuprofen (p.64·2).
Upper respiratory-tract disorders.

Advil Cold *Wyeth Lederle, Austria; Wyeth, Cz.; Wyeth, Hung.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; sinusitis.

Advil Cold & Flu *Wyeth Consumer, Irl.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Advil Cold & Sinus *Wyeth Consumer, Canad.; Whitehall, USA.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Coadvil in the *USA*.
Cold and influenza symptoms; sinusitis.

Advil Cold & Sinus Plus *Wyeth Consumer, Canad.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic symptoms; sinusitis.

Advil CS *Wyeth Consumer, S.Afr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Advil Mono *PSI, Belg.*
Ibuprofen (p.64·2).
Fever; pain.

Advil PM *Wyeth Consumer, USA.*
Diphenhydramine citrate (p.577·2); ibuprofen (p.64·2).

A-D-Vit *Meyer, Venez.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2); calcium phosphate (p.1676·2).
Osteoporosis; rickets.

AD-vitamin *ACO, Swed.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2).
Vitamin supplement.

ADX *Sigma, Arg.*
Ginseng; catuaba; guarana; damiana; saw palmetto; ginkgo biloba; arginine; zinc; bovine testicle hydrolysate; pollen; vitamin E (p.1922·1).

Adyston *Krewel, Ger.†.*
⊗ Pholedrine sulfate (p.1371·1); norfenefrine hydrochloride (p.1361·1).
Hypotension.

Adytenn *Ultra, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Aedolac *Rottapharm, Ital.*
Emollient.

Aegis *Pliva, Ital.*
Bacillus subtilis.
Restoration of gastrointestinal flora.

Aegrosan *Opfermann, Ger.†.*
Dimeticone (p.1770·2).
Reduction of gastrointestinal gas.

Aeknil *Therapeutic, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

A-E-Mulsin *Mucos, Austria; Mucos, Cz.†; Mucos, Ger.†.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Aequamen *Altana, Ger.*
Betahistine mesilate (p.2265·1).
Ménière's syndrome; vestibular disorders.

Aequifusine *Braun, Switz.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Aequiton-P *Sudmedica, Ger.†.*
Phenazone (p.116·1).
Fever; pain.

A-E-R *Birchwood, USA.*
Hamamelis (p.2318·2).
Anorectal disorders; vaginal irritation.

Aerflu *Boniscontro & Gazzone, Ital.*
⊗ Flunisolide (p.1531·1).
Respiratory-tract hypersensitivity; rhinitis.

Aerinaze *Schering-Plough, Cz.*
Desloratadine (p.576·1); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Aerius *Schering-Plough, Arg.; Schering-Plough, Austria; Schering-Plough, Belg.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, Venez.*
Desloratadine (p.576·1).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Aero Helpp Forte *ISA, Arg.†.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1); malathion (p.2046·1).
Pediculosis.

Aero Itan *Saval, Chile.*
Dimeticone (p.2032·1); metoclopramide (p.1747·3); chlordiazepoxide (p.968·1).
Dyspepsia; flatulence; gastrointestinal motility disorders; meteorism.

Aero Plus *BMS, Spain†.*
Dimeticone (p.1770·2); metoclopramide hydrochloride (p.1747·3).
Aerophagia; delayed gastric emptying.

Aero Red *Uriach, Spain.*
Dimeticone (p.1770·2).
Flatulence.

Aero Red Antiacido *Uriach, Spain.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Aero Red Complex *Uriach, Spain.*
Dimeticone (p.1770·2); lipolytic enzymes; amylolytic enzymes; proteolytic enzymes; cellulolytic enzymes.
Digestive system disorders.

Aeroaid *Graham-Field, USA; Health & Medical, USA.*
Thiomersal (p.1663·3).
Skin disinfection; wounds.

AeroBec *Ivax, Denm.; Ivax, Fin.; Ivax, Ger.; 3M, Irl.†; 3M, Neth.†; Ivax, Norw.; 3M, S.Afr.†; Ivax, Swed.; 3M, Switz.†; 3M, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

AeroBid *Forest Pharmaceuticals, USA.*
⊗ Flunisolide (p.1531·1).
Asthma.

Aerobin
Note. This name is used for preparations of different composition.
Farmasan, Ger.
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Farmasan, Thai.†; TTN, Thai.†.
Theophylline (p.1140·1).
Obstructive airways disease.

Aero-Bud *Andromaco, Chile.*
⊗ Budesonide (p.1520·1).
Asthma.

Aerocaine *Aeroceuticals, USA†.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1).
Skin disorders.

Aerocef *Fujisawa, Austria.*
Cefixime (p.224·3).
Bacterial infections.

Aerocort
Cipla, India.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3); beclometasone dipropionate (p.1516·2).
Asthma.

Cipla, Venez.
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Aerocortin *Fujisawa, Austria.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Aerodan *Medipharm, Chile.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; allergic skin disorders.

Aeroderm *Seid, Spain†.*
Lidocaine hydrochloride (p.1862·3).
Burns; insect stings; skin irritation.

Aeroderma *Pharmanik (Φαρμανικ), Gr.†.*
Bifonazole (p.527·3).
Fungal skin infections.

Aerodesin *Lysoform, Ger.*
⊗ Propyl alcohol (p.1660·2); alcohol (p.1625·2); glutaral (p.1645·2).
Surface disinfection.

Aerodini *Teuto, Braz.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Formerly known as Aerodine.
Obstructive airways disease.

Aerodiol *Servier, Arg.; Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.†; Servier, Hong Kong†; Servier, Irl.; Servier, Ital.; Servier, NZ; Servier, Neth.; Servier, Switz.; Servier, Turk.; Servier, UK†; Servier, Venez.*
Estradiol (p.2097·2).
Menopausal disorders.

Aerodur *AstraZeneca, Ger.; Stern, Ger.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Aerodyne *Fujisawa, Austria†.*
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Aerofagil *Geymonat, Ital.†.*
Sodium citrate (p.1673·3); dimeticone (p.1770·2).
Aerophagia; meteorism.

Aeroflat *Roche, Chile†; Biosarto, Spain.*
Metoclopramide (p.1747·3); simeticone (p.1770·2).
Aerophagia; aid in gastrointestinal radiology; delayed gastric emptying; gastrointestinal disorders; nausea and vomiting.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Aeroflux
Note. This name is used for preparations of different composition.
GSK, Braz.
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Obstructive airways disease.

GSK, Mex.; GSK, Venez.
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3).
Asthma; bronchitis; respiratory-tract disorders with increased mucus.

Aerofreeze *Graham-Field, USA.*
Dichlorodifluoromethane (p.1689·1); trichlorofluoromethane (p.1689·1).
Topical anaesthesia.

Aerogal *Panalab, Arg.*
Silicone oil (p.2032·1).
Barrier preparation.

Aerogastrol *Medipharm, Chile.*
Metoclopramide (p.1747·3); simeticone (p.1770·2); chlordiazepoxide (p.968·1).
Dyspepsia; flatulence; gastrointestinal motility disorders; meteorism.

Aerogel *BMS, Spain.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2).
Dyspepsia; flatulence; gastrointestinal hyperacidity.

Aerogreen *Greenpharma, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

AeroHist Plus *Aero, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Aerojet *Farmalab, Braz.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

AeroKid *Aero, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Aerolate *Fleming, USA.*
Theophylline (p.1140·1).
Obstructive airways disease.

Aerolid *Piam, Ital.*
⊗ Flunisolide (p.1531·1).
Respiratory-tract hypersensitivity; rhinitis.

Aerolin
GSK, Braz.; GSK, Gr.; Ivax, Irl.
⊗ Salbutamol sulfate (p.1131·3).
Asthma; chronic respiratory failure; obstructive airways disease.

GSK, Chile.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Aeromax
Note. This name is used for preparations of different composition.
GSK, Ger.
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Medinfar, Port.
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps.

Aeromed *Medipharm, Chile.*
Ivy (p.2328·1).
Cough.

Aerometrol Plus *Andromaco, Chile.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma.

Aeromicrosona C *ICN, Arg.†.*
⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Aeromuc *Fujisawa, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Aeron *Arrow, Austral.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Aeronix *Menarini, Spain.*
Zafirlukast (p.1150·2).
Asthma.

Aero-Om *OM, Port.*
Simeticone (p.1770·2).
Diarrhoea; flatulence.

Aeropax *Orion, Denm.; Sandoz, Neth.*
Dimeticone (p.1770·2).
Aid in radiography and gastroscopy; aid to gastroscopy; flatulence; infant colic; meteorism.

Aeropaxyn *Lannacher, Austria†.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchitis.

Aero-Ped *Stiefel, Braz.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aero-Plus *Andromaco, Chile.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Aero-Sal *Andromaco, Chile†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Aeroseb
Note. This name is used for preparations of different composition.
Panalab, Arg.
Shampoo: Pyrithione zinc (p.1611·2); cade oil (p.1616·1).
Scalp disorders.

Panalab, Arg.
Soap: Pyrithione zinc (p.1611·2).
Seborrhoea.

Aeroseb-Dex *Allergan Herbert, USA.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Aerosial *Ivax, Mex.*
⊗ Budesonide (p.1520·1).
Asthma; bronchitis.

Aerosil *Degussa, UK.*
Colloidal silicon dioxide (p.2146·2).
Pharmaceutical formulation aid.

Aerosol Spitzner N *Spitzner, Ger.†.*
Pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); siberian fir oil; noble pine oil.
Respiratory-tract disorders.

Aerosolv *Fujisawa, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Aerosoma *Etex, Chile.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Aeroson *Soho, Indon.*
Dimeticone (p.1770·2).
Abdominal distension; dyspepsia; flatulence; meteorism.

Aerosonit *GSK, Pol.*
Isosorbide dinitrate (p.1317·3).
Ischaemic heart disease; myocardial infarction.

AeroSpan *Forest Laboratories, USA.*
⊗ Flunisolide (p.1531·1).
Asthma.

Aerosporin *GSK, Philipp.*
Polymyxin B sulfate (p.317·3).
Bacterial ear infections.

Aerotamol *Royton, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Aerotec *Sanofi Synthelabo, Ital.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aerotide *GSK, Braz.*
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Asthma.

Aerotina *Raffo, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Aerotrat *Cazi, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aerotrop *Cassara, Arg.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

AeroTuss 12 *Aero, USA.*
Dextromethorphan tannate (p.1556·1).
Cough.

Aerovac *Sankyo, Austria.*
Lysates of *Staphylococcus aureus*; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Aerovac G *Casasco, Arg.*
Haemophilus influenzae; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; streptococcus.
Respiratory-tract infections.

Aerovent
Note. This name is used for preparations of different composition.
Cassara, Arg.
⊗ Budesonide (p.1520·1).

Teva, Israel.
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Aerovial *Lafi, Chile; Recalcine, Chile.*
⊗ Budesonide (p.1520·1).
Asthma.

Aerovit *Ufavita, Rus.*
Vitamin preparation with rutoside (p.1922·1).

Aerox *Torrex Chiesi, Hung.*
⊗ Budesonide (p.1520·1).
Asthma.

Aeroxina *Elea, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Aerozoin *Graham-Field, USA.*
Compound benzoin tincture.
Barrier preparation.

AErrane *Baxter, Austral.; Baxter, Cz.; Baxter, Hung.; Kalbe, Indon.; Baxter, Israel; Baxter, Ital.; Baxter, NZ; Baxter, Neth.; Baxter, Philipp.; Baxter, Pol.; AstraZeneca, S.Afr.; Baxter, Spain; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter Anaesthesia, UK.*
Isoflurane (p.1785·3).
General anaesthesia.

Aeruginox *Shenzhen, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Aescorin Forte *Steigerwald, Ger.*
Aesculus (p.2248·2).
Soft-tissue injury; venous insufficiency.

Aescorin N *Steigerwald, Ger.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2).
Haemorrhoids; vascular disorders.

Aescosulf N *Truw, Ger.*
Homoeopathic preparation.

Aesculaforce *Aponova, Austria; Bioforce, Switz.*
Aesculus (p.2248·2).
Venous insufficiency.

AesculaMed *Bioforce, Switz.*
Aesculus (p.2248·2).
Venous insufficiency.

Aesculan *Herbapol Poznan, Pol.; Herbapol Wroclaw, Pol.*
Esculoside (p.2248·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Aesculo Gel L *Medice, Ger.*
Coconut oil (p.2029·2).
Pediculosis.

Aesculus Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Aescusan
Note. This name is used for preparations of different composition.
Pharma Wernigerode, Rus.
Aescin (p.2248·2); thiamine hydrochloride (p.1976·1).
Haemorrhoids; venous insufficiency.

Riemser, Ger.
Cream: Aesculus (p.2248·2); hamamelis (p.2318·2).
Soft-tissue inflammation; venous insufficiency.

Jenapharm, Ger.
Delayed-release tablets; tablets: Aesculus (p.2248·2).
Venous insufficiency.

Aescuven *Cesra, Ger.; Cesra, Pol.*
Aesculus (p.2248·2).
Oedema; soft-tissue inflammation; venous insufficiency.

Aesim *Lamsa, Arg.*
Simeticone (p.1770·2).
Flatulence.

Aesol *Leiras, Fin.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Vitamins A and E deficiency; vitamins A and E supplement.

Aet *Craveri, Arg.*
Lauromacrogol 400 (p.1916·1).
Varices.

Aethoxysclerol *BSN, Austral.†; Teuto, Braz.†.*
Lauromacrogol 400 (p.1916·1).
Varices.

Aethoxysklerol *Nycomed, Austria; Codali, Belg.; Kreussler, Cz.; Kreussler, Denm.; Kreussler, Fin.; Kreussler, Ger.; IFET (ΙΦΕΤ), Gr.; Kreussler, Hung.; Sigma-Tau, Neth.; Kreussler, Pol.; Inverdia, Swed.; Kreussler, Switz.; Kreussler, Thai.†; Cem, Turk.*
Lauromacrogol 400 (p.1916·1).
Dilated cutaneous veins; haemorrhoids; varices.

Aethroma *Mepha, Hong Kong†.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Aetoxisclerol *Kreussler, Fr.*
Lauromacrogol 400 (p.1916·1).
Formerly known as Veinosclerol.
Varices.

Aetoxy Sklerol *Dominguez, Arg.*
Lauromacrogol 400 (p.1916·1).
Varices.

AF
Note. This name is used for preparations of different composition.
Valdecasas, Mex.
Folic acid (p.1940·1).
Folic acid deficiency; prevention of neural tube defects.

Lennon, S.Afr.
Zinc undecenoate (p.549·3); undecenoic acid (p.549·2); terpineol (p.2396·1).
Fungal skin infections.

Afacort *Anfarm, Gr.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Bacterial eye infections with inflammation.

Afalpi Tiptipot *CTI, Israel.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Afaxin *Sanofi Synthelabo, Philipp.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Afazol *Grin, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Afazol Z *Grin, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Eye disorders.

AFBM *Sigma, Braz.*
Vitamin A palmitate; pyridoxine hydrochloride; tocoferil acetate (p.1922·1).

Afebril *Bago, Arg.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Afebrin
Note. This name is used for preparations of different composition.
Legrand, Braz.†.
Phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1); phenyltoloxamine citrate (p.588·1); carbinoxamine maleate (p.570·2).
Cold and influenza symptoms.

Westmont, Hong Kong†; Konimex, Indon.
Paracetamol (p.108·1).
Fever; pain.

Afebryl *SMB, Belg.; Galephar, Fr.†; Azevedos, Port.; Galepharma, Turk.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; inflammation; pain.

Afecton *Help, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Afeditab *Watson, USA.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Afeksin *Actavis, Denm.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Afeme *Cetus, Arg.*
Dexchlorpheniramine (p.572·2).
Hypersensitivity reactions.

Afenexil *Temis, Arg.*
Paroxetine hydrochloride (p.414·2).
Depression.

Afenil
Note. This name is used for preparations of different composition.
Abbott, Gr.
Trandolapril (p.1416·2).
Hypertension.

Piam, Ital.
Food for special diets (p.1922·1).
Phenylketonuria.

Afenoxin *Faran, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

A-ferin
Note. This name is used for preparations of different composition.
Bilim, Turk.
Capsules: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Respiratory-tract congestion.

Bilim, Turk.
Forte tablets; paediatric suspension: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Bilim, Turk.
Sachets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Bilim, Turk.
Sinus tablets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Respiratory-tract congestion.

Afexil *Zentiva, Cz.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Affectine *Galpharma, Israel.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Affex *Astellas, Irl.*
Fluoxetine (p.397·3).
Bulimia; depression; obsessive-compulsive disorder.

Afiancen *Buxton, Arg.*
Leflunomide (p.75·3).

AFI-B-Total *Nycomed, Norw.†.*
Vitamin B substances (p.1922·1).
Alcoholism; megaloblastic anaemia; vitamin B deficiency.

AFI-D_2 *Nycomed, Norw.*
Ergocalciferol (p.1987·1).
Hypoparathyroid tetany.

Afid Plus *Fresenius Kabi, Ger.*
Didecyloxethylmethylammoniumpropionate; cocospropylenediamineguanidinium diacetate.
Instrument disinfection.

A-Fil *GenDerm, USA.*
Meradimate (p.1604·2); titanium dioxide (p.1617·3).
Sunscreen.

Afilan *Quesada, Arg.*
⊗ Mazindol (p.2157·3).
Obesity.

Afilite *Argiletz, Fr.†.*
Nutritional supplement (p.1922·1).

Afipran *Nycomed, Norw.*
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Afiten *Medochemie, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

A-Flam *EBN, Fr.*
Fish oil (p.1362·2); grape (p.2316·3).
Joint and soft-tissue inflammation.

Aflamid *Anchor, Mex.*
Meloxicam (p.80·3).
Ear, nose, and throat inflammation.

Aflamin
Note. This name is used for preparations of different composition.
Gedeon Richter, Hung.
Aceclofenac (p.14·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Hexal, S.Afr.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Aflarex *Alcon, Chile; Alcon, Venez.*
⊗ Fluorometholone acetate (p.1533·1).
Inflammatory eye disorders.

Aflat *Omega, Arg.*
Simeticone (p.1770·2).
Flatulence; infant colic.

Aflegan *ICN, Pol.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Aflem *Jumont, Philipp.*
Carbocisteine (p.1553·2).
Coughs; respiratory-tract congestion.

Aflen *Galenica, Gr.*
Triflusal (p.1418·3).
Thrombosis prophylaxis.

Aflex *Pharmaland, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Afligec *Filadams, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Afloben *Benedetti, Ital.*
Benzydamine hydrochloride (p.27·3).
Puerperal vaginal hygiene; vaginitis.

Afloderm *Belupo, Cz.; Belupo, Rus.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Aflogen *Faran, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Aflogol *Sanitas, Chile.*
Calcium aminosalicylate (p.201·2).
Skin and hair disorders.

Aflorix *Gramon, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Afloxan *Rottapharm, Chile†; Rotta, Hong Kong; Rottapharm, Ital.; Pharmalink, Philipp.; Rotta, Philipp.; Rotta, Thai.*
Proglumetacin maleate (p.119·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Afloyan *Alter, Spain.*
Mirtazapine (p.409·2).
Depression.

Aflubin *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Aflukin C *IPS, Neth.*
Quinine sulfate (p.612·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Aflumicort *Cafar, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Aflumycin *Agis, Israel.*
⊗ Prednisolone (p.1540·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Afluon *Viatris, Gr.; Viatris, Spain.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Afluria *ZLB, Neth.; CSL, USA.*
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Aflusil *Loeffler, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Afluta *Kwizda, Austria.*
Flutamide (p.725·1).
Prostatic cancer.

Afobam *Anpharm, Pol.; Egis, Pol.*
Alprazolam (p.960·1).
Anxiety; panic attacks.

Afoklin *Roemmers-Klinos, Venez.*
Folic acid (p.1940·1).
Antidote to folic acid antagonists; folic acid deficiency; prevention of neural tube defects in pregnancy.

Afongan *AB-Consult, Austria; Galderma, Mex.; Galderma, Port.†.*
Omoconazole nitrate (p.544·1).
Fungal and Gram-positive bacterial infections.

Afonilum *Abbott, Austria; Abbott, Cz.; Abbott, Ger.; Abbott, Pol.*
Theophylline (p.1140·1).
Obstructive airways disease.

Afonilum novo *Abbott, Ger.*
Theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Afonina *Farmacoope, Port.*
Benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Afonisan *Purissimus, Arg.*
Sulfadiazine (p.336·2); allantoin (p.1588·1).
Mouth and throat disorders.

Afopic *Teuto, Braz.*
Folic acid (p.1940·1).

Aforinol *Rekah, Israel.*
⊗ Mepyramine maleate (p.585·2); xylometazoline hydrochloride (p.1575·1); hamamelis (p.2318·2).
Nasal congestion.

Afos *Salus, Ital.†.*
Fosfomycin calcium (p.278·2).
Bacterial infections.

afpred-DEXA *Riemser, Ger.*
⊗ Dexamethasone sodium metasulfobenzoate (p.1526·2).
Obstructive airways disease.

afpred-THEO *Riemser, Ger.*
Theophylline (p.1140·1).
Cor pulmonale; neonatal apnoea; obstructive airways disease.

Afrazine *Schering-Plough, UK.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

African Gold *Strickland, Canad.†.*
Hydroquinone (p.1598·2).

Afrin
Note. This name is used for preparations of different composition.
Mantecorp, Braz.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Pol.; Schering-Plough, Singapore; Schering-Plough, Venez.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Aid in intranasal examination; middle ear infections; nasal congestion; ocular congestion.

Schering-Plough, USA.
Nasal drops; nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Schering-Plough, USA.
Tablets: Pseudoephedrine sulfate (p.1571·2).
Nasal congestion.

Afrin Moisturizing Saline Mist *Schering-Plough, USA.*
Sodium chloride (p.1686·1).
Formerly called Afrin Saline Mist.
Inflammation and dryness of nasal membranes.

Afrin Natural *Mantecorp, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Afrinex *Schering-Plough, Mex.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Nasal congestion.

Afrinex Infantil *Schering-Plough, Mex.*
Aspirin (p.20·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; fever; nasal congestion; pain.

Afro *Casel, Turk.*
⊗ Testosterone (p.2129·3).
Androgen deficiency.

Afrodita *Duncan, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Afrodor
Note. This name is used for preparations of different composition.
Farco, Cz.; Farco, Ger.; Farco, Hung.†; Farco, Rus.
Acecarbromal (p.959·2); quebracho (p.2377·1); alpha tocopheril acetate (p.1922·1).
Tonic.

Farmanic, Gr.
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Afron *Neves, Port.†.*
Genistein (p.2391·2); daidzein (p.2391·2); glicitein.
Menopausal disorders; menstrual disorders.

Afronis *Elanda, Pol.*
Boric acid (p.2268·1); menthol (p.2340·1); resorcinol (p.1612·1); thymol (p.1664·3).
Skin disorders.

Aftab *Rottapharm, Fin.; Opfermann, Ger.; Rottapharm, Ital.*
⊗ Triamcinolone acetonide (p.1544·3).
Aphthous ulcer; gingivitis; stomatitis.

Aftach *Teijin, Hong Kong; Teijin, Jpn; Angelini, Port.*
⊗ Triamcinolone acetonide (p.1544·3).
Aphthous ulcer.

Af-Taf *Sam-On, Israel.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Aftagel *Cooperation Pharmaceutique, Fr.*
Lidocaine hydrochloride (p.1862·3); zinc sulfate (p.1999·2).
Inflammatory mouth disorders.

Aftajuventus *Ern, Spain.*
⊗ Benzalkonium chloride (p.1629·1); hydrocortisone hydrogen succinate (p.1535·3).
Stomatitis.

Aftasone *Vinas, Spain.*
⊗ Hydrocortisone hydrogen succinate (p.1535·3).
Mouth ulcers.

Aftasone B C *Vinas, Spain.*
⊗ Ascorbic acid (p.1983·3); hydrocortisone hydrogen succinate (p.1535·3); pyridoxine (p.1979·1); riboflavin (p.1977·2).
Mouth ulcers.

Aftate *Schering-Plough, Hong Kong; Schering-Plough, USA.*
Tolnaftate (p.548·3).
Fungal skin infections; tinea pedis.

After 10 *Step, Arg.†.*
Pregnancy test (p.2372·1).

After Bite *Tender, Canad.; Pensa, Spain; Meda, Switz.; Ardern, UK.*
Ammonia (p.2256·1).
Insect bites; stings.

After Burn
Note. This name is used for preparations of different composition.
Tender, Cz.†.
Lidocaine hydrochloride (p.1862·3); aloe vera (p.1588·2).
Burns; skin irritation.

Tender, Israel.
Lidocaine (p.1862·3).
Pain and minor skin irritation.

After Sun *Dermoteca, Port.*
Moisturiser.

Afterbite *Tender, Israel.*
Ammonia (p.2256·1).
Bites and stings.

Afterburn *Tender, Canad.*
Lidocaine hydrochloride (p.1862·3).

After-Work *Hamilton, Austral.†.*
Emollient.
Dry skin.

Aftil *Elmor, Venez.*
Salicylic acid (p.1612·2); benzoin resin (p.2394·2); cinnamon (p.2283·1).
Aphthous ulcers; herpes labialis.

Aftine *Cifarma, Braz.*
Neomycin sulfate (p.305·1); bismuth sodium tartrate (p.1712·1); menthol (p.2340·1); procaine hydrochloride (p.1869·1).
Mouth and throat disorders.

Af-Tipa *Perrigo, Israel.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Aftir Gel *Biochimici, Ital.*
Malathion (p.2046·1).
Pediculosis.

Aftir Shampoo *Biochimici, Ital.*
Hydroxyquinoline sulfate (p.2323·1).
For use after Aftir Gel; pediculosis.

Aftosium *Ferrier, Fr.*
Homoeopathic preparation.

Afugin *Hexal, Pol.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Afumix *Senosiain, Mex.*
Fluconazole (p.532·1); tinidazole (p.848·3).
Vaginal infections.

Afungil *Senosiain, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Afunginal *ACME, Philipp.*
Nystatin (p.543·2).
Oral candidiasis.

Agaffin *Merck, Austria.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Agapurin *Zentiva, Cz.; Medphano, Ger.; Zentiva, Pol.; Slovakofarma, Singapore†; Slovakofarma, Thai.; Roemmers-Klinos, Venez.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Agaricus comp *Weleda, Ger.*
Homoeopathic preparation.

Agarol
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer, Hong Kong; Pfizer, Thai.
Liquid paraffin (p.2030·3).
Formerly contained liquid paraffin and phenolphthalein in *Thai.*
Constipation.

Pfizer, Braz.
Liquid paraffin (p.2030·3); sodium picosulfate (p.1771·1); agar (p.2140·3).
Formerly contained liquid paraffin, phenolphthalein, and agar.
Constipation.

Pfizer, Chile.
Liquid paraffin (p.2030·3); phenolphthalein (p.1762·1); agar (p.2140·3); glycerol (p.2314·2).
Constipation.

Pfizer, India†; Pfizer, Venez.†.
Liquid paraffin (p.2030·3); phenolphthalein (p.1762·1); agar (p.2140·3).
Constipation.

Elea, Arg.
Capsules; oral liquid: Liquid paraffin (p.2030·3); sodium picosulfate (p.1771·1); agar (p.2140·3).
Constipation.

Interbelle, Arg.
Chewing gum; gelcaps: Sodium picosulfate (p.1771·1).
Constipation.

Agarol CM *Warner-Lambert, Ital.†.*
Liquid paraffin (p.2030·3).
Constipation.

Agarol Extra *Numark, Canad.*
Senna (p.1769·2).
Constipation.

Agarol Fibras Naturales *Elea, Arg.†.*
Ispaghula (p.1737·1).
Constipation.

Agarol N *Pfizer Consumer, Ger.†.*
Liquid paraffin (p.2030·3).
Constipation.

Agarol Plain
Note. This name is used for preparations of different composition.
Numark, Canad.
Liquid paraffin (p.2030·3); glycerol (p.2314·2).
Constipation.

Pfizer, Gr.
Liquid paraffin (p.2030·3).
Constipation.

Agarol with Sennosides *Numark, Canad.*
Senna (p.1769·2).
Constipation.

Agarol Soft *Pfizer Consumer, Switz.*
Fig (p.1731·3); sorbitol (p.1965·1).
Constipation.

Agarolax *Pfizer, Venez.†.*
Phenolphthalein (p.1762·1).
Constipation.

Agaroletten *Pfizer Consumer, Ger.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Agasten *Novartis, Braz.*
Clemastine fumarate (p.573·2).
Hypersensitivity.

Agathol *Iderne, Fr.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3); peru balsam (p.2365·3).
Burns.

AGB *Cassara, Arg.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Age Block *Avon, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Agedin Plus *GD, Ital.*
Eicosapentaenoic acid (p.1362·1); ubidecarenone (p.2407·2); methionine (p.1450·1); betacarotene (p.1930·3).
Nutritional supplement.

A-Gel
Note. A similar name is used for preparations of different composition (see below).
Pharmatel, NZ†.
Lubricating gel.
Personal and surgical lubricant.

Agel
Note. A similar name is used for preparations of different composition (see above).
Andromaco, Venez.†.
Chlorquinaldol (p.242·3).
Mouth and throat disorders.

Agelan *Antigen, Hong Kong†; Antigen, Irl.†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Agelmin *Kleva, Gr.; Kleva, Singapore†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Agen
Note. This name is used for preparations of different composition.
Zentiva, Cz.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Zentiva, Hung.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Embil, Turk.
Polysaccharide polysulfuric acid ester; nonoxinol (p.1917·2).
Contraceptive.

A-gen 53
Note. This name is used for preparations of different composition.
ICN, Austria.
Polysaccharide polysulfuric acid ester.
Contraceptive.

Riemser, Ger.
Cellulose poly(sulfuric acid ester), trisodium salt; nonoxinol 9 (p.1917·2).
Contraceptive.

Agenerase *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.†; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.†; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; IFET, Gr.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.†; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Spain; GSK, Swed.†; GSK, Switz.; GSK, Turk.; GSK, UK†; Glaxo Wellcome, USA†; GSK, Venez.*
Amprenavir (p.865·3).
HIV infection.

Agermin *Andromaco, Chile†.*
Chlorhexidine (p.1635·2).
Disinfection of skin and wounds.

Ageroplas *Farma Lepori, Spain.*
Ditazole (p.1271·2).
Thromboembolism prophylaxis.

Agerpen *Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Agglad *Sophia, Mex.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Agglad Ofteno *Volta, Chile; Elmor, Venez.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Aggovask *Faran, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Aggrastat *MSD, Austral.; MSD, Austria; MSD, Belg.; Merck Frosst, Canad.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA.*
Tirofiban hydrochloride (p.1414·1).
Myocardial infarction; prevention of ischaemic cardiac complications during angioplasty or atherectomy; unstable angina.

Aggrastat *MSD, S.Afr.*
Tirofiban hydrochloride (p.1414·1).
Prevention of cardiac ischaemia in angioplasty or atherectomy.

Aggravan *Ferron, Indon.*
Cilostazol (p.1245·2).
Arterial occlusion; intermittent claudication.

Aggrenox *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, USA.*
Dipyridamole (p.1268·1); aspirin (p.20·3).
Cerebral ischaemia; ischaemic stroke; thromboembolic disorders.

Aggribloc *Nicholas Piramal, India.*
Tirofiban hydrochloride (p.1414·1).
Myocardial infarction; unstable angina.

Agilam *Elmor, Venez.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Agilan *Fujisawa, Austria.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Agilex *Mertens, Arg.*
Indometacin (p.66·3).
Fever; inflammation; pain.

Agilisin *Sankyo, Braz.*
Indometacin (p.66·3).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Agilo *Fujisawa, Austria†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Agilomed *Stada, Austria.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Agilona *Vinas, Spain.*
Benzydamine flufenamate (p.27·3).
Inflammation; pain; peri-articular and soft-tissue disorders.

Agin *Nordin, Mex.*
Aspirin (p.20·3); sulfadiazine (p.336·2).

Aginax *Q-Med, Ital.†.*
Barrier preparation.

Aginax Solution *CAG, Fr.*
Soap substitute.
Skin irritation.

Agiobita *SJA, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Agiobulk *Altana Madaus, S.Afr.*
Ispaghula (p.1737·1).
Constipation; diarrhoea.

Agiocur *Madaus, Austria; Meda, Fin.; Madaus, Ger.; Madaus, Hong Kong; Madaus, Israel; Madaus, Port.; Madaus, Thai.†.*
Ispaghula (p.1737·1).
Colostomy management; constipation; diarrhoea; diverticular disease; inflammatory bowel disease; irritable bowel syndrome; regulation of faecal consistency; stool softener.

Agiofibe *Abbott, Austral.; Zuoz, Venez.*
Ispaghula (p.1737·1).
Constipation; dietary fibre supplement.

Agiofibra *Nycomed, Braz.; Altana, Mex.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement.

Agiofibras *Phoenix, Arg.*
Ispaghula (p.1737·1).
Constipation; hypercholesterolaemia.

Agiofibre *Madaus, Ital.*
Ispaghula (p.1737·1).
Dietary fibre supplement.

Agiogel *Altana Madaus, S.Afr.†.*
Ispaghula (p.1737·1).
Constipation; diverticulitis; irritable bowel syndrome.

Agiolax *Phoenix, Arg.; Abbott, Austral.; Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Madaus, Cz.; Meda, Fin.; Madaus, Fr.; Madaus, Ger.; Madaus, Hong Kong; Madaus, Israel; Madaus, Ital.; Altana, Mex.; Madaus, Neth.; Madaus, Norw.; Madaus, Pol.; Neo-Farmaceutica, Port.; Altana Madaus, S.Afr.; Madaus, Spain; Meda, Swed.; Madaus, Switz.; Madaus, Thai.; Zuoz, Venez.*
Ispaghula (p.1737·1); senna (p.1769·2).
Bowel evacuation; constipation; haemorrhoids; stool softener.

Agiolax mite *Madaus, Switz.*
Ispaghula (p.1737·1).
Constipation; irritable bowel syndrome; stool softener.

Agiolax Pico *Madaus, Cz.; Madaus, Ger.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Agiopic *Madaus, Austria.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Agioslim *Madaus, Ital.*
Ispaghula (p.1737·1); glucomannan (p.2312·3).
Slimming aid.

AgioStop *Madaus, Ger.*
Saccharomyces cerevisiae (p.1998·3).
Acne; diarrhoea.

Agioten *Gerolymatos, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Agipiu *Candioli, Ital.†.*
Silver carbonate (p.2387·1); alkylbenzyldimethylammonium saccharinate (p.1629·3).
Burn and wound disinfection.

Agiserc *Agis, Israel.*
Betahistine (p.2265·1).
Vestibular disorders.

Agispor *Agis, Israel.*
Bifonazole (p.527·3).
Fungal skin infections; seborrhoeic dermatitis.

Agispor Onychoset *Agis, Israel.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Agisten *Agis, Israel.*
Clotrimazole (p.530·1).
Fungal skin infections; vaginitis.

Agisten with Aloe Vera *Agis, Israel.*
Clotrimazole (p.530·1); aloe vera (p.1588·2).
Fungal skin infections.

Agit *Sanol, Ger.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headaches; varices.

Agit plus *Sanol, Ger.†.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Aglan *Zentiva, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Aglio *Veresne, Arg.*
Garlic (p.2309·2); acetic acid (p.2244·2).
Pediculosis.

Aglucide *Beta, Arg.*
Gliclazide (p.440·3).
Diabetes mellitus.

Aglucil *Elofar, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Aglucose *Sigma, Braz.*
Acarbose (p.436·2).
Diabetes mellitus.

Aglumet *Probiomed, Mex.*
Metformin (p.453·3).
Diabetes mellitus.

Aglutella *Plada, Ital.*
Range of gluten-free food for special diets (p.1922·1).

Agnesin *Hevert, Ger.*
Homoeopathic preparation.

Agnicin *Parggon, Mex.*
Amikacin (p.200·2).
Bacterial infections.

Agnofem *Madaus, Austria.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Agnolyt *Madaus, Ger.; Madaus, Switz.*
Vitex agnus castus (p.2249·1).
Mastalgia; menstrual disorders; premenstrual syndrome.

Agno-Sabona *Sabona, Ger.†.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Agnu Gyne *Medikon, Indon.*
Agnus castus (p.2249·1).
Female infertility; mastalgia; menstrual disorders.

Agnucaston *Austroplant, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Hung.; Bionorica, Indon.; Darya-Varia, Indon.; Bionorica, Rus.†; Bionorica, Thai.†; Biomeks, Turk.*
Agnus castus (p.2249·1).
Female infertility; mastalgia; menstrual disorders.

Agnufemil *Steigerwald, Ger.†.*
Agnus castus (p.2249·1).
Mastalgia; premenstrual syndrome.

Agnukliman *Gebro, Austria.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Agnumens *Gebro, Austria.*
Agnus castus (p.2249·1).
Menstrual disorders; premenstrual syndrome.

Agnurell *Sanorell, Ger.*
Homoeopathic preparation.

Agnus castus comp *Hevert, Ger.*
Homoeopathic preparation.

Agnus femin *Hevert, Ger.*
Homoeopathic preparation.
Formerly known as Agnus castus.

Agobilina *Biol, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Agofell *Janssen-Cilag, S.Afr.*
Diisopromine hydrochloride (p.1724·1); sorbitol (p.1965·1).
Biliary-tract disorders.

Agofenac *Ogera, Switz.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Agofollin *Biotika, Cz.*
Estradiol benzoate (p.2097·2) or estradiol dipropionate (p.2097·3).
Menopausal disorders; menstrual disorders.

Agolutin *Biotika, Cz.; Hoechst Biotika, Cz.*
Progesterone (p.2125·1).
Menstrual disorders.

Agon *Therapharm, Austral.†.*
Felodipine (p.1285·3).
Hypertension.

Agoprim *Ogera, Switz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Agopton *Takeda, Austria; Takeda, Ger.; Takeda, Switz.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Agoral *Warner-Lambert, USA.*
Liquid paraffin (p.2030·3); phenolphthalein (p.1762·1); agar (p.2140·3).
Constipation.

Agorex *Ogera, Switz.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Agorhino *Ogera, Switz.†.*
Phenylephrine hydrochloride (p.1568·1); dimenhydrinate (p.576·2); caffeine (p.1116·3).
Cold symptoms; nasal and sinus congestion; rhinitis.

Agovirin *Biotika, Cz.*
⊗ Testosterone isobutyrate (p.2131·3).
Breast cancer; male hypogonadism; menstrual disorders.

A/G-Pro *Miller, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Agradil *Sanofi-Aventis, Ital.*
Veralipride (p.1035·2).
Menopausal disorders.

A-Gram *Pierre Fabre, Fr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Agrastat *MSD, Arg.; MSD, Braz.; MSD, Chile; MSD-Chibret, Fr.; MSD, Mex.; MSD, Spain; MSD, Venez.*
Tirofiban hydrochloride (p.1414·1).
Ischaemic heart disease; myocardial infarction; prevention of ischaemic cardiac complications during angioplasty or atherectomy; unstable angina.

Agreal *Sanofi-Aventis, Belg.†; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Grunenthal, Fr.†; Sanofi-Aventis, Port.†; Sanofi-Aventis, Spain†.*
Veralipride (p.1035·2).
Menopausal disorders.

Agre-Calvit *Solvay, Philipp.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Agregamina *Irex, Port.†.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Agre-Gola *Vemedia, Neth.*
Cetylpyridinium chloride (p.1635·1); phenol (p.1656·1); menthol (p.2340·1).
Sore throat.

Agrelid *Ariston, Arg.*
Anagrelide hydrochloride (p.2257·1).
Thrombocythaemia.

Agremol *Eurodrug, Thai.*
Dipyridamole (p.1268·1).
Ischaemic heart disease; thromboembolic disorders.

Agrenox *Boehringer Ingelheim, Arg.*
Dipyridamole (p.1268·1); aspirin (p.20·3).
Cerebrovascular ischaemia.

Agretik *Ilsan, Turk.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Agrezol *Meprofarm, Indon.*
Cilostazol (p.1245·2).
Arterial occlusion; intermittent claudication.

Agrimel *Ortoquimica, Braz.†.*
Aconite (p.2246·1); rorippa nasturtium aquaticum; tolu (p.1574·2); ipecacuanha (p.1562·3).
Coughs.

Agrip *Plata, Arg.*
Paracetamol (p.108·1); bromhexine (p.1552·2); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Agrippal *Elea, Arg.; Novartis, Braz.; Chiron, Cz.†; Chiron Vaccin, Fr.; Gerolymatos, Gr.; Chiron Vaccines, Hong Kong; Chiron, Hung.; Chiron Vaccines, Irl.; Chiron, Israel; Chiron Vaccines, Ital.; Ivax, Mex.; Chiron, Neth.; Chiron Vaccines, Philipp.; Biovac, S.Afr.; Novartis Vaccines, Singapore; Chiron, Swed.; Meda, Swed.; Chiron, Thai.; Berk, Turk.; Wyeth, UK.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Agrippin *Bernofarm, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Cold symptoms.

Agrisen *Alpharma, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Agrumina *Also, Ital.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Agruvit *Sanofi-Aventis, Ital.*
Ascorbic acid (p.1983·3); calcium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

Agrylin *Orphan, Austral.; Sigma, Braz.†; Shire, Canad.; IFET (ΙΦΕΤ), Gr.†; Shire, Hong Kong; Fahrenheit, Indon.; Roberts, Israel; Shire, Philipp.; Tema, S.Afr.; Shire, USA.*
Anagrelide hydrochloride (p.2257·1).
Essential thrombocythaemia.

Agua del Carmen
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Melissa oil (p.2339·3); lemon oil (p.2332·3); rosemary oil (p.2381·3); peppermint oil (p.1761·2); clove oil (p.2285·1); cinnamon oil (p.2283·2).
Insomnia; nervous disorders.

Fardi, Spain.
Coriander seeds (p.2288·1); matricaria (p.2279·3); melissa (p.2339·3); tilia (p.2402·2); lemon verbena (p.2333·1); cinnamon (p.2283·1); angelica (p.2258·1); nutmeg (p.2355·2); hyssop (p.2323·3).
Menstrual disorders; nervous disorders.

Agua Inglesa *Catarinense, Braz.*
Broom; cinchona; pear.
Reduced appetite.

Agua Melisa Carminativa *Sanitas, Chile.*
Melissa oil (p.2339·3); lemon oil (p.2332·3); clove oil (p.2285·1); nutmeg oil (p.2355·3); peppermint oil (p.1761·2); rosemary oil (p.2381·3); neroli oil (p.2351·1); cinnamon oil (p.2283·2).
Anxiety; dyspepsia; excess gastrointestinal gas.

Agua Sulfatada Picrica *Volta, Chile.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2); camphorated alcohol; trinitrophenol (p.2404·3).

Aguala *Royal, Chile.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Agucort *LKM, Arg.*
Oseltamivir (p.901·1).
Influenza.

Agudil *Sigma-Tau, Spain.*
Glutamine (p.1947·2); asparagine (p.1929·3); pyridoxine hydrochloride (p.1978·2); phosphoserine (p.2367·1).
Tonic.

Agufam *ST, Thai.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Agufem *Biofarm, Pol.*
Agnus castus (p.2249·1).
Menstrual disorders.

Aguipental *Solfran, Mex.*
Benzylpenicillin (p.213·1); streptomycin (p.333·3).

Agulan *Darya-Varia, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Agurin
Note. This name is used for preparations of different composition.
Recalcine, Chile†.
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Combined oral contraceptive; dysmenorrhoea.

Nolver, Venez.
Paracetamol (p.108·1).
Fever; pain.

Agyr *Tyrol, Austria†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Agyrax *UCB, Belg.; Vedim, Fr.*
Meclozine hydrochloride (p.584·3).
Motion sickness; nausea; vertigo; vomiting.

AH 3 N *Rodleben, Ger.*
Hydroxyzine hydrochloride (p.581·2).
Pruritus; urticaria.

AH-chew *Dexo, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

AH-chew D *WE, USA.*
Phenylephrine hydrochloride (p.1568·1) or phenylephrine tannate (p.1568·3).
Nasal congestion.

AHD 2000 *Lysoform, Ger.; Sonix, Philipp.*
⊗ Alcohol (p.1625·2).
Hand disinfection; skin disinfection.

AHF *CSL, Austral.†; CSL, NZ.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; von Willebrand's disease.

Ahiston *Teva, Israel.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Ahiston Compound *Teva, Israel.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Hypersensitivity reactions.

Ahora Test *Step, Arg.†.*
Pregnancy test (p.2372·1).

AHP 200 *Rosen, Ger.*
Oxaceprol (p.2359·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

A-Hydrocort *Abbott, Canad.†; Hospira, USA.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Aicamin *Esfar, Port.*
Orazamide (p.2357·3).
Liver disorders.

Aidar *Pharmaland, Thai.†.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Aidol *Farmanic, Gr.*
Mefenamic acid (p.80·1).
Inflammation; musculoskeletal and joint disorders; pain.

Aigin *Hevert, Ger.†.*
Kava (p.2328·3).
Anxiety.

Aiglonyl *Fumouze, Fr.†.*
Sulpiride (p.1028·3).
Anxiety; behaviour disorders in children.

Ailax *Galen, Irl.; Focus, UK†.*
Dantron (p.1722·2); poloxamer 188 (p.1918·1).
These ingredients can be described by the British Approved Name Co-danthramer.
Constipation.

Aimafix *Kedrion, Arg.; Biosano, Chile; Kedrion, Ital.; Kedrion, Rus.; Kocsel, Turk.*
Factor IX (p.1068·3).
Haemorrhagic disorders.

Ainedif *Penn, Arg.*
Diclofenac (p.44·2).
Inflammation.

Ainek *Keyerson, Mex.†.*
Piroxicam (p.117·3).
Inflammation; pain.

Ainelac *Hexal, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Ainex
Note. This name is used for preparations of different composition.
Schering-Plough, Chile; Schering-Plough, Venez.
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Sandoz, Mex.
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Air Citronella *Antipiol, Ital.†.*
Citronella oil (p.2284·2); geranium oil (p.2311·1).
Insect repellent.

Air Salonpas *Hisamitsu, NZ†; Pharmaco, NZ†; Hisamitsu, USA.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain.

Airbeclosona *Northia, Arg.*
⊗ Beclometasone (p.1517·2).
Asthma.

Airbronal *Baliarda, Arg.†.*
Theophylline (p.1140·1); ketotifen fumarate (p.582·2).
Obstructive airways disease.

Airbude *Northia, Arg.*
⊗ Budesonide (p.1520·1).

Airclin *Ache, Braz.*
⊗ Triamcinolone acetonide (p.1544·3).
Nasal disorders.

Aircort *Italchimici, Ital.*
⊗ Budesonide (p.1520·1).
Asthma; nasal polyps; rhinitis.

Airest *Caber, Ital.†.*
Bamifylline hydrochloride (p.1116·1).
Asthma; bronchospasm.

Airex *Medhaus, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Airfen *Cofasa, Venez.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Airol *Pierre Fabre, Cz.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Israel; Pierre Fabre, Ital.; Pierre Fabre, Philipp.; Pierre Fabre, Switz.*
Tretinoin (p.1618·1).
Acne.

Airomet *Masa, Thai.*
Omeprazole (p.1753·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Airomir
3M, Arg.†; 3M, Austral.; UCB, Belg.; 3M, Canad.; Ivax, Denm.; Ivax, Fin.; Ivax, Fr.; 3M, Hong Kong; Ivax, Irl.; 3M, Malaysia; 3M, NZ; Ivax, Neth.; 3M, Philipp.; 3M, Singapore†; Ivax, Swed.; 3M, Switz.†; 3M, Thai.†; Ivax, UK.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease.

3M, Chile; Ivax, Norw.; 3M, S.Afr.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Airon *Oftalmi, Venez.*
Montelukast sodium (p.1126·2).
Allergic rhinitis; asthma.

Airrox *Millimed, Thai.*
Simeticone (p.1770·2).
Aid to gastroscopy and X-ray examination; excess gastrointestinal gas.

Airsalbu *Northia, Arg.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Airtab *Millimed, Thai.*
Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Air-Tal *Almirall, Belg.*
Aceclofenac (p.14·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Airtal *Almirall, Chile†; Almirall, Ital.; Almirall, Port.; Almirall, Rus.; Almirall, Spain; Gentek, Venez.†.*
Aceclofenac (p.14·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Airtal Difucrem *Almirall, Spain.*
Aceclofenac (p.14·3).
Peri-articular and soft-tissue disorders.

Airum *Recalcine, Chile.*
⊗ Clenbuterol (p.1120·1).
Bronchospasm.

Air-X *RX, Hong Kong; RX, Thai.*
Simeticone (p.1770·2).
Aid to gastroscopy and X-ray examination; excess gastrointestinal gas; flatulence.

Aisoskin *Fidia, Ital.*
Isotretinoin (p.1599·2).
Acne.

Aitornet *Bajamed, Mex.*
Ketorolac (p.75·2).
Pain.

Ajan *3M, Ger.†.*
Nefopam hydrochloride (p.94·2).
Pain.

Ajatin *Profarma, Cz.*
Benzododecinium bromide (p.1631·2).
Disinfection of skin and wounds.

Ajo 1000 + C *Garden House, Arg.*
Garlic (p.2309·2); vitamin C (p.1983·3).
Dietary supplement.

Ajo Forte *Provefarma, Arg.*
Garlic (p.2309·2); ascorbic acid (p.1983·3); acerola.
Dietary supplement.

Ajolip *Natufarma, Arg.*
Garlic (p.2309·2); bearberry (p.2263·3).
Dietary supplement.

Ajomast *Monserrat, Arg.*
Garlic (p.2309·2).
Hyperlipidaemia.

Ajomast Circulatorio *Monserrat, Arg.†.*
Garlic (p.2309·2); rutoside (p.2305·1).
Circulatory disorders; haemorrhoids; venous insufficiency.

Ajuta *Hermes, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Ak Vernacon *Akorn, Canad.*
Pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Akabar *AF, Mex.*
Nifuroxazide (p.307·2).
Bacterial infections of the gastrointestinal tract.

Akacin *Diba, Mex.; Atlantic, Thai.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Akaderm N *Gepepharm, Ger.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Skin disorders.

Akamin *Alphapharm, Austral.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Akamon *Medochemie, Hong Kong; Medochemie, Malaysia.*
Bromazepam (p.964·3).
Anxiety.

Akarin *Nycomed, Denm.*
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Depression; panic attacks.

Akarpine *Akorn, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Akatinol *Phoenix, Arg.; Merz, Cz.†.*
Memantine hydrochloride (p.367·1).
Mental function disorders; movement disorders; parkinsonism; spasticity.

Ak-Beta *Akorn, USA.*
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma; ocular hypertension.

Ak-Chlor *Akorn, USA†.*
Chloramphenicol (p.239·3).
Eye infections.

Ak-Con *Akorn, Canad.; Akorn, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye disorders; minor eye irritation.

Ak-Dilate *Akorn, Canad.†; Akorn, USA.*
Phenylephrine hydrochloride (p.1568·1).
Funduscopy; open-angle glaucoma; ophthalmic examination; production of mydriasis; refraction without cycloplegia; uveitis.

AKE *Fresenius Kabi, Ger.; Fresenius Kabi, Neth.; Fresenius Kabi, Switz.†; Fresenius Kabi, Turk.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Akeprul *Loeffler, Mex.*
Benzoyl peroxide (p.1590·2).
Acne.

Akerat
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.; Avene, Fr.; Medifarm Avene, Venez.
⊗ Urea (p.1620·2); salicylic acid (p.1612·2); lactic acid (p.2329·3).
Dry skin; keratinisation disorders; skin disorders.

Silesia, Chile.
⊗ Urea (p.1620·2); salicylic acid (p.1612·2); lactic acid (p.2329·3); almond oil (p.2252·2).
Skin disorders.

Akevir *Kener, Mex.*
Aciclovir (p.862·3).

Akezol *Kener, Mex.*
⊗ Acetazolamide (p.1875·1).

Ak-Fluor *Akorn, USA.*
Fluorescein sodium (p.2306·1).
Ophthalmic diagnostic agent.

Akicin *General Drugs, Thai.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Akilen
Note. This name is used for preparations of different composition.
Medochemie, Hong Kong†; Medochemie, Malaysia.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Sanbe, Indon.
Ofloxacin (p.310·2).
Bacterial infections.

Akineton
Abbott, Arg.; Abbott, Austria; Knoll, Braz.; SIT, Cz.; SIT, Denm.; SIT, Fin.; Desma, Ger.; Vianex (Βιανέξ), Gr.; SIT, Hung.; DMS, Ital.; Abbott, Mex.; Abbott, Neth.; Abbott, Norw.†; Abbott, Philipp.; Desma, Port.; Abbott, S.Afr.; Desma, Spain; Abbott, Swed.†; Desma, Switz.; Abbott, Turk.; Abbott, Venez.
Biperiden hydrochloride (p.797·2) or biperiden lactate (p.797·3).
Bronchospasm; drug-induced extrapyramidal disorders; head injury; nicotine poisoning; organophosphorus poisoning; parkinsonism; phosphorus poisoning; spasticity; trigeminal neuralgia.

Abbott, Austral.; Pharmacobel, Belg.; Abbott, Canad.; DB, Fr.; Abbott, Irl.; Desma, Pol.; Abbott, Rus.†; Abbott, USA.
Biperiden hydrochloride (p.797·2).
Drug-induced extrapyramidal disorders; head injury; nocturnal cramps; parkinsonism; spasticity; trigeminal neuralgia.

Abbott, Chile.
Biperiden (p.797·2).
Parkinsonism.

Akinspray *Urgo, Belg.*
Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Akirol *Sedabel, Braz.†.*
Sulfur (p.1614·1); benzoyl peroxide (p.1590·2).
Acne.

Akistin *Pharmaselect, Austria.*
Diethylamine salamidacetate (p.121·2).
Musculoskeletal and joint disorders; neuralgias.

Aklonin *Wernigerode, Ger.†.*
Phenamazide hydrochloride (p.1761·3).
Smooth muscle cramp; vomiting.

Aklovir *Ilsan, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ak-NaCl *Akorn, USA.*
Sodium chloride (p.1686·1).
Corneal oedema.

Akne Cordes *Ichthyol, Austria; Ichthyol, Ger.†.*
Erythromycin (p.269·2).
Acne.

Aknecide *Galderma, Cz.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknecolor *Spirig, Cz.*
Clotrimazole (p.530·1).
Acne.

Aknederm Ery *Gepepharm, Ger.*
Erythromycin (p.269·2).
Acne.

Aknederm Neu *Gepepharm, Ger.*
Ictasol (p.1599·1); zinc oxide (p.1621·2).
Skin disorders.

Aknederm Oxid *Gepepharm, Ger.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknefug *Wolff, Cz.†.*
Estradiol (p.2097·2); hexachlorophene (p.1646·1).
Acne.

Aknefug BP *Orva, Turk.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknefug Doxy *Wolff, Ger.*
Doxycycline hyclate (p.267·1).
Acne.

Aknefug Iso *Wolff, Ger.*
Isotretinoin (p.1599·2).
Acne.

Aknefug Mino *Wolff, Ger.*
Minocycline hydrochloride (p.300·3).
Acne.

Aknefug simplex *Wolff, Ger.†.*
Hexachlorophene (p.1646·1).
Acne; rosacea.

Aknefug-EL *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
Erythromycin (p.269·2).
Acne.

Aknefug-Emulsion *Wolff, Ger.†.*
Estradiol (p.2097·2); hexachlorophene (p.1646·1).
Acne.

Aknefug-liquid *Wolff, Ger.*
Salicylic acid (p.1612·2).
Acne.

Aknefug-liquid N *Wolff, Hung.†.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Acne; seborrhoeic dermatitis.

Aknefug-oxid *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknefug-Simplex *Wolff, Cz.†.*
Hexachlorophene (p.1646·1).
Acne.

Aknemin *Merck, Neth.; Crookes Healthcare, UK.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Akne-Mycin *Hermal, Port.; Coria, USA.*
Erythromycin (p.269·2).
Acne.

Aknemycin
Note. This name is used for preparations of different composition.
Hermal, Austria; Boots Healthcare, Belg.; Hermal, Cz.; Hermal, Hong Kong; Hermal, Hung.; Hermal, Malaysia; Boots Healthcare, Neth.; Herrmann, Pol.; Hermal, Singapore.
Erythromycin (p.269·2).
Acne.

Hermal, Israel.
Erythromycin (p.269·2); ichthammol (p.1599·1).
Acne.

Hermal, Ger.
Lotion; ointment: Erythromycin (p.269·2).
Acne.

Boots Healthcare, Switz.
Ointment; topical solution: Erythromycin (p.269·2).
Acne.

Hermal, Ger.; Boots Healthcare, Switz.
Topical emulsion: Erythromycin (p.269·2); ichthammol (p.1599·1).
Acne.

Aknemycin compositum *Hermal, Austria.*
Erythromycin (p.269·2); light ammonium bituminosulfonate (p.1599·1).
Acne.

Aknemycin Plus *Hermal, Cz.; Hermal, Ger.; Hermal, Israel; Hermal, Malaysia; Herrmann, Pol.; Hermal, Singapore; Crookes Healthcare, UK.*
Erythromycin (p.269·2); tretinoin (p.1618·1).
Acne.

Aknenormin *Hermal, Cz.; Hermal, Ger.; Hermal, Hung.; Herrmann, Pol.*
Isotretinoin (p.1599·2).
Acne.

Ak-Neo-Dex *Akorn, USA.*
⊗ Neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).
Eye inflammation with bacterial infection.

Aknepur *Infusia, Cz.†.*
Colloidal sulfur (p.1614·1).
Acne.

Akne-Puren *Alpharma-Isis, Ger.†.*
Minocycline hydrochloride (p.300·3).
Acne.

Akneroxid *Hermal, Austria; Boots Healthcare, Belg.; Hermal, Cz.; Hermal, Ger.; Hermal, Hung.; Hermal, Malaysia; Boots Healthcare, Neth.; Herrmann, Pol.; Hermal, Singapore; Boots Healthcare, Switz.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknesil *Farmanic, Gr.*
Isotretinoin (p.1599·2).
Acne.

Aknex *Gebro, Switz.*
Benzoyl peroxide (p.1590·2).
Acne.

Aknex Cleaning *Gebro, Switz.*
Cetrimonium bromide (p.1635·1).
Acne; skin cleansing.

Aknicare *Dermoteca, Port.*
Pyruvic acid; triclosan (p.1665·2).
Soap substitute for acne-prone skin.

Aknicare Cleanser *General Topics, Ital.*
Pyruvic acid; triclosan (p.1665·2).
Acne.

Aknichthol *Ichthyol, Austria.*
Ictasol (p.1599·1); salicylic acid (p.1612·2); colloidal sulfur (p.1614·1).
Acne.

Aknichthol Creme *Ichthyol, Ger.*
Ictasol (p.1599·1).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Aknichthol N
Note.This name is used for preparations of different composition.
Ichthyol, Ger.
Ictasol (p.1599·1); salicylic acid (p.1612·2).
Acne.
Ichthyol, Switz.
Sodium bituminosulfonate (p.1599·1); salicylic acid (p.1612·2).
Acne.

Aknil Sunthi Sepuri, Indon.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Aknilox Drossapharm, Switz.; Assos, Turk.
Erythromycin (p.269·2).
Acne.

Aknin-Mino Sanofi Synthelabo, Ger.†.
Minocycline hydrochloride (p.300·3).
Acne.

Aknin-N Sanofi, Switz.
Minocycline hydrochloride (p.300·3).
Acne.

Aknoral IBSA, Switz.
Minocycline hydrochloride (p.300·3).
Acne.

Aknoren Bochemie, Cz.
Azelaic acid (p.1589·3).
Acne.

Aknosan Hermal, Ger.
Minocycline hydrochloride (p.300·3).
Acne.

Akorazol Collins, Mex.
Ketoconazole (p.539·1).
Fungal infections.

Ak-Pentolate Akorn, USA.
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Ak-Poly-Bac Akorn, USA.
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Eye infections.

Ak-Pred Akorn, USA†.
⊗ Prednisolone sodium phosphate (p.1541·2).
Eye inflammation.

AkPro Akorn, USA.
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Akratol Rafarm, Gr.
Nabumetone (p.91·2).
Inflammation; musculoskeletal and joint disorders; pain.

Akriderm Akrikhin, Rus.
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Akriderm Genta Akrikhin, Rus.
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Akriderm GK Akrikhin, Rus.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Akriderm SK Akrikhin, Rus.
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Akridipin Marvel, Rus.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Akrinor Viatris, Austria; AWD, Ger.†; Adcock Ingram, S.Afr.
⊗ Cafedrine hydrochloride (p.1238·2); theodrenaline hydrochloride (p.2400·1).
Circulatory disorders; hypotension.

Ak-Rinse Akorn, USA.
Electrolytes (p.1667·1).
Eye irrigation.

Akripamide Akrikhin, Rus.
⊗ Indapamide (p.1314·1).
Hypertension.

Akrofen Nufarindo, Indon.
Phenylbutazone (p.117·1).
Musculoskeletal, joint, and peri-articular disorders; thrombophlebitis.

Akrofolline Biofarma, Turk.
Estradiol propionate (p.2097·3).
Menopausal disorders.

Ak-Rose Akorn, Canad.
Rose bengal sodium (p.2381·1).
Ophthalmic diagnostic agent.

Aksef Nobel, Turk.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Aksil Embil, Turk.
Benzoyl peroxide (p.1590·2).
Acne.

Aksoderm Gemi, Pol.
Vitamin A (p.1971·2).
Skin disorders.

Ak-Spore Akorn, USA.
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Eye infections.

Ak-Sulf Akorn, Canad.; Akorn, USA.
Sulfacetamide sodium (p.335·3).
Eye infections.

Akt-3 Lupin, India.
1 Capsule, rifampicin (p.325·3); 1 tablet, ethambutol (p.275·2); isoniazid (p.288·1).
Tuberculosis.

Akt-4 Lupin, India.
1 Capsule, rifampicin (p.325·3); 2 tablets, pyrazinamide (p.320·2); 1 tablet, ethambutol (p.275·2); isoniazid (p.288·1).
Tuberculosis.

Akta Nicholas, Indon.
Vitamin preparation (p.1922·1).

Aktace Nicholas, Indon.
Ascorbic acid; vitamin B substances (p.1922·1).
Vitamin B and C deficiency.

Ak-Taine Akorn, Canad.; Akorn, USA.
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Ak-Tate Sandoz, Canad.
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Aktibol Nevzat, Turk.
Cobamamide (p.1980·2).
Megaloblastic anaemia.

Aktiferrin Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.
Ferrous sulfate (p.1939·3).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Aktiferrin Compositum
Note.This name is used for preparations of different composition.
Ratiopharm, Austria; Merckle, Rus.
Ferrous sulfate (p.1939·3) folic acid (p.1940·1).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron deficiency; iron-deficiency anaemia.
Ratiopharm, Cz.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Aktiferrin N Merckle, Ger.
Ferrous sulfate (p.1939·3).
Iron deficiency.

Aktiferrin-F
Note.This name is used for preparations of different composition.
Mepha, Israel; Mepha, Malaysia.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
-Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.
Mepha, Singapore.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Serine (p.1962·1) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Aktil Gedeon Richter, Hung.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Aktiosan Hexal, Arg.†.
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Aktivanad
Nycomed, Austria.
Oral liquid: Liver extract; yeast; rose fruit; caffeine (p.1922·1).
Tonic.
Nycomed, Austria; Aventis, S.Afr.†.
Syrup: Liver extract; yeast; rose fruit; ferric glycerophosphate; lysine (p.1922·1).
Tonic.
Aventis, S.Afr.†.
Tablets: Haematoporphyrin; liver extracts; amino acids; vitamins; caffeine; yeast extract; ferric glycerophosphate (p.1922·1).
Tonic.

Aktivanad-N
Rentschler, Ger.
Oral liquid: Liver extract; yeast extract; caffeine (p.1922·1).
Tonic.
Rentschler, Ger.†.
Tablets: Vitamin B substances; vitamin C; caffeine (p.1922·1).
Tonic.

Aktivin Michallik, Ger.
Isopropyl alcohol (p.1650·3).
Skin disinfection.

AkTob Akorn, USA.
Tobramycin (p.354·1).

Akton Exel, Belg.
Cloxazolam (p.981·1).
Anxiety; premedication; sleep disorders.

Ak-Tracin Akorn, USA†.
Bacitracin (p.210·3).
Eye infections.

Aktren Bayer, Austria; Bayer, Ger.
Ibuprofen (p.64·2).
Fever; pain.

Ak-Trol Akorn, USA†.
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye inflammation with bacterial infection.

Akutol Aveflor, Pol.
Acrylic copolymer aerosol.
Wounds.

Akwa Tears
Note.This name is used for preparations of different composition.
Akorn, Canad.
Wool fat (p.2033·2); liquid paraffin (p.2030·3); yellow soft paraffin (p.2031·3).
Dry eyes.
Akorn, USA.
Eye drops: Polyvinyl alcohol (p.2145·3).
Dry eyes.
Akorn, USA.
Eye ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

al 110 Nestle, Braz.; Nestle, Fr.; Nestle, Hong Kong; Nestle, Ital.; Nestle, Philipp.; Nestle, Port.†.
Food for special diets (p.1922·1).
Diarrhoea; lactose intolerance.

Alacetan Asconex, Ger.†.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; inflammation; pain.

Alacetan NNA Asconex, Ger.
Naproxen sodium (p.92·3).
Fever; pain.

Alacol DM Ballay, USA.
Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Alacor Durascan, Denm.†.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ala-Cort Del-Ray, USA.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Alacramyn Bioclon, Mex.
Scorpion venom antisera (p.2237·2).
Scorpion stings.

Alacre Neo-Farmaceutica, Port.
St John's wort (p.422·3).
Depression.

Alacta-NF Mead Johnson Nutritionals, Thai.†.
Food supplement with vitamins and minerals (p.1922·1).

Alager Denver, Arg.
Azelastine hydrochloride (p.568·2).
Allergic eye disorders.

Alaidol Byk, Arg.†.
Proglumetacin maleate (p.119·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Alamag Goldline, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Hyperacidity.

Alamag Plus Goldline, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Alamast Vistakon, USA.
Pemirolast potassium (p.1129·3).
Allergic conjunctivitis.

Alamin David, India.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Alampen Spefar, Venez.
Ampicillin (p.204·1).
Bacterial infections.

Alanase Pacific, NZ.
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; rhinitis.

Alandiem Zimaia, Port.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Alanox Darya-Varia, Indon.
Thioctic acid (p.2400·2).
Nutritional supplement in diabetes mellitus.

Alantamida Meyer, Venez.
Dequalinium chloride (p.1641·3); allantoin (p.1588·1).

Alantan Unia, Pol.
Allantoin (p.1588·1).
Burns; skin disorders; wounds.

Alantan-Plus Unia, Pol.
Allantoin (p.1588·1); dexpanthenol (p.2362·1).
Burns; skin disorders; wounds.

Alantavit Coel, Pol.
Allantoin (p.1588·1); vitamin A (p.1971·2); colecalciferol (p.1986·2).
Burns; skin disorders; ulcers; wounds.

Alapren Ranbaxy, S.Afr.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Alapril
Note.This name is used for preparations of different composition.
S Med, Austria.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.
Mediolanum, Ital.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Alapryl Menarini, Spain.
Halazepam (p.1000·1).
Anxiety.

Alarin Biofarma, Turk.
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alasenn Schworer, Ger.
Senna (p.1769·2); ononis (p.2357·1); achillea (p.2245·2); taraxacum (p.2395·1).
Constipation.

Alastik
Note.This name is used for preparations of different composition.
Grunenthal, Chile†.
Cream; lotion: Glycolic acid (p.1598·1).
Acne; dry skin; eye contour disorders; photoageing of the skin; seborrhoea; skin pigmentation disorders.
Grunenthal, Chile†.
Topical gel: Glycolic acid (p.1598·1); hydroquinone (p.1598·2); kojic acid (p.1603·3).
Skin pigmentation disorders.

Alasulf Major, USA.
Sulfanilamide (p.343·1); aminoacridine hydrochloride (p.1625·1); allantoin (p.1588·1).
Vaginal infections.

Alateris Ransom, UK.
Glucosamine (p.2313·2).
Knee osteoarthritis.

Alavac-S Teomed, Switz.†.
House-dust mite allergen extracts (p.2250·2) (p.2251·1).
Allergen immunotherapy.

Alavert Wyeth-Ayerst, USA.
Loratadine (p.583·3).
Hypersensitivity reactions.

Alavert Allergy & Sinus D Wyeth Consumer, USA.
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Alaway Bausch & Lomb, USA.
Ketotifen fumarate (p.582·2).
Eye irritation.

Alax Herbapol Poznan, Pol.
Aloes (p.1705·2); belladonna (p.2263·3); frangula bark (p.1732·2); liquorice (p.1740·3).
Constipation.

Alaxa Angelini, Ital.
Bisacodyl (p.1710·1).
Constipation.

Alaxan
Note.This name is used for preparations of different composition.
Great Eastern, Thai.; Therapharma, Thai.
Carisoprodol (p.1894·1); phenylbutazone calcium (p.117·1).
Musculoskeletal and joint disorders.
United Laboratories, Philipp.
Capsules; tablets: Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; pain.
United Laboratories, Philipp.
Topical gel: Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Alaxan PI Great Eastern, Thai.; Therapharma, Thai.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal pain.

Alba
Note. A similar name is used for preparations of different composition (see below).
Biem, Turk.; SNBTS, UK†.
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; plasma volume expansion.

Alba-3
Note. A similar name is used for preparations of different composition (see above).
IQB, Braz.
Albendazole (p.139·2).
Worm infections.

Albalon Allergan, Austral.; Allergan, Belg.†; Allergan, Canad.; Allergan, Hong Kong; Allergan, Malaysia; Allergan, NZ†; Allergan, Neth.; Allergan, Switz.; Allergan, Thai.; Allergan, USA.
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation; ocular congestion.

Albalon Relief Allergan, Austral.; Allergan, NZ†.
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Albalon-A Allergan, Austral.; Allergan, Canad.; Allergan, NZ†; Allergan, S.Afr.†.
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1).
Eye irritation; ocular congestion.

Albapure Dexa, Indon.
⊗ Albumin (p.1052·1).
Hypoproteinaemia; hypovolaemia.

Albarel
Egis, Cz.
Rilmenidine phosphate (p.1388·3).
Hypertension.
Egis, Rus.
Rilmenidine (p.1388·3).
Hypertension.

Albasol Allergan, Chile†.
⊗ Naphazoline hydrochloride (p.1565·2).
Eye congestion.

Albasol A *Allergan, Chile†.*
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1).
Eye disorders.

Albatel *TO-Chemicals, Thai.*
Albendazole (p.139·2).
Worm infections.

Albay
Note. This name is used for preparations of different composition.
Thomson, Austral.; Ebos, NZ; Miles, USA.
Honey bee venom (p.2251·1), wasp venom proteins (p.2251·1), or yellow jacket venom (p.2250·2).
Allergen immunotherapy; diagnosis of hypersensitivity to insect stings.
Bayer, S.Afr.
Bee venom (p.2251·1) (p.2250·2).
Diagnosis of allergy to bee stings; hyposensitisation to bee sting.

Albec *Psicofarma, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Albel *Geolab, Braz.*
Albendazole (p.139·2).
Worm infections.

Alben *Infabra, Braz.†; Biolab, Thai.*
Albendazole (p.139·2).
Worm infections.

Albenda *Milano, Thai.; Julphar, UAE.*
Albendazole (p.139·2).
Worm infections.

Albendol *Eurodrug, Malaysia.*
Albendazole (p.139·2).
Worm infections.

Albendrox *Royton, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Albendy *Galenogal, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Albenix *Globo, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Albensil *Arlex, Mex.*
Albendazole (p.139·2).
Worm infections.

Albentel *Teuto, Braz.*
Albendazole (p.139·2).
Worm infections.

Albenza *SmithKline Beecham, USA.*
Albendazole (p.139·2).
Cysticercosis; echinococcosis.

Albenzonil *Ducto, Braz.*
Albendazole (p.139·2).
Worm infections.

Albeoler *Andromaco, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Albepir *Albephar, Venez.*
Pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Alber T *Unison, Hong Kong†; Unison, Thai.*
Tolnaftate (p.548·3); triacetin (p.549·1).
Fungal skin infections.

Albert Tiafen *Aventis, Canad.†.*
Tiaprofenic acid (p.129·2).
Osteoarthritis; rheumatoid arthritis.

Albesin *Biotech, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Albesine Biotic *Indeco, Arg.*
Amoxicillin (p.202·2); diclofenac (p.44·2).

Albetol *Leiras, Fin.*
⊗ Labetalol hydrochloride (p.1321·1).
Angina pectoris; hypertension.

Albey
Note. This name is used for preparations of different composition.
Stallergenes, Fr.
Bee venom (p.2251·1) or wasp venom (p.2251·1) (p.2250·2).
Formerly known as Albay.
Allergen immunotherapy of bee or wasp stings; diagnosis of hypersensitivity to bee or wasp stings.
Medi Challenge, S.Afr.
Bee venom (p.2251·1) (p.2250·2).
Hyposensitisation.

Albezin *Brasterapica, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Albezol *SM, Venez.*
Albendazole (p.139·2).
Worm infections.

Albezole *Khandelwal, India.*
Albendazole (p.139·2).
Worm infections.

Albicansan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Albicar
Note. This name is used for preparations of different composition.
Casasco, Arg.
Levocarnitine (p.1932·2).
Carnitine deficiency.
Elmor, Venez.
Albendazole (p.139·2).
Worm infections.

Albicon *Farmalab, Braz.*
Potassium chloride (p.1684·3); benzocaine (p.1854·1); sodium bicarbonate (p.1673·2).
Formerly contained borax, potassium chloride, benzocaine, and sodium carbonate.
Local disinfection and anaesthesia.

Albicort *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Neth.†.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Albicort Compositum *Sanofi Synthelabo, Neth.†.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Keratinisation disorders; psoriasis.

Albintil *Solvay, Spain.*
Multivitamin preparation (p.1922·1).

Albios *Giuliani, Ital.*
Dietary fibre supplement with minerals (p.1922·1).

Albiotic *Pharmacia, Ger.†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Albiotin *Kalbe, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Albistin *Cazi, Braz.*
Nystatin (p.543·2).
Fungal infections.

Albital
Note. This name is used for preparations of different composition.
Cristalia, Braz.†.
Acetyltryptophan sodium; potassium caprylate; protein (p.1922·1).
Parenteral nutrition.
Hardis, Ital.; Serono, Mex.†.
⊗ Albumin (p.1052·1).
Hypoalbuminaemia.

Albizia Complex *Mediherb, Austral.*
Albizia; skullcap (p.2388·2); feverfew (p.622·2).
Hypersensitivity reactions.

Albocresil *Altana, Arg.; Nycomed, Braz.; Grunenthal, Chile†.*
Policresulen (p.1077·2).
Haemorrhage; mucous membrane inflammation in the mouth; skin ulcers and burns; vaginal disorders.

Alboral *Silanes, Mex.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; epilepsy; insomnia; premedication; skeletal muscle spasm; tetany.

Albothyl *Altana, Ger.; Altana, Hong Kong; Altana, Indon.; Pharos, Indon.; Altana, Malaysia; Altana, Mex.; Altana, Philipp.; Altana, Pol.; Altana, Singapore.*
Policresulen (p.1077·2).
Anogenital warts; aphthous ulcers; burns; cervical and vaginal disorders; haemorrhage; skin and mucous membrane disorders; ulcers; wounds.

Albotyl *Medicus, Gr.†.*
Nicergoline (p.2352·1).
Vasodilator.

Alboz *Collins, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Albraton *Steigerwald, Ger.†.*
Homoeopathic preparation.

Albucid *Chauvin ankerpharm, Ger.†; Allergan, India; Nicholas, Indon.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Albulair *Cassara, Arg.*
⊗ Levosalbutamol sulfate (p.1125·3).
Obstructive airways disease.

Albuman *Berna, Ital.†; Berna, Switz.; Berna, Turk.*
⊗ Albumin (p.1052·1).
Burns; hypoalbuminaemia; hypovolaemic shock; plasma volume expansion.

Albumar *Grossman, Mex.†.*
⊗ Albumin (p.1052·1).
Plasma volume expansion; shock.

Albumarc *American Red Cross, USA.*
⊗ Albumin (p.1052·1).

Albumax *Blausiegel, Braz.†; Green Cross, Philipp.*
⊗ Albumin (p.1052·1).
Burns; neonatal hyperbilirubinaemia; plasma volume expansion.

Albumex *CSL, Austral.; CSL, NZ.*
⊗ Albumin (p.1052·1).
Adult respiratory distress syndrome; burns; cardiopulmonary bypass surgery; haemodialysis; hypoproteinaemia; hypovolaemia; plasma exchange; plasma volume expansion; shock.

Albuminar *CSL, Braz.; ZLB Behring, Hong Kong; Centeon, Israel; Aventis Pasteur, Philipp.; ZLB Behring, Philipp.; Farma-Tek, Turk.; CSL Behring, USA.*
⊗ Albumin (p.1052·1).
Burns; hypoalbuminaemia; hypoproteinaemia; hypovolaemia; hypovolaemic shock; plasma volume expansion.

Albuminativ *Octapharma, Austria; Octapharma, Fin.; Octapharma, Neth.†; Octapharma, Swed.*
⊗ Albumin (p.1052·1).
Hypovolaemia.

Albumyn *Bioclon, Mex.†.*
⊗ Albumin (p.1052·1).
Hypoproteinaemia; plasma volume expansion.

Alburaas *Combiphar, Indon.; Shanghai RAAS, Thai.*
⊗ Albumin (p.1052·1).
Hypoproteinaemia; hypovolaemia.

Alburex
Note. This name is used for preparations of different composition.
Demo, Gr.
⊗ Plasma protein fraction (p.1076·2).
ZLB, Ital.
⊗ Albumin (p.1052·1).
Plasma volume expansion.

Albusol *NBI, S.Afr.*
⊗ Albumin (p.1052·1).
Hypoproteinaemia; hypovolaemia.

Albustix *Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer, NZ; Bayer Diagnostics, UK; Bayer, USA.*
Test for protein in urine.

Albutamol *Centaur, India.*
⊗ Etofylline (p.1121·1); salbutamol (p.1131·2); bromhexine (p.1552·2).
Obstructive airways disease.

Albutein *Grifols, Hong Kong; Grifols, Indon.; Tempo Scan Pacific, Indon.; Alpha Therapeutic, Ital.; Grifols, Malaysia; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, UK; Alpha Therapeutic, USA.*
⊗ Albumin (p.1052·1).
Burns; cardiopulmonary bypass procedures; dialysis; hyperbilirubinaemia; hypoalbuminaemia; hypoproteinaemia; hypovolaemia; hypovolaemic shock; neonatal hyperbilirubinaemia.

Albyl minor *Recip, Swed.*
Aspirin (p.20·3).
Fever; pain.

Albyl-E *Nycomed, Norw.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Alca-C *Novartis Consumer, Switz.*
Carbasalate calcium (p.33·3); ascorbic acid (p.1983·3).
Cold symptoms.

Alcacat *Baxter, Mex.†.*
Sodium chloride (p.1686·1).

Alcachofa Plus *Tecnonat, Arg.*
Cynara (p.2291·2).

Alcachofrax *Catarinense, Braz.*
Cynara (p.2291·2).
Lipid disorders.

Alcacyl *Novartis Consumer, Switz.*
Carbasalate calcium (p.33·3).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Alcacyl instantanee *Novartis Consumer, Switz.*
Lysine aspirin (p.79·1).
Fever; pain.

Alcafelol *Luper, Braz.†.*
Choline citrate (p.1934·2); cynara (p.2291·2); boldo (p.2267·2); magnesium sulfate (p.1679·3).
Liver disorders.

Alcaflor *Luper, Braz.†.*
Cynara (p.2291·2); boldo (p.2267·2).
Liver disorders.

Alcaine *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Mex.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, Singapore; Alcon, Switz.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Alcalergin *Herbarium, Braz.*
Liquorice (p.1740·3).
Cough.

Alcalinos Gelos *Gelos, Spain.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); sodium bicarbonate (p.1673·2); dibasic sodium phosphate (p.1682·3).
Gastrointestinal hyperacidity.

Alcalone Plus *Bunker, Braz.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Alcalosio *SIT, Ital.*
Anhydrous glucose (p.1945·3); potassium citrate (p.1673·2); pyridoxine hydrochloride (p.1978·2); sodium bicarbonate (p.1673·2); sodium citrate (p.1673·3).
Acetonaemia; gastrointestinal hyperacidity; vomiting.

Alca-Luftal *BMS, Braz.*
Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Flatulence; gastric hyperacidity.

Alcamex *Cooper (Κοπερ), Gr.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Alcan *Sons, Mex.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Alcaphor *Pharmadeveloppement, Fr.*
⊗ Trometamol citrate (p.2405·2); sodium acid citrate (p.1673·2); dipotassium citrate (p.1674·2).
Metabolic acidosis; renal calculi.

Alcare *Calgon Vestal, USA.*
⊗ Alcohol (p.1625·2).
Antiseptic.

Alcasedine *Will-Pharma, Neth.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; heartburn.

Alcasol *Meda, Belg.*
Sodium bicarbonate (p.1673·2); borax (p.2268·1); sodium chloride (p.1686·1).
Conjunctivitis; dry eyes.

Alcatex *Medix, Mex.†.*
Cimetidine (p.1716·2).

Alcavixin *Korea United, Philipp.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Alcelam *Pharmasant, Thai.*
Alprazolam (p.960·1).
Anxiety; insomnia; mixed anxiety depressive states.

Alcep *Hasco-Lek, Pol.*
Onion (p.2356·3).
Upper respiratory-tract infections.

Alcepalan *Herbapol Poznan, Pol.*
Onion (p.2356·3); heparin sodium (p.1301·2).
Keloids; scars.

Alchera *Pharmacare, S.Afr.*
Zopiclone (p.1039·1).
Insomnia.

Alcidolin *Sanofarm, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alcinal *Rekah, Israel.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Coughs and cold symptoms.

Alcinal New *Rekah, Israel.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Alcinal Plus *Rekah, Israel.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Coughs and cold symptoms; fever; pain.

Alcis *Chiesi, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Alciton *Kleva, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Alco *Interbat, Indon.*
Pseudoephedrine hydrochloride (p.1571·2).
Influenza symptoms.

Alco Plus *Interbat, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Influenza symptoms.

Alco Plus DMP *Interbat, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Cough; influenza symptoms.

Alco-Aloe *Ansell, Fr.*
⊗ Alcohol (p.1625·2); aloes (p.1705·2); chlorhexidine gluconate (p.1635·3); phenoxyethanol (p.1657·1).
Hand disinfection.

Alcobon *ICN, NZ†.*
Flucytosine (p.534·2).
Fungal infections.

Alcoderm
Note. This name is used for preparations of different composition.
Bajer, Arg.
Coal tar (p.1616·2).
Skin disorders.
Galderma, Irl.†.
Liquid paraffin (p.2030·3).
Dry skin.

Alcodin *Alcon, Ital.*
Myrtillus (p.2349·3).
Capillary fragility.

Alcohocel *Perez Gimenez, Spain.*
⊗ Alcohol (p.1625·2); cetylpyridinium chloride (p.1635·1).
Skin disinfection.

Alcohol Benzalconio *Viviar, Spain.*
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1).
Skin, wound, and surface disinfection.

Alcohol Cetil *Noriega, Spain†.*
⊗ Alcohol (p.1625·2); cetylpyridinium chloride (p.1635·1).
Skin disinfection.

Alcohol Cetilpi Cuve *Perez Gimenez, Spain†.*
⊗ Alcohol (p.1625·2); cetylpyridinium chloride (p.1635·1).
Skin disinfection.

Alcohol CL Benz *Betamadrileno, Spain.*
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1).
Skin, wound, and surface disinfection.

Alcohol Poten *Maxfarma, Spain.*
⊗ Alcohol (p.1625·2); benzethonium chloride (p.1630·1).
Skin, wound, and surface disinfection.

Alcohol Potenciado *Viviar, Spain.*
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1).
Skin, wound, and surface disinfection.

Alcojel *Wellspring, Canad.†.*
Isopropyl alcohol (p.1650·3).
Skin disorders.

Alcolex *Labomed, Chile.*
⊗ Benzoxonium chloride (p.1631·2); alcohol (p.1625·2).
Disinfection of instruments, skin, and wounds.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Alcomicin *Alcon, Canad.*
Gentamicin sulfate (p.282·1).
Eye infections.

Alcon Adequad *Alcon, Belg.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Alcon AE *Alcon, Arg.*
Vitamin A; vitamin E (p.1922·1).
Dietary supplement.

Alcon Eye Gel *Alcon, Belg.*
Carbomer (p.2141·3).
Dry eyes.

Alcon Lagrimas
Note.This name is used for preparations of different composition.
Alcon, Arg.
Eye drops: ⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Alcon, Arg.
Eye ointment: Liquid paraffin (p.2030·3); wool fat (p.2033·2); white soft paraffin (p.2031·2).
Dry eyes.

Alconmide *Alcon, Philipp.*
Lodoxamide trometamol (p.2334·2).
Allergic eye disorders.

Alcontar *Galderma, Arg.†.*
Coal tar (p.1616·2).
Eczema; psoriasis.

Alcoolat de Melisse *Weleda, Switz.†.*
Melissa (p.2339·3); nutmeg (p.2355·2); cinnamon (p.2283·1); angelica (p.2258·1); coriander (p.2288·1); clove (p.2284·3); lemon oil (p.2332·3).
Digestive system disorders; headache; menstrual cramps; sleep disorders; toothache.

Alcophyllex *Propan, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Bronchospasm.

Alcophyllin *Propan, S.Afr.*
Theophylline (p.1140·1).
Obstructive airways disease.

Alcortin *Primus, USA.*
⊗ Hydrocortisone (p.1535·2); diiodohydroxyquinoline (p.832·1).
Skin disorders.

Alcos-Anal
Note.This name is used for preparations of different composition.
BMS, Ger.†; Meda, Norw.
Lauromacrogol 400 (p.1916·1); 5-chlorocarvacrol (p.1639·3); sodium oleate (p.2139·1).
Anorectal disorders.

Meda, Swed.
Sodium oleate (p.2139·1); 2-hydroxy-5-chlorothymol.
Anorectal disorders.

Alco-Screen *Marco, Austral.†; Aptus, NZ†.*
Test for alcohol in saliva.

Alcosept *Floris, Israel.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Skin disinfection.

Alcover *Gerot, Austria; Gerot, Hung.†; CT, Ital.*
Sodium oxybate (p.1794·2).
Alcohol withdrawal syndrome.

Alcowipe *SSL, UK.*
Isopropyl alcohol (p.1650·3).
Hard surface disinfection.

Alcoxidine *Vitamed, Israel.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Alcrin-M *Anglo-French Drugs, India.*
Thioctic acid (p.2400·2); chromium polynicotinate; inositol (p.2325·2); mecobalamin (p.1981·1).
Peripheral neuropathy.

Alcur *Gea, Denm.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Alcusal *Alcusal, Austral.*
Copper salicylate.
Musculoskeletal and joint disorders; sports injuries.

Alcysten *Lachema, Cz.†.*
Cytarabine (p.705·1).
Leukaemias; non-Hodgkin's lymphoma.

Alcytam *Torrent, Braz.*
Citalopram (p.385·3).
Alcohol withdrawal syndrome; depression.

Alda *TNP, Thai.†.*
Albendazole (p.139·2).
Worm infections.

Aldactacine *Pfizer, Spain.*
⊗ Altizide (p.1209·1); spironolactone (p.1400·1).
Ascites; hypertension; oedema.

Aldactazida *Pfizer, Venez.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Aldactazide *Pfizer, Canad.; SPA, Ital.; Ali, Turk.; Searle, USA.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; liver cirrhosis with oedema or ascites; nephrotic syndrome.

Aldactazine *Continental Pharma, Belg.; Pfizer, Fr.; Pfizer, Port.*
⊗ Altizide (p.1209·1); spironolactone (p.1400·1).
Ascites; hypertension; nephrotic syndrome; oedema.

Aldactide *Pfizer, Irl.; Pharmacia, UK.*
⊗ Spironolactone (p.1400·1); hydroflumethiazide (p.1311·3).
These ingredients can be described by the British Approved Name Co-flumactone.
Heart failure; hypertension.

Aldacton *Ali, Turk.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; liver cirrhosis with ascites or oedema; nephrotic syndrome.

Aldactone
Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Continental Pharma, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; RPG, India; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Lepetit, Ital.; Pfizer, Mex.; Pharmacia, NZ†; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Port.; Searle, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Searle, USA; Pfizer, Venez.
⊗ Spironolactone (p.1400·1).
Aldosteronism; diagnosis of hyperaldosteronism; heart failure; hirsutism in women; hypertension; hypokalaemia; hypomagnesaemia; liver cirrhosis with ascites or oedema; myasthenia gravis; nephrotic syndrome; oedema.

Roche, Austria; Roche, Cz.; Roche, Ger.; Roche, Hung.†; Roche, Pol.
⊗ Potassium canrenoate (p.1374·1).
Heart failure; hyperaldosteronism; liver cirrhosis with ascites or oedema; nephrotic syndrome; oedema.

Aldactone Saltucin *Roche, Austria; Roche, Ger.†.*
⊗ Spironolactone (p.1400·1); butizide (p.1238·1).
Cor pulmonale; heart failure; hyperaldosteronism; hypertension; liver cirrhosis with ascites and oedema; nephrotic syndrome; oedema.

Aldactone-D *Pfizer, Arg.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Heart failure; hyperaldosteronism; liver cirrhosis with ascites; nephrotic syndrome; oedema.

Aldalix *Pfizer, Fr.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Heart failure.

Aldamin *Unipharm, Mex.*
Albendazole (p.139·2).
Worm infections.

Aldan *Polfarmex, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Aldara *Sidus, Arg.; 3M, Austral.; 3M, Belg.; Intendis, Braz.; 3M, Canad.; 3M, Chile; 3M, Cz.; 3M, Denm.; 3M, Fin.; 3M, Fr.; 3M, Ger.; Lavipharm, Gr.; 3M, Hong Kong; Meda, Hung.; 3M, Irl.; 3M, Israel; 3M, Ital.; 3M, Malaysia; 3M, Mex.; 3M, NZ; 3M, Neth.; 3M, Norw.; 3M, Philipp.; 3M, Pol.; Meda, Port.; 3M, S.Afr.; 3M, Singapore; 3M, Spain; 3M, Swed.; 3M, Switz.; 3M, Thai.; 3M, UK; Graceway, USA.*
Imiquimod (p.881·3).
Actinic keratosis; anogenital warts; basal cell carcinoma.

Aldarone *Cadila Pharma, India†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Aldazida
Note.This name is used for preparations of different composition.
Pfizer, Arg.; Pfizer, Braz.
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Heart failure; hyperaldosteronism; hypertension; liver cirrhosis with ascites and oedema; nephrotic syndrome; oedema.

Pfizer, Mex.
⊗ Spironolactone (p.1400·1); butizide (p.1238·1).
Ascites; hepatic cirrhosis; hypertension; oedema.

Aldazide *Pfizer, Indon.; Pfizer, Philipp.; Pharmacia, S.Afr.*
⊗ Spironolactone (p.1400·1); butizide (p.1238·1).
Heart failure; hypertension; liver cirrhosis; nephrotic syndrome; oedema.

Aldazine *Alphapharm, Austral.; Alphapharm, Malaysia†; Merck, Malaysia†; Pacific, NZ.*
Thioridazine hydrochloride (p.1031·2).
Agitation; alcohol withdrawal syndrome; anxiety; behaviour disorders in children and the elderly; psychoses; schizophrenia.

Aldecin *Schering-Plough, Austral.†; Schering-Plough, Cz.; Schering-Plough, Hong Kong†; Schering-Plough, Hung.†; Schering-Plough, Neth.; Schering-Plough, Rus.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma; nasal polyps; obstructive airways disease.

Aldecina *Byk, Port.†; Schering-Plough, Venez.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; obstructive airways disease; rhinitis.

Alderil *Vita, Venez.†.*
Resorcinol (p.1612·1); salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne.

Aldex AN *Zyber, USA.*
Doxylamine succinate (p.578·2).

Aldiab *Merck, Indon.*
Glipizide (p.441·3).
Diabetes mellitus.

Aldiana *Sevapharma, Cz.†.*
A diphtheria vaccine (p.2209·3).
Active immunisation.

Aldic *Shiwa, Thai.†.*
⊗ Furosemide (p.1292·1).
Barbiturate poisoning; hypertension; oedema; renal impairment.

Aldin *Merck, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aldipin *Helvepharm, Switz.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Aldisa *Sanbe, Indon.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Alditeana *Sevapharma, Cz.†.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Alditepera *Sevapharma, Cz.†.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Aldivina *Farcoral, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Aldizem *Alkaloid, Cz.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension; Raynaud's syndrome.

Aldo Asma *Aldo, Spain.*
⊗ Ascorbic acid; phenylephrine hydrochloride (p.1568·1); isoprenaline hydrochloride (p.1316·3).
Obstructive airways disease.

Aldo Otico *Aldo, Spain†.*
⊗ Framycetin sulfate (p.279·1); lidocaine hydrochloride (p.1862·3); triamcinolone acetonide (p.1544·3); choline salicylate (p.36·3).
External ear disorders; otitis media.

Aldobronquial *Aldo, Spain.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aldoclor *Merck, USA.*
⊗ Methyldopa (p.1334·1); chlorothiazide (p.1243·1).
Hypertension.

Aldocumar *Aldo, Spain.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders; thrombosis prophylaxis.

Aldoderma *Aldo, Spain.*
⊗ Framycetin sulfate (p.279·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Aldofen *Tocogino, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Aldolan *Liba, Turk.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Aldoleo *Altana, Spain.*
⊗ Chlortalidone (p.1243·3); spironolactone (p.1400·1).
Hypertension; oedema.

Aldolor *CTI, Israel.*
Paracetamol (p.108·1).
Fever; headache; pain.

Aldomet
MSD, Arg.; MSD, Austral.; MSD, Belg.; MSD, Braz.; MSD, Denm.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Irl.; MSD, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; Pharmalink, Philipp.; MSD, Port.; MSD, S.Afr.; Biopat, Spain; MSD, Swed.; MSD, Switz.; M & H, Thai.; MSD, UK; MSD, Venez.
Methyldopa (p.1334·1).
Hypertension.

Merck Frosst, Canad.†.
Methyldopa (p.1334·1) or methyldopate hydrochloride (p.1334·2).
Hypertension.

Aldometil *MSD, Austria.*
Methyldopa (p.1334·1).
Hypertension.

Aldomin *MSD, Israel.*
Methyldopa (p.1334·1).
Hypertension.

Aldonar *Upsifarma, Port.*
⊗ Spironolactone (p.1400·1).
Hypertension.

Aldoretic *MSD, Austria; Chibret, Port.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3); methyldopa (p.1334·1).
Hypertension.

Aldoril *Merck, USA†.*
⊗ Methyldopa (p.1334·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Aldoron *Ivax, Arg.*
Nimesulide (p.95·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Aldoron NF *Ivax, Arg.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Aldo-Silverderma *Aldo-Union, Hong Kong.*
Sulfadiazine silver (p.337·2).
Burns; pressure sores and skin ulcers.

Aldosomnil *Aldo, Spain.*
Lormetazepam (p.1005·2).
Insomnia; premedication.

Aldospirone *Teva, Israel.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; hypertension; hypokalaemia; liver cirrhosis.

Aldospray *Aldo-Union, Rus.*
Mabuprofen (p.65·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Aldospray Analgesico *Aldo, Spain.*
Mabuprofen (p.65·2).
Peri-articular and soft-tissue disorders.

Aldosterin *Cellofarm, Braz.†.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; hypokalaemia; oedema.

Aldotensin *Teuto, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Aldozone *Pfizer, Switz.*
⊗ Spironolactone (p.1400·1); butizide (p.1238·1).
Heart failure; hypertension; liver cirrhosis with ascites; nephrotic syndrome; oedema.

Aldribid *Aldril, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Aldricin *Aldril, Philipp.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Aldromax *Gap, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Aldronac *Roemmers-Klinos, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Aldrox
Note.This name is used for preparations of different composition.
Pasteur, Chile.
Alendronate sodium (p.1088·1).
Osteoporosis.

Vargas, Venez.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Aldurazyme *Genzyme, Belg.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Israel; Genzyme, Ital.; Medra, NZ; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Spain; Genzyme, Swed.; Genzyme, UK; Genzyme, USA.*
Laronidase (p.2330·3).
Mucopolysaccharidosis I.

Aledron *IQFA, Mex.*
Oxolamine citrate (p.1567·1).
Coughs.

Alefos *Faran, Gr.*
Alendronic acid (p.1088·1).
Osteoporosis.

Alegi *Lapi, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Alegysal *Ferron, Indon.; Santen, Indon.; Mitsubishi, Jpn; Santen, Philipp.*
Pemirolast potassium (p.1129·3).
Allergic rhinitis; asthma; conjunctivitis.

Aleli *Bernabo, Arg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Alembicol D *Alembic Products, UK.*
Fractionated coconut oil (p.1956·3).
Food for special diets; malabsorption syndromes.

Alemelano *Elvetium, Arg.†.*
Bifemelane hydrochloride (p.363·2).

Alenat *Arrow, Swed.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alenato *Valeant, Arg.; ICN, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Alenbit *Chrispa (Χρισπα), Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Alencast *Chrispa (Χρισπα), Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Alendil *Farmoquimica, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendil Calcio D *Farmoquimica, Braz.*
Tablets, alendronate sodium (p.1088·1); tablets, calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Alendo *Polychronus, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendral *Biospray, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendro *Arrow, Austral.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendrogen *Generics, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendromax *Arrow, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendron *Sandoz, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

AlendronHexal *Hexal, Austria.*
Alendronic acid (p.1088·1).
Osteoporosis.

Alendro-Q *Juta, Ger.; Q-Pharm, Ger.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alendros *Abiogen, Ital.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alenia *Biosintetica, Braz.*
⊗ Formoterol fumarate (p.1122·1); budesonide (p.1520·1).
Asthma.

Alenic Alka
Note. This name is used for preparations of different composition.
Rugby, USA.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Hyperacidity.
Rugby, USA.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Hyperacidity.

A-Lennon *Pharmacare, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Alenstran *Chrispa (Χρισπα), Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Alental *Chobet, Arg.*
Fluoxetine hydrochloride (p.391·2).
Depression; eating disorders; obsessive-compulsive disorder.

Alentol *Farmo Quimica, Chile.*
Fluoxetine (p.397·3).
Bulimia; depression.

Alenwin *Arrow, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alenzantyl *Chrispa (Χρισπα), Gr.*
Azelaic acid (p.1589·3).
Acne.

Aleot *Apomedica, Austria.*
⊗ Chlorphenesin (p.529·2); diphenhydramine hydrochloride (p.577·2); chlorobutanol (p.1639·2); benzalkonium chloride (p.1629·1); urea (p.1620·2).
Ear disorders.

Alepa *Duopharm, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Alepam *Alphapharm, Austral.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Aleprozil *Diba, Mex.*
Omeprazole (p.1753·1).
Aspiration syndrome; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alepsal
Note. This name is used for preparations of different composition.
Spedrog, Arg.; Sanofi Synthelabo, Mex.
Phenobarbital (p.492·2).
Epilepsy; sedative.
Genevrier, Fr.
Phenobarbital (p.492·2); caffeine (p.1116·3).
Epilepsy.

Alepsal Compuesto *Sanofi Synthelabo, Mex.*
Phenobarbital (p.492·2); phenytoin sodium (p.495·2).
Epilepsy.

Alerbak *Pfizer, Chile.*
Sodium spaglumate (p.2327·2).
Allergic conjunctivitis.

Alercina *Cinfa, Spain.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Alercortil *Allergan, Arg.†.*
⊗ Hydrocortisone (p.1535·2); naphazoline hydrochloride (p.1565·2).
Conjunctivitis.

Alercrom *Grin, Mex.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Alerdex *Armoxindo, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Alerdil *Diba, Mex.*
Chlorphenamine (p.572·2).
Hypersensitivity.

Alerdina *Cafar, Venez.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Aler-Dryl *Reese, USA.*
Diphenhydramine hydrochloride (p.577·2).

Alerdual *Thea, Fr.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

Alerfan *Anpharm, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alerfed *Guardian, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; sinusitis.

Alerfedine *Lazar, Arg.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Alerfedine D *Lazar, Arg.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Alerfin
Note. This name is used for preparations of different composition.
Farmalab, Braz.
⊗ Beclometasone dipropionate (p.1516·2).
Liferpal, Mex.
Loratadine (p.583·3).
Hypersensitivity.

Alerfin Ex *Liferpal, Mex.*
Loratadine (p.583·3); ambroxol (p.1550·3).

Alerfrin *Allergan, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Ocular congestion and irritation.

Alerfur *Ivax, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Alerg *IA, Ger.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Alergaliv *Legrand, Braz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Alergan *Chemopharma, Chile.*
Loratadine (p.583·3).
Allergic eye disorders; allergic rhinitis; allergic skin disorders; urticaria.

Alergi *Raymos, Arg.*
⊗ Dexamethasone (p.1526·1); chlorphenamine (p.572·2).
Hypersensitivity reactions.

Alergibon *Galderma, Braz.†; Galderma, Mex.*
Emollient; soap substitute.
Barrier preparation; dry skin; skin disorders.

Alergical
Note. This name is used for preparations of different composition.
Iquinosa, Spain.
Cream: ⊗ Betamethasone valerate (p.1519·1); fluocinolone acetonide (p.1531·3).
Skin disorders.
Juventus, Spain.
Syrup: ⊗ Chlorphenamine maleate (p.571·3); prednisolone metasulfobenzoate sodium (p.1541·1).
Hypersensitivity reactions; skin disorders.
Juventus, Spain.
Tablets: ⊗ Ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3); prednisolone (p.1540·3).
Hypersensitivity reactions; skin disorders.

Alergical Expect *Juventus, Spain.*
Chlorphenamine maleate (p.571·3); diprophylline (p.1120·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Bronchospasm; fever; pain.

Alergiderm *Prodotti, Braz.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions.

Alergidryl *Klonal, Arg.†.*
Chlorphenamine (p.572·2).
Hypersensitivity reactions.

Alergiftalmina *Davi, Port.*
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2).
Blepharospasm; conjunctivitis.

Alergin *Cipla, India.*
⊗ Ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1); phenobarbital (p.492·2).
Asthma; bronchospasm.

Alergipan *Benitol, Arg.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alergitanil *Prodotti, Braz.*
Mepyramine maleate (p.585·2).
Hypersensitivity reactions.

Alergitrat
Note. This name is used for preparations of different composition.
Fecofar, Arg.
Chlorphenamine (p.572·2).
Hypersensitivity reactions.
Eversil, Braz.†.
Mepyramine maleate (p.585·2); tripelennamine hydrochloride (p.592·2); strontium bromide (p.2269·3); calcium pantothenate; magnesium thiosulfate.
Hypersensitivity reactions.

Alergo Filinal *Eurofarma, Braz.*
Diphenhydramine hydrochloride (p.577·2); aminophylline (p.1114·2); guaifenesin (p.1561·3); pyridoxine hydrochloride (p.1978·2).
Respiratory-tract disorders.

Alergo Glucalbet *Arrow, Braz.†.*
Mepyramine maleate (p.585·2); pentoxyverine citrate (p.1567·3); calcium gluconate (p.1675·3); ammonium chloride (p.1551·3).
Coughs.

Alergocrom *Aldo, Spain; Medifarm, Venez.†.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchospasm.

Alergoftal *Alcon Cusi, Malaysia; Alcon Cusi, Spain; Alcon, Turk.*
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2).
Allergic conjunctivitis; allergic or inflammatory eye disorders.

Alergoliber *Recordati, Spain.*
Rupatadine fumarate (p.590·2).
Allergic rhinitis.

Alergolon *Biolab Sanus, Braz.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Alergonase *Montrose, Cz.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; nasal polyps.

Alergonil *Ducto, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Alergoral *Darrow, Braz.*
Allergen preparation (p.2250·2).
Allergen immunotherapy.

Alergosan *Klinger, Braz.†.*
Promethazine (p.588·2).
Hypersensitivity reactions.

Alergot *Oftalmi, Venez.*
Azelastine (p.568·2).
Allergic conjunctivitis.

Alergotox *Makros, Braz.†.*
Diphenhydramine hydrochloride (p.577·2); theophylline (p.1140·1); aminophylline (p.1114·2).
Hypersensitivity.

Alergotox Efedrina *Makros, Braz.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2); liver antitoxin.
Hypersensitivity.

Alergotox Expectorante *Makros, Braz.†.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); aminophylline (p.1114·2); liver antitoxin.
Respiratory-tract congestion.

Alergotox Nasal *Makros, Braz.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Alergovalle *Dovalle, Braz.†.*
Dexchlorpheniramine (p.572·2).
Hypersensitivity reactions.

Alergoxal *Bros, Gr.*
Cetirizine (p.571·1).
Hypersensitivity disorders.

Alergyo *Sanval, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Aleric *US Pharmacia, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alerid *UCB, Austria; Cipla, Cz.; Asche, Ger.†; Neopharma, Hung.; Cipla, India; UCB, Swed.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

Alerid Cold *Cipla, India.*
Cetirizine hydrochloride (p.570·3); phenylpropanolamine (p.1569·2); paracetamol (p.108·1).

Alerid D *Cipla, India.*
Cetirizine hydrochloride (p.570·3); phenylpropanolamine hydrochloride (p.1569·3).

Alerion *Filaxis, Arg.*
Clonazepam (p.478·2).
Anxiety disorders; epilepsy.

Alerjon *Edol, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Alerken *Kener, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Alerlisin *Menarini, Spain.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Alermed *Lek-Am, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Alermi *Offenbach, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Alermina *Lafedar, Arg.*
Diphenhydramine (p.577·1).
Hypersensitivity reactions.

Alermine *Royton, Braz.†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Alermizol *Pharmacia, Arg.†; Reig Jofre, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Alermuc *Elisium, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Alernex *Dabur, India†.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Alernitis *Ikapharmindo, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alerpriv *Montpellier, Arg.; Montpellier, Rus.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Alerpriv D *Montpellier, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Cold and influenza symptoms; otitis; rhinitis; sinusitis.

Alersan *Hexal, Braz.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Formerly contained mepyramine maleate and magnesium thiosulfate.
Hypersensitivity.

Alertec *Shire, Canad.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome.

Alerten *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.*
Ubidecarenone (p.2407·2).
Cardiovascular disorders; dietary supplement.

Alertidine *Schering-Plough, Venez.†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Alertonic *Sigma, Austral.†; Odan, Canad.; Adcock Ingram, S.Afr.*
Pipradrol hydrochloride (p.2162·3); vitamin B substances; minerals; trace elements (p.1922·1).
Tonic.

Alertop *Laboratorios Chile, Chile.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Alertop-D *Laboratorios Chile, Chile.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Alertrin *Plough, Port.*
Loratadine (p.583·3).
Allergic rhinitis; eye irritation; urticaria.

Alerxem *Kleva, Gr.*
⊗ Fluticasone (p.1533·2).
Hypersensitivity disorders.

Alerza *Ipca, Rus.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Alerzina *Lek-Am, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Alerzona *Silesia, Chile.*
⊗ Mepyramine maleate (p.585·2); prednisone acetate (p.1543·1).
Skin disorders.

Alesal *Zuoz, Venez.*
Diethylamine salicylate (p.47·2).
Musculoskeletal and joint disorders.

Alesion *Boehringer Ingelheim, Jpn.*
Epinastine hydrochloride (p.579·3).
Allergic rhinitis; asthma; pruritus.

Alespan *Intermed, Gr.*
Zolpidem (p.1038·2).
Insomnia.

Alesse *Wyeth, Canad.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Neth.; Wyeth-Ayerst, USA; Wyeth, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Androgen-associated acne in women; combined oral contraceptive.

Alestopor *Kleva, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Aletir *Bunker, Braz.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Aletris Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Aleucin *Piam, Ital.†.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

Aleudrina *Boehringer Ingelheim, Spain.*
⊗ Isoprenaline sulfate (p.1316·3).
Cardiac disorders; shock.

Aleva *OEP, Philipp.*
Ebastine (p.579·1).
Allergic rhinitis; urticaria.

Aleval *Sun, Mex.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Alevarin *Biofarma, Mex.*
Aesculus (p.2248·2).
Venous insufficiency.

Aleve *Bayer Consumer, Arg.; Roche Consumer, Austral.†; Bayer, Austria; Bayer, Belg.; Roche, Belg.; Bayer, Cz.; Bayer Sante, Fr.; Roche Consumer, Ger.; Bayer, Hung.; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Switz.; Mecom, Turk.; Procter & Gamble, USA.*
Naproxen sodium (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Alex *Glenmark, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); caffeine (p.1116·3).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, chlorphenamine maleate, paracetamol, and caffeine.
Cold symptoms; coughs.

Alex Cough
Note. This name is used for preparations of different composition.
Glenmark, India.
Lozenges: Dextromethorphan hydrobromide (p.1555·2).
Coughs; sore throat.
Glenmark, India.
Syrup: Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs.

Alex Paediatric *Glenmark, India.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Nasal congestion; nasal hypersensitivity reactions.

Alex Plus *Glenmark, Rus.*
Dextromethorphan hydrobromide (p.1555·2); terpin hydrate (p.1573·3); levomenthol.
Cough.

Alexa *Sigma, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Alexan *Ebewe, Austria; Pfizer, Chile; Ebewe, Cz.; Ebewe, Ger.; Neocorp, Ger.; Ebewe, Hong Kong; Ebewe, Hung.; Mack, Israel; Pfizer, Mex.†; EuroCept, Neth.; Ebewe, Pol.; Ferraz, Lynce, Port.†; Ebewe, Rus.; Intramed, S.Afr.; Mack, Singapore†; Mack, Thai.†; Eczacibasi, Turk.*
Cytarabine (p.705·1).
Formerly known as Cytovis in *Israel*.
Leukaemias; non-Hodgkin's lymphomas.

Alexia *Saval, Chile.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; allergic skin disorders.

Alexia D *Saval, Chile.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Alexin
Note. This name is used for preparations of different composition.
Dabur, India†.
Cefalexin (p.218·2).
Bacterial infections.

Farmoz, Port.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alexing *Farcoral, Mex.*
Ambroxol (p.1550·3); dextromethorphan (p.1555·2).
Coughs; respiratory-tract congestion.

Alexonal *Sandoz, Indon.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alex-P *Glenmark, India.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms; coughs.

Aleztem *Rayere, Mex.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Alfa
Note. This name is used for preparations of different composition.
Bergamon, Ital.
Didecyldimethylammonium chloride (p.1642·2).
Disinfection of burns, mucous membranes, and wounds.

Pfizer Consumer, Spain.
⊗ Naphazoline nitrate (p.1565·2).
Eye irritation.

Alfa Acid *Sinclair, Ital.*
Ammonium lactate (p.1589·2); salicylic acid (p.1612·2); dexpanthenol (p.2362·1).
Scalp disorders.

Alfa C *Bracco, Ital.*
Benzalkonium chloride (p.1629·1).
Eye irritation.

Alfa Calcimax *Gador, Arg.†.*
Alfacalcidol (p.1986·1).
Osteomalacia; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency.

Alfa D *Recalcine, Chile†.*
Alfacalcidol (p.1986·1).
Vitamin D supplement.

Alfa Kappa *Kedrion, Ital.*
Amino-acid preparation (p.1922·1).
Nutritional supplement in renal failure.

Alfa Lip *NCSN, Ital.*
Thioctic acid (p.2400·2); vitamins (p.1922·1).
Nutritional supplement.

Alfabase *Cassara, Arg.*
Emollient.

Alfabase 8 *Cassara, Arg.*
Glycolic acid (p.1598·1).
Photoageing of skin.

Alfacaina *Dentsply, Ital.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Alfacalcil *Zwitter, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alfaciclina *Vargas, Venez.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Alfacid *Grunenthal, Ger.*
Rifabutin (p.323·3).
Mycobacterium-avium complex infections in AIDS patients; tuberculosis.

Alfacip *Cipla, India.*
Alfacalcidol (p.1986·1).

Alfacip Plus *Cipla, India.*
Alfacalcidol (p.1986·1); calcium (p.1675·2).

Alfacolin *Prieto, Arg.*
Colistin (p.257·2).
Bacterial infections.

Alfacort
Cassara, Arg.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Inflammatory eye disorders; skin disorders.

Julphar, UAE.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Alfacortone *Spirig, Switz.*
⊗ Hydrocortisone acetate (p.1535·2).
Burns; insect stings; skin disorders.

Alfacrist *Chrispa (Χρισπα), Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Alfad *Biosintetica, Braz.†; Altana, Mex.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency.

Alfadel *Polychronus, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alfadil *Pfizer, Swed.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Alfadiman *Lazar, Arg.*
Allopurinol (p.552·2).
Hyperuricaemia.

Alfadiol *GSK, Pol.*
Alfacalcidol (p.1986·1).
Hypocalcaemia; hypoparathyroidism; nephrotic syndrome; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Alfadopan *Etifar, Venez.†.*
Methyldopa (p.1334·1).
Hypertension.

Alfadoxin *Laboratorios Chile, Chile.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Alfadrops *Cipla, India.*
Apraclonidine hydrochloride (p.1877·3).
Glaucoma.

Alfaferone *Alfa Wassermann, Cz.; Wassermann, Ital.; Alfa Wassermann, Pol.*
Interferon alfa (p.885·1).
Anogenital warts; hepatitis B; hepatitis C; malignant neoplasms.

Alfaflor *INTES, Ital.*
⊗ Bottle A, betamethasone sodium phosphate (p.1518·3); naphazoline nitrate (p.1565·2); bottle B, tetracycline hydrochloride (p.347·2).
Inflammatory eye disorders.

Alfagamma *Humana, Ital.†.*
Essential fatty acids; vitamin E; vitamin B (p.1922·1).
Nutritional supplement.

Alfagen *Wassermann, Ital.†.*
Collagen (p.2286·1).
Ulcers; wounds.

Alfaken *Kendrick, Mex.*
Lisinopril (p.1325·2).
Hypertension.

Alfakinasi *Wassermann, Ital.†.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Alfalastin *LFB, Fr.*
Alpha -proteinase inhibitor (p.2253·2).
Alpha antitrypsin deficiency.

Alfalfa Sativa Compuesta *Hochstetter, Chile†.*
Alfalfa; avena sativa; papaya (p.1922·1).
Tonic.

Alfalfa Tonic *Boiron, Canad.; Homeocan, Canad.*
Homoeopathic preparation.

Alfamedin *Kade, Ger.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia.

Alfamet *Ulagay, Turk.*
Methyldopa (p.1334·1).
Hypertension.

Alfa-Mon *Biotech, Venez.*
Vitamin A (p.1971·2).

Alfamox *Teofarma, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Alfan *Alpharma, Mex.*
⊗ Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Cough; nasal congestion.

Alfaprost *Elfar, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Alfapsin *Hetero, India.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3).
Inflammation; oedema.

Alfare *Nestle, Austral.; Nestle, Braz.; Nestle, Fr.; Nestle, Ital.; Nestle, Mex.; Nestle, Philipp.; Nestle, Port.†; Nestle, Switz.; Nestle, Venez.*
Preparation for enteral nutrition (p.1922·1).
Diarrhoea; digestive disorders; hypersensitivity; malabsorption disorders; milk intolerance.

Alfarol *Chugai, Jpn.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal failure; rickets.

Alfasid *Fako, Turk.*
Sultamicillin (p.344·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Alfasilin *Fako, Turk.*
Ampicillin (p.204·1).
Bacterial infections.

Alfasin *Solvay, Braz.*
⊗ Finasteride (p.2188·3).
Alopecia; benign prostatic hyperplasia.

Alfason *Astellas, Ger.*
⊗ Hydrocortisone butyrate (p.1535·3).
Skin disorders.

Alfast *Cristalia, Braz.*
⊗ Alfentanil hydrochloride (p.16·2).
Pain.

Alfate *Stadmed, India.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Alfater *Hardis, Ital.*
Interferon alfa (p.885·1).
Anogenital warts; hepatitis B; hepatitis non-A non-B; malignant neoplasms.

Alfatil *Lilly, Fr.*
Cefaclor (p.217·2).
Bacterial infections.

Alfavit *Medgenix, Belg.†.*
⊗ Ephedrine tartrate (p.1559·1); vitamins (p.1922·1).
Tonic.

Alfavitil *DNR, Arg.†.*
Pronalen.
Cellulitis.

Alfazol *IQFA, Mex.*
Albendazole (p.139·2).
Worm infections.

Allergefon *SERP, Mon.*
Carbinoxamine maleate (p.570·2).
Hypersensitivity reactions.

Alfem *Nucitec, Mex.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide (p.1744·1).
Calcium, vitamin D, and magnesium supplement; osteomalacia; osteoporosis; rickets; tetany.

Alfener *Farmanust, Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Alfenta *Janssen-Ortho, Canad.; Taylor, USA.*
⊗ Alfentanil hydrochloride (p.16·2).
Analgesia during anaesthesia; analgesia in ventilated patients; induction of anaesthesia.

Alferm
Note. This name is used for preparations of different composition.
Schoning-Berlin, Ger.†.
Ointment: ⊗ Prednisolone (p.1540·3); thymol (p.1664·3).
Anorectal disorders.

Schoning-Berlin, Ger.†.
Suppositories: ⊗ Prednisolone (p.1540·3); thymol (p.1664·3); menthol (p.2340·1).
Anorectal disorders.

Alferon *Cryopharma, Mex.*
Interferon alfa-2a (recombinant) (p.885·1).
Hepatitis B; malignant neoplasms.

Alferon N *Interferon Sciences, USA.*
Interferon alfa-n3 (p.885·1).
Genital warts.

Alfetim *Sanofi-Aventis, Hung.; Sanofi Synthelabo, Spain†.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Alficetin *Nova Argentia, Arg.*
Colistimethate sodium (p.256·3).
Bacterial infections.

Alfin *Sanitas, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Alfinor *Medochemie, Malaysia.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Alfitar *Fardi, Spain.*
Coal tar (p.1616·2).
Psoriasis; seborrhoeic dermatitis.

Alflam *Mugi, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Al-Flor *Francia, Ital.†.*
Lactic-acid producing bacteria (p.2372·3); yeast; anise; lime; vitamin C; vitamin B substances (p.1922·1).
Restoration of gastrointestinal flora.

Alflutop *Biotehnos, Rus.*
Defatted and deproteinised sea fish extract.
Musculoskeletal and joint disorders.

Alfospas *Rottapharm, Ital.*
Tiropramide hydrochloride (p.2403·1).
Smooth muscle spasm.

Alfoxil *Abfar, Turk.*
Amoxicillin (p.202·2).
Bacterial infections.

Alfron *Sigma, Braz.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; panic disorder.

Alfuca *Kenyaku, Thai.*
Albendazole (p.139·2).
Worm infections.

Alfuprost *Farmedia, Gr.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Alfural *Rafarm, Gr.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Alfuzin *Biomedica-Chemica, Gr.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Alfuzina *Bunker, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Alfuzostad *Stada, Cz.; Stada, Hung.; Steigerwald, Pol.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Alganax *Guardian, Indon.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Alganex *Roche, Swed.*
Tenoxicam (p.128·2).
Dysmenorrhoea; inflammation; musculoskeletal, joint, and peri-articular disorders; postoperative pain.

Algedol *Pfizer, Arg.*
⊗ Morphine sulfate (p.86·3).
Pain.

Algedrox *De Mayo, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Algefit *Pharmaselect, Austria.*
Diclofenac sodium (p.44·3).
Soft-tissue and peri-articular disorders.

Algesal
Note. This name is used for preparations of different composition.
Raffo, Arg.; Solvay, Austria; Pharmaselect, Cz.; Biokanol, Ger.; Solvay, Hung.; Byk Gulden, Mex.†; CS, Port.; Solvay, Switz.†.
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Vemedia, Belg.; Solvay, Fin.; Solvay, Ital.†; Solvay, Neth.; Nycomed, Norw.; Solvay, Swed.; Frik, Turk.; Zeroderma, UK.
Diethylamine salicylate (p.47·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Stada, Spain.
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2) or myrtecaine laurilsulfate (p.1867·2).
Peri-articular and soft-tissue disorders.

Algesal Forte *Solvay, Neth.*
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Muscle and joint pain.

Algesal Superactive *Solvay, Indon.*
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Algesal Suractive *Pharmadeveloppement, Fr.; Solvay, Gr.; Frik, Turk.*
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Musculoskeletal and joint pain; soft-tissue disorders.

Algesalona *Solvay, Ger.†; Solvay, Switz.†.*
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2); flufenamic acid (p.60·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Algesalona E *Solvay, Ger.†.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Algex *Farmo Quimica, Chile.*
Mefenamic acid (p.80·1).
Pain.

Algexin *Cimed, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Algi *Mabo, Spain.*
Metamizole magnesium (p.49·3).
Fever; pain.

Algi Peralgin *Infabra, Braz.†.*
Oxyphenbutazone (p.107·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Algiasdin *Isdin, Spain.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Algibon *Galderma, Venez.*
Skin cleanser.

Algi-Butazolon
Note. This name is used for preparations of different composition.
Dovalle, Braz.†.
Oral solution: Diclofenac (p.44·2); paracetamol (p.108·1).

Dovalle, Braz.†.
Tablets: Diclofenac (p.44·2); paracetamol (p.108·1); carisoprodol (p.1894·1); caffeine (p.1116·3).

Algical Kalzarevet *Femi Agran, Israel.*
Calcium carbonate (p.1714·1); sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Algice *Cazi, Braz.*
Green tablets, dipyrone (p.49·2); sodium camsilate (p.2388·3); cineole (p.2282·3); guaifenesin (p.1561·3); niaouli oil (p.2351·3); yellow tablets, vitamin C (p.1983·3).
Cold and influenza symptoms.

Algicler
Note. This name is used for preparations of different composition.
Monserrat, Arg.
Tablets: Diclofenac (p.44·2); paracetamol (p.108·1).

Monserrat, Arg.
Topical gel: Diclofenac diethylamine (p.44·3).

Algicon
Note. This name is used for preparations of different composition.
Sanofi-Aventis, UK†.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium alginate (p.2141·1); magnesium carbonate (p.1743·1); potassium bicarbonate (p.1673·1).
Gastric hyperacidity; gastro-oesophageal reflux.

Aventis, Irl.†; Aventis, Neth.
Oral suspension: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1); potassium bicarbonate (p.1673·1); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Aventis, Mex.†.
Oral suspension: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Aventis, Mex.†.
Tablets: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Aventis, Neth.
Tablets: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1); potassium bicarbonate (p.1673·1).
Gastro-oesophageal reflux.

Algi-Cool *Qualiphar, Belg.*
Menthol (p.2340·1); dexpanthenol (p.2362·1); chamomile (p.2279·3); arnica (p.2260·2); devil's claw (p.39·1); camphor (p.2273·2).
Musculoskeletal and joint disorders.

Algicote
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Chile.
Chewable tablets: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1); potassium bicarbonate (p.1673·1).
Gastro-oesophageal reflux.

Sanofi-Aventis, Chile.
Oral suspension: Magnesium alginate (p.2141·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); potassium bicarbonate (p.1673·1).
Gastro-oesophageal reflux.

Algicum *Azevedos, Port.*
Diethylamine salicylate (p.47·2).
Musculoskeletal, joint, and soft-tissue disorders.

Algidente *Sedabel, Braz.†.*
Phenol (p.1656·1); procaine hydrochloride (p.1869·1); clove oil (p.2285·1).
Mouth disorders.

Algiderm *Finadiet, Arg.*
Erythromycin (p.269·2).
Bacterial skin infections.

Algiderma *Davi, Port.*
Diethylamine salicylate (p.47·2).
Musculoskeletal, joint, and soft-tissue disorders.

Algidol
Note. This name is used for preparations of different composition.
Vitae, Mex.
Ibuprofen (p.64·2).
Pain.

Almirall, Spain.
Paracetamol (p.108·1); codeine phosphate (p.37·2); ascorbic acid (p.1983·3).
Pain.

Algidrin *Fardi, Spain.*
Ibuprofen lysine (p.64·2).
Inflammation; pain.

Algifemin *Sanitas, Chile.*
Mefenamic acid (p.80·1).
Pain.

Algifen
Note. This name is used for preparations of different composition.
Sintofarma, Braz.†.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Zentiva, Cz.
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Painful smooth muscle spasm.

Algifen Neo *Ivax, Cz.*
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).
Painful smooth muscle spasm.

Algifene *Ferraz, Lynce, Port.*
Dextropropoxyphene (p.40·1); paracetamol (p.108·1).
Pain.

Algiflamanil *Neo Quimica, Braz.*
Oxyphenbutazone (p.107·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Algiflex *EMS, Braz.*
Ibuprofen (p.64·2).

Algifor *Vifor, Switz.*
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; juvenile idiopathic arthritis; pain.

Algi-Itamanil *Neo Quimica, Braz.†.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Algik *Azevedos, Port.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Algikey *Inkeysa, Spain.*
Ketorolac trometamol (p.74·2).
Pain.

Algimate *Jaba Recordati, Port.*
Clonixin lysine (p.37·1).
Pain.

Algimesil *Francia, Ital.*
Nimesulide (p.95·3).
Musculoskeletal and joint disorders.

Algina *Confar, Port.*
Methyl salicylate (p.85·3); menthol (p.2340·1); guaiacol (p.1561·2).
Musculoskeletal, joint, and soft-tissue disorders.

Alginatol *Nizhpharm, Rus.*
Sodium alginate (p.2141·1).

Algine *Adelco, Gr.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Alginete *KRKA, Cz.†.*
Alginic acid (p.2140·3); carmellose sodium (p.2142·1).
Obesity.

Alginex *Sanopharm, Switz.†.*
Ethyl salicylate (p.52·1); camphor (p.2273·2); menthol (p.2340·1); turpentine oil (p.2406·3).
Musculoskeletal, joint, and peri-articular disorders; sports injuries.

Alginor *Boehringer Ingelheim, Ital.*
Cimetropium bromide (p.1720·2).
Adjunct in gastrointestinal examinations and surgical procedures; gastrointestinal disorders.

Algin-Vek *Faran, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Algio Nervomax *TRB, Arg.*
Ampoule 1, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ampoule 2, diclofenac sodium (p.44·3).
Pain; peri-articular and soft-tissue disorders.

Algio Nervomax Fuerte *TRB, Arg.*
⊗ Ampoule 1, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ampoule 2, diclofenac sodium (p.44·3); betamethasone sodium phosphate (p.1518·3).
Musculoskeletal and joint disorders.

Algio-Bladuril *Casasco, Arg.*
Flavoxate hydrochloride (p.2190·1); propyphenazone (p.119·3).
Bladder disorders; female genital-tract spasm.

Algiodent *Ronnet, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); hexylresorcinol (p.1647·1); cresol (p.1641·1).
Mouth and throat disorders.

Algion *Saval, Chile.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm.

Algiopiret *Fada, Arg.†.*
Dipyrone (p.49·2).
Fever; pain.

Algioprofen *Lazar, Arg.†.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Algioprux *Sidus, Arg.†.*
Naproxen (p.92·3).
Inflammation; pain.

Algiospray *Novag, Mex.†.*
Peridilmethylamine.

Algio-Truxa *Raffo, Arg.†.*
Paracetamol (p.108·1); piroxicam (p.117·3).
Inflammation; pain.

Algioxib *Dupomar, Arg.*
Diclofenac sodium (p.44·3).
Formerly contained rofecoxib.
Inflammation.

Algipan
Note. This name is used for preparations of different composition.
Qualiphar, Belg.
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); mephenesin (p.1897·2).
Musculoskeletal pain; skeletal muscle spasm.

UCB, Fr.
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); histamine hydrochloride (p.2319·2); mephenesin (p.1897·2).
Muscle pain.

Wyeth, India.
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); capsicum oleoresin (p.2276·2); histamine hydrochloride (p.2319·2).
Muscle and joint pain; neuralgia.

Wyeth, Irl.
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); capsaicin (p.32·3).
Musculoskeletal and joint pain.

Algirem *Masterlek, Rus.*
Rimantadine hydrochloride (p.904·2).
Influenza.

Algi-Reumatril *Hertz, Braz.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Inflammation; pain.

Algirona *Bunker, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Algiseda *Sanitas, Arg.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal, joint, and peri-articular disorders.

Algisedal *Viatris, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Algiseptico *Fada, Arg.†.*
Piperacillin (p.315·2).
Bacterial infections.

Algisite *Smith & Nephew, Canad.†.*
Calcium alginate (p.1058·1).
Wounds.

Algispray
Note. A similar name is used for preparations of different composition (see below).
Casasco, Arg.
Dichlorodifluoromethane (p.1689·1); trichlorofluoromethane (p.1689·1).
Local anaesthesia; pain.

Algis-Spray
Note. A similar name is used for preparations of different composition (see above).
Qualiphar, Belg.
Turpentine oil (p.2406·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint pain.

Algistop *ISA, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Algi-Tanderil *Klinger, Braz.†.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1); carisoprodol (p.1894·1); caffeine (p.1116·3).
Inflammation; pain.

Algitrin *Schering-Plough, Mex.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Algix *Gentili, Ital.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Algo *Lokman, Turk.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Algo Bebe *Lokman, Turk.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Algobaz *CPH, Port.†.*
Mecobalamin (p.1981·1).
Megaloblastic anaemia.

Algoceanic *Proceane, Fr.†.*
Sea water; bladderwrack (p.2384·2); chondrus crispus; ascophyllum nodosum.
Mineral supplement.

Algocetil *Francia, Ital.*
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders; neuritis.

Algocod *SMB, Belg.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Algocor *Teofarma, Ital.*
Gallopamil hydrochloride (p.1295·3).
Angina pectoris; myocardial infarction.

Algofen *Chefaro, Ital.*
Ibuprofen (p.64·2).
Pain.

Algofina *Sanamed, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Algoflex
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Hung.
Tablets: Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Sanofi-Aventis, Hung.
Topical gel: Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue disorders.

Algoflex-M *Sanofi-Aventis, Hung.*
Round tablets, ibuprofen (p.64·2); oblong tablets, drotaverine hydrochloride (p.2298·1).
Dysmenorrhoea.

Algofren *Intermed, Gr.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Algogen *Nakornpatana, Thai.*
Paracetamol (p.108·1).
Pain.

Algolider *Siar, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Algolisina *Poliforma, Ital.†.*
Pridinol mesilate (p.1898·1); benzydamine hydrochloride (p.27·3); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Algolysin *Teva, Israel.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Algon *Lavipharm, Gr.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Algonapril *Crinos, Ital.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Algophene *SMB, Belg.*
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Pain.

Algopirina *Medisint, Ital.*
Aspirin (p.20·3); paracetamol (p.108·1).
Cold and influenza symptoms; pain.

Algoplaque
Note. This name is used for preparations of different composition.
Urgo, Fr.
A hydrocolloid dressing.
Burns; ulcers; wounds.

Urgo, Ger.
Carmellose sodium (p.2142·1).
Ulcers; wounds.

Algopyrin *Sanofi-Aventis, Hung.*
Dipyrone (p.49·2).
Fever; pain.

Algopyrin Complex *Sanofi-Aventis, Hung.*
Dipyrone (p.49·2); caffeine (p.1116·3); drotaverine hydrochloride (p.2298·1).
Headache; migraine.

Algoren *Ronava, Venez.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; migraine.

Algorex *Amnol, Ital.*
Maritime pine (p.2368·1); aesculus (p.2248·2); bromelains (p.2269·1); vitamin B substances (p.1922·1).
Inflammation; oedema.

Algosenac *Senese, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; painful smooth muscle spasm.

Algosfar *Medifarma, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Algostase *SMB, Belg.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Algostase Mono *SMB, Belg.*
Paracetamol (p.108·1).
Fever; pain.

Algosteril *Brothier, Fr.; Johnson & Johnson, Ger.†; Johnson & Johnson, Ital.; Smith & Nephew, UK.*
Calcium alginate (p.1058·1).
Haemostatic dressing; wounds.

Algosteril Trionic *Johnson & Johnson, Ger.†.*
Calcium alginate (p.1058·1); manganese gluconate (p.1956·2); zinc gluconate (p.1999·2).
Burns; ulcers; wounds.

Algosulid *Med-One, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Algotropyl *Alpharma, Fr.†.*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2).
Cold symptoms.

Algover *Iapharm, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Algo-Wax *Lokman, Turk.*
Menthol (p.2340·1); camphor (p.2273·2); capsicum oleoresin (p.2276·2); eucalyptus oil (p.2301·2); thyme oil (p.2401·2); turpentine oil (p.2406·3); lavender oil (p.2331·2).
Musculoskeletal and joint pain.

Algoxam *Alter, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Algozone *Ozone, Hung.*
Dipyrone (p.49·2).
Fever; pain.

Algut *Merck, Indon.*
Allopurinol (p.552·2).
Gout.

Algybrex *Northia, Arg.*
Celecoxib (p.34·2).

Algy-Flanderil *Vitapan, Braz.†.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Alho Rogoff *Crefar, Port.†.*
Garlic (p.2309·2).
Cardiovascular disorders; rheumatic disorders; senility; stress.

Alho-Arthrosan N *Wiedemann, Ger.*
Homoeopathic preparation.

Alho-Sedosan *Wiedemann, Ger.*
Homoeopathic preparation.

Alhydrate *Nestle, Fr.; Nestle, Ital.*
Maltodextrin; sucrose; sodium chloride; citric acid; potassium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Ali Veg *GSK Consumer, Spain.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Alib *Ibfarma, Braz.†.*
Albendazole (p.139·2).
Worm infections.

A-Lices *AFT, NZ; Hoe, Singapore.*
Malathion (p.2046·1).
Pediculosis.

Alici-A *Mallix, Philipp.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Alicron *Ferron, Indon.*
Thioctic acid (p.2400·2); biotin (p.1931·3); chromium polynicotinate.
Supplement in diabetes mellitus.

Alicura *Catarinense, Braz.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Alidase *Bernabo, Arg.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Alidial *Filaxis, Arg.*
Gabapentin (p.482·3).
Epilepsy; postherpetic neuralgia.

Alidol *Syntex, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Aliflus *Menarini, Ital.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma.

Alikal *GSK, Arg.*
Aspirin (p.20·3); caffeine (p.1116·3); sodium bicarbonate (p.1673·2); citric acid (p.2284·1); sodium carbonate (p.2389·1).
Dyspepsia; headache.

Alikal Dolor *GSK, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Alimax *Cristalia, Braz.*
Heparin sodium (p.1301·2).
Burns.

Alimentum *Abbott, Canad.; Abbott, Singapore; Ross, USA.*
Protein hydrolysate infant feed (p.1922·1).
Fat malabsorption; food allergies; lactose intolerance; protein intolerance.

Alimix *Janssen-Cilag, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Alimta *Lilly, Arg.; Lilly, Austral.; Lilly, Belg.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Pol.; Lilly, Rus.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA.*
Pemetrexed disodium (p.762·1).
Malignant pleural mesothelioma; non-small cell lung cancer.

Alin
Note.This name is used for preparations of different composition.
Lazar, Arg.
Ezetimibe (p.1284·3).
Hypercholesterolaemia.
Millet Roux, Braz.
Albendazole (p.139·2).
Worm infections.
Chinoin, Mex.
⊗ Dexamethasone (p.1526·1), dexamethasone isonicotinate (p.1526·1), or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.
Biofarma, Turk.
Phenolphthalein (p.1762·1).

Alin Nasal *Chinoin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Rhinitis; sinusitis.

Alin Oftalmico *Chinoin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye disorders.

Alinal *Julphar, UAE†.*
Pipenzolate bromide (p.1762·2); phenobarbital (p.492·2).
Gastrointestinal spasm.

Alinamin *Takeda, Indon.*
Fursultiamine (p.1975·3) with or without vitamin B (p.1977·2).
Vitamin B deficiency.

Alinamin B12
Note.This name is used for preparations of different composition.
Takeda, Malaysia†; Takeda, Singapore†.
Fursultiamine (p.1975·3); vitamin B (p.1980·2). Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Anaemias; megaloblastic anaemia; neuritis.
Takeda, Thai.†.
Fursultiamine hydrochloride (p.1976·3); vitamin B (p.1980·2).
Macrocytic anaemia; megaloblastic anaemia; neuritis.

Alinamin-F
Note.This name is used for preparations of different composition.
Takeda, Hong Kong.
Fursultiamine hydrochloride (p.1976·3); riboflavin (p.1977·2).
Arthralgia; myalgia; neuralgia; neuritis.
Takeda, Jpn.
Fursultiamine hydrochloride (p.1976·3).
Vitamin B deficiency; vitamin B supplement.
Takeda, Singapore.
Fursultiamine (p.1975·3); riboflavin (p.1977·2).
Arthralgia; beri-beri; CNS disorders; gastrointestinal motility disorders; myalgia; myocardial metabolic disorders; neuralgia; peripheral nerve paralysis; peripheral neuritis; vitamin B deficiency; Wernicke's encephalopathy.
Takeda, Thai.
Injection: Fursultiamine hydrochloride (p.1976·3).
Vitamin B deficiency.
Takeda, Thai.
Tablets: Fursultiamine hydrochloride (p.1976·3); riboflavin (p.1977·2).
Vitamin B deficiency.

Alindrin *Recip, Swed.*
Ibuprofen (p.64·2).
Fever; pain.

Alinia *Romark, USA.*
Nitazoxanide (p.842·3).
Cryptosporidiosis; giardiasis.

Alinol *Pharmasant, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alinor *Alpharma, Norw.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Alinvit *Collins, Mex.*
Multivitamin preparation (p.1922·1).

Alione *Coloplast, Ger.*
Carmellose (p.2142·1).
Burns; ulcers; wounds.

Alione Charbon *Coloplast, Fr.*
Activated charcoal (p.1435·2).
Burns; ulcers; wounds.

Aliot *Biotech, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Aliovital *Agropharm, Pol.*
Garlic (p.2309·2).
Atherosclerosis; hyperlipidaemias.

Alipal Forte *Arex, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Alipas *Bernabo, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Alipas Duo *Bernabo, Arg.*
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Hyperlipidaemias.

Alipride *Centaur, India.*
Cisapride (p.1720·3).
Delayed gastric emptying; gastro-oesophageal reflux.

Aliserin *Unifarm, Ital.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Aliseum *Formenti, Ital.*
Diazepam (p.986·3).
Anxiety disorders; epilepsy; insomnia.

Alista *Novell, Indon.*
Cilostazol (p.1245·2).
Arterial occlusion.

Alisyd *Darier, Mex.*
⊗ Prednicarbate (p.1540·2).
Skin disorders.

Alitest *Columbia, Mex.†.*
Carbon-13 (p.2277·1).
Diagnostic agent.

Alitol *KRKA, Pol.*
Garlic oil (p.2309·2).
Atherosclerosis.

Alitraq *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore†; Abbott, Turk.; Abbott Nutrition, UK†; Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).

Aliucillin *Aliud, Austria.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Aliudox *Aliud, Austria.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Alivax *Vivax, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Alive *Uniao Quimica, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Alivet *Leti, Venez.*
Paracetamol (p.108·1); chlorphenamine (p.572·2) or chlorphenamine maleate (p.571·3).
Cold symptoms.

Alivet Dia *Leti, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Alivetforte *Leti, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Alivetnoc *Leti, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Alivetos *Leti, Venez.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Alivetos Pediatrico *Leti, Venez.*
Guaifenesin (p.1561·3).
Coughs.

Aliviador *Biologia, Braz.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Aliviagrip *Denver, Arg.*
Ibuprofen (p.64·2); pseudoephedrine (p.1571·2).

Alivian
Note.This name is used for preparations of different composition.
Vitarum, Arg.
Ranitidine (p.1766·1).
Gastric hyperacidity; peptic ulcer.
Cazi, Braz.
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders.

Alivioderm *Hexal, Braz.†.*
Nitrofurazone (p.309·1).
Infected burns; skin infections.

Aliviodol *Centrum, Spain.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthrosis; rheumatoid arthritis.

Aliviol *Cifarma, Braz.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); turpentine oil (p.2406·3); mustard oil (p.2349·2); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Pain.

Aliviomas *Alacan, Spain.*
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Aliviosin *Alacan, Spain.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Alivium *Mantecorp, Braz.*
Ibuprofen (p.64·2).
Fever; pain.

Alizar *Gynopharm, Chile.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; hypocalcaemia; oedema.

Aljil *Yeni, Turk.*
Caffeine (p.1116·3); propyphenazone (p.119·3); paracetamol (p.108·1).
Fever; pain.

ALK
Scherax, Ger.
A range of allergen extracts (p.2250·2).
Allergen immunotherapy.
Trimedal, Switz.
A range of grass and tree pollen allergen extracts (p.2370·2) (p.2250·2).
Allergen immunotherapy.

Alka *Bayer Consumer, UK.*
Aspirin (p.20·3).
Fever; pain.

Alka XS Go *Bayer Consumer, UK†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Alkabel *Cypress, USA.*
Phenobarbital (p.492·2); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Enterocolitis; irritable bowel syndrome.

Alkadil *Alkaloid, Cz.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Alkafizz *Xeragen, S.Afr.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); anhydrous citric acid (p.2284·1); tartaric acid (p.2395·2).
Gastric hyperacidity; urinary alkalinisation.

Alkagel *EMS, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Alkagel Complex *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Alkagel IS *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Alkagin
Note.This name is used for preparations of different composition.
Ganassini, Ital.
Calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2).
Personal hygiene.
Ganassini, Fr.
Topical gel: Aloe vera (p.1588·2); panthenol (p.2362·1); calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2); peppermint (p.1761·2).
Genital pruritus.
Dermoteca, Port.
Topical gel: Calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2); aloe (p.1588·2); chlorhexidine gluconate (p.1635·3).
Personal hygiene.
Ganassini, Fr.
Topical solution: Cocoylamidopropylbetaine; TEA cocoylglutamate; calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2).
Personal hygiene.
Dermoteca, Port.
Topical solution: Calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2); triclosan (p.1665·2).
Personal hygiene.
Dermoteca, Port.
Wipes: Calendula (p.2273·1); mallow (p.2337·2); tilia (p.2402·2); dipotassium glycyrrhizate (p.2316·2); tocoferol acetate (p.1992·3).
Personal hygiene.

Alkala N *Sanum-Kehlbeck, Ger.*
Sodium citrate (p.1673·3); potassium bicarbonate (p.1673·1); sodium bicarbonate (p.1673·2).
Gastrointestinal hyperacidity.

Alkala T *Sanum-Kehlbeck, Ger.*
Sodium bicarbonate (p.1673·2).
Metabolic acidosis.

Alkaligen *Human, Cz.†; Teva, Hung.*
Sodium bicarbonate (p.1673·2).
Barbiturate and salicylate poisoning; metabolic acidosis.

Alkalit *Infusia, Cz.†.*
Potassium citrate (p.1673·2); sodium acid citrate (p.1673·2).
Hyperuricaemia; renal calculi.

Alkalite D *Garec, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); light magnesium oxide (p.1744·1).
Gastric hyperacidity.

Alkamine *ANB, Thai.*
Aluminium hydroxide gel (p.1706·2); magnesium trisilicate (p.1744·1); kaolin (p.1738·1); atropine sulfate (p.1219·3).
Gastric hyperacidity; peptic ulcer.

Alka-Mints *Bayer, USA.*
Calcium carbonate (p.1714·1).
Hyperacidity.

Alkanil *Inga, India.*
Sodium acid citrate (p.1673·2); dibasic potassium citrate (p.1674·2).
Adjunct to sulfonamide therapy; dysuria; metabolic acidosis; systemic alkaliniser.

Alka-Prim *Polpharma, Pol.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Alka-Seltzer
Note.This name is used for preparations of different composition.
Bayer Consumer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer Consumer, Canad.; Bayer, Cz.; Bayer, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Ital.; Bayer Consumer, Malaysia; Bayer, NZ; Bayer, Neth.; Bayer, Philipp.; Bayer, Port.; Bayer, Rus.; Bayer Healthcare, Singapore; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer Consumer, UK; Miles, USA; Bayer, Venez.
Aspirin (p.20·3); citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Dyspepsia; fever; hangover; headache; heartburn; pain.
Bayer, Israel; Bayer, Pol.
Aspirin (p.20·3).
Fever; musculoskeletal and joint disorders; pain; thrombosis prophylaxis.
Bayer, Spain.
Aspirin (p.20·3); calcium phosphate (p.1676·2); citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Fever; musculoskeletal and joint disorders; pain.

Alka-Seltzer Antacid *Miles Consumer Healthcare, USA.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); potassium bicarbonate (p.1673·1).
Gastrointestinal disorders.

Alka-Seltzer with Aspirin *Miles Consumer Healthcare, USA.*
Aspirin (p.20·3); citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Arthritis; fever; gastrointestinal disorders; myocardial infarction; pain.

Alka-Seltzer Doble Accion *Bayer Consumer, Arg.*
Aspirin (p.20·3); sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Gastrointestinal disorders; pain.

Alka-Seltzer Plus Cold *Miles Consumer Healthcare, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Alka-Seltzer Plus Cold & Cough *Miles Consumer Healthcare, USA.*
Capsules: Dextromethorphan (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Alka-Seltzer Plus Cold & Sinus *Bayer, USA.*
Capsules: Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms; nasal congestion.

Alka-Seltzer Plus Day Cold *Bayer, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms; cough.

Alka-Seltzer Plus Night-Time Cold *Miles Consumer Healthcare, USA.*
Capsules: Doxylamine succinate (p.578·2); dextromethorphan (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Alka-Seltzer Plus Nose & Throat *Bayer, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Alka-Seltzer XS *Bayer Consumer, UK.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Gastric discomfort; pain.

Alkasid *Leo, Denm.†; Julphar, UAE.*
Aluminium magnesium silicate (p.2141·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Alkasol *Stadmed, India.*
Sodium acid citrate (p.1673·2).
Dysuria; fever; metabolic acidosis; systemic alkaliniser.

Alkasol-P *Stadmed, India.*
Sodium acid citrate (p.1673·2); paracetamol (p.108·1); sorbitol (p.1965·1).
Alkali depletion; cold symptoms; fever; pain.

Alkasolve *Sam-On, Israel.*
Potassium citrate (p.1673·2); sodium citrate (p.1673·3).
Diabetic acidosis; urinary alkalinisation.

Alkastom *Panvifarm, Gr.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Alkavite *Vitality, USA.*
A multivitamin and mineral preparation (p.1922·1).

Alkcema *Valeant, Hung.*
⊗ Triamcinolone acetonide (p.1544·3); chlorhexidine hydrochloride (p.1635·3).
Infected skin disorders.

Alkenide *Zambon, Fr.†.*
Poloxamer 188 (p.1918·1).
Skin cleanser.

Alkeran
GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.
Melphalan (p.742·1).
Malignant neoplasms; polycythaemia vera.

GSK, Chile; GSK, NZ; GSK, Swed.; GSK, UK; Celgene, USA.
Melphalan (p.742·1) or melphalan hydrochloride (p.742·3).
Malignant neoplasms; polycythaemia vera.

IFET (ΙΦΕΤ), Gr.
Melphalan hydrochloride (p.742·3).
Breast cancer; multiple myeloma; ovarian cancer.

Alkerana *GSK, Arg.*
Melphalan (p.742·1).
Malignant neoplasms.

Alket
Note.This name is used for preparations of different composition.
Poen, Arg.
Epinastine hydrochloride (p.579·3).
Allergic conjunctivitis.

Difass, Ital.
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; phlebitis.

Alkets *Hauck, USA†; Roberts, USA†.*
Calcium carbonate (p.1714·1).
Hyperacidity.

Alkocean *Proceane, Fr.†.*
Shark-liver oil (p.2386·1).
Tonic.

Alksebor *Valeant, Hung.*
Chlorhexidine hydrochloride (p.1635·3); vitamin A (p.1971·2); tocoferil acetate (p.1992·3); dexpanthenol (p.2362·1).
Skin and scalp disorders.

Alkyloxan *Choongwae, Singapore†; Kocsel, Turk.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

All Clear *Bausch & Lomb, Hong Kong; Bausch & Lomb, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

All Pecium *Dermoteca, Port.†.*
Pyrithione zinc (p.1611·2); sulfur (p.1614·1).
Seborrhoeic dermatitis.

Allamin *Kyorin, Thai.†.*
Amino-acid preparation (p.1922·1).
Nutritional supplement.

Allanderm-T *Allan, USA.*
Trypsin (p.2405·3); Peru balsam (p.2365·3); castor oil (p.2278·1).

AllanEnzyme
Note.This name is used for preparations of different composition.
Allan, USA.
⊗ Papain (p.2362·3); urea (p.1620·2); with or without chlorophyllin copper complex sodium (p.1471·1).
Ulcers; wounds.

Allan, USA.
⊗ Papain (p.2362·3); urea (p.1620·2).
Formerly known as AllanZyme.

AllanfillEnzyme *Allan, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2); chlorophyllin copper complex (p.1471·1).
Formerly known as Allanfil.

Allapinin *Vilar, Rus.*
Lappaconitine hydrobromide (p.1323·1).
Arrhythmias.

Allavin Expectorant *CCM, Malaysia.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs and cold symptoms; rhinitis.

Allavin Plus Expectorant *CCM, Malaysia.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Allbee *Robins, USA.*
A range of vitamin preparations (p.1922·1).

Alleal *Pierre Fabre, Ital.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis.

Allecet *Cipla-Medpro, S.Afr.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Alledine *Arrow, Austral.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Alledryl *Prater, Chile.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Alledryl D *Prater, Chile.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Allegra *Aventis, Arg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, India; Aventis, Mex.; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Fexofenadine hydrochloride (p.579·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Allegra-D *Aventis, Arg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Mex.; Aventis, USA; Sanofi-Aventis, Venez.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Allegro
Note.This name is used for preparations of different composition.
Berlin-Chemie, Ger.
Frovatriptan succinate (p.622·3).
Migraine.

Trima, Israel.
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Allegron *Aspen, Austral.; King, UK.*
Nortriptyline hydrochloride (p.413·2).
Depression; nocturnal enuresis.

Allelock *Kyowa, Jpn.*
Olopatadine hydrochloride (p.586·3).
Allergic rhinitis; urticaria.

Allenik *Galen, Turk.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; motion sickness; vertigo.

Allenopar *Gerot, Austria.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Allens Chesty Cough *Allens, UK.*
Ammonium chloride (p.1551·3); tolu tincture (p.1574·2); squill tincture (p.1573·1); menthol (p.2340·1); marrubium (p.1564·1).
Coughs.

Allens Dry Tickly Cough *Allens, UK.*
Benzoin tincture (p.2394·2); ipecacuanha tincture (p.1562·3); capsicum tincture (p.2276·2); cetylpyridinium chloride (p.1635·1).
Coughs.

Allens Junior Cough *Allens, UK.*
Glycerol (p.2314·2); anhydrous citric acid (p.2284·1).
Coughs; sore throat.

Allens Pine & Honey *Allens, UK.*
Ipecacuanha (p.1562·3); liquorice (p.1740·3); pumilio pine oil (p.2376·3); squill oxymel.
Bronchitis; cold symptoms; coughs.

Allent *Ascher, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

AllePak *Everton, USA.*
Day tablets, pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2); night tablets, chlorphenamine maleate (p.571·3); hyoscine methonitrate.
Upper respiratory-tract disorders.

Aller-Aide *Rougier, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Allerax *Bangkok Lab & Cosmetic, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Allergic skin reactions; pruritus; sedative.

Allerbiocid S *Allerbio, Fr.†.*
Benzyl benzoate (p.2036·1); tannic acid (p.2394·3).
Insecticide and antifungal for bedding and upholstery.

Allercalm
Note.This name is used for preparations of different composition.
Amnol, Ital.
Zinc orotate; vitamin A (p.1922·1).
Nutritional supplement.

Actavis, UK.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allercept *Jamieson, Canad.†.*
Urtica (p.2409·3); perilla fruit.

Allercet *Micro, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Aller-Chlor *Rugby, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allercon *Parmed, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Allercreme *Carme, USA†.*
Emollient and moisturiser.

Allerdine *LBS, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Allerdrug *Med-One, Gr.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Allerdryl *Valeant, Canad.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity.

Allerest *Fisons, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Minor eye irritation.

Allerest Allergy & Sinus Relief *Heritage Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Allerest Headache Strength *Ciba, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Allerest 12 Hour Nasal *Ciba Consumer, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Allerest Maximum Strength *Ciba, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Allerest Sinus Pain Formula *Ciba, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

AllerEze
Note. A similar name is used for preparations of different composition (see below).
Alphapharm, Austral.
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Aller-Eze
Note. A similar name is used for preparations of different composition (see above).
Novartis Consumer, UK.
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Allerfen *Sella, Ital.†.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; insomnia.

Allerfre *Boots Healthcare, Neth.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Allerfrim *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Allerfrim with Codeine *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Allerg-Abak *Thea, Neth.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Allergan *Bouty, Ital.*
Diphenhydramine hydrochloride (p.577·2).
Insect bites; pruritus; sunburn.

Allergan Enzymatic *Allergan, USA.*
Papain (p.2362·3) (p.1622·2).
Cleansing solution for soft contact lenses.

Allergefon *SERP, Mon.*
Carbinoxamine maleate (p.570·2).
Hypersensitivity reactions.

Allergen *Goldline, USA.*
Benzocaine (p.1854·1); phenazone (p.116·1); glycerol (p.2314·2).
Ear pain.

Allergex *Adcock Ingram, S.Afr.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allergie-Injektopas *Pascoe, Ger.*
Homoeopathic preparation.

Allergies Relief *Homeocan, Canad.*
Homoeopathic preparation.

Allergika
Note.This name is used for preparations of different composition.
Illa, Ger.†.
Bath additive: Soya oil (p.1965·3).
Skin disorders.

Illa, Ger.†.
Cream; ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Skin disorders.

Allergin
Note.This name is used for preparations of different composition.
Propan, S.Afr.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

PP Lab, Thai.†.
Chlorphenamine maleate (p.571·3).
Hypersensitivity.

Allergo-COMOD *Croma, Austria; Ursapharm, Cz.; Ioltech, Fr.†; Ursapharm, Ger.; Ursapharm, Neth.; Ursapharm, Pol.; Ursapharm, Switz.; Biem, Turk.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Allergocrom *Ursapharm, Cz.; Ursapharm, Ger.; Ursapharm, Malaysia†; Ursapharm, Neth.†; Ursapharm, Pol.; Biem, Turk.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; vernal keratoconjunctivitis.

Allergocrom Kombi *Ursapharm, Cz.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Allergodil *Pharmadorf, Arg.; Viatris, Austria; Meda, Belg.; Grunenthal, Chile†; Meda, Cz.; Viatris, Denm.; Viatris, Fr.; Viatris, Ger.; Meda, Hung.; Viatris, Ital.; Viatris, Neth.; Viatris, Pol.; Meda, Port.; Viatris, Rus.; Viatris, Switz.; Ulagay, Turk.; Zuoz, Venez.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Allergofact *Doctum, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Allergojovis *Biomedica-Chemica, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Allergokatt *Kattwiga, Ger.*
Homoeopathic preparation.

Allergo-Loges *Loges, Ger.*
Homoeopathic preparation.

Allergopharma *ACM, Neth.*
A range of allergen extracts from pollen (p.2370·2) and house dust mite (p.2251·1) (p.2250·2).
Diagnosis of hypersensitivity.

Allergopos N *Ursapharm, Ger.*
⊗ Antazoline phosphate (p.567·1); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Allergospasmin *Viatris, Ger.*
⊗ Sodium cromoglicate (p.1136·3); reproterol hydrochloride (p.1131·1).
Obstructive airways disease.

Allergospasmine *Asta Medica, Switz.†.*
⊗ Sodium cromoglicate (p.1136·3); reproterol hydrochloride (p.1131·1).
Obstructive airways disease.

Allergospray *Viatris, Austria.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Allergostop *Biomedica-Chemica, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Allergosyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Allergotin *Cooper (Κοπερ), Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Allergoval *Kohler-Pharma, Ger.*
Sodium cromoglicate (p.1136·3).
Hypersensitivity reactions.

Allergovit
Allergopharma, Ger.; Allergopharma, Switz.
Allergen extracts (p.2250·2).
Allergen immunotherapy.

ACM, Neth.; Allergopharma, Pol.
Pollen allergens (p.2370·2) (p.2250·2).
Allergen immunotherapy; hyposensitisation.

Allergy *Parmed, USA.*
Chlorphenamine maleate (p.571·3).

Allergy Caplets *Tanta, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Allergy Drops *Bausch & Lomb, Canad.; Bausch & Lomb, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Allergy Elixir *Tanta, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Allergy Formula *Perrigo, Canad.; Vita Health, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Allergy Relief
Note. This name is used for preparations of different composition.
Brauer, Austral.
Homoeopathic preparation.
Apotex, Canad.
Cetirizine hydrochloride (p.570·3).
Unichem, UK; Zee, USA.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allergy Sinus *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Allerief *Orbis Consumer, UK.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allerin
Note. This name is used for preparations of different composition.
Medifarma, Indon.
⊗ Guaifenesin (p.1561·3); sodium citrate (p.1673·3); diphenhydramine hydrochloride (p.577·2); phenylpropanolamine hydrochloride (p.1569·3); alcohol (p.1625·2).
Cough.
United American, Singapore.
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1). Formerly contained diphenhydramine hydrochloride, guaifenesin, phenylpropanolamine hydrochloride, and sodium citrate.
Allergic rhinitis; cold symptoms; sinusitis; sore throat.
Great Eastern, Thai.; United American, Thai.
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Coughs and cold symptoms.

Allerin AH *United Laboratories, Philipp.*
Diphenhydramine hydrochloride (p.577·2).
Cough; motion sickness; rhinitis.

Allerin Reformulated *United Laboratories, Philipp.*
Diphenhydramine hydrochloride (p.577·2); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough; upper respiratory-tract inflammation.

Allerjin *Gunsa, Turk.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; motion sickness; vertigo.

Allerket *Pulitzer, Ital.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis.

Allerlux *Mediwhite, Ital.*
Liquorice (p.1740·3); calendula (p.2273·1); lappa (p.2330·3); helichrysum italicum.
Allergic disorders.

AllerMax
Note. This name is used for preparations of different composition.
Schering-Plough, Austral.†.
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis.
Pfeiffer, USA.
Diphenhydramine hydrochloride (p.577·2).
Insomnia; motion sickness; parkinsonism.

Allermed *Murdock, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Allermin *Synco, Hong Kong.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Allermine *Xixia, S.Afr.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Allernix *Rougier, Canad.*
Diphenhydramine hydrochloride (p.577·2).
Antihistamine.

Allernon *Lannacher, Austria.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Allerphed *Great Southern, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Allerphen *Malayan, Singapore†.*
Chlorphenamine maleate (p.571·3).
Hay fever; hypersensitivity reactions; insect bites; pruritus.

Allersan *Europharm, Hong Kong.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Allerset *Santa, Turk.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Allersil *Silom, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hay fever.

Allersol *Sanovel, Turk.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Allersoothe *AFT, NZ.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; premedication; sedative.

Allerta *United Laboratories, Philipp.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Aller-Tab *Silom, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hay fever.

Allertec *Polfa Warszawa, Pol.; Warsaw-Polfa, Rus.; Korean Drug, Singapore†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

AllerTek *Ratiopharm, UK.*
Cetirizine (p.571·1).
Allergic rhinitis; urticaria.

Allertyn *DHA, Hong Kong; DHA, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

AlleRx
Note. This name is used for preparations of different composition.
Adams, USA.
Suspension: Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract disorders.
Adams, USA.
Tablets: AM Tablets, pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2); PM tablets, chlorphenamine maleate (p.571·3); hyoscine methonitrate.
Cold symptoms; rhinitis; sinusitis.

Allerzil *Bruno, Ital.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Allestra *Ache, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Allevyn *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Smith & Nephew, Ger.†; Smith & Nephew, Irl.†; Smith & Nephew, Ital.; Smith & Nephew, UK.*
Hydrophilic polyurethane dressing (p.1611·1).
Ulcers; wounds.

Allfen *MCR, USA.*
Guaifenesin (p.1561·3).
Coughs.

Allfen-DM *MCR, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Alli *GSK, USA.*
Orlistat (p.2358·1).
Obesity.

Alliocaps *Madaus, Arg.*
Garlic (p.2309·2).

Alliofil *Herbapol Poznan, Pol.*
Garlic (p.2309·2); urtica (p.2409·3).
Atherosclerosis; gastrointestinal, urinary-tract, and respiratory-tract disorders.

Alliogal *Gal, Pol.†.*
Garlic (p.2309·2); evening primrose oil (p.2302·1).
Atherosclerosis; gastrointestinal disorders; hypercholesterolaemia; peripheral vascular disorders.

Alliorut *Herbapol Poznan, Pol.*
Garlic (p.2309·2); crataegus (p.2289·1); troxerutin (p.2305·1).
Hyperlipidaemias; peripheral vascular disorders.

Alliosan *Allmedica, Ger.†.*
Garlic (p.2309·2).
Atherosclerosis; hyperlipidaemias.

Allium Cepa Compose *Boiron, Fr.†.*
Homoeopathic preparation.

Allium Compuesto *Ximena Polanco, Chile.*
Homoeopathic preparation.

Allium Plus *Zeller, Switz.*
Ginkgo biloba (p.2311·1); garlic (p.2309·2).
Cerebrovascular disease.

Allixon *Leti, Venez.*
Vitamin A; vitamin D (p.1922·1).
Vitamin A and D deficiency.

All-Nite Cold Formula *Major, USA.*
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1). Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, doxylamine succinate, and paracetamol.
Coughs and cold symptoms.

Allnol *Merck, Hong Kong†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allo *ABZ, Ger.; CT, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

allo-basan *Schonenberger, Switz.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allobenz *Ana, Austria.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia; renal calculi.

Allobeta *Betapharm, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alloboxal *Hexal, Arg.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allochrysine *Solvay, Belg.†; Genopharm, Fr.*
Aurotioprol (p.26·3).
Rheumatoid arthritis.

Allo.comp. *Ratiopharm, Ger.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Allo-Efeka *Riemser, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alloferin *ICN, Austria†; Valeant, Ger.; ICN, Hong Kong†; ICN, Malaysia†; Pharmaco, S.Afr.; ICN, Singapore†.*
Alcuronium chloride (p.1901·3).
Competitive neuromuscular blocker.

Alloferine *ICN, Braz.†.*
Alcuronium chloride (p.1901·3).
Competitive neuromuscular blocker.

Allogut *Atabay, Turk.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allohex *Dankos, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Allohexal *Hexal, Austral.; Hexal, NZ.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allomaron *Aventis, Ger.†; Natrapharm, Philipp.; Aventis, S.Afr.†; Aventis, Thai.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Allonol *Ratiopharm, Fin.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; uric acid nephropathy.

Allopin *General Drugs, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Alloptrex *Pierre Fabre, Fr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Allopur *Nycomed, Norw.; Ecosol, Switz.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Allo-Puren *Alpharma-Isis, Ger.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alloril *Dexxon, Israel.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Allorin *Douglas, Austral.†; Douglas, NZ.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alloris *Sanbe, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Allosig *Fawns & McAllan, Austral.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allostad *Stada, Austria.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Allotyrol *Tyrol, Austria†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Allo-Urik *Sanli, Turk.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alloxygen *Tynor, Philipp.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Allpyral *Thomson, Austral.; Ebos, NZ†; Miles, USA.*
Range of allergen extracts (p.2250·2).
Allergen immunotherapy.

Allpyral Pure Mite *Bayer, S.Afr.*
D. pteronyssinus extracts (p.2251·1)(p.2250·2).
Hyposensitisation.

Allpyral Special Grass *Bayer, S.Afr.*
Grass pollen extracts (p.2370·2)(p.2250·2).
Hyposensitisation.

Allsan *Biomed, Switz.*
A range of vitamin preparations with or without minerals (p.1922·1).

Allstam *Biostam (Βιοσταμ), Gr.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Alltracel P *Synapse, Irl.†.*
Calcium cellulose (p.1075·1).
Haemorrhage.

Alltracel S *Synapse, Irl.†.*
Calcium cellulose (p.1075·1); chlorhexidine (p.1635·2).
Haemorrhage.

Allumag M *Camden, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Gastric hyperacidity.

Allumag MPS *Camden, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Alluna Nacht *GSK Consumer, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Allupol *Polfa Grodzisk, Pol.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allurase *Terramedic, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allurene *Schering, Austria; Schering, Neth.*
Estradiol (p.2097·2); drospirenone (p.2095·2).
Menopausal disorders; osteoporosis.

Allurit *Teofarma, Ital.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Allvoran *TAD, Ger.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Allya
Note. This name is used for preparations of different composition.
Pascoe, Ger.
Injection: Homoeopathic preparation.
Pascoe, Ger.†.
Ointment: St John's wort oil (p.423·2); camphor (p.2273·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.
Pascoe, Ger.
Tablets: Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Alma *Adcock Ingram, S.Afr.*
Peppermint oil (p.1761·2); cardamom (p.2277·1).
Carminative.

Almacon *Pyridam, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Almacone *Rugby, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Almag
Note. This name is used for preparations of different composition.
CT, Ger.; Hua, Thai.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.
Inquifave, Venez.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid.

Almagel *Atlas, Canad.; Actavis, Hung.; Balkanpharma, Rus.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid; dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Almagel A *Actavis, Hung.; Balkanpharma, Rus.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); benzocaine (p.1854·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Almagel Neo *Balkanpharma, Rus.*
Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Almagel Plus *Atlas, Canad.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Almarion *Chew, Thai.*
Theophylline (p.1140·1).
Obstructive airways disease.

Almarl *Sumitomo, Jpn.*
⊗ Arotinolol hydrochloride (p.1217·3).
Angina pectoris; hypertension; tachycardia; tremor.

Almarytm *3M, Ital.*
Flecainide acetate (p.1288·1).
Arrhythmias.

Almasal *Chew, Thai.*
⊗ Theophylline (p.1140·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Alma-Tar *Vita, Venez.†.*
Cade oil (p.1616·1).
Scalp psoriasis; seborrhoea.

Almax *Almirall, Mex.; Almirall, Spain.*
Almagate (p.1705·1).
Dyspepsia; gastric hyperacidity; hiatus hernia; oesophagitis; peptic ulcer.

Almay Protective Lip Care *Revlon, Canad.†.*
SPF 25: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Almebex Plus B_{12} *Dayton, USA.*
Vitamin B substances (p.1922·1).

Almepan *Spefar, Venez.†.*
Methyldopa (p.1334·1).
Hypertension.

Almevax *Chiron Vaccines, UK.*
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Almic *TS, Ital.*
Fish oil (p.1362·2).
Nutritional supplement.

Almide *Alcon, Fr.*
Lodoxamide trometamol (p.2334·2).
Allergic eye disorders.

Almigripe *Jaba, Port.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Almin *SAD, Denm.*
Aluminium glycinate (p.1706·2).
Gastric hyperacidity; gastro-oesophageal reflux; hyperphosphataemia in renal dysfunction; peptic ulcer.

Alminox *Nycomed, Denm.*
Aluminium glycinate (p.1706·2); magnesium oxide (p.1744·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Almiral
Medochemie, Cz.; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.†.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain; renal and biliary colic.

Medochemie, Hong Kong.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders.

Almirid *Poli, Cz.; Desitin, Ger.; Poli, Pol.*
Dihydroergocryptine mesilate (p.364·2).
Hyperprolactinaemia; lactation inhibition; migraine; parkinsonism.

Almiron *Nutricia, Thai.†.*
Infant feed (p.1922·1).
Lactase deficiency; lactose intolerance.

Almiron Pepti *Nutricia, Fin.*
Infant feed (p.1922·1).
Cow's milk and soya protein allergy.

Almodin *Nordin, Mex.*
Aesculus (p.2248·2); hamamelis (p.2318·2).
Haemorrhoids; varices.

Almogran *Almirall, Belg.; Almirall, Denm.; Leiras, Fin.; Almirall, Fr.; Almirall, Ger.; Organon, Irl.; Almirall, Ital.; Almirall, Neth.; Almirall, Norw.; Almirall, Port.; Almirall, Spain; Nycomed, Swed.; Organon, UK.*
Almotriptan malate (p.617·3).
Migraine.

Almora
Note. This name is used for preparations of different composition.
Elpen (Ελπεν), Gr.
Potassium chloride; sodium bicarbonate; sodium chloride (p.1672·2).
Oral rehydration solution.

Forest Pharmaceuticals, USA†.
Magnesium gluconate (p.1679·2).
Dietary supplement.

Almorsan *TRB, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Almotrex *Solvay, Ital.*
Almotriptan malate (p.617·3).
Migraine.

Almyrol *Lysoform, Ger.*
Guanidine derivative; alkylamine; didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Alna *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Alnagon *Zentiva, Cz.*
Aspirin (p.20·3); caffeine (p.1116·3); phenobarbital (p.492·2); codeine phosphate (p.37·2).
Pain.

Alnase *Taro, Israel.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); mepyramine maleate (p.585·2).
Cold symptoms; rhinitis; sinusitis.

Alnax *Masa, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Alnex *Pisa, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Alnok *Durascan, Denm.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; hay fever; urticaria.

Aloclair *Butler, Ger.; Forest Laboratories, UK.*
Povidone (p.2146·1).
Mouth pain.

Alocril *Allergan, Canad.; Allergan, USA.*
Nedocromil sodium (p.1127·3).
Allergic conjunctivitis.

Alodan *Gerot, Austria.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Alodont *Pfizer Sante, Fr.; Uhlmann-Eyraud, Switz.†.*
Cetylpyridinium chloride (p.1635·1); chlorobutanol (p.1639·2); eugenol (p.2301·2).
Mouth and throat disorders; mouth and throat infections.

Alodorm *Alphapharm, Austral.; Alphapharm, Thai.†; TTN, Thai.†.*
Nitrazepam (p.1011·2).
Insomnia.

Alodox *Ocusoft, USA.*
Doxycycline (p.267·1).
Bacterial infections.

Aloe Complex *Dolisos, Canad.†.*
Homoeopathic preparation.

Aloe Grande *Gordon, USA.*
Vitamin A (p.1971·2); vitamin E (p.1992·2); aloe vera (p.1588·2).
Skin disorders.

Aloe Vera Plus *GNLD, Austral.*
Aloe vera (p.1588·2); ascorbic acid; chamomile; eleutherococcus senticosis; passion flower (p.1922·1).
Digestive disorders; tonic.

Aloe Vesta *Convatec, USA.*
Emollient.

Aloebel *Fortbenton, Arg.*
⊗ Aloe vera (p.1588·2); urea (p.1620·2).

Aloelax *Knop, Chile.*
Cape aloes (p.1705·2); linseed (p.2333·3).
Constipation.

Alofedina *Coll, Spain.*
Aloes (p.1705·2); belladonna (p.2263·3); ipecacuanha (p.1562·3); nux vomica (p.2355·3); podophyllum (p.1610·2).
Formerly contained aloin, belladonna, phenolphthalein, ipecacuanha, nux vomica, and podophyllum.
Constipation.

Alofresh *Garden House, Arg.†.*
Sunflower oil (p.1970·3); parsley oil (p.2363·2).
Dietary supplement; halitosis.

Alogesia *Seid, Spain.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Aloid *Janssen-Cilag, Mex.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Alois *Apsen, Braz.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease; parkinsonism.

Alomen *Benedetti, Ital.*
Ceftezole sodium (p.235·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Alomide *Alcon, Arg.; Alcon, Austria†; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Norw.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.†; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Lodoxamide trometamol (p.2334·2).
Allergic conjunctivitis; keratitis; vernal keratoconjunctivitis.

Alonet *Pharmachemie, Singapore†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Alopam *Alpharma, Denm.; Alpharma, Fin.†; Alpharma, Norw.*
Oxazepam (p.1014·2).
Anxiety; insomnia; neuroses; restlessness.

Alopate *Wolfs, Belg.*
Zinc oxide (p.1621·2); titanium oxide (p.1617·3); kaolin (p.1738·1).
Skin disorders.

Alopek *Royal, Chile.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Aloperidin *Janssen-Cilag, Gr.*
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Huntington's chorea; psychoses; tics.

Alopexy *Pierre Fabre, Fr.; Pierre Fabre, Israel; Pierre Fabre, Neth.; Pierre Fabre, Spain; Pierre Fabre, Switz.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Alophen *Numark, Canad.; Numark, USA.*
Bisacodyl (p.1710·1).
Constipation.

Aloplastine *Wolfs, Belg.; Medix, Fr.*
Zinc oxide (p.1621·2); glycerol (p.2314·2); purified talc (p.1615·2).
Napkin rash; skin disorders; skin irritation.

Alopon *Resinag, Switz.†.*
Aluminium chlorohydrate (p.1588·3).
Anorectal disorders.

Alopresin *Sanofi-Aventis, Spain†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Alopresin Diu *Sanofi-Aventis, Spain†.*
⊗ Hydrochlorothiazide (p.1307·3); captopril (p.1239·2).
Hypertension.

Aloprim *Nabi, USA.*
Allopurinol sodium (p.553·3).
Hyperuricaemia during cancer chemotherapy.

Alor *Atley, USA.*
Hydrocodone tartrate (p.63·1); aspirin (p.20·3).
Pain.

Alora
Note. This name is used for preparations of different composition.
Pharos, Indon.
Vitamin and mineral preparation (p.1922·1).
Pre- and postnatal supplement.

Nobel, Turk.
Passion flower (p.2363·2).
Anxiety; sleep disorders.

Procter & Gamble, USA.
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency.

Alorin *Essex, Ital.†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Aloset *Recalcine, Chile†.*
Methyldopa (p.1334·1).
Carcinoid syndrome; hypertension.

Alosfar *Esfar, Port.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alosol *Aventis, Mex.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat infections.

Alostil
Note. This name is used for preparations of different composition.
Pfizer Sante, Fr.
Minoxidil (p.1342·1).
Alopecia androgenetica.

Prafa, Indon.
Amikacin sulfate (p.200·3).
Bacterial infections.

Alotec *Boehringer Ingelheim, Jpn.*
⊗ Orciprenaline sulfate (p.1129·1).

Alovell *Novell, Indon.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Alovent *Boehringer Ingelheim, Venez.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Alovir *Caber, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Alox *Andromaco, Chile†.*
Oxcarbazepine (p.490·3).
Epilepsy.

Aloxan Derma *Resinag, Israel.*
Aluminium chlorohydrate (p.1588·3).
Burns; skin disorders; skin ulceration; wounds.

Aloxi *Medicom, Cz.; Galenica, Gr.; Helsinn Birex, Hung.; Helsinn Birex, Irl.; Italfarmaco, Ital.; Helsinn Birex, Neth.; Helsinn Birex, Pol.; Maelor, UK; MGI, USA.*
Palonosetron hydrochloride (p.1759·3).
Nausea and vomiting associated with cancer chemotherapy.

Aloxid *Interbat, Indon.*
Minoxidil (p.1342·1).
Alopecia.

Aloxidil *IDI, Ital.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Alozur *Ozone, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Alpagelle *Pharmadeveloppement, Fr.*
Miristalkonium chloride (p.1653·3).
Contraceptive.

Alpara *Molex Ayus, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cough; influenza symptoms.

Alpaz *Royal, Chile.*
Zopiclone (p.1039·1).
Insomnia.

Alpenaso *Soho, Indon.*
Terfenadine (p.590·3).
Allergic rhinitis; allergic skin disorders.

Alperol *Pharmasant, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; tremor.

Alpertan *Raffo, Arg.*
Valsartan (p.1420·2).
Hypertension.

1-Alpha *Leo, Belg.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Alpha Cade *Dermoteca, Port.*
Salicylic acid (p.1612·2); cade oil (p.1616·1); cedar oil (p.2400·3).
Psoriasis; seborrhoeic dermatitis.

Alpha D3 *Sidus, Arg.; Teva, Cz.; Gerolymatos, Gr.; Teva, Hong Kong; Teva, Hung.; GSK, India; Teva, Israel; Teva, Ital.; Teva, Rus.; Teva, Singapore; Teva, Thai.; Med, Turk.; Vivax, Venez.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypoparathyroidism; neonatal hypocalcaemia; osteomalacia; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets; vitamin D deficiency.

Alpha 5 DS *Merck Medication Familiale, Fr.†.*
Glycolic acid (p.1598·1); piroctone olamine (p.1610·1); alpha hydroxy acid esters; levomenol (p.2333·3); allantoin (p.1588·1); vitamin A palmitate (p.1973·1); vitamin E acetate (p.1992·3).
Skin disorders.

Alpha Keri
Note. This name is used for preparations of different composition.
BMS, Austral.; BMS, Hong Kong; BMS, NZ; BMS, UK.
Liquid paraffin (p.2030·3); lanolin oil (p.2033·2).
Bath additive; dry skin disorders; nappy rash; pruritus.

BMS, Canad.†; Novartis, USA.
Bath oil: Liquid paraffin (p.2030·3); liquid lanolin (p.2033·2).
Dermatitis; dry, pruritic skin disorders.

BMS, USA†.
Cleansing bar: Skin cleanser.

Alpha Septol *Dermoteca, Port.*
Pyrithione zinc (p.1611·2); piroctone olamine (p.1610·1); salicylic acid (p.1612·2).
Seborrhoeic dermatitis.

Alpha Toothache Essence *Adco, S.Afr.*
Phenol (p.1656·1); clove oil (p.2285·1).
Toothache.

Alpha UV *LED, Fr.†.*
SPF 15; SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Alpha-Amoxi *Apotex, NZ.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Alpha-Amoxyclav *Alpha, NZ.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Alphabikal *Demo, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphacaine *Dentsply, Fr.; Simaport, Port.; Heck, Switz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Alphacal *Energon, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphacedre *Dermoteca, Port.*
Vitamin B substances (p.1922·1); chlorhexidine gluconate (p.1635·3); cedar oil (p.2400·3).
Scalp disorders.

Alphacin *Alphapharm, Austral.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Alphacutanee *Leurquin, Fr.†.*
Chymotrypsin (p.2281·3).
Oedema.

Alphaderm *Alliance, Irl.; Alliance, UK.*
⊗ Hydrocortisone (p.1535·2); urea (p.1620·2).
Skin disorders.

Alphadinal *Alpharma, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Alphadine
Note. This name is used for preparations of different composition.
Minerva (Μινερβα), Gr.
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Nicholas Piramal, India†.
Povidone-iodine (p.1659·2).
Bacterial and fungal infections of the skin and mucous membranes; skin disinfection.

Alphadol *Panacea, India.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypoparathyroidism; osteoporosis.

Alphadopa *Wockhardt, India.*
Methyldopa (p.1334·1).
Hypertension.

Alpha-Due *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphaflam *Winthrop, Ger.*
Thioctic acid (p.2400·2).
Diabetic polyneuropathy.

Alphagan *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Hung.†; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Malaysia; Allergan, Mex.; Allergan, NZ; Allergan, Neth.; Allergan, Norw.; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA; Allergan, Venez.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Alphahist *Apex, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic skin disorders; reduced appetite.

Alphakeptol *Dermoteca, Port.†.*
Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2); piroctone olamine (p.1610·1).
Scalp disorders.

Alpha-Lipogamma *Worwag, Ger.*
Thioctic acid (p.2400·2), meglumine thioctate (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Alpha-Lipon
Note. This name is used for preparations of different composition.
Stada, Cz.†.
Thioctic acid (p.2400·2).
Diabetic polyneuropathy; liver disorders.

Aliud, Ger.; Stada, Ger.
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Alphalox-D *Alpharma, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dicycloverine hydrochloride (p.1722·3).
Dyspepsia; gastric hyperacidity.

Alphamid *Actavis, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Alphamol *Molex Ayus, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Alphamox *Alphapharm, Austral.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Alphanate *Grifols, Hong Kong; Alpha Therapeutic, Ital.; Grifols, Malaysia; Grifols, Neth.; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, UK; Grifols, USA.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Alphanine *Grifols, Ger.; Grifols, Hong Kong; Alpha Therapeutic, Ital.; Grifols, Malaysia; Grifols, Neth.; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, UK; Grifols, USA.*
A factor IX preparation (p.1068·3).
Factor IX deficiency; haemophilia B.

Alphaparin *Grifols, UK†.*
Certoparin sodium (p.1242·3).
Venous thromboembolism prophylaxis.

Alphapen *Unipharm, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Alpha-Plus *Genepharm, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphapress *Alphapharm, Austral.*
Hydralazine hydrochloride (p.1305·3).
Hypertension.

Alphapril *Alphapharm, Austral.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Alpharegul *Arlor, Fr.*
Cucurbita oil; urtica; borage oil; soya lecithin; beeswax; zinc oxide; vitamin E; pyridoxine hydrochloride (p.1922·1).
Hair loss.

Alpharexin *Alpharma, Mex.*
Vitamin B substances; vitamin C; ferrous sulfate; zinc sulfate (p.1922·1).

Alphasidol *AG Therapy, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphastria *Zambon, Switz.*
Sodium hyaluronate (p.2320·1); vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3); dexpanthenol (p.2362·1); allantoin (p.1588·1); camphor (p.2273·2); menthol (p.2340·1).
Prevention of skin striae.

Alphatrex *Savage, USA†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

alpha-Vibolex *Rosen, Ger.*
Thioctic acid (p.2400·2).
Diabetic polyneuropathy.

Alpha-Zedex *Wockhardt, India†.*
Terfenadine (p.590·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cold symptoms; coughs.

Alphazol *Vocate, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Alphazole *Dermoteca, Port.†.*
Climbazole (p.529·3); salicylic acid (p.1612·2); cedar oil (p.2400·3).
Scalp disorders.

Alphexine *Lilly, Fr.†.*
Cefaclor (p.217·2).
Bacterial infections.

Alphosyl
Note. This name is used for preparations of different composition.
Block, Austria; GSK Sante, Fr.†; Stafford-Miller, Israel†; Meda, Swed.†; Stafford-Miller, Switz.†.
Allantoin (p.1588·1); coal tar (p.1616·2).
Psoriasis; skin disorders.

Stafford-Miller, Irl.†.
Coal tar (p.1616·2).
Scalp disorders.

GSK Consumer, Spain.
Cream; topical solution: Allantoin (p.1588·1); coal tar (p.1616·2).
Psoriasis; seborrhoeic dermatitis.

Stafford-Miller, Austral.; GSK, S.Afr.
Lotion: Allantoin (p.1588·1); coal tar (p.1616·2).
Psoriasis.

GSK, S.Afr.
Scalp application: Coal tar (p.1616·2).
Skin and scalp disorders.

Stafford-Miller, Austral.; GSK Consumer, Spain.
Shampoo: Coal tar (p.1616·2).
Scalp disorders.

Alphosyl 2 in 1 *GSK, Israel; GSK Consumer, UK.*
Coal tar (p.1616·2).
Scalp disorders.

Alphosyl HC
Note. This name is used for preparations of different composition.
Stafford-Miller, Irl.†.
⊗ Coal tar (p.1616·2); hydrocortisone (p.1535·2).
Psoriasis.

Stafford-Miller, Israel†; GSK Consumer, UK.
⊗ Allantoin (p.1588·1); coal tar (p.1616·2); hydrocortisone (p.1535·2).
Psoriasis.

Alphosyle *Balverda, Ital.†.*
Allantoin (p.1588·1); coal tar (p.1616·2).
Psoriasis.

Alpicort
Note. This name is used for preparations of different composition.
Montavit, Austria.
⊗ Prednisolone (p.1540·3); salicylic acid (p.1612·2); coal tar (p.1616·2); colloidal sulfur (p.1614·1); thymol (p.1664·3).
Scalp disorders.

Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Wolff, Pol.
⊗ Prednisolone (p.1540·3); salicylic acid (p.1612·2).
Alopecia areata; eczema; psoriasis; scalp disorders.

Alpicort E *Wolff, Pol.*
⊗ Prednisolone (p.1540·3); salicylic acid (p.1612·2); estradiol benzoate (p.2097·2).
Alopecia.

Alpicort F *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Medika, Switz.*
⊗ Prednisolone (p.1540·3); salicylic acid (p.1612·2); estradiol benzoate (p.2097·2).
Alopecia; scalp disorders.

Alpider *Velka, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Alpin *Arlex, Mex.*
Hyoscine butylbromide (p.1734·1).

Alpirex *Berman, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Alplax *Gador, Arg.*
Alprazolam (p.960·1).
Anxiety; panic attacks.

Alplax Digest *Gador, Arg.*
Alprazolam (p.960·1); sulpiride (p.1028·3).
Somatic disorders.

Alplax Net *Gador, Arg.*
Alprazolam (p.960·1); domperidone (p.1726·2); simeticone (p.1770·2).
Anxiety with gastrointestinal disorders.

Alpovex *Rivero, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Alpoxen *Alpharma, Fin.; Alpharma, Norw.†; Alpharma, Swed.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Alpralid *CTI, Israel.*
Alprazolam (p.960·1).
Anxiety; panic disorders.

Alpram *Valmor, Venez.*
Alprazolam (p.960·1).
Anxiety; depression; panic disorder.

Alpranax *YSP, Malaysia.*
Alprazolam (p.960·1).
Anxiety; depression; panic disorder.

Alprastad *Stada, Austria.*
Alprazolam (p.960·1).
Anxiety.

Alpratyrol *Tyrol, Austria†.*
Alprazolam (p.960·1).
Anxiety disorders.

Alpravecs *Marvecs, Ital.*
Alprazolam (p.960·1).
Anxiety disorders; panic disorders.

Alprax *Arrow, Austral.; Arrow, Hong Kong; Torrent, India; Torrent, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Alpraz *SMB, Belg.*
Alprazolam (p.960·1).
Anxiety; depression; panic disorder.

Alprazig *Baldacci, Ital.*
Alprazolam (p.960·1).
Anxiety disorders.

Alprazol *Casasco, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Alprazomed *Ethimed, Belg.*
Alprazolam (p.960·1).
Anxiety disorders.

Alprazomerck *Generics, Pol.*
Alprazolam (p.960·1).
Anxiety.

Alpress *Pfizer, Fr.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Alprim *Alphapharm, Austral.; Alphapharm, Malaysia; Alphapharm, Singapore; Merck, Singapore.*
Trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

Alprocontin *Modi-Mundipharma, India.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Alpron *Aldril, Philipp.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Alpronax *Merck, Port.†.*
Alprazolam (p.960·1).
Anxiety disorders.

Alprostan *Zentiva, Cz.; Zentiva, Rus.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus; peripheral vascular disorders.

Alprostapint *Gebro, Austria; Pint, Austria; Pint, Cz.; Pint, Hung.; Pint, Israel.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus; peripheral arterial occlusion.

Alprostar *Recordati, Ital.*
Alprostadil alfadex (p.2183·3).
Thromboangiitis obliterans.

Alprox *Orion, Denm.; Orion, Fin.; Orion, Irl.; Orion, Israel; Orion, Pol.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; panic disorder.

Alpurase *Biolink, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Alpuric *Socobom, Belg.*
Allopurinol (p.552·2).
Gout; renal calculi.

Alquen *GSK, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alquimid *Sanfer, Mex.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Alra *Medi-Test, Fr.†.*
A range of skin-care preparations containing aloe vera (p.1588·2) for use in oncology patients.

Alres *Elmor, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); dexchlorpheniramine maleate (p.572·1).
Influenza symptoms.

Alrex *Bausch & Lomb, Arg.; Bausch & Lomb, Braz.†; Bausch & Lomb, USA.*
⊗ Loteprednol etabonate (p.1537·3).
Allergic conjunctivitis.

Alrheumun *Teofarma, Ger.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal and joint disorders.

Alrin *Teva, Israel.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Alrinte *Ativus, Braz.*
Rosemary (p.2381·2).
Dyspepsia; liver and biliary-tract disorders.

Alrof *David, India†.*
Rofecoxib (p.121·1).
Osteoarthritis; pain; rheumatoid arthritis.

Alsart *Meyer, Venez.*
Valsartan (p.1420·2).
Hypertension.

Alsartan *Aristo, India.*
Losartan potassium (p.1326·1).
Hypertension.

Alsartan-AM *Aristo, India.*
Losartan potassium (p.1326·1); amlodipine besilate (p.1214·1).
Hypertension.

Alsartan-H *Aristo, India.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Alserine *Samakeephaesaj, Thai.†.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Alsidexten *Lemery, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Alsidrine *Alsi, Canad.†.*
Ammonium chloride (p.1551·3); cocillana (p.1554·3).

Alsimine with Vitamins A & D *Alsi, Canad.†.*
Multivitamins with calcium and iron (p.1922·1).

Alsiphene *Alsi, Canad.†.*
Paracetamol (p.108·1).

Alsirub *Alsi, Canad.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3).

Alsogil *Also, Ital.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms; pain.

Alsol
Note. This name is used for preparations of different composition.
EGIS, Hung.
Aluminium acetotartrate (p.2255·1).
Skin disorders.

Athenstaedt, Ger.
Ointment: Basic aluminium acetotartrate (p.2255·1).
Superficial wounds.

Athenstaedt, Ger.†.
Topical solution: Basic aluminium acetotartrate (p.2255·1).
Hyperhidrosis; soft-tissue injury.

Alsol N *Athenstaedt, Ger.†.*
Basic aluminium acetotartrate (p.2255·1).
Napkin rash; skin disorders; wounds.

Alsoy *Nestle, Braz.; Nestle, Canad.; Nestle, Ital.†; Nestle, Thai.†.*
Soya preparation (p.1922·1).
Cow's milk intolerance; lactose intolerance; nutritional supplement.

Alstat *David, India.*
Etamsylate (p.1064·3).
Haemorrhage; menorrhagia.

Alsucral *Orion, Fin.; Orion, Malaysia; Orion, Singapore.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Alsylax *Boehringer Ingelheim, Chile.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Altabax *GSK, USA.*
Retapamulin (p.323·2).
Impetigo.

Altace *Aventis, Canad.; King, USA; Sanofi-Aventis, Venez.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Altace Plus *Sanofi-Aventis, Venez.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Altacef *Glenmark, India.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Altacet *Lek, Pol.*
Aluminium acetotartrate (p.2255·1).
Oedema.

Altacid *Bosnalijek, Rus.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Altacite *Roussel, S.Afr.*
Hydrotalcite (p.1733·3).
Gastric hyperacidity.

Altacite Plus *Peckforton, UK.*
Hydrotalcite (p.1733·3); simeticone (p.1770·2).
These ingredients can be described by the British Approved Name Co-simalcite.
Gastrointestinal disorders.

Altaclor *CT, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Altacura Ipragocce *Alta Care, Ital.*
Chamomile (p.2279·3); hamamelis (p.2318·2); euphrasia (p.2301·3).
Eye irritation.

Altadrine
Note. This name is used for preparations of different composition.
Alta Care, Ital.
Topical gel: ⊗ Garcinia cambogia (p.2309·2); caffeine (p.1116·3); simmondsia chinensis; aesculus (p.2248·2); capsicum (p.2276·2); urea (p.1620·2); methyl nicotinate (p.85·3).
Cellulitis.

Alta Care, Ital.
Transdermal patch: Avena (p.2262·1); green tea (p.2416·1); butcher's broom (p.2270·3); garcinia cambogia (p.2309·2); lemon (p.2332·3); magnesium chloride; ananas sativa; caffeine (p.1116·3).
Slimming-aid.

Altaflora Probiotici *Alta Care, Ital.*
Lactobacillus rhamnosus; *Streptococcus thermophilus*; *Lactobacillus acidophilus*; *Lactobacillus casei* (p.2372·3).
Restoration of gastrointestinal flora.

Altan *Rottapharm, Ital.*
Promelase (p.2373·3).
Haematomas; inflammation; oedema; respiratory-system disorders.

Altargo *GSK, Cz.; GSK, UK.*
Retapamulin (p.323·2).
Bacterial skin infections; impetigo; infected wounds.

Altaryl Childrens Allergy *Altaire, USA.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Altat *Teikoku, Jpn.*
Roxatidine acetate hydrochloride (p.1769·1).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; premedication; Zollinger-Ellison syndrome.

Altea (Specie Composta) *Dynacren, Ital.†.*
Althaea (p.2253·3); thyme (p.2401·1); fennel (p.2302·3); ribwort plantain (p.2379·1); liquorice (p.1740·3); iceland moss (p.2324·1).
Herbal tea; respiratory-tract congestion.

Alteana *Sevapharma, Cz.*
A tetanus vaccine (p.2240·1).
Active immunisation.

Alteis *Menarini, Fr.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Alteisduo *Menarini, Fr.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Altemol *Andromaco, Mex.†.*
Interferon alfa-n3 (p.885·1).
Anogenital warts.

Alten *Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Singapore.*
Tretinoin (p.1618·1).
Acne.

Altenal *Rayere, Mex.*
Clotrimazole (p.530·1).
Balanitis; fungal skin infections; trichomoniasis; vulvovaginal candidiasis.

Altercor *Farmaprojects, Neth.†.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Altergen *IBSA, Ital.*
Sodium hyaluronate (p.2320·1); sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Alter-H$_2$ *Church, Mex.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Altermon *Faran, Gr.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Alterna *Abbott, Arg.*
Preparation for enteral nutrition (p.1922·1).

ALternaGEL *J&J-Merck, USA.*
Dried aluminium hydroxide gel (p.1706·2).
Hyperacidity symptoms.

Alternus *Recalcine, Chile.*
Haloperidol (p.1000·2).

Altersol *IBSA, Ital.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Altezerod *Altius, Arg.*
Tegaserod maleate (p.1776·1).

Altezym *Alter, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Althaea Complex *Blackmores, Austral.*
Maize (p.2288·1); althaea (p.2253·3); buchu (p.2269·3); bearberry (p.2263·3); *d*-alpha tocoferil acid succinate (p.1993·1); vitamin A acetate (p.1973·1).
Urinary-tract disorders.

Althagem *Gemi, Pol.*
Althaea (p.2253·3).
Respiratory-tract disorders.

Althamel *Gemi, Pol.*
Althaea (p.2253·3).
Respiratory-tract disorders.

Althea *Pond's, Philipp.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Acne and hirsutism; combined oral contraceptive; menstrual disorders.

Althrocin *Alembic, India.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Altiazem
Menarini, Cz.†.
Diltiazem resinate (p.1267·1).
Angina pectoris; hypertension; myocardial infarction.

Menarini, Hong Kong; Lusofarmaco, Ital.; Lusofarmaco, Rus.; Menarini, Thai.†.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension; myocardial infarction.

Alticort *Silesia, Chile.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Alti-CPA *Altimed, Canad.†.*
Cyproterone acetate (p.2088·2).

Altim *Sanofi-Aventis, Fr.*
⊗ Cortivazol (p.1524·3).
Corticosteroid.

Alti-MPA *Altimed, Canad.†.*
Medroxyprogesterone acetate (p.2113·1).

Altior *Pensa, Spain.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Altisben *Alter, Spain.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Altiva *Ranbaxy, Braz.; Medico Uno, Hung.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; hypersensitivity reactions; urticaria.

Altiva-D *Ranbaxy, Malaysia.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Altiver *Maver, Mex.*
Captopril (p.1239·2).
Hypertension.

Altix *Herba Studio, Pol.*
Aluminium acetotartrate (p.2255·1).
Musculoskeletal, joint, and soft-tissue injury; skin disorders.

Altizem *Nobel, Turk.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Altocel *Irex, Fr.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Altofen *Sanbe, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Altone *Pharmasant, Thai.*
⊗ Spironolactone (p.1400·1).
Heart failure; liver cirrhosis with ascites; oedema.

Altoprev *First Horizon, USA.*
Lovastatin (p.1328·2).
Formerly known as Altocor.
Hyperlipidaemias.

Altoram *Med-One, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Altosec *Pharmacare, S.Afr.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Altosone *Essex, Ital.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Altramet *Lek, Pol.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome acid aspiration.

Altraz *Alkem, India.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Altreet Ag *Coloplast, Fr.*
Sulfadiazine silver (p.337·2); carmellose sodium (p.2142·1).
Infected burns and wounds.

Altrical *Pisa, Mex.*
Calcitriol (p.1986·2).
Hypocalcaemia; hypoparathyroidism; osteoporosis; rickets.

Altrol *Gelcaps, Mex.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Altrox *Torrent, Braz.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Altruline *Pfizer, Chile; Pfizer, Mex.*
Sertraline hydrochloride (p.421·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Altuss *SIFFRA, Ital.*
Senega (p.1572·3); althaea (p.2253·3); red-poppy (p.1472·3); marrubium (p.1564·1); pinus montana (p.2376·3); eucalyptus leaf (p.2301·2); propolis (p.2373·3); carpinus betulus; thyme oil (p.2401·2).
Cough.

Alu-3 *Germania, Austria.*
Aluminium tyrosinate.
Gastrointestinal disorders; hyperphosphataemia.

Alubifar *Rottapharm, Spain.*
Almasilate (p.1705·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Alu-Cap *IFET (IΦET), Gr.; 3M, Israel; 3M, UK; 3M, USA†.*
Aluminium hydroxide (p.1706·2).
Antacid; gastric hyperacidity; hyperphosphataemia; peptic ulcer.

Alucid
Note. This name is used for preparations of different composition.
Labima, Belg.
Aluminium glycinate (p.1706·2); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence; gastric hyperacidity.

CCM, Malaysia.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; heartburn.

Alucinol *Franco-Indian, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Alucol *Sanova, Austria; Melisana, Switz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastric irritation; gastro-oesophageal reflux; peptic ulcer.

Alucol Silicona *Farmasierra, Spain.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity and flatulence.

Aluctyl *Astellas, Ital.*
Aluminium lactate (p.2255·1).
Mouth and throat disorders.

Aludal *Teva Tuteur, Arg.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Aludix *Sons, Mex.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Aludonna
Note. This name is used for preparations of different composition.
Armoxindo, Indon.
Oral suspension: Aluminium oxide (p.1585·3); magnesium oxide (p.1744·1); hyoscyamine hydrobromide (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Armoxindo, Indon.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); calcium carbonate (p.1714·1); caffeine (p.1116·3); amylase (p.2256·3); chlorphenamine maleate (p.571·3); hyoscine hydrobromide (p.1734·1).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Aludonna D *Armoxindo, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn.

Aludrox
Note. This name is used for preparations of different composition.
Riemser, Ger.; Wyeth, India; Pfizer Consumer, Irl.
Aluminium hydroxide (p.1706·2).
Dyspepsia; gastric hyperacidity; heartburn; hyperphosphataemia; peptic ulcer.

Wyeth-Ayerst, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Pfizer Consumer, UK†.
Oral liquid: Aluminium hydroxide (p.1706·2).
Dyspepsia; hyperphosphataemia.

Wyeth, Gr.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Antacid.

Wyeth, Gr.
Tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Aludrox II *Bago, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Aludrox AC *Bago, Arg.†.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity.

Aludrox Forte *Bago, Arg.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Aludrox MH *Wyeth, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity; peptic ulcer.

Aludroxil *Sanval, Braz.*
Aluminium hydroxide (p.1706·2).
Antacid.

Alugastrin *Polfa Lodz, Pol.*
Dihydroxyaluminum sodium carbonate (p.1723·3).
Gastric hyperacidity; peptic ulcer.

Alugel *Atlas, Canad.; Chefaro, Spain.*
Aluminium hydroxide (p.1706·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; gastrointestinal hyperacidity; hyperphosphataemia.

Alugel Magnesiado
Note. This name is used for preparations of different composition.
Chefaro, Spain.
Chewable tablets: Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Dyspepsia; gastrointestinal hyperacidity.

Chefaro, Spain†.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastrointestinal hyperacidity.

Alujel *Deva, Turk.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Alukon *Acupharm, S.Afr.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Alum Milk *Aventis, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastritis; peptic ulcer.

Alumag
Note. This name is used for preparations of different composition.
Plata, Arg.†; Trianon, Canad.; Teva, Israel†; Novag, Mex.; Polfa Grodzisk, Pol.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Beacons, Singapore.
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

TC Pharma-Chem, Thai.
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); kaolin (p.1738·1); atropine sulfate (p.1219·3).
Gastric hyperacidity; peptic ulcer.

Alumag D *MDI, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Gastric hyperacidity.

Alumag Plus *Beacons, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Abdominal retention; flatulence.

Alumagall *Interdelta, Switz.†.*
Dried aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); allantoin (p.1588·1).
Gastric hyperacidity.

Aluman *Corsalud, Venez.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Alumite D *Xixia, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Gastric hyperacidity.

Alumpak *Valeant, Arg.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Alupent *Boehringer Ingelheim, Austral.†; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Canad.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; German Remedies, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.†.*
⊗ Orciprenaline sulfate (p.1129·1).
Beta blocker overdosage; bradycardia; bronchospasm; digitalis intoxication; obstructive airways disease; premature labour; Stokes-Adams attacks; threatened miscarriage.

Alupent Expectorant *Boehringer Ingelheim, Irl.*
⊗ Orciprenaline sulfate (p.1129·1); bromhexine hydrochloride (p.1552·2).
Obstructive airways disease.

Alupep *Sripasit, Thai.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); kaolin (p.1738·1); atropine sulfate (p.1219·3).
Gastric hyperacidity; peptic ulcer.

Aluprex *Collins, Mex.*
Sertraline hydrochloride (p.421·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Aluprol *Rowe-Fleming, Venez.†.*
Allopurinol (p.552·2).
Hyperuricaemia.

Aluron *Ronava, Venez.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Alusal *Polfa Grodzisk, Pol.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity; hyperphosphataemia; peptic ulcer.

Alustal *Stallergenes, Ger.; Stallergenes, Ital.; Trimedal, Switz.*
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.

Alusulin *Teva, Hung.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Alu-Tab *3M, Austral.; 3M, Canad.†; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Philipp.; 3M, Singapore; 3M, USA.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity; hyperphosphataemia; peptic ulcer.

Alutan *Medika, Switz.*
Citalopram hydrobromide (p.385·3).
Depression.

Alutard
ALK, Neth.
A range of allergen extracts (p.2250·2).
Hyposensitisation.

ALK, Norw.
Allergen extracts from timothy (*Phleum pratense*) (p.2370·2) or birch (*Betula verrucosa*) (p.2250·2).
Allergen immunotherapy.

Alutard SQ *ALK, Cz.; ALK, Denm.; ALK, Fin.; Alk-Abello, Pol.; ALK, Swed.; Trimedal, Switz.*
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.

Alutop
Note. This name is used for preparations of different composition.
General Drugs, Thai.
Oral gel: Dried aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; meteorism; peptic ulcer.

General Drugs, Thai.
Tablets: Dried aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; peptic ulcer.

Alvear *SIT, Ital.*
Royal jelly (p.2382·1).
Nutritional supplement.

Alvear con Ginseng *SIT, Ital.*
Ginseng (p.2312·1); honey (p.1948·2); royal jelly (p.2382·1); myrtillus (p.2349·3).
Nutritional supplement.

Alvedon *Multicare, Philipp.; AstraZeneca, Swed.; AstraZeneca, UK.*
Paracetamol (p.108·1).
Fever; pain.

Alvedrin *Offenbach, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Alven *Wassermann, Ital.*
Diosmin (p.2304·2).
Peripheral vascular disorders.

Alvena *Diba, Mex.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract disorders.

Alvent *Farmalab, Braz.†.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Alveofact *Boehringer Ingelheim, Austria†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Pol.*
Bovine pulmonary surfactant (p.2375·3).
Neonatal respiratory distress syndrome.

Alveofen *Prieto, Arg.*
⊗ Fenoterol (p.1121·1).
Obstructive airways disease.

Alveoten *IBI, Ital.*
Neltenexine (p.1566·1).
Respiratory-tract disorders.

Alvercol *Norgine, Austral.†; Norgine, S.Afr.†.*
Sterculia (p.1772·1); alverine citrate (p.1708·1).
Hyperkinetic disorders of the colon; hypertonic constipation; irritable bowel syndrome.

Alvesco *Altana, Arg.; Altana, Austral.; Nycomed, Braz.; Grunenthal, Chile; Altana, Cz.; Altana, Gr.; Altana, Hong Kong; Altana, Hung.; Altana, Irl.; Altana, Malaysia; Altana, Mex.; Altana, Neth.; Altana, Pol.; Altana Madaus, S.Afr.; Nycomed, UK; Sepracor, USA; Grunenthal, Venez.*
⊗ Ciclesonide (p.1521·3).
Asthma; obstructive airways disease.

Alvesin *Berlin-Chemie, Ger.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Alvidina *Farcoral, Mex.†.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Alvis *Novartis Ophthalmics, Arg.†.*
Pilocarpine hydrochloride (p.1884·3).
Ocular hypertension; production of miosis.

Alvisan Neo *Leros, Cz.*
Mistletoe (p.2345·3); St John's wort (p.422·3); equisetum (p.2299·3); crataegus (p.2289·1); peppermint leaf (p.1761·2); melissa (p.2339·3); chamomile (p.2279·3).
Hypertension; pre-sclerotic states.

Alvi-Tec *Tecnofarma, Mex.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Alvityl *Solvay, Fr.; Solvay, Rus.*
Multivitamin preparation (p.1922·1).
Tonic; vitamin deficiency.

Alvium *Columbia, Mex.†.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Cold symptoms.

Alviumito *Columbia, Mex.†.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Nasal congestion.

Alviumthe *Columbia, Mex.†.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Cold symptoms.

Alviz *Pharos, Indon.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Alvo *Taisho, Jpn.*
Oxaprozin (p.105·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Alvo Nasal *Lafedar, Arg.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Alvofact *Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Neth.†.*
Bovactant (p.2375·3).
Neonatal respiratory distress syndrome.

Alvogil *Prats, Spain.*
Butyl aminobenzoate (p.1857·1); eugenol (p.2301·2); iodoform (p.1650·2).

Alvogyl
Note. This name is used for preparations of different composition.
Septodont, Cz.
Lidocaine (p.1862·3); eugenol (p.2301·2).
Dental disorders.

Septodont, Switz.
Butyl aminobenzoate (p.1857·1); iodoform (p.1650·2); eugenol (p.2301·2); spearmint oil (p.2391·3); penghawar djambi fibra.
Alveolitis; pain following tooth extraction.

Alxil *Bernofarm, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Alymphon *Iso, Ger.†.*
Homoeopathic preparation.

Alyostal
Note. This name is used for preparations of different composition.
Stallergenes, Belg.
Venoms of bee (p.2251·1) and wasp (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Stallergenes, Cz.; Stallergenes, Fr.; Stallergenes, Pol.; Trimedal, Switz.
A range of allergen extracts (p.2250·2).
Allergen immunotherapy; diagnosis of hypersensitivity; hyposensitisation.

Alyrane *Zeneca, Israel; AstraZeneca, Philipp.; Baxter Anaesthesia, UK†.*
Enflurane (p.1782·2).
General anaesthesia.

Alz *Curamed, Ger.†.*
Ginkgo biloba (p.2311·1).
Mental function impairment; peripheral vascular disorders; tinnitus; vertigo.

Alzaimax *Rontag, Arg.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Alzam *Psicofarma, Mex.; Adcock Ingram, S.Afr.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety disorders; panic disorder.

Alzar *Medika, Switz.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Alzaten *Ariston, Arg.*
Phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Hypotension.

Alzen *Tecnifar, Port.*
Quetiapine fumarate (p.1022·2).
Mania; schizophrenia.

Alzene *Alphapharm, Austral.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Alzental *Shin Poong, Singapore.*
Albendazole (p.139·2).
Worm infections.

Alzex *Ativus, Braz.*
Multivitamin preparation (p.1922·1).

Alzim *Fahrenheit, Indon.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Alzoben *Biofarma, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Alzol *Pharmasant, Thai.*
Albendazole (p.139·2).
Worm infections.

Alzolam *Sun, Rus.*
Alprazolam (p.960·1).
Anxiety.

Alzomed-F *Farcoral, Mex.†.*
Benzonatate (p.1552·1).
Coughs.

Alzyr *Alpharma, Fin.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Alzytec *Samchully, Singapore.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

AM *New Vision, Canad.†.*
Multivitamin preparation (p.1922·1).

AM Treatment *Shaklee, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Ama *Atlantic, Thai.*
Chlorpromazine hydrochloride (p.969·2); amobarbital (p.961·3).
Anxiety; psychoses; tension.

Amace-BP *Systopic, India.*
Amlodipine besilate (p.1214·1); benazepril (p.1223·3).
Hypertension.

Amacin *Asian Pharm, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amacone *Hua, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Gastric hyperacidity; meteorism; peptic ulcer.

Amadiab *Lapi, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amadol *TAD, Ger.; Viatris, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Amagesan *Ritsert, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amalium *Janssen-Cilag, Austria.*
Flunarizine hydrochloride (p.580·2).
Migraine.

Aman
Note. A similar name is used for preparations of different composition (see below).
Hexal, Ger.†.
Amantadine sulfate (p.793·1).
Drug-induced extrapyramidal disorders; influenza A; parkinsonism.

Am-An
Note. A similar name is used for preparations of different composition (see above).
Berman, Mex.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Amanda *Unison, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Amanol *Medika, Switz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Amant *Faromed, Austria.*
Amantadine sulfate (p.793·1).
Influenza A; parkinsonism.

Amanta
ABZ, Ger.
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Azupharma, Ger.†.
Amantadine hydrochloride (p.792·3) or amantadine sulfate (p.793·1).
Influenza A; parkinsonism.

Amantadol *Hexal, Cz.*
Amantadine sulfate (p.793·1).
Influenza; parkinsonism.

Amantagamma *Worwag, Ger.*
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Amantan *Altana, Belg.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Amantix *Merz, Pol.*
Amantadine sulfate (p.793·1).
Parkinsonism.

A-Mantle *Doak, USA.*
An ointment base.
Formerly known as Acid Mantle.

Amantrel *Cipla, India.*
Amantadine (p.792·3).
Herpes zoster infections; influenza A; parkinsonism.

Amaphen with Codeine *Trimen, USA.*
Codeine phosphate (p.37·2); paracetamol (p.108·1); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Amara *Weleda, S.Afr.*
Absinthium (p.2244·1); achillea (p.2245·2); cichorium; centaury (p.2279·1); gentian (p.2310·3); imperatoria ostruthium; juniper (p.2328·2); sage (p.2382·3); taraxacum (p.2395·1).
Gastrointestinal disorders.

Amara-Pascoe *Pascoe, Ger.*
Gentian (p.2310·3); cinchona bark (p.2282·3); absinthium (p.2244·1); cinnamon bark (p.2283·1).
Formerly known as Amara-Tropfen-Pascoe.
Gastrointestinal disorders.

Amara-Tropfen *Weleda, Ger.*
Absinthium (p.2244·1); cichorium intybus; centaury (p.2279·1); gentian (p.2310·3); imperatoria; juniper (p.2328·2); achillea (p.2245·2); sage (p.2382·3); taraxacum (p.2395·1).
Gastrointestinal disorders.

Amarel *Sanofi-Aventis, Fr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amargozin *Pascual, Philipp.*
Karela.
Food supplement for blood sugar management.

Amaro Medicinale *Giuliani, Ital.*
Rhubarb (p.1768·3); cascara (p.1715·2); gentian (p.2310·3); boldo (p.2267·2).
Appetite loss; constipation; digestive disorders.

Amarosal *Herbapol Wroclaw, Pol.*
Achillea (p.2245·2); fennel (p.2302·3); melissa (p.2339·3); marrubium (p.1564·1).
Dyspepsia; meteorism; reduced appetite.

Amarwin *Winthrop, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amaryl *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Ger.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amarylle *Sanofi-Aventis, Belg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amasulin *Takeda, Jpn.*
Carumonam sodium (p.217·1).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Amatine *Shire, Canad.*
⊗ Midodrine hydrochloride (p.1341·1).
Orthostatic hypotension.

Amatol *Liferpal, Mex.*
Mebendazole (p.148·3).
Worm infections.

Amavio *Altana, Gr.*
⊗ Ciclesonide (p.1521·3).
Asthma.

Ambacamp *Pharmacia, Ger.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Ambamida *Sintesina, Arg.*
Erythromycin (p.269·2).
Bacterial infections.

Ambaxino *Pharmacia, Spain†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Ambe 12 *Merckle, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Amben *Medochemie, Hong Kong.*
Cefadroxil (p.218·1).
Bacterial infections.

Ambenat *Ratiopharm, Austria.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); heparin sodium (p.1301·2).
Muscle, nerve, and joint pain.

Ambene
Note. This name is used for preparations of different composition.
Ratiopharm, Austria.
⊗ Ampoule A, phenylbutazone sodium (p.117·1); sodium salamidacetate (p.121·2); dexamethasone (p.1526·1); ampoule B, cyanocobalamin (p.1980·2). Lidocaine hydrochloride (p.1862·3) is included in both ampoules to alleviate the pain of injection.
Arthritis; degenerative spinal disorders; neuralgias; neuritis.

Merckle, Ger.
Phenylbutazone (p.117·1) or phenylbutazone sodium (p.117·1).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Ankylosing spondylitis; gout; rheumatoid arthritis.

Merckle, Rus.
⊗ Solution A: phenylbutazone (p.117·1); sodium salamidacetate (p.121·2); dexamethasone (p.1526·1); Solution B: cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to reduce the pain of injection.
Gout; musculoskeletal and joint disorders; neuralgia; neuritis.

Ambene Comp *Merckle, Ger.†.*
Ampoule 1, phenylbutazone sodium (p.117·1); ampoule 2, cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in each ampoule to alleviate the pain of injection.
Gout; musculoskeletal and joint-disorders.

Ambene N
Note. This name is used for preparations of different composition.
Merckle, Ger.
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Ratiopharm, Austria.
Suppositories: Phenylbutazone (p.117·1); cyanocobalamin (p.1980·2).
Gout; musculoskeletal, joint, soft-tissue, and periarticular disorders; neuritis; superficial thrombophlebitis.

Ratiopharm, Austria.
Tablets: Phenylbutazone (p.117·1); thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2).
Aluminium glycinate (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; musculoskeletal, joint, soft-tissue, and periarticular disorders; neuritis; superficial thrombophlebitis.

Ambenyl Cough Syrup *Forest Pharmaceuticals, USA.*
Codeine phosphate (p.37·2); bromazine hydrochloride (p.569·1).
Allergic upper respiratory symptoms; coughs and cold symptoms.

Ambenyl-D *Forest Pharmaceuticals, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Ambese *Biotech, Venez.*
Secnidazole (p.846·3).
Protozoal infections.

Ambeven *Medikon, Indon.*
Graptophyllum pictum; sophora japonica; rubia cordifolia; coleus atropurpureus; burnet (p.2270·3); kaempferia angustifolia; curcuma heyneana.
Haemorrhoids.

Ambeven Plus *Medikon, Indon.*
Graptophyllum pictum; troxerutin (p.2305·1).
Haemorrhoids.

Ambex *Walmark, Cz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambezetal *Cimed, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

Ambi 10
Note. This name is used for preparations of different composition.
Kiwi, USA.
Cream: Benzoyl peroxide (p.1590·2).
Acne.

Kiwi, USA.
Soap: Triclosan (p.1665·2).

AMBI 60/580 *AMBI, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

AMBI 60/580/30 *AMBI, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; respiratory-tract congestion.

AMBI 1000/5 *AMBI, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cough.

AMBI 1000/55 *AMBI, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Ambidrin *Collins, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Ambien *Sanofi-Aventis, Hung.; Sanofi, USA.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Ambilan
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Orion, Fin.
Emollient.

Ambilan Bid *Laboratorios Chile, Chile.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ambiopi *Mersifarma, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ambiosol *Solfran, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Ambirix *GSK, Cz.; GSK, Neth.; GSK, Port.; GSK, Swed.†; GSK, UK.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p.2217·1).
Active immunisation.

AmBisome *Gador, Arg.; Gilead, Austral.; Fresenius Kabi, Austria; UCB, Belg.; United Medical, Braz.†; Astellas, Canad.; Gilead, Denm.; Orphan, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hong Kong; Gilead, Hung.; Gilead, Irl.; Nexstar, Israel; Gilead, Ital.; Astellas, Jpn; Gilead, NZ; Gilead, Neth.; Gilead, Norw.; Gilead, Pol.; Gilead, Port.; Gilead, Rus.; Key Oncologics, S.Afr.; Gilead, Singapore; Gilead, Spain; Swedish Orphan, Swed.; Fresenius Kabi, Switz.; Gilead, Thai.†; Er-Kim, Turk.; Gilead, UK; Fujisawa, USA.*
Liposomal amphotericin B (p.523·2) (p.523·2).
Fungal infections; leishmaniasis.

Ambistryn-S *Sarabhai Piramal, India.*
Streptomycin sulfate (p.333·3).
Tuberculosis.

Ambiz *Unichem, India.*
Zolpidem (p.1038·2).
Insomnia.

Ambodil-C *Arlex, Mex.*
⊗ Ambroxol (p.1550·3); clenbuterol (p.1120·1).
Coughs.

Amboneural *Arcana, Austria.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Amboral *Remek, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Ambotetra *Janssen-Cilag, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Ambotonin *Ebewe, Austria.*
Proteolytic peptide from porcine brain (Cerebrolysin) (p.2337·3).
Alzheimer's disease; cerebral disorders.

Ambra Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Ambra Oligoplex *Madaus, Arg.*
Mineral preparation (p.1922·1).

Ambrace *APT, Hong Kong.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Ambramicina *Scharper, Ital.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Ambra-Sinto T *Medley, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Ambre Solaire *Garnier, UK.*
Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Ambredin *Solco, Austria.*
⊗ Theophylline (p.1140·1); aceverine hydrochloride; octodrine phosphate (p.1361·1).
Obstructive airways disease.

Ambreks *Nobel, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambrexin *Ivax, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Ambril *Merck, Arg.; Desma, Ger.; Merck, Indon.; Merck, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambrix *GSK, UK.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p.2217·1).
Active immunisation.

Ambrizol *Biofarma, Braz.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambro *ABZ, Ger.; Hemopharm, Ger.; Hexal, Pol.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambrobene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ambrobeta *Betapharm, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambrobion *Medicus, Gr.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Ambroclar *Schering-Plough, Venez.*
Loratadine (p.583·3); ambroxol (p.1550·3).

Ambrodil
Note. This name is used for preparations of different composition.
Aristo, India.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Farmoz, Port.
Zidovudine (p.913·3).
HIV infection.

Ambrodil Plus *Aristo, India.*
Ambroxol (p.1550·3); guaifenesin (p.1561·3); phenylpropanolamine (p.1569·2); chlorphenamine maleate (p.571·3); menthol (p.2340·1).
Bronchitis; cold symptoms; rhinitis; sinusitis.

Ambrodil-S *Aristo, India.*
⊗ Ambroxol (p.1550·3); salbutamol (p.1131·2).
Asthma; smokers' cough.

Ambrodoc *Docpharm, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambrodoxy *Hexal, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections with increased or viscous mucus.

Ambrofur *Ivax, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambrohexal
Hexal, Austria; Hexal, Ger.; Sandoz, Hung.; Hexal, Rus.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Hexal, Pol.
Ambroxol (p.1550·3) or ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambroinfant *Rubiepharm, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambroksol *Altana, Pol.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambrol
Brasterapica, Braz.†.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Shiwa, Thai.†.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ambrolan *Lannacher, Austria.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Ambrolex *GSK, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Ambrolitic *Chiesi, Spain.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Ambrolos *Hexal, Austria†; Hexal, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders; respiratory-tract disorders with viscous mucus.

Ambrolytic *Samakeephaesaj, Thai.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ambromucil *Malesci, Ital.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Ambromuco *Cafar, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambromuco Compositum *Cafar, Venez.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Ambromyc *Farmedia, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Ambronorm *Genericon, Austria.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambropp *Dermapharm, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with increased or viscous mucus.

Ambro-Puren *Alpharma-Isis, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ambrosan *ProMed, Cz.; ProMed, Pol.; Promed, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambrosil *Globo, Braz.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Ambrosol
Pliva Krakow, Pol.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Pliva, Rus.
Ambroxol hydrochloride (p.1550·3).

Ambrospray *Medicom, Cz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambroten *Marjan, Braz.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Ambrotos *Recalcine, Chile.*
Ambroxol hydrochloride (p.1550·3); ammonium citrate (p.2256·3).
Respiratory-tract disorders.

Ambrotus *Epifarma, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Ambrox
Sinterapico, Braz.†.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

TNP, Thai.†; SM, Venez.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ambroxan *M & H, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Ambroxol AL comp *Aliud, Ger.*
Ambroxol hydrochloride (p.1550·3); doxycycline hyclate (p.267·1).
Respiratory-tract infections.

Ambroxol comp *Ratiopharm, Ger.*
Ambroxol hydrochloride (p.1550·3); doxycycline hyclate (p.267·1).
Respiratory-tract infections.

Ambufen *Macrophar, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ambulase *Grunenthal, Pol.; Grunenthal, Pol.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Amcef *Antibioticos, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Amchafibrin *Rottapharm, Spain.*
Tranexamic acid (p.1080·3).
Haemorrhage; hereditary angioedema.

Amciderm *Hermal, Ger.; Pharmasant, Thai.*
⊗ Amcinonide (p.1516·2).
Skin disorders.

Amcidil *Macrophar, Thai.*
Dicloxacillin (p.265·2).
Gram-positive bacterial infections.

Amcillin
Actavis, Indon.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Dumex-Alpharma, Thai.†.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Amcin *Cadila, India.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amcinafal *Relyo, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Amclo *Nicholas Piramal, India†.*
Amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Amco *Polipharm, Thai.*
Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Amcof *Cipla, India.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol (p.1131·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Amcold *Cipla, India.*
Cetirizine hydrochloride (p.570·3); ambroxol (p.1550·3).
Cold symptoms.

Amcopan *Macrophar, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Amcopan Plus *Macrophar, Thai.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm and pain.

Amcoral *Meiji, Jpn†.*
Amrinone (p.1215·1).
Heart failure.

Amcort
Note. This name is used for preparations of different composition.
Taro, Canad.
⊗ Amcinonide (p.1516·2).
Skin disorders.

Keene, USA†.
⊗ Triamcinolone diacetate (p.1544·3).
Corticosteroid.

Amc-Puren *Alpharma-Isis, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amdarone *Berlin Pharm, Thai.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amdepin *Cadila, India.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amdepin-AT *Cadila, India.*
⊗ Amlodipine besilate (p.1214·1); atenolol (p.1217·3).
Angina pectoris; hypertension.

Amdipin *Labomed, Chile.*
Amlodipine besilate (p.1214·1).
Hypertension; ischaemic heart disease.

Amdixal *Sandoz, Indon.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amdox-Puren *Alpharma-Isis, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections with viscous mucus.

Amebamagma *Wyeth, India.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Ameban
Note. This name is used for preparations of different composition.
Parggon, Mex.
Oral suspension: Diiodohydroxyquinoline (p.832·1); kaolin (p.1738·1); pectin (p.2145·2).
Amoebiasis.

Parggon, Mex.
Tablets: Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Amebil *Lafit, Braz.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Ameblin *Degorts, Mex.*
Metronidazole benzoate (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Amebyl *Offenbach, Mex.*
Metronidazole (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis; bacterial infections; giardiasis.

Amebysol *Rayere, Mex.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Ameciron *Am-Europharma, Philipp.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid supplement; iron-deficiency anaemia.

Amecladin *Am-Europharma, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Ameclina *Offenbach, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amedran *Farmedia, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Amefin *Pfizer, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Amefur *Ivax, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Ameket *SM, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Amekrin *Pfizer, Denm.; Pfizer, Fin.†; Pfizer, Swed.*
Amsacrine (p.681·1).
Acute leukaemias.

Amelox *Square, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amen *Carnrick, USA†.*
Medroxyprogesterone acetate (p.2113·1).
Abnormal uterine bleeding; secondary amenorrhoea.

Amender *Serral, Mex.*
Methyldopa (p.1334·1).
Hypertension.

Amenicil *Phoenix, Arg.*
St John's wort (p.422·3).
Depression.

Amenite A *Amenite, Arg.†.*
Vitamin A (p.1971·2).
Skin disorders.

Amenite Cap *Amenite, Arg.†.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Amenite E *Amenite, Arg.†*
Collagen (p.2286·1); elastin (p.2286·1).
Skin disorders.

Amenite Plus *Amenite, Arg.†*
Wheat germ (p.2415·1); collagen (p.2286·1).
Hair disorders.

Amenopam *Barrenne, Braz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Amenox *Sanofi Synthelabo, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Amerge *GSK, Canad.; Glaxo Wellcome, USA.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Americaine *Novartis Consumer, USA†.*
Benzocaine (p.1854·1).
Anorectal disorders.

Americaine Anesthetic *Celltech, USA†.*
Benzocaine (p.1854·1).
Local anaesthesia; lubrication.

Americaine First Aid *Fisons, USA†.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1).
Skin disorders.

Americaine Otic *Celltech, USA†.*
Benzocaine (p.1854·1).
Pain and pruritus in otitis.

Americet *MCR, USA.*
Paracetamol (p.108·1); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Ameride *BMS, Spain.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Amerifed *AMBI, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).

Amerigel
Note. This name is used for preparations of different composition.
Amerx, USA.
Lotion: Oak (p.2355·3).
Nappy rash.

Amerx, USA.
Ointment: Oak bark (p.2355·3); meadowsweet (p.2338·1); zinc acetate (p.1999·1).
Skin disorders.

Amerituss AD *AMBI, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).

Amermycin *Unison, Hong Kong; Unison, Thai.*
Doxycycline (p.267·1).
Bacterial infections.

Amerol *Tempo Scan Pacific, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Amersan *Austroplant, Austria; Austroplant, Cz.*
Agrimony herb (p.2249·2); achillea (p.2245·2); peppermint oil (p.1761·2); rose fruit (p.2381·2); berberis; black currant (p.2267·1); myrtillus (p.2349·3).
Digestive disorders; liver and biliary tract disorders.

Amerscan DMSA *Nycomed, Cz.†; Amersham, Neth.†; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) succimer.
Radionuclide imaging of the kidney.

Amerscan Hepatate *GE, Cz.; GE Healthcare, Neth.; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) colloidal tin.
Radionuclide imaging of the liver and spleen.

Amerscan Medronate *GE, Cz.; GE Healthcare, Neth.; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) medronate.
Bone scintigraphy.

Amerscan Pentetate *Nycomed, Cz.†; Amersham, Neth.†; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) pentetate.
Assessment of renal function; radionuclide imaging of the brain, heart, and lungs; studies of gastro-oesophageal reflux and gastric emptying.

Amerscan Pulmonate *Nycomed, Cz.†; Nycomed Amersham, UK.*
⊗ Technetium-99m (p.2055·3) labelled albumin macroaggregate.
Radionuclide imaging of the lung.

Amerscan Stannous *GE, Cz.; GE Healthcare, Neth.; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) stannous medronate.
Red blood cell labelling for blood pool scintigraphy.

Amertec *Nycomed, Cz.†; Nycomed Amersham, UK.*
Technetium-99m (p.2055·3) as sodium pertechnetate.
Radionuclide imaging.

Amertil *Biofarm, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Ameryl *Medi-Rx, Philipp.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis.

Amet *IFA, Mex.*
Desiccated thyroid (p.2177·1).
Hypothyroidism.

A-Methapred
Abbott, Israel†.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Hospira, USA.
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Ametic
Note. A similar name is used for preparations of different composition (see below).
Garec, S.Afr.†.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Ametik
Note. A similar name is used for preparations of different composition (see above).
Kurtsan, Turk.
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Ametop
Smith & Nephew, Canad.
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Smith & Nephew, Hong Kong; Smith & Nephew, Irl.†; Smith & Nephew, NZ†; Smith & Nephew Healthcare, UK.
Tetracaine (p.1871·2).
Local anaesthesia.

Ametricid *Medix, Mex.†.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Ametycine *Sanofi-Aventis, Fr.; Biosyn, Ger.*
Mitomycin (p.752·1).
Malignant neoplasms.

Ameu
Lichtwer, Ger.
Marine fish oil (p.1362·2).
Hyperlipidaemias.

Democal, Switz.†.
Omega-3 triglycerides (p.1362·1).
Hyperlipidaemias.

Ameustyn *Am-Europharma, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with excess mucus.

Amevive *Raffo, Arg.; Biogen, Canad.; Biogen, Israel; Biogen Dompe, Switz.; Biogen, USA.*
Alefacept (p.1587·3).
Psoriasis.

Amfamox *MSD, Austral.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Amfobase *Herba Studio, Pol.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Barrier preparation; skin disorders.

Amfostat *BMS, Arg.†; BMS, Mex.*
Amphotericin B (p.523·2).
Fungal infections; leishmaniasis.

Amgenal Cough *Goldline, USA.*
Bromazine hydrochloride (p.569·1); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Amgrip *Collins, Mex.*
Caffeine (p.1116·3); dextromethorphan (p.1555·2); phenylephrine (p.1568·1); chlorphenamine (p.572·2); moroxydine hydrochloride (p.898·2).
Cold and influenza symptoms.

Amiada *Intendis, Ger.*
Terbinafine hydrochloride (p.546·3).
Fungal nail and skin infections.

Amias *Eureco, Neth.; Takeda, UK.*
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension.

Amibriz *Janssen-Cilag, Mex.†.*
Mebendazole (p.148·3); quinfamide (p.846·2).
Amoebiasis; worm infections.

Amic *Jaba Recordati, Port.*
Amikacin (p.200·2).
Bacterial infections.

Amicacil *Teuto, Braz.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amicagel *Med-One, Gr.†.*
Amikacin (p.200·2).
Bacterial skin infections.

Amicalin *Royton, Braz.†.*
Amikacin (p.200·2).
Bacterial infections.

Amicaliq *Tanabe, Jpn†.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Amicar *Wyeth, Austral.†; Wyeth-Ayerst, Canad.†; Wyeth, Mex.†; Wyeth, NZ†; Xanodyne, USA.*
Aminocaproic acid (p.1053·2).
Fibrinolysis; haemorrhage.

Amicasil *Phoinix Pharm (Φοινιξ Φαρμ), Gr.; Pharmatex, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amicets *Elmor, Venez.*
Benzydamine hydrochloride (p.27·3); menthol (p.2340·1); thymol (p.1664·3).
Mouth and throat disorders.

Amicic *Novartis, Fr.†.*
Amino-acid preparation (p.1922·1).
Corneal ulcers.

Amicil *Unipharm, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Amicilon *Ariston, Braz.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amicin *Biochem, India.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amicina *Kener, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amicip *Cipla, India.*
Amikacin (p.200·2).
Bacterial infections.

Amicla *Erfa, Belg.*
⊗ Amcinonide (p.1516·2).
Skin disorders.

Amiclair *Abatron, UK.*
Enzymatic contact lens cleanser (p.1622·2).

Amiclaran *Zentiva, Cz.*
⊗ Amiloride hydrochloride (p.1209·2).
Hypertension; liver cirrhosis with ascites; oedema.

Amiclav *Ashbourne, UK†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
These ingredients can be described by the British Approved Name Co-amoxiclav.
Bacterial infections.

Amicloton *Zentiva, Cz.*
⊗ Amiloride hydrochloride (p.1209·2); chlortalidone (p.1243·3).
Hypertension.

Amico *SIT, Ital.*
Amino-acid preparation with cobamamide (p.1922·1).
Tonic.

Amicof *Union Drug, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Amico-L *TO-Chemicals, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Amicor *Samarth, India.*
Amrinone lactate (p.1215·1).
Heart failure.

Amicosol *Ecosol, Switz.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amicrobin *Quimifar, Spain.*
Norfloxacin (p.309·2).
Genito-urinary tract infections.

Amidalin *Hexal, Braz.†.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Amidarone 200 *TO-Chemicals, Thai.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amidate *Hospira, USA.*
Etomidate (p.1783·3).
General anaesthesia.

Amidiaz *Richmond, Arg.*
⊗ Morphine (p.86·3).
Pain.

Amidolite *Braun, Ital.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Hypovolaemia; shock.

Amidona *Grunenthal, Chile†.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal; pain.

Amidrin *Fardi, Spain.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; sinus congestion.

Amidrox *Crinos, Ital.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; multiple myeloma; osteolytic metastases in breast cancer.

Amifarin *Wandel, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Amifen *Meyer, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Amigdagen *Prodotti, Braz.*
Neomycin sulfate (p.305·1); tyrothricin (p.358·2); benzocaine (p.1854·1); menthol (p.2340·1).
Mouth and throat disorders.

Amigdalol *Delta, Braz.*
Tyrothricin (p.358·2); cetrimonium bromide (p.1635·1); vitamin C (p.1983·3); lidocaine (p.1862·3).
Mouth and throat disorders.

Amigdamicin *Sedabel, Braz.†.*
Neomycin sulfate (p.305·1); tyrothricin (p.358·2); benzocaine (p.1854·1); menthol (p.2340·1).
Mouth and throat disorders.

Amigdobis *Chinoin, Mex.*
Bismuth ethylhexanoate.
Sore throat.

Amigesic *Amide, USA.*
Salsalate (p.122·1).
Fever; inflammation; pain.

Amignul *Almirall, Port.; Uriach, Spain.*
Almotriptan malate (p.617·3).
Migraine.

Amigrenin *Veropharm, Rus.*
Sumatriptan succinate (p.625·2).
Migraine.

Ami-Hydrotride *CCM, Malaysia.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amik *Farmigea, Ital.*
Amikacin sulfate (p.200·3).
Skin infections.

Amikacide *United American, Philipp.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikafur *Ivax, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikal *Gea, Denm.†.*
⊗ Amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Amikalem *Lemery, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikan *Anfarm, Gr.; SoSe, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikasol *Samakeephaesaj, Thai.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikasons *Sons, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikavax *Vivax, Venez.*
Amikacin (p.200·2).
Bacterial infections.

Amikavi *Mavi, Mex.*
Amikacin (p.200·2).
Bacterial infections.

Amikayect *Grossman, Mex.; Novapharma, Venez.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amiketem *Ulagay, Turk.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Amikin *BMS, Austral.; BMS, Canad.†; BMS, Cz.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Philipp.; BMS, Pol.; BMS, S.Afr.; BMS, Singapore; BMS, Switz.; BMS, Thai.; BMS, UK; Apothecon, USA.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amiklin *BMS, Fr.†; BMS, Turk.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amikozit *Eczacibasi, Cz.†; Eczacibasi, Rus.; Eczacibasi, Turk.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amilamont *Rosemont, UK.*
⊗ Amiloride hydrochloride (p.1209·2).
Heart failure; hepatic cirrhosis with ascites; hypertension.

Amilande *Sanofi Synthelabo, Spain†.*
Amisulpride (p.961·1).
Schizophrenia.

Amilco *OBA, Denm.; Ivax, Hong Kong†; Ivax, Irl.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hepatic cirrhosis with ascites; hypertension; oedema.

Amil-Co *Ivax, UK.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-amilozide.
Ascites; heart failure; hepatic cirrhosis; hypertension.

Amilene *Tecnofarma, Chile.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Amilin *Hua, Thai.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Amilitrap *Dosa, Arg.*
Lamivudine (p.895·1).

Amilo-basan *Schonenberger, Switz.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Amiloclor *Klonal, Arg.†.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Amilocomp beta *Betapharm, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amiloferm *Nordic, Swed.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Amilopil *Cifarma, Braz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amiloral/HCT *Aliud, Austria.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; liver cirrhosis with ascites; oedema.

Amiloretic *Pharmacare, S.Afr.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amiloretik *Hexal, Austria; Hexal, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Amilorid comp *Genericon, Austria; CT, Ger.; Ratiopharm, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; liver cirrhosis with ascites; oedema.

Amilorid Comp *BMS, Hung.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; liver cirrhosis; oedema.

Amiloride Composto *Ratiopharm, Port.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).

Amiloride/HCTZ *Helvepharm, Switz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Amilorid/HCT *Aliud, Cz.; Aliud, Ger.; Sandoz, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amilostad *Stada, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amilostad HCT *Stada, Austria.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Amilozid *CT, Ger.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amilozid-B *Teva, Hung.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; liver cirrhosis with ascites; oedema.

Amimox *AstraZeneca, Swed.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections; peptic ulcer associated with Helicobacter pylori.

Amin 21 K *Italfarmacia, Ital.*
Amino-acid preparation with potassium (p.1922·1).
Nutritional supplement.

Amin-Aid *R&D, USA.*
Preparation for enteral nutrition in renal failure (p.1922·1).

Aminazin *Akrikhin, Rus.*
Chlorpromazine hydrochloride (p.969·2).

Amindan *Desitin, Ger.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Aminefron *Dexa, Indon.*
Amino acids (p.1922·1).
Dietary supplement in renal failure.

Aminess
Pharmacia, Hong Kong†; Recip, Norw.; Recip, Swed.; Ilsan, Turk.
Amino-acid preparation (p.1922·1).
Dietary supplement in renal impairment.

Clintec, USA.
Amino-acid infusion (p.1922·1).
parenteral nutrition in renal impairment.

Aminess-N *Recip, Fin.; Recip, Neth.*
Amino-acid preparation (p.1922·1).
Dietary supplement.

Amineurin *Hexal, Ger.*
Amitriptyline hydrochloride (p.376·1).
Depression; pain.

Amino *Natural Life, Arg.*
Amino-acid preparation (p.1922·1).
Dietary supplement.

Amino 3 *Fiori, Ital.*
Amino-acid preparation (p.1922·1).

Aminobrane *More, Philipp.*
A multivitamin, amino-acid, and mineral preparation (p.1922·1).

Aminocardol *Novartis, Turk.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Amino-Cerv *Milex, Canad.; Cooper, USA.*
⊗ Cystine (p.1937·1); inositol (p.2325·2); methionine (p.1450·1); sodium propionate (p.545·3); urea (p.1620·2).
Cervicitis; post cauterisation; post conisation; post cryosurgery; postpartum cervical tears.

Aminocid *Faria, Braz.†.*
Dipyrone (p.49·2); thiamine (p.1976·3); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Neuritis.

Aminocina *Biochimico, Braz.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Aminocont *Mundipharma, Fin.*
Aminophylline hydrate (p.1114·3).
Obstructive airways disease.

Aminodrip *Wockhardt, India.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Aminoefedrison *Rhein, Mex.*
Theophylline (p.1140·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Aminofilin *Phoenix, Arg.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Aminofluid *Otsuka, Jpn.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminofusin Hepar *Baxter, Ger.; Kalbe, Indon.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition in liver disease.

Aminofusin L *Kalbe, Indon.*
Amino-acid, carbohydrate, vitamin, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminofusin N *Baxter, Ger.†.*
Amino-acid, xylitol, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminofusin Paed *Kalbe, Indon.*
Amino-acid, vitamin, and electrolyte infusion (p.1922·1).
Parenteral nutrition in neonates and infants.

Aminofusin 10% Plus *Baxter, Ger.†.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminogran *UCB, Austral.; UCB, Irl.; Euromed, Ital.; Pharmabroker, NZ; UCB, Swed.; UCB, UK†.*
Food for special diets (p.1922·1).
Phenylketonuria.

Aminogran Mineral Mixture *UCB, Austral.; UCB, Irl.†.*
Mineral preparation (p.1922·1).
Mineral supplement; phenylketonuria (in conjunction with Aminogran).

Aminoima *IMA, Braz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Aminoleban *Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Philipp.; Thai Otsuka, Thai.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in hepatic encephalopathy and liver disorders.

Aminoleban EN *Otsuka, Hong Kong; Otsuka, Jpn.*
Preparation for enteral nutrition (p.1922·1).
Hepatic encephalopathy; liver failure.

Aminoleban Oral *Otsuka, Indon.; Otsuka, Philipp.; Thai Otsuka, Thai.*
Preparation for enteral nutrition (p.1922·1).
Formerly known as Aminoleban EN in *Thai*.
Hepatic encephalopathy; liver failure.

Aminoliv *Teuto, Braz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Aminomal
Note.This name is used for preparations of different composition.
Malesci, Ital.
Delayed-release tablets; injection; suppositories; tablets: Aminophylline (p.1114·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection; lidocaine (p.1862·3) is also included in the suppositories.
Obstructive airways disease.

Malesci, Ital.
Elixir: Theophylline (p.1140·1).
Obstructive airways disease.

Aminomel *Baxter, Pol.*
A range of amino-acid infusions with or without electrolytes (p.1922·1).
Parenteral nutrition.

Amino-Mel G *Fresenius Kabi, Austria; Leopold, Cz.†; Fresenius Kabi, Hung.†.*
Amino-acid, electrolyte, and glucose infusion (p.1922·1).
Parenteral nutrition.

Amino-Mel hepa *Fresenius Kabi, Austria.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition in liver disease.

Amino-Mel nephro *Fresenius Kabi, Austria.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal disease.

Amino-Mel Nephro *Fresenius Kabi, Cz.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal disease.

Aminomel nephro *Baxter, Ger.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Amino-Min-D *Tyson, USA.*
Calcium with vitamin D and minerals (p.1922·1).
Calcium deficiency; dietary supplement.

Aminomix *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.†; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.*
A range of amino-acid, carbohydrate, and electrolyte infusions (p.1922·1).
Parenteral nutrition.

Aminomux *Gador, Arg.; Pasteur, Chile; Leti, Venez.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolysis of malignancy; osteoporosis; Paget's disease of bone.

Amino-Opti-C *Tyson, USA.*
Lemon bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3); vitamin C (p.1983·3); rose hips (p.2381·2).
Capillary bleeding.

Aminopad *Fresenius Kabi, Austria; Baxter, Ger.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Aminopan *UCB, Ger.†.*
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage; postoperative pancreatic disorders.

Aminoplasmal *Braun, Arg.; Braun, Austria; Braun, Chile; Braun, Cz.; Braun, Denm.; Braun, Fin.; Braun, Ger.; Bioser (Βιοσερ), Gr.; Braun, Hong Kong; Braun, Hung.; Braun, Indon.; Braun, Israel; Braun Melsungen, Ital.; Braun, Neth.; Braun, Pol.; Braun, Port.; Braun, Singapore†; Braun, Spain; Braun, Swed.†; Braun, Thai.; Braun, Turk.; Braun, UK.*
A range of amino-acid infusions with or without electrolytes (p.1922·1).
Parenteral nutrition.

Aminoplex *Sidus, Arg.†.*
Amino acids; vitamin B substances (p.1922·1).
Dietary supplement.

Aminopro *Euro-Med, Philipp.*
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Aminopt *Sigma, Austral.*
Aminoacridine hydrochloride (p.1625·1).
Eye infections.

Aminoram *Fresenius Kabi, Ital.*
Food for special diets (p.1922·1).
Liver disorders.

Aminoroztok Neo *Infusia, Cz.†.*
Amino-acid and electrolyte infusion with or without carbohydrate (p.1922·1).
Parenteral nutrition.

Aminosam *Szama, Arg.*
Biotin (p.1931·3).
Alopecia.

Aminoserin *Amnol, Ital.†.*
Amino acids; phosphatidyl serine; minerals; vitamin A palmitate (p.1922·1).
Nutritional supplement.

Aminosol *Abbott, Mex.; Hemofarm, Rus.; Thai Otsuka, Thai.*
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Aminosol Neo-E *Hemofarm, Rus.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminosolut *DeltaSelect, Ger.†.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminostab *Fresenius Kabi, Fr.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Aminosteril *Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Baxter, Fin.†; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Mex.; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.*
A range of amino-acid infusions with or without electrolytes (p.1922·1).
Parenteral nutrition.

Aminosteril N Hepa *Fresenius Kabi, Cz.; Fresenius Kabi, Hong Kong†; Fresenius Kabi, Malaysia; Fresenius Kabi, Neth.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in liver failure.

Aminostress *Lafare, Ital.†.*
Nutritional supplement (p.1922·1).

Aminosyn *Hospira, USA.*
A range of amino-acid infusions with or without glucose and electrolytes (p.1922·1).
Parenteral nutrition.

Aminoterapia
Defuen, Arg.†.
Cream: Vitamin A; vitamin E acetate; ceramide; amino acids (p.1922·1).
Nail disorders.

Defuen, Arg.
Oral powder; tablets: Cystine; gelatin (p.1922·1).
Skin, hair, and nail disorders.

Defuen, Arg.†.
Tablets: Cystine; gelatin; cellulose (p.1922·1).
Skin, hair, and nail disorders.

Aminoterapia Capilar *Defuen, Arg.*
Cystine; hydrolysed animal protein; hydrolysed hair keratin; tocopheryl acetate; ascorbyl palmitate (p.1922·1).
Hair disorders.

Aminotool *Volchem, Ital.*
Amino-acid preparation (p.1922·1).

Aminotox *Teuto, Braz.†.*
Adenosine (p.1202·1); methionine (p.1450·1); betaine hydrochloride (p.2265·2); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2).
Liver disorders.

Aminotrans *GHP, Thai.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Aminotripa *Otsuka, Jpn.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Aminotrophylle-88 *Proel, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Aminovac *Nikkho, Braz.*
Allergen preparation (p.2250·2).
Allergen immunotherapy.

Aminoveinte *Madariaga, Spain.*
Multivitamin and amino-acid preparation (p.1922·1).
Tonic.

Aminovel *Otsuka, Indon.*
Amino-acid, sorbitol, electrolyte, and vitamin infusion (p.1922·1).
Parenteral nutrition.

Aminoven *Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Spain; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.*
Amino-acid infusion with or without glucose and electrolytes (p.1922·1).
Parenteral nutrition.

Aminovenoes N Paed *Fresenius Kabi, Cz.; Fresenius Kabi, Thai.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in neonates.

Aminovenos *Fresenius Kabi, Neth.; Fresenius Kabi, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in infants.

AminoVita *Cardinal, Philipp.*
A vitamin and amino-acid preparation (p.1922·1).

Aminoxidin *Fada, Arg.†.*
Ampicillin (p.204·1).
Bacterial infections.

Aminoxidin Sulbactam *Fada, Arg.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Aminoyodarsencal *Italmex, Mex.*
Calcium formate; calcium gluconate; calcium lactate; lysine hydrochloride; orthoiodine; tryptophan (p.1922·1).
Calcium deficiency; dietary supplement.

Aminozim *Balverda, Ital.†.*
Amino-acid preparation (p.1922·1).
Tonic.

Aminozyme *Stadmed, India.*
Protein hydrolysate; vitamin B substances; zinc sulfate (p.1922·1).
Burns; enzyme deficiency; hypoproteinaemia; nutritional supplement.

Amiobal *Baldacci, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiobeta *Betapharm, Ger.†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiocar *Klonal, Arg.*
Amiodarone (p.1210·2).
Arrhythmias.

Amiod *IA, Ger.†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiodacore *CTI, Israel.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias; heart failure.

Amiodar *Sigma-Tau, Ital.; Sandoz, Switz.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Amiodarex *Sanofi Synthelabo, Ger.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiodura *Merck dura, Ger.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiogamma *Worwag, Ger.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiohexal *Hexal, Cz.; Hexal, Ger.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiokordin *KRKA, Cz.; KRKA, Hung.†; KRKA, Pol.; KRKA, Rus.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amiopia *Medical, Spain.*
Vitamins, minerals, amino acids (p.1922·1); isoniazid (p.288·1).
Eye disorders.

Amiorel *Boehringer Ingelheim, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with increased or viscous mucus.

Amiorel Compuesto *Boehringer Ingelheim, Arg.*
⊗ Bromhexine hydrochloride (p.1552·2); diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Amioron *Geolab, Braz.†.*
Amiodarone (p.1210·2).
Arrhythmias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Amioxid *Neuraxpharm, Ger.*
Amitriptylinoxide (p.381·1).
Depression.

Amiparen *Otsuka, Indon.; Otsuka, Jpn; Thai Otsuka, Thai.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Amiphos *Dabur, India.*
Amifostine (p.1436·3).
Radiation-associated xerostomia; reduction of nephrotoxicity due to cisplatin; reduction of neutropenia due to cyclophosphamide and cisplatin therapy for ovarian cancer.

Amiprid *Keri, Hung.*
Amisulpride (p.961·1).
Psychoses.

Amira *Alphapharm, Austral.*
Moclobemide (p.411·1).
Depression.

Amirel *Medipharm, Chile.*
Mirtazapine (p.409·2).
Depression.

Amiretic *Biolab Sanus, Braz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Amirine *Rivopharm, Switz.*
Mianserin hydrochloride (p.408·1).
Depression.

Amirone *Julphar, UAE.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Amisol *Medica Korea, Singapore.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Amisulid *Temmler, Ger.*
Amisulpride (p.961·1).
Schizophrenia.

Amitacon *Egis, Thai.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Amithiazide *Jean-Marie, Hong Kong.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Amitiza *Takeda, USA.*
Lubiprostone (p.1742·3).
Chronic idiopathic constipation.

Amitone
Note.This name is used for preparations of different composition.
Unison, Hong Kong.
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.
Menley & James, USA†.
Calcium carbonate (p.1714·1).
Hyperacidity.

Amitrex *Sanofi-Aventis, Hung.; Sanofi-Aventis, Port.*
Amisulpride (p.961·1).
Schizophrenia.

Amitrexyl *BMS, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amitrid *Leiras, Fin.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Amitrip *Pacific, NZ.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Amitron *Torlan, Spain.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infection.

Amivia *Coloplast, Fr.†.*
Calcium alginate (p.1058·1); carmellose sodium (p.2142·1).
Ulcers; wounds.

Amix
Note. A similar name is used for preparations of different composition (see Amixx, below).
Ashbourne, UK.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amixen *Bernabo, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amixen Clavulanico *Bernabo, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amixen Plus *Bernabo, Arg.*
Amoxicillin trihydrate (p.202·2); diclofenac potassium (p.44·3).
Bacterial infections with inflammation.

Amixide *Sun, Rus.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Anxiety; depression.

Amixin *Masterlek, Rus.*
Tilorone.
Viral infections.

Amixx
Note. A similar name is used for preparations of different composition (see Amix, above).
Krewel, Ger.
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Amiyec *IQFA, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amiyu *Ajinomoto, Thai.; Biotek, Turk.*
Amino-acid preparation (p.1922·1).
Nutritional supplement; renal failure.

Amizal *Vida, Port.*
Idebenone (p.367·1).
Mental impairment associated with cerebrovascular disorders.

Amizepin *Polpharma, Pol.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; neuralgia.

Amizet 10 *Tanabe, Jpn†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Amizet 10X *Tanabe, Jpn†.*
Amino-acid and carbohydrate infusion (p.1922·1).
Parenteral nutrition.

Amizide *Alphapharm, Austral.; Alphapharm, Malaysia; Pacific, NZ.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Amizin *Giempi, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

AMK *Pisa, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amlactin *Upsher-Smith, USA.*
Ammonium lactate (p.1589·2).
Dry skin.

AmLactin AP *Upsher-Smith, USA.*
Pramocaine hydrochloride (p.1868·1); lactic acid (p.2329·3).

Amlate *Reddy, S.Afr.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlibon
Sandoz, Gr.; Sandoz, Venez.
Amlodipine (p.1214·2).
Angina pectoris; heart failure; hypertension.
Sandoz, Mex.
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlibon B *Sandoz, Venez.*
Amlodipine (p.1214·2); benazepril (p.1223·3).
Hypertension.

Amlid *Pinewood, Irl.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlidual *Sandoz, Mex.*
Amlodipine mesilate (Amlibon) (p.1214·2); simvastatin (Simplaqor) (p.1390·2).

Amlip *SM, Venez.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlist *Gerard, Irl.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlo *Wolff, Neth.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlo eco *Ecosol, Switz.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlo Tad *TAD, Ger.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlo Wolff *Wolff, Ger.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlobeta *Betapharm, Ger.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amloc
Pfizer, Arg.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Bago, Chile; Pfizer, Venez.†.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.
Pharma Dynamics, S.Afr.
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlocard *AWD, Ger.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amloclair *Hennig, Ger.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlocor *Torrent, Braz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlo-corax *corax, Ger.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlodac *Zydus, India.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlodanorm *Genericon, Austria.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlode *Rowex, Irl.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlodep *Extractum, Hung.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlodeq *Rottapharm, Spain†.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlodigamma
Worwag, Cz.; Worwag, Hung.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Worwag, Ger.
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlodil
Gap, Gr.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.
Bosnalijek, Rus.
Amlodipine besilate (p.1214·1).

Amlodin *Sumitomo, Jpn.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlodine *Quesada, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlodis *Eczacibasi, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlodoc *Docpharm, Ger.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlodowin *Chinoin, Hung.*
Amlodipine (p.1214·2).

Amlogal *SMB, Belg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlogard *Pfizer, India.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlo-Isis *Alpharma-Isis, Ger.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlokard *Sanovel, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

AmloLich *Winthrop, Ger.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlonor *Norpharm, Neth.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlopen *Elpen (Ελπεν), Gr.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlopin
Lek, Pol.; Farma, Venez.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Spirig, Switz.
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlopine *Berlin Pharm, Thai.*
Amlodipine besilate (p.1214·1).
Angina pectoris; congestive heart failure; hypertension.

Amlopp *Cipla, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amloprax *Teuto, Braz.†.*
Amlodipine besilate (p.1214·1).
Hypertension.

Amlopres *Cipla, India.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlopres AT *Cipla, India.*
⊗ Amlodipine besilate (p.1214·1); atenolol (p.1217·3).
Hypertension.

Amlopres L *Cipla, India.*
Amlodipine besilate (p.1214·1); lisinopril (p.1325·2).
Hypertension.

Amlopres Z *Cipla, India.*
Amlodipine besilate (p.1214·1); losartan potassium (p.1326·1).
Hypertension.

Amlopress *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlopril *Pfizer, Arg.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Amlo-Q *Juta, Ger.; Q-Pharm, Ger.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlor *Pfizer, Belg.; Pfizer, Fr.; Binesa, Spain.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amloratio *Ratiopharm, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amloreg *Ratiopharm, Austria.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amloretin *Biomedica-Chemica, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlosafe *Otsira, India†.*
Amlodipine besilate (p.1214·1).

Amlosafe-AT *Otsira, India†.*
⊗ Amlodipine besilate (p.1214·1); atenolol (p.1217·3).

Amlosafe-LS *Otsira, India†.*
Amlodipine besilate (p.1214·1); lisinopril (p.1325·2).

Amlosilat *AG Therapy, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlostad *Stada, Neth.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlostat *Biochem, India.*
Amlodipine besilate (p.1214·1).

Amlostat-AT *Biochem, India.*
⊗ Amlodipine besilate (p.1214·1); atenolol (p.1217·3).

Amlostin *Schein, UK.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlosyl *Norpharm, Neth.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlosyn *Generix, S.Afr.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlotabs *Cantabria, Spain†.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlotens *Klonal, Arg.; Specifar, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amlotenz *Belupo, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlotop *Makiz-Pharma, Rus.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlotrust *Centaur, India.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Amlovas *Unique, Rus.; Drogsan, Turk.; Megat, Venez.*
Amlodipine besilate (p.1214·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Amlovasc
Hexal, Braz.†.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Streuli, Switz.
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Amlow *Unipharm, Israel.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Amlozek *Adamed, Cz.; Adamed, Hung.; Adamed, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Ammeltz *Kobayashi, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); nonivamide (p.96·2).
Musculoskeletal pain; soft-tissue disorders.

Ammidene *Macrophar, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Ammiformin *Macrophar, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Ammi-Indocin *Macrophar, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Ammilazo *Macrophar, Thai.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Amminac *Macrophar, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Ammirox *Macrophar, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Ammitram *Macrophar, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Ammi-Votara *Macrophar, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ammonaps *Swedish Orphan, Cz.; Orphan, Fr.†; Orphan, Ger.†; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Swedish Orphan, Port.; Orphan, Spain; Swedish Orphan, UK.*
Sodium phenylbutyrate (p.2390·2).
Urea cycle disorders.

Ammonul *Ucyclyd, USA.*
Sodium phenylacetate (p.2390·2); sodium benzoate (p.1630·2).
Hyperammonaemia.

Amnesteem *Mylan, USA.*
Isotretinoin (p.1599·2).
Acne.

Amniolina *Reig Jofre, Spain.*
Talc (p.1615·2); zinc oxide (p.1621·2).
Nappy rash.

Amnivent *Ashbourne, UK†.*
Aminophylline (p.1114·2).
Bronchospasm.

Amnolake *Shinyaku, Jpn.*
Tamibarotene (p.772·3).
Acute promyelocytic leukaemia.

AMO Endosol *Advanced Medical Optics, Austral.; Allergan, Braz.†; Allergan, USA.*
Electrolytes (p.1667·1).
Irrigation solution during surgery.

Amo Resan *Alacan, Spain†.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

AMO Vitrax *Advanced Medical Optics, Austral.; Advanced Medical Optics, NZ†; Genop, S.Afr.; AMO, Singapore†; Allergan, USA.*
Sodium hyaluronate (p.2320·1).
Aid in ocular surgery.

Amobay *Bayer, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amobay CL *Bayer, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amobiotic
Laboratorios Chile, Chile.
Amoxicillin (p.202·2).
Bacterial infections.

Bernofarm, Indon.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amobronc *Ist. Chim. Inter., Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-system disorders.

Amocasin *Northia, Arg.*
⊗ Salbutamol (p.1131·2).
Asthma.

Amocetin *Remedina, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Amocid *Lysoform, Ger.*
Orthophenylphenol (p.1655·1).
Surface disinfection.

Amocillin *Caps, S.Afr.*
Amoxicillin sodium (p.202·2).
Bacterial infections.

Amocla
Penmix, Singapore.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Kuhnil, Thai.
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoclan
Hexal, Austria; Katwijk, Neth.; Hexal, Rus.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Hexal, Hung.†.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2) or potassium clavulanate (p.250·2).
Bacterial infections.

Westward, USA.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoclane *Eurogenerics, Belg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoclav
Casasco, Arg.; Hexal, Ger.; 1A, Hung.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Biomedis, Philipp.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoclavam *BA Farma, Port.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoclave *Bial, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoclen *Zentiva, Cz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amocol *Offenbach, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Amocomb *Bernofarm, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amocrin *Epifarma, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amodex *Bouchara-Recordati, Fr.*
Amoxicillin trihydrate (p.202·2) or amoxicillin sodium (p.202·2).
Bacterial infections.

Amodion *Schering-Plough, Venez.*
⊗ Ammonium acetate (p.1551·2); sodium benzoate (p.1630·2); ephedrine hydrochloride (p.1558·2).
Cough.

Amodipan *Santa, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amodivyr *Copernico, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Amodormin *Omicron, Arg.*
Diphenhydramine (p.577·1).
Insomnia.

Amoebriz *Janssen-Cilag, Mex.*
Mebendazole (p.148·3); quinfamide (p.846·2).
Amoebiasis; worm infections.

Amofar *Cafar, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amofat *Protein, Mex.†.*
Famotidine (p.1730·1).
Peptic ulcer.

Amofen *Pediapharm, Chile.*
Diclofenac (p.44·2).
Fever; inflammation; pain.

Amofil *Veripalvelu, Fin.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemophilia A.

Amofilin *Pisa, Mex.*
Aminophylline (p.1114·2).

Amoflamisan *Beecham, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoflux *Bergamo, Braz.†; Lampugnani, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amofur *Ivax, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Amogal *Galena, Cz.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amohexal *Hexal, Austral.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoklavin *Deva, Turk.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoksiklav
Lek, Cz.; Lek, Pol.; Lek, Rus.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Lek, Hong Kong; Lek, Thai.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoksilav *Ilsan, Turk.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoksilin *Nobel, Turk.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoksina *Nevzat, Turk.*
Amoxicillin (p.202·2).
Bacterial infections.

Amol
Note. A similar name is used for preparations of different composition (see below).
Altana, Cz.
Peppermint oil (p.1761·2); citronella oil (p.2284·2); clove oil (p.2285·1); cinnamon oil (p.2283·2); lavender oil (p.2331·2); lemon oil (p.2332·3); menthol (p.2340·1).
Cold symptoms; coughs; digestive disorders; sore throat.

Altana, Pol.
Peppermint oil (p.1761·2); clove oil (p.2285·1); cinnamon oil (p.2283·2); lavender oil (p.2331·2); lemon oil (p.2332·3); menthol (p.2340·1); melissa oil (p.2339·3).
Cold symptoms; eczema; gastrointestinal disorders; headache; insect bites; musculoskeletal and joint disorders; nervous disorders; neuralgia; oral hygiene; toothache.

A-Mol
Note. A similar name is used for preparations of different composition (see above).
Siam Bheasach, Thai.
Paracetamol (p.108·1).
Fever; pain.

Amol Heilkrautergeist N *Altana, Ger.*
Melissa oil (p.2339·3); clove oil (p.2285·1); cinnamon oil (p.2283·2); lemon oil (p.2332·3); peppermint oil (p.1761·2); lavender oil (p.2331·2); menthol (p.2340·1).
Capillary disorders; gastrointestinal disorders.

A-Mol Plus *Siam Bheasach, Thai.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; nasal congestion.

Amolex *Andromaco, Chile.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amolgen *Solfran, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Amolin
Note. A similar name is used for preparations of different composition (see below).
APT, Hong Kong.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ergha, Irl.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Am-O-Lin
Note. A similar name is used for preparations of different composition (see above).
Bayer, NZ.
Almond oil (p.2252·2); calamine (p.1591·2); salicylic acid (p.1612·2); zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Amoltex *Aldril, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Amonate *Dafra, Belg.*
White tablets, artesunate (p.598·2); yellow tablets, amodiaquine (p.597·2).
Malaria.

Amoram *LPC, UK.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amorion *Orion, Fin.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amosan
Note.This name is used for preparations of different composition.
Oral-B, Austral.; Gillette, Belg.
Sodium perborate (p.1662·1); sodium bitartrate.
Mouth disorders.

Oral-B, Canad.; Oral-B, USA.
Sodium perborate (p.1662·1).
Oral disinfection; oral lesions.

Amosept *Lysoform, Ger.*
Didecyldimethylammonium chloride (p.1642·2).
Hand disinfection.

Amosin *Sintez, Rus.; Sanli, Turk.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amosine *Mugi, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amosol *SoSe, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amospes *Specifar (Σπεσιφαρ), Gr.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Amosyt *Bioglan, Swed.*
Dimenhydrinate (p.576·2).
Ménière's syndrome; motion sickness; nausea; vertigo.

Amotaks *Polfa Tarchomin, Pol.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amotein *Chiesi, Spain.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Amoval *Saval, Chile.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoval Duo *Saval, Chile.*
Amoxicillin (p.202·2).
Bacterial infections.

Amovin *Cofasa, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Amox
EMS, Braz.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

KG, Ital.; SM, Thai.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxa *Atlantic, Hong Kong†; Atlantic, Singapore†; Atlantic, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxadene *Cifarma, Braz.*
Amoxicillin trihydrate (p.202·2).

Amoxal
Hexal, Austria.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

GSK, Venez.
Amoxicillin (p.202·2).
Bacterial infections.

Amoxapen *Remedica, Hong Kong; Remedica, Singapore.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxaren *Areu, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxcillin *Greater Pharma, Thai.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxclav *Sandoz, Ger.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amox-G *Klonal, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amox-G Bronquial *Klonal, Arg.*
Amoxicillin (p.202·2); bromhexine (p.1552·2).
Bacterial infections.

Amoxi
Mar, Arg.
Amoxicillin (p.202·2).
Bacterial infections.

SMB, Belg.†; 1A, Ger.; CT, Ger.; Sandoz, Ger.; Sanol, Ger.; Schwarz, Ger.; Generics, Israel; Pharmachemie, Neth.; TO-Chemicals, Thai.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi Gobens *Normon, Spain.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi Gobens Mucolitico *Normon, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Amoxi Plus *Mar, Arg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoxi Respiratorio *Mar, Arg.†.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Amoxibacter *Rubio, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

amoxi-basan *Schonenberger, Switz.†.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxibeta *Betapharm, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxibiot *Investi, Arg.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxibron
Note.This name is used for preparations of different composition.
Kinder, Braz.
Amoxicillin (p.202·2).
Bacterial infections.

GSK, Mex.
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Amoxicap
Globo, Braz.†.
Amoxicillin (p.202·2).
Bacterial infections.

Hovid, Singapore.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxicilina Duo *Plata, Arg.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxicillin comp *Sandoz, Austria; Ratiopharm, Ger.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxicina *Oriental, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxiclav *Alpharma-Isis, Ger.; Basics, Ger.; Betapharm, Ger.; CT, Ger.; Teva, Israel; Pisa, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

AmoxiClavulan *1A, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxi-Clavulan *1A, Ger.; Aliud, Ger.; Stada, Ger.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxicler *Monserrat, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxiclide *Rimsa, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2); nimesulide (p.95·3).
Respiratory-tract infections.

Amoxicom *Eversil, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxicomp *Genericon, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxi-Cophar *Cophar, Switz.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxidal *Roemmers, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxidal Duo *Roemmers, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxidal Respiratorio
Note.This name is used for preparations of different composition.
Roemmers, Arg.
Injection: Amoxicillin sodium (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Roemmers, Arg.
oral suspension; Tablets: Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Amoxidal Respiratorio Duo *Roemmers, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Amoxident *LPC, UK.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxidil *Cifarma, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi-Diolan *Meda, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxidoc *Docpharm, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxiduo *Roemmers-Klinos, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxidura Plus *Merck dura, Ger.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxifar *Zambon, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxifur *Ivax, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxiga *Elter, Venez.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxigran *Hovid, Singapore.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxigrand *Ahimsa, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxigrand Bronquial *Ahimsa, Arg.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Amoxigrand Compuesto *Ahimsa, Arg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoxi-Hefa *Riemser, Ger.; Wernigerode, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxihexal *Hexal, Austria; Hexal, Cz.; Hexal, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxil
GSK, Austral.; GSK, Gr.; GSK, Indon.; GSK, Irl.; GSK, Mex.; GSK, S.Afr.; GSK, UK.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

GSK, Braz.; German Remedies, India; GSK, NZ; GSK, Philipp.; GSK, Thai.; GSK, USA.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

GSK, Singapore.
Amoxicillin (p.202·2).
Bacterial infections.

Amoxilag *Lagap, Neth.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxilan *Lannacher, Austria; Meyer, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxillat *Azupharma, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxillat-Clav *Azupharma, Ger.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxillin
Pharos, Indon.
Amoxicillin (p.202·2).
Bacterial infections.

Benedetti, Ital.; Alpharma, Norw.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoximed *Cimed, Braz.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoximedical *Medical, Spain†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi-Mepha *Mepha, Switz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoximerck *Merck dura, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoximex *Cimex, Switz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxin *Ratiopharm, Fin.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxin Comp *Ratiopharm, Fin.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxina
Hexal, Braz.†.
Amoxicillin (p.202·2).
Bacterial infections.

Aesculapius, Ital.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxinovag *Novag, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi-Ped *Stiefel, Braz.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxipen *Biochimico, Braz.†; Drovepat, Venez.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxipenil *Montpellier, Arg.; Bago, Chile.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxipenil Bronquial *Montpellier, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Amoxiplus *Ratiopharm, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxipoten *Del Bel, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxi-Puren *Alpharma-Isis, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi-saar plus *MIP, Ger.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxisol *Rimsa, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxistad *Stada, Austria.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxistad plus *Stada, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amoxi-Tablinen *Winthrop, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxitan *Bunker, Braz.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxitenk *Biotenk, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxitenk Plus *Biotenk, Arg.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Amoxitenk Respiratorio *Biotenk, Arg.†.*
Amoxicillin (p.202·2); ambroxol hydrochloride (p.1550·3).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Respiratory-tract infections.

Amoxival *Valmor, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxivan *Khandelwal, India.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxivet *Valeant, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxi-Wolff *Wolff, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxol *Cassara, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Amoxsan *Sanbe, Indon.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxy *Hua, Thai.; M & H, Thai.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxyfizz *Schwulst, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxylin *Biomedis, Thai.; Great Eastern, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxypen *Socobom, Belg.; Grunenthal, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amoxyplus *Novag, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ampakine *Rontag, Arg.*
Amantadine (p.792·3).
Drug-induced extrapyramidal disorders; influenza; parkinsonism.

Ampamet *Menarini, Ital.*
⊗ Aniracetam (p.363·2).
Mental function impairment.

Amparax *Wyeth, Chile.*
Lorazepam (p.1004·1).
Anxiety; nausea and vomiting; premedication.

Amparo *Mibe, Ger.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Ampavit *ANB, Thai.*
Vitamin B (p.1980·2).
Megaloblastic anaemia.

Ampecyclal *Erempharma, Fr.*
⊗ Heptaminol adenosine phosphate (p.2319·1).
Haemorrhoids; metrorrhagia; venous insufficiency.

Ampen *Pfizer, Venez.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampenina *Behrens, Venez.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Ampex *Pharmacos, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Amphadase *Amphastar, USA.*
Hyaluronidase (p.2321·1).
Adjunct in subcutaneous urography; adjuvant to increase the absorption and dispersion of injected drugs; hypodermoclysis.

Amphiprol *Proel, Gr.*
Amphotericin B (p.523·2).
Fungal infections.

Amphisept *Goldschmidt, Switz.†.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Amphisept E *Bode, Ger.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Amphochol *Herbapol Lodz, Pol.*
Fumitory (p.2307·2).
Biliary-tract disorders.

Amphocil *Mayne, Austral.; Torrex, Austria; Zodiac, Braz.; Torrex, Cz.; Samaritan, Gr.; Mayne, Hong Kong†; Torrex, Hung.; Alza, Irl.; Sequus, Israel; Three Rivers, Malaysia; Lemery, Mex.; Intermune, Neth.; Torrex, Pol.; Farmoz, Port.; Intermune, Singapore†; Sequus, Spain; Mayne, Thai.; Beacon, UK.*
Amphotericin B-sodium cholesteryl sulfate complex (p.523·2) (p.523·2).
Fungal infections; leishmaniasis.

Amphocycline *BMS, Fr.*
Amphotericin B (p.523·2); tetracycline (p.347·1).
Vaginitis.

Amphodyn
Fujisawa, Austria.
⊗ Etilefrine hydrochloride (p.1284·1); aescin (p.2248·2).
Circulatory disorders; hypotension.

Klinge, Ger.†.
⊗ Etilefrine hydrochloride (p.1284·1); aesculus (p.2248·2).
Circulatory disorders; hypotension.

Amphoglucamin *Sintez, Rus.*
Amphotericin B (p.523·2).
Fungal infections.

Amphojel *Aurium, Canad.; Whitehall, NZ†; Akromed, S.Afr.; Wyeth-Ayerst, USA.*
Aluminium hydroxide (p.1706·2).
Antacid; gastric hyperacidity.

Ampho-Moronal *Dermapharm, Austria; Dermapharm, Ger.; Dermapharm, Switz.*
Amphotericin B (p.523·2).
Fungal infections.

Amphosca *Homeocan, Canad.*
Homoeopathic preparation.

Amphosca a l'orchitine *Lehning, Fr.*
Homoeopathic preparation.

Amphosca a l'ovarine *Lehning, Fr.*
Homoeopathic preparation.

Amphotec
Raffo, Arg.; Sequus, USA; Nolver, Venez.
Amphotericin B (p.523·2).
Fungal infections.

Oryx, Canad.†.
Amphotericin B-sodium cholesteryl sulfate complex (p.523·2)(p.523·2).
Aspergillosis.

Ampi
Arion, Arg.†; Prodotti, Braz.
Ampicillin (p.204·1).
Bacterial infections.

Interbat, Indon.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampibac *CT, Ital.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Ampibactan *Behrens, Venez.*
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Ampibal *Collins, Mex.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampi-Bis *Northia, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Ampi-Bis Plus *Northia, Arg.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Ampicidar *Columbia, Mex.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampiciflan *Bunker, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampiciklyna *Balldarassi, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicil *Medley, Braz.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Ampicilab *Multilab, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicilase *Teuto, Braz.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Ampicilib *Ibfarma, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicilil *Greenpharma, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicilon *Delta, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicimax *Royton, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicin *Westmont, Philipp.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampicinal *Globo, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampicler *Monserrat, Arg.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampiclox
GSK, Cz.†.
Ampicillin sodium (p.204·1); cloxacillin sodium (p.256·1).
Bacterial infections.

GSK, Hong Kong†.
Ampicillin (p.204·1); cloxacillin sodium (p.256·1).
Bacterial infections.

GSK, Irl.†; GSK, S.Afr.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

GSK, Thai.
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Ampiclox-D *GSK, Mex.*
Ampicillin trihydrate (p.204·2); dicloxacillin sodium (p.265·2).
Bacterial infections.

Ampicyn
Aspen, Austral.
Ampicillin sodium (p.204·1).
Bacterial infections.

Siam Bheasach, Thai.
Ampicillin (p.204·1).
Bacterial infections.

Ampidrat *Collins, Mex.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampifar *Farmoquimica, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampifen *Malayan, Singapore†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Ampiga *Elter, Venez.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampigen *Fabra, Arg.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampigen SB
Note.This name is used for preparations of different composition.
Fabra, Arg.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Fabra, Arg.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Ampigran *Legrand, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampigrand *Ahimsa, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Ampigrin *Collins, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Ampikyy *Vitabalans, Fin.*
⊗ Hydrocortisone (p.1535·2).
Snake bites; wasp and bee stings.

Ampilan *Meyer, Venez.*
Ampicillin (p.204·1).
Bacterial infections.

Ampilevel *Ern, Spain.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Formerly contained ampicillin benzathine, ampicillin sodium, and bromhexine hydrochloride.
Bacterial infections.

Ampilin
Hetero, India; Atlantic, Malaysia.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Atlantic, Singapore; Atlantic, Thai.
Ampicillin sodium (p.204·1).
Bacterial infections.

Ampilisa *Lisapharma, Ital.†.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampillin *PP Lab, Thai.†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampilon *Loren, Mex.†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampilox *Biochem, India.*
Ampicillin (p.204·1), ampicillin sodium (p.204·1), or ampicillin trihydrate (p.204·2); cloxacillin (p.256·1) or cloxacillin sodium (p.256·1).
Bacterial infections.

Ampilox-LB *Biochem, India.*
Ampicillin (p.204·1); cloxacillin (p.256·1); lactobacillus spores (p.2372·3).
Bacterial infections.

Ampilozin *Ducto, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Ampilux *Tubilux, Ital.*
Ampicillin sodium (p.204·1).
Eye infections.

Ampimax *Hexal, S.Afr.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampimex *Arlex, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Ampina *Penn, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders.

Ampine *Biomedica-Chemica, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ampinex *Medopharm, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Ampinox *Frasca, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Ampipen *Wyeth, India; Caps, S.Afr.*
Ampicillin (p.204·1).
Bacterial infections.

Ampiplus
Note.This name is used for preparations of different composition.
Menarini, Ital.†.
Ampicillin sodium (p.204·1); dicloxacillin sodium (p.265·2).
Bacterial infections.

Tecefarma, Spain.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampiplus Simplex *Menarini, Ital.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Ampi-Quim *Quimica y Farmacia, Mex.*
Ampicillin (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampirovix *Farmedia, Gr.*
Tenoxicam (p.128·2).
Inflammatory disorders.

Ampiset *Collins, Mex.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampisid
Note.This name is used for preparations of different composition.
Nevzat, Turk.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Nevzat, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Ampisina *Nevzat, Turk.*
Ampicillin (p.204·1).
Bacterial infections.

Ampisyn *Cipla, India.*
Ampicillin (p.204·1).
Bacterial infections.

Ampitasol *Pharmex (Φαρμεξ), Gr.*
Triclosan (p.1665·2).
Disinfection.

Ampi-Tecno *Tecnofarma, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Ampitenk *Biotenk, Arg.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampitrat *Vitapan, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampitren *Ronava, Venez.†.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Ampival *Sanval, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Ampixen *Oriental, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Ampixin *Neckerman, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Amplacilina *Eurofarma, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Amplacin *Cifarma, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Amplal *Gallia, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Amplamox *Biolab Sanus, Braz.†; Tecnifar, Port.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amplamox Plus *Tecnifar, Port.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amplavit *Cimed, Braz.*
Multivitamin preparation (p.1922·1).

Amplexol *Ethypharm, Port.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Ampliactil *Aventis, Arg.*
Chlorpromazine hydrochloride (p.969·2).
Behaviour disorders in children; nausea and vomiting; pain; pruritus; psychoses.

Ampliar *Casasco, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Ampliar Duo *Casasco, Arg.*
Atorvastatin (p.1219·1); ezetimibe (p.1284·3).
Hypercholesterolaemia.

Amplibac *Bergamo, Braz.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Amplibenzatin Bronquial *Ivax, Arg.*
1 Ampoule, ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); 1 ampoule, clonixin lysine (p.37·1); chlorphenamine maleate (p.571·3); bromhexine hydrochloride (p.1552·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Amplictil *Sanofi-Aventis, Braz.*
Chlorpromazine hydrochloride (p.969·2).
Nausea and vomiting; premedication; psychoses; tetanus.

Amplidermis *Medea, Spain.*
⊗ Acedoben (p.2244·2); allantoin (p.1588·1); chlorquinaldol (p.242·3); dexamethasone (p.1526·1); mepyramine maleate (p.585·2); vitamin F (p.2308·2).
Infected burns, skin ulcers, and wounds; infected skin disorders.

Amplifar *Tecnifar, Port.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampligen *HemispheRx, USA.*
Poly I.poly C12U (p.902·1).
AIDS and HIV infection; chronic fatigue syndrome; invasive metastatic melanoma; renal cell carcinoma.

Ampliron *Rhein, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amplital *Pharmacia, Ital.*
Ampicillin (p.204·1), ampicillin sodium (p.204·1), or ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampliton *Makiz-Pharma, Rus.*
Tablets, amlodipine besilate (p.1214·1); tablets, cilazapril (p.1244·3).
Hypertension.

Amplium
Note.This name is used for preparations of different composition.
Farmasa, Braz.
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Sigma-Tau, Ital.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Amplium-G *Farmasa, Braz.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Amplizer *OFF, Ital.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Amplobid *Bergamo, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Amplobiotic *Prati-Donaduzzi, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Amplofen *Merck, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Amplospec *Biochimico, Braz.†.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Amplotal *Medley, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

Amplus
Note.This name is used for preparations of different composition.
Szama, Arg.
Salicylic acid (p.1612·2); pilocarpine hydrochloride (p.1884·3); dexpanthenol; vitamin B .
Scalp disorders.

Jagson, India.
Capsules; tablets: Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1); lactic-acid-producing organisms (p.2372·3).
Bacterial infections.

Jagson, India.
Injection: Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Ampoxin *Unichem, India.*
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Ampoxin-LB *Unichem, India.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1); lactic-acid-producing organisms (p.2372·3).
Bacterial infections.

Ampra *M & H, Thai.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Amprace *MSD, Austral.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Amprexyl
Unison, Hong Kong.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Unison, Thai.
Ampicillin (p.204·1).
Bacterial infections.

Amprexyn *Liferpal, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Amprilan *KRKA, Cz.; KRKA, Hung.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction.

Amprilan H *KRKA, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Amprilan HD *KRKA, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Amprilan HL *KRKA, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ampro *TNP, Thai.†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ampromed *Millimed, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Amrix *ECR, USA.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Amsa PD *Erfa, Canad.*
Amsacrine (p.681·1).
Acute leukaemias.

Amsalyo *OTL, Fr.†.*
Amsacrine (p.681·1).
Acute leukaemias.

Amsapen *Antibioticos, Mex.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Amsati *Antibioticos, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Amsaxilina *Antibioticos, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amsidine *Pfizer, Belg.; Goldshield, Irl.; Pfizer, Neth.; Goldshield, UK.*
Amsacrine (p.681·1).
Acute leukaemias.

Amsidyl *Pfizer, Austral.; Godecke, Cz.†; Godecke, Ger.†; Pfizer, Switz.*
Amsacrine (p.681·1).
Acute leukaemias.

Amsupros *Pharmacia, Arg.†.*
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

AMT *Acis, Ger.†.*
Amantadine sulfate (p.793·1).
Influenza; parkinsonism.

Amtuss *Unison, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Amuchina *Pisa, Mex.†.*
Sodium hypochlorite (p.1661·1); sodium chloride (p.1686·1).
Mucous membrane, skin, surface, and wound disinfection.

Amuchina Med *Galephar, Switz.*
Sodium chloride (p.1686·1); sodium hypochlorite (p.1661·1).
Hand, skin, and wound disinfection.

Amuclan *Wolff, Ger.†; Wolff, Neth.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Amuclean *Amuchina, Ital.*
Benzalkonium chloride (p.1629·1).
Burn and wound disinfection.

Amuclor Med *Amuchina, Ital.*
Tosylchloramide sodium (p.1665·1).
Skin disinfection and cleansing.

Amuctol *Grunenthal, Arg.†.*
Erdosteine (p.1560·1).
Respiratory-tract disorders with viscous mucus.

Amuelle *Angelini, Ital.*
Pregnancy test (p.2372·1).

Amukin *BMS, Belg.; BMS, Neth.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Amukine *Gifrer Barbezat, Fr.*
Sodium hypochlorite (p.1661·1); sodium chloride (p.1686·1).
Skin, mucous membrane and wound cleansing.

Amukine Med *Amuchina, Ital.*
Sodium hypochlorite (p.1661·1).
Disinfection of burns, skin, wounds, and mucous membranes.

A-Mulsin *Mucos, Cz.†; Mucos, Ger.†.*
Vitamin A palmitate (p.1973·1).
Adjunct in cytotoxic therapy or radiotherapy; keratinisation disorders; vitamin A deficiency.

Amunovax *Sanofi Pasteur, Spain†.*
A measles vaccine (attenuated Enders' Edmonston strain) (p.2221·3).
Active immunisation.

Amusa *Icon, Philipp.*
Amoxicillin (p.202·2).
Bacterial infections.

Amvaz *Reddy, USA†.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amvey *APT, Hong Kong.*
Zopiclone (p.1039·1).
Insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Amvisc *Bio-Fizik, Turk.; Bausch & Lomb, USA.*
Sodium hyaluronate (p.2320·1).
Aid in ophthalmic surgery.

AMX *Pisa, Mex.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Amxol *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Amyben *Lexon, UK.*
Amiodarone hydrochloride (p.1210·2).
Tachyarrhythmias.

Amyclon *Nizpharm, Rus.†.*
Clotrimazole (p.530·1).
Fungal skin and nail infections.

Amycor *Merck-Lipha, Fr.*
Bifonazole (p.527·3).
Fungal skin infections.

Amycor Onychoset *Merck-Lipha, Fr.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Amydramine *Julphar, UAE.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Amydramine II *Julphar, UAE.*
Diphenhydramine hydrochloride (p.577·2).
Cold symptoms; coughs; hypersensitivity reactions.

Amydramine Paediatric *Julphar, UAE.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Amygdorectol *Merck Medication Familiale, Fr.†; Merck-Lipha, Switz.*
Bismuth camphocarbonate (p.1712·1).
Mouth and throat disorders.

Amykon *Engelhard, Ger.†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Amylin *Roemmers Rowe, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Amytal *Lilly, Austral.†; Lilly, Canad.†; Flynn, UK; Lilly, USA.*
Amobarbital sodium (p.961·3).
Hypnotic; insomnia; sedative; status epilepticus.

Amytril *Cristalia, Braz.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Amyx *Zentiva, Cz.; Zentiva, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Amyzol *Lek, Rus.*
Amitriptyline hydrochloride (p.376·1).

Amze *Penn, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Amzepril *Richmond, Arg.†.*
Amlodipine (p.1214·2); benazepril (p.1223·3).
Hypertension.

Amziax *Chobet, Arg.*
Alprazolam (p.960·1).
Alcoholism; anxiety; delirium tremens.

AN 1 *Krugmann, Ger.†.*
⊗ Amfetaminil (p.2150·2).
Narcoleptic syndrome.

Anabact *Bioglan, Irl.†; Cambridge Healthcare, UK.*
Metronidazole (p.837·1).
Malodorous fungating tumours; malodorous skin ulcers.

Anabar *Lunsco, USA.*
Paracetamol (p.108·1); salicylamide (p.121·2); phenyltoloxamine citrate (p.588·1).

Anabet *BMS, Port.*
⊗ Nadolol (p.1345·2).
Hypertension.

Anabion *Berlico Mulia, Indon.*
Vitamin B substances; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Anabol *British Dispensary, Thai.*
⊗ Methandienone (p.2116·3).
Anabolic.

Anaboline Depot *Adelco, Gr.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic.

anabol-loges *Loges, Ger.*
Alpha tocoferil acetate (p.1992·3); magnesium hydrogen phosphate; terra silicea; St John's wort (p.422·3).
Tonic.

Anabrest *Synthon, Cz.*
⊗ Anastrozole (p.681·2).

Anabron *Millet Roux, Braz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Anacal
Note.This name is used for preparations of different composition.
Ciclum, Port.
⊗ A heparinoid (p.1305·2); lauromacrogol 400 (p.1916·1); prednisolone (p.1540·3); hexachlorophene (p.1646·1).
Anorectal disorders.

Genus, UK.
A heparinoid (p.1305·2); lauromacrogol 400 (p.1916·1).
Anorectal disorders.

Anacalcit *Belmac, Spain.*
Sodium cellulose phosphate (p.1463·1).
Hypercalcaemia; hypercalciuria; osteopetrosis; vitamin D intoxication.

Anacaps *Ducray, Fr.*
Soya isoflavones (p.2391·2); bamboo extract; watercress extract; vitamins; evening primrose oil; zinc (p.1922·1).
Hair and scalp disorders.

Anacardio con Fosforo *Ximena Polanco, Chile.*
Homoeopathic preparation.

Anacervix *Lepori, Port.; Farma Lepori, Spain.*
Piracetam (p.368·2); vincamine (p.2414·1).
Cerebral trauma; cerebrovascular disorders.

Anacetine *Berlico Mulia, Indon.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Anacid *Ivax, Cz.; Ivax, Hung.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Anacid S *Ivax, Cz.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Anacidol
Note.This name is used for preparations of different composition.
Menarini, Ital.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2); milk powder.
Gastrointestinal disorders.

Spirig, Switz.†.
Calcium carbonate (p.1714·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastric disorders.

Anacin *Wyeth Consumer, Canad.; Wyeth Consumer, Chile; Wyeth Consumer, Hong Kong; ICC, Israel†; Whitehall, Israel†; Wyeth Consumer, Singapore†; Robins, USA; Wyeth, Venez.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Anacin Advanced Headache *Insight, USA.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Anaclosil *IFET (ΙΦΕΤ), Gr.; Reig Jofre, Spain.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Anacold *Darou Pakhsh, Rus.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Anacrodyne *Rekah, Israel.*
Vitamin B (p.1978·2).
Vitamin B deficiency.

Anacyclin *Novartis, Braz.†.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3). 28-Day packs also contain 6 inert tablets.
Combined oral contraceptive.

Anadar *Liptis, USA.*
Ibuprofen (p.64·2).

Anadar Cold & Flu *Liptis, USA.*
Ibuprofen (p.64·2); pseudoephedrine (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Anadekin *Collins, Mex.*
Vitamins A, D, and K (p.1922·1).

Anadent
Note.This name is used for preparations of different composition.
Taro, Israel.
Topical gel: Benzocaine (p.1854·1).
Mouth disorders.

Taro, Israel†.
Topical solution: Benzocaine (p.1854·1); phenylephrine hydrochloride (p.1568·1).
Mouth disorders.

Anadex *Interbat, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.

Anadil *Liferpal, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Fever; muscle spasm; pain.

Anadin
Note.This name is used for preparations of different composition.
Wyeth, Irl.
Aspirin (p.20·3); caffeine (p.1116·3); quinine sulfate (p.612·3).
Cold symptoms; pain.

SA Druggists Self Med, S.Afr.; Wyeth Consumer, UK.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Anadin-3 *SA Druggists Self Med, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Anadin Extra *Wyeth, Irl.; Home, Port.†; Wyeth Consumer, UK.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Anadin Ibuprofen *Wyeth Consumer, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Anadin Joint Pain *Wyeth Consumer, UK.*
Ibuprofen (p.64·2).
Joint pain.

Anadin Maximum Strength *Wyeth, Irl.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold and influenza symptoms; pain.

Anadin Paracetamol *Wyeth, Irl.; Home, Port.; Wyeth Consumer, UK.*
Paracetamol (p.108·1).
Fever; pain.

Anadin Ultra *Wyeth Consumer, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Anadol *TO-Chemicals, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Anador *Boehringer Ingelheim, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Anadrol *Unimed, USA.*
⊗ Oxymetholone (p.2123·3).
Anaemias.

Anadvil *Wyeth Sante, Fr.; Home, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Anadvil Rhume *Wyeth Sante, Fr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Anaebell *Bell, India†.*
Acriflavinium chloride (p.1625·1); lidocaine (p.1862·3); thymol (p.1664·3).
Skin disorders.

Anaemodoron *Weleda, Austria.*
Fragaria vesca; urtica dioica (p.2409·3).
Iron-deficiency anaemia.

Anaerobex *Gerot, Austria.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; Helicobacter pylori infections.

Anaerocid *Sigma, Braz.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Anaeromet *GSK, Belg.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Anaestalgin *Streuli, Switz.*
Procaine hydrochloride (p.1869·1); caffeine (p.1116·3).
Pain.

Anaesthecomp N *Ritsert, Ger.*
Lidocaine hydrochloride (p.1862·3); diphenhydramine hydrochloride (p.577·2).
Allergic rashes; insect stings; sunburn.

Anaestherit *Sanova, Austria.*
Benzocaine (p.1854·1).
Anorectal disorders; skin disorders.

Anaesthesin *Ritsert, Ger.*
Benzocaine (p.1854·1).
Local anaesthesia.

Anaesthesin N *Ritsert, Ger.*
Benzocaine (p.1854·1).
Local anaesthesia.

Anaesthesin-Rivanol *Ritsert, Ger.*
Benzocaine (p.1854·1); ethacridine lactate (p.1625·1).
Painful throat infections.

Anaesthesol *Nizpharm, Rus.*
Benzocaine (p.1854·1); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); menthol (p.2340·1).
Anorectal disorders.

Anaesthesulf *Ritsert, Ger.*
Lauromacrogol 400 (p.1916·1).
Pruritic skin disorders.

Anaesthetic Ear Drops *Vitamed, Israel.*
Tetracaine (p.1871·2); phenazone (p.116·1).
Otitis.

Anaesthetica *Pharmachemie, Neth.*
Bismuth subgallate (p.1711·1); lidocaine (p.1862·3); zinc oxide (p.1621·2).
Anorectal disorders.

Anafen *Bernofarm, Indon.*
Ibuprofen (p.64·2).
Fever; pain.

Anafertin *Armstrong, Mex.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Injectable contraceptive; menstrual disorders.

Anaflam *David, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ana-Flex
Note. A similar name is used for preparations of different composition (see below).
Gunther, Braz.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Anaflex
Note. A similar name is used for preparations of different composition (see above).
Bago, Arg.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Geistlich, Hung.†; Geistlich, Singapore; Geistlich, UK.
Polynoxylin (p.1658·3).
Burns; infected skin disorders; wounds.

Anafortan
Note.This name is used for preparations of different composition.
Khandelwal, India.
Injection: Camylofin (p.2274·1).
Smooth muscle spasm.

Khandelwal, India.
Tablets: Camylofin (p.2274·1); paracetamol (p.108·1).
Smooth muscle spasm.

Anafranil *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Oryx, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Lynapharm, Fr.; Dolorgiet, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Biofutura, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ†; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Polfa Kutno, Pol.; Defiante, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore†; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Clomipramine hydrochloride (p.386·3).
Cataplexy; depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain syndromes; panic disorder; sleep disorders; social phobia.

Anagastra *Madaus, Spain.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anagen *Cassara, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Anagraine *Aspen, Austral.*
Metoclopramide (p.1747·3); paracetamol (p.108·1).
Migraine.

Anagregal *Gentili, Ital.†.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Ana-Guard *Bayer, S.Afr.*
⊗ Adrenaline hydrochloride (p.1203·3).
Anaphylaxis.

Anahelp *Stallergenes, Fr.*
⊗ Adrenaline (p.1203·2).
Anaphylaxis.

Ana-Kit *Bayer, USA.*
Combination pack: ⊗ Injection, adrenaline hydrochloride (p.1203·3); 4 chewable tablets, chlorphenamine maleate (p.571·3).
Anaphylaxis.

Anakonidin *Konimex, Indon.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cough.

Analab *Biolab, Malaysia; Biolab, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Analcid *Terramedic, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Analept *Faran, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Analergin *Ivax, Cz.; Ivax, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

Analeric *Vianex (Βιανέξ), Gr.*
Diflunisal (p.47·2).
Inflammation; pain.

Analfin *Tecnofarma, Mex.*
⊗ Morphine sulfate (p.86·3).
Pain.

Anal-Gen
Note. A similar name is used for preparations of different composition (see below).
Psorimed, Switz.†.
Hamamelis water (p.2318·2); melissa oil (p.2339·3).
Anogenital skin disorders.

Analgen
Note. A similar name is used for preparations of different composition (see above).
Liomont, Mex.
Naproxen (p.92·3).
Inflammation; pain.

Johnson & Johnson, Braz.†.
Ointment: Turpentine oil (p.2406·3); methyl salicylate (p.85·3); camphor (p.2273·2); mustard oil (p.2349·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Aventis, S.Afr.
Tablets: Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Johnson & Johnson, Braz.†.
Topical gel: Menthol (p.2340·1).
Musculoskeletal and joint disorders.

Analgen Forte *Liomont, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Inflammation; pain.

Analgen-SA *Noristan, S.Afr.†.*
Aluminium aspirin (p.19·1); paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); chlorphenoxamine hydrochloride (p.572·3); phenobarbital (p.492·2).
Fever; pain.

Analgesia Creme *Rugby, USA.*
Trolamine salicylate (p.132·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Analgesic Balm *Watkins, Canad.; Geritrex, USA; Goldline, USA; Major, USA; URL, USA.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Analgesic Cream Extra Strength *Confab, Hong Kong.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Musculoskeletal pain and stiffness.

Analgesic/Calmative *Sandoz, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Pain.

Analgesico Dental *Hofmann, Chile.*
Eugenol (p.2301·2).
Toothache.

Analgesil *Kinder, Braz.*
Dipyrone (p.49·2).
Pain.

Analgesin *Teuto, Braz.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Analget *Polfa Grodzisk, Pol.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Analgex *Uniao Quimica, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Analgil *Azevedos, Port.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); guaiacol (p.1561·2).
Musculoskeletal and joint disorders.

Analgilasa *Ipsen, Spain.*
Caffeine (p.1116·3); codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Analgin
Note. This name is used for preparations of different composition.
BB, Cz.
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Smooth muscle spasm.

Medphano, Ger.; Balkanpharma, Rus.; Pharmachim, Rus.
Dipyrone (p.49·2).
Fever; pain.

Analgin C-R *EMS, Braz.*
Green tablets, dipyrone (p.49·2); chlorphenamine maleate (p.571·3); orange tablets, vitamin C (p.1983·3).
Cold and influenza symptoms.

Analgina *Lafedar, Arg.*
Dipyrone (p.49·2).
Fever; pain.

Analgin-Chinin *Pharmachim, Rus.*
Dipyrone (p.49·2); quinine hydrochloride (p.612·3).
Fever; pain.

Analgine *Sterop, Belg.*
Dipyrone (p.49·2).
Fever; pain.

Analgiplus *Faes, Spain.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Analgol *Profarm, Pol.*
Camphor (p.2273·2); juniper oil (p.2328·3); menthol (p.2340·1); pine oil (p.2368·2); turpentine oil (p.2406·3).
Catarrh; musculoskeletal and joint pain; neuralgia.

Analgolan *Profarm, Pol.*
Camphor (p.2273·2); methyl salicylate (p.85·3); pine oil (p.2368·2); turpentine oil (p.2406·3).
Musculoskeletal and joint pain; neuralgia.

Analgosedan *Brasmedica, Braz.†.*
Dipyrone (p.49·2); homatropine methylbromide (p.1881·3); adiphenine (p.2247·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Analka *Medic, Denm.*
Docusate sodium (p.1725·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Analmorph *Gray, Arg.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

Analog LCP *Scientific Hospital Supplies, Irl.†.*
Food for special diets (p.1922·1).
Phenylketonuria.

Analog MSUD *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

Analog P-AM *SHS, Cz.†.*
Preparation for enteral nutrition (p.1922·1).

Analog RVHB *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Homocystinuria; hypermethioninaemia.

Analog XMTVI *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Formerly known as Analog Xmet, Thre, Val, Isoleu.
Methylmalonic or propionic acidaemia.

Analog XP *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

Analog Xphen, Tyr *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Analpan *Duopharma, Hong Kong.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Analphen *Randall, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Analpram-HC *Ferndale, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Analsik *Sanbe, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Analspec *Metiska, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Analtrix *Faria, Braz.†.*
Oxyphenbutazone (p.107·3); paracetamol (p.108·1). Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain.

Analux *Alcon Cusi, Malaysia†; Alcon Cusi, Spain†.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Analverin *Dovalle, Braz.†.*
Hyoscyamine hydrobromide (p.1736·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Analverin Composto *Dovalle, Braz.†.*
Dipyrone (p.49·2); hyoscine (p.1733·3).
Muscle spasm; pain.

Analverin Plus *Dovalle, Braz.†.*
Paracetamol (p.108·1); hyoscine (p.1733·3).
Muscle spasm; pain.

Anamai *TNP, Thai.†.*
21 Tablets, norethisterone (p.2119·3); mestranol (p.2116·2); 7 tablets, inert.
Combined oral contraceptive.

AnaMantle HC *Kenwood, USA.*
⊗ Hydrocortisone acetate (p.1535·2); lidocaine hydrochloride (p.1862·3).

Anamix *SHS, Fr.*
Food for special diets (p.1922·1).
Phenylketonuria.

Anamorph *Fawns & McAllan, Austral.*
⊗ Morphine sulfate (p.86·3).
Pain.

Ananase *Rottapharm, Ital.; Delta, Port.; Vargas, Venez.*
Bromelains (p.2269·1).
Soft-tissue inflammation and oedema.

Ananase Forte *Sanofi-Aventis, Chile.*
Bromelains (p.2269·1).
Episiotomy; inflammation.

Anandron *Aventis, Arg.†; Aventis, Austral.; Sanofi-Aventis, Braz.; Aventis, Canad.; Aventis, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Aventis, Mex.; Aventis, Neth.; Sanofi-Aventis, Port.; Aventis, Swed.*
Nilutamide (p.756·2).
Prostatic cancer.

Anangor *Biosintetica, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Ananty *Plusandex, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Anapen *Lincoln, Cz.; Allerbio, Fr.; Beckmann, Ger.; Allertec, Gr.; Lincoln, Hung.; Celltech, Irl.; Lincoln Medical, Pol.; Decomed, Port.; Medeca, Swed.; Lincoln, UK.*
⊗ Adrenaline (p.1203·2).
Anaphylaxis.

Anapenil
Note. This name is used for preparations of different composition.
Grossman, Mex.
Injection: Clemizole penicillin (p.251·1); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Grossman, Mex.
Oral solution; tablets: Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Anaphase *Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.*
Tocoferil nicotinate (p.1415·1); vitamin B substances (p.1922·1).
Hair disorders.

Anaphyl *Sam-On, Israel†.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Anapirol *Dinafarma, Braz.†.*
Dipyrone (p.49·2); caffeine (p.1116·3); orphenadrine citrate (p.812·1).
Smooth muscle spasm.

Anaplas *Unipharma, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Anaplex *ECR, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Anaplex DM *ECR, USA.*
Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Anaplex HD *ECR, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Coughs and cold symptoms.

Anapolon *Abdi, Turk.*
⊗ Oxymetholone (p.2123·3).
Anaemias.

Anapran *Polfa Pabianice, Pol.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Anapres *Lemery, Mex.*
Prazosin (p.1376·2).
Hypertension.

Anapril *Merck, Hong Kong; Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Anaprilin *Akrikhin, Rus.*
⊗ Propranolol (p.1381·1).

Anaprol *Provit, Mex.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Anaprolina *Silesia, Chile.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic; breast cancer; osteoporosis.

Anaprotab *Sanli, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Anaprox *Roche, Austral.; Roche, Canad.; Minerva (Μινερβα), Gr.; Roche, USA.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Anapsique *Psicofarma, Mex.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Anapsyl *Novag, Mex.*
Naproxen sodium (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Anaptivan *Help, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Anapyrol *Maypo, Mex.*
Dipyrone (p.49·2).

Anara *Chinoin, Mex.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Anarex *CCM, Malaysia; Beacons, Singapore.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Dysmenorrhoea; skeletal muscle spasm.

Anargil *Medochemie, Cz.†; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Thai.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; female infertility; gynaecomastia; hereditary angioedema; menorrhagia; precocious puberty.

Anaribes Plus *Farmachimici, Ital.*
Black currant; betacarotene; vitamin C; vitamin E (p.1922·1).
Nutritional supplement.

Anarthril *Minerva (Μινερβα), Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Anartrit
Note. This name is used for preparations of different composition.
Garden House, Arg.
Calcium (p.1675·2); magnesium (p.1678·3); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Hexal, Braz.†.
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Anased *Potter's, UK.*
Lupulus (p.2335·2); Jamaica dogwood (p.2328·1); wild lettuce (p.2415·2); passion flower (p.2363·2); pulsatilla (p.2376·3).
Pain; tension.

Anaseptil *Farmasa, Braz.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); zinc peroxide (p.1666·3).
Bacterial skin infections.

Anasilpiel *Euroexim, Spain.*
⊗ Neomycin undecenoate (p.305·2); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Anaskebir *Aspen, Arg.*
⊗ Anastrozole (p.681·2).

Anasma *Alter, Spain.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma.

Anasmol *Roemmers Rowe, Venez.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Anaspaz *Ascher, USA.*
Hyoscyamine sulfate (p.1736·1).
Smooth muscle spasm.

Anassa *TO-Chemicals, Thai.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Anastase *Motima, Fr.*
Vegetable extracts from phaseolus vulgaris; cyprus; hamamelis; watercress; lemon; pineapple (p.1922·1).

Anasten Plus *Errekappa, Ital.*
Arginine; magnesium; potassium; creatine; levocarnitine; ubidecarenone; vitamin C (p.1922·1).
Nutritional supplement.

Anasterol *Terapeutico, Ital.*
Cyclanthera pedata; lespedeza capitata; oryzanol (p.2358·3); vitamins.
Hypercholesterolaemia.

Anastil
Note. This name is used for preparations of different composition.
Vargas, Venez.†.
Oxazepam (p.1014·2).
Anxiety.

Eberth, Ger.†.
Thyme (p.2401·1).
Bronchitis; catarrh; coughs.

Anastim con RTH *Pierre Fabre Dermo-Cosmetique, Arg.*
RTH extract; α-pinene (p.2368·3); saw palmetto (p.2192·3); crotamiton (p.1593·2); enoxolone (p.50·1).
Scalp disorders.

Anastol *Remedina, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Anastraze *Sandoz, Arg.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Anatac *Arafarma, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Anatensol
BMS, Austral.†; BMS, Indon.; BMS, Ital.; BMS, NZ.
Fluphenazine hydrochloride (p.998·1).
Anxiety; behavioural disorders; psychoses; tension.

Sarabhai Piramal, India; BMS, Port.
Fluphenazine decanoate (p.998·1).
Anxiety; schizophrenia.

BMS, Neth.
Fluphenazine decanoate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Anatetall *Chiron Vaccines, Ital.; Chiron, Thai.†; Berk, Turk.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Anatine *Pharmacia, Arg.†.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Anatoxal Adulti *Berna, Ital.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Formerly known as Anatoxal Di Te.
Active immunisation.

Anatoxal Te *Vieira, Port.†; Berna, Spain; Berna, Switz.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Anatoxal Di Te *Berna, Spain†; Berna, Switz.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Anatoxal Te Di *Berna, Spain.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of children and adults.

Anatoxal Di Te Berna *Faran, Gr.†.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Anatoxal Di Te Per *Faran, Gr.†; Berna, Spain†.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Anatoxal-TE-Berna *Faran, Gr.†.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Anatrast *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Anatyl *Sanval, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Anauran *Zambon, Ital.; Zambon, Rus.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Anaus *Beta, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Anausin *Viatris, Fr.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Anautin *SAD, Denm.*
Dimenhydrinate (p.576·2).
Allergic rhinitis; hay fever; motion sickness; urticaria.

Anavan *Fuji, Jpn.*
Diclofenac sodium (p.44·3).
Fever; inflammation; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Anavenol
Note.This name is used for preparations of different composition.
Zentiva, Cz.
⊗ Dihydroergocristine mesilate (p.364·2); esculoside (p.2248·2); rutoside (p.2305·1) or rutoside sodium sulfate (p.2305·2).
Thrombophlebitis; venous insufficiency.

Zentiva, Pol.; Leciva, Rus.
Dihydroergocristine mesilate (p.364·2); esculoside (p.2248·2); rutoside (p.2305·1).
Cerebrovascular disorders; intermittent claudication; migraine; venous insufficiency.

Anavit *Nufarindo, Indon.*
Vitamins A, B, and D (p.1922·1).
Nutritional supplement.

Anavix *Demo, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Anax *Millimed, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Anaxeryl *Bailly, Fr.*
Dithranol (p.1595·2); ichthammol (p.1599·1); salicylic acid (p.1612·2); resorcinol (p.1612·1); peru balsam (p.2365·3).
Formerly contained dithranol, ichthammol, salicylic acid, resorcinol, peru balsam, and birch tar oil.
Alopecia; psoriasis.

Anaya *Tauret, Cz.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Anazo *Medicine Products, Thai.*
Phenazopyridine hydrochloride (p.116·2).
Dysuria; urinary-tract pain.

Anbacim *Sanbe, Indon.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Anbegele *Home, Port.†.*
Cetylpyridinium chloride (p.1635·1); chlorocresol (p.1640·1); lidocaine (p.1862·3).
Mouth disorders.

Anbesol
Note.This name is used for preparations of different composition.
Wyeth Consumer, Canad.; Wyeth Consumer, Chile.
Benzocaine (p.1854·1).
Minor skin abrasions; mouth pain.

SSL, Irl.; SA Druggists Self Med, S.Afr.; SSL, UK.
Lidocaine hydrochloride (p.1862·3); chlorocresol (p.1640·1); cetylpyridinium chloride (p.1635·1).
Aphthous stomatitis; cold sores; denture irritation; gingival pain; teething.

Whitehall, USA.
Topical gel: Benzocaine (p.1854·1); phenol (p.1656·1).
Oral lesions.

Whitehall, USA.
Topical liquid: Benzocaine (p.1854·1); phenol (p.1656·1); menthol (p.2340·1); camphor (p.2273·2); povidone-iodine (p.1659·2).
Mouth and throat disorders.

Anbesol Baby *Wyeth Consumer, Canad.*
Benzocaine (p.1854·1).
Teething.

Anbesol Cold Sore Therapy *Wyeth Consumer, USA.*
Benzocaine (p.1854·1); allantoin (p.1588·1); camphor (p.2273·2).
Herpes labialis.

Anbesol Extra Strength *Wyeth Consumer, Canad.*
Benzocaine (p.1854·1).
Mouth pain.

Anbesol Maximum Strength *Wyeth Consumer, Canad.*
Benzocaine (p.1854·1); phenol (p.1656·1); camphor (p.2273·2); menthol (p.2340·1).
Minor skin abrasions; mouth pain.

Anbifen *ANB, Thai.*
Ibuprofen (p.64·2).
Fever; pain.

Anbikan *ANB, Thai.*
Kanamycin (p.291·3).
Gram-negative bacterial infections.

Anbikin *ANB, Thai.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Anbin *Grifols, Ital.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Anbinex *Grifols, Cz.; Grifols, Ger.; Grifols, Spain.*
Antithrombin III (p.1054·1).
Formerly known as Anbin in *Spain*.
Antithrombin III deficiency.

Anbiolid *Meprofarm, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Ancamin *PP Lab, Thai.†.*
Calamine (p.1591·2); zinc oxide (p.1621·2); chlorphenamine maleate (p.571·3).
Insect bites; pruritus; skin irritation.

Ancaron *Taisho, Jpn.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Ancef *Hospira, USA†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Ancefa *Meprofarm, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Anceron *Schering-Plough, S.Afr.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Ancet *C & M, USA.*
Skin cleanser.

Anchocalm *Genepharm, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Anchostam-100 *Biostam (Βιοσταμ), Gr.†.*
Ticlopidine (p.1412·1).
Antiplatelet therapy.

Ancid *Hexal, Ger.*
Hydrotalcite (p.1733·3).
Gastrointestinal hyperacidity; heartburn; peptic ulcer.

Ancine *Arlex, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Ancivin *Cantabria, Spain.*
Famciclovir (p.876·1).
Herpesvirus infections.

Ancla *Meprofarm, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Anclomax *Blausiegel, Braz.*
Aciclovir (p.862·3).

Ancobon *ICN, USA.*
Flucytosine (p.534·2).
Candidiasis; cryptococcosis.

Anconevron *Pharmanik (Φαρμανικ), Gr.†.*
Bromazepam (p.964·3).
Anxiety disorders.

Ancopir *Grossmann, Hong Kong; Grossmann, Switz.*
Vitamin B substances (p.1922·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Adjuvant in radiation therapy; alcoholism; lumbago; neuralgia; neuritis; sciatica; vitamin B deficiency.

Ancoren *Sanitas, Port.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ancoron *Libbs, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Ancotil *Valeant, Arg.; Valeant, Austral.; ICN, Austria; ICN, Denm.; CSP, Fr.; Valeant, Ger.; IFET (ΙΦΕΤ), Gr.; Valeant, Hong Kong; ICN, Irl.; ICN, Ital.; ICN, Malaysia†; ICN, NZ; ICN, Neth.; ICN, Pol.; Valeant, Singapore†; Medilink, Swed.; Valeant, Switz.; ICN, UK.*
Flucytosine (p.534·2).
Formerly known as Alcobon in the *UK*.
Fungal infections.

Ancotyl *Valeant, Rus.*
Flucytosine (p.534·2).
Fungal infections.

Andalpha *Actavis, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Andante
Note.This name is used for preparations of different composition.
Boehringer Ingelheim, Ger.
Bunazosin hydrochloride (p.1237·3).
Hypertension.

Gedeon Richter, Rus.
Zaleplon (p.1035·3).
Sleep disorders.

Sanovel, Turk.
Alendronic acid (p.1088·1).
Osteoporosis.

Andantol *Ache, Braz.; Asta Medica, Indon.; Sanfer, Mex.*
Isothipendyl hydrochloride (p.582·1).
Allergic skin disorders; burns; skin irritation.

Andantol Jalea *Zuoz, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); chamomile (p.2279·3); arnica (p.2260·2); calendula (p.2273·1); aloe vera (p.1588·2).
Burns; insect bites and stings; pruritus; sunburn.

Andapsin *Orion, Swed.*
Sucralfate (p.1772·2).
Gastrointestinal haemorrhage; peptic ulcer.

Andaxin *EGIS, Hung.*
Meprobamate (p.1006·2).
Alcoholism; anxiety disorders; spasticity.

Andazol *Biofarma, Turk.*
Albendazole (p.139·2).
Hydatid disease; strongyloidiasis.

Andehist
Note.This name is used for preparations of different composition.
Cypress, USA†.
Oral drops: Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Cypress, USA†.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Upper respiratory-tract disorders.

Andehist DM
Note.This name is used for preparations of different composition.
Silarx, USA†.
Oral drops: Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Cypress, USA†.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Andelux *Novartis, Braz.*
Cyproterone acetate (p.2088·2).

Andep *Medikon, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Andepin *Synteza, Pol.*
Fluoxetine (p.397·3).
Bulimia; depression; obsessive-compulsive disorder.

Andikap *Supra Ferbindo, Indon.*
Activated attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Andil *Recalcine, Chile†.*
Paracetamol (p.108·1); adiphenine hydrochloride (p.2248·1).
Colic; fever; pain.

Andilex *CT, Ital.†.*
Nicorandil (p.1349·1).
Angina pectoris.

A-N-Dix *Provit, Mex.*
Nalidixic acid (p.303·3).
Bacterial infections of the urinary tract.

Andociclina Balsamica *Andromaco, Mex.†.*
Oxytetracycline (p.312·2); guaifenesin (p.1561·3); cineole (p.2282·3).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract disorders.

Andolba *Eurofarma, Braz.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1); menthol (p.2340·1); hydroxyquinoline benzoate (p.2323·2).
Gynaecological disorders.

Andolex *3M, Denm.; 3M, S.Afr.; 3M, Swed.*
Benzydamine hydrochloride (p.27·3).
Painful inflammation of the mouth and throat.

Andolex-C
Note.This name is used for preparations of different composition.
3M, S.Afr.
Lozenge; oral gel: Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Inflammation and infection of the mouth and throat.

3M, S.Afr.
Mouthwash: Benzydamine hydrochloride (p.27·3); chlorhexidine gluconate (p.1635·3).
Inflammation and infection of the mouth and throat.

Andolor
Note.This name is used for preparations of different composition.
Krewel, Ger.
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Ulagay, Turk.
Dipyrone (p.49·2).
Fever; pain.

Andonex *Meprofarm, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine (p.1568·1); guaifenesin (p.1561·3); ipecacuanha (p.1562·3).
Cough.

Andopan *Atlantis, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Andoprim *Andromaco, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Andox *Atlantis, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Andractim *Besins, Belg.; Besins, Fr.; Piette, Thai.†.*
⊗ Androstanolone (p.2082·3).
Gynaecomastia; lichen sclerosus; male hypogonadism.

Andraxan *Medicom, Cz.; PH&T, Gr.; Mayne, Thai.; Onko, Turk.*
Flutamide (p.725·1).
Prostatic cancer.

Andre *Andre, India.*
⊗ Boric acid (p.2268·1); chlorphenamine maleate (p.571·3); sodium chloride (p.1686·1); zinc sulfate (p.1999·2); chlorobutanol (p.1639·2); naphazoline hydrochloride (p.1565·2).
Conjunctivitis.

Andreafol *Andreabal, Switz.*
Folic acid (p.1940·1).
Neural tube defect prophylaxis.

Andregen *Andre, India.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Andre-I-Kul *Andre, India.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); menthol (p.2340·1); camphor (p.2273·2).
Eye irritation.

Andrews *GSK Consumer, Irl.; GSK Consumer, UK.*
Citric acid (p.2284·1); magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2).
Constipation; dyspepsia.

Andrews Antacid *GSK Consumer, Irl.; GSK Consumer, UK.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dyspepsia; gastric hyperacidity; heartburn.

Andrews Tums Antacid *GSK Consumer, Austral.*
Calcium carbonate (p.1714·1).
Calcium supplement; dyspepsia; heartburn.

Andrin *Casasco, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Andrioderma *Andromaco, Arg.*
Vitamin A (p.1971·2).
Skin disorders.

Andriodermol
Note.This name is used for preparations of different composition.
Uniao Quimica, Braz.
Topical liquid: Undecenoic acid (p.549·2); sodium undecenoate (p.549·3); propionic acid (p.545·2); sodium propionate (p.545·3); hexylresorcinol (p.1647·1).
Skin infections.

Uniao Quimica, Braz.
Topical paint: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); calcium propionate (p.545·3); hexylresorcinol (p.1647·1).
Skin infections.

Andriol *Organon, Austral.; Organon, Austria; Organon, Canad.; Organon, Denm.; Organon, Ger.; Organon, Hong Kong; Organon, Hung.; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Port.; Organon, Rus.; Organon, Singapore; Organon, Switz.; Organon, Thai.; Organon, Venez.*
⊗ Testosterone undecylate (p.2130·2).
Delayed puberty; hypopituitarism; male hypogonadism; male infertility; masculinisation in transexuals; osteoporosis; testosterone deficiency.

Andriol Testocaps *Organon, Indon.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; osteoporosis.

Androbloc *Torrex, Austria.*
Flutamide (p.725·1).
Prostatic cancer.

Androcur *Gobbi, Arg.; Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Berlex, Canad.; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Jenapharm, Ger.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Schering, Hung.; Schering, Indon.; Schering, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Bayer, UK; Schering, Venez.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; male sexual deviation; male virilisation; precocious puberty; prostatic cancer.

Androderm *Mayne, Austral.; Paladin, Canad.; AstraZeneca, Ger.†; Promed, Ger.†; IFET (ΙΦΕΤ), Gr.; Schwarz, Ital.†; Mayne, NZ; CEPA, Spain; AstraZeneca, Switz.; SmithKline Beecham, USA.*
⊗ Testosterone (p.2129·3).
Male hypogonadism; testosterone deficiency.

Andro-Diane *Schering, Austria.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Androdor *Andromaco, Chile†.*
Flutamide (p.725·1).
Prostatic cancer.

Androfemon *Jenapharm, Ger.†.*
⊗ Estradiol valerate (p.2097·3); testosterone enantate (p.2130·1).
Menopausal disorders.

Androfin *Lannacher, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Androfloxin *Teuto, Braz.*
Norfloxacin (p.309·2).
Urinary-tract infections.

AndroGel *Besins, Belg.; Solvay, Canad.; Besins, Cz.; Besins, Fr.; Besins, Israel; Solvay, Ital.; Besins, Neth.; Besins, Port.; Besins, Rus.; Unimed, USA; Biopas, Venez.*
⊗ Testosterone (p.2129·3).
Male hypogonadism; testosterone deficiency.

Andrographis Complex *Mediherb, Austral.*
Andrographis; echinacea (p.2298·1); ocimum sanctum.
Liver disorders; respiratory-tract disorders.

Andrographis Compound *Phytomedicine, Austral.*
Andrographis; echinacea (p.2298·1); skullcap (p.2388·2).
Cold symptoms.

Android *Valeant, USA.*
⊗ Methyltestosterone (p.2117·1).
Breast cancer; cryptorchidism; male hypogonadism.

Androlic *British Dispensary, Thai.*
⊗ Oxymetholone (p.2123·3).
Anabolic; anaemias; cachexia.

Androlip *Teuto, Braz.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Androlistica *Holistica, Fr.*
Cucurbita oil; palm-nut oil; onion; omega-3 marine triglycerides; borage oil; yam extract; sea lettuce (p.1922·1).
Male menopause.

Androlon *Meprofarm, Indon.*
⊗ Mesterolone (p.2116·1).
Androgen deficiency; male infertility.

Androlone *Beta, Arg.*
⊗ Testosterone (p.2129·3).
Hypogonadism.

Androlone-D *Keene, USA.*
⊗ Nandrolone decanoate (p.2118·2).
Anaemia in renal disease.

Androneo *Neo Quimica, Braz.*
Cyproterone acetate (p.2088·2).
Androgen-dependent disorders in females; hypersexuality in males; prostatic cancer.

Andropatch *IFET (ΙΦΕΤ), Gr.; GSK, Irl.; GSK, UK.*
⊗ Testosterone (p.2129·3).
Hypogonadism; testosterone deficiency.

Andropel *Fortbenton, Arg.*
⊗ Finasteride (p.2188·3).
Alopecia.

Andros *Biomedis, Philipp.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Androskat *Altana, Austria; Altana, Neth.*
Papaverine hydrochloride (p.2191·3); phentolamine mesilate (p.1370·2).
Erectile dysfunction.

Androstat
Note. This name is used for preparations of different composition.
Bioprofarma, Arg.
Cyproterone acetate (p.2088·2).
Prostatic cancer.

Orion, Irl.
Flutamide (p.725·1).
Prostatic cancer.

Androsten *Herbarium, Braz.*
Gokhru (p.2404·1).

Androsteron *Bergamo, Braz.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in females; prostatic cancer; sexual deviation in males.

Androtag *Rontag, Arg.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Androtardyl *Schering, Fr.*
⊗ Testosterone enantate (p.2130·1).
Male hypogonadism.

Androtin *Andromaco, Mex.*
Famotidine (p.1730·1).
Dyspepsia.

Androtop *Solvay, Ger.*
⊗ Testosterone (p.2129·3).
Testosterone deficiency.

Androvite *Optimox, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Androxicam *Andromaco, Mex.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint and peri-articular disorders; pain.

Androxinon *Schering, Arg.†.*
Bicalutamide (p.686·2).
Prostatic cancer.

Androxon *Organon, Braz.; Organon, Israel; Organon, Norw.†; Donmed, S.Afr.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism.

Androxy *Upsher-Smith, USA.*
⊗ Fluoxymesterone (p.2103·3).
Breast cancer; delayed puberty; hypogonadism.

Androxyl *Duopharma, Hong Kong.*
Cefadroxil (p.218·1).
Bacterial infections.

Andursil
Novartis, Braz.; Sanopharm, Switz.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Anebol *Gador, Arg.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Anebron *Protein, Mex.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Anectine *GSK, Irl.; GSK, Mex.; GSK, Spain; GSK, UK; Glaxo Wellcome, USA.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Anekain *Pliva, Rus.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Anekron *EMS, Braz.*
Choline citrate (p.1934·2); betaine hydrochloride (p.2265·2); methionine (p.1450·1); adenosine (p.1202·1); vitamin B (p.1978·2); sorbitol (p.1965·1).
Liver disorders.

Anemagen *Ethex, USA†.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); stomach extract (p.2326·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Anemagen OB *Ethex, USA†.*
Ferrous fumarate (p.1938·3); calcium; vitamins (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Anemet *Aventis, Ger.; Aventis, Hung.†.*
Dolasetron mesilate (p.1725·3).
Nausea and vomiting.

Anemicon Plus *San Marino, Philipp.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemia in pregnancy; iron and folic acid deficiency.

Anemidox
Note. This name is used for preparations of different composition.
Merck, Arg.
Folic acid; thiamine; riboflavin; pyridoxine; cyanocobalamin; nicotinamide (p.1922·1).
Anaemias; vitamin B deficiency.

Merck, India.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2); calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Vitamin C (p.1983·3) is included to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Anemidox Folico *Merck, Arg.*
Folic acid (p.1940·1).
Megaloblastic anaemia; prevention of neural tubes defects.

Anemidox-Ferrum *Merck, Arg.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Anemidox-Solutab *Merck, Arg.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia; vitamin B deficiency.

Anemifer *Pharma Line, Gr.*
Iron sucrose (p.1953·2).
Anaemia.

Anemiplus *Globo, Braz.†.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Anemital *Basi, Port.†.*
Ferrous gluconate (p.1939·1).
Anaemias.

Anemix *Hebron, Braz.†.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Anaemias.

Anemofer *Marjan, Braz.†.*
Cyanocobalamin (p.1980·2); ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in the tablet preparation to increase the absorption and availability of iron.
Anaemias.

Anerex *AF, Mex.*
Vitamin B substances with iron (p.1922·1).
Anaemias; tonic.

Anerobia *Pfizer, Philipp.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; trichomoniasis.

Anerocid *Ferron, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Anerocin *Aldril, Philipp.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Anervan *Recip, Fin.; Recip, Norw.; Recip, Swed.*
Ergotamine tartrate (p.620·1); chlorcyclizine hydrochloride (p.571·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Cluster headache; migraine.

Anerzol *Liferpal, Mex.*
Astemizole (p.567·2).

Anesdente do Bebe *Loprofar, Braz.†.*
Tetracaine hydrochloride (p.1871·3); menthol (p.2340·1).
Teething pain.

Anesject *Danpac, Indon.*
Ketamine hydrochloride (p.1787·1).
Anaesthesia; analgesia in obstetrics.

Anespas *Rudefsa, Mex.*
Prifinium bromide (p.1764·2).
Muscle spasm; pain.

Anespro *Behrens, Venez.*
Propofol (p.1791·1).
General anaesthesia.

Anestacon *PolyMedica, USA.*
Lidocaine hydrochloride (p.1862·3).
Urethral pain.

Anestafoam *Onset, USA.*
Lidocaine (p.1862·3).
Local anaesthesia.

Anestalcon *Alcon, Arg.; Alcon, Braz.; Alcon, Chile.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Anestesi Doble *Alcon Cusi, Spain.*
Oxybuprocaine hydrochloride (p.1867·3); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Anestesia Loc Braun S/A *Braun, Spain.*
Cinchocaine hydrochloride (p.1857·3); procaine hydrochloride (p.1869·1).
Local anaesthesia.

Anestesia Topi Braun C/A *Braun, Spain.*
⊗ Tetracaine hydrochloride (p.1871·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Anestesia Topi Braun S/A *Braun, Spain.*
Tetracaine (p.1871·2).
Local anaesthesia.

Anestesico *Allergan, Braz.; Alcon Cusi, Spain.*
Tetracaine hydrochloride (p.1871·3).
Naphazoline hydrochloride (p.1565·2) or phenylephrine hydrochloride (p.1568·1) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Anestesiol *Loprofar, Braz.†.*
Thymol (p.1664·3); menthol (p.2340·1); camphor (p.2273·2); tetracaine hydrochloride (p.1871·3); phenazone (p.116·1); clove oil (p.2285·1).
Mouth disorders.

Anesthal *Jagson, India.*
Thiopental sodium (p.1795·2).
General anaesthesia; status epilepticus.

Anestocil *Edol, Port.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Anestol *Ilsan, Turk.*
Lidocaine (p.1862·3).
Local anaesthesia.

Anethaine *Torbet Laboratories, UK.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Aneurin *Teva, Ger.†.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Aneurol *Lacer, Spain.*
Diazepam (p.986·3).
Contains pyridoxine hydrochloride.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Anevrase
Note. This name is used for preparations of different composition.
Cazi, Braz.†.
Oral solution: Passion flower (p.2363·2); mulungu (p.2348·1); valerian (p.2410·1); melmendro; crataegus (p.2289·1); melissa (p.2339·3).
Sedative.

Cazi, Braz.†.
Tablets: Passion flower (p.2363·2); mulungu (p.2348·1); valerian (p.2410·1); melmendro; crataegus (p.2289·1).
Sedative.

Anevrasi *Donini, Ital.*
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1).
Insomnia.

Anew
Note. This name is used for preparations of different composition.
Avon, Canad.
SPF 15 cream; SPF 15 lotion: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Avon, Canad.
SPF 15 eye cream: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Anew Force Extra *Avon, Canad.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Anew Luminosity *Avon, Canad.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Anew Positivity *Avon, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Anew Revital-Air *Avon, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Anexa *Microsules, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Anexate *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Canad.; Roche, Cz.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK.*
Flumazenil (p.1445·2).
Benzodiazepine overdosage; reversal of benzodiazepine-induced sedation.

Anexsia *Andrx, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Anextuss *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cough.

Anfagladin *Anfarm, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Anfer *Anfarm, Gr.; Anfarm, Thai.†; TTN, Thai.†.*
Nabumetone (p.91·2).
Inflammatory disorders; osteoarthritis; pain; rheumatoid arthritis.

Anfertil *Wyeth, Braz.*
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Anflat *Cazi, Braz.†.*
Simeticone (p.1770·2).
Flatulence.

Anflatox *Ares, Mex.†.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Anflene *Teuto, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Anfocort *BMS, Ital.*
⊗ Halcinonide (p.1535·1); amphotericin B (p.523·2).
Infected skin disorders.

Anfogen *Richmond, Arg.*
Liposomal amphotericin B (p.523·2) (p.523·2).
Fungal infections.

Anfokali *Bano, Austria.*
Homoeopathic preparation.

Anfolic *TRB, Arg.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Anforicin B *Cristalia, Braz.*
Amphotericin B (p.523·2).
Fungal infections.

Anfoterin *Teuto, Braz.†.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).
Vaginal infections.

Anfozan *Proel, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis.

Anfree *Sincerity, Hong Kong.*
Flupentixol (p.997·1); melitracen (p.408·1).
Anxiety; depression.

Anfugine *Blausiegel, Braz.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Trichomoniasis; vaginal candidiasis.

Anfugitarin *Blausiegel, Braz.*
Miconazole nitrate (p.541·3).
Perianal and vulvovaginal candidiasis.

Anfuhex *Hexpharm, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Angass *Medice, Ger.*
Bismuth subnitrate (p.1711·2); bismuth aluminate (p.1710·3).
Peptic ulcer.

Angass S *Medice, Ger.†.*
Bismuth subnitrate (p.1711·2).
Peptic ulcer.

Ange *Teikoku, Jpn.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Angeliq
Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Bayer Schering, Cz.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Bayer Schering, Hung.; Schering, Indon.; Schering, Irl.; Agis, Israel; Schering, Ital.; Schering, Mex.; Schering, Neth.; Schering, Philipp.; Schering, Pol.; Berlex, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Spain; Schering, Thai.; Schering, UK; Bayer, USA.
Estradiol (p.2097·2); drospirenone (p.2095·2).
Menopausal disorders; osteoporosis.

Schering, Turk.
Estradiol valerate (p.2097·3); drospirenone (p.2095·2).
Menopausal disorders; osteoporosis.

Angemin *Schering, Denm.; Schering, Swed.*
Drospirenone (p.2095·2); estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Angenol *APT, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Angenovag *Novag, Mex.*
⊗ Dequalinium chloride (p.1641·3); enoxolone (p.50·1); hydrocortisone acetate (p.1535·2); tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Angettes *BMS, UK.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Angeze *Opus, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Anghostam-100 *Biostam (Βιοσταμ), Gr.*
Ticlopidine (p.1412·1).
Thromboembolic disorders.

Angibosan *Bock, Ger.†.*
Homoeopathic preparation.

Angicon *Royal, Chile.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Angicor *Aventis, Denm.*
Nicorandil (p.1349·1).
Angina pectoris.

Angidil *Errekappa, Ital.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angidine *Vifor, Switz.*
Gramicidin (p.286·1); benzethonium chloride (p.1630·1); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Angifonil *Diviser Aquilea, Spain†.*
Cetylpyridinium chloride (p.1635·1).
Bacterial mouth infections.

Angil *Sanval, Braz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Angileptol *Sigma-Tau, Spain.*
Enoxolone (p.50·1); benzocaine (p.1854·1); chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

Angilol *Douglas, NZ; DDSA Pharmaceuticals, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma; tremor.

Angimet *Bergamo, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Angina MCC *Streuli, Switz.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Mouth and throat disorders.

Angina-Gastreu S R1 *Reckeweg, Ger.*
Homoeopathic preparation.

Anginamide *Medgenix, Belg.*
Sulfacetamide sodium (p.335·3).
Infections of the mouth and throat.

Anginazol *Intermedica, Switz.*
Dichlorobenzyl alcohol (p.1642·1); cetylpyridinium chloride (p.1635·1); chlorquinaldol (p.242·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat infections.

Anginesin *Grossmann, Switz.†.*
Aluminium acetotartrate (p.2255·1); sage (p.2382·3).
Mouth and throat pain.

Angin-Heel S *Heel, Cz.*
Homoeopathic preparation.

Anginin *Delta, Port.†.*
Pyricarbate (p.2377·1).

Anginine *Sigma, Austral.; GSK, NZ†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Anginol *Labima, Belg.*
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Anginol-Lidocaine *Labima, Belg.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Anginomycin *Chephasaar, Ger.†.*
Tyrothricin (p.358·2); bacitracin (p.210·3).
Mouth and throat infections.

Angino-Rub *Eurofarma, Braz.*
Benzydamine hydrochloride (p.27·3); cineole (p.2282·3); turpentine oil (p.2406·3); camphor (p.2273·2); thymol (p.1664·3); menthol (p.2340·1).
Mouth and throat disorders.

Anginotrat *Purissimus, Arg.*
Gentamicin embonate (p.284·2); sulfadiazine (p.336·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Anginotricin *Sanval, Braz.*
Neomycin sulfate (p.305·1); tyrothricin (p.358·2); benzocaine (p.1854·1); sodium perborate (p.1662·1).
Mouth and throat disorders.

Anginova
Note. This name is used for preparations of different composition.
Confar, Port.
Dequalinium chloride (p.1641·3); benzocaine (p.1854·1); trypsin (p.2405·3).
Mouth and throat disorders.

Medinova, Switz.†.
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Anginovag *Novag, Spain.*
⊗ Dequalinium chloride (p.1641·3); enoxolone (p.50·1); hydrocortisone acetate (p.1535·2); lidocaine hydrochloride (p.1862·3); tyrothricin (p.358·2).
Mouth and throat disorders.

Anginovin H *Pfluger, Ger.†.*
Homoeopathic preparation.

Angin-San *Sandipro, Belg.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Angiocine *Wolfs, Belg.*
Lidocaine hydrochloride (p.1862·3); chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

Angiocis *CIS, Port.; Schering, UK.*
Technetium-99m stannous pyrophosphate (p.2055·3).
Red blood cell labelling for blood pool scintigraphy.

Angiodarona *Cazi, Braz.*
Amiodarone (p.1210·2).
Arrhythmias.

Angiodel *Organon, Turk.*
Bencyclane fumarate (p.1224·1).

Angiodrox *Solvay, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angiofilina *Fabra, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Angiofluor *Poen, Arg.†.*
Fluorescein sodium (p.2306·1).
Adjunct in eye examination.

Angioflux *Mitim, Ital.*
A heparinoid (p.1305·2).
Thrombosis prophylaxis.

Angioftal *Allergan, Arg.†.*
Chromocarb diethylamine (p.2281·1).
Conjunctivitis.

Angiografin *Schering, Austral.†; Schering, Neth.†; Schering, S.Afr.†.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Angiografina *Schering, Arg.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Angiolingual *Royal, Chile.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Angiolit *Pharmacia, Arg.†.*
Nicergoline (p.2352·1); flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; circulatory disorders of the ear and eye.

Angiolong *Farmalab, Braz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Angiomax
Medison, Israel.
Bivalirudin (p.1234·2).
Thromboembolism prophylaxis in patients undergoing percutaneous coronary interventions.

Bago, Arg.; CSL, Austral.; Oryx, Canad.; CSL, NZ.; Medicines Company, USA.
Bivalirudin trifluoroacetate (p.1234·3).
Thromboembolism prophylaxis in patients undergoing percutaneous coronary interventions.

Angiomiron *Schering, Venez.†.*
Meglumine iodamide (p.1481·3); sodium iodamide (p.1482·1).
Radiographic contrast medium.

Angioneurina *Baxter, Arg.†.*
C esterase inhibitor (p.2287·1).

Angionorm *Farmasan, Ger.*
Dihydroergotamine mesilate (p.618·2).
Circulation disorders; hypotension; migraine.

Angiopas *Pascoe, Ger.†.*
Homoeopathic preparation.

Angiophtal *MSD-Chibret, Fr.†.*
Chromocarb diethylamine (p.2281·1).
Capillary fragility in the eye.

Angiopine *Ashbourne, UK†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Angiopril
Note. This name is used for preparations of different composition.
Diffucap, Braz.†.
Enalapril maleate (p.1276·1).
Hypertension.

Torrent, Rus.
Captopril (p.1239·2).

Angiopurin *Dexcel, Hung.†.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Angiorex *Lampugnani, Ital.†.*
Myrtillus (p.2349·3).
Capillary disorders.

Angiorex Complex *Lampugnani, Ital.*
Rose fruit (p.2381·2); myrtillus (p.2349·3); butcher's broom (p.2270·3); centella (p.1592·3).
Venous insufficiency.

Angiosan *Novartis, Austria.*
Valsartan (p.1420·2).
Hypertension.

Angioten *Kalbe, Indon.*
Losartan potassium (p.1326·1).
Hypertension.

Angioton
Note. This name is used for preparations of different composition.
GD, Ital.
Cream: Ginkgo biloba (p.2311·1); centella (p.1592·3); menthol (p.2340·1); bioflavonoids (p.2304·1).
Peripheral vascular disorders.

GD, Ital.
Tablets: Centella (p.1592·3); myrtillus (p.2349·3); rutoside (p.2305·1); vitamins (p.1922·1).
Venous disorders.

Angioton S *DHU, Ger.*
Homoeopathic preparation.

Angiotrofin *Armstrong, Mex.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angioval *Galenica, Gr.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Angiovan *Giempi, Venez.*
Amlodipine besilate (p.1214·1).
Angina pectoris; heart failure; hypertension.

Angiovein *Piam, Ital.*
Thioctic acid (p.2400·2); vitis vinifera (p.2316·3); centella (p.1592·3); aesculus (p.2248·2); andrographis; ginkgo biloba (p.2311·1); garlic (p.2309·2); vitamin B substances (p.1922·1).
Circulatory disorders.

Angiovist *Schering, Chile.*
Sodium amidotrizoate (p.1475·3); meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Angiox *Nycomed, Cz.; Medicines Company, Denm.; Leiras, Fin.; Nycomed, Fr.; Nycomed, Ger.; Medicines Company, Gr.; Medicines Company, Hung.; Nycomed, Ital.; Nycomed, Neth.; Medicines Company, Norw.; Medicines Company, Port.; Ferrer, Spain; Nycomed, Swed.; Medicines Company, UK.*
Bivalirudin (p.1234·2).
Acute coronary syndromes; thromboembolism prophylaxis in percutaneous coronary interventions.

Angiozem *Littman, Philipp.; Ashbourne, UK†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angipec *Lamsa, Arg.*
Amlodipine besilate (p.1214·1).

Angipina *Azevedos, Port.*
Nifedipine (p.1350·1).
Angina pectoris.

Angipress
Note. This name is used for preparations of different composition.
Biosintetica, Braz.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Crinos, Ital.†.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angipress CD *Biosintetica, Braz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Angirel *Unison, Philipp.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; Ménière's disease.

Angised *GSK, Hong Kong; GSK, India; GSK, Israel†; GSK, S.Afr.; GSK, Singapore; GSK, Thai.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Angi-Spray *Akromed, S.Afr.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

Angistad *Stada, Philipp.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; ischaemic heart disease; pulmonary hypertension.

Angitak *LPC, UK.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Angitil *Trinity, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Angitrate *Akromed, S.Afr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Angitrit *Ranbaxy, Thai.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Angizem *Sanofi-Aventis, Ital.; Sun, Thai.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Anglix *Novartis, Mex.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Anglopen *Liomont, Mex.*
Ampicillin (p.204·1), ampicillin sodium (p.204·1), or ampicillin trihydrate (p.204·2).
Bacterial infections.

Anglotex *Arlex, Mex.*
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Anglucid *Collins, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Angocin Anti-Infekt N *Repha, Ger.*
Tropaeolum majus (p.2264·3); horseradish (p.2320·1).
Respiratory-tract infections; urinary-tract infections.

Angocin Bronchialtropfen *Repha, Ger.*
Marrubium vulgare (p.1564·1).
Catarrh.

Angoron *Sanofi-Aventis, Gr.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias; wolff-Parkinson-White syndrome.

Angoten *Microsules, Arg.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Angrip *Giempi, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Angrip Noche *Giempi, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Angstrom Corpo *Chefaro, Ital.*
Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Angstrom Viso
Note. This name is used for preparations of different composition.
Chefaro, Ital.
Cream: Octinoxate (p.1608·2); avobenzone (p.1589·3); vitamin E acetate (p.1992·3); dimethicone (p.2032·1); betacarotene (p.1930·3); allantoin (p.1588·1); sodium pidolate (p.1614·1); triclosan (p.1665·2).
Barrier preparation; sunscreen.

Chefaro, Ital.
Stick: Octinoxate (p.1608·2); avobenzone (p.1589·3); vitamin E acetate (p.1992·3); betacarotene (p.1930·3).
Barrier preparation; sunscreen.

Anguilce *TRB, Arg.†.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Angular *Fada, Arg.†.*
Bromazepam (p.964·3).
Anxiety.

Angurate Magentee *Alsitan, Ger.†.*
Mentzelia cordifolia.
Gastrointestinal disorders.

Angyton *Royton, Braz.†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Anhidrot *Stiefel, Arg.†.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Anhissen *Sunthi Sepuri, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Anhista *Sriprasit, Thai.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms.

Anhydrol Forte *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Anice (Specie Composta) *Dynacren, Ital.†.*
Aniseed (p.2258·2); chamomile (p.2279·3); caraway (p.2276·3); peppermint leaf (p.1761·2); fennel (p.2302·3).
Gastrointestinal disorders; herbal tea.

Aniduv *LKM, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders.

Aniflazime *Seber, Port.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Aniflazym *Takeda, Ger.*
Serrapeptase (p.2385·3).
Inflammation.

Anikef *Duopharma, Hong Kong.*
Cefuroxime (p.238·2).
Bacterial infections.

Anilar *LKM, Arg.*
Sertraline (p.422·1).
Depression.

Anilid *Kener, Mex.*
⊗ Chlortalidone (p.1243·3).

Animal Shapes *Major, USA.*
Multivitamin preparation (p.1922·1).

Animal Shapes + Iron *Major, USA.*
Multivitamin preparation with iron (p.1922·1).

Animativ *BioSaude, Port.†.*
Multivitamin preparation with iron (p.1922·1).

Animex-On *Bernabo, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Animi-3 *PBM, USA.*
Omega-3 triglycerides (p.1362·1); vitamin B ; vitamin B ; folic acid (p.1922·1).
Dietary supplement.

Animic *Vinas, Spain.*
St John's wort (p.422·3).
Sleep disorders; tonic.

Animine
Note. This name is used for preparations of different composition.
McGloin, Austral.
Cream: Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1).
Bites; pruritus; stings.

McGloin, Austral.
Lotion: Lidocaine hydrochloride (p.1862·3); benzalkonium chloride (p.1629·1); calamine (p.1591·2).
Bites; pruritus; stings.

Anionen-Spurenelement *Fresenius Kabi, Austria.*
Electrolytes for infusion (p.1667·1).
Parenteral nutrition.

Anios DD *Anios, Fr.*
Quaternary ammonium compound; guanidinium acetate; propyl alcohol (p.1660·2).
Cleaning and disinfection of surfaces and instruments.

Aniospray 29 *Anios, Fr.*
⊗ Didecyldimethylammonium chloride (p.1642·2); polihexanide (p.1658·2); alcohol PE (p.1625·2); glycolic acid (p.1598·1).
Instrument and surface disinfection.

Aniospray 41 *Anios, Fr.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Disinfection of instruments and surfaces.

Aniosyme *Anios, Fr.*
Didecyldimethylammonium chloride (p.1642·2); chelators; proteases; lipases; amylases.
Instrument disinfection.

Anioxyde *Anios, Fr.*
Peracetic acid (p.1655·2); hydrogen peroxide (p.1647·3).
Instrument disinfection.

Anipen *Choongwae, Philipp.; Unimex, Philipp.*
Cilastatin (p.243·2); imipenem (p.286·3).
Bacterial infections.

Aniran *Rontag, Arg.*
⊗ Aniracetam (p.363·2).
Mental function disorders.

Anisan *Pascoe, Ger.†.*
Menthol (p.2340·1); bismuth subgallate (p.1711·1); aluminium acetotartrate (p.2255·1); St John's wort oil (p.423·2); hamamelis (p.2318·2); liver oil.
Anorectal disorders.

Anisimol *Medipharm, Chile.*
Fluoxetine (p.397·3).
Bulimia; depression.

Anistal *Silanes, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Anitid *Bernofarm, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastric hypersecretory disorders; peptic ulcer.

Anitrim *Italmex, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Anival *Errekappa, Ital.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Anixon *Kramer, Philipp.*
Vitamin B substances (p.1922·1); ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron-deficiency anaemia; nutritional supplement.

Anksen *Sanovel, Turk.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Anlene *Fonterra, Indon.; Fonterra, Malaysia; Fonterra, Philipp.*
A range of nutritional supplements (p.1922·1).

Anlo *Sigma, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Anlodibal *Baldacci, Braz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Anlos *Sandoz, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Anlostin *Biovena, Pol.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Anmerob *Medikon, Indon.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Anmum *Fonterra, Indon.; Fonterra, Malaysia.*
Nutritional supplement for pregnancy and breast feeding (p.1922·1).
Nutritional supplement.

Anna *TNP, Thai.†.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Annadine *Unison, Thai.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Annita *Farmoquimica, Braz.*
Nitazoxanide (p.842·3).
Worm infections.

Annoxen *Siam Bheasach, Thai.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Anodan-HC *Odan, Canad.*
⊗ Hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2).
Anorectal disorders.

Anodesyn *Thornton & Ross, UK.*
Lidocaine hydrochloride (p.1862·3); allantoin (p.1588·1).
Anorectal disorders.

Anoflam *Pharma Nutria, Philipp.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Anolor *Blansett, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).

Anopyrin *Zentiva, Cz.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Anore *Kalbe, Indon.*
Norethisterone (p.2119·3).
Dysfunctional bleeding; endometriosis; postponement of menstruation; premenstrual syndrome.

Anore Dolor *Schwarzwalder, Ger.†.*
Homoeopathic preparation.

Anore X N *Schwarzwalder, Ger.†.*
Absinthium (p.2244·1); gentian (p.2310·3); angelica (p.2258·1).
Appetite loss; dyspepsia; meteorism.

Anore rheumatic N *Schwarzwalder, Ger.*
Homoeopathic preparation.

Anoreine
Note. This name is used for preparations of different composition.
Janssen-Cilag, Austria.
Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Anorectal disorders.

McNeil, Fr.
Carrageenan (p.2142·3); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2).
Anorectal disorders.

Anoreine mit Lidocain *Janssen-Cilag, Austria.*
Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); lidocaine (p.1862·3).
Anorectal disorders.

Anorfin *Hexal, Denm.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Anorsia *Asian Pharm, Thai.*
Pizotifen malate (p.624·2).
Anorexia; vascular headache.

102 Anos *ISA, Arg.*
A range of dietary supplements (p.1922·1).

Anovate *USV, India.*
⊗ Beclometasone dipropionate (p.1516·2); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Anovulatorio Micro-Dosis *Laboratorios Chile, Chile; Mintlab, Chile.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Anovulatorios *Laboratorios Chile, Chile.*
Lynestrenol (p.2112·3); mestranol (p.2116·2).
Combined oral contraceptive; menstrual disorders.

A-Nox *Aroma, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Anoxant *Eagle, Austral.*
A vitamin, mineral, amino-acid, and herbal antoxidant preparation (p.1922·1).

Anoxen *Roemmers, Venez.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Anoxid *Volchem, Ital.*
Vitamins A, C, and E (p.1922·1).
Nutritional supplement.

Anoxolan *Neo Quimica, Braz.*
Cloxazolam (p.981·1).
Anxiety; epilepsy.

Anpec *Alphapharm, Austral.; Alphapharm, Malaysia†; Merck, Malaysia†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Anpeval *Vir, Spain.*
Triflusal (p.1418·3).
Thromboembolic disorders.

Anphechlor *Medhaus, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Anpiride *Sanbe, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Anplag *Mitsubishi, Jpn.*
Sarpogrelate hydrochloride (p.1390·1).
Occlusive arterial disease.

Anposel *Medipharm, Chile.*
Meloxicam (p.80·3).
Osteoarthritis; pain; rheumatoid arthritis.

Anpre *Wermar, Mex.*
Meloxicam (p.80·3).
Dysmenorrhoea; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Anpress *Condrugs, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Anquil *Janssen-Cilag, Irl.†; Concord, UK.*
Benperidol (p.964·1).
Deviant sexual behaviour.

Anremed *Bajamed, Mex.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Ansaid *Pfizer, Canad.; Pfizer, Chile; Pharmacia, Cz.†; Pfizer, Mex.; Upjohn, USA.*
Flurbiprofen (p.61·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ansal *Novartis, Denm.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis.

Ansar *Bioclon, Mex.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Ansatipin *Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.†; Kenfarma, Spain; Pfizer, Swed.*
Rifabutin (p.323·3).
Nontuberculous mycobacterial infections; tuberculosis.

Ansatipine *Pfizer, Fr.*
Rifabutin (p.323·3).
Mycobacterial infections; tuberculosis.

Anselol *Douglas, Austral.; Douglas, NZ†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ansentron *Biosintetica, Braz.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Anseren *Novartis, Ital.*
Ketazolam (p.1002·2).
Anxiety disorders.

Ansi *Bernofarm, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Ansial *Pharmacia, Arg.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Ansielix *Craveri, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Ansielix Digest *Craveri, Arg.*
Alprazolam (p.960·1); domperidone (p.1726·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Ansienon *Cazi, Braz.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Ansieten *Ivax, Arg.*
Ketazolam (p.1002·2).
Anxiety.

Ansietil *Tecnofarma, Chile.*
Ketazolam (p.1002·2).
Anxiety.

Ansilan
Note. This name is used for preparations of different composition.
Lek, Cz.
Medazepam (p.1006·1).
Anxiety; nervous disorders.

Cosmopharm, Gr.
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Giempi, Venez.
Alprazolam (p.960·1).
Anxiety; panic disorder.

Ansilive *Libbs, Braz.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Ansilor *Sofex, Port.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; insomnia; premedication.

Ansimar *ABC, Ital.; OEP, Philipp.*
Doxofylline (p.1120·3).
Obstructive airways disease.

Ansiokey *Inkeysa, Spain.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Ansiolin *Almirall, Ital.*
Diazepam (p.986·3).
Anxiety; epilepsy; insomnia; premedication.

Ansiopax *Hebron, Braz.†.*
Kava (p.2328·3).
Sedative.

Ansiotex *Cimed, Braz.*
Pimethixene (p.588·1).
Hypersensitivity reactions.

Ansitec *Libbs, Braz.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Ansiten *Azevedos, Port.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders.

Ansium *Lesvi, Spain.*
Diazepam (p.986·3); sulpiride (p.1028·3).
Anxiety.

Ansiven *Abbott, Switz.†.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Anso
Note. This name is used for preparations of different composition.
Lacer, Hong Kong.
⊗ Hexetidine (p.1647·1); lidocaine hydrochloride (p.1862·3); triamcinolone acetonide (p.1544·3); pentosan polysulfate (p.1367·1).
Anorectal disorders.

Lacer, Spain.
⊗ Lidocaine hydrochloride (p.1862·3); triamcinolone acetonide (p.1544·3); pentosan polysulfate sodium (p.1367·1).
Formerly contained hexetidine, lidocaine hydrochloride, triamcinolone acetonide, and pentosan polysulfate sodium.
Anorectal disorders.

Anstrep *Solas, Indon.*
Psidium guajava; curcuma longa; betel pepper; cimicifuga racemosa (p.2282·1).
Diarrhoea.

Ansudor *Galderma, Ger.†.*
Aluminium chlorohydrate (p.1588·3); triclocarban (p.1665·2).
Hyperhidrosis; intertrigo; wound exudate.

Answell *Cadila, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Answer *Carter, Austral.†; Carter-Wallace, USA.*
Pregnancy test (p.2372·1).

Answer Now *Carter Horner, Canad.†.*
Pregnancy test (p.2372·1).

Anta *Pharmasant, Thai.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; insomnia; muscle relaxation.

Antabus *Chemomedica, Austria; Farmo Quimica, Chile; Alpharma, Cz.; Alpharma, Denm.; Alpharma, Fin.; Altana, Ger.; Alpharma, Neth.; Alpharma, Norw.; Bohm, Spain; Alpharma, Swed.; Team Medica, Switz.; Nobel, Turk.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Antabuse *Orphan, Austral.; Sanofi-Aventis, Belg.; Alpharma, Irl.; Wyeth-Ayerst, Israel†; Sirton, Ital.; CSL, NZ; Pharmacare, S.Afr.; Dumex-Alpharma, Thai.†; Alpharma, UK; Barr, USA; Duramed, USA.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Antacaine *Quality, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1) or magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Dyspepsia; gastritis; heartburn; peptic ulcer; reflux oesophagitis.

Antacal *Errekappa, Ital.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Antacia-SM *The Forty-Two, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Antacid
Note. This name is used for preparations of different composition.
DC Labs, Canad.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).

Geneva, USA.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Hyperacidity.

Goldline, USA.
Tablets: Calcium carbonate (p.1714·1).
Hyperacidity.

Antacid Chewable Tablets *Vitelle, Austral.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Antacid Plus Antiflatulant *DC Labs, Canad.†; Stanley, Canad.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Antacid Suspension *Pharmel, Canad.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).

Antacide Suspension *Therapex, Canad.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).

Antacide Suspension avec Antiflatulent *Therapex, Canad.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Antacidum *Pfizer, Austria.*
Dihydroxyaluminum sodium carbonate (p.1723·3).
Dyspepsia; hyperacidity; peptic ulcer.

Antacil
Note. This name is used for preparations of different composition.
TNP, Thai.†.
Oral suspension: Aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; peptic ulcer.

TNP, Thai.†.
Tablets: Magnesium trisilicate (p.1744·1); dried aluminium hydroxide gel (p.1706·2); kaolin (p.1738·1).
Gastric hyperacidity; peptic ulcer.

Antacin-D *Quality, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; heartburn; hiatus hernia; oesophagitis; peptic ulcer.

Antacsal *Alpharma, Mex.*
Aspirin (p.20·3).
Fever; pain.

Antadar *FHC, Port.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Antaderm *Darier, Mex.*
Allantoin (p.1588·1); coal tar (p.1616·2).
Psoriasis; seborrhoeic dermatitis.

Antadex-H *Continentales, Mex.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Antadine *Sanofi Omnimed, S.Afr.†.*
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; influenza A; parkinsonism.

Antaethyl *Sanofi-Aventis, Hung.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Antafit *Polipharm, Thai.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Antag *MedGen, Philipp.*
Cimetidine (p.1716·2).
Dyspepsia; gastro-intestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Antagel
Note.This name is used for preparations of different composition.
PannonPharma, Hung.
Magnesium oxide (p.1744·1); aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Centrafarm, Neth.; Katwijk, Neth.; Kring, Neth.; Pharmachemie, Neth.; Ratiopharm, Neth.; Sandoz, Neth.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders associated with hyperacidity.

Antagel M *PannonPharma, Hung.*
Magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Antagon
Note.This name is used for preparations of different composition.
Ativus, Braz.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Organon, USA†.
Ganirelix acetate (p.2105·1).
Now known as Ganirelix Acetate Injection.
Inhibition of premature luteinising hormone surges in controlled ovarian hyperstimulation.

Antagon 1 *Liomont, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Antagonil *Astellas, Ger.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Antak *GSK, Braz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Antalfebal *McNeil, Ital.*
Ibuprofen (p.64·2).
Fever; pain.

Antalfort *McNeil, Ital.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Antalgic *Caps, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Antalgil *McNeil, Ital.*
Ibuprofen (p.64·2).
Pain.

Antalgin
Note.This name is used for preparations of different composition.
Berlico Mulia, Indon.; Corsa, Indon.; Soho, Indon.
Dipyrone (p.49·2).
Fever; pain.

Medix, Mex.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Roche, Spain.
Naproxen sodium (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Antalgo *Selvi, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Antalin *Saval, Chile.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Mixed anxiety depressive states.

Antalisin *McNeil, Ital.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Antalyre *Boehringer Ingelheim, Fr.*
Salicylic acid (p.1612·2).
Formerly contained chlorhexidine gluconate and oxedrine tartrate.
Conjunctival irritation.

Antamin *Pascual, Philipp.; Pharex, Philipp.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Antanax *Novartis, Gr.†.*
Alprazolam (p.960·1).
Anxiety disorders.

Antanazol *Shin Poong, Singapore.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Antapiril *Pharmacos, Mex.*
Aspirin (p.20·3); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Influenza symptoms.

Antara *Reliant, USA.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Antarene *Elerte, Fr.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Antares *Krewel Meuselbach, Cz.†.*
Kava (p.2328·3).
Anxiety; nervous disorders.

Antasten *Cetus, Arg.*
Captopril (p.1239·2).
Hypertension.

Antasten-Privin *Novartis Ophthalmics, Swed.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2); boric acid (p.2268·1); borax (p.2268·1).
Allergic conjunctivitis.

Antaxon *Zambon, Hung.*
Naltrexone hydrochloride (p.1455·2).
Opioid withdrawal.

Antaxone *Zambon, Ital.; Zambon, Port.; Zambon, Rus.; Pharmazam, Spain.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Antazallerge *Siam Bheasach, Thai.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Conjunctivitis.

Antazoline-V *Rugby, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1).
Eye irritation.

Antebe *Rafarm, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Antebor *Wolfs, Belg.; Medix, Fr.†.*
Sulfacetamide sodium (p.335·3).
Acne; skin infections.

Antebor N *Sanofi, Switz.*
Chlorhexidine (p.1635·2); triclosan (p.1665·2).
Acne; seborrhoea.

Antelepsin *Dresden, Cz.†; Desitin, Ger.*
Clonazepam (p.478·2).
Bipolar disorder; epilepsy; panic attacks.

Antemin *Streuli, Switz.*
Dimenhydrinate (p.576·2).
Nausea and vomiting.

Antemin compositum *Streuli, Switz.*
Dimenhydrinate (p.576·2); caffeine (p.1116·3); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Anten *Pacific, NZ.*
Doxepin hydrochloride (p.389·1).
Depression.

Antenex *Alphapharm, Austral.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm; spasticity.

Anteovin *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Antepan *Sanofi Synthelabo, Austria; Henning, Ger.; Sanofi Synthelabo, Ger.*
Protirelin (p.2175·3).
Assessment of pituitary and thyroid function.

Antepsin *Boehringer Ingelheim, Arg.; Orion, Denm.; Orion, Fin.; Chugai, Irl.; Baldacci, Ital.; Orion, Norw.; Bilim, Turk.; Chugai, UK; Merck, UK.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer.

Antergan *TNP, Thai.†.*
⊗ Hydrocortisone acetate (p.1535·2); mepyramine maleate (p.585·2).
Pruritus; skin irritation.

Anthel
Note.This name is used for preparations of different composition.
Alphapharm, Austral.
Pyrantel embonate (p.155·1).
Worm infections.

Shiwa, Thai.†.
Albendazole (p.139·2).
Worm infections.

Anthelios
Note.This name is used for preparations of different composition.
Roche-Posay, Canad.
Cream, SPF 30; cream, SPF 60: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Canad.
Lotion, SPF 45: Avobenzone (p.1589·3); titanium dioxide (p.1617·3); ecamsule (p.1596·1); octocrilene (p.1608·3).
Sunscreen.

Roche-Posay, Arg.†.
SPF 10; SPF 20; SPF 40; SPF 50; SPF 60: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Fr.
SPF 20; SPF 40; SPF 50: Octocrilene (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3); drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1).
Sunscreen.

Roche-Posay, Irl.
SPF 40: Octocrilene (p.1608·3); avobenzone (p.1589·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Irl.
SPF 60: Octocrilene (p.1608·3); avobenzone (p.1589·3); drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Polymorphous light eruption; sunscreen.

Roche-Posay, Canad.
Topical spray, SPF 30: Avobenzone (p.1589·3); titanium dioxide (p.1617·3); ecamsule (p.1596·1); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Anthelios Helioblock *Roche-Posay, Braz.*
SPF 20; SPF 30; SPF 60: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Anthelios Helioblock Dermopediatrics *Roche-Posay, Braz.*
SPF 40; SPF 60: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Anthelios Helioblock Spray *Roche-Posay, Braz.*
SPF 20: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3); octil triazone (p.1608·1).
Sunscreen.

Anthelios Helioblock W30 *Roche-Posay, Braz.*
SPF 30: Ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3); octil triazone (p.1608·1).
Sunscreen.

Anthelios Helioblock W40 *Roche-Posay, Braz.*
SPF 40: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Anthelios SX *Roche-Posay, USA.*
SPF 15: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3).
Sunscreen.

Anthelios XL Extreme *Roche-Posay, Singapore.*
Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1).
Sunscreen.

Antherpos
Note.This name is used for preparations of different composition.
Roche-Posay, Braz.
Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Irl.
Enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Lip protectant; sunscreen.

Roche-Posay, Arg.†.
SPF 50: Ecamsule (p.1596·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Canad.
SPF 50: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Fr.
SPF 50: Octocrilene (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3); ecamsule (p.1596·1).
Sunscreen.

Anthisan *Aventis, Hong Kong; Sanofi-Aventis, Irl.; Aventis, NZ; Aventis, S.Afr.; Aventis, UK.*
Mepyramine maleate (p.585·2).
Allergic skin disorders; insect bites and stings; nettle rash; pruritus.

Anthisan Plus *Aventis, UK.*
Mepyramine maleate (p.585·2); benzocaine (p.1854·1).
Bites and stings.

Anthogenol *Phytologic, Austral.*
Grape (p.2316·3); ascorbic acid (p.1983·3).
Antoxidant; varicose veins.

Anthozym *Petrasch, Austria.*
Beta vulgaris; lactic acid; ferrous lactate; ascorbic acid; calcium lactate; potassium aspartate; magnesium aspartate; black currant juice (p.1922·1).
Tonic.

Anthracin *Dabur, Thai.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Anthra-Derm *Dermik, USA†.*
Dithranol (p.1595·2).
Psoriasis.

Anthraforte *Medican, Canad.*
Dithranol (p.1595·2).
Psoriasis.

Anthramed *Surya Dermato, Indon.*
Dithranol (p.1595·2).
Psoriasis.

Anthranol *Medican, Canad.; Stiefel, S.Afr.*
Dithranol (p.1595·2).
Psoriasis.

Anthrascalp *Medican, Canad.*
Dithranol (p.1595·2).
Psoriasis.

Anthraxiton *Medinova (Μεντινοβα), Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Anthrom *Yung Shin, Philipp.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Anti *Antula, Swed.*
Aciclovir (p.862·3).
Herpes labialis.

Anti Anorex Triple *Lesvi, Spain.*
⊗ Cyproheptadine hydrochloride (p.575·1); deanol aceglumate (p.2152·3); metoclopramide hydrochloride (p.1747·3).
Tonic.

Anti Itch
Note. A similar name is used for preparations of different composition (see Anti-Itch, below).
Medibrands, Israel.
Pramocaine hydrochloride (p.1868·1).
Pruritus; skin irritation; stings.

Anti-Ac
Note. A similar name is used for preparations of different composition (see below).
Clement-Thekan, Fr.†.
Pirimiphos-methyl (p.2049·2); permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
House dust mite acaricide.

Antiac
Note. A similar name is used for preparations of different composition (see above).
Salcura, UK.
Aloe vera (p.1588·2); manuka (p.2337·3).
Acne.

Antiacid
Note.This name is used for preparations of different composition.
Garden House, Arg.
Magnesium carbonate (p.1743·1); menthol (p.2340·1); calcium carbonate (p.1714·1).
Antacid; dietary supplement.

Lemax, Arg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Anti-Acido
Note. A similar name is used for preparations of different composition (see below).
Giuliani, Ital.
Aluminium hydroxide dried gel (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Aerophagia; gastric hyperacidity; meteorism.

Antiacido
Note. A similar name is used for preparations of different composition (see above).
GC, Venez.
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Antiacil *Sedabel, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1).
Antacid.

Antiacne
Note. A similar name is used for preparations of different composition (see below).
Drag, Chile†.
Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Anti-Acne
Note. A similar name is used for preparations of different composition (see above).
MDM, Ital.
Sublimed sulfur (p.1614·1); meclocycline sulfosalicylate (p.297·2); nicoboxil (p.95·1).
Acne.

Anti-Acne Control Formula *Clinique, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Antiacneicos Ac-Sal *Isdin, Port.†.*
Salicylic acid (p.1612·2); triclosan (p.1665·2); aloe vera (p.1588·2); polyglyceryl methacrylate.
Acne.

Antiacneicos Niacex *Isdin, Port.†.*
Niseiramida; glycerol (p.2314·2); sodium carbomer.
Acne.

Antiadipositum *Riemser, Ger.*
Phenylpropanolamine hydrochloride (p.1569·3); thiamine hydrochloride; pyridoxine hydrochloride; ascorbic acid (p.1922·1).
Obesity.

Antiadipositum X-112 *Hanseler, Switz.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Antiadipositum X-112 T *Riemser, Ger.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Antiadiposo *Teofarma, Ital.*
Iodocasein (p.2170·1); thiamine nitrate (p.1976·2).
Metabolic activator.

Anti-Age Energy *Argenfarma, Arg.*
Vitamin and mineral preparation (p.1922·1).

Anti-Ageing Kalmia *Homeocan, Canad.†*
Homoeopathic preparation.

Antiamox *Epicaris, Arg.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Antianem *Suan, Gr.*
Iron polymaltose (p.1953·1).
Anaemia.

Anti-Asidoz *Assos, Turk.*
Sodium bicarbonate (p.1673·2).
Dyspepsia; metabolic acidosis; urinary alkalinisation.

Anti-Asmatico *CPH, Port.*
⊗ Aminophylline (p.1114·2); phenobarbital (p.492·2); ephedrine hydrochloride (p.1558·2).
Asthma.

Antiax *Saval, Chile.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Antib *Biogam, Arg.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Antibacin
Elpen (Ελπεν), Gr.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Elpen, Singapore.
Ceftriaxone (p.238·1).
Bacterial infections.

Antibacter *Biol, Arg.†*
Sodium hypochlorite (p.1661·1); magnesium hypochlorite.
Disinfection.

Antibacter Forte *Bayer, Gr.*
Triclocarban (p.1665·2).
Disinfection.

Antibacterial Honey Barrier *Medihoney, Austral.*
Honey (p.1948·2).
Formerly known as Antibacterial Wound Gel.
Burns; ulcers; wounds.

Antibeksin *Fako, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); sodium citrate (p.1673·3); sulfogaiacol (p.1573·2); pheniramine maleate (p.587·3).
Respiratory-tract congestion.

Antiben *Liferpal, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Antibex *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Anti-Bio *Anpharm (Ανφαρμ), Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Antibiocilina *Fada, Arg.†*
Amoxicillin (p.202·2).
Bacterial infections.

Antibiocort *Eczane, Arg.†*
⊗ Hydrocortisone (p.1535·2); naphazoline (p.1565·1); neomycin (p.305·1); gramicidin (p.286·1).
Infected eye disorders.

Antibiopen *Reig Jofre, Spain.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Antibiophilus *Germania, Austria; Azevedos, Port.*
Lactobacillus rhamnosus (p.2372·3).
Diarrhoea.

Antibioptal
Note. This name is used for preparations of different composition.
Poen, Arg.
Tobramycin (p.354·1); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Farmila, Ital.
Chloramphenicol (p.239·3); neomycin sulfate (p.305·1).
Bacterial eye infections.

Antibiostad *Stada, Austria.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Antibio-Synalar *Jolly-Jatel, Fr.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Otitis externa.

Antibi-Otic *Seng, Thai.*
Chloramphenicol (p.239·3).
Bacterial ear infections.

Antibiotic Cold Sore Ointment *Columbia, Canad.*
Polymyxin B sulfate (p.317·3); tyrothricin (p.358·2); camphor (p.2273·2); menthol (p.2340·1); benzocaine (p.1854·1).
Herpes labialis.

Antibiotic Cream *Technilab, Canad.†*
Gramicidin (p.286·1); polymyxin B sulfate (p.317·3).

Antibiotic Simplex *Howmedica, NZ.*
Erythromycin gluceptate (p.269·3); colistimethate sodium (p.256·3); polymethylmethacrylate/methylmethacrylate copolymer (p.2343·3).
Bone cement for orthopaedic surgery.

Antibiotique Onguent *Prodemdis, Canad.*
Bacitracin (p.210·3); polymyxin B sulfate (p.317·3).

Antibiotrex *Stiefel, Fr.*
Isotretinoin (p.1599·2); erythromycin (p.269·2).
Acne.

Antibiotulle Lumiere *Solvay, Fr.; Hefa, Ger.†*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Burns; burns, ulcers; infected wounds; wounds.

Antibioxime *Atral, Port.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Anti-Bit *Eczacibasi, Rus.; Eczacibasi, Turk.*
Phenothrin (p.2048·3).
Pediculosis.

Antibloc *Craveri, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Antiblut *Genepharm, Gr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Antibron *Potter's, UK.*
⊗ Lobelia (p.2157·2); wild lettuce (p.2415·2); coltsfoot (p.1555·1); euphorbia (p.2301·3); pleurisy root (p.2370·1); senega (p.1572·3).
Coughs.

Antican *Elpen (Ελπεν), Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Anticatarral *Edigen, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, guaiazulene, muramidase hydrochloride, and paracetamol.
Cold and influenza symptoms.

Anticepim *Verisfield, Gr.*
Cefepime (p.224·1).
Bacterial infections.

Anticerumen *Desma, Spain.*
Sodium laurilsulfate (p.2138·3).
Removal of ear wax.

Antichloric *Therabel, Belg.*
Calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1).
Peptic ulcer.

Antichol *Medicus, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Anticholium *Kohler, Austria; Kohler, Cz.; Kohler, Ger.; IFET (ΙΦΕΤ), Gr.*
Physostigmine salicylate (p.1883·3).
Alcohol withdrawal syndrome; antimuscarinic poisoning; central anticholinergic syndrome.

Anticina *Ivax, Mex.*
Ranitidine (p.1766·1).
Gastric hyperacidity.

Anticol *Polfa Warszawa, Pol.*
Disulfiram (p.2296·2).
Alcoholism.

Anticold
Note. This name is used for preparations of different composition.
Andromaco, Chile.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Cold and influenza symptoms.

Christo, Hong Kong.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Colds; influenza.

Anticon *Uniderm, Israel.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Anticongestiva *Sanofi-Aventis, Spain.*
Zinc oxide (p.1621·2).
Skin irritation.

Anticorizza *Ogna, Ital.†*
Paracetamol (p.108·1); salicylamide (p.121·2); caffeine (p.1116·3); tripelennamine hydrochloride (p.592·2).
Cold and influenza symptoms.

Anticors Diable Vert *Colin, Belg.*
Salicylic acid (p.1612·2).
Warts.

Anticude
IFET (ΙΦΕΤ), Gr.
Edrophonium chloride (p.630·3).
Myasthenia gravis.

UCB, Spain.
Edrophonium bromide (p.630·3).
Diagnosis of myasthenia gravis; reversal of competitive neuromuscular blockade.

Anti-D *Upha, Malaysia†; Beacons, Singapore.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Antidep *Torrent, India.*
Imipramine hydrochloride (p.400·3).
Depression; narcoleptic syndrome; nocturnal enuresis.

Anti-Dessechement *Lierac, Fr.*
⊗ Urea (p.1620·2).
Dry skin; keratinisation disorders.

Antidia *Bernofarm, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Antidiab *KRKA, Cz.†; KRKA, Pol.*
Glipizide (p.441·3).
Diabetes mellitus.

Antidiar *Ahimsa, Arg.†*
Phthalylsulfathiazole (p.315·1); menadione (p.1995·2).
Diarrhoea.

Anti-Diarrheal *Stanley, Canad.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Antidifar *Alpharma, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Antidin *Teuto, Braz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Antidine *Kimia, Indon.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Antidol
Note. This name is used for preparations of different composition.
Elvetium, Arg.†
Rofecoxib (p.121·1).
Osteoarthritis; pain.

Gerbex, Canad.
Aspirin (p.20·3); caffeine (p.1116·3).

Quimica y Farmacia, Mex.; Cinfa, Spain.
Paracetamol (p.108·1).
Fever; pain.

Lek, Pol.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Antidot *Sistas, Turk.*
Menthol (p.2340·1); camphor (p.2273·2); boric acid (p.2268·1); methyl salicylate (p.85·3).
Minor cuts and abrasions.

Antidotum Thallii-Heyl *Heyl, Ger.*
Prussian blue (p.1461·3).
Thallium poisoning.

Antidral *Polfa Kutno, Pol.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Antidrasi *Visufarma, Ital.*
⊗ Diclofenamide (p.1880·2) or diclofenamide sodium (p.1880·2).
Control of intra-ocular pressure during eye surgery; glaucoma.

Antidry
Note. This name is used for preparations of different composition.
Merz, Switz.
Bath oil: Liquid paraffin (p.2030·3); almond oil (p.2252·2).
Skin disorders.

Merz, Switz.
Ointment: Pansy (p.2415·2); zinc oxide (p.1621·2); almond oil (p.2252·2).
Skin disorders.

Merz, Switz.
Shower oil: Liquid paraffin (p.2030·3); soya oil (p.1965·3); levomenol (p.2333·3).
Skin disorders.

Merz, Switz.
Topical lotion: Sodium lactate (p.1673·3); almond oil (p.2252·2).
Skin disorders.

Antiedema *Alcon Cusi, Spain.*
Sodium chloride (p.1686·1).
Corneal oedema.

Anti-Em *Adeka, Turk.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vertigo; vestibular disorders.

Antiemorroidali *AFOM, Ital.*
Ichthammol (p.1599·1); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); belladonna (p.2263·3).
Haemorrhoids.

Antiespasmodico *Veinfar, Arg.*
Homatropine (p.1881·2).
Smooth muscle spasm.

Antiestrias *Isdin, Port.*
Centella (p.1592·3); borage oil (p.2267·3); *dl*-alpha tocoferil acetate (p.1992·3); jojoba oil.
Firming cream.

Antietanol *Sanofi-Aventis, Braz.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Antifebrin *Royton, Braz.†*
Aspirin (p.20·3).
Fever; inflammation; pain.

Antifect *Potter's, UK.*
Garlic (p.2309·2); garlic oil (p.2309·2); echinacea (p.2298·1).
Catarrh; nasal congestion; rhinitis.

Antiflam *Rolab, S.Afr.†*
Ibuprofen (p.64·2).
Fever; pain.

Antiflammin H *Pfluger, Ger.†*
Homoeopathic preparation.

Antiflat *Lannacher, Austria; Mecom, Turk.*
Simeticone (p.1770·2).
Aid in gastrointestinal radiography; detergent poisoning; excess gastrointestinal gas.

Antiflog *FIRMA, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Antiflogil *Farmasa, Braz.†*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Antiflogol *Poen, Arg.*
⊗ Betamethasone (p.1518·2); tetryzoline hydrochloride (p.1574·1); chloramphenicol (p.239·3).
Infected eye disorders.

Antiflu
Note. This name is used for preparations of different composition.
Altana, Ital.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Sagmel, Rus.
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Pharmco, S.Afr.†
Paracetamol (p.108·1); mepyramine maleate (p.585·2); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3); codeine phosphate (p.37·2); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Antiflu Forte *Synco, Hong Kong.*
Paracetamol (p.108·1); salicylamide (p.121·2); phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms; rhinitis.

Antiflu-Des *Chinoin, Mex.*
Amantadine hydrochloride (p.792·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Influenza symptoms.

Antiflu-N-Forte *Synco, Hong Kong.*
⊗ Paracetamol (p.108·1); salicylamide (p.121·2); ephedrine hydrochloride (p.1558·2); phenylephrine hydrochloride (p.1568·1); dexchlorpheniramine maleate (p.572·1); caffeine (p.1116·3).
Cold and influenza symptoms; rhinitis.

AntiFocal *Vitorgan, Ger.*
Homoeopathic preparation.

AntiFocal N *Vitorgan, Ger.*
Homoeopathic preparation.

AntiFocal Nr 69-Sol L *Vitorgan, Ger.*
Homoeopathic preparation.

AntiFocal pro inj (Revitorgan-Dilution Nr 69) *Vitorgan, Ger.*
Homoeopathic preparation.

Antifom *Vargas, Venez.*
Simeticone (p.1770·2).
Flatulence.

Antifort *Christo, Hong Kong.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis; upper respiratory-tract congestion.

Anti-Fosfat Ca *Assos, Turk.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Anti-Fosfat Cc *Assos, Turk.*
Calcium carbonate (p.1714·1).
Hyperphosphataemia.

Antifungal
Note. This name is used for preparations of different composition.
Fortbenton, Arg.
Sulconazole nitrate (p.546·2).
Fungal skin infections.

YSP, Malaysia; Yung Shin, Singapore.
Miconazole nitrate (p.541·3).
Fungal skin and vaginal infections; fungal skin and vulvovaginal infections.

Antifungal Foot Deodorant *Or-Dov, Austral.†*
Tolnaftate (p.548·3).
Tinea pedis.

Antifungol
Note. This name is used for preparations of different composition.
Hexal, Rus.
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Hexal, Ger.
Cream; lotion; pessaries; topical spray; vaginal cream: Clotrimazole (p.530·1).
Fungal infections of the skin and genito-urinary tract.

Hexal, Ger.
Paste: Clotrimazole (p.530·1); zinc oxide (p.1621·2).
Fungal skin infections.

Antigeron *Farmasa, Braz.*
Cinnarizine (p.573·1).
Vestibular disorders.

Antiglan *Potter's, UK.*
Saw palmetto (p.2192·3); equisetum (p.2299·3); hydrangea (p.2321·2).
Formerly contained kava, saw palmetto, equisetum, and hydrangea.
Bladder discomfort.

Antigram *Armstrong, Mex.*
Lysine aspirin (p.79·1); metoclopramide (p.1747·3).
Migraine; vascular headache.

Anti-Granulocyte BW *CIS, Cz.†*
Technetium-99m (p.2055·3) labelled anti-granulocyte monoclonal antibody.
Bone-marrow scintigraphy; inflammation scintigraphy.

Antigreg *Piam, Ital.; Vecchi, Malaysia; Piam, Singapore.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Antigrietun *Casen Fleet, Spain.*
⊗ Allantoin (p.1588·1); aminoacridine (p.1625·2); peru balsam (p.2365·3); prednisolone (p.1540·3).
Allergic skin disorders; cracked nipples; mastitis; superficial burns.

Antigripal Compuesto *Vent-3, Arg.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Anti-Gripe *Plough, Port.†.*
Aconite (p.2246·1); belladonna (p.2263·3); codeine (p.37·2); caffeine (p.1116·3); paracetamol (p.108·1).
Cold symptoms; fever; pain.

Anti-Gripe Asclepius *Plough, Port.*
Paracetamol (p.108·1).
Fever; pain.

Antigriphine *GSK Consumer, Belg.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Antigrippin-ANVI *Antiviral, Rus.*
Green capsules: aspirin (p.20·3); ascorbic acid (p.1983·3); rutoside (p.2305·1); white capsules: dipyrone (p.49·2); diphenhydramine (p.577·1); calcium gluconate (p.1675·3).
Influenza symptoms; sARS.

Antigrippine
Note.This name is used for preparations of different composition.
GSK Consumer, Neth.
Paracetamol (p.108·1); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Fever; pain.

GSK Consumer, Port.
Paracetamol (p.108·1); mepyramine (p.585·1); caffeine (p.1116·3).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, and paracetamol.
Fever; pain.

Anti-H *Eisai, Fr.†.*
Aluminium sodium silicate (p.1707·3); kaolin (p.1738·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Flatulence; gastrointestinal pain.

Antihemorroidal
Note.This name is used for preparations of different composition.
Denver, Arg.
⊗ Lidocaine hydrochloride (p.1862·3); betamethasone valerate (p.1519·1); phenylephrine hydrochloride (p.1568·1).
Haemorrhoids.

Sertex, Arg.
Zinc oxide (p.1621·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Cinfa, Spain.
⊗ Benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); tannic acid (p.2394·3).
Anorectal disorders.

ICN, Spain†.
Ointment: ⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); promethazine hydrochloride (p.588·2); vitamin A (p.1971·2).
Anorectal disorders.

Antihep *Microgen, Rus.†.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Antihist *Merck, S.Afr.*
Mepyramine maleate (p.585·2).
Hypersensitivity reactions.

Antihistaminico *Llorens, Spain.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions of the eye.

Anti-Homocysteine Factor *Eagle, Austral.*
Amino acids, vitamin B substances; minerals (p.1922·1).
Elevated homocysteine levels.

Antihydral *Robugen, Ger.; Iromedica, Switz.*
Methenamine (p.298·3).
Hyperhidrosis; skin infections.

Antihydral M *Robugen, Ger.†; Robugen, Hong Kong†.*
Methenamine (p.298·3); sulfur (p.1614·1).
Fungal skin infections; hyperhidrosis.

Antihypertonicum Forte *Hevert, Ger.*
Homoeopathic preparation.

Antihypertonicum S *Schuck, Ger.*
Betula (p.2266·3); crataegus (p.2289·1); mistletoe (p.2345·3); olive (p.2356·2); rhododendron leaf; rutoside (p.2305·1); proxyphylline (p.1130·3).
Atherosclerosis; hypertension.

Antihypertonicum-Tropfen N *Schuck, Ger.*
Homoeopathic preparation.

Antihypertonicum-Weliplex *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Anti-Itch
Note. A similar name is used for preparations of different composition (see Anti Itch, above).
Taro, USA.
Diphenhydramine hydrochloride (p.577·2); zinc acetate (p.1999·1).
Pruritus.

Anti-Kalium *Medice, Ger.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Antikataraktikum N *Ursapharm, Ger.*
Disodium inosinate (p.2296·1).
Visual disturbances.

Antikatarata *Novartis Ophthalmics, Arg.†.*
Disodium inosinate (p.2296·1); nicotinamide (p.1957·3); magnesium aspartate (p.1679·1); sodium glycerophosphate (p.2315·2).
Cataracts.

Antikatarata Plus *Novartis, Arg.*
Potassium iodide (p.2169·2); sodium iodide (p.2169·2).
Cataracts.

Antikeloides Creme *Widmer, Switz.*
⊗ Dexamethasone (p.1526·1); urea (p.1620·2); vitamin A palmitate (p.1973·1).
Scars.

Antikun *Interbat, Indon.*
Piracetam (p.368·2).
Cerebral infarction.

Antil *Carnot, Mex.†.*
Cimetidine (p.1716·2).

Antilerg *Valeant, Arg.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis.

Antilergal *Medix, Mex.*
Loratadine (p.583·3).
Hypersensitivity reactions; rhinitis.

Antilerg-F *Demo, Gr.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Bacterial infections with inflammation.

Antilipid *Kleva, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Antilirium *Forest Pharmaceuticals, USA.*
Physostigmine salicylate (p.1883·3).
Reversal of drug-induced CNS antimuscarinic effects.

Antilysin *Spofa, Cz.†.*
Aprotinin (p.1055·1).
Haemorrhagic disorders.

Antimast N *Pharmakon, Ger.*
Homoeopathic preparation.

Antimast T *Selz, Ger.†.*
Homoeopathic preparation.

Antimast TN *Pharmakon, Ger.*
Homoeopathic preparation.

Antimed *Bajamed, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Antimeningococica A+C *Sanofi Pasteur, Arg.*
A meningococcal vaccine (group A and C) (p.2224·1).
Active immunisation.

Antimet *Antigen, Irl.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Antimic *Chew, Thai.*
Isoniazid (p.288·1).
Tuberculosis.

Antimicon *Lafit, Braz.†.*
Iodine (p.2169·2); benzoic acid (p.1630·2); salicylic acid (p.1612·2).

Antimicotica Solforata *AFOM, Ital.*
Sodium thiosulfate (p.1466·1); tartaric acid (p.2395·2).
Fungal skin infections.

Antimicotico *Savoma, Ital.*
Cream: Clotrimazole (p.530·1).
Fungal infections.

Antimicotico Martel *Hertz, Braz.*
Clotrimazole (p.530·1).
Fungal skin infections.

Antimigren *Pascoe, Ger.*
Homoeopathic preparation.

Antimigrin *Gebro, Austria.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Antiminth
Note.This name is used for preparations of different composition.
Pfizer, USA†.
Pyrantel embonate (p.155·1).
Worm infections.

Costec, Arg.
Shampoo: Pyrithione zinc (p.1611·2).
Scalp disorders.

Costec, Arg.
Soap: Chlorhexidine gluconate (p.1635·3).
Skin cleanser.

Anti-Mosquito *Premia, UK.*
Menthoglycol.
Insect repellent.

Antimycotic *Biospray, Gr.*
⊗ Miconazole nitrate (p.541·3); fluprednidene acetate (p.1533·1).
Infected skin disorders.

Antinaus *Pacific, NZ.*
Prochlorperazine maleate (p.1020·1).
Anxiety; Ménière's disease; nausea and vomiting; psychoses; vertigo.

Anti-Nauseant *Stanley, Canad.*
Dimenhydrinate (p.576·2).
Nausea.

Antinephrin M *Hanosan, Ger.*
Homoeopathic preparation.

Antinerveux Lesourd *Lesourd, Fr.*
Lotus petal; melilot (p.2339·2).
Insomnia; irritability.

Antineuralgica
Note.This name is used for preparations of different composition.
EGIS, Hung.
Caffeine (p.1116·3); aminophenazone (p.19·1); phenacetin (p.115·3).
Fever; pain.

Alpharma, Norw.
Caffeine (p.1116·3); phenazone (p.116·1).
Pain.

Antineurina *Mabo, Spain.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Neuritis; vitamin B deficiency.

Antinevralgico Dr Knapp *Montefarmaco, Ital.†.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Antinicoticum mono *Pharmakon, Ger.*
⊗ Homoeopathic preparation.

Antinicoticum sine (Rowo-100) *Pharmakon, Ger.†.*
Homoeopathic preparation.

Antio *Pentamedical, Ital.*
Zinc ricinoleate (p.2417·3).
Body odour.

Antiobiocilina *Fada, Arg.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Antiopiaz *Richmond, Arg.*
Naloxone (p.1454·1).
Opioid withdrawal.

Antiotic *Grossmann, Switz.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Antiox *Janssen, Philipp.*
Mebendazole (p.148·3).
Worm infections.

Antioxidans E *Hevert, Ger.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Antioxidant Formula *Nutrifarma, Turk.*
Multivitamin and mineral preparation (p.1922·1).

Antioxidant Forte Tablets *Vitelle, Austral.*
Betacarotene (p.1930·3); riboflavin (p.1977·2); ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); *d*-alpha tocoferil acid succinate (p.1993·1); zinc amino acid chelate (p.2000·1); folic acid (p.1940·1); milk thistle (p.1452·1); vitis vinifera (p.2316·3).
Antioxidant; vitamin A, C, E, and B , folic acid, and zinc deficiencies.

Antioxidant Tablets *Cenovis, Austral.; Vitelle, Austral.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); betacarotene (p.1930·3); *d*-alpha tocoferil acid succinate (p.1993·1); zinc amino acid chelate (p.2000·1); riboflavin (p.1977·2).
Antioxidant; vitamin A, C, E, B , and zinc deficiencies.

Antioxidante Natural *Framingham, Arg.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Antioxidante Plus *ISA, Arg.*
Vitamins; selenium (p.1922·1).

Antioxidante Vital *AM, Arg.*
Vitamin and mineral preparation (p.1922·1).

Antioxycaps with Selenium *Minskinterkaps, Rus.*
Ascorbic acid; α-tocopherol acetate; betacarotene; selenium yeast (p.1922·1).
Vitamin and selenium deficiency.

Anti-oxydant 200 *Synergia, Fr.*
Vitamin C; vitamin E; betacarotene; lycopene; lutein; selenium (p.1922·1).
Antoxidant preparation.

Anti-oxydant F4 *Synergia, Fr.*
Vitamin C; citroflavonoids; green tea; myrtillus; grape extract; vitamin E; carotenoids; lycopene; selenium (p.1922·1).
Antoxidant preparation.

Antipain *Nida, Singapore.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Insect bites; musculoskeletal disorders.

Antiparkin *Viatris, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Antipasmol *Monserrat, Arg.*
Belladonna (p.2263·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Antipeol
Note.This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Zinc oxide (p.1621·2); ichthammol (p.1599·1); salicylic acid (p.1612·2).
Skin disorders.

Medico-Biological Laboratories, UK.
⊗ Zinc oxide (p.1621·2); ichthammol (p.1599·1); salicylic acid (p.1612·2); urea (p.1620·2).
Skin disorders.

Antiphlogistine
Note.This name is used for preparations of different composition.
CIF, Braz.†.
Boric acid (p.2268·1); salicylic acid (p.1612·2); iodine (p.2169·2); peppermint oil (p.1761·2); sweet birch oil (p.86·2); eucalyptus oil (p.2301·2).
Inflammation.

Fumouze, Fr.†.
Kaolin (p.1738·1); salicylic acid (p.1612·2).
Muscle and connective tissue pain.

Doetsch, Grether, Switz.
Salicylic acid (p.1612·2); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2).
Inflammation; pain.

Antiphlogistine Rub A-535 *Church & Dwight, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Musculoskeletal pain.

Antiphlogistine Rub A-535 Capsaicin *Church & Dwight, Canad.*
Capsaicin (p.32·3).
Musculoskeletal and joint disorders.

Antiphlogistine Rub A-535 Ice *Church & Dwight, Canad.*
Menthol (p.2340·1).
Musculoskeletal pain.

Antiphlogistine Rub A-535 No Odour *Church & Dwight, Canad.*
Trolamine salicylate (p.132·3).
Musculoskeletal pain.

Anti-Phosphat *Brady, Austria; Gry, Ger.*
Aluminium hydroxide (p.1706·2).
Hyperphosphataemia.

Anti-phosphate *Bichsel, Switz.*
Dried aluminium hydroxide (p.1706·2).
Hyperphosphataemia.

Antipiol *Denolin, Belg.*
Ichthammol (p.1599·1); zinc oxide (p.1621·2).
Skin disorders.

Antiplaq *Penn, Arg.*
Clopidogrel bisulfate (p.1250·2).

Anti-Plaque Chewing Gum *Or-Dov, Austral.†.*
Chlorhexidine acetate (p.1635·2).
Dental plaque.

Anti-potasium *Assos, Turk.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Antipres
Note.This name is used for preparations of different composition.
Sandoz, Indon.
Sertraline (p.422·1).
Depression.

Giempi, Venez.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Antipressan *Teva, Hong Kong; Berk, UK.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Antiprestin *Pharos, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Antiprex *Elpen (Ελπεν), Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Antiprotin *Julphar, UAE.*
Bromocriptine mesilate (p.798·1).
Acromegaly; benign breast disorders; female infertility; hyperprolactinaemia; menstrual disorders; parkinsonism.

Antiprurit *Kade, Ger.†.*
⊗ Cell components and metabolic products of *Staphylococcus aureus*; *Enterococcus faecalis* (p.2372·3); *Pseudomonas aeruginosa*; and *Escherichia coli*; hydrocortisone (p.1535·2).
Skin disorders.

Antipsichos *Proel, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Antipulmina *Lisapharma, Ital.†.*
Peppermint oil (p.1761·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2).
Respiratory-tract disorders.

Antipyn *Garec, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Formerly contained paracetamol, codeine phosphate, and caffeine.
Fever; pain.

Antipyn Forte *Garec, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain associated with tension.

Antireumina *Teofarma, Ital.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Antirevmaticky Caj *Leros, Cz.*
Meadowsweet (p.2338·1); equisetum (p.2299·3); pansy (p.2415·2); devil's claw root (p.39·1); salix (p.121·3); solidaginis (p.2391·1); calluna.
Influenza symptoms; rheumatism.

Antirrinum *Reig Jofre, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Anti-rugas C *Dermoteca, Port.*
Ascorbic acid (p.1983·3).
Sun-induced skin damage.

Antis *Gerolymatos, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Antiscabbia Candioli al DDT Terapeutico
Candioli, Ital.
Benzyl benzoate (p.2036·1); benzocaine (p.1854·1); clofenotane (p.2038·2).
Scabies.

Antiscabbia CM *Candioli, Ital.*
Benzyl benzoate (p.2036·1); benzocaine (p.1854·1); permethrin (p.2048·2).
Scabies.

Antiscabiosum *Strathmann, Ger.*
Benzyl benzoate (p.2036·1).
Scabies.

Antisept *Cadila, India.*
Bergenia ligulata; leptadenia reticulata; mallotus philippinensis; rubia cordifolia; berberis aristata; shorea robusta.
Burns; skin infections; wounds.

Antisepthic Plus *Florida, Arg.*
Benzalkonium chloride (p.1629·1); chlorhexidine (p.1635·2).
Disinfection.

Antiseptic Mouthwash
Note.This name is used for preparations of different composition.
Scott, Canad.; Sutton, Canad.; Trillium, Canad.
Cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3).
Thornton & Ross, UK.
Sodium salicylate (p.124·2); thymol (p.1664·3); menthol (p.2340·1).
Mouth disorders.

Antiseptic Ointment *National Care, Canad.†.*
Chloroxylenol (p.1640·2).
Skin protection.

Antiseptic Skin Cream
Note.This name is used for preparations of different composition.
National Care, Canad.†.
Benzalkonium chloride (p.1629·1).
National Care, Canad.†.
Benzethonium chloride (p.1630·1); vitamin A (p.1971·2); vitamin D (p.1986·1).
Ostomy care; skin irritation.

Antiseptic Throat Lozenges
Note.This name is used for preparations of different composition.
Sutton, Canad.
Hexylresorcinol (p.1647·1).
Unichem, UK.
Amylmetacresol (p.1628·3).
Sore throat.

Antiseptic Wound & Skin Cleanser *MPM, USA.*
Benzethonium chloride (p.1630·1).
Disinfection of skin and wounds.

Antiseptico *Fidex, Arg.*
Povidone-iodine (p.1659·2).

Antiseptico Hertz *Hertz, Braz.*
Lidocaine (p.1862·3); benzethonium.

Antiseptin
Note.This name is used for preparations of different composition.
Hertz, Braz.†.
Bacitracin (p.210·3); neomycin (p.305·1); zinc (p.1999·1).
Skin infections.
Sanitas, Chile.
Triclosan (p.1665·2).
Disinfection of hands; skin infection.

Antiseptique Pastilles *Prodemdis, Canad.*
Domiphen bromide (p.1643·1).

Antisettico Astringente Sedativo *Bruschettini, Ital.*
⊗ Zinc phenolsulfonate (p.1621·3); sulfacetamide sodium (p.335·3); naphazoline hydrochloride (p.1565·2); lidocaine hydrochloride (p.1862·3).
Conjunctivitis.

Antisol *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Antispa *TP, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Antispas *Keene, USA.*
Dicycloverine hydrochloride (p.1722·3).
Functional bowel syndrome; irritable bowel syndrome.

Antispasmina *Hexa, Arg.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3).
Pain; smooth muscle spasm.

Antispasmina Colica
Note.This name is used for preparations of different composition.
Recordati, Ital.
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3); hyoscyamine (p.1736·1).
Gastrointestinal spasm.
Lepori, Port.
Papaverine (p.2191·3); belladonna (p.2263·3); valerian (p.2410·1).
Smooth muscle spasm.

Antispasmodic Elixir *Morton Grove, USA.*
Phenobarbital (p.492·2); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).

Antistax *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Fher, Ital.; Boehringer Ingelheim, Spain; Pharmaton, Switz.; Boehringer Ingelheim, UK.*
Red vine (p.2316·3).
Venous insufficiency.

Antisterin *Unipharma, Gr.*
Pravastatin sodium (p.1374·3).
Hyperlipidaemias.

Antistina-Privin *Novartis, Denm.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis.

Antistine-Privine *Novartis, Austral.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis; eye irritation.

Antistin-Privin *Novartis, Fin.†; Novartis, Ger.; Novartis, Israel†; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis.

Antistin-Privina *Novartis, Ital.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis.

Antitensin *Teuto, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Antitis *Potter's, UK.*
Buchu leaf (p.2269·3); clivers (p.2284·3); couch-grass (p.2288·2); equisetum (p.2299·3); shepherd's purse (p.2386·2); bearberry (p.2263·3).
Cystitis; urinary or bladder discomfort.

Antitos
Note. A similar name is used for preparations of different composition (see below).
Plata, Arg.†.
Senega (p.1572·3); sulfogaiacol (p.1573·2).
Coughs.

Antitoss
Note. A similar name is used for preparations of different composition (see above).
Kleva, Gr.
Butamirate citrate (p.1553·1).
Cough.

Antitrom *Lazar, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Anti-Tuss *Century, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Antitussivum Burger *Ysatfabrik, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Antitussivum Burger N *Ysatfabrik, Ger.†.*
Dihydrocodeine tartrate (p.48·1); thyme oil (p.2401·2).
Coughs.

Anti-Uron *Pliva Krakow, Pol.*
Mesna (p.1449·2).
Prevention of urotoxicity associated with cyclophosphamide, ifosfamide, or trofosfamide.

Antivenin (Latrodectus Mactans) *Merck Frosst, Canad.*
Black widow spider antiserum (p.2239·2).
Black widow spider bite.

Antiverrugas *Isdin, Spain.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Antivert *Pfizer, USA.*
Meclozine hydrochloride (p.584·3).
Motion sickness; vertigo.

Anti-Ves *Novartis, Ital.*
Soya oil; vitamins (p.1922·1).
Nutritional supplement.

Antivipmyn *Bioclon, Mex.*
Polyvalent crotalidae antiserum (p.2238·2).
Snake envenomation.

Antivir *Sanofi-Aventis, Pol.*
Aciclovir (p.862·3).
Herpesvirus infections.

Antivirax *EMS, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Antivom
Note.This name is used for preparations of different composition.
Unipharma, Gr.
Betahistine hydrochloride (p.2265·1).
Menière's disease; vertigo.
Teva, Hung.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Anti-Vomit *Deva, Turk.*
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Anti-Worm *Leidapharm, Neth.*
Mebendazole (p.148·3).
Worm infections.

Antix *Antula, Fin.*
Aciclovir (p.862·3).
Herpes labialis.

Antiza *Coronet, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough; fever.

Antizid *Lilly, S.Afr.*
Nizatidine (p.1751·2).
Heartburn; hyperacidity.

Antizine *Pharmasant, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions; sedative.

Antizol *Paladin, Canad.; Orphan Medical, Israel; IDIS, UK; Medisource, UK; Jazz, USA.*
Fomepizole (p.1446·3).
Available on a named-patient basis only in the *UK*.
Ethylene glycol poisoning; methanol poisoning.

Antodox *Juta, Ger.; Q-Pharm, Ger.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Antomiopic *Allergan, Braz.†; Novartis, Spain†.*
Vitamins and amino acids (p.1922·1); myrtillus (p.2349·3).
Eye disorders.

Antopal *Bama, Spain†.*
Binifibrate (p.1234·1).
Hyperlipidaemias.

Antopar *Lek, Cz.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Antoral *Recordati, Ital.*
Tibezonium iodide (p.2402·1).
Mouth and throat disinfection.

Antorcin *Antor, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Antoril *Teva Tuteur, Arg.*
Gemcitabine hydrochloride (p.727·3).
Malignant neoplasms.

Antotalgin *Farmina, Pol.*
Phenazone (p.116·1).
Earache.

Antox *Pharma Nord, Irl.*
Methionine (p.1450·1); vitamin C; vitamin E; selenium (p.1961·1) (p.1922·1).
Chronic pancreatitis.

Antoxyl *Tablets, India.*
Vitamins; amino acids; minerals; spirulina (p.1922·1).

Antra
AstraZeneca, Ger.
Omeprazole magnesium (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.
AstraZeneca, Ital.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.
AstraZeneca, Switz.
Omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Antrain *Interbat, Indon.*
Dipyrone (p.49·2).
Pain.

Antral *Carnot, Mex.†.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Antramups *AstraZeneca, Switz.*
Omeprazole magnesium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Antran *Solfran, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Antrenyl *Novartis, India.*
Oxyphenonium bromide (p.1759·2).
Adjunct in diarrhoea; gastritis; gastrointestinal hyperacidity; gastrointestinal hypermotility; peptic ulcer.

Antrex *Orion, Cz.†; Orion, Fin.; Atafarm, Turk.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Antrizine *Major, USA.*
Meclozine hydrochloride (p.584·3).
Motion sickness; vertigo.

Antrolin *NewFaDem, Ital.*
Nifedipine (p.1350·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Antroquoril *Schering-Plough, Austral.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Antup R *Teijin, Jpn.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; ischaemic heart disease; myocardial infarction.

Anturan *Amdipharm, UK.*
Sulfinpyrazone (p.559·2).
Gout; hyperuricaemia.

Anturane *Novartis, USA.*
Sulfinpyrazone (p.559·2).
Gouty arthritis.

Antussia
Note.This name is used for preparations of different composition.
Asian Pharm, Thai.
Capsules; tablets: Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).
Coughs and cold symptoms.
Asian Pharm, Thai.
Syrup: Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Antust *Medicine Products, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); terpin hydrate (p.1573·3).
Coughs.

Antux *Ache, Braz.; Leti, Venez.*
Levodropropizine (p.1557·3).
Cough.

Antygrypin *Galenus, Pol.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Anu-Aide *Technilab, Canad.†.*
Zinc sulfate (p.1999·2).
Haemorrhoids.

Anuar
Note.This name is used for preparations of different composition.
Tecnofarma, Chile.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-induced acne, alopecia, and hirsutism in women.
Pfizer, Arg.
Injection: Chloramphenicol sodium succinate (p.240·1).
Formerly contained chloramphenicol sodium succinate, colistimethate sodium, cinchocaine hydrochloride, dipyrone, guaifenesin, and chlorphenamine.
Bacterial infections.
Pharmacia, Arg.†.
Tablets: Roxithromycin (p.331·1).
Bacterial infections.

Anubis *Investi, Arg.*
84 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Anucare *YSP, Malaysia.*
Benzyl benzoate (p.2036·1); peru balsam (p.2365·3); zinc oxide (p.1621·2).
Anorectal disorders.

Anucet
Note.This name is used for preparations of different composition.
Sanobia, Port.
Ointment: ⊗ Hydrocortisone acetate (p.1535·2); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3); tetracaine hydrochloride (p.1871·3).
Anorectal disorders.
Sanobia, Port.†.
Suppositories: ⊗ Hydrocortisone acetate (p.1535·2); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3); tetracaine hydrochloride (p.1871·3); belladonna (p.2263·3).
Anorectal disorders.

Anucort-HC *G & W, USA.*
⊗ Hydrocortisone acetate (p.1535·2).

Anugesic
Note.This name is used for preparations of different composition.
Pfizer Consumer, S.Afr.
Ointment: Pramocaine hydrochloride (p.1868·1).
Anorectal disorders.
Pfizer Consumer, S.Afr.
Suppositories: Bismuth subgallate (p.1711·1); bismuth oxide (p.1710·3); resorcinol (p.1612·1); bismuth oxyiodide (p.1712·1); peru balsam (p.2365·3); benzyl benzoate (p.2036·1); zinc oxide (p.1621·2); boric acid (p.2268·1); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Anugesic-HC
Note.This name is used for preparations of different composition.
Pfizer Consumer, Canad.
⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2).
Anorectal disorders.
Pfizer, Irl.
Cream: ⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); zinc oxide (p.1621·2); peru balsam (p.2365·3); benzyl benzoate (p.2036·1); bismuth oxide (p.1710·3); resorcinol (p.1612·1).
Anorectal disorders.
Pfizer, UK.
Cream: ⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); bismuth oxide (p.1710·3); peru balsam (p.2365·3); zinc oxide (p.1621·2); benzyl benzoate (p.2036·1).
Anorectal disorders.
Pfizer, Irl.; Pfizer, UK.
Suppositories: ⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); peru balsam (p.2365·3); benzyl benzoate (p.2036·1); bismuth oxide (p.1710·3).
Anorectal disorders.

Anulbet *Alpes Chemie, Chile†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anulette *Silesia, Chile.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Anu-Med
Note. A similar name is used for preparations of different composition (see below).
Major, USA.
Phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Anumed
Note. A similar name is used for preparations of different composition (see above).
Major, USA.
Bismuth subgallate (p.1711·1); bismuth resorcinol compound (p.1712·1); benzyl benzoate (p.2036·1); zinc oxide (p.1621·2); peru balsam (p.2365·3).
Anorectal disorders.

Anumed HC *Major, USA.*
⊗ Hydrocortisone acetate (p.1535·2); bismuth subgallate (p.1711·1); bismuth resorcinol compound (p.1712·1); benzyl benzoate (p.2036·1); peru balsam (p.2365·3); zinc oxide (p.1621·2).
Anorectal disorders.

Anumedin *Kade, Ger.†.*
⊗ Prednisolone acetate (p.1541·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Anusol
Note. This name is used for preparations of different composition.
Elea, Arg.
Bismuth resorcinol compound (p.1712·1); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); peru balsam (p.2365·3); bismuth oxyiodide (p.1712·1); boric acid (p.2268·1).
Haemorrhoids.
Pfizer Consumer, Belg.
Lidocaine hydrochloride (p.1862·3); zinc oxide (p.1621·2).
Haemorrhoids.
Pfizer Consumer, Canad.
Zinc sulfate (p.1999·2).
Anorectal disorders.
Pfizer Sante, Fr.; Pfizer Consumer, S.Afr.
Bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2).
Anorectal disorders.
Pfizer Consumer, Ger.†.
Bismuth oxide-bismuthoxyiodide-1,3-bis-(ammoniumoxy)-benzol-4,5-(bismuthylsulfonate); zinc oxide (p.1621·2); peru balsam (p.2365·3).
Anorectal disorders.
Pfizer, Hong Kong; Parke, Davis, Israel†.
Peru balsam (p.2365·3); bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2).
Anorectal disorders.
Pfizer, Indon.
Bismuth subgallate (p.1711·1); bismuth resorcinol compound (p.1712·1); bismuth oxyiodide (p.1712·1); zinc oxide (p.1621·2).
Anal fissures; haemorrhoids.
Pfizer Consumer, Ital.
Resorcinol (p.1612·1); yellow bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); bismuth oxyiodide (p.1712·1); peru balsam (p.2365·3); zinc oxide (p.1621·2).
Anorectal disorders.
Pfizer, Malaysia; Pfizer, NZ.
Zinc oxide (p.1621·2); peru balsam (p.2365·3); benzyl benzoate (p.2036·1).
Anorectal disorders.
Nizhpharm, Rus.
Belladonna (p.2263·3); zinc sulfate (p.1999·2); bismuth tribromphenate (p.1712·1).
Anorectal disorders.
Pfizer, Thai.
Peru balsam (p.2365·3); benzyl benzoate (p.2036·1); bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); resorcinol (p.1612·1); zinc oxide (p.1621·2).
Haemorrhoids; pruritus ani.
Pfizer Consumer, Irl.; Pfizer Consumer, UK.
Cream: Zinc oxide (p.1621·2); bismuth oxide (p.1710·3); peru balsam (p.2365·3).
Anorectal disorders.
Pfizer Consumer, Singapore.
Ointment: Zinc oxide (p.1621·2); peru balsam (p.2365·3); benzyl benzoate (p.2036·1).
Formerly contained peru balsam, benzyl benzoate, bismuth oxide, bismuth subgallate, bismuth oxyiodide, and resorcinol.
Anorectal disorders.
Warner-Lambert, USA.
Ointment: Zinc oxide (p.1621·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.
Pfizer Consumer, Austral.
Ointment; suppositories: Zinc oxide (p.1621·2); peru balsam (p.2365·3); benzyl benzoate (p.2036·1).
Anorectal disorders.
Pfizer Consumer, Irl.; Pfizer Consumer, UK.
Ointment; suppositories: Bismuth subgallate (p.1711·1); bismuth oxide (p.1710·3); peru balsam (p.2365·3); zinc oxide (p.1621·2).
Anorectal disorders.
Pfizer Consumer, Singapore.
Suppositories: Zinc oxide (p.1621·2); Peru balsam (p.2365·3); benzyl benzoate (p.2036·1).
Formerly contained peru balsam, benzyl benzoate, bismuth oxide, bismuth subgallate, resorcinol, and zinc oxide.
Anorectal disorders.
Pfizer Consumer, Austral.
Wipes: Hamamelis water (p.2318·2); glycerol (p.2314·2).
Anorectal irritation.

Anusol Duo *Elea, Arg.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Anusol Duo S *Elea, Arg.*
⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); benzyl benzoate (p.2036·1); bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); peru balsam (p.2365·3); zinc oxide (p.1621·2).
Anorectal disorders.

Anusol Plus *Pfizer Consumer, Canad.*
Pramocaine hydrochloride (p.1868·1); zinc sulfate (p.1999·2).
Anorectal disorders.

Anusol-A *Elea, Arg.*
Pramocaine hydrochloride (p.1868·1); zinc oxide (p.1621·2); peru balsam (p.2365·3); benzyl benzoate (p.2036·1); kaolin (p.1738·1); calcium phosphate (p.1676·2).
Haemorrhoids.

Anusol-HC
Note. This name is used for preparations of different composition.
Elea, Arg.
⊗ Hydrocortisone acetate (p.1535·2).
Anorectal disorders.
Pfizer, Braz.
⊗ Hydrocortisone acetate (p.1535·2); bismuth resorcinol compound (p.1712·1); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); peru balsam (p.2365·3); benzyl benzoate (p.2036·1).
Anorectal disorders.
Pfizer Consumer, Canad.
⊗ Zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2).
Anorectal disorders.
Pfizer, Hong Kong†.
⊗ Peru balsam (p.2365·3); benzyl benzoate (p.2036·1); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); hydrocortisone acetate (p.1535·2); bismuth oxide (p.1710·3).
Anorectal disorders.
Pfizer, Indon.
⊗ Hydrocortisone acetate (p.1535·2); bismuth subgallate (p.1711·1); bismuth resorcinol compound (p.1712·1); bismuth oxyiodide (p.1712·1); zinc oxide (p.1621·2).
Anal pruritus; haemorrhoids.
Pfizer Consumer, Irl.
⊗ Hydrocortisone acetate (p.1535·2); benzyl benzoate (p.2036·1); bismuth subgallate (p.1711·1); bismuth oxide (p.1710·3); peru balsam (p.2365·3); zinc oxide (p.1621·2); resorcinol (p.1612·1).
Anorectal disorders.

Anusol-HC, Plus HC *Pfizer Consumer, UK.*
⊗ Bismuth subgallate (p.1711·1); bismuth oxide (p.1710·3); peru balsam (p.2365·3); zinc oxide (p.1621·2); hydrocortisone acetate (p.1535·2); benzyl benzoate (p.2036·1).
Anusol HC formerly contained bismuth subgallate, bismuth oxide, peru balsam, zinc oxide, hydrocortisone acetate, benzyl benzoate, and resorcinol.
Anorectal disorders.

Anuzinc *Sandoz, Canad.*
Zinc sulfate (p.1999·2).
Anorectal disorders.

Anuzinc HC *Sandoz, Canad.*
⊗ Zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Anuzinc HC Plus *Sabex, Canad.*
⊗ Zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Anuzinc Plus *Sandoz, Canad.*
Pramocaine hydrochloride (p.1868·1); zinc sulfate (p.1999·2).
Anorectal disorders.

Anvitoff *Abbott, Ger.†; Knoll, Switz.†.*
Tranexamic acid (p.1080·3).
Fibrinolytic states; haemorrhagic disorders.

Anvitol *Azevedos, Port.†.*
Haematoporphyrin hydrochloride; glycine; cyanocobalamin (p.1922·1).
Tonic.

Anvomer B6 *Dexa, Indon.*
Parathiazine teoclate; vitamin B (p.1979·1).
Motion sickness; vomiting.

Anvomin *Christo, Hong Kong.*
Promethazine teoclate (p.588·3).
Motion sickness; nausea; vertigo; vestibular disorders.

Anxer *Unison, Hong Kong; Unison, Thai.†.*
Cefalexin (p.218·2).
Bacterial infections.

Anxicalm *Clonmel, Irl.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm; spasticity.

Anxielax *Macrophar, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Anxietum *Ferrier, Fr.*
Homoeopathic preparation.

Anxiety/Stress L72 *Homeocan, Canad.†.*
Homoeopathic preparation.

Anxiolan *Medochemie, Thai.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Anxiolit *Gerot, Austria; Vifor, Switz.*
Oxazepam (p.1014·2).
Anxiety; insomnia.

Anxiolit plus *Gerot, Austria.*
Oxazepam (p.1014·2); methylbenactyzium bromide (p.1747·2).
Anxiety disorders.

Anxipress-D *Pharmaland, Thai.†.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Depression.

Anxira *Condrugs, Thai.*
Lorazepam (p.1004·1).
Anxiety disorders.

Anxirid *Aspen, S.Afr.†.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Anxiron *ICN, Cz.†; Valeant, Hung.*
Buspirone hydrochloride (p.965·3).
Anxiety; mixed anxiety depressive states; nervous disorders.

Anxium *Knop, Chile.*
St John's wort (p.422·3).
Depression.

Anxol *Svizera, India.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; insomnia; seizures; skeletal muscle spasm; tetanus.

Anxoral *IPRAD, Fr.†.*
Crataegus (p.2289·1); passion flower (p.2363·2); valerian (p.2410·1).
Formerly contained crataegus, passion flower, valerian, and phenobarbital.
Anxiety; insomnia.

Anxut *Eisai, Ger.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Anxyrex *Irex, Fr.†.*
Bromazepam (p.964·3).
Alcohol withdrawal syndrome; anxiety.

Any *Homme de Fer, Fr.*
Mequinol (p.1604·2).
Hyperpigmentation.

Anzac *Bangkok Lab & Cosmetic, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Anzatax *Mayne, Austral.; Mayne, Cz.; Mayne, Hong Kong; Tempo Scan Pacific, Indon.; Mayne, Ital.; Hospira, Malaysia; Pharmaplan, S.Afr.; Mayne, Singapore; Mayne, Thai.; Orna, Turk.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Anzemet *Aventis, Arg.†; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.; Aventis, Cz.†; Aventis, Fin.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Aventis, Mex.; Aventis, Neth.; Aventis, Switz.; Amdipharm, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Dolasetron mesilate (p.1725·3).
Nausea and vomiting.

Anzidin *Stadmed, India.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Anzilum *Cadila, India†.*
Alprazolam (p.960·1).
Anxiety.

Anzion *Farmaline, Thai.†.*
Alprazolam (p.960·1).
Anxiety.

Anzolden *Denver, Arg.*
Fluoxetine hydrochloride (p.391·2).

Anzopac *UCI, Braz.†.*
Capsules, lansoprazole (p.1739·2); tablets, clarithromycin (p.248·2); capsules, amoxicillin trihydrate (p.202·2).
Peptic ulcer.

Anzoprol *UCI, Braz.†.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AODrops *Ciba Vision, Canad.†.*
Lubricant for contact lenses (p.1622·2).

Aofen *Medicine Products, Thai.*
Griseofulvin (p.535·2).
Fungal infections of skin, hair, and nails.

AOFlow *Ciba Vision, Canad.†.*
Cleansing solution for contact lenses (p.1622·2).

Aosept *Ciba Vision, Austral.; Ciba Vision, Braz.†; Ciba Vision, Canad.; Ciba Vision, NZ; Ciba Vision, USA.*
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting solution for contact lenses.

Aosept Clear Care *Ciba Vision, Canad.*
Cleaning, disinfecting, and protein removal solution for soft contact lenses (p.1622·2).

Aosept Plus *Ciba Vision, Arg.*
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting solution for contact lenses.

A-Ostin-D3 *Farmedia, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Aotal *Merck-Lipha, Fr.*
Acamprosate calcium (p.958·3).
Alcoholism.

Aova *Velka, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

AP *Steigerwald, Ger.*
A range of homoeopathic preparations.

AP Inyect Cloruro Potasico *Fresenius Kabi, Spain.*
Potassium chloride (p.1684·3).
Hypokalaemia.

APA
Note. This name is used for preparations of different composition.
Lannacher, Austria.
Suppositories: Paracetamol (p.108·1); propyphenazone (p.119·3).
Fever; pain.
Lannacher, Austria.
Tablets: Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Pain.

Apacef *AstraZeneca, Belg.†; AstraZeneca, Fr.†.*
Cefotetan disodium (p.229·3).
Bacterial infections.

Apacet *Parmed, USA.*
Paracetamol (p.108·1).
Fever; pain.

Apadex *EGIS, Hung.*
⊗ Indapamide (p.1314·1).
Hypertension.

Apagen *Stomygen, Ital.*
Hydroxyapatite (p.2323·1).
Dental disorders.

Apain *AstraZeneca, Denm.*
Ibuprofen (p.64·2).
Pain.

Apaisac
Note. This name is used for preparations of different composition.
Biorga, Hong Kong.
Lip balm: Vitamin E (p.1992·2); phytosqualanes (p.2032·3) in an emollient basis.
Emollient.
Biorga, Hong Kong.
Topical emulsion: Aloe (p.1588·2); lecithin (p.2332·2); glycerol (p.2314·2); soya oil (p.1965·3).
Emollient.

Apaisance
Note. This name is used for preparations of different composition.
Lierac, Fr.
Cream: Tilia (p.2402·2); enoxolone (p.50·1); helichrysum; pilewort (p.2368·1).
Skin disorders.
Lierac, Fr.†.
Topical spray: Tilia (p.2402·2); levomenol (p.2333·3); chamomile (p.2279·3).
Skin disorders.

Apalin *Duopharma, Hong Kong.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Apamid *Pfizer, Fin.†; Weifa, Norw.; Parke, Davis, Swed.†; Weifa, Thai.†.*
Glipizide (p.441·3).
Diabetes mellitus.

Apamox *FS Profas, Spain; Pliva, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Apap *US Pharmacia, Pol.; Cypress, USA.*
Paracetamol (p.108·1).
Fever; pain.

Apap C Plus *US Pharmacia, Pol.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Apap Extra *US Pharmacia, Pol.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Apap Noc *US Pharmacia, Pol.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Pain with insomnia.

A-Par *Omega, Fr.*
Esdepallethrine (p.2042·3); piperonyl butoxide (p.2049·1).
Destruction of scabies mite, fleas and lice in textiles and adjunct to treatment.

A-Parkin *Dexxon, Israel.*
Amantadine sulfate (p.793·1).
Influenza A; parkinsonism.

Aparo *Kwizda, Austria†.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic attacks; social-anxiety disorder.

Aparoxal *Pierre Fabre, Fr.*
Phenobarbital (p.492·2).
Epilepsy.

Aparsonin N *Merckle, Ger.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased mucus.

Apasmil *Cordoba, Arg.†.*
An antilymphocyte immunoglobulin (p.1817·3).

Apasmo *Sidus, Arg.*
Camylofin hydrochloride (p.2274·1); dipyrone (p.49·2).
Muscle spasm; pain.

Apasmo Compuesto *Sidus, Arg.*
Pargeverine (p.1761·1); dipyrone (p.49·2).
Smooth muscle spasm.

Apatate *Kenwood, USA†.*
Vitamin B complex (p.1922·1).

Apatate with Fluoride *Kenwood, USA†.*
Vitamin B substances (p.1922·1) with sodium fluoride (p.1962·2).

Apatef *Wyeth, Austral.†; AstraZeneca, Ital.†; Wyeth, NZ†; AstraZeneca, Port.†.*
Cefotetan disodium (p.229·3).
Bacterial infections.

Apatinac *Herbapol Wroclaw, Pol.*
St John's wort (p.422·3).
Depression.

Apatite *Weleda, UK.*
Homoeopathic preparation.

Apaurin *KRKA, Cz.; KRKA, Rus.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; eclampsia; epilepsy; pre-eclampsia; premedication; skeletal muscle spasm; tetanus.

APC *Vomelin, Hung.†; Healthypharm, Neth.; Katwijk, Neth.; Leidapharm, Neth.; Marel, Neth.; Sameko, Neth.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Apecitab *Dosa, Arg.†.*
Capecitabine (p.691·3).
Malignant neoplasms.

Apegmone *Lipha Sante, Fr.†.*
Tioclomarol (p.1413·3).
Thromboembolic disorders.

A-Pen
Note. A similar name is used for preparations of different composition (see below).
Orion, Fin.
Ampicillin sodium (p.204·1).
Bacterial infections.

Apen
Note. A similar name is used for preparations of different composition (see above).
Xixia, S.Afr.
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Apenorm *Cipla, India†.*
Cyproheptadine hydrochloride (p.575·1).

Apeplus
Note.This name is used for preparations of different composition.
Lafedar, Arg.
Cyproheptadine (p.575·2); carnitine hydrochloride; levoglutamine; pyridoxine hydrochloride (p.1922·1).
Reduced appetite.

Mediderm, Chile†.
⊗ Finasteride (p.2188·3).
Alopecia.

A-Per *Aroma, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Aperdan *ABC, Ital.*
Naproxen cetrimonium (p.93·3).
Vulvovaginal disorders.

Apergan *Panzera, Ital.*
Royal jelly (p.2382·1); glucose (p.1945·3); ginseng (p.2312·1).
Nutritional supplement.

Aperisan *Dentinox, Cz.†; Dentinox, Ger.; Dentinox, Pol.*
Sage (p.2382·3).
Mouth and throat inflammation.

Aperomid *Masterlek, Rus.†.*
Pipecuronium bromide (p.1908·2).
Competitive neuromuscular blocker.

Apertia
Lundbeck, Austria†.
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic attacks.

Lundbeck, Cz.†.
Citalopram hydrochloride (p.385·3).
Depression; obsessive-compulsive disorder; panic attacks.

Apetibe *Luper, Braz.†.*
Buclizine (p.570·1); amino acids; vitamins (p.1922·1).
Reduced appetite; tonic.

Apetil
Note.This name is used for preparations of different composition.
Bunker, Braz.
Buclizine hydrochloride (p.570·1); amino acids; vitamin B substances (p.1922·1).
Reduced appetite; tonic.

Ram, USA†.
Multivitamin and mineral preparation (p.1922·1).

Apetitol Forte *Mertens, Arg.*
Cyproheptadine hydrochloride (p.575·1); vitamins (p.1922·1).
Reduced appetite.

Apetivit BC *Cifarma, Braz.*
Cyproheptadine hydrochloride (p.575·1); vitamin B substances; vitamin C (p.1922·1).
Reduced appetite; vitamin deficiency.

Apetiviton BC *Cifarma, Braz.*
Cyproheptadine hydrochloride (p.575·1); vitamin B substances; vitamin C (p.1922·1).
Reduced appetite.

Apeton *IPI, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic skin disorders; rhinitis.

Apetrol *Medipharm, Chile.*
Cyproheptadine hydrochloride (p.575·1); vitamins (p.1922·1).
Reduced appetite.

Apevitin BC *EMS, Braz.*
Cyproheptadine hydrochloride (p.575·1); vitamin B substances; ascorbic acid (p.1922·1).
Reduced appetite; tonic.

Apex Repel Natural *Apex, Austral.; Apex, NZ.*
Lavender oil (p.2331·2); melaleuca oil (p.2338·2); eucalyptus oil (p.2301·2); lemon grass oil (p.2333·1); citronella oil (p.2284·2).
Insect repellent.

Apex Repel Super
Note.This name is used for preparations of different composition.
Apex, Austral.; Apex, NZ.
Lotion: Diethyltoluamide (p.2041·1); ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Apex, Austral.; Apex, NZ.
Roll-on: Diethyltoluamide (p.2041·1).
Insect repellent.

Apex, Austral.; Apex, NZ.
Topical spray: Diethyltoluamide (p.2041·1); 1,3-di(4-imidazolino-2-methoxyphenoxy)propane.
Insect repellent.

Apex Repel Ultra *Apex, Austral.; Apex, NZ.*
Diethyltoluamide (p.2041·1); ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

ApexiCon *PharmaDerm, USA.*
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

APF *Cypress, USA†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Aphenylbarbit *Streuli, Switz.*
Phenobarbital (p.492·2).
Epilepsy; febrile convulsions; sedative.

Aphilan
Note.This name is used for preparations of different composition.
UCB, Fr.
Cream: ⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

UCB, Fr.
Tablets: Buclizine hydrochloride (p.570·1).
Allergic conjunctivitis; allergic rhinitis; motion sickness; urticaria.

A-P-Histallin *Medichem, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cold symptoms.

Aphloine P *DB, Fr.*
Aphloia; hamamelis (p.2318·2); viburnum (p.2267·1); esculoside (p.2248·2).
Haemorrhoids; peripheral vascular insufficiency.

Aphlox *Herbacos, Cz.†.*
Boric acid (p.2268·1); salicylic acid (p.1612·2); methyl salicylate (p.85·3); iodine (p.2169·2); potassium iodide (p.2169·2).
Inflammation; peri-articular and soft-tissue disorders.

Aphrenil *Euro-Med, Philipp.*
Chloramphenicol (p.239·3).
Bacterial infections.

Aphrodyne *Star, USA.*
Yohimbine hydrochloride (p.2200·2).

Aphrofem *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p.2311·1).

Aphtagone *Trima, Israel.*
Aloe vera (p.1588·2); benzalkonium chloride (p.1629·1); enoxolone (p.50·1); povidone (p.2146·1); sodium hyaluronate (p.2320·1).
Oral lesions.

Aphthasol *Block, USA.*
Amlexanox (p.1115·2).
Aphthous ulcers.

Aphtin *Aflofarm, Pol.; Coel, Pol.; Farmina, Pol.; Galenowe Olsztyn, Pol.; Microfarm, Pol.; Prolab, Pol.*
Borax (p.2268·1).
Mouth infections.

Aphtoral *Pierre Fabre, Fr.*
Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3); ascorbic acid (p.1983·3).
Mouth and throat disorders.

Api Baby *Sanitalia, Ital.*
Pollen (p.2370·2); royal jelly (p.2382·1); fructose; myrtillus (p.2349·3).
Nutritional supplement.

Apialys *Lapi, Indon.*
Vitamins; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Apidra *Aventis, Arg.; Sanofi-Aventis, Austral.; Aventis, Denm.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Aventis, Neth.; Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, S.Afr.; Aventis, Swed.; Sanofi-Aventis, Switz.; Aventis, UK; Aventis, USA.*
⊗ Insulin glulisine (p.449·3).
Diabetes mellitus.

ApiHelix *Apipol, Pol.*
Ivy (p.2328·1); liquorice (p.1740·3); thyme (p.2401·1).
Respiratory-tract inflammation.

Apihepar *Madaus, Austria; Viatris, Austria.*
Milk thistle (p.1452·1).
Liver disorders.

Apikobal *Santa, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Apilac *Tallinn, Rus.*
Royal jelly (p.2382·1).
Tonic.

Apilaxe *Cooperation Pharmaceutique, Fr.†.*
Sorbitol (p.1965·1); althaea leaf (p.2253·3).
Constipation.

Apilcav *Libbs, Braz.†.*
Alprostadil (p.2183·2).
Erectile dysfunction.

Apilepsin *KRKA, Rus.*
Sodium valproate (p.508·2).

Apimid *Apogepha, Ger.†.*
Flutamide (p.725·1).
Prostatic cancer.

Apinorm *Apipol, Pol.*
Aloes (p.1705·2); caraway (p.2276·3); aniseed (p.2258·2).
Bowel evacuation; constipation.

Apiocolina *Bruschettini, Ital.†.*
Escherichia coli lysate.
Anorectal inflammation.

Apipulmol *Apipol, Pol.*
Ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2).
Cough.

Apir Clorurado *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Apir Glucosado *Fresenius Kabi, Spain.*
Glucose (p.1945·3).
Fluid and electrolyte disorders; parenteral nutrition.

Apir Glucosalino *Fresenius Kabi, Spain.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Apir Ringer *Fresenius Kabi, Spain.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte depletion.

Apir Ringer Lactato *Fresenius Kabi, Spain.*
Electrolyte infusion with sodium lactate (p.1667·1).
Fluid and electrolyte depletion.

Apiret *Oftalmi, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Apiretal *Ern, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Apiretal Codeina *Ern, Spain.*
Paracetamol (p.108·1); codeine (p.37·2).
Pain.

Apirol *MSD, Israel.*
Norfloxacin (p.309·2).
Bacterial infections.

Apiron *Delta, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Apis Compuesto *Ximena Polanco, Chile.*
Homoeopathic preparation.

Apisarthron *Esparma, Cz.; Esparma, Rus.*
Bee venom extract (p.2251·1); methyl salicylate (p.85·3); volatile mustard oil (p.2349·2).
Musculoskeletal pain; musculoskeletal, peri-articular, and soft-tissue disorders; neuralgia; neuritis.

Apisate *Sunthi Sepuri, Indon.; Wyeth, Indon.*
⊗ Diethylpropion hydrochloride (p.2154·3); vitamin B substances (p.1922·1).
Obesity.

Apiserum *DB, Fr.*
Royal jelly (p.2382·1).
Tonic.

Apiserum con Telergon I *Medicalfarm, Ital.*
Wine; acacia honey (p.1948·2); royal jelly (p.2382·1).
Nutritional supplement.

Apisgel *Dolisos, Canad.*
Homoeopathic preparation.

Apis-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

Apistress *Sanitalia, Ital.*
Royal jelly (p.2382·1); pollen (p.2370·2); propolis (p.2373·3).
Nutritional supplement.

Apitussic *Apipol, Pol.*
Sulfogaiacol (p.1573·2).
Respiratory-tract disorders.

Apixol *Columbia, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Apizel *Apipol, Pol.*
Propolis (p.2373·3).
Burns; insect bites; skin disorders.

APL *Wyeth, Chile†; Akromed, S.Afr.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; infertility; male hypogonadism.

Aplacaina *Richmond, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Aplacasse *Menarini, Arg.*
Lorazepam (p.1004·1).
Anxiety.

Aplace *Kyorin, Jpn.*
Troxipide (p.1778·1).
Gastritis; peptic ulcer.

Aplacid *ITF, Chile.*
Sulpiride (p.1028·3).
Depression.

Aplactin *BMS, Ital.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hyperlipidaemias.

Aplaket *Rottapharm, Cz.†; Rotta, Hong Kong; Rottapharm, Ital.; Rotta, Malaysia; Delta, Port.; Rotta, Singapore; Rotta, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Maintenance of extracorporeal circulation; thromboembolism prophylaxis.

Aplatic *Ratiopharm, Hung.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Aplause *Marjan, Braz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Aplical *Grunenthal, Chile†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Aplical-D *Grunenthal, Chile†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteomalacia; osteoporosis.

Aplicav *Libbs, Braz.*
Alprostadil (p.2183·2).
Erectile dysfunction.

Apligraf *Novartis, USA.*
Bioengineered human skin equivalent (p.1613·3).
Diabetic foot ulcers; venous leg ulcers.

Aplisol *JHP, USA.*
Tuberculin purified protein derivative (p.2405·3).
Diagnosis of tuberculosis.

Aplom *Valmor, Venez.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Aplona *Athenstaedt, Ger.*
Apple powder; colloidal silicon dioxide (p.2146·3).
Diarrhoea.

Aplonit *Intermed, Gr.*
⊗ Celiprolol hydrochloride (p.1242·2).
Hypertension.

Aplosyn *Pascual, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Aplosyn C *Pascual, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Aplosyn N *Pascual, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Aplosyn-Otic *Pascual, Hong Kong; Pascual, Philipp.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); fluocinolone acetonide (p.1531·3).
Infected ear disorders.

Apmed *Cimed, Braz.*
Cyproheptadine hydrochloride (p.575·1); vitamins (p.1922·1).
Reduced appetite.

Apnol *Pharmaland, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Apo-Acebutol *Apotex, Cz.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Apoacor *Curex, Israel.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Apo-Alpraz *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Alprazolam (p.960·1).
Anxiety; sedative.

Apo-Amilzide *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Apo-Amlo *Apotex, Cz.; Apotex, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Apo-Amoxi
Apotex, Canad.; Apotex, Cz.†; Apotex, NZ; Apotex, Pol.; Apotex, Singapore.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Apotex, Hong Kong.
Amoxicillin (p.202·2).
Bacterial infections.

Apo-Amoxi Clav *Apotex, Canad.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Apo-Ampi *Apotex, Canad.; Apotex, Cz.†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Apo-Asa *Apotex, Cz.†.*
Aspirin (p.20·3).
Fever; pain.

Apo-Atenidone *Apotex, Canad.; Apotex, Malaysia.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Apo-Atenol *Apotex, Canad.; Apotex, Cz.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Apobace *Protein, Mex.†.*
Carbamazepine (p.471·3).
Epilepsy.

Apobacyn *Gerolymatos, Gr.*
Neomycin (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Apobase *Alpharma, Fin.*
Emollient.

Apo-Benztropine *Apotex, Cz.*
Benzatropine mesilate (p.797·1).
Dystonia; parkinsonism.

Apo-C *Apotex, Cz.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Apo-Cal *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Apo-Capto *Apotex, Canad.; Apotex, Cz.†; Apotex, Hong Kong; Apotex, Malaysia†; Apotex, Rus.; Apotex, Singapore.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Apocard *3M, Belg.; Meda, Port.; 3M, Spain.*
Flecainide acetate (p.1288·1).
Arrhythmias.

Apo-Carve *Apotex, Cz.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Apocatil *Protein, Mex.†.*
Dequalinium (p.1641·3).
Mouth and throat disorders.

Apo-Cephalex *Apotex, Canad.*
Cefalexin (p.218·2).
Bacterial infections.

Apo-Chlorax *Apotex, Canad.; Apotex, Malaysia†; Apotex, Singapore.*
Chlordiazepoxide hydrochloride (p.968·2); clidinium bromide (p.1722·1).
Gastrointestinal disorders with associated anxiety.

Apociclina *Protein, Mex.†.*
Doxycycline (p.267·1).
Bacterial infections.

Apocillin *Alpharma, Norw.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Apocit *Apogepha, Ger.*
Potassium sodium hydrogen citrate (p.1674·2).
Renal calculi.

Apo-Cital *Apotex, Cz.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Apoclavox *Apotex, Mex.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Apo-Clodin *Apotex, Pol.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis.

Apo-Cloxi *Apotex, Canad.; Apotex, Hong Kong.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Apocort *Alpharma, Fin.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Apo-Cromolyn *Apotex, Canad.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis; asthma.

Apocyclin *Alpharma, Fin.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Apodasi *Protein, Mex.†.*
Didanosine (p.870·2).

Apodefil *Apotex, Mex.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Apodepi *Apotex, Hung.*
Paroxetine (p.414·2).
Depression; panic disorder; post-traumatic stress disorder.

Apoderm *Nycomed, Austria.*
Deproteinised derivative of calf blood (p.2337·3).
Burns; ulcers; wounds.

Apo-Diclo
Apotex, Canad.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.

Apotex, Cz.; Apotex, Malaysia†; Apotex, NZ; Apotex, Rus.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Apotex, Hong Kong; Apotex, Pol.
Diclofenac (p.44·2).
Inflammation; musculoskeletal and joint disorders; pain.

Apo-Diltiaz *Apotex, Canad.; Apotex, Hong Kong.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Apodorm *Alpharma, Denm.; Alpharma, Norw.; Alpharma, Swed.*
Nitrazepam (p.1011·2).
Epilepsy; infantile spasm; insomnia.

Apo-Doxan *Apotex, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Apodoxin *Alpharma, Fin.*
Doxycycline (p.267·1).
Bacterial infections.

Apo-Doxy
Apotex, Canad.; Apotex, Cz.†; Apotex, Rus.†.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Apotex, Singapore.
Doxycycline (p.267·1).
Bacterial infections.

Apodrolen *Apotex, Mex.*
Alendronic acid (p.1088·1).
Osteoporosis.

Apo-Erythro
Apotex, Canad.
Erythromycin (p.269·2), erythromycin ethyl succinate (p.269·3), or erythromycin stearate (p.270·1).
Bacterial infections.

Apotex, Hong Kong.
Erythromycin (p.269·2).
Bacterial infections.

Apofarm *Gezzi, Arg.*
Aciclovir (p.862·3).

Apo-Fedipisal *Protein, Mex.†.*
Nifedipine (p.1350·1).
Hypertension.

Apo-Feno *Apotex, Canad.; Apotex, Cz.; Apotex, Pol.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Apo-Feno-Micro *Apotex, Hong Kong; Apotex, Malaysia.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Apo-Fide *Apotex, Mex.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Apofin *Chiesi, Ital.*
Apomorphine hydrochloride (p.795·1).
Parkinsonism.

Apo-Finas *Apotex, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Apoflox *Protein, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Apo-Fluoxetine *Apotex, Rus.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Apo-Flutam *Apotex, Pol.*
Flutamide (p.725·1).
Prostatic cancer.

Apoflux *Santa, Gr.†.*
Sodium fluoride (p.1962·2).
Prophylaxis of dental caries.

Apo-Fosinop *Apotex, Cz.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Apo-Gab *Apotex, Cz.*
Gabapentin (p.482·3).
Epilepsy; peripheral neuropathy.

Apo-Gain *Apotex, Canad.; Apotex, Hong Kong†; Apotex, Malaysia.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Apo-Galant *Apotex, Cz.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Apogastine *Curex, Israel.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apogeo *Progen, Ital.*
Soya isoflavones (p.2391·2); vitamin E (p.1992·2).
Nutritional supplement for the menopause.

Apo-Glimep *Apotex, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Apogly *Apotex, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

APO-go *Biochemie, Austria; Medeva, Cz.; Cephalon, Ger.; ITF, Gr.; Forum, Hung.†; Teva, Israel; Forum, Neth.; Forum, Port.; Italfarmaco, Spain; Gen, Turk.; Britannia Pharmaceuticals, UK.*
Apomorphine hydrochloride (p.795·1).
Parkinsonism.

Apo-Hepat *Pekana, Ger.†.*
Homoeopathic preparation.

Apo-Hydro *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Apo-Hydroxyquine *Apotex, Canad.*
Hydroxychloroquine sulfate (p.604·2).
Malaria; rheumatoid arthritis.

Apo-Indap *Apotex, Pol.*
⊗ Indapamide (p.1314·1).
Hypertension.

Apo-Infekt *Pekana, Ger.†.*
Homoeopathic preparation.

Apo-Ipravent *Apotex, Canad.; Apotex, NZ.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease; rhinitis.

Apo-ISDN *Apotex, Canad.; Apotex, Cz.†; Apotex, Hong Kong; Apotex, Malaysia†; Apotex, Singapore.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Apo-K *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Apo-Kesol *Protein, Mex.†.*
Ketoconazole (p.539·1).
Fungal infections.

Apo-Keto *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal and joint disorders; pain.

Apokinon *Rontag, Arg.†; Aguettant, Fr.†.*
Apomorphine hydrochloride (p.795·1).
Parkinsonism.

Apokyn *Bertek, USA.*
Apomorphine hydrochloride (p.795·1).
Parkinsonism.

Apol *Etifar, Venez.*
Vitamin and mineral preparation (p.1922·1).

Apolar *Alpharma, Fin.; Actavis, Indon.; Alpharma, Norw.; Alpharma, Swed.†.*
⊗ Desonide (p.1525·1).
Skin disorders.

Apolar med dekvalin *Alpharma, Norw.*
⊗ Desonide (p.1525·1); dequalinium chloride (p.1641·3).
Infected skin disorders.

Apolar-N *Actavis, Indon.*
⊗ Desonide (p.1525·1); neomycin sulfate (p.305·1).
Anogenital pruritus; infected skin disorders; otitis externa.

Apo-Lato *Apotex, Mex.*
Sucralfate (p.1772·2).
Peptic ulcer.

Apo-Levocarb *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, NZ.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Apolide *Apotex, Mex.*
Nimesulide (p.95·3).
Inflammation; pain.

Apoliz *Apotex, Mex.*
Cetirizine (p.571·1).
Hypersensitivity.

Apollo *Philusa, Philipp.*
Soft paraffin (p.2031·2).
Barrier preparation.

Apollonset *Farmanic, Gr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; premedication; skeletal muscle spasm; sleep disorders; status epilepticus; tetanus.

Apo-Lova *Apotex, Pol.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Apomastina *Apotex, Mex.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Apo-Medroxy *Apotex, Canad.*
Medroxyprogesterone acetate (p.2113·1).
Progestogenic.

Apometglu *Apotex, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Apo-Methazide *Apotex, Canad.*
⊗ Methyldopa (p.1334·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Apo-Methoprazine *Apotex, Canad.*
Levomepromazine maleate (p.1003·1).

Apo-Metoclop *Apotex, Canad.; Apotex, Rus.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Apomiclin *Apotex, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Apomin *APT, Hong Kong.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Apo-Mina *Protein, Mex.*
Dimenhydrinate (p.576·2).
Nausea; vertigo.

Apomine *Mayne, Austral.; Mayne, NZ.*
Apomorphine hydrochloride (p.795·1).
Parkinsonism.

Apo-Moclob *Apotex, Cz.*
Moclobemide (p.411·1).
Depression; social phobia.

Apo-Nadol *Apotex, Canad.; Apotex, Hong Kong.*
⊗ Nadolol (p.1345·2).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine.

Aponal *Roche, Ger.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; insomnia; withdrawal syndromes.

Apo-Napro-Na *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
Naproxen sodium (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Aponeusak *Protein, Mex.†.*
Fluoxetine (p.397·3).
Depression.

Apo-Nifed *Apotex, Canad.; Apotex, Singapore.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; Raynaud's syndrome.

Aponil
Note.This name is used for preparations of different composition.
Glaxo Allen, Ital.
Lacidipine (p.1322·2).
Hypertension.

Medochemie, Rus.
Nimesulide (p.95·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Aponistan V *Protein, Mex.*
Nystatin (p.543·2).
Fungal infections.

Apo-Norflox *Apotex, Canad.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Apo-Oflox *Apotex, Canad.; Apotex, Malaysia†.*
Ofloxacin (p.310·2).
Bacterial infections.

Apo-Ome *Apotex, Cz.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apo-Oxpar *Apotex, Mex.*
Paroxetine (p.414·2).
Depression.

Apo-Panto *Apotex, Cz.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Apo-Paradex *Apotex, NZ†.*
Paracetamol (p.108·1); dextropropoxyphene napsilate (p.40·1).
Pain.

Apo-Parox *Apotex, Cz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Apo-Pentox *Apotex, Pol.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Apo-Pen-VK *Apotex, Canad.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Apo-Pera *Apotex, Mex.*
Loperamide (p.1741·3).

Apo-Perindo *Apotex, Cz.*
Perindopril erbumine (p.1368·3).
Cardiac ischaemia; heart failure; hypertension.

Apophage *Curex, Israel.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Apo-Pindol *Apotex, Canad.; Apotex, Cz.†.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Apopiran *Protein, Mex.†.*
Piroxicam (p.117·3).
Rheumatism.

Apoplectal N *Fujisawa, Ger.†.*
⊗ Aesculus (p.2248·2); buphenine hydrochloride (p.2270·2).
Cerebrovascular disorders.

Apo-Prava *Apotex, Pol.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Apopraza *Apotex, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Apo-Prazo *Apotex, Canad.; Apotex, Hong Kong; Apotex, NZ; Apotex, Singapore.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's disease.

Apoprin *Protein, Mex.†.*
Ranitidine (p.1766·1).
Peptic ulcer.

Apo-Probutol *Protein, Mex.†.*
Ethambutol (p.275·2).

Apo-Prochlorazine *Apotex, Canad.*
Prochlorperazine maleate (p.1020·1).

Apoprod *Apotex, Mex.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Apo-Pulm *Pekana, Ger.†.*
Homoeopathic preparation.

Apo-Pyl *Apotex, Mex.*
Enalapril (p.1276·1).
Hypertension.

A-Por *Aspen, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal fungal infections.

Aporex *Alpharma, Norw.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Aporil *Qualiphar, Belg.*
Salicylic acid (p.1612·2); acetic acid (p.2244·2); lactic acid (p.2329·3); thuja (p.2400·3); greater celandine (p.2317·1).
Warts.

Apo-Risper *Apotex, Cz.*
Risperidone (p.1024·2).
Mania; schizophrenia.

Aposada *Apotex, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Apo-Salvent
Apotex, Canad.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Apotex, Cz.†; Apotex, NZ.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease; status asthmaticus.

Apotex, Hong Kong†; Apotex, Mex.
⊗ Salbutamol (p.1131·2).
Asthma.

Apo-Seleg *Apotex, Cz.*
⊗ Selegiline hydrochloride (p.817·1).
Alzheimer's disease; parkinsonism.

Apo-Selin *Apotex, Pol.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Apo-Sertral *Apotex, Cz.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Apo-Simva *Apotex, Cz.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Apostavina *Protein, Mex.†.*
Stavudine (p.907·1).
HIV infection.

Apo-Sulfatrim *Apotex, Canad.; Apotex, Cz.†; Apotex, NZ; Apotex, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Apo-Sulin *Apotex, Canad.; Apotex, Malaysia†; Apotex, Singapore.*
Sulindac (p.126·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Apo-Tamis *Apotex, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Apo-Tamox *Apotex, Canad.; Apotex, Hong Kong; Apotex, Singapore.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer.

Apotel *Unipharma, Gr.*
Paracetamol (p.108·1).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Fever; pain.

Apotel C-500 *Unipharma, Gr.*
Paracetamol (p.108·1); vitamin C (p.1983·3).
Fever; pain.

Apotel Extra *Unipharma, Gr.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Apoteoprol *Protein, Mex.†.*
Theophylline (p.1140·1).

Apo-Tetra *Apotex, Canad.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Apo-Theo *Apotex, Canad.; Apotex, Malaysia; Apotex, Singapore.*
Theophylline (p.1140·1).
Bronchospasm; obstructive airways disease.

Apo-Tic *Apotex, Cz.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Apo-Timol *Apotex, Canad.; Apotex, NZ.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Apo-Timop *Apotex, Canad.; Apotex, Hong Kong; Apotex, NZ.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Apo-Tinole *Protein, Mex.†.*
Allopurinol (p.552·2).
Gout.

Apotoke *Apotex, Mex.*
Ketorolac (p.75·2).
Inflammation; pain.

Apo-Triazide *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia†; Apotex, Rus.; Apotex, Singapore.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Hypertension; oedema.

Apo-Triazo *Apotex, Canad.*
Triazolam (p.1033·2).
Insomnia.

Apo-Trihex *Apotex, Canad.; Apotex, Hong Kong; Apotex, Malaysia; Apotex, Singapore.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Apo-Trimip *Apotex, Canad.*
Trimipramine maleate (p.426·3).
Depression.

Apo-Trina *Apotex, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Apo-Trinelax *Apotex, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Apo-Tuss *Pekana, Ger.†.*
Homoeopathic preparation.

Apoven *Douglas, Austral.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Apovent *Curex, Israel.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Apo-Verap *Apotex, Canad.; Apotex, Cz.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; obstructive cardiomyopathy.

Apo-Vir *Apotex, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Apozema *Apomedica, Austria.*
Turmeric oil (p.1473·2); *p*,α-dimethylbenzyl alcohol (p.2294·2); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); camphor (p.2273·2); menthol (p.2340·1).
Digestive disorders; gastrointestinal disorders.

Apozema Allium Cepa compositum *Apomedica, Austria.*
Homoeopathic preparation.

Apozema Apis compositum *Apomedica, Austria.*
Homoeopathic preparation.

Apozemia *Apotex, Mex.*
Metformin (p.453·3).
Diabetes mellitus.

Apozepam *Alpharma, Denm.; Alpharma, Swed.†.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; insomnia; premedication; restlessness; skeletal muscle spasm; spasticity.

Appearex *Merz, USA.*
Biotin (p.1931·3).
Nail disorders.

Appebon
United Laboratories, Philipp.
Syrup: Buclizine hydrochloride (p.570·1); vitamin B substances; lysine hydrochloride (p.1922·1).
Appetite stimulant.

United Laboratories, Philipp.
Tablets: Buclizine hydrochloride (p.570·1); vitamin B substances; vitamin C (p.1922·1).
Appetite stimulant.

Appebon with Iron
Note. This name is used for preparations of different composition.
United Laboratories, Philipp.
Capsules: Buclizine hydrochloride (p.570·1); vitamin B substances (p.1922·1); ferrous fumarate (p.1938·3).
Appetite stimulant.

United Laboratories, Philipp.
Syrup: Buclizine hydrochloride (p.570·1); vitamin B substances (p.1922·1); lysine hydrochloride; ferrous sulfate (p.1939·3).
Appetite stimulant.

Appedrine *Chattem, Canad.†.*
Benzocaine (p.1854·1); ferrous fumarate (p.1938·3); carmellose sodium (p.2142·1); vitamins (p.1922·1).
Obesity.

Appelin-B12 *Savoy, Singapore.*
Benzoic acid; inositol; lysine; sorbitol; vitamin B ; vitamin C (p.1922·1).
Tonic.

Appetason
Note. This name is used for preparations of different composition.
Ad-Drugstel, Philipp.
Capsules: Vitamin B substances (p.1922·1); ferrous sulfate (p.1939·3); buclizine hydrochloride (p.570·1).
Reduced appetite.

Ad-Drugstel, Philipp.
Syrup: Vitamin B substances; ferrous sulfate (p.1939·3); lysine hydrochloride (p.1922·1).
Reduced appetite.

Appetens *Novartis, Philipp.*
Pizotifen (p.624·2) or pizotifen malate (p.624·2); vitamin B substances (p.1922·1).
Reduced appetite.

Appetiser Mixture *Potter's, UK.*
Chamomile (p.2279·3); calumba (p.2273·2); compound gentian infusion (p.2310·3).
Flatulence; tonic.

Appeton *Kotra, Malaysia.*
A range of vitamin preparations with or without minerals, ginseng, lysine, or taurine (p.1922·1).

Appeton Lysine *Kotra, Hong Kong.*
A range of vitamin preparations with lysine (p.1922·1).

Appeton Memocap *Kotra, Malaysia†.*
Ginkgo biloba (p.2311·1).
Peripheral vascular disorders.

Appeton Weight Gain *Kotra, Hong Kong; Kotra, Malaysia†.*
A preparation for enteral nutrition (p.1922·1).

Applicaine
Note. This name is used for preparations of different composition.
Carter, Austral.
Oral gel: Choline salicylate (p.36·3).
Oral pain; teething.

Carter, Austral.
Topical liquid: Benzocaine (p.1854·1).
Mouth ulcers; oral pain; teething.

APR Cream *Curacel, Austral.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); capsicum oleoresin (p.2276·2); copper sulfate (p.1935·3); eicosapentaenoic acid (p.1362·1); melaleuca oil (p.2338·2); zinc sulfate (p.1999·2).
Musculoskeletal and joint disorders.

Apra *Altaire, USA.*
Paracetamol (p.108·1).
Fever; pain.

Apracur
Note. This name is used for preparations of different composition.
Serch, Arg.†.
Paracetamol (p.108·1); phenylephrine (p.1568·1); clemizole (p.574·1).
Influenza symptoms.

Trahan, Thai.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); clemizole hydrochloride (p.574·1); salicylamide (p.121·2).
Cold symptoms.

Apracur Antifebril *Higate, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Apracur Biotic *Serch, Arg.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Apracur Bucofaringeo *Serch, Arg.†.*
Hexylresorcinol (p.1647·1); benzocaine (p.1854·1).

Apracur Descongestivo *HMA, Arg.*
Paracetamol (p.108·1); phenylephrine (p.1568·1).
Cold symptoms.

Apracur Expectorante *HMA, Arg.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Apracur Nasal *HMA, Arg.*
⊗ Oxymetazoline (p.1567·2).
Nasal congestion.

Apraljin *Deva, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Apranax
Roche, Belg.; Valeant, Hung.; Roche, Switz.; Abdi, Turk.; Roche, Venez.†.
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Roche, Fr.
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Inflammatory disorders; musculoskeletal and joint disorders; pain.

Apraz *Mantecorp, Braz.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; panic disorder.

Aprazol *Bilim, Turk.; Husnu, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aprednislon *Merck, Austria.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Apresazide *Novartis, USA†.*
⊗ Hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Apresolin *Novartis, Norw.; Novartis, Swed.*
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension.

Apresolina *Novartis, Braz.; Novartis, Mex.; Novartis, Venez.†.*
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension.

Apresoline *Novartis, Austral.; SteriMax, Canad.; Novartis, Hong Kong†; Novartis, Irl.; Novartis, NZ; Novartis, Philipp.; Novartis, S.Afr.; Novartis, Thai.; Amdipharm, UK; Novartis, USA.*
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension; hypertensive crisis.

Apress *Gerolimatos (Γερολυματος), Gr.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Apri *Duramed, USA.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Aprical
Note. This name is used for preparations of different composition.
Raffo, Arg.†.
Ranitidine (p.1766·1).

Rentschler, Cz.†; Shire, Ger.
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

April *Gador, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

AprilGen *Generics, Pol.*
Quinapril (p.1382·3).
Heart failure; hypertension.

Aprinol *Anfarm, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Aprinox *Abbott, Austral.; Sovereign, UK.*
⊗ Bendroflumethiazide (p.1224·1).
Hypertension; oedema; suppression of lactation.

Aprix-DN *Recalcine, Chile†.*
Yellow tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); blue tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Influenza symptoms.

Aprodine *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Aprodine with Codeine *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Aprofen *Medicine Products, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Aprol *Bilim, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Apromed *Kocak, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Aprostal *Solvay, Philipp.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Aproten *Diet Erba, NZ; Ultrapharm, UK.*
Low-protein, gluten-free foods for special diets (p.1922·1).

Aprotex *Veropharm, Rus.*
Aprotinin (p.1055·1).

Aprotilin *Kleva, Gr.†.*
Maprotiline hydrochloride (p.407·2).
Depression.

Aprovel *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi, Denm.; BMS, Fin.; BMS, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; BMS, Irl.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; BMS, Neth.; Sanofi, Neth.; Sanofi BMS, Norw.; Sanofi Synthelabo, Philipp.; BMS, Pol.; Sanofi-Aventis, Pol.; BMS, Port.; Sanofi Synthelabo, Port.; Sanofi Winthrop, Rus.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; BMS, Swed.; Sanofi Synthelabo, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi Synthelabo, Thai.; BMS, UK; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
Irbesartan (p.1316·1).
Diabetic nephropathy; hypertension.

Aprovel HCT *Sanofi Synthelabo, Hong Kong†; Sanofi Synthelabo, Thai.†.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Aprowell *Ali, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Aproxal *Elpen (Ελπεν), Gr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Aprozide *Sanofi-Aventis, Braz.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

APS Balneum *APS, Cz.†.*
Chamomile oil (p.2279·3).
Bath additive; skin disorders.

APSI/AQ *Stallergenes, Cz.†.*
Allergen extracts (p.2250·2).
Hyposensitisation.

Apsoderm *Alice Loren, Gr.*
Salicylic acid (p.1612·2).
Skin disorders.

Apsomol *Farmasan, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Apsor *Merck-Lipha, Fr.*
Tacalcitol (p.1615·1).
Psoriasis.

Aptamil I *Support, Braz.†.*
Infant feed (p.1922·1).
Colic; constipation.

Aptamil AR *Milupa, Port.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Aptamil HA *Milupa, Port.*
Infant feed (p.1922·1).
Milk intolerance.

APT-Ampicloxa *Merck, Hong Kong.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Apteor *Solvay, Port.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Aptha-X *CTI, Israel.*
Aloe vera (p.1588·2); benzalkonium chloride (p.1629·1); enoxolone (p.50·1); povidone (p.2146·1); sodium hyaluronate (p.2320·1).
Oral lesions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Aptivium Liver Support *Cynergen, Indon.*
Silymarin (p.1452·2); turmeric (p.1473·2); thioctic acid (p.2400·2); vitamin B substances; ascorbic acid; vitamin E (p.1922·1).
Liver disorders.

Aptivium Optimum Joint Formula *Cynergen, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); vitamin C (p.1983·3).
Osteoarthritis; rheumatoid arthritis.

Aptivus *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.*
Tipranavir (p.909·3).
HIV infection.

Aptodin Plus *GD, Ital.*
Vitamin, mineral, and amino-acid preparation (p.1922·1).

Apton *Delta, Port.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Aptor *Nicholas, Indon.*
Aspirin (p.20·3).
Fever; pain.

Aptus Amphetamine *Aptus, NZ†.*
Test for amfetamine in urine.

Aptus Benzodiazepine *Aptus, NZ†.*
Test for benzodiazepines in urine.

Aptus Cannabis *Aptus, NZ†.*
Test for THC in urine.

Aptus Cocaine *Aptus, NZ†.*
Test for cocaine in urine.

Aptus Methadone *Aptus, NZ†.*
Test for methadone in urine.

Aptus Methamphetamine *Aptus, NZ†.*
Test for methamfetamine in urine.

Aptus Opiate *Aptus, NZ†.*
Test for opiates in urine.

Apulein *Gedeon Richter, Cz.†; Gedeon Richter, Hung.†.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Apurin
Hexal, Austria†; Gea, Denm.; Sandoz, Fin.
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Hexal, Neth.
Allopurinol (p.552·2) or allopurinol sodium (p.553·3).
Gout; hyperuricaemia.

Apurol *Leciva, Cz.†; Siegfried, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Apurone *Substipharm, Fr.*
Flumequine (p.278·1).
Bacterial infections of the urinary tract.

Apuzin *YSP, Malaysia.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Apydan *Desitin, Denm.; Algol, Fin.; Desitin, Hung.; Desitin, Pol.*
Oxcarbazepine (p.490·3).
Epilepsy.

Apyrene *Vincenti, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Apyrol *Salusif, Port.†.*
Sodium hydroxyquinoline sulfate (p.2323·2); camphor (p.2273·2).
Muscular pain; soft-tissue disorders; wounds.

Aqium *Ego, Austral.*
Barrier cream.

Aqsia *Abdi, Turk.*
Electrolyte solution (p.1667·1).
Eye irrigation.

Aqua Ban *Lane, UK; Thompson, USA.*
Ammonium chloride (p.1551·3); caffeine (p.1116·3).
Premenstrual water retention.

Aqua Ban Herbal *Lane, UK.*
Lappa (p.2330·3); bearberry (p.2263·3); clivers (p.2284·3).
Water retention.

Aqua Ban Plus *Thompson, USA.*
Ammonium chloride (p.1551·3); caffeine (p.1116·3); ferrous sulfate (p.1939·3).
Premenstrual water retention.

Aqua Dermis *Bio-Pharmaceuticals, Malaysia†.*
Soap substitute.

Aqua Ear *Wyeth Consumer, Austral.; Whitehall, NZ†.*
Glacial acetic acid (p.2244·2); isopropyl alcohol (p.1650·3).
Otitis externa.

Aqua Emoform *Altana, Ital.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Gingival inflammation; oral hygiene.

Aqua Lent Colirio *Inmunolab, Arg.*
⊗ Ephedrine (p.1558·1); phenazone (p.116·1).
Eye disorders.

Aqua Lent Lagrima *Inmunolab, Arg.†.*
Carmellose sodium (p.2142·1).
Dry eyes.

Aqua Lent Limpia Cristales *Inmunolab, Arg.*
Sodium chloride (p.1686·1) (p.1622·2).
Contact lens care.

Aqua Lent Lubricante *Inmunolab, Arg.*
Carmellose sodium (p.2142·1).
Dry eyes; eye irritation.

Aqua Lub *Probifasa, Mex.†.*
Lubricant for vaginal and rectal use.

Aqua Maris *Jadran, Rus.*
Sea water with natural salts and trace elements.
Nasal disorders.

AquaBalm *Quintessa, USA.*
Emollient.
Dry skin.

Aquabase *Avene, Fr.; Paddock, USA.*
Vehicle for topical preparations.

Aquablock *Pfizer, NZ.*
SPF 30+: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Aquacare *Allergan, Austral.; Allergan, NZ; Menley & James, USA.*
⊗ Urea (p.1620·2).
Dry skin; eczema; keratinisation disorders.

Aquacel *Convatec, Arg.; Convatec, Austral.†; Convatec, Canad.†; Convatec, Fr.; Convatec, Port.†.*
Carmellose sodium (p.2142·1).
Burns; skin ulcers; wounds.

Aquacel Ag *Convatec, Fr.; Convatec, Ital.*
Silver (p.2387·1); carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Aquachloral *PolyMedica, USA.*
Cloral hydrate (p.979·1).
Sedative.

Aquacort *Lindopharm, Ger.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Aquaderm
Note. This name is used for preparations of different composition.
Paladin, Canad.†.
Emollient.

Pendopharm, Canad.
SPF 15: Octisalate (p.1608·2); avobenzone (p.1589·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Baker Cummins, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Pendopharm, Canad.
SPF 30: Avobenzone (p.1589·3); octocrilene (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Aquadetrim *Medana, Rus.*
Colecalciferol (p.1986·2).
Hypoparathyroidism; osteomalacia; osteoporosis; rickets; tetany; vitamin D deficiency.

Aquadon *Rekah, Israel.*
⊗ Chlortalidone (p.1243·3).
Hypertension; liver cirrhosis; oedema; renal failure.

Aquadrate *Alliance, Irl.; Alliance, UK.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Aquae *Hamilton, Austral.; Hamilton, Hong Kong.*
Carmellose sodium (p.2142·1); sorbitol (p.1965·1); electrolytes (p.1667·1).
Artificial saliva.

Aqua-E *Yasoo, USA.*
Vitamin E (p.1992·2).

Aquafilme *Sofex, Port.†.*
Emollient.

Aquafor *Asta Medica, Ital.†.*
⊗ Xipamide (p.1434·1).
Hypertension.

Aquaform *Maersk, UK.*
Hydrogel dressing.
Ulcers; wounds.

Aquagel *Adams, Hong Kong.*
Lubricating jelly.

Aquagen SQ *ALK, Denm.; ALK, Fin.; ALK, Swed.*
Allergen extracts (p.2250·2).
Allergen immunotherapy; diagnosis of hypersensitivity.

Aqualan *Orion, Fin.*
Emollient.

Aqualane *Roux-Ocefa, Arg.*
Beeswax (p.2028·1); liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Barrier cream.

Aqualarm *Chauvin, Fr.*
Carbomer 980 (p.2141·3).
Dry eyes.

Aqualcium *Delta, Fr.†.*
Mineral preparation (p.1922·1).
Calcium deficiency.

Aqualette *Lichtwer, UK.*
Taraxacum (p.2395·1); equisetum (p.2299·3).

Aqualibra *Medice, Ger.*
Ononis (p.2357·1); java tea (p.2328·2); solidago (p.2391·1).
Urinary-tract disorders.

Aquamag *Delta, Fr.†.*
Mineral preparation (p.1922·1).
Magnesium deficiency.

Aquamephyton *Merck, USA†.*
Phytomenadione (p.1995·3).
Coagulation disorders associated with vitamin K deficiency, due to faulty formation of factors II, VII, IX, and X.

Aquamycetin-N *Winzer, Ger.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Aquanil
Note. This name is used for preparations of different composition.
Dispolab, Chile; Person & Covey, USA.
Soap-free skin cleanser.

OmniVision, Denm.; Novartis, Fin.†; OmniVision, Norw.; OmniVision, Swed.†.
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Darier, Mex.
Sodium laurilsulfate (p.2138·3).
Skin disorders.

Aquanil HC *Dispolab, Chile; Darier, Mex.; Person & Covey, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Aquaphar *Albephar, Venez.*
⊗ Urea (p.1620·2).

Aquaphilic *Medco, USA.*
Vehicle for topical preparations.

Aquaphor
Note. This name is used for preparations of different composition.
Lilly, Ger.
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Beiersdorf, USA.
Yellow soft paraffin; liquid paraffin; mineral wax; wool wax alcohol.
Barrier ointment; ointment base.

Aquaphor Healing Ointment *Beiersdorf, USA.*
Soft paraffin; liquid paraffin; ceresin; wool alcohols; panthenol; bisabolol.
Dry skin disorders.

Aquaphoril *Viatris, Austria.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Aquaphyllin *Ferndale, USA†.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

Aquapred *Winzer, Ger.*
⊗ Chloramphenicol (p.239·3); prednisolone sodium phosphate (p.1541·2).
Inflammatory disorders and infections of the eye.

Aquareduct *Azupharma, Ger.†.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Aquaretic *Azupharma, Ger.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Aquarid *Schwulst, S.Afr.*
⊗ Furosemide (p.1292·1).
Oedema.

Aquarius *Demo, Gr.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Aquasalina *Bruschettini, Ital.†.*
Sodium chloride (p.1686·1); borax (p.2268·1); boric acid (p.2268·1).
Eye and nasal irrigation.

Aquasept *Medlock Medical, UK.*
Triclosan (p.1665·2).
Skin disinfection.

Aquasite *Novartis Ophthalmics, USA†.*
⊗ Macrogol 400 (p.2336·3); dextran 70 (p.1059·3); polycarbophil (p.1763·3).
Dry eyes.

Aqua-Soap *Remexa, Mex.*
Soap substitute.

Aquasol *SSL, UK.*
Purified water (p.2414·3).

Aquasol A
Note. This name is used for preparations of different composition.
Minerva (Μινερβα), Gr.†.
Vitamin A (p.1971·2); panthenol (p.2362·1).

Hospira, USA.
Vitamin A (p.1971·2).
Vitamin A deficiency.

Aquasol AD *Grossman, Mex.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Aquasol A+D *Minerva (Μινερβα), Gr.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1).
Vitamin A and D deficiency.

Aquasol E *Columbia, Canad.; Mayne, USA.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Aquasport *Also, Ital.†.*
Mineral preparation (p.1922·1).

Aquasteril *Boxter, Fin.*
Water for injections (p.2414·3).

Aquasun
Note. This name is used for preparations of different composition.
Pfizer, NZ.
Lotion SPF 18: Octinoxate (p.1608·2); avobenzone (p.1589·3); oxybenzone (p.1608·3); octocrilene (p.1608·3).
Sunscreen.

Pfizer, NZ†.
SPF 4; SPF 8: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Pfizer, NZ.
SPF 30+ cream; SPF 30+ lotion: Octinoxate (p.1608·2); avobenzone (p.1589·3); octil triazone (p.1608·1).
Sunscreen.

Pfizer, NZ†.
Stick SPF 30: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Aquatab C *Adams, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly contained guaifenesin, phenylpropanolamine hydrochloride, and dextromethorphan hydrobromide.
Coughs.

Aquatab D *Adams, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly contained guaifenesin and phenylpropanolamine hydrochloride.
Nasal congestion.

Aquatab DM *Adams, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Aquatabs *Sovedis, Fr.*
Troclosene sodium (p.1665·3).
Water disinfection.

Aquatabs (Puritabs) *Dermatech, Austral.*
Troclosene sodium (p.1665·3).
Water disinfection.

Aquatain *Wyeth Consumer, Canad.*
Emollient.

AquaTears
Note. A similar name is used for preparations of different composition (see below).
Novartis, Austria.
Carbomer 974P (p.2141·3).
Dry eyes.

Aquatears
Note. A similar name is used for preparations of different composition (see above).
Cipla, India.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Aquatensen *Wallace, USA†.*
⊗ Methyclothiazide (p.1334·1).
Hypertension; oedema.

Aquaviron *Nicholas Piramal, India.*
⊗ Testosterone (p.2129·3).
Cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism; osteoporosis.

Aquavit-E *Cypress, USA.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Aquazide *Sun, India.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Aqucilina *Reig Jofre, Spain.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Aqucilina D A *Reig Jofre, Spain.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Aquedux *Sanofi Synthelabo, Port.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Aquella *Lifeplan, UK.*
Boldo; kelp; cider vinegar; lappa; taraxacum (p.1922·1).
Herbal supplement.

Aqueous Charcodote *Pharmascience, Singapore.*
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Aquex *Gry, Ger.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Aquiflav *Uriach Aquilea OTC, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Aquify *Ciba Vision, Arg.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Aquim *Ego, NZ†.*
Dimeticone (p.2032·1).
Barrier preparation.

Aquitol *Teva, Israel†.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin A and D supplement.

Aquitos *Uriach Aquilea OTC, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Aquo-Cytobion *Merck, Ger.†.*
Hydroxocobalamin acetate (p.1980·3).
Vitamin B deficiency.

Aquo-Trinitrosan *Merck, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension; myocardial infarction.

Aqupla *Shionogi, Jpn.*
Nedaplatin (p.755·2).
Malignant neoplasms.

Aqurea *ICM, Singapore.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Arabine *Mayne, Denm.; Mayne, Fin.; Mayne, Swed.*
Cytarabine (p.705·1).
Acute leukaemias.

Arabloc *Aventis, Austral.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Aracaf *TNP, Thai.†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; cough; nasal congestion.

ARA-cell *Stada, Austria; Cell Pharm, Ger.; Cell Pharm, Port.; Asos, Turk.*
Cytarabine (p.705·1).
Acute leukaemias; non-Hodgkins lymphoma.

Arachitol *Solvay, India.*
Colecalciferol (p.1986·2).
Hypoparathyroidism; rickets, osteomalacia.

Aracmyn *Bioclon, Mex.*
Spider venom antiserum (p.2239·2).
Spider bites (Latrodectus mactans, Loxosceles).

Aracytin *Janssen-Cilag, Arg.†; Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pharmacia, Ital.*
Cytarabine (p.705·1).
Acute leukaemias; lymphomas; myelodysplastic syndrome.

Aracytine *Pfizer, Fr.*
Cytarabine (p.705·1).
Leukaemias; myelodysplasia.

Aradix *Drugtech, Chile.*
⊗ Methylphenidate (p.2160·1).
Attention-deficit hyperactivity disorder; narcolepsy.

Aradois *Biolab Sanus, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Aradois H *Biolab Sanus, Braz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Aragest *Dexxon, Israel.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menstrual disorders.

Aralast *Alpha Therapeutic, USA.*
Alpha -proteinase inhibitor (p.2253·2).
Alpha -proteinase deficiency.

Aralen
Sanofi Synthelabo, Canad.†; Sanofi Synthelabo, Philipp.; Sanofi Winthrop, USA.
Chloroquine phosphate (p.599·3).
Amoebiasis; malaria.

Sanofi Synthelabo, Mex.
Chloroquine (p.599·2).
Amoebiasis; malaria.

Aralia Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Aralis *Pfluger, Ger.*
Homoeopathic preparation.

Aramin *Cristalia, Braz.*
⊗ Metaraminol tartrate (p.1333·2).
Hypotension.

Aramine *MSD, Austral.; IFET (ΙΦΕΤ), Gr.†; MSD, NZ; MSD, Norw.†; MSD, Thai.†; Merck, USA.*
⊗ Metaraminol tartrate (p.1333·2).
Hypotension; shock.

Aramix *Elea, Arg.*
Escitalopram (p.391·1).
Depression.

Aranelle *Barr, USA.*
21 Tablets, norethisterone (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Aranesp *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Genesis, Gr.; Amgen, Hong Kong; Amgen, Hung.; Amgen, Irl.; Amgen, Israel; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Eczacibasi, Turk.; Amgen, UK; Amgen, USA.*
⊗ Darbepoetin alfa (p.1058·2).
Anaemias.

Araniforce-forte *Weber & Weber, Ger.*
Homoeopathic preparation.

Aranisan-N *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Aranox *APT, Hong Kong.*
Itraconazole (p.536·3).
Fungal infections.

Arasena-A *Mochida, Jpn.*
Vidarabine (p.912·2).
Herpesvirus infections.

Aratac *Alphapharm, Austral.; Alphapharm, Malaysia; Pacific, NZ; Alphapharm, Singapore; Merck, Singapore; Merck, Thai.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Aratan *Andromaco, Chile.*
Losartan potassium (p.1326·1).
Hypertension.

Aratan D *Andromaco, Chile.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Arava *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Leflunomide (p.75·3).
Psoriatic arthritis; rheumatoid arthritis.

Arbid *Kolassa, Austria; Vifor, Switz.*
⊗ Buphenine hydrochloride (p.2270·2); diphenylpyraline hydrochloride (p.578·2).
Rhinitis; sinusitis.

Arbid N *Gepepharm, Ger.†.*
Diphenylpyraline hydrochloride (p.578·2).
Cold symptoms.

Arbidol *Masterlek, Rus.*
6-Bromo-5-hydroxy-1-methyl-4-dimethylaminomethyl-2-phenylthiomethylindole-3 carboxylic acid hydrochloride ethyl ester monohydrate.
Viral infections.

Arbid-top *Vifor, Switz.*
Phenylephrine hydrochloride (p.1568·1); dequalinium chloride (p.1641·3); muramidase hydrochloride (p.2348·1).
Nasal congestion.

Arbil *Ranbaxy, UK.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Arbistin *Altana, Mex.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Arbixil *Meyer, Venez.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol (p.1120·1) or clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Arbum *Jaldes, Fr.*
Lappa (p.2330·3); zinc; selenium; vitamins (p.1922·1).
Seborrhoea.

Arbuz *Bittermedizin, Ger.†.*
Papain (p.2362·3); pancreatin (p.2360·1).
Digestive disorders.

Arca-Be *Arcana, Austria.*
Thiamine disulfide (p.1976·3); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis.

Arcablock *Arcana, Austria.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Arcablock comp *Amat, Austria.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Arca-Enzym *Arcana, Austria.*
Pancreatin (p.2360·1); cellulase (p.2279·1); ox bile (p.2266·3); bromelains (p.2269·1).
Digestive disorders.

Arcalen *Herbapol Poznan, Pol.*
Arnica (p.2260·2); calendula (p.2273·1); esculoside (p.2248·2).
Soft-tissue injury.

Arcalion *Servier, Braz.; Grunenthal, Chile; Therval, Fr.; Servier, Gr.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Malaysia; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Spain; Servier, Switz.; Servier, Thai.; Servier, Turk.; Servier, Venez.*
Sulbutiamine (p.1976·1).
Asthenia; tonic; vitamin B deficiency.

Arcalyst *Regeneron, USA.*
Rilonacept (p.2379·2).
Cryopyrin-associated periodic syndromes.

Arcamox *Armoxindo, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Arcanafenac *Merck, S.Afr.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Arcapec *Meprofarm, Indon.*
Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Arcasin
Note. This name is used for preparations of different composition.
Meda, Ger.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Esteve, Spain†.
Cisapride (p.1720·3).
Gastroparesis.

Arcavit A *Merck, Austria†.*
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Arcavit A/E *Arcana, Austria.*
Vitamin A palmitate (p.1973·1); *dl*-alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Arcefal *Arlex, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Arceligasol *Gezzi, Arg.*
Hyssop (p.2323·3); bladderwrack (p.2384·2); fennel (p.2302·3); coltsfoot (p.1555·1); cynara (p.2291·2); equisetum (p.2299·3); peppermint (p.1761·2).

Arcental *FS Profas, Spain; Pliva, Spain.*
Ketoprofen (p.73·1).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Arche-cerin *Archea, Ger.†.*
Homoeopathic preparation.

Arche-gripal *Archea, Ger.†.*
Homoeopathic preparation.

Arche-septin *Archea, Ger.†.*
Homoeopathic preparation.

Archidex *TP, Thai.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin (p.305·1).
Infected eye or ear disorders.

Archifen
Note. This name is used for preparations of different composition.
Archifar, Thai.
Ear drops: Chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Bacterial ear infections.

Archifar, Thai.
Eye drops: Chloramphenicol (p.239·3).
Bacterial eye infections.

Arcid *Diafarm, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Arclonac *Condrugs, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Arcobee with C *Nature's Bounty, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Arcocilin *Biofarma, Venez.*
Ampicillin (p.204·1).
Bacterial infections.

Arcocillin *Armoxindo, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Arcodryl *Armoxindo, Indon.*
Diphenhydramine hydrochloride (p.577·2).
Allergic disorders.

Arcoiran *Alter, Spain.*
Sumatriptan succinate (p.625·2).
Migraine.

Arcolan *Galderma, Braz.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Arcolane *Galderma, Chile; Galderma, India; Galderma, Venez.*
Ketoconazole (p.539·1).
Pityriasis versicolor; scalp disorders; seborrhoeic dermatitis.

Arcored *Armoxindo, Indon.*
Vitamin B (p.1980·2).
Anaemias; nutritional supplement.

Arcosal *Rosco, Denm.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Arcostrong *Eadriex, Philipp.*
Vitamins; minerals; ginseng; choline; inositol; methionine (p.1922·1).
Tonic.

Arcoxia *MSD, Arg.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Indon.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Port.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Thai.; MSD, UK; MSD, Venez.*
Etoricoxib (p.53·1).
Ankylosing spondylitis; osteoarthritis; pain; rheumatoid arthritis.

Arctuvan *Klinge, Ger.*
Bearberry leaves (p.2263·3).
Urinary-tract infections.

Ardeaelytosol *Ardeapharma, Cz.*
A range of electrolyte infusions (p.1667·1).

Ardeanutrisol G *Ardeapharma, Cz.*
Anhydrous glucose (p.1945·3).
Hypoglycaemia; ketoacidosis; parenteral nutrition.

Ardeanutrisol SO *Ardeapharma, Cz.†.*
Sorbitol (p.1965·1).
Parenteral nutrition.

Ardeaosmosol MA *Ardeapharma, Cz.*
⊗ Mannitol (p.1330·2).
Acute renal failure; forced diuresis; intra-ocular hypertension; intracranial hypertension.

Ardey-aktiv *Ardeypharm, Ger.*
Ginseng (p.2312·1).
Tonic.

Ardeyceryl P *Ardeypharm, Ger.†.*
Pyritinol hydrochloride (p.369·1).
Mental function disorders.

Ardeycholan *Ardeypharm, Ger.*
Cynara (p.2291·2).
Biliary-tract disorders; dyspepsia.

Ardeycordal mono *Ardeypharm, Ger.*
Crataegus (p.2289·1).
Heart failure.

Ardeycordal N *Ardeypharm, Ger.†.*
Crataegus (p.2289·1); potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Arrhythmias.

Ardeydorm *Ardeypharm, Ger.*
Tryptophan (p.427·1).
Sleep disorders.

Ardeydystin *Ardeypharm, Ger.†.*
Kava (p.2328·3).
Nervous disorders.

Ardeyhepan *Emonta, Austria; Ardeypharm, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Ardeynephron *Ardeypharm, Ger.*
Java tea (p.2328·2).
Urinary-tract disorders.

Ardeysedon *Ardeypharm, Ger.*
Valerian root (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Ardeytropin *Ardeypharm, Ger.*
Tryptophan (p.427·1).
Depression; sleep disorders.

Ardin *Korea Pharma, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Ardine *Disprovent, Arg.†; Columbia, Mex.†; Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ardine Bronquial *Antibioticos, Spain†.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Ardineclav *Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ardinex *Abbott, Austria; AstraZeneca, Cz.†; Abbott, Fin.; Abbott, Pol.; Mundipharma, Swed.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Fever; pain.

Ardium *Servier, Indon.*
Flavonoids (hesperidin (p.2304·3), diosmin (p.2304·2)).
Haemorrhoids; phlebitis; venous insufficiency.

Ardoral *Cinfa, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Arduan *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Pipecuronium bromide (p.1908·2).
Competitive neuromuscular blocker.

Arecamin *Northia, Arg.*
Cefalotin (p.220·2).
Bacterial infections.

Arechin *Polfa Pabianice, Pol.*
Chloroquine phosphate (p.599·3).
Amoebiasis; lambliasis; lupus erythematosus; malaria; rheumatoid arthritis.

Arecid *Allertec, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Aredia *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile†; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ†; Novartis, Neth.; Novartis, Norw.†; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.†; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore†; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.†.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; metastatic bone pain; osteolytic bone metastases; osteoporosis; Paget's disease of bone.

Aredronet *Sun, India†.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolytic lesions and bone pain in multiple myeloma and in bone metastases associated with breast cancer; Paget's disease of bone.

Aregen *Novartis, Gr.; Normal, Port.*
Pimecrolimus (p.1609·1).
Atopic dermatitis; atopic eczema.

Arelix
Aventis, Austria; Aventis, Ger.
⊗ Piretanide (p.1372·3) or piretanide sodium (p.1372·3).
Forced diuresis; heart failure; hypertension; oedema; renal failure.

Sanofi-Aventis, Braz.; Sanofi-Aventis, Irl.; Sanofi Synthelabo, S.Afr.; Aventis, Switz.
⊗ Piretanide (p.1372·3).
Hypertension; oedema.

Arelix ACE *Aventis, Ger.*
⊗ Piretanide (p.1372·3); ramipril (p.1385·3).
Hypertension.

Areloger *Gerard, Irl.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Arem *Pharmacare, S.Afr.*
Nitrazepam (p.1011·2).
Insomnia.

Aremin *Difass, Ital.*
Suleparoid (p.1406·3).
Soft-tissue injury; thromboembolic disorders.

Aremis *Esteve, Spain.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Arendal *Ivax, Arg.; Pharma Investi, Chile.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Areplex *Adamed, Pol.*
Clopidogrel bisulfate (p.1250·2).
Thrombosis prophylaxis.

Ares *Uniao Quimica, Braz.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Arestal *Janssen-Cilag, Fr.; Norgine, Neth.*
Loperamide oxide (p.1741·2).
Diarrhoea.

Arestin *Orapharma, Port.; OraPharma, USA.*
Minocycline hydrochloride (p.300·3).
Periodontitis.

Aretensin *Takeda, Ger.*
⊗ Ramipril (p.1385·3); piretanide (p.1372·3).
Hypertension.

Areuma *Ecobi, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Areuzolin *Areu, Spain.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Arfarel *Pharmanik (Φαρμανικ), Gr.*
Clindamycin phosphate (p.251·2).
Acne.

Arfen
Note. This name is used for preparations of different composition.
Medochemie, Hong Kong; Medochemie, Malaysia.
Paracetamol (p.108·1).
Fever; pain.

Lisapharma, Ital.
Ibuprofen lysine (p.64·2).
Gynaecological inflammatory disorders; musculoskeletal and joint disorders; radiculitis.

Medinfar, Port.
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Arfen Plus *Medochemie, Hong Kong.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Arficin *Belupo, Cz.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and leprosy.

Arfloxina *Arlex, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Arflur *FDC, India†.*
Flurbiprofen (p.61·2).
Musculoskeletal and joint disorders; pain.

Arganova *Mitsubishi, Neth.*
Argatroban (p.1217·1).
Heparin-induced thrombocytopenia.

Argaryn *Arlex, Mex.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Argatroban *SmithKline Beecham, USA.*
Argatroban (p.1217·1).
Heparin-induced thrombocytopenia.

Argeal *Pierre Fabre, Arg.; Ducray, Fr.*
Kaolin (p.1738·1); saw palmetto (p.2192·3).
Seborrhoeic dermatitis.

Argeflox *Nova Argentia, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Argemol *Loeffler, Mex.*
Sulfadiazine silver (p.337·2).
Burns.

Argenpal *Braun, Port.†; Braun, Spain.*
Silver nitrate (p.2387·2).
Aphthous ulcers; skin disorders; verrucas; wounds.

Argent *Katadyn, Switz.†.*
Heavy kaolin (p.1738·1); silver (p.2387·1).
Burns; wounds.

Argentafil *Valeant, Mex.*
Sulfadiazine silver (p.337·2).
Burns; skin disorders; ulcers; wounds.

Argental *Liferpal, Mex.*
Sulfadiazine silver (p.337·2).
Infected skin disorders.

Argent-Eze *Lennon, S.Afr.*
Sulfadiazine silver (p.337·2).
Burns.

Argentocromo *Bucca, Spain†.*
Merbromin (p.1652·1); silver (p.2387·1).
Gingivitis; mouth infection.

Argentofenol *Bucca, Spain†.*
Phenol (p.1656·1); methylthioninium chloride (p.1450·3); silver nitrate (p.2387·2).
Aphthous stomatitis; oral bleeding; tonsillitis.

Argentum Complexe no 98 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 98.

Argentum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Argesic *Econo Med, USA†.*
Methyl salicylate (p.85·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Argesic-SA *Econo Med, USA.*
Salsalate (p.122·1).
Fever; inflammation; pain.

Argidam *Terapeutico, Ital.*
L-arginine; damiana; muira puama; zinc gluconate; vitamin E (p.1922·1).
Nutritional supplement.

Argiletz *Argiletz, Fr.†.*
Nutritional supplement (p.1922·1).

Argin *Volchem, Ital.*
Protein supplement (p.1922·1).
Arginine deficiency.

Arginaid Extra *Novartis Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).

Arginitric *Innopharm, Malaysia.*
Arginine (p.1928·2).
Dietary supplement.

Arginotri-B *Bouchara-Recordati, Fr.; Bouchara, Switz.*
Arginine hydrochloride (p.1928·2); thiamine hydrochloride; pyridoxine hydrochloride (p.1922·1).
Pain; tonic; vitamin B deficiency.

Argirofedrina *Vaillant, Ital.†.*
⊗ Ephedrine sulfate (p.1558·2); anhydrous sodium sulfate (p.1771·3); mild silver protein (p.2387·3).
Nasal congestion.

Argirol *Allergan, Braz.*
Mild silver protein (p.2387·3).
Eye infections.

Argisept *Centaur, India†.*
Sulfadiazine silver (p.337·2); chlorhexidine gluconate (p.1635·3).
Burns; pressure sores; ulcers.

Argisone *Teofarma, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); mild silver protein (p.2387·3).
Bacterial eye infections.

Argital *ISA, Arg.†.*
Multivitamin and mineral preparation (p.1922·1).

Argivit *Aesculapius, Ital.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).
Nutritional supplement.

Argocian *Biol, Arg.*
⊗ Hexoprenaline sulfate (p.1123·2).
Premature labour.

Argofan *Zentiva, Cz.*
Venlafaxine hydrochloride (p.427·3).
Anxiety disorders; depression.

Argol Essenza Balsamica *Alba Thyment, Pol.*
Cinnamon oil (p.2283·2); melissa oil (p.2339·3); mint oil (p.2345·2); clove oil (p.2285·1); thyme oil (p.2401·2); lemon oil (p.2332·3); nutmeg oil (p.2355·3); coriander oil (p.2288·1); menthol (p.2340·1).
Digestive disorders; insect bites; motion sickness; musculoskeletal and joint pain; pruritus; respiratory-tract disorders.

Argol Grip *Alba Thyment, Pol.*
Melissa oil (p.2339·3); cinnamon oil (p.2283·2); clove oil (p.2285·1); nutmeg oil (p.2355·3); thyme oil (p.2401·2); lemon oil (p.2332·3); coriander oil (p.2288·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); niaouli oil (p.2351·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint disorders; respiratory-tract disorders.

Argol Rheuma *Alba Thyment, Pol.*
Melissa oil (p.2339·3); cinnamon oil (p.2283·2); clove oil (p.2285·1); nutmeg oil (p.2355·3); thyme oil (p.2401·2); lemon oil (p.2332·3); coriander oil (p.2288·1); peppermint oil (p.1761·2); rosemary oil (p.2381·3); cajuput oil (p.2271·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Argosulfan *Jelfa, Cz.†; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
Sulfathiazole silver (p.343·3).
Burns; infected skin disorders; infected ulcers; radiation-damaged skin; wounds.

Argotone *Bracco, Ital.*
⊗ Ephedrine hydrochloride (p.1558·2); mild silver protein (p.2387·3).
Nasal congestion.

Argun *Merckle, Ger.†.*
Lonazolac calcium (p.77·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Argyrophedrine *Merck, Belg.*
⊗ Ephedrine levulinate (p.1559·1); mild silver protein (p.2387·3).
Respiratory-tract congestion.

Arhemapectine Antihemorragique *Aerocid, Fr.†.*
Pectin (p.2145·2).
Haemorrhage.

Arheumacare *Health Perception, UK.*
Tablets, glucosamine sulfate (p.2313·2); turmeric (p.1473·2); ginger (p.1732·3); capsules, cod-liver oil (p.1935·2); borage oil (p.2267·3).
Joint disorders.

Aria *Lichtwer, UK.*
Soya isoflavones (p.2391·2); calcium; folic acid; B vitamins; selenium (p.1922·1).
Nutritional supplement.

Arial *Dompe, Ital.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Arianna *Schering, Ital.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Aricept *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Eisai, Fr.; Eisai, Ger.; Pfizer, Ger.; Pfizer, Gr.; Eisai, Hong Kong; Pfizer, Hung.; Eisai, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Eisai, Jpn; Eisai, Malaysia; Pfizer, NZ; Pfizer, Norw.; Eisai, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Eisai, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Eisai, Thai.; Pfizer, Turk.; Pfizer, UK; Eisai, USA; Pfizer, USA.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease; vascular dementia.

Aricilina *Ariston, Braz.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Ariclaim *Lilly, Cz.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Neth.; Lilly, Port.*
Duloxetine hydrochloride (p.389·3).
Diabetic peripheral neuropathy; stress urinary incontinence in women.

Aricodiltosse *Menarini, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Aridex *Gentex, USA.*
Phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2); pentoxyverine citrate (p.1567·3).
Upper respiratory-tract disorders.

Aridil *CP Pharmaceuticals, UK.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Ascites; oedema.

Arifenicol *Ariston, Braz.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Ariflam *Ultra, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Ariflam Forte *Ultra, Mex.*
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Musculoskeletal pain; neuralgia; neuropathy.

Arifon *Socofar, Port.; Servier, Rus.*
⊗ Indapamide (p.1314·1).
Hypertension.

Arilin *Wolff, Ger.; Medika, Switz.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections; trichomoniasis.

Arilvax *Evans, Fin.†; Evans, Irl.†; Evans Medical, Israel; Chiron Vaccines, Neth.; Medpro, S.Afr.; Celltech, Singapore†; SBL, Swed.†; Evans Vaccines, Switz.†; Chiron Vaccines, UK.*
A yellow fever vaccine (17D strain) (p.2243·2).
Active immunisation.

Arima *Alphapharm, Austral.*
Moclobemide (p.411·1).
Depression.

Arimidex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Anastrozole (p.681·2).
Breast cancer; prostatic cancer.

Arinate *Dafra, Belg.*
Artesunate (p.598·2).
Malaria.

Arindap *Medana, Rus.*
⊗ Indapamide (p.1314·1).
Hypertension.

Arintapin *Sandoz, Denm.*
Mirtazapine (p.409·2).
Depression.

Arionecs *Liconsa, Cz.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Aripax *Erfar, Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Ariproxina *Ariston, Braz.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Aristaloe *Neo Dermos, Arg.*
Aloe vera (p.1588·2); elastin (p.2286·1).

Aristamed *Nordmark, Thai.†.*
Sulfisomidine (p.344·1).
Bacterial skin infections.

Aristen *Aristopharma, Hong Kong.*
Clotrimazole (p.530·1).
Fungal skin infections.

Aristin-C *Anfarm, Gr.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Aristo
Note. This name is used for preparations of different composition.
Steiner, Ger.
St John's wort (p.422·3).
Depression.

Aristopharma, Hong Kong.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Aristobet-N *Aristopharma, Hong Kong.*
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
Infected or inflammatory eye, ear, or nose disorders.

Aristochol *Steiner, Ger.†.*
Greater celandine (p.2317·1); cape aloe (p.1705·2).
Constipation.

Aristochol CC *Steiner, Ger.†.*
Greater celandine (p.2317·1); turmeric (p.1473·2).
Gastrointestinal spasm.

Aristochol N *Steiner, Ger.†.*
Greater celandine (p.2317·1); achillea (p.2245·2); taraxacum (p.2395·1); gnaphalii flowers; absinthium (p.2244·1).
Biliary disorders.

Aristocillin *Aristo, India.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Aristocor *Kwizda, Austria.*
Flecainide acetate (p.1288·1).
Arrhythmias.

Aristocort
Sigma, Austral.; Valeo, Canad.; Lederle, Hong Kong†; Zuellig, NZ; Wyeth-Ayerst, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Astellas, USA†.
⊗ Triamcinolone (p.1544·2) or trimacinolone acetonide (p.1544·3).
Corticosteroid.

Aristoforat *Steiner, Ger.*
St John's wort (p.422·3).
Depression.

Aristogyl *Aristo, India.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis.

Aristogyl Plus *Aristo, India.*
Metronidazole (p.837·1); diloxanide furoate (p.832·2); simeticone (p.1770·2).
Amoebiasis.

Aristogyl-F
Note. This name is used for preparations of different composition.
Aristo, India.
Oral suspension: Metronidazole benzoate (p.837·1); furazolidone (p.834·3).
Bacterial and protozoal gastrointestinal infections.

Aristo, India.
Tablets: Metronidazole (p.837·1); furazolidone (p.834·3); simeticone (p.1770·2).
Bacterial and protozoal gastrointestinal infections.

Aristomox *Aristo, India.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Aristomycin *Farmanic, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Aristophen *Aristopharma, Hong Kong.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Aristopramida *Ariston, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Aristospan *Valeo, Canad.; Fujisawa, USA.*
⊗ Triamcinolone hexacetonide (p.1544·3).
Corticosteroid; musculoskeletal and joint disorders.

Aristozyme
Note. This name is used for preparations of different composition.
Aristo, India.
Capsules: Amylase (p.2256·3); pepsin (p.2365·1); simeticone (p.1770·2).
Dyspepsia.

Aristo, India.
Oral liquid: Amylase (p.2256·3); pepsin (p.2365·1).
Dyspepsia.

Aristrol *Otsira, India†.*
Calcitriol (p.1986·2).

Aristrol Forte *Otsira, India†.*
Calcitriol (p.1986·2); calcium (p.1675·2); zinc (p.1999·1).

Aritmal *Biosel, Turk.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Arixtra *GSK, Austral.; GSK, Belg.; Sanofi Synthelabo, Braz.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; Sanofi Synthelabo, Hong Kong†; GSK, Indon.; GSK, Ital.; GSK, Malaysia; GSK, Mex.; Sanofi Synthelabo, NZ†; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, USA.*
Fondaparinux sodium (p.1291·1).
Deep-vein thrombosis; myocardial infarction; pulmonary embolism; thromboembolism prophylaxis; unstable angina.

Arjun *Arjun, UK.*
Menthol (p.2340·1) in aqueous cream.

Arkamin *Unichem, India.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Arkamin-H *Unichem, India.*
⊗ Clonidine hydrochloride (p.1247·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Arket *Lemery, Mex.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders.

Arketin *Lesvi, Spain.*
Risperidone (p.1024·2).
Behaviour disorders in children; bipolar disorder; psychoses.

Arketis *Medochemie, Cz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Arkine *Pyridam, Indon.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

Arkocaps *Arkopharma, Switz.†.*
Frangula bark (p.1732·2).
Constipation.

Arkocapsulas Carbon Vegetal *Arkochim, Spain.*
Activated charcoal (p.1435·2).
Diarrhoea.

Arkocapsulas Hiperico *Arkochim, Spain.*
St John's wort (p.422·3).
Tonic.

Arkogelules *Arkopharma, Fr.*
A range of herbal preparations.

Arkophytum *Arkomedika, Fr.†.*
Devil's claw root (p.39·1); black currant (p.2267·1); salix (p.121·3).
Painful joint disorders.

Arkotux *Arkochim, Spain.*
Ivy (p.2328·1).
Respiratory-tract congestion.

Arkovital C *Arkopharma, Fr.*
Ascorbic acid (p.1983·3).
Cold symptoms; tonic; vitamin C deficiency.

Arlecyn-K *Ultra, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Arlemide *Rontag, Arg.*
Aripiprazole (p.962·3).
Schizophrenia.

Arlette *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Arlevert *Hennig, Cz.; Hennig, Ger.; Henning, Hung.; Ashbourne, UK.*
Cinnarizine (p.573·1); dimenhydrinate (p.576·2).
Vertigo.

Arlevid *Arlex, Mex.*
Zalcitabine (p.912·3).
HIV infection.

Arlexen *Arlex, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Arlexen B *Arlex, Mex.*
Cefalexin (p.218·2); bromhexine (p.1552·2).
Respiratory-tract infections.

Arlexicam *Arlex, Mex.*
Piroxicam (p.117·3).
Fever; inflammation; rheumatism.

Arlidin *Erfa, Canad.; USV, India; Grossman, Mex.*
⊗ Buphenine hydrochloride (p.2270·2).
Cerebral and peripheral vascular disorders; organic mental disorders.

Arlina *Rafarm, Gr.*
Aceclofenac (p.14·3).
Inflammatory disorders.

Arlitene *Meda, Port.†.*
Moxisylyte hydrochloride (p.1344·3).

Arluy *Asofarma, Mex.*
Mebeverine (p.1744·3).
Gastrointestinal spasm.

Armament *Faran, Gr.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma.

Armanor *Servier, Pol.; Servier, Rus.*
Almitrine dimesilate (p.2149·3).
Respiratory failure with hypoxaemia.

Armaya *Centrum, Spain.*
Polypodium leucotomos.
Eczema; psoriasis.

Armil *BMS, Spain†.*
Benzalkonium chloride (p.1629·1).
Skin and mucous membrane disinfection.

Arminol *Krewel, Ger.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vestibular disorders.

Armisetin *Gunsa, Turk.*
Chloramphenicol (p.239·3).
Bacterial infections.

Armistor *Servier, Mex.*
Estradiol (p.2097·2).
Menopausal disorders.

Armix *Servier, Hung.*
Perindopril arginine (p.1368·2) or perindopril erbumine (p.1368·3).
Heart failure; hypertension; myocardial infarction.

Armix Komb *Servier, Hung.*
⊗ Indapamide (p.1314·1); perindopril erbumine (p.1368·3).
Hypertension.

Armix Prekomb *Servier, Hung.*
⊗ Indapamide (p.1314·1); perindopril erbumine (p.1368·3).
Hypertension.

Armocur *Agis, Israel†.*
Cyproterone acetate (p.2088·2).
Prostatic cancer; sexual disorders.

Armoglobulina *CSL, Braz.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; passive immunisation.

Armolev *Armoxindo, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Armonil
Note. This name is used for preparations of different composition.
Ivax, Arg.
Tilia (p.2402·2); passion flower (p.2363·2); valerian (p.2410·1).
Insomnia.

Recordati, Ital.
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Armonil Noche *Ivax, Arg.*
Melatonin (p.2338·3).
Jet-lag symptoms.

Armonyl *Maver, Chile.*
Valerian (p.2410·1); passion flower (p.2363·2); crataegus (p.2289·1).
Insomnia.

Armotraz *Cipla, India.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Armovit *Armoxindo, Indon.*
Royal jelly; ginseng (p.2312·1); vitamins; minerals; rutoside (p.1922·1).
Nutritional supplement; tonic.

Armoxin *Arlex, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Arnecrem *Casasco, Arg.†.*
Permethrin (p.2048·2); benzyl benzoate (p.2036·1); benzocaine (p.1854·1).
Pediculosis.

Arnela *Andromaco, Chile.*
Clotrimazole (p.530·1).
Fungal vulvovaginal infections.

Arnetin *Fisiopharma, Cz.†; Medochemie, Malaysia.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Arnica + *Homeocan, Canad.*
Homoeopathic preparation.

Arnica Comp
Note. This name is used for preparations of different composition.
DHU, Ger.
Homoeopathic preparation.

DHU, Malaysia†.
Arnica (p.2260·2); calendula (p.2273·1).
Minor wounds; soft-tissue disorders.

Arnica comp/Apis *Weleda, Ger.*
Homoeopathic preparation.

Arnica Complexe no 1 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 1.

Arnica Compuesta *Ximena Polanco, Chile.*
Homoeopathic preparation.

Arnica Hamamelis Compuesta *Knop, Chile.*
Homoeopathic preparation.

Arnica Hevert Complex *Hevert, Ger.*
Homoeopathic preparation.

Arnica Komplex *Richter, Austria.*
Homoeopathic preparation.

Arnica Massage Balm *Weleda, UK.*
Arnica flower oil; birch leaf oil (p.86·2); lavender oil (p.2331·2); rosemary oil (p.2381·3).
Rheumatic and muscular pain.

Arnica Massage Oil *Weleda, S.Afr.*
Arnica flower oil (p.2260·2); calendula oil (p.2273·1); birch leaf oil (p.2266·3); rosemary oil (p.2381·3); lavender oil (p.2331·2); lavandine oil.
Muscle and joint pain; skin disorders.

Arnica Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Arnica Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Arnica/Betula comp *Weleda, Ger.*
Homoeopathic preparation.

Arnicadol *Phytomedica, Fr.*
Arnica (p.2260·2); menthol (p.2340·1).
Soft-tissue injury.

Arnicaid *Hylands, Canad.*
Homoeopathic preparation.

Arnicalm *Boiron, Canad.†.*
Homoeopathic preparation.

Arnican *Melisana, Belg.; Cooperation Pharmaceutique, Fr.*
Arnica (p.2260·2).
Soft-tissue disorders.

Arnicare *Nelson, UK.*
Arnica (p.2260·2).
Bruising.

Arnica/Symphytum comp *Weleda, Ger.*
Homoeopathic preparation.

Arnicet *Metochem, Austria.*
Arnica (p.2260·2); hamamelis (p.2318·2).
Muscle pain; skin irritation; soft-tissue disorders.

Arnicon *Pan Quimica, Spain†.*
Arnica (p.2260·2); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain; soft-tissue disorders.

Arnid *Pharos, Indon.*
Nimesulide (p.95·3).
Osteoarthritis; pain; rheumatoid arthritis.

Arnidol *Harras-Curarina, Cz.*
Glycol salicylate (p.62·3); arnica (p.2260·2).
Musculoskeletal, joint, and soft-tissue disorders.

Arniflor *VSM, Neth.*
Homoeopathic preparation.

Arnigel
Note. This name is used for preparations of different composition.
Boiron, Fr.
Homoeopathic preparation.

Boiron, Port.
Arnica (p.2260·2).
Muscle pain; soft-tissue injuries.

Arnikaderm *Knop, Chile.*
Arnica (p.2260·2).
Inflammation; oedema.

Arnikamill *Biomo, Ger.†.*
Chamomile (p.2279·3); arnica flowers (p.2260·2).
Haemorrhoids; skin disorders; soft-tissue inflammation; wounds.

Arnikatinktur *Hetterich, Ger.*
Arnica (p.2260·2).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Arnilite *Eulite, Neth.*
Homoeopathic preparation.

Arnisol *Profarm, Pol.*
Aesculus (p.2248·2); arnica (p.2260·2); oak (p.2355·3).
Soft-tissue injury.

Arnol *Cetus, Arg.*
Pancreatin (p.2360·1); dehydrocholic acid (p.2292·2); cellulase (p.2279·1); diazepam (p.986·3).

Arobon *Sanova, Austria; Nestle, Ital.*
Ceratonia (p.2143·2).
Diarrhoea.

Arofexx *Neopharmed, Ital.†.*
Rofecoxib (p.121·1).
Osteoarthritis; rheumatoid arthritis.

Arola Rosebalm *Pharmaceutical Enterprises, S.Afr.*
Bismuth subnitrate (p.1711·2); dimeticone (p.2032·1); allantoin (p.1588·1); zinc oxide (p.1621·2).
Skin disorders.

Arolac *Lisapharm, Fr.*
Lisuride maleate (p.811·1).
Erectile dysfunction; gynaecomastia in males; hyperprolactinaemia; lactation inhibition.

Aroltex *LKM, Arg.*
Pergolide (p.813·1).
Parkinsonism.

Aromadetox *Omega, Fr.*
Honey; black radish; rosemary; cynara; lemon oil; rosemary oil; basil oil; dill oil; peppermint oil; anise oil; wild carrot oil; orange oil; bay oil; nutmeg oil; almond oil (p.1922·1).
Aid to detoxification.

Aromadigest *Omega, Fr.*
Vervain; taragon; taraxacum; lemon oil; basil oil; dill oil; peppermint oil; rosemary oil; anise oil; cardamom oil; ginger oil; bay oil; nutmeg oil; juniper oil (p.1922·1).
Digestive disorders.

Aromag *ICM, Singapore.*
Light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Dyspepsia; gastric hyperacidity; heartburn.

Aromagel *Hasco-Lek, Pol.*
Camphor (p.2273·2); Peru balsam (p.2365·3); rosemary oil (p.2381·3); eucalyptus oil (p.2301·2).
Respiratory-tract disorders; rheumatism.

Aromasil *Pfizer, Spain.*
⊗ Exemestane (p.719·3).
Breast cancer.

Aromasin *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pharmacia, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗ Exemestane (p.719·3).
Breast cancer; prostatic cancer.

Aromasine *Pfizer, Fr.*
⊗ Exemestane (p.719·3).
Breast cancer.

Aromasol *Plantes et Medecines, Fr.*
Clove oil (p.2285·1); peppermint oil (p.1761·2); pine oil (p.2368·2); lavender oil (p.2331·2); cinnamon oil (p.2283·2); rosemary oil (p.2381·3); wild thyme oil (p.2415·3).
Respiratory-tract congestion.

Aromatol *Hasco-Lek, Pol.*
Melissa (p.2339·3); clove oil (p.2285·1); cinnamon oil (p.2283·2); lemon oil (p.2332·3); peppermint oil (p.1761·2); lavender oil (p.2331·2); menthol (p.2340·1).
Circulatory disorders; cold symptoms; gastrointestinal disorders; headache; insomnia; neuralgia; rheumatism.

Aromavital *Omega, Fr.*
Fruit juice; honey; royal jelly; acerola; ginseng; cinnamon oil; turmeric oil; ginger oil; lemon grass oil; clove oil; nutmeg oil; peppermint oil; cumin oil (p.1922·1).
Tonic.

Aromazen *Omega, Fr.*
Melissa; honey; tilia; orange; vervain; basil oil; dill oil; orange oil; chamomile oil; santalum austrocaledonicum oil; lemon verbena oil (p.1922·1).
Sleep disorders.

Aromek *Celon, Pol.*
⊗ Letrozole (p.740·2).
Breast cancer.

Aromenal *Panalab, Arg.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Aronal Forte *Teva, Israel.*
Vitamin A (p.1971·2); guaiazulene (p.2317·3); aluminium lactate (p.2255·1); aldioxa (p.1587·2).
Sensitive gums; toothpaste.

Aronomag *Herbapol Wroclaw, Pol.*
Aronia melanocarpa; dibasic magnesium citrate.
Magnesium deficiency.

Aropax *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Braz.; Novartis, Mex.; GSK, NZ; GSK, S.Afr.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Aroselin *Leovan, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Arovit
Bayer Consumer, Arg.
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Roche, Braz.; Bayer, Ital.
Vitamin A acetate (p.1973·1) or vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Bio-Sante, Canad.
Vitamin A (p.1971·2).

Bayer Sante, Fr.†; Bayer, S.Afr.; Roche, Swed.; Roche, Switz.†.
Vitamin A palmitate (p.1973·1).
Keratinisation disorders; vitamin A deficiency.

Arowash *Cadila, India.*
Black catechu (p.2267·1); liquorice (p.1740·3); clove oil (p.2285·1).
Halitosis; mouth ulcers; toothache.

Aroxat *GSK, Chile.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic attacks; social phobia.

Aroxin *DHA, Hong Kong; DHA, Singapore.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Arpha Hustensirup *Urgo, Ger.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Arphos *Fournier, Fr.*
Calcium glycerophosphate; magnesium gluconate (p.1922·1).
Tonic.

Arpicolin *Rosemont, UK.*
Procyclidine hydrochloride (p.814·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Arpilon *Enzypharm, Austria†.*
Pipecuronium bromide (p.1908·2).
Competitive neuromuscular blocker.

Arpisen *Arlex, Mex.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Arranon *GSK, USA.*
Nelarabine (p.755·3).
Lymphoblastic leukaemia; lymphoblastic lymphoma.

Arrestin *Svizera, India.*
Aceclofenac (p.14·3).
Inflammation; pain.

Arret *Janssen-Cilag, Irl.; Johnson & Johnson MSD Consumer, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Arretin *Valeant, Mex.; ICN, Pol.*
Tretinoin (p.1618·1).
Acne; hyperkeratosis; photoageing of the skin.

Arrhythmie-Gastreu N *Reckeweg, Ger.*
Homoeopathic preparation.

Arrumalon *Sidus, Arg.†.*
Glycosaminoglycans; peptides; cartilage (p.2277·3); bone marrow.
Osteoarthritis.

Arscolloid *SIT, Ital.*
Dichlorobenzyl alcohol (p.1642·1); silver protein (p.2387·3).
Oral disinfection.

Arsen *Arlex, Mex.*
Senna (p.1769·2).
Constipation.

Arsenal *IQFA, Mex.*
Naproxen (p.92·3).
Inflammation.

Arsenal Compuesto *IQFA, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Arsicort *Arsmedendi, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Arsinal *Meprofarm, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E.
Fatigue; migraine; neuralgia; neuritis.

Arsipor *Arsmedendi, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Arsitam *Meprofarm, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Arsitec *Arsmedendi, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Arsorb *Arrow, Austral.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Arstatin *Arsmedendi, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Art *Negma, Fr.; Negma, Israel.*
Diacerein (p.41·3).
Osteoarthritis.

Artagen *Ranbaxy, India.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Artal *Pharmia, Fin.*
Pentoxifylline (p.1367·2).
Peripheral and cerebral vascular disorders; vascular eye disorders.

Artamin *Sandoz, Austria; Sandoz, Malaysia.*
Penicillamine (p.1456·2).
Benign hyperglobulinaemic purpura; chronic active hepatitis; cystinosis; cystinuria; heavy metal poisoning; primary biliary cirrhosis; rheumatoid arthritis; scleroderma; Wilson's disease.

Artandyl *Synco, Hong Kong.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Artane *Wyeth, Arg.; Sigma, Austral.; Torrex, Austria; PSI, Belg.; Wyeth, Braz.; Wyeth, Chile†; Sanofi-Aventis, Fr.; Teofarma, Ger.; IFET, Gr.; Wyeth, Hong Kong; Lederle, Indon.; Wyeth, Irl.†; Lederle, Israel†; Teofarma, Ital.; Wyeth, Mex.†; Teofarma, Neth.; Teofarma, Port.; Wyeth, S.Afr.; Teofarma, Spain; Wyeth-Ayerst, Thai.†.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Artaxan *Malesci, Ital.*
Nabumetone (p.91·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artaxol *Loeffler, Mex.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Artecef *Artecef, Neth.*
Artemotil (p.598·1).
Malaria.

Artecholin *Phytofarm Kleka, Pol.*
Artemisia abrotanum; milk thistle (p.1452·1); peppermint leaf (p.1761·2); cnicus benedictus (p.2285·2); greater celandine (p.2317·1); achillea (p.2245·2); taraxacum (p.2395·1).
Biliary-tract disorders.

Artecholwex *Herbapol Lodz, Pol.*
Artemisia abrotanum; milk thistle (p.1452·1); cnicus benedictus (p.2285·2); achillea (p.2245·2); peppermint leaf (p.1761·2); taraxacum (p.2395·1); greater celandine (p.2317·1).
Biliary-tract disorders.

Artedil *Chiesi, Spain.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Artedin *GD, Ital.*
Garlic; ginkgo biloba; curcubita; policosanol; vitamin C; vitamin E (p.1922·1).
Nutritional supplement.

Artelac *Bausch & Lomb, Arg.; Riel, Austria; Tramedico, Belg.; Bausch & Lomb, Braz.†; Santen, Denm.; Santen, Fin.; Chauvin, Fr.; Mann, Ger.; Mann, Hung.†; Mann, Irl.; Bausch & Lomb, Mex.; Santen, Norw.; Bausch & Lomb, Philipp.; Mann, Pol.; Lepori, Port.; Santen, Swed.; Pharma-Global, UK.*
Hypromellose (p.2144·2).
Dry eyes.

Artelife *Diba, Mex.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; circulatory disorders of the eyes and ears.

Artemal *Ipca, India†.*
Artesunate (p.598·2); sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Artemidis *Sigma, Braz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in women; combined oral contraceptive.

Artemisol *Herbapol Krakow, Pol.*
Absinthium (p.2244·1); tansy (p.2395·1).
Pediculosis.

Artemodi *Holley-Cotec, China.*
Artesunate (p.598·2); amodiaquine (p.597·2).
Malaria.

Artenolol *Ronava, Venez.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Arteolol *Lacer, Spain.*
⊗ Carteolol hydrochloride (p.1241·1).
Angina pectoris; arrhythmias; hypertension.

Arteopilo *Bausch & Lomb, Switz.*
⊗ Carteolol hydrochloride (p.1241·1); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Arteoptic *Novartis, Austria; Chauvin, Belg.; Novartis, Cz.; Novartis, Denm.†; Novartis, Fin.†; Novartis, Ger.; Otsuka, Hong Kong; Novartis Ophthalmics, Hung.†; Chauvin, Neth.; Novartis, Pol.; OM, Port.; Novartis Ophthalmics, Swed.†; Bausch & Lomb, Switz.; Otsuka, Thai.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Arterase *Clement, Fr.*
Equisetum (p.2299·3); garlic (p.2309·2); cypress (p.2291·2); aesculus (p.2248·2).
Capillary fragility; venous insufficiency.

Arterenol *Aventis, Ger.*
⊗ Noradrenaline hydrochloride (p.1360·2).
Shock.

Artergin *Orion, Fin.†.*
Codergocrine mesilate (p.363·3).
Mental function disorders in the elderly.

Arteria-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Arterioflexin *Lannacher, Austria.*
Clofibrate (p.1246·2).
Hyperlipidaemias.

Arteriol *Godor, Arg.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders; Raynaud's syndrome.

Arteriosan *Bernabo, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Arteriosan Plus *Bernabo, Arg.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Arteriotrat *Purissimus, Arg.*
Folic acid; vitamin B ; vitamin B (p.1922·1).

Arteriovinca *Lepori, Port.; Farma Lepori, Spain†.*
Vincamine (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; mental function impairment; vestibular disorders.

Arterodiet *Yves Ponroy, Fr.†.*
Fish oil (p.1922·1).
Nutritional supplement.

Arteron *Ariston, Braz.*
Pentoxifylline (p.1367·2).

Arterosan *Royal, Chile†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Arterosan Plus *Doetsch, Grether, Switz.*
Crataegus (p.2289·1); melissa (p.2339·3); garlic oil (p.2309·2); ginkgo biloba (p.2311·1).
Cerebrovascular disorders.

Arterosol *Minerva (Μινέρβα), Gr.†.*
Piracetam (p.368·2).
Central nervous system disorders.

Artesiane *Dafra, Belg.*
Artemether (p.598·1).
Malaria.

Artesol *Drugtech, Chile.*
Cilostazol (p.1245·2).
Intermittent claudication.

Arteven *Boehringer Ingelheim, Ital.*
Suleparoid (p.1406·3).
Thrombosis prophylaxis.

Artevil *Drugtech, Chile.*
Clopidogrel (p.1251·1).
Atherosclerosis.

Artex *Therval, Fr.; Servier, Neth.; Servier, Port.*
⊗ Tertatolol hydrochloride (p.1411·1).
Hypertension.

Artexal *Servier, Denm.; Servier, Irl.*
⊗ Tertatolol hydrochloride (p.1411·1).
Hypertension.

Artezine *Shchelkovskii, Rus.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Artflex *Ivax, Arg.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis of the knee; shoulder pain.

Arth-A Oligocan *Homeocan, Canad.†.*
Homoeopathic preparation.

Artha-G *Williams, USA.*
Salsalate (p.122·1).
Fever; inflammation; pain.

Arth-B Oligocan *Homeocan, Canad.†.*
Homoeopathic preparation.

Arthotec *Pharmacia, Ger.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Arthramina *Pharma Nord, Port.*
Glucosamine sulfate potassium chloride (p.2313·2).
Osteoarthritis.

Arthrease *DePuy, Ger.†; Biotechnology, Israel; DePuy, UK.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis of the knee.

Arthremin *Leciva, Cz.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Arthrexin *Alphapharm, Austral.; Alphapharm, Malaysia†; Merck, Malaysia†; Pacific, NZ; Pharmacare, S.Afr.*
Indometacin (p.66·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Arthribosan B 31 *Bock, Ger.†.*
Homoeopathic preparation.

ArthriCare *MD, Singapore.*
Glucosamine hydrochloride (p.2313·2) or glucosamine sulfate (p.2313·2).
Dietary supplement; joint disorders.

Arthricare Double Ice *Commerce, USA; Del, USA.*
Menthol (p.2340·1); camphor (p.2273·2).
Muscle and joint pain.

Arthricare Odor Free *Commerce, USA; Del, USA.*
Menthol (p.2340·1); methyl nicotinate (p.85·3); capsaicin (p.32·3).
Muscle and joint pain.

Arthricare Triple Medicated *Del, Canad.†; Commerce, USA; Del, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); methyl nicotinate (p.85·3).
Muscle and joint pain.

Arthricare for Women Extra Moisturizing *Del, Canad.†.*
Capsaicin (p.32·3).
Formerly known as Arthricare Hand & Body.

Arthricare for Women Multi-Action *Del, Canad.†.*
Menthol (p.2340·1); methyl nicotinate (p.85·3); capsaicin (p.32·3).
Formerly known as Arthricare Odor Free.

Arthrifen *Armoxindo, Indon.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Arthrifid S *Heel, Ger.*
Homoeopathic preparation.

Arthriflex *Sante Naturelle, Canad.*
Menthol (p.2340·1); cineole (p.2282·3).

Arthriforte *Blackmores, Austral.*
Fish oil (p.1362·2); eicosapentaenoic acid (p.1362·1); vitamin A (p.1971·2); turmeric (p.1473·2); devil's claw root (p.39·1); celery seed oil (p.2278·3); vitamin E (p.1992·2).
Arthritis; inflammation; rheumatism.

Arthril *Sons, Mex.*
Ketoprofen (p.73·1).
Inflammation.

Arthrimel *Clonmel, Irl.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Arthriselect *Dreluso, Ger.*
Homoeopathic preparation.

Arthritic Pain Herbal Formula 1 *Vitelle, Austral.*
Celery (p.2278·3); juniper (p.2328·2); devil's claw root (p.39·1); salix alba (p.121·3).
Arthritis; rheumatism.

Arthritic Pain L10 *Homeocan, Canad.†.*
Homoeopathic preparation.

Arthritic Pain Relief *Homeocan, Canad.*
Homoeopathic preparation.

Arthritil *Marching, Hong Kong.*
Glucosamine hydrochloride (p.2313·2).
Joint disorders.

Arthritil Plus *Marching, Hong Kong.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Arthritis Free *Young Again Products, USA.*
Vitamins; minerals; glucosamine; boswellic acid (p.1922·1).

Arthritis Hot Creme *Thompson, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Arthritis Pain Formula
Note. This name is used for preparations of different composition.
Hylands, Canad.
Homoeopathic preparation.

Whitehall, USA.
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Arthritis; fever; pain.

Arthritis Pain Formula Aspirin Free *Whitehall, USA.*
Paracetamol (p.108·1).
Fever; pain.

Arthritis Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Arthrixyl N *Syxyl, Ger.†.*
Homoeopathic preparation.

arthro akut *Byk Gulden, Ger.†; Byk Tosse, Ger.†.*
Lonazolac calcium (p.77·3).
Inflammation; musculoskeletal and joint disorders; pain.

Arthrocine *Substipharm, Fr.*
Sulindac (p.126·3).
Musculoskeletal, joint, and peri-articular disorders.

Arthrodeformat P *Ziethen, Ger.†.*
⊗ Pituitary extract (p.1543·3); rosemary oil (p.2381·3).
Rheumatic disorders.

Arthrodestal N *Krugmann, Ger.†.*
Glycol salicylate (p.62·3); camphor (p.2273·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Arthrodont *Pierre Fabre, Fr.; Pierre Fabre, S.Afr.*
Enoxolone (p.50·1).
Gum disorders.

Arthrodynat N *Ziethen, Ger.†.*
Urtica (p.2409·3).
Rheumatic disorders.

Arthrodynat P *Ziethen, Ger.†.*
Rosemary oil (p.2381·3); camphor (p.2273·2); St John's wort oil (p.423·2).
Rheumatic disorders.

Arthrofar *Vocate, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Arthrofen *Ashbourne, UK.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Arthro-Flex *Biotech, Singapore.*
Glucosamine sulfate (p.2313·2); manganese amino acid chelate (p.1956·3).
Musculoskeletal and joint disorders.

Arthrofluor *Teva, Hung.*
Sodium fluoride (p.1962·2).
Musculoskeletal and joint disorders.

Arthrokatt *Kattwiga, Ger.*
Homoeopathic preparation.

Arthrokehlan A *Sanum-Kehlbeck, Ger.*
Formoltoxoid from *Propionibacterium acnes* (p.702·1).
Musculoskeletal and joint disorders.

Arthrokehlan U *Sanum-Kehlbeck, Ger.*
Formol toxoid from Corynebacterium spp.
Tonic.

Arthrolib *EBN, Fr.*
Fish oil (p.1362·2); bamboo; ginger (p.1732·3); colecalciferol (p.1986·2); pyridoxine hydrochloride (p.1978·2).
Joint disorders.

Arthropan *Purdue Frederick, USA†.*
Choline salicylate (p.36·3).
Fever; inflammation; pain.

Arthrorein *Aurora, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Arthrorell *Sanorell, Ger.*
Homoeopathic preparation.

Arthrose-Echtroplex *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Arthrose-Gastreu R73 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Arthrosenex AR *Riemser, Ger.*
Arnica (p.2260·2).
Musculoskeletal and joint disorders.

Arthrosetten H *Riemser, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Arthrosin *Ashbourne, UK†.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Arthrotabs *Duopharm, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Arthrotec *Pfizer, Austral.; Sanova, Austria; Continental Pharma, Belg.; Pfizer, Canad.; Searle, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, Irl.; Pfizer, Israel; Pfizer, Neth.; Pfizer, Norw.; Pharmacia, Pol.; Pfizer, Port.; Searle, Rus.†; Pharmacia, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.†; Pfizer, UK; Searle, USA; Pfizer, Venez.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Arthrox *Polychronus, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Arthroxen *CP Pharmaceuticals, UK.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders.

Arthru-Derm *Meyer Zall, S.Afr.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Arthrum H *LCA, Fr.*
Sodium hyaluronate (p.2320·1).
Joint disorders.

Arthryl *Rottapharm, Fin.; Rottapharm, Pol.*
Glucosamine sulfate (p.2313·2).
Degenerative knee disorders; osteoarthritis.

Articaina C/E *Inibsa, Spain.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Articlox *Unipharma, Gr.*
Hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; vitamin B12 deficiency.

Articolase *SIRC, Singapore†.*
Collagen (p.2286·1).
Peri-articular disorders.

Articolase (w/glucosamine) *SIRC, Singapore.*
Collagen (p.2286·1); glucosamine sulfate (p.2313·2).
Joint disorders.

Articulaire Serocytol *Serolab, Switz.*
An immunoglobulin (equine).
Musculoskeletal and joint disorders.

Articulan *Pentafarma, Port.*
Etodolac (p.52·2).
Musculoskeletal and joint disorders.

Articurell *Sanorell, Ger.*
Homoeopathic preparation.

Artifene *Northia, Arg.*
Dextropropoxyphene (p.40·1); dipyrone (p.49·2).
Pain.

Artific *Farma Lepori, Spain.*
Hypromellose (p.2144·2).
Dry eyes.

Artificial Tears
Note. This name is used for preparations of different composition.
Alcon, Canad.
⊗ Dextran (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Ivax, Canad.; Pharmascience, Canad.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Bausch & Lomb, USA.
Hypromellose (p.2144·2).
Dry eyes.

Artificial Tears Extra *Pharmascience, Canad.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Formerly known as PMS-Artificial Tears Extra.
Dry eyes.

Artificial Tears Plus *Ivax, Canad.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Artifleur *Bloem Beheer, Neth.*
Homoeopathic preparation.

Artiflex *Gelcaps, Mex.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Artilog *Pharmacia, Ital.†.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Artin
Note. This name is used for preparations of different composition.
Sanova, Austria.
Aloes (p.1705·2); frangula bark (p.1732·2).
Constipation; stool softener.

Biogal-Teva, Hung.†.
⊗ Aloin (p.1705·3); phenolphthalein (p.1762·1); strychnine (p.2393·1); ipecacuanha (p.1562·3); belladonna (p.2263·3).
Constipation.

Artinibsa *Inibsa, Port.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artinizona *Teuto, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Artinor *Valeant, Mex.†.*
Piroxicam (p.117·3).
Inflammation; pain.

Artinostrum *Nostrum, Port.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Artirem *Codali, Belg.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Neth.; Guerbet, Switz.*
Meglumine gadoterate (p.1480·2).
Contrast medium for magnetic resonance imaging.

Artisial *Dexo, Fr.*
Electrolytes (p.1667·1); carmellose sodium (p.2142·1); sorbitol (p.1965·1).
Saliva substitute.

Artiss
Note. This name is used for preparations of different composition.
Baxter, USA.
Powder for topical solution: Total protein; fibrinogen (p.1070·1); fibrinolysis inhibitor; thrombin (p.1080·1); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Skin-graft adhesion.

Baxter, USA.
Topical solution: Total protein; fibrinogen (p.1070·1); thrombin (p.1080·1);
This forms a fibrin glue (p.1069·3).
Skin-graft adhesion.

Artistry *Amway, Canad.†.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Artocoron *Abbott, Ger.†.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral vascular disorders.

Artofen *Teva, Israel; Vifor, Switz.*
Ibuprofen (p.64·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Artok *Nycomed, Austria.*
Lornoxicam (p.77·3).
Musculoskeletal and joint disorders; pain.

Artonil *Hexal, Swed.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Artosin *Roche, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Artotec *Pfizer, Fr.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Artra *Unipharm, Rus.*
Chondroitin sulfate sodium (p.2280·3); glucosamine hydrochloride (p.2313·2).
Osteoarthritis.

Artragil *Faes, Spain†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Artrait *TRB, Arg.*
Methotrexate (p.745·2) or methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Artren
Merck, Braz.; Merck, Venez.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Merck, Chile.
Diclofenac (p.44·2), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Artrenac *Merck, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Artrenac Pro *Merck, Mex.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Artrene *Merck, Mex.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Artrex
Note. This name is used for preparations of different composition.
Spedrog, Arg.
Allopurinol (p.552·2); colchicine (p.556·1).
Gout; hyperuricaemia.

Bio-Ved, Singapore†.
Withania somnifera; boswellia serrata (p.2307·1); turmeric (p.1473·2); ginger (p.1732·3).
Musculoskeletal, joint, and soft-tissue disorders.

Artri *Medical, Spain.*
Adenosine phosphate (p.2247·2); indometacin (p.66·3).
Fever; inflammation; pain.

Artribid *MSD, Port.*
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Artricol *Medosan, Ital.*
Amtolmetin guacil (p.19·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artricom *Combiphar, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Artriden *Degorts, Mex.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Artridol
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Rimsa, Mex.
⊗ Indometacin (p.66·3); betamethasone (p.1518·2); methocarbamol (p.1897·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Merck, Port.
Hydroxymethoxy ethyl benzoate; phenylpropyl salicylate.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artridol Duo *Laboratorios Chile, Chile.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Artrifenil *Teuto, Braz.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Artril
Note. This name is used for preparations of different composition.
Farmasa, Braz.; Eczacibasi, Turk.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Advance, Singapore.
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Artril C *Advance, Singapore.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Artrilan *Offenbach, Mex.*
⊗ Prednisolone (p.1540·3); salicylamide (p.121·2); meprobamate (p.1006·2).
Musculoskeletal and joint disorders.

Artrilase *Bago, Arg.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Artrilase Complex *Bago, Arg.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Arthroses.

Artrilom *ProMed, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Artrilox *Combiphar, Indon.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Artriman *Biofarma, Mex.*
Glucosamine (p.2313·2).
Osteoarthritis.

Artrimax *Prater, Chile.*
Collagen UC-II (type 2, denatured) (p.2286·1).
Osteoarthritis; rheumatoid arthritis.

Artrimod *Labomed, Chile.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Artrinid *Uniao Quimica, Braz.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Artrinovo *Llorens, Spain.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Artriox *Medikon, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); zinc (p.1999·1).
Osteoarthritis.

Artritapsin *Maver, Chile.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; inflammation; pain.

Artritec *Pharlab, Braz.†.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Artritin *Teguhsindo, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1).
Osteoarthritis.

Artritol
Note. This name is used for preparations of different composition.
Bio-Sante, Canad.
Capsules: Paracetamol (p.108·1).

Bio-Sante, Canad.
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1).

Artriunic *Novag, Spain.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint and peri-articular disorders.

Artrizona *Silesia, Chile.*
Diacerein (p.41·3).
Degenerative joint disorders.

Artroben *Euromex, Mex.*
Benzydamine hydrochloride (p.27·3).
Inflammation; pain.

Artrocaptin
Note. This name is used for preparations of different composition.
Spedrog, Arg.
Chondroitin sulfate sodium (p.2280·3); glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Estedi, Spain.
Tolmetin sodium (p.130·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artrocel *Biotecnoquimica, Venez.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Artrodar *TRB, Arg.; TRB, Braz.; TRB, Cz.; TRB, Indon.; Chemedica, Malaysia; Chemedica, Thai.; Leti, Venez.*
Diacerein (p.41·3).
Degenerative joint disorders; osteoarthritis.

Artrodesmol Extra *Nupel, Spain.*
⊗ Dimethyl sulfoxide (p.2022·1); phenylbutazone (p.117·1); fluocinolone acetonide (p.1531·3); methyl salicylate (p.85·3).
Peri-articular and soft-tissue disorders.

Artrodol *AGIPS, Ital.*
Diflunisal (p.47·2).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Artrodue *MDM, Ital.*
Collagen (p.2286·1); mucopolysaccharides; vitamins; copper (p.1922·1).
Joint disorders.

Artrofenac *SoSe, Ital.†.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; painful smooth muscle spasm.

Artrofene *Sankyo, Port.†.*
Ketoprofen lysine (p.73·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Artroglobina *Elvetium, Arg.†.*
Diacerein (p.41·3).
Musculoskeletal and joint disorders.

Artrolive *Ache, Braz.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Artrolyt *Madaus, Austria; Neo-Farmaceutica, Port.*
Diacerein (p.41·3).
Osteoarthritis.

Artromed *Medosan, Ital.*
Amtolmetin guacil (p.19·2).
Musculoskeletal and joint disorders; pain.

Artron *Liomont, Mex.†.*
Naproxen (p.92·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artronil *Eurodrug, Malaysia; Eurodrug, Singapore; Eurodrug, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders; osteoarthritis.

Artroplex *Knop, Chile.*
Homoeopathic preparation.

Artrosamin *Lapreven, Venez.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); collagen (p.2286·1).
Arthroses.

Artrosil *Ache, Braz.*
Ketoprofen lysine (p.73·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Artrosilen *Dompe, Rus.*
Ketoprofen lysine (p.73·3).
Pain.

Artrosilene *Dompe, Ital.*
Ketoprofen lysine (p.73·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Artrotec *Pharmacia, Ital.; Pfizer, Mex.; Pfizer, Neth.; Continental, Spain.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; musculoskeletal and joint disorders; pain.

Artrox *Pfizer, Swed.*
Glucosamine hydrochloride (p.2313·2).
Osteoarthritis.

Artroxicam
Note. This name is used for preparations of different composition.
Medichrom, Gr.
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

SoSe, Ital.
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Artruic *IFET (ΙΦΕΤ), Gr.†.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Artu
Note. This name is used for preparations of different composition.
Artu, Neth.
A range of allergen extracts (p.2250·2).
Diagnosis of hypersensitivity.

Gunsa, Turk.
⊗ Promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Respiratory-tract congestion.

Arturic *Alpharma, Fin.; Alpharma, Norw.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Artuvac *Artu, Neth.*
Dermatophagoides pteronyssinus extracts (p.2250·2) (p.2251·1).
Allergen immunotherapy.

Artyflam *Rayere, Mex.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders.

Artz *AstraZeneca, Denm.; MDM, Ital.; Daiichi Sankyo, Port.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis.

Artzal *Sankyo, Austria; AstraZeneca, Fin.; AstraZeneca, Swed.*
Sodium hyaluronate (p.2320·1).
Arthrosis of the knee.

Aru C *Chauvin ankerpharm, Ger.†.*
Clotrimazole (p.530·1).
Corynebacterium skin infections; fungal skin infections.

Arubendol *Alpharma-Isis, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Aruclonin *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.†; Chauvin Ankerpharm, Hung.*
Clonidine hydrochloride (p.1247·1).
Glaucoma; ocular hypertension.

Arudel *Alter, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias; secondary prophylaxis of ischaemic heart disease.

Arufil *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.*
Povidone (p.2146·1).
Dry eyes.

Arufil C *Chauvin ankerpharm, Ger.*
Carbomer (p.2141·3).
Dry eyes.

Arutimol *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.; Chauvin, Rus.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Arutrin *Chauvin ankerpharm, Ger.†.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Aruzilina *Megat, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Arvastatil *Pharmanel, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Arvekap *Ipsen, Gr.*
⊗ Triptorelin (p.2135·2) or triptorelin embonate (p.2135·3).
Endometriosis; female infertility; prostatic cancer; uterine fibroids.

Arvenum
Note.This name is used for preparations of different composition.
Stroder, Ital.
Diosmin (p.2304·2).
Peripheral vascular disorders.

Sermedica, Port.
Bioflavonoids (p.2304·1).

Arvifax *Arriani, Gr.*
Venlafaxine (p.430·1).
Depression.

Arviron *Masterlek, Rus.*
Ribavirin (p.902·3).

Arvo *Phoenix, Arg.*
Travoprost (p.1886·1).
Glaucoma; ocular hypertension.

Arwin *Abbott, Austria.*
Ancrod (p.1215·3).
Peripheral vascular disorders.

Arxen *Arlex, Mex.*
Naproxen (p.92·3).
Inflammation; rheumatism.

Arxen Compositum *Arlex, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Inflammation; rheumatism.

Arycor
Sanofi Synthelabo, S.Afr.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Sanofi Synthelabo, Venez.†.
Amiodarone (p.1210·2).
Arrhythmias.

Arythmol *Abbott, Irl.; Abbott, Port.; Abbott, UK.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Arzedyn *Leovan, Gr.*
Cetirizine hydrochloride (p.570·3).

Arzepam *Solfran, Mex.*
Diazepam (p.986·3).
Anxiety; sedative.

Arzide *David, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Arzimol *Belmac, Spain.*
Cefprozil (p.232·2).
Bacterial infections.

Arzomeba *Pisa, Mex.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Arzomicin *Altana, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Arzomicina *APS, Port.†.*
Azithromycin (p.207·1).
Bacterial infections.

Arzomidol *Dollder, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

AS Cor *Sanfer, Mex.*
⊗ Norfenefrine hydrochloride (p.1361·1).
Hypotension.

AS 101 VA N *Staufen, Ger.†.*
Homoeopathic preparation.

ASA *German Remedies, India; Liomont, Mex.; Curtis, Pol.; Streuli, Switz.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Asa Right Powder *Eagle, Austral.*
Vitamin and mineral preparation with equisetum and ginger (p.1922·1).
Respiratory congestion.

Asa Tones *Eagle, Austral.*
Grindelia camporum (p.2317·2); ivy (p.2328·1); potassium iodide (p.2169·2); crataegus (p.2289·1); euphorbia hirta (p.2301·3); liquorice (p.1740·3); polygala tenuifolia (p.1572·3); drosera longifolia (p.2297·3).
Upper respiratory-tract symptoms.

Asabium *Otto, Indon.*
Clobazam (p.477·2).
Anxiety.

Asabon *Merck, Mex.*
Piroxicam (p.117·3).
Inflammation.

Asabrin *Ilsan, Turk.*
Aspirin (p.20·3).
Fever; pain.

Asacard *Flamel, Neth.; Flamel, Port.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Asacol *Altana, Belg.†; Procter & Gamble, Canad.; Medimport, Cz.; Schering, Denm.; Leiras, Fin.; Faran, Gr.; Tillotts, Hong Kong; Keri, Hung.; Win-Medicare, India; Tillotts, Israel; Giuliani, Ital.; Altana, Mex.; Baxter, NZ; Tillotts, NZ; Altana, Neth.; Schering, Norw.; Vitoria, Port.; Aventis, S.Afr.; Tillotts, Singapore; Schering, Swed.; Sanofi Synthelabo, Switz.; Tillotts, Thai.†; Biofarma, Turk.; Procter & Gamble, UK; Procter & Gamble, USA.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Asacolitin *Meduna, Ger.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Asacolon *Tillotts, Irl.*
Mesalazine (p.1745·1).
Crohn's disease; proctitis; ulcerative colitis.

ASAD *Stallergenes, Cz.†; Stallergenes, Fr.†; Stallergenes, Switz.†.*
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.

Asafen *Sanofi Synthelabo, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Pain.

Asafen Nueva Formula *Sanofi Synthelabo, Chile†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); caffeine (p.1116·3).
Nasal congestion; upper respiratory-tract disorders.

Asaflow *Sandipro, Belg.*
Aspirin (p.20·3).
Cardiovascular and cerebrovascular disorders.

Asalazin *Medichrom, Gr.†.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Asalen *Adcock Ingram, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Asalex *Chiesi, Ital.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Asalis *Rowe-Fleming, Venez.†.*
Lysine aspirin (p.79·1).
Fever; inflammation; pain.

Asalit *Merck, Braz.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Asam *Landson, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Asamax *Astellas, Ital.; Astellas, Neth.; Astellas, Pol.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Asamnex *Metiska, Indon.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Asaphen *Pharmascience, Canad.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Asapiuci *E-Pharma, Ital.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Asaprim *Primera, Philipp.*
Aspirin (p.20·3).
Fever; juvenile rheumatoid arthritis; pain; thrombosis prophylaxis.

Asaprol *Leti Gentek, Venez.*
Aspirin (p.20·3).
Fever; pain.

ASA-ratio *Ratiopharm, Ital.*
Aspirin (p.20·3).
Fever; pain.

Asarid *Boehringer Ingelheim, Belg.†.*
Aspirin (p.20·3).
Cardiovascular disorders; fever; pain.

Asarum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Asasantin *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim Promeco, Mex.†; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, UK.*
Dipyridamole (p.1268·1); aspirin (p.20·3).
Thromboembolism prophylaxis.

Asasantine *Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Switz.*
Dipyridamole (p.1268·1); aspirin (p.20·3).
Stroke prophylaxis; thromboembolic disorders.

Asatab *TO-Chemicals, Thai.*
Aspirin (p.20·3).
Thromboembolic disorders.

Asavixin *Madaus, Ital.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Asax *Pasteur, Chile.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Asazine *Tillotts, Switz.*
Mesalazine (p.1745·1).
Ulcerative colitis; ulcerative proctitis.

Asbunyl *IAE, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asbunyl Plus *IAE, Philipp.*
⊗ Salbutamol (p.1131·2); guaifenesin (p.1561·3).
Cough.

ASC *Geritrex, USA.*
Triclosan (p.1665·2).
Skin cleanser.

Ascabiol
Note.This name is used for preparations of different composition.
Aventis, Austral.; Aventis, Irl.†; Pharmacare, S.Afr.; Aventis, UK.
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Zambon, Fr.
Benzyl benzoate (p.2036·1); sulfiram (p.2050·3).
Scabies.

Nicholas Piramal, India.
Lindane (p.2045·3).
Pediculosis; scabies.

Ascafyl *Meyer, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Ascal *Viatris, Neth.; Meda, Port.; Farmasierra, Spain.*
Carbasalate calcium (p.33·3).
Fever; pain; thromboembolism prophylaxis.

Ascalan *Lannacher, Austria.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Ascalcin *Polfa Lodz, Pol.*
Aspirin (p.20·3); calcium lactate gluconate (p.1676·2).
Fever; pain.

Ascalcin Plus *Polfa Lodz, Pol.*
Aspirin (p.20·3); calcium lactate gluconate (p.1676·2); ascorbic acid (p.1983·3).
Fever; pain.

Ascardia *Pharos, Indon.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Ascarical *Farmoquimica, Braz.*
Pyrantel embonate (p.155·1).
Worm infections.

Ascaridil *Janssen-Cilag, Braz.*
Levamisole hydrochloride (p.147·2).
Ascariasis.

Ascarinase *Ibefar, Braz.†.*
Piperazine hydrate (p.153·1).
Worm infections.

Ascariobel *Sedabel, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Ascarizole *Globo, Braz.†.*
Tetramisole hydrochloride (p.156·1).
Worm infections.

Ascedor *Globo, Braz.†.*
Aspirin (p.20·3).

Ascencia *Bayer, Chile.*
Test system for measuring glucose in blood (p.2314·1).

Ascensia *Bayer, Arg.; Bayer, Austral.; Bayer Diagnostics, Fr.; Bayer Diagnostici, Ital.*
Test for glucose in blood (p.2314·1).

Ascensia Elite *Bayer, Canad.*
Test for glucose in blood (p.2314·1).

Ascensia Glucodisc *Bayer Diagnostics, UK.*
Test for glucose in blood (p.2314·1).

Asche Basis *Asche Chiesi, Ger.*
Emollient.
Skin disorders.

Asco-Caps *Key, USA.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Ascocid
Note.This name is used for preparations of different composition.
Volchem, Ital.
Peptide, lipid, and carbohydrate preparation with vitamin C (p.1922·1).
Nutritional supplement.

Key, USA.
Calcium ascorbate (p.1984·1).
Vitamin C supplement.

Ascodan *Polpharma, Pol.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Cough; fever; pain.

Ascodyne *Chemedica, Switz.†.*
Multivitamin preparation with amino acids (p.1922·1).
Tonic.

Ascof *Pascual, Philipp.*
Agnus castus (p.2249·1).
Cough; obstructive airways disease.

Ascofer
Note.This name is used for preparations of different composition.
Gerda, Fr.
Ferrous ascorbate (p.1938·2).
Iron-deficiency anaemias.

Espefa, Pol.
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ascomp with Codeine *Breckenridge, USA.*
Codeine phosphate (p.37·2); aspirin (p.20·3); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Asconvita *Medic+Aid, Philipp.*
Ascorbic acid (p.1983·3).
Scurvy; vitamin C deficiency.

Ascopen *Vendiz, Philipp.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Ascor *McGuff, USA.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Ascorbex *Sante Naturelle, Canad.†.*
Ascorbic acid (p.1983·3).

Ascorbin *Montavit, Austria; Orion, Fin.; Orion, Malaysia; Orion, Singapore.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Ascorbine *IFET (ΙΦΕΤ), Gr.†.*
Vitamin C (p.1983·3).

Ascorbisal *Lannacher, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; musculoskeletal and joint disorders; pain.

Ascorcee *Virgo, Philipp.*
Ascorbic acid (p.1983·3).
Methaemoglobinaemia; scurvy; wound healing.

Ascorell *Sanorell, Ger.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Ascorgem *Gemi, Pol.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Ascoril +
Note.This name is used for preparations of different composition.
Glenmark, India.
Syrup: ⊗ Bromhexine (p.1552·2); terbutaline sulfate (p.1138·3) guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Glenmark, India.
Tablets: ⊗ Bromhexine (p.1552·2); terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs.

Ascoril Expectorant *Glenmark, Rus.*
⊗ Salbutamol sulfate (p.1131·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Respiratory-tract disorders.

Ascoril-C *Glenmark, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Ascoril-D+ *Glenmark, India.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); triprolidine hydrochloride (p.592·3); menthol (p.2340·1).
Coughs.

Ascortonyl *Gerda, Fr.*
Ascorbic acid (p.1983·3); magnesium potassium aspartate.
Tonic.

Ascorutical
Note. This name is used for preparations of different composition.
Jelfa, Pol.
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); calcium hydrogen phosphate (p.1676·1); rutoside (p.2305·1).
Capillary fragility; cold and influenza symptoms; hypersensitivity reactions.

Jelfa, Rus.
Ascorbic acid (p.1983·3); rutoside (p.2305·1); calcium carbonate (p.1714·1).

Ascorutin *Zentiva, Cz.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3).
Capillary fragility; haemorrhage.

Ascorvit *Jenapharm, Ger.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Ascosal *Grossmann, Switz.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms.

Ascot *Polipharm, Thai.†.*
Aspirin (p.20·3).
Inflammation; pain; thromboembolic disorders.

Ascotodin *Bruschettini, Ital.*
Mebechinium metilsulfate; thonzylamine hydrochloride (p.592·1).
Eye disorders.

AscoTop *AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.*
Zolmitriptan (p.628·1).
Migraine.

Ascoxal
Note. This name is used for preparations of different composition.
AstraZeneca, Arg.†.
Ascorbic acid (p.1983·3); sodium percarbonate (p.1662·2).
Gingivitis.

AstraZeneca, Austral.; AstraZeneca, Fin.†; AstraZeneca, Mex.; AstraZeneca, Norw.†; AstraZeneca, Swed.†.
Ascorbic acid (p.1983·3); sodium percarbonate (p.1662·2); copper sulfate (p.1935·3).
Mouth and throat disorders; oral hygiene.

Ascredar *Roche, Austria.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolytic bone metastases; Paget's disease of bone.

Ascriptin *Aventis, Gr.†; Aventis, Israel†; Sanofi-Aventis, Ital.; Aventis, Mex.; Novartis, USA; Vargas, Venez.*
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) or aluminium hydroxide (p.1706·2), calcium carbonate (p.1714·1), and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; myocardial infarction; pain; thromboembolic disorders; thrombosis prophylaxis; transient ischaemic attacks.

Asdron *Marjan, Braz.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Asedas *Pyridam, Indon.*
Vitamins; minerals; docosahexaenoic acid; curcuma; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Aselli
Note. This name is used for preparations of different composition.
Weifa, Norw.
Cream: Cetylpyridinium chloride (p.1635·1); zinc tannate.
Minor skin disorders; skin disinfection; sunburn.

Weifa, Norw.
Ointment: Zinc tannate; zinc oxide (p.1621·2); titanium dioxide (p.1617·3); cod-liver oil (p.1935·2).
Minor skin disorders.

Asemin *Flupal, Venez.†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Asendin *Lederle, Indon.; Lederle, USA†.*
Amoxapine (p.382·2).
Depression.

Asendis *Goldshield, UK†.*
Amoxapine (p.382·2).
Depression.

Asendra *Pascoe, Ger.†.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Asenlix *Aventis, Mex.*
⊗ Clobenzorex hydrochloride (p.2152·3).
Obesity.

Asenta *Agis, Israel.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Asentra *KRKA, Cz.; KRKA, Hung.; KRKA, Neth.; KRKA, Pol.; KRKA, Rus.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

ASEP *Galen, UK.*
Glutaral (p.1645·2).
Instrument disinfection.

Asepar *Gunsa, Turk.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Asepsan *Zambon, Ital.*
Povidone-iodine (p.1659·2).
Disinfection of vaginal mucosa.

Asepta *Konimex, Indon.*
Povidone-iodine (p.1659·2).
Disinfection.

Aseptalum *ICN, Arg.†.*
Aluminium subacetate (p.2255·1).
Astringent.

Aseptisol *Bode, Ger.†.*
Glutaral (p.1645·2); formaldehyde (p.1644·2); didecylmethyloxethylammonium propionate.
Instrument disinfection.

Aseptobron
Note. This name is used for preparations of different composition.
Temis, Arg.
Inhalation: Menthol (p.2340·1); cineole (p.2282·3); niaouli (p.2351·3); camphor (p.2273·2); terpinol (p.2396·1); pinus pinaster oil (p.2368·1).
Respiratory-tract disorders.

Temis, Arg.
Injection: Cineole (p.2282·3); niaouli oil (p.2351·3); guaiacol (p.1561·2); iodoform (p.1650·2).
Formerly contained camphor, cineole, niaouli, guaiacol, and iodoform.
Respiratory-tract disorders.

Temis, Arg.
Syrup: Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Aseptobron Ampicilina *Temis, Arg.†.*
Ampicillin sodium (p.204·1); clonixin lysine (p.37·1); cineole (p.2282·3); niaouli oil (p.2351·3); terpineol (p.2396·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Aseptobron Antigripal *Temis, Arg.*
Levophenylephrine hydrochloride (p.1568·3); paracetamol (p.108·1); vitamin C (p.1983·3).
Cold and influenza symptoms.

Aseptobron Bromexina *Temis, Arg.*
Oxeladin citrate (p.1567·1); bromhexine hydrochloride (p.1552·2).
Coughs.

Aseptobron C *Temis, Arg.*
Oxeladin citrate (p.1567·1); carbinoxamine maleate (p.570·2).

Aseptobron Caramelos *Temis, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Aseptobron Descongestivo *Temis, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Aseptobron Expectorante *Temis, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with increased or viscous mucus.

Aseptobron N
Note. This name is used for preparations of different composition.
Temis, Arg.
Mouth and throat spray: Benzocaine (p.1854·1); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Mouth and throat disorders.

Temis, Arg.
Pastilles: Benzocaine (p.1854·1); gramicidin (p.286·1); neomycin sulfate (p.305·1); cineole (p.2282·3); menthol (p.2340·1).
Mouth and throat disorders.

Aseptobron Respiratorio *Temis, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Aseptobron Unicap *Temis, Arg.*
Hydrocodone resinate; chlorphenamine resinate (p.572·2).

Asepto-Glutaral *Preston, Arg.†.*
Glutaral (p.1645·2).
Disinfection.

Aseptol *Akdeniz, Turk.*
Cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Aseptone *Duopharma, Malaysia.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome.

Aseptosyl *Sanofi Synthelabo, Belg.†.*
Potassium hydroxyquinoline sulfate (p.2323·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Aserbine *Pharmaco, S.Afr.; Goldshield, UK†.*
Benzoic acid (p.1630·2); malic acid (p.2337·1); salicylic acid (p.1612·2); propylene glycol (p.2374·1).
Burns; skin ulcers; wounds.

Asercit *Itaca, Braz.†.*
Dacarbazine (p.706·3).
Hodgkin's lymphoma; malignant melanoma.

Asering *Otsuka, Indon.*
Electrolyte infusion with or without glucose (p.1667·1).
Carbohydrate source; fluid replacement.

Aseroprin *Itaca, Braz.†.*
Azathioprine (p.1818·2).
Rheumatoid arthritis; transplant rejection.

Asestor *Spedrog, Arg.*
Simeticone (p.1770·2); homatropine methylbromide (p.1881·3).
Flatulence; gastrointestinal spasm.

Asetisin *Pharlab, Braz.†.*
Aspirin (p.20·3).

Asfeina *Bial, Port.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Asfrenon *Terramedic, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm.

Asfrenon GF *Terramedic, Philipp.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Cough.

Asgoviscum N *AstraZeneca, Ger.†.*
Mistletoe (p.2345·3); crataegus (p.2289·1); garlic (p.2309·2).
Cardiac disorders.

Ashbourne Emollient Medicinal Bath Oil *Ashbourne, UK†.*
Liquid paraffin (p.2030·3); acetylated wool alcohols (p.2033·2).
Skin disorders.

Ashton & Parsons Infants Powders *Group, S.Afr.; SSL, UK.*
Chamomile (p.2279·3).
Colic; gastrointestinal disorders; teething.

Asiabron *Asian Pharm, Thai.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Asialax *Asian Pharm, Thai.*
Carisoprodol (p.1894·1); phenylbutazone (p.117·1).
Musculoskeletal and joint disorders.

Asialum *Asian Pharm, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; peptic ulcer.

Asiamox *Asian Pharm, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Asiatapp *Asian Pharm, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Asthma; cold symptoms.

Asiazole *Asian Pharm, Thai.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Asiazole-TN *Asian Pharm, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Asic
Note. This name is used for preparations of different composition.
Cesam, Port.†.
Bearberry (p.2263·3); carboxyethylgermanium; titanium dioxide (p.1617·3); methoxycinnamate.
Hyperpigmentation.

Pharmaceutical Enterprises, S.Afr.
Dicycloverine hydrochloride (p.1722·3); doxylamine succinate (p.578·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting in pregnancy.

Asidal *Eczacibasi, Turk.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Asidopan Plus *Wyeth, Turk.*
Magaldrate (p.1742·3); simeticone (p.1770·2).

Asidrat *Pharos, Indon.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Gastric hyperacidity; peptic ulcer.

Asig *Sigma, Austral.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Asilon *Akdeniz, Turk.*
Pipenzolate bromide (p.1762·2); simeticone (p.1770·2).

Asilone
Note. This name is used for preparations of different composition.
Roche, S.Afr.†.
Aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastric hyperacidity.

Thornton & Ross, UK.
Oral gel; oral suspension: Aluminium hydroxide (p.1706·2); light magnesium oxide (p.1744·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; hiatus hernia.

Daudt, Braz.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence.

Daudt, Braz.†; Thornton & Ross, UK.
Tablets: Aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Asilone Windcheaters *Thornton & Ross, UK†.*
Simeticone (p.1770·2).
Flatulence.

Asimat *Mersifarma, Indon.*
Mefenamic acid (p.80·1).
Pain.

Asimil B12 *Torlan, Spain†.*
Mecobalamin (p.1981·1).
Vitamin B12 deficiency.

Asinis *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Asinpirine *Ulagay, Turk.*
Aspirin (p.20·3).
Fever; pain.

Asiolex *Pharmacia, Arg.†.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Asipral *Labomed, Chile†.*
Azithromycin (p.207·1).
Bacterial infections.

Asisdun *Duncan, Arg.†.*
Cyproterone (p.2089·2).

Asist *Bilim, Turk.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory disorders with increased mucus.

Asiviral *Terra, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Askamex *Konimex, Indon.*
Levamisole hydrochloride (p.147·2).
Ankylostoma; ascariasis.

Askaripar *Aksu, Turk.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Askina
Note. This name is used for preparations of different composition.
Braun, Fr.†.
Hydrogel dressing.
Ulcers; wounds.

Braun, UK.
Sodium chloride (p.1686·1).
Wound cleansing and irrigation.

Askina Biofilm *Braun, Fr.†; Braun, Port.†.*
Carmellose (p.2142·1).
Wounds.

Askina Carbsorb *Braun, Port.†.*
Activated charcoal (p.1435·2).
Ulcers; wounds.

Askina Gel *Braun, Port.†.*
Hydrogel dressing.
Ulcers; wounds.

Askina Hydro *Braun, Port.†.*
Hydrocolloid dressing.
Burns; ulcers; wounds.

Askina Sorb
Braun, Fr.†.
Calcium alginate (p.1058·1); carmellose sodium (p.2142·1).
Wounds.

Braun, Port.†.
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Ulcers; wounds.

Askit *Askit, UK.*
Aspirin (p.20·3); aloxiprin (p.18·3); caffeine citrate (p.1116·3).
Fever; pain.

Asko *Pasifik, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Askorbin *Kimia, Indon.*
Ascorbic acid (p.1983·3).
Capillary bleeding; vitamin C deficiency.

ASL *Normon, Spain.*
Lysine aspirin (p.79·1).
Fever; inflammation; pain; thromboembolism prophylaxis.

Aslavital
Note. This name is used for preparations of different composition.
Sanova, Austria.
Injection: Procaine hydrochloride (p.1869·1); glutamic acid (p.1947·1).
Tonic.

Sanova, Austria.
Tablets: Procaine hydrochloride (p.1869·1); pyridoxine hydrochloride (p.1978·2); inositol (p.2325·2).
Tonic.

Asmabec *UCB, Fr.; UCB, Irl.; Celltech, Spain†; UCB, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Asmabiol *Biol, Arg.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Asmacaire *Aldo-Union, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asmacare *Kimia, Indon.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asmacortone *NCSN, Ital.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Asmadex *Dexa, Indon.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2).
Asthma; bronchitis.

Asmafen *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Pacific, NZ; Xepa-Soul Pattinson, Singapore†.*
Ketotifen fumarate (p.582·2).
Allergic bronchitis; allergic conjunctivitis; allergic rhinitis; allergic skin disorders; asthma.

Asmafilin *Casel, Turk.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Asmafin *Cazi, Braz.*
Aminophylline hydrate (p.1114·3).
Obstructive airways disease.

Asmaflu *Max Farma, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic disorders of the respiratory tract.

Asmafort *Julphar, UAE.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Asmag *Farmapol, Pol.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Asmakil *Elofar, Braz.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asmalergin *Merck, Braz.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Asmalia *Umeda, Thai.*
Aminophylline (p.1114·2).
Asthma; heart failure.

Asmalin *United American, Philipp.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asmalin Broncho *United American, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol (p.1131·2).
Bronchospasm; cough.

Asmaline *Polipharm, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Asmaliv *Legrand, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asmalix *Century, USA.*
Theophylline (p.1140·1).
Obstructive airways disease.

Asmanex *Aesca, Austria; Schering-Plough, Braz.†; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.†; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Irl.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Port.; Schering-Plough, Spain†; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗ Mometasone furoate (p.1539·3).
Asthma.

Asmano *Corsa, Indon.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2).
Obstructive airways disease.

Asmanoc *Shiwa, Thai.†.*
Ketotifen fumarate (p.582·2).
Asthma; bronchitis; hay fever.

Asmanon *Cazi, Braz.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Asmapax *Nicholas Piramal, India.*
⊗ Ephedrine (p.1558·1); theophylline (p.1140·1); phenobarbital (p.492·2).
Obstructive airways disease.

Asmapen *Neo Quimica, Braz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Asmaral-K *Serral, Mex.*
Ketotifen (p.582·2).
Asthma.

Asmasal
UCB, Fr.; UCB, Irl.; Celltech, Spain†; UCB, UK.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Silom, Thai.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asmasal Expectorant *Silom, Thai.†.*
⊗ Salbutamol (p.1131·2); guaifenesin (p.1561·3).
Bronchospasm associated with respiratory-tract congestion.

Asmasolon
Note.This name is used for preparations of different composition.
Probus, Indon.
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2).
Obstructive airways disease.

Westmont, Philipp.; Great Eastern, Thai.; Westmont, Thai.
Theophylline (p.1140·1).
Obstructive airways disease.

Asmatec *UCB, Port.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Asmaten *Duopharma, Hong Kong.*
Ketotifen fumarate (p.582·2).
Allergic bronchitis; asthma; hypersensitivity disorders.

Asmatil *Alodial, Port.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Asmatiron *Ibefar, Braz.†.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); homatropine methylbromide (p.1881·3); diphenhydramine hydrochloride (p.577·2); lobelia (p.2157·2); stramonium (p.2392·3).
Obstructive airways disease.

Asmatol *Roux-Ocefa, Arg.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asmavent
Note.This name is used for preparations of different composition.
Mintlab, Chile.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

United American, Philipp.
⊗ Budesonide (p.1520·1).
Asthma.

Asmavent-B *Mintlab, Chile.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Asmax *Ativus, Braz.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Asmen *Farmalab, Braz.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Asmeren *Labomed, Chile.*
⊗ Clenbuterol (p.1120·1).
Obstructive airways disease.

Asmetic *Farmilia, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Asmeton *Sankyo, Hong Kong; Sankyo, Thai.†.*
⊗ Methoxyphenamine hydrochloride (p.1564·2); aminophylline (p.1114·2); chlorphenamine maleate (p.571·3); noscapine (p.1566·2).
Asthma; bronchitis; coughs.

Asmifen *Bunker, Braz.*
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Asmigen *Pacific, NZ.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asmodrin *Sanval, Braz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Asmofen *Teuto, Braz.*
Ketotifen fumarate (p.582·2).
Asthma.

Asmol
Alphapharm, Austral.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Pacific, NZ†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asmo-Lavi *Vitoria, Port.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Asmopul
Note.This name is used for preparations of different composition.
Asmopul, Arg.†.
⊗ Atropine (p.1219·2); adrenaline (p.1203·2).
Asthma.

Cassara, Arg.
⊗ Fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Asmoquinol *Ducto, Braz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Asmotone Plus *East India Pharma, India.*
⊗ Bromhexine hydrochloride (p.1552·2); terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Asmovent *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aso DDI *Raffo, Arg.†.*
Didanosine (p.870·2).
HIV infection.

Asodal *Sandipro, Belg.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); tiemonium iodide (p.1776·3).
Colic; muscle spasm and pain.

Asodocel *Asofarma, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Asoflon *Asofarma, Mex.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Asoflut *Raffo, Arg.*
Flutamide (p.725·1).

Asofurtal *Raffo, Arg.*
Tegafur (p.776·1); uracil (p.2407·3).
Malignant neoplasms.

Asoglutan *Asofarma, Arg.; Raffo, Arg.*
Glucosamine sulfate (p.2313·2).
Arthroses.

Asoifos *Asofarma, Arg.†.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Asolmicina *Defuen, Arg.†.*
Minocycline (p.300·3).
Bacterial infections.

A-Solmicina-C *Richet, Arg.†.*
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Asolmicina.dox *Defuen, Arg.*
Doxycycline (p.267·1).
Bacterial infections; malaria.

Asomal *Radyum, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Asomutan *Raffo, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Asonacor *Abbott, Austria†.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Asonor *Pharma-Export, UK.*
Sodium chloride (p.1686·1); glycerol (p.2314·2); polysorbate 80 (p.1919·2).
Snoring.

Asotax *Raffo, Arg.; Asofarma, Mex.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Asotecan *Raffo, Arg.*
Topotecan (p.780·2).
Malignant neoplasms.

Asoteron
Raffo, Arg.
Cyproterone (p.2089·2).
Prostatic cancer.

Nolver, Venez.
Cyproterone acetate (p.2088·2).
Female androgenisation; precocious puberty; prostatic cancer.

Asotrex *Raffo, Arg.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Musculoskeletal and joint disorders.

Asovit *Valmor, Venez.†.*
Vitamin B substances (p.1922·1).

Asovit-Mineral *Valmor, Venez.†.*
Vitamin and mineral preparation (p.1922·1).

Asovon *Medicine Products, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Asovorin *Raffo, Arg.*
Calcium levofolinate (p.1943·3).
Malignant neoplasms.

ASP *Medinfar, Port.*
Aspirin (p.20·3).
Fever; pain.

Aspacardin *Terapia, Hung.†.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Arrhythmias; heart failure; magnesium and potassium supplement; myocardial infarction.

Aspagin *Proel, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Aspalgin *Fawns & McAllan, Austral.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Aspapirine *Erkimya, Turk.*
Aspirin (p.20·3).
Fever; pain.

Aspar *Tanabe, Indon.*
Potassium aspartate; magnesium aspartate; bisbentiamine; vitamin B (p.1922·1).
Nutritional supplement; tonic.

Asparagus-P *Grunwalder, Ger.*
Asparagus; parsley (p.2363·2).
Oedema; renal calculi.

Aspargin *Espefa, Pol.; Farmapol, Pol.; Filofarm, Pol.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Arrhythmias.

Aspartatol *Eagle, Austral.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1); glutamine (p.1947·2).
Tonic.

Asparten *Grunenthal, Port.*
Arginine aspartate (p.1928·2).
Asthenia; urea cycle disorders.

Aspartil *Munir, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Aspartina *Bouty, Ital.*
Aspartame (p.1930·1).
Sugar substitute.

A-Spas *Hyrex, USA†.*
Hyoscyamine sulfate (p.1736·1).
Gastrointestinal disorders.

Aspaserine B6 Tranq *UCB, Spain†.*
Diazepam (p.986·3).
Contains pyridoxine.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Aspasmine *Sterop, Belg.†.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Aspasmon N *Norgine, Ger.†.*
Peppermint oil (p.1761·2); anise oil (p.2258·2); caraway oil (p.2277·1).
Catarrh; gastrointestinal disorders.

Aspav *Alpharma, UK.*
Aspirin (p.20·3); papaveretum (p.105·2).
Pain.

Aspec *PSM, NZ; Hizon, Philipp.; Pharmaspec, Philipp.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Aspecton *Krewel, Ger.*
Thyme (p.2401·1).
Respiratory-tract congestion.

Aspecton Eukaps *Krewel, Ger.*
Eucalyptus oil (p.2301·2).
Respiratory-tract congestion.

Aspecton-Balsam *Krewel, Ger.†.*
Camphor (p.2273·2); thyme oil (p.2401·2); eucalyptus oil (p.2301·2).
Cold symptoms; coughs.

Aspectonetten N *Krewel, Ger.†.*
Gypsophila saponins.
Respiratory-tract catarrh.

Aspegic *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Malaysia†; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Switz.*
Lysine aspirin (p.79·1).
Fever; gout; inflammation; musculoskeletal and joint disorders; neuralgia; pain; thrombosis prophylaxis.

Aspegic Codeine *Sanofi-Aventis, Fr.†.*
Lysine aspirin (p.79·1); codeine phosphate (p.37·2).
Pain.

Aspent *Ranbaxy, Thai.*
Aspirin (p.20·3).
Myocardial infarction; osteoarthritis; rheumatoid arthritis; transient ischaemic attacks.

Aspercreme *Chattem, Canad.; Thompson, USA.*
Trolamine salicylate (p.132·3).
Muscle and joint pain; muscle, joint, and soft-tissue pain; neuralgia.

Aspergum *Heritage, Canad.; Schering-Plough, USA.*
Aspirin (p.20·3).
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Aspergun *ICN, Arg.†.*
Piroctone olamine (p.1610·1); collagen (p.2286·1).
Dandruff.

Asperivo *Rivopharm, Switz.†.*
Aspirin (p.20·3).
Fever; pain.

Aspex *Rekah, Israel.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Asphaline *Vifor, Switz.†.*
Camphor (p.2273·2); thymol (p.1664·3); paraformaldehyde (p.1655·2); zinc oxide (p.1621·2).
Root canal infections.

Aspicalm *Medichrom, Gr.*
Lysine aspirin (p.79·1).
Fever; pain.

Aspicam *Biofarm, Pol.*
Meloxicam (p.80·3).
Degenerative joint disorders; osteoarthritis.

Aspicot *Concept, India.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Aspidol *Piam, Ital.†.*
Lysine aspirin (p.79·1).
Pain.

Aspidor *Zeler, Port.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Aspiglicina *Antonetto, Ital.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Neuralgia.

Aspil *Fahrenheit, Indon.*
Cefotiam (p.230·1).
Bacterial infections.

Aspilets *United American, Hong Kong; Medifarma, Indon.; Imperial, Philipp.; Great Eastern, Thai.; United American, Thai.*
Aspirin (p.20·3).
Angina pectoris; fever; myocardial infarction; pain; pregnancy-induced hypertension; thromboembolic disorders.

Aspimag *Espefa, Pol.*
Aspirin (p.20·3).
Magnesium oxide (p.1744·1) is included in this preparation in an to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Aspimed *Cassara, Arg.†.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Aspinal *Munir, Turk.*
Aspirin (p.20·3).
Fever; pain.

Aspinat Cardio *Shchelkovskii, Rus.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Aspinfantil *Diviser Aquilea, Spain†.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Aspipur *Attavet, Fr.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1); methoprene (p.2046·3); tannins; tetramethrin (p.2051·1).
Insecticide.

Aspiretina *Andromaco, Venez.†.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Aspiricor *Bayer, Austria.*
Aspirin (p.20·3).
Migraine; thromboembolism prophylaxis.

Aspirin Activ *Bayer, Pol.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Aspirin Backache *Bayer Consumer, Canad.*
Aspirin (p.20·3); methocarbamol (p.1897·3).
Back pain.

Aspirin C *Bayer, Cz.; Bayer, Fin.; Bayer, Gr.; Bayer, Israel; Bayer, Pol.; Bayer, Rus.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; musculoskeletal and joint disorders; pain; thrombosis prophylaxis.

Aspirin + C *Bayer, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Aspirin Cardio *Bayer, Fin.; Bayer, Rus.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Aspirin Complex
Note. This name is used for preparations of different composition.
Bayer, Austria; Bayer, Ger.
Aspirin (p.20·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; fever; nasal congestion; pain.

Bayer, Rus.
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); phenylephrine acid tartrate (p.1568·1).
Cold and influenza symptoms.

Aspirin Extra *Bayer, Gr.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Aspirin Forte *Bayer, Ger.; Bayer, Hung.†; Bayer, Turk.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Aspirin Free Anacin *Robins, USA.*
Paracetamol (p.108·1).
Formerly known as Anacin-3.

Aspirin Free Anacin PM *Whitehall, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia; pain.

Aspirin Free Excedrin *BMS, USA.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Aspirin Free Pain Relief *Hudson, USA.*
Paracetamol (p.108·1).
Fever; pain.

Aspirin plus C *Bayer, Ger.; Bayer, Hung.; Bayer, Turk.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms; fever; inflammation; pain.

Aspirin Protect *Bayer, Hung.; Bayer, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Aspirin with Stomach Guard *Bayer Consumer, Canad.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1), magnesium carbonate (p.1743·1), and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain.

Aspirin Zipp *Bayer, Fin.*
Aspirin (p.20·3).
Cold symptoms; fever; pain.

Aspirina
Benitol, Arg.; Duncan, Arg.; Fabra, Arg.; Fecofar, Arg.; Gezzi, Arg.; Klonal, Arg.; Richet, Arg.; Vent-3, Arg.
Aspirin (p.20·3) or lysine aspirin (p.79·1).
Calcium carbonate (p.1714·1) and magnesium oxide (p.1744·1) are included in some preparations in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain; thromboembolism prophylaxis.

Bayer, Braz.; Bayer, Chile; Bayer, Ital.; Bayer, Port.; Bayer, Spain; Gervasi, Spain.
Aspirin (p.20·3).
Fever; inflammation; musculoskeletal, joint, and periarticular disorders; pain; thromboembolism prophylaxis.

Aspirina 03 *Bayer, Ital.*
Aspirin (p.20·3).
Magnesium hydroxide (p.1743·2) and aluminium glycinate (p.1706·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Aspirina C *Bayer, Braz.; Bayer, Chile; Bayer, Ital.; Bayer, Port.; Bayer, Spain.*
Aspirin (p.20·3); vitamin C (p.1983·3).
Fever; musculoskeletal disorders; pain.

Aspirina Complex *Bayer, Spain.*
Aspirin (p.20·3); phenylephrine acid tartrate (p.1568·1); chlorphenamine maleate (p.571·3).
Formerly contained aspirin, phenylpropanolamine tartrate, and chlorphenamine maleate.
Cold and influenza symptoms.

Aspirina Forte *Bayer, Braz.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Aspirina Plus *Bayer, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Aspirina Protect *Bayer, Mex.*
Aspirin (p.20·3).
Thromboembolic disorders.

Aspirine *Bayer, Belg.; BMS, Fr.; Bayer, Fr.*
Aspirin (p.20·3).
Fever; pain; thromboembolism prophylaxis.

Aspirine C *Bayer, Belg.; Bayer, Neth.; Bayer, Switz.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Aspirine Cardio *Bayer, Switz.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Aspirine Duo *Bayer, Belg.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Aspirine pH8 *3M, Fr.†.*
Aspirin (p.20·3).
Fever; pain.

Aspirine Protect *Bayer, Neth.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Aspirine vitamine C *UPSA, Fr.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Aspirinetas *Bayer Consumer, Arg.*
Aspirin (p.20·3).
Fever; pain.

Aspirinetta *Bayer, Ital.*
Aspirin (p.20·3).
Fever; pain.

Aspirin-Free Bayer Select Allergy Sinus *Sterling Health, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Aspirin-Free Bayer Select Head & Chest Cold *Sterling Health, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).

Aspirisucre *Arkomedika, Fr.*
Aspirin (p.20·3).
Fever; pain.

Aspi-Rub *Sidus, Arg.†.*
Methyl salicylate (p.85·3).

Aspisol *Bayer, Ger.†.*
Lysine aspirin (p.79·1).
Fever; pain; rheumatism; thromboembolic disorders.

Aspitopic *Bayer, Spain.*
Etofenamate (p.53·1).
Inflammation; pain.

Aspitrate *Otsira, India†.*
Isosorbide mononitrate (p.1318·3); aspirin (p.20·3).

Asprimox *Invamed, USA†.*
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2), calcium carbonate (p.1714·1), and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Aspro *Bayer Consumer, Austral.; Klosterfrau, Austria; Bayer, Belg.; Roche, Belg.; Roche Nicholas, Cz.†; Bayer Sante, Fr.; Bayer, Ger.; Bayer, Irl.; Bayer, Ital.; Bayer, NZ; Bayer, Neth.; Roche, Port.†; Roche Consumer, Singapore; Bayer, Switz.; Roche Consumer, UK.*
Aspirin (p.20·3).
Cold and influenza symptoms; fever; inflammation; pain; thromboembolism prophylaxis.

Aspro C *Roche Nicholas, Cz.†; Bayer, Hung.; Bayer, Ital.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms; fever; inflammation; pain.

Aspro mit Vitamin C *Klosterfrau, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Aspro vitamine C *Bayer Sante, Fr.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Asproaccel *Roche Nicholas, Fr.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Asprocard *ICN, Pol.*
Aspirin (p.20·3).
Glycine [589-y] is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thrombosis prophylaxis.

Asprocol *ICN, Pol.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Asquam *Pierre Fabre Dermatologie, Cz.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Asrina *Pharmasant, Thai.*
Aspirin (p.20·3).
Inflammation; pain; rheumatism.

ASS *Genericon, Austria; Hexal, Austria; Ratiopharm, Austria; 1A, Ger.; Aliud, Ger.; Alpharma-Isis, Ger.; CT, Ger.; Hexal, Ger.; RAN, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Stada, Ger.; Worwag, Ger.; Mepha, Switz.*
Aspirin (p.20·3).
Fever; inflammation; pain; rheumatism; thromboembolic disorders.

ASS + C *Hexal, Austria; Hexal, Ger.; Ratiopharm, Ger.; BMS, Hung.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms; fever; inflammation; pain.

ASS plus Vit C *1A, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Assal *Salus, Mex.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).

Assalix *Bionorica, Ger.; Bionorica, Switz.*
Salix (p.121·3).
Fever; pain; rheumatism.

Assan *Permamed, Switz.*
Flufenamic acid (p.60·3); glycol salicylate (p.62·3); heparin sodium (p.1301·2).
Musculoskeletal and joint pain; peripheral vascular disease; soft-tissue injury.

Assan thermo *Permamed, Switz.*
Flufenamic acid (p.60·3); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); heparin sodium (p.1301·2).
Musculoskeletal and joint disorders.

Assenzio (Specie Composta) *Dynacren, Ital.†.*
Absinthium (p.2244·1); gentian (p.2310·3); dried bitter-orange peel (p.2357·1); centaury (p.2279·1); cinnamon (p.2283·1).
Appetite loss; herbal tea.

Assepium *Gross, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Assepium Balsamico *Gross, Braz.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Respiratory-tract infections.

Asseptic *Neo Quimica, Braz.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Assert *Eurofarma, Braz.*
Sertraline hydrochloride (p.421·3).
Depression.

Assieme *Simesa, Ital.; AstraZeneca, Neth.; Tecnifar, Port.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Assist *GD, Ital.*
Soya oil; lutein; zinc (p.1922·1).
Nutritional supplement.

Assival *Teva, Israel.*
Diazepam (p.986·3).
Anxiety; epilepsy; insomnia; skeletal muscle spasm.

Assocals *SJA, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Assocort *BMS, Ital.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Infected skin disorders.

Assolid *Konpharma, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic respiratory-tract disorders.

Assoprol *SJA, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Assoral *Savio, Ital.*
Roxithromycin (p.331·1).
Bacterial infections.

Assosept-S *SJA, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Assplant *Robugen, Ger.*
Salix (p.121·3).
Rheumatism.

Assy Crema de Enjuague *Assistance, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Assy Espuma *Assistance, Arg.; Andromaco, Chile†.*
Permethrin (p.2048·2).
Pediculosis.

Astafen *Ilsan, Turk.*
Ketotifen (p.582·2).
Asthma.

Astagen *Genesis, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Astaplatin *Asta Oncologia, Braz.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Astat
Note. This name is used for preparations of different composition.
Acis, Hung.†.
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Tsumura, Jpn.
Lanoconazole (p.540·3).
Fungal skin infections.

Astebron *Integrated Pharmaceutical, Philipp.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Astelin *Sanfer, Mex.; Wallace, USA.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Astemina *Diba, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Astenol *Farmabraz, Braz.†.*
Erythroxylon catuaba; guarana (p.2416·1); thiamine; pepsin (p.1922·1).
Tonic.

Astenolit *Altana, Spain.*
Vitamin, mineral and amino-acid preparation (p.1922·1).
Tonic.

Astergina *Flupal, Venez.*
Codergocrine (p.364·1).

Astergyl *Aster, Braz.†.*
Metronidazole (p.837·1).

Asteriodine *Aster, Braz.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Astesen *Senosiain, Mex.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Astezol *ICN, Arg.†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Asthacrom *Cipla, India.*
⊗ Salbutamol (p.1131·2); sodium cromoglicate (p.1136·3).
Asthma.

Asthalin
Cipla, Cz.†; Cipla, India.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Cipla, Venez.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Asthalin AX *Cipla, India.*
⊗ Ambroxol (p.1550·3); salbutamol (p.1131·2).
Obstructive airways disease.

Asthalin Expectorant *Cipla, India.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Asthavent
Cipla-Medpro, S.Afr.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Cansin, Turk.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asthenal *Grossmann, Switz.†.*
Sodium dimethyl aminophenylphosphinate; glutamic acid; thiamine hydrochloride; ascorbic acid (p.1922·1).
Tonic.

Astherin *Pyridam, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Asthma *CCM, Malaysia.*
⊗ Ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1).
Bronchial asthma; chronic bronchitis.

Asthma & Catarrh Relief *Herbal Concepts, UK.*
⊗ Ipecacuanha (p.1562·3); lobelia (p.2157·2); marrubium (p.1564·1); liquorice (p.1740·3).
Asthma; catarrh.

Asthma 23 D *Sanova, Austria.*
⊗ Ephedrine hydrochloride (p.1558·2); belladonna (p.2263·3); papaverine hydrochloride (p.2191·3); caffeine-naphthylacetic sodium; theophylline (p.1140·1).
Obstructive airways disease.

Asthma Efeum *Apomedica, Austria.*
⊗ Proxyphylline (p.1130·3); phenazone (p.116·1); ethaverine sulfamate (p.2300·1); ephedrine hydrochloride (p.1558·2); diphenhydramine hydrochloride (p.577·2).
Obstructive airways disease.

Asthma H *Pfluger, Ger.†.*
Homoeopathic preparation.

Asthma 6-N *Hobein, Ger.†.*
⊗ Ephedrine hydrochloride (p.1558·2); grindelia (p.2317·2); senega root (p.1572·3).
Obstructive airways disease.

Asthma Soho *Soho, Indon.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2).
Asthma.

Asthma-Bomin H *Pfluger, Ger.*
Homoeopathic preparation.

AsthmaHaler Mist *Numark, USA.*
⊗ Adrenaline acid tartrate (p.1203·2).
Bronchospasm.

Asthma-Hilfe *Agepha, Austria.*
⊗ Aminophylline (p.1114·2); theobromine (p.1140·1); ephedrine hydrochloride (p.1558·2); sulfogaiacol (p.1573·2).
Obstructive airways disease.

Asthmakhell N *Steigerwald, Ger.*
Homoeopathic preparation.

Asthmalitan *MIT, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

AsthmaNefrin *Menley & James, USA.*
⊗ Racepinefrine hydrochloride (p.1204·2).
Obstructive airways disease.

Asthmasian *Asian Pharm, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Asthmatee EF-EM-ES *Smetana, Austria.*
Enulae root; marrubium vulgare (p.1564·1); origanum (p.2357·3); aniseed (p.2258·2); arnica (p.2260·2); cacao husk (p.2400·1).
Obstructive airways disease.

Asthmavowen-N *Weber & Weber, Ger.*
Homoeopathic preparation.

Asthmaxine *Synco, Hong Kong.*
Bromhexine hydrochloride (p.1552·2).
Respiratory disorders associated with viscous mucus.

Asthmino *Jagson, India†.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2).
Obstructive airways disease.

Asthmolin *Pharmasant, Thai.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asthmoprotect *Azupharma, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Asthmotrat *Intermed, Gr.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; chronic respiratory failure.

Astho-Med *Interdelta, Switz.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Astifat *Fatol, Ger.†.*
Ketotifen fumarate (p.582·2).
Asthma; bronchitis; hypersensitivity reactions.

Astifen *Christo, Hong Kong; Hexpharm, Indon.*
Ketotifen fumarate (p.582·2).
Allergic bronchitis; allergic conjunctivitis; allergic rhinitis; asthma; hypersensitivity disorders.

Astika *Ikapharmindo, Indon.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Astin *Probiomed, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia.

Astizole *Cadila, India.*
Astemizole (p.567·2).

Astmerole *Fako, Turk.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Astmopent *Polfa Warszawa, Pol.; GSK, Rus.*
⊗ Orciprenaline sulfate (p.1129·1).
Arrhythmias; asthma; premature labour.

Asto-Chol *Mediapharm, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Astomera *Bittner, Austria.*
Homoeopathic preparation.

Astonin *Merck, Spain.*
Fludrocortisone (p.1530·1).
Adrenocortical insufficiency; hypotension.

Astonin H *Merck, Austria; Merck, Ger.; Merck, Hung.*
Fludrocortisone (p.1530·1).
Adrenocortical insufficiency; congenital adrenal hyperplasia; hypotension; orthostatic hypotension.

Astracaine *AstraZeneca, Canad.†.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Astragalus Complex *Mediherb, Austral.*
Astragalus; echinacea (p.2298·1); Siberian ginseng (p.2386·3).
Tonic.

Astramorph *Astra, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Astrasept *Fermenta Biotech, Rus.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1).
Sore throat.

Astrexine *UCB, Belg.*
Chlorhexidine hydrochloride (p.1635·3).
Wound and skin disinfection.

Astrijesan *Farmo Quimica, Chile.*
Mint oil (p.2345·2); menthol (p.2340·1); methyl salicylate (p.85·3); myrrh (p.2349·2); eugenol (p.2301·2); zinc chloride (p.1999·1).
Mouth disorders.

Astrin *Medeus, Spain†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Astrix *Faulding, Austral.; Mayne, Hong Kong; Teva, Hung.; Faulding, Singapore†.*
Aspirin (p.20·3).
Thromboembolic disorders.

Astro *Eurofarma, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Astrocast *Chrispa (Χρισπα), Gr.*
⊗ Budesonide (p.1520·1).
Topical corticosteroid.

Astrofen *Liferpal, Mex.*
Phenylbutazone (p.117·1).
Inflammation; rheumatism.

Astroglide *Biofilm, USA.*
Glycerol (p.2314·2); propylene glycol (p.2374·1); polyquaternium-5.
Vaginal lubricant.

Astronautal *Strallhofer, Austria.*
Diphenylpyraline hydrochloride (p.578·2); pyridoxine hydrochloride (p.1978·2).
Motion sickness; nausea; vertigo.

Astudal *Almirall, Spain.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Astyl *Laphal, Fr.†.*
⊗ Deanol bisorcate (p.2152·3).
Tonic.

Astymin-3 *Tablets, India.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Astymin Forte *Tablets, India.*
Amino-acids and multivitamin preparation (p.1922·1).
Hypoproteinaemia; tonic.

Asucrose *Wockhardt, India.*
Acarbose (p.436·2).
Diabetes mellitus.

Asulblan *Fada, Arg.*
Amiodarone (p.1210·2).
Arrhythmias.

Asumalife *YSP, Malaysia; Yung Shin, Singapore.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma; pruritus; urticaria.

Asverin *Tanabe, Jpn.*
Tipepidine hibenzate (p.1574·2).
Coughs.

Asvex *Tanabe, Indon.*
Tipepidine hibenzate (p.1574·2).
Cough; upper respiratory-tract congestion.

Asvimol *Virgo, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Asytec *Actavis, Denm.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; hay fever; urticaria.

AT III *Baxter, Ger.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

AT 10 *Merck, Austria; Merck, Belg.†; Bayer, Ger.; Merck, Hung.†; Bayer, S.Afr.; Bayer, Switz.; Intrapharm, UK.*
Dihydrotachysterol (p.1986·3).
Hypocalcaemia of hypoparathyroidism; hypocalcaemic tetany; hypoparathyroidism; osteomalacia; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Atac *Megahealth, Chile.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Atacand *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; Teva, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; Astra, USA; AstraZeneca, Venez.*
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension; left-ventricular dysfunction.

Atacand HCT *AstraZeneca, Braz.; AstraZeneca, USA.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Atacand Plus *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Fin.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; Teva, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, Venez.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Atacand-D *AstraZeneca, Arg.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

AtacandZid *AstraZeneca, Denm.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Atalak *Sons, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Atalin *Gemballa, Braz.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Ataline *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma; obstructive airways disease.

Atamel *Pfizer, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Atamel Plus *Pfizer, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Atamelco *Pfizer, Venez.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Atamet *Athena Neurosciences, USA.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Atamir *Sandoz, Denm.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; rheumatoid arthritis; Wilson's disease.

Atano *Milano, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety disorders; hypersensitivity reactions; pruritus.

Atanol *Remedina, Gr.*
Trimetazidine (p.1419·2).

Atapec *Gemballa, Braz.†.*
Homatropine methylbromide (p.1881·3); furazolidone (p.834·3); pectin (p.2145·2).
Diarrhoea.

Atapryl *Athena Neurosciences, USA.*
⊗ Selegiline hydrochloride (p.817·1).

Ataralgin *Medicamenta, Cz.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); caffeine (p.1116·3).
Influenza symptoms; pain.

Atarax
Note.This name is used for preparations of different composition.
UCB, Austria; UCB, Belg.; Erfa, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; UCB, Gr.; UCB, Hong Kong; UCB, Hung.; UCB, India; UCB, Ital.; UCB, Malaysia; UCB, Mex.; UCB, Neth.; UCB, Norw.; UCB, Pol.; UCB, Rus.; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, Thai.; UCB, Turk.; Pfizer, UK; Pfizer, USA†.
Hydroxyzine hydrochloride (p.581·2).
Alcohol withdrawal syndrome; allergic skin reactions; anxiety; hypersensitivity reactions; insomnia; motion sickness; nausea and vomiting; nervous disorders; premedication; pruritus; urticaria.

Mersifarma, Indon.
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

UCB, Port.; UCB, Singapore.
Hydroxyzine (p.581·2).
Anxiety; premedication; pruritus.

Ataraxone *Lazar, Arg.*
Hydroxyzine hydrochloride (p.581·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; anxiety.

Atarin *Leiras, Fin.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Ataroc *Novell, Indon.*
⊗ Procaterol hydrochloride (p.1130·2).
Dyspnoea.

Atarva *Duncan, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Atarviton *Erfar, Gr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; premedication; skeletal muscle spasm; sleep disorders; status epilepticus; tetanus.

Atasol
Note. A similar name is used for preparations of different composition (see below).
Church & Dwight, Canad.
Paracetamol (p.108·1).
Fever; pain.

Atasol-8, -15, -30 *Church & Dwight, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine citrate (p.1116·3).
Fever; pain.

Ataspin *Atabay, Turk.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Atassol
Note. A similar name is used for preparations of different composition (see above).
Solfran, Mex.
Dextromethorphan (p.1555·2).
Coughs.

Atazid *AstraZeneca, Denm.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Atcard *Utopian, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atd *Biolab, Hong Kong; Biolab, Thai.†.*
Fluoxetine hydrochloride (p.391·2).
Anxiety; depression.

Ate *ABZ, Ger.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Ate Lich *Winthrop, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ate Lich comp *Winthrop, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atebemyxine *Chauvin, Fr.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Ateben *Pharmacia, Arg.†.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Atebeta *Betapharm, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Ateblocor *ProMed, Cz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atecard *Cazi, Braz.; Dabur, India†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atecard-D *Dabur, India†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atecilina *Gramon, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Atecor *Rowex, Irl.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atecor CT *Rowex, Irl.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atecortin *Jelfa, Pol.*
⊗ Hydrocortisone acetate (p.1535·2); oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Infected ear or eye disorders.

Atedon *Pharmavit, Cz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atedurex *Ecosol, Switz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atege *Inde, Spain.*
Antithymocyte immunoglobulin (rabbit) (p.1817·3).
Transplant rejection.

Atehexal *Hexal, Austral.; Hexal, Austria; Hexal, Cz.; Hexal, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atehexal comp *Hexal, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atehexal Compositum *Hexal, Rus.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atel
Note.This name is used for preparations of different composition.
Investi, Arg.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; heart failure; hypertension; myocardial infarction.

Betapharm, Ger.
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atel C *Hexal, Arg.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atel N *Hexal, Arg.†.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Atelec *Mochida, Jpn.*
Cilnidipine (p.1245·2).
Hypertension.

Atem *Promedica, Ital.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Atemaron N R30 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Atemperator
Note.This name is used for preparations of different composition.
Ivax, Arg.
Bromazepam (p.964·3).
Anxiety; delirium tremens.

Drugtech, Chile.
Magnesium valproate (p.511·3) or sodium valproate (p.508·2).
Epilepsy.

Armstrong, Mex.
Magnesium valproate (p.511·3).
Bipolar disorder; epilepsy; migraine.

Atemur *GSK, Ger.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Aten *Cadila, India.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Atenase *UCI, Braz.†.*
Niclosamide (p.151·1).
Cestode infections.

Atenativ *Octapharma, Austria; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Gr.; Octapharma, Hung.; Kedrion, Ital.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Spain; Octapharma, Swed.; Octapharma, Switz.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency; thromboembolic disorders.

Atenblock *Merck, Fin.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Atend *ZLB Behring, Mex.*
An antithrombin III preparation (p.1054·1).
Antithrombin III deficiency.

Atendol *Pohl, Ger.†.*
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Atenegran *Legrand, Braz.*
⊗ Atenolol (p.1217·3).
Hypertension.

Ateneo *Neo Quimica, Braz.*
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension.

Atenet *Nycomed, Denm.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenetic *Gerard, Irl.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenfar *Medipharm, Chile.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Ateni *Gerard, Irl.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

AteNif beta *Betapharm, Ger.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Atenigron *Mitim, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenil *Ecosol, Switz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenix
Note. This name is used for preparations of different composition.
Raffo, Arg.
Sertraline (p.422·1).
Depression.

Tecnofarma, Chile.
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Ashbourne, UK.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

AtenixCo *Ashbourne, UK.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Ateno *Alpharma-Isis, Ger.; Jean-Marie, Hong Kong†.*
⊗ Atenolol (p.1217·3).
Alcohol withdrawal syndrome; angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Ateno comp *Alpharma-Isis, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenobal *Baldacci, Braz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

ateno-basan *Schonenberger, Switz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

ateno-basan comp *Schonenberger, Switz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenobene *Ratiopharm, Cz.; Ratiopharm, Hung.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenoblock *Klonal, Arg.*
⊗ Atenolol (p.1217·3).
Hypertension.

Atenoblok *Triomed, S.Afr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Atenoblok Co *Triomed, S.Afr.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenoclor *Vitapan, Braz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenodan *Pharmacodane, Denm.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenogamma *Worwag, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atenogamma comp *Worwag, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenogen *Antigen, Irl.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenokin *Kinder, Braz.*
⊗ Atenolol (p.1217·3).
Hypertension.

Atenol *AstraZeneca, Braz.; Pfizer, Fin.; CT, Ital.; Merck, Mex.; TO-Chemicals, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Atenolab *Multilab, Braz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenolac *Lacer, Port.†.*
⊗ Atenolol (p.1217·3).

Atenolan *Lannacher, Austria; Lannacher, Rus.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenolan comp *Lannacher, Austria.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenolol AL comp *Aliud, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenolol comp *Genericon, Austria; Ratiopharm, Austria; Aliud, Ger.; CT, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Stada, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenolol Comp *BMS, Hung.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenolol Compositum *Merckle, Cz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenomel *PannonPharma, Hung.; Clonmel, Irl.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenopress *Hexal, Braz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atenor *Sandoz, Denm.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenoric *Neo Quimica, Braz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenorm *Cifarma, Braz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Atenos
Note. This name is used for preparations of different composition.
UCB, Austria.
Pentoxyverine (p.1567·3), pentoxyverine citrate (p.1567·3), or pentoxyverine hydrochloride (p.1567·3).
Coughs.

UCB, Ger.; UCB, Port.†.
⊗ Tulobuterol hydrochloride (p.1150·1).
Obstructive airways disease.

Atenotop *Topgen, Belg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atenotyrol *Tyrol, Austria†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenotyrol comp *Tyrol, Austria†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atenoval *Valmor, Venez.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Atenovit *Vitarum, Arg.*
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension.

Atens *Farmasa, Braz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Atens H *Farmasa, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Atensec *Neo Quimica, Braz.*
Ramipril (p.1385·3).
Hypertension.

Atenses *Novag, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Atensin *Medochemie, Thai.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Atensina *Boehringer Ingelheim, Braz.*
Clonidine hydrochloride (p.1247·1).
Hypertension; opioid withdrawal syndrome.

Atenual *Tecnofarma, Chile.*
Clomipramine (p.387·1).
Depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain.

Atenuol *Greenpharma, Braz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atenuol CRT *Greenpharma, Braz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Atepadene *Sidus, Arg.†; Mayoly-Spindler, Fr.*
Adenosine triphosphate disodium (p.2247·3).
Fibromyalgia; fibromyositis; pain.

Atepodin *Medix, Spain.*
Adenosine triphosphate sodium (p.2247·3).
Arrhythmias; muscular dystrophies; prevention of anoxia.

Atepress *Teuto, Braz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ateran *Eurofarmaco, Ital.†.*
A heparinoid (p.1305·2).
Thrombosis prophylaxis.

Aterax *UCB, S.Afr.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions; premedication; sedative.

Aterina *Tedec Meiji, Spain.*
Sulodexide (p.1406·3).
Atherosclerosis; hyperlipidaemias; thromboembolic disorders.

Aterkey *Inkeysa, Spain.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Atermin *Magis, Ital.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ateroclar
Note. This name is used for preparations of different composition.
Beta, Arg.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Drugtech, Chile.
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Medibase, Ital.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Ateroclar Duo *Beta, Arg.*
Ezetimibe tablets (p.1284·3); atorvastatin calcium tablets (p.1218·3).
Hypercholesterolaemia.

Ateroid *Cornelli, Ital.*
A heparinoid (p.1305·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Thrombosis prophylaxis.

Aterostat *Leksir, Rus.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Ateroxide *Difass, Ital.*
A heparinoid (p.1305·2).
Venous ulcer.

Atesifar *Siphar, Switz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Atestad *Stada, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

At-Eze *Douglas, NZ.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

ATG *Fresenius, Belg.; Fresenius Biotech, Cz.; Fresenius, Hong Kong; Fresenius, Israel; Fresenius Kabi, Neth.; Fresenius Medical, Pol.; Fresenius Hemocare, Singapore†; Fresenius Medical, Swed.; Fresenius Medical, Switz.; Fresenius Biotech, Thai.*
An antithymocyte immunoglobulin (rabbit) (p.1817·3).
Graft-versus-host disease; transplant rejection.

Atgam *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pharmacia Upjohn, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pharmacia, Spain†; Pfizer, Switz.†; Upjohn, USA; Pfizer, Venez.*
Antithymocyte immunoglobulin (horse) (p.1817·3).
Aplastic anaemia; immunosuppressant; renal transplant rejection.

Athenol *SMB, Belg.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Athera *Lane, UK.*
Parsley (p.2363·2); vervain (p.2413·3); senna leaf (p.1769·2); clivers (p.2284·3).
Menopausal symptoms.

Atherovit *Beres, Hung.*
Folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B deficiency; vitamin B supplement.

Athimil *Organon, Chile; Organon, Venez.†.*
Mianserin hydrochloride (p.408·1).
Depression.

Athletes Foot *Schering, Arg.†; Scholl, Hung.†; Scholl, Israel.*
Tolnaftate (p.548·3).
Tinea pedis.

Athos
Note. This name is used for preparations of different composition.
Roemmers, Arg.
Ivy (p.2328·1).
Respiratory-tract disorders.

Medix, Mex.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Athril *TO-Chemicals, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Athrofen *Amino, Switz.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Athymil *Organon, Fr.*
Mianserin hydrochloride (p.408·1).
Depression.

Atibax C *Fabop, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Atifan *KRKA, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Atiflan *Ederka, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Atimos *Torrex, Cz.; Torrex, Hung.; Chiesi, Ital.; Torrex, Pol.; Chiesi, Port.; Chiesi, Rus.*
⊗ Formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Atimos Modulite *Trinity, UK.*
⊗ Formoterol fumarate (p.1122·1).
Asthma.

Atinac *Diffucap, Braz.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

A-Tinic *Polipharm, Thai.†.*
Tretinoin (p.1618·1).
Sun-induced skin damage.

Atinorm
Note. This name is used for preparations of different composition.
Chrispa (Χρισπα), Gr.
Citalopram (p.385·3).
Depression.

Bioprogress, Ital.
⊗ Atenolol (p.1217·3); indapamide (p.1314·1).
Hypertension.

Atiramin *Juste, Spain.*
Azatadine maleate (p.568·1); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Atisuril *Altana, Mex.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Atiten *Bayer, Ital.*
Dihydrotachysterol (p.1986·3).
Hypoparathyroidism; pseudohypoparathyroidism.

Ativan *Sigma, Austral.; Wyeth, Canad.; IFET (ΙΦΕΤ), Gr.; Wyeth, Hong Kong†; Wyeth, India; Sunthi Sepuri, Indon.; Wyeth, Indon.; Wyeth, Irl.; Wyeth, Malaysia; Wyeth, Mex.; Healthcare Logistics, NZ; Akromed, S.Afr.; Wyeth, Singapore; Wyeth-Ayerst, Thai.†; Wyeth, Turk.; Wyeth, UK; Biovail, USA; Wyeth, Venez.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; mania; mixed anxiety depressive states; nausea and vomiting; premedication; sedative; status epilepticus.

Atizor *Medipharm, Chile.*
Azithromycin (p.207·1).
Bacterial infections.

Atkinson & Barker's Gripe Mixture *Torbet Laboratories, UK.*
Sodium bicarbonate (p.1673·2); caraway oil (p.2277·1); dill oil (p.2293·3).
Formerly contained light magnesium carbonate, sodium bicarbonate, fennel oil, and dill oil.
Infant colic.

Atlacne *Atlas, Arg.*
Isotretinoin (p.1599·2).
Acne.

Atlamicin *Atlas, Arg.*
Erythromycin (p.269·2).
Acne.

Atlansil *Roemmers, Arg.; Sanofi-Aventis, Braz.; Pharma Investi, Chile.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Atma *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Atmadisc *Sanol, Ger.; Schwarz, Ger.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Atmocol *Adams, UK.*
A deodorant spray for use with colostomies and ileostomies.

Atmos
Note. This name is used for preparations of different composition.
Eurofarma, Braz.
Amlodipine besilate (p.1214·1); enalapril maleate (p.1276·1).
Hypertension.

AstraZeneca, Fin.; AstraZeneca, Norw.; AstraZeneca, Swed.
⊗ Testosterone (p.2129·3).
Erectile dysfunction; hypogonadism; osteoporosis.

Atmose *Morishita, Philipp.*
Mefenamic acid (p.80·1).
Osteoarthritis; pain; rheumatoid arthritis.

Atoactive *Biodue, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Atock *Astellas, Jpn; Astellas, Philipp.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Atodel *Remedica, Malaysia; Remedica, Thai.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Atoderm
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Arg.†.
Dimeticone (p.2032·1).
Barrier preparation.

Bioderma, Ital.; Bioderma, Venez.
Emollient.
Dry skin disorders.

Atoderm creme *Bioderma, Fr.*
Emollient.
Dry skin disorders.

Atoderm moussant *Bioderma, Fr.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Cleansing of dry skin.

Atogal *Ingers, Cz.*
Atorvastatin (p.1219·1).

Atoken *Kendrick, Mex.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Atoksilin *Atabay, Turk.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Atolant *Mitsubishi, Jpn.*
Neticonazole hydrochloride (p.543·1).
Fungal skin infections.

Atolone *Major, USA.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Atomase *Douglas, Malaysia†; Douglas, NZ; Douglas, Singapore†; Douglas, Thai.; TTN, Thai.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Atomax *Makiz-Pharma, Rus.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Atomic Enema *Health Chemical, Hong Kong.*
Sodium chloride (p.1686·1).
Constipation.

Atomide *Douglas, NZ†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Atomo Desinflamante *Imvi, Arg.*
Amyl salicylate (p.19·3); camphor (p.2273·2); menthol (p.2340·1); terpineol (p.2396·1); cineole (p.2282·3); guaiacol (p.1561·2).
Musculoskeletal, joint, and peri-articular disorders.

Atomo Desinflamante C *Imvi, Arg.*
Amyl salicylate (p.19·3); camphor (p.2273·2); turpentine oil (p.2406·3); salicylic acid (p.1612·2); capsaicin (p.32·3).
Musculoskeletal and joint disorders; neuralgia.

Atomo Desinflamante Depor *Imvi, Arg.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Atomo Desinflamante Familiar *Imvi, Arg.*
Camphor (p.2273·2); menthol (p.2340·1); amyl salicylate (p.19·3); cineole (p.2282·3); terpineol (p.2396·1); guaiacol (p.1561·2).
Musculoskeletal, joint, and soft-tissue disorders.

Atomo Desinflamante G *Imvi, Arg.*
Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3); terpineol (p.2396·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Atomo Desinflamante Geldic *Imvi, Arg.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; oedema.

Atomo Desinflamante Ibu *Imvi, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Atomoderma A *Imvi, Arg.*
Vitamin A (p.1971·2).
Skin disorders.

Atomoderma A-D *Imvi, Arg.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); cod-liver oil (p.1935·2).
Skin disorders.

Atomoderma A-E *Imvi, Arg.*
Vitamin A palmitate (p.1973·1); tocoferil acetate (p.1992·3); allantoin (p.1588·1).
Skin disorders.

Atomoderma Plus *Imvi, Arg.*
⊗ Hydrocortisone (p.1535·2); fish-liver oil; cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Anorectal disorders; skin disorders.

Atopic
Note. This name is used for preparations of different composition.
Dermoteca, Port.†.
Bath gel: Lactic acid (p.2329·3).
Dry skin disorders.

Dermoteca, Port.†.
Cream; topical emulsion: Evening primrose oil (p.2302·1); lactic acid (p.2329·3).
Dry skin disorders.

Atopiclair *Ashbourne, UK; Graceway, USA.*
Enoxolone (p.50·1); piroctone olamine (p.1610·1); allantoin (p.1588·1); grape (p.2316·3); sodium hyaluronate (p.2320·1); telmesteine (p.1573·3).
Atopic eczema; skin disorders.

Atopil *IDI, Ital.†.*
Borage oil; vitamins; selenium (p.1922·1).
Nutritional supplement.

Ator *Sanovel, Turk.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Ator-Chol *Farmedia, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorgon *Proel, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atoris
KRKA, Cz.; KRKA, Hung.; KRKA, Rus.
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

KRKA, Pol.
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Atorlip *Pharmavita, Chile; Cipla, India.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Atorolnga *Lamda (Λαμδα), Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorpharm *Medis, Cz.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Atorsan *Sandoz, Indon.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Atorstat *Specifar (Σπεσιφαρ), Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorva *Teva, Hung.; Zydus, India.*
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Atorval *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorvanox *Verisfield, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorvastan *Biotenk, Arg.*
Atorvastatin (p.1219·1).
Atherosclerosis; hypercholesterolaemia.

Atorvin *Aurora, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atorvox *Gedeon Richter, Hung.*
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Atosil *Bayer, Ger.*
Promethazine hydrochloride (p.588·2).
Agitation; hypersensitivity reactions; insomnia; nausea and vomiting; restlessness.

Atossa *Anpharm, Pol.; ICN, Pol.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Atossion *Elofar, Braz.*
Dropropizine (p.1557·3).
Coughs.

Atossisclerol Kreussler *Gloria, Ital.*
Lauromacrogol 400 (p.1916·1).
Sclerotherapy of varices.

Atostan *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Somatostatin (p.1809·1).

Atouxx *Schwarz, Fr.*
Isomyrtol; pholcodine (p.1570·2).
Cough.

Atovarol *Vivax, Venez.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Atoxecar *Beta, Arg.†.*
Oxcarbazepine (p.490·3).
Epilepsy.

ATP *Hebron, Braz.†.*
Amino-acid preparation (p.1922·1).

ATP-Daiichi *Daiichi, Hong Kong.*
Adenosine triphosphate, disodium salt (p.2247·3).
Cardiovascular disorders; eye disorders; vestibular disorders.

Atractil *Trenker, Hong Kong; Trenker, Thai.*
⊗ Diethylpropion (p.2154·3).
Obesity.

Atralcilina *Atral, Port.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Atralidon *Atral, Port.*
Paracetamol (p.108·1).
Fever; pain.

Atralin *Coria, USA.*
Tretinoin (p.1618·1).
Acne.

Atralmicina *Atral, Port.*
Benethamine penicillin (p.212·1); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Atralxitina *Atral, Port.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Atram *Zentiva, Cz.; Zentiva, Pol.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Atranac *Corsa, Indon.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Atrederm *Pliva Krakow, Pol.*
Tretinoin (p.1618·1).
Acne.

Atretol *Athena Neurosciences, USA†.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Atrexel *Schering-Plough, Mex.*
Methotrexate (p.745·2).
Rheumatoid arthritis.

Atriance *GSK, Cz.; GSK, UK.*
Nelarabine (p.755·3).
Acute lymphoblastic leukaemia; lymphoblastic lymphoma.

Atrican *Innotech, Fr.; Innotech, Rus.*
Tenonitrozole (p.848·1).
Urogenital trichomoniasis.

Atridox *Sidus, Arg.; Atrix, Denm.†; Meda, Fin.†; Atrix, Ger.; Curasan, Ger.; Ebedent, Gr.; Essential Dental, NZ†; Atrix, Neth.; Atrix, Port.; Meda, Swed.; Heinimann, Switz.; Oraldent, UK; CollaGenex, USA.*
Doxycycline hyclate (p.267·1).
Bacterial mouth infections.

Atrilon *Byk, Port.†.*
Lonazolac calcium (p.77·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Atrimon
Note. This name is used for preparations of different composition.
Ivax, Arg.
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Combined injectable contraceptive.

Nolver, Venez.
Zolpidem tartrate (p.1037·3).
Insomnia.

Atripla *Gilead, UK; BMS, USA.*
Efavirenz (p.872·3); emtricitabine (p.873·3); tenofovir disoproxil fumarate (p.908·3).
HIV infection.

Atriscal *Lacer, Spain.*
Dexibuprofen (p.39·2).
Dysmenorrhoea; osteoarthritis; pain.

Atriser *Serral, Mex.*
Sulindac (p.126·3).
Inflammation.

Atrisol *Quimica y Farmacia, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension.

Atrisolon *Andre, India.*
⊗ Atropine sulfate (p.1219·3); prednisolone (p.1540·3).
Inflammatory eye disorders.

Atrium *Sapos, Hung.†.*
Febarbamate (p.996·1); difebarbamate (p.994·2); phenobarbital (p.492·2).
Alcohol withdrawal syndrome.

Atrival *Defuen, Arg.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Atrivex *Multicare, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with abnormal mucus; upper respiratory-tract inflammation.

Atro Grin *Grin, Mex.†.*
Atropine sulfate (p.1219·3).
Production of mydriasis.

Atro Ofteno *Sophia, Mex.*
Atropine (p.1219·2).
Production of mydriasis and cycloplegia.

Atrobel
Note. This name is used for preparations of different composition.
Fawns & McAllan, Austral.†.
Belladonna herb (p.2263·3).
Peptic ulcer; reduction of secretions; smooth muscle spasm.

Ronava, Venez.
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3); hyoscyamus (p.2323·3); paregoric (p.105·1); star anise (p.2392·1).

Atrodual *Boehringer Ingelheim, Fin.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Atrogel *Bioforce, UK.*
Arnica (p.2260·2).
Bruises; muscle pain.

Atroil *Rafarm, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Atrombin *Leiras, Fin.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Atromicin *Teuto, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Atromid-S *AstraZeneca, Port.†.*
Clofibrate (p.1246·2).

Atromizin *Cafar, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Atronase *Boehringer Ingelheim, Belg.*
Ipratropium bromide (p.1124·1).
Rhinitis.

Atrop *Upha, Malaysia†.*
Atropine sulfate (p.1219·3).
Production of mydriasis and cycloplegia.

AtroPen *Meridian, USA.*
Atropine sulfate (p.1219·3).
Organophosphorus or carbamate pesticide poisoning.

Atrophena *Spefar, Venez.†.*
Papaverine hydrochloride (p.2191·3).

Atropicel *Oftalmi, Venez.†.*
Atropine sulfate (p.1219·3).
Production of cycloplegia and mydriasis.

Atropinol *Winzer, Ger.†.*
Atropine (p.1219·2).
Production of mydriasis.

Atropion *Ariston, Braz.*
Atropine sulfate (p.1219·3).
Arrhythmias.

Atropisa *Pisa, Mex.*
Atropine (p.1219·2).

Atropisol *Novartis Ophthalmics, Canad.†.*
Atropine sulfate (p.1219·3).
Production of mydriasis and cycloplegia.

Atropocil *Edol, Port.*
Atropine sulfate (p.1219·3).
Production of mydriasis and cycloplegia.

Atropt *Sigma, Austral.; Healthcare Logistics, NZ.*
Atropine sulfate (p.1219·3).
Production of cycloplegia and mydriasis; production of mydriasis and cycloplegia.

Atropulm *Julphar, UAE.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Atrosan *Bioforce, UK.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Atrosept *Geneva, USA.*
Methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1); benzoic acid (p.1630·2); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

Atrosol *Sanovel, Turk.*
Atropine sulfate (p.1219·3).
Production of mydriasis and cycloplegia.

Atrospan *Fischer, Israel.*
Atropine sulfate (p.1219·3).
Production of cycloplegia and mydriasis.

Atrost *Gap, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atrosterol *Kleva, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atrotil *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Atrovent *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Teijin, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.*
Ipratropium bromide (p.1124·1).
Allergic rhinitis; asthma; obstructive airways disease; rhinorrhoea.

Atrovent Beta *Boehringer Ingelheim, S.Afr.*
⊗ Ipratropium bromide (p.1124·1); fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Atrovent Comp *Boehringer Ingelheim, Fin.*
⊗ Ipratropium bromide (p.1124·1); fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Atroveran *Vargas, Venez.*
Papaverine (p.2191·3); belladonna (p.2263·3); hyoscyamus (p.2323·3).
Smooth muscle spasm.

Atrovita *Faran, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Atrox *Biofarm, Pol.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Atrozol *Vipharm, Pol.*
⊗ Anastrozole (p.681·2).
Breast cancer.

ATryn *Leo, Cz.; Leo, Port.; Leo, UK.*
Antithrombin alfa (p.1054·2).
Antithrombin III deficiency.

ATS *Hoechst Marion Roussel, USA.*
Erythromycin (p.269·2).
Acne.

Atse *1A, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with excess and viscous mucus.

Attain *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Attempta *Ratiopharm, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Attenta *Alphapharm, Austral.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Attenuvax *Aventis Pasteur, Denm.†; MSD, Neth.†; Sanofi Pasteur, Switz.; Merck, USA.*
A live measles vaccine (Enders' Edmonston strain) (p.2221·3).
Active immunisation.

Attor *Biochem, India.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Aturgyl
Note. This name is used for preparations of different composition.
GSK, Braz.†.
⊗ Fenoxazoline hydrochloride (p.1560·3).
Nasal congestion.

Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinopharyngeal congestion.

Atus *Metapharma, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Atusil *Pediapharm, Chile.*
Promolate (p.1571·2).
Coughs.

Atuss DM *Atley, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs and associated respiratory-tract disorders.

Atuss-12 DM *Atley, USA.*
Pseudoephedrine polistirex (p.1572·1); chlorphenamine polistirex (p.572·2); dextromethorphan polistirex (p.1556·1).
Upper respiratory-tract disorders.

Atuss DS *Atley, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Atuss-12 DX *Atley, USA.*
Dextromethorphan polistirex (p.1556·1); guaifenesin (p.1561·3).
Coughs.

Atuss EX *Atley, USA†.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.

Atuss G *Atley, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.

Atuss HC *Atley, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Atuss HD *Atley, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).

Atuss HS *Atley, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Atuss HX *Atley, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Cough.

AT-V *Offenbach, Mex.†.*
Diazepam (p.986·3).

Atzirut X *CTI, Israel.*
Bisacodyl (p.1710·1).
Constipation.

AU 4 Regeneresen *Dyckerhoff, Ger.*
Ribonucleic acid (p.2379·1).
Ear disorders.

Aubeline *Arkopharma, Belg.; Arkopharma, Fr.*
Crataegus (p.2289·1).
Cardiac disorders; nervous disorders.

Aubril *Novartis, India.*
Trimethoprim (p.355·2); sulfadiazine (p.336·2).
Respiratory-tract infections; urinary-tract infections.

Aucic *Poen, Arg.*
Carmellose sodium (p.2142·1).
Dry eyes.

Aucusik *Andromaco, Chile.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1); benzyl alcohol (p.1631·3); menthol (p.2340·1).
Pruritus.

Audax *Mundipharma, Ger.†; SSL, Irl.; SSL, UK†.*
Choline salicylate (p.36·3).
Ear wax removal; earache.

Audazol *Lesvi, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Audi Baby *Diepharmex, Fr.*
Sea water.
External ear hygiene.

Audicort *Wyeth, Irl.†; Goldshield, UK†.*
⊗ Neomycin undecenoate (p.305·2); triamcinolone acetonide (p.1544·3).
Inflammatory ear disorders with bacterial infection; otitis externa.

Audifluor *Diba, Mex.*
Sodium fluoride (p.1962·2).
Otosclerosis.

Audione *Serra Pamies, Spain.*
Vitamins (p.1922·1); potassium iodide (p.2169·2).
Ear disorders; eye disorders.

Audispray *Diepharmex, Fr.*
Sea water.
External ear hygiene.

Audocaina *Organifar, Venez.†.*
Lidocaine (p.1862·3); phenazone (p.116·1); glycerol (p.2314·2).
Ear disorders.

Aufbaukalk I *Weleda, S.Afr.*
Homoeopathic preparation.

Aufbaukalk II *Weleda, S.Afr.*
Homoeopathic preparation.

Augclav *Pharmahof, Thai.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augelit *Catarinense, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Augenschutz NA *Salushaus, Ger.*
Vitamin A palmitate (p.1973·1).
Night-blindness.

Augentonicum *Medserve, Switz.*
Digitalis (p.1258·3); esculoside (p.2248·2).
Eye disorders.

Augentonikum N *Stulln, Ger.*
Digitalin (p.2293·3).
Eyestrain.

Augentropfen Mucokehl D5 *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Augentropfen Similasan *Jacoby, Austria.*
Homoeopathic preparation.

Augentropfen Stulln *Sanova, Austria.*
Digitalis (p.1258·3); esculoside (p.2248·2).

Augentropfen Stulln Mono *Stulln, Ger.*
Digitalis leaf (p.1258·3); esculoside (p.2248·2).
Eyestrain.

Augmaxcil *Triomed, S.Afr.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augmentan *GSK, Ger.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augmentin
GSK, Austral.; GSK, Chile; GSK, Fin.; GSK, Israel; GSK, USA.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; Teva, Hung.; GSK, Irl.; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Venez.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Braz.
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, India.
Amoxicillin (p.202·2), amoxicillin sodium (p.202·2), or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Indon.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Turk.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

GSK, UK.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
These ingredients can be described by the British Approved Name Co-amoxiclav.
Bacterial infections.

Augmentin Bid
GSK, Chile.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Venez.†.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augmentin-Duo *GSK, Cz.; GSK, Hung.; GSK, UK.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
These ingredients can be described by the British Approved Name Co-amoxiclav.
Bacterial infections.

Augmentine *GSK, Spain.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augmentin-Extra *GSK, Hung.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augmex
Korea United, Philipp.; Pharmatrix, Philipp.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Korea United, Singapore†.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Augort *Andromaco, Spain†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Augpen *Emcure, Thai.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Augurcin *Aldril, Philipp.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Aulcer *Alacan, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aulin *Grunenthal, Arg.†; CSC, Austria; Essex, Chile†; Medicom, Cz.; Lavipharm, Gr.; Helsinn Birex, Indon.; Helsinn Birex, Irl†.; Roche, Ital.; Essex, Philipp.; Medicom, Pol.; Angelini, Port.; Vifor, Switz.; Schering-Plough, Venez.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Aulo Gelio Pie *Aulo Gelio, Arg.*
Camphor (p.2273·2); vitamin A (p.1971·2).
Foot disorders.

Aulo Gelio Repelente *Aulo Gelio, Arg.*
Citronella oil (p.2284·2).
Insect repellent.

Aulo Repelente De Piojos *Aulo Gelio, Arg.*
Citronella oil (p.2284·2); rue (p.2382·2); quassia (p.2377·1); eucalyptus citriodora oil.
Insect repellent.

Aunativ *Octapharma, Austria†; Pharmacia, Cz.†; Octapharma, Denm.†; Octapharma, Gr.; Octapharma, Norw.†; Octapharma, Swed.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Auradol *Lusofarmaco, Ital.*
Frovatriptan succinate (p.622·3).
Migraine.

Auralgan
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.; Wyeth Consumer, Canad.; Whitehall, NZ.
Benzocaine (p.1854·1); phenazone (p.116·1); glycerol (p.2314·2).
Ear wax removal; earache; otitis media.

Wyeth, Philipp.
Phenazone (p.116·1); benzocaine (p.1854·1); hydroxyquinoline sulfate (p.2323·1).
Ear wax removal; otitis media.

Wyeth-Ayerst, Thai.†.
Benzocaine (p.1854·1); phenazone (p.116·1).
Ear wax removal; otitis media.

Deston, USA.
Benzocaine (p.1854·1); phenazone (p.116·1); acetic acid (p.2244·2); polycosanol; glycerol (p.2314·2).
Acute otitis media; ear wax removal.

Auralyt
Note. This name is used for preparations of different composition.
Wyeth Consumer, Mex.
Benzocaine (p.1854·1).

SA Druggists Self Med, S.Afr.
Glycerol (p.2314·2); phenazone (p.116·1); benzocaine (p.1854·1).
Ear wax removal; otitis media.

Auram *Ache, Braz.*
Oxcarbazepine (p.490·3).
Epilepsy; trigeminal neuralgia.

Auramin *ICN, Austria.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Aurantin *Pfizer, Ital.*
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy.

Auraphene-B *Reese, USA.*
Urea hydrogen peroxide (p.1666·2).

Aurasept *Adcock Ingram, S.Afr.*
Benzocaine (p.1854·1); phenazone (p.116·1).
Otitis.

Auratek hCG *Bio Merieux, UK†.*
Pregnancy test (p.2372·1).

Aureciclina *Sanval, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Aurecil *Edol, Port.†.*
Chlortetracycline hydrochloride (p.243·1).
Bacterial eye infections.

Aurene *Ivax, Arg.*
Oxcarbazepine (p.490·3).
Epilepsy.

Aureocort *Dermapharm, Austria; Teofarma, Ital.; Goldshield, UK.*
⊗ Chlortetracycline hydrochloride (p.243·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Aureocrem *Puebla, Arg.*
Polysaccharides of *Pseudomonas aeruginosa*.

Aureodelf *Lederle, Ger.†.*
⊗ Chlortetracycline hydrochloride (p.243·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Aureodermil *Edol, Port.†.*
Chlortetracycline hydrochloride (p.243·1).
Bacterial skin infections.

Aureomicina *Wyeth Lederle, Ital.; Alcon Cusi, Spain.*
Chlortetracycline hydrochloride (p.243·1).
Bacterial infections.

Aureomix *SIT, Ital.*
Chlortetracycline hydrochloride (p.243·1); sulfacetamide sodium (p.335·3).
Ear, nose, mouth, throat, and eye infections.

Aureomycin
Dermapharm, Austria; Erfa, Belg.; Riemser, Ger.; Wyeth Lederle, Norw.†; US Summit, Thai.
Chlortetracycline hydrochloride (p.243·1).
Bacterial infections.

Wyeth, Hong Kong†.
Chlortetracycline (p.242·3).
Bacterial infections.

Aureomycin N *Wyeth, Ger.†.*
Chlortetracycline hydrochloride (p.243·1); nystatin (p.543·2).
Vaginal infections.

Aureomycine *Meda, Belg.; Cooperation Pharmaceutique, Fr.; UCB, Fr.*
Chlortetracycline hydrochloride (p.243·1).
Eye and skin infections.

Aurex *Hexal, Pol.*
Citalopram hydrobromide (p.385·3).
Depression.

Auricam *Collins, Mex.*
Meloxicam (p.80·3).
Inflammation.

Auricid *Day, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Auricularum *Grimberg, Fr.; Grimberg, Israel.*
⊗ Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2); nystatin (p.543·2).
Otitis.

Auricum *Dolisos, Canad.†.*
Homoeopathic preparation.

Aurid *Pharmathen, Gr.*
⊗ Budesonide (p.1520·1).

Auriderm K2
Medstyle, Chile.
Vitamin K (p.1995·2).
Skin discoloration.

Auriga, Hong Kong.
Vitamin K (p.1995·3).
Erythema; haematomas; pre- and post- injection of wrinkle-filling product; pre- and post- sclerotherapy; purpura.

Auridonal *Ducto, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial ear infections.

Aurigen *Mavi, Mex.†.*
Allopurinol (p.552·2).
Gout.

Aurigoutte *Merck Medication Familiale, Fr.*
Hexamidine isetionate (p.1646·3); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Aurimel *MSD, Venez.†.*
Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2).
Cough.

Auristan *Monin, Fr.†.*
Phenylephrine hydrochloride (p.1568·1).
Otitis externa.

Auritricin *Delta, Braz.*
Tyrothricin (p.358·2); etyl metaborate; chlorobutanol (p.1639·2).
Ear infections.

Aurituss *Pediapharm, Chile; Recalcine, Chile.*
⊗ Salmeterol (p.1135·3); fluticasone (p.1533·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Auro *Del, USA.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Auroanalin N *Hevert, Ger.†.*
Glycol salicylate (p.62·3).
Inflammation; rheumatism.

Auroanalin Thermo *Hevert, Ger.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Aurobemid *Stada, Austria.*
Moclobemide (p.411·1).
Depression.

Aurobin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
⊗ Prednisolone caproate (p.1541·1); lidocaine hydrochloride (p.1862·3); dexpanthenol (p.2362·1); triclosan (p.1665·2).
Anorectal disorders.

Aurocalcin *Farmilia, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Aurochobet *Chobet, Arg.*
Calcium gold keratinate (p.62·3).
Musculoskeletal and joint disorders.

Auroclim *Juste, Spain.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Aurodipine *Aurora, Gr.*
Nimodipine (p.1357·2).
Ischaemic nervous system disorders.

Aurodren *Aurora, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Auro-Dri *Del, Canad.; Del, USA.*
Isopropyl alcohol (p.1650·3).
Ear disorders; water in the ear.

Aurofox *Salus, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Auroguard Otic *SDA, USA.*
Benzocaine (p.1854·1); phenazone (p.116·1); hydroxyquinoline sulfate (p.2323·1).
Ear disorders.

Auroken *Kendrick, Mex.†.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive disorders.

Aurolate *Pasadena, USA.*
Sodium aurothiomalate (p.122·2).

Auromelid *Farmilia, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Auromyose *Organon, Neth.†.*
Aurothioglucose (p.26·2).
Rheumatoid arthritis.

Auronal *Egis, Cz.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Aurone *Lennon, S.Afr.*
Phenazone (p.116·1).
Earache.

Aurone Forte *SA Druggists Self Med, S.Afr.*
Phenazone (p.116·1); benzocaine (p.1854·1); chlorobutanol (p.1639·2).
Inflammatory ear disorders with infection.

Auropan *KRKA, Rus.*
Auranofin (p.25·3).

Auroplatin *Steigerwald, Ger.*
Homoeopathic preparation.

Aurorex *Roche, Mex.*
Moclobemide (p.411·1).
Depression; social phobia.

Aurorix *Roche, Arg.†; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Malaysia; Roche, NZ†; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.*
Moclobemide (p.411·1).
Depression; panic disorder; social anxiety disorder; social phobia.

Aurostatin *Aurora, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Aurosyx N *Syxyl, Ger.†.*
Homoeopathic preparation.

Auroto *Barre-National, USA†.*
Benzocaine (p.1854·1); phenazone (p.116·1).
Earache.

Auroxicam *Aurora, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Auroxidol *Aurora, Gr.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Aurum-Gastreu S R2 *Reckeweg, Ger.*
Homoeopathic preparation.

Aurumheel *Peithner, Austria.*
Homoeopathic preparation.

Auscap *Sigma, Austral.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Auscard *Sigma, Austral.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Ausclav *Sigma, Austral.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ausentron *Laboratorios Chile, Chile.*
Clomipramine (p.387·1).
Depression; nocturnal enuresis; obsessive-compulsive disorder; premature ejaculation.

Ausfam *Arrow, Austral.; Arrow, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ausgem *Sigma, Austral.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Auspilic *Pharos, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Auspril *Sigma, Austral.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ausran *Sigma, Austral.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aussie Tan
Note. This name is used for preparations of different composition.
Or-Dov, Austral.†.
SPF 4: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Or-Dov, Austral.
SPF 7: Octinoxate (p.1608·2); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Or-Dov, Austral.
SPF 15 Lotion: Octinoxate (p.1608·2); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Or-Dov, Austral.
SPF 15 Topical gel: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Aussie Tan Pre-Tan *Or-Dov, Austral.*
Tyrosine (p.1971·1); tyrosinase.
To accelerate tanning.

Aussie Tan Skin Moisturiser *Or-Dov, Austral.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).

Aussie Tan Sunstick *Or-Dov, Austral.*
Salol (p.122·1).
Sunscreen.

Austrapen *Lennon, Austral.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Austrophyllin *Petrasch, Austria†.*
Diprophylline (p.1120·2).

Aut *Elea, Arg.†.*
Pyrantel embonate (p.155·1).
Gastrointestinal worm infections.

Autdol *Laboratorios Chile, Chile.*
Diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Aution Sticks 10EA *Menarini Diagnostics, Port.†.*
Test for glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrites, and leucocytes in urine.

Autoderm Extra *Ecolab, Ger.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3); benzyl alcohol (p.1631·3).
Skin disinfection.

Autohaler *Cipla, India†.*
⊗ Isoprenaline sulfate (p.1316·3).
Obstructive airways disease.

Autohelios *Roche-Posay, Arg.†; Roche-Posay, Braz.*
Dihydroxyacetone (p.1594·1).
Sunscreen adjunct.

Autoplasme Vaillant *SERP, Mon.*
Black mustard (p.2349·1).
Respiratory-tract congestion.

Autoplex *Baxter, Ger.†; Baxter, Swed.†.*
A factor VIII inhibitor bypassing fraction (p.1068·2).
Haemorrhage in patients with inhibitors to factor VIII.

Autoplex T *Baxter, Malaysia†; Nabi, USA†.*
A factor VIII inhibitor bypassing fraction (p.1068·2).
Haemorrhage in patients with inhibitor to factor VIII.

Autrin
Note. This name is used for preparations of different composition.
Wyeth, India; Wyeth, Mex.†; Pharmacare, S.Afr.
Ferrous fumarate (p.1938·3); folic acid; vitamin B (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Wyeth, Venez.†.
Capsules: Ferrous sulfate (p.1939·3); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Wyeth, Venez.†.
Syrup: Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Autrinic Compuesto *Wyeth, Arg.†.*
Ferrous fumarate (p.1938·3); ascorbic acid; vitamin B ; intrinsic factor; folic acid (p.1922·1).
Anaemias.

Autritis *Pentafarma, Port.*
Indometacin (p.66·3).

Auxib *MSD, Austria; MSD, Neth.*
Etoricoxib (p.53·1).
Arthritic gout; gout; osteoarthritis; rheumatoid arthritis.

Auxiloson *Boehringer Ingelheim, Ger.†.*
⊗ Dexamethasone isonicotinate (p.1526·1).
Respiratory-tract disorders.

Auxina A + E *Chiesi, Spain.*
Vitamin A palmitate (p.1973·1); tocoferil acetate (p.1992·3).
Deficiency of vitamins A and E; eye disorders; infertility; recurrent miscarriage; skin disorders.

Auxina A Masiva *Chiesi, Spain.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Auxina E *Chiesi, Spain.*
Tocoferil acetate (p.1992·3).
Biliary-tract disorders; cystic fibrosis; hypoproteinaemia; vitamin E deficiency.

Auxitrans *Aerocid, Fr.*
Pentaerythritol (p.1761·1).
Constipation.

Auxofer *Magis, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Auxxil *Laboratorios Chile, Chile.*
Levofloxacin (p.292·2).
Bacterial infections.

Avaden *Schering, Braz.; Schering, Chile; Schering, Cz.†; Schering, Mex.; Schering, Neth.†; Schering, Venez.*
16 Tablets, estradiol (p.2097·2); 12 tablets estradiol; gestodene (p.2105·2).
Menopausal disorders; osteoporosis.

Avadene *Schering, Fr.; Bayer, Port.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; gestodene (p.2105·2).
Menopausal disorders; osteoporosis.

Avafontan *Alpharma, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Avafortan *Therabel, Fr.†.*
Camylofin hydrochloride (p.2274·1) or camylofin noramidopyrine mesilate (p.2274·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Avagard CHG *3M, Canad.*
⊗ Alcohol (p.1625·2); chlorhexidine gluconate (p.1635·3).

Avagard D *3M, Canad.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Avage *Allergan, USA.*
Tazarotene (p.1617·1).
Facial wrinkles; skin pigmentation disorders.

Avaglim *GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hung.; GSK, Port.*
Rosiglitazone maleate (p.458·2); glimepiride (p.441·1).
Diabetes mellitus.

Avail *Menley & James, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Avala *Farmasa, Mex.; DHU, Spain.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Avaldrian *Alpharma, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Avalide *BMS, Canad.; Sanofi Synthelabo, Canad.; BMS, Mex.; BMS, USA.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Avallone *Novartis, Austria.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Avalon *Difa, Ital.*
Avena (p.2262·1).
Emollient skin cleanser.

Avalox *Bayer, Braz.; Bayer, Ger.; Bayer, Ital.; Bayer, Switz.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections; bacterial infections of the respiratory tract.

Avamigran
Note. This name is used for preparations of different composition.
Viatris, Austria.
Ergotamine tartrate (p.620·1); mecloxamine citrate (p.1744·3); camylofin hydrochloride (p.2274·1); caffeine (p.1116·3); propyphenazone (p.119·3).
Cluster headache; migraine.

Transfarma, Philipp.
Ergotamine tartrate (p.620·1).
Vascular headache.

Viatris, Port.†.
Ergotamine tartrate (p.620·1); propyphenazone (p.119·3).
Cluster headache; vascular headache.

Meda, Thai.; Pharmalink, Thai.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and related vascular headaches.

Avamigran N *AWD, Ger.†.*
Ergotamine tartrate (p.620·1); propyphenazone (p.119·3).
Cluster headache; migraine.

Avamys *GSK, Austral.; GSK, Cz.*
⊗ Fluticasone furoate (p.1533·2).
Allergic rhinitis.

Avance *Medlock Medical, UK.*
Hydropolymer wound dressing containing silver (p.2387·1).
Exudating wounds.

Avancel
Note. This name is used for preparations of different composition.
Bago, Arg.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Oral contraceptive in women with androgenic symptoms.

Bago, Chile†.
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Avancort *Polifarma, Ital.*
⊗ Methylprednisolone aceponate (p.1539·1).
Skin disorders.

Avandamet *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, USA; GSK, Venez.*
Rosiglitazone maleate (p.458·2); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Avandaryl *GSK, Indon.; GSK, USA.*
Rosiglitazone maleate (p.458·2); glimepiride (p.441·1).
Diabetes mellitus.

Avandia *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; SmithKline Beecham, USA; GSK, Venez.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Avant *Medochemie, Malaysia†.*
Haloperidol (p.1000·2).
Behavioural disorders; hiccups; movement disorders; psychomotor agitation; psychoses; stuttering; tics; vomiting.

Avantrin *UCB, Ital.†.*
Trapidil (p.1416·3).
Ischaemic heart disease.

Avanza *British Pharmaceuticals, Austral.*
Mirtazapine (p.409·2).
Depression.

Avapena *Sandoz, Mex.*
Chloropyramine hydrochloride (p.571·3).
Hypersensitivity.

Avapro *BMS, Arg.; BMS, Austral.; BMS, Braz.; BMS, Canad.; Sanofi Synthelabo, Canad.; BMS, Mex.; BMS, USA; Sanofi Winthrop, USA.*
Irbesartan (p.1316·1).
Diabetic nephropathy; hypertension.

Avapro HCT *BMS, Arg.; BMS, Austral.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Avar *Tiber, USA.*
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne.

Avaron *Bioton, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Avastar *Vianex (Βιανεξ), Gr.†.*
Tirofiban (p.1414·2).
Antiplatelet therapy.

Avastin *Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Genentech, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Genentech, USA.*
Bevacizumab (p.684·3).
Breast cancer; colorectal cancer; non-small cell lung cancer; renal cell cancer.

Avastinee *APT, Hong Kong.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Avastoph *Medic+Aid, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Avatratin *Iator, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Avaxim *Sanofi Pasteur, Arg.; Aventis Pasteur, Austral.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Pasteur Merieux, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; MSD, NZ; Sanofi Pasteur, Neth.; Aventis Pasteur,*

Philipp.; Aventis Pasteur, Pol.; Sanofi Pasteur, Port.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.; Aventis Pasteur, UK.
An inactivated hepatitis A vaccine (p.2214·2).
Separate preparations are available for children and for adolescents and adults.
Active immunisation.

Avazinc *Rekah, Israel.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

AVC *Theramed, Canad.†.*
Sulfanilamide (p.343·1).
Vulvovaginal candidiasis.

Avecyde *3M, Malaysia†; Galderma, Mex.; 3M, Singapore†.*
Lactic acid (p.2329·3).
Skin cleansing; skin irritation; soap substitute.

Avedorm duo *Eberth, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Agitation; sleep disorders.

Avedox-FC *Continentales, Mex.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Aveendix *Darier, Mex.*
Avena (p.2262·1); borage (p.2267·3); lactyl glutamate; vitamin E acetate (p.1992·3); levomenol (p.2333·3).
Dry skin; skin irritation.

Aveeno *Rydelle, USA.*
Soap-free skin cleanser; emollient and moisturiser.

Aveeno Anti-Itch *Johnson & Johnson, Canad.*
Calamine (p.1591·2); pramocaine hydrochloride (p.1868·1).
Skin disorders.

Aveeno Cleansing Bar *Rydelle, USA.*
Sulfur (p.1614·1); salicylic acid (p.1612·2); colloidal oatmeal (p.2262·1).
Acne.

Aveeno Diaper Rash *Johnson & Johnson, Canad.*
Zinc oxide (p.1621·2).
Nappy rash.

Aveeno Preparations *Johnson & Johnson, Canad.; Johnson & Johnson, Ital.; Dermoteca, Port.; Johnson & Johnson, UK.*
A range of preparations containing avena (p.2262·1).
Skin care; skin cleansing; skin disorders.

Avegon *Menarini, Gr.*
Vitamin A (p.1971·2); vitamin E (p.1992·2).

Avelon *Bayer, S.Afr.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Avelox *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Irl.; Shionogi, Jpn; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Philipp.; Bayer, Pol.; BayHealth, Port.; Bayer, Rus.; Bayer, Singapore; Bayer, Swed.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Schering-Plough, USA; Bayer, Venez.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Avemar *Er-Kim, Turk.*
Preparation for enteral nutrition (p.1922·1).

Avena Complex *Blackmores, Austral.*
Rosemary (p.2381·2); avena (p.2262·1); vervain (p.2413·3); kola (p.2416·1); vitamin B substances (p.1922·1).
Tonic.

Avena Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Avena Rihom Komplex *Richter, Austria.*
Homoeopathic preparation.

Avena Sativa Comp *Weleda, S.Afr.; Weleda, UK.*
Avena (p.2262·1); coffea tosta; lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; restlessness; sedative; to aid relaxation.

Avenaforce *Bioforce, Switz.†.*
Avena (p.2262·1).
Insomnia; nervousness.

Avene Antirougeurs *Avene, Fr.*
⊗ Butcher's broom (p.2270·3); dextran sulfate (p.2293·1); hesperidin methyl chalcone (p.2305·2).
Skin redness.

Avene Creme Protectrice and Lait Protecteur *Avene, Fr.†.*
SPF 12B 12A: Cinnamate.
Sunscreen.

Avene Ecran Extreme
Note. This name is used for preparations of different composition.
Avene, Fr.†.
SPF 50B 15A: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Avene, Fr.†.
SPF 60B 60A: Cinnamate.
Sunscreen.

Avene Ecran Jour *Avene, Fr.†.*
SPF 15: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Avene Ecran Tres Haute Protection
Note. This name is used for preparations of different composition.
Avene, Fr.†.
Cream SPF 20B 20A: Cinnamate.
Sunscreen.

Avene, Fr.†.
SPF 20B 15A: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Avene, Fr.†.
Stick SPF 20B 20A: Cinnamate; titanium dioxide (p.1617·3).
Sunscreen.

Avene 50 Proteccion Extrema *Silesia, Chile.*
SPF 50: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Avene 20 Proteccion Total
Note. This name is used for preparations of different composition.
Silesia, Chile.
Cream SPF 20: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); cinnamate.
Sunscreen.

Silesia, Chile.
Stick SPF 20: Titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Avene Spray 50+ *Silesia, Chile.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); bisoctrizole (p.1591·2); Tinosorb S (p.1590·2).
Sunscreen.

Aveno
Note. This name is used for preparations of different composition.
Szama, Arg.
Avena (p.2262·1); melaleuca oil (p.2338·2).
Skin disorders.

Galderma, Braz.
Barrier preparation; skin cleanser.

Avenoc
Note. This name is used for preparations of different composition.
Boiron, Cz.
Pilewort (p.2368·1); paeonia officinalis; adrenaline; amylocaine hydrochloride (p.1853·3).
Anorectal disorders; haemorrhoids.

Boiron, Canad.; Boiron, Port.
Homoeopathic preparation.

Avensyl *Elmor, Venez.*
Ispaghula (p.1737·1); avena (p.2262·1).
Constipation.

Aventyl *Pharmascience, Canad.; Lilly, USA.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Aveptol *Aledicine, Gr.*
Levocarnitine (p.1932·2).

Averpan *Neovita, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Avertex *Beta, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Avertin *Avefarm, Cz.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Avesoap *ICN, Arg.†.*
Soap substitute for sensitive skin.

Aviane *Duramed, USA.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Aviant *Schering-Plough, Mex.*
Desloratadine (p.576·1).
Allergic rhinitis; allergic skin disorders.

Avibon *Sanofi-Aventis, Fr.*
Vitamin A palmitate (p.1973·1).
Skin disorders.

Avicap *Kocak, Turk.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Avicis *Galderma, Braz.*
Estradiol (p.2097·2).
Alopecia.

A-Vicon *Collins, Mex.†.*
Vitamin A (p.1971·2).

A-Vicotrat *Heyl, Ger.†.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Avidart *GSK, Spain.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

Avidazine *Bell, India.*
Cinnarizine (p.573·1).
Ménière's disease; tinnitus; vertigo.

Avigen *Aksu, Turk.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Avigilen
Note. This name is used for preparations of different composition.
Sanova, Austria.
Alpha tocoferil acetate (p.1992·3).
Intermittent claudication; muscle and connective tissue disorders.

Riemser, Ger.
Piracetam (p.368·2).
Mental function disorders.

Avil
Aventis, Austral.; Hexal, Austria; Aventis, India; Sanofi-Aventis, Indon.; Aventis, NZ†; Ilsan, Turk.
Pheniramine maleate (p.587·3).
Allergic disorders; cold symptoms; motion sickness; pruritus; rhinitis; vestibular disorders.

Avil Decongestant *Aventis, Austral.*
Pheniramine maleate (p.587·3); ammonium chloride (p.1551·3); menthol (p.2340·1).
Bronchial and nasal congestion; coughs.

Avil Expectorant *Hub, India.*
Pheniramine maleate (p.587·3); ammonium chloride (p.1551·3); menthol (p.2340·1).
Bronchitis; coughs; respiratory-tract hypersensitivity.

Avilac *Agis, Israel.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Avinal-Ex *Sons, Mex.†.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Avintac *Mavi, Mex.*
Ranitidine (p.1766·1).

Avinza *King, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Aviomarin *Pliva Krakow, Pol.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting.

Avipur *Taro, Israel.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Avir *Roemmers-Klinos, Venez.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aviral *Medley, Braz.; Mepha, Switz.; Pliva, UK.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avirase *Lampugnani, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avirax *Fabrigen, Canad.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avirex-T *Tecnofarma, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Aviril H
Note. This name is used for preparations of different composition.
Leciva, Cz.†.
Ointment: Cinchocaine hydrochloride (p.1857·3); lysates of: *Escherichia coli*; *Staphylococcus*; *Pseudomonas aeruginosa*; *Streptococcus*; hamamelis (p.2318·2); calcium hydroxide (p.2272·2).
Anorectal disorders; haemorrhoids.

Leciva, Cz.†.
Suppositories: Hydroxyquinoline sulfate (p.2323·1); potassium sulfate (p.1684·3); cinchocaine hydrochloride (p.1857·3); lysates of: *Escherichia coli*; *Staphylococcus*; *Pseudomonas aeruginosa*; *Streptococcus*.
Anorectal disorders; haemorrhoids.

Avirin
Note. This name is used for preparations of different composition.
Royal, Chile†.
Amlodipine (p.1214·2).
Hypertension; ischaemic heart disease.

Eurofarmaco, Ital.†.
Inosine pranobex (p.884·2).
Viral infections.

Avirostat *Varifarma, Arg.*
Interferon alfa-2a (p.885·1).
Anogenital warts; hepatitis; malignant neoplasms.

Avirox *Sandoz, Denm.*
Aciclovir (p.862·3).
Herpes labialis.

Avishot *Organon, Jpn.*
Naftopidil (p.2190·2).
Benign prostatic hyperplasia.

A-Vita
Note. A similar name is used for preparations of different composition (see below).
Leiras, Fin.
Vitamin A palmitate (p.1973·1); menthol (p.2340·1).
Nasal dryness.

Avita
Note. A similar name is used for preparations of different composition (see above).
Penederm, USA.
Tretinoin (p.1618·1).
Acne.

A-Vitamiini *Leiras, Fin.†.*
Vitamin A (p.1971·2).
Scalp and skin disorders.

A-vitamin *Medic, Denm.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Avitan *Neckerman, Braz.†.*
Vitamin A (p.1971·2).

Avitana *Pfizer, Chile.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Avitcid *Orion, Fin.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders.

A-Vite *Neves, Port.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

A-Vitel *Medipharma, Arg.*
Vitamin A palmitate (p.1973·1).
Skin disorders.

A-Vitel E *Medipharma, Arg.*
Vitamin A (p.1971·2); alpha tocopherol (p.1992·2).
Skin disorders.

Avitene *Bard, Hong Kong†; Shionogi, USA.*
Microfibrillar collagen (p.2286·1).
Haemorrhage in surgical procedures.

Avitil *Roemmers Medihe, Venez.*
Extramel.
Pigmentation disorders; vitiligo.

Avitol *Lannacher, Austria.*
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Avitracid *Adroka, Switz.†.*
Isopropyl alcohol (p.1650·3).
Hand disinfection.

Avix *Ibirn, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avixis *Galderma, Arg.; Galderma, Mex.*
⊗ Alfatradiol (p.2082·1).
Alopecia androgenetica.

Avlocardyl *AstraZeneca, Fr.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; oesophageal varices; tremor.

Avloclor *AstraZeneca, Indon.; AstraZeneca, Irl.; Zeneca, Israel; AstraZeneca, UK.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Avlosulfon *Wyeth-Ayerst, Israel†.*
Dapsone (p.261·2).
Dermatitis herpetiformis; leprosy.

Avmigran *Ulagay, Turk.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); mecloxamine citrate (p.1744·3); paracetamol (p.108·1).
Migraine.

Avoca *Bray, UK.*
⊗ Silver nitrate (p.2387·2); potassium nitrate (p.1658·3).
Verrucas; warts.

Avocin *Wyeth Lederle, Ital.†.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Avodart *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; GSK, USA.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

Avogin *Lapi, Indon.*
Ginger (p.1732·3); vitamin B (p.1979·1).
Nausea and vomiting.

Avolve *GSK, Austria; Alenfarma, Port.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

Avomine *Sanofi-Aventis, Austral.; Nicholas Piramal, India; Aventis, NZ; Pharmacare, S.Afr.; Manx, UK.*
Promethazine teoclate (p.588·3).
Motion sickness; nausea and vomiting.

Avonex *Abbott, Arg.; Biogen, Austral.; Biogen, Austria; Biogen, Belg.; Abbott, Braz.; Biogen, Canad.; Abbott, Chile; Biogen, Cz.; Biogen, Denm.; Biogen, Fin.; Biogen, Fr.; Biogen, Ger.; Genesis, Gr.; Biogen, Hung.; Biogen, Irl.; Biogen, Israel; Dompe Biotec, Ital.; Abbott, Mex.; Biogen, NZ; Biogen, Neth.; Biogen, Norw.; Biogen, Pol.†; Biogen, Port.; Biogen, Rus.; Pharmaplan, S.Afr.; Biogen, Spain; Biogen, Swed.; Biogen Dompe, Switz.; Gen, Turk.; Biogen, UK; Biogen, USA; Abbott, Venez.*
Interferon beta-1a (p.891·2).
Multiple sclerosis.

Avorax *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections of the skin and mucous membranes.

Avrazor *Zentiva, Cz.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Avril *Teofarma, Spain.*
Cod-liver oil (p.1935·2); aluminium acetotartrate (p.2255·1); benzalkonium chloride (p.1629·1); zinc oxide (p.1621·2).
Burns; wounds.

Avural *LKM, Arg.*
Indinavir (p.884·2).
HIV infection.

Avuxilan *Arlex, Mex.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Avyclor *Uno, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avyplus *Epifarma, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Avysal *Selvi, Ital.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Awayke *Panacea, India†.*
Loratadine (p.583·3).
Cold symptoms; hypersensitivity reactions.

Awesome Animals *Nu-Life, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Awestatin *AWD, Hung.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Awirol *ICN, Pol.*
Aciclovir (p.862·3).
Herpesvirus skin infections.

Axagon *Simesa, Ital.*
Esomeprazole magnesium (p.1729·2) or esomeprazole sodium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Axal
Note. This name is used for preparations of different composition.
Duopharma, Malaysia.
Benfluorex hydrochloride (p.1224·3).
Hyperlipidaemias.
Randall, Mex.†.
Aspirin (p.20·3).

Axalan *Medifarma, Indon.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Axalin *Cipla, India†.*
⊗ Salbutamol sulfate (p.1131·3); ambroxol (p.1550·3); guaifenesin (p.1561·3); menthol (p.2340·1).

Axalin-AX *Cipla, India.*
⊗ Salbutamol (p.1131·2); ambroxol hydrochloride (p.1550·3).
Obstructive airways disease.

Axamon *Pik, Rus.*
Ipidacrine (p.631·2).
Alzheimer's disease; CNS and peripheral nervous system disorders; demyelinating disease; gastrointestinal atony; myasthenia.

Axant *Mintlab, Chile.*
Lactulose (p.1738·2).

Axasol *Andromaco, Chile.*
Clotrimazole (p.530·1).
Balanitis; fungal vaginal infections.

Axcel Dextrozine *Kotra, Malaysia.*
Dextromethorphan hydrobromide (p.1555·2); promethazine hydrochloride (p.588·2).
Cough; respiratory-tract congestion.

Axcel Fusi-Corte *Kotra, Malaysia.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Axcel Tridine *Kotra, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; respiratory-tract congestion; rhinitis; sinusitis.

Axed *Grin, Mex.*
Vitamin A; ergocalciferol (p.1922·1).
Vitamin A and E deficiency.

Axelabron *Ferakon, Gr.*
Risperidone (p.1024·2).
Psychoses.

Axelan *Proel, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Axelanol *Ferakon, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Axelorax *Proel, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Axelovert *Ferakon, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Axelvin *Proel, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Axepim *BMS, Fr.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Axer *Wassermann, Ital.†.*
Naproxen sodium (p.92·3).
Musculoskeletal and joint disorders; pain.

Axerophthol *Biotika, Cz.*
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Axert *Janssen-Ortho, Canad.; Ortho McNeil, USA.*
Almotriptan malate (p.617·3).
Migraine.

Axetine
GSK, Belg.
Cefuroxime axetil (p.238·2).
Bacterial infections.
Medochemie, Cz.; Medochemie, Hong Kong†; Medochemie, Rus.; Medochemie, Thai.†.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Axiago *Beta, Spain.*
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Axibin *Korea United, Philipp.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Axid
Farmoquimica, Braz.; Pharmel, Canad.; Lilly, Gr.†; Lilly, Hong Kong; Lilly, Indon.; Flynn, Irl.; Lilly, Malaysia†; Lilly, Mex.; Lilly, Neth.; Norgine, Neth.; GSK, Philipp.; Lilly, Thai.†; Lilly, Turk.; Flynn, UK; Braintree, USA; GSK, USA; Wyeth Consumer, USA; Lilly, Venez.†.
Nizatidine (p.1751·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Axilin *Ivax, Mex.*
Flunarizine (p.580·3).
Migraine.

Axilium *Pulitzer, Ital.*
Lormetazepam (p.1005·2).
Insomnia.

Aximad *Boniscontro & Gazzone, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Axis *Labinca, Arg.†.*
Piroxicam (p.117·3).

Axistal *Asian Pharm, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Axit *Alphapharm, Austral.*
Mirtazapine (p.409·2).
Depression.

Axmaxolv *Jewim, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Axobat *Lisapharma, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Axocillin *Malayan, Singapore†.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Axofin *Eurodrug, Mex.*
Doxofylline (p.1120·3).
Obstructive airways disease.

Axofor *Aventis, Mex.*
Hydroxocobalamin acetate (p.1980·3).
Anaemias; neuralgias; neuritis; neuropathies; vitamin B deficiency.

Axokine *Rontag, Arg.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; rheumatoid arthritis.

Axol *YSP, Malaysia; Bayer, Mex.; Yung Shin, Singapore.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Axone *Cadila, India.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Axonyl *Pfizer, Fr.†.*
Piracetam (p.368·2).
Dyslexia in children; mental function disorders; vertigo.

Axoren *GSK, Ital.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Axotide *GSK, Switz.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Axsain *Zeneus, Irl.; Cephalon, UK; Rodlen, USA.*
Capsaicin (p.32·3).
Diabetic neuropathy; post-herpetic neuralgia.

Axtar *Unipharm, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Axtil *Adamed, Pol.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction; non-diabetic glomerulonephropathy.

Axtin *Mavi, Mex.*
Fluoxetine (p.397·3).
Depression.

Axtrim *Unipharm, Mex.*
Piroxicam (p.117·3).
Inflammation.

Axura *Merz, Austria; Merz, Cz.; Merz, Ger.; Merz, Neth.; Merz, Pol.; Grunenthal, Port.; Andromaco, Spain; Merz, Switz.*
Memantine hydrochloride (p.367·1).
Formerly known as Akatinol in *Ger.*
Alzheimer's disease.

Axurocef *China Chem & Pharma, Thai.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Aydolid *Farma Lepori, Spain.*
Fosfosal (p.62·1).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Aydolid Codeina *Farma Lepori, Spain.*
Codeine phosphate (p.37·2); fosfosal (p.62·1).
Pain.

Aygestin *Barr, USA.*
Norethisterone acetate (p.2119·3).
Abnormal uterine bleeding; endometriosis; secondary amenorrhoea.

Aylide *Alphapharm, Austral.*
Glimepiride (p.441·1).
Diabetes mellitus.

Ayoral *Rayere, Mex.†.*
Dipyrone (p.49·2); papaverine (p.2191·3).
Fever; muscle spasm; pain.

Ayoral Simple *Rayere, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Ayr-5 *SMB, Chile.*
⊗ Urea (p.1620·2).
Skin disorders.

Ayr Saline *Ascher, USA.*
Sodium chloride (p.1686·1).
Nasal irritation.

Ayr con urea *SMB, Chile.*
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Ayra *Sanovel, Turk.*
Candesartan cilexetil (p.1238·3).
Hypertension.

Ayrementol *SMB, Chile.*
Menthol (p.2340·1); camphor (p.2273·2).
Dry skin; skin irritation.

Ayrton's Antiseptic *McGloin, Austral.*
Zinc oxide (p.1621·2); dichlorobenzyl alcohol (p.1642·1).
Superficial skin infections.

Ayrton's Chilblain *McGloin, Austral.*
Camphor (p.2273·2); benzocaine (p.1854·1); peru balsam (p.2365·3); phenol (p.1656·1).
Chilblains.

Ayton *Maigal, Arg.*
Vegetable oils; soya lecithin (p.2332·2).
Skin disorders.

AZ *Elmor, Venez.*
Azelastine hydrochloride (p.568·2).
Eye disorders.

AZ 15 *Procter & Gamble, Ital.*
Sodium chloride (p.1686·1); benzalkonium chloride (p.1629·1); azulene (p.2262·3).
Gum protection; oral hygiene.

Az Ofteno *Volta, Chile.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

AZ Ofteno *Sophia, Mex.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

AZ Protezione Gengive *Procter & Gamble, Ital.*
Triclosan (p.1665·2); pyrophosphate; sodium fluoride (p.1962·2).
Gum disorders.

AZ Tartar Control *Procter & Gamble, Ital.*
Sodium fluoride (p.1962·2); potassium and sodium pyrophosphates (p.2390·3).
Dental caries prophylaxis; dental tartar.

AZ Verde *Procter & Gamble, Ital.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Aza 20 *Pharmacore, Indon.*
Azelaic acid (p.1589·3).
Acne.

Azaallen *Allen, Austria.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Azacard *Oftalmi, Venez.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Azacid *Fako, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Azacleus *Nucleus, Neth.*
Azithromycin ethanolate (p.207·3).
Bacterial infections.

Azacortid *Aventis, Arg.; Sanofi-Aventis, Chile.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Azacortine *Omega, Belg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Azactam *BMS, Arg.†; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; Sanofi-Aventis, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Irl.; BMS, Israel†; BMS, Ital.; Eisai, Jpn; BMS, NZ; BMS, Norw.; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, UK; BMS, USA; BMS, Venez.*
Aztreonam (p.209·2).
Gram-negative bacterial infections.

Azadose *Pfizer, Fr.*
Azithromycin (p.207·1).
Nontuberculous mycobacterial infections.

Azafalk *EciFarma, Chile†; Falk, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; rheumatoid arthritis; transplant rejection.

Azaglax *GSK, Austria.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Azahexal *Hexal, Austral.*
Azathioprine (p.1818·2).
Autoimmune disorders; transplant rejection.

Azalia *Gedeon Richter, Cz.*
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Azamedac *Medac, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Azamun *Douglas, Austral.; Leiras, Fin.; Douglas, Hong Kong†; Douglas, NZ; Pharmaplan, S.Afr.*
Azathioprine (p.1818·2).
Auto-immune disorders; immunosuppressant; transplant rejection.

Azanplus *GSK, Mex.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Azantac *GSK, Fr.; GSK, Mex.; PCO, Neth.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Azaphen *Makiz-Pharma, Rus.*
Pipofezine or pipofezine hydrochloride (p.420·1).
Depression.

Azapin
Note. This name is used for preparations of different composition.
Arrow, Austral.
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.
Pharmathen, Gr.
Mirtazapine (p.409·2).
Depression.

Azapress *Bodene, S.Afr.*
Azathioprine (p.1818·2).
Transplant rejection.

Azaprin *Nolver, Venez.*
Azathioprine (p.1818·2).
Transplant rejection.

Azaprine *Ivax, Cz.*
Azathioprine (p.1818·2).
Auto-immune disorders; idiopathic thrombocytopenic purpura; transplant rejection.

Aza-Q *Juta, Ger.; Q-Pharm, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Azaran *Hemofarm, Rus.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Azarek *Hexal, Austria†; Ecosol, Switz.*
Azathioprine (p.1818·2).
Auto-immune disorders; idiopathic thrombocytopenic purpura; transplant rejection.

Azaron
Note. This name is used for preparations of different composition.
Sanova, Austria; Chefaro, Cz.†; Chefaro, Ger.; Chefaro, Neth.; Chefaro, Spain.
Tripelennamine hydrochloride (p.592·2).
Bites and stings; burns; hypersensitivity reactions; urticaria.
Omega, Belg.
Diphenhydramine hydrochloride (p.577·2).
Pruritus; skin irritation.

Azasan *Salix, USA.*
Azathioprine (p.1818·2).
Rheumatoid arthritis; transplant rejection.

AzaSite *Inspire, USA.*
Azithromycin (p.207·1).
Bacterial conjunctivitis.

Azathiodura *Merck dura, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Azatill *Prodotti, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azatrilem *Lemery, Mex.*
Azathioprine (p.1818·2).
Immunosuppressant.

Azatyl *Remedina, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Azecar *Bago, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Azectol *Help, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Azedose *Faran, Gr.*
Azelaic acid (p.1589·3).
Acne.

Azee *Cipla, India.*
Azithromycin (p.207·1).
Bacterial infections.

Azelac *Med-One, Gr.*
Azelaic acid (p.1589·3).
Acne.

Azelan *Intendis, Braz.*
Azelaic acid (p.1589·3).
Acne.

Azelast *Sigma, Braz.†.*
Azelastine hydrochloride (p.568·2).
Hypersensitivity reactions.

Azelaxine *Velka, Gr.*
Azelaic acid (p.1589·3).
Acne.

Azelderm *Kleva, Gr.; Orva, Turk.*
Azelaic acid (p.1589·3).
Acne.

Azelex *Allergan, USA.*
Azelaic acid (p.1589·3).
Acne.

Azelone *Korea United, Philipp.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis; allergic skin disorders; urticaria.

Azeltin *Biofarma, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Azelvin *Novartis, Norw.; Novartis, Swed.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Azenam *Aristo, India.*
Aztreonam (p.209·2).
Gram-negative bacterial infections.

Azenil *Pfizer, Israel.*
Azithromycin (p.207·1).
Bacterial infections.

Azep *Sigma, Austral.; Viatris, Hong Kong; German Remedies, India; Asta Medica, Malaysia†; Transfarma, Philipp.; Meda, Port.; Asta Medica, Singapore†; Transfarma, Thai.†.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Azepal *ICN, Hung.†.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias.

Azepam *Macrophar, Thai.*
Diazepam (p.986·3).
Anxiety; autonomic disorders; musculoskeletal spasm; psychoneurotic disorders.

Azetavir *Tecnofarma, Mex.*
Zidovudine (p.913·3).
Viral infections.

Azi *Sigma, Braz.; Sandoz, Hung.*
Azithromycin (p.207·1).
Bacterial infections.

Aziac *Infabra, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity.

Aziatop *Elea, Arg.*
Omeprazole (p.1753·1).
Peptic ulcer.

Azibact *Ipca, India.*
Azithromycin (p.207·1).
Bacterial infections.

Azibactron *Faran, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azibiot *Cimprich, Cz.; Euromex, Mex.; KRKA, Pol.*
Azithromycin (p.207·1).
Bacterial infections.

Azicid *Generics, Hung.*
Azithromycin (p.207·1).
Bacterial infections.

Aziclav *Spirig, Switz.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Azidina *Cipan, Port.*
Zidovudine (p.913·3).
HIV infection.

Azidromic *Royton, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Azifarm *Mediapharm, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azifast *Ipca, India.*
Azithromycin (p.207·1).
Bacterial infections.

Azigram *Vivax, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Azilect *Lundbeck, Belg.; Teva, Cz.; Teva, Denm.; Lundbeck, Fin.; Lundbeck, Fr.; Lundbeck, Ger.; Teva, Ger.; Lundbeck, Gr.; Lundbeck, Irl.; Teva, Israel; Teva, Neth.; Teva, Norw.; Teva, Pol.; Lundbeck, Port.; Teva, Spain; Lundbeck, UK; Teva, USA.*
Rasagiline mesilate (p.815·3).
Parkinsonism.

Aziliv *Delta, Braz.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Azilline *Spirig, Switz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Azimakrol *Roemmers-Klinos, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Azimax *Pfizer, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Azime *Sedabel, Braz.†.*
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive disorders; flatulence.

Azimed *Cimed, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azimix *Ativus, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azimycin *Polfa Tarchomin, Pol.*
Azithromycin (p.207·1).
Bacterial infections.

Azinc *Arkopharma, Fr.; Arkochim, Spain; Arkopharma, UK.*
A range of vitamin and mineral preparations (p.1922·1).

Aziphar *Ares, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Aziram *Uniao Quimica, Braz.*
Aluminium hydroxide (p.1706·2).
Antacid.

Azirox *Aurora, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azirutec *Zwitter, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azithral *Verisfield, Gr.; Alembic, India.*
Azithromycin (p.207·1).
Bacterial infections.

Azithrin *Alet, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azithrox *Farmstandart, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Azithrus *Synthesis, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Aziton *Labesfal, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Azitral *Sanitas, Arg.; Shreya, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrax *Farmoquimica, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrin *Delta, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrix *Pentafarma, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Azitro
Merck, Neth.
Azithromycin ethanolate (p.207·3).
Bacterial infections.

Deva, Turk.
Azithromycin (p.207·1).
Bacterial infections.

Azitrocin *Pfizer, Ital.; Pfizer, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrogal *Sant Gall, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrogran *Legrand, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrohexal *Sandoz, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrolab *Multilab, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrolan *Lanpharm, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrolid *Minerva (Μινερβα), Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrom *Laboratorios Chile, Chile; SM, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Azitromax *Pfizer, Norw.; Pfizer, Swed.*
Azithromycin (p.207·1).
Bacterial infections.

Azitromicil *Greenpharma, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azitromin *Farmasa, Braz.†; Farma, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Azitron *Cifarma, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrona *Klonal, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Azitronax *Pharlab, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Azitrox *Lamsa, Arg.; Zentiva, Cz.; Zentiva, Pol.*
Azithromycin (p.207·1).
Bacterial infections.

Azitroxil *De Mayo, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Azivirus *Suan, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Aziwok *Wockhardt, India; Wockhardt, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Azlaire *Schering-Plough, Mex.; Schering-Plough, Venez.*
Pranlukast (p.1130·2).
Allergic rhinitis; asthma.

Azmacon
Cipla, Hong Kong.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Armoxindo, Indon.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Azmacort *Sanofi-Aventis, Braz.; Aventis, Cz.†; KOS, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Asthma; obstructive airways disease.

Azmasol *Beximco, Singapore.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Azo Gantrisin *Roche, Turk.*
Sulfafurazole (p.338·3); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Azoazol *Gador, Arg.†.*
Zidovudine (p.913·3).
HIV infection.

Azodac *Eurolab, Arg.*
Levocarnitine fumarate; fructose; acetylcarnitine; vitamin E; citric acid; vitamin C (p.1922·1).
Dietary supplement.

Azoflu *Suan, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Azoflune *Tecnimede, Port.*
Fluconazole (p.532·1).
Fungal infections.

Azofur *Ivax, Mex.*
Phenazopyridine (p.116·3).
Urinary-tract pain.

Azogen *Degorts, Mex.*
Phenazopyridine hydrochloride (p.116·2); nalidixic acid (p.303·3).
Bacterial infections of the urinary tract.

Azol
Note.This name is used for preparations of different composition.
Alphapharm, Austral.; Merck, Indon.; Alphapharm, Malaysia; Alphapharm, Singapore; Merck, Singapore.
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; gynaecomastia; hereditary angioedema; menorrhagia.

Kern, Spain.
Sulfanilamide (p.343·1).
Skin infections.

Azolac Folico *Altana, Arg.*
Folic acid (p.1940·1).
Anaemias.

Azolin *Biochem, India.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Azoline *Fischer, Israel.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Allergic conjunctivitis; eye irritation.

Azolmen *Menarini, Ital.*
Bifonazole (p.527·3).
Fungal skin infections.

Azo-Mandelamine *Pfizer, Venez.*
Methenamine mandelate (p.298·3); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Azo-Max *Unipharm, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Azomax *Kocak, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Azomid *Adcock Ingram, S.Afr.*
⊗ Acetazolamide (p.1875·1).
Glaucoma.

Azomir *Sanofi Synthelabo, Philipp.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain and irritation.

Azomycin *Julphar, UAE.*
Azithromycin (p.207·1).
Bacterial infections.

Azomyr *Kirby, Arg.†; Schering-Plough, Cz.; Essex, Ital.; Schering-Plough, Mex.; Schering-Plough, Neth.; Schering-Plough, Port.; Menarini, Spain.*
Desloratadine (p.576·1).
Allergic rhinitis; allergic skin disorders; urticaria.

Azona
Note.This name is used for preparations of different composition.
Orion, Fin.
Trazodone hydrochloride (p.424·3).
Depression; insomnia; psychoses.

Keton, Mex.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Azopi *Generics, Israel.*
Azathioprine (p.1818·2).
Auto-immune disorders; rheumatoid arthritis; transplant rejection.

Azopt *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Pacific, NZ; Alcon, Neth.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
⊗ Brinzolamide (p.1879·1).
Glaucoma; ocular hypertension.

Azoptic *Alcon, S.Afr.*
⊗ Brinzolamide (p.1879·1).
Glaucoma; ocular hypertension.

Azor
Note.This name is used for preparations of different composition.
Pharmacare, S.Afr.
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Daiichi Sankyo, USA.
Amlodipine besilate (p.1214·1); olmesartan medoxomil (p.1361·1).
Hypertension.

Azoran
Note.This name is used for preparations of different composition.
RPG, India.
Azathioprine (p.1818·2).
Auto-immune disorders; organ transplantation.

Columbia, Mex.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Azosilin *Fako, Turk.*
Ampicillin (p.204·1); phenazopyridine hydrochloride (p.116·2).
Bacterial infections.

Azo-Standard *Amerifit, USA.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Azostix *Bayer, Austral.; Bayer, NZ†; Bayer Diagnostics, UK; Bayer, USA.*
Test for urea in blood.

Azotine *Ivax, Arg.†.*
Zidovudine (p.913·3).
HIV infection.

Azo-Uronalin *Vitae, Mex.*
Nalidixic acid (p.303·3); phenazopyridine (p.116·3).
Urinary-tract infections.

Azovir
Note.This name is used for preparations of different composition.
Medikon, Indon.
Aciclovir (p.862·3).
Herpesvirus infections.

ICN, Pol.
Zidovudine (p.913·3).
HIV infection.

Azo-Wintomylon *Sanofi Synthelabo, Mex.*
Nalidixic acid (p.303·3); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Azpencil *Degorts, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Azro *Eczacibasi, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Azromax *Gerard, Irl.*
Azithromycin (p.207·1).
Bacterial infections.

Aztemin *Apotex, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Aztil *Offenbach, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Aztreotic *Kleva, Gr.†.*
Aztreonam (p.209·2).
Bacterial infections.

Aztrin *Pharos, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Aztrolen *Degorts, Mex.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Azuben *Ipsen, Spain†.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Azubronchin *Azupharma, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Azucalcit *Azupharma, Ger.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Azucalen *Herbapol Wroclaw, Pol.*
Calendula (p.2273·1); chamomile (p.2279·3).
Vulvovaginal disorders.

Azucaps *Medix, Mex.†.*
Phenformin (p.437·2).
Diabetes mellitus.

Azucimet *Azupharma, Ger.†.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Azucort *Collins, Mex.*
⊗ Triamcinolone (p.1544·2).
Skin disorders.

Azudoxat *Azupharma, Ger.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Azudoxat comp *Azupharma, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Azufibrat *Azupharma, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Azufracid *Bajer, Arg.*
Sulfur (p.1614·1); sodium thiosulfate (p.1466·1).
Formerly contained sulfur and iodine.
Skin cleanser.

Azuglucon *Azupharma, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Azukon *Torrent, Braz.*
Gliclazide (p.440·3).
Diabetes mellitus.

Azulan *Herbapol Wroclaw, Pol.; Phytofarm Kleka, Pol.*
Chamomile (p.2279·3).
Gastrointestinal spasm; skin and mucous membrane inflammation.

Azulen *Provita, Austria.*
Guaiazulene (p.2317·3).
Hypersensitivity and inflammatory disorders.

Azulenal *Agepha, Austria.*
Guaiazulene (p.2317·3).
Hypersensitivity disorders; mucus membrane inflammation; skin disorders.

Azulene *Thea, Fr.†.*
Guaiazulene (p.2317·3).
Conjunctival irritation.

Azulenol *Teva, Hung.*
Guaiazulene (p.2317·3).
Skin disorders.

Azulfidina *Pfizer, Mex.*
Sulfasalazine (p.1773·2).
Rheumatoid arthritis; ulcerative colitis.

Azulfidine *Pfizer, Arg.; Pfizer, Chile; Pharmacia, Ger.; Santen, Jpn; Pharmacia Upjohn, USA; Pfizer, Venez.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Azulfin *Apsen, Braz.*
Sulfasalazine (p.1773·2).
Rheumatoid arthritis; ulcerative colitis.

Azulina *Llorens, Spain.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Formerly contained methylthioninium chloride and tetryzoline hydrochloride.
Eye disorders.

Azulipont *Azupharma, Ger.†.*
Thioctic acid (p.2400·2).
Diabetic polyneuropathy.

Azulix *Torrent, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Azulon
Note. This name is used for preparations of different composition.
Szama, Arg.
Guaiazulene (p.2317·3).
Hypersensitivity reactions; inflammation.
Baxter, Ger.
Chamomile (p.2279·3).
Skin disorders.

Azumetop *Azupharma, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Azumetop HCT *Azupharma, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Azunaftil *Azupharma, Ger.†.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral vascular disorders.

Azunol
Note. This name is used for preparations of different composition.
Shinyaku, Hong Kong†.
Azulene sodium sulfonate (p.2262·3).
Gastric ulcer; gastritis; mouth and throat disorders.
Shinyaku, Jpn.
Sodium gualenate (p.2262·3).
Mouth and throat disorders.

Azupamil *Azupharma, Ger.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Azupanthenol *Parke, Davis, Ger.†.*
Guaiazulene (p.2317·3); sodium pantothenate (p.1960·1).
Gastrointestinal disorders.

Azupentat *Azupharma, Ger.†.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Azuperamid *Azupharma, Ger.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Azuprostat *Sandoz, Ger.*
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Azuprostat Sabal *Sandoz, Ger.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Azuprostat Urtica *Sandoz, Ger.†.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Azur
Note. This name is used for preparations of different composition.
Steiner, Ger.
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.
Biores, Ital.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Azur compositum *Steiner, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Azur compositum SC *Steiner, Ger.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Azuranit *Azupharma, Ger.†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Azuril *Pharmanel, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Azuseptol *Hasco-Lek, Pol.*
Chamomile (p.2279·3).
Gastrointestinal spasm; skin and mucous membrane inflammation.

Azutan *Arex, Venez.*
Benzydamine hydrochloride (p.27·3).
Inflammation; mouth and throat disorders.

Azuthidrona *Lafedar, Arg.; Valuge, Arg.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Azutranquil *Azupharma, Ger.†.*
Oxazepam (p.1014·2).
Anxiety; insomnia.

Azutrimazol *Azupharma, Ger.†.*
Clotrimazole (p.530·1).
Fungal skin and genito-urinary tract infections.

Azymol *Drugtech, Chile.*
Aripiprazole (p.962·3).
Schizophrenia.

Azyr *SIFI, Ital.*
Vitamin and mineral preparation (p.1922·1).

Azyrol *Sons, Mex.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Azytan *Medilat, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

B1-12-15 *Italmex, Mex.*
Pangamic acid (p.2362·1); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2).
Anaemias; neuralgia; neuritis.

3B *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neural disorders.

B-6 *Pharmasant, Thai.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

B15 *Natural Life, Arg.†.*
Pangamic acid (p.2362·1).
Vitamin B supplement.

B_{12} Ankermann *Worwag, Cz.†; Worwag, Ger.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; vitamin B deficiency.

B Chabre *Expanpharm, Fr.*
Vitamin B substances (p.1922·1).

B Complex *Au Naturel, Canad.; Flora, Canad.; Holista, Canad.; Nutricorp, Canad.; CTI, Israel†; CCM, Malaysia; Vesco, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

B-100 Complex *TP, Thai.*
Vitamin B (p.1976·1); vitamin B (p.1977·2); vitamin B (p.1978·2); nicotinamide (p.1957·3).
Peripheral neuritis; vitamin B deficiency.

B Complex 50 *Jamieson, Hong Kong.*
Vitamin B substances; choline; inositol (p.1922·1).
Dietary supplement.

B Complex C 550 *Adams, Canad.*
Vitamin B substances and vitamin C (p.1922·1).

B complex with Minerals *Sisu, Canad.†.*
Vitamin B substances with minerals (p.1922·1).

B Complex plus C *Bio Vita, Canad.; Jamieson, Canad.; Nutricorp, Canad.; Pharmetics, Canad.*
Vitamin B substances and vitamin C (p.1922·1).

B Complex with Vitamin C *Pharmetics, Canad.*
Vitamin B substances; vitamin C (p.1922·1).

B_{12} compositum *Helvepharm, Switz.†.*
Cyanocobalamin; iron sucrose; calcium glycerophosphate (p.1922·1).
Tonic.

B Compound *Swiss Herbal, Canad.*
Vitamin B substances (p.1922·1).

B Compound with Vitamin C *Swiss Herbal, Canad.*
Vitamin B substances; vitamin C (p.1922·1).

B_{12} Depot-Hevert *Hevert, Ger.*
Hydroxocobalamin acetate (p.1980·3).
Vitamin B deficiency.

B12 Depot-Rotexmedica *Rotexmedica, Ger.*
Hydroxocobalamin acetate (p.1980·3).
Vitamin B deficiency.

B Dexol *Pharmasant, Thai.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

B_{12} Fol-Vicotrat *Heyl, Ger.†.*
Cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Vitamin B and folic acid deficiency.

B 12-L 90 *Loges, Ger.†.*
Cyanocobalamin (p.1980·2).
Anaemias; tonic; vitamin B deficiency.

B & O Supprettes No. 15A *Amerifit, USA.*
Prepared opium (p.105·1); powdered belladonna extract (p.2263·3).
Ureteral spasm pain.

B & O Supprettes No. 16A *Amerifit, USA.*
Prepared opium (p.105·1); powdered belladonna extract (p.2263·3).
Ureteral spasm pain.

B plus C *Novopharm, Canad.; Vita Health, Canad.*
Vitamin B substances and vitamin C (p.1922·1).

B12 Rotexmedica *Rotexmedica, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

B12 Steigerwald *Steigerwald, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

B Stress C plus Iron & Vitamins *Stanley, Canad.†.*
Vitamin preparation with iron (p.1922·1).

B Stress Select *Sisu, Canad.†.*
Vitamin B substances (p.1922·1).

B_1 Vicotrat *Heyl, Ger.†.*
Thiamine nitrate (p.1976·2).
Vitamin B deficiency.

B_6 Vicotrat *Heyl, Ger.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

B_{12} Vicotrat *Heyl, Ger.†.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

B_6 Vigen *Aksu, Turk.*
Pyridoxine hydrochloride (p.1978·2).
Idiopathic sideroblastic anaemia; isoniazid neuropathy; premenstrual syndrome; vitamin B deficiency.

B Virol *Rolmex, Canad.*
Multivitamin preparation (p.1922·1).

Babcon *Eisai, Thai.†; Toho, Thai.†.*
Dimethicone (p.1770·2).
Excess gastrointestinal gas; preparation for gastrointestinal examinations.

Babee *Pfeiffer, USA.*
Benzocaine (p.1854·1); cetalkonium chloride (p.1634·1); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3).
Oral lesions.

Babefen Sus *Polipharm, Thai.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Babic *Teva, Israel.*
Sodium bicarbonate (p.1673·2).
Infant colic.

Babicum *Natur Produkt, Pol.*
Ribwort plantain (p.2379·1); honey (p.1948·2).
Catarrh; cough.

Babiforton *Sanofi Synthelabo, Ger.†.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2); peppermint oil (p.1761·2).
Nasal congestion.

Babigoz Crema Protettiva *Guigoz, Ital.*
Zinc oxide (p.1621·2); chamomile (p.2279·3); wheatgerm oil (p.2415·1).
Nappy rash.

Babi-Lyte *SEA Pharm, Thai.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Babinoks *Sistas, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Babix *Stiefel, Arg.*
Liquid paraffin (p.2030·3).
Skin cleansing.

Babix-Inhalat N *Mickan, Ger.*
Eucalyptus oil (p.2301·2); Norway spruce oil.
Respiratory-tract disorders.

Babix-Wundsalbe N *Mickan, Ger.†.*
Zinc oxide (p.1621·2); lemon oil (p.2332·3); chamomile oil (p.2279·3).
Skin disorders.

Baby A + D *Vitamed, Israel.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Vitamin A and D supplement.

Baby AF *Sam-On, Israel.*
Sodium chloride (p.1686·1).
Nasal congestion.

Baby Agisten *Agis, Israel.*
Clotrimazole (p.530·1).
Fungal skin infections.

Baby Anbesol *Whitehall, USA.*
Benzocaine (p.1854·1).
Teething pain.

Baby Block *Estee Lauder, Canad.†.*
SPF 25: Titanium dioxide (p.1617·3).
Sunscreen.

Baby Cough with Antihistamine *Atlantic, Hong Kong; Atlantic, Thai.*
Acetic acid (p.2244·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); glycerol (p.2314·2); tolu balsam (p.1574·2); chlorphenamine maleate (p.571·3).
Coughs.

Baby Cough Syrup Atlantic *Atlantic, Thai.*
Acetic acid (p.2244·2); ammonium chloride (p.1551·3); glycerol (p.2314·2); sodium citrate (p.1673·3); tolu syrup (p.1574·2).
Coughs.

Baby Cough Syrup Greater *Greater Pharma, Thai.*
Ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Baby Fact B *Gemepe, Arg.*
Pulmonary surfactant (p.2375·3).
Neonatal respiratory distress syndrome.

Baby Gas-X *Novartis Consumer, USA.*
Simeticone (p.1770·2).
Infant colic.

Baby Gel *Medibrands, Israel.*
Benzocaine (p.1854·1).
Teething pain.

Baby Gripe *TO-Chemicals, Thai.*
Dill oil (p.2293·3); sodium bicarbonate (p.1673·2).
Flatulence; infant bloating.

Baby Gum *Rafa, Israel.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Mouth pain.

Baby Luuf *Apomedica, Austria.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); majoram oil (p.2358·1).
Respiratory-tract disorders.

Baby Orajel *Del, Canad.; Sanitas, Chile†; Hand-Prod, Pol.; Del, USA.*
Benzocaine (p.1854·1).
Teething pain.

Baby Orajel Tooth and Gum Cleanser *Del, USA.*
Poloxamer 407 (p.1918·2); simeticone (p.1770·2).
Dental hygiene.

Baby Paste *Vitamed, Israel.*
Zinc oxide (p.1621·2); starch (p.1968·1).
Nappy rash; skin irritation.

Baby Paste + Chamomile *Vitamed, Israel.*
Chamomile (p.2279·3); sage (p.2382·3); calamine (p.1591·2); zinc oxide (p.1621·2).
Skin disorders.

Baby Sebamed *Sebapharma, Thai.*
A range of skin cleansers and emollients.

Baby Shield *Hoe, Malaysia†; Hoe, Singapore†.*
Barrier lotion.
Nappy rash; skin irritation.

Baby Shield Plus *Hoe, Malaysia; Hoe, Singapore.*
Chlorhexidine gluconate (p.1635·3).
Nappy rash.

Baby Zanzara *Bouty, Ital.*
Ammonia (p.2256·1); almond oil (p.2252·2).
Bites.

BabyBIG *California Department of Health, USA.*
Botulism immunoglobulin (p.2207·3).
Botulism in infants.

Babycheck-Plus *Veda, Fr.*
Pregnancy test (p.2372·1).

Babycold *Pharmasant, Thai.*
Brompheniramine maleate (p.569·2).
Allergic rhinitis; hypersensitivity reactions.

Babydent *Stada, Cz.; Stada, Hung.*
Benzocaine (p.1854·1).
Teething pain.

Baby-Drax *Uniao Quimica, Braz.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration.

Babyfen *Qualiphar, Belg.*
Fennel oil (p.2303·1).
Infant colic.

Babygella
Note. This name is used for preparations of different composition.
Rottapharm, Fr.
Zinc oxide (p.1621·2).
Nappy rash.
Rottapharm, Ital.
Cream: Calendula (p.2273·1); chamomile (p.2279·3); zinc oxide (p.1621·2).
Barrier preparation.
Rottapharm, Ital.
Topical paste: Squalane; sweet almond oil; lactic acid; zinc oxide (p.1621·2).
Barrier preparation.

Babygencal *Qualiphar, Belg.*
Chamomile (p.2279·3).
Teething pain.

Babylax *Mann, Irl.; Fleet, Philipp.*
Glycerol (p.2314·2).
Constipation.

Babymed *Cimed, Braz.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); zinc (p.1999·1).
Nappy rash.

Babynose *Cooper (Κοπερ), Gr.†.*
Sodium chloride (p.1686·1).
Drying of nasal mucosa.

Babypasmil *Lafedar, Arg.*
Dicycloverine (p.1723·1).

Babypiril *Zambon, Spain.*
Ibuprofen arginine (p.65·2).
Fever; inflammation; pain.

Babyprin *Pfizer, Turk.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Baby-Rinolo *Bruno, Ital.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Formerly contained phenylpropanolamine hydrochloride, chlorphenamine maleate, and paracetamol.
Respiratory-tract disorders.

Babys Own Cough Syrup *Mentholatum, S.Afr.*
Ammonium chloride (p.1551·3); camphor (p.2273·2).
Coughs.

Babys Own Ointment *Block, Canad.†.*
Zinc oxide (p.1621·2).
Nappy rash.

Babys Own Teething Gel *Block, Canad.†.*
Benzyl alcohol (p.1631·3).
Teething pain.

Babys own Tummy Tablets *Hyde, S.Afr.*
Magnesium hydroxide (p.1743·2).
Constipation; gastric hyperacidity.

Babysan Powder *Szama, Arg.*
Alcloxa (p.1587·2).
Hyperhidrosis; skin disorders.

Babysiton *Faes, Spain.*
Cetylpyridinium chloride (p.1635·1); zinc oxide (p.1621·2).
Skin disorders.

Babyskin *Albephar, Venez.*
Barrier preparation.

Babysteril *Eurospital, Ital.*
Zinc oxide (p.1621·2); almond oil (p.2252·2); wheat-germ oil (p.2415·1); vitamin A (p.1971·2); vitamin E (p.1992·2).
Napkin rash.

Baby-Tex *Sertex, Arg.*
Vitamin A (p.1971·2); zinc oxide (p.1621·2); boric acid (p.2268·1).
Skin disorders.

Babyzim *Sam-On, Israel.*
Pepsin (p.2365·1); lactic acid (p.2329·3); sodium glycerophosphate (p.2315·2); nicotinic acid (p.1957·3).
Gastrointestinal disorders.

Bacacil *Rottapharm, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacagen *Boniscontro & Gazzone, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacal *Nakornpatana, Thai.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Bacampicin *Pharmacia, Belg.†; Pharmacia Upjohn, Port.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacampicine *Pharmacia, Fr.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacard *Chew, Thai.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin and wound disinfection.

Bacard Antiseptic *Chew, Thai.*
Chlorhexidine gluconate (p.1635·3).
Skin, hand, and wound disinfection.

Bacasint *Piam, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacattiv *Uno, Ital.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

bacbutINH *Armoxindo, Indon.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Bacbutol *Armoxindo, Indon.*
Ethambutol (p.275·2).
Tuberculosis.

Baccalin *Bode, Ger.†.*
Benzalkonium chloride (p.1629·1); didecyldimethylammonium chloride (p.1642·2).
Disinfection.

Baccidal *Kyorin, Jpn; Abbott, Spain.*
Norfloxacin (p.309·2).
Bacterial infections.

Bacda-B *Millimed, Thai.*
⊗ Clotrimazole (p.530·1); betamethasone (p.1518·2).
Fungal skin infections.

Bacfar *Elofar, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bacferol *Grisi, Mex.†.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Bach Rescue Remedy *Bach, UK.*
Helianthemum nummularium; clematis vitalba; impatiens glandulifera; prunus cerasifera; ornithogalum umbellatum.

Bacibact *Orion, Fin.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Bacicoline *MD Vision, Fr.*
⊗ Bacitracin (p.210·3); colistimethate sodium (p.256·3); hydrocortisone acetate (p.1535·2).
Eye disorders.

Bacicoline-B *MSD, Neth.*
⊗ Colistimethate sodium (p.256·3); bacitracin (p.210·3); hydrocortisone acetate (p.1535·2).
Inflammatory ear infections.

Bacid
Note. This name is used for preparations of different composition.
Erfa, Canad.
Lactobacillus rhamnosus (p.2372·3).
Diarrhoea; stomatitis.

Uno, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Ciba, USA.
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

Bacidal *Medichem, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Baciderm *SM, Venez.*
Bacitracin (p.210·3).
Skin infections.

Bacidermа *Confar, Port.*
Bacitracin (p.210·3); neomycin (p.305·1).
Bacterial skin infections.

Bacidermina *Greenpharma, Braz.*
Neomycin (p.305·1); bacitracin (p.210·3).
Skin infections.

Bacifim *Medipharma, Arg.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Bacifurane *Melisana, Belg.†.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Bacigen *Cazi, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Skin infections.

Baciguent *Johnson & Johnson, Canad.*
Bacitracin (p.210·3).
Infected burns and wounds.

Bacigyl *Aristo, India.*
Norfloxacin (p.309·2).
Bacterial infections.

Bacigyl-N *Aristo, India†.*
Norfloxacin (p.309·2); metronidazole (p.837·1).

Baci-IM *Pharma Tek, USA.*
Bacitracin (p.210·3).
Bacterial infections.

Baciject *SteriMax, Canad.*
Bacitracin (p.210·3).
Bacterial infections.

Bacilexin *Danlex, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Bacillin *Lafare, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bacillocid rasant *Bode, Ger.†.*
Glutaral (p.1645·2); benzalkonium chloride (p.1629·1); didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Bacillol *Bode, Ger.*
⊗ Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3); alcohol (p.1625·2); 1,6-dihydroxy-2,5-dioxahexane (p.1642·3); mecetronium etilsulfate (p.1652·1).
Surface disinfection.

Bacillol AF *Bode, Ger.*
⊗ Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3); alcohol (p.1625·2).
Surface disinfection.

Bacillol plus *Bode, Ger.*
Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3); glutaral (p.1645·2).
Surface disinfection.

Bacilor *Lyocentre, Fr.*
Lactobacillus casei var *rhamnosus* (p.2372·3).
Diarrhoea.

Bacimycin
Note. This name is used for preparations of different composition.
Grossmann, Hong Kong.
Bacitracin (p.210·3); neomycin (p.305·1).
Burns; infected skin disorders; wounds.

Alpharma, Norw.
Bacitracin zinc (p.210·3); chlorhexidine acetate (p.1635·2).
Infected skin disorders.

Grossmann, Switz.
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Bacimyxin *Pharmascience, Canad.*
Polymyxin B sulfate (p.317·3); bacitracin (p.210·3).
Bacterial skin infections.

Bacin *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacinantrat *Globo, Braz.†.*
Neomycin (p.305·1); bacitracin (p.210·3).
Skin infections.

Bacineo *Luper, Braz.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Bacipro *Biogalenic, Venez.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Bacirom *Aristo, India†.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Bacisporin *Alcala, Spain.*
⊗ Bacitracin zinc (p.210·3); hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected skin disorders.

Bacitin *Pharmascience, Canad.*
Bacitracin (p.210·3).
Bacterial skin infections.

Bacitopic *Laboratorios Chile, Chile†.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Bacterial skin infections; infected burns and wounds.

Bacitopic Compuesto *Laboratorios Chile, Chile.*
⊗ Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); antazoline phosphate (p.567·1); xylometazoline hydrochloride (p.1575·1).
Cold symptoms; rhinitis; sinusitis.

Bacitracina Zimaia *Generis, Port.*
Bacitracin (p.210·3); vitamin A (p.1971·2).
Bacterial skin infections.

Bacitracina-Neo *Zimaia, Port.†.*
Bacitracin (p.210·3); neomycin (p.305·1).
Bacterial skin infections.

Bacitracin-N *YSP, Malaysia.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected burns; infected wounds.

Backache
Note. This name is used for preparations of different composition.
Potter's, UK.
Oral mixture: Bearberry (p.2263·3); juniper (p.2328·2); clivers (p.2284·3); taraxacum (p.2395·1); lappa (p.2330·3).
Backache.

Potter's, UK.
Tablets: Gravel root (p.2317·1); hydrangea root (p.2321·2); buchu (p.2269·3); bearberry (p.2263·3).
Backache.

Backache with Arnica *Hylands, Canad.*
Homoeopathic preparation.

Backache Ledum *Homeocan, Canad.†.*
Homoeopathic preparation.

Backache Maximum Strength Relief *BMS, USA.*
Magnesium salicylate (p.79·2).

Backache Relief *Herbal Concepts, UK.*
Buchu (p.2269·3); bearberry (p.2263·3); parsley piert (p.2363·2).
Backache.

Back-Aid *Rougier, Canad.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).

BackOsamine *Health Perception, UK.*
Glucosamine (p.2313·2); chondroitin; bromelains (p.2269·1); turmeric (p.1473·2).
Back disorders.

Baclo *Douglas, Austral.*
Baclofen (p.1888·1).
Skeletal muscle spasm.

Baclodox *Indeco, Arg.*
Baclofen (p.1888·1).
Skeletal muscle spasm or spasticity.

Baclohexal *Hexal, Austral.†.*
Baclofen (p.1888·1).
Skeletal muscle spasm.

Baclon *Uniao Quimica, Braz.; Leiras, Fin.*
Baclofen (p.1888·1).
Skeletal muscle spasm; spasticity.

Baclopar *Merck, Fin.; Gerard, Irl.*
Baclofen (p.1888·1).
Spasticity.

Baclosal *Unipharm, Israel; M & H, Thai.*
Baclofen (p.1888·1).
Spasticity.

Baclosan *Polpharma, Rus.*
Baclofen (p.1888·1).
Skeletal muscle spasm.

Baclospas *Ashbourne, UK†.*
Baclofen (p.1888·1).
Skeletal muscle spasm or spasticity.

Bacmin *Marnel, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Bacnutri *Grisi, Mex.*
Cod-liver oil (p.1935·2).
Vitamin A and D supplement.

Bacopa Complex *Mediherb, Austral.*
Becopa; schisandra (p.2384·2); Siberian ginseng (p.2386·3); rosemary oil (p.2381·3).
Anxiety; tonic.

Bacotan *TO-Chemicals, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Bacpiryl *Parggon, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacproin *Best, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bacprotin *Prodotti, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacqure *Ranbaxy, Malaysia.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Bacris *Cristalia, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Bacrocin *Valeant, Braz.*
Mupirocin (p.302·3).
Bacterial skin infections.

Bac-Sulfitrin *Ducto, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacta *Masa, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactacin *Osoth, Thai.*
Nitrofurazone (p.309·1).
Burns; skin ulcers; wounds.

Bactalin *Genepharm, Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Bactamox *Grunenthal, Venez.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bactedene *Macrophar, Thai.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, burns, and umbilicus.

Bactelan *Quimica y Farmacia, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacteomycine *Merck Medication Familiale, Fr.†.*
Neomycin sulfate (p.305·1).
Infected skin disorders.

Bacteracin *Teuto, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Bacterian *Musa, Braz.†.*
Benzalkonium chloride (p.1629·1).
Disinfection.

Bacterianos D *Anios, Fr.†.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Disinfection of surfaces.

Bacteric *Hexal, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bacterinil *Luper, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Bacterix *Gifrer Barbezat, Fr.*
Nifuroxazide (p.307·2).

Bacternil *Maffioli, Ital.*
Sulfadiazine silver (p.337·2).
Infected burns and ulcers; infected skin disorders.

Bacterol *Pharmabiotics, Chile.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacteroskin *Stiefel, Arg.†.*
Coco fatty acids; undecenoic acid (p.549·2); triclocarban (p.1665·2).
Feminine hygiene; soap substitute.

Bactesyn *Kalbe, Indon.*
Sultamicillin (p.344·1).
Bacterial infections.

Bacteval *Valmor, Venez.*
Sulfamethizole (p.339·3); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Bactex *Union Drug, Thai.*
Mupirocin (p.302·3).
Bacterial skin infections.

Bacticef *Mitim, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Bacticel *Bago, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bacticide *Euro-Med, Philipp.*
Povidone-iodine (p.1659·2).
Skin cleanser; skin disinfection; vaginal cleansing; wounds.

Bacti-Cleanse *Pedinol, USA.*
Benzalkonium chloride (p.1629·1).
Skin cleanser.

Bacticlor *Ranbaxy, UK.*
Cefaclor (p.217·2).
Bacterial infections.

Bacticort *Montpellier, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Bacticort Complex *Montpellier, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); nystatin (p.543·2).
Infected skin disorders.

Bactidan *Pierre Fabre, Ital.*
Enoxacin (p.268·3).
Urinary-tract and respiratory-tract infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Bactide *Collins, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactident *UPSA Conseil, Fr.*
Sodium perborate (p.1662·1); sodium carbonate (p.2389·1); sodium phosphate (p.1682·3); sodium laurilsulfate (p.2138·3).
False teeth hygiene.

Bactidol *Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia†; Pfizer, Philipp.; Pfizer Consumer, Singapore.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Bactidron *Aventis, S.Afr.†.*
Enoxacin (p.268·3).
Cystitis; gonorrhoea.

Bactiflox *Mepha, Malaysia.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bactifree *United Laboratories, Philipp.*
Mupirocin (p.302·3).
Skin infections.

Bactigent *Filadams, Philipp.; Generics Pharmacal, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bactigram *Magis, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Bactigras *Smith & Nephew, Austral.; Smith & Nephew, Canad.; Braun, Ger.†; Smith & Nephew, Hong Kong†; Smith & Nephew, Ital.; Smith & Nephew, Malaysia; Smith & Nephew, Philipp.; Smith & Nephew, S.Afr.; Smith & Nephew, Thai.; Smith & Nephew, UK.*
Chlorhexidine acetate (p.1635·2).
Burns; scalds; skin infections; ulcers; wounds.

Bactil *CEPA, Spain.*
Ebastine (p.579·1).
Hypersensitivity reactions.

Bactilen *Cryopharma, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactilene *Bergamon, Ital.*
Dimethyldidecylammonium chloride; enoxolone (p.50·1).
Genital irritation.

Bactilina *Richmond, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Bactille *More, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactimed
Note. This name is used for preparations of different composition.
3DDD, Belg.
Amoxicillin (p.202·2).
Bacterial infections.
MedGen, Philipp.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Bactine
Note. This name is used for preparations of different composition.
Bayer Consumer, Canad.
Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).
Skin disorders; wound cleansing.
Miles, USA.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Bactine Antiseptic *Miles, USA.*
Lidocaine (p.1862·3); benzalkonium chloride (p.1629·1).
Skin disorders.

Bactine Pain Relieving Cleansing
Note. This name is used for preparations of different composition.
Bayer, USA.
Topical spray: Lidocaine (p.1862·3); benzalkonium chloride (p.1629·1).
Bayer, USA.
Topical wipes: Pramocaine hydrochloride (p.1868·1); benzalkonium chloride (p.1629·1).

Bactio Rhin *Altana, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Bactio Rhin Prednisolona *Altana, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); prednisolone (p.1540·3).
Allergic rhinitis; sinusitis.

Bactiprox *Erlimpex, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bactisona *Lafedar, Arg.*
⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Skin infections.

Bactisubtil *Sanofi Synthelabo, Belg.†; Cassella-med, Ger.†; Aventis, Port.†; Sanofi-Aventis, Rus.*
Bacillus cereus IP 5832.
Diarrhoea; gastrointestinal disorders; restoration of the gastrointestinal flora.

Bacti-Uril *Bago, Arg.*
Co-trimoxazole (p.258·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Bactiv *YSS, Philipp.*
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bactiver *Maver, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactizon *Sanbe, Philipp.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Bactocef *Garec, S.Afr.†.*
Cefradine (p.233·1).
Bacterial infections.

Bactocin
Note. This name is used for preparations of different composition.
Bunker, Braz.
Mupirocin (p.302·3).
Bacterial skin infections.
Scharper, Ital.
Lactobacillus plantarum.
Vulvovaginitis.
Hormona, Mex.
Ofloxacin (p.310·2).
Bacterial infections.

Bactoclav *OEP, Philipp.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bactoderm
Note. This name is used for preparations of different composition.
Hertz, Braz.
Neomycin (p.305·1); bacitracin (p.210·3).
Skin infections.
Ikapharmindo, Indon.; Agis, Israel†.
Mupirocin (p.302·3).
Bacterial skin infections; skin infections.

Bactof *Svizera, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Bactofen *Teleflex, Ital.*
Benzoxonium chloride (p.1631·2).
Disinfection of skin, mucous membranes, and instruments.

Bactoflox
Note. This name is used for preparations of different composition.
Aurantis, Braz.†; Biochimico, Braz.†.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.
Pentafarma, Port.
Ofloxacin (p.310·2).
Bacterial infections.

Bactomax *Cristalia, Braz.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Bactomicin *Sigma, Braz.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Bactopen *EMS, Braz.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Bactoprim Combi *Combiphar, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactopumon *Cinfa, Spain.*
Tolu balsam (p.1574·2); bromhexine hydrochloride (p.1552·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bactoquin *Otsira, India†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bactoreduct *Azupharma, Ger.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bactoscrub *Vitamed, Israel.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Bactosept *Vitamed, Israel.*
Chlorhexidine gluconate (p.1635·3).
Burn cleansing; disinfection of instruments and skin; wound cleansing.

BactoShield *Amsco, USA.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin disinfection.

Bactox *Innotech, Fr.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bactracid *Apogepha, Ger.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Bactramin *Chugai, Jpn.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bactrazine *Smith & Nephew, S.Afr.*
Sulfadiazine silver (p.337·2).
Infected ulcers and burns.

Bactricid *Soho, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactrim *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Fr.; Piramal, India; Roche, Indon.; Roche, Ital.; Roche, Mex.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, USA.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Bactrim Balsamico *Roche, Arg.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Bactrim Compositum *Roche, Mex.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Bactrimel *Roche, Chile; Roche, Gr.; Roche, Neth.; Roche, Venez.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Bactrisan *Sanval, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bactrizol
Note. This name is used for preparations of different composition.
IMA, Braz.; Corsa, Indon.
Co-trimoxazole (p.258·1).
Bacterial infections.
Behrens, Venez.
Metronidazole (p.837·1).

Bactroban
GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Pol.; GSK, S.Afr.; GSK, Swed.; GSK, Switz.; GSK, UK; SmithKline Beecham, USA.
Mupirocin (p.302·3) or mupirocin calcium (p.302·3).
Bacterial skin infections; elimination of nasal staphylococci; infected burns and wounds.
GSK, Braz.; GSK, Gr.; GSK, India; GSK, Indon.; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Rus.; GSK, Singapore; GSK, Thai.; GSK, Turk.; GSK, Venez.
Mupirocin (p.302·3).
Bacterial skin and wound infections; elimination of nasal staphylococci.
GSK, Fr.; GSK, Hong Kong; GSK, Jpn; Beecham, Port.; GSK, Spain.
Mupirocin calcium (p.302·3).
Bacterial skin infections; elimination of nasal staphylococci.

Bactrobandos *GSK, Venez.†.*
Mupirocin calcium (p.302·3).
Bacterial skin infections.

Bactrocin *LBS, Thai.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Bactrocine *Help, Gr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Bactron *Ronava, Venez.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bactroneo *Neo Quimica, Braz.*
Mupirocin (p.302·3).
Bacterial skin infections.

Bactropin *Cimed, Braz.; Sons, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bactylisine *Peters, Fr.†.*
Mixed quaternary ammonium salts; polyalkylamine.
Surface disinfection.

Bacxal *Pharmacare, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Baczole *San Marino, Philipp.; Nakornpatana, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Badiaga Complexe no 47 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 47.

Badyket
Note. This name is used for preparations of different composition.
Menarini, Arg.
Bemiparin (p.1223·2).
Thromboembolic disorders.
Tecefarma, Spain†.
Dexketoprofen trometamol (p.73·1).
Inflammation; pain.

Baflox *Galeno, Venez.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Bafucin *Pfizer, Fin.; Pfizer, Swed.*
Benzocaine (p.1854·1); gramicidin (p.286·1); cetylpyridinium chloride (p.1635·1); dichlorobenzyl alcohol (p.1642·1).
Mouth and throat disorders.

Bages *Unison, Malaysia; Unison, Thai.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Bagno Oculare *AFOM, Ital.†; Ogna, Ital.†.*
Zinc sulfate (p.1999·2); boric acid (p.2268·1); borax (p.2268·1).
Eye irritation.

Bagobutam *Bago, Chile†.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Bagociletas *Bago, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Bagociletas con Anestesia *Bago, Arg.*
Nitrofurantoin (p.308·1); tetracaine dibudinate (p.1871·3).
Mouth and throat disorders.

Bagociletas sin Anestesia *Bago, Arg.†.*
Nitrofurantoin (p.308·1); cetrimonium bromide (p.1635·1); hexylresorcinol (p.1647·1).
Mouth and throat disorders.

Bagoderm *Bago, Arg.*
Sodium acexamate (p.2245·2); cetrimonium bromide (p.1635·1).
Burns; cracked nipples; nappy rash; wounds.

Bagohepat *Bago, Arg.; Armstrong, Mex.*
Cynara (p.2291·2); dehydrocholic acid (p.2292·2).
Digestive disorders; liver disorders.

Bagomet *Montpellier, Rus.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Bagomicina *Bago, Chile.*
Minocycline (p.300·3).
Bacterial infections.

Bagopril *Bago, Rus.*
Enalapril maleate (p.1276·1).

Bagothyrox *Montpellier, Rus.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Bagovit A
Bago, Arg.
Vitamin A (p.1971·2).
Skin disorders.
Bago, Chile.
Vitamin A palmitate (p.1973·1).
Skin disorders.

Bagovit A Plus *Bago, Arg.*
⊗ Vitamin A palmitate (p.1973·1); triamcinolone acetonide (p.1544·3).
Skin disorders.

Bagovit Avant Piel *Bago, Arg.*
Vitamin A (p.1971·2); methylsilanol manuronate; dimethylsilanol hyaluronate.
Skin disorders.

Bagovit Solar *Bago, Arg.*
A range of sunscreen preparations.

Bagren *Serono, Braz.*
Bromocriptine mesilate (p.798·1).
Acromegaly; benign breast disorders; female infertility; lactation inhibition; menstrual disorders; parkinsonism; polycystic ovary; prolactinomas.

Bagton *Loeffler, Mex.*
Clioquinol (p.254·1).
Burns; skin infections.

Baikadent *Herbapol Wroclaw, Pol.*
Skullcap (p.2388·2).
Mouth disorders.

Bain antirhumatismal *Kneipp, Switz.†.*
Juniper oil (p.2328·3); sweet birch oil (p.86·2).
Bath additive; musculoskeletal and joint disorders.

Bain de Bouche Lipha *Merck Medication Familiale, Fr.*
Veratrol; menthol (p.2340·1); resorcinol (p.1612·1) cloral hydrate (p.979·1).
Mouthwash.

Bain contre les refroidissements *Kneipp, Switz.†.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2).
Bath additive; coughs and colds.

Bain extra-doux dermatologique *Widmer, Switz.*
Ichthammol (p.1599·1); chamomile (p.2279·3); guaiazulene (p.2317·3).
Skin disorders.

Bain de Soleil *Procter & Gamble, USA.*
SPF 4: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Bain de Soleil All Day
Note. This name is used for preparations of different composition.
Procter & Gamble, USA.
SPF 4; SPF 8: Octinoxate (p.1608·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.
Procter & Gamble, USA.
SPF 15; SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Bain de Soleil Color
Note. This name is used for preparations of different composition.
Procter & Gamble, USA.
SPF 8+: Octinoxate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.
Procter & Gamble, USA.
SPF 15+; SPF 30+: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Luminessence *Schering-Plough, Canad.†.*
SPF 4; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Oil Free Faces *Schering-Plough, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Oil-Free Protecteur *Schering-Plough, Canad.†.*
SPF 25: Avobenzone (p.1589·3); homosalate (p.1598·1); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Orange
Note. This name is used for preparations of different composition.
Schering-Plough, Canad.†.
SPF 4: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Schering-Plough, Canad.†.
SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Tanning Mist
Note. This name is used for preparations of different composition.
Schering-Plough, Canad.†.
SPF 4: Octocrilene (p.1608·3); octinoxate (p.1608·2). Formerly known as Bain de Soleil Mega Tan.
Sunscreen.

Schering-Plough, Canad.†.
SPF 8: Octocrilene (p.1608·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Bain de Soleil Tropical Schering-Plough, Canad.†.
SPF 4: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Bains Romains Couzian, Fr.
St John's wort oil (p.423·2).
Bath additive; dry skin; skin irritation.

Bainto TP, Thai.
Gamma-aminobutyric acid (p.2308·1).
Amnesia; hypertension; mental function impairment; palsy; speech disorders.

Bajaten
Note. This name is used for preparations of different composition.
Merck, Arg.
⊗ Indapamide (p.1314·1).
Hypertension.

Sanitas, Chile.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Bajaten D Sanitas, Chile.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Bajumol Poen, Arg.†.
Mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1); phenazone (p.116·1).
Eye inflammation and irritation.

Bakam De Salute, Ital.
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bakamsilin Kocak, Turk.
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Bakol Arkomedika, Fr.
Phytosterols (p.1373·1); vitamin E (p.1992·2).
Hypercholesterolaemia.

Baktisef Sanovel, Turk.
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bakton Ilsan, Turk.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Baktonium Bode, Ger.†.
Benzalkonium chloride (p.1629·1).
Hand and skin disinfection.

Bakumondo-to Tsumura, Jpn.
Ophiopogon tuber; pinellia tuber; jujube; liquorice; ginseng; brown rice.
Traditional Kampo medicine.

Balacet Cornerstone, USA.
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Pain.

Balad Korean Drug, Singapore†.
Sodium fusidate (p.279·3).
Bacterial skin infections; infected wounds and burns.

Baladex Aflofarm, Pol.
Guaifenesin (p.1561·3); theophylline (p.1140·1).
Obstructive airways disease.

Balanca Grunenthal, Ger.
Ethinylestradiol (p.2101·3); chlormadinone acetate (p.2084·3).
Combined oral contraceptive.

Balance Fresenius Medical, Cz.; Fresenius Medical, Fin.; Fresenius Medical, Hung.; Fresenius Medical, Neth.; Fresenius Medical, Port.; Fresenius Medical, Swed.
Sodium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose monohydrate (p.1670·3).
A range of peritoneal dialysis solutions.

Balance Elastin E Bio-Pharmaceuticals, Malaysia†.
Elastin (p.2286·1); vitamin E (p.1992·2).
Dry skin disorders.

Balance Glucosa Calcio Fresenius Medical, Spain.
Calcium chloride; magnesium chloride; sodium chloride; sodium lactate; glucose (p.1670·3).
Peritoneal dialysis.

balance glucose calcium Fresenius Kabi, Denm.
Glucose; calcium chloride; magnesium chloride; sodium chloride; sodium lactate (p.1670·3).
Peritoneal dialysis.

Balanced B Adams, Canad.; General Nutrition, Canad.; Hall, Canad.; Pharmetics, Canad.; Vitality, Canad.
Vitamin B substances (p.1922·1).

Balanced B Complex plus Vitamins C & E Pharmavite, Canad.†.
Vitamin B substances, vitamin C, and Vitamin E (p.1922·1).

Balanced C Complex Jamieson, Canad.†.
Ascorbic acid (p.1983·3).

Balanced Cal-Mag Quest, UK.
Calcium, magnesium, and vitamin D preparation (p.1922·1).

Balanced Irrigating Salt Solution Teva, Israel.
Electrolyte solution (p.1667·1).
Irrigation of eyes, ears, nose, and throat.

Balanced Salt Solution Alcon, NZ†; Euro-Med, Philipp.; Abbott, USA; Akorn, USA; Bausch & Lomb, USA.
Electrolyte solution (p.1667·1).
Eye irrigation.

Balancid Novum AstraZeneca, Denm.; AstraZeneca, Fin.
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Balans Labomed, Chile.
Betacarotene; alpha tocopherol; ascorbic acid (p.1922·1).
Vitamin supplement.

Balansol Teva, Hung.
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium acetate; sodium malate; sorbitol (p.1965·1) (p.1667·1).
Fluid and electrolyte disorders.

Balbek Provit, Mex.
Dextromethorphan (p.1555·2).
Coughs.

B-Alcerin Medicus, Gr.†.
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Balcor Baldacci, Braz.; Baldacci, Port.†.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Baldin-CE Neckerman, Braz.†.
Dipyrone (p.49·2); sodium camsilate (p.2388·3); ascorbic acid (p.1983·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3).
Cold and influenza symptoms.

Baldmin Mintlab, Chile.
Pipenzolate bromide (p.1762·2); phenobarbital (p.492·2).

Baldorm Klein, Ger.
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Baldracin Austroplant, Austria; Austroplant, Cz.
Valerian (p.2410·1); peppermint leaf (p.1761·2); melissa (p.2339·3); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Baldrian AMA Kwizda, Austria.
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Baldrian-Dispert Solvay, Swed.
Valerian (p.2410·1).
Anxiety; sleep disorders.

Baldrian-Dispert Nacht Solvay, Ger.
Valerian (p.2410·1); lupulus (p.2335·2).
Insomnia.

Baldrinetten Solvay, Austria†.
Valerian (p.2410·1).
Sedative.

Baldriparan Whitehall-Robins, Switz.
Valerian (p.2410·1); melissa (p.2339·3); lupulus (p.2335·2).
Nervous disorders.

Baldriparan N Stark Whitehall-Much, Ger.†.
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Baldriparan pour la nuit Whitehall-Robins, Switz.
Valerian (p.2410·1).
Sleep disorders.

Baldriparan Stark Whitehall-Much, Ger.†.
Valerian (p.2410·1).
Sleep disorders.

Baldrisedon Wild, Switz.†.
Valerian (p.2410·1).
Anxiety; sleep disorders.

Baldrisedon plus Wild, Switz.†.
Valerian (p.2410·1); melissa (p.2339·3); peppermint leaf (p.1761·2).
Nervous disorders; sleep disorders.

Baldrivit Rodisma, Ger.
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Baldurat Pohl, Ger.
Valerian (p.2410·1).
Nervous tension; sleep disorders.

Balepton Leovan, Gr.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Baliartrin Baliarda, Arg.
Glucosamine sulfate (p.2313·2).
Musculoskeletal and joint disorders.

Baliartrin Duo Baliarda, Arg.
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Arthroses.

Balidon Recalcine, Chile.
Triazolam (p.1033·2).
Sleep disorders.

Balidorm Baliarda, Arg.†.
Zolpidem tartrate (p.1037·3).

Baliglue Baliarda, Arg.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Balin Atlantic, Malaysia; Atlantic, Singapore.
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Bacterial infections.

Balisa Riemser, Ger.
⊗ Urea (p.1620·2).
Keratinisation disorders.

Balisa VAS Riemser, Ger.
⊗ Urea (p.1620·2); tretinoin (p.1618·1).
Keratinisation disorders.

Balkis
Note. This name is used for preparations of different composition.
Dolorgiet, Ger.†.
Capsules: Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Colds; hay fever.

Dolorgiet, Ger.
Nasal drops; nasal spray: ⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Ball Argenfarma, Arg.†.
Aspirin (p.20·3).

Balm of Gilead Potter's, UK.
⊗ Balm of Gilead (p.2371·1); squill (p.1573·1); lobelia (p.2157·2); lungwort.
Coughs.

Balmandol
Spirig, Cz.; Spirig, Switz.
Almond oil (p.2252·2); light liquid paraffin (p.2031·1).
Skin disorders.

Orva, Turk.
Almond oil (p.2252·2); liquid paraffin (p.2030·3).
Eczema; psoriasis; seborrhoeic dermatitis.

Balmed Hermal Boots Healthcare, Switz.
Soya oil (p.1965·3).
Bath additive; skin disorders.

Balmed Hermal F Boots Healthcare, Switz.
Arachis oil (p.2259·1); liquid paraffin (p.2030·3).
Bath additive; skin disorders.

Balmed Hermal Plus Boots Healthcare, Switz.
Soya oil (p.1965·3); lauromacrogol 400 (p.1916·1).
Bath additive; skin disorders.

Balmex
Note. This name is used for preparations of different composition.
GSK, Arg.†.
Zinc oxide (p.1621·2).
Nappy rash.

GSK, Braz.
Zinc oxide (p.1621·2); liquid paraffin (p.2030·3); beeswax (p.2028·1); silicone (p.2032·1); peru balsam (p.2365·3).
Skin disorders.

Balmex Baby Macsil, USA.
Zinc oxide (p.1621·2); peru balsam (p.2365·3); corn starch (p.1968·1); calcium carbonate (p.1714·1).
Nappy rash.

Balmex Emollient Chattem, USA.
Emollient and moisturiser.

Balmikel Minorock Mandiri, Indon.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3).
Muscle and joint pain.

Balminil Elfar, Spain†.
Nitrendipine (p.1358·2).
Hypertension.

Balminil Codeine Night-Time+Expectorant Rougier, Canad.
Codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs; respiratory-tract congestion.

Balminil Codeine+Decongestant+Expectorant Rougier, Canad.
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Balminil Cough & Flu Rougier, Canad.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Congestion; coughs.

Balminil DM Rougier, Canad.; Rougier, Hong Kong†.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Balminil DM+Decongestant Rougier, Canad.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Balminil DM D.
Congestion; coughs.

Balminil DM+Decongestant+Expectorant Rougier, Canad.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly known as Balminil DM D E.
Congestion; cough.

Balminil DM+Expectorant Rougier, Canad.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Formerly known as Balminil DM E.
Coughs.

Balminil Expectorant Rougier, Canad.
Guaifenesin (p.1561·3).
Coughs.

Balminil Nasal Decongestant Rougier, Canad.
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Balminil Night-Time Rougier, Canad.
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Congestion; coughs.

Balminil Suppositories Rougier, Canad.
Eucalyptus oil (p.2301·2); niaouli oil (p.2351·3); menthol (p.2340·1); sodium dibunate (p.1573·1).
Coughs.

Balm-Mint Andrae, Austria†.
Melissa (p.2339·3).
Insomnia; nervous disorders.

Balmosa Forest Laboratories, UK.
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, and soft-tissue pain.

Balmox Beecham, Port.; Alloga, Switz.
Nabumetone (p.91·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Balneoconzen N S & K, Ger.
Soya oil (p.1965·3).
Skin disorders.

Balneol Solvay, USA.
Skin cleanser.

Balneovit BioLife, Ger.
Soya oil (p.1965·3).
Bath additive; skin disorders.

Balnetar Westwood-Squibb, Canad.; Westwood-Squibb, USA.
Coal tar (p.1616·2).
Dermatitis; psoriasis; skin disorders.

Balneum
Note. This name is used for preparations of different composition.
Hermal, Austria; Boots Healthcare, Ger.; Hermal, Ger.; Boots Healthcare, Irl.; Hermal, Israel; Crookes Healthcare, UK.
Soya oil (p.1965·3).
Bath additive; dry skin conditions.

Hermal, Hong Kong.
White soft paraffin (p.2031·2); wool fat (p.2033·2); light liquid paraffin (p.2031·1).
Skin disorders.

Hermal, Malaysia; Hermal, Singapore; Boots, Thai.†; Hermal, Thai.†.
Bath oil: Light liquid paraffin (p.2031·1).
Bath additive; dry skin disorders; pruritus.

Hermal, Malaysia; Hermal, Singapore; Boots, Thai.†; Hermal, Thai.†.
Cream; lotion: Wool fat (p.2033·2); light liquid paraffin (p.2031·1); white soft paraffin (p.2031·2).
Dry skin disorders.

Balneum F Hermal, Austria; Boots Healthcare, Ger.; Hermal, Ger.; Hermal, Israel.
Arachis oil (p.2259·1); light liquid paraffin (p.2031·1).
Bath additive; skin disorders.

Balneum Hermal Hermal, Cz.; Boots Healthcare, Ital.; Herrmann, Pol.; Boots Healthcare, Switz.†.
Soya oil (p.1965·3).
Bath additive; dry skin disorders; pruritus.

Balneum Hermal F Hermal, Cz.; Herrmann, Pol.; Boots Healthcare, Switz.†.
Arachis oil (p.2259·1); liquid paraffin (p.2030·3).
Bath additive; dry skin disorders; pruritus.

Balneum Hermal Forte Boots Healthcare, Ital.
Arachis oil (p.2259·1); liquid paraffin (p.2030·3).
Bath additive; skin disorders.

Balneum Hermal Plus
Hermal, Cz.; Herrmann, Pol.
Soya oil (p.1965·3); lauromacrogol 400 (p.1916·1).
Bath additive; dry skin disorders; pruritus.

Boots Healthcare, Switz.†.
Soya oil (p.1965·3); macrogol lauril ethers (p.1916·1).
Skin disorders.

Balneum Intensiv
Note. This name is used for preparations of different composition.
Hermal, Hong Kong; Hermal, Malaysia.
⊗ Urea (p.1620·2).
Dry skin disorders.

Hermal, Singapore; Boots, Thai.†; Hermal, Thai.†.
Cream; lotion; wash: ⊗ Urea (p.1620·2).
Dry skin disorders.

Hermal, Singapore.
Shower gel: Soap substitute.

Boots, Thai.†; Hermal, Thai.†.
Shower lotion: Emollient; moisturiser.

Balneum Intensiv Plus
Hermal, Hong Kong; Hermal, Malaysia; Boots, Thai.†; Hermal, Thai.†.
⊗ Lauromacrogol (p.1916·1); urea (p.1620·2).
Dry skin disorders; pruritus.

Hermal, Singapore.
⊗ Macrogol lauril ether (p.1916·1); urea (p.1620·2).
Skin disorders.

Balneum Plus
Hermal, Austria; Boots Healthcare, Ger.; Hermal, Ger.
Soya oil (p.1965·3); lauromacrogol 400 (p.1916·1).
Bath additive; skin disorders.

Boots Healthcare, Irl.; Hermal, Israel.
Soya oil (p.1965·3); laureth compounds (p.1916·1).
Bath additive; dry skin; pruritus.

Crookes Healthcare, UK.
Bath additive: Soya oil (p.1965·3); macrogol lauril ethers (p.1916·1).
Dry skin; pruritus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Crookes Healthcare, UK.
Cream: ⊗ Macrogol lauril ethers (p.1916·1); urea (p.1620·2).
Skin disorders.

Balnox *Guidotti, Gr.*
Lacidipine (p.1322·2).
Hypertension.

Balpril *Baldacci, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Balsabit *Pensa, Spain.*
Pramocaine hydrochloride (p.1868·1).
Burns; insect bites; pruritus.

Balsader *Drovepat, Venez.†; Kimiceg, Venez.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Rubefacient.

Balsam Mentholi compositum *Chema-Elektromet, Pol.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders; neuralgia.

Balsam Sakti *Konimex, Indon.*
Menthol (p.2340·1); camphor (p.2273·2); clove oil (p.2285·1); peppermint oil (p.1761·2); cajuput oil (p.2271·2).
Nasal congestion; pain.

Balsam Szostakowskiego (Vinilinum) *ICN, Pol.*
Polyvinox.
Burns; chilblains; gastric hyperacidity; peptic ulcer; ulcers; wounds.

Balsamex *Konimex, Indon.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Muscle and joint pain.

Balsamico *Sella, Ital.*
Cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Cold symptoms.

Balsamicum *Weleda, UK.*
Homoeopathic preparation.

Balsamina *Ahimsa, Arg.*
Hexylresorcinol (p.1647·1); benzocaine (p.1854·1).
Formerly known as Balsamin.
Mouth and throat disorders.

Balsamina Kroner *Ceccarelli, Ital.*
Sulfogaiacol (p.1573·2); mepyramine maleate (p.585·2).
Catarrh; coughs.

Balsamo Alesida *Pfizer, Venez.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Balsamo Analgesico
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain.

Gestafarma, Port.
Salicylic acid (p.1612·2); benzyl nicotinate (p.28·1); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Balsamo Analgesico Basi *Basi, Port.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Formerly contained salicylic acid, menthol, and methyl salicylate.
Musculoskeletal, joint, and soft-tissue disorders.

Balsamo Analgesico con Fenilbutazona *Sanitas, Chile.*
Phenylbutazone (p.117·1); dimeticones (p.2032·1); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and peri-articular pain.

Balsamo Analgesico Labesfal *Labesfal, Port.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Formerly contained methyl salicylate (.
Musculoskeletal, joint, and soft-tissue disorders.

Balsamo Analgesico Sanitas *Upsifarma, Port.*
Methyl salicylate (p.85·3); salicylic acid (p.1612·2); menthol (p.2340·1); belladonna (p.2263·3).
Formerly contained methyl salicylate, salicylic acid, menthol, and capsicum (.
Musculoskeletal and joint pain.

Balsamo Bengue *EMS, Braz.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Balsamo Branco *Catarinense, Braz.*
Lavender (p.2331·1); melissa (p.2339·3); caraway (p.2276·3); aniseed (p.2258·2); cinnamon (p.2283·1); clove (p.2284·3); lemon (p.2332·3).
Dyspepsia.

Balsamo Ifusa *Ifusa, Mex.*
Methyl salicylate (p.85·3); pine oil (p.2368·2); peppermint oil (p.1761·2).
Musculoskeletal and joint pain.

Balsamo Italstadium *Falqui, Ital.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint pain.

Balsamo Kneipp *Boehringer Ingelheim, Spain†.*
Camphor (p.2273·2); Peru balsam (p.2365·3); cineole (p.2282·3); pine silvestris oil (p.2368·2); thymol (p.1664·3); menthol (p.2340·1).
Respiratory-tract disorders.

Balsamo Leon *Beiersdorf, Chile†.*
Menthol (p.2340·1); camphor (p.2273·2); thymol (p.1664·3); pine oil (p.2368·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); anfocerina K.
Coughs and cold symptoms.

Balsamo Nordin *Nordin, Mex.*
Arnica (p.2260·2); chamomile (p.2279·3); methyl salicylate (p.85·3).
Soft-tissue disorders.

Balsamo Nordin Unguento *Nordin, Mex.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Balsamo Nostrum *Nostrum, Port.*
Menthol (p.2340·1); methyl salicylate (p.85·3); camphor (p.2273·2).

Balsamo Primi Denti *Sanofi-Aventis OTC, Ital.*
Milk serum.
Teething pain.

Balsamo Sifcamina *Teofarma, Ital.*
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3).
Musculoskeletal disorders.

Balsamorhinol *Pierre Fabre, Fr.*
Chlorobutanol (p.1639·2); menthol (p.2340·1).
Rhinitis.

Balsan *Labinca, Arg.†.*
Sodium chloride; polysorbate 80 (p.1919·2); benzalkonium chloride.
Snoring.

Balsasulf *Fabra, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Balsatux *Edmond Pharma, Ital.†.*
Sulfogaiacol (p.1573·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Balsedrina *IQFA, Mex.*
Dextromethorphan (p.1555·2).
Coughs.

Balsem Sulphuris *Lennon, S.Afr.*
Turpentine oil (p.2406·3); precipitated sulfur (balsem sulfuris) (p.1614·1).
Backache; kidney disorders.

Balsem Vita GEEL *Lennon, S.Afr.*
Spike lavender oil (p.2392·1); rosemary oil (p.2381·3); clove oil (p.2285·1); cassia oil (p.2278·1); nutmeg oil (p.2355·3); lemon oil (p.2332·3); thyme oil (p.2401·2).
Colic; flatulence.

Balsem Vita ROOI *Lennon, S.Afr.*
Spike lavender oil (p.2392·1); clove oil (p.2285·1); cassia oil (p.2278·1); nutmeg oil (p.2355·3); lemon oil (p.2332·3); rosemary oil (p.2381·3); thyme oil (p.2401·2).
Colic; flatulence.

Balsem Vita WIT *Lennon, S.Afr.*
Cassia oil (p.2278·1); spike lavender oil (p.2392·1); clove oil (p.2285·1); nutmeg oil (p.2355·3); thyme oil (p.2401·2).
Colic; flatulence.

Balsem-Kopiva *Lennon, S.Afr.*
Balsam copaiba.
Bladder and kidney disorders.

Balsibron *Liferpal, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Balsibron-C *Liferpal, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders with viscous mucus.

Balsoclase *UCB, Neth.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Balsoclase Antitussivum *UCB, Belg.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Balsoclase Compositum *UCB, Neth.*
Pentoxyverine citrate (p.1567·3); cineole (p.2282·3); sodium citrate (p.1673·3); terpin hydrate (p.1573·3); thyme (p.2401·1).
Coughs.

Balsoclase Expectorans
Note. This name is used for preparations of different composition.
UCB, Belg.
Oral solution; syrup: Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Coughs.

UCB, Belg.
Suppositories: Pentoxyverine (p.1567·3); guaifenesin (p.1561·3); cineole (p.2282·3).
Balsoclase suppositories formerly contained pentoxyverine, guaifenesin, cineole, terpineol, and terpin hydrate.
Coughs.

Balsoclase-E *UCB, Neth.*
Pentoxyverine (p.1567·3); cineole (p.2282·3).
Coughs.

Balsofumine *Sanofi-Aventis, Fr.*
Peru balsam (p.2365·3); sumatra benzoin (p.2394·2); eucalyptus (p.2301·2); lavender oil (p.2331·2); thyme oil (p.2401·2).
Respiratory-tract congestion.

Balsofumine Mentholee *Sanofi Synthelabo OTC, Fr.*
Peru balsam (p.2365·3); sumatra benzoin (p.2394·2); eucalyptus (p.2301·2); lavender oil (p.2331·2); thyme oil (p.2401·2); menthol (p.2340·1).
Respiratory-tract congestion.

Balsolan *Gemi, Pol.*
Peru balsam (p.2365·3).
Burns; chilblains; ulcers.

Balsolene *Cooperation Pharmaceutique, Fr.*
Eucalyptus oil (p.2301·2); niaouli oil (p.2351·3); menthol (p.2340·1); siam benzoin (p.2386·2).
Respiratory-tract congestion.

Balsoprim *Juste, Spain.*
Bromhexine hydrochloride (p.1552·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bals-Sulphur *Sulphur Zdroj, Pol.*
Sodium chloride; bromide; iodide; borate (p.1667·1); sulfur (p.1614·1); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Balta Intimo *Boots Healthcare, Ital.†.*
Menthol (p.2340·1); cineole (p.2282·3); Iceland moss (p.2324·1); undecenoic acid (p.549·2).
Personal hygiene.

Balta-Crin Tar *Boots Healthcare, Ital.†.*
Tar (p.1616·2); allantoin (p.1588·1).
Seborrhoeic dermatitis.

Balticina *Rowe-Fleming, Venez.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Balto Foot Balm *Lane, UK.*
Camphor (p.2273·2); menthol (p.2340·1); zinc oxide (p.1621·2); precipitated sulfur (p.1614·1).
Aching feet; excessive perspiration; hard skin.

Baludol *Balu, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Balurol *Baldacci, Braz.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Balya *Sanofi Synthelabo, Turk.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).

Balzide *Malesci, Ital.*
Balsalazide sodium (p.1709·2).
Ulcerative colitis.

Balziva *Barr, USA.*
21 Tablets, ethinylestradiol (p.2101·3); norethisterone (p.2119·3); 7 tablets, inert.
Combined oral contraceptive.

Bamalite *Tecnobio, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Bambec *AstraZeneca, Austria; AstraZeneca, Braz.; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Ger.; Stern, Ger.; AstraZeneca, Hong Kong†; AstraZeneca, Hung.†; AstraZeneca, Ital.†; AstraZeneca, Malaysia†; AstraZeneca, NZ; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Singapore; Epsilon, Spain; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK.*
⊗ Bambuterol hydrochloride (p.1115·3).
Asthma; obstructive airways disease.

Bambudil *Cipla, India.*
⊗ Bambuterol hydrochloride (p.1115·3).
Obstructive airways disease.

Bamgetol *Mersifarma, Indon.*
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Bamifix *Farmalab, Braz.; Chiesi, Ital.*
Bamifylline hydrochloride (p.1116·1).
Obstructive airways disease.

Bamixol *Pulitzer, Ital.†.*
Bamifylline hydrochloride (p.1116·1).
Asthma; bronchospasm.

Bamycor *Hassle, Swed.†.*
Aspirin (p.20·3).
Cardiovascular and cerebrovascular disorders.

Bamyl *Ellem, Swed.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Bamyl koffein *Ellem, Swed.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Bamyl S *Ellem, Swed.*
Aspirin (p.20·3).
Fever; pain.

Bamyl S koffein *Ellem, Swed.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Bamyxin *Rekah, Israel.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Ban Pain
Note. This name is used for preparations of different composition.
Pharmacare, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Pharmacare, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain with tension.

Banadroxin *Pharmanik (Φαρμανικ), Gr.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Banadyne-3 *Norstar, USA.*
⊗ Lidocaine (p.1862·3); menthol (p.2340·1); alcohol (p.1625·2).
Herpes labialis.

Banalg *Forest Pharmaceuticals, USA.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Banan *Sankyo, Hong Kong; Sandoz, Indon.; Sankyo, Jpn; Pharmalink, Philipp.; Sankyo, Philipp.; Sankyo, Thai.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Banana Boat Active Kids
Note. This name is used for preparations of different composition.
Banana Boat, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat, Canad.†.
SPF 50: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Active Sport *Banana Boat, Canad.†.*
SPF 25: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Aloe Vera Lip Balm Sunblock
Playtex, Canad.
SPF 30: Padimate O (p.1609·1); octinoxate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1).
Sunscreen.

Banana Boat Baby Sunblock *Playtex, Canad.*
SPF 50: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat Cool Coloring *Banana Boat, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat Cool Colorz *Banana Boat, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat Dark Tanning
Note. This name is used for preparations of different composition.
Playtex, Canad.
Lotion SPF 4: Padimate O (p.1609·1).
Sunscreen.

Playtex, Canad.
Oil SPF 4: Padimate O (p.1609·1); octinoxate (p.1608·2).
Sunscreen.

Playtex, Canad.
Oil SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3); padimate O (p.1609·1).
Sunscreen.

Banana Boat Faces Plus *Banana Boat, Canad.†.*
SPF 23: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Formerly contained octinoxate, octisalate, oxybenzone, homosalate, titanium dioxide.
Sunscreen.

Banana Boat Funky Fruit Lip Balm *Banana Boat, Canad.†.*
SPF 15: Padimate O (p.1609·1); homosalate (p.1598·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Kids Sunblock
Note. This name is used for preparations of different composition.
Playtex, Canad.
Cream SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Playtex, Canad.
SPF 50: Octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat, Canad.†.
Spray SPF 48: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat, Canad.
Stick SPF 30: Homosalate (p.1598·1); octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Quik Blok Kids *Playtex, Canad.*
SPF 25: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Quik Dry *Banana Boat, Canad.†.*
SPF 15; SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Sooth-A-Caine *Playtex, Canad.*
Menthol (p.2340·1); lidocaine (p.1862·3).

Banana Boat Sport
Note. This name is used for preparations of different composition.
Playtex, Canad.
Cream SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Playtex, Canad.
Lip balm SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); oxybenzone (p.1608·3); padimate O (p.1609·1).
Sunscreen.

Playtex, Canad.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Playtex, Canad.
Stick SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Sunscreen Banana Boat, Canad.†.
SPF 8: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Banana Boat Ultra Banana Boat, Canad.; Playtex, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat Ultra Plus
Note.This name is used for preparations of different composition.
Playtex, Canad.
Lotion SPF 50: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3).
Sunscreen.

Banana Boat, Canad.†.
Spray SPF 48: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Banana Boat Vitamin E Lip Balm Sunblock
Playtex, Canad.†.
SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3); padimate O (p.1609·1).
Sunscreen.

Banatin Remedina, Gr.
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Bancap HC Forest Pharmaceuticals, USA.
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Band Aid Spruhpflaster Johnson & Johnson, Ger.†.
Cellaburat; octyldiphenylphosphate.
Skin ulcers; wounds.

Band-Aid Antibiotic Johnson & Johnson, Canad.
Bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).

Band-Aid Anti-Itch Johnson & Johnson, Canad.
Camphor (p.2273·2).
Skin disorders.

Bandax Lloyd, Philipp.
Cefalexin (p.218·2).
Bacterial infections.

Bandol Pharmacia, Spain†.
Paracetamol (p.108·1).
Fever; pain.

Bandotan Teva Tuteur, Arg.†.
Didanosine (p.870·2).
HIV infection.

Bandrobon Dupomar, Arg.
Ibandronate sodium (p.1098·3).
Hypercalcaemia of malignancy; myeloma; osteolysis of malignancy; osteoporosis; Paget's disease of bone.

Banedif
Note.This name is used for preparations of different composition.
Maxfarma, Spain.
Bacitracin (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Infected skin disorders.

Bago, Chile.
Ointment: Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Bacterial skin infections.

Bago, Chile.
Topical powder: Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); aluminium hydroxide (p.1706·2).
Bacterial skin infections.

Banedif Oftalmico Bago, Chile.
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial eye infections.

Banedif Oftalmico con Prednisolona Bago, Chile.
⊗ Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Infected eye disorders with inflammation.

Baneocin
Sandoz, Austria.
Bacitracin (p.210·3) or bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial infections.

Sandoz, Hung.; Sandoz, Malaysia; Sandoz, Pol.; Sandoz, Rus.; Sandoz, Singapore.
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial infections.

Baneopol Streuli, Switz.
Bacitracin (p.210·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Infected eye and skin disorders.

Banflex Forest Pharmaceuticals, USA.
Orphenadrine citrate (p.812·1).
Musculoskeletal pain.

Banholeum Sofex, Port.
Soya oil (p.1965·3).
Skin disorders.

Banholeum Composto Sofex, Port.
Soya oil (p.1965·3); coal tar (p.1616·2).
Bath additive; skin disorders.

Banholeum Gele Sofex, Port.
Soya oil (p.1965·3); liquid paraffin (p.2030·3).
Skin disorders.

Banidor Hertz, Braz.†.
Caffeine (p.1116·3); dipyrone (p.49·2); orphenadrine (p.812·2).

Banimed Bajamed, Mex.
Minocycline (p.300·3).
Bacterial infections.

Banish II Smith & Nephew, Austral.
Zinc ricinoleate (p.2417·3); dipropylene glycol.
Colostomy and ileostomy odour.

Banishing Cream Avon, Canad.
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Banlice Pfizer Consumer, Austral.
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Banner Protein Osotspa, Thai.
A preparation for enteral nutrition (p.1922·1).

Bano Meditop, Hung.
Calcium citrate (p.1675·3).
Calcium deficiency; calcium supplement; osteoporosis.

Bano Coloide Arlex, Mex.
Soya bean (p.1965·3); povidone-iodine (p.1659·2).
Skin disorders.

Bano Liquido con Eucalipto Johnson & Johnson, Arg.†.
Menthol (p.2340·1); cineole (p.2282·3); rosemary oil (p.2381·3).

Bano Ocular Poen, Arg.
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Bano Ocular Agrand Ahimsa, Arg.
⊗ Naphazoline (p.1565·1).
Eye disorders.

Banocide GSK, India.
Diethylcarbamazine citrate (p.143·1).
Worm infections.

Banocin
Note.This name is used for preparations of different composition.
Nakornpatana, Thai.
Ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Burns; ulcers; wounds.

Nakornpatana, Thai.
Topical powder: Clioquinol (p.254·1); bacitracin (p.210·3); neomycin sulfate (p.305·1); zinc stearate (p.2139·3).
Burns; ulcers; wounds.

Banoclus Frasca, Arg.; Lamsa, Arg.
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3).
Fever; inflammation; pain.

Banoftal Alcon, Arg.†; Alcon Cusi, Spain.
Hamamelis (p.2318·2); calendula (p.2273·1); boric acid (p.2268·1); borax (p.2268·1).
Eye disorders.

Banophen Allergy Major, USA.
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; insomnia; motion sickness.

Banophen Decongestant Major, USA.
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Hypersensitivity reactions; insomnia; motion sickness.

Ban-Sol Remexa, Mex.
SPF 30; SPF 50: Avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

Bansor Thornton & Ross, UK†.
Cetrimide (p.1634·1).
Sore gums.

Bantel TNP, Thai.†.
Pyrantel embonate (p.155·1).
Worm infections.

Bantenol Abello, Spain†.
Mebendazole (p.148·3).
Worm infections.

Bantif Child Caprifarmindo, Indon.; Sanbe, Indon.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Bantix Mediderm, Chile.
Mupirocin calcium (p.302·3).
Elimination of nasal staphylococci; skin infections.

Bantizol Blue Sky, Philipp.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bapex Probiomed, Mex.
Gabapentin (p.482·3).
Epilepsy.

Bapixied Bajamed, Mex.
Piroxicam (p.117·3).
Inflammation; pain.

Baquinor Sanbe, Indon.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Baraclude BMS, Arg.; BMS, Austral.; BMS, Cz.; BMS, Fr.; BMS, Gr.; BMS, Hung.; BMS, Indon.; BMS, Malaysia; BMS, NZ; BMS, Philipp.; BMS, Port.; BMS, Singapore; BMS, UK; BMS, USA.
Entecavir (p.875·1).
Chronic hepatitis B.

Baralgan Albert, S.Afr.†.
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Colic; genital-tract spasm.

Baralgetas Jugoremedia, Rus.†.
Fenpiverinium bromide (p.2303·2); dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).

Baralgin GSK, Braz.
Dipyrone (p.49·2).
Fever; pain.

Baralgin M Sanofi-Aventis, Rus.; Pharmagen, Turk.
Dipyrone (p.49·2).
Fever; pain.

Baralgina M Sanofi-Aventis, Chile.
Dipyrone (p.49·2).
Fever; pain.

Baratol Shire, Irl.†; Akromed, S.Afr.; Amdipharm, UK.
Indoramin hydrochloride (p.1315·1).
Hypertension.

Barazan Dieckmann, Ger.
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Barbamin Streuli, Switz.†.
Propyphenazone (p.119·3); diphenhydramine hydrochloride (p.577·2).
Fever; pain.

Barbidonna Wallace, USA†.
Atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); hyoscyamine hydrobromide (p.1736·1) or hyoscyamine sulfate (p.1736·1); phenobarbital (p.492·2).
Gastrointestinal disorders.

Barbitron Sanval, Braz.
Phenobarbital (p.492·2).
Convulsions.

Barbloc Alphapharm, Austral.
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Barcan UCB, Denm.; UCB, Fin.; UCB, Norw.; UCB, Swed.
Aceclofenac (p.14·3).
Inflammation; musculoskeletal and joint disorders.

Barex Dominguez, Arg.
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Barexal Ipsen, Belg.
Smectite (p.1771·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Diarrhoea.

Bargonil Roemmers Rowe, Venez.
Tribenoside (p.2403·3); a heparinoid (p.1305·2); lidocaine hydrochloride (p.1862·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Bariclor Degorts, Mex.
Chloramphenicol (p.239·3).
Bacterial infections.

Baricol E-Z-EM, Neth.
Barium sulfate (p.1477·2).
Radiography of the gastrointestinal tract.

Baricon Mallinckrodt, USA.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Baridium Pfeiffer, USA.
Phenazopyridine hydrochloride (p.116·2).
Irritation of the lower urinary tract.

Bariederm Uriage, Fr.
Barrier cream.

Barigesic Degorts, Mex.
⊗ Aspirin (p.20·3); prednisone (p.1542·3).
Inflammation; pain.

Barigraf Justesa Imagen, Arg.; Schering, Chile†; Juste, Spain.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Barilux Waldheim, Austria; Sanochemia, Ger.; IFET (ΙΦΕΤ), Gr.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Barilux Brausetabletten Sanochemia, Ger.†.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); dimethicone (p.1770·2).
Adjunct in gastrointestinal radiography.

Barin Roemmers Osmoph, Venez.
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Bario Bioquimico, Arg.; Denver, Arg.; Temis, Arg.
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Bario Dif Rovi, Spain.
Barium sulfate (p.1477·2).
Dimeticone (p.1770·2) is included in this preparation to eliminate gas from the gastrointestinal tract before radiography.
Contrast medium for gastrointestinal radiography.

Bario Llorente Llorente, Spain†.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Bariofarma Varifarma, Arg.
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Bariogel Cristalia, Braz.; Organifar, Venez.†.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Bariotin Etifar, Venez.†.
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Bariplex Degorts, Mex.
Multivitamin preparation (p.1922·1).

Baripril Lesvi, Spain.
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Baripril Diu Lesvi, Spain.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Baritex ICM, Singapore.
Dimeticone (p.2032·1).
Barrier cream.

Baritop Sanochemia, UK.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal tract radiography.

Barium Med Complex Dynamit, Austria.
Homoeopathic preparation.

Barmicil Sons, Mex.†.
Gentamicin sulfate (p.282·1).
Bacterial infections.

Barmicil Compuesto Sons, Mex.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Barnetil Sanofi Synthelabo, Belg.†; Sanofi-Aventis, Fr.†; Synthelabo, Port.†.
Sultopride hydrochloride (p.1029·3).
Aggression; delirium; mania; psychoses; schizophrenia.

Barnotil Sanofi Synthelabo, Ital.†.
Sultopride hydrochloride (p.1029·3).
Psychoses.

Barobag Mallinckrodt, USA.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Baroc
Bayer, Cz.
Ibuprofen sodium (p.65·2).
Fever; pain.

Bayer, Port.
Ibuprofen (p.64·2).
Fever; pain.

Baro-cat Mallinckrodt, USA.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Barokaton
Note.This name is used for preparations of different composition.
Sanova, Austria.
Injection: ⊗ 1-(β-Diethylaminoethyl)-theobromin-ethylbromide; 2-diethylaminoethanol hydrochloride (p.2154·3).
Asthma; cardiovascular disorders.

Sanova, Austria.
Tablets: 1-(β-Diethylaminoethyl)-theobromin-ethylbromide.
Asthma; cardiovascular disorders.

Barominic Am-Europharma, Philipp.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Baropyrine Am-Europharma, Philipp.
Paracetamol (p.108·1).
Fever; pain.

Baros Mallinckrodt, USA.
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); simeticone (p.1770·2).
Adjunct in gastrointestinal radiography.

Barosperse Mallinckrodt, Arg.; Mallinckrodt, USA.
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography; radiographic contrast medium.

Barotonal Alpharma-Isis, Ger.†.
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Baroxal Remek, Gr.
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Barrier Cream National Care, Canad.†.
Dimeticone (p.2032·1).
Skin disorders.

Barriere Wellspring, Canad.
Dimeticone (p.2032·1).
Nappy rash; skin irritation.

Barriere-HC Shire, Canad.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Barrycidal Barry, Ital.
Alkylbenzyldimethylammonium chloride (p.1629·1); benzethonium chloride (p.1630·1); diisobutylcresoxyethoxyethylbenzyldimethylammonium chloride.
Instrument disinfection.

Bartolium Nufarindo, Indon.
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Baruden Anpharm (Ανφαρμ), Gr.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Barzepin Novell, Indon.
Oxcarbazepine (p.490·3).
Epilepsy.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Basab *BA Farma, Port.†.*
Lomefloxacin (p.295·3).

Basalflex *Braun, Ital.*
Amino acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Basaljel *Aurium, Canad.*
Aluminium hydroxide (p.1706·2).
Hyperphosphataemia.

Basan *Leiras, Fin.*
Basis for topical preparations.

Bascardial *Bastian, Ger.†.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Coronary circulation disorders with magnesium and potassium deficiency.

Basdene *Bouchara-Recordati, Fr.*
Benzylthiouracil (p.2167·2).
Hyperthyroidism.

Bas-Dextrano *Braun, Port.*
⊗ Dextran 40 (p.1059·1) in glucose or sodium chloride.
Plasma volume expansion; thromboembolic disorders.

Basen *Takeda, Jpn; Takeda, Philipp.; Takeda, Thai.*
Voglibose (p.464·2).
Diabetes mellitus.

Baserin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Basicaina *Senese, Ital.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Basifen *Basi, Port.*
Fenbufen (p.54·3).
Musculoskeletal, joint, and peri-articular disorders.

Basikol *Arkopharma, Hong Kong.*
Phytosterols (p.1373·1); vitamin E (p.1992·2).
Hypercholesterolaemia.

Basilicao *Simoes, Braz.†.*
Colophony (p.2286·2); turpentine.
Acne.

Basina *T Man, Thai.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Basinal *Basi, Port.*
Naltrexone hydrochloride (p.1455·2).
Opioid withdrawal syndrome.

Basireuma *Basi, Port.†.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders.

Basiron *Galderma, Fin.; Galderma, Norw.; Galderma, Rus.; Galderma, Swed.; Galderma, Switz.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Basiron AC *Galderma, Cz.*
Benzoyl peroxide (p.1590·2).
Acne.

Basiter *Galderma, Ger.†.*
Coal tar (p.1616·2).
Eczema; psoriasis.

Basiton *Sarabhai Piramal, India.*
Vitamin B substances; vitamin C; folic acid (p.1922·1).
Vitamin B and C deficiency.

B1-ASmedic *Dyckerhoff, Ger.*
Thiamine nitrate (p.1976·2).
Vitamin B deficiency.

B2-ASmedic *Dyckerhoff, Ger.*
Riboflavin (p.1977·2).
Riboflavin deficiency.

B6-ASmedic *Dyckerhoff, Ger.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

B_{12}-ASmedic *Dyckerhoff, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Basocef *DeltaSelect, Ger.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Basocin *Galderma, Ger.*
Clindamycin phosphate (p.251·2).
Acne.

Basodexan *Hermal, Ger.*
⊗ Urea (p.1620·2).
Skin disorders.

Basofortina *Novartis, Arg.*
Methylergometrine maleate (p.2011·1).
Postpartum atony; postpartum haemorrhage; uterine subinvolution.

Basoplex *Riemser, Ger.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Basoquin *Pfizer, India.*
Amodiaquine (p.597·2).
Malaria.

Basotar *Galderma, Denm.†.*
Coal tar (p.1616·2).
Eczema; psoriasis.

Bassado *Pharmacia, Ital.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Basti-Cal *Bastian, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Basticrat *Bastian, Ger.†.*
Crataegus (p.2289·1).
Cardiac disorders.

Basti-Mag *Bastian, Ger.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Bastiverit *Bastian, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Bat *Zeta, Ital.*
Cetylpyridinium chloride (p.1635·1).
Disinfection of wounds and burns.

Batasalgin *Copernico, Ital.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Bateral *Allen, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bath E45 *Crookes Healthcare, UK.*
Bath additive.
Dry skin.

Batinel *Teva Tuteur, Arg.*
Mitoxantrone (p.754·3).
Malignant neoplasms.

Batiodin *Oro, Turk.*
Povidone-iodine (p.1659·2).
Minor cuts and abrasions; skin disinfection.

Batistol *Serch, Arg.†.*
Pentane (p.2026·1); butane (p.1688·2).
Local anaesthesia.

Batixim *SoSe, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Batmen *Menarini, Spain.*
⊗ Prednicarbate (p.1540·2).
Skin disorders.

Batrafen
Aventis, Austria; Aventis, Hong Kong.
Ciclopirox (p.529·2).
Fungal nail infections.

Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Indon.; Aventis, Irl.†; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Abbott, Switz.
Ciclopirox olamine (p.529·2).
Fungal skin, nail, and vulvovaginal infections.

Aventis, Ger.; Sanofi-Aventis, Hung.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Venez.
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin, nail and vaginal infections.

Sanofi-Aventis, NZ.
Cream; nail lacquer; topical solution: Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin and nail infections.

Batramycin *Geistlich, Singapore.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Bacterial skin infections.

Batramycine
Note. This name is used for preparations of different composition.
Geistlich, Switz.†.
Nasal ointment: Bacitracin (p.210·3); neomycin sulfate (p.305·1); octacaine hydrochloride (p.1867·2).
Bacterial nasal infections.

Geistlich, Switz.
Ointment; topical powder: Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Infected wounds or burns.

Batrevac *Solvay, Austria; Solvay, Neth.; Solvay, Port.; SBL, Swed.†.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Batrizol *Medimport, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Batrox *Bergamo, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Batticon *Adeka, Turk.*
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection; skin disorders.

Batugin *Kimia, Indon.*
Strobilanthes crispus; sonchus arvensis.
Renal colic.

Baudry *Boiron, Canad.†.*
Homoeopathic preparation.

Baume *Zeller, Switz.†.*
Achillea (p.2245·2); absinthium (p.2244·1); poppy flowers (p.1472·3); guaiacum wood; tormentil root (p.2403·2); cinnamon bark (p.2283·1); benzoin (p.2394·2); myrrh (p.2349·2); tolu balsam (p.1574·2).
Gastrointestinal disorders.

Baume Analgesique *Multi-Pro, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2).

Baume Analgesique Medicamente *Prodemdis, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Baume Aroma *Mayoly-Spindler, Fr.*
Clove oil (p.2285·1); capsicum oil; methyl salicylate (p.85·3).
Muscle and joint pain.

Baume Bengue *Beaufour, Fr.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle and joint pain.

Baume du Chalet *Plan, Switz.*
Lavender oil (p.2331·2); citronella oil (p.2284·2); spike lavender oil (p.2392·1); terebinthin (p.2406·3).
Skin disorders; wounds.

Baume de Chine Temple of Heaven blanc *Panax, Switz.*
Menthol (p.2340·1); camphor (p.2273·2); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); clove oil (p.2285·1); cinnamon oil (p.2283·2).
Musculoskeletal and joint disorders; soft-tissue injury.

Baume Esco *Streuli, Switz.*
Salicylic acid (p.1612·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Baume Esco Forte *Streuli, Switz.*
Salicylic acid (p.1612·2); menthol (p.2340·1); methyl salicylate (p.85·3); ethyl nicotinate (p.52·1).
Musculoskeletal and joint pain.

Bausch & Lomb Computer Eye Drops *Bausch & Lomb, Austral.*
Glycerol (p.2314·2).
Dry eyes; eye irritation.

Bausch & Lomb Concentrated Cleaner *Bausch & Lomb, Austral.*
Cleansing solution for gas permeable and hard contact lenses (p.1622·2).

Bausch & Lomb Conditioning Solution *Bausch & Lomb, Austral.; Bausch & Lomb, S.Afr.*
Disinfecting and storage solution for gas permeable and hard contact lenses (p.1622·2).

Bausch & Lomb Daily Cleaner *Bausch & Lomb, S.Afr.*
Cleaning solution for soft contact lenses (p.1622·2).

Bausch & Lomb FizziClean *Bausch & Lomb, S.Afr.*
Proteolytic enzyme cleaner (p.1622·2).
Cleaner for contact lenses.

Bausch & Lomb Lens Lubricant *Bausch & Lomb, S.Afr.*
Wetting solution for hard and soft contact lenses (p.1622·2).

Bausch & Lomb Moisture Drops *SofLens, S.Afr.†.*
Wetting solution for contact lenses (p.1622·2).

Bausch & Lomb Multi-Purpose *Bausch & Lomb, S.Afr.*
Cleaning, disinfecting, and storage solution for soft contact lenses (p.1622·2).

Bausch & Lomb ReNu Lubricating & Rewetting Drops *Bausch & Lomb, Austral.*
Lubricating and wetting solution for soft contact lenses (p.1622·2).

Bausch & Lomb ReNu Multiplus Multi-purpose Solution *Bausch & Lomb, Austral.*
Solution for soft contact lens care (p.1622·2).

Bausch & Lomb ReNu Multipurpose Solution *Bausch & Lomb, Austral.*
Cleaning, disinfecting, rinsing, and storage solution for soft contact lenses (p.1622·2).

Bausch & Lomb Sensitive Eyes Daily Cleaner *Bausch & Lomb, Austral.*
Cleansing solution for soft contact lenses (p.1622·2).

Bausch & Lomb Sensitive Eyes Protein Removal *Bausch & Lomb, Austral.*
Proteolytic enzyme (p.1622·2).
Cleanser for soft contact lenses.

Bausch & Lomb Sensitive Eyes Saline *Bausch & Lomb, Austral.*
Sodium chloride (p.1686·1) (p.1622·2).
Saline solution for soft contact lenses.

Bauxol *Mintlab, Chile.*
Bromhexine (p.1552·2); clofedanol (p.1554·2).
Coughs.

Baxamed *Bajamed, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Baxan *BMS, UK.*
Cefadroxil (p.218·1).
Bacterial infections.

Baxapril *Brasmedica, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Baxedin *Omega, Canad.*
Chlorhexidine gluconate (p.1635·3).
Disinfection and antisepsis.

Baxedin 2% - 70% *Omega, Canad.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Disinfection.

Baxidin *Sanitas, Ital.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Disinfection of wounds and burns.

Baxidyme *Bosch, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Baxi-K *Baxter, Mex.†.*
Amikacin sulfate (p.200·3).

Baxil *Erfa, Belg.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Baxima *Sandoz, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Baxo *Toyama, Jpn.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Baxolyn *Bosch, Philipp.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayagel
Note. This name is used for preparations of different composition.
Bayer Consumer, Arg.
Etofenamate (p.53·1); pine oil (p.2368·2); eucalyptus oil (p.2301·2).
Musculoskeletal, joint, and soft-tissue pain.

Bayer, Chile.
Etofenamate (p.53·1).
Musculoskeletal and joint pain.

Bayaspirina *Bayer, Arg.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Bayaspirina C *Bayer, Arg.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms; fever; pain.

Baycaron *Bayer, Neth.†.*
⊗ Mefruside (p.1332·1).
Hypertension; oedema.

Baycidal *Bayer, Ital.†.*
Triflumuron (p.2051·3).
Insecticide.

Baycillin *Bayer, Ger.*
Propicillin potassium (p.319·3).
Bacterial infections.

Baycip
Bayer, Chile.
Ciprofloxacin (p.243·3), ciprofloxacin hydrochloride (p.243·3), or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayer, Spain.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Baycuten
Note. This name is used for preparations of different composition.
Bayer, Braz.; Bayer, Port.
⊗ Clotrimazole (p.530·1); dexamethasone (p.1526·1).
Infected skin disorders.

Bayer, Chile; Bayer, Cz.; Bayer, Ger.†; Bayer, Philipp.
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Infected skin disorders.

Bayer, Mex.
⊗ Clotrimazole (p.530·1); dexamethasone (p.1526·1); neomycin (p.305·1).
Infected skin disorders.

Baycuten HC *Bayer, Ger.*
⊗ Clotrimazole (p.530·1); hydrocortisone (p.1535·2).
Infected skin disorders.

Baycuten N
Note. This name is used for preparations of different composition.
Bayer Schering, Malaysia.
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Fungal skin infections.

Bayer, Mex.; Bayer, Venez.
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Baycuten-N *Bayer, Indon.*
⊗ Dexamethasone acetate (p.1526·1); clotrimazole (p.530·1).
Infected skin disorders.

Bayer Extra Strength Back & Body Pain *Bayer, USA.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Bayer Low Adult Strength *Sterling Health, USA.*
Aspirin (p.20·3).

Bayer Select Chest Cold *Sterling Health, USA.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Bayer Select Flu Relief *Sterling Health, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).

Bayer Select Head Cold *Sterling Health, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Bayer Select Maximum Strength Backache *Sterling Health, USA.*
Magnesium salicylate (p.79·2).

Bayer Select Maximum Strength Night Time Pain Relief *Sterling Health, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia; pain.

Bayer Select Maximum Strength Sinus Pain Relief *Sterling Health, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; pain.

Bayer Select Night Time Cold *Sterling Health, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3).

Bayer Womens Aspirin Plus Calcium *Bayer, USA.*
Aspirin (p.20·3); calcium (p.1675·2).
Pain.

Bayers Tonic *Bayer, India.*
Liver extract; sodium acid phosphate; yeast extract; alcohol (p.1922·1).
Tonic.

Baygam *Bayer, Canad.†.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Baygon *Skills, Ital.*
Propoxur (p.2049·2); tetramethrin (p.2051·1); piperonyl butoxide (p.2049·1).
Insecticide.

BayHep *Bayer, Israel.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

BayHep B *Bayer, Canad.†; Bayer Biological, Hong Kong; Bayer, Philipp.; GenAsia, Philipp.; Bayer, Singapore†; Biem, Turk.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Baylotensin *Mitsubishi, Jpn.*
Nitrendipine (p.1358·2).
Angina pectoris; hypertension.

Baymycard *Bayer, Ger.; Bayer, Hung.*
Nisoldipine (p.1358·1).
Angina pectoris; hypertension.

Baynas *Shinyaku, Jpn.*
Ramatroban (p.2377·3).
Allergic rhinitis.

Bayolin *Bayer, Gr.; Bayer, Hung.†.*
A heparinoid (p.1305·2); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bayotensin *Bayer, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Baypen *Bayer, Austria; Bayer, Fr.; Bayer, Ger.; Bayer, Israel†; Bayer, Ital.*
Mezlocillin sodium (p.299·3).
Bacterial infections.

Baypresol *Bayropharm, Spain.*
Nitrendipine (p.1358·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Baypress *Bayer, Austria; Bayer, Belg.; Bayer, Cz.; Bayer, Denm.; Bayer, Fr.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Ital.; Bayer, Mex.†; Bayer, Neth.; Bayer, Port.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, Venez.*
Nitrendipine (p.1358·2).
Hypertension.

Baypril *Bayer, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; unstable angina.

BayRab *Bayer, Canad.†; Bayer Biological, Hong Kong; Bayer, Israel; Probifasa, Mex.†; Bayer, Philipp.; GenAsia, Philipp.; Bayer, Singapore†.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

BayRho-D *Gador, Arg.†; Bayer, Canad.†; Bayer, Chile†; Bayer Biological, Hong Kong; Bayer, Israel; Probifasa, Mex.†; Bayer, Singapore†; Biem, Turk.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Bayro *Bayer, Braz.; Bayer, Chile†; Viatris, Ital.; Bayer, Mex.*
Etofenamate (p.53·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Bayro Termo *Bayer, Mex.*
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and peri-articular disorders.

Bayrogel *Bayer, Arg.†.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bayro-Therm *Bayer, Chile†.*
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Baytalcid *Bayer, Venez.†.*
Hydrotalcite (p.1733·3).
Antacid.

BayTet *Bayer, Canad.†; Bayer Biological, Hong Kong; Bayer, Israel; Probifasa, Mex.†; Bayer, Philipp.; GenAsia, Philipp.; Bayer, Singapore†; Bayer, USA.*
A tetanus immunoglobulin (p.2239·3).
Formerly known as Hyper-Tet in the *USA*.
Passive immunisation.

Baythion EC *Bayer, Ital.†.*
Phoxim (p.2049·1).
Insecticide.

Bayzolam *Bayer, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Bazalin *Astellas, Spain.*
⊗ Coal tar (p.1616·2); fluocinolone acetonide (p.1531·3); salicylic acid (p.1612·2).
Keratinisation disorders; psoriasis.

Bazetham
Pliva Krakow, Pol.
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Pliva, UK.
Tamsulosin (p.2197·2).

Bazoton *Abbott, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Bazuctril *Chrispa (Χρισπα), Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Bazuka *Dendron, UK.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; verrucas; warts.

BB Test *Innotech, Fr.*
Pregnancy test (p.2372·1).

BBdent Gel Topico *Maver, Chile.*
Benzocaine (p.1854·1).

B-Beta *Ferron, Indon.*
⊗ Bisoprolol fumarate (p.1234·1).
Hypertension.

BB-K8 *BMS, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

BC *GSK Consumer, USA.*
Aspirin (p.20·3); salicylamide (p.121·2); caffeine (p.1116·3).
Pain.

BC Allergy Sinus Headache *GSK Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

BCAD *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Leucinosis.

BCAD 1 *Mead Johnson, Hong Kong.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

BCAD 2 *Mead Johnson Nutritionals, USA.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

B-Caroteno *AM, Arg.*
Betacarotene (p.1930·3).
Skin pigmentation.

B-C-Bid *Roberts, USA†.*
Vitamin B complex with vitamin C (p.1922·1).

B-Combin *SAD, Denm.*
Vitamin B substances (p.1922·1).

B-Complex *BMS, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

B-Complex Threshold *GNLD, Austral.*
Vitamin B substances (p.1922·1); rutoside (p.2305·1).
Vitamin B deficiencies.

B-Cool *Julphar, UAE.*
Oxybuprocaine hydrochloride (p.1867·3); cetylpyridinium chloride (p.1635·1); tyrothricin (p.358·2).
Throat disorders.

B-Dol *Be-Tabs, S.Afr.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain with tension.

Beacodyl *Beacons, Singapore.*
Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Allergic rhinitis; cough; urticaria.

Beacolux *CCM, Malaysia†.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Beacolytic *CCM, Malaysia.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with viscous mucus.

Beacon K *CCM, Malaysia.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Beacons *Beacons, Singapore.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Beacons Cough *Beacons, Singapore.*
⊗ Ammonium chloride (p.1551·3); ephedrine hydrochloride (p.1558·2); ipecacuanha (p.1562·3).
Cough.

Beacons DQ *Beacons, Singapore.*
Dequalinium chloride (p.1641·3).
Sore throat.

Beactafed *Beacons, Singapore.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion; urticaria.

Beactafed Co *Beacons, Singapore.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Formerly known as Beactafed.
Allergic rhinitis; cough; nasal congestion; respiratory-tract congestion.

Beafemic *CCM, Malaysia; Beacons, Singapore.*
Mefenamic acid (p.80·1).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Beaflu-Plus *Beacons, Singapore.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Fever; hypersensitivity reactions; pain.

Beafort *Beacons, Singapore.*
Thiamine hydrochloride; riboflavin; pyridoxine hydrochloride; cyanocobalamin; nicotinamide; calcium pantothenate (p.1922·1).
Vitamin B supplement.

Beagenco *Beacons, Singapore†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dexchlorpheniramine maleate (p.572·1).
Fever; hypersensitivity reactions; pain.

Beagenta *CCM, Malaysia.*
Gentamicin sulfate (p.282·1).
Bacterial skin, eye, and ear infections.

Beaglobe *CCM, Malaysia.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Bacterial infections.

Beagocrine *Upha, Malaysia†.*
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Beagyne *Effik, Fr.*
Fluconazole (p.532·1).
Vaginal and perineal candidiasis.

Beahexol *Beacons, Singapore.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Beakopectin *Upha, Malaysia†; Beacons, Singapore.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Beamodium *CCM, Malaysia.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Beamotil *CCM, Malaysia; Beacons, Singapore.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Colostomy and ileostomy management; diarrhoea.

Beamoxy *CCM, Malaysia.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Be-Ampicil *Be-Tabs, S.Afr.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Beanamine *Beacons, Singapore.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Allergic rhinitis; cough; urticaria.

Beano *GSK Consumer, Canad.; Stafford-Miller, UK; AkPharma, USA.*
Alpha galactosidase A (p.2252·3).
Flatulence arising from ingestion of complex carbohydrates.

Beapen *CCM, Malaysia.*
Phenoxymethylpenicillin potassium (p.314·2).
Gram-positive bacterial infections.

Beaphenicol *CCM, Malaysia; Beacons, Singapore†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Beapizide *Beacons, Singapore.*
Glipizide (p.441·3).
Diabetes mellitus.

Beaplex *Beacons, Singapore.*
Thiamine hydrochloride; riboflavin; pyridoxine hydrochloride; cyanocobalamin; nicotinamide; folic acid (p.1922·1).
Vitamin B supplement.

Bearantel *Beacons, Singapore.*
Pyrantel embonate (p.155·1).
Worm infections.

Bearax *Beacons, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections.

Bearcef *Daewoong, Singapore.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Bear-E-Yum *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Beatacycline
CCM, Malaysia.
Tetracycline (p.347·1).
Bacterial infections.

Beacons, Singapore.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Beatafed *CCM, Malaysia.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; sinusitis; upper respiratory-tract congestion.

Beatafed Compound *Upha, Malaysia†.*
Codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3).
Coughs.

Beathorphan *Beacons, Singapore.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Beathricin *Beacons, Singapore.*
Lidocaine hydrochloride (p.1862·3); tyrothricin (p.358·2).
Mouth and throat infections.

Beatifen *Beacons, Singapore.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma.

Beatizem *Beacons, Singapore.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Beatoconazole *Beacons, Singapore.*
Ketoconazole (p.539·1).
Fungal skin infections.

Beatolin *CCM, Malaysia.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Beatolin Expectorant *Upha, Malaysia†.*
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Coughs.

Beatrolol *Upha, Malaysia†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism.

Beavate *CCM, Malaysia.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Beavate N *CCM, Malaysia.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Beazyme *CCM, Malaysia.*
Papain (p.2362·3).
Inflammatory disorders; oedema.

Beba HA *Nestle, Cz.†.*
Infant feed (p.1922·1).
Food hypersensitivity.

Bebecrem *Lacefa, Arg.†.*
Barrier preparation.

Bebegel *Viatris, Fr.; Meda, Port.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Bebektin *Janssen-Cilag, Mex.*
Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Infected skin disorders.

Bebelac EC *Global Eramas, Indon.; Lyempf, Indon.; Tempo Scan Pacific, Indon.; Dumex, Malaysia.*
Infant feed (p.1922·1).
Gastrointestinal disorders.

Bebelac FL *Global Eramas, Indon.; Lyempf, Indon.; Tempo Scan Pacific, Indon.; Dumex, Malaysia.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Beben *Pfizer Consumer, Ital.*
⊗ Betamethasone benzoate (p.1518·3).
Skin disorders.

Beben Clorossina *Pfizer Consumer, Ital.*
⊗ Betamethasone benzoate (p.1518·3); chloroxine (p.242·2).
Infected skin disorders.

Bebesales *Pharmacia, Spain†.*
Calcium lactate pentahydrate; citric acid monohydrate; magnesium sulfate; potassium chloride; sodium bicarbonate; sodium chloride; glucose (p.1672·2).
Oral rehydration therapy.

Bebexin *Demo, Gr.*
Cetirizine (p.571·1).
Antihistamine.

Bebidol *TNP, Thai.†.*
Dill oil (p.2293·3); sodium bicarbonate (p.1673·2).
Flatulence; infant bloating.

Bebilon Amino *Nutricia, Pol.*
Infant feed (p.1922·1).
Colic; food allergy.

Bebilon Pepti *Nutricia, Pol.*
A range of infant feeds (p.1922·1).
Colic; diarrhoea; food allergy.

Bebilon Sojowy *Nutricia, Pol.*
Soy-based infant feed (p.1922·1).
Cows milk intolerance; fructosaemia; galactosaemia; lactose and sucrose intolerance.

Bebimix *Sella, Ital.*
Honey (p.1948·2); royal jelly (p.2382·1); myrtillus (p.2349·3).
Nutritional supplement.

Bebol *Wyeth, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Bebulin *Immuno, Braz.†.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Bebulin VH *Immuno, USA.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Bec *Maruko, Jpn.*
Aranidipine (p.1216·3).
Hypertension.

Becacort *Upha, Malaysia†.*
⊗ Hydrocortisone (p.1535·2); miconazole nitrate (p.541·3).
Infected skin disorders.

Becadexamin *GSK, India.*
Multivitamin and mineral preparation (p.1922·1).

Became *Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Singapore.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Becantex *CPH, Port.; Sanofi Synthelabo, Thai.†.*
Sodium dibunate (p.1573·1).
Coughs.

Becantosse *Dinafarma, Braz.†.*
Sodium dibunate (p.1573·1); potassium iodide (p.2169·2).
Coughs.

Becardin *Remedica, Hong Kong†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma; tremor; variceal haemorrhage.

Becarin *CCM, Malaysia.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Bece *Codilab, Port.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin supplement.

BECeco *Ecosol, Switz.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Becede *Vannier, Arg.*
Alprazolam (p.960·1).
Anxiety.

Becedyn *Bayer, Philipp.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C deficiency.

Becenun *BMS, Braz.*
Carmustine (p.694·3).
Malignant neoplasms.

Becetamol *Gebro, Austria; Gebro, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Beceze *Norton, S.Afr.†; Ivax, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma.

Bechilar *Montefarmaco, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bechlomin *Jean-Marie, Hong Kong.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions; inflammatory eye disorders.

Becilan *DB, Fr.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Beclase *De Mayo, Braz.*
⊗ Sodium dibunate (p.1573·1); mepyramine maleate (p.585·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Beclasma *Raffo, Arg.; Raffo, Chile†.*
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Asthma; obstructive airways disease.

Beclate *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia; Cipla-Medpro, S.Afr.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma; nasal polyps; skin disorders.

Beclate-C *Cipla, India.*
⊗ Beclometasone dipropionate (p.1516·2); clioquinol (p.254·1).
Infected skin disorders.

Beclate-N *Cipla, India.*
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Beclazone *Galena, Cz.†; Ivax, Cz.†; Ivax, Hong Kong; Ivax, Irl.; Ivax, Malaysia; Ivax, Mex.; Airflow, NZ; Norton, Rus.; Ivax, Singapore†; Norton Healthcare, Singapore†; Ivax, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

Beclo *Sandoz, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclo Asma *Aldo-Union, Hong Kong†; Aldo-Union, Singapore; Aldo, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclo Rino *Estedi, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; rhinitis.

Beclo Siozwo *Febena, Ger.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Beclobreathe *Sandoz, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Beclodin *Chiesi, Neth.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Becloenema *Estedi, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Ulcerative colitis.

Becloforte *GSK, Austral.†; GSK, Cz.; GSK, Hong Kong†; GSK, Israel; GSK, Malaysia†; GSK, Neth.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore†; GSK, Spain; GSK, Switz.†; GSK, Thai.†; GSK, Turk.; Allen & Hanburys, UK†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclofortil *Medifarm, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclogen
Note. This name is used for preparations of different composition.
Tocogino, Mex.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin (p.284·2).
Infected skin disorders.

Generics, UK.
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Beclohale *Julphar, UAE.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclohexal *Hexal, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclojet *Chiesi, Fr.; Chiesi, Rus.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclomet *Lannacher, Austria; Orion, Cz.; Meda, Denm.; Orion, Fin.; Orion, Ger.; Galenica, Gr.†; Orion, Hung.†; Actavis, Indon.; Orion, Malaysia; Meda, Norw.; Orion, Singapore; Ferrer, Spain; Meda, Swed.; Orion, Switz.†; Orion, Thai.; Elmor, Venez.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma; nasal polyps.

Beclomet Compositum *Elmor, Venez.†.*
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Obstructive airways disease.

Beclometatop *Topgen, Belg.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Beclomin *Jean-Marie, Hong Kong†.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions; inflammatory eye disorders.

Beclonarin *Rappai, Switz.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; polyps.

Beclonasal *Orion, Fin.; Orion, Hung.*
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; rhinitis.

Beclonato *Ducto, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Beclone *Leurquin, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclophar *Teva, Belg.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclo-Rhino *Viatris, Fr.; Goldshield, Irl.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; rhinitis.

Beclorhinol *Asche Chiesi, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Beclorino *Medifarm, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Beclosal *Biogalenic, Venez.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Beclosema *Etex, Chile.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclosil *Medifarm, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclosol *GSK, Braz.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; nasal polyps; rhinitis.

Beclosona *Spyfarma, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Beclospin *Chiesi, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beclotaide *Alenfarma, Port.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Becloturmant *Asche Chiesi, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Beclovent *GSK, Chile†; Glaxo Wellcome, USA.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Beco *Mepha, Switz.*
Vitamin B substances (p.1922·1).
Alcoholism; liver disorders; neuritis; vitamin B deficiency.

Becodisk *GSK, Pol.; GSK, Rus.; GSK, Switz.; GSK, Thai.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Becodisks *GSK, Cz.; GSK, Hong Kong; Allen & Hanburys, Irl.†; GSK, S.Afr.†; GSK, Turk.; Allen & Hanburys, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Becof *Caps, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Becogem *APT, Hong Kong.*
⊗ Betamethasone (p.1518·2); gentamicin sulfate (p.282·1); clotrimazole (p.530·1).
Infected skin disorders.

Becolex *Chiesi, Gr.*
⊗ Beclometasone (p.1517·2).
Corticosteroid.

Becolim *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore†; Atlantic, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Becoloxin *Upha, Malaysia†.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Motion sickness; nausea and vomiting.

Becom *British Dispensary, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Becombion *Merck, Indon.; Merck, Malaysia; Merck, Singapore†.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Becombion Extra Lysine *Merck, Indon.*
Vitamin B substances; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Becomplex *Alpharma, Malaysia†; Alpharma, Singapore†.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Becomplina Fuerte *Labomed, Chile.*
Thiamine; riboflavin; pyridoxine; cyanocobalamin; nicotinamide; calcium pantothenate (p.1922·1).
Vitamin B supplement.

Beconase *GSK Consumer, Austral.; GSK, Austria; GSK, Belg.; GSK, Chile†; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Hong Kong; GSK, Indon.; Allen & Hanburys, Irl.; GSK, Israel†; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Port.; GSK, Rus.†; GSK, S.Afr.; Allen, Spain; GSK, Switz.; GSK, Thai.; GSK Consumer, UK; Glaxo Wellcome, USA; GSK, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Beconase Allergy *GSK Consumer, Austral.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Beconase Aquosum *GSK, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Beconase Hayfever *GSK Consumer, Austral.; GSK, NZ.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Beconasol *GSK, Switz.*
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; rhinitis.

Becoplex Ido *Novo Nordisk, S.Afr.†.*
Vitamin B substances (p.1922·1).

Becortem *Bergamo, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Becortin *Purissimus, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin embonate (p.284·2); clotrimazole (p.530·1).
Infected skin and mucous membrane disorders.

Becosol *GHP, Thai.†.*
Vitamin B substances, glucose, and sodium chloride infusion (p.1922·1).
Parenteral nutrition.

Becosules *Pfizer, India.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Becosym *Roche Consumer, Irl.†.*
Vitamin B substances (p.1922·1).

Becotal *Streuli, Switz.*
Vitamin B substances (p.1922·1).
Neuropathies; vitamin B deficiency.

Becotide *GSK, Austral.; GSK, Austria; GSK, Belg.†; GSK, Cz.; GSK, Fin.†; GSK, Fr.; Glaxo Wellcome, Gr.†; GSK, Hong Kong; GSK, Indon.; Allen & Hanburys, Irl.; GSK, Israel†; Lusofarmaco, Ital.; GSK, Malaysia†; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore†; GSK, Spain; GSK, Swed.; GSK, Switz.†; GSK, Thai.†; GSK, Turk.; Allen & Hanburys, UK†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; nasal polyps; obstructive airways disease; rhinitis.

Becotide A *GSK, Ital.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Nose, sinus, and throat disorders; obstructive airways disease.

Becovigen *Aksu, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Becovit *Julphar, UAE.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Becovital *Kocak, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Becovital-C *Kocak, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Becozym *Bayer Consumer, Arg.; Roche, Israel; Bayer, Ital.; Bayer, Swed.*
Vitamin B substances (p.1922·1).
Alcoholism; neuralgia; neuropathies; vitamin B deficiency.

Becozym-C *Roche, Arg.†.*
Vitamin B substances; vitamin C (p.1922·1).

Becozyme *Roche, Belg.; Bayer Sante, Fr.; IFET, Gr.; Bayer, Port.; Bayer, Switz.; Roche, Turk.*
Vitamin B substances (p.1922·1).
Alcoholism; liver disorders; nausea and vomiting in pregnancy; neuralgia; neuritis; tonic; vitamin B deficiency.

Becozyme C *Bayer, Port.; Roche, Turk.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Becozyme C Forte *Piramal, India; Roche, Spain.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Becozyme-S *Bayer, Gr.; IFET (ΙΦΕΤ), Gr.*
Multivitamin preparation (p.1922·1).
Vitamin B deficiency.

Bectam *Labomed, Chile.*
Paroxetine hydrochloride (p.414·2).
Depression.

Bectosan *Liferpal, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Bed Wetting *Hylands, Canad.*
Homoeopathic preparation.

Bed Wetting Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Bedelix *Beaufour, Fr.*
Montmorillonite beidellitique.
Gastrointestinal disorders.

Bedena *SM, Venez.*
Bromhexine hydrochloride (p.1552·2).
Cough; respiratory-tract congestion.

Bediatil *Pasteur, Chile.*
Ibuprofen (p.64·2).
Fever; pain.

Bedice *Genepharm, Gr.†.*
Flurbiprofen (p.61·2).
Inflammatory disorders; pain.

Bedicort G *Jelfa, Pol.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Bedin *Pharmasant, Thai.*
⊗ Dihydroergocristine mesilate (p.364·2); clopamide (p.1250·1); reserpine (p.1387·3).
Hypertension.

Bedix *Bernabo, Arg.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Bedix-D *Bernabo, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Bedoce-Cal *Aventis, Mex.*
Calcium phosphate (p.1676·2); cyanocobalamin (p.1980·2).
Anaemias; calcium supplement.

Bedocil *Allen, Mex.†.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1).
Anaemias; neuritis.

Bedodeka *Teva, Israel.*
Vitamin B (p.1980·2).
Anaemias; vitamin B deficiency.

Bedodeka Antineuralgica *Biogal, Israel†.*
Procaine hydrochloride (p.1869·1); vitamin B substances (p.1922·1).
Arthralgia; neuralgia.

Bedol *Resource Medical, UK.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Bedorma *Vifor, Switz.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Bedovit Compuesto *Inquifave, Venez.*
Thiamine; pyridoxine; cyanocobalamin (p.1922·1).
Vitamin supplement.

Bedovit Pharmaton *Boehringer Ingelheim, Chile.*
Ginseng; deanol tartrate; vitamins; rutin; minerals; soya lecithin (p.1922·1).
Tonic.

Bedovit Simple *Inquifave, Venez.*
Cyanocobalamin (p.1980·2).

Bedoxine *Meuse, Belg.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Bedoyecta
Note. This name is used for preparations of different composition.
Grossman, Mex.
Calcium ascorbate; vitamin B substances; inositol; rutoside (p.1922·1).

Farma, Venez.
Hydroxocobalamin (p.1980·3); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Neuralgia; neuritis.

Bedoyecta Ped *Grossman, Mex.*
Vitamin B substances (p.1922·1).

Bedoyecta Tri *Grossman, Mex.*
Vitamin B substances (p.1922·1).

Bedoz *Nadeau, Canad.†.*
Cyanocobalamin (p.1980·2).

Bedoze *Merck, Port.†.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; neuralgias; neuritis.

Bedozil *Bunker, Braz.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; vitamin B supplement.

Bedranol *Sandoz, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; hypertension.

Beducen *Roche, Venez.†.*
Panthenol (p.2362·1).
Skin disorders.

Beech Nut Cough Drops
Note. This name is used for preparations of different composition.
Beta, Canad.†.
Black: Menthol (p.2340·1); anise oil (p.2258·2).
Beta, Canad.†.
Honey-Lemon; wild cherry: Menthol (p.2340·1); eucalyptus (p.2301·2).
Beta, Canad.†.
Menthol: Menthol (p.2340·1); anethole (p.2258·1); eucalyptus oil (p.2301·2).

Beecham Lemon *GSK Consumer, Spain.*
Ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Beechams Active Cold Relief *GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Beechams All-In-One *GSK Consumer, UK.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Beechams Cold & Flu *GSK Consumer, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Beechams Decongestant Plus with Paracetamol *GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Beechams Flu-Plus
Note. This name is used for preparations of different composition.
SmithKline Beecham Consumer, Irl.†.
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.
GSK Consumer, UK.
Oral liquid: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); vitamin C (p.1983·3).
Cold and influenza symptoms.
GSK Consumer, UK.
Tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Beechams Hot Lemon *GSK, Hong Kong†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Beechams Hot Lemon Decongestant *SmithKline Beecham Consumer, Irl.†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Beechams Hot Remedies *GSK Consumer, Irl.†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Beechams Max Strength Sore Throat Relief *GSK Consumer, UK.*
Hexylresorcinol (p.1647·1); benzalkonium chloride (p.1629·1).
Sore throat.

Beechams for Natural Defence *GSK Consumer, UK.*
Ascorbic acid (p.1983·3) with zinc.

Beechams Powders *GSK Consumer, UK.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold and influenza symptoms; pain.

Beechams Powders Capsules *GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Beechams Throat-Plus *GSK Consumer, UK.*
Benzalkonium chloride (p.1629·1); hexylresorcinol (p.1647·1).
Sore throat.

Beefolic *Sriprasit, Thai.*
Vitamin B substances with folic acid (p.1922·1).
Vitamin B deficiency, neuritis.

Beehive Balsam *Ayrton, UK.*
Purified honey (p.1948·2); glycerol (p.2314·2); ipecacuanha (p.1562·3).
Coughs.

Beelith *Beach, USA.*
Pyridoxine hydrochloride (p.1978·2); magnesium oxide (p.1744·1).
Dietary supplement.

Beesix *SA Druggists Self Med, S.Afr.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Beespan *Garec, S.Afr.*
Vitamin B substances (p.1922·1).
Vitamin B deficiencies.

Beetrion *Franco-Indian, India.*
Multivitamin and mineral preparation (p.1922·1).

Bee-Zee *Rugby, USA.*
Multivitamin and mineral preparation (p.1922·1).

Befact *SMB, Belg.*
Vitamin B substances (p.1922·1).
Alcoholism; neuritis; vitamin B deficiency.

Befar *Nexmed, Hong Kong.*
Alprostadil (p.2183·2).
Erectile dysfunction.

Befarin *Berlin Pharm, Thai.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Befelka-Oel *Befelka, Ger.*
St John's wort oil (p.423·2); calendula oil (p.2273·1); chamomile oil (p.2279·3); viola tricoloris oil.
Skin disorders.

Beferon
Note. A similar name is used for preparations of different composition (see below).
Cristalia, Braz.
Interferon alfa (p.885·1).

Beferron
Note. A similar name is used for preparations of different composition (see above).
Gache, Venez.
Ferric ammonium citrate (p.1938·1); vitamin B (p.1980·2).
Anaemias.

Befibrat *Hennig, Ger.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Befimat *Biomedica-Chemica, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Befitec *Tecnofarma, Mex.*
Bezafibrate (p.1232·1).

Befizal *Roche, Fr.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Beflavine *Bayer Sante, Fr.*
Riboflavin (p.1977·2).
Vitamin B deficiency.

Be-Flex Plus *Larken, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1); salicylamide (p.121·2).
Pain.

Befol
Note. This name is used for preparations of different composition.
Biotenk, Arg.
Diclofenac potassium (p.44·3).
Formerly contained rofecoxib.
Fever; inflammation; pain.
Farma, Venez.
Vitamin B substances (p.1922·1).
Hyperhomocysteinaemia.

Befol Plus *Biotenk, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Beforal *Leciva, Cz.†.*
Butorphanol tartrate (p.32·1).
Pain; premedication.

Beforplex *Eumedica, Belg.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Befosfin *Cafar, Venez.*
Cocarboxylase (p.1975·2); vitamin B (p.1980·2); riboflavin phosphate.
Neuritis; vitamin B deficiency.

Befucil *Biomedica-Chemica, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Begadon *Berman, Mex.*
Vitamin B substances (p.1922·1).

Begalin *Pfizer, Gr.*
Sultamicillin (p.344·1) or sultamicillin tosilate (p.344·1).
Bacterial infections.

Begalin-P *Pfizer, Gr.*
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Begesic
Note. This name is used for preparations of different composition.
Berlin, Hong Kong; Berlin Pharm, Thai.†.
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Formerly contained methyl salicylate, menthol, eugenol, and cajuput oil.
Lumbago; musculoskeletal and joint pain; sciatica.
Littman, Philipp.; Berlin Pharm, Singapore.
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2); cajuput oil (p.2271·2).
Insect bites; musculoskeletal, joint, and soft-tissue disorders; pain.

Begincalm *Genepharm, Gr.†.*
Indometacin (p.66·3).
Inflammatory disorders.

Beglan *Faes, Spain.*
⊗ Salmeterol xinafoate (p.1135·1).
Asthma; bronchitis.

Begrivac *Grunenthal, Austria; Novartis Vaccines, Cz.; Meda, Fin.; Chiron Behring, Ger.†; Novartis, Hung.; Wyeth, Irl.†; Chiron, Ital.; Multichem, NZ†; Chiron Behring, Norw.; Chiron Behring, Pol.; Meda, Swed.; Wyeth, UK.*
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Begrocit *Grossmann, Switz.†.*
Vitamin B substances; vitamin C; calcium (p.1922·1).
Dietary supplement.

Behepan
Note. This name is used for preparations of different composition.
Pfizer, Swed.
Injection: Hydroxocobalamin acetate (p.1980·3).
Megaloblastic anaemia; Schilling test; sprue; vitamin B deficiency.
Pfizer, Swed.
Tablets: Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; sprue; vitamin B deficiency.

Beheptal *Biosel, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Behexine *Osotspa, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Behistin *Pharmasant, Thai.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Behkacin *Behrens, Venez.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Behoedmiddel vir Kinders *Pharmacare, S.Afr.*
Magnesium carbonate (p.1743·1); chalk (p.1716·1).
Gastric hyperacidity.

Behrisol *Behrens, Venez.†.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Beiklin *Scherer, Singapore†.*
Multivitamin and mineral preparation (p.1922·1).

Beilande *HPP, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Bekalen *Megat, Venez.†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Bekamin C *Kimia, Indon.*
Ascorbic acid (p.1983·3).
Capillary bleeding; vitamin C deficiency.

Bekarbon *Kimia, Indon.*
Activated charcoal (p.1435·2).
Diarrhoea; flatulence.

Bekesina *Ultra, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Bekesina-S *Ultra, Mex.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Bekfan-C *Arlex, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Bekidiba *Diba, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Bekidiba Dex *Diba, Mex.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Beklamet *Biosel, Turk.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Beklazon *Bilim, Turk.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Beknol *Kener, Mex.*
Benzonatate (p.1552·1).
Coughs.

Beko *Orion, Fin.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Bekunis
Note. This name is used for preparations of different composition.
Schulke & Mayr, Austria; Lavipharm, Gr.†; Roha, Israel; Farmasa, Mex.; Roha, Pol.; Roha, Switz.
Senna (p.1769·2).
Bowel evacuation; constipation.
Abdi, Turk.
Bisacodyl (p.1710·1); senna (p.1769·2).
Roha, Port.
Tablets: Senna (p.1769·2); bisacodyl (p.1710·1).
Constipation.
Roha, Port.
Tea: Senna (p.1769·2).
Constipation.

Bekunis Bisacodyl *Roha, Ger.; Roha, Neth.*
Bisacodyl (p.1710·1).
Constipation.

Bekunis Complex *Diafarm, Spain.*
Bisacodyl (p.1710·1); senna (p.1769·2).
Bowel evacuation; constipation.

Bekunis Dragees *Roha, Switz.*
Bisacodyl (p.1710·1).
Constipation.

Bekunis Herbal Tea *Thursday, Austral.*
Senna (p.1769·2).
Constipation.

Bekunis Instant *Thursday, Austral.; Roha, Ger.*
Senna (p.1769·2).
Constipation.

Bekunis Plantaardig *Roha, Neth.*
Senna (p.1769·2).
Constipation.

Bekunis Senna *Roha, Neth.*
Senna (p.1769·2).
Constipation.

Bekunis-Krautertee N *Roha, Ger.*
Senna (p.1769·2).
Constipation.

BeL *Winthrop, Ger.*
Simvastatin (p.1390·2).
Coronary heart disease secondary prophylaxis; hypercholesterolaemia.

Bel Labial *Uriach, Spain.*
Aciclovir (p.862·3).
Herpes simplex infections.

Belachin-Gastreu R1 *Reckeweg, Neth.*
Homoeopathic preparation.

Belacid *Nakornpatana, Thai.*
Charcoal (p.1435·2); magnesium hydroxide (p.1743·2); belladonna (p.2263·3); peppermint oil (p.1761·2).
Gastric hyperacidity.

Belacodid
Note. This name is used for preparations of different composition.
Climax, Braz.†.
Injection: Codeine phosphate (p.37·2); sparteine sulfate (p.2391·2); homatropine methonitrate (p.1881·3).
Smooth muscle spasm.
Climax, Braz.†.
Oral drops: ⊗ Codeine (p.37·2); phenethylamine citrate; pentetrazol (p.2162·1); homatropine methonitrate (p.1881·3).
Cough.
Climax, Braz.†.
Syrup: ⊗ Codeine phosphate (p.37·2); phenethylamine citrate; trolamine thymolsulphonate; pentetrazol (p.2162·1); homatropine methonitrate (p.1881·3).
Cough.

Belagin *IMA, Braz.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2); aluminium (p.2254·1); menthol (p.2340·1); benzalkonium chloride (p.1629·1).
Gynaecological infections.

Belanette
Schering, Cz.
Drospirenone (p.2095·2); ethinylestradiol betadex clathrate (p.2102·1).
Combined oral contraceptive.
Schering, Neth.
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Belara *Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Fr.; Grunenthal, Ger.; Grunenthal, Hung.; Tec-O-Pharm, Israel; Formenti, Ital.; Grunenthal, Mex.; Grunenthal, Port.; Grunenthal, Rus.; Andromaco, Spain; Grunenthal, Switz.; Grunenthal, Venez.*
Ethinylestradiol (p.2101·3); chlormadinone acetate (p.2084·3).
Androgenisation in women; combined oral contraceptive.

Be-Lax *Be-Tabs, S.Afr.*
Magnesium sulfate (p.1679·3); magnesium carbonate (p.1743·1).
Constipation.

Belbar *Luar, Arg.*
⊗ Neomycin (p.305·1); polymyxin B (p.318·2); dexamethasone (p.1526·1).
Infected eye disorders.

Belcetin *Sedabel, Braz.†.*
Bacitracin (p.210·3); neomycin (p.305·1).
Bacterial skin infections.

Belcid
Biolab, Malaysia†.
Aluminium oxide (p.1585·3); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.
Biolab, Thai.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Belcomycine *Aventis, Neth.†.*
Colistin sulfate (p.256·2).
Bacterial infections.

Belestar *Biol, Arg.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Belexa *Farmasa, Braz.*
Vitamin B substances (p.1922·1).

Bel-Gel *Sedabel, Braz.†.*
Diclofenac diethylamine (p.44·3).

Beliam *Abbott, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Belidral *Almirall, Belg.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites; heart failure; hypertension; oedema.

Belifax *Pharmathen, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; peptic ulcer; reflux oesophagitis; Zollinger-Ellison syndrome.

Be-Lis *Galeno, Venez.†.*
Vitamin B substances (p.1922·1).
Dietary supplement.

Belisina *CPH, Port.*
Lysine hydrochloride; vitamin B substances (p.1922·1).
Tonic.

Belivon *Organon, Austria†; JC Healthcare, Ital.; Janssen-Cilag, Neth.; Janssen-Cilag, Port.†.*
Risperidone (p.1024·2).
Psychoses; schizophrenia.

Bell Diono Resolvent *Bell, India.*
⊗ Ethylmorphine (p.52·2); allylthiourea; hydrocortisone (p.1535·2); yellow mercuric oxide (p.2341·2).
Corneal scars, ulcers, and opacities.

Bell Pentolate *Bell, India.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Bell Pino-Atrin *Bell, India.*
Atropine sulfate (p.1219·3).
Production of mydriasis and cycloplegia; uveitis.

Bell Resolvent *Bell, India.*
⊗ Ethylmorphine (p.52·2); allylthiourea; hydrocortisone (p.1535·2); yellow mercuric oxide (p.2341·2).
Corneal scars, ulcers, and opacities.

Bella *Hexal, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Acne and hirsutism in women.

Bellacane *Treiner, USA.*
Hyoscyamine sulfate (p.1736·1); phenobarbital (p.492·2).
Gastrointestinal disorders.

Bellacid *Soho, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Belladonna Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Belladonna-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

Belladonnysat Burger *Ysatfabrik, Ger.*
Belladonna (p.2263·3).
Smooth muscle spasm.

Bellafit N *Streuli, Switz.*
Atropine sulfate (p.1219·3).
Colic; hyperhidrosis; sialorrhoea.

Bellagotin *Streuli, Switz.†.*
Belladonna (p.2263·3); diphenhydramine hydrochloride (p.577·2); ergotamine tartrate (p.620·1).
Nervous disorders.

Bellahist-D *Cypress, USA.*
Phenylephrine hydrochloride (p.1568·1); hyoscyamine sulfate (p.1736·1); hyoscine hydrobromide (p.1734·1); chlorphenamine maleate (p.571·3); atropine sulfate (p.1219·3).
Upper respiratory-tract disorders.

Bellamine *Major, USA.*
Levorotatory alkaloids of belladonna (p.2263·3); phenobarbital (p.492·2); ergotamine tartrate (p.620·1).
Gastrointestinal disorders.

Bellamox *Soho, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bellanorm *Rosch & Handel, Austria.*
Belladonna (p.2263·3).
Bronchospasm; gastrointestinal disorders; motion sickness; night sweats.

Bellapan *Farmapol, Pol.*
Belladonna (p.2263·3).
Dystonia; hyperhidrosis; Ménière's disease; migraine; motion sickness; smooth muscle spasm.

Bellapheen *Soho, Indon.*
Belladonna (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Autonomic disorders; gastrointestinal disorders; hypermenorrhoea; menopausal disorders.

Bellaspon *Zentiva, Cz.†.*
Ergotamine tartrate (p.620·1); belladonna (p.2263·3); phenobarbital (p.492·2).
Menopausal disorders; nervous disorders.

Bellatal *Richwood, USA.*
Phenobarbital (p.492·2); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Hypnotic; sedative.

Bellatotal *Cetus, Arg.*
Homatropine (p.1881·2); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Bellatram *Soho, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Belle Cream *Bell, India†.*
Zinc oxide (p.1621·2).
Photodermatoses; sunscreen.

Bellergal *Triton, Canad.; Novartis, Thai.†; Novartis, Turk.*
Laevorotatory alkaloids of belladonna (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Cardiovascular disorders; endocrine disorders; gastrointestinal disorders; menopausal disorders; nervous system disorders.

Bellergal Retardado *Novartis, Chile†.*
Total belladonna alkaloids (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Circulatory disorders; endocrine disorders; gastrointestinal disorders; nervous disorders.

Bellergal-S *Novartis, USA.*
Laevorotatory alkaloids of belladonna (Bellafoline) (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Cardiovascular disorders; gastrointestinal disorders; menopausal disorders; recurrent throbbing headache.

Bellergot *Herbapol Wroclaw, Pol.*
Belladonna (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Dysmenorrhoea; menopausal disorders; neuroses; vascular headache.

Bellgyn *Ratiopharm, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, and hirsutism in women.

Belloform *Tentan, Switz.†.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Bells Muscle Rub *Bell, UK.*
Sweet birch oil (p.86·2); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal disorders.

Belmacina *Pliva, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Belmalax *Belmac, Spain.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Belmalen *Cetus, Arg.*
Diclofenac (p.44·2); orphenadrine (p.812·2).
Inflammation; pain.

Belmalen Plus *Cetus, Arg.*
Glucosamine (p.2313·2).
Musculoskeletal and joint disorders.

Belmalip *Belmac, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias; secondary prophylaxis of ischaemic heart disease.

Belmazol *Daquimed, Port.; Belmac, Spain.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Belmycetin-C *Bell, India.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected eye disorders.

Belnif *Mibe, Ger.*
⊗ Metoprolol tartrate (p.1338·1); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Beloc
Note. This name is used for preparations of different composition.
AstraZeneca, Arg.†; AstraZeneca, Austria; AstraZeneca, Ger.; Promed, Ger.; AstraZeneca, Switz.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Recalcine, Chile.
⊗ Acebutolol (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

AstraZeneca, Turk.
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine.

Alian, Venez.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Beloc comp *Sanova, Austria.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Beloc COR *AstraZeneca, Switz.†.*
⊗ Metoprolol tartrate (p.1338·1).
Heart failure.

Beloc-Zok *AstraZeneca, Ger.; Promed, Ger.; AstraZeneca, Switz.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Beloc-Zok comp *Pharmacia, Ger.*
⊗ Metoprolol succinate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Beloderm
Belupo, Cz.
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Belupo, Rus.
⊗ Betamethasone (p.1518·2).
Skin disorders.

Belogent *Belupo, Cz.; Belupo, Rus.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Beloken *AstraZeneca, Spain.*
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Belomet *Recalcine, Chile.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Asthma.

Belosalic
Belupo, Cz.
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Infected skin disorders.

Belupo, Rus.
⊗ Betamethasone (p.1518·2) or betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Belozok *AstraZeneca, Arg.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

Bel-Phen-Ergot S *Goldline, USA.*
Phenobarbital (p.492·2); ergotamine tartrate (p.620·1); belladonna (p.2263·3).

Belprazol *Sedabel, Braz.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Belsar *Menarini, Belg.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Beltrax Uno *Baliarda, Arg.*
Saw palmetto (p.2192·3).

Belup *Luper, Braz.†.*
Multivitamin preparation (p.1922·1).

Belupan *Grunenthal, Chile†.*
Papaverine (p.2191·3); phenobarbital (p.492·2); belladonna liquid extract (p.2263·3).
Colic.

Beluron *Neo-Farmaceutica, Port.*
Paracetamol (p.108·1).
Fever; pain.

Belustine *OTL, Neth.*
Lomustine (p.741·1).
Malignant neoplasms.

Bemag *Altana, Pol.*
Magnesium lactogluconate; magnesium aspartate (p.1679·1); vitamin B .
Magnesium deficiency.

Bemase *Okasa, Thai.; TTN, Thai.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Bemaz *Laboratorios Chile, Chile.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Bemecor *Lek, Pol.*
Metildigoxin (p.1336·2).
Arrhythmias; heart failure.

Bemedrex *HRA, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Bemetrazole *Be-Tabs, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Bemetson *Orion, Fin.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Bemetson-K *Orion, Fin.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Bemicin *Northia, Arg.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Bemiks *Eczacibasi, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Bemiks C *Eczacibasi, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Beminal *Eurofarma, Braz.; Overseas, India†; Akromed, S.Afr.; Whitehall, USA.*
Vitamin B substances with vitamin C (p.1922·1).
Vitamin deficiency.

Beminal Plus *Eurofarma, Braz.*
Vitamin B substances; vitamin C; vitamin E; minerals (p.1922·1).

Beminex *Sons, Mex.*
⊗ Dexamethasone phosphate (p.1526·2).
Eye disorders.

Bemofil *Veripalvelu, Fin.†.*
A factor IX preparation (p.1068·3).

Bemolan *Altana, Spain.*
Magaldrate (p.1742·3).
Gastric hyperacidity.

Bemon *Riemser, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Bemonalcool *Sanitas, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Disinfection of skin and wounds.

Bemplas *Casasco, Arg.*
⊗ Clonidine hydrochloride (p.1247·1); chlortalidone (p.1243·3).
Hypertension.

Bena
Note. This name is used for preparations of different composition.
Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†.
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3).
Coughs; respiratory-tract congestion.

General Drug, Philipp.
Guaifenesin (p.1561·3).
Cough.

Benace *Novartis, India.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Benacid *Chew, Thai.*
⊗ Probenecid (p.558·2).
Gout; gouty arthritis.

Benacilina *Ivax, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benacne *Home, Port.*
Benzoyl peroxide (p.1590·2).
Acne.

Benacol DTM *Kalbe, Indon.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Benacol Expectorant *Kalbe, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Cold symptoms; cough; nasal congestion; sinusitis.

Benacort *Pulmomed, Rus.*
⊗ Budesonide (p.1520·1).
Asthma.

Benactiv *Boots Healthcare, Ital.*
Flurbiprofen (p.61·2).
Mouth and throat pain and inflammation.

Benaday *Pfizer, Denm.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; hay fever; urticaria.

Benaderma *Confar, Port.*
Diphenhydramine hydrochloride (p.577·2).
Skin disorders.

Benaderma com Calamina *Confar, Port.*
Calamine (p.1591·2); camphor (p.2273·2); diphenhydramine hydrochloride (p.577·2).
Skin disorders.

Benaderma Pruridermase *Confar, Port.†.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Skin disorders.

Benadon *Bayer Consumer, Arg.; Bayer, Ital.; Bayer, Port.; Bayer, Spain; Roche, Swed.; Bayer, Switz.; Roche, Venez.†.*
Pyridoxine hydrochloride (p.1978·2).
Alcoholism; anaemias; nausea and vomiting; neuritis; vitamin B deficiency.

Benadrex *Pfizer Consumer, Mex.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2).
Cough.

Benadryl
Note. This name is used for preparations of different composition.
Elea, Arg.; Pfizer, Gr.; Pfizer, Hong Kong†; Pfizer, Indon.; Pfizer Consumer, Mex.; Pfizer Consumer, Spain; Pfizer, Thai.; Parke, Davis, USA; Warner-Lambert, USA; Pfizer, Venez.
Diphenhydramine hydrochloride (p.577·2).
Allergic disorders; cough; insomnia; minor skin irritation; motion sickness; parkinsonism.

Pfizer, Braz.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Pfizer Consumer, Canad.; Pfizer, India.
Diphenhydramine hydrochloride (p.577·2) or diphenhydramine (p.577·1).
Hypersensitivity reactions; nausea and vomiting; sedative.

Pfizer, Denm.; Pfizer, Fin.
Acrivastine (p.566·1).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hay fever; urticaria.

Pfizer Consumer, Irl.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Allergic skin disorders; skin irritation.

Pfizer, Malaysia.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Formerly known as Benadryl Cough.
Coughs and cold symptoms; rhinitis.

Pfizer, Austria.
Oral drops; oral liquid: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); menthol (p.2340·1); sodium citrate (p.1673·3).
Cold and influenza symptoms; coughs.

Warner-Lambert, Ital.†.
Syrup: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Benadryl 24 *Elea, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Benadryl Allergy *Pfizer, USA.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Benadryl Allergy Oral Solution *Pfizer Consumer, UK.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Benadryl Allergy Relief *Pfizer Consumer, UK.*
Acrivastine (p.566·1).
Allergic rhinitis; urticaria.

Benadryl Allergy/Cold *Warner-Lambert, USA.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Benadryl Allergy/Congestion *Warner-Lambert, USA.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).

Benadryl Allergy/Sinus Headache *Pfizer Consumer, Canad.; Warner-Lambert, USA.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Eye irritation; headache; upper respiratory-tract disorders.

Benadryl Antialergico *Parke, Davis, Arg.†.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; motion sickness; parkinsonism.

Benadryl Antihistamine *Pfizer, Philipp.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Benadryl Antitusivo *Elea, Arg.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); menthol (p.2340·1); sodium citrate (p.1673·3).
Coughs.

Benadryl CD
Note. This name is used for preparations of different composition.
Pfizer, Malaysia†; Pfizer, Singapore†.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Cold symptoms; coughs.

Pfizer, Thai.†.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Benadryl Chesty Cough and Nasal Congestion *Johnson & Johnson, NZ.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Benadryl Chesty Forte *Johnson & Johnson, NZ.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Coughs.

Benadryl Childrens Allergy *Pfizer, USA.*
Diphenhydramine citrate (p.577·2).
Hypersensitivity reactions.

Benadryl CM *Pfizer, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1); alcohol (p.1625·2).
Cough.

Benadryl Cold Nighttime Formula *Parke, Davis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Benadryl Complex *Warner-Lambert, Ital.†.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Benadryl Cough
Note. This name is used for preparations of different composition.
Parke, Davis, India†; Pfizer, Thai.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; respiratory-tract congestion; sneezing.

Pfizer Consumer, Singapore.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Cold symptoms; coughs.

Benadryl 24 D *Elea, Arg.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).

Benadryl Day & Night *Elea, Arg.*
Day tablets, paracetamol (p.108·1); pseudoephedrine (p.1571·2); night tablets, paracetamol; diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Benadryl Decongestant *Pfizer, Thai.; Parke, Davis, USA.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; upper respiratory-tract symptoms.

Benadryl Descongestivo *Elea, Arg.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).

Benadryl DM Compuesto *Elea, Arg.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3).
Coughs.

Benadryl DMP
Note. This name is used for preparations of different composition.
Pfizer, Indon.
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Cough and cold symptoms.

Pfizer, Thai.
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; respiratory-tract congestion.

Benadryl DMP Child *Pfizer, Indon.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough and cold symptoms.

Benadryl Dry Cough and Nasal Congestion *Johnson & Johnson, NZ.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Benadryl Dry Forte *Johnson & Johnson, NZ.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benadryl E *Pfizer Consumer, Mex.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3).
Cough.

Benadryl Expectorant *Pfizer, Philipp.*
Guaifenesin (p.1561·3).
Chest congestion.

Benadryl for the Family Chesty Cough & Nasal Congestion *Pfizer Consumer, Austral.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Benadryl for the Family Chesty Forte *Pfizer Consumer, Austral.†.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Coughs.

Benadryl for the Family - Dry *Pfizer Consumer, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).
Coughs and cold symptoms.

Benadryl for the Family Dry Cough and Nasal Congestion *Pfizer Consumer, Austral.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Benadryl for the Family Dry Forte *Pfizer Consumer, Austral.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benadryl for the Family Original *Pfizer Consumer, Austral.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Allergic rhinitis; cough and cold symptoms.

Benadryl Itch
Note. This name is used for preparations of different composition.
Warner-Lambert, USA.
Cream; topical spray; topical stick: Diphenhydramine hydrochloride (p.577·2); zinc acetate (p.1999·1).
Hypersensitivity reactions.

Warner-Lambert, USA.
Topical gel: Diphenhydramine hydrochloride (p.577·2).
Pruritus.

Benadryl N *Parke, Davis, Cz.†; Pfizer Consumer, Ger.†.*
Diphenhydramine hydrochloride (p.577·2).
Coughs, colds and associated respiratory-tract disorders.

Benadryl Nightime *Johnson & Johnson, NZ.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2).
Coughs and cold symptoms.

Benadryl One A Day *Pfizer Consumer, UK.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Benadryl Original *Johnson & Johnson, NZ.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Benadryl Plus *Pfizer Consumer, UK.*
Acrivastine (p.566·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Benadryl Skin Allergy Relief *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); zinc oxide (p.1621·2).
Allergic skin disorders; skin irritation.

Benadryl Total/Allergy *Pfizer Consumer, Canad.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Eye irritation; headache; upper respiratory-tract disorders.

Benagol *Boots Healthcare, Ital.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Oral hygiene.

Benagol Mentolo-Eucaliptolo *Boots Healthcare, Ital.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1).
Oral hygiene.

Benagol Vitamina C *Boots Healthcare, Ital.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3).
Adjunct in cold symptoms; oral hygiene.

Benal *Berman, Mex.*
Thiamine (p.1976·3).
Vitamin B deficiency.

Benalapril *Berlin-Chemie, Ger.; Berlin-Chemie, Pol.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Benalapril Plus *Berlin-Chemie, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Benalcon *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds.

Benalet *Pfizer, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).

Benalgin *Balkanpharma, Rus.*
Dipyrone (p.49·2); thiamine hydrochloride (p.1976·1); caffeine (p.1116·3).
Fever; pain.

Benalgis *Franco-Indian, India.*
Vitamin B (p.1975·2).
Beri-beri; neuritis.

Benapen *Biolab Sanus, Braz.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Benaprost *Bago, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Benarin *Pulmomed, Rus.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Benatux *Cifarma, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Benaxil *Yoo Young, Philipp.*
Diphenhydramine hydrochloride (p.577·2).
Angioedema; conjunctivitis; pruritus; rhinitis; urticaria.

Benaxima *Ivax, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Benaxona *Ivax, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Benazeplus *Aliud, Ger.; Stada, Ger.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Benazepril comp *1A, Ger.; Betapharm, Ger.; Hexal, Ger.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Benazepril HCT *AWD, Ger.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Bencard Priktestoplossing *Artu, Neth.*
A range of allergen extracts (p.2250·2).
Diagnosis of hypersensitivity.

Bencard Skin Testing Solutions *Allergy Therapeutics, UK.*
Allergen extracts (single and mixed) (p.2250·2).
Diagnosis of hypersensitivity.

Bencelin *Antibioticos, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Bencelin Combinado *Antibioticos, Mex.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Bencid *Geno, India; Pharmaland, Thai.*
⊗ Probenecid (p.558·2).
Gout; gouty arthritis; hyperuricaemia.

Benciefredil *Novag, Mex.*
Guaifenesin (p.1561·3); dextromethorphan (p.1555·2).
Coughs.

Bencifem *Prieto, Arg.*
Benzydamine hydrochloride (p.27·3).

Bencil Scab *Fabra, Arg.*
Permethrin (p.2048·2); benzyl benzoate (p.2036·1).
Pediculosis.

Benclamid *Craveri, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Benclamin *Cazi, Braz.; Polipharm, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Benclav *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bencocan *Teuto, Braz.*
Benzyl benzoate (p.2036·1).

Bencole *Adcock Ingram, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Benda *TNP, Thai.†.*
Mebendazole (p.148·3).
Worm infections.

Bendacor *Corsalud, Venez.*
Mebendazole (p.148·3).
Worm infections.

Bendalina *Angelini, Ital.; Angelini, Philipp.; Lepori, Port.; Elmor, Venez.*
Bendazac lysine (p.27·1).
Cataracts.

Bendamen *Meyer, Venez.*
Mebendazole (p.148·3).
Worm infections.

Bendapar *Ivax, Mex.*
Albendazole (p.139·2).
Worm infections.

Bendex *Cipla, India; Cipla-Medpro, S.Afr.*
Albendazole (p.139·2).
Giardiasis; worm infections.

Bendigon N *Gepepharm, Ger.†.*
⊗ Mefruside (p.1332·1); reserpine (p.1387·3).
Hypertension.

Bendracol *Synco, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); terpin hydrate (p.1573·3); menthol (p.2340·1).
Coughs; respiratory-tract congestion.

Bendrax *Haller, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Bendzon *Dzwon, India.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Benecid *Valdecasas, Mex.*
⊗ Probenecid (p.558·2).
Adjunct to beta-lactam antibacterials; gout.

Benectrin *Legrand, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Benectrin Balsamico *Legrand, Braz.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Bacterial infections.

Benecut *Sanova, Austria.*
Naftifine hydrochloride (p.542·3).
Fungal skin infections.

Benedorm
Note. This name is used for preparations of different composition.
Ariston, Arg.
Bromazepam (p.964·3).
Alcohol withdrawal syndrome; anxiety.

Valeant, Mex.
Melatonin (p.2338·3).
Sleep disorders.

Benefiber *Novartis Consumer, Austral.†; Novartis, Braz.†; Novartis Nutrition, USA.*
Guar gum (p.442·3).
Constipation; diarrhoea; dietary fibre supplement.

Benefix
Note. This name is used for preparations of different composition.
Wyeth, Arg.; Wyeth, Austral.; Genetics Institute, Austria; Baxter, Belg.; Wyeth, Braz.†; Wyeth, Canad.; Wyeth, Chile†; Wyeth, Cz.; Wyeth, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Ital.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Norw.; Wyeth Lederle, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Wyeth, UK.
Nonacog alfa (p.1068·3).
Factor IX deficiency; haemophilia B.

Wyeth, Mex.†; Wyeth, USA.
A factor IX preparation (recombinant) (p.1068·3).
Factor IX deficiency.

Beneflora *Cedar Health, UK.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium* spp; *Streptococcus thermophilus* (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Bifidobacterium longum* (p.2372·3); fructo oligosaccharides; pea fibres.
Maintenance of normal gastrointestinal flora.

Beneflur *Schering, Mex.; Schering, Spain.*
Fludarabine phosphate (p.721·1).
Chronic lymphocytic leukaemia.

Benegel *Legrand, Braz.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); rosemary oil (p.2381·3); lavender oil (p.2331·2); turpentine oil (p.2406·3); mustard oil (p.2349·2).
Musculoskeletal and joint disorders.

Benemicin *Polfa, Cz.; Tarchomin, Rus.*
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis.

Benemid *IFET (ΙΦΕΤ), Gr.; MSD, Thai.†; Merck, USA.*
⊗ Probenecid (p.558·2).
Adjunct to beta-lactam antibacterials; gout; hyperuricaemia.

Benemide *Bouchara-Recordati, Fr.*
⊗ Probenecid (p.558·2).
Adjunct to beta-lactam antibacterials; gout; hyperuricaemia.

Benepax *Apsen, Braz.*
Paroxetine hydrochloride (p.414·2).
Depression.

Benera *TO-Chemicals, Thai.*
Belladonna alkaloids (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Menopausal disorders; migraine; neurocirculatory asthenia; psychosomatic disorders.

Benergina *Merck, Port.*
Diphenhydramine hydrochloride (p.577·2).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Beneroc *Bayer, Braz.*
Vitamin B preparation (p.1922·1).

Benerva *Roche, Belg.; Roche, Braz.; Bayer Sante, Fr.; IFET (ΙΦΕΤ), Gr.; Roche Consumer, Irl.†; Bayer, Ital.; Bayer Consumer, Mex.; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Roche Consumer, UK.*
Thiamine hydrochloride (p.1976·1).
Alcoholism; beri-beri; neuritis; neuropathies; vitamin B deficiency; Wernicke's encephalopathy.

Benestan *Sanofi-Aventis, Port.; Sanofi-Aventis, Spain.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Benet *Takeda, Jpn.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Benetazon *Leciva, Hung.†.*
Tribuzone.
Musculoskeletal and joint disorders.

Benetor *Menarini, Fin.; Galen, Irl.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Benetransit *Kalisterra, Fr.*
Cassia (p.1715·3); cynara (p.2291·2); fennel (p.2302·3); yogurt.
Digestive disorders.

Benetussin *Janssen-Cilag, Port.*
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3).
Coughs.

Beneum *Teuto, Braz.*
Thiamine hydrochloride (p.1976·1).
Vitamin B supplement.

Beneuran *Nycomed, Austria.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Beneuran compositum *Nycomed, Austria.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Cervical syndrome; funicular myelosis; herpes zoster infection; nervous exhaustion; neuralgia; neuritis; pregnancy induced vomiting.

Beneuran Vit B-Komplex *Nycomed, Austria†.*
Riboflavin sodium phosphate (p.1977·3); pyridoxine hydrochloride (p.1978·2); dexpanthenol (p.2362·1); thiamine hydrochloride (p.1976·1); nicotinamide (p.1957·3).
Eye disorders; gastrointestinal disorders; liver disorders; mouth and throat disorders; neurological disorders; obstetric disorders; skin disorders; vitamin deficiency.

Beneurol *Meuse, Belg.*
Thiamine hydrochloride (p.1976·1).
Beri-beri; neuritis; vitamin B deficiency; Wernicke's encephalopathy.

Beneuron Forte *Franco-Indian, India.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Benevat *Teuto, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Benevolus *Schwabe, Arg.†.*
Silymarin (p.1452·2).
Liver disorders.

Benevran *Legrand, Braz.*
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Benexol *Roche, Turk.*
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Benexol B12
Note. This name is used for preparations of different composition.
Bayer Consumer, Mex.; Bayer, Switz.
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Alcoholism; megaloblastic and sideroblastic anaemias; neuritis; neuropathies; vitamin B deficiency.

Bayer, Ital.
Injection: Cocarboxylase (p.1975·2); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3).
Neuropathies; vitamin B , B , and B deficiency; vomiting.

Bayer, Ital.
Tablets: Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuropathies; vitamin B , B , and B deficiency; vomiting.

Benexol B1 B6 B12 *Bayer, Spain.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Benflogin
Note. This name is used for preparations of different composition.
Ache, Braz.
Benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Angelini, Ital.
Ibuprofen guaiacol ester (p.65·2).
Fever; inflammation; pain.

Benflux *Atral, Port.; Polinac, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Benfofen *Sanofi Synthelabo, Ger.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Benfogamma *Worwag, Cz.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.*
Benfotiamine (p.1975·2).
Vitamin B deficiency.

Benfol *Andromaco, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Painful smooth muscle spasm.

Ben-Gay *Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Israel; Pfizer, Pol.; Pfizer, Rus.; Pfizer Consumer, Singapore†; Pfizer, Turk.; Pfizer, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and soft-tissue pain; neuralgia; sports injuries.

Bengay *Pfizer, Indon.; Ponce, Venez.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain; soft-tissue injury.

Bengay Arthritis *Pfizer Consumer, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Bengay Greaseless *Pfizer, Philipp.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Muscle pain.

Bengay Ice *Pfizer Consumer, Canad.†.*
Menthol (p.2340·1).
Muscle and joint pain.

Bengay Muscle Pain Regular (Original) *Pfizer Consumer, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle and joint pain.

Bengay Muscle Pain Ultra *Pfizer Consumer, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle and joint pain.

Bengay No Odor *Pfizer Consumer, Canad.*
Trolamine salicylate (p.132·3).
Muscle and joint pain.

Ben-Gay Patch *Pfizer, USA.*
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Bengay Plus *Pfizer, Indon.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal pain; soft-tissue injury.

Ben-Gay Ultra *Pfizer, Hong Kong; Pfizer Consumer, Singapore†; Pfizer, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle, joint, and soft-tissue pain; neuralgia; sports injuries.

Bengay Ultra *Pfizer, Philipp.*
Menthol (p.2340·1); methyl salicylate (p.85·3); camphor (p.2273·2).
Musculoskeletal and joint pain.

Ben-Gay Ultrastrength *Pfizer, Israel.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint pain.

Ben-Gay Vanishing *Pfizer, USA.*
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Benglau *CSC, Austria.*
Dapiprazole hydrochloride (p.2292·2).
Reversal of mydriasis.

Benhex *PSM, NZ.*
Lindane (p.2045·3).
Scabies.

Benical *Bayer, Switz.; Roche, Turk.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

Benical Cold *Roche, Turk.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Benicar *Sankyo, Braz.; Sankyo, USA; Sankyo, Venez.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Benicar HCT *Sankyo, Braz.; Sankyo, USA.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

beni-cur *Sabona, Ger.†.*
Garlic (p.2309·2).
Atherosclerosis.

Beniforte *Pharmatechnica, Philipp.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3); vitamin B (p.1980·2).
Anaemias.

Benil
Note. This name is used for preparations of different composition.
Vianex (Βιανέξ), Gr.
Brimonidine (p.1878·3).
Glaucoma.

Akdeniz, Turk.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Respiratory-tract congestion.

Benilin *Medikon, Indon.*
Dextromethorphan (p.1555·2); phenylpropanolamine (p.1569·2); diphenhydramine (p.577·1).
Upper respiratory-tract disorders.

Benilylin *Pfizer, Turk.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Respiratory-tract congestion.

Beniod *Chiesi, Spain.*
Delapril hydrochloride (p.1256·2).
Hypertension.

Benisan *Fabra, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Benison *Biosel, Turk.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; motion sickness; vertigo.

Benistina *Ortoquimica, Braz.†.*
Mepyramine maleate (p.585·2); pyridoxine (p.1979·1).
Hypersensitivity reactions.

Benitol *Benitol, Arg.*
Bismuth salicylate (p.1711·1); sodium bicarbonate (p.1673·2); magnesium oxide (p.1744·1); magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); belladonna (p.2263·3).
Formerly contained bismuth salicylate and sodium bicarbonate.
Antacid.

Benitrom *Ivax, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Bennasone *Silom, Thai.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Bennatuss
Note. This name is used for preparations of different composition.
Hoe, Malaysia.
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2).
Cough; nasal congestion.

Hoe, Singapore.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; nasal congestion.

Bennetts Colic Mixture *Bennetts, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); belladonna (p.2263·3).
Infant colic.

Benocetam *Bernofarm, Indon.*
Piracetam (p.368·2).
Cerebrovascular disorders.

Benocten *Medinova, Singapore; Medinova, Switz.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Benodent
Note. This name is used for preparations of different composition.
IMS, Ital.
Capsules: Chlorhexidine gluconate (p.1635·3).
Mouth infections; oral hygiene.

IMS, Ital.
Mouthwash: Sodium fluoride (p.1962·2); chlorhexidine (p.1635·2).
Dental caries prophylaxis; dental hygiene.

Benodent CLX *IMS, Ital.*
Chlorhexidine gluconate (p.1635·3).
Dental disorders.

Benodent Gel Gengivale *IMS, Ital.†.*
⊗ Chlorhexidine (p.1635·2); potassium nitrate (p.1658·3); enoxolone potassium (p.50·1).
Gum disorders.

Benofomin *Bernofarm, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Benol *Aksu, Turk.*
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Benomox *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Benoquin
Note. This name is used for preparations of different composition.
Ivax, Arg.
Balsalazide (p.1709·3).
Ulcerative colitis.

Valeant, Canad.; Mac, India†; Valeant, USA.
Monobenzone (p.1607·3).
Final depigmentation in extensive vitiligo; post-inflammatory melasma; skin hyperpigmentation.

Benoral
Note. This name is used for preparations of different composition.
Sanofi, Irl.†; Sanofi Synthelabo, UK†.
Benorilate (p.27·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

BioSaude, Port.
Dichlorobenzyl alcohol (p.1642·1) benzydamine hydrochloride (p.27·3).
Mouth disorders.

Reig Jofre, Spain.
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Santa, Turk.
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Benormal *Cristalia, Braz.*
Vitamin B substances with calcium (p.1922·1).
Nutritional supplement.

Benosid *Farmasan, Ger.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Benoson *Bernofarm, Indon.*
⊗ Betamethasone (p.1518·2) or betamethasone valerate (p.1519·1).
Corticosteroid.

Benoson V *Bernofarm, Indon.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Benoson G *Bernofarm, Indon.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Benoson M *Bernofarm, Indon.*
⊗ Betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Benoson N *Bernofarm, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Skin disorders.

Benostan *Bernofarm, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Benovit C *Bernofarm, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C supplement.

Benoxi *Unimed, Cz.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Benoxid *Astellas, Ital.*
Benzoyl peroxide (p.1590·2).
Acne; skin disinfection.

Benoxinat *Agepha, Austria.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Benoxinat SE *Alcon, Ger.†.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Benoxinate *Alcon, Hong Kong†; Liba, Turk.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Benoxuric *Bernofarm, Indon.*
Allopurinol (p.552·2).
Hyperuricaemia.

Benoxygel *Stiefel, Port.; Stiefel, Spain.*
Benzoyl peroxide (p.1590·2).
Acne.

Benoxyl *Stiefel, Canad.; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Venez.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Benozym *Bernofarm, Indon.*
Pancreatin (p.2360·1); bromelains (p.2269·1); ox bile extract (p.2266·3).
Digestive enzyme and pancreatic deficiencies.

Benpen *CSL, Austral.; CSL, NZ.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Benph *Gerard, Irl.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Benpine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety; skeletal muscle spasm.

Benquil *Concord, UK†.*
Benperidol (p.964·1).
Deviant sexual behaviour.

Bens *Tender, Canad.†; Ardern, UK.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Bens Natural *Ardern, UK.*
Lemon eucalyptus.
Insect repellent.

Bensal HP *7 Oaks, USA.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2).
Fungal skin infections.

Bensolmin *Continentales, Mex.*
Mebendazole (p.148·3).
Amoebiasis; worm infections.

Bensulf *Fada, Arg.*
Thiopental sodium (p.1795·2).

Bensulfoid *ECR, USA.*
Cream: Colloidal sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Ben-Tann *Midlothian, USA.*
Diphenhydramine tannate (p.577·3).
Hypersensitivity reactions.

Bentasil
Note. This name is used for preparations of different composition.
Carter Horner, Canad.†.
Black currant lozenges; orange lozenges for kids; strawberry lozenges for kids: Menthol (p.2340·1).
Sore throat.

Carter Horner, Canad.†.
Cherry lozenges; honey-lemon lozenges: Anethole (p.2258·1); menthol (p.2340·1).
Coughs; sore throats.

Bentasil Eucalyptus *Carter Horner, Canad.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Coughs; nasal congestion; sore throat.

Bentasil Licorice with Echinacea *Carter Horner, Canad.†.*
Ammonium chloride (p.1551·3); anethole (p.2258·1); echinacea (p.2298·1); liquorice (p.1740·3); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Sore throat.

Bentasil Menthol *Carter Horner, Canad.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Coughs; nasal congestion; sore throat.

Bentelan *Biofutura, Ital.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Bentiamin *Haller, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Bentifen *Novartis, Ital.; Novartis, Neth.; Novartis, Port.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis.

Bentix *Sons, Mex.*
⊗ Clioquinol (p.254·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Bentonine *IFET (ΙΦΕΤ), Gr.†.*
Bentonite (p.2141·2).
Paraquat poisoning.

Bentophyto
Note.This name is used for preparations of different composition.
Panalab, Arg.
Soap: Undecenoic acid diethanolamide (p.549·3).
Fungal skin infections.

Panalab, Arg.
Topical powder: Undecenoic acid diethanolamide (p.549·3); triclosan (p.1665·2); salicylic acid (p.1612·2); boric acid (p.2268·1); alum (p.2254·1); precipitated sulfur (p.1614·1).
Fungal skin infections.

Bentos *Kaken, Jpn; Europhta, Mon.*
⊗ Befunolol hydrochloride (p.1878·2).
Glaucoma; ocular hypertension.

Bentyl *Medley, Braz.; Aventis, Mex.; Duncan, Philipp.; Axcan, USA.*
Dicycloverine hydrochloride (p.1722·3).
Functional bowel syndrome; irritable bowel syndrome; smooth muscle spasm.

Bentylol *Axcan, Canad.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm.

Benur *Bioindustria, Ital.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia.

Ben-u-ron *Sigmapharm, Austria; Bene, Cz.; Bene, Ger.; Novartis Consumer, Ger.; Bene-Chemie, Hong Kong; Bene, Hung.; Neo-Farmaceutica, Port.; Milupa, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Benursil *Benedetti, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders; cholesterol gallstones.

Benuryl *Valeant, Canad.*
⊗ Probenecid (p.558·2).
Hyperuricaemia.

Benutrex *Organon, Venez.*
Vitamin B substances; vitamin C (p.1922·1).

Benutrex 1000 *Organon, Chile.*
Thiamine hydrochloride; riboflavin; pyridoxine hydrochloride; nicotinamide; dexpanthenol; cyanocobalamin; hydroxocobalamin (p.1922·1).
Neuralgia; neuritis; vitamin B deficiency.

Benutrex B12 *Organon, Venez.*
Vitamin B substances (p.1922·1).

Benutrex C *Organon, Philipp.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Benuvit-C *Tai Yu, Philipp.*
Vitamin B substances; vitamin C; glucose (p.1922·1).
Parenteral nutrition.

Benylan *Pfizer, Denm.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Formerly contained diphenhydramine hydrochloride, ammonium chloride, and menthol.
Coughs; hypersensitivity.

Benylin
Note.This name is used for preparations of different composition.
Pfizer Consumer, Belg.
Diphenhydramine hydrochloride (p.577·2).
Formerly known as Benylin Antihistaminicum.
Hypersensitivity reactions.

Pfizer, Chile.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Pfizer Consumer, Irl.; Janssen-Cilag, Port.
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Coughs.

Pfizer, Switz.†.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Benylin a la codeine N *Pfizer Consumer, Switz.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Benylin a la codeine contained diphenhydramine hydrochloride, codeine phosphate, ammonium chloride.
Coughs.

Benylin Active Response *Pfizer Consumer, UK†.*
Echinacea purpurea (p.2298·1).
Upper respiratory-tract infections.

Benylin Adult *Warner-Lambert, USA†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Antitusivo *Pfizer Consumer, Spain†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Bronchospect *Pfizer Consumer, S.Afr.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs.

Benylin CD *Pfizer, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Benylin Chesty *Pfizer Consumer, S.Afr.*
⊗ Orciprenaline sulfate (p.1129·1); bromhexine hydrochloride (p.1552·2).
Coughs.

Benylin Chesty Coughs Non-Drowsy *Pfizer Consumer, UK.*
Guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Benylin Chesty Coughs Original *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Coughs.

Benylin Childrens Chesty Coughs *Pfizer Consumer, Irl.; Pfizer Consumer, UK.*
Guaifenesin (p.1561·3).
Coughs.

Benylin Childrens Cough and Cold *Pfizer Consumer, Irl.*
Dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Benylin Childrens Coughs & Colds *Pfizer Consumer, UK.*
Dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Benylin Childrens Dry Cough
Note. A similar name is used for preparations of different composition (see below).
Pfizer Consumer, Irl.
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Benylin Childrens Dry Coughs
Note. A similar name is used for preparations of different composition (see above).
Pfizer Consumer, UK.
Pholcodine (p.1570·2).
Coughs.

Benylin Childrens Night Coughs *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Coughs; hypersensitivity symptoms of the respiratory tract.

Benylin Clear Action *Pfizer Consumer, Irl.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Benylin with Codeine
Note.This name is used for preparations of different composition.
Pfizer Consumer, Irl.; Pfizer Consumer, UK†.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); menthol (p.2340·1).
Coughs.

Pfizer Consumer, S.Afr.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Benylin Cold & Flu
Note.This name is used for preparations of different composition.
Pfizer Consumer, UK.
Capsules: Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Pfizer Consumer, UK.
Sachets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Benylin 1 Cold and Flu *Pfizer Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Formerly known as Benylin 4 Flu.
Coughs and cold symptoms.

Benylin 2 Cold and Flu with Codeine *Pfizer Consumer, Canad.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly known as Benylin Codeine D-E.
Coughs; nasal congestion.

Benylin 1 Cold and Flu Day Night *Pfizer Consumer, Canad.*
Day caplets, paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); night caplets, paracetamol; pseudoephedrine hydrochloride; diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Benylin 1 Cold and Flu Nightime *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Benylin Compuesto *Pfizer, Venez.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2).
Cough.

Benylin Cough *Pfizer, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Benylin Cough & Congestion *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Benylin D *Pfizer Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Benylin Day & Night *Pfizer Consumer, Irl.; Pfizer Consumer, UK.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; diphenhydramine hydrochloride (p.577·2).
Day tablets formerly contained paracetamol and phenylpropanolamine hydrochloride.
Cold and influenza symptoms.

Benylin Descongestivo *Pfizer Consumer, Spain.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Benylin DM *Pfizer Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2) or dextromethorphan polistirex (p.1556·1).
Coughs.

Benylin DM-D *Pfizer Consumer, Canad.; Pfizer Consumer, S.Afr.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Benylin DM-D-E *Pfizer Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Benylin DM-E *Pfizer Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Benylin Dry Cough
Note.This name is used for preparations of different composition.
Pfizer Consumer, Irl.
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Pfizer Consumer, S.Afr.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Dry Coughs Non-Drowsy *Pfizer Consumer, UK.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Dry Coughs Original *Pfizer Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1).
Coughs.

Benylin Dual Action Chesty *Pfizer Consumer, Irl.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Benylin Dual Action Dry *Pfizer Consumer, Irl.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3).
Coughs.

Benylin E *Pfizer Consumer, Canad.*
Guaifenesin (p.1561·3).
Coughs.

Benylin Energy Boosting *Pfizer Consumer, Canad.†.*
Siberian ginseng (p.2386·3).
Fatigue following colds and influenza.

Benylin Expectorant *Warner-Lambert, USA†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Benylin First Defense *Pfizer Consumer, Canad.†.*
Echinacea (p.2298·1); menthol (p.2340·1).
Cough and cold symptoms.

Benylin 4 Flu
Pfizer Consumer, Irl.; Pfizer Consumer, UK.
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Benylin Four Flu *Pfizer Consumer, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Benylin Multi-Symptom *Warner-Lambert, USA†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Cough and cold symptoms.

Benylin Non-Drowsy Chesty Cough *Pfizer Consumer, Irl.*
Guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Benylin Non-Drowsy Dry Cough *Pfizer Consumer, Irl.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Original *Pfizer Consumer, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Benylin Pediatric *Warner-Lambert, USA†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Benylin Sore Throat Lozenge *Pfizer Consumer, UK†.*
Hexylresorcinol (p.1647·1).
Sore throat.

Benylin Tickly Coughs *Pfizer Consumer, UK.*
Glycerol (p.2314·2).
Coughs.

Benylin Wet Cough *Pfizer Consumer, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Benza *Century, USA.*
Benzalkonium chloride (p.1629·1).
Eye, bladder, urethra, and body cavity irrigation; skin, mucous membrane, and wound disinfection; vaginal douching.

Benzac *Galderma, Austral.; Galderma, Belg.; Galderma, Canad.; Galderma, Chile; Galderma, Ital.; Galderma, NZ; Galderma, Neth.; Galderma, Port.; Galderma, Singapore; Galderma, Switz.; Galderma, Thai.; Galderma, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzac AC *Galderma, Braz.; Galderma, Hong Kong; Galderma, India; Galderma, Israel; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, S.Afr.; Liba, Turk.; Galderma, Venez.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzac Eritromicina *Galderma, Braz.†.*
Erythromycin (p.269·2); benzoyl peroxide (p.1590·2).
Acne.

Benzac Plus *Galderma, Chile; Galderma, Mex.*
Benzoyl peroxide (p.1590·2); erythromycin estolate (p.269·3).
Acne.

Benzaclin
Dermik, Canad.; Darier, Mex.
Clindamycin phosphate (p.251·2); benzoyl peroxide (p.1590·2).
Acne.

Dermik, USA.
Clindamycin (p.251·1); benzoyl peroxide (p.1590·2).
Acne.

Benzacne *Altana, Pol.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzac-W *Lavipharm, Gr.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzaderm
Note.This name is used for preparations of different composition.
Remexa, Mex.
Soap.
Skin cleansing.

Remexa, Mex.
Topical gel: Benzoyl peroxide (p.1590·2).
Acne.

Benzafur *Ivax, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzagel *Columbia, Canad.†; Dermik, Canad.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzaknen *AB-Consult, Austria; Galderma, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzalcor *Corsalud, Venez.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzalcream *Argenfarma, Arg.†.*
Benzalkonium chloride (p.1629·1).
Mucous membrane disinfection.

Benzalcrem *Gezzi, Arg.*
Zinc oxide (p.1621·2); white soft paraffin (p.2031·2).
Nappy rash.

Benzaltex *Innothera, Switz.†.*
Benzalkonium chloride (p.1629·1).
Contraceptive; genital hygiene.

Benzamycin *Ingens, Arg.†; Trenker, Belg.; Dermik, Canad.; Finn Vita, Chile†; Papaellinas (Παπαελληνας), Gr.†; Dermik, Hong Kong; Schwarz, Irl.; Dermik, Israel; Darier, Mex.; Dermik, Singapore; Tek, Turk.; Schwarz, UK†; Dermik, USA.*
Benzoyl peroxide (p.1590·2); erythromycin (p.269·2).
Acne.

Benzamycine *UCB, S.Afr.†.*
Benzoyl peroxide (p.1590·2); erythromycin (p.269·2).
Acne.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Benzanil Compuesto *Roche, Mex.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Benzanil Simple *Roche, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzantine H *Rekah, Israel.*
⊗ Diphenhydramine hydrochloride (p.577·2); hydrocortisone (p.1535·2).
Skin disorders; skin irritation.

Benzapen *Tum, Turk.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzapen 6.3.3 *Tum, Turk.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Benzapen G *Teuto, Braz.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Benzapur *Herbapol Poznan, Pol.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzatec *Caps, S.Afr.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Benzatron *Ariston, Braz.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzecilin *Teuto, Braz.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Benzedrex *Ascher, USA.*
⊗ Propylhexedrine (p.2163·1).
Nasal congestion.

Benzemul *McGloin, Austral.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzet *Premier, S.Afr.†.*
Cetrimide (p.1634·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Benzetacil *Wyeth, Arg.; Eurofarma, Braz.; Sandoz, Mex.; Reig Jofre, Spain.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzetacil 3-3 *Sandoz, Venez.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1); benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzetacil 6-3-3 *Sandoz, Venez.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Benzetacil Combinado *Sandoz, Mex.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Benzetacil Compuesta *Reig Jofre, Spain.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2); benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzetacil L-A *Sandoz, Venez.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Benzevit *Elofar, Braz.*
Nystatin (p.543·2); zinc oxide (p.1621·2).
Skin infections.

Benzibel *Luper, Braz.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzidan *Deva, Turk.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat pain and inflammation.

Benzihex *Galderma, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzin
Note. This name is used for preparations of different composition.
Globo, Braz.†.
Benzyl benzoate (p.2036·1).
Scabies.

Vida, Port.
Lisinopril (p.1325·2).

Benziq *Graceway, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzirin *Fater, Ital.*
Benzydamine hydrochloride (p.27·3).
Inflammatory mouth and throat disorders.

Benzitrat *Biolab Sanus, Braz.*
Benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Benzoax *Ducto, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzoben *Osorio de Moraes, Braz.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzo-Bencil *Vita, Venez.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzocaine PD *Produits Dentaires, Switz.*
Benzocaine (p.1854·1); hydroxyquinoline sulfate (p.2323·1); eugenol (p.2301·2).
Dental pain.

Benzocan *Teuto, Braz.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzodent *Procter & Gamble, USA.*
Benzocaine (p.1854·1).
Oral lesions.

Benzoderm Myco *Athenstaedt, Ger.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Benzodiazol *Meyer, Venez.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Benzodit *Drovepat, Venez.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzogal *Rafarm, Gr.*
Benzyl benzoate (p.2036·1).
Lice infestations.

Benzo-Ginestryl *Aventis, Mex.*
Estradiol benzoate (p.2097·2).
Menopausal disorders; menstrual disorders; osteoporosis.

Benzo-Ginoestril *Sanofi-Aventis, Braz.*
Estradiol hexahydrobenzoate (p.2097·3).
Menopausal disorders; osteoporosis.

Benzol
Note. This name is used for preparations of different composition.
Greenpharma, Braz.
Albendazole (p.139·2).
Worm infections.

Teuto, Braz.†.
Tiabendazole (p.156·2).
Worm infections.

Benzolac *Surya Dermato, Indon.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzolac Cl *Surya Dermato, Indon.*
Benzoyl peroxide (p.1590·2); clindamycin phosphate (p.251·2).
Acne.

Benzolato *Sedabel, Braz.†.*
Benzyl benzoate (p.2036·1).
Scabies.

Benzoleks *Sanofi Synthelabo, Turk.*
Phenyltoloxamine citrate (p.588·1); guaifenesin (p.1561·3); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Respiratory-tract congestion.

Benzolina *Biofarma, Braz.†.*
Benzyl benzoate (p.2036·1).
Scabies.

Benzolom *Osorio de Moraes, Braz.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Benzomel *Granado, Braz.†.*
Sodium benzoate (p.1630·2); mepyramine maleate (p.585·2); sulfogaiacol (p.1573·2); belladonna (p.2263·3); passion flower (p.2363·2).
Coughs.

Benzomid *Surya Dermato, Indon.*
Benzocaine (p.1854·1); cetrimide (p.1634·1).
Burns; insect bites; minor wounds; skin irritation; sunburn.

Benzonal *Cryopharma, Mex.*
Benzonatate (p.1552·1).
Coughs.

Benzopin *Schwulst, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; premedication.

Benzoral *Billiet, Arg.†.*
Cyanocobalamin (p.1980·2).
Anaemias.

Benzosed *Troika, Venez.*
Midazolam (p.1007·3).
General anaesthesia; premedication.

Benz-O-Sthetic *Geritrex, USA.*
Benzocaine (p.1854·1).
Local anaesthesia.

Benzotal *Cifarma, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

Benzotisan *Sanval, Braz.*
Benzyl benzoate (p.2036·1).
Scabies.

Benzotripen *Sons, Mex.*
Procaine benzylpenicillin (p.319·2).
Respiratory-tract infections.

Benzoyt *Riemser, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Benzperox *Medphano, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Benztrop *Pharmalab, Austral.; AFT, NZ.*
Benzatropine mesilate (p.797·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Benzyme *Collins, Mex.*
Diazepam (p.986·3).

Beocid Puroptal *Metochem, Austria.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Beof *Saval, Chile.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Beofenac *UCB, Austria†; Almirall, Ger.*
Aceclofenac (p.14·3).
Ankylosing spondylitis; musculoskeletal and joint disorders; osteoarthritis; rheumatoid arthritis.

Beofta *Columbia, Mex.†.*
⊗ Betaxolol (p.1231·2).

Be-Oxytet *Be-Tabs, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Bepanten *Bayer, Ital.*
Dexpanthenol (p.2362·1).
Intestinal atony.

Bepanthen
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.
Benzalkonium chloride (p.1629·1).
Formerly contained panthenol.
Minor skin lesions; skin irritation.

Bayer, Cz.; Bayer, Fin.; Bayer Sante, Fr.; Bayer, Ger.; Bayer, Hung.; Bayer, Indon.; Roche, Israel; Bayer Consumer, Mex.; Bayer, Pol.; Bayer Consumer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, UK.
Dexpanthenol (p.2362·1).
Dry skin disorders; eye disorders; minor burns and wounds; nappy rash; nasal disorders; skin and mucous membrane disorders; skin irritation; sunburn.

Roche, NZ.
Panthenol (p.2362·1).
Burns; skin irritation; skin lesions.

Bayer, Austria.
Cream; ointment: Dexpanthenol (p.2362·1).
Skin damage; wounds.

Bayer, Austria.
Solution: Dexpanthenol (p.2362·1); domiphen bromide (p.1643·1).
Gastrointestinal disorders; mouth and throat disorders; nasal disorders; respiratory tract disorders; skin damage.

Bepanthen Antiseptische *Bayer, Ger.*
Dexpanthenol (p.2362·1); chlorhexidine gluconate (p.1635·3).
Wounds.

Bepanthen Plus *Bayer, Austria; Bayer, Cz.; Bayer, Hung.; Roche, Israel; Bayer, Pol.; Bayer Consumer, Rus.*
Dexpanthenol (p.2362·1); chlorhexidine hydrochloride (p.1635·3).
Burns; skin disorders; wounds.

Bepanthene
Note. This name is used for preparations of different composition.
Bayer Sante, Fr.; Bayer, Spain; Bayer, Switz.; Roche, Turk.
Dexpanthenol (p.2362·1).
Alopecia; gastrointestinal disorders; mouth and throat disorders; nasal disorders; respiratory-tract disorders; skin disorders; wounds.

Bayer, Port.
Cream; ointment: Dexpanthenol (p.2362·1).
Skin disorders; wounds.

Bayer, Port.
Lotion: Dexpanthenol (p.2362·1); chlorhexidine hydrochloride (p.1635·3).
Skin disorders; wounds.

Bepanthene Plus
Bayer, Port.; Roche, Turk.
Dexpanthenol (p.2362·1); chlorhexidine hydrochloride (p.1635·3).
Skin disorders; wounds.

Bayer, Switz.
Dexpanthenol (p.2362·1); chlorhexidine gluconate (p.1635·3) or chlorhexidine hydrochloride (p.1635·3).
Skin disorders; ulcers; wounds.

Bepantol *Roche, Braz.; Bayer, Chile; Roche Consumer, S.Afr.†; Merkez, Turk.*
Dexpanthenol (p.2362·1).
Burns; skin disorders; wounds.

Beparine
Note. This name is used for preparations of different composition.
Biological E, India.
Cream: Heparin sodium (p.1301·2); benzyl nicotinate (p.28·1).
Superficial thrombophlebitis.

Biological E, India.
Injection: Heparin sodium (p.1301·2).
Thromboembolic disorders.

Bepeben *Teuto, Braz.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Bepeno *Milano, Thai.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Nasal congestion; respiratory-tract disorders.

Bepeno-G *Milano, Thai.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Beplex *Anglo-French Drugs, India; Darou Pakhsh, Rus.*
Vitamin B substances with or without vitamin C (p.1922·1).
Vitamin B deficiency.

Beplexaron *Ariston, Braz.*
Vitamin B substances (p.1922·1).

Beplex-Zee *Anglo-French Drugs, India; Anglo-French Drugs, Thai.†.*
Multivitamin preparation with zinc (p.1922·1).

Beplus
Note. This name is used for preparations of different composition.
Cazi, Braz.
Vitamin B substances (p.1922·1).

Plusandex, Venez.
Thiamine (p.1976·3); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; vitamin B deficiency.

Bepro *Wallace Mfg Chem., UK.*
Codeine phosphate (p.37·2).
Coughs.

Beprogel *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Beprogent *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Beprogenta *Chew, Thai.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected inflammatory skin disorders.

Beprolic *Hoe, Thai.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Bepronate *Pharmasant, Thai.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Beprosalic *Hoe, Malaysia; Hoe, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Beprosone *Hoe, Malaysia; Hoe, Singapore; Chew, Thai.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Beprospen *Biotech, Venez.*
⊗ Betamethasone phosphate (p.1519·1); betamethasone dipropionate (p.1518·3).
Corticosteroid.

Bepsar *Nabiqasim, Philipp.*
Losartan potassium (p.1326·1).
Hypertension.

Beptazine *MM, India.*
⊗ Propranolol hydrochloride (p.1380·3); dihydralazine sulfate (p.1264·3).
Hypertension.

Beptazine-H *MM, India.*
⊗ Propranolol hydrochloride (p.1380·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Bequidril *Teuto, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Bequium *Saval, Chile.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); codeine (p.37·2).
Coughs; nasal congestion.

Beramicina *Berman, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Beramikin *Berman, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Berberell *Sanorell, Ger.*
Homoeopathic preparation.

Berberil *Mann, Pol.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Conjunctivitis; eye irritation.

Berberil Dry Eye *Mann, Ger.*
Hypromellose (p.2144·2).
Dry eyes.

Berberil N *Mann, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Berberis Complex *Blackmores, Austral.*
Berberis vulgaris; taraxacum (p.2395·1); greater celandine (p.2317·1); boldo (p.2267·2); lecithin (p.2332·2); methionine (p.1450·1); thiamine hydrochloride (p.1976·1).
Constipation; dyspepsia; liver disorders.

Berberis Cosmoplex *Peithner, Austria.*
Homoeopathic preparation.

Berberis Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Berberis Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Berberis/Cantharis Comp *Weleda, S.Afr.*
Homoeopathic preparation.

Bercetina *Bernabo, Arg.*
Flunarizine (p.580·3).

Berciclina *Berman, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Berciclina Enzimatica *Berman, Mex.*
Tetracycline (p.347·1) with enzymes.
Bacterial infections.

Berclomine *Polipharm, Thai.*
Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Gastrointestinal colic and spasm; irritable bowel syndrome.

Beres *Beres, Hung.*
Trace element preparation (p.1922·1).
Nutritional supplement.

Beres B1 *Beres, Hung.*
Thiamine nitrate (p.1976·2).
Vitamin B deficiency.

Beres B6 *Beres, Hung.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Beres C *Beres, Hung.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Beres Calcium *Beres, Hung.*
Calcium carbonate (p.1714·1).
Allergic disorders; calcium supplement; osteoporosis.

Beres Drops Plus *Beres, Rus.*
Mineral and trace element preparation (p.1922·1).

Beres Magnezium + B_6 *Beres, Hung.*
Magnesium oxide (p.1744·1); magnesium citrate (p.1743·2); pyridoxine hydrochloride (p.1978·2).
Magnesium deficiency; magnesium supplement.

Berex *Leiras, Fin.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Berex Cee *Leiras, Fin.*
Vitamin B substances; ascorbic acid; calcium carbonate; calcium glycerophosphate (p.1922·1).
Calcium supplement; vitamin B supplement; vitamin C supplement.

Bergacid *Bergamon, Ital.*
Boric acid (p.2268·1); bergamot oil (p.2265·1).
Fungal skin and vaginal infections.

Bergagyn *Bergamon, Ital.*
Benzalkonium chloride (p.1629·1).
Vaginal disinfection.

Bergamol *Medichrom, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Bergamon Sapone *Bergamon, Ital.*
Tribromsalan (p.1632·3).
Skin cleansing.

Berggeist *Kur und Stadtapotheke, Austria.*
⊗ Arnica tincture (p.2260·2); urtica tincture (p.2409·3); formic acid (p.2306·3); menthol (p.2340·1); methyl nicotinate (p.85·3); juniper oil (p.2328·3); lavender oil (p.2331·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); pumilio pine oil (p.2376·3).
Bruising; musculoskeletal and joint disorders; neuralgia.

Bergon *MC, Ital.†.*
Orthophenylphenol (p.1655·1); glutaral (p.1645·2); isopropyl alcohol (p.1650·3).
Disinfection of endoscopes.

Beriate *Aventis, Austria.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency.

Beriate P *Aventis Behring, Arg.; CSL, Braz.; ZLB, Ger.; CSL, Hung.; ZLB, Ital.; CSL, Port.; ZLB, Spain; Aventis Behring, Swed.†; ZLB, Switz.; Farma-Tek, Turk.; Aventis Behring, UK.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemophilia A.

Beribumin *CSL, Braz.*
⊗ Albumin (p.1052·1).
Plasma volume expansion.

Bericard *Provita, Austria.*
Crataegus (p.2289·1).
Cardiovascular disorders.

Berifen *Mepha, Indon.; Sunthi Sepuri, Indon.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Beriglobin *ZLB, Austria; ZLB, Denm.; ZLB, Ger.; Mirren, S.Afr.; ZLB, Swed.; ZLB, Switz.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; mucositis; passive immunisation.

Beriglobin P *Aventis Behring, Israel.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Beriglobina *Aventis Behring, Arg.; CSL, Braz.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Beriglobina P *Sanofi Pasteur, Chile; ZLB Behring, Mex.; ZLB, Spain.*
Normal immunoglobulins (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Berigripina *Elea, Arg.†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Berinert *ZLB, Austria; CSL, Cz.; ZLB, Ger.; ZLB, Switz.*
Complement C1 esterase inhibitor (p.2287·1).
Hereditary angioedema.

Berinert P *Aventis Behring, Arg.; CSL, Hung.*
Complement C1 esterase inhibitor (p.2287·1).
Hereditary angioedema.

Berinin *CSL, Braz.; ZLB, Ger.*
A factor IX preparation (p.1068·3).
Factor IX deficiency; haemophilia B.

Berinin HS *ZLB, Switz.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Berinin P *Aventis Behring, Arg.; CSL, Hung.; ZLB Behring, Mex.; ZLB, Spain; Farma-Tek, Turk.*
A factor IX preparation (p.1068·3).
Factor IX deficiency; haemophilia B.

Beriplast *Aventis, Austria; Nycomed, Fr.; ZLB, Ger.; Dexa, Indon.; ZLB, Indon.; Aventis Behring, Israel; ZLB, Ital.; Centeon, Pol.*
1 Ampoule: fibrinogen (p.1070·1); factor XIII (p.1069·2); 1 ampoule, aprotinin (p.1055·1); 1 ampoule: thrombin (p.1080·1); 1 ampoule, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Beriplast P
Note.This name is used for preparations of different composition.
Aventis Behring, Arg.; CSL, Braz.; Sanofi Pasteur, Chile; ZLB, Gr.; Aventis Behring, Hong Kong; CSL, Hung.; ZLB Behring, Mex.; ZLB, Neth.; ZLB, Switz.; Farma-Tek, Turk.
1 Ampoule, fibrinogen (p.1070·1); factor XIII (p.1069·2); 1 ampoule, aprotinin (p.1055·1); 1 ampoule, thrombin (p.1080·1); 1 ampoule, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Beriplast P Combi *ZLB, Spain.*
1 Vial, fibrinogen (p.1070·1); factor XIII (p.1069·2); 1 vial, aprotinin (p.1055·1); 1 vial thrombin (p.1080·1); 1 vial, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Beriplex *ZLB, Austria; ZLB, Switz.*
A factor IX preparation (p.1068·3).
Anticoagulant overdose; factor II, VII, IX, and X deficiency; haemorrhagic disorders.

Beriplex PN *Aventis Behring, Arg.; CSL, Braz.; ZLB, Ger.; CSL, Hung.; CSL, UK.*
A factor IX preparation (p.1068·3).
Anticoagulant overdose; haemorrhagic disorders.

Berirab *ZLB, Austria; ZLB, Ger.; Aventis Behring, Israel; ZLB, Switz.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Berirab-P *Zydus, India; ZLB Behring, Mex.; Aventis Pasteur, Philipp.; ZLB Behring, Philipp.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Berivine *Meuse, Belg.*
Riboflavin (p.1977·2).
Vitamin B deficiency.

Berko-Fiz *Berko, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Berk-Oral *Berk, Turk.*
Sodium chloride; sodium citrate; potassium chloride; anhydrous glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Berko-Setamol *Berko, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Berlactone *Berlin Pharm, Thai.†.*
⊗ Spironolactone (p.1400·1).
Hypertension; oedema and ascites of heart failure; primary aldosteronism.

Berlamin Modular *Berlin-Chemie, Rus.*
Preparation for enteral nutrition (p.1922·1).

Berlex *Duncan, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Berlicetin
Note.This name is used for preparations of different composition.
Wernigerode, Ger.
Ear drops: ⊗ Chloramphenicol (p.239·3); prednisolone (p.1540·3).
Bacterial ear infections with inflammation.

Chauvin ankerpharm, Ger.
Eye drops: Azidamfenicol (p.206·3).
Bacterial eye infections.

Berlicort
Note.This name is used for preparations of different composition.
Berlin-Chemie, Ger.†; Berlin-Chemie, Rus.
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Berlico Mulia, Indon.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Berlifed *Berlico Mulia, Indon.*
⊗ Promethazine hydrochloride (p.588·2); pseudoephedrine hydrochloride (p.1571·2); sodium citrate (p.1673·3); ammonium chloride (p.1551·3); alcohol (p.1625·2).
Cough; influenza symptoms.

Berlinsulin H 30/70 *Berlin-Chemie, Ger.*
⊗ Mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Berlinsulin H Basal *Berlin-Chemie, Ger.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Berlinsulin H Normal *Berlin-Chemie, Ger.*
⊗ Insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Berlipril *Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Berlin-Chemie, Rus.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Berlison *Intendis, Braz.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Berlithion *Berlin-Chemie, Rus.*
Thioctic acid (p.2400·2).
Alcoholic polyneuropathy; diabetic polyneuropathy.

Berlizon *Berlico Mulia, Indon.*
Phenylbutazone (p.117·1).
Gout; musculoskeletal and joint disorders.

Berlocid *Berlin-Chemie, Cz.†; Berlin-Chemie, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Berlocombin *Berlin-Chemie, Ger.†.*
Trimethoprim (p.355·2); sulfamerazine (p.339·3).
Bacterial infections.

Berlofen *Elea, Arg.*
Aceclofenac (p.14·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Berlosid *Berlico Mulia, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Berlosin *Berlin-Chemie, Ger.*
Dipyrone (p.49·2).
Fever; pain.

Berloson-N *Berlico Mulia, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Berlthyrox *Berlin-Chemie, Ger.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Bermacia *CIF, Braz.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Bernacin *Am-Europharma, Philipp.*
Vitamin B ; vitamin B ; vitamin B   (p.1922·1).
Vitamin B deficiency.

Bernadine *Shiwa, Thai.†.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, burns, and mucous membranes; mouth and throat inflammation.

Bernesten *Berlico Mulia, Indon.*
Clotrimazole (p.530·1).
Fungal skin infections.

Berniter *Galderma, Ger.*
Coal tar (p.1616·2).
Scalp disorders.

Bernoflox *Bernofarm, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Berocca *Bayer Consumer, Arg.; Bayer Consumer, Austral.; Bayer, Austria; Roche, Cz.†; Bayer Sante, Fr.; Bayer, Hong Kong; Bayer, Hung.; Roche, Ital.†; Bayer Consumer, Mex.; Bayer, NZ; Bayer, Philipp.; Roche Consumer, Singapore; Roche, Swed.†; Roche, Thai.; Roche Consumer, UK; Roche, USA; Roche, Venez.†.*
Vitamin B substances; vitamin C; with or without minerals (p.1922·1).
Dietary supplement; vitamin B and C deficiency.

Berocca Calcio e Magnesio *Bayer, Port.*
Vitamin B substances; vitamin C; calcium; magnesium (p.1922·1).
Vitamin deficiency.

Berocca Calcium *Roche, Cz.†.*
Vitamin B substances; vitamin C; calcium (p.1922·1).

Berocca Calcium and Magnesium *Roche, Cz.†; Roche, Israel†.*
Vitamin B substances; vitamin C; calcium; magnesium (p.1922·1).
Nutritional supplement.

Berocca Calcium & Magnesium *Bayer Consumer, Rus.*
Vitamin B substances; ascorbic acid; calcium; magnesium (p.1922·1).

Berocca calcium, magnesium + zinc *Bayer, Switz.*
Vitamin B substances; vitamin C; calcium; magnesium; zinc (p.1922·1).
Alcoholism; vitamin deficiency.

Berocca Plus
Note.This name is used for preparations of different composition.
Bayer Consumer, Arg.; Bayer, Chile; Bayer, Fin.
Vitamin B substances; vitamin C; calcium; magnesium; zinc (p.1922·1).

Roche, USA.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Berocca plus Zink *Bayer, Austria.*
Vitamin B substances; ascorbic acid; magnesium salts; calcium salts; zinc citrate (p.1922·1).
Vitamin B and C deficiency; zinc deficiency.

Berocca-C *Roche, Venez.†.*
Vitamin B substances; vitamin C (p.1922·1).

Beroccal *Roche, Braz.*
Vitamin B substances; vitamin C; calcium; magnesium; zinc (p.1922·1) 406 Formerly contained vitamin b substances, vitamin C, calcium, and magnesium =(prvademecum.com 05.05).

Berodual *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong†; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain†; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Asthma; obstructive airways disease.

Berodualin *Boehringer Ingelheim, Austria.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Berofin *Sanofi Synthelabo, Arg.*
Biperiden hydrochloride (p.797·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Beromin *Condrugs, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; vitamin B deficiency.

Beromun *Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Fr.†; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.*
Tasonermin (p.783·3).
Soft-tissue sarcoma.

Berosolvon *Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.†.*
⊗ Fenoterol hydrobromide (p.1121·1); bromhexine hydrochloride (p.1552·2).
Obstructive airways disease; respiratory-tract disorders.

Berotec *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.†; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile†; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hong Kong†; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.†; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain†; Boehringer Ingelheim, Swed.†; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.†.*
⊗ Fenoterol hydrobromide (p.1121·1).
Asthma; dyspnoea; obstructive airways disease; premature labour; uterine hypertonia.

Berovent *Boehringer Ingelheim, Gr.*
⊗ Salbutamol sulfate (p.1131·3); ipratropium bromide (p.1124·1).
Asthma; obstructive airways disease.

Berry Vision *Sanbe, Indon.*
Myrtillus (p.2349·3); vitamin A; vitamin E; betacarotene (p.1922·1).
Dietary supplement for eye health.

Bersen *Pasteur, Chile.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Bersol *Bernofarm, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Berthyco *Bernofarm, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Bertocil *Edol, Port.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Beruhigungs- und Schlaftropfen fur Kinder Nr 4 *Doskar, Austria.*
Homoeopathic preparation.

Berzymplex *Bernofarm, Indon.*
Pancreatin (p.2360·1); ox bile extract (p.2266·3); dimeticone (p.1770·2); vitamin B substances (p.1922·1).
Flatulence; pancreatic enzyme deficiency; vitamin B deficiency.

Besavar *Winthrop, UK.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Besedan *Wyeth, Braz.†.*
Butamirate citrate (p.1553·1).
Coughs.

Besemax *Adcock Ingram, S.Afr.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal spasm; pain.

Besenol *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); orphenadrine citrate (p.812·1).
Musculoskeletal spasm; pain.

Beserol *Sanofi-Aventis, Braz.*
Diclofenac sodium (p.44·3); carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Muscle spasm; pain.

Beseroldos *Sanofi-Aventis, Venez.*
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Pain; skeletal muscle spasm.

Beserol-S *Sanofi-Aventis, Chile.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Musculoskeletal spasm; pain.

Besflox *Labesfal, Port.*
Norfloxacin (p.309·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Besidin *Coup, Gr.†.*
Cimetidine (p.1716·2).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Besitran *Pfizer, Spain.*
Sertraline hydrochloride (p.421·3).
Anxiety post-traumatic stress disorder; depression; obsessive-compulsive disorder.

Besix *Remek, Gr.*
Pyridoxine hydrochloride (p.1978·2).
Hyperoxaluria; sideroplastic anaemia; vitamin B6 deficiency.

Besobrial *Merck, S.Afr.*
Acamprosate calcium (p.958·3).
Chronic alcoholism.

Besone *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Besone-N *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Bespar *BMS, Ger.; Hormosan, Ger.; Vianex (Βιανεξ), Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Bessasone *Pharmaland, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Best *Konsuma, Venez.*
dl-Alpha tocoferil acetate (p.1992·3).
Antoxidant.

Best Balm *Minorock Mandiri, Indon.*
Camphor (p.2273·2); peppermint oil (p.1761·2).
Insect bites; muscle pain.

Bestafen *Best, Mex.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Bestalen *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Bestalin *Lapi, Indon.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Bestatin
Note.This name is used for preparations of different composition.
Kayaku, Cz.†; Kayaku, Jpn.
Ubenimex (p.784·1).
Restoration of immune function following chemotherapy.

Berlin Pharm, Thai.
Simvastatin (p.1390·2).
Hypercholesterolaemia.

BestBreast *Milte, Ital.*
Vitamin and mineral preparation (p.1922·1).

Bestcall *Takeda, Jpn.*
Cefmenoxime hydrochloride (p.225·2).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bestcilina-A *Best, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Bestelar *Best, Mex.*
Mebendazole (p.148·3).
Worm infections.

Bester Complex *Salvat, Spain.*
Thiamine hydrochloride (p.1976·1); hydroxocobalamin acetate (p.1980·3); pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Bestocin *Best, Mex.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Bestocol *Tanabe, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Cold and influenza symptoms.

Beston *Tanabe, Indon.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Bestozyme
Note.This name is used for preparations of different composition.
Biological E, India.
Capsules: Amylase (p.2256·3); papain (p.2362·3) simeticone (p.1770·2).
Dyspepsia.

Biological E, India.
Paediatric Syrup: Amylase (p.2256·3); papain (p.2362·3); anise oil (p.2258·2); caraway oil (p.2277·1); cinnamon oil (p.2283·2); dill oil (p.2293·3).
Dyspepsia.

Biological E, India.
Syrup: Amylase (p.2256·3); papain (p.2362·3).
Dyspepsia.

Bestpirin *Polfa Kutno, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Bestrol *Cetus, Arg.*
Alprazolam (p.960·1).
Anxiety; depression.

Bestron *Senju, Jpn.*
Cefmenoxime hydrochloride (p.225·2).
Bacterial eye infections.

Bestum *Wockhardt, Rus.*
Ceftazidime (p.234·1).
Bacterial infections.

Be-Supra *Irex, Port.†.*
Vitamin B substances and vitamin C (p.1922·1).

Beta
Note.This name is used for preparations of different composition.
Lichtenstein, Cz.†; Pacific, NZ; Jean-Marie, Philipp.; Chew, Thai.
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Stadmed, India.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

CCM, Malaysia.
⊗ Betamethasone sodium phosphate (p.1518·3).
Inflammatory eye and ear disorders.

Beta 21 *IDI, Ital.*
⊗ Betamethasone valero-acetate (p.1519·1).
Skin disorders.

Beta A-C
Note.This name is used for preparations of different composition.
Eagle, Austral.
Oral powder: Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); calcium ascorbate (p.1984·1); *dl*-alpha tocoferil acetate (p.1992·3); rutoside (p.2305·1); zinc amino acid chelate (p.2000·1); betacarotene (p.1930·3).
Vitamin supplement.

Eagle, Austral.
Tablets: Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); calcium ascorbate (p.1984·1); *dl*-alpha tocoferil acetate (p.1992·3); rutoside (p.2305·1); zinc amino acid chelate (p.2000·1); betacarotene (p.1930·3); bioflavonoids (p.2304·1).
Vitamin supplement.

Beta Adenil *Adesil, Arg.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Beta Alcanforado *Betamadrileno, Spain.*
⊗ Camphor (p.2273·2); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue pain.

Beta C E with Selenium *Stanley, Canad.†.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

Beta Long *Uniao Quimica, Braz.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Skin disorders.

Beta Micoter *Leo, Spain.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Beta Nicardia *Unique, India†; Unique, Singapore.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Beta Nicip *Cipla, India.*
Nimesulide betadex (p.95·3).

Beta Opthiole *Kite (Κιτε), Gr.*
⊗ Metipranolol hydrochloride (p.1883·2); benzalkonium chloride (p.1629·1).
Formerly known as Beta-Ophtiole.
Glaucoma.

Beta plus Vitamins C, E & Selenium *Quest, Canad.†.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

Beta Romero *Betamadrileno, Spain.*
⊗ Alcohol (p.1625·2); rosemary oil (p.2381·3).
Musculoskeletal pain and fatigue.

Beta-Adalat *Bayer, Austria; Bayer, Belg.†; Bayer, Irl.; Bayer, Switz.; Bayer, UK.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Beta-Adalate *Bayer, Fr.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Betabion
Note.This name is used for preparations of different composition.
Merck, Ger.; Merck, Swed.
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Bioton, Pol.
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betabioptal
Farmitalia, Cz.†.
⊗ Betamethasone (p.1518·2); chloramphenicol (p.239·3).
Infected eye disorders.

Farmila, Ital.
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3); chloramphenicol (p.239·3).
Infected eye disorders.

Betabiot *Serral, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Betabiotic *Benedetti, Ital.*
Flucloxacillin sodium (p.277·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Betabloc
Note. A similar name is used for preparations of different composition (see below).
USV, India.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Betablok
Note. A similar name is used for preparations of different composition (see above).
Hexpharm, Indon.
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Be-Tabs Antacid *Be-Tabs, S.Afr.*
Magnesium trisilicate (p.1744·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastrointestinal disorders associated with hyperacidity.

Betac *Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris; arrhythmias; hypertension; hypertrophic cardiomyopathy; myocardial infarction.

Beta-C *Chew, Thai.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betacade *Dermoteca, Port.†.*
Salicylic acid (p.1612·2); cade oil (p.1616·1); cedar oil (p.2278·3); liquid paraffin (p.2030·3).
Skin irritation.

Betacaine *Canderm, Canad.; Darier, Mex.*
Lidocaine (p.1862·3).
Local anaesthesia.

Betacap *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders.

Betacar *Sanofi-Aventis, Chile.*
⊗ Atenolol (p.1217·3).
Hypertension.

Betacard *Torrent, Rus.*
⊗ Atenolol (p.1217·3).

Beta-Cardone *UCB, UK.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Betacarpin *Riel, Austria.*
⊗ Pilocarpine hydrochloride (p.1884·3); metipranolol hydrochloride (p.1883·2).
Glaucoma.

Betacef *Biochimico, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Betachek *California Scientific, Arg.; National Diagnostic, Austral.†.*
Test for glucose in blood (p.2314·1).

Betacid *Meditop, Hung.*
Pepsin (p.2365·1); betaine hydrochloride (p.2265·2).
Hypochlorhydria.

Betacin
Note.This name is used for preparations of different composition.
CCM, Malaysia.
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Be-Tabs, S.Afr.
Indometacin (p.66·3).
Formerly known as Famethacin.
Gout; musculoskeletal and joint disorders.

Betaclar *Angelini, Ital.*
⊗ Befunolol hydrochloride (p.1878·2).
Glaucoma.

Betaclav *Ranbaxy, Braz.; Corsa, Indon.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Betaclomin *Be-Tabs, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); dried aluminium hydroxide gel (p.1706·2); light magnesium oxide (p.1744·1).
Gastrointestinal hyperacidity.

Betaclopramide *Be-Tabs, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea.

Betacomplesso *Medosan, Ital.*
Vitamin B substances (p.1922·1).
Tonic; vitamin B deficiency.

Betacort
Note.This name is used for preparations of different composition.
Biospray, Gr.
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Skin disorders.

SM, Venez.
⊗ Betamethasone (p.1518·2).
Skin disorders.

Cassara, Arg.
Cream: ⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Cassara, Arg.
Injection: ⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Cassara, Arg.
Oral drops: ⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betacort Plus *Cassara, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Betacorten *Trima, Israel; Trima, Singapore; Unipharm, Singapore.*
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Betacorten-G *Trima, Israel.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Betacorton
Note.This name is used for preparations of different composition.
Spirig, Cz.
⊗ Halcinonide (p.1535·1).
Skin disorders.

Orva, Turk.
⊗ Halcinonide (p.1535·1); urea (p.1620·2).
Skin disorders.

Betacorton S *Spirig, Cz.*
⊗ Halcinonide (p.1535·1); salicylic acid (p.1612·2).
Skin disorders.

Betacorton U *Spirig, Cz.*
⊗ Halcinonide (p.1535·1); urea (p.1620·2).
Skin disorders.

Betacortone
Note.This name is used for preparations of different composition.
Spirig, Switz.
Cream: ⊗ Halcinonide (p.1535·1); urea (p.1620·2).
Skin disorders.

Spirig, Switz.
Topical solution: ⊗ Halcinonide (p.1535·1).
Skin disorders.

Betacortone S *Spirig, Switz.*
⊗ Halcinonide (p.1535·1); salicylic acid (p.1612·2).
Skin disorders.

Betacream
Note. A similar name is used for preparations of different composition (see below).
Epifarma, Ital.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

BetaCreme
Note. A similar name is used for preparations of different composition (see above).
Winthrop, Ger.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betaderm
Note.This name is used for preparations of different composition.
Stiefel, Braz.; Taro, Canad.; Biotech, Venez.
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders; skin disorders.

Beta, Ital.
Salicylic acid (p.1612·2); aluminium acetate (p.2255·1); zinc oxide (p.1621·2).
Skin disinfection.

Betaderm con Gentamicina *Biotech, Venez.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Betaderm N *Stiefel, Braz.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betaderma *Safire, Hong Kong.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betadermic *Galen, Ger.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Betadine *Faulding, Austral.; Purdue, Canad.; Egis, Cz.; Leiras, Fin.; Viatris, Fr.; Lavipharm, Gr.; Mundipharma, Hong Kong; EGIS, Hung.; Win-Medicare, India; Mahakam Beta, Indon.; Mundipharma, Indon.; SSL, Irl.; Viatris, Ital.; Mahakam Beta, Malaysia; Baxter, NZ; Viatris, Neth.; Mundipharma, Philipp.; Pascual, Philipp.; Egis, Pol.; Meda, Port.; Egis, Rus.; Adcock Ingram, S.Afr.; Mundipharma, Singapore; Gervasi, Spain; Viatris, Spain; Mundipharma, Switz.; Mundipharma, Thai.; Molnlycke, UK; Purdue Frederick, USA; Novapharm, Venez.*
Povidone-iodine (p.1659·2).
Burns; disinfection of burns, mucous membranes, skin, skin ulcers, and wounds; infections of the skin, mucous membranes, vagina, and oropharynx; lubricant in catheterisation; oral hygiene; seborrhoeic dermatitis; ulcers; wounds.

Betadine First Aid Antibiotics + Moisturizer
Purdue Frederick, USA.
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Minor cuts and burns.

Betadine Plus First Aid Antibiotics & Pain Reliever *Purdue Frederick, USA.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); pramocaine hydrochloride (p.1868·1).
Minor cuts and burns.

Betadine-AD *Win-Medicare, India.*
Povidone-iodine (p.1659·2).
Scalp disorders.

Beta-Dipo *TNP, Thai.†.*
⊗ Betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Skin disorders.

Betadipresan *Fides Ecopharma, Spain†.*
⊗ Hydralazine hydrochloride (p.1305·3); propranolol hydrochloride (p.1380·3).
Hypertension.

Betadipresan Diu *Fides Ecopharma, Spain†.*
⊗ Bendroflumethiazide (p.1224·1); hydralazine hydrochloride (p.1305·3); propranolol hydrochloride (p.1380·3).
Hypertension.

Betadiur *Siphar, Switz.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver failure with ascites; oedema.

Betadona *Mundipharma, Austria.*
Povidone-iodine (p.1659·2).
Infected wounds and burns.

Betadorm D *McNeil, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Betadorm-A *Woelm, Ger.†.*
Diphenhydramine hydrochloride (p.577·2); 8-chlorotheophylline.
Sleep disorders.

Betadrenol *Desma, Ger.*
⊗ Bupranolol hydrochloride (p.1238·1).
Hypertension; ischaemic heart disease; myocardial infarction.

Betadrin *Polfa Warszawa, Pol.; Polfa, Rus.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline nitrate (p.1565·2).
Allergic rhinitis; conjunctivitis; eye disorders.

Betaeffe Complex *Mavi, Ital.*
Carotenoids; vitamin E; vitamin C; vitis vinifera (p.1922·1).
Nutritional supplement.

Betaeffe Plus *Mavi, Ital.*
Betacarotene, vitamin E, and selenium preparation (p.1922·1).
Nutritional supplement.

Betafact *Lab Francais du Fractionnement, Fr.; Vianex (Βιανεξ), Gr.; Omrix, Israel; Lab Francais du Fractionnement, Neth.; LFB, Port.; Er-Kim, Turk.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Betafed *Be-Tabs, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Betaferon *Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering-Plough, Gr.; Schering, Hong Kong; Schering, Hung.; German Remedies, India; Schering, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Schering, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Schering, UK.*
Interferon beta-1b (p.891·2).
Multiple sclerosis.

Betafloroto *INTES, Ital.*
⊗ Betamethasone sodium phosphate (p.1518·3); tetracycline hydrochloride (p.347·2).
Ear infections; rhinitis.

Betafoam *Cipla, India.*
⊗ Betamethasone (p.1518·2).

Betafusin *Pharmex (Φαρμεξ), Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Betagalen *Galen, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betagan *Allergan, Arg.; Allergan, Austral.; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Denm.; Allergan, Fr.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Israel; Allergan, Malaysia†; Allergan, Mex.; Allergan, NZ; Allergan, Neth.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma; ocular hypertension.

Betagard *GNLD, Austral.*
Vitamin, mineral, and amino-acid preparation (p.1922·1).

Betagen
Note.This name is used for preparations of different composition.
Allergan, Chile.
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma; ocular hypertension.

Generics, Hung.
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

CCM, Malaysia.
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin sulfate (p.282·1).
Infected eye and ear disorders.

Biotech, Venez.
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betagen Solspen *Biotech, Venez.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Betagenot *Lekko, Rus.*
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin sulfate (p.282·1).
Infected ear and eye disorders.

Betagentam *Winzer, Ger.; Sanbe, Indon.*
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin sulfate (p.282·1).
Infected eye disorders.

Betagesic *Adcock Ingram, S.Afr.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Betaglau *Edol, Port.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betaglid *Pliva Krakow, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Betaglim *Panacea, India†.*
Glimepiride (p.441·1).
Diabetes mellitus.

Betaglim M *Panacea, India†.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Betagranulos *Medihealth, Mex.; Roemmers Medihe, Venez.*
Polyethylene granules (p.1585·3).
Acne.

Betahist *Cipla, India†.*
Betahistine hydrochloride (p.2265·1).

Betahist-B *Farmaline, Thai.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Betahistop *Topgen, Belg.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; vertigo.

Betaimune *Pharmadass, UK.*
Vitamins A, C, and E; selenium; zinc (p.1922·1).
Antoxidant preparation.

Betaine Digestive Aid *GNLD, Austral.*
Betaine hydrochloride (p.2265·2); pepsin (p.2365·1); papain (p.2362·3); pectin (p.2145·2); natural dried beet; rhubarb (p.1768·3); liquorice (p.1740·3).
Digestive disorders.

Betaisodona *Mundipharma, Austria; Mundipharma, Ger.*
Povidone-iodine (p.1659·2).
Burns; mouth and throat infections; skin and mucous membrane disinfection; skin infections; skin ulcers; vaginal infections; wounds.

Betaject *Sandoz, Canad.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Betaklav *KRKA, Cz.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Betakon *Aroma, Turk.*
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection.

Betaksim *Nevzat, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Betalbee *Wellhealth, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Dietary supplement.

Betaleukin *Gosnii, Rus.*
Interleukin-1 (p.2325·3).
Leucopenia; secondary immunodeficiency.

Betalgon *Nizhpharm, Rus.*
Nicoboxil (p.95·1); nonivamide (p.96·2).
Musculoskeletal, joint, peri-articular and soft-tissue disorders; neuralgia.

Betalin *Be-Tabs, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Betaliver *Luper, Braz.†.*
Methionine (p.1450·1); adenosine (p.1202·1); betaine hydrochloride (p.2265·2); pyridoxine hydrochloride (p.1978·2); choline citrate (p.1934·2).
Liver disorders.

Betalmic *Unimed, Cz.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betaloc
AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, India; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Philipp.; AstraZeneca, Thai.; AstraZeneca, UK.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

AstraZeneca, Cz.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; EGIS, Hung.; AstraZeneca, NZ; AstraZeneca, Pol.; AstraZeneca, Singapore.
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Betaloc Comp *AstraZeneca, Hong Kong.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Betaloc ZOK *AstraZeneca, Rus.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

Betalol *Berlin Pharm, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety disorders; arrhythmias; hypertension; tremor.

Betalor *Biosintetica, Braz.*
⊗ Amlodipine besilate (p.1214·1); atenolol (p.1217·3).
Angina pectoris; hypertension.

Betama-EN *Samakeephaesaj, Thai.†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betamaks *Grindex, Rus.*
Sulpiride (p.1028·3).
Delirium; depression; irritable bowel syndrome; neuroses; peptic ulcer; schizophrenia; vestibular disorders.

Betamann *Mann, Ger.; Mann, Pol.*
⊗ Metipranolol hydrochloride (p.1883·2).
Glaucoma; ocular hypertension.

Betamatic *Medichrom, Gr.†.*
⊗ Betamethasone valerate (p.1519·1).
Topical corticosteroid.

Betamed *Kwizda, Austria.*
⊗ Bupranolol hydrochloride (p.1238·1); diazepam (p.986·3).
Anxiety disorders.

Betamesol *Proge, Ital.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Betametagen *Kinder, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betametasona B12 *Roux-Ocefa, Arg.*
⊗ Betamethasone sodium phosphate (p.1518·3); hydroxocobalamin (p.1980·3).
Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Betameth *Osoth, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betamethason comp *Hexal, Ger.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Betamethason Plus *Heumann, Ger.†.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Betamethasone Clo *Pharmaniaga, Malaysia.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Formerly known as Dermal C.
Fungal skin infections.

Betamethasone G *Pharmaniaga, Malaysia.*
⊗ Betamethasone (p.1518·2); gentamicin sulfate (p.282·1).
Formerly known as Dermal G.
Infected skin disorders.

Betamethasone N *Pharmaniaga, Malaysia.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Formerly known as Dermasole N.
Infected skin disorders.

Betamethasone SA *Pharmaniaga, Malaysia.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Formerly known as Dermal SA.
Skin disorders.

Betameth-N *Osoth, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betamican *Alter, Spain.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Beta-Micoter *Leo, Port.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Betamida *Alcon Cusi, Spain†.*
⊗ Betamethasone sodium phosphate (p.1518·3); sulfacetamide sodium (p.335·3).
Eye disorders.

Betamil-GM *Merck, India.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Betamil-M *Merck, India.*
⊗ Betamethasone dipropionate (p.1518·3); miconazole nitrate (p.541·3).
Infected skin disorders.

Betamin *Aventis, Austral.; Sanitas, Chile†.*
Thiamine hydrochloride (p.1976·1).
Neuralgia; neuritis; vitamin B deficiency.

Betamine *Wolfs, Belg.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency; Wernicke's encephalopathy.

Betamoclav *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Betam-Ophtal *Winzer, Ger.†; Sanbe, Indon.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Inflammatory eye disorders.

Betamotil *Ipca, India.*
Artemotil (p.598·1).
Malaria.

Betamox
Note.This name is used for preparations of different composition.
Duopharma, Hong Kong; Be-Tabs, S.Afr.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Cipan, Port.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Betamycin *Be-Tabs, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Beta-N *Chew, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betanase *Cadila, Cz.†; Cadila, Rus.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Betanicomylon *Nizhpharm, Rus.*
Nicoboxil (p.95·1); nonivamide (p.96·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; peripheral vascular disorders.

Betanoid *Pharmacare, S.Afr.*
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betanoid N *Aspen, S.Afr.†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betanorm *Ali, Turk.*
Gliclazide (p.440·3).
Diabetes mellitus.

Beta-Ophtiole *Riel, Austria; Tramedico, Belg.; Mann, Malaysia†; Tramedico, Neth.; Bausch & Lomb, Philipp.; Lepori, Port.; SofLens, S.Afr.; Mann, Singapore†; Bausch & Lomb, Thai.†; Mann, Thai.†.*
⊗ Metipranolol hydrochloride (p.1883·2).
Glaucoma; ocular hypertension.

Betapace *Berlex, USA.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Betapam *Be-Tabs, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; premedication.

Betapect *Be-Tabs, S.Afr.*
Light kaolin (p.1738·1); apple pectin (p.2145·2).
Formerly known as Pectikon.
Diarrhoea.

Betapen *Be-Tabs, S.Afr.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Betaperamide *Adcock Ingram, S.Afr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Betaphlem *Be-Tabs, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased mucous.

Betapirox *Medihealth, Mex.; Roemmers Medihe, Venez.*
Piroctone olamine (p.1610·1).
Dandruff; seborrhoeic dermatitis.

Betaplex *Drugtech, Chile.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Betapred *Orphan, Fin.; Swedish Orphan, Swed.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betapress *Polipharm, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; tremor.

Betapressin *Wolff, Ger.*
⊗ Penbutolol sulfate (p.1366·2).
Arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Betaprid *Tiefenbacher, Neth.*
Tiapride hydrochloride (p.1032·1).
Drug-induced extrapyramidal disorders.

Betaprofen *Be-Tabs, S.Afr.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Beta-Prograne *Tillomed, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; essential tremor; hypertension; hyperthyroidism; migraine; prophylaxis of upper gastrointestinal bleeding.

Betaprospan *Uniao Quimica, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betapyn *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2); caffeine (p.1116·3).
Fever; pain.

Betapyr *Wolfs, Belg.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Alcoholic polyneuritis; prophylaxis during isoniazid therapy; vitamin B and/or B deficiency.

Betarelix *Wolff, Ger.*
⊗ Penbutolol sulfate (p.1366·2); piretanide (p.1372·3).
Hypertension.

Betaren *Dexxon, Israel.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Betarene *Darya-Varia, Indon.*
Carotenoids.
Antoxidant.

Betaretic *Be-Tabs, S.Afr.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Betarhin *Mahakam Beta, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Betarretin *Roemmers Medihe, Venez.*
Tretinoin (p.1618·1).
Acne.

Betaryx *Integrated Pharmaceutical, Philipp.; Swiss Pharma, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; hyperthyroidism; migraine; tachycardia.

Beta-S *Chew, Thai.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2).
Skin disorders.

BetaSalbe *Winthrop, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betasalic
Andromaco, Arg.
⊗ Betamethasone (p.1518·2); salicylic acid (p.1612·2).
Skin disorders.

Cipla, India.
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2).
Skin disorders.

Betasan *Mundipharma, Austria.*
Povidone-iodine (p.1659·2).
Infected burns and wounds.

Betasel *Alcon, Arg.*
⊗ Betaxolol hydrochloride (p.1231·2).

Betaselen *Arkopharma, Fr.*
Multivitamin and mineral preparation (p.1922·1).
Tonic.

Betasemid *Wolff, Ger.*
⊗ Penbutolol sulfate (p.1366·2); furosemide (p.1292·1).
Hypertension.

Betasept *Purdue Frederick, USA.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Betaseptic
Note.This name is used for preparations of different composition.
Mundipharma, Austria; Viatris, Ital.
Povidone-iodine (p.1659·2).
Medicated dressing; skin disinfection.

Mundipharma, Ger.; Mundipharma, Switz.
⊗ Povidone-iodine (p.1659·2); isopropyl alcohol (p.1650·3); alcohol (p.1625·2).
Skin and hand disinfection; skin disinfection.

Betaserc *Solvay, Austria; Solvay, Belg.; Solvay, Braz.; Solvay, Cz.; Solvay, Denm.; Solvay, Fin.; Solvay, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; Solvay, Malaysia; Solvay, Neth.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, Singapore; Solvay, Switz.; Eczacibasi, Turk.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; nausea and vomiting; tinnitus; vertigo; vestibular disorders.

Betaseron *Berlex, Canad.; Berlex, USA.*
Interferon beta-1b (p.891·2).
Multiple sclerosis.

Betasid *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Betasin *Otto, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Betasleep *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Betaslim *GMP, Indon.*
Poliglusam (p.2370·1); garcinia cambogia (p.2309·2); levocarnitine; chromium tripicolinate; vitamin C (p.1922·1).
Weight reduction.

Betasoda *Restan, S.Afr.†.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Urinary alkalinisation.

Beta-Sol
Note. A similar name is used for preparations of different composition (see below).
Fawns & McAllan, Austral.†.
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Betasol
Note. A similar name is used for preparations of different composition (see above).
Upha, Malaysia†; Chew, Thai.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Herbapol Pruszkow, Pol.
Phaseolus; lappa (p.2330·3); ononis (p.2357·1); rhubarb (p.1768·3); equisetum (p.2299·3); buckwheat (p.2270·1); sambucus (p.2383·1); birch leaf (p.2266·3).
Urinary-tract inflammation.

Betason *Kimia, Indon.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betasone
DHA, Hong Kong; Vida, Hong Kong; DHA, Malaysia; DHA, Singapore.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Lekko, Rus.
⊗ Betamethasone sodium phosphate (p.1518·3).
Inflammatory eye disorders; otitis externa.

Julphar, UAE.
Cream; ointment: ⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Julphar, UAE.
Tablets: ⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betasone-G *Klonal, Arg.*
⊗ Betamethasone (p.1518·2), betamethasone sodium phosphate (p.1518·3), or betamethasone valerate (p.1519·1).
Corticosteroid.

Betasone-G Compuesto *Klonal, Arg.*
⊗ Betamethasone (p.1518·2); neomycin (p.305·1).
Infected skin disorders.

Betasone-G 12 Horas *Klonal, Arg.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betason-N *Kimia, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Skin disorders.

Betaspan
Note.This name is used for preparations of different composition.
Delta, Braz.
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

GSK, India.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; hypertension; hyperthyroidism; migraine; tremor.

Betaspore *Aristo, India†.*
Cefalexin (p.218·2).
Bacterial infections.

Betasporina *Atral, Port.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Beta-Stulln *Stulln, Ger.†.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Inflammatory eye disorders.

Betasyn *Jacoby, Austria.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Beta-Synto *Codal Synto, Hong Kong.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Betatab *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; hyperthyroidism.

Beta-Tablinen *Winthrop, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; migraine.

Betaton *Hovid, Malaysia†.*
Vitamin and mineral preparation with lecithin (p.1922·1).

Betaton with Ginseng *Hovid, Malaysia†.*
Multivitamin and mineral preparation with rutoside, lecithin, and ginseng (p.1922·1).

Betatop *IPRAD, Fr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Betatopic *Andromaco, Arg.*
⊗ Betamethasone (p.1518·2).
Skin disorders.

Betatrinta *Eurofarma, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betatul *Viatris, Spain.*
Povidone-iodine (p.1659·2).
Infected skin disorders; skin disinfection.

Beta-Turfa *Worwag, Ger.*
⊗ Propranolol hydrochloride (p.1380·3); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Beta-Val *Lemmon, USA.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

BetaVent *WraSer, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cough.

Betavert *Hennig, Ger.*
Betahistine mesilate (p.2265·1).
Vestibular disorders.

Betavit *Cipla, India; Terramedic, Philipp.*
Multivitamin preparation (p.1922·1).

Betavite *Nicholas Piramal, India†.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Betavix *Genepharm, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Beta-Wolff *Wolff, Ger.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betaxa *Zentiva, Cz.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris; hypertension.

Betaxin *Abbott, Canad.†.*
Thiamine hydrochloride (p.1976·1).

Betaxina *Terapeutico, Ital.†.*
Nalidixic acid (p.303·3).
Gram-negative genito-urinary tract infections.

Betaxol *Oftalmi, Venez.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betaxon *Alcon, USA†.*
⊗ Levobetaxolol hydrochloride (p.1882·3).
Glaucoma; ocular hypertension.

Betazide *AstraZeneca, Philipp.*
⊗ Hydrochlorothiazide (p.1307·3); metoprolol tartrate (p.1338·1).
Hypertension.

Betazidim *Lapreven, Venez.*
Ceftazidime (p.234·1).
Bacterial infections.

Betazim *Sam-On, Israel.*
Betaine hydrochloride (p.2265·2); pepsin (p.2365·1).
Anorexia; diarrhoea; gastritis; gastrointestinal hypoacidity.

Betazok *AstraZeneca, Philipp.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Betazol Cort *Delta, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Betazone *APT, Hong Kong.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Beten *Svizera, India; CCM, Malaysia.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic subaortic stenosis; myocardial infarction; tremor.

Betesil *IBSA, Cz.; Genevrier, Fr.; IBSA, Hung.; IBSA, Ital.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betfu *Medimar, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Bethacil *Bioindustria, Ital.*
Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bethasone *Greater Pharma, Thai.*
⊗ Betamethasone (p.1518·2).
Skin disorders.

Bethasone-N *Greater Pharma, Thai.*
⊗ Betamethasone (p.1518·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Bethiol *Nizhpharm, Rus.*
Belladonna (p.2263·3); ichthammol (p.1599·1).

Betiga *Solas, Indon.*
Aluminium chlorohydrate (p.1588·3); menthol (p.2340·1); salicylic acid (p.1612·2); triclosan (p.1665·2); zinc oxide (p.1621·2).
Hyperhidrosis.

Betim *ICN, UK.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; hypertension; migraine; myocardial infarction.

Betimol *Novartis Ophthalmics, USA.*
⊗ Timolol (p.1413·1).
Glaucoma; ocular hypertension.

Betiral *Roche, Gr.†.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Betistine *Rafa, Israel.*
Betahistine hydrochloride (p.2265·1).
Vestibular disorders.

Betitotal *Adcock Ingram, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Betlife *Grunenthal, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Betnasol *Defiante, Port.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betnecip *Cipla, India.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Betnecort *Cipla, India.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betnederm *Cipla, India.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnederm C *Cipla, India.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnederm GM *Cipla, India.*
⊗ Betamethasone valerate (p.1519·1); gentamicin (p.284·2); miconazole nitrate (p.541·3).
Infected skin disorders.

Betnederm N *Cipla, India.*
⊗ Betamethasone valerate (p.1519·1); neomycin (p.305·1).
Infected skin disorders.

Betnelan
Farmoquimica, Braz.; GSK, India; UCB, Irl.; GSK, Philipp.; UCB, UK.
⊗ Betamethasone (p.1518·2).
Corticosteroid.

GSK, Neth.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnelan-V *GSK, Belg.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnelan-VC *GSK, Belg.†.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnesalic *GSK, Fr.†; GSK, Hong Kong†; Alloga, Switz.; GSK, Thai.†.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2).
Skin disorders.

Betnesalic mono *Meda, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnesol
GSK, Austria; Shire, Canad.; Sigma-Tau, Fr.; GSK, India; UCB, Irl.; Devries, Israel; GSK, Malaysia†; GSK, NZ; Defiante, Neth.; Pharmacare, S.Afr.; Sigma-Tau, Switz.; UCB, UK.
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

IFET (ΙΦΕΤ), Gr.
⊗ Betamethasone (p.1518·2).
Inflammatory bowel disease.

Sigma-Tau, Ger.
⊗ Betamethasone sodium phosphate (p.1518·3).
Ulcerative colitis.

Betnesol Aqueous *GSK, NZ.*
⊗ Betamethasone sodium phosphate (p.1518·3); naphazoline nitrate (p.1565·2).
Nasal congestion and inflammation.

Betnesol-N *GSK, Austria; GSK, India; UCB, Irl.; Devries, Israel; GSK, Malaysia†; Pharmacare, S.Afr.; UCB, UK.*
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
Infected inflammatory eye, ear or nose disorders.

Betnesol-N Nasal *GSK, India.*
⊗ Betamethasone sodium phosphate (p.1518·3); naphazoline nitrate (p.1565·2); neomycin sulfate (p.305·1).
Nasal disorders.

Betnesol-V *GSK, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betneton *GSK, Philipp.*
⊗ Betamethasone (p.1518·2); chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Betneval *GSK, Fr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betneval-Neomycine *GSK, Fr.†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betnolon *Cifarma, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnor *Indoco, India.*
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
Inflammatory eye and ear disorders.

Betnosone *Hoe, Malaysia.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnosone N *Hoe, Malaysia.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betnovat *GSK, Denm.; GSK, Fin.; GSK, Norw.; GSK, Swed.*
⊗ Betamethasone valerate (p.1519·1).
Otitis externa; skin and scalp disorders.

Betnovat Comp *Meda, Fin.†.*
⊗ Betamethasone valerate (p.1519·1); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Betnovat med Chinoform *GSK, Denm.; GSK, Norw.; GSK, Swed.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnovat med Neomycin *GSK, Swed.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betnovat Rektal *Meda, Denm.†.*
⊗ Betamethasone valerate (p.1519·1); lidocaine hydrochloride (p.1862·3); phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Betnovat-C *GSK, Fin.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnovate *GSK, Arg.; Sigma, Austral.; GSK, Austria; GSK, Braz.; GSK, Chile†; GSK, Cz.; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; UCB, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Betnovate Antihemorroidal *GSK, Arg.†.*
⊗ Betamethasone valerate (p.1519·1); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Betnovate Capilar *GSK, Arg.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders.

Betnovate RD (Ready Diluted) *GSK, UK.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betnovate-C *GSK, Arg.; GSK, Austria; GSK, Gr.; GSK, Hong Kong†; GSK, India; GSK, Irl.; GSK, Israel; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Switz.; GSK, Thai.; GSK, Turk.; Chemidex, UK.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnovate-GM *GSK, India.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Betnovate-M *GSK, India.*
⊗ Betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Betnovate-N *GSK, Arg.; GSK, Austria; GSK, Braz.; GSK, Chile†; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Switz.; GSK, Thai.; Chemidex, UK.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Betnovate-Q *GSK, Braz.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Betnovate-S *GSK, India.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2).
Skin disorders.

Beto *1A, Pol.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Betodermin *Mugi, Indon.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betolvex
Alpharma, Denm.; Alpharma, Fin.
Cyanocobalamin (p.1980·2) or cyanocobalamin tannate (p.1981·3).
Megaloblastic anaemia; vitamin B deficiency.

Alpharma, Norw.; Team Medica, Switz.
Cyanocobalamin tannate (p.1981·3).
Megaloblastic anaemia; vitamin B deficiency.

Alpharma, Swed.
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Betolvidon *Abigo, Swed.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Betonin *Knoll, India.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Betonvit *Recalcine, Chile†.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); procaine hydrochloride (p.1869·1).
Neuralgia; neuritis; neuropathy; tonic.

Betopic *Armoxindo, Indon.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betoptic *Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Neth.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betoptima *Alcon, Ger.; Alcon, Indon.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betoquin *Ioquin, Austral.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Betosalic *TO-Chemicals, Thai.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2).
Skin disorders.

Betosone *TO-Chemicals, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betosone-CE *TO-Chemicals, Thai.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Be-Total *Carlo Erba OTC, Ital.; Pfizer Consumer, Ital.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Betozone
Note. This name is used for preparations of different composition.
De Mayo, Braz.
Capsules: Ferrous fumarate (p.1938·3); folic acid (p.1940·1); ascorbic acid; vitamin B substances (p.1922·1).
Anaemias.

De Mayo, Braz.
Oral liquid: Ferrous sulfate (p.1939·3); vitamin B substances; lysine hydrochloride (p.1922·1).
Anaemias.

Betrat B *Ativus, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betres AP *Offenbach, Mex.*
Vitamin B substances (p.1922·1).

Betrigen *IQFA, Mex.*
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1); gentamicin (p.284·2).
Infected skin disorders.

Betrilol *Boehringer Ingelheim, Jpn†.*
⊗ Bunitrolol hydrochloride.

Betrimine *Help, Gr.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).

Betrion *Otto, Indon.*
Thiamine disulfide (p.1976·3); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Neuralgia; neuritis; rheumatism; vitamin B deficiency.

Betron R *Italfarmaco, Ital.†.*
Interferon beta (human, recombinant) (p.891·2).
Malignant neoplasms; viral infections.

Betrospam *Legrand, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Betrox *Serral, Mex.*
Hydroxocobalamin acetate (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Metabolic disorders; neuralgias; neuropathies; vitamin B deficiency.

Betsol Z *Zafiro, Mex.*
Sodium bicarbonate (p.1673·2).
Metabolic acidosis.

Betsona *Neo Quimica, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Betsuril *Almirall, Spain†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Bettamousse *Celltech, Denm.; Berren, Fin.; Celltech, Irl.; UCB, Irl.; Evans Medical, Israel; Mipharm, Ital.; Vitaflo, Norw.; UCB, Spain; Vitaflo, Swed.; UCB, UK.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders; skin disorders.

Better Cholesterol *Young Again Products, USA.*
Sitosterol (p.1373·2); beta-glucan (p.2333·1); soya isoflavones (p.2391·2).

Better Prostate *Young Again Products, USA†.*
Sitosterol (p.1373·2); zinc citrate (p.1999·2).
Dietary supplement.

Betuline *Ferndale, USA.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Betulla (Specie Composta) *Dynacren, Ital.†.*
Birch leaf (p.2266·3); couch-grass (p.2288·2).
Herbal tea; water retention.

Beurises *Be-Tabs, S.Afr.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Bevalex *Molex Ayus, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Bevi Dam *Vincenti, Venez.*
Benzydamine hydrochloride (p.27·3).
Inflammation.

Bevigen *Aksu, Turk.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Bevindazol *Vincenti, Venez.*
Albendazole (p.139·2).
Worm infections.

Beviplex *Meuse, Belg.†; ICN, Cz.†.*
Vitamin B substances (p.1922·1).
Neuritis; vitamin B deficiency.

Beviplex forte *Abigo, Swed.*
Vitamin B substances (p.1922·1).
Alcoholism; neuropathies; vitamin B deficiency.

Bevispas *Pharmacare, S.Afr.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Bevit Forte *Hexal, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous system disorders.

Bevitab *Kocak, Turk.*
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Bevitamel *Westlake, USA.*
Melatonin (p.2338·3); vitamin B (p.1980·2); folic acid (p.1940·1).
Aid in homocysteine metabolism; sleep disorders.

Bevitece *Azevedos, Port.*
Vitamin B substances; vitamin C (p.1922·1).

Bevitex
Note. This name is used for preparations of different composition.
Prater, Chile.
Pargeverine hydrochloride (p.1761·1).
Aid in endoscopy or colonoscopy; nausea and vomiting; smooth muscle spasm.

Manon, Israel.
Vitamin B (p.1980·2).
Vitamin supplement.

Bevitin *Abbott, Ital.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Bevitin-C *Abfar, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Bevitine *DB, Fr.*
Thiamine hydrochloride (p.1976·1).
Beri beri; neuritis; vitamin B deficiency.

Bevitol
Note. This name is used for preparations of different composition.
Lannacher, Austria.
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Munir, Turk.
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Bevitotal comp *Recip, Swed.*
Vitamin B substances with vitamin C (p.1922·1).
Alcoholism; neuropathies; vitamin B and C deficiency.

Bevonazole *Bevo, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Bevoren *Almirall, Belg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Bevostatin *Bevo, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Bex *Roche Consumer, Austral.†.*
Aspirin (p.20·3).
Fever; pain.

Bexacal *Sandoz, Mex.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Bexalcor *Sandoz, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bexatus *Bexal, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bexce *Tempo Scan Pacific, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Nutritional supplement.

Bexce Plus *Tempo Scan Pacific, Indon.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Bexicortil *Isdin, Spain.*
⊗ Fluorometholone (p.1532·3); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Bexid *ACO Hud, Swed.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Bexident
Note. This name is used for preparations of different composition.
Isdin, Port.
Dental gel; dental spray; mouthwash: Chlorhexidine (p.1635·2).
Gingivitis.

Isdin, Port.
Paediatric dental gel: Dipotassium glycyrrhizate (p.2316·2); dexpanthenol (p.2362·1).
Gum protection.

Isdin, Port.
Toothpaste: Triclosan (p.1665·2); sodium fluoride (p.1962·2).
Gingivitis.

Bexident Pediatrics *Rhein, Mex.†.*
Dipotassium glycyrrhizate (p.2316·2); dexpanthenol (p.2362·1).
Gum care.

Bexidermil *Isdin, Spain.*
Trolamine salicylate (p.132·3).
Peri-articular disorders; soft-tissue disorders.

Bexilon *Plusandex, Venez.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bexine
Note. This name is used for preparations of different composition.
Collins, Mex.
⊗ Dexamethasone (p.1526·1); phenylephrine (p.1568·1); neomycin (p.305·1).
Formerly contained dexamethasone.

Spirig, Switz.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bexinor *Beacons, Singapore.*
Norfloxacin (p.309·2).
Bacterial infections.

Bexistar *Barcino, Spain.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Bexon
Note. This name is used for preparations of different composition.
Gobbi, Arg.
Pessaries: ⊗ Metronidazole (p.837·1); nystatin (p.543·2); hydrocortisone (p.1535·2).
Vaginal infections.

Gobbi, Arg.
Tablets: Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Bextra
Note. This name is used for preparations of different composition.
Pfizer, Belg.†; Pfizer, Braz.†; Pfizer, Canad.†; Pharmacia, Chile†; Pfizer, Cz.†; Pfizer, Fin.†; Pfizer, Fr.†; Pfizer, Ger.†; Pharmacia, Ger.†; Pfizer, Gr.†; Pharmacia, Hong Kong†; Pfizer, Indon.†; Pfizer, Irl.†; Pfizer, Malaysia†; Pfizer, NZ†; Pfizer, Norw.†; Pfizer, Port.†; Pharmacia, S.Afr.†; Pfizer, Singapore†; Pfizer, Swed.†; Pfizer, Thai.†; Pfizer, UK†; Pfizer, USA†; Pharmacia, USA†; Pharmacia, Venez.†.
Valdecoxib (p.132·3).
Dysmenorrhoea; osteoarthritis; pain; rheumatoid arthritis.

Pfizer, Switz.†.
Injection: Parecoxib sodium (p.111·3).
Postoperative pain.

Pfizer, Switz.†.
Tablets: Valdecoxib (p.132·3).
Osteoarthritis; pain; rheumatoid arthritis.

Bexxar *Corixa, USA; GSK, USA.*
Iodine-131 tositumomab (p.2054·3) (see also Tositumomab (p.781·2)).
Non-Hodgkin's lymphoma.

Beysonit *Leovan, Gr.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Beytina *Linker, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Beza *ABZ, Ger.; Otsira, India†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezabeta *Betapharm, Ger.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezacur *Investi, Arg.; Pharma & Co, Austria; Hexal, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezadoc *Docpharm, Ger.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezafisal *Cryopharma, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezagamma *Worwag, Ger.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezagen *Generics, UK.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezalex *Pharmacos Abug, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezalip *Roche, Arg.; Roche, Austria; Roche, Canad.; Roche, Fin.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Nicholas Piramal, India; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Swed.; Roche, Thai.; Roche, UK; Roche, Venez.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezalip Mono *Roche, UK.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezamerck *Merck dura, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezamidin *Pliva Krakow, Pol.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezamil *Milano, Thai.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezanin *Farmanic, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Bezapham *Phamos, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Beza-Puren *Alpharma-Isis, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezaretard *Genericon, Austria.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezastad *Stada, Austria; Stada, Philipp.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Bezpa *Wockhardt, Rus.*
Drotaverine hydrochloride (p.2298·1).

B-Feron *Greater Pharma, Thai.†.*
Multivitamin and mineral preparation (p.1922·1).

BFI *Numark, USA.*
Bismuth-formic-iodide (p.1712·1); zinc phenolsulfonate (p.1621·3); alum (p.2254·1); bismuth subgallate (p.1711·1); boric acid (p.2268·1); menthol (p.2340·1); cineole (p.2282·3); thymol (p.1664·3).
Antiseptic.

B-G Prot *Merind, India.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

BGB Norflox *Pond's, Thai.†.*
Norfloxacin (p.309·2).
Bacterial infections.

B-Gel *Vida, Hong Kong.*
Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1).
Oral lesions.

Bgramin *Douglas, Austral.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

B-Gurup *Sanli, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Bi Moxal *Elea, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bi Moxal Duo *Elea, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bi Predonium *Servier, Port.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Bi Preterax *Servier, Belg.; Servier, Port.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Biactol Liquid *Crookes Healthcare, UK.*
Phenoxypropanol (p.1657·2).
Acne.

Biaferone *Kedrion, Ital.*
Interferon alfa (p.885·1).
Anogenital warts; hepatitis; malignant neoplasms.

Biafine
Note.This name is used for preparations of different composition.
Craveri, Arg.; D & M, Chile; Medix, Fr.; Medix, Hong Kong; Medix, Israel; Medix, Malaysia†; Medix, Singapore†; Interdelta, Switz.; Ortho Neutrogena, USA; Medifarm, Venez.
Trolamine (p.2405·1).
Burns; erythema; scars; sunburn; ulcers; wounds.

Medix, Pol.†.
Paraffin; avocado oil.
Burns; ulcers.

Upsifarma, Port.
Sodium alginate (p.2141·1).
Formerly contained trolamine.
Burns; wounds.

Bi-Aglut *Plada, Ital.; Novartis Consumer, UK.*
A range of gluten-free and lactose-reduced foods (p.1922·1).
Gluten and lactose intolerance; gluten intolerance.

Bialcol *Novartis, Chile; Novartis Consumer, Ital.*
Benzoxonium chloride (p.1631·2).
Disinfection of instruments, skin, surfaces, and wounds.

Bialerge *Elofar, Braz.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Nasal congestion.

Bialminal *Bial, Port.*
Phenobarbital (p.492·2).
Alcohol withdrawal syndrome; epilepsy; sedative.

Bialzepam *Medibial, Port.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; skeletal muscle spasm.

Biamotil *Allergan, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye and ear infections.

Biamotil-D *Allergan, Braz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Bianco Val *Edmond Pharma, Ital.†.*
Valerian (p.2410·1); crataegus (p.2289·1).
Hyperexcitability; insomnia.

Biarison *ICN, Hung.†; Novartis, Turk.*
Proquazone (p.119·3).
Gout; inflammation; musculoskeletal and joint disorders; musculoskeletal, joint, and peri-articular disorders.

Biartac *MSD, Belg.†.*
Diflunisal (p.47·2).
Arthrosis; polyarthritis.

Biascor *Biol, Arg.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Biasquin F *Best, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Biasten *Pulmomed, Rus.*
⊗ Salbutamol hemisuccinate (p.1133·2); budesonide (p.1520·1).
Obstructive airways disease.

Biatain
Note.This name is used for preparations of different composition.
Coloplast, Fr.
Carmellose sodium (p.2142·1).
Ulcers; wounds.

Coloplast, Ger.
Polyurethane foam.
Ulcers; wounds.

Biatain Argent *Coloplast, Fr.*
Silver (p.2387·1); carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Biatain-Ibu *Coloplast, UK.*
Ibuprofen (p.64·2).
Pain in chronic wounds.

Biatos *Cimed, Braz.*
Ketotifen (p.582·2).
Asthma.

Biatron *Pharos, Indon.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Biavax II *MSD, USA.*
A rubella and mumps vaccine (Wistar RA 27/3 and Jeryl Lynn (B level) strains respectively) (p.2237·2).
Active immunisation.

Biaven *Biagini, Cz.†; Kedrion, Ital.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency.

Biaxin *Abbott, Canad.; Abbott, Ger.; Abbott, USA.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori infections.

Biaxsig *Aventis, Austral.*
Roxithromycin (p.331·1).
Bacterial infections.

BiaZinc *Medix, Fr.†.*
Zinc oxide (p.1621·2); copper pidolate (p.1614·1); vitamin E (p.1992·2).
Barrier preparation; dry skin.

Biberon *Martin, Spain; Pharmacia, Spain.*
Glucose (p.1945·3).
Fluid disorders; parenteral nutrition.

Bibien *BJ, Gr.*
Citalopram (p.385·3).
Depression.

Bibivit Light *Lampugnani, Ital.*
Multivitamin and carbohydrate preparation with fruit and plant extracts (p.1922·1).
Nutritional supplement.

Bibix *Lemery, Mex.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Bibol Leloup *Hexa, Arg.*
Silymarin (p.1452·2); dehydrocholic acid (p.2292·2); pancreatin (p.2360·1); bile salts (p.2266·2); homatropine methylbromide (p.1881·3).
Liver disorders.

Bibora *Berko, Turk.*
Borax (p.2268·1).

Bica *Finadiet, Arg.†.*
Calcium carbonate (p.1714·1).
Antacid.

Bicaflac *Edwards, Austria; Braun, Denm.†; Edwards, Spain.*
A range of haemofiltration solutions (p.1670·3).
Haemofiltration.

Bicain *Orion, Fin.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bicaluplex *Ingers, Cz.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bicalut *Alvia (Αλβια), Gr.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bicam *Biolab, Thai.†.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Bicamide *Genepharm, Gr.*
Bicalutamide (p.686·2).
Prostatic cancer.

bicaNorm *Fresenius Medical, Ger.*
Sodium bicarbonate (p.1673·2).
Metabolic acidosis.

bicaNova *Fresenius Medical, Cz.*
Sodium chloride; calcium chloride; magnesium chloride; sodium bicarbonate; glucose (p.1670·3).
A range of peritoneal dialysis solutions.

Bicaprost *Pharmacia, Arg.†.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bicarnat *Pisa, Mex.*
Sodium bicarbonate (p.1673·2).
Electrolyte disorders.

Bicatlon *Medico Uno, Hung.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bicavera *Fresenius Medical, Cz.; Fresenius Medical, Fin.; Fresenius Medical, Neth.; Fresenius Medical, Port.; Fresenius Medical, Swed.; Fresenius Medical, Switz.*
Sodium chloride; calcium chloride; magnesium chloride; sodium bicarbonate; glucose (p.1670·3).
A range of peritoneal dialysis solutions.

Bicavera Glucosa *Fresenius Medical, Spain.*
Sodium chloride; calcium chloride; magnesium chloride; glucose (p.1670·3).
Peritoneal dialysis.

Bicavera Glucose *Fresenius Medical, Denm.*
Glucose; calcium chloride; magnesium chloride; sodium chloride; sodium bicarbonate (p.1670·3).
Peritoneal dialysis.

Bicavine *Cazi, Braz.*
Dipyrone (p.49·2); thiamine (p.1976·3); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Neuritis; pain.

Bicetil *Menarini, Spain.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Bicholate *Sabex, Canad.*
Bile salts (p.2266·2); cascara (p.1715·2); aloin (p.1705·3); bisacodyl (p.1710·1).
Constipation.

Bicidal Plus *Kee, India.*
Amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1); *Lactobacillus sporogenes* (p.2372·3).
Bacterial infections.

Bicide *Fischer, Israel.*
Lindane (p.2045·3).
Scabies.

Bicillin-1 *Sintez, Rus.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Bicillin-3 *Sintez, Rus.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin sodium (p.213·1) or benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections; leishmaniasis.

Bicillin-5 *Sintez, Rus.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Bicillin C-R *Monarch, USA.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Bicillin L-A *Aspen, Austral.; Healthcare Logistics, NZ; Akromed, S.Afr.; Monarch, USA.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Bicirkan *Pierre Fabre, Fr.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); vitamin C (p.1983·3).
Venous insufficiency.

Biciron *Alcon, Ger.*
⊗ Tramazoline hydrochloride (p.1574·3).
Eye disorders.

Bicitra *Alza, USA.*
Sodium citrate (p.1673·3); citric acid monohydrate (p.2284·1).
Chronic metabolic acidosis; urine alkalinising agent.

Bi-Citrol *Tonipharm, Fr.†.*
Monosodium citrate (p.1674·2); sodium citrate (p.1673·3).
Dyspepsia.

Bicitron *Medichem, Indon.; Medifarma, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neuritis; neuropathy; vitamin B supplement.

Biclar *Abbott, Belg.*
Clarithromycin (p.248·2).
Bacterial infections.

Biclin *BMS, Mex.; BMS, Port.; BMS, Spain.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Biclinocilline *Sanofi-Aventis, Fr.*
Benethamine penicillin (p.212·1); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Biclomet *Biomedis, Philipp.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in intestinal intubation; nausea and vomiting.

BiCNU *BMS, Arg.; BMS, Austral.; Bristol, Canad.; BMS, Chile; BMS, Cz.; BMS, Fr.; BMS, Hong Kong; BMS, Hung.; BMS, Irl.; BMS, Israel†; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Philipp.; BMS, S.Afr.; BMS, Singapore; BMS, UK†; BMS Oncology, USA.*
Carmustine (p.694·3).
Malignant neoplasms.

Bicobon *PP Lab, Thai.†.*
Sodium bicarbonate (p.1673·2); activated charcoal (p.1435·2); peppermint oil (p.1761·2).
Diarrhoea; flatulence; gastrointestinal disorders.

Bicofen *Iapharm, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Bicolax *Armoxindo, Indon.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Bicold *Labima, Belg.†.*
Diphenylpyraline hydrochloride (p.578·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract congestion.

Bicomplex *ABC, Ital.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Bicompo *Bernofarm, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Biconcor *Merck, Braz.; Merck, Mex.; Merck, Venez.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bicor *Alphapharm, Austral.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Bicox-E *Overseas, India†.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Bicozene *Novartis, USA.*
Benzocaine (p.1854·1); resorcinol (p.1612·1).
Local anaesthesia.

Bicrinol *Ingens, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections.

Bicrolid *Sanbe, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Bicromil *Cetus, Arg.*
Sertraline (p.422·1).
Depression.

Bidanzen *GSK, India.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; hyphaema; inflammation; pain; pericoronitis; respiratory-tract congestion.

Bidecar *Baliarda, Arg.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Bideon *Fecofar, Arg.*
⊗ Phenazone (p.116·1); naphazoline (p.1565·1); lidocaine (p.1862·3).
Eye disorders.

Bideren *Novopharm, Philipp.; Pascual, Philipp.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Biderit *Merck, Mex.*
Isosorbide dinitrate (p.1317·3).

Bidex-A *Stewart Jackson, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Bidex-DMI *Stewart Jackson, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Bidhist *Cypress, USA.*
Brompheniramine maleate (p.569·2).
Rhinitis.

Bidiabe *Sanofi-Aventis, Ital.*
Chlorpropamide (p.438·3); phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Bidiam *Menarini, Port.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).

Bidicef *Medikon, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Bidiclin *Chiesi, Gr.*
⊗ Beclometasone (p.1517·2).
Corticosteroid.

Bidien *IDI, Ital.*
⊗ Budesonide (p.1520·1).
Skin disorders.

BiDil *NitroMed, USA.*
Isosorbide dinitrate (p.1317·3); hydralazine hydrochloride (p.1305·3).
Heart failure in black patients.

Bidiprox *Medikon, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Biditin *Medikon, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Bi-Dizalon *Rayere, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Bidocef *Cofasa, Venez.*
Cefalexin (p.218·2).
Bacterial infections.

Bidoflox *Kee, India†.*
Ofloxacin (p.310·2).
Bacterial infections.

Bidoflox-Oz *Kee, India†.*
Ofloxacin (p.310·2); ornidazole (p.843·1).
Infections.

Bidor *Weleda, UK.*
Homoeopathic preparation.

Bidrolar *Spyfarma, Spain.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Bidrostat *Bioprofarma, Arg.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bidroxyl *BMS, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Bidrozil *Collins, Mex.*
⊗ Nystatin (p.543·2); triamcinolone (p.1544·2).
Skin disorders.

Bidryl Expectorant *Hexpharm, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Biduret *GSK, India.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Bienfait Multi-vital
Note. This name is used for preparations of different composition.
Lancome, Canad.
SPF 15: Ensulizole (p.1597·1); octinoxate (p.1608·2).
Sunscreen.
Lancome, Canad.
SPF 30: Avobenzone (p.1589·3); octisalate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

Bienfait Total *Lancome, Canad.†*
SPF 15: Avobenzone (p.1589·3); octisalate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

Biennol *Dunner, Switz.*
Evening primrose oil (p.2302·1).
Dietary supplement in hyperlipidaemias.

Bienterico *Caldeira & Marques, Port.*
Streptomycin sulfate (p.333·3); neomycin sulfate (p.305·1).
Bowel sterilisation; diarrhoea; hepatic coma.

Bi-Euglucon
Note. This name is used for preparations of different composition.
Roche, Ital.†
Glibenclamide (p.440·1); phenformin hydrochloride (p.455·3).
Diabetes mellitus.
Roche, Venez.
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Bi-Euglucon M *Roche, Chile; Roche, Ital.; Roche, Mex.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Bifardol *Liferpal, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Bifaren *Biomep, Mex.*
Bezafibrate (p.1232·1).
Hypercholesterolaemia.

Bifazol *Bayer, Ital.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifebral *Aventis, Mex.*
Ketoprofen sodium (p.73·3); paracetamol (p.108·1).
Fever; pain.

Bifen *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Bifena *Panalab, Arg.*
Lotion 1, salicylic acid (p.1612·2); undecenoic acid amide (p.549·3); resorcinol monoacetate (p.1612·1); sulfur (p.1614·1); capsicum tincture (p.2276·2); lotion 2, pantothenic acid (p.1959·3); inositol (p.2325·2); yeast (p.1998·3); cinchona (p.2282·3).
Hair disorders.

Bifenac *Pharmacia Upjohn, Mex.†*
Tolfenamic acid (p.130·1).
Fever; gout; inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Biferce *Sanbe, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Bifidosa *Nutricia-Bago, Arg.*
Lactulose (p.1738·2); ferrous sulfate; vitamin B substances (p.1922·1).
Restoration of normal gastrointestinal flora.

Bifiform *Ferrosan, Rus.*
Bifidobacterium; *Enterococcus faecium* (p.2372·3).
Restoration of normal gastrointestinal flora.

Bifilac *Tablets, India.*
Enterococcus faecalis (p.2372·3); *Clostridium butyricum*; *Bacillus mesentericus*; *Lactobacillus sporogenes* (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Bifilact *Fidia, Ital.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus lactis* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3); *Bifidobacterium bifidum* (p.2372·3); *Lactobacillus sporogenes* (p.2372·3); vitamin B substances; brewers yeast (p.1998·3).
Maintenance of normal gastrointestinal flora.

Bifinorma *Merckle, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Bifiteral *Solvay, Austria; Solvay, Belg.; Solvay, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic coma; hepatic encephalopathy; stool softener.

Bifix
Note. This name is used for preparations of different composition.
Bayer Sante, Fr.
Nifuroxazide (p.307·2).
Diarrhoea.
Medichem, Philipp.
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Bifized *Farmanic, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifluorid *Voco, Cz.†; Voco, Denm.; New Ulros, Ital.†; Voco, Pol.; Meda, Swed.*
Calcium fluoride (p.1932·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth; sensitive gums.

Bifokey *Inkeysa, Spain.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifomyk *Riemser, Ger.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifon *Dermapharm, Ger.; Genepharm, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifonal *Fortbenton, Arg.†*
Bifonazole (p.527·3).
Fungal skin infections.

Bifort
Note. This name is used for preparations of different composition.
Finadiet, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.
Merck, Spain†.
⊗ Cafedrine hydrochloride (p.1238·2); theodrenaline hydrochloride (p.2400·1).
Hypotension.

Bifosa *Troikaa, India.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Bifosin *Sintez, Rus.*
Bifonazole (p.527·3).
Fungal skin infections.

Bifotik *Sanbe, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Bifril *Silesia, Chile; Lusofarmaco, Ital.; Menarini, Swed.†*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Bifrizide *Lusofarmaco, Ital.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Big-Ben *Greater Pharma, Thai.*
Mebendazole (p.148·3).
Worm infections.

Bigenol *Grisi, Mex.*
⊗ Methyltestosterone (p.2117·1); calcium glycerophosphate; calcium anhydroxymethylenediphosphate; magnesium anhydroxymethylenediphosphate; glutamic acid; thiamine hydrochloride; nux vomica (p.2355·3).
Anabolic.

Biger *BI, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Bigetric *Casasco, Arg.*
Domperidone (p.1726·2); simeticone (p.1770·2).
Dyspepsia; flatulence; nausea and vomiting.

Bigomet *Otsira, India†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Bigonist *Sanofi-Aventis, Fr.*
⊗ Buserelin acetate (p.2083·2).
Prostatic cancer.

Bigpen *GSK, Spain†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Biguanex *Denver, Arg.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Biherpan *ICN, Pol.*
Heparin sodium (p.1301·2); zinc sulfate (p.1999·2).
Herpes infections of the skin and mucous membranes.

Bikalm *Altana, Ger.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Bikipen *Ivax, Mex.*
Biperiden (p.797·2).
Parkinsonism.

Biklin *BMS, Arg.; BMS, Austria; BMS, Fin.; BMS, Ger.; BMS, Swed.; BMS, Venez.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Bil 13 *Bago, Arg.*
Choline orotate (p.2358·3); dehydrocholic acid (p.2292·2); deoxycholic acid (p.2266·3); casanthranol (p.1715·1); boldine (p.2267·3).
Constipation; liver and biliary-tract disorders.

Bil 13 Enzimatico *Bago, Arg.*
Metoclopramide hydrochloride (p.1747·3); dehydrocholic acid (p.2292·2); pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders; flatulence.

Bilagit *Sanofi Synthelabo, Hung.†*
Choleinic sodium; phenolphthalein (p.1762·1); methenamine (p.298·3); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3); menthol (p.2340·1).
Biliary-tract disorders.

Bilagit Mono *Temmler, Ger.†*
Javanese turmeric (p.2406·3).
Dyspepsia.

Bilagol *Lazar, Arg.*
Bile salts (p.2266·2); dehydrocholic acid (p.2292·2); domperidone (p.1726·2); simeticone (p.1770·2).
Digestive disorders; dyspepsia.

Bilamide *Ethnor, India.*
Hydroxymethylnicotinamide (p.2323·1).
Anorexia; constipation; dyspepsia; flatulence.

Bilaten *Medipharm, Chile.*
Candesartan cilexetil (p.1238·3).
Hypertension.

Bilaten-D *Medipharm, Chile.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Bilatin *Stada, Austria.*
Lecithin (p.2332·2); liver extract (p.2337·3).
Tonic.

Bilaxil *Bayer, Chile.*
Ispaghula husk (p.1737·1); senna (p.1769·2).
Bowel evacuation; constipation.

Bilberin *Hasco-Lek, Pol.*
Myrtillus (p.2349·3).
Circulatory eye disorders.

Bilberry Formula *Quest, Canad.†*
Myrtillus; carrot; citrus bioflavonoids; hesperidin (p.1922·1).

Bilberry Plus *Eagle, Austral.*
Myrtillus (p.2349·3); euphrasia (p.2301·3); fenugreek (p.2303·3); hydrastis (p.2321·3).
Eye fatigue.

Bilberry Plus Eye Health *Cenovis, Austral.*
Myrtillus (p.2349·3); ginkgo biloba (p.2311·1); tagetes erecta; riboflavin; *dl*-alpha tocoferil acetate; ascorbic acid; zinc gluconate; betacarotene (p.1922·1).
Eye fatigue; eye irritation.

Bilduretic *Bangkok Lab & Cosmetic, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Bileco *Ivax, Arg.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bilem
Lemery, Mex.
⊗ Tamoxifen (p.775·1).
Lemery, Rus.†; Lemery, Thai.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Bilenor *Schwarz, Ital.*
Magnesium trihydrate salt of chenodeoxycholic and ursodeoxycholic acids (p.2280·1) (p.2408·1).
Biliary dyspepsia; gallstones.

Bilenzima *Elofar, Braz.*
Bromopride (p.1713·3).
Gastrointestinal disorders.

Biletan *Gador, Arg.*
Thioctic acid (p.2400·2).
Liver disorders.

Biletan Enzimatico *Gador, Arg.*
Thioctic acid (p.2400·2); pancreatin (p.2360·1); cellulase (p.2279·1); simeticone (p.1770·2).
Digestive disorders.

Bilicanta *Roche, Spain†.*
Hymecromone (p.2323·2).
Biliary-tract disorders.

Bilicura Forte *Muller Goppingen, Ger.†*
Kava (p.2328·3); cynara (p.2291·2).
Biliary disorders; dyspepsia.

Bilidren *Lanpharm, Arg.*
Cascara (p.1715·2); cynara (p.2291·2); bile salts (p.2266·2).
Biliary-tract disorders.

Biliepar *Ibirn, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; gallstones.

Bilifel *Neckerman, Braz.†*
Cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3); fig (p.1731·3).
Constipation.

Biliflux *Eurofarma, Braz.†*
Diisopromine hydrochloride (p.1724·1); sorbitol (p.1965·1).
Liver disorders.

Bilifuge *Plan, Switz.*
Cynara (p.2291·2); berberis vulgaris; java tea (p.2328·2); kinkeliba (p.2329·2).
Digestive disorders.

Bili-Labstix *Bayer Diagnostici, Ital.†; Bayer, USA.*
Test for pH, protein, glucose, ketones, bilirubin, and blood in urine.

Bilina *Esteve, Spain.*
Levocabastine hydrochloride (p.583·1).
Allergic conjunctivitis; allergic rhinitis.

Bilinum Complexe no 113 *Lehning, Fr.*
Homoeopathic preparation.

Biliosan Compuesto *Hexa, Arg.†*
Carqueja; boldo (p.2267·2); cynara (p.2291·2); bile salts (p.2266·2); homatropine methylbromide (p.1881·3); peppermint oil (p.1761·2).
Biliary-tract disorders; digestive disorders.

Bilipax *Taphlan, Switz.†*
Naphthylacetic acid (p.2350·2); methylphenylethyl nicotinate.
Adjuvant in cholangiography; digestive disorders.

Bilipeptal Mono *Evisco, Ger.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Biliranin *Pharmaten (Φαρματεν), Gr.†*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Bilisan Duo *Repha, Ger.*
Milk thistle (p.1452·1); Javanese turmeric (p.2406·3).
Biliary-tract disorders; dyspepsia; liver disorders.

Biliscopin *Schering, Austral.; Schering, Austria; Schering, Ger.; IFET (ΙΦΕΤ), Gr.; Schering, NZ; Schering, Swed.†; Schering, Switz.; Bayer, UK.*
Meglumine iotroxate (p.1486·1).
Contrast medium for biliary-tract radiography.

Bilisegrol *Schering, Spain†.*
Meglumine iotroxate (p.1486·1).
Contrast medium for biliary-tract radiography.

Billerol *Lehning, Fr.*
Homoeopathic preparation.

Biloban *Cipan, Port.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Bilobene *Ratiopharm, Austria; Merckle, Ger.; Ratiopharm, Hung.*
Fumitory (p.2307·2).
Biliary-tract disorders.

Bilobil *Teva, Hung.; KRKA, Pol.; KRKA, Rus.*
Gingko biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function impairment.

Bilocor *Pharma Dynamics, S.Afr.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bilogink *Naturex, Mex.†*
Ginkgo biloba (p.2311·1).

Biloina *Andromaco, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Bilokan *Santa, Turk.*
Ginkgolides (p.2311·3).
Dementia; peripheral vascular disorders; vertigo; vestibular disorders.

Bilol *Ecosol, Switz.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hyperkinetic heart syndrome; hypertension.

Biloptin *IFET (ΙΦΕΤ), Gr.†; Schering, UK†.*
Sodium iopodate (p.1484·3).
Contrast medium for biliary-tract radiography.

Bilozen *Klonal, Arg.*
Ketotifen (p.582·2).
Eye disorders.

Bilron *Aspen, S.Afr.†*
Iron bile salts (p.2266·2).
Bile salt deficiency; biliary-tract disorders.

Bilsan *Abbott, Hong Kong.*
Choline bicitrate (p.1934·2); inositol (p.2325·2); methionine (p.1450·1); vitamin B substances (p.1922·1); dehydrocholic acid (p.2292·2); ox bile (p.2266·3).
Biliary disorders; liver disorders.

Biltricid *Bayer, Rus.*
Praziquantel (p.153·3).
Worm infections.

Biltricide *Bayer, Austral.; Bayer, Canad.; Bayer, Fr.; Bayer, Ger.; IFET (ΙΦΕΤ), Gr.; Bayer, Hong Kong; Bayer, Israel; Bayer, Neth.; Bayer, S.Afr.; Schering, USA.*
Praziquantel (p.153·3).
Worm infections.

Biluen Enzimatico *Altana, Arg.*
Azintamide (p.2262·2); pancreatin (p.2360·1); cellulase (p.2279·1); simeticone (p.1770·2).
Liver and biliary-tract disorders.

Bilugen *Roche Diagnostics, Austral.*
Test for urobilinogen and bilirubin in urine.

Bilumid *Veropharm, Rus.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bilutamid *PharmaConsult, Hung.*
Bicalutamide (p.686·2).
Prostatic cancer.

Bim *Ivax, Arg.†*
Bacteria; muramidase hydrochloride (p.2348·1).
Respiratory-tract infections.

Bimanol *Polfa Pabianice, Pol.*
⊗ Deanol (p.2152·3).
Atherosclerotic encephalopathy; depression; faecal incontinence; nocturia; reduced concentration in children; schizophrenia; tonic.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Bimetdad *Bajamed, Mex.*
Enalapril (p.1276·1).
Hypertension.

Bimicot *Euroderm, Arg.*
Bifonazole (p.527·3).
Fungal skin infections.

Bimidal *Bajamed, Mex.*
Losartan (p.1327·2).
Hypertension.

Bi-Miotic *Bell, India.*
Pilocarpine nitrate (p.1884·3); physostigmine salicylate (p.1883·3).
Glaucoma.

Bimixin *Sanofi-Aventis, Ital.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Enteric infections.

Bimolin *Drugtech, Chile†.*
⊗ Pemoline (p.2161·2).

Bimoxan *Hexal, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bimoxin *Biofarma, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Binafex *Serral, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Binafin
Vitapan, Braz.†.
Terbinafine (p.546·3).
Fungal skin infections.

Shreya, Rus.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Binaldan *Vifor, Switz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Binanidda *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Binarin *Pisa, Mex.*
Epirubicin (p.716·2).
Malignant neoplasms.

Binazin *Polfa Pabianice, Pol.*
Todralazine hydrochloride (p.1415·1).
Hypertension.

Bindazac *Norma (Νορμα), Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Bi-Nerisona *Intendis, Braz.; Schering, Chile; Intendis, Mex.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Binerisona *Schering, Venez.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Biniwas *Chiesi, Spain†.*
Binifibrate (p.1234·1).
Hyperlipidaemias.

Binko *Hexal, Braz.†.*
Ginkgo biloba (p.2311·1).

Binoclar *Biochemie, Hong Kong; Sandoz, Venez.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Binocrit *Sandoz, Cz.; Sandoz, UK.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Binoctrin *Cazi, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Binocular *Sandoz, Malaysia.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication in peptic ulcer.

Binodian *Schering, Mex.*
⊗ Estradiol valerate (p.2097·3); prasterone enantate (p.2124·2).
Menopausal disorders.

Binoklar *Sandoz, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Binordiol *Wyeth Lederle, Belg.†; Wyeth, Switz.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive; menstrual disorders.

Binospan *Cazi, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Fever 406 Formerly known as Binospan Composto =(prvademecum.com 05.05).; pain.

Binotal
Bayer, Braz.; Bayer, Mex.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Grunenthal, Ger.
Ampicillin sodium (p.204·1).
Bacterial infections.

Bayer, Indon.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Binovum *Janssen-Cilag, UK.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Binozyt *Sandoz, Indon.; Sandoz, Thai.; Sandoz, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

B-Insulin *Berlin-Chemie, Ger.†.*
⊗ Insulin injection (pork) (p.443·2).
Diabetes mellitus.

Bintamox *Hexpharm, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Binvex *Ivax, Arg.*
Pargeverine hydrochloride (p.1761·1); dihydroxydibutylether (p.2293·3).
Liver and biliary-tract disorders.

Bio-200 *Dermofarma, Ital.*
Royal jelly (p.2382·1); pollen (p.2370·2).
Nutritional supplement.

Bio Ace *Blackmores, Austral.*
Betacarotene; ascorbic acid; *d*-alpha tocoferil acid succinate; vitamin B ; calcium pantothenate; vitamin B ; vitamin K ; zinc; ginseng; garlic (p.1922·1).
Tonic.

Bio Ace Excell *Blackmores, Austral.*
Vitis vinifera; milk thistle; betacarotene; vitamin C; *d*-alpha tocopherol; calcium pantothenate; vitamin B ; zinc; vitamin B ; folic acid; thiamine nitrate (p.1922·1).
Tonic.

Bio Acidophilus *Bioceuticals, UK.*
Lactobacillus acidophilus (p.2372·3).

Bio C *Blackmores, Austral.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); calcium ascorbate (p.1984·1); bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3); rose fruit (p.2381·2); acerola.
Vitamin C supplement.

Bio Cabal *Dallas, Arg.†.*
⊗ Dexamethasone (p.1526·1); astemizole (p.567·2).
Hypersensitivity reactions.

Bio Fibralax Bi-Attivo *Giuliani, Ital.*
Dietary fibre (p.1712·3); *Lactobacillus acidophilus* (p.2372·3).
Dietary supplement.

Bio Flora *DermoDuemila, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins; minerals (p.1922·1).
Gastrointestinal disorders.

Bio Grip C *Gramon, Arg.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms.

Bio Grip Classic *Gramon, Arg.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); bromhexine (p.1552·2).
Respiratory-tract disorders.

Bio Grip Plus *Gramon, Arg.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); pentoxyverine citrate (p.1567·3); ascorbic acid (p.1983·3); vitamin B .
Cold and influenza symptoms.

Bio Grip-T *Gramon, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Bio Iron *Blackmores, Austral.*
Ferrous fumarate (p.1938·3); folic acid; vitamin B ; urtica (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency.

Bio Magnesium *Blackmores, Austral.*
Magnesium (p.1678·3); calcium ascorbate (p.1984·1); vitamin B (p.1978·2); colecalciferol (p.1986·2); manganese (p.1956·1).
Muscle cramps.

Bio Max *Shchelkovskii, Rus.*
Vitamins; minerals; rutoside (p.1922·1).

Bio Slim Silueta *Natrahealth, UK.*
Poliglusam (p.2370·1).
Slimming aid.

Bio Star *Novag, Spain.*
Ginseng (p.2312·1).
Tonic.

Bio Tarbun *Duncan, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Bio Tears *Maurino, Arg.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Bio Zinc *Blackmores, Austral.*
Vitamin A acetate; pyridoxine hydrochloride; magnesium phosphate; zinc amino-acid chelate (p.1922·1).
Skin disorders; wounds.

Bioacne *Ikapharmindo, Indon.*
Cetrimide (p.1634·1); resorcinol (p.1612·1); sulfur (p.1614·1).
Acne.

Bioactiv *Knop, Chile.*
A range of homoeopathic preparations.

Bioaler *Giscard, Arg.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Bio-Amoksiclav *Biotech, S.Afr.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Bio-Antioxydant *Pharma Nord, Fr.†.*
Vitamin and mineral preparation (p.1922·1).
Antioxidant.

Bioarginina *Damor, Ital.*
Arginine (p.1928·2) or arginine hydrochloride (p.1928·2).
Asthenia; hyperammonaemia.

Bioarginol-C *Bioresearch, Mex.*
Sulfadiazine (p.336·2).
Bacterial skin infections.

Bioaron C *Phytofarm Kleka, Pol.*
Aloes (p.1705·2); aronia melanocarpa; vitamin C (p.1983·3).
Infection prophylaxis; reduced appetite.

Bio-Arscolloid *SIT, Ital.*
Dichlorobenzyl alcohol (p.1642·1); silver protein (p.2387·3); tyrothricin (p.358·2).
Bacterial mouth infections.

Biobase
Note. This name is used for preparations of different composition.
Odan, Canad.
⊗ Alcohol (p.1625·2).
Antiseptic vehicle for topical preparations.

Bioderma, Fr.
Vehicle for topical preparations.

Biobase-G *Odan, Canad.*
⊗ Alcohol (p.1625·2); glycolic acid (p.1598·1).
Antiseptic vehicle for topical preparations.

Biobeclasona *Biogalenic, Venez.*
⊗ Beclometasone (p.1517·2).
Allergic rhinitis.

Biobeclod *Biogalenic, Venez.*
⊗ Beclometasone (p.1517·2).
Obstructive airways disease.

Biobees *Bioceuticals, UK.*
A range of preparations containing royal jelly (p.2382·1).

Biobin *Biochem, India.*
Cytarabine (p.705·1).
Malignant neoplasms.

Bio-C
Uniao Quimica, Braz.
Ascorbic acid (p.1983·3).

Pharma Nord, Norw.; Pharma Nord, Thai.
Calcium ascorbate (p.1984·1).
Vitamin C deficiency.

Bio-C Complex *Blackmores, Austral.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); calcium ascorbate (p.1984·1); lemon bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3); acerola.
Vitamin C preparation.

Biocadmio *Uriach, Spain.*
Cadmium sulfide (p.2271·2).
Skin and scalp disorders.

Bio-Cal *YSP, Malaysia.*
Boron; calcium; colecalciferol; magnesium; iodine; selenium (p.1922·1).
Dietary supplement.

Biocalcin *Esseti, Ital.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; sympathetic pain syndrome.

Biocalcio *Sedabel, Braz.†.*
Calcium phosphate; cyanocobalamin; ergocalciferol; sodium fluoride; sodium iodide (p.1922·1).
Vitamin and mineral supplement.

Biocalcium *Bioprogress, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Biocalcium D3 *Bioprogress, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Bio-Calcium + D$_3$ *Pharma Nord, Irl.*
Calcium (p.1675·2); magnesium (p.1678·3); colecalciferol (p.1986·2).
Calcium deficiency.

Bio-Calcium + D$_3$ + K *Pharma Nord, Irl.*
Calcium (p.1675·2); colecalciferol (p.1986·2); vitamin K (p.1995·2).

Bio-Calcium + D3 + K *Pharma Nord, Thai.*
Calcium (p.1675·2); colecalciferol (p.1986·2); vitamin K (p.1995·2).
Calcium supplement; osteoporosis.

Biocalm
Note. This name is used for preparations of different composition.
Lizofarm, Ital.
Valerian (p.2410·1); passion flower (p.2363·2); peppermint leaf (p.1761·2).
Insomnia.

Biolab, Thai.
Tolperisone hydrochloride (p.1899·3).
Obliterative vascular diseases; parkinsonism; skeletal muscle spasticity and spasm.

Biocalron *Biomedis, Thai.; Great Eastern, Thai.*
Calcium lactate (p.1676·1); ferrous fumarate (p.1938·3); vitamin C (p.1983·3); rutoside (p.2305·1).
Calcium and iron supplement.

BioCalth *BioCalth, UK.*
Calcium -threonate (p.1677·1).
Calcium supplement.

Biocalyptol
Note. This name is used for preparations of different composition.
Zambon, Fr.
Pholcodine (p.1570·2).
Formerly contained pholcodine, cineole, and guaiacol.
Coughs.

Laphal, Hong Kong†.
Pholcodine (p.1570·2); cineole (p.2282·3); guaiacol (p.1561·2).
Coughs.

Biocalyptol S *Laphal, Cz.†.*
Pholcodine (p.1570·2); cineole (p.2282·3); guaiacol (p.1561·2).
Coughs.

Biocanol *Fako, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Bio-Caps *Bio-Health, UK.*
Multivitamin and mineral preparation (p.1922·1).

Biocaps *Biotech Naturis, Venez.*
Betacarotene; vitamin C; vitamin D; vitamin E (p.1922·1).
Dietary supplement.

Biocarb *Biochem, India.*
Carboplatin (p.693·1).
Malignant neoplasms.

Biocarbo *Biosintetica, Braz.*
Carboplatin (p.693·1).
Malignant neoplasms.

Biocard
Note. This name is used for preparations of different composition.
Niche, Irl.
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Fako, Turk.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Biocarde
Note. A similar name is used for preparations of different composition (see above).
Lehning, Fr.
Crataegus (p.2289·1); passion flower (p.2363·2); avena (p.2262·1); valerian (p.2410·1); melissa (p.2339·3); motherwort (p.2347·3).
Insomnia; nervous disorders.

BioCardine *Scandinavian Laboratories, Pol.*
Fish oil (p.1362·2).
Cardiovascular disorders; hyperlipidaemias.

Biocarn *Medice, Ger.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Biocarnil *Abiogen, Ital.†.*
Carnitine hydrochloride (p.1933·1); -lysine hydrochloride (p.1955·1).
Carnitine deficiency.

Biocarotine *Bioceuticals, UK.*
Betacarotene (p.1930·3).

Biocatalase *Fournier SA, Spain†.*
Catalase (p.2278·2).
Burns; skin disorders; ulcers; wounds.

Biocebe *Nutergia, Fr.*
Vitamin, bioflavonoid, and zinc preparation (p.1922·1).
Nutritional supplement.

Biocef
Note. This name is used for preparations of different composition.
Sandoz, Austria.
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Otto, Indon.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Zambon, Spain.
Ceftibuten (p.235·3).
Bacterial infections.

International Ethical, USA†.
Cefalexin (p.218·2).
Bacterial infections.

Biocefazon *Bioton, Pol.*
Cefoperazone sodium (p.227·1).
Gram-negative bacterial infections.

Biocefra *Laquifa, Port.*
Cefradine (p.233·1).
Bacterial infections.

Bioceftrax *Biogalenic, Venez.*
Ceftriaxone (p.238·1).
Bacterial infections.

Bio-Cest *Bioresearch, Mex.†.*
Praziquantel (p.153·3).
Cysticercosis.

Biochetasi
Sigma-Tau, Ital.
Injection; suppositories: Vitamin B substances and electrolytes (p.1922·1).
Fluid and electrolyte disorders; liver disorders.

Sigma-Tau, Ital.
Oral granules: Vitamin B substances, electrolytes, and carbohydrate (p.1922·1).
Fluid and electrolyte disorders; liver disorders.

Biochin *Biolab, Thai.†.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Biocholes *Medikon, Indon.*
Cynara (p.2291·2); vitamin C; nicotinamide (p.1957·3); vitamin E; chromium tripicolinate (p.1934·3).
Hyperlipidaemias.

Bio-Ci *Ceccarelli, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Biociclin *Francia, Ital.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Biocid *Biochem, India.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Biocidan
Note. This name is used for preparations of different composition.
Menarini, Fr.
Eye drops: Cethexonium bromide (p.1634·1).
Minor eye infections.
Menarini, Fr.
Nasal spray: Cethexonium bromide (p.1634·1); phenyltoloxamine citrate (p.588·1).
Rhinitis.

Biocil
Note. This name is used for preparations of different composition.
Ibirn, Ital.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.
Pharmaniaga, Malaysia†; Raza, Malaysia†.
Ampicillin trihydrate (p.204·2).
Bacterial infections.
Formula, NZ.
Povidone-iodine (p.1659·2).
Herpes labialis; minor cuts and burns; skin disinfection.

Biocilin *Biochem, India.*
Ampicillin (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Biocilina
Note. A similar name is used for preparations of different composition (see below).
Biogalenic, Venez.
Oxacillin sodium (p.311·3).
Bacterial infections.

Bio-Cillin
Note. A similar name is used for preparations of different composition (see above).
Biotech, S.Afr.
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Biocin *Atral, Port.†.*
Doxycycline (p.267·1).
Bacterial infections.

Biocine Test *Biovac, S.Afr.*
Tuberculin (p.2405·3).
Diagnosis of tuberculosis.

Biocine Test PPD *Chiron Vaccines, Ital.*
Tuberculin purified protein derivative (p.2405·3).
Test for hypersensitivity to tubercle bacillus.

Biocip
Biochem, India.
Ciprofloxacin (p.243·3).
Bacterial infections.
Ranbaxy, S.Afr.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Biocipro *Biospray, Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Biocip-TZ *Biochem, India.*
Ciprofloxacin (p.243·3); tinidazole (p.848·3).
Bacterial infections.

Biocitronil *SMB, Chile†.*
Bifonazole (p.527·3).
Fungal skin infections.

Bioclar *Biochem, India.*
Clarithromycin (p.248·2).
Bacterial infections.

Bioclaril *GNR, Ital.†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Bioclate *Armour, USA†.*
A factor VIII preparation (p.1067·1).
Haemophilia A.

Bioclavid *Sandoz, Arg.; Sandoz, Denm.; Sandoz, Fin.; Sandoz, Gr.; Sandoz, Neth.; Sandoz, Philipp.; Sandoz, Swed.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Bioclin Kera *Dermoteca, Port.†.*
Borage; cystine; glycine; zinc gluconate; methionine; arginine; cucurbita; vitis vinifera; calcium pantothenate; biotin; copper gluconate (p.1922·1).
Hair and nail disorders.

Bioclin Sebo Care
Note. This name is used for preparations of different composition.
Dermoteca, Port.†.
Capsules: Borage oil (p.2267·3); Iceland moss (p.2324·1); zinc (p.1999·1); cucurbita oil (p.2290·2).
Seborrhoea.
Dermoteca, Port.
Topical gel: Glycolic acid (p.1598·1); piroctone olamine (p.1610·1); salicylic acid (p.1612·2); lactic acid (p.2329·3).
Acne.

Bioclindax *Biogalenic, Venez.*
Clindamycin (p.251·1).
Bacterial infections.

Bioclox *Biochem, India.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Bioclusive *Johnson & Johnson, Ital.*
Polyurethane dressing (p.1611·1).
Wounds.

Biocobal *Lemery, Mex.*
Hydroxocobalamin (p.1980·3).
Anaemias; neuritis.

Biocodone *UCB, Belg.*
Hydrocodone bitartrate (p.63·1).
Coughs.

Biocolchid *Biogalenic, Venez.*
Thiocolchicoside (p.1898·2).

Biocombin *Meprofarm, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neuritis; vitamin B deficiency.

Biocord *Medipharm, Chile.*
Vitamins; minerals; ginseng; soya lecithin; procaine hydrochloride; rutin (p.1922·1).
Skin, hair, and nail disorders; tonic.

Biocord Active *Medipharm, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Biocord-E *Medipharm, Chile.*
Vitamins; minerals; rutoside; ginseng; soya lecithin; procaine hydrochloride (p.1922·1).
Dietary supplement.

Biocort
Note. This name is used for preparations of different composition.
Biosintex, Arg.
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections.
Medikon, Indon.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.
Adcock Ingram, S.Afr.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Biocortin *Eczane, Arg.†.*
⊗ Hydrocortisone (p.1535·2); neomycin (p.305·1); tetryzoline (p.1574·1).
Eye disorders.

Biocoryl *Uriach, Spain.*
Procainamide hydrochloride (p.1377·2).
Arrhythmias.

Biocos *APS, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Biocream *Merck, Indon.*
Moisturiser.

Biocrin *Biofarma, Braz.†.*
Vitamin A (p.1971·2).

Biocrinal *Sofex, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Biocrist *Biosintetica, Braz.†.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Biocristine *Biochem, India.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Bio-Cuivre *Herbaxt, Fr.*
Copper pidolate; manganese pidolate (p.1922·1).
Nutritional supplement.

Biocure *Qualiphar, Belg.*
A range of multivitamin and mineral preparations (p.1922·1).

Bio-C-Vitamin *Pharma Nord, Fin.*
Calcium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

BioCyst *CytoChemia, Ger.*
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1); java tea (p.2328·2).
Urinary-tract disorders.

Bio-Dac *Bioresearch, Mex.*
Sulindac (p.126·3).
Inflammation; rheumatism.

Biodaclin *Rayere, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Biodacyna *Bioton, Pol.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Biodalgic *Biocodex, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Biodan
Note. This name is used for preparations of different composition.
Bioresearch, Mex.
Phenytoin sodium (p.495·2).
Epilepsy.
Biomedis, Thai.†; Great Eastern, Thai.†.
Sulfaguanidine (p.339·2); activated charcoal (p.1435·2); bismuth subcarbonate (p.1711·1); pectin (p.2145·2); dicycloverine hydrochloride (p.1722·3).
Diarrhoea.

Biodantyl-C *Bioresearch, Mex.*
Miconazole (p.541·2).
Fungal skin infections.

Biodasin *Promed, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Bio-Delta Cortilen *SIFI, Ital.*
⊗ Prednisolone acetate (p.1541·1); neomycin sulfate (p.305·1).
Eye infections.

Bioderm
Note. This name is used for preparations of different composition.
Odan, Canad.
Polymyxin B sulfate (p.317·3); bacitracin (p.210·3).
Bacterial skin infections.
Galenium, Indon.
Gentamicin sulfate (p.282·1).
Skin infections.

Biodermatin *Lafare, Ital.*
Biotin (p.1931·3).
Biotin deficiency.

Bio-Dermis *Sidus, Arg.*
Aloe arborescens.
Skin disorders.

Biodexan *Sophia, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Biodexin *Silesia, Chile†.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Infected burns, ulcers, and wounds; skin infections.

Biodezil *Bioresearch, Mex.*
Captopril (p.1239·2).
Hypertension.

Biodiar *Sandoz, Indon.*
Activated attapulgite (p.1709·1).
Diarrhoea.

Biodif *Bago, Chile.*
Betacarotene; vitamin E; vitamin C; minerals (p.1922·1).

Biodinam *Roux-Ocefa, Arg.*
Vitamin and trace element preparation (p.1922·1).

Biodine *Major, USA.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Bio-Disc *Blackmores, Austral.*
Minerals; vitamins (p.1922·1); silicon dioxide (p.2146·2); bromelains (p.2269·1); papain (p.2362·3).
Delayed bone healing; muscular and joint pain.

Biodobutin *Biosintetica, Braz.†.*
Dobutamine hydrochloride (p.1271·2).

Biodol
Note. This name is used for preparations of different composition.
Biofarma, Braz.†.
Miconazole (p.541·2).
Fungal skin infections.
Niche, Irl.
Tramadol hydrochloride (p.130·3).
Pain.

Biodone *Biomed, Austral.†; Biomed, NZ.*
⊗ Methadone hydrochloride (p.82·3).
Opioid dependence; opioid withdrawal syndrome.

Biodophilus *Bioceuticals, UK.*
Lactobacillus acidophilus (p.2372·3).

Biodoxan *Biogalenic, Venez.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Biodoxi *Biochem, India.*
Doxycycline (p.267·1).
Bacterial infections.

Biodramina *Uriach, Spain.*
Dimenhydrinate (p.576·2).
Motion sickness.

Biodramina Cafeina *Uriach, Spain.*
Caffeine (p.1116·3); dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Motion sickness; vertigo.

Biodribin *IBA, Pol.*
Cladribine (p.701·1).
Leukaemias; lymphoma.

Biodrop *Sidus, Arg.†.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Biodrox *Biofarma, Braz.†.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Biodroxil *Sandoz, Austria; Novartis, Chile†; Sandoz, Cz.; Biochemie, Hong Kong; Biochemie, Hung.†; Sandoz, Indon.; Sandoz, Israel; Sandoz, Pol.*
Cefadroxil (p.218·1).
Bacterial infections.

Biodruff *Farmamust, Gr.*
Tenoxicam (p.128·2).
Inflammatory disorders.

Bio-E
Teguhsindo, Indon.
Vitamin E (p.1992·2).
Antioxidant; vitamin E deficiency.
Pharma Nord, Thai.
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Bioelementa *Dekaz, Gr.*
⊗ Mometasone (p.1540·1).
Inflammatory skin disorders.

Bio-Energol Plus *Yabrofarma, Port.*
Arginine aspartate (p.1928·2).
Tonic.

Bio-Enhanced Calcium Plus *Abbott, Malaysia.*
Calcium (p.1675·2); ergocalciferol (p.1987·1).
Dietary supplement.

Bioenterine *DB, Fr.*
Nutritional supplement (p.1922·1).
Maintenance of gastrointestinal flora.

Bioepicyna *IBA, Pol.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

BIO-EPL *Medikon, Indon.*
Lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1); methionine (p.1450·1).
Liver disorders.

Bioequiseto *Cabassi, Ital.*
Equisetum (p.2299·3).
Nutritional supplement.

Bioesse Plus *Mavi, Ital.*
Amino acids; biotin; selenium; saw palmetto (p.1922·1).
Nutritional supplement.

Bioestril Blu *Viatris, Ital.*
Soya; red clover; cimicifuga; urtica; valerian; agnus castus; vitamin E (p.1922·1).
Nutritional supplement for women.

Bioestril Rosso *Viatris, Ital.*
Soya; red clover; cimicifuga; agnus castus; ginseng; crataegus; vitamin E (p.1922·1).
Nutritional supplement for women.

Bio-E-Vitamin *Pharma Nord, Fin.; Pharma Nord, Norw.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Biofanal *Pfleger, Ger.*
Nystatin (p.543·2).
Candidiasis.

Biofax *Maver, Chile.*
Vitamin E; betacarotene; vitamin C; selenium; zinc gluconate (p.1922·1).

Biofaxil *Lepori, Port.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Biofazolin *Bioton, Pol.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Biofem
Note. This name is used for preparations of different composition.
Biotenk, Arg.†.
⊗ Raloxifene (p.2128·3).
Osteoporosis.
Biotenk, Arg.
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.
Hexal, Ger.; Ilsan, Turk.
Vitex agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Biofem 35 *Biotenk, Arg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Biofem Test *Biotenk, Arg.*
Pregnancy test (p.2372·1).

Biofenac
Note. This name is used for preparations of different composition.
Almirall, Belg.; Galenica, Gr.; Almirall, Neth.; Almirall, Port.
Aceclofenac (p.14·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Ache, Braz.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Bio-Fer
Note. A similar name is used for preparations of different composition (see below).
Herbaxt, Fr.
Iron pidolate; folic acid; ascorbic acid (p.1922·1).
Nutritional supplement.

Biofer
Note. A similar name is used for preparations of different composition (see above).
Bioresearch, Mex.
Paracetamol (p.108·1).
Fever; pain.

Bioferal *Bioprogress, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Bioferina *Bioresearch, Mex.*
Phenazopyridine (p.116·3).
Urinary-tract infections.

Bioferon *Sidus, Arg.; Bio Sidus, Thai.*
Interferon alfa-2b (recombinant) (p.885·1).
Anogenital warts; hepatitis; malignant neoplasms.

Bioferon Hepakit *Sidus, Arg.*
Capsules, ribavirin (p.902·3); injection, interferon alfa-2b (recombinant) (p.885·1).
Chronic hepatitis C.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Bioferro *Prospa, Port.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Bioff *Biochem, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Biofiber *Enila, Braz.†.*
Guar gum (p.442·3).

Biofilen *Degorts, Mex.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Biofilm *Braun, UK.*
Hydrocolloid dressing.
Ulcers; wounds.

Biofim *Uniao Quimica, Braz.†.*
14 Tablets, mestranol (p.2116·2); 7 tablets, norethisterone (p.2119·3); mestranol; 7 tablets, inert.
Biphasic oral contraceptive.

Bioflac *Cristalia, Braz.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Bioflam *Rider, Chile.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Bioflavin *Herbarium, Braz.*
Ginkgo biloba (p.2311·1).

Bioflevin *Biomedica-Chemica, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Bioflex *Rottapharm, Chile.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Degenerative joint disorders.

Bioflogil *Spedrog, Arg.*
Chondroitin sulfate sodium (p.2280·3).
Osteoarthritis; osteoporosis.

Bioflor *Biocodex, Hong Kong.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea; irritable bowel syndrome.

Bioflora
Note. A similar name is used for preparations of different composition (see below).
Sidus, Arg.
Lactobacillus casei (p.2372·3); *Lactobacillus plantarum*; *Enterococcus faecalis* (p.2372·3); *Bifidobacterium brevis* (p.2372·3).
Restoration of gastrointestinal flora.

Bio-Flora
Note. A similar name is used for preparations of different composition (see above).
Maver, Chile.
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Bioflorin
Note.This name is used for preparations of different composition.
Sanova, Austria.
Live *Enterococcus faecium* (p.2372·3).
Gastrointestinal disorders.

Hebron, Braz.†.
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea; restoration of gastrointestinal flora.

Sanofi-Aventis, Ital.; Sanofi Synthelabo, Switz.
Lactic-acid-producing enterococci (p.2372·3).
Gastrointestinal disorders.

Bioflox *Bioresearch, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Biofloxcin *Niche, Irl.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Biofloxin *Biochem, India.*
Norfloxacin (p.309·2).
Bacterial infections.

Bioflox-TZ *Biochem, India.*
Norfloxacin (p.309·2); tinidazole (p.848·3).
Bacterial infections.

Bioflu *United Laboratories, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; cold and influenza symptoms; sinusitis.

Biofluor Ortodoncia *Distrifarma, Port.†.*
Sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Biofluor Plus *Distrifarma, Port.†.*
Chlorhexidine gluconate (p.1635·3); sodium fluoride (p.1962·2).
Oral hygiene.

Biofluor Prevencao *Distrifarma, Port.†.*
Chlorhexidine gluconate (p.1635·3); sodium fluoride (p.1962·2).
Oral hygiene.

Biofluor Sensitive *Distrifarma, Port.†.*
⊗ Potassium nitrate (p.1658·3); cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).
Gingivitis; sensitive teeth.

Bioflusin *Bioresearch, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Hay fever.

Bioflutin *Sudmedica, Ger.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Biofolic *Esseti, Ital.*
Calcium mefolinate pentahydrate (p.1932·2).
Antidote to folic acid antagonists; folic acid deficiency; reduction of aminopterin and methotrexate toxicity.

Biofos *Meprofarm, Indon.*
Echinacea (p.2298·1); curcuminoid; fructo oligosaccharide; taurine (p.2395·2); phyllanthus niruri.
Digestive disorders; immunostimulant; reduced appetite.

Biofreeze
Note.This name is used for preparations of different composition.
Shield, Irl.
Isopropyl alcohol (p.1650·3); maté (p.2416·1); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint pain.

Lane, UK.
Menthol (p.2340·1); maté (p.2416·1).
Musculoskeletal and joint pain.

Biofrin *Sophia, Mex.*
⊗ Polymyxin B (p.318·2); neomycin (p.305·1); naphazoline (p.1565·1).
Eye disorders.

Biofructose *Bunker, Braz.*
Vitamin B substances, ascorbic acid, and fructose (p.1922·1).

Biofrut *Neckerman, Braz.†.*
Fructose (p.1945·1); ascorbic acid (p.1983·3).

Bioftal *Lafedar, Arg.*
Chloramphenicol (p.239·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).

Biofurex *KBR, Ital.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Biofurin *Bioresearch, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Biofuroksym *Bioton, Pol.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Biofuroso *Bioresearch, Mex.*
Ferrous fumarate (p.1938·3).
Iron deficiency anaemia.

Biogal *Gal, Pol.†.*
Borage oil (p.2267·3).
Atherosclerosis; cardiovascular disorders; eczema.

Biogam *Biogam, Switz.†.*
Trace element preparations (p.1922·1).

Biogamma *Asubio, Jpn.*
Interferon gamma-1a (p.893·3).
Skin lymphoma.

Biogaracin *Biochem, India.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Biogastron *Bernofarm, Indon.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); dimeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Biogat *Biochem, India†.*
Gatifloxacin (p.281·1).
Bacterial infections.

Biogaze
Note.This name is used for preparations of different composition.
OJG, Belg.
Dodeclonium bromide (p.1642·3); lidocaine hydrochloride (p.1862·3).
Skin disorders.

Zambon, Fr.†.
Niaouli oil (p.2351·3); thyme oil (p.2401·2).
Burns.

Biogel
Note.This name is used for preparations of different composition.
Prater, Chile.
Ketoconazole (p.539·1).
Fungal scalp infections.

Ghimas, Ital.
Royal jelly (p.2382·1).

Biogelat Vitamin E *Metochem, Cz.†.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Bio-Gelin *Northia, Arg.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Biogena Dermo *Valetudo, Ital.*
Soap substitute.

Biogenol *Chemopharma, Chile; Hakay, Turk.*
Vitamin A palmitate; calcium ascorbate; alpha tocoferil acetate; selenium yeast; zinc gluconate; copper gluconate (p.1922·1).
Nutritional supplement; vitamin B deficiency.

Biogesic *Biomedis, Hong Kong; Biomedis, Indon.; Probus, Indon.; Biomedis, Malaysia; United Laboratories, Philipp.; Biomedis, Singapore; Biomedis, Thai.; Great Eastern, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Bioget *Michallik, Ger.†.*
Tannic acid (p.2394·3); cetylpyridinium chloride (p.1635·1).
Burns; wounds.

BioGinkgo
Note. A similar name is used for preparations of different composition (see below).
Pharmanex, USA.
Ginkgo biloba (p.2311·1).
Nutritional supplement.

Bioginko
Note. A similar name is used for preparations of different composition (see above).
Indofarma, Pol.
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Mental function impairment; tonic.

Bioglan Acidophilus *Bioglan, Austral.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Bioglan Arthri Plus *Bioglan, Austral.*
Celery seed oil (p.2278·3); evening primrose oil (p.2302·1); fish oil (p.1362·2); devil's claw root (p.39·1); salix (p.121·3).
Arthritis; rheumatism; sports injuries.

Bioglan 3B Beer Belly Buster *Bioglan, Austral.*
Garcinia (p.2309·2); chromium trichloride (p.1934·3); pectin (p.2145·2); methylcellulose (p.2145·1); guarana (p.2416·1); St John's wort (p.422·3).
Obesity.

Bioglan Bioage Peripheral *Bioglan, Austral.*
Viola tricolor (p.2415·2); crataegus (p.2289·1); olive (p.2356·2); magnesium orotate (p.2358·3); *d*-alpha tocoferil acid succinate (p.1993·1).
Peripheral circulatory disorders.

Bioglan The Blue One *Bioglan, Austral.*
Avena (p.2262·1); tribulus terrestris (p.2404·1); damiana (p.2292·1); capsicum (p.2276·2); eschscholtzia californica; zinc amino acid chelate (p.2000·1); rutoside (p.2305·1).
Tonic for males.

Bioglan Cal C *Bioglan, Austral.*
Calcium ascorbate (p.1984·1).
Vitamin C supplement.

Bioglan Cirflo *Bioglan, Austral.†.*
Rutoside (p.2305·1); bioflavonoids (p.2304·1); nicotinic acid (p.1957·3); calcium ascorbate (p.1984·1); calcium gluconate (p.1675·3); aesculus (p.2248·2); hamamelis (p.2318·2); pulsatilla (p.2376·3); butcher's broom (p.2270·3).
Peripheral circulatory disorders.

Bioglan Cranbiotic Super *Bioglan, Austral.*
Cranberry (p.2289·1); taraxacum (p.2395·1); bearberry (p.2263·3); buchu (p.2269·3); solidago virgaurea (p.2391·1).
Cystitis.

Bioglan Daily Plus *Bioglan, Austral.*
Vitamin and mineral preparation (p.1922·1).

Bioglan Daily Plus Max *Bioglan, Austral.*
Ginseng; garlic; milk thistle; bladderwrack; lecithin; vitamins; minerals (p.1922·1).
Tonic.

Bioglan Digestive Zyme *Bioglan, Austral.*
Betaine hydrochloride (p.2265·2); glutamic acid (p.1947·1); pepsin (p.2365·1).
Achlorhydria; hypochlorhydria.

Bioglan Discone *Bioglan, Austral.†.*
Vitamin and mineral preparation (p.1922·1) with bromelain (p.2269·1) and papain (p.2362·3).
Arthritis; rheumatism; sports injuries.

Bioglan Easy Bronz *Bioglan, Austral.*
Lycopersicon esculatum.
Skin tanning.

Bioglan Formula Four *Bioglan, Austral.*
Vitamin and mineral preparation (p.1922·1).

Bioglan Ginger-Vite Forte *Bioglan, Austral.*
Ginger oil (p.1732·3); ginger (p.1732·3); evening primrose oil (p.2302·1).
Arthritis; rheumatism; sports injuries.

Bioglan Ginsynergy *Bioglan, Austral.*
Ginseng (p.2312·1); eleutherococcus senticosis root (p.2386·3); withania somnifera; panax quinquefolium.
Tonic.

Bioglan Hemo Factor *Bioglan, Austral.*
Vitamin preparation with iron and folic acid (p.1922·1).
Anaemia.

Bioglan Joint Mobility *Bioglan, Austral.*
Glucosamine sulfate (p.2313·2); turmeric (p.1473·2); boswellia serrata (p.2307·1); capsicum (p.2276·2); zinc gluconate (p.1999·2); manganese amino acid chelate (p.1956·3).
Musculoskeletal and joint disorders.

Bioglan Liver-Vite *Bioglan, Austral.*
Milk thistle (p.1452·1).
Liver disorders.

Bioglan Maxepa *Bioglan, Austral.*
Fish oil (p.1362·2).
Atherosclerosis; hypertriglyceridaemia.

Bioglan Mega C *Bioglan, Austral.*
Ascorbic acid (p.1983·3); rose fruit (p.2381·2); hesperidin (p.2304·3).
Vitamin C supplement.

Bioglan Mens Super Soy/Clover *Bioglan, Austral.*
Red clover (p.2285·1); soya bean (p.1965·3); saw palmetto (p.2192·3); damiana (p.2292·1); calcium hydrogen phosphate (p.1676·1).
Male menopausal disorders.

Bioglan Micelle A plus E *Bioglan, Austral.*
Vitamin A (p.1971·2); *d*-alpha tocoferil acetate (p.1992·3).
Fat malabsorption syndromes; vitamin A and E supplement.

Bioglan Micelle E *Bioglan, Austral.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Bioglan Natural E *Bioglan, Austral.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Bioglan Neo Stress *Bioglan, Austral.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Bioglan Organic Mineral *Bioglan, Austral.*
Mineral supplement (p.1922·1).

Bioglan Panazyme *Bioglan, Austral.*
Pancreatin (p.2360·1).
Digestive enzyme supplement.

Bioglan PMT-Eze *Bioglan, Austral.*
Multivitamin and mineral preparation with herbs (bladderwrack, juniper, alchemilla, bearberry, viburnum opulus, vitex agnus castus) (p.1922·1).
Menstrual disorders.

Bioglan Primrose Micelle *Bioglan, Austral.*
Evening primrose oil (p.2302·1).
Eczema; mastalgia.

Bioglan Primrose-E *Bioglan, Austral.*
Evening primrose oil (p.2302·1); *d*-alpha tocopherol (p.1992·2).
Premenstrual syndrome.

Bioglan Pro-Guard *Bioglan, Austral.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Bioglan Psylli-Mucil Plus *Bioglan, Austral.*
Ispaghula (p.1737·1); slippery elm (p.2388·2); peppermint leaf (p.1761·2); ginger (p.1732·3); pectin (p.2145·2).
Bowel cleanser.

Bioglan Pygno-Vite *Bioglan, Austral.*
Vitis vinifera (p.2316·3); myrtillus (p.2349·3).
Peripheral circulatory disorders.

Bioglan Silica-Vite *Bioglan, Austral.*
Equisetum (p.2299·3).
Skin disorders; wounds.

Bioglan Soy Power Plus *Bioglan, Austral.*
Red clover (p.2285·1); soya bean (p.1965·3); dioscorea villosa; calcium hydrogen phosphate (p.1676·1).
Isoflavone and calcium supplement.

Bioglan Stress-Relax *Bioglan, Austral.*
St John's wort (p.422·3).
Anxiety; nervous disorders.

Bioglan Sucro *Bioglan, Austral.*
Vitamin and mineral preparation (p.1922·1).

Bioglan Super Cal C *Bioglan, Austral.*
Calcium ascorbate (p.1984·1); citrus bioflavonoids (p.2304·1); hesperidin (p.2304·3); rutoside (p.2305·1); rose fruit (p.2381·2).
Vitamin C supplement.

Bioglan Supercarotene C&E *Bioglan, Austral.*
Betacarotene; *d*-alpha tocoferil acid succinate; ascorbic acid (p.1922·1).
Tonic.

Bioglan Superdophilus *Bioglan, Austral.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Bioglan Synergy B *Bioglan, Austral.*
Vitamin B substances with vitamin C and magnesium (p.1922·1).

Bioglan Vision-Eze *Bioglan, Austral.*
Myrtillus (p.2349·3); ginkgo biloba (p.2311·1).
Eye fatigue; peripheral circulatory disorders; poor night vision.

Bioglan Water Soluble E *Bioglan, Austral.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Bioglan Zellulean with Escin *Bioglan, Austral.*
Aesculus (p.2248·2); ginkgo biloba (p.2311·1); vitis vinifera (p.2316·3); bladderwrack (p.2384·2); bioflavonoids (p.2304·1); lecithin (p.2332·2); pectin (p.2145·2); tyrosine (p.1971·1); evening primrose oil (p.2302·1); omega-3 marine triglycerides (p.1362·2); yellow sweet clover (p.2339·2).
Aid to skin tissue repair; obesity.

Bioglan Zinc Chelate *Bioglan, Austral.*
Zinc amino acid chelate (p.2000·1).
Zinc deficiency.

Bioglan Zn-A-C *Bioglan, Austral.*
Ascorbic acid (p.1983·3); vitamin A (p.1971·2); zinc amino acid chelate (p.2000·1); calcium pantothenate (p.1959·3); rutoside (p.2305·1).
Vitamin and mineral supplement.

Bioglic *Biolab Sanus, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Bioglobina *Vargas, Venez.*
Vitamin preparation (p.1922·1).

Bioglufer *Euro-Pharma, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Bioglusil *Bioresearch, Mex.†.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Biogreen *Euro-Pharma, Ital.*
Sodium monofluorophosphate (p.1964·3); propolis (p.2373·3); tabebuia; plant extracts.
Mouth disorders.

Bio-Grip C *Gramon, Arg.*
Aspirin (p.20·3); vitamin C (p.1983·3).
Cold symptoms.

Biogrip Forte *Sanitas, Chile.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Biogyl *Biolab, Thai.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Biohep *Kee, India†.*
Ornithine aspartate (p.1959·2); pancreatin (p.2360·1).
Liver disorders.

Biohepax *Ducto, Braz.*
Adenosine (p.1202·1); methionine (p.1450·1); betaine (p.2265·2); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2).
Biliary-tract disorders.

Bio-Hep-B *Biotechnology, Israel.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Biohes *Biosel, Turk.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Plasma volume expansion.

Biohist *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2); calamine (p.1591·2); phenol (p.1656·1).
Skin disorders.

Biohist-LA *Ivax, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly contained carbinoxamine maleate and pseudoephedrine hydrochloride.
Cold symptoms.

Bio-H-Tin *e+b, Austria; e+b, Ger.; e+b, Hung.; Gebro, Switz.*
Biotin (p.1931·3).
Biotin deficiency; hair and nail disorders.

Biohulin 70/30, 80/20, and 90/10 *Biobras, Braz.†.*
⊗ A mixture of isophane insulin injection(human, monocomponent) and insulin injection (human, monocomponent) (p.443·2) in the proportions indicated.
Diabetes mellitus.

Biohulin C *Novo Nordisk, Arg.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Biohulin Lenta *Biobras, Braz.†.*
⊗ Insulin zinc suspension (human, monocomponent) (p.443·2).
Diabetes mellitus.

Biohulin N *Novo Nordisk, Arg.*
⊗ Protamine zinc insulin (human) (p.443·2).
Diabetes mellitus.

Biohulin NPH *Biobras, Braz.*
⊗ Isophane insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Biohulin Regular *Biobras, Braz.*
⊗ Insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Biohulin Ultralenta *Biobras, Braz.†.*
⊗ Insulin zinc suspension (crystalline) (human, monocomponent) (p.443·2).
Diabetes mellitus.

Bio-Insulin I *Guidotti, Ital.†.*
⊗ Isophane insulin (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Bio-Insulin 30/70 and 50/50 *Guidotti, Ital.†.*
⊗ Mixtures of insulin injection (human, biosynthetic) and isophane insulin injection (human, biosynthetic) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Bio-Insulin L *Guidotti, Ital.†.*
⊗ Insulin zinc suspension (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Bio-Insulin R *Guidotti, Ital.†.*
⊗ Insulin (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Bio-Insulin U *Guidotti, Ital.†.*
⊗ Insulin zinc suspension (crystalline) (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Bioiodine *Bioceuticals, UK.*
Potassium iodate (p.2169·2).

Biojument Plus *Acti Diffusion, Fr.*
Amino-acid, vitamin, mineral, trace-element, and enzyme preparation (p.1922·1).

Biokacin *Rayere, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Biokadin *Kansuk, Turk.*
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection; vaginal infections.

Biokid *Medikon, Indon.*
Vitamins; minerals; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Biokids *Biotherm, Canad.†.*
SPF 35: Avobenzone (p.1589·3); enzacamene (p.1597·1); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Bioklysm *Biospray, Gr.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Biokonik *Apotex, Mex.*
Vitamin and mineral preparation (p.1922·1).

Biokur *Biocur, Ger.†.*
Biotin (p.1931·3).
Biotin deficiency.

Biol Preo *Biol, Arg.*
Escherichia coli; *Staphylococcus aureus*; alpha haemolytic streptococcus; *Streptococcus pyogenes*; non-haemolytic streptococcus; *Enterococcus faecalis* (p.2372·3); *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Pseudomonas aeruginosa*.
Respiratory-tract infections.

Biolac *Angelini, Ital.†.*
Lactulose (p.1738·2).
Constipation.

Biolactine *Sella, Ital.*
Vitamin B substances (p.1922·1), lactic-acid-producing organisms (p.2372·3); myrtillus (p.2349·3).
Nutritional supplement.

Biolactona *Bioresearch, Mex.*
⊗ Spironolactone (p.1400·1).
Hypertension; oedema.

Biolactus *Rider, Chile.*
Lactobacillus rhamnosus (p.2372·3).
Diarrhoea.

Biolactyl *DB, Fr.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus casei* var *rhamnosus* (p.2372·3).
Maintenance of gastrointestinal flora.

Biolaif *Medix, Mex.*
⊗ Prasterone (p.2124·2).
Tonic.

Biolan *Santen, Ger.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Biolane *Prater, Chile.*
Pyrithione zinc (p.1611·2).
Dandruff.

Biolanz *Biogalenic, Venez.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Biolastin *Ikapharmindo, Indon.*
Collagen (p.2286·1); hydrolastan.
Aid in maintaining skin elasticity.

Biolau *Luchon, Fr.*
Linalol; geraniol (p.2310·3); neroli; d-borneol (p.2268·3); cinol; cineole (p.2282·3); sodium chloride (p.1686·1).
Nasal and oral hygiene.

Biolax *Chatfield Laboratories, UK.*
Bisacodyl (p.1710·1).
Constipation.

Biolectra Calcium *Hermes, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Biolectra Magnesium 240 *Hermes, Ger.*
Magnesium oxide (p.1744·1).
Muscular disorders associated with magnesium deficiency.

Biolectra Magnesium 365 *Hermes, Ger.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Magnesium deficiency.

Biolectra Zink *Hermes, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Bioleine *Nutergia, Fr.*
Evening primrose oil (p.2302·1).
Nutritional supplement.

Biolergy *Konimex, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders; insect bites; rhinitis; urticaria.

Biolfolic *Biol, Arg.*
Folic acid (p.1940·1).
Megaloblastic anaemia; prevention of neural tube defects.

Biolid
Note. This name is used for preparations of different composition.
Bioresearch, Mex.†.
Loperamide (p.1741·3).
Diarrhoea.

Rovi, Spain.
Ispaghula (p.1737·1).
Constipation; diarrhoea.

Biolina *Bioceuticals, UK.*
Spirulina (p.2392·1).

Biolincom *Otto, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Biolix *Bioresearch, Mex.*
Domperidone (p.1726·2).
Dyspepsia.

Bio-Logos *Sigma-Tau, Switz.*
Hydroxocobalamin; amino acids (p.1922·1).
Tonic.

Biolon *Ophtapharma, Canad.†; Laboratorios Chile, Chile; Stulln, Ger.; Biotechnology, Israel; Cryopharma, Mex.; Pharmafrica, S.Afr.; Abdi, Turk.*
Sodium hyaluronate (p.2320·1).
Aid in ophthalmic surgery.

Biolone *Pharmafrica, S.Afr.*
Sodium hyaluronate (p.2320·1).
Aid in eye surgery.

Biolorat *Technobio, Mex.; Biogalenic, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity.

Biolutam *Biotenk, Arg.*
Bicalutamide (p.686·2).
Prostatic cancer.

Biolyse *Key Oncologics, S.Afr.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer.

Biolysin *Bernofarm, Indon.*
Vitamins; lysine hydrochloride; NZA (p.1922·1).
Vitamin supplement.

Biomag
Note. This name is used for preparations of different composition.
Baliarda, Arg.
Magnesium pidolate (p.1679·3).
Magnesium supplement.

Lehning, Canad.; Lehning, Fr.
Homoeopathic preparation.

Boniscontro & Gazzone, Ital.
Cimetidine (p.1716·2).
Gastrointestinal hyperacidity; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Sanofi-Aventis, Pol.
Magnesium lactate (p.1679·2).
Magnesium deficiency.

Biomag Vital *Baliarda, Arg.*
Levocarnitine; magnesium pidolate; vitamin B substances; vitamin C (p.1922·1).
Tonic.

Biomagnesin *Madaus, Ger.*
Dibasic magnesium phosphate (p.1680·1); dibasic magnesium citrate.
Magnesium deficiency.

Bio-Magnesium *Phytomed, Switz.*
Homoeopathic preparation.

Bio-Marine Plus *Pharma Nord, Fr.†.*
Omega-3 marine triglycerides (p.1362·2); folic acid; vitamin B (p.1922·1).
Nutritional supplement.

Biomaterna *Biogalenic, Venez.*
Vitamin and mineral preparation (p.1922·1).

Biomax Kid *Biofarma, Mex.*
Vitamins; echinacea (p.1922·1).

Biomega
Note. A similar name is used for preparations of different composition (see below).
Graha, Indon.
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

BiOmega
Note. A similar name is used for preparations of different composition (see above).
Usana, Malaysia.
Fish oil; natural tocopherols (p.1922·1).
Dietary supplement.

Biomega-3
Note. This name is used for preparations of different composition.
Usana, Hong Kong†.
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1); omega-3 triglycerides (p.1362·1).
Fatty acid supplement.

Usana, Singapore.
Fish oil; mixed natural tocopherols (p.1922·1).
Dietary supplement.

Bio-Melatonin *Pharma Nord, Hung.*
Melatonin (p.2338·3).
Regulation of sleep-wake cycle.

Biomelox *Biogalenic, Venez.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Bioment *Fako, Turk.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Biomesina *Biomep, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Biomesina Compuesta *Biomep, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Biometacin *Bioresearch, Mex.*
Indometacin (p.66·3).
Rheumatism.

Biometrix *Schering-Plough, Mex.*
Vitamins; minerals; ginkgo biloba; ginseng (p.1922·1).

Biometrox *Biosintetica, Braz.*
Methotrexate sodium (p.745·2).
Malignant neoplasms.

Biomex *Actavis, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neuralgia; neuritis; vomiting of pregnancy.

Biomicovo *Biotecnoquimica, Venez.†.*
Arnica (p.2260·2); hamamelis (p.2318·2); St John's wort (p.422·3); calendula (p.2273·1).

Biomida *Biosintetica, Braz.†.*
Flutamide (p.725·1).

Biomin H *Biomin, Cz.*
Calcium; magnesium; phosphorus; trace elements (p.1922·1).
Mineral supplement.

Biomina *Precimex, Mex.†.*
⊗ Albumin (human) (p.1052·1).

Biomineral *Biochimici, Ital.*
Mineral preparation with cystine (p.1922·1).
Nutritional supplement.

Biomineral 5-Alfa *Biochimici, Ital.*
Cucurbita oil; soya oil; evening primrose oil; zinc-rich yeast; green tea; biotin (p.1922·1).
Nutritional supplement; seborrhoea; thinning hair.

Biomineral 5-Alfa Shampoo *Biochimici, Ital.*
Green tea (p.2416·1); biotin; pyridoxine; keratin; collagen (p.2286·1); panthenol.
Seborrhoeic scalp disorders.

Biomineral Donna *Biochimici, Ital.*
Amino acids; minerals; vitamins; millet; cimicifuga; Steromax (palm oil phytosterol) (p.1922·1).
Nutritional supplement for menopausal women.

Bio-Mineral Formula *Blackmores, Austral.*
Mineral preparation (p.1922·1).

Biomineral One *Biochimici, Ital.*
Vitamin and mineral preparation with cystine and methionine (p.1922·1).

Biomineral Plus *Biochimici, Ital.*
Multivitamin and mineral preparation with cystine and methionine (p.1922·1).
Nutritional supplement.

Biomineral Unghie *Biochimici, Ital.*
Amino-acid preparation with vitamins and minerals (p.1922·1).
Nail disorders.

Biominol A *Alter, Spain.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Biominol A D *Alter, Spain.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Deficiency of vitamins A and D.

Biomira *Ingens, Arg.*
Ketotifen (p.582·2).
Allergic eye disorders.

Biomisen *Bioresearch, Mex.†.*
⊗ Furosemide (p.1292·1).

Biomitin *Bioresearch, Mex.*
Difenidol (p.1723·2).
Nausea and vomiting; vertigo.

Biomoist *Ikapharmindo, Indon.*
Moisturiser.

Biomo-lipon *Biomo, Ger.*
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Biomona *Bioresearch, Mex.*
Metronidazole (p.837·1).
Vaginitis.

Biomont *Pharmonta, Austria.*
Multivitamin preparation (p.1922·1).

Biomousse *Clement-Thekan, Fr.†.*
Soap substitute.
Feminine hygiene.

Biomoxil *Biochem, India.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Biomoxil-LB *Biochem, India.*
Amoxicillin (p.202·2); lactobacillus (p.2372·3).
Bacterial infections.

Biomunil *Lusofarmaco, Ital.*
Klebsiella pneumoniae ribosomes and membrane fraction; *Streptococcus pneumoniae* ribosomes; *Streptococcus pyogenes* ribosomes; *Haemophilus influenzae* ribosomes.
Immunostimulant.

Biomunyl uno *Zambon, Ger.*
Ribosomal fraction from *Klebsiella pneumoniae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Haemophilus influenzae*; membrane fraction from *Klebsiella pneumoniae*.
Respiratory-tract infections.

Biomycetin *JRalph, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Bion 3 *Merck, Chile.*
Lactobacillus gasseri (p.2372·3); *Bifidobacterium bifidum*; *Bifidobacterium longum*; vitamins; minerals (p.1922·1).
Dietary supplement.

Bion 3 Adultes *Merck Medication Familiale, Fr.*
Vitamins; minerals; probiotics (p.1922·1).
Tonic.

Bion 3 Seniors *Merck Medication Familiale, Fr.*
Vitamins; minerals; probiotics; ginseng; lutein; myrtillus (p.1922·1).
Tonic.

Bion Tears *Alcon, Austral.; Alcon, Canad.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Singapore; Alcon, Swed.; Alcon, Thai.; Alcon, USA.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Bion Transit *Merck Medication Familiale, Fr.*
Lactobacillus plantarum.
Digestive disorders; maintenance of gastrointestinal flora.

Bionafil *Bioresearch, Mex.*
Enalapril (p.1276·1).
Hypertension.

Bionagre *Phytobiolab, Fr.*
Evening primrose oil (p.2302·1).
Atopy; dry skin disorders; premenstrual syndrome.

Bionagre plus E *Bio-Sante, Canad.*
Linoleic acid (p.2308·2); linolenic acid (p.1362·1); vitamin E (p.1992·2).

Bionagrol *Biophytarom, Fr.*
Evening primrose oil (p.2302·1).
Nutritional supplement.

Bionagrol Plus *Biophytarom, Fr.*
Evening primrose oil (p.2302·1); omega-3 fatty acids (p.1362·1).
Nutritional supplement.

Bionaryl *Bioresearch, Mex.*
Diphenhydramine (p.577·1).
Hypersensitivity.

Bionder-C *Bioresearch, Mex.*
Clioquinol (p.254·1).
Skin infections.

Bionect *JSJ, USA.*
Sodium hyaluronate (p.2320·1).
Facial wrinkles and folds.

Bionet *Church & Dwight, Canad.*
Benzocaine (p.1854·1); cetalkonium chloride (p.1634·1).
Mouth and throat disorders.

Bioneural B12 *Labinca, Arg.†.*
Ibuprofen (p.64·2); hydroxocobalamin (p.1980·3).
Pain.

Bioneuril *Bioresearch, Mex.*
Carbamazepine (p.471·3).
Epilepsy.

Bionicard *Rottapharm, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Bionif *Bioprogress, Ital.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Bionit *Technobio, Mex.*
Nitazoxanide (p.842·3).
Amoebiasis; lambliasis; trichomoniasis; worm infections.

Bionobal *Bioresearch, Mex.*
Hydralazine (p.1307·2).
Hypertension; oedema.

Bionokaltran *Bioresearch, Mex.*
Calcium (p.1675·2).
Calcium deficiency.

Bionol *Bioresearch, Mex.*
Allopurinol (p.552·2).
Hyperuricaemia.

Bionolip *Bioresearch, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

bioNorm mit Konjak *Merck, Ger.†.*
Glucomannan (p.2312·3).
Obesity.

Bionoxol *Bioresearch, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract disorders.

Bionutrin *Biomedis, Thai.; Great Eastern, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Bionutrion *Mugi, Indon.*
Vitamin B substances; vitamin D; vitamin E; calcium hypophosphite; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Biopafen *Bioresearch, Mex.*
Propafenone (p.1380·2).
Arrhythmias.

Biopank *Kee, India†.*
Pancreatin (p.2360·1).
Digestive disorders.

Bioparox *Servier, Cz.; Servier, Hung.; Servier, Pol.; Egis-Servier, Rus.*
Fusafungine (p.279·2).
Respiratory-tract infections.

Biopatch *Johnson & Johnson, Ital.*
Hydrophilic polyurethane dressing (p.1611·1); chlorhexidine gluconate (p.1635·3).
Wounds.

Biopause *Monin, Fr.*
Soya bean (p.1965·3); magnesium lactate (p.1679·2); yam.
Menopausal disorders.

Biopause solution intime *Monin, Fr.*
Soya bean (p.1965·3); plantain (p.2369·3); macadamia oil.
Personal hygiene during the menopause.

Biopaxel *Biosintetica, Braz.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Bio-Pen *Biotech, S.Afr.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Biopensyn *Biomedis, Indon.; Medifarma, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Biopental *OM, Port.*
Lysates of *Streptococcus pneumoniae*; *Moraxella catarrhalis*; *Staphylococcus aureus*; *Klebsiella pneumoniae*; *Haemophilus influenzae*; *Streptococcus pyogenes*.
Respiratory-tract infections.

Bioperazone *Biopharma, Ital.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Biophase *Ecofarm, Ital.*
Soap substitute.

Biophase Shampoo *Ecofarm, Ital.*
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2); glycolic acid (p.1598·1); cinnamon (p.2283·1); clove (p.2284·3); gaultheria procumbens.
Seborrhoeic scalp disorders.

Biophase Zinco Amidata *Ecofarm, Ital.*
Barrier preparation.

Biophen *Ilsan, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Biophenicol *Biochem, India.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Biopime *Biochem, India.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Biopin *Biopin, Rus.†.*
Pine resin (p.2286·2).
Burns; musculoskeletal, joint, and soft-tissue disorders; skin disorders; ulcers; wounds.

Biopiper *Bioprogress, Ital.†.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Biopirox *Biogalenic, Venez.†.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders.

Bioplacenton *Kalbe, Indon.*
Neomycin sulfate (p.305·1); placenta extract (p.2337·3).
Burns; skin infections; ulcers; wounds.

Bioplak *Ern, Spain.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

bioplant-Kamillenfluid *Serum-Werk Bernburg, Ger.†.*
Chamomile (p.2279·3); calendula (p.2273·1).
Bedsores; mouth inflammation; skin inflammation.

Bioplasma FDP *NBI, S.Afr.*
⊗ Plasma protein fraction (p.1076·2).
Fluid depletion; haemorrhagic disorders.

Bioplatinex *Biogalenic, Venez.*
Carboplatin (p.693·1).
Malignant neoplasms.

Bioplatino *Biosintetica, Braz.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Bioplazma *Biosel, Turk.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Plasma volume expansion.

Bioplex
Note. This name is used for preparations of different composition.
Sante Naturelle, Canad.; Fresenius Kabi, Ital.
Vitamin B substances (p.1922·1).
Parenteral nutrition.

Teva, UK†.
Carbenoxolone sodium (p.1714·3).
Mouth ulcers.

Bioplus *Adcock Ingram, S.Afr.*
Caffeine; vitamins; calcium (p.1922·1).
Tonic.

Bioposide *Biochem, India.*
Etoposide (p.718·1).
Malignant neoplasms.

Biopram *Bioresearch, Mex.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Bioprazol *Klinger, Braz.†; Biofarm, Pol.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Biopril *Biochem, India.*
Lisinopril (p.1325·2).

Biopril-AM *Biochem, India†.*
Lisinopril (p.1325·2); amlodipine besilate (p.1214·1).

Bioprim *Norma (Νορμα), Gr.†; Bioresearch, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Bioprofol *Biosintetica, Braz.†.*
Propofol (p.1791·1).
General anaesthesia.

Bioprol *Bioresearch, Mex.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Bioprost
Note. This name is used for preparations of different composition.
Indofarma, Pol.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Intelpharm, Rus.
Cucurbita oil (p.2290·2); thymol (p.1664·3).
Benign prostatic hyperplasia; prostatitis.

Bioprotect *Grossman, Mex.*
Vitamin and mineral preparation (p.1922·1).

Bioprotus *Carrare, Fr.*
Lactic-acid-producing organisms (p.2372·3).
Maintenance of gastrointestinal flora.

Bioptan *Biofarma, Turk.*
Propyphenazone (p.119·3); caffeine (p.1116·3).
Pain.

Biopten *Asubio, Jpn.*
Sapropterin hydrochloride (p.2383·2).
Genetic metabolic disease.

Bioptic *Bausch & Lomb, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Bioptic DX *Bausch & Lomb, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Bioptimum *Boiron, Port.*
A range of amino-acid, vitamin and mineral preparations (p.1922·1).

Biopto-E *Jenapharm, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Biopulmin *Grunenthal, Chile.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Bioquel *Biotecnoquimica, Venez.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Bioquidan *Bioresearch, Mex.*
Dextromethorphan (p.1555·2).
Coughs.

Bioquil *Atral, Port.*
Ofloxacin (p.310·2).
Bacterial infections.

Bioquin
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Erythromycin ethyl succinate (p.269·3); sulfafurazole (p.338·3).
Bacterial infections.

Ikapharmindo, Indon.
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Bio-Quinon Q10 Super *Pharma Nord, Fr.†.*
Ubidecarenone (p.2407·2).
Nutritional supplement.

Bio-Quinone *Pharma Nord, Malaysia; Pharma Nord, Thai.*
Ubidecarenone (p.2407·2).
Heart failure.

Bioracef *Bioton, Pol.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Bioral *Smith & Nephew, Austral.; Merck Consumer, UK†.*
Carbenoxolone sodium (p.1714·3).
Mouth ulcers.

Bioralin *Bioresearch, Mex.*
⊗ Chlortalidone (p.1243·3).
Heart failure; hypertension.

Bioran *Bioresearch, Mex.*
Methenamine (p.298·3).
Urinary-tract infections.

Biordyn *Bioresearch, Mex.*
⊗ Isosorbide (p.1317·2).

Bioregime *Azevedos, Port.†.*
Glucomannan (p.2312·3).
Obesity.

Bioregime Fort *Azevedos, Port.†.*
Glucomannan (p.2312·3); yeast (p.1998·3).
Obesity.

Bioregime SlimKit
Note. This name is used for preparations of different composition.
Azevedos, Port.†.
Capsules: Glucomannan (p.2312·3); bromelains (p.2269·1).
Obesity.

Azevedos, Port.†.
Topical gel: Caffeine (p.1116·3).
Obesity.

Biorenyn *Bioresearch, Mex.*
⊗ Salbutamol (p.1131·2).
Asthma.

Bioretin *Medikon, Indon.*
Betacarotene (p.1930·3); myrtillus (p.2349·3); tribulus terrestris (p.2404·1).
Dietary supplement for eye health.

Bioreucam *Angenerico, Port.†.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Bioreunil *Bioresearch, Mex.†.*
Carbamazepine (p.471·3).
Epilepsy.

Biorevit Gel *DNR, Arg.†.*
Aloe vera (p.1588·2).
Skin disorders.

Biorevit Labial *DNR, Arg.*
Oxybenzone (p.1608·3).

Biorevit Solar 15 *DNR, Arg.†.*
Titanium dioxide (p.1617·3); aminobenzoic acid (p.1589·1).
Sunscreen.

Biorgan
Note. This name is used for preparations of different composition.
Ivax, Arg.
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders.

Royal, Chile†.
Vitamin B substances; methionine; cystine; zinc; gelatin (p.1922·1).
Hair and nail disorders.

Biorgan B *Ivax, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).
Gastrointestinal disorders.

Biorgasept *Biorga, Fr.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin and wounds; skin infections.

Biorinil *Farmila, Ital.*
⊗ Betamethasone (p.1518·2); tetryzoline hydrochloride (p.1574·1).
Rhinitis; rhinopharyngitis; sinusitis.

Biorisan *Vocate, Gr.*
Amikacin (p.200·2).
Bacterial infections.

Bio-Ritmo *Medinfar, Port.†.*
Arginine aspartate; pyridoxine hydrochloride; pangamic acid (p.1922·1).
Tonic.

Biormon *Amsa, Ital.†.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Amenorrhoea; oligomenorrhoea.

Biorox *Biochem, India.*
Roxithromycin (p.331·1).
Bacterial infections.

Biorphen *Alliance, UK.*
Orphenadrine hydrochloride (p.812·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Biorrub *Biosintetica, Braz.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Biortan *Biogalenic, Venez.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Biortho *Nutergia, Fr.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Biorubina *IBA, Pol.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Bios Life *Unicity, Singapore.*
Guar gum; acacia; ceratonia; pectin; oat fibre; vitamins; phytosterols; calcium carbonate; beta-glucan; chrysanthemum morifolium; policosanol; zinc gluconate; selenium yeast; chromium yeast (p.1922·1).
Dietary supplement.

Biosal
Note. This name is used for preparations of different composition.
Yauyip, Austral.†.
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3).
Arthritis pain.

Bioprogress, Ital.†.
Nimesulide (p.95·3).
Fever; inflammation; pain.

Biosal Arthritis *Yauyip, Austral.*
Thurfyl salicylate (p.129·1); methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3).
Arthritis.

Biosan E *Hexal, Ger.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Biosan Zink *Biocur, Ger.†.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Biosanbe *Sanbe, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid (p.1940·1); cyanocobalamin (p.1980·2); intrinsic factor (p.2326·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Bioscalin *Giuliani, Ital.*
Multivitamin and mineral preparation with methionine (p.1922·1).
Hair and nail disorders.

Bioscalin Tricoage+ *Giuliani, Ital.*
Multivitamin and mineral preparation (p.1922·1).
Hair disorders.

Bioscefal *Unibios, Spain†.*
Cefalexin (p.218·2).
Bacterial infections.

Bioscina Composta *Biochimico, Braz.†.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Biosedon *Sabona, Ger.†.*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Anxiety disorders; sleep disorders.

Bio-Sel *Ache, Braz.†.*
Betacarotene; selenium; alpha tocoferol; ascorbic acid (p.1922·1).

Bio-Selenium *Herbaxt, Fr.*
Selenium (p.1961·1) from *Saccharomyces cerevisiae*; alpha tocoferil acetate (p.1992·3); wheat-germ oil (p.2415·1).
Muscular disorders; skin disorders.

Bioselenium *Uriach, Spain.*
Selenium sulfide (p.1613·1).
Skin and scalp disorders.

Bio-Selenium Zinc *Pharma Nord, Thai.*
Multivitamin preparation with selenium (p.1961·1) and zinc (p.1999·1) (p.1922·1).
Selenium and zinc deficiencies.

Biosemida *Biogalenic, Venez.*
⊗ Furosemide (p.1292·1).

Biosern *Bioprogress, Ital.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Biosetron *Medicus, Gr.*
Ondansetron (p.1756·3).

Biosil *Enzpharma, NZ†.*
Orthosilicic acid (p.2146·2).
Nutritional supplement.

BioSil *Bio Minerals, Philipp.*
Silicon dioxide (p.2146·2); choline; glycerol; water.
Silicon supplement.

Biosim *Biochem, India†.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Biosint *Liomont, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Biosonida *Biogalenic, Venez.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; obstructive airways disease.

Biosonide *Medicus, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Biosorb *Nutricia, Turk.*
A range of preparations for enteral nutrition (p.1922·1).

Biosotal *Sanofi-Aventis, Pol.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Biosoviran *Bioprogress, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Biospasmil *Biomed Lublin, Pol.*
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3).
Smooth muscle spasm.

Bio-Sport *Pharma Nord, Fr.†.*
Capsules, fish oil; borage oil; tablets, betacarotene; vitamins; minerals (p.1922·1).
Nutritional supplement.

Biostan *Bioresearch, Mex.*
Astemizole (p.567·2).

Biostate *CSL, Austral.; CSL, NZ.*
A factor VIII preparation (human) (p.1067·1).
Haemophilia A.

Biostatik *Pharos, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Bi-Osteo *Synergia, Fr.*
Calcium carbonate; fish oil; evening primrose oil (p.2302·1); vitamins; minerals (p.1922·1).
Nutritional supplement.

Bioster *Terramedic, Philipp.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Biosteron *Lek-Am, Pol.*
⊗ Prasterone (p.2124·2).
Prasterone deficiency.

Biostim *Sanofi-Aventis, Braz.; Aventis, Cz.; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Ital.; Aventis, Mex.; Aventis, Port.†.*
Klebsiella pneumoniae glycoprotein (p.2329·2).
Burns; prophylaxis of respiratory-tract infection; ulcers; wounds.

Biostimol *Vita Health, Switz.*
Citrulline malate (p.1935·1).
Asthenia.

Biostin
Note. This name is used for preparations of different composition.
Teva, Hung.
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Bioresearch, Mex.
Glibenclamide (p.440·1).
Diabetes mellitus.

Biostop *Vezedes, Fr.*
Coconut oil (p.2029·2); fruit acids.
Insect repellent.

Bio-Strath
Note. This name is used for preparations of different composition.
Bio-Strath, Cz.†.
Valerian (p.2410·1); passion flower (p.2363·2); peppermint leaf (p.1761·2).
Nervous disorders.

Crefar, Port.†.
Amino-acid, vitamin, and mineral preparation (p.1922·1).
Tonic.

Cedar Health, UK.
Saccharomyces cerevisiae (p.1998·3).

Bio-Strath Artichoke Formula *Cedar Health, UK.*
Cynara (p.2291·2); thistle seeds (p.2285·2); peppermint leaf (p.1761·2); yeast plasmolysate (p.1998·3).
Dyspepsia.

Bio-Strath Valerian Formula *Cedar Health, UK.*
Valerian (p.2410·1); passion flower (p.2363·2); peppermint leaf (p.1761·2); yeast plasmolysate (p.1998·3).
Insomnia; irritability; tension.

Bio-Strath Willow Formula *Cedar Health, UK.*
Salix (p.121·3); primula root (p.2372·2); yeast plasmolysate (p.1998·3).
Musculoskeletal and joint pain.

Bio-Strep *Biotech, S.Afr.*
Streptomycin sulfate (p.333·3).
Bacterial infections.

Biostrogen *Biogalenic, Venez.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Biostrum *Lapi, Indon.*
Bovine colostrum; docosahexaenoic acid; cod-liver oil; lysine hydrochloride; vitamins; zinc picolinate (p.2001·1) (p.1922·1).
Nutritional supplement.

Biostymina *Phytofarm Kleka, Pol.*
Aloes (p.1705·2).
Immunostimulant; respiratory-tract infections.

Biosulidd L *Biopharm, Philipp.*
⊗ An insulin zinc injection (human) (p.443·2).
Diabetes mellitus.

Biosulin N *Marvel, Rus.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Biosulin R *Marvel, Rus.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Biotad *Biomedica, Ital.*
Vitamin C; glutathione; thioctic acid; vitamin E (p.1922·1).
Dietary supplement.

Biotaer an Caramelos *Investi, Arg.*
Bacitracin (p.210·3); neomycin (p.305·1); tyrothricin (p.358·2).
Mouth and throat infections.

Biotaer Gamma *Hexal, Arg.†.*
⊗ Immunoglobulin (p.2225·3); neomycin (p.305·1); bacitracin (p.210·3); tyrothricin (p.358·2); phenylephrine hydrochloride (p.1568·1); beclometasone dipropionate (p.1516·2); nystatin (p.543·2).

Biotaer Nasal *Investi, Arg.*
⊗ Framycetin sulfate (p.279·1); gramicidin (p.286·1); triamcinolone hexacetonide (p.1544·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); naphazoline nitrate (p.1565·2).
Nasal congestion.

Biotaer Nebulizable *Investi, Arg.*
⊗ Nystatin (p.543·2); beclometasone dipropionate (p.1516·2); neomycin (p.305·1); bacitracin (p.210·3); tyrothricin (p.358·2); phenylephrine hydrochloride (p.1568·1).

Biotaer Ultrason Nebulizable *Disprovent, Arg.†.*
⊗ Neomycin (p.305·1); bacitracin (p.210·3); tyrothricin (p.358·2); dexamethasone (p.1526·1); phenylephrine hydrochloride (p.1568·1).

Biotaksym *Bioton, Pol.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Biotamoxal *Hexa, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Biotanica Feminine *Medikem, Fr.†.*
Soya bean; lupulus; borage oil; spinach leaf; vitamin E; grape extract; vitamin B ; folic acid (p.1922·1).
Nutritional supplement.

Biotanica Ginsemag *Medikem, Fr.†.*
Magnesium glycerophosphate; magnesium lactate; magnesium oxide; ginseng; vitamin B (p.1922·1).
Nutritional supplement.

Biotanica Nocturn *Medikem, Fr.†.*
Melissa; valerian; lupulus; wheat germ; spinach leaf; orange leaf; vitamin B (p.1922·1).
Nutritional supplement; sleep disorders.

Biotanica Pro Energy *Medikem, Fr.†.*
Dried yeast; ginseng; kola; shiitake mushrooms; camelia sinensis; vitamin C; royal jelly; grape extract; B vitamins (p.1922·1).
Nutritional supplement.

Biotanica Regenerance *Medikem, Fr.†.*
Marine carotenoids; omega-3 triglycerides; pumpkin seed; grape extract; selenium; vitamin C; zinc sulfate; camelia sinensis; vitamin E; pantothenic acid; folic acid (p.1922·1).
Nutritional supplement.

Biotanica Uricalm *Medikem, Fr.†.*
Heather flower; meadowsweet; melissa; lithothamme; zinc sulfate; pumpkin seed (p.1922·1).
Micturition disorders; nutritional supplement.

Biotarson N *Ifusa, Mex.*
⊗ Hydrocortisone acetate (p.1535·2); gramicidin (p.286·1); neomycin (p.305·1).
Bacterial nose infections.

Biotarson O *Ifusa, Mex.*
⊗ Naphazoline (p.1565·1); gramicidin (p.286·1); neomycin (p.305·1).
Bacterial eye infections.

Biotase *YSP, Malaysia; Yung Shin, Singapore.*
Biodiastase (mixed digestive enzymes) (p.2257·1); lipase (p.2360·3); newlase.
Digestive disorders.

Biotassina *Teofarma, Ital.*
Amino acids; vitamin B substances (p.1922·1); calcium gluconate (p.1675·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Asthenia.

Biotax
Note. This name is used for preparations of different composition.
Biochem, India.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Faulding, Israel.
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small-cell lung cancer; ovarian cancer.

Biotaxel *Medicus, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Biotaxime *Biolab, Thai.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Biotax-O *Biochem, India.*
Cefixime (p.224·3).
Bacterial infections.

Biotazol *Bioresearch, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Biotecan *Biotenk, Arg.; Biosintetica, Braz.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Biotel kidney *Biotel, USA†.*
Test for haemoglobin, red blood cells, and albumin in urine.

Biotene *Laclede, Singapore.*
Glucose oxidase (p.2313·3); lactoperoxidase (p.2330·2); muramidase (p.2348·1); lactoferrin (p.2330·1).
Mouth disorders.

Biotene with Calcium *Laclede, USA.*
Propylene glycol (p.2374·1); hyetellose (p.2143·3); aloe vera (p.1588·2); zinc gluconate; calcium lactate; lactoferrin (p.2330·1); muramidase (p.2348·1); lactoperoxidase (p.2330·2); glucose oxidase (p.2313·3).
Dry mouth.

Biotene Dry Mouth *Anglian, UK.*
Lactoperoxidase (p.2330·2); glucose oxidase (p.2313·3); lactoferrin (p.2330·1); muramidase (p.2348·1).
Dry mouth.

Biotene Oralbalance *Anglian, UK.*
Lactoperoxidase (p.2330·2); glucose oxidase (p.2313·3); xylitol (p.1998·2).
Dry mouth.

Biotenor *Biofarma, Braz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Biotenzol *Bioresearch, Mex.†.*
Methyldopa (p.1334·1).
Hypertension.

Bioteral *Northia, Arg.; Itaca, Braz.†.*
Ceftriaxone (p.238·1).
Bacterial infections.

Biotermin AS *Terramedic, Philipp.*
Vitamins (p.1922·1); buclizine hydrochloride (p.570·1).
Appetite stimulant; nutritional supplement.

Bio-Termin Plus with Lecithin *Terramedic, Philipp.*
Vitamins; lecithin; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Bioterona *Biosintetica, Braz.†.*
Cyproterone acetate (p.2088·2).

Biotherm *Biotherm, Canad.*
SPF 15; SPF 25; SPF 30: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Aquasource *Biotherm, Canad.†.*
SPF 15: Ensulizole (p.1597·1); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Gelee Fraiche Bronzante Hydratante *Biotherm, Canad.†.*
SPF 8: Octinoxate (p.1608·2); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Gelee Fraiche Hydrantante *Biotherm, Canad.†.*
SPF 10; SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Lait Bronzant *Biotherm, Canad.†.*
SPF 8: Octinoxate (p.1608·2); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Lait Protecteur *Biotherm, Canad.†.*
SPF 15: Octinoxate (p.1608·2); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Soin des Levres *Biotherm, Canad.†.*
SPF 8: Octinoxate (p.1608·2).
Sunscreen.

Biotherm Soin Solaire *Biotherm, Canad.†.*
SPF 8: Octinoxate (p.1608·2); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Biotherm Soin Solaire Autobronzant *Biotherm, Canad.†.*
SPF 8: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1).
Sunscreen.

Biotherm UV Protectant *Biotherm, Canad.†.*
SPF 25: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Biothicol *Sanbe, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Biothrax *Bioport, USA.*
An adsorbed anthrax vaccine (p.2204·1).
Active immunisation.

Biothymus DS
Note. This name is used for preparations of different composition.
Biochimici, Ital.
Face wash: Levomenol (p.2333·3); enoxolone (p.50·1); piroctone olamine (p.1610·1); salix (p.121·3).
Seborrhoeic dermatitis.

Biochimici, Ital.
Scalp lotion: Piroctone olamine (p.1610·1); urtica (p.2409·3); salix (p.121·3); salicylic acid (p.1612·2); menthol (p.2340·1).
Seborrhoeic dermatitis.

Biochimici, Ital.
Shampoo: Pyrithione zinc (p.1611·2); dipotassium glycyrrhizate (p.2316·2).
Seborrhoeic dermatitis.

Biothymus F Urto *Biochimici, Ital.*
Paeonia suffruticosa.
Prevention of hair loss.

Biothymus M Urto *Biochimici, Ital.*
Paeonia suffruticosa; saw palmetto (p.2192·3).
Prevention of hair loss.

Biotic *TRB, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bioticaps *Richet, Arg.*
Chloramphenicol (p.239·3).
Bacterial infections.

Bioticic *PS, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Biotifen *Bioresearch, Mex.*
Ketotifen (p.582·2).
Asthma; hypersensitivity.

Biotin-Asmedic *Dyckerhoff, Ger.*
Biotin (p.1931·3).
Biotin deficiency.

Biotine *ICM, Singapore.*
Tetracycline hydrochloride (p.347·2).
Skin infections.

Biotisan *Hubner, Fin.*
Biotin (p.1931·3).
Biotin deficiency.

Bioton *Sella, Ital.*
Honey (p.1948·2); ginseng (p.2312·1); royal jelly (p.2382·1).
Nutritional supplement.

Biotone *Laphal, Fr.†.*
Kola (p.2416·1); phosphoric acid (p.2367·1); manganese glycerophosphate (p.2315·2).
Tonic.

Biotonus *Gynopharm, Chile.*
Betacarotene; vitamin E; ascorbic acid; minerals (p.1922·1).

Biotrakson *Bioton, Pol.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Biotravel *Carrare, Fr.*
Lactic-acid-producing organisms (p.2372·3).
Maintenance of gastrointestinal flora.

Biotredine *Biomedica-Chemica, Gr.†.*
Etidronate disodium (p.1097·1).
Paget's disease; postmenopausal osteoporosis.

Biotrefon L *Italmex, Mex.*
Cobamamide (p.1980·2).
Tonic.

Biotrefon Plus *Wyeth Consumer, Ital.*
Pollen (p.2370·2); royal jelly (p.2382·1); liver extract (p.2337·3).

Biotrex *Sinterapico, Braz.†.*
Tetracycline (p.347·1).
Bacterial infections.

Biotrexate *Biochem, India.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Biotriamin *Sophia, Mex.*
⊗ Triamcinolone (p.1544·2); polymyxin B (p.318·2).
Skin disorders.

Biotriax *Sandoz, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Biotricina *Bioresearch, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Biotril *Bioresearch, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Biotrim *Nutravite, Canad.†.*
Thioctic acid (p.2400·2); citrus aurantium (p.2357·1); CLA one; garcinia cambogia (p.2309·2); green tea extract (p.2416·1); guggul lipid extract.
Slimming aid.

Biotrivin *Bioresearch, Mex.*
Vitamin B substances (p.1922·1).
Neuritis; vitamin B supplement.

Biotrixina *Benedetti, Ital.†.*
Cefatrizine (p.221·3).
Bacterial infections.

Biotron *Adcock Ingram, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Biotropin *Ivax, Arg.; Enila, Braz.†.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Bio-Tropin *Biotechnology, Israel.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Bio-TT *Bio Farma, Thai.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Biotum *Bioton, Pol.*
Ceftazidime (p.234·1).
Bacterial infections.

Biotuss *Spitzner, Ger.*
Thyme (p.2401·1).
Respiratory-tract congestion.

Biotussil *Biomedica, Cz.*
Gentian (p.2310·3); cowslip (p.2372·2); plantaginis (p.2379·1); sambucus (p.2383·1); thyme (p.2401·1); liquorice (p.1740·3); fennel oil (p.2303·1); anise oil (p.2258·2).
Respiratory-tract disorders.

Biovac HB *Elea, Arg.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Biovac-B *Wockhardt, Rus.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Bio-Vagin *Elofar, Braz.*
Metronidazole benzoate (p.837·1); nystatin (p.543·2).
Gynaecological infections.

Bioval *Biochem, India†.*
Valdecoxib (p.132·3).

Bioval-P *Biochem, India†.*
Parecoxib (p.112·1).

Biovancomin *Biosintetica, Braz.†.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Biovent *Biomedis, Thai.; Great Eastern, Thai.*
⊗ Salbutamol (p.1131·2); guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Biovicam *Bioresearch, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Biovicam Ex *Bioresearch, Mex.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Biovicerin *Geyer, Braz.†.*
Bacillus cereus.
Diarrhoea.

Biovigor *IBSA, Switz.*
Hydroxocobalamin chloride; amino acids (p.1922·1).
Tonic.

Biovinate *Biomedis, Philipp.*
Carboplatin (p.693·1).
Ovarian cancer.

Biovir
Note. This name is used for preparations of different composition.
Ivax, Arg.
Adefovir dipivoxil (p.865·1).
Chronic hepatitis B.

GSK, Braz.
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Bioviraz *Bioresearch, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Biovision *Indofarma, Pol.*
Myrtillus (p.2349·3); betacarotene (p.1930·3); vitamin C (p.1983·3); vitamin B (p.1977·2); procyanidin (p.2304·1).
Vascular eye disorders.

Biovit
Note. This name is used for preparations of different composition.
Gerot, Austria.
Multivitamin preparation with iron (p.1922·1).

Biospray, Gr.
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Biovit-A *Bioceuticals, UK.*
Vitamin A (p.1971·2).

Biovital
Note. This name is used for preparations of different composition.
EMS, Braz.; Roche Consumer, Irl.†; Bayer, Pol.; Nattermann, Rus.
Multivitamin and mineral preparation (p.1922·1).
Tonic; vitamin and iron deficiencies.

Famac, Ital.
Royal jelly (p.2382·1).
Nutritional supplement.

Roche Consumer, Hung.†.
Oral solution: Ferric sodium citrate (p.1950·3); crataegus (p.2289·1); motherwort (p.2347·3); vitamins (p.1922·1).
Iron deficiency; tonic.

Roche Consumer, Hung.†.
Tablets: Ferrous sulfate (p.1939·3); ferric citrate; crataegus (p.2289·1); motherwort (p.2347·3); vitamins (p.1922·1).
Iron deficiency; tonic.

Biovital A, E + Spec B-Komplex *Roche Consumer, Hung.†.*
Multivitamin preparation (p.1922·1).

Biovital Aktiv
Note. This name is used for preparations of different composition.
Roche Consumer, Ger.†.
Oral liquid: Crataegus (p.2289·1); caffeine citrate (p.1116·3); ferrous gluconate (p.1939·1); vitamins.
Tonic.

Roche Consumer, Ger.†.
Tablets: Crataegus (p.2289·1); motherwort (p.2347·3); ferrous sulfate (p.1939·3); vitamins (p.1922·1).
Tonic.

Biovital Classic *Bad Heilbrunner, Ger.*
Crataegus (p.2289·1); motherwort (p.2347·3); ferric sodium citrate (p.1950·3); vitamins.
Tonic.

Biovital Ginseng *Bayer, Switz.*
⊗ Ginseng (p.2312·1); caffeine (p.1116·3); lecithin (p.2332·2); rutoside sodium sulfate (p.2305·2); vitamins; minerals (p.1922·1).
Tonic.

Biovital N *Bayer, Pol.*
Crataegus (p.2289·1); motherwort (p.2347·3); iron; vitamins.
Tonic.

Bio-Vitas *Kyorin, Thai.†.*
Chlorphenamine maleate (p.571·3); -methionine (p.1450·2); vitamin B substances (p.1922·1).
Skin disorders.

Biovitol-C *Bioresearch, Mex.*
Tretinoin (p.1618·1).
Skin disorders.

Biovorin *Biochem, India.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists.

Bioxan *Bioresearch, Mex.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders.

Bioxel *Bioresearch, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Bioxetin *Sanofi-Aventis, Pol.*
Fluoxetine (p.397·3).
Bulimia; depression; obsessive-compulsive disorder.

Bioxifeno *Biosintetica, Braz.*
⊗ Tamoxifen citrate (p.772·3).
Malignant neoplasms.

Bioxil *Biomep, Mex.*
Captopril (p.1239·2).
Hypertension.

Bioxilina *Northia, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Bioxilina Plus *Northia, Arg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Bioximicina *Bioresearch, Mex.*
Doxycycline (p.267·1).
Bacterial infections.

Bioximil *Bioresearch, Mex.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders.

Bioxon *Otto, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

BioXtra *Molar, UK†.*
Lactoperoxidase (p.2330·2); lactoferrin (p.2330·1); muramidase (p.2348·1); whey colostrum (p.2208·1); xylitol (p.1998·2).
Dry mouth; oral hygiene; xerostomia.

BioXtra Programme *Pamex, Irl.*
Artificial saliva, toothpaste, and mouthrinse.
Dry mouth.

Bioxyllin *Biomedis, Indon.; Medifarma, Indon.*
Amoxicillin (p.202·2).
Bacterial infections.

Bioxyol *Richard, Fr.*
Zinc oxide (p.1621·2); zinc peroxide (p.1666·3); titanium dioxide (p.1617·3).
Ulcers.

Bioyetin *Probiomed, Mex.*
⊗ Erythropoietin (p.1061·1).
Anaemias.

Biozac *Niche, Irl.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Biozendi *Roemmers Osmoph, Venez.*
Benzydamine hydrochloride (p.27·3).
Inflammation; mouth and throat disorders.

Biozidima *Biogalenic, Venez.*
Ceftazidime (p.234·1).
Bacterial infections.

Bio-Zinc *Herbaxt, Fr.*
Zinc pidolate; vitamin A; vitamin B (p.1922·1).
Nutritional supplement.

Biozirox *Biomedica-Chemica, Gr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Biozitra *BioSaude, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Biozitrom *Biofarma, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Biozole *Biolab, Malaysia; Biolab, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Biozolene *Bioindustria, Ital.†.*
Fluconazole (p.532·1).
Fungal infections.

Biozolin *Novartis, Gr.†; Sandoz, Indon.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Biozoral *Bioresearch, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Biozosin *Niche, Denm.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Bipasmin
Note. This name is used for preparations of different composition.
Anchor, Mex.
Oral drops: Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Anchor, Mex.
Tablets: Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Bipasmin Compuesto *Anchor, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Formerly contained pargeverine hydrochloride and metamizole magnesium.
Smooth muscle pain and spasm.

Bipasmin Compuesto N *Anchor, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Bipasmin Compuesto NF *Boehringer Ingelheim Promeco, Mex.†.*
Hyoscine butylbromide (p.1734·1); ibuprofen (p.64·2).
Smooth muscle pain and spasm.

Bipasmin N *Anchor, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Bipectinol *Adcock Ingram, S.Afr.*
Kaolin (p.1738·1); pectin (p.2145·2); electrolytes (p.1667·1).
Diarrhoea.

Bipencil *Biochimico, Braz.†.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Bipensaar *MIP, Ger.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Biperidys *Pierre Fabre, Fr.*
Domperidone (p.1726·2).
Nausea and vomiting.

Biphasil *Wyeth, Austral.†; Akromed, S.Afr.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Biphasic oral contraceptive; menstrual disorders.

Biphaston *Agis, Israel†.*
Dydrogesterone (p.2096·2).
Infertility; menorrhagia; menstrual disorders.

Biplatrix *BSN, Fr.*
Dried calcium sulfate (p.2273·1).
External splinting.

Bipodial *Pisa, Mex.†.*
Sodium bicarbonate; sodium chloride (p.1670·3).
Haemodialysis.

Bipolam *GSK, Austria.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Bipomax *Janssen-Cilag, Spain.*
Topiramate (p.506·2).
Epilepsy; migraine.

Bi-Pradia *Liferpal, Mex.*
Glibenclamide (p.440·1); metformin (p.453·3).
Diabetes mellitus.

Bipranix *Ashbourne, UK†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bipredonium *Danval, Spain†.*
⊗ Indapamide (p.1314·1); perindopril (p.1368·2).
Hypertension.

Bipreterax *Servier, Arg.; Therval, Fr.; Servier, Irl.; Servier, S.Afr.; Servier, Spain; Servier, Venez.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Bi-Preterax *Servier, Philipp.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Biprin *Vivax, Venez.*
Pyridoxine (p.1979·1).
Neuritis; premenstrual syndrome; vitamin B deficiency; vomiting.

Bipro *Kenyaku, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Bi-Profenid *Sanofi-Aventis, Braz.; Aventis, Cz.†; Sanofi-Aventis, Fr.; Aventis, Pol.*
Ketoprofen (p.73·1).
Inflammation; migraine; musculoskeletal, joint, and peri-articular disorders.

Biprol *Makiz-Pharma, Rus.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bipronyl *Pharmachemie, Singapore†.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Biquin *AstraZeneca, Canad.*
Quinidine bisulfate (p.1383·1).
Arrhythmias.

Biquinate *Aventis, Austral.*
Quinine bisulfate (p.612·2).
Diagnosis of myasthenia gravis; malaria; muscle cramps; myotonia congenita.

Birac *Pharmacia, Arg.†.*
Stavudine (p.907·1).
HIV infection.

Biral *Altana Madaus, S.Afr.*
Valerian (p.2410·1); passion flower (p.2363·2).
Anxiety; minor nervous disorders.

Biravid *Biex, Irl.*
Ofloxacin (p.310·2).
Bacterial infections.

Birkenkohle comp *Weleda, Austria; Weleda, Ger.*
Homoeopathic preparation.

Birley's *Torbet Laboratories, UK.*
Dried aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); light magnesium carbonate (p.1743·1).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Birodogyl *Sanofi-Aventis, Fr.*
Spiramycin (p.333·1); metronidazole (p.837·1).
Bacterial mouth infections.

Bi-Rofenid *Sanofi-Aventis, Belg.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Biron *Douglas, NZ.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Biroxol *Salus, Ital.†.*
Ciclopirox olamine (p.529·2).
Fungal infections.

Birvac *Pharmacia, Arg.†.*
Lamivudine (p.895·1).
HIV infection.

Bisacolax *Valeant, Canad.*
Bisacodyl (p.1710·1).
Constipation.

Bisakol *Yeni, Turk.*
Bisacodyl (p.1710·1).

Bisalax *Aspen, Austral.; Uniao Quimica, Braz.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Bisa-Lax *Bergen Brunswig, USA.*
Bisacodyl (p.1710·1).
Constipation.

Bisatum *Pliva, Cz.*
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Biscotto Plasmon *Plasmon, Ital.†.*
Protein, carbohydrate, and lipid preparation with minerals and vitamins (p.1922·1).
Nutritional supplement.

Bisco-Zitron *Biscova, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Bisectron *Corsalud, Venez.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Biseko
Note. This name is used for preparations of different composition.
Biotest, Austria; Biotest, Cz.†; Biotest, Ger.; Biotest, Hung.; Biotest, Thai.
⊗ A plasma protein fraction (p.1076·2).
Haemodilution; hypoalbuminaemia; hypogammaglobulinaemia; hypoproteinaemia; hypovolaemia; passive immunisation; plasma volume expansion.

Biotest, Hong Kong; Biotest, Pol.
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; hypogammaglobulinaemia; hypoproteinaemia; passive immunisation; plasma volume expansion.

Rak, Turk.
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation.

Biselic *ICN, Mex.†.*
Tripotassium dicitratobismuthate (p.1711·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Biseptine *Bayer Sante, Fr.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); benzyl alcohol (p.1631·3).
Bacterial skin infections; skin and wound disinfection.

Biseptol *Polfa, Cz.; Medana, Pol.; Polfa Pabianice, Pol.; Pabianice, Rus.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Biserol-Potassium *Bichsel, Switz.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Bisidim *Best, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

BI-Sifrol *Boehringer Ingelheim, Jpn.*
Pramipexole (p.814·2).

Bisil *Sriprasit, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Bisincof *Loeffler, Mex.*
Ambroxol hydrochloride (p.1550·3); loratadine (p.583·3).
Coughs; respiratory-tract congestion.

Biskapect *Adcock Ingram, S.Afr.*
Light kaolin (p.1738·1); apple pectin (p.2145·2); bismuth subcarbonate (p.1711·1).
Diarrhoea.

Bislan *YSP, Malaysia; Yung Shin, Singapore.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bisma Rex
Note. A similar name is used for preparations of different composition (see below).
Novartis Consumer, S.Afr.†.
Bismuth aluminate (p.1710·3); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); magnesium carbonate (p.1743·1).

Bismag *Wyeth Consumer, Singapore.*
Heavy magnesium carbonate (p.1743·1); light magnesium carbonate; sodium bicarbonate (p.1673·2).
Dyspepsia; gastric hyperacidity.

Bisma-Rex
Note. A similar name is used for preparations of different composition (see above).
3M, UK.
Bismuth subcarbonate (p.1711·1); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); magnesium carbonate (p.1743·1); peppermint oil (p.1761·2).
Dyspepsia; flatulence.

Bismatrol *Major, USA.*
Bismuth salicylate (p.1711·1).
Diarrhoea; dyspepsia; nausea.

Bismed *Technilab, Canad.†; Quimica y Farmacia, Mex.*
Bismuth salicylate (p.1711·1).
Diarrhoea; dyspepsia.

Bismofarma *Farmasa, Mex.*
Tripotassium dicitratobismuthate (p.1711·2).
Peptic ulcer.

Bismolan *Bittermedizin, Ger.†.*
Bismuth subnitrate (p.1711·2); butoxycaine hydrochloride (p.1856·3); zinc oxide (p.1621·2).
Anorectal disorders.

Bismolan H Corti *Bittermedizin, Ger.*
⊗ Prednisolone acetate (p.1541·1); bismuth oxychloride (p.1712·1); zinc oxide (p.1621·2).
Anorectal disorders.

Bismolan N *Bittermedizin, Ger.†.*
Procaine hydrochloride (p.1869·1); bismuth oxychloride (p.1712·1); zinc oxide (p.1621·2).
Anorectal disorders.

Bismomagnesie *Yeni, Turk.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).

Bismoral *Zentiva, Cz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bismorectal *Vifor, Switz.*
Bismuth succinate (p.1712·1); bismuth hydroxyquinoline (p.1712·1); eucalyptus oil (p.2301·2); sage oil (p.2382·3).
Mouth and throat disorders.

Bismu-Jet *Legrand, Braz.*
Neomycin sulfate (p.305·1); bismuth sodium tartrate (p.1712·1); menthol (p.2340·1); procaine hydrochloride (p.1869·1).
Mouth and throat disorders.

Bismultin *Rafarm, Gr.*
Econazole nitrate (p.531·1).
Fungal skin and vaginal infections.

Bismutal *Rougier, Canad.*
Bismuth camphocarbonate (p.1712·1); guaifenesin (p.1561·3).
Sore throat.

Bismuto con Pectina *Chobet, Arg.*
Bismuth hydroxide (p.1712·1); pectin (p.2145·2).
Formerly known as Bismuto Comprimidos.
Digestive disorders.

Biso *Hennig, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Biso comp *ABZ, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Biso Lich *Winthrop, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

BisoAPS *APS, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisobeta *Betapharm, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisobeta comp *Betapharm, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisobloc *Azupharma, Ger.†; Keri, Neth.†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisoblock *Extractum, Cz.; Keri, Hung.; Keri, Neth.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisocard *Polfa, Cz.; Valeant, Hung.; ICN, Pol.; Valeant, Rus.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisocombin *Kwizda, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisocor *Kwizda, Austria; Actavis, Denm.; Niche, Irl.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Bisodol
Note. This name is used for preparations of different composition.
Forest Laboratories, Port.
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence.

Forest, Irl.; SA Druggists Self Med, S.Afr.; Forest Laboratories, UK.
Oral powder: Heavy magnesium carbonate (p.1743·1); light magnesium carbonate; sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Forest, Irl.; SA Druggists Self Med, S.Afr.; Forest Laboratories, UK.
Tablets: Calcium carbonate (p.1714·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Bisodol Extra *Forest Laboratories, UK.*
Magaldrate (p.1742·3); alginic acid (p.2140·3); sodium bicarbonate (p.1673·2).
Antacid.

Bisodol Extra Strong Mint Tablets *Forest, Irl.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence; heartburn.

Bisodol Heartburn Relief *Forest Laboratories, UK.*
Alginic acid (p.2140·3); magaldrate (p.1742·3); sodium bicarbonate (p.1673·2).
Dyspepsia; heartburn.

Bisodol Wind Relief *Forest Laboratories, UK.*
Calcium carbonate (p.1714·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); simeticone (p.1770·2).
Formerly known as Bisodol Extra.
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Bisogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Rus.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisogen *Merck, Hung.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisohexal *Hexal, Ger.; Hexal, Pol.; Hexal, S.Afr.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension; ischaemic heart disease.

Bisohexal plus *Hexal, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisolangin *Boehringer Ingelheim, Austria†.*
Ambroxol hydrochloride (p.1550·3).
Sore throat.

Bisolapid *Boehringer Ingelheim, Switz.†.*
Acetylcysteine (p.1548·2).
Excess respiratory mucus.

Bisolaryn *Boehringer Ingelheim, Austria.*
Ambroxol hydrochloride (p.1550·3).
Sore throat.

Bisolax *Seng, Thai.*
Bisacodyl (p.1710·1); docusate sodium (p.1725·1); carmellose sodium (p.2142·1).
Constipation.

Bisolbruis *Boehringer Ingelheim, Neth.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased mucus.

Bisolgrip *Boehringer Ingelheim, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Catarrh; cold and influenza symptoms.

Bisolgrip T *Unilfarma, Port.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; inflammation; pain.

Bisolgripin *Boehringer Ingelheim, Neth.†.*
Aspirin (p.20·3).
Pain.

BisoLich comp *Lichtenstein, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisolnasal *Boehringer Ingelheim, Neth.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Bisolol *Rafa, Israel.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisolpent *Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Venez.†.*
⊗ Bromhexine hydrochloride (p.1552·2); orciprenaline sulfate (p.1129·1).
Asthma; bronchospasm; cough.

Bisolpent Ex *Boehringer Ingelheim Promeco, Mex.*
⊗ Bromhexine hydrochloride (p.1552·2); orciprenaline sulfate (p.1129·1).
Respiratory-tract disorders.

Bisolsinus *Boehringer Ingelheim Promeco, Mex.*
Gentian (p.2310·3); primula flower (p.2372·2); sorrel (p.2391·1); sambucus (p.2383·1); vervain (p.2413·3).
Respiratory-tract disorders.

Bisolspray *Boehringer Ingelheim, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Upper respiratory-tract congestion and inflammation.

Bisoltab *Macrophar, Thai.*
Bromhexine hydrochloride (p.1552·2).
Coughs; respiratory-tract congestion.

Bisoltus *Boehringer Ingelheim, Spain.*
Codeine hydrochloride (p.37·2).
Cough.

Bisoltussin *Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Port.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Bisolvon *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia†; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.*
Bromhexine hydrochloride (p.1552·2).
Formerly known as Bisolvon Chesty in *NZ.*
Cough; respiratory-tract congestion; Sjögren's syndrome.

Bisolvon A *Boehringer Ingelheim Promeco, Mex.*
Ampicillin trihydrate (p.204·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Bisolvon Antitusivo *Boehringer Ingelheim, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bisolvon Chesty *Boehringer Ingelheim, Austral.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bisolvon Compositum *Boehringer Ingelheim, Spain.*
⊗ Bromhexine hydrochloride (p.1552·2); codeine hydrochloride (p.37·2); diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Bisolvon Compositum NF *Boehringer Ingelheim, Arg.*
⊗ Bromhexine hydrochloride (p.1552·2); codeine hydrochloride (p.37·2); diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Bisolvon Dry *Boehringer Ingelheim, Austral.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bisolvon E *Boehringer Ingelheim Promeco, Mex.*
Bromhexine hydrochloride (p.1552·2); erythromycin ethyl succinate (p.269·3).
Respiratory-tract infections.

Bisolvon EX *Boehringer Ingelheim, Thai.*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bisolvon Extra *Boehringer Ingelheim, Indon.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cough.

Bisolvon Linctus *Boehringer Ingelheim, Switz.*
Bromhexine hydrochloride (p.1552·2); ammonium chloride (p.1551·3).
Respiratory-tract disorders.

Bisolvon Linctus DA *Boehringer Ingelheim, S.Afr.*
⊗ Bromhexine hydrochloride (p.1552·2); orciprenaline sulfate (p.1129·1).
Cough associated with wheeziness.

Bisolvon Sinus *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, NZ†.*
Bromhexine hydrochloride (p.1552·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Bisomerck *Merck, Fin.; Merck dura, Ger.; Merck, Swed.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisomerck Plus *Merck dura, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisopine *Pinewood, Irl.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisoplus *Aliud, Ger.; Stada, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisopral *Alpharma, Fin.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisoprolol comp *Ratiopharm, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisoprolol Comp *Ratiopharm, Fin.; CT, Ger.; Ratiopharm, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisoprolol HCT *Sandoz, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisoprolol Plus *1A, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisoprolol-HCT *Arcana, Austria; Ratiopharm, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisopromerck *Merck, Pol.*
⊗ Bisoprolol fumarate (p.1234·1).
Hypertension; ischaemic heart disease.

Bisoprotop *Topgen, Belg.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Biso-Puren *Alpharma-Isis, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Biso-Puren comp *Alpharma-Isis, Ger.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisoratio *Ratiopharm, Pol.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension; ischaemic heart disease.

Bisostad *Stada, Austria.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bisostad plus *Stada, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bisotyrol *Tyrol, Austria†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Bis-Pectin *Biotech, Austral.†.*
Codeine phosphate (p.37·2); kaolin (p.1738·1); aluminium hydroxide (p.1706·2); pectin (p.2145·2).
Diarrhoea.

Bisphonal *Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Incadronate disodium (p.1099·3).
Hypercalcaemia of malignancy.

Bissel 12 *Keton, Mex.*
Vitamin B (p.1980·2).

Bistatin V *Bioresearch, Mex.*
Nystatin (p.543·2).
Fungal vaginal infections.

Biston *Zentiva, Cz.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; neuralgia.

Bistrepen *Alembic, India.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Bistryl *Roux-Ocefa, Arg.†.*
Ibuprofen (p.64·2).
Fever; pain.

Bisuisan *DM, Braz.†.*
Sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); bismuth subcarbonate (p.1711·1); belladonna (p.2263·3); rhubarb (p.1768·3); menthol (p.2340·1).
Gastrointestinal hyperacidity.

Bisultrim *Biomep, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Bisval *Valdecasas, Mex.*
Bismuth salicylate (p.1711·1).
Diarrhoea; gastrointestinal hyperacidity.

Bitakebir *Aspen, Arg.*
Bicalutamide (p.686·2).

Bite & Itch Lotion *Reese, USA.*
Diphenhydramine hydrochloride (p.577·2); pramocaine hydrochloride (p.1868·1).

Bite Rx *International Lab Tech, USA.*
Aluminium acetate (p.2255·1).
Insect bites.

Bitecan AA *Cetus, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); metoclopramide (p.1747·3).
Gastrointestinal disorders.

Bitensil *Q Pharma, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Bitensil Diu *Q Pharma, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Biteral *Roche, Turk.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Bithiol *Qualiphar, Belg.*
Ichthammol (p.1599·1).
Skin disorders.

Bi-Tildiem *Sanofi-Aventis, Fr.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Bitiron *Abdi, Turk.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Hypothyroidism.

Bitobionil *SJA, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Biulan *Flupal, Venez.†.*
⊗ Bumetanide (p.1237·1).

Biureol *Plurilab, Port.*
Piperazine hydrate (p.153·1); avocado (p.2262·2); phyllanthus niruri.
Urinary-tract disorders.

Bivacyn *Medphano, Ger.†; Lek, Hong Kong; Teva, Hung.; Lek, Pol.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial eye infections; burns; otitis externa; otitis media; skin and mucous membrane infections; ulcers; urinary-tract infections; wounds.

Bivalos *Servier, Rus.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Bi-Vaspit *Asche, Ger.†.*
⊗ Fluocortin butyl (p.1532·2); isoconazole nitrate (p.536·2).
Nappy rash.

Bivate *Douglas, NZ.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Bivaxol *Ivax, Cz.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Biviol *Organon, Ger.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Bivitasi *Kedrion, Ital.†.*
Cocarboxylase hydrochloride (p.1975·2).
Vitamin B deficiency.

Bivitox *Terapeutico, Ital.†.*
Cogalactoisomerase disodium (p.2285·3).
Liver disorders.

Bivorilan *Medinova (Μεντινοβα), Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bixen *Biomep, Mex.*
Naproxen (p.92·3).
Pain.

Bixon *Biores, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

B-Ject *Hyrex, USA†.*
Vitamin B substances (p.1922·1).
Parenteral nutrition.

B-Jen *Lafedar, Arg.*
Permethrin (p.2048·2).
Pediculosis.

BK
Note.This name is used for preparations of different composition.
3M, NZ†.
Liquid soap: Lactic acid (p.2329·3).
Soap substitute in skin disorders.

3M, NZ.
Lotion: Liquid paraffin (p.2030·3); oil-soluble dewaxed lanolin fraction (p.2033·2).
Dry skin disorders; pruritus.

BK HC *3M, NZ.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

B-kombin *Leiras, Fin.†; ACO, Swed.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

B-Komplex *Zentiva, Cz.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

B-Komplex forte *Hevert, Ger.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

B-Laboterol *Labomed, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections with inflammation.

Black Forest *Novartis Consumer, S.Afr.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Black Seed *Be-Tabs, S.Afr.†.*
Nutritional supplement (p.1922·1).

Blackcurrant Coldrex Hot *GSK Consumer, Hung.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Black-Draught
Note.This name is used for preparations of different composition.
Chattem, USA†.
Syrup: Casanthranol (p.1715·1); senna (p.1769·2); rhubarb (p.1768·3).
Constipation.

Chattem, USA.
Tablets: Senna (p.1769·2).
Constipation.

Blackmores B Plus C *Blackmores, Thai.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B deficiency; vitamin C deficiency.

Blackmores Bio *Blackmores, Thai.*
A range of vitamin preparations with or without minerals (p.1922·1).

Blackmores Exec B's *Blackmores, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Blackmores Naturetime Buffered C *Blackmores, Thai.*
Calcium ascorbate; ascorbic acid; bioflavonoids; rutin; hesperidin; rose fruit (p.1983·3).

Blacor *LKM, Arg.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Bladder Irritation *Hylands, Canad.*
Homoeopathic preparation.

Bladderon *Shinyaku, Jpn.*
Flavoxate hydrochloride (p.2190·1).
Pollakisuria.

Blader *Fada, Arg.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Bladex *Pharma Investi, Chile†.*
Ibuprofen (p.64·2).
Fever.

Bladiron *Anfarm, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Bladuril *Casasco, Arg.; Tecnofarma, Chile; Aventis, Mex.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Blahungstee N *Abtswinder, Cz.†.*
Aniseed (p.2258·2); fennel (p.2302·3); peppermint leaf (p.1761·2); caraway (p.2276·3); melissa (p.2339·3); cinnamon (p.2283·1); centaurea cyanus; calendula (p.2273·1).
Digestive disorders.

Blairex Lens Lubricant *Blairex, USA.*
Range of solutions for soft contact lenses (p.1622·2).

Blamy *Duncan, Arg.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2); miconazole (p.541·2).
Infected skin disorders.

Blanc Dient *Bernabo, Arg.*
Urea hydrogen peroxide (p.1666·2).
Dental whitener.

Blancaler
Note.This name is used for preparations of different composition.
Galderma, Mex.
Cream: Titanium dioxide (p.1617·3).
Skin hyperpigmentation.

Galderma, Mex.
Topical gel: Achillea (p.2245·2).
Skin hyperpigmentation.

Blanel *Pfleger, Ger.*
Potassium sodium hydrogen citrate (p.1674·2).
Renal calculi.

Blanoxan *BMS, Mex.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Blasen- und Nierentee *Abtswinder, Cz.†.*
Bearberry (p.2263·3); phaseolus; equisetum (p.2299·3); birch leaf (p.2266·3); peppermint leaf (p.1761·2); liquorice (p.1740·3); calendula (p.2273·1).
Kidney and bladder disorders.

Blasentee St Severin *Smetana, Austria.*
Birch leaf (p.2266·3); herniaria (p.2319·1); equisetum (p.2299·3); calluna vulgaris.
Formerly known as Blasentee EF-EM-ES.
Kidney and bladder disorders.

Blastivin *Pharmachemie, Neth.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Blastocarb *Laboratorios Chile, Chile†; Lemery, Mex.; Lemery, Rus.; Lemery, Thai.*
Carboplatin (p.693·1).
Malignant neoplasms.

Blastoestimulina
Note.This name is used for preparations of different composition.
Almirall, Spain†.
Eye drops: Centella (p.1592·3).
Eye disorders.

Almirall, Spain.
Ointment: Centella (p.1592·3); neomycin sulfate (p.305·1).
Burns; skin infections; ulcers; wounds.

Almirall, Spain.
Pessaries: Centella (p.1592·3); miconazole nitrate (p.541·3); metronidazole (p.837·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Vulvovaginal infections.

Almirall, Spain.
Topical aerosol: Centella (p.1592·3); tetracaine (p.1871·2).
Burns; ulcers; wounds.

Almirall, Spain.
Topical powder: Centella (p.1592·3).
Burns; ulcers; wounds.

Blastoferon *Sidus, Arg.*
Interferon beta (p.891·2).
Multiple sclerosis.

Blastolem *Laboratorios Chile, Chile; Lemery, Mex.; Lemery, Rus.; Lemery, Thai.*
Cisplatin (p.698·2).
Malignant neoplasms.

Blaston *Lacer, Spain.*
Cinitapride acid tartrate (p.1720·3).
Gastro-oesophageal reflux; gastroparesis.

Blastop *TRB, Arg.*
Folic acid (p.1940·1); vitamin B (p.1978·2); vitamin B (p.1980·2).
Atherosclerosis; cerebrovascular disorders; dietary supplement; hyperhomocysteinaemia.

Blastovin *Teva Tuteur, Arg.; Teva, Israel.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Blaubimax *Blausiegel, Braz.*
⊗ Albumin (p.1052·1).
Plasma volume expansion.

Blaubumin *Blausiegel, Braz.†.*
⊗ Albumin (p.1052·1).
Plasma volume expansion.

Blauferon *Blausiegel, Braz.*
Interferon alfa-2b (p.885·1).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Blauimuno *Blausiegel, Braz.†.*
Immunoglobulin (p.2225·3).

Blavin *Baliarda, Arg.*
Terazosin (p.1410·3).
Benign prostatic hyperplasia.

Blecidex *Sanbe, Indon.*
⊗ Neomycin sulfate (p.305·1); gramicidin (p.286·1); dexamethasone sodium metasulfobenzoate (p.1526·2).
Infected eye disorders; otitis externa.

Bledilait *Bledina, Fr.*
A range of infant feeds (p.1922·1).
Allergic disorders; diarrhoea; regurgitation.

Bledstop *Caprifarmindo, Indon.; Sanbe, Indon.*
Methylergometrine maleate (p.2011·1).
Management of third-stage labour; uterine haemorrhage.

Bleduran *Anpharm (Ανφαρμ), Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Blef-10 *Allergan, Mex.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Blefamide
Note.This name is used for preparations of different composition.
Allergan, Arg.
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Allergan, Mex.
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Eye disorders.

Allergan, Chile.
Eye drops: ⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Allergan, Chile.
Eye ointment: ⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Eye disorders.

Blefamide-F *Allergan, Mex.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Blefarida *Alcon Cusi, Spain.*
⊗ Chloramphenicol (p.239·3); cortisone acetate (p.1524·2).
Infected eye disorders.

Blefarolin *Bruschettini, Ital.*
Tannic acid (p.2394·3); resorcinol (p.1612·1); menthol (p.2340·1).
Eye disorders.

Blefarosan *Lersan, Arg.*
Sulfathiazole sodium (p.343·3).
Bacterial eye infections.

Blemaren *Esparma, Rus.*
Citric acid (p.2284·1); sodium citrate (p.1673·3); potassium bicarbonate (p.1673·1).
Hyperuricaemia; porphyria cutanea tarda; renal calculi.

Blemaren N
Esparma, Cz.
Citric acid (p.2284·1); sodium citrate (p.1673·3); potassium bicarbonate (p.1673·1).
Hyperuricaemia; porphyria cutanea tarda; renal calculi.

Esparma, Ger.; Esparma, Hung.
Citric acid (p.2284·1); anhydrous sodium citrate (p.1673·3); potassium bicarbonate (p.1673·1).
Hyperuricaemia; porphyria cutanea tarda; renal calculi.

Bleminol *Gepepharm, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Blemish Control *Kay, Canad.*
Salicylic acid (p.1612·2).
Acne.

Blemix *Ashbourne, UK†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Blenamax *Sigma, Austral.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Teva, Rus.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Blend-a-Med *Procter & Gamble, Cz.†.*
Sodium phosphate (p.1682·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth.

Blendera *Otsuka, Thai.*
Preparation for enteral nutrition (p.1922·1).

Blendox *Degorts, Mex.*
Chlorphenamine (p.572·2).

Blenox *Antibioticos, Spain.*
⊗ Amoxicillin (p.202·2).
Probenecid (p.558·2) is included in this preparation to reduce renal tubular excretion of amoxicillin.
Bacterial infections.

Blenoxane *BMS, Austral.; BMS, Braz.; Bristol, Canad.; BMS, NZ; BMS, Philipp.; BMS, S.Afr.; BMS Oncology, USA.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleo *Kyowa, UK.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleo-cell *Cell Pharm, Ger.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleochem *Biochem, India.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleocin
Kayaku, Cz.; Vianex (Βιανεξ), Gr.; Kayaku, Hong Kong; Kayaku, Hung.; Khandelwal, India; Kalbe, Indon.; Kayaku, Indon.; Kayaku, Jpn; Kayaku, Singapore; Masu, Thai.; Onko, Turk.
Bleomycin hydrochloride (p.688·2).
Malignant neoplasms.

Kayaku, Malaysia; Euro Nippon Kayaku, Pol.
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleocip *Cipla, India.*
Bleomycin (p.688·2).
Malignant neoplasms.

Bleocris *LKM, Arg.*
Bleomycin (p.688·2).
Malignant neoplasms.

Bleolem *Lemery, Mex.; Key Oncologics, S.Afr.; Lemery, Thai.; Atafarm, Turk.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleomedac *Medac, Ger.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bleomin *Teva, Belg.*
Bleomycin (p.688·2).
Malignant neoplasms.

Bleo-S *Kayaku, Jpn; Masu, Thai.*
Bleomycin sulfate (p.687·1).
Skin cancer.

Bleph-10 *Allergan, Austral.; Allergan, Hong Kong; Allergan, NZ; Allergan, Thai.†; Allergan, USA.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Blephagel *Pfizer, Arg.; Allergan, Braz.; Thea, Fr.; Thea, Philipp.; Pfizer, Singapore; Pfizer, Venez.*
Eyelid cleanser.

Blephamid *Abdi, Turk.*
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Blephamide
Note.This name is used for preparations of different composition.
Allergan, Canad.; Allergan, Ger.; Allergan, Switz.; Allergan, USA.
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Blepharitis; conjunctivitis; eye disorders; eye infections; eye inflammation with bacterial infection.

Alvia (Αλβια), Gr.†; Allergan, Hong Kong; Allergan, Malaysia†; Allergan, Singapore.
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Blepharitis; conjunctivitis.

Allergan, Israel; Allergan, NZ.
Eye drops: ⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Blepharitis; conjunctivitis.

Allergan, Israel.
Eye ointment: ⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Blephasol *Pharmacia, Singapore†.*
Eyelid cleanser.

BLES *Bles, Canad.*
Bovine lipid extract surfactant (p.2375·3).
Neonatal respiratory distress syndrome.

Blesifen *Sanbe, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Blexit *Laboratorios Chile, Chile.*
Bleomycin (p.688·2).
Malignant neoplasms.

Blezamont *Farmanic, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Blindafe *Nucitec, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Blink *Advanced Medical Optics, UK.*
Polyvinyl alcohol (p.2145·3); sodium chloride (p.1686·1) (p.1622·2).
Dry eyes in contact lens wearers.

Blink Contacts
Amo, Arg.; Visiontech, Arg.
Sodium hyaluronate (p.2320·1); OcuPure.
Dry eyes.

AMO, Austral.
Sodium hyaluronate (p.2320·1); Ocupure (p.1622·2).
Lubricating drops for contact lenses.

Blink-N-Clean
Note.This name is used for preparations of different composition.
Amo, Arg.; Visiontech, Arg.
Cleansing drops for contact lenses (p.1622·2).

AMO, Austral.
⊗ Hypromellose (p.2144·2); tyloxapol (p.1921·3); trometamol (p.2405·1) (p.1622·2).
Cleansing and lubrication of contact lenses.

Blinx *Pilkington Barnes-Hind, USA.*
Electrolytes (p.1667·1).
Eye irrigation.

Blio *Mayne, Port.†.*
Bleomycin sulfate (p.687·1).

Blis K12 Throat Guard *Blis, NZ.*
Streptococcus thermophilus (p.2372·3).
Restoration of normal throat bacterial flora.

Blisprotex *Rider, Chile.*
Zinc oxide (p.1621·2); dimeticone (p.2032·1).
Nappy rash.

BlisterGard *Medtech, USA.*
Topical barrier preparation.

Blistex
Note.This name is used for preparations of different composition.
Rider, Chile.
Phenol (p.1656·1); camphor (p.2273·2).
Chapped lips.

Pharmaceutical Enterprises, S.Afr.
Allantoin (p.1588·1); phenol (p.1656·1); camphor (p.2273·2); menthol (p.2340·1).
Dry lips; herpes labialis.

Blistex, USA.
Camphor (p.2273·2); phenol (p.1656·1); allantoin (p.1588·1).
Oral lesions.

Blistex Complete Moisture *Blistex, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Blistex DCT Lip Balm *Blistex, Canad.*
SPF 20: Octinoxate (p.1608·2); oxybenzone (p.1608·3); menthol (p.2340·1); phenol (p.1656·1); camphor (p.2273·2).
Chapped lips; sunscreen.

Blistex Fruit Smoothies *Rider, Chile.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Blistex Fruit Smoothies Lipbalm *Blistex, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Blistex Herbal Answer *Blistex, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Blistex Herbal Lip Protector *Key, Austral.*
SPF 16: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Blistex Lip Balm
Note.This name is used for preparations of different composition.
Blistex, Canad.
SPF 10: Padimate O (p.1609·1); oxybenzone (p.1608·3); dimeticone (p.2032·1).
Chapped lips; sunscreen.

Blistex, USA.
SPF 10: Camphor (p.2273·2); phenol (p.1656·1); allantoin (p.1588·1); dimethicone (p.2032·1); padimate O (p.1609·1); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Blistex Lip Conditioner *Key, Austral.*
SPF 16: Octinoxate (p.1608·2); padimate O (p.1609·1).
Sunscreen.

Blistex Lip Medex *Blistex, Canad.*
Menthol (p.2340·1); camphor (p.2273·2); phenol (p.1656·1).
Chapped lips; cold sores.

Blistex Lip Ointment *Blistex, Hong Kong†.*
Allantoin (p.1588·1); camphor (p.2273·2); phenol (p.1656·1); menthol (p.2340·1).
Chapped lips; herpes labialis.

Blistex Lip Revitalizer *Key, Austral.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Dry lips; sunscreen.

Blistex Lip Tone *Key, Austral.*
SPF 18: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Dry lips; sunscreen.

Blistex Medicated Lip Balm *Key, Austral.*
SPF 16: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Dry lips; sunscreen.

Blistex Medicated Lip Conditioner *Key, Austral.*
SPF 20: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Dry lips; sunscreen.

Blistex Medicated Lip Conditioner Jar *Blistex, Canad.†.*
SPF 15: Camphor (p.2273·2); menthol (p.2340·1); meradimate (p.1604·2); octinoxate (p.1608·2); phenol (p.1656·1).
Chapped lips; herpes labialis.

Blistex Medicated Lip Ointment
Note.This name is used for preparations of different composition.
Blistex, Canad.
Allantoin (p.1588·1); camphor (p.2273·2); phenol (p.1656·1).
Chapped lips; herpes labialis.

Key, Austral.
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3); allantoin (p.1588·1); camphor (p.2273·2).
Dry lips; sunscreen.

Blistex Relief Cream *DDD, UK.*
Strong ammonia solution (p.2256·1); ammonia solution aromatic; phenol (p.1656·1).
Formerly known as Blisteze.
Chapped and cracked lips; herpes labialis.

Blistex Silk and Shine Lipbalm *Blistex, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Blistex Ultra Lip Balm *Key, Austral.*
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); meradimate (p.1604·2); homosalate (p.1598·1).
Dry lips; sunscreen.

Blistex Ultra Protection *Blistex, USA.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); meradimate (p.1604·2); homosalate (p.1598·1).
Sunscreen.

Blistex Ultra Protection Lip Balm *Blistex, Canad.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); meradimate (p.1604·2); homosalate (p.1598·1); dimeticone (p.2032·1).
Chapped lips; sunscreen.

Blistik *Rider, Chile.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Blis-To-Sol
Note.This name is used for preparations of different composition.
Oakhurst, USA.
Topical liquid: Tolnaftate (p.548·3).
Fungal skin infections.

Oakhurst, USA.
Topical powder: Zinc undecenoate (p.549·3).
Fungal skin infections.

Bliz *Grisi, Mex.*
Boldo (p.2267·2).
Constipation.

Blizer *Ibirn, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Blocacid
Note.This name is used for preparations of different composition.
Ipca, India†; IPCA, Singapore†.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Collins, Mex.
Naproxen (p.92·3); carisoprodol (p.1894·1).
Inflammation; pain.

Blocadren *MSD, Austria; MSD, Belg.; SIT, Ital.; MSD, Mex.; MSD, Norw.; MSD, Port.†; MSD, Swed.; Merck, USA.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; arrhythmias; glaucoma; heart failure; hypertension; migraine; myocardial infarction; ocular hypertension.

Blocalcin *Lachema, Cz.; Pliva, Hung.; Pliva Lachema, Pol.; Lachema, Rus.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Blocamicina *Gador, Arg.*
Bleomycin hydrochloride (p.688·2).
Malignant neoplasms.

Blocanol *MSD, Fin.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; glaucoma; hypertension; migraine; myocardial infarction; ocular hypertension.

Blocar *Bago, Chile.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Blocatens *Unipharma, Gr.*
⊗ Bisoprolol (p.1234·2).
Hypertension.

Blocatril *Tecnofarma, Mex.*
Enalapril (p.1276·1).
Hypertension.

Blocksol *Albephar, Venez.*
Octinoxate (p.1608·2); titanium dioxide (p.1617·3); oxybenzone (p.1608·3).
Sunscreen.

Blocotenol *Azupharma, Ger.†; Sandoz, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Blocotenol comp *Azupharma, Ger.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Bloculcer *Labesfal, Port.*
Ranitidine hydrochloride (p.1766·1).

Blodex *Estedi, Spain†.*
Vegetable oil (p.2413·1).
Adjunct in cholecystography and cholangiography.

Bloflex *Blooming Fields, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Bloicin-S *Korea United, Philipp.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bloken *Degorts, Mex.*
Phenylbutazone (p.117·1).
Inflammation; pain.

Blokium
Note.This name is used for preparations of different composition.
Casasco, Arg.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Prodes, Hung.; Almirall, Port.†; Romofarm, Spain; Gentek, Venez.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Blokium B12 *Casasco, Arg.*
⊗ Diclofenac potassium (p.44·3); betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Musculoskeletal and joint disorders.

Blokium Cox *Casasco, Arg.†.*
Rofecoxib (p.121·1).
Osteoarthritis; pain.

Blokium Diu *Prodes, Hung.; Probios, Port.†; Romofarm, Spain.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Blokium Flex *Casasco, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Blokium Gesic *Casasco, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Blokiuret *Gentek, Venez.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Blonax *Mintlab, Chile.*
Clonixin lysine (p.37·1).
Pain.

Blood Builder *Nutrifarma, Turk.*
Iron (p.1949·1); vitamin B (p.1980·2); folic acid (p.1940·1).

Blootec *Ibfarma, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Bloprazol *Fresenius Kabi, Port.*
Omeprazole sodium (p.1753·1).

Blopresid *Takeda, Ital.; Euro Registratie, Neth.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Blopress *Takeda, Austria; Abbott, Braz.; Abbott, Chile; Grunenthal, Cz.†; Takeda, Ger.; Takeda, Hong Kong; Takeda, Indon.; Takeda, Ital.; Takeda, Jpn; Takeda, Malaysia; Abbott, Mex.; Euro Registratie, Neth.; Takeda, Philipp.; Seber, Port.; Takeda, Spain; Takeda, Switz.; Takeda, Thai.; Abbott, Venez.*
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension; left-ventricular dysfunction.

Blopress Comp *Seber, Port.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Blopress D *Abbott, Chile.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Blopress 16 mg + 12,5 mg *Seber, Port.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Blopress Plus *Takeda, Austria; Takeda, Ger.; Takeda, Hong Kong; Takeda, Indon.; Abbott, Mex.; Takeda, Philipp.; Takeda, Switz.; Takeda, Thai.; Abbott, Venez.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Blosyn *Gufic, India.*
⊗ Haemoglobin (p.1072·3); ferric ammonium citrate (p.1938·1); vitamin B (p.1980·2); vitamin B (p.1979·1) folic acid (p.1940·1).
Anaemias.

Blotex *Sandoz, Mex.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

B-Lovatin *Medicus, Gr.†.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Blow-X *T Man, Thai.*
Simeticone (p.1770·2).
Excess gastrointestinal gas.

Blox *Saval, Chile.*
Candesartan cilexetil (p.1238·3).
Hypertension.

Bloxang *Chauvin, Fr.*
⊗ Gelatin (porcine) (p.1072·1).
Haemostatic.

Blox-D *Saval, Chile.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Bluboro *Allergan Herbert, USA†.*
Aluminium sulfate (p.2255·1); calcium acetate (p.1675·2).
Bruises; skin inflammation.

Bluco *Hua, Thai.*
Codeine phosphate (p.37·2); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Bluderm *Quimioterapica, Braz.†.*
Boric acid (p.2268·1); glycerol (p.2314·2); quillaia (p.1920·1).
Skin disinfection.

Blue *Ambix, USA; Moore, USA.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Blue Caps *SM, Venez.*
Pyrithione zinc (p.1611·2).
Skin disorders.

Blue Ice Gel *Geritrex, USA.*
Menthol (p.2340·1); isopropyl alcohol (p.1650·3).

Blue Patent *Guerbet, Israel.*
Dye for contrast media.

Bluesteril *IMS, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection.

Bluetest *Delta, Fr.†.*
Pregnancy or fertility test (p.2372·1).

Blueye *Sam Chun Dang, Hong Kong.*
Hypromellose (p.2144·2).
Dry eyes.

Blum *Ahimsa, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Blumen *Luper, Braz.†.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Barrier preparation; skin disorders.

Blumol *Farmanic, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Bluna *Faes, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Blustark *Savio, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Blutwurz *Ratiopharm, Ger.*
Tormentil (p.2403·2).
Diarrhoea.

BM Lactato *Roche, Arg.*
Test for lactic acid in blood.

BM-Accutest *Roche Diagnostics, Irl.; Roche Diagnostics, UK.*
Test for glucose in blood (p.2314·1).
For use with Accutrend blood glucose meters.

BM-Test 1-44 *Roche Diagnostics, Irl.†; Roche Diagnostics, NZ†; Roche Diagnostics, UK.*
Test for glucose in blood (p.2314·1).
Formerly known as BM-Test Glycemie 1-44.

BM-Test BG *Roche Diagnostics, Austral.*
Test for glucose in blood (p.2314·1).

BM-Test Glycemie *Roche Diagnostics, Fr.†.*
Test for glucose in blood (p.2314·1).

BM-Test Glycemie 20-800 *Roche Diagnostics, Austral.*
Test for glucose in blood (p.2314·1).

BM-Test GP *Roche Diagnostics, Austral.*
Test for glucose and protein in urine.

B-Mycin *YSP, Malaysia.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

BN 53 *Staufen, Ger.†.*
Homoeopathic preparation.

BN dolo *Staufen, Ger.*
Homoeopathic preparation.

BNIL *Millimed, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

BNP Ointment *Vendiz, Philipp.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected skin disorders.

Bobodent *Hasco-Lek, Pol.*
Chamomile (p.2279·3); thyme (p.2401·1); lidocaine hydrochloride (p.1862·3).
Mouth disorders.

Bobotic *Medana, Pol.*
Simeticone (p.1770·2).
Excess gastrointestinal gas; preparation for gastrointestinal procedures.

Bo-Cal *Fibertone, USA†.*
Calcium with vitamins B and D, and magnesium (p.1922·1).

Bocasan *Gillette, Neth.*
Sodium perborate (p.1662·1).
Mouth disorders.

Bocatriol *Leo, Austria; Leo, Denm.; Leo, Ger.; Leo, Switz.†.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency.

Bocytin *Asian Pharm, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Bo-D-Fense *Green Leaf, Philipp.*
Andrographis; ginger (p.1732·3); black pepper (p.2364·3); vitamin C (p.1983·3); zinc gluconate (p.1999·2).
Upper respiratory-tract disorders.

Bodi Care Lotion *Geritrex, USA.*
Liquid paraffin (p.2030·3); soft paraffin (p.2031·2).
Dry skin.

Bodi Kleen *Geritrex, USA.*
Trolamine laurilsulfate (p.2138·3); phenoxyethanol (p.1657·1); hexylene glycol (p.2319·1); aloe vera (p.1588·2).

Bodi Line Action *Geritrex, USA.*
⊗ Alcohol (p.1625·2).
Hand cleanser.

Bodi Oil *Geritrex, USA.*
Liquid paraffin (p.2030·3); lanolin oil (p.2033·2); aloe vera oil.
Dry skin.

Bodi Protect *Geritrex, USA.*
Barrier ointment.

Bodisan *Medinfar, Port.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bodivitin *Hua, Thai.*
Multivitamin preparation with calcium (p.1922·1).

Bodrex *Tempo Scan Pacific, Indon.*
Caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Bodrex Forte *Tempo Scan Pacific, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Bodrexin
Note. This name is used for preparations of different composition.
Bode, Indon.; Tempo Scan Pacific, Indon.
Syrup: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Cold and influenza symptoms; cough.

Tempo Scan Pacific, Indon.
Tablets: Aspirin (p.20·3).
Fever; pain.

Body Peel *Lierac, Fr.*
⊗ Salicylic acid (p.1612·2); glycolic acid (p.1598·1); urea (p.1620·2).
Sun-induced skin damage.

Body Rox *Usana, Hong Kong†.*
A multivitamin and mineral preparation with bioflavonoids (p.1922·1).

Body Smarts *Adams, Canad.†.*
Vitamin or mineral preparations (p.1922·1).

Body-Calcin *Unipharma, Gr.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Bodyguard *Sanitalia, Ital.*
Echinacea (p.2298·1); salix (p.121·3); devil's claw root (p.39·1); propolis (p.2373·3).
Nutritional supplement.

Boestrol *Antigen, Irl.*
Diethylstilbestrol (p.2094·1).
Breast cancer; prostatic cancer.

Boflavin *Milano, Thai.*
Riboflavin (p.1977·2).
Vitamin B deficiency.

Bofutsushosan *Tsumura, Jpn.*
Scutellaria root; liquorice; platycodon root; gypsum; atractylodes rhizome; rhubarb; schizonepeta spike; gardenia fruit; peony root; cnidium rhizome; Japanese angelica root; mentha; saposhnikovia root; ephedra; forsythia fruit; ginger; talc; mirabilitum.
Traditional Kampo medicine.

Boi K *BOI, Spain.*
Potassium ascorbate (p.1685·1).
Potassium depletion.

Boi K Aspartico *BOI, Spain.*
Potassium ascorbate (p.1685·1).
Potassium depletion.

Boi K Gluconato *BOI, Spain.*
Potassium gluconate (p.1684·3).
Hypokalaemia.

Boie Carminative (Carminasen) *Boie, Philipp.*
Liquorice (p.1740·3); rhubarb (p.1768·3); senna (p.1769·2).
Colic; flatulence; gastrointestinal spasm; indigestion.

Boil Ease
Note. This name is used for preparations of different composition.
Del, Canad.†.
Benzocaine (p.1854·1); ichthammol (p.1599·1); sulfur (p.1614·1); cade oil (p.1616·1); camphor (p.2273·2); phenol (p.1656·1); zinc oxide (p.1621·2); thymol (p.1664·3).

Commerce, USA; Del, USA.
Benzocaine (p.1854·1); ichthammol (p.1599·1); sulfur (p.1614·1); cade oil (p.1616·1); camphor (p.2273·2); phenol (p.1656·1); zinc oxide (p.1621·2); thymol (p.1664·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Boils.

Boi-ogi-to *Tsumura, Jpn.*
Astragalus root; sinomenium stem; atractylodes lancea rhizome; jujube; liquorice; ginger.
Traditional Kampo medicine.

Bokey *Yung Shin, Hong Kong; Yung Shin, Singapore.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Bo-Lax *Cipla, India.*
Bisacodyl (p.1710·1).
Constipation.

Bolbamox *Sons, Mex.†.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Bolbasalt *Bajamed, Mex.†.*
⊗ Salbutamol (p.1131·2).
Asthma.

Bolchipen *Cruz, Spain†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bolcitol *Lesourd, Fr.*
Fumitory (p.2307·2); boldo (p.2267·2); sage (p.2382·3); fennel (p.2302·3).
Biliary disorders; gastrointestinal disorders; kidney disorders.

Boldaloin *Herbapol Wroclaw, Pol.*
Aloes (p.1705·2); boldine (p.2267·3).
Constipation; digestive disorders; liver and biliary-tract disorders.

Boldex *Potter's, UK.*
Taraxacum (p.2395·1); butternut bark; boldo (p.2267·2); bladderwrack (p.2384·2).
Slimming aid.

Boldina *Plata, Arg.*
Boldo (p.2267·2); carqueja; cynara (p.2291·2).
Liver disorders.

Boldina He *Teofarma, Ital.*
Boldine (p.2267·3); aloin (p.1705·3).
Constipation.

Boldocynara *Bioforce, Switz.*
Cynara (p.2291·2); taraxacum (p.2395·1); boldo (p.2267·2); peppermint leaf (p.1761·2).
Formerly contained cynara, silybum marianum, taraxacum, boldo, and peppermint leaf.
Digestive disorders.

Boldolaxin *Diviser Aquilea, Spain†.*
Belladonna (p.2263·3); bisacodyl (p.1710·1); boldo leaves (p.2267·2); calcium phosphate (p.1676·2); docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Boldopeptan *Neo Quimica, Braz.†.*
Cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3); liver extract (p.2337·3).
Liver disorders.

Boldovera *Aflofarm, Pol.*
Aloes (p.1705·2); fumitory (p.2307·2); boldine (p.2267·3).
Constipation; digestive disorders; gastrointestinal spasm.

Bolidol *Kern, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Bolinan *Bayer Sante, Fr.*
Povidone (p.2146·1).
Gastrointestinal disorders.

Bolinet *BMS, Pol.*
Ibuprofen (p.64·2).
Fever; pain.

Bolisegna *Rafarm, Gr.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory disorders associated with viscous mucus.

Boljuprima *Prima, Braz.†.*
Boldo (p.2267·2); solanum paniculatum.
Biliary-tract disorders.

Bollinol *Viofar, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Boloxen *Kato, Pol.*
Naproxen sodium (p.92·3).
Fever; pain.

Boltin *Organon, Spain.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Bolus Adstringens *EGIS, Hung.*
Albumin tannate (p.1704·2); bismuth subgallate (p.1711·1); kaolin(p.1738·1).
Gastrointestinal disorders.

Bolus alba comp *Wala, Ger.*
Homoeopathic preparation.

Bolus Eucalypti Comp
Note. This name is used for preparations of different composition.
Weleda, Austria; Weleda, UK.
Homoeopathic preparation.

Weleda, S.Afr.
Apis (p.2258·3); belladonna (p.2263·3); eucalyptus leaf (p.2301·2); kaolin (p.1738·1).
Mouth and throat disorders.

Bolus Laxans *EGIS, Hung.*
Rhubarb (p.1768·3); sulfur (p.1614·1); senna (p.1769·2); kaolin (p.1738·1).
Constipation; dyspepsia; flatulence; meteorism.

Bolutol *Farmasierra, Spain†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Boma *Ogna, Ital.*
Borax (p.2268·1); benzocaine (p.1854·1).
Nausea; oral hygiene.

Bomacorin *Hevert, Ger.*
Crataegus (p.2289·1).
Heart failure.

Bomagall mono *Hevert, Ger.†.*
Fumitory (p.2307·2).
Biliary-tract spasm; gastrointestinal spasm.

Bomagall N *Hevert, Ger.*
Homoeopathic preparation.

Bomaklim *Hevert, Ger.†.*
Homoeopathic preparation.

Bomaklim Complex *Hevert, Ger.*
Homoeopathic preparation.

Bomapect *Hevert, Ger.*
Homoeopathic preparation.

Bomarthros *Hevert, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Bomex *YSP, Malaysia; Yung Shin, Singapore†.*
Brompheniramine maleate (p.569·2).
Hypersensitivity reactions.

Bomexin *Pond's, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bomine
Note. This name is used for preparations of different composition.
Mayo, Mex.
Dimenhydrinate (p.576·2); pyridoxine (p.1979·1).
Nausea and vomiting.

Pharmasant, Thai.
Brompheniramine maleate (p.569·2).
Allergic rhinitis.

Bomix *Bode, Ger.*
Clorophene (p.1641·1); orthophenylphenol (p.1655·1); chlorocresol (p.1640·1).
Instrument disinfection.

Bomvital *Diamond, Philipp.*
Vitamins; lysine; lecithin; calcium carbonate; omega 3-fatty acid; Chlorella growth factor (p.1922·1).
Nutritional supplement.

Bonadoxina *Pfizer, Mex.; Pfizer, Venez.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Lidocaine (p.1862·3) is included in the injection to alleviate the pain of injection.
Nausea and vomiting; vertigo.

Bonair *Solara, Mex.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Bonalen
Note. This name is used for preparations of different composition.
Uniao Quimica, Braz.; Ingers, Cz.
Alendronate sodium (p.1088·1).
Osteoporosis.

Vitae, Mex.
Meclozine (p.585·1); pyridoxine (p.1979·1).
Nausea and vomiting.

Bonalet-Cee *Am-Europharma, Philipp.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Bonalfa *White, Arg.†; Schering-Plough, Chile; Teijin, Jpn; Schering-Plough, Mex.; Isdin, Port.; Isdin, Spain; Schering-Plough, Venez.†.*
Tacalcitol (p.1615·1).
Ichthyosis; psoriasis.

Bonalon *Teijin, Jpn.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Bonamina *Pfizer, Chile.*
Meclozine hydrochloride (p.584·3).
Nausea and vomiting; vertigo.

Bonamine *Pfizer Consumer, Canad.; Pfizer, Philipp.*
Meclozine hydrochloride (p.584·3).
Nausea; vertigo; vestibular disorders; vomiting.

Bonanoti *Novag, Mex.*
Diphenhydramine (p.577·1).
Insomnia.

Bonapetit *Sinterapico, Braz.†.*
Cyproheptadine hydrochloride (p.575·1); vitamins (p.1922·1).
Reduced appetite.

Bonaplatin *Baxter, Philipp.*
Carboplatin (p.693·1).
Malignant neoplasms.

Bonar *Biosintetica, Braz.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Bonasanit *Biokanol, Ger.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Bonat *Roche, Israel.*
Ibandronate sodium (p.1098·3).
Prevention of skeletal events associated with breast cancer and bone metastases.

Bonatol-R *Coup, Gr.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal and joint disorders; pain.

Bonaven
Note. This name is used for preparations of different composition.
Medihealth, Mex.
Avena (p.2262·1); sodium cocoyl isetionate (p.2138·3).
Skin cleanser.

Roemmers Medihe, Venez.
Soap substitute with avena (p.2262·1).

Bonazin *Collins, Mex.*
Pyridoxine (p.1979·1); meclozine (p.585·1).
Nausea and vomiting.

Boncilin *Rowe-Fleming, Venez.†.*
Chlorphenamine maleate (p.571·3); sodium salicylate (p.124·2).
Influenza symptoms.

Boncol *Sojar, Arg.*
Phytoestriols.
Hypercholesterolaemia.

Boncordin *Sandoz, Arg.†.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Bondenza *Roche, Cz.; Roche, Neth.; Roche, Port.*
Ibandronate sodium (p.1098·3).
Osteoporosis.

Bondil *Meda, Norw.; Meda, Swed.*
Alprostadil (p.2183·2).
Erectile dysfunction.

Bondiol *Gry, Ger.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Bondormin *Rafa, Israel.*
Brotizolam (p.965·2).
Insomnia.

Bondronat *Roche, Austria; Roche, Belg.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Ital.; Syntex, Mex.; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK.*
Ibandronate sodium (p.1098·3).
Hypercalcaemia of malignancy; metastatic bone disease.

Bo-Ne-Ca *ST, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

BoneCare *MD, Singapore.*
Calcium (p.1675·2); vitamin D (p.1986·1).
Dietary supplement.

Bonedron *Minerva (Μινερβα), Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Bonefos *Aventis, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Berlex, Canad.; Bayer, Cz.; Schering, Denm.; Schering, Fin.; Medac, Ger.; Schering, Ger.; IFET (ΙΦΕΤ), Gr.; Schering, Hong Kong; Schering, Hung.; Schering, Indon.; Schering, Irl.; Leiras, Israel; Bayer Schering, Malaysia; Schering, Mex.; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Lusalfarma, Port.; Schering, Rus.; Schering, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Er-Kim, Turk.; Bayer, UK.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; Paget's disease of bone.

Bonemax *Dincsa, Turk.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Bonephos *Key Oncologics, S.Afr.*
Clodronate (p.1095·2).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Bonesoy Optima *Nature's Way, Philipp.*
Calcium citrate; soy isoflavones; vitamins; minerals (p.1922·1).
Nutritional supplement.

Bongreen *Welfide, Singapore†.*
Alfacalcidol (p.1986·1).
Osteoporosis; vitamin D metabolic disorders.

Bonic *Ethica, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); vitamins; minerals (p.1922·1).
Osteoarthritis.

Bonidon *Mepha, Cz.†; Mepha, Switz.*
Indometacin (p.66·3).

Aluminium glycinate (p.1706·2) is included in the tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Bonifen *Merck, Mex.†; Merck, Port.†; Merck, Venez.*
Pyritinol hydrochloride (p.369·1).
Cerebrovascular disorders; mental function disorders.

Bonil *Pediapharm, Chile.*
Ketoprofen (p.73·1).
Fever; pain.

Bonine *Pfizer, Rus.; Insight, USA.*
Meclozine hydrochloride (p.584·3).
Motion sickness; vertigo.

Bonine for Kids *Insight, USA.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea and vomiting.

Bonitrop *Cofasa, Venez.*
Pyritinol hydrochloride (p.369·1).
Fatigue.

Boniva *Roche, USA.*
Ibandronate sodium (p.1098·3).
Osteoporosis.

Bonjedex *Loyal Advance, Hong Kong.*
⊗ Betamethasone sodium phosphate (p.1518·3); chlorphenamine maleate (p.571·3); oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Bonjela *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Reckitt Benckiser, Israel; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Herpes labialis; mouth pain and inflammation; teething pain.

Bonjela Teething Gel *Reckitt Benckiser, UK.*
Lidocaine (p.1862·3); cetalkonium chloride (p.1634·1).
Infant teething.

Bon-Ker *Baxter, Mex.†.*
Calcium gluconate (p.1675·3).

Bonmax *Zydus, India.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Bonmin *Aksu, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Bonningtons Irish Moss
Note. This name is used for preparations of different composition.
GSK Consumer, Austral.
Carrageenan (p.2142·3); camphor (p.2273·2); menthol (p.2340·1).
Coughs; sore throat.

GSK, NZ.
Carrageenan (p.2142·3); camphor (p.2273·2); menthol (p.2340·1); liquorice (p.1740·3).
Coughs.

Bonnisan *Himalaya Herbal, Malaysia.*
Dill oil; tinospora cordifolia; capparis spinosa; piper longum; emblica officinalis; cichorium intybus; cassia occidentalis; terminalia chebula; cardamom; achillea; tamarix gallica; tribulus terrestris; punarnava.
Tonic.

Bonocef *Baldacci, Port.†.*
Cefixime (p.224·3).
Bacterial infections.

Bon-One *Teijin, Hong Kong; Dipa, Indon.; Teijin, Indon.; Teijin, Philipp.; Teijin, Singapore; Teijin, Thai.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypoparathyroidism; malabsorption of calcium; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Bonoq *Grunenthal, Ger.†.*
Gatifloxacin (p.281·1).
Bacterial infections.

Bonserin *Rafa, Israel.*
Mianserin hydrochloride (p.408·1).
Depression.

Bontal *Continentales, Mex.*
Diiodohydroxyquinoline (p.832·1); phthalylsulfathiazole (p.315·1); homatropine (p.1881·2).
Diarrhoea.

Bontoss *Neo Quimica, Braz.†.*
Guaifenesin (p.1561·3); potassium iodide (p.2169·2).
Coughs.

Bontril *Valeant, USA.*
⊗ Phendimetrazine tartrate (p.2162·1).
Obesity.

Bonviva
Roche, Arg.; Roche, Cz.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Neth.; Roche, Philipp.; Roche, Pol.†; Roche, Port.; GSK, Swed.; Roche, Swed.
Ibandronate sodium (p.1098·3).
Osteoporosis.

Roche, Chile; Roche, Gr.; Roche, Malaysia; Roche, Singapore; GSK, UK; Roche, UK.
Ibandronic acid (p.1098·3).
Osteoporosis.

Bonyl *Orion, Denm.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Bonzol
Note. This name is used for preparations of different composition.
Mitsubishi, Jpn†.
⊗ Danazol (p.2090·2).
Endometriosis.

Bajamed, Mex.
Lansoprazole (p.1739·2).
Peptic ulcer.

Boost
Note. This name is used for preparations of different composition.
Mead Johnson Nutritionals, Canad.†; Mead Johnson Nutritionals, USA.
A range of lactose-free preparations for enteral nutrition (p.1922·1).

Seven Seas, UK.
Caffeine (p.1116·3); glucose; vitamin B substances; taurine (p.1922·1).
Fatigue.

Boostim *Svizera, India.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Boostrix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Norw.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Thai.; GSK, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Boostrix IPV *GSK, Austral.; GSK, NZ.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Boostrix Polio *GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Norw.; GSK, Port.; GSK, Swed.; GSK, Switz.*
An adsorbed diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Boostrixtetra *GSK, Fr.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Boots Antenatal Massage Cream *Boots Healthcare, Malaysia†.*
Aloe vera (p.1588·2); vitamin E (p.1992·2).
Stretch marks.

Boots Chesty Cough Syrup 1 Year Plus *Boots, UK.*
Guaifenesin (p.1561·3).
Coughs.

Boots Cold & Flu Relief *Boots, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1) caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Boots Cold & Flu Relief Hot Lemon *Boots, UK.*
Paracetamol (p.108·1); vitamin C (p.1983·3).
Cold and influenza symptoms.

Boots Cough & Decongestant Syrup 2 Years Plus *Boots, UK.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Boots Cough Syrup 3 Months Plus *Boots, UK.*
Glycerol (p.2314·2).
Coughs.

Boots Decongestant Capsules *Boots, UK.*
Phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Boots Decongestant Tablets *Boots, UK.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Boots Dry Cough Syrup 1 Year Plus *Boots, UK.*
Pholcodine (p.1570·2).
Coughs.

Boots Gripe Mixture 1 Month Plus *Boots, UK.*
Sodium bicarbonate (p.1673·2).
Dyspepsia.

Boots Maximum Strength Cold & Flu Relief *Boots, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Boots Nightime Cough Syrup 1 Year Plus *Boots, UK.*
Diphenhydramine hydrochloride (p.577·2); pholcodine (p.1570·2).
Coughs.

Boots Pain Relief Suspension 6 Years Plus *Boots, UK.*
Paracetamol (p.108·1).
Fever; pain.

Boots Threadworm Tablets 2 Years Plus *Boots, UK.*
Mebendazole (p.148·3).
Threadworm.

Boots Wind Relief *Boots, UK.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia.

B.O.P. *PPDH, Fr.*
Olive leaf (p.2356·2); birch leaf (p.2266·3).
Oedema.

Boplatex *Pisa, Mex.*
Carboplatin (p.693·1).
Malignant neoplasms.

Boracap
Note. A similar name is used for preparations of different composition (see below).
Sriprasit, Thai.
Multivitamin preparation with iron, calcium and folic acid (p.1922·1).

Boracaps
Note. A similar name is used for preparations of different composition (see above).
Tentan, Switz.
Borage oil (p.2267·3).
Dietary supplement in hyperlipidaemias.

Boracough *Sriprasit, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Boradrine
Note. This name is used for preparations of different composition.
Thea, Belg.
Borax (p.2268·1); boric acid (p.2268·1); phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Thea, Neth.
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Borafen *Sriprasit, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Borag *Ativus, Braz.*
Fish oil (p.1362·2); borage oil (p.2267·3); soya oil (p.1965·3).
Dietary supplement.

Borakid *Sriprasit, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Boraline *McNeil, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Boramint *Andromaco, Venez.†.*
Menthol (p.2340·1); borax (p.2268·1); sodium benzoate (p.1630·2); sodium bicarbonate (p.1673·2).
Mouth and throat disorders.

Boramycin *Sriprasit, Thai.*
Tetracycline phosphate complex (p.347·2).
Bacterial infections.

Borasol *Prolab, Pol.*
Boric acid (p.2268·1).
Burns; oedema; skin disorders.

Borbalan *Spyfarma, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Borea *Madaus, Spain.*
Megestrol acetate (p.2114·3).
Anorexia and cachexia associated with AIDS or cancer; breast cancer; endometrial cancer.

Boref *Andromaco, Venez.†.*
⊗ Ephedrine (p.1558·1).
Nasal congestion.

Bori-Zinc *SM, Venez.†.*
Salicylic acid (p.1612·2); zinc oxide (p.1621·2); sulfur (p.1614·1); boric acid (p.2268·1).
Fungal skin infections.

Born *Riemser, Ger.*
Crataegus (p.2289·1).
Cardiac disorders.

Borneral *Ilsan, Turk.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Bornilene *Euphar, Ital.*
Xibornol (p.361·3).
Mouth and throat infections.

Borocaina *Wassermann, Ital.*
Benzyl alcohol (p.1631·3); sodium benzoate (p.1630·2).
Mouth and throat disinfection.

Borocaina Gola *Wassermann, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

Borocanfor *Vita, Venez.*
Calamine (p.1591·2); zinc oxide (p.1621·2); menthol (p.2340·1); salicylic acid (p.1612·2); boric acid (p.2268·1); camphor (p.2273·2).
Fungal foot infections.

Borocarpin-S *Winzer, Ger.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.

Borocell *Neutron Technology, USA.*
Sodium monomercaptoundecahydro-closo-dodecaborate.
Glioblastoma multiforme.

Boroclarine *Europhta, Mon.*
Borax (p.2268·1); boric acid (p.2268·1); phenylephrine hydrochloride (p.1568·1).
Conjunctivitis.

Borofair Otic *Major, USA.*
Acetic acid (p.2244·2); aluminium acetate (p.2255·1).

Borofax *Warner-Wellcome, USA.*
Zinc oxide (p.1621·2).
Formerly contained boric acid.
Skin irritation.

Borogin *Roemmers Osmoph, Venez.*
Cetylpyridinium chloride (p.1635·1); hydroxyquinoline sulfate (p.2323·1); boric acid (p.2268·1); alum (p.2254·1).
Vaginal infections.

Boronex *Remedina, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Boropak *Glenwood, USA†.*
Aluminium sulfate (p.2255·1); calcium acetate (p.1675·2).
Inflammatory skin disorders.

Borophen *Dekaz, Gr.*
Clindamycin (p.251·1).
Bacterial infections.

Boro-Scopol *Winzer, Ger.*
Hyoscine hydrobromide (p.1734·1).
Eye disorders; production of mydriasis and cycloplegia.

Borostyrol
Note. This name is used for preparations of different composition.
ACP, Belg.
Thymol (p.1664·3); salol (p.122·1); menthol (p.2340·1); boric acid (p.2268·1); benzoin (p.2394·2).
Mouth disorders.

Mayoly-Spindler, Fr.
Thymol (p.1664·3); salol (p.122·1); levomenthol; boric acid (p.2268·1); siam benzoin (p.2386·2).
Insect stings; minor skin and mouth disorders.

Borostyrol N *Uhlmann-Eyraud, Switz.†.*
Thymol (p.1664·3); salol (p.122·1); menthol (p.2340·1); Siam benzoin (p.2386·2).
Mouth disorders.

Borraginol-N *Takeda, Hong Kong; Takeda, Indon.*
Benzocaine (p.1854·1); cinchocaine hydrochloride (p.1857·3); diphenhydramine hydrochloride (p.577·2); cetrimide (p.1634·1); radix lithospermi.
Anorectal disorders.

Borraginol-S *Takeda, Indon.*
⊗ Prednisolone (p.1540·3); lidocaine (p.1862·3); benzocaine (p.1854·1); cetrimide (p.1634·1); radix lithospermi.
Anorectal disorders.

Borsdruppels *Lennon, S.Afr.*
Liquorice (p.1740·3); fennel oil (p.2303·1); anise oil (p.2258·2).
Bronchitis; coughs; croup.

Borstol Cold and Flu Powders with Vitamin C *Group, S.Afr.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Borstol Cough Remedy *Group, S.Afr.*
Ammonium chloride (p.1551·3); senega root (p.1572·3); buchu (p.2269·3); camphor (p.2273·2); cinchona (p.2282·3); aristolochia (p.2260·1); balsam sulphuris; turpentine gum.
Coughs.

Borstol Linctus *Group, S.Afr.*
Guaifenesin (p.1561·3).
Cough.

Bort *Megat, Venez.†.*
Tiemonium iodide (p.1776·3); dipyrone (p.49·2).
Muscle spasm; pain.

Borymycin *YSP, Malaysia; Yung Shin, Singapore.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Bosconar *Teva Tuteur, Arg.*
Bicalutamide (p.686·2).
Malignant neoplasms.

Bosea *Sevapharma, Cz.†.*
Botulism antitoxins (A, B, and E) (p.2207·3).
Botulism.

Bosisto's Eucalyptus Inhalant *Felton, Austral.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Cold symptoms.

Bosisto's Eucalyptus Rub *Felton, Austral.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Muscular aches and pains.

Bosisto's Eucalyptus Spray *Felton, Austral.*
Eucalyptus oil (p.2301·2).
Muscular aches and pains.

Bosisto's Vaporising Ointment *Felton, Austral.*
Eucalyptus oil (p.2301·2); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2); rosemary oil (p.2381·3).
Cold symptoms.

Bosporon *Grunenthal, Port.; Tedec Meiji, Spain.*
Lornoxicam (p.77·3).
Inflammation; musculoskeletal and joint disorders; pain.

Boston *Bausch & Lomb, Braz.†; Bausch & Lomb, Canad.; Chauvin, Fr.; Polymer Technology, USA.*
Cleaning solution for contact lenses (p.1622·2).

Boswellia Complex *Mediherb, Austral.*
Boswellia serrata (p.2307·1); celery (p.2278·3); ginger (p.1732·3).
Musculoskeletal and joint disorders.

Boswellia Compound *Phytomedicine, Austral.*
Boswellia serrata (p.2307·1); devil's claw root (p.39·1); ginger (p.1732·3); guaiacum resin (p.2317·3).
Arthritis.

Botaderm *Biospray, Gr.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Botafex *Farmex, Gr.*
Minoxidil (p.1342·1).

Botamiral *Biospray, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Botamycin-N *Biospray, Gr.*
Clindamycin phosphate (p.251·2).
Acne.

Botanica Hayfever *Botanica, NZ.*
Chamomile (p.2279·3); lavender (p.2331·1); melissa (p.2339·3); quercetin (p.2305·1); vitamin C (p.1983·3).
Prevention of minor allergic reactions in the upper respiratory tract.

Botastin *Biospray, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Botox *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; GSK, Jpn; Allergan, Malaysia; Allergan, Mex.; Allergan, NZ; Allergan, Neth.; Allergan, Norw.; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, Rus.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA; Allergan, Venez.*
Botulinum A toxin (p.1890·1).
Achalasia; anal fissures; bladder instability; blepharospasm; bruxism; cervical dystonia; foot spasticity associated with paediatric cerebral palsy; glabellar lines; hemifacial spasm; hyperhidrosis; spasmodic torticollis; strabismus; tremor; upper limb spasticity following stroke.

Botropase *Abbott, Ital.†.*
Batroxobin (p.1056·1).
Haemorrhagic disorders.

Bottom Better *InnoVisions, USA.*
Yellow soft paraffin (p.2031·3); wool fat (p.2033·2).
Nappy rash.

Boucren *Bouzen, Arg.*
Cetrimide (p.1634·1).
Skin infections.

Bounty Bears *Nature's Bounty, USA.*
A range of vitamin preparations (p.1922·1).

Boutavixal *Proel, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Bovisan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Bowa *TNP, Thai.†.*
Aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; peptic ulcer.

Boxazin plus C *Boehringer Ingelheim, Ger.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Boxocalm *Cheplapharm, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety; insomnia.

Boxogetten S *Cheplapharm, Ger.*
Phenylpropanolamine hydrochloride (p.1569·3).
Obesity.

Boxol *Pharmacia, Spain†.*
Dalteparin sodium (p.1255·1).
Deep-vein thrombosis; myocardial infarction; thrombosis prophylaxis; unstable angina pectoris.

Boxolam *Mayo, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Boxolip *Cheplapharm, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Boyol Salve *Pfeiffer, USA.*
Ichthammol (p.1599·1); benzocaine (p.1854·1).
Skin disorders.

Bozaktral *Chrispa (Χρισπα), Gr.*
Cisapride (p.1720·3).
Diabetic gastroparesis resistant to other therapy.

BP Poly-650 *Brookstone, USA.*
Paracetamol (p.108·1); phenyltoloxamine citrate (p.588·1).
Pain.

B-Platin *Blausiegel, Braz.*
Carboplatin (p.693·1).
Malignant neoplasms.

B-Plex *Stanley, Canad.†.*
Vitamin B substances (p.1922·1).

B-Plex C *Stanley, Canad.†.*
Vitamin B substances and vitamin C (p.1922·1).

B-Plus *Biolab, Thai.†.*
Vitamin B substances (p.1922·1).

BPNorm *Westmont, Philipp.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

B-Prime *Primera, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

BPzide *Stadmed, India.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

BQL *Cadila, India.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

B-Quick *Brassora, Arg.*
Pregnancy test (p.2372·1).

Bradelmin *Degorts, Mex.*
Albendazole (p.139·2).
Worm infections.

Bradimox *Astellas, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bradoral *Novartis Consumer, Ital.*
Domiphen bromide (p.1643·1).
Mouth and throat disinfection.

Bradosol
Note. This name is used for preparations of different composition.
Novartis Consumer, Austria.
Domiphen bromide (p.1643·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); anise oil (p.2258·2).
Sore throat.
Columbia, Canad.
Hexylresorcinol (p.1647·1).
Sore throat.
Novartis Consumer, UK.
Benzalkonium chloride (p.1629·1).
Sore throat.

Bradoxil *Pharmawealth, Philipp.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Brady's-Magentropfen *Brady, Austria.*
Cinchona bark (p.2282·3); cinnamon (p.2283·1); aniseed (p.2258·2); coriander (p.2288·1); fennel (p.2302·3); myrrh (p.2349·2); santalum album (p.2383·2); gentian (p.2310·3); zedoary.
Gastrointestinal disorders.

Bragg's Medicinal Charcoal *Bragg, UK.*
Activated charcoal (p.1435·2).
Dyspepsia; flatulence; heartburn.

Brainact *Kalbe, Indon.*
Citicoline (p.2283·3).
Cerebral infarction; head injury; hemiplegia.

Brainal *Grunenthal, Chile†; Andromaco, Cz.†; Andromaco, Rus.†; Librapharm, Spain.*
Nimodipine (p.1357·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Brainox *Grunenthal, Port.*
Nimodipine (p.1357·2).
Cerebral ischaemia after subarachnoid haemorrhage.

Brain-Spect *Medi-Radiopharma, Cz.*
Technetium-99m (p.2055·3) exametazime.
Radionuclide imaging of the CNS.

Braintop *Exel, Belg.*
Piracetam (p.368·2).
Mental function impairment.

Braito *Konimex, Indon.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Allergic eye disorders; eye irritation.

Brakhor *Psicofarma, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hyperlipidaemias.

Bral *Biotech, Venez.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Bralifex *Sanbe, Indon.*
Tobramycin (p.354·1).
Bacterial eye infections.

Bralifex Plus *Sanbe, Indon.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Bralin *Bernofarm, Indon.*
Citicoline (p.2283·3).
Cerebral infarction; head injury; hemiplegia.

Bralix *Remedica, Hong Kong.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Dysmenorrhoea; gastrointestinal disorders; nocturnal enuresis; ureteral spasm.

Bramedil *Grunenthal, Chile.*
Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Bramedil Compuesto *Grunenthal, Chile.*
Pargeverine hydrochloride (p.1761·1); metamizole magnesium (p.49·3).
Colic; dysmenorrhoea.

Bramicil *Fisiopharma, Ital.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Bramin *Degorts, Mex.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Influenza symptoms.

Bramin-hepa *Merz, Ger.†.*
Isoleucine (p.1954·1); leucine (p.1954·3); valine (p.1971·1); pyridoxine hydrochloride (p.1978·2).
Hepatic encephalopathy.

Bramitob *Torrex Chiesi, Cz.; Chiesi, Ital.; Promedica, Port.*
Tobramycin (p.354·1).
Pseudomonal infections in cystic fibrosis.

BranchAmin *Clintec, USA.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in hepatic encephalopathy.

Brand- u. Wundgel-Medice N *Medice, Ger.*
⊗ Benzethonium chloride (p.1630·1); lauromacrogol 400 (p.1916·1); urea (p.1620·2).
Burns; insect stings; skin disorders; wounds.

Brand- und Wundgel *Funcke, Cz.†.*
Dexpanthenol (p.2362·1); allantoin (p.1588·1); lidocaine hydrochloride (p.1862·3); cetylpyridinium chloride (p.1635·1).
Burns; insect stings; wounds.

Brand- und Wund-Gel Eu Rho *Eu Rho, Ger.†.*
Lidocaine hydrochloride (p.1862·3); allantoin (p.1588·1); cetylpyridinium chloride (p.1635·1); dexpanthenol (p.2362·1).
Burns; insect stings; skin disorders; wounds.

Brandiazin *Medphano, Ger.*
Sulfadiazine silver (p.337·2).
Burns.

Branigen *GSK, Ital.*
Acetylcarnitine hydrochloride (p.1932·2).
Peripheral nerve disorders.

Branitil *OFF, Ital.*
Acetylcarnitine hydrochloride (p.1932·2).
Cerebrovascular disorders; peripheral nerve disorders.

Brasan *Vianex (Βιανεξ), Gr.*
Serrapeptase (p.2385·3).
Inflammatory disorders.

Brasivol *Stiefel, Austral.; Stiefel, Fr.; Stiefel, Hong Kong†; Stiefel, Irl.; Stiefel, S.Afr.; Stiefel, UK.*
Aluminium oxide (p.1585·3).
Acne.

Brasmatic *Darya-Varia, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Brassel *Pharmacia, Ital.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; parkinsonism.

Bratofil *Inquifave, Venez.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Bratofil c Neomicina *Inquifave, Venez.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Braunoderm *Braun, Austria; Braun, Belg.; Braun, Ger.; Braun, Ital.; Braun, Port.; Braun, Switz.*
Povidone-iodine (p.1659·2); isopropyl alcohol (p.1650·3).
Skin disinfection; wounds.

Braunol *Braun, Austria; Braun, Belg.; Braun, Cz.; Braun, Ger.; Ratiopharm, Ger.; Braun, Ital.; Braun, Neth.; Braun, Port.; Braun, Switz.*
Povidone-iodine (p.1659·2).
Burns; disinfection of the skin, mucous membranes, and wounds; skin infections.

Braunosan *Braun, Switz.*
Povidone-iodine (p.1659·2).
Hand disinfection.

Braunosan H Plus *Braun, Switz.*
Povidone-iodine (p.1659·2).
Hand and skin disinfection.

Braunovidon *Braun, Austria; Braun, Cz.; Braun, Ger.; Braun, Pol.; Braun, Switz.*
Povidone-iodine (p.1659·2).
Burns; infected skin disorders; skin and wound infections; ulcers.

Bravelle *Ferring, Canad.; Ferring, Gr.; Ferring, Neth.; Ferring, Port.; Ferring, USA.*
⊗ Urofollitropin (p.2136·3).
Female infertility.

Brax *Biomep, Mex.*
Paracetamol (p.108·1); naproxen (p.92·3).
Pain.

Braxan *Armstrong, Mex.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Braxidin *Sanbe, Indon.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal disorders; smooth muscle spasm.

Brazepam *Pharmacare, S.Afr.*
Bromazepam (p.964·3).
Anxiety.

Breacol
Note. A similar name is used for preparations of different composition (see below).
Valeant, Hong Kong; Valeant, Singapore.
Guaifenesin (p.1561·3).
Coughs; sore throat.

Bre-A-Col
Note. A similar name is used for preparations of different composition (see above).
Grossman, Mex.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Breacol Decongestant & Cough Suppressant *ICN, Malaysia†.*
Codeine phosphate (p.37·2); phenylephrine hydrochloride (p.1568·1).
Coughs; upper respiratory-tract congestion.

Breaflu *Grossman, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Respiratory-tract disorders; rhinitis.

Breathe Free *Thompson, USA.*
Sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Breathe More *Homeocan, Canad.*
Homoeopathic preparation.

Breatheze *Rolab, S.Afr.†.*
⊗ Salbutamol (p.1131·2).
Bronchospasm.

Breathquality-UBT *AB, Ital.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for gastroduodenal Helicobacter pylori infection.

Breator *Raffo, Arg.†.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Bredinin *Asahi, Jpn.*
Mizoribine (p.1835·1).
Immunosuppressant.

Bredon *Organon, Mex.*
Oxolamine citrate (p.1567·1).
Coughs.

Breeze 2 *Bayer, UK.*
Test for glucose in blood (p.2314·1).

Breezee Mist Antifungal *Pedinol, USA†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Breezee Mist Foot Powder *Pedinol, USA.*
Aluminium chlorohydrate (p.1588·3); menthol (p.2340·1); undecenoic acid (p.549·2).
Formerly known as Breezee Mist Antifungal.
Fungal skin infections.

Brefar *Farcoral, Mex.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Brefus *Hebron, Braz.†.*
Liquorice (p.1740·3).
Coughs.

Bregamin *Continentales, Mex.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Allergic conjunctivitis; respiratory-tract congestion; rhinitis.

Breinox *Farma, Venez.*
Piracetam (p.368·2).
Mental function impairment.

Brek *TRB, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Brelcip *Micro, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Brellercet *Brown & Burk, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Brelomax *Abbott, Ger.*
⊗ Tulobuterol hydrochloride (p.1150·1).
Obstructive airways disease.

Brelox *Brel, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Bremagan Flu *Boehringer Ingelheim Promeco, Mex.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; hay fever.

Bremax *Abbott, Austria; Abbott, Mex.; Abbott, Philipp.; Abbott, Venez.†.*
⊗ Tulobuterol hydrochloride (p.1150·1).
Obstructive airways disease.

Bremecina *Collins, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Bremide *AstraZeneca, Norw.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Otitis media.

Breminal *Gobbi, Arg.*
Tolterodine (p.2198·2).
Bladder instability.

Bremon *Pensa, Spain.*
Clarithromycin (p.248·2).
Bacterial infections.

Bremotel *Alpharma, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Bren Fort *Collins, Mex.†.*
Multivitamin preparation (p.1922·1).

Brenax *Sandoz, Indon.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Brenazol *Durascan, Denm.†.*
Miconazole nitrate (p.541·3).
Fungal infections.

Brenda-35 ED *Alphapharm, Austral.*
21 Tablets, cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3); 7 inert tablets.
Androgenisation in females; combined oral contraceptive.

Brenoxil *Tecnofarma, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Brentacort *Janssen-Cilag, Denm.*
⊗ Hydrocortisone (p.1535·2); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Brentan
Note. This name is used for preparations of different composition.
Janssen-Cilag, Denm.
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections.
Janssen-Cilag, Indon.; Esteve, Spain.
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal skin infections with inflammation.

Bres *Farmacologico Milanese, Ital.†.*
Bromelains (p.2269·1); aescin (p.2248·2).
Peripheral vascular disorders.

Bresal *Berman, Mex.*
Phenylbutazone (p.117·1).
Inflammation; musculoskeletal and joint disorders.

Bresben *Sandoz, Ger.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Bresec *Vocate, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Brethal *Fako, Turk.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Brethine *aai, USA.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bretol *Flupal, Venez.*
⊗ Tulobuterol hydrochloride (p.1150·1).
Obstructive airways disease.

Bretylate *GSK, Israel†.*
Bretylium tosilate (p.1236·2).
Ventricular arrhythmias.

Bretylol *Sanofi Omnimed, S.Afr.†.*
Bretylium tosilate (p.1236·2).
Ventricular arrhythmias.

Breva *Valeas, Ital.*
⊗ Salbutamol (p.1131·2); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Brevafen *Janssen-Cilag, Arg.*
⊗ Alfentanil hydrochloride (p.16·2).
Analgesia in anaesthesia.

Brevex *Bago, Chile.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Muscle spasm; pain.

Brevibloc *Sidus, Arg.†; Boots Healthcare, Austral.; Torrex, Austria; Baxter, Belg.; Cristalia, Braz.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.†; Baxter, Ger.; Baxter, Gr.; Boots, Hong Kong†; Du Pont, Hong Kong†; Baxter, Hung.; Baxter, Irl.; Du Pont, Israel†; Baxter, Ital.; BMS, Malaysia†; Aventis, Mex.†; AFT, NZ; Baxter, Neth.; Baxter, Port.; Sanofi Synthelabo, S.Afr.; BMS, Singapore†; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, USA.*
⊗ Esmolol hydrochloride (p.1282·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Brevicon *Pfizer, Canad.; Searle, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Brevimytal *Lilly, Ger.*
Methohexital sodium (p.1788·3).
General anaesthesia.

Brevinaze *Intramed, S.Afr.*
Ketamine hydrochloride (p.1787·1).
Analgesia in painful procedures; general anaesthesia.

Brevinor *Pfizer, Austral.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, NZ; Searle, S.Afr.†; Pfizer, UK.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Brevital *Monarch, USA.*
Methohexital sodium (p.1788·3).
General anaesthesia.

Brevoxyl *Stiefel, Austral.; Sanova, Austria; Stiefel, Belg.; Stiefel, Fin.; Stiefel, Fr.; Stiefel, Ger.; Gabriel, Gr.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, NZ; Stiefel, Norw.; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, S.Afr.; Stiefel, Singapore; Sylak, Swed.; Stiefel, Thai.; Stiefel, UK; Stiefel, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Brewers Yeast
Note. This name is used for preparations of different composition.
Greater Pharma, Thai.
Dried yeast (p.1998·3).
Vitamin B deficiency.

Seven Seas, UK.
Yeast (p.1998·3); vitamin B substances (p.1922·1).

Nature's Bounty, USA; Sundown, Venez.†.
Vitamin B substances (p.1922·1).

Brexecam *Adcock Ingram, S.Afr.*
Piroxicam betadex (p.117·3).
Gout; musculoskeletal and joint disorders.

Brexicam *Pierre Fabre, Mex.*
Piroxicam betadex (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Brexic-DT *Wockhardt, India.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Brexidol *Torrex, Austria; Biovail, Canad.†; Nycomed, Denm.†; Nycomed, Fin.†; Asche Chiesi, Ger.; Nycomed, Norw.; Nycomed, Swed.; Chiesi, Switz.†; Trinity, UK.*
Piroxicam betadex (p.117·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Brexin
Note. This name is used for preparations of different composition.
Torrex, Austria; Gross, Braz.; Pierre Fabre, Fr.; Chiesi, Gr.; Torrex Chiesi, Hung.; Promedica, Ital.; Chiesi, Malaysia; Neo-Farmaceutica, Port.; Chiesi, Singapore†; Chiesi, Thai.
Piroxicam betadex (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Cofasa, Venez.
Paracetamol (p.108·1).
Fever; pain.

Brexine *Christiaens, Belg.; Nycomed, Neth.*
Piroxicam betadex (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Brexinil *Chiesi, Spain.*
Piroxicam betadex (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Brexivel *Promedica, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Brexodin *Quimica y Farmacia, Mex.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Brexon *Essex, Chile†.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Burns; skin disorders; wounds.

Brexonase *Etex, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Brexotide *Etex, Chile.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Brexovent *Etex, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Brezal *Novartis, Ital.*
Choline alfoscerate (p.363·3).
Mental function impairment in the elderly.

Briazide *Pierre Fabre, Fr.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Bricalin *Teva, Israel.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bricanil *AstraZeneca, Venez.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bricanyl *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; 3M, Cz.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Stern, Ger.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; Astra, Mex.†; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour; pulmonary-function tests.

Bricanyl comp *AstraZeneca, Austria; AstraZeneca, Ger.†; Stern, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Bricanyl Composto *AstraZeneca, Braz.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Bricanyl EX *AstraZeneca, Mex.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Bricanyl Expectorant *AstraZeneca, Hong Kong†; AstraZeneca, Irl.; AstraZeneca, Philipp.; AstraZeneca, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Cough; obstructive airways disease.

Bricarex *AstraZeneca, India.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Asthma; coughs.

Bricasma *AstraZeneca, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bricasma Expectorant *AstraZeneca, Indon.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Bridatec *GE Healthcare, Neth.; GE, Port.*
Technetium-99m mebrofenin (p.2055·3).
Radionuclide imaging of the biliary-tract and liver.

Bridic *Menarini, Port.*
Brivudine (p.867·3).
Herpes zoster infections.

Briem *Pierre Fabre, Fr.*
Benazepril hydrochloride (p.1223·2).
Hypertension.

Brietal *Lilly, Austral.; Lilly, Austria; Lilly, Israel†; Lilly, Neth.; Lilly, Pol.; Lilly, Rus.*
Methohexital sodium (p.1788·3).
General anaesthesia; hypnotic.

Brighser *Solvang, Philipp.*
Vitamins; lysine hydrochloride (p.1922·1).

Briklin *Vianex (Βιανέξ), Gr.*
Amikacin (p.200·2).
Bacterial infections.

Brimex *Biomep, Mex.*
Aciclovir (p.862·3).
Viral infections.

Brimodin *Cipla, India.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Brimodin P *Cipla, India.*
Brimonidine tartrate (p.1878·3); oxychlorocomplex.

Brimodine *Faran, Gr.*
Brimonidine (p.1878·3).
Glaucoma.

Brimo-Klonal *Klonal, Arg.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Brimopress *Poen, Arg.; Poen, Chile.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Brinaf *Slovakofarma, Cz.†.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Brinal *Biomedica-Chemica, Gr.*
Brimonidine (p.1878·3).
Glaucoma.

Brinaldix *Novartis, Ger.†; EGIS, Hung.; Novartis, India.*
⊗ Clopamide (p.1250·1).
Hypertension; oedema.

Brinerdin *Novartis, Austria; Novartis, S.Afr.; Novartis, Thai.*
⊗ Clopamide (p.1250·1); dihydroergocristine mesilate (p.364·2); reserpine (p.1387·3).
Hypertension.

Brinerdina *Teofarma, Ital.; Novartis, Spain†.*
⊗ Clopamide (p.1250·1); dihydroergocristine mesilate (p.364·2); reserpine (p.1387·3).
Hypertension.

Brinerdine *Novartis, Port.†; Novartis, Switz.*
⊗ Clopamide (p.1250·1); dihydroergocristine mesilate (p.364·2); reserpine (p.1387·3).
Hypertension.

Brinidin *Pharmanel, Gr.*
Brimonidine (p.1878·3).
Glaucoma.

Brinix *Guidotti, Spain.*
Brivudine (p.867·3).
Herpes zoster infections.

Brintenal *Beta, Arg.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Brintoverilte *Nycomed, Denm.; SAD, Denm.*
Hydrogen peroxide (p.1647·3).
Mouth infections; oral disinfection; wounds.

Briofil *Teofarma, Ital.*
Bamifylline hydrochloride (p.1116·1).
Obstructive airways disease.

Briogen *IBC, Ital.†.*
Glutamine (p.1947·2); -phosphoserine (p.2367·1); cyanocobalamin (p.1980·2).
Tonic.

Briomet *Farma, Venez.*
Cobamamide (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Myalgia; myopathy; neuropathy.

Briomotil *DMG, Ital.*
Inulin; arginine; glutamine; electrolytes (p.1922·1).

Brionil *Lesvi, Spain.*
Nedocromil sodium (p.1127·3).
Asthma.

Brionot *Casasco, Arg.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Brioplus *Piam, Ital.*
Tryptophan (p.427·1); griffonia simplicifolia (p.2317·2); vitamin B substances (p.1922·1).
Low mood.

Briovitan *Montefarmaco, Ital.*
Multivitamin and mineral preparation with flavonoids (p.1922·1).
Nutritional supplement.

Briovitase *Montefarmaco, Ital.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Magnesium and potassium deficiency.

Briovitase Sostegno *Montefarmaco, Ital.*
Vitamins; minerals; carnitine; papaya (p.1922·1).

Brisair *GSK, Spain.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Briscocough *Quatromed, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Briscopyn *Quatromed, S.Afr.*
Paracetamol (p.108·1); caffeine (p.1116·3); meprobamate (p.1006·2); codeine phosphate (p.37·2).
Pain with tension.

Briserin N *Novartis, Ger.*
⊗ Clopamide (p.1250·1); reserpine (p.1387·3).
Hypertension.

Brisfirina *BMS, Spain.*
Cefapirin sodium (p.221·2).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Brismucol *BMS, Braz.; BMS, Mex.*
Ambroxol acefyllinate (p.1114·2).
Respiratory-tract disorders.

Brisomax *Bialfar, Port.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Brisoral *BMS, Spain.*
Cefprozil (p.232·2).
Bacterial infections.

Brisovent *Bialfar, Port.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Brispen *Hormona, Mex.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Bristaciclina Dental *Pfizer, Spain.*
Benzydamine hydrochloride (p.27·3); chymotrypsin (p.2281·3); tetracycline hydrochloride (p.347·2); trypsin (p.2405·3).
Mouth and upper respiratory-tract infections.

Bristacol *Juste, Spain.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia; myocardial infarction.

Bristacycline *Bristol, USA.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Bristaflam *BMS, Arg.†; BMS, Chile†; Almirall, Mex.; Elmor, Venez.*
Aceclofenac (p.14·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Bristamox *BMS, Fr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

BrisTaxol *BMS, Mex.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Bristopen *BMS, Fr.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Britamox *Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2).
Formerly known as Halitol.
Bacterial infections.

Britapen *Reig Jofre, Spain.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Britaxol *BMS, Chile.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

British Army Foot Powder *Regal, Canad.†.*
Boric acid (p.2268·1); formaldehyde (p.1644·2); salicylic acid (p.1612·2); zinc oxide (p.1621·2).
Tinea pedis.

Britlofex *Britannia Pharmaceuticals, UK.*
Lofexidine hydrochloride (p.1449·1).
Opioid withdrawal symptoms.

Brivex *Menarini, Switz.*
Brivudine (p.867·3).
Varicella-zoster infections.

Brivir *Menarini, Gr.*
Brivudine (p.867·3).
Herpes zoster infections.

Brivirac *Menarini, Ital.*
Brivudine (p.867·3).
Herpes zoster infections.

Brixia *Poen, Arg.; Poen, Chile; Roemmers Poen, Venez.*
Azelastine hydrochloride (p.568·2).
Allergic eye disorders.

Brixilon *Leti, Venez.*
Ambroxol acefyllinate (p.1114·2).
Asthma.

Brixopan *Epifarma, Ital.*
Bromazepam (p.964·3).
Anxiety disorders; psychosomatic disorders; tension.

Brixoral *Biospray, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Brizolina *BMS, Spain.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Broad Spectrum Sunblock *Avon, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Broadced *Kalbe, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Brocaden *Pharmasant, Thai.*
Bromocriptine mesilate (p.798·1).
Hyperprolactinaemia; parkinsonism.

Brocalcio D3 *Roemmers, Venez.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Brocantol *Cofasa, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Brochlor *Sanofi-Aventis, UK.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Brocil *Berman, Mex.*
Chloramphenicol succinate (p.241·3).
Bacterial infections.

Brocof *Vamsler, Philipp.*
Ambroxol (p.1550·3).
Respiratory-tract disorders with abnormal mucus.

Brocolan *Berman, Mex.*
Dextromethorphan (p.1555·2).

Brodacid *Inco Veritas, Pol.*
Dimethyl sulfoxide (p.2022·1); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Brodifac *Mintlab, Chile.*
Ketorolac (p.75·2).
Inflammation; pain.

Brodil *Sanovel, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Brodilan *Zuoz, Venez.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Bronchospasm.

Brodilin *Zuoz, Venez.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Bronchospasm.

Broend *Parggon, Mex.*
Guaifenesin (p.1561·3); sodium dibunate (p.1573·1).
Coughs.

Brofed
Note.This name is used for preparations of different composition.
Pharmaland, Thai.
Bromperidol (p.965·1).
Psychoses.

Marnel, USA.
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Broflex *Alliance, UK.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Brogal *Rayere, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Brogal Compositum *Rayere, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Brogal-T *Rayere, Mex.*
Ambroxol hydrochloride (p.1550·3); dextromethorphan hydrobromide (p.1555·2).
Cough; respiratory-tract congestion.

Brogamax *Rayere, Mex.*
Co-trimoxazole (p.258·1); ambroxol (p.1550·3).
Bacterial infections of the respiratory tract.

Broksin *Tripharma, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Brolamina *Ivax, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Brolene
Aventis, Austral.; Sanofi-Aventis, Irl.; Aventis, NZ; Aventis, UK.
Dibrompropamidine isetionate (p.1642·1) or propamidine isetionate (p.1660·1).
Eye infections.

Genop, S.Afr.
Propamidine isetionate (p.1660·1).
Eye infections.

Brolene Cool Eyes *Aventis, UK.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Brolexan *Medifarma, Indon.; UAP, Indon.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Brolin
Note.This name is used for preparations of different composition.
D & M, Chile.
Cysteine; zinc; pyridoxine; biotin (p.1922·1).
Hair and nail disorders.

Vedim, Spain†.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Brolin Forte *D & M, Chile.*
Cysteine; vitamins; minerals (p.1922·1).
Hair and nail disorders.

Broluidan *Kenfarma, Spain†.*
Letosteine (p.1563·3).
Respiratory-tract disorders.

Bromace *Ace, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with abnormal mucus.

Bromacef *Ad-Drugstel, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with abnormal mucus.

Bromadine-DM *Cypress, USA.*
Brompheniramine hydrochloride (p.569·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bromalex *Vitoria, Port.*
Bromazepam (p.964·3).
Anxiety.

Bromalgina *Climax, Braz.†.*
Codeine diethylbarbiturate (p.38·3); dipyrone (p.49·2); homatropine methylbromide (p.1881·3).
Painful muscle spasm.

BromaLich *Lichtenstein, Ger.†.*
Bromazepam (p.964·3).
Anxiety; sleep disorders.

Bromam *Sandoz, Denm.*
Bromazepam (p.964·3).
Anxiety.

Bromarest DX *Warner Chilcott, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Bromatan Plus *Cypress, USA.*
Pseudoephedrine tannate (p.1572·1); dextromethorphan tannate (p.1556·1); dexchlorpheniramine tannate (p.572·2).
Allergic rhinitis; cold symptoms; cough; sinusitis.

Bromatan-DM *Cypress, USA.*
Brompheniramine tannate (p.569·3); phenylephrine tannate (p.1568·3); dextromethorphan tannate (p.1556·1).
Coughs; nasal congestion.

Bromatane DX *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bromatanil *Investi, Arg.*
Bromazepam (p.964·3).
Anxiety.

Bromatop *Topgen, Belg.*
Bromazepam (p.964·3).
Anxiety; sleep disorders.

Bromavon *Hua, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion; respiratory-tract disorders.

Bromax *Pentafarma, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Bromaz *1A, Ger.†.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Bromazanil *Hexal, Ger.*
Bromazepam (p.964·3).
Anxiety; tension.

Bromaze *Hexal, S.Afr.*
Bromazepam (p.964·3).
Anxiety.

Bromazep *CT, Ger.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Bromazepan *Dovalle, Braz.†.*
Bromazepam (p.964·3).
Anxiety.

Bromazolo *Baldacci, Ital.*
Thiamazole (p.2176·3); dibromotyrosine (p.2169·1).
Hyperthyroidism.

Bromed *Kolassa, Austria.*
Bromocriptine mesilate (p.798·1).
Acromegaly; galactorrhoea; lactation inhibition; menstrual disorders; parkinsonism; prolactinoma.

Bromedrina *Sankyo, Venez.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromek *Kocak, Turk.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromeksin *Oro, Turk.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromel *Antibioticos, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Bromelin *Hebron, Braz.†.*
Bromelains (p.2269·1); invertase; glucose oxidase (p.2313·3); ribonuclease (p.2378·3); amylase (p.2256·3).
Coughs.

Bromelip *Maver, Mex.*
Dextromethorphan (p.1555·2).
Cough.

Bromergon *2K, Denm.†; Lek, Pol.; Lek, Rus.; Sandoz, Thai.*
Bromocriptine mesilate (p.798·1).
Acromegaly; amenorrhoea; galactorrhoea; hyperprolactinaemia; hypertension; hypogonadism; lactation inhibition; mastalgia; parkinsonism; prolactinoma.

Bromesep Elixir *Siam Bheasach, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; nasal congestion.

Bromesep Expectorant *Siam Bheasach, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Allergic rhinitis; coughs; nasal congestion.

Brometix *Etifar, Venez.†.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Brometos *Lafedar, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromex *Qualiphar, Belg.; Cipla, India; PP Lab, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Bronchiectasis; obstructive bronchopneumonopathies; respiratory-tract disorders associated with increased or viscous mucus; sinusitis; Sjögren's syndrome.

Bromexidryl *Klonal, Arg.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Bromexol *Galeno, Venez.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Bromfed *Verum, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; nasal congestion.

Bromfed-DM *Verum, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Allergic rhinitis; coughs; vasomotor rhinitis.

Bromfed-PD *Verum, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; nasal congestion.

Bromfenex *Ethex, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract disorders.

Bromhexine Compound *Vida, Hong Kong.*
⊗ Codeine phosphate (p.37·2); bromhexine hydrochloride (p.1552·2); ephedrine hydrochloride (p.1558·2); brompheniramine maleate (p.569·2); papaverine hydrochloride (p.2191·3).
Catarrh; coughs; nasal congestion.

Bromhist *Cypress, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Bromhist PDX
Note.This name is used for preparations of different composition.
Cypress, USA.
Oral drops: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Cypress, USA.
Syrup: Brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).

Bromhist-DM
Note.This name is used for preparations of different composition.
Cypress, USA.
Oral drops: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; upper respiratory-tract congestion.

Cypress, USA.
Syrup: Brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Bromhist-NR *Cypress, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).

Bromhistop *Neo Dermos, Arg.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Bromicof *Loeffler, Mex.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromidem *Sandipro, Belg.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Bromidrastina *Ibefar, Braz.†.*
Sodium bromide (p.2269·2); hydrastis (p.2321·3); hamamelis (p.2318·2); black haw (p.2267·1); gossypium herbaceum.
Menstrual disorders.

Bromifen *Neo Quimica, Braz.*
⊗ Fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Bromika *Ikapharmindo, Indon.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Bromil
Note.This name is used for preparations of different composition.
EMS, Braz.
Pastilles: Menthol (p.2340·1); terpineol (p.2396·1); cineole (p.2282·3); ascorbic acid (p.1983·3); benzocaine (p.1854·1).
Mouth and throat disorders.

EMS, Braz.
Syrup: Cineole (p.2282·3); terpineol (p.2396·1); menthol (p.2340·1).
Coughs.

Bromi-Lotion *Gordon, USA.*
Aluminium chlorohydrate (p.1588·3).
Bromhidrosis; hyperhidrosis.

Brominol-C *Sons, Mex.*
Dextromethorphan (p.1555·2); ambroxol (p.1550·3).
Coughs.

Bromiramin *Norma (Νορμα), Gr.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory disorders associated with viscous mucus.

Bromivec *Precimex, Mex.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Bromixen *Maver, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Brommer *Mersifarma, Indon.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Bromo Madelon *St Laurent, Canad.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).

Bromo Seltzer
Note.This name is used for preparations of different composition.
Tower, Canad.
Sodium citrate (p.1673·3).
Dyspepsia; gastric hyperacidity.

Warner-Lambert, USA.
Paracetamol (p.108·1).
Fever; pain.

Bromo Seltzer Effervescent Granules *Warner-Lambert, USA.*
Sodium bicarbonate (p.1673·2); paracetamol (p.108·1); citric acid (p.2284·1).
Hyperacidity.

Bromocal *Caldeira & Metelo, Port.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromocalcio *Pasteur, Chile.*
Calcium bromolactobionate (p.967·3).
Insomnia; nervous disorders.

Bromocod N *Streuli, Switz.*
Codeine phosphate (p.37·2); belladonna (p.2263·3); drosera (p.2297·3); ipecacuanha (p.1562·3); opium (p.105·1); terpin hydrate (p.1573·3).
Coughs.

Bromocorn *Filofarm, Pol.*
Bromocriptine (p.800·3).
Hyperprolactinaemia; lactation inhibition; male and female infertility; menstrual disorders; parkinsonism; prolactinoma.

Bromocrel *Hexal, Ger.†.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism.

Bromodel *Organifar, Venez.†.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Bromodol *Janssen-Cilag, Arg.*
Bromperidol (p.965·1) or bromperidol decanoate (p.965·1).
Psychoses.

Bromohexal *Hexal, Austral.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism; prolactinomas.

Bromo-Kin *Winthrop, Fr.*
Bromocriptine mesilate (p.798·1).
Hyperprolactinaemia; lactation inhibition; parkinsonism; prolactinomas.

Bromolactin *Sigma, Austral.†.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism.

Bromolin *Cipla, India.*
Bromhexine (p.1552·2); amoxicillin (p.202·2).
Respiratory-tract infections.

Bromophar *Qualiphar, Belg.*
Codeine phosphate (p.37·2).
Coughs.

Bromopirin *Sigma, Braz.*
Bromazepam (p.964·3); sulpiride (p.1028·3).
Psychoses.

Bromoprid *Teuto, Braz.†.*
Bromopride (p.1713·3).
Nausea and vomiting.

Bromoson *Unison, Hong Kong; Unison, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromotec *Teuto, Braz.*
⊗ Fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Bromotiren *Baldacci, Ital.*
Dibromotyrosine (p.2169·1).
Hyperthyroidism.

Bromotuss with Codeine *Rugby, USA.*
Bromazine hydrochloride (p.569·1); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Bromovent *Bergamo, Braz.*
Ipratropium bromide (p.1124·1).
Asthma.

Bromox *Etifar, Venez.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Bromoxil *Vitae, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Bromoxon *Sanval, Braz.*
Bromazepam (p.964·3).
Anxiety.

Bromped *Hua, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic respiratory-tract disorders; nasal congestion.

Bromphen DX Cough *Muro, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Bromphenex *Ethex, Hong Kong.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Brompheniramine Cough *Geneva, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Brom-PP *Jean-Marie, Hong Kong.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract disorders.

Brom-Ramine Compound *Universal, Hong Kong.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract disorders.

Bromso *TO-Chemicals, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromso-Ex *TO-Chemicals, Thai.*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromtine *Duopharma, Hong Kong.*
Bromocriptine (p.800·3).
Acromegaly; hyperprolactinaemia; parkinsonism.

Bromtussia *Asian Pharm, Thai.*
Guaifenesin (p.1561·3); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

Bromtussia DC *Asian Pharm, Thai.†.*
Guaifenesin (p.1561·3); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2).
Coughs; nasal congestion.

Bromuc *Ariston, Braz.; Fujisawa, Ger.†; Klinge, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromurex *Pisa, Mex.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Bromxin *Masa, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Bromxine *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.; General Drugs, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bromycil *Ace, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excess mucus.

Bron 6 *Capo Sole, Ital.†.*
Chestnut honey; propolis; althaea; erisimo; thyme; wild rose; niaouli oil (p.1922·1).
Food supplement; tonic.

Bronacim *Valmor, Venez.†.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Bronalide *Boehringer Ingelheim, Gr.†.*
⊗ Flunisolide (p.1531·1).
Asthma.

Bronar *Degorts, Mex.*
Ambroxol hydrochloride (p.1550·3); loratadine (p.583·3).
Respiratory-tract disorders.

Bronax *Roemmers, Arg.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Broncafect *Mediherb, Austral.*
Pleurisy root (p.2370·1); echinacea (p.2298·1); liquorice (p.1740·3); marrubium (p.1564·1); thyme (p.2401·1); ginger (p.1732·3).
Cold and influenza symptoms; coughs.

Broncaire Expectorant *Biolab, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol (p.1131·2).
Obstructive airways disease.

Broncal *Novel, Ital.†.*
Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2).
Coughs.

Broncalene *McNeil, Fr.*
Pholcodine (p.1570·2); chlorphenamine maleate (p.571·3); sodium benzoate (p.1630·2).
Coughs.

Broncalene Nourisson *McNeil, Fr.*
Chlorphenamine maleate (p.571·3); sodium benzoate (p.1630·2); tolu balsam (p.1574·2).
Coughs.

Broncard *Labomed, Chile.*
Levodropropizine (p.1557·3).
Coughs.

Broncasma *Berna, Port.†.*
An inactivated bacterial vaccine containing lysates of *Haemophilus influenzae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Neisseria t.*; pneumococcus; staphylococcus; *Streptococcus haemolyticus*; *Streptococcus viridans*.

Broncatar *Cazi, Braz.*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Broncelix *Pfizer Consumer, NZ.*
Choline theophyllinate (p.1119·3); guaifenesin (p.1561·3).
Coughs.

Bronchalis-Heel *Peithner, Austria; Heel, Cz.*
Homoeopathic preparation.

Bronchathiol *Aventis, Belg.†; McNeil, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Bronchenolo
Note. This name is used for preparations of different composition.
GSK Consumer, Ital.†.
Pastilles: Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

GSK Consumer, Ital.
Syrup: Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2); ammonium acetate (p.1551·2).
Coughs.

GSK Consumer, Ital.
Tablets: Dextromethorphan hydrobromide (adsorbed onto magnesium trisilicate) (p.1555·2).
Coughs.

Bronchenolo Antiflu *GSK, Ital.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Bronchette *Pharmacare, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excess and viscous mucus.

Bronchex *Hilarys, Canad.†.*
Ammonium chloride (p.1551·3); ammonia (p.2256·1); ammonium carbonate (p.1551·3); glycerol (p.2314·2); liquorice (p.1740·3); menthol (p.2340·1); siberian fir oil; white pine compound.

Bronchial *Atlas, Canad.; Theralab, Canad.*
Ammonium chloride (p.1551·3); senega (p.1572·3); white pine compound.

Bronchial Cough
Note. This name is used for preparations of different composition.
Hylands, Canad.
Homoeopathic preparation.

Pendopharm, Canad.
Ammonium chloride (p.1551·3); aralia racemosa; poplar buds (p.2371·1); sanguinaria (p.2383·2); senega (p.1572·3); white pine; wild cherry (p.2415·2).
Cough.

Bronchialbalsam *Ratiopharm, Ger.†.*
Pine needle oil (p.2368·2); eucalyptus oil (p.2301·2).
Catarrh.

Bronchialtee N *Abtswinder, Cz.†.*
Liquorice (p.1740·3); plantaginis (p.2379·1); fennel (p.2302·3); thyme (p.2401·1); viola tricolor (p.2415·2); wild thyme (p.2415·3); cowslip (p.2372·2).
Upper respiratory-tract disorders.

Bronchiase *Lafare, Ital.*
Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2).
Coughs.

Bronchicough *Aventis, S.Afr.†.*
⊗ Cimicifuga (p.2282·1); grindelia (p.2317·2); burnet saxifrage (p.2270·3); cowslip (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1); ephedrine hydrochloride (p.1558·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); saponin.
Coughs.

Bronchicum
Note. This name is used for preparations of different composition.
Cassella-med, Ger.
Thyme (p.2401·1); cowslip root (p.2372·2).
Respiratory-tract disorders associated with viscous mucus.

Aventis, Neth.
Thyme (p.2401·1); primula root (p.2372·2); grindelia (p.2317·2); burnet saxifrage root (p.2270·3); anise oil (p.2258·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); saponin.
Coughs.

Nattermann, Pol.†.
Quebracho (p.2377·1); soapwort (p.2388·2); thyme (p.2401·1); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Catarrh.

Aventis, Rus.
Grindelia (p.2317·2); saxifraga; primula (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1).
Respiratory-tract disorders.

Aventis, S.Afr.†.
⊗ Cimicifuga (p.2282·1); grindelia (p.2317·2); burnet saxifrage (p.2270·3); cowslip (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1); ephedrine hydrochloride (p.1558·2); menthol (p.2340·1); sodium bromide (p.2269·2); eucalyptus oil (p.2301·2); saponin.
Bronchitis.

Bronchicum Balsam mit Eukalyptusol *Nattermann, Ger.†.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); pine silvestris oil (p.2368·2).
Catarrh; cold symptoms.

Bronchicum Eliksir *Nattermann, Pol.*
Grindelia (p.2317·2); burnet saxifrage (p.2270·3); primrose root (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Catarrh.

Bronchicum Elixir *Aventis, Cz.†.*
Grindelia (p.2317·2); burnet saxifrage (p.2270·3); cowslip (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1).
Bronchitis; coughs.

Bronchicum Elixir N *Nattermann, Ger.†.*
Grindelia (p.2317·2); burnet saxifrage (p.2270·3); primula root (p.2372·2); quebracho (p.2377·1); thyme (p.2401·1).
Bronchial congestion; coughs.

Bronchicum Elixir Plus *Nattermann, Ger.†.*
Thyme (p.2401·1); ribwort plantain (p.2379·1); primula root (p.2372·2).
Bronchial congestion; coughs.

Bronchicum Elixir S *Cassella-med, Ger.*
Thyme (p.2401·1); cowslip root (p.2372·2).
Bronchitis; catarrh; coughs.

Bronchicum Extra Sterk *Aventis, Neth.*
Codeine phosphate (p.37·2).
Formerly contained ephedrine hydrochloride, codeine phosphate, and vegetable extracts.
Coughs.

Bronchicum Husten
Note. This name is used for preparations of different composition.
Aventis, Rus.
Pastilles: Thyme (p.2401·1).
Cough.

Aventis, Rus.
Syrup: Thyme (p.2401·1); rose fruit (p.2381·2); saxifraga; primula (p.2372·2); grindelia (p.2317·2); honey (p.1948·2).
Cough.

Bronchicum Husten-Pastillen *Aventis, Cz.†.*
Thyme (p.2401·1).
Coughs; sore throat.

Bronchicum Hustensirup *Aventis, Cz.†.*
Grindelia (p.2317·2); burnet saxifrage (p.2270·3); cowslip (p.2372·2); thyme (p.2401·1); rose fruit (p.2381·2).
Catarrh.

Bronchicum Medizinal-Bad *Cassella-med, Ger.†.*
Thyme oil (p.2401·2).
Bath additive; respiratory-tract disorders.

Bronchicum Mono Codein *Cassella-med, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Bronchicum N *Nattermann, Pol.*
Thyme (p.2401·1).
Catarrh; cough.

Bronchicum Pastillen *Cassella-med, Ger.†.*
Thyme (p.2401·1).
Coughs; sore throat.

Bronchicum Pflanzlicher *Nattermann, Ger.†.*
Thyme (p.2401·1); drosera (p.2297·3).
Cold symptoms; coughs.

Bronchicum Pflanzlicher Hustenstiller *Aventis, Cz.†.*
Drosera (p.2297·3); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Cold symptoms; coughs.

Bronchicum Sekret-Loser *Aventis, Cz.†; Nattermann, Ger.†.*
Eucalyptus oil (p.2301·2); thyme (p.2401·1); cowslip (p.2372·2).
Upper respiratory-tract disorders; upper respiratory-tract disorders with viscous mucus.

Bronchicum T *Nattermann, Pol.*
Thyme (p.2401·1).
Catarrh; cough.

Bronchicum Thymian *Nattermann, Ger.†.*
Primula root (p.2372·2); thyme (p.2401·1).
Bronchitis; coughs.

Bronchicum Tropfen *Aventis, Cz.†.*
Quebracho (p.2377·1); soapwort (p.2388·2); thyme (p.2401·1); eucalyptus oil (p.2301·2).
Bronchitis.

Bronchicum Tropfen N *Nattermann, Ger.†.*
Quebracho (p.2377·1); soapwort (p.2388·2); thyme (p.2401·1).
Bronchitis.

Bronchi-Do *Grasler, Ger.*
Homoeopathic preparation.

Bronchiflu *Aventis, S.Afr.†.*
Mepyramine maleate (p.585·2); menthol (p.2340·1); ammonium chloride (p.1551·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; coughs.

Bronchikatt *Kattwiga, Ger.†.*
Homoeopathic preparation.

Bronchil *Siam Bheasach, Thai.*
Guaifenesin (p.1561·3); theophylline (p.1140·1).
Obstructive airways disease.

Bronchilet *Nicholas Piramal, India†.*
⊗ Salbutamol sulfate (p.1131·3); etofylline (p.1121·1).
Obstructive airways disease.

Bronchilin *Flordis, Austral.†.*
Primrose; thyme (p.2401·1).
Coughs.

Bronchilite *Eulite, Neth.*
Homoeopathic preparation.

Bronchilon *Cesra, Ger.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Bronchi-Mereprine *Novum, Belg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with viscous mucus.

Bronchiole *Bevo, Gr.†.*
Carbocisteine (p.1553·2).

Bronchi-Pertu *Pekana, Ger.†.*
Homoeopathic preparation.

Bronchipret
Note. This name is used for preparations of different composition.
Austroplant, Austria; Bionorica, Rus.
Thyme (p.2401·1); ivy (p.2328·1).
Bronchitis; respiratory-tract disorders.

Bionorica, Cz.; Bionorica, Philipp.; Pharmalink, Philipp.
Primula (p.2372·2); thyme (p.2401·1).
Bronchitis; respiratory-tract disorders.

Bionorica, Ger.
Oral drops; oral liquid: Thyme (p.2401·1); ivy (p.2328·1).
Bronchitis.

Bionorica, Hung.
Oral drops; syrup: Thyme (p.2401·1); ivy (p.2328·1).
Bronchitis.

Bionorica, Ger.
Pastilles: Thyme (p.2401·1).
Bronchitis; cold symptoms; coughs.

Bionorica, Indon.; Darya-Varia, Indon.
Syrup: Thyme (p.2401·1); ivy (p.2328·1).
Respiratory-tract disorders.

Bionorica, Ger.; Bionorica, Hung.; Bionorica, Indon.; Darya-Varia, Indon.
Tablets: Primula root (p.2372·2); thyme (p.2401·1).
Bronchitis; respiratory-tract disorders.

Bronchipret TP *Bionorica, Rus.*
Primula root (p.2372·2); thyme (p.2401·1).
Respiratory-tract disorders.

Bronchiselect *Dreluso, Ger.*
Homoeopathic preparation.

Bronchithym *Austroplant, Austria.*
Thyme (p.2401·1); cowslip (p.2372·2).
Bronchitis.

Bronchitin *Nufarindo, Indon.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Bronchitussin *Vramed, Rus.*
⊗ Glaucine hydrobromide (p.1561·1); ephedrine hydrochloride (p.1558·2); basil oil (p.2263·2).

Broncho D *Sam-On, Israel.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs; respiratory-tract congestion.

Broncho Fertiginhalat *Astellas, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Broncho Inhalat *Astellas, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Broncho Munal *Medice, Ger.†; Abiogen, Ital.; Lek, Rus.*
Haemophilus influenzae; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Moraxella catarrhalis*.
Respiratory-tract infections.

Broncho Saline *Blairex, USA.*
Sodium chloride (p.1686·1).
Diluent for bronchodilator solutions for inhalation.

Bronchobest *CT, Ger.†.*
Spike lavender oil (p.2392·1).
Bronchitis.

Bronchobos *Bosnalek, Rus.*
Carbocisteine (p.1553·2).
Otitis media; respiratory-tract disorders associated with increased or viscous mucus.

Bronchocin *Balkanpharma, Rus.*
⊗ Glaucine hydrobromide (p.1561·1); ephedrine hydrochloride (p.1558·2); basil oil (p.2263·2).
Respiratory-tract disorders.

Bronchocort *Astellas, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Bronchodam *Filadams, Philipp.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bronchodex Pastilles *Prodemdis, Canad.*
Domiphen bromide (p.1643·1).

Bronchodex Pastilles Antiseptiques *Prodemdis, Canad.*
Hexylresorcinol (p.1647·1).

Bronchodex Vapo *Theralab, Canad.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1).

Bronchodex-Rub *Theralab, Canad.†.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Bronchodine *Pharmacobel, Belg.*
Codeine phosphate (p.37·2).
Coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Bronchodual *Boehringer Ingelheim, Fr.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Bronchodurat N *Pohl, Ger.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Bronchitis; cold symptoms.

Broncho-Euphyllin *Altana, Ger.*
Theophylline (p.1140·1); ambroxol hydrochloride (p.1550·3).
Obstructive airways disease.

Bronchofen *Pharma Nutria, Philipp.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; rhinitis; sinusitis.

Bronchofluid N *DP-Medica, Switz.†.*
Guaifenesin (p.1561·3); drosera (p.2297·3); ivy (p.2328·1); ribwort plantain (p.2379·1); senega (p.1572·3); thyme (p.2401·1); anise oil (p.2258·2).
Coughs with excessive mucus.

Bronchoforton
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Austria†.
Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2); peppermint oil (p.1761·2).
Cold and influenza symptoms.

Winthrop, Ger.
Capsules: Eucalyptus oil (p.2301·2); anise oil (p.2258·2); peppermint oil (p.1761·2).
Catarrh.

Winthrop, Ger.
Ointment: Eucalyptus oil (p.2301·2); Norway spruce oil; peppermint oil (p.1761·2).
Catarrh; cold symptoms.

Winthrop, Ger.
Oral liquid: Ivy (p.2328·1).
Bronchitis; catarrh.

Bronchoforton Kinderbalsam *Winthrop, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Coughs; respiratory-tract congestion.

Bronchofyl *Remedina, Gr.*
Butamirate (p.1553·1).
Cough.

Bronchohexal *Hexal, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Broncho-Kid *Sam-On, Israel.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Bronchokod *Sanofi-Aventis, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bronchol *Streuli, Switz.*
Guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Broncholate
Note. This name is used for preparations of different composition.
Sam-On, Israel.
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract disorders.

Sanofi Winthrop, USA.
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

Broncholate Forte *Sam-On, Israel.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Respiratory-tract disorders.

Broncholate Plus *Sam-On, Israel.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Broncholine *TO-Chemicals, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Broncholit *Nicholas, Indon.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Broncholysin *Spofa, Cz.†.*
Acetylcysteine (p.1548·2).
Paracetamol overdosage; respiratory-tract disorders associated with increased or viscous mucus.

Broncholytin *Sopharma, Rus.*
⊗ Glaucine hydrobromide (p.1561·1); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Bronchonyl
Note. This name is used for preparations of different composition.
Pharmasant, Thai.
Syrup: Terbutaline hydrochloride; guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Pharmasant, Thai.
Tablets: ⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bronchoparat *Astellas, Ger.*
Theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Bronchopect *Herbapol Poznan, Pol.*
Ivy (p.2328·1).
Catarrh.

Broncho-pectoralis Pholcodine *Medgenix, Belg.*
Pholcodine (p.1570·2); sulfogaiacol (p.1573·2).
Coughs and nasal congestion.

Bronchoped *Adcock Ingram, S.Afr.*
⊗ Terbutaline sulfate (p.1138·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs with bronchospasm.

Bronchophan DM *Atlas, Canad.*
Dextromethorphan hydrobromide (p.1555·2).

Bronchophan Expectorant *Atlas, Canad.*
Guaifenesin (p.1561·3).
Cough.

Bronchophen *Sunthi Sepuri, Indon.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

Bronchophylin *Darya-Varia, Indon.*
Theophylline (p.1140·1).
Asthma.

Bronchoplus *Nycomed, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Bronchoprex Expectorant *Kenyaku, Thai.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2).
Catarrh; coughs.

Bronchoprex Syrup *Kenyaku, Thai.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract disorders.

Bronchopront
Grunenthal, Chile†; Mack, Cz.†; Pfizer Consumer, Ger.; Mack, Hong Kong; Mack, Hung.†; Combiphar, Indon.; Ferraz, Lynce, Port.†; Mack, Singapore†; Mack, Thai.†.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Zuoz, Venez.
Ambroxol (p.1550·3) or ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Bronchorectine au Citral *Mayoly-Spindler, Fr.*
Citral (p.2284·1); guaiacol (p.1561·2); terpin hydrate (p.1573·3); pine silvestris oil (p.2368·2); wild thyme oil (p.2415·3).
Respiratory disorders.

Bronchoretard *Astellas, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

Broncho-Rivo
Note. This name is used for preparations of different composition.
Rivopharm, Switz.†.
Adult: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Rivopharm, Switz.†.
Paediatric: Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Bronchosan *Zentiva, Cz.*
Bromhexine hydrochloride (p.1552·2); menthol (p.2340·1); fennel oil (p.2303·1); anise oil (p.2258·2); origanum oil (p.2358·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Bronchosan Nouvelle formule *Bioforce, Switz.†.*
Ivy (p.2328·1); thyme (p.2401·1); liquorice (p.1740·3).
Coughs.

Bronchosedal
Note. This name is used for preparations of different composition.
Janssen-Cilag, Belg.
Oral liquid: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Janssen-Cilag, Belg.
Syrup: Codeine phosphate (p.37·2).
Coughs.

Broncho-Sern *Truw, Ger.*
Ribwort plantain (p.2379·1).
Cold symptoms; inflammation of mouth and throat.

Bronchosol *Phytofarm Kleka, Pol.*
Thyme (p.2401·1); primrose root (p.2372·2); thymol (p.1664·3).
Cough; respiratory-tract congestion.

Bronchosolvin *Ipca, India.*
⊗ Bromhexine hydrochloride (p.1552·2); terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs; respiratory-tract disorders associated with viscous mucus.

Bronchospasmin *Viatris, Ger.*
⊗ Reproterol hydrochloride (p.1131·1).
Status asthmaticus.

Bronchospect *Pfizer Consumer, S.Afr.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs.

Bronchospray *Astellas, Ger.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Bronchostad Hustenloser *Stada, Ger.*
Ivy (p.2328·1).
Cold symptoms.

Bronchostop
Note. This name is used for preparations of different composition.
Metochem, Cz.†.
Guaifenesin (p.1561·3); thyme (p.2401·1); chamomile (p.2279·3); anise oil (p.2258·2).
Cold symptoms; coughs.

Metochem, Austria.
Capsules: Mentholum valerianicum; guaifenesin (p.1561·3); eucalyptus oil (p.2301·2); camphor (p.2273·2).
Coughs.

Metochem, Austria.
Ointment: Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); pumilio pine oil (p.2376·3); thyme oil (p.2401·2).
Catarrh; colds; cough; sore throat.

Metochem, Austria.
Oral drops: Guaifenesin (p.1561·3); thyme (p.2401·1); chamomile (p.2279·3); anise oil (p.2258·2).
Coughs.

Bronchosyx comp *Syxyl, Ger.*
Homoeopathic preparation.

Bronchosyx N *Syxyl, Ger.†.*
Liquorice (p.1740·3); thyme (p.2401·1).
Cold symptoms.

Broncho-Truw Erkaltungsbalsam *Truw, Ger.*
Eucalyptus oil (p.2301·2).
Cold symptoms.

Bronchotussine
Note. This name is used for preparations of different composition.
Adelco, Gr.
Bromhexine hydrochloride (p.1552·2).
Respiratory disorders associated with viscous mucus.

Vifor, Switz.
Butetamate citrate (p.1553·1); codeine phosphate (p.37·2).
Coughs.

Broncho-Tyrosolvetten *Byk Gulden, Ger.†; Roland, Ger.†.*
Cetylpyridinium chloride (p.1635·1); ammonium chloride (p.1551·3); liquorice (p.1740·3).
Mouth and throat infections; respiratory-tract catarrh.

Broncho-Vaxom
Note. This name is used for preparations of different composition.
Casasco, Arg.; Altana, Austria; Solvay, Belg.; Nycomed, Braz.; Andromaco, Chile; OM, Cz.; Altana, Ger.; OM, Hung.; Altana, Ital.; Grunenthal, Mex.; OM, Philipp.; Pharmalink, Philipp.; OM, Pol.; OM, Port.; OM, Rus.; OM, Switz.
Lysate of: *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Moraxella catarrhalis*.
Respiratory-tract infections.

Gap, Gr.; OM, Hong Kong.
Bacterial lysate.
Respiratory-tract infections.

Bronchowern *Wernigerode, Ger.; Wernigerode, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Broncimucil *Uriach, Spain.*
Brovanexine hydrochloride (p.1553·1).
Respiratory-tract disorders associated with increased mucus.

Broncivent *Boehringer Ingelheim, Spain†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Bronclear
Note. A similar name is used for preparations of different composition (see below).
Polipharm, Thai.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncleer
Note. A similar name is used for preparations of different composition (see above).
Adcock Ingram, S.Afr.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Broncleer with Codeine *Adcock Ingram, S.Afr.; Propan, S.Afr.*
Codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Bronco Aseptilex Fuerte *Chiesi, Spain.*
Bromhexine hydrochloride (p.1552·2); co-trimoxazole (p.258·1); guaiacol cinnamate (p.1561·2).
Respiratory-tract infections.

Bronco Asmo *Pond's, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bronco Asmol *Herbes Universelles, Canad.*
Ammonium bicarbonate (p.1551·3); anethole (p.2258·1); tolu balsam (p.1574·2); benzoic acid (p.1630·2); camphor (p.2273·2); squill (p.1573·1).

Bronco Biotaer *Disprovent, Arg.†.*
Ambroxol hydrochloride (p.1550·3); clofedanol hydrochloride (p.1554·2); pseudoephedrine sulfate (p.1571·2); astemizole (p.567·2).

Bronco Etersan *Dallas, Arg.*
Terpineol (p.2396·1); cineole (p.2282·3); pine silvestris oil (p.2368·2); turpentine oil (p.2406·3).
Respiratory-tract disorders.

Bronco Medical *Medical, Spain.*
Sulfogaiacol (p.1573·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Bronco Tonic *Vir, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Bronco-Amoxil *GSK, Braz.†.*
Amoxicillin (p.202·2); bromhexine hydrochloride (p.1552·2).
Bacterial infections.

Broncocalmine *Oriental, Arg.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Broncocent *Blue Sky, Philipp.*
Carbocisteine (p.1553·2).
Coughs.

Broncoclar
Note. This name is used for preparations of different composition.
UPSA, Fr.
Granules for oral solution: Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

UPSA, Fr.
Syrup: Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncodeina *Pasteur, Chile.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); belladonna liquid extract (p.2263·3); menthol (p.2340·1); sodium benzoate (p.1630·2); terpin hydrate (p.1573·3).
Coughs.

Broncodiazina *Vitoria, Port.*
⊗ Ammonium chloride (p.1551·3); pentetrazol (p.2162·1); sodium benzoate (p.1630·2); sulfadiazine (p.336·2); drosera (p.2297·3); tolu balsam (p.1574·2).
Respiratory-tract disorders.

Broncodual *Laboratorios Chile, Chile.*
Clobutinol (p.1554·2).
Coughs.

Broncodual Compuesto *Laboratorios Chile, Chile.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1); ammonium chloride (p.1551·3).
Coughs; obstructive airways disease.

Broncofama *FAMA, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Broncofenil *Zurita, Braz.*
Guaifenesin (p.1561·3).
Formerly contained guaifenesin, lobelia, and aconite.
Cough.

Broncofisin *Luper, Braz.†.*
Tolu balsam (p.1574·2); potassium iodide (p.2169·2); sulfogaiacol (p.1573·2).
Coughs.

Broncofluid *Recofarma, Ital.*
Prenoxdiazine hibenzate (p.1571·1); carbocisteine (p.1553·2).
Coughs.

Broncoflux *Farmasa, Braz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broncofol *Ipca, India†.*
⊗ Theophylline (p.1140·1); ephedrine (p.1558·1); phenobarbital (p.492·2).
Asthma.

Broncofol-P *Ipca, India†.*
⊗ Theophylline (p.1140·1); ephedrine (p.1558·1).
Asthma.

Broncoformo Muco Dexa *Gayoso, Spain.*
⊗ Dexamethasone (p.1526·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2).
Respiratory-tract disorders.

Broncokin *Geymonat, Ital.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Broncol
Note. This name is used for preparations of different composition.
Delta, Braz.
Eucalyptus (p.2301·2); ginger (p.1732·3); siparuna apiosyce; lantana camara; mikania glomerata; belladonna (p.2263·3); jaborandi.
Coughs.

Crown, S.Afr.†.
Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); panthenol (p.2362·1).
Coughs.

Pharmaland, Thai.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Broncolex *Legrand, Braz.†.*
⊗ Guaifenesin (p.1561·3); etafedrine hydrochloride (p.1560·2); bufylline (p.1116·3); doxylamine succinate (p.578·2).
Coughs.

Broncoliber *Tecnimede, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Broncomega *Almirall, Spain†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Broncomnes *Bracco, Ital.*
Ambroxol acefyllinate (p.1114·2).
Bronchospasm.

Broncomucil *GSK, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with excess or viscous mucus.

Bronconait *GSK, Ital.†*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Bronconal *Cifarma, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Bronconex *Schering-Plough, NZ.*
⊗ Mometasone furoate (p.1539·3).
Asthma.

Broncophilina *Behrens, Venez.*
Aminophylline (p.1114·2).
Asthma.

Broncopinol *Luper, Braz.†*
⊗ 1 Ampoule, dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); myrtol (p.2349·3); suprarenal cortex (p.1543·3); chlorophyllin copper complex potassium (p.1471·1); cineole (p.2282·3); 1 ampoule, chlorphenamine maleate (p.571·3); vitamin C (p.1983·3).
Cold and influenza symptoms.

Bronco-Polimoxil *Legrand, Braz.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Bacterial infections.

Broncopulmo *Merck, Port.†*
Sobrerol (p.1572·3).
Coughs.

Broncoral *Ferrer, Spain.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Broncorinol Expectorant *Bayer Sante, Fr.†*
Carbocisteine (p.1553·2).
Viscous bronchial secretions.

Broncorinol maux de gorge *Roche Nicholas, Fr.†*
Cetylpyridinium chloride (p.1635·1); tetracaine hydrochloride (p.1871·3); ascorbic acid (p.1983·3).
Sore throat.

Broncorinol rhinites *Roche Nicholas, Fr.†*
Cetrimide (p.1634·1); tyrothricin (p.358·2).
Upper respiratory-tract infections.

Broncorinol rhume *Roche Nicholas, Fr.†*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Broncorinol toux seche *Bayer Sante, Fr.†*
Pholcodine (p.1570·2); sodium benzoate; senega; eucalyptus.
Formerly contained pholcodine, sodium benzoate, aconite, hyoscyamus, lobelia, senega, and eucalyptus.
Coughs.

Broncort *Boehringer Ingelheim, Switz.†*
⊗ Flunisolide (p.1531·1).
Obstructive airways disease.

Broncosed *Noos, Ital.*
Thyme (p.2401·1); castanea vesca.

Broncosedina *FAMA, Ital.*
Cocillana (p.1554·3); eriodictyon (p.1560·2); marrubium (p.1564·1); grindelia (p.2317·2); juniper (p.2328·2); compound thyme (p.2401·1); pumilio pine oil (p.2376·3); mint oil (p.2345·2).
Respiratory-tract disorders.

Broncoserum *Ifusa, Mex.*
Sulfogaiacol (p.1573·2).
Coughs.

Broncosil *Basi, Port.†*
Camphor (p.2273·2); quinine (p.612·2).

Broncospasmine *Asta Medica, Ital.†*
⊗ Reproterol hydrochloride (p.1131·1).
Asthma.

Broncot *K2 Pharmacare, Chile.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Broncoten *Farmion, Braz.†*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Broncoteril *Farmanic, Gr.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Broncoterol
Note. This name is used for preparations of different composition.
Bago, Chile†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Azevedos, Port.
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Broncoterol-B *Bago, Chile†.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Broncotosil *Bago, Chile†.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Broncotron-D *Seyer, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Bronco-Turbinal *Valeas, Ital.†*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Broncovaleas *Valeas, Cz.†; Valeas, Ital.*
⊗ Salbutamol (p.1131·2).
Bronchospasm; obstructive airways disease.

Broncovanil *Skills, Ital.*
Guaifenesin (p.1561·3).
Respiratory-tract disorders.

Broncovir *Vir, Spain.*
Co-trimoxazole (p.258·1); sulfogaiacol (p.1573·2).
Respiratory-tract infections.

Broncovital
Note. This name is used for preparations of different composition.
Ifusa, Mex.
Chlorphenamine (p.572·2); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Puerto Galiano, Spain†.
⊗ Cineole (p.2282·3); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); niaouli oil (p.2351·3); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); belladonna (p.2263·3); drosera (p.2297·3); quebracho (p.2377·1); senega (p.1572·3).
Respiratory-tract disorders.

Broncozol *Mugi, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Brondal *Upha, Malaysia†.*
Guaifenesin (p.1561·3); theophylline (p.1140·1).
Obstructive airways disease.

Brondecon *Pfizer Consumer, NZ.*
Choline theophyllinate (p.1119·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Brondecon Elixir *Pfizer Consumer, Austral.*
Choline theophyllinate (p.1119·3).
Obstructive airways disease.

Brondecon Expectorant *Pfizer Consumer, Austral.*
Choline theophyllinate (p.1119·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Brondil *Great Eastern, Thai.; Therapharma, Thai.*
⊗ Etafedrine hydrochloride (p.1560·2); theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Brondil (Reformulated) *United American, Philipp.*
Theophylline (p.1140·1).
Obstructive airways disease.

Brondilat
Note. This name is used for preparations of different composition.
Ache, Braz.
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Pediapharm, Chile; Pharmabiotics, Chile.
Montelukast (p.1126·3).
Asthma.

Brondilax *Vitarum, Arg.*
Bromhexine (p.1552·2).

Brondilex *Biomedis, Indon.; Medifarma, Indon.*
Theophylline (p.1140·1).
Asthma.

Brondix *Pentafarm, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Bronfilil *Cifarma, Braz.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Bronica *Takeda, Jpn.*
Seratrodast (p.1136·2).
Asthma.

Bronilide *Boehringer Ingelheim, Cz.†*
⊗ Flunisolide (p.1531·1).
Asthma.

Bronilis *Leti, Venez.*
Ambroxol acefyllinate (p.1114·2).

Bronkaid Dual Action *Sterling, USA.*
⊗ Ephedrine sulfate (p.1558·2); guaifenesin (p.1561·3).

Bronkar *Nobel, Turk.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Bronkar-A *Nobel, Turk.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Bronkasma *Sanofi Synthelabo, Arg.†*
⊗ Theophylline (p.1140·1); ephedrine sulfate (p.1558·2).
Asthma.

Bronkese *Pharmacare, S.Afr.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with viscous mucus.

Bronkese Compound *Pharmacare, S.Afr.*
⊗ Bromhexine hydrochloride (p.1552·2); orciprenaline sulfate (p.1129·1).
Coughs.

Bronkids *Great Southern, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).

Bronkirex *Irex, Fr.†*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Bronkitose Mielimon *Biofarma, Mex.*
Cineole (p.2282·3); verbascum (p.2413·3); sambucus (p.2383·1).
Respiratory-tract infections.

Bronklast *Farma, Venez.*
⊗ Budesonide (p.1520·1).
Asthma.

Bronkolin *Adeka, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Bronkotrat *Hexal, Braz.†*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Bronkotuss Expectorant *Hyrex, USA.*
⊗ Ephedrine sulfate (p.1558·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs.

Bronkyl *Weifa, Norw.*
Acetylcysteine (p.1548·2).
Chronic bronchitis; cystic fibrosis.

Bronmycin *Biolab, Malaysia†; Biolab, Singapore; Biolab, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Bronoday *Okasa, Thai.; TTN, Thai.*
Theophylline (p.1140·1).
Obstructive airways disease.

Bronolban *Sons, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Bronolban-M *Sons, Mex.*
⊗ Ambroxol (p.1550·3); clenbuterol (p.1120·1).
Respiratory-tract congestion.

Bro-N-Pain *Brovar, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Bronpax *Schering-Plough, Mex.*
Benzonatate (p.1552·1).
Coughs.

Bronpect-D *Kenyaku, Hong Kong; Kenyaku, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Bronpul *Soria Natural, Spain†.*
Eucalyptus (p.2301·2); verbascum flower (p.2413·3); althaea (p.2253·3); elecampane (p.1558·1); liquorice (p.1740·3).
Lower respiratory-tract infections.

Bronq-C *Bernabo, Arg.*
⊗ Clenbuterol (p.1120·1) or clenbuterol hydrochloride (p.1120·1).

Bronquial *OM, Port.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Respiratory-tract congestion.

Bronquiasmol *Confar, Port.†*
⊗ Ephedrine (p.1558·1); ethylmorphine (p.52·2); sodium benzoate (p.1630·2).
Coughs.

Bronquicisteina *Iquinosa, Spain.*
Carbocisteine (p.1553·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bronquidex *Farmalab, Braz.*
⊗ Potassium iodide (p.2169·2); guaifenesin (p.1561·3); diphenhydramine hydrochloride (p.577·2); sodium benzoate (p.1630·2); ammonium chloride (p.1551·3); belladonna (p.2263·3); lobelia (p.2157·2).
Respiratory-tract congestion.

Bronquidiazina CR *Faes, Spain.*
Tolu balsam (p.1574·2); bromhexine (p.1552·2); sodium benzoate (p.1630·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bronquil *Vitapan, Braz.†*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Bronquimar *Decrox, Spain.*
Guaifenesin (p.1561·3); sodium benzoate (p.1630·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bronquimucil
Note. This name is used for preparations of different composition.
Arrow, Braz.; Prospa, Port.†.
Brovanexine hydrochloride (p.1553·1).
Respiratory-tract congestion; respiratory-tract disorders.

Uriach, Spain†.
Brovanexine hydrochloride (p.1553·1); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Bronquiogem *Prodotti, Braz.*
Yucca (p.2416·3); rorippa nasturtium aquaticum; mikania glomerata; lantana camara; passion flower (p.2363·2); erva silvina; oleo vermelho; sodium benzoate (p.1630·2).
Respiratory-tract disorders.

Bronquisedan *Gramon, Arg.*
Clobutinol hydrochloride (p.1554·1); ambroxol hydrochloride (p.1550·3).
Formerly contained theophylline glycinate, clobutinol hydrochloride, and ambroxol hydrochloride.
Bronchitis; coughs.

Bronquisedan Elixir *Gramon, Arg.*
Bromhexine hydrochloride (p.1552·2).
Bronchitis; catarrh.

Bronquisedan Mucolitico *Gramon, Arg.*
Ambroxol hydrochloride (p.1550·3); clobutinol hydrochloride (p.1554·1).
Coughs.

Bronquisedan Paediatrico *Gramon, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Bronquitos *Legrand, Braz.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); theophylline (p.1140·1); vitamin B (p.1978·2).
Obstructive airways disease.

Bronsal *UCB, Spain.*
⊗ Betamethasone sodium phosphate (p.1518·3); diprophylline (p.1120·2); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Bronsema *F5 Profas, Spain.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Bronsema Expectorante *Pliva, Spain.*
Erythromycin ethyl succinate (p.269·3); guaifenesin (p.1561·3).
Respiratory-tract infections.

Bronsol *Vita, Venez.†*
Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Bronsolvan *Kalbe, Indon.*
Theophylline (p.1140·1).
Asthma.

Bronsul *Del Bel, Arg.*
Canthaxanthin (p.1470·2); betacarotene (p.1930·3).
Suntanning aid.

Brontal *Sanitas, Chile.*
Bromhexine hydrochloride (p.1552·2); clofedanol hydrochloride (p.1554·2).
Coughs; respiratory-tract congestion.

Brontex *Procter & Gamble, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Brontoss *Teuto, Braz.*
⊗ Potassium iodide (p.2169·2); belladonna (p.2263·3); lobelia (p.2157·2); diphenhydramine hydrochloride (p.577·2).
Coughs.

Brontus *Chinta, Thai.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Coughs; respiratory-tract congestion.

Bronuck *Senju, Jpn.*
Bromfenac sodium (p.28·2).
Inflammatory eye disorders; postoperative eye inflammation.

Bronx *Lisapharma, Ital.†*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Bronxol *Cifarma, Braz.; Labialfarma, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Bronzearte *Gramon, Arg.*
Canthaxanthin (p.1470·2).
Suntanning aid.

Brooklax *Group, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Brooklax Pills *Group, S.Afr.*
Yellow phenolphthalein (p.1762·1); aloin (p.1705·3); capsicum oleoresin (p.2276·2).
Constipation.

Bropamil *Offenbach, Mex.†*
Bromazepam (p.964·3).
Anxiety.

Bropil *Pediapharm, Chile.*
⊗ Salbutamol (p.1131·2).

Broptin *IQFA, Mex.*
Bromocriptine (p.800·3).
Hyperprolactinaemia.

Broquixol *Schering-Plough, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Bros
Note. This name is used for preparations of different composition.
TRB, Arg.†.
Cerebral phospholipids (porcine) (p.2337·3).
Mental function impairment; tonic.

TRB, Braz.
Phosphatidyl serine (p.2367·1).
Cerebrovascular disorders.

Brosidon *Bros, Gr.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; Paget's disease of bone.

Brosiral *Bros, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Brosolan *Collins, Mex.*
Ambroxol (p.1550·3).
Coughs.

Brosolan C *Collins, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion.

Brosoline-Rectocaps *Mepha, Switz.†*
Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3).
Bronchial disorders.

Brospec *Prafa, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Brospina *Pisa, Mex.*
⊗ Buprenorphine (p.29·1).
Pain.

Brota Rectal Balsamico *Escaned, Spain.*
⊗ Camphor (p.2273·2); cineole (p.2282·3); ephedrine hydrochloride (p.1558·2); niaouli oil (p.2351·3); quinine sulfate (p.612·3); sulfogaiacol (p.1573·2).
Respiratory-tract disorders.

Brotazona *Escaned, Spain.*
Feprazone (p.60·2).
Gout; musculoskeletal and joint disorders.

Brovana *Sepracor, USA.*
⊗ Arformoterol tartrate (p.1115·3).
Obstructive airways disease.

Brovex PD *MCR, USA.*
Pseudoephedrine tannate (p.1572·1); brompheniramine tannate (p.569·3).
Upper respiratory-tract disorders.

Brovicarpine *Rafarm, Gr.†.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension.

Brovicton *Bros, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Brovon *GSK, India; Torbet Laboratories, UK.*
⊗ Adrenaline (p.1203·2); atropine methonitrate (p.1219·3); papaverine hydrochloride (p.2191·3).
Bronchospasm; emphysema.

Brown Mixture
Note.This name is used for preparations of different composition.
Vickmans, Hong Kong.
Liquorice (p.1740·3); camphorated opium (p.105·1).
Catarrh; coughs.
British Dispensary, Thai.
Liquorice fluid extract (p.1740·3); antimony potassium tartrate (p.141·2); camphorated opium tincture.
Coughs.

Broxal *Bernofarm, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broxamel *Andromaco, Venez.†.*
Bromhexine (p.1552·2); oxolamine phosphate (p.1567·1).
Cough.

Broxan *Dynamic, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with abnormal mucus.

Broxaquim *Quimica y Farmacia, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broxifil *Filadams, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broxil *GSK, Neth.*
Pheneticillin potassium (p.314·1).
Bacterial infections.

Broxil-M *Metz, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with abnormal mucus.

Broxine *Malayan, Singapore†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Broxitrol *Pharmacare, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Coughs with abnormal mucous secretion.

Broxo al Fluoro *SIT, Ital.*
Levomenol (p.2333·3); sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Gum disorders; halitosis.

Broxodin
Note.This name is used for preparations of different composition.
SIT, Ital.†.
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.
Vargas, Venez.
⊗ Bromhexine hydrochloride (p.1552·2); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders.
SIT, Ital.
Oral drops; oral gel: Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Broxofar *Farcoral, Mex.*
Ambroxol hydrochloride (p.1550·3).

Broxofar Compuesto *Farcoral, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders with viscous mucus.

Broxoffler *Loeffler, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broxol
Note.This name is used for preparations of different composition.
Mundipharma, Austria; Boniscontro & Gazzone, Ital.; Carnot, Mex.; Masa, Thai.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders; respiratory-tract disorders associated with increased or viscous mucus; respiratory-tract disorders with viscous mucus.
Galeno, Venez.
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Cough.

Broxol Air *Carnot, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders.

Broxol Plus *Carnot, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders with viscous mucus.

Broxolflem *Galeno, Venez.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Broxolgrip Dia *Galeno, Venez.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Cold symptoms.

Broxolgrip Noche *Galeno, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine (p.1571·2).
Cold symptoms.

Broxolim *Tocogino, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Broxolim-AM *Tocogino, Mex.†.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Broxolim-C *Tocogino, Mex.*
⊗ Ambroxol (p.1550·3); clenbuterol (p.1120·1).
Respiratory-tract disorders.

Broxolvan *Novo Pharm, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Broxsa *Silom, Thai.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Broxytone *IAE, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Bro-Zedex *Wockhardt, India.*
⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs associated with obstructive airways disease.

Brozepax *Biosintetica, Braz.†.*
Bromazepam (p.964·3).
Anxiety.

Brozil *YSP, Malaysia; Yung Shin, Singapore.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Bruace *Jagson, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Brucam *Bruluart, Mex.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Brucap *Bruluart, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension.

Bruciaporri *Giovanardi, Ital.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Verrucas; warts.

Brucilina *Bruluagsa, Mex.*
Ampicillin (p.204·1); dicloxacillin sodium (p.265·2).
Bacterial infections.

Brudol *Elmor, Venez.*
Ibuprofen (p.64·2); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Vascular headache.

Brufen
Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Gr.; Abbott, Hong Kong†; Knoll, India; Abbott, Irl.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Philipp.; Abbott, Port.; Abbott, S.Afr.; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK.
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.
Abbott, Ital.
Ibuprofen (p.64·2) or ibuprofen sodium (p.65·2).
Musculoskeletal and joint disorders; pain; soft-tissue injuries.

Brugesic *Pharmaniaga, Malaysia†; Raza, Malaysia†; Garec, S.Afr.†; Elmor, Venez.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Brugesina *Elmor, Venez.*
Ibuprofen (p.64·2); hyoscine butylbromide (p.1734·1).
Pain with spasm.

Bruise Cream *Medipharma, Hong Kong†.*
A heparinoid (p.1305·2).
Bruising.

Bruiseze *Bayer Consumer, UK.*
A heparinoid (p.1305·2).
Soft-tissue injury.

Brulamycin
Torrex, Austria; Medphano, Ger.†; Teva, Hung.; Biogal, Rus.
Tobramycin sulfate (p.354·2).
Bacterial infections.
Biogal, Cz.
Tobramycin (p.354·1).
Bacterial eye infections.

Brulex *Bailly, Fr.*
Phenazone (p.116·1); zinc oxide (p.1621·2); peru balsam (p.2365·3); phenol (p.1656·1); sodium salicylate (p.124·2).
Burns; sunburn.

Brulidine *Aspen, Austral.; Aventis, Norw.; Manx, UK.*
Dibrompropamidine isetionate (p.1642·1).
Burns; napkin rash; otitis externa; skin abrasions; skin infections.

Brulstop *Agepharm, Fr.†.*
Hydrocolloid dressing.
Burns.

Brumax *Bruluagsa, Mex.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Brumed *LSP, Thai.†.*
Ibuprofen (p.64·2).
Fever; pain.

Brumetidina *Bruschettini, Ital.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Brumeton Colloidale S *Bruschettini, Ital.*
⊗ Betamethasone (p.1518·2); sulfacetamide sodium (p.335·3).
Eye and ear disorders.

Brumixol *Bruschettini, Ital.*
Ciclopirox olamine (p.529·2).
Fungal skin and vulvovaginal infections.

Brunac *Bruschettini, Ital.; Bio-Gen, Turk.*
Acetylcysteine (p.1548·2).
Dry eyes.

Brunacod *Brunel, S.Afr.*
⊗ Promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2).
Coughs.

Brunacol *Bruluart, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Brunal *Fada, Arg.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Brunavera *Euroderm, Arg.*
Aloe vera (p.1588·2); calendula (p.2273·1); alpha tocopherol (p.1992·2).
Dry skin.

Brunazine *Brunel, S.Afr.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; motion sickness; nausea; vomiting.

Brunicrom *Bruschettini, Ital.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Brunocillin *Mepha, Switz.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Brunomol *Brunel, S.Afr.†.*
Paracetamol (p.108·1).
Fever; pain.

Brupen *Bruluagsa, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Brupen Compuesto *Bruluagsa, Mex.*
Ampicillin trihydrate (p.204·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Bruprin *Condrugs, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Brushtox *Dentox, UK.*
⊗ Denatured alcohol (p.1625·2); hydroxybenzoate esters (p.1648·3); zinc chloride (p.1999·1).
Disinfection of toothbrushes.

Brusil *Silom, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Brust- und Hustentee *Bad Heilbrunner, Ger.*
Thyme (p.2401·1); primula root (p.2372·2).
Respiratory-tract disorders with viscous mucus.

Brust- und Hustentee St Severin *Smetana, Austria.*
Castanea vulgaris; ribwort plantain (p.2379·1); verbascum leaf (p.2413·3); thyme (p.2401·1); elecampane (p.1558·1).
Respiratory-tract disorders.

Brustan *Ranbaxy, Philipp.; Ranbaxy, Rus.; Ranbaxy, Thai.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Brux *Cinetic, Arg.*
Omeprazole (p.1753·1).
Gastric hyperacidity.

Bruxel *Ivax, Arg.*
Proglumetacin maleate (p.119·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Bruxicam *Bruschettini, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Brylcreem Anti-Dandruff *Combe, Canad.*
Pyrithione zinc (p.1611·2).
Dandruff.

Bryorheum *DHU, Ger.*
Homoeopathic preparation.

BS *Xepa-Soul Pattinson, Singapore†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

BS Carino *Carinopharm, Ger.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

BSI Medicated Spray *Tungfa, Philipp.*
⊗ Nux vomica (p.2355·3); pinelliae tuber; drynariae rhizoma; liquorice (p.1740·3); ginseng (p.2312·1); lycopodium serratum; menthol (p.2340·1); methyl salicylate (p.85·3); alcohol (p.1625·2).
Muscle pain.

B-Six *Sam-On, Israel.*
Vitamin B (p.1978·2).
Vitamin B deficiency.

BS-ratiopharm *Ratiopharm, Ger.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

BSS *Alcon, Austral.; Alcon, Canad.; Alcon, Fr.; Alcon, Ger.; Serag-Wiessner, Ger.; Alkon (Αλκον), Gr.†; Alcon, Hong Kong†; Alcon, Hung.†; Alcon, Irl.†; Alcon, Israel; Alcon, Malaysia; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, UK; Alcon, USA; Alcon, Venez.†.*
Electrolyte solution (p.1667·1).
Eye irrigation; irrigation of ear, nose, and throat.

BSS Plus
Note.This name is used for preparations of different composition.
Alcon, Austral.; Alcon, Austria; Alcon, Canad.; Alcon, Fr.; Alcon, Ger.; Alcon, Hong Kong†; Alcon, Hung.; Alcon, Israel; Alcon, Malaysia; Alcon, Singapore; Alcon, Switz.†; Alcon, Thai.; Alcon, USA.; Alcon, Venez.†.
Electrolytes (p.1667·1) glucose (p.1945·3); oxiglutatione (p.1448·1).
Eye irrigation.
Alkon (Αλκον), Gr.†.
An electrolyte solution (p.1667·1).
Ocular irrigation during ophthalmic surgery.
Alcon, S.Afr.
Electrolytes (p.1667·1); glucose (p.1945·3); glutathione (p.1448·1).
Eye irrigation.

BT Enema *Yenisehir, Turk.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

B-Tablock *Latinofarma, Braz.*
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma.

B-Tasone-G *Beacons, Singapore.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

BTK-Plus *Geritrex, USA.*
Clorophene (p.1641·1); orthophenylphenol (p.1655·1); amylphenol.
Disinfectant.

BTXA *LIBP, Hong Kong.*
Botulinum A toxin (p.1890·1).
Blepharospasm; hemifacial spasm; strabismus.

BTX-HA Ofteno *Sophia, Mex.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

BU Pangramin SLIT *Alk-Scherax, Ger.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Buateron *Farmedia, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Bubil *Jaka, Rus.*
Pyrethrins (p.2049·3); acetic acid (p.2244·2).

Bucagel *Meda, Port.*
Choline salicylate (p.36·3).
Mouth disorders.

Bucain *Curasan, Austria; DeltaSelect, Ger.; Bernofarm, Indon.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bucaine *DeltaSelect, Hung.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bucanil *YSP, Malaysia; Yung Shin, Singapore†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Bucaril *Pharmaland, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Buccalin
Note.This name is used for preparations of different composition.
Kwizda, Austria.
Haemophilus influenzae; pneumococci; streptococci; staphylococcus aureus; ox bile extract (p.2266·3).
Prophylaxis of bacterial infections in patients with colds.
SIT, Ital.
Streptococcus pneumoniae I, II, and III; *Streptococcus haemolyticus*; *Staphylococcus aureus*; *Haemophilus influenzae*.
Prophylaxis of bacterial infections in patients with influenza.

Buccaline
Note.This name is used for preparations of different composition.
Qualiphar, Belg.; Berna, Hong Kong†; Pharmabroker, NZ; Berna, Thai.†.
Pneumococcus; streptococcus; staphylococcus; *Haemophilus influenzae*; ox bile extract (p.2266·3).
Common cold prophylaxis.
Desma, Switz.
Streptococcus haemolyticus; *Streptococcus pneumoniae*; *Staphylococcus aureus*; *Haemophilus influenzae*; ox bile (p.2266·3).
Common cold prophylaxis.

Buccalsone *Will-Pharma, Belg.†; Will-Pharma, Neth.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Aphthous stomatitis; mouth ulcers.

Buccapol *Berna, Turk.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Buccard *AstraZeneca, Denm.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Buccastem *Reckitt Benckiser, Irl.; Reckitt Benckiser, NZ; Reckitt Benckiser, UK.*
Prochlorperazine maleate (p.1020·1).
Migraine; nausea and vomiting; vertigo; vestibular disorders.

Buccosan *Pfizer Consumer, Belg.†.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Bucco-Tantum *Bayer, Switz.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation.

Buchex *Bernabo, Arg.*
Hexetidine (p.1647·1); benzydamine hydrochloride (p.27·3).
Mouth disorders.

Buchzine *Upha, Malaysia†.*
Buclizine hydrochloride (p.570·1).
Appetite loss; hypersensitivity reactions.

Bucin *Masa, Thai.†.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Buckleys *Nycomed, Neth.*
Ammonium carbonate (p.1551·3); balsam canadense; camphor (p.2273·2); potassium bicarbonate (p.1673·1); menthol (p.2340·1).

Buckley's Bedtime *Buckley, Canad.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Cold symptoms; coughs.

Buckleys Chest Congestion *Novartis, USA.*
Guaifensin (p.1561·3).
Cough.

Buckleys Cough *Novartis, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Buckley's Cough, Cold & Flu Daytime Relief *Buckley, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms; coughs.

Buckley's Cough, Cold & Flu Nighttime Relief *Buckley, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; coughs.

Buckley's DM *Buckley, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Dry cough.

Buckley's DM Decongestant *Buckley, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Buckleys Kinderhoestsiroop *Nycomed, Neth.*
Acetic acid (p.2244·2); ascorbic acid (p.1983·3); ipecacuanha (p.1562·3).

Buckley's Mixture *Buckley, Canad.*
Ammonium carbonate (p.1551·3); potassium bicarbonate (p.1673·1); menthol (p.2340·1); camphor (p.2273·2).
Cough.

Buckleys Pain Relief *Buckley, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle and joint pain.

Buckley's Sinus Pain Relief *Buckley, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Sinus pain.

Buckley's White Rub *Buckley, Canad.†.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); thymol (p.1664·3).
Cold symptoms; muscle and joint pain.

Bucladin-S Softab *Stuart, USA.*
Buclizine hydrochloride (p.570·1).
Motion sickness.

Buclamin *Teuto, Braz.†.*
Buclizine hydrochloride (p.570·1); tryptophan; lysine hydrochloride; pyridoxine; cyanocobalamin (p.1922·1).
Reduced appetite; tonic.

Buclen *Alian, Venez.*
⊗ Clenbuterol (p.1120·1).

Buclifen-Vit *Profarb, Braz.†.*
Buclizine hydrochloride (p.570·1); lysine; vitamin B (p.1922·1).
Reduced appetite; tonic.

Buclimax *Ducto, Braz.*
Buclizine hydrochloride (p.570·1); lysine; vitamin B substances (p.1922·1); caffeine (p.1116·3).
Reduced appetite; tonic.

Buclina *Sanofi-Aventis, Braz.; Vedim, Port.*
Buclizine hydrochloride (p.570·1).
Migraine; motion sickness; pruritus; reduced appetite.

Bucliplex *Dovalle, Braz.†.*
Buclizine hydrochloride (p.570·1); vitamin B substances (p.1922·1).
Reduced appetite; tonic.

Buclorhex *Sertex, Arg.*
Chlorhexidine hydrochloride (p.1635·2); sodium fluoride (p.1962·2).
Dental caries prophylaxis; mouth disorders.

Buco Bleu *Ilsan, Turk.*
Methylthioninium chloride (p.1450·3); resorcinol (p.1612·1).
Mouth and throat disorders.

Buco Regis *Ramon Sala, Spain.*
Ipecacuanha (p.1562·3); methyl salicylate (p.85·3); myrrh (p.2349·2); sulfanilamide (p.343·1); zinc chloride (p.1999·1); menthol (p.2340·1).
Mouth and throat inflammation; pyorrhoea.

Bucoangin N *Northia, Arg.*
Gramicidin (p.286·1); neomycin (p.305·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Bucodrin *Fardi, Spain.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Bucogel *Gador, Arg.*
Chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis; mouth disinfection; oral hygiene.

Bucometasana *Solvay, Spain.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Bucomicina *Pisa, Mex.*
Streptomycin (p.333·3).
Bacterial infections.

Buconif *Nycomed, Austria.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease; Raynaud's syndrome.

Bucort *Orion, Fin.*
⊗ Hydrocortisone butyrate (p.1535·3).
Skin disorders.

Bucoseptil *Sanitas, Chile.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders; oral hygiene.

Bucospray *Teofarma, Spain.*
Chlorhexidine gluconate (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Bucotricin *Monserrat, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Budamax *PMC, Austral.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps.

Budapp *Dermapharm, Ger.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Budasmal *Laboratorios Chile, Chile.*
⊗ Budesonide (p.1520·1).
Asthma.

Budecol *AstraZeneca, Gr.*
⊗ Budesonide (p.1520·1).
Inflammatory bowel disease.

Budecort *AstraZeneca, Braz.; Astellas, Ger.; Cipla, India†; Hoe, Malaysia; AstraZeneca, Philipp.; Cipla, Thai.; Oftalmi, Venez.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; asthma; nasal polyps; obstructive airways disease.

Budefarma *ICN, Arg.†.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Budefat *Fatol, Ger.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Budeflam *Cipla-Medpro, S.Afr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; asthma.

Budemar *Biostam (Βιοσταμ), Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Budenas *Oftalmi, Venez.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Budenase *Cipla, Hong Kong; Cipla, India†; Cipla, Malaysia.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps.

Budenite *Aurora, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Budenofalk *Codali, Belg.; Biotoscana, Chile; Falk, Cz.; Falk, Denm.; Meda, Fin.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Darya-Varia, Indon.; Falk, Indon.; Falk, Irl.; Tramedico, Neth.; Falk, Philipp.; Pharmalink, Philipp.; Falk, Pol.; Falk, Singapore; Falk, Spain; Meda, Swed.; Vifor, Switz.; Ali, Turk.; Provalis, UK.*
⊗ Budesonide (p.1520·1).
Inflammatory bowel disease.

Budeprion *Teva, USA.*
Bupropion hydrochloride (p.383·1).
Depression.

Budeprol *Proel, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Buderen *Balu, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Buderhin *GSK, Pol.*
⊗ Budesonide (p.1520·1).
Rhinitis.

Budes *Hexal, Ger.*
⊗ Budesonide (p.1520·1).
Nasal polyps; obstructive airways disease; rhinitis.

Budesal *Cipla, India†.*
⊗ Budesonide (p.1520·1); salbutamol (p.1131·2).
Asthma.

Budesan *Biospray, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Budesoderm *Pharmex (Φαρμεξ), Gr.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Budesogen *Generics, Hung.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Budeson *Altana, Arg.; Falk, Israel.*
⊗ Budesonide (p.1520·1).
Asthma; Crohn's disease; nasal polyps; rhinitis.

Budesonal *Verisfield, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Budiair *Torrex, Austria; Farmalab, Braz.; Torrex Chiesi, Cz.; Asche Chiesi, Ger.; Chiesi, Gr.; Chiesi, Malaysia.*
⊗ Budesonide (p.1520·1).
Asthma; obstructive airways disease.

Budicort *Teva, Israel.*
⊗ Budesonide (p.1520·1).
Asthma.

Budon *Lindopharm, Ger.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Budo-san *Merck, Austria; Falk, Port.*
⊗ Budesonide (p.1520·1).
Crohn's disease.

Budosan *Farmasa, Mex.*
⊗ Budesonide (p.1520·1).
Crohn's disease.

Buenas Noches *ISA, Arg.*
Melatonin (p.2338·3).
Sleep disorders.

Buenoson N *Zilly, Ger.†.*
St John's wort oil; wheat-germ oil; avocado oil; birch tar oil; thiamine hydrochloride; dilute formic acid; garlic juice; birch leaf; juniper berry; gentian root; lupulus; clove; male fern leaf.
Herbal preparation.

Buer Lecithin Plus *Altana, Ger.*
Soya phospholipids; vitamins (p.1922·1).
Tonic.

Buerlecithin
Note. This name is used for preparations of different composition.
Thursday, Austral.; Roland, Cz.†; Altana, Ger.
Lecithin (p.2332·2).
Hypercholesterolaemia; tonic.

Altana, Austria.
Lecithin (p.2332·2) with or without vitamins (p.1922·1).
Tonic.

Buerlecithin Compact *Byk, Austria; Altana, Switz.†.*
Soya lecithin (p.2332·2).
Tonic.

Bufacyl *Medipharm, Chile.*
Octatropine methylbromide (p.1752·1); phenobarbital (p.492·2).
Colic; dysmenorrhoea; vomiting in infants.

Bufect *Sanbe, Indon.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; pain.

Bufederm *Galen, Ger.†.*
Bufexamac (p.28·3).
Skin disorders.

Bufedil *Abbott, Braz.; Abbott, Ger.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Bufencon *YSP, Malaysia; Yung Shin, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Bufex *Dermapharm, Austria.*
Bufexamac (p.28·3).
Skin disorders.

Bufexan
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Lannacher, Austria.
Bufexamac (p.28·3).
Inflammatory skin disorders.

Bufexine *Continental Pharma, Belg.†.*
Bufexamac (p.28·3).
Arthritis; peri-articular inflammation.

Buffered C *Quest, UK.*
Calcium ascorbate (p.1984·1).

Buffered C 500 *Bio-Health, UK.*
Calcium ascorbate (p.1984·1).

Buffered Pirin *Pennex, Israel.*
Aspirin (p.20·3) and buffering agents.
Fever; musculoskeletal and joint disorders; pain; thrombosis prophylaxis.

Bufferin *BMS, Arg.†; BMS, Braz.; BMS, Canad.; BMS, Ital.†; BMS, Singapore†; Novartis, USA.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1), magnesium carbonate (p.1743·1), and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; myocardial infarction; pain; thromboembolism prophylaxis; transient ischaemic attacks.

Bufferin AF Nite Time *BMS, USA†.*
Diphenhydramine citrate (p.577·2); paracetamol (p.108·1).
Insomnia.

Bufferin Low Dose *BMS, Malaysia†.*
Aspirin (p.20·3).
Thromboembolic disorders.

Buffex *Roberts, USA.*
Aspirin (p.20·3).
Aluminium glycinate (p.1706·2) and magnesium carbonate (p.1743·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Bufidol *Behrens, Venez.*
Nalbuphine (p.92·2).
Pain.

Bufigen
Note. This name is used for preparations of different composition.
Antigen, Irl.
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders; pain; soft-tissue injuries.

Pisa, Mex.
Nalbuphine hydrochloride (p.91·3).
Pain.

Bufilem *Lemery, Mex.*
Nalbuphine (p.92·2).
Pain.

Buflan *Fournier, Ital.*
Buflomedil hydrochloride (p.1236·3).
Vascular disorders.

Buflo *ABZ, Ger.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflocit *CT, Ital.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Buflodil *Medichrom, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflofar *Upsamedica, Ital.†.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Buflohexal *Hexal, Austria; Hexal, Ger.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflomed
Scott-Cassara, Arg.
Buflomedil (p.1237·1).
Cerebral and peripheral vascular disorders.

Genericon, Austria.
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflomemed *Ethimed, Belg.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Buflo-POS *Ursapharm, Ger.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflo-Puren *Alpharma-Isis, Ger.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Buflotop *Topgen, Belg.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Buflox *Hexal, Pol.*
Buflomedil hydrochloride (p.1236·3).
Intermittent claudication; obstructive arterial disease.

Buftyl *Hexal, Austria.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Bug zzz Away *Naltek, Canad.†.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Bugazon *Pharmacos Abug, Mex.*
Captopril (p.1239·2).
Hypertension.

Bugesic *Cipla, Austral.†.*
Ibuprofen (p.64·2).

Bugs Bunny *Bayer Consumer, Canad.; Bayer Healthcare, Singapore†; Miles, USA.*
Multivitamins or multivitamins with minerals (p.1922·1).

Bugumentol *Drogsan, Turk.*
Cineole (p.2282·3); menthol (p.2340·1); peppermint oil (p.1761·2); turpentine oil (p.2406·3).
Respiratory-tract disorders.

Bugusan *Kurtsan, Turk.*
Cineole (p.2282·3); menthol (p.2340·1).
Respiratory-tract disorders.

Buguseptil *Santa, Turk.*
Benzoin tincture (p.2394·2); menthol (p.2340·1); niaouli oil (p.2351·3); cineole (p.2282·3); turpentine oil (p.2406·3).
Respiratory-tract disorders.

Bukatel *Panacea, India†.*
Prochlorperazine (p.1020·1).
Nausea and vomiting.

Bukosan *Slovakofarma, Cz.†.*
Rhubarb (p.1768·3); salicylic acid (p.1612·2).
Oral inflammation and pain.

Bukuryoingohangekobokuto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; atractylodes lancea rhizome; magnolia bark; citrus unshiu peel; ginseng; perilla herb; immature orange; ginger.
Traditional Kampo medicine.

Bulasan *Quimica y Farmacia, Mex.*
Cinnarizine (p.573·1).
Peripheral vascular disease.

Bulboid *Melisana, Switz.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Bulboshap *Farmagan, Ital.*
Shampoo containing achillea, chamomile, cinchona, cornflower, gentian, lilly, and almond.
Seborrhoeic dermatitis.

Bulgarolax *Laboratorios Chile, Chile.*
Phenolphthalein (p.1762·1); cascara (p.1715·2); aloes (p.1705·2).
Constipation.

Bulk *Agepha, Austria.*
Methylcellulose (p.2145·1).
Constipation.

Bullfrog
Note.This name is used for preparations of different composition.
Chattem, USA.
Gel SPF 18: Oxybenzone (p.1608·3); octocrilene (p.1608·3); octinoxate (p.1608·2).
Sunscreen.
Chattem, USA.
SPF 36: Oxybenzone (p.1608·3); octocrilene (p.1608·3); octinoxate (p.1608·2).
Sunscreen.
Chattem, USA.
Stick SPF 18: Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Bullfrog for Kids *Chattem, USA.*
SPF 18: Octocrilene (p.1608·3); octinoxate (p.1608·2) octisalate (p.1608·2).
Sunscreen.

Bullfrog Sport *Chattem, USA.*
SPF 18: Oxybenzone (p.1608·3); octocrilene (p.1608·3); octinoxate (p.1608·2) octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Bumaflex N *Altana, Arg.*
Naproxen (p.92·3).
Inflammation.

Bumed *Medifive, Thai.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Bumedyl *Atlantis, Mex.†.*
⊗ Bumetanide (p.1237·1).
Cirrhosis with ascites; heart failure; hypertension; oedema.

Bumeftyl *Faran, Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Bumelex *Roemmers Rowe, Venez.*
⊗ Bumetanide (p.1237·1).
Hypertension; oedema.

Bumetin *Galeno, Venez.*
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders.

Bumetone *Greater Pharma, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Bumex *Roche, USA.*
⊗ Bumetanide (p.1237·1).
Oedema.

Buminate *Baxter Immuno, Arg.; Baxter, Hong Kong; Baxter, Malaysia; Baxter, Mex.†; Baxter, Thai.; Baxter, USA.*
⊗ Albumin (p.1052·1).
Adult respiratory distress syndrome; burns; cardiopulmonary bypass surgery; haemolytic disease of the newborn; hypoalbuminaemia; hypoproteinaemia; hypovolaemia; neonatal hyperbilirubinaemia; nephrosis; plasma volume expansion.

Bumps and Bruises *Hylands, Canad.*
Homoeopathic preparation.

Bunafon *Intermed, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Bunase *Okasa, Thai.; TTN, Thai.*
⊗ Budesonide (p.1520·1).
Rhinitis.

Bunda *Nutricia, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement in pregnant and lactating women.

Bunil *Ovation, Port.*
Melperone (p.1006·2).
Agitation; alcohol withdrawal syndrome; behaviour disorders; confusion; psychoses.

Bunondol *Polfa Warszawa, Pol.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Buona *Eurofarma, Braz.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Bup
Note. A similar name is used for preparations of different composition (see below).
Eurofarma, Braz.
Bupropion hydrochloride (p.383·1).

BUP-4
Note. A similar name is used for preparations of different composition (see above).
UCB, Jpn.
Propiverine hydrochloride (p.2192·2).
Urinary frequency; urinary incontinence.

Bupafen *Biomed, NZ.*
⊗ Bupivacaine hydrochloride (p.1854·3); fentanyl citrate (p.55·3).
Epidural analgesia.

Bupap *ECR, USA.*
Butalbital (p.967·2); paracetamol (p.108·1).
Pain.

Buphenyl *Ucyclyd, USA.*
Sodium phenylbutyrate (p.2390·2).
Urea cycle disorders.

Bupiabbott *Abbott, Braz.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bupiabbott Plus *Abbott, Braz.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupibil *Mayne, Ital.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bupicain *Monico, Ital.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupicaina *Scott-Cassara, Arg.*
Bupivacaine (p.1855·3).
Local anaesthesia.

Bupicaine *Lekko, Rus.†.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bupiforan *Baxter, Ital.; Baxter, Neth.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupigobbi *Gobbi, Arg.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Bupinex *Richmond, Arg.*
Bupivacaine (p.1855·3).
Local anaesthesia.

Bupinostrum *Nostrum, Port.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) may be included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupisen *Senese, Ital.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupisolver *AltaSelect, Ital.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupixamol *Molteni, Ital.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bupleurum Complex *Mediherb, Austral.*
Bupleurum; danshen; milk thistle (p.1452·1).
Liver disorders.

Bupleurum Compound *Phytomedicine, Austral.*
Bupleurum; milk thistle (p.1452·1); fennel (p.2302·3); berberis vulgaris.
Liver disorders.

Bupogesic *APT, Hong Kong.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Bupren *Valeant, Hung.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Buprenex *Reckitt & Colman, USA.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Buprex *Schering-Plough, Port.; Schering-Plough, Spain.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Buprifen *Farma, Venez.†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Buprine *Siam Bheasach, Thai.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Buprodol *Cafar, Venez.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Buprophar *Teva, Belg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Buram *Leo, Denm.; Leo, Irl.*
⊗ Amiloride hydrochloride (p.1209·2); bumetanide (p.1237·1).
Oedema.

Burana *Orion, Fin.; Orion, Rus.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Burana-C *Orion, Fin.*
Ibuprofen (p.64·2); ascorbic acid (p.1983·3).
Influenza symptoms.

Buraton 10 F *Schulke & Mayr, Ger.*
Glyoxal (p.1646·1); formaldehyde (p.1644·2); glutaral (p.1645·2); ethylhexanal (p.1644·1).
Surface disinfection.

Burgerstein CELA *Antistress, Switz.*
Multivitamin and mineral preparation (p.1922·1).

Burgerstein Geriatrikum *Antistress, Switz.*
Multivitamin and mineral preparation (p.1922·1).
Tonic.

Burgerstein S *Antistress, Switz.†.*
Vitamin and mineral preparation (p.1922·1).
Liver disorders.

Burgerstein TopVital *Antistress, Switz.*
Multivitamin and mineral preparation with ginseng (p.1922·1)(p.2312·1).
Tonic.

Burinax *Solvay, Braz.*
⊗ Bumetanide (p.1237·1).
Oedema.

Burinex *CSL, Austral.; Leo, Austria; Leo, Belg.; Leo, Canad.; Leo, Denm.; Leo, Fr.; Leo, Ger.; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Irl.; Leo, Malaysia; CSL, NZ; Leo, NZ; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Adcock Ingram, S.Afr.; Leo, Singapore; Leo, Swed.; Leo, Switz.; Leo, Thai.†; Leo, UK.*
⊗ Bumetanide (p.1237·1).
Forced diuresis; heart failure; hypertension; liver cirrhosis; oedema; renal failure; sodium retention.

Burinex A *Leo, UK.*
⊗ Bumetanide (p.1237·1); amiloride hydrochloride (p.1209·2).
Oedema.

Burinex K *Leo, Irl.†; Leo, Malaysia†; Leo, Norw.; Adcock Ingram, S.Afr.; Leo, Singapore; Leo, UK†.*
⊗ Bumetanide (p.1237·1); potassium chloride (p.1684·3).
Oedema.

Burinex med kaliumklorid *Leo, Denm.*
⊗ Bumetanide (p.1237·1); potassium chloride (p.1684·3).
Hypertension; oedema.

Burmicin *Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Burn Cream *Medipharma, Hong Kong†.*
Aminoacridine hydrochloride (p.1625·1); thymol (p.1664·3); allantoin (p.1588·1); lidocaine hydrochloride (p.1862·3).
Burns.

Burn Healing Cream *Brauer, Austral.†.*
Homoeopathic preparation.

Burnaid *Rye, Singapore.*
Melaleuca oil (p.2338·2); triclosan (p.1665·2).
Burns; scalds.

Burnazin *Darya-Varia, Indon.*
Sulfadiazine silver (p.337·2).
Burns.

Burneze *SSL, UK.*
Benzocaine (p.1854·1).
Burns; scalds.

Burnheal *Cipla, India†.*
Sulfadiazine silver (p.337·2); chlorhexidine (p.1635·2).
Burns.

Burnil *Kurtsan, Turk.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Burnol Plus
Note.This name is used for preparations of different composition.
Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.
Aminoacridine hydrochloride (p.1625·1); cetrimide (p.1634·1).
Formerly contained aminoacridine hydrochloride, cetrimide, and thymol.
Burns; insect bites; skin rashes; wounds.
Boots, Thai.
Aminoacridine hydrochloride (p.1625·1); cetrimide (p.1634·1); thymol (p.1664·3).
Burns; insect bites; skin rashes; wounds.

Burns Cream *Nelson, UK.*
Homoeopathic preparation.

Burnshield *Burnshield, Israel.*
Melaleuca oil (p.2338·2).
Burns; scalds.

Burnshield Gel *Travel-Safe, UK.*
Melaleuca oil (p.2338·2).
Burns; scalds.

Burofix *ICN, Hung.†.*
Calcium acetate (p.1675·2); aluminium sulfate (p.2255·1).
Soft-tissue disorders.

Buronil *Lundbeck, Austria; Pharma Logistics, Belg.; Ovation, Cz.; Ovation, Denm.; Lundbeck, Fin.†; Swedish Orphan, Swed.*
Melperone hydrochloride (p.1006·2).
Agitation; anxiety; confusion; dementia; depression; disturbed behaviour; drug and alcohol withdrawal syndromes; pain; psychoses; sleep disorders.

Buronon *Abbott, Turk.*
Melperone hydrochloride (p.1006·2).
Agitation; anxiety; behaviour disorders.

Buro-Sol *Trans Canaderm, Canad.; Doak, USA†.*
Aluminium acetate (p.2255·1).
Ear disorders; skin disorders.

Burow's *Rugby, USA.*
Acetic acid (p.2244·2); aluminium acetate (p.2255·1).
Ear infections.

Burten *Laboratorios Chile, Chile.*
Ketorolac trometamol (p.74·2).
Pain.

Busansil *Rega, Port.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buscadol *Boehringer Ingelheim, Venez.†.*
Metamizole magnesium (p.49·3).
Fever; pain.

Buscalm *Wockhardt, India.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buscalma *Grunenthal, Port.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buscapina *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p.1734·1).
Adjuvant in gastrointestinal radiography; smooth muscle spasm.

Buscapina Compositum *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Colic; painful smooth muscle spasm.

Buscapina Compositum N *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Painful smooth muscle spasm.

Buscapina Fem *Boehringer Ingelheim, Arg.*
Hyoscine butylbromide (p.1734·1); ibuprofen (p.64·2).
Smooth muscle spasm and pain.

Buscapina Plus *Boehringer Ingelheim, Venez.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Pain; smooth muscle spasm.

Buscofem *Boehringer Ingelheim, Gr.*
Ibuprofen (p.64·2).
Pain.

Buscofen *Boehringer Ingelheim, Ital.*
Ibuprofen (p.64·2).
Pain.

Buscolysin *Pharmachim, Cz.†; Medphano, Ger.†; Sopharma, Pol.*
Hyoscine butylbromide (p.1734·1).
Aid in endoscopy; gastrointestinal disorders; gastrointestinal radiography; smooth muscle spasm.

Buscomed *Medlink, Philipp.*
Hyoscine butylbromide (p.1734·1).
Peptic ulcer; smooth muscle spasm.

Busconet *Sons, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Painful smooth muscle spasm.

Buscono *Milano, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Buscopalamin *Synco, Hong Kong.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm.

Buscopamol *Boehringer Ingelheim, Austria.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Pain; smooth muscle spasm.

Buscopan *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; German Remedies, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Eczacibasi, Turk.; Boehringer Ingelheim, UK.*
Hyoscine butylbromide (p.1734·1).
Aid in radiology or endoscopy; colic pain; irritable bowel disease; smooth muscle spasm.

Buscopan Compositum
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, S.Afr.; Eczacibasi, Turk.
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Boehringer Ingelheim, Ital.
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm.

Buscopan Compositum N *Unilfarma, Port.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm.

Buscopan Composto *Boehringer Ingelheim, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Buscopan Plus *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Thai.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Painful smooth muscle spasm.

Buscoveran Composto *Bunker, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Busepan *Offenbach, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Busetal *Uriach, Spain†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Bush Formula *Or-Dov, Austral.†.*
Chlorhexidine gluconate (p.1635·3).
Acne; skin rashes.

Bushi *Andromaco, Arg.*
Calendula (p.2273·1); allantoin (p.1588·1).
Nipple care.

Busidril *Omega, Spain†.*
Ebastine (p.579·1).
Hypersensitivity reactions.

Busilvex *Pierre Fabre, Cz.; Pierre Fabre, Denm.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Ital.; Pierre Fabre, Neth.; Pierre Fabre, Norw.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Spain; Pierre Fabre, Swed.; Robapharm, Switz.; Pierre Fabre, UK.*
Busulfan (p.690·2).
Haematopoietic stem-cell transplantation; malignant neoplasms.

Busina *Jofrain, Mex.*
Hyoscine butylbromide (p.1734·1).

Busonal *Bevo, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Busonid *Biosintetica, Braz.*
⊗ Budesonide (p.1520·1).
Corticosteroid.

Busopin *Jean-Marie, Hong Kong; Jean-Marie, Philipp.*
Hyoscine butylbromide (p.1734·1).
Dyskinesia; peptic ulcer; post-operative vomiting; smooth muscle spasm.

Busp *Hexal, Ger.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders.

Buspanil *Novartis, Braz.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buspar *BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Cz.†; BMS, Denm.; BMS, Fin.; Orion, Fin.; BMS, Fr.; BMS, Hong Kong; BMS, Irl.; BMS, Ital.; BMS, Mex.; BMS, NZ; BMS, Norw.; BMS, Port.; BMS, S.Afr.; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, UK; BMS, USA.*
Buspirone hydrochloride (p.965·3).
Anxiety; mixed anxiety depressive states.

Buspimen *Menarini, Ital.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buspirex *Technilab, Canad.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buspirol *BMS, Israel†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buspium *Tecnifar, Port.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Buspon *Deva, Turk.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Busprina *Farcoral, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Busprina-S *Farcoral, Mex.†.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Bustrix *GSK, Arg.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Busulfex *ESP, Canad.; Kirin, Hong Kong; Orphan Medical, Israel; Biem, Turk.; ESP, USA.*
Busulfan (p.690·2).
Haematopoietic stem cell transplantation; malignant neoplasms.

Buta *PD, Thai.†.*
Phenylbutazone sodium (p.117·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gout; musculoskeletal and joint disorders.

Buta Pee Dee *PD, Thai.†.*
Phenylbutazone (p.117·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Buta Rut B12 *Fabra, Arg.*
Cyanocobalamin (p.1980·2); piroxicam (p.117·3).
Inflammation; pain.

Butacodin *Zarbi (Ζαρμπη), Gr.*
Butamirate citrate (p.1553·1).
Cough.

Butacort *Alphapharm, Malaysia; Pacific, NZ.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Butadion
Gedeon Richter, Rus.
Phenylbutazone (p.117·1).

Streuli, Switz.
Phenylbutazone (p.117·1) or phenylbutazone sodium (p.117·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gout; musculoskeletal and joint disorders; phlebitis; sft-tissue disorders.

Butafen *Ipca, India†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Butagan *Anpharm (Ανφαρμ), Gr.*
Butamirate (p.1553·1).
Cough.

Butahale
Reddy, Malaysia†; Reddy, Singapore.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Biofarma, Venez.†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Butalen *Allen, Mex.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders.

Butalin *Julphar, UAE.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Butaline *CCM, Malaysia.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Butaliret *Fatol, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Butalitab *Fatol, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Butamidon *Otto, Indon.*
Phenylbutazone (p.117·1); propyphenazone (p.119·3); thiamine nitrate (p.1976·2).
Musculoskeletal and joint disorders.

Butamine *Taro, Israel.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Butamir *Pharmanel, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Butamol *Lafedar, Arg.; Arrow, Austral.; Pharmaland, Thai.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Butanil *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma.

Butaparin *Streuli, Switz.*
Heparin sodium (p.1301·2); phenylbutazone (p.117·1); thymol (p.1664·3).
Peripheral vascular disorders.

Butapirazol *Polfa Warszawa, Pol.*
Phenylbutazone (p.117·1).
Lidocaine hydrochloride is included in the intramuscular injection to alleviate the pain of injection.
Gout; musculoskeletal, joint, and peri-articular disorders.

Buta-Proxyvon
Note. This name is used for preparations of different composition.
Wockhardt, India.
Capsules: Diclofenac sodium (p.44·3); dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Inflammation; musculoskeletal and joint disorders.

Wockhardt, India.
Topical gel: Diclofenac diethylamine (p.44·3); linseed oil (p.2334·1); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Butarion *Chew, Thai.*
Phenylbutazone (p.117·1); dipyrone (p.49·2).
Gout; musculoskeletal and joint disorders.

Butartrol *Sanitas, Chile.*
Ibuprofen (p.64·2); meprobamate (p.1006·2).
Aluminium glycinate (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; musculoskeletal, joint, and peri-articular disorders.

Butasona *Fabra, Arg.*
⊗ Betamethasone (p.1518·2), betamethasone sodium phosphate (p.1518·3), or betamethasone valerate (p.1519·1).
Corticosteroid.

Butasona RL *Fabra, Arg.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Butavate *GSK, Gr.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Butayonacol *Ifusa, Mex.*
Salicylamide (p.121·2); phenylbutazone (p.117·1); colchicine (p.556·1).
Inflammation; musculoskeletal and joint disorders.

Butazil *Neo Quimica, Braz.†.*
Phenylbutazone (p.117·1); paracetamol (p.108·1).
Fever; inflammation; pain.

Butazolidin *Novartis, Belg.; Fagron, Neth.*
Phenylbutazone (p.117·1).
Ankylosing spondylitis; arthritis; gout.

Butazolidina
Novartis, Braz.; Novartis, Spain.
Phenylbutazone (p.117·1).
Lidocaine (p.1862·3) may be included in the injection to alleviate the pain of injection.
Ankylosing spondylitis; gout; musculoskeletal, joint, and peri-articular disorders; rheumatoid arthritis.

Sandoz, Mex.
Phenylbutazone sodium (p.117·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Ankylosing spondylitis; arthrosis; gout; rheumatoid arthritis.

Butazolidine *Novartis, Fr.†.*
Phenylbutazone (p.117·1).
Ankylosing spondylitis; gout; peri-articular disorders.

Butazolon *Dovalle, Braz.†.*
Phenylbutazone (p.117·1).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal tract.
Gout; musculoskeletal, joint, and peri-articular disorders.

Butazona *Boehringer Ingelheim, Braz.*
Phenylbutazone calcium (p.117·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Butazonil *Teuto, Braz.†.*
Phenylbutazone (p.117·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Butecam *LKM, Arg.*
Bromazepam (p.964·3).
Anxiety.

Butekont *Med-One, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Butesin *Abbott, Chile.*
Butyl aminobenzoate picrate (p.1857·1); nitromersol (p.1654·1).
Burns; insect bites.

Butesin Picrate *Abbott, Austral.†.*
Butyl aminobenzoate picrate (p.1857·1); nitromersol (p.1654·1).
Burns; skin abrasions.

Butex *Athlon, USA.*
Paracetamol (p.108·1); butalbital (p.967·2).
Pain.

Butibel *Wallace, USA.*
Belladonna (p.2263·3); secbutabarbital sodium (p.1027·2).
Gastrointestinal disorders.

Buticrem *Raffo, Arg.†.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Butidiona
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.†.
Cream: Ibuprofen (p.64·2); benzyl nicotinate (p.28·1).
Inflammation.

Roux-Ocefa, Arg.
Tablets: Ibuprofen (p.64·2).
Inflammation.

Butilamin *Sanval, Braz.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Butilamina Compuesta *Plusandex, Venez.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Butilene *Inter, Venez.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Butimaxil *Bruluagsa, Mex.*
Dicloxacillin sodium (p.265·2).
Staphylococcal infections.

Butimerin
Note. This name is used for preparations of different composition.
Ariston, Arg.
Paste: Benzethonium chloride (p.1630·1) butimerin; titanium dioxide (p.1617·3).
Cracked nipples; infected skin disorders; nappy rash.

Ariston, Arg.
Topical powder: Bacitracin (p.210·3); neomycin sulfate (p.305·1); papain (p.2362·3); butimerin.
Burns; skin infections; ulcers; wounds.

Butin *YSP, Malaysia†; Yung Shin, Singapore†.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism.

Butinat *Sanofi Synthelabo, Arg.†.*
⊗ Bumetanide (p.1237·1).
Heart failure; hepatic cirrhosis; hypertension; oedema.

Butineuron *Lafedar, Arg.*
Gamma-aminobutyric acid (p.2308·1); pyridoxine hydrochloride (p.1978·2).

Butiral *Rayere, Mex.*
Hyoscine butylbromide (p.1734·1).
Muscle spasm.

Butiran *Ecobi, Ital.*
Butamirate citrate (p.1553·1).
Coughs.

Butisel *Diba, Mex.*
⊗ Dexamethasone (p.1526·1); phenylbutazone (p.117·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders.

Butisol *Medpointe, USA.*
Secbutabarbital sodium (p.1027·2).
Insomnia; sedative.

Buti-Spirobene *Ratiopharm, Austria.*
⊗ Butizide (p.1238·1); spironolactone (p.1400·1).
Aldosteronism; oedema.

Butix *Pierre Fabre, Fr.*
Diphenhydramine hydrochloride (p.577·2).
Insect stings; pruritus; urticaria.

Buto Air *Aldo, Spain.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Buto Asma
Aldo-Union, Hong Kong†; Aldo-Union, Singapore†; Aldo-Union, Thai.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Aldo, Spain.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Butoas *Biogalenic, Venez.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Butobloc *Pharmacare, S.Afr.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

Butocort *Cassara, Arg.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Asthma.

Buton *Mintlab, Chile.*
Papaverine hydrochloride (p.2191·3); atropine sulfate (p.1219·3).
Muscle spasm.

Butop *Cipla, India†.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Butopan *Biofarma, Turk.*
Hyoscine butylbromide (p.1734·1).

Butosali *Valdecasas, Mex.*
⊗ Furosemide (p.1292·1).
Diuretic.

Butosol *Northia, Arg.; Aldo, Spain; Medifarm, Venez.*
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Asthma; obstructive airways disease.

Butotal *Grunenthal, Chile; Kener, Mex.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Butotal B *Grunenthal, Chile.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Butovent *Farmalab, Braz.; Chiesi, Cz.†; Chiesi, Neth.; Chiesi, Thai.*
⊗ Salbutamol (p.1131·2).
Asthma; obstructive airways disease.

BuTrans *Napp, Irl.; Napp, UK.*
⊗ Buprenorphine (p.29·1).
Pain.

Butrew *Bioquimed, Mex.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Butrin *Farmilia, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Butropina *Vincenti, Venez.*
Atropine methonitrate (p.1219·3); secbutabarbital sodium (p.1027·2).

Butrum *Aristo, India.*
Butorphanol tartrate (p.32·1).
Pain; premedication.

Buttercup Infant Cough Syrup *Chefaro, UK.*
Ipecacuanha (p.1562·3); glucose (p.1945·3); menthol (p.2340·1).
Coughs; sore throat.

Buttercup Syrup *Chefaro, UK.*
Squill liquid extract (p.1573·1); capsicum tincture (p.2276·2).
Coughs.

Buttercup Syrup (Blackcurrant flavour)
Chefaro, UK.
Ipecacuanha (p.1562·3); glucose (p.1945·3); menthol (p.2340·1).
Coughs.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Buttercup Syrup (Honey and Lemon flavour) *Chefaro, UK.*
Ipecacuanha (p.1562·3); glucose (p.1945·3); menthol (p.2340·1); honey (p.1948·2).
Coughs.

Butt-Out *Paradise, Canad.*
⊗ Lobelia (p.2157·2).
Aid to smoking withdrawal.

Butyl *Masa, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Butylin *Hovid, Hong Kong†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Buvacaina *Pisa, Mex.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Buvasodil *ICN, Pol.*
Buflomedil hydrochloride (p.1236·3).
Obstructive peripheral vascular disorders.

Buvastin *Elpen (Ελπεν), Gr.*
Butamirate citrate (p.1553·1).
Cough.

Buventol
Lannacher, Austria; Orion, Cz.; Meda, Denm.; Orion, Fin.; HRA, Fr.; Berlin-Chemie, Hung.; Menarini, Hung.; Orion, Malaysia; Douglas, NZ; Meda, Norw.; Orion, Singapore; Meda, Swed.; Orion, Switz.†.
⊗ Salbutamol sulfate (p.1131·3).
Asthma; obstructive airways disease.

Galenica, Gr.†; Actavis, Indon.; Orion, Thai.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Buxon *Saval, Chile.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Buzz Away *Purity Life, Canad.†.*
Citronella oil (p.2284·2).
Insect repellent.

B-Vasc *Garec, S.Afr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

B-Vesil
Note.This name is used for preparations of different composition.
Daudt, Braz.
Oral solution: Dehydrocholic acid (p.2292·2); glycine (p.1947·3); choline chloride (p.1934·2).
Digestive disorders.

Daudt, Braz.
Tablets: Dehydrocholic acid (p.2292·2); bovine bile extract (p.2266·3).
Digestive disorders.

B-Vit *Cazi, Braz.†.*
Vitamin B substances (p.1922·1).

BVK Roche plus C *Roche Consumer, Ger.†.*
Vitamin B substances with ascorbic acid (p.1922·1).
Vitamin B and C deficiency.

By-Ache *Cypress, USA.*
Paracetamol (p.108·1); salicylamide (p.121·2); phenyltoloxamine citrate (p.588·1).
Pain.

Byakko-ka-ninjin-to *Tsumura, Jpn.*
Gypsum; anemarrhena rhizome; liquorice; ginseng; brown rice.
Traditional Kampo medicine.

Byanodine *Biogal-Teva, Hung.†.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; hepatitis; rheumatoid arthritis; scleroderma; Wilson's disease.

Byclomine *Major, USA.*
Dicycloverine hydrochloride (p.1722·3).
Functional bowel/irritable bowel syndrome.

Bycolen *Landson, Indon.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; cough.

Byetta *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Cz.; Lilly, Port.; Lilly, UK; Amylin, USA.*
Exenatide (p.439·2).
Diabetes mellitus.

Bykomycin *Altana, Austria; Byk Gulden, Ger.†.*
Neomycin sulfate (p.305·1).
Hepatic coma.

Byl *Medical, Port.†.*
Agar (p.2140·3); ox bile (p.2266·2); phenolphthalein (p.1762·1).
Constipation.

By-Madol *Ergha, Irl.*
Tramadol hydrochloride (p.130·3).
Pain.

Bymeniere *Toho, Hong Kong.*
Betahistine mesilate (p.2265·1).
Ménière's disease.

By-Mycin *Ergha, Irl.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Byodinoral *MDM, Ital.*
Multivitamin preparation with thioctic acid (p.2400·2) (p.1922·1).
Neuropathies.

Bysclas *BYS, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections; toxoplasmosis.

BySec *Biex, Irl.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

ByStat *Biex, Irl.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Bystolic *Forest Laboratories, USA.*
⊗ Nebivolol (p.1347·1).
Hypertension.

Bystrumgel *Akrikhin, Rus.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ByTrite *Biex, Irl.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; nephropathy.

By-Vertin *Ergha, Irl.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; tinnitus; vertigo.

ByZestra *Biex, Irl.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

B-Z Vit *Utopian, Thai.*
Multivitamin preparation with zinc (p.1922·1).
Vitamin supplement.

C-20 *Osoth, Thai.*
Chlorhexidine gluconate (p.1635·3).
Mouth infections.

C-86 *Valuge, Arg.*
Ketoconazole (p.539·1).
Scalp disorders.

C500 *Rekah, Israel.*
Vitamin C (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

C2 with Codeine *Wampole, Canad.†.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Cardiovascular disorders; fever; inflammation; pain.

C Factors "1000" Plus *Solgar, USA.*
Vitamin C (p.1983·3); rose hips (p.2381·2); citrus bioflavonoids complex (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3).
Capillary bleeding.

C1 Inattivatore Umano *Baxter, Ital.†.*
Complement C1 esterase inhibitor (p.2287·1).
Hereditary angioedema.

C Mon *PP Lab, Thai.†.*
Ascorbic acid (p.1983·3).
Scurvy.

C Monovit *Esseti, Ital.*
Sodium ascorbate (p.1984·1).
Vitamin C deficiency.

C Pal *Eagle, Austral.*
Vitamin and mineral preparation with lysine (p.1922·1).

C Supa + Bioflavonoids *Vitaplex, Austral.†.*
Calcium ascorbate (p.1984·1); citrus bioflavonoids (p.2304·1); hesperidin (p.2304·3); rutoside (p.2305·1); rose fruit (p.2381·2).
Vitamin C deficiency.

Ca Lac *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Calcium lactate (p.1676·1).
Calcium deficiency.

Caas *EMS, Braz.†.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Cabagin *Kowa, Jpn.*
Methiosulfonium chloride (p.2343·3); sodium bicarbonate (p.1673·2); swertia; biodiastase 2000 (p.2257·1); lipase AP12.
Antacid; carminative; flatulence.

Cabal *Dallas, Arg.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cabal-D *Dallas, Arg.*
Pseudoephedrine sulfate (p.1571·2); cetirizine hydrochloride (p.570·3).
Allergic rhinitis.

Cabalex *Andromaco, Chile†.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Cabaser *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Norw.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pharmacia, UK.*
Cabergoline (p.802·1).
Hyperprolactinaemia; lactation inhibition; parkinsonism.

Cabaseril *Pfizer, Austria; Pharmacia, Ger.*
Cabergoline (p.802·1).
Parkinsonism.

Cabe 2 *Kowa, Jpn.*
Methiosulfonium chloride (p.2343·3); sodium bicarbonate (p.1673·2); magnesium carbonate (p.1743·1); aluminium hydroxide (p.1706·2); aluminium magnesium silicate (p.2141·2); ursodeoxycholic acid (p.2408·1).
Antacid; flatulence; peptic ulcer.

Cabera *Teva, Cz.*
Cabergoline (p.802·1).
Adenoma; hyperprolactinaemia; lactation inhibition.

Caberlin *Sun, India.*
Cabergoline (p.802·1).
Hyperprolactinaemia.

Caberpar *Rontag, Arg.*
Cabergoline (p.802·1).
Parkinsonism.

Cabioten *Biofarma, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Cabral *Frik, Turk.*
Fenyramidol hydrochloride.
Skeletal muscle spasm.

Ca-C
Note.This name is used for preparations of different composition.
Novartis Sante, Fr.†.
Ascorbic acid (p.1983·3); calcium lactate gluconate (p.1676·2).
Asthenia.

Novartis, Hong Kong†; Novartis OTC, Singapore; Novartis Consumer, Switz.†; Novartis, Thai.
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); calcium lactate gluconate (p.1676·2).
Adjunct in colds and influenza; calcium and vitamin C deficiency.

Novartis Consumer, Port.
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); calcium gluconate (p.1675·3).

Caceff *Lupin, India.*
Cefalexin (p.218·2); carbocisteine (p.1553·2).
Otitis media; respiratory-tract infections.

Cachexan *Polfarmex, Pol.*
Megestrol acetate (p.2114·3).
AIDS-associated cachexia; cancer-associated cachexia.

Cachexon *Telluride, USA.*
Glutathione (p.1448·1).
AIDS-associated cachexia.

Cacit
Note.This name is used for preparations of different composition.
Procter & Gamble, Belg.; Procter & Gamble, Fr.; Procter & Gamble, Irl.†; Procter & Gamble, Ital.; Procter & Gamble, Neth.; Procter & Gamble, UK.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Vita, Port.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cacit D3 *Procter & Gamble, UK.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cacit mit Vitamin D_3 *Viatris, Austria.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cacit Vitamina D3 *Procter & Gamble, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cacit Vitamine D_3 *Procter & Gamble, Belg.; Procter & Gamble, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cactus compositum *Peithner, Austria.*
Homoeopathic preparation.

CaD *Will-Pharma, Neth.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cadafen *Drovepat, Venez.†.*
Paracetamol (p.108·1).
Fever; pain.

Cadafen Grip *Kimiceg, Venez.†.*
Paracetamol (p.108·1); dexchlorpheniramine maleate (p.572·1).
Cold and influenza symptoms.

Cade L *Pharmavita, Chile.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Cadencial Plus *Lafedar, Arg.*
Cinnarizine (p.573·1); gamma-aminobutyric acid (p.2308·1); vitamin B (p.1979·1).
Cerebrovascular disorders.

Cadens *Zambon, Fr.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Cadevit *Gynopharm, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Cadex *Dexcel, Israel.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cadexcin-N *TNP, Thai.†.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Bacterial eye and ear infections.

Cadicoff *Cadila, India†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Coughs.

Cadicon *Pharmasant, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Cadifen *CaDiGroup, Ital.*
Fennel (p.2302·3); aniseed (p.2258·2); chamomile (p.2279·3); liquorice (p.1740·3); caraway (p.2276·3); coriander (p.2288·1).
Bloating; digestive disorders.

Cadiflur *Cadila, India.*
Flurbiprofen (p.61·2).

Cadimasol *Viatris, Ital.*
Vitamin D and mineral preparation (p.1922·1).

Cadimint *CaDiGroup, Ital.*
Peppermint (p.1761·2); fennel (p.2302·3); aniseed (p.2258·2); chamomile (p.2279·3); liquorice (p.1740·3); caraway (p.2276·3); coriander (p.2288·1).
Gastrointestinal bloating.

Cadinol *Andromaco, Chile†.*
Dimeticone (p.2032·1).
Flatulence.

Cadinyl *Medifive, Thai.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); zinc oxide (p.1621·2).
Skin irritation.

Cadiphylate *Zydus, India.*
⊗ Acefylline piperazine (p.1114·1); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Cadisper C *Cadila, India.*
Methyl hesperidin; rutoside (p.2305·1); vitamin C (p.1983·3); carbazochrome (p.1058·2); menadione sodium bisulfite (p.1995·3); calcium hydrogen phosphate (p.1676·1).
Haemorrhage.

Caditam *Cadila, India.*
⊗ Tamoxifen citrate (p.772·3).

Caditar *Tradiphar, Fr.*
Cade oil (p.1616·1).
Psoriasis; seborrhoeic dermatitis.

Caditrex *Cadila, India.*
Methotrexate (p.745·2).
Malignant neoplasms.

Cadolac *Cadila, India.*
Ketorolac trometamol (p.74·2).
Pain.

Cadpres *Cadila, India.*
⊗ Atenolol (p.1217·3).

Cadramine *Atlantic, Thai.*
Calamine (p.1591·2); zinc oxide (p.1621·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); menthol (p.2340·1).
Skin irritation.

Cadramine-V *Atlantic, Hong Kong.*
Calamine (p.1591·2); zinc oxide (p.1621·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); menthol (p.2340·1).
Skin disorders.

Cadraten *GSK, Ital.*
Cadralazine (p.1238·2).
Hypertension.

Cadria *Cadila, India.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Cadrox *Dinafarma, Braz.†.*
Calcium carbonate (p.1714·1); aluminium hydroxide (p.1706·2).
Gastrointestinal hyperacidity.

Cadtre *New Research, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Caduet *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Hung.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, USA; Pfizer, Venez.*
Amlodipine besilate (p.1214·1); atorvastatin calcium (p.1218·3).
Angina pectoris; cardiovascular risk reduction; hypercholesterolaemia; hypertension in patients with cardiovascular risk factors.

Caduril *Mediphar, Venez.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2).
Seborrhoea.

Caduzinc *Mediphar, Venez.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Cadvion *Merck, India.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1); vitamin E (p.1992·2).
Hypertriglyceridaemia.

Cadyoil *Cady, Ital.*
Emollient.

Caedax *Aesca, Austria†; Schering-Plough, Gr.†; Schering-Plough, Port.*
Ceftibuten (p.235·3).
Bacterial infections.

Caelyx *Schering-Plough, Arg.†; Schering-Plough, Austral.; Sequus, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Sequus, Israel†; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-*

Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Venez.
Liposomal doxorubicin hydrochloride (p.712·2) (p.712·2).
Breast cancer; Kaposi's sarcoma; multiple myeloma; ovarian cancer.

Caext *Dallas, Arg.*
Benzocaine (p.1854·1); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Mouth and throat disorders.

Cafalena *Dinafarma, Braz.†.*
Dipyrone (p.49·2); sodium camsilate (p.2388·3).
Cold and influenza symptoms.

Cafatine *Major, USA.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Cafatine-PB *Major, USA.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); belladonna (p.2263·3); pentobarbital sodium (p.1016·1).
Migraine.

Cafcit *IFET (ΙΦΕΤ), Gr.; Mead Johnson Nutritionals, USA.*
Caffeine citrate (p.1116·3).
Acute alcohol intoxication; apnoea of prematurity; lumbar puncture headache.

Cafe-Kit *Aristo, India†.*
1 Capsule, iron carbonyl (p.1950·3); folic acid (p.1940·1); 1 tablet, calcium (p.1675·2); colecalciferol (p.1986·2).

Cafenol *Elmor, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Cafergot *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Alliance, UK; Novartis, USA; Novartis, Venez.†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Cafergot N *Novartis, Ger.†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Headache including migraine.

Cafergot-PB
Note. This name is used for preparations of different composition.
Novartis, Canad.†.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); laevorotatory alkaloids of belladonna (p.2263·3); pentobarbital (p.1016·1).
Migraine and related vascular headache.

Novartis, Chile†; Novartis, S.Afr.†; Novartis, Spain†; Novartis, Switz.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); total belladonna alkaloids (p.2263·3); butalbital (p.967·2).
Migraine and related vascular headache.

Caffedrine *Thompson, USA.*
Caffeine (p.1116·3).
Fatigue.

Caffeine Withdrawal Support *Homeocan, Canad.†.*
Homoeopathic preparation.

Caffetin *Alkaloid, Rus.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Cafgesic Forte *Cypress, USA.*
Paracetamol (p.108·1); magnesium salicylate (p.79·2); phenyltoloxamine citrate (p.588·1); caffeine (p.1116·3).
Fatigue; pain.

Cafiaspirina *Bayer Consumer, Arg.; Bayer, Braz.; Bayer, Chile; Bayer, Port.; Bayer, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Cafinitrina *Berenguer Infale, Spain.*
Caffeine citrate (p.1116·3); glyceryl trinitrate (p.1296·2).
Angina pectoris; biliary-tract spasm; vasospasm.

Cafox *Cafar, Venez.*
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Cough.

Caftar *Quimica y Farmacia, Mex.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and related vascular headache.

Caginal *Pond's, Thai.*
Clotrimazole (p.530·1).
Trichomoniasis; vaginal candidiasis.

Caien *Aulo Gelio, Arg.*
Almond oil (p.2252·2); sodium laurilsulfate (p.2138·3); stearyl alcohol (p.2033·1); cetyl alcohol (p.2028·3); carbomer 23278-p.
Insecticide.

Caina G *Gray, Arg.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Caj z Hlohu *Megafyt-R, Cz.*
Crataegus (p.2289·1).
Cardiac disorders; hypertension.

Caj z Kvetu Bezu Cerneho *Megafyt-R, Cz.*
Sambucus (p.2383·1).
Cold symptoms; mild diuretic.

Caj z Listu Senny *Megafyt-R, Cz.*
Senna (p.1769·2).
Constipation.

Caj ze Salveje *Megafyt-R, Cz.*
Sage (p.2382·3).
Gastrointestinal disorders; gingivitis; stomatitis; upper respiratory-tract inflammation.

Cajova Smes pri Nachlazeni *Megafyt-R, Cz.*
Fennel (p.2302·3); sambucus (p.2383·1); tilia (p.2402·2); plantaginis (p.2379·1); liquorice (p.1740·3).
Catarrh; coughs; fever.

Cajova Smes pri Redukcni Diete *Megafyt-R, Cz.†.*
Bladderwrack (p.2384·2); achillea (p.2245·2); St John's wort (p.422·3); birch leaf (p.2266·3); liquorice (p.1740·3); peppermint leaf (p.1761·2).
Slimming aid.

Cal-95 *Lapi, Indon.*
Coral calcium (p.1675·2); soy isoflavone (p.2391·2); colecalciferol (p.1986·2); vitamin K ; magnesium; zinc; boron (p.1922·1).
Calcium supplement; osteoporosis.

Cal-500 *Pro Doc, Canad.*
Calcium carbonate (p.1714·1).

Cal Alkyline *Eagle, Austral.*
Calcium carbonate (p.1714·1); slippery elm (p.2388·2); glycine (p.1947·3); equisetum (p.2299·3); dibasic sodium phosphate (p.1682·3); spirulina (p.2392·1); magnesium carbonate (p.1743·1); ginger (p.1732·3).
Gastric hyperacidity.

Cal D *Pro Doc, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Cal Extra *Multi-Pro, Canad.*
Calcium; iron; magnesium; zinc; vitamin D (p.1922·1).

Cal Mag plus Vitamin D *Quest, Canad.*
Calcium, magnesium, and vitamin D (p.1922·1).

Cal Mag with Vitamin D *Jamieson, Hong Kong.*
Calcium; magnesium; colecalciferol (p.1922·1).
Dietary supplement.

Cal Mag with Zinc *Jamieson, Hong Kong.*
Calcium; magnesium; zinc (p.1922·1).
Dietary supplement.

Cal Mo Dol *Herbes Universelles, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3); turpentine oil (p.2406·3); peppermint oil (p.1761·2).

CAL Ocean *Proceane, Fr.*
Calcium (from oyster shells) (p.1675·2).
Calcium supplement.

Calaband *SSL, Austral.; Medlock Medical, UK.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Eczema; leg ulcers; medicated bandage.

Calabren *Teva, Hong Kong†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Calabron *Hoechst Biotika, Cz.†; Slovakofarma, Cz.†.*
Calcium bromolactobionate (p.967·3).
Nervous disorders.

Calacort *Galenium, Indon.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Caladaryl Panal *Parke, Davis, Arg.†.*
Zinc oxide (p.1621·2).
Nappy rash.

Caladerm
Note. This name is used for preparations of different composition.
Klinger, Braz.†.
Diphenhydramine (p.577·1) or diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Pruritus; skin irritation.

Macrophar, Thai.†.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2).
Pruritus; skin irritation.

Caladine
Note. This name is used for preparations of different composition.
Galenium, Indon.
Cream; topical powder: Calamine (p.1591·2); zinc oxide (p.1621·2); camphor (p.2273·2); menthol (p.2340·1).
Skin irritation.

Galenium, Indon.
Foam: Skin cleanser.

Galenium, Indon.
Lotion: Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); zinc oxide (p.1621·2).
Miliaria; nappy rash; sunburn; urticaria.

Caladryl
Note. This name is used for preparations of different composition.
Elea, Arg.; Omega, Belg.; Pfizer, Philipp.; Pfizer Consumer, S.Afr.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2).
Allergic skin reactions; insect bites; skin irritation.

Pfizer, Braz.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Chefaro, Port.; Pfizer, Thai.; Pfizer, Turk.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Allergic skin reactions; heat rash; insect bites; pruritus; skin irritation; sunburn.

Pfizer Consumer, Canad.; Warner-Lambert, USA.
Pramocaine hydrochloride (p.1868·1); calamine (p.1591·2).
Formerly contained diphenhydramine hydrochloride and calamine.
Pruritus; skin irritation.

Pfizer Consumer, Mex.; Pfizer, Venez.†.
Calamine (p.1591·2); camphor (p.2273·2).
Pruritus; skin irritation.

Chefaro, Spain.
Cream: Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2).
Formerly contained diphenhydramine hydrochloride and calamine.
Pruritus; skin irritation.

Chefaro, Spain.
Topical solution: Diphenhydramine (p.577·1); zinc oxide (p.1621·2).
Formerly contained diphenhydramine, camphor, and zinc oxide.
Pruritus; skin irritation.

Caladryl Clear
Note. This name is used for preparations of different composition.
Pfizer, Chile.
Pramocaine hydrochloride (p.1868·1); camphor (p.2273·2); zinc acetate (p.1999·1).
Skin irritation; urticaria.

Pfizer Consumer, Mex.; Warner-Lambert, USA.
Pramocaine hydrochloride (p.1868·1); zinc acetate (p.1999·1).
Skin irritation.

Caladryl D *Elea, Arg.*
Diphenhydramine hydrochloride (p.577·2).
Pruritus.

Caladryl Incoloro *Elea, Arg.*
Diphenhydramine hydrochloride (p.577·2); zinc acetate (p.1999·1) or zinc oxide (p.1621·2).
Skin irritation.

Calafol *Alaven, USA.*
Vitamin B ; vitamin B ; folic acid; calcium; colecalciferol (p.1922·1).

Calagin *SIFFRA, Ital.*
Lactobacillus acidophilus (p.2372·3).
Maintenance of vaginal flora.

Cal-Aid *Indoco, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Calalgin *Geritrex, USA.*
Calcium alginate (p.1058·1).
Wounds.

Calamec *Mecosin, Indon.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Skin irritation; urticaria.

Calamed *Cimed, Braz.*
Calamine (p.1591·2); diphenhydramine (p.577·1); camphor (p.2273·2).
Sunburn.

Calamina *Bunker, Braz.*
Diphenhydramine (p.577·1) or diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Pruritus; skin irritation.

Calamine Antihistamine *RW, Canad.; Rougier, Canad.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Pruritus.

Calamine Lotion
Note. This name is used for preparations of different composition.
McGloin, Austral.
Calamine (p.1591·2); zinc oxide (p.1621·2); phenol (p.1656·1).
Insect bites; skin irritation; sunburn.

Floris, Israel; Sam-On, Israel; Vitamed, Israel.
Calamine (p.1591·2); zinc oxide (p.1621·2).
Pruritus.

Calamine-D *Medipharma, Hong Kong†.*
Calamine (p.1591·2); zinc oxide (p.1621·2); kaolin (p.1738·1); diphenhydramine hydrochloride (p.577·2).
Pruritus.

Calaminol *Vita, Venez.*
Calamine (p.1591·2); menthol (p.2340·1); camphor (p.2273·2).
Skin irritation.

Calaminol Simple *Vita, Venez.†.*
Calamine (p.1591·2); zinc oxide (p.1621·2); menthol (p.2340·1).
Pruritus.

Calamycin *Pfeiffer, USA.*
Zinc oxide (p.1621·2); calamine (p.1591·2); benzocaine (p.1854·1); chloroxylenol (p.1640·2); mepyramine maleate (p.585·2).
Pruritus.

Calamyn *Neo Quimica, Braz.*
Calamine (p.1591·2); diphenhydramine (p.577·1); camphor (p.2273·2).
Formerly known as Calamina Composta.
Pruritus; skin irritation.

Calan *Searle, USA.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Calanda *Atlantis, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Calanol *Nakornpatana, Thai.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2).
Skin irritation.

Cal-Antagon *Ferring, Port.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Calaphyl *Greenpharma, Braz.†.*
Calamine (p.1591·2).

Calapol *GSK, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Calapro *Medicine Products, Thai.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Skin irritation.

Calaptin *Nicholas Piramal, India.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Calarex *Apex, Indon.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Pruritus; skin irritation.

Calasthetic *Adcock Ingram, S.Afr.*
Calamine (p.1591·2); benzocaine (p.1854·1); pheniramine maleate (p.587·3); phenol (p.1656·1).
Pruritus; skin irritation.

Calasyl Original *SM, Venez.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Barrier preparation; skin irritation.

Calasyl Transparente *SM, Venez.*
Zinc acetate (p.1999·1); zinc oxide (p.1621·2); camphor (p.2273·2).
Barrier preparation; skin irritation.

Calatrim *Trima, Israel†.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Sunburn; urticaria.

Calatrim cum Sulphur *Trima, Israel†.*
Calamine (p.1591·2); zinc oxide (p.1621·2); sulfur (p.1614·1).
Pruritus.

Calax *Odan, Canad.*
Docusate calcium (p.1724·3).
Constipation.

Calbisan *Pantafarm, Ital.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calbrun *Caldeira & Metelo, Port.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Calburst *Pharmavite, Canad.†.*
Vitamin D (p.1986·1); calcium carbonate (p.1714·1).

Cal-C *Key, USA.*
Calcium citrate (p.1675·3).
Calcium supplement.

Calcalcin *Eisai, Thai.; Sato, Thai.*
Calcium carbonate (p.1714·1); calcium citrate (p.1675·3); calcium gluconate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcanate *ST, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Cal-Car *Selvi, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calcar *Unison, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Calcarb with Vitamin D *Ivax, USA.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Calcarbonate *Millimed, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Calcarea fluor Compuesta *Ximena Polanco, Chile.*
Homoeopathic preparation.

Calcascorbin *Pharmonta, Austria.*
Calcium ascorbate (p.1984·1).
Vitamin C deficiency.

Calcea Wund- und Heilcreme *Wala, Ger.*
Homoeopathic preparation.

Calcebion *Merck, Venez.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1).

Calcebone *Icon, Philipp.*
Calcium ascorbate (p.1984·1); calcium hydrogen phosphate (p.1676·1).
Calcium supplement.

Calcefor *Laboratorios Chile, Chile.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcefor Cap *Laboratorios Chile, Chile.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcefor D *Laboratorios Chile, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cal.Cell *Lapreven, Venez.*
Calcium carbonate (p.1714·1); ergocalciferol (p.1987·1).
Osteoporosis.

Calcemin *Sagmel, Rus.*
Calcium citrate (p.1675·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); zinc oxide; copper oxide; manganese sulfate; sodium borate (p.1922·1).
Dietary supplement; osteoporosis.

Calcemin Advance *Sagmel, Rus.*
Calcium citrate (p.1675·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide; zinc oxide; copper oxide; manganese sulfate; boron sulfate (p.1922·1).

Calceos *koGen, UK.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Calcet *Mission Pharmacal, USA.*
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium supplement.

Calcet Plus *Mission Pharmacal, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Low-calcium leg cramping; nursing mothers; osteoporosis; patients with milk allergies; pre- and postoperative patients.

Calcetat *Giovanardi, Ital.*
Calcium acetate (p.1675·2).
Calcium supplement.

Calcevita *Bayer, Neth.; Bayer, Swed.*
Multivitamin preparation with calcium (p.1922·1).
Calcium and vitamin deficiency.

Calchan *Ranbaxy, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Calcheck
Note. A similar name is used for preparations of different composition (see below).
Apotex, Philipp.; Pharma 3, Philipp.
Nifedipine (p.1350·1).
Hypertension.

Calchek
Note. A similar name is used for preparations of different composition (see above).
Ipca, India.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Ipca, Rus.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Calchek L *Ipca, India.*
Amlodipine besilate (p.1214·1); lisinopril (p.1325·2).
Hypertension.

Calchew *Ranbaxy, Thai.*
Calcium carbonate (p.1714·1); calcium gluconate (p.1675·3).
Calcium supplement; hypocalcaemia.

Calci *Hexal, Ger.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Calci-10 *Pharmathen, Gr.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Calcia
Note. This name is used for preparations of different composition.
Medexus, Canad.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Assos, Turk.
Calcium with vitamins and iron (p.1922·1).

Peter Black, UK.
Calcium carbonate (p.1714·1) with vitamins and iron (p.1922·1).

Calci-Aid *Bayer, Philipp.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcial D *Alacan, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcianta *Armoxindo, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

CalciAPS D3 *APS, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calciben *FIRMA, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; prevention of fracture in osteoporosis; reflex sympathetic dystrophy.

Calcibind *Mission Pharmacal, USA.*
Sodium cellulose phosphate (p.1463·1).
Idiopathic hypercalcaemia.

Calcibloc *Therapharma, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; bradycardia; hypertension.

Calcibon
Note. This name is used for preparations of different composition.
Biomet Merck, Ger.
Hydroxyapatite (p.2323·1).
Bone reconstruction.

Masa, Thai.†; Novapharma, Venez.
Calcium citrate (p.1675·3).
Calcium deficiency; calcium supplement; osteoporosis.

Calcibon D *Novapharma, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteoporosis.

Calcibon D Magnesio *Novapharm, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); magnesium oxide (p.1744·1).
Dietary supplement.

Calcibon D Soya *Novapharm, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); magnesium oxide (p.1744·1); soya isoflavones (p.2391·2).
Dietary supplement.

Calcibon Natal *Novapharm, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); folic acid (p.1940·1).
Dietary supplement for pregnant women.

Calcibronat *Teofarma, Ital.; Novartis, Mex.†; Granions, Mon.*
Calcium bromolactobionate (p.967·3).
Nervous disorders; sleep disorders.

CalciCaps *Nion, USA.*
Calcium with vitamin D and phosphorus (p.1922·1).
Calcium deficiency; dietary supplement.

CalciCaps with iron *Nion, USA.*
Calcium with vitamin D, phosphorus, and iron (p.1922·1).
Calcium deficiency; dietary supplement.

CalciCaps M-Z *Nion, USA.*
Calcium with vitamins A and D, and minerals (p.1922·1).

Calcicarb *Parma, Hung.*
Calcium carbonate (p.1714·1).
Hyperphosphataemia in renal dialysis patients.

Calcicard
Note. This name is used for preparations of different composition.
Pharma Dynamics, S.Afr.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Ivax, UK.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Calcichell *Ativus, Braz.*
Calcium amino acid chelate.
Calcium supplement.

Calci-Chew *Christiaens, Belg.; Nycomed, Neth.; R&D, USA.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Calcichew *Leiras, Fin.; Nycomed, Hong Kong†; Nycomed, Hung.; Shire, Irl.; Pharmacia, S.Afr.; Shire, UK.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteomalacia; osteoporosis; phosphate-binder in renal dialysis.

Calcichew D_3 *BNS, Austria; Nycomed, Cz.; Nycomed, Denm.; Leiras, Fin.; Nycomed, Hong Kong†; Nycomed, Hung.; Shire, Irl.; Nycomed, Israel; Nycomed, Swed.; Shire, UK.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteomalacia; osteoporosis.

Calci-Chew D3 *Nycomed, Neth.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcicold3 *Fidia, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcicontrol *Polychronus, Gr.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Calciday *Medisys, Philipp.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Calcidef *Tecnofarma, Mex.*
Calcium (p.1675·2).
Calcium supplement.

Calcideron *Mediapharm, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calcidia *Bayer Sante, Fr.*
Calcium carbonate (p.1714·1).
Hypocalcaemia and hyperphosphoraemia related to kidney disorders; renal osteodystrophy.

Calcidin
Note. This name is used for preparations of different composition.
Otto, Indon.
Syrup: Calcium hydrogen phosphate (p.1676·1); calcium gluconate (p.1675·3); vitamins (p.1922·1).
Calcium supplement.

Otto, Indon.
Tablets: Calcium hydrogen phosphate (p.1676·1); calcium lactate (p.1676·1); vitamin C; colecalciferol (p.1986·2).
Calcium supplement.

Calcidina *Rafarm, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcidine *Biofarma, Turk.*
Calcium magnesium fytate; calcium gluconate (p.1675·3); ergocalciferol (p.1987·1).
Calcium and vitamin D supplement.

Calcidol *Kimia, Indon.*
Vitamins; calcium; phosphorus; docosahexaenoic acid; lysine (p.1922·1).
Nutritional supplement.

Calcidon *Bayer, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcidose *Opocalcium, Fr.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcidose Vitamine D *Opocalcium, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcidrine *Abbott, USA.*
Codeine (p.37·2); calcium iodide (p.1553·2).
Coughs.

Calcidrops *Medilat, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Calcifar *Farcoral, Mex.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calciferol *Biotika, Cz.; Schwarz, USA.*
Ergocalciferol (p.1987·1).
Familial hypophosphataemia; gastrointestinal, liver, or biliary disease associated with malabsorption of vitamin D; hypoparathyroidism; refractory rickets; vitamin D deficiency.

Calciferol B12 *EMS, Braz.†.*
Ergocalciferol; vitamin B ; calcium chloride; calcium phosphate; sodium fluoride (p.1922·1).
Vitamin and mineral supplement.

Calcifix B12 *Cifarma, Braz.*
Calcium phosphate (p.1676·2); ergocalciferol (p.1987·1); sodium fluoride (p.1962·2); cyanocobalamin (p.1980·2).
Vitamin and mineral supplement.

Calcifix Irradiado *Cifarma, Braz.*
Calcium phosphate (p.1676·2); ergocalciferol (p.1987·1); sodium fluoride (p.1962·2).
Vitamin D and mineral supplement.

Calcifluol *Cimed, Braz.*
Calcium chloride; ergocalciferol; sodium fluoride; sodium phosphate; lysine (p.1922·1).
Nutritional supplement.

Calcifluor *Crinex, Fr.†.*
Calcium fluoride (p.1932·1).
Dental caries prophylaxis.

Calcifolin *Kleva, Gr.; Ibirn, Ital.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency; megaloblastic anaemia.

Calcifort *Labinca, Arg.†.*
Disodium calcium edetate; ergocalciferol; cyanocobalamin (p.1922·1).
Calcium and vitamin supplement.

Calciforte
Note. This name is used for preparations of different composition.
Grimberg, Fr.
Oral liquid: Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); calcium gluceptate (p.1675·3); calcium chloride (p.1675·2); yeast (*Saccharomyces cerevisiae*) (p.1998·3).
Calcium deficiency; osteoporosis.

Grimberg, Fr.
Powder for oral solution: Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); calcium gluceptate (p.1675·3); calcium chloride (p.1675·2); calcium carbonate (p.1714·1); yeast (*Saccharomyces cerevisiae*) (p.1998·3).
Calcium deficiency; osteoporosis.

Calciforte Vitamin D_3 *Grimberg, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); yeast (*Saccharomyces cerevisiae*) (p.1998·3).
Calcium and vitamin D deficiency; osteoporosis.

Calcifox *Diba, Mex.*
Calcium phosphate (p.1676·2).
Calcium and phosphorus deficiency.

Calcigamma *Worwag, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcigard *Torrent, India; Steinbach, Philipp.; Torrent, Rus.; Torrent, Singapore; Torrent, Thai.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; ischaemic heart disease; peripheral vascular disorders; Raynaud's disease.

Calcigen *Cadila, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).

Calcigen D *Opfermann, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcigenol
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Calcium phosphate (p.1676·2); sodium fluoride (p.1962·2).

Korangi, Port.
Calcium phosphate (p.1676·2); ergocalciferol (p.1987·1).
Calcium and vitamin D supplement; osteoporosis; rickets; tetany.

Calcigenol B12 *Millet-Franklin, Arg.*
Calcium phosphate; calciferol; vitamin B (p.1922·1).
Osteoporosis; vitamin and calcium supplement.

Calcigenol Doble *Aventis, Mex.*
Calcium phosphate (p.1676·2).
Calcium supplement.

Calcigran
Note. This name is used for preparations of different composition.
Labomed, Chile.
Calcium carbonate (p.1714·1); calcium hydrogen phosphate (p.1676·1); ascorbic acid (p.1983·3); ergocalciferol (p.1987·1).
Calcium and vitamin D deficiency; osteoporosis.

Nycomed, Norw.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteoporosis.

Calcigran D *Labomed, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

Calci-Gry *Gry, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcihep *Aventis, Austral.†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Calcihexal *Hexal, Pol.*
Calcitonin (salmon) (p.1093·1).
Bone metastases; hypercalcaemia; osteoporosis; Paget's disease of bone.

Calciject *Omega, Canad.*
Calcium chloride (p.1675·2).
Calcium supplement.

Calcijex *Abbott, Austral.; Abbott, Austria; Abbott, Braz.; Abbott, Canad.; Abbott, Cz.; Abbott, Fin.†; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.†; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Turk.; Abbott, UK; Abbott, USA.*
Calcitriol (p.1986·2).
Hyperparathyroidism; hypocalcaemia in dialysis patients; hypoparathyroidism; osteomalacia; renal osteodystrophy; rickets.

Calcilac KT *Jenapharm, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calciless *Sam-On, Israel.*
Dibasic sodium phosphate (p.1682·3); monobasic potassium phosphate (p.1682·2).
Calcium oxalate renal calculi.

Calcilo XD *Ross, USA.*
Low calcium, vitamin D-free infant feed (p.1922·1).
Hypercalcaemia; osteopetrosis.

Calcimag *Chance, Pol.*
Ascorbic acid; vitamin B substances; calcium gluconate; magnesium aspartate; potassium citrate (p.1922·1).
Dietary supplement.

Calcimagon *Orion, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; hyperphosphataemia; osteoporosis.

Calcimagon-D3 *BNS, Austria; Orion, Ger.; Nycomed, Switz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcimar *Aventis, Canad.; Rhone-Poulenc Rorer, USA.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Calcimax
Note. This name is used for preparations of different composition.
Gador, Arg.
Calcium citrate (p.1675·3).
Calcium supplement; hypocalcaemia; osteoporosis.

Wallace Mfg Chem., UK.
Calcium levulinate (p.1676·2); calcium chloride (p.1675·2); vitamins (p.1922·1).

Calcimax D3
Gador, Arg.; Pasteur, Chile.
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; hypocalcaemia; osteomalacia; osteoporosis.

Basel, Turk.
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Calcimax Magnesio *Gador, Arg.*
Colecalciferol (p.1986·2); pyridoxine hydrochloride (p.1978·2); minerals (p.1922·1).
Dietary supplement; osteoporosis.

Calcimed *Hermes, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcimed D_3 *Hermes, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcimega *Solas, Indon.*
Calcium hydrogen phosphate (p.1676·1); docosahexaenoic acid; omega-3 fatty acids; vitamins (p.1922·1).
Calcium supplement.

Calcimex *Frisian Flag, Indon.; Dutch Lady, Malaysia†.*
Preparation for enteral nutrition (p.1922·1).
Calcium supplement; osteoporosis.

Calcimin *Mintlab, Chile.*
Calcium gluconate (p.1675·3).
Calcium supplement.

Calci-Mix *R&D, USA.*
Calcium carbonate (p.1714·1).
Calcium deficiency; dietary supplement.

Calcimon *Altana, Port.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteolytic bone pain; osteoporosis; Paget's disease of bone.

Calcimonio *SM, Venez.*
Oxolamine phosphate (p.1567·1).
Respiratory-tract disorders.

Calcimore *Taro, Israel.*
Calcium carbonate (p.1714·1).
Calcium supplement; gastritis; gastrointestinal hyperacidity; heartburn; peptic ulcer.

Calcimusc *Gedeon Richter, Hung.*
Calcium gluconate (p.1675·3).
Hyperkalaemia; hypersensitivity reactions; hypocalcaemia; inflammation; oxalic acid, citrate, fluoride, and sodium edetate poisoning; tetany.

Calcinatal *Pfizer Consumer, Spain†.*
Multivitamin and mineral preparation (p.1922·1).

Calcinol
Note. This name is used for preparations of different composition.
Raptakos, India.
Oral powder: Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Raptakos, India.
Syrup: Calcium lactate (p.1676·1); calcium gluconate (p.1675·3); colecalciferol (p.1986·2); vitamin B (p.1980·2); magnesium chloride (p.1679·1).
Calcium deficiency; calcium supplement.

Raptakos, India.
Tablets: Calcium carbonate (p.1714·1); calcium phosphate (p.1676·2); calcium fluoride (p.1932·1); magnesium hydroxide (p.1743·2); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Calcinol Complexo *EMS, Braz.*
Calcium chloride (p.1675·2); calcium phosphate (p.1676·2); ergocalciferol (p.1987·1); sodium fluoride (p.1962·2); vitamin B (p.1980·2).
Vitamin D and mineral supplement.

Calcinor D *Medifarm, Venez.*
Calcium citrate (p.1675·3); vitamin D (p.1986·1); magnesium (p.1678·3).
Calcium and vitamin D supplement; osteoporosis; pre-eclampsia.

Calcio *Valma, Chile.*
Calcium carbonate (p.1714·1).

Calcio 20 *Madariaga, Spain†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcio 520 *Knop, Chile.*
Calcium phosphate (p.1676·2); calcium gluconate (p.1675·3); calcium carbonate (p.1714·1); magnesium oxide (p.1744·1); alfalfa (p.2249·2) rose fruit (p.2381·2).
Calcium supplement; osteoporosis.

Calcio Acido *Biotenk, Arg.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calcio Cit *TRB, Arg.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis; renal calculi; renal osteodystrophy.

Calcio Cit Simple *TRB, Arg.*
Calcium citrate (p.1675·3).
Calcium supplement; osteoporosis; renal calculi; renal osteodystrophy.

Calcio Cm *Labomed, Chile.*
Calcium carbonate (p.1714·1); calcium phosphate (p.1676·2); magnesium sulfate; vitamin C (p.1922·1).
Calcium supplement; osteoporosis.

Calcio 20 Complex *Madariaga, Spain.*
Ascorbic acid (p.1983·3); calcium phosphate (p.1676·2); calcium pantothenate (p.1959·3); cyanocobalamin (p.1980·2); colecalciferol (p.1986·2); vitamin A palmitate (p.1973·1).
Calcium deficiency; osteoporosis.

Calcio D *Arkochim, Spain; Isdin, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcio Day D *Silesia, Chile†.*
Calcium carbonate (p.1714·1); magnesium oxide (p.1744·1); vitamin D (p.1986·1).
Calcium, magnesium, and vitamin D supplement; osteoporosis.

Calcio Dobetin *Angelini, Ital.*
Cyanocobalamin (p.1980·2); calcium gluconate (p.1675·3); calcium gluceptate (p.1675·3).
Calcium and vitamin B deficiency.

Calcio 20 Emulsion *Madariaga, Spain.*
Calcium phosphate (p.1676·2).
Calcium deficiency; osteomalacia; osteoporosis.

Calcio 20 Fuerte *Madariaga, Spain.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Calcio Masticable *AM, Arg.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium supplement.

Calcio Nil *Andromaco, Chile†.*
Calcium phosphate (p.1676·2); calcium lactate (p.1676·1); sodium chloride; magnesium oxide; calciferol (p.1922·1).
Calcium deficiency.

Calcio Nil Forte *Andromaco, Chile†.*
Calcium carbonate (p.1714·1); calcium citrate (p.1675·3); calcium lactate (p.1676·1); calcium phosphate (p.1676·2); ergocalciferol (p.1987·1); magnesium oxide (p.1744·1).
Calcium deficiency; osteomalacia; osteoporosis.

Calcio Ostelin *Farma, Venez.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calciobion *Ibefar, Braz.†.*
Calcium phosphate; ergocalciferol; vitamin B ; sodium fluoride (p.1922·1).
Nutritional supplement.

Calcioday-D
Eurodrug, Hong Kong; Eurodrug, Malaysia†; Eurodrug, Singapore†.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide (p.1744·1).
Calcium, magnesium, and vitamin D supplement.

Eurodrug, Thai.†.
Calcium (p.1675·2); colecalciferol (p.1986·2); magnesium (p.1678·3).
Calcium, magnesium and vitamin D supplement.

Calciodie *SPA, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calciofar D *Elmor, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium supplement.

Calciofem *Biofarma, Mex.*
Calcium (p.1675·2); ergocalciferol (p.1987·1).
Osteoporosis.

Calciofix *Damor, Ital.*
-Arginine (p.1928·2); -lysine (p.1955·1); glycerophosphoric acid (p.2315·2).
Bone and dental disorders; tonic.

Calciogenol *Etifar, Venez.*
Calcium gluconate (p.1675·3); colecalciferol (p.1986·2).

Calciokatabios *SIT, Ital.†.*
Calcium and vitamin preparation (p.1922·1).
Nutritional supplement.

Calciomag D *Tecnonat, Arg.*
Calcium; vitamin D; magnesium (p.1922·1).
Dietary supplement.

Calcion *Meyer, Venez.*
Calcium carbonate (p.1714·1).

Calcion D Plus *Meyer, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium supplement.

Calcional *Spedrog, Arg.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcional Citrato *Spedrog, Arg.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis.

Calcional D3 *Spedrog, Arg.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calciopiu *Lafare, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calcior *Delta, Port.*
Calcium carbonate (p.1714·1).

Calcioral *Nycomed, Gr.; Novartis Consumer, Port.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; hypoparathyroidism; osteomalacia; osteoporosis; pseudohypoparathyroidism; rickets.

Calcioral D3 *Nycomed, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcior-D *Delta, Port.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calciosint *Pulitzer, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Calcioton *San Carlo, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Calciovit Puro *Laboratorios Chile, Chile.*
Vitamin D (p.1986·1); calcium hydrogen phosphate (p.1676·1).
Hypocalcaemia; osteomalacia; rickets.

Calciozim *Balverda, Ital.†.*
Colecalciferol (p.1986·2); calcium gluconate (p.1675·3); calcium gluceptate (p.1675·3).
Bone metabolic disorders; calcium deficiency.

Calciparin *Sanofi Synthelabo, Ger.; Choay, Israel.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Calciparina *Italfarmaco, Ital.; Sanofi Synthelabo, Port.†; Sanofi Synthelabo, Spain†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Calciparine *Sanofi Synthelabo, Arg.; Sanofi Synthelabo, Austral.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi, Irl.†; Adcock Ingram, S.Afr.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Turk.; Sanofi-Aventis, UK†.*
Heparin calcium (p.1301·2).
Disseminated intravascular coagulation; thromboembolic disorders.

Calci-Ped *Stiefel, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Calcipen *Leo, Denm.; Leo, Norw.†.*
Phenoxymethylpenicillin calcium (p.314·2).
Bacterial infections.

Calciphar *Pharmex (Φαρμεξ), Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calciphedrin *ICN, Hung.†.*
⊗ Calcium hydrogen phosphate (p.1676·1); calcium gluconate (p.1675·3); ephedrine hydrochloride (p.1558·2).
Hypersensitivity reactions.

Calcipiryna *Polpharma, Pol.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal tract.
Fever; pain; thromboembolism prophylaxis.

Calciplex *Vitaplex, Austral.†.*
Mineral and vitamin D preparation (p.1922·1).
Calcium deficiency; osteoporosis.

Calciplus *Alvia (Αλβια), Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calcipot *3M, Ger.*
Calcium citrate (p.1675·3); calcium hydrogen phosphate (p.1676·1).
Calcium deficiency.

Calcipot C *Kolassa, Austria.*
Vitamin C (p.1983·3); rutoside (p.2305·1); calcium citrate (p.1675·3); calcium glycerophosphate (p.1676·1).
Calcium and vitamin C deficiency.

Calcipot D_3 *Kolassa, Austria.*
Colecalciferol (p.1986·2); calcium citrate (p.1675·3); calcium glycerophosphate (p.1676·1).
Calcium and vitamin D deficiency.

Calciprat *IPRAD, Fr.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calciprat D_3 *IPRAD, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calci-Rav *Asta Medica, Israel.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calciretard *Kohler-Pharma, Ger.*
Calcium aspartate (p.1677·1).
Calcium deficiency.

Calcirol *Cadila, India.*
Colecalciferol (p.1986·2).
Osteomalacia; rickets.

Calcisan *Petrasch, Austria.*
Calcium hydrogen phosphate (p.1676·1); calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcisan B + C *Petrasch, Austria.*
Calcium hydrogen phosphate (p.1676·1); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3); thiamine hydrochloride (p.1976·1).
Calcium, vitamin B , and vitamin C deficiency; osteoporosis.

Calcisan C *Petrasch, Austria.*
Calcium hydrogen phosphate (p.1676·1); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Calcium and vitamin C deficiency.

Calcisan D *Petrasch, Austria.*
Calcium hydrogen phosphate (p.1676·1); calcium carbonate (p.1714·1); ergocalciferol (p.1987·1).
Calcium and vitamin D deficiency; osteoporosis.

Calcisedron-D *Gedeon Richter, Hung.*
4 Tablets, alendronate sodium (p.1088·1) (Sedron); 28 tablets, colecalciferol (p.1986·2); calcium carbonate (p.1714·1) (CalciviD).
Osteoporosis.

Calcispren *Veltipharm, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calcit *Soho, Indon.; Zydus Cadila, Thai.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Calcitab *ITF, Port.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Calcitab D *ITF, Port.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Calcitar *Sanofi-Aventis, Port.*
Calcitonin (salmon) (p.1093·1).

Calcite *Riva, Canad.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcite D *Riva, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Dietary supplement.

Calcitherapy *AG Therapy, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calciton *Biospray, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calcitonin *Novartis, Austria; Jelfa, Pol.*
Calcitonin (salmon) (p.1093·1).
Bone loss following immobilisation; hypercalcaemia; osteoporosis; Paget's disease of bone.

Calcitonina *Novartis, Ital.; Onko, Turk.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Calcitoran *Teikoku, Jpn.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Calcitran B12 *Eversil, Braz.†.*
Cyanocobalamin; ergocalciferol; calcium phosphate; calcium glycerophosphate; sodium fluoride (p.1922·1).
Vitamin and mineral supplement.

Calcitrat *Merckle, Ger.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis.

Cal-Citrate *Bio-Tech, USA.*
Calcium citrate (p.1675·3).
Calcium supplement.

Calcitrex *Oftalmi, Venez.*
Calcium citrate (p.1675·3).
Calcium supplement; osteoporosis.

Calcitrex D3 *Oftalmi, Venez.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calcitridin
Note. This name is used for preparations of different composition.
Opfermann, Ger.†.
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Rottapharm, Ital.†.
Sodium monofluorophosphate (p.1964·3); calcium carbonate (p.1714·1).
Osteoporosis.

Calcitugg *Nycomed, Swed.*
Calcium carbonate (p.1714·1).
Calcium deficiency; hyperphosphataemia; osteoporosis.

Calcium-600
Note. A similar name is used for preparations of different composition (see below).
Key, USA.
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcium 600
Note. A similar name is used for preparations of different composition (see above).
Wyeth Lederle, Port.†.
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).

Calcium Ad *Armoxindo, Indon.*
Calcium gluconate (p.1675·3); calcium hydrogen phosphate (p.1676·1); vitamin A; vitamin D (p.1922·1).
Calcium deficiency; calcium, vitamin A, and vitamin D deficiency.

Calcium AL *Aliud, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium beta *Betapharm, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Braun *Braun, Ger.*
Calcium gluconate (p.1675·3); calcium saccharate (p.2272·3).
Calcium deficiency.

Calcium C
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Sodium calcium edetate (p.1462·2); ascorbic acid (p.1983·3).

Slovakofarma, Cz.†.
Calcium lactoglucoheptonate lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Influenza; respiratory-tract infections.

Farmaco, Pol.; Polfa Lodz, Pol.
Calcium lactate gluconate (p.1676·2); ascorbic acid (p.1983·3).
Calcium and vitamin C supplement.

Calcium C Neo *Zentiva, Cz.*
Calcium glubionate (p.1675·3); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Osteoporosis; tonic.

Calcium Calfit *Herbapol Lublin, Pol.*
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency; osteoporosis.

Calcium Central Poly *Pharmasant, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calcium Citrate *Perrigo, Israel.*
Calcium citrate (p.1675·3); vitamin D (p.1986·1).
Calcium supplement.

Calcium Clear *Nutraceuticals, UK.*
Calcium lactate (p.1676·1); magnesium carbonate (p.1743·1).
Calcium supplement.

Calcium D
Note. This name is used for preparations of different composition.
Novartis, Arg.†.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Trianon, Canad.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Hermes, Port.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Pharmasant, Thai.
Calcium carbonate (p.1714·1); calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calcium D$_3$ *Aliud, Ger.; Betapharm, Ger.; CT, Ger.; Ratiopharm, Ger.; Stada, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium D3
Note.This name is used for preparations of different composition.
Novartis, Braz.
Effervescent tablets: Calcium carbonate (p.1714·1); calcium lactate gluconate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Novartis, Braz.
Tablets: Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calcium 500D *Polfa Lodz, Pol.*
Calcium lactogluconate; colecalciferol (p.1986·2); vitamin C (p.1983·3).
Calcium supplement; immobilisation; osteomalacia; osteoporosis; rickets.

Calcium 600 + D *Nature's Bounty, USA.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Calcium D Sauter *Labatec, Switz.*
Calcium hydrogen phosphate (p.1676·1); calcium gluconate (p.1675·3); calcium lactate (p.1676·1); ergocalciferol (p.1987·1); ascorbic acid (p.1983·3).
Calcium supplement; disorders of calcium and phosphorus metabolism; vitamin C and D deficiencies.

Calcium Dago *Steiner, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Eifelfango *Eifelfango, Ger.†.*
Calcium gluconate (p.1675·3); calcium levulinate (p.1676·2).
Calcium deficiency.

Calcium and Ergocalciferol Tablets *Alpharma, UK.*
Calcium lactate 300 mg (p.1676·1); calcium phosphate 150 mg (p.1676·2); ergocalciferol 10 μg (p.1987·1).
Each tablet contains 400 units of vitamin-D activity. They should be crushed or chewed before administration.
Distinguish from Calcium with Vitamin D Tablets (BPC 1973).
Calcium and vitamin D deficiency.

Calcium Factor *Novartis, Chile.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; rickets.

Calcium Forte D *Novartis, Chile.*
Calcium lactogluconate; calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Hypocalcaemia; osteoporosis.

Calcium Fresenius
Note.This name is used for preparations of different composition.
Fresenius Kabi, Austria.
Calcium gluconate (p.1675·3); calcium saccharate (p.2272·3).
Hypocalcaemia; osteoporosis.

Fresenius Kabi, Ger.†.
Calcium gluconate (p.1675·3); calcium gluceptate (p.1675·3); calcium saccharate (p.2272·3).
Calcium deficiency.

Calcium Heumann *Heumann, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Hexal *Hexal, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Magnesium Plus *Shaklee, Canad.†.*
Vitamin D (p.1986·1); calcium phosphate (p.1676·2); magnesium carbonate (p.1743·1).

Calcium Oyster Shell *Novopharm, Canad.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcium Picken *Adeka, Turk.*
Calcium gluconate (p.1675·3); calcium levulinate (p.1676·2).
Calcium deficiency; calcium supplement.

Calcium Plus
Note.This name is used for preparations of different composition.
Viatris, Austria.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

General Nutrition, Canad.
Multivitamin and mineral preparation (p.1922·1).

Calcium Resonium *Sanofi Synthelabo, Austral.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Gr.†; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Irl.; Aventis, NZ; Sanofi-Aventis, Pol.; Sanofi Synthelabo, UK.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Calcium Rich Rolaids *Warner-Lambert, USA.*
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Hyperacidity.

Calcium Stada *Stada, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Stanley *Stanley, Canad.†.*
Calcium gluceptate (p.1675·3); calcium gluconate (p.1675·3).
Calcium deficiency; calcium supplement.

Calcium Syrop *Hasco-Lek, Pol.*
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency; heavy metal poisoning; osteomalacia; rickets.

Calcium Unison *Unison, Hong Kong; Unison, Thai.*
Calcium lactate (p.1676·1).
Calcium deficiency; calcium supplement.

Calcium Verla *Verla, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium Verla D *Verla, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium Vida *Vida, Hong Kong.*
Calcium gluconate (p.1675·3); calcium hydrogen phosphate (p.1676·1).
Calcium deficiency.

Calcium Vitis *Neopharma, Ger.†.*
Sodium calcium edetate (p.1462·2).
Heavy-metal poisoning.

Calcium von CT *CT, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calciumade *BioFemme, Philipp.*
High-calcium drink for women (p.1922·1).

Calciumcafe *Candioli, Ital.*
Calcium (p.1675·2); vitamin D (p.1986·1).
Nutritional supplement.

Calcium-D *Beacons, Singapore.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Calcium-D3 Nycomed *Nycomed, Rus.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-D-Redoxon *Bayer, Hong Kong; Bayer, Indon.; Bayer, Singapore; Roche, Thai.†.*
Vitamin B ; vitamin C; vitamin D; calcium (p.1922·1).
Calcium and vitamin deficiency; nutritional supplement.

Calcium-D-Sandoz *Novartis Consumer, Austria; Novartis Consumer, Ger.†; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Port.; Novartis, Turk.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-D3-Sandoz *Novartis Consumer, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Calcium-dura *Merck dura, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calcium-dura Vit D$_3$ *Merck dura, Ger.*
Calcium carbonate (p.1714·1) or calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-EAP *Kohler-Pharma, Ger.*
Phosphorylcolamine calcium.
Multiple sclerosis.

Calciumfolinat *Ebewe, Hong Kong.*
Folinic acid (p.1943·3).
Reduction of methotrexate toxicity.

Calcium-Rougier *Rougier, Canad.†.*
Calcium gluceptate (p.1675·3); calcium gluconate (p.1675·3).
Calcium supplement.

Calcium-Rutinion *Biomo, Ger.†.*
Rutoside (p.2305·1); calcium gluconate (p.1675·3).
Capillary disorders; hypersensitivity reactions.

Calcium-Sandoz
Note.This name is used for preparations of different composition.
Novartis, Arg.; Novartis, Hong Kong†; Novartis Consumer, Hung.; Novartis Consumer, Ital.; Novartis, Mex.; Novartis, NZ; Novartis Consumer, Port.; Novartis OTC, Singapore; Novartis, Thai.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Bone demineralisation; calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Novartis, Braz.
Calcium gluconate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency.

Novartis, Chile.
Calcium lactogluconate; calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; rickets.

Novartis, India.
Calcium carbonate (p.1714·1) or calcium glubionate (p.1675·3).
Calcium deficiency.

Novartis, Indon.
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium supplement.

Novartis, Philipp.
Calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Novartis Consumer, Spain†.
Calcium glubionate (p.1675·3).
Calcium deficiency.

Novartis, Denm.; Sandoz, Ger.; Novartis Consumer, Israel; Novartis, Norw.; Novartis Consumer, S.Afr.; Novartis, Swed.; Novartis, Turk.; Novartis, Venez.
Effervescent tablets: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets.

Novartis Consumer, Austria; Novartis, Fin.
Effervescent tablets; oral powder: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; osteomalacia; osteoporosis.

Novartis Sante, Fr.
Effervescent tablets; oral solution: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Sandoz, Switz.
Effervescent tablets; powder for oral solution: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Allergic disorders; calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Novartis Consumer, Austria; Novartis, Denm.; Novartis, Fin.; Novartis Consumer, Israel; Novartis Consumer, Neth.; Novartis, S.Afr.†; Novartis, Swed.; Sandoz, Switz.; Novartis, Turk.
Injection: Calcium glubionate (p.1675·3).
Allergic skin disorders; calcium deficiency; hyperkalaemia; hypocalcaemia; tetrachloromethane poisoning; osteomalacia; osteoporosis; poisoning with lead, fluorides, or magnesium; rickets; tetanus; tetany.

Sandoz, Ger.
Injection: Calcium gluconate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency.

Novartis Consumer, Neth.
Oral powder; tablets: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Novartis, Irl.†; Alliance, UK; Novartis, Venez.
Syrup: Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency; calcium supplement; osteoporosis.

Novartis Consumer, Canad.†.
Tablets: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calcium-Sandoz C *Novartis, Turk.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); vitamin C (p.1983·3).
Calcium deficiency.

Calcium-Sandoz + D *Novartis, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz D3 *Sandoz, Switz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz D Osteo *Sandoz, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcium-Sandoz F *Novartis, Braz.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency.

Calcium-Sandoz FF *Novartis, Cz.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; renal osteodystrophy; tetany.

Calcium-Sandoz Forte
Note.This name is used for preparations of different composition.
Novartis, Cz.
Calcium glubionate (p.1675·3) or calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; renal osteodystrophy; tetany.

Novartis, Indon.; Novartis, Malaysia†; Novartis, Rus.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Novartis Consumer, Pol.
Calcium carbonate (p.1714·1); calcium lactogluconate.
Calcium supplement; osteomalacia; osteoporosis; rickets.

Novartis Consumer, Spain.
Calcium carbonate (p.1714·1); calcium glubionate (p.1675·3).
Calcium deficiency; hypoparathyroidism; osteomalacia; osteoporosis; rickets.

Calcium-Sandoz Forte D
Note.This name is used for preparations of different composition.
Novartis, Chile.
Calcium carbonate (p.1714·1); calcium lactobionate (p.1676·2); vitamin D (p.1986·1).
Hypocalcaemia; osteoporosis.

Novartis Consumer, Spain.
Calcium gluceptate (p.1675·3); colecalciferol(p.1986·2); calcium carbonate (p.1714·1).
Deficiencies of calcium and vitamin D; osteoporosis.

Calcium-Sandoz Junior Growth *Novartis, Indon.*
Calcium; iron; zinc (p.1922·1).
Calcium supplement.

Calcium-Sandoz Junior Strength *Novartis, Indon.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcium-Sandoz Vit C *Novartis, Indon.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Calcium supplement.

Calcium-Sandoz + Vit C *Novartis Consumer, Israel.*
Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); calcium carbonate (p.1714·1); vitamin C (p.1983·3).
Calcium and vitamin C supplement.

Calcium-Sandoz + Vitamin C
Note.This name is used for preparations of different composition.
Novartis Consumer, Hung.; Novartis Consumer, Malaysia.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Calcium and vitamin C deficiency; calcium and vitamin C supplement; cold and influenza symptoms.

Novartis Consumer, Pol.
Calcium carbonate (p.1714·1); calcium lactogluconate; ascorbic acid (p.1983·3).
Calcium and vitamin C supplement.

Calcium-Sandoz + Vitamina C *Novartis, Braz.*
Calcium carbonate (p.1714·1); calcium lactobionate (p.1676·2); ascorbic acid (p.1983·3).
Calcium and vitamin C supplement.

Calciumvit *Viternat, Braz.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Calciumvit Infantil *Viternat, Braz.†.*
Calcium carbonate (p.1714·1); cod-liver oil (p.1935·2).
Nutritional supplement.

Calcival *Valdecasas, Mex.*
Calcium citrate (p.1675·3).
Calcium deficiency; calcium supplement; osteomalacia, rickets; osteoporosis.

Calcivid *Beres, Hung.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcivit *UB, Switz.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calcivit D *Hexal, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calcivit F *Hexal, Ger.†.*
Calcium carbonate (p.1714·1); sodium fluorophosphate (p.1964·3).
Osteoporosis.

calcivitase *Biosyn, Ger.†.*
Calcium citrate (p.1675·3); calcium gluconate (p.1675·3); calcium glycerophosphate (p.1676·1); calcium silicate (p.1676·3); colecalciferol (p.1986·2).
Calcium deficiency.

Calcivoran *Vocate, Gr.*
Calcium folinate (p.1943·3).
Folic acid antidote; megaloblastic anaemia.

Calcivorin *Mintlab, Chile.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calcivorin D *Mintlab, Chile.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Calciyodina *Manuell, Mex.*
Calcium caseinate (p.1934·1); calcium gluconate (p.1675·3); calcium lactate (p.1676·1); iodocasein (p.2170·1).
Calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Calco *Kwizda, Austria; Pharmanik (Φαρμανικ), Gr.; Lisapharma, Hung.; Medico Uno, Hung.; Lisapharma, Ital.†; Lisapharma, Singapore†; Lisapharma, Thai.*
Calcitonin (salmon) (p.1093·1).
Bone loss following immobilisation; hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Calcodol-D3 *Farmanic, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

CalCold *Pfizer Consumer, UK.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Calcom *Panacea, India.*
Calcium carbonate (p.1714·1); calcitriol (p.1986·2).
Formerly contained alfacalcidol.
Osteoporosis.

Calcort *Sanofi-Aventis, Braz.; Galen, Ger.; Shire, Irl.; Aventis, Mex.; Aventis, Switz.; Shire, UK; Sanofi-Aventis, Venez.*
⊗ Deflazacort (p.1524·3).
Corticosteroid; rheumatoid arthritis.

Calc-Os *Erlimpex, Indon.*
Oyster shell (p.1675·2); vitamin D (p.1986·1).
Calcium supplement; osteoporosis.

Calcos Vitamine D$_3$ *Arkomedika, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

CalCough Chesty *Pfizer Consumer, UK.*
Guaifenesin (p.1561·3).
Cough.

CalCough Tickly *Pfizer Consumer, UK.*
Glycerol (p.2314·2).
Cough.

Calcufel Aqua *Hevert, Ger.†.*
Solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Calculi H *Pfluger, Ger.†.*
Homoeopathic preparation.

Calculina *Ferro, Arg.†.*
No 1, podophyllum (p.1610·2); no 2, cascara (p.1715·2); rhubarb (p.1768·3); senna (p.1769·2); no 3, olive oil (p.2356·2); no 4, castor oil (p.2278·1); no 5, methenamine (p.298·3).
Biliary-tract disorders.

Calcusan *Monserrat, Arg.*
Calamine (p.1591·2); diphenhydramine (p.577·1).
Allergic skin reactions; skin irritation.

Calcusan Bebe *Monserrat, Arg.*
Vitamin A (p.1971·2); zinc oxide (p.1621·2); boric acid (p.2268·1).

Cal-C-Vita
Bayer Consumer, Arg.; Bayer, Austria; Bayer, Gr.; Bayer, S.Afr.; Bayer, Switz.
Calcium carbonate (p.1714·1); vitamins (p.1922·1).
Bone and teeth disorders; calcium and vitamin deficiency; fractures; nutritional supplement; tonic; wounds.

Roche, Israel.
Calcium; vitamins (p.1922·1).
Nutritional supplement.

Cal-C-Vita Fluor *Bayer Consumer, Arg.*
Calcium carbonate (p.1714·1); sodium fluoride (p.1962·2); vitamins (p.1922·1).
Calcium and fluoride supplement.

CalD *PSM, NZ.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Cal+D *Verisfield, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Cal-D3 *Cotek, Singapore†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Cald 3-Therapy *AG Therapy, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Caldar-D *Medipharm, Chile.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium deficiency; osteoporosis.

Cal-De *Novartis, Austria; Novartis, Switz.†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Calde *Marjan, Braz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Caldea *ICN, Hung.†.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); calcium hydrogen phosphate (p.1676·1); calcium lactate (p.1676·1).
Hypocalcaemia; osteomalacia; tetany.

Caldease *Roche Consumer, Irl.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Burns; nappy rash; skin irritation; wounds.

CaldeCort *Novartis Consumer, USA.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Skin disorders.

Calderol *Organon, USA.*
Calcifediol (p.1986·1).
Hypocalcaemia associated with renal dialysis; metabolic bone disease.

Caldesene
Note. This name is used for preparations of different composition.
Roche Consumer, Irl.
Calcium undecenoate (p.549·3).
Nappy rash; skin irritation.

Insight, USA.
Ointment: Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin disorders.

Insight, USA.
Topical powder: Calcium undecenoate (p.549·3).
Bromhidrosis; fungal skin infections; hyperhidrosis; minor skin irritation; nappy rash.

Caldesil *Chiesi, Gr.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Caldetrin *Polfa Pabianice, Pol.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis.

Caldeval *Saval, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

Caldine
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Fr.
Lacidipine (p.1322·2).
Hypertension.

Takeda, Philipp.
Manidipine hydrochloride (p.1330·2).
Hypertension.

Cal-D-or *Nycomed, Austria.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Caldoxon *Millimed, Thai.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); vitamin C; vitamin B (p.1922·1).
Calcium and vitamin supplement; osteoporosis.

Cal-D-Vita
Bayer, Austria; Bayer, Swed.; Roche, Turk.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Bayer, Thai.
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calel-D *Rhone-Poulenc Rorer, USA.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Nutritional supplement.

Calendaderm *Knop, Chile.*
Homoeopathic preparation.

Calendolon *Weleda, UK.*
Calendula (p.2273·1).
Minor wounds and abrasions.

Calendula + *Homeocan, Canad.*
Homoeopathic preparation.

Calendula Complexe no 89 *Lehning, Fr.*
Homoeopathic preparation.

Calendula Concreta *Simoes, Braz.†.*
Calendula (p.2273·1); zinc oxide (p.1621·2).
Skin disorders.

Calendula Echinacea Comp *Knop, Chile.*
Homoeopathic preparation.

Calendula Nappy Change Cream *Weleda, UK.*
Calendula (p.2273·1); chamomile (p.2279·3); almond oil (p.2252·2).
Nappy rash.

Calendulan
Note. This name is used for preparations of different composition.
VSM, Neth.
Cream; ointment; topical gel; topical spray: Homoeopathic preparation.

VSM, Neth.
Topical emulsion: Homoeopathic preparation.

Calendulene *Thea, Fr.*
Calendula (p.2273·1).
Eye hygiene.

Calendulin *Herbapol Wroclaw, Pol.*
Calendula (p.2273·1).
Vulvovaginal disorders.

Calendumed
Note. This name is used for preparations of different composition.
Peithner, Austria; DHU, Ger.
Homoeopathic preparation.

Peithner, Cz.†.
Calendula (p.2273·1).
Skin ulcers; wounds.

Calfadol *Faran, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Calfa-Plus *Kee, India.*
Alfacalcidol (p.1986·1); calcium carbonate (p.1714·1).
Hyperparathyroidism; hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy.

Calfate *Angelini, Port.*
Sucralfate (p.1772·2).
Duodenitis; gastritis; gastro-oesophageal reflux; peptic ulcer.

Calferon *Delta, Braz.*
Ergocalciferol; vitamin B ; calcium gluconate; calcium phosphate; sodium fluoride (p.1922·1).
Formerly known as Calciferol Composto.
Vitamin and mineral supplement.

Calfetos *Medipharm, Chile.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Calfolex *Sirton, Ital.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency; reduction of aminopterin and methotrexate toxicity.

Calfolin *Eurofarma, Braz.†.*
Calcium folinate (p.1943·3).
Adjunct to antineoplastic therapy; anaemias; antidote to folic acid antagonists.

Calfosina *Grunenthal, Chile†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Calfovit D3 *Menarini, UK.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cal-G *Key, USA.*
Calcium gluconate (p.1675·3).
Calcium supplement.

Calgayan *Grossman, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract disorders.

Calgel *McNeil, Cz.; GSK, Pol.; GSK, Rus.; GSK, Turk.; Pfizer Consumer, UK; GSK, Venez.†.*
Lidocaine hydrochloride (p.1862·3); cetylpyridinium chloride (p.1635·1).
Gingivitis; teething pain.

Calibral
Note. This name is used for preparations of different composition.
Pharmacare, Philipp.
Mefenamic acid (p.80·1).
Fever; pain.

Solvay, Port.†.
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Calicida Indiano
Note. This name is used for preparations of different composition.
Gestafarma, Port.
Ointment: Salicylic acid (p.1612·2); phenol (p.1656·1); turpentine oil (p.2406·3).
Formerly contained salicylic acid and acetic acid (.
Callosities; verrucas.

Gestafarma, Port.
Topical solution: Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Callosities; verrucas.

Calicida Moreno *Moreno, Port.*
Salicylic acid (p.1612·2).
Calluses; warts.

Caliderm *Darier, Mex.*
Calcium hydroxide (p.2272·2); almond oil (p.2252·2).
Skin disorders.

Calidiol *Servier, Hung.; Servier, Pol.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Califig
Note. This name is used for preparations of different composition.
Merck Consumer, UK.
Chewable bar: Senna (p.1769·2); fig (p.1731·3); dietary fibre (p.1922·1).
Constipation.

Merck Consumer, UK.
Oral liquid: Senna (p.1769·2); fig (p.1731·3).
Constipation.

Calimal *Sussex, UK.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Calinat *Aesculapius, Ital.*
Calcium folinate (p.1943·3).
Folate deficiency; reduction of aminopterin and methotrexate toxicity.

Calinofen *Medimport, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Calinol *Adipharm, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Caliprene *Lemery, Mex.*
Pilocarpine hydrochloride (p.1884·3).
Sjögren's syndrome; xerostomia.

Calista *Ecobrands, UK.*
Fertility test (p.2372·1).

Calisvit *Menarini, Ital.; Menarini, Neth.*
Colecalciferol (p.1986·2); calcium phosphate (p.1676·2).
Calcium and vitamin D deficiency; osteoporosis.

Calix *Meprofarm, Indon.*
Calcium pidolate; curcuminoid; fructo-oligosaccharide; vitamins (p.1922·1).
Nutritional supplement.

Calixta *Belupo, Cz.*
Mirtazapine (p.409·2).
Depression.

Cal-Lac *Bio-Tech, USA.*
Calcium lactate (p.1676·1).
Calcium supplement.

Callicida
Note. This name is used for preparations of different composition.
Cabuchi, Arg.
Salicylic acid (p.1612·2); lactic acid (p.2329·3); phenol (p.1656·1); acetic acid (p.2244·2); benzocaine (p.1854·1); collodion.
Callus removal.

Gezzi, Arg.
Salicylic acid (p.1612·2).
Callus removal.

Lauria, Arg.†.
Salicylic acid (p.1612·2); resorcinol (p.1612·1); lactic acid (p.2329·3).
Callus removal.

El Monje, Arg.
Ointment: Salicylic acid (p.1612·2).
Callus removal.

El Monje, Arg.
Topical solution: Salicylic acid (p.1612·2); lactic acid (p.2329·3); zinc chloride (p.1999·1).
Callus removal.

Callicida 2 *Schering-Plough, Arg.†.*
Salicylic acid (p.1612·2); Canada balsam; acetone; collodion.
Callus removal.

Callicida Brum *Brum, Spain†.*
Flexible collodion; salicylic acid (p.1612·2); trichloroacetic acid (p.1620·1).
Callosities.

Callicida Cor Pik *Quimifar, Spain.*
Acetic acid (p.2244·2); flexible collodion; lactic acid (p.2329·3); castor oil; salicylic acid (p.1612·2).
Callosities.

Callicida Gras *Quimifar, Spain.*
Salicylic acid (p.1612·2).
Callosities.

Callicida Rojo *Escaned, Spain.*
Acetic acid (p.2244·2); flexible collodion; benzocaine (p.1854·1); salicylic acid (p.1612·2); iodine tincture (p.2169·2).
Callosities.

Callicida Salve *Cederroth, Spain.*
Salicylic acid (p.1612·2).
Callosities.

Callifugo *Mediplants, Gr.*
Salicylic acid (p.1612·2).
Keratolytic.

Callimon
Note. This name is used for preparations of different composition.
Grossmann, Hong Kong.
Calcium (p.1675·2); vitamin C (p.1983·3).
Calcium and vitamin C supplement.

Grossmann, Switz.†.
Calcium carbonate (p.1714·1); calcium lactate (p.1676·1); ascorbic acid (p.1983·3).
Vitamin C and calcium supplement.

Callivoro Marthand *Martinez Llenas, Spain.*
Salicylic acid (p.1612·2); benzocaine (p.1854·1).
Callosities.

Callix *Perez Gimenez, Spain.*
Flexible collodion; benzocaine (p.1854·1); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Callosities.

Callofin *Alcor, Spain.*
Salicylic acid (p.1612·2).
Callosities.

Callous *SSL, Cz.; SSL, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns.

Calm *Brauer, Austral.*
Passion flower (p.2363·2); aconitum nap; belladonna; chamomilla.
Formerly known as Infant Calm.
Insomnia; irritability or restlessness in children.

Calma *Uno, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Calma D3 *Uno, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calmaben *Montavit, Austria.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; sedative.

Calmador *Finadiet, Arg.*
Tramadol hydrochloride (p.130·3).
Pain.

Calmador Plus *Finadiet, Arg.*
Paracetamol (p.108·1); tramadol hydrochloride (p.130·3).
Pain.

Calmafher *Fher, Spain†.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Cal-Mag *Quest, Malaysia.*
Calcium; magnesium; vitamin D (p.1922·1).
Dietary supplement.

Calmag *Jamieson, Philipp.*
Calcium; magnesium; vitamin D (p.1922·1).
Calcium deficiency; osteoporosis.

Cal-Mag Citrate with Vitamin D & Zinc *Swiss Herbal, Canad.*
Calcium, magnesium, zinc, and vitamin D (p.1922·1).

Cal-Mag Complete with Zinc, C & D *Quest, Canad.*
Calcium, magnesium, zinc, vitamin C, and vitamin D (p.1922·1).

Calmag D *Gerbex, Canad.*
Calcium, magnesium, and vitamin D (p.1922·1).

CalMag Plus *Usana, Hong Kong†; USANA, USA.*
Colecalciferol; calcium citrate; magnesium chelate; silicon chelate; boron chelate (p.1922·1).
Nutritional supplement.

Cal-Mag Plus *Quest, UK.*
Mineral supplement (p.1922·1).

Cal-Mag plus Vitamin D *Quest, Canad.*
Calcium, magnesium, and vitamin D (p.1922·1).

Cal-Mag Vitamin C & Zinc *Swiss Herbal, Canad.†.*
Calcium, magnesium, zinc, and vitamin C (p.1922·1).

Cal-Mag with Vitamin D & Zinc *Swiss Herbal, Canad.*
Calcium, magnesium, zinc, and vitamin D (p.1922·1).

Cal-Mag & Vitamins C & D *Swiss Herbal, Canad.*
Calcium and magnesium with vitamins C and D (p.1922·1).

Calmagrip *Perez Gimenez, Spain.*
Ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Calman *Ativus, Braz.*
Passion flower (p.2363·2); crataegus (p.2289·1); salix (p.121·3).
Anxiety; insomnia.

Calmanervin
Note. This name is used for preparations of different composition.
Sam-On, Israel.
Elixir: Passion flower (p.2363·2); valerian (p.2410·1).
Anxiety; insomnia.

Sam-On, Israel.
Tablets: Passion flower (p.2363·2); valerian (p.2410·1); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Anxiety; insomnia.

Calmante de Aftas *Drag, Chile†.*
Lidocaine (p.1862·3); methylrosanilinium chloride (p.1653·1).

Calmante de Denticion *Drag, Chile†.*
Lidocaine (p.1862·3).

Calmante Vitaminado PG *Perez Gimenez, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); thiamine (p.1976·3).
Fever; pain.

Calmante Vitaminado PG Efervescente *Perez Gimenez, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); thiamine nitrate (p.1976·2); ascorbic acid (p.1983·3).
Fever; pain.

Calmante Vitaminado Rinver *Monik, Spain.*
Aspirin (p.20·3); thiamine (p.1976·3).
Fever; inflammation; pain.

Calmanticold *Perez Gimenez, Spain†.*
Paracetamol (p.108·1).
Fever; pain.

Calmapax *Delta, Braz.*
Chamomile (p.2279·3); erythrina mulungu (p.2348·1); melissa (p.2339·3); passion flower (p.2363·2).
Sedative.

Calmapica *Perez Gimenez, Spain.*
Ammonia (p.2256·1).
Insect bites; stings.

Calmapir *Elvetium, Arg.†.*
Piroxicam (p.117·3).
Inflammation; osteoarthritis; pain; rheumatoid arthritis; tendinitis.

Calmapir-P *Elvetium, Arg.†.*
Piroxicam (p.117·3); paracetamol (p.108·1).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Calmaril *Siam Bheasach, Thai.†.*
Thioridazine hydrochloride (p.1031·2).
Anxiety; behaviour disorders; mania; schizophrenia.

Calmarum *Medical, Port.†.*
⊗ Sulfogaiacol (p.1573·2); ephedrine hydrochloride (p.1558·2); ethylmorphine (dionina) (p.52·2); sodium benzoate (p.1630·2); aconite (p.2246·1); thyme (p.2401·1); senega (p.1572·3).
Coughs.

Calmason *Terapeutico, Ital.*
Lupulus (p.2335·2); giuggiolo; valerian (p.2410·1); passion flower (p.2363·2); rosolaccio; melissa (p.2339·3); green tea (p.2416·1); griffonia (p.2317·2); vitamin B substances (p.1922·1); magnesium (p.1678·3).
Sleep disorders.

Calmate *Blue Sky, Philipp.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calmatel *Almirall, Spain.*
Piketoprofen hydrochloride (p.117·2).
Peri-articular and soft-tissue disorders.

Calmatol *Farmo Quimica, Chile.*
Scholtzia; chamomile (p.2279·3); tilia (p.2402·2); mint oil (p.2345·2); fennel oil (p.2303·1).
Teething pain.

Calmatoss *Herbarium, Braz.†.*
Grindelia (p.2317·2); guaco; tolu balsam (p.1574·2); propolis (p.2373·3); copaiba; nasturtium; honey (p.1948·2).
Coughs.

Calmatron *Fabop, Arg.*
Lorazepam (p.1004·1).
Anxiety.

Calmaverine *Taphlan, Switz.†.*
Caroverine (p.2277·3) or caroverine hydrochloride (p.2277·3).
Smooth muscle spasm.

Calmax *Ergha, Irl.*
Alprazolam (p.960·1).
Anxiety.

Calmaxid *Norgine, Switz.†.*
Nizatidine (p.1751·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Calmazin *Ibefar, Braz.†.*
Papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3); passion flower (p.2363·2); adonis vernalis (p.2248·1); crataegus (p.2289·1).
Sedative.

Calmday *Will-Pharma, Belg.*
Nordazepam (p.1012·1).
Anxiety.

Calmerphan-L *Doetsch, Grether, Switz.*
Dextromethorphan resin (p.1556·1).
Bronchitis; coughs.

Calmese *Themis Chemicals, India.*
Lorazepam (p.1004·1).
Premedication.

Calmesine *Mepha, Switz.*
Dextromethorphan resin (p.1556·1).
Coughs.

Calmettes *Solvay, S.Afr.*
Valerian (p.2410·1).
Anxiety; nervous disorders.

Calmex
Note. This name is used for preparations of different composition.
Novopharm, Canad.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Roerig, Chile.
Doxylamine succinate (p.578·2).
Insomnia.

Calmicort *Clement-Thekan, Fr.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Calmiderm *Tilman, Hong Kong.*
Chamomile (p.2279·3); calendula (p.2273·1); urtica (p.2409·3); menthol (p.2340·1); lavender oil (p.2331·2).
Dry skin; skin irritation.

Calmina *Pharbio, Pol.*
Lupulus (p.2335·2); melissa (p.2339·3); valerian (p.2410·1).
Insomnia.

Calmin-AF *Combiphar, Indon.*
Vitamins; ferrous fumarate (p.1938·3); calcium lactate; iodine (p.1922·1).
Anaemias; nutritional supplement in pregnancy.

Calmine *Bouty, Ital.*
Ibuprofen (p.64·2).
Pain.

Calminex Atleta *Mantecorp, Braz.*
Methyl salicylate (p.85·3); belladonna (p.2263·3); camphor (p.2273·2).
Musculoskeletal and joint disorders.

Calminex H *Mantecorp, Braz.*
Methyl salicylate (p.85·3); zinc oxide (p.1621·2); belladonna (p.2263·3); peru balsam (p.2365·3); camphor (p.2273·2).
Musculoskeletal and joint disorders.

Calmiphase *Arkomedika, Fr.†.*
Chamomile (p.2279·3); centella (p.1592·3).
Skin disorders.

Calmiplan *Bunker, Braz.*
Passion flower (p.2363·2); crataegus (p.2289·1); salix (p.121·3).
Sedative.

Calmiton *Bunker, Braz.†.*
Kava (p.2328·3).
Anxiety.

Calmix *Overseas, India†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium; manganese; zinc; copper (p.1922·1).
Calcium supplement; osteoporosis.

Calmixene *Novartis, Fr.*
Pimethixene (p.588·1).
Coughs.

Calmlet *Sunthi Sepuri, Indon.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Calmo *Eagle, Austral.*
Mistletoe (p.2345·3); valerian (p.2410·1); vervain (p.2413·3); gentian (p.2310·3); avena (p.2262·1); passion flower (p.2363·2); skullcap (p.2388·2); tansy (p.2395·1); pulsatilla (p.2376·3).
Hypnotic; tension; tension headache.

Calmobrul *SVR, Fr.*
Proline; water lilly flower; allantoin; dexpanthenol; vitamin E.
Formerly contained St John's wort oil, wheat-germ oil, allantoin, vitamin E, niaouli oil, and rosemary oil.
Skin irritation; sunburn.

Calmociteno *Medley, Braz.*
Diazepam (p.986·3).
Anxiety.

Calmodor *Gerolymatos, Gr.*
Paracetamol (p.108·1).
Fever; pain.

Calmoflex *Gezzi, Arg.*
Diclofenac sodium (p.44·3).
Pain.

Calmoflorine *Coup, Gr.*
Sulpiride (p.1028·3).
Psychoses.

Calmogel *Sanofi-Aventis, Ital.*
Isothipendyl hydrochloride (p.582·1).
Insect bites; pruritus; sunburn.

Calmogenol *Brasmedica, Braz.†.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; nausea and vomiting; premedication; sedative.

Calmol
Note. This name is used for preparations of different composition.
Temis, Arg.
Alprazolam (p.960·1).
Anxiety; panic disorder.

Mentholatum, USA.
Zinc oxide (p.1621·2); bismuth subgallate (p.1711·1).
Anorectal disorders.

CalmolinADD *Tribest, S.Afr.*
Evening primrose oil (p.2302·1); vitamins; minerals (p.1922·1).
Dietary supplement.

Calmonal *Aura, Cz.*
Salix; urtica; lavender; peppermint leaf; chamomile; lupulus.
Bath additive; musculoskeletal and joint disorders.

Calmonex *Delta, Braz.*
Kava (p.2328·3).
Anxiety.

Calmophytum *Holistica, Fr.*
Tilia (p.2402·2); orange buds (p.2357·1); chamomile (p.2279·3); vervain (p.2413·3); hibiscus (p.2319·2).
Insomnia.

Calmopirin *Fada, Arg.*
Dextropropoxyphene (p.40·1); dipyrone (p.49·2).
Fever; pain.

Calmoplex *Teofarma, Spain.*
Codeine phosphate (p.37·2); hydroxyzine hydrochloride (p.581·2); propyphenazone (p.119·3).
Coughs; fever; pain.

Calmose *Welt, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium carbonate (p.1743·1).
Antacid.

Calmosedan *Recalcine, Chile.*
Chlormezanone (p.968·3); diazepam (p.986·3).
Anxiety; muscle spasm.

Calmoseptine
Note. This name is used for preparations of different composition.
Calmoseptine, Philipp.
Zinc oxide (p.1621·2); calamine (p.1591·2); menthol (p.2340·1); phenol (p.1656·1); thymol (p.1664·3); chlorothymol (p.1640·1).
Barrier preparation; skin irritation.

Calmoseptine, USA.
Menthol (p.2340·1); zinc oxide (p.1621·2).

Calmosine *Legras, Fr.†.*
Dill seed (p.2293·3); dill oil (p.2293·3).
Infant colic.

Calmox *Meyer, Venez.†.*
Meloxicam (p.80·3).
Inflammation; pain; rheumatic disorders.

Calmpose *Ranbaxy, India; Ranbaxy, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal; alcohol withdrawal syndrome; anxiety; convulsions; muscle spasm; premedication; skeletal muscle spasm; status epilepticus; tetanus.

Calms *Hylands, Canad.†.*
Homoeopathic preparation.

Calms Forte *Hylands, Canad.*
Homoeopathic preparation.

Calmtabs *Natural Life, Arg.†.*
Valerian (p.2410·1); passion flower (p.2363·2); celery (p.2278·3); cataria; lupulus (p.2335·2); dried orange peel (p.2357·1).
Sedative.

Calm-U *Wilson, NZ.*
Diphenhydramine hydrochloride (p.577·2); salicylamide (p.121·2).
Anxiety; insomnia.

Calmuderm *Leo, Indon.; Roi Surya, Indon.*
⊗ Urea (p.1620·2).
Dry skin disorders; hyperkeratosis.

Calmurid
Note. This name is used for preparations of different composition.
Ronnet, Arg.
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Galderma, Austral.; AB-Consult, Austria; Galderma, Belg.†; Galderma, Ger.†; Galderma, Irl.; Galpharma, Israel; Galderma, NZ†; Galderma, Neth.; Jaba, Port.; Galderma, Switz.; Galderma, UK.
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin; eczema; ichthyosis; keratinisation disorders.

Royal, Chile.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Calmurid HC
Note. This name is used for preparations of different composition.
AB-Consult, Austria; Galderma, Irl.; Galderma, Israel†; Galderma, Neth.; Galderma, Switz.†; Galderma, UK.
⊗ Urea (p.1620·2); lactic acid (p.2329·3); hydrocortisone (p.1535·2).
Dry eczema; inflammatory skin disorders; keratinisation disorders.

Galderma, S.Afr.†.
⊗ Urea (p.1620·2); hydrocortisone (p.1535·2).
Skin disorders.

Calmuril *ACO Hud, Fin.; ACO Hud, Swed.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin; eczema; ichthyosis; keratinisation disorders.

Calm-X *Republic, USA.*
Dimenhydrinate (p.576·2).
Motion sickness.

Calmylin *Rougier, Canad.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); codeine phosphate (p.37·2).

Calmylin Ace *Rougier, Canad.*
Guaifenesin (p.1561·3); pheniramine maleate (p.587·3); codeine phosphate (p.37·2).
Coughs.

Calmylin with Codeine *Rougier, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).

Calmylin No 1 *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Calmylin Original with Codeine *Rougier, Canad.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); codeine phosphate (p.37·2).
Coughs.

Calnat *Combiphar, Indon.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Cal-Nate *Ethex, USA.*
Vitamin and mineral preparation (p.1922·1).

Calner *Medipharm, Chile.*
Dipotassium clorazepate (p.980·1).
Alcohol withdrawal; anxiety; insomnia; premedication.

Calnier-D *Vannier, Arg.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calnif *Cadila, India.*
Nifedipine (p.1350·1).

Calnisan *Gynopharm, Chile; Vivax, Venez.†.*
Calcitonin (salmon) (p.1093·1).
Metastatic bone pain; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Calnit *Sandoz, Spain.*
Nimodipine (p.1357·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Calogen
Note. This name is used for preparations of different composition.
Scientific Hospital Supplies, Austral.; Nutricia, Fin.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Nutricia, NZ; Nutricia Clinical, UK.
Arachis oil (p.2259·1).
Carbohydrate malabsorption; dietary supplement; disorders of amino acid metabolism; food for special diets; ketogenic diet in epilepsy.

Probios, Port.†; Elfar, Spain.
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; tumour-induced bone pain.

CaloMist *Fleming, USA.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Calope *Simoes, Braz.†.*
Phenylacetic acid; lactic acid (p.2329·3); thuja (p.2400·3).
Keratinisation disorders.

Caloplast *Adco, S.Afr.*
Glycerol (p.2314·2); boric acid (p.2268·1).
Boils; carbuncles; skin inflammation.

Caloreen *Nestle, Fr.; IFET (ΙΦΕΤ), Gr.†; Nestle, UK.*
Dextrin (p.1937·1).
Food for special diets.

Calorex *Konimex, Indon.*
Chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine (p.1569·2).
Cold and influenza symptoms.

Calorub Forte *Hofmann, Chile.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Calorub Nueva Formula *Hofmann, Chile.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal and joint disorders.

Calos *Fahrenheit, Indon.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Cal-Os *Siam Bheasach, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Calosbon *Teguhsindo, Indon.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); isoflavone (p.2391·2).
Menopausal disorders; osteoporosis.

Calostrum *Meprofarm, Indon.*
Bovine colostrum; docosahexaenoic acid; cod-liver oil; lysine hydrochloride; vitamins; minerals (p.1922·1).
Nutritional supplement.

Calotrat *Galenogal, Braz.†.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Hyperkeratosis.

Calox *Medipharma, Hong Kong†.*
Diphenhydramine hydrochloride (p.577·2).
Pruritus.

Calox Super *Qualiphar, Belg.*
Denture fixative.

Calpal D *Arex, Venez.†.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Calparine *Sanofi-Aventis, Belg.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Calperos *Bouchara-Recordati, Fr.; Pliva Krakow, Pol.; Robapharm, Switz.*
Calcium carbonate (p.1714·1).
Allergic disorders; calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets.

Calperos D_3 *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Robapharm, Switz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calpharma *Quimpharma, Mex.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Calphosan *Glenwood, USA.*
Calcium glycerophosphate (p.1676·1); calcium lactate (p.1676·1).
Calcium deficiency.

Calphron *Nephro-Tech, USA.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Calpix *Euro-Labor, Port.†; Grunenthal, Port.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Calplus MZ *Nupharma, Thai.*
Calcium; magnesium; zinc (p.1667·1).
Dietary supplement.

CalplusD3 *Guidotti, Ital.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calpol *McNeil, Cz.; GSK, Hong Kong†; GSK, India; Pfizer Consumer, Irl.; GSK, Philipp.; GSK, Pol.; Janssen-Cilag, Port.†; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Thai.; GSK, Turk.; Pfizer Consumer, UK.*
Paracetamol (p.108·1).
Fever; pain.

Calpol Night *Pfizer Consumer, UK.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold symptoms; fever; pain.

Calporo *Eagle, Austral.*
Vitamin and mineral supplement with rose fruit, irish moss, echinacea, equisetum, lysine, and bone powder (p.1922·1).
Bone disorders; mineral supplement.

Calporosis D *Mersifarma, Indon.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D deficiency; calcium supplement.

Calpred *Grossmann, Switz.*
⊗ Prednisolone acetate (p.1541·1); mepyramine maleate (p.585·2); calcium levulinate (p.1676·2).
Skin disorders.

Calpres *Temis, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Calprimum *Iderne, Fr.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Calprofen *Pfizer Consumer, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Calron *East India Pharma, India.*
Multivitamin and mineral preparation (p.1922·1).

Calrub *Pfizer Consumer, UK.*
Eucalyptus (p.2301·2); menthol (p.2340·1).
Respiratory-tract congestion.

Cal-Rutina *Valeant, Mex.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Capillary fragility.

Calsal *Balu, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Calsalettes *Torbet Laboratories, UK.*
Aloin (p.1705·3).
Constipation.

Calsan *Novartis, Braz.; Novartis Consumer, Canad.; Novartis, Indon.; Novartis, Mex.; Wander, Philipp.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Calsed *Sumitomo, Jpn.*
Amrubicin hydrochloride (p.680·3).
Lung cancer.

Calsein *Manuell, Mex.*
Calcium caseinate (p.1934·1).

Calshake *Fresenius Kabi, Irl.; Fresenius Kabi, UK.*
Preparation for enteral nutrition (p.1922·1).

Calsical *Teguhsindo, Indon.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Calslot *Takeda, Jpn.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Calsorp *Thaipharmed, Thai.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis; rickets.

Calsuba *Group, S.Afr.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Calsum *Sriprasit, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteomalacia; osteoporosis; rickets.

Cal-Sup *3M, Austral.; 3M, Malaysia; 3M, Singapore†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Calsyn *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Calsynar
Aventis, Arg.†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Cz.†; Sanofi-Aventis, Gr.; Sanofi-Aventis, Spain; Aventis, UK†.
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; metastatic bone pain; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Aventis, Ger.†.
Calcitonin (salmon) acetate (p.1094·1).
Bone pain in malignancy; hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Caltab *Masa, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Caltab W/Vitamin D *Millimed, Thai.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Caltanid *Gentek, Venez.†.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Caltec *Zwitter, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Caltera *Verisfield, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Caltheon *Chephasaar, Ger.†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Calthicon *Pharmasant, Thai.†.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Calthrox *Cadila, India.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Caltine *Ferring, Canad.; Ferring, Cz.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; metastatic bone pain; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Caltoson Balsamico *Rottapharm, Spain.*
Cineole (p.2282·3); benzocaine (p.1854·1); pholcodine (p.1570·2); cherry-laurel; terpineol (p.2396·1); menthol (p.2340·1).
Respiratory-tract disorders.

Caltrate
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.; Wyeth Consumer, Canad.; Wyeth Sante, Fr.; Wyeth Consumer, Hong Kong; Lederle, Israel; Wyeth Consumer, Malaysia; Wyeth Consumer, Mex.; Wyeth Consumer, NZ; Wyeth Consumer, S.Afr.; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.; Lederle, USA; Wyeth, Venez.†.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Wyeth Consumer, Ital.; Wyeth, Turk.
Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Caltrate + D
Wyeth-Whitehall, Arg.; Wyeth Consumer, Thai.; Wyeth, Venez.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium supplement; hypocalcaemia; osteoporosis.

Wyeth Consumer, Braz.; Wyeth Consumer, Malaysia; Wyeth Consumer, Mex.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetany.

Wyeth Consumer, Hong Kong.
Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis.

Caltrate + Iron & Vitamin D *Lederle, USA.*
Calcium carbonate (p.1714·1); ferrous fumarate (p.1938·3); vitamin D (p.1986·1).
Calcium and iron deficiency.

Caltrate + M *Wyeth Consumer, Braz.; Wyeth Consumer, Mex.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); minerals (p.1922·1).
Calcium, vitamin D, and mineral supplement; osteomalacia; osteoporosis; rickets; tetany.

Caltrate Plus
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.; Wyeth, Cz.; Wyeth Consumer, Malaysia; Whitehall, Pol.; Wyeth Consumer, Port.†.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide; zinc oxide; copper oxide; manganese sulfate (p.1922·1).
Calcium, vitamin D, and mineral deficiency; dietary supplement; osteomalacia; osteoporosis.

Wyeth Consumer, Canad.; Wyeth Consumer, Singapore.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1); copper oxide; magnesium oxide; manganese sulfate; zinc oxide (p.1922·1).

Wyeth Consumer, Hong Kong; Wyeth, Philipp.; Wyeth Consumer, Thai.
Calcium (p.1675·2); vitamin D (p.1986·1); copper; magnesium; manganese; zinc (p.1922·1).
Calcium deficiency; calcium supplement; osteomalacia; osteoporosis.

Wyeth Consumer, Irl.
Calcium (p.1675·2); vitamin D; boron; copper; magnesium; manganese; zinc (p.1922·1).
Calcium deficiency; calcium supplement.

Wyeth Consumer, UK; Lederle, USA.
Calcium (p.1675·2); colecalciferol (p.1986·2); boron; copper; magnesium; manganese; zinc (p.1922·1).
Bone disorders; calcium deficiency.

Caltrate Plus Mastigavel *Wyeth Consumer, Port.†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium; zinc; copper; manganese; boron (p.1922·1).
Osteoporosis.

Caltrate + S *Wyeth Consumer, Mex.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); soya bean (p.1965·3).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetany.

Caltrate Select *Wyeth Consumer, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium supplement.

Caltrate + Soy *Wyeth Consumer, Hong Kong; Wyeth Consumer, Singapore.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1); soya isoflavones (p.2391·2).
Calcium and vitamin D supplement; calcium deficiency; osteomalacia; osteoporosis.

Caltrate + Vit D
Lederle, Israel.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Wyeth Consumer, Singapore.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Caltrate with Vitamin D *Wyeth Consumer, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium supplement.

Caltrate + Vitamin D
Wyeth Consumer, Austral.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium supplement; osteomalacia; osteoporosis.

Lederle, USA.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium deficiency.

Caltrate Vitamine D_3 *Wyeth Sante, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Caltrate + Witamina D *Whitehall, Pol.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Caltrec *Columbia, Mex.†.*
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium supplement.

Caltren *Libbs, Braz.*
Nitrendipine (p.1358·2).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Caltriject *Faran, Gr.*
Calcitriol (p.1986·2).
Vitamin D deficiency.

Caltrivat *VSM, Neth.*
Homoeopathic preparation.

Caltro *Geneva, USA.*
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Caltron *Pyridam, Indon.*
Calcium carbonate (p.1714·1); colecalciferol; magnesium; zinc; copper; manganese; boron (p.1922·1).
Calcium and vitamin D deficiency; calcium supplement.

Caltum *Ethica, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Caltusine *Rudefsa, Mex.*
Guaifenesin (p.1561·3); oxolamine citrate (p.1567·1).
Formerly contained carbocisteine and oxolamine citrate.
Respiratory-tract disorders.

Calumid *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Bicalutamide (p.686·2).
Prostatic cancer.

Caluran *Ranbaxy, India.*
Bicalutamide (p.686·2).
Prostatic cancer.

Calutide *Cipla, India.*
Bicalutamide (p.686·2).
Prostatic cancer.

Calutol *Nolver, Venez.*
Bicalutamide (p.686·2).
Prostatic cancer.

Calvakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Calvasc *Douglas, NZ.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Calvepen *Clonmel, Irl.*
Phenoxymethylpenicillin calcium (p.314·2).
Bacterial infections.

Calvidin *Faran, Gr.; Ergha, Irl.; Rottapharm, Irl.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Calvin *Biolab, Thai.*
Calcium (p.1675·2).
Osteoporosis.

Calvin Plus *Biolab, Thai.*
Calcium (p.1675·2); vitamin D (p.1986·1); boron; copper; magnesium; manganese; zinc (p.1922·1).
Osteoporosis.

Calvit *Multicare, Philipp.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium supplement; osteoporosis.

Calvita B12 *De Mayo, Braz.*
Calcium lactate; calcium phosphate; sodium fluoride; colecalciferol; vitamin B (p.1922·1).

Calvitalis *Julphar, UAE.*
Vitamin preparation with calcium (p.1922·1).
Dietary supplement.

Calvite P & D *Cypress, USA.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).

Calvitran *Landson, Indon.*
Vitamins; sodium hypophosphite; calcium hypophosphite; calcium gluconate (p.1922·1).
Nutritional supplement.

Calvonin *Kalbe, Indon.*
Isoflavone (p.2391·2).
Menopausal disorders; osteoporosis.

Calypsol *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia†; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Thai.*
Ketamine hydrochloride (p.1787·1).
Analgesic sedative; general anaesthesia.

Calyptol *Sanofi-Aventis, Ital.*
Cineole (p.2282·3); terpineol (p.2396·1); pine oil (p.2368·2); thyme oil (p.2401·2); rosemary oil (p.2381·3).
Respiratory-tract congestion.

Calzem *Cazi, Braz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Cam
Note. A similar name is used for preparations of different composition (see below).
Laboratorios Chile, Chile.
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

CAM
Note. A similar name is used for preparations of different composition (see above).
Cambridge Healthcare, UK.
⊗ Ephedrine hydrochloride (p.1558·2).
Bronchospasm; cough.

Cama Arthritis Pain Reliever *Novartis, USA.*
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2) and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Arthritis; pain.

Camazol *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Cambem *UCI, Braz.†.*
Cambendazole (p.142·2).
Strongyloidiasis.

Camcolit *Norgine, Belg.; Norgine, Hong Kong; Norgine, Irl.; Norgine, Neth.; Norgine, S.Afr.; Norgine, Singapore; Norgine, UK.*
Lithium carbonate (p.401·3).
Aggressive or self-mutilating behaviour; bipolar disorder; depression; mania.

Camelox *PannonPharma, Hung.*
Meloxicam (p.80·3).

Cameo *Medco, USA.*
Emollient.

Camforte *Svizera, India†.*
Cabergoline (p.802·1).
Hyperprolactinaemia.

Camgesic *Camden, Singapore.*
Paracetamol (p.108·1); orphenadrine citrate (p.812·1).
Musculoskeletal pain and spasm.

Camigesik *Lucas Djaja, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Camil *Martin, Spain†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Camilia *Boiron, Canad.; Boiron, Fr.*
Homoeopathic preparation.

Camiline *Arkopharma, Fr.*
Green tea (p.2416·1).
Asthenia; slimming aid.

Caminol *Geminis, Arg.†.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Callus removal.

Camirox *Norma (Νορμα), Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Camnovate *Camden, Singapore.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Camoderm *Goldshield, Hong Kong; Goldshield, Singapore†.*
Chamomile (p.2279·3).
Cracked and sore nipples; nappy rash; skin irritation.

Camolyn *Oftalmi, Venez.*
Chamomile (p.2279·3); hamamelis (p.2318·2).
Eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Camolyn Plus *Oftalmi, Venez.*
⊗ Naphazoline hydrochloride (p.1565·2); chamomile (p.2279·3); hamamelis (p.2318·2).
Eye irritation.

Camomila *Catarinense, Braz.*
Aloes (p.1705·2); paregoric (p.105·1); aniseed (p.2258·2); peppermint leaf (p.1761·2); melissa (p.2339·3); chamomile (p.2279·3); centaury (p.2279·1); condurango (p.2287·1); Fuller's earth (p.1447·1); gentian (p.2310·3); absinthium (p.2244·1); quassia (p.2377·1); rhubarb (p.1768·3); bixa orellana.
Digestive disorders.

Camomilina C *Igefarma, Braz.*
Chamomile (p.2279·3); liquorice (p.1740·3); colecalciferol; vitamin C; calcium phosphate (p.1922·1).
Nutritional supplement.

Camomilla (Specie Composta) *Dynacren, Ital.†*
Valerian (p.2410·1); chamomile (p.2279·3); caraway (p.2276·3); peppermint leaf (p.1761·2).
Herbal tea; sedative.

Camoquin *Pfizer, India.*
Amodiaquine hydrochloride (p.597·2).
Malaria.

Camoxin *Klinger, Braz.†*
Amoxicillin (p.202·2).
Bacterial infections.

Campal *Meyer, Venez.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Campath *Schering, Arg.; Schering, Braz.; Schering, Rus.; Berlex, USA.*
Alemtuzumab (p.677·2).
Chronic lymphocytic leukaemia.

Campel *Chiesi, Fr.*
Chromocarb diethylamine (p.2281·1).
Circulatory disorders; haemorrhoids.

Camphoderm N *Li-il, Ger.*
Camphor (p.2273·2).
Catarrh; musculoskeletal, joint, and soft-tissue disorders.

Camphodionyl *Distri B3, Fr.*
Sulfogaiacol (p.1573·2); codeine (p.37·2).
Coughs.

Campho-Phenique *Sterling, USA; Winthrop Consumer, USA.*
Phenol (p.1656·1); camphor (p.2273·2).
Burns; cuts; herpes labialis; infections; insect bites; pain.

Campho-Phenique Cold Sore Treatment & Scab Relief *Bayer, USA.*
Pramocaine hydrochloride (p.1868·1).

Camphopin *Schoning-Berlin, Ger.*
Methyl salicylate (p.85·3); benzyl nicotinate (p.28·1); camphor (p.2273·2).
Frostbite; neuralgia; rheumatic disorders; sciatica; tendinitis.

Camphor Linctus Compound *McGloin, Austral.*
Camphor (p.2273·2); tolu balsam (p.1574·2).
Coughs.

Camphrice Du Canada *Homme de Fer, Fr.*
Camphor (p.2273·2).
Skin disorders.

Campicillin *Cadila, India.*
Ampicillin (p.204·1).
Bacterial infections.

Campicillin Plus *Cadila, India.*
Ampicillin trihydrate (p.204·2); *Lactobacillus sporogenes* (p.2372·3).
Bacterial infections.

Campilox *Cadila, India.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Campirex *IQFA, Mex.*
Piroxicam (p.117·3).
Inflammation.

Campixen *IBI, Ital.†*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Campral *Merck, Arg.†; Alphapharm, Austral.; Merck, Austria; Merck, Belg.; Merck, Braz.†; Merck, Chile; Merck, Cz.; Merck Sante, Denm.; AWD, Ger.; Merck Sante, Hong Kong; Merck, Hung.; Merck, Irl.; Merck, Mex.; Merck, Neth.; Merck, Norw.; Merck, Pol.; Merck, Port.; Merck, Singapore†; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, Turk.; Merck, UK; Forest Laboratories, USA.*
Acamprosate calcium (p.958·3).
Alcoholism.

Campto *Pfizer, Austria; Pfizer, Belg.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Aventis, Rus.; Aventis, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Aventis, Turk.; Pfizer, UK.*
Irinotecan hydrochloride (p.737·1).
Cervical cancer; colorectal cancer; gastric cancer; small cell lung cancer.

Camptosar *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Mex.; Pfizer, NZ; Pharmacia, USA; Pfizer, Venez.*
Irinotecan hydrochloride (p.737·1).
Breast cancer; colorectal cancer.

Canadine *TNP, Thai.†*
Clotrimazole (p.530·1).
Fungal skin infections.

Canadiol *Esteve, Spain.*
Itraconazole (p.536·3).
Fungal infections.

Canalba *Aspen, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Canasa *Axcan, USA.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Canasone *TNP, Thai.†*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections.

Canazol *TO-Chemicals, Thai.*
Clotrimazole (p.530·1).
Fungal skin, oropharyngeal, and vaginal infections; trichomoniasis.

Canazol-BE *TO-Chemicals, Thai.*
⊗ Clotrimazole (p.530·1); betamethasone valerate (p.1519·1).
Fungal skin infections.

Cancid *Sunthi Sepuri, Indon.*
Fluconazole (p.532·1).
Fungal infections.

Cancidas *MSD, Arg.; MSD, Austral.; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Caspofungin acetate (p.528·2).
Aspergillosis; candidiasis.

Cancina *Mayo, Mex.*
Kanamycin (p.291·3).
Bacterial infections.

Candacide *Be-Tabs, S.Afr.*
Nystatin (p.543·2).
Oral candidiasis.

Candacort *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗ Clotrimazole (p.530·1); hydrocortisone (p.1535·2).
Fungal skin infections with inflammation.

Candalba *Brauer, Austral.†*
Homoeopathic preparation.

Candaspor *Be-Tabs, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Candazol *Apogepha, Ger.†*
Clotrimazole (p.530·1).
Fungal and bacterial vaginal infections; trichomoniasis.

Candazole *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Candepressin *Liptis, USA.*
Candesartan cilexetil (p.1238·3).

Candepressin Plus *Liptis, USA.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Canderel *Ali, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Canderm *Legrand, Braz.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Formerly known as Canderme.

Candermil *LKM, Arg.*
Nystatin (p.543·2).
Fungal infections.

Candesar *Stancare, India.*
Candesartan (p.1239·1).
Hypertension.

Candibec *Glenmark, Philipp.*
⊗ Beclometasone dipropionate (p.1516·2); clotrimazole (p.530·1).
Fungal skin infections.

Candibene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.*
Clotrimazole (p.530·1).
Fungal and bacterial skin and vaginal infections; vaginal trichomoniasis.

Candibiotic *Glenmark, India; Glenmark, Rus.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Candicort *Ache, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Candid *Glenmark, India; Glenmark, Malaysia; Neves, Port.†; Glenmark, Rus.; Glenmark, Thai.*
Clotrimazole (p.530·1).
Fungal skin, scalp, mouth, and vaginal infections; trichomoniasis.

Candid B *Glenmark, India; Glenmark, Rus.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2).
Infected skin disorders.

Candid Ear Drops *Glenmark, India.*
Clotrimazole (p.530·1); lidocaine hydrochloride (p.1862·3).
Fungal ear infections.

Candid V6 *Glenmark, Philipp.; Glenmark, Rus.*
Clotrimazole (p.530·1).
Fungal vaginal infections; vaginal infections.

Candida Yeast *Homeocan, Canad.*
Homoeopathic preparation.

Candiden *Akita, UK†.*
Clotrimazole (p.530·1).
Fungal infections.

Candiderm *Ache, Braz.*
Ketoconazole (p.539·1).
Fungal skin infections.

Candiderma *Glenmark, India†.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); gentamicin sulfate (p.282·1).
Bacterial and fungal skin infections.

Candiderma + *Glenmark, India.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1).
Bacterial and fungal skin infections.

Candidias *Fabra, Arg.*
Nystatin (p.543·2).
Fungal infections.

Candidin *Toprak, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Candid-TV *Glenmark, India.*
Clotrimazole (p.530·1); selenium sulfide (p.1613·1).
Scalp disorders.

Candilax *Cevallos, Arg.*
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Constipation.

Candimicol *Quesada, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Candimon *Andromaco, Mex.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Candimyc *Viofar, Gr.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Candinox *Charoen, Thai.*
Clotrimazole (p.530·1).
Fungal mouth, throat, and vaginal infections; trichomoniasis.

Candio *Hermal, Austria; Hermal, Ger.*
Nystatin (p.543·2).
Fungal infections.

Candio-Hermal Plus *Hermal, Ger.*
⊗ Nystatin (p.543·2); fluprednidene acetate (p.1533·1).
Inflammatory skin disorders with fungal infection.

Candiphen *Sons, Mex.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Candipres *Precimex, Mex.*
Amphotericin B (p.523·2).
Fungal infections.

Candistat *Merck, India.*
Itraconazole (p.536·3).
Fungal infections.

Candistatin *Teuto, Braz.†; BMS, Canad.*
Nystatin (p.543·2).
Fungal infections.

Candistin *Pharos, Indon.*
Nystatin (p.543·2).
Candidiasis.

Canditral *Glenmark, India; Glenmark, Malaysia; Glenmark, Singapore†; Glenmark, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Canditrat *Teuto, Braz.*
Nystatin (p.543·2).
Fungal infections.

Candix *Prodotti, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Candizol *Ache, Braz.; Sandoz, Indon.; Ivax, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Candizole *Pharmacare, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Candizole-T *Unichem, India.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1).
Vaginal candidiasis.

Candoral *Ache, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Candyl *Douglas, Austral.†; Douglas, NZ.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Canef *AstraZeneca, Denm.; AstraZeneca, Fin.; Astra, Mex.†; AstraZeneca, Neth.; Jaba, Port.; AstraZeneca, Swed.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Canelin *Square, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Canephron *Bionorica, Ger.*
Centaury (p.2279·1); lovage (p.2335·1); rosemary (p.2381·2).
Renal calculi; urinary-tract disorders.

Canephron N *Bionorica, Rus.*
Centaury (p.2279·1); lovage (p.2335·1); rosemary (p.2381·2).
Urinary-tract disorders.

Canephron novo *Bionorica, Ger.†*
Birch leaf (p.2266·3); java tea (p.2328·2); solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Canephron S *Bionorica, Ger.*
Solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Canergy *Meprofarm, Indon.*
Levocarnitine fumarate; thioctic acid; ubidecarenone; vitamin B substances; ascorbic acid (p.1922·1).
Nutritional supplement.

Canesoral Duo *Bayer, Austral.*
1 Capsule, fluconazole (p.532·1); cream, clotrimazole (Canesten) (p.530·1).
Vaginal candidiasis.

Canesten *Bayer, Austral.; Bayer, Austria; Bayer, Braz.; Bayer Consumer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer Consumer, Malaysia; Bayer Consumer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Norw.; Bayer, Philipp.; Bayer, Pol.; Bayer, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Thai.; Bayer, Turk.; Bayer Consumer, UK; Bayer, Venez.*
Clotrimazole (p.530·1).
Fungal and bacterial infections of the skin and vagina; vaginal trichomoniasis.

Canesten AF Once Daily *Bayer Consumer, UK†.*
Bifonazole (p.527·3).
Athlete's foot.

Canesten Bifonazol *Bayer, Austria.*
Bifonazole (p.527·3).
Fungal foot infections.

Canesten Bifonazol comp *Bayer, Austria.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Canesten Combi *Bayer Consumer, UK.*
Combination pack containing Canesten Cream and Canesten 1 pessary: Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

Canesten Extra *Bayer, Ger.*
Bifonazole (p.527·3).
Fungal skin infections.

Canesten Extra Nagelset *Bayer, Ger.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Onychomycosis.

Canesten Fluconazole *Bayer, NZ.*
Fluconazole (p.532·1).
Vaginal candidiasis.

Canesten HC *Bayer, Ger.†; Bayer, Hong Kong; Bayer, Irl.; Bayer, Singapore; Bayer Consumer, UK.*
⊗ Clotrimazole (p.530·1); hydrocortisone (p.1535·2).
Fungal infections with inflammation.

Canesten Oasis *Bayer Consumer, UK.*
Sodium citrate (p.1673·3).
Cystitis.

Canesten Once Daily *Bayer Consumer, Austral.*
Bifonazole (p.527·3).
Fungal skin infections.

Canesten Oral *Bayer Consumer, UK.*
Fluconazole (p.532·1).
Candidal balanitis; vaginal candidiasis.

Canestene *Bayer, Belg.; Bayer, Switz.*
Clotrimazole (p.530·1).
Balanitis; fungal and bacterial skin infections; fungal nail infections; vulvovaginal candidiasis.

Canestene Derm Bifonazole *Bayer, Belg.*
Bifonazole (p.527·3).
Fungal skin infections.

Canex
Note. This name is used for preparations of different composition.
Wolff, Ger.
Fluconazole (p.532·1).
Fungal infections.

Alliance, S.Afr.
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Canferon *Takeda, Jpn.*
Interferon alfa-2a (p.885·1).
Hepatitis B; hepatitis C; multiple myeloma; renal cancer.

Canfomenol *Brasmedica, Braz.†*
⊗ Niaouli oil (p.2351·3); camphor (p.2273·2); cineole (p.2282·3); guaiacol (p.1561·2); menthol (p.2340·1); ephedrine (p.1558·1).
Respiratory-tract congestion.

Canfosalicilica *Farmatre, Ital.†; Ogna, Ital.†; Sella, Ital.†.*
Camphor (p.2273·2); methyl salicylate (p.85·3).
Muscle and joint pain.

Canicol *Caprifarmindo, Indon.; Sanbe, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Canidazol *Arex, Venez.†*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Canifug *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
Clotrimazole (p.530·1).
Fungal and bacterial skin and vaginal infections; vaginal trichomoniasis.

Canifug Itra *Wolff, Ger.*
Itraconazole (p.536·3).
Fungal infections.

Cankerol N *Coradol, Ger.†.*
Homoeopathic preparation.

Canoderm *ACO Hud, Swed.*
⊗ Urea (p.1620·2).
Dry skin.

Canol *Jolly-Jatel, Fr.*
Cynara (p.2291·2); chimaphila; aphloia.
Promotor of digestion and renal function.

Canolen *Biofarma, Turk.*
Ciclopirox olamine (p.529·2).
Fungal skin infections; vaginal candidiasis.

Canovex *Microsules, Arg.†.*
Dipyrone (p.49·2); dextropropoxyphene napsilate (p.40·1) or dextropropoxyphene hydrochloride (p.40·1).
Fever; pain.

Canrenol *Grunenthal, Belg.; SPA, Cz.†.*
⊗ Potassium canrenoate (p.1374·1).
Cirrhosis; electrolyte disturbances; heart failure; hyperaldosteronism; hypertension; nephrotic syndrome.

Canri *Mayne, Cz.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Canstat *Pharmacare, S.Afr.*
Nystatin (p.543·2).
Candidiasis.

Cantabilin *Formenti, Ital.*
Hymecromone (p.2323·2).
Biliary-tract disorders; liver disorders.

Cantabiline *Merck, Belg.; Merck-Lipha, Fr.; Ilsan, Turk.*
Hymecromone (p.2323·2).
Biliary-tract disorders; dyspepsia.

Cantadrill *Pierre Fabre Sante, Fr.*
Erysimum.
Mouth and throat disorders.

Cantalene *Cooperation Pharmaceutique, Fr.*
Muramidase hydrochloride (p.2348·1); chlorhexidine acetate (p.1635·2); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Cantel *Pisa, Mex.*
Ketotifen (p.582·2).

Canthacur *Paladin, Canad.*
Cantharidin (p.2276·1).
Molluscum contagiosum; warts.

Canthacur-PS *Paladin, Canad.*
Cantharidin (p.2276·1); podophyllum resin (p.1610·2); salicylic acid (p.1612·2).
Molluscum contagiosum; warts.

Cantharis Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Cantharone *Dormer, Canad.*
Cantharidin (p.2276·1).
Molluscum contagiosum; warts.

Cantharone Plus *Dormer, Canad.*
Cantharidin (p.2276·1); podophyllum resin (p.1610·2); salicylic acid (p.1612·2).
Warts.

Cantil *AstraZeneca, Swed.†; Hoechst Marion Roussel, USA.*
Mepenzolate bromide (p.1745·1).
Adjunctive therapy in peptic ulcer; spasmodic disorders of the colon.

Cantipal *Loren, Mex.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine (p.572·2); phenylephrine (p.1568·1).
Cold symptoms.

Cantril *Talcris, Arg.†.*
⊗ Clobetasol (p.1522·2).
Skin disorders.

Canusal *CP Pharmaceuticals, UK.*
Heparin sodium (p.1301·2).
To maintain patency of in-dwelling intravascular lines.

Caobe *Mayo, Mex.*
Oxolamine (p.1567·1); ammonium acetate (p.1551·2); sodium citrate (p.1673·3).
Cough.

Caopecfar *Alpharma, Mex.*
Furazolidone (p.834·3); pectin (p.2145·2); kaolin (p.1738·1).
Diarrhoea.

Caosina *Ern, Spain.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Caosina D *Ern, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Capabiotic *Fahrenheit, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

Capace *Hexal, Austria; Cipla, India; Garec, S.Afr.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Capacit *Liferpal, Mex.*
⊗ Salbutamol (p.1131·2).

Capadex *Fawns & McAllan, Austral.; Healthcare Logistics, NZ.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Caparin *Osotspa, Thai.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Capasal *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Scalp disorders.

Capastat *Lilly, Austral.; Lilly, Austria; Lilly, Cz.†; IFET (ΙΦΕΤ), Gr.; Lilly, Rus.; Dista, Spain; King, UK; Dura, USA.*
Capreomycin sulfate (p.215·3).
Tuberculosis.

CAPD *Fresenius Medical, Hung.; Fresenius, Israel; Fresenius Medical, Port.; Fresenius Medical, Spain.*
A range of electrolyte solutions with glucose (p.1670·3).
Peritoneal dialysis.

CAPD/DPCA *Fresenius Medical, Cz.; Fresenius Medical, Denm.; Fresenius Medical, Fin.; Fresenius Medical, Hung.; Fresenius Medical, Neth.; Fresenius Medical, Port.; Fresenius Medical, Spain; Fresenius Medical, Swed.†.*
A range of electrolyte solutions with glucose (p.1670·3).
Peritoneal dialysis.

Capel *Ache, Braz.*
Ketoconazole (p.539·1); panthenol (p.2362·1).
Seborrhoeic dermatitis.

Capella *Tentan, Switz.*
Homoeopathic preparation.

Capent
Note. This name is used for preparations of different composition.
Andromaco, Chile.
Loperamide (p.1741·3).
Diarrhoea.

Novartis, Mex.
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Capergyl *Bailleul, Fr.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Capex *Galderma, Canad.; Galderma, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Scalp disorders.

Capginvit *Atlantic, Hong Kong; Atlantic, Thai.*
Multivitamin preparation (p.1922·1).

Capibaryne *Osorio de Moraes, Braz.†.*
Vitamin B substances with minerals (p.1922·1).

Capila Savon *Kurtsan, Turk.*
Sulfur (p.1614·1).
Acne.

Capilarema *Baldacci, Braz.; Baldacci, Port.; Zambon, Spain†.*
Aminaphthone (p.1053·1).
Capillary disorders; haemorrhage.

Capill *Pharma Italia, Ital.*
Centella (p.1592·3); aesculus (p.2248·2); red vine (p.2316·3); myrtillus (p.2349·3); vitamin C (p.1983·3); vitamin E (p.1992·2).
Capillary disorders; oedema.

Capill Venogel *Pharma Italia, Ital.*
Centella (p.1592·3); biorusol; rutoside (p.2305·1); aesculus (p.2248·2); butcher's broom (p.2270·3); melilot (p.2339·2).
Peripheral vascular disorders.

Capillarema *Baldacci, Ital.*
Aminaphthone (p.1053·1).
Capillary disorders.

Capillaron *Madaus, Ger.†.*
Homoeopathic preparation.

Capillaron Vertigo *Madaus, Ger.*
Homoeopathic preparation.

Capin *Biogal-Teva, Hung.†.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Capistan *Pierre Fabre, Cz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Capital with Codeine *Carnrick, USA.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Capital Soleil
Note. This name is used for preparations of different composition.
Vichy, Fr.
Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); octocrilene (p.1608·3); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Vichy, USA.
SPF 20: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Capitis
Note. This name is used for preparations of different composition.
Fecofar, Arg.
Cream: Permethrin (p.2048·2).
Pediculosis.

Fecofar, Arg.†.
Lotion: Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis.

Capitrol *Westwood-Squibb, USA.*
Chloroxine (p.242·2).
Seborrhoeic dermatitis.

Capiven *Servier, Denm.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Venous insufficiency.

Capivit A + E *GSK, Pol.*
Vitamin A acetate (p.1973·1); *dl*-alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Caplenal *Berk, UK.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Capmerin *Korea United, Philipp.*
Mercaptopurine (p.744·1).
Leukaemias.

Capobal *Baldacci, Braz.*
Captopril (p.1239·2).
Hypertension.

Capocard *Dar Al Dawa, Hong Kong†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Capomed *Medlink, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infection.

Caposan *Adler, Switz.†.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Capostad *Stada, Austria.*
Captopril (p.1239·2).
Heart failure; hypertension.

Caposten *Chinoin, Mex.*
Hydroxyprogesterone (p.2110·3).

Capoten *BMS, Austral.; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, Hong Kong; BMS, Indon.; BMS, Irl.; BMS, Ital.; BMS, Malaysia†; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Philipp.; BMS, Port.; Akrikhin, Rus.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore†; BMS, Spain; BMS, Swed.; BMS, Thai.; BMS, UK; Par, USA; BMS, Venez.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Capotena *BMS, Mex.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Capotrat *Uniao Quimica, Braz.*
Captopril (p.1239·2).
Hypertension.

Capotril *Neo Quimica, Braz.†.*
Captopril (p.1239·2).
Hypertension.

Capox *Geolab, Braz.*
Captopril (p.1239·2).
Heart failure; hypertension.

Capox H *Geolab, Braz.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Capozid *BMS, Denm.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Capozide *BMS, Austria; BMS, Ger.; BMS, Indon.; BMS, Irl.; BMS, Mex.; BMS, NZ; BMS, Neth.†; Akrikhin, Rus.; BMS, Rus.; BMS, S.Afr.; BMS, Switz.; BMS, UK; Par, USA; BMS, Venez.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3) .
These ingredients can be described by the British Approved Name Co-zidocapt.
Heart failure; hypertension.

Capril *Teuto, Braz.; APT, Hong Kong.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Caprilate *Eagle, Austral.*
Sodium octanoate (p.2356·1); berberis vulgaris; magnesium chloride (p.1679·1); zinc gluconate (p.1999·2); lithium chloride (p.406·1); sorbic acid (p.1662·2).
Inhibition of gastrointestinal yeast growth.

Caprill *Pinewood, Irl.*
Captopril (p.1239·2).
Heart failure; hypertension.

Caprilon
Note. This name is used for preparations of different composition.
Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Scientific Hospital Supplies, UK.
Preparation for enteral nutrition containing medium-chain triglycerides (p.1956·3).
Disorders of fat metabolism; hepatobiliary disorders; malabsorption syndromes; pancreatic disorders; stagnant-loop syndrome; steatorrhoea.

Leiras, Fin.
Tranexamic acid (p.1080·3).
Fibrinolysis; hereditary angioedema.

Capriltop *Topgen, Belg.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Caprimida *Megahealth, Chile.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis; rickets; tetanus.

Caprimida D *Megahealth, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetanus.

Caprimida D Balance *Megahealth, Chile.*
Calcium (p.1675·2); colecalciferol (p.1986·2); magnesium; zinc; manganese; copper; boron.
Calcium and vitamin D deficiency; osteoporosis.

Caprin *Pinewood, Irl.; Pinewood, UK.*
Aspirin (p.20·3).
Fever; inflammation; pain; rheumatic disorders; thrombosis prophylaxis.

Caprisana *Zeppenfeldt, Ger.†.*
Camphor (p.2273·2); juniper oil (p.2328·3); rosemary oil (p.2381·3); turpentine oil (p.2406·3); larch oil.
Musculoskeletal and joint disorders.

Caprisset *Solfran, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Capritin *Atral, Port.*
Captopril (p.1239·2).

Caproamin *Rottapharm, Spain; Surgimed, Venez.*
Aminocaproic acid (p.1053·2).
Haemorrhage.

Caprofides Hemostatico *Rottapharm, Spain.*
⊗ Aminocaproic acid (p.1053·2); esculoside (p.2248·2); hesperidin methyl chalcone (p.2305·2); menadione (p.1995·2); creatinine sulfate.
Haemorrhage.

Caprolisin *Malesci, Ital.*
Aminocaproic acid (p.1053·2).
Haemorrhagic disorders.

Capros *Medac, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

Capsalgine *Aroma, Turk.*
Salicylic acid (p.1612·2); capsicum oleoresin (p.2276·2); camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2).
Musculoskeletal and joint pain.

Capsamol *Worwag, Ger.*
Capsicum (p.2276·2).
Musculoskeletal and joint pain.

Capsamol N *Worwag, Ger.†.*
Benzyl nicotinate (p.28·1); capsaicin (p.32·3).
Rheumatic disorders.

Capsella Complex *Mediherb, Austral.*
Shepherd's purse (p.2386·2); dong quai (p.2297·3); paeonia lactiflora; helonias (p.2318·3).
Female genito-urinary tract disorders.

Capsic *Pierre Fabre Sante, Fr.*
Capsaicin (p.32·3); methyl nicotinate (p.85·3).
Muscle cramp.

Capsicam *Tallinn, Rus.*
Benzyl nicotinate (p.28·1); vanillylnonamide (p.96·2); camphor (p.2273·2); turpentine oil (p.2406·3); dimethyl sulfoxide (p.2022·1).
Musculoskeletal and joint pain.

Capsicin *Vinas, Spain.*
Capsaicin (p.32·3).
Musculoskeletal and joint pain.

Capsicof *Gelcaps, Mex.*
Benzonatate (p.1552·1).
Cough.

Capsicolle *Chemopharma, Cz.*
Capsaicin (p.32·3); belladonna (p.2263·3).
Muscle pain.

Capsicum + Arthri-Cream *Homeocan, Canad.*
Homoeopathic preparation.

Capsicum Farmaya *Alacan, Spain.*
Capsaicin (p.32·3).
Musculoskeletal and joint pain.

Capsidol *Janssen-Cilag, Mex.; Vinas, Spain.*
Capsaicin (p.32·3).
Musculoskeletal and joint disorders; musculoskeletal and joint pain; pain.

Capsiflu *Gelcaps, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Capsi-Gel *Biosel, Turk.*
Capsicum oleoresin (p.2276·2); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Capsigel N *Herbapol Poznan, Pol.*
Camphor (p.2273·2); capsaicin (p.32·3); eucalyptus oil (p.2301·2); salicylic acid (p.1612·2); turpentine oil (p.2406·3).
Musculoskeletal and joint pain; neuralgia.

Capsin *Fleming, USA.*
Capsaicin (p.32·3).
Neuralgia; pain.

Capsina *Bioglan, Norw.; Bioglan, Swed.*
Capsaicin (p.32·3).
Postherpetic neuralgia.

Capsinat *Caprifarmindo, Indon.; Sanbe, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Capsion *CIS, Cz.; CIS, Neth.; CIS, Port.; Schering, UK.*
Iodine-131 (p.2054·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Capso *RDC, Ital.*
Capsicum oleoresin (p.2276·2); aloe vera (p.1588·2).
Skin disorders.

Capsoid *Caps, S.Afr.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Capsolin *Chefaro, Ital.*
Capsicum oleoresin (p.2276·2); camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2).
Joint and muscle pain; soft-tissue disorders.

Capson *Pharmatrix, Arg.*
Aloe vera (p.1588·2).
Skin disorders.

Capsugen *Vitalink, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Capsulas Handel *Casasco, Arg.†.*
Castor oil (p.2278·1).
Constipation.

Capsules-vital *Biomed, Switz.*
Ginkgo biloba (p.2311·1); glutamic acid; magnesium glycerophosphate; magnesium orotate; lecithin (p.1922·1).
Tonic.

Capsuvac *Galen, UK.*
Dantron (p.1722·2); docusate sodium (p.1725·1).
These ingredients can be described by the British Approved Name Co-danthrusate.
Constipation.

Captagon *Meda, Belg.; Viatris, Ger.†.*
⊗ Fenetylline hydrochloride (p.2156·2).
Hyperactivity disorders; narcoleptic syndrome.

Captaton *Biotenk, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Captea *Sanofi-Aventis, Fr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captensin *Kalbe, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Capti *Genpharm, Israel†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captil *Hebron, Braz.†.*
Captopril (p.1239·2).
Hypertension.

Captimer *MIT, Ger.*
Tiopronin (p.1467·1).
Cystinuria; heavy metal poisoning; liver disorders; Wilson's disease.

Captin *Krewel, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Capto *Alpharma-Isis, Ger.; CT, Ger.; Winthrop, Ger.; corax, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Capto Comp *1A, Ger.; ABZ, Ger.; CT, Ger.; Winthrop, Ger.; corax, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Capto Plus *Alpharma-Isis, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

capto-basan *Schonenberger, Switz.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Captobel *Sedabel, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captobeta *Betapharm, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captobeta Comp *Betapharm, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Capto-Co *Ivax, UK.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-zidocapt.
Hypertension.

Captocomp *Ebewe, Austria.*
Verapamil hydrochloride (p.1421·1); captopril (p.1239·2).
Hypertension.

Captocord *Globo, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captodan *Pharmacodane, Denm.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captodoc *Docpharm, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captodoc Comp *Docpharm, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Capto-dura M *Merck dura, Ger.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captoflux *Hennig, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captogamma *Worwag, Ger.; Worwag, Hung.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Captogamma HCT *Worwag, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captohexal *Hexal, Austral.; Hexal, Ger.; Hexal, NZ; Hexal, S.Afr.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captohexal Comp *Hexal, Austria; Salutas, Cz.†; Hexal, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captol
Note. This name is used for preparations of different composition.
Sandoz, Denm.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.
Pacific, NZ†.
⊗ Oxprenolol hydrochloride (p.1365·1).
Angina pectoris; arrhythmias; hypertension.

Captolab *Multilab, Braz.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captolane *Sanofi-Aventis, Fr.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captolin *HB, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captomax *Adcock Ingram, S.Afr.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Captomed *Ebewe, Austria; Cimed, Braz.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captomerck *Merck dura, Ger.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captomin *Ratiopharm, Fin.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Capton *Royton, Braz.†.*
Captopril (p.1239·2).
Hypertension.

Captophar *Julphar, UAE.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captopiril *Bunker, Braz.*
Captopril (p.1239·2).
Hypertension.

Captopress
Note. This name is used for preparations of different composition.
Lindopharm, Ger.
Captopril (p.1239·2).
Heart failure; hypertension.
Genepharm, Gr.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captopril Comp *ABZ, Ger.; Basics, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captopril Compositum *Faromed, Austria; Mayrhofer, Austria.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captopril HCT *Aliud, Ger.; Sandoz, Ger.; Stada, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captopril Plus *Verla, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captopril-HCT *Ratiopharm, Austria.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captoprimed *Ethimed, Belg.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captopron *Cifarma, Braz.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captor *Hexal, Austria; Rowex, Irl.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captoretic *Hexal, S.Afr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captor-HCT *Rowex, Irl.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captosen *Pharlab, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captoser *Serral, Mex.*
Captopril (p.1239·2).
Hypertension.

Captosif *Sinterapico, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captosina *VP, Spain.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captosol *Ecosol, Switz.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Captosol comp *Ecosol, Switz.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Captospes+H *Alet, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captostad *Berner, Fin.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captotec *Hexal, Braz.†.*
Captopril (p.1239·2).
Hypertension.

Captotec + HCT *Hexal, Braz.†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Captotyrol *Tyrol, Austria†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Captozen *Vitapan, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Captral *Silanes, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Captral ASA *Silanes, Mex.*
Captopril (p.1239·2); aspirin (p.20·3).
Diabetic nephropathy; heart failure; hypertension; thromboembolic disorders.

Captrizin *Prodotti, Braz.*
Captopril (p.1239·2).
Hypertension.

Captus *Laboratorios Chile, Chile.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); noscapine (p.1566·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Capurate *Sigma, Austral.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Capval *Dreluso, Ger.*
Noscapine resinate or noscapine hydrochloride (p.1566·3).
Coughs and associated respiratory-tract disorders.

Capxidin *Malayan, Singapore†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Capyla *Sigma, Braz.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Capzacin *Combiphar, Indon.*
Capsaicin (p.32·3).
Neuropathic pain; osteoarthritis.

Capzasin-HP *Chattem, USA.*
Capsaicin (p.32·3).
Pain.

Capzasin-P *Chattem, USA.*
Capsaicin (p.32·3).
Pain.

Car *Lindopharm, Ger.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Carac *Dermik, USA.*
Fluorouracil (p.722·2).
Actinic keratoses.

Carace *BMS, Irl.; BMS, UK.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Carace Plus *BMS, Irl.; BMS, UK.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Caradine *Millimed, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hay fever.

Carafate *Aspen, Austral.; Healthcare Logistics, NZ; Axcan, USA.*
Sucralfate (p.1772·2).
Peptic ulcer.

Caralpha *Alpharma, UK.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Caramelle alle Erbe Digestive *Giuliani, Ital.*
Gentian (p.2310·3); rhubarb (p.1768·3); boldo (p.2267·2).
Aid to digestion.

Caramelos Agua del Carmen *Fardi, Spain†.*
Cineole (p.2282·3); melissa (p.2339·3); menthol (p.2340·1).
Nasal congestion.

Caramelos Antibioticos
Note. This name is used for preparations of different composition.
Fecofar, Arg.; Richet, Arg.
Benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.
HMA, Arg.; Raymos, Arg.
Hexylresorcinol (p.1647·1); benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Caramelos Antibioticos Bucoangin *Northia, Arg.†.*
Hexylresorcinol (p.1647·1); neomycin (p.305·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Caramelos Antibioticos Lefmar *Biosintex, Arg.*
Tyrothricin (p.358·2); hexylresorcinol (p.1647·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Caramelos Oriental *Oriental, Arg.*
Hexylresorcinol (p.1647·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Carasel *Almirall, Spain.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Carb PSE 12 DM *Rivers Edge, USA.*
Dextromethorphan tannate (p.1556·1); carbinoxamine tannate; pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Carb Pseudo-Tan *Hi-Tech, USA.*
Pentoxyverine tannate (p.1567·3); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Carba *CT, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbabeta *Betapharm, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbac *Syntex, Mex.†.*
Loracarbef (p.295·3).
Bacterial infections.

Carbacontin *Modi-Mundipharma, India.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy.

Carbactive *Cooperation Pharmaceutique, Fr.*
Activated charcoal (p.1435·2).
Gastrointestinal disorders.

Carbactol Retard *Laboratorios Chile, Chile†.*
Carbamazepine (p.471·3).
Diabetes insipidus; epilepsy; neuralgia.

Carbaderme *Lepori, Port.†.*
Emollient.

Carbadura *Merck dura, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbafen *Liferpal, Mex.*
Paracetamol (p.108·1); methocarbamol (p.1897·3).
Painful skeletal muscle spasm.

Carbaflux *Hennig, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbagamma *Worwag, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbagen *Generics, UK.*
Carbamazepine (p.471·3).
Epilepsy.

Carbager-Plus *Streger, Mex.*
Methocarbamol (p.1897·3); ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint and periarticular disorders; pain.

Carbaglu *Orphan, Belg.; Orphan Europe, Cz.; Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan, UK.*
Carglumic acid (p.2277·2).
Hyperammonaemia.

Carbagramon *Gramon, Arg.*
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Carbaica *Pharmafar, Ital.†.*
Urazamide (p.2407·3).
Liver disorders.

Carbalan *Quimica y Farmacia, Mex.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; neuralgias.

Carbalax *Forest Laboratories, UK.*
Monobasic sodium phosphate (p.1682·3); sodium bicarbonate (p.1673·2).
Bowel evacuation; constipation.

Carbalepsin *Akrikhin, Rus.*
Carbamazepine (p.471·3).
Epilepsy.

Carbamann *Mann, Ger.*
Carbachol (p.1879·2).
Glaucoma.

Carbamat *Pfizer, Arg.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; deafferentation pain; diabetes insipidus; diabetic neuropathy; epilepsy; trigeminal neuralgia.

Carbamid + VAS *Widmer, Ger.*
⊗ Tretinoin (p.1618·1); urea (p.1620·2).
Skin disorders.

Carbamide Creme *Widmer, Switz.*
⊗ Urea (p.1620·2); vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1).
Skin disorders.

Carbamide Emulsion *Widmer, Switz.*
⊗ Urea (p.1620·2).
Skin disorders.

Carbamide + VAS *Widmer, Switz.*
⊗ Tretinoin (p.1618·1); urea (p.1620·2); dexpanthenol (p.2362·1).
Skin disorders.

Carbamox *Offenbach, Mex.*
Methocarbamol (p.1897·3); aspirin (p.20·3).
Fever; muscle spasm; pain.

Carbapin *Hemofarm, Rus.*
Carbamazepine (p.471·3).

Carbargal *Roemmers Osmoph, Venez.*
Activated charcoal (p.1435·2); simeticone (p.1770·2).
Flatulence.

Carbargal con Atropina *Roemmers Osmoph, Venez.*
Activated charcoal (p.1435·2); simeticone (p.1770·2); atropine sulfate (p.1219·3).
Gastrointestinal disorders.

Carbasal *Salus, Mex.*
Carbamazepine (p.471·3).
Epilepsy.

Carbastat *Novartis Ophthalmics, Canad.†; Novartis Ophthalmics, USA.*
Carbachol (p.1879·2).
Production of miosis.

Carbatab *GM, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cough; respiratory-tract congestion.

Carbatil
Note. This name is used for preparations of different composition.
Loren, Mex.†.
Mebendazole (p.148·3).
Worm infections.

Biotech, Venez.
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Carbatol *Torrent, Singapore; Torrent, Thai.†.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; glossopharyngeal neuralgia; mania; trigeminal neuralgia.

Carbatrol *Shire Richwood, USA.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Carbaval *Valdecasas, Mex.*
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Carbazene *Medifive, Thai.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Carbazep *Cryopharma, Mex.*
Carbamazepine (p.471·3).
Diabetic neuropathy; epilepsy; neuralgias.

Carbazina *Psicofarma, Mex.*
Carbamazepine (p.471·3).
Alcohol and drug withdrawal syndromes; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias.

Carbecin *GSK, Mex.†.*
Carbenicillin sodium (p.216·2).
Bacterial infections.

Carbellon *Torbet Laboratories, UK.*
Activated charcoal (p.1435·2); magnesium hydroxide (p.1743·2); peppermint oil (p.1761·2).
Dyspepsia; flatulence; gastric hyperacidity.

Carbenin *Sankyo, Jpn.*
Panipenem (p.313·2); betamipron (p.215·2).
Bacterial infections.

Carbex
Note. This name is used for preparations of different composition.
Ferring, Irl.†; Nordic, UK..
Oral granules, sodium bicarbonate (p.1673·2); simeticone (p.1770·2); solution, citric acid (p.2284·1).
Double contrast radiography of the gastrointestinal tract.

Endo, USA.
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Carbi *Gerard, Israel.*
Carbamazepine (p.471·3).
Bipolar disorder; diabetes insipidus; epilepsy; mania; trigeminal neuralgia.

Carbicalcin *Procter & Gamble, Ital.†; Chiesi, Spain.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Carbidol *Teuto, Braz.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Carbilepp *Katwijk, Philipp.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Carbilev *Pharmacare, S.Afr.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Carbin *Rowe-Fleming, Venez.†.*
Pentoxyverine citrate (p.1567·3); pentoxyverine hydrochloride (p.1567·3).
Cough.

Carbinib *Edol, Port.*
⊗ Acetazolamide (p.1875·1).
Glaucoma; ocular hypertension; pulmonary hypertension.

Carbinoxamine Compound *Morton Grove, USA†.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Carbiset *Nutripharm, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2).
Upper respiratory-tract symptoms.

Carbistad *Stada, Austria.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Carbital *Teuto, Braz.*
Phenobarbital (p.492·2).
Epilepsy.

Carbium *Hexal, Ger.†.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Carbloc *Labomed, Chile†.*
Nifedipine (p.1350·1).
Hypertension.

Carbloxal *Sandoz, Indon.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Carbo *Max Farma, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Carbo Betulae Comp *Weleda, S.Afr.*
Carbo betulae; antimonit; chamomile (p.2279·3).
Gastrointestinal disorders.

Carbo D3 *Sofar, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Carbo Konigsfeld *Muller Goppingen, Ger.*
Carbo coffea (p.2416·1).
Diarrhoea.

Carbobel *Medgenix, Belg.*
Activated charcoal (p.1435·2); methenamine (p.298·3); magnesium citrate (p.1743·2).
Diarrhoea; dyspepsia; poisoning.

Carbocain *AstraZeneca, Denm.; Dentsply, Norw.; AstraZeneca, Swed.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbocaina
Note. This name is used for preparations of different composition.
AstraZeneca, Ital.
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Bucca, Spain†.
Phenol (p.1656·1); methyl salicylate (p.85·3); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Carbocaine *AstraZeneca, Austral.; Hospira, Canad.; AstraZeneca, Fr.; Adcock Ingram, S.Afr.; Hospira, USA.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia; regional anaesthesia.

Carbocaine with Neo-Cobefrin *Cook-Waite, USA.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Corbadrine (p.2287·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbocal *Madariaga, Spain; Unison, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency; hypocalcaemia; osteoporosis.

Carbocal D *Madariaga, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Carbocalc *Unison, Thai.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Carbo-cell *Cell Pharm, Ger.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carbocin *Cimed, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Carbocit
Note. This name is used for preparations of different composition.
Imuna, Cz.
Activated charcoal (p.1435·2); bismuth subgallate (p.1711·1); citric acid monohydrate (p.2284·1).
Diarrhoea.

CT, Ital.
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Carbocter *Pharmasant, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Carbodec *Rugby, USA.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Carbodec DM *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2).
Coughs and cold symptoms.

Carbodex DM
Note. This name is used for preparations of different composition.
Tri-Med, USA.
Oral drops: Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Tri-Med, USA.
Syrup: Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Carbo-Dome *Sandoz, UK.*
Coal tar (p.1616·2).
Psoriasis.

Carbofan *Bunker, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Carboflem *Danlex, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excess or viscous mucus.

Carboflex
Note. This name is used for preparations of different composition.
Convatec, Austral.†; Convatec, Fr.
Activated charcoal (p.1435·2); alginate.
Wounds.

Convatec, Canad.†; Convatec, Port.†.
Calcium-sodium alginate (p.1058·1)(p.2141·1); carmellose sodium (p.2142·1); activated charcoal (p.1435·2).
Ulcers; wounds.

Carboflot *Glenmark, India†.*
Iron carbonyl (p.1950·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Anaemias.

Carbogasol
Note. This name is used for preparations of different composition.
Montpellier, Arg.
Oral drops: Simeticone (p.1770·2).
Meteorism; preparation for radiography.

Montpellier, Arg.
Tablets: Simeticone (p.1770·2); charcoal (p.1435·2).
Formerly contained simeticone, charcoal, and homatropine methylbromide.
Dyspepsia; meteorism.

Carbogasol Antiacido *Montpellier, Arg.†.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Carbogasol Digestivo *Montpellier, Arg.*
Pancreatin (p.2360·1); simeticone (p.1770·2); thioctic acid (p.2400·2); deoxycholic acid (p.2266·3); dehydrocholic acid (p.2292·2).
Dyspepsia.

Carbogasol Forte *Montpellier, Arg.*
Simeticone (p.1770·2).
Dyspepsia; meteorism; preparation for radiography.

Carbohidrato 100 *Survival, Arg.*
Maltodextrin (p.1955·3).
Dietary supplement.

Carbohydrate-Free Mixture *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).

Carbokebir *Aspen, Arg.*
Carboplatin (p.693·1).

Carbolactanose *Melisana, Belg.*
Lactococcus lactis (p.2372·3); activated charcoal (p.1435·2).
Diarrhoea; enterocolitis; meteorism; re-establishment of gastrointestinal flora.

Carbolevure
Vedim, Fr.
Saccharomyces cerevisiae (p.1998·3); activated charcoal (p.1435·2).
Gastrointestinal disorders.

UCB, Switz.
Dried yeast (p.1998·3); activated charcoal (p.1435·2).
Gastrointestinal disorders.

Carbolim *Arrow, Braz.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; migraine and vascular headaches; neutropenia; schizophrenia.

Carbolit *Raffo, Chile; Psicofarma, Mex.*
Lithium carbonate (p.401·3).
Bipolar disorder; migraine; obsessive-compulsive disorder; psychoses; schizophrenia.

Carbolith *Valeant, Canad.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Carbolithium *Elan, Ital.*
Lithium carbonate (p.401·3).
Adjunct in drug-induced leucopenia; cluster headache; psychiatric disorders.

Carbolitium *Eurofarma, Braz.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; migraine and vascular headaches; neutropenia; schizophrenia.

Carbomed *Medicine Products, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Carbomedac *Medac, Ger.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carbomix *Leiras, Fin.; Omega, Fr.; IFET (ΙΦΕΤ), Gr.†; Mayne, Irl.; Vaillant, Ital.; Selena, Swed.; Meadow, UK.*
Activated charcoal (p.1435·2).
Acute diarrhoea; acute poisoning; drug overdosage; flatulence.

Carbomox *Win-Medicare, India.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); carbocisteine (p.1553·2).
Otitis media; respiratory-tract infections.

Ca-R-Bon *Greater Pharma, Thai.*
Activated charcoal (p.1435·2).
Abdominal distension; diarrhoea; poisoning.

Carbon Sulfaguanidina *Valma, Chile.*
Activated charcoal (p.1435·2); sulfaguanidine (p.339·2).
Gastrointestinal infections.

Carbon Tabs *Hexa, Arg.*
Activated charcoal (p.1435·2); phthalylsulfathiazole (p.315·1); homatropine methylbromide (p.1881·3).
Gastrointestinal disorders.

Carbone Composto *AFOM, Ital.; Zeta, Ital.*
Vegetable charcoal (p.1435·3); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastrointestinal disorders.

Carbonesia *Geymonat, Ital.*
Activated charcoal (p.1435·2); magnesium oxide (p.1744·1); calcium carbonate (p.1714·1); magnesium peroxide (p.1651·3).
Gastrointestinal disorders.

Carbonet *Smith & Nephew, Fr.; Smith & Nephew, Irl.; Smith & Nephew, UK.*
Activated charcoal (p.1435·2).
Malodorous wounds; suppurating wounds; ulcers.

Carbonex *Legras, Fr.*
Magnesium hydroxide (p.1743·2).
Formerly contained sublimed sulfur and magnesium hydroxide.
Constipation.

Carbonpectate *Chew, Thai.*
Activated charcoal (p.1435·2); magnesium carbonate (p.1743·1); pectin (p.2145·2).
Diarrhoea; flatulence; gastrointestinal disorders.

Carbophos *Tradiphar, Fr.*
Vegetable charcoal (p.1435·3); calcium carbonate (p.1714·1); calcium phosphate (p.1676·2).
Gastrointestinal disorders.

Carboplamin *Vianex (Βιανεξ), Gr.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carboplat *Pfizer, Arg.; BMS, Ger.; Asofarma, Mex.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carboplex *LKM, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Carboplyin *Dentsply, Denm.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Carboron *Royal, Chile.*
Lithium carbonate (p.401·3).
Alcohol withdrawal; bipolar disorder; migraine; obsessive-compulsive disorder; schizophrenia.

Carbosan *Rowa, Hung.; Rowa, Irl.*
Carbenoxolone sodium (p.1714·3).
Aphthous stomatitis; herpes labialis.

Carbosen *Senese, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carboseptol *Herbes Universelles, Canad.†.*
Menthol (p.2340·1); cineole (p.2282·3); methyl salicylate (p.85·3); thymol (p.1664·3); zinc oxide (p.1621·2).

Carbosin *Teva, Belg.; Nycomed, Fin.†; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Asta Medica, NZ†; NZ Medical & Scientific, NZ†; Pharmachemie, Neth.; Nycomed, Norw.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.; Er-Kim, Turk.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carbosint *Boniscontro & Gazzone, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Carbosol
Note. This name is used for preparations of different composition.
Sanova, Austria.
Carboplatin (p.693·1).
Malignant neoplasms.

Morishita, Philipp.
Carbocisteine (p.1553·2).
Cough; respiratory-tract congestion.

Carbosorb *Pharmalab, Austral.; Imuna, Cz.*
Activated charcoal (p.1435·2).
Diarrhoea; drug overdose; poisoning.

Carbosorb X *AFT, NZ.*
Activated charcoal (p.1435·2).
Drug overdose; poisoning.

Carbosorb S *Pharmalab, Austral.; AFT, NZ†.*
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Drug overdose; poisoning.

Carbosorb XS *AFT, NZ.*
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Drug overdose; poisoning.

Carbospare *Abbott, Fin.†.*
Preparation for enteral nutrition (p.1922·1).

Carbostesin *AstraZeneca, Austria; AstraZeneca, Ger.; AstraZeneca, Switz.*
Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Carbosylane *Grimberg, Fr.; Lilly, Gr.; Grimberg, Israel.*
Activated charcoal (p.1435·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastrointestinal distension; meteorism.

Carbosymag *Grimberg, Fr.*
Activated charcoal (p.1435·2); simeticone (p.1770·2); magnesium oxide (p.1744·1).
Dyspepsia; meteorism.

Carbotec *Columbia, Mex.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carboticon *Interdelta, Switz.*
Activated charcoal (p.1435·2); simeticone (p.1770·2).
Digestive disorders; flatulence.

Carbotinol *Korea United, Philipp.*
Carboplatin (p.693·1).
Ovarian cancer; small cell lung cancer.

Carbotop *Pulitzer, Ital.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Carbotoss *Greenpharma, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Carbotox *Imuna, Cz.*
Activated charcoal (p.1435·2); sodium thiosulfate (p.1466·1).
Diarrhoea; poisoning.

Carbotural *Valeant, Mex.*
Activated charcoal (p.1435·2).
Diarrhoea; dyspepsia; flatulence; halitosis.

Carboxil *Lafit, Braz.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Carboxine *Cypress, USA†.*
Carbinoxamine maleate (p.570·2).
Rhinitis.

Carboxine-PSE *Cypress, USA.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Carboxtie *Bioprofarma, Arg.*
Carboplatin (p.693·1).
Malignant neoplasms.

Carboyoghurt *SIT, Ital.*
Vegetable charcoal (p.1435·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Carbozor *Chrispa (Χρισπα), Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Cardace *Sanofi-Aventis, Fin.; Aventis, India; Aventis, Indon.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure; heart failure following myocardial infarction; hypertension; myocardial infarction.

Cardace Comp *Sanofi-Aventis, Fin.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Cardactona *Pasteur, Chile.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; hypertension; oedema.

Cardalin *Solvay, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Cardanat *Temmler, Ger.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Cardaxen *Spirig, Switz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Cardaxen plus *Spirig, Switz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Cardcor *Teuto, Braz.*
Digoxin (p.1259·3).
Arrhythmias.

Cardec DM *Qualitest, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Cardegic *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Neth.*
Lysine aspirin (p.79·1).
Thromboembolic disorders.

Cardeloc *TO-Chemicals, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Cardem *Sanofi-Aventis, Spain.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Cardenalin *Pfizer, Jpn†.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Cardene *Yamanouchi, Irl.†; Astellas, Neth.; Astellas, UK; Wyeth-Ayerst, USA.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Cardenol *TO-Chemicals, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; tremor.

Cardensiel *Merck-Lipha, Fr.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Cardepine *Imperial, Malaysia; Imperial, Philipp.; Great Eastern, Thai.; Westmont, Thai.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; heart failure; hypertension.

Card-Floe II *Sisu, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Cardiac D-Dimer *Roche Diagnostics, Mex.*
Test for D-dimer in blood.
Diagnosis of venous thrombosis and pulmonary embolism.

Cardiac M Myoglobin *Roche Diagnostics, Mex.*
Test for myoglobin in blood.
Diagnosis of myocardial infarction.

Cardiac T Troponin T *Roche Diagnostics, Mex.*
Test for troponin T in blood.
Diagnosis of myocardial damage.

Cardiace *Triomed, S.Afr.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Cardiactiv *Herbapol Krakow, Pol.*
Crataegus (p.2289·1); rosemary (p.2381·2).
Heart failure.

Cardiaforce *Bioforce, Switz.*
Crataegus (p.2289·1); melissa (p.2339·3); Malaga wine.
Nervous disorders; palpitations.

Cardiagen *APS, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Cardiagen HCT *APS, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Cardial *Meprofarm, Indon.*
Dipyridamole (p.1268·1).
Angina pectoris.

Cardialgine *MIP, Ger.†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Cardiamid-Coffein *Polfa Pabianice, Pol.*
⊗ Caffeine (p.1116·3); nikethamide (p.2161·2); strychnine (p.2393·1).
Tonic.

Cardiamidum *Polfa Pabianice, Pol.*
⊗ Nikethamide (p.2161·2).
Hypotension.

CardiASK *Kanonfarma, Rus.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Cardiavis N *Truw, Ger.*
Homoeopathic preparation.

Cardiax *Sidus, Arg.*
Aspirin (p.20·3); vitamin C (p.1983·3); vitamin E (p.1992·2).
Thrombosis prophylaxis.

Cardiazem *Sanitas, Chile.*
Nitrendipine (p.1358·2).
Hypertension.

Cardiazol-Dicodid *Nicholas Piramal, India†.*
⊗ Pentetrazol (p.2162·1); hydrocodone hydrochloride (p.63·1).
Coughs.

Cardiazol-Paracodina *Abbott, Ital.*
⊗ Pentetrazol (p.2162·1); dihydrocodeine thiocyanate (p.48·3).
Coughs.

Cardibisana *Riemser, Ger.†.*
⊗ Crataegus (p.2289·1); cinchona bark (p.2282·3); kola (p.2416·1); convallaria (p.2287·3); cereus (p.2279·2); ephedra (p.1558·1); ginseng (p.2312·1); camphora; thiamine hydrochloride; veratrum; strophanthus; phosphor; glonoinum; ars. alb.
Cardiovascular disorders.

Cardibloc
Note. A similar name is used for preparations of different composition (see below).
Imperial, Singapore.
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Cardiblok
Note. A similar name is used for preparations of different composition (see above).
Xixia, S.Afr.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; phaeochromocytoma; tachycardia; tremor.

Cardicap *Pharmaspec, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Cardicon *Labomed, Chile.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction.

Cardicor *Merck, Denm.; Merck, Irl.; Bayer, Ital.; Merck, Neth.†; Merck, S.Afr.; Merck, UK.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Cardicoron *Teuto, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cardif Beta *Concept, India.*
⊗ Nitrendipine (p.1358·2); atenolol (p.1217·3).
Hypertension.

Cardifen *Pharmacare, S.Afr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cardiflor *VSM, Neth.*
Homoeopathic preparation.

Cardiject *Danpac, Indon.; Pharmaplan, S.Afr.; Sun, Thai.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Cardiket *Schwarz, Cz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Cardil *Orion, Denm.; Santa, Gr.; Orion, Malaysia; Orion, Rus.; Orion, Singapore; Orion, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cardilan *BB, Cz.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Cardiac disorders; magnesium and potassium depletion.

Cardilat *Triomed, S.Afr.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cardilate MR *Ivax, Hong Kong†; Ivax, UK.*
Nifedipine (p.1350·1).
The name Cardilate has also been used for preparations containing eritrityl tetranitrate.
Angina pectoris; hypertension.

Cardiloc *Unipharm, Israel.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Cardilol
Note. This name is used for preparations of different composition.
Libbs, Braz.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Julphar, UAE.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; phaeochromocytoma; tremor.

Cardilom *Osorio de Moraes, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Cardilopin *Egis, Cz.; EGIS, Hung.; Egis, Pol.; Egis, Rus.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Cardin *Schwarz, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Cardinit *Abbott, Mex.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Cardinol *Pacific, NZ.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma; tremor.

Cardinorm
Note. This name is used for preparations of different composition.
Hexal, Austral.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

New Research, Ital.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Cardinorma *Pekana, Ger.†.*
Homoeopathic preparation.

Cardio AAS *Sigma, Braz.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Cardio Aspirin *Bayer, Indon.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Cardioace *Vitabiotics, Hong Kong; Vitabiotics, UK.*
Omega-3 fish oil; garlic; lecithin; vitamins; minerals (p.1922·1).

Cardioaspirin *Bayer, Ital.*
Aspirin (p.20·3).
Thromboembolic disorders.

Cardioaspirina *Bayer Consumer, Arg.; Bayer, Chile.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Cardioaspirine *Bayer, Belg.*
Aspirin (p.20·3).
Thromboembolic disorders.

Cardiobil *Biologici Italia, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Cardioblock *Lafedar, Arg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Cardiobonisol *Bonimed, Pol.*
Crataegus (p.2289·1); cynara (p.2291·2); echinacea purpurea (p.2298·1); ginkgo biloba (p.2311·1).
Cardiovascular disorders.

Cardiobron *Fada, Arg.*
Alprostadil (p.2183·2).

Cardiocalm *Pharmastra, Fr.*
Crataegus (p.2289·1).
Formerly contained crataegus and phenobarbital.
Insomnia; nervous disorders.

CardioCare *MD, Singapore.*
Fish oil (salmon) (p.1362·2); eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Dietary supplement.

Cardiochek *Pentafarma, Chile.*
Tests for cholesterol, glucose, or triglycerides.

Cardiocor *Merck, Austria; Wyeth, Fr.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Cardiodarone *Novosibkhimfarm, Rus.; Shchelkovskii, Rus.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cardiodopa *Royton, Braz.†.*
Methyldopa (p.1334·1).
Hypertension.

Cardiodoron
Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.
Hyoscyamus niger; onopordum acanthium; cowslip flower (p.2372·2).
Cardiac disorders; circulatory disorders; sleep disorders.

Weleda, Switz.†.
Hyoscyamus (p.2323·3); onopordum acanthium; cowslip flower (p.2372·2).
Circulatory disorders.

Cardio-Essentials *Unicity, Singapore.*
Ubidecarenone; levocarnitine; L-taurine; crataegus (p.1922·1).
Dietary supplement.

Cardiofenone *Polifarma, Ital.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Cardiofil *Filofarm, Pol.*
Aspirin (p.20·3).
Magnesium oxide (p.1744·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis.

Cardiogen *UCB, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Cardiogoxin *Medipharma, Arg.*
Digoxin (p.1259·3).

Cardio-Green *Becton Dickinson, USA†.*
Indocyanine green (p.2324·3).
Diagnostic aid.

Cardioguard *Clonmel, Irl.†.*
Folic acid (p.1940·1).
Hyperhomocysteinaemia.

Cardioject *Syxyl, Ger.*
Homoeopathic preparation.

Cardioket *Adeka, Turk.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Cardio-Kreislauf-Longoral *Artesan, Ger.; Cassella-med, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1); crataegus (p.2289·1).
Formerly Cardio-Longoral.
Cardiovascular disorders.

Cardiol
Note. This name is used for preparations of different composition.
Roche, Fin.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Bialport, Port.
Fluvastatin sodium (p.1290·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Cardiol C *Herbapol Wroclaw, Pol.*
Caffeine (p.1116·3); kola (p.2416·1); convallaria (p.2287·3); crataegus (p.2289·1); valerian (p.2410·1).
Cardiovascular disorders; tonic.

Cardiolen *Sanitas, Chile.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Cardiolite *BMS, Austral.; New England Nuclear, Austria; BMS, Belg.†; BMS, Cz.; Du Pont, Fr.†; Du Pont, Irl.†; BMS, Ital.; BMS, Neth.; APS, Port.; BMS, Spain; BMS, UK; Du Pont, USA.*
Technetium-99m sestamibi (p.2055·3).
Assessment of myocardial function; diagnosis and investigation of hyperparathyroidism; diagnosis and location of myocardial infarction; diagnosis of breast cancer; diagnosis of ischaemic heart disease.

Cardiom3 *Isodisnatura, Fr.*
Fish oil (p.1362·2); vitamin E; selenium (p.1922·1).
Nutritional supplement.

Cardiomagnyl *Nycomed, Rus.*
Aspirin (p.20·3); magnesium hydroxide (p.1743·2).
Thromboembolism prophylaxis.

Cardi-Omega 3 *Thompson, USA.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Cardiomin *Andromaco, Chile†.*
Aminophylline (p.1114·2).
Obstructive airways disease; status asthmaticus.

Cardionil
Note. This name is used for preparations of different composition.
Ducto, Braz.
Digoxin (p.1259·3).

Alacan, Spain.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Cardionox *Alodial, Port.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Cardiopine *Julphar, UAE.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cardioplegia *IFET (ΙΦΕΤ), Gr.; Mayne, Hong Kong; DBL, Indon.; Tempo Scan Pacific, Indon.; Hospira, Malaysia; Mayne, Singapore; Mayne, Thai.*
Magnesium chloride (p.1679·1); potassium chloride (p.1684·3); procaine hydrochloride (p.1869·1).
Induction of cardiac arrest during cardiopulmonary bypass and open-heart surgery.

Cardioplegia A *Baxter, Austral.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3); magnesium chloride (p.1679·1); calcium chloride (p.1675·2).
Induction of cardiac arrest during heart surgery.

Cardioplegia Concentrate *Mayne, Austral.*
Magnesium chloride (p.1679·1); potassium chloride (p.1684·3); procaine hydrochloride (p.1869·1).
Induction of cardiac arrest during open heart surgery.

Cardioplegin N *Kohler, Ger.†.*
Magnesium aspartate (p.1679·1); procaine hydrochloride (p.1869·1); xylitol (p.1998·2).
Cardioplegia in open-heart surgery.

Cardioplen *Trinity, UK.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Cardioplus *Ipca, India.*
Multivitamin and mineral preparation (p.1922·1).

Cardiopranol *Sedabel, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Cardiopril *Pfizer, Switz.†.*
Spirapril hydrochloride (p.1399·3).
Hypertension.

Cardioprotect *Janssen-Cilag, Mex.*
Aspirin (p.20·3); *dl*-alpha tocoferil acetate (p.1992·3).
Thromboembolism prophylaxis.

Cardioreg *Rhone-Poulenc Rorer, Ital.†.*
Tablets: β-Acetyldigoxin (p.1201·2).
Heart failure.

Cardiorex *Bago, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; heart failure; hypertension.

Cardiorona *Columbia, Mex.†.*
Amiodarone (p.1210·2).
Angina pectoris; arrhythmias.

Cardiosedantol *Recalcine, Chile.*
Pentaerithrityl tetranitrate (p.1366·3); diazepam (p.986·3); chlormezanone (p.968·3).
Anxiety.

Cardiosel *UAP, Indon.; Imperial, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Cardioselect N *Dreluso, Ger.*
Homoeopathic preparation.

Cardiosolupsan *BMS, Fr.*
Lysine aspirin (p.79·1).
Formerly contained carbasalate calcium.
Thromboembolism prophylaxis.

Cardio-Spect *Medi-Radiopharma, Cz.*
Technetium-99m (p.2055·3) sestamibi.
Diagnosis of myocardial infarction; diagnosis of myocardial ischaemia and ventricular dysfunction.

Cardiostat *Apotex, Philipp.; Pharma 3, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension.

Cardiostatin *Makiz-Pharma, Rus.*
Lovastatin (p.1328·2).
Coronary atherosclerosis; hypercholesterolaemia.

Cardiostenol *Molteni, Ital.*
⊗ Morphine hydrochloride (p.86·3); atropine sulfate (p.1219·3).
Adjuvant in anaesthesia; pain.

Cardiotab *Interhealthcare, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Cardiotek Rx *Stewart Jackson, USA.*
Vitamin B ; vitamin B ; folic acid; arginine hydrochloride (p.1922·1).

Cardioten
Note. This name is used for preparations of different composition.
OFF, Ital.
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Verheilen, Philipp.
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Cardiotensin *Schwarz, Pol.*
Moexipril hydrochloride (p.1343·2).
Hypertension.

Cardiotone *VHB, India†.*
Amrinone lactate (p.1215·1).
Heart failure.

Cardiotonic *Herbapol Krakow, Pol.*
Crataegus (p.2289·1); valerian (p.2410·1).
Heart failure.

Cardiovas *Abbott, Spain.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Cardiovasc *Rottapharm, Ital.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Cardiover *Landson, Indon.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris.

Cardiovert *Sanofi Synthelabo, Philipp.*
Adenosine (p.1202·1).
Diagnosis of supraventricular tachycardia; paroxysmal supraventricular tachycardia.

Cardioxane
Note. This name is used for preparations of different composition.
CSC, Austria; Zodiac, Braz.; Novartis, Cz.; Chiron, Denm.; Novartis, Fr.; Novartis, Hung.; Novartis, Irl.; Chiron, Israel; Chiron, Ital.; Asofarma, Mex.; Chiron, Pol.; Novartis, UK; Nolver, Venez.
Dexrazoxane hydrochloride (p.1443·1).
Prevention of anthracycline cardiotoxicity.

Tecnofarma, Chile.
Razoxane (p.767·1).
Prevention of doxorubicin cardiotoxicity.

Cardioxin *Novartis, India†.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Cardip *Francia, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Cardiphar *Teva, Belg.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Cardipin *Spirig, Switz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction.

Cardipirina *Zuoz, Venez.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Cardiplant *Schwabe, Cz.†; Schwabe, Pol.; Schwabe, Switz.*
Crataegus (p.2289·1).
Arrhythmias; cardiac disorders; heart failure.

Cardiplast *Schwarz, Gr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Cardipril
Note. This name is used for preparations of different composition.
Liomont, Mex.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Bial, Port.
Imidapril hydrochloride (p.1313·3).
Hypertension.

Cardiprin *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ†; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis; thrombosis prophylaxis.

Cardirenal *Lafage, Arg.†.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Cardirene *Sanofi-Aventis, Ital.*
Lysine aspirin (p.79·1).
Thrombosis prophylaxis.

Cardiser *Merck, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cardisorb *Valeant, Hung.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Cardispan *Grossman, Mex.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Cardispray *Julphar, UAE†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Carditril *Eversil, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Cardium *DHA, Hong Kong; DHA, Singapore.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cardivas
Note. This name is used for preparations of different composition.
Sidus, Arg.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Sun, Rus.
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Cardix *Multilab, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Cardizem *Aventis, Austral.; Boehringer Ingelheim, Braz.; Biovail, Canad.; Ferrosan, Denm.; Pfizer, Fin.; Aventis, NZ; Pfizer, Norw.; Pfizer, Swed.; Abbott, USA.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Cardol *Alphapharm, Austral.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Cardonit *Polfa Warszawa, Pol.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Cardopar *DHA, Singapore.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Cardopax *Orion, Denm.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Cardoral *Pfizer, Israel.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cardosin *Actavis, Denm.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cardoxan *Douglas, NZ.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cardoxin *Rafa, Israel.*
Dipyridamole (p.1268·1).
Adjunct to cardiac imaging; nephrotic syndrome; pre-eclampsia; thrombosis prophylaxis.

Cardoxone *Remedica, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; migraine.

Cards HCG-Urine *Point of Care Diagnostics, NZ†.*
Pregnancy test (p.2372·1).

Cardugen *Merck, S.Afr.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Cardular *Pfizer, Ger.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cardules *Nicholas Piramal, India.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cardules Plus *Nicholas Piramal, India.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Carduokatt N *Kattwiga, Ger.†.*
Homoeopathic preparation.

Cardura *Pfizer, Arg.; AstraZeneca, Canad.; Roerig, Chile; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Carduran *Pfizer, Braz.; Pfizer, Denm.; Pfizer, Norw.; Pfizer, Spain.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Cardyl *Euro Registratie, Neth.; Pfizer, Spain.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Careflu *Uno, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic disorders of the respiratory tract.

Carena *Biofarma, Turk.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Carencil *Bonafarma, Port.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Carencyl *IPRAD, Fr.*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).
Tonic.

Caresel *Wassen, Ital.*
Vitamin C; vitamin E; selenium; zinc; betacarotene; astaxanthin (p.1922·1).
Nutritional supplement.

Caress *Schering-Plough, Swed.*
⊗ Urea (p.1620·2).
Dry skin.

Carexan *Pisa, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Carexidil *Cantabria, Spain.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Careza *Silesia, Chile.*
24 Tablets, ethinylestradiol (p.2101·3); gestodene (p.2105·2); 4 tablets, inert.
Combined oral contraceptive.

CareZee *Pharmacare, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Carfosid *Palmares, Ital.*
Iron-rich yeast (p.1949·1); levocarnitine (p.1932·2); calcium folinate (p.1943·3).
Anaemias.

Cargespril *Gelcaps, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Carginine *Coraltis, Israel†.*
L-Arginine (p.1928·2).
Amino-acid deficiency.

Cargosil *Genepharm, Gr.*
Aciclovir (p.862·3).
Herpes simplex infections.

Cariamyl
Note. This name is used for preparations of different composition.
Corsa, Indon.; Sanofi Synthelabo, Indon.
Heptaminol acefyllinate (p.1123·2).
Asthma; bronchitis; dyspnoea.

Prater, Chile.
Cream: Menthol (p.2340·1); camphor (p.2273·2); triclosan (p.1665·2); benzocaine (p.1854·1).
Skin irritation.

Prater, Chile.
Lotion: Camphor (p.2273·2); triclosan (p.1665·2); benzocaine (p.1854·1).
Skin irritation.

Cariax *Pasteur, Chile.*
Chlorhexidine gluconate (p.1635·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; oral hygiene.

Cariban *Inibsa, Spain.*
Doxylamine succinate (p.578·2); pyridoxine hydrochloride (p.1978·2).
Nausea; vomiting.

Caricef *Antibioticos, Spain.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Carident *Jelfa, Pol.*
Framycetin sulfate (p.279·1); papain (p.2362·3).
Mouth disorders.

Cariderm *Pharlab, Braz.†.*
Zinc (p.1999·1); vitamin A (p.1971·2); ergocalciferol (p.1987·1); boric acid (p.2268·1).
Skin disorders.

Carig *Cadila, India.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Caril *Nutricia, Fr.*
Carrots, rice, dextrin-maltose, glucose, and electrolytes (p.1672·2).
Diarrhoea.

Carilax *Strallhofer, Austria.*
Fig (p.1731·3); senna (p.1769·2).
Bowel evacuation; constipation.

Carimune *CSL Behring, USA.*
A normal immunoglobulin (p.2225·3).

Carin *CCM, Hong Kong; CCM, Malaysia; CCM, Singapore.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Carinose *Community Pharmacy, Thai.†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hay fever.

Carinox *CCM, Malaysia.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Carisano *Truw, Ger.†.*
Garlic (p.2309·2).
Lipid disorders.

Cariso-Co *PP Lab, Thai.†.*
Paracetamol (p.108·1); carisoprodol (p.1894·1).
Musculoskeletal disorders.

Carisoma *Wallace, India; Forest Laboratories, UK†.*
Carisoprodol (p.1894·1).
Skeletal muscle spasm.

Carisoma Compound
Note. This name is used for preparations of different composition.
Wallace, India.
Carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Musculoskeletal pain.

Carter Horner, Thai.†.
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal and joint disorders.

Caristop
Note. This name is used for preparations of different composition.
Maver, Chile.
Mouthwash: Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Maver, Chile.
Toothpaste: Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2); sodium benzoate (p.1630·2).
Dental caries prophylaxis.

Caritasone *Chinta, Thai.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal and joint disorders.

Caritec *Stancare, India.*
Benidipine hydrochloride (p.1224·3).
Angina pectoris; hypertension.

Carito mono *Maxmedic, Ger.*
Java tea (p.2328·2).
Urinary-tract disorders.

Carl Baders Divinal *Apotheke Heiligen Rupertus, Austria.*
Camphor and camphor spirit (p.2273·2); methyl salicylate (p.85·3); salicylic acid (p.1612·2); salol (p.122·1); turpentine oil (p.2406·3); rosemary oil (p.2381·3); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Carlets 9 11 *Keton, Mex.*
Vitamin preparation (p.1922·1).

CarLich *Winthrop, Ger.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carloc *Cipla, India; Cipla-Medpro, S.Afr.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Carloxan *Orion, Denm.†.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Carlytene *Viatris, Fr.*
Moxisylyte hydrochloride (p.1344·3).
Mental function impairment; Raynaud's syndrome.

Carmapine *Pharmasant, Thai.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; diabetic neuropathy; epilepsy; glossopharyngeal neuralgia; trigeminal neuralgia.

Carmazin *Teuto, Braz.*
Carbamazepine (p.471·3).
Epilepsy.

Carmed *Surya Dermato, Indon.*
⊗ Urea (p.1620·2).
Hyperkeratotic skin disorders.

Carmen *Berlin-Chemie, Ger.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Carmian *Teofarma, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Carmicide *Indoco, India; Indoco, Thai.†.*
Sodium citrate (p.1673·3); citric acid (p.2284·1); ginger (p.1732·3); aromatic cardamom tincture (p.2277·1); cinnamon tincture (p.2283·1).
Colic; dyspepsia; flatulence.

Carmicina *Irex, Port.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Carminagal N *Galenika, Ger.†.*
Cynara (p.2291·2).
Dyspepsia.

Carminativo Ibys *Pharmacia, Spain†.*
Anise oil (p.2258·2); sodium bicarbonate (p.1673·2).
Aerophagia.

Carminativo Juventus *Juventus, Spain.*
Anise oil (p.2258·2); belladonna tincture (p.2263·3); sodium bicarbonate (p.1673·2).
Aerophagia; meteorism; vomiting.

Carminativum Babynos *Dentinox, Cz.†; Dentinox, Ger.†.*
Fennel (p.2302·3); coriander (p.2288·1); chamomile (p.2279·3).
Appetite loss; dyspepsia; flatulence; gastrointestinal spasm.

Carminativum Hofmann *Hofmann & Sommer, Ger.*
Peppermint leaf (p.1761·2); chamomile (p.2279·3); caraway (p.2276·3).
Dyspepsia.

Carminativum-Hetterich *Madaus, Ger.*
Chamomile (p.2279·3); peppermint leaf (p.1761·2); caraway (p.2276·3); fennel (p.2302·3); dried bitter-orange peel (p.2357·1).
Gastrointestinal disorders.

Carminativum-Pascoe *Pascoe, Ger.†.*
Peppermint leaf (p.1761·2); chamomile (p.2279·3); caraway (p.2276·3).
Dyspepsia.

Carminex *Adcock Ingram, S.Afr.*
Magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); sodium citrate (p.1673·3).
Gastric hyperacidity.

Carmint *Sofar, Ital.*
Peppermint oil (p.1761·2).
Gastrointestinal disorders.

Carmitol *Medinfar, Port.*
⊗ Urea (p.1620·2); panthenol (p.2362·1).
Dry skin; pruritus.

Carmol
Note. This name is used for preparations of different composition.
Doak, Hong Kong; Doak, USA.
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Iromedica, Switz.
Drops: Lemon grass oil (p.2333·1); sage oil (p.2382·3); clove oil (p.2285·1); cinnamon oil (p.2283·2); lavender oil (p.2331·2); nutmeg oil (p.2355·3); anise oil (p.2258·2); thyme oil (p.2401·2); lemon oil (p.2332·3); menthol (p.2340·1); melissa (p.2339·3).
Gastrointestinal disorders; headache; motion sickness; muscle and joint pain; respiratory-tract disorders.

Iromedica, Switz.
Massage fluid; sport gel: Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); anise oil (p.2258·2); clove oil (p.2285·1); lavender oil (p.2331·2); nutmeg oil (p.2355·3); lemon grass oil (p.2333·1); sage oil (p.2382·3); thyme oil (p.2401·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); pine oil (p.2368·2); rosemary oil (p.2381·3).
Musculoskeletal, joint, and soft-tissue disorders.

Iromedica, Switz.
Ointment: Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); anise oil (p.2258·2); clove oil (p.2285·1); nutmeg oil (p.2355·3); lemon grass oil (p.2333·1); sage oil (p.2382·3); thyme oil (p.2401·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Iromedica, Switz.
Spray: Mint oil (p.2345·2).
Soft-tissue disorders.

Carmol HC *Doak, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Corticosteroid.

Carmol Magen-Galle-Darm *Omegin, Ger.*
Taraxacum (p.2395·1); peppermint leaf (p.1761·2); cynara (p.2291·2).
Biliary-tract disorders.

Carmol Plus *Iromedica, Switz.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); anise oil (p.2258·2); clove oil (p.2285·1); nutmeg oil (p.2355·3); lemon grass oil (p.2333·1); sage oil (p.2382·3); thyme oil (p.2401·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); cayenne pepper (p.2276·2); citral (p.2284·1); allantoin (p.1588·1).
Musculoskeletal and joint disorders.

Carmol Scalp Treatment *Doak, USA.*
Sulfacetamide sodium (p.335·3).
Scalp infections.

Carmolis
Note. This name is used for preparations of different composition.
Schmidgall, Pol.
Anise oil (p.2258·2); clove oil (p.2285·1); cinnamon oil (p.2283·2); lemon oil (p.2332·3); lavender oil (p.2331·2); citronella oil (p.2284·2); sage oil (p.2382·3); thyme oil (p.2401·2); menthol (p.2340·1); melissa (p.2339·3).
Anxiety; gastrointestinal disorders; headache; insect bites; insomnia; mood disturbances; musculoskeletal and joint disorders; neuralgia; pruritus; respiratory-tract disorders.

Schmidgall, Rus.†.
Menthol (p.2340·1); thyme oil (p.2401·2); anise oil (p.2258·2); Chinese schisandra oil (p.2384·2); clove oil (p.2285·1); lemon oil (p.2332·3); lavender oil (p.2331·2); spike lavender oil (p.2392·1); Indian mint oil; sage oil (p.2382·3); nutmeg oil (p.2355·3).
Dyspepsia; headache; musculoskeletal and joint disorders; nervous disorders; neuritis; pruritus; respiratory-tract inflammation.

Carmolis Fluid *Iromedica, Rus.†.*
Menthol (p.2340·1); pine oil (p.2368·2); methyl salicylate (p.85·3); camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); lavender oil (p.2331·2); rosemary oil (p.2381·3); thyme oil (p.2401·2); Indian mint oil; sage oil (p.2382·3); nutmeg oil (p.2355·3); anise oil (p.2258·2); clove oil (p.2285·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Carmubris *BMS, Austria; BMS, Ger.; IFET (ΙΦΕΤ), Gr.*
Carmustine (p.694·3).
Malignant neoplasms.

Carnabol *Ache, Braz.*
Buclizine (p.570·1); caffeine (p.1116·3); lysine; vitamin B substances (p.1922·1).
Reduced appetite; tonic.

Carnation
Note. This name is used for preparations of different composition.
Cuxson, Gerrard, Canad.; Cuxson, Gerrard, UK.
Salicylic acid (p.1612·2).
Calluses; corns; verrucas.

Nestle, Canad.†.
A range of preparations for enteral nutrition (p.1922·1).

Carnation Calcium Plus with Fiber *Nestle, Philipp.*
Preparation for enteral nutrition (p.1922·1).

Carnicor
Labomed, Chile; Pascual, Philipp.; Sigma-Tau, Philipp.
Levocarnitine (p.1932·2).
Angina pectoris; arrhythmias; carnitine deficiency; heart failure; myocardial ischaemia.

Sigma-Tau, Spain.
Carnitine (p.1932·2).
Carnitine deficiency.

Carnidose *Faran, Gr.*
Levocarnitine (p.1932·2).
Cardiomyopathy; carnitine deficiency.

Carnigen *Aventis, Austria; Cassella-med, Ger.*
⊗ Oxilofrine hydrochloride (p.1364·3).
Circulatory disorders; hypotension.

Carnil *Anfarm, Gr.*
Levocarnitine (p.1932·2).
Cardiomyopathy; carnitine deficiency.

Carnisin *Leti, Venez.*
Levocarnitine (p.1932·2).

Carniten *Sigma-Tau, Rus.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Carnitene *Sigma-Tau, Hong Kong; Sigma-Tau, Ital.; Santa, Turk.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Carnitolo *Recofarma, Ital.*
Levocarnitine hydrochloride (p.1932·3).
Carnitine deficiency.

Carnitop *Infosint, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Carnitor *Sigma-Tau, Canad.; Sigma-Tau, Hong Kong; Elder, India; Shire, UK; Sigma-Tau, USA.*
Levocarnitine (p.1932·2).
Cardiac disorders; carnitine deficiency.

Carnivit *Polfa Kutno, Pol.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Carnot Colutorio *Esme, Arg.*
Bacitracin (p.210·3); gramicidin (p.286·1); benzocaine (p.1854·1); lidocaine (p.1862·3).
Mouth disorders.

Carnot Topico *Esme, Arg.*
Aluminium chloride (p.1588·2); acriflavinium chloride (p.1625·1); lidocaine hydrochloride (p.1862·3).
Mouth disorders.

Carnotprim *Carnot, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; migraine; nausea and vomiting.

Carnovis *Glaxo Allen, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Carnum *FIRMA, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Carobel *Cow & Gate, Irl.; Cow & Gate, UK.*
Ceratonia (p.2143·2).
Dysphagia; feed thickener to control vomiting; nausea and vomiting in pregnancy.

Carofril *Arlex, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Carogil *Novartis Nutrition, Fr.†.*
Carrots, rice, dextrin-maltose, and electrolytes (p.1672·2).
Diarrhoea.

Caroid *Lepori, Port.†.*
Capsicum (p.2276·2); cascara (p.1715·2); phenolphthalein (p.1762·1); papain (p.2362·3); bile salts (p.2266·2).
Constipation.

Caromin *Ipca, India†.*
Multivitamin and mineral preparation (p.1922·1).

Carominthe *Lehning, Fr.*
Homoeopathic preparation.

Carone *IQFA, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Carotaben *Hermal, Austria; Hermal, Cz.; Hermal, Ger.; Boots Healthcare, Switz.*
Betacarotene (p.1930·3).
Erythropoietic protoporphyria; photodermatitis; skin pigmentation disorders.

Carotana *Twardy, Ger.†.*
Betacarotene (p.1930·3).
Vitamin A deficiency.

Carotenoplos *Laboratorios Chile, Chile†.*
Betacarotene; *dl*-alpha tocoferil acetate; calcium ascorbate; zinc sulfate; selenium yeast (p.1922·1).
Nutritional supplement.

Carotenos *Natufarma, Arg.*
Ascorbic acid; betacarotene; alfa tocopherol (p.1922·1).
Vitamin supplement.

Carotin *Twardy, Ger.*
Betacarotene (p.1930·3); biotin (p.1931·3); calcium pantothenate (p.1959·3).
Suntanning aid.

Carotinora *Twardy, Ger.*
Betacarotene (p.1930·3).
Vitamin A deficiency.

Carovigen *Aksu, Turk.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Carovit
Note. This name is used for preparations of different composition.
Biochimici, Ital.
Betacarotene with vitamins C and E (p.1922·1).
Nutritional supplement.

Kocak, Turk.
Betacarotene (p.1930·3).
Vitamin A deficiency.

Carovit Forte *Biochimici, Ital.*
Betacarotene with vitamins E and C (p.1922·1).
Nutritional supplement.

Carovit Melanin *Biochimici, Ital.*
Amino-acid preparation with vitamins and minerals (p.1922·1).
Nutritional supplement.

Carovit Repair *Biochimici, Ital.*
Evening primrose oil; fish oil; zinc-rich yeast; vitamin E; dried yeast; betacarotene (p.1922·1).
Nutritional supplement.

Carpantin *Sanofi Synthelabo, Ital.†.*
Pantethine (p.1365·3); carnitine chloride (p.1933·1); cyproheptadine hydrochloride (p.575·1).
Anorexia; insufficient body weight.

Carpiaton *Fahrenheit, Indon.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; hypertension; oedema.

Carpilo *Chauvin, Fr.*
⊗ Pilocarpine hydrochloride (p.1884·3); carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Carpin *Novag, Mex.*
Carbamazepine (p.471·3).
Diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias; polydipsia; polyuria.

Carpine *Atlantic, Thai.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Carpo-Miotic *Bell, India.*
Pilocarpine nitrate (p.1884·3).
Glaucoma.

Car-Q *Kalbe, Indon.*
Ubidecarenone (p.2407·2); levocarnitine fumarate (p.1933·1).
Antoxidant; cardiovascular function.

Carrasyn *Carrington, USA.*
Acemannan (p.2244·2).
Wounds.

Carreldon *Bama, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Carres Parapsyllium *IPRAD, Fr.*
Ispaghula (p.1737·1); fig (p.1731·3); prune (p.1765·1); tamarind (p.1775·3); rhubarb (p.1768·3); guar gum (p.442·3); fibre.
Constipation.

Carrier
Note. This name is used for preparations of different composition.
Casasco, Arg.
Memantine hydrochloride (p.367·1).
Alzheimer's disease; muscle spasticity.

Chiesi, Ital.†.
Levocarnitine (p.1932·2).
Carnitine deficiency.

Carsil *Sopharma, Rus.*
Silymarin (p.1452·2).
Liver disorders.

Carsol *Ecosol, Switz.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; neuralgias.

Carsuquin *Degorts, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis; trichomoniasis.

Cartago *Lampugnani, Ital.*
Chondroitin sulfate sodium (p.2280·3); glucosamine hydrochloride (p.2313·2); devil's claw root (p.39·1); vitamin C; colecalciferol (p.1986·2).
Joint disorders.

Cartan *Quesada, Arg.*
Losartan (p.1327·2).
Hypertension.

Cartazid *Megat, Venez.†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Carteabak *Thea, Fr.; Thea, Neth.; Thea, Port.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Carteodose *Lamda (Λαμδα), Gr.†.*
⊗ Carteolol (p.1241·2).
Glaucoma.

Carteol *Meda, Belg.; Mann, Cz.; Chauvin, Fr.; SIFI, Ital.; Abdi, Turk.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Carteopil *Meda, Belg.*
⊗ Pilocarpine hydrochloride (p.1884·3); carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Carters *Therabel, Belg.*
Bisacodyl (p.1710·1).
Constipation.

Carters Little Pills *Church & Dwight, Canad.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Carthamex *Rolmex, Canad.*
Vitamin B (p.1979·1) in safflower oil.

Car-ti buron flex *Lafarmen, Arg.*
Glucosamine (p.2313·2); cartilage (shark) (p.2277·3); magnesium hydroxide (p.1743·2).

Cartia
Note. This name is used for preparations of different composition.
GSK, Austral.; GSK, Hong Kong; GSK, Israel; GSK, NZ; Lusofarmaco, Port.
Aspirin (p.20·3).
Thromboembolism prophylaxis; thrombosis prophylaxis.

Andrx, USA.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Car-ti-buron Lafarmen, Arg.
Cartilage (shark) (p.2277·3).
Musculoskeletal and joint disorders.

Cartidont Curaden, Ital.
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Cartiflex
Note. This name is used for preparations of different composition.
ISA, Arg.
Cream: Diethylamine salicylate (p.47·2); benzocaine (p.1854·1).
ISA, Arg.
Tablets: Cartilage (shark) (p.2277·3); minerals; vitamin D; carbohydrate; protein; lipids (p.1922·1).

Cartiflex Forte ISA, Arg.
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Degenerative joint disorders.

Cartilade Cartilade, Arg.†.
Cartilage (shark) (p.2277·3).
Dietary supplement.

Cartilag Eagle, Austral.
Cartilage (bovine) (p.2277·3).
Dietary supplement.

Cartilago Compuesto Hochstetter, Chile†.
Cartilage (p.2277·3); potassium dichromate.
Arthritis.

Cartilago T-500 Knop, Chile.
Shark cartilage (p.2277·3); soya lecithin (p.2332·2); silicon dioxide (p.2146·2).
Joint disorders.

Cartilago Vital AM, Arg.
Cartilage (shark) (p.2277·3).
Dietary supplement.

Cartimax Argenfarma, Arg.
Cartilage (shark) (p.2277·3).
Arthroses; dietary supplement.

Cartimin Velin, Neth.
Glucosamine sulfate sodium chloride (p.2313·2).
Osteoarthritis of the knee.

Cartin Plus Combiphar, Indon.
Chondroitin sulfate (p.2280·3); glucosamine (p.2313·2); vitamins (p.1922·1).
Osteoarthritis.

Cartine Tecnifar, Port.
Levocarnitine (p.1932·2).

Cartipro Recon, Singapore.
Glucosamine sulfate (p.2313·2); ascorbic acid (p.1983·3).
Joint disorders.

Cartisorb Bioiberica, Spain.
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Cartivix Jaba, Port.
Diacerein (p.41·3).
Osteoarthritis.

Cartonic Yamanouchi, Jpn†.
Amrinone (p.1215·1).
Heart failure.

Cartrax Pfizer, Braz.
Tioconazole (p.548·2); tinidazole (p.848·3).
Vulvovaginal infections.

Cartrex Almirall, Fr.
Aceclofenac (p.14·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Cartrilet Fahrenheit, Indon.
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Cartril-S
CCM, Hong Kong.
Glucosamine sulfate (p.2313·2).
Osteoarthritis.
CCM, Malaysia.
Glucosamine hydrochloride (p.2313·2) or glucosamine sulfate (p.2313·2).
Osteoarthritis.

Cartrimox Ace, Philipp.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Cartrol Abbott, USA.
⊗ Carteolol hydrochloride (p.1241·1).
Hypertension.

Caruderma Europharm, Hong Kong.
⊗ Urea (p.1620·2).
Dry skin.

Carvas Meprofarm, Indon.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Carvasin Teofarma, Ital.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Carve TAD, Ger.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvecard AWD, Ger.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvedexxon Dexcel, Israel.
⊗ Carvedilol (p.1241·3).
Heart failure.

Carvedigamma Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvedil Bago, Arg.; Behrens, Venez.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvedil D Bago, Arg.
⊗ Carvedilol (p.1241·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Carvedilat Sigma, Braz.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvedilen Specifar, Gr.
⊗ Carvedilol (p.1241·3).
Hypertension.

Carvel Hexal, Arg.†.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvepen Elpen (Ελπεν), Gr.
⊗ Carvedilol (p.1241·3).
Hypertension.

Carve-Q Juta, Ger.; Q-Pharm, Ger.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvesan Medopharm, Cz.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvetone Durascan, Denm.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvetrend Pliva, Cz.; Pliva Krakow, Pol.; Pliva, Rus.; Pharma Dynamics, S.Afr.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvicum Duopharm, Ger.†.
Taraxacum (p.2395·1).
Appetite loss; biliary disorders; digestive disorders; diuretic.

Carvidil Grindex, Rus.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvil Zydus, India.
⊗ Carvedilol (p.1241·3).
Hypertension.

Carvipress Gentili, Ital.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvol Teva, Hung.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Carvomin Wernigerode, Ger.†.
Angelica (p.2258·1); cnicus benedictus (p.2285·2); peppermint leaf (p.1761·2).
Gastrointestinal disorders.

Carvomin Magentropfen mit Pomeranze Madaus, Ger.†.
Bitter-orange peel (p.2357·1).
Dyspepsia.

Carvon Weleda, Switz.†.
Activated charcoal (p.1435·2); cumin oil.
Colic; digestive disorders; flatulence.

Carxasin M & H, Thai.
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Carylderm SSL, UK.
Carbaryl (p.2037·1).
Pediculosis.

Caryolysine Genopharm, Fr.; IFET (ΙΦΕΤ), Gr.
Chlormethine hydrochloride (p.697·3).
Lymphomas; malignant effusions; malignant neoplasms; mycosis fungoides; psoriasis.

Carzem Baldacci, Port.†; Unison, Thai.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Carzepin Hovid, Hong Kong.
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Carzepine Condrugs, Thai.
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; diabetes insipidus; diabetic neuropathy; epilepsy; trigeminal neuralgia.

Carzilasa Manuell, Mex.
Cocarboxylase (p.1975·2).
Cardiovascular, cerebrovascular, and metabolic disorders.

Carzodelan Gaschler, Ger.†.
Pancreatin (p.2360·1).
Inflammatory disorders.

Casacol Helsinn Birex, Irl.
⊗ Methoxyphenamine hydrochloride (p.1564·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Coughs.

Casalm Pfizer, Austria; Pharmacia, Ger.†.
Calcitonin (salmon) (p.1093·1).
Bone loss following immobilisation; hypercalcaemia; osteolysis; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Casbame Bajamed, Mex.
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Casbol Fournier SA, Spain.
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Cascade Lane, UK.
Bearberry (p.2263·3); clivers (p.2284·3); lappa root (p.2330·3).
Water retention.

Cascalax Will-Pharma, Belg.†; Will Pharma, Neth.
Casanthranol (p.1715·1).
Constipation.

Cascara Sagrada Bouzen Bouzen, Arg.†.
Cascara (p.1715·2); belladonna (p.2263·3); bile salts (p.2266·2); phenolphthalein (p.1762·1).
Constipation.

Cascara Sagrada Oligoplex Madaus, Arg.
Sodium picosulfate (p.1771·1); belladonna (p.2263·3); cascara (p.1715·2).
Constipation.

Cascara Sagrada Puler Serch, Arg.†.
Cascara (p.1715·2); phenolphthalein (p.1762·1).
Constipation.

Cascara-Salax Ferring, Austria.
Powder, dried magnesium sulfate (p.1680·1); tablets, cascara (p.1715·2).
Bowel evacuation.

Cascor Ranbaxy, Malaysia; Ranbaxy, Thai.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Casec Mead Johnson Nutritionals, Canad.†; Mead Johnson, Israel; Mead Johnson Nutritionals, USA.
Calcium caseinate (p.1934·1).
Protein supplement.

Caseical Support, Braz.†.
Preparation for enteral nutrition (p.1922·1).

Caseincal Novag, Mex.†.
Calcium caseinate (p.1934·1).
Dietary supplement.

Casen Mikroklysma De Witt, Neth.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3).
Constipation.

Casenfilus Casen Fleet, Spain.
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Casenglicol Casen Fleet, Spain.
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Casfen Menarini, Port.†.
Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Casicot Be-Tabs, S.Afr.
Co-trimoxazole (p.258·1).
Bacterial infections.

Casilan Glaxo Wellcome, Mex.†.
Protein supplement (p.1922·1).

Casipril Tunggal Idaman, Indon.
Captopril (p.1239·2).
Heart failure; hypertension.

Caslot Ranbaxy, Malaysia.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Casodex AstraZeneca, Arg.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Zeneca, USA; AstraZeneca, Venez.
Bicalutamide (p.686·2).
Prostatic cancer.

Caspacil Cazi, Braz.
Selenium sulfide (p.1613·1).
Dandruff.

Caspiselenio Kin, Spain.
Selenium sulfide (p.1613·1).
Scalp disorders.

Casprin YSP, Malaysia.
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Cassadan Temmler, Ger.
Alprazolam (p.960·1).
Anxiety.

Castaderm Lannett, USA.
Resorcinol (p.1612·1); boric acid (p.2268·1); phenol (p.1656·1).
Fungal skin infections.

Castagnus Herbapol Wroclaw, Pol.
Agnus castus (p.2249·1).
Menstrual disorders.

Castal APT, Hong Kong.
Cefaclor (p.217·2).
Bacterial infections.

Castanha de India Composta Infabra, Braz.†.
Aesculus (p.2248·2); rutoside (p.2305·1); vitamin C (p.1983·3).
Venous insufficiency.

Castel Sysset, USA.
Resorcinol (p.1612·1).
Fungal skin infections.

Castellani mit Miconazol Hollborn, Ger.
Miconazole (p.541·2).
Fungal and bacterial skin infections.

Castilium Sanofi-Aventis, Port.
Clobazam (p.477·2).
Anxiety disorders.

Castoria Boie, Philipp.
Senna (p.1769·2); cucurbita (p.2290·2); santonica; potassium sodium tartrate (p.1764·1); sodium bicarbonate (p.1673·2).
Constipation.

Castufemin Ardeypharm, Ger.
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Catabex UCB, Belg.
Dropropizine (p.1557·3).
Coughs.

Catabex Expectorans UCB, Belg.†.
Dropropizine (p.1557·3); guaifenesin (p.1561·3).
Coughs.

Catabina Tecnifar, Port.
Dropropizine (p.1557·3).
Coughs.

Catabina Expectorante Tecnifar, Port.
Dropropizine (p.1557·3); guaifenesin (p.1561·3).
Coughs.

Cataclot Ono, Jpn.
Ozagrel sodium (p.2359·2).
Cerebrovascular disorders.

Catacol Alcon, Fr.
Disodium inosinate (p.2296·1).
Lens opacities.

Cataflam
Novartis, Arg.†; Novartis, Indon.; Novartis, Philipp.; Novartis, Singapore.
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Novartis, Belg.
Diclofenac (p.44·2) or diclofenac potassium (p.44·3).
Inflammation; pain.
Novartis, Braz.; Novartis, Chile; Novartis, Venez.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.
Novartis, Gr.†; Novartis, Hong Kong; Novartis, Irl.; Novartis, Israel; Novartis Consumer, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Normal, Port.; Novartis, S.Afr.; Novartis, Thai.; Novartis, Turk.; Novartis, USA.
Diclofenac potassium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Novartis, Hung.
Diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.
Novartis, Malaysia.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.
Novartis, Mex.
Diclofenac (p.44·2), diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Cataflex Cifarma, Braz.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Inflammation.

Cataflexym Cifarma, Braz.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Catalet Biomed Krakow, Pol.
Pollen allergen extracts (p.2370·2) (p.2250·2).
Hyposensitisation.

Catalgem Ibfarma, Braz.†.
Diclofenac potassium (p.44·3).

Catalgine Aerocid, Fr.†.
Sodium aspirin (p.23·3).
Fever; musculoskeletal and joint disorders; myocardial infarction; pain.

Catalgine Vitamine C Medipha, Fr.†.
Sodium aspirin (p.23·3); ascorbic acid (p.1983·3).
Fever; pain.

Catalin
Allergan, Arg.†; Vianex (Βιανέξ), Gr.; Allergan, India; Senju, Jpn; Senju, Pol.; Takeda, Thai.
Pirenoxine (p.2369·1).
Cataract.
Takeda, Hong Kong; Takeda, Indon.; Takeda, Malaysia†; Takeda, Philipp.; Takeda, Singapore.
Pirenoxine sodium (p.2368·3).
Cataract.

Catalip Solvay, Port.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Catanac Ethica, Indon.; Pharmasant, Thai.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Catapres *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Hong Kong†; Zydus, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA.*
Clonidine hydrochloride (p.1247·1).
Hypertension; menopausal flushing; migraine and vascular headache.

Boehringer Ingelheim, NZ.
Clonidine (p.1247·1) or clonidine hydrochloride (p.1247·1).
Hypertension.

Catapres Diu *Zydus, India.*
⊗ Clonidine hydrochloride (p.1247·1); chlortalidone (p.1243·3).
Hypertension.

Catapresan *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Unilfarma, Port.; Fher, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Venez.*
Clonidine hydrochloride (p.1247·1).
Hypertension; menopausal disorders; migraine; opioid withdrawal syndrome.

Boehringer Ingelheim, Ital.
Clonidine (p.1247·1) or clonidine hydrochloride (p.1247·1).
Hypertension.

Boehringer Ingelheim Promeco, Mex.
Clonidine (p.1247·1).
Hypertension.

Catapressan *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fr.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Catarest *Centaur, India.*
Potassium iodide (p.2169·2); sodium chloride (p.1686·1); calcium chloride (p.1675·2).
Cataracts.

Cataridol *Novartis Ophthalmics, Fr.†.*
Calcium chloride (p.1675·2); magnesium chloride (p.1679·1); sodium chloride (p.1686·1).
Lens opacities.

Catarrh Cream *Weleda, UK.*
Homoeopathic preparation.

Catarrh Mixture *Potter's, UK.*
Boneset (p.2267·3); blue flag (p.2327·1); lapp root (p.2330·3); hyssop (p.2323·3); capsicum (p.2276·2).
Catarrh.

Catarrh-eeze *Chefaro, UK.*
Marrubium (p.1564·1); achillea (p.2245·2); elecampane (p.1558·1).
Catarrh.

Catarrh-Ex *Thompson, UK.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); caffeine (p.1116·3).
Cold symptoms.

Catarrosan *Tentan, Switz.†.*
Homoeopathic preparation.

Catarrosine *Fecofar, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Catarstat *Chauvin, Fr.; Bausch & Lomb, Philipp.; Bausch & Lomb, Switz.*
Pyridoxine hydrochloride (p.1978·2); amino acids.
Cataract; cataracts; lens opacities.

Catazyme-P
Note. This name is used for preparations of different composition.
Stadmed, India.
Oral drops: Amylase (p.2256·3); cinnamon oil (p.2283·2); caraway oil (p.2277·1); cardamom oil (p.2277·2).
Dyspepsia; flatulence.

Stadmed, India.
Syrup: Amylase (p.2256·3); papain (p.2362·3).
Dyspepsia; flatulence.

CAT-Barium (E-Z-CAT) *Bracco, Switz.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Categ *Sofar, Ital.*
Green tea (chinese) (p.2416·1).
Nutritional supplement.

Categor *Sandoz, Arg.*
Capecitabine (p.691·3).
Malignant neoplasms.

Catenol *Cadila, Cz.†; Cadila, Rus.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Caterol *Pharmasant, Thai.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Catex *Cantabria, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Catexan *Biogaran, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Cathejell
Note. This name is used for preparations of different composition.
Montavit, Austria; Montavit, Israel.
Diphenhydramine hydrochloride (p.577·2); chlorhexidine hydrochloride (p.1635·3).
Cystoscopy; endoscopy; lubrication for catheter insertion.

Hospithera, Belg.; Montavit, Philipp.; Montavit, Port.
Chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Catheterisation.

Cathejell with Lidocaine *Montavit, Malaysia; Montavit, Rus.†; Pharmaplan, S.Afr.; Montavit, Thai.; Mediplus, UK.*
Chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Catheterisation; instrument insertion.

Cathejell mit Lidocain *Montavit, Austria; Pfleger, Ger.*
Chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Catheterisation; instrument insertion.

Cathejell S *Pfleger, Ger.*
Chlorhexidine hydrochloride (p.1635·3).
Catheterisation.

Catheter Preparation *Pfizer, Austral.*
Chlorhexidine gluconate (p.1635·3).
Genital disinfection before bladder catheterisation.

Cathflo *Roche, Canad.*
Alteplase (p.1207·2).
Venous catheter occlusion.

Catiz Plus *Merck, Arg.*
Saw palmetto (p.2192·3); pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Catlep *Sumitomo, Jpn; Teikoku Seiyaku, Jpn.*
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Cato-Bell *Bell, India.*
Potassium iodide (p.2169·2); sodium chloride (p.1686·1); calcium chloride (p.1675·2).
Cataract; lens opacities.

Catogen *Galeno, Venez.†.*
Gentamicin (p.284·2).
Bacterial skin infections.

Catona *Mavi, Mex.*
Captopril (p.1239·2).
Hypertension.

Catonet *Nycomed, Denm.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Catonin *Magis, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Catoplin *Beacons, Singapore.*
Captopril (p.1239·2).
Heart failure; hypertension.

Catoprol *Medley, Braz.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Catrigel *Vocate, Gr.*
⊗ Miconazole nitrate (p.541·3); fluprednidene acetate (p.1533·1).
Infected skin disorders.

Catrix
Note. This name is used for preparations of different composition.
Valeant, Ger.; ICN, Port.†; Valeant, UK†.
Collagen (p.2286·1).
Burns; ulcers; wounds.

Donell DerMedex, USA.
Emollient and moisturiser.

Catrix Correction *Donell DerMedex, USA.*
SPF 15: Octinoxate (p.1608·2); meradimate (p.1604·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Catrix Lip *Donell DerMedex, USA.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Cats Claw Complex *Mediherb, Austral.*
Cat's claw; tabebuia avellanedae; echinacea (p.2298·1).
Cold symptoms; tonic.

Caulophyllum Complex *Dolisos, Canad.†.*
Homoeopathic preparation.

Causalon *Phoenix, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Causalon Bronquial *Phoenix, Arg.*
Clofedanol hydrochloride (p.1554·2); guaifenesin (p.1561·3); oxatomide (p.587·1).
Coughs.

Causalon Gesic *Phoenix, Arg.†.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; inflammation; pain.

Causalon Grip *Phoenix, Arg.*
Paracetamol (p.108·1); oxatomide (p.587·1); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Causalon Ibu *Phoenix, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Causalon Pro *Phoenix, Arg.†.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Fever; pain.

Causat *Sanofi Synthelabo, Austria.*
Procaine hydrochloride (p.1869·1); atropine sulfate (p.1219·3).
Migraine; neuralgia; neuritis.

Caustinerf forte *Septodont, Switz.†.*
Lidocaine (p.1862·3); phenol (p.1656·1); paraformaldehyde (p.1655·2).
Dental pain.

Cauterex *Ache, Braz.*
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1); gentamicin sulfate (p.282·1).
Wounds.

Cauteridol *Ederka, Mex.*
Ranitidine (p.1766·1).

Cavel *Duopharma, Malaysia.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Caveril *Remedica, Thai.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Caverject
Pharmacia, Arg.†; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.†; Pharmacia, USA; Pfizer, Venez.
Alprostadil (p.2183·2).
Diagnostic aid; erectile dysfunction.

Pfizer, UK.
Alprostadil (p.2183·2) or alprostadil alfadex (p.2183·3).
Erectile dysfunction.

Caverta *Ranbaxy, India.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Caviamina *De Mayo, Braz.*
Vitamin B substances; vitamin C; fructose (p.1922·1).

CaviD *Nycomed, Denm.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cavigen *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p.2311·1).

Cavilon *3M, Arg.†; 3M, Canad.†; 3M, Fr.; 3M, UK.*
A barrier film.
Ostomy care.

Cavimet *Rowe-Fleming, Venez.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cavinton *Bago, Arg.†; Gedeon Richter, Cz.; Celltech, Ger.†; Gedeon Richter, Hung.; Richter, Pol.; BioSaude, Port.; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Gedeon Richter, Thai.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; dementia; mental function impairment; vascular eye and ear disorders; vestibular disorders.

Cavirox *Roux-Ocefa, Arg.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Cavirox Cit *Roux-Ocefa, Arg.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cavirox Junior *Roux-Ocefa, Arg.†.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Cavit D3 *Merck, Indon.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Cavit-D3 *Merck, Singapore.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Cavodan *Lacefa, Arg.†.*
Hyoscine butylbromide (p.1734·1); nitrazepam (p.1011·2); oxazepam (p.1014·2).
Sedative.

Cavodine *Biolab, Thai.†.*
Povidone-iodine (p.1659·2).
Skin, burn, and wound disinfection.

Cavumox *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Caxin *Hovid, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Caye Rheuma-Balsam *Cheplapharm, Ger.*
Glycol salicylate (p.62·3); sodium salamidacetate (p.121·2); benzyl nicotinate (p.28·1); capsicum (p.2276·2); coumarin (p.2288·2).
Musculoskeletal, joint, and soft-tissue disorders.

Cayenne Plus *Nutravite, Canad.†.*
Cayenne (p.2276·2); ginger root (p.1732·3).

Cazaprol *KRKA, Cz.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Caziderm *Cazi, Braz.*
Nitrofurazone (p.309·1).
Burns; skin infections.

Cazigeran *Cazi, Braz.*
Vitamin B substances; vitamin E; magnesium aspartate; potassium aspartate (p.1922·1).

Cazmar *Fucus, Arg.*
Vitamin A (p.1971·2).
Skin disorders.

Cazole *Malpharm, Hong Kong; Malaysia Chemist, Singapore†.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Cazosin *Millimed, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

C-Bildz *Alcon, Austria.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

C-1000-C
Note. This name is used for preparations of different composition.
Novartis, Chile†.
Ascorbic acid (p.1983·3); calcium lactobionate (p.1676·2); calcium carbonate (p.1714·1).
Calcium and vitamin C supplement.

Novartis, Mex.
Ascorbic acid (p.1983·3); calcium lactate gluconate (p.1676·2).
Calcium and vitamin C supplement.

C-Calcio *EMS, Braz.*
Vitamin C; calcium carbonate; colecalciferol; vitamin B (p.1922·1).
Calcium and vitamin supplement.

C-Calcium *Streuli, Switz.*
Calcium gluconate (p.1675·3); ascorbic acid (p.1983·3); calcium saccharate (p.2272·3).
Vitamin C and calcium deficiency.

CCK *Sanitas, Arg.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders.

CCK Flunarizina *Sanitas, Arg.†.*
Codergocrine mesilate (p.363·3); flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; vestibular disorders.

CC-Nefro *Medice, Ger.*
Calcium carbonate (p.1714·1).
Hyperphosphataemia.

CCNU *Medac, UK.*
Lomustine (p.741·1).
Malignant neoplasms.

C-Dose *Medgenix, Belg.†.*
Ascorbic acid (p.1983·3).
Scurvy; vitamin C deficiency.

CDR *Bayer, Thai.*
Calcium; vitamin B ; vitamin C; vitamin D (p.1922·1).
Calcium and vitamin supplement; osteoporosis.

CDR Fortos *Bayer, Indon.*
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis.

CDT *CSL, Austral.; CSL, NZ.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of infants and young children.

Cealb *Sanquin, Neth.; Centurion, Turk.*
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; plasma volume expansion.

Ceanel *Quinoderm, Irl.†; Ferndale, UK.*
Cetrimide (p.1634·1); phenethyl alcohol (p.1655·3); undecenoic acid (p.549·2).
Dandruff; psoriasis; seborrhoea; seborrhoeic dermatitis.

CEA-Scan *Immunomedics, Cz.†; Altana, Ital.; Nucliber, Spain; Immunomedics, UK; Immunomedics, USA.*
Technetium-99m (p.2055·3) arcitumomab.
Detection of colorectal cancer.

Cebactam *LBS, Thai.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Cebedex *Abdi, Turk.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye and ear disorders.

Cebedexacol *Chauvin, Fr.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Eye infections.

Cebemyxine *Chauvin, Fr.; Bausch & Lomb, Hong Kong; Chauvin, Hong Kong; Abdi, Turk.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Cebenicol *Chauvin, Fr.†.*
Chloramphenicol (p.239·3).
Eye infections.

Cebera *Irex, Fr.†.*
Alibendol (p.2250·2).
Dyspepsia.

Cebesin *Bausch & Lomb, Switz.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Cebesine *Chauvin, Fr.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Cebex *Otto, Indon.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Cebexin *Indian Drugs, India.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Cebiolon *Merck, Port.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cebion *Merck, Arg.†; Merck, Austria; Merck, Braz.; Merck, Chile; Merck, Cz.†; Merck, Ger.; Galenica, Gr.†; Merck, Hung.; Merck, Indon.; Bracco, Ital.; Merck, Pol.; Merck, Port.; Merck Consumer, Singapore; Merck, Spain; Merck, Venez.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cebion Calcico *Merck, Chile.*
Vitamin C; calcium carbonate; rutoside; colecalciferol (p.1922·1).
Calcium supplement; tonic.

Cebion Calcio *Merck, Braz.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1).
Calcium and vitamin C supplement.

Cebion Erkaltungs *Merck, Ger.†.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms; fever; pain.

Cebion N *Merck, Ger.†.*
Sodium ascorbate (p.1984·1).
Methaemoglobinaemia; vitamin C deficiency.

Cebion Plus Magnesio *Merck, Braz.†.*
Ascorbic acid (p.1983·3); magnesium carbonate (p.1743·1).
Nutritional supplement.

Cebion Plus Com Minerais *Merck, Braz.†.*
Ascorbic acid (p.1983·3); minerals.
Nutritional supplement.

Cebion plus Rutin *Merck, Austria.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Nutritional supplement.

Cebion Zinco *Merck, Braz.*
Ascorbic acid (p.1983·3); zinc (p.1999·1).
Vitamin C and zinc supplement.

Cebionmulti *Merck, Pol.*
Vitamin preparation (p.1922·1).

Cebragil *Medimar, Gr.*
Piracetam (p.368·2).

Cebralat *Libbs, Braz.*
Cilostazol (p.1245·2).
Cerebral and peripheral vascular disorders.

Cebran *Deafarma, Ital.*
Nicergoline (p.2352·1).
Cerebrovascular disorders.

Cebrilin *Libbs, Braz.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Cebrocal
Note.This name is used for preparations of different composition.
Temis, Arg.
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Recalcine, Chile.
Gamma-aminobutyric acid; gamma-amino beta-hidroxybutyric acid; acetylglutamin; vitamin B (p.1922·1).

Cebrofort *Baliarda, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders.

Cebrolux *Tubilux, Ital.*
Vitamins; citicoline (p.1922·1).
Nutritional supplement.

Cebronfilina *Neo Quimica, Braz.*
Ambroxol acefyllinate (p.1114·2).
Respiratory-tract disorders.

Cebrotex *Janssen-Cilag, Port.†.*
Glutamine (p.1947·2).

Cebrotex Forte *Lusomedicamenta, Port.*
Benfotiamine (p.1975·2); calcium magnesium fytate; glutamine (p.1947·2).

Cebroton *Tubilux, Ital.*
Citicoline sodium (p.2283·3).
Parkinsonism.

Cebrotonin *Ritter, Malaysia†; Ritter, Singapore.*
Piracetam (p.368·2).
Mental function impairment in the elderly.

Cebutid *Shire, Fr.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Cec *Hexal, Arg.†; Hexal, Austria; Salutas, Cz.†; Hexal, Ger.; Hexal, Mex.; Hexal, S.Afr.*
Cefaclor (p.217·2).
Bacterial infections.

Cecap *Atlantic, Hong Kong; Atlantic, Malaysia.*
Vitamin C (p.1983·3).
Tonic; vitamin C deficiency.

Cecenu *Medac, Ger.*
Lomustine (p.741·1).
Malignant neoplasms.

Ceclobid *EL, Philipp.; YSS, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Ceclor *Aspen, Austral.; Arcana, Austria; Lilly, Belg.; Lilly, Braz.†; Pharmel, Canad.; Lilly, Cz.; Lilly, Gr.; APPI, Hong Kong; Keri, Hung.; Lilly, Indon.; Lilly, Israel†; Altana, Mex.; EuroCept, Neth.; GSK, Philipp.; Polfa Kutno, Pol.; Medinfar, Port.; Lilly, Rus.; Lilly, S.Afr.†; Biomed, Spain; Sigma-Tau, Switz.; Lilly, Turk.; Lilly, USA; Farma, Venez.*
Cefaclor (p.217·2).
Bacterial infections.

Ceclorbeta *Betapharm, Ger.*
Cefaclor (p.217·2).
Bacterial infections.

Ceclordox *Altana, Mex.*
Cefaclor (p.217·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Cecloretta *Keri, Hung.*
Cefaclor (p.217·2).
Bacterial infections.

Cecnoin *Ranbaxy, Braz.*
Isotretinoin (p.1599·2).
Acne.

Cecoflan *Vitapan, Braz.†.*
Aceclofenac (p.14·3).
Musculoskeletal and joint disorders.

Cecold *Pharmasant, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Cecon *Pharmacia, India; Abbott, Philipp.; Abbott, Port.; Abbott, USA.*
Ascorbic acid (p.1983·3).
Scurvy; vitamin C deficiency.

Cecrisina *Janssen-Cilag, Port.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cecural *Demo, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Cecure *Cadila, India.*
Folic acid; vitamin B ; vitamin B ; vitamin E; vitamin C (p.1922·1).

Cedantron *Soho, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Cedax *White, Arg.†; SIFI, Cz.†; Schering-Plough, Cz.†; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Neth.; Schering-Plough, Philipp.; Schering-Plough, Pol.; SIFI, Rus.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Shionogi, USA; Schering-Plough, Venez.*
Ceftibuten (p.235·3).
Bacterial infections.

Cedelate *TNP, Thai.†.*
Flunarizine (p.580·3).
Migraine; vestibular disorders.

Cedetrin-T *Exbio, Cz.†.*
Muromonab-CD3 (p.1835·2).
Transplant rejection.

Cedilanid *Novartis, Mex.*
Lanatoside C (p.1322·3).
Cardiac disorders.

Cedilanide *Novartis, Braz.*
Deslanoside (p.1257·2).
Heart failure; supraventricular arrhythmias.

Cedine *Rowex, Irl.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Cedium *Qualiphar, Belg.*
Benzalkonium chloride (p.1629·1).
Disinfection of the skin, wounds, and hands.

Cedium Chlorhexidine *Qualiphar, Belg.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Cedixen *Aventis, Austria.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Cedizim *Uno, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Cedocard *Altana, Austria; Altana, Belg.; Paladin, Canad.†; Altana, Indon.; Darya-Varia, Indon.; Altana, Neth.; Cedona, Neth.; Pharmacia, UK.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Cedovix *Specifar (Σπεσιφαρ), Gr.*
Camphor (p.2273·2); cineole (p.2282·3); menthol (p.2340·1).
Topical analgesic.

Cedozelin *Sigma, Braz.†.*
Vitamin B substances; fructose; vitamin C (p.1922·1).
Anaemias.

Cedric *Elea, Arg.*
Ivy (p.2328·1).
Cough.

Cedrilax *Pharlab, Braz.†.*
Paracetamol (p.108·1); diclofenac sodium (p.44·3); caffeine (p.1116·3); carisoprodol (p.1894·1).

Cedrin *Mantecorp, Braz.*
Pseudoephedrine sulfate (p.1571·2); azatadine maleate (p.568·1).
Nasal congestion.

Cedrox *Hikma, Cz.†; Hexal, Ger.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Cedroxim *Leti, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Cedur *Roche, Belg.; Roche, Braz.; Roche, Ger.; Roche, Switz.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Ceelin *Pediatrica, Malaysia; Pediatrica, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

CeeNU *BMS, Arg.; BMS, Austral.; Bristol, Canad.; BMS, Chile; BMS, Cz.; BMS, Hong Kong; BMS, Israel†; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Philipp.; BMS, S.Afr.; BMS, Singapore†; BMS Oncology, USA.*
Lomustine (p.741·1).
Malignant neoplasms.

Ceerexin *Leiras, Fin.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

CEF-3 *Dankos, Philipp.; Siam Bheasach, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cef-4 *Siam Bheasach, Malaysia.*
Ceftazidime (p.234·1).
Bacterial infections.

CEF-4 *Siam Bheasach, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefa Resan *Alacan, Spain†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefaben *Cazi, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefabene *Cefak, Ger.*
Stipites dulcamarae (p.2298·1).
Eczema.

Cefabiot *Hexal, Arg.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefabiotic *Bernofarm, Indon.*
Cefalexin (p.218·2).
Bacterial infections.

Cefabiozim *IPA, Ital.†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefabol *Robert, Spain.*
Sodium cytidine monophosphate (p.2291·3); gamma-aminobutyric acid (p.2308·1); aminohydroxybutyric acid (p.471·2); magnesium glutamate hydrobromide (p.2337·1); trisodium uridine triphosphate (p.2408·1); pyridoxine hydrochloride (p.1978·2).
Mental function disorders; tonic.

Cefabrina *Neo Quimica, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Cefabroxil *Maver, Mex.*
Cefalexin (p.218·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Cefacar *BMS, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefacar Mucolitico *BMS, Arg.†.*
Cefadroxil (p.218·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Cefacene *Centrum, Spain†.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefacet *Norgine, Fr.*
Cefalexin (p.218·2).
Bacterial infections.

Cefaciclina *Rowe-Fleming, Venez.†.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefacidal *BMS, Belg.; BMS, Fr.†; BMS, Mex.†; BMS, Neth.; BMS, S.Afr.; BMS, Venez.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefacile *BMS, Port.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefacilina *Montpellier, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefacilina Bronquial *Montpellier, Arg.*
Cefadroxil (p.218·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Cefacin-M *Bright Future, Hong Kong.*
Cefalexin (p.218·2).
Bacterial infections.

Cefaclen *Zentiva, Cz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefacloren *Neo Quimica, Braz.*
Cefaclor (p.217·2).
Bacterial infections.

Cefacloril *Remek, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Cefacolin *Northia, Arg.; Itaca, Braz.†.*
Cefotaxime (p.229·1).
Bacterial infections.

Cefacure *Orchid, Hong Kong.*
Cefalexin (p.218·2).
Bacterial infections.

Cefacynar *Cefak, Ger.*
Cynara (p.2291·2).
Biliary-tract disorders.

Cefaday *Biofarma, Turk.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefade *Klonal, Arg.†.*
Cefalotin (p.220·2).
Bacterial infections.

Cefadian *Cefak, Ger.†.*
Potentilla anserina.
Dysmenorrhoea.

Cefadin
Note.This name is used for preparations of different composition.
Genepharm, Gr.
Cefamandole (p.220·3).
Bacterial infections.

Atlantic, Singapore; Vana, Thai.†.
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefadol *Atlantic, Thai.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Cefadolor *Cefak, Ger.*
Guaiacum wood.
Rheumatic disorders.

Cefadolor H *Cefak, Ger.†.*
Homoeopathic preparation.

Cefadrex *Vir, Spain.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the injection to alleviate the pain of injection.
Bacterial infections.

Cefadril
AGIPS, Ital.; LSP, Thai.†.
Cefadroxil (p.218·1).
Bacterial infections.

Gentek, Venez.†.
Cefadroxil (p.218·1) or cefadroxil lysine (p.218·2).
Bacterial infections.

Cefadrin
Note.This name is used for preparations of different composition.
Cifarma, Braz.
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Cefak, Ger.
⊗ Ephedra (p.1558·1); thyme (p.2401·1); ammi visnaga (p.2256·1).
Formerly known as Cefedrin N.
Asthma; coughs.

Cefadrox *Cassara, Arg.; LA, Arg.; Salutas, Cz.†; Aristo, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefadroxon *Sanval, Braz.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefadur *Cipla, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefafloria *Cefak, Ger.†.*
Ethyl linoleate (p.2308·2).
Formerly known as Floriabene.
Skin disorders.

Cefagel *Multilab, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefagen *Maver, Mex.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefager *Gerard, Irl.*
Cefaclor (p.217·2).
Bacterial infections.

Cefagil *Cefak, Ger.*
Homoeopathic preparation.

Cefagon *Ibfarma, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Cefagran *Legrand, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefakliman *Cefak, Ger.*
Homoeopathic preparation.

Cefakliman mono *Cefak, Ger.; Cefak, Hung.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Cefaklon *Klonal, Arg.†.*
Cefaclor (p.217·2).
Bacterial infections.

Cefalan *Merck, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Cefaldina *IMA, Braz.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Migraine.

Cefalekol *Teva, Hung.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefalektin *Cefak, Ger.*
Mistletoe (p.2345·3).
Malignant neoplasms.

Cefalex *Bago, Arg.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Migraine.

Cefalexan *Sanval, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Cefalexgobens *Normon, Spain.*
Cefalexin (p.218·2).
Bacterial infections.

Cefalexi *Arion, Arg.†.*
Cefalexin (p.218·2).
Bacterial infections.

Cefalgin *Polfa Pabianice, Pol.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Cefalin
Note.This name is used for preparations of different composition.
EMS, Braz.
Cefalotin sodium (p.219·2).
Bacterial infections.

Generics, Israel†; BioFemme, Philipp.
Cefalexin (p.218·2).
Bacterial infections.

Atlantic, Thai.
Cefazolin sodium (p.222·1).
Bacterial infections.

Cefaline Hauth *Homme de Fer, Fr.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Cefaline-Pyrazole *Homme de Fer, Fr.†.*
Dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Cefalium *Ache, Braz.*
Paracetamol (p.108·1); dihydroergotamine mesilate (p.618·2); metoclopramide hydrochloride (p.1747·3); caffeine (p.1116·3).
Migraine.

Cefaliv *Ache, Braz.*
Dihydroergotamine mesilate (p.618·2); dipyrone (p.49·2); caffeine (p.1116·3).
Migraine.

Cefalmin
Note.This name is used for preparations of different composition.
Sanitas, Chile.
Ergotamine tartrate (p.620·1); dipyrone (p.49·2); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Migraine and other vascular headache.

Labesfal, Port.
Cefradine (p.233·1).
Bacterial infections.

Cefaloga *Elter, Venez.†.*
Cefalexin (p.218·2).
Bacterial infections.

Cefaloject *BMS, Fr.*
Cefapirin sodium (p.221·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefalom *Help, Gr.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefalomicina *Bago, Arg.*
Cefazolin (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Cefalor *APT, Hong Kong; Vitamed, Israel.*
Cefaclor (p.217·2).
Bacterial infections.

Cefalot *Teuto, Braz.†.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefalotil *Uniao Quimica, Braz.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefaluna *Cefak, Ger.†.*
Valerian (p.2410·1).
Anxiety; sleep disorders.

Cefalver *Maver, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Cefam
Note.This name is used for preparations of different composition.
Pharma-Marketing, Hung.; Magis, Ital.
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Dollder, Venez.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefamadar *Cefak, Ger.*
Homoeopathic preparation.

Cefamanit *Cefak, Ger.*
Homoeopathic preparation.

Cefamar
Note.This name is used for preparations of different composition.
Mar, Arg.
Cefadroxil (p.218·1).
Bacterial infections.

Menarini, Thai.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cefamezin *Gador, Arg.; Fujisawa, Hong Kong; Teva, Israel; Pharmacia, Ital.; Astellas, Jpn; Astellas, Neth.; Hikma, Port.; Eczacibasi, Rus.; Astellas, Thai.; Eczacibasi, Turk.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefamig *Merck Medication Familiale, Fr.*
Chamomile (p.2279·3).
Headache.

Cefamox *BMS, Braz.; BMS, Chile; BMS, Mex.; BMS, Swed.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefan *Cefak, Ger.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Cefanal *Bunker, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefanex *Apothecon, USA.*
Cefalexin (p.218·2).
Bacterial infections.

Cefanorm *Cefak, Ger.; Cefak, Hung.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Cefantral *Lupin, Cz.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefanyl *Faran, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Cefaperos
BMS, Belg.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

BMS, Fr.†.
Cefatrizine (p.221·3) or cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Cefapoten *Del Bel, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Cefapulmon mono *Cefak, Ger.†.*
Ivy (p.2328·1).
Bronchial catarrh.

Cefaricida *Pentafarma, Port.†.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefarinol *Gramon, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Cefariston *Ariston, Braz.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefarizon *Pharmakin, Venez.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Cefasabal *Cefak, Ger.*
Saw palmetto (p.2192·3); solidago virgaurea (p.2391·1); aesculus (p.2248·2).
Prostatic disorders.

Cefasedativ *Cefak, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2).
Formerly contained valerian, lupulus, and crataegus.
Anxiety disorders; insomnia.

Cefasel *Cefak, Ger.*
Sodium selenite (p.1961·1).
Selenium deficiency.

Cefasept *Cefak, Ger.*
Homoeopathic preparation.

Cefasin *Sintesina, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefasliymarin *Cefak, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Cefasporina *Oriental, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Cefassin *Cefak, Ger.†.*
Symphoricarpus; euphorbium cypariss.; gold in form of tetrachlorogold acid (p.2316·3).
Formerly known as Cefossin H.
Joint disorders.

Cefastad *Stada, Austria.*
Cefaclor (p.217·2).
Bacterial infections.

Cefasyn *Cipla, India; Cipla-Medpro, S.Afr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefat
Note.This name is used for preparations of different composition.
Sanbe, Indon.
Cefadroxil (p.218·1).
Bacterial infections.

Sintez, Rus.
Cefamandole nafate (p.220·3).
Bacterial infections.

Cefatec *Cefak, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Cefatenk *Biotenk, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefatin *Roche, Turk.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefatox
Note.This name is used for preparations of different composition.
Cefak, Ger.†.
Echinacea purpurea (p.2298·1).
Respiratory-tract infections.

Biofarma, Venez.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefatrex *BMS, Gr.†.*
Cefapirin sodium (p.221·2).
Bacterial infections.

Cefatrexyl *BMS, Cz.†.*
Cefapirin sodium (p.221·2).
Bacterial infections.

Cefatrix *Levofarma, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Cefaval *Valmor, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefavora *Cefak, Ger.*
Homoeopathic preparation.

Cefawell *Cefak, Ger.†.*
Calendula (p.2273·1); arnica (p.2260·2).
Skin disorders; wounds.

Cefa-Wolff *Wolff, Ger.†.*
Cefaclor (p.217·2).
Bacterial infections.

Cefax
Note.This name is used for preparations of different composition.
1A, Austria.
Cefaclor (p.217·2).
Bacterial infections.

Inga, Malaysia†.
Cefalexin (p.218·2).
Bacterial infections.

Cefaxon
Note.This name is used for preparations of different composition.
Ariston, Braz.
Cefalexin (p.218·2).
Bacterial infections.

Kimia, Indon.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefaxona *Pisa, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefaxone *Lupin, Cz.†; Shin Poong, Malaysia; Shin Poong, Singapore.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefazid *Biochem, India.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefazil *Italfarmaco, Ital.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefazillin *TP, Thai.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Cefazima *Biochimico, Braz.†.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefazime *Cheil, Singapore.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefazink *Cefak, Ger.*
Zinc gluconate (p.1999·2).
Zinc deficiency.

Cefazol *Kalbe, Indon.; General Drugs, Thai.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Cefazone *Teuto, Braz.†.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cef-Dime *Millimed, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Cef-Diolan *Meda, Ger.*
Cefaclor (p.217·2).
Bacterial infections.

Cefditran *Ranbaxy, India.*
Cefditoren (p.223·2).
Bacterial infections.

Cefec *Tecnifar, Port.†.*
Cefetamet pivoxil hydrochloride (p.224·2).
Bacterial infections.

Cefecon D *Nizpharm, Rus.*
Paracetamol (p.108·1).
Fever; pain.

Cefecon N *Nizpharm, Rus.*
Naproxen (p.92·3); caffeine (p.1116·3); salicylamide (p.121·2).
Fever; inflammation; pain.

Cefelen *Solara, Mex.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cefen *Pharmasant, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Cefepen *Cellofarm, Braz.†.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Ceferro *Teofarma, Ger.*
Ferrous sulfate (p.1939·3).
Iron-deficiency; iron-deficiency anaemias.

Cefexin *Unison, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Cefexina *Greenpharma, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Cefgram
Note.This name is used for preparations of different composition.
Bennett, Gr.
Cefprozil (p.232·2).
Bacterial infections.

Behrens, Venez.
Ceftazidime (p.234·1).
Bacterial infections.

Ceficad *Cadila, India.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cefimen-K *Klonal, Arg.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cefimix *Tecnimede, Port.*
Cefixime (p.224·3).
Bacterial infections.

Cefin
Note.This name is used for preparations of different composition.
Remedina, Gr.
Ceftazidime (p.234·1).
Bacterial infections.

Korea United, Singapore†; Pharmakin, Venez.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefine *TNP, Thai.†.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefir *Fahrenheit, Indon.*
Cefpirome (p.231·3).
Bacterial infections.

Cefirax *Saval, Chile.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Cefiton *Labesfal, Port.*
Cefixime (p.224·3).
Bacterial infections.

Cefix
Note.This name is used for preparations of different composition.
Cipla, India.
Cefixime (p.224·3).
Bacterial infections.

Dollder, Venez.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefix LB *Cipla, India.*
Cefixime (p.224·3); lactobacillus (p.2372·3).
Bacterial infections.

Cefixdura *Merck dura, Ger.*
Cefixime (p.224·3).
Bacterial infections.

Cefixoral *Menarini, Ital.*
Cefixime (p.224·3).
Bacterial infections.

Cefizel *Zeler, Port.*
Cefixime (p.224·3).
Bacterial infections.

Cefizox *GSK, Canad.; Hikma, Cz.†; Aventis, Fr.†; GSK, India; Kalbe, Indon.; Promeco, Mex.†; Astellas, Neth.; Hikma, Port.; Eczacibasi, Turk.; Fujisawa, USA.*
Ceftizoxime sodium (p.236·2).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefkor *Douglas, Austral.*
Cefaclor (p.217·2).
Bacterial infections.

Ceflacid *Collins, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Ceflavit *Aurora, Gr.†.*
Carbocisteine (p.1553·2).
Mucolytic.

Ceflax *Hikma, Port.†*
Cefalexin (p.218·2).
Bacterial infections.

Ceflen *Lapreven, Venez.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Ceflexin *Luper, Braz.†*
Cefalexin (p.218·2).
Bacterial infections.

Ceflour *YSP, Malaysia.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Ceflux *Ahimsa, Arg.†*
Cefuroxime (p.238·2).
Bacterial infections.

Cefmandol *General Drugs, Thai.*
Cefamandole (p.220·3).
Bacterial infections.

Cefmetazon *Sankyo, Hong Kong†; Sankyo, Jpn†.*
Cefmetazole sodium (p.225·3).
Bacterial infections.

Cefmix *Cadila, India.*
Cefalexin (p.218·2).
Bacterial infections.

Cefnax *Teuto, Braz.†*
Cefixime (p.224·3).
Bacterial infections.

Cefnos *Pharos, Indon.*
Cefpirome (p.231·3).
Bacterial infections.

Cefobacter *AGIPS, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefobetox *Pentafarma, Port.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefobid *Pfizer, Arg.†; Pfizer, Austria; Pfizer, Chile; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Jpn†; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, Singapore; Farmasierra, Spain†; Pfizer, Thai.; Pfizer, Turk.; Pfizer, USA†; Pfizer, Venez.†.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cefocef *Centaur, India.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefocef-LB *Centaur, India.*
Cefixime (p.224·3); lactobacilli (p.2372·3).
Bacterial infections.

Cefociclin *Francia, Ital.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoclin *Carbel, Mex.†*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefodie *Cristalfarma, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injections to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefodime *LBS, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefodox *Sanofi-Aventis, Irl.; Scharper, Ital.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Cefofix *Hikma, Neth.; Hikma, Port.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cefogen *Cadila, India; Cadila, Thai.†*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cefoger *De Salute, Ital.†*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefogram *Richmond, Arg.†*
Cefuroxime (p.238·2).
Bacterial infections.

Cefok *KBR, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefol *Abbott, Hong Kong; Abbott, USA.*
Multivitamin preparation (p.1922·1).

Cefomax *Bago, Arg.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefomic *LBS, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefomit *Magis, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefomycin *Cadila, India.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cefonax *Elmor, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Cefoneg *Tosi, Ital.†*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoper *Menarini, Ital.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoperazin *Taisho, Jpn.*
Cefoperazone sodium (p.227·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefophar *Pharos, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cefoplus *Aesculapius, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefoprim *DRD, Gr.†; Esseti, Ital.*
Cefuroxime sodium (p.238·2).
Lidocaine hydrochloride (p.1862·3) may be included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cefoprox *Cipla, India.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Cefor *Meiji, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ceforal
Note. This name is used for preparations of different composition.
Teva, Israel.
Cefalexin (p.218·2).
Bacterial infections.

Grunenthal, Port.
Cefadroxil (p.218·1).
Bacterial infections.

Ceforan *Uniao Quimica, Braz.; General Drugs, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefortam *Glaxo Wellcome, Port.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceforth *Biochem, India†.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Cefosin *Sintez, Rus.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefosporen *TRB, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Cefosporin *Esseti, Ital.†*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefotan *Wyeth-Ayerst, Canad.†; Zeneca, USA.*
Cefotetan disodium (p.229·3).
Bacterial infections.

Cefotas *Roemmers-Klinos, Venez.†*
Cefotaxime (p.229·1).
Bacterial infections.

Cefotax *T3A Pharma, Hung.†; Atlantic, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefotex *Precimex, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefotrix *Eberth, Denm.; Eberth, Ger.; T3A Pharma, Hung.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefovell *Novell, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefovit *Vitamed, Israel.*
Cefalexin (p.218·2).
Bacterial infections.

Cefoxal *Sandoz, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefoxan *Royton, Braz.*
Cefoxitin (p.230·3).
Bacterial infections.

Cefoxim *Biochem, India.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefoxin *Royton, Braz.; M & H, Thai.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefozin *Bilim, Turk.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cefozone *Atlantic, Singapore; Vana, Thai.†*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cefper *Biolab, Thai.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Cefpro *Verisfield, Gr.*
Cefprozil (p.232·2).
Bacterial infections.

Cefra *OM, Port.†*
Cefadroxil (p.218·1).
Bacterial infections.

Cefrabiotic *Prospa, Ital.†*
Cefradine (p.233·1).
Bacterial infections.

Cefracin *Corsalud, Venez.†*
Cefradine (p.233·1).
Bacterial infections.

Cefraden *Merck, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefradil *Merck, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefradol *Ferron, Indon.*
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

Cefradur
Note. This name is used for preparations of different composition.
Atral, Port.
Cefradine (p.233·1).
Bacterial infections.

Eczacibasi, Turk.
Cefadroxil (p.218·1).
Bacterial infections.

Cefral *Lilly, Arg.†*
Cefaclor (p.217·2).
Bacterial infections.

Cefralon *Aldril, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Cefriex *Novell, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Cefril *BMS, S.Afr.*
Cefradine (p.233·1).
Bacterial infections.

Cefrin
Note. This name is used for preparations of different composition.
Dexa, Indon.
Cefpirome (p.231·3).
Bacterial infections.

Julphar, UAE.
Cefalexin (p.218·2).
Bacterial infections.

Cefrix *Tecnimede, Port.†*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefrom *Aventis, Austral.; Aventis, Austria; Aventis, Belg.†; Aventis, Cz.†; Sanofi-Aventis, Fr.; Hoechst Marion Roussel, Gr.†; Aventis, India; Sanofi-Aventis, Indon.; Aventis, Irl.†; Aventis, Mex.; Sanofi-Aventis, NZ†; Aventis, Neth.; Sanofi-Aventis, Port.†; Aventis, S.Afr.; Aventis, Thai.; Aventis, UK†.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Cefspan *Grunenthal, Chile†; Kalbe, Indon.; Astellas, Jpn; Astellas, Thai.*
Cefixime (p.224·3).
Bacterial infections.

Ceft *Sanval, Braz.†*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ceftal *Rowex, Irl.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Ceftanorth *Itaca, Braz.†*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftaran *TNP, Thai.†*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ceftaridem *Vocate, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftax *Hikma, Cz.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ceftaxan *Umeda, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ceftaz *Cipla, India.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftazidon *Ariston, Braz.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftazim *Atral, Port.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftazin *Remedina, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Ceften *Teuto, Braz.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftidin *Hetero, India.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceftil *Hanmi, Singapore.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Ceftim *Glaxo Allen, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Ceftin *GSK, Canad.; GSK, USA.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Ceftina *Probiomed, Mex.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Ceftix *Gador, Arg.†*
Ceftizoxime (p.236·3).
Bacterial infections.

Ceftizon *Bago, Arg.†*
Ceftizoxime sodium (p.236·2).
Bacterial infections.

Ceftomax *Solara, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cefton *Ariston, Braz.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Ceftoral *Vianex (Βιανεξ), Gr.*
Cefixime (p.224·3).
Bacterial infections.

Ceftrat *Uniao Quimica, Braz.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Ceftrex *Biolab, Malaysia; Columbia, Mex.; Biolab, Thai.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftrialin *Behrens, Venez.*
Ceftriaxone (p.238·1).
Bacterial infections.

Ceftriax *Sigma, Braz.*
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftriaz *Klonal, Arg.†*
Ceftriaxone (p.238·1).
Bacterial infections.

Ceftrifin *Wockhardt, Rus.*
Ceftriaxone (p.238·1).
Bacterial infections.

Ceftrilem *Lemery, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ceftrinal *Farmedia, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Ceftriphin *General Drugs, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ceftrixon *Verisfield, Gr.*
Ceftriaxone (p.238·1).
Bacterial infections.

Ceftrox *Meiji, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ceftum *Ferron, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Cefu *TAD, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefudura *Merck dura, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefuhexal *Hexal, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefu-Hexal *Hexal, S.Afr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefulton *Fulton, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Cefumax *SoSe, Ital.†*
Cefuroxime sodium (p.238·2).

Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cefunorth *Itaca, Braz.†.*
Cefuroxime (p.238·2).
Bacterial infections.

Cefur *Vianex (Βιανέξ), Gr.; Eurofarmaco, Ital.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cefuracet *Rhein, Mex.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefuran *Royton, Braz.†.*
Cefuroxime (p.238·2).
Bacterial infections.

Cefurax *Lindopharm, Ger.; Lindopharm, Israel.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefurex *Salus, Ital.†.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Cefurim
Teva, Belg.; General Drugs, Thai.
Cefuroxime (p.238·2).
Bacterial infections.

Ecosol, Switz.
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefurin *Pharma-Marketing, Hung.; Magis, Ital.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cefuroprol *Proel, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefuro-Puren *Alpharma-Isis, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefurox
GSK, Arg.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Prafa, Indon.
Cefuroxime (p.238·2).
Bacterial infections.

Cefurox-Wolff *Wolff, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefuzime *Julphar, UAE.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cefxin *Community Pharmacy, Thai.†.*
Cefalexin (p.218·2).
Bacterial infections.

Cefxitin *Siam Bheasach, Thai.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Cefxon *Lapi, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cefzil *BMS, Braz.; BMS, Canad.; BMS, Cz.; BMS, Hung.; BMS, Indon.; BMS, Pol.; BMS, UK†; BMS, USA.*
Cefprozil (p.232·2).
Bacterial infections.

Cefzolin *Utopian, Thai.*
Cefazolin (p.222·1).
Bacterial infections.

Cefzon *Astellas, Jpn.*
Cefdinir (p.223·1).
Bacterial infections.

Cef-Zone *Millimed, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ceglution *Ariston, Arg.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Cegripe *Janssen-Cilag, Port.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); hesperidin (p.2304·3); ascorbic acid (p.1983·3).
Cold symptoms.

Cegrovit *Grossmann, Hong Kong; Grossmann, Switz.†.*
Vitamin C (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cehapark *Sanova, Austria.*
Bromocriptine mesilate (p.798·1).
Acromegaly; parkinsonism.

Cehasol *Sanova, Austria.*
Sulfur-rich shale oil (Cehasol); vitamin F-glycerinester (p.2308·2).
Skin disorders.

Cek *Hexal, Pol.*
Cefaclor (p.217·2).
Bacterial infections.

Ceklin *Klinger, Braz.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Celamine *Pharmasant, Thai.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis; pain; panic attacks; parkinsonism.

Celance *Roemmers, Arg.; Lilly, Braz.; Lilly, Chile†; Lilly, Fr.; Lilly, Gr.; Lilly, Hong Kong†; Lilly, Irl.; Lilly, Singapore†; Lilly, Thai.†; Lilly, UK.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Celapram *Alphapharm, Austral.; Pacific, NZ.*
Citalopram hydrobromide (p.385·3).
Depression.

Celascon *Zentiva, Rus.*
Ascorbic acid (p.1983·3).

Celaskon *Zentiva, Cz.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Celatrac
Note. This name is used for preparations of different composition.
Age D'or, Singapore.
Capsules: Fish oil (p.1362·2); soya oil (p.1965·3).
Joint disorders.

Age D'or, Singapore.
Cream: Menthol (p.2340·1).
Musculoskeletal and soft-tissue disorders.

Celay *Cofasa, Venez.*
Cetirizine hydrochloride (p.570·3).

Celco *Unison, Thai.*
Cefaclor (p.217·2).
Bacterial infections.

Celcox *Trima, Israel.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Celebra *Pfizer, Braz.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Fin.; Mack, Israel; Pfizer, Norw.; Pharmacia, Norw.; Pfizer, Swed.*
Celecoxib (p.34·2).
Familial adenomatous polyposis; osteoarthritis; pain; rheumatoid arthritis.

Celebrex *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Searle, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Searle, USA; Pharmacia, Venez.†.*
Celecoxib (p.34·2).
Ankylosing spondylitis; colorectal polyps; degenerative joint disorders; familial adenomatous polyposis; inflammation; juvenile rheumatoid arthritis; osteoarthritis; pain; rheumatoid arthritis.

Celectan *Farma, Venez.*
Nitazoxanide (p.842·3).
Amoebiasis; giardiasis; worm infections.

Celectol *Aventis, Cz.†; Sanofi-Aventis, Fr.; Winthrop, UK.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Celedol *Ipca, India.*
Celecoxib (p.34·2).
Familial adenomatous polyposis; osteoarthritis; pain; rheumatoid arthritis.

Celemax *Ivax, Arg.†.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Celemin *Probiomed, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Celen *Ranbaxy, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Celenid *Biopharm, Hong Kong†; Biolab, Malaysia†; Biolab, Singapore; Biolab, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; nausea; peripheral vascular disorders; vertigo; vestibular disorders.

Celer C *IAE, Philipp.*
Lysine hydrochloride; vitamin B substances (p.1922·1).
Tonic.

Celerg *Legrand, Braz.*
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).

Celermin *Pascual, Philipp.*
Vitamins; Chlorella growth factor; lysine; taurine (p.1922·1).
Dietary supplement.

Celery Plus *Swiss Bio, Malaysia†.*
Celery (p.2278·3); stellaria media; devil's claw root (p.39·1); lappa (p.2330·3); salix (p.121·3).
Musculoskeletal and joint pain.

Celesdepot *Schering-Plough, Port.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Celesemine *Schering-Plough, Spain.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Celestamil *Teuto, Braz.†.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Celestamin *Aesca, Austria.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity disorders.

Celestamincort *Schering-Plough, Venez.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).

Celestamine *Schering-Plough, Arg.; Mantecorp, Braz.; Schering-Plough, Chile; Schering-Plough, Fr.; Essex, Ger.†; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Mex.†; Essex, Philipp.; Schering-Plough, S.Afr.; Essex, Switz.; Schering-Plough, Venez.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders; inflammatory eye disorders; rhinitis; skin disorders.

Celestamine N *Essex, Ger.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Celestamine NS *Schering-Plough, Mex.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).
Hypersensitivity.

Celestamine-F *Schering-Plough, Mex.†.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity.

Celestamine-L *Schering-Plough, Arg.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).
Hypersensitivity reactions.

Celestan
Aesca, Austria.
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3) and betamethasone acetate (p.1518·2).
Corticosteroid.

Teuto, Braz.†.
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celestan Depot *Essex, Ger.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Celestan solubile *Essex, Ger.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celestan-V *Essex, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Celestene
Schering-Plough, Fr.
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

IFET (ΙΦΕΤ), Gr.
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Celestene Chronodose *Schering-Plough, Fr.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Celestoderm *Schering, Canad.†; Schering-Plough, Fin.; Schering-Plough, Fr.; Schering-Plough, Neth.; Key, Spain; Schering-Plough, Venez.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders; skin disorders.

Celestoderm cum Chinoform *Schering-Plough, Fin.†.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Celestoderm cum Garamycin *Schering-Plough, Fin.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestoderm con Gentalyn *Schering-Plough, Venez.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestoderm Gentamicina *Key, Spain.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestoderm-V *Schering-Plough, Cz.†; Schering-Plough, Gr.; Schering-Plough, Hong Kong†; Schering-Plough, Indon.; Schering-Plough, Ital.†; Schering-Plough, Malaysia†; Schering-Plough, Mex.†; Schering-Plough, Rus.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore†; Key, Spain; Essex, Switz.; Schering-Plough, Turk.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Celestoderm-V with Garamycin *Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Rus.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore†.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestoderm-V with Neomycin *Schering-Plough, Singapore†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Celestoderm-V/GA *Schering-Plough, Gr.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celeston
Note. This name is used for preparations of different composition.
Schering-Plough, Denm.
Cream; ointment; topical emulsion: ⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Schering-Plough, Denm.; Schering-Plough, Norw.
Injection: ⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Schering-Plough, Swed.
Injection: ⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celeston bifas *Schering-Plough, Swed.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celeston Chronodose *Schering-Plough, Fin.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celeston med Chinoform *Schering-Plough, Denm.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Celeston valerat *Schering-Plough, Swed.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Celeston valerat comp *Schering-Plough, Swed.†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Celeston valerat med chinoform *Schering-Plough, Swed.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders; otitis externa.

Celeston valerat med gentamicin *Schering-Plough, Swed.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestone
Schering-Plough, Arg.; Schering-Plough, Belg.; Schering-Plough, Hung.†; Schering-Plough, Ital.; Schering-Plough, Mex.; Schering-Plough, Neth.; Schering-Plough, Singapore†; Essex, Switz.; Schering-Plough, Venez.
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Mantecorp, Braz.; IFET (ΙΦΕΤ), Gr.; Schering-Plough, Hong Kong†; Schering-Plough, Philipp.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering, USA.
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Pol.; Schering-Plough, Spain.
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celestone V *Schering-Plough, Austral.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Celestone Chronodose *Schering-Plough, Austral.; Schering-Plough, Belg.; Schering-Plough, Gr.; Schering-Plough, Israel; Schering-Plough, NZ; Schering-Plough, Neth.; Essex, Switz.; Schering-Plough, Turk.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Celestone Cronodose *Schering-Plough, Arg.; Schering-Plough, Ital.; Schering-Plough, Spain.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Celestone M *Schering-Plough, Austral.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Celestone S *Schering-Plough, Spain.*
⊗ Betamethasone (p.1518·2); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Celestone Soluspan *Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Mex.; Schering-Plough, S.Afr.; Schering, USA; Schering-Plough, Venez.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celestone VG *Schering-Plough, Austral.†.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Celestrat *Uniao Quimica, Braz.*
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

Celetil *Geolab, Braz.*
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

Celeuk *Takeda, Jpn.*
Celmoleukin (p.735·1).
Angiosarcoma.

Celevac *Shire, Irl.; Amdipharm, UK.*
Methylcellulose (p.2145·1).
Constipation; diarrhoea; dietary fibre supplement; diverticular disease; obesity; ostomy management; ulcerative colitis.

Celex
Note. This name is used for preparations of different composition.
Farmo Quimica, Chile.
Clonixin lysine (p.37·1).
Pain.

Millimed, Thai.
Cefalexin (p.218·2).
Bacterial infections.

Celexa *Lundbeck, Canad.; Forest Pharmaceuticals, USA.*
Citalopram hydrobromide (p.385·3).
Depression.

Celexin *Mantecorp, Braz.; Hovid, Malaysia; Hovid, Singapore; Atlantic, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Celfax *Degorts, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Celib *Unichem, India.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Celibron *Elpen (Ελπεν), Gr.*
Ambroxol (p.1550·3).
Mucolytic.

Ce-Limo *Viatris, Austria.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Ce-Limo plus 10 Vitamine *Viatris, Austria.*
Multivitamin preparation (p.1922·1).

Ce-Limo-Calcium *Viatris, Austria.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1).
Calcium and vitamin C deficiency.

Celin *GSK, Hong Kong†; GSK, India.*
Vitamin C (p.1983·3).
Adjunct in wounds and infections; scurvy; vitamin C supplement.

Celinax *Infabra, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Celiol *Sandoz, Austria.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Celip *Basics, Ger.*
⊗ Celiprolol hydrochloride (p.1242·2).
Hypertension.

Celipres *Ranbaxy, Pol.*
⊗ Celiprolol hydrochloride (p.1242·2).
Hypertension.

Celipro *Winthrop, Ger.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Celiprogamma *Worwag, Ger.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Celit *Fada, Arg.†.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Celius *Gerolymatos, Gr.*
Citalopram (p.385·3).
Depression.

Cellasene *Cinetic, Arg.*
Bearberry; melilotus; ginkgo biloba; bladderwrack; centella; fish oil; borage oil; soya lecithin; fatty acids (p.1922·1).
Antoxidant; cellulitis.

Cellavie *Ferrosan, Fin.†.*
d-Alpha tocoferil acetate (p.1992·3); ascorbic acid (p.1983·3).
Vitamin E and vitamin C deficiency.

Cellblastin *Cell Pharm, Ger.†.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

CellCept
Roche, Arg.; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Gr.; Roche, Hong Kong; Roche, Indon.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, USA; Roche, Venez.
Mycophenolate mofetil (p.1836·2).
Transplant rejection.

Roche, Austral.; Roche, Austria; Roche, Canad.; Roche, Ger.; Roche, Irl.; Roche, Port.; Roche, UK.
Mycophenolate mofetil (p.1836·2) or mycophenolate mofetil hydrochloride (p.1836·2).
Transplant rejection.

Roche, Hung.
Mycophenolate mofetil hydrochloride (p.1836·2).
Transplant rejection.

Cellcristin *Cell Pharm, Ger.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Celldolor *Cell Pharm, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Cellidrin *Hennig, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Cellidrine *Sanofi, Switz.*
Allopurinol (p.552·2).
Hyperuricaemia.

Cellmune *Cipla, India.*
Mycophenolate mofetil (p.1836·2).
Transplant rejection.

cellmustin *Cell Pharm, Ger.*
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Cellobexon *Agepha, Austria.*
Hymetellose (p.2143·3).
Formerly contained methylcellulose, thiamine hydrochloride, and vitamin C.
Constipation; obesity.

Celloid Compounds Magcal Plus *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); magnesium phosphate (p.1679·2); calcium phosphate (p.1676·2); dibasic potassium phosphate (p.1682·2); iron phosphate (p.1950·3).

Celloid Compounds Sodical Plus *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); calcium phosphate (p.1676·2); iron phosphate (p.1950·3).

Celloids CF 43 *Blackmores, Austral.*
Homoeopathic preparation.

Celloids CP 57 *Blackmores, Austral.*
Calcium phosphate (p.1676·2).

Celloids CS 36 *Blackmores, Austral.*
Calcium sulfate (p.2272·3).

Celloids IP 82 *Blackmores, Austral.*
Iron phosphate (p.1950·3).

Celloids MP 65 *Blackmores, Austral.*
Magnesium phosphate (p.1679·2).

Celloids PC 73 *Blackmores, Austral.*
Potassium chloride (p.1684·3).

Celloids PP 85 *Blackmores, Austral.*
Potassium phosphate (p.1682·2).

Celloids PS 29 *Blackmores, Austral.*
Potassium sulfate (p.1684·3).

Celloids S 79 *Blackmores, Austral.*
Silicon dioxide (p.2146·2).

Celloids SP 96 *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3).

Celloids SS 69 *Blackmores, Austral.*
Anhydrous sodium sulfate (p.1771·3).

Cellosorb
Note.This name is used for preparations of different composition.
Urgo, Fr.
Carmellose (p.2142·1); white soft paraffin (p.2031·2).
Burns; wounds.

Urgo, Ger.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Cellozina *Biofarma, Venez.*
Cefazolin (p.222·1).
Bacterial infections.

Cellskinlab C + AHA *Dispolab, Arg.*
Ascorbic acid (p.1983·3); glycolic acid (p.1598·1); lactic acid (p.2329·3).
Light-induced skin damage.

Cellskinlab C + E *Dispolab, Arg.*
Ascorbic acid (p.1983·3); alpha tocopherol (p.1992·2).
Light-induced skin damage.

Cellskinlab Hydragel B5 *Dispolab, Arg.*
Hyaluronic acid (p.2320·1); pantothenic acid (p.1959·3).
Dry skin disorders.

Cellskinlab Phyto Spot *Dispolab, Arg.*
Arbutin (p.1589·2); kojic acid (p.1603·3); thyme (p.2401·1); cucurbita (p.2290·2).
Skin pigmentation disorders.

Cellskinlab Serum 15 *Dispolab, Arg.*
Ascorbic acid (p.1983·3).
Light-induced skin damage.

Celltech Gold *K2 Pharmacare, Chile.*
Ginkgo biloba (p.2311·1); fucus vesiculosus (p.2384·2); grape (p.2316·3); melilot (p.2339·2); borage (p.2267·3); fish oils (p.1362·2).
Cellulite.

Celltop *Baxter, Belg.; Baxter Oncology, Fr.*
Etoposide (p.718·1).
Malignant neoplasms.

Cellufluid
Allergan, Cz.; Allergan, Port.; Allergan, Switz.
Carmellose sodium (p.2142·1).
Dry eyes.

Alvia (Αλβια), Gr.
Carmellose (p.2142·1).
Dry eyes.

Cellufresh
Allergan, Arg.†; Allergan, Austral.; Allergan, Braz.; Allergan, Ger.; Allergan, Ital.; Allergan, NZ†; Allergan, Philipp.; Allergan, S.Afr.; Allergan, Spain; Allergan, Thai.
Carmellose sodium (p.2142·1)(p.1622·2).
Dry eyes; eye irritation; lubricating solution for contact lens.

Cellugel *Alcon, Ger.; Alcon, Malaysia; Alcon, S.Afr.*
Hypromellose (p.2144·2).
Adjunct in ophthalmic surgery.

Cellular Formula *General Nutrition, Canad.*
Multivitamin and trace element preparation (p.1922·1).

Cellulin Retinale *INTES, Ital.*
Retina extract (p.2337·3).
Eye disorders.

Cellumed *Allergan, Ger.*
Carmellose sodium (p.2142·1).
Dry eyes.

Celluspan *Fischer, Israel.*
Cellulose derivatives (p.2143·1); electrolytes (p.1667·1).
Aid in gonioscopy.

Celluvisc *Allergan, Arg.†; Allergan, Austral.; Allergan, Austria; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Irl.; Allergan, Ital.; Allergan, Mex.†; Allergan, NZ†; Allergan, Neth.; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Allergan, UK; Allergan, USA.*
Carmellose sodium (p.2142·1).
Dry eyes; eye irritation.

Cellvital *Pharma Investi, Chile.*
Selenium yeast; zinc gluconate; copper gluconate; vitamins (p.1922·1).
Dietary supplement.

Celobar *Enila, Braz.†.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Celocid *Dexa, Indon.; Ferron, Indon.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Celocort *Legrand, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Celocurin *Ipex, Swed.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Celocurine *CSP, Fr.†.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Celoftal *Alcon, Ger.; Alcon, Venez.†.*
Hypromellose (p.2144·2).
Aid in eye surgery.

Celol *Pacific, NZ.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Celonfex *Indeco, Arg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Celontin *Erfa, Canad.; Parke, Davis, Israel†; Pfizer, Neth.; Parke, Davis, USA.*
Mesuximide (p.490·1).
Absence seizures.

Celox *Barrenne, Braz.*
Grape (p.2316·3).

Celoxin *Vitapan, Braz.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Celozol *Cellofarm, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Celsentri *Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, UK.*
Maraviroc (p.897·3).
HIV infection.

Celtect *Kyowa, Jpn.*
Oxatomide (p.587·1).

Celtium *Saval, Chile.*
Escitalopram oxalate (p.391·1).
Depression.

Celu-Atlas *Atlas, Arg.*
Centella (p.1592·3); ivy (p.2328·1); bladderwrack (p.2384·2); butcher's broom (p.2270·3); caffeine (p.1116·3).
Cellulitis.

Celucrem *ICN, Arg.†.*
Lactic acid (p.2329·3).
Skin disorders.

Celu-Ikx *Ikx, Arg.*
Siloxanetriol alginate; caffeine (p.1116·3); methylsilanol manuronate.
Cellulite.

Cel-U-Jec *Hauck, USA.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Celulase *Rider, Chile.*
Centella (p.1592·3).
Burns; fibrosis; lipodystrophy; ulcers; venous insufficiency; wounds.

Celulase Con Neomicina *Rider, Chile.*
Centella (p.1592·3); neomycin sulfate (p.305·1).
Burns; skin infections; ulcers; wounds.

Celulase Plus *Rider, Chile.*
Centella (p.1592·3).
Burns; fibrosis; lipodystrophy; ulcers; wounds.

Celulose *Grin, Mex.*
Hypromellose (p.2144·2).
Aid in ophthalmic procedures; dry eyes.

Celunaf *Grin, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Celupan *Lacer, Spain.*
Naltrexone hydrochloride (p.1455·2).
Alcoholism; opioid withdrawal.

Celuvital *Beta, Arg.†.*
Vitamin A palmitate (p.1973·1); collagen (p.2286·1).
Barrier cream.

Celvista *Lilly, Thai.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Celyth's *Natiris, Venez.*
Cynodon dactylon; bengal gram; centella (p.1592·3); taraxacum (p.2395·1).

Cemado *Francia, Ital.*
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cemaflavone *Bailleul, Fr.*
Citroflavonoids (p.2304·1); magnesium ascorbate (p.1679·1).
Haemorrhoids; venous insufficiency; visual disorders.

Cemalyt *Saros, Spain.*
⊗ Triamcinolone (p.1544·2); centella (p.1592·3).
Skin disorders.

Cemaquin *Cimex, Cz.†; Cimex, Hong Kong†; Cimex, Switz.*
Benzethonium chloride (p.1630·1); ascorbic acid (p.1983·3).
Mouth and throat infections.

Cemax *Biochimico, Braz.†.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cementin *DHA, Hong Kong; DHA, Singapore.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cemidin *Dexxon, Israel.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cemidon *IFET (ΙΦΕΤ), Gr.; Chiesi, Spain.*
Isoniazid (p.288·1).
Tuberculosis.

Cemidon B6 *Chiesi, Spain.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Cemina *Medix, Mex.†.*
Ascorbic acid (p.1983·3).
Vitamin supplement.

Cemirit *Bayer, Ital.*
Aspirin (p.20·3).
Fever; inflammation; influenza symptoms; pain.

Cemol *Pharmasant, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Cemol Cold *Pharmasant, Thai.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever.

Cenacert *Phoenix, Arg.†.*
Oxatomide (p.587·1).
Hypersensitivity reactions.

Cenafed *Century, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Cenafed Plus *Century, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Cenai *The Forty-Two, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disease; vestibular disorders.

Cena-K *Century, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Cenalfan *Sigma, Braz.†.*
Vitamins A, C, and E (p.1922·1).

Cenalfan Plus *Sigma, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Cenamin *Pharmasant, Thai.*
Multivitamin preparation with iron and iodine (p.1922·1).

Cenasic *Pharmasant, Thai.*
Paracetamol (p.108·1); orphenadrine citrate (p.812·1).
Muscle pain.

Cenat *Madaus, Spain.*
Ispaghula (p.1737·1).
Constipation; functional diarrhoeas.

Cenbufen *Pharmasant, Thai.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Cencamet *Pharmasant, Thai.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Cencanyl *Pharmasant, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Cencenag *Pharmasant, Thai.*
Diclofenac sodium (p.44·3).
Rheumatoid arthritis.

Cencold *Pharmasant, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever.

Cencopan *Pharmasant, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Cendalex *Aldril, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Cendalon *Teva Tuteur, Arg.*
⊗ Letrozole (p.740·2).

Cendexsone *Pharmasant, Thai.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Ceneo *Pensa, Spain.*
⊗ Hydrocortisone buteprate (p.1535·2).
Skin disorders.

Cenestin *Duramed, USA.*
Synthetic conjugated estrogens, A (p.2087·2).
Menopausal disorders.

Cenevit *Legrand, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cenilene *Schering-Plough, Port.†.*
Fluphenazine hydrochloride (p.998·1).

Cenlidac *Pharmasant, Thai.*
Sulindac (p.126·3).
Musculoskeletal, joint, and peri-articular disorders.

Cenogen Ultra *US Pharmaceutical, USA.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).

Cenogen-OB *US Pharmaceutical, USA†.*
Multivitamin and mineral preparation with iron (p.1922·1).

Cenolate *Hospira, USA.*
Sodium ascorbate (p.1984·1).
Scurvy; vitamin C deficiency.

Cenopec *Pharmasant, Thai.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Cenpadol *Pharmasant, Thai.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal pain and spasm.

Cenparkin *China Chem & Pharma, Thai.†.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Cenpidine *Pharmasant, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Centa Vite *Cypress, USA.*
Vitamin and mineral preparation (p.1922·1).

Centabel *Andromaco, Chile.*
Centella (p.1592·3).
Burns; ulcers; venous insufficiency; wounds.

Centabio *Sanbe, Indon.*
Neomycin sulfate (p.305·1); placenta extract (p.2337·3).
Burns; skin infections; ulcers; wounds.

Centagin *Pharmasant, Thai.*
Dipyrone (p.49·2).
Fever; pain.

Centany *Ortho Dermatological, USA.*
Mupirocin (p.302·3).
Bacterial skin infections.

Centapp *Pharmasant, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; nasal congestion.

Centaurea (Specie Composta) *Dynacren, Ital.†.*
Centaury (p.2279·1); taraxacum (p.2395·1); gentian (p.2310·3).
Gastrointestinal disorders; herbal tea.

Centelax *Catarinense, Braz.*
Centella (p.1592·3).
Vascular disorders.

Centella Asiatica Compuesta *Lafarmen, Arg.*
Centella (p.1592·3); nicotinamide (p.1957·3); selenium (p.1961·1).

Centella Asiatica Diates *Provefarma, Arg.*
Centella (p.1592·3); alpha tocopherol (p.1992·2).
Dietary supplement.

Centella Asiatica Vital *AM, Arg.*
Centella (p.1592·3); vitamin E (p.1992·2).
Dietary supplement.

Centella Complex
Note. This name is used for preparations of different composition.
Peter, Ital.
Tablets: Centella (p.1592·3); hamamelis (p.2318·2); aesculus (p.2248·2); pineapple; vitamin C (p.1983·3).
Circulatory disorders; nutritional supplement.

Peter, Ital.
Topical gel: Centella (p.1592·3); aesculus (p.2248·2); pineapple; hamamelis (p.2318·2); allantoin (p.1588·1).

Centella Incaico *Incaico, Arg.*
Centella (p.1592·3); green tea (p.2416·1); vitamin B (p.1979·1).

Centella Queen Complex
Note. This name is used for preparations of different composition.
Temis, Arg.
Cream: Centella (p.1592·3); marine algae; equisetum (p.2299·3).
Cellulitis.

Temis, Arg.
Tablets: Bladderwrack; vitamin E; centella; ginkgo biloba (p.1922·1).
Dietary supplement.

Centella Queen Reductora *Temis, Arg.*
Centella (p.1592·3); fibre (p.1712·3).
Slimming aid.

Centellacrom *Framingham, Arg.*
Centella (p.1592·3); chromium tripicolinate (p.1934·3).
Dietary supplement.

Centellase *Sanofi-Aventis, Ital.; Tai Guk, Singapore.*
Centella (p.1592·3).
Burns; scars; skin ulcers; venous insufficiency; wounds.

Centellase de Centella Queen *Temis, Arg.*
Centella (p.1592·3); bladderwrack (p.2384·2); ginkgo biloba (p.2311·1); vitamin E (p.1992·2).
Cellulitis.

Centellase Gel *Temis, Arg.*
Centella (p.1592·3); equisetum (p.2299·3); caffeine (p.1116·3); algae (p.2384·2).
Cellulitis.

Centella-Vit *Fontovit, Braz.*
Centella (p.1592·3).

Center-Al *Center, USA.*
Range of allergen extracts (p.2250·2).
Allergen immunotherapy.

Centeril H
Note. This name is used for preparations of different composition.
Errekappa, Ital.
Cream: Zinc oxide (p.1621·2); centella (p.1592·3); hamamelis (p.2318·2); aesculus (p.2248·2); peppermint (p.1761·2); menthol (p.2340·1).
Anorectal disorders.

Errekappa, Ital.
Topical solution: Centella (p.1592·3); hamamelis (p.2318·2); aesculus (p.2248·2).
Anorectal disorders.

Centiax *Errekappa, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Centica *Samjin, Singapore.*
Centella (p.1592·3).
Burns; scars; skin ulcers; wounds.

Centilux *Alcon Cusi, Spain.*
⊗ Methylthioninium chloride (p.1450·3); naphazoline hydrochloride (p.1565·2).
Eye disorders.

Centocort *Pharmasant, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Centrac *Pfizer, Gr.*
Prazepam (p.1019·3).
Anxiety disorders.

Centracetam *UCB, Port.†.*
Piracetam (p.368·2); vincamine (p.2414·1).

Centramin *Rosch & Handel, Austria.*
Glycine (p.1947·3); magnesium chloride (p.1679·1); calcium chloride (p.1675·2); potassium chloride (p.1684·3).
Pruritus; tetany.

Centravim *Terramedic, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Centravit *Pharmasant, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Centravita Expletus *Unipharm, Mex.*
Vitamin and mineral preparation (p.1922·1).

Centrax *Pfizer, Irl.*
Prazepam (p.1019·3).
Anxiety disorders.

Centrifal *Quimica y Farmacia, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Centromicina *Boehringer Ingelheim, Arg.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Centron *Torrent, India.*
⊗ Ormeloxifene (p.2123·1).
Oral contraceptive.

Centropain
Note. This name is used for preparations of different composition.
Pharmasant, Thai.
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal pain.

Pharmasant, Thai.
Gel: Menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Centrophene *Zydus, Fr.†.*
Trimetazidine hydrochloride (p.1419·2).
Now known as Trimetazidine Zydus.
Angina pectoris; vertigo; visual disorders.

Centrovite *Rugby, USA.*
A range of multivitamin and mineral preparations with iron and folic acid (p.1922·1).

Centrum
Note. This name is used for preparations of different composition.
Wyeth-Whitehall, Arg.; Wyeth Consumer, Austral.; Wyeth Lederle, Austria; Wyeth Consumer, Braz.; Wyeth Consumer, Canad.; Wyeth Consumer, Chile; Lederle, Cz.†; Wyeth Consumer, Hong Kong; Wyeth, Hung.†; Wyeth, Irl.; Lederle, Israel; Wyeth Consumer, Malaysia; Wyeth Consumer, Mex.; Wyeth, Philipp.; Wyeth Consumer, Port.†; Wyeth, Rus.; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.; Wyeth, Turk.; Wyeth Consumer, UK; Wyeth-Ayerst, USA; Wyeth, Venez.
Vitamin and mineral preparation (p.1922·1).

Polifarma, Ital.
Cytidine (p.2291·3); uridine (p.2407·3).
Mental function impairment.

Centural Gold *Goldshield, Singapore†.*
Multivitamin and mineral preparation (p.1922·1).

Centurion A–Z *Mission Pharmacal, USA†.*
Iron (p.1949·1); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Centyl *Leo, Denm.; Leo, Irl.; Leo, Norw.*
⊗ Bendroflumethiazide (p.1224·1).
Diabetes insipidus; eclampsia; hypertension; oedema; renal calcium stones.

Centyl K *Leo, Irl.; Leo, Swed.; Leo, UK.*
⊗ Bendroflumethiazide (p.1224·1); potassium chloride (p.1684·3).
Hypertension; oedema; renal calculi.

Centyl med Kaliumklorid *Leo, Denm.; Leo, Norw.*
⊗ Bendroflumethiazide (p.1224·1); potassium chloride (p.1684·3).
Diabetes insipidus; hypertension; oedema; renal calcium stones.

Ceolat *Solvay, Cz.†; Riemser, Ger.; Solvay, Gr.†; Vemedia, Neth.†; Solvay, Norw.†.*
Dimeticone (p.1770·2).
Adjunct in gastrointestinal investigations; flatulence.

Ceolat Compositum *Lannacher, Austria.*
Dimeticone (p.2032·1); metoclopramide (p.1747·3).
Gastrointestinal disorders.

Ceo-Two *Beutlich, USA.*
Sodium bicarbonate (p.1673·2); potassium acid tartrate (p.1764·1).
Constipation.

Ceoxil *Magis, Ital.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Ceoxx *MSD, Austria†; MSD, Chile†; MSD, Irl.†; MSD, Port.†; MSD, Spain†.*
Rofecoxib (p.121·1).
Osteoarthritis; pain; rheumatoid arthritis.

Cepa Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Cepacaina *Sanofi-Aventis, Braz.; Aventis, Mex.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacaine
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.; Roche, NZ.
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Adcock Ingram, S.Afr.
Lozenges: Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Adcock Ingram, S.Afr.†.
Mouthwash: Benzocaine (p.1854·1); cinchocaine hydrochloride (p.1857·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacilina *Reig Jofre, Spain.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections; rheumatic fever.

Cepacilina 633 *Reig Jofre, Spain.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2); benzathine benzylpenicillin (p.212·1).
Bacterial infections; rheumatic fever.

Cepacol
Note. This name is used for preparations of different composition.
Combe, Canad.; Aventis, Hong Kong; Roche, NZ; Sanofi-Aventis, Singapore; Aventis, Thai.; Sanofi-Aventis, Venez.
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders; oral hygiene.

Adcock Ingram, S.Afr.
Linctus: Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); sodium citrate (p.1673·3); cetylpyridinium chloride (p.1635·1).
Coughs.

Adcock Ingram, S.Afr.
Lozenges; mouthwash: Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacol Anaesthetic *Bayer Consumer, Austral.; Roche, NZ.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacol Anesthetic *JB Williams, USA.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

Cepacol Antibacterial
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.
Eucalyptus and Menthol: Cetylpyridinium chloride (p.1635·1); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Mouth and throat disorders.

Roche Consumer, Austral.
Honey and Lemon; Orange Citrus: Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacol Antiseptic Throat Lozenges *Bayer Consumer, Austral.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Cepacol Cough Discs
Note. This name is used for preparations of different composition.
Roche, NZ.
Dextromethorphan hydrobromide (p.1555·2); cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1); menthol (p.2340·1).
Coughs; mouth and throat disorders.

Adcock Ingram, S.Afr.
Dextromethorphan hydrobromide (p.1555·2); cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Coughs; sore throat.

Cepacol Cough & Sore Throat *Bayer Consumer, Austral.*
Dextromethorphan hydrobromide (p.1555·2); cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1); menthol (p.2340·1).
Coughs; sore throat.

Cepacol Extra Strength *Combe, Canad.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Formerly known as Cepacol Citrus.
Mouth and throat disorders.

Cepacol with Fluoride *Combe, Canad.*
Cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).

Cepacol Maximum Strength Sore Throat
Note. This name is used for preparations of different composition.
JB Williams, USA.
Lozenges: Benzocaine (p.1854·1); menthol (p.2340·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

JB Williams, USA.
Throat spray: Dyclonine hydrochloride (p.1861·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

Cepacol Menta *Sanofi-Aventis, Braz.*
Cetylpyridinium chloride (p.1635·1); menthol (p.2340·1).
Oral hygiene.

Cepacol Mint *Bayer Consumer, Austral.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders; oral hygiene.

Cepacol Mouthwash *JB Williams, USA.*
Cetylpyridinium chloride (p.1635·1).
Minor mouth or throat disorders.

Cepacol Regular *Bayer Consumer, Austral.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders; oral hygiene.

Cepacol Regular Strength *JB Williams, USA.*
Menthol (p.2340·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

Cepacol Sore Throat Post Nasal Drip *Combe, USA.*
Menthol (p.2340·1).

Cepacol Spray *Combe, Canad.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Cepacol Throat *JB Williams, USA.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Cepacol Ultra Sore Throat Plus Cough *Combe, USA.*
Benzocaine (p.1854·1); dextromethorphan hydrobromide (p.1555·2).
Cough; sore throat.

Cepacol Viractin *GSK Consumer, Canad.†.*
Tetracaine hydrochloride (p.1871·3).

Cepacol Viractin Cold Sore Treatment *JB Williams, USA.*
Tetracaine (p.1871·2) or tetracaine hydrochloride (p.1871·3).
Topical anaesthesia.

Cepacol-BE *Sanofi-Aventis, Venez.*
Cetylpyridinium chloride (p.1635·1); lidocaine (p.1862·3).
Mouth and throat disorders.

Cepadont *Agis, Israel.*
Cetylpyridinium chloride (p.1635·1); chlorobutanol (p.1639·2).
Mouth disinfection.

Cepal
Note. This name is used for preparations of different composition.
Demo, Gr.†.
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Pharmasant, Thai.
Fenbufen (p.54·3).
Musculoskeletal and joint disorders.

Cepan *Unia, Pol.*
Allantoin (p.1588·1); onion (p.2356·3); chamomile (p.2279·3); heparin sodium (p.1301·2).
Keloids; scars.

Ceparidin *Centrum, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Cepasmel *Gemi, Pol.*
Onion (p.2356·3); garlic (p.2309·2).
Respiratory-tract disorders.

Cepastat
Note. This name is used for preparations of different composition.
Combe, Canad.; SmithKline Beecham Consumer, USA.
Phenol (p.1656·1); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Mouth and throat disorders; sore throat.

Aventis, Hong Kong; Sanofi-Aventis, Singapore.
Phenol (p.1656·1); menthol (p.2340·1).
Mouth and throat disorders; sore throat.

Cepastat Cherry *SmithKline Beecham Consumer, USA.*
Phenol (p.1656·1); menthol (p.2340·1).
Sore throat.

Cepastil *Gemi, Pol.*
Onion (p.2356·3); garlic (p.2309·2).
Respiratory-tract disorders.

Cepazine *Novaxo, Fr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cepexin *GSK, Austria.*
Cefalexin (p.218·2).
Bacterial infections.

Cepezet *Mersifarma, Indon.*
Chlorpromazine hydrochloride (p.969·2).
Behaviour disorders; psychoses.

Cephadex *Cipla, India.*
Cefalexin (p.218·2).
Bacterial infections.

Cephadex LB *Cipla, India.*
Cefalexin (p.218·2); lactobacillus (p.2372·3).
Bacterial infections.

Cephadol *Shinyaku, Hong Kong; Shinyaku, Jpn; Shinyaku, Malaysia; Shinyaku, Philipp.; Shinyaku, Singapore†; Shinyaku, Thai.*
Difenidol hydrochloride (p.1723·2).
Postoperative vomiting; vertigo; vestibular disorders.

Cephaflox *Guardian, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Cephalen *Beximco, Singapore.*
Cefalexin (p.218·2).
Bacterial infections.

Cephalex *CT, Ger.*
Cefalexin (p.218·2).
Bacterial infections.

Cephalexyl *Bangkok Lab & Cosmetic, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Cephalgan *UPSA, Cz.†; BMS, Fr.†.*
Carbasalate calcium (p.33·3); metoclopramide hydrochloride (p.1747·3).
Migraine.

Cephalite *Eulite, Neth.*
Homoeopathic preparation.

Cephalobene *Ratiopharm, Austria.*
Cefalexin (p.218·2).
Bacterial infections.

Cephalodoc *Docpharm, Ger.†.*
Cefaclor (p.217·2).
Bacterial infections.

Cephaloplant *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Cephanmycin *Yung Shin, Singapore.*
Cefalexin (p.218·2).
Bacterial infections.

Cephanol *Riva, Canad.*
Paracetamol (p.108·1).

Cephation *Meiji, Indon.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Cephaxin *Biochem, India.*
Cefalexin (p.218·2).
Bacterial infections.

Cephaxon *Toprak, Turk.*
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Cephin *General Drugs, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Cephoral *Merck, Ger.; Fujisawa, Switz.*
Cefixime (p.224·3).
Bacterial infections.

Cephos *CT, Ital.*
Cefadroxil (p.218·1).
Bacterial infections.

Cephulac *Hoechst Marion Roussel, USA.*
Lactulose (p.1738·2).
Hepatic encephalopathy.

Cephyl
Note. This name is used for preparations of different composition.
Boiron, Cz.†; Boiron, Port.
Aspirin (p.20·3); ethenzamide (p.51·3); caffeine (p.1116·3); belladonna; iridis versicoloris; strychni; spigeliae; gelsemii.
Fever; pain.

Boiron, Fr.
Aspirin (p.20·3); caffeine (p.1116·3); belladonna; iris versicolor; nux vomica; spigelia; gelsemium.
Formerly contained aspirin, ethenzamide, caffeine hydrate, belladonna, iris versicolor, nux vomica, spigelia, and gelsemium.
Fever; pain.

Cepifran *Juste, Spain†.*
Ceftibuten (p.235·3).
Bacterial infections.

Cepim *Polifarma, Ital.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cepimax *BMS, Philipp.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cepimex *BMS, Ital.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Cepin *Roemmers Medihe, Venez.*
Vitamin C (p.1983·3); hyaluronic acid (p.2320·1); dexpanthenol (p.2362·1).
Antoxidant.

Ceplac *Manx, UK.*
Erythrosine (p.1471·3).
Disclosing agent for plaque.

Ceplon *Rowe-Fleming, Venez.†.*
Captopril (p.1239·2).
Hypertension.

Cepobrom *Maver, Mex.*
Cefalexin (p.218·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Cepodem *Stancare, India; Ranbaxy, S.Afr.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Ceporacin *Bioniche, Canad.†.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Ceporex *GSK, Belg.†; GSK, Hong Kong; GSK, Irl.†; GSK, Ital.; GSK, Malaysia†; GSK, Mex.; GSK, Philipp.; Glaxo Wellcome, Port.; GSK, Singapore†; GSK, Thai.†; Galen, UK.*
Cefalexin (p.218·2).
Bacterial infections.

Ceporexin *Investi, Arg.; GSK, Braz.†; Aventis, Ger.†; GSK, Ger.†.*
Cefalexin (p.218·2).
Bacterial infections.

Ceporexine *GSK, Fr.*
Cefalexin (p.218·2).
Bacterial infections.

Ceposil *Pisa, Mex.*
Potassium acetate (p.1684·2).

Cepotec *Tecnofarma, Mex.*
Cefadroxil (p.218·1).
Bacterial infections.

Cepramine *Pharmasant, Thai.*
Vitamin and mineral preparation (p.1922·1).

Ceprandal *Sigma-Tau, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ceprater *Richmond, Arg.*
Cyproterone (p.2089·2).

Ceprazol *Laboratorios Chile, Chile.*
Albendazole (p.139·2).
Worm infections.

Ceprimax *Fides Ecopharma, Spain†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ceprin *Dolisos, Canad.*
Homoeopathic preparation.

Cepriser *Serral, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Ceprof *Epicaris, Arg.*
Cefprozil (p.232·2).
Bacterial infections.

Ceprofen *Neo Quimica, Braz.*
Ketoprofen (p.73·1).

Ceprotin *Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.*
Protein C (p.1077·3).
Protein C deficiency; thromboembolic disorders.

Ceptaz *GSK, Canad.†; Glaxo Wellcome, USA.*
Ceftazidime (p.234·1).
Bacterial infections.

Ceptik *Interbat, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Cepton *LPC, UK.*
Chlorhexidine gluconate (p.1635·3).
Acne.

Cequinyl *GSK Sante, Fr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); ascorbic acid (p.1983·3).
Fever; nasal congestion; pain.

Ceractiv *Andromaco, Chile.*
⊗ Pemoline (p.2161·2).
Attention-deficit hyperactivity disorder.

Ceradolan
Takeda, Indon.; Takeda, Philipp.
Cefotiam hexetil hydrochloride (p.230·1) or cefotiam hydrochloride (p.230·1).
Bacterial infections.

Takeda, Singapore; Takeda, Thai.
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

Ceraklin *Innoderm, Philipp.*
Ceramide.
Dry skin; soap substitute.

Ceralan *Orion, Fin.*
Emollient.
Dry skin.

Ceralip *Roche-Posay, Arg.†; Roche-Posay, Braz.; Roche-Posay, Fr.; Roche-Posay, Irl.*
Emollient.
Dry lips; mucous membrane damage.

Ceramil *Pharmanel, Gr.*
Cefotaxime (p.229·1).
Bacterial infections.

Ceranid *Hexal, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal hypersecretion; peptic ulcer.

Cerasorb *Curasan, Ger.*
Calcium phosphate (p.1676·2).
Artificial bone and dental enamel.

Cerat Inalterable *Roche-Posay, Fr.*
Titanium dioxide (p.1617·3); aluminium silicate (p.1707·3); white beeswax (p.2028·1); light liquid paraffin (p.2031·1).
Barrier ointment.

Ceratio *Ratiopharm, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cerax
Note. This name is used for preparations of different composition.
Millet-Franklin, Arg.
Benzocaine (p.1854·1).
Removal of ear wax.

Pharmasant, Thai.
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions; sedative.

Cerazet *Organon, Spain.*
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Cerazette *Organon, Arg.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hung.; Organon, Indon.; Organon, Israel; Organon, Ital.; Organon, Mex.; Organon, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Organon, Swed.; Organon, Switz.; Organon, UK; Organon, Venez.*
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Cerbon *Confar, Port.*
Pyritinol hydrochloride (p.369·1).
Cerebrovascular disorders; mental function disorders.

Cerclerol *Beta, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Cere *Kolassa, Austria.*
Ornithine aspartate (p.1959·2).
Hepatic encephalopathy.

Cerebokan *Austroplant, Austria.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Cerebral-Do *Grasler, Ger.*
Homoeopathic preparation.

Cerebrex *Luper, Braz.†.*
Vitamin B substances; glutamic acid; calcium glycerophosphate; calcium phosphate (p.1922·1).
Nutritional supplement.

Cerebrino *Mandri, Spain.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Influenza symptoms; pain.

Cerebroad *Chinta, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; peripheral vascular disorders; vestibular disorders.

Cerebrofort AA+DHA *Kalbe, Indon.*
Docosahexaenoic acid; arachidonic acid; eicosapentaenoic acid; glutamic acid; vitamins (p.1922·1).
Nutritional supplement.

Cerebrofort Gold *Kalbe, Indon.*
Arachidonic acid; docosahexaenoic acid; eicosapentaenoic acid; glutamic acid; biotin; lysine monohydrochloride; vitamins (p.1922·1).
Nutritional supplement.

Cerebroforte *Azupharma, Ger.†.*
Piracetam (p.368·2).
Mental function disorders.

Cerebrol *Actipharm, Switz.†.*
Codeine phosphate (p.37·2); caffeine (p.1116·3); paracetamol (p.108·1); propyphenazone (p.119·3).
Pain.

Cerebrol sans codeine *Actipharm, Switz.†.*
Caffeine (p.1116·3); paracetamol (p.108·1).
Pain.

Cerebrolysin *Ebewe, Austria; Ebewe, Cz.; Ebewe, Ger.; Ebewe, Hong Kong; Ebewe, Rus.; Ebewe, Thai.*
Porcine brain extract (p.2337·3).
Alzheimer's disease; brain injury; cerebrovascular disorders; dementia; depression; epilepsy; mental function impairment; nervous system disorders; parkinsonism; stroke.

Cerebrolysine *Bio Portugal, Port.*
Porcine brain extract (p.2337·3).
Brain injury; dementia.

Cerebropan *Kedrion, Ital.†.*
Piracetam (p.368·2).
Mental function impairment.

Cerebrotonin *Ebewe, Austria.*
Porcine brain protein (p.2337·3).
Cerebral disorders.

Cerebrovit Active *Kalbe, Indon.*
Ginseng (p.2312·1); guaranine; levoglutamic acid; folic acid; vitamins; zinc (p.1922·1).
Tonic.

Cerebroxine *Therabel, Belg.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Cerebryl *Kwizda, Austria; Kwizda, Cz.†; Kwizda, Hung.*
Piracetam (p.368·2).
Cerebral disorders; mental function disorders.

Cerebyx *Erfa, Canad.; Parke, Davis, USA.*
Fosphenytoin sodium (p.481·3).
Epilepsy; seizures during neurosurgery.

Ceredase *Genzyme, Israel†; Genzyme, Jpn†; Genzyme, USA.*
Alglucerase (p.2249·2).
Gaucher disease.

Ceredist *Tanabe, Jpn.*
Taltirelin (p.2394·3).
Spinocerebellar degeneration.

Cerefolin *Pan American, USA.*
Calcium mefolinate (p.1932·2); riboflavin (p.1977·2); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Hyperhomocysteinaemia.

Ceregen *Diba, Mex.; Vargas, Venez.†.*
Multivitamin and mineral preparation (p.1922·1).

Cereginkgo *Pfluger, Ger.†.*
Homoeopathic preparation.

Ceregumil *Azevedos, Port.†.*
Preparation for enteral nutrition (p.1922·1).

Cerekinon *Tanabe, Hong Kong; Tanabe, Jpn; Tanabe, Malaysia; Tanabe, Singapore; Tanabe, Thai.*
Trimebutine maleate (p.2404·3).
Gastritis; irritable bowel syndrome.

Cerelac *Nestle, Braz.; Nestle, Port.†.*
Preparation for enteral nutrition (p.1922·1).
Gluten intolerance.

Cerella *Asche, Ger.†.*
Estradiol (p.2097·2).
Menopausal disorders.

Cereloid *Sun, India.*
Codergocrine mesilate (p.363·3).
Dementia.

Cereluc *Beta, Arg.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Ceremin
Note. This name is used for preparations of different composition.
Austroplant, Austria.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Polipharm, Thai.
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Ceremir *Rottapharm, Spain.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Cereneu *Parke, Davis, Spain.*
Fosphenytoin sodium (p.481·3).
Epilepsy.

Cereon *Biogal, Israel†.*
Ascorbic acid (p.1983·3).
Scurvy.

Cerepar *Mepha, Switz.*
Cinnarizine (p.573·1).
Vertigo; vestibular disorders.

Cerepar N *Merckle, Ger.*
Piracetam (p.368·2).
Mental function impairment.

Cerepro *Veropharm, Rus.*
Choline alfoscerate (p.363·3).
Cerebrovascular disorders; mental function disorders.

Cereron *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; motion sickness; peripheral vascular disorders; vestibular disorders.

Cerestabon *Seber, Port.*
Idebenone (p.367·1).
Cerebrovascular disorders; mental function disorders.

Cerestar *Ranbaxy, Malaysia†.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Tonic.

Ceretec *Amersham, Austral.; Amersham, Austria; GE, Cz.; Amersham, Ital.; GE Healthcare, Neth.; GE, Port.; Amersham, Spain; Nycomed Amersham, UK.*
Technetium-99m exametazime (p.2055·3).
Cerebral blood flow scintigraphy; leucocyte labelling.

Cereton *Meprofarm, Indon.*
Ginkgo biloba (p.2311·1); d-methyl amino ethanol; pine bark; nicotinamide (p.1957·3).
Cerebral and peripheral vascular disorders.

Cerex *Hexal, Cz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cerezyme *Genzyme, Austral.; Genzyme, Austria; Genzyme, Belg.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Genzyme, Israel; Genzyme, Ital.; Genzyme, Jpn; Medra, NZ; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Pharmaplan, S.Afr.; Genzyme, Spain; Genzyme, Swed.; Genzyme, Switz.; Genzyme, UK; Genzyme, USA.*
Imiglucerase (p.2249·3).
Gaucher disease.

Cergem *Organon, Ger.*
Gemeprost (p.2010·2).
Cervical dilatation.

Cergodun *Duncan, Arg.; Duncan, Hong Kong.*
Nicergoline (p.2352·1).
Cerebral and peripheral circulatory disorders.

Ceriax *Farmoz, Port.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ceridal *Stiefel, Fin.*
Emollient.

Cerina *Wyeth, Switz.†.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Cerini *Sanbe, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Ceri-Nutrina *Prospa, Port.†.*
Preparation for enteral nutrition (p.1922·1).

Ceris *Madaus, Fr.*
Trospium chloride (p.2198·3).
Bladder instability.

Ceritec *YSP, Malaysia.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; rhinitis; urticaria.

Cerivikehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Cermox *Rontag, Arg.*
Ciclosporin (p.1822·2).
Transplant rejection.

Cernevit *Baxter Immuno, Arg.; Baxter, Austral.†; Baxter, Austria; Clintec, Belg.; Baxter, Cz.; Clintec, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Ital.; Baxter, NZ; Clintec, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, USA.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Cernilton *Temis, Arg.; Strathmann, Ger.; Fuso, Jpn.*
Pollen (Cernitin T-60) (p.2370·2).
Benign prostatic hyperplasia; prostatitis.

Cerofene *Medicus, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cerofor *Schering-Plough, Venez.†.*
Lysine hydrochloride; vitamin B substances (p.1922·1).
Dietary supplement.

Ceron *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Rhinitis.

Ceron-DM *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cough; upper respiratory-tract symptoms.

Ceropid *Novell, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cerose DM *Wyeth-Ayerst, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Coughs and cold symptoms.

Cerosel *Biochefa, Pol.*
Selenium yeast (p.1961·1).
Selenium deficiency.

Cerosporin GS *Medac, Arg.†.*
Phenazone (p.116·1); neomycin sulfate (p.305·1); cetrimide (p.1634·1).
Ear wax removal.

Cerosteril *Bouty, Ital.*
Benzalkonium chloride (p.1629·1); quaternium-14; allantoin (p.1588·1).
Disinfection and cleansing of wounds and burns.

Cerotor *Torrex Chiesi, Cz.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Cerotto Bertelli Arnikos *Kelemata, Ital.*
Capsicum oleoresin (p.2276·2).
Musculoskeletal disorders.

Cerovite *Rugby, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Cerox *Bouty, Ital.†.*
Benzalkonium chloride (p.1629·1); allantoin (p.1588·1); quaternium-14.
Skin, wound, and burn disinfection.

Ceroxim *Ranbaxy, Hung.; Ranbaxy, Pol.; Ranbaxy, S.Afr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Ceroxmed Tex *Bouty, Ital.*
Zinc oxide (p.1621·2).
Medicated dressing.

Cerozon *Ethica, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Cerson *Riemser, Ger.*
⊗ Flumetasone pivalate (p.1531·1).
Skin disorders.

Certagen
Note. This name is used for preparations of different composition.
Goldline, USA.
Oral liquid: Multivitamin and mineral preparation (p.1922·1).
Goldline, USA.
Tablets: Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Certagen Senior *Goldline, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Certalac *Celltech, Belg.†.*
Lactulose (p.1738·2).
Constipation.

Certa-Vite *Major, USA†.*
Multivitamin and mineral preparation (p.1922·1).

Certican *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Venez.*
Everolimus (p.1833·3).
Transplant rejection.

Certified Decongestant *Prodemdis, Canad.*
⊗ Xylometazoline hydrochloride (p.1575·1).

Certified Ice *Prodemdis, Canad.*
Menthol (p.2340·1).

Certified Nasal *Prodemdis, Canad.*
Sodium chloride (p.1686·1).

Certomycin *Aesca, Austria; Essex, Ger.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Certonal *Riemser, Ger.†.*
Moxaverine hydrochloride (p.2347·3).
Circulatory disorders.

Certorun *Faran, Gr.*
Sertraline (p.422·1).
Depression.

Certuss *Prodotti, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Ceru Spray *Ghimas, Ital.*
Chamomile (p.2279·3).
Aural hygiene.

Cerubidin *Aventis, Denm.; Sanofi-Aventis, Irl.; Aventis, Norw.; Aventis, S.Afr.†; Aventis, Swed.†.*
Daunorubicin hydrochloride (p.709·1).
Acute leukaemias.

Cerubidine *Sanofi-Aventis, Belg.; Erfa, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.†; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Aventis, Israel; Aventis, Neth.; Aventis, Switz.; Bedford, USA.*
Daunorubicin hydrochloride (p.709·1).
Malignant neoplasms.

Cerucal *AWD, Cz.; Temmler, Ger.; AWD, Hung.; AWD, Rus.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; gastrointestinal motility disorders; nausea and vomiting.

Cerulisina *Bouty, Ital.*
Xylene (p.2027·3).
Ear wax removal.

Cerulyse *Chauvin, Fr.*
Xylene (p.2027·3).
Ear wax removal.

Cerulyx *Chauvin, Belg.*
Xylene (p.2027·3).
Ear wax removal.

Cerumenex *Purdue, Canad.; Noristan, S.Afr.†; Mundipharma, Switz.; Purdue Frederick, USA†.*
Trolamine polypeptide oleate-condensate (p.2405·1).
Ear wax removal.

Cerumenex N *Mundipharma, Ger.*
Trolamine polypeptide oleate-condensate (p.2405·1).
Ear wax removal.

Cerumenol
Note. This name is used for preparations of different composition.
McNeil, Fr.
Polysorbate 80 (p.1919·2).
Ear wax removal.
Desma, Spain.
Potassium hydroxide (p.2371·3).
Ear wax removal.
Interdelta, Switz.
Paradichlorobenzene (p.2363·1); chlorobutanol hemihydrate (p.1639·2); turpentine oil (p.2406·3); orthodichlorobenzene (p.2358·3); methoxybutyl acetate.
Ear wax removal.

Cerumex *Cassara, Arg.*
Docusate sodium (p.1725·1).
Ear wax removal.

Cerumin *Alcon, Braz.*
Hydroxyquinoline borate (p.2323·2); trolamine (p.2405·1).
Ear wax removal.

Cerumol
Note. This name is used for preparations of different composition.
Culver, Austral.
Paradichlorobenzene (p.2363·1); chlorobutanol (p.1639·2); orthodichlorobenzene (p.2358·3); arachis oil (p.2259·1).
Ear wax removal.
Paladin, Canad.
Paradichlorobenzene (p.2363·1); chlorobutanol (p.1639·2); turpentine oil (p.2406·3).
Ear wax removal.
Laboratories for Applied Biology, Irl.; Tamar, Israel; Pharmafrica, S.Afr.; Laboratories for Applied Biology, Singapore; Laboratories for Applied Biology, UK.
Paradichlorobenzene (p.2363·1); chlorobutanol (p.1639·2); arachis oil (p.2259·1).
The name Cerumenol has also been used for this preparation in the UK.
Ear wax removal.
Laboratories for Applied Biology, Malaysia.
Paradichlorobenzene (p.2363·1); chlorobutanol (p.1639·2).
Ear wax removal.

Ceruspray *Chauvin, Fr.*
Polysorbate 80 (p.1919·2); sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1).
Ear irrigation for wax removal.

Cerutil *Alpharma-Isis, Ger.†.*
⊗ Meclofenoxate hydrochloride (p.2338·1).
Cerebrovascular disorders; mental function impairment.

Cerutin *Polfarmex, Pol.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Vitamin C deficiency.

Ceruxim *Antor, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cervagem *Aventis, Austral.; Aventis, Denm.; Aventis, Fin.†; Aventis, Hong Kong†; Sanofi-Aventis, Malaysia; Aventis, NZ; Aventis, Norw.†; Sanofi-Aventis, Singapore; Aventis, Swed.*
Gemeprost (p.2010·2).
Cervical dilatation; termination of pregnancy.

Cervageme *Sanofi-Aventis, Fr.*
Gemeprost (p.2010·2).
Cervical dilatation prior to uterine procedures; termination of pregnancy.

Cervarix *GSK, Cz.; GSK, UK.*
A human papillomavirus vaccine (types 16, 18) (p.2217·3).
Active immunisation.

Cervep *Menarini, Arg.*
Heparin sodium (p.1301·2).
Soft-tissue injury; thrombophlebitis.

Cervicum *Pharmasant, Thai.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cervidil
Note. This name is used for preparations of different composition.
CSL, Austral.; Ferring, Canad.; CSL, NZ; Forest Pharmaceuticals, USA.
Dinoprostone (p.2007·1).
Labour induction.
Serono, Ital.
Gemeprost (p.2010·2).
Cervical dilatation.

Cervilan *Aventis, Mex.*
Lomifylline (p.2334·3); dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders.

Cervilane *Aventis, Arg.; Sanofi-Aventis, Chile; Roussel, Port.†.*
Lomifylline (p.2334·3); dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders; vestibular disorders.

Cervin *Pasteur, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cervinca *Basi, Port.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Cerviprime *AstraZeneca, India.*
Dinoprostone (p.2007·1).
Cervical dilatation.

Cervitec *DAB, Swed.†.*
Chlorhexidine acetate (p.1635·2).
Dental hygiene.

Cervoxan *Almirall, Fr.; Decomed, Port.; Mabo, Spain.*
Vinburnine (p.2414·1).
Cerebrovascular disorders; mental function impairment; vascular eye disorders.

Cervusen *Hamilton, Hong Kong.*
Deer antler cartilage (p.2277·3); ginseng (p.2312·1); deer ligament.
Osteoarthritis; rheumatoid arthritis.

Cerylana *Intra, Venez.*
Diphenhydramine hydrochloride (p.577·2); wild lettuce (p.2415·2); cocillana (p.1554·3); wild cherry (p.2415·2).
Cough.

Cerzine *Mepha, Switz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

CES *Valeant, Canad.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis; prostatic cancer.

Cesamet *Valeant, Arg.; Valeant, Canad.; Lilly, Irl.†; Valeant, USA.*
⊗ Nabilone (p.1750·3).
Nausea and vomiting associated with cancer chemotherapy.

Cesbron *Sanofi Synthelabo, Port.*
⊗ Clenbuterol (p.1120·1).

Cesia *Prasco, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic combined oral contraceptive.

Cesol *Merck, Chile; Merck, Ger.; Merck, Mex.*
Praziquantel (p.153·3).
Worm infections.

Cesoline *Pharmasant, Thai.*
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension.

Cesplon *Esteve, Spain.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Cesplon Plus *Esteve, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); captopril (p.1239·2).
Hypertension.

Cesradyston *Cesra, Cz.†; Cesra, Ger.*
St John's wort (p.422·3).
Depression; nervous disorders.

Cesrasanol *Cesra, Ger.†.*
Chamomile; hamamelis; calendula; arnica; achillea; centaury.
Inflammation; spasms.

Cessagripe *Neckerman, Braz.†.*
Nux vomica (p.2355·3).

Cessatosse *Regius, Braz.†.*
Sodium dibunate (p.1573·1); sulfogaiacol (p.1573·2); belladonna (p.2263·3); sodium benzoate (p.1630·2).
Coughs.

Cestop *Drag, Chile†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cestop B *Drag, Chile†.*
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1).
Infected skin disorders.

Cestox *Merck, Braz.; Merck, Venez.*
Praziquantel (p.153·3).
Worm infections.

Cet-10 *Biosis, Philipp.; Taiwan Biotech, Philipp.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cet eco *Ecosol, Switz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Ceta *C & M, USA.*
Skin cleanser.

Ceta Plus *Seatrace, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Cetabon *Great Eastern, Thai.; Therapharma, Thai.*
⊗ Stanozolol (p.2129·1); vitamin B substances (p.1922·1).
Anabolic.

Cetabrium *Soho, Indon.*
Chlordiazepoxide hydrochloride (p.968·2).
Agitation; anxiety; delirium tremens.

Cetabutol *Soho, Indon.*
D-Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Cetacaine *Cetylite, USA.*
Benzocaine (p.1854·1); butyl aminobenzoate (p.1857·1); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Cetacillin *Soho, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Cetacol *Soho, Indon.*
Nicotinyl alcohol tartrate (p.1349·3).
Peripheral vascular disorders.

Cetacort *Healthpoint, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cetacycline-P *Soho, Indon.*
Tetracycline phosphate complex (p.347·2).
Bacterial infections.

Cetadexon *Soho, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Cetadop *Ethica, Indon.*
Dopamine hydrochloride (p.1273·2).
Cardiogenic shock.

Cetafloxo *Soho, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cetaflu-forte *Atabay, Turk.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Cetafrin *Luper, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Cetaklenz *Geritrex, USA.*
Glycerol (p.2314·2); sodium laurilsulfate (p.2138·3).
Soap-free skin cleanser.

Cetal *Pfizer, Austria†; Pfizer, Switz.†.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Cetalerg *AWD, Ger.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

CetAlergin *ICN, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetalgin *Soho, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Cetalgin-T *Soho, Indon.*
Dipyrone (p.49·2); vitamin B ; vitamin B ; vitamin B (p.1922·1); caffeine (p.1116·3).
Pain.

Cetallerg *Ecosol, Switz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetalmic *Soho, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Cetam *Yung Shin, Singapore†.*
Piracetam (p.368·2).
Mental function disorders.

Cetamid *ACME, Philipp.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma; heart failure; oedema.

Cetamide *Alcon, Canad.; Alcon, USA.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Cetamine *Wolfs, Belg.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cetampril *Labesfal, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Cetan
Note.This name is used for preparations of different composition.
HPP, Hong Kong†.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Pharmasant, Thai.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Cetanorm *Norma, UK.*
Benzalkonium chloride (p.1629·1); aldioxa (p.1587·2); chlorobutanol (p.1639·2); cetrimide (p.1634·1).
Nappy rash; wounds.

Cetaphil *Galderma, Austral.; Galderma, Braz.; Galderma, Canad.†; Galderma, Chile; Galderma, Fr.; Galderma, Hong Kong; Galderma, India; Galderma, Malaysia; Galderma, Mex.; Galderma, NZ; Galderma, Philipp.; Galderma, Port.†; Galderma, Singapore; Galderma, Spain†; Galderma, Thai.; Galderma, UK; Galderma, USA.*
Soap substitute.

Cetaphil Antibacterial *Galderma, Mex.*
Soap substitute with triclosan (p.1665·2).
Skin disorders.

Cetaphil Daily Facial *Galderma, Canad.*
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3).
Sunscreen.

Cetapred *Alcon, Mex.; Alcon, Philipp.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Bacterial eye infections with inflammation.

Cetapril *Dainippon, Jpn.*
Alacepril (p.1206·3).
Hypertension.

Cetapyrin *Soho, Indon.*
Phenylbutazone (p.117·1); propyphenazone (p.119·3).
Musculoskeletal and joint disorders.

Cetasix *Soho, Indon.*
⊗ Furosemide (p.1292·1).
Ascites; heart failure; nephrotic syndrome; oedema.

Cetathiacol *Soho, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Cetathrocin *Soho, Indon.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Cetatrex *Soho, Indon.*
Sumatriptan succinate (p.625·2).
Migraine.

Cetavlex
Note.This name is used for preparations of different composition.
Tramedico, Belg.
Cetrimonium bromide (p.1635·1); chlorhexidine gluconate (p.1635·3).
Disinfection of wounds, burns, skin, and hands; skin disorders.

Bioglan, Irl.†; Bioglan, Malaysia†; CS, Port.; Centrapharm, UK.
Cetrimide (p.1634·1).
Disinfection of skin, minor wounds and burns; nappy rash; skin disorders.

Cetavlon *Pierre Fabre Sante, Fr.; Cana, Gr.; AstraZeneca, Spain†.*
Cetrimide (p.1634·1).
Antiseptic; bacterial skin infections; burns; disinfection; wounds.

Cetavol *Pharmasant, Thai.*
Fluphenazine hydrochloride (p.998·1); nortriptyline hydrochloride (p.413·2).
Mixed anxiety depressive states.

Cetaxim *TRB, Arg.†.*
Cefixime (p.224·3).
Bacterial infections.

Cetaxima *YSP, Malaysia†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cetaz *Uniao Quimica, Braz.*
Ceftazidime (p.234·1).
Bacterial infections.

Cetazime *T3A Pharma, Hung.*
Ceftazidime (p.234·1).
Bacterial infections.

Cetazin *Sigmapharm, Austria.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Cetazum *Landson, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Cetcip *Cipla, India.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetebe *GSK Consumer, Austria; GSK Consumer, Ger.; GSK Consumer, Hung.; GSK Consumer, Pol.; GSK Consumer, Port.†; GSK Consumer, Switz.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Ceterifug *Wolff, Ger.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cethaphil *Galderma, Venez.*
A range of skin care products.

Cethexal *Hexal, Mex.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders.

Cethixim *Ethica, Indon.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Ceti *TAD, Ger.†.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetialfa *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Ceticad *Cadila, India.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetidac *Eurolab, Arg.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetiderm *Dermapharm, Austria; Dermapharm, Ger.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetidura *Merck dura, Ger.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetigen *Generics, Hung.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetihexal *Hexal, Braz.†.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetihis *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cetil *CT, Ger.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetildrops *Luper, Braz.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

CetiLich *Winthrop, Ger.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetilsan *Sella, Ital.*
Cetylpyridinium chloride (p.1635·1).
Oral hygiene; skin and wound disinfection.

Cetimil *Lesvi, Spain.*
Nedocromil sodium (p.1127·3).
Asthma.

Cetimin *Mergers Drugfil, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Cetinject *Lamda (Λαμδα), Gr.†.*
Paracetamol (p.108·1).
Fever; pain.

Cetiprin
Pharmacia, Austria†.
Emepronium carrageenate (p.2188·2).
Incontinence; tenesmus; urinary frequency.

Darrow, Braz.†; Pfizer, Denm.†; Pharmacia, Neth.†.
Emepronium bromide (p.2188·1).
Neurogenic bladder; urinary frequency; urinary incontinence.

Pharmacia, Norw.†; Pharmacia, Swed.†.
Emepronium bromide (p.2188·1) or emepronium carrageenate (p.2188·2).
Bladder disorders; pancreatitis; smooth muscle spasm; tenesmus; urinary frequency; urinary incontinence.

Cetiprin Novum *Pharmacia, Fin.†.*
Emepronium carrageenate (p.2188·2).
Bladder disorders.

Ceti-Puren *Alpharma-Isis, Ger.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetiram *Alet, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Cetirex *Elter, Venez.*
Cetirizine (p.571·1).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cetirgen *Gabriel, Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Cetirhexal *Hexal, Austria.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; asthma.

Cetirigamma *Worwag, Ger.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetirin *Quality, Hong Kong.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetirinax *Actavis, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Cetiristad *Stada, Austria.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetirivax *Vivax, Venez.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Cetirivax D *Vivax, Venez.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine sulfate (p.1571·2).
Hypersensitivity reactions.

Cetirlan *Krewel, Ger.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetirocol *Approved Prescription Services, UK†.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetiva AE *Farmasa, Braz.*
Vitamins A, C, and E (p.1922·1).

Cetivit *Ducto, Braz.*
Ascorbic acid (p.1983·3).

Cetix *Medinfar, Port.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetizine *Lazar, Arg.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetobeta *Bunker, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); ketoconazole (p.539·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Cetocomp *Europharm, Hong Kong.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Cetocona *HB, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Cetoconalab *Multilab, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetocort *Teuto, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); ketoconazole (p.539·1).
Infected skin disorders.

Cetocorten *Cifarma, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone (p.1518·2).
Fungal skin infections.

Cetoglutaran *Tradiphar, Fr.*
Calcium di-oxoglurate.
Asthenia.

Cetohexal *Hexal, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Cetomed *Cimed, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetomicoss *Globo, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Cetomizol *Greenpharma, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetonax *Janssen-Cilag, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetoneo *Neo Quimica, Braz.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Cetonil *Stiefel, Arg.; Stiefel, Braz.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections; pityriasis; scalp disorders.

Cetonin *Cifarma, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetopic *Medihealth, Mex.*
Sodium ascorbyl phosphate; hyaluronic acid (p.2320·1); tocoferil acetate (p.1992·3); dexpanthenol (p.2362·1).
Erythema; melasma.

Cetoquina Y *Solfran, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Cetor *Sanquin, Neth.*
Complement C1 esterase inhibitor (p.2287·1).
C1 esterase deficiency.

Cetornan *Chiesi, Fr.*
Ornithine oxoglurate (p.1959·2).
Nutritional supplement.

Cetoros *Pharos, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Cetoteron *Eurofarma, Braz.*
Cyproterone acetate (p.2088·2).

Cetoxil *Ivax, Mex.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Cetoxol *SA Druggists Self Med, S.Afr.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

Cetozan *Royton, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetozaz *Biofarma, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Cetozol *Cazi, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Cetozone *De Mayo, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cetraben *Hetero, India.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Skin disorders.

Cetraben Emollient
Note.This name is used for preparations of different composition.
Genus, UK.
Bath additive: Light liquid paraffin (p.2031·1).
Dry skin; eczema.

Genus, UK.
Cream: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry skin; eczema.

Cetrakam *LKM, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Cetral *Meyer, Venez.*
Cetirizine (p.571·1).

Cetralon *Julphar, UAE.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Cetrasol *IAE, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cetraxal *Salvat, Spain.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cetraxal Plus *Salvat, Spain.*
⊗ Ciprofloxacin (p.243·3); fluocinolone acetonide (p.1531·3).
Otitis externa.

Cetrazil *Infosint, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Cetrexidin *Vebas, Ital.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Mouth disinfection.

Cetriderm con Triclosan *Gedis, Ital.*
Triclosan (p.1665·2).
Skin cleansing.

Cetril *Royal, Chile.*
Baclofen (p.1888·1).
Skeletal muscle spasticity in multiple sclerosis.

Cetrilan *Theraskin, Braz.*
Cetrimide (p.1634·1); benzalkonium chloride (p.1629·1).
Skin disinfection.

Cetriler *Roux-Ocefa, Arg.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Cetriler D *Roux-Ocefa, Arg.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Cetrimed *Medifive, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; insect bites.

Cetrin
Note.This name is used for preparations of different composition.
Teva, Hung.
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Vitamed, Israel.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Disinfectant.

Cetrine *Rowex, Irl.; Reddy, Rus.; Reddy, Singapore; Spirig, Switz.; Reddy, Thai.; Biofarma, Venez.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; angioedema; hypersensitivity reactions; insect bites; pruritus; urticaria.

Cetrinets *Westmont, Hong Kong; Westmont, Malaysia†; United Laboratories, Philipp.; Westmont, Singapore†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cetrinox *Magis, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Cetripharm Actavis, Hung.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; conjunctivitis; urticaria.

Cetrisan Gedis, Ital.
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Surface disinfection.

Cetriscabin Sanofi-Aventis, Pol.
Benzyl benzoate (p.2036·1); cetrimonium bromide (p.1635·1).
Pediculosis; scabies.

Cetrivax Norton, Pol.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetriwal Wallace, India.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetrixal Sandoz, Indon.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetrizen Norton, Pol.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetrizet Sun, India; Sun, Thai.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Cetrizin
Note. This name is used for preparations of different composition.
Solvay, Braz.; TO-Chemicals, Thai.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; insect bites.

Elpen (Ελπεν), Gr.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Cetrizine Cadila, India.
Cetirizine (p.571·1).

Cetrolac Genom, Braz.
Ketorolac trometamol (p.74·2).
Eye disorders.

Cetron Raffo, Arg.
Ondansetron (p.1756·3).
Nausea and vomiting.

Cetrotide Serono, Arg.; Serono, Austral.; Serono, Austria; Serono, Belg.; Serono, Braz.; Serono, Canad.; Novartis, Chile; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Hung.; Serum Institute, India; DKSH, Indon.; Serono, Indon.; Serono, Irl.; Baxter, Israel; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Douglas, NZ; Serono, Neth.; Serono, Norw.; Serono, Philipp.; Serono, Pol.; Serono, Port.; Baxter, Rus.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.
Cetrorelix acetate (p.2084·2).
Controlled ovarian stimulation.

Cetryn Abdi Ibrahim, Indon.; Abdi, Turk.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cety Yung Shin, Hong Kong.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Cetyl Aksu, Turk.
Cetrimide (p.1634·1).
Skin disinfection.

Cetylcide II Cetylite, USA.
Alkyldimethylbenzylammonium chloride (p.1629·1); alkyldimethylethylbenzylammonium chloride.
Surface disinfection.

Cetylcide-G Cetylite, USA.
Glutaral (p.1645·2).
Instrument disinfection.

Cetylpyridinium B Pharmaniaga, Malaysia.
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Cetylyre UPSA Conseil, Fr.†.
Cetylpyridinium chloride (p.1635·1).
Eye disorders.

Cetymin Galenium, Indon.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cetynol Brasmedica, Braz.†.
Paracetamol (p.108·1).
Fever; pain.

Cetyrol Biochemie, Austria†.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cetyryzyna Egis, Pol.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cevaderm Cevallos, Arg.
⊗ Betamethasone valerate (p.1519·1); tolnaftate (p.548·3); gentamicin (p.284·2).
Skin infections.

Cevadil GMP, Indon.
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Cevalin Bayer Consumer, Mex.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cevanil Pharmasant, Thai.†.
Pirenzepine hydrochloride (p.1762·3).
Peptic ulcer.

Cevas Cadila, India.
⊗ Carvedilol (p.1241·3).

Cevax Vivax, Venez.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cevi-Bid Geriatric Pharm. Corp., USA.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cevicort Cevallos, Arg.
⊗ Betamethasone (p.1518·2).
Skin disorders.

Cevicort NC Cevallos, Arg.
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Cevi-drops Centrapharm, Belg.
Ascorbic acid (p.1983·3); calcium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

Cevi-Fer Geriatric Pharm. Corp., USA†.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1). Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Cevigen Bros, Gr.
Azelaic acid (p.1589·3).
Acne.

Cevikap Medana, Pol.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cevilor Antor, Gr.†.
Cisapride (p.1720·3).
Gastric motility disorders.

Cevimin Flupal, Venez.
Indometacin (p.66·3).

Cevinolon Bros, Gr.
Aciclovir (p.862·3).
Herpes simplex infections.

Cevirin Esseti, Ital.†.
Aciclovir (p.862·3).
Herpesvirus infections.

Ce-Vi-Sol BMS, Mex.; Mead Johnson, Philipp.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cevit Plusandex, Venez.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cevita Teuto, Braz.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Cevi-Tabs Ferrosan, Fin.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cevitol Lannacher, Austria.
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Ceviton Ariston, Braz.
Ascorbic acid (p.1983·3).

Cewin Sanofi Synthelabo, Arg.; Sanofi-Aventis, Braz.
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cexb Behrens, Venez.
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Cexidal Otico Salvat, Spain†.
⊗ Ciprofloxacin (p.243·3); fluocinolone acetonide (p.1531·3).
Otitis externa.

Cexim Lilly, Hung.†.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Ceza Pharmaland, Thai.
Cetirizine hydrochloride (p.570·3).
Allergic skin disorders; rhinitis.

Cezane Hexa, Arg.†.
Astemizole (p.567·2).
Allergic rhinitis; urticaria.

Cezin UAD, USA.
Multivitamin and mineral preparation (p.1922·1).

Ceziren Pharmanel, Gr.†.
Cetirizine (p.571·1).
Allergic disorders.

Cezolin
Note. This name is used for preparations of different composition.
Biochimico, Braz.†.
Cefazolin sodium (p.222·1).
Bacterial infections.

Remedina, Gr.
Ketoconazole (p.539·1).
Fungal infections.

Cezox Pharmasant, Thai.
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle pain and spasm.

CF Vite Cypress, USA†.
Multivitamin and zinc preparation (p.1922·1).
Dietary supplement.

C-Film Lucchini, Switz.†.
A nonoxinol (p.1917·1).
Contraceptive.

C-Flox Alphapharm, Austral.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

C-Floxacin SM, Thai.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

C-G ICN, Arg.†.
Sulfacetamide sodium (p.335·3); sulfur (p.1614·1).
Acne; rosacea; seborrhoeic dermatitis.

CGT Libbs, Braz.
Multivitamin and mineral preparation (p.1922·1).

CGU WC Elge, USA.
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cough.

Chamberlains Cough Remedy Honey and Liquorice Pfizer Consumer, S.Afr.
Guaifenesin (p.1561·3).
Coughs.

Chamberlains Cough Remedy Peppermint Pfizer Consumer, S.Afr.
Guaifenesin (p.1561·3).
Coughs.

Chamberlains Cough Remedy Regular Pfizer Consumer, S.Afr.
Liquorice (p.1740·3); ipecacuanha (p.1562·3).
Coughs.

Chamberlains Traditional Colic Remedy Pfizer Consumer, S.Afr.
Chlorobutanol (p.1639·2); ether (p.2023·2); blackberry root.
Colic; flatulence.

Chamo S Ysatfabrik, Ger.†.
Chamomile flowers (p.2279·3).
Anorectal disorders; gastrointestinal disorders; mouth and throat inflammation; respiratory-tract disorders; skin disorders; vaginitis; wounds.

Chamoca M Hanosan, Ger.
Homoeopathic preparation.

Chamodent VSM, Neth.
Homoeopathic preparation.

Chamomile Blend Lifeplan, UK.
Valerian; chamomile; lupulus; passion flower (p.1922·1).
Herbal supplement.

Chamomilla Comp Weleda, Ger.†.
Homoeopathic preparation.

Chamomilla/Millefolium Comp Weleda, S.Afr.
Homoeopathic preparation.

Championyl Sanofi-Aventis, Ital.
Sulpiride (p.1028·3).
Dysthymia; psychoses.

Champix
Pfizer, Austral.; Pfizer, Braz.; Pfizer, Cz.; Pfizer, Gr.; Pfizer, NZ; Pfizer, Port.; Pfizer, UK.
Varenicline tartrate (p.2411·1).
Aid to smoking withdrawal.

Pfizer, Fr.; Pfizer, Hung.
Varenicline (p.2411·1).
Aid to smoking withdrawal.

Champs C Upha, Indon.; Upha, Singapore.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Champs C with Lysine Upha, Indon.; Upha, Singapore.
Ascorbic acid (p.1983·3); lysine hydrochloride (p.1955·1).
Vitamin C supplement.

Champs DHA Upha, Indon.; CCM, Malaysia; Upha, Singapore.
Fish oil (p.1362·2).
Nutritional supplement.

Champs D-Worms CCM, Malaysia.
Albendazole (p.139·2).
Worm infections.

Champs Junior CCM, Hong Kong.
Vitamin C (p.1983·3).
Vitamin C supplement.

Champs M Upha, Singapore.
Vitamin preparation with or without lysine (p.1922·1).

Champs M with Lysine CCM, Hong Kong; Upha, Indon.
A vitamin preparation with lysine (p.1922·1).
Dietary supplement; nutritional supplement.

Champuacid Bajer, Arg.
Zinc undecenoate (p.549·3); salicylic acid (p.1612·2); coal tar (Alcoderm) (p.1616·2).
Scalp disorders.

Chantaline Altana, Spain†.
Theophylline (p.1140·1).
Asthma; bronchospasm; heart failure; paroxysmal dyspnoea.

Chantix Pfizer, USA.
Varenicline tartrate (p.2411·1).
Smoking cessation.

Chap Stick
Note. This name is used for preparations of different composition.
Whitehall, NZ†.
Lip Balm Classic SPF 4: Padimate O (p.1609·1).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Balm SPF 15: Oxybenzone (p.1608·3); padimate O (p.1609·1).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Balm Strawberry SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Balm Ultra SPF 30+: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Wyeth Consumer, NZ.
Lip Conditioner SPF 15: Aloe vera (p.1588·2) octinoxate (p.1608·2); oxybenzone (p.1608·3); vitamin E (p.1992·2).
Chapped lips; sunscreen.

Chapstick
Note. This name is used for preparations of different composition.
Robins, USA.
Lip balm SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Whitehall, Braz.†.
Lipbalm: Padimate O (p.1609·1); camphor (p.2273·2); titanium dioxide (p.1617·3).
Dry or chapped lips; sunscreen.

Whitehall, Braz.†.
Lipbalm SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3); camphor (p.2273·2); titanium dioxide (p.1617·3).
Dry or chapped lips; sunscreen.

Robins, USA.
Ointment SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Wyeth Consumer, Austral.
SPF 4: Padimate O (p.1609·1).
Dry or chapped lips; sunscreen for lips.

Wyeth Consumer, Austral.
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Dry or chapped lips; sunscreen for lips.

Chapstick Lip Balm Whitehall-Robins, Canad.
Padimate O (p.1609·1).
Sunscreen.

Chapstick Lip Moisturizer Wyeth Consumer, Canad.; Wyeth Consumer, Chile.
Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Chapstick Medicated Wyeth Consumer, Chile.
White soft paraffin (p.2031·2); camphor (p.2273·2); menthol (p.2340·1); phenol (p.1656·1).
Chapped lips.

Chapstick Medicated Lip Balm
Whitehall-Robins, Canad.†.
Camphor (p.2273·2); menthol (p.2340·1); soft paraffin (p.2031·2); phenol (p.1656·1).

Robins, USA.
Yellow soft paraffin (p.2031·3); camphor (p.2273·2); menthol (p.2340·1); phenol (p.1656·1).

Chapstick Mint Wyeth Consumer, Chile.
Padimate O (p.1609·1).
Chapped lips; sunscreen.

Chapstick Regular Wyeth Consumer, Chile.
Padimate O (p.1609·1); titanium dioxide (p.1617·3).
Chapped lips; sunscreen.

Chapstick Sunblock
Note. This name is used for preparations of different composition.
Whitehall-Robins, Canad.†.
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Wyeth Consumer, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Chapstick Ultra Wyeth Consumer, Chile.
SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Chapped lips; sunscreen.

Charac Omega, Canad.
Activated charcoal (p.1435·2).
Poison antidote.

Charac Tol Omega, Canad.
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Poison antidote.

Charantia Herbcare, Philipp.
Karela.
Supplement for diabetics.

Charbon de Belloc Omega, Fr.
Activated charcoal (p.1435·2).
Gastrointestinal disorders.

Charcoaid Requa, USA.
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Charcoal Plus Kramer, USA.
Activated charcoal (p.1435·2).
Formerly contained simeticone and activated charcoal.
Flatulence.

Charcocaps Key, Austral.; Requa, USA.
Activated charcoal (p.1435·2).
Diarrhoea; flatulence; poisoning.

Charcodote
Note. This name is used for preparations of different composition.
Pharmascience, Canad.; Genmedix, Israel.
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Emergency treatment of poisoning; poison antidote.

Pharmascience, Hong Kong; Pliva, UK.
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Charcodote Aqueous *Pharmascience, Canad.*
Activated charcoal (p.1435·2).
Poison antidote.

Charflo Aqua *SSM, Turk.*
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Charflo Sorbitol *SSM, Turk.*
Activated charcoal (p.1435·2); sorbitol (p.1965·1).
Emergency treatment of poisoning.

Charlieu Antipelliculaire *Nigy, Fr.*
Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Charlieu Anti-Poux *Mayoly-Spindler, Cz.†; Mayoly-Spindler, Fr.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Charlieu Topic *Nigy, Fr.†.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Charlieu Topicrem *Nigy, Fr.*
⊗ Urea (p.1620·2); glycerol (p.2314·2).
Dry skin disorders.

Charlyn *Krugher, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic respiratory-tract disorders.

Chase Kolik Gripe Water *Stella, Canad.*
⊗ Alcohol (p.1625·2); ginger (p.1732·3); dill oil (p.2293·3); sodium bicarbonate (p.1673·2).

Chase Kolik Gripe Water Alcohol-Free *Stella, Canad.*
Fennel oil (p.2303·1); sodium bicarbonate (p.1673·2).

Chebil *Basi, Port.†.*
Chenodeoxycholic acid (p.2280·1).

Check-Mate *BHR, UK.*
Pregnancy test (p.2372·1).

CheeTah *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Chefarine *Chefaro, Neth.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Chefir *Drug Research, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Cheiranthol *Klein, Ger.†.*
Cheiranthus cheiri; milk thistle (p.1452·1); cnicus benedictus (p.2285·2); achillea (p.2245·2); St John's wort (p.422·3).
Liver disorders.

Chek-Stix *Bayer, Austral.*
Positive and negative controls for tests for glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leucocytes in urine.

Chelated Bone Meal *Swiss Herbal, Canad.†.*
Calcium; phosphorus (p.1922·1).

Chelated Cal-Mag *GNLD, Austral.*
Calcium glycinate (p.1677·1); magnesium glycinate (p.1680·1); fish-liver oil.
Calcium and magnesium deficiency.

Chelated Cal-Mag plus Vitamin *Swiss Herbal, Canad.*
Calcium; magnesium; vitamin C; vitamin D (p.1922·1).

Chelated Dol Mite *Swiss Herbal, Canad.†.*
Calcium; magnesium (p.1922·1).

Chelated Solamins *Solgar, UK.*
Minerals as amino-acid chelates (p.1922·1).

Chelatran *SERB, Fr.*
Disodium edetate (p.1463·3).
Digitalis intoxication.

Chelicur *Hasco-Lek, Pol.*
Greater celandine (p.2317·1); turmeric (p.1473·2).
Biliary-tract disorders; liver disorders.

Chelidonium comp *Wala, Ger.; Weleda, Ger.*
Homoeopathic preparation.

Chelidonium Compose *Boiron, Fr.†.*
Homoeopathic preparation.

Chelintox *Braun, Switz.†.*
Sodium calcium edetate (p.1462·2).
Heavy-metal poisoning.

Cheltin *Pharma Investi, Chile.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Chemacin *CT, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Chemcard *Marco, Austral.†.*
Test for cholesterol in blood.

Chemet *Ovation, USA.*
Succimer (p.1466·2).
Lead poisoning.

Chemicetina
Fournier, Ital.
Chloramphenicol (p.239·3).
Bacterial infections.
Inde, Spain.
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Chemiderm *Farmanic, Gr.*
Terbinafine (p.546·3).
Fungal infections.

Chemilaic *Iasis, Gr.†.*
Azelaic acid (p.1589·3).
Acne.

Chemionazolo *NCSN, Ital.†.*
Econazole nitrate (p.531·1).
Fungal and bacterial skin and vulvovaginal infections.

Chemisolv *Farmanic, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Chemists Own Chesty Cough *Sigma, Austral.*
Bromhexine hydrochloride (p.1552·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly known as Chemists Own Mucotuss.
Coughs and cold symptoms.

Chemists Own Chesty Mucus Cough *Sigma, Austral.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Formerly known as Chemists Own Noesude.
Coughs and cold symptoms.

Chemists Own Childrens Cough & Cold *Herron, Austral.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Chemists Own Clozole *Herron, Austral.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Chemists Own Cold & Allergy *Sigma, Austral.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Formerly known as Chemists Own Zaymaz.
Cold symptoms; hypersensitivity reactions.

Chemists Own Cold & Flu Day/Night *Chemists Own, Austral.*
Day tablets, Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Chemists Own Cold & Flu Relief *Chemists Own, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Cold and influenza symptoms.

Chemists Own Cold Sore *Sigma, Austral.*
Aciclovir (p.862·3).
Herpes labialis.

Chemists Own Coldeze *Chemists Own, Austral.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; hay fever.

Chemists Own Cough Suppressant *Sigma, Austral.*
Ammonium chloride (p.1551·3); codeine phosphate (p.37·2); menthol (p.2340·1).
Cough.

Chemists Own Decongestant Nasal Spray *Herron, Austral.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Chemists Own Diarrhoea Mixture *Herron, Austral.†.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); catechu tincture (p.2278·2); codeine phosphate (p.37·2); kaolin (p.1738·1); magnesium trisilicate (p.1744·1).
Diarrhoea.

Chemists Own Diarrhoea Relief *Sigma, Austral.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Chemists Own Difenacol *Sigma, Austral.*
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1); sodium citrate (p.1673·3).
Coughs.

Chemists Own Dry Cough *Sigma, Austral.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Chemists Own Dry Raspy Cough *Sigma, Austral.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Chemists Own Dexolix.
Coughs and cold symptoms.

Chemists Own Expectalix *Sigma, Austral.*
Ammonium chloride (p.1551·3); codeine phosphate (p.37·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Chemists Own Hayfever Sinus Relief *Sigma, Austral.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly known as Chemists Own Allergy Hayfever Sinus Relief.
Hay fever; nasal and sinus congestion.

Chemists Own Kiddicol *Sigma, Austral.*
Ammonium chloride (p.1551·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); pholcodine (p.1570·2).
Cold symptoms; cough.

Chemists Own Natural Laxative with Softener *Sigma, Austral.*
Docusate sodium (p.1725·1); senna leaf (p.1769·2); sennosides (p.1769·3).
Constipation.

Chemists Own Pain *Chemists Own, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Chemists Own Pain & Fever *Chemists Own, Austral.*
Paracetamol (p.108·1).
Fever; pain.

Chemists Own Peetalix *Herron, Austral.†.*
Alimemazine tartrate (p.566·2).

Chemists Own Period Pain Tablets *Sigma, Austral.*
Naproxen sodium (p.92·3).
Dysmenorrhoea.

Chemists Own Sinus Relief *Sigma, Austral.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Chemists Own Sinus-Pain Relief *Sigma, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; sinusitis.

Chemists Own De Worm *Sigma, Austral.*
Mebendazole (p.148·3).
Worm infections.

Chemisulide *Iasis, Gr.†.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Chemitrim *Biomedica, Hong Kong†; Biomedica, Ital.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Chemix *YSP, Malaysia; Yung Shin, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Chemopent *Diffucap, Braz.†.*
Pentoxifylline (p.1367·2).

Chemoprim *Biolab, Hong Kong; Biolab, Singapore; Biolab, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Chemotrex *Medichem, Indon.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Chemstrip 6 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, leukocytes, and pH in urine.

Chemstrip 7 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, bilirubin, leukocytes, and pH in urine.

Chemstrip 8 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, leukocytes, and pH in urine.

Chemstrip 9 *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes, and pH in urine.

Chemstrip bG *Boehringer Mannheim Diagnostics, USA.*
Test for glucose in blood (p.2314·1).

Chemstrip 2 GP *Boehringer Mannheim, USA.*
Test for glucose and protein in urine.

Chemstrip K *Roche Diagnostics, Canad.; Boehringer Mannheim, USA.*
Test for ketones in urine.

Chemstrip 2 LN *Boehringer Mannheim, USA.*
Test for nitrite and leukocytes in urine.

Chemstrip Micral *Boehringer Mannheim, USA.*
Test for albumin in urine.

Chemstrip 4 the OB *Boehringer Mannheim, USA.*
Test for glucose, protein, blood, and leukocytes in urine.

Chemstrip 10 with SG *Boehringer Mannheim, USA.*
Test for nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, leucocytes, and specific gravity in urine.

Chemstrip uG *Roche Diagnostics, Canad.; Boehringer Mannheim, USA.*
Test for glucose in urine (p.2314·1).

Chemstrip uG 5000K *Roche Diagnostics, Canad.*
Test for glucose and ketones in urine.

Chemstrip uGK *Boehringer Mannheim, USA.*
Test for glucose and ketones in urine.

Chemstrip uG/K *Roche Diagnostics, Canad.*
Test for glucose and ketones in urine.

Chemydur *Sovereign, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Chenofalk *Merck, Austria†; Codali, Belg.†; Falk, Ger.; Falk, Hong Kong†; Falk, Hung.†; Darya-Varia, Indon.; Falk, Indon.; Rafa, Israel; Farmasa, Mex.†; Tramedico, Neth.; Ali, Turk.*
Chenodeoxycholic acid (p.2280·1).
Cholesterol gallstones.

Chepamed *Promed, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Chephapyrin N *MIP, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Cheracap *Pharmacia, Venez.†.*
Chlorphenamine maleate (p.571·3); aspirin (p.20·3); caffeine (p.1116·3).
Cold symptoms.

Cheracap S *Pharmacia, Braz.*
Chlorphenamine maleate (p.571·3); aspirin (p.20·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Cheracol
Note. This name is used for preparations of different composition.
Shire, Canad.†.
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Coughs.
Pfizer, Chile.
⊗ Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); methoxyphenamine hydrochloride (p.1564·2).
Cold symptoms.
Pfizer Consumer, Mex.
Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Formerly contained aspirin, caffeine, chlorphenamine maleate, and methoxyphenamine hydrochloride.
Allergic rhinitis; cold and influenza symptoms.

Cheracol Cough *Roberts, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Cheracol D Cough *Roberts, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Cheracol Duo *Pfizer Consumer, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Cheracol Plus *Lee, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Formerly contained phenylpropanolamine hydrochloride, chlorphenamine maleate, and dextromethorphan hydrobromide.
Coughs and cold symptoms.

Cheracol Sore Throat *Roberts, USA.*
Phenol (p.1656·1).
Sore throat.

Chericof *Ranbaxy, Malaysia.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Cherifer *Tynor, Philipp.*
A range of nutritional supplements containing Chlorella growth factor and vitamins with or without minerals (p.1922·1).

Chest Mixture *Potter's, UK.*
⊗ Horehound (p.1564·1); pleurisy root (p.2370·1); senega (p.1572·3); lobelia (p.2157·2); acetum scillae (p.1573·1).
Catarrh; coughs.

Cheston *Cipla, India.*
Bromhexine hydrochloride (p.1552·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Coughs.

Cheston Cold *Cipla, India.*
Cetirizine hydrochloride (p.570·3); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cold symptoms.

Cheston CS *Cipla, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Cheston DT *Cipla, India.*
Bromhexine (p.1552·2); chlorphenamine (p.572·2); phenylpropanolamine (p.1569·2).
Respiratory-tract disorders.

Chesty Cough Relief *Herbal Concepts, UK.*
Senega (p.1572·3); catechu (p.2278·2); liquorice (p.1740·3); tolu (p.1574·2); coltsfoot (p.1555·1).
Coughs.

Chetofen *Boniscontro & Gazzone, Ital.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis.

Chetonex *Humana, Ital.*
Vitamins; minerals (p.1922·1); alanine (p.1928·1).
Acetonaemia; ketosis.

Chew-C *Key, USA.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C supplement.

Chew-E *Eagle, Austral.*
d-Alpha tocoferil acid succinate (p.1993·1).
Vitamin E supplement.

Chewette C *Hovid, Malaysia.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Chewy C *Be-Tabs, S.Afr.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Chexid *Otsira, India.*
Lansoprazole (p.1739·2).

Chiana *Bio-Diät, Ger.†.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome.

Chiana-Oel *Bonamedis, Switz.*
Peppermint oil (p.1761·2).
Cold symptoms; gastrointestinal disorders; headache; muscular pain.

Chibretico *Chibret, Port.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Chibro-Cadron *Thea, Fr.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye disorders.

Chibro-Proscar *MSD-Chibret, Fr.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Chibro-Timoptol *Chibret, Ger.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Chibroxin *MSD, Arg.†; MSD, Braz.†; MSD, Chile†; Thea, Ger.; MSD, Israel†; MSD, Malaysia†; Thea, Pol.; MSD, Singapore†; Thea, Spain; MSD, Venez.†.*
Norfloxacin (p.309·2).
Bacterial eye infections.

Chibroxine *Thea, Fr.*
Norfloxacin (p.309·2).
Eye infections.

Chibroxol *Thea, Belg.; Thea, Neth.; Thea, Port.; MSD, Switz.†.*
Norfloxacin (p.309·2).
Bacterial eye infections.

Chiclida *Andromaco, Mex.; Torrens, Spain.*
Meclozine hydrochloride (p.584·3).
Motion sickness.

Chicovit Pharmaton *Boehringer Ingelheim, Chile.*
Lysine hydrochloride; calcium; phosphorus; vitamins (p.1922·1).
Tonic.

Chiggerex *Scherer, USA.*
Benzocaine (p.1854·1); camphor (p.2273·2); menthol (p.2340·1).
Skin disorders.

Chigger-Tox *Scherer, USA.*
Benzocaine (p.1854·1).
Local anaesthesia.

Chikujountanto *Tsumura, Jpn.*
Pinellia tuber; bupleurum root; ophiopogon tuber; poria sclerotium; platycodon root; immature orange; cyperus rhizome; citrus unshiu peel; coptis rhizome; liquorice; ginger; ginseng; bamboo trunk.
Traditional Kampo medicine.

Chil Kid Plus DHA *Morinaga, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement.

Chil School *Morinaga, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement.

Chilblain Formula *Vitaplex, Austral.†.*
Nicotinamide (p.1957·3); acetomenaphthone (p.1995·2).
Chilblains; poor peripheral circulation.

Chilblains Cream *Nelson, UK.*
Homoeopathic preparation.

Chilcee *Blue Sky, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Child Chesty Cough *Numark, UK.*
Diphenhydramine (p.577·1).
Coughs.

Child Formula *Avon, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Childrens Advil Cold *Wyeth Consumer, Canad.; Whitehall-Robins, USA.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; sinusitis; upper respiratory-tract disorders.

Children's Allergy Formula *Pharmascience, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Childrens Cepacol *JB Williams, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Childrens Cherry Sucrets *SmithKline Beecham, Israel†.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Childrens Chewable *Adams, Canad.; GFR, Canad.; Jamieson, Canad.; Natures Sunshine, Canad.; Novopharm, Canad.*
Multivitamin preparations with or without minerals (p.1922·1).

Childrens Chewable Vita-Mins *Seroyal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Childrens Chewables *Sisu, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Children's Choice *Swiss Herbal, Canad.†.*
Multivitamin preparation with or without iron (p.1922·1).

Children's Clusivol *Wyeth, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Childrens Cold and Flu Relief *Brauer, Austral.*
Homoeopathic preparation.

Childrens Coltalin with Vit B_1 *Fortune, Hong Kong†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); vitamin B (p.1976·3).
Respiratory-tract disorders.

Childrens Diarrhoea Mixture *Unichem, UK.*
Kaolin (p.1738·1).
Diarrhoea.

Childrens Dynafed Jr *BDI, USA†.*
Paracetamol (p.108·1).
Fever; pain.

Childrens Feverhalt *Pendopharm, Canad.*
Paracetamol (p.108·1).
Fever; pain.

Children's Formula Cough *Pharmakon, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Childrens Ibuprofen Cold *Major, USA.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Children's Kaopectate *Pharmacia, USA.*
Bismuth salicylate (p.1711·1).
Formerly contained attapulgite.
Diarrhoea.

Childrens Mapap *Major, USA.*
Paracetamol (p.108·1).
Fever; pain.

Childrens Motion Sickness Liquid *Tanta, Canad.*
Dimenhydrinate (p.576·2).

Childrens Motrin Cold *McNeil Consumer, USA.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Childrens Mult *Vitaplex, Austral.†.*
Multivitamin and mineral preparation with lysine hydrochloride (p.1922·1).

Children's Multivitamins *Cenovis, Austral.; Vitelle, Austral.*
Multivitamin and mineral preparation (p.1922·1).

Children's Nostril *Ciba, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Childrens NyQuil *Procter & Gamble, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Childrens Panadol *GSK Consumer, Austral.*
Paracetamol (p.108·1).
Fever; pain.

Childrens Panadol Cold & Flu *GSK, Singapore†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Childrens Panadol Cold Relief Elixir *GSK Consumer, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly known as Panadol Childrens Cold.
Cold symptoms; fever; nasal congestion; pain.

Childrens Panadol Drops for Infants *GSK, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Childrens PediaCare Nighttime Cough *Pfizer, USA.*
Diphenhydramine hydrochloride (p.577·2).
Cough.

Childrens Sudafed Cold & Cough *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Childrens Sudafed Nasal Decongestant *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Children's SunKist Multivitamins Complete *Ciba, USA.*
Multivitamin and mineral preparation (p.1922·1).

Children's SunKist Multivitamins + Extra C *Ciba, USA.*
Multivitamin preparation (p.1922·1).

Children's Tylenol *Johnson & Johnson, Hong Kong†.*
Paracetamol (p.108·1).
Fever; pain.

Children's Tylenol Cold Plus Cough *Johnson & Johnson, Hong Kong†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Childrevit *Diviser Aquilea, Spain†.*
Cyproheptadine hydrochloride (p.575·1); amino acids and vitamins (p.1922·1).
Tonic.

Chilvax *Proel, Gr.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Chilvit-Cee *Essenpharma, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Chimar *Menarini, Port.*
Chymotrypsin (p.2281·3); trypsin (p.2405·3).
Adjunct to antibiotics; inflammation; oedema; respiratory-tract congestion.

Chimax *Chiron, UK.*
Flutamide (p.725·1).
Prostatic cancer.

Chimodil *Yamanouchi, Ital.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia.

Chimono *Lusofarmaco, Ital.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

China Diarrhea L107 *Homeocan, Canad.†.*
Homoeopathic preparation.

China Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

China Oel *Bio-Diet, Israel; Pronovo, Turk.*
Peppermint oil (p.1761·2).
Cold symptoms; gastrointestinal disorders; respiratory-tract disorders.

China-Balsam *Bio-Diat, Ger.†.*
Camphor (p.2273·2); clove oil (p.2285·1); eucalyptus oil (p.2301·2); Norway spruce oil; menthol (p.2340·1).
Catarrh; fatigue; headache; musculoskeletal and joint disorders; toothache.

Chinacin-T *Chinta, Thai.*
Clindamycin (p.251·1).
Acne.

China-Eisenwein *Mayrhofer, Austria.*
Mace flowers (p.2336·1); gentian (p.2310·3); bitter-orange peel (p.2357·1); centaury (p.2279·1); ceratonia (p.2143·2); cinchona bark (p.2282·3); cinnamon (p.2283·1); ferrous citrate (p.1950·3); ferrous ascorbate (p.1938·2).
Tonic.

China-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

China-Oel *Bio-Diat, Cz.†; Bio-Diat, Ger.†.*
Peppermint oil (p.1761·2).
Cold symptoms; neuromuscular pain; smooth muscle spasm.

Chinclonac *Chinta, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Chingazol *Chinta, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections; trichomoniasis; vaginal candidiasis.

Chinofungin *Sanofi-Aventis, Hung.*
Tolnaftate (p.548·3).
Fungal skin and nail infections.

Chinoidina *Giovanardi, Ital.†.*
Cinchona calisaya (p.2282·3); gentian (p.2310·3); kola (p.2416·1).
Dyspepsia.

Chinopamil *PannonPharma, Hung.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Chinoplus *Angelini, Ital.*
Prulifloxacin (p.320·1).
Bacterial infections.

Chinosol *Chinosolfabrik, Ger.*
Hydroxyquinoline sulfate (p.2323·1); potassium sulfate (p.1684·3).
Skin disinfection.

Chinotal *PannonPharma, Hung.*
Pentoxifylline (p.1367·2).
Peripheral and cerebral vascular disorders; vascular eye disorders.

Chintaral *Chinta, Thai.*
Ketoconazole (p.539·1).
Scalp disorders.

Chinteina *Lafare, Ital.*
Quinidine sulfate (p.1383·2).
Arrhythmias.

Chiosan *Lafedar, Arg.*
⊗ Tetryzoline hydrochloride (p.1574·1).

Chipil *Fontelabor, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Chiro Des *Kosmidis, Gr.*
Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3).
Disinfection.

Chirocaina *Abbott, Chile; Abbott, Venez.*
Levobupivacaine hydrochloride (p.1862·1).
Local anaesthesia.

Chirocaine *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Cz.; Abbott, Fin.; Abbott, Fr.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Ital.; Abbott, NZ†; Abbott, Neth.; Abbott, Norw.; Abbott, Port.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Swed.; Abbott, Switz.; Abbott, Turk.; Abbott, UK; Purdue Frederick, USA†.*
Levobupivacaine hydrochloride (p.1862·1).
Local anaesthesia; pain.

Chirocane *Abbott, Spain.*
Levobupivacaine hydrochloride (p.1862·1).
Local anaesthesia.

Chiroflu *Novartis Vaccines, Port.; Esteve, Spain.*
An inactivated influenza vaccine (subunits) (p.2218·2).
Active immunisation.

Chirofossat N *Dreluso, Ger.*
Homoeopathic preparation.

Chiromas *Esteve, Spain.*
An influenza vaccine (p.2218·2).
Active immunisation.

Chiron Barrier Cream *Portex, UK.*
Aluminium chlorohydrate (p.1588·3).

Chiron IL-2 *Key Oncologics, S.Afr.*
Aldesleukin (p.735·1).
Metastatic melanoma; metastatic renal cell cancer.

Chironair Odour Control Liquid *Coloplast, UK.*
A deodorant for use with colostomies and ileostomies.

Chiroplexan H *Pfluger, Ger.*
Homoeopathic preparation.

ChiRhoStim *ChiRhoClin, USA.*
Secretin (p.2384·3).
Assessment of pancreatic function; diagnosis of gastrinoma.

Chitaq *Chitin, Hong Kong.*
N-Acetyl glucosamine (p.2313·2).
Arthritis.

Chitodine *IMS, Ital.*
Iodine (p.2169·2).
Skin and wound disinfection.

Chito-Lafarmen *Lafarmen, Arg.*
Poliglusam (p.2370·1).
Obesity.

Chiton *INTES, Ital.*
Vitamin B substances; methionine; copper; zinc; omega-3 and omega-6 marine triglycerides (p.1922·1).
Nutritional supplement.

Chitosan C *YSP, Malaysia†.*
Vitamin C (p.1983·3); poliglusam (p.2370·1).
Nutritional supplement.

Chitosano *SIRC, Singapore.*
Poliglusam (p.2370·1); citrus aurantium (p.2357·1); garcinia cambogia (p.2309·2); iodine; chromium; vitamin C; guar gum; zinc sulfate; ferrous gluconate; vanadium pentoxide (p.1922·1).
Dietary aid in weight reduction.

Chlamydicin *Heremco, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Chlo-Amine *Hollister-Stier, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlobax *Beacons, Singapore.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal disorders.

Chloe *Zentiva, Cz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-induced acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Chloment *Denk, Hong Kong†.*
Chloramphenicol (p.239·3).
Eye infections.

Chlomide *Malayan, Singapore†.*
Chlorpropamide (p.438·3).
Diabetes insipidus; diabetes mellitus.

Chlomy-P *Sankyo, Hong Kong†.*
⊗ Chloramphenicol (p.239·3); neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Infected skin disorders.

Chlor-3 *Fleming, USA.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3); magnesium chloride (p.1679·1).
Medical condiment; table salt substitute.

Chloracil *Siam Bheasach, Thai.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Chloraethyl *Henning, Hung.†.*
Ethyl chloride (p.1861·2).
Local anaesthesia.

Chloraethyl Dr Henning *Henning Walldorf, Ger.; Henning, Israel.*
Ethyl chloride (p.1861·2).
Local anaesthesia.

Chlorafed *Roberts, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Chloraldurat *Pohl, Ger.; Pohl, Switz.*
Cloral hydrate (p.979·1).
Insomnia; nervous disorders; sedative; sleep disorders.

Chloram-D *Duopharma, Hong Kong.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Eye inflammation with bacterial infection.

Chloramex *Actavis, Indon.; Pharmacare, S.Afr.*
Chloramphenicol (p.239·3).
Bacterial eye infections; bacterial infections.

Chloramin T *Lysoform, Ger.*
Tosylchloramide sodium (p.1665·1).
Hand disinfection; surface disinfection.

Chloramine
Upha, Malaysia†.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Beacons, Singapore.
Chlorphenamine (p.572·2).
Allergic rhinitis; allergic skin disorders.

Chlorammonic *Chiesi, Fr.†.*
Ammonium chloride (p.1551·3).
Alkalosis; urinary-tract disorders.

Chloramno *Milano, Thai.*
Chloramphenicol (p.239·3).
Bacterial infections.

Chloramon *Streuli, Switz.*
Ammonium chloride (p.1551·3).
Bronchitis; metabolic alkalosis.

Chloramphecort *Kimia, Indon.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Chloramphecort-H *Kimia, Indon.*
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3).
Infected skin disorders.

Chloramsaar N *Chephasaar, Ger.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Chloranic *Norma (Νορμα), Gr.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Chlorapred *Demo, Gr.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Bacterial eye infections with inflammation.

ChloraPrep *Enturia, UK.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin disinfection.

Chloraseptic Kids Sore Throat Spray *Prestige, USA.*
Phenol (p.1656·1).
Formerly known as Childrens Vicks Chloraseptic Spray.
Sore throat.

Chloraseptic Lozenges *Prestige, Canad.*
Benzocaine (p.1854·1); menthol (p.2340·1).
Sore throat and mouth.

Chloraseptic Sore Throat
Note. This name is used for preparations of different composition.
Prestige, USA.
Lozenges: Benzocaine (p.1854·1); menthol (p.2340·1).
Formerly known as Vicks Chloraseptic Sore Throat.
Sore throat.

Prestige, USA.
Throat spray: Phenol (p.1656·1).
Formerly known as Vicks Chloraseptic.
Minor mouth or throat irritation.

Chloraseptic Spray *Prestige, Canad.*
Phenol (p.1656·1).
Sore throat.

Chloraseptine *Sterop, Belg.*
Tosylchloramide sodium (p.1665·1).
Disinfection; water purification.

Chlorasol *Seton, Israel; SSL, UK†.*
Sodium hypochlorite (p.1661·1).
Cleansing of skin ulcers and pressure sores; skin disinfection.

Chloraxin *Cipla, India.*
Chloramphenicol (p.239·3), chloramphenicol palmitate (p.239·3), or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Chlorazin *Streuli, Switz.*
Chlorpromazine hydrochloride (p.969·2).
Nausea; pain; pruritus; psychoses; vertigo; vomiting.

Chlorazol *Qualiphar, Belg.*
Tosylchloramide sodium (p.1665·1).
Disinfection.

Chlorbiotic *Bernofarm, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Chlorchinaldin H *Chema-Elektromet, Pol.*
⊗ Chlorquinaldol (p.242·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Chlorcol *Adcock Ingram, S.Afr.*
Chloramphenicol (p.239·3).
Bacterial infections.

Chlordex GP *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Chlordrine *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Chloresium *Rystan, USA.*
Chlorophyllin copper complex (p.1471·1).
Relief of malodour of wounds and ulcers; wound healing.

Chlorestrol *Pond's, Thai.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Chlorethyl *Adroka, Switz.*
Ethyl chloride (p.1861·2).
Local anaesthesia.

Chlorex-A *Cypress, USA.*
Phenyltoloxamine citrate (p.588·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis.

Chlorformin *Cadila, India†.*
Chlorpropamide (p.438·3); phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Chlorgest *Ranbaxy, Thai.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Chlorhex *Milano, Thai.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Chlorhexamed *GSK, Austria; GSK Consumer, Ger.; GSK Consumer, Neth.; GSK Consumer, Switz.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat infections; oral hygiene.

Chlorhex-C *Milano, Thai.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Chlorhist *Propan, S.Afr.†.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlorhist Baby Cough *Sriprasit, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Chlorhist Cough *Sriprasit, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1).
Coughs.

Chlorhistan *Hua, Thai.†.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms; nasal congestion.

Chlorispray *Anios, Fr.†.*
⊗ Chlorhexidine gluconate (p.1635·3); formaldehyde (p.1644·2); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2); alcohol (p.1625·2).
Surface disinfection.

Chlorleate *Silom, Thai.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions; insect bites.

Chlorleate Expectorant *Silom, Thai.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; nasal congestion.

Chlormazine *Pharmasant, Thai.†.*
Chlorpromazine (p.969·1).
Nausea and vomiting; psychoses.

Chlor-Mes *Cypress, USA.*
Chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; upper-respiratory-tract allergies.

Chlor-Mes D *Cypress, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Respiratory-tract congestion; rhinitis; sinusitis.

Chlor-Mes Jr *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; upper respiratory-tract symptoms associated with allergies.

Chlormine *DHA, Malaysia.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlormixin *Noir, India.*
Polymyxin B sulfate (p.317·3); chloramphenicol (p.239·3).
Bacterial eye infections.

Chlornamol *Upha, Malaysia†; Beacons, Singapore.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms; fever; hypersensitivity reactions; pain.

Chlorochin *Streuli, Switz.*
Chloroquine phosphate (p.599·3).
Lupus erythematosus; malaria; polyarthritis.

Chlorocid *EGIS, Hung.†.*
Chloramphenicol (p.239·3).
Bacterial skin infections.

Chlorocid-H *EGIS, Hung.†.*
⊗ Hydrocortisone acetate (p.1535·2); chloramphenicol (p.239·3).
Bacterial eye and skin infections.

Chlorocyclinum *Chema-Elektromet, Pol.*
Chlortetracycline hydrochloride (p.243·1).
Infected skin disorders.

Chlorofarm-S *Biostam (Βιοσταμ), Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Chlorofoz *Am-Europharma, Philipp.*
Chloroquine phosphate (p.599·3).
Amoebic infections; lupus erythematosus; malaria.

Chlorohex
Geistlich, Singapore.
Chlorhexidine (p.1635·2).
Skin and wound disinfection.

Geistlich, Switz.†.
Chlorhexidine gluconate (p.1635·3) and/or chlorhexidine hydrochloride (p.1635·3).
Skin and hand disinfection.

Colgate-Palmolive, UK.
Chlorhexidine gluconate (p.1635·3).
Mouth infections; oral hygiene.

Chlorohistol *Julphar, UAE.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity.

Chloromag *Merit, USA.*
Magnesium chloride (p.1679·1).

Chloro-Magnesion *PPDH, Fr.†.*
Magnesium chloride (p.1679·1); calcium chloride (p.1675·2).
Magnesium deficiency.

Chloromycetin
Elea, Arg.
Chloramphenicol (p.239·3), chloramphenicol palmitate (p.239·3); or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Pfizer, Austral.; Pfizer, NZ.
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Erfa, Canad.
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Pfizer, Chile; Pfizer, India.
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Pfizer, Fin.; Goldshield, Irl.; Pfizer, S.Afr.; Pfizer, Spain†; Pfizer, Swed.; Goldshield, UK; Monarch, USA; Pfizer, Venez.†.
Chloramphenicol (p.239·3).
Bacterial infections.

Pfizer, Mex.
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Pfizer, Philipp.
Chloramphenicol palmitate (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Chloromycetin Ear Drops *Pfizer, India.*
Chloramphenicol (p.239·3); benzocaine (p.1854·1).
Bacterial ear infections.

Chloronguent *Sterop, Belg.*
Tosylchloramide sodium (p.1665·1).
Wounds.

Chloropect *Adcock Ingram, S.Afr.*
⊗ Kaolin (p.1738·1); pectin (p.2145·2); bismuth subcarbonate (p.1711·1); chloroform and morphine tincture (p.86·3).
Diarrhoea.

Chloropernazinum *Labor, Pol.*
Prochlorperazine maleate (p.1020·1).
Mania; migraine; nausea and vomiting; schizophrenia; vestibular disorders.

Chloroph *Seng, Hong Kong; Seng, Thai.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Chlorophyl liquid "Schuh" *Coradol, Ger.†.*
Chlorophyllin (p.1471·1); crataegus (p.2289·1).
Asthenia; deodorant.

Chlorophyll *Potter's, UK.*
Kola nut (p.2416·1); chlorophyllin (p.1471·1).
Tonic.

Chlorophyllin Salbe "Schuh" *Coradol, Ger.†.*
Chlorophyllin (p.1471·1); chamomilla; arnica; hamamelis (p.2318·2).
Wounds.

Chloropotassuril *Melisana, Belg.*
Potassium chloride (p.1684·3).
Potassium depletion.

Chloroptic *Allergan, Israel; Allergan, S.Afr.†; Allergan, USA†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Chloro-S *Medic+Aid, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Chlorosan *PannonPharma, Hung.†.*
Chlorquinaldol (p.242·3).
Skin infections.

Chlorosin *General Drugs, Thai.*
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Chlorotracin *Chew, Thai.*
Chloramphenicol (p.239·3); clioquinol (p.254·1); phthalylsulfathiazole (p.315·1).
Gastrointestinal infections.

Chlorphed-LA *Hauck, USA; Roberts, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Chlorphedrine SR *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Chlorphemin *Tanabe, Indon.*
⊗ Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); alcohol (p.1625·2).
Cough; respiratory-tract congestion.

Chlorphen *Caps, S.Afr.*
Chloramphenicol (p.239·3).
Bacterial infections.

Chlorphenicol *Rekah, Israel.*
Chloramphenicol (p.239·3).
Bacterial skin infections.

Chlorpheno *Milano, Thai.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlorphenon *Ethica, Indon.; Soho, Indon.*
Chlorphenamine maleate (p.571·3).
Allergic disorders.

Chlor-Pro *Schein, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlorpromanyl *Technilab, Canad.†.*
Chlorpromazine hydrochloride (p.969·2).
Nausea and vomiting; psychoses.

Chlorpromasit *Sriprasit, Thai.*
Chlorpromazine (p.969·1).
Behaviour disorders in children; nausea and vomiting; psychoses.

Chlorpromed *Medifive, Thai.*
Chlorpromazine hydrochloride (p.969·2).
Mania; nausea and vomiting; schizophrenia; sedation.

Chlorpyrimine *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlorquin *Aspen, Austral.; Healthcare Logistics, NZ.*
Chloroquine phosphate (p.599·3).
Amoebic hepatitis; lupus erythematosus; malaria; rheumatoid arthritis and related collagen disease.

Chlorsedyl *Beacons, Singapore.*
⊗ Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Cough; hypersensitivity reactions; respiratory-tract congestion.

Chlorsig *Sigma, Austral.; Sigma, Hong Kong; Healthcare Logistics, NZ; Sigma, Philipp.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Chlorsuccillin *Jelfa, Pol.*
Suxamethonium (p.1912·1).
Depolarising neuromuscular blocker.

ChlorTan *Cypress, USA.*
Chlorphenamine tannate (p.572·2).
Hay fever.

ChlorTan D *Cypress, USA.*
Chlorphenamine tannate (p.572·2); phenylephrine tannate (p.1568·3).
Hay fever; sinusitis.

Chlortralim *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlortetracycline hydrochloride (p.243·1).
Bacterial eye infections.

Chlor-Trimeton *Schering-Plough, Philipp.; Schering-Plough, S.Afr.†; Schering-Plough, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Chlor-Trimeton 4 Hour Relief *Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Chlor-Trimeton 12 Hour Relief *Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Chlor-Tripolon *Schering, Canad.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity disorders; pruritus.

Chlor-Tripolon Decongestant *Schering, Canad.†.*
Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Chlor-Tripolon ND *Schering, Canad.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Chlorvescent
Note. This name is used for preparations of different composition.
Aspen, Austral.
Potassium chloride (p.1684·3); potassium bicarbonate (p.1673·1); potassium carbonate.
Potassium deficiency.

Healthcare Logistics, NZ.
Potassium chloride (p.1684·3).
Potassium deficiency.

Chlorvytol *Tolmann, Philipp.*
Vitamin B substances; ascorbic acid; lysine; taurine; Chlorella pyrenoidosa (p.1922·1).
Nutritional supplement.

Chlorzide *Malayan, Singapore†.*
⊗ Chlorothiazide (p.1243·1).
Hypertension; oedema.

Chlorzox *Pharmasant, Thai.†.*
Chlorzoxazone (p.1894·3).
Skeletal muscle pain and spasm.

Chlotenor *Sandoz, Gr.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Choanol N *Hanosan, Ger.*
Homoeopathic preparation.

Choats Extract of Lettuce Cough Mixture
Pfizer Consumer, S.Afr.
Lettuce (p.2415·2); tolu balsam (p.1574·2); honey (p.1948·2).
Coughs.

Chocaton *Mirren, S.Afr.*
Multivitamin preparation (p.1922·1).

Chocovite *Torbet, Irl.*
Calcium gluconate (p.1675·3); ergocalciferol (p.1987·1).
Calcium deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Chofabol *Allen, Mex.*
Magnesium sulfate (p.1679·3); boldo (p.2267·2); cynara (p.2291·2); belladonna (p.2263·3); peptone.
Biliary-tract disorders.

Chofitol *Millet-Franklin, Arg.*
Cynara (p.2291·2).
Biliary-tract disorders; diuretic; hypercholesterolaemia.

Chofranina *De Mayo, Braz.*
Cascara (p.1715·2); cynara (p.2291·2); carmellose (p.2142·1).
Constipation.

Choice DM
Note. This name is used for preparations of different composition.
Mead Johnson Nutritionals, Canad.†; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.†; BMS, USA.
Preparation for enteral nutrition (p.1922·1).
Abnormal glucose tolerance.

BMS, USA.
Test for glycated haemoglobin in blood (p.2314·1).

Choice DM Daily Moisturizing *BMS, USA.*
Emollient.

Choice DM Gentle Care *BMS, USA.*
Cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Cholac *Alra, USA†.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Cholagogum *Cassella-med, Ger.*
Cynara (p.2291·2).
Dyspepsia.

Cholagogum F *Nattermann, Ger.†.*
Turmeric (p.1473·2); greater celandine (p.2317·1).
Biliary-tract disorders.

Cholagogum N *Nattermann, Ger.†.*
Greater celandine (p.2317·1); turmeric (p.1473·2); peppermint oil (p.1761·2).
Biliary disorders; gallstones.

Cholagol
Note. This name is used for preparations of different composition.
Galena, Cz.; Ivax, Cz.
Frangula bark (p.1732·2); magnesium salicylate (p.79·2); turmeric (p.1473·2); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2).
Biliary and liver disorders.

Ivax, Hung.
Frangula (p.1732·2); magnesium salicylate (p.79·2); turmeric (p.1473·2).
Biliary-tract disorders.

Galena, Rus.
Emodin buckthorn; magnesium salicylate (p.79·2); turmeric (p.1473·2); essential oils.

Cholagutt *Korangi, Port.†.*
Greater celandine (p.2317·1); milk thistle (p.1452·1); peppermint leaf (p.1761·2); lavender (p.2331·1); calamus (p.2271·3); podophyllum (p.1610·2).
Biliary tract disorders.

Cholagutt-N *Biocur, Ger.†.*
Greater celandine (p.2317·1); spike lavender (p.2391·3); peppermint leaf (p.1761·2).
Biliary disorders; gallstones.

Chol-Aid *Chefaro, UK.*
Policosanol (p.1373·3); omega-3 fish oil (p.1362·2).
Dietary supplement.

Cholal Modificado *Italmex, Mex.*
Liver antitoxin (p.2337·3); sodium sulfate; magnesium sulfate; sodium chloride; potassium nitrate (p.1667·1).
Biliary-tract disorders; liver disorders.

Cholamid *Polfa Pabianice, Pol.*
Nicotinyl methylamide.
Biliary-tract and liver disorders.

Cholan-HMB *Ciba Consumer, USA.*
Dehydrocholic acid (p.2292·2).
Biliary stasis; constipation.

Chol-Arbuz NF *Bittermedizin, Ger.*
Pancreatin (p.2360·1); turmeric (p.1473·2).
Chol-Arbuz N formerly contained papain, pancreatin, and turmeric.
Digestive disorders.

Cholarist *Steiner, Ger.*
Greater celandine (p.2317·1).
Smooth muscle spasm.

Cholasyn *Rolmex, Canad.†.*
Cascara (p.1715·2); senna (p.1769·2).

Cholasyn II *Rolmex, Canad.*
Cascara (p.1715·2); senna (p.1769·2).
Constipation.

Cholavisol *Herbapol Krakow, Pol.*
Taraxacum (p.2395·1); helichrysum; peppermint leaf (p.1761·2); achillea (p.2245·2); frangula bark (p.1732·2); greater celandine (p.2317·1).
Digestive disorders.

Cholax *Maver, Chile.*
Senna (p.1769·2).
Constipation.

Cholbalance *Ikapharmindo, Indon.*
Plant stanol ester (p.1373·2).
Hyperlipidaemias.

Choldestal *Krugmann, Ger.†.*
Capsules: Turmeric (p.1473·2).
Dyspepsia.

Chol-Do *Grasler, Ger.*
Homoeopathic preparation.

Cholebine *Mitsubishi, Jpn.*
Colestilan (p.1252·2).
Hypercholesterolaemia.

Cholebrine *Viatris, Neth.†.*
Iocetamic acid (p.1481·3).
Contrast medium for cholecystography.

Cholecis *Schering, UK.*
Technetium-99m mebrofenin (p.2055·3).
Assessment of liver function; hepatobiliary imaging.

Chole-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.
Chole-cyl Ho-Len-Complex formerly contained apocynum, belladonna, berberis, carduus mar, chamomilla, cholesterinum, colocynthis, and taraxacum.

Cholecysmon *Riemser, Ger.†.*
Ox bile extract (p.2266·3).
Liver, bile, and pancreas disorders.

Choledian *Mediam, Neth.*
Technetium-99m mebrofenin (p.2055·3).
Radionuclide imaging of the liver and biliary-tract.

Choledyl *Erfa, Canad.; Galenica, Gr.; Warner Chilcott, USA†.*
Choline theophyllinate (p.1119·3).
Asthma; obstructive airways disease.

Choledyl Expectorant *Erfa, Canad.*
Choline theophyllinate (p.1119·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Cholegerol *Holistica, Fr.†.*
Soya lecithin (p.2332·2); wheat germ; shiitake; herbs (p.1922·1).
Cholesterol reduction.

Cholemed *3DDD, Belg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Choleodoron
Note. This name is used for preparations of different composition.
Weleda, Austria; Weleda, S.Afr.; Weleda, Switz.†.
Greater celandine (p.2317·1); Javanese turmeric (p.2406·3).
Liver and biliary-tract disorders; liver and gallbladder disorders.

Weleda, Fr.; Weleda, Ger.; Weleda, Neth.; Weleda, UK.
Homoeopathic preparation.

Cholescreen *Omega, Fr.†.*
Test for total cholesterol in blood.

Cholesol *Herbapol Wroclaw, Pol.*
Chamomile (p.2279·3); equisetum (p.2299·3); frangula (p.1732·2); St John's wort (p.422·3); rose fruit (p.2381·2); taraxacum (p.2395·1); coriander (p.2288·1); juniper (p.2328·2); helichrysum; knotgrass (p.2329·2).
Biliary-tract disorders; liver disorders.

Cholespar *Pharos, Indon.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Cholestabyl *Fournier, Ger.*
Colestipol hydrochloride (p.1252·2).
Hypercholesterolaemia.

Cholestad *Littman, Philipp.*
Simvastatin (p.1390·2).
Coronary heart disease; hyperlipidaemias.

Cholestagel *Genzyme, Cz.; Genzyme, Neth.; Genzyme, Port.; Genzyme, UK.*
Colesevelam hydrochloride (p.1252·1).
Hypercholesterolaemia.

Cholestat *Kalbe, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Cholesterol Reducing Plan *Natural Life, Arg.†.*
Sitosterol (p.1373·2); omega-3 fish oil (p.1362·2); ispaghula (p.1737·1); lecithin (p.2332·2); avena (p.2262·1); chromium (p.1934·3); vitamins.
Hypercholesterolaemia.

Cholesterol Support *Reese, USA.*
Sitosterol (p.1373·2); zinc citrate (p.1999·2).

Cholestil *Polfa, Cz.; Polfa Pabianice, Pol.*
Hymecromone (p.2323·2).
Biliary-tract disorders; liver disorders.

Cholestin *Pharmanex, USA.*
Citrus polymethoxylated flavones; geraniol (p.2310·3); omega-3 fatty acids (p.1362·1); tocotrienols.
Formerly contained policosanol.
Nutritional supplement.

Cholest-X L112 *Homeocan, Canad.†.*
Homoeopathic preparation.

Cholesvit *Graha, Indon.*
Lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1).
Hypercholesterolaemia.

Choletec *Bracco, USA.*
Technetium-99m mebrofenin (p.2055·3).
Hepatobiliary imaging.

Cholex *Silanes, Mex.*
Menthol (p.2340·1); pinene (p.2368·3); menthone (p.2340·2); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3).
Biliary-tract disorders.

Cholhepan *Doctum, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Cholhepan N *Schuck, Ger.*
Milk thistle (p.1452·1); greater celandine (p.2317·1); aloes (p.1705·2).
Constipation.

Choliatron *Seber, Port.*
Trepibutone (p.2403·3).
Biliary-tract disorders.

Cholinex *GSK, Pol.*
Choline salicylate (p.36·3).
Mouth and throat disorders.

Cholinogo *Pasteur, Chile.*
Peptone magnesium sulfate (p.1679·3).
Biliary-tract and liver disorders.

Cholinoid *Goldline, USA.*
Vitamin B substances with vitamin C (p.1922·1); lemon bioflavonoids (p.2304·1).

Cholipin *Vargas, Venez.*
Fenipentol (p.2302·3); octibenzonium bromide.
Biliary-tract disorders.

Cholipravin *Kleva, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Cholirene *Unipharma, Gr.*
Hymecromone (p.2323·2).
Spasmolytic.

Cholisal *Jelfa, Rus.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Mouth disorders.

Cholitol *Herbapol Krakow, Pol.*
Belladonna (p.2263·3); greater celandine (p.2317·1); turmeric (p.1473·2); peppermint leaf (p.1761·2); taraxacum (p.2395·1); valerian (p.2410·1).
Biliary-tract disorders.

Cholit-Ursan *Stada, Ger.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones.

Chol-Kugeletten Neu *Dolorgiet, Ger.*
Greater celandine (p.2317·1); aloes (p.1705·2).
Constipation.

Chol-Less *Rafa, Israel†.*
Colestyramine (p.1252·3).
Atherosclerosis; hypercholesterolaemia; myocardial infarction; pruritus in partial biliary obstruction.

Cholofalk *Falk, Ger.*
Ursodeoxycholic acid (p.2408·1).
Primary biliary cirrhosis.

Chologrfin *Squibb Diagnostics, USA.*
Meglumine adipiodone (p.1475·2).
Contrast medium for biliary-tract radiography.

Cholonerton *Sanova, Austria.*
Hymecromone (p.2323·2).
Liver and gallbladder disorders.

Cholosom Phyto N *Hevert, Ger.*
Greater celandine (p.2317·1); turmeric (p.1473·2).
Liver and bile disorders.

Cholosom SL *Hevert, Ger.†.*
Greater celandine (p.2317·1); Javanese turmeric (p.2406·3); taraxacum (p.2395·1).
Liver and bile disorders.

Cholosom-Tee *Hevert, Ger.*
Caraway (p.2276·3); Javanese turmeric (p.2406·3); taraxacum (p.2395·1); milk thistle (p.1452·1); peppermint leaf (p.1761·2).
Biliary-tract disorders; gastrointestinal disorders.

Cholspasmin *Dolorgiet, Ger.*
Hymecromone (p.2323·2).
Biliary-tract disorders.

Cholspasmin Phyto *Merck, Ger.†.*
Greater celandine (p.2317·1).
Biliary and gastrointestinal spasm.

Cholspasminase N *Merck, Ger.; Nordmark, Ger.*
Pancreatin (p.2360·1).
Pancreatic disorders.

Chol-Spasmoletten *Dolorgiet, Ger.*
Hymecromone (p.2323·2).
Biliary disorders.

Cholstat
Note. This name is used for preparations of different composition.
Alphapharm, Austral.; Ivax, Irl.
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia; hyperlipidaemias.

Bayer, Cz.†.
Cerivastatin sodium.
Hypercholesterolaemia.

Cholvastin *Sanbe, Indon.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Chomelanum *Brady, Austria; Schur, Ger.*
Choline stearate.
Burns; insect stings; skin disorders; soft-tissue disorders; sports injuries; wounds.

Chondril *Hovid, Malaysia.*
Chondroitin sulfate (p.2280·3).
Dietary supplement.

Chondroitine-Akos
Note. This name is used for preparations of different composition.
Sintez, Rus.
Capsules: Chondroitin sulfate (p.2280·3).
Osteoarthritis.

Sintez, Rus.
Ointment: Chondroitin sulfate (p.2280·3); dimethyl sulfoxide (p.2022·1).
Degenerative joint disorders.

Chondrolon *Microgen, Rus.†.*
Chondroitin sulfate sodium (p.2280·3).
Degenerative joint disorders.

Chondro-PA *Landson, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); minerals; vitamin C (p.1922·1).
Osteoarthritis.

Chondrosteo *Equilibre Attitude, Fr.†.*
Glucosamine sulfate; maltodextrin; chondroitin sulfate; harpagophytum; meadowsweet; black currant; bamboo; minerals (p.1922·1).
Musculoskeletal and joint disorders; nutritional supplement.

Chondrosulf *Genevrier, Fr.*
Chondroitin sulfate sodium (p.2280·3).
Osteoarthritis of the knee and hip.

Chondroxide *Nizpharm, Rus.*
Chondroitin sulfate (p.2280·3); dimethyl sulfoxide (p.2022·1).
Degenerative joint disorders; soft-tissue injury.

Chooz *Schering-Plough, USA.*
Calcium carbonate (p.1714·1).
Hyperacidity.

Chophytol *Millet Roux, Braz.; Rosa-Phytopharma, Fr.; Rosa-Phytopharma, Rus.; Rosa-Phytopharma, Switz.*
Cynara (p.2291·2).
Atherosclerosis; dyspepsia; gastrointestinal disorders; kidney disorders; liver and biliary-tract disorders; obesity.

Chopintac *Nufarindo, Indon.*
Ranitidine hydrochloride (p.1766·1).
Pathological hypersecretory disorders; peptic ulcer.

Choragon *Ferring, Belg.; Ferring, Braz.†; Ferring, Ger.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Malaysia; Ferring, Mex.; Ferring, Neth.; Ferring, Pol.; Ferring, Rus.; Er-Kim, Turk.; Ferring, UK.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism; male and female infertility.

Chorei-to *Tsumura, Jpn.*
Alisma rhizome; polyporus sclerotium; poria sclerotium; gelatin; talc.
Traditional Kampo medicine.

Chorex *Hyrex, USA†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Male and female infertility; male hypogonadism; prepubertal cryptorchidism.

Chorigon *Teva, Israel†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; female infertility; male hypogonadism.

Choriomon *IBSA, Hong Kong; CORNE, Mex.; IBSA, Switz.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; male and female infertility; male hypogonadism.

Choron *Forest Pharmaceuticals, USA.*
⊗ Chorionic gonadotrophin (p.2085·1).
Male and female infertility; male hypogonadism; prepubertal cryptorchidism.

Choto-san *Tsumura, Jpn.*
Gypsum; citrus unshiu peel; ophiopogon tuber; pinellia tuber; poria sclerotium; ginseng; saposhnikovia root; liquorice; ginger; uncaria thorn; chrysanthemum flower.
Traditional Kampo medicine.

Chributan *Chrispa (Χρισπα), Gr.*
Butamirate citrate (p.1553·1).
Cough.

Chricetyl *Sanofarm, Gr.*
Acetylcysteine (p.1548·2).

Chrisracol *Christo, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); terpin hydrate (p.1573·3); menthol (p.2340·1).
Cold symptoms; coughs; nasal congestion.

Christamol *Christo, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Christatin *Chrispa (Χρισπα), Gr.*
Simvastatin (p.1390·2).

Chromagen *Ther-Rx, USA.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); intrinsic factor (stomach preparation) (p.2326·3).
Succinic acid and vitamin C (p.1983·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen FA *Ther-Rx, USA.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Succinic acid and vitamin C (p.1983·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen Forte *Ther-Rx, USA.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Succinic acid and vitamin C (p.1983·3) are included in this preparation to increase the absorption and availability of iron.
Anaemias.

Chromagen OB *Savage, USA.*
Multivitamin and mineral preparation (p.1922·1).

Chroma-Pak *Smith & Nephew SoloPak, USA.*
Chromium trichloride (p.1934·3).
Additive for intravenous total parenteral nutrition solutions.

Chromargon *Richard, Fr.*
Hydroxyquinoline sulfate (p.2323·1); acriflavinium chloride (p.1625·1).
Skin infections.

Chromasvelt *Pharma Nord, Fr.*
Chromium trichloride (p.1934·3).
Appetite suppressant.

Chrome *Eagle, Austral.*
Chromium amino acid chelate (p.1934·3).
Dietary supplement.

Chromelin Complexion Blender *Summers, USA.*
Dihydroxyacetone (p.1594·1).
Hypopigmentation; vitiligo.

Chromo-Z *Lewison, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Chronadalate *Bayer, Fr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Chron-ASA *Sigma, Braz.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Chronocard *Cesra, Pol.*
Crataegus (p.2289·1).
Arrhythmias; heart failure.

Chronocard N *Cesra, Ger.*
Crataegus (p.2289·1).
Heart failure.

Chronocorte *Streuli, Switz.*
⊗ Dexamethasone (p.1526·1); dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Chrono-Indocid *MSD-Chibret, Fr.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Chronophyllin *Byk Madaus, S.Afr.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Chronovera *Pfizer, Canad.; Searle, Neth.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Chronulac *Hoechst Marion Roussel, USA.*
Lactulose (p.1738·2).
Constipation.

Chrysocor *Sanum-Kehlbeck, Ger.†.*
Placenta extracts (human) (p.2337·3).
Sexual disorders.

Chuker
Merisant, Arg.
Oral liquid: Saccharin sodium (p.1960·3); aspartame (p.1930·1).
Formerly contained saccharin sodium and sodium cyclamate.
Sugar substitute.

Merisant, Arg.
Tablets: Saccharin sodium (p.1960·3); aspartame (p.1930·1).
Formerly contained saccharin sodium, sodium cyclamate, and calcium cyclamate.
Sugar substitute.

CHX Dental Gel *Dentsply, Ger.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Chymodiactin *Link, Austral.; Eight, Spain†.*
Chymopapain (p.2281·2).
Herniated lumbar intervertebral disc.

Chymol *Anglian, UK.*
Eucalyptus oil (p.2301·2); terpineol (p.2396·1); methyl salicylate (p.85·3); phenol (p.1656·1).
Bruises; chapped skin; chilblains; sprains.

Chymoral *Cooper (Κοπερ), Gr.*
Chymotrypsin (p.2281·3); trypsin (p.2405·3).
Inflammatory disorders.

Ciagen *Craveri, Arg.*
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Cialis *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Tadalafil (p.2196·2).
Erectile dysfunction.

Cianofer *Vincenti, Venez.*
Ferric ammonium citrate (p.1938·1); copper sulfate (p.1935·3); cyanocobalamin (p.1980·2).
Anaemias.

Cianomin *Offenbach, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Cianon B12 *Ducto, Braz.*
Cyanocobalamin (p.1980·2).

Cianotrat *Delta, Braz.*
Vitamin B substances (p.1922·1).

Cianotrat-Dexa *Delta, Braz.*
⊗ Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); dexamethasone (p.1526·1) or dexamethasone phosphate (p.1526·2).
Procaine hydrochloride (p.1869·1) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis.

Ciapar *Fada, Arg.†.*
⊗ Isoprenaline (p.1316·3).

Ciatyl-Z *Bayer, Ger.*
Zuclopenthixol acetate (p.1040·3), zuclopenthixol decanoate (p.1040·3), or zuclopenthixol hydrochloride (p.1040·3).
Psychoses.

Ciazil
Note. This name is used for preparations of different composition.
Douglas, Austral.
Citalopram hydrobromide (p.385·3).
Depression.

Genepharm, Gr.
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Ciba Vision Cleaner For Sensitive Eyes *Ciba Vision, USA.*
Cleaning solution for soft contact lenses (p.1622·2).

Cibacalcin *Novartis, Austria; Novartis, Ger.†; Novartis, Israel.*
Calcitonin (human) (p.1093·1).
Hypercalcaemia; osteolysis; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Cibacalcina *Novartis, Braz.†; Novartis, Port.†.*
Calcitonin (human) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Cibacalcine *Novartis, Fr.*
Calcitonin (human) (p.1093·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Cibace *Novartis, S.Afr.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Cibacen *Novartis, Belg.; Meda, Denm.; Meda, Ger.; Novartis, Gr.; Novartis, Indon.; Meda, Irl.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Neth.; Novartis, Philipp.; Meda, Spain; Novartis, Switz.; Novartis, Turk.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension; renal failure.

Cibacene *Meda, Fr.*
Benazepril hydrochloride (p.1223·2).
Glomerulonephropathy; hypertension.

Cibadrex *Meda, Fr.; Meda, Ger.; Novartis, Gr.; Novartis, Ital.; Novartis, Neth.; Novartis, S.Afr.; Meda, Spain; Novartis, Switz.; Novartis, Turk.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Cibaflam *Novartis, Ger.*
⊗ Fluorometholone (p.1532·3); gentamicin sulfate (p.282·1).
Inflammatory eye infections.

Cibalena A *Novartis, Braz.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Cibalgin Compositum N *Novartis, Ger.†.*
Propyphenazone (p.119·3); codeine phosphate (p.37·2).
Pain.

Cibalgina Due Fast *Novartis Consumer, Ital.*
Ibuprofen (p.64·2).
Fever; influenza symptoms; pain.

Cibenol *Astellas, Jpn.*
Cibenzoline succinate (p.1244·2).
Tachyarrhythmias.

Cibis *Siam Bheasach, Thai.*
Chlorphenamine maleate (p.571·3); lidocaine hydrochloride (p.1862·3); hexachlorophene (p.1646·1); methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Dermatitis; eczema; insect bites; pruritus; scalds; wounds.

Ciblex *Drugtech, Chile.*
Mirtazapine (p.409·2).
Depression.

Ciblor *Pierre Fabre Sante, Fr.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Cibral *Ranbaxy, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Cibren *Ethica, Indon.*
Citicoline (p.2283·3).
Head injury; hemiplegia.

Cibrogan *Roux-Ocefa, Arg.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Cibronal *Liferpal, Mex.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Cica-Care *Smith & Nephew, Fr.; Smith & Nephew, Ital.; Smith & Nephew, Philipp.; Smith & Nephew Healthcare, UK.*
Silicone (p.2032·1).
Hypertrophic scars; keloids.

Cicactive *Uriage, Fr.*
Barrier cream.

Cicaderma
Note. This name is used for preparations of different composition.
Boiron, Canad.
Homoeopathic preparation.

Boiron, Cz.; Boiron, Fr.; Boiron, Port.
Ledum palustre; pulsatilla (p.2376·3); calendula (p.2273·1); St John's wort (p.422·3); achillea (p.2245·2).
Burns; insect stings; wounds.

Cicadin *Nordin, Mex.*
Calendula (p.2273·1).

Cicafem *koGen, UK.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.
Androgen-dependent acne and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Cicafissan *Uhlmann-Eyraud, Switz.*
Casein hydrolysate (p.1934·1); kaolin (p.1738·1); bismuth subnitrate (p.1711·2); zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Cicalfate *Silesia, Chile; Avene, Fr.*
Sucralfate (p.1772·2); copper sulfate (p.1935·3); zinc sulfate (p.1999·2); zinc oxide (p.1621·2).
Minor wounds; skin irritation.

Cicamosa *Boots Healthcare, Fr.*
Mimosa tenuiflora.
Skin disorders.

Cicaplast *Roche-Posay, Fr.*
Zinc gluconate (p.1999·2); manganese gluconate (p.1956·2); sodium hyaluronate (p.2320·1); copper gluconate (p.1935·3).
Skin lesions.

Cicapost
Isdin, Chile.
Dexpanthenol (p.2362·1); rose oil (p.2381·2); glycerol (p.2314·2); nicotinamide (p.1957·3); centella triterpenes (p.1592·3); alfa tocoferil acetate; dextran sulfate (p.2293·1).
Cicatrisation.

Isdin, Port.
Dexpanthenol (p.2362·1); rose oil (p.2381·2); glycerol (p.2314·2); nicotinamide; cravagem asiatica triterpenes; alfa tocoferil acetate; dextran sulfate (p.2293·1).
Cicatrisation.

Cicatral *Uriach Aquilea OTC, Spain.*
Peru balsam (p.2365·3); ergocalciferol (p.1987·1); estrone (p.2101·2); benzocaine (p.1854·1); vitamin A (p.1971·2); tyrothricin (p.358·2).
Burns; skin disorders; ulcers; wounds.

Cicatrene
Note. This name is used for preparations of different composition.
Farmoquimica, Braz.
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); cysteine; glycine; threonine.
Skin infections.

Pfizer Consumer, Ital.
Cream; topical powder: Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Skin infections.

Pfizer Consumer, Ital.
Topical spray: Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Skin infections.

Cicatrex *Investi, Arg.; GSK, Austria; GSK, Ger.†; Pfizer Consumer, Switz.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); -cysteine; -threonine; glycine.
Bacterial skin infections; burns; ulcers; wounds.

Cicatrex Baby *Investi, Arg.*
Barrier preparation.

Cicatridine *HRA, Fr.*
Sodium hyaluronate (p.2320·1); centella (p.1592·3); calendula (p.2273·1); aloe vera (p.1588·2); melaleuca oil (p.2338·2).
Vaginal atrophy; vaginal injury.

Cicatrin
Pfizer Consumer, Austral.; GSK, Canad.; GSK, Irl.; GSK Consumer, Port.; Pfizer Consumer, S.Afr.; GSK, UK†.
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); -cysteine; glycine; -threonine.
Anorectal disorders; burns; infected skin disorders; skin ulcers; wounds.

Cicatrina *Fada, Arg.*
Zinc oxide (p.1621·2); ichthammol (p.1599·1).
Skin disorders.

Cicatrizan *Johnson & Johnson, Braz.†.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); cysteine; glycine; threonine.
Skin infections.

Cicatrizol *Ronnet, Arg.*
Sodium acexamate (p.2245·2); gentamicin sulfate (p.282·1).
Burns; wounds.

Cicatrol *Hexa, Arg.*
Zinc undecenoate (p.549·3); zinc oxide (p.1621·2); sodium propionate (p.545·3); salicylic acid (p.1612·2); coal tar (p.1616·2).
Burns; fungal skin infections; ulcers; wounds.

Cicatryl *UCB, Fr.*
Allantoin (p.1588·1); guaiazulene (p.2317·3); chlorocresol (p.1640·1); alpha tocoferil acetate (p.1992·3).
Superficial burns and wounds.

Cicatul *ICN, Arg.*
Wheat germ (p.2415·1); phenoxyethanol (p.1657·1).
Vulvo-vaginal disorders; wounds.

Cicladol *Farmalab, Braz.; Master Pharma, Ital.*
Piroxicam betadex (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ciclafast *Master Pharma, Ital.†.*
Piroxicam pivalate (p.118·2).
Musculoskeletal, joint, and peri-articular disorders.

Ciclamil
Note. This name is used for preparations of different composition.
LKM, Arg.
Cyproterone (p.2089·2).

Silesia, Chile.
Cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal spasm.

Ciclan *Rowe-Fleming, Venez.†.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm.

Ciclavix *Luper, Braz.†.*
Aciclovir (p.862·3).

Ciclem *Pharmacare, Philipp.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cicletan *Pharmanel, Gr.†.*
Lorazepam (p.1004·1).
Anxiety disorders.

Cicletex *Phoenix, Arg.*
⊗ Ciclesonide (p.1521·3).
Asthma.

Ciclidon *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ciclidoxan *Richmond, Arg.*
Doxycycline (p.267·1).
Bacterial infections.

Ciclinil *Farmoz, Port.*
Clarithromycin (p.248·2).
Bacterial infections.

Ciclisan *Sanval, Braz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Ciclo *Uniao Quimica, Braz.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ciclobiotico
Note. This name is used for preparations of different composition.
Atral, Port.†.
Capsules: Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Atral, Port.†.
Eye ointment; ointment: ⊗ Tetracycline hydrochloride (p.347·2); prednisolone (p.1540·3).
Bacterial infections.

Ciclobrain *Coronet, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Ciclochem *Novag, Spain.*
Ciclopirox olamine (p.529·2).
Fungal skin and nail infections; vulvovaginal candidiasis.

Ciclocris *Cristalia, Braz.†.*
Aciclovir (p.862·3).

Ciclocur *Schering, Arg.*
White tablets, estradiol valerate (p.2097·3); coloured tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; menstrual disorders.

Cicloderm *Trima, Israel; Trima, Thai.†.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Cicloderm-C *Trima, Israel.*
⊗ Ciclopirox olamine (p.529·2); clobetasone butyrate (p.1522·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Ciclodin *Unison, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciclodrax *Cellofarm, Braz.†.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Ciclofalina *Almirall, Spain.*
Piracetam (p.368·2).
Cortical myoclonia; mental function impairment.

Ciclofast *Pharmacia, Venez.†.*
Piroxicam betadex (p.117·3).
Ankylosing spondylitis; dysmenorrhoea; osteoarthritis; rheumatoid arthritis.

Ciclofemme *Cifarma, Braz.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Cicloferon *Liomont, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Cicloftal *Oftalmi, Venez.†.*
Cyclopentolate hydrochloride (p.1879·3).
Production of cycloplegia and mydriasis.

Ciclohexal *Hexal, S.Afr.*
Ciclosporin (p.1822·2).
Graft-versus-host disease; psoriasis; transplant rejection.

Ciclokapron *Pfizer, Venez.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Ciclokebir *Aspen, Arg.*
Cyclophosphamide (p.702·1).

Ciclolato *Latinofarma, Braz.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Ciclolux *Allergan, Ital.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Ciclomex *Gynopharm, Chile.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
28-Day packs contain 24 active tablets and 4 inert tablets.
Combined oral contraceptive.

Ciclomidrin *Latinofarma, Braz.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Ciclon *Haller, Braz.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ciclopenal *Alcon, Arg.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Cicloplant *Abbott, Mex.*
Agnus castus (p.2249·1).
Menstrual disorders.

Cicloplegicedol *Edol, Port.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis.

Cicloplegico *Allergan, Braz.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Cicloplejico *Alcon Cusi, Spain; Llorens, Spain.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis; uveitis.

Ciclopoli *Taurus, Ger.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Cicloprimogyna *Schering, Braz.*
White tablets, estradiol valerate (p.2097·3); red tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders.

Cicloral *Hexal, Austral.; Hexal, Ger.*
Ciclosporin (p.1822·2).
Atopic eczema; graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Cicloralhexal *Hexal, Austria.*
Ciclosporin (p.1822·2).
Atopic dermatitis; auto-immune disorders; graft-versus-host disease; nephrotic syndrome; rheumatoid arthritis; transplant rejection.

Ciclosol *Ecosol, Switz.*
Ciclosporin (p.1822·2).
Atopic eczema; graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Ciclospasmol *Yamanouchi, Ital.†.*
Cyclandelate (p.1254·1).
Cerebral and peripheral vascular disorders.

Ciclostar *Medinfar, Port.*
Ciclosporin (p.1822·2).
Atopic eczema; graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplantation rejection; uveitis.

Ciclotal *Lemery, Mex.; Lemery, Rus.*
Medroxyprogesterone acetate (p.2113·1).
Malignant neoplasms; progestogen-only contraceptive.

Ciclotetryl *Fortbenton, Arg.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Ciclotos *Recalcine, Chile.*
Codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Ciclotran *Beta, Arg.†.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Cicloven *AGIPS, Ital.*
Pyricarbate (p.2377·1).
Vascular disorders.

Cicloviral *Medinfar, Port.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Ciclovulon *Sanval, Braz.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Combined oral contraceptive.

Ciclox
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Clonazepam (p.478·2).
Epilepsy; obsessive-compulsive disorder; panic disorder.
Oboi, Philipp.
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Ciclozinil *Aesculapius, Ital.*
Gentamicin sulfate (p.282·1).
Infected skin disorders.

Cicnor *Sanofi Synthelabo, Port.†.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).

Ciconazol *Cimed, Braz.*
Miconazole (p.541·2).
Fungal infections.

Cidacid *Tai Yu, Philipp.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Cidalin *Agis, Israel.*
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Cidegol C *Hofmann & Sommer, Ger.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Cidermex
Note. This name is used for preparations of different composition.
Panalab, Arg.
Pantothenic acid (p.1959·3).
Scalp disorders.
UCB, Fr.
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Eye disorders.

Cidetox *Offenbach, Mex.*
Aluminium hydroxide (p.1706·2); magnesium (p.1678·3); dimeticone (p.1770·2).
Gastric hyperacidity.

Cidex *Johnson & Johnson Medical, Fr.†; Johnson & Johnson, Ger.†; Johnson & Johnson Medical, USA.*
Glutaral (p.1645·2).
Instrument disinfection.

Cidex OPA *Johnson & Johnson, Fr.†; Johnson & Johnson, Ger.; Advanced Sterilization Products, USA.*
o-Phthaldialdehyde (p.1658·1).
Instrument disinfection.

Cidezyme *Johnson & Johnson, Fr.†.*
Proteolytic enzymes.
Instrument disinfection.

Cidilin *Errekappa, Ital.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; parkinsonism.

Cidine
Note. This name is used for preparations of different composition.
Recordati, Spain.
Cinitapride acid tartrate (p.1720·3).
Gastro-oesophageal reflux; gastroparesis.
Medifive, Thai.
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Cidoclar *Teva, Hung.*
Clarithromycin (p.248·2).
Bacterial infections.

Cidomel *Clonmel, Irl.†.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Cidominet *Rafarm, Gr.*
Calcium carbonate (p.1714·1); calcium lactate (p.1676·1); vitamin C (p.1922·1).
Formerly known as Cidominent.
Breast-feeding; osteoporosis; pregnancy.

Cidomycin *Sanofi-Aventis, Irl.; Aventis, Israel†; Aventis, S.Afr.; Aventis, UK; Beacon, UK.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Cidoston *Med-One, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Cidoten *Schering-Plough, Chile.*
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Cidoten V *Schering-Plough, Chile.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Cidoten Rapilento *Schering-Plough, Chile.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Lidocaine (p.1862·3) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Cidren *Vocate, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Dry mouth.

Cidrin *Abbott, Chile.*
⊗ Metamfetamine hydrochloride (p.2158·1).
Attention-deficit hyperactivity disorder.

Cidron *Hexal, Denm.; Gea, Fin.†; Hexal, Swed.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Cidrops *Faran, Gr.†.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

Cidroxal *Pharmathen, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciechocinski *Uzdrowisko Ciechocinek, Pol.*
Electrolyte solution (p.1667·1).
Musculoskeletal and joint disorders; neuralgia; peripheral vascular disorders; respiratory-tract disorders; skin disorders.

Cieldom *Teva Tuteur, Arg.*
Cabergoline (p.802·1).
Hyperprolactinaemia; inhibition of lactation; parkinsonism.

Ciella *Cooperation Pharmaceutique, Fr.*
Salicylic acid (p.1612·2).
Eye disorders.

Cif Candioli *Papaellinas (Παπαελληνας), Gr.*
Tetramethrin (p.2051·1); phenothrin (p.2048·3).
Head, body, and crab lice.

Cifarcaina *Behrens, Venez.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Cifespasmo *Northia, Arg.*
Hyoscine butylbromide (p.1734·1).
Muscle spasm.

Cifespasmo Compuesto *Northia, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Muscle spasm; pain.

Cifin *Pharmacodane, Denm.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciflan *Azevedos, Port.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciflo *Masa, Thai.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cifloc *Reddy, S.Afr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciflocina *Cibran, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciflogex *Cimed, Braz.*
Benzydamine hydrochloride (p.27·3).
Inflammation; pain.

Ciflolan *Olan-Kemed, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciflon *Lapi, Indon.*
Citrus bioflavonoids (p.2304·1); diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Ciflos *Guardian, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciflosin *Deva, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciflox
Note. This name is used for preparations of different composition.
Lannacher, Austria; Medley, Braz.; Roemmers Rowe, Venez.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.
Alcon, Denm.
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Infected ear disorders.
Bayer, Fr.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cifloxager *Gerard, Irl.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cifloxan *Vitapan, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cifloxin
Pharmabiotics, Chile; Quality, Hong Kong.
Ciprofloxacin (p.243·3).
Bacterial infections.
Sandoz, Hung.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.
Siam Bheasach, Malaysia.
Ciprofloxacin lactate (p.243·3).
Bacterial infections.
Siam Bheasach, Thai.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cifloxinal *ProMed, Cz.; Promed, Rus.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cifloxtron *Ariston, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cifluron *Il-ko, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cifoxim *Taiwan Biotech, Philipp.*
Cefazolin (p.222·1).
Bacterial infections.

Cifran
Ranbaxy, Cz.; Ranbaxy, Hung.; Merck, Mex.; Douglas, NZ; Ranbaxy, Pol.; Ranbaxy, S.Afr.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.
Ranbaxy, India; Ranbaxy, Rus.; Ranbaxy, Thai.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.
Ranbaxy, Malaysia.
Ciprofloxacin (p.243·3).
Bacterial infections.

Cigamet *General Drugs, Thai.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer.

Cigamete *Prodotti, Braz.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ciganclor *Richmond, Arg.*
Ganciclovir (p.879·1).
Viral infections.

Cigmadil *Collins, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Cig-Ridettes *Or-Dov, Austral.†.*
⊗ Lobeline hydrochloride (p.2157·2).
Aid to smoking withdrawal.

Cikavit *Knop, Chile.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Skin irritation; wounds.

Cikedrix *CKD, Philipp.; Unimex, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

CIL *Winthrop, Ger.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Cilab *Biolab, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cilacil *Aventis, Turk.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Cilamin *Panacea, India.*
Penicillamine (p.1456·2).
Cystinuria; rheumatoid arthritis; Wilson's disease.

Cilamox *Sigma, Austral.; Sigma, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Cilanem *Ranbaxy, India.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Cilatron *Quesada, Arg.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Cilaxoral *Ferring, Swed.*
Sodium picosulfate (p.1771·1).
Constipation.

Cilclar *Novartis Ophthalmics, Braz.; Novartis, Venez.*
Preparation for eye cleansing.
Blepharitis.

Cilest *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Codepharma, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Cileste *Janssen-Cilag, Austria.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Cilestoderme *Schering-Plough, Port.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Ciletin *Korea United, Philipp.*
Cilostazol (p.1245·2).
Occlusive arterial disease; peripheral vascular disorders.

Cilex
Note. This name is used for preparations of different composition.
Douglas, Austral.
Cefalexin (p.218·2).
Bacterial infections.
AWD, Ger.†.
Citalopram hydrobromide (p.385·3).
Depression.

Cilfam *Pharma Nutria, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Cilferon-A *Janssen-Cilag, Ital.†.*
Interferon alfa (p.885·1).
Anogenital warts; hepatitis; malignant neoplasms.

Cilicaine *Healthcare Logistics, NZ.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Cilicaine V *Fawns & McAllan, Austral.*
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Cilicaine Syringe *Sigma, Austral.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Cilicaine VK *Fawns & McAllan, Austral.; Healthcare Logistics, NZ.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Cilift *Pharmacare, S.Afr.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Cilin *Labesfal, Port.†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Cilinafosal *Medical, Spain.*
⊗ Ephedrine hydrochloride (p.1558·2); sulfanilamide sodium mesilate (p.343·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Dihidroestreptomicina *Medical, Spain.*
⊗ Dihydrostreptomycin sulfate (p.266·1); ephedrine hydrochloride (p.1558·2); sulfanilamide sodium mesilate (p.343·1).
Formerly known as Cilinafosal DHD Estrep.
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Hidrocortisona *Medical, Spain.*
⊗ Ephedrine hydrochloride (p.1558·2); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); sulfanilamide sodium mesilate (p.343·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinafosal Neomicina *Medical, Spain.*
⊗ Ephedrine hydrochloride (p.1558·2); neomycin sulfate (p.305·1).
Nasal congestion and infection; sinusitis; throat infections.

Cilinase *Dovalle, Braz.†.*
Ciclacillin (p.243·1).
Bacterial infections.

Cilinon *Ariston, Braz.*
Ampicillin (p.204·1).

Cilipen *Elofar, Braz.*
Ampicillin (p.204·1).
Bacterial infections.

Cilkanol *Zentiva, Cz.*
Troxerutin (p.2305·1).
Chronic venous insufficiency; circulatory disorders; haemorrhoids.

Cillimicina *Normon, Spain.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Cilodac *Lupin, India.*
Cilostazol (p.1245·2).
Intermittent claudication.

Cilodex *Alcon, Braz.; Alcon, Chile; Alcon, Mex.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Cilon *Sandoz, Pol.*
Citalopram hydrobromide (p.385·3).
Depression.

Cilopen VK *Douglas, Austral.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Cilopress *Biospray, Gr.*
Citalopram (p.385·3).
Depression.

Ciloprin cum Anaesthetico *Janssen-Cilag, Austria†; Janssen-Cilag, Fin.†.*
Acediasulfone (p.200·2); cinchocaine (p.1857·2); oxymethurea (p.1655·1).
Ear disorders.

Ciloprin ca *Janssen-Cilag, Switz.†.*
Acediasulfone (p.200·2); cinchocaine (p.1857·2); oxymethurea (p.1655·1).
Otitis.

Ciloquin *Ioquin, Austral.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Cilostal *Merck, Arg.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Cilovas *Baliarda, Arg.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Cilox *Alcon, Indon.; Alcon, Norw.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial keratitis; eye infections.

Ciloxacin *Alcon, Chile.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Ciloxadex *Alcon, Arg.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Ciloxan *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Cz.; Alcon, Denm.; Alcon, Fr.; Alcon, Ger.; Alkon (Αλκον), Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Neth.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections; bacterial eye infections.

Cilpen *Antibioticos, Mex.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Cilpier *Pierrel, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Cilroton *Janssen-Cilag, Gr.*
Domperidone (p.1726·2).
Acid aspiration; aid in diagnostic procedures; delayed gastric emptying; gastro-oesophageal reflux disease; nausea and vomiting.

Ciltiren *Vocate, Gr.*
Cefotaxime (p.229·1).
Bacterial infections.

Cim *Decomed, Port.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatic insufficiency; peptic ulcer; Zollinger-Ellison syndrome.

Cimaas *Cimed, Braz.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Cimagen *Antigen, Irl.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Cimal
Note.This name is used for preparations of different composition.
Drugtech, Chile.
Citalopram hydrobromide (p.385·3).
Depression.

Specifar (Σπεσιφαρ), Gr.†.
Etofenamate (p.53·1).
Inflammatory disorders; pain.

Alpharma, Norw.
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimascal *Belmac, Spain.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Cimascal D *Belmac, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Cime *ABZ, Ger.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimebec *Farcoral, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimebeta *Betapharm, Ger.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimecard *Cimed, Braz.*
Digoxin (p.1259·3).

Cimecid *Rotexmedica, Philipp.*
Cimetidine hydrochloride (p.1716·3).
Gastro-oesophageal reflux; peptic ulcer.

Cimecodan *Pharmacodane, Denm.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimecort *Cimed, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone (p.1518·2); neomycin (p.305·1).
Infected skin disorders.

Cimedine *Dar Al Dawa, Hong Kong.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimedul *Offenbach, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimefer
Note. A similar name is used for preparations of different composition (see below).
Cimed, Braz.
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Cimeffer
Note. A similar name is used for preparations of different composition (see above).
Reuffer, Mex.
Cimetidine (p.1716·2).
Peptic ulcer.

Cimegast *ICN, Pol.*
Cimetidine (p.1716·2).
Dyspepsia; gastric hyperacidity; heartburn.

Cimegripe *Cimed, Braz.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); phenylephrine (p.1568·1).
Influenza symptoms.

Cimehexal
Hexal, Austral.
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hexal, Ger.
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimeldine *Clonmel, Irl.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Cimelide *Cimed, Braz.*
Nimesulide (p.95·3).
Inflammation; pain.

Cimelin *Sanova, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Cimet *Thiemann, Ger.†; Ipca, India†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimeta *Jean-Marie, Hong Kong.*
Cimetidine (p.1716·2).
Dyspepsia; peptic ulcer.

Cimetag
GSK, Austria.
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Anaphylactoid reactions; gastrointestinal disorders associated with hyperacidity.

Teva, Israel; Julphar, UAE.
Cimetidine (p.1716·2).
Dyspepsia; gastric hypersecretion; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimetase *Liomont, Mex.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimetetax *Biofarma, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimetidan *Cimed, Braz.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimetil *Infabra, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimetilab *Multilab, Braz.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimetin *Cristalia, Braz.†.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimetina *Hexal, Braz.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimetinax *Ducto, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimetine *Sriprasit, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimetival *Sanval, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimetix *Drovepat, Venez.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimeton *Novartis, Gr.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cimet-P *PP Lab, Thai.†.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer.

Cimexol *Solas, Indon.*
Cimetidine (p.1716·2).
Gastric hypersecretion; gastro-oesophageal reflux; peptic ulcer.

Cimexyl *Sanova, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Cimi *Gerard, Israel†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer.

Cimicifuga comp *Steigerwald, Ger.*
Homoeopathic preparation.

Cimicifuga Compound *Phytomedicine, Austral.*
St John's wort (p.422·3); cimicifuga (p.2282·1); dioscorea villosa; lavender (p.2331·1).
Menopausal disorders.

Cimicifuga Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Cimicifuga Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Cimicin *Stada, Hung.*
Cimicifuga (p.2282·1).
Menstrual symptoms.

Cimidine *Berlin Pharm, Thai.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; mastocytosis; peptic ulcer; Zollinger-Ellison syndrome.

Cimifemine *Zeller, Switz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Cimille *Qualifarma, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cimipax *IPRAD, Fr.*
Cimicifuga (p.2282·1).
Insomnia; nervous disorders.

Cimisan *APS, Cz.; APS, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

CimLich *Artesan, Cz.†; Winthrop, Ger.*
Cimetidine (p.1716·2).
Acid aspiration; acute pancreatitis; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cimlok *Be-Tabs, S.Afr.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cimogal *Probiomed, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cimulcer *Biopharm, Hong Kong†; Biolab, Malaysia; Standard, Philipp.; Biolab, Singapore; Biolab, Thai.†.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Cimzia *UCB, Switz.; UCB, USA.*
Certolizumab pegol (p.1715·3).
Crohn's disease.

Cinababy *VSM, Neth.*
Homoeopathic preparation.

Cinabel
Note.This name is used for preparations of different composition.
Andromaco, Chile.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dipyrone (p.49·2); chlorphenamine maleate (p.571·3).
Migraine and other vascular headaches.

Columbia, Mex.†.
Clotrimazole (p.530·1).

Andromaco, Venez.†.
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Cinacris *Ivax, Arg.*
Cinnarizine (p.573·1); dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders.

Cinactiv *Labomed, Chile.*
Erythromycin-zinc complex (p.269·2).
Acne.

Cinadine *Garec, S.Afr.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; upper gastrointestinal haemorrhage; Zollinger-Ellison syndrome.

Cinaebosan *Bock, Ger.†.*
Homoeopathic preparation.

Cinaflan *Brasterapica, Braz.†.*
Diclofenac potassium (p.44·3).

Cinalong *UCB, Jpn.*
Cilnidipine (p.1245·2).
Hypertension.

Cinam *Sanbe, Indon.*
Sultamicillin (p.344·1).
Bacterial infections.

Cinapen *Elpen (Ελπεν), Gr.*
Citalopram (p.385·3).
Depression.

Cinaran *Cazi, Braz.*
Cinnarizine (p.573·1).

Cinaren *Dollder, Venez.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cinarepa *Cristalfarma, Ital.*
Cynara (p.2291·2); taraxacum (p.2395·1); turmeric (p.1473·2); rosemary oil (p.2381·3).
Nutritional supplement for liver disorders.

Cinarin *Galeno, Venez.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cinarivert *Biofarma, Braz.†.*
Cinnarizine (p.573·1).
Vestibular disorders.

Cinarix *Royton, Braz.†.*
Cinnarizine (p.573·1).

Cinaryl *Themis, India.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Allergic rhinitis; cold symptoms; sinusitis.

Cinatrex *Cifarma, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Cinaz *Pentafarma, Port.*
Cetirizine hydrochloride (p.570·3).

Cinaziere *Ashbourne, UK†.*
Cinnarizine (p.573·1).

Cinazin *Vitapan, Braz.†.*
Cinnarizine (p.573·1).
Vestibular disorders.

Cinazon *Sanval, Braz.*
Cinnarizine (p.573·1).

Cinazyn *Italchimici, Ital.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cincain *Ophtha, Denm.; Ipex, Swed.*
Cinchocaine (p.1857·2).
Eye disorders.

Cincofarm *Lepori, Port.; Farma Lepori, Spain.*
Oxitriptan (p.414·1).
Depression; epilepsy; migraine.

Cinco-Fu *Pharmacia, Arg.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Cincol *Polfa Warszawa, Pol.*
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Conjunctivitis.

Cincordil *Sigma, Braz.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Cincuental *Schwabe, Arg.†.*
Vincamine (p.2414·1).
Mental function impairment.

Cindala *Medikon, Indon.*
Clindamycin (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Cinebil *Jaba Recordati, Port.*
Sucralfate (p.1772·2).

Cinedil *Alkaloid, Cz.†.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Cinegel *Med-One, Gr.*
Amikacin (p.200·2).
Bacterial skin infections.

Cineprac *Liferpal, Mex.*
Trimebutine (p.2404·3).
Gastrointestinal disorders.

Cinergil *Labomed, Chile.*
Cinnarizine (p.573·1).
Mental function impairment; peripheral vascular disorders; vertigo.

Cinerine *Pharmasant, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; motion sickness; peripheral vascular disorders; vestibular disorders.

Cinet *Medinfar, Port.*
Domperidone (p.1726·2).
Dyspepsia; nausea; vomiting.

Cinetic *Teofarma, Ital.*
Thyroid (p.2177·1).
Hypothyroidism.

Cinetol *Cristalia, Braz.*
Biperiden hydrochloride (p.797·2).
Parkinsonism.

Cinfacromin *Cinfa, Spain.*
Merbromin (p.1652·1).
Skin disinfection.

Cinfamar *Cinfa, Spain.*
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Cinfamar Cafeina *Cinfa, Spain.*
Caffeine (p.1116·3); dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Cinfatos *Cinfa, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Cinfatos Complex *Cinfa, Spain.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Cinfloxine *Medicine Products, Thai.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cinie *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.*
Sumatriptan succinate (p.625·2).
Migraine.

Cinigest *Baliarda, Arg.*
Cinitapride (p.1720·2).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Cinkef-U *Hospira, Port.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Cinkona *Ipca, India.*
Quinine dihydrochloride (p.612·3) or quinine sulfate (p.612·3).
Malaria.

Cinkos *Med-Care, Turk.*
Zinc oxide (p.1621·2); white soft paraffin (p.2031·2); purified talc (p.1615·2).
Barrier preparation.

Cinmik *Karnataka, Philipp.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Cinna *YSP, Malaysia; Yung Shin, Singapore; Millimed, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Cinnabene *Ratiopharm, Austria; Ratiopharm, Cz.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Cinnabsin *DHU, Rus.*
Homoeopathic preparation.

Cinnageron *Streuli, Switz.*
Cinnarizine (p.573·1).
Cochlear disorders; motion sickness; vestibular disorders.

Cinnamed *Medika, Switz.†.*
Cinnarizine (p.573·1).
Vestibular disorders.

Cinnar *Atlantic, Singapore; Atlantic, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Cinnaron *Remedica, Malaysia; Remedica, Singapore.*
Cinnarizine (p.573·1).
Motion sickness; vestibular disorders.

Cinnarplus *Gerot, Austria.*
⊗ Cinnarizine (p.573·1); etamivan (p.2156·1).
Cerebral and peripheral vascular disease.

Cinnaza *Pharmaland, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; peripheral vascular disorders; vestibular disorders.

Cinobac *Bruno, Ital.; Lilly, USA†.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Cinobactin *Lilly, Gr.†.*
Cinoxacin (p.243·2).
Bacterial infections.

Cinocil *Uno, Ital.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Cinoflax *Ativus, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cinogenta *Ferron, Indon.*
⊗ Gentamicin sulfate (p.282·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Cinolon *Sanbe, Indon.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cinolon-N *Sanbe, Indon.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Cinon *Azevedos, Port.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Cinopal *Wyeth-Ayerst, Thai.†; Turgut, Turk.*
Fenbufen (p.54·3).
Musculoskeletal and joint disorders; pain.

Cinotec *Medipharma, Hong Kong†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cinoxen *Ibirn, Ital.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Cinq sur Cinq
Note.This name is used for preparations of different composition.
Bayer, Fr.
Cream; lotion: Ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Bayer, Fr.
Diffuser cartridge: Esdepallethrine (p.2042·3).
Insect repellent.

Bayer, Fr.
Diffuser liquid: Esdepallethrine (p.2042·3); butylated hydroxytoluene (p.1633·2).
Insect repellent.

Bayer, Fr.
Mosquito net: Deltamethrin (p.2040·1).
Insect repellent.

Cinquerix *GSK, Ital.†.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Cinrizine *Medifive, Thai.*
Cinnarizine (p.573·1).
Circulatory disorders; migraine; motion sickness; vestibular disorders.

Cintalux *Sandoz, Austria.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Cintidina *Greenpharma, Braz.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cintigo *Wallace, India.*
Cinnarizine (p.573·1).
Ménière's disease; tinnitus; vertigo.

Cintilan *Medley, Braz.*
Piracetam (p.368·2).
Alcoholism; behaviour disorders in children; cerebrovascular disorders; senile dementia; vertigo.

Cinton *Ariston, Braz.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Cintsu *YSP, Malaysia†.*
Verapamil hydrochloride (p.1421·1).
Hypertension.

Ciocar *Mavi, Mex.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Cional *Nycomed, Austria.*
Aluminium formate (p.1706·2); chamomile (p.2279·3); sage (p.2382·3); arnica (p.2260·2).
Mouth and throat disorders.

Cip eco *Ecosol, Switz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipadur *Cipla-Medpro, S.Afr.*
Cefadroxil (p.218·1).
Bacterial infections.

Cipalat *Cipla-Medpro, S.Afr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cipamox *Cipan, Port.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Cipancin *Cipan, Port.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Cipanfeno *Cipan, Port.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; asthma.

Cipasid *Siam Bheasach, Thai.*
Cisapride (p.1720·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis; intestinal pseudo-obstruction.

Cipcal *Cipla, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Cipcal M *Cipla, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); minerals (p.1922·1).
Calcium and vitamin D deficiency.

Cipcorlin *Cipla, India.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Ciperico *Cimed, Braz.*
St John's wort (p.422·3).
Depression.

Ciperina *Gache, Venez.*
Piperazine (p.152·3).
Worm infections.

Cipex *Cipla-Medpro, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Cipflocin *Asian Pharm, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipflox *Pacific, NZ.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipgen *Cadila, India.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipgen TZ *Cadila, India.*
Ciprofloxacin (p.243·3); tinidazole (p.848·3).
Bacterial infections; protozoal infections.

Cipgesic *Cipla, India.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Cipgesic Plus *Cipla, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Ciphin
Zentiva, Cz.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Zentiva, Hung.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Zentiva, Pol.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipide *APT, Hong Kong.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipiram *Tecnimede, Port.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Cipla-Actin *Cipla-Medpro, S.Afr.*
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; pruritus.

Ciplacef *Cipla, India; Cipla, Venez.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ciplactin *Cipla, India.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; migraine.

Cipladine *Cipla, India.*
Povidone-iodine (p.1659·2).
Disinfection.

Ciplar *Cipla, India.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Ciplar-H *Cipla, India.*
⊗ Propranolol hydrochloride (p.1380·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ciplatec *Cipla-Medpro, S.Afr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ciplazin *Prater, Chile†.*
St John's wort (p.422·3).
Depression.

Ciplexal *Hexal, Philipp.; Salutas, Philipp.*
Cisplatin (p.698·2).
Malignant neoplasms.

Ciplin *Cipla, India.*
Co-trimoxazole (p.258·1).
Bacterial infections; Pneumocystis pneumonia; toxoplasmosis.

Ciploric *Cipla, India.*
Allopurinol (p.552·2).
Hyperuricaemia.

Ciplox
Cipla, Cz.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipla, Hong Kong; Neopharma, Hung.; Cipan, Port.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipla, India.
Ciprofloxacin (p.243·3), ciprofloxacin hydrochloride (p.243·3), or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipla, Israel.
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciplox D *Cipla, India.*
⊗ Ciprofloxacin (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Ciplox TZ *Cipla, India.*
Ciprofloxacin (p.243·3); tinidazole (p.848·3).
Bacterial infections.

Ciploxx *Cipla-Medpro, S.Afr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipobacter *Rubio, Spain†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipocal *Pharmex (Φαρμεξ), Gr.*
Calcipotriol (p.1591·3).
Psoriasis.

Cipofix *Cipla-Medpro, S.Afr.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cipon *Unison, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprager *Gerard, Irl.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Ciprain *Maver, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipralan
Continental Pharma, Belg.; BMS, Fr.
Cibenzoline succinate (p.1244·2).
Arrhythmias.

BMS, Fr.
Injection: Cibenzoline succinate (p.1244·2); cibenzoline (p.1244·1).
Arrhythmias.

Cipralex *Lundbeck, Austria; Lundbeck, Canad.; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Hung.; Lundbeck, India; Lundbeck, Indon.; Lundbeck, Israel; Lundbeck, Ital.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Turk.; Lundbeck, UK.*
Escitalopram oxalate (p.391·1).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Cipram
Lundbeck, Austria†.
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Cz.; Lundbeck, Hong Kong; Lundbeck, Indon.; Lundbeck, Malaysia; Lundbeck, Singapore; Lundbeck, Thai.; Lundbeck, Turk.
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Anpharm (Ανφαρμ), Gr.
Citalopram (p.385·3).
Depression.

Cipramil
Lundbeck, Austral.; Silesia, Chile; Lundbeck, Israel; Healthcare Logistics, NZ; Lundbeck, Norw.; Lundbeck, Pol.; Lundbeck, Rus.; Lundbeck, S.Afr.
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Belg.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ger.; Lundbeck, Irl.; Lundbeck, Neth.; Lundbeck, Swed.; Lundbeck, UK.
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorder; phobias.

Lundbeck, Braz.
Citalopram (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Ciprane *Teuto, Braz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in women.

Cipramine *Pinewood, Irl.; Pinewood, Neth.*
Citalopram hydrobromide (p.385·3).
Depression.

Ciprasid *Yeni, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprenit Otico *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Ciprex *Bosnalijek, Rus.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipridanol *Richmond, Arg.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Cipride *Biolab, Thai.†.*
Cisapride (p.1720·3).
Anorexia nervosa; constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis; intestinal pseudo-obstruction.

Cipril *Cipla, Hong Kong; Cipla, India.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Cipril-H *Cipla, India.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Cipríne *Pfizer, Switz.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprinol
KRKA, Cz.; KRKA, Pol.; KRKA, Rus.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

KRKA, Hung.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

KRKA, Neth.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprivax *Vivax, Venez.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprix *Geolab, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro
Bayer, Arg.; Bayer, Braz.; Bayer, Canad.; Bayer, USA.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

1A, Ger.; Basics, Ger.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bayer, Mex.; Biofarma, Turk.
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipro HC *Alcon, Arg.; Alcon, Braz.; Alcon, Canad.; Alcon, Hong Kong; Alcon, Malaysia†; Alcon, USA.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Infected ear disorders; otitis externa.

Ciproant *Eversil, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprobac *Pisa, Mex.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciprobay
Note. This name is used for preparations of different composition.
Bayer, Cz.; Bayer Schering, Malaysia; Bayer, Philipp.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Thai.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayer, Ger.
Ciprofloxacin (p.243·3), ciprofloxacin hydrochloride (p.243·3), or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Alkon (Αλκον), Gr.†; Bayer, Pol.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Alcon, Hung.†.
Ear drops: ⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Bacterial ear infections.

Bayer, Hung.
Injection; tablets: Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciprobay HC
Alcon, S.Afr.
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Alcon, Singapore.
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciprobay HC Otic *Alcon, Cz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciprobel *Socobom, Belg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprobeta *Betapharm, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprobid
Cadila, Cz.†.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cadila, India; Cadila, Rus.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Zydus Cadila, Thai.
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprobiot *Hexal, Braz.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprobiotic *Cryopharma, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro-Cent *Centaur, India.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Ciprocep *TO-Chemicals, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprocilin *Legrand, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprocina *Zeus, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprocort
Note. This name is used for preparations of different composition.
Beta, Arg.
Cream; topical spray: ⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Burns; skin disorders.

Beta, Arg.
Injection: ⊗ Dexamethasone sodium phosphate (p.1526·2); cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions.

Beta, Arg.
Pessaries: ⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2); metronidazole (p.837·1).
Vaginal infections.

Ciprocort D *Beta, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract disorders.

Ciprocort L *Beta, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Hypersensitivity reactions.

Ciproctal *Inkeysa, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprodac *Cadila, India.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciprodex
Note. This name is used for preparations of different composition.
Alcon, Canad.
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Bacterial ear infections.

Saval, Chile; Alcon, USA.
⊗ Ciprofloxacin (p.243·3); dexamethasone (p.1526·1).
Bacterial eye infections with inflammation; infected ear disorders; otitis media.

Dexcel, Israel.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro-Dexol *Collins, Mex.†.*
Cyproheptadine (p.575·2); vitamins (p.1922·1).
Appetite loss.

Ciprodine *Sanval, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprodoc *Docpharm, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprodura *Merck dura, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprofal *Vocate, Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprofar *Elofar, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprofarma *Varifarma, Arg.*
Cyproterone (p.2089·2).

Ciprofat *Fatol, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprofin *Utopian, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproflonax *Pharlab, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproflox
Hebron, Braz.†; Elmor, Venez.
Ciprofloxacin (p.243·3).
Bacterial infections.

CT, Ger.; Spirig, Switz.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Senosiain, Mex.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciprofloxacin HY *Alkon (Αλκον), Gr.†.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Bacterial ear infections.

Ciprofloxil *Greenpharma, Braz.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproflox-Otic *Sertex, Arg.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciproflox-Puren *Alpharma-Isis, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprofur *Ivax, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprogamma *Worwag, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprogen *Xixia, S.Afr.; General Drugs, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprogis *Agis, Israel.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproglen *Glenmark, Thai.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprohexal
Hexal, Ger.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Hexal, Mex.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro-Hexal *Hexal, S.Afr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproktan *Kocak, Turk.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprol *Arrow, Austral.; Arrow, Hong Kong.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprolen *AC Helcor, Hung.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprolet
Reddy, Rus.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Reddy, Singapore.
Ciprofloxacin (p.243·3).
Bacterial infections.

Reddy, Thai.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Biofarma, Venez.†.
Ciprofloxacin (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipro-Lich *Lichtenstein, Ger.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprolisina *AF, Mex.*
Cyproheptadine hydrochloride (p.575·1); cyanocobalamin (p.1980·2).
Tonic.

Ciprolone *Lek, Rus.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Cipromax *Verheilen, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipromed
S Med, Austria; Alpharma, Fin.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Promed, Rus.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Eye or ear infections.

Cipro-Med *Medika, Switz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipromet
Note. This name is used for preparations of different composition.
Metro, Philipp.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Giempi, Venez.†.
⊗ Cyproheptadine hydrochloride (p.575·1); dexamethasone (p.1526·1).

Cipron-H *M & H, Thai.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipromizin *Biofarma, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipromycin *Medichrom, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipronal *Cazi, Braz.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipronax *Vivax Optipharm, Venez.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Cipronex *Polpharma, Pol.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipronom *Genom, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro-Otico *Alcon, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Cipropharm *Actavis, Hung.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproplex *Teva Tuteur, Arg.*
Cyproterone (p.2089·2).

Cipropol *Polfa Grodzisk, Pol.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipro-Q *Juta, Ger.; Q-Pharm, Ger.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproquin *Behrens, Venez.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciproquinol *Ferring, Port.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipro-saar *MIP, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproser *Serral, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipropses *Alet, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprostad *Stada, Austria.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprostat *Apsen, Braz.*
Cyproterone acetate (p.2088·2).

Ciprosun *Sun, Rus.; Sun, Thai.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprotan *Clonmel, Irl.*
Citalopram hydrobromide (p.385·3).
Depression.

Ciprotec *Reuffer, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciprotenk *Biotenk, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprotor *Torrent, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproval *Saval, Chile.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprovid *Millimed, Thai.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciproviron *Schering, Chile†.*
Cyproterone acetate (p.2088·2).
Androgen-induced acne, alopecia, hirsutism, or seborrhoea in women; prostatic cancer; sexual deviation in men.

Ciprovit Calcio *Beta, Arg.*
Cyproheptadine hydrochloride (p.575·1); calcium phosphate; cyanocobalamin (p.1922·1).
Tonic.

Ciprovit Energizante *Beta, Arg.*
Cyproheptadine hydrochloride (p.575·1); vitamins; ginkgo biloba; pyritinol hydrochloride (p.1922·1).
Tonic.

Ciprovit Magnesico *Beta, Arg.*
Cyproheptadine hydrochloride (p.575·1); vitamins; magnesium chloride (p.1922·1).
Tonic.

Ciprowin *Alembic, India.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cipro-Wolff *Wolff, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprox *Lindopharm, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproxan
Royton, Braz.†; Pond's, Thai.
Ciprofloxacin (p.243·3).
Bacterial infections.

Bayer, Jpn.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproxen *Cifarma, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproxil *Haller, Braz.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciproxin
Bayer, Austral.; Bayer, Denm.; Bayer, Fin.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer, Norw.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayer, Austria; Bayer, NZ; Bayer, Neth.; Bayer, Swed.; Bayer, UK.
Ciprofloxacin (p.243·3), ciprofloxacin hydrochloride (p.243·3), or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayer, Israel; Bayer, Turk.
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproxin HC *Alcon, Austral.; Alcon, Israel; Alcon, NZ; Alcon, Switz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Infected ear disorders; otitis externa.

Ciproxina
Note. This name is used for preparations of different composition.
Bayer, Mex.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Bayer, Port.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

M4, Spain.
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Bayer, Venez.
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproxina HC *Alcon, Mex.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciproxina Simple *M4, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Ciproxine
Bayer, Belg.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Bayer, Switz.
Ciprofloxacin (p.243·3), ciprofloxacin hydrochloride (p.243·3), or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ciproxin-Hydrocortison *Alcon, Fin.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciproxino *Andromaco, Chile.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciproxyl
Bangkok Lab & Cosmetic, Hong Kong.
Ciprofloxacin (p.243·3).
Bacterial infections.

Farmaline, Thai.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ciprum
Pliva, Cz.; Pliva, Hung.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Pliva Krakow, Pol.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cipstryn *Cipla, India.*
Streptomycin sulfate (p.333·3).
Bacterial infections.

Ciptini *Cipla, India.*
Ciprofloxacin (p.243·3); tinidazole (p.848·3).
Bacterial infections.

Cipzen *Cipla, India.*
Serrapeptase (p.2385·3).

Cipzen D *Cipla, India.*
Serrapeptase (p.2385·3); diclofenac (p.44·2).

Cipzen N *Cipla, India.*
Serrapeptase (p.2385·3); nimesulide (p.95·3).

Cip-Zox *Cipla, India.*
Diclofenac (p.44·2); paracetamol (p.108·1); chlorzoxazone (p.1894·3).

Ciqfadin *IQFA, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cirantan *AstraZeneca, Neth.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Circadin *Lundbeck, Port.; Lundbeck, UK.*
Melatonin (p.2338·3).
Insomnia.

Circanetten *Eversil, Braz.†; Evers, Thai.*
Potassium acid tartrate (p.1764·1); senna (p.1769·2); sulfur (p.1614·1).
Haemorrhoids; varices; vascular disorders.

Circanol *3M, Ger.†.*
Codergocrine mesilate (p.363·3).
Hypertension; mental function disorders.

Circarol *Jin Yang, Malaysia.*
Crataegus (p.2289·1); melissa (p.2339·3); ginkgo biloba (p.2311·1); garlic oil (p.2309·2).
Circulatory disorders.

Circavite-T *Circle, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Circo-Maren *Krewel, Ger.†.*
Nicergoline (p.2352·1).
Mental function disorders.

Circonyl *TRB, Arg.*
Quinine sulfate (p.612·3).
Nocturnal leg cramps.

Circulan
Note. This name is used for preparations of different composition.
Dong-A, Philipp.; Macropharma, Philipp.
Crataegus (p.2289·1); ginkgo biloba (p.2311·1); garlic oil (p.2309·2); melissa (p.2339·3).
Circulatory disorders.

Adroka, Switz.
Crataegus (p.2289·1); passion flower (p.2363·2).
Cardiac disorders.

Circulat *Polpharma, Pol.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders.

Circulation *Homeocan, Canad.†.*
Homoeopathic preparation.

Circulatonic *Phytomedica, Fr.*
Menthol (p.2340·1); camphor (p.2273·2); cypress oil (p.2291·2).
Circulatory disorders.

Circumax *ISA, Arg.†.*
Ginkgo biloba; centella; selenium; garlic (p.1922·1).
Dietary supplement.

Circupon *Kolassa, Austria.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Circus Chews *Sundown, Venez.†.*
Vitamin preparation (p.1922·1).

Circuvit *Ariston, Arg.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Circuvit E *Wernigerode, Ger.†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Cirflox-G *Klonal, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciriax *Roemmers, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciriax Otic *Roemmers, Arg.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Ciriax Otic L *Roemmers, Arg.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2); lidocaine hydrochloride (p.1862·3).
Otitis externa.

Cirizine *Biospray, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cirkan *Pierre Fabre, Fr.*
⊗ Butcher's broom (p.2270·3); ascorbic acid (p.1983·3); hesperidin methyl chalcone (p.2305·2).
Haemorrhoids; metrorrhagia; venous insufficiency.

Cirkan a la Prednacinolone *Pierre Fabre, Fr.*
⊗ Desonide (p.1525·1); lidocaine hydrochloride (p.1862·3); vitamin A palmitate (p.1973·1); ruscosides; tocoferil acetate (p.1992·3); heparin sodium (p.1301·2).
Anorectal disorders.

Cirku Sed *Roha, Hong Kong†.*
Valerian (p.2410·1).
Insomnia.

Cirkused *Roha, Pol.; Diafarm, Spain†.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Cirloid *Fahrenheit, Indon.*
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Cirok
Korea United, Philipp.; Korea United, Singapore†.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Pharmakin, Venez.
Ciprofloxacin (p.243·3).
Bacterial infections.

Ciroxin *Jin Yang, Singapore†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cirrus *UCB, Austria; UCB, Belg.; UCB, Fin.; UCB, Hong Kong; UCB, Indon.; UCB, Malaysia; Vedim, Pol.; UCB, Port.; UCB, Singapore†; UCB, Turk.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Ciruela Fibra *Garden House, Arg.*
Senna (p.1769·2).

Ciruelax Comp *Ivax, Mex.*
Senna (p.1769·2).
Constipation.

Ciruelax Jalea *Ivax, Mex.*
Senna (p.1769·2); prune (p.1765·1).
Constipation.

Ciruelax TE *Ivax, Mex.*
Senna (p.1769·2).
Constipation.

Cirulan *Novag, Mex.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders.

Cirulaxia
Note. This name is used for preparations of different composition.
Altana, Arg.
Chewable tablets: Sodium picosulfate (p.1771·1).
Constipation.

Altana, Arg.
Syrup: Prune (p.1765·1); senna (p.1769·2).
Constipation.

Cirus *Ventaglio, Chile.*
Ketoprofen (p.73·1).
Osteoarthritis; pain; rheumatoid arthritis.

Cisaken *Kendrick, Mex.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; motion sickness; vestibular disorders.

Cisalone *Sigma, India†.*
Cisapride (p.1720·3).
Delayed gastric emptying; gastro-oesophageal reflux.

Cisamod *Dollder, Venez.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Cisanplat *Dakota, Cz.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cisap *Dominguez, Arg.†.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Cisapin *LSP, Thai.†.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastroparesis.

Cisaprid *Med-One, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Cisaride *Pharmasant, Thai.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux.

Ciscomax *Eczane, Arg.†.*
Ranitidine (p.1766·1).
Gastritis; peptic ulcer; Zollinger-Ellison syndrome.

Ciscutan *Pelpharma, Austria.*
Isotretinoin (p.1599·2).
Acne.

Cis-Gry *Gry, Ger.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cishexal *Hexal, Austria.*
Cisplatin (p.698·2).
Malignant neoplasms.

Ciskebir *Aspen, Arg.*
Cisplatin (p.698·2).

Ci-Sons *Sons, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cisordinol *Lundbeck, Austria; Silesia, Chile; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Hung.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Port.; Lundbeck, Spain; Lundbeck, Swed.*
Zuclopenthixol acetate (p.1040·3), zuclopenthixol decanoate (p.1040·3), or zuclopenthixol hydrochloride (p.1040·3).
Psychoses.

Cisplamol *Vianex (Βιανέξ), Gr.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cisplat *Biochem, India.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cisplatex *Eurofarma, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cisplatyl *Sanofi-Aventis, Fr.; Aventis, Gr.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cispride *Klonal, Arg.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Cistalgan *Recordati, Ital.*
Flavoxate hydrochloride (p.2190·1); propyphenazone (p.119·3).
Spasm of the female genital tract; urinary-tract disorders.

Cistalgina *Fortbenton, Arg.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Cistamine *LBS, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic skin disorders; rhinitis.

Cisteine *TNP, Thai.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Cisteinol *Galeno, Venez.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Cisticid *Merck, Braz.; Merck, Chile; Merck, Mex.; Merck, Venez.†.*
Praziquantel (p.153·3).
Cestode infections; cysticercosis; neurocysticercosis; trematode infections.

Cistidac *Eurolab, Arg.*
-cystine; -methionine; zinc; biotin; vitamin B (p.1922·1).
Hair and nail disorders.

Cistidil *IDI, Ital.*
-Cystine (p.1937·1).
Skin disorders.

Cistimax
Fortbenton, Arg.
Lotion: Methionine; pyridoxine; zinc (p.1922·1).
Hair loss.

Fortbenton, Arg.
Tablets: Cystine; vitamins; minerals; gelatin (p.1922·1).

Cistimax Ungueal *Fortbenton, Arg.*
Biotin; vitamin E; formaldehyde (p.1644·1) (p.1922·1).
Nail disorders.

Cistobil *Bracco, Ital.†.*
Iopanoic acid (p.1484·1).
Contrast medium for biliary-tract radiography.

Cistomid *Uno, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Cistopax *Zimaia, Port.†.*
Oxolinic acid (p.312·2).
Urinary-tract infections.

Cistoquine Plus *Casasco, Arg.†.*
Dihydroxydibutylether (p.2293·3); simeticone (p.1770·2).
Biliary-tract disorders; flatulence.

Cistus canadensis Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Cita *Sanofi-Aventis, Cz.*
Citalopram hydrobromide (p.385·3).
Depression.

Citab *Eurofarma, Braz.†.*
Cytarabine hydrochloride (p.706·1).
Malignant neoplasms.

Citabion *Medicus, Gr.*
Cytarabine (p.705·1).
Malignant neoplasms.

Citadep *Cipla, India.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citadur *Sandoz, Denm.*
Citalopram hydrobromide (p.385·3).
Depression; panic attacks.

Citadura *Merck dura, Ger.*
Citalopram hydrobromide (p.385·3).
Depression.

Citagen *Generics, Hung.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citagenin *Ivax, Arg.*
Cytarabine (p.705·1).
Malignant neoplasms.

Citaham *Actavis, Denm.*
Citalopram hydrobromide (p.385·3).
Depression; panic attacks.

Cital
Note. This name is used for preparations of different composition.
Eurodrug, Hong Kong; Biovena, Pol.
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Bichsel, Switz.†.
⊗ Mannitol (p.1330·2); sorbitol (p.1965·1).
Irrigation solution.

Citalax *Indeco, Arg.*
Escitalopram oxalate (p.391·1).
Anxiety; depression.

Citalec *Zentiva, Cz.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Citalgan *Merck, Mex.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Citalhexal *Hexal, Austria†.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

CitaLich *Winthrop, Ger.*
Citalopram hydrobromide (p.385·3).
Depression.

Citalodep *Extractum, Hung.*
Citalopram hydrobromide (p.385·3).

CitaloHexal *Hexal, S.Afr.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Citalon *Biochemie, Austria†; Sandoz, Cz.; Krewel, Ger.; Sandoz, Hung.*
Citalopram hydrobromide (p.385·3).
Depression.

Citalo-Q *Juta, Ger.; Q-Pharm, Ger.*
Citalopram hydrobromide (p.385·3).
Depression.

Citalor *Pfizer, Braz.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Citalostad *Stada, Austria.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

Citalowin *Zentiva, Hung.*
Citalopram hydrobromide (p.385·3).
Depression.

Citaloxan *Hospira, Port.*
Cytarabine (p.705·1).

Citalvir *Vir, Spain.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Citanest *AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.†; AstraZeneca, NZ; AstraZeneca, Neth.; Inibsa, Spain; AstraZeneca, Swed.; AstraZeneca, Turk.; AstraZeneca, UK; Dentsply, UK; Astra, USA.*
Prilocaine hydrochloride (p.1868·2).
Adrenaline (p.1203·2), adrenaline acid tartrate (p.1203·2), or felypressin (p.2302·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

Citanest Dental *Dentsply, Austral.*
⊗ Prilocaine hydrochloride (p.1868·2).
Adrenaline (p.1203·2) or felypressin (p.2302·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest Octapresin *Astra, Mex.†.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest Octapressin *Dentsply, Denm.; Dentsply, Fin.; Dentsply, Norw.; Inibsa, Spain; Dentsply, Swed.; Globopharm, Switz.; AstraZeneca, Turk.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest con Octapressin *Dentsply, Ital.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest with Octapressin *Dentsply, NZ†; Dentsply, UK.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citanest Octapressine *Dentsply, Neth.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citapram *Sandoz, Hung.*
Citalopram hydrobromide (p.385·3).
Depression.

Citara *Fako, Turk.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citaratio *Ratiopharm, Cz.; Ratiopharm, Pol.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citarax *Blausiegel, Braz.*
Cytarabine (p.705·1).
Malignant neoplasms.

Citarcana *Arcana, Austria.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citavi *Labocor, Port.†.*
Ascorbic acid (p.1983·3).
Tonic.

Citavie *Actavis, Swed.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Citax F *Biogam, Arg.*
A normal immunoglobulin (p.2225·3).
Auto-immune disorders; idiopathic thrombocytopenic purpura; passive immunisation.

Citaxin *Pliva Krakow, Pol.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citaz *Kalbe, Indon.*
Cilostazol (p.1245·2).
Arterial occlusion.

Citazon *Kocak, Turk.*
Thioacetazone (p.351·2).
Tuberculosis.

Citdolal *Ciclum, Spain†.*
Metamizole magnesium (p.49·3).
Fever; pain.

Citemul S *Medopharm, Ger.†.*
Mesulphen (p.1604·3).
Scabies; skin disorders.

Citiclor *CT, Ital.†.*
Cefaclor (p.217·2).
Bacterial infections.

Citidine *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Citifar *Lafare, Ital.†.*
Citicoline (p.2283·3).
Parkinsonism.

Citiflux *CT, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; rhinitis.

Citilat *CT, Ital.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease.

Citinoides *Serra Pamies, Spain.*
Lithium carbonate (p.401·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Dyspepsia; gastrointestinal hyperacidity.

Cition *Eurofarmaco, Ital.†.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; parkinsonism.

Citivir *CT, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Citizem *CT, Ital.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Citizol *Aristo, India.*
Ciprofloxacin (p.243·3); tinidazole (p.848·3).

Citocaina *Cristalia, Braz.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Citocartin *Molteni, Ital.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Citodon *Durascan, Denm.†; AstraZeneca, Swed.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Citodox *Pfizer, Arg.*
Etoposide (p.718·1).
Malignant neoplasms.

Citofolin *Bracco, Ital.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency; reduction of aminopterin and methotrexate toxicity.

Citofur *Lusofarmaco, Ital.†.*
Tegafur (p.776·1).
Malignant neoplasms.

Citogel *Gebro, Austria; Geymonat, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal disorders associated with hyperacidity; peptic ulcer.

Cito-Guakalin *Stada, Ger.†.*
Sodium dibunate (p.1573·1); guaifenesin (p.1561·3); thyme (p.2401·1).
Coughs and associated respiratory-tract disorders.

Citoken T *Kendrick, Mex.†.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders; pain.

Citol
Tripharma, Rus.
Citalopram (p.385·3).
Depression.

Abdi, Turk.
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citolap *Tum, Turk.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citomid *Laboratorios Chile, Chile; Lemery, Cz.†; Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.*
Vincristine sulfate (p.787·1).
Idiopathic thrombocytopenic purpura; malignant neoplasms.

Citoneurin *Merck, Braz.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B deficiency; vitamin B supplement.

Citoneuron *Andromaco, Chile.*
Sodium cytidine monophosphate (p.2291·3); trisodium uridine triphosphate (p.2408·1); hydroxocobalamin (p.1980·3).
Myopathy; neuralgia; neuritis.

Citonina *Pharmacia, Arg.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; metastatic bone pain; osteoporosis; Paget's disease of bone; pancreatitis; sympathetic dystrophy.

Citopam *Sun, India.*
Citalopram (p.385·3).
Depression; panic disorder.

Citophase *Farmila, Ital.*
Cytochrome-c peroxidase (p.2291·3).
Corneal disorders.

Citoplatino *Sanofi-Aventis, Ital.*
Cisplatin (p.698·2).
Malignant neoplasms.

Citoplax *Bergamo, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Citor *Torrex, Austria.*
Citalopram hydrobromide (p.385·3).
Anxiety disorders; depression; panic disorder.

Citorsal *Ern, Spain.*
Calcium lactate; citric acid; magnesium sulfate; potassium chloride; sodium citrate; sodium chloride; tribasic sodium phosphate; glucose (p.1672·2).
Oral rehydration.

Citos *Nordin, Mex.*
Tolu balsam (p.1574·2); drosera (p.2297·3).
Coughs.

Citostal *BMS, Braz.*
Lomustine (p.741·1).
Malignant neoplasms.

Citovirax *Roche, Ital.*
Ganciclovir (p.879·1) or ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Citox *Sun, Mex.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Citra pH *ValMed, USA.*
Sodium citrate (p.1673·3).
Hyperacidity.

Citracal
Note. This name is used for preparations of different composition.
Mission, Austral.†; Mission Pharmacal, Hong Kong; Mission Pharmacal, Malaysia†; Mission Pharmacal, Singapore; Mission Pharmacal, USA; Vivax, Venez.
Calcium citrate (p.1675·3).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Bruno, Ital.†.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Citracal Creamy Bites *Mission Pharmacal, USA†.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Citracal D *Vivax, Venez.*
Calcium citrate (p.1675·3); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Citracal + D
Note. This name is used for preparations of different composition.
Mission Pharmacal, Hong Kong; Mission Pharmacal, Malaysia†.
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Mission Pharmacal, Singapore.
Calcium citrate (p.1675·3); vitamin D (p.1986·1).
Calcium deficiency; osteoporosis.

Mission Pharmacal, USA.
Calcium citrate (p.1675·3); ergocalciferol (p.1987·1).

Citracal Plus with Magnesium *Mission Pharmacal, USA.*
Calcium (p.1675·2); vitamin D (p.1987·1); pyridoxine; minerals (p.1922·1).

Citracal Prenatal *Mission Pharmacal, USA.*
Vitamin and mineral preparation (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement for pregnant and postnatal women.

Citracal Prenatal + DHA *Mission Pharmacal, USA.*
Tablets, vitamin and mineral preparation with iron and folic acid (p.1922·1); capsules, docosahexaenoic acid (p.1362·1).
Docusate sodium (p.1725·1) is included in the tablets to reduce the constipating effects of iron.
Dietary supplement.

CitraFleet *De Witt, UK.*
Sodium picosulfate (p.1771·1); magnesium citrate (p.1743·2).
Bowel evacuation.

Citralamina *SM, Venez.*
Oxolamine citrate (p.1567·1).
Respiratory-tract disorders.

Citralite *Aventis, Austral.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); tartaric acid (p.2395·2).
Urinary alkalinisation.

Citralka *Pfizer, India.*
Sodium acid citrate (p.1673·2).
Acidosis.

Citra-Lock *Dirinco, Neth.*
Sodium citrate (p.1673·3).
To maintain patency of central venous catheters.

Citramag *Sanochemia, UK.*
Magnesium citrate (p.1743·2).
Bowel evacuation.

Citramar *Dupomar, Arg.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis.

Citramar D *Dupomar, Arg.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteopenia; osteoporosis.

Citramin *Engelhard, Ger.†.*
Alum (p.2254·1).
Mouth and throat disorders.

Citranacea *Nutravite, Canad.†.*
Echinacea (p.2298·1).

Citrargine *Laphal, Cz.†.*
⊗ Arginine citrate (p.1928·3); betaine hydrochloride (p.2265·2); betaine (p.2265·2).
Liver disorders.

Citrarginine *Laphal, Fr.†.*
⊗ Neutral arginine citrate (p.1928·3); betaine (p.2265·2); betaine hydrochloride (p.2265·2).
Liver disorders.

Citrato Espresso Gabbiani *Montefarmaco, Ital.*
Magnesium oxide (p.1744·1); magnesium carbonate (p.1743·1).
Gastrointestinal disorders.

Citrato Espresso S. Pellegrino *Sanofi-Aventis, Ital.*
Magnesium hydroxide (p.1743·2).
Constipation.

Citravescent
Note. This name is used for preparations of different composition.
Aventis, Austral.; Aventis, Malaysia†.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); tartaric acid (p.2395·2).
Urinary alkalinisation.

Pacific, NZ.
Sodium citrotartrate (p.1674·2).
Acidosis; gastric hyperacidity; urinary alkalinisation.

Citravit *Farmstandart, Rus.*
Ascorbic acid (p.1983·3).

Citravite
Pharmed, India.
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Adjunct in wounds and infections; scurvy.

Boots Healthcare, NZ†.
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Citredici UBT Kit *Cortex, Ital.*
⊗ Carbon-13 labelled urea (p.2277·1).
Diagnosis of gastroduodenal Helicobacter pylori infection.

Citrex Vitamin C *Pharmaniaga, Malaysia.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Citrex Vitamin E *Pharmaniaga, Malaysia.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Citri Slim+Trim *Bioglan, Austral.*
Garcinia (p.2309·2); chromium trichloride (p.1934·3); pectin (p.2145·2); methylcellulose (p.2145·1); magnesium amino acid chelate (p.1680·1).
Dietary supplement; obesity.

Citrihexal *Hexal, Austral.*
Calcitriol (p.1986·2).
Hypocalcaemia; hypoparathyroidism; osteoporosis; rickets.

Citrimax *Natural Life, Arg.†.*
Garcinia cambogia (p.2309·2).
Slimming aid.

Citrizan *IDI, Ital.*
Catalase (equine) (p.2278·2).
Burns; skin ulceration.

Citrizan Antibiotico *IDI, Ital.*
Catalase (equine) (p.2278·2); gentamicin sulfate (p.282·1).
Infected burns and skin ulcers.

Citro Jod *Esoform, Ital.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Citro-C
Note. This name is used for preparations of different composition.
Forder, Arg.†.
Sodium ascorbyl phosphate.
Vitamin C supplement.

Knop, Chile.
Echinacea (p.2298·1); ascorbic acid (p.1983·3).
Respiratory-tract infections.

Citrocarbonate *Hauck, USA; Roberts, USA.*
Sodium bicarbonate (p.1673·2); anhydrous sodium citrate (p.1673·3).
Hyperacidity.

Citrocholine
Note. This name is used for preparations of different composition.
Bailleul, Fr.
Oral powder: Sodium citrate (p.1673·3); magnesium citrate (p.1743·2); choline citrate (p.1934·2).
Dyspepsia.

Bailleul, Fr.
Oral solution: Choline citrate (p.1934·2); sodium acid citrate (p.1673·2); citric acid monohydrate (p.2284·1); light magnesium carbonate (p.1743·1).
Dyspepsia.

Citrocil *Reig Jofre, Spain.*
Dihydrostreptomycin sulfate (p.266·1).
Gastrointestinal infections.

Citrocit *Premier, S.Afr.†.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Urinary alkalinisation.

Citroclorex *Esoform, Ital.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Skin disinfection.

Citrocola *Argenfarma, Arg.*
Ascorbic acid (p.1983·3).

Citroepatina *Roche, Ital.*
Betaine monocitrate (p.2265·2); sorbitol (p.1965·1); sodium bicarbonate (p.1673·2); anhydrous citric acid (p.2284·1).
Digestive disorders.

Citro-Flav *Goldline, USA.*
Citrus bioflavonoids complex (p.2304·1).
Capillary bleeding.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Citrokalcium *Pharma Patent, Hung.*
Calcium citrate (p.1675·3).
Calcium supplement; osteomalacia; osteoporosis; rickets.

Citrokehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Citrol *Rowex, Irl.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Citrolithin *Farmanic, Gr.*
Citric acid (p.2284·1); sodium citrate (p.1673·3).

Citrolyt *Filofarm, Pol.*
Citric acid (p.2284·1); potassium citrate (p.1673·2); sodium citrate (p.1673·3).
Gout; renal calculi.

Citro-Mag *Rougier, Canad.; Rougier, Hong Kong†.*
Magnesium citrate (p.1743·2).
Bowel evacuation; constipation.

Citromed *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin disinfection.

Citromed 80 and 85 *Esoform, Ital.*
⊗ Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Skin disinfection.

Citromed Chirurgico *Esoform, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2); chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Citromed Chlor *Esoform, Ital.*
Tosylchloramide sodium (p.1665·1).
Surface disinfection.

Citromed Soap *Esoform, Ital.*
Cetylpyridinium chloride (p.1635·1).
Skin disinfection.

Citromedics Disinfettante *Esoform, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Surface disinfection.

Citromedics Pronto *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Instrument disinfection.

Citromel *Knop, Chile.*
Melissa (p.2339·3).
Anxiety; gastrointestinal disorders.

Citron *Infabra, Braz.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Citron Chaud DM *Prodemdis, Canad.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); dextromethorphan hydrobromide (p.1555·2); ascorbic acid (p.1983·3).

Citropepsin *Altana, Ger.†; ICN, Pol.*
Pepsin (p.2365·1); citric acid (p.2284·1).
Digestive disorders; gastrointestinal disorders.

Citropiperazina *Bruno, Ital.*
Piperazine citrate (p.152·3).
Urinary alkalinisation.

Citroplex *Neo Quimica, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Citroplus *Medley, Braz.†; Whitehall, Ital.†.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal procedures; gastrointestinal motility disorders; nausea and vomiting.

Citrosan *Boots Healthcare, Neth.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); sodium citrate (p.1673·3).
Cold and influenza symptoms.

Citrosil *Manetti Roberts, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of skin, burns, and wounds.

Citrosil Alcolico Azzurro *Manetti Roberts, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2); sodium nitrite (p.1464·3).
Instrument disinfection.

Citrosil Alcolico Bruno *Manetti Roberts, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Skin and wound disinfection.

Citrosil Alcolico Incolore *Manetti Roberts, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Skin and wound disinfection.

Citrosil Nubesan *Manetti Roberts, Ital.*
Benzalkonium chloride (p.1629·1); benzoin resin (p.2394·2).
Surface disinfection.

Citrosil Sapone *Manetti Roberts, Ital.*
Triclocarban (p.1665·2).
Skin cleansing.

Citro-Soda *Adcock Ingram, S.Afr.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); citric acid (p.2284·1).
Antacid; urinary alkalinisation.

Citrosodina *Bayer, Ital.*
Sodium citrate (p.1673·3).
Gastric hyperacidity.

Citrosodine
Note. This name is used for preparations of different composition.
Prima, Braz.†.
Oral granules: Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); sodium citrate (p.1673·3).
Gastric hyperacidity.

Prima, Braz.†.
Tablets: Sodium citrate (p.1673·3).
Gastrointestinal hyperacidity.

Citrosteril Ambiente *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1).
Linen disinfection.

Citrosteril Aspiratori *Sanitas, Ital.*
Orthophenylphenol (p.1655·1).
Disinfection of aspirators.

Citrosteril Deterferri *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection.

Citrosteril Impronte *Sanitas, Ital.*
Glutaral (p.1645·2); benzalkonium chloride (p.1629·1).
Disinfection in dentistry.

Citrosteril Pronto *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1); chlorhexidine (p.1635·2).
Disinfection in dentistry.

Citrosteril Sterilferri *Sanitas, Ital.*
Glutaral (p.1645·2).
Instrument disinfection.

Citrosteril Strumenti *Sanitas, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Instrument disinfection.

Citrosystem *Antipiol, Ital.*
Citronella oil (p.2284·2); basil oil (p.2263·2); lavender oil (p.2331·2).
Insect repellent.

Citrotein *Sandoz Nutrition, USA.*
Lactose-, cholesterol-, and gluten-free preparation for enteral nutrition (p.1922·1).

Citrovenot *Bros, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Citrovit *Sanofi-Aventis, Braz.; McNeil, Spain.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Citrovita
Note. This name is used for preparations of different composition.
Argenfarma, Arg.
Chewable tablets: Ascorbic acid (p.1983·3); zinc (p.1999·1).
Dietary supplement.

Argenfarma, Arg.
Oral solution: Ascorbic acid (p.1983·3).

Citrucel *GSK, USA.*
Methylcellulose (p.2145·1).
Bowel evacuation; constipation.

Citrus-flav C *Fibertone, USA.*
Citrus bioflavonoids complex (p.2304·1); vitamin C (p.1983·3); hesperidin (p.2304·3); acerola; rutoside (p.2305·1).
Capillary bleeding.

Citta *Eurofarma, Braz.*
Citalopram (p.385·3).
Anxiety; depression.

Civalex *Hovid, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Civell *Novell, Indon.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Civeran *Lesvi, Spain.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Civertim *Geolab, Braz.*
Cinnarizine (p.573·1).
Vestibular disorders.

Civicor *Douglas, NZ†; Douglas, Thai.†; TTN, Thai.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Civigel *Novartis, Fr.*
Carbomer 980 (p.2141·3).
Dry eyes.

Cixin *Geolab, Braz.*
Colchicine (p.556·1).
Gout.

Cixtor *Solvang, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Cizetol *Cipla, India.*
Carbamazepine (p.471·3).
Epilepsy.

Cizo *Bosch, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Cizoren *Stadmed, India†.*
Haloperidol (p.1000·2).
Childhood behaviour disorders; psychoses.

CK-2 *Degorts, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; rhinitis.

C-4-Kids *Terramedic, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

CKP *Bell, India.*
Vitamin C (p.1983·3); carbazochrome salicylate (p.1058·2); menadione sodium bisulfite (p.1995·3); rutoside (p.2305·1); calcium hydrogen phosphate (p.1676·1).
Haemorrhagic disorders.

C-L90 *Loges, Ger.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

CL tre *Nova Argentia, Ital.*
Trichloroacetic acid (p.1620·1).
Warts.

Clabat *Interbat, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Claben *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Clabin
Note. This name is used for preparations of different composition.
Chefaro, Ger.
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; warts.

Interdelta, Switz.
Salicylic acid (p.1612·2); lactic acid (p.2329·3); resorcinol (p.1612·1).
Calluses; corns; verrucas; warts.

Clacee *Abbott, S.Afr.*
Clarithromycin (p.248·2).
Bacterial infections.

Clacef *Inmark, Indon.; Dexa, Singapore.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clacin *APT, Hong Kong.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Clacina *BioSaude, Port.*
Clarithromycin (p.248·2).
Bacterial infections.

Clacine *Kalbe, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Cladex *Dexa, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cladostad *Stada, Cz.; Stada, Hung.*
Itraconazole (p.536·3).
Fungal infections.

Clafetam *Ahn-Gook, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Claforan *Aventis, Austral.†; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; ICN, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Lepetit, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Clafordil *Ariston, Braz.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clafoxim *Kalbe, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clairette *Stragen, UK.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne or hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Clairo *Weleda, S.Afr.*
Caraway (p.2276·3); clove (p.2284·3); erythraea centaury (p.2279·1); peppermint leaf (p.1761·2); achillea (p.2245·2); hoyae carnosae; aniseed (p.2258·2); senna (p.1769·2).
Constipation; digestive disorders.

Clalodine *Pharmasant, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Clamarvit *Clariana, Spain†.*
Ascorbic acid (p.1983·3); vitamin B substances (p.1922·1); ferrous gluconate (p.1939·1); ferrous glucoptate (p.1938·3).
Anaemias; tonic.

Clambusil *Loeffler, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clamentin *Xixia, S.Afr.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clamiben *Teuto, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Clamicin *Medley, Braz.*
Clarithromycin (p.248·2).
Bacterial infections.

Clamide *Hovid, Hong Kong; Hovid, Singapore.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Clamist *Wander, India.*
Clemastine fumarate (p.573·2).
Hypersensitivity reactions.

Clamohexal *Hexal, Austral.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clamonex *Yungjin, Singapore.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clamovid *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Philipp.; Hovid, Singapore.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Formerly known as Amoxiclav in *Malaysia*.
Bacterial infections.

Clamox *GSK, Fin.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Clamoxin *Maver, Mex.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Clamoxyl
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Austria; GSK, Ger.†; GSK, Neth.; Beecham, Port.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

GSK, Belg.; GSK, Fr.; GSK, Spain; GSK, Switz.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Clamoxyl Mucolitico *GSK, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Clamycin *Julphar, UAE.*
Clarithromycin (p.248·2).
Bacterial infections.

Claneksi
Sanbe, Indon.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Sanbe, Philipp.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Clanza *One Pharma, Philipp.*
Aceclofenac (p.14·3).
Inflammation; musculoskeletal and joint disorders; pain.

Clanzoflat *Wyeth, Spain.*
Dimeticone (p.1770·2); clebopride (p.1722·1).
Gastrointestinal disorders.

Clapharin Comp *Alternova, Fin.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clapharma *Actavis, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarac *Douglas, Austral.; Douglas, NZ.*
Clarithromycin (p.248·2).
Bacterial infections.

Claradol *Bayer, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Claradol Cafeine *Bayer, Fr.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Claradol Codeine *Bayer, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Claragine *Bayer, Fr.*
Aspirin (p.20·3).
Fever; pain.

Claral *Intendis, Spain.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Claral Plus *Intendis, Spain.*
⊗ Chlorquinaldol (p.242·3); diflucortolone valerate (p.1529·2).
Infected skin disorders.

Claramax *Schering-Plough, Austral.; Schering-Plough, NZ.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Claramid *Zambon, Belg.†; Pfizer, Fr.*
Roxithromycin (p.331·1).
Bacterial infections.

Claranta *OEP, Philipp.; Ajanta, Venez.*
Clarithromycin (p.248·2).
Bacterial infections; leprosy; protozoal infections.

Clararcana *Arcana, Austria.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarasol *Oftalmi, Venez.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Claratyne *Schering-Plough, Austral.; Schering-Plough, NZ.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Claravis *Barr, USA.*
Isotretinoin (p.1599·2).
Acne.

Claraxim *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clarbac *Pentafarma, Port.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarbact *Ipca, India; Ipca, Rus.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarelux *Pierre Fabre, Gr.; Pierre Fabre, Neth.; Pierre Fabre Dermo-Cosmetique, Port.; 3M, UK.*
⊗ Clobetasol propionate (p.1522·2).
Scalp disorders; skin disorders.

Clarema *Damor, Ital.*
Suleparoid (p.1406·3).
Superficial vascular disorders; thrombosis prophylaxis.

Clarens *Alfa Biotech, Ital.*
Sulodexide (p.1406·3).
Venous ulcers.

Clarex
Note. This name is used for preparations of different composition.
Phoenix, Arg.
Erythromycin lactobionate (p.270·1).
Bacterial conjunctivitis.
Pharmacos, Mex.
Phenylephrine (p.1568·1); boric acid (p.2268·1).
Eye disorders.

Clarex Compuesto *Phoenix, Arg.*
Erythromycin lactobionate (p.270·1); colistimethate sodium (p.256·3).
Bacterial eye infections.

Clarexid *Pliva, Cz.*
Clarithromycin (p.248·2).
Bacterial infections.

Clargotil *Gedeon Richter, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

Clari *Hanmi, Singapore.*
Clarithromycin (p.248·2).
Bacterial infections.

Claribactron *Faran, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Claribel *Loyal Advance, Hong Kong.*
Clindamycin phosphate (p.251·2).
Acne.

Claribid *Pharmacia, India.*
Clarithromycin (p.248·2).
Bacterial infections.

Claribiotic *Baliarda, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Claricide *Bilim, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Claricina *Lafedar, Arg.; Biofarma, Braz.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Claricip *Cipla, India.*
Clarithromycin (p.248·2).
Bacterial infections.

Claricort *Undra, Mex.†; Schering-Plough, Philipp.; Schering-Plough, Venez.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).
Hypersensitivity reactions.

Clarid *Biolab, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Clariderm *Stiefel, Thai.*
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Claridex *Schering-Plough, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Claridexultra *Schering-Plough, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Claridon *Schering-Plough, Port.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Clarifex *Difa, Ital.*
Chlorhexidine gluconate (p.1635·3).
Soap substitute.

Clariflu *Schering-Plough, Hong Kong; Schering-Plough, Mex.; Schering-Plough, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1).
Allergic rhinitis; cold symptoms; influenza symptoms.

Clarifriol *Schering-Plough, Arg.; Schering-Plough, Mex.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1).
Allergic rhinitis; cold symptoms; influenza symptoms.

Clariget *Getz, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarigrip *Schering-Plough, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1).
Allergic rhinitis; influenza symptoms.

ClariHexal *Hexal, S.Afr.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarihis *Lapi, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Claril *Alcon, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Ocular congestion.

Clarilerg *Hexal, Braz.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Clarimac *Cadila, India.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarimax *Montpellier, Arg.; Andromaco, Chile.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarimex *Pharmex (Φαρμεξ), Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarimid *Epicaris, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarimir *Andromaco, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Clarimir F *Andromaco, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic eye disorders; eye irritation.

Clarinase *Schering-Plough, Austral.; Aesca, Austria; Schering-Plough, Belg.; Essex, Chile; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Mex.†; Schering-Plough, NZ†; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Singapore; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, Venez.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold and influenza symptoms; upper respiratory-tract congestion.

Clarineo *Neo Quimica, Braz.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarinese *Pharmacare, S.Afr.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Clarinex *Schering, USA.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Clarinex-D *Schering, USA.*
Desloratadine (p.576·1); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract disorders.

Claripel *Stiefel, Arg.; Stiefel, Braz.; Stiefel, USA.*
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Claripen *Elpen (Ελπεν), Gr.; Elpen, Singapore.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarisco *Teofarma, Ital.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Clarisens *Farmstandart, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Clarisoft *Vannier, Arg.*
⊗ Phenazone (p.116·1); ephedrine (p.1558·1).
Eye disorders.

Clariteyes *Schering-Plough, UK.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Clarith *Taisho, Jpn; LBS, Thai.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Clarithro *Arrow, Austral.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarithrobeta *Betapharm, Ger.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori-associated peptic ulcer.

Claritic *SM, Venez.*
Clarithromycin (p.248·2).
Bacterial infections.

Claritin *Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Indon.; Shionogi, Jpn; Schering-Plough, Philipp.; Schering-Plough, USA.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Claritin Allergic Congestion Relief *Schering, Canad.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Claritin Allergy & Sinus *Schering, Canad.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Claritin Extra *Schering, Canad.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Claritin Eye Allergy Relief *Schering, Canad.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis.

Claritin Skin Itch Relief *Schering, Canad.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Claritin-D *Mantecorp, Braz.; Schering, USA.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; nasal congestion.

Claritine *Schering-Plough, Belg.; Schering-Plough, Cz.; Schering-Plough, Hung.; Schering-Plough, Neth.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Essex, Switz.; Schering-Plough, Turk.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

Claritone *Fischer, Israel.*
Comfort solution for contact lens (p.1622·2).
Dry eyes; eye irritation.

Claritromax *Prodotti, Braz.*
Clarithromycin (p.248·2).
Bacterial infections.

Claritron *Cellofarm, Braz.†; Biofarma, Venez.*
Clarithromycin (p.248·2).
Bacterial infections.

Claritur *Cantabria, Spain†.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarituss Plus *Pharmacare, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Cough.

Clarityn
Note. This name is used for preparations of different composition.
Aesca, Austria; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Irl.†; Schering-Plough, Ital.; Schering-Plough, Norw.; Schering-Plough, Swed.
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; asthma; urticaria.
Schering-Plough, UK.
Eye drops: Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.
Schering-Plough, UK.
Syrup; tablets: Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Clarityne *Schering-Plough, Arg.; Essex, Chile; Schering-Plough, Fr.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Thai.; Schering-Plough, Venez.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; pruritus; urticaria.

Clarityne Cort *Schering-Plough, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Hypersensitivity reactions.

Clarityne D *Schering-Plough, Arg.; Schering-Plough, Gr.; Schering-Plough, Mex.; Schering-Plough, S.Afr.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic disorders; allergic rhinitis; cold symptoms; upper respiratory-tract congestion.

Clarivax *Vivax, Venez.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Clarivit *Vitapan, Braz.†.*
⊗ Naphazoline (p.1565·1).
Allergic rhinitis.

Clarix
Note. This name is used for preparations of different composition.
Cooperation Pharmaceutique, Fr.
Erysimum; pholcodine (p.1570·2).
Coughs.
Oftalmi, Venez.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Allergic conjunctivitis; nasal congestion.

Claro *ITF, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Clarobiotico *Tecnimede, Port.*
Clarithromycin (p.248·2).
Bacterial infections.

Claroft *Alcon, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Claroftal *Poen, Arg.*
Sodium cromoglicate (p.1136·3).
Blepharitis; conjunctivitis.

Clarograf *Justesa Imagen, Arg.; Schering, Spain.*
Iopromide (p.1485·1).
Radiographic contrast medium.

Claromycin *Gap, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Claromycine *Spirig, Switz.*
Clarithromycin (p.248·2).
Bacterial infections.

Claron *Siam Bheasach, Thai.*
Clarithromycin (p.248·2).
Bacterial infections.

Claropram *Spirig, Switz.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Clarosip *Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Irl.; Grunenthal, Neth.; Grunenthal, Port.; Grunenthal, UK.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarotadine *Akrikhin, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Clarover *Novartis, Ital.*
Povidone (p.2146·1).
Dry eyes.

Clarovil *Beta, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Clarus
Note. This name is used for preparations of different composition.
Josper, Braz.†.
Bromhexine (p.1552·2).
Respiratory-tract disorders.
Prempharm, Canad.
Isotretinoin (p.1599·2).
Acne.

Clarvisan *Allergan, Ital.; Hormona, Mex.†; Seber, Port.; Alcon Cusi, Spain.*
Pirenoxine sodium (p.2368·3).
Cataracts.

Clarvisol *Allergan, Braz.*
Pirenoxine sodium (p.2368·3).
Cataracts.

Clarvisor *Alcon, Ger.†.*
Pirenoxine sodium (p.2368·3).
Cataracts.

Clarvix *Beta, Arg.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Clasifel *Stiefel, Chile; Stiefel, Mex.*
Hydroquinone (p.1598·2); oxybenzone (p.1608·3); padimate O (p.1609·1); dioxybenzone (p.1594·2).
Skin pigmentation disorders.

Classic *Kimia, Indon.*
⊗ Furosemide (p.1292·1).
Hypertension; nephrotic syndrome; oedema.

Classic Swiss One *Swiss Herbal, Canad.†.*
Multivitamin and mineral preparation with methionine (p.1922·1).

Clast *Meiji, Indon.*
Clebopride malate (p.1722·1).
Gastrointestinal disorders.

Clasteon *Abiogen, Ital.; Beacon, UK.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolytic tumours; osteoporosis.

Clastidin *Nutrifar, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Clastoban *Schering, Fr.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Clatatin *Molex Ayus, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Clatax *Fahrenheit, Indon.*
Cefotaxime (p.229·1).
Bacterial infections.

Clatic *Pasteur, Chile.*
Clarithromycin (p.248·2).
Bacterial infections.

Clatorin *Royton, Braz.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Clatrocin *Ivax, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Clatromicin *Sandoz, Arg.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Claudemor
Note. This name is used for preparations of different composition.
Sankyo, Braz.
Thromboplastin (p.1080·2); benzocaine (p.1854·1); procaine hydrochloride (p.1869·1); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); peru balsam (p.2365·3).
Anorectal disorders.
Sankyo, Port.†.
Thromboplastin (p.1080·2); benzocaine (p.1854·1); procaine (p.1869·2); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); peru balsam (p.2365·3).
Anorectal disorders.
Sankyo, Venez.†.
Rectal ointment: Thromboplastin (p.1080·2); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1).
Haemorrhoids.
Sankyo, Venez.†.
Suppositories: Thromboplastin (p.1080·2); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1); benzocaine (p.1854·1); Peru balsam (p.2365·3).
Haemorrhoids.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Clauden *Lohmann, Ger.*
A range of dressings impregnated with thromboplastin (p.1080·2).
Haemorrhage.

Claudia *Sandoz, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Claudicat *Altana, Ger.; Altana, Port.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Clauparest *Pekana, Ger.†.*
Homoeopathic preparation.

Clav-Air *Biofarma, Braz.†.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavamel *Clonmel, Irl.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavamox
Sandoz, Austria.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Kalbe, Indon.; Taro, Israel; Bial, Port.; Grunenthal, Switz.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavant *Columbia, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Claventin
Note. This name is used for preparations of different composition.
GSK, Fr.
Ticarcillin sodium (p.352·2); potassium clavulanate (p.250·2).
Bacterial infections.

Kalbe, Philipp.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Clavepen *Clintex, Port.; Almirall, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Claversal *Merck, Austria; Tramedico, Belg.; Merckle, Ger.; GSK, Ital.; GSK, Neth.; Altana, Port.; Faes, Spain.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Clavex *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavigrenin *Galena, Cz.†; Ivax, Cz.†; Hormosan, Ger.†.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine; migraine and related vascular headaches; nervous disorders.

Clavinex *Saval, Chile.*
Potassium clavulanate (p.250·2); amoxicillin (p.202·2).
Bacterial infections.

Clavinex Duo *Saval, Chile.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Clavocef *Oboi, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clavolek *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavoplus *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavoxel *Metz, Philipp.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavoxil *Haller, Braz.†.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavoxilina Bid *Pharmabiotics, Chile.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

clavu-basan *Schonenberger, Switz.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavucar *Geymonat, Ital.†.*
Ticarcillin sodium (p.352·2); potassium clavulanate (p.250·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Clavucid *Astellas, Belg.; Recordati, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavucyd *Unipharm, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavulanex *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavulin
Arrow, Austral.; GSK, Canad.; Fournier, Ital.; Sanfer, Mex.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

GSK, Braz.
Amoxicillin (p.202·2); clavulanic acid (p.250·2) or potassium clavulanate (p.250·2).
Bacterial infections.

Clavulox *GSK, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavulox Duo *GSK, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavumox
GSK, Hung.†.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Group, S.Afr.; Pfizer, Spain; Dollder, Venez.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavurion *Orion, Fin.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavuser *Serral, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clavuxal *Alpharma, Fin.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Clawkit *Ximena Polanco, Chile.*
Homoeopathic preparation.

Clax *Cadila, India.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1); *Lactobacillus sporogenes* (p.2372·3).
Bacterial infections.

Cleactor *Eisai, Jpn.*
Monteplase (p.1344·1).
Myocardial infarction; pulmonary embolism.

Clean & Clear Blackhead Clearing Astringent *Johnson & Johnson, Canad.*
Salicylic acid (p.1612·2).

Clean & Clear Continuous Control *Johnson & Johnson, Canad.*
Benzoyl peroxide (p.1590·2).
Acne.

Clean & Clear Continuous Control Acne Wash *Johnson & Johnson, Canad.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Deep Cleaning Astringent *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Foaming Facial Cleanser *Johnson & Johnson, Canad.*
Triclosan (p.1665·2).
Acne.

Clean & Clear Gel Secativo *Johnson & Johnson, Braz.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Hidratante *Johnson & Johnson, Braz.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Invsible Blemish Treatment *Johnson & Johnson, Canad.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Locao Adstringente *Johnson & Johnson, Braz.*
Salicylic acid (p.1612·2).
Acne.

Clean & Clear Persa Gel *Johnson & Johnson, Canad.*
Benzoyl peroxide (p.1590·2).
Acne.

Clean & Clear Sabonete Liquido Facial *Johnson & Johnson, Braz.*
Triclosan (p.1665·2).
Acne.

Clean & Clear Sabonete Liquido Refrecante *Johnson & Johnson, Braz.†.*
Salicylic acid (p.1612·2).
Acne.

Clean Hair *Neo Quimica, Braz.*
Permethrin (p.2048·2).
Pediculosis.

Clean Skin Anti Acne *Mentholatum, Austral.*
Melaleuca oil (p.2338·2).
Acne.

Clean Skin Face Wash *Mentholatum, Austral.*
Melaleuca oil (p.2338·2); benzalkonium chloride (p.1629·1).
Acne.

Clean-AC
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.
Cucurbita (p.2290·2); zinc gluconate (p.1999·2).
Acne.

Avene, Fr.
Zinc gluconate (p.1999·2); levomenol (p.2333·3).
Dry skin following acne treatment.

Clean-AF *Floris, Israel.*
Sodium chloride (p.1686·1).
Nasal congestion.

Cleanal *Mitsubishi, Jpn.*
Fudosteine (p.1561·1).
Respiratory-tract congestion.

Cleanance
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
Cucurbita (p.2290·2); zinc gluconate (p.1999·2).
Seborrhoea.

Silesia, Chile.
Topical emulsion: Cucurbita (p.2290·2); zinc gluconate (p.1999·2); salicylic acid (p.1612·2).
Seborrhoea.

Avene, Fr.
Topical emulsion; topical gel: Zinc gluconate (p.1999·2); cucurbita (p.2290·2).
Seborrhoea.

Silesia, Chile.
Topical gel: Cucurbita (p.2290·2); zinc gluconate (p.1999·2).
Seborrhoea.

Avene, Fr.
Topical lotion: Zinc gluconate (p.1999·2); cucurbita (p.2290·2); salicylic acid (p.1612·2).
Seborrhoea.

Cleanance K *Avene, Fr.*
Glycolic acid (p.1598·1); lactic acid (p.2329·3); salicylic acid (p.1612·2); zinc gluconate (p.1999·2); cucurbita (p.2290·2).
Seborrhoea.

Cleanbac *Prati-Donaduzzi, Braz.†.*
Nitrofurazone (p.309·1).
Burns; skin infections; ulcers; wounds.

Cleancef *Shin Poong, Singapore.*
Cefaclor (p.217·2).
Bacterial infections.

CleanEars *Naveh, Israel.*
Liquid paraffin (p.2030·3); squalane (p.2032·3).
Ear wax removal.

Cleansa Plus *Swiss Bio, Malaysia†.*
Lappa (p.2330·3); passion flower (p.2363·2); red clover (p.2285·1); queen's delight; sarsaparilla (p.2383·3); urtica (p.2409·3).
Dietary supplement; skin disorders.

Cleansing Herbs *Potter's, UK.*
Buckthorn (p.1713·3); psyllium (p.1737·1); senna leaves (p.1769·2); sambucus (p.2383·1); fennel seed (p.2302·3); maté (p.2416·1).
Cleansing Herb Tablets formerly contained senna leaves, aloes, cascara, taraxacum, and fennel seed.
Constipation.

Cleanxate *Sam Chun Dang, Singapore.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Clear Away *Schering-Plough, Austral.†.*
Salicylic acid (p.1612·2).
Warts.

Clear Blue
Note. This name is used for preparations of different composition.
Volta, Chile.
Pregnancy test (p.2372·1).

Leurquin, Hong Kong.
⊗ Naphazoline nitrate (p.1565·2); methylthioninium chloride (p.1450·3).
Eye irritation.

Clear Blue Easy *Wyeth, Venez.†.*
Pregnancy test (p.2372·1).

Clear Cough *Be-Tabs, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Clear Ear *Co-Pharma, UK.*
Docusate sodium (p.1725·1).
Ear wax removal.

Clear Eyes *Abbott, Austral.†; Prestige, Canad.; Abbott, NZ; Ross, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Clear Eyes ACR *Abbott, NZ†.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Clear Eyes Allergy *Prestige, Canad.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).

Clear Eyes CLR *Ross, USA.*
Sodium chloride (p.1686·1); hypromellose (p.2144·2) (p.1622·2).
Moistening drops for contact lenses.

Clear Eyes Contact Lens Relief *Medtech, USA.*
Sorbic acid (p.1662·2); edetic acid (p.1445·1) (p.1622·2).

Clear Eyes for Dry Eyes *Medtech, USA.*
Carmellose sodium (p.2142·1).
Dry eyes.

Clear Eyes Plus Redness Relief *Medtech, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Clear Eyes Seasonal Relief *Medtech, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Formerly known as Clear Eyes ACR.
Eye irritation.

Clear Plus Easy *Wyeth, Venez.†.*
Pregnancy test (p.2372·1).

Clear Tussin 30 *Goldline, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

ClearAc *Hylands, Canad.*
Homoeopathic preparation.

ClearAc Cleanser *Hylands, Canad.*
Homoeopathic preparation.

Clearamed *Boots Healthcare, Neth.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Clearamox *Boehringer Ingelheim, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Clearasil
Note. This name is used for preparations of different composition.
Boots Healthcare, NZ.
Sulfur (p.1614·1); triclosan (p.1665·2).
Acne.

Richardson-Vicks Personal Care, USA.
Benzoyl peroxide (p.1590·2).
Acne.

Clearasil 3 in 1 *Reckitt Benckiser, Singapore.*
Salicylic acid (p.1612·2).
Soap substitute.

Clearasil Acne Control *Reckitt Benckiser, Canad.*
Resorcinol (p.1612·1); sulfur (p.1614·1).

Clearasil Acne Cream *Reckitt Benckiser, Canad.*
Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Clearasil Acne Treatment Cream *Procter & Gamble, Austral.*
Sulfur (p.1614·1); triclosan (p.1665·2).
Acne.

Clearasil Active Treatment Cream *Crookes Healthcare, UK.*
Triclosan (p.1665·2); sulfur (p.1614·1).
Formerly known as Clearasil Treatment Cream.
Acne.

Clearasil Antibacterial *Richardson-Vicks Personal Care, USA.*
Triclosan (p.1665·2); glycerol (p.2314·2); titanium dioxide (p.1617·3).
Acne.

Clearasil Benzoyl P *Procter & Gamble, S.Afr.*
Benzoyl peroxide (p.1590·2).
Acne.

Clearasil B.P. Plus *Reckitt Benckiser, Canad.*
Benzoyl peroxide (p.1590·2).
Acne.

Clearasil Cleanser *Reckitt Benckiser, Canad.*
Salicylic acid (p.1612·2).
Acne.

Clearasil Clearstick *Procter & Gamble, Canad.†; Procter & Gamble, USA.*
Salicylic acid (p.1612·2).
Acne.

Clearasil Daily Face Wash
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.
Phenoxyisopropanol (p.1657·2).
Acne.

Procter & Gamble, USA.
Triclosan (p.1665·2).

Clearasil 3 in 1 Deep Cleansing Wash *Reckitt Benckiser, Malaysia.*
Salicylic acid (p.1612·2).
Soap substitute.

Clearasil Double Action Pads *Crookes Healthcare, UK.*
Salicylic acid (p.1612·2).
Formerly known as Clearasil Dual Action Pads.
Acne.

Clearasil Double Clear *Richardson-Vicks, USA.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2); hamamelis (p.2318·2).

Clearasil Double Textured Pads *Procter & Gamble, USA.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).

Clearasil Face Wash *Procter & Gamble, Canad.†.*
Triclosan (p.1665·2).
Acne.

Clearasil Facial Cleansing *Boots, Singapore.*
Triclosan (p.1665·2).
Soap substitute.

Clearasil Ice Wash *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Salicylic acid (p.1612·2).
Acne; seborrhoea; soap substitute.

Clearasil Medicated Facial Cleanser *Procter & Gamble, S.Afr.*
⊗ Allantoin (p.1588·1); alcohol (p.1625·2); salicylic acid (p.1612·2).
Acne.

Clearasil Medicated Wipes *Procter & Gamble, Austral.*
Salicylic acid (p.1612·2).
Acne.

Clearasil Overnight Defence *Boots, Singapore.*
Salicylic acid (p.1612·2); triclosan (p.1665·2).
Acne.

Clearasil Pads *Boots Healthcare, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clearasil Pimple Treatment *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Triclosan (p.1665·2); sulfur (p.1614·1); bentonite (p.2141·2).
Acne.

Clearasil Pore Cleansing Lotion *Crookes Healthcare, UK.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Formerly known as Clearasil Medicated Lotion.
Acne.

Clearasil Stayclear *Boots Healthcare, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clearasil T *Procter & Gamble, S.Afr.*
Sulfur (p.1614·1); triclosan (p.1665·2); bentonite (p.2141·2).
Acne.

Clearasil Ultra *Procter & Gamble, Austral.; Boots Healthcare, NZ; Boots, Pol.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Clearasil Ultra Deep Pore *Reckitt Benckiser, Malaysia.*
Salicylic acid (p.1612·2).
Acne; soap substitute.

Clear-Atadine *Major, USA.*
Loratadine (p.583·3).
Allergic rhinitis.

Clearblue *Unipath, Canad.; Unipath, Israel; Unipath, Ital.; Pfizer, NZ; Whitehall-Robins, Switz.; Unipath, UK.*
Pregnancy test (p.2372·1).

Clearblue Easy *Wyeth Consumer, Braz.; Whitehall, USA.*
Pregnancy test (p.2372·1).

Clearblue Easy Ovulation *Unipath, USA.*
Fertility test (p.2372·1).

Clearblue One Step *Pfizer Consumer, Austral.†.*
Pregnancy test (p.2372·1).

Clearblue test d'ovulation *Polive, Fr.*
Fertility test (p.2372·1).
Formerly known as Clearplan.

Clearblue test de grossesse *Polive, Fr.*
Pregnancy test (p.2372·1).

Cleardent *Medibrands, Israel.*
Chlorhexidine gluconate (p.1635·3).
Mouth infections; oral hygiene.

Clearex *Medibrands, Israel.*
Salicylic acid (p.1612·2).
Acne.

Clearex Cover Up *Medibrands, Israel.*
Benzoyl peroxide (p.1590·2).
Acne.

Clearex for Sensitive Skin *Medibrands, Israel.*
Salicylic acid (p.1612·2).
Acne.

Clearine *Dominion, India.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Clearize *Abbott, Venez.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Clearplan *Unipath, Canad.; Wyeth Consumer, Chile†; Unipath, Ital.; Pfizer, NZ; Whitehall-Robins, Switz.*
Fertility test (p.2372·1).

Clearplan Easy *Whitehall, USA†.*
Fertility test (p.2372·1).

Clearplan One Step *Pfizer Consumer, Austral.†.*
Fertility test (p.2372·1).

Clearsing *Duncan, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Clearskin Acne Defense Stick *Avon, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clearskin Antibacterial
Note. This name is used for preparations of different composition.
Avon, Canad.
Cream: Benzethonium chloride (p.1630·1).
Acne.

Avon, Canad.†.
Soap: Triclosan (p.1665·2).
Acne.

Clearskin Cleansing *Avon, Canad.*
Salicylic acid (p.1612·2).
Acne.

Clearskin Medicated Cleanser *Avon, Canad.†.*
Triclosan (p.1665·2).
Acne.

Clearskin Medicated Wash *Avon, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clearskin Overnight Acne Treatment *Avon, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Clearskin Targeted Blemish Remover *Avon, Canad.*
Salicylic acid (p.1612·2).
Acne.

Clearsore *Pinewood, UK.*
Aciclovir (p.862·3).
Herpes simplex infections of the lips and face.

Clear-View
Note. A similar name is used for preparations of different composition (see below).
Colgate Oral Care, Austral.
Demisting solution for dental mirrors and spectacles.

Clearview HCG
Note. A similar name is used for preparations of different composition (see above).
Pfizer Consumer, Austral.; Unipath, UK; Wampole, USA.
Pregnancy test (p.2372·1).

Clearwax *Cipla, India.*
Paradichlorobenzene (p.2363·1); benzocaine (p.1854·1); chlorobutanol (p.1639·2); turpentine oil (p.2406·3).
Ear wax removal.

Clebofex *Azevedos, Port.*
Clebopride malate (p.1722·1).
Gastrointestinal disorders.

Cleboril *Almirall, Spain.*
Clebopride malate (p.1722·1).
Gastrointestinal disorders; nausea and vomiting.

Clebudan *Grunenthal, Chile.*
⊗ Budesonide (p.1520·1).
Nasal polyps; obstructive airways disease; rhinitis.

Clebutec *Almirall, Port.*
Clebopride malate (p.1722·1).
Gastrointestinal disorders.

Cledist *Jaldes, Fr.*
Selenium; zinc citrate; ascorbic acid; vitamin E; betacarotene; tagetes; tomato; turmeric; grape; myrtillus; urtica doica (p.1922·1).
Nutritional supplement.

Cleeravue-M *Stonebridge, USA.*
Minocycline (p.300·3).
Bacterial infections.

Clematis III Oligoplex *Madaus, Arg.†.*
Hamamelis (p.2318·2); clematis recta; sanguinaria (p.2383·2).
Inflammation.

Clembroxol *Pentafarma, Port.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion and bronchospasm.

Clembumar *Dupomar, Arg.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Clemental *Therabel, Fr.†.*
Tiapride hydrochloride (p.1032·1).
Aggression; agitation; childhood behaviour disorders; choreas; pain; Tourette's syndrome.

Clements Iron *Felton, Austral.*
Multivitamin, mineral, and glucose preparation with iron (p.1949·1)(p.1922·1).
Iron deficiency; nutritional anaemia.

Clements Tonic *Felton, Austral.*
Vitamin and mineral preparation with ginseng (p.2312·1) and ginkgo biloba (p.2311·1) (p.1922·1).
Formerly a mineral preparation with malt, honey, thiamine and yeast.
Dietary supplement; tonic.

Clenasma *Biomedica, Hong Kong†; Biomedica, Ital.†.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Clenbunal *Roemmers Rowe, Venez.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Clenbuxol *Roemmers Rowe, Venez.*
⊗ Clenbuterol (p.1120·1); ambroxol (p.1550·3).
Respiratory-tract disorders.

Clendazaf *Zafiro, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clenia *Upsher-Smith, USA.*
Sulfacetamide sodium (p.335·3); sulfur (p.1614·1).
Acne.

Cleniderm *Soho, Indon.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Clenigen *Chiesi, Cz.†.*
⊗ Beclometasone dipropionate (p.1516·2); gentamicin sulfate (p.282·1); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Clenil *Torrex, Austria; Farmalab, Braz.; Chiesi, Cz.; Chiesi, Gr.†; Chiesi, Ital.; Chiesi, Malaysia; Chiesi, Neth.; Chiesi, Port.; Chiesi, Rus.; Rolab, S.Afr.†; Chiesi, Singapore†; Chiesi, Thai.; Trinity, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma; nasal polyps; obstructive airways disease; sinusitis.

Clenil Compositum
Farmalab, Braz.; Promedica, Ital.
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Chiesi, Singapore†; Chiesi, Thai.
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Obstructive airways disease.

Clenil Forte Jet *Chiesi, Gr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Clenil Rino *Chiesi, Gr.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Clenilexx *Promedica, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Clens-100 *Alcon, Braz.; Alcon, Canad.; Alcon, Fr.*
Cleaning solution for contact lenses (p.1622·2).

Clen-Zym *Alcon, UK.*
Pancreatin (p.2360·1) (p.1622·2).
Soft contact lens cleanser.

Cleocin
Pfizer, Austral.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Pfizer, Austria; Pharmacia, USA.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Pharmacia, Ital.
Clindamycin phosphate (p.251·2).
Bacterial vaginosis.

Eczacibasi, Turk.
Clindamycin hydrochloride (p.251·1), clindamycin palmitate (p.252·3), or clindamycin phosphate (p.251·2).
Bacterial injections.

Cleocin T *Eczacibasi, Turk.; Pharmacia, USA.*
Clindamycin phosphate (p.251·2).
Acne.

Cleridium *IPRAD, Fr.†.*
Dipyridamole (p.1268·1).
Thromboembolism prophylaxis.

Cleron *Aegis, Hong Kong; Aegis, Singapore.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Clerz
Note. This name is used for preparations of different composition.
Ciba Vision, Canad.†.
Poloxamer 407 (p.1918·2) (p.1622·2).
Lubricating solution for contact lenses.

Alcon, USA.
Range of solutions for contact lenses (p.1622·2).

Cletal *Tolmann, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Cletonol *Merck, Arg.†.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Clever *Chiesi, Ital.*
Ebastine (p.579·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Cleveron *TRB, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Clevia *Hermal, Ger.*
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Clevian *Aesculapius, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Clevosan
Note. This name is used for preparations of different composition.
Baliarda, Arg.
Ointment: Centella (p.1592·3); neomycin sulfate (p.305·1).
Skin disorders.

Baliarda, Arg.
Topical powder: Centella (p.1592·3); neomycin (p.305·1); zinc undecenoate (p.549·3); zinc oxide (p.1621·2).
Skin disorders.

Baliarda, Arg.
Topical spray: Centella (p.1592·3); tetracaine (p.1871·2).
Skin disorders.

Clexane *Aventis, Arg.; Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Sanofi-Aventis, NZ; Aventis, Neth.; Aventis, Philipp.; Aventis, Pol.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Venez.*
Enoxaparin sodium (p.1277·2).
Deep-vein thrombosis; myocardial infarction; prevention of clotting in extracorporeal circuits; pulmonary embolism; thromboembolism prophylaxis; unstable angina.

Clexane anti Xa-IU *Sanofi-Aventis, Cz.*
Enoxaparin sodium (p.1277·2); anti-Xa.
Myocardial infarction; prevention of clotting during haemodialysis; thromboembolic disorders; unstable angina.

Clexiclor *Uno, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Cliacil *Aventis, Austria.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Cliad *Interbat, Indon.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Enterocolitis; irritable bowel syndrome; peptic ulcer.

Cliane *Schering, Braz.; Schering, Chile; Schering, Mex.; Schering, NZ; Schering, Venez.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Cliarvas *Baliarda, Arg.†.*
Losartan potassium (p.1326·1).
Hypertension.

Clibite *Korea United, Philipp.; Pharma 3, Philipp.*
Gliclazide (p.440·3).
Diabetes mellitus.

Clibium *Klinger, Braz.†.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Clidacin *Vianex (Βιανέξ), Gr.*
Clindamycin (p.251·1).
Bacterial infections.

Clidam *Biochemie, Austria†.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clidan *Cassara, Arg.*
Clindamycin phosphate (p.251·2).
Acne.

Clidan B *Cassara, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Clidets
Stiefel, Chile.
Clindamycin phosphate (p.251·2).
Acne.

Stiefel, Mex.
Clindamycin (p.251·1).
Acne.

Clifemin *Herbarium, Braz.*
Cimicifuga (p.2282·1).
Menopausal symptoms.

Clifenal *Biofarma, Mex.*
Cimicifuga (p.2282·1).
Menopausal disorders; menstrual disorders.

Climabelle *Schering, Austria†.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Climaclod *Mastelli, Ital.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Climacteron *Sandoz, Canad.*
⊗ Testosterone enantate benzilic acid hydrazone (p.2131·3); estradiol dienanthate (p.2097·3); estradiol benzoate (p.2097·2).
Menopausal disorders; osteoporosis.

Climadan
Note. This name is used for preparations of different composition.
Dankos, Singapore†.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Dankos, Indon.
Capsules: Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Kalbe, Indon.
Topical gel: Clindamycin phosphate (p.251·2); zinc acetate (p.1999·1).
Acne.

Climaderm *Wyeth, Arg.†; Wyeth, Braz.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Venez.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Climadil *Marjan, Braz.*
Red clover (p.2285·1).
Menopausal symptoms.

Climafen *Andromaco, Chile.*
⊗ Tibolone (p.2134·1).
Oestrogen deficiency; osteoporosis.

Climagest *Novartis, UK.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; norethisterone (p.2119·3).
Menopausal disorders.

Climanor *Resource Medical, UK.*
Medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Climara *Schering, Austral.; Schering, Austria; Schering, Belg.; Berlex, Canad.; Bayer Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Berlipharm, Irl.; Schering, Ital.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Bayer, USA.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Climara Duo *Schering, Cz.†; Schering, Fin.†; Schering, Port.†.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; levonorgestrel (p.2121·2).
Hormone replacement therapy; menopausal disorders.

ClimaraPro *Berlex, USA.*
Estradiol (p.2097·2); levonorgestrel (p.2121·2).
Menopausal disorders.

Climarest *Wyeth, Ger.†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Climasoy *Konsuma, Venez.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Climaston
Solvay, Fr.
Tablets 1mg/5mg: Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Solvay, Fr.
Tablets 1mg/10mg; tablets 2mg/10mg: 14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Climaston Continu *Euro Registratie, Neth.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Climatidine *Climax, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Climatix *Investi, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Climatrol Continuo *Gynopharm, Chile.*
35 Tablets, conjugated oestrogens (p.2087·2); 35 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Climatrol E *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Climatrol HT *Gynopharm, Chile.*
17 Tablets, conjugated oestrogens (p.2087·2); 13 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Climatrol HT Ciclico *Vivax, Venez.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Climatrol HT Continuo *Gynopharm, Chile; Vivax, Venez.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Climaval *Novartis, UK.*
Estradiol valerate (p.2097·3).
Menopausal disorders.

Climavita *Permamed, Switz.*
Cimicifuga root (p.2282·1).
Menopausal disorders.

Climaxol *Lehning, Fr.*
Hamamelis (p.2318·2); viburnum (p.2267·1); butcher's broom (p.2270·3); hydrastis (p.2321·3); aesculus (p.2248·2).
Peripheral vascular disorders.

Climen *Schering, Austral.; Schering, Austria; Schering, Belg.; Bayer Schering, Cz.; Schering, Denm.; Schering, Ger.; Schering, Hung.; Schering, Ital.; Bayer Schering, Malaysia; Schering, Norw.†; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Switz.; Schering, Thai.; Schering, Turk.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, cyproterone acetate (p.2088·2); estradiol valerate.
28-Day packs contain 16 and 12 tablets, respectively.
Hormone replacement therapy; menopausal disorders; menstrual disorders; oestrogen deficiency; osteoporosis.

Climen 28 *Schering, Hong Kong; Schering, Indon.; Schering, Philipp.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; cyproterone acetate (p.2088·2).
Menopausal disorders; menstrual disorders; osteoporosis.

Climene *Schering, Arg.; Schering, Braz.; Schering, Chile; Schering, Fr.; Schering, Mex.; Schering, Neth.; Schering, Venez.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; cyproterone acetate (p.2088·2).
28-Day packs contain 16 and 12 tablets, respectively.
Menopausal disorders; osteoporosis.

Climesse *Novartis, UK.*
Estradiol valerate (p.2097·3); norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

Climil-80 *Wassen, Ital.*
Soya (p.1965·3); cimicifuga (p.2282·1).

Climil Complex *Wassen, Ital.*
Soya (p.1965·3); cimicifuga (p.2282·1); griffonia simplicifolia (p.2317·2).

Climil Gel *Wassen, Ital.*
Soya isoflavones (p.2391·2); mimosa tenuiflora.

Climodien *Schering, Austria; Schering, Belg.; Schering, Denm.; Schering, Ger.; Schering, Gr.†; Schering, Neth.; Schering, Norw.; Bayer, Port.; Schering, Rus.; Schering, Spain; Schering, Swed.; Schering, Turk.*
Estradiol valerate (p.2097·3); dienogest (p.2094·1).
Menopausal disorders; osteoporosis.

Climodiene *Schering, Fr.*
Estradiol valerate (p.2097·3); dienogest (p.2094·1).
Menopausal disorders.

Climopax *Wyeth, Ger.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Climopax Cyclo *Wyeth, Ger.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Climopax mono *Wyeth, Ger.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Climycen *Help, Gr.*
Clindamycin (p.251·1).
Vaginal infections.

Clin *Ulagay, Turk.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clinac
Note. This name is used for preparations of different composition.
Pacific, Hong Kong.
Clindamycin (p.251·1).
Acne.

Pacific, NZ†.
Clindamycin phosphate (p.251·2).
Acne.

Edol, Port.
Erythromycin (p.269·2).
Acne.

Clinac BPO *Ferndale, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Clinac OC *Ferndale, Hong Kong; World Pioneer, Hong Kong.*
Acrylate copolymer; macrogol 400 (p.2336·3); carbomer 940 (p.2141·3).
Seborrhoea.

Clinadil *Stada, Spain.*
Cinnarizine (p.573·1); dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders.

Clinadil Compositum *Ciclum, Spain.*
Cinnarizine (p.573·1); codergocrine mesilate (p.363·3); heptaminol acefyllinate (p.1123·2).
Cerebrovascular disorders.

Clinadol *Gador, Arg.*
Flurbiprofen (p.61·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Clinadryl *Bangkok Lab & Cosmetic, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Bronchitis; cold symptoms; hypersensitivity reactions.

Clinagel *Stiefel, Braz.*
Clindamycin phosphate (p.251·2).
Acne.

Clinal
Note. This name is used for preparations of different composition.
Andromaco, Arg.
Sulfanilamide (p.343·1); zinc oxide (p.1621·2); vitamin A.
Formerly contained sulphanilamide, zinc oxide, vitamin A, and vitamin D.
Skin disorders.

Andromaco, Venez.†.
Neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Infected skin disorders.

Clinamsa *Antibioticos, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clinax *Cinetic, Arg.*
Minocycline (p.300·3).
Bacterial infections.

Clinbaxef *Bosch, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Clinbercin *Bernofarm, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clincina *Labesfal, Port.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clincor *Corsalud, Venez.†.*
Tetracycline hydrochloride (p.347·2).
Amoebiasis; bacterial infections.

Clincorp *Valeant, Arg.*
Soap substitute.

Clinda *Winthrop, Ger.; Wolff, Ger.*
Clindamycin hydrochloride (p.251·1) or clindamycin palmitate hydrochloride (p.251·1).
Bacterial infections.

Clindabeta *Betapharm, Ger.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindac
Hexal, Austria; Ranbaxy, Malaysia.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Intramed, S.Afr.
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindac A *Galderma, India.*
Clindamycin phosphate (p.251·2).
Acne.

Clindacin
Panalab, Arg.; Akrikhin, Rus.
Clindamycin phosphate (p.251·2).
Acne; bacterial vaginosis.

Cellofarm, Braz.†.
Clindamycin (p.251·1).
Bacterial infections.

Lannacher, Pol.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindacne
Theraskin, Braz.
Clindamycin (p.251·1).
Acne.

Homeofarm, Pol.
Clindamycin phosphate (p.251·2).
Acne.

Clindacur *Cinetic, Arg.*
Clindamycin phosphate (p.251·2); benzoyl peroxide (p.1590·2).
Acne.

Clindagel
Vocate, Gr.
Clindamycin (p.251·1).
Vaginal infections.

Galderma, Singapore; Galderma, USA.
Clindamycin phosphate (p.251·2).
Acne.

Clindahexal
Hexal, Ger.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Hexal, S.Afr.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindal
Note. This name is used for preparations of different composition.
Merck, Braz.
Azithromycin (p.207·1).
Bacterial infections.

One Pharma, Philipp.
Clindamycin (p.251·1).
Bacterial infections.

Clindalaf *Lafedar, Arg.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Clindalin *Union Drug, Thai.*
Clindamycin phosphate (p.251·2).
Skin infections.

ClindaMax *PharmaDerm, USA.*
Clindamycin phosphate (p.251·2).
Acne.

Clindamin C *Teuto, Braz.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindapack *Darier, Mex.*
Clindamycin phosphate (p.251·2); benzoyl peroxide (p.1590·2).
Acne.

Clindarix *Ariston, Braz.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clinda-saar *MIP, Ger.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Clindastad *Stada, Ger.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindatech *Dermatech, Austral.; Dermatech, Hong Kong; Dermatech, Philipp.; Dermatech, Singapore.*
Clindamycin hydrochloride (p.251·1).
Acne.

Clindaval *Valmor, Venez.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindavid *Millimed, Thai.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindazyn *Lemery, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindesse *KV, USA.*
Clindamycin phosphate (p.251·2).
Bacterial vaginosis.

Clindets *Stiefel, Canad.; Stiefel, USA.*
Clindamycin phosphate (p.251·2).
Acne.

Clindex *Chelsea, USA.*
Clidinium bromide (p.1722·1); chlordiazepoxide hydrochloride (p.968·2).
Gastrointestinal disorders.

Clindexcin *Mugi, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clindo *Hexal, Pol.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Clindopax *Lagos, Arg.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindox *Behrens, Venez.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clindoxyl *Stiefel, Arg.; Sanova, Austria; Stiefel, Braz.; Stiefel, Canad.*
Benzoyl peroxide (p.1590·2); clindamycin phosphate (p.251·2).
Acne.

Clinensol *Allergan, Braz.†.*
Miranol (p.1622·2).
Cleansing solution for contact lenses.

Clinesfar *Essex, Ger.†.*
Erythromycin (p.269·2); tretinoin (p.1618·1).
Acne.

Clinet *Ativus, Braz.*
Red clover (p.2285·1).

Clinfar *Merck, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Clinfol *Nolver, Venez.*
Clindamycin (p.251·1).
Bacterial vaginosis.

Clinic *Jamieson, Hong Kong†.*
Vitamin E (p.1992·2).
Moisturiser.

Clinic A Retinol Vital Day *Jamieson, Canad.†.*
SPF 20: Meradimate (p.1604·2); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Clinical Program Thickened Juice *Nutricia, Austral.†.*
Food thickener (p.1922·1).
Dysphagia.

Clinidac *Pharos, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Cliniderm
Note. This name is used for preparations of different composition.
Wild, Switz.
Cream: Polyethylene granules (abrasive) (p.1585·3); salicylic acid (p.1612·2).
Acne; seborrhoea.

Wild, Switz.
Topical solution: Triclosan (p.1665·2).
Acne; seborrhoea.

Clinigel *Orion, Austral.; Orion, NZ.*
Lubricating gel.

Clinika *Ikapharmindo, Indon.*
Clindamycin (p.251·1) or clindamycin phosphate (p.251·2).
Acne.

Clinikold *Bangkok Lab & Cosmetic, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Clinimet *Bangkok Lab & Cosmetic, Thai.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Clinimix *Clintec, Austria; Baxter, Cz.; Clintec, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Kalbe, Indon.; Baxter, Ital.; Clintec, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.†; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.; Baxter, UK.*
A range of amino-acid and glucose infusions with or without electrolytes (p.1922·1).
Parenteral nutrition.

Clinimycin *Galen, Irl.*
Oxytetracycline (p.312·2).
Bacterial infections.

Clinisorb *CliniMed, UK.*
Activated charcoal (p.1435·2).
Malodorous wounds.

Clinistix *Bayer, Austral.; Bayer, Canad.; Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer, NZ; Bayer, Port.; Bayer Diagnostics, UK; Bayer, USA.*
Test for glucose in urine (p.2314·1).

clinit *Hormosan, Ger.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Clinit N *Hormosan, Ger.†.*
Sodium salamidacetate (p.121·2).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Joint disorders; severe pain.

Clinitar *Cambridge Healthcare, UK.*
Coal tar (Stantar) (p.1616·2).
Dandruff; eczema; psoriasis; seborrhoeic dermatitis.

Clinitek HCG *Bayer, Austral.†.*
Pregnancy test (p.2372·1).

Clinitek Microalbumin *Bayer, Austral.*
Test for albumin and creatinine in urine.

Clinitek Microalbuminuria/Creatinina *Bayer, Arg.*
Test for albumin and creatine in urine.

Clinitest *Bayer, Austral.; Bayer, Canad.; Bayer Diagnostics, Fr.†; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, Mex.; Bayer, NZ; Bayer Diagnostics, UK; Bayer, USA.*
Test for sugar in urine (p.2314·1).
In the *UK* these are described in the Drug Tariff as Copper Solution Reagent Tablets.

Clinium
Note.This name is used for preparations of different composition.
Sanitas, Chile.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.
Ethnor, India; Janssen-Cilag, S.Afr.
Lidoflazine (p.1325·1).
Angina pectoris; ischaemic heart disease; myocardial infarction.
Interbat, Indon.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Clinivate *Bangkok Lab & Cosmetic, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Clinivate-N *Bangkok Lab & Cosmetic, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Clinjos *Meprofarm, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clinmas *Lapi, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Clinoderm *Bangkok Lab & Cosmetic, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clinofar *SmithKline Beecham, Gr.†.*
Sodium chloride (p.1686·1).
Nasal congestion.

Clinofem *Pharmacia, Ger.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menopausal disorders; menstrual disorders; test of ovarian function.

Clinofug D *Wolff, Ger.†.*
Doxycycline hyclate (p.267·1).
Acne.

Clinogel *Viatris, Fr.*
Isopropyl alcohol (p.1650·3); triclosan (p.1665·2).
Hand disinfection.

Clinoleic
Baxter Immuno, Arg.; Clintec, Austria; Baxter, Cz.; Clintec, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Clintec, Israel; Baxter, Ital.; Baxter, Mex.†; Clintec, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.; Baxter, UK.
Olive oil (p.2356·2); soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Clinomel
Baxter Immuno, Arg.; Clintec, Austria; Clintec, Cz.†; Baxter, Fin.†; Baxter, Fr.†; Baxter, Ger.†; Baxter, Gr.; Baxter, Hong Kong†; Baxter, Hung.†; Baxter, Ital.†; Baxter, Mex.†; Baxter, Pol.; Adcock Ingram Critical Care, S.Afr.; Baxter, Spain†; Baxter, Swed.†; Baxter, Thai.; Eczacibasi-Baxter, Turk.
Amino-acid, glucose, electrolyte, and lipid (from soya oil (p.1965·3)) infusion (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Clinomyn *Bergamon, Ital.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Clinopront *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Clinorette *Resource Medical, UK.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone (p.2119·3).
Menopausal disorders.

Clinoril *MSD, Austral.†; MSD, Austria; MSD, Belg.; MSD, Cz.†; MSD, Denm.†; MSD, Hong Kong; MSD, Irl.; Neopharmed, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, NZ; MSD, Norw.; MSD, Swed.; MSD, Switz.†; M & H, Thai.; MSD, UK; Merck, USA; MSD, Venez.†.*
Sulindac (p.126·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Clinott *Macrophar, Thai.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Clinovir
Note.This name is used for preparations of different composition.
Pharmacia, Ger.
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.
Pharos, Indon.; Bangkok Lab & Cosmetic, Thai.
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes; herpesvirus infections.

Clin-Sanorania *Winthrop, Ger.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clintopic *Valeant, Arg.*
Clindamycin hydrochloride (p.251·1).
Acne.

Clinutren *Nestle, Fr.; Nestle Clinical, Irl.; Nestle, Ital.; Nestle, Rus.; Nestle, UK.*
A range of nutritional supplements (p.1922·1).

Clinvit *Plants, Ital.*
Royal jelly (p.2382·1).
Nutritional supplement.

Clinwas *Chiesi, Spain.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Clio-Betnovate *Glaxo Wellcome, Mex.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Clioderm-H *Sons, Mex.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Infected skin disorders.

Cliogan *Juste, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Clionara *Besins, Ger.; Kade, Ger.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Cliovyl *SJA, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Clip Ampoules *Pierre Fabre Sante, Fr.*
Carmellose (p.2142·1).
Wounds.

Clip Blessures *Pierre Fabre Sante, Fr.*
Hydrophilic polyurethane dressing (p.1611·1).
Wounds.

Clip Brulures *Pierre Fabre Sante, Fr.*
Carmellose (p.2142·1).
Burns.

Clip Derm *Pierre Fabre Sante, Fr.*
Polyurethane dressing (p.1611·1).
Wounds.

Clip Hemo *Pierre Fabre Sante, Fr.*
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Wounds.

Clip Strip *Pierre Fabre Sante, Fr.*
Polyurethane foam dressing (p.1611·1).
Wounds.

Clipostat *Hexal, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Clipper *Chiesi, Ital.; Trinity, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Ulcerative colitis.

Clipto *Quimifar, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Cliptol *Pierre Fabre Sante, Fr.*
Ibuprofen (p.64·2); menthol (p.2340·1).
Soft-tissue disorders.

Cliptol Sport
Note.This name is used for preparations of different composition.
Pierre Fabre Sante, Fr.†.
Ointment: Methyl nicotinate (p.85·3); capsaicin (p.32·3).
Massage ointment for muscle strain.
Pierre Fabre Sante, Fr.†.
Topical spray: Butane (p.1688·2); isobutane (p.1690·1); propane (p.1691·3); peppermint (p.1761·2).
Muscle cramps; sports injuries.

Clirbest *Best, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

C-Lisa *Lisapharma, Ital.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Clisflex *Sella, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Clisin *Juste, Spain†.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets estradiol valerate; cyproterone acetate (p.2088·2).
Menopausal disorders; osteoporosis.

Clisma Fleet *Bergamon, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Clisma-Lax *Sofar, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Constipation.

Clison *Alpharma, Mex.*
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Clisteran *Lainco, Spain.*
Sodium lauril sulfoacetate (p.2138·3); sodium citrate (p.1673·3).
Bowel evacuation; constipation.

Clistin
Note.This name is used for preparations of different composition.
Klinger, Braz.†.
Loratadine (p.583·3).
Hypersensitivity reactions.
Ethnor, India.
Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Clitax *Tecnimede, Port.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Clitaxel *Pfizer, Arg.; Nolver, Venez.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Cliten *Biomedica-Chemica, Gr.*
Tetracycline hydrochloride (p.347·2).
Acne.

Clivarin *Abbott, Austria; Abbott, Cz.; Abbott, Denm.†; Abbott, Ger.; Abbott, Gr.; Abbott, Hung.; Abbott, Pol.; Abbott, Port.*
Reviparin sodium (p.1388·2).
Thromboembolic disorders.

Clivarina *Schwarz, Ital.*
Reviparin sodium (p.1388·2).
Thromboembolic disorders.

Clivarine *Knoll, Fr.†; Abbott, Hong Kong; Abbott, India; Abbott, UK†.*
Reviparin sodium (p.1388·2).
Thromboembolic disorders.

Clivasol *Eczane, Arg.†.*
Povidone-iodine (p.1659·2).
Disinfection.

Clivoten *Italfarmaco, Ital.*
Isradipine (p.1319·2).
Hypertension.

Cliz *Integra, Philipp.; Samjin, Philipp.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Clizid *Sandoz, Philipp.*
Gliclazide (p.440·3).
Diabetes mellitus.

Clo *Sigma, Braz.*
Clomipramine hydrochloride (p.386·3).
Depression.

Clo-5 *Danes, Arg.†.*
Sodium cromoglicate (p.1136·3).
Bronchospasm.

Clobasol *Jean-Marie, Hong Kong.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobasone *Pharmaland, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobatos *Bago, Chile†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Clobederm *Jelfa, Pol.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobegalen *Galen, Ger.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobemix *Douglas, Austral.*
Moclobemide (p.411·1).
Depression.

Clobendian *Efarmes, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cloben-G *Indoco, India.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); gentamicin (p.284·2).
Allergic skin disorders; fungal skin infections.

Clobeplus *Defuen, Arg.*
⊗ Clobetasol propionate (p.1522·2); ammonium lactate (p.1589·2).
Skin disorders.

Clobesol LA *Valeant, Arg.*
⊗ Clobetasol propionate (p.1522·2); ammonium lactate (p.1589·2).
Skin disorders.

Clobesol *Valeant, Arg.; Valeant, Braz.; Aristopharma, Hong Kong; GSK, Ital.; Valeant, Mex.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobeson *Dong Kook, Singapore†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobet
Note.This name is used for preparations of different composition.
Angelini, Ital.
⊗ Clobetasone butyrate (p.1522·3).
Eye disorders.
Biolab, Malaysia; Biolab, Thai.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobeta-G *Loyal Advance, Hong Kong.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); clotrimazole (p.530·1); clioquinol (p.254·1).
Infected skin disorders.

Clobetate *Polipharm, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clobex *Galderma, Arg.; Galderma, Canad.; Galderma, Cz.; Galderma, Hong Kong; Galderma, Neth.; Galderma, USA.*
⊗ Clobetasol propionate (p.1522·2).
Skin and scalp disorders.

Clobioxal *Bioresearch, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Clobium *Ferron, Indon.*
Clobazam (p.477·2).
Anxiety.

Clob-X *Galderma, Braz.; Galderma, Chile.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clocan *IQFA, Mex.*
Clotrimazole (p.530·1).
Fungal infections.

Clocef *Teuto, Braz.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Clocip *Cipla, India.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Clocip B *Cipla, India.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2).
Infected skin disorders.

Clocip NB *Cipla, India.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); neomycin (p.305·1).
Infected skin disorders.

Clociver *Maver, Mex.*
Aciclovir (p.862·3).
Viral infections.

Clocktower *Group, S.Afr.*
Zinc oxide (p.1621·2).
Minor cuts and abrasions; skin disorders.

Clocream
Note. A similar name is used for preparations of different composition (see below).
Roberts, USA.
Cod-liver oil (p.1935·2); colecalciferol (p.1986·2); vitamin A palmitate (p.1973·1).
Skin disorders.

Clocreme
Note. A similar name is used for preparations of different composition (see above).
Pacific, Hong Kong; Pacific, NZ.
Clotrimazole (p.530·1).
Erythrasma; fungal skin infections; vulvovaginal candidiasis.

Clodavan *Medipharm, Chile.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clodeosten *Boniscontro & Gazzone, Ital.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Cloder *Nobel, Turk.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Cloderm
Note.This name is used for preparations of different composition.
Dermapharm, Ger.
Clotrimazole (p.530·1).
Fungal skin infections.
Cipla, India; Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.
⊗ Clobetasol propionate (p.1522·2).
Skin and scalp disorders.
Ikapharmindo, Indon.
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.
Coria, USA.
⊗ Clocortolone pivalate (p.1523·1).
Skin disorders.

Cloderm GM *Cipla, India.*
⊗ Clobetasol propionate (p.1522·2); gentamicin (p.284·2); miconazole nitrate (p.541·3).
Skin disorders.

Clodian *Sandoz, Arg.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolic disorders.

Clodoxin *Plusandex, Venez.*
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Clodrel *Baliarda, Arg.†.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolic disorders.

Clodron *1A, Ger.; Hexal, Ger.; Fidia, Ital.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Clodron beta *Betapharm, Ger.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Clody *Promedica, Ital.*
Clodronate disodium (p.1095·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Cloel *Aesculapius, Ital.*
Cloperastine fendizoate (p.1554·3).
Coughs.

Clofamox *Lamsa, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Clo-Far *Farcoral, Mex.*
Diclofenac potassium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Clofaren *Royton, Braz.†.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal and joint disorders.

Clofec *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Clofeme *Hexal, Austral.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Clofen
Note. This name is used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Malaysia.
Baclofen (p.1888·1).
Skeletal muscle spasm; spasticity.

Neckerman, Braz.†.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).

Zeler, Port.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Julphar, UAE.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dollder, Venez.
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Inflammation; pain; peri-articular disorders.

Clofenac *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Singapore; Vivax Optipharm, Venez.*
Diclofenac sodium (p.44·3).
Gout; inflammatory eye disorders; musculoskeletal and joint disorders; pain.

Clofenak *Medley, Braz.*
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Clofend *Fidia, Ital.*
Levocloperastine fendizoate (p.1554·3).
Coughs.

Clofenid *Cifarma, Braz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Clofenix *Aldril, Philipp.*
Diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Clofert *Svizera, India.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Clofexan *Bago, Chile.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Clofil *Filadams, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Cloflow *Otsira, India.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis.

Cloflow Plus *Otsira, India†.*
Clopidogrel bisulfate (p.1250·2); aspirin (p.20·3).

Clofon *YF Chem, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Clofozine *AstraZeneca, India.*
Clofazimine (p.254·2).
Lepra reactions; leprosy.

Clofranil *Sun, Rus.; Sun, Thai.†.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; obsessive-compulsive disorder; phobic states.

Cloftal *Oftalmi, Venez.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Clogar *Self-Care Products, UK.*
Cod-liver oil (p.1935·2); garlic (p.2309·2).

Cloisone *Psicofarma, Mex.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Clo-Kit *Indoco, India.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Clolar *Genzyme, USA.*
Clofarabine (p.701·3).
Acute lymphoblastic leukaemia.

Clomacin *Quimica y Farmacia, Mex.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Clomazen *Uniao Quimica, Braz.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clomazol *Cifarma, Braz.; Multichem, NZ.*
Clotrimazole (p.530·1).
Fungal and bacterial skin infections; vulvovaginal candidiasis.

Clomazole *Idaman, Malaysia.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cloment *Pharmaplan, S.Afr.*
Clozapine (p.981·1).
Schizophrenia.

Clomhexal *Hexal, Austral.; Hexal, Cz.; Hexal, Ger.*
⊗ Clomifene citrate (p.2086·1).
Female infertility; male infertility.

Clomicin *IQFA, Mex.*
Chloramphenicol (p.239·3).
Formerly contained dicloxacillin sodium.
Bacterial infections.

Clomid *Aventis, Austral.; Aventis, Belg.; Medley, Braz.; Aventis, Canad.; Sanofi-Aventis, Fr.; Aventis, Hong Kong†; Sanofi-Aventis, Irl.; Bruno, Ital.; Sanofi-Aventis, Malaysia; Aventis, Neth.; Duncan, Philipp.; Adcock Ingram, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Switz.; Aventis, Thai.; Aventis, UK; Hoechst Marion Roussel, USA.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; diagnosis of hypothalamic-pituitary function; male infertility.

Clomidep *Pharmaplan, S.Afr.*
Clomipramine hydrochloride (p.386·3).
Depression.

Clomifen *Leiras, Fin.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; male infertility.

Clomifeno *Casen Fleet, Spain†.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; male infertility.

Clomifil *Sunthi Sepuri, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Clomihexal *Hexal, S.Afr.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Clomin
Note. This name is used for preparations of different composition.
Medinova (Μεντινοβα), Gr.†.
Cefatrizine (p.221·3).
Bacterial infections.

Quatromed, S.Afr.†.
Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Clominal *Randall, Mex.*
Dicycloverine (p.1723·1).
Nausea and vomiting.

Clomipram *Casasco, Arg.†.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain; panic disorder.

Clomipran *Uniao Quimica, Braz.*
Clomipramine hydrochloride (p.386·3).
Depression; nocturnal enuresis; obsessive-compulsive disorder; pain; panic disorder.

Clomirex *Mipharm, Ital.*
Chlorhexidine (p.1635·2).
Vaginal infections.

Clomycin *Neo-Pharma, India.*
Clotrimazole (p.530·1); gentamicin (p.284·2).
Skin and nail infections.

Clonabay *Bayer, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Clonac *Arrow, Austral.; Faran, Gr.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Clonagin *Baliarda, Arg.*
Clonazepam (p.478·2).
Anxiety; epilepsy; panic attacks.

Clonalgin *Chemopharma, Chile.*
Clonixin lysine (p.37·1).
Pain.

Clonalgin Compuesto *Chemopharma, Chile.*
Clonixin lysine (p.37·1); ergotamine tartrate (p.620·1).
Migraine and other vascular headaches.

Clonamox *PannonPharma, Hung.; Clonmel, Irl.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Clonamp *Clonmel, Irl.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Clonapam *ICN, Canad.†; Laboratorios Chile, Chile; ICN, Hung.*
Clonazepam (p.478·2).
Anxiety; convulsions; epilepsy; panic attacks; sleep disorders.

Clonaren *Metz, Philipp.*
Diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Clonarol *Merck, Austria.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Clonate *Hoe, Philipp.; Marketlink, Philipp.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clonax *Beta, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Clonazen 2 *Bouzen, Arg.*
Clonazepam (p.478·2).
Anxiety; epilepsy.

Clonazine *Clonmel, Irl.*
Chlorpromazine hydrochloride (p.969·2).
Hypothermia induction; premedication; schizophrenia; sedative; vomiting.

Clonazone *Lagepha, Belg.*
Tosylchloramide sodium (p.1665·1).
Disinfection.

Clonea *Alphapharm, Austral.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cloner *Vannier, Arg.*
Clonazepam (p.478·2).
Anxiety disorders; epilepsy.

Clonesina *Teuto, Braz.†.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Clonex
Note. This name is used for preparations of different composition.
Saval, Chile; Teva, Israel.
Clonazepam (p.478·2).
Epilepsy; panic disorder; panic disorders.

Corsa, Indon.
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Clonfolic *Clonmel, Irl.*
Folic acid (p.1940·1).
Prevention of fetal neural tube defects.

Clonid-Ophtal *Winzer, Ger.*
Clonidine hydrochloride (p.1247·1).
Glaucoma; ocular hypertension.

Clonidural *Richmond, Arg.*
Clonidine (p.1247·1).
Hypertension.

Clonipres *Rowe-Fleming, Venez.†.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Clonistada *Stada, Ger.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Clonitia *Tunggal Idaman, Indon.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clonix *Janssen-Cilag, Port.*
Clonixin (p.37·1).
Pain.

Clonixil *Richmond, Arg.*
Clonixin lysine (p.37·1).
Fever; inflammation; pain.

Clonnirit *Rafa, Israel.*
Clonidine hydrochloride (p.1247·1).
Menopausal flushing; migraine and other vascular headaches.

Clonocid *Clonmel, Irl.*
Clarithromycin (p.248·2).
Bacterial infections.

Clonodifen *Tecnofarma, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Clonogal *Biogal-Teva, Hung.†.*
Clonazepam (p.478·2).
Anxiety disorders; epilepsy.

Clonotril *Torrent, Braz.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Clonovate *TO-Chemicals, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clont *Infectopharm, Ger.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Clop *Quim-Far, Venez.†.*
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Clopact *Ipca, India.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis.

Clopact A *Ipca, India.*
Clopidogrel bisulfate (p.1250·2); aspirin (p.20·3).
Atherosclerosis.

Clopamon *Pharmacare, S.Afr.*
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; gastrointestinal radiography; nausea and vomiting.

Clopan
Note. This name is used for preparations of different composition.
Cristalia, Braz.
Clonazepam (p.478·2).
Epilepsy.

FIRMA, Ital.†.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Clopes *Metiska, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Clopin *Ecosol, Switz.*
Clozapine (p.981·1).
Schizophrenia.

Clopina *Rowe-Fleming, Venez.†.*
Aluminium hydroxide (p.1706·2); dicycloverine hydrochloride (p.1722·3); magnesium oxide (p.1744·1).
Antacid.

Clopine *Mayne, Austral.; Douglas, NZ.*
Clozapine (p.981·1).
Schizophrenia.

Clopirim *Quimioterapica, Braz.†.*
Chloroquine phosphate (p.599·3).
Malaria.

Clopivas *Cipla, India.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolic disorders.

Clopivas AP *Cipla, India.*
Clopidogrel bisulfate (p.1250·2); aspirin (p.20·3).
Thromboembolic disorders.

Clopixol
Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Belg.; Lundbeck, Braz.; Lundbeck, Canad.; Lundbeck, Fr.; Lundbeck, Hong Kong; Lundbeck, India; Lundbeck, Irl.; Lundbeck, Ital.; Lundbeck, Malaysia; Lundbeck, Mex.; Lundbeck, NZ; Lundbeck, Pol.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Singapore; Axofarma, Spain; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.; Lundbeck, UK.
Zuclopenthixol acetate (p.1040·3), zuclopenthixol decanoate (p.1040·3), or zuclopenthixol hydrochloride (p.1040·3).
Aggression; agitation; behaviour disorders; bipolar disorder; dementia; mania; mental function impairment; psychomotor hyperexcitability; psychoses.

Lundbeck, Gr.
Zuclopenthixol (p.1040·3) or zuclopenthixol decanoate (p.1040·3).
Psychoses.

Lundbeck, Israel; Euro Registratie, Neth.; Lundbeck, Philipp.
Zuclopenthixol decanoate (p.1040·3), or zuclopenthixol hydrochloride (p.1040·3).
Behavioural disorders; bipolar disorder; dementia; psychoses.

Clopod *Biochem, India.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolic disorders.

Clopod-A *Biochem, India.*
Clopidogrel bisulfate (p.1250·2); aspirin (p.20·3).
Thromboembolic disorders.

Clopra
Ortoquimica, Braz.†.
Metoclopramide (p.1747·3).
Nausea and vomiting.

Quantum, USA†.
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Clopram *Douglas, Austral.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; obsessive-compulsive disorder.

Clopramel *Novell, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Clopreg *Kee, India.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Clopress *Alphapharm, Malaysia†; Merck, Malaysia†; Pacific, NZ.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain; panic disorder.

Clopsine *Psicofarma, Mex.*
Clozapine (p.981·1).
Bipolar disorder; schizophrenia; tremor; withdrawal syndromes.

Cloptison *MSD, Norw.†.*
⊗ Clobetasone butyrate (p.1522·3).
Eye disorders.

Cloptison-N *MSD, Arg.†.*
⊗ Clobetasone butyrate (p.1522·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Clorace *Cofasa, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Cloracef *Ethica, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

CloraCEF *Ranbaxy, S.Afr.†.*
Cefaclor (p.217·2).
Bacterial infections.

Clorad *ACS Dobfar, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Cloradex *Tubilux, Ital.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Infected inflammatory eye disorders.

Clorafen *Merck, Mex.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Clorafenil *Teuto, Braz.*
Chloramphenicol (p.239·3).
Bacterial infections.

Cloraldin *Medinfar, Port.*
Chlorhexidine gluconate (p.1635·3).

Cloram Zinc *Llorens, Spain.*
⊗ Chloramphenicol (p.239·3); naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Formerly known as Cloranfenic Zinc.
Bacterial eye infections.

Cloramed
Note. This name is used for preparations of different composition.
Medimport, Mex.
Chloramphenicol (p.239·3).
Bacterial infections.

Medifive, Thai.
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Cloramfen *Nuovo ISM, Ital.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cloramfeni *Sophia, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cloramfesa *Organifar, Venez.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Cloramidina *Armoxindo, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clorampast *Pasteur, Chile.*
Chloramphenicol (p.239·3).
Vulvovaginal infections.

Clorampler *Arlex, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Cloran *Grin, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cloran Hemidex *Llorens, Spain.*
⊗ Boric acid (p.2268·1); chloramphenicol (p.239·3); dexamethasone phosphate (p.1526·2).
Infected eye disorders.

Cloran Otico *Grin, Mex.*
Chloramphenicol (p.239·3); benzocaine (p.1854·1).
Bacterial ear infections.

Clorana *Sanofi-Aventis, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema; renal calculi.

Cloranfenic *Laus, Spain†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cloranfenil *Sanval, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Cloranmicron *Alcon, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cloranpectina *Basi, Port.†.*
Chloramphenicol (p.239·3); phthalylsulfathiazole (p.315·1); pectin (p.2145·2).
Gastrointestinal infections.

Cloranxen *Polfa Kutno, Pol.*
Dipotassium clorazepate (p.980·1).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Cloraseptic *Legrand, Braz.*
Phenol (p.1656·1); sodium phenolate; borax (p.2268·1); thymol (p.1664·3); menthol (p.2340·1).
Mouth and throat disorders.

Clorasona *Oftalmi, Venez.*
⊗ Chloramphenicol (p.239·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Cloratadd D *EMS, Braz.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Cloraxene *TO-Chemicals, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Clorazer *ACS Dobfar, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Clorazin *Tecnofarma, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clorcin-Ped *Stiefel, Braz.*
Cefaclor (p.217·2).
Bacterial infections.

Clorcorticil *Edol, Port.†.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Bacterial eye infections with inflammation.

Clordil *Diba, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clordilon *Vitapan, Braz.†.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Clordox *Teuto, Braz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Cloretilo Chemirosa *Ern, Spain.*
Ethyl chloride (p.1861·2).
Local anaesthesia.

Clorexan *IMS, Ital.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Wound disinfection.

Clorexan Ferri *IMS, Ital.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Instrument disinfection.

Clorfenil *Rayere, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clorfibrase *Elea, Arg.*
Chloramphenicol (p.239·3); fibrinolysin (p.1287·3); dornase alfa (p.1557·1).
Wounds.

Clorfriol *Rayere, Mex.†.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); ascorbic acid (p.1983·3); moroxydine hydrochloride (p.898·2).
Cold and influenza symptoms.

Clorhexitulle *Aventis, Austral.†.*
Chlorhexidine acetate (p.1635·2).
Burns; infected skin disorders; skin ulcers; wounds.

Cloriflox *TS, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Cloril *Atlantic, Thai.*
Clozapine (p.981·1).
Schizophrenia.

Clorimet-Z *Zafiro, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Clorina *Lysoform, Ger.; BMS, Spain.*
Tosylchloramide sodium (p.1665·1).
Linen disinfection; skin and wound disinfection; surface disinfection.

Clorix *Pharma Dynamics, S.Afr.*
Moclobemide (p.411·1).
Depression; social phobia.

Clorizin *Cifarma, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Cirrhosis with ascites; heart failure; hypertension; oedema.

Clor-K-Zaf *Zafiro, Mex.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Clorocil *Edol, Port.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Clorofunon *Parggon, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clorom *Rowex, Irl.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Clorosan *Lachifarma, Ital.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin, wounds, and burns.

Clorotan *Reuffer, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Clorotir *Biochemie, NZ; Novartis, NZ; Sandoz, Philipp.; Sandoz, Thai.*
Cefaclor (p.217·2).
Bacterial infections.

Cloro-Trimeton *Schering-Plough, Mex.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity.

Clorotrimeton *Schering-Plough, Venez.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Clorpactin WCS-90 *Guardian, USA.*
Oxychlorosene sodium (p.1655·1).
Disinfection; skin infections.

Clorpamina *Andromaco, Mex.†.*
Dopamine hydrochloride (p.1273·2).
Heart failure; shock.

Clorpax *Sandoz, Austral.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Clorpres *Bertek, USA.*
⊗ Clonidine hydrochloride (p.1247·1); chlortalidone (p.1243·3).
Hypertension.

Clorprimeton *Essex, Chile.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Clorpromaz *Uniao Quimica, Braz.*
Chlorpromazine hydrochloride (p.969·2).
Psychoses.

Clorpromini *Biofarma, Braz.†.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Clortalil *Legrand, Braz.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema; renal calculi.

Clortanol *CT, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Clortil *Teuto, Braz.*
⊗ Chlortalidone (p.1243·3).
Hypertension.

Clortilen *Sankyo, Venez.*
Clotrimazole (p.530·1).
Fungal infections.

Clorton *Pharlab, Braz.†.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Clorxil *Pan Quimica, Spain†.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin and wounds.

Cloryvil *Giempi, Venez.*
Aciclovir (p.862·3).
Herpesvirus infections.

Clorzin *Neckerman, Braz.†.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Closanasol *Jelfa, Hung.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Closcript *Ranbaxy, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Closderm *Yung Shin, Philipp.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Closin *Holsten, Ger.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; psychoses; sleep disorders.

Closina *Aspen, Austral.*
Cycloserine (p.260·2).
Tuberculosis; urinary-tract infections.

Closol *Fahrenheit, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Clostedal *Silanes, Mex.*
Carbamazepine (p.471·3).
Alcohol and benzodiazepine withdrawal syndromes; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias; polydipsia; polyuria.

Clostet *Chiron Vaccines, UK†.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Clostil *Egis, Philipp.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Clostilbegyt *Egis, Cz.; Egis, Hong Kong; EGIS, Hung.; Egis, Malaysia; Egis, Pol.; Egis, Rus.; Egis, Singapore.*
⊗ Clomifene citrate (p.2086·1).
Galactorrhoea; male and female infertility.

Clotam *Gea, Denm.†; Sandoz, Fin.; Faran, Gr.; Hexal, Neth.; Ecosol, Switz.†; koGen, UK.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Clotan *Grunenthal, Venez.†.*
Tolfenamic acid (p.130·1).
Dysmenorrhoea.

Clotassio *Bunker, Braz.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Clotest *Bripharm, Irl.*
Test for *Helicobacter pylori* from biopsy specimens.

Clotidone *Apotex, Philipp.; Pharma 3, Philipp.*
Ticlopidine hydrochloride (p.1411·2).
Prevention of platelet loss during extracorporeal stenting; thromboembolic disorders.

Clotigen
Note. This name is used for preparations of different composition.
Vitapan, Braz.
Clotrimazole (p.530·1).
Fungal skin infections.

Dynamic, Philipp.
Menadione sodium bisulfite (p.1995·3).
Haemorrhage.

Cloton *TNP, Thai.†.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Coughs; nasal congestion; rhinitis.

Clotramid *Molteni, Ital.†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Mouth disinfection.

Clotrason *Schering-Plough, Denm.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Clotrasone *Essex, Philipp.; Schering-Plough, Singapore†; Desarrollo, Spain; Schering-Plough, Thai.†.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Clotreme *Hexal, Austral.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotren *Teuto, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Clotri *Polipharm, Thai.†.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Clotricin *Seng, Thai.*
Clotrimazole (p.530·1).
Fungal vaginal infections; trichomoniasis.

Clotricina *Diba, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Clotri-Denk *Denk, Hong Kong.*
Clotrimazole (p.530·1).
Fungal and bacterial vaginal infections; fungal skin infections; trichomoniasis.

Clotriderm *Greenpharma, Braz.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotrigalen *Galen, Ger.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotrihexal *Hexal, NZ.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Clotrimaderm *Taro, Canad.; Taro, Israel; AFT, NZ.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal candidiasis.

Clotrimin *Medipharm, Chile.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Clotrimin-B *Medipharm, Chile.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections with inflammation.

Clotrimix *Eversil, Braz.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotrinolon *Jean-Marie, Hong Kong.*
⊗ Clotrimazole (p.530·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections with inflammation.

Clotri-Q *Q-Pharma, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotrisone *Taro, Israel.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Clotrix *Lamsa, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Clotrizan *Prodotti, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Clotrizol
Note. This name is used for preparations of different composition.
Celloform, Braz.†.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Calox, Venez.
Clotrimazole (p.530·1).
Fungal infections.

Cloval *Saval, Chile.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Cloval Compuesto *Saval, Chile.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1).
Coughs.

Clovate *UCB, Spain.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Cloverin *Proula, Venez.†.*
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3); hyoscyamus (p.2323·3); star anise (p.2392·1).

Clovertil *Meprofarm, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Clovex *Arlex, Mex.*
Aciclovir (p.862·3).
Viral infections.

Clovicol *General Drugs House, Philipp.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Clovillin *General Drugs House, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Clovimax *Vamsler, Philipp.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Clovin *Nakornpatana, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Clovir *Cazi, Braz.*
Aciclovir (p.862·3).

Clovira *M & H, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Clovirax *Cooper (Κοπερ), Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Clovirex *Flupal, Venez.†.*
Aciclovir (p.862·3).

Clovixime *General Drugs House, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Cloviz *General Drugs House, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Clox *Caber, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Cloxa *Hua, Thai.; M & H, Thai.; TO-Chemicals, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxacap *Hovid, Singapore†.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Cloxalin *Siam Bheasach, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxam
Note. This name is used for preparations of different composition.
Jaba, Port.
Cloxazolam (p.981·1).
Anxiety disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pharmacare, S.Afr.
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Macrophar, Thai.
Cloxacillin (p.256·1).
Bacterial infections.

Cloxan
Note.This name is used for preparations of different composition.
Orion, Fin.†.
Chlorprothixene hydrochloride (p.977·2).
Psychoses.

Biomep, Mex.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Cloxanbin *ANB, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxapan *TNP, Thai.†.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxapen *Pasteur, Chile†.*
Cloxacillin (p.256·1).
Bacterial infections.

Cloxasian *Asian Pharm, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxgen *General Drugs, Thai.*
Cloxacillin (p.256·1) or cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxib *Klonal, Arg.†.*
Celecoxib (p.34·2).

Cloxigen *Dynamic, Philipp.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxil *Duopharma, Hong Kong†; Ranbaxy, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloxillin
Note.This name is used for preparations of different composition.
Ibirn, Ital.
Flucloxacillin sodium (p.277·1).
Bacterial infections.

British Dispensary, Thai.†.
Cloxacillin sodium (p.256·1).
Bacterial infections.

Cloximar Duo *Dupomar, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Cloxin
DHA, Hong Kong.
Cloxacillin (p.256·1).
Staphylococcal infections.

Pharmacare, S.Afr.
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Cloxina *Lewison, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Cloxona-O *Sons, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Cloxy *Jean-Marie, Philipp.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cloxydin *Biomedis, Thai.; Great Eastern, Thai.*
Dicloxacillin (p.265·2).
Bacterial infections.

Clozal *Sankyo, Braz.*
Cloxazolam (p.981·1).
Anxiety.

Clozan *Pfizer, Belg.*
Clotiazepam (p.980·3).
Anxiety disorders.

Clozanil *Sanitas, Chile.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Clozaril *Novartis, Austral.; Novartis, Canad.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Malaysia; Novartis, NZ; Novartis, Singapore; Novartis, Thai.; Novartis, UK; Novartis, USA.*
Clozapine (p.981·1).
Psychoses associated with parkinsonism; schizophrenia.

Clozol *Cipla, India; Ilsan, Turk.*
Clotrimazole (p.530·1).
Fungal skin infection; fungal skin infections.

Clozole *Jean-Marie, Hong Kong.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Clusivol
Wyeth Consumer, Braz.; Wyeth, Philipp.; Wyeth, Venez.
Multivitamin and mineral preparation (p.1922·1).

Akromed, S.Afr.
Chewable tablets: Multivitamin preparation (p.1922·1).

Akromed, S.Afr.
Syrup; tablets: Multivitamin and mineral preparation (p.1922·1).

Clusivol Composto *Wyeth Consumer, Braz.*
Vitamin, amino-acid, and mineral preparation (p.1922·1).

Clusivol Pediatric *Wyeth, Philipp.*
Vitamin preparation (p.1922·1).

Cluvax *Gynopharm, Chile.*
Clindamycin phosphate (p.251·2).
Bacterial vaginosis.

Cluvimin *Scherer, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Cluyer *Fada, Arg.*
⊗ Pethidine (p.115·1).
Pain.

Clys-Go *Megat, Venez.†.*
Docusate sodium (p.1725·1); sorbitol (p.1965·1).
Bowel evacuation.

Clysmol *Pharmacia, Austria.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Clyss-Go *Novag, Mex.; Prospa, Port.*
Docusate sodium (p.1725·1); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Clyvorax *Unipharm, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

CMD *TNP, Thai.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; hypersensitivity reactions; peptic ulcer; Zollinger-Ellison syndrome.

C-Mox *Columbia, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

CMP *Klonal, Arg.†.*
Carbamazepine (p.471·3).
Epilepsy.

CMV Immunoglobulin *CSL, Austral.*
A cytomegalovirus immunoglobulin (human) (p.2208·3).
Passive immunisation.

CMW *DePuy, Ger.*
Polymethylmethacrylate (p.2343·3).
Bone cement for orthopaedic surgery.

CMW Gentamicin *Johnson & Johnson, NZ.*
Polymethylmethacrylate (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

CMW mit Gentamicin *DePuy, Ger.*
Polymethylmethacrylate (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

C-Mycin *Hoe, Malaysia†; Hoe, Singapore†.*
Clindamycin phosphate (p.251·2).
Acne.

CN-25 *Masa, Thai.†.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; peripheral vascular disorders.

C'Nergil *Medinfar, Port.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

CNN *Ipca, India†.*
Minocycline (p.300·3).
Acne.

Co Amoxin *Coll, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Co Bucal *Biomed, Spain.*
Alum (p.2254·1); procaine hydrochloride (p.1869·1); salicylic acid (p.1612·2); sodium chlorate (p.2389·1); thymol (p.1664·3); cherry laurel water; peppermint oil.
Gingivitis; pyorrhoea; stomatitis.

Co Fluocin Fuerte *Smaller, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

CO_2 Granulat *Guerbet, Austria; Guerbet, Cz.†; Guerbet, Ger.†.*
Betaine hydrochloride (p.2265·2); sodium bicarbonate (p.1673·2); dimeticone (p.1770·2); colloidal silicon dioxide (p.2146·3).
Adjunct in double contrast radiography.

Co-Acepril *Spirig, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Acetan *Kwizda, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

CoActifed
Note.This name is used for preparations of different composition.
GSK, Canad.
Expectorant: Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

GSK, Canad.
Syrup; tablets: Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Coalgan *Brothier, Fr.*
Calcium alginate (p.1058·1).
Haemorrhage.

Co-Amilorid *Cophar, Switz.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Co-Amiloride *Teva, Belg.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Coamox *Community Pharmacy, Thai.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Co-Amoxi
Ratiopharm, Belg.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Ratiopharm, Hung.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Mepha, Switz.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Co-Amoxicilline *Sandoz, Switz.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Co-Amoxilan *Eurogenerics, Belg.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Co-Amoxyclav *Sandoz, S.Afr.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Co-Angiosan *Novartis, Austria.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Apap *Rugby, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Coaparin *Polfa Warszawa, Pol.*
Heparin sodium (p.1301·2).
Thromboembolism prophylaxis.

CoAprovel *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi, Denm.; BMS, Fr.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; BMS, Neth.; Sanofi Synthelabo, Neth.; Sanofi BMS, Norw.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Port.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; BMS, Swed.; Sanofi Synthelabo, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi Synthelabo, Thai.; BMS, UK; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Arinate *Dafra, Belg.*
3 Tablets, artesunate (p.598·2); 3 tablets, sulfametopyrazine (p.342·2); pyrimethamine (p.610·2).
Malaria.

Coarol *Andromaco, Chile.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Coartem *Novartis, S.Afr.; Novartis, Thai.*
Artemether (p.598·1); lumefantrine (p.605·1).
Malaria.

Co-Artesiane *Dafra, Belg.*
Artemether (p.598·1); lumefantrine (p.605·1).
Malaria.

Co-Atenolol *Cophar, Switz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Coaxil
Servier, Cz.; Servier, Hung.; Servier, Pol.
Tianeptine sodium (p.423·3).
Alcohol withdrawal syndrome; depression.

Servier, Rus.
Tianeptine (p.424·1).
Depression.

Cobactin *Zambon, Braz.*
Cyproheptadine hydrochloride (p.575·1); cobamamide (p.1980·2).
Reduced appetite; tonic.

Cobadex *Maver, Mex.*
Ambroxol hydrochloride (p.1550·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; respiratory-tract congestion.

Cobadex Forte *GSK, India.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Cobaforte *EG, Ital.*
Cobamamide (p.1980·2).
Vitamin B deficiency.

Cobaglobal *Legrand, Braz.*
Cobamamide (p.1980·2); cyproheptadine hydrochloride (p.575·1).
Tonic.

Cobalatec *Caps, S.Afr.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Cobaldoze *Kinder, Braz.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Cobalfer *Biotech, Venez.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2); copper sulfate (p.1935·3).
Anaemias.

Cobalin-H *Link, UK.*
Hydroxocobalamin (p.1980·3).
Anaemia due to B deficiency; Leber's atrophy; tobacco amblyopia.

Cobalti *Rega, Port.†.*
Ferric ammonium citrate (p.1938·1).
Anaemias; tonic.

Cobamet *Roussel, Port.†.*
Mecobalamin (p.1981·1).
Anaemias.

Cobamin *Santen, Hong Kong.*
Cyanocobalamin (p.1980·2).
Eye disorders.

Cobamol *Maver, Mex.*
⊗ Salbutamol (p.1131·2).

Cobantril *Interdelta, Switz.*
Pyrantel embonate (p.155·1).
Nematode infections.

Cobanzyme *Aclae, Fr.*
Cobamamide (p.1980·2).
Megaloblastic anaemia.

Cobavit *Cifarma, Braz.*
Cyproheptadine hydrochloride (p.575·1); cobamamide (p.1980·2).
Reduced appetite.

Cobavital *Solvay, Braz.*
Cobamamide (p.1980·2); cyproheptadine hydrochloride (p.575·1).
Reduced appetite; tonic.

Cobaxid *Tecnifar, Port.*
Cobamamide (p.1980·2).
Anaemias; neuralgias; neuritis; tonic.

Cobay *Millimed, Thai.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cobazim *Interbat, Indon.*
Cobamamide (p.1980·2).
Anorexia; malnutrition; pernicious anaemia.

Co-Becetamol *Gebro, Switz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Cobederm-H *Sarabhai Piramal, India.*
⊗ Halcinonide (p.1535·1); econazole nitrate (p.531·1).
Infected skin disorders.

Cobefen *Sanitas, Chile.*
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

Cobenexol Forte *Bayer Consumer, Arg.*
Cocarboxylase (p.1975·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuritis; radiotherapy-induced vomiting; vitamin B deficiency; vomiting of pregnancy.

Cobenexol Fuerte *Bayer Consumer, Arg.*
Vitamin B (p.1975·2); vitamin B (p.1978·2); vitamin B (p.1980·2).
Neuralgias; neuritis; vitamin B deficiency.

Cobenzil Compuesto *Abbott, Arg.†.*
⊗ Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2); ephedrine hydrochloride (p.1558·2); ipecacuanha (p.1562·3); ammonium chloride (p.1551·3); tolu balsam (p.1574·2).
Coughs.

Co-Betaloc *Pharmacia, Irl.; Pfizer, UK†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

cobidec n *Pfizer Consumer, Ger.†.*
Multivitamin and mineral preparation (p.1922·1).

Cobiona *Esteve, Spain.*
Oxatomide (p.587·1).
Hypersensitivity reactions.

Cobirolyte *Allen, Mex.†.*
Oral rehydration therapy (p.1672·2).

Co-Bisoprolol *Eurogenerics, Belg.; Ratiopharm, Belg.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cobix *Cipla, India.*
Celecoxib (p.34·2).

Cobotiaxina *Ifusa, Mex.*
Cyanocobalamin (p.1980·2); pyridoxine (p.1979·1); thiamine (p.1976·3).
Anaemias; neuritis.

Co-Captopril *Genericon, Austria.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Captotyrol *Tyrol, Austria†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Captral *Silanes, Mex.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Carnetina B12 *Sigma-Tau, Ital.*
Cobamamide (p.1980·2); levocarnitine (p.1932·2).
Tonic.

Coccila
Note. This name is used for preparations of different composition.
TNP, Thai.†
Syrup: Furazolidone (p.834·3); neomycin (p.305·1); kaolin (p.1738·1).
Gastrointestinal infections.
TNP, Thai.†
Tablets: Diiodohydroxyquinoline (p.832·1); neomycin sulfate (p.305·1); phthalylsulfathiazole (p.315·1); light kaolin (p.1738·1); furazolidone (p.834·3).
Gastrointestinal infections.

Cocculine *Boiron, Canad.; Boiron, Cz.; Boiron, Fr.; Boiron, Port.*
Homoeopathic preparation.

Cocculus Complexe no 73 *Lehning, Fr.*
Homoeopathic preparation.

Cocculus Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Cocculus-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

Cochic *Masa, Thai.*
Colchicine (p.556·1).
Gout.

Coci-Fedra *Marching, Hong Kong.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); squill (p.1573·1); senega (p.1572·3); cocillana (p.1554·3).
Cold symptoms; cough; hay fever; nasal congestion.

Coci-Fedra-C *Marching, Hong Kong.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); squill (p.1573·1); senega (p.1572·3); cocillana (p.1554·3).
Coughs; hypersensitivity reactions; nasal congestion.

Cocillana *Orion, Fin.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Cocillana Christo *Christo, Hong Kong.*
Cocillana (p.1554·3); euphorbia (p.2301·3); senega (p.1572·3); squill (p.1573·1); menthol (p.2340·1).
Coughs.

Cocillana Co *Adcock Ingram, S.Afr.*
Cocillana (p.1554·3); squill (p.1573·1); menthol (p.2340·1).
Coughs.

Cocillana Compound
Note. This name is used for preparations of different composition.
Synco, Hong Kong.
Cocillana (p.1554·3); euphorbia (p.2301·3); senega (p.1572·3); squill (p.1573·1); menthol (p.2340·1).
Formerly contained cocillana, euphorbia, senega, squill, antimony potassium tartrate, and menthol.
Coughs; respiratory-tract congestion.
Universal, Hong Kong.
Cocillana (p.1554·3); euphorbia (p.2301·3); squill (p.1573·1); senega (p.1572·3); codeine phosphate (p.37·2).
Coughs.
Vida, Hong Kong.
Cocillana (p.1554·3); euphorbia (p.2301·3); squill (p.1573·1).
Cold symptoms; coughs.

Cocillana-Etyfin *Ellem, Swed.*
Ethylmorphine hydrochloride (p.52·2); senega (p.1572·3); cocillana (p.1554·3).
Coughs.

Co-Cof *Millimed, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Cocois *Bioglan, Hong Kong†; UCB, Irl.; Bioglan, Malaysia†; AFT, NZ†; Central Clinical, Pol.; UCB, UK.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); precipitated sulfur (p.1614·1).
Scalp disorders.

Coco-Scalp *AFT, NZ.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Scaly scalp disorders.

Cocydal *Xixia, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cocyntal *Boiron, Canad.*
Homoeopathic preparation.

Co-Cyproterone *Sandoz, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Cod Efferalgan *BMS, Spain.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

COD N 70 *Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Codabrol *Rekah, Israel.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Cod-Acamol Forte *Teva, Israel.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Codaewon *Daewon, Hong Kong.*
⊗ Dihydrocodeine tartrate (p.48·1); guaifenesin (p.1561·3); methylephedrine hydrochloride (p.1564·3); chlorphenamine maleate (p.571·3).
Cough.

Co-Dafalgan *BMS, Spain; Upsamedica, Switz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Codafen Continus *Napp, Irl.†; Napp, UK†.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Codalax *Napp, Irl.; Douglas, NZ†; Napp, UK.*
Dantron (p.1722·2); poloxamer 188 (p.1918·1).
These ingredients can be described by the British Approved Name Co-danthramer.
Constipation.

Codal-DH *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Allergic rhinitis; coughs and cold symptoms.

Codal-DM *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Allergic rhinitis; coughs and cold symptoms.

Codalgin *Fawns & McAllan, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Codalgin Plus *Sigma, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Fever; pain.

Co-Dalzad *Novartis, Gr.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Codant *Antigen, Irl.*
Codeine phosphate (p.37·2).
Pain.

Codapane *Alphapharm, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Codaphed *Julphar, UAE.*
⊗ Ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs.

Codaphed Plus *Julphar, UAE.*
⊗ Ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Codaten *Novartis, Braz.*
Diclofenac (p.44·2); codeine phosphate (p.37·2).
Inflammation; pain.

Codebromil *Vincenti, Venez.*
Codeine (p.37·2); thyme (p.2401·1); drosera (p.2297·3); Desessartz syrup.
Cough.

Codebup *Richmond, Arg.*
Bicalutamide (p.686·2).

Codedrill *Pierre Fabre Sante, Fr.*
Codeine phosphate (p.37·2).
Formerly known as Pectoral Edulcor.
Coughs.

Codef *Be-Tabs, S.Afr.*
⊗ Codeine phosphate (p.37·2); mepyramine maleate (p.585·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Codehist DH *Geneva, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Codein-Acisal *ICN, Hung.†.*
Codeine phosphate (p.37·2); aspirin (p.20·3).
Cold symptoms; coughs.

Codeine Contin *Purdue, Canad.*
Codeine (p.37·2); codeine sulfate (p.37·3).
Pain.

Codeipar *Andromaco, Chile.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Codeisan *Belmac, Spain.*
Codeine phosphate (p.37·2).
Cough.

Codelac *Farmstandart, Rus.*
Codeine (p.37·2); sodium bicarbonate (p.1673·2); liquorice (p.1740·3); thermopsia lanceolata.
Cough.

Codelac Phyto *Farmstandart, Rus.*
Codeine phosphate (p.37·2); thyme (p.2401·1); liquorice (p.1740·3); thermopsia.
Coughs.

Codelasa
Note. This name is used for preparations of different composition.
Andromaco, Arg.
Codeine (p.37·2); guaifenesin (p.1561·3).
Coughs.
Andromaco, Chile.
Codeine (p.37·2); ethylmorphine (p.52·2); homatropine methylbromide (p.1881·3).
Coughs.
Zuoz, Venez.
Codeine (p.37·2); chlorphenamine maleate (p.571·3).

Codelsol *Ulagay, Turk.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Inflammatory eye and ear disorders.

Codelton *Ulagay, Turk.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Codelum *Sanova, Austria.*
Thyme (p.2401·1); codeine phosphate (p.37·2).
Coughs.

Codenfan *Bouchara-Recordati, Fr.*
Codeine phosphate (p.37·2).
Pain.

Codepect *Neopharm, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cold symptoms; coughs; nasal congestion.

Coderetta N *Valeant, Hung.*
⊗ Codeine hydrochloride (p.37·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Codergine *Shiwa, Thai.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; peripheral vascular disorders.

Coderit *Chinoin, Mex.*
⊗ Codeine hydrochloride (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Coderit N *Valeant, Hung.*
⊗ Codeine hydrochloride (p.37·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Coderol *Almirall, Spain.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Codesan Comp *Leiras, Fin.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); diphenhydramine hydrochloride (p.577·2); cocillana (p.1554·3).
Coughs.

Codesan N *Leiras, Fin.†.*
Noscapine (p.1566·2); cocillana (p.1554·3).
Coughs.

Codesia *Asian Pharm, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Codesic *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Codetabs *Leiras, Fin.*
Cocillana (p.1554·3).
Coughs.

Codethyline *Erfa, Belg.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Codetol *Laboratorios Chile, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

Codetol PM *Laboratorios Chile, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); avocado leaf (p.2262·2); eucalyptus leaf (p.2301·2).
Coughs; nasal congestion.

Codetricine *Madaus, Fr.†.*
Tyrothricin (p.358·2).
Mouth and throat disorders.

Codetricine vitamine C *Madaus, Fr.†.*
Tyrothricin (p.358·2); tetracaine hydrochloride (p.1871·3); ascorbic acid (p.1983·3).
Mouth and throat disorders.

Codeverin *Luper, Braz.†.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3).
Muscle spasm; pain.

Codex
Note. This name is used for preparations of different composition.
Uniao Quimica, Braz.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.
Zambon, Ital.
Saccharomyces boulardii (p.2372·3).
Gastrointestinal disorders.

Codexial *Spirig, Fr.*
A range of emollients.

Codexial Zinc *Spirig, Fr.*
White soft paraffin (p.2031·2); zinc oxide (p.1621·2).
Skin disorders.

Codexine-R *Coup, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Cod-Guaiacol *Vitamed, Israel.*
Sulfogaiacol (p.1573·2); codeine phosphate (p.37·2).
Coughs.

codi OPT *Optimed, Ger.*
Codeine phosphate (p.37·2).
Pain.

Codiasp *Codilab, Port.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain; thrombosis prophylaxis.

Codical *Sam-On, Israel.*
Codeine phosphate (p.37·2).
Coughs.

Codicaps *Thiemann, Ger.†.*
Codeine (p.37·2); chlorphenamine maleate (p.571·3).
Catarrh; coughs.

Codicaps mono *UCB, Ger.*
Codeine (p.37·2).
Coughs.

Codicaps N *Thiemann, Ger.†.*
Codeine (p.37·2).
Coughs.

Codicaps Neo *UCB, Ger.*
Codeine (p.37·2).
Coughs.

Codicet *Hua, Thai.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Codiclear DH *Victory, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Codicompren *Desma, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Codicontin *Mundipharma, Belg.; Mundipharma, Switz.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Codidol *Mundipharma, Austria.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Codifos *Cipla, India.*
Codeine phosphate (p.37·2).

Codigesic *Bangkok Lab & Cosmetic, Thai.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Co-Dilatrend *Roche, Austria.*
⊗ Carvedilol (p.1241·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Codilergi *Codilab, Port.*
Diphenhydramine (p.577·1).
Skin irritation.

Codimal DH *Victory, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); dexchlorpheniramine maleate (p.572·1).
Formerly contained hydrocodone tartrate, phenylephrine hydrochloride, and mepyramine maleate.
Coughs and cold symptoms.

Codimal DM *Victory, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Coughs.

Codimal PH *Victory, USA.*
Codeine phosphate (p.37·2); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Coughs and cold symptoms.

Codimin *Biomedica-Chemica, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Codinex *Pinewood, Irl.*
Codeine phosphate (p.37·2).
Coughs.

Co-Diovan *Novartis, Austria; Novartis, Cz.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Diovane *Novartis, Belg.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Codipar
Note. This name is used for preparations of different composition.
GSK, Pol.
Paracetamol (p.108·1).
Fever; pain.
Goldshield, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

Codipar Plus *GSK, Pol.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Codipertussin
Fujisawa, Austria.
Codeine polistirex (p.38·3).
Bronchitis; coughs.
Tussin, Ger.
Codeine phosphate (p.37·2).
Coughs.

Codiphen *Pfizer Consumer, Austral.*
Codeine phosphate (p.37·2); aspirin (p.20·3).
Fever; pain.

Codipront
Pfizer, Austria; Mack, Cz.†; Slovakofarma, Cz.†; CTS, Hong Kong; Bracco, Ital.†; Ferraz, Lynce, Port.; Pfizer, Switz.; Mack, Thai.†.
Codeine polistirex (p.38·3); phenyltoloxamine polistirex (p.588·1).
Coughs.
Grunenthal, Chile†; Kimia, Indon.; Mack, Singapore†; Pfizer, Spain†; Zuoz, Venez.
Codeine resin (p.37·2); phenyltoloxamine resin (p.588·1).
Cough.
Mack, Illert., Ger.†.
Codeine phosphate (p.37·2) or codeine polistirex (p.38·3); phenyltoloxamine citrate (p.588·1) or phenyltoloxamine polistirex (p.588·1).
Coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Codipront cum Expectorans
Note.This name is used for preparations of different composition.
Pfizer, Switz.†.
Capsules: Codeine resinate (p.38·3); phenyltoloxamine resinate (p.588·1); guaifenesin (p.1561·3).
Coughs.

Pfizer, Switz.†.
Syrup: Codeine resinate (p.38·3); phenyltoloxamine resinate (p.588·1); guaifenesin (p.1561·3); thyme (p.2401·1).
Coughs.

Codipront cum Expectorant
Note.This name is used for preparations of different composition.
Kimia, Indon.
Capsule: Codeine (p.37·2); phenyltoloxamine (p.588·1); guaifenesin (p.1561·3).
Cough.

Kimia, Indon.
Syrup: Codeine (p.37·2); phenyltoloxamine (p.588·1); guaifenesin (p.1561·3); thyme (p.2401·1).
Cough.

Codipront Mono *Pfizer, Austria; Mack, Illert., Ger.†; Zuoz, Venez.*
Codeine polistirex (p.38·3).
Coughs.

Codipront N
Galenica, Gr.†.
Codeine polistirex (p.38·3); codeine phosphate (p.37·2).
Cough.

Mack, Hong Kong†.
Codeine polistirex (p.38·3).
Coughs.

Codis *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, UK.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Codisal Forte *Rafa, Israel.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Cold symptoms; coughs; fever; pain.

Coditam *Kimia, Indon.*
Codeine (p.37·2); paracetamol (p.108·1).
Pain.

Coditard *Fujisawa, Austria.*
Codeine polistirex (p.38·3).
Coughs.

Codivis *CTI, Israel.*
Codeine (p.37·2); phenyltoloxamine (p.588·1).
Coughs.

Codoformo *Silva, Venez.†.*
Codeine (p.37·2); belladonna (p.2263·3); terpin (p.1573·3); guaifenesin (p.1561·3).
Cough.

Codol
Note.This name is used for preparations of different composition.
Confar, Port.
Codeine (p.37·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Formerly contained codeine and vegetable extract (.
Cough.

Mundipharma, Switz.†.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Codolax
Note.This name is used for preparations of different composition.
Vickmans, Hong Kong.
Syrup: Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); papaverine hydrochloride (p.2191·3); guaifenesin (p.1561·3).
Coughs.

Vickmans, Hong Kong.
Tablets: Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); papaverine hydrochloride (p.2191·3).
Coughs.

Codoliprane *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Codomex Orange *Medipharma, Hong Kong†.*
Codeine phosphate (p.37·2); papaverine hydrochloride (p.2191·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Codomex Purple *Medipharma, Hong Kong†.*
Codeine phosphate (p.37·2); papaverine hydrochloride (p.2191·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Cold and influenza symptoms.

Codomill *Brunel, S.Afr.†.*
Mepyramine maleate (p.585·2); codeine phosphate (p.37·2).
Coughs.

Codoplex
Note.This name is used for preparations of different composition.
Jean-Marie, Hong Kong.
Syrup: Codeine phosphate (p.37·2); papaverine hydrochloride (p.2191·3); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Cough.

Jean-Marie, Hong Kong.
Tablets: Codeine phosphate (p.37·2); papaverine hydrochloride (p.2191·3); chlorphenamine maleate (p.571·3); terpin hydrate (p.1573·3); caffeine (p.1116·3).
Cough.

Codotusil *Medifarma, Mex.†.*
⊗ Ammonium chloride (p.1551·3); diphenhydramine (p.577·1); ephedrine hydrochloride (p.1558·2).
Coughs.

Codotussyl Expectorant
Note.This name is used for preparations of different composition.
Wyeth Sante, Fr.
Oral solution: Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Wyeth Sante, Fr.
Syrup: Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Codotussyl Maux de Gorge *Wyeth Sante, Fr.*
Lidocaine hydrochloride (p.1862·3); sodium benzoate (p.1630·2); benzyl alcohol (p.1631·3).
Mouth and throat disorders.

Codotussyl Toux Seche
Note.This name is used for preparations of different composition.
Wyeth Sante, Fr.
Capsules: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Wyeth Sante, Fr.
Syrup: Pholcodine (p.1570·2).
Coughs.

Codox *Boots Healthcare, Austral.*
Aspirin (p.20·3); dihydrocodeine tartrate (p.48·1).
Cough; fever; pain.

Codoxol *Be-Tabs, S.Afr.*
Codeine phosphate (p.37·2); doxylamine succinate (p.578·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain with tension.

Codral Cold & Flu *Johnson & Johnson, NZ.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Cold and influenza symptoms.

Codral Cough, Cold & Flu Day & Night *Johnson & Johnson, NZ.*
Day capsules, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); night capsules, paracetamol; dextromethorphan hydrobromide; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Codral Daytime/Nightime *Johnson & Johnson, NZ.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); night tablets, paracetamol; pseidoephedrine hydrochloride; triprolidine hydrochloride (p.592·3).
Cold and influenza symptoms; nasal congestion.

Codral Dry Cough *Pfizer Consumer, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs; nasal congestion.

Codral 4 Flu *Pfizer Consumer, Austral.; Johnson & Johnson, NZ.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Codral Forte *GSK, Austral.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Coughs; pain.

Codral Linctus *Pfizer, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Cold symptoms; coughs.

Codral Original Chesty Cough *Pfizer Consumer, Austral.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; coughs.

Codral Original Cold & Flu *Pfizer Consumer, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Cold and influenza symptoms.

Codral Original Day & Night Cold & Flu *Pfizer Consumer, Austral.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); night tablets, paracetamol; pseudoephedrine hydrochloride; triprolidine hydrochloride (p.592·3).
Cold and influenza symptoms.

Codral Original Dry Cough *Pfizer Consumer, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Codral Pain Relief *Pfizer Consumer, Austral.; Pfizer, NZ†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Codral PE Cold & Flu *Pfizer Consumer, Austral.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2).
Formerly contained paracetamol, pseudoephedrine hydrochloride, and codeine phosphate.
Cold and influenza symptoms.

Codral PE Cold & Flu + Cough *Johnson & Johnson, Austral.*
Day capsules, paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); night capsules, paracetamol; dextromethorphan hydrobromide; chlorphenamine maleate (p.571·3).
The day capsules formerly contained paracetamol, pseudoephedrine hydrochloride, and dextromethorphan hydrobromide.
Coughs and cold symptoms.

Codral PE Day & Night *Johnson & Johnson, Austral.*
Day tablets, paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2); night tablets, paracetamol; phenylephrine hydrochloride; chlorphenamine maleate (p.571·3).
Formerly contained day tablets: paracetamol, pseudoephedrine hydrochloride, and codeine phosphate and night tablets: paracetamol, pseudoephedrine hydrochloride, and triprolidine hydrochloride.
Cold and influenza symptoms.

Codral PE Nightime *Pfizer, Austral.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Codrinan *Cimed, Braz.*
Theophylline (p.1140·1).
Obstructive airways disease.

Codulin *Medea, Spain.*
Codeine phosphate (p.37·2).
Cough.

Coduretas *Reig Jofre, Spain†.*
⊗ Codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2).
Formerly known as Gragenil.
Cough; respiratory-tract disorders.

Codyl *Actavis, Denm.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Pain.

Codylex *Anglo-French Drugs, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Codylex Plus *Anglo-French Drugs, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms; upper respiratory-tract disorders.

Coease *Advance, USA.*
Sodium hyaluronate (p.2320·1).
Aid in eye surgery.

Coedieci *Mitim, Ital.†.*
Ubidecarenone (p.2407·2).
Coenzyme Q10 deficiency.

Co-Efferalagan *BMS, Ital.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Co-En Q *Corsa, Indon.*
Ubidecarenone (p.2407·2).
Nutritional supplement.

Co-Enac *Hexal, Austria.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enalapril *1A, Austria; Eurogenerics, Belg.; Ratiopharm, Belg.; Sandoz, Belg.; Ratiopharm, Hung.; Sandoz, Hung.; Sandoz, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enalil *Kinder, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enaprotec *Hexal, Braz.†.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enaran *Kwizda, Austria.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enatec *Mepha, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Enatyrol *Biochemie, Austria†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coenrelax *Centrum, Spain.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Co-Epril *Ecosol, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coex *Farmasa, Braz.†.*
Ubidecarenone (p.2407·2).

Co-Exaliv *Maver, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion; rhinitis.

Cof Q
Note.This name is used for preparations of different composition.
Cipla, India.
Lozenge: Dextromethorphan (p.1555·2); amylmetacresol (p.1628·3).
Coughs.

Cipla, India.
Tablets: Paracetamol (p.108·1); bromhexine (p.1552·2); guaifenesin (p.1561·3); chlorphenamine (p.572·2); phenylpropanolamine (p.1569·2).
Coughs.

Cof QD *Cipla, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine (p.572·2); phenylpropanolamine (p.1569·2).
Coughs.

Cof QX *Cipla, India.*
⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Coughs.

Cofact *Sanquin, Neth.*
Factor VIII inhibitor bypassing fraction (p.1068·2).
Coumarin anticoagulant overdose; haemorrhagic disorders.

Cofbron *Macrophar, Thai.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Cofdex *Cipla, India.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Cofdex CC *Cipla, India.*
Dextromethorphan (p.1555·2); phenylephrine (p.1568·1); diphenhydramine (p.577·1); pseudoephedrine (p.1571·2); paracetamol (p.108·1).
Respiratory-tract disorders.

Cofdex Forte
Note.This name is used for preparations of different composition.
Cipla, India.
Expectorant: Bromhexine (p.1552·2); phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2).
Coughs.

Cipla, India.
Syrup: Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2).
Coughs.

Cofdex P *Cipla, India.*
Dextromethorphan (p.1555·2); bromhexine (p.1552·2); phenylpropanolamine (p.1569·2); menthol (p.2340·1).
Coughs.

Cofdex Plus *Cipla, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine (p.572·2).

Cofed *M & H, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever.

Cofedron *Azevedos, Port.*
Paracetamol (p.108·1).
Fever; pain.

Cofen *ICM, Singapore.*
Guaifenesin (p.1561·3).
Coughs.

Cofenac
Note.This name is used for preparations of different composition.
Cipla, India.
Tablets: Diclofenac (p.44·2); paracetamol (p.108·1).
Inflammation; pain.

Cipla, India.
Topical gel: Diclofenac sodium (p.44·3).
Inflammation; pain.

Cofendyl *Aspen Consumer, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Coffalon N *Stark, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Coffecorn *Filofarm, Pol.*
Caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Headache including migraine.

Coffedon *Jaka-80, Rus.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Coffeemed N *Passauer, Ger.†.*
Caffeine (p.1116·3); phenazone (p.116·1).
Pain.

Coffekapton *Strallhofer, Austria.*
Caffeine (p.1116·3).
Fatigue; vascular headache.

Coffepirine *Marcmed, Pol.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Coffo Selt *Rosch & Handel, Austria.*
Phenazone (p.116·1); caffeine (p.1116·3).
Pain.

Coff-Rest *Garec, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Coff-Up *Universal, S.Afr.*
Pheniramine maleate (p.587·3); menthol (p.2340·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Respiratory-tract congestion.

Cofihist *Cipla, India.*
Diphenhydramine (p.577·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Respiratory-tract disorders.

Cofi-Tabs *Vitabalans, Fin.*
Caffeine (p.1116·3).
Fatigue.

Co-Flem *Pharmacare, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Cofles *Euro-Med, Philipp.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Coflic *Baliarda, Arg.*
Folic acid (p.1940·1).
Anaemias; folic acid deficiency.

Coflic B6-B12 *Baliarda, Arg.*
Folic acid; pyridoxine hydrochloride; vitamin B (p.1922·1).
Folic acid and vitamin B deficiency.

Cofnil-N *Idaman, Malaysia.*
⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); ammonium chloride (p.1551·3).
Cough; nasal congestion.

Cofol *Cipla, India.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Cofol Z *Cipla, India.*
Iron carbonyl (p.1950·3); folic acid (p.1940·1); zinc (p.1999·1).

Cofrel *Pfizer, Hong Kong.*
Benproperine (p.1552·1).
Coughs.

Cofron *Abbott, Arg.; Abbott, Chile†.*
Clofedanol hydrochloride (p.1554·2); bromhexine hydrochloride (p.1552·2).
Coughs.

Cofryl *Cipla, India.*
Diphenhydramine hydrochloride (p.577·2).
Coughs.

Cofsed *Greater Pharma, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; nasal congestion.

Cofsils *Cipla, India†.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Throat disorders.

Cofton
Note. This name is used for preparations of different composition.
Cipla, India.
Syrup: Chlorphenamine maleate (p.571·3); sodium citrate (p.1673·3).
Coughs.
Cipla, India.
Tablets: Chlorphenamine maleate (p.571·3).

Cofton SF *Cipla, India.*
⊗ Chlorphenamine (p.572·2); ammonium chloride (p.1551·3); ephedrine (p.1558·1); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Cofvyn *Cipla, India.*
Bromhexine (p.1552·2); pseudoephedrine (p.1571·2).
Respiratory-tract disorders.

Co-Gel *Pharmacare, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); light magnesium oxide (p.1744·1).
Gastric hyperacidity.

Cogenate *General Drugs, Thai.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Cogentin *MSD, Austral.; MSD, Austria; Merck Frosst, Canad.†; MSD, Denm.†; MSD, Hong Kong; MSD, Irl.†; Healthcare Logistics, NZ; MSD, Norw.†; MSD, Port.†; MSD, Thai.; IDIS, UK; Merck, USA.*
Benzatropine mesilate (p.797·1).
Drug-induced extrapyramidal disorders; dystonias; parkinsonism.

Co-Gesic
Note. This name is used for preparations of different composition.
Brainware, S.Afr.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.
Schwarz, USA.
Paracetamol (p.108·1); hydrocodone tartrate (p.63·1).
Pain.

Cogetine *General Drugs, Thai.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Cogiton *Biofarm, Pol.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Cogitum *GSK Sante, Fr.†; Korangi, Port.†.*
Bipotassium *N*-acetylaspartate.
Asthenia.

Cognex *Genesis, Gr.†; OTL, Spain†; Parke, Davis, USA.*
Tacrine hydrochloride (p.370·2).
Alzheimer's disease.

Cognitiv
Note. This name is used for preparations of different composition.
Rontag, Arg.†.
Tacrine hydrochloride (p.370·2).
Alzheimer's disease.
Ebewe, Austria; Ebewe, Cz.; Ebewe, Hung.; Ebewe, Rus.
⊗ Selegiline hydrochloride (p.817·1).
Alzheimer's disease; parkinsonism.

Cognito *Health Perception, UK.*
Phosphatidyl serine (p.2367·1).
Memory impairment.

Cohemin *Orion, Fin.*
Hydroxocobalamin acetate (p.1980·3).
Megaloblastic anaemia; neuropathies; vitamin B deficiency.

Co-Hist *Roberts, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine (p.572·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Cohistan *Biomedis, Indon.; Medifarma, Indon.; Biomedis, Thai.; Great Eastern, Thai.*
Chlorphenamine maleate (p.571·3).
Allergic disorders.

Cohistan Expectorant *Medifarma, Indon.; Great Eastern, Thai.; Pediatrica, Thai.*
Guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Cough.

Cohortan *Boehringer Ingelheim, Spain.*
⊗ Hydrocortisone (p.1535·2); tyrothricin (p.358·2); isopropyl benzatropine mesilate.
Anorectal disorders.

Co-Hypert *Pekana, Ger.†.*
Homoeopathic preparation.

Co-Hypomed *Interpharm, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Coid *Lamsa, Arg.*
⊗ Betamethasone (p.1518·2) or betamethasone valerate (p.1519·1).
Corticosteroid.

Co-Inhibace *Roche, Belg.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Cokenzen *Takeda, Fr.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Cola Tonic *Fiori, Ital.†.*
Fructose; kola; ginseng; fieno greco; guarana (p.1922·1).
Nutritional supplement.

Colace *Wellspring, Canad.; Purdue, USA.*
Docusate sodium (p.1725·1).
Constipation.

Colace Infant/Child *Purdue, USA.*
Glycerol (p.2314·2).
Constipation.

Colachofra *EMS, Braz.*
Sorbitol (p.1965·1); betaine hydrochloride (p.2265·2); cynara (p.2291·2); boldo (p.2267·2); solanum paniculatum.
Liver disorders.

Coladren *Coop. Farm., Ital.*
Cascara (p.1715·2); boldo (p.2267·2).
Constipation.

Colagenan *Herbarium, Braz.*
⊗ Gelatin (p.1072·1).

Colageno + C *Sigma, Arg.*
Bovine collagen (p.2286·1); vitamin C; magnesium (p.1922·1).
Arthroses.

Colain *Darya-Varia, Indon.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Colatan *Allen, Spain†.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Colatus *TNP, Thai.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Colax
Note. This name is used for preparations of different composition.
OFF, Ital.
Senna (p.1769·2); rhubarb (p.1768·3); cynara (p.2291·2); boldo (p.2267·2).
Constipation; digestive disorders; loss of appetite.
Mediherb, Austral.
Oral liquid: Dill (p.2293·3); butternut; cascara (p.1715·2); chamomile (p.2279·3); yellow dock (p.2416·3); taraxacum (p.2395·1).
Constipation.
Mediherb, Austral.
Tablets: Dill (p.2293·3); cascara (p.1715·2); chamomile (p.2279·3); yellow dock (p.2416·3); taraxacum (p.2395·1).
Constipation.

Colazal *Salix, USA.*
Balsalazide sodium (p.1709·2).
Ulcerative colitis.

Colazid *Shire, Norw.; Meda, Swed.*
Balsalazide sodium (p.1709·2).
Ulcerative colitis.

Colazide *Pharmatel, Austral.; AstraZeneca, Cz.†; Shire, UK.*
Balsalazide sodium (p.1709·2).
Ulcerative colitis.

ColBenemid *Merck, USA.*
⊗ Probenecid (p.558·2); colchicine (p.556·1).
Chronic gouty arthritis.

Colbiocin
Note. This name is used for preparations of different composition.
SIFI, Ital.; SIFI, Rus.
Eye drops: Rolitetracycline (p.330·3); chloramphenicol (p.239·3); colistimethate sodium (p.256·3).
Bacterial eye infections.
SIFI, Ital.; SIFI, Rus.
Eye ointment: Tetracycline (p.347·1); chloramphenicol (p.239·3); colistimethate sodium (p.256·3).
Bacterial eye infections.

Colcaps
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Capsules: Phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2); caffeine (p.1116·3); salicylamide (p.121·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; nasal congestion; rhinitis.
Adcock Ingram, S.Afr.
Effervescent tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); vitamin C (p.1983·3).
Cold and influenza symptoms.
Adcock Ingram, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; nasal congestion; rhinitis.

Colchicum comp *Pfluger, Ger.*
Homoeopathic preparation.

Colchicum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Colchicum-Dispert *Solvay, Hung.; Frik, Turk.*
Colchicine (p.556·1).
Gout.

Colchily *Pharmasant, Thai.*
Colchicine (p.556·1).
Gout.

Colchimax
Note. This name is used for preparations of different composition.
Opocalcium, Fr.
Colchicine (p.556·1); tiemonium metilsulfate (p.1776·3); opium powder (p.105·1).
Gout; inflammatory disorders.
Seid, Spain.
Colchicine (p.556·1); dicycloverine hydrochloride (p.1722·3).
Gout.

Colchin *Greenpharma, Braz.*
Colchicine (p.556·1).
Gout.

Colchiquim *Quimica y Farmacia, Mex.*
Colchicine (p.556·1).
Biliary and hepatic cirrhosis; gout.

Colchis *Apsen, Braz.*
Colchicine (p.556·1).
Familial Mediterranean fever; gout; psoriasis; sarcoidosis; scleroderma.

Colchysat *Ysatfabrik, Ger.*
Colchicum autumnale (p.558·1).
Gout.

Colcina *Jean-Marie, Hong Kong.*
Colchicine (p.556·1).
Gout.

Colcine *Pharmahof, Thai.*
Colchicine (p.556·1).
Gout.

Colcleer *Adcock Ingram, S.Afr.*
⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Cold Cap *Nufarindo, Indon.*
⊗ Salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Cough; influenza symptoms.

Cold Care *Dossier, Neth.*
Homoeopathic preparation.

Cold Control *Reese, USA.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms.

Cold Cream *Vita, Venez.*
Soap substitute.
Dry or sensitive skin.

Cold Cream Avene *Silesia, Chile.*
White beeswax (p.2028·1); liquid paraffin (p.2030·3).
Dry skin disorders.

Cold Cream Naturel
Roche-Posay, Arg.†.
Cetyl esters wax (p.2029·1); white beeswax (p.2028·1); light liquid paraffin (p.2031·1).
Nappy rash; vehicle for dermatological agents.
Roche-Posay, Fr.
Cetyl palmitate; white beeswax (p.2028·1); light liquid paraffin (p.2031·1).
Skin dryness and irritation.

Cold Cream Salicyle *Roche-Posay, Fr.†.*
Salicylic acid (p.1612·2); titanium dioxide (p.1617·3).
Skin disorders.

Cold and Flu Relief *Brauer, Austral.†.*
Ascorbic acid (p.1983·3); echinacea angustifolia (p.2298·1); zinc gluconate (p.1999·2); apis mel.; arsen. alb.; aurum met.; baptisia tinct.; belladonna; bryonia; ferrum phos.; merc. sol.
Cold and influenza symptoms.

Cold & Flu Respatona Cough Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Cold & Flu Respatona Decongestant Cough Relief *Brauer, Austral.†.*
Anise oil; marshmallow; white bryony; Iceland moss; chamomile; thyme; urtica; aconite; ammonia; coccus cacti; corallium rubrum; drosera rotundifolia; ipecacuanha; kali bich.; kreosotum; spongia tosta; sticta pulmonaria.
Cough.

Cold & Flu Respatona Dry Cough Relief *Brauer, Austral.†.*
Anise oil; marshmallow; white bryony; Iceland moss; echinacea; chamomile; thyme; urtica; aconite; ammonia; coccus cacti; corallium rubrum; drosera rotundifolia; ipecacuanha; kali bich.; kreosotum; spongia tosta; sticta pulmonaria.
Cough.

Cold & Flu Respatona Flu & Fever Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Cold & Flu Respatona Head Cold Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Cold & Flu Respatona Sore Throat Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Cold & Flu Tablets Non Drowsy *Or-Dov, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); citrus bioflavonoids (p.2304·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms; hay fever.

Cold Medication D *Prodemdis, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Cold Medication Extra-Strength Daytime
Confab, Hong Kong.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Cold Medication Extra-Strength Nightime
Confab, Hong Kong.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Cold Medication N *Prodemdis, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Cold Relief
Note. This name is used for preparations of different composition.
Unichem, UK.
Capsules: Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.
Unichem, UK.
Oral powders: Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Cold Sore *ICN, NZ.*
Menthol (p.2340·1); camphor (p.2273·2); benzoin (p.2394·2).
Herpes labialis.

Cold Sore Lotion *Rougier, Canad.*
Benzoin (p.2394·2); camphor (p.2273·2); menthol (p.2340·1).
Herpes labialis.

Cold Sore Relief *Vitaplex, Austral.†.*
Lysine hydrochloride (p.1955·1); ascorbic acid (p.1983·3); zinc amino acid chelate (p.2000·1).
Herpes labialis.

Cold Sores & Fever Blisters *Hylands, Canad.*
Homoeopathic preparation.

Cold Tablets with Zinc *Hylands, Canad.*
Homoeopathic preparation.

Colda *Sigmapharm, Austria.*
Sage oil (p.2382·3); thuja oil (p.2400·3); pumilio pine oil (p.2376·3); camphor (p.2273·2); pine silvestris oil (p.2368·2); dexpanthenol (p.2362·1); eucalyptus oil (p.2301·2).
Respiratory-tract disorders.

Coldacrom *Sigmapharm, Austria.*
Sodium cromoglicate (p.1136·3).
Conjunctivitis.

Coldact Broncho *Ranbaxy, Rus.†.*
Ambroxol hydrochloride (p.1550·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).

Coldact Flu Plus *Ranbaxy, Rus.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).

Coldact Lorpils *Ranbaxy, Rus.†.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).

Coldadolin *Sigmapharm, Austria.*
Ethenzamide (p.51·3); paracetamol (p.108·1); caffeine (p.1116·3); butetamate citrate (p.1553·1).
Smooth muscle spasm and pain.

Coldagrippin *Sigmapharm, Austria.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Coldaid *Rayere, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; hay fever.

Coldan *Sigmapharm, Austria; Kotsopoulos (Κωτσοπουλος), Gr.*
⊗ Naphazoline hydrochloride (p.1565·2).
Adjunct in rhinoscopy; conjunctivitis; ocular irritation; rhinitis; sinusitis; sore throat.

Coldangin *Sigmapharm, Austria.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Mouth and throat disorders.

Coldargan
Sigmapharm, Austria.
⊗ Silver protein (p.2387·3); ephedrine levulinate (p.1559·1); calcium levulinate (p.1676·2); sodium levulinate.
Mouth and throat disorders; rhinitis; sinusitis.

Sigmapharm, Hung.
⊗ Silver protein (p.2387·3); ephedrine levulinate (p.1559·1); calcium levulinate (p.1676·2).
Mouth and throat disorders; rhinitis; sinusitis.

Coldastop
Note. This name is used for preparations of different composition.
Desitin, Cz.
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3); terpineol (p.2396·1); lemon oil (p.2332·3); orange oil (p.2357·2).
Rhinitis.

Desitin, Ger.; Desitin, Hung.
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Cold symptoms; rhinitis.

Coldcap-A *Christo, Hong Kong.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); noscapine (p.1566·2); caffeine (p.1116·3); terpin hydrate (p.1573·3).
Cold and influenza symptoms.

Coldec D *Breckenridge, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2).
Upper respiratory-tract disorders.

Coldec DM *Silarx, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Coldeks *Deva, Turk.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); noscapine (p.1566·2).
Respiratory-tract congestion.

Coldenza *Nelson, UK.*
Homoeopathic preparation.

Coldex *Teva, Israel.*
Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms; hypersensitivity reactions; sinusitis.

Coldin *Sanofi-Aventis, Chile.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with viscous mucus.

Coldistan
Note. This name is used for preparations of different composition.
Sigmapharm, Hung.†.
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Allergic eye disorders.

Sigmapharm, Austria.
Eye drops; nasal drops: ⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Allergic eye disorders; eye irritation; rhinitis; sinusitis.

Sigmapharm, Austria.
Nasal ointment: Diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1); calcium levulinate (p.1676·2); cetylpyridinium chloride (p.1635·1); dexpanthenol (p.2362·1); sage oil (p.2382·3).
Hay fever; rhinitis; sinusitis.

Coldistop *Sigmapharm, Austria; Proreo, Switz.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Nasal and sinus disorders; rhinitis.

Coldmist *Breckenridge, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Coldoff *Stadmed, India.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Coldophthal *Sigmapharm, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2); mercuric oxycyanide (p.2342·2); boric acid (p.2268·1).
Conjunctivitis; eye irritation.

Coldosian *Asian Pharm, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Coldrex
Note. This name is used for preparations of different composition.
GSK Consumer, Cz.
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); terpin monohydrate (p.1573·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

GSK, Fin.
Aspirin (p.20·3); guaifenesin (p.1561·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

GSK, Hong Kong†.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); vitamin C (p.1983·3); noscapine (p.1566·2); terpin hydrate (p.1573·3); caffeine (p.1116·3).
Cold and influenza symptoms; sinusitis.

GSK Consumer, Pol.
Benzalkonium chloride (p.1629·1); hexylresorcinol (p.1647·1).
Sore throat.

GSK Consumer, Hung.
Oral powder: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

GSK Consumer, Hung.
Tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3); terpin hydrate (p.1573·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Coldrex Broncho *GSK Consumer, Cz.; GSK Consumer, Hung.*
Guaifenesin (p.1561·3).
Coughs.

Coldrex Day/Night *GSK, NZ†.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, chlorphenamine maleate (p.571·3); paracetamol; pseudoephedrine hydrochloride.
Cold and influenza symptoms; nasal congestion.

Coldrex Head & Chest Cold *GSK, NZ†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Coldrex Head Cold *GSK, NZ†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Sinusitis.

Coldrex Hotrem *GSK, Cz.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Coldrex HotRem *GSK Consumer, Pol.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Coldrex HotRem Lemon *GSK Consumer, Rus.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Influenza symptoms.

Coldrex Laryplus *GSK Consumer, Cz.; GSK Consumer, Hung.†.*
Hexylresorcinol (p.1647·1); benzalkonium chloride (p.1629·1).
Sore throat.

Coldrex MaxGrip *GSK Consumer, Cz.; GSK, Hung.; GSK Consumer, Pol.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Coldrex MaxGrip C *GSK Consumer, Pol.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3); caffeine (p.1116·3) terpin hydrate (p.1573·3).
Cold and influenza symptoms.

Coldrex MaxGrip Lemon *GSK Consumer, Rus.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Influenza symptoms.

Coldrex Nite *GSK Consumer, Cz.*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Coldrex Reformulated *Sanofi Synthelabo, Philipp.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; rhinitis; sinusitis.

Coldrin
Note. This name is used for preparations of different composition.
Janssen-Cilag, Braz.
Cinnarizine (p.573·1); phenylephrine hydrochloride (p.1568·1); pentoxyverine citrate (p.1567·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Influenza symptoms.

Shinyaku, Hong Kong†; Shinyaku, Singapore†.
Clofedanol hydrochloride (p.1554·2).
Coughs.

Coldrine *Hauck, USA; Roberts, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Coldstat *Prater, Chile†.*
Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine (p.572·2).
Cold and influenza symptoms.

Coldtab-2 *Christo, Hong Kong.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); noscapine (p.1566·2); caffeine (p.1116·3); terpin hydrate (p.1573·3).
Cold and influenza symptoms.

Coldvac *Byk Madaus, S.Afr.†.*
Pneumococci; streptococci; staphylococci; *Haemophilus influenzae*.
Respiratory-tract disorders.

Coldvico
Note. This name is used for preparations of different composition.
Merck, S.Afr.
Capsules: Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Merck, S.Afr.
Syrup: Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Coleb *AstraZeneca, Ger.; Promed, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Coledis *Sidus, Arg.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Coledos *Prospa, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Colega-3 *Biofarma, Mex.*
Eicosapentaenoic acid (p.1362·1).
Dietary supplement.

Colegraf *Estedi, Spain.*
Iopanoic acid (p.1484·1).
Contrast medium for biliary-tract radiography.

Colemin *Biohorm, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Colenon *SIRC, Singapore.*
Poliglusam (p.2370·1); garcinia cambogia (p.2309·2); hydroxycitric acid; chromium; vitamin C (p.1922·1).
Dietary aid.

Colepak *Rowe-Fleming, Venez.†.*
Iopanoic acid (p.1484·1).
Radiographic contrast medium.

Colepren *Randall, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Colergis *Dexa, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Colerin *Nostrum, Port.*
Azintamide (p.2262·2).
Digestive insufficiency.

Colerin-F *Nostrum, Port.*
Azintamide (p.2262·2); pancreatin (p.2360·1); cellulase (p.2279·1).
Digestive insufficiency.

Colese *Alphapharm, Austral.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Colesken *Kendrick, Mex.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; cerebrovascular risk reduction; hypercholesterolaemia.

Colesom *Temis, Arg.†.*
Iopanoic acid (p.1484·1).
Contrast medium for cholecystography.

Colestase *Sanofi-Aventis, Braz.*
Furazolidone (p.834·3); diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Colesterase *Sinclair, Ital.*
Vitamin E (p.1992·2); policosanol (p.1373·3); fermented red rice.
Hypercholesterolaemia.

Colesterminol *Omicron, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Colesthexal *Hexal, Ger.†.*
Colestyramine (p.1252·3).
Hyperlipidaemias.

Colestid *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pharmacia, Cz.†; Pharmacia, Ger.; Pharmacia, Irl.†; Pharmacia, Israel; Pfizer, Mex.†; Pharmacia, NZ; Pharmacia, Neth.†; Pfizer, Port.; Pfizer, Spain; Pfizer, Switz.; Pharmacia, UK; Pharmacia Upjohn, USA.*
Colestipol hydrochloride (p.1252·2).
Hypercholesterolaemia.

Colesto Cero *Garden House, Arg.†.*
Indian bdellium.
Dietary supplement.

Colestyr *CT, Ger.*
Colestyramine (p.1252·3).
Biliary-tract disorders; hyperlipidaemias.

Colesvir *Vir, Spain.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Coleus Complex *Mediherb, Austral.*
Coleus forskohlii; crataegus (p.2289·1); valerian (p.2410·1).
Hypertension.

Colevix *Royal, Chile†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Colex *Tramedico, Neth.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Colexklysma *Tramedico, Belg.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Colfarit *Bayer, Hung.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Colfed-A *Parmed, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Colfene *Elmor, Venez.*
Ibuprofen (p.64·2); thiocolchicoside (p.1898·2).
Pain with spasm.

Colfin *Nufarindo, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); phenylpropanolamine hydrochloride (p.1569·3).
Cough; influenza symptoms.

Colfur
Note. This name is used for preparations of different composition.
Church, Mex.
Oral suspension: Colistin sulfate (p.256·2); furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal infections.

Church, Mex.
Tablets: Colistin sulfate (p.256·2); furazolidone (p.834·3).
Gastrointestinal infections.

Colgate Total *Colgate-Palmolive, Ital.*
Sodium fluoride (p.1962·2); triclosan (p.1665·2).
Dental caries prophylaxis; oral hygiene.

Colgen Kowa Bien Soft Mini *Kowa, Jpn.*
Chlorphenamine maleate (p.571·3); belladonna alkaloids (p.2263·3); phenylephrine hydrochloride (p.1568·1); dipotassium glycyrrhizate (p.2316·2).

Colgen Kowa IB Toumei *Kowa, Jpn.*
⊗ Ibuprofen (p.64·2); dexchlorpheniramine maleate (p.572·1); dihydrocodeine phosphate (p.48·1); guaifenesin (p.1561·3); methylephedrine hydrochloride (p.1564·3); caffeine (p.1116·3).
Cold symptoms.

Colgout *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ.*
Colchicine (p.556·1).
Gout; polyarthritis associated with sarcoidosis.

Colhidrol *Teva Tuteur, Arg.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Colibiogen *Laves, Ger.*
Peptide extract from *Escherichia coli*.
Gastrointestinal disorders; hypersensitivity; musculoskeletal and joint disorders; skin disorders.

Colic *Hylands, Canad.*
Homoeopathic preparation.

Colic Relief *Brauer, Austral.*
Homoeopathic preparation.

Colicon *Reese, USA.*
Simeticone (p.1770·2).

Colidium *Solas, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Colief *Clonmel, Irl.; Britannia Health, UK.*
Tilactase (p.2402·1).
Colic associated with lactose intolerance; infant colic.

Colifagina *ABC, Ital.*
Lysate of *Escherichia coli*; *Bacillus pumilus*; *Morganella morgani*; *Alcaligenes faecalis*; *Shigella flexneri*; *Enterococcus faecalis* (p.2372·3); *Bacillus subtilis*; *Proteus vulgaris*.
Gastrointestinal infections; genito-urinary infections.

Coli-Fagina S *ABC, Port.*
Lysates of *Escherichia coli*; *Bacillus morgani*; *B. faecalis alcaligenes*; *E. pseudodysenteriae*; *Bacillus subtilis*; *Proteus vulgaris*; *Enterococcus faecalis* (p.2372·3); *B. mesentericus*.
Gastrointestinal infections; genito-urinary infections.

Colifilm *Quesada, Arg.*
Loperamide (p.1741·3).
Diarrhoea; ileostomy management.

Colifoam *Aspen, Austral.; Montavit, Austria; Meda, Denm.; Meda, Fin.; Meda, Ger.; Kite (Κιτε), Gr.; Meda, Irl.; Alloga, Ital.; Stafford-Miller, NZ; Schwarz, Norw.; Meda, Port.; Omnimed, S.Afr.†; Meda, Swed.; Meda, UK.*
⊗ Hydrocortisone acetate (p.1535·2).
Inflammatory bowel disease.

Colifossim *Day, Ital.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Colimax *Qualiphar, Belg.†.*
⊗ Ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); aconite (p.2246·1); belladonna (p.2263·3); thyme (p.2401·1); wild thyme (p.2415·3); maidenhair fern.
Coughs.

Colimet *Collins, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Colimex
Note. This name is used for preparations of different composition.
Wallace, India.
Oral drops: Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Flatulence; gastrointestinal spasm.

Wallace, India.
Tablets: Dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1).
Colic; dysmenorrhoea.

Colimicina
Quimifar, Spain.
Colistin sulfate (p.256·2).
Bacterial infections.

UCB, Ital.
Injection: Colistimethate sodium (p.256·3).
Gram-negative bacterial infections.

UCB, Ital.
Oral drops; tablets: Colistin sulfate (p.256·2).
Gram-negative bacterial infections of the gastrointestinal tract.

Colimil *Milte, Ital.*
Melissa (p.2339·3); chamomile (p.2279·3); fennel (p.2302·3).
Infant colic.

Colimix *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Flatulence and abdominal discomfort; gastrointestinal spasm; infant colic.

Colimune *Aventis, Ger.*
Sodium cromoglicate (p.1136·3).
Food hypersensitivity.

Colimycin *Lundbeck, Denm.; Lundbeck, Norw.*
Colistimethate sodium (p.256·3).
Bacterial infections; Gram-negative bacterial infections.

Colimycine
Aventis, Cz.†; Aventis, Neth.†.
Colistimethate sodium (p.256·3).
Bacterial infections.

Sanofi-Aventis, Fr.
Colistin sulfate (p.256·2) or colistimethate sodium (p.256·3).
Bacterial infections.

Colin *Strand, Malaysia†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; status asthmaticus.

Colina *Intersan, Ger.*
Smectite (p.1771·1).
Diarrhoea.

Colina Spezial *Intersan, Ger.*
Smectite (p.1771·1); aluminium hydroxide-magnesium carbonate gel (p.1707·2).
Diarrhoea; gastrointestinal disorders.

Colinfant *Dyntec, Cz.*
Escherichia coli.
Gastrointestinal infections.

Colinsan *Ferring, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; dermatomyositis; idiopathic thrombocytopenic purpura; inflammatory bowel disease; polyarteritis nodosa; rheumatoid arthritis; transplant rejection.

Colintest-Gastreu R37 *Reckeweg, Neth.*
Homoeopathic preparation.

Colintil *Inibsa, Port.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Coli-Om *OM, Port.†.*
Lysate of *Escherichia coli.*
Gastrointestinal infections; urinary-tract infections.

Coliopan *Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Singapore†.*
Butropium bromide (p.1713·3).
Painful gastrointestinal spasm.

Coliper *Mintlab, Chile.*
Loperamide (p.1741·3).
Diarrhoea.

Coliquifilm *Allergan, Ger.; Allergan, Switz.*
White soft paraffin (p.2031·2); wool alcohols (p.2033·2); light liquid paraffin (p.2031·1).
Eye disorders.

Coliracin *Rafa, Israel.*
Colistimethate sodium (p.256·3).
Bacterial infections.

Colircusi Anestesico *Alcon, Port.*
⊗ Tetracaine hydrochloride (p.1871·3); naphazoline hydrochloride (p.1565·2).
Eye disorders.

Colircusi Cicloplejico *Alcon Cusi, Malaysia.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Coliria *Gezzi, Arg.*
⊗ Ephedrine (p.1558·1); phenazone (p.116·1).
Eye irritation.

Colirid *Cadila, India.*
Dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1); simeticone (p.1770·2).
Colic; dysmenorrhoea; irritable bowel syndrome.

Colirio Antibiotico CNH *Lafedar, Arg.*
⊗ Hydrocortisone (p.1535·2); chloramphenicol (p.239·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Colirio Iris *Ponce, Venez.*
⊗ Ephedrine sulfate (p.1558·2).
Eye congestion.

Colirio Legrand *Legrand, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Ocular congestion.

Colirio Moura Brasil *Sanofi-Aventis, Braz.*
⊗ Zinc sulfate (p.1999·2); naphazoline hydrochloride (p.1565·2).
Ocular congestion.

Colirio Teuto *Teuto, Braz.*
⊗ Zinc sulfate (p.1999·2); naphazoline hydrochloride (p.1565·2).
Ocular congestion.

Coliriocilina *Medical, Spain†.*
Benzylpenicillin potassium (p.213·1).
Eye infections.

Coliriocilina Adren Astr *Medical, Spain.*
⊗ Boric acid (p.2268·1); adrenaline hydrochloride (p.1203·3); naphazoline hydrochloride (p.1565·2); procaine hydrochloride (p.1869·1); zinc sulfate (p.1999·2).
Eye disorders.

Coliriocilina Espectro *Medical, Spain†.*
Neomycin sulfate (p.305·1); oxytetracycline (p.312·2).
Bacterial eye infections.

Coliriocilina Gentam *Medical, Spain†.*
Gentamicin sulfate (p.282·1).
Eye infections.

Coliriocilina Prednisona *Medical, Spain.*
⊗ Neomycin sulfate (p.305·1); prednisone (p.1542·3).
Eye disorders.

Colisil *Silva, Venez.†.*
Colistin (p.257·2).
Bacterial infections.

Co-Lisinopril *Eurogenerics, Belg.; Ratiopharm, Belg.; Sandoz, Belg.; Teva, Belg.; Sandoz, Switz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Lisinostad *Stada, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Colistate *Atlantic, Thai.*
Colistimethate sodium (p.256·3).
Gram-negative bacterial infections.

Colistineb *Pharma Logistics, Belg.*
Colistimethate sodium (p.256·3).
Gram-negative bacterial infections.

Colistop *Hexa, Arg.*
Phthalylsulfathiazole (p.315·1); bismuth subcarbonate (p.1711·1); homatropine methylbromide (p.1881·3).
Gastro-enteritis.

Colistoral *BMS, Arg.†.*
Phthalylsulfathiazole (p.315·1); bismuth subgallate (p.1711·1).
Diarrhoea; gastroenteritis.

Colitan *GSK, Pol.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Colitofalk *Codali, Belg.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Colitromin *Collins, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Colixane *Sanitas, Arg.*
Trimebutine maleate (p.2404·3).

Colixane B *Sanitas, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).

Colixin *Pharmis, Port.*
Colistimethate sodium (p.256·3).
Gram-negative bacterial infections.

Colizin *Sedabel, Braz.†.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Ocular congestion.

Colizole *East India Pharma, India.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Collagen T2-Gag *Formoterapia, Arg.†.*
Collagen (p.2286·1); cartilage (p.2277·3).
Nutritional supplement.

Collapat II *Biomet, Ger.*
Hydroxyapatite (p.2323·1); collagen (p.2286·1).
Bone reconstruction.

Collatamp EG *Schering-Plough, UK.*
Collagen (p.2286·1); gentamicin sulfate (p.282·1).
Haemorrhage.

Collatamp G *Schering-Plough, Fr.†.*
Collagen (bovine) (p.2286·1); gentamicin sulfate (p.282·1).
Haemorrhage.

Collazin *Selmag, Switz.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Collerin Expectorant *Coronet, Indon.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3); phenylpropanolamine hydrochloride (p.1569·3).
Cough.

Collicort *Collins, Mex.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Collins Elixir *Collins Elixir, UK.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Collins Elixir Decongesant Pasilles *Collins Elixir, UK.*
Menthol (p.2340·1); eucalyptus (p.2301·2).
Coughs; nasal congestion.

Collirio Alfa *Bracco, Ital.*
⊗ Naphazoline nitrate (p.1565·2).
Eye irritation.

Collirio Alfa Antistaminico *Bracco, Ital.*
⊗ Thonzylamine hydrochloride (p.592·1); naphazoline nitrate (p.1565·2).
Conjunctival disorders.

Collis Browne's
Note.This name is used for preparations of different composition.
Thornton & Ross, UK.
Oral mixture: ⊗ Morphine (p.86·3); peppermint oil (p.1761·2).
Coughs; diarrhoea.

Thornton & Ross, UK.
Tablets: ⊗ Light kaolin (p.1738·1); morphine hydrochloride (p.86·3); heavy calcium carbonate (p.1714·1).
Diarrhoea.

Collite *Eulite, Neth.*
Homoeopathic preparation.

Collodene *Universal, S.Afr.*
Pectin (p.2145·2); light kaolin (p.1738·1).
Diarrhoea.

Colloidal 75 *Douglas, NZ†.*
Mineral (p.1667·1) and trace-element preparation (p.1922·1).
Nutritional supplement.

Collomack *Mack, Illert., Ger.†; Mack, Hong Kong; Mack, Malaysia†; Mack, Singapore†; Mack, Thai.†; Zuoz, Venez.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3); lauromacrogol 400 (p.1916·1).
Calluses; corns; warts.

Collosol *Solvay, India.*
Iodine (p.2169·2).
Hyperthyroidism; hypothyroidism.

Colloss *Biomet, Ger.*
Collagen (bovine) (p.2286·1).
Bone reconstruction.

Collubiazol
Note.This name is used for preparations of different composition.
Millet-Franklin, Arg.
Pastilles: Tyrothricin (p.358·2); benzocaine (p.1854·1); hexylresorcinol (p.1647·1).
Formerly contained sulfachrysoidine sodium, benzocaine, and cetylpyridinium chloride.
Mouth and throat disorders.

Millet-Franklin, Arg.
Spray: Sulfachrysoidine sodium; benzocaine (p.1854·1).
Mouth and throat disorders.

Collu-Blache *Zydus, Fr.†; Bausch & Lomb, Switz.*
Chlorhexidine gluconate (p.1635·3); oxybuprocaine hydrochloride (p.1867·3).
Mouth and throat disorders.

Colludol *Melisana, Belg.; Cooperation Pharmaceutique, Fr.*
Hexamidine isetionate (p.1646·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Collu-Hextril *Pfizer Sante, Fr.; Janssen-Cilag, Port.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Collunosol-N *Sanofi, Switz.*
Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Collunovar
Note.This name is used for preparations of different composition.
Dexo, Fr.
Mouthwash; throat spray: Chlorhexidine gluconate (p.1635·3).
Mouth and throat infections.

Dexo, Fr.†.
Pastilles: Bacitracin zinc (p.210·3); tyrothricin (p.358·2).
Mouth and throat infections.

Collustan *UPSA, Fr.†.*
Chlorhexidine gluconate (p.1635·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Collylarm *Vifor, Switz.*
Povidone (p.2146·1); polyvinyl alcohol (p.2145·3).
Dry eyes.

Collypan *Vifor, Switz.*
⊗ Tetryzoline hydrochloride (p.1574·1); zinc sulfate (p.1999·2); digitalis (p.1258·3); hamamelis (p.2318·2); euphrasia (p.2301·3).
Eye irritation.

Collyre Alpha *Bracco, Switz.†.*
⊗ Naphazoline nitrate (p.1565·2); camphor (p.2273·2).
Eye irritation.

Collyre Bleu
Note.This name is used for preparations of different composition.
Sabex, Canad.†.
⊗ Methylthioninium chloride (p.1450·3); naphazoline hydrochloride (p.1565·2).

Leurquin, Fr.
⊗ Methylthioninium chloride (p.1450·3); naphazoline nitrate (p.1565·2).
Eye irritation.

Collyre Bleu Laiter *Leurquin, Switz.*
⊗ Methylthioninium chloride (p.1450·3); naphazoline nitrate (p.1565·2).
Eye irritation.

Collyria *Nova Argentia, Ital.†.*
Benzalkonium chloride (p.1629·1); guaiazulene (p.2317·3); polyvinyl alcohol (p.2145·3).
Eye hygiene; eye irritation.

Collyrium Fresh *Wyeth-Ayerst, USA†.*
⊗ Tetryzoline hydrochloride (p.1574·1); glycerol (p.2314·2).
Eye irritation.

Collyrium for Fresh Eyes *Bausch & Lomb, USA.*
Borax (p.2268·1); boric acid (p.2268·1).
Eye irrigation.

Colmax *Andromaco, Chile.*
Clonixin lysine (p.37·1).
Pain.

Colme
Note.This name is used for preparations of different composition.
Croma, Austria; Ipsen, Rus.; Ipsen, Spain.
Calcium carbimide (p.2271·3).
Alcoholism.

Interbat, Indon.
Chloramphenicol (p.239·3).
Bacterial infections.

Colnidin *Reig Jofre, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Colobil *Sidepal, Braz.†.*
Homoeopathic preparation.

Colobolina *Fabra, Arg.*
Hyoscine butylbromide (p.1734·1).
Muscle spasm.

Colobolina D *Fabra, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Muscle spasm; pain.

Colocarb *Expanpharm, Fr.*
Activated charcoal (p.1435·2).
Gastrointestinal disorders.

ColoCare *Helena, Canad.; Helena, USA.*
Test for occult blood in faeces.

Colocort *Paddock, USA.*
⊗ Hydrocortisone (p.1535·2).
Anorectal disorders.

Colodium *Hovid, Hong Kong†; Hovid, Singapore†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Colofac *Solvay, Austral.; Solvay, Austria; Solvay, Irl.; Solvay, NZ; Solvay, S.Afr.; Solvay, Thai.; Solvay, UK.*
Mebeverine hydrochloride (p.1744·2).
Abdominal pain; gastrointestinal spasm; irritable bowel syndrome.

Colofiber *Madaus, Belg.*
Ispaghula (p.1737·1).
Colopathy; constipation.

Colofoam *Meda, Fr.*
⊗ Hydrocortisone acetate (p.1535·2).
Inflammatory bowel disease.

Colofort *Ipsen, Belg.; Ipsen, Neth.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Colognost *Sanochemia, Ger.*
Radio-opaque polyvinyl chloride O-ring.
Diagnosis of colon transit time.

Cololyt *Spirig, Switz.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Colomba spezial *Mauermann, Ger.*
Homoeopathic preparation.

Colominte *Vitoria, Port.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome.

Colomycin
Forest Laboratories, Cz.
Colistimethate sodium (p.256·3).
Bacterial infections.

Forest, Irl.; Pharmax, Irl.; Forest Laboratories, UK.
Colistin sulfate (p.256·2) or colistimethate sodium (p.256·3).
Bacterial infections.

Colonac *Uniao Quimica, Braz.*
Lactulose (p.1738·2).
Constipation.

Colonaid *Recalcine, Chile.*
Tegaserod (p.1776·2).
Irritable bowel syndrome in women.

Colonel *Astellas, Jpn.*
Polycarbophil calcium (p.1763·3).
Irritable bowel syndrome.

Colonic Lavage Powder *Biotech, Austral.†.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Colonil *Quesada, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Colonlytely *Dendy, Austral.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Colonorm *Mundipharma, Austria.*
Senna (p.1769·2).
Anorectal disorders; constipation.

Colonorm N *Mundipharma, Ger.†.*
Macrogol 3350 (p.2336·3) electrolytes (p.1667·1).
Bowel evacuation.

Colonprep *Dendy, Austral.†.*
1 Sachet, macrogol 3350 (p.2336·3); electrolytes (p.1667·1) (Colonlytely); 2 sachets, sodium picosulfate (p.1771·1) (Picolax).
Bowel evacuation.

Colonsoft *Orion, Fin.*
Electrolytes (p.1667·1); macrogol 4000 (p.2336·3).
Constipation.

Colonsteril *Orion, Fin.*
Electrolytes (p.1667·1); macrogol 4000 (p.2336·3).
Bowel evacuation; constipation.

Colopeg *Bayer, Belg.; Bayer, Fr.*
Electrolytes (p.1667·1); macrogol 3350 (p.2336·3).
Bowel evacuation.

Colophos *Spirig, Switz.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Coloplast OAD (Sween) *Coloplast, UK.*
A deodorant for stoma care.

Colo-Pleon *Sanofi Synthelabo, Austria; Sanofi Synthelabo, Ger.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease.

Coloplex *Andromaco, Venez.†.*
Zipeprol hydrochloride (p.1575·3).
Cough.

Colo-Prep *Anmarate, S.Afr.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Colopriv *Expanscience, Fr.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal and biliary-tract disorders.

Colopten *Fournier, Ital.*
Purified antigenic fraction of *Staphylococcus aureus*; *Escherichia coli*; *Klebsiella pneumoniae*; *Proteus vulgaris*.
Diarrhoea.

Colosan mite *Vifor, Switz.*
Sterculia (p.1772·1).
Constipation; obesity.

Colosan plus *Vifor, Switz.*
Sterculia (p.1772·1); frangula (p.1732·2).
Constipation.

Coloscreen *Biolab, NZ; Helena, USA.*
Test for faecal occult blood.

Coloserod *Lazar, Arg.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome in women.

Colosoft *Medichemie, Switz.†.*
Ispaghula (p.1737·1).
Constipation.

Colo-Sol *Vifor, Switz.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Colospa *Solvay, India.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Colospan *Hovid, Malaysia†; Hovid, Singapore†.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Colostrum
Note. This name is used for preparations of different composition.
Eagle, Austral.
Milk extract (p.1922·1).
Dietary supplement.

Nathura, Ital.
Colostrum (p.2208·1); melaleuca viridiflora; cypress (p.2291·2).
Skin disorders; wounds.

Colotal *Agis, Israel.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal disorders.

Coloxyl
Note. This name is used for preparations of different composition.
Fawns & McAllan, Austral.; Sigma, NZ.
Enema; tablets: Docusate sodium (p.1725·1).
Bowel evacuation; bowel evacuation (enema); constipation.

Fawns & McAllan, Austral.; Sigma, NZ.
Oral drops: Poloxamer 188 (p.1918·1).
Constipation; faecal softener.

Fawns & McAllan, Austral.; Sigma, NZ.
Suppositories: Docusate sodium (p.1725·1); bisacodyl (p.1710·1).
Bowel evacuation; constipation; faecal softener.

Coloxyl with Senna *Fawns & McAllan, Austral.; Pharmaco, NZ.*
Docusate sodium (p.1725·1); sennosides (p.1769·3).
Constipation.

Colpagex N *Marjan, Braz.*
Neomycin sulfate (p.305·1); tyrothricin (p.358·2); nystatin (p.543·2); sodium propionate (p.545·3); boric acid (p.2268·1).
Vulvovaginal infections.

Colpatrin *Teuto, Braz.*
Metronidazole (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1).
Vulvovaginal infections.

Colpermin *Germania, Austria; Medimport, Cz.; Faran, Gr.; Tillotts, Hong Kong; Pfizer Consumer, Irl.; Tillotts, Israel; Schering-Plough, Mex.†; Tillotts, Singapore; Tillotts, Switz.; Tillotts, Thai.; Adeka, Turk.; Pfizer Consumer, UK.*
Peppermint oil (p.1761·2).
Abdominal pain; bloating; irritable bowel syndrome.

Colphen *Adcock Ingram, S.Afr.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); sodium salicylate (p.124·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); cetylpyridinium chloride (p.1635·1).
Coughs.

Colpica *Tropica Mas, Indon.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Colpist *Ativus, Braz.*
Metronidazole benzoate (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1).
Vulvovaginal infections.

Colpistar *Farmoquimica, Braz.*
Vaginal cream: Metronidazole (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1); muramidase (p.2348·1).
Vulvovaginal infections.

Colpistatin *Ache, Braz.*
Metronidazole benzoate (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1).
Vulvovaginal infections.

Colpixol *Lundbeck, S.Afr.*
Zuclopenthixol acetate (p.1040·3).
Psychoses.

Colpocin-T *Demo, Gr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Colpo-Cleaner *Dolhay, Hung.*
Povidone-iodine (p.1659·2).
Vaginitis.

Colpoestriol *Temis, Arg.*
Estriol (p.2101·1).
Urinary incontinence; vulvovaginal disorders.

Colpofilin *Lazar, Arg.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Colpogyn *Angelini, Ital.*
Estriol (p.2101·1).
Cervical erosion; menopausal disorders.

Colpolase
Note. This name is used for preparations of different composition.
De Mayo, Braz.
Topical solution: Neomycin sulfate (p.305·1); tyrothricin (p.358·2); hydroxyquinoline sulfate (p.2323·1); lactic acid (p.2329·3); menthol (p.2340·1).
Vulvovaginal infections.

De Mayo, Braz.
Vaginal capsules; vaginal cream: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); nystatin (p.543·2); tinidazole (p.848·3).
Vulvovaginal infections.

Colposeptine *Theramex, Cz.†; Merck-Theramex, Hong Kong; Merck, Turk.*
Chlorquinaldol (p.242·3); promestriene (p.2127·3).
Colpitis; gonorrhoea; leucorrhoea; vaginal disorders.

Colpotrofin *BOI, Spain.*
Promestriene (p.2127·3).
Vulvovaginal disorders.

Colpotrofina *Gentek, Venez.†.*
Promestriene (p.2127·3).
Vaginal disorders.

Colpotrofine *Nycomed, Braz.*
Promestriene (p.2127·3).
Menopausal disorders.

Colpotrophine *Merck, Arg.; Theramex, Cz.†; Merck-Theramex, Hong Kong; Theramex, Ital.; Merck, Mex.; Theramex, Port.; Merck, Singapore; Vifor, Switz.; Merck, Turk.*
Promestriene (p.2127·3).
Vulvovaginal disorders.

Colpradin *Biomep, Mex.*
Pravastatin (p.1375·1).
Hypercholesterolaemia.

Colprin *Ronava, Venez.†.*
Paracetamol (p.108·1).
Fever; pain.

Colpro *Wyeth Lederle, Belg.†; Wyeth, S.Afr.†; Wyeth, Spain†; Wyeth, Switz.†.*
Medrogestone (p.2113·1).
Benign breast disorders; endometriosis; functional uterine bleeding; infertility; menopausal disorders; menorrhagia; menstrual disorders; prostatic hyperplasia.

Colpron *Wyeth Lederle, Austria.*
Medrogestone (p.2113·1).
Hormone replacement therapy; menorrhagia; secondary amenorrhoea.

Colprone *Biodim, Fr.; Wyeth, Hong Kong†; Wyeth Lederle, Ital.†.*
Medrogestone (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; fibroids; functional uterine bleeding; infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Colpuril *Nova Argentia, Arg.*
Allopurinol (p.552·2); colchicine (p.556·1).
Gout; hyperuricaemia.

Colsanac *Pierre Fabre, Port.*
Lactulose (p.1738·2).
Constipation; hepatic coma; hepatic encephalopathy.

Colsancetine *Sanbe, Indon.*
Chloramphenicol (p.239·3), chloramphenicol palmitate (p.239·3), or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Colser *Serral, Mex.*
Bezafibrate (p.1232·1).
Hypercholesterolaemia.

Colsor
Note. This name is used for preparations of different composition.
Seng, Thai.
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Pickles, UK.
Phenol (p.1656·1); menthol (p.2340·1); tannic acid (p.2394·3).
Herpes labialis.

Colsprin *Reckitt Benckiser, India.*
Aspirin (p.20·3).
Prophylaxis of cerebrovascular disorders or myocardial infarction after by-pass surgery.

Colstat *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); atropine sulfate (p.1219·3).
Cold and influenza symptoms.

Coltalin with Vit B_1 *Fortune, Hong Kong†.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); vitamin B_1 (p.1976·3).
Respiratory-tract disorders.

Colther *Farmamust, Gr.*
Tobramycin (p.354·1).
Eye infections.

Coltix *Medical, Arg.†.*
Salicylic acid (p.1612·2); resorcinol (p.1612·1); lactic acid (p.2329·3); benzocaine (p.1854·1).
Calluses.

Coltramyl *Sanofi-Aventis, Fr.; Korangi, Port.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Coltrax *Sanofi-Aventis, Braz.; Sanofi-Aventis, Venez.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Colufase *Columbia, Mex.†.*
Sodium benzoate (p.1630·2).
Hyperammonaemia.

Columbia Antiseptic Powder *Sturtevant, USA.*
Zinc oxide (p.1621·2); talc (p.1615·2); phenol (p.1656·1); boric acid (p.2268·1).

Columina *Columbia, Mex.†.*
Cimetidine (p.1716·2).

Colutoide *Cimed, Braz.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1); bismuth sodium tartrate (p.1712·1); procaine hydrochloride (p.1869·1).
Mouth and throat disorders.

Colval *Valmor, Venez.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Colvan
Note. This name is used for preparations of different composition.
Dynamic, Philipp.
Capsules: Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Colds; coughs.

Dynamic, Philipp.
Oral drops; syrup: Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold symptoms; nasal congestion; rhinitis; sinusitis.

Colvastina *Farmoz, Port.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Colver *Farmochimica, Ital.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Coly-Mycin M *Link, Austral.; Erfa, Canad.; Pfizer, NZ†; Monarch, USA.*
Colistimethate sodium (p.256·3).
Bacterial infections.

Coly-Mycin S Otic *King, USA.*
⊗ Colistin sulfate (p.256·2); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); tonzonium bromide (p.2403·2).
Bacterial ear infections.

Colypan *Farma, Venez.*
Trimebutine maleate (p.2404·3).
Dyspepsia; irritable bowel syndrome.

CoLyte *Pharmascience, Canad.; Schwarz, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Colza *Bintang Toedjoe, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Cold and influenza symptoms.

Comafusin Hepar *Baxter, Ger.; Kalbe, Indon.*
Amino-acid, vitamin, and electrolyte infusion with xylitol (p.1922·1).
Hepatic coma; hepatic insufficiency.

Comagis *Agis, Israel.*
⊗ Bifonazole (p.527·3); fluocinonide (p.1532·1).
Infected skin disorders.

Comarol *Sanofi-Aventis, Pol.*
Diphenhydramine hydrochloride (p.577·2); lidocaine hydrochloride (p.1862·3).
Skin irritation.

Comat *Milano, Thai.*
Clotrimazole (p.530·1).
Fungal and bacterial vaginal infections; trichomoniasis.

Combacid N *Streuli, Switz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity.

Combactam *Pfizer, Austria; Pfizer, Ger.*
Sulbactam sodium (p.335·1).
Adjunct to beta-lactam antibiotics; bacterial infections.

Combactan *Bergamo, Braz.*
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Combact-HIB *Aventis, S.Afr.*
An adsorbed diphtheria, tetanus, pertussis and haemophilus influenzae conjugate vaccine (p.2211·1).
Active immunisation.

Combair *Torrex Chiesi, Cz.*
⊗ Beclometasone dipropionate (p.1516·2); formoterol fumarate (p.1122·1).
Asthma.

CombAmox *Arcana, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Combanal *Etifar, Venez.†.*
Dipyrone (p.49·2).
Fever; pain.

Combantrin *Pfizer Consumer, Austral.; Infectopharm, Austria; Pfizer Consumer, Canad.; Pfizer, Chile; Teofarma, Fr.; Pfizer, Gr.†; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Israel†; Pfizer, Ital.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer Consumer, S.Afr.; Pfizer, Venez.*
Pyrantel embonate (p.155·1).
Worm infections.

Combantrin-1 *Pfizer, NZ.*
Mebendazole (p.148·3).
Worm infections.

Combantrin-1 with Mebendazole *Pfizer Consumer, Austral.*
Mebendazole (p.148·3).
Worm infections.

Combantrin-A *Pfizer, India.*
Albendazole (p.139·2).
Worm infections.

Combar *Stada, Denm.*
Mirtazapine (p.409·2).
Depression.

Combaren *Novartis, Ger.; Novartis, Venez.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Inflammation; pain.

Combaron *Etifar, Venez.†.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Combes *Meprofarm, Indon.*
Poliglusam (p.2370·1); garcinia cambogia (p.2309·2); levocarnitine; chromium tripicolinate; ubidecarenone; ascorbic acid (p.1922·1).
Weight reduction.

Combetasi *Kedrion, Ital.†.*
Vitamin B substances (p.1922·1).
Tonic.

ComBgen *Ethex, USA.*
Vitamin B ; vitamin B ; folic acid (p.1922·1).

Combi *Farmanic, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Infected skin disorders.

Combi Flu *Combiphar, Indon.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); phenylpropanolamine (p.1569·2).
Cold and influenza symptoms.

Combi-Cal *Asta Medica, Thai.†.*
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Combicef *Combiphar, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Combicetin *Combiphar, Indon.*
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Combicid
Note. This name is used for preparations of different composition.
Bilim, Thai.†; TTN, Thai.†.
Sultamicillin tosilate (p.344·1).
Bacterial infections.

Bilim, Turk.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Bilim, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Combicitrine *Berlico Mulia, Indon.*
Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Combid *GSK, Thai.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Combiderm
Note. This name is used for preparations of different composition.
Convatec, Austral.†.
Hydrocolloid dressing.
Skin ulcers; wounds.

Kalbe, Singapore.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Combiflam *Aventis, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Combiflex
Note. This name is used for preparations of different composition.
Braun, Indon.
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Breckenridge, USA.
Paracetamol (p.108·1); salicylamide (p.121·2); caffeine (p.1116·3); phenyltoloxamine citrate (p.588·1).
Pain.

Combiflex ES *Breckenridge, USA.*
Paracetamol (p.108·1); magnesium salicylate (p.79·2); caffeine (p.1116·3); phenyltoloxamine citrate (p.588·1).
Pain.

Combifusin *Baxter, Ger.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Combigan *Allergan, Arg.; Allergan, Austral.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Cz.; Alvia (Αλβια), Gr.; Allergan, Hung.; Allergan, Irl.; Allergan, NZ; Allergan, Port.; Allergan, Switz.; Allergan, UK; Allergan, USA.*
⊗ Brimonidine tartrate (p.1878·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Combigan-D *Allergan, Mex.*
⊗ Brimonidine tartrate (p.1878·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

CombiKids *Sandoz, Philipp.*
Syrup, rifampicin (p.325·3) (Rimactane); oral suspension, pyrazinamide (p.320·2) (PZA-Ciba); syrup, isoniazid (Nicetal) (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in the Nicetal syrup for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Combilax
Note. This name is used for preparations of different composition.
Mundipharma, Austral.
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Constipation.

KG, Ital.
Lactulose (p.1738·2); senna (p.1769·2); cascara (p.1715·2); vitamin B substances (p.1922·1).
Gastrointestinal disorders.

Combi-Methoxan *Ad-Drugstel, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Combina *Omega, Irl.*
Test for glucose, ketones, nitrates, pH, specific gravity, bilirubin, urobilinogen, protein, and blood in urine.

Combina 2 *Omega, Irl.*
Test for glucose and ketones in urine.

Combina 3 *Omega, Irl.*
Test for glucose, pH, and protein in urine.

Combina Glucose *Omega, Irl.*
Test for glucose in urine (p.2314·1).

Combinacion PI *Pisa, Mex.†.*
Glucose (p.1945·3); electrolytes (p.1667·1).

Combinacion Rubin-Calcagno *Pisa, Mex.†.*
Electrolyte infusion (p.1667·1).

Combined *Gador, Arg.†.*
Olanzapine (p.1012·1); fluoxetine hydrochloride (p.391·2).
Bipolar disorder.

Combinovita *Sedabel, Braz.†.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).
Tonic.

Combinplex *Hua, Thai.*
Vitamin B substances (p.1922·1).
Vitamin supplement.

CombiPack *Sandoz, Philipp.*
1 Tablet, rifampicin (p.325·3); 1 tablet, isoniazid (p.288·1); 3 tablets, pyrazinamide (p.320·2).
Tuberculosis.

CombiPatch *Novartis, USA.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders.

Combiplasmal *Braun, Ger.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Combiplex *Berlico Mulia, Indon.*
Thiamine hydrochloride; riboflavin; pyridoxine hydrochloride; nicotinamide; calcium pantothenate (p.1922·1).
Vitamin B deficiency.

Combipres *Boehringer Ingelheim, USA†.*
⊗ Clonidine hydrochloride (p.1247·1); chlortalidone (p.1243·3).
Hypertension.

Combipresan *Boehringer Ingelheim, Ger.†.*
⊗ Clonidine hydrochloride (p.1247·1); chlortalidone (p.1243·3).
Hypertension.

Combipul *Cipla, Philipp.*
⊗ Ipratropium bromide (p.1124·1); salbutamol (p.1131·2).
Obstructive airways disease.

Combirex *Ipca, India†.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Combirice *Baldacci, Ital.*
Rice flour; maltodextrin; sodium citrate; sodium chloride; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration.

Combiron *Ache, Braz.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Combisartan *Menarini, Ital.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Combiseven *Bracco, Ital.*
Patch 1, estradiol (p.2097·2); patch 2, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Combistix *Bayer, USA.*
Test for pH, protein, and glucose in urine.

Combithyrex *Sandoz, Austria.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Hypothyroidism.

Combivent *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease.

Combivir *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Combivite *SA Druggists Self Med, S.Afr.*
Multivitamin preparation (p.1922·1).

Combivitol *Lannacher, Austria.*
Multivitamin preparation (p.1922·1).

Combizar *Therapharma, Philipp.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Combizym
Note. This name is used for preparations of different composition.
Sankyo, Austria; Sankyo, Fin.; Sankyo, Ger.†; Sankyo, Hong Kong; Sankyo, Hung.†; Sankyo, Ital.†; Wilson, NZ†; Will-Pharma, Neth.; Sankyo, Norw.; Sankyo, Pol.; Sankyo, Port.; Selena, Swed.; Medinova, Switz.; Medinova, Thai.
Pancreatin (p.2360·1); enzymes from *Aspergillus oryzae*.
Cystic fibrosis; digestive disorders; meteorism; pancreatic insufficiency.

Sanofi Synthelabo, Chile†.
Digestive enzymes; bile salts (p.2266·2).
Digestive disorders.

Combizym Compositum *Sankyo, Austria; Silesia, Chile; Sankyo, Cz.; Sankyo, Fin.; Sankyo, Ger.†; Sankyo, Hung.†; Sankyo, Port.†; Selena, Swed.; Medinova, Switz.; Medinova, Thai.*
Pancreatin (p.2360·1); enzymes from *Aspergillus oryzae*; ox bile (p.2266·3).
Digestive disorders; meteorism; pancreatic insufficiency.

Combizym Composto *Sankyo, Braz.†.*
Enzymes from *Aspergillus oryzae*; pancreatin (p.2360·1).

Combizym Forte *Sankyo, Venez.*
Enzymes from *Aspergillus oryzae*; pancreatin (p.2360·1); ox bile (p.2266·3).
Liver and bile disorders; pancreatic insufficiency.

Combudoron
Note. This name is used for preparations of different composition.
Weleda, Ger.; Weleda, S.Afr.; Weleda, Switz.
Arnica (p.2260·2); urtica (p.2409·3).
Burns; insect bites; insect stings; skin irritation.

Weleda, UK.
Homoeopathic preparation.

Combunex *Lupin, India.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Tuberculosis.

Combunox *Forest Laboratories, USA.*
⊗ Oxycodone hydrochloride (p.106·2); ibuprofen (p.64·2).
Pain.

Combur 3 *Roche Diagnostics, Irl.*
Test for pH, protein, and glucose in urine.

Combur 7 *Roche Diagnostics, Irl.*
Test for pH, protein, glucose, ketones,leucocytes, nitrite, and blood in urine.

Combur 8 *Roche Diagnostics, Irl.†.*
Test for nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, and blood in urine.

Combur 9 *Roche Diagnostics, Irl.*
Test for pH, protein, glucose, ketones, leucocytes, nitrite, blood, urobilinogen, and bilirubin in urine.

Combur 10 *Roche Diagnostics, Irl.*
Test for specific gravity, nitrite, pH, leucocytes, protein, glucose, ketones, urobilirubin, and blood in urine.

Combur 4 D *Roche Diagnostics, Irl.†.*
Test for protein, glucose, ketones, and blood in urine.

Combur 5 D *Roche Diagnostics, Fr.; Roche Diagnostics, Irl.*
Test for pH, protein, glucose, ketones, and blood in urine.

Combur Test *Roche Diagnostics, Austral.*
Test for pH, protein, and glucose in urine.

Combur 3 Test *Roche Diagnostics, Fr.*
Test for pH, protein, and glucose in urine.

Combur 7 Test *Roche Diagnostics, Austral.; Roche Diagnostics, Fr.*
Test for pH, protein, glucose, ketones, bilirubin, urobilinogen, and blood in urine.

Combur 8 Test *Roche Diagnostics, Austral.*
Test for ketones, urobilinogen, bilirubin, blood, nitrite, pH, protein, and glucose in urine.

Combur 9 Test *Roche Diagnostics, Austral.*
Test for leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, and blood in urine.

Combur 10 Test *Roche Diagnostics, Austral.; Roche Diagnostics, Fr.*
Test for specific gravity, leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, and blood in urine.

Combur 5 Test D *Roche Diagnostics, Austral.†.*
Test for pH, protein, glucose, ketones, and blood in urine.

Combur 3 Test E *Roche Diagnostics, Austral.†.*
Test for protein, glucose, and blood in urine.

Combur 2 Test LN *Roche Diagnostics, Fr.*
Test for leucocytes and nitrite in urine.

Comburic *Therabel, Belg.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Combustin Heilsalbe *Combustin, Ger.*
Bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); benzocaine (p.1854·1).
Burns; frostbite; haemorrhoids; skin disorders; skin ulceration; wounds.

Combutol *Lupin, India.*
Ethambutol (p.275·2).
Tuberculosis.

Comdasin *Combiphar, Indon.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Acne; gastrointestinal infections.

Comelian *Kowa, Jpn.*
Dilazep hydrochloride (p.1265·1).
Angina pectoris; nephropathy.

Comenter *Raffo, Arg.; Asofarma, Mex.; Nolver, Venez.*
Mirtazapine (p.409·2).
Depression.

Co-Mepril *Kwizda, Austria.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Comfeel
Note. This name is used for preparations of different composition.
Coloplast, Arg.; Coloplast, Fr.; Coloplast, S.Afr.
Carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Coloplast, UK.
Barrier cream.
Peristomal care.

Coloplast, UK.
Medicated dressing: Carmellose sodium (p.2142·1).
Wounds.

Comfeel Plus
Coloplast, Arg.; Coloplast, UK.
Calcium alginate (p.1058·1); carmellose sodium (p.2142·1).
Burns; pressure sores; wounds.

Coloplast, Ger.
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Ulcers; wounds.

Comfeel Plus Transparente *Coloplast, Arg.*
Carmellose sodium (p.2142·1).
Burns; pressure sores; wounds.

Comfeel Plus Transparenter *Coloplast, Ger.*
Carmellose (p.2142·1).
Ulcers; wounds.

Comfeel Purilon *Coloplast, Arg.†.*
Calcium alginate (p.1058·1); carmellose sodium (p.2142·1).
Ulcers; wounds.

Comfeel SeaSorb
Note. This name is used for preparations of different composition.
Coloplast, Arg.†.
Calcium alginate (p.1058·1); sodium alginate (p.2141·1); carmellose sodium (p.2142·1).
Ulcers; wounds.

Coloplast, UK.
Calcium sodium alginate (p.1058·1) (p.2141·1).
Exudating wounds.

Comfort Eye Drops *Pilkington Barnes-Hind, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Minor eye irritation.

Comfort Tears *Pilkington Barnes-Hind, USA.*
Hyetellose (p.2143·3).
Dry eyes.

Comfortcare Dual Action *Allergan, Canad.†.*
Subtilisin (p.2393·3); poloxamer 228 (p.1622·2).
Cleanser for gas permeable contact lenses.

Comfortcare GP *Pilkington Barnes-Hind, USA.*
Disinfecting, wetting, and soaking solution for gas permeable contact lenses (p.1622·2).

Comfortcare Wetting & Soaking *Allergan, Canad.†.*
Wetting and soaking solution for gas permeable contact lenses (p.1622·2).

Comfrelieve *Seven Seas, UK.*
Comfrey (p.2286·3).
Joint pain and inflammation.

Comfrey Plus *Herbal, Israel.*
Comfrey (p.2286·3); allantoin (p.1588·1).
Burns; cuts; insect bites; nappy rash; soft-tissue injury.

Comfy *Polipharm, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); ammonium chloride (p.1551·3).
Cold symptoms; coughs; nasal congestion.

Comhist LA *Procter & Gamble, USA.*
Chlorphenamine maleate (p.571·3); phenyltoloxamine citrate (p.588·1); phenylephrine hydrochloride (p.1568·1).
Nasal congestion; rhinorrhoea.

Co-Micardis *Boehringer Ingelheim, S.Afr.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Comilorid *Mepha, Switz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Comizial *Ogna, Ital.†.*
Phenobarbital (p.492·2).
Chorea; epilepsy.

Commit *GSK, USA.*
Nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

Comoprin *British Dispensary, Thai.†.*
Aspirin (p.20·3).
Fever; pain.

Comosup *Farmasierra, Spain.*
Glycerol (p.2314·2).
Constipation.

Compact Sorb *Esoform, Ital.*
Sodium polyacrylate.
Spillage of biological fluids.

Compagel *Sanofi Synthelabo, Spain†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magaldrate (p.1742·3).
Gastrointestinal hyperacidity.

Compagen *Solfran, Mex.*
Vitamin and mineral preparation (p.1922·1).

Compaser *Aurora, Gr.†.*
Bifonazole (p.527·3).
Fungal skin infections.

Compaz *Cristalia, Braz.*
Diazepam (p.986·3).
Anxiety.

Compazine *SmithKline Beecham, USA.*
Prochlorperazine (p.1020·1), prochlorperazine edisilate (p.1020·1), or prochlorperazine maleate (p.1020·1).
Non-psychotic anxiety; psychoses; severe nausea and vomiting.

Compeedmed *Johnson & Johnson Consumer, Belg.*
Salicylic acid (p.1612·2).

Compendium *Polifarma, Ital.*
Bromazepam (p.964·3).
Anxiety disorders; insomnia.

Compensal *Provit, Mex.*
Cyanocobalamin (p.1980·2).

Compensan *Lannacher, Austria.*
⊗ Morphine hydrochloride (p.86·3).
Opioid withdrawal syndrome.

Competact *Takeda, Cz.; Takeda, Fr.; Lilly, Port.; Takeda, UK.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Compete *Mission Pharmacal, USA.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Complamin
Note. This name is used for preparations of different composition.
Riemser, Ger.
Buflomedil hydrochloride (p.1236·3).
Formerly contained xantinol nicotinate.
Peripheral vascular disorders.

Sanofi-Aventis, Ital.; GSK, Neth.; Doetsch, Grether, Switz.
Xantinol nicotinate (p.1433·1).
Cerebral and peripheral vascular disorders; hypercholesterolaemia.

Complamin spezial *Riemser, Ger.*
Xantinol nicotinate (p.1433·1).
Lipid disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Complamina *German Remedies, India.*
Xantinol nicotinate (p.1433·1).
Cerebral and peripheral vascular disorders.

Complan *Glaxo Wellcome, Mex.†; Heinz-Wattie, NZ; Heinz, UK.*
Preparation for enteral nutrition (p.1922·1).

Compleal *Macanthy, Mon.*
A range of dietary supplements (p.1922·1).

Compleat *Novartis, Arg.†; Novartis, Braz.; Novartis Nutrition, Hong Kong; Sandoz Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).

Complegel Novo *Boehringer Ingelheim, Arg.*
Citicoline (p.2283·3).
Cerebrovascular disorders.

Complejo B *AM, Arg.; Bioresearch, Mex.; Italmex, Mex.; Biogalenic, Venez.; Cofasa, Venez.; Medifarm, Venez.; Spefar, Venez.; Vivax Colmed, Venez.*
Vitamin B substances (p.1922·1).

Complejo B Compositum *Polinac, Venez.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Neuralgia; neuritis.

Complementa *Carlo Erba OTC, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).

Complenatal FF *Pharmaceutical Enterprises, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Complesso B *Carlo Erba OTC, Ital.†.*
Vitamin B substances (p.1922·1).
Vitamin deficiency.

Completax Plus *Silesia, Chile†.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Complete *AMO, UK.*
A range of preparations for contact lens care (p.1622·2).

Complete All-In-One *AMO, Canad.*
A cleansing, rinsing, disinfecting and lubricating solution for soft contact lenses (p.1622·2).

Complete Comfort Plus *Visiontech, Arg.; Allergan, Braz.†; Advanced Medical Optics, NZ.*
Preparation for contact lens care (p.1622·2).

Complete Moisture Plus *Amo, Arg.; Visiontech, Arg.*
Disinfectant solution for contact lenses (p.1622·2).

Complete Multi Pre- and Post-Natal *Wampole, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Complete Multi-Adult *Wampole, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Complete Protein Remover *AMO, Austral.; Allergan, Canad.†.*
Subtilisin A (p.2393·3) (p.1622·2).
Protein remover for soft contact lenses.

Complete Solution *AMO, Austral.*
Cleaning, rinsing, disinfecting, storage, and lubricating solution for soft contact lenses (p.1622·2).

Completia *Nature's Way, Philipp.*
Vitamins; minerals; docosahexaenoic acid; peppermint oil; raspberry leaf; taraxacum; urticaria; peppermint leaf; diatomaceous plant; inositol, choline bitartrate (p.1922·1).
Prenatal supplement.

Compleven
Note. This name is used for preparations of different composition.
Fresenius Kabi, Austria†; Fresenius Kabi, Fin.†; Fresenius Kabi, Ger.†; Fresenius Kabi, Pol.; Fresenius Kabi, Swed.†; Fresenius Kabi, UK†.
Amino-acid, glucose, lipid (from soya oil (p.1965·3)), and electrolyte infusion (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Fresenius Kabi, Gr.; Fresenius Kabi, Port.†; Fresenius Kabi, Switz.
Amino acid and carbohydrate infusion (p.1922·1).
Parenteral nutrition.

Complevit
Note. This name is used for preparations of different composition.
EMS, Braz.
Buclizine (p.570·1); gamma-aminobutyric acid (p.2308·1).
Reduced appetite; tonic.

Pharma Investi, Chile.
Vitamin and mineral preparation (p.1922·1).

Complevit Pediatrico *Pharma Investi, Chile.*
Vitamin preparation (p.1922·1).

Complevitan *Bunker, Braz.*
Vitamin B substances (p.1922·1).

Complex 15
Note. This name is used for preparations of different composition.
Schering-Plough, Canad.†.
Dimeticone (p.2032·1); lecithin (p.2332·2).
Emollient.

Schering-Plough, USA.
Emollient and moisturiser.

Complex ADC *Plata, Arg.*
Vitamins A, C, and D (p.1922·1).
Nutritional supplement.

Complex B *Plata, Arg.*
Vitamin B substances; vitamin C (p.1922·1).

Complex B Calcio Y Magnesio *Plata, Arg.*
Vitamin B substances; vitamin C; calcium carbonate; magnesium oxide (p.1922·1).
Nutritional supplement.

Complexe Assistance *Deva, Fr.*
Clematis; star of Bethlehem; sunflower; impatiens; lotus; prunus.
Stress.

Complexe B Compose *Bio-Sante, Canad.*
Vitamin B substances (p.1922·1).

Complexe *Lehning, Fr.*
A range of homoeopathic preparations.

Compleximed B *Globo, Braz.†.*
Vitamin B substances (p.1922·1).

Compleximed B+C *Globo, Braz.†.*
Multivitamin preparation (p.1922·1).

Complexo B *Bayer, Braz.; EMS, Braz.; Roche, Braz.; Basi, Port.†.*
Vitamin B substances (p.1922·1).

Complidermol *Medea, Spain†.*
Multivitamins and amino acids (p.1922·1); inositol (p.2325·2).
Skin disorders.

Complivit *Farmstandart, Rus.*
Vitamin and mineral preparation (p.1922·1).

Comploment Continus *SSL, Irl.; Mundipharma, Switz.†.*
Pyridoxine hydrochloride (p.1978·2).
Premenstrual syndrome; vitamin B deficiency.

Complutine *Novartis Consumer, Spain.*
Diazepam (p.986·3).
Contains pyridoxine hydrochloride.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Comply *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Composto Anticelulitico *Infabra, Braz.†.*
Ginkgo biloba (p.2311·1); bearberry (p.2263·3); bladderwrack (p.2384·2); centella (p.1592·3).

Composto Emagrecedor *Viternat, Braz.†.*
Cynara (p.2291·2); bladderwrack (p.2384·2); centella (p.1592·3); dried yeast (p.1998·3); passion flower (p.2363·2); cascara (p.1715·2).
Slimming aid.

Compound Inhalation of Menthol *McGloin, Austral.*
Menthol (p.2340·1); siberian fir oil; creosote (p.1555·1).
Cold symptoms.

Compound W *Medtech, Canad.; SSL, Irl.; SA Druggists Self Med, S.Afr.; SSL, UK; Medtech, USA.*
Salicylic acid (p.1612·2).
Hyperkeratosis; verrucas; warts.

Compound W Freeze Off *Medtech, USA.*
Dimethyl ether (p.1689·2); propane (p.1691·3); isobutane (p.1690·1).
Warts.

Compound W Plus *Medtech, Canad.*
Salicylic acid (p.1612·2).
Warts.

Compoz Night-time Sleep Aid *Medtech, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Compral *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Compralgyl *Gifrer Barbezat, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Formerly contained aspirin and codeine phosphate.
Fever; pain.

Compraz *Combiphar, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Comprilex *Pediatrica, Philipp.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Comprimes a croquer Estomac *Zeller, Switz.*
Calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1).
Dyspepsia; gastric hyperacidity; meteorism.

Comprimes analgesiques "S" *Synpharma, Switz.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); propyphenazone (p.119·3).
Fever; pain.

Comprimes contre la toux *Zeller, Switz.†.*
Ivy (p.2328·1).
Bronchial disorders with viscous mucus.

Comprimes somniferes "S" *Synpharma, Switz.*
Diphenhydramine (p.577·1).
Agitation; insomnia; nervousness.

Compro *Paddock, USA.*
Prochlorperazine (p.1020·1).
Nausea and vomiting.

Computer Eye Drops *Bausch & Lomb, Hong Kong; Bausch & Lomb, Philipp.; Bausch & Lomb, USA†.*
Glycerol (p.2314·2).
Dry eyes; eye irritation.

Comsikla *Combiphar, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Comsporin *Combiphar, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Comstrong *Unison, Thai.*
Vitamin B substances (p.1922·1).
Vitamin supplement.

Comtan *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, USA; Novartis, Venez.*
Entacapone (p.804·1).
Parkinsonism.

Comtaplex *Greater Pharma, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Comtess *Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Orion, Irl.; Orion, Neth.; Orion, Norw.; Orion, Port.; Orion, Swed.; Orion, UK.*
Entacapone (p.804·1).
Parkinsonism.

Comthycol *Combiphar, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Comtrex *Bristol-Myers Products, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Comtrex Acute Head Cold *BMS, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Comtrex Allergy-Sinus *Bristol-Myers Products, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Comtrex Cold *BMS, Gr.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); chlorphenamine (p.572·2).
Cold symptoms.

Comtrex Day & Night Maximum Strength *Bristol-Myers Products, USA.*
Orange caplets, dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); blue tablets, dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Comtrex Day & Night Multi-Symptom *Bristol-Myers Products, USA.*
Orange caplets, dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); yellow tablets, dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Comtrex Day/Night Flu Therapy *BMS, USA.*
Day caplets, pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night caplets, pseudoephedrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Formerly known as Comtrex Flu Therapy & Fever Relief Day & Night Multi-Symptom.
Upper respiratory-tract disorders.

Comtrex Hot Flu Relief *Bristol-Myers Products, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Comtrex Maximum Strength Night-time Cold & Cough *BMS, USA.*
Dextromethorphan (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Comtrex Maximum Strength Sore Throat *BMS, USA.*
Paracetamol (p.108·1).
Sore throat.

Comtrex Multi-Symptom Deep Chest Cold *BMS, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Comtrex Sinus & Nasal Decongestant *BMS, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Comtro *Combiphar, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Comtusi *Combiphar, Indon.*
Oxomemazine (p.587·1); guaifenesin (p.1561·3).
Cough.

Comvax *CSL, Austral.; MSD, Mex.; MSD, NZ; Merck, USA.*
A haemophilus influenzae and hepatitis B vaccine (p.2213·3).
Active immunisation; active immunisation in infants.

Comvita C *Interbat, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Nutritional supplement.

Comvita C Plus *Interbat, Indon.*
Vitamin B substances; ascorbic acid; vitamin A; vitamin D (p.1922·1).
Nutritional supplement.

Comvufen *Precimex, Mex.*
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; pre-eclampsia.

Con Con *Hua, Thai.*
Salicylic acid (p.1612·2); liquefied phenol (p.1656·1).
Corns; warts.

Conacid *Purissimus, Arg.*
Folic acid (p.1940·1).
Anaemias; prevention of neural tube defects.

Conal *Cypress, USA.*
Chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Nasal congestion.

Conamed *Bajamed, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Conamic *Pharmasant, Thai.*
Mefenamic acid (p.80·1).
Inflammation; musculoskeletal and joint disorders; pain.

Conan *Mitsubishi, Jpn.*
Quinapril hydrochloride (p.1382·2).
Hypertension.

Conasol *Actavis, Denm.*
Fluconazole (p.532·1).
Fungal infections.

Conazine *Condrugs, Thai.*
Perphenazine (p.1017·1).
Anxiety; nausea and vomiting.

Conazol
Note. This name is used for preparations of different composition.
Alet, Gr.
⊗ Miconazole nitrate (p.541·3); fluprednidene acetate (p.1533·1).
Infected skin disorders.

Liomont, Mex.
Ketoconazole (p.539·1).
Fungal infections.

Conazole *DHA, Hong Kong; DHA, Singapore.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Conbutol *Continental-Pharm, Thai.†.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Concatag *Lafedar, Arg.*
Neomycin sulfate (p.305·1).
Bacterial eye infections.

Concavit *Wallace Mfg Chem., UK.*
Multivitamin preparation (p.1922·1).

Conceive Ovulation Predictor *Quidel, USA†.*
Fertility test (p.2372·1).

Conceive Pregnancy *Quidel, USA.*
Pregnancy test (p.2372·1).

Concentrado Acido *Reccius, Chile.*
Sodium chloride; calcium chloride; magnesium chloride; potassium chloride; acetic acid; glucose (p.1670·3).
Haemodialysis.

Concentrado Basico *Reccius, Chile.*
Sodium chloride (p.1686·1); sodium bicarbonate (p.1673·2).
Haemodialysis.

Concentrated Cleaner *Bausch & Lomb, NZ†.*
Cleaning solution for contact lens care (p.1622·2).

Concentrated Milk of Magnesia-Cascara *Roxane, USA.*
Magnesium hydroxide (p.1743·2); cascara (p.1715·2).

Concentrin *CT, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Conceplan M *Grunenthal, Ger.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Combined oral contraceptive.

Concepnor *Neo Quimica, Braz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Concept *Sea-Band, UK.*
Pregnancy test (p.2372·1).

Concerta *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; McNeil Pharmaceutical, USA; Janssen-Cilag, Venez.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Conchae comp. *Weleda, UK.*
Homoeopathic preparation.

Concor *Merck, Arg.; Merck, Austria; Merck, Braz.; Merck, Chile; Merck, Cz.; Merck, Ger.; Merck, Hong Kong; Merck, Hung.; Merck, India; Merck, Indon.; Merck, Israel; Bracco, Ital.; Merck, Malaysia; Merck, Mex.; Merck, Pol.; Merck, Port.; Merck, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Switz.; Merck, Thai.; Santa, Turk.; Merck, Venez.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; anxiety; aortic aneurysm; arrhythmias; heart failure; hypertension; hyperthyroidism; ischaemic heart disease; myocardial infarction; obstructive cardiomyopathy.

Concor Cor *Merck, Cz.; Merck, Hung.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Concor Plus *Merck, Austria; Merck, Cz.†; Merck, Ger.; Merck, Hung.; Merck, Port.; Merck, Switz.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Concore *Merck, Philipp.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure; hypertension.

Condep *Duopharma, Malaysia.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer; endometriosis; progestogen-only injectable contraceptive; renal cancer.

Condiabet *Armoxindo, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Conditioning Solution *Bausch & Lomb, NZ†.*
Chlorhexidine gluconate (p.1635·3); disodium edetate (p.1463·3) (p.1622·2).
Soaking and wetting of contact lens.

Condiuren *Gentili, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Condral
Note. This name is used for preparations of different composition.
SPA, Cz.; SPA, Pol.
Chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.
SPA, Ital.
A heparinoid (p.1305·2).
Osteoarthritis; pain.

Condress *Abiogen, Ital.*
Collagen (p.2286·1).
Cicatrisation of wounds and skin ulcers.

Condro San *Bioiberica, Spain.*
Chondroitin sulfate (p.2280·3).
Osteoarthritis.

Condro Sorb *Andromaco, Chile†.*
Chondroitin sulfate (p.2280·3).
Osteoarthritis; rheumatoid arthritis.

Condrocaps *Geymonat, Ital.*
Collagen; mucopolysaccharides; vitamins; minerals (p.1922·1).
Nutritional supplement.

Condrodin *Bioiberica, Spain†.*
Chondroitin sulfate (p.2280·3).
Osteoarthritis.

Condrofer *UCB, Ital.†.*
Chondroitin sulfate A-iron complex (p.1934·2).
Iron deficiency; iron deficiency anaemias.

Condroflex *Zodiac, Braz.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.

Condroitina *Dominguez, Arg.†.*
Chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.

Condrosamina *Andromaco, Chile†.*
Chondroitin sulfate (p.2280·3); glucosamine hydrochloride (p.2313·2).
Osteoarthritis; rheumatoid arthritis.

Condrosulf *Pharmacia, Arg.†; Sanova, Austria; Labomed, Chile; IBSA, Cz.; IBSA, Hung.; CORNE, Mex.; IBSA, Port.; Farma Lepori, Spain; IBSA, Switz.*
Chondroitin sulfate sodium (p.2280·3).
Degenerative joint disorders; osteoarthritis.

Conducat *Baxter, Mex.†.*
Magnesium sulfate (p.1679·3).

Conducil *Dollder, Venez.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction.

Conductasa *Teofarma, Spain.*
Pyridoxine oxoglurate (p.1979·1).
Vitamin B6 deficiency.

Conducton *Fujisawa, Austria†; Fujisawa, Ger.†.*
⊗ Carazolol (p.1240·3).
Angina pectoris; arrhythmias; cardiac disorders; heart failure; hypertension; myocardial infarction.

Condugesic *IFET (ΙΦΕΤ), Gr.†.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Condyline *Hamilton, Austral.; Canderm, Canad.; Galderma, Denm.; Galderma, Fin.; Astellas, Fr.; Nycomed, Hung.; Newport, Irl.; Nycomed, Irl.; Astellas, Ital.; CSL, NZ; Yamanouchi, NZ; Astellas, Neth.; Galderma, Norw.; Astellas, Pol.; Astellas, Port.; Yamanouchi, Rus.; Galderma, Swed.; Nycomed, Switz.; Ardern, UK.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Condylox *Gerot, Austria; Wolff, Ger.; Agis, Israel; Oclassen, USA.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Conectol *Ivax, Arg.†.*
⊗ Aniracetam (p.363·2).
Mental function impairment.

Conef *Defuen, Arg.†.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Conevit *Loren, Mex.†.*
Vitamin preparation with lysine and iron (p.1922·1).

Conexine
Note. This name is used for preparations of different composition.
Beta, Arg.
Memantine hydrochloride (p.367·1).
Alzheimer's disease; mental function impairment; spasticity.
Nolver, Venez.
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Confer *Merck, Chile.*
Ferrous fumarate; folic acid; cyanocobalamin (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Dietary supplement.

Conferma 3 Plus *Sanofi-Aventis OTC, Ital.*
Pregnancy test (p.2372·1).

Confetti Lassativi CM *Giuliani, Ital.*
Senna (p.1769·2); boldo (p.2267·2); cascara (p.1715·2).
Constipation.

Confetto CM *Falqui, Ital.*
Bisacodyl (p.1710·1).
Constipation.

Confetto Falqui *Montefarmaco, Cz.†.*
Phenolphthalein (p.1762·1).
Constipation.

Confiance *Helsinn, Port.†; Wassen, UK.*
Multivitamin and mineral preparation (p.1922·1).

Confiance Donna *Wassen, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Confidelle Progress *Bouty, Ital.*
Pregnancy test (p.2372·1).

Confirm *Durex, Canad.*
Pregnancy test (p.2372·1).

Confit *Procter & Gamble, Austria.*
⊗ Verapamil hydrochloride (p.1421·1); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Confludin N *Truw, Ger.*
Homoeopathic preparation.

Confobos *Smaller, Spain.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Conforgel *Grin, Mex.*
Carbomer (p.2141·3).
Dry eyes.

Conformal *Ivax, Arg.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; trigeminal neuralgia.

Conformil *Milupa, Port.†.*
Infant feed (p.1922·1).
Milk intolerance.

Confor-Tar *ICN, Arg.†.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2); coal tar (p.1616·2).
Skin disorders.

Confortel *Forder, Arg.†.*
Levomenol (p.2333·3); pilewort (p.2368·1).
Skin disorders.

Confortid
Alpharma, Denm.; Alpharma, Norw.
Indometacin (p.66·3) or indometacin sodium (p.66·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain; renal and biliary colic.
Alpharma, Fin.; Alpharma, Swed.
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; renal and biliary colic.
Alpharma-Isis, Ger.
Indometacin sodium (p.66·3).
Renal and biliary colic.

Confosept Zuurstofwater *Conforma, Belg.*
Hydrogen peroxide (p.1647·3).
Disinfection.

Congen *Jean-Marie, Philipp.*
Crotamiton (p.1593·2).
Insect bites and stings; pruritus; scabies.

Congescor *Merck, Ital.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Congest *Trianon, Canad.*
Conjugated oestrogens (p.2087·2).
Oestrogen therapy.

Congest Aid *Zee, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).

Congestac *Ascher, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Congestaid *Zee, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Congestant *Rugby, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Congestex *Pediapharm, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); noscapine (p.1566·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Congestril (Reformulated) *Roddensers, Philipp.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

Congex *Buxton, Arg.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Congox *Wermar, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Conidrin *Arrow, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); mepyramine maleate (p.585·2).
Nasal congestion.

Coniel *Kyowa, Jpn; Kyowa Hakko, Philipp.*
Benidipine hydrochloride (p.1224·3).
Angina pectoris; hypertension.

Conjugen *Fujisawa, Austria†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Conjuncain-EDO *Mann, Ger.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Conjunctilone *Allergan, Port.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Conjunctilone-S *Allergan, Port.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Conjunctisan-A *Vitorgan, Ger.*
Homoeopathic preparation.

Conjunctisan-B *Vitorgan, Ger.*
Homoeopathic preparation.

Conlax *Continental-Pharm, Thai.*
Bisacodyl (p.1710·1).
Constipation.

Conludag *Pfizer, Norw.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Conmag *Pharmasant, Thai.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); kaolin (p.1738·1); menthol (p.2340·1).
Gastric hyperacidity; peptic ulcer.

Conmel *Farmasa, Braz.; Recalcine, Chile; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Port.†; Sanofi-Aventis, Venez.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Conmy *Taiwan Biotech, Philipp.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Conmycin *Armoxindo, Indon.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Connettivina *Kolassa, Austria; Fidia, Hong Kong; Fidia, Ital.; Fidia, Thai.†.*
Sodium hyaluronate (p.2320·1).
Burns; ulcers; varices; wounds.

Connettivina Plus *Fidia, Ital.*
Sodium hyaluronate (p.2320·1); sulfadiazine silver (p.337·2).
Burns; skin ulceration; wound.

Conotrane *Yamanouchi, Irl.†; Astellas, UK.*
Benzalkonium chloride (p.1629·1); dimeticone (p.2032·1).
Barrier cream.

Conpin *TAD, Cz.; TAD, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Conpremin *Wyeth, Chile.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Conpremin Pak *Wyeth, Chile.*
White tablets, conjugated oestrogens (p.2087·2); blue tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Conpremin Pak Plus *Wyeth, Chile.*
28 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Conpres *Ranbaxy, Hung.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Conprim *Condrugs, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Conranin *Armoxindo, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastritis; pathological hypersecretory disorders; peptic ulcer.

Conrax *Fada, Arg.*
Chlorpromazine (p.969·1).
Nausea and vomiting; premedication; psychoses.

Conray
Mallinckrodt, Arg.; Bracco, Ital.†; Mallinckrodt, UK; Mallinckrodt, USA.
Meglumine iotalamate (p.1485·3) or sodium iotalamate (p.1485·3).
Radiographic contrast medium.
Tyco, Canad.
Meglumine iotalamate (p.1485·3).
Radiographic contrast medium.

Conray 30 *Tyco, Ger.†.*
Meglumine iotalamate (p.1485·3).
Radiographic contrast medium.

Conray 60 *Tyco, Ger.†.*
Meglumine iotalamate (p.1485·3).
Radiographic contrast medium.

Conray 280 *Mallinckrodt, Austral.*
Meglumine iotalamate (p.1485·3).
Radiographic contrast medium for urography and angiography.

Consec *Jagson, India.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Consil *Barnes Hind, Arg.*
Polyvinyl alcohol (p.2145·3); chlorhexidine gluconate (p.1635·3) (p.1622·2).
Disinfecting and wetting solution for gas permeable contact lenses.

Consil Clean *Barnes Hind, Arg.*
Miranol; norfox (p.1622·2).
Cleaning of gas permeable contact lenses.

Consinut *Continental-Pharm, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; nasal congestion.

Consolin *Dolisos, Canad.*
Homoeopathic preparation.

Constante *Uniao Quimica, Braz.*
Alprazolam (p.960·1).
Anxiety.

Constilac *Alra, USA.*
Lactulose (p.1738·2).
Constipation.

Constilax *Bros, Gr.*
Norfloxacin (p.309·2).
Urinary tract infections.

Constipal *Plough, Port.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract congestion.

Constipation L106 *Homeocan, Canad.†.*
Homoeopathic preparation.

Constipen *Combiphar, Indon.*
Lactulose (p.1738·2).
Constipation; encephalopathy.

Constriction *Neo Quimica, Braz.*
Dopamine hydrochloride (p.1273·2).

Constrilia *Alcon, Fr.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Constulose *Barre-National, USA.*
Lactulose (p.1738·2).
Constipation.

Consudine *Condrugs, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms; hypersensitivity reactions; nasal congestion; rhinitis.

Consupren *Galena, Cz.†; Ivax, Cz.†; Galena, Rus.; Galena, Thai.; SPB, Thai.*
Ciclosporin (p.1822·2).
Auto-immune disorders; graft-versus-host disease; lupus; nephrotic syndrome; polymyositis; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Contac *GSK, Chile; GSK, Cz.†.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; hay fever; sinusitis.

Contac AM *GSK, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Contac Cold Chest Congestion Non Drowsy *GSK Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Contac Cold & Fever *GSK Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).

Contac Cold + Flu *GSK Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Contac Cold + Flu Day & Night *GSK Consumer, USA.*
Day tablets, phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); night tablets, phenylephrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Contac Cold Nasal Congestion Nondrowsy *GSK Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).

Contac Cold & Sore Throat *GSK Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Contac Cold & Sore Throat Non Drowsy *GSK Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).

Contac Complete Cough Cold and Flu Day & Night *GSK Consumer, Canad.*
Yellow caplets, pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); blue caplets,

diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride; paracetamol.
Cold symptoms.

Contac Day & Night Allergy Sinus *SmithKline Beecham Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).

Contac Day and Night Cold & Flu Caplets *SmithKline Beecham Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Contac Erkaltungs-Trunk *GSK Consumer, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Contac Erkaltungs-Trunk Forte *GSK Consumer, Ger.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; coughs.

Contac Head & Chest Congestion *GSK Consumer, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Contac 12 Hour Allergy *SmithKline Beecham Consumer, USA.*
Clemastine fumarate (p.573·2).

Contac Non Drowsy *GSK Consumer, UK.*
Pseudoephedrine hydrochloride (p.1571·2).
Contac 400 formerly contained chlorphenamine maleate and phenylpropanolamine hydrochloride.
Cold symptoms.

Contac PM *GSK, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Contac Rhume *SmithKline Beecham Consumer, Switz.†.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; hay fever.

Contac Sinus *GSK Consumer, Canad.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Sinus pain and congestion.

Contac Toux *SmithKline Beecham Consumer, Switz.†.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Contac Ultra *GSK, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Rhinitis.

Contac-CC *GSK, India†.*
Phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Coughs; influenza symptoms; nasal congestion; sinusitis.

Contagrin *Grin, Mex.*
Solution for contact lens care (p.1622·2).

Contalax *Omega, Fr.; Fischer, Israel.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Contalgin *Pfizer, Denm.*
⊗ Morphine sulfate (p.86·3).
Pain.

Contaren *Almirall, Belg.†.*
⊗ Canrenone (p.1239·2).
Hypertension; oedema.

Contasoft *Grin, Mex.*
Solution for contact lens care (p.1622·2).

Contefur *Loren, Mex.†.*
Furazolidone (p.834·3); clioquinol (p.254·1); homatropine (p.1881·2); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Contem *Ahimsa, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Contemnol *Zentiva, Cz.†.*
Lithium carbonate (p.401·3).
Bipolar disorder; mania.

Conthram *Pacific, NZ†.*
Dantron (p.1722·2); poloxamer (p.1918·1).
Constipation.

Contiabe *Cazi, Braz.†.*
Vitamin B substances (p.1922·1).

Contiflo *Ranbaxy, Braz.; Ranbaxy, UK.*
Tamsulosin hydrochloride (p.2197·1).

Contigen *Baxter, NZ; Bard, UK.*
Bovine dermal collagen (p.2286·1).
Urinary incontinence.

Contilen *Legrand, Braz.†.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Contimit *Lindopharm, Ger.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Continex *Baliarda, Arg.†.*
Oxybutynin (p.2190·3).

Continuin *Gedeon Richter, Hung.†.*
Etynodiol diacetate (p.2103·2).
Progestogen-only oral contraceptive.

Continukit *Pascual, Philipp.*
1 Tablet, ethambutol hydrochloride (p.274·1) (Ethonah); 1 tablet, isoniazid (p.288·1) (Nyadin); 1 capsule, rifampicin (p.325·3) (Ricyn).
Tuberculosis.

Continukit Plus *Pascual, Philipp.*
1 Tablet, ethambutol hydrochloride (p.274·1); 1 tablet, isoniazid (p.288·1); 1 capsule, rifampicin (p.325·3); 1 tablet, multivitamin and minerals (p.1922·1) (Vitalivin-E).
Tuberculosis.

Continupack *Pascual, Philipp.*
1 Tablet, isoniazid (p.288·1) (Nyadin); 1 capsule, rifampicin (p.325·3) (Ricyn).
Tuberculosis.

Contiphyllin *Lindopharm, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

Contour *Columbia, Arg.†.*
Etofenamate (p.53·1).

Contracep *Sigma, Braz.; TNP, Thai.†.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Contraceptin T *Nizhpharm, Rus.*
Hydroxyquinoline sulfate (p.2323·1); boric acid (p.2268·1); tannic acid (p.2394·3).

Contracer *Instituto Tecnologico PET, Port.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide agent for detection of malignant neoplasms by positron emission tomography.

Contracide *Norgine, Fr.†; Norgine, Ital.†.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); dimeticone (p.1770·2).
Aerophagia; gastrointestinal hyperacidity; meteorism.

Contracne *Biorga, Fr.*
Isotretinoin (p.1599·2).
Acne.

Contra-Coff *Universal, S.Afr.*
Pholcodine (p.1570·2); squill (p.1573·1).
Coughs.

Contractubex *Phoenix, Arg.; Kolassa, Austria; Biolab Sanus, Braz.; Merz, Cz.; Merz, Ger.; Merz, Hong Kong; Merz, Hung.; Win-Medicare, India; Merz, Philipp.; Organon, Philipp.; Merz, Pol.; Merz, Rus.; Merz, Switz.*
Onion (p.2356·3); heparin sodium (p.1301·2) allantoin (p.1588·1).
Contractures; keloids; scars.

Contradol *Gemballa, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Contraforte *Sanochemia, Austria†.*
Propyphenazone (p.119·3); dextropropoxyphene (p.40·1); caffeine (p.1116·3).
Pain.

Contragel Vert *Bivea, Fr.*
Lactic acid (p.2329·3); sodium lactate (p.1673·3).
For use with vaginal contraceptive devices.

Contral *Corsa, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Contralgen *Pietrasanta, Ital.†.*
Paracetamol (p.108·1); aspirin (p.20·3).
Cold and influenza symptoms; fever; pain.

Contralmor *Laboratorios Chile, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); lidocaine (p.1862·3); zinc oxide (p.1621·2).
Anorectal disorders.

Contralum Ultra *Boots Healthcare, Neth.*
Enzacamene (p.1597·1); avobenzone (p.1589·3); sodium 2-phenyl-1*H*-benzimidazole-5-sulfonate (p.1597·1).
Photosensitive skin disorders; sunscreen.

Contram *Armoxindo, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Contramal *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Fr.; Grunenthal, Hung.; Teva, Hung.; Sarabhai Piramal, India; Formenti, Ital.; Abdi, Turk.*
Tramadol hydrochloride (p.130·3).
Pain.

Contramareo *Torrens, Spain.*
Dimenhydrinate (p.576·2).
Motion sickness.

Contramutan *Cassella-med, Ger.*
Homoeopathic preparation.

Contraneural *Pfleger, Ger.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Contraneural Paracetamol/Codeine *Pfleger, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Contraspan *Galena, Cz.†; Ivax, Cz.†.*
Belladonna (p.2263·3); papaverine hydrochloride (p.2191·3); phenobarbital (p.492·2); camphor (p.2273·2); absinthium (p.2244·1); valerian (p.2410·1); chamomile (p.2279·3); caraway oil (p.2277·1); fennel oil (p.2303·1); peppermint oil (p.1761·2).
Smooth muscle spasm.

Contraspasmin *Viatris, Ger.†.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Contratemp *Mugi, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Contrathion
Aventis, Arg.; Sanofi-Aventis, Braz.; SERB, Fr.; IFET, Gr.; Sanofi-Aventis, Ital.
Pralidoxime metilsulfate (p.1460·2).
Organophosphorus poisoning.

Keymen, Turk.
Pralidoxime mesilate (p.1460·2).
Organophosphorus insecticide poisoning.

Contravert B_6 *Sanochemia, Austria.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Motion sickness; vertigo; vomiting.

Contraxen *Liferpal, Mex.*
Naproxen (p.92·3); carisoprodol (p.1894·1).

Contre-Coups de l'Abbe Perdrigeon *Pionneau, Fr.*
Aloes (p.1705·2).
Skin disorders; soft-tissue injury; superficial wounds.

Contre-Douleurs *Wild, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Colloidal aluminium hydroxide (p.1706·2) is included in the tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Contre-Douleurs C *Wild, Switz.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold symptoms; fever.

Contre-Douleurs P *Wild, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Contre-Douleurs plus *Wild, Switz.*
Aspirin (p.20·3); caffeine (p.1116·3).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Contreet *Coloplast, Ger.; Coloplast, UK.*
Hydrocolloid silver dressing (ionic) (p.2387·1).
Burns; ulcers; wounds.

Contrex *Supra Ferbindo, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Contrexyn *Supra Ferbindo, Indon.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Contril *US Pharmacia, Pol.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Contrin *Geneva, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); intrinsic factor (p.2326·3); vitamin B substances (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Control
Note. This name is used for preparations of different composition.
Farmasa, Braz.
Poliglusam (p.2370·1); fruit oligosaccharides; sodium ascorbate; citric acid.

Bio-Sante, Canad.
Cascara (p.1715·2); sennosides A and B (p.1769·3).
Constipation.

Bayer, Ital.
Lorazepam (p.1004·1).
Convulsions; nervous disorders; sedative.

Control K *Merck, Arg.*
Potassium chloride (p.1684·3).
Potassium deficiency.

Controlacne *Pharmalab, Arg.*
Glycolic acid (p.1598·1); lactic acid (p.2329·3); salicylic acid (p.1612·2); resorcinol (p.1612·1); camphor (p.2273·2); aloe (p.1588·2); calendula (p.2273·1).
Acne.

Controlip *Abbott, Mex.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Controller *Alta Care, Ital.*
St John's wort (p.422·3); crataegus (p.2289·1); kava (p.2328·3); passion flower (p.2363·2); lavender oil (p.2331·2); St John's wort oil (p.423·2); verbena oil; neroli oil (p.2351·1).
Nervous disorders.

Controloc
Nycomed, Cz.; Sanofi-Aventis, Gr.; Altana, Hung.; Altana, Malaysia; Bayer, S.Afr.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Agis, Israel; Altana, Singapore; Altana, Thai.; Schering-Plough, Thai.
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Altana, Pol.
Pantoprazole (p.1760·1) or pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Controlpros *Rontag, Arg.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

ControlRx *Omnii, USA.*
Sodium fluoride (p.1962·2); dimeticone (p.2032·1); poloxamer 407 (p.1918·2).
Dental caries prophylaxis.

Controlvas *Shire, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Contromet *Adcock Ingram, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastrointestinal disorders.

Contrykal *AWD, Rus.*
Aprotinin (p.1055·1).
Haemorrhage; pancreatitis.

Contugesic *Mundipharma, Spain†.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Contumax
Note. This name is used for preparations of different composition.
Asofarma, Mex.
Macrogol 3350 (p.2336·3).
Bowel evacuation; constipation.

Casen Fleet, Spain.
Sodium picosulfate (p.1771·1).
Constipation.

Contusin
Note. This name is used for preparations of different composition.
Lacer, Spain.
Diethylamine salicylate (p.47·2); aesculus (p.2248·2).
Musculoskeletal, joint, and soft-tissue disorders.

Herbamed, Switz.
Homoeopathic preparation.

Contuxin *Continentales, Mex.*
Oxolamine (p.1567·1).
Cough.

Conucol *Armoxindo, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Convacard *Cheplapharm, Ger.†.*
Convallaria glycosides (p.2287·3).
Heart failure.

Conva-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Convaden *Schering, Cz.†.*
Estradiol (p.2097·2); gestodene (p.2105·2).
Menopausal disorders; osteoporosis.

Convafort *Herbapol Krakow, Pol.*
Convallaria (p.2287·3).
Circulatory disorders.

Convalemin *Cipla, Cz.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Convallocor Herztropfen N *Hevert, Ger.*
Homoeopathic preparation.

Convallocor-SL *Hevert, Ger.*
Crataegus (p.2289·1); convallaria (p.2287·3).
Cardiac disorders.

Convastabil *Klein, Ger.*
Convallaria (p.2287·3); crataegus (p.2289·1).
Cardiac disorders.

Convertal *Tecnimede, Port.†.*
Captopril (p.1239·2).

Converten *Gentili, Ital.*
Enalapril maleate (p.1276·1).
Asymptomatic left-ventricular dysfunction; heart failure; hypertension.

Convertin *MSD, Israel.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Convifer con Hierro *Degorts, Mex.*
Vitamins with iron and lysine (p.1922·1).
Tonic.

Conviron-TR *Ranbaxy, India.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B (p.1980·2); vitamin B (p.1979·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Convulex
Note. This name is used for preparations of different composition.
Gerot, Austria; Altana, Belg.; Gerot, Cz.; Lundbeck, Ger.; Gerot, Hung.; Gerot, Neth.†; Gerot, Pol.; Altana Madaus, S.Afr.; Gerot, Switz.; Liba, Turk.
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Bipolar disorder; epilepsy; mania; migraine; psychoses.

Gerot, Rus.; Gerot, Singapore; Pharmacia, UK.
Valproic acid (p.508·2).
Bipolar disorder; epilepsy; febrile convulsions.

Meyer, Venez.
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Convulsan
Note.This name is used for preparations of different composition.
Sanval, Braz.
Carbamazepine (p.471·3).
Epilepsy.

Actavis, Rus.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Convulsofin *Dresden, Cz.†; AWD, Rus.*
Calcium valproate (p.511·3).
Bipolar disorder; epilepsy.

AWD, Ger.; Wernigerode, Ger.
Calcium valproate (p.511·3) or sodium valproate (p.508·2).
Epilepsy.

Conzace *Biomedis, Philipp.*
Vitamin A; vitamin E; vitamin C; zinc sulfate (p.1922·1).
Nutritional supplement.

Conzila *Medinova (Μεντινοβα), Gr.*
Piroxicam (p.117·3).
Inflammatory disorders.

Cool B *Sisu, Canad.*
Vitamin B substances (p.1922·1).

Cool Mint Listerine
Note.This name is used for preparations of different composition.
Pfizer, Hong Kong.
Thymol (p.1664·3); cineole (p.2282·3); methyl salicylate (p.85·3); menthol (p.2340·1); copper gluconate (p.1935·3).
Halitosis.

Pfizer Consumer, S.Afr.
Thymol (p.1664·3).
Mouth and throat disorders.

Cool Tears *Valeant, Arg.*
Hypromellose (p.2144·2).
Eye irritation.

Coolby Cough *Pharmasant, Thai.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Coolips *Mintlab, Chile.*
Cetirizine hydrochloride (p.570·3).

Coolmetec *Sankyo, Fr.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coordinax *Janssen-Cilag, Hung.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Copal
Note.This name is used for preparations of different composition.
Biomet, Ger.
Polymethylmethacrylate methylmethacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1); clindamycin hydrochloride (p.251·1).
Bone infections.

Probiomed, Mex.
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Copal Chest Rub *Guardian, Indon.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold and influenza symptoms; insect bites; stomach ache.

Copalia *Novartis, Cz.; Novartis, Gr.; Novartis, Port.*
Valsartan (p.1420·2); amlodipine besilate (p.1214·1).
Hypertension.

Copamide *Dey's, India†.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Copan *Duopharma, Hong Kong.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Copastin *YSP, Malaysia.*
Cloperastine hydrochloride (p.1554·3).
Coughs.

Copaxone *Teva Tuteur, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Biosintetica, Braz.; Teva, Canad.; Teva, Cz.; Teva, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Teva, Ger.; Sanofi-Aventis, Gr.; Teva, Hung.; Sanofi-Aventis, Irl.; Teva, Israel; Sanofi-Aventis, Ital.; Lemery, Mex.; Sanofi-Aventis, NZ; Teva, Neth.; Teva, Norw.; Teva, Pol.; Sanofi-Aventis, Port.; Teva, Rus.; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Med, Turk.; Aventis, UK; Teva, UK; Teva, USA.*
Glatiramer acetate (p.2312·2).
Multiple sclerosis.

Cope *Mentholatum, USA.*
Aspirin (p.20·3); caffeine (p.1116·3).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Copegus *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, UK; Roche, USA.*
Ribavirin (p.902·3).
For use with interferon alfa-2a or peginterferon alfa-2a.
Chronic hepatitis C.

Copercilex *Cooper (Κοπερ), Gr.*
Ampicillin sodium (p.204·1).
Eye infections.

Cophadyl *ICM, Singapore.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Cophadyl-E *ICM, Singapore.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Cophene No. 2 *Dunhall, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Cophene XP *Dunhall, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Coughs.

Cophenylcaine *Paedpharm, Austral.*
Phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3).
Aid in upper respiratory-tract investigations; epistaxis; preparation of nasal mucosa for surgical procedures.

Cophylac *Valeo, Canad.*
Oral solution: ⊗ Normethadone hydrochloride (p.1566·2); oxilofrine hydrochloride (p.1364·3).
Coughs.

6 Copin
Note.This name is used for preparations of different composition.
Ariston, Arg.
Injection: Hyoscine methobromide (p.1734·1); chlorpromazine hydrochloride (p.969·2); pyridoxine hydrochloride (p.1978·2).
Vomiting.

Ariston, Arg.
Oral drops; tablets: Hyoscine methobromide (p.1734·1); chlorpromazine hydrochloride (p.969·2); pyridoxine hydrochloride (p.1978·2); procaine hydrochloride (p.1869·1).
Vomiting.

Copinal *Vinas, Spain.*
Zinc acexamate (p.2245·2).
Peptic ulcer.

Copiron *Microsules, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Coplaxil *Haller, Braz.†.*
Teicoplanin (p.344·3).
Bacterial infections.

Coplexina *Sanofi Synthelabo, Arg.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders.

Copovan *Mayne, Ital.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Copper-T *Kimia, Indon.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Coppertone
Note.This name is used for preparations of different composition.
Balmar, NZ†.
Lotion SPF 4+: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Balmar, NZ.
Lotion SPF 15+: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Balmar, NZ.
Lotion SPF 30+: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Balmar, NZ†.
Oil SPF 2: Homosalate (p.1598·1).
Sunscreen.

Coppertone Bug & Sun Adult *Schering-Plough, USA.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); homosalate (p.1598·1).
Sunscreen.

Coppertone Bug & Sun Kids *Schering-Plough, USA.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3).
Sunscreen.

Coppertone Bug & Sunblock
Note.This name is used for preparations of different composition.
Schering-Plough, Canad.†.
SPF 15: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); diethyltoluamide (p.2041·1).
Insect repellent; sunscreen.

Schering-Plough, Canad.†.
SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); diethyltoluamide (p.2041·1).
Insect repellent; sunscreen.

Coppertone Kids
Note.This name is used for preparations of different composition.
Schering-Plough, USA.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3).
Sunscreen.

Coppertone Kids Colorblok *Schering-Plough, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Kids Glitter *Schering-Plough, Canad.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Kids Spray'n Play *Schering-Plough, Canad.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Kids Sunblock *Schering-Plough, Canad.*
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Kids Sunblock Foam *Schering-Plough, Canad.†.*
SPF 40: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Lipkote *Schering-Plough, USA.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Mist *Schering-Plough, Canad.†.*
SPF 4: Homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Moisturizing
Note.This name is used for preparations of different composition.
Schering-Plough, USA.
SPF 2: Homosalate (p.1598·1).
Sunscreen.

Schering-Plough, USA.
SPF 15; SPF 4; SPF 6; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 25; SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 45: Octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Oil-Free
Note.This name is used for preparations of different composition.
Schering-Plough, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, Canad.
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering, Canad.
SPF 45: Avobenzone (p.1589·3); homosalate (p.1598·1); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Formerly contained homosalate, octinoxate, octisalate, and oxybenzone.
Sunscreen.

Coppertone Oil-Free Faces *Schering-Plough, Canad.*
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Sport
Note.This name is used for preparations of different composition.
Schering, Canad.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 15; SPF 4; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Sport Gel *Schering, Canad.*
SPF 15; SPF 30: Avobenzone (p.1589·3); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Sport Spray *Schering, Canad.*
SPF 15; SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Sunscreen *Schering, Canad.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Suntan *Schering-Plough, Canad.*
SPF 4: Octinoxate (p.1608·2); octocrilene (p.1608·3).
Formerly contained octinoxate and oxybenzone.
Sunscreen.

Coppertone Tan Magnifier
Note.This name is used for preparations of different composition.
Schering-Plough, USA.
Gel SPF 4: Ensulizole (p.1597·1).
Sunscreen.

Schering-Plough, USA.
Lotion SPF 4: Octinoxate (p.1608·2).
Sunscreen.

Schering-Plough, USA.
SPF 2: Trolamine salicylate (p.132·3).
Sunscreen.

Coppertone Waterbabies *Schering, Canad.; Schering-Plough, USA.*
SPF 30; SPF 45: Homosalate (p.1598·1); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Coppertone Waterproof Spray *Schering-Plough, Canad.†.*
SPF 15; SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Coppertone Waterproof Sunblock
Note.This name is used for preparations of different composition.
Schering-Plough, Canad.†.
Gel SPF 15; Gel SPF 30: Avobenzone (p.1589·3); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, Canad.†.
Lotion SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, Canad.†.
Lotion SPF 30; Lotion SPF 45: Octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, Canad.†.
Lotion Spray SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Co-Prenessa *KRKA, Hung.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Co-Pressoless *Cifarma, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Pressotec *Teuto, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coptin *Axcan, Canad.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

Copyrkal *Berlin-Chemie, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Copyrkal N *Berlin-Chemie, Ger.†.*
Propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Co-Pyronil *Lilly, Thai.†.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Co-Q-10
Note.This name is used for preparations of different composition.
Swiss Herbal, Canad.†; Larkhall Laboratories, UK†; Carlson, USA†.
Ubidecarenone (p.2407·2).
Metabolic disorders.

Merck, Indon.
Cod-liver oil (p.1935·2); eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1); vitamins (p.1922·1); ubidecarenone (p.2407·2).
Adjunct in cardiac disease; tonic.

Coquelusedal *Elerte, Fr.*
Grindelia (p.2317·2); gelsemium (p.2310·1).
Formerly contained niaouli oil, grindelia, and gelsemium.
Coughs.

Coquelusedal Paracetamol *Elerte, Fr.*
Paracetamol (p.108·1); grindelia (p.2317·2); gelsemium (p.2310·1).
Formerly contained paracetamol, niaouli oil, grindelia, and gelsemium.
Respiratory-tract disorders.

Coquevit *Brasmedica, Braz.†.*
⊗ Sodium dibunate (p.1573·1); ephedrine (p.1558·1); vitamin C (p.1983·3).
Coughs.

Co-Quinapril *Eurogenerics, Belg.; Sandoz, Belg.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

CoQuinone *Usana, Hong Kong†; Usana, Singapore; USANA, USA.*
Ubidecarenone (p.2407·2).
Coenzyme Q10 supplement; dietary supplement.

Coqun *Visufarma, Ital.*
Ubidecarenone (p.2407·2); tocofersolan (p.1993·3).
Dry eyes.

Cor-30, Cor-80 *Pascual, Philipp.*
Aspirin (p.20·3).
Thromboembolic disorders.

Cor Mio *Hexal, Braz.†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

cor tensobon *Schwarz, Ger.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension.

Cora *Erbiode, Austria.*
Homoeopathic preparation.

Coraben *Medic, Braz.†.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Succinic acid is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Coracil *Gador, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Coracten *Vianex (Βιανέξ), Gr.; ICN, Hong Kong†; ICN, Thai.; UCB, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Coradol
Note. This name is used for preparations of different composition.
Slovakofarma, Cz.†.
Magnesium aspartate (p.1679·1); magnesium chloride (p.1679·1).
Hypertension; ischaemic heart disease; magnesium deficiency.

Coradol, Ger.†.
Homoeopathic preparation.

Coradona *Farma, Venez.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Corafen *Bernabo, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Coral
Note. This name is used for preparations of different composition.
SoSe, Ital.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Wermar, Mex.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Coralan *Servier, Austral.*
Ivabradine hydrochloride (p.1320·2).
Angina pectoris.

Coralen *Alter, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Coralmyn *Bioclon, Mex.*
Snake venom antiserum (p.2238·2).
Micrurus spp bites.

Coralzul *Farcoral, Mex.*
Furazolidone (p.834·3); homatropine (p.1881·2); kaolin (p.1738·1); pectin (p.2145·2); diiodohydroxyquinoline (p.832·1).
Gastrointestinal disorders.

Coramedan *Medice, Ger.†.*
Digitoxin (p.1259·1).
Arrhythmias; heart failure.

Coramil *Sanofi Synthelabo, Swed.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Coramine Glucose *Novartis Sante, Fr.*
⊗ Nikethamide (p.2161·2); glucose monohydrate (p.1945·3).
Asthenia; fainting.

Corangin *Novartis, Ger.; Novartis, Hong Kong†; Novartis, NZ.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Corangin Nitrospray *Novartis, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; myocardial infarction.

Corangine *Novartis, Switz.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Coraphene *Vedim, Port.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; premedication; pruritus.

Coras *Alphapharm, Austral.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Corase *Medac, Ger.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Coraspin *Bayer, Turk.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Coraspir *Armstrong, Mex.*
Lysine aspirin (p.79·1).
Fever; pain; thromboembolism prophylaxis.

Coraspirina *Bayer, Venez.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Coratol *Scan Lab, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Coraxan *Servier, Rus.*
Ivabradine hydrochloride (p.1320·2).
Angina pectoris.

Corazem *Mundipharma, Austria†; Farma, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Corazet *Mundipharma, Ger.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Corbar *Adcock Ingram, S.Afr.*
⊗ Guaifenesin (p.1561·3); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); co. cocillana syrup (p.1554·3).
Coughs.

Corbeta *Sarabhai Piramal, India.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris.

Corbetazine *Sarabhai Piramal, India.*
⊗ Propranolol hydrochloride (p.1380·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Corbeton *Alphapharm, Austral.*
⊗ Oxprenolol hydrochloride (p.1365·1).
Angina pectoris; arrhythmias; hypertension.

Corbin *Pharmadica, Thai.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Corbionax *Sanofi-Aventis, Fr.; Winthrop, Port.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Corbis *Roemmers, Arg.; Unichem, Rus.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Corbis D *Roemmers, Arg.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Corcanfol *Lafage, Arg.†.*
⊗ Etilefrine (p.1284·1).
Hypotension.

Corciclen *Allergan, Braz.*
⊗ Chlortetracycline hydrochloride (p.243·1); cortisone acetate (p.1524·2); bismuth loretinate.
Infected eye disorders.

Cordafen *Polpharma, Cz.†; Polpharma, Pol.; Polpharma, Rus.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; ischaemic heart disease; migraine; peripheral vascular disorders.

Cordaflex *EGIS, Hung.; Egis, Rus.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction; Raynaud's syndrome.

Cordalat *Kimia, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cordalin *AWD, Ger.†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Cordan *Sandoz, Denm.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cordanum *Dresden, Cz.†; AWD, Ger.; Pliva, Rus.*
⊗ Talinolol (p.1409·1).
Arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Cordapur Novo *APS, Ger.*
Crataegus (p.2289·1).
Heart failure.

Cordarex
Biosintetica, Braz.
Amlodipine besilate (p.1214·1).
Hypertension; ischaemic heart disease.

Sanofi Synthelabo, Ger.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cordarone *Sanofi-Aventis, Belg.; Wyeth, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi Torrent, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.; Wyeth-Ayerst, USA.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Cordarone X *Sanofi Synthelabo, Austral.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Sanofi Synthelabo, S.Afr.; Sanofi Synthelabo, UK.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cordazem *Benecor, Philipp.; Pascual, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Cordes Beta *Ichthyol, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Cordes BPO *Ichthyol, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Cordes Estriol *APS, Ger.*
Estriol (p.2101·1).
Vaginal disorders.

Cordes VAS *Ichthyol, Ger.*
Tretinoin (p.1618·1).
Acne.

Cordesin *Serag-Wiessner, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Heart failure; myocardial infarction; potassium and magnesium deficiency.

Cordesyl *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Cordex *Prosel, Philipp.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Cordiax *Crinos, Ital.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Cordicant *Mundipharma, Ger.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cordichin *Abbott, Ger.*
Verapamil hydrochloride (p.1421·1); quinidine (p.1383·1).
Arrhythmias.

Cordil
Note. This name is used for preparations of different composition.
Teuto, Braz.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Dexxon, Israel.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Cordilat
Note. This name is used for preparations of different composition.
Cristalia, Braz.
Verapamil hydrochloride (p.1421·1).

Tecnofarma, Mex.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Cordilox *Abbott, Austral.; Ivax, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Cordimedil *Kleva, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Cordinal *Spedrog, Arg.*
Bifemelane hydrochloride (p.363·2).
Mental function impairment.

Cordinate *AWD, Ger.*
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Cordinate plus *AWD, Ger.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Cordiodoron *Weleda, Ger.*
Homoeopathic preparation.

Cordipatch *Schwarz, Fr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Cordipin *KRKA, Cz.; KRKA, Hung.†; KRKA, Pol.; KRKA, Rus.; KRKA, Singapore.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; migraine; peripheral vascular disorders; Raynaud's syndrome.

Cordipina *Farmasa, Braz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Cordiplast *Gebro, Austria; CEPA, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Cordiron *Diffucap, Braz.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Cordisil *Flupal, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cordisol *Bioprogress, Ital.†.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Cordizem *Kimia, Indon.*
Diltiazem (p.1267·1).
Angina pectoris.

Cordodopa *Sanofi Synthelabo, Port.*
Dopamine hydrochloride (p.1273·2).
Shock.

Cordran *Watson, USA.*
⊗ Fludroxycortide (p.1530·3).
Skin disorders.

Cordron-D *Cypress, USA.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Cordron-DM *Cypress, USA.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Cordron-HC *Cypress, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Cordymax *Pharmanex, USA.*
Cordyceps sinensis mushroom mycelia.
Fatigue.

Corectin *Biofarm, Pol.*
⊗ Bisoprolol fumarate (p.1234·1).
Hypertension; ischaemic heart disease.

Coredopril *Sandoz, Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coredryl *GMP, Indon.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Cough.

Coreg
Roche, Braz.; GSK, Canad.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure.

GSK, USA.
⊗ Carvedilol (p.1241·3) or carvedilol phosphate (p.1241·3).
Heart failure; hypertension.

Corega *GSK, Braz.*
Sterculia (p.1772·1).

Coreine *Germania, Austria.*
Carrageenan (p.2142·3).
Constipation.

Corenistad *Stada, Austria.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Renitec *MSD, Arg.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Denm.†; MSD-Chibret, Fr.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Philipp.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Venez.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Reniten *MSD, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Corenza C *Adcock Ingram, S.Afr.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); moroxydine hydrochloride (p.898·2).
Cold and influenza symptoms.

Coreptil *Sanofi Synthelabo, Ital.†.*
⊗ Heptaminol hydrochloride (p.2319·1).
Adjunct in overdosage with neuroleptics and barbiturates; cardiac disorders.

Coretec *Eisai, Jpn.*
Olprinone hydrochloride (p.1361·3).
Heart failure.

Coreton *Slovakofarma, Cz.†.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Corex *Pfizer, India.*
Chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); menthol (p.2340·1).
Coughs.

Corex Dx *Pfizer, India.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1).
Coughs.

Corexan *Biotech, Venez.†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; hypersensitivity reactions; urticaria.

Corexin *Otto, Indon.*
Salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Corfen-DM *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

Corflo *Wockhardt, India.*
Nicorandil (p.1349·1).
Angina pectoris.

Corgard *BMS, Arg.; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; Sanofi-Aventis, Fr.; BMS, Hong Kong†; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, S.Afr.; BMS, Spain; BMS, Switz.; Sanofi Synthelabo, UK; Monarch, USA; BMS, Venez.*
⊗ Nadolol (p.1345·2).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; obstructive cardiomyopathy.

Corgaretic *BMS, Mex.; BMS, S.Afr.; Sanofi Synthelabo, UK†.*
⊗ Nadolol (p.1345·2); bendroflumethiazide (p.1224·1).
Hypertension.

Corgic *Jumont, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Corhinza *Hexpharm, Indon.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cough; influenza symptoms.

Corhydron *Jelfa, Pol.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Coric *BMS, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Coric Plus *BMS, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Coricide le Diable *Sodia, Fr.*
Salicylic acid (p.1612·2).
Callosities; corns; verrucae.

Coricidil-D *Plough, Port.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; rhinitis; sinusitis.

Coricidin
Note. This name is used for preparations of different composition.
Schering-Plough, Indon.
⊗ Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); alcohol (p.1625·2).
Respiratory-tract allergic reactions; sinusitis.

Schering-Plough, Ital.†.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Allergic rhinitis; cold symptoms; sinusitis.

Schering-Plough, Spain†.
Ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); salicylamide (p.121·2).
Fever; nasal congestion; pain.

Schering-Plough, USA; Schering-Plough, Venez.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; upper respiratory-tract symptoms.

Coricidin II Chest Congestion and Cough *Schering-Plough, Canad.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Coricidin II Cold and Flu *Schering-Plough, Canad.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Coricidin II Cough and Cold *Schering-Plough, Canad.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).

Coricidin Expec *Schering-Plough, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Coricidin II Extra Strength Cold and Flu *Schering-Plough, Canad.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Coricidin F *Schering-Plough, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Nasal congestion.

Coricidin HBP Chest Congestion & Cough *Schering-Plough, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Coricidin Pediatrico NF *Schering-Plough, Mex.†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract congestion.

Coridil *Ecosol, Switz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Corifam *Coronet, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Corifeo *UCB, Ger.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Corifin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract congestion.

Corifina *Farma Lepori, Spain.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Corilax *Community Pharmacy, Thai.†.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain; neuralgia; tension headache.

Corilin *Schering-Plough, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hypersensitivity reactions.

Corilin F *Schering-Plough, Mex.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Nasal congestion.

Corilisina *Pensa, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Corindocomb *Schering, Ger.†.*
⊗ Mepindolol sulfate (p.1333·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Corindolan *Schering, Ger.*
⊗ Mepindolol sulfate (p.1333·1).
Angina pectoris; cardiac hyperkinetic syndrome; hypertension.

Corinfar *Dresden, Cz.; AWD, Ger.; AWD, Hung.; AWD, Rus.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Coriodal *Sanitas, Chile.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; migraine.

Corion *Win-Medicare, India.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; habitual miscarriage; male and female infertility; male hypogonadism; pituitary dwarfism.

Coriosta Vitaltonikum N *Niedermaier, Ger.†.*
Ginseng (p.2312·1).
Tonic.

Coriovaccine *Columbia, Arg.*
Staphylococcus; *Micrococcus*; *Pneumococcus*; *Streptococcus*; *Klebsiella*; *Moraxella catarrhalis*; *Haemophilus influenzae*; vitamin C (p.1983·3).

Corisol *Ecosol, Switz.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections; trichomoniasis.

Coristina D *Mantecorp, Braz.*
Dexchlorpheniramine maleate (p.572·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); aspirin (p.20·3).
Cold and influenza symptoms.

Coristina R *Mantecorp, Braz.*
Salicylamide (p.121·2); dexchlorpheniramine maleate (p.572·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Influenza symptoms.

Coristine-DH *Technilab, Canad.†.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).
Coughs.

Coritab *Atlantic, Hong Kong.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, phenylpropanolamine hydrochloride, and chlorphenamine maleate.
Cold symptoms; nasal congestion; rhinitis.

Coritensil *Roux-Ocefa, Arg.*
⊗ Carvedilol (p.1241·3).

Coritex *Bago, Chile.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Coritrope *Sanofi-Aventis, Indon.*
Milrinone acetate.
Heart failure.

Coritussal *Mack, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine (p.1569·2); carbinoxamine maleate (p.570·2).
Formerly contained dextromethorphan hydrobromide, phenylephrine hydrochloride, and carbinoxamine maleate.
Coughs; rhinitis.

Coriver *Maver, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Corixa *Biotenk, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Corixil *Bracco, Ital.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Corizin *Greenpharma, Braz.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2).

Corizina *Cetus, Arg.*
Ascorbic acid (p.1983·3); paracetamol (p.108·1); diphenhydramine (p.577·1).
Influenza symptoms.

Corizzina *SIT, Ital.†.*
⊗ Tetracaine hydrochloride (p.1871·3); naphazoline nitrate (p.1565·2).
Nasal congestion.

cor-L 90 N *Loges, Ger.†.*
Homoeopathic preparation.

Corlan *UCB, Irl.; UCB, UK.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Aphthous stomatitis.

Corlentor *Servier, Cz.; Servier, Fr.; Servier, Neth.; Servier, Port.*
Ivabradine hydrochloride (p.1320·2).
Angina pectoris.

Corlisina *Corsalud, Venez.†.*
Vitamin B substances (p.1922·1).
Dietary supplement.

Cor-loges *Loges, Ger.*
Homoeopathic preparation.
Formerly contained squill and convallaria.

Corlopam *Elan, Irl.†; Zeneus, Ital.; Elan, Neth.; Hospira, USA.*
Fenoldopam mesilate (p.1287·1).
Hypertension.

Cormac *Megat, Venez.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Cormagnesin
Viatris, Austria; Worwag, Cz.†; Worwag, Ger.; Worwag, Hung.; Worwag, Rus.
Magnesium sulfate (p.1679·3).
Arrhythmias; bronchospasm; CNS hyperexcitability; eclampsia; magnesium deficiency; magnesium supplement; myocardial infarction; premature labour.

Worwag, Port.
Magnesium aspartate (p.1679·1).
Magnesium supplement.

Cormatic *Megat, Venez.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cormax *Watson, USA.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Cormelian *Khandelwal, India.*
Dilazep hydrochloride (p.1265·1).
Ischaemic heart disease.

Cormisin *Gunsa, Turk.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Corn *SSL, Pol.*
Salicylic acid (p.1612·2).
Corns.

Corn and Callous *SSL, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns.

Corn and Callous Removal Liquid *Scholl, Israel.*
Salicylic acid (p.1612·2); camphor (p.2273·2).
Formerly known as Corn Removing Liquid.
Corns and callouses.

Corn Huskers *Warner-Lambert, USA.*
Emollient and moisturiser.

Cornalgin *Corsa, Indon.*
Dipyrone (p.49·2).
Fever; pain.

Cornaron *TAD, Ger.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Cornel *Berenguer Infale, Spain†.*
Nisoldipine (p.1358·1).
Angina pectoris; hypertension.

Corneregel *Riel, Austria; Mann, Ger.; Kite (Κιτε), Gr.; Mann, Hung.; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.; Mann, Pol.; Mann, Rus.*
Dexpanthenol (p.2362·1).
Corneal lesions; eye disorders; keratitis.

Corni Limp *Sophia, Mex.*
Sodium chloride (p.1686·1).

Cornina
Note. This name is used for preparations of different composition.
Beiersdorf, Chile†.
Triclosan (p.1665·2); dichlorobenzyl alcohol (p.1642·1).
Bacterial and fungal foot infections.

Beiersdorf, Spain†.
Salicylic acid (p.1612·2).
Corns.

Cornkil *Norgine, Austral.†.*
Benzocaine (p.1854·1); salicylic acid (p.1612·2); lactic acid (p.2329·3).
Corns.

Corobion *Coronet, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; hyperemesis gravidarum; muscular weakness; neuralgia; neuritis; paraesthesia.

Corocrat *Biomo, Ger.†.*
Crataegus (p.2289·1).
Heart failure.

Corocyd *Coronet, Indon.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Coroday *Generics, UK†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Corodil *Hexal, Denm.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Corodil Comp *Hexal, Denm.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Corodin *Drugtech, Chile.*
Losartan potassium (p.1326·1).
Hypertension.

Corodin D *Drugtech, Chile.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Corodoc S *Fides, Ger.†.*
Homoeopathic preparation.

Corodrox *Fabop, Arg.*
Diltiazem (p.1267·1).
Angina pectoris.

Corodyn *Schmidgall, Austria†.*
Crataegus tincture (p.2289·1); camphor (p.2273·2); menthol (p.2340·1).
Cardiovascular disorders.

Coroflex *Coronet, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Corogal *Probiomed, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Corolater *Sandoz, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Corolin *Leiras, Fin.†.*
Simvastatin (p.1390·2).
Coronary artery disease; hypercholesterolaemia.

Coromert *Mertens, Arg.*
Flunarizine (p.580·3).
Migraine; vertigo.

Coronair *Socobom, Belg.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Coronar *Biolab Sanus, Braz.*
Isosorbide mononitrate (p.1318·3).
Formerly contained propatylnitrate.
Angina pectoris.

Coronaril *Sigma, Braz.*
Verapamil hydrochloride (p.1421·1).

Coronax *Fabop, Arg.*
Amiodarone (p.1210·2).
Arrhythmias.

Coronex *Pacific, NZ†.*
Isosorbide dinitrate (p.1317·3).

Coronipin *Dexa, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Coro-Nitro *3M, Ger.†; Ayrton, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Coronorm *Wolff, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Coronovo
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Recalcine, Chile.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Coronur *Roche, Spain.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Coropres *Roche, Spain.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension; ischaemic heart disease.

Cororell *Sanorell, Ger.*
Homoeopathic preparation.

Corosan *Farmacologico Milanese, Ital.*
Dipyridamole (p.1268·1).
Vascular disorders.

Corotal *Rosch & Handel, Austria.*
β-Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Corotenol *Mepha, Cz.†; Mepha, Malaysia†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Corotrend *Rhein, Mex.; Medika, Switz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; ischaemic heart disease; myocardial infarction.

Corotrop
Sanofi Synthelabo, Austria; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Switz.
Milrinone (p.1341·2).
Heart failure.

Sanofi Synthelabo, Swed.
Milrinone lactate (p.1341·2).
Heart failure.

Corotrope
Sanofi Synthelabo, Arg.; Sanofi-Aventis, Chile; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Venez.
Milrinone lactate (p.1341·2).
Heart failure.

Sanofi-Aventis, Belg.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain.
Milrinone (p.1341·2).
Circulatory failure; heart failure.

Coroval *Sandoz, Arg.*
Amlodipine besilate (p.1214·1).
Hypertension.

Coroval B *Sandoz, Arg.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Corozell *Fresenius Kabi, Austria.*
Potassium chloride (p.1684·3); magnesium aspartate (p.1679·1).
Potassium and magnesium deficiency.

Corpamil *Helvepharm, Switz.†.*
Verapamil hydrochloride (p.1421·1).
Angina; arrhythmias; hypertension.

Corpaz *Indeco, Arg.*
⊗ Atenolol (p.1217·3).
Hypertension.

Corpea *Normon, Spain.*
Molsidomine (p.1343·3).
Angina pectoris.

Corpendol *Sanofi Synthelabo, Port.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; essential tremor; gastrointestinal haemorrhage; hypertension; migraine; myocardial infarction; obstructive cardiomyopathy; thyrotoxicosis.

Corplus *Bago, Arg.†.*
Lysine aspirin (p.79·1).
Thromboembolism prophylaxis.

Corpotasin CL *Armstrong, Mex.*
Potassium bicarbonate (p.1673·1); potassium chloride (p.1684·3); lysine hydrochloride (p.1955·1).
Digitalis intoxication; potassium and chloride supplement.

Corpotasin GK *Armstrong, Mex.*
Potassium gluconate (p.1684·3).
Digitalis intoxication; hypokalaemia.

Corpotasin LP *Armstrong, Mex.*
Potassium chloride (p.1684·3).
Digitalis intoxication; hypokalaemia.

Corpress *Neves, Port.†.*
Amlodipine besilate (p.1214·1).
Angina pectoris.

Corpril *Ranbaxy, Hung.; Ranbaxy, Thai.*
Ramipril (p.1385·3).
Congestive heart failure; hypertension; myocardial infarction.

Corprilin *Streuli, Switz.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Corprilor *Rubio, Singapore; Rubio, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Corpriretic *Streuli, Switz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Corque *Geneva, USA.*
⊗ Hydrocortisone (p.1535·2); clioquinol (p.254·1).
Skin disorders.

Correcteur Anti-Taches *Lierac, Fr.*
Glycolic acid (p.1598·1); lactic acid (p.2329·3).
Skin hyperpigmentation.

Correctol
Note. This name is used for preparations of different composition.
Schering, Canad.; Schering-Plough, USA.
Bisacodyl (p.1710·1).
Formerly contained docusate sodium and phenolphthalein.
Constipation.

Alcon, Fr.
Disodium inosinate (p.2296·1).
Visual disturbances.

Schering-Plough, Mex.†.
Docusate sodium (p.1725·1).
Constipation.

Correctol Stool Softener *Schering, Canad.*
Docusate sodium (p.1725·1).
Constipation.

Corsabalm *Corsa, Indon.*
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); menthol (p.2340·1); cinnamon oil (p.2283·2); clove oil (p.2285·1); citronella oil (p.2284·2).
Musculoskeletal and soft-tissue pain; neuralgia.

Corsaben *Corsalud, Venez.†.*
Ammonium acetate (p.1551·2); Desessartz syrup; polygala (p.1572·3); sodium benzoate (p.1630·2).
Cough.

Corsabutol *Corsa, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Corsacillin *Corsa, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Corsacin *Corsa, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Corsaderm *Corsa, Indon.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Corsadryl *Corsa, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough.

Corsafen *Corsa, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Corsafer *Corsalud, Venez.†.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Corsagrip *Corsa, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Corsagyl *Corsa, Indon.*
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Corsal *Ulagay, Turk.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract congestion.

Corsamag *Corsa, Indon.*
Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Epigastric pain; gastric bloating; gastric hyperacidity; nausea associated with peptic ulcer.

Corsamet *Corsa, Indon.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Corsamox *Corsa, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Corsamycin *Corsa, Indon.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Corsamyl *Corsa, Indon.*
Dextromethorphan hydrobromide (p.1555·2); dexchlorpheniramine maleate (p.572·1).
Bronchitis; cold and influenza symptoms; cough.

Corsaneuron *Corsa, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Diabetic neuropathy; myalgia; neuralgia; neuritis; paraesthesia.

Corsanural *Corsa, Indon.*
Dipyrone (p.49·2); vitamin B ; vitamin B ; vitamin B (p.1922·1).
Pain.

Corsasep *Corsa, Indon.*
Povidone-iodine (p.1659·2).
Wounds.

Corsatet *Corsa, Indon.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Corsatrocin *Corsa, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Corsazinamid *Corsa, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Corsel *Fahrenheit, Indon.*
Ubidecarenone (p.2407·2); levocarnitine (p.1932·2).
Nutritional supplement.

Cor-Select
Note. This name is used for preparations of different composition.
Dreluso, Ger.†.
Ointment: Crataegus (p.2289·1); valerian (p.2410·1); camphor (p.2273·2); ol. sinapis (p.2349·2); benzyl nicotinate (p.28·1); peppermint oil (p.1761·2); melissa oil (p.2339·3).
Cardiovascular disorders.

Dreluso, Ger.
Oral drops: Homoeopathic preparation.

Corsifar *Siphar, Switz.†.*
Molsidomine (p.1343·3).
Ischaemic heart disease.

Corsim *ProMed, Cz.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Corsodyl *GSK Consumer, Belg.; GSK Consumer, Cz.; GSK, Fin.; GSK Sante, Fr.; GSK, Hong Kong; GSK Consumer, Irl.; GSK, Israel; GSK, Ital.; GSK Consumer, Neth.; GSK, Norw.; GSK Consumer, Port.; Group, S.Afr.; GSK Consumer, Swed.; GSK Consumer, Switz.; GSK Consumer, UK.*
Chlorhexidine gluconate (p.1635·3).
Mouth infections; mouth ulcers; oral hygiene.

CorSotalol *Merck dura, Ger.†.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Corstanal *Corsa, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Corstat *Medreich, Hong Kong.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hyperlipidaemias.

Cortafrin *Streger, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Fever; nasal congestion; pain.

Cortafriol C *Sanofi-Aventis, Spain.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); ascorbic acid (p.1983·3).
Fever; influenza and cold symptoms; pain.

Cortafriol Complex *Sanofi-Aventis, Spain.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Cor-Tagrip *Benitol, Arg.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); bromhexine (p.1552·2).
Formerly contained paracetamol, pseudoephedrine, astemizole, and bromhexine.
Influenza symptoms.

Cortaid
Dermatech, Austral.†; Carlo Erba OTC, Ital.†.
⊗ Hydrocortisone acetate (p.1535·2).
Anogenital pruritus; skin disorders.

Pharmacia Upjohn, USA.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Skin disorders.

Cortaid with Aloe *Pharmacia, Singapore†.*
⊗ Hydrocortisone acetate (p.1535·2); aloe vera (p.1588·2).
Skin disorders.

Cortal *GSK, Philipp.*
Aspirin (p.20·3).
Fever; pain.

Cortal for Adults *GSK, Hong Kong.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Cortal for Children *GSK, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Cortalen C *Ativus, Braz.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Cortaler Novo *Phoenix, Arg.†.*
⊗ Dexamethasone (p.1526·1); terfenadine (p.590·3).
Hypersensitivity reactions.

Cortamide *Ottolenghi, Ital.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cortancyl *Sanofi-Aventis, Fr.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Cortane-B *Blansett, USA.*
⊗ Chloroxylenol (p.1640·2); pramocaine hydrochloride (p.1868·1); hydrocortisone (p.1535·2).

Cortanest Plus *Piam, Ital.*
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3).
Anogenital disorders; burns; skin disorders.

Cortapaisyl *Merck Medication Familiale, Fr.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortare *Ivax, Pol.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Cortate
Note. This name is used for preparations of different composition.
Aspen, Austral.
⊗ Cortisone acetate (p.1524·2).
Oral corticosteroid.

Schering-Plough, Canad.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortatrigen *Goldline, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Cortax *Ativus, Braz.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Cort-Dome *Miles, USA.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Anorectal disorders; skin disorders.

Cortef
Dermatech, Austral.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

McNeil Consumer, Canad.; McNeil Consumer, Canad.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Corticosteroid.

Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia Upjohn, Rus.
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Upjohn, USA.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone cipionate (p.1535·3).
Corticosteroid.

Cortef Feminine Itch *Upjohn, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Pruritus.

Cortenem *Pharmacia, Arg.†.*
⊗ Hydrocortisone (p.1535·2).
Inflammatory bowel disease.

Cortenema
Note. This name is used for preparations of different composition.
Axcan, Canad.; Solvay, USA†.
⊗ Hydrocortisone (p.1535·2).
Inflammatory bowel disease; ulcerative colitis.

Casen Fleet, Spain.
⊗ Allantoin (p.1588·1); hydrocortisone hydrogen succinate (p.1535·3); homatropine methylbromide (p.1881·3); zinc oxide (p.1621·2).
Anorectal disorders.

Corteroid *Montpellier, Arg.*
⊗ Betamethasone (p.1518·2), betamethasone sodium phosphate (p.1518·3), or betamethasone valerate (p.1519·1).
Corticosteroid.

Corteroid Gesic *Montpellier, Arg.*
⊗ Betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3); diclofenac sodium (p.44·3); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Gout; musculoskeletal, joint, and peri-articular disorders; neuritis.

Corteroid Retard *Montpellier, Arg.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone acetate (p.1518·2).
Corticosteroid.

Cortespasmo *Northia, Arg.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Cortexin *Geropharm, Rus.*
Polypeptide brain extract (bovine/porcine) (p.2337·3).
Cerebral palsy; cerebrovascular disorders; cranial-cerebral trauma; dystonia; encephalitis; encephalomyelitis; encephalopathy; epilepsy; mental function impairment.

Corti Biciron N *S & K, Ger.*
⊗ Dexamethasone isonicotinate (p.1526·1); oxytetracycline hydrochloride (p.312·3).
Infected eye disorders.

Corti Jaikal *S & K, Ger.†.*
⊗ Hydrocortisone acetate (p.1535·2); sodium thiosulfate (p.1466·1); salicylic acid (p.1612·2).
Acne.

Corti-Arscolloid *SIT, Ital.*
⊗ Dichlorobenzyl alcohol (p.1642·1); silver protein (p.2387·3); dexamethasone sodium phosphate (p.1526·2).
Stomatitis.

Cortic *Sigma, Austral.*
⊗ Hydrocortisone acetate (p.1535·2).
Anogenital pruritus; skin disorders.

Cortic ND *Everett, USA.*
⊗ Hydrocortisone (p.1535·2); pramocaine hydrochloride (p.1868·1); chloroxylenol (p.1640·2); benzalkonium chloride (p.1629·1).
Inflammatory ear disorders.

Corticaine
Note. This name is used for preparations of different composition.
UCB, USA.
Cream: ⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Glaxo, USA.
Rectal cream: ⊗ Hydrocortisone acetate (p.1535·2); cinchocaine (p.1857·2).
Anorectal disorders.

Cortical *Caber, Ital.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Corticel *Serono, Arg.†.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Corticetine *Chauvin, Fr.; Bausch & Lomb, Switz.†.*
⊗ Framycetin sulfate (p.279·1); dexamethasone sodium phosphate (p.1526·2).
Ear disorders; otitis.

Corticil T *Edol, Port.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Corticin *Medipharma, Hong Kong†.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Corticina *Roemmers-Klinos, Venez.*
⊗ Hydrocortisone buteprate (p.1535·2) or hydrocortisone hydrogen succinate (p.1535·3).
Corticosteroid.

Corti-Clyss *Braun, Switz.†.*
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1).
Crohn's disease; ulcerative colitis.

Corticoderm *Meda, Swed.†.*
⊗ Fluprednidene acetate (p.1533·1).
Eczema.

Corticorp *Organifar, Venez.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Corticorten *Neo Quimica, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Corticosan *Fabra, Arg.*
Losartan potassium (p.1326·1).
Hypertension.

Corticotulle Lumiere *Solvay, Fr.†; Hefa, Ger.†.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); triamcinolone acetonide (p.1544·3).
Burns; ulcers; wounds.

Cortidax *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Cortidene *Berna, Spain.*
⊗ Paramethasone acetate (p.1540·2).
Corticosteroid.

Cortiderma *Mertens, Arg.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Cortidex *Pharlab, Braz.†; Sanbe, Indon.; Rayere, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid; skin disorders.

Cortidexason *Dermapharm, Ger.†.*
⊗ Dexamethasone (p.1526·1).
Skin and scalp disorders.

Cortidexason comp *Dermapharm, Ger.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Cortidro *Sofar, Ital.*
⊗ Hydrocortisone acetate (p.1535·2).
Bites and stings; burns; eczema; pruritus.

Corti-Dynexan *Kreussler, Ger.†.*
⊗ Prednisolone acetate (p.1541·1); lauromacrogol 400 (p.1916·1); dequalinium chloride (p.1641·3).
Inflammatory disorders of the mouth.

Cortiespec *Sesderma, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cortifenol H *Novartis, Chile†.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Bacterial eye infections with inflammation.

Cortifluid N *Streuli, Switz.*
⊗ Calcium pantothenate (p.1959·3); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Corti-Fluoral *Schering, Ital.*
⊗ Josamycin propionate (p.291·1); diflucortolone valerate (p.1529·2).
Mouth disorders.

Cortifoam *GSK Consumer, Canad.; Agis, Israel; Schwarz, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Colitis; proctitis; ulcerative proctitis.

Cortifung-C *Tocogino, Mex.*
Clioquinol (p.254·1).
Skin infections.

Cortifung-N *Tocogino, Mex.*
⊗ Fluocinolone (p.1531·3); neomycin (p.305·1).
Infected skin disorders.

Cortifung-S *Tocogino, Mex.*
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Cortifung-Y *Tocogino, Mex.*
⊗ Fluocinolone (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Cortigrin
Note.This name is used for preparations of different composition.
Collins, Mex.†.
Tetracycline (p.347·1).
Bacterial infections.

Collins, Mex.
Chlorphenamine (p.572·2); aspirin (p.20·3).
Cold and influenza symptoms.

Cortigrip *Medipharm, Chile.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Cold and influenza symptoms.

Cortigrip Dia/Noche *Medipharm, Chile.*
Day tablets, pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night tablets, pseudoephedrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Cortigripe *Generis, Port.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Formerly contained aspirin and hydrocortisone.
Influenza; pain.

Cortilate *Micro, India.*
⊗ Halcinonide (p.1535·1).
Skin disorders.

Cortilate-S *Micro, India.*
⊗ Halcinonide (p.1535·1); salicylic acid (p.1612·2).
Skin disorders.

Cortilona *Offenbach, Mex.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cortilona Compuesta *Offenbach, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Skin disorders.

Cortimar *Mar, Arg.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Cortimycin
Note.This name is used for preparations of different composition.
Medical Ophthalmics, USA.
Eye drops: ⊗ Hydrocortisone (p.1535·2); neomycin (p.305·1); polymyxin B (p.318·2).
Infected eye disorders.

Medical Ophthalmics, USA.
Eye ointment: ⊗ Hydrocortisone (p.1535·2); neomycin (p.305·1); bacitracin (p.210·3); polymyxin B (p.318·2).
Infected eye disorders.

Cortimycine
Note.This name is used for preparations of different composition.
Abdi, Turk.
⊗ Hydrocortisone acetate (p.1535·2).
Inflammatory eye disorders.

Drossapharm, Switz.
Cream: ⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); dexpanthenol (p.2362·1).
Infected skin disorders.

Drossapharm, Switz.
Cream; ointment: ⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Cortimyk *CCS, Swed.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal skin infections with inflammation.

Cortimyxin
Note.This name is used for preparations of different composition.
Sandoz, Canad.
Ear drops: ⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Ear disorders.

Sandoz, Canad.
Eye ointment: ⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Infected eye disorders.

Cort-Inal *Teofarma, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); diprophylline (p.1120·2).
Bronchial catarrh.

Cortinasal *Spirig, Switz.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Cortineff *Jelfa, Pol.; Polfa Pabianice, Pol.; Pabianice, Rus.*
Fludrocortisone acetate (p.1530·1).
Adrenocortical insufficiency; adrenogenital syndrome; hypotension; inflammatory eye disorders.

Cortiphenol H
Novartis, Gr.
⊗ Chloramphenicol (p.239·3); hydrocortisone (p.1535·2).
Bacterial eye infections with inflammation.

Novartis, Hong Kong.
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected eye disorders.

Cortiprex *Laboratorios Chile, Chile.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Cortipyren B *Gador, Arg.*
⊗ Meprednisone (p.1538·1).
Corticosteroid.

Cortirel *Curatis, Ger.*
⊗ Corticorelin triflutate (p.1523·2).
Diagnosis of corticotrophic pituitary function.

Cortirell *Sanorell, Ger.*
Homoeopathic preparation.

Cortiron *Schering, Ital.*
Desoxycortone acetate (p.1525·3) or desoxycortone enantate (p.1525·3).
Adrenocortical insufficiency.

Cortisal *Dexo, Fr.*
⊗ Dipropylene glycol mono- and disalicylate (p.62·3); prednisolone (p.1540·3).
Peri-articular and soft-tissue disorders.

Cortisdin Urea *Isdin, Spain.*
⊗ Fluorometholone (p.1532·3); urea (p.1620·2).
Skin disorders.

Cortisedermyl *Cooper, Fr.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortisol *Laboratorios Chile, Chile.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Cortisolona *Klonal, Arg.†.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Cortison Chemicet Topica *Teofarma, Spain.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Cortison Chemicetina *Fournier, Ital.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected eye or skin disorders.

Cortison Kemicetin *Sanochemia, Austria.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Bacterial eye infections; inflammation.

Cortison Kemicetine *Mac, India†.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Cortisonal *Uniao Quimica, Braz.*
⊗ Hydrocortisone acetate (p.1535·2) or hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Cortispec *Euroderm, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Infected skin disorders.

Cortisporin
Note.This name is used for preparations of different composition.
GSK, Mex.; GSK, Philipp.
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Infected ear disorders; otitis externa.

Monarch, USA.
Cream: ⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

GSK, Canad.
Ear drops; eye drops: ⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Bacterial infections with inflammation.

Monarch, USA†.
Eye ointment; ointment: ⊗ Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Infected skin and eye disorders.

GSK, Canad.
Ointment: ⊗ Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Bacterial infections with inflammation.

Monarch, USA.
Ophthalmic suspension: ⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Infected eye disorders.

Cortisporin-TC *JHP, USA.*
⊗ Colistin sulfate (p.256·2); neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2); tonzonium bromide (p.2403·2).
Infected ear disorders.

Cortistamin L *Bago, Arg.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).
Hypersensitivity reactions.

Cortistamin NF *Bago, Arg.†.*
⊗ Betamethasone (p.1518·2); terfenadine (p.590·3).
Hypersensitivity reactions.

Cortisteron *Streuli, Switz.*
Desoxycortone acetate (p.1525·3).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Adrenocortical insufficiency.

Cortiston *Ariston, Braz.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Cortisumman *Winzer, Ger.†.*
⊗ Dexamethasone (p.1526·1).
Eye disorders.

Cortisyl *Aventis, UK.*
⊗ Cortisone acetate (p.1524·2).
Corticosteroid.

Cortitop *Multilab, Braz.*
⊗ Dexamethasone acetate (p.1526·1).
Skin disorders.

Cortival *Fawns & McAllan, Austral.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Cortivent *Leiras, Fin.†.*
⊗ Budesonide (p.1520·1).
Asthma.

Cortixide *Farmedia, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis; allergic skin disorders.

Cortizan *Innoderm, Philipp.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortizol *EMS, Braz.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Cortizon *Prodotti, Braz.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Cortizone *Pfizer, Israel; Pfizer Consumer, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortizul
Note.This name is used for preparations of different composition.
Lersan, Arg.
Eye drops: ⊗ Prednisolone (p.1540·3); phenylephrine hydrochloride (p.1568·1).
Inflammatory eye disorders.

Lersan, Arg.
Eye ointment: ⊗ Prednisolone (p.1540·3).
Inflammatory eye disorders.

Cortoderm
Note.This name is used for preparations of different composition.
Taro, Canad.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Pharmacare, S.Afr.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cortoderm-C *Lennon, S.Afr.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Cortoftal *Alcon Cusi, Malaysia†; Alcon Cusi, Spain†.*
⊗ Clobetasone butyrate (p.1522·3).
Inflammatory eye disorders.

Cortogen *Schering-Plough, S.Afr.†.*
⊗ Cortisone acetate (p.1524·2).
Corticosteroid.

Cortola-m *East India Pharma, India.*
⊗ Sulfacetamide sodium (p.335·3); hydrocortisone acetate (p.1535·2).
Infected eye disorders.

Cortomycetin *Nizhpharm, Rus.*
⊗ Chloramphenicol (p.239·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Cortone *Merck Frosst, Canad.†; Ist. Chim. Inter., Ital.; Merck, USA.*
⊗ Cortisone acetate (p.1524·2).
Corticosteroid.

Cortop *Mayne, Ital.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Cortopic *Laboratorios Chile, Chile.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Cortopin *Pinewood, Irl.; Lexon, UK.*
⊗ Hydrocortisone (p.1535·2).
Insect bites; skin disorders.

Cortoquinol *East India Pharma, India.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Fungal skin infections.

Cortos *Raffo, Arg.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Corto-Tavegil
Note.This name is used for preparations of different composition.
Novartis Consumer, Ger.†.
Tablets: ⊗ Clemastine fumarate (p.573·2); dexamethasone (p.1526·1).
Hypersensitivity reactions.

Novartis Consumer, Ger.†.
Topical gel: ⊗ Clemastine fumarate (p.573·2); clocortolone pivalate (p.1523·1).
Insect stings; skin disorders; sunburn.

Cortran *Rider, Chile.*
Citalopram hydrobromide (p.385·3).
Depression.

Cortril *Pfizer, Belg.†.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Eye disorders; skin disorders.

Cortropin *Pinewood, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cortrosyn
Amphastar, Canad.; Organon (Οργανον), Gr.; Organon, Israel†; Organon, Ital.†; Amphastar, USA.
⊗ Tetracosactide (p.1543·3).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency; infantile spasm; multiple sclerosis.

Organon, Hong Kong; Organon, Thai.
⊗ Tetracosactide hexa-acetate (p.1544·1).
Diagnosis of adrenocortical insufficiency.

Organon, Neth.†.
⊗ Tetracosactide (p.1543·3) or tetracosactide hexaacetate (p.1544·1).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency.

Cortuss *Pharmaland, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Cortynase *Oftalmi, Venez.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; sinusitis.

Corubin
Note.This name is used for preparations of different composition.
Lazar, Arg.
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Farmanic, Gr.
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Corubin B1 *Inter, Venez.†.*
Vitamin B ; vitamin B (p.1922·1).
Dietary supplement.

Coruno *Therabel, Belg.*
Molsidomine (p.1343·3).
Angina pectoris.

Corus *Biosintetica, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Corus H *Biosintetica, Braz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coruzol *Schlatter, Switz.†.*
Acetic acid (p.2244·2); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Hard skin.

Corvadil *Unichem, Rus.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Corvasal
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Fr.†.
Injection: Linsidomine hydrochloride (p.1325·1).
Angina pectoris; cardiac investigations; coronary arterial spasm.

Sanofi-Aventis, Fr.
Tablets: Molsidomine (p.1343·3).
Angina pectoris.

Corvatard *Therabel, Belg.†.*
Molsidomine (p.1343·3).
Angina pectoris.

Corvaton *Therabel, Belg.; Sanofi-Aventis, Cz.; Aventis, Ger.; Sanofi-Aventis, Hung.; Therabel, Port.†; Aventis, Switz.*
Molsidomine (p.1343·3).
Angina pectoris; heart failure; myocardial infarction.

Cor-Vel *Truw, Ger.*
Camphor (p.2273·2); menthol (p.2340·1); Norway spruce oil; rosemary oil (p.2381·3).
Cardiac disorders.

Corvert *Pfizer, Austria; Pharmacia, Cz.†; Pfizer, Fin.; Pfizer, Fr.†; Gerolymatos, Gr.; Pharmacia, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Swed.; Pfizer, Switz.; Pharmacia Upjohn, USA.*
Ibutilide fumarate (p.1312·2).
Arrhythmias.

Corvita C *Provefarma, Arg.*
Ascorbic acid (p.1983·3); bixa orellana.
Dietary supplement.

Corvita Lax *Provefarma, Arg.*
Magnesium; wheat bran (p.1922·1).
Dietary supplement.

Corvitol *Berlin-Chemie, Cz.†; Berlin-Chemie, Rus.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Corvo *TAD, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Corvo HCT *TAD, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Coryfin C *SIT, Ital.*
Menglytate (p.1564·2); ascorbic acid (p.1983·3).
Coughs; hoarseness.

Coryol *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Coryx
Note. This name is used for preparations of different composition.
Mirren, S.Afr.
Effervescent tablets: Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Mirren, S.Afr.
Syrup: Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); vitamin C (p.1983·3).
Cold and influenza symptoms.

Coryzalia *Boiron, Canad.; Boiron, Cz.; Boiron, Fr.; Boiron, Port.*
Homoeopathic preparation.

Corzide *Monarch, USA.*
⊗ Nadolol (p.1345·2); bendroflumethiazide (p.1224·1).
Hypertension.

Cosaar *MSD, Austria; MSD, Switz.*
Losartan potassium (p.1326·1).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension.

Cosaar Plus *MSD, Austria; MSD, Switz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cosaldon
Note. This name is used for preparations of different composition.
Aventis, Ger.†.
Pentifylline (p.1366·3).
Cerebrovascular insufficiency; vascular eye disorders; vestibular disorders.

Aventis, S.Afr.†.
Pentifylline (p.1366·3); nicotinic acid (p.1957·3).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Cosalgesic *Alpharma, Hong Kong; Cox, Hong Kong; Alpharma, UK†.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
These ingredients can be described by the British Approved Name Co-proxamol.
Pain.

Co-Salt *Pfizer, Arg.*
Potassium chloride (p.1684·3).
Salt substitute.

Cosamin *Nutramax, USA.*
Glucosamine hydrochloride; chondroitin sulfate sodium; manganese ascorbate (p.1922·1).
Nutritional supplement.

Cosamine *Hovid, Malaysia.*
Glucosamine sulfate potassium (p.2313·2).
Osteoarthritis.

Cosantin *Kee, India†.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin E; vitamin C; manganese (p.1922·1).
Dietary supplement; osteoarthritis.

Cosavil *Hub, India.*
Pheniramine maleate (p.587·3); paracetamol (p.108·1).
Cold symptoms.

Coscopin *Biological E, India.*
Noscapine (p.1566·2); citric acid (p.2284·1); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Coughs.

Coscopin BR *Biological E, India.*
Pseudoephedrine (p.1571·2); bromhexine hydrochloride (p.1552·2); menthol (p.2340·1).
Coughs.

Coscopin Plus *Biological E, India.*
Noscapine (p.1566·2); citric acid (p.2284·1); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Coughs.

Cose-Anal *Will-Pharma, Belg.*
Sodium oleate (p.2139·1); lauromacrogol 400 (p.1916·1).
Haemorrhoids.

Cosiden *Rowe-Fleming, Venez.†.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Cosig *Sigma, Austral.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cosil *Alian, Venez.*
Enalapril maleate (p.1276·1).
Hypertension.

Cosivatin *Med-One, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Coslan *Parke, Davis, Spain.*
Mefenamic acid (p.80·1).
Fever; inflammation; pain.

Coslyte *CFL, India.*
Potassium chloride; sodium chloride; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

Cosmaxil *Cosmofarma, Port.†.*
⊗ Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2); theophylline (p.1140·1).
Obstructive airways disease.

Cosmegen *Bioprofarma, Arg.; MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Fin.; MSD-Chibret, Fr.; IFET (ΙΦΕΤ), Gr.; MSD, Hong Kong; MSD, Irl.; MSD, Ital.; MSD, Malaysia†; MSD, NZ; MSD, Norw.; MSD, Philipp.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.†; MSD, Turk.; IDIS, UK; Merck, USA.*
Dactinomycin (p.707·2).
Malignant neoplasms.

Cosmiciclina *INTES, Ital.*
Oxytetracycline hydrochloride (p.312·3); chloramphenicol (p.239·3); sulfacetamide sodium (p.335·3).
Bacterial infections of the eye or ear.

CosmoDerm *Inamed, Singapore.*
Collagen (p.2286·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Scars; wrinkles.

Cosmodex Depigmenten *Lierac, Fr.†.*
Liposomes of TPE; AHA complex; oryzanol (p.2358·3).
Hyperpigmentation.

Cosmodex Uniwhite *Lierac, Fr.†.*
Liposomes of TPE; glycolic acid (p.1598·1); sodium lactate (p.1673·3).
Hyperpigmentation.

Cosmofer *Nebo, Denm.; Gry, Ger.; Demo, Gr.; Nebo, Hong Kong†; Schwarz, Hong Kong†; Vitaline, Irl.; Nebo, Norw.; Nebo, Philipp.; Pharmacosmos, Port.; Nebo, Thai.; Say, Turk.; Vitaline, UK; Nebo, Venez.*
Iron dextran (p.1951·1).
Iron deficiency; iron-deficiency anaemia.

CosmoPlast *Inamed, Singapore.*
Collagen (p.2286·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Scars; wrinkles.

Cosmopril *Cosmopharm, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Coso *McGloin, Austral.*
Menthol (p.2340·1); camphor (p.2273·2); benzyl alcohol (p.1631·3).
Herpes labialis.

Cosolve *Vargas, Venez.*
Ketotifen (p.582·2).
Hypersensitivity reactions.

Cosome *Merck, India.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine (p.1568·1); chlorphenamine maleate (p.571·3).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, and chlorphenamine maleate.
Cold symptoms; coughs; nasal congestion.

Cosooth *Sensomed, Philipp.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Cosopt *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Chibret, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; Pharmalink, Philipp.; MSD, Pol.; Chibret, Port.; MSD, S.Afr.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Cospanon *Eisai, Jpn.*
Flopropione (p.2305·3).
Smooth muscle spasm.

Cost *Fada, Arg.*
Ketamine (p.1788·1).
General anaesthesia.

Costazole *Crisdy-Na, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Costi *Medochemie, Hong Kong.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Costil *Pyridam, Indon.*
Domperidone (p.1726·2).
Dyspepsia; epigastric discomfort; flatulence; hiccups; nausea and vomiting.

Cosudex *AstraZeneca, Austral.; AstraZeneca, NZ.*
Bicalutamide (p.686·2).
Prostatic cancer.

Co-Sultrin *Valmor, Venez.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cosuric *DDSA Pharmaceuticals, UK.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Cosylan *Pfizer, Norw.*
Ethylmorphine hydrochloride (p.52·2); cascara (p.1715·2); menthol (p.2340·1).
Coughs; respiratory-tract irritation.

Cosyr
Note. This name is used for preparations of different composition.
Medifarma, Indon.; UAP, Indon.
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Cough.

Great Eastern, Thai.; United American, Thai.
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs.

Cosyr (Reformulated) *United American, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Cotalbex *Streuli, Philipp.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Cotamox *Asian Pharm, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cotar *Flupal, Venez.†.*
Dipyrone (p.49·2); salicylamide (p.121·2); carisoprodol (p.1894·1).
Pain.

Cotareg *Biosintetica, Braz.†; Novartis, Fr.; Novartis, Ital.; Euro Registratie, Neth.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Co-Tareg *Jaba, Port.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Cotaryl *FDC, India.*
⊗ Urea (p.1620·2); calcium lactate (p.1676·1); lactic acid (p.2329·3); potassium chloride (p.1684·3); magnesium chloride (p.1679·1); glycine (p.1947·3); monobasic sodium phosphate (p.1682·3); ammonium chloride (p.1551·3); sodium chloride (p.1686·1).
Hyperkeratosis; ichthyosis.

Co-Tasian *Asian Pharm, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cotaso *Union Drug, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Cotazym
Note. This name is used for preparations of different composition.
Organon, Braz.; UCB, Ger.
Pancreatin (p.2360·1).
Pancreatic enzyme deficiency.

Organon, Canad.; Organon, NZ.
Pancrelipase (p.2360·1).
Pancreatic enzyme deficiency.

Cotazym Forte *Organon, Indon.*
Pancreatin (p.2360·1); ox bile extract (p.2266·3); cellulase (p.2279·1).
Digestive disorders; pancreatic deficiency.

Cotazym S Forte *Organon, Austral.*
Pancrelipase (p.2360·1).
Pancreatic enzyme deficiency.

Cotazym-S *Organon, Neth.†.*
Pancrelipase (p.2360·1).
Pancreatic insufficiency.

Cotecxin *Holley-Cotec, China.*
Artenimol (p.598·3).
Malaria.

Cotenol *TP, Thai.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Cotenolol-Neo *Mepha, Switz.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Cotensil *Giempi, Venez.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Cotesifar *Siphar, Switz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Cotet *Adcock Ingram, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Coteveten *Solvay, Fr.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cotibin Compuesto
Note. This name is used for preparations of different composition.
Andromaco, Chile†.
Oral suspension: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Andromaco, Chile.
Tablets: Paracetamol (p.108·1).
Fever; pain.

Cotibin Dia y Noche *Andromaco, Chile.*
Day tablets, pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night tablets, pseudoephedrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Cotibin Flu *Andromaco, Chile†.*
Paracetamol (p.108·1); noscapine (p.1566·2); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Cotina *Sanitas, Chile.*
Nicotinic acid (p.1957·3).
Chilblains; hyperlipidaemias; peripheral vascular disorders; venous ulcers.

Cotinazin *Pfizer, Gr.*
Tioconazole (p.548·2).
Fungal skin and vaginal infections.

Co-Tioctan *Purissimus, Arg.*
Cocarboxylase (p.1975·2); thioctic acid (p.2400·2).
Liver disorders; metabolic disorders; poisoning.

Cotofin *Loren, Mex.†.*
Paracetamol (p.108·1); chlorphenamine (p.572·2).
Hypersensitivity.

Cotone Emostatico *Nova Argentia, Ital.*
Ferric chloride (p.2303·3).
Styptic.

Cotrane *Sanofi-Aventis, Belg.*
Dimethoxanate hydrochloride (p.1557·1).
Coughs.

Cotrazol *Valomed, Spain.*
Guaifenesin (p.1561·3); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Cotren *Biopharm, Hong Kong; Biolab, Malaysia†; Biolab, Singapore; Biolab, Thai.*
Clotrimazole (p.530·1).
Fungal and bacterial vaginal infections; fungal skin infections; trichomoniasis.

Cotriatec *Sanofi-Aventis, Fr.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Cotribene *Ratiopharm, Austria.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrim *Ratiopharm, Belg.; Ratiopharm, Fin.; 1A, Ger.; ABZ, Ger.; CT, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Wernigerode, Ger.; Medochemie, Hong Kong; Pyridam, Indon.; Medochemie, Malaysia; Ratiopharm, Port.†; Spirig, Switz.; Lemmon, USA.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrim-Diolan *Meda, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; fungal mycetoma; paracoccidioidomycosis.

Co-Trimed *Medifive, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Co-Trimexazole *Beacons, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections.

CotrimHefa *Riemser, Ger.; Wernigerode, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrimhexal *Hexal, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrimol *Ipca, India†; UAP, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cotrimox-Wolff *Wolff, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrimstada *Stada, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; paracoccidioidomycosis; pneumocystis pneumonia.

Cotripharm *Praxipharm, Hung.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Cotrisan *Sanitas, Chile.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cotrizol-G *Klonal, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Cotron *Pinewood, Irl.*
Dantron (p.1722·2); poloxamer 188 (p.1918·1).
Constipation.

Co-Tuss V *Rugby, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Cotussin *TP, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; nasal congestion.

Co-Tylenol *Janssen-Cilag, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Cough & Cold *Homeocan, Canad.*
Oral pellets: Homoeopathic preparation.

Cough & Cold L52 *Homeocan, Canad.*
Homoeopathic preparation.

Cough Drops
Note. This name is used for preparations of different composition.
Zee, Canad.
Menthol (p.2340·1).

Weleda, UK.
Homoeopathic preparation.

Cough Elixir
Note. This name is used for preparations of different composition.
Weleda, S.Afr.
Thyme (p.2401·1); aniseed (p.2258·2); ipecacuanha (p.1562·3); dulcamara (p.2298·1); marrubium (p.1564·1); althaea (p.2253·3); malt extract (p.1955·2); drosera (p.2297·3); pulsatilla (p.2376·3).
Coughs.

Weleda, UK.
Homoeopathic preparation.

Cough EN Expectorant *Metiska, Indon.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Cough EN Plus *Metiska, Indon.*
Dextromethorphan (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine (p.1569·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough; respiratory-tract congestion.

Cough & Flu Syrup *Technilab, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).

Cough Formula Comtrex *Bristol-Myers Products, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Cough L64 *Homeocan, Canad.†.*
Homoeopathic preparation.

Cough Lozenges *Sutton, Canad.*
Menthol (p.2340·1).

Cough Nurse *GSK Consumer, UK.*
Diphenhydramine (p.577·1); pholcodine (p.1570·2).
Coughs.

Cough Relief *Brauer, Austral.†.*
Anise oil (p.2258·2); althaea (p.2253·3); bryonia (p.2269·3); Iceland moss (p.2324·1); echinacea (p.2298·1); chamomile (p.2279·3); thyme (p.2401·1); urtica (p.2409·3); aconitum nap.; coccus cacti; corallium rub.; drosera; ipecacuanha; kali bich.; kreosotum; spongia tosta; sticta pulm.
Cough.

Cough Syrup
Note. This name is used for preparations of different composition.
Rougier, Canad.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Goldline, USA.
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Cough Syrup with Codeine *Rougier, Canad.*
Guaifenesin (p.1561·3); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).

Cough Syrup DM *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2).

Cough Syrup DM Decongestant *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Cough Syrup DM Decongestant for Children *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Cough Syrup DM Decongestant Expectorant *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Cough Syrup DM Expectorant *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Cough Syrup DM-D-E *WestCan, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Cough Syrup DM-E *WestCan, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Cough Syrup Expectorant *Jamp, Canad.*
Guaifenesin (p.1561·3).

Cough Syrup with Guaifenesin & Dextromethorphan *Tanta, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Cough Syrup with Honey *Hylands, Canad.*
Homoeopathic preparation.

Coughcod *Pharmacare, S.Afr.*
⊗ Ephedrine hydrochloride (p.1558·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); codeine phosphate (p.37·2); mepyramine maleate (p.585·2).
Coughs.

Cough-eeze *Perrigo, UK.*
Ipecacuanha (p.1562·3); marrubium (p.1564·1); elecampane (p.1558·1).
Coughs.

Cough-EN *Xepa-Soul Pattinson, Hong Kong†; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Coughs; respiratory-tract congestion.

Coughlax *Malaysia Chemist, Singapore†.*
⊗ Ammonium chloride (p.1551·3); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs; respiratory-tract congestion; sneezing.

Coughmin *Kyorin, Thai.†.*
⊗ Sodium dibunate (p.1573·1); chlorphenamine maleate (p.571·3); *dl*-methylephedrine hydrochloride (p.1564·3).
Coughs.

Coughnadryl *Condrugs, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; nasal congestion; sneezing.

Cough-X *Ascher, USA.*
Dextromethorphan hydrobromide (p.1555·2); benzocaine (p.1854·1).
Coughs.

Couldespir *Alter, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Couldina *Alter, Spain.*
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Couldina C *Alter, Spain.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3); phenylephrine (p.1568·1).
Cold and influenza symptoms.

Couldina Instant *Alter, Spain.*
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Coulergin *Alter, Spain.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Coumadin *BMS, Arg.; Sigma, Austral.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Ger.; Taro, Israel; BMS, Ital.; BMS, Malaysia; BMS, Mex.; Healthcare Logistics, NZ; Boots, Philipp.; Sanofi Omnimed, S.Afr.†; BMS, Singapore; Eczacibasi, Turk.; BMS, USA; BMS, Venez.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Coumadine *BMS, Fr.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Counterpain
Note. This name is used for preparations of different composition.
BMS, Gr.; BMS, Indon.; BMS, Philipp.; BMS, S.Afr.; BMS, Singapore; BMS, Thai.
Eugenol (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders; respiratory-tract congestion.
BMS, Hong Kong.
Cream: Eugenol (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal pain.
BMS, Hong Kong.
Topical gel: Menthol (p.2340·1).
Musculoskeletal pain.

Counterpain Cool *BMS, Indon.; BMS, Singapore; BMS, Thai.*
Menthol (p.2340·1).
Musculoskeletal and soft-tissue disorders.

Counterpain Plus *BMS, Thai.*
Eugenol (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3); piroxicam (p.117·3).
Osteoarthritis.

Counterpain-PXM *BMS, Indon.*
Eugenol (p.2301·2); levomenthol; methyl salicylate (p.85·3); piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Courage *Soho, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Couvrance *Pierre Fabre, UK.*
SPF 30: A range of covering creams with sunscreens (titanium dioxide (p.1617·3); octinoxate (p.1608·2)).
Concealment of skin imperfections.

Covadenyl *Luar, Arg.*
Collagen (p.2286·1).
Dietary supplement.

Co-Vals *Esteve, Spain.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Covamet *Adcock Ingram, S.Afr.*
Cyclizine hydrochloride (p.574·2).
Nausea; vestibular disorders; vomiting.

Covan *Pharmascience, Canad.†.*
Codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Covancaine *Adcock Ingram, S.Afr.*
⊗ Phenazone (p.116·1); urea (p.1620·2); sulfacetamide sodium (p.335·3); benzocaine (p.1854·1).
Otitis externa; otitis media.

Covance *Ranbaxy, India.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; hypertension; stroke prophylaxis.

Covance-D *Ranbaxy, India.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Covapril *Duopharma, Malaysia.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Covarex *MZ, S.Afr.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Covaryx *Centrix, USA.*
⊗ Esterified oestrogens (p.2097·1); methyltestosterone (p.2117·1).
Menopausal disorders.

Co-Vasocor *Medika, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Covastin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Solvay, Singapore.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; coronary heart disease; hypercholesterolaemia.

Covatine *Bailly, Fr.*
Captodiame hydrochloride (p.967·3).
Anxiety.

Covaxis *Sanofi Pasteur, Ger.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Covedaspen *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Covemarin *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Covemedal *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Coventrol *Gentek, Venez.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Covepet *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Covera *Searle, USA.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Coverdosyn *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Coverdyne *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Coverene *Servier, Arg.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Coverex *Egis, Cz.; EGIS, Hung.; Egis, Neth.; Egis, Pol.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Coverex Komb *EGIS, Hung.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Coverex Prekomb *EGIS, Hung.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Covermark *MDM, Fr.; Epiderm, UK.*
A range of covering creams.
Concealment of birth marks, scars, and disfiguring skin disease.

Coversidin *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Coversum *Servier, Austria; Servier, Ger.; Servier, Switz.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Coversum Combi *Servier, Ger.; Servier, Switz.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Coversyl
Servier, Austral.; Servier, Belg.; Servier, Braz.; Servier, Canad.; Grunenthal, Chile; Servier, Denm.; Servier, Fin.; Servier, Fr.; Servier, Gr.; Serdia, India; Servier, Ital.; Daiichi, Jpn; Servier, Malaysia; Sanfer, Mex.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Singapore; Servier, Spain; Servier, Thai.; Servier, Turk.; Servier, Venez.
Perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction; stroke prophylaxis.
Servier, Irl.; Servier, Neth.; Servier, Port.; Servier, UK.
Perindopril arginine (p.1368·2) or perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction.

Coversyl Comp *Servier, Denm.; Servier, Fin.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Coversyl Plus
Servier, Austral.; Eutherapie, Belg.; Servier, Braz.; Servier, Canad.; Serdia, India; Servier, Malaysia; Servier, NZ; Servier, S.Afr.; Servier, Singapore; Servier, Turk.
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.
Servier, Irl.; Servier, Neth.; Servier, UK.
⊗ Perindopril arginine (p.1368·2) or perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Coversyspes *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Covethanar *Medialyse, Cz.*
Perindopril erbumine (p.1368·3).
Cerebrovascular disorders; heart failure; hypertension.

Co-Vibedoze *Delta, Port.*
Cobamamide (p.1980·2).
Vitamin B supplement.

Coviogal *Teva, Hung.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Covitasa B12 *Seid, Spain.*
Cyproheptadine hydrochloride (p.575·1); cobamamide (p.1980·2).
Tonic.

Covitol *Aspen, Austral.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Nappy rash; skin disorders.

Covocef-N *Anfarm, Gr.*
Cefixime (p.224·3).
Bacterial infections.

Covochol *Covan, S.Afr.*
Acetylcholine chloride (p.1877·1).
Production of miosis in eye surgery.

Covocort *Premier, S.Afr.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Covomycin *Adcock Ingram, S.Afr.*
⊗ Chloramphenicol (p.239·3); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).
Eye, ear, and nose infections.

Covomycin-D *Adcock Ingram, S.Afr.*
⊗ Chloramphenicol (p.239·3); neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye and ear infections.

Covonia Bronchial Balsam *Thornton & Ross, UK.*
Dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1).
Coughs.

Covonia Cold & Flu *Thornton & Ross, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Cold and influenza symptoms.

Covonia Mentholated *Thornton & Ross, UK.*
Menthol (p.2340·1); squill tincture (p.1573·1); liquorice (p.1740·3).
Coughs.

Covonia Night-Time *Thornton & Ross, UK.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2).
Coughs.

Covonia Throat Spray *Thornton & Ross, UK.*
Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3).
Sore throat.

Covonia Vapour Drops *Thornton & Ross, UK.*
Menthol (p.2340·1); peppermint oil (p.1761·2).
Nasal congestion.

Covorit *Laboratorios Chile, Chile.*
Folinic acid (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Covosan *Adcock Ingram, S.Afr.*
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1); sulfacetamide sodium (p.335·3).
Conjunctivitis.

Covospor *Adcock Ingram, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Covostet *Adcock Ingram, S.Afr.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Covosulf *Covan, S.Afr.†.*
Sulfacetamide sodium (p.335·3).
Conjunctivitis.

Covotop *Adcock Ingram, S.Afr.*
Chloramphenicol (p.239·3); benzocaine (p.1854·1).
Ear infections.

Cow & Gate Formula-S *Nutricia, Hong Kong.*
Infant feed (p.1922·1).
Lactose intolerance; milk protein allergy.

Cow & Gate Pepti-Junior *Nutricia, Hong Kong.*
Infant feed (p.1922·1).
Diarrhoea; food hypersensitivity; malabsorption syndromes; malnutrition; short-bowel syndrome.

Coxa-cyl Ho-Len-Complex *Liebermann, Ger.†.*
Homoeopathic preparation.

Coxalgan *Anpharm, Pol.*
Nabumetone (p.91·2).
Degenerative joint disorders; rheumatoid arthritis.

Coxanturenasi *Teofarma, Ital.*
Pyridoxine hydrochloride (p.1978·2); pyridoxal phosphate (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Vitamin B and its co-enzyme deficiency.

Coxel *Beta, Arg.†.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Coxeton *Polfa Pabianice, Pol.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Coxflam *Cipla-Medpro, S.Afr.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Coxina-3 *Aristo, India.*
1 Capsule rifampicin (p.325·3); 1 tablet, isoniazid (p.288·1); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Coxina-4 *Aristo, India.*
1 Capsule rifampicin (p.325·3); 1 tablet isoniazid (p.288·1); ethambutol hydrochloride (p.274·1); 2 tablets pyrazinamide (p.320·2).
Tuberculosis.

Coxinex *Aristo, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Coxiro *Dosa, Arg.†.*
Rofecoxib (p.121·1).
Inflammation; pain.

Coxtenk *Biotenk, Arg.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Coxtral *Zentiva, Cz.; Zentiva, Rus.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Coxumadol *Italfarmaco, Spain.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Coxxil *MSD, Austria†; Gentili, Ital.†; Ferraz, Lynce, Port.†.*
Rofecoxib (p.121·1).
Osteoarthritis; rheumatoid arthritis.

Cozaar *MSD, Austral.; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.†; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Losartan potassium (p.1326·1).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; left ventricular hypertrophy.

Cozaar Comp *MSD, Denm.; MSD, Fin.; MSD, Irl.; MSD, Norw.; MSD, S.Afr.; MSD, Swed.; MSD, UK.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cozaar Plus *MSD, Belg.; MSD, Neth.; MSD, Port.; MSD, Spain.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cozaarex *MSD, Arg.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Cozaarex D *MSD, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Cozep *Pharmasant, Thai.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety.

Cozole *Metz, Philipp.; Be-Tabs, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

CP Tannic *Cypress, USA†.*
Chlorphenamine tannate (p.572·2); pseudoephedrine tannate (p.1572·1).
Nasal congestion; rhinitis; sinusitis.

CP-Acne *Pharmatrix, Arg.*
Clindamycin (p.251·1); benzoyl peroxide (p.1590·2).
Acne.

CP-Atenol *Christo, Hong Kong.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

CPB WC *Elge, USA.*
Brompheniramine maleate (p.569·2); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

CP-Carba *Christo, Hong Kong.*
Carbamazepine (p.471·3).
Alcohol withdrawal; bipolar disorder; diabetic neuropathy; epilepsy; mania; trigeminal neuralgia.

CP-Colchi *Christo, Hong Kong.*
Colchicine (p.556·1).
Gout.

CPD *Ivax, Arg.†.*
Cyproterone acetate (p.2088·2).
Androgen-induced acne, alopecia, hirsutism, and seborrhoea in women; male sexual deviation; precocious puberty; prostatic cancer.

C-Pela *TNP, Thai.†.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness; nausea and vomiting; vestibular disorders.

CP-Fluoxet *Christo, Hong Kong.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

CP-Furo *Christo, Hong Kong.*
⊗ Furosemide (p.1292·1).
Hypertension; liver cirrhosis with ascites; oedema.

CP-Gliz *Christo, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

C-plan *Polifarma, Turk.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

C-Platin *Blausiegel, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

CP-Loradine *Christo, Hong Kong.*
Loratadine (p.583·3).
Hypersensitivity reactions.

C-Plus *Hylands, Canad.*
Homoeopathic preparation.

CP-Lyso *Christo, Hong Kong.*
Muramidase hydrochloride (p.2348·1).
Chronic sinusitis; minor haemorrhage; respiratory-tract disorders associated with viscous mucus.

CPM PSE MSC *Cypress, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2).
Rhinitis.

CP-Metform *Christo, Hong Kong.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

CP-Metolol *Christo, Hong Kong.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

CP-Metolol Co *Christo, Hong Kong.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

CPM/PE/MSC *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Allergic rhinitis.

CPP *Synco, Hong Kong.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; nasal congestion.

CP-Pirox *Christo, Hong Kong.*
Piroxicam (p.117·3).
Musculoskeletal disorders; osteoarthritis.

CP-Prazo *Christo, Hong Kong.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's disease.

CP-PTU *Christo, Hong Kong.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

CP-Pyridine *Christo, Hong Kong.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract disorders.

CPS Pulver *Brady, Austria; Gry, Ger.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

CPT *Varifarma, Arg.†.*
Irinotecan (p.738·1).
Malignant neoplasms.

CP-Theo *Christo, Hong Kong.*
Theophylline (p.1140·1).
Obstructive airways disease.

CP-Tran *Christo, Hong Kong.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders.

Craegium *Hexal, Ger.*
Crataegus (p.2289·1).
Heart failure.

Crafilm *Francia, Ital.*
Sucralfate (p.1772·2).
Gastrointestinal disorders associated with hyperacidity.

Cralonin *Peithner, Austria; Heel, Ger.*
Homoeopathic preparation.

Crampex *Thornton & Ross, UK.*
Calcium gluconate (p.1675·3); nicotinic acid (p.1957·3); colecalciferol (p.1986·2).
Night cramps.

Crampeze Stomach Cramps *Brands Worldwide, Austral.*
Chamomile (p.2279·3); fennel (p.2302·3); peppermint oil (p.1761·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; heartburn; irritable bowel syndrome.

Crampiton *Orion, Fin.*
Quinine hydrochloride (p.612·3); meprobamate (p.1006·2).
Muscle spasm.

Cran Max *Swiss Herbal, Canad.†.*
Cranberry (p.2289·1).

Cranagil *Marien, Austria.*
Homoeopathic preparation.

Cranberry Complex
Note. This name is used for preparations of different composition.
Cenovis, Austral.
Cranberry (p.2289·1); buchu (p.2269·3); bearberry (p.2263·3); ascorbic acid (p.1983·3).
Cystitis; fluid retention.

Mediherb, Austral.
Bearberry (p.2263·3); buchu (p.2269·3); crataeva nurvala; cranberry (p.2289·1).
Cystitis.

Cran-C *Holista, Canad.†.*
Cranberry (p.2289·1); vitamin C (p.1983·3).

Cranio-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Cranoc *Astellas, Ger.*
Fluvastatin sodium (p.1290·2).
Hypercholesterolaemia.

Crantex *Breckenridge, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Crataegan *Austroplant, Austria.*
Crataegus (p.2289·1).
Cardiac disorders.

Crataegisan *Bioforce, Switz.*
Crataegus (p.2289·1).
Cardiac disorders.

Crataegitan *Amino, Switz.*
Crataegus (p.2289·1).
Cardiac disorders.

Crataegus Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Crataegutt *Peithner, Austria; Schwabe, Ger.; ASI, Hung.†.*
Crataegus (p.2289·1).
Cardiac disorders; heart failure.

Crataegysat *Ysatfabrik, Ger.*
Crataegus (p.2289·1).
Cardiac disorders.

Cratae-Loges *Loges, Ger.*
Crataegus (p.2289·1).
Heart failure.

Crataepas *Pascoe, Ger.†.*
Crataegus (p.2289·1).
Heart failure.

Cratecor *Bionorica, Ger.†.*
Crataegus (p.2289·1).
Heart failure.

Cratenox *Knop, Chile.*
Crataegus (p.2289·1).
Cardiovascular disorders.

Cratex *Corsalud, Venez.†.*
Passion flower (p.2363·2); valerian (p.2410·1); crataegus (p.2289·1); hyoscyamus (p.2323·3).
Nervous disorders.

Cratonic *Herbapol Wroclaw, Pol.*
Crataegus (p.2289·1).
Arrhythmias; heart failure.

Craun *Fada, Arg.†.*
Paracetamol (p.108·1); diphenhydramine (p.577·1); dipyrone (p.49·2).

Craveril *Craveri, Arg.*
Fenofibrate (p.1286·2).
Hypercholesterolaemia.

Cravisol *Phytofarm Kleka, Pol.*
Crataegus (p.2289·1); melissa (p.2339·3); mistletoe (p.2345·3).
Atherosclerosis; heart failure; hypertension; peripheral vascular disorders.

Cravit *Daiichi, Hong Kong; Santen, Hong Kong; Ferron, Indon.; Kalbe, Indon.; Daiichi, Jpn; Santen, Jpn; Daiichi, Malaysia; Daiichi, Singapore; Santen, Singapore; Daiichi, Thai.; Santen, Thai.; Fako, Turk.*
Levofloxacin (p.292·2).
Bacterial infections.

Cravox *Lapi, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Creacal *Diviser Aquilea, Spain†.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Creagin *Infosint, Ital.†.*
Multivitamin and mineral preparation with creatine, ginkgo biloba and ginseng (p.1922·1).
Tonic.

Cream E45 *Boots Healthcare, NZ.*
Emollient.
Dry skin.

Creamalin *Valeant, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; heartburn.

Creamalin HM *Valeant, Philipp.*
Aluminium hydroxide (p.1706·2); homatropine methylbromide (p.1881·3).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer; pyrosis.

Creamy Tar *C & M, USA.*
Coal tar (p.1616·2).
Scalp disorders.

Creanolona *Bohm, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin (p.305·1); polymyxin B (p.318·2).
Skin infections with inflammation.

Creatile *Fargim, Ital.*
Creatine (p.2289·2).
Nutritional supplement.

Creatyl *Volchem, Ital.*
Amino-acid preparation or amino-acid and carbohydrate preparation (p.1922·1).
Nutritional supplement.

Creavit *Medisint, Ital.*
Carnitine; creatine; minerals; vitamins (p.1922·1).
Tonic.

Crecil *Vinas, Spain.*
Cystine (p.1937·1).
Cystine deficiency.

Credaxol *Quimica y Farmacia, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; mastocytosis; peptic ulcer; Zollinger-Ellison syndrome.

Crelisin *Corsalud, Venez.†.*
Vitamin preparation (p.1922·1).
Dietary supplement.

Crelo Blanco *Wellpharma, Ital.*
Emollient.
Dry skin disorders; pharmaceutical base.

Crema Antiinflamatoria *Spineda, Arg.*
Diethylamine salicylate (p.47·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Crema Axel *Grisi, Mex.†.*
Sulfur (p.1614·1); triclosan (p.1665·2); resorcinol (p.1612·1).
Acne.

Crema Bier *Bier, Ital.*
Barrier preparation.

Crema De Bismuto *Chobet, Arg.; Denver, Arg.; Lemax, Arg.; Vannier, Arg.*
Bismuth hydroxide (p.1712·1); pectin (p.2145·2).
Diarrhoea.

Crema Blanca *Bustillos, Mex.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation disorders.

Crema Coloreada de Proteccion Total *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); cinnamate.
Sunscreen.

Crema Compensadora Avene *Silesia, Chile.*
Emollient.
Eczema.

Crema Contracepti Lanzas *Ipsen, Spain.*
Benzalkonium chloride (p.1629·1).
Contraceptive.

Crema Facial De Dia AHA Formula 405 *Dermaclin, Mex.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Crema Facial De Noche AHA Formula 405 *Dermaclin, Mex.†.*
Moisturiser.

Crema Invisible de Proteccion Total *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); cinnamate.
Sunscreen.

Crema de Ordene
Note. This name is used for preparations of different composition.
Florida, Arg.; Nolt, Arg.
Vitamin A (p.1971·2); alpha tocopherol (p.1992·2); aloe vera (p.1588·2).
Dry skin disorders.

Spineda, Arg.
Vitamin A (p.1971·2); benzalkonium chloride (p.1629·1); zinc (p.1999·1).
Skin disorders.

Crema Para Paspaduras *Florida, Arg.*
Allantoin (p.1588·1); wool fat (p.2033·2); zinc (p.1999·1).
Barrier cream.

Crema Para Pieles Intolerantes Avene *Silesia, Chile.*
Emollient.
Dry skin.

Crema de Proteccion Extrema 50B *Pierre Fabre Dermo-Cosmetique, Arg.†.*
SPF 50: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Cremaffin *Abbott, India.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Cremag *Zuoz, Venez.*
Magaldrate (p.1742·3).
Antacid.

Cremalax *Abbott, India.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Cremalgin *Co-Pharma, UK.*
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); capsicum oleoresin (p.2276·2).
Musculoskeletal and joint pain.

Cremalon *Zuoz, Venez.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Antacid; flatulence.

Creme Ecran Total
Lancome, Canad.†.
SPF 40: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Vichy, Canad.
SPF 45: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Creme et Lait Solaire *Eucerin, Fr.†.*
SPF 25: Avobenzone (p.1589·3); octinoxate (p.1608·2); ensulizole (p.1597·1); enzacamene (p.1597·1).
Sunscreen.

Creme Gordo Barral *Lepori, Port.†.*
Emollient.

Creme Labiale Ecran Opaque *Juvex, Fr.*
SPF 50: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Lip protection; sunscreen.

Creme Laser Hidrante *Dermoteca, Port.*
⊗ Squalane (p.2032·3); proline (p.1960·2); urea (p.1620·2); lactic acid (p.2329·3); citric acid (p.2284·1); *dl*-alpha tocopherol (p.1992·2); butcher's broom (p.2270·3).
Dry skin; skin irritation.

Creme au Melilot Composee *Avene, Fr.*
Dextran sulfate (p.2293·1); melilot (p.2339·2); butcher's broom (p.2270·3).
Skin redness.

Creme Rap *IPRAD, Fr.*
Scoparium (p.2384·2); arnica (p.2260·2); aesculus (p.2248·2).
Soft-tissue disorders; venous insufficiency.

Creme Solaire Bronzage Rapide *Clarins, Canad.*
SPF 10: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Creme Solaire Bronzage Securite Special *Clarins, Canad.†.*
SPF 15: Avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Creme Solaire Haute Protection *Lancome, Canad.†.*
SPF 15: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Creme Solaire Haute Protection Special *Clarins, Canad.*
SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Creme Solaire Tres Haute Protection Special Intolerances *Clarins, Canad.*
SPF 30: Ensulizole (p.1597·1); octinoxate (p.1608·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Creme Universal *Merck, Braz.*
Emollient.

Cremederme *Bunker, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Cremicort *Chefaro, Neth.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cremicort-H *Omega, Belg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Creminem *Mintlab, Chile.*
Clotrimazole (p.530·1).
Fungal skin infections.

Creminem-B *Mintlab, Chile.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections.

Cremirit *Mintlab, Chile.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Cremisona
Note. This name is used for preparations of different composition.
ICN, Arg.†.
⊗ Sodium lactate (p.1673·3); urea (p.1620·2); squalane (p.2032·3); hyaluronic acid (p.2320·1).
Dry skin disorders.

Diba, Mex.
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Cremol-Ritter *Gebro, Switz.*
A range of skin cleansing and emollient preparations.
Skin disorders.

Cremor capsici comp *Pharmachemie, Neth.*
Capsicum (p.2276·2); glycol salicylate (p.62·3); histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Cremor Capsici compositus *Ratiopharm, Neth.*
Capsicum (p.2276·2); glycol salicylate (p.62·3); histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Cremor Neoaquasorb *Profarma, Cz.†.*
Emollient.
Skin disorders.

Cremor Refrigerans *Profarma, Cz.†.*
Emollient.
Skin disorders.

Cremosan *Quimica y Farmacia, Mex.*
Ketoconazole (p.539·1).
Fungal skin infections.

Cremsol *Quimifar, Spain.*
⊗ Linseed oil; calcium hydroxide (p.2272·2); benzocaine (p.1854·1); sulfathiazole (p.343·2); triamcinolone acetonide (p.1544·3); zinc oxide (p.1621·2).
Infected skin disorders.

Cremsor N *LKM, Arg.*
⊗ Allantoin (p.1588·1); coal tar (p.1616·2); urea (p.1620·2).
Skin disorders.

Creolina *Pearson, Ital.*
Cresol (p.1641·1).
Surface disinfection.

Creomulsion *Summit, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Creon *Altana, Arg.; Solvay, Austral.; Solvay, Belg.; Solvay, Braz.; Solvay, Canad.; Grunenthal, Chile; Solvay, Denm.; Solvay, Fin.; Solvay, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Irl.; Solvay, Israel; Solvay, Ital.; Solvay, Malaysia; Altana, Mex.; Boehringer Ingelheim, NZ; Solvay, Neth.; Solvay, Norw.; Solvay, Philipp.; Schering, S.Afr.; Solvay, Singapore; Solvay, Swed.; Solvay, Switz.; Solvay, Thai.; Solvay, UK; Solvay, USA.*
Pancreatin (p.2360·1).
Cystic fibrosis; digestive disorders; pancreatic disorders; pancreatic insufficiency.

Creo-Rectal *Sandoz, Canad.*
Diphenylpyraline hydrochloride (p.578·2); guaiacol carbonate (p.1561·2); camphor (p.2273·2).
Coughs.

Creosedin *Rontag, Arg.*
Bromazepam (p.964·3).
Anxiety.

Creosoto Composto *Ogna, Ital.*
Creosote (p.1555·1); phenol (p.1656·1); lidocaine hydrochloride (p.1862·3); eugenol (p.2301·2).
Dental pain.

Creo-Terpin *Lee, USA.*
Dextromethorphan hydrobromide (p.1555·2).

Cresadex *Drugtech, Chile.*
Rosuvastatin calcium (p.1389·1).
Hyperlipidaemias.

Crescom *Esoform, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Instrument disinfection; surface disinfection.

Cresophene
Note. This name is used for preparations of different composition.
Prats, Spain.
⊗ Dexamethasone (p.1526·1); hexachlorophene (p.1646·1); prajmalium bitartrate (p.1374·2); parachlorophenol (p.1655·2).
Dental caries; oral disinfection.

Septodont, Switz.†.
⊗ Dexamethasone acetate (p.1526·1); thymol (p.1664·3); parachlorophenol (p.1655·2); camphor (p.2273·2).
Root canal infections.

Crestor *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; Shionogi, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Rosuvastatin calcium (p.1389·1).
Atherosclerosis; hypercholesterolaemia.

Cresylate *Recsei, USA.*
m-Cresyl acetate (p.1641·1); isopropyl alcohol (p.1650·3).
Ear infection.

Crevet *Prater, Chile.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Crevet Calcio + D3 + C *Prater, Chile.*
Calcium (p.1675·2); colecalciferol (p.1986·2); ascorbic acid (p.1983·3).
Calcium supplement.

Crevet L *Prater, Chile.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Crevet-E *Prater, Chile.*
Vitamin E (p.1992·2).

Crevytin *Tolmann, Philipp.*
Vitamins; lysine; taurine (p.1922·1).

CRH *Ferring, Austria; Ferring, Ger.; Ferring, Neth.*
⊗ Corticorelin triflutate (p.1523·2).
Diagnosis of adrenal disorders; diagnosis of Cushing's syndrome.

Crialix *Filaxis, Arg.*
Donepezil (p.365·2).
Alzheimer's disease.

Criam *Psicofarma, Mex.*
Magnesium valproate (p.511·3).
Epilepsy.

Criax *Meprofarm, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Crilem *Lemery, Mex.*
Bromocriptine mesilate (p.798·1).

Crima *Fada, Arg.*
Ceftazidime (p.234·1).
Bacterial infections.

Crimanex *Drossapharm, Switz.*
Dipyrithione (p.1595·1); undecenoic acid diethanolamide (p.549·3).
Scalp disorders.

Crinalsofex *Sofex, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Criniton *Richter, Austria; Atzinger, Ger.†.*
Thymol (p.1664·3); salicylic acid (p.1612·2); rosemary oil (p.2381·3).
Scalp disorders.

Crino Cordes *Ichthyol, Austria.*
Sodium bituminosulfonate (p.1599·1); sodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3).
Scalp disorders.

Crino Cordes N *Ichthyol, Ger.†.*
Ictasol (p.1599·1).
Scalp disorders; skin disorders.

Crinohermal *Hermal, Port.*
⊗ Estradiol (p.2097·2); fluprednidene acetate (p.1533·1).
Alopecia in females.

Crinohermal fem *Hermal, Ger.*
⊗ Fluprednidene acetate (p.1533·1); estradiol (p.2097·2).
Female hair loss.

Crino-Kaban N *Asche, Ger.†.*
⊗ Clocortolone pivalate (p.1523·1); salicylic acid (p.1612·2).
Scalp disorders.

Crinone *Serono, Arg.; Serono, Austral.; Serono, Belg.; Serono, Braz.; Serono, Canad.; Novartis, Chile†; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serum Institute, India; DKSH, Indon.; Serono, Indon.; Serono, Irl.; Serono, Israel; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Douglas, NZ; Serono, Norw.; Serono, Philipp.; Serono, Port.; Serono, Rus.; Serono, S.Afr.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
Progesterone (p.2125·1).
Adjuvant in oestrogen replacement therapy; dysfunctional uterine bleeding; female infertility; gynaecological disorders; in-vitro fertilisation; menopausal disorders; menstrual disorders; progesterone deficiency.

Crinoren *Uriach, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Crinoretic *Uriach, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Criotonal *Amnol, Ital.*
Aescin; caffeine; ruscus; centella; arnica; hedera; capsicum; ginkgo biloba; menthol.
Skin disorders.

Cripar *Hormosan, Ger.; Taurus, Ger.; Merz, Switz.*
Dihydroergocryptine mesilate (p.364·2).
Migraine; parkinsonism.

Cripofen
Note. This name is used for preparations of different composition.
Arlex, Mex.
Oral drops: Paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Influenza symptoms.

Arlex, Mex.
Tablets: Paracetamol (p.108·1); phenylephrine (p.1568·1); brompheniramine (p.569·3).
Influenza symptoms.

Cripsa *Caprifarmindo, Indon.; Sanbe, Indon.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; parkinsonism; premenstrual syndrome.

Criptamine *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Bromocriptine mesilate (p.798·1).
Acromegaly; benign breast disorders; galactorrhoea; hyperprolactinaemia; hypogonadism; male and female infertility; menstrual disorders; parkinsonism.

CRI-regen *Pekana, Ger.†.*
Homoeopathic preparation.

Crisabon *Teva Tuteur, Arg.*
Epirubicin (p.716·2).
Malignant neoplasms.

Crisacide *LKM, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Crisafeno *LKM, Arg.*
⊗ Tamoxifen (p.775·1).

Crisapla *LKM, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Crisarfam *Pharmacare, Philipp.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis, leprosy, and gonorrhoea.

Crisasma *Sintesina, Arg.*
Theophylline (p.1140·1).
Obstructive airways disease.

Crisazet *LKM, Arg.*
Zidovudine (p.913·3).
HIV infection.

Crisdazol *Cristalia, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Crislaxo *Quimifar, Spain.*
Aloes (p.1705·2); aniseed (p.2258·2); cascara (p.1715·2); senna (p.1769·2); fennel (p.2302·3); rhubarb (p.1768·3); sulfur (p.1614·1); belladonna (p.2263·3).
Constipation.

Crismol *Royal, Chile.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Crisofimina *Teva Tuteur, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Crisomet *Juste, Spain.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Crisplus *Elea, Arg.*
Orlistat (p.2358·1).
Obesity.

Cristaclar *Beta, Arg.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Cristadoce *Intra, Venez.*
Vitamin B (p.1980·2).
Dietary supplement; reduced appetite.

Cristalcrom *Cinfa, Spain.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Cristalmina *Salvat, Spain.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Cristalomicina
Note. This name is used for preparations of different composition.
Ivax, Arg.
Ear drops: ⊗ Kanamycin sulfate (p.291·2); hydrocortisone (p.1535·2); phenazone (p.116·1); benzocaine (p.1854·1).
Otitis externa; otitis media.

Ivax, Arg.
Injection: Kanamycin sulfate (p.291·2).
Tuberculosis.

Cristalpen *Biolab Sanus, Braz.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Cristan *Shin Poong, Singapore.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal candidiasis.

Cristane *Cardinal, Philipp.*
Betacarotene; vitamin C; vitamin E; zinc (p.1922·1).
Dietary supplement.

Cristerona *Gador, Arg.*
Estradiol (p.2097·2); progesterone (p.2125·1).
Menstrual disorders.

Cristil *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Cristopal *Alcon, Fr.†.*
Calcium chloride (p.1675·2); sodium succinate (p.2391·1); magnesium aspartate (p.1679·1); glycine (p.1947·3).
Lens opacities.

Criten *Tecnofarma, Chile.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; parkinsonism.

Criticare HN *Mead Johnson, Austral.; Mead Johnson Nutritionals, Canad.†; Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).

Critichol *Angelini, Ital.*
Fenipentol hemisuccinate (p.2302·3); cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3).
Constipation.

Crivion *Farmanust, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Crixan *Ranbaxy, Malaysia; Ranbaxy, Singapore; Ranbaxy, Thai.*
Clarithromycin (p.248·2).
Bacterial infections.

Crixivan *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; Banyu, Jpn; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Indinavir sulfate (p.882·2).
HIV infection.

Cro 50 *Investigaciones Filosoficas y Cientificas, Mex.*
Ribonuclease (p.2378·3).
Inflammation.

Croben *Wassen, Ital.*
Chromium (p.1934·3).
Nutritional supplement.

Crobextin *Hexal, Philipp.; Salutas, Philipp.*
Carboplatin (p.693·1).
Malignant neoplasms.

Crocalcin *Boehringer Ingelheim, Gr.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; Paget's disease of bone.

Crocin *GSK, India; Solvay, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

CroFab *Altana, USA.*
Crotalidae polyvalent immune fab (p.2238·3).
Rattlesnake bites.

Crofed *Coronet, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; upper respiratory-tract allergy.

Croferron *Degorts, Mex.*
Ferrous fumarate (p.1938·3).
Iron deficiency.

Croglina *Edol, Port.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Crohnezine *Vianex (Βιανεξ), Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Croix Blanche *SMB, Belg.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Crolidin *Kleva, Gr.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Crolisil *Loeffler, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Crolix *Rayere, Mex.*
Roxithromycin (p.331·1).
Bacterial infections.

Crolom *Dura, USA.*
Sodium cromoglicate (p.1136·3).
Inflammatory disorders of the eye.

Crom *Selvi, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Cromabak *Thea, Belg.; Allergan, Braz.; Thea, Fr.; Pharmex (Φαρμεξ), Gr.; Thea, Hong Kong; Thea, Ital.; Thea, Philipp.; Thea, Port.; Genop, S.Afr.†; Pfizer, Singapore; Thea, Switz.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Cromadoses *Thea, Fr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Cromal *Mundipharma, Austria†; Cipla, Hong Kong; Cipla, India.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders; allergic rhinitis; asthma; obstructive airways disease.

Cromantal *Alcon, Ital.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Cro-Man-Zin *Freeda, USA.*
Chromium, manganese, and zinc preparation (p.1922·1).
Mineral supplement.

Cromatodol *Croma, Austria.*
Tramadol hydrochloride (p.130·3).
Pain.

Cromatonbic B12 *Menarini, Spain.*
Cyanocobalamin (p.1980·2).
Vitamin B12 deficiency.

Cromatonbic Ferro *Menarini, Arg.†; Menarini, Spain.*
Ferrous lactate (p.1939·2).
Iron deficiency; iron-deficiency anaemia.

Cromatonbic Folinico *Menarini, Arg.†; Menarini, Spain.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; folate deficiency; megaloblastic anaemia; methotrexate toxicity.

Cromatonferro *Menarini, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in the tablets to increase the absorption and availability of iron.
Anaemias; iron deficiency.

Cromer Orto *Normon, Spain.*
Merbromin (p.1652·1).
Skin and wound disinfection.

Cromese *Pfizer, Austral.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromex *Davi, Port.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Cromezin *SoSe, Ital.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Cromidin *Royal, Chile.*
Tacrolimus (p.1843·1).
Atopic eczema.

Cromifusin *Pisa, Mex.†.*
Chromium trichloride (p.1934·3).

Cromisol *Vivax Optipharm, Venez.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Cromo *1A, Ger.; CT, Ger.; Ratiopharm, Ger.; Stulln, Ger.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma; hypersensitivity reactions.

Cromo Asma *Aldo, Spain†.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchospasm.

Cromobene *Ratiopharm, Cz.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis; asthma.

Cromocato *Neo Quimica, Braz.*
Sodium cromoglicate (p.1136·3).

Cromocur *Tipomark, Ital.†.*
Merbromin (p.1652·1).
Wound disinfection.

Cromodal *Zwitter, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Cromodyn *Rappai, Switz.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Cromoftal *Oftalmi, Venez.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Cromogen *Galena, Cz.†; Ivax, Cz.†; Ivax, Irl.; Norton, Israel†; Norton, Pol.; Ivax, UK†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromoglicin *Heumann, Ger.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma.

Cromoglin *Ratiopharm, Austria; Merckle, Rus.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders; allergic rhinitis; obstructive airways disease.

Cromohexal *Hexal, Cz.; Hexal, Ger.; Sandoz, Hung.; Hexal, Pol.; Hexal, Rus.; Hexal, S.Afr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma.

Cromolerg *Allergan, Braz.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Cromolergin UD *Pharmanel, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Cromolind *Lindopharm, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromolux *AFT, NZ.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Cromolyn *Pharmascience, Canad.; Orion, Cz.†; Orion, Hung.†; Genmedix, Israel.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma.

Cromonez-Pos *Ursapharm, Belg.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Cromophtal *Agepha, Austria.*
Sodium cromoglicate (p.1136·3).
Conjunctivitis.

Crom-Ophtal *Winzer, Ger.; Sanbe, Indon.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Cromophta-Pos *Ursapharm, Belg.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Cromoplex *Otsira, India.*
Vitamin preparation with chromium and zinc (p.1922·1).

Cromo-POS *Farmex, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Cromopp *Dermapharm, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromoptic *Chauvin, Fr.; Vitamed, Israel.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic eye disorders.

Cromosan *Medici, Ital.†.*
Sodium cromoglicate (p.1136·3).
Food hypersensitivity.

Cromosoft *Thea, Fr.†.*
Sodium cromoglicate (p.1136·3).

Cromosol *ICN, Pol.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Cromosol ophta *Ecosol, Switz.*
Sodium cromoglicate (p.1136·3).
Conjunctivitis.

Cromosol UD *Ecosol, Switz.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromo-Spray *Oftalmi, Venez.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromotex *Medix, Mex.*
Chromium dinicotinate (ChromeMate).
Chromium supplement.

Cromovisus *DMG, Ital.†.*
Calcium phosphate; bioflavonoids; yeast; vitamins (p.1922·1).
Nutritional supplement.

Cromoxal *Hexal, Pol.*
Sodium cromoglicate (p.1136·3).
Asthma.

Cromoxin K *Rius, Spain†.*
Carbazochrome (p.1058·2); phytomenadione (p.1995·3).
Haemorrhage.

Cromozil *Tubilux, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1); sodium cromoglicate (p.1136·3).
Conjunctivitis.

Cromycin *Croma, Austria.*
Tobramycin (p.354·1).
Bacterial eye infections.

Cronal *Valdecasas, Mex.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity.

Cronase *Vitamed, Israel.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Cronasma *Orion, Ger.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Cronavit *Degorts, Mex.*
Multivitamin preparation with iron (p.1922·1).
Tonic.

Cronemet *Special Product's Line, Ital.*
Gliclazide (p.440·3).
Diabetes mellitus.

Croneparina *Ivax, Arg.; UCB, Gr.†; UCB, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Cronitin *GMP, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Cronizat *Caber, Ital.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Cronobe *Biolab Sanus, Braz.*
Cobamamide (p.1980·2).
Tonic.

Cronocaps *Medix, Mex.*
Melatonin (p.2338·3).
Insomnia.

Cronocef *ICN, Ital.*
Cefprozil (p.232·2).
Bacterial infections.

Cronocol *Schering-Plough, Port.*
Gentamicin sulfate (p.282·1).
Bone infections.

Cronocorteroid *Montpellier, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Cronodine *Alacan, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Cronoferril *Grunenthal, Chile†.*
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); folic acid (p.1940·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Cronogeron *Arrow, Braz.*
Cinnarizine (p.573·1).
Peripheral vascular disorders; vestibular disorders.

Cronol *Solvay, Spain.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cronolax *Andromaco, Chile.*
Sodium picosulfate (p.1771·1).
Constipation.

Cronolevel *Schering-Plough, Arg.; Essex, Chile; Schering-Plough, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Lidocaine (p.1862·3) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Cronomet *MSD, Braz.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Cronopen *Elea, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Cronopen Balsamico *Elea, Arg.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); dipyrone (p.49·2); guaifenesin (p.1561·3).
Respiratory-tract infections.

Cronoplex
Note. This name is used for preparations of different composition.
Delta, Braz.
Oral solution: Sodium picosulfate (p.1771·1).
Constipation.

Delta, Braz.
Suppositories; tablets: Bisacodyl (p.1710·1).
Constipation.

Cronovera *Pharmacia, Braz.†; Pfizer, Mex.; Pfizer, Venez.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Cronus *Tecnofarma, Chile.*
Paracetamol (p.108·1); tramadol hydrochloride (p.130·3).
Pain.

Cropoz *GSK, Rus.*
Sodium cromoglicate (p.1136·3).

Cropoz G *GSK, Pol.*
Sodium cromoglicate (p.1136·3).
Food allergy.

Cross Brand Corn Plasters *Wrapsa, S.Afr.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Crotamitex *Gepepharm, Ger.*
Crotamiton (p.1593·2).
Scabies.

Crotamiton H *Pharmaniaga, Malaysia.*
⊗ Hydrocortisone (p.1535·2); crotamiton (p.1593·2).
Formerly known as H-C.
Skin disorders.

Crotanol *Roemmers Osmoph, Venez.*
Crotamiton (p.1593·2).
Pediculosis; pruritus; scabies.

Crotorax *Sarabhai Piramal, India; Idaman, Malaysia.*
Crotamiton (p.1593·2).
Pediculosis; pruritus; scabies.

Crotorax-HC *Sarabhai Piramal, India.*
⊗ Crotamiton (p.1593·2); hydrocortisone (p.1535·2).
Pruritus.

Crovalen *Degorts, Mex.*
Multivitamin preparation with iron (p.1922·1).

Crowne *Master, Chile.*
⊗ Potassium nitrate (p.1658·3).
Hypersensitive teeth.

Croxilex *Ulagay, Turk.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Crucial *Nestle, Fr.*
Preparation for enteral nutrition (p.1922·1).

Cruex
Note. This name is used for preparations of different composition.
Novartis Consumer, USA.
Aerosol; cream: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Bromhidrosis; fungal skin infections; hyperhidrosis; minor skin irritation; nappy rash.

Novartis Consumer, USA.
Topical powder: Calcium undecenoate (p.549·3).
Bromhidrosis; fungal skin infections; hyperhidrosis; minor skin irritation; nappy rash.

Crupodex *Biogal-Teva, Hung.†.*
Dextranomer (p.1593·3).
Burns; ulcers; wounds.

Cruscasohn *Antonetto, Ital.*
Cereal fibre; guar gum (p.442·3); pectin (p.2145·2).
Constipation.

Crusken *GSK Consumer, Ital.*
A range of dietary fibre supplements (p.1712·3).
Delayed gastrointestinal transit.

Cruzafen *Meditrina, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by cancer chemotherapy.

Cruzzy *SIT, Ital.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Cruzzy Shampoo Potenziato alla Sumitrina *SIT, Ital.*
Phenothrin (p.2048·3).
Pediculosis.

Cryaxon *Bosch, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Cryobutol *Cryopharma, Mex.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Cryocriptina *Cryopharma, Mex.*
Bromocriptine (p.800·3).
Hyperprolactinaemia; lactation inhibition.

Cryogenine Plus *Andromaco, Chile†.*
Paracetamol (p.108·1).
Fever; pain.

Cryogesic *Acorus, UK.*
Ethyl chloride (p.1861·2).
Local anaesthesia; testing of regional blockade; testing of tooth vitality.

Cryometasona *Cryopharma, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Cryoperacid *Cryopharma, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Cryopina *Cryopharma, Mex.*
Hyoscine butylbromide (p.1734·1).

Cryoplex *Cryopharma, Mex.*
Vitamin B substances (p.1922·1).
Anaemias; neuritis.

Cryopril *Cryopharma, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension.

Cryosolona *Cryopharma, Mex.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Cryotol *Cryopharma, Mex.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Cryo-Tropin *Cryopharma, Mex.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Cryoxet *Cryopharma, Mex.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Cryoxifeno *Pizzard, Mex.*
⊗ Tamoxifen (p.775·1).

Cryptal *Fahrenheit, Indon.*
Fluconazole (p.532·1).
Fungal infections.

Cryptocur *Aventis, Neth.*
⊗ Gonadorelin (p.2106·2).
Cryptorchidism.

Crysanal *Roche, Austral.*
Naproxen sodium (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

CrySelle *Barr, USA.*
21 Tablets, ethinylestradiol (p.2101·3); norgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Crystacide *Tramedico, Belg.†; Riemser, Ger.; Bioglan, Hong Kong†; Bioglan, Irl.†; Bioglan, Israel†; Mipharm, Ital.; AFT, NZ; CS, Port.; Celltech, Spain†; GP, UK.*
Hydrogen peroxide (p.1647·3).
Skin infections.

Crystacit *Be-Tabs, S.Afr.*
Potassium citrate (p.1673·2); citric acid (p.2284·1).
Urinary alkalinisation.

Crystal Clear *ACS, Austral.†; Douglas, NZ.*
Pregnancy test (p.2372·1).

Crystamine *Dunhall, USA.*
Cyanocobalamin (p.1980·2).
Schilling test; vitamin B deficiency.

Crystapen *Bioniche, Canad.; Britannia Pharmaceuticals, Irl.; Britannia Pharmaceuticals, UK.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Crystepin *Zentiva, Cz.; Leciva, Rus.*
⊗ Clopamide (p.1250·1); reserpine (p.1387·3); dihydroergocristine mesilate (p.364·2).
Hypertension.

Crysti 1000 *Hauck, USA; Roberts, USA.*
Cyanocobalamin (p.1980·2).
Schilling test; vitamin B deficiency.

Crysticillin *Apothecon, USA.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Crystodigin *Lilly, USA.*
Digitoxin (p.1259·1).
Atrial flutter and fibrillation; heart failure; supraventricular tachycardia.

Crytion *Temis, Arg.*
Sodium aurotiosulfate (p.124·2).
Rheumatoid arthritis.

Crytioro *Drag, Chile.*
Sodium aurotiosulfate (p.124·2).
Ankylosing spondylitis; juvenile rheumatoid arthritis; lupus erythematosus; pemphigus; psoriatic arthritis; rheumatoid arthritis.

C-Sik *Frankin, Hong Kong†.*
Cinnarizine (p.573·1); pyridoxine (p.1979·1).
Motion sickness.

C-Solve *Syosset, USA.*
Vehicle for topical preparations.

CST *Pose, Thai.*
Clotrimazole (p.530·1).
Fungal vaginal infections; trichomoniasis.

CT1000 *Sigma, Arg.*
Cartilage glycosaminoglycans (shark) (p.2277·3).
Musculoskeletal and joint disorders; osteoporosis.

CT Ointment *Life, Israel†.*
Coal tar (p.1616·2); dead sea minerals.
Psoriasis; seborrhoeic dermatitis.

CT Pommade *Life, Israel†.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); dead sea minerals.
Psoriasis of the scalp.

CT Shampoo *Life, Israel†.*
Coal tar (p.1616·2); tar (p.1616·2); cade oil (p.1616·1); dead sea minerals.
Psoriasis; seborrhoeic dermatitis.

C-Tabs *Ferrosan, Fin.*
Ascorbic acid (p.1983·3).
Dietary supplement; vitamin C deficiency.

C-Tamin *Rekah, Israel.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

C-Tan D *Centurion, USA.*
Phenylephrine tannate (p.1568·3); brompheniramine tannate (p.569·3).
Upper respiratory-tract disorders.

C-Tanna 12D *Prasco, USA.*
Pentoxyverine tannate (p.1567·3); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

C-Tard *Wyeth Consumer, Ital.*
Ascorbic acid (p.1983·3).
Adjunct in stomatitis and gingivitis; vitamin C deficiency.

CTM *Berlico Mulia, Indon.*
Chlorphenamine maleate (p.571·3).
Allergic disorders.

CTR *Liptis, USA.*
Atorvastatin (p.1219·1).

CTZ *Syncom, India.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Cuadel *Cetus, Arg.*
Diazepam (p.986·3).
Anxiety; muscle spasm.

Cuait D *Ariston, Arg.*
Trifluoperazine hydrochloride (p.1034·2); tranylcypromine sulfate (p.424·1).
Depression.

Cuait N *Ariston, Arg.*
Trifluoperazine hydrochloride (p.1034·2); amobarbital (p.961·3).
Insomnia.

Cuantil *Teva Tuteur, Arg.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Cuarcic *Monte Verde, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Cuassicum *Nucleopharm, Arg.*
Quassia (p.2377·1); thyme oil (p.2401·2).
Pediculosis.

Cuassicum Prevent 2 en 1 *Nucleopharm, Arg.*
Quassia (p.2377·1).
Pediculosis.

Cuatroderm *Desarrollo, Spain.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3).
Infected skin disorders.

Cuatroepi *Varifarma, Arg.*
Epirubicin (p.716·2).
Malignant neoplasms.

Cuatromin *Grunenthal, Chile.*
Vitamin preparation (p.1922·1).

Cubicin *Novartis, Cz.; Novartis, Gr.; Cubist, Israel; Novartis, Port.; Novartis, UK; Cubist, USA.*
Daptomycin (p.264·1).
Gram-positive skin and skin structure infections; right-sided infective endocarditis.

Cubison *Nutricia, Austral.†; Nutricia, Fin.; Nutricia, Ital.; Nutricia, Port.*
Preparation for enteral nutrition (p.1922·1).
Bedsores; dietary management of wounds.

Cubitan *Nutricia, Austral.†; Support, Braz.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.*
Preparation for enteral nutrition (p.1922·1).
Bedsores; pressure sores.

Cucurbita Compuesta *Hochstetter, Chile†.*
Homoeopathic preparation.

Cuerpo Amarillo Fuerte *Hormona, Mex.*
Progesterone (p.2125·1).
Menstrual disorders; threatened miscarriage.

Cuidaderma *Caldeira & Metelo, Port.*
Zinc oxide (p.1621·2); almond oil (p.2252·2); starch (p.1968·1); talc (p.1615·2).
Skin irritation.

Cuidado Intimo *Beiersdorf, Chile.*
Lactic acid (p.2329·3); levomenol (p.2333·3).
Feminine hygiene.

Cuidafem *Bernabo, Arg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Culat *Roche, Austria.*
⊗ Epoetin beta (p.1061·1).
Anaemia of prematurity, chronic renal failure or malignant disease; autologous blood transfusions.

Cullens Headache Powders *Cullen & Davison, UK.*
Aspirin (p.20·3); caffeine (p.1116·3).

Cultivo BCG *Lemery, Mex.*
BCG vaccine (p.2205·3).
Bladder cancer.

Culture Care *Lifeplan, UK.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactococcus lactis* (p.2372·3); *Bifidobacterium bifidum* (p.2372·3); fructo-oligosaccharides.
Maintenance of normal gastrointestinal flora.

Culturelle
Note. This name is used for preparations of different composition.
Pharma Dynamics, S.Afr.
Bifidobacterium longum (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3).
Restoration of intestinal flora.

Pharma Dynamics, S.Afr.
Capsule; chewable tablets: Bifidobacterium longum (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3).
Restoration of intestinal flora.

Culturelle VC *Pharma Dynamics, S.Afr.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus paracasei* (p.2372·3).
Restoration of vaginal flora.

Culuflex H *Celudrop, Arg.*
Hyaluronic acid (p.2320·1); vitamin B (p.1959·3); vitamin E (p.1992·2); octinoxate (p.1608·2).
Skin disorders.

Cumadren *NAM, Ital.*
Melilot; manna; vitamins; rutin; minerals (p.1922·1).
Nutritional supplement.

Cumar *Medifarm Ducray, Venez.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Cumarol *Elea, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Cumatil L *Bayer, Arg.*
Phenytoin (p.495·2); methylphenobarbital (p.490·2); phenobarbital (p.492·2).
Epilepsy.

Cunesin *Recordati, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cupanol *Guardian, Indon.; Ern, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Cuparcen HM *Pfluger, Ger.†.*
Homoeopathic preparation.

Cupax *Kleva, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Cuplaton *Orion, Fin.; Orion, Malaysia; Orion, Singapore.*
Dimethicone (p.1770·2).
Abdominal discomfort; aid in gastrointestinal radiography and gastroscopy; flatulence; meteorism.

Cuplex *Smith & Nephew, Irl.; Crawford, UK.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; warts.

Cuprenil *Polfa Kutno, Pol.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; rheumatoid arthritis; Wilson's disease.

Cupressin *Takeda, Malaysia†; Takeda, Philipp.; Takeda, Singapore; Takeda, Thai.†.*
Delapril hydrochloride (p.1256·2).
Hypertension.

Cupridium *DHU, Ger.†.*
Homoeopathic preparation.

Cuprifusin *Pisa, Mex.†.*
Copper sulfate (p.1935·3).

Cuprimine *MSD, Arg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Hong Kong†; MSD, Israel†; MSD, Norw.†; MSD, Thai.; Aton, USA.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; rheumatoid arthritis; Wilson's disease.

Cupripen *Omedir, Arg.; IFET (ΙΦΕΤ), Gr.†; Rubio, Spain.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; rheumatoid arthritis; Wilson's disease.

Cuprocept CCL *Cuprocept, S.Afr.†.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Cuprofen *SSL, UK.*
Ibuprofen (p.64·2).
Cold and influenza symptoms; fever; inflammation; pain.

Cuprofen Plus *SSL, UK.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Pain.

Cuprosodio *Bier, Ital.*
Cetrimide (p.1634·1); copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Personal hygiene.

Cuprosodio Plus *Bier, Ital.*
Chlorhexidine gluconate (p.1635·3); copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Genital hygiene.

Curacao *Age D'or, Singapore.*
Aloe vera (p.1588·2).
Wound disinfection.

Curacid *Finadiet, Arg.*
Fatty acid glycerides; fatty acid triglycerides; vitamin A; vitamin D.
Haemorrhoids; skin disorders; vaginal disorders.

Curacil *Kalbe, Indon.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Curacit *Nycomed, Norw.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Curacleanse *Curacel, Austral.†.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Curacne *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Gr.; Pierre Fabre Dermatologie, Pol.*
Isotretinoin (p.1599·2).
Acne.

Curaderm *Curacel, Austral.†.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2); melaleuca oil (p.2338·2); linolenic acid (p.1362·1); solasodine glycosides.
Actinic keratoses; sunspots.

Curadon *AstraZeneca, Swed.*
Paracetamol (p.108·1).
Fever; pain.

Curadona *Lainco, Spain.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Curafil *Betamadrileno, Spain.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Curakne *Pierre Fabre, Switz.*
Isotretinoin (p.1599·2).
Acne.

Curalest *Pharmachemie, Neth.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Curam
Sandoz, Austral.; Sandoz, Austria; Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.; Sandoz, Venez.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Biochemie, Hong Kong; Sandoz, S.Afr.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Sandoz, Malaysia; Sandoz, Singapore.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Sandoz, Thai.
Amoxicillin (p.202·2), amoxicillin sodium (p.202·2), or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2) or potassium clavulanate (p.250·2).
Bacterial infections.

Curanail *Galderma, UK.*
Amorolfine (p.523·1).
Fungal nail infections.

Curandron *Schering, Austria; Berlipharm, Neth.*
Cyproterone acetate (p.2088·2).
Androgen dependent acne, alopecia, hirsutism, and seborrhoea in women; prostatic cancer; sexual behaviour disorders.

Curantyl *Berlin-Chemie, Rus.*
Dipyridamole (p.1268·1).
Cerebrovascular disorders; microcirculatory disorders; placental insufficiency; thromboembolism prophylaxis.

Curantyl N *Berlin-Chemie, Cz.†; Berlin-Chemie, Ger.†.*
Dipyridamole (p.1268·1).
Thromboembolism prophylaxis; thrombosis prophylaxis.

Curare comp *Hanosan, Ger.†.*
Homoeopathic preparation.

Curarine *Taro, Israel†.*
Tubocurarine chloride (p.1912·3).
Competitive neuromuscular blocker.

Curasan *Kohler, Cz.†.*
Hyaluronic acid (p.2320·1).
Synovial fluid replacement.

Curasept *Curaprox, UK.*
Chlorhexidine (p.1635·2).
Oral hygiene.

Curash *Carter-Wallace, Philipp.*
Zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Curash Anti-Rash *Carter, Austral.*
Zinc oxide (p.1621·2).
Hyperhidrosis; nappy rash; skin irritation.

Curash Baby Wipes *Carter, Austral.*
Vitamin E (p.1992·2); sorbolene.
Skin cleanser and moisturiser.

Curash Babycare *Carter, Austral.*
dl-Alpha tocoferil acetate (p.1992·3); zinc oxide (p.1621·2); almond oil (p.2252·2).
Nappy rash.

Curasten *Therabel, Fr.*
Lysine hydrochloride (p.1955·1); calcium gluceptate (p.1675·3).
Asthenia.

Curatane *Douglas, Israel.*
Isotretinoin (p.1599·2).
Acne.

Curatin
Note. This name is used for preparations of different composition.
Carter, Austral.
Tolnaftate (p.548·3).
Fungal skin infections.

Sanova, Austria.
Biotin (p.1931·3).
Hair and nail disorders.

Curatoderm *Hermal, Austria; Boots Healthcare, Belg.; Hermal, Cz.; Hermal, Ger.; Hermal, Hung.; Hermal, Israel; Herrmann, Pol.; Boots Healthcare, Switz.; Crookes Healthcare, UK.*
Tacalcitol (p.1615·1).
Psoriasis.

Curaven *Boehringer Ingelheim, Ital.†.*
Aesculus (p.2248·2).
Peripheral vascular disorders.

Curavisc *Margalit, Israel.*
Sodium hyaluronate (p.2320·1).
Degenerative joint disorders.

Curazid (Reformulated) *Natrapharm, Philipp.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Curazink *Stada, Ger.*
Zinc histidinate (p.2000·1).
Zinc deficiency.

Curban *Rafarm, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Curcuma Plus *Soho, Indon.*
Vitamin B substances; betacarotene; curcuminoid (p.1922·1).
Reduced appetite.

Curcumen *Temmler, Ger.*
Javanese turmeric (p.2406·3).
Dyspepsia.

Curcu-Truw *Truw, Ger.*
Javanese turmeric (p.2406·3).
Dyspepsia.

Curel *Bausch & Lomb, USA.*
Emollient and moisturiser.

Curethyl *Tradiphar, Fr.*
⊗ Alcohol (p.1625·2).
Alcohol withdrawal syndrome.

Curfos *Interbat, Indon.*
Curcuminoid; fructo-oligosaccharide; docosahexaenoic acid; arachidonic acid; vitamin B substances (p.1922·1).
Reduced appetite; vitamin supplement.

Curicap *MDS, Cz.; MDS, Port.; Nucliber, Spain.*
Iodine-131 as sodium iodide (p.2054·3).
Hyperthyroidism; thyroid cancer.

Curine *Leti, Spain†.*
Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).
Pain; pruritus.

Curinflam
Duncan, Arg.
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3).
Inflammation; pain.

Duncan, Hong Kong.
Diclofenac diethylamine (p.44·3).
Inflammation; pain.

Curinflam Plus *Duncan, Arg.*
Diclofenac (p.44·2); pridinol (p.1898·2).

Curiosin
Note. This name is used for preparations of different composition.
Gedeon Richter, Cz.†.
Sodium hyaluronate (p.2320·1); zinc chloride (p.1999·1).
Acne; skin ulcers; wounds.

Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Rus.
Zinc hyaluronate (p.2320·2).
Acne; fistulas; skin disorders; ulcers; wounds.

Curisept *Excelentia, Arg.†.*
Piroxoline; hydroxyquinoline (p.2323·2).
Wounds.

Curlem *Lemery, Mex.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Curliv *Soho, Indon.*
Schisandra (p.2384·2); javanese turmeric (p.2406·3); liquorice (p.1740·3); choline bitartrate (p.1934·2); vitamin B (p.1922·1).
Liver disorders.

Curliv Plus
Note. This name is used for preparations of different composition.
Soho, Indon.
Capsules: Silymarin (p.1452·2); schisandra (p.2384·2); Javanese turmeric (p.2406·3); liquorice (p.1740·3); choline bitartrate (p.1934·2); vitamin B (p.1922·1).
Liver disorders.

Soho, Indon.
Syrup: Silymarin (p.1452·2); schisandra (p.2384·2); Javanese turmeric (p.2406·3); liquorice (p.1740·3); vitamin B (p.1922·1).
Liver disorders.

Curmunos *Fahrenheit, Indon.*
Echinacea (p.2298·1); curcumin; bovine colostrum; lysine hydrochloride; docosahexaenoic acid; vitamins (p.1922·1).
Maintenance of healthy immune system.

Curocef
GSK, Austria.
Cefuroxime sodium (p.238·2).
Bacterial infections.

GSK, Chile.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Curon-B *Intramed, S.Afr.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Curosurf *Douglas, Austral.; Nycomed, Austria; Pharma Logistics, Belg.; Farmalab, Braz.; Chiesi, Cz.; Nycomed, Denm.; Leiras, Fin.; Chiesi, Fr.; Nycomed, Ger.; Chiesi, Gr.; Chiesi, Hung.; Trinity, Irl.; SLE, Israel; Chiesi, Ital.; Douglas, NZ; Nycomed, Neth.; Nycomed, Norw.; Chiesi, Pol.; Lepori, Port.; Chiesi, Rus.; Safeline, S.Afr.; Chiesi, Spain; Nycomed, Swed.; Nycomed, Switz.; Chiesi, Thai.; Trinity, UK; Dey, USA.*
Poractant alfa (p.2376·1).
Neonatal respiratory distress syndrome.

Curoxim *GSK, Ital.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Curoxima *GSK, Spain.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Curoxime *Glaxo Wellcome, Port.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Curpol *Pfizer Consumer, Belg.*
Paracetamol (p.108·1).
Fever; pain.

Curson *Soho, Indon.*
Javanese turmeric (p.2406·3); lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1).
Hepatitis.

Curvit *Soho, Indon.*
Vitamin B substances; calcium gluconate; curcuminoid (p.1922·1).
Calcium supplement; reduced appetite; vitamin supplement.

Curvit CL *Soho, Indon.*
Vitamins; calcium hypophosphite; arachidonic acid; docosahexaenoic acid; fructo oligosaccharides; cod-liver oil; curcuma (p.1922·1).
Nutritional supplement; tonic.

Curyken *Kendrick, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus; urticaria.

Cusate *Pharmasant, Thai.*
Docusate sodium (p.1725·1).
Constipation.

Cuscutine *Geymonat, Ital.*
Senna (p.1769·2); aloin (p.1705·3).
Constipation.

Cusibel *Cusi, Venez.†.*
⊗ Tetryzoline (p.1574·1).
Eye congestion.

Cusicrom *Alcon, Cz.; Alcon, Hung.†; Alcon Cusi, Malaysia; Alcon, Pol.; Alcon, Port.†; Alcon Cusi, Spain; M4, Spain.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders; allergic rhinitis.

Cusimolol *Alcon, Hung.; Alcon, Ital.; Alcon Cusi, Malaysia; Alcon, Pol.; Alcon, Port.†; Alcon Cusi, Spain; Alcon, Turk.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Cusiviral *Alcon, Hong Kong; Alcon Cusi, Malaysia; Alcon, Pol.; Alcon, Singapore.*
Aciclovir (p.862·3).
Herpes simplex keratitis.

Custey *Microsules, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Custodial *Schwabe, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Custodiol *Kohler, Austria; Tramedico, Belg.†; Kohler, Cz.†; Kohler, Ger.; IFET (ΙΦΕΤ), Gr.; Tramedico, Neth.*
Organ perfusion solution (p.1667·1).
Cardioplegia; transplant preservation.

Custoplex *Biogam, Arg.*
Organ perfusion solution (p.1667·1).

Cuta Crema *Fortbenton, Arg.*
⊗ Gentamicin sulfate (p.282·1); betamethasone (p.1518·2); miconazole nitrate (p.541·3).
Infected skin disorders.

Cutacelan *Schering, Arg.; Schering, Mex.†; Schering, Venez.*
Azelaic acid (p.1589·3).
Acne.

Cutaclin *Valeant, Mex.*
Clindamycin phosphate (p.251·2).
Acne; pyodermas.

Cutacnyl *Galderma, Fr.*
Benzoyl peroxide (p.1590·2).
Acne.

Cutaderm *Schering-Plough, S.Afr.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Cutanil *ITF, Chile.*
Clotrimazole (p.530·1); zinc oxide (p.1621·2).
Fungal skin infections.

Cutaninfant *Rubiepharm, Ger.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Cutanit *Astellas, Spain.*
⊗ Fluclorolone acetonide (p.1529·3).
Skin disorders.

Cutanplast *Mascia Brunelli, Ital.*
⊗ Gelatin (p.1072·1).
Haemostasis.

Cutanum *Jenapharm, Ger.*
Estradiol (p.2097·2).
Menopausal disorders.

Cutasept *Bode, Ger.; Pharma-Chemie, Gr.; Beiersdorf, Switz.*
Isopropyl alcohol (p.1650·3); benzalkonium chloride (p.1629·1).
Skin disinfection.

Cutemol *Summers, USA.*
Emollient and moisturiser.

Cutenox *Biochimico, Braz.†.*
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders; unstable angina.

Cuteplex *Jumont, Philipp.*
Vitamin preparation with or without ferrous sulfate (p.1922·1).

Cuteral *Panalab, Arg.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Cuterpes *Chauvin, Fr.*
Ibacitabine (p.881·2).
Herpes labialis.

Cuticerin *Smith & Nephew, Fr.*
Hard paraffin (p.2030·3); white soft paraffin (p.2031·2).
Burns; ulcers; wounds.

Cuticlin *Vivax, Venez.*
Isotretinoin (p.1599·2).
Acne.

Cuticura
Note. This name is used for preparations of different composition.
Novartis Consumer, S.Afr.†.
Hydroxyquinoline (p.2323·2); sulfur (p.1614·1); phenol (p.1656·1).

DEP, USA†.
Triclocarban (p.1665·2).
Skin cleanser.

Cutiderm *Prodotti, Braz.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Skin infections.

Cutidermin *Phoenix, Arg.†.*
Resorcinol (p.1612·1); bismuth salicylate (p.1711·1).
Skin disorders.

Cuti-Do *Grasler, Ger.†.*
Homoeopathic preparation.

Cutimix *Metochem, Austria; Metochem, Cz.†.*
Zinc oxide (p.1621·2); talc (p.1615·2).
Skin disorders.

Cutinorm *Ipca, India†.*
⊗ Beclometasone dipropionate (p.1516·2); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Bacterial and fungal skin infections.

Cutinova *Smith & Nephew Healthcare, UK.*
Polyurethane foam dressing (p.1611·1).
Burns; ulcers; wounds.

Cutinova Alginate *Nuova Signorini, Ital.*
Calcium alginate (p.1058·1).
Wounds.

Cutinova Hydro *Smith & Nephew, Ital.*
Polyurethane dressing (p.1611·1).
Skin ulcers.

Cutiphile *Braun, Fr.†.*
Bismuth subgallate (p.1711·1); bismuth subnitrate (p.1711·2); zinc oxide (p.1621·2).
Skin disorders.

Cutisan *Boots Healthcare, Fr.*
Triclocarban (p.1665·2).
Skin disorders.

Cutisanol
Note. This name is used for preparations of different composition.
Millet Roux, Braz.
Ointment: Magnesium silicate (p.2144·3); thymol iodide (p.1664·3); zinc oxide (p.1621·2); bismuth subgallate (p.1711·1).
Skin disorders.

Millet Roux, Braz.
Topical gel: Zinc oxide (p.1621·2); bismuth subgallate (p.1711·1).
Skin disorders.

Cutisoft *Ipca, India.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Cutisorb *BSN, Fr.*
Dialkylcarbamoyl chloride (DACC).
Wound dressing.

cutistad *Stada, Ger.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Cutivat *GSK, Denm.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Cutivate *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK Consumer, Canad.; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Israel†; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Turk.; GSK, UK; PharmaDerm, USA; GSK, Venez.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Cutter *United, Canad.†.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Cuvalit *Schering, Ger.†.*
Lisuride maleate (p.811·1).
Migraine.

Cuvefilm *Perez Gimenez, Spain.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Cuxabrain *TAD, Ger.†.*
Piracetam (p.368·2).
Mental function disorders.

Cuxafenon *TAD, Ger.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Cuxanorm *TAD, Ger.*
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension; ischaemic heart disease.

Cu-Zn *Uriage, Fr.*
A range of preparations containing copper pidolate (p.1614·1) and zinc pidolate (p.1614·1) or copper gluconate (p.1935·3) and zinc gluconate (p.1999·2).
Skin irritation.

C-Vex *Zentiva, Philipp.*
Pentoxifylline (p.1367·2).
Circulatory disorders.

C-vimin *AstraZeneca, Fin.; AstraZeneca, Swed.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

C-Vit *Novartis Consumer, Austria.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

C-Vitamin *BMS, Cz.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

CVP *Sterling, India.*
Citrus bioflavonoids (p.2304·1); vitamin C (p.1983·3).
Capillary fragility.

CVP B1 B6 B12 *Phoenix, Arg.†.*
Vitamin B (p.1976·1); vitamin B (p.1978·2); vitamin B (p.1980·2); vitamin C (p.1983·3); bioflavonoids (p.2304·1).
Capillary disorders; neuralgias; neuritis; vitamin B and C supplement.

CVP Duo *Phoenix, Arg.*
Bioflavonoids (p.2304·1); ascorbic acid (p.1983·3).
Vascular disorders.

CVP Flebo *Phoenix, Arg.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Haemorrhoids; varices.

CVP Forte *Phoenix, Arg.*
Ascorbic acid (p.1983·3); bioflavonoids (p.2304·1).
Arteriopathy; phlebopathy.

CV-Sprin *Cadila, India.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

C-Will *Will-Pharma, Belg.; Will-Pharma, Neth.; SPB, Thai.; Willpharma, Thai.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Cx-3 *Cadila, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Cx-4 *Cadila, India.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1); 1 tablet ethambutol (p.275·2).
Tuberculosis.

Cx-5 *Cadila, India.*
1 Capsule, rifampicin (p.325·3); 2 tablets, pyrazinamide (p.320·2); 1 tablet, ethambutol (p.275·2); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

CX Powder *Adams, UK.*
Chlorhexidine acetate (p.1635·2).
Skin disinfection.

Cyanide Antidote Package *Lilly, USA.*
Combination pack: 2 Ampoules, sodium nitrite (p.1464·3); 2 ampoules, sodium thiosulfate (p.1466·1); 12 aspirols, amyl nitrite (p.1437·3).
Cyanide poisoning.

Cyanokit *Merck-Lipha, Fr.; Merck Sante, Hong Kong; Dey, USA.*
Hydroxocobalamin (p.1980·3).
Cyanide poisoning.

Cyater *Sigma-Tau, Spain.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Cybufen *Lederle, Indon.*
Fenbufen (p.54·3).
Musculoskeletal and joint disorders.

Cybutol *Pharmachemie, Hong Kong; World Pioneer, Hong Kong; Pharmachemie, S.Afr.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Cycin *Dong, Singapore.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cyclabil *Schering, Fin.; Schering, Norw.; Schering, Swed.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; menstrual disorders; oestrogen deficiency; osteoporosis.

Cyclacur *Schering, Austria; Schering, Gr.; Schering, Switz.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2).
Hormone replacement therapy; menopausal disorders; menstrual disorders.

Cycladol
Chiesi, Fr.; Chiesi, Spain.
Piroxicam betadex (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ulagay, Turk.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Cyclan *BPL-Meizler, Braz.†.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Cyclate *Cadila, India.*
Cyclopentolate hydrochloride (p.1879·3).

Cycleane *Organon, Fr.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Cyclen *Janssen-Ortho, Canad.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Cyclergine *Poirier, Fr.†.*
Cyclandelate (p.1254·1).
Peripheral vascular disorders.

Cyclessa *Organon, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Cyclidox *Xixia, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Cyclimorph *Amdipharm, Irl.; Aspen, S.Afr.; CeNeS, UK.*
⊗ Morphine tartrate (p.87·2); cyclizine tartrate (p.574·2).
Pain.

Cyclimycin *Pharmacare, S.Afr.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Cycline *Kleva, Gr.*
Minocycline (p.300·3).
Bacterial infections.

Cyclinex *Ross, USA.*
A range of preparations for enteral nutrition including an infant feed (p.1922·1).
Gyrate atrophy; urea cycle disorder.

Cyclivex *Pharmacare, S.Afr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Cyclo 3
Note. This name is used for preparations of different composition.
Pierre Fabre, Arg.; Pierre Fabre, Port.
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Haemorrhoids; venous insufficiency.

Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre, Singapore.
Butcher's broom (p.2270·3); melilot (p.2339·2).
Circulatory disorders; haemorrhoids; lymphatic insufficiency; venous insufficiency.

Cyclo 3 Fort *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Pol.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, Thai.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Bleeding during oral contraceptive or intra-uterine device use; circulatory disorders; haemorrhoids; lymphatic insufficiency; menstrual disorders; venous insufficiency.

Cyclo 3 Forte *Pharmafabre (Φαρμαφαμπρ), Gr.*
Butcher's broom (p.2270·3); hesperidin (p.2304·3); ascorbic acid (p.1983·3).
Vascular disorders.

Cyclobiol *Andromaco, Chile†.*
Estradiol (p.2097·2).
Breast cancer; menopausal disorders; osteoporosis; prostatic cancer.

Cycloblastin *Pfizer, Austral.; Pfizer, NZ; Pharmacia, S.Afr.*
Cyclophosphamide (p.702·1).
Auto-immune diseases; malignant neoplasms; transplant rejection.

Cyclocort *Stiefel, Canad.; Astellas, USA†.*
⊗ Amcinonide (p.1516·2).
Skin disorders.

Cyclocur *Schering, Belg.; Schering, Neth.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2).
Menopausal disorders; menstrual disorders; osteoporosis.

Cycloderm *CSC, Austria.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Cyclodynon *Bionorica, Rus.*
Agnus castus (p.2249·1).
Menstrual disorders.

Cyclofem *Master, Chile†; Tunggal Idaman, Indon.*
Medroxyprogesterone acetate (p.2113·1); estradiol cipionate (p.2097·2).
Combined injectable contraceptive.

Cyclofemina *Millet Roux, Braz.; Carnot, Mex.*
Estradiol cipionate (p.2097·2); medroxyprogesterone acetate (p.2113·1).
Combined injectable contraceptive.

Cycloferon *Polisan, Rus.*
Arachidonic acid.
Bacterial and fungal infections; connective tissue disorders; degenerative-dystrophic joint disorders; viral infections.

Cyclogest *Alpharma, Hong Kong; Cox, Hong Kong; Actavis, Malaysia; Aventis, S.Afr.; Actavis, Singapore; Aventis, Thai.; Assos, Turk.; Actavis, UK.*
Progesterone (p.2125·1).
Female infertility; postnatal depression; premenstrual syndrome.

Cyclogesterin *Pharmacia, Venez.†.*
Natural equine oestrogens (p.2087·2); progesterone (p.2125·1).
Endometriosis; menstrual disorders.

Cyclogyl *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.†; Alcon, Denm.; Alcon, Gr.; Alcon, Hong Kong; Andre, India; Alcon, Malaysia; Alcon, NZ; Alcon, Neth.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, USA; Alcon, Venez.*
Cyclopentolate hydrochloride (p.1879·3).
Production of cycloplegia and mydriasis.

Cyclomandol *Yamanouchi, Swed.†.*
Cyclandelate (p.1254·1).
Vascular disorders.

Cyclomed
Note. This name is used for preparations of different composition.
Medibrands, Israel.
Aciclovir (p.862·3).
Herpes simplex infections.

Promed, Rus.
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis.

Cyclo-Meff *Indoco, India.*
Mefenamic acid (p.80·1); dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Cyclomen *Sanofi Synthelabo, Canad.*
⊗ Danazol (p.2090·2).
Endometriosis; mastalgia; primary menorrhagia.

Cyclo-Menorette *Wyeth, Cz.†; Wyeth, Ger.; Wyeth, Hung.†.*
11 Tablets, estradiol valerate (p.2097·3); estriol (p.2101·1); 10 tablets, estradiol valerate; estriol; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Cyclominol *Noel, India.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm; irritable bowel syndrome.

Cyclomydri *Alcon, Neth.†.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Cyclomydril *Alcon, Malaysia; Alcon, S.Afr.; Alcon, Singapore; Alcon, USA.*
Cyclopentolate hydrochloride (p.1879·3); phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

CycloOstrogynal *Asche, Cz.†; Schering, Ger.*
11 Tablets, estradiol valerate (p.2097·3); estriol (p.2101·1); 10 Tablets, estradiol valerate; estriol; levonorgestrel (p.2121·2).
Menopausal disorders.

Cyclopam
Note. This name is used for preparations of different composition.
Indoco, India.
Injection: Dicycloverine hydrochloride (p.1722·3).
Colic; dysmenorrhoea; irritable bowel syndrome.

Indoco, India.
Oral drops; oral suspension: Dicycloverine hydrochloride (p.1722·3); dimeticone (p.1770·2).
Colic; dysmenorrhoea; irritable bowel syndrome.

Indoco, India.
Tablets: Dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1).
Colic; dysmenorrhoea; irritable bowel syndrome.

Cyclopentol *Viatris, Belg.†.*
Cyclopentolate hydrochloride (p.1879·3).
Prevention of iridocrystalline adherences; prevention of synechiae; production of mydriasis and cycloplegia.

Cyclopentolate *Rafa, Israel†.*
Cyclopentolate hydrochloride (p.1879·3); lidocaine (p.1862·3).
Production of mydriasis and cycloplegia.

Cycloplatin *Pliva, Cz.; Pliva, Hung.; Pliva Lachema, Pol.; Pliva, Rus.*
Carboplatin (p.693·1).
Malignant neoplasms.

Cyclo-Premella *Wyeth, Cz.†; Wyeth, Hung.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Cyclo-Premella ST *Wyeth, Switz.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency.

Cyclo-Progynon *Schering, Denm.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Cyclo-Progynova *Schering, Ger.; Schering, Indon.; Schering, Pol.; Schering, Rus.; Schering, Thai.; Schering, Turk.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2).
Menopausal disorders; menstrual disorders; osteoporosis.

Cyclo-Progynova 1 mg *Viatris, UK.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders.

Cyclo-Progynova 2 mg *Viatris, UK.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2).
Menopausal disorders.

Cyclorax *Atlantic, Hong Kong†; Atlantic, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Cycloreg *Jagson, India.*
Norethisterone (p.2119·3).
Endometriosis; menstrual disorders; postponement of menstruation.

Cyclorel *Zydus, Fr.†.*
Naringin sodium.
Circulatory disorders.

Cyclorine *Lupin, India.*
Cycloserine (p.260·2).
Tuberculosis.

Cyclosa *Organon, Ger.*
7 Tablets, ethinylestradiol (p.2101·3); 15 tablets, ethinylestradiol; desogestrel (p.2093·2).
Menstrual disorders.

Cycloserine *King, UK.*
Cycloserine (p.260·2).
Tuberculosis; urinary-tract infections.

Cycloson *Pharmachemie, Hong Kong; World Pioneer, Hong Kong; Pharmachemie, S.Afr.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Cyclospasmol *Yamanouchi, Belg.†; Yamanouchi, Fin.†; Yamanouchi, Neth.; Yamanouchi, Port.†.*
Cyclandelate (p.1254·1).
Peripheral and cerebral vascular disorders.

Cyclostad *Stada, Philipp.*
Aciclovir (p.862·3).
Herpesvirus infections.

Cyclostin *Pharmacia, Ger.†.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Cyclotrax *Shin Poong, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Cyclovax *Remedica, Hong Kong; Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Cycloven Forte N *CT, Ger.*
Aesculus (p.2248·2); esculoside (p.2248·2); rutoside (p.2305·1).
Peripheral vascular disorders; venous insufficiency.

Cyclovent *Pharmachemie, Hong Kong; World Pioneer, Hong Kong.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Cyclovir *Medichrom, Gr.†; Cadila, India; Cadila, Rus.*
Aciclovir (p.862·3).
Herpes simplex infections; herpesvirus infections.

Cycloviran *Medichrom, Gr.; Sigma-Tau, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Cycloxan *Biochem, India.*
Cyclophosphamide (p.702·1).
Immunosuppressant; malignant neoplasms.

Cycofed *Cypress, USA†.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Cycomin *Rotexmedica, Philipp.*
Phytomenadione (p.1995·3).
Hypoprothrombinaemic haemorrhage.

Cycortide *Pharmachemie, Hong Kong; World Pioneer, Hong Kong.*
⊗ Budesonide (p.1520·1).
Asthma.

Cycrin *Wyeth, Arg.†; Wyeth, Braz.; Wyeth, Mex.†; ESI, USA†.*
Medroxyprogesterone acetate (p.2113·1).
Abnormal uterine bleeding; menopausal disorders; secondary amenorrhoea.

Cydec *Cypress, USA†.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).

Cydec DM *Cypress, USA†.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Cydifar *Ifars, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic disorders.

Cydonin *EGIS, Hung.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cydoxmine-B *PD, Thai.†.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Megaloblastic anaemia; nausea and vomiting; neuritis; polyneuritis.

Cyfenol *Cifarma, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Cyflox *Greater Pharma, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cyfloxin *Marching, Hong Kong.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cy-Gesic *Cypress, USA.*
Phenylephrine hydrochloride (p.1568·1); phenazone (p.116·1); benzocaine (p.1854·1).
Earache.

Cyheptine *Greater Pharma, Thai.*
Cyproheptadine (p.575·2).
Hypersensitivity reactions; pruritus; reduced appetite.

Cyklo-F *Pharmacia, Swed.*
Tranexamic acid (p.1080·3).
Menorrhagia.

Cyklokapron *Pfizer Consumer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pharmacia, Cz.†; Pfizer, Denm.; Meda, Fin.; Pharmacia, Ger.; Pfizer, Hong Kong; Meda, Irl.; Pfizer Consumer, NZ; Pfizer, Neth.; Meda, Norw.; Pfizer, Norw.; Pfizer, Philipp.; Pharmacia, S.Afr.; Pfizer, Singapore; Meda, Swed.; Pfizer, Swed.; Pfizer, Switz.; Meda, UK; Pfizer, UK; Pfizer, USA.*
Tranexamic acid (p.1080·3).
Dental extraction in haemophiliacs; fibrinolytic haemorrhage; hereditary angioedema; hyphaemia; menorrhagia; surgical procedures in those with coagulopathies; upper-gastrointestinal haemorrhage.

Cylat *Lapi, Indon.*
Cyproheptadine (p.575·2).
Allergic disorders.

Cylert *Abbott, Chile; Abbott, Israel; Abbott, USA†.*
⊗ Pemoline (p.2161·2).
Attention deficit hyperactivity disorder.

Cylex *Pharmakon, USA.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Sore throat.

Cyllind *Abbott, Ger.*
Clarithromycin (p.248·2).
Bacterial infections.

Cylocide *Shinyaku, Jpn.*
Cytarabine (p.705·1).
Acute leukaemias.

Cylocort *Genom, Braz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Cylowam *Konimex, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Cyltabs *Solvay, India.*
Multivitamin and mineral preparation with liver (p.1922·1).
Tonic.

Cymalon *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Sodium citrate (p.1673·3); anhydrous citric acid (p.2284·1); sodium bicarbonate (p.1673·2); sodium carbonate (p.2389·1).
Cystitis.

Cymalon Cranberry *Thornton & Ross, UK.*
Potassium citrate (p.1673·2).
Cystitis; urinary-tract infections.

Cymbalta *Lilly, Arg.; Lilly, Austral.; Lilly, Belg.; Lilly, Braz.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Boehringer Ingelheim, Ger.; Lilly, Ger.; Lilly, Gr.; Boehringer Ingelheim, Hong Kong; Lilly, Hong Kong; Lilly, Hung.; Boehringer Ingelheim, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Boehringer Ingelheim, Philipp.; Lilly, Philipp.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, UK; Lilly, USA.*
Duloxetine hydrochloride (p.389·3).
Depression; diabetic peripheral neuropathy.

Cymerin *Mitsubishi, Jpn.*
Ranimustine (p.766·3).
Malignant neoplasms; polycythaemia vera; thrombocythaemia.

Cymerion *Azevedos, Port.*
Zolpidem tartrate (p.1037·3).
Insomnia; sedative.

Cymevan *Roche, Fr.*
Ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Cymeven *Roche, Ger.*
Ganciclovir (p.879·1) or ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Cymevene
Roche, Arg.; Roche, Chile; Roche, Hong Kong; Recordati, Ital.; Roche, Singapore; Roche, Turk.; Roche, Venez.
Ganciclovir (p.879·1).
Cytomegalovirus infections.

Roche, Austral.; Roche, Austria; Roche, Cz.; Roche, Gr.; Roche, Hung.; Roche, Mex.; Roche, NZ.
Ganciclovir (p.879·1) or ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Roche, Belg.; Roche, Braz.; Roche, Denm.; Roche, Fin.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK.
Ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Cymex *Actavis, UK.*
⊗ Urea (p.1620·2); dimethicone (p.2032·1); cetrimide (p.1634·1); chlorocresol (p.1640·1).
Cracked lips; herpes labialis.

Cymi *Lennon, S.Afr.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Cymine *Pharmasant, Thai.*
Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Gastrointestinal colic and spasm.

Cyna Bilisan *Repha, Ger.†.*
Cynara (p.2291·2).
Dyspepsia.

Cynacholin *Phytofarm Kleka, Pol.*
Cynara (p.2291·2).
Atherosclerosis; gastrointestinal disorders; hyperlipidaemias.

Cynacur *Hexal, Ger.*
Cynara (p.2291·2).
Dyspepsia.

Cynalip duo *Sabona, Ger.†.*
Cynara (p.2291·2).
Dyspepsia.

Cynara Compuesta *Ximena Polanco, Chile.*
Homoeopathic preparation.

Cynarex *Roux-Ocefa, Arg.; Herbapol Wroclaw, Pol.*
Cynara (p.2291·2).
Atherosclerosis; hypercholesterolaemia; liver disorders.

Cynarix *Montavit, Austria.*
Cynara (p.2291·2).
Liver and biliary disorders.

Cynarix comp *Montavit, Austria.*
Cynara (p.2291·2); salverine hydrochloride (p.2383·1).
Biliary disorders.

Cynarix N *Sabona, Ger.†.*
Cynara (p.2291·2).
Dyspepsia.

Cynaro Bilina *Nutridiver, Spain.*
Cynara (p.2291·2); aloes (p.1705·2).
Biliary-tract disorders; constipation.

Cynarol *Pharmethic, Belg.*
Cynara (p.2291·2).
Biliary-tract disorders.

Cynarosan *Slovakofarma, Cz.†.*
Cynara (p.2291·2); rhubarb (p.1768·3); taraxacum (p.2395·1); agrimony (p.2249·2); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Liver and biliary-tract disorders.

Cynarzym N *Altana, Ger.†.*
Cynara (p.2291·2); boldo (p.2267·2); greater celandine (p.2317·1).
Digestive disorders; liver disorders.

Cynascool *Natiris, Venez.*
Cynara (p.2291·2); boldo (p.2267·2); rhubarb (p.1768·3); solanum melongena.

Cyndal HD *Cypress, USA†.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).

Cyne *Novartis, Gr.†.*
Butamirate citrate (p.1553·1).
Cough.

Cynocuatro *Grossman, Mex.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Cynomel *Enila, Braz.†; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.†; Grossman, Mex.*
Liothyronine sodium (p.2174·1).
Diagnosis of hyperthyroidism; hypothyroidism.

Cynomycin *Wyeth, India.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Cynoplus *Grossman, Mex.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Hypothyroidism.

Cynovit *Julphar, UAE.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; vitamin B deficiency; vitamin B supplement.

Cynozet *Glenmark, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Cynt
Note. This name is used for preparations of different composition.
Lilly, Braz.; Solvay, Cz.; Lilly, Ger.; Solvay, Gr.; Lilly, Hung.; Lilly, Rus.†; Lilly, Turk.
Moxonidine (p.1345·1).
Hypertension.

Dollder, Venez.
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Cyomin *Forest Pharmaceuticals, USA.*
Cyanocobalamin (p.1980·2).
Schilling test; vitamin B deficiency.

Cyotic *Cypress, USA.*
⊗ Hydrocortisone (p.1535·2); pramocaine hydrochloride (p.1868·1); chloroxylenol (p.1640·2).
External ear disorders.

Cypestra *Mepha, Switz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Cypex *Cypress, USA.*
Guaifenesin (p.1561·3); sulfogaiacol (p.1573·2).
Coughs.

Cypral *Alian, Venez.*
Ciprofloxacin (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Cyprest *Polfa Pabianice, Pol.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Cypretyl *Ratiopharm, Fin.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, hirsutism, and seborrhoea in women; oral contraceptive in women with androgen-associated symptoms.

Cyproderm *Dermapharm, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Cyprodex *Roemmers-Klinos, Venez.*
⊗ Cyproheptadine hydrochloride (p.575·1); dexamethasone acetate (p.1526·1).
Hypersensitivity disorders.

Cyprodin *Roemmers-Klinos, Venez.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity disorders.

Cyprodiol *Eurogenerics, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Cyprogin *Atlantic, Hong Kong; Atlantic, Thai.*
Cyproheptadine hydrochloride (p.575·1).
Anorexia; hypersensitivity reactions; migraine; pruritus; reduced appetite.

Cyprohexal *Sandoz, Austral.*
Cyproterone acetate (p.2088·2).
Androgenisation in women; prostatic cancer.

Cypromix *Stragen, Hung.*
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Androgen-dependent acne and hirsutism in women; combined oral contraceptive in women with androgenic symptoms.

Cypron *Generics, Israel.*
Cyproterone acetate (p.2088·2).
Androgenisation; male sexual disorders; prostatic cancer.

Cyprone *Alphapharm, Austral.*
Cyproterone acetate (p.2088·2).
Androgenisation in females; prostatic cancer; sexual deviation in men.

Cypronette *Aliud, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Cyprono *Milano, Thai.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; pruritus; reduced appetite.

Cyproplex *Teva, Belg.; Teva, Cz.; Pharmachemie, Malaysia; Pharmachemie, S.Afr.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in females; female infertility; male sexual deviation; precocious puberty; prostatic cancer.

Cyprosian *Asian Pharm, Thai.*
Cyproheptadine hydrochloride (p.575·1).
Anorexia; hypersensitivity reactions; pruritus.

Cyprostat *Schering, Austral.; Bayer, UK.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in females; prostatic cancer; sexual deviation in men.

Cyprostol *Pfizer, Austria.*
Misoprostol (p.2013·2).
Peptic ulcer.

Cyprotec *Chew, Thai.*
Cyproheptadine hydrochloride (p.575·1).
Anorexia; hypersensitivity reactions; pruritus.

Cyprotin *Beacons, Singapore.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; migraine and other vascular headaches.

Cyral *Gerot, Austria.*
Primidone (p.503·2).
Epilepsy.

Cyress *Astellas, Neth.; Astellas, Port.*
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Cyriamine *Pharmasant, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Vitamin B deficiency.

Cyrpon *Kolassa, Austria.*
Meprobamate (p.1006·2).
Anxiety.

Cys Control *Arkomedika, Fr.*
Cranberry (p.2289·1).
Urinary-tract disorders.

Cysdexpel *Ad-Drugstel, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Cysporin *Mayne, Austral.*
Ciclosporin (p.1822·2).
Atopic dermatitis; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection.

Cystadan *Orphan Medical, Israel.*
Betaine (p.2265·2).
Homocystinaemia; homocystinuria.

Cystadane *Orphan, Austral.; Orphan Medical, Canad.; Orphan Europe, Cz.; Orphan Europe, Port.; Rare Disease Therapeutics, USA.*
Betaine (p.2265·2).
Homocystinuria.

Cystagon *Orphan, Austral.; Orphan, Belg.; Orphan Europe, Cz.; Orphan, Denm.; Orphan, Fin.; Orphan, Fr.; Orphan, Ger.; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Swedish Orphan, Swed.; Orphan, UK.*
Mercaptamine bitartrate (p.2340·3).
Nephropathic cystinosis.

Cystel Antipelliculaire *Bailleul, Fr.†.*
Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Cystel Shampooing Antiseborrheique *Bailleul, Fr.†.*
Cade oil (p.1616·1); zinc sulfate (p.1999·2).
Formerly known as Cystelle Shampooing Cheveux Gras.
Seborrhoea.

Cystemme *Abbott, UK.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2).
Cystitis.

Cystex
Note. This name is used for preparations of different composition.
EMS, Braz.
Acriflavinium chloride (p.1625·1); methenamine (p.298·3); methylthioninium chloride (p.1450·3); belladonna (p.2263·3).
Urinary-tract infections.

Numark, USA.
Methenamine (p.298·3); sodium salicylate (p.124·2); benzoic acid (p.1630·2).
Urinary-tract infections.

Cystibosin B 48 *Bock, Ger.†.*
Homoeopathic preparation.

Cysticide *Merck, Ger.; Merck, S.Afr.*
Praziquantel (p.153·3).
Neurocysticercosis.

Cystine B$_6$ *Bailleul, Fr.*
Cystine (p.1937·1); pyridoxine hydrochloride (p.1978·2).
Eye disorders; nail and hair disorders.

Cystinex *Sofex, Port.†.*
Gelatin; cystine; pyridoxine hydrochloride; zinc gluconate; vitamin A acetate (p.1922·1).
Hair loss; nail disorders.

Cystinol Akut *Schaper & Brummer, Ger.*
Bearberry (p.2263·3).
Urinary-tract inflammation.

Cystinol Long *Schaper & Brummer, Ger.*
Solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Cystinol N *Schaper & Brummer, Ger.*
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1).
Cystinol formerly contained birch leaf, equisetum, solidago virgaurea, and bearberry.
Urinary-tract disorders.

Cystistat *Bioniche, Canad.; Pliva, UK.*
Sodium hyaluronate (p.2320·1).
Interstitial cystitis; replacement of bladder glycosaminoglycan.

Cystitis Juniperus *Homeocan, Canad.†.*
Homoeopathic preparation.

Cystitis Relief *Galpharm, UK; Numark, UK; Thornton & Ross, UK.*
Sodium citrate (p.1673·3).
Cystitis.

Cystium Solidago *Wernigerode, Ger.*
Solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Cystium-wern *Wernigerode, Ger.†.*
Fennel oil (p.2303·1); camphor oil (p.2273·3).
Renal calculi.

Cysti-Z *Bailleul, Fr.†.*
-Methionine (p.1450·2); zinc sulfate (p.1999·2); pyridoxine hydrochloride (p.1978·2).
Alopecia; seborrhoea.

Cysto Fink Mono *GSK Consumer, Ger.†.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Cysto Hevert *Hevert, Ger.*
Homoeopathic preparation.

Cystocalm *Galpharm, UK.*
Sodium citrate (p.1673·3).
Cystitis.

Cysto-Conray *Mallinckrodt, Arg.; Tyco, Canad.; Mallinckrodt, USA.*
Meglumine iotalamate (p.1485·3).
Radiographic contrast medium.

Cysto-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Cysto-Gastreu R18 *Reckeweg, Neth.*
Homoeopathic preparation.

Cysto-Gastreu S R18 *Reckeweg, Ger.*
Homoeopathic preparation.

Cystografin *Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Cysto-Myacyne N *Schur, Ger.*
Neomycin sulfate (p.305·1).
Urinary-tract infections.

Cystone
Note. This name is used for preparations of different composition.
Himalaya Herbal, Malaysia.
Didymocarpus pedicellata; saxifraga ligulata; rubia cordifolia; cyperus scariosus; achyranthes aspera; onosma bracteatum; vernonia cinerea; lime silicate; asphalt.
Urinary-tract disorders.

Himalaya, Rus.
Shilapuspha (Didymocarpus pedicellata); Pasanabheda (Saxifraga ligulata); Manjishtha (Rubia cordifolia); Nagarmusta (Cyperus scariosus); Apamarga (Achyranthes aspera); Gojiha (Onosma bracteatum); Sahadevi (Vernonia cinerea); Shilajeet (Purified); Hajrul yahood bhasma.
Ayurvedic remedy; urinary-tract disorders.

Cystonorm *Esparma, Ger.†.*
Oxybutynin (p.2190·3).
Bladder instability; neurogenic bladder.

Cystopurin *Bayer, Irl.; Roche Consumer, Irl.; Roche Consumer, UK.*
Potassium citrate (p.1673·2).
Cystitis; lower urinary-tract infection.

Cysto-Saar *MIP, Ger.*
Nitroxoline (p.309·2).
Urinary-tract infections.

Cystosol *Unimedic, Swed.†.*
Sorbitol (p.1965·1).
Bladder irrigation.

Cystospaz *PolyMedica, USA.*
Hyoscyamine (p.1736·1).
Urinary-tract spasm.

Cysto-Urgenin *Madaus, Ger.*
Cucurbita oil (p.2290·2).
Bladder irritability.

Cystrin *Sanofi Synthelabo, Austria; Leiras, Cz.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Sanofi Synthelabo, Neth.†; Sanofi-Aventis, Pol.; Sanofi Synthelabo, UK.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder disorders; nocturnal enuresis; urinary frequency; urinary incontinence.

Cyta-Cell *Eurogenerics, Belg.*
Cytarabine (p.705·1).
Malignant neoplasms.

Cytacon *Goldshield, Irl.; Goldshield, UK.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; tropical sprue; vitamin B deficiency.

Cytadren *Novartis, Austral.; Novartis, NZ†; Novartis, USA†.*
⊗ Aminoglutethimide (p.679·1).
Breast cancer; Cushing's syndrome; prostatic cancer.

Cytagon *Pharmaland, Thai.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Cytamen *Mayne, Austral.; UCB, Irl.; UCB, UK.*
Cyanocobalamin (p.1980·2).
Anaemia due to B deficiency; macrocytic anaemias; Schilling test; vitamin B deficiency.

Cytamid *Esparma, Hung.†.*
Flutamide (p.725·1).
Prostatic cancer.

Cytarine *Dabur, India; Dabur, Thai.*
Cytarabine (p.705·1).
Malignant neoplasms.

Cyteal *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, UK.*
Chlorhexidine gluconate (p.1635·3); chlorocresol (p.1640·1); hexamidine isetionate (p.1646·3).
Disinfection of skin and mucous membranes; hand disinfection; skin infections; vulvovaginal infections; wound disinfection.

Cytelium *Ducray, Fr.; Medifarm A-Derm, Venez.*
Avena (p.2262·1); zinc oxide (p.1621·2).
Skin disorders.

Cytine *Douglas, NZ.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Cyto-Bifidus *Eagle, Austral.*
Lactobacillus acidophilus; *L. bulgaricus*; *L. rhamnosus*; *L. casei*; *L. plantarum*; *L. salivarius*; *L. brevis*; *L. lactis* (p.2372·3).
Gastrointestinal disorders.

Cytobion *Merck, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Cytoblastin *Cipla, India.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Cytocarb *Cipla, India.*
Carboplatin (p.693·1).
Ovarian cancer; small-cell lung cancer.

Cytocristin *Cipla, India.*
Vincristine sulfate (p.787·1).
Acute leukaemias.

Cytodrox *Cipla, India.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Cytofos *Sun, Thai.*
Amifostine (p.1436·3).
Radiotherapy-induced adverse effects; reduction of toxicity due to alkylating agents and platinum-containing cytotoxics.

CytoGam *Purissimus, Arg.†; Medimmune, USA.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Cytoglobin *Bayer, Austria; Bayer, Ger.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Cytolog *Zydus, India.*
Misoprostol (p.2013·2).
Peptic ulcer.

Cytomel *Theramed, Canad.; GSK, Neth.; Jones, USA.*
Liothyronine sodium (p.2174·1).
Evaluation of thyroid function; hypothyroidism; nontoxic goitre.

Cytomid *Cipla, India.*
Flutamide (p.725·1).
Prostatic cancer.

Cytonal *Atafarm, Turk.*
Cytarabine (p.705·1).
Acute myeloid leukaemia.

Cytophosphan *Taro, Israel.*
Cyclophosphamide (p.702·1).
Malignant neoplasms; systemic lupus erythematosus.

Cytoplatin *Cipla, India; Cipla, Venez.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cytorest *Mochida, Jpn.*
Cytochrome C (p.2291·3).
Leucopenia.

Cytorich *Richmond, Arg.*
Bleomycin (p.688·2).
Malignant neoplasms.

Cytosar *Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pharmacia, Denm.†; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Irl.†; Pharmacia, Israel; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.†; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore†; Pharmacia, Swed.†; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Venez.*
Cytarabine (p.705·1).
Leukaemias; non-Hodgkin's lymphoma.

Cytosar-U *Pfizer, Indon.; Pfizer, Malaysia; Pfizer, Philipp.; Gensia, USA†.*
Cytarabine (p.705·1).
Leukaemias; non-Hodgkin's lymphoma.

Cytosplat *Korea United, Philipp.*
Cisplatin (p.698·2).
Malignant neoplasms.

Cytotam *Cipla, India.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Cytotec *Pfizer, Austral.; Continental Pharma, Belg.; Pfizer, Braz.; Pharmacia, Canad.†; Searle, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.†; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Searle, Pol.; Pfizer, Port.; Searle, Rus.†; Pharmacia, S.Afr.; Pharmacia, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Ali, Turk.; Pharmacia, UK; Searle, USA; Pfizer, Venez.*
Misoprostol (p.2013·2).
Gastrointestinal haemorrhage; peptic ulcer; termination of pregnancy.

Cytotect *Biotest, Austria; Pentafarma, Chile; Biotest, Cz.; Biotest, Ger.; Biotest, Hong Kong; Biotest, Hung.; Biotest, Ital.; Biotest, Pol.; Biotest, Switz.; Biotest, Turk.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Cytovene
Rontag, Arg.†.
Ganciclovir (p.879·1).
Cytomegalovirus infections.

Roche, Canad.; Roche, USA.
Ganciclovir (p.879·1) or ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Cytovit *Ipca, India.*
Vitamin and mineral preparation (p.1922·1).

Cytoxan *BMS, Canad.; BMS, Cz.†; BMS, Hung.; BMS, Israel†; BMS, NZ; BMS, Philipp.; BMS Oncology, USA†.*
Cyclophosphamide (p.702·1).
Auto-immune disorders; glomerular kidney disease in children; malignant neoplasms; nephrotic syndrome.

Cytra-2 *Cypress, USA.*
Citric acid monohydrate (p.2284·1); sodium citrate (p.1673·3).
Metabolic acidosis; urinary alkalinisation.

Cytra-3 *Cypress, USA.*
Citric acid monohydrate (p.2284·1); potassium citrate (p.1673·2); sodium citrate (p.1673·3).
Metabolic acidosis; urinary alkalinisation.

Cytragen *Vonnace, Philipp.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Cytra-K *Cypress, USA.*
Citric acid monohydrate (p.2284·1); potassium citrate (p.1673·2).
Metabolic acidosis; urinary alkalinisation.

Cytra-LC *Cypress, USA.*
Citric acid monohydrate (p.2284·1); potassium citrate (p.1673·2); sodium citrate (p.1673·3).
Metabolic acidosis; urinary alkalinisation.

Cytur Test *Roche Diagnostics, Austral.*
Test for leucocytes in urine.

Cytuss HC *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).

Cytuss-HC NR *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); dexbrompheniramine maleate (p.569·2).
Allergic rhinitis; cold symptoms; cough.

Cyzine *Pharmasant, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic skin disorders; rhinitis.

Czynnik VIII (Metoda M) *Imed, Pol.*
A factor VIII preparation (p.1067·1).
Factor VII deficiency.

4D *Sandoz, Philipp.*
1 Strip, ethambutol (p.275·2); isoniazid (p.288·1); pyrazinamide (p.320·2); rifampicin (p.325·3).
Tuberculosis.

D-204 *Gambro, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis solution.

D-248 *Gambro, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis solution.

D-300 *Gambro, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis solution.

D-326 *Gambro, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis solution.

D 4 *Fouchard, Chile†.*
Hydroquinone (p.1598·2); kojic acid (p.1603·3); glycolic acid (p.1598·1).
Skin pigmentation disorders.

D Biotin *Jamieson, Canad.†.*
Biotin (p.1931·3).

d Epifrin *Allergan, Cz.†; Allergan, Ger.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

D_3 Vicotrat *Heyl, Ger.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

DA II *Dura, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

DA Chewable *Dura, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Allergic rhinitis; cold symptoms; sinusitis.

Daben *Solfran, Mex.*
Mebendazole (p.148·3).
Worm infections.

Dabenzol *Filaxis, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Dabetil *Liferpal, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Dabex *Merck, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Dabinese *Pfizer, Venez.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Dabonal *Lesvi, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Dabonal Plus *Lesvi, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); enalapril maleate (p.1276·1).
Hypertension.

Dabrin *Pasteur, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Parenteral corticosteroid.

Dabroson *Norma (Νορμα), Gr.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Dabsan *Nordin, Mex.*
Cantharis vesicatoria.
Burns; keratosis.

Daburex *Alternavida, Mex.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Dacam *Laboratorios Chile, Chile.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Dacam RL *Laboratorios Chile, Chile.*
⊗ Betamethasone acetate (p.1518·2); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Dacarb *Eurofarma, Braz.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Dacarbion *Medicus, Gr.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Dacarin *VHB, India.*
Dacarbazine hydrochloride (p.707·1).
Malignant neoplasms.

Dacatic *Orion, Fin.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Dacef *Pharmacare, S.Afr.*
Cefadroxil (p.218·1).
Bacterial infections.

Dacex-A *Cypress, USA.*
Carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Dacex-DM *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Dacex-PE *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

Dacin
Note. This name is used for preparations of different composition.
Mersifarma, Indon.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Lipomed, Switz.
Dacarbazine (p.706·3).
Malignant neoplasms.

Dacin-F *Farmaline, Thai.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Daclin
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Clindamycin phosphate (p.251·2).
Bacterial infections.

Tempo Scan Pacific, Indon.
Clindamycin (p.251·1).
Bacterial infections.

Pacific, NZ.
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Dacmozen *VHB, India.*
Dactinomycin (p.707·2).
Malignant neoplasms.

Dacogen *MGI, USA.*
Decitabine (p.710·1).
Myelodysplastic syndromes.

Dacortin *Merck, Spain.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Dacortin H *Merck, Spain†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Dacotin *Reddy's, India.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Dacovo *Tafir, Spain†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Dacplat *Pfizer, Arg.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Dacrin *MSD, Austria.*
⊗ Hydrastinine hydrochloride (p.2321·2); oxedrine tartrate (p.1364·3).
Conjunctivitis.

Dacrio Gel *Alcon, Gr.*
Carbomer (p.2141·3).
Dry eyes.

Dacriogel *Alcon, Ital.*
Carbomer (p.2141·3).
Dry eyes.

Dacriose *Novartis Ophthalmics, USA.*
Electrolytes (p.1667·1).
Eye irrigation.

Dacriosol *Alcon, Denm.; Alcon, Ital.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Dacrodil *Teva Tuteur, Arg.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Dacrolux *Alcon, Hung.; Alcon Cusi, Malaysia; Cusi, Singapore†; Alcon Cusi, Spain; Alcon, Turk.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Dacryne *McNeil, Fr.*
⊗ Oxedrine tartrate (p.1364·3); chlorhexidine gluconate (p.1635·3).
Formerly known as Dacryoseptil.
Eye disorders.

Dacryoboraline *McNeil, Fr.*
⊗ Oxedrine tartrate (p.1364·3); borax (p.2268·1); boric acid (p.2268·1).
Eye irritation.

Dacryolarmes *Martin-Johnson & Johnson, Fr.†.*
Methylcellulose 4000 (p.2145·1).
Dry eyes; protection during eye examinations.

Dacryoserum *McNeil, Fr.*
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation.

Dacryum *McNeil, Fr.*
Borax (p.2268·1); boric acid (p.2268·1).
Eye irritation.

Dacten *Phoenix, Arg.*
Candesartan cilexetil (p.1238·3).
Hypertension.

Dacten D *Phoenix, Arg.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Dactil OB
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Piperidolate hydrochloride (p.1762·2); hesperidin (p.2304·3); ascorbic acid (p.1983·3).
Smooth muscle spasm.

Aventis, Mex.
Piperidolate hydrochloride (p.1762·2).
Dysmenorrhoea; premature labour; threatened miscarriage.

Dactron *Darya-Varia, Indon.*
Dipyrone (p.49·2); vitamin B ; vitamin B ; vitamin B (p.1922·1).
Pain.

Dactylen *Fahrenheit, Indon.*
⊗ Alcohol (p.1625·2); cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Mouth and throat disorders; oral hygiene.

Dacudoses *Thea, Fr.*
Boric acid (p.2268·1); borax (p.2268·1).
Eye irritation.

Dadicil *Best, Mex.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dadosel *Farma Lepori, Spain.*
Ibuprofen sodium (p.65·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Dadumir *Krugher, Ital.*
Delorazepam (p.986·1).
Anxiety; insomnia.

Daedalon *Gedeon Richter, Hung.; Pharmamagist, Hung.*
Dimenhydrinate (p.576·2).
Motion sickness; vestibular disorders.

Daedalonetta *Pharmamagist, Hung.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting.

Daewo
Note. This name is used for preparations of different composition.
Costec, Arg.
Soap: Triclosan (Irgasan DP-300) (p.1665·2).
Skin and hand disinfection.

Costec, Arg.†.
Topical solution: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Dafalgan *BMS, Belg.; BMS, Fr.; BMS, Port.; Esteve, Spain; Upsamedica, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Dafalgan Codeina *BMS, Port.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dafalgan Codeine *BMS, Belg.; UPSA, Cz.†; BMS, Fr.; BMS, Pol.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dafalgan plus C *Upsamedica, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms; fever; pain.

Dafex *Phoenix, Arg.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Dafiro *Novartis, Cz.; Novartis, Gr.; Novartis, Port.*
Amlodipine besilate (p.1214·1); valsartan (p.1420·2).
Hypertension.

Daflon
Note. This name is used for preparations of different composition.
Servier, Arg.; Servier, Austria; Servier, Belg.; Servier, Gr.; Servier, Hong Kong; Sanfer, Mex.; Servier, Philipp.; Servier, Port.; Servier, Thai.; Servier, Turk.; Servier, Venez.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhage; haemorrhoids; vascular disorders; venous insufficiency.

Servier, Braz.
Diosmin (p.2304·2).
Haemorrhoids; menorrhagia; venous insufficiency.

Servier, Fr.
Bioflavonoids (p.2304·1).
Vascular disorders.

Daflon 500 *Servier, Braz.; Grunenthal, Chile; Servier, Ital.; Servier, Malaysia; Servier, Singapore; Servier, Spain; Servier, Switz.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; vascular disorders; venous insufficiency.

Dafloxen *Liomont, Mex.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Dafloxen-F *Liomont, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Dafne *Omega, Arg.*
Dicycloverine hydrochloride (p.1722·3); diazepam (p.986·3); aluminium glycinate (p.1706·2); magnesium oxide (p.1744·1); lidocaine (p.1862·3); simeticone (p.1770·2).
Dyspepsia; gastrointestinal motility disorders; peptic ulcer.

Dafnegil *Lepori, Port.*
Nifuratel (p.841·3); nystatin (p.543·2).
Vulvovaginal infections.

Dafnegil Neo *Merz, Switz.*
Ciclopirox olamine (p.529·2).
Vulvovaginal candidiasis.

Dafnegin *Poli, Cz.; Pharmanel, Gr.†; Pharmacia, Ital.; Poli, Pol.*
Ciclopirox olamine (p.529·2).
Candidiasis of the skin and vagina.

Dafomin *TO-Chemicals, Thai.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Dafor *Gerolymatos, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Daforin *Sigma, Braz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Dafrafin *Dafra, Belg.*
Sulfametopyrazine (p.342·2); pyrimethamine (p.610·2).
Malaria.

Daga *Aventis, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Dagan *Tedec Meiji, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Dagenol *Mediphar, Venez.*
Menthol (p.2340·1); camphor (p.2273·2); avena (p.2262·1).
Pruritus.

Dagol *Cetus, Arg.*
Sodium picosulfate (p.1771·1).
Constipation.

Dagotil *Royal, Chile.*
Risperidone (p.1024·2).
Schizophrenia.

Dagragel *Meda, Port.*
⊗ Gelatin (p.1072·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Dagravit *Meda, Port.*
A range of vitamin preparations with or without minerals (p.1922·1).

Dagravit A Forte *Viatris, Neth.†.*
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Dagravit A-E Forte *Viatris, Neth.†.*
Vitamin A palmitate (p.1973·1); *dl*-alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Dagravit Totaal 8 *Viatris, Neth.†.*
Multivitamin preparation (p.1922·1).

Dagrilan *Pharmacypria, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Dagynil *Teofarma, Neth.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Dahlia *ITF, Chile.*
21 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Daiet B *Humana, Ital.*
Fatty-acid, lipid, and vitamin preparation (p.1922·1).
Nutritional supplement.

Dai-kenchu-to *Tsumura, Jpn.*
Ginseng; zanthoxylum fruit; ginger.
Traditional Kampo medicine.

Dailat *Pharmasant, Thai.*
Serrapeptase (p.2385·3).
Inflammation; swelling.

Daily *Pierre Fabre Sante, Fr.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Triphasic oral contraceptive.

Daily Benefits *Kay, Canad.†.*
Multivitamin and mineral preparations (p.1922·1).

Daily Complete + Nutrient *Awareness, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Daily Conditioning *Blistex, USA.*
SPF 20: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Daily Fatigue Relief *Herbal Concepts, UK.*
Kola (p.2416·1); damiana (p.2292·1); saw palmetto (p.2192·3).
Fatigue.

Daily Gold Pack *Solgar, UK.*
Multivitamin and mineral preparation (p.1922·1).

Daily Multi *Vitaplex, Austral.†.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Daily One *Nutrifarma, Turk.*
Multivitamin and mineral preparation (p.1922·1).

Daily Overwork & Mental Fatigue Relief *Herbal Concepts, UK.*
Avena (p.2262·1); zanthoxylum (p.2417·1).
Tonic.

Daily Protection Moisturizer *Kay, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Daily Tension & Strain Relief *Herbal Concepts, UK.*
Asafetida (p.2261·3); valerian (p.2410·1); avena (p.2262·1); passion flower (p.2363·2).
Strain; tension.

Dailyvit *Beacons, Singapore.*
Vitamin preparation with or without minerals (p.1922·1).

Daily-Vite *Rugby, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Daimeton *Drag, Chile†.*
Paracetamol (p.108·1).
Fever; pain.

Daio-kanzo-to *Tsumura, Jpn.*
Rhubarb; liquorice.
Traditional Kampo medicine.

Dairy Ease *Blistex, USA.*
Tilactase (p.2402·1).
Lactase insufficiency.

Dairyaid *Tanta, Canad.*
Tilactase (p.2402·1).
Lactase insufficiency.

Dairywilf *Keton, Mex.*
Multivitamin preparation (p.1922·1).

Daisaikoto *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; scutellaria root; peony root; jujube; immature orange; ginger; rhubarb.
Traditional Kampo medicine.

Daisamox *Pharmacare, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Daiticin *Erlimpex, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Daiv *Fada, Arg.*
Diazepam (p.986·3).
Anxiety; muscle spasm.

Daivobet *CSL, Austral.; Roche, Braz.; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Leo, Malaysia; Valeant, Mex.; CSL, NZ; Leo, Norw.; Leo, Philipp.; Leo, Pol.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.*
⊗ Calcipotriol (p.1591·3); betamethasone dipropionate (p.1518·3).
Psoriasis.

Daivonex *Andromaco, Arg.; CSL, Austral.; Leo, Belg.; Schering-Plough, Braz.; Andromaco, Chile; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.; Win-Medicare, India; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Valeant, Mex.; CSL, NZ; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Leo, Pol.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.; Leti, Venez.†.*
Calcipotriol (p.1591·3).
Psoriasis; vitiligo.

Dakar *Sanofi-Aventis, Belg.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Dakin *Cooperation Pharmaceutique, Fr.*
Sodium hypochlorite (p.1661·1).
Skin, mucous membrane, and wound disinfection.

Dakincooper *Melisana, Belg.*
Sodium hypochlorite (p.1661·1).
Skin and mucous membrane disinfection.

Dakin's Solution *Century, Canad.*
Sodium hypochlorite (p.1661·1).

Daknax *Pharlab, Braz.†.*
Miconazole (p.541·2).
Fungal infections.

Daksol
Note. This name is used for preparations of different composition.
Pharmavita, Chile.
Lamotrigine (p.485·1).
Epilepsy.

Galeno, Venez.
Secnidazole (p.846·3).
Protozoal infections.

Daktacort
Janssen-Cilag, Belg.; Orion, Fin.; Janssen, Hong Kong; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.†; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK.
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal and Gram-positive bacterial skin infections with inflammation.

Ethnor, India.
⊗ Miconazole nitrate (p.541·3); hydrocortisone acetate (p.1535·2).
Infected skin and nail disorders.

Daktacort HC *Johnson & Johnson MSD Consumer, UK.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Daktagold *Janssen-Cilag, Austral.†; Janssen-Cilag, NZ.*
Ketoconazole (p.539·1).
Fungal skin infections; seborrhoeic dermatitis.

Daktar
Janssen-Cilag, Belg.†; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

McNeil, Ger.
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections.

Daktarin
Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.†; Orion, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; McNeil, Neth.; Janssen, Philipp.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Janssen-Cilag, Venez.
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections; fungal nail and mouth infections.

Janssen-Cilag, Braz.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Ethnor, India; Janssen-Cilag, Malaysia; Janssen-Cilag, Pol.; Janssen-Cilag, Singapore; Janssen-Cilag, Thai.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin, mucous membrane, and nail infections.

Janssen-Cilag, Chile; Pharmasol, Rus.
Miconazole (p.541·2).
Candidiasis; tinea pedis.

Daktarin Diaper *Janssen-Cilag, Indon.*
Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Nappy rash.

Daktarin Gold *Johnson & Johnson MSD Consumer, UK.*
Ketoconazole (p.539·1).
Fungal skin infections.

Daktazol *Neo Quimica, Braz.*
Miconazole nitrate (p.541·3).
Fungal infections.

Daktodor *Janssen-Cilag, Gr.*
⊗ Hydrocortisone (p.1535·2); miconazole nitrate (p.541·3).
Fungal skin infections with inflammation.

Daktozin *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.†; Janssen-Cilag, NZ†; Janssen-Cilag, Venez.*
Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Fungal skin infections; nappy rash with fungal infection.

Dal *Gynopharm, Chile.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 5 tablets, ethinylestradiol; 2 tablets, placebo.
Biphasic oral contraceptive.

D-Al *Sevapharma, Cz.*
Allergen extracts (p.2250·2).
Diagnosis of hypersensitivity.

Dalacin
Pfizer, Arg.†; Pfizer, Chile; Pfizer, Cz.; Pfizer, Hung.; Pharmacia, India; Pfizer, Irl.; Pfizer, UK.
Clindamycin phosphate (p.251·2).
Bacterial infections.

Pfizer, Austria; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.
Clindamycin hydrochloride (p.251·1), clindamycin palmitate hydrochloride (p.251·1), or clindamycin phosphate (p.251·2).
Bacterial infections.

Pfizer, Denm.; Pfizer, Rus.; Pfizer, Spain; Pfizer, Venez.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Pfizer, Belg.
Lotion: Clindamycin phosphate (p.251·2).
Formerly known as Dalcin Topical.
Acne.

Pfizer, Belg.
Vaginal gel: Clindamycin phosphate (p.251·2).
Formerly known as Dalacin Vaginal.
Bacterial vaginosis.

Dalacin V
Pfizer, Austral.; Pfizer, Chile; Pfizer, Mex.; Pfizer, Port.; Pfizer, Switz.
Clindamycin phosphate (p.251·2).
Bacterial vaginitis.

Pfizer, Braz.
Clindamycin hydrochloride (p.251·1).
Bacterial vaginitis.

Dalacin C
Pfizer, Arg.; Pfizer, Austral.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pharmacia, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections; malaria; pneumocystis pneumonia; toxoplasmosis.

Pfizer, Belg.; Pfizer, Canad.; Pfizer, Hung.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Switz.
Clindamycin hydrochloride (p.251·1), clindamycin palmitate hydrochloride (p.251·1), or clindamycin phosphate (p.251·2).
Bacterial infections.

Pfizer, Braz.; Pharmacia, Israel; Pfizer, Port.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Dalacin ST *Pfizer, Arg.*
Clindamycin phosphate (p.251·2).
Acne.

Dalacin T *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pharmacia, NZ†; Pfizer, Neth.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.*
Clindamycin phosphate (p.251·2).
Acne; bacterial infections.

Dalacin T Prewash *Pharmacia, NZ.*
Triclosan (p.1665·2).
Skin cleansing.

Dalacin Vaginal *Paladin, Canad.; Pharmacia, Israel.*
Clindamycin phosphate (p.251·2).
Bacterial vaginitis.

Dalacin VC *Pharmacia, S.Afr.*
Clindamycin phosphate (p.251·2).
Bacterial vaginosis.

Dalacine *Pfizer, Fr.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Dalacine T *Pfizer, Fr.*
Clindamycin phosphate (p.251·2).
Acne.

Dalagis T *Agis, Israel.*
Clindamycin phosphate (p.251·2).
Acne.

Dalalone *Forest Pharmaceuticals, USA.*
⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Dalam *Penn, Arg.; Richmond, Arg.*
Midazolam (p.1007·3).
Induction of anaesthesia; premedication; sedative.

Dalamon *Alter, Spain†.*
⊗ Cyanocobalamin (p.1980·2); dexamethasone sodium diacid phosphate (p.1526·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Myalgia; neuralgia; neuritis; rheumatism.

Dalamon Inyectable *Alter, Spain.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dalap *Biosintetica, Braz.*
Adapalene (p.1587·1).
Acne.

Dalatina *Euromex, Mex.*
Clindamycin (p.251·1).
Acne.

Dalatina V *Euromex, Mex.*
Clindamycin (p.251·1).
Vaginal infections.

Dalcap *Unichem, India.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Dalcept *Cuprocept, S.Afr.†.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Dalcipran *Roche, Arg.; Germania, Austria; Pierre Fabre, Cz.; Reprefar, Port.*
Milnacipran hydrochloride (p.409·2).
Depression.

Dal-E *Dal-Vita, Austral.*
d-Alpha tocoferil acetate (p.1992·3).
Burns; minor wounds; skin irritation.

Daleron *KRKA, Cz.; KRKA, Rus.*
Paracetamol (p.108·1).
Fever; pain.

Daleron C *KRKA, Rus.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).

Daleron proti chripce a nachlazeni *KRKA, Cz.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; cough.

Dalet Med Balsam *Mauermann, Ger.†.*
Guaiacol (p.1561·2); methyl salicylate (p.85·3); belladonna (p.2263·3); menthol (p.2340·1).
Hallux valgus; inflammation of big toe joint.

Dalex *Vargas, Venez.*
Epirizole (p.50·2).

Dalfarol *Darya-Varia, Indon.*
d-Alpha tocopherol (p.1992·2).
Cardiovascular disorders; vitamin E supplement.

Dalfaz *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Pol.; Sanofi Winthrop, Rus.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Dalgen *Recordati, Spain.*
Fepradinol hydrochloride (p.60·2).
Peri-articular disorders; soft-tissue disorders.

Dalgex *Daudt, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine (p.1116·3).
Pain; skeletal muscle spasm.

Dalhis *Pharmasant, Thai.*
Mebhydrolin (p.584·3).
Hypersensitivity reactions.

Dalidome *Serral, Mex.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2); camphor (p.2273·2).
Skin disorders.

Dalisol
Note. This name is used for preparations of different composition.
Lemery, Mex.; Lemery, Rus.†.
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; antidote to folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity.

Lemery, Thai.
Folinic acid (p.1943·3).
Adjunct to fluorouracil in colorectal cancer and breast cancer; antidote to folic acid antagonists; folate deficiency; megaloblastic anaemia; reduction of methotrexate toxicity.

Dalivit *Ariston, Braz.†; LPC, UK.*
Vitamin B substances; vitamin C; fructose (p.1922·1).

Dallamizol-D *Dallas, Arg.†.*
Pseudoephedrine sulfate (p.1571·2); astemizole (p.567·2).

Dallapasmo *Dallas, Arg.*
Homatropine methylbromide (p.1881·3).
Muscle spasm.

Dallergy *Laser, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

Dallergy DM *Laser, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Cold symptoms; cough.

Dallergy-D
Note. This name is used for preparations of different composition.
Laser, USA.
Capsules: Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Laser, USA.
Syrup: Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Dallergy-JR *Laser, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Allergic rhinitis; nasal congestion.

Dalmacol *Riva, Canad.*
⊗ Hydrocodone tartrate (p.63·1); etafedrine hydrochloride (p.1560·2); sodium citrate (p.1673·3); doxylamine succinate (p.578·2).
Respiratory-tract disorders.

Dalmadorm
Valeant, Braz.; Valeant, Hong Kong; Combiphar, Indon.; Valeant, Indon.; ICN, Neth.; Valeant, Singapore; Valeant, Switz.
Flurazepam hydrochloride (p.999·1).
Insomnia.

Valeant, Ger.; ICN, Ital.; Valeant, Port.; Pharmaco, S.Afr.; ICN, Thai.
Flurazepam monohydrochloride (p.999·1).
Anxiety; insomnia.

Dalmane
Valeant, Canad.†; Valeant, Irl.; Valeant, USA†.
Flurazepam hydrochloride (p.999·1).
Insomnia.

ICN, UK.
Flurazepam monohydrochloride (p.999·1).
Insomnia.

Dalmasin *Ferring, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Dalminette *Norma (Νορμα), Gr.†.*
Paracetamol (p.108·1).
Fever; pain.

Dalparan *Farma Lepori, Spain.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Dalpas *Biotech, Venez.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Dalsan *Egis, Cz.; EGIS, Hung.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Dalsin *Offenbach, Mex.*
Dipyrone (p.49·2).
Fever; muscle spasm; pain.

Dalsy *Knoll, Braz.; Abbott, Spain.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Daltazen *Giempi, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension.

Daltroid *Lemery, Mex.†.*
Levothyroxine sodium (p.2171·2).

Dalun *Medipharm, Chile.*
Hydroxyzine hydrochloride (p.581·2).
Agitation; anxiety; hypersensitivity reactions.

Dalycrid *Pasteur, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dalys *Dosa, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Dalzad *Novartis, Gr.*
Valsartan (p.1420·2).
Hypertension.

Dalzolston *Ariston, Braz.*
Metronidazole (p.837·1).

Dam *Terapeutico, Ital.*
Damiana (p.2292·1); muira-puama; santoreggia; kola (p.2416·1); cinnamon (p.2283·1).
Erectile dysfunction.

DAM Antacidum *Corifel, Switz.*
Calcium carbonate (p.1714·1); glycine (p.1947·3); liquorice (p.1740·3).
Gastric hyperacidity.

Damaben *Caprifarmindo, Indon.; Sanbe, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; gastroparesis; nausea and vomiting.

Dama-Lax *Schering-Plough, Spain†.*
Docusate sodium (p.1725·1).
Constipation.

Damason-P *Mason, USA.*
Hydrocodone tartrate (p.63·1); aspirin (p.20·3).
Pain.

Damax *Offenbach, Mex.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).

Damiana and Kola Tablets *Dorwest, UK.*
Kola (p.2416·1); damiana (p.2292·1); saw palmetto (p.2192·3).
Tonic.

Damiana-Sarsaparilla Formula *Quest, Canad.†.*
Damiana leaf (p.2292·1); kelp (p.2384·2); liquorice root (p.1740·3); sarsaparilla root (p.2383·2); saw palmetto berry (p.2192·3); ginseng root (p.2312·1).

Damiclin *Ivax, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Damicol *Biol, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Damide *Benedetti, Ital.*
⊗ Indapamide (p.1314·1).
Hypertension.

Daminate *Sriprasit, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Cold symptoms; coughs; nasal congestion.

Damira *Hero, Switz.*
Preparation for enteral nutrition (p.1922·1).
Cow's milk intolerance.

Damixa *Merck, Arg.†.*
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal colic.

Damixan *Medipharm, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Damizen *Farmo Quimica, Chile.*
Serrapeptase (p.2385·3).
Inflammation.

Damizol *Specifar, Gr.*
Midazolam (p.1007·3).

Damoxy *Dabur, India†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Dampo *Bayer, Neth.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold symptoms.

Dampo bij droge hoest *Bayer, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dampo Solvopect *Bayer, Neth.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Damsel *Gador, Arg.*
21 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Damurgin *Gedeon Richter, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Damuvit *Pyridam, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C deficiency.

Dan Shen Compound *Phytomedicine, Austral.*
Danshen; crataegus (p.2289·1); valerian (p.2410·1); coleus forskohlii.
Circulatory disorders.

Danabol *Body Research, Thai.†.*
⊗ Methandienone (p.2116·3).
Androgen.

Danac *Lemery, Mex.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Danalem *Lemery, Mex.*
⊗ Danazol (p.2090·2).

Danalgin *Kalbe, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Danantizol *Gador, Arg.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Danasin *Kocak, Turk.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; hereditary angioedema.

Danasone *Hexpharm, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Danatrol *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; hereditary angioedema; menorrhagia; precocious puberty.

Danazant *Antigen, Irl.†.*
⊗ Danazol (p.2090·2).
Benign breast disorders; dysfunctional uterine bleeding; endometriosis; gynaecomastia.

Danbutol *Danlex, Philipp.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Dancimin-C *Dankos, Singapore.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Dancor *Merck, Austria; Merck, Neth.; Merck, Port.; Merck, Spain; Merck, Switz.*
Nicorandil (p.1349·1).
Angina pectoris.

Dancow *Nestle, Indon.*
A range of preparations for enteral nutrition (p.1922·1).

Dandelion Complex *Swiss Bio, Malaysia†.*
Capsicum (p.2276·2); cynara (p.2291·2); ginger (p.1732·3); lappa (p.2330·3); peppermint oil (p.1761·2); taraxacum (p.2395·1).
Aid to fat digestion; promotion of hepatobiliary function.

Dandrazol *Transdermal, UK.*
Ketoconazole (p.539·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Dandrid *Sandoz, UK.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Dandruff Control Pert 2 in 1 *Procter & Gamble, Austral.*
Pyrithione zinc (p.1611·2).
Dandruff.

Dandruff Shampoo plus Conditioner *Sutton, Canad.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Danemet *Ivax, Cz.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Daneuron *Hexpharm, Indon.; Dankos, Singapore.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Hyperemesis gravidarum; neuritis; peripheral nerve pain; vitamin B deficiency.

Danferane *Rivero, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Danfree *Cipla, India; Valmor, Venez.†.*
Ketoconazole (p.539·1).
Scalp disorders.

Dan-Gard *Faulding, Austral.; Valeo, Canad.*
Pyrithione zinc (p.1611·2).
Dandruff.

Danilax *Danipharm, Denm.†; Danipharm, Hong Kong.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Danilon
Note. This name is used for preparations of different composition.
Esteve, Spain.
Suxibuzone (p.128·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Biotech, Venez.
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Danitin *Yung Shin, Philipp.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Danitrin *Deva, Turk.*
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris.

Danium *Zentiva, Cz.*
Calcium dobesilate (p.2272·1).
Diabetic retinopathy; haemorrhoids; venous insufficiency.

Danium Compositum *Leciva, Cz.†.*
Calcium dobesilate (p.2272·1); carboxycellulose calcium; zinc oxide (p.1621·2).
Anal fissures; haemorrhoids.

Dank *Ilsan, Turk.*
Dihydroxyaluminum sodium carbonate (p.1723·3).

Danka *Angelini, Ital.*
Levodropropizine (p.1557·3).
Coughs.

Dankit *Rafarm, Gr.*
Erythromycin (p.269·2).
Acne.

Danlax *Sovereign, UK.*
Dantron (p.1722·2); poloxamer 188 (p.1918·1).
Constipation.

Danlox *Casasco, Arg.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Danoclav *Actavis, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Danocrine *Sanofi Synthelabo, Austral.; Sanofi Winthrop, Denm.†; Sanofi Synthelabo, Fin.†; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Indon.; Aventis, NZ†; Sanofi Synthelabo, Norw.†; Sanofi Synthelabo, Swed.†; Sanofi Winthrop, USA†.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; hereditary angioedema; mastalgia; menorrhagia.

Danoflox *Kalbe, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Danogar *Sanofi Synthelabo, Chile†.*
⊗ Danazol (p.2090·2).
Benign breast disorders; dysfunctional uterine bleeding; endometrial thinning; endometriosis; hereditary angioedema.

Danogen *Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; hereditary angioedema; mastalgia; menorrhagia.

Danokrin *Sanofi Synthelabo, Austria.*
⊗ Danazol (p.2090·2).
Endometriosis; gynaecomastia; hereditary angioedema; precocious puberty.

Danol *Sanofi Synthelabo, Cz.†; Sanofi, Irl.; Sanofi Synthelabo, Israel; Sanofi Synthelabo, UK.*
⊗ Danazol (p.2090·2).
Formerly known as Danocrine in *Israel*.
Benign breast disorders; dysfunctional uterine bleeding; endometriosis; hereditary angioedema; mastalgia; menorrhagia; precocious puberty.

Danoprox *Chemedica, Ger.†.*
Oxaprozin (p.105·3).
Musculoskeletal, joint, and peri-articular disorders.

Danoptin *Pliva-Lachema, Cz.; Pliva Krakow, Pol.*
Lamotrigine (p.485·1).
Epilepsy.

Danovag *Novag, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Danoval *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; hereditary angioedema; menstrual disorders; precocious puberty.

Danovir *Dankos, Indon.; Dankos, Singapore†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Danox *Zuoz, Venez.†.*
Alprazolam (p.960·1).
Anxiety.

Danoxilin *Actavis, Indon.*
Amoxicillin (p.202·2).
Bacterial infections.

Danruf *Torrent, India.*
Ketoconazole (p.539·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Dansera *Otto, Indon.*
Serrapeptase (p.2385·3); thiamine nitrate; riboflavin; pyridoxine hydrochloride; cyanocobalamin; nicotinamide; tocoferil acetate (p.1922·1).
Nutritional supplement.

Danssan *Duopharma, Hong Kong.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Dantalin *Cazi, Braz.*
Phenytoin (p.495·2).
Epilepsy.

Dantamacrin *Procter & Gamble, Ger.; Vifor, Switz.*
Dantrolene sodium (p.1896·1).
Skeletal muscle spasm; spasticity.

Dan-Tar Plus *Stiefel, Canad.*
Polytar (a blend of wood and mineral tars) (p.1616·1); dipyrithione (p.1595·1).
Dandruff.

Dantenk *Biotenk, Arg.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Dantifar *Organifar, Venez.†.*
Bencyclane fumarate (p.1224·1).
Cerebral and peripheral vascular disorders.

D-Antihist *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Dantoinal *Biotech, Venez.*
Phenytoin sodium (p.495·2).
Epilepsy.

Dantrium *Pfizer, Austral.; Procter & Gamble, Belg.; Procter & Gamble, Canad.; Farmo Quimica, Chile; Procter & Gamble, Denm.; Merck-Lipha, Fr.; IFET (ΙΦΕΤ), Gr.; Procter & Gamble, Hong Kong†; Procter & Gamble, Irl.; Procter & Gamble, Israel; Formenti, Ital.; Pfizer, NZ; Procter & Gamble, Neth.; Normal, Port.†; Pharmaco, S.Afr.; Procter & Gamble, UK; Procter & Gamble, USA.*
Dantrolene sodium (p.1896·1).
Malignant hyperthermia; skeletal muscle spasm; spasticity.

Dantrolen *Cristalia, Braz.; IFET (ΙΦΕΤ), Gr.*
Dantrolene sodium (p.1896·1).
Malignant hyperthermia; skeletal muscle spasm.

Dantron
Hexal, S.Afr.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Unison, Thai.
Ondansetron (p.1756·3).
Nausea and vomiting.

Dantroxal *Sandoz, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Dantum *Europharm, Hong Kong.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation.

Danubial *Atlantis, Mex.†.*
Ornidazole (p.843·1).
Amoebiasis; giardiasis; trichomoniasis.

Dany *The Forty-Two, Thai.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; nausea and vomiting.

Danzen *Casasco, Arg.; Takeda, Hong Kong; Takeda, Ital.; Takeda, Malaysia; Hormona, Mex.; Takeda, Singapore; Takeda, Thai.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; cystitis; epididymitis; inflammation; oedema; respiratory-tract congestion; sinusitis; wisdom tooth pericoronitis; wounds.

Danzyme *Medicine Products, Thai.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; cystitis; epididymitis; inflammation; pericoronitis; respiratory-tract congestion; sinusitis.

Daohair-S *Farmex, Gr.*
Pyrithione zinc (p.1611·2).
Pityriasis; seborrhoeic dermatitis.

Daonil *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Aventis, Denm.; Aventis, Fin.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel†; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, Neth.; Aventis, Norw.†; Aventis, Philipp.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, UK; Sanofi-Aventis, Venez.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Daono *Milano, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Daopar *Hoechst Marion Roussel, Gr.†.*
Glibenclamide (p.440·1); phenformin hydrochloride (p.455·3).
Diabetes.

Dapa *Alphapharm, Malaysia; Merck, Malaysia.*
⊗ Indapamide (p.1314·1).
Hypertension.

Dapamax *Adcock Ingram, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension; oedema.

Daparox *Angelini, Ital.*
Paroxetine mesilate (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Dapa-Tabs *Alphapharm, Austral.; Alphapharm, Hong Kong; Alphapharm, Singapore; Merck, Singapore.*
⊗ Indapamide (p.1314·1).
Hypertension.

Daphne
Note. This name is used for preparations of different composition.
Mithra, Belg.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.
Famy, Philipp.
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Dapoder *Duncan, Arg.*
Amino acids; vitamin B (p.1922·1).
Tonic.

Dapotum *Sanofi Synthelabo, Austria; BMS, Ger.; Sanofi Synthelabo, Ger.; BMS, Switz.*
Fluphenazine decanoate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Mania; psychoses; schizophrenia.

Dapril *Medochemie, Cz.; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Dapriton *Marching, Hong Kong.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Daps *Pfizer, Arg.*
Dapsone (p.261·2).
Leprosy.

Dapsoderm-X *Remexa, Mex.*
Dapsone (p.261·2).
Bacterial mycetoma; dermatitis herpetiformis; leprosy.

Daptacel *Aventis Pasteur, USA.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Daptaral *Wyeth-Ayerst, Thai.†.*
Multivitamin and mineral preparation (p.1922·1).

Daptril *Qestmed, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Dapyrin *Hexpharm, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Daquiran *Boehringer Ingelheim, Neth.†.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism.

Daralix *Aspen, S.Afr.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; nausea; vomiting.

Daram *Bittner, Austria.*
Homoeopathic preparation.

Daramal *GSK, S.Afr.*
Chloroquine sulfate (p.599·3).
Discoid lupus erythematosus; malaria; rheumatoid arthritis.

Daramal-Paludrine *Zeneca, S.Afr.†.*
Chloroquine sulfate (p.599·3); proguanil hydrochloride (p.609·2).
Malaria.

Daranide *Merck, USA†.*
⊗ Diclofenamide (p.1880·2).
Glaucoma.

Daraprim *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Ger.; Wellcome, Irl.†; Wellcome, Israel†; GSK, Mex.; GSK, Neth.; GSK, Pol.; GSK, S.Afr.; GSK, Spain; GSK, Switz.; GSK, Thai.†; GSK, UK; Glaxo Wellcome, USA.*
Pyrimethamine (p.610·2).
Malaria; toxoplasmosis.

Daraprin *Farmoquimica, Braz.*
Pyrimethamine (p.610·2).
Malaria.

Darat *Danlex, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Darax *Pond's, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions.

Darbalan *Merck, Austria.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Darbalan Plus *Merck, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Darbin *Darrow, Braz.*
Cytarabine (p.705·1).
Malignant neoplasms.

Darcipireno *Fabra, Arg.*
Biperiden (p.797·2).
Parkinsonism.

Dardex *Pliva, Spain†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Dardokef *Darya-Varia, Indon.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Dardum *Lisapharma, Ital.; Lisapharma, Pol.; Lisapharma, Singapore.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Darebon *Novartis, Austria; Novartis, Ger.†.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Daren
Note. This name is used for preparations of different composition.
Organon, Jpn.
Emedastine fumarate (p.579·2).
Allergic rhinitis; allergic skin disorders.
Delta, Singapore†.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Dargol *Kleva, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Daribur *Darier, Mex.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2); camphor (p.2273·2).
Hyperhidrosis; skin disorders.

Daric *Phoenix, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Daricon *Pfizer, Hong Kong; Pfizer, Thai.†.*
Oxyphencyclimine hydrochloride (p.1759·2).
Irritable bowel syndrome; peptic ulcer.

Darilin *Recordati, Ital.*
Valganciclovir hydrochloride (p.911·3).
Cytomegalovirus retinitis.

Dariseb *Darier, Mex.*
Coal tar (p.1616·2); menthol (p.2340·1).
Scalp disorders.

Daritex A *Alternavida, Mex.*
Irinotecan hydrochloride (p.737·1).
Malignant neoplasms.

Darkene *Bayer, Ital.*
Flunitrazepam (p.996·2).
Insomnia.

Darleton *Anfarm, Gr.*
Sulpiride (p.1028·3).
Psychoses.

Darlin *Sandipro, Belg.*
Senna fruit (p.1769·2).
Constipation.

Darmen Salt *Ern, Spain.*
Magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2); dibasic sodium phosphate (p.1682·3); sodium sulfate (p.1771·3).
Constipation; dyspepsia; gastric hyperacidity.

Darmol
Note. This name is used for preparations of different composition.
Schmidgall, Austria; Iromedica, Switz.
Senna (p.1769·2).
Constipation.
Schmidgall, Cz.†; Omegin, Ger.†; Schmidgall, Hung.
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Darmol Pico *Omegin, Ger.*
Sodium picosulfate (p.1771·1).
Constipation.

Daro *Heca, Neth.*
Paracetamol (p.108·1).
Fever; pain.

Daro APC *Heca, Neth.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Pain.

Daro Hoofdpijnpoeders *Heca, Neth.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Headache.

Darob *Abbott, Arg.†; Ebewe, Austria; Knoll, Cz.†; Abbott, Ger.; Abbott, Pol.; Abbott, Port.; Abbott, Turk.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Daroderm Trekzalf *Heca, Neth.*
Ichthammol (p.1599·1).
Boils.

Daroderm Zinkzalf *Heca, Neth.*
Zinc oxide (p.1621·2).
Skin disorders.

Darolan Hoestprikkeldempende *Heca, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Darolan Slijmoplossende *Heca, Neth.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with viscous mucus.

Daromefan *Heca, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Daromide *Aspen, S.Afr.*
Merbromin (p.1652·1); sulfanilamide (p.343·1); acriflavinium chloride (p.1625·1); cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin infections; wounds.

Daronda *Abbott, Gr.; Stephar, Neth.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; female infertility; prostatic cancer; uterine fibroids.

Daronrix *GSK, Cz.*
An influenza vaccine (H5N1) (p.2218·2).
Active immunisation in influenza pandemics.

Darosal *Heca, Neth.*
Aspirin (p.20·3).
Pain.

Darrow-Liq *Brunel, S.Afr.†.*
Sodium chloride; potassium chloride; sodium citrate dihydrate; glucose (p.1672·2).
Oral rehydration therapy.

Darrowped *SA Druggists Self Med, S.Afr.*
Potassium chloride; sodium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Darstin *Seid, Spain.*
Progesterone (p.2125·1).
Benign breast disorders.

Dartelin *Lek, Pol.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; vascular eye and ear disorders.

Dartobcin *Darya-Varia, Indon.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Dartrizon *Degorts, Mex.*
⊗ Oxyphenbutazone (p.107·3); prednisolone (p.1540·3).
Rheumatism.

Daruma *Wyeth Lederle, Ital.†.*
Idebenone (p.367·1).
Mental and movement disturbances associated with cerebrovascular disorders.

Darvalidol *Darnica, Pol.*
Menthyl isovalerate.
Gastrointestinal spasm; hepatic colic; migraine.

Darvocet *aai, USA.*
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Pain.

Darvocet-N *aai, USA.*
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Fever; pain.

Darvolin *Eczacibasi, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Darvon
Lilly, Spain†.
Dextropropoxyphene napsilate (p.40·1).
Pain.
Lilly, USA.
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Darvon Compound *aai, USA†.*
Dextropropoxyphene hydrochloride (p.40·1); aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Darvon Simple *Lilly, Mex.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Darvon-N *Paladin, Canad.; Lilly, USA.*
Dextropropoxyphene napsilate (p.40·1).
Pain.

Darvon-N Compuesto *Lilly, Mex.†.*
Dextropropoxyphene napsilate (p.40·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Daryant-Tulle *Darya-Varia, Indon.*
Framycetin sulfate (p.279·1).
Burns; infected skin disorders; wounds.

Darzitil *Fabra, Arg.*
Amoxicillin trihydrate (p.202·2) or amoxicillin sodium (p.202·2).
Bacterial infections.

Darzitil Plus *Fabra, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Darzitil SB *Fabra, Arg.*
Amoxicillin trihydrate (p.202·2) or amoxicillin sodium (p.202·2); pivsulbactam (p.335·1) or sulbactam sodium (p.335·1).
Bacterial infections.

Darzune *Merck, Mex.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Dasabion *Kimia, Indon.*
Ferrous fumarate (p.1938·3); vitamins (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Dasc *EMS, Braz.*
Pancrelipase (p.2360·1); bile salts (p.2266·2); cellulase (p.2279·1).
Digestive disorders.

Dasen *Takeda, Jpn.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Daskil *Novartis, Austria; LPB, Ital.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Daskyl *Azevedos, Port.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Daslin *RPG, India.*
⊗ Diphenhydramine (p.577·1); ammonium chloride (p.1551·3); alcohol (p.1625·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Dasmetrol *Tocogino, Mex.*
Metronidazole (p.837·1).
Acne; amoebiasis.

Dastonil *Montpellier, Arg.*
⊗ Cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3); prasterone sodium sulfate (p.2124·2) procaine hydrochloride (p.1869·1).
Tonic.

Dastosin *Astellas, Spain.*
Dimemorfan phosphate (p.1557·1).
Coughs.

Dastusin *Shiwa, Thai.†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; coughs.

Dasuglor *Fada, Arg.*
Cefalotin (p.220·2).
Bacterial infections.

Datan *Pyridam, Indon.*
Mefenamic acid (p.80·1).
Pain.

Dateril *Merck, Mex.*
Carbamazepine (p.471·3).
Bipolar disorder; diabetic neuropathy; epilepsy; neuralgias.

Datevan *Rontag, Arg.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Datisan *Duncan, Arg.†.*
Mitomycin (p.752·1).
Malignant neoplasms.

Datolan *Faes, Spain.*
Zopiclone (p.1039·1).
Insomnia.

Datril *BMS, Mex.*
Paracetamol (p.108·1).
Fever; pain.

DaTSCAN *GE, Cz.; Amersham, Fr.; Amersham, Ital.; GE Healthcare, Neth.; GE, Port.; Nycomed Amersham, UK.*
Iodine-123 (p.2054·2) as ioflupane.
Diagnosis of parkinsonism.

Daunoblastin *Pfizer, Austria; Pharmacia, Ger.; Pharmacia, S.Afr.*
Daunorubicin hydrochloride (p.709·1).
Leukaemias; neuroblastoma; rhabdomyosarcoma.

Daunoblastina *Pfizer, Arg.; Pharmacia, Braz.; Pharmacia, Hong Kong†; Pfizer, Hung.; Pharmacia, Ital.; Pfizer, Port.†; Pfizer, Singapore; Kenfarma, Spain; Pfizer, Venez.*
Daunorubicin hydrochloride (p.709·1).
Malignant neoplasms.

Daunocin *BPL-Meizler, Braz.†.*
Daunorubicin hydrochloride (p.709·1).
Malignant neoplasms.

Daunotec *Cipla, India.*
Daunorubicin hydrochloride (p.709·1).
Kaposi's sarcoma.

DaunoXome
Nexstar, Austral.; Gilead, Fr.; Gilead, Irl.
Liposomal daunorubicin hydrochloride (p.709·1) (p.709·1).
HIV-related Kaposi's sarcoma.
Fresenius Kabi, Austria; United Medical, Braz.†; Gilead, Denm.; Orphan, Fin.; Gilead, Ger.; Gilead, Gr.; Gilead, Ital.; Gilead, Neth.; Diatos, Port.; Gilead, Spain†; Swedish Orphan, Swed.; Fresenius, Switz.†; Diatos, UK; Nexstar, USA.
Liposomal daunorubicin citrate (p.709·3) (p.709·1).
Kaposi's sarcoma.
Nexstar, Rus.
Liposomal daunorubicin (p.709·3) (p.709·1).
Kaposi's sarcoma.

Daurocina *Laboratorios Chile, Chile.*
Daunorubicin (p.709·3).
Malignant neoplasms.

Dauxona *Northia, Arg.*
Glyceryl trinitrate (p.1296·2).

Davedax *Bracco, Ital.*
Reboxetine mesilate (p.420·3).
Depression.

D'Aveia *Dermoteca, Port.†.*
A range of skin, scalp, and vaginal preparations containing avena (p.2262·1).

Davercin *Polfa Tarchomin, Pol.*
Erythromycin cyclocarbonate.
Bacterial infections.

Daverium *Pharmanel, Gr.; Pharmacia, Ital.*
α-Dihydroergocryptine mesilate (p.364·2).
Hyperprolactinaemia; parkinsonism.

Davicrome *Davi, Port.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Davilla *Rekah, Israel.*
Opium (p.105·1); rhubarb (p.1768·3); cinnamon (p.2283·1); peppermint oil (p.1761·2).
Gastrointestinal disorders.

Davilose *Davi, Port.*
Hypromellose (p.2144·2).
Dry eyes.

Davimicina *Davi, Port.†.*
⊗ Bacitracin (p.210·3); hydrocortisone (p.1535·2); neomycin (p.305·1).
Infected eye disorders.

Davinefrina *Davi, Port.*
Phenylephrine hydrochloride (p.1568·1).
Eye congestion; glaucoma; ocular hypertension; production of miosis; ptosis.

Davitamon Fem *Chefaro, UK.*
A range of vitamin, mineral, and nutritional supplements (p.1922·1).

Davixolol *Davi, Port.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Davixon *New Research, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Dawnex *Micro, Thai.*
Fluoxetine hydrochloride (p.391·2).
Cataplexy; depression; narcolepsy; obsessive-compulsive disorder.

Daxet *Fahrenheit, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Daxim *Abbott, Chile; Abbott, Venez.*
Levosimendan (p.1324·3).
Heart failure.

Daxon *Rhein, Mex.*
Nitazoxanide (p.842·3).
Amoebiasis; giardiasis; trichomoniasis; worm infections.

Daxotel
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Dabur, India; Dabur, Thai.†; Biogalenic, Venez.
Docetaxel (p.710·3).
Breast cancer; non-small cell lung cancer.

Day & Night *Pfizer Consumer, Irl.*
15 Tablets, paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); 5 tablets, paracetamol; diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Day & Night Cold & Flu *Pfizer Consumer, Austral.; Pfizer, NZ.*
Day capsules, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); night capsules, paracetamol; dextromethorphan hydrobromide; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Day & Night Nurse *GSK Consumer, UK.*
Day capsules, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); pholcodine (p.1570·2); night capsules, paracetamol; promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Day Nurse *GSK Consumer, Irl.; GSK Consumer, UK.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); pholcodine (p.1570·2).
Formerly contained paracetamol, dextromethorphan hydrobromide, and phenylpropanolamine hydrochloride.
Cold and influenza symptoms.

Day Peel *Lierac, Fr.*
⊗ Salicylic acid (p.1612·2); glycolic acid (p.1598·1); urea (p.1620·2).
Sun-induced skin damage.

Dayalets *Abbott, Hong Kong†; Abbott, USA†.*
Multivitamin preparation (p.1922·1).

Dayalets + Iron *Abbott, USA.*
Multivitamin preparation with iron and folic acid (p.1922·1).

Dayalets plus Iron *Abbott, Hong Kong†.*
Multivitamin preparation with iron (p.1922·1).

Dayamin *Abbott, Venez.*
Vitamin preparation (p.1922·1).

Dayamineral *Abbott, Arg.; Abbott, Chile†; Abbott, Spain; Abbott, Venez.*
Multivitamin and mineral preparation (p.1922·1).

Day-Cal *Sanbe, Indon.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide (p.1744·1).
Calcium and vitamin D deficiency.

Daycee *Medisys, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Daycef *SarPharm, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Daygrip *Lafedar, Arg.*
Paracetamol (p.108·1); levophenylephrine hydrochloride (p.1568·3); vitamin C (p.1983·3).
Cold and influenza symptoms.

Dayhist *The Forty-Two, Thai.*
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Dayhist-1 *Major, USA.*
Clemastine fumarate (p.573·2).
Allergic rhinitis; urticaria.

Daypro *Pfizer, Canad.; Pharmacia, USA.*
Oxaprozin (p.105·3).
Osteoarthritis; rheumatoid arthritis.

DayQuil *Procter & Gamble, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms.

DayQuil Sinus *Procter & Gamble, Canad.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Dayrun *CSC, Cz.; CSC, Ger.†.*
Oxaprozin (p.105·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Days *Merck, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Daytime Cold & Flu *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Daytrana *Shire, USA.*
⊗ Methylphenidate (p.2160·1).
Attention-deficit hyperactivity disorder.

Daytrix *CT, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Dayvit *Ache, Braz.*
Vitamin and mineral preparation (p.1922·1).

Dayvital *Will Pharma, Neth.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Daywear *Estee Lauder, Canad.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Dazamide *Major, USA†.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma; oedema; symptoms associated with acute mountain sickness.

Dazen *Takeda, Fr.*
Serrapeptase (p.2385·3).
Oedema; respiratory-tract congestion.

Dazid *Macrophar, Thai.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Dazine *PP Lab, Thai.†.*
Thioridazine hydrochloride (p.1031·2).
Anxiety; mania; schizophrenia.

Dazithin *Cryopharma, Mex.*
Thioridazine (p.1031·2).
Psychoses.

Dazocan *Apotex, Mex.*
Albendazole (p.139·2).
Parasitic infections.

Dazolic *Sun, Rus.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Dazolin
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Drugtech, Chile.
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Offenbach, Mex.
Albendazole (p.139·2).
Worm infections.

Dazomet *Fabop, Arg.*
Mebendazole (p.148·3).

Dazotron *Fabop, Arg.*
Metronidazole (p.837·1).

DBI *USV, India†.*
Phenformin hydrochloride (p.455·3).
Diabetes mellitus.

DBI AP *Montpellier, Arg.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

DBI Duo *Montpellier, Arg.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

DC Softgels *Goldline, USA.*
Docusate calcium (p.1724·3).
Constipation.

D-Calcium *Mediapharm, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

D-Calsor *Orion, Fin.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Calcium supplement; vitamin D deficiency.

DCCK *Shire, Ger.*
Codergocrine mesilate (p.363·3).
Cerebrovascular insufficiency; hypertension; mental function impairment.

D-Coate *Hua, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

D'Contract *EBN, Fr.*
Dried yeast (p.1998·3); grape (p.2316·3); magnesium oxide (p.1744·1); zinc gluconate (p.1999·2).
Musculoskeletal disorders.

D-Cure *SMB, Belg.*
Colecalciferol (p.1986·2).
Dietary supplement; hypoparathyroidism; osteoporosis; pseudohypoparathyroidism; vitamin D deficiency.

D-cycloserin *IFET (ΙΦΕΤ), Gr.*
Cycloserine (p.260·2).
Tuberculosis.

DDAVP
Ferring, Canad.; Ferring, Chile; IFET (ΙΦΕΤ), Gr.; Ferring, Irl.; Ferring, Port.; Ferring, UK; Aventis, USA.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemophilia A; headache resulting from lumbar puncture; multiple sclerosis associated nocturia; nocturnal enuresis; polydipsia; polyuria; test of fibrinolytic response; test of renal concentrating capacity; von Willebrand's disease.

Remexa, Mex.†; Ferring, S.Afr.
Desmopressin (p.2185·2).
Diabetes insipidus; haemophilia A; nocturnal enuresis; polydipsia; polyuria; renal function testing; von Willebrand's disease.

DDD
Note. This name is used for preparations of different composition.
DDD, UK.
Cream: Thymol (p.1664·3); menthol (p.2340·1); methyl salicylate (p.85·3); chlorobutanol (p.1639·2); titanium dioxide (p.1617·3).
Cuts; grazes; rashes; spots.

DDD, UK.
Lotion: Thymol (p.1664·3); menthol (p.2340·1); salicylic acid (p.1612·2); chlorobutanol (p.1639·2); methyl salicylate (p.85·3).
Rashes; spots.

DDD, Austria.
Lotion; ointment: Salicylic acid (p.1612·2); methyl salicylate (p.85·3); thymol (p.1664·3); camphor (p.2273·2).
Skin disorders.

De A a Zinc Grossesse *Arkopharma, Fr.*
Multivitamin and mineral preparation (p.1922·1).

De Icin *Viatris, Belg.†.*
⊗ Dexamethasone sodium metasulfobenzoate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

De Icol *Meda, Belg.; Alcon Cusi, Malaysia.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Infected eye disorders.

de STAT *Sherman, USA.*
Range of solutions for contact lenses (p.1622·2).

De Witt's Analgesic *De Witt, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

De Witt's Antacid
Note. This name is used for preparations of different composition.
De Witt, UK.
Oral powder: Magnesium trisilicate (p.1744·1); light magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); light kaolin (p.1738·1); peppermint oil (p.1761·2).
Dyspepsia; gastric hyperacidity; heartburn.

De Witt, UK.
Tablets: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1); peppermint oil (p.1761·2).
Dyspepsia; gastric hyperacidity; heartburn.

De Witt's K & B Pills *De Witt, UK.*
Bearberry (p.2263·3); buchu (p.2269·3).
Fluid retention.

De Witts New Pills *Fleet, Austral.*
Bearberry (p.2263·3); buchu (p.2269·3).
Fluid retention.

De Witts Pills *De Witt, NZ†.*
Bearberry (p.2263·3); buchu (p.2269·3); caffeine (p.1116·3); methylthioninium chloride (p.1450·3).
Fluid retention.

Deacos *Indian Drugs, India†.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cold symptoms; coughs.

Deacura *Dermapharm, Ger.*
Biotin (p.1931·3).
Biotin deficiency.

Deafort *Collins, Mex.†.*
Multivitamin preparation (p.1922·1).

Deaftol avec lidocaine *Wild, Switz.*
Aluminium lactate (p.2255·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Dealan *Silanes, Mex.*
Coal tar (p.1616·2); clioquinol (p.254·1); allantoin (p.1588·1).
Dandruff.

Dealgic *Pharmacia, Ital.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dealyd *Rosch & Handel, Austria.*
Polyphloroglucinol phosphate (p.1611·1).
Burns; skin disorders; wounds.

Deamcilina *Degorts, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Deana-Caps *Collins, Mex.†.*
Multivitamin preparation (p.1922·1).

Deanxit *Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Hong Kong; Lundbeck, Ital.†; Lundbeck, Singapore; Lundbeck, Spain; Lundbeck, Switz.; Lundbeck, Thai.*
Flupentixol hydrochloride (p.997·2); melitracen hydrochloride (p.408·1).
Anxiety; asthenia; depression; migraine; mixed anxiety-depression; psychosomatic disorders.

Deaten *Andromaco, Chile.*
Atomoxetine hydrochloride (p.2151·1).
Attention-deficit hyperactivity disorder.

Deb *Pharmacia, Ital.*
Tetridamine maleate (p.129·1).
Cervicitis; vulvovaginitis.

Debacterol *Epien, USA.*
Sulfuric acid (p.2394·1); sulfonated phenols (p.1656·1).
Mouth and gum disorders.

Debax *Gebro, Austria.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Debby *TNP, Thai.†.*
Nifuroxazide (p.307·2).
Colitis; diarrhoea; dysentery.

Debecylina *Polfa Tarchomin, Pol.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Debeina *CPH, Port.†.*
Phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Debelex *Pharmacia, Arg.†.*
Azapropazone (p.26·3).
Gout; inflammation.

Debelizyna *Herbapol Pruszkow, Pol.*
Dolichos biflorus.
Renal calculi.

Debenal *Med-One, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Debeone *Armstrong, Mex.*
Metformin hydrochloride (p.453·2).
Formerly contained phenformin hydrochloride.
Diabetes mellitus.

Debequin *Degorts, Mex.*
Dextromethorphan (p.1555·2).
Coughs.

Debequin C *Degorts, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Debisor *Novag, Mex.*
Isosorbide dinitrate (p.1317·3).

Deblaston *Madaus, Austria; Madaus, Ger.; Altana Madaus, S.Afr.*
Pipemidic acid (p.315·1).
Bacterial infections of the urinary tract.

Debonal *Cryopharma, Mex.*
Sodium bicarbonate (p.1673·2).
Metabolic acidosis.

Debridat
Pfizer, Arg.; Parke, Davis, Austria; Enila, Braz.†; Pfizer, Chile; Sigma-Tau, Ital.; Pfizer, Port.; Pfizer, Singapore; Abdi, Turk.
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders; irritable bowel syndrome.

Pfizer, Fr.; Pfizer, Hung.†; Parke, Davis, Pol.; Uhlmann-Eyraud, Switz.
Trimebutine (p.2404·3) or trimebutine maleate (p.2404·3).
Gastrointestinal and biliary-tract disorders.

GSK, Mex.; Farma, Venez.†.
Trimebutine (p.2404·3).
Gastrointestinal disorders.

Debridat B *Pfizer, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).
Gastrointestinal disorders.

Debril *Monserrat, Arg.*
Naproxen (p.92·3).
Fever; inflammation; pain.

Debrisan *Pharmacia, Belg.†; Pharmacia, Hong Kong†; Pharmacia, Irl.†; Pharmacia, Ital.; Pharmacia Upjohn, Mex.†; Pharmacia, S.Afr.; Pfizer, UK†; Johnson & Johnson, USA.*
Dextranomer (p.1593·3).
Burns; exudating and infected wounds and ulcers.

Debrisorb *Pharmacia, Ger.†.*
Dextranomer (p.1593·3).
Wounds.

Debrox *Euroderm OTC, Ital.; Marion Merrell Dow, USA.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Debrum *Sigma-Tau, Ital.*
Trimebutine maleate (p.2404·3); medazepam (p.1006·1).
Gastrointestinal spasm with a component of anxiety.

Debrumyl *Pierre Fabre Sante, Fr.; Pierre Fabre, Port.*
⊗ Deanol pidolate (p.2152·3); heptaminol hydrochloride (p.2319·1).
Asthenia; mental function disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Debtan YSP, Malaysia†; Yung Shin, Thai.
Glibenclamide (p.440·1).
Diabetes mellitus.

DEC
Note. A similar name is used for preparations of different composition (see below).
Synco, Hong Kong.
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); dexchlorpheniramine maleate (p.572·1); ammonium chloride (p.1551·3).
Coughs.

Dec
Note. A similar name is used for preparations of different composition (see above).
PP Lab, Thai.†.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Deca Atlantic, Malaysia; Atlantic, Thai.
Fluphenazine decanoate (p.998·1).
Schizophrenia.

Decadran Neomicina MSD, Spain†.
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye or ear disorders.

Decadron
Note. This name is used for preparations of different composition.
Sidus, Arg.
⊗ Dexamethasone (p.1526·1), dexamethasone acetate (p.1526·1), or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

MSD, Belg.†; MSD, Denm.†; MSD, Fin.†.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Ache, Braz.; IFET (ΙΦΕΤ), Gr.; Visufarma, Ital.; MSD, Malaysia†; MSD, Norw.†; MSD, Swed.†; Merck, USA.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Merck Frosst, Canad.†; MSD, Irl.†; MSD, Mex.; MSD, Neth.†; MSD, S.Afr.; MSD, Switz.†; M & H, Thai.; MSD, UK†.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

MSD, Venez.†.
Eye drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

MSD, Venez.†.
Injection: ⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Medinfar, Port.; MSD, Venez.†.
Tablets: ⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Decadron con Ciprofloxina Sidus, Arg.
⊗ Dexamethasone (p.1526·1); ciprofloxacin hydrochloride (p.243·3).
Infected eye disorders.

Decadron Colirio Ache, Braz.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Formerly known as Decadron Colirio com Neomicina.
Infected eye disorders.

Decadron med Neomycin MSD, Denm.†.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Decadron Nasal Ache, Braz.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Infected nasal disorders.

Decadron con Neomicina
Sidus, Arg.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

MSD, Mex.
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
External ear disorders; infected eye disorders.

Decadron com Neomicina Medinfar, Port.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Decadron cum neomycin MSD, Swed.†.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Decadron with Neomycin MSD, Thai.†.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Decadron con Nistatina MSD, Mex.
⊗ Dexamethasone (p.1526·1); nystatin (p.543·2).
Formerly contained dexamethasone tebutate, diiodohydroxyquinoline, and nystatin.
Vaginitis.

Decadron con Tobramicina Sidus, Arg.
⊗ Dexamethasone (p.1526·1); tobramycin (p.354·1).
Infected eye disorders.

Decadronal Ache, Braz.; MSD, Mex.
⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Deca-Durabol Organon, Swed.
⊗ Nandrolone decanoate (p.2118·2).
Anaemia; osteoporosis.

Deca-Durabolin Organon, Arg.; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Canad.; Organon, Chile; Organon, Cz.†; Organon, Fin.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, India; Organon, Indon.; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Pol.; Organon, Port.; Donmed, S.Afr.; Organon, Singapore; Organon, Spain; Organon, Switz.; Organon, Thai.; Organon, UK; Organon, USA; Organon, Venez.
⊗ Nandrolone decanoate (p.2118·2).
Anabolic; anaemias; breast cancer; long-term corticosteroid treatment; osteoporosis; renal failure.

Decafar Lafare, Ital.
Ubidecarenone (p.2407·2).
Coenzyme Q deficiency.

Decagen Goldline, USA.
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Decahist-DM Cypress, USA†.
Carbinoxamine maleate (p.570·2); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; upper respiratory-tract congestion.

Decain Dexa, Indon.
Bupivacaine hydrochloride (p.1854·3).
Intrathecal anaesthesia.

Decal
Note. This name is used for preparations of different composition.
Menarini, Gr.
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Rice Steele, Irl.
Calcium lactate (p.1676·1); calcium gluconate (p.1675·3); calcium phosphate (p.1676·2); ergocalciferol (p.1987·1).
Calcium and vitamin D deficiency.

Decalcit Neves, Port.; Geistlich, Switz.
Colecalciferol (p.1986·2); calcium hydrogen phosphate (p.1676·1).
Formerly contained ergocalciferol and calcium hydrogen phosphate in *Switz.*
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

Decaldol Polfa Warszawa, Pol.
Haloperidol decanoate (p.1000·2).
Chorea; psychoses; tics.

Deca-Lentermina Complex Biotech, Venez.
Hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); vitamin B (p.1979·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis; vitamin B deficiency.

Decalogiflox Biocodex, Fr.
Lomefloxacin hydrochloride (p.295·2).
Urinary-tract infections.

Decalona Biotech, Venez.
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Decamedin Tanabe, Indon.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Decan
Note. This name is used for preparations of different composition.
Aguettant, Fr.†; Clintec, Neth.; Baxter, Port.; Baxter, Spain; Baxter, UK.
Electrolyte (p.1667·1) and trace element preparation (p.1922·1).
Parenteral nutrition.

YSP, Malaysia.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Yung Shin, Philipp.
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Yung Shin, Singapore.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Decan Haloper Uniao Quimica, Braz.
Haloperidol decanoate (p.1000·2).
Psychoses.

Decaneurabol Cadila, India†.
⊗ Nandrolone decanoate (p.2118·2).
Anabolic; osteoporosis.

Decanobral Allen, Mex.
Vitamin and mineral preparation (p.1922·1).

Decapeptyl
Sidus, Arg.; Ferring, Austria; Tecnofarma, Chile; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Ger.; Ferring, India; Ferring, Neth.; Ipsen, Port.; Ferring, Switz.; Er-Kim, Turk.
⊗ Triptorelin acetate (p.2135·3).
Benign prostatic hyperplasia; breast cancer; endometriosis; female infertility; ovarian cancer; precocious puberty; prostatic cancer; uterine fibroids.

Ipsen, Belg.; Beaufour, Fr.; Ipsen, Ital.
⊗ Triptorelin (p.2135·2) or triptorelin embonate (p.2135·3).
Breast cancer; endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Ferring, Hong Kong; Ipsen, Irl.; Ferring, Malaysia; Pharmaplan, S.Afr.; Ferring, Singapore; Ferring, Thai.
⊗ Triptorelin (p.2135·2).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Ferring, Hung.; Ferring, Pol.; Ferring, Rus.; Ipsen, UK.
⊗ Triptorelin (p.2135·2) or triptorelin acetate (p.2135·3).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Ferring, Israel; Ipsen, Spain.
⊗ Triptorelin acetate (p.2135·3), or triptorelin embonate (p.2135·3).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Ferring, Swed.; Nolver, Venez.
⊗ Triptorelin embonate (p.2135·3).
Endometriosis; precocious puberty; prostatic cancer.

Decapinol Sinclair, UK.
Delmopinol hydrochloride (p.2292·2).
Gingivitis.

Decaquinon Eisai, Thai.
Ubidecarenone (p.2407·2).
Heart failure.

Decarb Cipla, India.
Dacarbazine (p.706·3).
Malignant neoplasms.

Decaris Gedeon Richter, Cz.†; Janssen, Hong Kong; Gedeon Richter, Hung.; Janssen-Cilag, Mex.; Gedeon Richter, Rus.; Janssen-Cilag, Venez.†.
Levamisole hydrochloride (p.147·2).
Worm infections.

Deca-Scab Lafedar, Arg.†.
Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis; scabies.

Decasept N Streuli, Switz.
Dequalinium chloride (p.1641·3); calcium pantothenate (p.1959·3); lauromacrogol 400 (p.1916·1).
Mouth and throat disorders.

Decasona Alter, Spain†.
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Decasone Pharmacare, S.Afr.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Decaspray Merck, USA.
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Decatylen Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore.
Dequalinium chloride (p.1641·3); cinchocaine hydrochloride (p.1857·3).
Mouth and throat disorders.

Decatylene Mepha, Switz.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Decatylene Neo Mepha, Switz.
Dequalinium chloride (p.1641·3); cinchocaine hydrochloride (p.1857·3).
Mouth and throat disorders.

Decatyleno Mepha, Port.
Cinchocaine hydrochloride (p.1857·3); dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Decaugh Fortune, Hong Kong†.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Decavac Aventis Pasteur, USA.
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Decaven
Note. This name is used for preparations of different composition.
Baxter, Gr.†; Baxter, Ital.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Oftalmi, Venez.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye or ear disorders.

Deca-Vi-Sol BMS, Mex.
Vitamin preparation (p.1922·1).

Decavit Rowa, Irl.; Charoen Bhaesaj, Malaysia; Kocak, Turk.
Multivitamin preparation (p.1922·1).
Dietary supplement.

Decdan Merind, India.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Decdan-N Merind, India.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye disorders.

Decentan
Merck, Austria; Merck, Spain.
Perphenazine (p.1017·1).
Anxiety; depression; pain; psychoses; vomiting.

Merck, Ger.
Perphenazine (p.1017·1) or perphenazine enantate (p.1017·2).
Nausea; psychoses; vomiting.

De-Chlor DM Cypress, USA.
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

De-Chlor DR Cypress, USA.
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

De-Chlor G Cypress, USA.
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

De-Chlor HC Cypress, USA.
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms; cough.

De-Chlor HD Cypress, USA†.
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms.

De-Chlor MR Cypress, USA.
Hydrocodone tartrate (p.63·1); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Cough; nasal congestion.

De-Chlor NX Cypress, USA.
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Decho Milano, Thai.
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Decholin Miles, USA.
Dehydrocholic acid (p.2292·2).
Constipation.

Decidex Roemmers, Arg.
Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract congestion.

Decidex Compuesto Roemmers, Arg.
Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1).
Influenza symptoms.

Decidex Plus Roemmers, Arg.
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Decilina Klonal, Arg.†.
Ampicillin (p.204·1).
Bacterial infections.

Decilone Westmont, Indon.; Westmont, Philipp.
⊗ Dexamethasone (p.1526·1).
Corticosteroid; oral corticosteroid.

Decipar Sanofi-Aventis, Spain.
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders.

Decitriol Richmond, Arg.
Lysine aspirin (p.79·1).
Inflammation; pain.

Decliten Ariston, Arg.
Prazosin hydrochloride (p.1375·2).
Hypertension.

Decloban Leo, Spain.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Declofon Pharmanel, Gr.
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Declomycin Wyeth, Canad.; Glades, USA.
Demeclocycline hydrochloride (p.264·3).
Bacterial infections; intestinal amoebiasis.

Declovir Hoe, Malaysia.
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Decnazol Pharlab, Braz.†.
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Decobel Ronava, Venez.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Decocon A Sensomed, Philipp.
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Inflammatory eye disorders.

Decocort Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal and Gram-positive bacterial skin infections with inflammation.

Decoderm Hermal, Austria; Boots Healthcare, Belg.; Hermal, Ger.; Merck, Indon.; Boots Healthcare, Switz.
⊗ Fluprednidene acetate (p.1533·1).
Skin disorders.

Decoderm 3 Merck, Indon.
⊗ Fluprednidene (p.1533·1); neomycin (p.305·1); cloxiquine (p.530·3).
Infected skin disorders.

Decoderm Basiscreme Hermal, Ger.
Emollient.
Skin disorders.

Decoderm bivalent Boots Healthcare, Switz.
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Decoderm Comp Hermal, Ger.
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Decoderm Compositum Hermal, Austria; Boots Healthcare, Belg.
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Decoderm tri Hermal, Ger.
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Decoderm trivalent *Hermal, Austria.*
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1); cloxiquine (p.530·3).
Infected skin disorders.

Decofam Cough
Note. This name is used for preparations of different composition.
DHA, Hong Kong.
⊗ Ammonium chloride (p.1551·3); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

DHA, Singapore.
⊗ Ammonium chloride (p.1551·3); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Decofed *Barre-National, USA; Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Decohistine DH *Morton Grove, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Decol *Idaman, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Decolgen
Note. This name is used for preparations of different composition.
Unilab, Malaysia.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

United Laboratories, Philipp.
Phenylpropanolamine hydrochloride (p.1569·3).

Westmont, Singapore.
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Formerly contained ascorbic acid, chlorphenamine maleate, paracetamol, and phenylpropanolamine hydrochloride.
Cold symptoms; upper respiratory-tract disorders.
Nasal congestion.

Great Eastern, Thai.; Westmont, Thai.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; hay fever; sinusitis.

Probus, Indon.
Oral liquid; oral powder: Paracetamol (p.108·1); phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2) or chlorphenamine maleate (p.571·3).
Cold symptoms; upper respiratory-tract disorders.

Probus, Indon.
Tablets: Paracetamol (p.108·1); phenylpropanolamine (p.1569·2); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Cold symptoms; upper respiratory-tract disorders.

Decolgen DE *Great Eastern, Thai.; Westmont, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; hay fever; sinusitis.

Decolgen Forte *United Laboratories, Philipp.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Decolgen No-Drowse *United Laboratories, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cold and influenza symptoms; rhinitis.

Decolgen Plus *Great Eastern, Thai.; Westmont, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; hay fever; sinusitis.

Decolgen Prin *Great Eastern, Thai.; Westmont, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; hay fever; sinusitis.

Decolsin *Probus, Indon.*
⊗ Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); etafedrine hydrochloride (p.1560·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Decolsin Reformulated *Westmont, Philipp.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cough; fever; headache; nasal congestion.

Decomed *Elmor, Venez.*
Benzalkonium chloride (p.1629·1).
Antiseptic.

Decomit *Beximco, Singapore.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; nasal polyps.

Decomyk *Hermal, Ger.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive skin infections.

Decon *Cadila Pharma, India.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Decon Lavanda *IP, Ital.*
Levomenol (p.2333·3); chlorhexidine gluconate (p.1635·3); lactic acid (p.2329·3); lysates of lactobacillus (p.2372·3).
Restoration of vaginal flora.

Decon Nasale *IP, Ital.*
Sodium carboxymethyl betaglucan.
Nasal hygiene.

Decon Ovuli *IP, Ital.*
Triticum vulgare (p.2415·1); phenoxyethanol (p.1657·1); calendula (p.2273·1); hamamelis (p.2318·2).
Vaginal mucosal disorders.

Deconamine *Kenwood, Hong Kong; Kenwood, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion; sinusitis.

Deconamine CX *Bradley, USA.*
Guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Deconex DM *Poly, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cough; respiratory-tract congestion.

Deconex 50FF *Borer, Thai.†.*
Glyoxal (p.1646·1); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Surface and instrument disinfection.

Deconex 53IN *Borer, Thai.†.*
Alkylamine; didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Decongest *Technilab, Canad.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Decongestant *Rugby, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Decongestant Nasal Mist *Prodemdis, Canad.*
⊗ Oxymetazoline hydrochloride (p.1567·2).

Decongestant Nasal Spray *Jamp, Canad.; Pharmascience, Canad.; Prodemdis, Canad.; Rougier, Canad.; Confab, Hong Kong.*
⊗ Xylometazoline hydrochloride (p.1575·1).

Decongestant Nose Drops *Prodemdis, Canad.*
⊗ Xylometazoline hydrochloride (p.1575·1).

Decongestant Tablets *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2).

Decongex Plus *Ache, Braz.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Decongex Plus Expectorante *Ache, Braz.†.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Nasal congestion.

Decono *Milano, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Deconomed *Iopharm, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Deconsal II *Cornerstone, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Formerly contained pseudoephedrine hydrochloride and guaifenesin.
Coughs; nasal congestion.

Decontractyl
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Fr.
Ointment: Mephenesin (p.1897·2); methyl nicotinate (p.85·3).
Painful muscular disorders.

Sanofi-Aventis, Fr.
Tablets: Mephenesin (p.1897·2).
Painful muscular disorders.

Decontril *Boniscontro & Gazzone, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Decordex *Nida, Singapore.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Decorenone *Italfarmaco, Ital.*
Ubidecarenone (p.2407·2).
Co-enzyme Q deficiency.

Decorex *Pisa, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Decorfen *Greenpharma, Braz.*
Potassium (p.1684·2).

Decorpa *Pierre Fabre, Ger.†.*
Sterculia (p.1772·1).
Obesity.

Decortilen *Merck, Ger.*
⊗ Prednylidene (p.1543·1).
Corticosteroid.

Decortin *Merck, Ger.*
⊗ Prednisone (p.1542·3).
Oral corticosteroid.

Decortin H *Merck, Ger.*
⊗ Prednisolone (p.1540·3).
Oral corticosteroid.

Decos *Sriprasit, Thai.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Decosil *Collins, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Decostriol *Jenapharm, Ger.; Jenapharm, Hong Kong; Jenapharm, Thai.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; phosphate excretion disorders; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Decozol *Hoe, Malaysia; Hoe, Singapore.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Decramp *IPRAD, Fr.*
Magnesium phosphate (p.1679·2); potassium chloride (p.1684·3); copper (p.1935·2); arnica (p.2260·2).
Skeletal muscle spasm.

Decrelip *Ferrer, Spain†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Decresco *BMS, Spain†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Dectancyl *Sanofi-Aventis, Fr.*
⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Decubal *Alpharma, Fin.; Actavis, Indon.; Alpharma, Port.†; Assos, Turk.; Alpharma, UK.*
Emollient; moisturiser.
Bedsores; dry skin disorders; nappy rash.

Deculin *Dexa, Indon.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Decurin *Gray, Arg.*
Tubocurarine chloride (p.1912·3).
Competitive neuromuscular blocker.

Decylenes *Rugby, USA.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Bromhidrosis; fungal skin infections; hyperhidrosis; minor skin irritation; nappy rash.

Decyline
Note. This name is used for preparations of different composition.
Corsa, Indon.
Cream: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Corsa, Indon.
Ointment: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); sodium propionate (p.545·3); salicylic acid (p.1612·2).
Fungal skin infections.

Corsa, Indon.
Topical powder: Zinc undecenoate (p.549·3); calcium propionate (p.545·3).
Fungal skin infections.

Dedile *Ivax, Arg.*
Flutamide (p.725·1).

Dediol *Sanofi-Aventis, Ital.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Dedolor *Fujisawa, Austria.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dedostryl *Antor, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Dedralen *Italfarmaco, Ital.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Dedrei *Opfermann, Ger.*
Colecalciferol (p.1986·2).
Osteoporosis; vitamin D deficiency.

Dedrogyl *Pharmacobel, Belg.; DB, Fr.; Desma, Ger.; IFET (ΙΦΕΤ), Gr.; Desma, Port.*
Calcifediol (p.1986·1).
Hypocalcaemia; hypoparathyroidism; osteomalacia; renal osteodystrophy; renal osteopathy; rickets; vitamin D deficiency.

Deep Cold *Mentholatum, Canad.*
Menthol (p.2340·1).

Deep Freeze *Mentholatum, UK.*
Menthol (p.2340·1); pentane (p.2026·1).
Musculoskeletal, joint, and soft-tissue disorders.

Deep Freeze Cold Gel *Mentholatum, UK.*
Menthol (p.2340·1).
Musculoskeletal, joint, and peri-articular disorders.

Deep Heat
Note. This name is used for preparations of different composition.
Mentholatum, Austral.; Hyde, S.Afr.
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscular aches and pains.

Vianex (Βιανέξ), Gr.
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); menthol (p.2340·1).
Topical analgesia.

Mentholatum, Pol.†.
Cream: Eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Musculoskeletal, join, and soft-tissue disorders; neuralgia.

Mentholatum, Austral.; Mentholatum, Pol.
Topical spray: Methyl salicylate (p.85·3); ethyl salicylate (p.52·1); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal, join, and soft-tissue disorders; neuralgia.

Deep Heat Maximum Strength *Mentholatum, UK.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Deep Heat Rub *Mentholatum, Israel; Hyde, S.Afr.; Mentholatum, UK.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Musculoskeletal and joint pain; musculoskeletal, joint, and soft-tissue disorders; musculoskeletal, joint, and soft-tissue pain.

Deep Heat Spray *Mentholatum, Israel; Mentholatum, S.Afr.; Mentholatum, UK.*
Methyl nicotinate (p.85·3); glycol salicylate (p.62·3); ethyl salicylate (p.52·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deep Heating
Note. This name is used for preparations of different composition.
Mentholatum, Canad.
Cream; lotion: Methyl salicylate (p.85·3); menthol (p.2340·1).

Mentholatum, Canad.
Transdermal patch: Methyl salicylate (p.85·3).

Deep Heating Rub *Mentholatum, Singapore†.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue pain.

Deep Heating Spray *Mentholatum, Singapore†.*
Methyl salicylate (p.85·3); ethyl salicylate (p.52·1); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain.

Deep Relief *Gezzi, Arg.†; Mentholatum, Hung.; Mentholatum, Pol.†; Mentholatum, UK.*
Ibuprofen (p.64·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deep Woods OFF *Johnson, Canad.†.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Deep-Down Rub *SmithKline Beecham, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Deetipat *Ferrosan, Fin.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Defam *Andromaco, Mex.*
Nimesulide (p.95·3).
Inflammation; pain; peri-articular and soft-tissue disorders.

Defanac *Ranbaxy, UK.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Defanyl *Eisai, Fr.*
Amoxapine (p.382·2).
Depression.

Defarol *Adipharm (Αδηφαρμ), Gr.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Defas *Rontag, Arg.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Defatig *Farmasa, Braz.*
Vitamin B substances; potassium aspartate; magnesium aspartate (p.1922·1).
Nutritional supplement.

Defaxina *Smaller, Spain†.*
Cefalexin (p.218·2).
Bacterial infections.

DeFed *Ferndale, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Defeks *Berk, Turk.*
⊗ Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2).
Respiratory-tract congestion.

Defenac *Ranbaxy, UK.*
Diclofenac (p.44·2).

Defen-LA *Horizon, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Defibrase *Gerot, Austria.*
Batroxobin (p.1056·1).
Thromboembolic disorders.

Deficial B12 *Gross, Braz.*
Calcium phosphate; sodium fluoride; colecalciferol; cyanocobalamin (p.1922·1).
Nutritional supplement.

Defiltran *Dexo, Fr.*
⊗ Acetazolamide (p.1875·1).
Soft-tissue injury.

Defin *Liferpal, Mex.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Definity *BMS, Canad.; BMS, Chile; BMS, Israel; Lantheus, USA.*
Perflutren (p.1488·2) in lipid coated microspheres.
Contrast medium for echocardiography and abdominal ultrasound.

Defirin *Chemipharma, Gr.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemophilia; von Willebrand's disease.

Defislez *Synthesis, Rus.*
Hypromellose (p.2144·2).
Eye disorders.

Defix *SNBTS, UK†.*
Factor IX (p.1068·3).
Haemorrhagic disorders.

Defixal *Megat, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Deflaimmun *Sigma, Braz.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Deflam *Akromed, S.Afr.*
Oxaprozin (p.105·3).
Musculoskeletal, joint, and peri-articular disorders.

Deflamat
Fujisawa, Austria; Actavis, Indon.; Sankyo, Ital.; Fujisawa, Switz.†; Trip-harma, Turk.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Andromaco, Chile.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain.

Deflamm *Fujisawa, Austria.*
Diclofenac sodium (p.44·3).
Musculoskeletal pain and inflammation.

Deflamol *Fumouze, Fr.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Deflamon *Bieffe, Cz.†; SPA, Ital.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Deflamox *Hormona, Mex.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Deflamox Plus *Hormona, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Deflan *Guidotti, Ital.*
⊗ Deflazacort (p.1524·3).
Oral corticosteroid.

Deflanil *Libbs, Braz.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Deflaren *Sanval, Braz.*
⊗ Dexamethasone (p.1526·1) or dexamethasone acetate (p.1526·1).
Corticosteroid.

Deflatop *Astellas, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders.

Deflegmin *ICN, Pol.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Deflogen *Genom, Braz.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Deflogix *Vedim, Port.†.*
Ketoprofen lysine (p.73·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Deflox
Note. This name is used for preparations of different composition.
Merck, Mex.
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Inflammation; pain.

Abbott, Spain.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Deflu *Yeni, Turk.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Defluin *Merck, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Defluin Plus *Merck, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Defluina
Note. This name is used for preparations of different composition.
Ebewe, Austria.
Raubasine (p.1386·3) or raubasine hydrochloride (p.1386·3); dihydroergocristine mesilate (p.364·2); dihydroergotamine mesilate (p.618·2).
Cerebral and peripheral vascular disease.

Aventis, Ger.
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Teofarma, Ital.†.
Dihydroergocristine mesilate (p.364·2).
Cerebral and peripheral vascular disorders; headache; hypertension.

Defluina N *Aventis, Ger.†.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Deflux
Note. This name is used for preparations of different composition.
Lafit, Braz.†.
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Q-Med, USA.
Dextranomer (p.1593·3); hyaluronic acid (p.2320·1).
Vesicoureteral reflux.

Defobin *Zentiva, Cz.†.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety disorders; muscle spasm; spasticity.

Defomag *Pharmasant, Thai.†.*
Aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastric hyperacidity.

Defomil *Nakornpatana, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Deforan *Deva, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Defradil *Merck, Mex.*
Cefotaxime (p.229·1).
Bacterial infections.

Deftan *Merck, Spain†.*
Lofepramine hydrochloride (p.407·1).
Depression.

Defungin *Innoderm, Philipp.*
Miconazole (p.541·2).
Fungal skin and nail infections.

Defungo *Siam Bheasach, Thai.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections; trichomoniasis.

Degabina *Rivero, Arg.*
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

DeGalin *Riemser, Ger.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; folic acid deficiency; prevention of methotrexate toxicity.

Degan *Lek, Cz.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastrointestinal disorders.

Degas *Wyeth Consumer, Austral.; Invamed, USA†.*
Simeticone (p.1770·2).
Flatulence.

De-Gas *Wyeth Consumer, NZ.*
Simeticone (p.1770·2).
Flatulence.

Degas Extra *Wyeth Consumer, Austral.*
Simeticone (p.1770·2); calcium carbonate (p.1714·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence.

Degas Infant Drops *Wyeth Consumer, Austral.†.*
Simeticone (p.1770·2).
Infant colic.

Degastrol *Deva, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Degest *Akorn, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Minor eye irritation.

Degest 2 *Barnes Hind, NZ†.*
⊗ Naphazoline hydrochloride (p.1565·2); phenazone (p.116·1).
Eye irritation.

Degirol *Darya-Varia, Indon.*
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Degoran *Novartis Consumer, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); pheniramine maleate (p.587·3).
Cold and influenza symptoms.

Degoran C *Novartis Consumer, S.Afr.*
Paracetamol (p.108·1); vitamin C (p.1983·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Degoran Cold & Flu *Novartis Consumer, S.Afr.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Degoran Cough *Novartis Consumer, S.Afr.†.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Degoran Plus *Novartis Consumer, S.Afr.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Degorflan *Degorts, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Degorvit-Plus *Degorts, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Degraler *Bago, Chile.*
Levocetirizine hydrochloride (p.583·2).
Hypersensitivity reactions.

Degran *Ranbaxy, Thai.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Degranol *Pharmacare, S.Afr.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Degrium *Ferron, Indon.*
Flunarizine (p.580·3).
Migraine; peripheral vascular disorders.

Dehace *Lannacher, Austria.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Dehalid *Gal, Pol.†.*
Borage oil (p.2267·3); cod-liver oil (p.1935·2); vitamin E (p.1992·2).
Atherosclerosis; atopic eczema; rheumatoid arthritis; vitamin A and D deficiency.

Dehidrobenzperidol *OTL, Port.; Kern, Spain†.*
Droperidol (p.994·3).
General anaesthesia; neuroleptanalgesia; premedication.

Dehistine *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Dehydral *Valeo, Canad.*
Methenamine (p.298·3).
Hyperhidrosis.

dehydro sanol tri *Sanol, Ger.*
⊗ Bemetizide (p.1223·1); triamterene (p.1417·2).
Leg pain associated with venous insufficiency.

Dehydrobenzperidol *LCA, Belg.; Janssen-Cilag, Cz.†; OTL, Denm.; OTL, Fin.; IFET (ΙΦΕΤ), Gr.†; OTL, Neth.; Janssen-Cilag, Thai.†.*
Droperidol (p.994·3).
Agitation; induction of anaesthesia; nausea and vomiting; neuroleptanalgesia; postoperative nausea and vomiting; premedication; sedation.

Dehydrosol *San Marino, Philipp.*
Sodium chloride; sodium citrate; potassium chloride; anhydrous glucose (p.1672·2).
Diarrhoea; oral rehydration.

Deicol *Leti, Venez.†.*
⊗ Chloramphenicol (p.239·3); dexamethasone (p.1526·1).
Infected eye disorders.

Deilem *Nucitec, Mex.*
Preparation for enteral nutrition (p.1922·1).

Deiten *ABC, Ital.*
Nitrendipine (p.1358·2).
Hypertension.

Deixim *Benedetti, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Dek *Materfarma, Port.*
Benzocaine (p.1854·1); dequalinium chloride (p.1641·3).
Mouth and throat disorders.

DEKA
Note. A similar name is used for preparations of different composition (see below).
Dayton, USA.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dexbrompheniramine maleate (p.569·2).

Dekamin *Monico, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Dekar 2 *Pentamedical, Ital.*
Benzyl benzoate (p.2036·1); quassia (p.2377·1).

Dekatin *Ativus, Braz.*
Crataegus (p.2289·1).
Heart failure.

Dekinet *Rafa, Israel.*
Biperiden hydrochloride (p.797·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Dekka
Note. A similar name is used for preparations of different composition (see above).
Pond's, Thai.
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection of skin, wounds, and instruments.

Dekort *Deva, Turk.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dekristol *Jenapharm, Ger.*
Colecalciferol (p.1986·2).
Rickets; vitamin D deficiency.

Deksalon *Sanli, Turk.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Deksamet *Biosel, Turk.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Deksan *Deva, Turk.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Del Aqua *Del-Ray, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Delabarre *Fumouze, Fr.*
Tamarind (p.1775·3).
Teething pain.

Delabarre Bio-adhesif *Fumouze, Fr.*
Oak bark (p.2355·3); rhatany root (p.2378·3); triclosan (p.1665·2).
Oral lesions.

Delacard *Torrex, Austria; Chiesi, Gr.*
Delapril hydrochloride (p.1256·2).
Hypertension.

Delacet *Herbapol Krakow, Pol.*
Delphinium consolida.
Pediculosis.

De-Lact *Nutricia, Austral.*
Infant feed (p.1922·1).
Lactose intolerance.

Delagil
Note. This name is used for preparations of different composition.
ICN, Cz.; Valeant, Hung.
Chloroquine phosphate (p.599·3).
Amoebiasis; ankylosing spondylitis; lupus erythematosus; malaria; photodermatoses; rheumatoid arthritis.

Dermapharm, Ger.
Phenol-formaldehyde-urea polycondensate sodium sulfate.
Skin disorders.

Valeant, Rus.
Chloroquine (p.599·2).
Malaria.

Delak *Raffo, Arg.*
Oxybutynin (p.2190·3).
Urinary-tract disorders.

Delaket *Chiesi, Ital.*
Delapril (p.1256·2).
Heart failure; hypertension.

Delakete *Farmalab, Braz.†.*
Delapril hydrochloride (p.1256·2).
Hypertension.

Delapride
Torrex, Austria.
⊗ Delapril hydrochloride (p.1256·2); indapamide (p.1314·1).
Hypertension.

Promedica, Ital.
⊗ Delapril (p.1256·2); indapamide (p.1314·1).
Hypertension.

Delatar *Lek, Cz.; Lek, Pol.*
Coal tar (p.1616·2).
Eczema; keratinisation disorders; lichen planus; psoriasis.

Delatestryl *Theramed, Canad.; Savient, USA.*
⊗ Testosterone enantate (p.2130·1).
Androgen therapy; breast cancer; delayed puberty (males); male hypogonadism.

Delazinc *Mericon, USA.*
Zinc oxide (p.1621·2).
Skin disorders.

Delbiase *Chiesi, Fr.†.*
Magnesium chloride (p.1679·1); magnesium bromide (p.1680·1).
Magnesium deficiency.

Delbulasa *Alpharma, Mex.†.*
Phenylbutazone (p.117·1).
Inflammation; musculoskeletal and joint disorders.

Delcoprep *DeltaSelect, Ger.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Delecit *MDM, Ital.*
Choline alfoscerate (p.363·3).
Mental function impairment.

Delegol *Bayer, Ital.*
Partially chlorinated benzylphenol.
Surface disinfection.

Delepsine *Orion, Denm.*
Sodium valproate (p.508·2).
Epilepsy.

Deleptin *Stada, Austria.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; diabetes insipidus; diabetic neuropathy; epilepsy; mania; neuralgias.

Delestrogen *Theramed, Canad.†; JHP, USA.*
Estradiol valerate (p.2097·3).
Breast cancer; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; menopausal disorders; menstrual disorders; prostatic cancer; vulval and vaginal atrophy.

Deletus *Nicholas Piramal, India.*
Dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3); phenylpropanolamine hydrochloride (p.1569·3).
Formerly contained dextromethorphan hydrobromide, triprolidine hydrochloride, and pseudoephedrine hydrochloride.
Coughs.

Deletus A *Nicholas Piramal, India†.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Asthmatic cough.

Deletus D *Nicholas Piramal, India.*
Dextromethorphan hydrobromide (p.1555·2); triprolidine hydrochloride (p.592·3); phenylpropanolamine hydrochloride (p.1569·3); menthol (p.2340·1).
Formerly contained dextromethorphan hydrobromide, triprolidine hydrochloride, pseudoephedrine hydrochloride, and menthol.
Coughs.

Deletus P *Nicholas Piramal, India.*
Bromhexine hydrochloride (p.1552·2); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Formerly contained bromhexine hydrochloride, pseudoephedrine hydrochloride, and guaifenesin.
Coughs associated with viscous mucus.

Delfen *Janssen-Cilag, Arg.†; Janssen-Cilag, Austria†; Johnson & Johnson, Canad.; Cilag, Cz.†; Ethnor, India; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel†; Janssen-Cilag, Port.†; Janssen-Cilag, S.Afr.; Janssen-Cilag, Switz.†; Janssen-Cilag, UK†; Advanced Care, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Delfos *AGIPS, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Delgacin Fibras *Higate, Arg.†.*
Lecithin; glucomannan; bladderwrack (p.1922·1).
Dietary supplement.

Delgadol *K2 Pharmacare, Chile.*
Phaseolus vulgaris.
Obesity.

Delgadol Fibra *K2 Pharmacare, Chile.*
Phaseolus vulgaris; soluble fibre (carmellose & glucomannan) (p.2142·1) (p.2312·3).
Obesity.

Delgadol Vita *K2 Pharmacare, Chile.*
Phaseolus vulgaris; vitamins.
Obesity.

Delical *DHN, Fr.*
Food for special diets (p.1922·1).
Diarrhoea; lactose intolerance; nutritional supplement.

Delicate Skin Pasta *RCA, Ital.*
Zinc oxide (p.1621·2).
Skin irritation.

Delidose *HRA, Fr.*
Estradiol (p.2097·2).
Menopausal disorders.

delimmun *Syner, Ger.*
Inosine pranobex (p.884·2).
Viral infections.

Delimon *Pharmathen, Gr.*
Diclofenac sodium (p.44·3).
Prevention of miosis in ophthalmic surgery.

Delin *Atlantic, Hong Kong; Atlantic, Malaysia.*
Dequalinium chloride (p.1641·3).
Gingivitis; sore throat.

Delinar *Teva Tuteur, Arg.*
Mesna (p.1449·2).

Delipoderm *Reig Jofre, Spain.*
Promestriene (p.2127·3).
Acne; seborrhoea.

Delipost *Rafarm, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Delipramil *E-Pharma, Ital.*
Metoclopramide hydrochloride (p.1747·3).
Gastric hyperacidity.

Deliproct *Intendis, Fr.*
⊗ Prednisolone caproate (p.1541·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Delirex *Sanova, Austria.*
Caroverine hydrochloride (p.2277·3).
Alcohol and drug withdrawal syndromes.

Delisan *Baliarda, Arg.*
⊗ Fluorometholone (p.1532·3); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Delisprin *Otsira, India.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Delitab-HCT *Tiefenbacher, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Delitan *Gynopharm, Chile.*
⊗ Esterified oestrogens (p.2097·1); methyltestosterone (p.2117·1).
Menopausal disorders.

Delitex N *Infectopharm, Ger.*
Lindane (p.2045·3).
Pediculosis.

Delitroxin *Pharmathen, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Deliver *Mead Johnson, Austral.; Mead Johnson, NZ†.*
Preparation for enteral nutrition (p.1922·1).
Fluid or volume restriction; hypermetabolic states.

Delix *Aventis, Ger.; Aventis, Turk.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction.

Delix Plus *Aventis, Ger.; Aventis, Turk.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Dellamethasone *Darya-Varia, Indon.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dellasidrex *Darya-Varia, Indon.*
⊗ Reserpine (p.1387·3); dihydralazine (p.1264·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Del-Lend *Eversil, Braz.†.*
Deltamethrin (p.2040·1).

Dellova *Clement, Fr.†.*
Bladderwrack (p.2384·2); java tea (p.2328·2).
Obesity.

Delmuno *Aventis, Ger.*
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Del-Mycin *Del-Ray, USA.*
Erythromycin (p.269·2).

Delnil *Sandoz, Denm.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Delok *Nicholas Piramal, India.*
Duloxetine hydrochloride (p.389·3).
Depression.

Delonal *Essex, Ger.; Essex, Switz.†.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Delos *Dallas, Arg.*
Roxithromycin (p.331·1).
Bacterial infections.

Delos Otic *Dallas, Arg.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Ear disorders.

Delpeg *Vanden Bogaerde, Belg.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Delph Sun Lotion
Note. This name is used for preparations of different composition.
Fenton, UK.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.
Fenton, UK.
SPF 25; SPF 30; SPF 50: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Delphi *Erfa, Belg.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Delphicol *Wyeth, India.*
Tricholine citrate (p.1934·2); acetyl dimethionine; inositol (p.2325·2); vitamin B (p.1980·2).
Liver disorders.

Delphicort *Dermapharm, Austria; Riemser, Ger.*
⊗ Triamcinolone (p.1544·2), triamcinolone acetonide (p.1544·3), or triamcinolone diacetate (p.1544·3).
Corticosteroid.

Delphimix *Riemser, Ger.†.*
⊗ Triamcinolone diacetate (p.1544·3).
Musculoskeletal and joint disorders.

Delphinac *Lederle, Ger.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Delpral *Sanofi Synthelabo, Austria.*
Tiapride hydrochloride (p.1032·1).
Alcohol withdrawal syndrome; movement disorders.

Delrosa
Note. This name is used for preparations of different composition.
Valeant, Hong Kong.
Vitamin C (p.1983·3).
Vitamin C supplement.
Valeant, Philipp.
Rose fruit (p.2381·2); ascorbic acid (p.1983·3).
Vitamin C supplement.

Delsacid *Selvi, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Delsal *Meyer, Venez.*
Dipyrone (p.49·2).
Fever; pain.

Delsoralen *Darya-Varia, Indon.*
Methoxsalen (p.1605·1).
Psoriasis; vitiligo.

Delsym
Novartis Consumer, Canad.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.
Bayer, Irl.; Roche Consumer, Irl.; Adams, USA.
Dextromethorphan resinate (p.1556·1).
Coughs.

Delta 80 *IDI, Ital.*
Benzoyl peroxide (p.1590·2); cetylpyridinium chloride (p.1635·1).
Acne; skin disinfection.

Delta Charcoal *Sriprasit, Thai.*
Charcoal (p.1435·2); magnesium hydroxide (p.1743·2); belladonna (p.2263·3); peppermint oil (p.1761·2).
Diarrhoea; flatulence; poisoning.

Delta 80 Plus *IDI, Ital.*
Benzoyl peroxide (p.1590·2); cetylpyridinium chloride (p.1635·1).
Acne; skin disinfection.

Delta T *APT, Hong Kong.*
Clindamycin phosphate (p.251·2).
Acne.

Delta Tomanil B12 *Altana, Arg.*
⊗ Diclofenac sodium (p.44·3); prednisolone (p.1540·3); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Musculoskeletal and joint disorders; pain.

Deltacef *Pulitzer, Ital.†.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Deltacid *Solvay, Braz.*
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Deltacid Plus *Solvay, Braz.*
Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis; scabies.

Deltacillin *Lagamed, S.Afr.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Delta-Cortef *Upjohn, USA†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Deltacortene *Bruno, Ital.*
⊗ Prednisone (p.1542·3).
Oral corticosteroid.

Deltacortril *Pfizer, Belg.†; Pfizer, Gr.; Phoenix, Irl.; Pfizer, Turk.; Pfizer, UK.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Delta-D *Freeda, USA.*
Colecalciferol (p.1986·2).
Dietary supplement; vitamin D deficiency.

Delta-Diona *Reuffer, Mex.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Deltaflan *Delta, Braz.*
Nimesulide (p.95·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Deltaflogin *Delta, Braz.*
Diclofenac diethylamine (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Delta-Hadensa *Kolassa, Austria.*
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1); chlorcarvacrol (p.1639·3); ichthammol (p.1599·1); menthol (p.2340·1); with or without chamomile oil (p.2279·3).
Anorectal disorders.

Deltajonin *DeltaSelect, Ger.*
A range of electrolyte infusions with or without carbohydrate (p.1667·1).
Fluid and electrolyte disorders.

Deltalab *Multilab, Braz.*
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Deltalaf *Lanpharm, Arg.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Deltalipid *DeltaSelect, Ger.*
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Deltamannit *DeltaSelect, Ger.*
⊗ Mannitol (p.1330·2).
Forced diuresis; oedema; renal failure.

Deltamid *Volta, Chile; Sophia, Mex.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Eye disorders; infected eye disorders.

Deltamidrina *Tubilux, Ital.*
⊗ Prednisolone acetate (p.1541·1); atropine sulfate (p.1219·3); phenylephrine hydrochloride (p.1568·1).
Inflammatory eye disorders.

Deltamin *DeltaSelect, Ger.*
A range of amino-acid infusions with or without electrolytes and xylitol (p.1922·1).
Parenteral nutrition.

Deltamitren *Teuto, Braz.†.*
Deltamethrin (p.2040·1).

Deltapio *Luper, Braz.†.*
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Deltar *Phoenix, Arg.*
⊗ Prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Deltaran *Strathmann, Ger.*
Dexibuprofen (p.39·2).
Musculoskeletal and joint disorders; pain.

Deltaren *Delta, Braz.*
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Deltarhinol *Aventis, Turk.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Deltarhinol-Mono *Melisana, Belg.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Deltarinolo *Sanofi-Aventis, Ital.*
⊗ Ephedrine hydrochloride (p.1558·2); naphazoline nitrate (p.1565·2).
Nasal congestion.

Deltasay *Biofarma, Braz.†.*
Deltamethrin (p.2040·1).
Pediculosis.

Deltasone *Upjohn, USA.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Deltasoralen *Delta, Irl.*
Methoxsalen (p.1605·1).
Leucoderma; mycosis fungoides; psoriasis; vitiligo.

Deltastab *Sovereign, UK.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Delta-Tritex *Dermol, USA†.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Deltavac *Trimen, USA.*
Sulfanilamide (p.343·1); aminoacridine hydrochloride (p.1625·1); allantoin (p.1588·1).
Vaginal infections.

Deltavagin *Finderm, Ital.*
⊗ Betamethasone (p.1518·2); tyrothricin (p.358·2); norvaline.
Vaginitis.

Deltavit *Delta, Braz.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Deltazen *Irex, Fr.*
Diltiazem hydrochloride (p.1265·1).
Hypertension.

Deltisan *Valma, Chile.*
Zinc (p.1999·1); cod-liver oil (p.1935·2).
Skin disorders.

Deltison *Recip, Swed.*
⊗ Prednisone (p.1542·3).
Magnesium trisilicate (p.1744·1) and calcium hydrogen phosphate (p.1676·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Corticosteroid.

Deltisona B *Aventis, Arg.*
⊗ Meprednisone (p.1538·1) or meprednisone hemisuccinate (p.1538·1).
Corticosteroid.

Delto-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Deltoram-GP *Continentales, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Nasal congestion; rhinitis; sinusitis.

Deltron *Pharmacos, Mex.*
⊗ Prednisolone (p.1540·3); chlorphenamine (p.572·2).
Eye disorders.

Deltrox *Dupomar, Arg.†.*
Cefuroxime (p.238·2) or cefuroxime axetil (p.238·2).
Bacterial infections.

Delufen *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Delursan *Axcan, Fr.*
Ursodeoxycholic acid (p.2408·1).
Gallstones; liver and biliary disorders.

Demac *Osotspa, Thai.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Demacort *Andromaco, Arg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Demadex *Roche, USA.*
⊗ Torasemide (p.1415·3).
Hypertension; oedema.

Demalgon *Extractum, Hung.*
Aminophenazone (p.19·1); carbromal (p.967·3).
Fever; pain.

Demalgonil *Zentiva, Hung.*
Allobarbital (p.959·3); aminophenazone (p.19·1); urethane.
Fever; pain.

Demalit *Baldacci, Ital.*
Soya (p.1965·3); dioscorea composita.
Menopausal disorders.

Demar *Polinac, Venez.†.*
Lindane (p.2045·3).
Pediculosis; scabies.

Dematrac *Dem, Turk.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Demazin
Note. This name is used for preparations of different composition.
Schering-Plough, Austral.; Schering-Plough, NZ†.
Delayed-release tablets: Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.
Schering-Plough, Austral.; Schering-Plough, NZ; Schering-Plough, S.Afr.
Syrup: Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Hypersensitivity reactions; upper respiratory-tract congestion.

Schering-Plough, Austral.
Tablets: Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory tract congestion.

Demazin Anti-Allergy *Schering-Plough, S.Afr.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Demazin Anti-Tussive *Schering-Plough, S.Afr.†.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3).
Coughs.

Demazin Clear *Schering-Plough, Austral.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory tract congestion.

Demazin Cold & Flu *Schering-Plough, Austral.*
Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms; sinusitis.

Demazin Cold Relief *Schering-Plough, Austral.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory tract congestion.

Demazin Cough & Cold *Schering-Plough, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); pholcodine (p.1570·2); chlorphenamine maleate (p.571·3).
Cold symptoms; cough.

Demazin Cough, Cold & Flu *Schering-Plough, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms; cough.

Demazin Day & Night *Schering-Plough, Austral.*
Day-time tablets, paracetamol (p.108·1); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); night-time tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold symptoms.

Demazin Day/Night Relief *Schering-Plough, Austral.; Schering-Plough, NZ†.*
Day tablets, pseudoephedrine sulfate (p.1571·2); night tablets, dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate.
Upper respiratory-tract congestion.

Demazin Decongestant *Schering-Plough, S.Afr.†.*
Pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Demazin Expectorant *Schering-Plough, S.Afr.†.*
Dexchlorpheniramine maleate (p.572·1) pseudoephedrine sulfate (p.1571·2) guaifenesin (p.1561·3).
Coughs.

Demazin Non-Drowsy *Schering-Plough, NZ†.*
Pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Upper respiratory-tract congestion.

Demazin NS *Schering-Plough, S.Afr.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Rhinitis.

Demazin Sinus *Schering-Plough, Austral.†.*
Pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Demeprazol *Deva, Turk.*
Omeprazole (p.1753·1).

Demergin *Demo, Gr.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage.

Demerol *Sanofi Synthelabo, Canad.; Abbott, Chile†; Abbott, Philipp.; Sanofi Winthrop, USA; Abbott, Venez.†.*
⊗ Pethidine hydrochloride (p.113·2).
Adjunct in anaesthesia; pain; premedication.

Demerung *Biotecnoquimica, Venez.*
Fucus (p.2384·2); greater celandine (p.2317·1); coffea arabica (p.2416·1); equisetum (p.2299·3).
Slimming aid.

Demetil *Farmila, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye congestion.

Demetrin *Pfizer, Austria; Parke, Davis, Ger.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Switz.*
Prazepam (p.1019·3).
Anxiety; nervous disorders; skeletal muscle spasm; sleep disorders; tension.

Demex *Berlin-Chemie, Ger.*
Propyphenazone (p.119·3).
Fever; pain.

Demi Canderel *Ali, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Demiax *Merck, Spain†.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Demiderm *Schering-Plough, Venez.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Demi-Regroton *Rhone-Poulenc Rorer, USA.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Demix *Ashbourne, UK†.*
Doxycycline hyclate (p.267·1).

Demo Elixir pectoral N *Vifor, Switz.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); belladonna (p.2263·3); drosera (p.2297·3); ivy (p.2328·1); ipecacuanha (p.1562·3).
Coughs.

Demo pommade contre les refroidissements *Democal, Switz.†.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2); peru balsam (p.2365·3); camphor (p.2273·2); thyme oil (p.2401·2).
Cold symptoms.

Demo-Cineol *Sandoz, Canad.*
Cineole (p.2282·3); guaiacol (p.1561·2); camphor (p.2273·2).
Coughs.

Democyl *Vifor, Neth.; Democal, Switz.†.*
Paracetamol (p.108·1).
Fever; pain.

Demodek *Drag, Chile†.*
Nitrofurazone (p.309·1).
Bacterial skin infections.

Demodon Neo *Vifor, Switz.*
Senna (p.1769·2).
Constipation.

Demogripal *Democal, Switz.†.*
Paracetamol (p.108·1).
Fever; pain.

Demogripal C *Vifor, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Demoksil *Deva, Turk.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Demolaxin *Vifor, Switz.*
Bisacodyl (p.1710·1).
Constipation.

DemoLibral *Vifor, Switz.*
Acetylcysteine (p.1548·2).
Coughs.

Demolox *Wyeth Lederle, Denm.†; Wyeth, India.*
Amoxapine (p.382·2).
Depression.

Demonatur Capsules contre les refroidissements *Vifor, Switz.*
Brown capsules, thyme oil (p.2401·2); origanum oil (p.2358·1); savory oil (p.2394·3); green capsules, echinacea purpurea (p.2298·1).
Influenza symptoms.

Demonatur Dragees pour les reins et la vessie *Vifor, Switz.*
Bearberry (p.2263·3); solidago virgaurea (p.2391·1); ononis (p.2357·1); echinacea (p.2298·1); Java tea (p.2328·2).
Urinary-tract disorders.

Demonatur Ginkgo *Vifor, Switz.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disease.

Demonatur Gouttes pour le foie et la bile *Vifor, Switz.*
Vial no 1: gentian (p.2310·3); taraxacum (p.2395·1); cynara (p.2291·2); vial no 2: milk thistle (p.1452·1); celandine (p.2317·1); berberis.
Gastrointestinal disorders.

DemoPectol
Note. This name is used for preparations of different composition.
Vifor, Switz.
Oral drops: Thyme (p.2401·1); ivy (p.2328·1); liquorice (p.1740·3).
Coughs.

Vifor, Switz.
Syrup: Thyme (p.2401·1); cowslip (p.2372·2); ivy (p.2328·1).
Coughs.

DemoPectol Junior *Vifor, Switz.*
Ivy (p.2328·1).
Coughs.

Demostan N
Note. This name is used for preparations of different composition.
Vifor, Switz.
Cream: Mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3); calcium levulinate (p.1676·2); menthol (p.2340·1).
Allergic, pruritic or inflamed skin conditions.

Vifor, Switz.
Topical gel: Mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3); dexpanthenol (p.2362·1).
Allergic, pruritic and inflamed skin conditions.

Demotest *Pierre Fabre, Spain.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Demotherm Pommade contre le rhumatisme *Democal, Switz.†.*
Benzyl nicotinate (p.28·1); glycol salicylate (p.62·3).
Musculoskeletal and joint pain.

DemoTussil *Vifor, Switz.*
Noscapine (p.1566·2); drosera (p.2297·3); liquorice (p.1740·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2).
Bronchitis; coughs; laryngitis; sinusitis.

DemoTussol *Vifor, Switz.*
Butamirate citrate (p.1553·1).
Coughs.

Demovarin *Vifor, Switz.*
Heparin sodium (p.1301·2).
Superficial vascular disorders.

Demoven N *Vifor, Switz.*
Troxerutin (p.2305·1); aesculus (p.2248·2).
Soft-tissue disorders; venous insufficiency.

Demovit *Vifor, Switz.*
A range of multivitamin and mineral preparations (p.1922·1).
Dietary supplementation.

Demovit C *Vifor, Switz.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Demoxate *Demo, Gr.*
Flumazenil (p.1445·2).
Benzodiazepine overdosage.

Dempol *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3).
Hand disinfection.

Demser *Aton, USA.*
Metirosine (p.1337·1).
Phaeochromocytoma.

Demsil *Vocate, Gr.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Demucine *Leti, Venez.†.*
Sulglicotide (p.1775·3).
Peptic ulcer.

Demulcin *Scanpharm, Denm.*
Codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Demulen *Pfizer, Canad.; Searle, USA†.*
Etynodiol diacetate (p.2103·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Demusin *Nupel, Spain.*
Albumin tannate (p.1704·2); amylase (p.2256·3); ethylmorphine hydrochloride (p.52·2).
Diarrhoea.

Denacen *Marjan, Braz.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Denaclof *Novartis, Gr.*
Diclofenac sodium (p.44·3).
Prevention of miosis in ophthalmic surgery.

Denamol *TO-Chemicals, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Denan *Boehringer Ingelheim, Ger.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Denapril *Medinfar, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Denason *Greenpharma, Braz.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Denavir *SmithKline Beecham Consumer, USA.*
Penciclovir (p.901·2).
Herpes labialis.

Denaxpren *Coll, Spain.*
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Denazox *Remedica, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Dencorub
Note. This name is used for preparations of different composition.
Carter, Austral.
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3).
Musculoskeletal pain.

Ponce, Venez.
Topical gel: Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Ponce, Venez.
Topical spray: Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Dencorub Anti-Inflammatory *Carter-Wallace, Austral.†.*
Diclofenac sodium (p.44·3).
Peri-articular and soft-tissue disorders.

Dencorub Arthritis *Carter, Austral.*
Trolamine salicylate (p.132·3).
Arthritis; muscle pain.

Dencorub Arthritis Ice *Carter-Wallace, Austral.*
Menthol (p.2340·1).
Musculoskeletal pain.

Dencorub Extra Strength *Carter-Wallace, Austral.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle pain.

Dencorub Ice *Ponce, Venez.*
Menthol (p.2340·1).
Musculoskeletal and joint pain.

Dencorub Pain Relieving Cream *Carter-Wallace, Austral.†.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3).

Dencorub Uncion *Ponce, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Dendracin Neurodendtraxcin *Physicians Science & Nature, USA.*
Benzocaine (p.1854·1); menthol (p.2340·1); methyl salicylate (p.85·3).

Denerel *Medochemie, Malaysia; Medochemie, Thai.†.*
Ketotifen fumarate (p.582·2).
Allergic bronchitis; allergic rhinitis; allergic skin disorders; asthma; hypersensitivity reactions.

Denerval *Jaba, Port.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Denex *Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; myocardial infarction.

Denfos *Biofarma, Venez.†.*
Alendronic acid (p.1088·1).
Osteoporosis.

Deniban *Sanofi-Aventis, Cz.; Sanofi-Aventis, Ital.*
Amisulpride (p.961·1).
Depression.

Denim *Hua, Thai.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; radiation sickness.

Denium *Strand, Malaysia†.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Denkacort *Denk, Hong Kong†.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Denkan *Duopharma, Malaysia.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

De-Nol *Yamanouchi, Cz.†; Gerolymatos, Gr.; Gerolymatos, Hong Kong; Yamanouchi, Hung.†; Astellas, Ital.; CSL, NZ; Yamanouchi, NZ; Astellas, Neth.; Yamanouchi, Port.†; Yamanouchi, Rus.; Astellas, S.Afr.; Brocades, Singapore; Eczacibasi, Turk.*
Tripotassium dicitratobismuthate (p.1711·2).
Dyspepsia; gastritis; irritable bowel syndrome; peptic ulcer.

De-Noltab *Yamanouchi, Irl.†; Astellas, UK.*
Tripotassium dicitratobismuthate (p.1711·2).
Dyspepsia; gastritis; peptic ulcer.

Denomix *Combiphar, Indon.*
⊗ Desoximetasone (p.1525·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Denoral
Note. This name is used for preparations of different composition.
Theraplix, Fr.†.
Clocinizine hydrochloride (p.574·1); pholcodine (p.1570·2).
Formerly contained buzepide metiodide, clocinizine hydrochloride, and pholcodine.
Coughs.

Aventis, Ital.†.
Buzepide metiodide (p.1714·1); clocinizine hydrochloride (p.574·1); phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Denorex
Note. This name is used for preparations of different composition.
Wyeth, Irl.; Wyeth Consumer, Neth.; Wyeth Consumer, Singapore†.
Coal tar (p.1616·2); menthol (p.2340·1).
Dandruff; psoriasis; seborrhoeic dermatitis.

Whitehall, Israel†; SA Druggists Self Med, S.Afr.
Coal tar (p.1616·2).
Dandruff; psoriasis; seborrhoeic dermatitis.

Denorex Daily *Whitehall, Braz.†.*
Salicylic acid (p.1612·2).
Scalp disorders.

Denorex Everyday *Denorex, Canad.*
Pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Denorex Herbal *Wyeth Consumer, Chile†.*
Coal tar (p.1616·2); menthol (p.2340·1).
Scalp disorders.

Denorex Medicated *Denorex, Canad.*
Coal tar (p.1616·2); menthol (p.2340·1).
Dandruff; pruritus; psoriasis; seborrhoeic dermatitis.

Denorex Original *Wyeth, Venez.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Denorex Plus *Whitehall, Braz.†.*
Salicylic acid (p.1612·2).
Scalp disorders.

Denovir *Novartis Consumer, Port.*
Penciclovir (p.901·2).

Denpru *Fada, Arg.*
Protamine (p.1461·1).
Heparin overdose.

Denquel *Procter & Gamble, USA.*
⊗ Potassium nitrate (p.1658·3).
Sensitive teeth.

Densical *Zambon, Fr.; Rubio, Spain.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Densical D *Vitoria, Port.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiencies; osteoporosis.

Densical vitamine D_3 *Zambon, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiencies; osteoporosis.

Denson *Siam Bheasach, Thai.*
⊗ Prednisolone (p.1540·3); nitrofurazone (p.309·1).
Infected skin disorders.

Densopax *Justesa Imagen, Arg.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Densulin *Denver, Arg.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Denta Plus *Rising Pharmaceuticals, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

DentaGel *Rising Pharmaceuticals, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentagesic *Maver, Chile.*
Clonixin lysine (p.37·1).
Pain.

Dentaliv *Mintlab, Chile.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Dentalivio *IMA, Braz.†.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth disorders.

Dentan *Ipex, Swed.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentapaine *Reese, USA.*
Benzocaine (p.1854·1); clove oil (p.2285·1).
Toothache.

Dentaton *Ghimas, Ital.*
Chlorhexidine (p.1635·2); mallow (p.2337·2).
Oral hygiene.

Dentex *Colgate-Palmolive, Fr.*
Hydrogen peroxide (35%) (p.1647·3).
Mouth irritation; oral hygiene.

Denticare *Trima, Israel†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Denticelso *Alcor, Spain.*
Sulfacetamide (p.335·3); tyrothricin (p.358·2).
Mouth infections.

Dentigel *Gouka, Neth.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentikrisos *Quimifar, Spain.*
Benzocaine (p.1854·1); tetracaine hydrochloride (p.1871·3); menthol (p.2340·1).
Formerly contained creosote, benzocaine, tetracaine hydrochloride, and menthol.
Toothache.

Dentin *Rekah, Israel.*
Eugenol (p.2301·2); benzocaine (p.1854·1); chlorobutanol (p.1639·2).
Toothache.

Dentinale *Montefarmaco, Ital.*
Amylocaine hydrochloride (p.1853·3); sodium benzoate (p.1630·2).
Teething pain.

Dentinox
Note. This name is used for preparations of different composition.
DDD, Israel; DDD, Singapore.
Simeticone (p.1770·2); dill oil (p.2293·3).
Infant colic.

Vemedia, Neth.
Lidocaine hydrochloride (p.1862·3).
Teething pain.

Abdi, Turk.
Lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1); chamomile (p.2279·3).
Teething pain.

Altana, Austria.
Dental gel: Chamomile (p.2279·3); lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1).
Teething pain.

Altana, Austria.
Oral drops: Chamomile tincture (p.2279·3); myrrh tincture (p.2349·2); cetylpyridinium chloride (p.1635·1); lauromacrogol 400 (p.1916·1).
Teething pain.

Dentinox Colic Drops *DDD, Hong Kong; DDD, Malaysia; DDD, UK.*
Simeticone (p.1770·2).
Infant colic.

Dentinox Cradle Cap *DDD, Malaysia; DDD, Singapore; DDD, UK.*
Sodium lauril ether sulfosuccinate; sodium lauril ether sulfate (p.2138·3).
Cradle cap.

Dentinox N *Dentinox, Cz.†; Dentinox, Ger.; Dentinox, Hung.; Dentinox, Pol.*
Chamomile (p.2279·3); lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1).
Teething pain.

Dentinox Teething Gel *DDD, Hong Kong; DDD, Malaysia; DDD, Singapore; DDD, UK.*
Lidocaine hydrochloride (p.1862·3); cetylpyridinium chloride (p.1635·1).
Denture irritation; sore gums; teething pain.

Dentipatch *Noven, USA.*
Lidocaine (p.1862·3).
Local anaesthesia.

Dentirol Fluor *Dentirol, Swed.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentisan *Multilab, Braz.*
Procaine hydrochloride (p.1869·1); phenol (p.1656·1); menthol (p.2340·1); clove oil (p.2285·1).
Dental pain.

Dentispray *Andromaco, Chile; Ferraz, Lynce, Port.; Vinas, Spain.*
Benzocaine (p.1854·1).
Local anaesthesia; mouth pain; teeth and gum pain; toothache.

Dentix *Trima, Israel.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; oral hygiene.

Dentocaine *Phoenix, Philipp.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Dentocar *PannonPharma, Hung.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentogen *Anglian, UK.*
Clove oil (p.2285·1).
Toothache.

Dentohexine *Streuli, Switz.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders; oral hygiene.

Dent-O-Kain *Geritrex, USA.*
Benzocaine (p.1854·1).
Local anaesthesia.

Dentol Topico *Perez Gimenez, Spain.*
Camphor (p.2273·2); saffron (p.1472·3); clove oil (p.2285·1); cloral hydrate (p.979·1); procaine hydrochloride (p.1869·1); menthol (p.2340·1).
Toothache.

Dentolina Plus *Fucus, Arg.*
Dipyrone (p.49·2); caffeine (p.1116·3).
Fever; pain.

Dentomicin *Seid, Spain.*
Saffron (p.1472·3); tamarind (p.1775·3).
Toothache.

Dentomycin
Note. This name is used for preparations of different composition.
Kreussler, Ger.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Blackwell, UK.
Minocycline hydrochloride (p.300·3).
Bacterial mouth infections.

Dentopain *Sandoz, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Dentophar *Qualiphar, Belg.*
Amylocaine hydrochloride (p.1853·3); cloral hydrate (p.979·1); chloroform (p.1781·1); menthol (p.2340·1); thymol (p.1664·3); eugenol (p.2301·2) =www.bcfi.be 1.07.
Dental pain.

Dentosan Azione Intensiva *Pfizer Consumer, Ital.*
Chlorhexidine gluconate (p.1635·3); peppermint oil (p.1761·2); geranium oil (p.2311·1); melissa oil (p.2339·3); clove oil (p.2285·1); spearmint oil (p.2391·3).
Oral hygiene.

Dentosan Carie & Alito *Pfizer Consumer, Ital.†.*
Sanguinaria (p.2383·2); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Dentosan Clorexidina *Pfizer Consumer, Ital.*
Chlorhexidine (p.1635·2).
Gum disorders.

Dentosan Extra Fluor *Pfizer Consumer, Ital.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentosan Junior *Pfizer Consumer, Ital.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentosan Mese *Pfizer Consumer, Ital.*
Peppermint oil (p.1761·2); geranium oil (p.2311·1); melissa oil (p.2339·3); clove oil (p.2285·1); spearmint oil (p.2391·3); chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Dentosan Parodontale *Pfizer Consumer, Ital.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Dentosan Placca & Carie *Pfizer Consumer, Ital.*
Chlorhexidine gluconate (p.1635·3); sodium fluoride (p.1962·2); peppermint oil (p.1761·2).
Oral hygiene.

Dentosan Prevent *Pfizer Consumer, Ital.†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Dentosan Sensibile *Pfizer Consumer, Ital.*
⊗ Potassium nitrate (p.1658·3) sodium fluoride (p.1962·2).
Gingivitis; hypersensitive teeth.

Dentosedina *Teofarma, Ital.*
Procaine hydrochloride (p.1869·1); benzocaine (p.1854·1).
Dental pain.

Dentosept *Phytofarm Kleka, Pol.*
Arnica (p.2260·2); chamomile (p.2279·3); peppermint (p.1761·2); oak bark (p.2355·3); sage leaf (p.2382·3); thyme (p.2401·1); couch-grass (p.2288·2).
Mouth disorders.

Dentosept A *Phytofarm Kleka, Pol.*
Arnica (p.2260·2); chamomile (p.2279·3); peppermint (p.1761·2); oak bark (p.2355·3); sage leaf (p.2382·3); thyme (p.2401·1); calamus (p.2271·3); benzocaine (p.1854·1); borax (p.2268·1).
Mouth disorders.

Dentosmin P *Riemser, Ger.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Dentoxil *Master, Chile.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Dentromin *Denver, Arg.*
Enalapril (p.1276·1).
Hypertension.

Dentron *Santa, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Dent's Extra Strength Toothache Gum *Dent, USA.*
Benzocaine (p.1854·1).

Dent's Maximum Strength Toothache Drops *Dent, USA.*
Benzocaine (p.1854·1).

Dentsiblen
Note. This name is used for preparations of different composition.
GSK, Mex.
Mouthwash: ⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3); xylitol (p.1998·2).
Dental hypersensitivity; oral hygiene.

GSK, Mex.
Toothpaste: ⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3); aldioxa (p.1587·2).
Dental hypersensitivity; oral hygiene.

Dentyl pH *Grafton, UK.*
Triclosan (p.1665·2); fluoride (p.1962·2).
Oral hygiene.

Denubil *Pierre Fabre, Spain.*
⊗ Heptaminol hydrochloride (p.2319·1); deanol pidolate (p.2152·3).
Mental function disorders.

Denufam *Caprifarmindo, Indon.; Sanbe, Indon.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Denulcer *Ciclum, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Denvar *Merck, Mex.; Merck, Spain.*
Cefixime (p.224·3).
Bacterial infections.

Denvercrem *Denver, Arg.*
⊗ Gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Denyl *Cristalia, Braz.*
Citalopram (p.385·3).
Depression; obsessive-compulsive disorder; panic attacks.

Denzapine *Merz, UK.*
Clozapine (p.981·1).
Psychoses associated with parkinsonism; schizophrenia.

Denzo *TO-Chemicals, Thai.*
Serrapeptase (p.2385·3).
Inflammation; swelling.

Deo *Milano, Thai.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Deocil *Diffucap, Braz.†.*
Ketorolac trometamol (p.74·2).
Inflammation; pain.

De-Ol *Hoe, Philipp.; Marketlink, Philipp.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Deolin *Unison, Thai.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Deopens *Brunel, S.Afr.†.*
Magnesium hydroxide (p.1743·2).
Gastro-oesophageal reflux.

Deopid *Masa, Thai.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Deotrin *Bunker, Braz.*
Deltamethrin (p.2040·1).

Deoxical *Galeno, Venez.*
Calcium dobesilate (p.2272·1).
Varices; venous insufficiency.

Deoxymykoin *Medicamenta, Cz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Depacon *Abbott, USA.*
Sodium valproate (p.508·2).
Epilepsy.

Depade *Mallinckrodt, USA†.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal.

Depakene
Abbott, Arg.; Abbott, Indon.
Valproic acid (p.508·2).
Epilepsy.

Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Mex.; Abbott, Philipp.; Sanofi Synthelabo, Philipp.; Abbott, USA.
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

Kyowa, Jpn.
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; mania.

Depakin
Sanofi Synthelabo, Ital.
Sodium valproate (p.508·2).
Epilepsy.

Sanofi Synthelabo, Turk.
Sodium valproate (p.508·2) or valproic acid (p.508·2).
Epilepsy.

Depakin Chrono *Sanofi Synthelabo, Ital.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Bipolar disorder; epilepsy.

Depakine
Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Winthrop, Rus.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Abbott, Venez.
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; febrile convulsions; infantile convulsions.

Sanofi Synthelabo, Neth.
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

Depakine Chrono *Sanofi Synthelabo, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Winthrop, Rus.; Sanofi Synthelabo, Switz.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Bipolar disorder; epilepsy; mania.

Depakine Chronosphere *Sanofi Synthelabo, Austria; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Bipolar disorder; epilepsy.

Depakine Crono *Sanofi-Aventis, Spain.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Depakote *Abbott, Braz.; Sanofi-Aventis, Fr.; Abbott, Indon.; Abbott, Philipp.; Sanofi Synthelabo, UK; Abbott, USA.*
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; mania; migraine.

Depalept *Sanofi Synthelabo, Israel.*
Sodium valproate (p.508·2).
Epilepsy; porphyria.

Depalept Chrono *Sanofi Synthelabo, Israel.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Depalgos *Molteni, Ital.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Depamag *Sigma-Tau, Ital.*
Magnesium valproate (p.511·3).
Epilepsy.

Depamide *Sanofi-Aventis, Fr.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Spain.*
Valpromide (p.508·3).
Aggression; bipolar disorder; depression; epilepsy; mania; psychomotor agitation.

Depan-F *Unison, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Deparex *Viofar, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Deparkin *Leciva, Cz.†.*
Diethazine hydrochloride (p.803·3).
Drug-induced extrapyramidal disorders; dyskinesia; meniere's disease; parkinsonism.

Deparoc *Pharmacare, S.Afr.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Deparon
Note. This name is used for preparations of different composition.
Westmont, Indon.
Dipyrone (p.49·2); meprobamate (p.1006·2).
Pain.

Great Eastern, Thai.; Westmont, Thai.
Dipyrone (p.49·2).
Pain.

Depas *Fournier, Ital.; Mitsubishi, Jpn.*
Etizolam (p.996·1).
Anxiety; anxiety states; psychosomatic disorders; sleep disorders.

Depatox *Progen, Ital.*
Curcumin (p.1471·2); thioctic acid (p.2400·2); silymarin (p.1452·2).
Liver disorders.

Depen *Carter Horner, Canad.†; Wallace, USA.*
Penicillamine (p.1456·2).
Cystinuria; rheumatoid arthritis; Wilson's disease.

Dependex *Orpha-Devel, Austria.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome.

Depersolon *Gedeon Richter, Cz.†; Gedeon Richter, Hung.†.*
⊗ Mazipredone hydrochloride (p.1537·3).
Corticosteroid.

Depesert *Merck, Spain.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; obsessive-compulsive disorder; post-traumatic stress disorder.

depGynogen *Forest Pharmaceuticals, USA.*
Estradiol cipionate (p.2097·2).
Female hypogonadism; menopausal vasomotor symptoms.

Depicor *Merck, India.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Depiderm *Uriage, Fr.*
Liquorice (p.1740·3).
Skin hyperpigmentation.

Depigoid *Leti, Ger.; Novartis, Ger.*
Allergen extracts (p.2250·2).
Hyposensitisation.

Depin *Cadila, India.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Depin-E *Cadila, Rus.*
Nifedipine (p.1350·1).

Depixol
Lundbeck, Irl.
Flupentixol decanoate (p.997·1).
Psychoses.
Lundbeck, UK.
Flupentixol decanoate (p.997·1) or flupentixol hydrochloride (p.997·2).
Psychoses.

Depizide *Pond's, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Deplecat *Baxter, Mex.†.*
Potassium phosphate (p.1682·2).

Deplin *Pamlab, USA.*
Calcium mefolinate (p.1932·2).
Megaloblastic anaemia.

depMedalone *Forest Pharmaceuticals, USA.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Depnil *Cipla-Medpro, S.Afr.*
Moclobemide (p.411·1).
Depression; social phobia.

Depnon *Organon, India.*
Mianserin hydrochloride (p.408·1).
Depression.

Depo Moderin *Pharmacia, Spain†.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Depo-Clinovir *Pharmacia, Ger.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Depocon
Note. This name is used for preparations of different composition.
Pfizer, Austria.
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.
Duopharma, Malaysia.
Norethisterone enantate (p.2120·1).
Progestogen-only injectable contraceptive.

DepoCyt *Paladin, Canad.†; Enzon, USA.*
Liposomal cytarabine (p.705·1) (p.705·1).
Lymphomatous meningitis.

DepoCyte *Mundipharma, Belg.; Mundipharma, Cz.; Skyepharma, Denm.; Mundipharma, Fin.; Mundipharma, Fr.; Mundipharma, Ger.; Mundipharma, Ital.; Skyepharma, Neth.; Skyepharma, Norw.; SkyePharma, Pol.; Mundipharma, Spain; Mundipharma, Swed.; Napp, UK.*
Liposomal cytarabine (p.705·1) (p.705·1).
Lymphomatous meningitis.

Depocyte *Mundipharma, Port.*
Liposomal cytarabine (p.705·1)(p.705·1).
Lymphomatous meningitis.

Depo-Dilar *Abdi, Turk.*
⊗ Paramethasone acetate (p.1540·2).
Corticosteroid.

DepoDur *Endo, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Depo-Eligard *Astellas, Belg.*
⊗ Leuprorelin acetate (p.2111·1).
Prostatic cancer.

Depofin *Allen, Mex.*
Diiodohydroxyquinoline (p.832·1); kaolin (p.1738·1); pectin (p.2145·2).
Amoebiasis; diarrhoea.

Depogen *Hyrex, USA.*
Estradiol cipionate (p.2097·2).
Female hypogonadism; menopausal vasomotor symptoms.

Depo-Gestin *ANB, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; progestogen-only injectable contraceptive.

Depolan
Note. This name is used for preparations of different composition.
Lannacher, Denm.; Nordic Drugs, Fin.; Nordic, Swed.
⊗ Morphine hydrochloride (p.86·3).
Pain.
Gap, Gr.
Risperidone (p.1024·2).
Psychoses.

Depolut *Taro, Israel†.*
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; endometriosis; functional uterine bleeding; uterine cancer.

Depo-M *Vesco, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; progestogen-only injectable contraceptive.

Depo-Medrate *Pharmacia, Ger.†.*
⊗ Methylprednisolone acetate (p.1538·2).
Parenteral corticosteroid.

Depo-Medrol *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, India; Pfizer, Indon.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pharmacia, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.†; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Eczacibasi, Turk.; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗ Methylprednisolone acetate (p.1538·2).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Corticosteroid.

Depo-Medrol cum Lidocain *Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol com Lidocaina *Pfizer, Port.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol + Lidocaina *Pharmacia, Ital.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol with Lidocaine *Pfizer, Canad.; Pfizer, Hong Kong; Pharmacia, Israel; Pharmacia, NZ; Pfizer, S.Afr.; Pfizer, Thai.†.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol Lidocaine *Pfizer, Switz.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol + Lidocaine *Pfizer, Belg.; Pfizer, Neth.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depo-Medrol mit Lidocain *Pfizer, Austria.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal and joint disorders.

Depo-Medrol z Lidokaina *Pfizer, Pol.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Joint disorders.

Depo-Medrone *IFET (ΙΦΕΤ), Gr.†; Pfizer, Irl.; Pfizer, UK.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Depo-Medrone with Lidocaine *Pfizer, Irl.; Pfizer, UK.*
⊗ Methylprednisolone acetate (p.1538·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal, joint, and peri-articular disorders.

Depon *BMS, Gr.*
Paracetamol (p.108·1).
Fever; pain.

Depon Extra *BMS, Gr.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Depon Maximum *BMS, Gr.*
Paracetamol (p.108·1).
Fever; pain.

Depon Odis *BMS, Gr.*
Paracetamol (p.108·1).
Fever; pain.

Depo-Nisolone *Pfizer, Austral.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Deponit *Gebro, Austria; Altana, Belg.; Schwarz, Cz.†; Schwarz, Fin.; Schwarz, Ger.; Schwarz, Hong Kong; Schwarz, Irl.; Schwarz, Israel; Schwarz, Ital.; Schwarz, Malaysia; Altana, Neth.; Schwarz, Philipp.; Schwarz, Rus.; Ranbaxy, Singapore; Schwarz, Singapore; Schwarz, Switz.; Adeka, Turk.; UCB, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; coronary heart disease; heart failure; ischaemic heart disease; prophylaxis of phlebitis and extravasation.

Depon+Vit. C *BMS, Gr.*
Paracetamol (p.108·1); vitamin C (p.1983·3).
Fever; pain.

Depopred *Hyrex, USA†.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Depo-Prodasone *Pfizer, Chile; Pfizer, Fr.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; malignant neoplasms.

Depo-Progesno *Milano, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Depo-Progesta *General Drugs, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; progestogen-only injectable contraceptive.

Depo-Progevera *Pfizer, Spain.*
Medroxyprogesterone acetate (p.2113·1).
Endometrial cancer; progestogen-only injectable contraceptive.

Depo-Provera *Pharmacia, Arg.†; Pfizer, Austral.; Pfizer, Belg.; Pharmacia, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, India; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.†; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.†; Eczacibasi, Turk.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; breast cancer; dysfunctional uterine bleeding; endometrial cancer; endometriosis; menopausal disorders; ovarian cancer; precocious puberty; progestogen-only injectable contraceptive; prostatic cancer; renal cancer.

Depo-Ralovera *Pfizer, Austral.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; malignant neoplasms; progestogen-only injectable contraceptive.

Deposilin *Ulagay, Turk.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Deposilin 6.3.3 *Ulagay, Turk.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Depostat *Schering, Cz.; Schering, Ger.†; Schering, Ital.†; Schering, Rus.; Schering, Spain†; Schering, Switz.†.*
Gestonorone caproate (p.2105·3).
Benign prostatic hyperplasia; breast cancer; endometrial cancer; prostatic adenoma.

Deposteron *Sigma, Braz.*
⊗ Testosterone cipionate (p.2129·3).
Androgen deficiency; breast cancer; delayed puberty (males); male hypogonadism.

Depo-subQ Provera *Pharmacia Upjohn, USA.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; progestogen-only injectable contraceptive.

Depo-Testadiol *Upjohn, USA.*
⊗ Estradiol cipionate (p.2097·2); testosterone cipionate (p.2129·3).
Menopausal vasomotor symptoms; prevention of postpartum breast engorgement.

Depotestogen *Hyrex, USA.*
⊗ Estradiol cipionate (p.2097·2); testosterone cipionate (p.2129·3).
Menopausal vasomotor symptoms; prevention of postpartum breast engorgement.

Depot-Hal
Hal, Ger.
Allergen extracts of pollen (p.2370·2), fungi, house dust mites (p.2251·1) and skin (p.2251·1) (p.2250·2).
Allergen immunotherapy.
Hal, Neth.
Allergen extracts from house-dust mites (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Depot-Insulin *Aventis, Ger.†.*
⊗ Insulin injection (bovine) (p.443·2).
Diabetes mellitus.

Depot-Insulin S *Aventis, Ger.†.*
⊗ Insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Depotrone *Adcock Ingram, S.Afr.*
⊗ Testosterone cipionate (p.2129·3).
Gynaecomastia; lactation suppression; male hypogonadism; mastitis; menstrual disorders.

Depotrust *Umeda, Philipp.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Deprakine *Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi Synthelabo, Norw.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; mania.

Deprakine Depot *Sanofi-Aventis, Fin.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Bipolar disorder; epilepsy.

Depral *Alkaloida, Hung.*
Sulpiride (p.1028·3).
Depression; dizziness; nausea and vomiting; schizophrenia; vertigo.

Depramil *Cipla-Medpro, S.Afr.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Depramina *Teuto, Braz.*
Imipramine hydrochloride (p.400·3).
Depression.

Deprancol *Parke, Davis, Spain.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Deprax
Note. This name is used for preparations of different composition.
Ache, Braz.
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.
Saval, Chile.
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.
Farma Lepori, Spain.
Trazodone hydrochloride (p.424·3).
Depression; dyskinesias; mood disorders; premedication; tremor.

Deprazolin *Zentiva, Cz.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension.

Deprecalm *Lazar, Arg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Deprece *Tecnobio, Spain†.*
Almagate (p.1705·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Deprectal *Psicofarma, Mex.*
Oxcarbazepine (p.490·3).
Epilepsy; neuropathic pain.

Depredon *Kleva, Gr.*
Risperidone (p.1024·2).
Psychoses.

Deprefax *Pharmacia, Arg.†.*
Nefazodone (p.413·1).
Depression.

Depreger *Gerard, Irl.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Depreks *Abdi, Turk.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Deprelin *Farmo Quimica, Chile.*
Clomipramine hydrochloride (p.386·3).
Depression; nocturnal enuresis; panic disorder.

Deprelio *Estedi, Spain.*
Amitriptyline hydrochloride (p.376·1).
Bulimia nervosa; depression; neuropathic pain; nocturnal enuresis; postherpetic neuralgia.

Deprenil *Terra, Turk.*
Opipramol hydrochloride (p.414·1).
Depression.

Deprenon *Slovakofarma, Cz.†.*
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder.

Deprenorm *Kanonfarma, Rus.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; vascular eye disorders; vestibular disorders.

Deprenyl *HRA, Fr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Depreram *Kleva, Gr.*
Mirtazapine (p.409·2).
Depression.

Depress *Uniao Quimica, Braz.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Depressan *Altana, Ger.; Altana, Hung.*
Dihydralazine sulfate (p.1264·3).
Hypertension.

Deprex
Note. This name is used for preparations of different composition.
Zentiva, Cz.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.
Interbat, Indon.
Oxitriptan (p.414·1); vitamin B (p.1979·1); ascorbic acid (p.1983·3).
Depression; headache; insomnia; myalgia.

Deprexan *Unipharm, Israel.*
Desipramine hydrochloride (p.387·3).
Depression.

Deprexen *Lisapharma, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Deprexetin *ICN, Pol.*
Fluoxetine (p.397·3).
Bulimia; depression; obsessive-compulsive disorder.

Deprexin *Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Singapore.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Deprexone *Apotex, Philipp.; Pharma 3, Philipp.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Depridol *Extractum, Hung.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal; pain.

Deprilan *Biosintetica, Braz.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Deprilept *Lundbeck, Ger.*
Maprotiline hydrochloride (p.407·2).
Depression.

Deprim *Lek, Cz.†; Lek, Pol.; Lek, Rus.*
St John's wort (p.422·3).
Anxiety; depression.

Deprimil *Merck, Port.†.*
Lofepramine hydrochloride (p.407·1).
Depression.

Deprizac Intas, Philipp.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Deprocid Sanofi Pasteur, Chile.
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Deproist Expectorant with Codeine Geneva, USA.
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Depronal Pfizer, Belg.; Pfizer, Neth.
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Deproxin Siam Bheasach, Thai.
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Deprozan Meridian, S.Afr.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Deprozel Pliva Krakow, Pol.
Paroxetine mesilate (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Deprozin Offenbach, Mex.
Fluoxetine (p.397·3).
Depression.

Deprozol Ache, Braz.
Secnidazole (p.846·3).
Bacterial infections; protozoal infections.

Depsan Biogal-Teva, Hung.†.
Trazodone hydrochloride (p.424·3).
Depression; mixed anxiety-depressive states.

Depsonil Sarabhai Piramal, India.
Imipramine hydrochloride (p.400·3) or imipramine embonate (p.400·3).
Depression; nocturnal enuresis.

Depsonil-DZ Sarabhai Piramal, India.
Imipramine hydrochloride (p.400·3); diazepam (p.986·3).
Mixed anxiety depressive states.

Depten Cadila, India.
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Deptral
Meprofarm, Indon.
Sertraline hydrochloride (p.421·3).
Depression.

Bajamed, Mex.
Sertraline (p.422·1).
Depression.

Deptran
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
Doxepin hydrochloride (p.389·1).
Depression.

Enila, Braz.†.
Bromazepam (p.964·3).
Anxiety; insomnia.

Depulol Hasco-Lek, Pol.
Eucalyptus oil (p.2301·2); Peru balsam (p.2365·3); rosemary oil (p.2381·3).
Cold and influenza symptoms; cough.

Depuran McNeil, Ger.; Aspen, S.Afr.
Senna (p.1769·2).
Constipation.

Depuratif des Alpes
Note. This name is used for preparations of different composition.
Tilman, Belg.
Iodine (p.2169·2); frangula (p.1732·2); liquorice (p.1740·3); senna (p.1769·2).
Constipation.

Sodia, Fr.
Frangula bark (p.1732·2).
Constipation.

Depuratif Parnel Poirier, Fr.
Lappa (p.2330·3); viola tricolor (p.2415·2); soapwort (p.2388·2); fumitory (p.2307·2).
Gastrointestinal disorders.

Depuratif Richelet Richelet, Fr.†.
Walnut leaves; cresson leaves; cochlearia armoracia root; cochlearia officinalis leaves; menyanthes leaves; cinnamon bark; bitter orange; gentian; tannic acid; magnesium chloride; magnesium bromide; nicotinamide (p.1922·1).
Tonic.

Depurativo Richelet Vitafarma, Spain.
Gentian (p.2310·3); potassium iodide (p.2169·2); salicylic acid (p.1612·2); tannic acid (p.2394·3); iodine (p.2169·2); cinnamon oil (p.2283·2); magnesium chloride (p.1679·1); magnesium bromide (p.1680·1); nicotinamide (p.1957·3).
Detoxification.

Depuratum Lehning, Fr.
Birch leaf (p.2266·3); rosemary leaf (p.2381·2); juniper (p.2328·2); rhapontic root (p.1768·3); fumitory (p.2307·2); thyme (p.2401·1); ononis (p.2357·1).
Gastrointestinal disorders.

Depurol Royal, Chile.
Venlafaxine hydrochloride (p.427·3).
Depression.

Depygon Sripasit, Thai.†.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Depyrel Abic, Israel†.
Trazodone hydrochloride (p.424·3).
Depression.

Depyret TO-Chemicals, Thai.
Paracetamol (p.108·1).
Fever; pain.

Depzac Cipla, India.
Fluoxetine hydrochloride (p.391·2).
Depression.

Deq Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.
Dequalinium chloride (p.1641·3); tyrothricin (p.358·2).
Mouth and throat disorders.

Dequacaine Boots Healthcare, Irl.; Crookes Healthcare, UK.
Benzocaine (p.1854·1); dequalinium chloride (p.1641·3).
Sore throat.

Dequa-Coff Aspen, S.Afr.
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Dequadin
Note. This name is used for preparations of different composition.
Farmoquimica, Braz.
Dequalinium chloride (p.1641·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Wellspring, Canad.; GSK, Hong Kong; Boots Healthcare, Irl.; Eurospital, Ital.; GSK, Philipp.; Aspen, S.Afr.†; GSK, Singapore; Inibsa, Spain†; GSK, Thai.; GSK, Turk.; Crookes Healthcare, UK; GSK Consumer, Venez.
Dequalinium chloride (p.1641·3).
Mouth and throat infections; sore throat.

Dequadin Mouth Paint Aspen Consumer, S.Afr.
Dequalinium chloride (p.1641·3); lidocaine (p.1862·3).
Mouth and throat disorders.

Dequa-Flu Aspen, S.Afr.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); phenyltoloxamine citrate (p.588·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Dequafungan Provita, Austria.
Dequalinium chloride (p.1641·3); undecenoic acid (p.549·2).
Skin infections.

Dequalid Wolfs, Belg.
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Dequalinetten Provita, Austria.
Dequalinium chloride (p.1641·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Dequa-loz Beacons, Singapore.
Dequalinium chloride (p.1641·3).
Sore throat.

Dequasine Miller, USA.
Vitamin C with minerals and amino-acids (p.1922·1).

Dequaspray Crookes Healthcare, UK.
Lidocaine hydrochloride (p.1862·3).
Formerly known as Strepsils Pain Relief Spray.
Sore throat.

Dequavagyn Provita, Austria.
Dequalinium chloride (p.1641·3).

Dequin Degorts, Mex.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract congestion.

Dequonal Nycomed, Austria; Kreussler, Ger.; Kreussler, Switz.
Dequalinium chloride (p.1641·3); benzalkonium chloride (p.1629·1).
Mouth and throat infections.

Dequosangola Eurospital, Ital.
Dequalinium chloride (p.1641·3).
Mouth disinfection.

Derain Leti, Venez.
Triticum aestivum (p.2415·1).
Wounds.

Deralbine Andromaco, Arg.
Miconazole nitrate (p.541·3).
Fungal infections.

Deralin Alphapharm, Austral.; Abic, Israel.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; hypertrophic subaortic stenosis; migraine; myocardial infarction; phaeochromocytoma; tremor.

Deratil Medicus, Gr.
Itraconazole (p.536·3).
Fungal infections.

Deratin Norman, Spain.
Chlorhexidine gluconate (p.1635·3).
Mouth and throat infections; skin and wound disinfection.

Derbac-M SSL, Irl.; SSL, NZ; SSL, UK.
Malathion (p.2046·1).
Pediculosis; scabies.

Dercason GMP, Indon.
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Dercolina Casasco, Arg.
Choline salicylate (p.36·3).
Mouth disorders.

Dercome Wolff, Ger.
Benzoyl peroxide (p.1590·2).
Acne.

Dercotex Sertex, Arg.
⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Dercut Pekana, Ger.†.
Homoeopathic preparation.

Dercutane Cantabria, Spain.
Isotretinoin (p.1599·2).
Acne.

Dereme Menarini, Spain.
⊗ Beclometasone salicylate (p.1517·2).
Skin disorders.

Dergentil Vivax, Venez.
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Dergesol Copernico, Ital.
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Derhotill Gemi, Pol.
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); turpentine oil (p.2406·3).
Cold and influenza symptoms; musculoskeletal pain.

Dericip Cipla, India.
Theophylline (p.1140·1); etofylline (p.1121·1).
Obstructive airways disease.

Dericip Plus Cipla, India.
⊗ Theophylline (p.1140·1); ephedrine (p.1558·1); diazepam (p.986·3).

Derifil Rystan, USA.
Chlorophyllin copper complex (p.1471·1).
Ostomy deodorant; reduction of faecal or urinary odour in incontinence.

Derihaler German Remedies, India.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Deril Ibirn, Ital.
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Derinat Technomedservis, Rus.
Sodium deoxyribonucleate (p.2292·3).
Burns; gastritis; haemorrhoids; infections; ischaemic heart disease; mucous membrane inflammation; obstructive airways disease; peptic ulcer; radiation trauma; reduction of cancer chemotherapy associated toxicity; rheumatoid arthritis; stimulating haemopoiesis; ulcers; urogenital disorders; venous insufficiency; wounds.

Derinox Therabel, Fr.
⊗ Prednisolone (p.1540·3); naphazoline nitrate (p.1565·2).
Rhinitis.

Deriphyllin German Remedies, India.
Etofylline (p.1121·1); theophylline (p.1140·1).
Cardiac disorders; oedema; respiratory disorders.

Deripil Galderma, Spain.
Erythromycin (p.269·2).
Acne.

Deriva Glenmark, India.
Adapalene (p.1587·1).
Acne.

Deriva-C Glenmark, India.
Adapalene (p.1587·1); clindamycin (p.251·1).
Acne.

Derivatio H Pfluger, Ger.
Homoeopathic preparation.

Derivoco Defuen, Arg.†.
⊗ Hydrocortisone acetate (p.1535·2); vitamin A (p.1971·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Derivon
Note. This name is used for preparations of different composition.
Rosch & Handel, Austria.
Cream: Benzyl nicotinate (p.28·1); diethylamine salicylate (p.47·2); heparin (p.1301·2).
Musculoskeletal and joint disorders; neuralgia; soft-tissue disorders.

Gerot, Austria.
Liniment: Benzyl nicotinate (p.28·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Soft-tissue, peri-articular, musculoskeletal, and joint disorders.

Derizic Bevo, Gr.
Clarithromycin (p.248·2).
Bacterial infections.

Derm A Dermpharma, Philipp.
Tretinoin (p.1618·1).
Skin disorders; sun-induced skin damage.

Derm Hydralin Bayer, Fr.
Glycine (p.1947·3).
Pruritus.

Derma Care
Note. A similar name is used for preparations of different composition (see Dermacare, below).
Fischer, Israel.
Salicylic acid (p.1612·2); hamamelis (p.2318·2); chamomile (p.2279·3); provitamin B .
Seborrhoea; skin cleansing.

Derma Viva Rugby, USA†.
Emollient and moisturiser.

Dermabase Paddock, USA.
Vehicle for topical preparations.

Dermabaz Sanofi Synthelabo, Hong Kong†.
Tretinoin (p.1618·1); erythromycin (p.269·2).
Acne.

Dermabel Royal, Chile.
Clindamycin phosphate (p.251·2).
Acne.

Dermabiolene Farmacologico Milanese, Ital.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Dermabion KRKA, Cz.†.
Dried yeast; vitamin B substances; vitamin A; zinc sulfate (p.1922·1).
Skin disorders.

Dermabiotic Elmor, Venez.
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Dermabiotico Saval, Chile.
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Burns; infected skin disorders; wounds.

Dermabiotik Medikon, Indon.
Gentamicin sulfate (p.282·1).
Skin infections.

Dermablend Cosmetique Active, UK.
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Dermablend Clarifying Stalder, Philipp.
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Skin cleanser.

Dermablend Cleansing Stalder, Philipp.
Skin cleanser.

Dermablend Skin Moisturizer Stalder, Philipp.
Emollient.

Dermabond Johnson & Johnson Medical, Arg.; Ethicon, Fr.; Ethicon, UK.
Ocrilate (p.2290·2).
Tissue adhesive for wound closure.

Dermabut Grunenthal, Port.
Colecalciferol (p.1986·2); vitamin A palmitate (p.1973·1); zinc oxide (p.1621·2).
Burns; skin disorders; varicose veins; wounds.

Dermac
Note. This name is used for preparations of different composition.
Stiefel, Mex.
Cream: Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Stiefel, Mex.
Soap: Sulfated castor oil (p.2139·3).
Acne; seborrhoea.

Dermac Crema Stiefel, Chile.
Sulfur (p.1614·1); resorcinol (p.1612·1); chloroxylenol (p.1640·2).
Acne.

Dermac Jabon Stiefel, Chile.
Soap substitute.
Acne.

Dermacalm-d Bayer, Switz.
⊗ Hydrocortisone acetate (p.1535·2); dexpanthenol (p.2362·1).
Skin disorders.

Dermacare
Note. A similar name is used for preparations of different composition (see Derma Care, above).
Darrow, Braz.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Derma-Care
Note. A similar name is used for preparations of different composition (see above).
Hermal, Israel.
⊗ Lauromacrogol 400 (p.1916·1); urea (p.1620·2).
Skin disorders.

Dermacerium Silvestre, Braz.
Sulfadiazine silver (p.337·2); cerous nitrate (p.1593·1).
Bacterial skin infections.

Dermacetin-Ped Stiefel, Braz.†.
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Dermachrome Sanofi-Aventis OTC, Fr.
Chlorhexidine gluconate (p.1635·3).
Formerly contained thiomersal and lidocaine hydrochloride.
Wounds.

Dermacid Darier, Mex.
Thymol (p.1664·3); benzalkonium chloride (p.1629·1).
Acne; seborrhoea.

Dermacide
Note. This name is used for preparations of different composition.
CS, Fr.
Soap: Tartaric acid (p.2395·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Cleansing of skin.

CS, Fr.
Topical solution: Hydroxyquinoline sulfate (p.2323·1); sodium propionate (p.545·3); salicylic acid (p.1612·2); tartaric acid (p.2395·2).
Bacterial skin infections; cleansing of skin.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dermaclean
Note. This name is used for preparations of different composition.
Lafedar, Arg.
Benzoyl peroxide (p.1590·2); clindamycin phosphate (p.251·2).
Acne.

STOM, Ital.
Soap substitute.

Dermaclob *Cinetic, Arg.*
⊗ Clobetasol (p.1522·2).
Skin disorders.

Dermaco *Mediherb, Austral.*
Sarsaparilla (p.2383·3); clivers (p.2284·3); berberis aquifolium; burdock (p.2330·3); yellow dock (p.2416·3).
Eczema; psoriasis.

Dermacoat *Century, USA.*
Benzocaine (p.1854·1); chloroxylenol (p.1640·2); menthol (p.2340·1).
Skin disorders.

Dermacol *Vitamed, Israel.*
Emollient.
Dry skin.

Dermacolor *Fox, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Dermacom *Tecnofarma, Chile.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Dermacombin
Taro, Israel.
⊗ Nystatin (p.543·2); neomycin sulfate (p.305·1); gramicidin (p.286·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Taro, Thai.
⊗ Nystatin (p.543·2); neomycin (p.305·1); gramicidin (p.286·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Dermacool *Pern, UK.*
Menthol (p.2340·1).
Pruritus; skin irritation.

Dermacort
Note. This name is used for preparations of different composition.
DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tanabe, Indon.
⊗ Hydrocortisone (p.1535·2); camphor (p.2273·2).
Skin disorders.

Genus, UK.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermacreme *Potter's, UK.*
Menthol (p.2340·1); methyl salicylate (p.85·3); liquefied phenol (p.1656·1).
Antiseptic for minor skin injuries.

Dermacrom *Galderma, Mex.*
Dihydroxyacetone (p.1594·1).
Tanning agent.

Dermacure *McNeil, Neth.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Dermacyd *Sanofi Synthelabo, Braz.*
Lactoserum; lactic acid (p.2329·3).
Skin disorders.

Dermades *Pharmacore, Indon.*
⊗ Desonide (p.1525·1).
Skin disorders.

Dermadex
Note. This name is used for preparations of different composition.
GSK, Arg.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Teofarma, Ital.
⊗ Dexamethasone valerate (p.1526·3).
Skin disorders.

Dermadex NN *GSK, Arg.*
⊗ Clobetasol propionate (p.1522·2); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Dermadine *Medpro, S.Afr.*
Povidone-iodine (p.1659·2).
Burns; mouth and throat disorders; skin disinfection; wounds.

Dermadrate *Dermatech, Austral.; Dermatech, Hong Kong; Balmar, NZ; Dermatech, Singapore.*
⊗ Lactic acid (p.2329·3); urea (p.1620·2); sodium pidolate (p.1614·1).
Dry skin.

Dermadrox
Note. This name is used for preparations of different composition.
Geritrex, USA.
Zinc acetate (p.1999·1).
Wounds.

Geritrex, USA.
Ointment: Aluminium hydroxide (p.1706·2); zinc chloride (p.1999·1); wool fat (p.2033·2); calcium carbonate; vitamin A.
Skin irritation.

Dermafacte *Marching, Hong Kong.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Dermafin *YSP, Malaysia.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Dermafleur *Bloem Beheer, Neth.*
Homoeopathic preparation.

Dermaflex *Neolab, Canad.*
⊗ Urea (p.1620·2).
Emollient; moisturiser.

Dermaflex HC *Neolab, Canad.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dermaflogil *NCSN, Ital.*
⊗ Diflucortolone valerate (p.1529·2); kanamycin sulfate (p.291·2).
Skin disorders.

Dermaflor
Note. This name is used for preparations of different composition.
ICN, Arg.†.
Ciclopirox olamine (p.529·2).
Fungal skin and nail infections.

NCSN, Ital.†.
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Dermaforine *PannonPharma, Hung.†.*
Methylrosanilinium chloride (p.1653·1); ammoniated mercury (p.1604·3); mercurous chloride (p.2341·2); yellow mercuric oxide (p.2341·2); bismuth subnitrate (p.1711·2); zinc oxide (p.1621·2).
Skin infections; ulcers.

Dermafree *Delta, Braz.*
Aspirin (p.20·3); lactic acid (p.2329·3).

Dermagen *Corsa, Indon.*
Gentamicin sulfate (p.282·1).
Skin infections.

Dermaglos
Note. This name is used for preparations of different composition.
Andromaco, Arg.
A range of moisturisers with or without sunscreens.
Dry skin.

Andromaco, Chile.
Vitamin A palmitate (p.1973·1); allantoin (p.1588·1); tocoferil acetate (p.1992·3).
Formerly contained vitamin A palmitate, ergocalciferol, benzethonium chloride, and allantoin.
Burns; skin disorders; wounds.

Dermaglos Plus *Andromaco, Chile†.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1); benzethonium chloride (p.1630·1); allantoin (p.1588·1); vitamin E acetate (p.1992·3); centella (p.1592·3).
Burns; skin disorders; wounds.

Dermagor *Dermoteca, Port.*
Emollient.

Dermagor Ecran Solar *Dermoteca, Port.*
Titanium dioxide (p.1617·3).
Sunscreen.

Dermagor-Antitranspirante *Dermoteca, Port.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Dermagraft *Smith & Nephew, S.Afr.; Smith & Nephew, UK; Smith & Nephew, USA.*
Human dermal tissue (p.1613·3).
Diabetic foot ulcers.

Dermagran
Note. This name is used for preparations of different composition.
Victus, Venez.
Ointment: Zinc (p.1999·1); vitamins and minerals.
Barrier preparation; burns; ulcers; wounds.

Victus, Venez.
Topical spray: Zinc (p.1999·1); vitamin B (p.1979·1).
Burns; ulcers; wounds.

Dermagran-B *Victus, Venez.*
Hydrophilic wound dressing.

Derm-Aid *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
⊗ Hydrocortisone (p.1535·2).
Anogenital pruritus; skin disorders.

Derma-Keri *Darier, Mex.*
⊗ Urea (p.1620·2).
Hyperkeratotic skin disorders.

Dermaknel *GSK, Pol.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Skin disorders.

Dermal Care *Bayer Diagnostici, Ital.*
⊗ Urea (p.1620·2).
Dry skin and nail disorders.

Dermalac *Taro, Canad.*
Lactic acid (p.2329·3).

Dermalact *Albephar, Venez.*
Lactic acid (p.2329·3).

Dermalar *Teva, Israel.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Dermalibour *Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.*
Avena (p.2262·1); zinc oxide (p.1621·2); zinc sulfate (p.1999·2); copper sulfate (p.1935·3).
Skin disorders.

Dermalife *Orion, NZ.*
Vitamin A (p.1971·2).
Skin disorders.

Dermalife Plus *Orion, Austral.*
Calamine (p.1591·2); vitamin A palmitate (p.1973·1); dimeticone (p.2032·1).
Burns; cradle cap; minor skin lesions; nappy rash; skin disorders.

Dermalin *United Laboratories, Philipp.*
Benzoic acid (p.1630·2); clioquinol (p.254·1); menthol (p.2340·1); salicylic acid (p.1612·2); sulfur (p.1614·1); cetyl alcohol (p.2028·3).
Skin infections.

Dermalisan *Prodotti, Braz.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); zinc oxide (p.1621·2).
Skin disorders.

Dermalite *Eulite, Neth.*
Homoeopathic preparation.

Dermallerg *Ratiopharm, Ger.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermalo
Note. A similar name is used for preparations of different composition (see below).
Dermal Laboratories, UK.
Liquid paraffin (p.2030·3); acetylated wool alcohols (p.2033·2).
Formerly known as Emmolate.
Dry skin.

Dermaloe
Note. A similar name is used for preparations of different composition (see above).
Forder, Arg.†.
Aloe vera (p.1588·2); allantoin (p.1588·1).
Barrier preparation.

Dermalog *BMS, Mex.*
⊗ Halcinonide (p.1535·1).
Skin disorders.

Dermalog-C *BMS, Mex.*
⊗ Halcinonide (p.1535·1); nystatin (p.543·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Dermamina *EMS, Braz.*
Calamine (p.1591·2); zinc oxide (p.1621·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); glycerol (p.2314·2).
Skin disorders.

Dermamist
Note. This name is used for preparations of different composition.
Caraderm, Irl.
White soft paraffin (p.2031·2).
Dry skin disorders.

Astellas, Ital.
Emollient.
Dry skin disorders.

Alliance, UK.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry skin disorders.

Dermamycin *Pfeiffer, USA.*
Diphenhydramine hydrochloride (p.577·2).

Derma-Mykotral *Rosen, Ger.*
Miconazole nitrate (p.541·3).
Fungal infections of the skin and mucous membranes.

Derman *CICSA, Mex.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Derman Plus *Amuchina, Ital.*
Triclosan (p.1665·2).
Hand disinfection.

Derman Talco *CICSA, Mex.*
Benzalkonium chloride (p.1629·1).

Dermana Crema *Humana, Ital.*
Gamolenic acid (p.2308·2); omega-3 triglyceride (p.1362·1); vitamin E (p.1992·2); vitamin A (p.1971·2).
Emollient.

Dermana Pasta *Humana, Ital.*
Gamolenic acid (p.2308·2); omega-3 triglyceride (p.1362·1); vitamin E (p.1992·2); vitamin A (p.1971·2); zinc oxide (p.1621·2).
Dry skin disorders; skin irritation.

DermaNail *Summers, USA.*
Alpha acetoxy acid.
Nail disorders.

Dermance
Note. This name is used for preparations of different composition.
Bio-Sante, Canad.†.
Liquid soap; soap: Triclosan (p.1665·2).
Acne.

Bio-Sante, Canad.†.
Lotion: Benzoyl peroxide (p.1590·2).
Acne.

Dermanide *Interbat, Indon.*
⊗ Desonide (p.1525·1).
Skin disorders.

Dermanios Scrub *Anios, Fr.*
Soap substitute.

Derman-Oil *Humana, Ital.*
Gamolenic acid (p.2308·2); omega-3 triglycerides (p.1362·1); vitamins A (p.1971·2); vitamin E (p.1992·2).
Bath additive.

Dermanol *Quimica y Farmacia, Mex.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium subacetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

Dermanol-C *ICM, Singapore.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Dermanova *Wierhom, Arg.*
Vitamin A (p.1971·2); rosa mosqueta; alpha tocopherol (p.1992·2).

Dermanox *Centrapharm, Belg.*
Enoxolone (p.50·1).
Burns; skin disorders; wounds.

Derman-Shampoo AF *Humana, Ital.†.*
Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2); climbazole (p.529·3).
Dandruff.

Dermaoral *Arrow, Denm.†.*
Isotretinoin (p.1599·2).
Acne.

Derma-Pax *Recsei, USA.*
Mepyramine maleate (p.585·2); chlorphenamine (p.572·2).
Pruritus.

Dermapharm Basis *Dermapharm, Ger.*
Emollient.
Skin disorders.

Dermapro *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermaral *Corsa, Indon.*
Ketoconazole (p.539·1).
Fungal skin infections.

Dermarell *Sanorell, Ger.*
Homoeopathic preparation.

Dermaren *Areu, Spain.*
⊗ Dichlorisone acetate (p.1529·1).
Skin disorders.

Dermarest
Note. This name is used for preparations of different composition.
Del, Canad.
Salicylic acid (p.1612·2).
Dandruff; psoriasis; seborrhoeic dermatitis.

Del, USA.
Diphenhydramine hydrochloride (p.577·2); resorcinol (p.1612·1).
Pruritus.

Dermarest Dri-Cort *Del, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dermarest Dricort Anti-Itch *Del, Canad.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermarest Plus *Del, Canad.; Del, USA.*
Diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Pruritus.

Derma-Rx Lightener *Derma-Rx, Hong Kong.*
Hydroquinone (p.1598·2).
Hyperpigmentation.

Dermase *Sanval, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Skin infections.

Dermaseb *Cassara, Arg.*
Sulfacetamide sodium (p.335·3).
Acne.

Dermasept Antifungal *Pharmakon, USA.*
Tannic acid (p.2394·3); zinc chloride (p.1999·1); benzocaine (p.1854·1); methylbenzethonium chloride (p.1653·1); tolnaftate (p.548·3); undecenoic acid (p.549·2).
Fungal skin infections.

Dermasil *Silom, Thai.†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Derma-Smoothe/FS *Hill, Canad.; Hill, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Dermasol *Olan-Kemed, Thai.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Dermasole *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Dermasole DP *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Dermasolon *Ikapharmindo, Indon.*
⊗ Fluocinolone (p.1531·3) or fluocinolone acetonide (p.1531·3).
Skin disorders.

Dermasone
Note. This name is used for preparations of different composition.
Technilab, Canad.†; Technilab, Hong Kong†.
⊗ Clobetasol propionate (p.1522·2).
Skin and scalp disorders.

ICM, Singapore.
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Dermaspraid Antiseptique *Bayer, Fr.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); benzyl alcohol (p.1631·3).
Formerly known as Dermaspray.
Wound disinfection.

Dermaspraid Demangeaison *Bayer, Fr.*
⊗ Hydrocortisone acetate (p.1535·2).
Nettle and insect stings; sunburn.

Dermaspray *Bayer, Austria; Roche, Belg.†.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); benzyl alcohol (p.1631·3).
Wound and burn disinfection; wound disinfection.

Dermasten *Offenbach, Mex.*
Clotrimazole (p.530·1).
Fungal skin infections.

Dermastir Solari *Alta Care, Ital.*
Octyl palmitate; octinoxate (p.1608·2); bustus chinensis; titanium dioxide (p.1617·3); avobenzone (p.1589·3); bisoctrizole (p.1591·2); ethylhexyl methoxycinnamate decyl glucoside.
Sunscreen.

Dermatar *IDI, Ital.*
⊗ Betamethasone valero-acetate (p.1519·1); salicylic acid (p.1612·2); ichthammol (p.1599·1).
Skin disorders.

Dermatech Liquid *Dermatech, Austral.*
⊗ Alcohol (p.1625·2); propylene glycol (p.2374·1).
Vehicle for topical drugs.

Dermatech Wart Treatment *Dermatech, Austral.; Dermatech, Hong Kong; Dermatech, Singapore.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Dermaten *Pharmasant, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Dermatin *Pfleger, Ger.*
Terbinafine hydrochloride (p.546·3).
Fungal nail and skin infections.

Dermatitis Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Dermatix *Valeant, Austral.; ICN, Fr.; Valeant, Ger.; Valeant, Irl.; ICN, Malaysia; Valeant, Philipp.; Valeant, Singapore; ICN, UK.*
Silicone gel (p.2032·1).
Hypertrophic and keloid scars.

Dermatix Catrix *ICN, Canad.†.*
Collagen (p.2286·1).
Burns; ulcers; wounds.

Dermatix Fitocream *Valeant, Canad.*
Wheat germ (p.2415·1).
Burns; wounds.

Dermatix Si *Valeant, Canad.*
Silicone liquid gel (p.2032·1).
Scars.

Dermatodoron
Note. This name is used for preparations of different composition.
Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.
Dulcamara (p.2298·1); lysimachia nummularia.
Eczema; psoriasis.

Weleda, UK.
Homoeopathic preparation.

Dermatol *Chinosolfabrik, Ger.†; Aroma, Turk.; Merkez, Turk.*
Bismuth subgallate (p.1711·1).
Burns; excoriations; skin disorders.

Dermatolona *Armstrong, Mex.*
Sodium acexamate (p.2245·2); cetrimonium bromide (p.1635·1).
Minor burns and wounds; skin irritation.

Dermatop *Sanofi-Aventis, Braz.; Dermik, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Ger.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Aventis, Thai.; Aventis, Turk.; Dermik, USA.*
⊗ Prednicarbate (p.1540·2).
Burns; skin disorders.

Dermatovate *GSK, Mex.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermatrans
Note. This name is used for preparations of different composition.
Rottapharm, Chile.
Estradiol (p.2097·2).
Menopausal disorders.

Bayer, Ital.; Rotta, Port.; Recordati, Spain.
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Derm'attive 10 *Sidone, Braz.†.*
Theophylline glycolate; centella (p.1592·3); guarana (p.2416·1).

Derm'attive Solaire *Sidone, Braz.†.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); ginkgo biloba (p.2311·1); aloe vera (p.1588·2).

Dermaval *FIRMA, Ital.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

DermaVeen
Note. This name is used for preparations of different composition.
Dermatech, Hong Kong.
A range of preparations containing colloidal oatmeal (p.2262·1) with or without sodium pidolate (p.1614·1).
Dry skin; skin irritation.

Dermatech, NZ.
Colloidal oatmeal (p.2262·1).
Dry skin; pruritus; soap-free cleanser.

DermaVeen Acne *Dermatech, Singapore†.*
Colloidal oatmeal (p.2262·1); salicylic acid (p.1612·2).
Soap-free cleanser.

DermaVeen Bath *Dermatech, Austral.; Dermatech, Singapore.*
Colloidal oatmeal (p.2262·1).
Bath additive; dry skin; pruritus; skin irritation.

DermaVeen Dry Skin *Dermatech, Austral.; Dermatech, Singapore.*
Colloidal oatmeal (p.2262·1).
Dry skin; pruritus; skin irritation; soap-free cleanser.

DermaVeen Moisturising
Note. This name is used for preparations of different composition.
Dermatech, Austral.
Colloidal oatmeal (p.2262·1); sodium pidolate (p.1614·1); white soft paraffin (p.2031·2).
Dry skin; pruritus.

Dermatech, Singapore.
Colloidal oatmeal (p.2262·1).
Dry skin; skin irritation.

DermaVeen Oatmeal Shampoo *Dermatech, Singapore.*
Colloidal oatmeal (p.2262·1).
Scalp disorders.

DermaVeen Shower & Bath *Dermatech, Austral.; Dermatech, Singapore.*
Colloidal oatmeal (p.2262·1); sodium pidolate (p.1614·1); liquid paraffin (p.2030·3).
Bath additive; dry skin; pruritus; soap-free skin cleanser.

DermaVeen Soap Free *Dermatech, Singapore.*
Colloidal oatmeal (p.2262·1).
Soap-free skin cleanser.

Dermavite *Stiefel, Braz.*
Vitamin and mineral preparation (p.1922·1).

DermaVite *Stiefel, USA.*
Multivitamin and mineral preparation (p.1922·1).

Dermax
Note. This name is used for preparations of different composition.
Galderma, Braz.
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne.

Fischer, Israel.
Triclosan (p.1665·2).
Acne; eczema; heat rash; impetigo; nappy rash.

Reddy, S.Afr.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Dermax Therapeutic Shampoo *Dermal Laboratories, UK.*
Benzalkonium chloride (p.1629·1).
Dandruff; seborrhoea.

Dermazellon *Kohler, Ger.†.*
Silver salt of 2-aminoethyl dihydrogen phosphate.
Burns; skin infections; wounds.

Dermazil *Pentafarma, Port.*
Azelaic acid (p.1589·3).

Dermazin *Pharmascience, Canad.†; Lek, Cz.; Lek, Hong Kong; Lek, Hung.; Lek, Pol.; Lek, Rus.; Lek, Thai.*
Sulfadiazine silver (p.337·2).
Bacterial skin infections; burns; ulcers; wounds.

Dermazinc *Sivaderm, Arg.*
Pyrithione zinc (p.1611·2).
Pityriasis.

Dermazine *Silvestre, Braz.*
Sulfadiazine silver (p.337·2).
Bacterial skin infections; infected burns; skin ulceration.

Dermazol *Sanval, Braz.; Bailleul, Fr.; Pharma 2000, Ital.†.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Dermazole
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, Hong Kong†; Ego, NZ†; Ego, Singapore†.
Econazole nitrate (p.531·1).
Fungal skin infections.

Hexal, S.Afr.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Dermazulen *Zentiva, Cz.*
Guaiazulene (p.2317·3); chamomile oil (p.2279·3).
Burns; skin ulcers; wounds.

Dermdryl *Teuto, Braz.†.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2).
Skin disorders.

Der-med *Permamed, Switz.*
Soap substitute.
Skin disorders.

Dermedal *Farmec, Ital.*
Tosylchloramide sodium (p.1665·1).
Disinfection of burns, wounds, and surfaces; genital hygiene.

Dermenet *Essex, Chile†.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Dermestril *Mayne, Austral.†; CSC, Austria; Besins, Belg.; Rottapharm, Cz.; Rottapharm, Fin.; Rottapharm, Fr.; Opfermann, Ger.; Faran, Gr.; Rotta, Hong Kong; Rottapharm, Hung.; Rottapharm, Irl.†; LTS, Israel; Rotta, Israel; Rottapharm, Ital.; Rottapharm, Neth.; Delta, Port.; Rottapharm, Spain; Sigma-Tau, Switz.†.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Dermex *Hamilton, Austral.*
Range of barrier creams.

Dermexane *Cassara, Arg.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermeze *Aspen, Austral.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Dry skin.

Derm-Freeze *Eagle, Austral.*
Trichlorofluoromethane (p.1689·1); dichlorodifluoromethane (p.1689·1).
Local anaesthesia; pain.

Dermic
Note. This name is used for preparations of different composition.
Valeant, Arg.
Zinc oxide (p.1621·2).
Skin disorders.

Kinder, Braz.
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne.

Dermichthol *Ichthyol, Ger.†.*
Ictasol (p.1599·1).
Skin disorders.

Dermicil *Cipla, India†.*
Chlorphenesin (p.529·2).
Prickly heat.

Dermicon *Bunker, Braz.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2); iodine (p.2169·2).
Fungal skin infections.

Dermi-cyl *Liebermann, Ger.*
Calcium hydroxide solution (p.2272·2).
Burns; skin disorders.

Dermi-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Dermidex *Thornton & Ross, UK.*
Lidocaine (p.1862·3); alcloxa (p.1587·2); chlorobutanol (p.1639·2); cetrimide (p.1634·1).
Skin irritation.

Dermifun *Ivax, Mex.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Dermikolin
Note. This name is used for preparations of different composition.
Radyum, Turk.
Ointment: Nitrofurazone (p.309·1).
Skin infections.

Radyum, Turk.
Topical powder: Bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); boric acid (p.2268·1); aluminium hydroxide (p.1706·2).
Skin disorders.

Dermilia Flebozin *Depofarma, Ital.*
Zinc oxide (p.1621·2); myrtillus (p.2349·3); echinacea (p.2298·1); hamamelis (p.2318·2); melilot (p.2339·2); centella (p.1592·3).
Tired legs.

Dermilon *Caesaro, Austria; Cesra, Ger.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Skin disorders.

Dermimade Bacitracina *Esfar, Port.†.*
Bacitracin (p.210·3); neomycin (p.305·1).
Skin infections.

Dermimade Cloranfenicol *Esfar, Port.*
Chloramphenicol (p.239·3).
Skin infections.

Dermimade Hidrocortisona *Esfar, Port.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Derminiol *Marvecs, Ital.; DHU, Spain.*
Hamamelis (p.2318·2).
Inflammation of skin and mucous membranes; skin irritation; superficial skin lesions and burns.

Derminoin *Med-One, Gr.†.*
Isotretinoin (p.1599·2).
Acne.

Derm'Intim *Ducray, Fr.*
Avena (p.2262·1); glycine (p.1947·3); glycerol (p.2314·2).
Personal hygiene.

Dermirit *Morgan, Ital.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dermisan *Armoxindo, Indon.*
Hexachlorophene (p.1646·1).
Skin disinfection.

Dermisdin *Isdin, Spain†.*
Fenticlor (p.531·3); miconazole nitrate (p.541·3); salicylic acid (p.1612·2).
Acne; scalp disorders; seborrhoea.

Dermisol *Albephar, Venez.*
⊗ Urea (p.1620·2).

Dermisone Epitelizante *Novartis Consumer, Spain.*
Amino acids (p.1922·1); chloramphenicol (p.239·3); vitamin A palmitate; vitamin F.
Wound healing.

Dermisone Tri Antibiotic *Novartis Consumer, Spain.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Skin infections.

Dermithan *Medical, Arg.*
Calamine (p.1591·2); diphenhydramine (p.577·1); camphorated phenol (p.1656·1); salol (p.122·1).
Pruritus; skin irritation.

Dermithan Incoloro *Medical, Arg.*
Diphenhydramine (p.577·1); zinc oxide (p.1621·2).
Pruritus; skin irritation.

Dermitina *Donini, Ital.*
Hamamelis (p.2318·2); sodium glutamate; fatty acids (p.1922·1).
Soap substitute.

Dermizan *Bunker, Braz.*
Azelaic acid (p.1589·3).
Acne.

Dermizin *Gerolymatos, Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Dermizol *Roux-Ocefa, Arg.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Dermizol G *Roux-Ocefa, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Dermizol Trio *Roux-Ocefa, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole (p.541·2).
Infected skin disorders.

Dermklobal *Technilab, Pol.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermo *APT, Hong Kong.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermo 6 *Pharmadeveloppement, Fr.*
Pyridoxine hydrochloride (p.1978·2).
Seborrhoea.

Dermo Bell *Remexa, Mex.*
Arachis oil (p.2259·1).
Skin disorders.

Dermo Halibut *Novartis Consumer, Spain.*
Dimeticone (p.2032·1); benzalkonium chloride (p.1629·1); vitamin A (p.1971·2); zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Dermo Hubber *Teofarma, Spain.*
⊗ Bacitracin zinc (p.210·3); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Dermo Posterisan *Kade, Ger.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermo Vagisil Crema *Combe, Arg.*
Benzocaine (p.1854·1); resorcinol (p.1612·1).

Dermo WAS *Wolff, Austria.*
Lecithin (p.2332·2).
Skin disorders.

Dermoangiopan *Abiogen, Ital.†.*
Troxerutin (p.2305·1); sulodexide (p.1406·3).
Soft-tissue disorders; vascular disorders.

Dermobacter *Innotech, Fr.; Innotech, Hong Kong.*
Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Skin and mucous membrane disinfection.

Dermobarrina
Note. This name is used for preparations of different composition.
Reccius, Chile.
Cream: Resorcinol (p.1612·1).

Reccius, Chile.
Lotion: Benzalkonium chloride (p.1629·1); menthol (p.2340·1).

Dermobase *Key, Arg.†.*
Emollient.
Skin disorders.

Dermobel *Sedabel, Braz.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin (p.305·1).
Infected skin disorders.

Dermobene *Legrand, Braz.*
Clotrimazole (p.530·1).
Fungal skin infections.

Dermobet *Infabra, Braz.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Dermobeta
Note. This name is used for preparations of different composition.
Betapharm, Ger.†.
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Krugher, Ital.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Dermobion *Serral, Mex.†.*
Filiferine; papain (p.2362·3).
Burns; wounds.

Dermobiotico *Davi, Port.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Skin infections.

Dermobras *Remexa, Mex.*
Aluminium oxide (p.1585·3); triclosan (p.1665·2).
Skin cleansing.

Dermocal *Panalab, Arg.†.*
Calcipotriol (p.1591·3).
Psoriasis.

Dermocare *Darier, Mex.*
Resorcinol (p.1612·1); calamine (p.1591·2).
Acne; seborrhoea.

Dermocica *Phytomedica, Fr.*
Arnica (p.2260·2); melaleuca oil (p.2338·2); mimosa; vervain oil.
Burns; scars; wounds.

Dermocinetic *Geymonat, Ital.*
Levothyroxine sodium (p.2171·2); aescin (p.2248·2).
Cellulite; local build up of adipose tissue.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dermocitran *Imvi, Arg.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Dermocort *Unipharma, Gr.*
⊗ Fluticasone (p.1533·2).
Skin disorders.

Dermocortal *Chefaro, Ital.*
⊗ Hydrocortisone (p.1535·2).
Burns; eczema; erythema; insect stings; pruritus.

Dermocrem *Ache, Braz.*
Wheat germ (p.2415·1).
Wounds.

Dermocridin *Neo Dermos, Arg.*
Lactic acid (p.2329·3); menthol (p.2340·1); panthenol (p.2362·1); vegetable extracts.
Seborrhoeic dermatitis.

Dermocuivre *Chauvin, Fr.*
Copper sulfate (p.1935·3); zinc oxide (p.1621·2).
Skin disorders.

Dermodan *ITF, Chile.*
Tretinoin (p.1618·1).
Acne; light-induced skin damage.

Dermodan Plus *ITF, Chile.*
Erythromycin (p.269·2); tretinoin (p.1618·1).
Acne.

Dermoden *Cifarma, Braz.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Skin disorders.

Dermodex *BMS, Braz.*
Zinc oxide (p.1621·2); nystatin (p.543·2).
Infected skin disorders.

Dermodrin *Montavit, Austria.*
Diphenhydramine hydrochloride (p.577·2).
Skin disorders.

Dermofenac *Whitehall, Fr.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermofibrin C *Biochimico, Braz.†.*
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1); chloramphenicol (p.239·3).
Wounds.

Dermofix *Darya-Varia, Indon.; Ferrer, Indon.; Azevedos, Port.; Ferrer, Spain.*
Sertaconazole nitrate (p.546·1).
Fungal skin, scalp, and nail infections; vulvovaginal candidiasis.

Dermofug *Wolff, Cz.*
Dodecylbenzenesulfonic acid; ammonium laurilsulfate (p.2138·3).
Acne; fungal skin infections; seborrhoeic dermatitis.

Dermoil *Dermofarma, Ital.*
Emollient.
Bath additive; dry skin disorders.

Dermojela *Jean-Marie, Hong Kong.*
Choline salicylate (p.36·3); benzalkonium chloride (p.1629·1); menthol (p.2340·1).
Mouth disorders.

Dermojuventus *Juventus, Spain.*
Tretinoin (p.1618·1).
Acne; sunlight-induced skin damage.

Dermokin *Kinder, Braz.*
Zinc oxide (p.1621·2); nystatin (p.543·2).
Skin disorders.

Dermol
Note. This name is used for preparations of different composition.
Simoes, Braz.†.
Benzalkonium chloride (p.1629·1); salicylic acid (p.1612·2); camphor (p.2273·2); iodo iodetata (p.2169·2); siam benzoin (p.2386·2); arnica (p.2260·2).
Pruritic skin disorders.

Adelco, Gr.
⊗ Prednisolone (p.1540·3); neomycin (p.305·1).
Infected skin disorders.

Pacific, NZ.
⊗ Clobetasol propionate (p.1522·2).
Skin and scalp disorders.

Dermal Laboratories, UK.
Benzalkonium chloride (p.1629·1); chlorhexidine hydrochloride (p.1635·3); liquid paraffin (p.2030·3); isopropyl myristate (p.2029·3).
Dry and pruritic skin disorders.

Dermol HC *Dermol, USA.*
⊗ Hydrocortisone (p.1535·2).

Dermolantyl *Chrispa (Χρισπα), Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Dermolate *Schering-Plough, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Dermolin
Note. This name is used for preparations of different composition.
Lafare, Ital.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Roberts, USA.
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); mustard oil (p.2349·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Dermomax *Biosintetica, Braz.*
Lidocaine (p.1862·3).
Local anaesthesia.

Dermomicin *Biofarma, Braz.†.*
Neomycin sulfate (p.305·1).
Skin infections.

Dermomycin *Sigma-Tau, Ital.*
Sodium fusidate (p.279·3).
Bacterial skin infections.

Dermomycose Liquido *Reig Jofre, Spain.*
Boric acid (p.2268·1); phenol (p.1656·1); rosaniline; resorcinol (p.1612·1).
Fungal skin infections.

Dermomycose Talco *Reig Jofre, Spain.*
Neomycin undecenoate (p.305·2); menthol (p.2340·1).
Skin infections.

Dermon
Unison, Hong Kong.
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Unison, Thai.
Miconazole (p.541·2).
Fungal infections of skin, mucous membranes, and nails.

Dermonil *Vitapan, Braz.†.*
⊗ Betamethasone (p.1518·2).
Skin disorders.

Dermopan *Pierre Fabre Dermo-Cosmetique, Arg.; Medifarm A-Derm, Venez.*
Avena (p.2262·1).
Skin cleansing.

Dermopanten *Chema-Elektromet, Pol.*
Dexpanthenol (p.2362·1).
Skin and mucous membrane disorders; wounds.

Dermoper *Defuen, Arg.*
Permethrin (p.2048·2).
Scabies.

Dermoperative *Giscard, Arg.*
⊗ Hydrocortisone (p.1535·2); gentamicin (p.284·2).
Infected skin disorders.

Dermopero *Defuen, Arg.*
Ivermectin (p.145·2).

Dermophenazol *Polfa Warszawa, Pol.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Insect bites and stings.

Dermophil Indien
Note. This name is used for preparations of different composition.
Dermophil Indien, Fr.†; Melisana, Switz.
Peru balsam (p.2365·3); levomenol (p.2333·3); salol (p.122·1).
Emollient.

Dermophil Indien, Fr.†.
Lipstick: Enzacamene (p.1597·1); isopropyldibenzoylmethane (p.1599·2).
Sunscreen.

Dermophil Indien, Fr.†.
Lipstick SPF 7: Enzacamene (p.1597·1).
Sunscreen.

Dermophil Indien, Fr.†.
Maxi-stick: Enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Dermoplast
Note. This name is used for preparations of different composition.
Remexa, Mex.
⊗ Urea (p.1620·2).
Dry skin disorders.

Medtech, USA.
Benzocaine (p.1854·1).
Painful conditions of the skin and perineum.

Dermoplast Antibacterial *Medtech, USA.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1).
Local anaesthesia.

Dermoplex Antifungal *CCM, Malaysia.*
Tolnaftate (p.548·3).
Fungal skin infections.

Dermoplex Antiseptic *CCM, Malaysia.*
Cetrimide (p.1634·1).
Insect bites and stings; minor wounds and burns; nappy rash.

Dermoplex Calamine *CCM, Malaysia.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Insect bites; nappy rash; skin irritation.

Dermoprolyn *Infosint, Ital.†.*
Aescin (p.2248·2); hamamelis (p.2318·2); butcher's broom (p.2270·3); ivy (p.2328·1).
Skin disorders.

Dermopur *Prolab, Pol.*
Benzocaine (p.1854·1); zinc oxide (p.1621·2); menthol (p.2340·1).
Skin disorders.

Dermoquinol *East India Pharma, India.*
Clioquinol (p.254·1).
Fungal skin infections.

Dermorelle *IPRAD, Fr.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Dermo-Rest *Eczacibasi, Turk.*
Tioconazole (p.548·2).
Fungal skin and nail infections.

Dermosa Aureomicina *Teofarma, Spain.*
Chlortetracycline hydrochloride (p.243·1).
Skin infections.

Dermosa Hidrocortisona *Teofarma, Spain.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dermosalic *Bunker, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Dermosan *Lafedar, Arg.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); benzocaine (p.1854·1); zinc oxide (p.1621·2).
Skin disorders.

Dermosavit *Coel, Pol.*
Vitamin A (p.1971·2).
Skin disorders.

Dermoscalp *Remexa, Mex.*
Salicylic acid (p.1612·2); coal tar (p.1616·2); resorcinol (p.1612·1).
Dandruff.

Dermosed *Makros, Braz.†.*
Tyrothricin (p.358·2); salicylic acid (p.1612·2); boric acid (p.2268·1).
Skin infections.

Dermoseptic *Ferrer, Spain.*
Sertaconazole nitrate (p.546·1).
Fungal skin, scalp, and nail infections.

Dermoskin *Remexa, Mex.†.*
Almond oil (p.2252·2).
Moisturiser.

Dermoskin C *Remexa, Mex.†.*
Sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3).
UV-induced skin damage.

Dermosol *YSP, Malaysia; Yung Shin, Singapore.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermosolon
Note. This name is used for preparations of different composition.
Dermapharm, Ger.
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Gedeon Richter, Rus.
⊗ Clioquinol (p.254·1); prednisolone (p.1540·3).
Infected skin disorders.

Dermosona
Note. This name is used for preparations of different composition.
Fecofar, Arg.
⊗ Miconazole (p.541·2); betamethasone valerate (p.1519·1); gentamicin (p.284·2).
Infected skin disorders.

Saval, Chile.
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Dermo-Sulfuryl *Legras, Fr.*
Precipitated sulfur (p.1614·1); copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Acne.

Dermosupril *Roemmers Medihe, Venez.*
⊗ Desonide (p.1525·1).
Skin disorders.

Dermosupril C *Roemmers Medihe, Venez.*
⊗ Desonide (p.1525·1); clioquinol (p.254·1).
Infected skin disorders.

DermOtic *Hill, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Otitis externa.

Dermotin A *Remexa, Mex.*
Vitamin A palmitate (p.1973·1).
Skin disorders.

Dermotivin *Galderma, Braz.; Galderma, Venez.*
Soap substitute.
Seborrhoea.

Dermo-Trosyd *Pfizer, Turk.*
Tioconazole (p.548·2).
Fungal skin and nail infections.

Dermovagisil *Combe, Spain.*
Lidocaine (p.1862·3).
Vaginal disorders.

Dermoval
Note. This name is used for preparations of different composition.
Luper, Braz.†.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

GSK, Fr.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Tocogino, Mex.
⊗ Betamethasone (p.1518·2).
Skin disorders.

Dermovan *Healthpoint, USA.*
Vehicle for topical preparations.

Dermovat
Note. This name is used for preparations of different composition.
Pharlab, Braz.†.
⊗ Betamethasone (p.1518·2).
Skin disorders.

GSK, Denm.; GSK, Fin.; GSK, Norw.; GSK, Swed.
⊗ Clobetasol propionate (p.1522·2).
Eczema; psoriasis; skin and scalp disorders; skin disorders.

Dermovate *GSK, Austria; GSK, Belg.; Taro, Canad.; GSK, Chile; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; Sekpharma, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
⊗ Clobetasol propionate (p.1522·2).
Skin and scalp disorders.

Dermovate-NN *GSK, Philipp.; Glaxo Wellcome, Port.†; GSK, Switz.; Chemidex, UK.*
⊗ Clobetasol propionate (p.1522·2); neomycin sulfate (p.305·1); nystatin (p.543·2).
Skin disorders with bacterial or fungal infection.

Dermovel *Ferron, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Dermovit *White, Arg.†.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Dermovit A *Coel, Pol.*
Vitamin A (p.1971·2).
Burns; chilblains; wounds.

Dermovit E *Coel, Pol.*
Vitamin E (p.1992·2).
Varicose ulcer.

Dermovit F *Coel, Pol.*
Vitamin F (p.2308·2).
Skin disorders.

Dermovitamina *Pasquali, Ital.*
Cod-liver oil (p.1935·2).
Skin disorders.

Dermowas *Wolff, Ger.*
Dodecylbenzolsulfonic acid trolamine; ammonium laurilsulfate (p.2138·3).
Skin disorders.

Dermowund *Adler, Austria.*
Acriflavinium chloride (p.1625·1); diacetylaminoazotoluene (p.1641·3); cod-liver oil (p.1935·2); linseed oil (p.2334·1); sodium propionate (p.545·3); zinc oxide (p.1621·2).
Wounds.

Dermox *Remexa, Mex.*
Methoxsalen (p.1605·1).
Psoriasis; vitiligo.

Dermoxin
Note. This name is used for preparations of different composition.
Bunker, Braz.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Skin disorders.

GSK, Ger.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermoxinale *GSK, Ger.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermoxyl
Note. This name is used for preparations of different composition.
ICN, Canad.†.
Benzoyl peroxide (p.1590·2).
Acne.

Laboratorios Chile, Chile.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Sinclair, Ital.
Urea hydrogen peroxide (p.1666·2).
Skin disinfection and cleansing.

Derms *Uniao Quimica, Braz.*
Tiabendazole (p.156·2); neomycin sulfate (p.305·1).
Skin infections.

Derm's Shampoo *LDA, Arg.*
Ciclopirox (p.529·2); salicylic acid (p.1612·2).
Dandruff; seborrhoeic dermatitis.

Dermtex HC with Aloe *Pfeiffer, USA.*
⊗ Hydrocortisone (p.1535·2); aloe vera (p.1588·2).
Skin disorders.

Dermum *Dermophil Indien, Fr.†.*
St John's wort (p.422·3).
Skin irritation.

Dermuspray *Warner Chilcott, USA.*
Trypsin (p.2405·3); peru balsam (p.2365·3); castor oil (p.2278·1).
Wounds.

Dermvien *Hautel, Arg.†.*
Aloe vera (p.1588·2); panthenol (p.2362·1).

Dermyc *Teva, Hung.*
Fluconazole (p.532·1).
Fungal infections.

Dermycose *Prima, Braz.†.*
Iodine (p.2169·2); sodium iodide (p.2169·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Fungal skin infections.

Dernilan *Herbapol Wroclaw, Pol.*
Camphor (p.2273·2); allantoin (p.1588·1); nicotinamide (p.1957·3); salicylic acid (p.1612·2).
Keratinisation disorders.

Derobin Skin *USV, India.*
Dithranol (p.1595·2); salicylic acid (p.1612·2); coal tar (p.1616·2).
Corns; psoriasis; ringworm.

Deroctyl *Gap, Gr.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Derofen Miel *Sanofi Synthelabo, Mex.†.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Deronga Heilpaste *Galderma, Ger.†.*
Natamycin (p.543·1).
Fungal skin infections.

Deroser *Serral, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Deroxat *GSK, Fr.; GSK, Switz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Derozin *Gap, Gr.*
Cinnarizine (p.573·1).
Vertigo.

Derpinol *Corsalud, Venez.†.*
Guaiacol (p.1561·2); pine oil (p.2368·2); cineole (p.2282·3); terpin hydrate (p.1573·3).
Respiratory-tract disorders.

Derrumal *Finadiet, Arg.*
Avocado (p.2262·2); soya (p.1965·3).
Arthritis.

Derso TCC *Pfizer, Braz.†.*
Triclocarban (p.1665·2).
Skin infections.

Dertrase *Q Pharma, Spain.*
Carbamoylglutamic acid; inositol (p.2325·2); methionine (p.1450·1); chymotrypsin (p.2281·3); ribonucleic acid (p.2379·1); trypsin (p.2405·3); nitrofurazone (p.309·1).
Burns; skin disorders; ulcers; wounds.

Dertrin *IQFA, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Derusil *Loeffler, Mex.*
Itraconazole (p.536·3).
Fungal skin and vaginal infections.

Dervanol *Kurtsan, Turk.*
Zinc oxide (p.1621·2); chlorhexidine hydrochloride (p.1635·3); betacarotene (p.1930·3).
Skin disorders.

Dervin *Boniscontro & Gazzone, Ital.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Derzid *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Derzid-C *Unison, Hong Kong; Unison, Thai.*
⊗ Betamethasone valerate (p.1519·1); clotrimazole (p.530·1).
Skin disorders with fungal infection.

Derzid-N *Unison, Hong Kong†; Unison, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Skin disorders with bacterial infection.

Desaflu *Drug Research, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic respiratory-tract disorders.

Desal *Biofarma, Turk.*
⊗ Furosemide (p.1292·1).
Oedema.

Desalex *Mantecorp, Braz.; Schering-Plough, Singapore†; Schering-Plough, Venez.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Desalfa
Note. This name is used for preparations of different composition.
INTES, Ital.
Cream; ointment: ⊗ Dexamethasone isonicotinate (p.1526·1); lidocaine hydrochloride (p.1862·3).
Haemorrhoids; skin disorders.

INTES, Ital.
Eye drops; eye ointment: ⊗ Dexamethasone isonicotinate (p.1526·1); phenylephrine hydrochloride (p.1568·1); neomycin (p.305·1).
Eye disorders.

INTES, Ital.
Lotion: ⊗ Dexamethasone isonicotinate (p.1526·1); neomycin (p.305·1).
Skin disorders.

INTES, Ital.
Nasal/ear drops: ⊗ Dexamethasone isonicotinate (p.1526·1); neomycin (p.305·1).
Nasal and ear infections.

Desamin Same *Savoma, Ital.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Desamix Effe *Savoma, Ital.*
⊗ Dexamethasone (p.1526·1); clotrimazole (p.530·1).
Infected skin disorders.

Desamix-Neomicina *Savoma, Ital.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Skin disorders.

Desamon *Streuli, Switz.*
Didecyldimethylammonium chloride (p.1642·2); isopropyl alcohol (p.1650·3).
Disinfection of instruments, clothing, hands, skin, and mucous membranes.

Desaquick extra fresh *Altana, Switz.†.*
Magnesium peroxide (p.1651·3); ascorbic acid (p.1983·3).
Halitosis.

Desaquick forte *Altana, Switz.†.*
Sodium percarbonate (p.1662·2); ascorbic acid (p.1983·3); cetylpyridinium chloride (p.1635·1).
Halitosis.

Desaquick fresh *Altana, Switz.†.*
Magnesium peroxide (p.1651·3); ascorbic acid (p.1983·3); menthol (p.2340·1).
Halitosis.

Desarell *Sanorell, Ger.*
Homoeopathic preparation.

Desarrol *Iquinosa, Spain.*
Cyproheptadine hydrochloride (p.575·1); amino acids (p.1922·1).
Tonic.

Descon *Farmasa, Braz.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Desconex *Reig Jofre, Spain†.*
Loxapine hydrochloride (p.1005·3) or loxapine succinate (p.1005·3).
Psychoses.

Descongestivo Cuve Nasal *Perez Gimenez, Spain†.*
Phenylephrine hydrochloride (p.1568·1); menthol (p.2340·1).
Nasal congestion.

Desconphar *ICN, Arg.†.*
Salicylic acid (p.1612·2).
Eye irritation.

Descutan *Fresenius Kabi, Swed.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Desdek *Edol, Port.*
Fusidic acid (p.279·3).
Bacterial infections.

Desderman N *Schulke & Mayr, Ger.†.*
⊗ Orthophenylphenol (p.1655·1); alcohol (p.1625·2).
Hand disinfection.

Desdol *Medipharm, Chile.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Musculoskeletal spasm.

Desec *TO-Chemicals, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux, Zollinger-Ellison syndrome; peptic ulcer.

Desefin *Deva, Turk.*
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Deselex *Schering-Plough, S.Afr.*
Desloratadine (p.576·1).
Allergic rhinitis.

Desenex
Novartis Consumer, Canad.; Roche Consumer, Irl.
Zinc undecenoate (p.549·3); undecenoic acid (p.549·2).
Fungal skin infections.

Novartis Consumer, USA.
Undecenoic acid (p.549·2) and/or zinc undecenoate (p.549·3).
Fungal skin infections; minor skin disorders.

DesenexMax *Novartis, USA.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Desenfriol *Schering-Plough, Arg.; Schering-Plough, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; fever; nasal congestion; pain.

Desenfriol C *Schering-Plough, Spain.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Fever; nasal congestion; pain.

Desenfriol Caramelos *Key, Arg.†.*
Cetylpyridinium chloride (p.1635·1); propyl aminobenzoate; gramicidin (p.286·1).
Sore throat.

Desenfriol D *Schering-Plough, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Fever; nasal congestion; pain.

Desenfriol D Plus *Schering-Plough, Mex.†.*
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Desenfriol Decongestivo *Schering-Plough, Arg.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Desenfriol Hiper T *Key, Arg.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Allergic respiratory-tract disorders; cold symptoms.

Desenfriol con Paracetamol *Schering-Plough, Chile†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Desenfriolito *Schering-Plough, Arg.*
Aspirin (p.20·3).
Cold and influenza symptoms.

Desenfriolito Con Paracetamol *Schering-Plough, Chile†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms.

Desenfriol-Ito Plus *Schering-Plough, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Formerly contained paracetamol, chlorphenamine maleate, and aspirin.
Allergic rhinitis; cold symptoms.

Desenfriol-Ito TF *Schering-Plough, Mex.†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Desensib *Wiedemann, Ger.†.*
Homoeopathic preparation.

Desensilium *Biokosma, Fr.*
Quail's eggs.
Allergic disorders.

Desensyl *Gador, Arg.*
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Sensitive teeth.

Desentol *Ipex, Swed.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Deserein *Medilat, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Deseril *Novartis, Austral.; Novartis, Belg.; Novartis, Ger.†; Novartis, Neth.; Novartis, S.Afr.†; Novartis, Switz.†; Alliance, UK.*
Methysergide maleate (p.623·1).
Cluster headache; diarrhoea associated with carcinoid disease; migraine and other vascular headaches.

Deserila *Novartis, Braz.*
Methysergide maleate (p.623·1).
Migraine.

Desernil *Novartis, Fr.*
Methysergide maleate (p.623·1).
Migraine; vascular facial pain.

Desert Pure Calcium *Cal-White, USA.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Desfatigan *Pentafarma, Port.*
Calcium pangamate (p.2362·1).

Desferal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Biofutura, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ†; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Desferrioxamine mesilate (p.1439·2).
Aluminium overload; iron overload.

Desferin *Novartis, Spain.*
Desferrioxamine mesilate (p.1439·2).
Aluminium overload; iron overload.

Desflam *Merck, Mex.*
Bumadizone calcium (p.28·3).
Inflammation; peri-articular and soft-tissue disorders.

Desfrin *Uniao Quimica, Braz.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Desicol *Pfizer, Chile.*
Pig bile (p.2266·2).
Adjuvant in absorption of fat-soluble vitamins; biliary-tract disorders.

Desicort *Taro, Israel.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Desifluvoxamin *Declimed, Ger.†.*
Fluvoxamine maleate (p.399·3).
Depression.

Desihex *SM, Venez.*
Soap substitute.

Desiken *Kendrick, Mex.*
Ribavirin (p.902·3).
Viral infections.

Desinax *Tecnimede, Port.*
Venlafaxine hydrochloride (p.427·3).
Depression; mixed anxiety-depressive states; social phobia.

Desinflam *Pharmacia, Arg.†.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Desinflam Biotic *Pharmacia, Arg.†.*
Amoxicillin trihydrate (p.202·2); diclofenac sodium (p.44·3).
Bacterial infections.

Desinflex *Diffucap, Braz.†.*
Diclofenac diethylamine (p.44·3).
Inflammation.

Desintan P *Stafford-Miller, Port.†.*
Permethrin (p.2048·2).
Pediculosis.

Desintex *Richard, Fr.*
Sodium thiosulfate (p.1466·1); magnesium thiosulfate (p.1466·1).
Dyspepsia; rhinitis; rhinopharyngitis.

Desintex Infantile *Richard, Fr.*
Sodium thiosulfate (p.1466·1); magnesium thiosulfate (p.1466·1); calcium gluconate (p.1675·3); calcium carbonate (p.1714·1).
Dyspepsia; rhinitis; rhinopharyngitis.

Desintex-Choline *Richard, Fr.*
Sodium thiosulfate (p.1466·1); magnesium thiosulfate (p.1466·1); choline chloride (p.1934·2).
Dyspepsia.

Desinvag *Casen Fleet, Spain.*
Benzalkonium chloride (p.1629·1); furazolidone (p.834·3).
Vaginal antiseptic; vulvovaginal trichomoniasis.

Desirel *Codal Synto, Thai.*
Trazodone hydrochloride (p.424·3).
Anxiety; depression.

Desital *Desitin, Norw.†.*
Citalopram hydrobromide (p.385·3).
Depression.

Desiticlopidin *Declimed, Ger.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Desitin
Note. This name is used for preparations of different composition.
Sigmapharm, Austria; Pfizer Consumer, Canad.; Desitin, Cz.†; Pfizer, Hong Kong; Pfizer, Israel; Pfizer Consumer, Mex.; Leeming, USA.
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Burns; nappy rash; skin disorders; skin irritation; wounds.

Pfizer, Philipp.; Pfizer, Rus.; Pfizer Consumer, Singapore†.
Zinc oxide (p.1621·2).
Formerly contained cod-liver oil and zinc oxide in *Singapore*.
Burns; cuts; nappy rash.

Desitin, Ger.
Ointment; topical spray: Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin disorders; wounds.

Desitin, Ger.†.
Topical powder: Zinc oxide (p.1621·2).
Burns; skin disorders.

Desitin Clear *Pfizer, USA.*
Barrier preparation.
Nappy rash.

Desitin Creamy
Note. This name is used for preparations of different composition.
Pfizer Consumer, Singapore†.
Zinc oxide (p.1621·2); aloe vera (p.1588·2); vitamin E (p.1992·2).
Nappy rash.

Pfizer, USA.
Zinc oxide (p.1621·2); liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Formerly known as Daily Care.
Nappy rash.

Desitin Daily Care *Pfizer, Hong Kong†.*
Zinc oxide (p.1621·2).
Nappy rash.

Desitin Nappy Rash Ointment *Pfizer Consumer, Austral.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Nappy rash.

Desitin with Zinc Oxide *Pfizer, USA.*
Corn starch (p.1968·1); zinc oxide (p.1621·2).

Desitur *Turimed, Switz.†.*
⊗ Alcohol (p.1625·2); cetrimonium bromide (p.1635·1).
Hand disinfection.

Desketo
Recalcine, Chile.
Dexketoprofen (p.73·3).
Pain.

Malesci, Ital.
Dexketoprofen trometamol (p.73·1).
Pain.

Deslor *Sun, India.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Deslorat *Oftalmi, Venez.*
Desloratadine (p.576·1).
Allergic rhinitis; allergic skin disorders; asthma.

Desmanol *Schulke & Mayr, Ger.†.*
Chlorhexidine gluconate (p.1635·3); propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3).
Hand disinfection.

Desmanol G *Merck, Thai.†; Schulke & Mayr, Thai.†.*
Chlorhexidine gluconate (p.1635·3).
Hand disinfection.

Desmin *Grunenthal, Ger.*
Ethinylestradiol (p.2101·3); desogestrel (p.2093·2).
Combined oral contraceptive.

Desmogalen *Galen, Ger.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; test of renal concentrating capacity.

DesmoMelt *Ferring, UK.*
Desmopressin (p.2185·2).

Desmopress *Ferring, Hung.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis.

Desmoprol *Proel, Gr.*
Desmopressin (p.2185·2).
Diabetes insipidus; haemorrhagic disorders.

Desmospray *Ferring, Cz.; Ferring, Irl.; Ferring, Port.; Ferring, UK.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturia associated with multiple sclerosis; nocturnal enuresis; polyuria; test of renal concentrating capacity.

Desmotabs *Ferring, Cz.; Ferring, Irl.; Ferring, UK.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturia; nocturnal enuresis.

Desobesi-M *Ache, Braz.*
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Desocol *Lampugnani, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; cholesterol gallstones.

Desocort
Note. This name is used for preparations of different composition.
Galderma, Canad.
⊗ Desonide (p.1525·1).
Skin disorders.

Chauvin, Fr.†.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Otitis externa.

Des-OD *Cadila, India.*
Desloratadine (p.576·1).

Desoform *Lysoform, Ger.†.*
Glyoxal (p.1646·1); formaldehyde (p.1644·2); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Desogen *Organon, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Desol *Geno, India.*
Docusate sodium (p.1725·1).
Ear wax removal.

Desolett *Organon, Swed.; Organon, Turk.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Desolex *Surya Dermato, Indon.*
⊗ Desonide (p.1525·1).
Skin disorders.

Desolex-N *Surya Dermato, Indon.*
⊗ Desonide (p.1525·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Desomedine *Sidus, Arg.†; Chauvin, Fr.; Bausch & Lomb, Singapore; Chauvin, Singapore; Bausch & Lomb, Switz.*
Hexamidine isetionate (p.1646·3).
Eye infections; rhinopharyngeal infections.

Desomex *Konimex, Indon.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Deson *Unison, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Desonax *LPB, Ital.*
⊗ Budesonide (p.1520·1).
Asthma.

Desonol *Medley, Braz.*
⊗ Desonide (p.1525·1).
Skin disorders.

Desopan *Mochida, Jpn.*
Trilostane (p.2404·2).
Adrenocortical suppressant.

Desoplus *Lagos, Arg.*
⊗ Desonide (p.1525·1).
Skin disorders.

Desorate *Pond's, Thai.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy.

Desorelle *Mithra, Belg.; Sandoz, Denm.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Desoren
Note. This name is used for preparations of different composition.
Grunenthal, Chile.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Vitamed, Israel.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Ear infections.

Desotap *Novo Pharm, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; rhinitis; sinusitis.

DesOwen *Galderma, Arg.; Galderma, Austral.; Galderma, Braz.†; Galderma, Chile; Galderma, Hong Kong; Galderma, India; Galderma, Mex.; Pacific, NZ†; Galderma, Philipp.; Galderma, Singapore; Galderma, USA; Galderma, Venez.*
⊗ Desonide (p.1525·1).
Skin disorders.

Desoxi *Optimapharma, Canad.†.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Desoxil *Boniscontro & Gazzone, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders.

Desoxyn *Abbott, USA.*
⊗ Metamfetamine hydrochloride (p.2158·1).
Attention deficit hyperactivity disorder; obesity.

Despacilina *BMS, Braz.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Despamen *AF, Mex.*
⊗ Estradiol valerate (p.2097·3); testosterone enantate (p.2130·1).
Menopausal disorders; osteoporosis.

Desparasil *Rimsa, Mex.†.*
Piperazine hydrate (p.153·1).
Nematode infections.

Despex *Alcon, Arg.†.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Despigmentante *Dermoteca, Port.*
Lactic acid (p.2329·3); kojic acid (p.1603·3); enoxolone (p.50·1); arbutin (p.1589·2).
Skin hyperpigmentation.

Desquam *Westwood-Squibb, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Desquaman *Hermal, Austria; Hermal, Israel.*
Pyrithione zinc (p.1611·2).
Dandruff; scalp infections; seborrhoeic dermatitis.

De-squaman N *Hermal, Ger.†.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Desquam-X *Westwood-Squibb, Canad.*
Benzoyl peroxide (p.1590·2).
Acne.

Dessensibilizante Chauvin *Prima, Braz.†.*
Sodium thiosulfate (p.1466·1); magnesium thiosulfate (p.1466·1).
Hypersensitivity reactions.

Dessolets *SMB, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye congestion.

Destamin *Medifarma, Mex.*
Histamine hydrochloride (p.2319·2).

Destap *Laboratorios Chile, Chile.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma; nasal polyps.

Destara *Roche, Neth.*
Ibandronate sodium (p.1098·3).
Hypercalcaemia of malignancy.

deSTAT 3 *Sherman, USA.*
Cleaning, disinfectant, and storage solution for gas permeable contact lenses (p.1622·2).

Destilbenol *Apsen, Braz.*
Diethylstilbestrol (p.2094·1).
Breast cancer; prostatic cancer.

Destolit *Sanofi-Aventis, Port.; Norgine, UK.*
Ursodeoxycholic acid (p.2408·1).
Biliary tract disorders; cholesterol gallstones.

Destoxican *Pentafarma, Port.*
Naltrexone hydrochloride (p.1455·2).
Alcohol dependence; opioid dependence.

Destralina *Mavi, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Destrepen *Proel, Gr.†.*
Cefoxitin (p.230·3).
Bacterial infections.

Destrobac *Teleflex, Ital.; Gebro, Switz.*
Povidone-iodine (p.1659·2).
Burns; infected skin disorders; skin disinfection; wounds.

Desugar *Stada, Austria.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Desuric *Sanofi Synthelabo, Belg.†; Sanfer, Mex.†; OTL, Neth.; Sanofi Synthelabo, Switz.†.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia.

Desurol *Leciva, Cz.†.*
Oxolinic acid (p.312·2).
Urinary-tract infections.

Desyrel *BMS, Canad.; Santa, Turk.; Apothecon, USA†.*
Trazodone hydrochloride (p.424·3).
Anxiety; depression.

DET MS *Shire, Ger.*
Dihydroergotamine mesilate (p.618·2).
Hypotension.

DET MS spezial *Shire, Ger.†.*
Dihydroergotamine mesilate (p.618·2).
Chronic venous insufficiency; hypotension; migraine and other vascular headaches.

Detametazon *Masterlek, Rus.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Detamol *PD, Thai.†.*
Paracetamol (p.108·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Fever; pain; post-immunisation reactions.

Detane *Del, Canad.†; Del, USA.*
Benzocaine (p.1854·1).
Genital desensitising lubricant; premature ejaculation.

Detantol *Eisai, Indon.; Eisai, Jpn; Eisai, Thai.*
Bunazosin hydrochloride (p.1237·3).
Hypertension.

Detarmon *Rowe-Fleming, Venez.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Detebencil
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.
Emulsion: Permethrin (p.2048·2); benzyl benzoate (p.2036·1); benzocaine (p.1854·1).
Pediculosis.

Roux-Ocefa, Arg.
Lotion: Permethrin (p.2048·2); benzyl benzoate (p.2036·1).
Pediculosis.

Detebencil Nit *Roux-Ocefa, Arg.*
Permethrin (p.2048·2); acetic acid (p.2244·2).
Pediculosis.

Deteclo *Goldshield, UK†.*
Tetracycline hydrochloride (p.347·2); chlortetracycline hydrochloride (p.243·1); demeclocycline hydrochloride (p.264·3).
Bacterial infections.

Detect Baby *Blausiegel, Braz.*
Pregnancy test (p.2372·1).

Detemes *Sanova, Austria.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and related vascular headaches; venous insufficiency.

Deten *Siam Bheasach, Thai.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Detenler *Duncan, Arg.*
Levomepromazine (p.1002·3).
Psychoses.

Detensiel *Merck-Lipha, Fr.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Detensor *Novartis Consumer, Switz.*
Diphenhydramine hydrochloride (p.577·2); 8-chlorotheophylline.
Sleep disorders.

Detergil *Manetti Roberts, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection; wound disinfection.

Dethamycin *Vitamed, Israel.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye, ear, and nose disorders.

Dethaphrine *Vitamed, Israel.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Infected eye, ear, and nose disorders.

Deticene *Aventis, Arg.†; Sanofi-Aventis, Chile; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Mex.†; Aventis, Neth.; Sanofi-Aventis, Port.; Aventis, Turk.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Detidron *Hexal, Austria.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Detilem *Lemery, Mex.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Detimedac *Medac, Ger.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Detoch *PD, Thai.†.*
Dequalinium chloride (p.1641·3); ascorbic acid (p.1983·3).
Mouth and throat infections.

Detofan *Quim-Far, Venez.†.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Detox *Reese, USA.*
Red clover; liquorice; peach bark; orange grape root; stillingla; cascara; sarsaparilla; lappa root; buckthorn (p.1922·1).
Dietary supplement.

Detox L37 *Homeocan, Canad.*
Homoeopathic preparation.

Detoxalgine *Organon, Fr.†.*
Glucuronamide (p.2314·2); aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; musculoskeletal and joint disorders; pain.

Detoxell *EBN, Fr.*
Brassica oleracea; taraxacum (p.2395·1); verbascum (p.2413·3); grape (p.2316·3).
Detoxification therapy.

Detoxergon *Baldacci, Port.*
Pirglutargine (p.2369·1); taurine (p.2395·2); pyridoxine hydrochloride (p.1978·2); citric acid (p.2284·1); sodium citrate; calcium citrate; potassium citrate; magnesium citrate.
Liver disorders.

Detoxicon *SIT, Ital.*
Glycine (p.1947·3); acetylmethionine (p.1450·2).
Tonic.

Detraine *Seid, Spain.*
⊗ Hydrocortisone (p.1535·2); propanocaine hydrochloride (p.1869·3).
Insect bites and stings; pruritus; skin disorders.

Detralex *Servier, Cz.; Servier, Hung.; Servier, Pol.; Servier, Rus.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Detramol *Filadams, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Detreomycyna *Chema-Elektromet, Pol.*
Chloramphenicol (p.239·3).
Bacterial skin infections.

Detrex *Vargas, Venez.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Detrican *Rowe-Fleming, Venez.†.*
Tenonitrozole (p.848·1).
Fungal infections.

Detrichol *GMP, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Detrol *Pfizer, Canad.; Pharmacia Upjohn, USA.*
Tolterodine tartrate (p.2198·1).
Bladder instability.

Detrovel *Fahrenheit, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Detrunorm *Apogepha, Port.†; Pharmafrica, S.Afr.; Amdipharm, UK.*
Propiverine hydrochloride (p.2192·2).
Bladder instability; neurogenic bladder.

Detrusan *Stada, Austria.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Detrusitol *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, India; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, Venez.*
Tolterodine tartrate (p.2198·1).
Bladder instability; urinary incontinence.

Detsel *Pfizer, Austria; Pfizer, Neth.†.*
Tolterodine tartrate (p.2198·1).
Bladder instability; irritable bladder; urinary incontinence.

Detska Cajova Smes *Megafyt-R, Cz.*
Peppermint leaf (p.1761·2); chamomile (p.2279·3); fennel (p.2302·3); althaea (p.2253·3); liquorice (p.1740·3).
Digestive system disorders.

Detsky Caj s Hermankem *Leros, Cz.*
Chamomile (p.2279·3); fennel (p.2302·3); peppermint leaf (p.1761·2); althaea (p.2253·3); raspberry leaf (p.2378·2); plantaginis (p.2379·1); lupulus (p.2335·2); wild thyme (p.2415·3); sambucus (p.2383·1); liquorice (p.1740·3).
Digestive system disorders.

Dettol
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Belg.; Vianex (Βιανέξ), Gr.; Reckitt Benckiser, Neth.
Chloroxylenol (p.1640·2).
Skin disinfection; wounds.

Reckitt Benckiser, Hong Kong†; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.
Cream: Chloroxylenol (p.1640·2); triclosan (p.1665·2).
Burns; insect bites and stings; skin and wound disinfection.

Reckitt Benckiser, NZ; Reckitt Benckiser, Singapore.
Topical liquid: Chloroxylenol (p.1640·2).
Skin and wound disinfection.

Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.
Topical solution: Chloroxylenol (p.1640·2).
Skin and wound disinfection.

Reckitt Benckiser, NZ.
Topical spray: Benzalkonium chloride (p.1629·1).
Skin disinfection.

Reckitt Benckiser, UK.
Topical spray: Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).
Bites and stings; minor burns; minor wounds.

Dettol Antiseptic Wash *Reckitt Benckiser, UK.*
Benzalkonium chloride (p.1629·1).
Wound disinfection.

Dettol Classic *Reckitt Benckiser, Austral.*
Chloroxylenol (p.1640·2).
Bath additive; bites and stings; burns; minor abrasions; skin disinfection.

Dettol Cream *Reckitt Benckiser, Austral.*
Chloroxylenol (p.1640·2); triclosan (p.1665·2).
Bites and stings; burns; minor abrasions; skin disorders; skin infections.

Dettol Fresh *Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Reckitt Benckiser, NZ; Reckitt Benckiser, UK.*
Benzalkonium chloride (p.1629·1).
Bites and stings; burns; minor abrasions; skin disinfection.

Dettol Liquid Wash *Reckitt Benckiser, Austral.*
Triclosan (p.1665·2).
Acne; skin cleansing.

Dettol Obstetric *Reckitt Benckiser, India.*
Chloroxylenol (p.1640·2); terpineol (p.2396·1).
Skin disinfection; vaginal lubricant.

Dettolin *Reckitt Benckiser, India.*
⊗ Chloroxylenol (p.1640·2); menthol (p.2340·1); alcohol (p.1625·2).
Gingivitis; oral hygiene; periodontitis.

Dettonjab *Defuen, Arg.*
Undecenoic acid diethanolamide (p.549·3); triclosan (p.1665·2).
Acne.

Detulin *McNeil, Ger.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Deturgylone *Sanofi-Aventis, Fr.*
⊗ Prednisolone sodium phosphate (p.1541·2); oxymetazoline hydrochloride (p.1567·2).
Rhinitis.

Deucoaler *Medipharm, Chile.*
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

Deucodol *Medipharm, Chile.*
Ibuprofen (p.64·2).
Fever; inflammation.

Deucodol Plus *Medipharm, Chile.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; nasal congestion; sinusitis.

Deucotos *Medipharm, Chile.*
Codeine (p.37·2); pseudoephedrine (p.1571·2); chlorphenamine (p.572·2).
Bronchitis; cold symptoms; coughs.

Deucoval *Medipharm, Chile.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Deursil *Sanofi-Aventis, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; gallstones.

De-ursil *Sanofi Synthelabo, Switz.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Devaljin *Deva, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Devapen *Deva, Turk.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Devaron *Solvay, Neth.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Devedryl *Klonal, Arg.*
Loratadine (p.583·3).

Develanid *Klonal, Arg.†.*
Lanatoside C (p.1322·3).

Deverol mit Thiazid *Sanochemia, Austria.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Ascites; heart failure; nephrotic syndrome; oedema.

Devikap *Medana, Pol.*
Colecalciferol (p.1986·2).
Osteomalacia; osteoporosis; rickets; tetany.

Devilan *Biomedica, Cz.*
2-Aminotridecane undecenoate; dipenditum.
Fungal skin infections.

Devils Claw Plus *Eagle, Austral.*
Devil's claw root (p.39·1); murraya; celery (p.2278·3); hesperidin (p.2304·3).
Arthritis; rheumatism.

Devincal *Prodes, Spain; Gentek, Venez.†.*
Piracetam (p.368·2); vincamine (p.2414·1).
Cerebrovascular disorders.

Devisol *Ifarm, Pol.*
Calcifediol (p.1986·1).
Hypocalcaemia; hypoparathyroidism; osteomalacia; renal osteodystrophy; rickets.

Devit-3 *Deva, Turk.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Devitol *Orion, Fin.*
Ergocalciferol (p.1987·1).
Vitamin D deficiency.

Devitre *Nycomed, Swed.†.*
Colecalciferol (p.1986·2).
Osteoporosis; vitamin D deficiency.

Devix *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Butamirate citrate (p.1553·1).
Cough.

Devotan *Menarini, Gr.*
Gliquidone (p.442·1).
Diabetes mellitus.

Devrom *Parthenon, USA.*
Bismuth subgallate (p.1711·1).
Ostomy deodorant.

Dewax *Ranbaxy, Thai.*
Docusate sodium (p.1725·1).
Ear wax removal.

Dex *PP Lab, Thai.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Dex4 Glucose *Can-Am Care, USA.*
Glucose (p.1945·3).
Hypoglycaemia.

Dexa *Merckle, Cz.†; CT, Ger.; Jenapharm, Ger.; Ratiopharm, Hung.; Shiwa, Thai.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexa Aminofilin *Phoenix, Arg.*
⊗ Theophylline (p.1140·1); dexamethasone (p.1526·1).
Asthma.

Dexa ANB *ANB, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexa Biciron *Alcon, Ger.*
⊗ Dexamethasone isonicotinate (p.1526·1); tramazoline hydrochloride (p.1574·3).
Allergic and inflammatory disorders of the eye.

Dexa Loscon mono *Galderma, Ger.*
⊗ Dexamethasone isonicotinate (p.1526·1).
Scalp disorders.

Dexa Polyspectran *Alcon, Ger.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).
Infected eye and ear disorders.

Dexa Tavegil *Novartis Consumer, Spain.*
⊗ Clemastine (p.573·3); dexamethasone (p.1526·1).
Hypersensitivity reactions; inflammatory eye disorders; insect bites and stings; sunburn.

Dexa Teosona *Phoenix, Arg.*
⊗ Theophylline (p.1140·1); dexamethasone (p.1526·1).
Obstructive airways disease.

Dexa-Allvoran *TAD, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexabene *Ratiopharm, Austria; Merckle, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexabeta *Betapharm, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexabion
Note. This name is used for preparations of different composition.
Merck, Mex.
⊗ Ampoule 1: thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ampoule 2: dexamethasone sodium phosphate (p.1526·2).
Lidocaine hydrochloride (p.1862·3) is included in ampoule 2 to alleviate the pain of injection.
Inflammation; neuralgias; neuritis; peri-articular disorders.

Merck, Arg.
Injection: ⊗ Ampoule 1, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ampoule 2, dexamethasone sodium phosphate (p.1526·2).
Inflammation; neuralgias; neuritis; rheumatoid arthritis.

Merck, Arg.†.
Tablets: ⊗ Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); dexamethasone (p.1526·1).
Inflammation; joint and peri-articular disorders; neuralgia; neuritis.

Dexacap *Dexa, Hong Kong†; Dexa, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Dexacef *Ferron, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Dexachlor *Cooper (Κοπερ), Gr.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Infected eye disorders.

Dexacid *Biosintex, Arg.†.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Dexacidin *Novartis Ophthalmics, USA†.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye inflammation with bacterial infection.

Dexacilin
Note. This name is used for preparations of different composition.
Prodotti, Braz.
Eye drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Prodotti, Braz.
Injection: ⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexacin *ANB, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye or ear disorders.

Dexacine *Novartis Ophthalmics, USA†.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Dexacip *Cipla, India.*
⊗ Dexamethasone (p.1526·1); dexamethasone phosphate (p.1526·2), or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexa-Citoneurin *Merck, Braz.*
⊗ Thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); dexamethasone (p.1526·1) or dexamethasone acetate (p.1526·1).
Neuritis.

dexa-clinit *Hormosan, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Parenteral corticosteroid.

Dexaclor *Hebron, Braz.†.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Infected skin disorders.

Dexacobal *Uniao Quimica, Braz.*
⊗ Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); dexamethasone acetate (p.1526·1).
Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Neuritis.

Dexacollyre *Cooper (Κοπερ), Gr.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexacort
Note. This name is used for preparations of different composition.
Gemballa, Braz.†.
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Skin disorders.

Teva, Israel.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Behrens, Venez.
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Dexacortal *Organon, Swed.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexacortin *Streuli, Switz.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexacortin-K *Streuli, Switz.†.*
⊗ Dexamethasone (p.1526·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Joint and peri-articular disorders.

Dexa-Cronobe *Biolab Sanus, Braz.*
⊗ Ampoule A, cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1); ampoule B, dexamethasone acetate (p.1526·1).
Neuritis.

Dexaden *Cifarma, Braz.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexadent *Chema-Elektromet, Pol.*
⊗ Dexamethasone acetate (p.1526·1); framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3).
Dental infections.

Dexadermil *Legrand, Braz.*
⊗ Dexamethasone acetate (p.1526·1).
Skin disorders.

Dexador *Ativus, Braz.*
⊗ Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); dexamethasone phosphate (p.1526·2).
Procaine hydrochloride (p.1869·1) is included in the injection to alleviate the pain of injection.
Neuritis.

Dexadoze *Teuto, Braz.*
⊗ Ampoule A, dexamethasone acetate (p.1526·1); ampoule B, thiamine hydrochloride (p.1976·1); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Neuritis.

Dexadutil *Parggon, Mex.*
⊗ Dexamethasone (p.1526·1); phenylbutazone (p.117·1).
Rheumatism.

DexaEDO *Mann, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexa-Effekton *Teofarma, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Rheumatic disorders.

Dexafarm *ICN, Arg.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexafed Cough *Mallard, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Dexafenicol *Allergan, Braz.*
⊗ Chloramphenicol (p.239·3); dexamethasone (p.1526·1).
Infected eye disorders.

Dexaflam *Winthrop, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Musculoskeletal, joint, and peri-articular disorders.

Dexaflan *Hebron, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexaflox *Dexa, Indon.*
Pefloxacin (p.313·3).
Bacterial infections.

Dexafree *Thea, Pol.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexafrin *Sophia, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Formerly contained dexamethasone sodium phosphate and phenylephrine hydrochloride.
Eye disorders.

Dexafurazon *Allergan, Arg.†.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).
Infected eye disorders.

Dexagalen *Galen, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexagel *Mann, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Dexagenta *Croma, Austria.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2); gentamicin sulfate (p.282·1).
Infected eye disorders.

Dexa-Gentamicin
Note. This name is used for preparations of different composition.
Ursapharm, Cz.
⊗ Dexamethasone (p.1526·1); gentamicin sulfate (p.282·1).
Infected eye disorders.

Ursapharm, Ger.; Ursapharm, Rus.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2); gentamicin sulfate (p.282·1).
Infected eye disorders.

Ursapharm, Malaysia†.
⊗ Dexamethasone sodium phosphate (p.1526·2); gentamicin sulfate (p.282·1).
Infected eye disorders.

Dexagenta-POS *Ursapharm, Belg.; Ursapharm, Neth.*
⊗ Dexamethasone sodium phosphate (p.1526·2); gentamicin sulfate (p.282·1).
Infected eye disorders.

Dexagil *Marjan, Braz.*
⊗ Dexamethasone phosphate (p.1526·2); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Procaine hydrochloride (p.1869·1) is included in the vitamin injection to alleviate the pain of injection.
Neuritis.

Dexagin *Farmo Quimica, Chile.*
⊗ Dexamethasone tebutate (p.1526·3); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1); boric acid (p.2268·1).
Vaginitis.

Dexagrane *Ioltech, Fr.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Dexagreen *Greenpharma, Braz.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Dexagrin *Grin, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexahexal *Hexal, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexak *Berlin-Chemie, Pol.*
Dexketoprofen trometamol (p.73·1).
Pain.

Dexal *Marcel, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexalaf *Lafedar, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexalergin
Note. This name is used for preparations of different composition.
Ivax, Arg.
Cream: ⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); chlorphenamine maleate (p.571·3).
Skin disorders.

Ivax, Arg.
Injection: ⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Ivax, Arg.
Nasal spray; nose drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); chlorphenamine maleate (p.571·3); naphazoline hydrochloride (p.1565·2).
Nasal disorders.

Ivax, Arg.
Syrup; tablets: ⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2); chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Dexalgen *Eurofarma, Braz.*
⊗ Ampoule I, hydroxocobalamin (p.1980·3); ampoule II, dipyrone (p.49·2); dexamethasone sodium phosphate (p.1526·2).
Neuritis.

Dexalgin 25 *Berlin-Chemie, Rus.*
Dexketoprofen trometamol (p.73·1).
Musculoskeletal and joint disorders; pain.

Dexalin *General Drugs, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); cajuput oil (p.2271·2); cineole (p.2282·3).
Lumbago; rheumatic conditions; sciatica.

Dexalocal
Note. This name is used for preparations of different composition.
Farmanic, Gr.
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Medinova, Switz.
⊗ Dexamethasone (p.1526·1).
Skin and scalp disorders.

Dexalocal-F *Medinova, Switz.*
⊗ Dexamethasone (p.1526·1); framycetin sulfate (p.279·1).
Infected skin disorders.

Dexalone
Note. A similar name is used for preparations of different composition (see below).
CCM, Malaysia.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

DexAlone
Note. A similar name is used for preparations of different composition (see above).
DexGen, USA.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexaltin *Kayaku, Cz.; Kayaku, Hong Kong; Kayaku, Malaysia; Kayaku, Singapore; ANB, Thai.*
⊗ Dexamethasone (p.1526·1).
Glossitis; mouth ulcers; stomatitis.

Dexa-M *Dexa, Indon.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexam Constric *Alcon Cusi, Spain†.*
⊗ Chloramphenicol succinate (p.241·3); dexamethasone sodium phosphate (p.1526·2); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Dexambutol *IFET (ΙΦΕΤ), Gr.*
Ethambutol (p.275·2).
Tuberculosis.

Dexamed
Medochemie, Cz.; Medochemie, Rus.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Medochemie, Hong Kong; Medochemie, Singapore.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexameral *LKM, Arg.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexameson *Cristalia, Braz.*
⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Dexametax *Galenogal, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Dexameth *Major, USA†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexametonal *Hexal, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexametrat *Globo, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Dexamex *Vitapan, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexamicin *Grin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Dexamilan *Parggon, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexamin
Note. This name is used for preparations of different composition.
Streuli, Switz.†.
⊗ Dexamfetamine sulfate (p.2153·1).
Obesity.

Vivax Optipharm, Venez.
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Dexaminor *Allergan, Braz.*
⊗ Dexamethasone (p.1526·1).
Eye disorders.

Dexamol *Dexxon, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Dexamol Cold Day *Dexxon, Israel.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Dexamol Cold Night *Dexxon, Israel.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Dexamol Kid *Dexxon, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Dexamol Plus *Dexxon, Israel.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Dexamol PM *Dexxon, Israel.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia; pain.

Dexamol Sinus Day *Dexxon, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Dexamol Sinus Night *Dexxon, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Dexamonozon *Medice, Ger.*
⊗ Dexamethasone (p.1526·1).
Oral corticosteroid.

Dexamonozon N *Medice, Ger.†.*
⊗ Dexamethasone (p.1526·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Dexamycin
Note. This name is used for preparations of different composition.
Alvia (Αλβια), Gr.
⊗ Dexamethasone (p.1526·1); tobramycin (p.354·1).
Infected eye disorders.

Teva, Israel.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Inflammatory eye disorders with infection.

Dexamytrex
Bausch & Lomb, Arg.; Mann, Ger.; Tramedico, Neth.; Bausch & Lomb, Philipp.; Lepori, Port.
⊗ Gentamicin sulfate (p.282·1); dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Bausch & Lomb, Braz.†; Kite (Κιτε), Gr.
⊗ Gentamicin sulfate (p.282·1); dexamethasone (p.1526·1).
Infected eye disorders.

Mann, Malaysia†; Mann, Pol.; Mann, Singapore.
⊗ Gentamicin sulfate (p.282·1); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Bausch & Lomb, Thai.; Mann, Thai.; Pharmalink, Thai.
⊗ Gentamicin sulfate (p.282·1); dexamethasone phosphate (p.1526·2).
Infected eye disorders.

Dexan *Recalcine, Chile.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Dexaneol *Cusi, Venez.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Infected eye disorders.

Dexa-Neuriberi *Haller, Braz.†.*
⊗ Dexamethasone (p.1526·1); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Neuritis.

Dexaneurin *Uniao Quimica, Braz.*
⊗ Ampoule A, cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); ampoule B, dexamethasone acetate (p.1526·1).
Procaine hydrochloride (p.1869·1) is included in ampoule A of this preparation to alleviate the pain of injection.
Neuritis.

Dexanevral *Hebron, Braz.†.*
⊗ Dexamethasone (p.1526·1); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuritis.

Dexanicol *Pascual, Philipp.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Dexanil
Note. This name is used for preparations of different composition.
Ducto, Braz.
Cream: ⊗ Dexamethasone acetate (p.1526·1); neomycin sulfate (p.305·1).

Ducto, Braz.
Injection: ⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexano *Milano, Thai.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexanta *Dexa, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Dex-Antihist *Pharmaniaga, Malaysia†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Dexantol *Medika, Switz.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Dexa-P *PP Lab, Thai.†.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexaphen-SA *Major, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Dexa-Phlogont L *Azupharma, Ger.†.*
⊗ Prednisolone (p.1540·3); dexamethasone (p.1526·1); lidocaine hydrochloride (p.1862·3).
Musculoskeletal and joint disorders.

Dexapolcort *Polfa Tarchomin, Pol.*
⊗ Dexamethasone (p.1526·1).
Allergic skin disorders.

Dexapolcort N *Tarchomin, Hung.; Polfa Tarchomin, Pol.*
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Infected skin disorders.

Dexa-Polyspectran New *Alcon, Belg.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Dexapos *Ursapharm, Cz.†; Ursapharm, Ger.; Ursapharm, Rus.*
⊗ Dexamethasone sodium sulfobenzoate (p.1526·2).
Allergic and inflammatory eye disorders.

Dexa-POS *Ursapharm, Neth.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexapostafen *Pfizer, Venez.*
⊗ Dexamethasone (p.1526·1); buclizine hydrochloride (p.570·1).
Hypersensitivity reactions.

Dexaprof D *Ivax, Arg.*
⊗ Loratadine (p.583·3); dexamethasone (p.1526·1).
Formerly contained astemizole and dexamethasone.
Hypersensitivity reactions.

Dexa-ratiopharm *Ratiopharm, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexa-Rhinaspray Duo *Boehringer Ingelheim, Irl.; Boehringer Ingelheim, UK†.*
⊗ Tramazoline hydrochloride (p.1574·3); dexamethasone isonicotinate (p.1526·1).
Allergic rhinitis.

Dexa-Rhinaspray-N *Boehringer Ingelheim, Gr.*
⊗ Dexamethasone (p.1526·1); tramazoline (p.1574·3).
Nasal congestion.

Dexa-Rhinospray *Boehringer Ingelheim, Belg.*
⊗ Tramazoline hydrochloride (p.1574·3); dexamethasone isonicotinate (p.1526·1).
Rhinitis.

Dexa-Rhinospray Mono *Mann, Ger.*
⊗ Dexamethasone isonicotinate (p.1526·1).
Formerly known as Dexa-Rhinospray M.
Allergic rhinitis.

Dexa-Rhinospray N *Boehringer Ingelheim, Arg.*
⊗ Tramazoline hydrochloride (p.1574·3); dexamethasone isonicotinate (p.1526·1).
Rhinitis.

Dexasalyl
Mayrhofer, Austria†.
⊗ Dexamethasone acetate (p.1526·1); salicylic acid (p.1612·2).
Skin disorders.

Medinova, Switz.
⊗ Dexamethasone (p.1526·1) or dexamethasone acetate (p.1526·1); salicylic acid (p.1612·2).
Skin and scalp disorders.

Dexasil *Silom, Thai.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Dexa-Sine *Alcon, Belg.; Liba, Turk.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Dexa-sine *Alcon, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Dexa-Siozwo *Febena, Ger.*
⊗ Dexamethasone acetate (p.1526·1); peppermint oil (p.1761·2).
Catarrh; rhinitis; sinusitis.

Dexason
Teuto, Braz.
⊗ Dexamethasone (p.1526·1), dexamethasone acetate (p.1526·1), or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

ICN, Cz.†.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexasone
Valeant, Canad.; Atlantic, Hong Kong; Cadila, India.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Hauck, USA.
⊗ Dexamethasone acetate (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexasporin *Moore, USA; Rugby, USA; URL, USA.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye inflammation with bacterial infection.

Dexaton *Vianex (Βιανεξ), Gr.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexatopic *Organon, Arg.†; Organon, Indon.; Organon, Neth.†.*
⊗ Dexamethasone (p.1526·1); nandrolone decanoate (p.2118·2); chlorhexidine hydrochloride (p.1635·3).
Skin disorders.

Dexatotal *Paylos, Arg.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexatrim *Chattem, Canad.†.*
Benzocaine (p.1854·1); vitamins; iron.
Obesity.

Dexatrim Plus Vitamins *Thompson, USA.*
Multivitamin and mineral preparation (p.1922·1).

Dexatussin *Espefa, Pol.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Dexaval *Tecnifar, Port.*
⊗ Dexamethasone valerate (p.1526·3).
Skin disorders.

Dexaval V *Tecnifar, Port.*
⊗ Dexamethasone valerate (p.1526·3); clioquinol (p.254·1).
Infected skin disorders.

Dexaval A *Tecnifar, Port.*
⊗ Dexamethasone valerate (p.1526·3); chlorphenamine maleate (p.571·3).
Skin disorders with pruritus.

Dexaval N *Tecnifar, Port.*
⊗ Dexamethasone valerate (p.1526·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Dexaval O *Tecnifar, Port.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Dexaven
Jelfa, Pol.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Jelfa, Rus.
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Dexavison *Teuto, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Dexazen *Luper, Braz.†.*
⊗ Dexamethasone acetate (p.1526·1), dexamethasone phosphate (p.1526·2), or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexazol *Dexa, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Dexazona
Note. This name is used for preparations of different composition.
Bunker, Braz.
Eye drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye disorders.

Bunker, Braz.
Injection; syrup; tablets: ⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Dexbroxine *Pharmasant, Thai.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexchloramine *CCM, Malaysia; Beacons, Singapore.*
Dexchlorpheniramine maleate (p.572·1).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Dexclor *Cristalia, Braz.†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Dexcof *Cipla, India.*
Dextromethorphan (p.1555·2); phenylpropanolamine (p.1569·2); diphenhydramine hydrochloride (p.577·2).
Coughs.

Dexcon-DM *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Dexcon-PE *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cough; nasal congestion.

Dexcophan *Hovid, Malaysia; Hovid, Singapore.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexcophan Cough *Hovid, Malaysia.*
⊗ Ammonium chloride (p.1551·3); dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2).
Coughs; nasal congestion.

Dexedrine *GSK, Canad.; UCB, UK; GSK, USA.*
⊗ Dexamfetamine sulfate (p.2153·1).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Dexef *Dexo, Fr.*
Cefradine (p.233·1).
Bacterial infections.

Dexefrin *Fischer, Israel.*
⊗ Dexamethasone sodium phosphate (p.1526·2); phenylephrine (p.1568·1); neomycin sulfate (p.305·1).
Inflammatory eye disorders with infection.

Dexelle *ITF, Chile.*
Dexibuprofen (p.39·2).
Fever; pain.

Dexemel *ML, Neth.†; ML Laboratories, UK†.*
Icodextrin (p.1937·2) with electrolytes.
Vehicle for intraperitoneal drug administration.

Dexeryl
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Fr.
Glycerol (p.2314·2); white soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry skin disorders; minor burns.

Pascual, Hong Kong.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

DexFerrum *American Regent, USA.*
Iron dextran (p.1951·1).
Iron deficiency.

DexFol *Rising Pharmaceuticals, USA.*
Vitamin B substances; vitamin C (p.1922·1).

Dexicam *OFF, Ital.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Dexicar *Provit, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexide *Rottapharm, Spain.*
Colextran hydrochloride (p.1254·1).
Hyperlipidaemias.

Deximune *Dexcel, Israel.*
Ciclosporin (p.1822·2).
Atopic eczema; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Dexion *Umeda, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexipan *Julphar, UAE.*
Dexpanthenol (p.2362·1).
Skin irritation; wounds.

Dexir *BMS, Belg.; UPSA Conseil, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexiron *Genpharm, Canad.*
Iron dextran (p.1951·1).
Iron deficiency.

Dexit *Leiras, Fin.*
Dexibuprofen (p.39·2).
Fever; pain.

Dexi-Tuss *3M, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexium *Sanofi Synthelabo, Ger.*
Calcium dobesilate (p.2272·1).
Vascular disorders.

Dexiven *Rivero, Arg.*
Calcitriol (p.1986·2).
Hypocalcaemia in dialysis patients.

Dexlerg *Cazi, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Dexlin *Arlex, Mex.*
Nimesulide (p.95·3).
Inflammation.

Dexmene *Biofarma, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexmetha *Synco, Hong Kong.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexmethsone *Aspen, Austral.; Aspen, Hong Kong.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexmin
Note. This name is used for preparations of different composition.
Neckerman, Braz.†.
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Daewon, Hong Kong†.
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic rhinitis; asthma; skin disorders.

Dexmolex *Molex Ayus, Indon.*
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2).
Cough; respiratory-tract allergic disorders.

Dexne
Note. This name is used for preparations of different composition.
Offenbach, Mex.
Ear drops: ⊗ Dexamethasone (p.1526·1); neomycin (p.305·1); lidocaine (p.1862·3).
Inflammatory ear disorders.

Offenbach, Mex.
Eye drops: ⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Inflammatory eye disorders.

Offenbach, Mex.
Nose drops: ⊗ Dexamethasone (p.1526·1); neomycin (p.305·1); phenylephrine (p.1568·1).
Inflammatory nose disorders.

Dexnon *Kern, Spain.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Dexo *Dominguez, Arg.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; cholesterol gallstones.

Dexocort *Kimia, Indon.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Dexodin *IQFA, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Dexofan *Nycomed, Denm.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dexofen *AstraZeneca, Swed.*
Dextropropoxyphene napsilate (p.40·1).
Pain.

Dexoket *Menarini, Cz.*
Dexketoprofen trometamol (p.73·1).
Pain.

Dexol
Note. This name is used for preparations of different composition.
SMB, Chile.
Borage (p.2267·3).
Barrier preparation; dry skin.

Andromaco, Mex.
Ambroxol (p.1550·3); dextromethorphan (p.1555·2).
Respiratory-tract congestion.

Dexolan *Streuli, Switz.*
⊗ Dexamethasone (p.1526·1); zinc oxide (p.1621·2).
Skin disorders.

Dexoline *Novartis, Ital.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Dexoltryn *Ultra, Mex.*
Dextromethorphan hydrobromide (p.1555·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Dexolut *Dexa, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with congestion.

Dexomon *Hillcross, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Dexon *General Drugs, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexona
Note. This name is used for preparations of different composition.
Cadila, Cz.†; Cadila, India.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Jofrain, Mex.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Cadila, Rus.
Ear/eye drops: ⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected ear and eye disorders.

Cadila, Rus.
Injection; tablets: ⊗ Dexamethasone (p.1526·1) or dexamethasone phosphate (p.1526·2).
Corticosteroid.

Dexona Eye/Ear *Cadila, India.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Bacterial eye infections; inflammatory ear disorders.

Dexone *Keene, USA.*
⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Dexoph
Seng, Hong Kong.
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected ear disorders; infected eye disorders.

Seng, Thai.
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

DexOptifen *Spirig, Switz.*
Dexibuprofen (p.39·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dexorange *Franco-Indian, India.*
Ferric ammonium citrate (p.1938·1); vitamin B (p.1980·2); folic acid (p.1940·1).
Anaemias.

Dexosyn Plus *Bell, India.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected inflammatory eye disorders.

Dexosyn-C *Bell, India.*
⊗ Chloramphenicol (p.239·3); dexamethasone (p.1526·1).
Corneal lesions; infected inflammatory eye disorders.

Dexosyn-N *Bell, India.*
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Corneal lesions; infected inflammatory eye disorders.

Dex-Otic *Teva, Israel.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected ear disorders.

DexPak *ECR, USA.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Dexphen M *Boca, USA.*
Dexchlorpheniramine maleate (p.572·1); hyoscine methonitrate (p.1734·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Dexpin *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p.1555·2); terpin hydrate (p.1573·3); chlorphenamine maleate (p.571·3).
Coughs.

Dexprofen *Polfa Kutno, Pol.*
Dexibuprofen (p.39·2).
Fever; inflammation; pain.

Dexprofeno *Richmond, Arg.*
Dextropropoxyphene (p.40·1); ibuprofen lysine (p.64·2).
Fever; pain.

Dexsal
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Austral.
Oral granules: Sodium citrotartrate (p.1674·2); tartaric acid (p.2395·2); glucose (p.1945·3); sodium bicarbonate (p.1673·2).
Dyspepsia.

Reckitt Benckiser, Austral.
Oral liquid: Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Dyspepsia; flatulence.

Dexsin *Christo, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Dexsol *Rosemont, UK.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexsul *Parggon, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Dextafen *Otto, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Dextamine
Note. This name is used for preparations of different composition.
Cifarma, Braz.
⊗ Dexchlorpheniramine maleate (p.572·1); betamethasone (p.1518·2).
Hypersensitivity reactions.

Phapros, Indon.
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Dextasona *Blausiegel, Braz.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexthasol *Olan-Kemed, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dexton *TP, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dextone *Tocogino, Mex.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Infected eye disorders.

Dextonil *Plusandex, Venez.*
Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3).
Cough.

Dextracin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia; Xepa-Soul Pattinson, Singapore.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Dextral *Molex Ayus, Indon.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Dextramet *Hua, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dextramine *Camden, Singapore.*
Dexchlorpheniramine maleate (p.572·1).
Allergic rhinitis; allergic skin disorders; insect bites.

Dextrarine Phenylbutazone *Sanofi-Aventis, Fr.*
Dextran sulfate (p.2293·1); phenylbutazone (p.117·1).
Tendinitis.

Dextrevit *Valeant, Mex.*
Vitamin B substances; vitamin C; glucose (p.1922·1).
Neuritis; vitamin deficiencies.

Dextricea *Durban, Spain.*
Rice; gelatin tannate (p.2394·3); pectin (p.2145·2); wheat germ.
Diarrhoea.

Dextrifer *Intermed, Gr.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Dextrifer-Fol *Intermed, Gr.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias.

Dextro *Osoth, Thai.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Coughs.

Dextro BS *Osoth, Thai.*
Dextromethorphan (p.1555·2); terpin hydrate (p.1573·3); chlorphenamine maleate (p.571·3).
Coughs.

Dextro + Dipirona *Richmond, Arg.*
Dextropropoxyphene (p.40·1); dipyrone (p.49·2).
Fever; pain.

Dextro GG *Jean-Marie, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Dextro OG-T *Roche, Ger.*
Mono- and oligosaccharide mixture.
Glucose tolerance test.

Dextro Plus *Jean-Marie, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Dextrocilla *Europharm, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); cocillana (p.1554·3); senega (p.1572·3); squill (p.1573·1).
Cough.

Dextrodip *Drawer, Arg.*
Dextropropoxyphene (p.40·1); dipyrone (p.49·2).
Pain.

Dextrodyl *CCM, Malaysia.*
Dextromethorphan hydrobromide (p.1555·2); promethazine hydrochloride (p.588·2).
Coughs.

Dextrolyte *Unipharma, Gr.; Tablets, India.*
Sodium chloride; potassium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dextrolyte-E *Tablets, India.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte imbalance.

Dextrolyte-G *Tablets, India.*
Electrolyte infusion (p.1667·1).
Forced diuresis; loss of gastric juice; mild alkalosis.

Dextrolyte-M *Tablets, India.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte imbalance; metabolic acidosis.

Dextrolyte-P *Tablets, India.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte imbalance; mild acidosis.

Dextrome *Christo, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dextromethorphan Compound *Pharmaniaga, Malaysia.*
Dextromethorphan hydrobromide (p.1555·2); promethazine hydrochloride (p.588·2).
Formerly known as Metofen Compound.
Coughs.

Dextromine *General Drugs, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Dextropirac *Montpellier, Arg.†.*
Dexibuprofen (p.39·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Dextroral *General Drugs, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dextroref *Chemical, Fr.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Dextro-Sal *Behrens, Venez.†.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Dextrosin
Note. This name is used for preparations of different composition.
Otto, Indon.
Syrup: Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Otto, Indon.
Tablets: Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Dextrosone *Quality, Hong Kong.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions; inflammatory eye disorders.

Dextrostat *Shire Richwood, USA.*
⊗ Dexamfetamine sulfate (p.2153·1).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Dextrostix *Bayer, Arg.; Bayer Diagnostics, Mex.*
Test for glucose in blood (p.2314·1).

Dextrotos *Lafedar, Arg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dextrovitase *Ache, Braz.†.*
Vitamin B substances; ascorbic acid; glucose (p.1922·1).
Nutritional supplement.

Dex-Tuss CV *Cypress, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cough.

Dex-Tuss DM *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Dexyclav *Dexa, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Dexycol *Dexa, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Dexylin *General Drugs, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Dexymox *Dexa, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Dezabil *Alpharma, Mex.*
Albendazole (p.139·2).
Worm infections.

Dezacor *Faes, Spain.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dezartal *Andromaco, Chile.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Dezcard *Siam Bheasach, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dezepan *Klonal, Arg.*
Diazepam (p.986·3).
Anxiety.

Dezor *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections; seborrhoeic dermatitis.

Dezoral *Hoe, Singapore†.*
Ketoconazole (p.539·1).
Fungal skin infections; seborrhoeic dermatitis.

Dezorol *Profarm, Pol.*
Methenamine (p.298·3); menthol (p.2340·1); salicylic acid (p.1612·2).
Hyperhidrosis of the feet.

DF 118 *GSK, Hong Kong; Galen, Irl.; GSK, Malaysia; Aspen, S.Afr.; Martindale Pharmaceuticals, UK.*
Dihydrocodeine tartrate (p.48·1).
. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Pain.

DF Expectorant NP *APT, Hong Kong.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

DF Multi-Symptom *APT, Hong Kong.*
Paracetamol (p.108·1); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); bromhexine hydrochloride (p.1552·2); salicylamide (p.121·2); caffeine (p.1116·3).
Upper respiratory-tract disorders.

DF Night Time *APT, Hong Kong.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

D-Feda II *WE, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

D-Flor *Berko, Turk.*
Sodium fluoride (p.1962·2); colecalciferol (p.1986·2).

D-Fluoretten *Aventis, Ger.*
Colecalciferol (p.1986·2); sodium fluoride (p.1962·2).
Dental caries prophylaxis; rickets prophylaxis.

DFN *Bajer, Arg.*
Diclofenac diethylamine (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

DG-6 *Craveri, Arg.*
Lapirium chloride.
Burns; skin infections; skin, surface, and equipment disinfection.

DG-6 Iodopovidona *Craveri, Arg.†.*
Povidone-iodine (p.1659·2).
Instrument disinfection; skin infections; wounds.

D-Gam *BPL, UK.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

D-Germ *Biocide, S.Afr.*
Chlorhexidine gluconate (p.1635·3).
Hand disinfection.

DHA *Baldacci, Ital.*
Omega-3 fish oil (p.1362·2); sunflower oil (p.1970·3).
Nutritional supplement.

Dhabesol *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dhacillin *DHA, Hong Kong†; DHA, Singapore.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Dhacodine *DHA, Malaysia.*
Pholcodine (p.1570·2).
Coughs.

Dhacold *DHA, Singapore†.*
Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Dhacopan *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Dhacort *DHA, Hong Kong; DHA, Malaysia†; DHA, Singapore.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dhactulose *DHA, Malaysia; DHA, Singapore.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Dhalgesic *DHA, Hong Kong; DHA, Singapore.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal, joint, and soft-tissue disorders.

Dhalumag *DHA, Malaysia; DHA, Singapore†.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Gastric hyperacidity; peptic ulcer.

Dhamol *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Dhamotil *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Dhaperazine *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Prochlorperazine maleate (p.1020·1).
Emotional and mental disturbances; Ménière's disease; migraine; nausea and vomiting.

Dhasedyl *DHA, Hong Kong; DHA, Singapore.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); promethazine hydrochloride (p.588·2).
Coughs.

Dhasedyl DM *DHA, Malaysia; DHA, Singapore.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); promethazine hydrochloride (p.588·2).
Cough; nasal congestion.

Dhasolone *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Dhatalin *DHA, Hong Kong.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma; bronchitis.

Dhatifen
DHA, Hong Kong.
Ketotifen fumarate (p.582·2).
Asthma; conjunctivitis; rhinitis.

DHA, Malaysia; DHA, Singapore.
Ketotifen (p.582·2).
Asthma; hypersensitivity reactions.

Dhatracin *DHA, Malaysia.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Dhatrin *DHA, Hong Kong; DHA, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections.

DHC *Mundipharma, Ger.; Extractum, Hung.; Mundipharma, Hung.*
Dihydrocodeine tartrate (p.48·1).
Pain.

DHC Continus *Mundipharma, Cz.; Napp, Irl.; Pharmaco, NZ; Norpharma, Pol.; Napp, UK.*
Dihydrocodeine tartrate (p.48·1).
Pain.

DHC Plus *Purdue Frederick, USA.*
Dihydrocodeine tartrate (p.48·1); paracetamol (p.108·1); caffeine (p.1116·3).

DHE *Ratiopharm, Austria; Ratiopharm, Ger.; Xcel, USA.*
Dihydroergotamine mesilate (p.618·2).
Cluster headache; hypotension; migraine and other vascular headaches; venous insufficiency.

DHS Sal *Dispolab, Chile.*
Salicylic acid (p.1612·2).
Dandruff.

DHS Tar *Person & Covey, USA.*
Coal tar (p.1616·2).
Scalp disorders; seborrhoea.

DHS Tar Gel *Dispolab, Chile.*
Coal tar (p.1616·2).
Psoriasis.

DHS Zinc *Dispolab, Chile; Person & Covey, USA.*
Pyrithione zinc (p.1611·2).
Scalp disorders; seborrhoeic dermatitis.

DHT *Roxane, USA.*
Dihydrotachysterol (p.1986·3).
Hypoparathyroidism; postoperative and idiopathic tetany.

Di Anatoxal *Pharmabroker, NZ.*
An adsorbed diphtheria vaccine (p.2209·3).
Active immunisation.

Di Dolko *Therabel, Fr.*
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Pain.

Di Retard *Llorens, Spain.*
Diclofenac sodium (p.44·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders; pain; renal colic.

Di Te Anatoxal *Berna, Malaysia†; Berna, Philipp.; Berna, Singapore†; Berna, Thai.†; Berna, Turk.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Di Te Per Anatoxal *Berna, Turk.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DI VP *Pharmavita, Chile.*
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; migraine.

Dia-Aktivanad-N *Rentschler, Ger.*
Bovine liver extract; yeast extract; caffeine (p.1922·1).
Tonic.

Diab Dos *Omedir, Arg.*
Metformin (p.453·3).
Diabetes mellitus.

DiaB Gel *Carrington, USA.*
Acemannan (p.2244·2).
Diabetic ulcers.

Diabact *Orexo, Denm.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Test for Helicobacter pylori infection.

Diabact UBT *Kibion, Swed.; Medical Diagnostics, UK.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Test for Helicobacter pylori infection.

Diabamyl *Expanpharm, Fr.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaban *Pascual, Philipp.*
Lagerstroemia speciosa.
Nutritional supplement for diabetics.

Diabe Pass *Omedir, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabecontrol *Sanval, Braz.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Diabeedol *Sriprasit, Thai.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Diabefar *Elpen (Ελπεν), Gr.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabemet *YSP, Malaysia†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabemide *Guidotti, Ital.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Diabemin *Lafedar, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diaben
Note. This name is used for preparations of different composition.
Elea, Arg.
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Kinder, Braz.
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabene *Lehning, Fr.*
Homoeopathic preparation.

Diabenol *Greater Pharma, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabenor *IFI, Ital†.*
Glisolamide (p.442·2).
Diabetes mellitus.

Diabenyl T *Chauvin ankerpharm, Ger.†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Diabenyl-Rhinex *Wernigerode, Ger.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Allergic rhinitis.

Diaberet *Visufarma, Ital.*
Vitamin E; Oligopin; ubidecarenone (p.1922·1).
Nutritional supplement.

Diabeside *Chew, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabesin *TAD, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabesor *Soria Natural, Spain†.*
Centaurea aspera; eucalyptus (p.2301·2); phaseolus vulgaris; sage (p.2382·3); lappa (p.2330·3).
Diabetes mellitus.

Diabest *Promed, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabestat *Andromaco, Chile†.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

DiaBeta *Aventis, Canad.; Hoechst Marion Roussel, USA.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabetamide *Ashbourne, UK†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabetan *Leros, Cz.*
Phaseolus; myrtillus (p.2349·3); sage (p.2382·3); galega; polygonum avicularis; taraxacum (p.2395·1); raspberry leaf (p.2378·2); fennel (p.2302·3); lappa (p.2330·3); liquorice (p.1740·3).
Adjuvant in diabetes mellitus.

Diabetan S *Schuck, Ger.†.*
Homoeopathic preparation.

Diabetase *Azupharma, Ger.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabetasol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition (p.1922·1).
Diabetes mellitus.

Diabetex *Germania, Austria.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabetic Tussin *Roberts, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine (p.1568·1).
Coughs.

Diabetic Tussin DM *Roberts, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Diabeticka Cajova Smes-Megadiabetin *Megafyt-R, Cz.*
Galega; phaseolus; myrtillus (p.2349·3); urtica (p.2409·3); sage (p.2382·3); taraxacum (p.2395·1).
Diabetes mellitus.

Diabetiks *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; bioflavonoids; myrtillus; ginkgo biloba; green tea; pine bark; acetylcysteine; taurine; ubidecarenone; lipoic acid (p.1922·1).
Tonic.

Diabetisource com Nutrishield *Novartis, Braz.*
Preparation for enteral nutrition (p.1922·1).

Diabetmin *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Singapore.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabetofort *Leki Natury, Pol.*
Phaseolus; birch leaf (p.2266·3); couch-grass (p.2288·2); blackberry leaf; rose fruit (p.2381·2).
Diabetes mellitus.

Diabetol *Polpharma, Pol.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Diabeton *Servier, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabetosol *Herbapol Krakow, Pol.*
Galega officinalis; phaseolus vulgaris; taraxacum (p.2395·1); couch-grass (p.2288·2); cranberry leaf (p.2289·1).
Diabetes mellitus.

Diabetty's *Neckerman, Braz.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabe-Tuss DM *Paddock, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Diabetussic *Hasco-Lek, Pol.*
Sulfogaiacol (p.1573·2).
Catarrh.

Diabex *Alphapharm, Austral.; Combiphar, Indon.; Merck, Neth.; Merck, Port.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabexil *Arrow, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diabezidum *Jelfa, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabiclor *Mavi, Mex.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Diabiformine *Pfizer, Switz.*
Chlorpropamide (p.438·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diabinax *Shreya, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabinese *Pfizer, Arg.; Pfizer, Belg.†; Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Israel†; Pfizer, Malaysia†; Pfizer, Mex.; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore†; Farmasierra, Spain; Pfizer, Thai.; Pfizer, Turk.; Pfizer, USA.*
Chlorpropamide (p.438·3).
Diabetes insipidus; diabetes mellitus.

Diabion
Note. This name is used for preparations of different composition.
Merck, Chile; Merck, Mex.
Vitamin and mineral preparation (p.1922·1).

Metiska, Indon.
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; vitamin B ; vitamin C; folic acid (p.1922·1).
Anaemias; nutritional supplement.

Diabitex *Rekah, Israel.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Diabitor *Unison, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diaborale *Pharmacia, Ital.*
Glycyclamide (p.442·3).
Diabetes mellitus.

Diabrezide *Molteni, Cz.†; Helsinn Birex, Irl.; Molteni, Ital.; Molteni, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diabur-5000 *Roche Diagnostics, NZ.*
Test for glucose in urine (p.2314·1).

Diabur-Test 5000 *Roche, Arg.†; Roche Diagnostics, Austral.; Roche Diagnostics, Irl.; Roche Diagnostics, Ital.; Roche Diagnostics, Mex.; Roche Diagnostics, UK.*
Test for glucose in urine (p.2314·1).

Diacarb *Polpharma, Rus.*
⊗ Acetazolamide (p.1875·1).
Altitude sickness; epilepsy; glaucoma; intracranial hypertension; oedema.

Diacard *Madaus, Ger.*
Homoeopathic preparation.

Diacardin *Pliva, Ital.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diacardyne *Ethypharm, Port.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Diacare *Be-Tabs, S.Afr.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diacepam *Silanes, Mex.†.*
Diazepam (p.986·3).
Anxiety; sedative.

Diacer *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Diaceril *Alvia (Αλβια), Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Diaclaron *Siam Bheasach, Thai.†.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diaclid *Integrated Pharmaceutical, Philipp.; Swiss Pharma, Philipp.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diaclide *Gerard, Irl.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diacneal *Pierre Fabre, Arg.; Silesia, Chile; Medifarm Avene, Venez.*
Retinaldehyde (p.1612·2); glycolic acid (p.1598·1); thermal water.
Acne.

Diaco *Mediherb, Austral.*
Achillea (p.2245·2); echinacea (p.2298·1); liquorice (p.1740·3); sambucus (p.2383·1); tilia (p.2402·2); ginger (p.1732·3).
Cold and influenza symptoms.

Diacol *Bial, Port.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dia-Colon *Piam, Ital.*
Lactulose (p.1738·2).
Constipation.

Diacomit *Biocodex, Cz.; Biocodex, Fr.; Biocodex, Port.*
Stiripentol (p.504·2).
Epilepsy.

Diacor
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Mebendazole (p.148·3).
Worm infections.

Dexo, Fr.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diacordin *Zentiva, Cz.; Zentiva, Pol.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diacron *Tempo Scan Pacific, Malaysia†.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diactal *Neuropharma, Arg.*
Diazepam (p.986·3).

Di-Actane *Menarini, Fr.*
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders; mental function impairment in the elderly.

Diactin *Beximco, Singapore.*
Glipizide (p.441·3).
Diabetes mellitus.

Diacure
Note. This name is used for preparations of different composition.
Lehning, Fr.
Taraxacum (p.2395·1); berberis; juglans; millefolium; myrtillus (p.2349·3); centaury (p.2279·1); natrum phosphoricum.
Metabolic disorders.

McNeil, Neth.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diadef *Sanli, Turk.*
Loperamide (p.1741·3).
Diarrhoea.

Diadermina *Plata, Arg.*
Ammonium stearate.

Diadex *Polinac, Venez.*
Dexpanthenol (p.2362·1); menthol (p.2340·1); camphor (p.2273·2).
Pruritus; skin irritation.

Diadex Phis *Polinac, Venez.*
Soap substitute.

Diadicon *Labomed, Chile.*
Bromhexine hydrochloride (p.1552·2); clofedanol hydrochloride (p.1554·2).
Coughs; respiratory-tract congestion.

Diadium *Lapi, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Di-Adreson-F
Organon, Fin.; Organon, Hung.; Organon, Neth.
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Organon, Hong Kong; Organon, Thai.
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Diadupsan *BMS, Fr.†.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Dia-Eptal *Montavit, Austria.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diafat *Sandoz, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diafit *Ikapharmindo, Indon.*
Preparation for enteral nutrition (p.1922·1).
Diabetes mellitus.

Diaforin *Ferrer, Spain.*
Risperidone (p.1024·2).
Behaviour disorders in children; bipolar disorder; psychoses.

Diaformin *Alphapharm, Austral.; Uniao Quimica, Braz.; Alphapharm, Hong Kong.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaformina *Roemmers, Venez.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaformina Plus *Roemmers, Venez.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Diaforte *Cipla, India.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diafuran
Note. This name is used for preparations of different composition.
Cazi, Braz.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Kramer, Philipp.
Furazolidone (p.834·3).
Gastrointestinal infections.

Diafuryl *Cooper, Fr.; Abdi, Turk.*
Nifuroxazide (p.307·2).
Diarrhoea; gastro-enteritis.

Diafusor *Schering-Plough, Belg.; Pierre Fabre, Fr.; Pierre Fabre, Port.; Gervasi, Spain; Pierre Fabre, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Diagesic *Biotech, Venez.*
Diclofenac potassium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Diagit *Interbat, Indon.*
Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Diaglim *Biochem, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Diaglip *Cipla, India.*
Glipizide (p.441·3).
Diabetes mellitus.

Diaglip M *Cipla, India.*
Glipizide (p.441·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaglit *Biochem, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Diaglitab *Biopharm, Chile.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaglitab Plus *Biopharm, Chile.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Diaglucide *Biogaran, S.Afr.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diaglyk *Ashbourne, UK.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diagnosis *Rottapharm, Ital.*
Pregnancy test (p.2372·1).

Diagran *Teofarma, Ital.*
Multivitamin preparation (p.1922·1).

Diagran Minerale *Teofarma, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Diagrin *Makros, Braz.†.*
Metoclopramide hydrochloride (p.1747·3); vitamin B (p.1978·2).
Nausea and vomiting.

Diahalt *Wampole, Canad.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diah-Limit *Wallis, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dial *Dial, Canad.†.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Dial Complete *Dial, Canad.*
Triclosan (p.1665·2).
Hand disinfection.

Dialac *Kalbe, Indon.*
Lactobacillus acidophilus (p.2372·3); ascorbic acid; calcium; nicotinamide; zinc oxide; thiamine hydrochloride; riboflavin; pyridoxine hydrochloride (p.1922·1).
Gastrointestinal disorders.

Dialacid *Collins, Mex.†.*
Loperamide (p.1741·3).
Diarrhoea.

Dialamine *Scientific Hospital Supplies, Austral.; SHS, Fr.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, Israel; Nutricia, NZ†; Scientific Hospital Supplies, NZ†; Scientific Hospital Supplies, UK.*
Preparation for enteral nutrition (p.1922·1).
Enteral nutrition; urea cycle disorders.

Dialar *Sandoz, UK.*
Diazepam (p.986·3).

Dialeli AF *Valdecasas, Mex.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3).
Iron-deficiency anaemia; prevention of neural tube defects.

Dialens
Note. This name is used for preparations of different composition.
Bausch & Lomb, Port.
Chlorhexidine gluconate (p.1635·3).
Contact lens care; tear deficiency.

Bausch & Lomb, Switz.
⊗ Dextran 70 (p.1059·3).
Dry eyes; wetting agent for contact lenses.

Dialgin *Collins, Mex.*
Diiodohydroxyquinoline (p.832·1); furazolidone (p.834·3); homatropine (p.1881·2).
Amoebiasis; diarrhoea.

Dialgine *Intermedica, Switz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Dialgine forte *Intermedica, Switz.†.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Dialgirex *Sanofi-Aventis, Fr.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Dialine *Teva, Israel.*
Glucose; sodium chloride; sodium lactate; calcium chloride; magnesium chloride (p.1670·3).
Peritoneal dialysis.

Dialisis Perit *Bieffe, Spain.*
Electrolytes; glucose monohydrate (p.1670·3).
Peritoneal dialysis.

Dialitica II *Argenfarma, Arg.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).

Diallertest *DBV, Fr.*
Patch test for cow's milk protein allergy (p.2250·2).

Dial-ND *Neo Dermos, Arg.*
Cystine; cysteine; methionine; vitamin F (p.1922·1).

Dialon
Note. This name is used for preparations of different composition.
Eisai, Indon.
Indometacin farnesil (p.68·1).
Musculoskeletal and joint disorders.

Julphar, UAE.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Dialon-T *Alet, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Dialope *Copyfarm, Denm.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dialosa *Specifar, Gr.; Valeant, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Dialster *Esoform, Ital.*
Troclosene sodium (p.1665·3).
Disinfection of surfaces, water, food, and feeding bottles.

Dialudon *Sigma, Braz.*
Phenytoin (p.495·2); diazepam (p.986·3).
Epilepsy.

Dialume *Rhone-Poulenc Rorer, USA.*
Aluminium hydroxide (p.1706·2).
Hyperacidity.

Dialuna *Genericon, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms.

Dialvit *Bichsel, Switz.*
Multivitamin preparation (p.1922·1).
Dietary supplement in renal failure.

Dialycal *DHN, Fr.†.*
Preparation for enteral nutrition (p.1922·1).

Dialycare *Abbott, Ital.*
Preparation for enteral nutrition (p.1922·1).
Renal dialysis.

Dialytan H *Aguettant, Fr.†.*
Haemodialysis solution (p.1670·3).

Dialyte *GHP, Thai.†; Gambro, USA.*
Glucose; electrolytes (p.1670·3).
Peritoneal dialysis solution.

Dialyvite *Hillestad, USA.*
Vitamin and mineral preparations (p.1922·1).

Diamaze *Macrophar, Thai.†.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diameb *Precimex, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Diamel *SM, Venez.*
Fumaric acid; wild lettuce; ascorbic acid; amino acids; zinc sulfate; vitamin B substances; cranberry (p.1922·1).
Nutritional supplement in diabetes mellitus.

Diamellitis *Cifarma, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Diameprid *Mecom, Turk.*
Glimepiride (p.441·1).
Diabetes mellitus.

Diamet *Weifa, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diamexon *TO-Chemicals, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diamicron *Servier, Arg.; Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, Canad.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Irl.; Servier, Ital.; Servier, Malaysia; Servier, Mex.; Servier, NZ; Servier, Neth.; Servier, Philipp.; Servier, Port.; Servier, S.Afr.; Servier, Singapore; Servier, Spain; Servier, Switz.; Servier, Thai.; Servier, Turk.; Servier, UK; Servier, Venez.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diamide *Pacific, NZ; Filadams, Philipp.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Diamig *Micro, India.*
Miglitol (p.454·3).
Diabetes mellitus.

Diamin
Note. This name is used for preparations of different composition.
Grossman, Mex.
α-Dihydroergocryptine mesilate (p.364·2).
Hyperprolactinaemia.

Malaysia Chemist, Singapore†.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaminocillina *Fournier, Ital.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Diamitex *Duopharma, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diamoril *Chiesi, Fr.†.*
Benzquercin (p.2304·1).
Peripheral vascular disorders.

Diamox
Wyeth, Arg.; Sigma, Austral.; Genom, Braz.; Wyeth, Canad.; Goldshield, Denm.†; IFET (ΙΦΕΤ), Gr.; Wyeth, Hong Kong; Wyeth, India; Lederle, Indon.; Lederle, Israel†; Teofarma, Ital.; Wyeth, Mex.†; Goldshield, Norw.; Wyeth, Philipp.; Pharmafrica, S.Afr.; Wyeth-Ayerst, Thai.; Barr, USA; Wyeth, Venez.†.
⊗ Acetazolamide (p.1875·1).
Absence seizures; acute mountain sickness; epilepsy; glaucoma; heart failure; oedema; premenstrual syndrome.

Wyeth Lederle, Austria; PSI, Belg.; Goldshield, Fin.; Sanofi-Aventis, Fr.; Goldshield, Ger.; Goldshield, Irl.; Healthcare Logistics, NZ; Goldshield, Neth.; Goldshield, Swed.†; Vifor, Switz.; Goldshield, UK.
⊗ Acetazolamide (p.1875·1) or acetazolamide sodium (p.1875·1).
Epilepsy; glaucoma; heart failure; hypercapnia; Ménière's disease; mountain sickness; ocular hypertension; oedema; pancreatic disorders; premenstrual syndrome; raised intra-ocular pressure; respiratory insufficiency.

Diamplicil *Pharmacia, Ital.†.*
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Diamprex *Liferpal, Mex.*
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Dianben *BOI, Spain.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diane *Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Berlex, Canad.; Schering, Chile; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Hong Kong; Schering, Hung.; German Remedies, India; Schering, Indon.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Berlifarma, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Schering, Venez.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms; polycystic ovary syndrome.

Dianeal *Baxter, Austral.; Baxter, Austria; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Hung.; Baxter, Indon.; Baxter, Israel; Baxter, Neth.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Venez.*
Glucose; sodium chloride; sodium lactate; magnesium chloride; calcium chloride (p.1670·3).
A range of solutions for peritoneal dialysis.

Dianette *Schering, Irl.; Schering, UK.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).

These ingredients can be described by the British Approved Name Co-cyprindiol.
Acne and hirsutism in females; oral contraceptive in women with severe acne.

Dianicotyl *IFET (ΙΦΕΤ), Gr.*
Isoniazid (p.288·1).
Tuberculosis.

Dianid *Biolab, Malaysia; Biolab, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diano *Milano, Thai.*
Diazepam (p.986·3).
Anxiety; autonomic disorders; insomnia; psychoneurotic disorders; skeletal muscle spasm.

Dianoct *Silesia, Chile.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Dianorm
Note. This name is used for preparations of different composition.
Eurodrug, Hong Kong; Merck, Philipp.; Eurodrug, Singapore.
Gliclazide (p.440·3).
Diabetes mellitus.

Tiefenbacher, Neth.†.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Kocak, Turk.
Glibenclamide (p.440·1).
Diabetes mellitus.

Dianormax *Grunenthal, Chile.*
Gliclazide (p.440·3).
Diabetes mellitus.

Dianova *Alternova, Denm.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea; oral contraceptive in women with androgenic symptoms.

Di-Antalvic *Sanofi-Aventis, Fr.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Diapam
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Chlormezanone (p.968·3); diazepam (p.986·3).
Anxiety; musculoskeletal spasm; sleep disorders.

Orion, Fin.; Greater Pharma, Thai.; Biosel, Turk.
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; autonomic disorders; febrile convulsions; insomnia; pain; premedication; psychoneurotic disorders; skeletal muscle spasm; status epilepticus.

Diapanil *Randall, Mex.†.*
Diazepam (p.986·3).
Anxiety.

Dia-Par Compuesto *Streger, Mex.*
Nifuroxazide (p.307·2); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Diaparene Corn Starch *Personal Care, USA.*
Corn starch (p.1968·1); aloes (p.1705·2).
Nappy rash.

Diaparene Diaper Rash *Personal Care, USA.*
Zinc oxide (p.1621·2).
Nappy rash.

Diapatol *Teofarma, Ital.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide hydrochloride (p.968·2).
Anxiety disorders; depression; insomnia.

Diapectolin *Medi-Rx, Philipp.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Diaper Guard *Del, USA.*
Dimeticone (p.2032·1); white soft paraffin (p.2031·2); vitamin A (p.1971·2); vitamin D (p.1986·1); vitamin E (p.1992·2).
Nappy rash.

Diaper Rash *Goldline, USA; Rugby, USA.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Nappy rash.

Diaperol *Diba, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diaperyl *Medi-Rx, Philipp.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Diapet *Soho, Indon.*
Coix lacrima-jobi semen; psidium guajava; phellodendri radix; turmeric (p.1473·2); rhizoma coptidis.
Diarrhoea.

Diaphage *SVUS, Cz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diaphal *Pierre Fabre, Ger.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Ascites; hypertension; oedema.

Diaphin *Diamo, Switz.*
⊗ Diamorphine hydrochloride (p.42·1).
Opioid dependence.

Diaphyllin *Extractum, Hung.; Gedeon Richter, Hung.*
Aminophylline (p.1114·2).
Asthma; cardiac disorders.

Diapine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; skeletal muscle spasm.

Diapiride *OM, Port.*
Glimepiride (p.441·1).
Diabetes mellitus.

Diapo *CCM, Malaysia; Beacons, Singapore.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; skeletal muscle spasm.

Diaprel *Servier, Cz.; Servier, Hung.; Anpharm, Pol.; Servier, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diapresan *Bago, Chile.*
Trazodone hydrochloride (p.424·3).
Depression.

Diapride *Arrow, Austral.; Eurodrug, Hong Kong; Eurodrug, Malaysia; Eurodrug, Singapore.*
Glimepiride (p.441·1).
Diabetes mellitus.

Diaquitte *Peach, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diaralia *Boiron, Fr.*
Homoeopathic preparation.

Diarcalm *McGloin, Austral.*
Light kaolin (p.1738·1); pectin (p.2145·2); catechu (p.2278·2); aluminium hydroxide (p.1706·2).
Diarrhoea; stomach pain.

Diarem *Pharmachemie, Neth.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diaren *Saval, Chile.*
Nifuroxazide (p.307·2); activated attapulgite (p.1709·1).
Diarrhoea.

Diarent *Chew, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diaretyl *Cooperation Pharmaceutique, Fr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diareze
Note. This name is used for preparations of different composition.
Boots, UK.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Key, Austral.
Oral suspension: Attapulgite (p.1709·1); pectin (p.2145·2); simeticone (p.1770·2).
Diarrhoea.

Key, Austral.
Tablets: Attapulgite (p.1709·1); pectin (p.2145·2); aluminium hydroxide (p.1706·2).
Diarrhoea.

Diarfin
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile†.
Oral suspension: Nifuroxazide (p.307·2).
Gastrointestinal infections.

Laboratorios Chile, Chile†.
Tablets: Nifuroxazide (p.307·2); activated attapulgite (p.1709·1).
Diarrhoea.

Diargal *bsa, Fr.*
Infant feed (p.1922·1).
Diarrhoea.

Diarigoz *Guigoz, Fr.*
Infant feed (p.1922·1).
Diarrhoea.

Diaril
Note. This name is used for preparations of different composition.
MC, Ital.†.
Glutaral (p.1645·2); phenol (p.1656·1); orthophenylphenol (p.1655·1).
Instrument disinfection.

Biofarm, Pol.
Glimepiride (p.441·1).
Diabetes mellitus.

Diarim *Rimsa, Mex.†.*
Nifuroxazide (p.307·2).

Diaris *Poen, Arg.*
Vitamin and mineral preparation (p.1922·1).

Diarlac *Urgo, Fr.†.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea.

Diarlop
Note. This name is used for preparations of different composition.
Jagson, India.
Capsules: Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Jagson, India.
Oral suspension: Nalidixic acid (p.303·3).
Diarrhoea.

Diarman *Berman, Mex.*
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Diarodil *Greater Pharma, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diarona *Vincenti, Venez.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Diaront mono *Rosen, Ger.*
Colistin sulfate (p.256·2).
Selective gastrointestinal tract decontamination.

Diarresec *Farmion, Braz.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diarrest RF *Galen, Irl.*
Loperamide hydrochloride (p.1741·1); potassium chloride; sodium chloride; sodium citrate.
Diarrhoea.

Diarret *Geymonat, Ital.†.*
Nifuroxazide (p.307·2).
Acute infective diarrhoea.

Diarrex *Hylands, Canad.*
Homoeopathic preparation.

Diarr-Eze *Pharmascience, Canad.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diarrhea Relief
Note. A similar name is used for preparations of different composition (see below).
Homeocan, Canad.
Homoeopathic preparation.

Diarrhoea Relief
Note. A similar name is used for preparations of different composition (see above).
Pharmascience, Canad.; Vita Health, Canad.
Loperamide hydrochloride (p.1741·1).

Diarrhoea Relief Tablets *Brauer, Austral.†.*
Homoeopathic preparation.

Diarrhoesan *Vitasan, Austria; Loges, Ger.*
Pectin (p.2145·2); chamomile extract (p.2279·3).
Diarrhoea.

Diarrocalmol *Benitol, Arg.*
Phthalylsulfathiazole (p.315·1); activated charcoal (p.1435·2).
Diarrhoea.

DiarrStope *Age D'or, Singapore.*
Lactobacillus acidophilus (p.2372·3).
Gastrointestinal disorders.

Diarsed *Sanofi-Aventis, Fr.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Diarstop *Giuliani, Ital.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diarzero *Unifarm, Ital.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diascan *Home Diagnostics, USA.*
Test for glucose in blood (p.2314·1).

Diascreen 3 *Marco, Austral.†.*
Test for glucose, protein, and pH in urine.

Diascreen 5 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, and blood in urine.

Diascreen 6 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, blood, and bilirubin in urine.

Diascreen 7 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, blood, bilirubin, and urobilinogen in urine.

Diascreen 8 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, blood, bilirubin, urobilinogen, and nitrite in urine.

Diascreen 9 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, blood, bilirubin, urobilinogen, nitrite, and leucocytes in urine.

Diascreen 10 *Marco, Austral.†.*
Test for glucose, protein, ketones, pH, blood, bilirubin, urobilinogen, nitrite, leucocytes, and specific gravity in urine.

Diascreen 40BL *Marco, Austral.†.*
Test for glucose, protein, blood, and leucocytes in urine.

Diascreen 2GK *Marco, Austral.†.*
Test for glucose and ketones in urine.

Diascreen Glucose *Marco, Austral.†.*
Test for glucose in urine (p.2314·1).
Formerly known as Diascreen 1G.

Diascreen 2GP *Marco, Austral.†.*
Test for glucose and protein in urine.

Diascreen 1K *Marco, Austral.†.*
Test for ketones in urine.

Diascreen 4NL *Marco, Austral.†.*
Test for glucose, protein, nitrite, and leucocytes in urine.

Diascreen 4PH *Marco, Austral.†.*
Test for glucose, protein, pH, and blood in urine.

Diasec *Hexal, Braz.†; Armoxindo, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diasectral *Aventis, Denm.; Sanofi-Aventis, Fin.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Diasef *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Diaseptyl *Pierre Fabre, Fr.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of superficial wounds; skin cleansing.

Diasgest *Siam Bheasach, Thai.*
Amylase (p.2256·3); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); aluminium magnesium silicate (p.2141·2); scopolia; vitamin B (p.1976·3).
Dyspepsia; gastric hyperacidity; gastritis; gastrointestinal motility disorders; heartburn.

Diasip *Nutricia-Bago, Arg.; Nutricia, Fin.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.*
Preparation for enteral nutrition (p.1922·1).
Diabetes mellitus.

Diasistol *Jaba Recordati, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Diason *Nutricia-Bago, Arg.; Nutricia, Fin.; Nutricia, Ital.; Nutricia, Pol.; Nutricia, Port.*
Preparation for enteral nutrition in diabetic patients (p.1922·1).
Impaired glucose tolerance.

Diasorane *Darier, Mex.*
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Diasorb *Columbia, USA.*
Activated attapulgite (p.1709·1).
The name Diasorb has also been used to describe a preparation containing loperamide.
Diarrhoea.

Diastabol *Sanofi Synthelabo, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Hung.; Sanofi Synthelabo, Mex.; Sanofi-Aventis, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Swed.†; Sanofi Synthelabo, Switz.*
Miglitol (p.454·3).
Diabetes mellitus.

Diastat *Shire, Canad.; Valeant, USA.*
Diazepam (p.986·3).
Convulsions; epilepsy.

Diastix *Bayer, Arg.; Bayer, Austral.; Bayer, Canad.; Bayer, India; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, Mex.; Bayer, NZ; Bayer Diagnostics, UK; Bayer, USA.*
Test for glucose in urine (p.2314·1).

Diastone *Microsules, Arg.*
Diclofenac sodium (p.44·3).
Fever; inflammation; pain.

Diastop *Pacific, NZ.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Diatabs Reformulated *Biomedis, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diatabs formerly contained attapulgite.
Diarrhoea.

Diatabs (Reformulated) *United Laboratories, Philipp.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Diatec *Neckerman, Braz.†.*
Meloxicam (p.80·3).

Diatelan *Reuffer, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Diatex *Medix, Mex.†.*
Diazepam (p.986·3).
Anxiety.

Diathynil *Sigma-Tau, Ital.*
Biotin (p.1931·3).
Biotin deficiency; digestive disorders; skin disorders.

Diatica *Unique, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diatin *Ferrer, Spain.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Diatol *Pacific, Hong Kong; Pacific, NZ.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Diatracin *Dista, Spain†.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Diatrim *Trima, Israel.*
Diacerein (p.41·3).
Osteoarthritis.

Diatrol *Sunward, Malaysia†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Diatussin *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); menthol (p.2340·1); ammonium chloride (p.1551·3); theophylline (p.1140·1).
Coughs.

Diatx *Pan American, USA.*
Vitamin B substances and vitamin C (p.1922·1).

Diatx Fe *Pan American, USA.*
Vitamin B substances; vitamin C; ferrous fumarate (p.1922·1).

Diaval *Valdecasas, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Diaxone *Europharma, Ital.*
Ceftriaxone sodium.

Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Diaz *Taro, Israel.*
Diazepam (p.986·3).
Anxiety; insomnia; skeletal muscle spasm.

Diazefast *Sigma, Braz.*
Diazepam (p.986·3).
Anxiety.

Diazem
Note. This name is used for preparations of different composition.
Medochemie, Rus.
Diltiazem hydrochloride (p.1265·1).

Deva, Turk.
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; muscle spasm; premedication; status epilepticus.

Diazemuls *Pfizer, Canad.; Alpharma, Hong Kong; Alpharma, Irl.; Teva, Ital.; CSL, NZ; Dumex, NZ; Alpharma, Neth.; Alpharma, UK.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; convulsions; epilepsy; premedication; sedative; skeletal muscle spasm; status epilepticus; tetanus; tetany.

Diazen *Korea United, Philipp.; Pharmatrix, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Diazep *ABZ, Ger.; CT, Ger.*
Diazepam (p.986·3).
Anxiety; premedication; skeletal muscle spasm; status epilepticus.

Diazepan *Brasmedica, Braz.†.*
Diazepam (p.986·3).
Anxiety.

Diazidan *ICN, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Diazol *EMS, Braz.*
Co-trimoxazole (p.258·1); calcium carbonate (p.1714·1); attapulgite (p.1709·1).
Diarrhoea.

Diazolen *Degorts, Mex.*
Mebendazole (p.148·3).
Worm infections.

Diazolin *Akrikhin, Rus.*
Mebhydrolin (p.584·3).

Diazomid *Sanofi Synthelabo, Turk.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma.

Diazon *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Diba *Manetti Roberts, Ital.*
Glutaral (p.1645·2).
Instrument disinfection; surface disinfection.

Dibacilina *Diba, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Dibact *Svizera, India†.*
Ceftriaxone (p.238·1); tazobactam (p.344·3).
Bacterial infections.

Dibapec Compuesto *Diba, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Dibaprim *Diba, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Dibase *Abiogen, Ital.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Dibasona *Diba, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Dibaterr *Diba, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Dibavytal *Diba, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Dibecon *Pharmasant, Thai.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Dibekan *Vargas, Venez.*
Dibekacin sulfate (p.265·2).
Bacterial infections.

Dibelet *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diben *Fresenius Kabi, Chile; Fresenius Kabi, Fin.; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Pol.*
Preparation for enteral nutrition (p.1922·1).
Diabetes mellitus; impaired glucose tolerance.

Dibendril
Note. This name is used for preparations of different composition.
Legrand, Braz.
Pastilles: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Formerly contained ampicillin benzathine and ampicillin sodium.
Coughs.

Legrand, Braz.
Syrup: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Dibendyl *Malaysia Chemist, Singapore†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs; respiratory-tract congestion; sneezing.

Dibendyl Forte CD *Malaysia Chemist, Singapore†.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; respiratory-tract congestion; sneezing.

Dibent *Hauck, USA.*
Dicycloverine hydrochloride (p.1722·3).
Functional bowel/irritable bowel syndrome.

Dibenyline *Link, Austral.; IFET (ΙΦΕΤ), Gr.; Goldshield, Hong Kong; Goldshield, Israel; Link, NZ; GSK, Neth.; SmithKline Beecham, S.Afr.; Forley, UK.*
Phenoxybenzamine hydrochloride (p.1369·3).
Acrocyanosis; benign prostatic hyperplasia; neurogenic bladder; phaeochromocytoma; Raynaud's syndrome; shock; urinary retention.

Dibenzyline *Wellspring, USA.*
Phenoxybenzamine hydrochloride (p.1369·3).
Phaeochromocytoma.

Dibenzyran *Procter & Gamble, Austria; Esparma, Ger.*
Phenoxybenzamine hydrochloride (p.1369·3).
Neurogenic bladder; phaeochromocytoma.

Dibertil *Sandipro, Belg.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal examination; nausea and vomiting.

Dibetam *Vitapan, Braz.†.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Dibetasol *Shin Poong, Malaysia; Shin Poong, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Dibetid *Arlex, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Dibetop *Davi, Port.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Dibetop Q *Davi, Port.†.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Dibicor *Pik, Rus.*
Taurine (p.2395·2).
Diabetes mellitus; glycoside intoxication; heart failure.

Dibional *Rivero, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Dibistic *Elvetium, Arg.†.*
Didanosine (p.870·2).
HIV infection.

Dibizide *Eurodrug, Malaysia†.*
Glipizide (p.441·3).
Diabetes mellitus.

Diblocin *AstraZeneca, Ger.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dibondrin *Montavit, Austria.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity disorders; prophylaxis against anaphylactic shock; sedative.

Dibose *Ranbaxy, Malaysia.*
Acarbose (p.436·2).
Diabetes mellitus.

Dibro-Be Mono *Dibropharm, Ger.*
Potassium bromide (p.2269·2).
Epilepsy.

Dibromol *Trommsdorff, Ger.*
Sodium 3,5-dibromo-4-hydroxybenzenesulphonate; bromchlorophen (p.1632·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Dibroxin *Tecnofarma, Mex.†.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Dibtrigen *Diba, Mex.*
Vitamin and mineral preparation (p.1922·1).

Dibufen *Diba, Mex.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Dibunafon *Royal, Chile.*
Sodium dibunate (p.1573·1).
Formerly contained sodium dibunate, chlorphenamine maleate, paracetamol, and sodium benzoate.
Coughs.

Dibutasona *Diba, Mex.*
⊗ Dexamethasone (p.1526·1); phenylbutazone (p.117·1).
Inflammation; rheumatism.

Dical
Note. This name is used for preparations of different composition.
Grunenthal, Mex.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement.

Abbott, USA.
Calcium with vitamin D and phosphorus (p.1922·1).
Calcium deficiency; dietary supplement.

Dicalcico *Etifar, Venez.†.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2); vitamin A (p.1971·2).
Calcium and vitamin supplement.

Di-Calci-Plex *Khandelwal, India.*
Multivitamin and mineral preparation with calcium (p.1922·1).
Calcium deficiency; vitamin deficiency.

Dicalcium *Abiogen, Ital.†.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); calcium carbonate (p.1714·1).
Vitamin or mineral deficiency.

Dical-D
Note. This name is used for preparations of different composition.
Abbott, Chile†.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; hypocalcaemia; osteomalacia; osteoporosis; rickets.

Abbott, Hong Kong.
Calcium with vitamin D and phosphorus (p.1922·1).
Dietary supplement.

Dicalm *Vita Health, Switz.†.*
Valerian (p.2410·1); lupulus (p.2335·2); ballota; passion flower (p.2363·2).
Nervous disorders; sleep disorders.

Dicalmir *Dicofarm, Ital.*
Fennel (p.2302·3); chamomile (p.2279·3); aniseed (p.2258·2); liquorice (p.1740·3); cumin; coriander (p.2288·1).
Colic; meteorism.

Dicalys 11 *Fresenius Medical, Swed.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration.

Dicalys 17 *Fresenius Medical, Swed.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate (p.1670·3).
Haemofiltration.

Dicap *Pacific, NZ.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dicasin *Medinova (Μεντινοβα), Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Dicel *Centrix, USA.*
Pseudoephedrine tannate (p.1572·1); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

Dicel DM *Centrix, USA.*
Dextromethorphan tannate (p.1556·1); chlorphenamine tannate (p.572·2); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Dicentril *Degorts, Mex.*
Aluminium (p.2254·1); magnesium (p.1678·3).
Gastric hyperacidity.

Dicetel *Raffo, Arg.; Solvay, Austria; Solvay, Belg.; Nycomed, Braz.; Solvay, Canad.; Solvay, Cz.; Solvay, Fr.; Solvay, Gr.; Solvay, Hung.; Solvay, Ital.; Altana, Mex.; Solvay, Port.; Solvay, Rus.; Solvay, Switz.; Solvay, Thai.; Frik, Turk.; Zuoz, Venez.*
Pinaverium bromide (p.2368·1).
Adjunct in gastrointestinal radiography; gastrointestinal and biliary-tract pain and spasm; gastrointestinal motility disorders; irritable bowel syndrome; smooth muscle spasm.

Dicfafena *IQFA, Mex.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal and joint disorders; pain.

Dichlotride *MSD, Austral.†; MSD, Denm.†; MSD, Malaysia†; MSD, Port.†; M & H, Thai.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema; premenstrual syndrome.

Diciclor *Spefar, Venez.†.*
Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Dicigel *Galeno, Venez.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Antacid; smooth muscle spasm.

Dicigon *Parggon, Mex.*
Dicycloverine (p.1723·1).
Smooth muscle spasm.

Dicil *Royal, Chile.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Dicillin *Sandoz, Denm.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Dicinone *Sanofi-Aventis, Braz.; Pensa, Spain.*
Etamsylate (p.1064·3).
Haemorrhage.

Dicitrate *Pharmascience, Canad.†; Pharmascience, Singapore.*
Sodium citrate dihydrate (p.1673·3); citric acid monohydrate (p.2284·1).
Acid aspiration; acidosis; gout; neutralising buffer; renal calculi; systemic alkaliniser.

Diclac
Investi, Arg.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Hexal, Austral.; Hexal, Austria; Hexal, Braz.†; Hexal, Ger.; Sandoz, Hung.; Rowex, Irl.; Sandoz, Mex.; Hexal, Pol.; Hexal, Rus.; Ecosol, Switz.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain.

Dicladox *Ivax, Arg.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Diclamina *Esteve, Spain.*
Cinnarizine (p.573·1); heptaminol acefyllinate (p.1123·2).
Vascular headache; vertigo.

Diclanil *Condrugs, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diclax *Douglas, NZ.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclaxol *Hexal, Austria.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclectin *Duchesnay, Canad.*
Doxylamine succinate (p.578·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting of pregnancy.

Diclen *Lamsa, Arg.*
Clonixin lysine (p.37·1).
Inflammation; pain.

Dicleophen *Sons, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Diclex *Meiji, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Diclo *1A, Ger.; ABZ, Ger.; Betapharm, Ger.; CT, Ger.; Carinopharm, Ger.; Kade, Ger.; Pinewood, Irl.; Camden, Singapore; Cophar, Switz.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclo P *Uniao Quimica, Braz.*
Diclofenac potassium (p.44·3).

Dicloabak *Thea, Port.*
Diclofenac sodium (p.44·3).
Inhibition of miosis during cataract surgery; prevention of inflammation and pain following ocular surgery.

Diclo-B *Lannacher, Austria.*
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Gout; musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis; pain.

diclo-basan *Sandoz, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; soft-tissue injuries.

Diclobene
Ratiopharm, Austria.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal and biliary colic.

Merckle, Rus.
Diclofenac sodium (p.44·3).

Dicloberl
Berlin-Chemie, Pol.
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Berlin-Chemie, Rus.
Diclofenac sodium (p.44·3).

Diclocil *BMS, Austral.; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, NZ; BMS, Norw.; BMS, Port.; BMS, Swed.; BMS, Thai.; BMS, Venez.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Diclocillin *TO-Chemicals, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Diclocular *Angelini, Ital.*
Diclofenac sodium (p.44·3).
Pain and inflammation of the eye.

Diclodan *Pharmacodane, Denm.*
Diclofenac (p.44·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclo-Denk *Denk, Hong Kong; Denk, Singapore†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Diclodent *GS, Port.*
Diclofenac (p.44·2).

Dicloderm Forte *Decrox, Spain.*
⊗ Dichlorisone acetate (p.1529·1).
Skin disorders.

Diclo-Divido *Alpharma-Isis, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Diclodoc *Docpharm, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

DicloDuo *BMS, Pol.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclof *Brasterapica, Braz.†.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclo-F *Promed, Rus.*
Diclofenac sodium (p.44·3).
Cystoid macular oedema following surgery; inflammatory eye disorders; inhibition of miosis in cataract surgery.

Diclofan *Boniscontro & Gazzone, Ital.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclofast *Specifar, Gr.*
Diclofenac potassium (p.44·3).
Inflammatory disorders.

Diclofemed *Ethimed, Belg.*
Diclofenac sodium (p.44·3).

Diclofen
Pharmacia, Braz.†.
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
SVUS, Cz.; Berlin Pharm, Thai.†.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Jean-Marie, Hong Kong.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclofen P *SM, Venez.*
Diclofenac potassium (p.44·3).
Fever; inflammation; pain.

Diclofenacol *Hyperion, Rus.*
Diclofenac sodium (p.44·3); menthol (p.2340·1).

Diclofenax *Infabra, Braz.†.*
Diclofenac potassium (p.44·3).

Diclofenbeta *Betapharm, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Diclofetamol *Ducto, Braz.*
Caffeine (p.1116·3); carisoprodol (p.1894·1); diclofenac sodium (p.44·3); paracetamol (p.108·1).

Dicloflam
Molex Ayus, Indon.; Pharmacare, S.Afr.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.
Santa, Turk.
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dicloflex *Dexcel, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dicloftal *Lepori, Port.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Dicloftil *Farmigea, Ital.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Diclogea *Gea, Denm.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclo-Gel *Sandoz, Ger.*
Diclofenac sodium (p.44·3).
Inflammation; soft-tissue disorders.

Diclogel *Polipharm, Thai.*
Diclofenac diethylamine (p.44·3).
Inflammation; pain.

Diclogenom *Genom, Braz.*
Diclofenac sodium (p.44·3).
Eye disorders.

Diclogenta *Centaur, India.*
Diclofenac sodium (p.44·3); gentamicin sulfate (p.282·1).
Bacterial eye infections with inflammation.

Diclogesic
TRB, Arg.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Biliary and renal colic; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.
Dar Al Dawa, Hong Kong.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclogesic Forte *TRB, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Diclogesic Plus B12 *TRB, Arg.*
⊗ Diclofenac potassium (p.44·3); betamethasone (p.1518·2); cyanocobalamin (p.1980·2).
Musculoskeletal and joint disorders; neuropathy.

Diclogesic Relax *TRB, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Diclogrand *Ahimsa, Arg.*
Diclofenac (p.44·2).
Inflammation; pain.

Diclohexal
Hexal, Austral.; Hexal, NZ.
Diclofenac sodium (p.44·3).
Dysmenorrhoea; gout; inflammation; musculoskeletal and joint disorders; pain.
Hexal, S.Afr.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclokalium *Prati-Donaduzzi, Braz.†.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclokin *Kinder, Braz.*
Chloroquine phosphate (p.599·3).
Malaria.

Diclolak *Grunenthal, Venez.†.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Diclolan *Olan-Kemed, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclomar *Mar, Arg.*
Diclofenac (p.44·2).
Inflammation; pain.

Diclomar Flex *Mar, Arg.*
Diclofenac (p.44·2); pridinol (p.1898·2).
Inflammation; muscle spasm; pain.

Diclomax *Provalis, Irl.; koGen, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclomec *Abdi Ibrahim, Indon.; Mecom, Turk.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain; renal and biliary colic.

Diclomel *PannonPharma, Hung.; Clonmel, Irl.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclomelan *Lannacher, Austria.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain; renal and biliary colic.

Diclometin *Merck, Fin.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Diclomex *Ratiopharm, Fin.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclomin *Atlantis, Mex.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm and hypermotility.

Diclomol
Note. This name is used for preparations of different composition.
Win-Medicare, Thai.
Diclofenac sodium (p.44·3).
Inflammation; osteoarthritis; rheumatoid arthritis.
Win-Medicare, India.
Injection; slow-release tablets: Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Win-Medicare, India.
Tablets: Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Win-Medicare, India.
Topical gel: Diclofenac diethylamine (p.44·3).
Soft-tissue disorders.

Diclon *Sandoz, Denm.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclonac *Lupin, India.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; pain.

Diclonaco *Ducto, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclonat *Pliva, Rus.*
Diclofenac sodium (p.44·3).

Diclonatrium *Prati-Donaduzzi, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclonax *Hertz, Braz.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclonex *Nexo, Arg.*
Diclofenac (p.44·2).
Inflammation; pain.

Diclonex Relax *Nexo, Arg.*
Diclofenac sodium (p.44·3); pridinol (p.1898·2).
Musculoskeletal and joint disorders.

Diclonil *Hertz, Braz.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclophlogont *Azupharma, Ger.†; Novartis, Gr.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dicloplast *Faran, Gr.; CTI, Israel.*
Diclofenac epolamine (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Diclo-Puren *Alpharma-Isis, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dicloral *IBN, Ital.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Mouth and throat disorders.

Dicloran
Unique, India†; Unique, Rus.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.
Randall, Mex.; Unique, Singapore.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dicloran MS *Unique, India.*
Diclofenac diethylamine (p.44·3); linolenic acid (p.1362·1); methyl salicylate (p.85·3); menthol (p.2340·1); benzyl alcohol (p.1631·3).
Soft-tissue disorders.

Dicloran Plus *Unique, Rus.*
Diclofenac diethylamine (p.44·3); methyl salicylate (p.85·3); menthol (p.2340·1); linseed oil (p.2334·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema.

Dicloran-A *Unique, India†.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Gout; musculoskeletal and joint disorders.

Dicloraster *Esoform, Ital.*
Troclosene (p.1665·3).
Water purification.

Dicloratio *Ratiopharm, Pol.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Lidocaine hydrochloride (p.1862·3) is included in the injection to reduce the pain of injection.
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclorengel *Trima, Israel.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dicloreum
Alfa Wassermann, Cz.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.
Wassermann, Ital.
Diclofenac epolamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Alfa Wassermann, Pol.
Diclofenac (p.44·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Diclo-saar *MIP, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Diclosal *Biofarma, Venez.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Diclosian *Asian Pharm, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclosifar *Siphar, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; thrombophlebitis.

Diclosod *HB, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclosodico *Multilab, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Diclosol *Solfran, Mex.*
Diclofenac (p.44·2).
Inflammation; pain.

Dicloson *Unison, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Diclospa *Cipla, India.*
Dicycloverine hydrochloride (p.1722·3); diclofenac potassium (p.44·3).
Musculoskeletal disorders.

Diclospray *Sanofi-Aventis, Port.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Diclostad *Stada, Austria.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal and biliary colic.

Diclostan *Biofarma, Venez.†.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; pain.

Diclosyl *Medicopharm, Austria.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diclotaren *Farmo Quimica, Chile.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Diclotears *Medivis, Ital.*
Diclofenac sodium (p.44·3).
Eye inflammation.

Diclotec *Technilab, Canad.†; Lepori, Port.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) may be included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Diclo-Tecno *Tecnofarma, Mex.*
Dicloxacillin (p.265·2).
Staphylococcal infections.

Diclotop *Topmed, Belg.*
Diclofenac sodium (p.44·3).

Diclovit
Note. This name is used for preparations of different composition.
Lannacher, Austria.
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Gout; musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.
Nizpharm, Rus.
Diclofenac sodium (p.44·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal and hepatic colic.

Diclovith-B *Sons, Mex.*
Ampoule 1, pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2); ampoule 2, diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; neuralgias; neuritis; neuropathy.

Diclovol *Arun, UK.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diclowal *Ritter, Hong Kong†; Ritter, Singapore†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diclox *PP Lab, Thai.†.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Dicloxaquim *Quimica y Farmacia, Mex.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Dicloxia *Asian Pharm, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Dicloxin *Olan-Kemed, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Dicloxman *T Man, Thai.†.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Dicloxno *Milano, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Dicloxsig *Sigma, Austral.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Diclozip *Ashbourne, UK.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Dicodid *Abbott, Ger.; Knoll, Switz.†.*
Hydrocodone hydrochloride (p.63·1) or hydrocodone tartrate (p.63·1).
Coughs; pain.

Dicodin *Mundipharma, Fr.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Dicodral *Dicofarm, Ital.*
Sodium chloride; potassium chloride; sodium bicarbonate or sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dicofan *Rivero, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Dicofen *Dicofarm, Ital.†.*
A range of preparations for enteral nutrition (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Dicoflor *Dicofarm, Ital.*
Food containing lactic-acid-producing organisms (p.2372·3).
Disturbances of the gastrointestinal flora.

Dicogel *Mintlab, Chile.*
Diclofenac diethylamine (p.44·3).
Inflammation.

Dicoman *Dicofarm, Ital.*
Dietary fibre supplement (p.1922·1).

Dicomin *Berlin Pharm, Thai.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm.

Diconal *Wellcome, Irl.†; CeNeS, UK.*
Dipipanone hydrochloride (p.49·1); cyclizine hydrochloride (p.574·2).
Pain.

Diconpin *TAD, Ger.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Dicopac *Nycomed, Cz.†; Nycomed Amersham, UK.*
1 capsule, cyanocobalamin (cobalt-57) (p.2053·2); 1 capsule, cyanocobalamin (cobalt-58) (p.2053·2); 1 ampoule, cyanocobalamin (p.1980·2).
Diagnosis of vitamin B malabsorption.

Dicoplus *Dicofarm, Ital.*
Glucomannan (p.2312·3).
Constipation; diverticulitis; irritable bowel syndrome.

Dicorantil *Sanofi-Aventis, Braz.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Dicortal *Avantgarde, Ital.†.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Dicortineff *Jelfa, Pol.; Polfa Warszawa, Pol.*
Fludrocortisone acetate (p.1530·1); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Infected eye or ear disorders.

Dicorvin *Valeant, Spain.*
Acetylspiramycin (p.333·2).
Bacterial infections.

Dicorynan *IFET (IΦET), Gr.; Sanofi-Aventis, Spain.*
Disopyramide (p.1269·1).
Arrhythmias.

Dicoterol *Gelcaps, Mex.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Dictyolone *Texinfine, Fr.*
Padina pavonica (p.2384·2).
Bone and joint disorders.

Dicymine *Christo, Hong Kong; Pharmasant, Thai.*
Dicycloverine hydrochloride (p.1722·3).
Flatulence; gastrointestinal spasm.

Dicymine Co *Christo, Hong Kong.*
Dicycloverine hydrochloride (p.1722·3); dimeticone (p.1770·2).
Flatulence; gastrointestinal spasm.

Dicynene *Sanofi-Aventis, Irl.; Sanofi Synthelabo, UK.*
Etamsylate (p.1064·3).
Menorrhagia; periventricular haemorrhage.

Dicynone *Sanofi-Aventis, Belg.; OM, Cz.; Sanofi-Aventis, Fr.; Teva, Hung.; Corsa, Indon.; OM, Indon.; Sanofi-Aventis, Ital.; Grunenthal, Mex.; Lek, Rus.; Sanofi-Aventis, Singapore†; OM, Switz.; Leti, Venez.*
Etamsylate (p.1064·3).
Haemorrhage; menorrhagia; metrorrhagia; vascular fragility.

Didamega *Larkhall Laboratories, UK.*
Multivitamin and mineral preparation (p.1922·1).

Didanox *Cristalia, Braz.†.*
Didanosine (p.870·2).
HIV infection.

Didasten *Landsteiner, Mex.*
Didanosine (p.870·2).
HIV infection.

Di-Delamine *Commerce, USA; Del, USA.*
Diphenhydramine hydrochloride (p.577·2); tripelennamine hydrochloride (p.592·2).
Pruritus.

Dideral *Sanofi Synthelabo, Turk.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction; phaeochromocytoma; tremor.

Didor *Viatris, Port.†.*
Dihydrocodeine tartrate (p.48·1).
Pain.

Didrex *Upjohn, USA.*
⊗ Benzfetamine hydrochloride (p.2152·1).
Obesity.

Didrica *Pensa, Spain.*
Calcium chloride; potassium chloride; sodium chloride; sodium lactate; glucose (p.1672·2).
Oral rehydration therapy.

Didrocal *Pfizer, Austral.; Procter & Gamble, Canad.*
28 White tablets, etidronate disodium (p.1097·1); 76 blue tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Didrogyl *IFET (IΦET), Gr.; Bruno, Ital.*
Calcifediol (p.1986·1).
Hypocalcaemia; hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency.

Didrokit *Procter & Gamble, Neth.*
Tablets, etidronate disodium (Didronel) (p.1097·1); tablets, calcium carbonate (Cacit) (p.1714·1).
Osteoporosis.

Didronat *Kocak, Turk.*
Etidronate disodium (p.1097·1).
Paget's disease of bone.

Didronate *Procter & Gamble, Denm.; Roche, Fin.; Roche, Swed.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Didronate Calcium *Procter & Gamble, Denm.*
14 Tablets, etidronate disodium (p.1097·1); 76 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Didronate + Calcium *Roche, Fin.; Roche, Swed.*
14 Tablets, etidronate disodium (p.1097·1); 76 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Didronate + Calsium *Procter & Gamble, Norw.*
14 Didronate tablets, etidronate disodium (p.1097·1); 76 calcium tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Didronel *Pfizer, Austral.; Aventis, Austria; Procter & Gamble, Belg.†; Procter & Gamble, Canad.; Procter & Gamble, Fr.; Procter & Gamble, Ger.; Procter & Gamble, Hong Kong†; Procter & Gamble, Irl.; Procter & Gamble, Israel; Procter & Gamble, Ital.†; Sumitomo, Jpn; Pfizer, NZ; Procter & Gamble, Neth.; Normal, Port.†; Vifor, Switz.; Procter & Gamble, UK; MGI, USA; Procter & Gamble, USA.*
Etidronate disodium (p.1097·1).
Ectopic ossification; hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Didronel Kit *Procter & Gamble, Ger.*
White tablets, etidronate disodium (p.1097·1); blue tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Didronel PMO *Procter & Gamble, Irl.; Procter & Gamble, UK.*
Tablets, etidronate disodium (Didronel) (p.1097·1); tablets, calcium carbonate (Cacit) (p.1714·1).
Osteoporosis.

Diemil *Almirall, Spain.*
Dihydroergocristine mesilate (p.364·2); piracetam (p.368·2).
Cerebrovascular disorders; head injury.

Diemon *Pfizer, Arg.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Dienpax *Sanofi-Aventis, Braz.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm; tetanus.

Dientrin *Sanofi-Aventis, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Diergo *Novartis, Belg.*
Dihydroergotamine mesilate (p.618·2).
Migraine.

Diergospray *Novartis, Fr.*
Dihydroergotamine mesilate (p.618·2); caffeine (p.1116·3).
Migraine.

Diertina *Pharmanel, Gr.; Pharmacia, Ital.†; Sankyo, Port.*
Dihydroergocristine mesilate (p.364·2).
Cerebral and peripheral vascular disorders; dopamine deficiency; headache; hypertension; migraine.

Diertine *Astellas, Spain.*
Dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders; tinnitus; vascular eye disorders; vertigo.

Di-Ertride *Malaysia Chemist, Singapore†.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema.

Diesan *CT, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorders.

Diespor *Biomedica, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Diestet *Darier, Mex.*
⊗ Mazindol (p.2157·3).
Obesity.

Diet Complet *Natural Life, Arg.*
Multivitamin preparation (p.1922·1).

Diet Sucaryl *Abbott, Ital.*
Sodium cyclamate (p.1936·3); saccharin (p.1960·2).
Sugar substitute.

Dietacil *IMA, Braz.*
Aspartame (p.1930·1).
Sugar substitute.

Dietamina *Neckerman, Braz.†.*
Aspartame (p.1930·1).
Sugar substitute.

Dietasal *Libbs, Braz.*
Sodium chloride; potassium chloride (p.1672·2).
Oral rehydration solution.

Dietene *Adcock Ingram, S.Afr.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Diethizine *Pond's, Thai.*
Diethylcarbamazine citrate (p.143·1).
Filariasis; loiasis.

Dietil *Trenker, Thai.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Dietline *NPC, Fr.*
A range of dietary supplements (p.1922·1).

Dietmann *Zydus, India.*
Glucomannan (p.2312·3).
Constipation; diabetes mellitus; hyperlipidaemias; obesity.

Dietoman *Teofarma, Ital.; Armstrong, Mex.*
Glucomannan (p.2312·3).
Diabetes mellitus; lipid disorders; obesity.

Di-Eudrin *Biotech, Venez.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Diezime *Recordati, Ital.*
Cefodizime sodium (p.226·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Diezol Compuesto *Galeno, Venez.†.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Dif Vitamin A Masivo *Roche, Spain†.*
Vitamin A acetate (p.1973·1).
Vitamin A deficiency.

Difadol *Polfa Warszawa, Pol.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Gout; inflammatory eye disorders; musculoskeletal, joint, and peri-articular disorders; pain.

Difarben *Rayere, Mex.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders.

Difaterol *Bial, Spain.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Difebril *Cifarma, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Di-Fedril *Quim-Far, Venez.†.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Difelene *TNP, Thai.†.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Difemic *Pharmasant, Thai.*
Dicycloverine hydrochloride (p.1722·3); mefenamic acid (p.80·1).
Gastrointestinal spasm with pain.

Difen
Note. This name is used for preparations of different composition.
Allergan, Braz.
Pranoprofen (p.119·1).
Inflammatory eye disorders.

Stulln, Ger.; Nakorn, Thai.
Diclofenac sodium (p.44·3).
Eye inflammation; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain; prevention of miosis in eye surgery.

Meyer, Venez.
Paracetamol (p.108·1); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Migraine.

Difenac
Lafedar, Arg.; DHA, Hong Kong; DHA, Singapore; TP, Thai.
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Dollder, Venez.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Difenac Forte *Lafedar, Arg.*
⊗ Diclofenac potassium (p.44·3); betamethasone (p.1518·2); cyanocobalamin (p.1980·2).
Musculoskeletal and joint disorders; neuritis.

Difenacol *Chemists Own, Austral.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cold symptoms; cough.

Difenak *Terra, Turk.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Difenan *Royton, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Difenax *GX, Philipp.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Difend *Medicus, Gr.†.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Difene *Fujisawa, Austria; Astellas, Irl.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal colic.

Difenet *Nycomed, Denm.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Difengesic *Bangkok Lab & Cosmetic, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Difenidrin *Cristalia, Braz.*
Diphenhydramine hydrochloride (p.577·2).

Difeno *Milano, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders.

Difenol *APT, Hong Kong.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Difensil *Humana, Ital.*
Sicillian red orange.
Tonic.

Diferbest *Best, Mex.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diferin *Grossman, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Difexon
Note. This name is used for preparations of different composition.
Bago, Chile.
Povidone-iodine (p.1659·2).
Burns; disinfection of mucous membranes and skin; skin infections; ulcers; vaginal infections; wounds.

Armstrong, Mex.†.
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Differin *Galderma, Arg.; Galderma, Austral.; AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Canad.; Galderma, Chile; Galderma, Fin.; Galderma, Ger.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Ital.; Galderma, Malaysia; Galderma, NZ; Galderma, Neth.; Galderma, Norw.; Galderma, Philipp.; Galderma, Pol.; Galderma, Port.; Galderma, Rus.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Swed.; Galderma, Switz.; Galderma, Thai.; Liba, Turk.; Galderma, UK; Galderma, USA; Galderma, Venez.*
Adapalene (p.1587·1).
Acne.

Differine *Galderma, Cz.; Galderma, Fr.; Galderma, Spain.*
Adapalene (p.1587·1).
Acne.

Difflam *3M, Austral.; 3M, Hong Kong; 3M, Irl.; 3M, NZ; 3M, Philipp.; 3M, Singapore; 3M, Thai.; 3M, UK.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation and pain; musculoskeletal, joint, and soft-tissue disorders; painful inflammatory disorders.

Difflam Anti-inflammatory Anti-Bacterial Lozenges *3M, Singapore.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Difflam Anti-inflammatory Lozenges
Note. This name is used for preparations of different composition.
3M, Hong Kong.
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

3M, Malaysia.
Benzydamine hydrochloride (p.27·3).
Mouth and throat pain and inflammation.

Difflam Anti-inflammatory Lozenges with Cough Suppressant *3M, Austral.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1); pholcodine (p.1570·2).
Formerly known as Difflam Anti-inflammatory Cough Lozenges.
Coughs; sore throat.

Difflam Anti-inflammatory Lozenges (with Antibacterial) *3M, Malaysia.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Difflam Anti-Inflammatory Lozenges (with cough suppressant) *3M, Malaysia.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1); pholcodine (p.1570·2).
Cough; mouth and throat disorders.

Difflam Anti-inflammatory Throat Spray *3M, Austral.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat pain.

Difflam Cough *3M, NZ.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1); pholcodine (p.1570·2).
Coughs; mouth and throat disorders.

Difflam Lozenges *3M, Austral.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat pain.

Difflam Mouth Gel *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Singapore.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth pain and inflammation.

Difflam Solution *3M, Austral.; 3M, Malaysia.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat pain and inflammation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Difflam-C *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Singapore.*
Benzydamine hydrochloride (p.27·3); chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders; oral hygiene.

Diffu-K *UCB, Fr.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Diffumal *Malesci, Ital.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

Diffumax *Menarini, Hung.; Berlin-Chemie, Pol.*
⊗ Formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Diffusyl *Farmasan, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Difil-G *Stewart Jackson, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Asthma.

Difilin *Deva, Turk.*
Diprophylline (p.1120·2).
Obstructive airways disease.

Difiram *Pharmasant, Thai.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Difix *Promedica, Ital.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Diflam *Interbat, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Diflapane *Danlex, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diflax *Columbia, Mex.†.*
Simeticone (p.1770·2).
Flatulence.

Diflazole *Pinewood, Irl.*
Fluconazole (p.532·1).
Fungal infections.

Diflazon *KRKA, Cz.; KRKA, Hung.†; KRKA, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Diflerix *Medochemie, Hong Kong; Medochemie, Malaysia.*
⊗ Indapamide (p.1314·1).
Hypertension.

Difloxin *Otto, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Diflucan *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn†; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Vinci, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Diflucohexal *Hexal, Austria.*
Fluconazole (p.532·1).
Fungal infections.

Difluena *Spofa, Cz.†.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Difluid *Bioprogress, Ital.†.*
Dihydroergocristine mesilate (p.364·2).
Cerebral and peripheral disorders; headache; hypertension; migraine.

Diflunazol *Klonal, Arg.†.*
⊗ Econazole (p.531·1); neomycin (p.305·1); diflucortolone (p.1529·2).
Infected skin disorders.

Diflusal *MSD, Belg.*
Diflunisal (p.47·2).
Pain.

Diflux *Quesada, Arg.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Hypertension.

Difluzol *Stada, Austria.*
Fluconazole (p.532·1).
Fungal infections.

Difluzole *Cipla-Medpro, S.Afr.*
Fluconazole (p.532·1).
Fungal infections.

Difmedol *Faran, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Difmetre *Solvay, Ital.*
Indometacin (p.66·3); caffeine (p.1116·3); prochlorperazine maleate (p.1020·1).
Headache; migraine.

Difnal
Ranbaxy, Malaysia.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ranbaxy, Singapore.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Difnan *Hikma, Port.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Difonate *Pharmanel, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Diformil *Faes, Spain.*
Metaformaldehyde (Trioxane).
Formerly contained formaldehyde.
Mouth infections.

Diformiltricina *Faes, Spain.*
Cetrimonium bromide (p.1635·1); benzocaine (p.1854·1); metaformaldehyde (Trioxane); tyrothricin (p.358·2).
Formerly contained cetrimonium bromide, benzocaine, formaldehyde, and tyrothricin.
Mouth and throat disorders.

Diformin *Leiras, Fin.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

DiFortan *Emo-Farm, Pol.*
Naproxen cholinate.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Difosfen *Omedir, Arg.; Rubio, Singapore; Rubio, Spain; Rubio, Thai.; TTN, Thai.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Difosfocin *Magis, Ital.*
Citicoline (p.2283·3).
Parkinsonism.

Difosfonal *SPA, Ital.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolytic tumours; osteoporosis.

Difoxacil *Quimica y Farmacia, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Difrarel
Note. This name is used for preparations of different composition.
Leurquin, Fr.; Sigma-Tau, Neth.
Myrtillus (p.2349·3); betacarotene (p.1930·3).
Vascular disorders.

Sigma-Tau, Ger.; Tecnifar, Port.
Myrtillus (p.2349·3).
Peripheral vascular disorders; vascular eye disorders.

Difrarel E
Note. This name is used for preparations of different composition.
Leurquin, Fr.; Leurquin Mediolanum, Hung.
Myrtillus (p.2349·3); vitamin E acetate (p.1992·3).
Myopias.

Leurquin, Hong Kong.
Vitamin E (p.1992·2); anthrocyanosides.
Myopias; poor night vision.

Difrin *Vitamed, Israel.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Diftavax *Sanofi Pasteur, Arg.†; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Spain; Sanofi Pasteur, UK†.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation; active immunisation of older children and adults.

Dif-Tet-All *Novartis, Braz.; Chiron Vaccines, Ital.; Chiron, Thai.†.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Difur *Cantabria, Spain.*
Polypodium leucotomos.
Skin disorders.

Difuran *The Forty-Two, Thai.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal infections.

Difusel *Medix, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Difusil *Ivax, Arg.*
Codergocrine mesilate (p.363·3); cinnarizine (p.573·1).
Mental function impairment.

Digacin *Mibe, Ger.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Digal *Probiomed, Mex.*
Dipyridamole (p.1268·1).

Digaol *Ioltech, Fr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Digaril *Solvay, Spain.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; hyperlipidaemias.

Digassim *Vitoria, Port.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Digastril *Brasmedica, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); kaolin (p.1738·1).
Gastric hyperacidity.

Digecap-Zimatico *Sigma, Braz.*
Bromopride (p.1713·3); dimeticone (p.1770·2); pancreatin (p.2360·1); cellulase (p.2279·1).
Digestive disorders Formerly contained bromopride, dimeticone, and pancreatin =(PRBraz.02).; nausea and vomiting.

Digedrat *Medley, Braz.*
Trimebutine maleate (p.2404·3).
Dyspepsia; irritable bowel syndrome; postoperative gastrointestinal atony.

Digedryl *Merck Medication Familiale, Fr.*
Anhydrous sodium sulfate (p.1771·3); monobasic sodium phosphate (p.1682·3).
Dyspepsia.

Di-Gel
Note. This name is used for preparations of different composition.
Plough, Port.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastric hyperacidity.

Schering-Plough, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Schering-Plough, Indon.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Cholecystitis; flatulence; gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Schering-Plough, Indon.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Cholecystitis; flatulence; gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Di-Gel Forte *Plough, Port.†.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity.

Digelax *Balverda, Ital.†.*
Boldo (p.2267·2); rhubarb (p.1768·3); cascara (p.1715·2); cynara (p.2291·2); croton eleuteria; inositol (p.2325·2).
Constipation.

Digenat *Natufarma, Arg.*
Cynara (p.2291·2); boldo (p.2267·2); carqueja.
Herbal supplement.

Digene
Note. This name is used for preparations of different composition.
Abbott, India.
Oral gel: Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); carmellose sodium (p.2142·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; heartburn; peptic ulcer.

Abbott, India.
Tablets: Aluminium hydroxide (p.1706·2); aluminium magnesium silicate (p.2141·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn; peptic ulcer.

Digenil *Saval, Chile.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders; flatulence.

Digenor *Rudefsa, Mex.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2).
Adjunct in gastrointestinal procedures; gastritis; hiatus hernia; nausea and vomiting; oesophagitis; peptic ulcer.

Digenor Plus *Rudefsa, Mex.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2); papain (p.2362·3).
Adjunct in gastrointestinal procedures; gastrointestinal disorders.

Digenorflat *Baliarda, Arg.*
Pancreatin (p.2360·1); simeticone (p.1770·2); dehydrocholic acid (p.2292·2).
Digestive disorders.

Digenormotil *Baliarda, Arg.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Digenormotil Plus *Baliarda, Arg.†.*
Cisapride (p.1720·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Digenta *Interbat, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Digeodren *Sevene, Fr.*
Homoeopathic preparation.

Digepepsin *Kenwood, USA.*
Pepsin (p.2365·1); pancreatin (p.2360·1); bile salts (p.2266·2).

Digeplex
Note. This name is used for preparations of different composition.
Shreya, India.
Oral drops: Amylase (p.2256·3); pepsin (p.2365·1); cardamom oil (p.2277·2); cinnamon oil (p.2283·2).
Digestive disorders.

Shreya, India.
Oral liquid: Amylase (p.2256·3); pepsin (p.2365·1).
Digestive disorders.

Digeplex-T *Shreya, India.*
Pancreatin (p.2360·1); ox-bile (p.2266·3); pepsin (p.2365·1); amylase (p.2256·3); dimeticone (p.1770·2).
Digestive disorders.

Digeplus *Ache, Braz.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2); dehydrocholic acid (p.2292·2); cellulase (p.2279·1); pepsin (p.2365·1); pancreatin (p.2360·1).
Digestive disorders.

Digerall *Falqui, Ital.†.*
Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Digerent *Polifarma, Ital.*
Trimebutine maleate (p.2404·3).
Gastrointestinal spasm; irritable colon; oesophageal motility disorders.

Digerex *De Mayo, Braz.*
Bromopride (p.1713·3).
Nausea and vomiting.

Digerfit *Body Spring, Ital.*
Papaya; pineapple; fennel; amino acids; pyridoxine (p.1922·1).
Digestive disorders; nutritional supplement.

Digervin *Coll, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity peptic ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Digesan *Sanofi-Aventis, Braz.*
Bromopride (p.1713·3).
Gastrointestinal motility disorders; nausea and vomiting.

Di-Gesic *Aspen, Austral.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Digeslit *Alodial, Port.†.*
Famotidine (p.1730·1).

Digespar *Sanofi-Aventis, Chile.*
Metoclopramide hydrochloride (p.1747·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Digesplen *Craveri, Arg.*
Pancreatin (p.2360·1); metoclopramide (p.1747·3); simeticone (p.1770·2); deoxycholic acid (p.2266·3).
Gastrointestinal disorders.

Digesprid *Neo Quimica, Braz.*
Bromopride (p.1713·3).
Nausea and vomiting.

Digest
Note. This name is used for preparations of different composition.
Mediherb, Austral.
Echinacea (p.2298·1); gentian (p.2310·3); chamomile (p.2279·3); milk thistle (p.1452·1); taraxacum (p.2395·1).
Digestive disorders.

Kalbe, Indon.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Digest Plus *Nutravite, Canad.†.*
Bromelain; cataria; fennel seed; ginger root; glutamic acid; pancreatin; papain; papaya fruit complex and leaf; peppermint root; pepsin; saw palmetto berries.

Digesta *Seaford, Canad.*
Amylase (p.2256·3); lipase (p.2360·3); tilactase (p.2402·1); sucrase; maltase (p.2245·3); cellulase (p.2279·1).
Digestive disorders.

Digestaid *Eagle, Austral.*
Betaine hydrochloride (p.2265·2); pepsin (p.2365·1); pancreatin (p.2360·1); ox bile salt (p.2266·2); bromelain (p.2269·1); papain (p.2362·3); maltase (p.2245·3); potassium chloride (p.1684·3); gentian (p.2310·3); fennel; peppermint oil (p.1761·2); chromium chelate (p.1934·3).
Gastrointestinal disorders.

Digestar *Brasmedica, Braz.†.*
Chamomile (p.2279·3); gentian (p.2310·3).
Gastrointestinal disorders.

Digestbem *Eurofarma, Braz.*
Sodium bicarbonate (p.1673·2); sodium carbonate (p.2389·1); citric acid (p.2284·1).
Gastrointestinal hyperacidity.

Digestelact *Nutricia, Austral.*
Food for special diets (p.1922·1).
Lactose intolerance.

Digestif Marga *Cooperation Pharmaceutique, Fr.*
Magnesium hydroxide (p.1743·2); dried aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1).
Gastrointestinal disorders.

Digestif Rennie *Bayer, Cz.; Bayer, Hung.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); papain (p.2362·3); pancreatin (p.2360·1).
Dyspepsia; gastrointestinal disorders associated with hyperacidity; pancreatic insufficiency.

Digestif-Ara *Rafa, Israel†.*
Magnesium carbonate (p.1743·1); magnesium peroxide (p.1651·3); magnesium oxide (p.1744·1); calcium carbonate (p.1714·1); kaolin (p.1738·1); peppermint oil (p.1761·2).
Calcium supplement; dyspepsia; flatulence; gastrointestinal hyperacidity.

Digestil *Teuto, Braz.*
Bromopride (p.1713·3).
Gastrointestinal disorders.

Digestin *Chew, Thai.*
Mamylase; amylase (p.2256·3); thiamine nitrate (p.1976·2); scopolia; sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); dried aluminium hydroxide gel (p.1706·2).
Gastrointestinal disorders.

Digestina *Uniao Quimica, Braz.*
Bromopride (p.1713·3).
Nausea and vomiting.

Digestion *Homeocan, Canad.*
Homoeopathic preparation.

Digestive *Dorwest, UK.*
Ginger (p.1732·3); hydrastis (p.2321·3); rhubarb (p.1768·3); valerian (p.2410·1).
Dyspepsia; gastric hyperacidity; heartburn; nausea.

Digestive Aid *Blackmores, Austral.*
Slippery elm (p.2388·2); fennel (p.2302·3); ginger (p.1732·3); gentian (p.2310·3); papain (p.2362·3); bromelains (p.2269·1); peppermint leaf (p.1761·2); anise oil (p.2258·2).
Digestive disorders.

Digestivo Antonetto *Antonetto, Ital.*
Anionic resin; glycine (p.1947·3); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Digestivo Giuliani *Giuliani, Ital.*
Domperidone (p.1726·2).
Dyspepsia.

Digestivum-Hetterich S *Galenika, Ger.†.*
Gentian (p.2310·3).
Bloating; flatulence; loss of appetite.

Digest-Merz *Merz, Ger.†.*
Turmeric (p.1473·2); dimethicone (p.1770·2).
Digestive system disorders.

Digestodoron
Note. This name is used for preparations of different composition.
Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.
Male fern (p.148·3); polypodium leaf; scolopendrium vulgare; salix leaf (p.121·3).
Gastrointestinal disorders.

Weleda, Fr.; Weleda, UK.
Homoeopathic preparation.

Digestomen *Menarini, Belg.*
Betaine hydrochloride (p.2265·2); pepsin (p.2365·1); papain (p.2362·3); amylase (p.2256·3); pancreatin (p.2360·1); pancrelipase (p.2360·1); cellulase (p.2279·1).
Digestive disorders due to pancreatic insufficiency.

Digestomen Complex *Menarini, Spain.*
White tablets, pepsin (p.2365·1); red tablets, papain (p.2362·3); amylase (p.2256·3); green tablets, pancreatin (p.2360·1).
Digestive disorders.

Digeston *Hexal, Braz.†.*
Bromopride (p.1713·3).
Nausea and vomiting.

Diges-Tonic *Herbapol Krakow, Pol.*
Chamomile (p.2279·3); fennel (p.2302·3); St John's wort (p.422·3); peppermint leaf (p.1761·2); rhubarb (p.1768·3); rose fruit (p.2381·2); coriander (p.2288·1).
Gastrointestinal disorders.

Digestopan *Menarini, Ital.†.*
Pepsin (p.2365·1); papain (p.2362·3); amylase (p.2256·3); pancreatin (p.2360·1); pancreatic lipase; cellulase (p.2279·1).
Digestive disorders.

Digestovital *Puerto Galiano, Spain†.*
Belladonna (p.2263·3); opium (p.105·1); sodium bicarbonate (p.1673·2); sodium citrate (p.1673·3); sodium sulfate (p.1771·3); star anise (p.2392·1); aniseed (p.2258·2) cardamom (p.2277·1).
Flatulence; gastric hyperacidity; gastrointestinal spasm; vomiting.

Digestron *Loprofar, Braz.†.*
Dehydrocholic acid (p.2292·2); aesculus (p.2248·2); drimys winterii; erythroxylon catuaba; cynara (p.2291·2); cnicus benedictus (p.2285·2); sodium phosphate (p.1682·3); liver extract (p.2337·3).
Liver disorders.

Digest-X Yucca L110 *Homeocan, Canad.†.*
Homoeopathic preparation.

Digezanol *Hormona, Mex.*
Albendazole (p.139·2).
Giardiasis; worm infections.

Digezin *Recalcine, Chile†.*
Fenipentol (p.2302·3); benoctonium bromide.
Gastrointestinal disorders.

Digezym *Quality, Hong Kong.*
Pancreatin (p.2360·1); amylase (p.2256·3); papain (p.2362·3); lysine (p.1955·1); vitamin B ; vitamin B (p.1922·1).
Digestive disorders.

Digherbal *Knop, Chile.*
Homoeopathic preparation.

Digi-Aldopur *Kwizda, Austria.*
⊗ Spironolactone (p.1400·1); β-acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Digibind *GSK, Austral.; GSK, Canad.; IFET (ΙΦΕΤ), Gr.†; GSK, UK; Glaxo Wellcome, USA.*
Digoxin-specific antibody fragments (p.1443·3).
Digoxin or digitoxin toxicity.

Digidot *Roche, Fr.†.*
Digoxin-specific antibody fragments (p.1443·3).
Digoxin or digitoxin toxicity.

DigiFab *IFET (ΙΦΕΤ), Gr.; Protherics, USA.*
Digoxin-specific antibody fragments (p.1443·3).
Digoxin toxicity.

Digifar *Farmila, Ital.†.*
Digitalin (p.2293·3); vitamin P (p.2304·1).
Eye disorders.

Digifungin *Wagner, Hung.*
Tolnaftate (p.548·3).
Fungal skin infections.

Digimed *corax, Ger.*
Digitoxin (p.1259·1).
Arrhythmias; heart failure.

Digimerck *Merck, Austria; Merck, Ger.; Merck, Hung.*
Digitoxin (p.1259·1).
Arrhythmias; heart failure.

Digitaline *Procter & Gamble, Belg.†; Barrenne, Braz.*
Digitoxin (p.1259·1).
Arrhythmias; heart failure.

Digitalis Antidot *Roche, Austria†; Roche, Belg.; Roche, Ger.; Roche, Swed.; Roche, Switz.*
Digoxin-specific antibody fragments (p.1443·3).
Digitalis poisoning.

Digitalis Antidote *Roche, Hong Kong.*
Digoxin-specific antibody fragments (p.1443·3).
Digitalis poisoning.

Digitalysat Scilla-Digitaloid *Ysatfabrik, Ger.†.*
Squill (p.1573·1).
Cardiac disorders.

Digitax *Greenpharma, Braz.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Digitek *UDL, USA.*
Digoxin (p.1259·3).
Atrial fibrillation; heart failure.

Digitrin *AstraZeneca, Swed.†.*
Digitoxin (p.1259·1).
Arrhythmias; heart failure.

Digixina *HB, Braz.†.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Diglexol *IQFA, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Dignobroxol *Sankyo, Cz.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Dignodolin *Sankyo, Ger.†.*
Flufenamic acid (p.60·3).
Musculoskeletal and joint disorders.

Dignofenac *Deutsche, Chile†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dignokonstant *Sankyo, Ger.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Digobal *Baldacci, Braz.*
Digoxin (p.1259·3).

Digocard-G *Klonal, Arg.*
Digoxin (p.1259·3).

Digophton *Chauvin ankerpharm, Ger.†.*
Digitalis (p.1258·3).
Eye strain.

Digoregen *RAN, Ger.†.*
Digoxin (p.1259·3).
Heart failure.

Digosin *Chugai, Jpn.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Digostada *Stada, Ger.*
β-Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Digotab *AWD, Ger.*
β-Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Digox
Note. This name is used for preparations of different composition.
Pharlab, Braz.†.
Digoxin (p.1259·3).
Arrhythmias; heart failure.

CT, Ger.
β-Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Digoxan *Vitapan, Braz.†.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Digoxen *Cifarma, Braz.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Digoxil *Legrand, Braz.*
Digoxin (p.1259·3).

Digoxin "Didier" *Hormosan, Ger.†.*
β-Acetyldigoxin (p.1201·2).
Heart failure.

Digton *Areu, Spain.*
Sulpiride (p.1028·3).
Anxiety disorders; psychoses; vertigo.

Di-Hydan *Genopharm, Fr.*
Phenytoin (p.495·2).
Epilepsy; facial neuralgias.

Dihydergot
Note. This name is used for preparations of different composition.
Novartis, Austral.; Novartis, Belg.; Novartis, Braz.†; Novartis, Cz.; Novartis, Ger.†; Novartis, Gr.; Novartis, India†; Novartis, Indon.; Novartis, Mex.; Novartis, Port.†; Novartis, Spain; Novartis, Venez.
Dihydroergotamine mesilate (p.618·2).
Cerebrovascular disorders; chronic fatigue; constipation; herpes; migraine and related vascular headache; orthostatic hypotension; urinary retention; venous insufficiency; vertigo.

Novartis, Austria.
Injection; oral drops; tablets: Dihydroergotamine mesilate (p.618·2).
Chronic functional constipation; hypotension; migraine and related vascular headache; venous disorders of the legs.

Novartis, Austria; Novartis, Switz.
Nasal spray: Dihydroergotamine mesilate (p.618·2); caffeine (p.1116·3).
Migraine.

Novartis, Switz.
Oral drops; tablets: Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headaches.

Dihydergot plus *Novartis, Ger.; Novartis, Switz.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Dihydral *Solvay, Neth.*
Dihydrotachysterol (p.1986·3).
Hypoparathyroidism; renal osteodystrophy; rickets.

Dihydrocodeine P *Pharmaniaga, Malaysia.*
Dihydrocodeine tartrate (p.48·1); paracetamol (p.108·1).
Formerly known as Codimol.
Pain.

DiHydro-CP *Cypress, USA.*
Dihydrocodeine tartrate (p.48·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

DiHydro-GP *Cypress, USA.*
Dihydrocodeine tartrate (p.48·1); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

DiHydro-PE *Cypress, USA.*
Dihydrocodeine tartrate (p.48·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cough; upper respiratory-tract congestion.

Dihytamin *Wernigerode, Ger.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headaches.

Diidergot *Teofarma, Ital.*
Dihydroergotamine mesilate (p.618·2).
Headache; vascular disorders.

Dijex
Note. This name is used for preparations of different composition.
SSL, UK†.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
These ingredients can be described by the British Approved Name Co-magaldrox.
Dyspepsia.

SSL, UK†.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Dyspepsia.

Dikacine *Continental Pharma, Belg.†.*
Dibekacin sulfate (p.265·2).
Gram-negative bacterial infections; staphylococcal infections.

Dikantal *Crinos, Ital.*
⊗ Potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypertension.

Diklason *Leti, Venez.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Diklonat P *Pliva Krakow, Pol.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dikloron
Note. This name is used for preparations of different composition.
Carlo Erba, Turk.; Deva, Turk.
Injection; suppositories; tablets: Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Carlo Erba, Turk.; Deva, Turk.
Topical gel: Diclofenac sodium (p.44·3); diclofenac diethylamine (p.44·3).
Musculoskeletal and joint pain.

Dikloziaja *Ziaja, Pol.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

DIKY *CSC, Cz.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Dilabar *Lesvi, Spain.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Dilabar Diu *Lesvi, Spain; Vita, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); captopril (p.1239·2).
Hypertension.

Dilacard *Royton, Braz.†.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension.

Dilaclan *CEPA, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilacor
Note. This name is used for preparations of different composition.
Temis, Arg.†.
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Teuto, Braz.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Watson, USA.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilacoran *Abbott, Mex.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; heart failure; hypertension; myocardial infarction.

Dilacoron *Abbott, Braz.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic cardiomyopathy; migraine and other vascular headaches.

Diladel *Sanofi-Aventis, Ital.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilaescol *Kolassa, Austria.*
⊗ Buphenine hydrochloride (p.2270·2); thiamine hydrochloride (p.1976·1); aesculus (p.2248·2).
Migraine; peripheral vascular disease; premenstrual syndrome; reflex sympathetic dystrophy.

Dilaflux *Medley, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Dilafurane *Sanofi Synthelabo, Spain†.*
Benziodarone (p.555·3).
Gout; hyperuricaemia.

Dilahex *Hexal, Philipp.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Dilahim *Ahimsa, Arg.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Dilam *Lamsa, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dilamax *Bialfar, Port.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Dilamet *Gramon, Arg.†.*
Lormetazepam (p.1005·2).
Anxiety.

Dilamol *Sanval, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Dilan *Gunal, Turk.*
Salicylic acid (p.1612·2); acetic acid (p.2244·2); cloral hydrate (p.979·1).
Calluses.

Dilanacin *AWD, Ger.†.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Dilanorm *Aventis, Neth.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Dilantin
Pfizer, Austral.; Pfizer, Canad.; Pfizer, India; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Parke, Davis, USA.
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; seizures associated with neurosurgery; trigeminal neuralgia.

Pfizer, Fr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia; Pfizer, Venez.
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; extrapyramidal syndrome; neuralgia; seizures associated with neurosurgery; status epilepticus.

Parke, Davis, Israel.
Phenytoin (p.495·2).
Epilepsy.

Dilantin with Phenobarbital *Pfizer, India.*
Phenytoin sodium (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Dilaplus *Roche, Austria.*
⊗ Carvedilol (p.1241·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Dilaprost *Biofarma, Turk.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Dilar *Syntex, Mex.*
⊗ Paramethasone acetate (p.1540·2).
Corticosteroid.

Dilarmine *Syntex, Mex.*
⊗ Paramethasone acetate (p.1540·2); chlorphenamine maleate (p.571·3).
Hypersensitivity; inflammation.

Dilartan *Duncan, Arg.*
Bamethan (p.1222·3).
Varices.

Dilasidom *Warsaw-Polfa, Rus.*
Molsidomine (p.1343·3).
Angina pectoris; heart failure.

Dilatam *Abic, Israel; Pascual, Philipp.; Teva, Philipp.; Pharmacare, S.Afr.; Novopharm, Singapore†; Pharmachemie, Singapore†; Teva, Singapore†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilateron-F *Offenbach, Mex.*
Cinnarizine (p.573·1).
Vertigo.

Dilatol
Note. This name is used for preparations of different composition.
Kolassa, Austria.
⊗ Buphenine hydrochloride (p.2270·2).
Inhibition of labour; peripheral vascular disease; uterine relaxant; vascular headache.

Jaba, Port.
Isradipine (p.1319·2).
Hypertension.

Dilatol-Chinin *Kolassa, Austria.*
⊗ Buphenine hydrochloride (p.2270·2); quinine sulfate (p.612·3).
Cramp.

Dilatrat *Cazi, Braz.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Dilatrate *Schwarz, USA.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Dilatrend *Roche, Arg.; Roche, Austral.; Roche, Austria; Asta Medica, Braz.†; Roche, Chile; Roche Diagnostics, Cz.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Philipp.; Roche, Pol.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Venez.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension; ischaemic heart disease; left-ventricular dysfunction.

Dilaudid *Abbott, Austral.; Abbott, Austria; Abbott, Canad.; Abbott, Ger.; Abbott, NZ†; Abbott, USA.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Dilaudid Cough *Knoll, USA.*
⊗ Hydromorphone hydrochloride (p.63·2); guaifenesin (p.1561·3).
Coughs.

Dilaudid-Atropin *Abbott, Swed.; Knoll, Switz.†.*
⊗ Hydromorphone hydrochloride (p.63·2); atropine sulfate (p.1219·3).
Pain; smooth muscle spasm.

Dilavenil *Unipharma, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Dilbloc *Roche, Indon.; Roche, Port.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension; ischaemic heart disease.

Dilcard *Alphapharm, Malaysia†; Merck, Malaysia†; Pacific, NZ†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Dilcardia *Unique, India†; Danlex, Philipp.; Unique, Rus.; Generics, UK.*
Diltiazem hydrochloride (p.1265·1).
Also known as Dizemont in *Philipp*.
Angina pectoris; hypertension.

Dilceren *Zentiva, Cz.*
Nimodipine (p.1357·2).
Ischaemic neurological deficit due to arterial vasospasm following subarachnoid haemorrhage.

Dilclor *Diba, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Dilcontin *Modi-Mundipharma, India.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilcor
Note. This name is used for preparations of different composition.
Norpharma, Denm.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

BOI, Spain.
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Dilcoran *Alpharma-Isis, Ger.*
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris.

Dilem *Ist. Chim. Inter., Ital.; Douglas, Malaysia†; Douglas, Thai.; TTN, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilena *Organon, Arg.†; Organon, Braz.; Organon, Hong Kong; Organon, Mex.; Organon, Port.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Diletan *Vitoria, Port.†.*
Sumatriptan succinate (p.625·2).
Cluster headache; migraine.

Dilex-G *Poly, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Asthma.

Dilfar *Solvay, Port.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilgard *Cipla, India.*
Diltiazem hydrochloride (p.1265·1).

Diligan
Note. This name is used for preparations of different composition.
UCB, Austria.
Hydroxyzine hydrochloride (p.581·2); meclozine hydrochloride (p.584·3); nicotinic acid (p.1957·3).
Vestibular disorders.

UCB, Ger.†.
Hydroxyzine hydrochloride (p.581·2); meclozine hydrochloride (p.584·3).
Ménière's disease; vertigo.

UCB, India.
Meclozine hydrochloride (p.584·3); nicotinic acid (p.1957·3).
Labyrinthitis; vertigo.

UCB, Port.†.
Hydroxyzine (p.581·2); meclozine (p.585·1); nicotinic acid (p.1957·3).

Dilinct *Adcock Ingram, S.Afr.*
Etofylline (p.1121·1); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Bronchodilator; coughs.

Dilinct Junior *Adcock Ingram, S.Afr.*
Guaifenesin (p.1561·3).
Cough.

Diliter *Boniscontro & Gazzone, Ital.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension.

Dilizem *Berlin Pharm, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilmen *Menarini, Indon.; Sanbe, Indon.*
Diltiazem hydrochloride (p.1265·1).
Hypertension.

Dilmin *Ratiopharm, Fin.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diloc *Tramedico, Neth.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilocaine *Hauck, USA.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Dilocar *Errekappa, Ital.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Dilocard *ICN, Pol.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilomil *Siam Bheasach, Thai.†.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Dilomin *Am-Europharma, Philipp.*
Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Dilongo *IPI, Port.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilopin *Munir, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Dilor *Savage, USA†.*
Diprophylline (p.1120·2).
Obstructive airways disease.

Dilostop *Collins, Mex.†.*
Loperamide (p.1741·3).
Diarrhoea.

Dilosyn *Sigma, Austral.†; GSK, India.*
Methdilazine hydrochloride (p.585·3).
Hypersensitivity reactions; neurodermatitis; pruritus; rhinitis.

Dilosyn Expectorant *GSK, India.*
Methdilazine hydrochloride (p.585·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Dilotab *Zee, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Dilotex *Dollder, Venez.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Dilox *Recalcine, Chile.*
Ketorolac trometamol (p.74·2).
Pain.

Diloxin *Pond's, Thai.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Dilper-INA *Ultra, Mex.*
Cinnarizine (p.573·1).

Dilpral *Orion, Fin.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilrene *Winthrop, Fr.; Sanofi-Aventis, Hung.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilsal *TAD, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dil-Sanorania *Winthrop, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilso *Soho, Indon.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilta *ABZ, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltabeta *Betapharm, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltahexal *Hexal, Austral.; Hexal, Austria; Hexal, Ger.; Hexal, NZ.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltam *Rowex, Irl.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltan *Mepha, Hong Kong†; Mepha, Hung.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltapham *Phamos, Ger.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltaretard *Betapharm, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilt-CD *Apotex, USA.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltec *Utopian, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension.

Diltelan
Faran, Gr.
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

OEP, Philipp.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltem *Neiadas (Νειάδας), Gr.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltenk *Biotenk, Arg.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Dilti *CT, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltia *Andrx, USA.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltiacor *Hexal, Arg.†; Biolab Sanus, Braz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Diltiagamma *Worwag, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltiangina *Tecnimede, Port.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Diltiastad *Stada, Austria.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilticard *Ilsan, Turk.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltiem *Sanofi-Aventis, Port.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltime *Zydus, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltin *Cimed, Braz.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Diltipress *Sigma, Braz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltiuc *Merck dura, Ger.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltiwas *Chiesi, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltix *Pliva, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Diltizem *Pharmacia, Braz.; Nevzat, Turk.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltor *Torrent, Braz.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Diltotal *Mintlab, Chile.*
Ginseng; lecithin; procaine hydrochloride (p.1869·1); vitamins; rutin; minerals (p.1922·1).

Dilt-XR *Apotex, USA.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilucid *Collins, Mex.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Dilucort *Triomed, S.Afr.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Dilufrin *Sophia, Mex.*
Phenylephrine (p.1568·1).
Eye congestion.

Dilum *Tecnifar, Port.*
Isoxsuprine hydrochloride (p.2327·3).
Cerebral and peripheral vascular disorders; relaxation of the uterus.

Diluplex *Steierl, Ger.*
Homoeopathic preparation.

Diluran *Zentiva, Cz.*
⊗ Acetazolamide (p.1875·1).
Glaucoma.

Dilusol *Dermtek, Canad.†.*
⊗ Alcohol (p.1625·2); isopropyl alcohol; propylene glycol; laureth-4.
Topical vehicle.

Dilusol AHA *Dermtek, Canad.†.*
⊗ Alcohol (p.1625·2); glycolic acid (p.1598·1); polyquaternium 10; polysorbate 20; propylene glycol.
Topical vehicle.

Dilutol
Note. This name is used for preparations of different composition.
Lazar, Arg.
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders.

Roche, Spain.
⊗ Torasemide sodium (p.1416·1).
Hypertension; oedema.

Diluxina *Diba, Mex.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Dilvas *Cipla, India.*
Enalapril maleate (p.1276·1).

Dilvas AM *Cipla, India.*
Enalapril maleate (p.1276·1); amlodipine besilate (p.1214·1).
Hypertension.

Dilzanol *Remedina, Gr.†.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Dilzanton *Juta, Ger.; Q-Pharm, Ger.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dilzem *Douglas, Austral.; Elan, Austria; Godecke, Cz.†; Orion, Fin.; Godecke, Ger.; Pfizer, Hung.; Torrent, India; Zeneus, Irl.; Douglas, NZ; Pfizer, Philipp.; Godecke, Pol.; Parke, Davis, Pol.; Pfizer, Switz.; Pharmasant, Thai.†; Cephalon, UK.*
Diltiazem hydrochloride (p.1265·1).
Adjunct in transluminal coronary angioplasty or bypass surgery; angina pectoris; arrhythmias; coronary spasm; hypertension; myocardial infarction; prevention of kidney transplant rejection; reduction of ciclosporin nephrotoxicity.

Dilzene *Sigma-Tau, Ital.*
Diltiazem hydrochloride (p.1265·1).
Arrhythmias; hypertension; ischaemic heart disease.

Dilzen-G *Klonal, Arg.*
Diltiazem (p.1267·1).
Angina pectoris.

Dilzicardin *Azupharma, Ger.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dima *Medochemie, Singapore.*
Nitrazepam (p.1011·2).
Insomnia.

Dimacol *Wyeth Consumer, Mex.; Robins, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Dimafit *Body Spring, Ital.*
Garcinia, chromium tripicolinate; taraxacum; birch leaf; camelia sinensis (p.1922·1).
Nutritional supplement; obesity.

Dimagrasi *Giuliani, Ital.†.*
Avena; soya lecithin; oligopeptides; vitamin E; betacarotene; chromium-rich yeast (p.1922·1).
Nutritional supplement; obesity.

Dimagrasicell *Giuliani, Ital.†.*
Bladderwrack; java tea; bioflavonoids; tilia; ginkgo biloba; chromium-rich yeast; centella; vitamin E (p.1922·1).
Cellulite; nutritional supplement.

Dimagrir *Gador, Arg.*
⊗ Mazindol (p.2157·3).
Obesity.

Dimagrir Triac *Gador, Arg.†.*
⊗ Mazindol (p.2157·3); tiratricol (p.2177·3).
Obesity.

Dimalan *Filaxis, Arg.*
Bicalutamide (p.686·2).

Dimanin R *Bayer, Ital.†.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Dim-Antos *Agepha, Austria; Pharmonta, Austria.*
Propyphenazone (p.119·3).
Fever; pain.

Dimase *Unison, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Dimate *APT, Hong Kong.*
Dimenhydrinate (p.576·2).
Motion sickness.

Dimaval
Note. This name is used for preparations of different composition.
Lazar, Arg.
Homatropine methylbromide (p.1881·3); benactyzine hydrochloride (p.383·1); pentobarbital (p.1016·1).
Smooth muscle spasm.

Heyl, Cz.; Heyl, Ger.
Unithiol (p.1468·1).
Antidote; heavy-metal poisoning.

Dimavyl *Leti, Venez.*
Glimepiride (p.441·1).
Diabetes mellitus.

Dimaxin *Medipharma, Hong Kong†.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Dimecaina *Grunenthal, Chile.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Dimedril *Vitapan, Braz.†.*
Dimenhydrinate (p.576·2); pyridoxine (p.1979·1).

Dimefor *Farmoquimica, Braz.; Rhein, Mex.; Lilly, Venez.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Dimegan
Note. This name is used for preparations of different composition.
Dexo, Fr.
Brompheniramine maleate (p.569·2).
Allergic disorders.

Senosiain, Mex.
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Dimegan D *Senosiain, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Dimen *Heumann, Ger.†.*
Dimenhydrinate (p.576·2).
Dizziness; motion sickness; nausea; vomiting.

Dimenate *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Dimenhydrinate (p.576·2).
Ménière's disease; motion sickness; nausea; vomiting.

Dimenformon *Organon, Belg.*
Estradiol benzoate (p.2097·2); estradiol phenylpropionate (p.2097·3).
Menstrual disorders; oestrogen replacement therapy.

Dimeno *Milano, Thai.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vertigo.

Dimeprost *Columbia, Mex.*
Diethylstilbestrol (p.2094·1).
Prostatic cancer.

Dimerrin *Unison, Philipp.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; rhinitis; sinusitis.

Dimesul *Lafare, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Dimeta-2 *Christo, Hong Kong.*
Brompheniramine maleate (p.569·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Dimetabs *Jones, USA.*
Dimenhydrinate (p.576·2).
Motion sickness.

Dimetane
Note. This name is used for preparations of different composition.
Wyeth, Fr.
Pholcodine (p.1570·2).
Formerly contained brompheniramine maleate and pholcodine.
Coughs.

Wyeth Consumer, Thai.; Robins, USA†.
Brompheniramine maleate (p.569·2).
Hay fever; hypersensitivity reactions.

Dimetane Decongestant *Robins, USA†.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract symptoms.

Dimetane Expectorant C *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Formerly contained brompheniramine maleate, phenylephrine hydrochloride, guaifenesin, codeine phosphate, and phenylpropanolamine hydrochloride.
Upper respiratory-tract disorders.

Dimetane Expectorant DC *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Formerly contained brompheniramine maleate, hydrocodone tartrate, guaifenesin, phenylephrine hydrochloride, and phenylpropanolamine hydrochloride.
Upper respiratory-tract disorders.

Dimetane Expectorant Enfant *Whitehall, Fr.†.*
Brompheniramine maleate (p.569·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2).
Upper respiratory-tract congestion.

Dimetapp
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.; Wyeth, Philipp.; Wyeth Consumer, Singapore.
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic conjunctivitis; allergic rhinitis; cold symptoms; hypersensitivity reactions; sinusitis.

Wyeth Consumer, Braz.; Wyeth Consumer, Mex.; Whitehall-Robins, USA.
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Formerly contained brompheniramine maleate, phenylpropanolamine hydrochloride, and phenylephrine hydrochloride in *Braz.*
Allergic rhinitis; nasal congestion; upper respiratory-tract symptoms.

SA Druggists Self Med, S.Afr.
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Wyeth, Venez.†.
Delayed-release tablets; elixir; paediatric oral drops: Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract disorders.

Wyeth Consumer, NZ.
Drops; elixir: Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Hay fever; nasal congestion.

Wyeth Consumer, Hong Kong.
Elixir: Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract symptoms.

Wyeth Consumer, Thai.
Elixir; oral drops: Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Wyeth, Venez.
Syrup: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract disorders.

Dimetapp Chesty Cough *Wyeth Consumer, Austral.*
Guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2).
Cough.

Dimetapp Childrens Cold & Fever *Wyeth Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Upper respiratory-tract disorders.

Dimetapp Children's Cough & Cold *Whitehall-Robins, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Dimetapp Cold *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; cold symptoms.

Dimetapp Cold, Cough & Flu
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.
Day & Night Liquid Capsules: Day capsules, dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night capsules, dextromethorphan hydrobromide; pseudoephedrine hydrochloride; doxylamine succinate (p.578·2); paracetamol.
Cold and influenza symptoms.

Wyeth Consumer, Austral.
Liquid Capsules: Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Cold and influenza symptoms; coughs.

Dimetapp Cold, Cough & Flu Day & Night *Whitehall, NZ†.*
Day capsules, dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night capsules, dextromethorphan hydrobromide; pseudoephedrine hydrochloride; doxylamine succinate (p.578·2); paracetamol.
Cold and influenza symptoms; cough.

Dimetapp Cold, Cough & Sinus *Wyeth Consumer, Austral.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Dimetapp Cold & Fever *Whitehall-Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); paracetamol (p.108·1).
Cold symptoms.

Dimetapp Cold & Flu *Wyeth Consumer, Austral.; Whitehall, NZ†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms; cough; coughs.

Dimetapp Cough & Congestion *Wyeth Consumer, Canad.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Dimetapp Daytime Cold *Wyeth Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; upper respiratory-tract disorders.

Dimetapp Decongestant *Whitehall-Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Dimetapp Decongestant Plus Cough *Whitehall-Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Dimetapp DM
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract symptoms.

Whitehall-Robins, USA.
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Dimetapp DM Cold & Cough *Wyeth Consumer, NZ.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms; cough; hay fever; nasal congestion.

Dimetapp DM Cough & Cold *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms; upper respiratory-tract disorders.

Dimetapp Expectorante *Wyeth Consumer, Braz.*
Guaifenesin (p.1561·3).
Formerly contained brompheniramine maleate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin.
Cough.

Dimetapp Headcold & Flu *Wyeth Consumer, Austral.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Dimetapp 12 Hour Nasal *Wyeth Consumer, Austral.; Wyeth Consumer, NZ.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Dimetapp Long Acting Cough Plus Cold *Wyeth Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Dimetapp New *Wyeth, Gr.†.*
Brompheniramine maleate (p.569·2); phenylpropanolamine hydrochloride (p.1569·3).
Hypersensitivity reactions.

Dimetapp Nighttime Cold *Wyeth Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms; upper respiratory-tract disorders.

Dimetapp Nighttime Flu *Whitehall-Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); brompheniramine maleate (p.569·2).
Coughs and cold symptoms.

Dimetapp Non-Drowsy Flu *Whitehall-Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Dimetapp Oral Infant Cold & Fever Drops *Wyeth Consumer, Canad.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Allergy symptoms; cold symptoms; fever.

Dimetapp Oral Infant Drops *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; hypersensitivity reactions.

Dimetapp Pain & Fever Relief *Wyeth Consumer, Austral.*
Ibuprofen (p.64·2).
Fever; pain.

Dimetapp Sinus
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.; Whitehall, NZ†.
Pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion.

Robins, USA.
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Nasal congestion.

Dimetapp-C *Wyeth Consumer, Canad.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2).
Cold symptoms; upper respiratory-tract disorders.

Dimethicream *Hamilton, Austral.*
Dimeticone (p.2032·1); cetrimide (p.1634·1).
Emollient barrier cream.

Dimetil *Mibe, Ger.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Dimetin-F *Farcoral, Mex.†.*
Dimenhydrinate (p.576·2).
Nausea and vomiting.

Dimetirol *Offenbach, Mex.*
Metamizole magnesium (p.49·3).
Fever; muscle spasm; pain.

Dimetofan *Vitae, Mex.*
Dextromethorphan (p.1555·2); pseudoephedrine (p.1571·2).
Coughs.

Dimetriose *Aventis, Austral.; Sanofi-Aventis, Malaysia; Aventis, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Aventis, Thai.; Distriphar, UK.*
⊗ Gestrinone (p.2106·1).
Endometriosis.

Dimetrose *Sanofi-Aventis, Braz.; Pharmacia, Ital.*
⊗ Gestrinone (p.2106·1).
Endometriosis.

Dimex *Cazi, Braz.†.*
Dipyrone (p.49·2); diphenhydramine hydrochloride (p.577·2).
Fever; pain.

Dimexol *Medicamenta, Cz.*
Mephenoxalone (p.1897·2).
Skeletal muscle spasm.

Dimezin *Teuto, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Dimicaps *Gelcaps, Mex.*
Dimenhydrinate (p.576·2).
Nausea and vomiting; vertigo.

Dimicin *Bergamo, Braz.†.*
Phthalylsulfacetamide (p.315·1); neomycin sulfate (p.305·1); aluminium hydroxide (p.1706·2).
Diarrhoea.

Dimicina *Codilab, Port.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Diarrhoea.

DiMill *SIT, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection; eye irritation.

Dimin *TNP, Thai.†.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting.

Diminex Antitusigeno *Vinas, Spain.*
Cineole (p.2282·3); chlorcyclizine hydrochloride (p.571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Diminon *Master, Chile.*
Clonixin lysine (p.37·1).
Inflammation; pain.

Diminor *Alphrema, Ital.*
Phaseolamin.
Slimming aid.

Diminual *Labocean, Fr.†.*
Avena; citrus documana murra; camelia sinensis; ananas tige; pectin; yeast; laminaria digitata; sweet marjoram (p.1922·1).
Nutritional supplement.

Diminut *Libbs, Braz.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Dimipress *Cifarma, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Dimirel *Aventis, Austral.*
Glimepiride (p.441·1).
Diabetes mellitus.

Dimiril *Chowgule, India†.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Dimitone *Roche, Belg.; Roche, Denm.; Abic, Israel.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Dimodan *Aventis, Mex.*
Disopyramide (p.1269·1).
Arrhythmias.

Dimol *Wallace, India.*
Simeticone (p.1770·2).
Adjunct in gastroscopy and abdominal x-ray; flatulence; infant colic.

Dimopen *Bruluagsa, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Dimophen DC *Nakornpatana, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Dimor *Nordic, Swed.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dimorf *Cristalia, Braz.*
⊗ Morphine sulfate (p.86·3).
Pain.

Dimotane *Goldshield, UK†.*
Brompheniramine maleate (p.569·2).
Allergic rhinitis; urticaria.

Dimotane Co *Wyeth Consumer, Irl.; Wyeth Consumer, UK.*
Brompheniramine maleate (p.569·2); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Dimotane Expectorant *Wyeth Consumer, UK.*
Brompheniramine maleate (p.569·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract congestion.

Dimotane Plus *Goldshield, UK†.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Dimotapp Expectorant *Wyeth, Fr.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Dimotil *Quality, Hong Kong.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea; ostomy management.

Dimzef *CKD, Philipp.; Unimex, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Dina *San Carlo, Ital.†.*
Cimetidine (p.1716·2).
Gastrointestinal disorders associated with hyperacidity.

Dinac *Douglas, Austral.; Sriprasit, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dinaclon *Vianex (Βιανέξ), Gr.†.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Dinacode
Note. This name is used for preparations of different composition.
Picot, Fr.†.
Cream: Turpentine oil (p.2406·3); pine oil (p.2368·2); rosemary oil (p.2381·3); wild thyme oil (p.2415·3); white thyme oil; niaouli oil (p.2351·3); cineole (p.2282·3); quinine sulfate (p.612·3).
Respiratory congestion.

Picot, Fr.†.
Paediatric suppositories: Sodium benzoate (p.1630·2); cineole (p.2282·3).
Formerly contained potassium borotartrate, sodium benzoate, sodium bromide, and phenobarbital.
Coughs.

Picot, Fr.†.
Paediatric syrup: Sodium benzoate (p.1630·2); grindelia (p.2317·2); wild thyme (p.2415·3); tolu balsam (p.1574·2).
Coughs.

Dinacode avec codeine
Note. This name is used for preparations of different composition.
Picot, Fr.†.
paediatric syrup; Syrup: Sodium benzoate (p.1630·2); wild thyme (p.2415·3); tolu balsam (p.1574·2); codeine (p.37·2).
Coughs.

Picot, Fr.†.
Suppositories: Codeine (p.37·2); cineole (p.2282·3).
Coughs.

Dinacode N
Note. This name is used for preparations of different composition.
Picot, Switz.†.
Syrup: Codeine (p.37·2); sodium benzoate (p.1630·2); thyme (p.2401·1); tolu balsam (p.1574·2).
Coughs.

Picot, Switz.†.
Tablets: Codeine (p.37·2); sodium benzoate (p.1630·2).
Coughs.

Dinaflex *Zodiac, Braz.; Tecnofarma, Chile.*
Glucosamine sulfate (p.2313·2).
Arthroses; degenerative joint disorders.

Dinaflex Duo *Tecnofarma, Chile.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Degenerative joint disorders.

Dinaflox *Quimica y Farmacia, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Dinagen *Hormona, Mex.*
Piracetam (p.368·2).
Cerebrovascular disease.

Dinalexin *Pharmathen, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Dinamel *Liferpal, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Dinamot *Giempi, Venez.*
Famotidine (p.1730·1).
Gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Dinamotonic *Pharma Investi, Chile†.*
Vitamin E; vitamin C; zinc; selenium (p.1922·1).
Tonic.

Dinapres *Chiesi, Gr.; Master Pharma, Ital.*
⊗ Delapril (p.1256·2); indapamide (p.1314·1).
Hypertension.

Dinaron *Pfizer, Arg.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; female infertility; hypogonadotrophic hypogonadism.

Dinasepte *Cosmofarma, Port.†.*
Povidone-iodine (p.1659·2).
Mouth and throat disorders; skin and vulvovaginal infections; skin disorders; skin, burn, and vaginal disinfection.

Dinate *Jaapharm, Canad.; Seatrace, USA.*
Dimenhydrinate (p.576·2).
Motion sickness.

Dinaton *Ache, Braz.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Dinavir *Cristalia, Braz.†.*
Indinavir sulfate (p.882·2).
HIV infection.

Dinavital C *Merck, Braz.*
Arginine (p.1928·2); ascorbic acid (p.1983·3).
Tonic.

Dinavital Ginseng *Raffo, Arg.†.*
Ginseng; pyritinol; B vitamins (p.1922·1).
Tonic.

Dinavital Q10 *Raffo, Arg.†.*
Betacarotene; ascorbic acid; *dl*-alpha tocoferol acetate; ubidecarenone (p.1922·1).
Antoxidant.

Dinavital Vascular *Raffo, Arg.†.*
Codergocrine; pyritinol; B vitamins; ginseng (p.1922·1).
Cerebrovascular disorders; tonic.

Dinaxil *Tecnifar, Port.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; asthma; hypersensitivity; urticaria.

Dinaxil Capilar *Serra Pamies, Spain.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Dinaxin *Rayere, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Dinazide *TO-Chemicals, Thai.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Dindevan *Sigma, Austral.; Biological E, India.*
Phenindione (p.1369·2).
Thromboembolic disorders.

Dinefec *British Dispensary, Thai.†.*
Diclofenac diethylamine (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Di-Neumobron
Note. This name is used for preparations of different composition.
Roemmers, Arg.
Oral solution: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Roemmers, Arg.
Soluble tablets: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); tipepidine hibenzate (p.1574·2).
Respiratory-tract disorders.

Roemmers, Arg.
Suppositories: Paracetamol (p.108·1); guaifenesin (p.1561·3); niaouli oil (p.2351·3); cineole (p.2282·3); camphor (p.2273·2); terpineol (p.2396·1).
Respiratory-tract disorders.

Dineurin *Drugtech, Chile.*
Gabapentin (p.482·3).
Epilepsy.

Dinex *Cipla, India.*
Didanosine (p.870·2).
HIV infection.

Dinid *Vargas, Venez.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Diniket *Schwarz, Ital.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Dinill *Allergan, Braz.*
Benzalkonium chloride (p.1629·1); boric acid (p.2268·1).
Formerly contained benzalkonium chloride, boric acid, borax, hamamelis, and chamomile.
Eye disorders.

Dinill-D *Allergan, Mex.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Dinisan *ProMed, Cz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Dinisor *Parke, Davis, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Dinistenile *Lepori, Port.†.*
⊗ Prasterone sodium sulfate (p.2124·2).
Anabolic; tonic.

Dinit *Leiras, Fin.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Dinitrile Ormovit *Biotech, Venez.†.*
⊗ Succinic dinitrile; vitamin B ; vitamin B (p.1922·1); methandriol.
Nervous disorders.

Dinitrile-Vit *Biotech, Venez.*
Succinic dinitrile; vitamin B ; vitamin B (p.1922·1).
Nervous disorders.

Dinitro-B *Cafar, Venez.*
Succinic dinitrile; vitamin B substances (p.1922·1).
Nervous disorders.

Dinitrobe *Cafar, Venez.*
Vitamin B substances (p.1922·1).

Dinnefords Teejel *SSL, UK†.*
Choline salicylate (p.36·3).
Denture irritation; herpes labialis; mouth ulcers; teething pain.

Dinobroxol *Sankyo, Spain.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Dinospray *Cipla-Medpro, S.Afr.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; myocardial infarction.

Dinostral *Helvepharm, Switz.†.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Dinoven *Sankyo, Spain.*
A heparinoid (p.1305·2).
Soft-tissue disorders; varices.

Dintoina *Recordati, Ital.*
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; trigeminal neuralgia.

Dintoinale *Recordati, Ital.*
Phenytoin sodium (p.495·2); methylphenobarbital (p.490·2).
Epilepsy.

Dinul *Tecnifar, Port.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dinyl *Slovakofarma, Cz.†.*
Aminophenazone (p.19·1); allobarbital (p.959·3); butobarbital (p.967·2); phenacetin (p.115·3); caffeine (p.1116·3).
Pain.

Dio *Sciencex, Fr.*
Diosmin (p.2304·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Dioalgo *Bouchara-Recordati, Fr.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Diocaine *Dioptic, Canad.†.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Diocalm Dual Action *SSL, UK.*
⊗ Morphine hydrochloride (p.86·3); attapulgite (p.1709·1).
Diarrhoea.

Diocalm Ultra *SSL, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diocam *Elisium, Arg.*
Clonazepam (p.478·2).
Anxiety; epilepsy; panic attacks; social phobia.

Diocaps *Berk, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Diocarpine *Dioptic, Canad.†.*
Pilocarpine hydrochloride (p.1884·3).
Cholinergic; production of miosis.

Diochloram *Dioptic, Canad.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Diocimex *Cimex, Switz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Diocla *Oriental, Arg.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Diocomb SI *Novartis, Braz.*
Tablets, valsartan (p.1420·2); tablets, simvastatin (p.1390·2).

Dioctyl *UCB, UK.*
Docusate sodium (p.1725·1).
Constipation.

Dioctyn *Dixon-Shane, USA.*
Docusate sodium (p.1725·1).
Constipation.

Diodarone *Prodotti, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Dioderm *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Diodex *Dioptic, Canad.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Diodolina *Mayo, Mex.*
Diiodohydroxyquinoline (p.832·1); metronidazole (p.837·1).
Amoebiasis.

Diodonato *Andromaco, Venez.†.*
Zinc undecenoate (p.549·3); calcium propionate (p.545·3); diiodohydroxyquinoline (p.832·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Fungal skin infections.

Diodoquin *Glenwood, Canad.; Pfizer, Mex.; Pfizer, Venez.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Diofen *Liptis, USA.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes.

Dioflam *Polychronus, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Diofluor *Dioptic, Canad.*
Fluorescein sodium (p.2306·1).
Aid to ophthalmic examination.

Diogent *Dioptic, Canad.†.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Diolan *Zentiva, Cz.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Diolaxil *Sanofi Synthelabo, Spain†.*
Sennosides A and B (p.1769·3).
Constipation.

Diomicete *Edol, Port.*
Clotrimazole (p.530·1).
Fungal eye infections.

Diomycin *Dioptic, Canad.†.*
Erythromycin (p.269·2).
Bacterial eye infections.

Diondel *Roemmers, Arg.*
Flecainide (p.1289·2).
Arrhythmias.

Dionephrine *Dioptic, Canad.*
Phenylephrine hydrochloride (p.1568·1).

Dionina *Merck, Arg.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Dionosil *GSK, Israel†.*
Propyliodone (p.1488·3).
Radiographic contrast medium for bronchography.

Diopentolate *Dioptic, Canad.†.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Diophenyl-T *Dioptic, Canad.†.*
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Diopine *Alvia (Αλβια), Gr.†; Allergan, Mex.†; Allergan, Neth.; Allergan, Spain; Allergan, Switz.†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Diopred *Dioptic, Canad.†.*
⊗ Prednisolone acetate (p.1541·1).
Eye inflammation.

Dioptears *Dioptic, Canad.*
Polysorbate 80 (p.1919·2).
Dry eyes.

Dioptec *Dergam, Fr.*
Evening primrose oil (p.2302·1); salmon oil (p.1362·1); calendula (p.2273·1); vitamins; minerals (p.1922·1).
Dry eyes.

Diopticon *Dioptic, Canad.*
⊗ Naphazoline hydrochloride (p.1565·2).

Diopticon A *Dioptic, Canad.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).

Dioptimyd *Dioptic, Canad.†.*
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Eye disorders.

Dioptrol *Dioptic, Canad.†.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); dexamethasone (p.1526·1).
Eye disorders.

Dioralyte *Sanofi-Aventis, Irl.; Aventis, Neth.; Korangi, Port.; Aventis, UK.*
Sodium chloride; potassium chloride; sodium acid citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dioralyte Effervescent *Aventis, UK†.*
Sodium chloride; sodium bicarbonate; potassium chloride; citric acid; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dioralyte Relief *Aventis, UK.*
Rice powder; sodium citrate; sodium chloride; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dioralyte Rice *Aventis, Neth.†.*
Rice powder; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Dioran *Andromaco, Chile†.*
Ibuprofen (p.64·2); dipyrone (p.49·2); chlormezanone (p.968·3).
Musculoskeletal spasm; pain.

Diorouge *Dioptic, Canad.*
Pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).

Diosmectal *Malesci, Ital.*
Diosmectite (p.1771·1).
Gastrointestinal disorders.

Diosmil *Cooperation Pharmaceutique, Fr.†.*
Diosmin (p.2304·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Diosmin *Ache, Braz.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Diosmina Complex *Amnol, Ital.*
Diosmin (p.2304·2); hesperidin (p.2304·3); melilot (p.2339·2); vitamins (p.1922·1).
Circulatory disorders.

Diosper *Kleva, Gr.; Kleva, Singapore.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; vascular disorders; venous insufficiency.

Diostate *Roberts, USA.*
Calcium with vitamin D and phosphorus (p.1922·1).
Calcium deficiency; dietary supplement.

Diosulf *Dioptic, Canad.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Diosven *CT, Ital.*
Diosmin (p.2304·2).
Peripheral vascular disorders.

Diotrope *Dioptic, Canad.†.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Diotroxin *Pharmacare, S.Afr.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Hypothyroidism.

Diotul *Faes, Spain.*
Dosmalfate (p.1727·3).
NSAID-induced peptic ulcer.

Diovan *Novartis, Arg.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Mochida, Jpn; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Valsartan (p.1420·2).
Heart failure; hypertension; left ventricular dysfunction; myocardial infarction.

Diovan A *Novartis, Arg.*
Valsartan (p.1420·2); amlodipine (p.1214·2).
Angina pectoris; hypertension.

Diovan Amlo *Novartis, Braz.*
Valsartan (p.1420·2); amlodipine besilate (p.1214·1).
Hypertension.

Diovan Comp *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Diovan D *Novartis, Arg.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Diovan HCT *Novartis, Braz.; Novartis, Canad.; Novartis, Hung.; Novartis, USA; Novartis, Venez.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Diovan Triple *Novartis, Arg.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3); amlodipine (p.1214·2).
Angina pectoris; hypertension.

Diovan/Amlibon *Novartis, Venez.*
14 Tablets, valsartan (Diovan) (p.1420·2); 14 tablets, amlodipine (Amlibon) (p.1214·2).
Angina pectoris; hypertension.

Diovane *Novartis, Belg.*
Valsartan (p.1420·2).
Hypertension.

Diovenor *Innothera, Fr.; Zuoz Innothera, Venez.*
Diosmin (p.2304·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Diovol
Note. This name is used for preparations of different composition.
Wallace, India.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium carbonate (p.1743·1); simeticone (p.1770·2).
Gastritis; gastrointestinal hyperacidity; hiatus hernia; peptic ulcer.

Church & Dwight, Canad.
Caplets; oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; heartburn.

Carter Horner, Thai.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Church & Dwight, Canad.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Dyspepsia; heartburn.

Carter Horner, Thai.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Diovol Ex *Church & Dwight, Canad.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Diovol Forte *Wallace, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastritis; gastrointestinal hyperacidity; hiatus hernia; peptic ulcer.

Diovol Forte DGL *Wallace, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2); liquorice (p.1740·3).
Gastritis; gastrointestinal hyperacidity; hiatus hernia; peptic ulcer.

Diovol Plus
Note. This name is used for preparations of different composition.
Church & Dwight, Canad.; Carter Horner, Hong Kong.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Church & Dwight, Canad.; Carter Horner, Hong Kong.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Diovol Plus AF *Church & Dwight, Canad.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; heartburn.

Dioxadol
Note. This name is used for preparations of different composition.
Montpellier, Arg.
Oral drops: Dipyrone (p.49·2); paracetamol (p.108·1).
Pain.

Montpellier, Arg.
Syrup; tablets: Dipyrone (p.49·2).
Pain.

Dioxaflex
Bago, Arg.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac epolamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Bago, Braz.
Diclofenac sodium (p.44·3).
Inflammation; pain.

Armstrong, Mex.
Diclofenac epolamine (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Dioxaflex B12 *Bago, Arg.*
⊗ Diclofenac sodium (p.44·3); betamethasone (p.1518·2); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Joint pain.

Dioxaflex Forte *Bago, Arg.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Pain.

Dioxaflex Gesic *Bago, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Dysmenorrhoea; soft-tissue disorders.

Dioxaflex Plus *Bago, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint, and peri-articular disorders.

Dioxicolagol *Fabra, Arg.*
Cynara (p.2291·2); boldo (p.2267·2); belladonna (p.2263·3); valerian (p.2410·1); espina colorada.
Digestive disorders.

Dioxis *Hexa, Arg.*
Aciclovir (p.862·3).
Herpesvirus infections.

Dip *Merck, Venez.*
Sucralfate (p.1772·2).
Peptic ulcer.

Dip Hot *Mentholatum, Pol.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Dip Rilif *Mentholatum, Pol.*
Ibuprofen (p.64·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dipamona *Roemmers Rowe, Venez.*
Dipyrone (p.49·2).
Fever; pain.

Dipana *Promed, Rus.*
Picrorhiza kurroa; andrographis paniculata; eclipta alba; phyllanthus niruri; black nightshade (p.2267·1); tinospora cordifolia; bacopa monnieri; punarnava (p.2376·3); ginger (p.1732·3); piper longum.
Liver disorders.

Dipankrin *Gedeon Richter, Hung.*
Pancreatin (p.2360·1); duodenum extract (p.2337·3).
Gastrointestinal disorders.

Dipatropin *Pasteur, Chile.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3).
Muscle spasm.

Dipaverina *Geyer, Braz.†.*
Papaverine hydrochloride (p.2191·3).

Dipazide *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Dipecfur *Parggon, Mex.*
Diiodohydroxyquinoline (p.832·1); activated charcoal (p.1435·2).
Diarrhoea.

Dipemina *Lazar, Arg.; Raffo, Chile.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Dipen *Elpen (Ελπεν), Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Dipentum *Pharmacia, Arg.†; UCB, Austral.; UCB, Austria; Pfizer, Canad.; Pfizer, Chile; Celltech, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; Pharmacia-Upjohn, Gr.†; UCB, Hong Kong; Pharmacia, Hung.†; UCB, Irl.; Pharmacia, Israel†; Pharmacia, Ital.†; Pharmabroker, NZ; UCB, Neth.; Celltech, Norw.; Pharmacia, S.Afr.; UCB, Swed.; UCB, Switz.; Eczacibasi, Turk.; UCB, UK; UCB, USA.*
Olsalazine sodium (p.1752·2).
Inflammatory bowel disease.

Dipep *Serum Institute, India.*
Papain (p.2362·3); amylase (p.2256·3); pepsin (p.2365·1); lipase (p.2360·3); cellulase (p.2279·1).
Dyspepsia.

Dipeptamin *Fresenius Kabi, Ger.*
-Alanyl- -glutamine (p.1947·2).
Parenteral nutrition.

Dipeptiven *Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK.*
-Alanyl- -glutamine (p.1947·2).
Parenteral nutrition.

Diperflox *Francia, Ital.*
Norfloxacin pivoxil (p.309·3).
Urinary-tract infections.

Dipergon *Schering, Gr.*
Lisuride (p.811·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; prolactinoma.

Diperil *Bioethical, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Diperpen *Francia, Ital.*
Pipemidic acid (p.315·1).
Bacterial infections of the urinary tract.

Dipezona *Omega, Arg.*
Diazepam (p.986·3).
Anxiety; epilepsy; muscle spasm; sedation.

Diphafen *Sons, Mex.*
Difenidol (p.1723·2).
Nausea and vomiting.

Diphamine *Medgenix, Belg.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; insect stings; pruritus; sunburn; urticaria.

Diphantoine
Wolfs, Belg.
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy.

Katwijk, Neth.
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; epilepsy.

Diphedan *EGIS, Hung.*
Phenytoin (p.495·2).
Epilepsy; trigeminal neuralgia.

Diphen *ICM, Singapore.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Bronchial congestion; cold symptoms; coughs.

Diphen AF *Morton Grove, USA.*
Diphenhydramine hydrochloride (p.577·2).

Diphen Tann/ PE Tann/ CT Tann *Brighton, USA.*
Pentoxyverine tannate (p.1567·3); diphenhydramine tannate (p.577·3); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Diphenal *Minerva (Μινερβα), Gr.*
Phenytoin (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Diphenamill *Brunel, S.Afr.†.*
Aminophylline (p.1114·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Diphendryl Expectorant *TO-Chemicals, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; nasal congestion.

Diphenhist *Rugby, USA.*
Diphenhydramine hydrochloride (p.577·2).

Diphenhydramine Compound Linctus *Medipharma, Hong Kong†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).

Diphenhydramine Constrictor *Viatris, Belg.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Hypersensitivity reactions.

Diphenhydramine Expectorant
Note. This name is used for preparations of different composition.
Pharmaniaga, Malaysia.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Formerly called Benalix.
Coughs; upper respiratory-tract congestion.

SA Druggists, S.Afr.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; respiratory-tract congestion.

Diphenhydramine Expectorant Syrup *Adco, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); chloroform (p.1781·1).
Coughs.

DiphenMax D *Rivers Edge, USA.*
Phenylephrine tannate (p.1568·3); diphenhydramine tannate (p.577·3).
Upper respiratory-tract disorders.

Diphereline
Beaufour, Cz.; Beaufour-Ipsen, Hung.
⊗ Triptorelin acetate (p.2135·3).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Beaufour-Ipsen, Hong Kong; Beaufour Ipsen, Pol.; Beaufour-Ipsen, Rus.
⊗ Triptorelin (p.2135·2).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Pharma Biotech, Israel; Ipsen, Thai.
⊗ Triptorelin embonate (p.2135·3).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroids.

Diphergan *Altana, Pol.; Jelfa, Pol.*
Promethazine hydrochloride (p.588·2).
Asthma; hypersensitivity reactions; motion sickness; premedication.

Diphlogen *Novartis Consumer, Austria.*
Aluminium sodium silicate (p.1707·3); eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diphos *Procter & Gamble, Ger.*
Etidronate disodium (p.1097·1).
Ectopic ossification; Paget's disease of bone.

Diphtheria *Commonwealth Serum, Hong Kong.*
A diphtheria immunoglobulin (equine).
Passive immunisation; treatment of diphtheria.

Dipidol *Behrens, Venez.*
Dipyrone (p.49·2).
Fever; pain.

Dipidolor *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Ger.; Janssen-Cilag, Neth.*
Piritramide (p.117·2).
Pain.

Dipigrand *Ahimsa, Arg.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Dipimax *Cimed, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Dipinal *Cifarma, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Dipiperon *Janssen-Cilag, Belg.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Neth.; Janssen-Cilag, Switz.*
Pipamperone hydrochloride (p.1019·1).
Aggressive states; behaviour disorders; drug withdrawal syndromes; psychoses; sleep disorders.

Dipirex *Geyer, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Dipirol *Royton, Braz.†.*
Dipyrone (p.49·2); adiphenine hydrochloride (p.2248·1); homatropine methylbromide (p.1881·3); papaverine hydrochloride (p.2191·3).
Muscle spasm; pain.

Dipiron *IMA, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Dipironax *Royton, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Dipix *Geolab, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Diplexil *Tecnifar, Port.*
Sodium valproate (p.508·2).
Epilepsy.

Diplexil-R *Tecnifar, Port.*
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; migraine and other headaches.

Diplovax *Biovac, S.Afr.*
A measles vaccine (Edmonston-Zagreb strain) (p.2221·3).
Active immunisation.

Dipni *Omega, Arg.*
Nystatin (p.543·2).
Candidiasis.

Dipofen *Arlex, Mex.*
Ibuprofen (p.64·2).
Inflammation.

Dipoquin *Ioquin, Austral.; Pacific, NZ†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Diposef *Unison, Thai.†.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Dipot *Asian Pharm, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Dipres *Precimex, Mex.*
Dipyridamole (p.1268·1).

Diprin *Geolab, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Diprivan *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.†; AstraZeneca, Fr.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; Nicholas Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Thai.†; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Propofol (p.1791·1).
General anaesthesia; sedation; sedative.

Di-Pro *Organon, Turk.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Endometriosis; menopausal disorders; menstrual disorders.

Dipro AS *Delta, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Psoriasis.

Diprobase
Note. This name is used for preparations of different composition.
Essex, Chile; Schering-Plough, Fr.; Schering-Plough, Hong Kong; Schering-Plough, Irl.; Schering-Plough, Port.†.
Emollient.
Skin disorders; topical vehicle.

Schering-Plough, Pol.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Skin disorders.

Schering-Plough, UK.
Cream: Emollient.
Dry skin conditions; topical vehicle.

Schering-Plough, UK.
Ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Emollient.

Diprobath *Schering-Plough, UK.*
Light liquid paraffin (p.2031·1); isopropyl myristate (p.2029·3); laureth 4.
Dry skin disorders; hyperkeratoses.

Diprobet *Polipharm, Thai.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprobeta *Bunker, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprocel *Key, Arg.†; Schering-Plough, Hong Kong; Schering-Plough, Malaysia; Schering-Plough, Singapore; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprocort *Cifarma, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diproderm *Aesca, Austria; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Norw.; Schering-Plough, Spain; Schering-Plough, Swed.*
⊗ Betamethasone dipropionate (p.1518·3).
Otitis externa; skin and scalp disorders.

Diprodin *Kotra, Malaysia.*
⊗ Diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2).
Allergic rhinitis; cold symptoms; cough.

Diprodol *Sons, Mex.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Diproex *Unichem, India.*
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; migraine.

Diprofast *Schering-Plough, Mex.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprofol *Taro, Israel.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Diproform *Schering-Plough, Ital.; Schering-Plough, Philipp.*
⊗ Betamethasone dipropionate (p.1518·3); clioquinol (p.254·1).
Infected skin disorders.

Diproformo *Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3); clioquinol (p.254·1).
Infected skin and scalp disorders.

Diproforte *Aesca, Austria.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprofos *Schering-Plough, Port.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprogen *Schering, Canad.†.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Diprogenta *Schering-Plough, Arg.; Aesca, Austria; Mantecorp, Braz.; Essex, Ger.; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Essex, Switz.; Schering-Plough, Thai.†; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Diprolen *Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Swed.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprolene *Schering-Plough, Belg.; Essex, Chile; Schering-Plough, Fr.; Schering-Plough, Israel; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, S.Afr.†; Essex, Switz.; Schering-Plough, Turk.; Schering, USA.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin and scalp disorders.

Diprolene Glycol *Schering, Canad.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Di-Promal
Note. A similar name is used for preparations of different composition (see below).
Mundipharma, Austria.
⊗ Ipratropium bromide (p.1124·1); salbutamol (p.1131·2).
Obstructive airways disease.

Dipromal
Note. A similar name is used for preparations of different composition (see above).
ICN, Pol.
Magnesium valproate (p.511·3).
Epilepsy.

Dipronova *Unipharm, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprophos *Aesca, Austria; Schering-Plough, Belg.; Schering-Plough, Cz.; Schering-Plough, Hung.; Schering-Plough, Pol.; Essex, Switz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diproquin *Essex, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); hydroxyquinoline iodochloride (p.2323·2).
Infected skin disorders.

Diprosalic *Schering-Plough, Arg.; Aesca, Austria; Schering-Plough, Belg.; Mantecorp, Braz.; Schering, Canad.; Essex, Chile; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.†; Schering-Plough, NZ†; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Essex, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, UK; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Keratinisation disorders; skin and scalp disorders.

Diprosen *Teuto, Braz.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprosept *Schering-Plough, Fr.†.*
⊗ Betamethasone dipropionate (p.1518·3); clioquinol (p.254·1).
Infected skin disorders.

Diprosis *Essex, Ger.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprosone *Schering-Plough, Arg.; Schering-Plough, Austral.; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering, Canad.; Schering-Plough, Cz.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Hong Kong; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3).
Corticosteroid; skin and scalp disorders.

Diprosone Depot *Essex, Ger.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Parenteral corticosteroid.

Diprosone G *Schering-Plough, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Diprosone Neomycine *Schering-Plough, Fr.*
⊗ Betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Diprosone Y *Schering-Plough, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); clioquinol (p.254·1).
Infected skin disorders.

Diprosone-OV *Schering-Plough, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Diprospan
Schering-Plough, Braz.; Schering-Plough, Denm.; Schering-Plough, Hong Kong; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Mex.; Essex, Philipp.; Schering-Plough, Rus.; Schering-Plough, Singapore; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, Venez.
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Essex, Chile.
Cream; ointment: ⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Essex, Chile.
Injection: ⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprospan G *Essex, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Diprosta *Konimex, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Diprostene *Schering-Plough, Fr.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Diprotop *Schering-Plough, Thai.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Dipsin *CPH, Port.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Dipxapen *Liferpal, Mex.†.*
Dicloxacillin (p.265·2).
Bacterial infections.

Dipydol *Valdecasas, Mex.*
Dipyrone (p.49·2).
Pain.

Dipyridan *Aventis, Belg.†.*
Dipyridamole (p.1268·1).
Angina pectoris; thromboembolism prophylaxis.

Dipyrin *Ratiopharm, Fin.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Dirahist *Teofarma, Ital.*
⊗ Triamcinolone (p.1544·2); chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Diralon *Biotech, Venez.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Dirastan *Zentiva, Cz.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Directim *Azevedos, Port.†.*
Amineptine hydrochloride (p.375·3).
Depression.

Direktan *Gerot, Austria.*
Sodium nicotinate (p.1958·3).
Decubitus ulcer; peripheral vascular disease; sports massage.

Dirfaben *Rayere, Mex.†.*
Pancreatin (p.2360·1); ox bile (p.2266·3); dimeticone (p.1770·2).
Digestive disorders.

Dirine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗ Furosemide (p.1292·1).
Diuretic; hypertension; oedema.

Dirinol *Cryopharma, Mex.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Diroquine *Atlantic, Thai.*
Chloroquine phosphate (p.599·3).
Amoebiasis; malaria; rheumatoid arthritis.

Diroseal *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile; Avene, Fr.*
⊗ Retinaldehyde (p.1612·2); HMC (p.2305·2); dextran sulfate (p.2293·1).
Rosacea; skin disorders; skin redness.

Diroton *Gedeon Richter, Cz.; Richter, Pol.; Gedeon Richter, Rus.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Dirox *Gramon, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Dirox Alergia *Gramon, Arg.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal and ocular symptoms of allergy.

Dirret *Best, Mex.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Dirtop *Medipharm, Chile.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Dirunez *Lamda (Λαμδα), Gr.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Dirytmin *Hassle, Swed.†.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Disalcid *3M, USA.*
Salsalate (p.122·1).
Musculoskeletal and joint disorders.

Disalgil *Also, Ital.†.*
Glycol salicylate (p.62·3); camphor (p.2273·2); capsaicin (p.32·3).
Musculoskeletal, joint, and soft-tissue disorders.

Disalgyl *Monin, Fr.†.*
Methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2); camphor (p.2273·2).
Musculoskeletal and joint pain.

Disalpin *AWD, Ger.†.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Disalunil *Berlin-Chemie, Ger.; Berlin-Chemie, Pol.†.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetic nephropathy; hypertension; oedema.

Disanal *Humana, Ital.*
Food for special diets (p.1922·1).
Gastrointestinal disorders.

Disbuspan *Prodotti, Braz.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Pain; smooth muscle spasm.

Disci Bamb *Pfluger, Ger.*
Homoeopathic preparation.

Dis-Cinil Complex *Menarini, Ital.*
Dihydroxydibutylether (p.2293·3); cascara (p.1715·2); rhubarb (p.1768·3); boldo (p.2267·2).
Constipation.

Disclo-Gel *Colgate Oral Care, Austral.*
Erythrosine (p.1471·3).
Disclosing agent for dental plaque.

Disclo-Plaque *Colgate Oral Care, Austral.*
Fluorescein (p.2306·1).
Disclosing agent for dental plaque.

Disclo-Tabs *Colgate Oral Care, Austral.*
Erythrosine (p.1471·3).
Disclosing agent for dental plaque.

Disco-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Discorid *Bros, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Discotrine *3M, Denm.; 3M, Fr.; Pfizer, Port.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; prevention of phlebitis and extravasation during intravenous infusion.

Discover *Carter-Wallace, UK.*
Pregnancy test (p.2372·1).

Discover One Step *Wilson, NZ.*
Pregnancy test (p.2372·1).

Discover Onestep *Carter, Austral.*
Pregnancy test (p.2372·1).

Discover Onestep Ovulation Prediction *Carter, Austral.*
Fertility test (p.2372·1).

DisCoVisc *Alcon, USA.*
Sodium hyaluronate (p.2320·1); chondroitin sulfate sodium (p.2280·3).
Adjunct in eye surgery.

Discozal *Bros, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Discretal *Beta, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Discus comp H *Heel, Neth.*
Homoeopathic preparation.

Disdolen *Uriach, Spain.*
Fosfosal (p.62·1).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Disdolen Codeina *Uriach, Spain.*
Codeine phosphate (p.37·2); fosfosal (p.62·1).
Pain.

Disebrin *Tubilux, Ital.*
Heparin sodium (p.1301·2).
Eye disorders.

Disel *Andromaco, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Disel Hidrocortisona *Andromaco, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); hydrocortisone (p.1535·2).
Nasal congestion.

Disento *Nakornpatana, Thai.*
Diiodohydroxyquinoline (p.832·1); furazolidone (p.834·3); neomycin sulfate (p.305·1); phthalylsulfathiazole (p.315·1); light kaolin (p.1738·1).
Diarrhoea; gastrointestinal infections.

Disento PF *Nakornpatana, Thai.*
Furazolidone (p.834·3); pectin (p.2145·2); light kaolin (p.1738·1).
Bacterial diarrhoea; enteritis.

Diseon *Teva, Ital.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Diseptil *Gedis, Ital.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Diseptyl *Rekah, Israel.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Disequens *Novo Nordisk, Arg.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Diser *Kee, India.*
Diclofenac potassium (p.44·3); serrapeptase (p.2385·3).
Inflammation; pain.

Diserim *Apsen, Braz.*
⊗ Bendroflumethiazide (p.1224·1); fluphenazine hydrochloride (p.998·1).
Obesity; oedema; premenstrual syndrome.

Diserinal *Boniscontro & Gazzone, Ital.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Disfabac *Prafa, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Disflatyl
Note. This name is used for preparations of different composition.
ICN, Austria; Solco, Cz.†; ICN, Fin.; Pharos, Indon.; Solco, Indon.; ICN, Malaysia; Valeant, Philipp.; ICN, Rus.; Valeant, Switz.; ICN, Thai.
Simeticone (p.1770·2).
Aerophagia; dyspepsia; excess gastrointestinal gas; flatulence; gastrointestinal bloating; meteorism; preparation for gastrointestinal investigations.

Valeant, Singapore.
Dimeticone (p.1770·2); silicon dioxide (p.2146·2).
Flatulence; preparation for gastrointestinal investigations.

Solco, Hong Kong.
Oral drops: Simeticone (p.1770·2).
Flatulence; preparation for gastrointestinal investigations.

Solco, Hong Kong.
Tablets: Dimeticone (p.1770·2); silicon dioxide (p.2146·2).
Flatulence; preparation for gastrointestinal investigations.

Disflux *Corsa, Indon.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Disfruta *Maver, Chile.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Antacid.

Disfrutab *Maver, Chile.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Disgren
Note. This name is used for preparations of different composition.
Bago, Arg.; Biosintetica, Braz.; Uriach, Hung.; Sanfer, Mex.; Uriach, Spain; Megat, Venez.
Triflusal (p.1418·3).
Myocardial infarction; stroke; thromboembolic disorders.

Pasteur, Chile.
Aspirin (p.20·3).
Fever; pain; thromboembolism prophylaxis.

Disifelit *Fada, Arg.*
⊗ Droperidol (p.994·3); fentanyl (p.55·3).
Neuroleptanalgesia.

Disigien *AFOM, Ital.*
Benzalkonium chloride (p.1629·1).
Skin and wound disinfection.

Disinal *Silanes, Mex.*
Clonixin lysine (p.37·1).
Pain.

Disinfecting *Teka, Turk.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Disinfene *AFOM, Ital.*
Chlorhexidine hydrochloride (p.1635·3); hydroxyquinoline sulfate (p.2323·1).
Skin and wound disinfection.

Disinol *Kocak, Turk.*
Chlorobutanol (p.1639·2); phenol (p.1656·1); clove oil (p.2285·1).
Mouth and throat pain; teething pain.

Disintryl *Aledicine, Gr.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Disintyl *Zeta, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds, burns, and external genitals.

Disipal *Astellas, Belg.; Yamanouchi, Denm.; Gerolymatos, Gr.; Astellas, Ital.; CSL, NZ; Yamanouchi, Norw.†; 3M, S.Afr.; Yamanouchi, Swed.†; Sovereign, UK.*
Orphenadrine hydrochloride (p.812·1).
Drug-induced extrapyramidal disorders; neuroleptic syndrome; parkinsonism; senile or presenile depression; skeletal muscle spasm; vertigo.

Disipan *Bernabo, Arg.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Disithrom *Sanofarm, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Diskets *Cebert, USA.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal.

Diskin *Federfarma, Ital.†.*
Dihydroxydibutylether (p.2293·3).
Constipation with digestive disorders.

Dislax *Makros, Braz.†.*
Bisacodyl (p.1710·1).
Constipation.

Dislembral *Sanofi Synthelabo, Arg.†.*
Hyoscine butylbromide (p.1734·1); diazepam (p.986·3).
Muscle spasm with anxiety.

Dislep *Bago, Arg.; Silesia, Chile; Ferrer-Novag, Mex.; Leti, Venez.*
Levosulpiride (p.1028·3).
Dyspepsia; gastrointestinal motility disorders; nausea and vomiting; vertigo.

Dislipin *Leti, Venez.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Dislipina *Merck, Port.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Dislipor *Andromaco, Chile.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Dismam *Merck, Chile.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Dismaren *Sanofi Synthelabo, Arg.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Dismegyn *Gynea, Spain.*
Agnus castus (p.2249·1).
Menstrual disorders.

Dismenol *Merz, Switz.*
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; pain.

Dismenol N *Simons, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Dismenol Neu *Medra, Austria.*
Ibuprofen (p.64·2).
Pain.

Dismifen *Best, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Dismolan
Rivero, Arg.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Lapreven, Venez.
Ondansetron (p.1756·3).
Nausea and vomiting.

Dismozon pur *Bode, Ger.*
Magnesium monoperoxyphthalate.
Surface disinfection.

Disnal *Ferrer, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Disneumon Mentol *Solvay, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion; sinusitis.

Disneumon Pernasal *Solvay, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Nasal and sinus congestion.

Disobrom *Geneva, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Disocor *Janssen-Cilag, Port.*
Carnitine (p.1932·2).
Carnitine deficiency.

Diso-Duriles *AstraZeneca, Ger.†.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Disofrin *Essex, Chile†.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract disorders.

Disofrol *Schering-Plough, Fin.†; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Nasal congestion; rhinitis; upper respiratory-tract disorders.

Disogel *Concept, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); liquorice (p.1740·3); simeticone (p.1770·2).
Gastro-oesophageal reflux; peptic ulcer.

Disogram *Ranbaxy, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Disol *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion; respiratory-tract disorders associated with increased or viscous mucus.

Disolina *Biotech, Venez.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Disomet *Orion, Fin.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Disons Dex *Sons, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Disopain *Mitsubishi-Tokyo, Jpn.*
Mofezolac (p.86·2).
Inflammation; pain.

Disophrol *Schering-Plough, Cz.; Schering-Plough, Hung.†; Schering-Plough, Pol.; Schering-Plough, Turk.; Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Allergic rhinitis; otitis media; respiratory-tract congestion; rhinosinusitis; sinusitis.

Disopranil *Prater, Chile.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Disoprivan *AstraZeneca, Ger.; AstraZeneca, Switz.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Disotat *Alpharma-Isis, Ger.†.*
Di-isopropylammonium dichloroacetate (p.1265·1) or di-isopropylammonium hydrochloride (p.1265·1).
Hypertension.

Disothiazide *Dexxon, Israel.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Disotron *Ariston, Braz.*
Heparin sodium (p.1301·2).

Dispaclonidin *OmniVision, Ger.*
Clonidine hydrochloride (p.1247·1).
Glaucoma; ocular hypertension.

Dispacromil *OmniVision, Ger.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Dispadex comp *OmniVision, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Bacterial infections and inflammation of the eye.

Dispadol *Aventis, Venez.†.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Dispasan *Ioltech, Ger.*
Sodium hyaluronate (p.2320·1).
Adjunct in ocular surgery.

Dispasmol *Andromaco, Chile†.*
Phenobarbital (p.492·2); atropine (p.1219·2).
Muscle spasm.

Dispatenol *OmniVision, Ger.*
Dexpanthenol (p.2362·1); polyvinyl alcohol (p.2145·3).
Dry eyes.

Dispatim *Novartis, Austria; Novartis, Ger.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dispedrol *Chrispa (Χρισπα), Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Dispello *Ayrton, UK.*
Salicylic acid (p.1612·2); zinc chloride (p.1999·1); hypophosphorous acid (p.2323·3); pyroxylin (p.1611·3); colophony resin (p.2286·2).
Corns; warts.

Dispepci *Pentafarma, Port.*
Lansoprazole (p.1739·2).
Gastric hyperacidity.

Dispeptal *Nicholas Piramal, India†.*
Pancreatin (p.2360·1); vegetable enzymes; bile salts (p.2266·2).
Dyspepsia; eructation; flatulence; heartburn.

Dispeptrin *Cifarma, Braz.*
Co-trimoxazole (p.258·1); calcium carbonate (p.1714·1); attapulgite (p.1709·1).
Bacterial infections.

Disperbarium *Rovi, Spain.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Dispercarpine *Novartis, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of mydriasis.

Disperin *Orion, Fin.*
Aspirin (p.20·3).
Fever; musculoskeletal and joint disorders; pain; thromboembolism prophylaxis.

DisperMox *Ranbaxy, USA.*
Amoxicillin (p.202·2).
Bacterial infections.

Dispersadron-C *Novartis, Gr.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Bacterial eye infections with inflammation.

Displata *Itaca, Braz.†.*
Carboplatin (p.693·1).
Malignant neoplasms.

Display *Solea, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection; eye irritation.

Dispneitrat *IMA, Braz.*
Aminophylline (p.1114·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Dispon *Balverda, Ital.†.*
Liothyronine (p.2174·2).
Cellulite; local accumulation of adipose tissue.

Dispril *Reckitt Benckiser, Belg.; Reckitt Benckiser, Norw.; Ali, Turk.*
Aspirin (p.20·3).
Fever; inflammation; pain; rheumatic disorders; thromboembolism prophylaxis.

Disprin *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, India; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, UK.*
Aspirin (p.20·3).
Cold symptoms; fever; inflammation; pain; thromboembolic disorders.

Disprin Direct *Reckitt Benckiser, Austral.; Reckitt Benckiser, UK.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain.

Disprin Extra *Reckitt Benckiser, UK.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Disprin Forte *Reckitt Benckiser, Austral.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Disprin Paracetamol *Reckitt Benckiser, India.*
Paracetamol (p.108·1).
Fever; pain.

Disprina *Sanofi Synthelabo, Mex.*
Aspirin (p.20·3).
Fever; pain.

Disprol *Reckitt Benckiser, Irl.; Reckitt Benckiser, NZ†; Reckitt Benckiser, UK.*
Paracetamol (p.108·1).
Fever; pain.

Dispromil *Diviser Aquilea, Spain†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Disques Coricides *SSL, Fr.*
Salicylic acid (p.1612·2).
Calluses; corns.

Dissen *Andromaco, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Dissenten *SPA, Cz.; SPA, Ital.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dissolursil *Uno, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; cholesterol gallstones.

Distaclor *Flynn, Irl.; Lilly, Malaysia†; Lilly, Singapore†; Lilly, Thai.; Flynn, UK.*
Cefaclor (p.217·2).
Bacterial infections.

Distalene *Ivax, Arg.*
⊗ Anastrozole (p.681·2).

Distalgesic
Lilly, Hong Kong†; Napp, Irl.†; Meda, Swed.†; Dista, Switz.†; Meda, UK†.
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
These ingredients can be described by the British Approved Name Co-proxamol.
Pain.

Aspen, S.Afr.
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Fever; pain.

Distalgic *Lilly, Belg.†.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Distamine *Alliance, Irl.; Lilly, NZ†; Alliance, UK.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; hepatitis; rheumatoid arthritis; Wilson's disease.

Distaph *Alphapharm, Austral.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Distasil *Milana, Ital.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Distaxid *Norgine, Spain.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Distedon *Adelco, Gr.*
Diazepam (p.986·3); clidinium bromide (p.1722·1).
Peptic and urinary tract disorders.

Distenil *Sun, India.*
Simeticone (p.1770·2); activated charcoal (p.1435·2).
Aerophagia; diverticulosis; dyspepsia; food intolerance; gastrointestinal spasm; irritable bowel syndrome; malabsorption syndrome; meteorism.

Distensan *Esteve, Spain.*
Clotiazepam (p.980·3).
Anxiety; neuroleptanalgesia; premedication.

Disteril *Lachifarma, Ital.*
Benzalkonium chloride (p.1629·1).
Genital hygiene; skin, wound, and burn disinfection.

Distex *Recalcine, Chile.*
Flurbiprofen (p.61·2).
Pain.

Distilbene *Gerda, Fr.*
Diethylstilbestrol (p.2094·1).
Prostatic cancer.

Distimax *Medipharm, Chile.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome in women.

Distinon *Samarth, India.*
Pyridostigmine bromide (p.633·3).
Myasthenia gravis.

Distobram *Lilly, Port.†.*
Tobramycin (p.354·1).
Bacterial infections.

Distonal *Royal, Chile.*
Desipramine hydrochloride (p.387·3).
Attention-deficit hyperactivity disorder; bulimia; cocaine withdrawal syndrome; depression; narcoleptic syndrome; pain; panic attacks.

Distop *Zeler, Port.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).

Distraneurin *AstraZeneca, Ger.; AstraZeneca, Switz.*
Clomethiazole (p.978·1) or clomethiazole edisilate (p.978·1).
Alcohol withdrawal syndrome; sedative; senile confusion; sleep disorders.

Distraneurine *AstraZeneca, Belg.†; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Spain.*
Clomethiazole (p.978·1).
Alcohol withdrawal syndrome; behaviour disorders in the elderly; insomnia; sedative.

Distreptaza *Biomed Lublin, Pol.; Biomed Warszawa, Pol.*
Streptodornase (p.2393·1); streptokinase (p.1402·3).
Fistulae; infections; inflammation; ulcers; wounds.

Disudrin
Note. This name is used for preparations of different composition.
Medifarma, Indon.; Pediatrica, Indon.
Pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Pediatrica, Philipp.
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Disufen *Angenerico, Ital.*
⊗ Sufentanil citrate (p.125·1).
General anaesthesia; neuroleptanalgesia.

Di-Su-Frone *Hua, Thai.†.*
Furazolidone (p.834·3); pectin (p.2145·2); kaolin (p.1738·1).
Gastrointestinal infections.

Disulone *Sanofi-Aventis, Fr.*
Dapsone (p.261·2); ferrous oxalate (p.1939·2).
Dermatitis herpetiformis; leprosy; pneumocystis pneumonia; polychondritis.

Disupril *Faria, Braz.†.*
Amino acids; vitamin B substances (p.1922·1).
Nutritional supplement.

Diswart *Dermatech, Austral.*
Glutaral (p.1645·2).
Common warts.

DIT1-2 *Dunhall, USA.*
Sulfanilamide (p.343·1); aminoacridine hydrochloride (p.1625·1); allantoin (p.1588·1).
Vaginal infections.

Ditalin *Otto, Indon.*
Phenytoin (p.495·2); phenobarbital sodium (p.492·2).
Arrhythmias; chorea; epilepsy; parkinsonism; trigeminal neuralgia.

Ditana *Bajamed, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Ditanrix *GSK, Ital.; GSK, Spain; GSK, Switz.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Ditaven *Merck, Austria†.*
Digitoxin (p.1259·1).
Haematomas; leg oedema; peripheral vascular disease; varicose ulcers; venous insufficiency.

Ditavene *Pharmadeveloppement, Fr.*
Melilot (p.2339·2); red vine (p.2316·3).
Capillary disorders.

Ditayod *Solfran, Mex.*
Phthalylsulfathiazole (p.315·1); clioquinol (p.254·1).
Amoebiasis.

DiTe Anatoxal *Berna, Hong Kong†; Pharmabroker, NZ.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1). Separate preparations are available for adults and children.
Active immunisation.

DiTe Booster *Statens Serum Institut, Denm.; Statens Serum Institut, Fin.; Statens Serum Institut, Norw.; SSI, Swed.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Ditec *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Rus.*
⊗ Fenoterol hydrobromide (p.1121·1); sodium cromoglicate (p.1136·3).
Obstructive airways disease.

Di-Te-Ki-Booster *Statens Serum Institut, Denm.*
A diphtheria, tetanus and pertussis vaccine (p.2210·3).
Active immunisation.

Di-Te-Kik *Statens Serum Institut, Fin.†; SSI, Swed.*
A diphtheria, tetanus and pertussis vaccine (p.2210·3).
Active immunisation.

Di-Te-Ki-Pol *Statens Serum Institut, Denm.; Statens Serum Institut, Fin.†; SSI, Swed.†.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Di-Te-Ki-Pol/Act-Hib *Statens Serum Institut, Denm.*
A diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Ditemer *Aventis Pasteur, Belg.†.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Ditenol *Eversil, Braz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Ditenside *Almirall, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Ditensor *Funk, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

DiTePer Anatoxal *Faran, Gr.†; Pharmabroker, NZ.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Dithiaden
Zentiva, Cz.
Bisulepin hydrochloride (p.569·1).
Hypersensitivity reactions.

Leciva, Hung.†.
Bisulepin (p.569·1).
Hypersensitivity reactions.

Dithiazide *Pharmalab, Austral.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Dithiol *Galephar, Fr.†.*
Ethylmorphine hydrochloride (p.52·2).
Coughs.

Dithrasal *Dermatech, Austral.; Dermatech, Hong Kong; Dermatech, Singapore.*
Dithranol (p.1595·2); salicylic acid (p.1612·2).
Psoriasis.

Dithrocream *Hamilton, Austral.†; Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Dithranol (p.1595·2).
Psoriasis.

Dithyron *Unipharma, Gr.*
Levothyroxine (p.2173·2); liothyronine (p.2174·2).
Thyroid disorders.

Ditide *GSK, India.*
⊗ Benzthiazide (p.1225·1); triamterene (p.1417·2).
Oedema.

Ditizem *Siam Bheasach, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Ditoin *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Phenytoin sodium (p.495·2).
Epilepsy; migraine; trigeminal neuralgia.

Ditomed *Medifive, Thai.*
Phenytoin sodium (p.495·2).
Epilepsy.

Ditonal N *Athenstaedt, Ger.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Ditopax
Note. This name is used for preparations of different composition.
Schering-Plough, Arg.
Chewable tablets: Simeticone (p.1770·2); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Essex, Chile.
Chewable tablets: Simeticone (p.1770·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Key, Arg.†; Essex, Chile; Schering-Plough, Mex.
Oral suspension: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Schering-Plough, Mex.
Tablets: Dimeticone (p.1770·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Ditopax-F *Schering-Plough, Mex.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Ditosil
Note. This name is used for preparations of different composition.
Schering-Plough, Venez.
Oral suspension: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Schering-Plough, Venez.
Tablets: Simeticone (p.1770·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Ditosil Plus *Schering-Plough, Venez.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Flatulence; gastric hyperacidity.

Ditral
Note. This name is used for preparations of different composition.
LA, Arg.
Dipyrone (p.49·2).
Fever; pain.

Berman, Mex.
Tetramethamizole guaiacol; vitamins (p.1922·1).
Bacterial infections.

Ditranex *Dipa, Indon.; Prafa, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; hereditary angioedema.

Ditrei *Italmex, Mex.*
Di-isopropylammonium dichloroacetate (p.1265·1).
Angina pectoris; myocardial infarction; vascular disorders.

Ditrenil *Siam Bheasach, Thai.*
Nitrendipine (p.1358·2).
Hypertension.

Ditrevit *Humana, Ital.*
Vitamin D (p.1986·1); docosahexaenoic acid (p.1362·1).
Nutritional supplement.

Ditrim *Orion, Fin.*
Trimethoprim (p.355·2); sulfadiazine (p.336·2).
Bacterial infections; pneumocystis pneumonia.

Ditripentat *Heyl, Cz.*
Pentetic acid (p.1459·3).
Antidote.

Ditripentat-Heyl *Heyl, Ger.*
Calcium trisodium pentetate (p.1460·1).
Poisoning with heavy or radioactive metals.

Ditropan *Phoenix, Arg.; Aventis, Austral.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Janssen-Ortho, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Malaysia†; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Synthelabo, S.Afr.; Sanofi Synthelabo, Singapore†; Sanofi-Aventis, Spain; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Janssen-Cilag, UK; Ortho-McNeil, USA.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; neurogenic bladder; nocturnal enuresis; urinary frequency; urinary incontinence; urinary urgency.

Ditrost *Boniscontro & Gazzone, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ditterolina *Ivax, Mex.*
Dicloxacillin (p.265·2) or dicloxacillin sodium (p.265·2).
Bacterial infections.

Ditum *TNP, Thai.†.*
Dicloxacillin (p.265·2).
Bacterial infections.

Ditustat *Ivax, Cz.*
Dropropizine (p.1557·3).
Coughs.

Diu Venostasin *Klinge, Ger.*
⊗ Tablets, triamterene (p.1417·2); hydrochlorothiazide (p.1307·3); controlled-release capsules, aesculus (p.2248·2).
Venous insufficiency.

Diu-Atenolol *Verla, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Diube *SIT, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Diubeloc *AstraZeneca, Arg.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Diucardin *Wyeth-Ayerst, USA†.*
⊗ Hydroflumethiazide (p.1311·3).
Hypertension; oedema.

Diucomb *Byk, Belg.†; Sanol, Ger.; Schwarz, Ger.*
⊗ Bemetizide (p.1223·1); triamterene (p.1417·2).
Hypertension; oedema.

Diucontin-K *Modi-Mundipharma, India.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).
Oedema.

Diulo *Desma, Port.*
⊗ Metolazone (p.1337·2).
Ascites associated with liver cirrhosis; hypertension; oedema.

diu-melusin *TAD, Ger.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Diumide-K *Mundipharma, Philipp.; Pascual, Philipp.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).
Oedema.

Diumide-K Continus *Napp, Irl.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).
Oedema.

Diupres
Note. A similar name is used for preparations of different composition (see below).
Merck, USA.
⊗ Reserpine (p.1387·3); chlorothiazide (p.1243·1).
Hypertension.

Diupress
Note. A similar name is used for preparations of different composition (see above).
Eurofarma, Braz.
⊗ Chlortalidone (p.1243·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Diuprol *Protein, Mex.†.*
⊗ Chlortalidone (p.1243·3).

Diuprotect *Silesia, Chile.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Diur Pot *Northia, Arg.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Diurace *BMS, Neth.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Diural
Note. This name is used for preparations of different composition.
LA, Arg.
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension.

Alpharma, Denm.; Alpharma, Norw.
⊗ Furosemide (p.1292·1).
Forced diuresis; hypertension; oedema; renal failure.

Silanes, Mex.
⊗ Piretanide (p.1372·3).
Hypertension; oedema; renal failure.

Diuramid *Medphano, Ger.; Polpharma, Pol.*
⊗ Acetazolamide (p.1875·1).
Altitude sickness; epilepsy; glaucoma; oedema.

Diuramin *Ratiopharm, Fin.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites; hypertension; oedema.

Diurana *Sanofi Synthelabo, Braz.*
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Hypertension; oedema.

Diurapid *Jenapharm, Ger.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; oliguria.

Diurefo *Pyridam, Indon.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Diurek *Boniscontro & Gazzone, Ital.*
⊗ Potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypertension.

Diuremid *Guidotti, Ital.*
⊗ Torasemide (p.1415·3) or torasemide sodium (p.1416·1).
Ascites; heart failure; oedema; renal failure.

Diuremida *Geolab, Braz.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Diurene *Winthrop, Port.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites associated with liver cirrhosis; heart failure; hypertension.

Diurepina *Prodotti, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension.

Diurese *American Urologicals, USA†.*
⊗ Trichlormethiazide (p.1418·3).
Hypertension; oedema.

Diuresin *Polfarmex, Pol.*
⊗ Indapamide (p.1314·1).
Hypertension.

Diuresix *Menarini, Ital.*
⊗ Torasemide (p.1415·3) or torasemide sodium (p.1416·1).
Ascites; heart failure; kidney disorders; oedema.

Diuret *Ibfarma, Braz.†.*
⊗ Furosemide (p.1292·1).
Hypertension.

Diuretabs *Potter's, UK.*
Buchu leaf (p.2269·3); juniper berry oil (p.2328·3); parsley piert (p.2363·2); bearberry (p.2263·3).
Fluid retention.

Diuretic *Royton, Braz.†.*
⊗ Hydrochlorothiazide (p.1307·3).

Diuretikum Verla *Verla, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Diuretil *Ducto, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension.

Diuret-P *PP Lab, Thai.†.*
⊗ Hydrochlorothiazide (p.1307·3).
Diuretic.

Diurette *Cederroth, Spain.*
Taraxacum (p.2395·1); equisetum (p.2299·3).
Oedema.

Diurevit Mono *Ruhrpharm, Ger.*
Java tea (p.2328·2).
Urinary-tract disorders.

Diurex
Note. This name is used for preparations of different composition.
Bago, Arg.
⊗ Hydrochlorothiazide (p.1307·3).
Ascites; heart failure; hypertension; nephrotic syndrome; pre-eclampsia.

Orion, Fin.
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Cirrhosis with ascites; heart failure; hypertension.

Lacer, Spain.
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Diurex A *Bago, Arg.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis; hypertension; oedema.

Diurexan *Meda, Port.; Mer-National, S.Afr.†; Viatris, UK.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Diurezin *Cazi, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema; renal calculi.

Diurezin-A *Cazi, Braz.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Diurigen *Goldline, USA.*
⊗ Chlorothiazide (p.1243·1).
Hypertension; oedema.

Diuril
Note. This name is used for preparations of different composition.
Pharma Nutria, Philipp.
⊗ Furosemide (p.1292·1).
Hypercalcaemia; hypertension; oedema.

Merck, USA.
⊗ Chlorothiazide (p.1243·1) or chlorothiazide sodium (p.1243·1).
Hypertension; oedema.

Diurin *Pacific, NZ.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; severe renal impairment.

Diurinat *Soria Natural, Spain.*
Betula alba (p.2266·3); equisetum (p.2299·3); corn silk (p.2288·1); couch-grass (p.2288·2).
Oedema.

Diurisa *Eurofarma, Braz.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Diurit *Neckerman, Braz.†.*
⊗ Furosemide (p.1292·1).
Hypertension.

Diurix *Teuto, Braz.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Diurmessel *Biomep, Mex.*
⊗ Furosemide (p.1292·1).

Diuronis *Hasco-Lek, Pol.*
Chamomile (p.2279·3); ononis (p.2357·1); solidago (p.2391·1); cowberry (p.2288·3).
Urinary-tract disorders.

Diursan *TAD, Ger.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Diuspec *Hizon, Philipp.; Pharmaspec, Philipp.*
⊗ Furosemide (p.1292·1).
Hypercalcaemia; hypertension; oedema; oliguria.

Diutensat *Azupharma, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Diutensat comp *Azupharma, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3); propranolol hydrochloride (p.1380·3).
Hypertension.

Diutensen-R *Wallace, USA†.*
⊗ Methyclothiazide (p.1334·1); reserpine (p.1387·3).
Hypertension.

Diutropan *Nupharma, Thai.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder disorders.

Diuver *Pliva-Lachema, Cz.; Pliva Krakow, Pol.; Pliva, Rus.*
⊗ Torasemide (p.1415·3).
Heart failure; hypertension; oedema.

Diuzine *I Farmacologia, Spain.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Diva
Note. This name is used for preparations of different composition.
Elea, Arg.
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Reddy, S.Afr.
21 Tablets, cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea; combined oral contraceptive in women with androgenic symptoms.

Zeroderma, UK.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
These ingredients can be described by the British Approved Name Co-cyprindiol.
Acne and hirsutism in women.

Diva Total *Elea, Arg.*
24 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 4, tablets inert.
Combined oral contraceptive.

Dival *Valmor, Venez.*
Diclofenac sodium (p.44·3).
Inflammation; pain; rheumatic disorders.

Divalio *Elpen (Ελπεν), Gr.†.*
Carbocisteine (p.1553·2).
Mucolytic.

Divalol W *Wernigerode, Ger.†.*
Javanese turmeric (p.2406·3); peppermint oil (p.1761·2).
Biliary disorders.

Divanon *Tecnofarma, Chile.*
Clindamycin phosphate (p.251·2).
Acne; bacterial vaginitis.

Divaril *Tecnofarma, Chile.*
Mirtazapine (p.409·2).
Depression.

Divarius *Chiesi, Fr.*
Paroxetine mesilate (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; social phobia.

Divascan *Berlin-Chemie, Ger.†; Berlin-Chemie, Hung.; Menarini, Hung.; Berlin-Chemie, Pol.*
Iprazochrome (p.623·1).
Diabetic retinopathy; headache; migraine.

Divascol *Spofa, Cz.*
Tolazoline hydrochloride (p.1415·2).
Peripheral vascular disorders.

Divegal *Sanochemia, Austria.*
Dihydroergotamine tartrate (p.618·3).
Migraine and related vascular headaches.

Divelol *Baldacci, Braz.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Diven *Organifar, Venez.†.*
Promethazine (p.588·2).

Divens *Dexa, Indon.*
Phyllanthus niruri.
Immunomodulator.

Divermil *Gross, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Divical *Rottapharm, Ital.†.*
Calcium folinate (p.1943·3).
Folate deficiency.

Divicil *BA Farma, Port.*
Aciclovir (p.862·3).
Herpesvirus infections.

Dividol *Zambon, Braz.; Zambon, Ital.*
Viminol hydroxybenzoate (p.133·2).
Pain.

Divifolin *Rottapharm, Ital.*
Calcium folinate (p.1943·3).
Folate deficiency; folic acid antagonist overdosage.

Divigel *Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Hung.; Win-Medicare, India; Orion, Irl.; Orion, Malaysia; Orion, Pol.; Orion, Rus.; Orion, Singapore; Orion, Swed.; Orion, Switz.; Orion, Thai.; Upsher-Smith, USA.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Divina
Note. This name is used for preparations of different composition.
Elea, Arg.
21 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Orion, Cz.; Orion, Denm.; Orion, Fin.; HRA, Fr.; Organon (Οργανον), Gr.; Orion, Hung.; Organon, Neth.†; Orion, Pol.; Orion, Rus.; Aspen, S.Afr.; Orion, Swed.†; Abdi, Turk.
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Hormone replacement therapy; menopausal disorders; menstrual disorders; oestrogen deficiency; osteoporosis.

Divina Plus *Orion, Denm.; Orion, Swed.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Diviplus *Eumedica, Belg.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Diviseq *Orion, Cz.; HRA, Fr.; Orion, Irl.†; Orion, Norw.†; Orion, Pol.; Orion, Rus.; Orion, Switz.; Orion, Thai.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Divitren *Orion, Fin.; Orion, Hung.†; Orion, Rus.*
70 Tablets, estradiol valerate (p.2097·3); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Diviva *Eumedica, Belg.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen replacement therapy.

Divoltar *Hexpharm, Indon.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dixabiox *Rivero, Arg.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Dixamid *Norma (Νορμα), Gr.†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Dixarit *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Malaysia†; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore†; Boehringer Ingelheim, UK.*
Clonidine hydrochloride (p.1247·1).
Headache; menopausal vasomotor disorders; migraine and other vascular headache.

Dixen *Maver, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Dixeran *Lundbeck, Austria; Lundbeck, Belg.†.*
Melitracen hydrochloride (p.408·1).
Depression.

Dixi *Vivax Gynopharm, Venez.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Dixi-35 *Gynopharm, Chile.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).

Dixidrol *Rivero, Arg.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Oral rehydration therapy.

Dixiflen *Farcoral, Mex.*
Ox bile (p.2266·3); pancreatin (p.2360·1); cellulase (p.2279·1); dimeticone (p.1770·2).
Digestive disorders; flatulence.

Dixine *Lavipharm, Gr.*
Risperidone (p.1024·2).
Psychoses.

Dixocillin *Siam Bheasach, Thai.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Dixonal *Medix, Mex.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Diyaben *Adeka, Turk.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Diyasorb *Yeni, Turk.*
Attapulgite (p.1709·1).

Diyenil *Gunsa, Turk.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Pruritus.

Diyet Tat *Eczacibasi, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Diyosul *Jofrain, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Dizan *Pharmaland, Thai.*
Diazepam (p.986·3).
Autonomic disorders; muscle spasm; psychoneurotic disorders.

Dizatec *Genetic, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Dizem *IQFA, Mex.*
Di-iodohomatropine.
Amoebiasis.

Dizepam *Masa, Thai.†.*
Diazepam (p.986·3).
Anxiety.

Dizilium *Medikon, Indon.*
Flunarizine (p.580·3).
Migraine; peripheral vascular disorders; vestibular disorders.

Dizinil *Julphar, UAE.*
Dimenhydrinate (p.576·2).
Nausea and vomiting; vestibular disorders.

Diziron *Glenmark, India.*
Cinnarizine (p.573·1).
Motion sickness; vestibular disorders.

Dizmiss *JMI, USA.*
Meclozine hydrochloride (p.584·3).
Motion sickness; vertigo.

Dizolam *Atlantic, Singapore†; Atlantic, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Dizole *Alphapharm, Austral.*
Fluconazole (p.532·1).
Fungal infections.

Dizolvin *Rayere, Mex.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Dizzinon *Unison, Philipp.*
Cinnarizine (p.573·1).
Migraine; motion sickness; nausea; peripheral vascular disorders; vestibular disorders; vomiting.

DK-Line *Abdi, Turk.*
⊗ Perflunafene (p.2365·2).
Aid in ophthalmic surgery.

DKTP-Hib *Nederlands Vaccin Instituut, Neth.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae B vaccine (p.2212·1).
Active immunisation.

Dlianos *Novartis, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).

D-Lisin *Collins, Mex.†.*
Vitamin preparation (p.1922·1).

D-Loratin *Cipla, India.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

DM Active *Giscard, Arg.*
⊗ Deanol (p.2152·3).

DM Children's Cough Syrup *Trillium, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

DM Cough Syrup
Note. This name is used for preparations of different composition.
Prodemdis, Canad.
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3).
Coughs.

Trillium, Canad.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

DM Creme *Altana, Port.*
Glycol salicylate (p.62·3); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis.

DM Decongestant *Trillium, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

DM Decongestant-Expectorant *Trillium, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

DM Decongestant-Expectorant-Analgesic *Trillium, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).

DM Expectorant *Trillium, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

DM Gel *Altana, Port.*
Glycol salicylate (p.62·3); menthol (p.2340·1); heparin sodium (p.1301·2).
Muscular pain; neuralgia; soft-tissue injury.

DM Plus *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

DM Plus Decongestant *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

DM Plus Decongestant Expectorant *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

DM Plus Expectorant *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

DM Sans Sucre *Trianon, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

4-DMAP *Kohler, Ger.; Tramedico, Neth.*
4-Dimethylaminophenol hydrochloride (p.1444·3).
Cyanide, hydrocyanic acid, nitrile, or hydrogen sulfide poisoning.

DMax *Great Southern, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2).
Upper respiratory-tract disorders.

DM-Cordyl *Christo, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Cold symptoms; cough.

DML *Person & Covey, USA.*
A range of moisturisers.

DML Facial *Dispolab, Chile.*
SPF 25: Octinoxate (p.1608·2); homosalate (p.1598·1); avobenzone (p.1589·3); octocrilene (p.1608·3).
Sunscreen.

DML Forte Con Pantenol *Dispolab, Chile.*
Emollient.
Dry skin.

DMS Control *INTES, Ital.*
Multivitamin preparation with vitis vinifera (p.1922·1).
Nutritional supplement.

Dnaren *Ariston, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

DNCG *Stada, Cz.†; Mundipharma, Ger.; Padia, Ger.; Penta, Ger.; Stada, Ger.; Trommsdorff, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma; conjunctivitis; food allergy; hypersensitivity reactions; rhinitis.

DNSM *Investigaciones Filosoficas y Cientificas, Mex.*
Dornase alfa (p.1557·1).
Inflammation.

Doak-Oil *Trans Canaderm, Canad.*
Liquid paraffin; isopropyl palmitate; coal tar (p.1616·2).
Skin disorders.

Doans
Note. This name is used for preparations of different composition.
Medipharma, Hong Kong†.
Zinc oxide (p.1621·2); phenol (p.1656·1).
Skin disorders.

Novartis Consumer, USA.
Magnesium salicylate (p.79·2).
Fever; inflammation; pain.

Doans Backache Pills
Note. This name is used for preparations of different composition.
Mentholatum, S.Afr.
Paracetamol (p.108·1); sodium salicylate (p.124·2); buchu (p.2269·3); aloin (p.1705·3).
Musculoskeletal pain.

LPC, UK.
Paracetamol (p.108·1); sodium salicylate (p.124·2).
Pain.

Dobacen *Brandt, Switz.†.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Dobendan *Boots Healthcare, Austria; Boots Healthcare, Ger.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Dobendan Direkt *Boots, Ger.*
Flurbiprofen (p.61·2).
Sore throat.

Dobendan Synergie *Boots, Ger.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Mouth infections.

Dobesifar *Alcon, Hong Kong†.*
Calcium dobesilate (p.2272·1).
Haemorrhagic eye disorders.

Dobesix *Brasmedica, Braz.†.*
⊗ Mazindol (p.2157·3); diazepam (p.986·3).
Obesity.

Dobet *Oftalmi, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dobetin *Angelini, Ital.; Elmor, Venez.*
Cyanocobalamin (p.1980·2).
Neuritis; tonic; vitamin B deficiency.

Dobetin Compuesto *Elmor, Venez.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuritis.

Dobetin Totale *Angelini, Ital.*
Hydroxocobalamin (p.1980·3); thiamine (p.1976·3); pyridoxine (p.1979·1).
Neuralgia.

Dobetin con Vitamina B1 *Angelini, Ital.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1).
Neuralgia; neuritis.

Dobexil *Valeant, Cz.*
Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Dobexil Plus *Leciva, Cz.†.*
⊗ Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Dobica *Nycomed, Cz.; Altana, Ger.*
Calcium dobesilate (p.2272·1).
Capillary fragility; diabetic retinopathy; haemorrhoids; venous insufficiency.

Dobil *Pharmaland, Thai.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever; nasal congestion; rhinitis.

Dobilet *Otsira, India.*
Calcium dobesilate (p.2272·1).
Diabetic retinopathy; haemorrhoids; varices.

Dobipro *Salus, Mex.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Dobiron *Legrand, Braz.*
Ferrous sulfate (p.1939·3); vitamin B substances; liver extract; gastric mucosa extract (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Doblexan *Quimifar, Spain.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Dobren *Teofarma, Ital.*
Sulpiride (p.1028·3).
Dysthymia; psychoses.

Dobriciclin *Quimifar, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Dobrofen *Boots Healthcare, Ger.†.*
Flurbiprofen (p.61·2).
Sore throat.

Dobroson *Steigerwald, Pol.*
Zopiclone (p.1039·1).
Insomnia.

Dobtan *Uniao Quimica, Braz.*
Dobutamine hydrochloride (p.1271·2).
Heart failure; shock.

Dobucard *Scott-Cassara, Arg.; Solvay, Malaysia†.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Dobucor *Schering, Port.; Juste, Spain.*
Dobutamine hydrochloride (p.1271·2).
Heart failure; shock.

Dobuject *Gautier, Arg.†; Bayer Schering, Cz.; Schering, Fin.; Dexa, Indon.; Leiras, Indon.; Leiras, Israel; Pisa, Mex.; Schering, Philipp.; Schering, Pol.; Leiras, Singapore†; Schering, Thai.*
Dobutamine hydrochloride (p.1271·2).
Circulatory failure; heart failure; shock.

Dobupal *Almirall, Spain.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social phobia.

Dobupum *Kyowa, Jpn.*
Dobutamine hydrochloride (p.1271·2).

Doburan *Pharmakin, Venez.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Dobutabbott *Abbott, Braz.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Dobutal *Biochimico, Braz.†.*
Dobutamine (p.1272·1).
Heart failure.

Dobutam *Rafa, Israel†.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Dobutan *Demo, Gr.*
Dobutamine hydrochloride (p.1271·2).

Dobutel *Novell, Indon.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Dobutil *BPL-Meizler, Braz.†.*
Dobutamine hydrochloride (p.1271·2).
Heart failure; shock.

Dobutina *Hospira, Port.*
Dobutamine hydrochloride (p.1271·2).

Dobuton *Ariston, Braz.*
Dobutamine (p.1272·1).

Dobutrex *Lilly, Arg.†; Aspen, Austral.; Lilly, Belg.†; Lilly, Braz.†; Lilly, Canad.†; Lilly, Chile†; Lilly, Cz.; Lilly, Denm.†; Lilly, Fin.†; Lilly, Fr.†; Lilly, Hong Kong†; Lilly, Hung.†; Nicholas Piramal, India; Lilly, Irl.†; Bayer, Ital.†; Lilly, Malaysia†; Sandoz, Mex.; Lilly, NZ†; Lilly, Norw.†; GSK, Philipp.; Sandoz, S.Afr.; Irisfarma, Spain†; Meda, Swed.; Medika, Switz.; Lilly, Thai.†; Lilly, UK†; Lilly, USA†; Lilly, Venez.†.*
Dobutamine hydrochloride (p.1271·2).
Cardiac stress testing; diagnosis of coronary artery disease; heart failure; hypoperfusion; shock.

Dobutrexmerck *Merck, Belg.*
Dobutamine (p.1272·1).
Hypotension.

Dobuxin *Behrens, Venez.*
Dobutamine hydrochloride (p.1271·2).
Heart failure.

Doc *Iller, Ger.*
Arnica (p.2260·2).
Musculoskeletal, joint, and soft-tissue disorders.

Docacetyl *Docpharma, Belg.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Docaciclo *Docpharma, Belg.*
Aciclovir (p.862·3).
Herpesvirus infections.

Docaine *M & H, Thai.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Docallopu *Docpharma, Belg.*
Allopurinol (p.552·2).
Gout; renal calculi.

Docalprazo *Docpharma, Belg.*
Alprazolam (p.960·1).
Anxiety.

Docamoclaf *Docpharma, Belg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Docamoxici *Docpharma, Belg.*
Amoxicillin (p.202·2).
Bacterial infections.

Docard *Dexxon, Israel; Dexxon, Philipp.*
Dopamine hydrochloride (p.1273·2).
Shock.

Docateno *Docpharma, Belg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Docatone *Wyeth, Spain†.*
Doxapram (p.2155·2).
CNS depression; respiratory depression.

Docbetahi *Docpharma, Belg.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; vertigo.

Docbisopro *Docpharma, Belg.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Docbromaze *Docpharma, Belg.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Docbudeso *Docpharma, Belg.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Docbuflome *Docpharma, Belg.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Doccaptopri *Docpharma, Belg.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Doccefaclo *Docpharma, Belg.*
Cefaclor (p.217·2).
Bacterial infections.

Doccefuro *Docpharma, Belg.*
Cefuroxime (p.238·2).
Bacterial infections.

Doccimeti *Docpharma, Belg.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer.

Docciproflo *Docpharma, Belg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Doccyproestra *Docpharma, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Docdiclofe *Docpharma, Belg.*
Diclofenac sodium (p.44·3).

Docdipyri *Docpharma, Belg.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Docdol *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain.

Docdomperi *Docpharma, Belg.*
Domperidone (p.1726·2).
Gastroparesis; nausea and vomiting.

Docdoxycy *Docpharma, Belg.*
Doxycycline (p.267·1).
Bacterial infections.

Doce Vida *Marjan, Braz.†.*
Aspartame (p.1930·1).
Sugar substitute.

Docebe B12 *Flupal, Venez.†.*
Vitamin B (p.1980·2).

Docechol *Lafedar, Arg.*
Pepsin (p.2365·1); amylase (p.2256·3); papain (p.2362·3); caffeine (p.1116·3).
Digestive disorders.

Docekebir *Aspen, Arg.*
Docetaxel (p.710·3).

Doce-Plex *Meyer, Venez.*
Vitamin B substances (p.1922·1).
Tonic; vitamin supplement.

Docetax *Cipla, India.*
Docetaxel (p.710·3).
Breast cancer; non-small-cell lung cancer.

Docetril *Loren, Mex.†.*
Liver extract; vitamin B substances (p.1922·1).

Docfenofi *Docpharma, Belg.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Docfluoxetine *Docpharma, Belg.*
Fluoxetine (p.397·3).
Depression.

Docfurose *Docpharma, Belg.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Docidrazin *AstraZeneca, Ger.†.*
⊗ Propranolol hydrochloride (p.1380·3); hydralazine hydrochloride (p.1305·3); bendroflumethiazide (p.1224·1).
Hypertension.

Docin *Pharmasant, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Docindapa *Docpharma, Belg.*
⊗ Indapamide (p.1314·1).
Hypertension.

Dociretic *Mibe, Ger.*
⊗ Propranolol hydrochloride (p.1380·3); bendroflumethiazide (p.1224·1).
Hypertension.

Dociron *Quim-Far, Venez.†.*
Ferric ammonium citrate (p.1938·1).
Iron-deficiency anaemia.

Docistin *Biomedis, Philipp.*
Cisplatin (p.698·2).
Malignant neoplasms.

Dociteren *Mibe, Ger.*
⊗ Propranolol hydrochloride (p.1380·3); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Dociton *Mibe, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; migraine; myocardial infarction.

Docitral *Vargas, Venez.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Docketoral *Docpharma, Belg.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Docline *Atlantic, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doclis *Bial, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Docloraze *Docpharma, Belg.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Doclormeta *Docpharma, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Docmebenda *Docpharma, Belg.*
Mebendazole (p.148·3).
Worm infections.

Docmeloxi *Docpharma, Belg.*
Meloxicam (p.80·3).

Docmetoclo *Docpharma, Belg.*
Metoclopramide (p.1747·3).
Gastroparesis; nausea and vomiting.

Docmorfine *Docpharma, Belg.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

Docofloxacine *Docpharma, Belg.*
Ofloxacin (p.310·2).
Bacterial infections.

Docomepra *Docpharma, Belg.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer.

Docostyl *Pentafarm, Spain†.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Docparacod *Docpharma, Belg.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Docpirace *Docpharma, Belg.*
Piracetam (p.368·2).
Cerebrovascular disorders.

Docpiroxi *Docpharma, Belg.*
Piroxicam (p.117·3).

Docraniti *Docpharma, Belg.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer.

Docril *Biomep, Mex.*
Diclofenac (p.44·2).
Pain.

Docroxithro *Docpharma, Belg.*
Roxithromycin (p.331·1).
Bacterial infections.

Docrub *Aspen Consumer, S.Afr.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); buchu oil (p.2269·3).
Cold symptoms; coughs; soft-tissue disorders.

Docrutosi *Docpharma, Belg.*
Troxerutin (p.2305·1).
Capillary impairment; venous insufficiency.

Docsalbuta *Docpharma, Belg.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Docsed *Aspen, S.Afr.*
⊗ Mepyramine maleate (p.585·2); codeine phosphate (p.37·2); pholcodine (p.1570·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Docsi *Biomep, Mex.*
Chlorphenamine (p.572·2).
Hypersensitivity.

Docsimvasta *Docpharma, Belg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Docspirochlor *Docpharma, Belg.*
⊗ Hydrochlorothiazide (p.1307·3); spironolactone (p.1400·1).

Docspirono *Docpharma, Belg.*
⊗ Spironolactone (p.1400·1).
Cirrhosis with ascites; heart failure; hyperaldosteronism; hypertension.

Docsulpiri *Docpharma, Belg.*
Sulpiride (p.1028·3).
Psychoses.

Doctadryle *Doctum, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Doctamine *Doctum, Gr.*
Butamirate (p.1553·1).
Cough.

Doctamoxifene *Docpharma, Belg.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Docticam *Doctum, Gr.†.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Doctinon *Doctum, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Doctiverine *Doctum, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Doctodermis *Medea, Spain.*
Biotin (p.1931·3); triclosan (p.1665·2).
Skin cleansing.

Doctofril Antiinflamat *Nupel, Spain.*
Phenylbutazone (p.117·1); lidocaine (p.1862·3); methyl nicotinate (p.85·3); vitamin F (p.2308·2).
Chilblains; rheumatic and muscle pain.

Doctomitil *Medea, Spain†.*
Cineole (p.2282·3); diethylamine salicylate (p.47·2); methyl nicotinate (p.85·3).
Soft-tissue disorders.

Doctor's Choice Fortified Bone Support *Vita Green, Hong Kong.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Doctor's Choice for Joints *Vita Green, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Joint disorders.

Doctor's Choice Multivitamins and Minerals for Eyes *Vita Green, Hong Kong.*
A vitamin and mineral preparation with linoleic acid, garlic, and ginkgo biloba (p.1922·1).
Dietary supplement.

Doctor's Choice Omega 3 *Vita Green, Hong Kong.*
Docosahexaenoic acid (p.1362·1); eicosapentaenoic acid (p.1362·1); vitamin E (p.1992·2).
Dietary supplement.

Doctramado *Docpharma, Belg.*
Tramadol hydrochloride (p.130·3).
Pain.

Doctril *McNeil, Spain.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Doculyse *Omega, Fr.*
Docusate sodium (p.1725·1); phenonip; citric acid (p.2284·1); sodium citrate (p.1673·3).
Irrigation solution for ear wax removal and hygiene.

Docusoft *Reese, USA.*
Docusate sodium (p.1725·1).
Constipation.

Docusoft Plus *Reese, USA.*
Docusate sodium (p.1725·1); casanthranol (p.1715·1).
Constipation.

Docusol *Typharm, UK.*
Docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Doc-Vite *Docmed, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Docviteee *Docpharma, Belg.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Docyl *Unison, Thai.*
Doxycycline (p.267·1).
Bacterial infections.

Dodds *Stella, Canad.†.*
Sodium salicylate (p.124·2).
Musculoskeletal pain.

Dodds Back Ease *Stella, Canad.*
Paracetamol (p.108·1); methocarbamol (p.1897·3).

Dodecavit *SERB, Fr.*
Hydroxocobalamin acetate (p.1980·3).
Vitamin B 2 deficiency.

Dodemina Tri *Valeant, Mex.*
Hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Metabolic acidosis; neuralgias; neuritis; vitamin B deficiency.

Dodemox *Fadim, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Dodepar *ABC, Port.*
Vitamin B substances (p.1922·1).
Anaemias; tonic.

Doderlein *Novartis Consumer, Austria.*
Lactobacillus gasseri.
Vaginal candidiasis.

Doderlein Med *Novartis Consumer, Ger.*
Lactobacillus gasseri.
Vaginal disorders.

Dodesept *Schulke & Mayr, Austria.*
⊗ Orthophenylphenol (p.1655·1); alcohol (p.1625·2); isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2).
Skin disinfection.

Dodesept Gefarbt *Schulke & Mayr, Austria.*
⊗ Orthophenylphenol (p.1655·1); alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Dodesept N *Schulke & Mayr, Austria.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Dodex *Deva, Turk.*
Vitamin B (p.1980·2).
Megaloblastic anaemia.

Do-Do ChestEze *Novartis Consumer, UK.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); caffeine (p.1116·3).
Bronchial coughs; respiratory-tract congestion; wheezing.

Dofacef *Sanbe, Indon.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Dofaxil *Continentales, Mex.*
Dextromethorphan hydrobromide (p.1555·2); ambroxol hydrochloride (p.1550·3).
Coughs; respiratory-tract congestion.

Dofedrin *Abbott, Mex.*
Pseudoephedrine (p.1571·2).
Upper respiratory-tract congestion.

Dofen
Note. This name is used for preparations of different composition.
Dexa, Indon.
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; pain.

Parggon, Mex.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders.

Dofene *Caldeira & Metelo, Port.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal and joint disorders.

Doffler *Loeffler, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Dofisan *Berman, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Doflex *Jagson, India.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; pain.

Doflex Plus *Jagson, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Gout; musculoskeletal and joint disorders; pain.

Dogistin *Temis, Arg.†.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Dogmatil *Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Hong Kong; Delagrange, Indon.; Soho, Indon.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore†; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Turk.*
Sulpiride (p.1028·3).
Anxiety; behaviour disorders; depression; gastrointestinal disorders; Ménière's disease; migraine; neuroses; obsessive-compulsive disorder; peptic ulcer; post-concussion syndrome; psychoses; psychosomatic disorders; schizophrenia; vertigo.

Dogmatyl *Sanofi-Aventis, Gr.; Astellas, Jpn.*
Sulpiride (p.1028·3).
Depression; peptic ulcer; psychoses; schizophrenia.

DOK *Major, USA.*
Docusate sodium (p.1725·1).
Constipation.

Doket *IQFA, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Doketrol *Rivero, Arg.*
Sodium nitroprusside (p.1397·1).
Hypertension.

Doksin *Nevzat, Turk.*
Doxycycline (p.267·1).
Bacterial infections; malaria; oral herpes simplex infections.

Doksura *Fako, Turk.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Doktacillin *AstraZeneca, Denm.†; AstraZeneca, Swed.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Doktor Mom
Note. This name is used for preparations of different composition.
Unique, Rus.
Ointment: Menthol (p.2340·1); camphor (p.2273·2); thymol (p.1664·3); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3).
Cold symptoms.

Unique, Rus.
Syrup: Ocimum sanctum; liquorice (p.1740·3); turmeric (p.1473·2); ginger (p.1732·3); adhatoda vasica; solanum indicum; inula racemosa; cubeb (p.2290·1); terminalia bellerica; aloes (p.1705·2); menthol (p.2340·1).
Coughs.

Doktor Mom Herbal Cough Lozenges *Unique, Rus.*
Liquorice (p.1740·3); ginger (p.1732·3); emblica; menthol (p.2340·1).
Upper respiratory-tract disorders.

Dol *Calox, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Migraine.

Dolac *Ethica, Indon.; Syntex, Mex.; Cadila, Rus.*
Ketorolac trometamol (p.74·2).
Pain.

Dolacen *Labesfal, Port.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolacet *Roberts, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Doladamon-P *Ulagay, Turk.*
Paracetamol (p.108·1); ciclonium bromide (p.1716·2); codeine phosphate (p.37·2).
Fever; pain.

Dolaforte *Chemists Own, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dolak
Note. This name is used for preparations of different composition.
Bama, Spain.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Dollder, Venez.
Ketorolac trometamol (p.74·2).
Pain.

Dolal
Note. This name is used for preparations of different composition.
Biocodex, Fr.
Ethylmethoxy salicylate; phenylpropyl salicylate.
Musculoskeletal and joint pain.

Remek, Gr.
Paracetamol (p.108·1).
Fever; pain.

Dolalgial *Grunenthal, Chile†; Sanofi-Aventis, Spain.*
Clonixin lysine (p.37·1).
Pain; peri-articular disorders.

Dolamin *Farmoquimica, Braz.*
Clonixin lysine (p.37·1).
Pain.

Dolamin Flex *Farmoquimica, Braz.*
Clonixin lysine (p.37·1); cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal pain and spasm.

Dolan
Note. This name is used for preparations of different composition.
Leiras, Fin.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Pediatrica, Philipp.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Dolana *Combiphar, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolanaest *Gebro, Austria; Strathmann, Ger.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia; pain syndromes.

Dolanet
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Arg.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Gramon-Bago, Urug.
Dipyrone (p.49·2).
Fever; pain.

Dolantin *Aventis, Ger.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Dolantina *Sanofi-Aventis, Braz.; Kern, Spain.*
⊗ Pethidine hydrochloride (p.113·2).
Pain; premedication; smooth muscle spasm.

Dolantine *Sanofi-Aventis, Belg.*
⊗ Pethidine hydrochloride (p.113·2).
Pain; premedication.

Dolaren
Note. This name is used for preparations of different composition.
AF, Mex.
Cream: Diclofenac diethylamine (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

AF, Mex.
Tablets: Diclofenac sodium (p.44·3); carisoprodol (p.1894·1).
Gout; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Dolargan
Sanofi-Aventis, Hung.
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Chinoin, Pol.
⊗ Pethidine (p.115·1).
Pain.

Dolased Analgesic Calmative *Chemists Own, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Pain.

Dolased Day/Night Pain Relief *Chemists Own, Austral.*
Day tablets, paracetamol (p.108·1); codeine phosphate (p.37·2); night tablets, paracetamol; codeine phosphate; doxylamine succinate (p.578·2).
Pain.

Dolaut *GiEnne, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Dolbufen *Bayer, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Dolce *Oro, Turk.*
Sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute.

Dolcet *Janssen, Philipp.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Dolcevin *Minerva (Μινερβα), Gr.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Dolcevita *Codilab, Port.†.*
Aspartame (p.1930·1).
Sugar substitute.

Dolcidium *SMB, Belg.*
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Dolcin *Biotoscana, Chile†.*
Mefenamic acid (p.80·1).
Pain.

Dolcispray *Olvos, Gr.*
Indometacin (p.66·3).
Inflammatory disorders.

Dolcol *Dainippon, Jpn.*
Pipemidic acid (p.315·1).
Bacterial infections.

Dolcontin *Mundipharma, Fin.; Pfizer, Norw.; Pfizer, Swed.*
⊗ Morphine sulfate (p.86·3).
Pain.

Dolcontral *Polfa Warszawa, Pol.*
⊗ Pethidine (p.115·1).
Pain.

Dolcopin
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Rottapharm, Spain.
Magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2); almasilate (p.1705·1); alginic acid (p.2140·3).
Dyspepsia; gastro-oesophageal reflux.

Dolcoplaz *Loeffler, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Dolcoxx *MSD, Ital.†.*
Rofecoxib (p.121·1).
Pain.

Dolean *Recalcine, Chile.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dolectran *LKM, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Dolemicin *Gayoso, Spain.*
Metamizole magnesium (p.49·3).
Fever; pain.

Dolenon *Strathmann, Ger.†.*
Cayenne pepper (p.2276·2).
Muscle pain; nerve pain.

Doleron *AstraZeneca, Swed.†.*
Aspirin (p.20·3); dextropropoxyphene napsilate (p.40·1); phenazone (p.116·1).
Pain.

Doleside *FD, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Dolestan
Note. This name is used for preparations of different composition.
Krewel, Ger.
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Krewel, Ger.
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Dolestan forte comp *Whitehall-Much, Ger.†.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3).
Sleep disorders.

Dolestine *Teva, Israel.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Dolex
Note. This name is used for preparations of different composition.
Ivax, Arg.
Clonixin lysine (p.37·1).
Pain.

Steierl, Ger.
Homoeopathic preparation.

IFI, Ital.†.
Furprofen (p.62·2).
Pain.

Dolexpel *Morishita, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Dolfen *Great Eastern, Thai.; Westmont, Thai.*
Mefenamic acid (p.80·1).
Pain.

Dolfenal *Medifarma, Indon.; Westmont, Philipp.; Great Eastern, Thai.†; Westmont, Thai.†.*
Mefenamic acid (p.80·1).
Fever; pain.

Dolflam *Rayere, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolgan *Bioresearch, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Dolgan Flash *Sanofi Synthelabo, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Dolgenal *Tecnofarma, Chile.*
Ketorolac trometamol (p.74·2).
Pain.

Dolgesic *Novag, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Dolgesic Codeina *Novag, Spain.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Dolgesik *Mersifarma, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolgic *Athlon, USA.*
Paracetamol (p.108·1); butalbital (p.967·2).
Pain.

Dolgic LQ *Athlon, USA.*
Paracetamol (p.108·1); butalbital (p.967·2); caffeine (p.1116·3).
Pain.

Dolgic Plus *Victory, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Dolgit *Sanova, Austria; Dolorgiet, Cz.; Merck-Lipha, Fr.; Dolorgiet, Ger.; Dolorgiet, Hung.; Dolorgiet, Pol.; Dolorgiet, Rus.; Adeka, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolgit-Diclo *Dolorgiet, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Dolgosin *Boniscontro & Gazzone, Ital.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Doli Rhume *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Doliactic *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Dolib *Panacea, India†.*
Rofecoxib (p.121·1).
Dysmenorrhoea; musculoskeletal and joint disorders; pain.

Dolibu *Fujisawa, Austria.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Dolical *Rekah, Israel.*
Morpholine salicylate (p.91·1).
Skeletal muscle spasm.

Dolicoccil *Dolisos, Canad.†; Dolisos, Cz.*
Homoeopathic preparation.

Dolider *Pasteur, Chile.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Dolidermil *Dolisos, Fr.*
Homoeopathic preparation.

Dolifebril *Dolisos, Fr.*
Homoeopathic preparation.

Dolikan *Collins, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Dolilite *Eulite, Neth.*
Homoeopathic preparation.

Dolilux *Uno, Ital.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dolinac *Teofarma, Ital.*
Felbinac (p.54·3).
Inflammation; pain.

Doline
Note. This name is used for preparations of different composition.
Alphapharm, Malaysia.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Tripharma, Turk.
Etofenamate (p.53·1).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Dolintol *Vir, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Doliprane *Sanofi-Aventis, Fr.; Nicholas Piramal, India†.*
Paracetamol (p.108·1).
Fever; pain.

Dolirelax *Dolisos, Fr.*
Homoeopathic preparation.

DolirhumePro *Sanofi-Aventis OTC, Fr.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; doxylamine succinate (p.578·2).
Cold symptoms.

Dolisedal *Dolisos, Fr.*
Homoeopathic preparation.

Dolistamine *Dolisos, Fr.*
Homoeopathic preparation.

Dolitabs *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Dolitravel *Dolisos, Fr.*
Homoeopathic preparation.

Dolium *Utopian, Thai.*
Domperidone (p.1726·2).
Flatulence; nausea and vomiting.

Dolizol *Unipharm, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Dolkin *Caber, Ital.†.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Dolko *Therabel, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Dolmal *Biolink, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolmatil *Sanofi-Aventis, Irl.; Sanofi Synthelabo, UK.*
Sulpiride (p.1028·3).
Schizophrenia.

Dolmed *Leiras, Fin.*
⊗ Methadone hydrochloride (p.82·3).
Opioid dependence; pain.

Dolmen
Note. This name is used for preparations of different composition.
Sigma-Tau, Ital.
Tenoxicam (p.128·2).
Musculoskeletal disorders.

Uriach, Spain.
Aspirin (p.20·3); ascorbic acid (p.1983·3); codeine phosphate (p.37·2).
Fever; influenza symptoms; pain.

Dolmetine *CNN, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Dolmigral *Prodes, Spain†.*
Sumatriptan succinate (p.625·2).
Migraine.

Dolmina *Zentiva, Cz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolmisin *Farcoral, Mex.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Dol-Mite *Swiss Herbal, Canad.*
Calcium carbonate; magnesium carbonate (p.1922·1).

Dolmitin *Nupel, Spain.*
Cineole (p.2282·3); diethylamine salicylate (p.47·2).
Soft-tissue disorders.

Dolmix *Apomedica, Austria.*
Ethenzamide (p.51·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Dolnefort *Farcoral, Mex.*
Dipyrone (p.49·2); vitamin B substances (p.1922·1).
Neuritis; pain.

Dolnix *Recalcine, Chile.*
Ibuprofen (p.64·2); dipyrone (p.49·2); chlormezanone (p.968·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolnot *ICN, Arg.†.*
Clonixin lysine (p.37·1).
Fever; inflammation; pain.

Dolo Demotherm *Vifor, Switz.*
Dimethyl sulfoxide (p.2022·1); benzyl nicotinate (p.28·1); glycol salicylate (p.62·3).
Musculoskeletal and joint pain.

Dolo Mobilat *Sankyo, Ger.†.*
Phenylephrine hydrochloride (p.1568·1); a heparinoid (p.1305·2); glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo Moff *Uniao Quimica, Braz.*
⊗ Morphine sulfate (p.86·3).
Pain.

Dolo Nervobion
Note. This name is used for preparations of different composition.
Merck, Arg.
Diclofenac sodium (p.44·3); thiamine (p.1976·3); pyridoxine hydrochloride (p.1978·2); mecobalamin (p.1981·1).
Inflammation; pain.

Merck, Spain.
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; renal colic.

Dolo Nervobion 10000 *Merck, Arg.*
Ampoule 1, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ampoule 2, diclofenac sodium (p.44·3). Ampoule 2 formerly contained dipyrone.
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Dolo Sanol *Sanol, Ger.; Schwarz, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Dolo Scanneuron *Tempo Scan Pacific, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Pain.

Dolo Target *Whitehall-Robins, Switz.†.*
Felbinac (p.54·3).
Musculoskeletal, joint, peri-articular, and soft-tissue injuries and disorders.

Dolo Tomanil *Altana, Arg.*
Diclofenac (p.44·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolo Winasorb *K2 Pharmacare, Chile.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Dolo-Arthrodynat *Ziethen, Ger.†.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Dolo-Arthrosenex *Whitehall-Robins, Switz.*
Glycol salicylate (p.62·3); heparin sodium (p.1301·2); camphor (p.2273·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosenex N *Riemser, Ger.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosenex NH *Riemser, Ger.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Arthrosenex sine Heparino *Whitehall-Robins, Switz.†.*
Glycol salicylate (p.62·3); camphor (p.2273·2); isopropyl alcohol (p.1650·3); lavender oil (p.2331·2); thyme oil (p.2401·2); Siberian fir oil.
Musculoskeletal, joint, peri-articular, and soft-tissue injuries and disorders.

Dolo-Arthrosetten H *Riemser, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Dolobene *Ratiopharm, Austria; Mepha, Braz.; Ratiopharm, Cz.; Merckle, Ger.; Mepha, Hong Kong; Ratiopharm, Hung.; Ratiopharm, Pol.; Merckle, Rus.; Mepha, Switz.*
Dimethyl sulfoxide (p.2022·1); heparin sodium (p.1301·2); dexpanthenol (p.2362·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis; oedema; pain; skin ulcers; superficial thrombophlebitis.

Dolobene pur *Merckle, Ger.*
Dimethyl sulfoxide (p.2022·1).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Dolobid *MSD, Austral.†; MSD, Irl.†; MSD, Israel†; MSD, Ital.†; MSD, Mex.†; MSD, Neth.; MSD, Port.†; Frosst, Spain; M & H, Thai.; MSD, UK†; Merck, USA†; MSD, Venez.†.*
Diflunisal (p.47·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolobis *MSD-Chibret, Fr.†.*
Diflunisal (p.47·2).
Pain.

Doloc *Sanitas, Chile.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Dolocalma *Neves, Port.*
Metamizole magnesium (p.49·3).
Colic; fever; pain.

Dolocam *Rimsa, Mex.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolocam Plus *Rimsa, Mex.*
Meloxicam (p.80·3); methocarbamol (p.1897·3).
Musculoskeletal, joint, and peri-articular disorders.

Dolocap *Erlimpex, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolocartigen *Rimsa, Mex.*
Meloxicam (p.80·3); diacerein (p.41·3).
Degenerative joint disorders.

Dolocid *MSD, Neth.*
Diflunisal (p.47·2).
Musculoskeletal and joint disorders; pain.

Dolocide K *Kee, India.*
Diclofenac potassium (p.44·3).
Musculoskeletal and joint disorders.

Dolocide KP *Kee, India.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Dolocide MR *Kee, India.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Pain; peri-articular disorders.

Dolocide Plus *Kee, India.*
Diclofenac diethylamine (p.44·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Pain; soft-tissue disorders.

Dolocin *Quality, Hong Kong.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

DoloCitran C *Novartis Consumer, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Dolocod *Fujisawa, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Dolocox *Baliarda, Arg.†.*
Ibuprofen (p.64·2).

Doloctaprin *Elvetium, Arg.†.*
Nimesulide (p.95·3).
Musculoskeletal, joint, and peri-articular disorders.

Doloctaprin Plus *Elvetium, Arg.†.*
Nimesulide (p.95·3); orphenadrine (p.812·2).
Musculoskeletal pain and spasm.

Dolo-cyl
Note. A similar name is used for preparations of different composition (see below).
Liebermann, Ger.
Arnica oil (p.2260·2); eucalyptus oil (p.2301·2); St John's wort oil (p.423·2); juniper oil (p.2328·3); lavender oil (p.2331·2); pumilio pine oil (p.2376·3); rosemary oil (p.2381·3).
Musculoskeletal pain.

Dolocyl
Note. A similar name is used for preparations of different composition (see above).
Novartis Consumer, Ital.; Novartis Consumer, Port.; Novartis Consumer, Switz.
Ibuprofen (p.64·2).
Fever; pain.

Dolodens *Nupel, Spain.*
Codeine phosphate (p.37·2); hydroxyzine hydrochloride (p.581·2); propyphenazone (p.119·3).
Pain.

Dolodent
Note. This name is used for preparations of different composition.
OBA, Denm.
Benzocaine (p.1854·1); myrrh (p.2349·2).
Mouth pain.

Gilbert, Fr.
Amylocaine hydrochloride (p.1853·3).
Teething pain.

Doloderm *Sanofi-Aventis, Ital.*
Methyl butetisalicylate (p.85·2).
Musculoskeletal and joint pain.

Dolo-Dismenol *Merz, Switz.*
Ibuprofen (p.64·2).
Pain.

Dolo-Dobendan *Boots Healthcare, Ger.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Dolodoc *Docpharm, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Dolodol *Cantabria, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolofar *Medipharm, Chile.*
Ketoprofen (p.73·1).
Gout; musculoskeletal and joint disorders; pain.

Dolofarma *Maxfarma, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Dolofast *Bracco, Ital.*
Ibuprofen lysine (p.64·2).
Musculoskeletal pain; soft-tissue disorders.

Dolofenac
Note. This name is used for preparations of different composition.
LA, Arg.
Diclofenac sodium (p.44·3).
Inflammation; pain.

Merck, Indon.
Diclofenac sodium (p.44·3); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Neuralgia; neuritis.

Arlex, Mex.
Diclofenac (p.44·2).
Inflammation; rheumatism.

Dolofen-F *Tempo Scan Pacific, Indon.*
Ibuprofen (p.64·2).
Pain.

Dolofin *Socobom, Belg.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Doloflam *Biolab, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; pain.

Doloflex *Altana, Ital.*
Paracetamol (p.108·1); aspirin (p.20·3).
Pain.

Dolofort *Fujisawa, Austria.*
Ibuprofen (p.64·2).
Pain.

Dolofrix *Penn, Arg.*
Paracetamol (p.108·1); codeine (p.37·2).
Pain.

Dolofur *Ivax, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Dologen *Kenyaku, Thai.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dologesic *Infinity, Venez.*
Ibuprofen (p.64·2).
Inflammation; pain.

Dologex *Cinfa, Spain†.*
Turpentine oil (p.2406·3); menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Dologinex *Roemmers Rowe, Venez.*
Clonixin lysine (p.37·1); pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Doloject *Syxyl, Ger.*
Homoeopathic preparation.

Dolokam *Cadila, India.*
Piroxicam (p.117·3).

Dolokapton *Strallhofer, Austria.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Dolo-Ketazon *Recalcine, Chile.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolokey *Inkeysa, Spain.*
Camphor (p.2273·2); lavender oil (p.2331·2); methyl salicylate (p.85·3); expressed mustard oil (p.2349·2); rosemary oil (p.2381·3); eucalyptus oil (p.2301·2); belladonna (p.2263·3); capsicum (p.2276·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Dolol *Nycomed, Austria; Nycomed, Denm.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolo-Licobion *Berlico Mulia, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Dolol-Instant *Sandipro, Belg.*
Paracetamol (p.108·1).
Fever; pain.

Dolomate *Jaba Recordati, Port.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Dolomax *Farma, Venez.*
Ketoprofen (p.73·1).
Pain.

DoloMed *Bioforce, Switz.†.*
Butterbur (p.2271·1).
Migraine; painful smooth muscle spasm.

Dolomedil *Almirall, Spain.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Dolo-Menthoneurin *Altana, Austria; Altana, Ger.†.*
Diethylamine salicylate (p.47·2); heparin sodium (p.1301·2); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Dolomin *Bago, Arg.†.*
Dexibuprofen (p.39·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolomite *Nature's Bounty, USA.*
Dolomite (p.2297·3).
Dietary supplement.

Dolomo *Fujisawa, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Dolomo TN *Astellas, Ger.*
White tablets, aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); blue tablets, aspirin; paracetamol; codeine phosphate (p.37·2).
Pain.

Dolomol *Hikma, Rus.*
Paracetamol (p.108·1).
Fever; pain.

Dolonase *Medipharm, Chile.*
Ibuprofen (p.64·2); dipyrone (p.49·2); chlormezanone (p.968·3).
Dysmenorrhoea; musculoskeletal and joint disorders.

Doloneitor *Driburg, Arg.*
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3).
Inflammation; pain.

Dolonerv *Gerot, Austria.*
Paracetamol (p.108·1); vitamin B substances (p.1922·1).
Pain.

Doloneuro *Merck, Ger.†.*
Diethylamine salicylate (p.47·2); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal, joint, and soft-tissue injury; neuralgia.

Dolo-Neurobion
Note. This name is used for preparations of different composition.
Merck, Austria.
Diclofenac sodium (p.44·3); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2).
Musculoskeletal and joint disorders; neuralgia; neuritis; pain.

Merck, Indon.
Paracetamol (p.108·1); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Merck, Mex.
Diclofenac sodium (p.44·3); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy.

Merck, Philipp.
Paracetamol (p.108·1); vitamin B (p.1976·2); vitamin B (p.1978·2); vitamin B (p.1980·2).
Neuralgia; neuritis; pain.

Dolo-Neurobion forte *Merck, Ger.†.*
Paracetamol (p.108·1); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Arthritis; back pain; neuralgia.

Dolo-Neurobion N *Merck, Ger.†.*
Paracetamol (p.108·1); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2).
Joint disorders; lumbago; neuralgia; neuritis; sciatica.

Dolo-Neurobionta *Merck, Chile†.*
Dipyrone (p.49·2); vitamin B substances.
Procaine (p.1869·2) is included in the injection to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Dolonex *Pfizer, India.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dolo-Niofen *K2 Pharmacare, Chile.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Dolono *RID, USA.*
Paracetamol (p.108·1).
Fever; pain.

Dolonovag *Gobbi, Arg.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Dolo-Octirona *Laboratorios Chile, Chile.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; musculoskeletal and joint disorders; pain.

Dolo-Pangavit *Church, Mex.*
Diclofenac sodium (p.44·3); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Musculoskeletal, joint, and peri-articular disorders; neuritis; neuropathy; pain.

Dolophine *Roxane, USA.*
⊗ Methadone hydrochloride (p.82·3).
Detoxification and treatment of opioid addiction; pain.

DoloPosterine N *Kade, Ger.*
Cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Doloproct *Schering, Denm.; Intendis, Ger.; Schering, Gr.; Intendis, Ital.*
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Doloproct Comp *Schering, Denm.*
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3); benzyl alcohol (p.1631·3).
Anorectal disorders.

Dolo-Puren *Alpharma-Isis, Ger.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Dolopyrine *Streuli, Switz.†.*
Propyphenazone (p.119·3); atropine methobromide (p.1219·2); papaverine hydrochloride (p.2191·3); diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2).
Pain.

Doloquim *Quimica y Farmacia, Mex.*
Aspirin (p.20·3).
Pain; thromboembolic disorders.

Dolor *Extractum, Hung.*
Ethylmorphine hydrochloride (p.52·2); aminophenazone (p.19·1); phenacetin (p.115·3).
Pain.

DolorA *Schwarzwalder, Ger.*
Homoeopathic preparation.

Dolorac
Note. This name is used for preparations of different composition.
Vita, Spain.
Ibuprofen lysine (p.64·2).
Inflammation; pain.

GenDerm, USA.
Capsaicin (p.32·3).
Pain.

Dolorecto *Capsifar, Port.*
Glycerol (p.2314·2).
Constipation.

Doloreduct *Azupharma, Ger.†.*
Paracetamol (p.108·1).
Fever; pain.

Dolorelax *Silesia, Chile†.*
Paracetamol (p.108·1); chlormezanone (p.968·3).
Musculoskeletal spasm; pain.

Dolores *Curtis, Pol.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Dolorex
Note. This name is used for preparations of different composition.
S Med, Austria†.
Diethylamine salicylate (p.47·2); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Mecom, Turk.
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dolor-loges *Loges, Ger.†.*
Homoeopathic preparation.

Dolormin
McNeil, Ger.
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; migraine; pain.

MSD, Port.
Ibuprofen lysine (p.64·2).
Fever; pain.

Dolormin mit Naproxen *McNeil, Ger.*
Naproxen (p.92·3).
Pain.

Dolorol *Pharmacare, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Dolorol Forte *Pharmacare, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Dolorosan *Leciva, Cz.†.*
Lysine aspirin (p.79·1).
Musculoskeletal, joint, and peri-articular disorders.

Dolorsin *Recalcine, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Dolorstad *Stada, Cz.*
Sumatriptan succinate (p.625·2).
Migraine.

Dolorsyn *Omega, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Dolorub *Maver, Chile.*
Ibuprofen (p.64·2).
Inflammation; pain.

Dolorub Capsico *Maver, Chile.*
Capsicum (p.2276·2).
Pain.

Dolo-Rubriment *Nordmark, Cz.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); heparin sodium (p.1301·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dolo-Rubriment H *Riemser, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, and soft-tissue disorders; neuritis.

Dolos *Tempo Scan Pacific, Indon.*
Mefenamic acid (p.80·1).
Pain.

Dolosal *Cristalia, Braz.*
⊗ Pethidine hydrochloride (p.113·2).
Pain; premedication.

Dolosarto *Biosarto, Spain†.*
Aspirin (p.20·3); benzydamine hydrochloride (p.27·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Dolospam *Laboratorios Chile, Chile.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Dolo-Spedifen *Zambon, Hong Kong†; Zambon, Switz.*
Ibuprofen arginine (p.65·2).
Fever; pain.

Dolostop
Note. This name is used for preparations of different composition.
Intermed, Gr.
Nimesulide (p.95·3).
Inflammatory disorders.

Gentili, Ital.†.
Rofecoxib (p.121·1).
Pain.

Bayer, Spain.
Paracetamol (p.108·1).
Fever; pain.

Zeller, Switz.†.
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

DoloStop nouvelle formule *Zeller, Switz.†.*
Paracetamol (p.108·1).
Fever; pain.

Dolosul *Soria Natural, Spain†.*
Devil's claw root (p.39·1); salix (p.121·3); meadowsweet (p.2338·1).
Rheumatic disorders.

Dolotandax *Sandoz, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Dolotec *Innotech, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Doloteffin *Ardeypharm, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Dolotemp *GSK, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Dolo-Tiaminal *Silanes, Mex.*
Dipyrone (p.49·2); cyanocobalamin (p.1980·2); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2).
Neuralgia; neuritis.

Dolotol 12 *Saval, Chile.*
Lysine aspirin (p.79·1); glycine (p.1947·3); hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

Dolotor *Roche, Mex.†.*
Ketorolac trometamol (p.74·2).
Pain.

Dolotral *Stada, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolotram *Pharmaplan, S.Afr.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolotramine *Streuli, Switz.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolotren *Faes, Spain.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal colic.

Dolo-Veniten *Whitehall-Robins, Switz.†.*
Glycol salicylate (p.62·3); a heparinoid (p.1305·2); aescin (p.2248·2).
Vascular disorders.

Doloverina *Saval, Chile.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal pain and spasm.

Dolovin *Atral, Port.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

DoloVisano M *Kade, Ger.*
Mephenesin (p.1897·2).
Cervical syndrome; lumbago; skeletal muscle spasm.

DoloVisano Salbe *Kade, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Circulatory disorders of the skin; muscle, joint, and soft-tissue disorders.

Dolo-Voltaren
Novartis Consumer, Austria.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Novartis, Spain.
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; renal colic.

Doloxene *Aspen, Austral.; NordMedica, Denm.; Lilly, Irl.†; Lilly, NZ†; Aspen, S.Afr.; Meda, Swed.*
Dextropropoxyphene napsilate (p.40·1).
Pain.

Doloxene Co *Pharmacare, S.Afr.*
Dextropropoxyphene napsilate (p.40·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Doloxene-A *Lilly, Braz.*
Dextropropoxyphene napsilate (p.40·1); aspirin (p.20·3).
Pain.

Doloxtren *Sintactica, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Dolpar *Esteve, Port.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolpasse *Fresenius Kabi, Austria.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolpaz *Pasteur, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolphin *Sanovel, Turk.*
Diflunisal (p.47·2).
Musculoskeletal and joint disorders; pain.

Dolpic Forte *Pasteur, Chile.*
Trimebutine maleate (p.2404·3).
Irritable bowel syndrome.

Dolpocetmol *Synco, Hong Kong.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Dolprin *Collins, Mex.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dolprofen *Collins, Mex.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Dolprone *Melisana, Belg.; Aventis, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Dolpyc *Teofarma, Ital.*
Capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, and soft-tissue pain.

Dolquine *Rubio, Spain.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; malaria; rheumatoid arthritis.

Dolsed *American Urologicals, USA†.*
Methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1); benzoic acid (p.1630·2); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dolsin *BB, Cz.*
⊗ Pethidine hydrochloride (p.113·2).
Pain; premedication.

Dolsiprim *Rowe-Fleming, Venez.†.*
Aspartame (p.1930·1).
Sugar substitute.

Dolsten *Medic+Aid, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Doltaque *EG, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Doltarac *Offenbacн, Mex.*
Diclofenac (p.44·2).
Inflammation.

Doltard
Note. This name is used for preparations of different composition.
Nycomed, Cz.†; Nycomed, Denm.; Nycomed, Pol.
⊗ Morphine sulfate (p.86·3).
Pain.

Ethypharm, Neth.
Tramadol hydrochloride (p.130·3).
Pain.

Dolten *Pfizer, Arg.*
Ketorolac trometamol (p.74·2).
Pain.

Doltren *Flupal, Venez.†.*
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3).
Inflammation; pain.

Dol-u-ron *Neo-Farmaceutica, Port.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Doluvital *Valdecasas, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Dolval *Randall, Mex.*
Ibuprofen (p.64·2).
Fever; pain.

Dolvan
Note. This name is used for preparations of different composition.
Gador, Arg.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Norma, UK.
⊗ Diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms; nasal congestion.

Dolvan Flex *Gador, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint and peri-articular disorders.

Dolven *Eczacibasi, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Dolver *Maver, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Dolviran
Note. This name is used for preparations of different composition.
Bayer, Belg.†; Bayer, Port.; Kern, Spain; Bayer, Turk.; Bayer, Venez.
Aspirin (p.20·3); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Bayer, Mex.
Paracetamol (p.108·1).
Fever; pain.

Dolviran N
Note. This name is used for preparations of different composition.
Tropon, Ger.
Aspirin (p.20·3); codeine phosphate (p.37·2).
Pain.

Bayer, Neth.†.
Aspirin (p.20·3); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Dolxen *Maver, Mex.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Dolyzinax *Genepharm, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Dolzam *Zambon, Belg.*
Tramadol hydrochloride (p.130·3).
Pain.

Dolzycam *Sons, Mex.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

DOM *Lapi, Indon.*
Domperidone (p.1726·2).
Dyspepsia; hiccups; nausea and vomiting.

Doma Grip *Dallas, Arg.*
Guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Doma Grip tablets formerly contained guaifenesin, astemizole, phenylephrine hydrochloride, and paracetamol.

Domar *Eurodrug, Hong Kong; Teofarma, Ital.; Eurodrug, Singapore; Eurodrug, Thai.*
Pinazepam (p.1019·1).
Alcoholism; anxiety; depression; epilepsy; insomnia; mixed anxiety depressive states; neuroses; psychoneurotic disorders.

Domcet *Cipla, India.*
Domperidone (p.1726·2); paracetamol (p.108·1).

Domeboro *Serral, Mex.; Miles, USA.*
Aluminium sulfate (p.2255·1); calcium acetate (p.1675·2).
Skin disorders.

Domedon *Tempo Scan Pacific, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Domenal *Collins, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Domenan *Kissei, Jpn.*
Ozagrel hydrochloride (p.2359·2).
Asthma.

Domeni *Tafir, Spain†.*
Vincamine (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Dome-Paste *Miles, USA.*
⊗ Zinc oxide (p.1621·2); calamine (p.1591·2); gelatin (p.1072·1).
Conditions of the extremities requiring protection and support.

Domer *Best, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Domerdon *Asian Pharm, Thai.*
Domperidone (p.1726·2).
Delayed gastric emptying; dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Domerid *Rowex, Irl.*
Domperidone maleate (p.1726·3).
Nausea; regurgitation; upper abdominal discomfort; vomiting.

Domeryl *Combiphar, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); alcohol (p.1625·2).
Cough; respiratory-tract congestion.

Domes *SoSe, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Domet *Hexpharm, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Dometa *Ikapharmindo, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Dometic *Kalbe, Indon.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Dometin *Nycomed, Neth.†.*
Indometacin (p.66·3).
Musculoskeletal, joint, and peri-articular disorders.

Domicap *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Domidin *YSP, Malaysia.*
Domiphen bromide (p.1643·1).
Sore throat.

Domidon *Gry, Ger.*
Domperidone maleate (p.1726·3).
Dyspepsia; nausea and vomiting.

Domidone *Milano, Thai.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; hiatus hernia; nausea and vomiting.

Domigel *Solfran, Mex.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Domiken *Kendrick, Mex.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Domin *Boehringer Ingelheim, Jpn.*
Talipexole hydrochloride (p.819·2).
Parkinsonism.

Dominadol *Craveri, Arg.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Dominal *Viatris, Austria; Meda, Belg.; AWD, Ger.*
Prothipendyl hydrochloride (p.1021·3).
Agitation; atopic dermatitis; eclampsia; gastrointestinal spasm; pain; premedication; pruritus; psychoses; sedative; sleep disorders; vomiting.

Dominans *Lundbeck, Ital.*
Nortriptyline hydrochloride (p.413·2); fluphenazine hydrochloride (p.998·1).
Mixed anxiety depressive states.

Dominium *Tecnofarma, Chile.*
Fluoxetine (p.397·3).
Bulimia; depression; obsessive-compulsive disorder.

Domitrone *Biomedis Oncology, Philipp.*
Mitoxantrone hydrochloride (p.754·1).
Breast cancer; chronic myeloid leukaemia; non-Hodgkin's lymphoma.

Domnamid *Lundbeck, Denm.†.*
Estazolam (p.995·1).
Premedication; sleep disorders.

Domol *Miles, USA.*
Bath additive.
Lubrication of the skin; pruritus.

Dompel *Samnam, Singapore.*
Domperidone (p.1726·2).
Dyspepsia.

Dompenyl *Korea United, Philipp.; Pharma 3, Philipp.; Korea United, Singapore†.*
Domperidone (p.1726·2).
Nausea and vomiting.

Dompeon *APT, Hong Kong.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Domper *YSP, Malaysia; Yung Shin, Singapore.*
Domperidone (p.1726·2).
Meteorism; nausea and vomiting.

Domperamol *Servier, UK†.*
Paracetamol (p.108·1); domperidone maleate (p.1726·3).
Migraine.

Domperdone *Polipharm, Thai.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; nausea and vomiting.

Domperi *Ipca, India.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; nausea and vomiting.

Domperitop *Topgen, Belg.*
Domperidone (p.1726·2).
Gastroparesis; nausea and vomiting.

Domper-M *Bangkok Lab & Cosmetic, Thai.*
Domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea and vomiting.

Domperol *Farmion, Braz.†.*
Domperidone (p.1726·2).
Nausea and vomiting.

Domperon *Cadila, India.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders; nausea and vomiting.

Dom-Polienzim *Sanitas, Arg.*
Domperidone (p.1726·2); lipase (p.2360·3); amylase (p.2256·3); protease; cellulase (p.2279·1); simeticone (p.1770·2).
Gastrointestinal disorders; pancreatic insufficiency.

Domsedan *Fortbenton, Arg.*
Vitamin A (p.1971·2).

Domstal *Torrent, India.*
Domperidone (p.1726·2).
Gastro-oesophageal reflux; gastroparesis; meteorism; nausea and vomiting.

Domtisona *Fortbenton, Arg.†.*
⊗ Triamcinolone (p.1544·2); coal tar (p.1616·2).
Skin disorders.

Domuderm *Fortbenton, Arg.*
Azulene (p.2262·3); hamamelis (p.2318·2).
Skin cleanser.

Domutussina *Proge, Ital.*
Dropropizine (p.1557·3).
Coughs.

Domuvar *Bioprogress, Ital.†.*
Spores of *Bacillus subtilis.*
Gastrointestinal disorders.

Domycotin *Help, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Dona *Rottapharm, Cz.; Rottapharm, Hung.; Helsinn Birex, Irl.; Rottapharm, Ital.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Osteoarthritis.

Dona 200-S *Opfermann, Ger.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Donalg *Dynacren, Ital.*
Tetracaine hydrochloride (p.1871·3); sulfogaiacol (p.1573·2); salicylic acid (p.1612·2); menthol (p.2340·1); sage (p.2382·3); chamomile (p.2279·3); salix (p.121·3); ginger (p.1732·3).
Dental pain.

Donalgin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Niflumic acid (p.95·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Donamet *Abbott, Ital.*
Ademetionine butanedisulfonate (p.2247·1).
Hepatic cholestasis.

Donaprox *Reuffer, Mex.*
Naproxen (p.92·3).
Pain.

Donaren *Apsen, Braz.*
Trazodone hydrochloride (p.424·3).
Depression; neurogenic pain.

Donarot *Faran, Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Donataxel *Bioprofarma, Arg.*
Docetaxel (p.710·3).
Breast cancer; non-small cell lung cancer; prostatic cancer.

Donatiol *AGIPS, Ital.*
Mecysteine hydrochloride (p.1564·2); guaifenesin (p.1561·3); camphor (p.2273·2).
Respiratory-tract disorders.

Donatussin
Note. This name is used for preparations of different composition.
Laser, USA.
Oral drops: Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Laser, USA.
Syrup: Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Donatussin DC *Laser, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Donatussin DM *Laser, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Donaz *Glenmark, India.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Donecept *Cipla, India.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Donegal *Medipharm, Chile.*
Domperidone (p.1726·2).
Gastro-oesophageal reflux; hiccups; nausea; vomiting.

Doneka *Lesvi, Spain.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Doneka Plus *Lesvi, Spain.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Donepes *Richmond, Arg.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Donepex *Celon, Pol.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Doneurin *Hexal, Ger.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; withdrawal syndromes.

Donexan *Meprofarm, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Cough; nasal congestion.

Donexan-DX *Meprofarm, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough; respiratory-tract congestion.

Dong Quai Complex *Blackmores, Austral.*
Dong quai (p.2297·3); avena (p.2262·1); cimicifuga (p.2282·1); vitex agnus castus (p.2249·1); vitamins and minerals (p.1922·1).
Menopausal disorders; premenstrual syndrome; uterine cramping.

Donix *Llorens, Spain.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety disorders; chemotherapy induced nausea and vomiting; insomnia; premedication.

Donna
Note. This name is used for preparations of different composition.
Eurofarma, Braz.†.
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Duopharma, Hong Kong; Duopharma, Malaysia.
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Donnagel
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.
Hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal disorders.

IQB, Braz.
⊗ Metronidazole (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1); urea (p.1620·2).
Vulvovaginal infections.

Donnalix *Wyeth Consumer, Austral.*
Hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Gastrointestinal disorders.

Donnamar *Marnel, USA.*
Hyoscyamine sulfate (p.1736·1).

Donnatab *Wyeth Consumer, Austral.*
Hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Gastrointestinal disorders.

Donnatal *Pharmacare, S.Afr.; Whitehall, Thai.†; PBM, USA.*
Hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); phenobarbital (p.492·2).
Acute enterocolitis; gastrointestinal disorders; genitourinary disorders; irritable bowel syndrome; motion sickness; smooth muscle spasm.

Donnina *Kwizda, Austria.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Donobid *MSD, Denm.†; MSD, Fin.†; MSD, Norw.; MSD, Swed.*
Diflunisal (p.47·2).
Inflammation; musculoskeletal and joint disorders; pain.

Donodol *Armstrong, Mex.*
Clonixin lysine (p.37·1).
Pain.

Donodol Compuesto *Armstrong, Mex.*
Clonixin lysine (p.37·1); hyoscine butylbromide (p.1734·1).
Smooth muscle pain and spasm.

Donomix *Laboratorios Chile, Chile.*
⊗ Clotrimazole (p.530·1); betamethasone (p.1518·2).
Fungal skin infections with inflammation.

Donorest *Wyeth Lederle, Port.†.*
Fentiazac (p.60·1).

Donormyl *UPSA Conseil, Fr.*
Doxylamine succinate (p.578·2).
Insomnia.

Don't Bug Me *Relax, UK.*
Vitamin B (p.1976·3); aloe vera (p.1588·2).
Insect repellent.

dontisanin *Aventis, Ger.*
Bromelain (p.2269·1).
Inflammation.

Dontisolon D *Aventis, Ger.*
⊗ Prednisolone (p.1540·3) or prednisolone acetate (p.1541·1).
Inflammatory disorders of the mouth.

Dontuxin *Continentales, Mex.*
Dextromethorphan (p.1555·2).
Cough.

Donulide *Rega, Port.*
Nimesulide (p.95·3).
Fever; pain.

Donum *M & H, Thai.*
Domperidone (p.1726·2).
Dyspepsia; gastro-oesophageal reflux; heartburn; nausea and vomiting.

Donzeimer *Indeco, Arg.*
Donepezil (p.365·2).
Alzheimer's disease.

Dopabane *Ariston, Braz.*
Dopamine hydrochloride (p.1273·2).

Dopac *Kalbe, Indon.*
Dopamine hydrochloride (p.1273·2).
Heart failure; hypotension; shock.

Dopacard *Speywood, Cz.†; Elan, Denm.; Zeneus, Fin.; Zeneus, Fr.; Zeneus, Ger.; Zeneus, Irl.; NZ Medical & Scientific, NZ†; Ipsen, Swed.†; Vifor, Switz.†; Cephalon, UK.*
⊗ Dopexamine hydrochloride (p.1274·2).
Adjunct in cardiac surgery; heart failure.

Dopacris *Cristalia, Braz.*
Dopamine hydrochloride (p.1273·2).

Dopadura C *Merck dura, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Dopaflex *Medphano, Ger.; PannonPharma, Hung.†.*
Levodopa (p.804·3).
Parkinsonism.

Dopagon *Schering, Arg.†.*
Lisuride maleate (p.811·1).
Acromegaly; female infertility; hyperprolactinaemia; lactation inhibition; menstrual disorders; parkinsonism.

Dopagrand *Ahimsa, Arg.*
Methyldopa (p.1334·1).
Hypertension.

Dopagyt *Themis Chemicals, India.*
Methyldopa (p.1334·1).
Hypertension.

Dopalux *Sandoz, Cz.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Dopamed
Note. This name is used for preparations of different composition.
Kolassa, Austria.
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

General Drugs, Thai.
Methyldopa (p.1334·1).
Hypertension.

Dopamet *Medochemie, Hong Kong; Actavis, Indon.; Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Methyldopa (p.1334·1).
Hypertension.

Dopametil *Bunker, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Dopamex *Biolab, Thai.*
Dopamine hydrochloride (p.1273·2).
Acute poisoning; hypotension; shock.

Dopaminex *Solvay, Thai.*
Dopamine hydrochloride (p.1273·2).
Shock.

Dopar *Shire, USA†.*
Levodopa (p.804·3).
Parkinsonism.

Dopareel *Toyo, Hong Kong.*
Zopiclone (p.1039·1).
Insomnia.

Doparid *Rafa, Israel.*
Tiapride hydrochloride (p.1032·1).
Choreas; dyskinesias; tics; tremor.

Doparl *Kyowa, Jpn.*
Levodopa (p.804·3).
Parkinsonism.

Dopasian *Asian Pharm, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Dopatral *LA, Arg.*
Methyldopa (p.1334·1).
Hypertension.

Dopatropin *Scott-Cassara, Arg.*
Dopamine (p.1274·1).

Dopegyt *Egis, Cz.; UCB, Ger.; Egis, Hong Kong; EGIS, Hung.; Egis, Malaysia; Egis, Pol.; Egis, Rus.; Egis, Singapore; Egis, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Dopergin *Schering, Austria; Schering, Ger.; Schering, Ital.; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Spain; Schering, Switz.†; Schering, Thai.†; Schering, Turk.*
Lisuride maleate (p.811·1).
Acromegaly; amenorrhoea; female infertility; galactorrhoea; galactostasis; hyperprolactinaemia; lactation inhibition; male hypogonadism; mastitis; parkinsonism; premenstrual syndrome; prolactinomas.

Dopergine *Schering, Fr.*
Lisuride maleate (p.811·1).
Erectile dysfunction; galactorrhoea; gynaecomastia in males; infertility; menstrual disorders; parkinsonism.

Dopicar *Teva, Israel.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Dopin *Pharmaland, Thai.†.*
Dosulepin hydrochloride (p.388·2).
Depression; mixed anxiety depressive states.

Dopina *Behrens, Venez.*
Dopamine hydrochloride (p.1273·2).
Hypotension; shock.

Dopinga *Inga, India.*
Dopamine hydrochloride (p.1273·2).
Shock.

Dopmin *Orion, Denm.; Orion, Fin.; Orion, Malaysia; Orion, Singapore†; Orion, Thai.; Drogsan, Turk.*
Dopamine hydrochloride (p.1273·2).
Heart failure; open heart surgery; shock.

Dopo Pik *Alckamed, Ital.*
Triclosan (Irgasan 300) (p.1665·2); trolamine (p.2405·1); propylene glycol (p.2374·1).
Skin disinfection.

Doppelherz Cardiovital *Queisser, Rus.*
Crataegus (p.2289·1).
Heart failure.

Doppelherz Energie-Tonikum *Queisser, Cz.*
Vitamin B substances; crataegus; valerian; lupulus (p.1922·1).
Tonic.

Doppelherz Energie-Tonikum N *Queisser, Ger.†.*
Vitamin B substances; crataegus; valerian; lupulus (p.1922·1).
Tonic.

Doppelherz Energotonik *Queisser, Rus.*
Vitamins; minerals; rutoside; choline citrate; sea salt; honey; invert sugar; mistletoe; hypericum; achillea; crataegus; angelica; valerian; lupulus; bitter orange; sage oil; rosemary oil; melissa oil; aromatic infusion; sodium glycerophosphate (p.1922·1).
Tonic.

Doppelherz Energovital Tonik *Queisser, Pol.*
Vitamins; minerals; rutoside; crataegus; St John's wort; equisetum; mistletoe; valerian; lupulus; bitter orange; melissa oil; sage oil; rosemary oil (p.1922·1).
Tonic.

Doppelherz Ginseng Aktiv *Queisser, Ger.†; Queisser, Rus.*
Ginseng (p.2312·1); pyridoxine hydrochloride; nicotinamide; caffeine (p.1116·3) (p.1922·1).
Tonic.

Doppelherz Melissa *Queisser, Rus.*
Melissa (p.2339·3); angelica (p.2258·1); cinnamon (p.2283·1); nutmeg (p.2355·2); bitter-orange peel (p.2357·1); citrus fruits peel (p.2332·3); clove (p.2284·3).

Doppelherz Melissengeist *Queisser, Ger.†.*
Melissa (p.2339·3); angelica (p.2258·1); cinnamon (p.2283·1); nutmeg (p.2355·2); bitter-orange peel (p.2357·1); clove (p.2284·3); lemon peel (p.2332·3).
Digestive disorders; skin circulatory disorders.

Doppelherz Nervotonik *Queisser, Rus.*
St John's wort (p.422·3).
Anxiety; nervous disorders.

Doppelherz Selevit *Queisser, Rus.*
Selenium yeast; vitamins (p.1922·1).

Doppelherz Vital Kapseln *Queisser, Pol.*
Garlic oil (p.2309·2); ginseng (p.2312·1); vitamins (p.1922·1).
Atherosclerosis; respiratory-tract disorders.

Doppelherz Vitalotonik *Queisser, Rus.*
Crataegus (p.2289·1); lupulus (p.2335·2); valerian (p.2410·1); melissa (p.2339·3); ginseng (p.2312·1).
Tonic.

Doppel-Spalt Compact *Whitehall-Much, Ger.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Dopram *Wyeth, Austral.†; Wyeth Lederle, Austria; Eumedica, Belg.; Meda, Denm.; Meda, Fin.; Genopharm, Fr.; Riemser, Ger.; IFET (ΙΦΕΤ), Gr.; Robins, Hong Kong†; Antigen, Irl.; Wyeth, NZ†; Bournonville, Neth.; Meda, Norw.; Bodene, S.Afr.; Wyeth, Switz.†; Anpharm, UK; Baxter, USA.*
Doxapram hydrochloride (p.2155·1).
Respiratory depression; respiratory failure.

Dopress *Pacific, NZ.*
Dosulepin hydrochloride (p.388·2).
Depression.

Doproct *Continental Pharma, Thai.*
⊗ Hydrocortisone acetate (p.1535·2); zinc oxide (p.1621·2); benzocaine (p.1854·1).
Anorectal disorders.

Dops
Note. This name is used for preparations of different composition.
Fuca, Fr.
Sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); calcium phosphate (p.1676·2); magnesium hydroxide (p.1743·2); titanium dioxide (p.1617·3); magnesium carbonate (p.1743·1).
Gastrointestinal hyperacidity.

Sumitomo, Jpn.
Droxidopa (p.803·3).
Orthostatic hypotension; parkinsonism.

Dopsan *Pond's, Thai.*
Dapsone (p.261·2).
Dermatitis herpetiformis; leprosy.

Doqua *Sriprasit, Thai.*
Thiamphenicol (p.351·1).
Bacterial infections.

Doral *Mitsubishi, Jpn; Questcor, USA.*
Quazepam (p.1022·1).
Insomnia; premedication.

Doralan *Wermar, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Doralan-Ax *Wermar, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Doralese
GSK, Irl.
Indoramin (p.1315·3).
Benign prostatic hyperplasia.

Chemidex, UK.
Indoramin hydrochloride (p.1315·1).
Benign prostatic hyperplasia.

Doralex *Vitapan, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Doralgex *Greenpharma, Braz.*
Dipyrone (p.49·2); orphenadrine (p.812·2); caffeine (p.1116·3).

Doralgina *Neo Quimica, Braz.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Muscle spasm; pain.

Doralin *Menarini, Gr.*
Otilonium bromide (p.2359·1).
Aid in gastrointestinal endoscopy; gastrointestinal smooth muscle spasm.

Doraplax *Luper, Braz.†.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Dorbantil *Drugtech, Chile; Recalcine, Chile.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dorbigot *Nufarindo, Indon.*
Paracetamol (p.108·1); acetylcysteine (p.1548·2).
Coughs; fever.

Dorcalor *BA Farma, Port.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dorciflex *Cifarma, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Muscle spasm; pain.

Dorcol Children's Cold Formula *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Dorcol Children's Cough Syrup *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dorcol Children's Decongestant *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Doregrippin *Rentschler, Ger.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Dorehydrin *Sanova, Austria.*
Codergocrine mesilate (p.363·3).
Cervical syndrome; hypertension; mental function impairment; migraine and related vascular headache; peripheral vascular disorders.

Dorend *Teuto, Braz.†.*
Paracetamol (p.108·1); phenylbutazone (p.117·1).

Doreperol N *Rentschler, Ger.†.*
Hexetidine (p.1647·1).
Mouth and throat disorders; oral hygiene.

Dores *Pyridam, Indon.*
Haloperidol (p.1000·2).
Anxiety; psychoses.

Doretrim *Novartis, Braz.†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Dorf *Ibirn, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Dorfan *Akdeniz, Turk.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Dorfebril *Neckerman, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Dorfen *Cazi, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Dorflan *Cazi, Braz.*
Diclofenac (p.44·2), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Inflammation; pain.

Dorflex *Sanofi-Aventis, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Skeletal muscle spasm.

Dorgen *Cazi, Braz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dorgex *Greenpharma, Braz.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Doriance Solaire *Plantes et Medecines, Fr.*
Dietary supplement (p.1922·1).
Tanning aid.

Dorib *Ibfarma, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Doribax *Ortho McNeil, USA.*
Doripenem (p.266·3).
Bacterial infections.

Doribel *Luper, Braz.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Dorical *Legrand, Braz.*
Vitamins; rutin; minerals (p.1922·1).
Nutritional supplement.

Doricin *EMS, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine citrate (p.1116·3).
Skeletal muscle spasm.

Dorico *Sanofi-Aventis, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Doricoflu *Farmila, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Doricum
Note. This name is used for preparations of different composition.
Farmila, Ital.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Eye, ear, and nose disorders.

Roche, Venez.
Midazolam maleate (p.1007·3) or midazolam (p.1007·3).
Sedative.

Doridamina *Angelini, Ital.†.*
Lonidamine (p.741·3).
Malignant neoplasms.

Doridina *Bunker, Braz.*
⊗ Isometheptene hydrochloride (p.2327·1) or isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Doridone *DHA, Hong Kong; DHA, Singapore.*
Domperidone (p.1726·2).
Nausea and vomiting.

Doriflan *Luper, Braz.†.*
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Dorigren *Soma, Braz.*
Ibuprofen (p.64·2).
Inflammation; pain.

Dorilan *Luper, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Dorilax *Ache, Braz.*
Paracetamol (p.108·1); carisoprodol (p.1894·1); caffeine (p.1116·3).
Skeletal muscle spasm.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dorilen *Legrand, Braz.*
Dipyrone (p.49·2); adiphenine (p.2247·3); promethazine (p.588·2).
Pain.

Doriless *Cifarma, Braz.*
Dipyrone (p.49·2); promethazine (p.588·2); adiphenine (p.2247·3).
Muscle spasm; pain.

Doriman *Vir, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Dorithricin
Note. This name is used for preparations of different composition.
Medice, Hung.; Rentschler, Singapore.
Tyrothricin (p.358·2); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Provita, Austria.
Eye ointment: Tyrothricin (p.358·2); neomycin sulfate (p.305·1).

Rentschler, Austria.
Lozenges: Tyrothricin (p.358·2); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Dorithricin Limone *Rentschler, Ger.†.*
Tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Dorithricin Original *Rentschler, Ger.*
Tyrothricin (p.358·2); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Dorival *Bayer, Spain.*
Ibuprofen (p.64·2).
Fever; pain.

Dorixina *Roemmers, Arg.; Rhein, Mex.; Roemmers, Venez.*
Clonixin lysine (p.37·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dorixina B1 B6 B12 *Roemmers, Arg.*
Clonixin lysine (p.37·1); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2) or hydroxocobalamin acetate (p.1980·3).
Inflammation; pain.

Dorixina Flex *Roemmers, Venez.*
Clonixin lysine (p.37·1); cyclobenzaprine hydrochloride (p.1895·2).
Painful smooth muscle spasm.

Dorixina Forte *Roemmers, Arg.*
Clonixin lysine (p.37·1); dextropropoxyphene napsilate (p.40·1).
Pain.

Dorixina Relax *Roemmers, Arg.*
Clonixin lysine (p.37·1); cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal pain.

Dorken *UCB, Spain.*
Dipotassium clorazepate (p.980·1); aminohydroxybutyric acid (p.471·2); pyridoxine hydrochloride (p.1978·2).
Anxiety disorders; behavioural disorders; epilepsy; insomnia.

Dorlamida *Atlas, Arg.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Dorlamida T *Atlas, Arg.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dorless *Uniao Quimica, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Dorlise *Menarini, Port.*
Frovatriptan succinate (p.622·3).
Migraine.

Dorlotyn *Extractum, Hung.†.*
Amobarbital (p.961·3).
Sleep disorders.

Dorm
Note. A similar name is used for preparations of different composition (see below).
Norma (Νορμα), Gr.
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Dormalon *Wernigerode, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Dormarist *Steiner, Ger.†.*
Valerian (p.2410·1); melissa (p.2339·3).
Sleep disorders.

Dorme
Note. A similar name is used for preparations of different composition (see above).
Noristan, S.Afr.†.
Quazepam (p.1022·1).
Insomnia.

Dormeasan *Bioforce, Ger.; Bioforce, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2).
Agitation; insomnia; nervous disorders.

Dormelox *Delta, Braz.*
Meloxicam (p.80·3).

Dormer 211 *Dormer, Canad.†.*
Emollient.
Dry skin.

Dormex
Note. This name is used for preparations of different composition.
Nobel, Canad.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Recalcine, Chile.
Brotizolam (p.965·2).
Insomnia.

Dormicum
Roche, Arg.; Roche, Gr.; Roche, Hong Kong; Roche, Indon.; Roche, Israel; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, S.Afr.; Roche, Singapore; Roche, Swed.; Roche, Thai.; Roche, Turk.
Midazolam (p.1007·3).
General anaesthesia; induction of anaesthesia; insomnia; premedication; sedative; status epilepticus.

Roche, Austria; Roche, Belg.; Roche, Denm.
Midazolam hydrochloride (p.1007·3).
General anaesthesia; premedication; sedative.

Roche, Cz.; Roche, Fin.; EGIS, Hung.; Roche, Malaysia; Roche, Switz.
Midazolam (p.1007·3) or midazolam maleate (p.1007·3).
Analgesia in anaesthesia; general anaesthesia; insomnia; premedication; sedative.

Roche, Ger.; Roche, Mex.; Roche, Neth.; Roche, Port.
Midazolam hydrochloride (p.1007·3) or midazolam maleate (p.1007·3).
General anaesthesia; insomnia; premedication; sedative.

Roche, Spain.
Midazolam maleate (p.1007·3).
General anaesthesia; insomnia; premedication; sedative.

Dormid *Scott-Cassara, Arg.*
Midazolam (p.1007·3).
Premedication; sedative.

Dormidina *Esteve, Port.; Pensa, Spain.*
Doxylamine succinate (p.578·2).
Insomnia.

Dormi-Gastreu S R14 *Reckeweg, Ger.*
Homoeopathic preparation.

Dormil *Milte, Ital.*
Eschscholtzia californica; passion flower (p.2363·2).
Sleep disorders.

Dormilam *Laboratorios Chile, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Dormilan *Baliarda, Arg.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Dormin *Randob, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Dorminoctil *Recalcine, Chile.*
Doxylamine succinate (p.578·2).
Sleep disorders.

Dormiphen *Lalco, Canad.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Dormiplant
Note. This name is used for preparations of different composition.
VSM, Belg.; Marvecs, Ital.; Schwabe, Pol.; DHU, Spain; Schwabe, Switz.
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia; nervous disorders; sleep disorders.

Schwabe, Neth.
Valerian (p.2410·1).

Dormire *Cristalia, Braz.*
Midazolam maleate (p.1007·3).
Insomnia; premedication.

Dormium *Uniao Quimica, Braz.*
Midazolam (p.1007·3).
Insomnia.

Dormixal *Demo, Gr.*
Midazolam (p.1007·3).

Dormizol *Sanofi-Aventis, Austral.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Dormodor *Valeant, Spain.*
Flurazepam hydrochloride (p.999·1).
Insomnia.

Dormonid
Roche, Braz.
Midazolam hydrochloride (p.1007·3) or midazolam maleate (p.1007·3).
Adjunct in anaesthesia; insomnia; premedication; sedative.

Roche, Chile.
Midazolam (p.1007·3) or midazolam hydrochloride (p.1007·3).
General anaesthesia; insomnia; premedication; sedative.

Dormonoct *Aventis, Arg.; Sanofi-Aventis, Belg.; Aventis, Neth.; Sanofi-Aventis, Port.; Aventis, S.Afr.*
Loprazolam mesilate (p.1003·3).
Insomnia; premedication.

Dormo-Puren *Alpharma-Isis, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Dormo-Sern *Riemser, Ger.†.*
Valerian (p.2410·1); passion flower (p.2363·2).
Nervous disorders; sleep disorders.

Dormosol *Raffo, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Dormosyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Dormoverlan *Verla, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Agitation; insomnia.

Dormutil N *Alpharma-Isis, Ger.†.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Dornal *Klinger, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Dorner *Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.; Yamanouchi, Thai.*
Beraprost sodium (p.1225·1).
Arterial occlusion; pulmonary hypertension; thromboembolic disorders.

Dornot *Uniao Quimica, Braz.*
⊗ Pethidine hydrochloride (p.113·2).
Pain.

Dorocoff-Paracetamol *Hevert, Ger.†.*
Paracetamol (p.108·1).
Fever; pain.

Dorofen *Liptis, USA.*
Glucosamine sulfate (p.2313·2); ginkgo biloba (p.2311·1).
Intermittent claudication; osteoarthritis.

Dorona *Ducto, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Dorosan *Rottapharm, Cz.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Dorox *M & H, Thai.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Doroxan *Rottapharm, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Dorpane *Macrophar, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Peri-articular disorders; skeletal muscle pain; tension headache.

Dorpiel *Fortbenton, Arg.*
Tretinoin (p.1618·1).
Acne.

Dorpinon *Ariston, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Dorsal *Silanes, Mex.*
Meloxicam (p.80·3); carisoprodol (p.1894·1).
Musculoskeletal and joint disorders.

Dorsanol *Multilab, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Dorscopena *Ariston, Braz.†.*
Dipyrone (p.49·2); chlorophenothiazinylscopine.
Skeletal muscle spasm.

Dorsedin *EMS, Braz.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Dorsiflex *Lek, Cz.; Will-Pharma, Neth.; Ilsan, Turk.*
Mephenoxalone (p.1897·2).
Skeletal muscle pain; skeletal muscle spasm.

Dorsilon *Ilsan, Turk.*
Mephenoxalone (p.1897·2); paracetamol (p.108·1).
Skeletal muscle spasm.

Dorsof T *Laboratorios Chile, Chile.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dorspan *EMS, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Skeletal muscle spasm.

Dorvan *Simoes, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Dorveran *Hexal, Braz.†.*
Belladonna (p.2263·3); hyoscyamus (p.2323·3); star anise (p.2392·1); boldo (p.2267·2).
Smooth muscle spasm.

Doryl *Merck, Fin.†; Merck, Ger.†; Merck, Switz.†.*
Carbachol (p.1879·2).
Gastrointestinal motility disorders; micturition disorders; urinary retention.

Doryx *Mayne, Austral.; Pfizer, Chile; Gerard, Norw.†; Faulding, Singapore†; Scand Pharm, Swed.†; Warner Chilcott, USA.*
Doxycycline hyclate (p.267·1).
Amoebiasis; bacterial infections; malaria.

Dorzoflax *Sidus, Arg.†.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dorzol *Oftalmi, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; intra-ocular hypertension.

Dorzone *Delta, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Dorzox *Cipla, India.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Dos Dias N
Note. This name is used for preparations of different composition.
Elea, Arg.
Injection: Estradiol benzoate (p.2097·2); hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea.

Elea, Arg.
Tablets: Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Amenorrhoea.

DOS Softgel *Goldline, USA.*
Docusate sodium (p.1725·1).
Constipation.

Dosaflex *Richwood, USA.*
Senna (p.1769·2).
Constipation.

Dosamont *Medinova (Μεντινοβα), Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Dosan *Pacific, NZ.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dosanac *Siam Bheasach, Thai.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dosano *Sandoz, Cz.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dosate *Pharmasant, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux, Zollinger-Ellison syndrome; peptic ulcer.

Dosavastatin *Dosa, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Dosberotec *Boehringer Ingelheim, Ital.*
⊗ Fenoterol hydrobromide (p.1121·1).
Respiratory-tract disorders.

Doscafis *Llorens, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Doses-O-Son *Realdyme, Fr.*
Bran (p.1712·3).
Dietary fibre supplement.

Dosier
Note. This name is used for preparations of different composition.
Casasco, Arg.
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Tecnofarma, Chile†.
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Dosil *Llorens, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Dosil Enzimatico *Llorens, Spain.*
Doxycycline hyclate (p.267·1); chymotrypsin (p.2281·3); trypsin (p.2405·3).
Bacterial infections.

Dosin *Andromaco, Chile.*
Domperidone (p.1726·2).
Diabetic gastroparesis; dyspepsia; gastro-oesophageal reflux; nausea; vomiting.

Dosiseptine *Gifrer Barbezat, Fr.*
Chlorhexidine gluconate (p.1635·3).
Wounds disinfection.

Dosmin *Remexa, Mex.*
Camphor (p.2273·2); menthol (p.2340·1).
Allergic skin disorders; pruritus; urticaria.

Dosodos *Beta, Arg.*
Butamirate citrate (p.1553·1).
Coughs.

Dosoxygenee *Gifrer Barbezat, Fr.*
Hydrogen peroxide (p.1647·3).
Wound disinfection.

Dospan Pento *Ivax, Arg.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; circulatory disorders of the eye and ear.

Dospir *Boehringer Ingelheim, Switz.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Doss *Gry, Ger.*
Alfacalcidol (p.1986·1).
Bone disorders; hypoparathyroidism.

Dostan *Prosel, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage; hereditary angioedema.

Dostein *Roche, Mex.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Dosteril *Biomep, Mex.*
Lisinopril (p.1325·2).
Hypertension.

Dostil *Triomed, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Dostinex *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Paladin, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong;*

Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia Upjohn, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Kenfarma, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pharmacia, UK; Pharmacia Upjohn, USA†; Pfizer, Venez.
Cabergoline (p.802·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism; pituitary adenoma; prolactinoma.

Dosturel *Bros, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Dosulfin Bronquial *Sandoz, Arg.*
⊗ Co-trimoxazole (p.258·1); bromhexine hydrochloride (p.1552·2); etamivan (p.2156·1); guaifenesin (p.1561·3); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Respiratory-tract infections.

Dosulfin Fuerte *Sandoz, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Dosyklin *Leiras, Fin.*
Doxycycline (p.267·1).
Bacterial infections.

Dotagil *Loeffler, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Dotalsec *Hexa, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dotarem *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Codali, Belg.; Guerbet, Braz.†; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; R+N, Gr.; Guerbet, Hung.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Martins & Fernandes, Port.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; Quifoven, Venez.*
Meglumine gadoterate (p.1480·2).
Contrast medium for magnetic resonance imaging.

Dotest *Mentholatum, Austral.†.*
Pregnancy test (p.2372·1).

Dothapax *Ashbourne, UK†.*
Dosulepin hydrochloride (p.388·2).

Dothep *Alphapharm, Austral.; Gerard, Irl.; Alphapharm, Malaysia.*
Dosulepin hydrochloride (p.388·2).
Depression; mixed anxiety-depressive states.

Dotin *Pfizer, Venez.†.*
Barrier preparation.

Dotrin *Medical, Arg.*
Neomycin sulfate (p.305·1); hexylresorcinol (p.1647·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Dotur *Sandoz, Austria; Sandoz, Indon.; Sandoz, Pol.*
Doxycycline hyclate (p.267·1).
Bacterial infections; protozoal infections.

Double M *Ipca, India†.*
Multivitamin and mineral preparation (p.1922·1).

Double-Action Toothache Kit *Dent, USA.*
Liquid, benzocaine (p.1854·1); tablets, paracetamol (p.108·1) (Maranox).

Doublebase *Dermal Laboratories, UK.*
Isopropyl myristate (p.2029·3); liquid paraffin (p.2030·3).
Dry skin; pruritus.

Doublecap *Breckenridge, USA.*
Capsaicin (p.32·3).
Musculoskeletal and joint pain.

Double-Tussin DM *Reese, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Douglan *3M, Ger.*
Pimecrolimus (p.1609·1).
Eczema.

Doulax *Bio-Sante, Canad.*
Cascara (p.1715·2); senna (p.1769·2).
Constipation.

Douzabox *Denk, Thai.; Sriprasit, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Vitamin B deficiency.

Doval *Pharmaceutical Enterprises, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; depression; premedication.

Dovalem *Novag, Mex.*
Ethambutol (p.275·2).
Tuberculosis.

Dovate *Pharmacare, S.Afr.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dovavixin *Help, Gr.†.*
Zipeprol hydrochloride (p.1575·3).
Cough.

Doven *Eurofarmaco, Ital.*
Diosmin (p.2304·2).
Capillary fragility; venous insufficiency.

Doveri *Rekah, Israel.*
Opium (p.105·1); ipecacuanha (p.1562·3).
Coughs; dyspnoea.

Dovidin *Anpharm (Ανφαρμ), Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Dovidox *Fabop, Arg.†.*
Povidone-iodine (p.1659·2).

Dovobet *Leo, Belg.; Leo, Canad.; Leo (Λεω), Gr.; Leo, Irl.; Formenti, Ital.; Leo, Neth.; Leo, UK.*
⊗ Calcipotriol (p.1591·3); betamethasone dipropionate (p.1518·3).
Psoriasis.

Dovonex *Leo, Canad.; Leo (Λεω), Gr.; Leo, Irl.; Teikoku Seiyaku, Jpn; Adcock Ingram, S.Afr.; Leo, UK; Westwood-Squibb, USA.*
Calcipotriol (p.1591·3).
Psoriasis.

Downtrat *Dosa, Arg.*
⊗ Sibutramine (p.2164·1).
Obesity.

Doxacar *Durascan, Denm.†.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxacard *Cipla, India.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Doxacin *Otto, Indon.*
Doxycycline (p.267·1).
Bacterial infections.

Doxacor *Hexal, Ger.; Ilsan, Turk.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxacyne *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxadura *Schein, UK.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxagal *Teva, Hung.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxagamma *Worwag, Ger.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxakne *Galen, Ger.*
Doxycycline (p.267·1).
Acne.

Doxal
Note. This name is used for preparations of different composition.
Agepha, Austria; CTS, Rus.†.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Sigma, Braz.
Pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Vitamin supplement.

Orion, Fin.
Doxepin hydrochloride (p.389·1).
Anxiety; depression; insomnia.

Doxaloc *Unipharm, Israel.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxam *TAD, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Doxamax *Esparma, Ger.†.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxamil *Quimica y Farmacia, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Doxano *Biochemie, Austria†.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxanorm *ICN, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxapen *Liferpal, Mex.*
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Doxapress *Kwizda, Austria.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxapril *Bago, Arg.*
Lisinopril (p.1325·2).
Hypertension.

Doxa-Puren *Alpharma-Isis, Ger.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxar *Polfa Kutno, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxaratio *Ratiopharm, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxasin *Fortbenton, Arg.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Doxasyn *Genthon, Hong Kong.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxatan *Clonmel, Irl.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxatensa *VP, Spain.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

DoxaUro *Hexal, Ger.†.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia.

Doxazoflo *Gry, Ger.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxazomerck *Merck dura, Ger.†.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxe *TAD, Ger.*
Doxepin hydrochloride (p.389·1).
Anxiety disorders; depression; withdrawal syndromes.

Doxederm *Lazar, Arg.†.*
Doxepin (p.389·2).
Pruritus.

Doxef *Kimia, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Doxemina *Collins, Mex.*
Hydroxocobalamin (p.1980·3); thiamine (p.1976·3); pyridoxine (p.1979·1).
Neuritis.

Doxepia *Temmler, Ger.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; sleep disorders; withdrawal syndromes.

Doxetal *Richmond, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Doxibiot *Investi, Arg.*
Doxycycline (p.267·1).
Bacterial infections.

Doxibiotic *CTI, Israel.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxican *Azevedos, Port.*
Tenoxicam (p.128·2).
Gout pain; musculoskeletal and joint disorders.

Doxicard *Apotex, Hung.*
Doxazosin (p.1275·2).
Hypertension.

Doxicin *Genexo, Pol.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxicip *Cipla, India.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxiclat *Pierre Fabre, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxiclival *Valmor, Venez.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxicon *Vendiz, Philipp.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxicor *Pharmacore, Indon.*
Doxycycline (p.267·1).
Bacterial infections.

Doxicrisol *Quimifar, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxidan
Note. This name is used for preparations of different composition.
Pharmacia, USA†.
Capsules: Docusate calcium (p.1724·3); phenolphthalein (p.1762·1).
Constipation.

Pharmacia, USA.
Delayed-release tablets: Bisacodyl (p.1710·1).
Constipation.

Doxidol *Savant, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Doxifen *Bago, Chile.*
Miconazole nitrate (p.541·3); tinidazole (p.848·3).
Balanitis; vaginal infections.

Doxi-Hem *Hemofarm, Rus.*
Calcium dobesilate (p.2272·1).
Capillary fragility; microangiopathy; venous insufficiency.

Doxil
Note. This name is used for preparations of different composition.
JC Healthcare, Israel; Ortho Biotech, USA.
Liposomal doxorubicin hydrochloride (p.712·2) (p.712·2).
AIDS-related Kaposi's sarcoma; breast cancer; multiple myeloma; ovarian cancer.

Merck, Mex.
Dicloxacillin (p.265·2).
Bacterial infections.

Doxilek *Lek, Hung.*
Calcium dobesilate (p.2272·1).
Chronic venous insufficiency; diabetic retinopathy; haemorrhoids; thrombophlebitis.

Doxilin *Malayan, Singapore†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxilina *Vitapan, Braz.†.*
Doxycycline (p.267·1).
Bacterial infections.

Doximal *Cipla-Medpro, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doximax Neo *Ferrer, Spain.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doximed *Ratiopharm, Fin.*
Doxycycline (p.267·1).
Bacterial infections.

Doximucol *Winthrop, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Bacterial infections of the respiratory tract associated with increased or viscous mucus.

Doximycin *Orion, Fin.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxin *Medichem, Indon.; BioFemme, Philipp.; Asian Pharm, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxinate
Note. This name is used for preparations of different composition.
Sigma, India.
Doxylamine succinate (p.578·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting in pregnancy.

Torlan, Spain†.
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxine *Pacific, NZ; Pacific, Singapore.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxi-Om *OM, Port.*
Calcium dobesilate (p.2272·1).
Vascular disorders.

Doxiproct
Note. This name is used for preparations of different composition.
OM, Cz.; OM, Hung.; Grunenthal, Mex.†; OM, Port.; OM, Switz.
Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Abiogen, Ital.
⊗ Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3); dexamethasone acetate (p.1526·1).
Anorectal disorders.

Doxiproct Plus *OM, Cz.; OM, Hung.; Grunenthal, Mex.; OM, Port.; OM, Switz.*
⊗ Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3); dexamethasone acetate (p.1526·1).
Anorectal disorders.

Doxitab *APT, Hong Kong; Medpro, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxiten Bio *Teofarma, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxiten Enzimatico *Teofarma, Spain.*
Doxycycline hyclate (p.267·1); chymotrypsin (p.2281·3); trypsin (p.2405·3).
Bacterial infections.

Doxithal *Royal, Chile.*
Doxycycline (p.267·1).
Bacterial infections.

Doxitin *Vitabalans, Fin.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxium *Altana, Arg.; Ebewe, Austria; Labomed, Chile; OM, Cz.; Ebewe, Hong Kong; Biogal-Teva, Hung.; Abiogen, Ital.; OM, Malaysia; Grunenthal, Mex.; OM, Philipp.; Pharmalink, Philipp.; OM, Pol.; Johnson & Johnson, S.Afr.; Esteve, Spain; OM, Switz.; Abdi, Turk.; Leti, Venez.*
Calcium dobesilate (p.2272·1).
Capillary disorders; diabetic retinopathy; haemorrhoids; haemostasis during surgery; microangiopathy; microcirculatory disorders; thrombophlebitis; vascular disorders; venous insufficiency.

Doxivenil *OM, Cz.†; Biogal-Teva, Hung.; OM, Port.; OM, Switz.; Leti, Venez.*
Calcium dobesilate (p.2272·1); dextran sulfate potassium (p.2293·1).
Inflammation; venous insufficiency.

Doxmil *Biotenk, Arg.†.*
Docetaxel (p.710·3).
Breast cancer; non-small cell lung cancer.

DOXO-Cell *Stada, Austria; Cell Pharm, Ger.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

DOXO-cell *Cell Pharm, Port.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxocris *LKM, Arg.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Doxofil *Itaca, Braz.†.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Doxokebir *Aspen, Arg.*
Doxorubicin (p.712·2).

Doxolbran *Phoenix, Arg.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxolem *CSC, Austria; Zodiac, Braz.; Medicom, Cz.; Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxonex *Polpharma, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Doxonolver *Nolver, Venez.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Doxopeg *Raffo, Arg.*
Doxorubicin (liposomal) (p.712·2) (p.712·2).

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Doxorbin *BMS, Arg.†.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxorubin *Nycomed, Austria; Teva, Belg.; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Malaysia; Asta Medica, NZ; NZ Medical & Scientific, NZ; Pharmachemie, Neth.; Pharmachemie, Singapore†; Pharmachemie, Thai.; Teva, Thai.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxotec *Columbia, Mex.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxotil *Genepharm, Gr.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxsig *Sigma, Austral.*
Doxycycline hyclate (p.267·1).
Adjunct in amoebiasis; bacterial infections; malaria.

Doxsol *Cazi, Braz.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Doxsyn *MDI, S.Afr.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain with tension.

Doxtie *Bioprofarma, Arg.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Doxtran *Phoenix-Elea, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Formerly contained rofecoxib.
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Doxtran B12 *Phoenix, Arg.*
⊗ Diclofenac sodium (p.44·3); betamethasone (p.1518·2); vitamin B (p.1980·2).
Musculoskeletal, joint, and peri-articular disorders; neuritis; neuropathy.

Doxtran Flex *Phoenix-Elea, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Doxtran Gesic *Phoenix, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Dysmenorrhoea; peri-articular disorders.

Doxy
Douglas, Austral.; Elerte, Fr.; Douglas, Hong Kong†; Vitamed, Israel; Strand, Malaysia†; Douglas, NZ; Masa, Thai.
Doxycycline hyclate (p.267·1).
Adjunct in amoebiasis; bacterial infections; malaria.

1A, Ger.; ABZ, Ger.; CT, Ger.; Meda, Ger.; S & K, Ger.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

USV, India; Pharmachemie, Neth.
Doxycycline (p.267·1).
Bacterial infections.

Doxy Comp *CT, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Doxy Komb *Meda, Ger.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxy Lindoxyl *Lindopharm, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Bacterial infections of the respiratory-tract associated with increased or viscous mucus.

Doxy M *Ratiopharm, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxy Plus *Stada, Ger.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Doxy-basan *Schonenberger, Switz.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxybene *Ratiopharm, Austria; Ratiopharm, Cz.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxycap *Hovid, Singapore.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxycillin *CCM, Malaysia.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxycin *Riva, Canad.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyclin *Pharmacare, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxycline
Spirig, Switz.
Doxycycline hyclate (p.267·1).
Bacterial infections.

General Drugs, Thai.
Doxycycline (p.267·1).
Bacterial infections.

Doxycyclin Al Comp *Aliud, Cz.*
Ambroxol hydrochloride (p.1550·3); doxycycline hyclate (p.267·1).
Respiratory-tract infections.

Doxycyl *Pharmacare, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Doxy-Dagra *Viatris, Neth.†.*
Doxycycline fosfatex (p.267·1).
Bacterial infections.

Doxyderm *Fujisawa, Austria.*
Doxycycline hyclate (p.267·1).
Acne.

Doxyderma *Dermapharm, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxy-Diolan *Meda, Ger.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxydoc *Docpharm, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxydyn *Fujisawa, Austria.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyfene *Adcock Ingram, S.Afr.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Doxyferm *Nordic, Swed.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxygram *Pharma 2000, Fr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyhexal
Hexal, Austral.; Hexal, S.Afr.
Doxycycline (p.267·1).
Adjunct in amoebiasis; bacterial infections; malaria.

Hexal, Austria; Hexal, Cz.; Hexal, Ger.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Amoebiasis; bacterial infections.

Doxy-HP *Riemser, Ger.; Wernigerode, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxylag *Lagap, Switz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylan *Lannacher, Austria.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylar *Sandoz, UK.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylcap *Bangkok Lab & Cosmetic, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylets *SMB, Belg.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylin
Alphapharm, Austral.; Dexxon, Israel; TP, Thai.
Doxycycline hyclate (p.267·1).
Amoebiasis; bacterial infections; malaria.

Alpharma, Norw.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyline *Yung Shin, Singapore.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxylis *Expanscience, Fr.*
Doxycycline (p.267·1).
Bacterial infections.

Doxylyn *Lloyd, Philipp.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxymerck *Merck dura, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxymono *Betapharm, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxymycin
Yung Shin, Hong Kong; YSP, Malaysia; Lennon, S.Afr.; Beacons, Singapore.
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Teva, Neth.†.
Doxycycline (p.267·1).
Bacterial infections.

Doxy-N-Tablinen *Winthrop, Ger.*
Doxycycline (p.267·1).
Bacterial infections.

Doxy-P *PP Lab, Thai.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxypal-DR *Jagson, India.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxypalu *Biorga, Fr.*
Doxycycline (p.267·1).
Malaria.

Doxypharm *Praxipharm, Hung.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyprotect *PannonPharma, Hung.*
Doxycycline (p.267·1).
Bacterial infections.

Doxy-Puren *Alpharma-Isis, Ger.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxyratio M *Ratiopharm, Pol.*
Doxycycline (p.267·1).
Bacterial infections.

Doxysol *Ecosol, Norw.†; Ecosol, Switz.*
Doxycycline (p.267·1).
Bacterial infections; malaria.

Doxysolvat *Betapharm, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Doxystad *Stada, Austria.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxytab *Socobom, Belg.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxytec *Technilab, Canad.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxytrex
Note. This name is used for preparations of different composition.
Unipharma, Gr.
Calcium dobesilate (p.2272·1).
Capillary disorders.

Sanobia, Port.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Doxytrim *Trima, Israel.*
Doxycycline hyclate (p.267·1).
Amoebiasis; bacterial infections; malaria.

Doxy-Wolff *Wolff, Ger.*
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Doxy-Wolff Mucolyt *Wolff, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections associated with increased or viscous mucus.

Doycur *Biomep, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Doyle *Raffo, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Dozbe *Profarb, Braz.†.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Dozefol *ITF, Port.*
Folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Dietary supplement.

Dozeneurin *Sigma, Braz.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1).
Vitamin B and B deficiency.

Dozic
Note. This name is used for preparations of different composition.
Raffo, Arg.
Risperidone (p.1024·2).
Psychoses.

Rosemont, UK.
Haloperidol (p.1000·2).
Anxiety; intractable hiccup; motor tics; nausea and vomiting; psychoses.

Dozile *Sunspot, Austral.; Pfizer Consumer, NZ.*
Doxylamine succinate (p.578·2).
Insomnia.

Dozol *Rice Steele, Irl.; Typharm, UK.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms; fever; pain.

Dozone *Ozone, Cz.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Dozozin *Umeda, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

D-P
Note. A similar name is used for preparations of different composition (see below).
Klonal, Arg.†.
Dextropropoxyphene (p.40·1); dipyrone (p.49·2).
Pain.

DP
Note. A similar name is used for preparations of different composition (see above).
Douglas, NZ.
Liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry skin; pruritus.

DP Barrier Cream *Douglas, NZ.*
Dimeticone (p.2032·1).

DP Gesic *Cadila, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).

DP Hand Rub *Douglas, NZ.*
Chlorhexidine (p.1635·2).
Skin disinfection.

DP Hydrocortisone *Douglas, NZ.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

DP Lotion - HC *Douglas, NZ.*
⊗ Hydrocortisone (p.1535·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Skin disorders.

DP Lubricating Gel *Douglas, NZ.*
Lubricating gel.

D-Pam *Douglas, NZ.*
Diazepam (p.986·3).
Anxiety; sedative; skeletal muscle spasm.

DPCA *Fresenius Medical, Switz.*
A range of glucose and electrolyte solutions with or without potassium (p.1670·3).
Peritoneal dialysis.

DP-Cipro *Douglas, NZ.*
Ciprofloxacin (p.243·3).
Bacterial infections.

D-Penamine *Alphapharm, Austral.; Pacific, NZ.*
Penicillamine (p.1456·2).
Cystinuria; heavy metal poisoning; rheumatoid arthritis; Wilson's disease.

DPH *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

DPN *Alclin, S.Afr.*
Nadide (p.2350·1).
Alcoholism; drug addiction.

DPT, DT COQ *Aventis Pasteur, Philipp.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DQM *Pharmaniaga, Malaysia.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Dr Amin *Eurolab, Arg.*
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Dr Calm *Wunderpharm, Arg.†.*
Thiamine (p.1976·3); melissa (p.2339·3); tilia (p.2402·2).
Sedative.

Dr Dermi-Heal *Quality Formulations, USA.*
Allantoin (p.1588·1); zinc oxide (p.1621·2); peru balsam (p.2365·3); castor oil (p.2278·1).
Skin disorders.

Dr Edwards Olive *Oakhurst, USA.*
Sennosides (p.1769·3).
Constipation.

Dr Grandel Granobil *Grandel, Ger.†.*
Usnea barbata (p.2409·3).
Bacterial infections of the mouth and throat.

Dr Janssens Teebohnen *Dr Janssen, Ger.†.*
Aloes (p.1705·2).
Constipation.

Dr Johnsons Nit & Lice *MPM, UK.*
Melaleuca oil (p.2338·2); azadirachta (p.2262·2).
Pediculosis.

Dr Mackenzies Veinoids *SA Druggists Self Med, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Dr Niedermaier Herztonikum *Niedermaier, Ger.*
Crataegus (p.2289·1).
Cardiovascular disorders.

Dr Reckeweg *Reckeweg, Cz.*
A range of homoeopathic preparations.

Dr Rentschler Halstabletten *Rentschler, Cz.†.*
Tyrothricin (p.358·2); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Dr Rentschler Hustenloser *Rentschler, Cz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Dr Rentschler Hustenstiller *Rentschler, Cz.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dr Rentschler Rachenspray *Rentschler, Cz.†.*
Hexetidine (p.1647·1).
Oral hygiene; upper respiratory-tract infections.

Dr Rentschler Rachenspulung *Rentschler, Cz.†.*
Hexetidine (p.1647·1).
Oral hygiene; upper respiratory-tract infections.

Dr Rentschler Snupfenspray *Rentschler, Cz.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Upper respiratory-tract congestion.

Dr Rentschler Snupfentropfen *Rentschler, Cz.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Upper respiratory-tract congestion.

Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee *Scheffler, Ger.*
Birch leaf (p.2266·3); java tea (p.2328·2); solidaga virgaurea (p.2391·1).
Urinary-tract disorders.

Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee Scheffler, Ger.
Thyme (p.2401·1); primula root (p.2372·2).
Respiratory-tract congestion.

Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee Scheffler, Ger.
Melissa (p.2339·3); passion flower (p.2363·2); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Dr Scholl's Athlete's Foot Schering-Plough, USA.
Tolnaftate (p.548·3).
Tinea pedis.

Dr Scholl's Callus Removers Schering-Plough, USA.
Salicylic acid (p.1612·2).

Dr Scholl's Clear Away Schering-Plough, USA.
Salicylic acid (p.1612·2).
Hyperkeratosis.

Dr Scholl's Corn Removers Schering-Plough, USA.
Salicylic acid (p.1612·2).

Dr Scholl's Corn/Callus Remover Schering-Plough, USA.
Salicylic acid (p.1612·2).
Hyperkeratosis.

Dr Scholl's Cracked Heel Relief Schering-Plough, USA.
Lidocaine (p.1862·3).

Dr Scholl's Wart Remover Schering-Plough, USA.
Salicylic acid (p.1612·2).

Dr Selby Sidus, Arg.
Zinc oxide (p.1621·2); vitamin D (p.1986·1); wool fat (p.2033·2); talc (p.1615·2).
Skin disorders.

Dr Smiths Beta, USA.
Zinc oxide (p.1621·2).
Skin disorders.

Dr Theiss Beinwell Salbe Naturwaren, Cz.†.
Comfrey (p.2286·3); alpha tocoferil acetate (p.1992·3).
Musculoskeletal and joint pain; skin trauma.

Dr Theiss Eucalyptus Erkaltungs-Balsam Naturwaren, Cz.†.
Eucalyptus oil (p.2301·2); pine oil (p.2368·2); camphor (p.2273·2).
Cold and influenza symptoms.

Dr Theiss Rheuma Creme Naturwaren, Cz.†.
Capsaicin (p.32·3); camphor (p.2273·2); aloes (p.1705·2); rhubarb (p.1768·3); myrrh (p.2349·2); zedoary; angelica (p.2258·1); carlina; senna (p.1769·2); saffron (p.1472·3); manna (p.1744·2); cimicifuga (p.2282·1); valerian (p.2410·1); cinnamon (p.2283·1); cardamom (p.2277·1).
Joint and peri-articular disorders.

Dr Theiss Ringelblumen Salbe Naturwaren, Cz.
Calendula (p.2273·1).
Infected skin ulcers.

Dr Theiss Schweden Krauter Naturwaren, Cz.
Aloes (p.1705·2); gentian (p.2310·3); rhubarb (p.1768·3); myrrh (p.2349·2); senna (p.1769·2); angelica (p.2258·1); zedoary; manna (p.1744·2); carlinae; saffron (p.1472·3).
Constipation.

Dr Theiss Schwedenbitter Naturwaren, Cz.
Aloes (p.1705·2); rhubarb (p.1768·3); cimicifuga (p.2282·1); cinnamon (p.2283·1); cardamom (p.2277·1); angelica (p.2258·1); valerian (p.2410·1); myrrh (p.2349·2); zedoary; dictamini alba; gentian (p.2310·3); carlina; camphor (p.2273·2); tormentil (p.2403·2); castorei; polyporus officinalis; mace (p.2336·1); senna (p.1769·2); nutmeg (p.2355·2); saffron (p.1472·3); calamus (p.2271·3).
Constipation; rheumatism.

Dr Theiss Spitzwegerich Hustensaft Naturwaren, Cz.†.
Plantaginis (p.2379·1); peppermint oil (p.1761·2).
Cold symptoms; coughs.

Dr Wiemanns Rheumatonikum Beethoven, Ger.
Birch leaf (p.2266·3); salix (p.121·3); devil's claw root (p.39·1); heisteria.
Musculoskeletal and joint disorders.

Dr Williams Pink Pills Mentholatum, S.Afr.
Ferrous sulfate; manganese sulfate; copper sulfate (p.1922·1).
Tonic.

Dracanyl AstraZeneca, Gr.
⊗ Terbutaline sulfate (p.1138·3).
Asthma.

Drafen Continentales, Mex.
Diphenhydramine hydrochloride (p.577·2).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Drafilyn-Z Zafiro, Mex.
Aminophylline (p.1114·2).
Obstructive airways disease.

Draganon Roche, Ital.†.
⊗ Aniracetam (p.363·2).
Mental function disorders.

Dragees antirhumatismales Zeller, Switz.
Salix (p.121·3); passion flower (p.2363·2).
Musculoskeletal and joint disorders.

Dragees aux figues avec du sene Zeller, Switz.
Fig (p.1731·3); senna (p.1769·2); butterbur (p.2271·1).
Constipation.

Dragees Fuca Fuca, Fr.
Frangula bark (p.1732·2); cascara (p.1715·2); bladderwrack (p.2384·2).
Constipation.

Dragees Neunzehn Wyeth Lederle, Austria†.
Aloes (p.1705·2); frangula (p.1732·2); cascara (p.1715·2); fel suis (p.2266·3).
Constipation.

Dragees Neunzehn Senna Wyeth Lederle, Austria†.
Senna (p.1769·2).
Constipation.

Dragees pour le coeur et les nerfs Zeller, Switz.
Crataegus (p.2289·1); passion flower (p.2363·2); lupulus (p.2335·2); valerian (p.2410·1).
Nervous disorders.

Dragees pour la detente nerveuse Zeller, Switz.
Butterbur (p.2271·1); valerian (p.2410·1); passion flower (p.2363·2); melissa (p.2339·3).
Nervous disorders.

Dragees pour le sommeil Zeller, Switz.
Valerian (p.2410·1); lupulus (p.2335·2).
Sleep disorders.

Dragees S contre la toux Hanseler, Switz.†.
Codeine phosphate (p.37·2); belladonna (p.2263·3); drosera (p.2297·3); ivy (p.2328·1); hyoscyamus (p.2323·3).
Coughs.

Dragees S pour les reins et la vessie Hanseler, Switz.
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1); bearberry (p.2263·3).
Urinary-tract disorders.

Dragees sedatives Dr Welti Welti, Switz.
Valerian (p.2410·1); lupulus (p.2335·2); crataegus (p.2289·1).
Nervous disorders; sleep disorders.

Dragees Vegetales Rex Lehning, Fr.
Frangula bark (p.1732·2); cascara (p.1715·2).
Constipation.

Dragon Balm Peter Black, UK.
Camphor (p.2273·2); menthol (p.2340·1); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); eucalyptus oil (p.2301·2); cassia oil (p.2278·1); pine oil (p.2368·2); thymol (p.1664·3); guaiacol (p.1561·2); peru balsam (p.2365·3).
Muscular aches.

Dragon Plaster 3-OL, Israel.
Capsicum (p.2276·2).
Musculoskeletal and joint disorders.

Drainactil Aerocid, Fr.
Boldo (p.2267·2); birch leaf (p.2266·3); black currant leaf (p.2267·1).
Gastrointestinal disorders; kidney disorders.

Drainuryl Erjean, Fr.
Green tea (p.2416·1); taraxacum (p.2395·1); meadowsweet (p.2338·1); couch-grass (p.2288·2); cherry.
Water retention.

Dralen Specifar (Σπεσιφαρ), Gr.†.
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Dralitem Raffo, Arg.
Temozolomide (p.776·3).

Dramamine Pfizer, Arg.; Pfizer Consumer, Austral.; Pfizer, Braz.; Pfizer, Fr.; Pfizer, Indon.; Pfizer Consumer, Irl.†; Searle, Israel†; Pfizer, Malaysia; Pfizer Consumer, Mex.; Pharmacia, NZ; Pharmacia, Port.†; Pfizer Consumer, Singapore†; Pharmacia, Switz.†; Pfizer, Thai.; Ali, Turk.; Upjohn, USA; Pharmacia, Venez.†.
Dimenhydrinate (p.576·2).
Motion sickness; nausea; radiation sickness; vertigo; vestibular disorders; vomiting.

Dramamine II Upjohn, USA.
Meclozine hydrochloride (p.584·3).
Motion sickness.

Dramamine-compositum Pfizer, Switz.†.
Dimenhydrinate (p.576·2); caffeine (p.1116·3).
Motion sickness.

Dramanate Pasadena, USA.
Dimenhydrinate (p.576·2).
Motion sickness.

Dramasine Pfizer, Indon.
Dimenhydrinate (p.576·2); vitamin B (p.1979·1).
Motion sickness; nausea and vomiting; vestibular disorders.

Dramavit Luper, Braz.†.
Dimenhydrinate (p.576·2).
Nausea and vomiting.

Dramavit B6 Luper, Braz.†.
Vitamin B (p.1978·2); dimenhydrinate (p.576·2).
Nausea and vomiting.

Dramelin Wescrib, Philipp.
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Dramigel Drug Research, Ital.
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Dramin Nycomed, Braz.
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Dramin B-6 Nycomed, Braz.
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Dramin B-6 DL Nycomed, Braz.
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2); glucose (p.1945·3); fructose (p.1945·1).
Nausea and vomiting; vertigo.

Dramina Jadran, Rus.
Dimenhydrinate (p.576·2).
Motion sickness; vestibular disorders.

Draminal Cavalheiro, Port.
Dimenhydrinate (p.576·2).
Nausea and vomiting; vertigo.

Dramine Uriach, Spain.
Meclozine hydrochloride (p.584·3).
Motion sickness.

Dramion Stroder, Ital.
Gliclazide (p.440·3).
Diabetes mellitus.

Dramnate RPG, India.
Dimenhydrinate (p.576·2).
Ménière's syndrome; nausea and vomiting; vertigo.

Dranat Remedina, Gr.
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Drapix Doctum, Gr.
Povidone-iodine (p.1659·2).
Disinfection.

Drapolene
Note. This name is used for preparations of different composition.
Farmoquimica, Braz.
Benzalkonium chloride (p.1629·1); cetrimonium bromide (p.1635·1).
Barrier preparation; skin disorders.

GSK, Hong Kong†; Wellcome, Irl.; GSK, Malaysia; GSK, Philipp.; GSK, Rus.; GSK, Singapore; GSK, Thai.; GSK, Turk.; Chefaro, UK.
Benzalkonium chloride (p.1629·1); cetrimide (p.1634·1).
Burns; cradle cap; nappy rash; prickly heat; skin disorders; urinary rash.

Drastirel Doctum, Gr.
Ketoprofen (p.73·1).
Inflammatory disorders.

Draverex IMO, Ital.
Frangula (p.1732·2); cascara (p.1715·2).
Constipation.

Dravom Specifar (Σπεσιφαρ), Gr.†.
Dimenhydrinate (p.576·2).
Nausea; vertigo; vomiting.

Dravyr Drug Research, Ital.; Drug Research, Singapore.
Aciclovir (p.862·3).
Herpesvirus infections.

Draxil Kener, Mex.
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

DraxImage MAA Draximage, Neth.
⊗ Technetium-99m albumin macroaggregates (p.2055·3).
Radionuclide imaging of the lungs; venous scintigraphy.

DraxImage MDP Draximage, Neth.
Technetium-99m medronate (p.2055·3).
Bone scintigraphy.

Drayacol DX Parggon, Mex.
Guaifenesin (p.1561·3); dextromethorphan (p.1555·2).
Coughs.

Drazine Pharmasant, Thai.
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions; motion sickness.

Dreemon Peach, UK.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Dreierlei Hofmann & Sommer, Ger.
Valerian (p.2410·1); mint oil (p.2345·2).
Digestive disorders.

Dreisacarb Brady, Austria; Gry, Ger.
Calcium carbonate (p.1714·1).
Calcium supplement; hyperphosphataemia.

Dreisafer Gry, Ger.
Ferrous sulfate (p.1939·3).
Iron deficiency.

DreisaFol Gry, Ger.
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Dreisavit Brady, Austria.
Multivitamin preparation (p.1922·1).

Dreisavit N Gry, Ger.; Bichsel, Switz.
Vitamin B substances with ascorbic acid (p.1922·1).
Dietary supplement; vitamin deficiency.

Dremo-K Silva, Venez.†.
Methyl hesperidin; rutoside (p.2305·1); ascorbic acid (p.1983·3); carbazochrome (p.1058·2); vitamin K (p.1995·2).

Drenalin Ariston, Braz.
⊗ Adrenaline (p.1203·2).

Drenex Medichem, Philipp.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Drenidra Cazi, Braz.
⊗ Chlortalidone (p.1243·3).
Hypertension.

Dreniformio Biolab Sanus, Braz.
⊗ Fludroxycortide (p.1530·3); clioquinol (p.254·1).
Skin disorders.

Drenison Biolab Sanus, Braz.
⊗ Fludroxycortide (p.1530·3).
Skin disorders.

Drenison N Biolab Sanus, Braz.
⊗ Fludroxycortide (p.1530·3); neomycin sulfate (p.305·1).
Skin disorders.

Dren'it Marfarma, Ital.
Pineapple; urtica; java tea; ruscus (p.1922·1).
Nutritional supplement.

Drenocol Lafage, Arg.†.
Magnesium sulfate (p.1679·3); boldo (p.2267·2) peptone.
Biliary-tract disorders.

Drenoflux Zeller, Port.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1); sodium benzoate (p.1630·2).
Coughs; respiratory-tract congestion.

Drenol Pfizer, Braz.
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema; renal calculi.

Drenovac Nikkho, Braz.†.
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Drenoxol Vitoria, Port.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Drenural Grossman, Mex.
⊗ Bumetanide (p.1237·1).
Hypertension; oedema; premenstrual syndrome.

Drepatil Fada, Arg.†.
Diphenhydramine (p.577·1).
Hypersensitivity reactions.

Dresan Phoenix, Arg.†.
Dipyrone (p.49·2); benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Dresan Biotic Phoenix, Arg.†.
Dipyrone (p.49·2); benzydamine hydrochloride (p.27·3); tetracycline (p.347·1).
Bacterial infections.

Dresplan Smaller, Spain.
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder.

Drexabion Eadriex, Philipp.
Vitamin B (p.1976·1); vitamin B (p.1978·2); vitamin B (p.1980·2).
Alcoholism; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Drexabion OB Eadriex, Philipp.
Vitamin B substances (p.1922·1); ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron-deficiency anaemia.

Drexel Elmor, Venez.
Nimesulide (p.95·3).
Inflammation; pain.

Driclor Stiefel, Austral.; Stiefel, Fr.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia†; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, UK.
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Dridase Sanofi Synthelabo, Ger.; Altana, Neth.
Oxybutynin hydrochloride (p.2190·3).
Bladder hyperactivity; neurogenic bladder.

Dridol ProStrakan, Swed.
Droperidol (p.994·3).
Nausea and vomiting associated with anaesthesia; neuroleptanalgesia.

Dri/Ear Pfeiffer, USA.
Boric acid (p.2268·1); isopropyl alcohol (p.1650·3).
Ear disorders.

Drifen Richmond, Arg.
Paclitaxel (p.759·1).
Malignant neoplasms.

Driges Grisi, Mex.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; peptic ulcer; Zollinger-Ellison syndrome.

DriHist Prasco, USA.
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Driken Kendrick, Mex.
Iron dextran (p.1951·1).
Iron-deficiency anaemia.

Drilix Be-Tabs, S.Afr.
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Drill
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Arg.; Pierre Fabre, Cz.; Pierre Fabre Sante, Fr.; Pierre Fabre, Port.; Pierre Fabre, Rus.
Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Pierre Fabre, Spain.
Chlorhexidine gluconate (p.1635·3); benzocaine (p.1854·1).
Mouth and throat infections.

Pierre Fabre, Hung.
Pastilles: Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Pierre Fabre, Hung.
Syrup: Dextromethorphan hydrobromide (p.1555·2).
Cough.

Drill Expectorant Pierre Fabre Sante, Fr.; Pierre Fabre, Hung.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Drill Mucolitico *Pierre Fabre, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Drill Tosse Seca *Pierre Fabre, Port.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Drill toux seche *Pierre Fabre Sante, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Drilozole *Aldril, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Drilyna *Bago, Arg.*
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Drimen *Coup, Gr.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vertigo.

Driminate *YSP, Malaysia.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Drimnorth *Northia, Arg.*
Midazolam (p.1007·3).

Drimpam *Alliance, S.Afr.†.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic attacks.

Drimux A *Gador, Arg.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; hypertension; liver cirrhosis with ascites; nephrotic syndrome; oedema.

Drin *Wassermann, Ital.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Drina *Silesia, Chile.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Drinamil *Sanitas, Chile.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Heart failure; hypertension; oedema.

Drinasal S *Merck, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Drinax *Andromaco, Venez.†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

DrinkaLax *acaSan, Austria.*
Macrogol 4000 (p.2336·3).
Constipation.

Drinus
Note. This name is used for preparations of different composition.
Kramer, Philipp.
Syrup: Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Kramer, Philipp.
Tablets: Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; rhinitis; sinusitis.

Drioquilen *Columbia, Mex.†.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Dripanina *Ariston, Braz.*
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders.

Driptane *Fournier, Belg.†; Fournier, Cz.†; Fournier, Fr.; Fournier, Philipp.; Fournier, Pol.; Fournier, Rus.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; neurogenic bladder; nocturnal enuresis.

Drisdol *Sanofi Synthelabo, Canad.; Sanofi Winthrop, USA.*
Ergocalciferol (p.1987·1).
Familial hypophosphataemia; hypoparathyroidism; rickets.

Drisentin *Sanovel, Turk.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Drisi-Ven *Truw, Ger.†.*
Troxerutin (p.2305·1).
Vascular disorders.

Drisofal *Help, Gr.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Dristan
Note. This name is used for preparations of different composition.
Wyeth Consumer, Chile.
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Wyeth, Turk.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Wyeth Consumer, Canad.
Caplets; tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; upper respiratory-tract disorders.

Wyeth Consumer, Canad.
Long-acting nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Wyeth Consumer, Canad.
Nasal spray: Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3).
Nasal congestion.

Wyeth, Irl.†; Pharmacare, S.Afr.
Nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Pharmacare, S.Afr.
Tablets: Aspirin (p.20·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Dristan Allergy *Whitehall, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Hypersensitivity reactions.

Dristan Analgesico *Wyeth-Whitehall, Arg.†.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Aluminium hydroxide (p.1706·2) and magnesium carbonate (p.1743·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Dristan Cold
Note. This name is used for preparations of different composition.
Wyeth Consumer, Hong Kong; Whitehall, USA.
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms; upper respiratory-tract symptoms.

Wyeth, India.
Phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); paracetamol (p.108·1).
Cold symptoms.

Dristan Cold Caplets *Whitehall, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Dristan Cold & Flu *Whitehall, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Dristan Cold Maximum Strength *Wyeth Consumer, Hong Kong.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; upper respiratory-tract symptoms.

Dristan Cold Maximum Strength Multi-symptom Formula *Whitehall, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Cold symptoms; hypersensitivity reactions.

Dristan Cold Maximum Strength No Drowsiness Formula *Whitehall, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Dristan Cold Multi-Symptom Formula *Whitehall, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Dristan Cold ND *SA Druggists Self Med, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Dristan Compuesto *Wyeth-Whitehall, Arg.*
Aspirin (p.20·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Aluminium hydroxide (p.1706·2) and magnesium carbonate (p.1743·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Influenza symptoms.

Dristan Decongestant Cough Medicine *SA Druggists Self Med, S.Afr.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Dristan Decongestant Nasal Mist *SA Druggists Self Med, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3).
Cold symptoms; hayfever; sinusitis.

Dristan Descongestivo *Wyeth-Whitehall, Arg.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).

Dristan Expectorant
Note. This name is used for preparations of different composition.
Wyeth, India.
Oral liquid: Codeine phosphate (p.37·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3); citric acid (p.2284·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs.

Wyeth, India†.
Tablets: Phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); aspirin (p.20·3).
Coughs.

Dristan 12-hr Nasal Decongestant Spray *Whitehall, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Dristan Juice Mix-in *Whitehall, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Dristan Long Lasting *Whitehall, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Dristan N D *Wyeth Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms; fever; headache; pain; upper respiratory-tract disorders.

Dristan Nasal *Wyeth-Whitehall, Arg.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Dristan Nasal Drops *Wyeth, India.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); menthol (p.2340·1); cineole (p.2282·3).
Nasal congestion.

Dristan Nasal Spray *Whitehall, USA.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3).
Nasal congestion.

Dristan Saline Spray *Whitehall, USA.*
Sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Dristan Sinus *Whitehall-Robins, Canad.†; Whitehall, USA.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Cold and influenza symptoms; sinusitis.

Dristancito *Wyeth-Whitehall, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Drithocreme *Dermik, USA†.*
Dithranol (p.1595·2).
Psoriasis.

Dritho-Scalp *Dermik, USA.*
Dithranol (p.1595·2).
Psoriasis.

Drivermide *Nakornpatana, Thai.*
Mebendazole (p.148·3).
Worm infections.

Drix Bisacodyl *Hermes, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Drixin *Schering-Plough, Denm.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinitis; sinusitis.

Drixine *Schering-Plough, NZ†; Schering-Plough, Philipp.; Schering-Plough, S.Afr.; Schering-Plough, Venez.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis; nasal congestion.

Drixine Nasal *Schering-Plough, Austral.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Drixomed *Iopharm, USA.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract disorders.

Drixoral
Note. This name is used for preparations of different composition.
Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Singapore†.
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Schering-Plough, USA.
Pseudoephedrine sulfate (p.1571·2); brompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Schering-Plough, Canad.
Nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Upper respiratory-tract congestion.

Schering-Plough, Canad.
Sustained release tablets: Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Drixoral Cold & Allergy *Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Drixoral Cold & Flu *Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Drixoral Cough & Congestion *Schering-Plough, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Drixoral Cough & Sore Throat *Schering-Plough, USA.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Drixoral Day/Night *Schering-Plough, Canad.*
Yellow tablets, pseudoephedrine sulfate (p.1571·2); white tablets, dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate.
Ear disorders; upper respiratory-tract congestion.

Drixoral ND *Schering-Plough, Canad.*
Pseudoephedrine sulfate (p.1571·2).
Ear disorders; upper respiratory-tract congestion.

Drixoral Non-Drowsy Formula *Schering, USA.*
Pseudoephedrine sulfate (p.1571·2).
Nasal congestion.

Drixoral Plus *Schering-Plough, USA.*
Pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1); dexbrompheniramine maleate (p.569·2).
Formerly known as Drixoral Allergy Sinus.
Upper respiratory-tract symptoms.

DRN 8103 *BSM, Austria.*
Thallium-201 chloride (p.2056·3).
Radionuclide imaging.

Droal *Vita, Spain.*
Ketorolac trometamol (p.74·2).
Pain.

Drocef *Vivax, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Drocon-CS *Cypress, USA.*
Hydrocodone tartrate (p.63·1); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; upper respiratory-tract congestion.

Drofaron *Vifor, Switz.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis.

Drofaxil *Royton, Braz.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Drofen *Andromaco, Venez.†.*
Tiabendazole (p.156·2).
Worm infections.

Drogenil
Note. This name is used for preparations of different composition.
Essex, Chile; Schering-Plough, Irl.; Essex, Ital.†; Schering-Plough, Neth.; Plough, Port.; Schering-Plough, UK.
Flutamide (p.725·1).
Prostatic cancer.

Plus, Gr.
Terbinafine (p.546·3).
Fungal skin infections.

Drolasona *Alter, Spain†.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Droleptan
Pharmalab, Austral.; ProStrakan, Fr.; IFET (ΙΦΕΤ), Gr.
Droperidol (p.994·3).
Aggression; general anaesthesia; nausea and vomiting; neuroleptanalgesia; premedication; psychoses.

AFT, NZ.
Droperidol tartrate (p.995·1).
Adjunct to anaesthesia; premedication; psychoses.

Drolex *Biosis, Philipp.; Taiwan Biotech, Philipp.*
Cefadroxil (p.218·1).
Bacterial infections.

Droll *Galenica, Gr.*
Ciprofloxacin (p.243·3).
Bacterial ear infections.

Dromadol *Teva, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Drometak *Precimex, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Drometox *Drovepat, Venez.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Dromil Sauco *Vargas, Venez.*
Ammonium acetate (p.1551·2); sodium benzoate (p.1630·2); drosera (p.2297·3); sambucus (p.2383·1); Desessartz; senega (p.1572·3).
Respiratory-tract congestion.

Dromos *Sigma-Tau, Ital.*
Propionyl- -carnitine hydrochloride (p.1932·3).
Cardiac disorders.

Dronadil *Ares, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Dronal *Sigma-Tau, Ital.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Dronalden *Denver, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Dronalent *Chrispa (Χρισπα), Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Dronat *Fortbenton, Arg.*
Alendronate (p.1088·1).
Osteoporosis.

Dronate-OS *BDH, India.*
Etidronate disodium (p.1097·1).
Hypercalcaemia of malignancy; Paget's disease of bone.

2-Drop *Soll (Σολλ), Gr.*
Salicylic acid (p.1612·2); camphor.
Corns.

Dropavix *Pharmanel, Gr.*
Levodropropizine (p.1557·3).
Cough.

Dropaxin *Italfarmaco, Ital.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Dropcina *Plough, Port.*
Gramicidin (p.286·1); cetylpyridinium chloride (p.1635·1); dichlorobenzyl alcohol (p.1642·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Droperdal *Cristalia, Braz.*
Droperidol (p.994·3).
Psychoses.

Droperol *Troikaa, India.*
Droperidol (p.994·3).
Agitation; neuroleptanalgesia; premedication.

Dropflam *Eupharmed, Ital.*
Diclofenac sodium (p.44·3).
Anterior eye inflammation.

Dropgel *Eupharmed, Ital.*
Carbomer 980 (p.2141·3).
Dry eyes.

Dropicine *Beta, Arg.*
Risperidone (p.1024·2).
Psychoses.

Dropid *Medicine Products, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Dropiltim *Faran, Gr.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Dropilton *Bruschettini, Ital.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Dropovit *Wyeth, India.*
Multivitamin preparation (p.1922·1).

Dropstar *Poen, Arg.; Farmigea, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Droptimol *Farmigea, Ital.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Dropyal *Bruschettini, Ital.*
Sodium hyaluronate (p.2320·1); carbomer 941 (p.2141·3); glycerol (p.2314·2).
Dry eyes.

Drosana Resiston avec vitamine C *Vifor, Switz.*
Echinacea purpurea (p.2298·1); red cherry (p.1472·2).
Cold symptoms.

Drosemiel *Ximena Polanco, Chile.*
Homoeopathic preparation.

Drosera Complexe no 64 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 64.

Drosera Komplex *Richter, Austria.*
Homoeopathic preparation.

Droserapect *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Drosera-Weliplex *Weber & Weber, Ger.*
Homoeopathic preparation.

Drosetux *Dolisos, Canad.; Boiron, Cz.; Dolisos, Fr.*
Homoeopathic preparation.

Drosinula *Bioforce, Switz.†.*
Norway spruce buds; drosera (p.2297·3); ivy (p.2328·1); pear.
Respiratory-tract disorders.

Drosithym-N *Ysatfabrik, Ger.*
Cowslip rhizome (p.2372·2); thyme (p.2401·1); drosera (p.2297·3).
Catarrh; coughs.

Drossadin *Drossapharm, Switz.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Drossafol *Drossapharm, Switz.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Drossanose *Drossapharm, Israel.*
Sea salt (p.1686·1).
Nasal disorders.

Drossa-Nose *Drossapharm, Switz.*
Sea salt (p.1686·1).
Nasal dryness.

Drosten *Vocate, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Drosyn *FDC, India.*
Phenylephrine hydrochloride (p.1568·1).
Production of cycloplegia and mydriasis; synechiae.

Drotin *Bushnell, India.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Drovera *Svizera, India†.*
Drotaverine (p.2297·3).
Muscle spasm.

Drovid *Drogsan, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

Drovitan *Vitae, Mex.*
Alendronate (p.1088·1).
Osteoporosis.

Droxaine *Daudt, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastrointestinal hyperacidity.

Droxaryl
Note. This name is used for preparations of different composition.
Pfizer Consumer, Belg.†; Continental, Cz.†; Sanofi Synthelabo, Neth.
Bufexamac (p.28·3).
Atopic eczema; contact dermatitis; inflammation; skin disorders; soft-tissue disorders.

Sanova, Austria.
Cream: Bufexamac (p.28·3).
Skin disorders.

Sanova, Austria.
Ointment: Bufexamac (p.28·3); alfa tocoferil acetate (p.1992·3).
Skin disorders.

Droxel *Recalcine, Chile.*
Propyphenazone (p.119·3); calcium ascorbate (p.1984·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); vitamin A (p.1971·2).
Cold and influenza symptoms.

Droxia *BMS Oncology, USA.*
Hydroxycarbamide (p.729·1).
Sickle-cell anaemia.

Droxiderm *Yung Shin, Philipp.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Droxifan *Meyer, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Droxil *Klonal, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Droximag *PP Lab, Thai.†.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); kaolin (p.1738·1); atropine sulfate (p.1219·3).
Alkaloid poisoning; gastrointestinal infection; peptic ulcer.

Droxiurea *Pfizer, Arg.†.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Droxivit *Pizzard, Mex.†.*
Hydroxocobalamin (p.1980·3).

Droxofor *Aventis, Venez.†.*
Hydroxocobalamin acetate (p.1980·3).
Neuralgia; neuritis.

Droxol *Microsules Bernabo, Arg.†.*
Pirenzepine hydrochloride (p.1762·3).
Peptic ulcer.

Droxyl *Pharmaland, Thai.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; peptic ulcer.

Drozid *Dexa, Philipp.*
Cefadroxil (p.218·1).
Bacterial infections.

Drufusan N *Syxyl, Ger.*
Homoeopathic preparation.

Drug Screen *Omega, Irl.*
A range of tests for drugs of abuse.

Druide Insect Repellent *Druide, Canad.†.*
Citronella oil (p.2284·2).
Insect repellent.

Druisel *Northia, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Drum *Pharmatrix, Arg.*
Fusidic acid (p.279·3).
Bacterial skin infections.

Drum B *Pharmatrix, Arg.*
⊗ Fusidic acid (p.279·3); betamethasone (p.1518·2).
Infected skin disorders.

Drunen *Andromaco, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Dry & Clear *SA Druggists Self Med, S.Afr.*
Benzoyl peroxide (p.1590·2).
Acne; rosacea.

Dry & Clear Medicated Skin Cleanser *SA Druggists Self Med, S.Afr.*
⊗ Salicylic acid (p.1612·2); benzoic acid (p.1630·2); benzethonium chloride (p.1630·1); alcohol (p.1625·2).
Acne.

Dry Cough Syrup *AAH, UK.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Dry Eye Gel *Alcon, Neth.*
Carbomer 934P (p.2141·3).
Dry eyes.

Dry Eyes
Note. This name is used for preparations of different composition.
Bausch & Lomb, USA.
Eye drops: Polyvinyl alcohol (p.2145·3).
Dry eyes.

Bausch & Lomb, USA.
Eye ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Dryears *Naveh, Israel.*
Isopropyl alcohol (p.1650·3); glycerol (p.2314·2).
Removal of trapped ear water.

Drygel *Compu, S.Afr.*
Povidone-iodine (p.1659·2).
Aphthous ulcers; burns; skin infections; wounds.

Drylin *Merckle, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Drynalken *Kendrick, Mex.*
Dopamine hydrochloride (p.1273·2).
Extracorporeal circulation; hypotension; shock.

Drynisan *Fecofar, Arg.*
⊗ Naphazoline (p.1565·1); mepyramine (p.585·1).

Dryptal *Berk, Cz.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Drysol *Dispolab, Arg.; Dispolab, Chile; Darier, Mex.; Person & Covey, USA.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Drytec *GE Healthcare, Neth.; Amersham, Spain.*
Technetium-99m (p.2055·3).
Diagnostic agent; radionuclide imaging.

Drytergent *C & M, USA.*
Skin cleanser.

Drytex *C & M, USA.*
Salicylic acid (p.1612·2); methylbenzethonium chloride (p.1653·1).
Acne.

Dryvax *Wyeth-Ayerst, USA.*
A smallpox vaccine (p.2238·1).
Active immunisation.

DS-24 *Pharmafrica, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

DS500 *INQ, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

DS Emulsion
Note. This name is used for preparations of different composition.
Biorga, Fr.
Copper pidolate (p.1614·1); zinc pidolate (p.1614·1).
Skin irritation.

Biorga, Hong Kong.
Copper pidolate (p.1614·1); zinc pidolate (p.1614·1); dimeticone (p.2032·1); tocoferil acetate (p.1992·3).
Facial skin irritation.

D-S-S *Warner Chilcott, USA.*
Docusate sodium (p.1725·1).
Constipation.

D-Stress
Fontovit, Braz.†.
Ginseng; vitamin B substances; ascorbic acid; rutoside (p.1922·1).

Synergia, Fr.
Magnesium glycerophosphate; arginine; taurine; vitamin B substances (p.1922·1).
Nervous disorders.

DT *Biomed Krakow, Pol.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

DT Coq *Vianex (Βιανέξ), Gr.†; Aventis Pasteur, Pol.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DT Polio *Sanofi Pasteur, Fr.*
A diphtheria, tetanus, and poliomyelitis vaccine (p.2212·2).
Active immunisation.

DT Vax *Aventis Pasteur, Arg.†; Aventis Pasteur, Braz.†; Vianex (Βιανέξ), Gr.; Aventis, S.Afr.; Aventis Pasteur, Thai.†.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

D-Tann *Midlothian, USA.*
Phenylephrine tannate (p.1568·3); diphenhydramine tannate (p.577·3).
Upper respiratory-tract disorders.

DTaP *SSI, Pol.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DTaP-IPV *SSI, Pol.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

D-Tarine *Macrophar, Thai.†.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm and spasticity.

D-Tato *Apotex, Mex.*
Benzonatate (p.1552·1).
Cough.

DTCoq/DTP *Aventis Pasteur, Braz.†; Pasteur Merieux, Israel; Sanofi Pasteur, Thai.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DTI *Korean United, Malaysia†.*
Dacarbazine (p.706·3).
Malignant melanoma; sarcoma.

DTIC *Bayer, Austral.; Bayer, Canad.†; VHB, India†; Bayer, Swed.; Medinova, Switz.*
Dacarbazine (p.706·3).
Malignant neoplasms.

DTIC-Dome *Bayer, Austria; Bayer, NZ†; Bayer, S.Afr.; Bayer, UK†; Bayer, USA.*
Dacarbazine (p.706·3).
Malignant neoplasms.

DT-Impfstoff *Aventis Pasteur, Ger.†; Chiron Behring, Ger.†.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of infants and young children.

DTM *Biochem, India.*
Diltiazem (p.1267·1).
Angina pectoris.

DTP *Biomed Krakow, Pol.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DTP Vaccine *Bio Farma, Thai.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DTPA *Rez, Cz.*
Technetium-99m (p.2055·3) pentetate.
Radionuclide imaging of the urinary tract and CNS.

DTP-Merieux *Aventis, S.Afr.; Sanofi Pasteur, Spain†.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

DT-reduct *Aventis Pasteur, Austria.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

D-Triol *Faran, Gr.*
Calcitriol (p.1986·2).
Prophylaxis and therapy of vitamin D deficiency.

DT-Vac *Serum Institute, India.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Duac *Stiefel, Austral.; Stiefel, Cz.; Stiefel, Hong Kong; Stiefel, Irl.; Sparks, NZ; Stiefel, Neth.; Stiefel, Pol.; Stiefel, Port.; Stiefel, Spain; Leo, Swed.; Stiefel, USA.*
Benzoyl peroxide (p.1590·2); clindamycin phosphate (p.251·2).
Acne.

Duac Once Daily *Stiefel, UK.*
Benzoyl peroxide (p.1590·2); clindamycin phosphate (p.251·2).
Acne.

Duact *GSK, Austria; GSK, Denm.; GSK, Fin.; GSK, Turk.*
Acrivastine (p.566·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; respiratory-tract congestion.

Duadacin Extra Strength Cold & Flu *Bradley, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Duafen *Pharmed, Austria.*
Ibuprofen (p.64·2).
Fever; pain.

Duagen *GSK, Gr.; GSK, Neth.; Jaba, Port.; GSK, Spain.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

Dual Antigen *Serum Institute, India.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Dualgan *ITF, Port.*
Etodolac (p.52·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Dualgos *Liferpal, Mex.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; pain.

Dualid
Note. This name is used for preparations of different composition.
Duncan, Arg.
Ranitidine (p.1766·1).
Peptic ulcer.

Biotech, Venez.
Oxantel embonate (p.152·2); pyrantel embonate (p.155·1).
Worm infections.

Dualid S *Ache, Braz.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Dualizol *Degorts, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Dual-Lax Extra Strong *Lane, UK.*
Senna (p.1769·2); aloin (p.1705·3); cascara (p.1715·2).
Constipation.

Dual-Lax Normal Strength *Lane, UK.*
Senna (p.1769·2); cape aloes (p.1705·2); cascara (p.1715·2).
Constipation.

Duals Nordin Adulto *Nordin, Mex.*
Vitamins (p.1922·1); aspirin (p.20·3); caffeine (p.1116·3).
Influenza symptoms.

Duals Nordin Infantil *Nordin, Mex.*
Vitamins (p.1922·1); aspirin (p.20·3).
Influenza symptoms.

Dualten *Saval, Chile.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension; ischaemic heart disease.

Duan *Pharmed, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Duaneo *Pharmed, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Duaneo mit Codein *Pharmed, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); codeine hydrochloride (p.37·2).
Pain.

Duaspir *Montrose, Cz.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Duavent *United American, Philipp.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Dubagest *Glenmark, India.*
Progesterone (p.2125·1).
Female infertility; menopausal disorders; menstrual disorders; threatened miscarriage.

Dubam
Note. This name is used for preparations of different composition.
Norma, UK.
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3).
Musculoskeletal pain.

Norma, UK.
Topical spray: Methyl salicylate (p.85·3); ethyl salicylate (p.52·1); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal pain.

Dube *Korean Drug, Singapore†.*
Lidocaine (p.1862·3).
Local anaesthesia.

Dublon *Fada, Arg.*
⊗ Esmolol (p.1282·3).
Hypertension; tachycardia.

Duboisine *Novartis, Fr.†.*
Hyoscyamine sulfate (p.1736·1).
Eye examination; uveitis.

Dubova Kura *Megafyt-R, Cz.*
Oak bark (p.2355·3).
Haemorrhoids; inflammatory disorders of the skin and mucous membranes.

Ducene *Sauter, Austral.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm; spasticity.

Duciclon *Degorts, Mex.*
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy.

Ducilamina *Theraskin, Braz.*
Calamine (p.1591·2).
Skin irritation.

Ducray Antipelliculaire *Ducray, Fr.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Ductelmin *Ducto, Braz.*
Mebendazole (p.148·3).
Worm infections.

Ductocina *Ducto, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ductogel *Ducto, Braz.*
Aluminium hydroxide (p.1706·2).
Antacid.

Ductomet *Ducto, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Ductonar *Roux-Ocefa, Arg.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Ductopan *Neo Quimica, Braz.†.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Ductopril *Ducto, Braz.*
Captopril (p.1239·2).
Hypertension.

Ductoveran *Ducto, Braz.*
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3); hyoscyamus (p.2323·3); boldo (p.2267·2); star anise (p.2392·1).

Ductovirax *Ducto, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Dudencer *Tempo Scan Pacific, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duellin *EGIS, Hung.; Egis, Rus.*
Carbidopa (p.803·1); levodopa (p.804·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Duet *Integrity, USA; Xanodyne, USA.*
Multivitamin and mineral preparation (p.1922·1).

Duet DHA *Xanodyne, USA.*
Tablets, vitamins; minerals (p.1922·1); capsules, omega-3 fatty acids (p.1362·2).
Dietary supplement.

Duetact *Takeda, USA.*
Pioglitazone hydrochloride (p.456·1); glimepiride (p.441·1).
Diabetes mellitus.

Dueva *Menarini, Ital.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Dufaston *Solvay, Ital.*
Dydrogesterone (p.2096·2).
Endometriosis; female infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Dufine *Effik, Port.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Duflegrip *Fecofar, Arg.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); bromhexine hydrochloride (p.1552·2); pseudoephedrine sulfate (p.1571·2).

Duflemina *Janssen-Cilag, Arg.†.*
Calcium dobesilate (p.2272·1).
Haemorrhoids; venous insufficiency.

Duflomex *Actavis, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Duinum *Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
⊗ Clomifene citrate (p.2086·1).
Amenorrhoea; anovulatory infertility; oligospermia; polycystic ovary syndrome.

Duiwelsdrekdruppels *Lennon, S.Afr.*
Asafetida (p.2261·3).
Coughs; flatulence.

Dukoral *Sanofi Pasteur, Austral.; Sanofi Pasteur, Canad.; SBL, Cz.; SBL, Denm.; SBL, Fin.; Socopharm, Fr.; Chiron, Ital.; Sanofi Pasteur, Malaysia; Aventis, NZ; SBL, Neth.; SBL, Norw.; Aventis Pasteur, Philipp.; SBL, Port.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Esteve, Spain; SBL, Swed.; Sanofi Pasteur, Thai.; Chiron, Turk.; Masta, UK.*
An oral cholera vaccine (p.2208·1).
Active immunisation.

Dularell Classic *Sanorell, Ger.†.*
Homoeopathic preparation.

Dularell N *Sanorell, Ger.*
Homoeopathic preparation.

Dulax *Antigen, Irl.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Dulcamara-Homaccord *Peithner, Austria.*
Homoeopathic preparation.

Dulcarhus-Gastreu R11 *Reckeweg, Neth.*
Homoeopathic preparation.

Dulcaryl *Bilim, Turk.*
Sodium cyclamate (p.1936·3); saccharin sodium dihydrochloride.
Sugar substitute.

Dulceril *Codilab, Port.†.*
Sodium cyclamate (p.1936·3); saccharin (p.1960·2).
Sugar substitute.

Dulcilarmes *Allergan, Fr.*
Povidone (p.2146·1).
Dry eyes.

Dulciphak *Allergan, Fr.*
Sodium monomethyltrisilanol orthohydroxybenzoate; parahydroxycinnamic acid.
Lens opacities.

Dulcivit *Abigo, Swed.*
Multivitamin preparation (p.1922·1).

Dulco Laxo *Boehringer Ingelheim, Spain; Gervasi, Spain.*
Bisacodyl (p.1710·1).
Constipation.

Dulcodruppels *Boehringer Ingelheim, Neth.*
Sodium picosulfate (p.1771·1).
Constipation.

DulcoEase *Boehringer Ingelheim, UK.*
Docusate sodium (p.1725·1).
Stool softener.

Dulcolactol *Boehringer Ingelheim, Indon.*
Lactulose (p.1738·2).
Constipation.

Dulcolan *Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Dulcolax
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; German Remedies, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.
Bisacodyl (p.1710·1).
Formerly known as Durolax in *Austral*.
Bowel evacuation; constipation.

Boehringer Ingelheim, UK.
Capsules: Sodium picosulfate (p.1771·1).
Constipation.

Boehringer Ingelheim, Arg.
Capsules; oral drops: Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Boehringer Ingelheim, USA.
Oral liquid: Magnesium hydroxide (p.1743·2).
Antacid.

Boehringer Ingelheim, UK.
Suppositories; tablets: Bisacodyl (p.1710·1).
Constipation.

Boehringer Ingelheim, Arg.; Boehringer Ingelheim, USA.
Tablets: Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Dulcolax Bowel Prep Kit *Boehringer Ingelheim, USA.*
Combination pack: 4 Tablets, bisacodyl (p.1710·1); docusate sodium (p.1725·1); 1 suppository, bisacodyl.
Pre-operative bowel preparation.

Dulcolax NP *Boehringer Ingelheim, Ger.*
Sodium picosulfate (p.1771·1).
Constipation.

Dulcolax Perles *Boehringer Ingelheim, Irl.*
Sodium picosulfate (p.1771·1).
Constipation.

Dulcolax Picosulphate *Boehringer Ingelheim, Belg.*
Sodium picosulfate (p.1771·1).
Constipation.

Dulcolax Stool Softener *Boehringer Ingelheim Consumer, USA.*
Docusate sodium (p.1725·1).
Constipation.

Dulcolite *Naturissima, Venez.†.*
Aspartame (p.1930·1).
Sugar substitute.

Dulcopearls *Boehringer Ingelheim, Neth.*
Sodium picosulfate (p.1771·1).
Constipation.

Dulcosil *Biotech Naturis, Venez.*
Aspartame (p.1930·1).
Sugar substitute.

Dulcosol *Piam, Ital.*
A nutritional supplement for infants (p.1922·1).

Dulinas *Royal, Chile†.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin disorders.

Dull-C *Freeda, USA.*
Ascorbic acid (p.1983·3).
Scurvy; vitamin C deficiency.

Dul-Suc *Prater, Chile.*
Saccharin sodium (p.1960·3).
Sugar substitute.

Dultavax *Sanofi Pasteur, Hung.*
A diphtheria, tetanus, and poliomyelitis vaccine (p.2212·2).
Active immunisation.

Dumex Lactose-Free *Dumex, Malaysia†; Dumex, Singapore†.*
Infant feed (p.1922·1).
Diarrhoea; lactose intolerance.

Dumex LF *Dumex, Philipp.*
Lactose-free infant feed (p.1922·1).
Diarrhoea; lactose intolerance.

Dumex Mama Plus *Dumex, Malaysia; Dumex, Philipp.*
Nutritional supplement for pregnant and lactating women (p.1922·1).

Dumex Plus *Dumex, Singapore†.*
A range of nutritional supplements (p.1922·1).

Dumicoat *Alpharma, Switz.†.*
Miconazole (p.541·2).
Denture stomatitis.

Dumin *Actavis, Indon.; Alpharma, Malaysia†.*
Paracetamol (p.108·1).
Fever; pain.

Dumirox *Solvay, Belg.†; Solvay, Ital.; Solvay, Spain.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Dumocalcin
Note. This name is used for preparations of different composition.
Actavis, Indon.
Calcium hydrogen phosphate (p.1676·1).
Calcium supplement.

Alpharma, Malaysia†; Alpharma, Singapore.
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Dietary supplement.

Dumocalcin Plus *Actavis, Indon.*
Calcium hydrogen phosphate (p.1676·1); calcium citrate (p.1675·3); vitamin D (p.1986·2).
Calcium and vitamin D supplement.

Dumocycline *Actavis, Indon.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Dumolid *Actavis, Indon.*
Nitrazepam (p.1011·2).
Insomnia.

Dumotrim *Actavis, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Dumovit C *Alpharma, Malaysia†; Alpharma, Singapore†.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C supplement.

Dumovital *Alpharma, Port.†.*
Multivitamin and mineral preparation (p.1922·1).

Dumoxin
Actavis, Indon.; Pharmacare, S.Afr.
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Alpharma, Norw.; Dumex-Alpharma, Thai.†.
Doxycycline (p.267·1).
Bacterial infections.

Dumozol *Actavis, Indon.; Actavis, Port.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections; rosacea.

Dumyrox *Solvay, Gr.; Solvay, Port.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Duna *Tedec Meiji, Spain.*
Pinazepam (p.1019·1).
Anxiety.

Dunason *Alcon, Arg.; Alcon, Braz.; Alcon, Mex.*
Chondroitin sulfate (p.2280·3).
Dry eyes.

Duncan *Pharmaland, Thai.*
Chlorpromazine hydrochloride (p.969·2).
Mania; schizophrenia; sedative.

Duncankil *Duncan, Arg.†.*
Permethrin (p.2048·2).
Pediculosis.

Dunox *Duncan, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Duo Celloids CPIP *Blackmores, Austral.*
Calcium phosphate (p.1676·2); iron phosphate (p.1950·3).

Duo Celloids CPMP *Blackmores, Austral.*
Calcium phosphate (p.1676·2); magnesium phosphate (p.1679·2).

Duo Celloids PCCP *Blackmores, Austral.*
Potassium chloride (p.1684·3); calcium phosphate (p.1676·2).

Duo Celloids PCIP *Blackmores, Austral.*
Potassium chloride (p.1684·3); iron phosphate (p.1950·3).

Duo Celloids PCMP *Blackmores, Austral.*
Potassium chloride (p.1684·3); magnesium phosphate (p.1679·2).

Duo Celloids PPIP *Blackmores, Austral.*
Potassium phosphate (p.1682·2); iron phosphate (p.1950·3).

Duo Celloids PPMP *Blackmores, Austral.*
Potassium phosphate (p.1682·2); magnesium phosphate (p.1679·2).

Duo Celloids PSMP *Blackmores, Austral.*
Potassium sulfate (p.1684·3); magnesium phosphate (p.1679·2).

Duo Celloids PSPC *Blackmores, Austral.*
Potassium sulfate (p.1684·3); potassium chloride (p.1684·3).

Duo Celloids SCF *Blackmores, Austral.*
Silicon dioxide (p.2146·2); calcium fluoride.

Duo Celloids SPCF *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); calcium fluoride.

Duo Celloids SPCP *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); calcium phosphate (p.1676·2).

Duo Celloids SPIP *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); iron phosphate (p.1950·3).

Duo Celloids SPMP *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); magnesium phosphate (p.1679·2).

Duo Celloids SPPC *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); potassium chloride (p.1684·3).

Duo Celloids SPPP *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); potassium phosphate (p.1682·2).

Duo Celloids SPPS *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); potassium sulfate (p.1684·3).

Duo Celloids SPS *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); silicon dioxide (p.2146·2).

Duo Celloids SPSS *Blackmores, Austral.*
Dibasic sodium phosphate (p.1682·3); sodium sulfate (p.1771·3).

Duo Celloids SSMP *Blackmores, Austral.*
Sodium sulfate (p.1771·3); magnesium phosphate (p.1679·2).

Duo Celloids SSPC *Blackmores, Austral.*
Sodium sulfate (p.1771·3); potassium chloride (p.1684·3).

Duo Celloids SSS *Blackmores, Austral.*
Sodium sulfate (p.1771·3); silicon dioxide (p.2146·2).

Duo Clindacin *Panalab, Arg.*
Gel, benzoyl peroxide (p.1590·2); topical solution, clindamycin phosphate (p.251·2).
Acne.

Duo Decadron *Sidus, Arg.*
⊗ Dexamethasone acetate (p.1526·1); dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Duo Minoxi *Finadiet, Arg.†.*
Ketoconazole (p.539·1); trolamine salicylate (p.132·3).
Dandruff.

Duo Reparation *Texinfine, Fr.*
Bottle A: isononyl isonanoate; padina pavonica (p.2384·2); bottle B: isononyl isonanoate; opuntia ficus-indica.
Scars.

Duo Vizerul *Montpellier, Arg.†.*
Ranitidine hydrochloride (p.1766·1); pirenzepine hydrochloride (p.1762·3).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Duo-Anglucid *Collins, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Duobact *Orion, Irl.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Duobak *Kocak, Turk.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Duobaktam
Note. This name is used for preparations of different composition.
Eczacibasi, Turk.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1). Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Eczacibasi, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Duobar *Scientific Hospital Supplies, Austral.; SHS, Fr.†; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Disorders of amino acid metabolism; kidney disorders; protein restriction.

Duobetic *Help, Gr.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Duobloc *Sidus, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Duo-C *Geymonat, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Duocaine *Amphastar, USA.*
Lidocaine hydrochloride (p.1862·3); bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Duocal *Scientific Hospital Supplies, Austral.; Nutricia, Fin.; SHS, Fr.; Scientific Hospital Supplies, Irl.; Nutricia, NZ; SHS, Singapore†; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).

Duocef *Bergamo, Braz.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Duocet *Mason, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Duocid
Note. This name is used for preparations of different composition.
Pfizer, Turk.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Pfizer, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Duocort *Orion, Fin.*
⊗ Hydrocortisone butyrate (p.1535·3); chlorhexidine gluconate (p.1635·3).
Skin disorders.

Duo-Cotecxin *Holley-Cotec, China.*
Artenimol (p.598·3); piperaquine phosphate (p.608·1).
Malaria.

Duoctrin *Haller, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Duo-CVP *Sanofi-Aventis, Chile.*
Citrobioflavonoids (p.2304·1); ascorbic acid (p.1983·3).
Capillary fragility; haemorrhage.

Duo-Decadron *Ache, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); dexamethasone acetate (p.1526·1).
Parenteral corticosteroid.

Duoderm
Note. This name is used for preparations of different composition.
Convatec, Arg.; Convatec, Austral.; Convatec, Fr.; Convatec, UK.
A range of hydrocolloid dressings.
Burns; ulcers; wounds.

Schering-Plough, S.Afr.†.
Tolnaftate (p.548·3); nystatin (p.543·2).
Fungal skin infections.

Orva, Turk.
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Warts.

Duodexa N *Kade, Ger.†.*
⊗ Dexamethasone (p.1526·1); dexamethasone sodium metasulfobenzoate (p.1526·2).
Skin disorders.

Duodil *Solvay, India.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Painful skeletal muscle spasm.

Duodopa *Torrent, Braz.; Solvay, Cz.; Neopharma, Denm.; Solvay, Fr.; Solvay, Ital.; Solvay, Neth.; Solvay, Norw.; Solvay, Port.; Solvay, Spain; Solvay, Swed.; Solvay, UK.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

DuoDote *Meridian, USA.*
Atropine (p.1219·2); pralidoxime chloride (p.1460·2).
Organophosphorus poisoning.

Duo-Extolen *Specifar (Σπεσιφαρ), Gr.†.*
Zipeprol hydrochloride (p.1575·3).
Cough.

Duofem
Note. A similar name is used for preparations of different composition (see below).
Hexal, Ger.
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Duofemme
Note. A similar name is used for preparations of different composition (see above).
Isdin, Spain.
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Duofer *Andreabal, Switz.*
Ferrous fumarate (p.1938·3); ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Duofer Fol *Andreabal, Switz.*
Ferrous fumarate (p.1938·3); ferrous gluconate (p.1939·1); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and folic acid deficiency.

Duofilm
Note. This name is used for preparations of different composition.
Sanova, Austria; Stiefel, Braz.; Stiefel, Chile; Stiefel, Cz.; Stiefel, Fr.; Stiefel, Ger.; Gabriel, Gr.; Stiefel, Hung.; Stiefel, Irl.; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Neth.; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Port.†; Stiefel, S.Afr.; Qualicare, Switz.; Stiefel, Thai.; Stiefel, UK; Stiefel, Venez.†.
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; hyperkeratosis; warts.

Stiefel, Belg.; Schering-Plough, USA.
Salicylic acid (p.1612·2).
Hyperkeratosis; warts.

Stiefel, Canad.
Patch; topical gel: Salicylic acid (p.1612·2).
Warts.

Stiefel, Arg.; Stiefel, Austral.; Stiefel, Hong Kong; Stiefel, NZ; Stiefel, Singapore.
Topical gel: Salicylic acid (p.1612·2).
Calluses; corns; warts.

Stiefel, Hong Kong; Stiefel, Singapore.
Topical liquid: Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; warts.

Stiefel, NZ.
Topical paint: Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Corns; warts.

Stiefel, Arg.; Stiefel, Austral.; Stiefel, Canad.
Topical solution: Salicylic acid (p.1612·2); lactic acid (p.2329·3); flexible collodion.
Warts.

Duoflam
Note. This name is used for preparations of different composition.
Cristalia, Braz.
⊗ Betamethasone dipropionate (p.1518·3); betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Svizera, India.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Duoflam Gel *Svizera, India.*
Diclofenac diethylamine (p.44·3); linseed oil (p.2334·1); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and soft-tissue disorders.

Duoflam Plus *Svizera, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; inflammation; pain.

Duoflex *Rayere, Mex.*
Diclofenac sodium (p.44·3); carisoprodol (p.1894·1).
Inflammation; musculoskeletal pain with muscle spasm; pain.

Duoflu *Fortbenton, Arg.*
⊗ Fluocinolone acetonide (p.1531·3).
Seborrhoeic dermatitis.

Duoform Novo *Mauermann, Ger.†.*
Butcher's broom (p.2270·3).
Haemorrhoids.

Duoforte *Stiefel, Arg.; Stiefel, Braz.†; Stiefel, Canad.*
Salicylic acid (p.1612·2).
Warts.

Duogas
Note. This name is used for preparations of different composition.
Bracco, Ital.
Sodium bicarbonate (p.1673·2); anhydrous citric acid (p.2284·1); dimeticone (p.1770·2).
Double-contrast radiography of the oesophagus and stomach.

Macrophar, Thai.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duogastril *Biolab, Philipp.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duogink *Duopharm, Ger.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders.

Duogynon *Duopharma, Malaysia.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Amenorrhoea.

Duohist DH *Breckenridge, USA.*
Chlorphenamine maleate (p.571·3); dihydrocodeine tartrate (p.48·1); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Duokapton *Strallhofer, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Duokliman *Kwizda, Austria.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Oestrogen deficiency; osteoporosis.

Duolaxan *Carlo Erba OTC, Ital.†.*
Ispaghula (p.1737·1); liquid paraffin (p.2030·3).
Constipation.

Duolin
Cipla, India; Cipla-Medpro, S.Afr.
⊗ Ipratropium bromide (p.1124·1); salbutamol (p.1131·2).
Obstructive airways disease.

Rex, NZ; Cipla, Venez.
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Duolip *Ratiopharm, Austria; Ratiopharm, Cz.; Merckle, Ger.; Mepha, Hong Kong; Mepha, Malaysia†; Mepha, Switz.†.*
Etofylline clofibrate (p.1284·2).
Hyperlipidaemias.

Duolube *Bausch & Lomb, Canad.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Corneal dryness.

Duoluton-L *German Remedies, India.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Endometriosis; menstrual disorders.

Duomet *Uniao Quimica, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Duomox *Astellas, Cz.; Yamanouchi, Hung.; Astellas, Pol.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Duonalc *Valeant, Canad.*
Isopropyl alcohol (p.1650·3).
Skin cleanser.

Duonalc-E *Valeant, Canad.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin cleanser.

Duonalc-E Mild *Valeant, Canad.*
⊗ Alcohol (p.1625·2).
Skin cleanser.

Duonasa *Normon, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Duonase *Cipla, India.*
⊗ Azelastine hydrochloride (p.568·2); fluticasone propionate (p.1533·2).
Allergic rhinitis.

Duonate *URL, USA.*
Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2).
Upper respiratory-tract disorders.

DuoNeb *Dey, USA.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Duopack *Altana, Arg.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Duoplant
Note. This name is used for preparations of different composition.
Stiefel, Canad.
Salicylic acid (p.1612·2); lactic acid (p.2329·3); formaldehyde (p.1644·2).
Plantar warts.

Stiefel, Mex.; Schering-Plough, USA.
Salicylic acid (p.1612·2).
Molluscum contagiosum; warts.

Duoplant Gel *Stiefel, Chile.*
Salicylic acid (p.1612·2).
Warts.

Duopres *Farma, Venez.*
Amlodipine besilate (p.1214·1); enalapril maleate (p.1276·1).
Hypertension.

Duopril
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

BMS, Hung.
⊗ Fosinopril (p.1292·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Duoran *Lisapharma, Ital.†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Duorol *Chefaro, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Duo-Scabil *Agis, Israel.*
Crotamiton (p.1593·2); sulfur (p.1614·1).
Scabies.

Duosol *Braun, Cz.; Braun, Neth.*
Sodium chloride; calcium chloride; magnesium chloride; sodium bicarbonate; glucose; with or without potassium chloride (p.1670·3).
Haemofiltration.

Duotec *Boehringer Ingelheim, Arg.†; Boehringer Ingelheim, Hung.†.*
⊗ Fenoterol hydrobromide (p.1121·1) sodium cromoglicate (p.1136·3).
Obstructive airways disease.

Duoton *TP, Thai.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Duo-Trach Kit *Astra, USA.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

DuoTrav *Alcon, Cz.; Alcon, Gr.; Alcon, Hung.; Pacific, NZ; Alcon, Pol.; Alcon, Port.; Alcon, UK.*
⊗ Travoprost (p.1886·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Duotric *Asian Pharm, Thai.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer.

Duova
Note. This name is used for preparations of different composition.
HRA, Fr.
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Cipla, India.
⊗ Tiotropium bromide (p.1148·3); formoterol fumarate (p.1122·1).
Obstructive airways disease.

Duoval *Saval, Chile.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Duovel *Sanovel, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Duovent *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, UK; Oftalmi, Venez.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Duoventrin *Schworer, Ger.*
Bismuth subnitrate (p.1711·2); linseed (p.2333·3); lactose.
Gastrointestinal disorders.

Duoventrinetten N *Schworer, Ger.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium trisilicate (p.1744·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; heartburn.

Duovir *Cristalia, Braz.†; Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Duovir N *Cipla, India.*
Lamivudine (p.895·1); zidovudine (p.913·3); nevirapine (p.899·1).
HIV infection.

Duovisc *Alcon, Austral.; Alcon, Ger.; Alcon, Hong Kong†; Alcon, Malaysia; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.*
1 Syringe, sodium hyaluronate (p.2320·1); chondroitin sulfate sodium (p.2280·3) (Viscoat); 1 syringe, sodium hyaluronate (Provisc).
Adjunct in eye surgery.

Duovit *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
20 Tablets, vitamins; 20 tablets, minerals and trace elements (p.1922·1).
Nutritional supplement; tonic.

Duovitan *Viatris, Austria.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Duozol *Blausiegel, Braz.*
Tinidazole (p.848·3); tioconazole (p.548·2).
Vaginal infections.

Duphafibra *Solvay, Spain.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement.

Duphalac *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Grunenthal, Chile; Solvay, Cz.; Solvay, Fin.; Solvay, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, India; Solvay, Indon.; Solvay, Irl.; Solvay, Ital.; Solvay, Malaysia; Solvay, Neth.; Solvay, Norw.; Solvay, Philipp.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Schering, S.Afr.; Solvay, Singapore; Solvay, Spain; Solvay, Swed.; Solvay, Switz.; Solvay, Thai.; Eczacibasi, Turk.; Solvay, UK; Solvay, USA.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy; salmonella enteritis.

Dupharon *CNN, Philipp.*
Folic acid (p.1940·1); vitamin B substances (p.1922·1); ferrous sulfate (p.1939·3).
Iron-deficiency anaemia; vitamin B deficiency.

Duphaston *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Solvay, Braz.; Grunenthal, Chile; Solvay, Cz.; Solvay, Fr.; Solvay, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, India; Solvay, Indon.; Solvay, Irl.; Solvay, Israel; Solvay, Malaysia; Duphar, NZ; Solvay, Neth.; Solvay, Philipp.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Schering, S.Afr.; Solvay, Singapore; Solvay, Swed.; Solvay, Switz.; Solvay, Thai.; Eczacibasi, Turk.; Solvay, UK†; Zuoz, Venez.*
Dydrogesterone (p.2096·2).
Cancer of breast, uterus, and kidney; dysfunctional uterine bleeding; endometriosis; female infertility; functional uterine bleeding; hormone replacement therapy; mastopathies; menopausal disorders; menstrual disorders; progestogen deficiency; threatened or recurrent miscarriage.

Dupla *Leti, Venez.†.*
Policosanol (p.1373·3).
Hypercholesterolaemia.

Duplex *C & M, USA†.*
Skin cleanser.

Duplicalcio 150 *Medical, Spain†.*
Isoniazid (p.288·1); pyridoxine (p.1979·1); calcium gluconate (p.1675·3).
Tuberculosis.

Duplicalcio B12 *Medical, Spain.*
Calcium gluconate (p.1675·3); calcium levulinate (p.1676·2) cyanocobalamin (p.1980·2); isoniazid (p.288·1).
Anaemias; tonic; tuberculosis.

Duplicalcio Hidraz *Medical, Spain†.*
Calcium gluconate (p.1675·3); calcium levulinate (p.1676·2); isoniazid (p.288·1).
Tonic; tuberculosis.

Duplicam *Hexal, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Duplide *Ethypharm, Port.†.*
Diltiazem hydrochloride (p.1265·1).

Duplotrast Weinsaure *Gerot, Austria.*
Tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2); simeticone (p.1770·2).
Double contrast gastrointestinal radiography.

Duplotrast Z *Gerot, Austria.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); simeticone (p.1770·2).
Adjunct in double contrast radiography.

Dupofol *Dupomar, Arg.*
Folic acid (p.1940·1).

Duprost *Cipla, India.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

dura AL *Merck dura, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Durabac Forte *Proethic, USA.*
Paracetamol (p.108·1); magnesium salicylate (p.79·2); caffeine (p.1116·3); phenyltoloxamine citrate (p.588·1).

Durabeta *Littman, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Durabiotic *Sandoz, Israel.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Durabolin *Organon, India; Organon, Neth.; Organon, USA.*
⊗ Nandrolone phenylpropionate (p.2118·3).
Anabolic; breast cancer; osteoporosis.

Durabronchal *Merck dura, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Duracain *Sintetica, Switz.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Duracaina *Behrens, Venez.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Duracaine *AstraZeneca, Arg.; AstraZeneca, Chile†.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Duracard *Sun, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Duracare
Note. This name is used for preparations of different composition.
Allergan, Braz.†.
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Cleansing solution for contact lenses.

Blairex, USA.
Cleansing solution for soft contact lenses (p.1622·2).

Duracef *BMS, Austria; BMS, Belg.; BMS, Cz.; BMS, Fin.; BMS, Hong Kong; BMS, Hung.; BMS, Israel†; BMS, Mex.; BMS, Pol.; BMS, S.Afr.; Juste, Spain.*
Cefadroxil (p.218·1).
Bacterial infections.

Duracef Expec *BMS, Mex.*
Cefadroxil (p.218·1); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Duraclon *aai, USA.*
Clonidine hydrochloride (p.1247·1).
Pain.

Duracoll *Schering-Plough, Belg.*
Gentamicin sulfate (p.282·1); collagen (bovine) (p.2286·1).
Bone infections.

duracoron *Merck dura, Ger.†.*
Molsidomine (p.1343·3).
Angina pectoris.

duracroman *Merck dura, Ger.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

duradermal *Merck dura, Ger.*
Bufexamac (p.28·3).
Skin disorders.

duradiuret *Merck dura, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Duradoce *Atlantis, Mex.*
Hydroxocobalamin (p.1980·3).
Neuritis; pernicious anaemia.

DuraDox *Julphar, UAE.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Duradrin *Duramed, USA†.*
⊗ Isometheptene mucate (p.2327·2); dichloralphenazone (p.994·2); paracetamol (p.108·1).
Migraine; tension headache.

durafenat *Merck dura, Ger.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Duraflu *Proethic, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

durafungol *Merck dura, Ger.*
Clotrimazole (p.530·1).
Fungal skin infections.

durafurid *Merck dura, Ger.†.*
⊗ Furosemide (p.1292·1) (p.1294·1).
Hypertension; oedema.

Duragel *SSL, UK†.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Duragesic *Janssen-Ortho, Canad.; Janssen, USA.*
⊗ Fentanyl (p.55·3).
Pain.

duraglucon N *Merck dura, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

duraH2 *Merck dura, Ger.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Durahist *Proethic, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Durahist D *Proethic, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dexchlorpheniramine maleate (p.572·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Duralex *American Urologicals, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

duralipon *Merck dura, Ger.*
Thioctic acid (p.2400·2).
Diabetic polyneuropathy.

Duralith *Janssen-Ortho, Canad.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Duralmor *Sanfer, Mex.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

duralopid *Merck dura, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

duralozam *Merck dura, Ger.†.*
Lorazepam (p.1004·1).
Anxiety; sleep disorders.

duramipress *Merck dura, Ger.†.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Duramist Plus *Pfeiffer, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

duramonitat *Merck dura, Ger.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Duramorph *Gray, Arg.; Baxter, USA; Elkins-Sinn, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

duramucal *Merck dura, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Duramycin *Pyridam, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Duran *TNP, Thai.†.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Duranest *Astra, USA†.*
⊗ Etidocaine hydrochloride (p.1861·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

duranifin *Merck dura, Ger.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

duranifin Sali *Merck dura, Ger.†.*
⊗ Nifedipine (p.1350·1); mefruside (p.1332·1).
Hypertension.

Duranil *Interbelle, Arg.; Pfizer, Chile.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

duranitrat *Merck dura, Ger.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Duranol *OEP, Philipp.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Durapen *De Mayo, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

durapenicillin *Merck dura, Ger.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

durapental *Merck dura, Ger.†.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Duraphat *Colgate-Palmolive, Austria; Colgate-Palmolive, Denm.; Colgate-Palmolive, Fin.; Colgate-Palmolive, Ger.; Colgate, Gr.; Woelm, Israel; Colgate-Palmolive, Ital.; Colgate-Palmolive, Norw.; Colgate Palmolive, Port.; Colgate-Palmolive, Swed.†; Colgate-Palmolive, Switz.; Colgate-Palmolive, UK.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; sensitive teeth.

Duraphen II *Proethic, USA†.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).

duraphyllin *Merck dura, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

durapindol *Merck dura, Ger.†.*
⊗ Pindolol (p.1372·1).
Cardiac hyperkinesis; hypertension; ischaemic heart disease.

durapirox *Merck dura, Ger.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

duraprednisolon *Merck dura, Ger.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Duraprox *Tramedico, Belg.; Sanofi Pasteur, Chile; Gerolymatos, Gr.*
Oxaprozin (p.105·3).
Gout; inflammatory disorders; musculoskeletal, joint, and peri-articular disorders.

durarese *Merck dura, Ger.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Durasal *Prasco, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Durascreen
Note. This name is used for preparations of different composition.
Pharmascience, Canad.†.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Pierre Fabre, USA.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Pharmascience, Canad.†; Pierre Fabre, USA.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); ensulizole (p.1597·1).
Sunscreen.

durasilymarin *Merck dura, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Durasolets *SMB, Chile.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry eyes.

durasoptin *Merck dura, Ger.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

duraspiron *Merck dura, Ger.†.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; liver cirrhosis with ascites; oedema.

duraspiron-comp *Merck dura, Ger.†.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; heart failure; hyperaldosteronism; oedema.

DuraTan Forte *Proethic, USA.*
Dextromethorphan tannate (p.1556·1); dexchlorpheniramine tannate (p.572·2); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Dura-Tap/PD *Dura, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Duratears
Note. This name is used for preparations of different composition.
Alcon, Austral.
Liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Alcon, Belg.; Alcon, Canad.†; Alcon, Chile; Alcon, Gr.; Alcon, Hong Kong; Alcon, Israel; Alcon, Singapore; Alcon, Thai.; Liba, Turk.
Liquid paraffin (p.2030·3); anhydrous liquid lanolin (p.2033·2); white soft paraffin (p.2031·2).
Dry eyes.

Alcon, Neth.
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Alcon, S.Afr.
Anhydrous liquid lanolin (p.2033·2).
Dry eyes.

Duratears Free *Alcon, Neth.*
Povidone (p.2146·1).
Dry eyes.

Duratears Naturale *Alcon, Malaysia; Alcon, USA.*
Liquid paraffin (p.2030·3); wool fat (p.2033·2); white soft paraffin (p.2031·2).
Dry eyes.

Duratears Z *Alcon, Neth.*
Liquid paraffin (p.2030·3); hydrous wool fat (p.2033·3); white soft paraffin (p.2031·2).
Dry eyes.

duratenol *Merck dura, Ger.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

duratenol comp *Merck dura, Ger.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Durater *Senosiain, Mex.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Durateston *Organon, Braz.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Anaemia; androgenic; breast cancer; delayed puberty; male hypogonadism.

Duration *Schering-Plough, Hong Kong; Schering-Plough, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Duratirs *Alcon, Ital.†.*
Liquid paraffin (p.2030·3).
Dry eyes.

Duratocin *Ferring, Arg.; Ferring, Austral.; Ferring, Canad.; Ferring, Cz.; Ferring, Hong Kong; Ferring, Malaysia; Ferring, Singapore.*
Carbetocin (p.2005·3).
Postpartum haemorrhage; uterine atony.

Duratuss *Victory, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Nasal congestion.

Duratuss A *Victory, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Duratuss AC *Victory, USA.*
Phenylephrine hydrochloride (p.1568·1); diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Duratuss CS *Victory, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cough.

Duratuss DM *Victory, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Duratuss G *UCB, USA†.*
Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Duratuss GP *Victory, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Formerly contained guaifenesin and pseudoephedrine hydrochloride.
Coughs.

Duratuss HD *Victory, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Coughs; nasal congestion.

Duratuss PE *Victory, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

duraultra *OmniVision, Ger.*
⊗ Vitamin A (p.1971·2); actinoquinol sodium (p.2246·3); naphazoline nitrate (p.1565·2).
Eye disorders.

Dura-Vent/DA *Dura, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

duravolten *Merck dura, Ger.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Duraxin *Portal, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1); salicylamide (p.121·2).
Upper respiratory-tract disorders.

durazanil *Merck dura, Ger.*
Bromazepam (p.964·3).
Anxiety disorders; insomnia.

durazepam *Merck dura, Ger.*
Oxazepam (p.1014·2).
Anxiety disorders; sleep disorders.

durazidum *Merck dura, Ger.†.*
Magnesium hydroxide gel (p.1743·2); aluminium hydroxide gel (p.1706·2).
Gastrointestinal disorders.

Dura-Zok *Durascan, Denm.†.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Durbis
Aventis, Denm.†.
Disopyramide (p.1269·1).
Arrhythmias.
Aventis, Norw.
Disopyramide phosphate (p.1269·2).
Arrhythmias.
Aventis, Swed.
Disopyramide (p.1269·1) or disopyramide phosphate (p.1269·2).
Ventricular arrhythmias.

Durekal *Leo, Fin.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Dur-Elix *3M, Philipp.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Duremesan
Note. This name is used for preparations of different composition.
Streuli, Switz.
Suppositories: Meclozine hydrochloride (p.584·3).
Nausea and vomiting.
Streuli, Switz.
Tablets: Meclozine hydrochloride (p.584·3); caffeine (p.1116·3).
Nausea and vomiting.

Duremid *Chobet, Arg.*
⊗ Indapamide (p.1314·1).
Hypertension.

Durex Sensilube *SSL, UK.*
Vaginal lubricant.
Formerly known as Senselle.

Duricef *BMS, Canad.; BMS, Indon.; BMS, Singapore; BMS, Turk.; BMS, USA†.*
Cefadroxil (p.218·1).
Bacterial infections.

Duride *Alphapharm, Austral.; Alphapharm, Malaysia; Pacific, NZ.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Durisal *Yeni, Turk.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Durnit *Sanofi Synthelabo, Arg.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Durobac *Pharmaceutical Enterprises, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Durobion *Olvos, Gr.*
⊗ Diethylaminoethanol malate (p.2154·3).
Tonic.

Durocin *Antor, Gr.*
Amikacin (p.200·2).
Bacterial infections.

Durodor *Sandoz, Mex.*
Tramadol hydrochloride (p.130·3).
Pain.

Duroferon *AstraZeneca, Fin.; AstraZeneca, Norw.; AstraZeneca, Swed.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Duroferon Vitamin *Hassle, Swed.†.*
Multivitamin preparation with iron (p.1922·1).
Iron-deficiency anaemia in pregnancy.

Durofolin *Biotrends, Gr.*
Calcium folinate (p.1943·3).
Folic acid antidote; megaloblastic anaemia.

Durogesic *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗ Fentanyl (p.55·3).
Pain.

Duro-K *Novartis, Austral.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Durol *Actavis, Indon.*
Vitamin B substances; minerals (p.1922·1).
Tonic.

Durolane *Kalbe, Indon.; Pharma Italia, Ital.*
Hyaluronic acid (p.2320·1).
Osteoarthritis.

Durolax X-Pack *Boehringer Ingelheim, Austral.†.*
Combination pack: 3 Tablets, bisacodyl (p.1710·1); 1 suppository, bisacodyl; 1 sachet, citric acid (p.2284·1); heavy magnesium carbonate (p.1743·1).
Bowel evacuation.

Durolax SP *Boehringer Ingelheim, Austral.*
Sodium picosulfate (p.1771·1).
Constipation.

Duromeran *Genepharm, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Duromine *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Philipp.; 3M, S.Afr.; 3M, Singapore; 3M, Thai.†.*
⊗ Phentermine (as an ion-exchange resin complex) (p.2162·2).
Obesity.

Duronitrin *AstraZeneca, Ital.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Durotan *Lilly, Ger.†.*
⊗ Xipamide (p.1434·1); reserpine (p.1387·3).
Hypertension.

Durotep *Kyowa, Jpn.*
⊗ Fentanyl (p.55·3).
Pain.

Duro-Tuss *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Singapore.*
Pholcodine (p.1570·2).
Coughs.

Duro-Tuss Chesty *3M, Austral.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cough.

Duro-Tuss Chesty Cough Plus Nasal Decongestant *3M, Austral.*
Bromhexine hydrochloride (p.1552·2); pseudoephedrine hydrochloride (p.1571·2).
Sinus and nasal congestion.

Duro-Tuss Cold & Allergy *3M, Austral.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract congestion.

Duro-Tuss Cough *3M, NZ.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Duro-Tuss Cough Lozenges *3M, Austral.; 3M, Singapore.*
Pholcodine (p.1570·2); cetylpyridinium chloride (p.1635·1).
Cough; sore throat.

Duro-Tuss Decongestant *3M, Austral.; 3M, Hong Kong; 3M, Singapore.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Duro-Tuss Dry Cough Plus Nasal Decongestant *3M, Austral.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; respiratory-tract congestion.

Duro-Tuss Expectorant *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Singapore.*
Pholcodine (p.1570·2); bromhexine hydrochloride (p.1552·2).
Coughs; respiratory-tract congestion.

Duro-Tuss Lozenges *3M, NZ.*
Pholcodine (p.1570·2); cetylpyridinium chloride (p.1635·1).
Coughs; sore throat.

Duro-Tuss Mucolytic *3M, Hong Kong; 3M, NZ†; 3M, Singapore.*
Bromhexine hydrochloride (p.1552·2).
Formerly known as Dur-Elix in *NZ.*
Respiratory-tract congestion.

Duro-Tuss Mucolytic Cough Liquid *3M, Austral.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Duro-Tuss Sinus *3M, Austral.; 3M, Malaysia.*
Bromhexine hydrochloride (p.1552·2); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; sinus congestion; upper respiratory-tract congestion.

Duroval *Valmor, Venez.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Durvitan *Seid, Spain.*
Caffeine (p.1116·3).
Asthenia.

Dusil *Alpharma, Malaysia†; Alpharma, Singapore.*
Aspirin (p.20·3).
Fever; influenza symptoms; pain.

Dusodril *Merck, Austria; Merck, Ger.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral vascular disorders; vascular disorders of the brain, ears, and eyes.

Duspatal
Grunenthal, Chile; Solvay, Neth.
Mebeverine embonate (p.1744·3) or mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm; irritable bowel syndrome.
Solvay, Ger.; Solvay, Ital.; Solvay, Port.
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm; irritable bowel syndrome.

Duspatalin *Altana, Arg.; Solvay, Belg.; Solvay, Braz.; Solvay, Cz.; Solvay, Denm.; Solvay, Fr.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; Solvay, Malaysia; Solvay, Philipp.; Solvay, Pol.; Solvay, Rus.; Solvay, Singapore; Solvay, Spain; Solvay, Switz.; Eczacibasi, Turk.*
Mebeverine hydrochloride (p.1744·2).
Biliary dyskinesia; enteritis; gastrointestinal spasm; irritable bowel syndrome.

Duspatin *Berlin Pharm, Thai.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal pain and spasm; irritable bowel syndrome.

Duspaverin *Ilsan, Turk.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm.

Dussedrine *Pharmacos, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Dutacor *Durascan, Denm.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Duticin *Korea United, Philipp.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Dutross *TNP, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Dutross-P200 *TNP, Thai.†.*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Duvadilan
Altana, Arg.; Solvay, Gr.†; Solvay, India; Solvay, Indon.; Solvay, Philipp.; Zuoz, Venez.
Isoxsuprine hydrochloride (p.2327·3).
Cerebral and peripheral vascular disorders; premature labour.
Duphar-Interfran, Thai.†.
Isoxsuprine hydrochloride (p.2327·3) or isoxsuprine resinate (p.2327·3).
Cerebral and peripheral vascular disorders; premature labour.

Duvagin *Infinity, Venez.*
Acetic acid (p.2244·2).
Vaginal disorders.

Duvaxan *Sandoz, Arg.†.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Duvig *Fada, Arg.*
Dobutamine (p.1272·1).

Duvira *Leciva, Cz.†.*
Dihydroxypropyladenine.
Herpes simplex infections.

Duvium *Zambon, Belg.†; Inpharzam, Switz.†.*
Benorilate (p.27·2).
Fever; musculoskeletal and joint disorders; pain.

Duvodine *Actavis, Indon.*
Povidone-iodine (p.1659·2).
Burns; skin and mucous membrane disinfection; wounds.

Duvoid *Shire, Canad.*
Bethanechol chloride (p.2265·3).
Urinary retention.

Duxaril *Servier, Hong Kong; Servier, Philipp.; Servier, Singapore; Servier, Thai.*
Almitrine dimesilate (p.2149·3); raubasine (p.1386·3).
Cerebrovascular disorders; chorioretinal ischaemia; cochleovestibular ischaemia; mental function impairment; stroke.

Duxetin *Gador, Arg.*
Duloxetine hydrochloride (p.389·3).
Depression; diabetic neuropathy.

Duxil
Note. This name is used for preparations of different composition.
Ardix, Fr.†.
Almitrine (p.2149·3) or almitrine dimesilate (p.2149·3); raubasine (p.1386·3).
Eye and ear disorders of vascular origin; mental function impairment in the elderly.
Galenica, Gr.
Carbocisteine lysine (p.1553·3).
Respiratory-tract congestion.
Servier, Port.
Almitrine dimesilate (p.2149·3); raubasine (p.1386·3).
Cerebral ischaemia; mental function impairment; retinal ischaemia; vestibular ischaemia.

Duxima *Ecobi, Ital.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Duxocin *Biochem, India.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Duxor *Servier, Spain†.*
Raubasine (p.1386·3); almitrine (p.2149·3) or almitrine besilate.
Cerebrovascular disorders; vestibular disorders.

Duzen *Prime, Singapore.*
Fusidic acid (p.279·3).
Bacterial skin infections.

Duzimicin *Prati-Donaduzzi, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

D-Vi-Sol *Mead Johnson Nutritionals, Canad.*
Colecalciferol (p.1986·2).
Formerly known as Enfalac D-Vi-Sol.
Vitamin D supplement for breast-fed infants.

D-Vital *Will-Pharma, Belg.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

DVN *Overseas, India.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

D-Void *Sun, India.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturia; nocturnal enuresis; test of renal concentrating capacity.

D-Worm *Triomed, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Dyalac *Towa, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Dyazide
Goldshield, Hong Kong; Goldshield, Irl.; GSK, Mex.; Decomed, Port.; Pharmafrica, S.Afr.; Doetsch, Grether, Switz.; Goldshield, Thai.; Goldshield, UK; SmithKline Beecham, USA.
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
These ingredients can be described by the British Approved Name Co-triamterzide.
Hypertension; oedema.

Dyclone *Astra, USA†.*
Dyclonine hydrochloride (p.1861·1).
Local anaesthesia.

Dycon *Hovid, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dyctiol *Texinfine, Fr.†.*
Padina pavonica (p.2384·2).
Dietary supplement.

Dyflex-G *Econo Med, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Bronchospasm.

Dyfrin *Oftalmi, Venez.†.*
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of cycloplegia and mydriasis.

Dy-G *Cypress, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Asthma.

Dygase *Cypress, USA.*
Pancreatin (p.2360·1).
Digestive enzyme deficiency.

Dygratyl *Solvay, Denm.; Solvay, Fin.; Solvay, Swed.*
Dihydrotachysterol (p.1986·3).
Hypocalcaemia; hypoparathyroidism; osteomalacia; pseudohypoparathyroidism; renal osteodystrophy; rickets; secondary hyperparathyroidism; vitamin D deficiency.

Dyline GG *Seatrace, USA†.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Bronchospasm.

Dylix *Lunsco, USA.*
Diprophylline (p.1120·2).

Dyloject *Javelin, UK.*
Diclofenac sodium (p.44·3).
Pain.

Dymadon *Pfizer Consumer, Austral.*
Paracetamol (p.108·1).
Fever; pain.

Dymadon Co *Pfizer Consumer, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dymadon Forte *GSK, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Dymaten *Continentales, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Dymelor *Lilly, USA†.*
Acetohexamide (p.437·1).
Diabetes mellitus.

Dymenate *Keene, USA.*
Dimenhydrinate (p.576·2).
Motion sickness.

Dymotil *Goldshield, UK.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
These ingredients can be described by the British Approved Name Co-phenotrope.
Diarrhoea.

Dyna Jets *Roche, S.Afr.†.*
Multivitamin preparation (p.1922·1).

Dynabac *Lilly, Chile†; Almirall, Fr.; Lilly, Gr.†; Lilly, Malaysia†; Abdi, Turk.; Muro, USA†.*
Dirithromycin (p.266·2).
Bacterial infections.

Dynabolon *Fournier, Ital.†.*
⊗ Nandrolone undecylate (p.2118·3).
Osteoporosis.

Dynacef *Dexa, Indon.*
Cefradine (p.233·1).
Bacterial infections.

Dynacide *Rivadis, Fr.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Dynacil *Sanol, Ger.; Schwarz, Ger.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Dynacil comp *Sanol, Ger.; Schwarz, Ger.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Dynacin *Medicis, USA.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Dynacirc *Novartis, Arg.†; Novartis, Chile†; Novartis, Hong Kong; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, S.Afr.; Novartis, Singapore; Novartis, Thai.; Novartis, Turk.; Novartis, USA; Novartis, Venez.†.*
Isradipine (p.1319·2).
Hypertension.

Dynafed Asthma Relief *BDI, USA†.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

Dynafed EX *BDI, USA†.*
Paracetamol (p.108·1).
Fever; pain.

Dynafed Plus *BDI, USA†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Dynafemme *Diepharmex, Fr.†.*
Vitamin, mineral, bladderwrack, and evening primrose oil preparation (p.1922·1).
Nutritional supplement.

Dynafloc *Pharma Dynamics, S.Afr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Dyna-Hex *Western Medical, USA.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Dynak *Pharma Dynamics, S.Afr.*
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Dynalgic *Bride, Cz.†; Bride, Hung.†.*
Aspirin (p.20·3); codeine phosphate (p.37·2); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Dynamin
Note. This name is used for preparations of different composition.
Ern, Spain.
Vitamin B substances; caffeine; glutamine (p.1922·1).
Tonic.
Berk, UK.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Dynamisan
Note. This name is used for preparations of different composition.
Novartis, Arg.
Vitamins; minerals; amino acids (p.1922·1); ginseng (p.2312·1).
Nutritional supplement.
Novartis, Chile; Novartis, Mex.
Vitamins; minerals; amino acids; ginseng (p.1922·1).
Tonic.
Novartis Sante, Fr.; Mipharm, Ital.
Arginine glutamate (p.1928·2).
Asthenia; tonic.
Novartis Consumer, Switz.
Arginine aspartate (p.1928·2).
Tonic.

Dynamo *Key, Austral.*
Caffeine (p.1116·3); glucose; thiamine hydrochloride; nicotinic acid (p.1922·1).
Drowsiness; mental fatigue.

Dynamogen *Faes, Spain.*
Arginine aspartate (p.1928·2); glutodina.
Anorexia; tonic; weight loss.

Dynamucil *Siphar, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucus.

Dynapen-3 *Zwitter, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Dynaphos-C *Sofar, Ital.*
Ascorbic acid (p.1983·3).
Gingivitis; stomatitis; vitamin C deficiency.

Dynasprin *USV, India.*
Aspirin (p.20·3); dipyridamole (p.1268·1).
Thromboembolic disorders.

Dynastat *Pfizer, Austral.; Pharmacia, Austria; Pfizer, Belg.; Pfizer, Cz.; Pharmacia, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pharmacia, Norw.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, Spain; Pfizer, Swed.; Pfizer, Thai.; Pharmacia, UK; Pharmacia, Venez.†.*
Parecoxib sodium (p.111·3).
Postoperative pain.

Dynatra *Almirall, Belg.; Zambon, Neth.*
Dopamine hydrochloride (p.1273·2).
Hypotension; shock.

Dynatussin
Note. This name is used for preparations of different composition.
Crisdy-Na, Philipp.
Capsules: Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.
Crisdy-Na, Philipp.
Syrup: Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); sodium citrate (p.1673·3).
Cold and influenza symptoms; cough.

Dynavit *Danlex, Philipp.*
Multivitamins (p.1922·1) with Chlorella growth factor.
Nutritional supplement.

Dynef *Sigma-Tau, Ger.†.*
Anthocyanins from myrtillus; alpha tocoferil acetate (p.1992·3).
Eye disorders.

Dynepo *Shire, Cz.; Shire, Neth.; Shire, Port.; Shire, UK.*
⊗ Epoetin delta (p.1061·1).
Anaemia in renal failure.

Dynergum *Biocodex, Port.*
Citrulline malate (p.1935·1).
Tonic.

Dynex VR *Athlon, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cough.

Dynexan
Note. This name is used for preparations of different composition.
Nycomed, Austria.
Tetracaine hydrochloride (p.1871·3); chamomile (p.2279·3); sage (p.2382·3); arnica (p.2260·2); aluminium formate (p.1706·2).
Mouth and throat disorders.
Kreussler, Fr.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia; painful mouth lesions.
Adcock Ingram, S.Afr.
Tetracaine hydrochloride (p.1871·3); chamomile (p.2279·3); arnica (p.2260·2); sage (p.2382·3); aluminium formate (p.1706·2).
Local anaesthesia.

Dynexan Herpescreme *Kreussler, Ger.*
Aciclovir (p.862·3).
Herpes labialis.

Dynexan Mundgel *Kreussler, Ger.*
Lidocaine hydrochloride (p.1862·3); benzalkonium chloride (p.1629·1).
Painful inflammatory disorders of the mouth.

Dynexan nouvelle formule *Kreussler, Switz.*
Lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Dynexan Zahnfleischtropfen *Kreussler, Ger.*
Aluminium formate (p.1706·2).
Formerly known as Cional S.
Mouth and throat inflammation.

Dynorm *Roche, Ger.*
Cilazapril (p.1244·3).
Hypertension.

Dynorm Plus *Roche, Ger.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Dynos *Intramed, S.Afr.*
Dopamine hydrochloride (p.1273·2).
Heart failure; shock.

Dyphylline-GG *Cypress, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Asthma; bronchospasm.

Dyprotex
Note. This name is used for preparations of different composition.
Blistex, Hong Kong†.
Dimethicone (p.2032·1); zinc oxide (p.1621·2); soft paraffin (p.2031·2).
Nappy rash.
Blistex, Israel.
Zinc oxide (p.1621·2).
Nappy rash.
Blistex, USA.
Dimethicone (p.2032·1); zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Nappy rash.

Dyrade-M *Cipla, India.*
Diloxanide furoate (p.832·2); metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis.

Dyrenium *GSK, Canad.†; SmithKline Beecham, USA.*
⊗ Triamterene (p.1417·2).
Oedema.

Dyrenium compositum *Doetsch, Grether, Switz.*
⊗ Triamterene (p.1417·2); benzthiazide (p.1225·1).
Hypertension; oedema.

Dysalfa *Fournier, Fr.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Dyscornut *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Dysfungal *Roi Surya, Indon.*
Ketoconazole (p.539·1).
Fungal skin infections.

Dysfur-M *Biological E, India†.*
Furazolidone (p.834·3); metronidazole (p.837·1); homatropine methylbromide (p.1881·3).
Intestinal infections.

Dyskinon *Nicholas Piramal, India†.*
Biperiden hydrochloride (p.797·2).
Cranial trauma; drug-induced extrapyramidal disorders; nicotine poisoning; parkinsonism; trigeminal neuralgia.

Dyslor *Biolatina, Chile.*
Botulinum A toxin (p.1890·1).
Blepharospasm; facial lines; foot spasticity in cerebral palsy; hemifacial spasm; spasmodic torticollis; spasticity.

Dysman *Ashbourne, UK†.*
Mefenamic acid (p.80·1).
Dysfunctional menorrhagia; fever; pain.

Dysmen
Note. This name is used for preparations of different composition.
Svizera, India.
Injection: Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.
Svizera, India.
Tablets: Mefenamic acid (p.80·1); dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Dysmen-500 *Sigma, India†.*
Mefenamic acid (p.80·1).
Dysmenorrhoea; pain.

Dysmen Forte *Sigma, India.*
Mefenamic acid (p.80·1); paracetamol (p.108·1).
Pain.

Dysmenalgit *Krewel, Ger.*
Naproxen (p.92·3).
Dysmenorrhoea.

Dysmenorm *DHU, Rus.*
Homoeopathic preparation.

Dysmenorrhoe-Gastreu S R75 *Reckeweg, Ger.*
Homoeopathic preparation.

Dyspagon *Pierre Fabre Sante, Fr.; Pierre Fabre, Port.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Dyspamet *Goldshield, Irl.; Goldshield, UK.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Dyspen *Biolab, Hong Kong†; Biolab, Thai.†.*
Mefenamic acid (p.80·1).
Fever; inflammation; pain.

Dyspepsin *Herbapol Krakow, Pol.*
Achillea (p.2245·2); calendula (p.2273·1); gentian (p.2310·3); peppermint leaf (p.1761·2); phaseolus; taraxacum (p.2395·1).
Dyspepsia.

Dysport *Sidus, Arg.; Ipsen, Austral.; Richter, Austria; Ipsen, Belg.; Biosintetica, Braz.; Beaufour-Ipsen, Cz.; Ipsen, Denm.; Ipsen, Fin.; Beaufour, Fr.; Ipsen, Ger.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Ipsen, Irl.; Ipsen, Israel; Ipsen, Ital.; Beaufour-Ipsen, Malaysia; Ipsen, NZ; NZ Medical & Scientific, NZ; Ipsen, Neth.; Ipsen, Norw.; Ipsen, Philipp.; Ipsen, Pol.; Ipsen, Port.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Spain; Ipsen, Swed.; Ipsen, Switz.; Ipsen, Thai.; Gen, Turk.; Ipsen, UK; Nolver, Venez.*
Botulinum A toxin (p.1890·1).
Blepharospasm; dystonia; foot spasticity associated with paediatric cerebral palsy; glabellar lines; hemifacial spasm; hyperhidrosis; spasmodic torticollis; upper limb spasticity following stroke.

Dystan *Medikon, Indon.*
Mefenamic acid (p.80·1).
Fever; menorrhagia; pain.

Dystolise *Motima, Fr.*
Melissa (p.2339·3); angelica (p.2258·1); sweet marjoram (p.2337·3).
Tonic.

dysto-loges *Loges, Ger.*
Homoeopathic preparation.
Formerly known as dysto-L 90 N.

dysto-loges N *Loges, Ger.*
Homoeopathic preparation.

dysto-lux *Loges, Ger.*
St John's wort (p.422·3).
Anxiety; depression.

Dystonal *Pharmacobel, Belg.*
Dihydroergotamine mesilate (p.618·2).
Migraine and other vascular headaches.

Dystophan *Kattwiga, Ger.*
Homoeopathic preparation.

Dysurgal *Maxmedic, Ger.*
Atropine sulfate (p.1219·3).
Reduction of gastrointestinal secretions; smooth muscle spasm.

Dytac *SMB, Belg.; GSK, Neth.†; Goldshield, UK.*
⊗ Triamterene (p.1417·2).
Ascites; heart failure; hypertension; oedema.

Dytan *Hawthorn, USA.*
Diphenhydramine tannate (p.577·3).
Hypersensitivity reactions.

Dytan-AT *Cypress, USA.*
Pentoxyverine tannate (p.1567·3); diphenhydramine tannate (p.577·3).
Cough.

Dytan-CD *Hawthorn, USA.*
Pentoxyverine tannate (p.1567·3); diphenhydramine tannate (p.577·3); phenylephrine tannate (p.1568·3).
Coryza; cough; nasal congestion.

Dytan-CS *Hawthorn, USA.*
Pentoxyverine tannate (p.1567·3); diphenhydramine tannate (p.577·3); phenylephrine tannate (p.1568·3).
Coughs.

Dytan-D *Hawthorn, USA.*
Diphenhydramine tannate (p.577·3); phenylephrine tannate (p.1568·3).
Cold symptoms; nasal congestion.

Dytan-DM *Cypress, USA.*
Phenylephrine tannate (p.1568·3); dextromethorphan tannate (p.1556·1); diphenhydramine tannate (p.577·3).
Cough; nasal congestion.

Dytan-HC *Hawthorn, USA.*
Hydrocodone tannate (p.63·2); phenylephrine tannate (p.1568·3); diphenhydramine tannate (p.577·3).
Cough; upper respiratory-tract congestion.

Dyta-Urese *SMB, Belg.; Goldshield, Neth.*
⊗ Triamterene (p.1417·2); epitizide (p.1279·1).
Hypertension; oedema.

Dytenzide *Astellas, Belg.; Goldshield, Neth.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Dyterene *Pharmasant, Thai.†.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Hypertension; oedema.

Dytide *Goldshield, UK.*
⊗ Triamterene (p.1417·2); benzthiazide (p.1225·1).
Oedema.

Dytide H *Procter & Gamble, Austria; Mibe, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Dytor *Cipla, India.*
⊗ Torasemide (p.1415·3).
Heart failure; hypertension; oedema.

Dytuss *Lunsco, USA.*
Diphenhydramine hydrochloride (p.577·2).

Dyzco *Mediherb, Austral.*
Blue cohosh (p.2267·2); cimicifuga (p.2282·1); dioscorea villosa; viburnum opulus; ginger (p.1732·3).
Dysmenorrhoea.

Dyzole *Douglas, NZ.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

D-Zol *Pacific, NZ.*
⊗ Danazol (p.2090·2).
Benign breast disease; endometriosis; hereditary angioedema; menorrhagia.

E45
Note. This name is used for preparations of different composition.
Boots Healthcare, Austral.
White soft paraffin (p.2031·2); light liquid paraffin (p.2031·1); wool fat (p.2033·2).
Dry skin.
Boots Healthcare, Irl.; Boots Healthcare, S.Afr.; Crookes Healthcare, UK.
Emollient.
Dry skin disorders.
Reckitt Benckiser, Pol.
Wool fat (p.2033·2); liquid paraffin (p.2030·3); soft paraffin (p.2031·2).
Skin disorders.

E45 Itch Relief *Crookes Healthcare, UK.*
⊗ Macrogol lauril ethers (p.1916·1); urea (p.1620·2).
Pruritus; scaling skin conditions.

E Mal *Themis Chemicals, India.*
Artemotil (p.598·1).
Malaria.

E Plus *Delta, Braz.*
dl-Alpha tocoferil acetate (p.1992·3).

E 200 Plus C *Bio-Sante, Canad.*
Vitamins C and E (p.1922·1).

E Radicaps *Legrand, Braz.*
Vitamin E (p.1992·2).
Vitamin E supplement.

E45 Sun
Note. This name is used for preparations of different composition.
Crookes Healthcare, UK.
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Formerly contained titanium dioxide and zinc oxide.
Sunscreen.
Crookes Healthcare, UK.
SPF 30: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

E45 Sun Reflective Sunscreen *Crookes Healthcare, UK.*
SPF 25; SPF 50: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

E Vita *Scherer, Malaysia†; Swiss Bio, Malaysia†.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Eaca Balsamico *Nikkho, Braz.*
Aminocaproic acid (p.1053·2); sodium benzoate (p.1630·2); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Respiratory-tract congestion.

Ealk *Medimar, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Eanox *Desitin, Cz.; Desitin, Denm.†.*
Zolpidem tartrate (p.1037·3).
Insomnia.

EAP-61 *Hanosan, Ger.†.*
Homoeopathic preparation.

Ear Clear *Key, Austral.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Ear Clear for Swimmer's Ear *Key, Austral.*
Acetic acid (p.2244·2); isopropyl alcohol (p.1650·3).
Otitis externa.

Earache *Hylands, Canad.*
Homoeopathic preparation.

Earache Relief *Brauer, Austral.; Homeocan, Canad.*
Homoeopathic preparation.

EarCalm *GSK Consumer, UK.*
Glacial acetic acid (p.2244·2).
Superficial ear infections.

Earclear *Wilson, NZ.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Ear-Dry *Scherer, USA.*
Boric acid (p.2268·1); isopropyl alcohol (p.1650·3).
Ear disorders.

Earex *SSL, UK.*
Arachis oil (p.2259·1); almond oil (p.2252·2); rectified camphor oil (p.2273·3).
Ear wax removal.

Earex Plus *SSL, UK.*
Choline salicylate (p.36·3); glycerol (p.2314·2).
Ear wax removal; earache.

Ear-Eze *Hyrex, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Early Bird
Note. This name is used for preparations of different composition.
Mentholatum, Austral.
Pyrantel embonate (p.155·1).
Enterobiasis.

Kent, UK.
Pregnancy test (p.2372·1).

EarSol-HC *Parnell, USA.*
⊗ Hydrocortisone (p.1535·2).
Ear inflammation.

EAS Pfrimmer *Kalbe, Indon.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Eascold *Quality, Hong Kong.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Allergic rhinitis; cold and influenza symptoms; nasal congestion.

Easepex *MedGen, Philipp.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Easi Breathe *Cipla, India.*
Camphor (p.2273·2); chlorothymol (p.1640·1); eucalyptus oil (p.2301·2); menthol (p.2340·1); terpineol (p.2396·1).
Respiratory-tract disorders.

Easi-Cort *Ivax, Cz.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Easiko *Medipharma, Hong Kong†.*
Mepyramine maleate (p.585·2); menthol (p.2340·1); camphor (p.2273·2).

Easiphen *SHS, Fr.; Scientific Hospital Supplies, Irl.*
Food for special diets (p.1922·1).
Phenylketonuria.

EAS-Oral *Fresenius Kabi, Turk.*
Amino-acid preparation (p.1922·1).
Nutritional supplement.

Easprin *Lotus, USA.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Easy Dayz *Cipla, India.*
Naproxen sodium (p.92·3).

Easy gel *Teva, Israel.*
Benzydamine hydrochloride (p.27·3).
Musculoskeletal and joint disorders.

Easylax
Note. This name is used for preparations of different composition.
Cipla, India.
Liquid paraffin (p.2030·3); magnesium hydroxide (p.1743·2).
Constipation.

Sam-On, Israel.
Phenolphthalein (p.1762·1).
Constipation.

Eatan N *Desitin, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Eau Des Carmes *Medgenix, Belg.*
Lemon peel; angelica; cinnamon; coriander; clove; melissa; nutmeg; watercress.
Tonic.

Eau pour les yeux *Zeller, Switz.*
Zinc sulfate (p.1999·2); fennel oil; saffron.
Eye irritation.

Eau Precieuse *Omega, Fr.*
Boric acid (p.2268·1); salicylic acid (p.1612·2); tannic acid (p.2394·3); glycerol; xylelol; sodium oleate; eucalyptus globulus; alcohol; menthol; cineole.
Seborrhoea.

Eau-de-vie de France avec huile de pin nain du Tirol *Doetsch, Grether, Switz.†.*
Menthol (p.2340·1); pumilio pine oil (p.2376·3).
Muscular pain and fatigue.

Eavit *Terapeutico, Ital.*
Gelatin; wheat-germ oil; carrot oil; soya lecithin; royal jelly; beeswax (p.1922·1).
Nutritional supplement.

Eavit Plus *Terapeutico, Ital.*
Gelatin; wheat-germ oil; carrot oil; lecithin; royal jelly; soya oil (p.1922·1).
Nutritional supplement.

Ebamin *Jin Yang, Hong Kong.*
Ginkgo biloba (p.2311·1).
Cerebral disorders; peripheral vascular disorders.

E-Base *Barr, USA.*
Erythromycin (p.269·2).
Bacterial infections.

Ebastel *Byk, Arg.†; Eurofarma, Braz.; Almirall, Chile†; Almirall, Ger.; Dainippon, Jpn; Almirall, Spain; Elmor, Venez.*
Ebastine (p.579·1).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; pruritus; urticaria.

Ebastel D *Byk, Arg.†; Eurofarma, Braz.*
Ebastine (p.579·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Ebefen *Ebewe, Austria.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Ebenol *Strathmann, Ger.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Ebeoxal *Ebewe, Cz.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Eberbiovac HB *Zuoz, Venez.†.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Ebernet *Salvat, Spain.*
Eberconazole nitrate (p.530·3).
Fungal skin infections.

Ebersedin *Bros, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Ebersept *Bros, Gr.*
Ketoconazole (p.539·1).
Fungal infections.

Ebertop *Salvat, Spain.*
Eberconazole nitrate (p.530·3).
Fungal skin infections.

Ebertuss *Bros, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Ebesupol *Chiesi, Spain.*
Eberconazole nitrate (p.530·3).
Fungal skin infections.

Ebetaxel *Ebewe, Austria; Ebewe, Israel.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Ebetrexat *Ebewe, Austria.*
Methotrexate (p.745·2) or methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Ebexid *Sigma, India.*
Thyroid (p.2177·1); vitamin B substances; vitamin E (p.1922·1).
Hypothyroidism.

Ebix *Lundbeck, Braz.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease; cerebral spasticity; parkinsonism.

Ebixa *Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Canad.; Lundbeck, Chile; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Fr.; Lundbeck, Ger.; Lundbeck, Gr.; Lundbeck, Hong Kong; Lundbeck, Hung.; Lundbeck, Irl.; Lundbeck, Israel; Lundbeck, Ital.; Lundbeck, Mex.; Healthcare Logistics, NZ; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Pol.; Lundbeck, Port.; Lundbeck, S.Afr.; Lundbeck, Singapore; Lundbeck, Spain; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.; Lundbeck, UK.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease; spasticity.

Ebov *Glenmark, India.*
Etoricoxib (p.53·1).
Ankylosing spondylitis; gout; osteoarthritis; pain; rheumatoid arthritis.

Ebrantil
Altana, Austria; Nycomed, Cz.; Altana, Ger.; Altana, Hung.
Urapidil (p.1419·3) or urapidil hydrochloride (p.1419·3).
Hypertension; production of controlled hypotension.

Altana, Belg.; Altana, Ital.; Bykomed, Port.; Altana, Switz.
Urapidil hydrochloride (p.1419·3).
Hypertension; production of controlled hypotension.

Altana, Neth.; Altana, Pol.
Urapidil (p.1419·3).
Hypertension.

Ebrimycin *PannonPharma, Hung.*
Primycin sulfate; lidocaine (p.1862·3).
Bacterial skin infections.

Ebromin *Degorts, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Ebromin P *Degorts, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion.

Ebufac *DDSA Pharmaceuticals, UK.*
Ibuprofen (p.64·2).

Eburdent *Dentsply, Ital.*
Sodium fluoride (p.1962·2).
Gum disorders.

Eburdent F *Dentsply, Ital.*
Miristalkonium saccharinate (p.1653·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; oral hygiene.

Eburnal *Chiesi, Ital.†.*
Vinburnine (p.2414·1).
Cerebrovascular disorders.

Eburnate *Vannier, Arg.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Eburos *Dentsply, Ital.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Ebutol *Novartis, Rus.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

E-Butol *Beacons, Singapore.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

EC *Cadila, India.*
Vitamin C; vitamin E (p.1922·1).
Antoxidant.

Eca Presan *BMS, Mex.*
Captopril (p.1239·2).
Hypertension.

Ecabil *Mayne, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Ecadiu *Sandoz, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); captopril (p.1239·2).
Hypertension.

Ecafast *Crinos, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Ecalin *Jaka-80, Rus.*
Econazole nitrate (p.531·1).
Fungal infections.

Ecalta *Pfizer, Cz.; Pfizer, Port.; Pfizer, UK.*
Anidulafungin (p.527·2).
Candidiasis.

Ecamais *Atral, Port.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Ecamannan *CaDiGroup, Ital.*
Glucomannan (p.2312·3); vitamin E (p.1992·2); vitamin C (p.1983·3); betacarotene (p.1930·3).
Gastrointestinal disorders; hypercholesterolaemia; obesity.

Ecanol *Sarabhai Piramal, India.*
Econazole nitrate (p.531·1).
Fungal and Gram-positive bacterial skin infections; vulvovaginal candidiasis.

Ecap *Glenmark, India.*
Vitamin E acetate (p.1992·3).
Vitamin E supplement.

Ecapril
Note. This name is used for preparations of different composition.
Hexal, Mex.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Atral, Port.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Ecaprilat *Lazar, Arg.*
Enalapril (p.1276·1).
Heart failure; hypertension.

Ecasil *Biolab Sanus, Braz.†.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Ecasolv *Benedetti, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Ecaten *Ivax, Mex.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Ecator *Torrent, Braz.*
Ramipril (p.1385·3).
Hypertension.

Ecator H *Torrent, Braz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ecatrol *Ethica, Indon.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Ecax *Bago, Chile.*
Meloxicam (p.80·3).
Inflammation; pain.

Ecazide *BMS, Fr.; BMS, Spain.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Eccarvit Plus *CaDiGroup, Ital.*
Vitamin C; vitamin E; betacarotene; ginkgo biloba; chromium tripicolinate (p.1922·1).
Nutritional supplement.

Eccelium *Manetti Roberts, Ital.†.*
Econazole sulfosalicylate (p.531·2).
Fungal infections; Gram-positive bacterial superinfections.

Eccoxolac *Viatris, UK.*
Etodolac (p.52·2).
Osteoarthritis; rheumatoid arthritis.

Ecee2 *German Remedies, India.*
Levonorgestrel (p.2121·2).
Postcoital contraceptive.

Ecee Plus *Edwards, USA.*
Vitamins C and E with minerals (p.1922·1).

Ecelecort *Iator, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Echan *Hexal, Ger.*
Echinacea purpura (p.2298·1).
Respiratory- and urinary-tract infections.

Echi-bosan *Bock, Ger.†.*
Homoeopathic preparation.

Echifit *Krewel, Ger.†.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Echiherb *Duopharm, Ger.†.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary- tract infections.

Echilite *Eulite, Neth.*
Homoeopathic preparation.

Echinacea
Note. This name is used for preparations of different composition.
Potter's, UK.
Elixir: Echinacea (p.2298·1); baptisia tinctoria; fumitory (p.2307·2).
Catarrh; immunostimulant; minor skin disorders.

Potter's, UK.
Tablets: Echinacea (p.2298·1).
Immunostimulant; skin disorders.

Echinacea 4000 *Procare, Austral.*
Echinacea (p.2298·1); calcium ascorbate (p.1984·1); zinc amino acid chelate (p.2000·1).
Upper respiratory-tract symptoms.

Echinacea ACE + Zinc *Blackmores, Austral.*
Echinacea pupurea (p.2298·1); vitamins (p.1922·1); zinc amino-acid chelate (p.2000·1).
Cold and influenza symptoms.

Echinacea comp *Hevert, Ger.†; Steigerwald, Ger.*
Homoeopathic preparation.

Echinacea Complex *Cenovis, Austral.*
Echinacea (p.2298·1); vitamins (p.1922·1); zinc amino acid chelate (p.2000·1).
Skin disorders; upper respiratory-tract infections; wounds.

Echinacea Complexe no 40 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 40.

Echinacea Goldenseal Formula *Quest, Canad.†.*
Astragalus; echinacea (p.2298·1); hydrastis (p.2321·3).

Echinacea L40 *Homeocan, Canad.*
Homoeopathic preparation.

Echinacea Lozenge *Blackmores, Austral.*
Echinacea purpurea (p.2298·1); sodium ascorbate (p.1984·1); eucalyptus oil (p.2301·2).
Cold and influenza symptoms.

Echinacea Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Echinacea Oligoplex *Madaus, Ger.†.*
Homoeopathic preparation.

Echinacea Plus *Herbal Science, Malaysia†; Swiss Bio, Malaysia†.*
Echinacea (p.2298·1); garlic (p.2309·2).
Tonic.

Echinacea Ro-Plex (Rowo-415) *Pharmakon, Ger.†.*
Homoeopathic preparation.

Echinacea Urtinktur *Hevert, Ger.*
Homoeopathic preparation.

Echinacea-Complex *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Echinacea-Cosmoplex *Peithner, Austria.*
Homoeopathic preparation.

Echinacea/Quarz comp *Wala, Ger.*
Homoeopathic preparation.

Echinacin *Thursday, Austral.; Madaus, Austria; Madaus, Belg.; Madaus, Cz.; Madaus, Ger.; Remek, Gr.; Madaus, Hung.; Madaus, Spain; Madaus, Switz.*
Echinacea purpurea (p.2298·1).
Cold symptoms; immunostimulant; respiratory- and urinary-tract infections; skin disorders; wounds.

Echinacin akut *Madaus, Ger.*
Homoeopathic preparation.

Echinaforce *Aponova, Austria; Bioforce, Ger.; Bioforce, Switz.; Bioforce, UK.*
Echinacea (p.2298·1).
Cold symptoms; fever; respiratory- and urinary-tract infections.

Echinaject *Syxyl, Ger.*
Homoeopathic preparation.

EchinaMed *Bioforce, Switz.*
Echinacea (p.2298·1).
Cold symptoms; fever.

Echinapur *Scheffler, Ger.; Herbapol Poznan, Pol.*
Echinacea purpura (p.2298·1).
Respiratory- and urinary-tract infections; wounds.

Echinarell *Sanorell, Ger.*
Homoeopathic preparation.

Echinart *Ceom, Ital.†.*
Homoeopathic preparation.

Echinasal *Herbapol Wroclaw, Pol.*
Echinacea purpurea (p.2298·1); ribwort plantain (p.2379·1); rose fruit (p.2381·2); thyme (p.2401·1); grindelia (p.2317·2).
Catarrh; cough.

Echinasyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Echinatur *Ritsert, Ger.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Echine *Eagle, Austral.*
Herbal and homoeopathic antiseptic.

Echinerba *Labofarm, Pol.*
Echinacea purpurea (p.2298·1).
Catarrh.

Echiplant *Schwabe, Switz.†.*
Echinacea purpurea (p.2298·1).
Respiratory-tract infections.

Echnatol *Gerot, Austria.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea and vomiting.

Echnatol B_6 *Rosch & Handel, Austria.*
Cyclizine hydrochloride (p.574·2); pyridoxine hydrochloride (p.1978·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Echovist *Schering, Austria; Berlex, Canad.†; Schering, Fin.†; Schering, Fr.; Schering, Ger.; Schering, Hung.; Schering, Israel; Schering, Neth.†; Schering, S.Afr.†; Schering, Swed.; Bayer, UK.*
Galactose (p.1481·1).
Ultrasound contrast medium.

Echte Sodener Mineral-Pastillen *Twardy, Ger.†.*
Minerals from spring or stream (p.1667·1).
Respiratory-tract congestion.

Echtronerval-N *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Echtrosept-N *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Echtrovit *Weber & Weber, Ger.†.*
Vitamins; rutoside (p.1922·1).
Tonic.

Eciclean *Biotoscana, Chile.*
Chamomile flowers (p.2279·3); sage leaf (p.2382·3).
Dry mouth; mouth disorders.

Eclaran *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Port.*
Benzoyl peroxide (p.1590·2).
Acne.

Eclipse Lip and Face *Triangle, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Eclipsol
Note. This name is used for preparations of different composition.
Darier, Mex.
baby SPF 30; cream SPF 30; SPF 20; SPF 27: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Darier, Mex.
gel SPF 30; SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Darier, Mex.
SPF 40: Octocrilene (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Darier, Mex.
SPF 50: Octocrilene (p.1608·3); octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Eclorion *Norma (Νορμα), Gr.†.*
Sulpiride (p.1028·3).
Psychoses.

Ecnagel *Valuge, Arg.*
Salicylic acid (p.1612·2); resorcinol (p.1612·1); hamamelis (p.2318·2).
Skin disorders.

Ecnagel E *Valuge, Arg.*
Salicylic acid (p.1612·2); resorcinol (p.1612·1); erythromycin (p.269·2).
Infected skin disorders.

Ecnagel PB *Valuge, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Eco Mi *Geymonat, Ital.*
Econazole nitrate (p.531·1).
Fungal skin or vulvovaginal infections.

Ecobec *Ivax, Cz.; Ivax, Fr.; Ivax, Hung.†; Teva, Port.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

ecobiosan *Ecosol, Switz.*
d-Alpha tocopherol (p.1992·2).
Muscle and connective-tissue disorders associated with dyslipoproteinaemias; vitamin E supplement.

Ecocain *Katsoupas, Gr.†; Molteni, Ital.; Julphar, UAE.*
Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ecocillin *Proge, Ital.†.*
Lactobacillus plantarum.
Vaginitis.

Ecocort *Hoe, Malaysia; Hoe, Singapore; Hoe, Thai.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections.

Ecodax
Note. This name is used for preparations of different composition.
Unique, India†.
⊗ Beclometasone dipropionate (p.1516·2); econazole nitrate (p.531·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Unique, Rus.
Econazole nitrate (p.531·1).
Fungal skin infections.

Ecodergin *Farmigea, Ital.*
Econazole nitrate (p.531·1).
Vulvovaginal or dermatological fungal and Gram-positive bacterial infections.

Ecoderm
Note. This name is used for preparations of different composition.
Hoe, Malaysia†; Johnson & Johnson, S.Afr.
Econazole nitrate (p.531·1).
Fungal skin infections.

Chew, Thai.
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections.

Ecodipine *Ecosol, Switz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Ecodolor *Ecosol, Switz.*
Tramadol hydrochloride (p.130·3).
Pain.

Ecodurex *Ecosol, Switz.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Ecofenac *Ecosol, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Ecofermenti *Echo, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins (p.1922·1).
Disturbances of the gastrointestinal flora.

Ecofibra *Echo, Ital.*
Dietary fibre supplement (p.1922·1) (p.1712·3).
Delayed gastrointestinal transit; obesity.

Ecofilm *Latinofarma, Braz.*
Carmellose sodium (p.2142·1).
Dry eyes.

Ecoflorina *Ecobi, Ital.*
Lactic-acid-producing organisms (p.2372·3).
Nutritional supplement.

Ecofol *Ecobi, Ital.*
Calcium folinate (p.1943·3).
Anaemias; antidote to overdosage with folic acid antagonists; folic acid deficiency.

Ecogyn *Vivax, Venez.†.*
Alfa tocopherol (p.1992·2).
Vitamin E deficiency.

Ecolicin *Chauvin ankerpharm, Ger.*
Erythromycin lactobionate (p.270·1); colistimethate sodium (p.256·3).
Bacterial eye infections.

Ecoline *Biomedica-Chemica, Gr.†.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Ecomer *Natumin, Pol.*
Greenland shark-liver oil (p.2386·1).
Infections.

Ecomikole *SPB, Rus.†.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Ecomucyl *Ecosol, Switz.*
Acetylcysteine (p.1548·2) or acetylcysteine sodium (p.1548·2).
Paracetamol overdosage; respiratory-tract disorders.

Econ
Note. This name is used for preparations of different composition.
Orion, Denm.†.
Ethinylestradiol (p.2101·3); norethisterone acetate (p.2119·3).
Combined oral contraceptive.

General Drugs, Thai.
Econazole nitrate (p.531·1).
Fungal skin infections.

Econac *Goldshield, UK.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Econacort *BMS, UK.*
⊗ Econazole nitrate (p.531·1); hydrocortisone (p.1535·2).
Infected skin disorders.

Econal-C *Janpharm, S.Afr.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Econazine *YSP, Malaysia; Yung Shin, Singapore.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections.

Econite *APT, Hong Kong.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Econokit *Pascual, Philipp.*
1 Tablet, isoniazid (p.288·1) (Nyadin); 1 capsule, rifampicin (p.325·3) (Ricyn); 3 tablets, pyrazinamide (p.320·2) (Zapedia); 1 tablet, ethambutol hydrochloride (p.274·1) (Ethonah).
Tuberculosis.

Econokit-MDR *Pascual, Philipp.*
2 Tablets, pyrazinamide (p.320·2); 1 capsule, rifampicin (p.325·3); 1 tablet, isoniazid (p.288·1); 1 tablet, ethambutol hydrochloride (p.274·1).
Tuberculosis.

Econopack *Pascual, Philipp.*
1 Tablet, isoniazid (p.288·1) (Nyadin); 1 capsule, rifampicin (p.325·3) (Ricyn); 3 tablets, pyrazinamide (p.320·2) (Zapedia).
Tuberculosis.

Econopred *Alcon, Singapore; Alcon, USA†.*
⊗ Prednisolone acetate (p.1541·1).
Eye disorders; inflammatory eye disorders.

Econormotil *Mepro, Chile.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Ecopace *Goldshield, UK.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Ecophane *Biorga, Fr.*
Nutritional supplement (p.1922·1).
Nail and hair tonic.

Ecopirin *Abdi, Turk.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Ecoprin *Sam-On, Israel.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Ecoprofen *Ecosol, Switz.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

E-Cor *Slovakofarma, Cz.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ecorex *Zambon, Ital.*
Econazole nitrate (p.531·1).
Fungal or bacterial skin or vulvovaginal infections.

Ecos *Uniao Quimica, Braz.*
Dropropizine (p.1557·3).
Coughs.

Ecosal *Ivax, Cz.; Ivax, Hung.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; obstructive airways disease.

Ecosamina *Penn, Arg.*
Chondroitin sulfate (p.2280·3); glucosamine (p.2313·2).
Arthroses.

Ecosette *TS, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Ecoshampoo *ICN, Arg.†.*
Acetic acid (p.2244·2).
Pediculosis.

Ecosone *Christo, Hong Kong.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Ecosporina *Ecobi, Ital.*
Cefradine (p.233·1).
Bacterial infections.

Ecosprin *Sidmak, India.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Ecostatin *BMS, Canad.; BMS, Irl.; BMS, UK.*
Econazole nitrate (p.531·1).
Fungal infections.

Ecosteril *Amsa, Ital.*
Econazole nitrate (p.531·1).
Fungal and Gram-positive skin and nail infections; vulvovaginitis.

Ecotam *Sesderma, Spain.*
Econazole nitrate (p.531·1).
Fungal skin and nail infections.

Ecotrin *Schering-Plough, Arg.; Link, Austral.†; GSK, Chile; Goldshield, Hong Kong; GSK, Mex.; Link, NZ; Pharmafrica, S.Afr.; GSK Consumer, USA.*
Aspirin (p.20·3).
Fever; inflammation; musculoskeletal and joint disorders; pain; thromboembolic disorders.

Ecotrixon *Bernofarm, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Ecoval *GSK, Ital.*
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Ecoval con Neomicina *GSK, Ital.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Ecovent *Ecosol, Switz.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Eco-Vita-Min *Ecobi, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).

Ecoxib *Anglo-French Drugs, India†.*
Etoricoxib (p.53·1).
Gout.

Ecradin *Med-One, Gr.*
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Ecran LEB Protection *Eucerin, Fr.*
SPF 15; SPF 25: Avobenzone (p.1589·3); octinoxate (p.1608·2); octil triazone (p.1608·1).
Sunscreen.

Ecran Protection Extreme *Eucerin, Fr.†.*
SPF 60: Bisoctrizole (p.1591·2); titanium dioxide (p.1617·3); ensulizole (p.1597·1); iscotrizinol (p.1599·2); octil triazone (p.1608·1); octinoxate (p.1608·2).
Sunscreen.

Ecran Solaires Haute Protection *Juvex, Fr.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); avobenzone (p.1589·3); ensulizole (p.1597·1); octinoxate (p.1608·2).
Sunscreen.

Ecreme *Pacific, NZ.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Ecridoxan *Help, Gr.†.*
Etodolac (p.52·2).
Inflammatory disorders; pain.

Ectaprim *Liomont, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Ectiban *Laboratorios Chile, Chile.*
Escitalopram oxalate (p.391·1).
Depression; panic disorder; social anxiety disorder.

Ectiva *Bracco, Ital.; Altana, Mex.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Ectofus *Coup, Gr.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Ectopal *Codal Synto, Thai.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; female infertility; gynaecomastia; hereditary angioedema; menorrhagia; precocious puberty.

Ectosone *Technilab, Hong Kong†.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders.

Ectospasmol *Rafarm, Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Ectren *Menarini, Spain.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Ectrin
Note. This name is used for preparations of different composition.
EMS, Braz.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

OEP, Philipp.
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Ectrin Balsamico *EMS, Braz.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Bacterial infections.

Ecuaderm *Roemmers Rowe, Venez.*
Benzoyl peroxide (p.1590·2).
Acne.

Ecuamon *Lazar, Arg.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Ecur Test *Roche Diagnostics, Austral.*
Test for glucose, protein, and blood in urine.

Ecur Test and Leucocytes *Roche Diagnostics, Austral.*
Test for protein, glucose, blood, and leucocytes in urine.

Ecural *Essex, Ger.*
⊗ Mometasone furoate (p.1539·3).
Scalp disorders; skin disorders.

Eczema Cream *Hamilton, Austral.*
Coal tar (p.1616·2); dimethicone (p.2032·1); zinc oxide (p.1621·2).
Dermatitis; eczema.

Eczema L87 *Homeocan, Canad.*
Homoeopathic preparation.

Eczema Ointment *Potter's, UK.*
Zinc oxide (p.1621·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2); stellaria media.
Eczema.

Eczema Relief
Note. This name is used for preparations of different composition.
Medherb, Austral.
Calendula (p.2273·1); myrrh (p.2349·2).
Eczema.

Homeocan, Canad.
Homoeopathic preparation.

Eczemol *Plymouth Pharmaceuticals, USA.*
Homoeopathic preparation.

Eczil *Wockhardt, Hung.†.*
⊗ Fluocinolone acetonide (p.1531·3); povidone-iodine (p.1659·2).
Skin disorders.

Eczo-Wokadine *Wockhardt, India.*
⊗ Fluocinolone acetonide (p.1531·3); povidone-iodine (p.1659·2).
Infected skin disorders.

Ed A-Hist *Edwards, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; nasal congestion.

Ed Chlor-PED D *Edwards, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

ED Tuss HC *Edwards, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Edalen *Temis, Arg.*
Risperidone (p.1024·2).
Psychoses.

Edamox *Remedica, Hong Kong.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Edason *Medicus, Gr.†.*
Clindamycin phosphate (p.251·2).
Acne.

Ed-Chlor-Tan *Edwards, USA.*
Chlorphenamine tannate (p.572·2).
Hypersensitivity reactions.

Ede 6 *Teofarma, Ital.†.*
Dimeticone (p.1770·2); pancreatin (p.2360·1).
Digestive disorders.

Edecam *Diba, Mex.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Edecrin
MSD, Austral.
⊗ Etacrynic acid (p.1283·1).
Formerly known as Edecril.
Ascites; heart failure; nephrotic syndrome; oedema.

MSD, Austria; Merck Frosst, Canad.; Aton, USA.
⊗ Etacrynic acid (p.1283·1) or sodium etacrynate (p.1283·2).
Ascites; heart failure; nephrotic syndrome; oedema.

Edecrina *MSD, Swed.†.*
⊗ Sodium etacrynate (p.1283·2).
Oedema.

Edefen *Diba, Mex.†.*
Oxyphenbutazone (p.107·3).
Rheumatoid disorders.

Edem *Wermar, Mex.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Edemann *Littman, Philipp.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Edemax *SIFI, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Edemid *Behrens, Venez.*
⊗ Furosemide (p.1292·1).
Hypertension.

Edemin *Ikapharmindo, Indon.*
⊗ Furosemide (p.1292·1).
Pulmonary oedema.

Edemox *Chiesi, Spain.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma; high-altitude disorders; oedema.

Edenil *Zambon, Ital.*
Ibuprofen isobutanolammonium (p.65·2).
Gynaecological disorders.

Edenol *Randall, Mex.*
⊗ Furosemide (p.1292·1).
Hypertension; liver cirrhosis with ascites; nephrotic syndrome; oedema.

Ederphyt
Note. This name is used for preparations of different composition.
Doetsch, Grether, Switz.
Cream: Phenyl undecenoate (p.549·3); thymol (p.1664·3); salicylic acid (p.1612·2).
Fungal foot infections.

Mavena, Switz.†.
Topical spray: Phenol undecenoate (p.549·3); menthol (p.2340·1); thymol (p.1664·3); salicylic acid (p.1612·2); phenoxyethanol (p.1657·1); isopropyl alcohol (p.1650·3).
Fungal foot infections.

Edetil *Biotecnoquimica, Venez.*
Disodium edetate (p.1463·3).
Digitalis toxicity; hypercalcaemia.

Edeven
Note. This name is used for preparations of different composition.
IBI, Ital.
Injection; tablets: Sodium aescinate (p.2248·2).
Capillary fragility.

IBI, Ital.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); diethylamine salicylate (p.47·2).
Capillary fragility.

E-devit *Framingham, Arg.*
Alpha tocopherol (p.1992·2); collagen (p.2286·1); elastin (p.2286·1).

E-devit Protectora *Framingham, Arg.*
Vitamin E (p.1992·2).

Edex
Schwarz, Cz.†.
Alprostadil alfadex (p.2183·3).
Erectile dysfunction.

Schwarz, Fr.; Lavipharm, Gr.†; Schwarz, USA.
Alprostadil (p.2183·2).
Erectile dysfunction.

Edhanol *Solvay, Braz.*
Phenobarbital (p.492·2).
Epilepsy.

Edicin *Lek, Cz.; Lek, Hung.†; Lek, Pol.; Lek, Rus.; Sandoz, Thai.*
Vancomycin hydrochloride (p.358·3).
Gram-positive bacterial infections.

Edictum *Phoenix, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Edifaringen *Gayoso, Spain.*
⊗ Bacitracin zinc (p.210·3); benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); potassium chlorate (p.2371·3).
Mouth and throat disorders.

Edigastrol *Serra Pamies, Spain.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Dyspepsia; gastrointestinal hyperacidity.

Edinol *Bayer, India.*
Multivitamin and mineral preparation (p.1922·1).

Ed-in-Sol *Edwards, USA†.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Edip *Ipca, India†.*
Nifedipine (p.1350·1).
Angina pectoris.

Edirel *Laphal, Fr.†.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Ediston *Pierre Fabre Sante, Fr.*
Nifuroxazide (p.307·2).
Diarrhoea.

Edmudo *Rafarm, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Ednapron *Grin, Mex.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Ednyt *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Pinewood, Irl.†; Richter, Pol.; Gedeon Richter, Rus.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ednyt HCT *Gedeon Richter, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Ednyt Plus *Gedeon Richter, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Edodes *Peter, Ital.*
Vitamin B substances; arginine; sodium CM-betaglucan (p.1922·1).
Tonic.

Edolar *Nevzat, Turk.*
Etodolac (p.52·2).
Osteoarthritis; rheumatoid arthritis.

Edolfene *Edol, Port.*
Flurbiprofen sodium (p.61·2).
Ocular inflammation; prevention of intra- and postoperative miosis.

Edolglau *Edol, Port.*
Clonidine hydrochloride (p.1247·1).
Glaucoma; ocular hypertension.

Edoltar *Edol, Port.†.*
Undecenoic acid monoethanolamide (p.549·3); coal tar (p.1616·2); salicylic acid (p.1612·2); resorcinol (p.1612·1); thymol (p.1664·3).
Skin and scalp disorders.

Edorame *Pisa, Mex.*
Magnesium valproate (p.511·3).
Epilepsy.

Edoti *Ethica, Indon.*
Vitamin E (p.1992·2).
Antoxidant; vitamin E deficiency.

Edoxil *Inibsa, Spain†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Edoxil Mucolitico *Inibsa, Spain†.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Edrigyl *Gerolymatos, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Edronax *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pharmacia, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Norw.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK.*
Reboxetine mesilate (p.420·3).
Depression.

E-Drops *Ranbaxy, Thai.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

ED-SPAZ *Edwards, USA.*
Hyoscyamine sulfate (p.1736·1).

ED-TLC *Edwards, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Edual *Recalcine, Chile†.*
St John's wort (p.422·3).
Depression.

Educiclina *Tecnofarma, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Edufil *Genepharm, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Edul *Infinity, Venez.*
Aspartame (p.1930·1).
Artificial sweetener.

Edul K-200 *Knop, Chile.*
Chromium tripicolinate (p.1934·3).
Chromium deficiency.

Edulsan *Framingham, Arg.*
Stevioside (p.1969·1).
Sugar substitute.

Edulsan Folic *Framingham, Arg.*
Folic acid (p.1940·1).
Dietary supplement.

Eduprim *F5 Profas, Spain†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Eduprim Mucolitico *F5 Profas, Spain.*
Carbocisteine (p.1553·2); guaifenesin (p.1561·3); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Edurid *Iromedica, Switz.†.*
Edoxudine (p.872·2).
Herpes simplex infections.

EEE *Cadila, India.*
Vitamin E (p.1992·2).

EES *Abbott, Austral.; Abbott, Canad.; Abbott, Hong Kong; Abbott, Indon.; Abbott, Malaysia; Abbott, NZ; Abbott, Singapore; Abbott, USA.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections; intestinal amoebiasis.

Eetless *Adcock Ingram, S.Afr.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Eeze *Antula, Fin.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Efabetic *Express Care, NZ†.*
Essential fatty acids; gamolenic acid; vitamin E (p.1922·1).
Dietary supplement in diabetic neuropathy.

Efacal *Nutricia, NZ†.*
Evening primrose oil (p.2302·1); essential fatty acids; fish oil (p.1362·2); calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Efaderm *Galderma, India.*
Sodium pidolate (p.1614·1); sodium lactate (p.1673·3); sunflower oil (p.1970·3).
Dry skin disorders.

Efadermin *Widmer, Ger.*
Lithium succinate (p.1604·1); zinc sulfate (p.1999·2).
Seborrhoeic dermatitis.

Efagel *Mavi, Ital.*
Gamolenic acid (p.2308·2); vitamin E (p.1992·2).
Nutritional supplement.

Efalex
Note. This name is used for preparations of different composition.
Efamol, Austral.†.
Evening primrose oil (p.2302·1); thyme oil (p.2401·2); tuna oil (p.1362·2).
Dietary supplement.

Nutricia, Canad.†; Nutricia, NZ; Wassen, UK.
Evening primrose oil (p.2302·1); thyme oil (p.2401·2); fish oil (p.1362·1).
Dietary supplement.

Efalith *Widmer, Austria; Widmer, Belg.; Scotia, Irl.; Widmer, Switz.*
Lithium succinate (p.1604·1); zinc sulfate (p.1999·2).
Seborrhoeic dermatitis.

Efamarine *Efamol, Austral.†; Nutricia, NZ; Efamol, UK.*
Evening primrose oil (p.2302·1); fish oil (p.1362·2).
Dietary supplement.

Efamast
Note. This name is used for preparations of different composition.
Scotia, Cz.†.
Evening primrose oil (p.2302·1).
Mastalgia.

Express Care, NZ.
Essential fatty acids; gamolenic acid (p.2308·2).
Mastalgia.

Efamax *Nutricia, NZ.*
Evening primrose oil (p.2302·1); fish oil (p.1362·2); vitamins and minerals (p.1922·1); herbs.
Dietary supplement.

Efamol *Primula, Arg.†; Efamol, Canad.†; Nutricia, NZ; Sidroga, Switz.; Efamol, UK.*
Evening primrose oil (p.2302·1).
Dietary supplement.

Efamol G *Covan, S.Afr.†.*
Gamolenic acid (p.2308·2); linoleic acid (p.2308·2).
Nutritional supplement.

Efamol PMP *Nutricia Dietary, UK.*
Evening primrose oil (p.2302·1); vitamins; minerals (p.1922·1).
Premenstrual syndrome.

Efanatal *Nutricia, NZ; Nutricia Dietary, UK.*
Polyunsaturated fatty acids; docosahexaenoic acid; arachidonic acid; gamolenic acid (p.1922·1).
Dietary supplement in pregnancy and breast feeding.

Efavilea *Elea, Arg.*
Efavirenz (p.872·3).
HIV infection.

Efavir *Cipla, India; Cipla, Venez.*
Efavirenz (p.872·3).
HIV infection.

Efcamon *Nizhpharm, Rus.*
Methyl salicylate (p.85·3); capsicum (p.2276·2); camphor (p.2273·2); clove oil (p.2285·1); mustard oil (p.2349·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); cloral hydrate (p.979·1); cinnamon oil (p.2283·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Efcorlin *GSK, India.*
⊗ Hydrocortisone (p.1535·2); naphazoline nitrate (p.1565·2).
Nasal congestion.

Efcortelan *Chemidex, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Efcortesol *Sovereign, UK.*
⊗ Hydrocortisone sodium phosphate (p.1535·3).
Corticosteroid.

Efdege *Iason, Austria; Iason, Cz.; Iason, Neth.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide agent for positron emission tomography.

Efecient *Panacea, India.*
Sodium ferric gluconate complex (p.1962·2).
Iron deficiency in haemodialysis renal failure.

Efecoryl Forte *Sidus, Arg.*
⊗ Phenylephrine hydrochloride (p.1568·1); prednisolone acetate (p.1541·1).
Eye disorders.

Efectin *Wyeth Lederle, Austria; Wyeth, Cz.; Wyeth, Hung.; Wyeth, Pol.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Efectine *Unipharm, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Efectine D *Unipharm, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Pruritus; rhinitis; upper respiratory-tract congestion; urticaria.

Efedrosan *Pasteur, Chile.*
⊗ Ephedrine hydrochloride (p.1558·2).
Asthma; bronchitis.

Efektolol *Alpharma-Isis, Ger.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; essential tremor; hypertension; hyperthyroidism; migraine.

Efemolin *Novartis, Ger.*
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Allergic and inflammatory disorders of the eye.

Efemolina *Novartis Ophthalmics, Arg.*
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Efemoline
Note. This name is used for preparations of different composition.
Novartis, Gr.
⊗ Fluorometholone (p.1532·3); gentamicin (p.284·2).
Infected eye disorders.

Novartis, Hong Kong; Novartis, Ital.; Novartis, Malaysia†; Novartis, Philipp.; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Allergic and inflammatory eye disorders.

Efensol *Faes, Spain.*
Colestyramine (p.1252·3).
Formerly contained filicol.
Hyperlipidaemias.

Eferox *Lindopharm, Ger.; Hexal, Pol.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; thyroid cancer.

Eferox Jod *Lindopharm, Ger.*
Levothyroxine sodium (p.2171·2); potassium iodide (p.2169·2).
Goitre; iodine deficiency.

E-Fertoc *Vitae, Mex.*
Alpha tocopherol (p.1992·2).

Efetamol *Italfarmaco, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Efeu *Madaus, Ger.; Ratiopharm, Ger.; Sandoz, Ger.*
Ivy (p.2328·1).
Catarrh; coughs.

Efevelone *Actavis, Rus.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Efexin *Medikon, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Efexor *Wyeth, Arg.; Wyeth, Austral.; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Indon.; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Sin-*

gapore; Wyeth, Swed.; Wyeth, Switz.; Wyeth-Ayerst, Thai.; Wyeth, Turk.; Wyeth, UK; Wyeth, Venez.
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; mixed anxiety depressive states; panic disorder; social phobia.

Effaclar
Note. This name is used for preparations of different composition.
Roche-Posay, Arg.†.
Zinc pidolate (p.1614·1).
Acne.

Roche-Posay, Braz.
Zinc pidolate (p.1614·1); iodopropynyl butyl carbamate (Glycacil) (p.2045·2); chlorhexidine gluconate (p.1635·3).

Roche-Posay, Fr.; Roche-Posay, Irl.
Zinc pidolate (p.1614·1); iodopropynyl butyl carbamate (Glycacil) (p.2045·2).
Acne.

Effaclar AI *Roche-Posay, Irl.*
Nicotinamide (p.1957·3); piroctone olamine (p.1610·1); lipo hydroxy acids; iodopropynyl butyl carbamate (Glycacil) (p.2045·2).
Acne.

Effaclar K
Note. This name is used for preparations of different composition.
Roche-Posay, Irl.
Lipo hydroxy acid; alkyl malate; salicylic acid (p.1612·2); thermal water; zinc PCA (p.1614·1); iodopropynyl butyl carbamate (Glycacil) (p.2045·2).
Acne.

Roche-Posay, Singapore.
Lipo-hydroxy acid; salicylic acid (p.1612·2); zinc pidolate (p.1614·1).
Acne.

Effacne *Roche-Posay, Fr.; Roche-Posay, Switz.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Effadiane *CS, Fr.*
A range of emollients and a soap substitute.
Dry skin.

Effadiane relipidantes *CS, Fr.*
Inulin (p.2326·3); *Bifidobacterium lactis*; fish oil (p.1362·2); borage oil (p.2267·3).
Skin irritation.

Effalpha *Roche-Posay, Arg.†.*
Glycolic acid (p.1598·1); zinc pidolate (p.1614·1).
Acne.

Effcal *Ranbaxy, Malaysia; Ranbaxy, Singapore; Ranbaxy, Thai.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Effect Comfort *Ivax, Cz.*
Paracetamol (p.108·1).
Fever; pain.

Effective Strength Cough Formula *Barre-National, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Effective Strength Cough Formula Liquid With Decongestant *Barre-National, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Effectsal *Shin Poong, Singapore.*
Norfloxacin (p.309·2).
Bacterial infections.

Effederm *CS, Fr.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders; warts.

Effegyn *Effik, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Effekton *Teofarma, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Effekton mit Ketoprofen *Teofarma, Ger.*
Ketoprofen (p.73·1).
Soft-tissue injury.

Efferalgan *BMS, Cz.; BMS, Fr.; BMS, Hung.; BMS, Israel†; BMS, Ital.; BMS, Pol.; BMS, Port.; BMS, Spain; BMS, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Efferalgan C *BMS, Belg.†; BMS, Hung.†; BMS, Ital.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Efferalgan Codeine *UPSA, Cz.†; BMS, Fr.; BMS, Israel†; BMS, Pol.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Efferalgan Vit C *BMS, Spain.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Efferalgan Vitamin C *BMS, Cz.; BMS, Pol.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Efferalgan Vitamine C *BMS, Fr.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Efferalganodis *UPSA Conseil, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Effercal D3 *Piam, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Effercet *Doctum, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Effercitrate *Typharm, UK.*
Potassium citrate (p.1673·2); citric acid (p.2284·1).
Cystitis.

Effer-K *Nomax, USA.*
Potassium bicarbonate (p.1673·1); potassium citrate (p.1673·2).
Hypokalaemia; potassium depletion.

Effersol *Pharmacare, S.Afr.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Acidosis; urinary alkalinisation.

Effervit Calcium *Altana, Pol.*
Calcium lactogluconate; ascorbic acid (p.1983·3).
Calcium and vitamin C deficiency.

Efferzyme *Bausch & Lomb, Canad.†.*
Subtilisin (p.2393·3) (p.1622·2).
Protein remover for soft contact lenses.

Effexor
Wyeth, Canad.; Wyeth-Ayerst, USA.
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Wyeth, Fr.
Venlafaxine (p.430·1) or venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Effia *Effik, Fr.*
Soya isoflavones (p.2391·2); vitamins; calcium (p.1922·1).
Menopausal disorders.

Effico
Forest, Irl.; Pharmax, Irl.
Nicotinamide; thiamine hydrochloride; caffeine (p.1922·1).
Tonic.

Forest Laboratories, UK.
Nicotinamide; thiamine hydrochloride; caffeine; compound gentian infusion (p.1922·1).
Tonic.

Efficort *Galderma, Arg.†; Galderma, Chile; Galderma, Fr.; Galderma, Hong Kong†; Galderma, Israel; Galderma, Ital.†; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Galderma, Venez.*
⊗ Hydrocortisone aceponate (p.1536·2).
Skin disorders.

Effidia *Ethicon, Fr.*
Sodium hyaluronate (p.2320·1).
Burns; ulcers; wounds.

Effidigest *Nutrisante, Fr.*
Nutritional supplement (p.1922·1).
Digestive disorders.

Effidrate
Note. This name is used for preparations of different composition.
Roche-Posay, Arg.†.
Glycerol; octoxin; aluminium (p.2254·1).
Acne.

Roche-Posay, Braz.†.
Glycerol (p.2314·2); ethylhexylglycerin (p.1644·1); aluminium starch octenylsuccinate.
Skin hydrating preparation.

Effigel *IBSA, Switz.*
Diclofenac epolamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Effiplen
Note. This name is used for preparations of different composition.
Effik, Port.
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Effik, Spain†.
Buspirone hydrochloride (p.965·3).
Anxiety; mixed anxiety depressive states.

Effiprev *Effik, Fr.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Effizinc *Expanscience, Fr.*
Zinc gluconate (p.1999·2).
Acne; acrodermatitis.

Efflumidex *Allergan, Cz.; Allergan, Ger.; Allergan, Hung.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Efflumycin *Allergan, Ger.†.*
⊗ Fluorometholone (p.1532·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Effontil *Boehringer Ingelheim, Venez.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Effortil *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Gr.; IFET (ΙΦΕΤ), Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Norw.†; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.*
⊗ Etilefrine hydrochloride (p.1284·1).
Cardiovascular collapse; hypotension; orthostatic hypotension; post-operative debility; vascular headache.

Effortil comp *Boehringer Ingelheim, Austria.*
⊗ Etilefrine hydrochloride (p.1284·1); dihydroergotamine mesilate (p.618·2).
Hypotension.

Effortil plus *Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Switz.*
⊗ Etilefrine hydrochloride (p.1284·1); dihydroergotamine mesilate (p.618·2).
Hypotension.

Effox *Schwarz, Cz.†; Schwarz, Pol.; Schwarz, Rus.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction; pulmonary hypertension.

Efherol *Vitemat, Braz.†.*
Vitamin E (p.1992·2).

Efidac 24 Chlorpheniramine *Hogil, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Efidac 24 Pseudoepehdrine *Hogil, USA.*
Pseudoephedrine hydrochloride (p.1571·2).

Efiken *Kendrick, Mex.*
Ketoprofen (p.73·1).
Osteoarthritis; pain; rheumatoid arthritis.

Efimag *Fornet, Fr.†.*
Magnesium pidolate (p.1679·3).
Magnesium deficiency.

Efimerol *Liferpal, Mex.*
Ketorolac (p.75·2).
Pain.

Efixano *Dosa, Arg.*
Irinotecan hydrochloride (p.737·1).
Malignant neoplasms.

Eflagen *Sanbe, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Eflevar *Altana, Arg.*
Calcium dobesilate (p.2272·1).
Haemorrhoids; venous insufficiency.

Eflin *Meprofarm, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic disorders; cold symptoms; sinusitis.

Eflone *Ciba Vision, USA.*
⊗ Fluorometholone acetate (p.1533·1).
Eye disorders.

Efloran *KRKA, Cz.; KRKA, Rus.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Efluvium Anti-caspa *Dermoteca, Port.*
Salicylic acid (p.1612·2); ichthammol (p.1599·1); saw palmetto (p.2192·3); climbazole (p.529·3); acetamide monoethanolamide.
Scalp disorders.

Efluvium Anti-seborreico
Note. This name is used for preparations of different composition.
Dermoteca, Port.
Lotion: Salicylic acid (p.1612·2); panthenol (p.2362·1); azeoglycine; acetamide monoethanolamide.
Scalp disorders.

Dermoteca, Port.
Shampoo: Salicylic acid (p.1612·2); ichthammol (p.1599·1); saw palmetto (p.2192·3); acetamide monoethanolamide.
Scalp disorders.

Efluvium Saquetas *Dermoteca, Port.*
Vitamins; minerals; amino-acids; gelatin (p.1922·1).
Nutritional supplement.

Efodil *Lafage, Arg.†.*
⊗ Ephedrine (p.1558·1); silver (p.2387·1).
Nasal congestion.

Efodine *Fougera, USA.*
Povidone-iodine (p.1659·2).
Skin disinfection.

E-Folic *Framingham, Arg.*
Folic acid; *d*-alpha tocopherol; vitamin B ; vitamin B (p.1922·1).
Dietary supplement.

Eformax *Teva, Port.*
⊗ Formoterol fumarate (p.1122·1).

Eforol *Yeni, Turk.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Efortil *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Spain.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Efotax *Meprofarm, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Efoxamina *Leti, Venez.†.*
⊗ Phenyltoloxamine (p.588·1); racephedrine (p.1559·1).

Efpa *Adeka, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Efrane *Abbott, Denm.†; Abbott, Fin.†; Abbott, Swed.†.*
Enflurane (p.1782·2).
General anaesthesia.

Efridol *Aesculapius, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Efrin *Fischer, Israel.*
Phenylephrine hydrochloride (p.1568·1).
Eye congestion; production of mydriasis.

Efrinol *Prolab, Pol.*
⊗ Ephedrine hydrochloride (p.1558·2).
Nasal congestion.

Efriviral *Aesculapius, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Eftapan *Ratiopharm, Austria; Merckle, Ger.*
Eprazinone hydrochloride (p.1559·3).
Coughs; respiratory-tract disorders.

Eftapan Tetra *Ratiopharm, Austria.*
Eprazinone hydrochloride (p.1559·3); tetracycline hydrochloride (p.347·2).
Bacterial respiratory-tract infections.

Eftiar Decalin *DORC, Neth.*
⊗ Perflunafene (p.2365·2).
Ophthalmic tamponade.

Eftiar Octane *DORC, Neth.*
Perfluorooctane (p.2365·3).
Ophthalmic tamponade.

Eftriax *CCM, Malaysia.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Eftrival *Valmor, Venez.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Eftry *Krugher, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Efudex *Valeant, Canad.; Valeant, USA.*
Fluorouracil (p.722·2).
Actinic keratoses; skin cancer.

Efudix *Valeant, Arg.; ICN, Austral.; Pharma Logistics, Belg.; Raffo, Chile; CSP, Fr.; Valeant, Ger.; ICN, Hong Kong†; Valeant, Hung.; Valeant, Irl.; ICN, Israel; ICN, Ital.; Valeant, Mex.; Pacific, NZ; ICN, Neth.; ICN, Pol.; Pharmaco, S.Afr.; Valeant, Singapore; Valeant, Spain†; Valeant, Switz.; ICN, UK.*
Fluorouracil (p.722·2).
Actinic keratoses; anogenital warts; Bowen's disease; premalignant skin lesions; senile keratosis; skin cancer; solar keratosis; warts.

Efurix *Valeant, Braz.*
Fluorouracil (p.722·2).
Actinic and senile keratoses; skin cancer.

Efurox *CCM, Malaysia.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Efxine *Pharmasant, Thai.†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Egarone *Farmalider, Spain†.*
⊗ Allantoin (p.1588·1); benzalkonium chloride (p.1629·1); muramidase hydrochloride (p.2348·1); oxymetazoline (p.1567·2).
Cold symptoms; rhinitis; sinusitis.

Egaten *Novartis, Fr.*
Triclabendazole (p.157·2).
Fascioliasis.

Egazil *AstraZeneca, Denm.; AstraZeneca, Fin.†; AstraZeneca, Norw.; AstraZeneca, Swed.*
Hyoscyamine sulfate (p.1736·1).
Biliary colic; bladder tenesmus; gastrointestinal spasm; hypersecretion; irritable bowel syndrome.

Egelif *Leovan, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

E-Gems *Carlson, USA.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

E-Gen-C *Schering, S.Afr.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Postcoital oral contraceptive.

Egerian *AGIPS, Ital.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Egery *Biorga, Fr.*
Erythromycin (p.269·2).
Bacterial infections.

Egestan *Elea, Arg.*
Folic acid (p.1940·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Egestan Hierro *Elea, Arg.*
Ferrous gluceptate (p.1938·3); folic acid (p.1940·1).
Anaemias; folic acid and iron supplement.

Egg Plus *Megapharm, Israel.*
⊗ Albumin (p.1052·1).
Nutritional protein supplement.

Egibren *Chiesi, Ital.*
⊗ Selegiline hydrochloride (p.817·1).
Psychiatric disorders.

Egicalm *Sanofi-Aventis, Gr.*
Lysine aspirin (p.79·1).
Fever; inflammation; pain.

Egicalm Cardio *Sanofi-Aventis, Gr.*
Lysine aspirin (p.79·1).
Thromboembolism prophylaxis.

Egiferon *Trigon, Hung.*
Interferon alfa (p.885·1).
Chronic myeloid leukaemia; hairy-cell leukaemia; hepatitis C; herpes simplex infections; warts.

Egifilin *EGIS, Hung.*
Theophylline (p.1140·1).
Obstructive airways disease.

Egilipid *Egis, Cz.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Egilok *Egis, Cz.; EGIS, Hung.; Egis, Rus.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; ischaemic heart disease; migraine; myocardial infarction.

Egistrozol *Synthon, Cz.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Eglandin *Welfide, Singapore†.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Eglek *Masterlek, Rus.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vestibular disorders.

Eglidon *Merck, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Eglonil *Sanofi-Aventis, Rus.*
Sulpiride (p.1028·3).

Eglonyl *Alkaloid, Cz.†; Sanofi Synthelabo, S.Afr.*
Sulpiride (p.1028·3).
Depression; disturbed behaviour; peptic ulcer; psychoses; psychosomatic symptoms; vertigo.

Eglymad *KRKA, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Ego Skin Cream
Note. This name is used for preparations of different composition.
Ego, Austral.
Emollient.

Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
Cetyl alcohol (p.2028·3); glycerol (p.2314·2); liquid paraffin (p.2030·3).
Barrier cream; dry skin; emollient.

Egocort *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Egoderm
Note. This name is used for preparations of different composition.
Ego, Austral.
Cream: Ichthammol (p.1599·1).
Skin disorders.

Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
Cream: Ichthammol (p.1599·1); allantoin (p.1588·1).
Skin disorders.

Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
Ointment: Ichthammol (p.1599·1); zinc oxide (p.1621·2).
Skin disorders.

Ego, NZ.
Ointment: Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Skin disorders.

Egogyn
Note. This name is used for preparations of different composition.
Gynopharm, Chile; Vivax Gynopharm, Venez.
Vitamin E (p.1992·2).
Dietary supplement; vitamin E deficiency.

Schering, Ital.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Egomycol *Ego, NZ†.*
Undecylenic alkanolamide (p.549·3); chlorhexidine gluconate (p.1635·3); salicylic acid (p.1612·2); benzoic acid (p.1630·2); resorcinol (p.1612·1).
Fungal skin and nail infections.

Egopsoryl TA
Note. This name is used for preparations of different composition.
Ego, Austral.
Sulfur (p.1614·1); phenol (p.1656·1); menthol (p.2340·1); glycerol (p.2314·2); coal tar (p.1616·2).
Psoriasis.

Ego, Hong Kong.
Sulfur (p.1614·1); phenol (p.1656·1); coal tar (p.1616·2); menthol (p.2340·1); allantoin (p.1588·1); glycerol (p.2314·2).
Eczema; psoriasis.

Ego, Malaysia; Ego, NZ; Ego, Singapore.
Sulfur (p.1614·1); phenol (p.1656·1); coal tar (p.1616·2); menthol (p.2340·1); allantoin (p.1588·1).
Formerly contained sulfur, phenol, and coal tar in *Singapore*.
Eczema; psoriasis.

Egosona *Altana, Arg.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; rhinitis.

Egotussano *Sedabel, Braz.†.*
Sodium sulfonate; sodium benzoate (p.1630·2); guaiacol (p.1561·2).
Coughs.

Egozinc
Pharmascience, Canad.
Zinc oxide (p.1621·2) or zinc sulfate (p.1999·2).
Haemorrhoids.

Pharmascience, Hong Kong.
Zinc sulfate (p.1999·2).
Burns; ulcers; wounds.

Egozinc-HC *Pharmascience, Canad.*
⊗ Zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2).
Formerly known as PMS-Egozinc-HC.
Anorectal disorders.

Egozite Baby *Ego, NZ.*
Zinc oxide (p.1621·2); dimeticone (p.2032·1); light liquid paraffin (p.2031·1).
Barrier cream; nappy rash.

Egozite Baby Cream *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
Zinc oxide (p.1621·2); dimeticone (p.2032·1); light liquid paraffin (p.2031·1).
Formerly contained zinc oxide, dimeticone, light liquid paraffin, glycerol, and dexpanthenol in *Singapore*.
Skin disorders.

Egozite Cradle Cap *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ.*
Salicylic acid (p.1612·2) in an oil basis.
Cradle cap; seborrhoeic dermatitis.

Egozite Protective Baby Lotion
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, Hong Kong; Ego, NZ.
Dimeticone (p.2032·1).
Barrier preparation; nappy rash.

Ego, Malaysia; Ego, Singapore†.
Dimeticone (p.2032·1); light liquid paraffin (p.2031·1); glycerol (p.2314·2).
Barrier preparation; nappy rash.

Egrin *Grin, Mex.*
Alpha tocopherol (p.1992·2).

EH Retard *Eco, S.Afr.†.*
Allergen extracts (p.2250·2).
Hyposensitisation.

Ehrenhofer-Salbe *Ehrenhofer, Austria.*
Colophony (p.2286·2); lovage root (p.2335·1).
Bronchitis; skin disorders; soft-tissue, peri-articular, musculoskeletal, and joint disorders.

Ehrlich *Farmex, Gr.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); camphor (p.2273·2); benzyl nicotinate (p.28·1); mink oil; Spanish bog extract.

Ehrlich Balsamo *Polinac, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); benzyl nicotinate (p.28·1); capsicum (p.2276·2).
Musculoskeletal and joint disorders.

Eicebaer *Merck, Austria.*
Thyme (p.2401·1); senega (p.1572·3); bitter orange (p.2357·1).
Cough; respiratory-tract congestion.

Eicof *Bangkok Lab & Cosmetic, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Eicosan *Truw, Ger.*
Marine fish oil (p.1362·2).
Hyperlipidaemias.

Eicosapen *Nefro, Austria; Truw, Ger.; Altana, Switz.*
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias.

Eicovis *NBF, Ital.*
Omega-3 triglycerides, vitamins, and minerals (p.1922·1).
Eye disorders; nutritional supplement.

Eidoca *Eicopen, Venez.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Eifel *Rafarm, Gr.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; raised intra-ocular pressure.

Eifelfango-Neuenahr *Eifelfango, Ger.†.*
Medicinal mud.
Gastrointestinal disorders; gout; musculoskeletal and joint disorders; neuralgia.

EinsAlpha *Leo, Ger.*
Alfacalcidol (p.1986·1).
Osteodystrophy; osteomalacia; osteoporosis; rickets; vitamin D deficiency.

Eiquinon *Eisai, Hong Kong.*
Ubidecarenone (p.2407·2).
Heart failure.

Eisen-Diasporal *Protina, Cz.†.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Eisendragees-ratiopharm *Ratiopharm, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Eisenkapseln *Forster, Ger.†.*
Ferrous sulfate (p.1939·3); yeast; nicotinamide; folic acid; cyanocobalamin; copper sulfate; manganese sulfate (p.1922·1).
Iron deficiency.

Eisen-Sandoz *Sandoz, Ger.*
Ferrous gluconate (p.1939·1).
Iron deficiency.

EK-3 *Wermar, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

EK Burger *Ysatfabrik, Ger.*
Homoeopathic preparation.

Eki Cabe *Kowa, Jpn.*
Hydrotalcite (p.1733·3); oxoamidine; ursodeoxycholic acid (p.2408·1); ginseng (p.2312·1).
Antacid; flatulence.

Ekian *Uriach Aquilea OTC, Spain.*
Echinacea (p.2298·1).
Infections.

Ekilid *Aventis, Mex.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vertigo.

Ekinase *Soho, Indon.*
Echinacea purpurea (p.2298·1); selenium (p.1961·1).
Immunostimulant.

Eklipid *Proel, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Eklips *Sanovel, Turk.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; hypertension.

Eklips Plus *Sanovel, Turk.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Eklivan *Proel, Gr.*
Somatostatin (p.1809·1).
Haemorrhage in the upper gastro-intestinal tract.

Ekogal *Gal, Pol.†.*
Greenland shark-liver oil (p.2386·1).
Infections.

Ekorinol *Yeni, Turk.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Ekosetol *Yeni, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Ekovit *Curtis, Pol.*
Vitamins; magnesium; selenium (p.1922·1).
Dietary supplement.

Eksedryl Expectorant *Ethica, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); alcohol (p.1625·2).
Cold symptoms; cough; respiratory-tract congestion.

Ekseme *Monin, Fr.*
Cardiospermum halicacabum; hamamelis (p.2318·2).
Dry skin; skin irritation.

Eksofed *Bilim, Turk.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Eksofed Ekspektoran *Bilim, Turk.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

ektebin *Riemser, Ger.; Wernigerode, Ger.*
Protionamide (p.320·1).
Tuberculosis.

Ektogan *Teofarma, Ital.*
Zinc peroxide (p.1666·3); zinc oxide (p.1621·2); magnesium peroxide (p.1651·3).
Skin disorders; wound disinfection.

Ektoselene *Robapharm, Switz.*
Selenium disulfide (p.1613·1); sulfur (p.1614·1).
Scalp disorders.

Ektrofil *Ecobi, Ital.*
Zinc oxide (p.1621·2); aloe vera (p.1588·2).
Emollient.

Ekuba *Teofarma, Ital.*
Vaginal douche: Chlorhexidine gluconate (p.1635·3).
Personal hygiene.

Ekvacillin *AstraZeneca, Fin.†; AstraZeneca, Norw.; AstraZeneca, Swed.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Ekxine *Strand, Malaysia†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with viscous mucus.

Ekzegamma *Viofar, Gr.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1); undecenoic acid (p.549·2).
Infected skin disorders.

Ekzemsalbe F *Agepha, Austria.*
⊗ Hydrocortisone acetate (p.1535·2).
Eczema.

Ekzevit *Biomedica-Chemica, Gr.†.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Ekzevowen *Weber & Weber, Ger.*
Homoeopathic preparation.

EL Diet *Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Elacur *Riemser, Ger.*
Propyl nicotinate (p.119·2).
Musculoskeletal and joint disorders; neuralgia.

Elacutan *Riemser, Cz.; Riemser, Ger.*
⊗ Urea (p.1620·2).
Skin disorders.

Elafax *Gador, Arg.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Elagen *Eladon, UK.*
Eleutherococcus senticosis (p.2386·3).
Tonic.

Elageno OS *Mavi, Ital.*
Folic acid; magnesium; omega 6 and omega 3 triglycerides; fatty acids (p.1922·1).
Formerly known as Pufolic.
Nutritional supplement.

Elamax *Biolab Sanus, Braz.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, cyproterone acetate (p.2088·2); estradiol valerate.
Menopausal disorders.

Elan *Schwarz, Ital.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; cardiac stenosis; heart failure; myocardial infarction.

Elana *OTW, Ger.*
Homoeopathic preparation.

Elana mono *OTW, Ger.†.*
Homoeopathic preparation.

Elandur *Sidus, Arg.†.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Elan-Forte *YSP, Malaysia.*
Chlorhexidine hydrochloride (p.1635·3); tolnaftate (p.548·3).
Fungal skin infections.

Elani *Libbs, Braz.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Elantan *Gebro, Austria; Sanol, Ger.; Schwarz, Ger.; Schwarz, Hong Kong; Schwarz, Irl.; Schwarz, Malaysia; Abbott, Mex.; Schwarz, Philipp.; Omnimed, S.Afr.; Ranbaxy, Singapore; Schwarz, Singapore; Schwarz, Thai.; UCB, UK; Farma, Venez.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction; pulmonary hypertension.

Elanver *Remedina, Gr.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Elaprase *Shire, Cz.; Shire, Port.; Shire, UK; Shire, USA.*
Idursulfase (p.2324·2).
Mucopolysaccharidosis II.

Elase *Pfizer, Chile; Pfizer, Fr.; Parke, Davis, Ital.†; Pfizer, Malaysia.*
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1).
Cervicitis; debridement of wounds; vaginitis.

Elaspol *Ono, Jpn.*
Sivelestat sodium (p.2388·1).
Acute lung injury associated with septicaemia.

Elastab *TO-Chemicals, Thai.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Elasterin *Phoenix, Arg.*
Ibandronate (p.1098·3).

Elatec *Servier, Mex.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Elater *Medipharm, Chile.*
Terbinafine (p.546·3) or terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Elatrol *Teva, Israel.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Elatrolet *Teva, Israel.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Elavil
Note. This name is used for preparations of different composition.
Merck Frosst, Canad.†; Substipharm, Fr.; DDSA Pharmaceuticals, UK; Zeneca, USA†.
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Am-Europharma, Philipp.
Allopurinol (p.552·2).
Hyperuricaemia; renal calculi.

Elawox *Riemser, Ger.*
Urea hydrogen peroxide (p.1666·2).
Infected wounds.

Elazor *Sigma-Tau, Ital.*
Fluconazole (p.532·1).
Fungal infections.

Elbaprid *Tiefenbacher, Neth.*
Tiapride hydrochloride (p.1032·1).
Neuroleptic-induced extrapyramidal disorders.

Elbat *Genepharm, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Elbrol *Pfleger, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Essential tremor; hypertension; hyperthyroidism; ischaemic heart disease; migraine.

Elbrus *Roemmers, Arg.*
Rasagiline mesilate (p.815·3).
Parkinsonism.

Elcal *Andromaco, Chile.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Elcal I *Andromaco, Chile†.*
Calcium gluconate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium deficiency.

Elcal-C Magnesio *Andromaco, Chile†.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); ascorbic acid (p.1983·3).
Calcium, magnesium and vitamin C deficiency.

Elcal-D *Andromaco, Chile.*
Calcium carbonate (p.1714·1) or calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteomalacia; osteoporosis; rickets.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Elcar *Pik, Rus.*
Levocarnitine (p.1932·2).
Carnitine deficiency; gastritis; hyperthyroidism; pancreatitis; skin disorders; tonic.

Elcimen *Nycomed, Austria†.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Elcion *Ranbaxy, India.*
Diazepam (p.986·3).
Alcohol withdrawal; anxiety; muscle spasm.

Elcitonin *Asahi, Jpn.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Elcodil *Faran, Gr.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Elcodrix *Pharlab, Braz.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Elcoman *Sandoz, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Elcrit *Parke, Davis, Ger.; Pfizer, Ger.*
Clozapine (p.981·1).
Schizophrenia.

Eldepryl *Douglas, Austral.; Meda, Belg.; Draxis, Canad.†; Orion, Denm.; Orion, Fin.; Orion, Irl.; Douglas, NZ; Viatris, Neth.; Orion, Norw.; Reckitt Benckiser, S.Afr.; Orion, Swed.; Orion, UK; Somerset, USA.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Eldertonic *Merz, USA.*
Vitamin B substances with minerals (p.1922·1).

Eldicet *Recalcine, Chile; Solvay, India; Solvay, Philipp.; Solvay, Spain.*
Pinaverium bromide (p.2368·1).
Biliary-tract dyskinesia; biliary-tract pain; constipation; gastrointestinal pain; gastrointestinal radiography; gastrointestinal spasm; irritable bowel syndrome.

Eldisin *Stada, Austria.*
Vindesine sulfate (p.788·2).
Malignant neoplasms.

Eldisine *Lilly, Arg.†; Aspen, Austral.†; Eurogenerics, Belg.; Lilly, Cz.†; Lilly, Fin.†; EG, Fr.; Cell Pharm, Ger.; IFET (ΙΦΕΤ), Gr.; Lilly, Irl.; Crinos, Ital.; Stada, Neth.; Lilly, S.Afr.†; Stada, Swed.; Medika, Switz.; Genus, UK.*
Vindesine sulfate (p.788·2).
Malignant neoplasms.

Eldopaque *Valeant, Canad.; Valeant, Hong Kong; Valeant, Malaysia; Valeant, Mex.; Valeant, Singapore; Crawford, UK; ICN, USA.*
Hydroquinone (p.1598·2) in a sunblocking basis.
Hyperpigmented skin disorders.

Eldoquin *Valeant, Canad.; Valeant, Hong Kong; Valeant, Malaysia; Valeant, Mex.; ICN, NZ; Valeant, Singapore; Crawford, UK; ICN, USA.*
Hydroquinone (p.1598·2).
Hyperpigmented skin disorders.

Eldoral *AWD, Ger.†.*
Trimipramine maleate (p.426·3).
Anxiety; depression.

Elebe *Medipharma, Arg.*
Carbamazepine (p.471·3).
Epilepsy; neuralgia.

Elebloc *Alcon, Arg.; Alcon Cusi, Spain.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma.

EleCare *Ross, USA.*
Elemental amino-acid based food for special diets (p.1922·1).
Food allergies; malabsorption; maldigestion; whole protein intolerance.

Elecor *Almirall, Spain.*
⊗ Eplerenone (p.1279·2).
Heart failure.

Electral *FDC, India.*
Potassium chloride; sodium chloride; sodium citrate; anhydrous glucose (p.1672·2).
Oral rehydration therapy.

Electric Blue Headlice
Note. This name is used for preparations of different composition.
Apotex, NZ.
Conditioner: Clove oil (p.2285·1); lavender oil (p.2331·2); lemon oil (p.2332·3); rosemary oil (p.2381·3); melaleuca oil (p.2338·2).
Detection of pediculosis.

Apotex, NZ.
Cream: Clove oil (p.2285·1); lavender oil (p.2331·2); melaleuca oil (p.2338·2).
Pediculosis.

Electrobion *Merck, India.*
Sodium chloride; potassium chloride; sodium citrate; anhydrous glucose (p.1672·2).
Oral rehydration therapy.

Electrolade *Eastern Pharmaceuticals, Irl.; Thornton & Ross, UK.*
Sodium chloride; potassium chloride; sodium bicarbonate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Electrolit *Pisa, Mex.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1672·2).
Oral rehydration therapy.

Electrolit Pediatrico *Pisa, Mex.*
Glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Electrolyte *Fresenius Kabi, Gr.*
Electrolyte infusion (p.1667·1).

Electropak *Mirren, S.Afr.*
Potassium chloride; sodium chloride; sodium bicarbonate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Electrorice *Naveh, Israel.*
Electrolytes in rice flour base (p.1672·2).
Diarrhoea; oral rehydration therapy.

Elegelin *Sun, Thai.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Elem *Andromaco, Chile†.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Elemental 028 *Scientific Hospital Supplies, Austral.; Nutricia, Fin.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, UK.*
Preparation for enteral nutrition (p.1922·1).

Elemental Zinc *Baxter, NZ†; DBL, NZ†.*
Zinc chloride (p.1999·1).
Zinc deficiency.

Elenium *Polfa, Cz.; Tarchomin, Hung.; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety; depression; insomnia; movement disorders; premedication; psychosomatic symptoms; spasticity.

Elenol *Gerda, Fr.*
Lindane (p.2045·3); amylocaine hydrochloride (p.1853·3).
Scabies.

Eleobron *Vamsler, Philipp.*
Guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Coughs.

Eleomox *Vamsler, Philipp.*
Amoxicillin (p.202·2).
Bacterial infections.

Eleparon *Sankyo, Braz.†.*
Silymarin (p.1452·2).
Liver disorders.

Eleprep *Norgine, Neth.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Elepril *Farmasa, Braz.*
⊗ Selegiline (p.818·1).
Parkinsonism.

Elepsin *Andromaco, Arg.*
Imipramine hydrochloride (p.400·3).
Depression.

Elequine *Janssen-Cilag, Mex.*
Levofloxacin (p.292·2).
Bacterial infections.

Elestat *Allergan, USA.*
Epinastine hydrochloride (p.579·3).
Allergic conjunctivitis.

Elestrin *Kenwood, USA.*
Estradiol (p.2097·2).
Menopausal disorders.

Eleu *Harras-Curarina, Ger.*
Siberian ginseng (p.2386·3).
Tonic.

Eleu-Kokk *Boehringer Ingelheim, Ger.*
Siberian ginseng root (p.2386·3).
Tonic.

Eleuphrat *Schering-Plough, Austral.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Eleutheroforce *Bioforce, Ger.*
Siberian ginseng root (p.2386·3).
Tonic.

Eleutherokokk *Arko, Ger.†.*
Siberian ginseng root (p.2386·3).
Tonic.

Eleutherosan *Alpa, Cz.†.*
Eleutherococcus (p.2386·3).
Tonic.

Eleu-Twardypharm *Twardy, Ger.†.*
Siberian ginseng (p.2386·3).
Tonic.

Eleva *Alphapharm, Austral.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder; social phobia.

Eleval *Drugtech, Chile.*
Sertraline (p.422·1).
Depression.

Elevat *Lagamed, S.Afr.†.*
⊗ Dronabinol (p.1728·1).
Anorexia with weight loss in AIDS; nausea and vomiting.

Elevex *Sensomed, Philipp.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Elevit *Bayer, Austral.; Bayer, Austria; Bayer, Braz.; Bayer, NZ; Roche, Switz.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement in pregnancy and breast feeding.

Elevit Geriatrico *Roche, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Elevit Pre-Nat *Bayer Consumer, Mex.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement during pregnancy and lactation.

Elevit Pronatal *Bayer, Cz.; Roche, Hong Kong; Bayer, Hung.; Bayer, Philipp.; Bayer, Pol.; Bayer, Port.; Rottendorf, Rus.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement in pregnancy and lactation.

Elevit Vitamine B_9 *Roche Nicholas, Fr.*
Multivitamin and mineral preparation (p.1922·1).

Elex E *Verla, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Elfaxone *MR Pharma, Neth.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Elferri *Sigma, India†.*
Vitamin B substances (p.1975·1); ferrous gluconate (p.1939·1); yeast (p.1998·3).
Tonic.

Elferri-Z *Svizera, India.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2); zinc sulfate (p.1999·2).
Iron and folic acid deficiency during pregnancy.

ELG Nil *Cadila, India.*
Cetirizine (p.571·1).

Elgadil *Altana, Spain.*
Urapidil hydrochloride (p.1419·3).
Hypertension.

Elgam *Sankyo, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Elgydium
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Arg.
Range of products containing nicomenthol hydrofluoride (p.1963·3) with or without chlorhexidine gluconate (p.1635·3).
Dental carries prophylaxis; dental hygiene.

Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore; Ceuta, UK.
Chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis; gum disorders; mouth disorders.

Elgydium Bicarbonate *Pierre Fabre Sante, Fr.†.*
Sodium bicarbonate (p.1673·2).
Dental hygiene.

Elgydium Dents Sensibiles *Pierre Fabre, Fr.*
Nicomethanol hydrofluoride (p.1963·3); chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis; sensitive gums.

Elgydium Dientes Sensibles *Pierre Fabre Oral Care, Arg.*
Nicomethanol hydrofluoride (p.1963·3); chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis; sensitive teeth.

Elgydium Junior *Pierre Fabre Oral Care, Arg.; Pierre Fabre, Fr.*
Nicomethanol hydrofluoride (p.1963·3).
Dental caries prophylaxis.

Elgydium Proteccion *Pierre Fabre Oral Care, Arg.*
Nicomethanol hydrofluoride (p.1963·3).
Dental caries prophylaxis.

Elgydium Protection Caries *Pierre Fabre, Fr.*
Nicomethanol hydrofluoride (p.1963·3).
Dental caries prophylaxis.

Elgyfluor
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Arg.†; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore.
Nicomethanol hydrofluoride (p.1963·3); chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis.

Pierre Fabre Sante, Fr.†.
Dental gel: Nicomethanol hydrofluoride (p.1963·3); chlorhexidine gluconate (p.1635·3).
Oral hygiene; sensitive gums.

Pierre Fabre Sante, Fr.†.
Toothpaste: Nicomethanol hydrofluoride (p.1963·3).
Oral hygiene.

Elgyfluor Junior *Pierre Fabre Sante, Fr.†.*
Nicomethanol hydrofluoride (p.1963·3).
Dental caries prophylaxis.

Elian *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Elibactin *Gerolymatos, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Eliben *Bennett, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Elica *Schering-Plough, Mex.; Schering-Plough, Philipp.; Schering-Plough, S.Afr.†; Essex, Spain.*
⊗ Mometasone furoate (p.1539·3).
Skin and scalp disorders.

Elicocin *Santen, Philipp.*
Erythromycin (p.269·2); colistimethate sodium (p.256·3).
Bacterial eye infections.

Elicodil *Menarini, Ital.†.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Elicor *Pharmanik (Φαρμανικ), Gr.†.*
Acetylcysteine (p.1548·2).
Respiratory disorders associated with viscous mucus.

Elidel *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Pimecrolimus (p.1609·1).
Atopic eczema.

Elidiur *BMS, Ital.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Elify *Medochemie, Cz.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Eligard *Raffo, Arg.; Mayne, Austral.; Sanofi Synthelabo, Canad.; Astellas, Cz.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Yamanouchi, Hung.; Mayne, NZ; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Astellas, Spain; Astellas, Swed.; Yamanouchi, Switz.; Sanofi Synthelabo, USA.*
⊗ Leuprorelin acetate (p.2111·1).
Formerly known as Leuprogel One-Month Depot in the *USA*.
Prostatic cancer.

Elimite *Allergan, USA.*
Permethrin (p.2048·2).
Scabies.

Elimitona *Brauer, Austral.*
Homoeopathic preparation.

Elimitona Slim & Detox *Brauer, Austral.*
Homoeopathic preparation.

Elimta *Lilly, Chile†.*
Pemetrexed disodium (p.762·1).
Malignant pleural mesothelioma; non-small cell lung cancer.

Elina *Reddy's, India.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Elinap *Kleva, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Elinatecan *Nolver, Venez.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Eliosid *New Research, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Elipa *Edol, Port.*
Ketorolac trometamol (p.74·2).
Allergic conjunctivitis; ocular inflammation.

Eliphorin *Elin, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Elisir Terpina *Teofarma, Ital.*
Terpin hydrate (p.1573·3); dropropizine (p.1557·3).
Coughs.

Elisor *BMS, Fr.*
Pravastatin sodium (p.1374·3).
Coronary atherosclerosis; hypercholesterolaemia.

Elissan *Serra Pamies, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Elitar *Daquimed, Port.*
Nabumetone (p.91·2).
Musculoskeletal, joint, and peri-articular disorders.

Elite *Bayer, Arg.; Bayer, Port.†.*
Test for glucose in blood (p.2314·1).
For use with Glucometer Elite.

Elitek *Sanofi Synthelabo, USA.*
Rasburicase (p.560·2).
Hyperuricaemia.

Eliten *BMS, Ital.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Elitiran *Mintlab, Chile.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Inflammation; pain.

Elitos *Andromaco, Arg.*
Oxeladin citrate (p.1567·1).
Coughs.

Elitos ET *Andromaco, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); tolu (p.1574·2).
Coughs.

Elityran *Vianex (Βιανεξ), Gr.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; female infertility; prostatic cancer; uterine fibroids.

Eliur *Northia, Arg.†.*
⊗ Furosemide (p.1292·1).

Eliwel *Sun, Rus.*
Amitriptyline hydrochloride (p.376·1).

Elixifilin *Martin, Spain.*
Theophylline (p.1140·1).
Obstructive airways disease.

Elixine *Saval, Chile.*
Theophylline (p.1140·1).
Obstructive airways disease.

Elixir 914 *Simoes, Braz.†.*
Potassium iodide (p.2169·2); star anise (p.2392·1).

Elixir Americano *Labortecne, Braz.†.*
Potassium iodide (p.2169·2).
Coughs.

Elixir Bonjean *Dexo, Fr.*
Melissa (p.2339·3); bitter-orange peel (p.2357·1); aniseed (p.2258·2); cumin seed; catechu (p.2278·2); peppermint oil (p.1761·2).
Digestive disorders.

Elixir Damiana and Saw Palmetto *Potter's, UK.*
Corn silk (p.2288·1); damiana (p.2292·1); saw palmetto (p.2192·3).
Tonic.

Elixir fortifiant *Phytomed, Switz.*
Ginkgo biloba; ginseng; calcium lactophosphate (p.1922·1).
Tonic.

Elixir frangulae compositum *Streuli, Switz.*
Frangula bark (p.1732·2).
Constipation.

Elixir Grez *Monin, Fr.†.*
Bitter orange (p.2357·1); gentian (p.2310·3); cinnamon (p.2283·1); citric acid monohydrate (p.2284·1).
Digestive disorders.

Elixir de Inhame *Goulart, Braz.†.*
Colocasia antiquorum; sarsaparilla (p.2383·3); honey (p.1948·2).

Elixir de Marinheiro *Phos-Kola, Braz.†.*
Potassium iodide (p.2169·2); cocillana (p.1554·3); sarsaparilla (p.2383·3); camphorated opium (p.105·1); anacardium occidentale.
Respiratory-tract congestion.

Elixir Paregorico *Catarinense, Braz.*
Camphorated opium (p.105·1).
Diarrhoea; opioid withdrawal syndrome.

Elixir de Passiflora *Sinterapico, Braz.†.*
Passion flower (p.2363·2); erythrina mulungu (p.2348·1); melissa (p.2339·3).

Elixir Spark *Poirier, Fr.*
Boldo (p.2267·2); cynara (p.2291·2).
Digestive disorders.

Elixir tonique N *Streuli, Switz.*
Condurango (p.2287·1); iron (p.1949·1).
Appetite loss; tonic.

Elixofilina *Schering, Mex.*
Theophylline (p.1140·1).

Elixomin *Cenci, USA†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Elixophyllin *Forest Pharmaceuticals, USA.*
Theophylline (p.1140·1).
Obstructive airways disease.

Elixophyllin-GG *Forest Pharmaceuticals, USA.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Elixophyllin-KI *Forest Pharmaceuticals, USA.*
Theophylline (p.1140·1); potassium iodide (p.2169·2).
Tenacious mucus in asthma and bronchitis.

ElixSure Childrens Congestion *Taro Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

ElixSure Childrens Cough *Taro Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Elizac *Mersifarma, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Elkapin *Pfizer, Ital.†.*
⊗ Etozolin (p.1284·2).
Hypertension; oedema.

ELKO-Mix *Baxter, Ger.*
Electrolyte infusion (p.1667·1).
Parenteral nutrition.

Elkostop *Minerva (Μινερβα), Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Elkotheran *Bros, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ellanco *Duopharma, Hong Kong.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Ellatun *Alcon, Ger.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Ell-Cranell alpha *Galderma, Ger.*
⊗ Alfatradiol (p.2082·1).
Alopecia androgenetica.

Ell-Cranell dexa *Galderma, Ger.*
⊗ Alfatradiol (p.2082·1); dexamethasone (p.1526·1).
Hair loss.

Elleacnelle *Stragen, Switz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Elleci *Lampugnani, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Ellence *Pharmacia Upjohn, USA.*
Epirubicin hydrochloride (p.716·1).
Breast cancer.

Elleste *Searle, Cz.†.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Elleste Duet Conti *Meda, UK.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Elleste-Duet *Meda, UK.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Elleste-Solo *Meda, UK.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Elle-Test *Gilbert, Fr.*
Pregnancy test (p.2372·1).

Ellgy *Hoe, Philipp.; Marketlink, Philipp.; Pharmalink, Philipp.; Hoe, Singapore.*
A range of moisturisers.

Ellgy H2O *Hoe, Malaysia.*
Saccharide isomerate; dipalmitoyl hydroxyproline.
Dry skin.

Ellgy Plus *Hoe, Malaysia.*
Saccharide isomerate; portulaca.
Dry, cracked heels.

Ellimans *Thornton & Ross, UK.*
Turpentine oil (p.2406·3); acetic acid (p.2244·2).
Musculoskeletal pain.

Elliots B *Orphan Medical, Israel.*
Electrolyte solution with glucose (p.1667·1).
Diluent for intrathecal administration of methotrexate sodium and cytarabine.

Ellisek-S *SJA, Gr.*
Butamirate (p.1553·1).
Cough.

Ellsurex *Galderma, Ger.*
Selenium sulfide (p.1613·1); colloidal sulfur (p.1614·1); allantoin (p.1588·1).
Scalp disorders.

Elmego *Chinta, Thai.*
Indometacin (p.66·3).
Musculoskeletal, joint, and peri-articular disorders.

Elmendos *GSK, Austral.; GSK, Ger.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Elmetacin *Stada, Cz.; Sankyo, Ger.; Sankyo, Hung.; Wilson, NZ†; Sankyo, Pol.; Ciclum, Port.; Pharmafrica, S.Afr.; Medinova, Switz.; Medinova, Thai.; Sankyo, Venez.*
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Elmetin *Medochemie, Hong Kong†.*
Mebendazole (p.148·3).
Worm infections.

Elmex
Note. This name is used for preparations of different composition.
GABA, Belg.; Vebas, Ital.
Olaflur (p.1959·2); dectaflur (p.1937·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

GABA, Port.
Dental gel: Olaflur (p.1959·2); sodium fluoride (p.1962·2); dectaflur (p.1937·1).
Dental caries prophylaxis.

GABA, Port.
Dental solution: Olaflur (p.1959·2); dectaflur (p.1937·1).
Dental caries prophylaxis.

GABA, Fr.†; Teva, Israel.
Mouthwash: Olaflur (p.1959·2); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

GABA, Fr.†.
Toothpaste: Olaflur (p.1959·2).
Dental caries prophylaxis.

Teva, Israel†.
Toothpaste: Olaflur (p.1959·2); hetaflur (p.1948·2).
Dental caries prophylaxis.

Teva, Israel†.
Toothpaste for sensitive teeth: Olaflur (p.1959·2).
Dental caries prophylaxis.

Gebro, Austria; GABA, Cz.; GABA, Fin.; GABA, Ger.; Biogal-Teva, Hung.; Teva, Israel; GABA, Neth.; GABA, Switz.
Topical gel: Olaflur (p.1959·2); dectaflur (p.1937·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis; sensitive teeth.

GABA, Ger.
Topical liquid: Olaflur (p.1959·2); dectaflur (p.1937·1).
Dental caries; sensitive teeth.

Gebro, Austria; GABA, Cz.; GABA, Fin.; Biogal-Teva, Hung.; GABA, Neth.; GABA, Switz.
Topical solution: Olaflur (p.1959·2); dectaflur (p.1937·1).
Dental caries prophylaxis; sensitive teeth.

Elmex Sensitive
Note. This name is used for preparations of different composition.
GABA, Fr.†.
Mouthwash: Olaflur (p.1959·2); potassium fluoride (p.1963·3).
Dental caries prophylaxis; dental hypersensitivity.

GABA, Fr.†.
Toothpaste: Olaflur (p.1959·2).
Dental caries prophylaxis; dental hypersensitivity.

Elmiron *Ivax, Arg.; Arthropharm, Austral.†; Janssen-Ortho, Canad.; Ivax, Hong Kong; Alza, USA.*
Pentosan polysulfate sodium (p.1367·1).
Interstitial cystitis.

Elo-admix *Fresenius Kabi, Austria.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Eloamin *Fresenius Kabi, Austria; Fresenius Kabi, Cz.†.*
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Elobact *GSK, Ger.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Elocin *Shiwa, Thai.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Elocom *Schering-Plough, Belg.; Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; Schering-Plough, Hung.; Schering-Plough, Israel; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, Spain; Essex, Switz.*
⊗ Mometasone furoate (p.1539·3).
Scalp disorders; skin disorders.

Elocom-S *Schering-Plough, Rus.*
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Skin disorders.

Elocon *Schering-Plough, Arg.; Schering-Plough, Austral.; Aesca, Austria; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Gr.; Fulford, India; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Ital.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Essex, Philipp.; Schering-Plough, S.Afr.; Schering-Plough, Swed.; Schering-Plough, Turk.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; atopic dermatitis; nasal polyps; psoriasis; seborrhoeic dermatitis; sinusitis; skin and scalp disorders.

Eloconex *Schering-Plough, Venez.†.*
⊗ Mometasone furoate (p.1539·3).
Asthma.

Elodrink *Stada, Austria.*
Sodium chloride; potassium chloride; sodium bicarbonate; glucose monohydrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Elofuran *Elofar, Braz.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Elohaes *Fresenius Kabi, Neth.; Fresenius Kabi, UK†.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Extracorporeal circulation; hypovolaemic shock; leucapheresis; plasma volume expansion.

Elohast *Fresenius Kabi, Austria; Fresenius Kabi, Cz.†.*
⊗ An etherified starch (p.1065·1) in sodium chloride or electrolytes.
Hypovolaemia; plasma volume expansion.

Elohes *Fresenius Kabi, Spain.*
⊗ An etherified starch (p.1065·1).
Plasma volume expansion.

Eloisin *Alcon Cusi, Spain.*
Eledoisin trifluoroacetate (p.2299·1).
Dry eyes.

Elolipid *Fresenius Kabi, Austria; Fresenius Kabi, Cz.†; Fresenius Kabi, Ital.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

ELO-MEL *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Hung.†.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Elomet *Schering-Plough, Hong Kong; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Port.; Schering-Plough, Singapore; Schering-Plough, Thai.; Schering-Plough, Venez.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Elon Dual Defense *Dartmouth, USA.*
Undecenoic acid (p.549·2).
Fungal skin infections.

Elongal *Royal, Chile†.*
Diazepam (p.986·3).
Epilepsy.

Elontril *GSK, Cz.; Bial, Port.*
Bupropion hydrochloride (p.383·1).
Depression.

Elopram *Recordati, Ital.*
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Elopro *Pharmacore, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Elorgan *Sanofi-Aventis, Spain.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Elorheo *Fresenius Kabi, Austria.*
⊗ Dextran 40 (p.1059·1) in electrolytes.
Fluid and electrolyte disorders.

Elosalic *White, Arg.†; Aesca, Austria; Essex, Ger.; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Pol.; Schering-Plough, S.Afr.; Schering-Plough, Swed.; Schering-Plough, Thai.†; Schering-Plough, Turk.; Schering-Plough, Venez.*
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Psoriasis; skin disorders.

Eloskin *Soho, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Elosone *Blau, Pol.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Elotin *Elofar, Braz.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Elotrace *Fresenius Kabi, Austria; Fresenius Kabi, Cz.*
An electrolyte (p.1667·1) and trace-element (p.1922·1) infusion.
Parenteral nutrition; trace element deficiency.

Elotrans *Stada, Ger.; Stada, Hung.; Helvepharm, Switz.*
Anhydrous glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Elovent *Aesca, Austria; Schering-Plough, Gr.†; Schering-Plough, Mex.; Schering-Plough, Neth.; Schering-Plough, Port.*
⊗ Mometasone furoate (p.1539·3).
Asthma; obstructive airways disease.

Elovera
Glenmark, India.
Aloe vera (p.1588·2); vitamin E acetate (p.1992·3).
Dry skin disorders.

Glenmark, Malaysia; Glenmark, Philipp.
Aloe vera (p.1588·2); vitamin E (p.1992·2).
Dry skin disorders; moisturiser.

Elovera-SPF *Glenmark, India.*
Aloe vera (p.1588·2); vitamin E acetate (p.1992·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Elox *Guardian, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Eloxatin *Sanofi Synthelabo, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Oxaliplatin (p.757·3).
Colorectal cancer; gastric cancer.

Eloxatine *Sanofi-Aventis, Fr.; Sanofi Winthrop, Rus.; Sanofi Synthelabo, Switz.*
Oxaliplatin (p.757·3).
Colorectal cancer; ovarian cancer.

Eloxil *Elin, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Elozell *Fresenius Kabi, Austria.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Cardiac disorders; digitalis toxicity; potassium and magnesium deficiency.

Elozell spezial *Fresenius Kabi, Austria.*
Potassium chloride (p.1684·3); potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Cardiac disorders; digitalis toxicity; potassium and magnesium deficiency.

Elozima *Elofar, Braz.†.*
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive disorders.

Elpegon *Elpen (Ελπεν), Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Elpi *Elea, Arg.*
Clofibrate (p.1246·2).
Hyperlipidaemias; thrombosis prophylaxis.

Elpi Lip *Elea, Arg.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Elpicef *Fahrenheit, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Elpradil *Streuli, Switz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Elpradil HCT *Streuli, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Elprazol *Pharlab, Braz.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Elroquil N *Rodleben, Ger.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety disorders; premedication; pruritus; sleep disorders.

Elrox *Biopharm, Rus.*
Roxithromycin (p.331·1).
Bacterial infections.

Elsazym
Note. This name is used for preparations of different composition.
Otto, Indon.
Oral granules: Pancreatin (p.2360·1); vitamin A; vitamin B ; folic acid (p.1922·1).
Digestive disorders.

Otto, Indon.
Tablets: Pancreatin (p.2360·1); bromelains (p.2269·1); dimeticone (p.1770·2).
Dyspepsia; supplement following gastrointestinal surgery.

Elsep *Wyeth, Fr.*
Mitoxantrone hydrochloride (p.754·1).
Multiple sclerosis.

Elspar *MSD, Braz.; MSD, Hong Kong†; Merck, USA.*
Asparaginase (p.682·1).
Acute lymphocytic leukaemia; malignant neoplasms.

Elstatin *Glenmark, Singapore.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Eltacin *Biotiki, Rus.*
Glycine (p.1947·3); glutamic acid (p.1947·1); cystine (p.1937·1).
Heart failure.

Eltair *Scharper, Ital.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore; Douglas, Thai.; TTN, Thai.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Elteans *Jaldes, Fr.*
Salmon oil (p.1362·1); borage oil (p.2267·3); carrot and soya oils; vitamin E.
Nutritional fatty acid supplement.

Elthyro *MJ Biopharm, Thai.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Elthyrone *Abbott, Belg.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Eltocin *Ipca, India.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eltor *Aventis, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion.

Eltroxin *GSK, Canad.; GSK, Cz.; GSK, Denm.; Sigma, Hong Kong; GSK, India; Goldshield, Irl.; GSK, Israel; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, S.Afr.; GSK, Singapore; GSK, Thai.; Goldshield, UK.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; thyroid cancer.

Eltroxine *Sigma-Tau, Switz.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Elucent Skin Refining Day Cream *Ego, Austral.*
SPF 20: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); avobenzone (p.1589·3); emollients.
Dry skin; sunscreen.

Eludril
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Arg.; Dolisos, Belg.; Pierre Fabre, Port.; Pierre Fabre, Singapore; Pierre Fabre, Spain.
Chlorhexidine gluconate (p.1635·3); chlorobutanol (p.1639·2).
Mouth and throat disorders.

Pierre Fabre, Rus.
Chlorhexidine gluconate (p.1635·3); chlorobutanol (p.1639·2); chloroform (p.1781·1).
Mouth disorders.

Pierre Fabre, Fr.
Mouth spray: Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Pierre Fabre, Switz.
Mouth and throat spray: Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Pierre Fabre, Fr.; Pierre Fabre, Switz.; Pierre Fabre, UK.
Mouthwash: Chlorhexidine gluconate (p.1635·3); chlorobutanol (p.1639·2).
Mouth and throat disorders.

Pierre Fabre, UK.
Throat spray: Chlorhexidine gluconate (p.1635·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Elugan *Asche Chiesi, Ger.*
Simeticone (p.1770·2).
Gastrointestinal disorders with excess gas.

Elugel *Pierre Fabre Oral Care, Arg.; Pierre Fabre, Fr.; Pierre Fabre, Rus.; Pierre Fabre, Singapore.*
Chlorhexidine gluconate (p.1635·3).
Gum disorders; mouth infections; oral hygiene.

Elum *Farmasa, Braz.*
Cloxazolam (p.981·1).
Anxiety.

Elumatic *CIS, Neth.; CIS, Port.*
Technetium-99m (p.2055·3).
Radionuclide imaging.

Elusanes *Dolisos, Fr.†.*
A range of herbal preparations.

Elusanes Harpagesic *Plantes et Medecines, Fr.*
Devil's claw root (p.39·1).
Joint pain.

Elutit-Calcium *Felgentrager, Ger.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Elutit-Natrium *Felgentrager, Ger.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Elvecis *Ivax, Arg.*
Cisplatin (p.698·2).
Malignant neoplasms.

Elvefocal *Ivax, Arg.*
Calcium folinate (p.1943·3).

Elven *Actavis, Hung.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Elvenavir *Ivax, Arg.*
Indinavir sulfate (p.882·2).
HIV infection.

Elvesil *Biomedica-Chemica, Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Elvorine *Wyeth, Belg.; Wyeth, Fr.*
Calcium levofolinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; adjuvant to fluorouracil therapy; folic acid antagonist toxicity; prevention of toxicity induced by methotrexate and other dihydrofolate reductase inhibitors.

E-Lyte *Fleet, Austral.†; Regional Health, NZ†.*
Sodium chloride; anhydrous citric acid; sodium bicarbonate; potassium chloride; anhydrous glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Elyzol
Chemomedica, Austria; Colgate-Palmolive, Denm.; Colgate-Palmolive, Fr.; Colgate-Palmolive, Ger.; CTI, Israel; Colgate-Palmolive, Ital.; Colgate-Palmolive, Norw.; Colgate-Palmolive, Switz.; Colgate-Palmolive, UK.
Metronidazole benzoate (p.837·1).
Bacterial mouth infections; periodontitis.

Colgate-Palmolive, Fin.; Alpharma, Hong Kong; Dumex-Alpharma, Thai.†.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; bacterial mouth infections; trichomoniasis.

Alpharma, Mex.; Alpharma, Swed.†; Colgate-Palmolive, Swed.†.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; rosacea; trichomoniasis.

Elyzol Dental *Colgate, Gr.*
Metronidazole benzoate (p.837·1).
Bacterial mouth infections.

Elzogram *Lilly, Ger.†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Elzym
Note. This name is used for preparations of different composition.
Sankyo, Thai.†.
Enzyme concentrate from *Aspergillus oryzae*; simeticone (p.1770·2); ethaverine hydrochloride (p.2299·3).
Gastrointestinal disorders with excess gas; preparation of gastrointestinal tract for radiological examination.

Sankyo, Venez.
Enzymes from *Aspergillus oryzae*; simeticone (p.1770·2).
Digestive disorders; flatulence.

Emadine *Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Neth.; Alcon, Norw.; Alcon, Pol.; Alcon, Port.; Alcon, S.Afr.; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA.*
Emedastine fumarate (p.579·2).
Allergic conjunctivitis.

Emaftol *Ogna, Ital.*
Policresulen (p.1077·2).
Mouth disinfection.

Emagel *Pierrel, Ital.*
⊗ Polygeline (p.1077·2).
Plasma volume expansion.

Emagrevit *Vitermat, Braz.†.*
Bladderwrack (p.2384·2); cynara (p.2291·2); cascara (p.1715·2); centella (p.1592·3); bearberry (p.2263·3); dried yeast (p.1998·3); boldo (p.2267·2); passion flower (p.2363·2).
Obesity.

Emagrex *Dinafarma, Braz.†.*
Bladderwrack (p.2384·2); thyroid (p.2177·1); bile salts (p.2266·2); phenolphthalein (p.1762·1).
Constipation; obesity.

Emagrip *Chemopharma, Chile.*
Dihydroergotamine mesilate (p.618·2); paracetamol (p.108·1); caffeine (p.1116·3).
Vascular headache.

Emama *Eurofarma, Braz.*
dl-Alpha tocoferil acetate (p.1992·3).

Emanthal *MM, India.*
Albendazole (p.139·2).
Worm infections.

Emantid *MM, India†.*
Furazolidone (p.834·3); berberine hydrochloride (p.2264·3); belladonna (p.2263·3).
Gastrointestinal infections.

Emarfen *Minerva (Μινέρβα), Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Emasex A *Eurim, Ger.†.*
Bamethan sulfate (p.1222·3).
Erectile dysfunction.

Emasex-A vitex *Eurim, Ger.*
Homoeopathic preparation.

Emasex-N *Eurim, Ger.†.*
Bamethan sulfate (p.1222·3); benzyl nicotinate (p.28·1).
Erectile dysfunction; tonic.

Emazian B12 *Pfizer, Ital.†.*
Thiamine hydrochloride (p.1976·1); riboflavin (p.1977·2); panthenol (p.2362·1); nicotinamide (p.1957·3); calcium folinate (p.1943·3); cyanocobalamin (p.1980·2).
Deficiency states; macrocytic anaemia.

EMB *Fatol, Ger.; Riemser, Ger.; Wernigerode, Ger.; Fatol, Hong Kong.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Embeline *Healthpoint, USA†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Embial *Merck, Ger.†.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

EMB-INH *Fatol, Ger.†.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Tuberculosis.

Embol *Yung Shin, Thai.*
Piracetam (p.368·2).
Alcohol withdrawal syndrome; cerebrovascular disorders; mental function impairment.

Embolex NM *Novartis, Ger.†.*
Certoparin sodium (p.1242·3); dihydroergotamine mesilate (p.618·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Thromboembolism prophylaxis.

Embrex *Andrx, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Embrocacion Gras *Quimifar, Spain.*
⊗ Alcohol (p.1625·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3); capsicum (p.2276·2).
Muscle and joint pain.

Emcolol *Gerard, Irl.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Emconcor *Merck, Belg.; Merck, Denm.; Merck, Fin.; Merck, Norw.; Merck, Spain; Merck, Swed.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Emconcor Comp *Merck, Fin.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Emcor *Merck, Irl.; Merck, Neth.; Merck, UK.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Emcoretic *Merck, Belg.; Merck, Neth.; Merck, Spain.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Emcredil *Unichem, India.*
Ethacridine lactate (p.1625·1).
Termination of pregnancy.

Emcyt *Pfizer, Canad.; Pfizer, Mex.; Pharmacia Upjohn, USA.*
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Emdalen *Merck, S.Afr.*
Lofepramine hydrochloride (p.407·1).
Depression.

Emdar *Merck, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Emebrid *Pharlab, Braz.†.*
Dimenhydrinate (p.576·2).
Nausea and vomiting; vertigo.

Emecort *Merck, Braz.†.*
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Emedal *Target, Gr.*
Metronidazole (p.837·1).
Acne rosacea.

Emediba *Diba, Mex.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Nausea; vertigo; vomiting.

Emedrin N *Streuli, Switz.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Emedur
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Turk.
Injection; tablets: Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Sanofi Synthelabo, Turk.
Suppositories: Trimethobenzamide hydrochloride (p.592·2); benzocaine (p.1854·1).
Nausea and vomiting.

Emedyl *Montavit, Austria.*
Dimenhydrinate (p.576·2).
Nausea and vomiting; vestibular disorders.

Emegar *Stada, Cz.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Emend
Note. This name is used for preparations of different composition.
MSD, Arg.; MSD, Austral.; MSD, Belg.; MSD, Braz.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, NZ; MSD, Norw.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, UK; Merck, USA; MSD, Venez.
Aprepitant (p.1708·2).
Nausea and vomiting associated with cancer chemotherapy.

Merck, USA.
Injection: Fosaprepitant meglumine (p.1732·1).
Nausea and vomiting associated with cancer chemotherapy.

Emeproton *Cantabria, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Emeral *Nova Argentia, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Emeran *Erlimpex, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Emergen *Laboratorios Chile, Chile.*
Sertraline (p.422·1).
Depression.

Emergent-Ez *Healthfirst, USA.*
Combination pack: ⊗ 2 Ampoules, adrenaline (p.1203·2); 1 ampoule, aminophylline (p.1114·2); 3 inhalants, ammonia (p.2256·1); 2 inhalants, amyl nitrite (p.1437·3); 2 ampoules, atropine (p.1219·2); 2 ampoules, diphenhydramine hydrochloride (Benadryl) (p.577·2); tablets, glyceryl trinitrate (p.1296·2); 1 vial, hydrocortisone sodium succinate (Solu-Cortef) (p.1536·1); 1 ampoule, pentazocine lactate (Talwin) (p.112·3); 1 ampoule, trimethobenzamide hydrochloride (Tigan) (p.592·2); 2 ampoules, diazepam (Valium) (p.986·3); 2 ampoules, mephentermine sulfate (Wyamine) (p.1332·3).
Emergency treatment.

Emerxil *Omega, Belg.*
Glycol salicylate (p.62·3); lidocaine hydrochloride (p.1862·3); methyl nicotinate (p.85·3).
Inflammation; pain.

Emesafene *Ace, Neth.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Nausea; vomiting.

Emesan *Lindopharm, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Nausea; vomiting.

Emeset *Cipla, Cz.; Cipla, India; Cipla, Thai.; Cipla, Venez.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Emeside *Chemidex, UK.*
Ethosuximide (p.479·3).
Absence seizures; myoclonic seizures.

Emestar Mono *Trommsdorff, Ger.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Emestar plus *Trommsdorff, Ger.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Emetal *Asian Pharm, Thai.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Emetic *Elofar, Braz.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Emetostop *Specifar (Σπεσιφαρ), Gr.*
Meclozine hydrochloride (p.584·3).
Vertigo.

Emetrol
Note. This name is used for preparations of different composition.
Aventis, Austral.†; Sanofi Winthrop, USA.
Fructose (p.1945·1); glucose (p.1945·3); phosphoric acid (p.2367·1).
Nausea; vomiting.

Gemballa, Braz.†.
Metoclopramide (p.1747·3); pyridoxine (p.1979·1).
Nausea and vomiting.

Aspen Consumer, S.Afr.
Sucrose (p.1969·2); phosphoric acid (p.2367·1).
Nausea.

Emetron *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Em-eukal *Soldan, Ger.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); pumilio pine oil (p.2376·3); thyme oil (p.2401·2); turpentine oil (p.2406·3); camphor (p.2273·2).
Coughs and cold symptoms.

Em-eukal Husten- und Brusttee *Soldan, Ger.†.*
Althaea (p.2253·3); fennel (p.2302·3); aniseed (p.2258·2); liquorice (p.1740·3); fennel oil (p.2303·1); anise oil (p.2258·2).
Coughs.

Emex *Mirren, S.Afr.*
Invert sugar (p.1949·1); phosphoric acid (p.2367·1).
Nausea.

Emflam *Merck, India.*
Ibuprofen (p.64·2).
Inflammation; pain.

Emflam Plus *Merck, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; pain.

Emflex *Merck, UK.*
Acemetacin (p.15·1).
Inflammation; pain; rheumatoid arthritis.

Emfor *Stadmed, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Emforal *Remedica, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; migraine; obstructive cardiomyopathy; tremor.

Emfrastop *Iapharm, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Emgecard *Kwizda, Austria.*
Magnesium aspartate hydrochloride (p.1680·1).
Magnesium deficiency; pre-eclampsia.

Emgel *Glaxo Wellcome, USA†.*
Erythromycin (p.269·2).
Acne.

Emgesan *Recip, Fin.; Recip, Swed.*
Magnesium hydroxide (p.1743·2).
Magnesium deficiency; renal calculi.

Emibion *Guardian, Indon.*
Ferrous gluconate (p.1939·1); folic acid; manganese sulfate; copper sulfate; vitamin B (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Emican *Alter, Spain†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Emicilin *EMS, Braz.*
⊗ Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Probenecid (p.558·2) is included in some of preparations to reduce renal tubular excretion of the antibiotic.
Bacterial infections.

Emidoxin *Magis, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Emidoxyn *Shreya, India.*
Prochlorperazine maleate (p.1020·1).
Nausea and vomiting.

Emidrat *EMS, Braz.*
Sodium chloride; potassium chloride; sodium citrate; sodium phosphate; calcium lactate; magnesium citrate; citric acid; saccharin sodium; glucose (p.1672·2).
Diarrhoea; oral rehydration solution.

Emiken *Kener, Mex.*
Domperidone (p.1726·2).
Nausea and vomiting.

E-Mil *Fontovit, Braz.†.*
dl-Alpha tocoferil acetate (p.1992·3).

Emilace *Astellas, Jpn.*
Nemonapride (p.1011·1).
Schizophrenia.

Emin *Cipla, India.*
Promethazine teoclate (p.588·3).
Nausea and vomiting.

Eminase *Carinopharm, Austria; Tramedico, Belg.†; Carinopharm, Ger.; Roberts, Israel†; Tramedico, Neth.†.*
Anistreplase (p.1216·1).
Myocardial infarction.

Emineton *Kalbe, Indon.*
Ferrous fumarate (p.1938·3); copper sulfate; cobalt sulfate; manganese sulfate; vitamin B ; vitamin B ; vitamin E; folic acid; calcium hydrogen phosphate (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Eminox *Pharmacore, Indon.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Emisgenta *EMS, Braz.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Emistin *EMS, Braz.*
⊗ Clemastine fumarate (p.573·2); dexamethasone acetate (p.1526·1).
Hypersensitivity reactions.

Emital *Ivax, Irl.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Emitex *Garec, S.Afr.†.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea; vestibular disorders; vomiting.

Emivox *Phoenix, Arg.†.*
Ondansetron (p.1756·3).
Vomiting.

Emizol *Lemery, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Emla *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Emlapatch *AstraZeneca, Fr.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Emlyte *MM, India.*
Sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Oral rehydration therapy.

Emlyte-S *MM, India.*
Sodium chloride; sodium citrate; potassium chloride; glucose; lactobacillus (p.1672·2).
Oral rehydration therapy.

Em-medical
Note. This name is used for preparations of different composition.
Soldan, Ger.†.
Oral drops: Eucalyptus leaf (p.2301·2); aniseed (p.2258·2); fennel (p.2302·3); thyme (p.2401·1).
Formerly known as Em-eukal.
Coughs.

Soldan, Ger.†.
Oral liquid: Dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1); cetylpyridinium chloride (p.1635·1); anise oil (p.2258·2); gypsophila saponin; thymol (p.1664·3).
Formerly known as Em-eukal.
Catarrh; coughs.

Em-medical forte *Soldan, Ger.†.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly known as Em-eukal forte N.
Catarrh; coughs.

Em-medical Mono *Soldan, Ger.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Formerly known as Em-eukal Mono.
Rhinitis.

Emmenoiasi *Titanpharma, Ital.*
Centella (p.1592·3); couch-grass (p.2288·2); lupulus (p.2335·2); melissa (p.2339·3); zinc (p.1999·1); copper (p.1935·2).
Nutritional supplement.

Emmenovis *Vitoria, Port.†.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Menstrual disorders; recurrent miscarriage.

Emnorm *Ipca, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Emoantitossina *Piam, Ital.†.*
Calcium folinate (p.1943·3); cyanocobalamin (p.1980·2); monophosphothiamine chloride (p.1976·3); riboflavin sodium phosphate (p.1977·3); pyridoxine hydrochloride (p.1978·2); nicotinamide (p.1957·3); panthenol (p.2362·1).
Anaemias; deficiency states.

Emocal *Gea, Fin.†.*
Citalopram hydrobromide (p.385·3).
Depression.

Emochol *Emo-Farm, Pol.†.*
Naproxen (p.92·3).
Musculoskeletal, joint, and soft-tissue disorders.

Emoclot *Kedrion, Arg.; Biosano, Chile; ISI, Cz.†; Kedrion, Ital.; Serono, Mex.†; Kedrion, Port.; Kedrion, Rus.; Onko, Turk.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Emo-Cort *Trans Canaderm, Canad.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Emocrat forte *Hevert, Ger.†.*
⊗ Crataegus; rutoside sodium sulfate (p.2305·2).
Arrhythmias; ischaemic heart disease.

Emocrat N *Hevert, Ger.*
Homoeopathic preparation.

Emodan *Korea United, Philipp.*
Ondansetron hydrochloride (p.1756·3).
Nausea; vomiting.

Emoderm *Theraskin, Braz.*
⊗ Urea (p.1620·2).
Skin disorders.

Emofix *DMG, Ital.*
Haemostatic barrier ointment with collagen (p.2286·1).

Emoform
Note. This name is used for preparations of different composition.
Nycomed, Braz.; Wild, Switz.
Electrolytes (p.1667·1).
Hypersensitive teeth; oral hygiene.

Pfizer Sante, Fr.
Stannous fluoride (p.1967·3).
Dental caries prophylaxis; sensitive gums.

Emoform Actisens *Altana, Ital.†.*
⊗ Titanium dioxide (p.1617·3); sodium fluoride (p.1962·2); potassium nitrate (p.1658·3).
Dental caries prophylaxis; sensitive teeth.

Emoform AP *Nycomed, Braz.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Emoform AT *Nycomed, Braz.*
Sodium monofluorophosphate (p.1964·3); potassium pyrophosphate.
Dental caries prophylaxis.

Emoform Clorofila *Nycomed, Braz.*
Electrolytes (p.1667·1); chlorophyll (p.1471·1).
Dental caries prophylaxis.

Emoform Dents Sensibles *Pfizer Sante, Fr.*
⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis; sensitive gums.

Emoform Dientes Sensibles *Gador, Arg.*
Electrolytes (p.1667·1).
Dental caries prophylaxis; hypersensitive teeth.

Emoform Gencives *Pfizer Sante, Fr.*
⊗ Potassium nitrate (p.1658·3); sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1).
Gingivitis; sensitive gums.

Emoform Total *Gador, Arg.*
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3); triclosan (p.1665·2); etidronate disodium (p.1097·1); sodium bicarbonate (p.1673·2); xylitol (p.1998·2).
Formerly contained sodium fluoride, sodium monofluorophosphate, and triclosan.
Dental caries prophylaxis.

Emoform-F au fluor *Wild, Switz.*
Electrolytes (p.1667·1); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis; oral hygiene; sensitive teeth.

Emoform-Tat *Altana, Ital.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental tartar.

Emoklar *Savio, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Emol *Fischer, Israel.*
Bath additive.
Dry skin.

Emolan
Note. This name is used for preparations of different composition.
Megahealth, Chile; Vivax Gynopharm, Venez.
Soap substitute.
Dermatitis.

Megahealth, Chile.
SPF 35: Octinoxate (p.1608·2); amiloxate (p.1589·1); avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Emolan Barra Protectora Labial *Megahealth, Chile.*
SPF 30: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Emolan Bloqueador Solar *Megahealth, Chile.*
SPF 60: Enzacamene (p.1597·1); titanium dioxide (p.1617·3); ensulizole (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Emolan Fotoprotector Mineral *Megahealth, Chile.*
SPF 60: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Emolan H *Megahealth, Chile.*
Padimate O (p.1609·1).
Sunscreen.

Emolan Protector Solar *Megahealth, Chile.*
SPF 20: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Emolan Spray *Megahealth, Chile.*
SPF 50: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Emolan Ultra *Megahealth, Chile.*
SPF 30: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Emolin Neo
Note. This name is used for preparations of different composition.
Medihealth, Mex.
Tocoferil acetate (p.1992·3); dexpanthenol (p.2362·1); hyaluronic acid (p.2320·1).
Dry skin; skin irritation.

Roemmers Medihe, Venez.
Moisturiser.

Emollia *Gordon, USA.*
Emollient and moisturiser.

Emollin *CD Medical, UK.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Emollient.

Emolytar *Stiefel, Spain.*
Tar (p.1616·2); juniper oil (p.2328·3); coal tar (p.1616·2); arachis oil (p.2259·1).
Skin disorders.

Emonorm *Aesculapius, Ital.†.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Emopon *Terapeutico, Ital.*
Calcium folinate (p.1943·3); cyanocobalamin (p.1980·2); ferric ammonium citrate (p.1938·1); thiamine hydrochloride (p.1976·1); nicotinamide (p.1957·3).
Macrocytic anaemia; tonic.

Emopremarin *Wyeth Lederle, Ital.†.*
Conjugated oestrogens (p.2087·2).
Haemorrhage.

Emorect *Emo-Farm, Pol.*
Aesculus (p.2248·2); arnica (p.2260·2).
Haematoma; oedema; phlebitis; venous insufficiency.

Emoren *Novasorel, Ital.*
Oxetacaine hydrochloride (p.1867·3).
Haemorrhoids.

Emorril *Chefaro, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); lidocaine hydrochloride (p.1862·3).
Adjunct in anorectal surgery; haemorrhoids.

Emortrofine *Alphrema, Ital.*
Vitamin E (p.1992·2); bioflavonoids (p.2304·1).
Capillary disorders; haemorrhoids.

Emorzim *Pfizer, Gr.*
Carboplatin (p.693·1).
Ovarian cancer; small-cell lung cancer.

Emosint *Kedrion, Arg.; Kedrion, Ital.; Kedrion, Rus.*
Desmopressin acetate (p.2185·3).
Haemophilia; von Willebrand's disease.

Emotion *Picot, Fr.*
Pregnancy test (p.2372·1).

Emotival
Note. This name is used for preparations of different composition.
Ivax, Arg.
Lorazepam (p.1004·1).
Anxiety; insomnia.

Klinger, Braz.†.
St John's wort (p.422·3).
Depression.

Emoton *Tentan, Switz.*
Agnus castus (p.2249·1).
Premenstrual disorders.

Emotpin *Meda, Swed.†.*
Aspirin (p.20·3).
Fever; pain.

Emotrip *Ipca, India.*
Amitriptyline (p.376·1); chlordiazepoxide (p.968·1).
Anxiety; depression.

Emovat *GSK, Denm.; GSK, Fin.; GSK, Swed.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Emovate *GSK, Austria; GSK, Ger.; GSK, Neth.; Glaxo Wellcome, Port.; UCB, Spain; GSK, Switz.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Emovis *Boniscontro & Gazzone, Ital.†.*
Calcium folinate (p.1943·3).
Anaemias; antidote to overdosage with folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Emoxen *Walmark, Cz.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders.

Emoxiron *Caber, Ital.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Empacod *Altana Madaus, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Empaped *Altana Madaus, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Empatil *Liferpal, Mex.*
Carisoprodol (p.1894·1); diclofenac (p.44·2).

Empecid *Bayer Consumer, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections; vaginal candidiasis.

Empecid Cort *Bayer, Arg.*
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Infected skin disorders.

Empecid Pie *Bayer Consumer, Arg.*
Bifonazole (p.527·3); crotamiton (p.1593·2); lidocaine (p.1862·3); enoxolone (p.50·1); menthol (p.2340·1).
Tinea pedis.

Empeecetin *Nufarindo, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Empenox *Demo, Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Emperal *Orion, Denm.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; irritable bowel syndrome; nausea and vomiting.

Empirin *Wellcome, USA.*
Aspirin (p.20·3).
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Empirin with Codeine *Wellcome, USA.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Pain.

Empirol *Norma (Νορμα), Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Emplasto Monopolis *Grisi, Mex.*
Copper acetate (p.2287·3); lead monoxide (p.2332·2).
Medicated dressing.

Emplatre antirhumatismal Isola Capsicum N *IVF, Switz.*
Capsaicin (p.32·3).
Musculoskeletal and joint pain; neuralgia.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Emplatre antirhumatismal Isola Capsicum N a l'huile essentielle de Gaultherie *IVF, Switz.*
Capsaicin (p.32·3); gaultheria.
Musculoskeletal and joint pain; neuralgia.

Emplatre Etoile *IVF, Switz.†.*
Capsaicin (p.32·3).
Musculoskeletal pain; rheumatism.

Emplatre Etoile salicyle *IVF, Switz.†.*
Capsaicin (p.32·3); methyl salicylate (p.85·3).
Musculoskeletal and joint pain; rheumatism.

Emplusal *Pharmacare, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Emportal *Novartis Consumer, Spain.*
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

Empracet *GSK, Canad.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Empurine *Dabur, Philipp.; Dabur, Thai.*
Mercaptopurine (p.744·1).
Crohn's disease; inflammatory bowel disease; leukaemias; ulcerative colitis.

Empynase *Kaken, Jpn.*
Pronase (p.2373·3).
Inflammation; respiratory-tract congestion.

Emquin *Merck, India.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Emren *Gedeon Richter, Hung.*
Ramipril (p.1385·3).
Hypertension.

EMS Expectorante *EMS, Braz.*
⊗ Guaifenesin (p.1561·3); etafedrine hydrochloride (p.1560·2); bufylline (p.1116·3); doxylamine succinate (p.578·2).
Respiratory-tract disorders.

Emsam *BMS, USA.*
⊗ Selegiline (p.818·1).
Depression.

Emscab *MM, India.*
Lindane (p.2045·3); aminoacridine hydrochloride (p.1625·1).
Pediculosis; scabies.

Emscort *EMS, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Emselex *Novartis, Cz.; Bayer, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Neth.; Novartis, Swed.; Novartis, UK.*
Darifenacin hydrobromide (p.2185·1).
Bladder instability.

Emser *Siemens, Ger.*
Natural emser salt (see Emser Salz) in isotonic solution.
Nasal congestion.

Emser Inhalationslosung *Siemens, Ger.*
Natural emser salt (see Emser Salz) in isotonic solution.
Respiratory-tract disorders.

Emser Nasensalbe *Hexal, Austria.*
Natural emser salt; azulene (p.2262·3); nutmeg oil (p.2355·3); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); cedar wood oil (p.2278·3); turpentine oil (p.2406·3); camphor (p.2273·2).
Colds; hay fever.

Emser Nasensalbe N *Siemens, Ger.†.*
Natural emser salz; azulene (p.2262·3); nutmeg oil (p.2355·3); pine needle oil (p.2368·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); cedar wood oil (p.2278·3); camphor (p.2273·2); turpentine oil (p.2406·3).
Colds; hay fever.

Emser Pastillen *Hexal, Austria; Siemens, Ger.*
Natural emser salt.
Respiratory-tract disorders; throat disorders.

Emser Pastillen mit Menthol *Hexal, Austria.*
Natural emser salt; menthol (p.2340·1); peppermint oil (p.1761·2).
Respiratory-tract disorders.

Emser Salz *Siemens, Ger.*
Natural emser salt (containing lithium, sodium, potassium, magnesium, calcium, manganese, ferrous, ferric, fluoride, chloride, bromide, iodide, nitrite, sulfate, bicarbonate, and carbonate ions).
Upper respiratory-tract disorders.

Emser sensitiv *Siemens, Ger.*
Natural emser salt (see Emser Salz).
Nasal congestion; rhinitis.

Emsgrip *EMS, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Ems-Max *EMS, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Emsogen *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Nutricia, NZ†; Scientific Hospital Supplies, NZ†.*
Preparation for enteral nutrition (p.1922·1).

Emsyn *Aspen, S.Afr.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Emthexat *Nycomed, Fin.†; Nycomed, Norw.; Nycomed, Swed.†.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Emthexate
Nycomed, Austria; Teva, Belg.; Nettopharma, Denm.†; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.
Methotrexate (p.745·2).
Auto-immune disorders; graft-versus-host disease; malignant neoplasms; psoriasis; rheumatoid arthritis.

Asta Oncologia, Braz.
Methotrexate (p.745·2) or methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

NZ Medical & Scientific, NZ; Pharmachemie, Neth.; Teva, Spain; Med, Turk.
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Emtriva *Gador, Arg.; Gilead, Austral.; UCB, Belg.; Gilead, Cz.; Gilead, Denm.; Orphan, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hung.; Gilead, Irl.; Gilead, Ital.; Stendhal, Mex.; Gilead, NZ; Gilead, Neth.; Gilead, Norw.; Gilead, Pol.; Gilead, Port.; Gilead, Spain; Swedish Orphan, Swed.; Chemedica, Switz.; Gilead, UK; Gilead, USA.*
Emtricitabine (p.873·3).
HIV infection.

Emulave
Note. This name is used for preparations of different composition.
Ovelle, Irl.
Soap substitute.

Johnson & Johnson, Ital.; Dermoteca, Port.
Avena (p.2262·1).
Emollient; soap substitute.

Emulax
Note. This name is used for preparations of different composition.
AstraZeneca, Swed.
Cascara (p.1715·2); docusate sodium (p.1725·1).
Constipation.

British Dispensary, Thai.
Oral liquid: Liquid paraffin (p.2030·3); phenolphthalein (p.1762·1); carmellose sodium (p.2142·1).
Constipation.

British Dispensary, Thai.
Tablets: Bisacodyl (p.1710·1).
Constipation.

Emuliquen Laxante *Lainco, Spain.*
Sodium picosulfate (p.1771·1); liquid paraffin (p.2030·3).
Constipation.

Emuliquen Simple *Lainco, Spain.*
Liquid paraffin (p.2030·3).
Constipation.

Emulsan *Pisa, Mex.†.*
Lipid infusion (p.1922·1).

Emulsao de Lipidos *Grifols, Port.*
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid emulsion for parenteral nutrition.

Emulsao Scott *GSK, Braz.*
Cod-liver oil; soya oil; vitamin A; vitamin D; electrolytes (p.1922·1).
Nutritional supplement.

Emulsao Universal *Merck, Braz.*
Emollient.

Emulsiderm *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Isopropyl myristate (p.2029·3); liquid paraffin (p.2030·3); benzalkonium chloride (p.1629·1).
Dry skin disorders.

E-Mulsin *Mucos, Ger.†.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Emulsion de Scott *GSK, Mex.*
Cod-liver oil (p.1935·2); calcium phosphate (p.1676·2).
Vitamin A, vitamin D, and calcium supplement.

Emulsoil *Paddock, USA.*
Castor oil (p.2278·1).
Constipation.

Emu-V *Pharmacia, Cz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Emuxel *Dynamic, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Emvit CAP *Cadila, India.*
Amino acids; vitamins (p.1922·1).
Dietary supplement.

E-Mycin
Alphapharm, Austral.; Pacific, NZ.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Pharmacia, Hong Kong†; Knoll, USA.
Erythromycin (p.269·2).
Bacterial infections.

Themis, India.
Erythromycin estolate (p.269·3).
Bacterial infections.

Emzaclear *Meyer Zall, S.Afr.*
Salicylic acid (p.1612·2).
Acne.

Emzok
Ivax, Cz.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

Galena, Rus.
⊗ Metoprolol (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

En *Abbott, Ital.*
Delorazepam (p.986·1).
Anxiety disorders; epilepsy; premedication; sleep disorders.

Ena *Hennig, Ger.; Stadmed, India.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

ena-basan *Schonenberger, Switz.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enabeta *Betapharm, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enabeta comp *Betapharm, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enablex *Novartis, S.Afr.; Novartis, USA.*
Darifenacin hydrobromide (p.2185·1).
Bladder instability.

Enabran *Casasco, Arg.*
Haloperidol (p.1000·2).
Psychoses; Tourette's syndrome.

Enac *Hexal, Austria.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Enacard *Approved Prescription Services, UK†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

EnAce *Nicholas Piramal, India.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

EnAce-D *Nicholas Piramal, India.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enacodan *Pharmacodane, Denm.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enacostad *Stada, Austria†; Stada, Neth.†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enacozid *Pharmacodane, Denm.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enadil *United Nordic, Denm.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enadiol *Laboratorios Chile, Chile.*
Estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

Enadiol CC *Laboratorios Chile, Chile.*
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Enadiol MP *Laboratorios Chile, Chile.*
12 tablets, estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1); 18 tablets, estradiol valerate.
Menopausal disorders.

Enadiol Neta *Laboratorios Chile, Chile.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

enadura *Merck dura, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enadura Plus *Merck dura, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enaf *Umeda, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; progestogen-only injectable contraceptive.

Enafarm *Farmakor, Rus.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enahexal
Hexal, Austral.; Hexal, NZ.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Hexal, Ger.
Enalapril maleate (p.1276·1) or enalaprilat (p.1276·2).
Heart failure; hypertension.

Enahexal comp *Hexal, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enahimine *Remedina, Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Enal *1A, Ger.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalabal *Baldacci, Braz.*
Enalapril maleate (p.1276·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Enalabell *Bellwether, Austral.*
Enalapril (p.1276·1).
Heart failure; hypertension.

Enaladex *Dexcel, Israel.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaladil *Rhein, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalafel *Asofarma, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalagamma *Worwag, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalagamma HCT *Worwag, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalamed *Cimed, Braz.*
Enalapril (p.1276·1).
Hypertension.

Enalanorm *Genericon, Austria.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Enalap *Saba, Turk.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalaplex *Pharlab, Braz.†.*
Enalapril (p.1276·1).
Hypertension.

Enalapoten *Del Bel, Arg.*
Enalapril (p.1276·1).
Hypertension.

Enalapril Comp *Arcana, Austria; Ratiopharm, Austria; Ratiopharm, Fin.; ABZ, Ger.; CT, Ger.; corax, Ger.; Ratiopharm, Norw.; Ratiopharm, Swed.; Sandoz, Swed.; Stada, Swed.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril HCT *AWD, Ger.; Sandoz, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril Hexal Plus *Sandoz, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril plus *1A, Ger.; Basics, Ger.; MIP, Ger.; Verla, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril-HCT *1A, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril/HCT *Kwizda, Austria; Ratiopharm, Austria; Sandoz, Austria; Stada, Austria.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalapril-saar Plus *MIP, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalaprin *Spefar, Venez.†.*
Enalapril (p.1276·1).
Hypertension.

Enala-Q comp *Juta, Ger.; Q-Pharm, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalatec *Greenpharma, Braz.*
Enalapril (p.1276·1).
Hypertension.

Enaldun
Duncan, Arg.
Enalapril (p.1276·1).
Hypertension.

Duncan, Hong Kong.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

EnaLich *Winthrop, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

EnaLich comp *Winthrop, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalil *Kinder, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Enalind *Lindopharm, Ger.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaloc *Leiras, Fin.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaloc Comp *Leiras, Fin.†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enalprin *Royton, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Enalten *Saval, Chile.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enalten D *Saval, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Enalten DN *Saval, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Enam *Reddy, Rus.; Reddy, Thai.; Biofarma, Venez.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaminoleban *Otsuka, Jpn†.*
Amino acid preparation for enteral nutrition (p.1922·1).
Hepatic encephalopathy; liver failure.

Enangel *Menarini, Spain.*
Dexketoprofen trometamol (p.73·1).
Inflammation; pain.

Enanton *Orion, Denm.†; Orion, Fin.; Orion, Norw.; Orion, Swed.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; precocious puberty; prostatic cancer; uterine fibroids.

Enantone *Takeda, Austria; Takeda, Fr.; Takeda, Ger.; Takeda, Hong Kong; Takeda, Ital.; Takeda, Thai.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; precocious puberty; prostatic cancer; stimulation of ovulation; uterine fibroids.

Enantone-Gyn *Takeda, Ger.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; uterine fibroids.

Enantyum *Menarini, Arg.; Menarini, Ital.; Menarini, Neth.; Menarini, Port.; Menarini, Spain.*
Dexketoprofen trometamol (p.73·1).
Pain.

Enap
KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.
Enalapril maleate (p.1276·1) or enalaprilat (p.1276·2).
Diabetic nephropathy; heart failure; hypertension.

Rowex, Irl.; Pharma Dynamics, S.Afr.; KRKA, Singapore.
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Enap H *KRKA, Pol.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enap HL *KRKA, Pol.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enap-Co *Pharma Dynamics, S.Afr.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enap-H *KRKA, Cz.; KRKA, Rus.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enap-HL *KRKA, Cz.; KRKA, Hung.; KRKA, Rus.; KRKA, Singapore.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enapirex *Chinoin, Cz.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaplus *Aliud, Ger.; Stada, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enapren *MSD, Ital.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; ischaemic heart disease.

Enapress *Berner, Fin.†; Stada, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enapril *Lannacher, Austria; Hexal, Cz.; Sandoz, Hung.; YSP, Malaysia; Intas, Thai.; Ilsan, Turk.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Enaprival *Valmor, Venez.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Enaprotec *Hexal, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Ena-Puren *Alpharma-Isis, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaran *Kwizda, Austria.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Enarenal *Polpharma, Pol.; Polpharma, Rus.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enaril *Biolab, Singapore; Biolab, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enasifar *Siphar, Switz.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enat *Mega Lifesciences, Philipp.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Enatec *Hebron, Braz.†; Mepha, Switz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enatec F *Hebron, Braz.†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enatia *Farmoz, Port.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Enaton *Tomnus, Braz.†.*
Enalapril (p.1276·1).
Hypertension.

Enatral *LA, Arg.*
Enalapril (p.1276·1).
Hypertension.

Enatrial *Investi, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enatus *Medisint, Ital.*
Iceland moss; plantago; althaea; aesculus; thyme; melissa; drosera; papaver.
Coughs.

Enatyrol *Tyrol, Austria†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enax *Ativus, Braz.*
Echinacea (p.2298·1).
Immunostimulant.

Enazil *Pliva Krakow, Pol.; Pliva, Rus.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enbrel *Wyeth, Arg.; Wyeth, Austral.; Wyeth, Belg.; Wyeth, Braz.; Amgen, Canad.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Hung.; Wyeth, India; Wyeth, Indon.; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain; Wyeth, Swed.; Wyeth, Switz.; Wyeth-Ayerst, Thai.; Wyeth, Turk.; Wyeth, UK; Amgen, USA; Wyeth, Venez.*
Etanercept (p.50·2).
Ankylosing spondylitis; juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis.

Enca *Prempharm, Canad.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Encare *Thompson, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Encaskin Cream *APR, Switz.*
Salnacedin (p.1613·1).
Acne.

Encaskin Creme *Farmalight, Port.†.*
Salnacedin (p.1613·1).
Acne.

Encaskin Detergente *Farmalight, Port.†.*
Salnacedin (p.1613·1).
Skin wash.

Encaskin Liquid Detergent *APR, Switz.*
Salnacedin (p.1613·1).
Skin wash.

Encebion *Medikon, Indon.*
Piracetam (p.368·2).
Cerebral trauma; learning difficulties in children; mental function impairment.

Encefabol *Mepro, Chile.*
Pyritinol hydrochloride (p.369·1).
Cerebrovascular disorders; mental function impairment.

Encepan *Interbat, Indon.*
Pyritinol (p.369·2).
Cerebral trauma; mental function impairment.

Encephabol
Merck, Austria; Merck, Cz.; Merck, India.
Pyritinol (p.369·2) or pyritinol hydrochloride (p.369·1).
Cerebrovascular disorders; dementia; mental function impairment; migraine; organic brain disorders.

Merck, Ger.; Merck, Hong Kong; Merck, Indon.; Merck, Malaysia†; Merck, Mex.; Merck, Philipp.; Merck, Rus.; Merck, S.Afr.; Merck, Singapore†; Merck, Thai.
Pyritinol hydrochloride (p.369·1).
Cerebral trauma; cerebrovascular disorders; dementia; mental function impairment; organic brain disorders.

Encepur *Grunenthal, Austria; Novartis Vaccines, Cz.; Meda, Fin.; Chiron Vaccines, Ger.; Novartis Vaccines, Hung.; Chiron Behring, Pol.; Meda, Swed.; Berna, Switz.*
An inactivated tick-borne encephalitis vaccine (p.2241·1).
Separate preparations are available for infants and children and for older children and adults.
Active immunisation.

Encevir *Microgen, Rus.*
An inactivated tick-borne encephalitis vaccine (p.2241·1).
Active immunisation.

Encialina *Bucca, Spain†.*
Aconite (p.2246·1); arnica (p.2260·2); ipecacuanha (p.1562·3); chamomile (p.2279·3); rhatany (p.2378·3); iodine (p.2169·2).
Mouth inflammation; pyorrhoea.

Encloxil *Pharmacare, Philipp.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Encopirin *Perrigo, Pol.*
Aspirin (p.20·3).
Fever; pain; thromboembolism prophylaxis.

Encorate *Sun, Rus.; Sun, Thai.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; migraine.

Encorate Chrono *Sun, Rus.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Encortolon *Polfa Pabianice, Pol.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Encorton *Polfa Pabianice, Pol.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Encypalmed *Trima, Israel.*
Pancreatin (p.2360·1); ox bile (p.2266·3); rhubarb (p.1768·3); frangula bark (p.1732·2); sodium bicarbonate (p.1673·2).
Dyspepsia; gastro-enteritis; meteorism.

Endace *Samarth, India.*
Megestrol (p.2115·1).
Breast cancer; endometrial cancer.

Endafed *UAD, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Allergic rhinitis; nasal congestion.

Endagen-HD *Abana, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Endak *Madaus, Austria; Madaus, Ger.*
⊗ Carteolol hydrochloride (p.1241·1).
Angina pectoris; arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Endal *Pediamed, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Endal Expectorant *Pediamed, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Formerly contained phenylpropanolamine hydrochloride, guaifenesin, and codeine phosphate.
Coughs.

Endal-HD *Pediamed, USA.*
Diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1); hydrocodone tartrate (p.63·1).
Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, and hydrocodone tartrate.
Coughs and cold symptoms.

Endal-HD Plus *Pediamed, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Endantadine *BMS, Canad.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Endcoff *EMS, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Endcol Cold & Flu *Pharmacare, S.Afr.*
Paracetamol (p.108·1); vitamin C (p.1983·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Endcol Cough Linctus *Aspen Consumer, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Endcol DM *Aspen Consumer, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Endcol Expectorant *Aspen Consumer, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Endcol Lozenges *Aspen Consumer, S.Afr.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Sore throat.

En-De-Kay *GSK Consumer, Neth.; Manx, UK.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Endep *Alphapharm, Austral.; Alphapharm, Malaysia†; Merck, Malaysia†.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Endhometrol *Boiron, Fr.*
Homoeopathic preparation.

Endial *Roemmers, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Endialop *Medphano, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Endiaron
Note. This name is used for preparations of different composition.
Herbacos, Cz.; Zentiva, Cz.
Chloroxine (p.242·2).
Amoebiasis; burns; disturbance of the intestinal flora; gastro-enteritis; giardiasis; infected skin disorders; wounds.

Medphano, Ger.†.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Endiform *Leciva, Cz.†.*
Chloroxine (p.242·2); oxyphenonium bromide (p.1759·2).
Gastro-enteritis.

Endium *Dexo, Fr.*
Diosmin (p.2304·2).
Haemorrhoids; peripheral vascular disorders.

Endobon *Biomet, Ger.*
Hydroxyapatite (p.2323·1).
Bone defects.

Endobulin *Baxter Immuno, Arg.; Baxter, Austria; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Immuno, Israel†; Baxter, Ital.; Baxter, Pol.; Adcock Ingram Critical Care, S.Afr.†; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenia; immunodeficiency disorders; Kawasaki disease; passive immunisation.

Endobuline *Baxter, Fr.; Immuno, Neth.†.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation.

Endocaina *Lafage, Arg.†.*
Procaine (p.1869·2).
Local anaesthesia.

Endocal *Pisa, Mex.†.*
Calcitonin (salmon) (p.1093·1).

Endocet *BMS, Canad.; Endo, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Fever; pain.

Endoclar *Baliarda, Arg.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Endocodone *Endo, USA†.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Endocorion *Elea, Arg.*
⊗ Chorionic gonadotrophin (p.2085·1).
Benign breast disorders; cryptorchidism; delayed puberty; habitual and threatened miscarriage; male and female infertility; menstrual disorders.

Endodan *BMS, Canad.*
⊗ Oxycodone hydrochloride (p.106·2); aspirin (p.20·3).
Fever; inflammation; pain.

Endofalk *Codali, Belg.; Falk, Ger.; Falk, Neth.; Falk, Port.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel cleansing for endoscopy; bowel evacuation.

Endofolin *Marjan, Braz.*
Folic acid (p.1940·1).
Anaemias; folic acid deficiency.

Endogel *Ioltech, Ger.*
Sodium hyaluronate (p.2320·1).
Adjunct in cataract surgery.

Endogel Esteril *Rider, Chile.*
Lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Endoscopy; urethral disinfection and anaesthesia.

Endogest *Siam Bheasach, Thai.†.*
Amylase (p.2256·3); vitamin B (p.1976·3); scopolia; sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Dyspepsia; gastric hyperacidity; gastritis; gastrointestinal motility disorders; heartburn.

Endol *Deva, Turk.*
Indometacin (p.66·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Endolac *Proge, Ital.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus delbrueckii*; *Streptococcus thermophilus* (p.2372·3).
Gastrointestinal disorders.

Endolipid *Darrow, Braz.†.*
Fractionated soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Endolipide *Braun, Fr.†; Braun, Port.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Endolor *Keene, USA.*
Paracetamol (p.108·1); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Endometril *Organon, Indon.*
Lynestrenol (p.2112·3).
Dysfunctional uterine bleeding; endometrial cancer; endometriosis; mastopathy; menstrual disorders.

Endometrin *Ferring, Hong Kong; Ferring, Israel; Ferring, USA.*
Progesterone (p.2125·1).
Female infertility.

Endomicina *Key, Arg.†.*
Neomycin (p.305·1); furazolidone (p.834·3); pectin (p.2145·2); kaolin (p.1738·1).
Diarrhoea.

Endomina *Farma Lepori, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Endomina Plus *Farma Lepori, Spain.*
Patch A, estradiol (p.2097·2); patch B, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Endone *Sigma, Austral.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Endoneutralio *SoSe, Ital.†.*
Sodium citrate (p.1673·3); potassium citrate (p.1673·2).
Gastric hyperacidity.

Endo-Paractol *Temmler, Ger.*
Simeticone (p.1770·2).
Adjuvant for endoscopy and double contrast radiography.

Endopeg *Braun, Belg.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Endoprost *Italfarmaco, Ital.*
Iloprost trometamol (p.1313·1).
Arterial ischaemia; Raynaud's syndrome; thromboangiitis obliterans.

Endorem *Guerbet, Austria; Codali, Belg.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Martins & Fernandes, Port.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.*
Ferumoxides (p.1478·1).
Contrast medium for magnetic resonance imaging of the liver.

Endosetin *Nobel, Turk.*
Indometacin (p.66·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Endosgel *Farco, Austria; Farco, Ger.; Farco, Neth.*
Chlorhexidine gluconate (p.1635·3); sodium lactate (p.1673·3).
Gynaecological and urinary-tract procedures.

Endosin *Akdeniz, Turk.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Endospray *Axcan, Canad.†.*
Benzocaine (p.1854·1); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Endotelon *Sanofi-Aventis, Chile; Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.*
Grape (p.2316·3).
Lymphoedema; peripheral vascular disorders; venous insufficiency.

Endothalyl *TC Pharma-Chem, Thai.*
Clioquinol (p.254·1); phthalylsulfathiazole (p.315·1).
Gastrointestinal infections.

Endotropina *Fada, Arg.*
Atropine (p.1219·2).

Endotussin *Prodotti, Braz.*
Potassium iodide (p.2169·2); theophylline calcium salicylate (p.1146·3).
Respiratory-tract congestion.

Endoxan *Sandoz, Arg.†; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Chile; Baxter, Cz.; Baxter Oncology, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; German Remedies, India; Baxter, Indon.; Baxter, Israel; Baxter, Ital.; Shionogi, Jpn†; Baxter Oncology, Malaysia†; Baxter, NZ; Baxter, Neth.; Baxter, Philipp.; Baxter Oncology, Pol.; Baxter, Port.; Aventis, S.Afr.; Baxter Oncology, Singapore; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
Cyclophosphamide (p.702·1).
Autoimmune disorders; haematopoietic stem cell transplantation; lupus erythematosus; malignant neoplasms; rheumatoid arthritis; transplant rejection.

Endoxana *Asta Medica, Irl.; Baxter Oncology, UK†.*
Cyclophosphamide (p.702·1).
Now known as Cyclophosphamide in the *UK*.
Malignant neoplasms.

Endrate *Abbott, USA.*
Disodium edetate (p.1463·3).
Digitalis-induced cardiac arrhythmias; hypercalcaemia.

Endrine
Note. This name is used for preparations of different composition.
Christiaens, Belg.
⊗ Ephedrine (p.1558·1); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Rhinopharyngeal congestion.

Wyeth, India.
⊗ Ephedrine (p.1558·1); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3).
Nasal congestion.

Endrine Doux *Christiaens, Belg.*
⊗ Ephedrine (p.1558·1); eucalyptus oil (p.2301·2).
Rhinopharyngeal congestion.

Endrine Mild *Wyeth, India.*
⊗ Ephedrine (p.1558·1); camphor (p.2273·2); cineole (p.2282·3).
Nasal congestion.

Endrolin *Kalbe, Indon.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; prostatic cancer.

Endronax *Solvay, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Endur-acin *Endurance, USA.*
Nicotinic acid (p.1957·3).
Hypercholesterolaemia.

Enduron *Abbott, Hong Kong†; Abbott, USA.*
⊗ Methyclothiazide (p.1334·1).
Hypertension; oedema.

Enduronyl *Abbott, Hong Kong†.*
⊗ Methyclothiazide (p.1334·1); deserpidine (p.1257·1).
Hypertension.

Endvir Simplex *Dicofarm, Ital.*
Lactoferrin (p.2330·1).
Herpesvirus infection.

Eneas *Merck, Ger.; Galenica, Gr.; Procter & Gamble, Port.; Vita, Spain.*
Enalapril maleate (p.1276·1); nitrendipine (p.1358·2).
Hypertension.

Enecal *Elmor, Venez.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; myocardial infarction.

Enecat *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Enelbin *Zentiva, Cz.*
Naftidrofuryl oxalate (p.1346·2).
Vascular disorders.

Enelbin-Paste N *Cassella-med, Ger.*
Zinc oxide (p.1621·2); salicylic acid (p.1612·2); aluminium silicate (p.1707·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Enelbin-Salbe *Cassella-med, Ger.*
Arnica (p.2260·2).
Soft-tissue injuries.

Enelbin-Salbe N *Cassella-med, Ger.†.*
Heparin sodium (p.1301·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, peri-articular and soft-tissue disorders; superficial vascular disorders.

Enelfa *Sanova, Austria; Dolorgiet, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Enema *RiC, Pol.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Enema Casen *Casen Fleet, Spain.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation.

Enema Cooper *Cooper (Κοπερ), Gr.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Enemac *Eurospital, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Enemark *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Enemol *Gador, Arg.; Dominion, Canad.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Ener-B *YSP, Malaysia.*
Vitamin B substances; vitamin C (p.1922·1).
Dietary supplement.

Enerbex *Medikon, Indon.*
Vitamins (p.1922·1); zinc sulfate (p.1999·2).
Nutritional supplement.

Enerbody *Body Spring, Ital.*
Maltodextrin; fructose; vitamins; minerals (p.1922·1).
Nutritional supplement; obesity.

Enerbol *Pliva, Cz.; Polfa, Hung.†; Ikapharmindo, Indon.; Pliva, Rus.*
Pyritinol hydrochloride (p.369·1).
Cerebral trauma; cerebrovascular disorders; mental function impairment; migraine; rheumatoid arthritis; trigeminal neuralgia.

Enercal *Wyeth Nutrition, Indon.*
A range of preparations for enteral nutrition (p.1922·1).

Enercal Plus *Wyeth, Hong Kong; Wyeth, Malaysia; Wyeth, Singapore.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Enerday *Megahealth, Chile.*
Ginseng; vitamins; erythroxylon catuaba; marapuama (p.1922·1).
Tonic.

Ener-E *Wassen, Ital.†.*
Vitamin E (p.1992·2); ubidecarenone (p.2407·2).
Nutritional supplement.

Ener-Forte *CNN, Philipp.*
Vitamin preparation with or without iron (p.1922·1).

Ener-G *General Dietary, UK.*
Gluten-free bread, rice bran, and pasta (p.1922·1).
Gluten-sensitive enteropathies.

Energavit *Roemmers, Arg.*
Iron sucrose (p.1953·2).
Iron deficiency.

Energeia *Sanitalia, Ital.*
Ginseng; ginkgo biloba; eleutherococcus; minerals (p.1922·1).
Nutritional supplement.

Energel *Arcolab, Philipp.*
Vitamins; minerals; ginseng; choline bitartrate; methionine (p.1922·1).
Dietary supplement.

Energen *Volchem, Ital.*
Glucose (p.1945·3) or maltodextrin (p.1955·3).
Energy loss; hypoglycaemia.

Energiclin *Hebron, Braz.*
Piracetam (p.368·2); vitamins (p.1922·1).
Tonic.

Energil C *EMS, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Energitum *Zambon, Fr.†.*
Arginine glutamate (p.1928·2).
Asthenia.

Energivit
Note. This name is used for preparations of different composition.
Scientific Hospital Supplies, Austral.; SHS, Fr.; Scientific Hospital Supplies, Irl.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Scientific Hospital Supplies, UK.
Nutritional supplement for infants and children (p.1922·1).

Ache, Braz.
Piracetam (p.368·2); fructose; vitamin B substances; ascorbic acid; tocopherol acetate (p.1922·1).
Alcoholism; behaviour disorders in children; cerebrovascular disorders; senile dementia; vertigo.

Energizante *AM, Arg.*
Vitamins; minerals; arginine; choline; royal jelly; guarana; pollen (p.1922·1).
Tonic.

Energizante Vital con ginseng *AM, Arg.*
Vitamins; minerals; arginine; choline; centella; ginseng; guarana; royal jelly; pollen (p.1922·1).
Tonic.

Energoplex *Libbs, Braz.*
Vitamins; fructose; arginine (p.1922·1).
Nutritional supplement.

Energotin aktiv *Stada, Ger.*
Taigawurzeln.
Tonic.

Energrip C *Vitapan, Braz.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Energy *Dolisos, Canad.*
Homoeopathic preparation.

Energy Plus
Note. This name is used for preparations of different composition.
Tecnonat, Arg.
Vitamins; minerals; ginseng (p.2312·1); guarana (p.2416·1) (p.1922·1).

Nutravite, Canad.†.
Ginseng (p.2312·1); kola (p.2416·1).

Energyn-T *DHA, Singapore.*
Multivitamin and mineral preparation (p.1922·1).

Energysor *Soria Natural, Spain†.*
Ginseng (p.2312·1); Siberian ginseng (p.2386·3); damiana (p.2292·1).
Fatigue; tonic.

Energyvit *Elmor, Venez.*
Ginseng; deanol tartrate; rutoside; vitamins; minerals (p.1922·1).
Tonic.

Enerion *Servier, Rus.*
Sulbutiamine (p.1976·1).
Asthenia.

Enerject-12 *Anglo-French Drugs, India.*
Vitamin B substances; vitamin C (p.1922·1).

Enerjets *Chilton, USA.*
Caffeine (p.1116·3).
Fatigue.

Ener-Mix *Also, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).

Enerplus *Soho, Indon.*
Adenosine triphosphate (p.2247·3); vitamin B substances; vitamin E (p.1922·1).
Fatigue; muscular weakness; myocardial disorders.

Enerseng *Herbarium, Braz.*
Ginseng (p.2312·1).
Asthenia.

Enerstress *Diamond, Philipp.*
Vitamin B substances; vitamin C (p.1922·1).

Enervit
EMS, Braz.
Succinic dinitrile; vitamin B substances (p.1922·1).
Nutritional supplement.

Also, Ital.
A range of nutritional supplements (p.1922·1).

Enervon Drops *General Drug, Philipp.*
Vitamin preparation (p.1922·1).

Enervon with E & Zinc *United American, Philipp.*
Vitamin preparation with zinc sulfate (p.1922·1).

Enervon with Ginseng & Vitamin E *United American, Malaysia.*
Ginseng; vitamins (p.1922·1).
Dietary supplement.

Enervon HP *Unilab, Philipp.*
Preparation for enteral nutrition (p.1922·1).

Enervon Prime *Unilab, Philipp.*
Preparation for enteral nutrition (p.1922·1).

Enervon-C
United American, Hong Kong; Medifarma, Indon.; United American, Malaysia; Great Eastern, Thai.; United American, Thai.
Vitamin B substances with vitamin C (p.1922·1).
Vitamin B and C supplement; vitamin deficiencies.

United American, Philipp.
Injection: Vitamin B substances; coenzyme A; nadide; vitamin C (p.1922·1).
Tonic.

United American, Singapore.
Syrup: Multivitamin preparation (p.1922·1).

United American, Philipp.; United American, Singapore.
Tablets: Vitamin B substances; vitamin C (p.1922·1).

Enervon-C Plus *United American, Hong Kong; United American, Malaysia; United American, Philipp.*
Multivitamin preparation (p.1922·1).

Enervon-E *United American, Philipp.*
d-Alpha tocopherol (p.1992·2).
Antioxidant.

Enervon-MV *Great Eastern, Thai.; United American, Thai.*
Multivitamin preparation with zinc (p.1922·1).

Enerzip *Cardinal, Philipp.*
Vitamin B substances; vitamin C; choline bitartrate; inositol (p.1922·1).

Enetege *Fada, Arg.*
Glyceryl trinitrate (p.1296·2).

Enfagrow *Mead Johnson, Indon.*
A range of preparations for enteral nutrition (p.1922·1).

Enfagrow A+ *Mead Johnson, Hong Kong.*
Preparation for enteral nutrition in infants (p.1922·1).

Enfagrow Lactofree *Mead Johnson, Philipp.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Enfakid A+ *Mead Johnson, Hong Kong; Mead Johnson, Indon.*
Preparation for enteral nutrition in children (p.1922·1).

Enfalac AR *Mead Johnson Nutritionals, Canad.†; Mead Johnson, Malaysia; Mead Johnson, Singapore; Mead Johnson Nutritionals, Thai.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Enfalac HA *Mead Johnson, Port.†; Mead Johnson Nutritionals, Thai.*
Infant feed (p.1922·1).
Cows' milk intolerance.

Enfalac Lactofree *Mead Johnson Nutritionals, Canad.†; Mead Johnson, Philipp.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Enfalac LF *Mead Johnson, Malaysia; Mead Johnson, Singapore.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Enfalac Nutramigen *Mead Johnson Nutritionals, Canad.†.*
Gluten-free, lactose-free casein hydrolysate preparation for special diets (p.1922·1).
Galactosaemia; protein sensitivity.

Enfalac Pregestimil *Mead Johnson Nutritionals, Canad.†.*
Infant feed (p.1922·1).
Malabsorption syndromes.

Enfalac Prosobee Soy *Mead Johnson Nutritionals, Canad.†.*
Soy based infant feed (p.1922·1).
Hypersensitivity to cow's milk.

Enfalyte *Mead Johnson Nutritionals, Canad.*
Rice syrup; sodium chloride; potassium citrate; sodium citrate; citric acid (p.1672·2).
Formerly known as Enfalac Enfalyte.
Diarrhoea; oral rehydration therapy.

EnfaMama *Mead Johnson, Indon.*
Nutritional supplement for pregnant and breast-feeding women (p.1922·1).

Enfamama *Mead Johnson, Philipp.*
Nutritional supplement for pregnant and lactating women (p.1922·1).

Enfamil AR *BMS, Arg.; Mead Johnson, Braz.; Mead Johnson, Chile; Mead Johnson, Fr.; BMS, Hong Kong; Mead Johnson, Irl.; Mead Johnson, Israel; BMS, Mex.; Mead Johnson, Port.†; Mead Johnson Nutritionals, UK; BMS, Venez.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Enfamil HA *Mead Johnson, Fr.*
Infant feed (p.1922·1).
Infants with a family history of allergy.

Enfamil Lactofree *Mead Johnson, Irl.*
Infant feed (p.1922·1).
Lactose intolerance.

Enfamil Natalins Rx *Mead Johnson Nutritionals, USA.*
Multivitamin and mineral preparation (p.1922·1).
Formerly known as Natalins Rx.

Enfamil Nutramigen *BMS, Arg.*
Infant feed (p.1922·1).
Diarrhoea; fructosaemia; galactosaemia; protein sensitivity.

Enfamil Poly-Vi-Sol *Mead Johnson, Austral.*
Multivitamin preparation (p.1922·1).

Enfamil Pregel *Mead Johnson, Ital.*
Infant feed (p.1922·1).
Regurgitation.

Enfamil Pregestimil *BMS, Arg.*
Infant feed (p.1922·1).
Diarrhoea; galactosaemia; lactose intolerance; pancreatic insufficiency; protein sensitivity; sucrose intolerance.

Enfamil Prosobee *Mead Johnson, Austral.*
Infant feed (p.1922·1).
Cow's milk intolerance; galactosaemia; lactose intolerance; sucrose intolerance.

Enfamil sin Lactosa *BMS, Arg.; Mead Johnson, Chile; BMS, Mex.*
Infant feed (p.1922·1).
Lactose intolerance.

Enfamil Soya *BMS, Arg.; Mead Johnson, Chile; Mead Johnson, Israel; BMS, Mex.*
Soy-based infant feed (p.1922·1).
Colic; cows' milk intolerance; diarrhoea; eczema; galactosaemia; gastro-oesophageal reflux; lactose or sucrose intolerance.

Enfapro Lactofree *Mead Johnson, Philipp.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Enfapro LF *Mead Johnson, Malaysia; Mead Johnson, Singapore.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Enfexia *Bilim, Turk.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Enflucide *Yenisehir, Turk.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Enfluthane *Baxter, Braz.*
Enflurane (p.1782·2).
General anaesthesia.

Enfol *Ativus, Braz.*
Folic acid (p.1940·1).

Enforan *Richmond, Arg.*
Enflurane (p.1782·2).
General anaesthesia.

Enfran *Pisa, Mex.*
Enflurane (p.1782·2).
General anaesthesia.

Enfriestop *Gayoso, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

En-Ga-Lax *Omega, Arg.*
Casanthranol (p.1715·1); bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Engerix-B *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA; GSK, Venez.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Separate preparations are available for children and for adults.
Active immunisation.

Engestol-Hyd *Pharmanik (Φαρμανικ), Gr.†.*
Codergocrine (p.364·1).
Peripheral vascular disorders.

Engystol *Peithner, Austria.; Heel, Cz.; Heel, Ger.*
Homoeopathic preparation.

Engystol N *Heel, S.Afr.*
Homoeopathic preparation.

Enhancer *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Enhancin
Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Mex.; Ranbaxy, Philipp.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ranbaxy, Malaysia.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2) or potassium clavulanate (p.250·2).
Bacterial infections.

Ranbaxy, Singapore.
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Enhansid *Interhealthcare, Philipp.*
Folic acid (p.1940·1).
Megaloblastic anaemia.

Enhos *Kansuk, Turk.*
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).

Eni *Grossman, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Enico *Eisai, Indon.*
Tocoferil nicotinate (p.1415·1).
Atherosclerosis; circulatory disorders; disorders of fat metabolism.

Enicul *Apomedica, Austria.*
Magnesium trisilicate (p.1744·1); algeldrate (p.1706·2); ammonium glycyrrhizate (p.2316·1).
Gastrointestinal disorders.

Enidap *Farmanic, Gr.*
Sertraline (p.422·1).
Depression.

Enidazol *East India Pharma, India.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis.

Enidin *Allergan, Austral.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Eniflex *Bago, Chile†.*
Glucosamine hydrochloride (p.2313·2); ascorbic acid (p.1983·3); lucerne; minerals.
Joint disorders.

Enison *IFET (ΙΦΕΤ), Gr.; Stada, Spain.*
Vindesine sulfate (p.788·2).
Malignant neoplasms.

Enit *Gap, Gr.; Procter & Gamble, Port.; Lacer, Spain.*
Enalapril maleate (p.1276·1); nitrendipine (p.1358·2).
Hypertension.

Enivac HB *Panacea, India.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Enjomin *Codilab, Port.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Enjool *Simoes, Braz.†.*
Metoclopramide hydrochloride (p.1747·3); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Enjuvia *Duramed, USA.*
Synthetic conjugated estrogens, B (p.2087·2).
Menopausal disorders.

Enkacetyn *Kimia, Indon.*
Chloramphenicol (p.239·3).
Skin infections.

Enkacort *Kimia, Indon.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Enkapyrin *Kimia, Indon.*
Phenylbutazone (p.117·1); propyphenazone (p.119·3).
Arthritis; neuralgia.

Enkasari *Kimia, Indon.*
Abrus (p.2244·1); liquorice (p.1740·3); betel; menthol (p.2340·1).
Scurvy.

Enlace *Wermar, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Enlinea *Elhoim, Arg.†.*
Centella (p.1592·3); caffeine (p.1116·3); levocarnitine (p.1932·2); seaweed extract.

Enlive *Abbott, Austral.; Abbott, Fin.†; Abbott, Fr.; Abbott, Irl.; Abbott, Mex.; Abbott Nutrition, UK; Abbott, USA.*
Preparation for enteral nutrition (p.1922·1).

Enlon *Baxter, Canad.; Baxter, USA†.*
Edrophonium chloride (p.630·3).
Adjunct in curare-induced respiratory depression; differential diagnosis of myasthenia gravis; reversal of competitive neuromuscular blockade.

Enlon-Plus *Baxter, USA†.*
Edrophonium chloride (p.630·3).
Atropine sulfate (p.1219·3) is included in this preparation to protect against the muscarinic actions.
Curare antagonist; reversal of competitive neuromuscular blockade.

Ennamax *Actavis, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Urticaria.

Ennos *Lannacher, Austria.*
Paroxetine mesilate (p.414·2).
Depression; obsessive-compulsive disorder; panic disorders; social anxiety disorder.

Eno
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Austral.; GSK, Hong Kong†; GSK, Israel; GSK Consumer, UK; GSK Consumer, Venez.
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); sodium carbonate (p.2389·1).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; nausea.

GSK Consumer, Canad.
Sodium citrate (p.1673·3).
Dyspepsia.

GSK Consumer, Port.
Citric acid (p.2284·1); sodium carbonate (p.2389·1).

Enofosforina Vigor *Serra Pamies, Spain.*
Calcium lactophosphate; magnesium glycerophosphate; kola; pyridoxine; sodium glycerophosphate; potassium glycerophosphate; nicotinamide; glycerol; manganese glycerophosphate (p.1922·1).
Tonic.

Enoksetin *Eczacibasi, Turk.*
Enoxacin (p.268·3).
Bacterial infections.

Enomdan *Pharmacia, Swed.†.*
Multivitamin preparation (p.1922·1).

Enoparin *Vivax, Venez.*
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders; unstable angina.

Enorden *Finadiet, Arg.*
Amisulpride (p.961·1).
Psychoses.

Enoton *Pensa, Spain.*
Cyproheptadine aspartate (p.575·2); mecobalamin (p.1981·1).
Anorexia; tonic; weight loss.

Enouvim *Pharmacare, Philipp.*
Vitamin preparation with lysine and taurine (p.1922·1).

Enoval *Novag, Mex.*
Enalapril (p.1276·1).
Hypertension.

Enoxen *EG, Ital.*
Enoxacin (p.268·3).
Bacterial infections.

Enoxin *CCM, Hong Kong; CCM, Malaysia.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Enoxor *Germania, Austria; Pierre Fabre, Fr.; Pierre Fabre, Ger.*
Enoxacin (p.268·3).
Bacterial infections.

Enper *Elea, Arg.*
Zidovudine (p.913·3).
HIV infection.

Enpicortyn *Nicholas, Indon.*
⊗ Tetracycline hydrochloride (p.347·2); hydrocortisone (p.1535·2).
Infected eye disorders.

Enpott *Ranbaxy, Thai.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Enpovax HDC *CSL, Austral.†.*
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

Enpresse *Barr, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Enprin *Galpharm, UK.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Enrich *Abbott, Cz.†; Abbott, Fin.; Abbott, Fr.; Abbott, Irl.; Abbott, Ital.†; Abbott, Turk.; Abbott Nutrition, UK.*
Preparation for enteral nutrition (p.1922·1).

Enromic *Microsules, Arg.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Enshake *Abbott, UK.*
Preparation for enteral nutrition (p.1922·1).

Ensial *Remedina, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Ensibest *Best, Mex.*
Prazosin hydrochloride (p.1375·2).
Frostbite; heart failure; hypertension; intermittent claudication; Raynaud's syndrome.

Ensinger Schiller-Quelle Heilwasser *Ensinger, Ger.†.*
Electrolytes (p.1667·1); silicic acid; boric acid (p.2268·1); carbon dioxide.
Gastrointestinal disorders; urinary-tract infections.

Ensini *Nutricia, Fin.; Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).

Ensure *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Cz.†; Abbott, Fin.; Abbott, Fr.; Abbott, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott Nutrition, UK; Ross, USA; Abbott, Venez.*
A range of preparations for enteral nutrition (p.1922·1).

Ensure Plus *Abbott, Irl.; Abbott, Ital.; Abbott, Singapore; Abbott Nutrition, UK.*
High calorie preparation for enteral nutrition (p.1922·1).

ENT
Note. This name is used for preparations of different composition.
Iomed, Hong Kong†.
Phenylpropanolamine hydrochloride (p.1569·3); brompheniramine maleate (p.569·2).
Nasal congestion; sinusitis.

Adcock Ingram, S.Afr.
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline nitrate (p.1565·2).
Nasal congestion.

Entact
Elpen (Ελπεν), Gr.; Lundbeck, Spain.
Escitalopram (p.391·1).
Depression; panic disorder; social phobia.

Recordati, Ital.
Escitalopram oxalate (p.391·1).
Depression; panic disorder.

Entacyl *Shire, Canad.†.*
Piperazine adipate (p.152·3).
Ascariasis; enterobiasis.

Entamizole *Abbott, India.*
Diloxanide furoate (p.832·2); metronidazole (p.837·1).
Amoebiasis; giardiasis.

Entasid
Note. This name is used for preparations of different composition.
Cadila, India.
Chewable tablets: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); almasilate (p.1705·1).

Cadila, India.
Oral suspension: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).

Entecet *Nutergia, Fr.*
Hordeum sativum germ; enzymes derived from aspergillus including amylase and protease; lipase derived from rhizopus.
Dyspepsia.

Entera *Fresenius Kabi, Mex.*
Preparation for enteral nutrition (p.1922·1).

Enteral *Vargas, Venez.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Enteraproct *Crinos, Ital.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Enterasin *Crinos, Ital.*
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Entereg *GSK, USA.*
Alvimopan (p.1708·1).
Postoperative ileus.

Enterex *K2 Pharmacare, Chile; Pisa, Mex.; Victus, Venez.*
Preparation for enteral nutrition (p.1922·1).

Enterin *Farmedia, Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Entermid *Nakornpatana, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Entero Micinovo *Bago, Chile.*
Co-trimoxazole (p.258·1); attapulgite (p.1709·1).
Diarrhoea.

Entero VU *Temis, Arg.; E-Z-EM, Israel.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Enterobacilli *Proge, Ital.*
Lactobacillus paracasei; *Lactobacillus salivarius*; vitamins (p.1922·1).
Disturbances of the intestinal flora.

Enterobacticel *Bago, Arg.*
Co-trimoxazole (p.258·1); attapulgite (p.1709·1).
Diarrhoea.

Enterobene *Ratiopharm, Austria; Ratiopharm, Hung.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Enterobion *Makros, Braz.†.*
Furazolidone (p.834·3); homatropine (p.1881·2); pectin (p.2145·2).
Diarrhoea.

Enterobios *Bioprogress, Ital.†.*
Bacillus subtilis spores.
Restoration of gastrointestinal flora.

Enterocid *Teuto, Braz.†.*
Pyrvinium embonate (p.155·3).
Worm infections.

Enterocin Compound *Synco, Hong Kong.*
Furazolidone (p.834·3); neomycin sulfate (p.305·1); pectin (p.2145·2); attapulgite (p.1709·1); papaverine hydrochloride (p.2191·3).
Diarrhoea; gastrointestinal infections.

Enterocir *AstraZeneca, Ital.†.*
⊗ Budesonide (p.1520·1).
Crohn's disease.

Entero-Diyod *Serral, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis; giardiasis; shigellosis; trichomoniasis.

Enterodyne *Adcock Ingram, S.Afr.*
⊗ Bismuth carbonate (p.1711·1); calcium carbonate (p.1714·1); chloroform and morphine tincture (p.86·3); aromatic ammonia liquid (p.2256·1); nutmeg oil (p.2355·3); clove oil (p.2285·1); cardamom tincture (p.2277·1); catechu tincture (p.2278·2); conc. cinnamon water; cinnamon oil (p.2283·2).
Gastrointestinal disorders.

Enterofigon *Hertz, Braz.*
Adenosine (p.1202·1); betaine (p.2265·2); choline (p.1934·2); methionine (p.1450·1).
Liver disorders.

Enterofuryl *Bosnalek, Rus.*
Nifuroxazide (p.307·2).
Diarrhoea.

Entero-Gastreu R4 *Reckeweg, Neth.*
Homoeopathic preparation.

Enterogermina
Note. This name is used for preparations of different composition.
Sanofi-Aventis OTC, Ital.
Spores of *Bacillus subtilis.*
Gastrointestinal disorders.

Sanofi Synthelabo, Mex.
Bacillus clausii spores.
Maintenance of gastrointestinal flora.

Enterogit *Soho, Indon.*
Activated attapulgite (p.1709·1).
Diarrhoea.

Enterokan *Farmasa, Mex.; Schwabe, Singapore†.*
Peppermint oil (p.1761·2); caraway oil (p.2277·1).
Dyspepsia; gastrointestinal disorders; irritable bowel syndrome.

Enterol
Note. This name is used for preparations of different composition.
Biodiphar, Belg.; Biocodex, Cz.; Teva, Hung.; Biocodex, Pol.; Merck, Port.†; Biocodex, Rus.
Saccharomyces boulardii (p.2372·3).
Antibiotic-associated colitis; diarrhoea; restoration of gastrointestinal flora.

Sanitas, Chile.
Phthalylsulfacetamide (p.315·1); activated attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Enterol Con Nifuroxacida *Sanitas, Chile.*
Phthalylsulfacetamide (p.315·1); nifuroxazide (p.307·2).
Gastrointestinal infections; gastrointestinal sterilisation.

Enterolactis *Sofar, Ital.*
Lactobacillus casei (p.2372·3) and vitamin B substances (p.1922·1) with or without inulin (p.2326·3).
Restoration of gastrointestinal flora.

Enterolidon *Ortoquimica, Braz.†.*
Furazolidone (p.834·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Enterolyte *Adcock Ingram, S.Afr.*
Kaolin (p.1738·1); pectin (p.2145·2); sodium lactate; potassium chloride; sodium chloride (p.1672·2).
Diarrhoea.

Enteromicina *Produfarma, Port.*
Neomycin sulfate (p.305·1).
Gastro-enteritis.

Enteromix *Bioprogress, Ital.†.*
Piromidic acid (p.316·3).
Bacterial infections of the gastrointestinal tract.

Enteropathyl *Merck Medication Familiale, Fr.*
Sulfaguanidine (p.339·2).

Enteroplant
Note. This name is used for preparations of different composition.
Spitzner, Ger.; Schwabe, Hung.
Peppermint oil (p.1761·2); caraway oil (p.2277·1).
Dyspepsia; gastrointestinal disorders.

Schwabe, Switz.†.
Peppermint oil (p.1761·2); cumin oil.
Dyspepsia.

Enteropride *Janssen-Cilag, Mex.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Enteroprin *Metro, Philipp.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Entero-Quinol *East India Pharma, India.*
Clioquinol (p.254·1).
Amoebic dysentery.

Enteroseven *Federfarma, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins; minerals; inulin (p.1922·1).
Disturbances of the intestinal flora; nutritional supplement.

Enterosilicona *Estedi, Spain.*
Dimeticone (p.1770·2).
Flatulence; infant colic; meteorism.

Enterosol *Phytofarm Kleka, Pol.*
Achillea (p.2245·2); greater celandine (p.2317·1); oak bark (p.2355·3); salix purpurea (p.121·3); sage (p.2382·3); thyme (p.2401·1); artemisia abrotanum.
Gastrointestinal disorders.

Enterostop *Teofarma, Ital.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Gastrointestinal infections.

Entero-Teknosal *Taco, Ger.*
Colloidal silicon dioxide (p.2146·3).
Diarrhoea.

Enter-Out *Medimar, Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).

Enter-Sal *Nevzat, Turk.*
Sodium salicylate (p.124·2).
Fever; pain.

Entertainer's Secret *KLI, USA.*
Aloe vera (p.1588·2); carmellose sodium (p.2142·1); glycerol (p.2314·2).
Formerly known as Moi-Stir 10.
Throat discomfort.

Enterum *Angelini, Ital.*
Spores of *Bacillus subtilis.*
Gastrointestinal disorders.

Entex
Note. This name is used for preparations of different composition.
Purdue, Canad.
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract congestion.

Andrx, USA.
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs and cold symptoms; nasal congestion.

Entex LA *Andrx, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Entex HC *Athlon, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly contained hydrocodone tartrate, phenylephrine hydrochloride, and guaifenesin.
Coughs.

Entex PSE *Athlon, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Entianthe *Rafarm, Gr.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Entir *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Entizol *Polpharma, Cz.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Entocir *AstraZeneca, Ital.*
⊗ Budesonide (p.1520·1).
Crohn's disease.

Entocord *AstraZeneca, S.Afr.; AstraZeneca, Spain.*
⊗ Budesonide (p.1520·1).
Crohn's disease; ulcerative colitis.

Entocort *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Eisai, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Singapore†; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
⊗ Budesonide (p.1520·1).
Inflammatory bowel disease.

Entodiba *Diba, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Entofoam *Cipla, India.*
⊗ Hydrocortisone acetate (p.1535·2).

Entom Nature *Dynacren, Ital.*
Geranium oil (p.2311·1).
Insect repellent.

Entonox *Afrox, S.Afr.; BOC, UK.*
Nitrous oxide (p.1789·3); oxygen (p.1690·2).
Obstructive airways disease; pain.

Entoplus *Diba, Mex.*
Albendazole (p.139·2).
Worm infections.

Entosec *Cipla, India.*
Secnidazole (p.846·3).
Amoebiasis; trichomoniasis.

Entosorbine-N *Bayer, Neth.*
Albumin tannate (p.1704·2).
Diarrhoea.

Entox-P *Wyeth Consumer, Malaysia†; Wyeth-Ayerst, Thai.†.*
Activated attapulgite (p.1709·1).
Diarrhoea.

Entrarin *Asian Pharm, Thai.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Entrasol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition (p.1922·1).

Entressdruppels HM *SA Druggists, S.Afr.*
Asafetida tincture (p.2261·3); valerian (p.2410·1); cassia bark (p.1715·3); nutmeg (p.2355·2); lavender oil (p.2331·2); rosemary oil (p.2381·3).
Flatulence; insomnia; nervous disorders.

Entrition *Clintec, USA.*
A range of lactose-free preparations for enteral nutrition (p.1922·1).

Entrobar *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Entrocalm
Note. This name is used for preparations of different composition.
Galpharm, UK.
Capsules: Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Galpharm, UK.
Tablets: Kaolin (p.1738·1).
Diarrhoea.

Entrocalm Replace *Galpharm, UK.*
Glucose monohydrate; sodium chloride; potassium chloride; sodium citrate; citric acid (p.1672·2).
Oral rehydration therapy.

Entrocel *Mallinckrodt, USA.*
Hypromellose (p.2144·2).
Adjunct in gastrointestinal radiography.

Entrodiar *Medikon, Indon.*
Psidium guajava; turmeric (p.1473·2); catechu (p.2278·2); coptis chinensus.
Diarrhoea.

Entrodyn *Ravensberg, Ger.†.*
Phenylephrine (p.1568·1); caffeine (p.1116·3).
Hypotension.

Entrogard *Mugi, Indon.*
Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Entrolate *Stadmed, India†.*
Tinidazole (p.848·3); diloxanide furoate (p.832·2).
Amoebiasis.

Entrolax *Galpharm, UK.*
Bisacodyl (p.1710·1).
Constipation.

Entron *Ethica, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Entrophen *Pendopharm, Canad.*
Aspirin (p.20·3).
Fever; musculoskeletal and joint disorders; myocardial infarction; pain; transient ischaemic attacks.

Entrozyme Plain *Stadmed, India.*
Clioquinol (p.254·1).
Amoebic dysentery.

Entrydil *Orion, Irl.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Entschlackender Abfuhrtee EF-EM-ES *Smetana, Austria.*
Senna (p.1769·2); equisetum (p.2299·3); sambucus (p.2383·1); delphinium consolida.
Constipation.

ENTsol *Bradley, Singapore.*
Sodium chloride (p.1686·1); monobasic potassium phosphate (p.1682·2); dibasic sodium phosphate (p.1682·3).
Nasal congestion; throat disorders.

Entumin *Novartis, Israel; Novartis, Ital.*
Clotiapine (p.980·2).
Alcohol withdrawal syndrome; anxiety; bipolar disorder; psychoses; restlessness; schizophrenia.

Entumine *Novartis, Switz.*
Clotiapine (p.980·2).
Alcohol withdrawal syndrome; anxiety disorders; hyperactivity; psychoses; sleep disorders.

Enturen *Medivis, Ital.*
Sulfinpyrazone (p.559·2).
Thromboembolic disorders.

Entuss Expectorant
Note. This name is used for preparations of different composition.
Hauck, USA; Roberts, USA.
Oral liquid: Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Hauck, USA; Roberts, USA.
Tablets: Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Entuss-D
Note. This name is used for preparations of different composition.
Roberts, USA.
Liquid: Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Roberts, USA.
Tablets: Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Entuss-D Jr *Roberts, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Entzundungstropfen *Heel, Ger.*
Homoeopathic preparation.

Enuclen *Alcon, Ger.†.*
Tyloxapol (p.1921·3).
Cleansing and lubrication of eye prostheses.

Enuclene *Alcon, Canad.; Alcon, NZ; Alcon, USA.*
Tyloxapol (p.1921·3).
Cleansing and lubrication of artificial eyes.

Enulid *Rottapharm, Ital.*
⊗ Moexipril hydrochloride (p.1343·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Enulose *Barre-National, USA.*
Lactulose (p.1738·2).
Hepatic encephalopathy.

EnurAid *Hylands, Canad.*
Homoeopathic preparation.

Enuroplant *DHU, Ger.*
Homoeopathic preparation.

Envacar *Pfizer, Philipp.*
Amlodipine besilate (p.1214·1); atorvastatin calcium (p.1218·3).
Angina pectoris; cardiovascular risk reduction; hyperlipidaemias.

Envas *Cadila Pharma, India; Cadila, Rus.; Cadila, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Enviage *Novartis, Cz.; Novartis, Port.*
Aliskiren (p.1207·1).
Hypertension.

Enviro-Stress *Vitaline, USA.*
Vitamin B substances with vitamin C and minerals (p.1922·1).

Envit Q_{10} *Polfa Pabianice, Pol.*
Ubidecarenone (p.2407·2).
Cardiovascular disorders; chronic fatigue syndrome; coenzyme Q10 deficiency.

Enxak *Cazi, Braz.*
Dihydroergotamine mesilate (p.618·2); dipyrone (p.49·2); caffeine (p.1116·3).
Migraine.

Enydrial *Johnson & Johnson Consumer, Fr.*
A range of cleansing agents and emollients.
Dry skin; skin irritation.

Enystin *Kalbe, Indon.*
Nystatin (p.543·2).
Oral candidiasis.

Enzace *Sigma, Austral.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Enzaprost
Faran, Gr.
Dinoprost (p.2006·3).
Termination of pregnancy.

Chinoin, Pol.
Dinoprost trometamol (p.2006·3).
Termination of pregnancy; uterine evacuation.

Enzaprost F *Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Chinoin, Rus.*
Dinoprost (p.2006·3).
Labour induction; termination of pregnancy.

Enziagil Magenplus *Riemser, Ger.†.*
Gentian (p.2310·3).
Digestive system disorders.

Enzian Anaemodoron Drops *Weleda, S.Afr.*
Honey (p.1948·2); gentian (p.2310·3); fragaria vesca; urtica (p.2409·3).
Anaemias; tonic.

Enzicoba *Farmasa, Braz.*
Cobamamide (p.1980·2).
Reduced appetite; tonic.

Enziflur *Bros, Gr.†.*
Serrapeptase (p.2385·3).
Inflammatory disorders.

Enzima de Lechoza *Sundown, Venez.†.*
Papaya; papain (p.2362·3); bromelains (p.2269·1).
Dietary supplement.

Enzine *Sandoz, Austria.*
Cefixime (p.224·3).
Bacterial infections.

Enzipan *Abbott, Ital.*
Pancrelipase (p.2360·1).
Pancreatic disorders.

Enziprid *Brasmedica, Braz.†.*
Bromopride (p.1713·3); lipase (p.2360·3); amylase (p.2256·3).
Digestive-system disorders; nausea and vomiting.

Enzira *Chiron Vaccines, UK.*
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Enzix *Hemofarm, Rus.*
⊗ Tablets, enalapril maleate (p.1276·1); tablets, indapamide (p.1314·1).
Hypertension.

Enzogenol *MD, Singapore†.*
Pinus radiata; vitamin C; vitamin E; linseed oil (p.1922·1).
Antoxidant preparation.

Enzone *UAD, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine (p.1868·2).

Enzyflat *Solvay, Austria†.*
Pancreatin (p.2360·1); dimethicone (p.1770·2).
Flatulence; meteorism; preparation for gastrointestinal radiography and ultrasound.

Enzymatic Cleaner *Alcon, USA.*
Pancreatin (p.2360·1) (p.1622·2).
Cleansing solution for soft contact lenses.

Enzyme
Note. This name is used for preparations of different composition.
GNLD, Austral.
Pancreatin (p.2360·1); pepsin (p.2365·1); ox bile (p.2266·3); papain (p.2362·3); amylase (p.2256·3).
Digestive disorders.

Nature's Bounty, USA.
Amylase (p.2256·3); cellulase (p.2279·1); lipase; protease.
Gastrointestinal disorders.

Enzyme Digest *Quest, UK.*
Betaine hydrochloride (p.2265·2); papain (p.2362·3); bromelain (p.2269·1); amylase (p.2256·3); lipase (p.2360·3); peppermint oil (p.1761·2).

Enzyme Plus *Lifeplan, UK.*
Betaine hydrochloride (p.2265·2); amylase (p.2256·3); pepsin (p.2365·1); lipase (p.2360·3).
Dietary supplement.

Enzymet *Ranbaxy, Thai.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive system disorders; flatulence.

Enzymfort *Kimia, Indon.*
Pancreatin (p.2360·1); vitamin B substances (p.1922·1); bile extract (p.2266·3).
Digestive disorders.

Enzym-Harongan *Schwabe, Ger.*
Haronga; Javanese turmeric (p.2406·3); pancreas (p.2337·3).
Digestive system disorders.

Enzym-Lefax *Bayer, Ger.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive system disorders.

Enzym-Wied *Wiedemann, Ger.†.*
Pancreatin (p.2360·1); bromelains (p.2269·1); papain (p.2362·3); triacylglycerollipase; amylase (p.2256·3); trypsin (p.2405·3); chymotrypsin (p.2281·3); rutoside (p.2305·1).
Atherosclerosis; soft-tissue injury; thrombosis; venous inflammation.

Enzynorm *Pharmaselect, Austria; Noristan, S.Afr.†.*
Gastric mucous membrane extract (p.2337·3).
Anaemia; digestive disorders; gastrointestinal disorders.

Enzynorm f *Abbott, Ger.*
Gastric mucous membrane extract (p.2337·3); amino acids (p.1922·1).
Gastrointestinal disorders.

Enzyplex
Note. This name is used for preparations of different composition.
Westmont, Hong Kong; Medifarma, Indon.; Westmont, Malaysia; Westmont, Singapore.
Amylase (p.2256·3); protease; lipase; deoxycholic acid (p.2266·3); dimethicone (p.1770·2); vitamin B substances (p.1922·1).
Digestive disorders associated with excess gas.

Great Eastern, Thai.; Westmont, Thai.
Rizolipase; amylase (p.2256·3); protease; deoxycholic acid (p.2266·3); simeticone (p.1770·2); vitamin B substances (p.1922·1).
Digestive system disorders with excess gas.

Enzystal *Torrent, Rus.*
Pancreatin (p.2360·1).

Eoline *Pfizer, Belg.†.*
⊗ Hydrocortisone (p.1535·2); nystatin (p.543·2); oxytetracycline calcium (p.312·3).
Infected skin disorders.

Eolus *Sigma-Tau, Ital.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Eostar *Gerot, Austria.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

Epabetina *OFF, Ital.†.*
Betaine glucuronate (p.2265·2); trigonelline.
Liver disorders.

Epabiol *Biophytarom, Fr.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Epacalcica *Ibirn, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Epacaps *Altana, Switz.*
Marine fish oil (p.1362·2).
Hyperlipidaemias; nutritional supplement.

Epadel *Mochida, Jpn.*
Icosapent ethyl (p.1362·1).
Arteriosclerosis obliterans; hyperlipidaemias.

Epaderm *Medlock Medical, UK.*
Yellow soft paraffin (p.2031·3); emulsifying wax (p.2029·2); liquid paraffin (p.2030·3).
Dry skin.

Epadoc *Faran, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Epadoren *Demo, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Epagest *Lampugnani, Ital.†.*
Fennel (p.2302·3); milk thistle (p.1452·1); cynara (p.2291·2); vitamin B substances (p.1922·1).
Dietary supplement; liver disorders.

Epailis *DHN, Fr.*
Nutritional supplement (p.1922·1).
Regurgitation.

Epalat EPS *OFF, Ital.*
Lactulose (p.1738·2).
Liver disorders.

Epalfen *Zambon, Ital.; Zambon, Neth.*
Lactulose (p.1738·2).
Constipation; liver disorders.

Epamin
Elea, Arg.; Pfizer, Mex.; Pfizer, Venez.
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; digitalis toxicity; epilepsy; migraine; myocardial infarction; psychoses; seizures associated with neurosurgery; trigeminal neuralgia.

Pfizer, Chile.
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; seizures associated with neurosurgery.

Epanutin
Pfizer, Austria; Pfizer, Belg.; Pfizer, Irl.; Pfizer, S.Afr.; Pfizer, Switz.†; Pfizer, UK.
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; migraine; non-epileptic convulsions; parkinsonism; seizures associated with neurosurgery or head injury; status epilepticus; Sydenham's chorea; trigeminal neuralgia.

Pfizer, Cz.; Parke, Davis, Ger.†; Pfizer, Hung.; Parke, Davis, Israel; Pfizer, Neth.; Davis, Spain; Pfizer, Swed.; Pfizer, Turk.
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; neuralgias; seizures associated with neurosurgery; status epilepticus; sympathetic pain syndromes; trigeminal neuralgia.

Pfizer, Gr.; Parke, Davis, Pol.
Phenytoin (p.495·2).
Arrhythmias caused by digoxin toxicity; epilepsy.

Epaplex 40 *Uno, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Sideropenic anaemia.

Epaq
Note. This name is used for preparations of different composition.
3M, Arg.†; 3M, Mex.
Metronidazole (p.837·1).
Vaginitis.

Arrow, Austral.; Ivax, Ger.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Eparema *Nycomed, Braz.; SIT, Ital.*
Cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3).
Constipation; liver disorders.

Eparema-Levul *SIT, Ital.*
Cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3); fructose (p.1945·1).
Constipation.

Epargriseovit *Pharmacia, Ital.; Deva, Turk.*
Cyanocobalamin (p.1980·2); folic acid (p.1940·1); nicotinamide (p.1957·3); ascorbic acid (p.1983·3).
Anaemias; peripheral neuropathies; tonic.

Eparical *Aventis, Ital.†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Eparinlider *Scharper, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Eparinovis *INTES, Ital.*
Heparin sodium (p.1301·2).
Eye disorders.

Eparmefolin *Bracco, Ital.*
Cyanocobalamin (p.1980·2); calcium folinate (p.1943·3).
Folate and vitamin B deficiency.

Eparven *Pantafarm, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Epasan *Biospray, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Epasan Omega 3 *Maver, Chile.*
Marine fish oils (p.1362·2).
Dietary supplement; hyperlipidaemias.

Epasol *Mendelejeff, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; cholesterol gallstones.

Epatin *Coronet, Indon.*
Lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1).
Dietary supplement.

Epativan *Cimed, Braz.*
Adenosine (p.1202·1); methionine (p.1450·1); choline (p.1934·2); vitamin B (p.1978·2).
Liver disorders.

Epatoxil *C & RF, Ital.†.*
Cogalactoisomerase sodium (p.2285·3).
Liver disorders.

Epax *Vivax, Venez.*
Omega-3 triglycerides (p.1362·1).
Hyperlipidaemias.

Epaxal *Scott-Cassara, Arg.; Docpharma, Belg.; Berna, Canad.†; Biosano, Chile; Berna, Cz.†; Berna, Denm.; Berna, Fin.; Niddapharm, Ger.†; Baxter, Gr.; Berna, Hong Kong; Droreth, Israel; Berna, Ital.; Berna, Malaysia; Berna, NZ; Pharmabroker, NZ; Berna, Neth.; Berna, Norw.; Berna, Philipp.; Berna, Port.; Berna, Singapore; Berna, Spain; SBL, Swed.; Berna, Switz.; Berna, Turk.; Masta, UK; Farma, Venez.†.*
An inactivated hepatitis A vaccine (RG-SB strain) (p.2214·2).
Active immunisation.

Epazin *Torrent, Philipp.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; neuropathic pain.

EP&C Essence *Potter's, UK.*
Bayberry bark (p.2263·2); hemlock spruce; sambucus (p.2383·1); peppermint oil (p.1761·2).
Colds; sore throat.

Epdantoin *Embil, Turk.*
Phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia.

Epelin *Ache, Braz.; Pfizer, Braz.*
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia.

Epexol *Sanbe, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

EPH *Investigaciones Filosoficas y Cientificas, Mex.*
Alpha tocoferiol acetate (p.1992·3).
Atherosclerosis; erectile dysfunction.

Ephedroides *Richelet, Fr.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Ephedronguent *Sterop, Belg.*
⊗ Ephedrine (p.1558·1).
Nasal congestion.

Ephedyl *Synco, Hong Kong.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Cold and influenza symptoms; coughs; rhinitis.

Ephelia *Stada, Ger.†; Ipsen, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Ephepect Blocker *Bolder, Hong Kong.*
Sodium dibunate (p.1573·1); dequalinium chloride (p.1641·3); anise oil (p.2258·2).
Coughs.

Ephepect-Blocker-Pastillen N *Bolder, Ger.*
Sodium dibunate (p.1573·1); dequalinium chloride (p.1641·3).
Coughs.

Ephepect-Pastillen N *Bolder, Ger.*
Thyme (p.2401·1); anise oil (p.2258·2); eucalyptus oil (p.2301·2); fennel oil (p.2303·1); peppermint oil (p.1761·2); ammonium chloride (p.1551·3).
Respiratory-tract disorders.

Epherit *Extractum, Hung.*
⊗ Ephedrine hydrochloride (p.1558·2).
Hypotension; narcoleptic syndrome; respiratory-tract disorders.

Ephron *Medhaus, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Ephydion
Note. This name is used for preparations of different composition.
Jolly-Jatel, Fr.
Oral drops: Ethylmorphine hydrochloride (p.52·2); sodium benzoate (p.1630·2); grindelia (p.2317·2).
Coughs.

Jolly-Jatel, Fr.
Syrup: Ethylmorphine hydrochloride (p.52·2); sulfogaiacol (p.1573·2); grindelia (p.2317·2).
Coughs.

Ephydrol
Note. This name is used for preparations of different composition.
CS, Fr.
Cream: Fioravanti; lavender oil (p.2331·2); bergamot oil (p.2265·1); lemon oil (p.2332·3); camphor (p.2273·2); menthol (p.2340·1); salicyl alcohol (p.2383·1); formaldehyde solution (p.1644·2).
Hyperhidrosis.

CS, Fr.
Topical solution (with brush or aerosol spray): Fioravanti; camphor (p.2273·2); menthol (p.2340·1); salicyl alcohol (p.2383·1); bergamot oil (p.2265·1); lemon oil (p.2332·3); lavender oil (p.2331·2); formaldehyde solution (p.1644·2); plantain (p.2369·3).
Hyperhidrosis.

CS, Fr.†.
Topical spray: Sanicula; fioravanti; camphor (p.2273·2); lavender oil (p.2331·2); bergamot oil (p.2265·1); lemon oil (p.2332·3); menthol (p.2340·1); salicyl alcohol (p.2383·1); formaldehyde solution (p.1644·2).
Hyperhidrosis.

Ephynal
Bayer Consumer, Arg.; Bayer, Austria; Roche, Belg.; Roche, Braz.; Bayer, Fr.†; IFET (ΙΦΕΤ), Gr.†; Roche Consumer, Irl.†; Roche, Israel†; Bayer, Ital.; Bayer, Port.; Bayer, S.Afr.; Bayer, Spain; Bayer, Switz.; Roche Consumer, UK.
Vitamin E (p.1992·3).
Vitamin E deficiency; vitamin E supplement.

Roche Consumer, Ger.†; Roche, Turk.; Roche, Venez.†.
Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Epianal *Will-Pharma, Neth.*
Sodium oleate (p.2139·1); a macrogol lauril ether (p.1916·1); chlorocarvacrol (p.1639·3).
Haemorrhoids.

Epi-C *Lafayette, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Epicef *FD, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Epi-Cell *Stada, Austria; Cell Pharm, Ger.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Epi-cell *Cell Pharm, Port.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Epicitrin *Neo Quimica, Braz.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial skin infections.

Epiclodina *Pisa, Mex.*
Clonidine (p.1247·1).
Hypertension.

Epicol *Loren, Mex.†.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3); tolu balsam (p.1574·2).
Coughs.

Epicol NF *Loren, Mex.†.*
Dextromethorphan (p.1555·2); ambroxol (p.1550·3).
Coughs.

Epicol Pediatrico *Loren, Mex.†.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Epicordin
Note. This name is used for preparations of different composition.
Solvay, Austria.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Solvay, Ger.†.
Captopril (p.1239·2).
Heart failure; hypertension.

Epicur *Obolenskoe, Rus.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Epident *Grands Espaces, Fr.*
Tooth extract.
Mucous membrane disorders of the nose and throat.

Epi-Derm *Dispolab, Chile.*
Silicon elastomer (p.2032·1).
Hypertrophic scars; keloids.

Epidona *Wyeth, Braz.†.*
Primidone (p.503·2).
Epilepsy.

Epidosin *TTK, India; Solvay, Indon.; Frik, Turk.*
Valethamate bromide (p.1778·3).
Cervical dilatation; smooth muscle spasm.

Epidosin Compozitum *Frik, Turk.*
Valethamate bromide (p.1778·3); paracetamol (p.108·1).
Smooth muscle spasm.

Epidoxo *LKM, Arg.*
Epirubicin (p.716·2).
Malignant neoplasms.

Epidrat *Mantecorp, Braz.*
Moisturiser.

Epidropal *Teofarma, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Epiduo *Galderma, Fr.*
Adapalene (p.1587·1); benzoyl peroxide (p.1590·2).
Acne.

Epiestrol *Rottapharm, Chile; Helsinn Birex, Irl.†; Pfizer, Ital.; Rotta, Port.; Rottapharm, Switz.†.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Epifil *Filaxis, Arg.*
Epirubicin (p.716·2).
Malignant neoplasms.

Epifoam *Schwarz, Israel; Alaven, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders; skin disorders.

Epifon *Biotech, Venez.†.*
Lamotrigine (p.485·1).
Epilepsy.

Epifrin *Allergan, USA†.*
⊗ Adrenaline hydrochloride (p.1203·3).
Open-angle glaucoma.

Epigen *Catalysis, Arg.; Medix, Mex.; Cheminova, Rus.*
Glycyrrhizic acid (p.2316·1).
Viral infections of skin and mucous membranes.

Epiglu *Meyer-Haake, Ger.; Synapse, Irl.; Schuco, UK.*
Ethyl 2-cyanoacrylate (p.2290·2); polymethylmethacrylate (p.2343·3).
Wound closure and suture support; wounds.

Epiject *Abbott, Canad.*
Sodium valproate (p.508·2).
Epilepsy.

Epikebir *Aspen, Arg.*
Epirubicin (p.716·2).
Malignant neoplasms.

Epikor *Korea United, Philipp.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; schizophrenia; trigeminal neuralgia.

Epikur *Agepha, Austria.*
Meprobamate (p.1006·2).
Anxiety; sleep disturbances.

Epilactal *Polpharma, Pol.*
Lamotrigine (p.485·1).
Epilepsy.

Epilan
Note. This name is used for preparations of different composition.
Gerot, Austria; Gerot, Cz.†.
Mephenytoin (p.490·1).
Epilepsy.

Anglo-French Drugs, India.
Phenytoin sodium (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Epilan-D *Gerot, Austria; Gerot, Cz.*
Phenytoin (p.495·2).
Epilepsy; neuralgias; seizures associated with neurosurgery.

Epilantin
Note. This name is used for preparations of different composition.
Streuli, Philipp.
Phenytoin sodium (p.495·2).
Epilepsy.

Otsuka, Spain†.
Phenytoin (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Epilantine *Streuli, Switz.†.*
Phenytoin sodium (p.495·2).
Epilepsy.

Epilem *Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Epilenil *Biolab Sanus, Braz.*
Valproic acid (p.508·2).
Epilepsy.

Epilepax *Ivax, Arg.*
Lamotrigine (p.485·1).
Epilepsy.

Epileptil *Teuto, Braz.*
Clonazepam (p.478·2).
Epilepsy.

Epilex *Abbott, India.*
Sodium valproate (p.508·2).
Epilepsy.

Epilfarmo *Farmoz, Port.*
Oxcarbazepine (p.490·3).
Epilepsy; trigeminal neuralgia.

Epilim *Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Irl.; Sanofi-Aventis, Malaysia; Aventis, NZ; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, UK.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; mania.

Epilim Chrono *Sanofi-Aventis, Irl.; Sanofi Synthelabo, UK.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

E-Pilo *Ciba Vision, USA†.*
⊗ Adrenaline acid tartrate (p.1203·2); pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure.

Epilobin *Leros, Cz.*
Epilobium; buchu (p.2269·3); solidago (p.2391·1); calendula (p.2273·1).
Urinary-tract disorders.

Epilon *Yung Shin, Hong Kong.*
Hyoscine butylbromide (p.1734·1) dicycloverine hydrochloride (p.1722·3) chlordiazepoxide (p.968·1) chlorophyllin copper complex sodium (p.1471·1) alu-

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

minium magnesium hydroxide magnesium oxide (p.1744·1) aluminium silicate (p.1707·3).
Dyspepsia; gastric hyperacidity; gastric pain; gastritis; gastrointestinal spasm; peptic ulcer.

Epi-Lyt *Valeo, Canad.; Stiefel, USA.*
Glycerol (p.2314·2); lactic acid (p.2329·3).
Dry skin.

Epimaz *Ivax, UK.*
Carbamazepine (p.471·3).

Epimil *Ivax, Cz.*
Lamotrigine (p.485·1).
Epilepsy.

Epinal *Alcon, USA.*
⊗ Adrenaline borate complex (p.1204·2).
Open-angle glaucoma.

Epinat *Nycomed, Norw.*
Phenytoin (p.495·2).
Epilepsy.

Epi-NC *Neocorp, Ger.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Epinerve *SIFI, Ital.*
Epigallocatechin gallate (p.1613·3).
Eye disorders.

Epinitril
Bouchara-Recordati, Fr.; Rottapharm, Gr.; Rottapharm, Irl.†; Rottapharm, Ital.; Delta, Port.; Rottapharm, Spain.
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Epione *Schering-Plough, Port.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Epipak *3M Espe, Ger.†.*
Aluminium chlorohydrate (p.1588·3); polyethyleneimine hydrochloride.
Mouth disorders.

EpiPen *Merck, Arg.; CSL, Austral.; ALK, Austria; ALK, Belg.; Allerex, Canad.; ALK, Cz.; ALK, Denm.; ALK, Fin.; IFET (ΙΦΕΤ), Gr.; ALK, Hung.; Center, Israel; Merck, Malaysia; CSL, NZ; ALK, Neth.; ALK, Norw.; Alk-Abello, Pol.; Merck, Port.; Merck, S.Afr.; ALK, Swed.; Trimedal, Switz.; ALK, UK; Dey, USA.*
⊗ Adrenaline (p.1203·2).
Anaphylaxis; status asthmaticus.

Epi-Pevaryl *McNeil, Ger.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Epi-Pevaryl Heilpaste *Janssen-Cilag, Ger.†.*
Econazole nitrate (p.531·1); zinc oxide (p.1621·2).
Fungal skin infections.

Epi-Pevaryl Pv *McNeil, Ger.*
Econazole (p.531·1).
Pityriasis versicolor.

Epipevisone *Janssen-Cilag, Ger.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal and Gram-positive bacterial skin infections.

Epiphane *Uriage, Fr.†.*
Piroctone olamine (p.1610·1); cade oil (p.1616·1); levomenol (p.2333·3).
Scalp disorders.

Epiprocto *Epicaris, Arg.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium acetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

Epipropane *Medgenix, Belg.*
⊗ Phenobarbital magnesium (p.494·1); amfetamine sulfate (p.2150·2).
Agitation; epilepsy; hypertension.

EpiQuin *SkinMedica, USA.*
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Epiral *Zentiva, Cz.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Epirub *Alvia (Αλβια), Gr.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Episcorit *Sanum-Kehlbeck, Ger.*
Echinacea purpura (p.2298·1).
Respiratory- and urinary-tract infections.

Episec *Odan, Canad.*
Liquid paraffin (p.2030·3); propylene glycol (p.2374·1); trolamine stearate.

Episenta *Beacon, UK.*
Sodium valproate (p.508·2).
Epilepsy.

Episoft *LED, Fr.†.*
Moisturiser.
Dry skin disorders.

Episol UVA *Mantecorp, Braz.*
SPF 30: Oxybenzone (p.1608·3); avobenzone (p.1589·3); octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2).
Sunscreen.

Episol UVA Guard *Schering-Plough, Braz.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Epistaxol *Medical, Spain.*
⊗ Adrenaline (p.1203·2); phenazone (p.116·1); naphazoline hydrochloride (p.1565·2); rutoside (p.2305·1).
Epistaxis; mucous membrane haemorrhage.

Epitaloe *Mediwhite, Ital.*
Aloe vera (p.1588·2).
Corneal trauma.

Epitec *Cipla-Medpro, S.Afr.*
Lamotrigine (p.485·1).
Epilepsy.

Epitege *Euromedex, Fr.†.*
Barrier cream.
Formerly known as Epiplaie Epitège.

Epiteliol-C *Spedrog, Arg.*
Vitamin C (p.1983·3); hesperidin (p.2304·3); vitamins A and E (p.1922·1).
Skin and capillary disorders.

Epitelizante *Novartis, Spain.*
Methionine (p.1450·1); gentamicin sulfate (p.282·1); vitamin A palmitate (p.1973·1).
Corneal damage.

Epitezan *Allergan, Braz.*
Vitamin A (p.1971·2); chloramphenicol (p.239·3); amino acids.
Eye infections.

Epithea *Thea, Fr.*
Cyanocobalamin (p.1980·2).
Corneal scarring.

Epithelial
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.†.
Avena (p.2262·1); vitamins A and E (p.1922·1).
Skin disorders.

Grossmann, Switz.†.
Ichthammol (p.1599·1); linseed oil (p.2334·1); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Burns; ulcers; wounds.

Epitheliale *Ducray, Fr.*
Avena (p.2262·1); vitamins A and E (p.1922·1).
Skin disorders.

Epitheliale A-Derma *Pierre Fabre Dermo-Cosmetique, Arg.*
Avena (p.2262·1); vitamin A (p.1971·2); vitamin E (p.1992·2).
Skin disorders.

Epitheliale AH *Pierre Fabre Dermo-Cosmetique, Arg.; Medifarm Ducray, Venez.*
Avena (p.2262·1); hyaluronic acid (p.2320·1).
Skin lesions.

Epitol *Lemmon, USA.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Epitomax *Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Euro Registratie, Neth.*
Topiramate (p.506·2).
Epilepsy; migraine.

Epitopic *Gerda, Fr.*
⊗ Difluprednate (p.1529·3).
Skin disorders.

Epitrel *Loeffler, Mex.*
Tretinoin (p.1618·1).
Acne; sun-induced skin damage.

Epitrigine *Actavis, Hung.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Epitril *Novartis, India.*
Clonazepam (p.478·2).
Epilepsy.

Epitrogine *Liptis, USA.*
Lamotrigine (p.485·1).

Epival
Gerot, Austria†.
Sodium valproate (p.508·2).
Epilepsy.

Abbott, Canad.; Abbott, Mex.; Abbott, Philipp.
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; mania; migraine.

Epiven *Novell, Indon.*
Gabapentin (p.482·3).
Epilepsy.

Epivir *GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; Glaxo, Jpn†; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA; GSK, Venez.*
Lamivudine (p.895·1).
Hepatitis B; HIV infection.

Epizam *Cipla, India.*
Clonazepam (p.478·2).

Epizon
Note. This name is used for preparations of different composition.
Mepha, Hong Kong†.
Rectocaps for children: Paracetamol (p.108·1); propyphenazone (p.119·3); guaifenesin (p.1561·3).
Fever; pain.

Mepha, Hong Kong†.
Rectocaps for infants: Paracetamol (p.108·1); propyphenazone (p.119·3); guaifenesin (p.1561·3); valerian (p.2410·1); passion flower (p.2363·2).
Fever; pain.

Epleptin *Pharmaplan, S.Afr.*
Gabapentin (p.482·3).
Epilepsy.

Eplonat *Infirmarius-Rovit, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

E.P.Mycin *Boryung, Thai.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Epoallen *Allen, Austria.*
Epoprostenol sodium (p.1279·3).
Pulmonary hypertension; thrombosis prophylaxis during haemodialysis.

Epocaldi *Novell, Indon.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); evening primrose oil (p.2302·1).
Osteoporosis; premenstrual syndrome.

Epocan *Merck, Arg.†.*
Pyritinol hydrochloride (p.369·1).
Cerebrovascular disorders.

Epocelin *Fujisawa, Jpn†.*
Ceftizoxime sodium (p.236·2).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Epocler *Wyeth Consumer, Braz.*
Adenosine (p.1202·1); methionine (p.1450·1); choline (p.1934·2); betaine hydrochloride (p.2265·2); vitamin B (p.1978·2).
Liver disorders.

Epocrin *Gosnii, Rus.; HPB, Rus.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Epogam *Scotia, Cz.†; Strathmann, Ger.; Pharmacia, Irl.†; Zeller, Switz.*
Evening primrose oil (p.2302·1).
Atopic eczema.

Epogen *Cassara, Arg.; Amgen, USA.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Epogin *Chugai, Jpn.*
⊗ Epoetin beta (p.1061·1).
Anaemias; autologous blood transfusion.

Epokelan *Medochemie, Malaysia†.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Epokine
PMG, Chile.
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood donation.

Cheil Jedang, Philipp.; Macropharma, Philipp.; CJ, Thai.
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Epol *Polinac, Venez.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Epolar *Keri, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Epomax
Lek, Cz.†.
⊗ Epoetin omega (p.1061·1).
Anaemias; autologous blood transfusion.

Cryopharma, Mex.
⊗ Epoetin (p.1061·1).
Anaemias.

Epopen *Pensa, Spain.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusions.

Eposal
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Chile.
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Galeno, Venez.
Chlordiazepoxide (p.968·1).
Anxiety; insomnia.

Eposerin *Pharmacia, Ital.*
Ceftizoxime sodium (p.236·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Eposido *Blausiegel, Braz.*
Etoposide (p.718·1).
Malignant neoplasms.

Eposin *Teva, Belg.; Nycomed, Fin.†; Pharmachemie, Malaysia; Nycomed, Norw.; Pharmachemie, Port.; Pharmachemie, S.Afr.; Tedec Meiji, Spain†; Teva, Swed.; Pharmachemie, Thai.; Teva, Thai.; Mert, Turk.; Medac, UK.*
Etoposide (p.718·1).
Malignant neoplasms.

Eposino *Shandong Kexing, Philipp.*
⊗ Epoetin alfa (p.1061·1).
Anaemia of chronic renal failure.

Epotin *Julphar, UAE.*
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood transfusions.

Epotrex-NP *Novell, Indon.*
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood transfusion.

Epoxide *PP Lab, Thai.†.*
Chlordiazepoxide hydrochloride (p.968·2).
Anxiety.

Epoxitin *JC Healthcare, Ital.†.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusions.

Eppy *Chauvin, Irl.†; Smith & Nephew, S.Afr.; Abigo, Swed.†.*
⊗ Adrenaline (p.1203·2).
Glaucoma; open-angle glaucoma.

EPR *Elvetium, Arg.†.*
Epirubicin (p.716·2).
Malignant neoplasms.

Epratenz *SmithKline Beecham, Gr.†.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Eprex *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Pentafarma, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Cilag, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Cilag, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Gurel, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Epril *Hexal, Pol.; Ecosol, Switz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Epril Plus *Ecosol, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

E-Prime *Usana, Hong Kong†; Usana, Singapore.*
Vitamin E substances (p.1992·2).
Vitamin E and antoxidant supplement.

Eprinoc *Sanbe, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Eprodine *Pond's, Thai.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Eprofil
Note. This name is used for preparations of different composition.
Andromaco, Chile†.
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Columbia, Mex.
Tiabendazole (p.156·2).
Pediculosis; scabies.

Vargas, Venez.
Mebendazole (p.148·3).
Worm infections.

Epsicaprom *Bial, Port.*
Aminocaproic acid (p.1053·2).
Fibrinolysis.

Epsidox *Laboratorios Chile, Chile.*
Etoposide (p.718·1).
Malignant neoplasms.

Epsilat *Coup, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Epsilon *Will-Pharma, Belg.*
Ibuprofen (p.64·2).
Fever; pain.

Epsin *GSK, Mex.*
Aciclovir (p.862·3).
Herpes labialis.

Epsipam *Will-Pharma, Belg.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Epsitron *Remedica, Hong Kong†; Remedica, Thai.*
Captopril (p.1239·2).
Heart failure; hypertension.

Epsoclar *Mayne, Ital.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Epsodil *Biologici Italia, Ital.†.*
Heparin sodium (p.1301·2).
Maintenance of patency of catheters and cannulas.

Epsodilave *Mayne, Ital.*
Heparin sodium (p.1301·2).
Maintenance of patency of catheters and cannulas.

Epsolin *Cadila, India.*
Phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia; ventricular arrhythmias.

Epsonal *Pyridam, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

ept Stick Test *Warner-Lambert, USA.*
Pregnancy test (p.2372·1).

Eptacor *Corsalud, Venez.†.*
Cyproheptadine hydrochloride (p.575·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Eptadone *Molteni, Ital.; Dee, UK.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal; pain.

Eptavit *Leurquin, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Eptoin *Abbott, India.*
Phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia.

Epulor *Vistapharm, USA.*
Preparation for enteral nutrition (p.1922·1).

Epuram *Pharmafarm, Fr.†.*
Citrulline (p.1935·1); arginine hydrochloride (p.1928·2); ornithine hydrochloride (p.1959·2).
Liver disorders.

Epzicom *GSK, USA.*
Abacavir (p.861·3); lamivudine (p.895·1).
HIV infection.

Equagesic
Note. This name is used for preparations of different composition.
Wyeth, India.
Aspirin (p.20·3); ethoheptazine citrate (p.52·1).
Dysmenorrhoea; pain.

Akromed, S.Afr.
Aspirin (p.20·3); meprobamate (p.1006·2); ethoheptazine citrate (p.52·1).
Musculoskeletal spasm; tension headache.

Leitner, USA.
Aspirin (p.20·3); meprobamate (p.1006·2).
Musculoskeletal pain.

Equal *Merisant, Canad.; Nutrasweet, NZ; Merisant, Thai.†; Calox, Venez.†.*
Aspartame (p.1930·1).
Sugar substitute.

Equalactin *Numark, USA.*
Polycarbophil calcium (p.1763·3).
Constipation; diarrhoea.

Equaleze *Aquamarine, UK.*
Sodium chloride (p.1686·1).
Nasal congestion.

Equaliv *Meyer, Venez.*
Valerian (p.2410·1); crataegus (p.2289·1); passion flower (p.2363·2).
Anxiety.

Equalsweet *Merisant, Arg.*
Sucrose (p.1969·2); aspartame (p.1930·1); acesulfame potassium (p.1928·1).
Sugar substitute.

Equanil *Sanofi-Aventis, Fr.; Akromed, S.Afr.*
Meprobamate (p.1006·2).
Alcohol withdrawal syndrome; anxiety; premedication; sedative; skeletal muscle spasm.

Equanox *Linde, UK.*
Nitrous oxide (p.1789·3); oxygen (p.1690·2).

Equasym *Celltech, Denm.; UCB, Ger.; UCB, Irl.; Celltech, Neth.; Celltech, Norw.; UCB, UK.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Equate *Pharmascience, Canad.*
Aspirin (p.20·3).

Equetro *Shire, USA.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Equiceft *Tum, Turk.*
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Equidan *Otsuka, Spain†.*
Belladonna alkaloids (p.2263·3); phenytoin (p.495·2); phenobarbital (p.492·2).
Anxiety; infantile spasms; insomnia; menopausal disorders; migraine.

Equiday *Algol, Fin.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Equiderm *Galderma, Mex.; Galderma, Venez.†.*
Emollient; moisturiser.

Equifan *Bajamed, Mex.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Equifem *Elea, Arg.*
Drospirenone (p.2095·2); estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Equilet *Mission Pharmacal, USA†.*
Calcium carbonate (p.1714·1).
Hyperacidity.

Equilibra *Darrow, Braz.†.*
St John's wort (p.422·3).
Depression.

Equilibrane *Temis, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Equilibrin *Aventis, Ger.*
Amitriptylinoxide (p.381·1).
Depression.

Equilibrium *Jagson, India.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety.

Equilid *Sanofi-Aventis, Braz.; Bruno, Ital.*
Sulpiride (p.1028·3).
Adjuvant in gastric ulcer; depression; nausea and vomiting; nervous disorders; psychoses; schizophrenia.

Equilium *Fumouze, Fr.†.*
Tiapride (p.1032·2).
Aggressive states; agitation; choreiform movements; pain.

Equilon *Chefaro, UK†.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Equilon Herbal *Chefaro, UK.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome.

Equin *Aldo-Union, Hong Kong; Aldo-Union, Singapore; Aldo, Spain.*
Conjugated oestrogens (p.2087·2).
Dysfunctional uterine bleeding; female hypogonadism; lactation inhibition; menopausal disorders; osteoporosis.

Equinacea *Herbarium, Braz.†.*
Echinacea (p.2298·1).

Equinorm *Aspen, S.Afr.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome.

Equipax *Parke, Davis, Spain†.*
Gabapentin (p.482·3).
Epilepsy.

Equirex *Jagson, India.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Irritable bowel syndrome; peptic ulcer.

Equisedin *Lazar, Arg.*
Bromazepam (p.964·3).
Anxiety.

Equisil N *Klein, Ger.*
Equisetum (p.2299·3); ribwort plantain (p.2379·1); castanea vulgaris; cowslip rhizome (p.2372·2); verbascum flowers (p.2413·3); thyme (p.2401·1); colloidal silicon dioxide (p.2146·3).
Coughs and associated respiratory-tract disorders.

Equi-Sleep *Equity, S.Afr.†.*
Doxylamine succinate (p.578·2).
Insomnia.

Equitam
Note. This name is used for preparations of different composition.
Euroforma, Braz.
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders.

Biotherapie, Fr.†.
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety.

Equiton *Bruschettini, Ital.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Equizolin *Tum, Turk.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Equoral *Ivax, Cz.; Ivax, Pol.; Ivax, Thai.; SPB, Thai.*
Ciclosporin (p.1822·2).
Atopic eczema; auto-immune disorders; graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

ER Cream *Curacel, Austral.†.*
Allantoin (p.1588·1); alpha tocoferil acetate (p.1992·3); eicosapentaenoic acid (p.1362·1); coal tar (p.1616·2); vitamin A palmitate (p.1973·1); zinc oxide (p.1621·2).
Skin disorders.

Era *Abbott, NZ.*
Erythromycin lactobionate (p.270·1) or erythromycin stearate (p.270·1).
Bacterial infections.

Erabutol Plus *Pyridam, Indon.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Eracid *Svizera, India†.*
Pantoprazole sodium (p.1760·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Eracillin *Chew, Thai.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Eraclox *Unison, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Eradacil *Sanofi-Aventis, Braz.; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Port.†.*
Rosoxacin (p.330·3).
Gonorrhoea; urinary-tract infections.

Eradipak *GSK, Cz.†.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Eradix *Kwizda, Austria.*
Famotidine (p.1730·1).
Peptic ulcer.

Eraldin *Richmond, Arg.*
Sevoflurane (p.1793·2).
General anaesthesia.

Eralga *Chew, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Eramox *Nycomed, Austria†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Eramycin *Wesley, USA.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eranz *Wyeth, Arg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Venez.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Eraphage *Guardian, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Erase *Aesthetic Plus, Singapore.*
Onion (p.2356·3); allantoin (p.1588·1); vitamin E acetate (p.1992·3); nicotinamide (p.1957·3); aesculus (p.2248·2).
Scars.

Erasol *McGloin, Austral.*
Phenazone (p.116·1).
Ear ache.

Erasul *Innoderm, Philipp.*
Bio-sulfur (p.1614·1).
Skin disorders.

Erathrom *Asian Pharm, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Eraverm *Gemballa, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Eraverm-T *Gemballa, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Eraxil *Gepepharm, Ger.*
Crotamiton (p.1593·2).
Scabies.

Eraxis *Pfizer, USA.*
Anidulafungin (p.527·2).
Candidiasis.

Erazaban *Healthcare Brands, Cz.*
Docosanol (p.872·2).
Herpes labialis.

Erazon *KRKA, Hung.†; KRKA, Rus.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders.

Erbacomplex *Pharmacia, Venez.†.*
Vitamin B substances (p.1922·1).

Erbazid *Pfizer, Mex.†.*
Isoniazid (p.288·1).
Tuberculosis.

Erbazide *Mac, India†.*
Methaniazide calcium (p.298·3).
Tuberculosis.

Erbitrax *Loeffler, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Erbitux *Merck, Arg.; Alphapharm, Austral.; Merck, Belg.; Merck, Chile; Merck, Cz.; Merck, Denm.; Merck, Fin.; Merck-Lipha, Fr.; Merck, Gr.; Merck, Hong Kong; Merck, Hung.; Merck, Irl.; Merck, Israel; Merck, Ital.; Merck, Malaysia; Pacific, NZ; Merck, Neth.; Merck, Norw.; Merck, Philipp.; Merck, Port.; Merck, Singapore; Merck, Spain; Merck, Swed.; Merck, Switz.; Merck, UK; BMS, USA.*
Cetuximab (p.695·3).
Colorectal cancer; head and neck cancer.

Erbolin *Biofarma, Turk.*
Omeprazole (p.1753·1).

Erbonda Noche *Boehringer Ingelheim, Arg.†.*
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia.

Ercaf *Geneva, USA.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and related vascular headache.

Ercar *Almirall, Spain†.*
Carboplatin (p.693·1).
Bladder cancer; head and neck cancer; ovarian cancer; small-cell lung cancer.

Ercefuryl *Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi Synthelabo, Philipp.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.*
Nifuroxazide (p.307·2).
Gastrointestinal infections.

Erceryl *Sanofi-Aventis, Fr.*
Nifuroxazide (p.307·2).
Diarrhoea.

Ercestop *Sanofi-Aventis, Fr.*
Loperamide hydrochloride (p.1741·1).
Formerly known as Delalande Diarrhée.
Diarrhoea.

Erco-Fer *Orion, Swed.*
Ferrous fumarate (p.1938·3).
Iron deficiency; iron-deficiency anaemia.

Ercoquin *Medic, Denm.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; malaria; photosensitivity; rheumatoid arthritis.

Ercoril *Medic, Denm.*
Propantheline bromide (p.1764·3).
Gastrointestinal spasm.

Ercycof *Pharmachemie, Neth.†.*
Ergotamine tartrate (p.620·1); cyclizine hydrochloride (p.574·2); caffeine (p.1116·3).
Migraine.

Erdomed *CSC, Austria; Medicom, Cz.; CSC, Hung.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Erdon *Aristopharma, Hong Kong.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Erdopect *Orion, Fin.*
Erdosteine (p.1560·1).
Respiratory-tract disorders.

Erdostin *Ilsan, Turk.*
Erdosteine (p.1560·1).
Respiratory disorders with increased mucus.

Erdotin *Asta Medica, Braz.†; Edmond, Denm.; Edmond Pharma, Ital.; Edmond, Port.; Galen, UK.*
Erdosteine (p.1560·1).
Bronchitis; respiratory-tract congestion.

Erectol *Northia, Arg.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Eremfat
Fatol, Austria; Fatol, Ger.
Rifampicin (p.325·3) or rifampicin sodium (p.328·2).
Brucellosis; Buruli ulcer; leprosy; meningococcal meningitis prophylaxis; staphylococcal infections; tuberculosis.

Fatol, Cz.
Rifampicin (p.325·3).

Eres N *Muller Goppingen, Ger.†.*
Verbascum flowers (p.2413·3).
Bronchial catarrh.

Erevan *Fournier, Ital.†.*
A heparinoid (p.1305·2).
Superficial vascular disorders; thrombosis prophylaxis.

Erevit *Biotika, Cz.; Zentiva, Cz.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Erfulyn *Nobel, Turk.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Erfuzide *Union Drug, Thai.*
Nifuroxazide (p.307·2).
Gastrointestinal infections.

Erg XXI *Farmorcore, Port.†.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders; hypertension.

Ergafein *Ulagay, Turk.*
Paracetamol (p.108·1); ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Fever; pain.

Ergalea *Taurus, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in women.

Ergam *Gedeon Richter, Hung.*
Ergotamine tartrate (p.620·1).
Migraine; postpartum atony; postpartum haemorrhage.

Ergamisol *Janssen-Cilag, Austral.†; Janssen-Cilag, Belg.†; Janssen-Ortho, Canad.†; Janssen-Cilag, Ger.†; IFET (ΙΦΕΤ), Gr.; Janssen-Cilag, Israel; Janssen-Cilag, Neth.†; Janssen-Cilag, S.Afr.†; Janssen, USA†.*
Levamisole hydrochloride (p.147·2).
Adjunct to fluorouracil in colon cancer; immunostimulant; nephrotic syndrome.

Erganton *Anto, Ger.†; Q-Pharm, Ger.†.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine; vascular disorders.

Ergenyl *Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Swed.*
Sodium valproate (p.508·2).
Epilepsy; mania.

Ergenyl Chrono *Sanofi Synthelabo, Ger.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Ergex *Rimsa, Mex.*
Ranitidine (p.1766·1); cisapride (p.1720·3).
Acid aspiration; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ergix
Note. This name is used for preparations of different composition.
Merck Medication Familiale, Fr.
Capsules: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Merck Medication Familiale, Fr.†.
Lozenges: Tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Sore throat.

Merck Medication Familiale, Fr.
Syrup: Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Merck Medication Familiale, Fr.
Tablets: Ibuprofen (p.64·2).
Fever; pain.

Ergix Toux Seche *Merck Medication Familiale, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly known as Taritux.
Coughs.

ergo sanol spezial N *Sanol, Ger.*
Ergotamine tartrate (p.620·1).
Migraine and other vascular headache.

Ergobel
Note. This name is used for preparations of different composition.
Kwizda, Ger.
Nicergoline (p.2352·1).
Mental function disorders.

Coup, Gr.
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Ergobelan *Labomed, Chile.*
Belladonna (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Vascular headache.

Ergocaf *Probiomed, Mex.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Ergocalm *Teofarma, Ger.*
Lormetazepam (p.1005·2).
Premedication; sleep disorders.

Ergoclavin *Bros, Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ergocrist *Sanofarm, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Ergodavur *Davur, Spain.*
Dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders; vascular ear, nose, throat and eye disorders; vestibular disorders.

Ergodesit *Desitin, Ger.*
Codergocrine mesilate (p.363·3).
Hypertension; mental function disorders.

Ergodilat *Diviser Aquilea, Spain†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; circulatory disorders.

Ergodose *Shire, Fr.†.*
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Ergodryl *Pfizer, Austral.†; Erfa, Canad.*
Ergotamine tartrate (p.620·1); caffeine citrate (p.1116·3); diphenhydramine hydrochloride (p.577·2).
Migraine and other vascular headaches.

Ergodryl Mono *Pfizer, Austral.†.*
Ergotamine tartrate (p.620·1).
Migraine and other vascular headaches.

Ergoffin *Temmler, Ger.†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Headache; migraine.

Ergofil *Vocate, Gr.*
Dihydroergocristine mesilate (p.364·2).
Peripheral vascular disorders.

Ergogin *Cipla, India.*
Methylergometrine (p.2011·2).

Ergohydrine *Streuli, Switz.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disease.

Ergokapton *Strallhofer, Austria.*
Ergotamine tartrate (p.620·1).
Migraine and related vascular headaches.

Ergokoffin *OBA, Denm.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Ergo-Kranit *Krewel, Ger.†.*
Ergotamine tartrate (p.620·1); propyphenazone (p.119·3); paracetamol (p.108·1).
Headache; migraine.

Ergo-Kranit Migrane *Krewel, Ger.*
Ergotamine tartrate (p.620·1).
Formerly known as Ergo-Kranit akut.
Migraine.

Ergolaktyna *Polfa Grodzisk, Pol.*
Bromocriptine (p.800·3).
Benign breast disorders; hyperprolactinaemia; infertility; lactation inhibition; parkinsonism; premenstrual syndrome; prolactinoma.

Ergolefrin *Gepepharm, Ger.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Ergo-Lonarid PD *Boehringer Ingelheim, Ger.†.*
Dihydroergotamine tartrate (p.618·3); paracetamol (p.108·1).
Headache; migraine.

Ergomar *Lotus, USA.*
Ergotamine tartrate (p.620·1).
Migraine and related vascular headache.

Ergomed *Kwizda, Austria.*
Codergocrine mesilate (p.363·3).
Cerebral insufficiency; hypertension; migraine and related vascular headache.

Ergomemor *Hexal, Braz.†.*
Glutamic acid; calcium glycerophosphate; tribasic calcium phosphate; vitamin B substances (p.1922·1).
Dietary supplement.

Ergometrin *Uniao Quimica, Braz.*
Methylergometrine maleate (p.2011·1).

Ergomicon *Offenbach, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Ergomimet *Fujisawa, Ger.†.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headaches; vascular disorders.

Ergomimet plus *Fujisawa, Ger.†.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Ergonef *ITF, Chile.*
Clonixin lysine (p.37·1); ergotamine tartrate (p.620·1).
Headache; migraine.

Ergont *Sigmapharm, Austria; Desitin, Ger.†.*
Dihydroergotamine mesilate (p.618·2).
Circulatory disorders; hypotension; migraine and related vascular headache; vascular disorders.

Ergosia *Asian Pharm, Thai.*
Ergotamine tartrate (p.620·1).
Migraine.

Ergospharma *Alpharma, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Ergotab *Jagson, India.*
Ergot (p.2010·1).
Menopausal haemorrhage; menorrhagia; postpartum haemorrhage; uterine atony.

ergotam *CT, Ger.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headaches; vascular disorders.

Ergotan *Salf, Ital.*
Ergotamine tartrate (p.620·1).
Migraine and related vascular headache.

Ergotika *Ikapharmindo, Indon.*
Codergocrine mesilate (p.363·3).
Mental function impairment.

Ergotonine *Streuli, Switz.*
Dihydroergotamine mesilate (p.618·2).
Fatigue; hypotension; migraine.

Ergotop *Kwizda, Austria; Ivax, Cz.; Kwizda, Hung.*
Nicergoline (p.2352·1).
Alzheimer's disease; mental function impairment; peripheral and cerebral vascular disorders; vestibular disorders.

ergotox *CT, Ger.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Ergotrate *Biolab Sanus, Braz.†; Armstrong, Mex.; Bedford, USA.*
Ergometrine maleate (p.2009·2).
Postpartum or postabortal haemorrhage.

Ergotyl *Sandoz, Thai.*
Methylergometrine maleate (p.2011·1).
Management of third stage of labour; postpartum haemorrhage; postpartum uterine atony.

Ergovasan *Montavit, Austria.*
Dihydroergotamine mesilate (p.618·2).
Circulatory disorders; hypotension; migraine and related vascular headaches.

Ergoxina *Klonal, Arg.†.*
Codergocrine (p.364·1).

Ergybiol *Nutergia, Fr.*
Mineral preparation (p.1922·1).

Ergymag *Nutergia, Fr.*
Vitamin B and mineral preparation (p.1922·1).

Ergyphilus *Nutergia, Fr.*
Lactobacillus rhamnosus (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Bifidobacterium bifidum* (p.2372·3).
Maintenance of normal gastrointestinal flora.

Eri *Andromaco, Arg.*
Erythromycin (p.269·2).

Eribec *Collins, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Eriber *Berman, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Eribiotic *Teuto, Braz.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Ericaf *Tempo Scan Pacific, Indon.*
Ergotamine (p.621·3); caffeine (p.1116·3).
Migraine.

Ericin *Chew, Thai.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eridamin *Brasmedica, Braz.†.*
Benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Eridosis *Orravan, Spain.*
Erythromycin (p.269·2).
Acne.

Eriflogin *Asta Medica, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Erifostine *Teva Tuteur, Arg.*
Amifostine (p.1436·3).
Reduction of haematotoxicity and nephrotoxicity associated with chemotherapy.

Eriglobin *Max Farma, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of the iron.
Iron-deficiency anaemia.

Erigon *Extractum, Hung.*
Codeine hydrochloride (p.37·2); sulfogaiacol (p.1573·2).
Coughs and cold symptoms.

Erigrand *Ahimsa, Arg.*
Erythromycin (p.269·2).
Bacterial infections.

Eriken *Kendrick, Mex.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Eril
Note. This name is used for preparations of different composition.
Savio, Ital.†.
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Asahi, Jpn†.
Fasudil hydrochloride (p.1285·2).
Cerebral vasospasm following subarachnoid haemorrhage.

Erilon *Biotech, Venez.*
⊗ Desonide (p.1525·1).
Skin disorders.

Erimicin
Note. This name is used for preparations of different composition.
Cassara, Arg.; D & M, Chile.
Benzoyl peroxide (p.1590·2); erythromycin (p.269·2).
Acne.

Sanli, Turk.
Erythromycin (p.269·2).
Bacterial infections.

Erimicina *Globo, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Erimit *TP, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erimycin *Siam Bheasach, Thai.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erinol *Homeocan, Canad.*
Homoeopathic preparation.

Eriogem *Eriochem, Arg.*
Gemcitabine (p.728·1).
Malignant neoplasms.

Erios *Mepha, Switz.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Eriox *Eriochem, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Erioxal *Eriochem, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Eripan *Biofarma, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Erisine *Lafedar, Arg.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erisol *Cassara, Arg.*
Erythromycin (p.269·2).
Acne.

Erispan *Maver, Mex.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Eristin *Atlas, Arg.*
Erythromycin lactobionate (p.270·1); colistimethate sodium (p.256·3).
Bacterial eye infections.

Erisuspen *Medifarma, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Erit *Duncan, Arg.*
Erythromycin (p.269·2).
Bacterial infections.

Eritax *Luper, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritimix *Etifar, Venez.†.*
Erythromycin (p.269·2).
Bacterial infections.

Eritina
Note. This name is used for preparations of different composition.
Cristalia, Braz.
⊗ Epoetin alfa (p.1061·1).
Anaemias.

Sanitas, Port.†.
Erythromycin propionate (p.270·1).
Bacterial infections.

Eritos *Biolab Sanus, Braz.*
Dropropizine (p.1557·3).
Coughs.

Eritrax *Luper, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritrazon *Cipan, Port.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eritrerba *Pfizer, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrex *Ache, Braz.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritrex A *Ache, Braz.*
Erythromycin (p.269·2); azulene (p.2262·3).
Bacterial skin infections.

Eritril
Note. This name is used for preparations of different composition.
Northia, Arg.
Enalapril (p.1276·1).
Hypertension.

Ortoquimica, Braz.†.
Erythromycin (p.269·2).
Bacterial infections.

Eritrin *Hebron, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritro *Kocak, Turk.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eritrobron *Casasco, Arg.*
Erythromycin estolate (p.269·3); bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Eritrocina
Abbott, Ital.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Amdipharm, Port.
Erythromycin ethyl succinate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial infections.

Eritroderm *Valeant, Arg.*
Erythromycin (p.269·2).
Acne.

Eritrofarm *Valeant, Arg.*
Erythromycin lactobionate (p.270·1).
Bacterial conjunctivitis.

Eritrofarmin *Rayere, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrogen *Bioprofarma, Arg.*
⊗ Epoetin beta (p.1061·1).
Anaemias; autologous blood transfusion.

Eritrogobens *Normon, Spain.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eritrolat *Liferpal, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Eritromax *Blausiegel, Braz.*
⊗ Epoetin (p.1061·1).
Anaemias.

Eritromed *Biocumed, Arg.*
Erythromycin (p.269·2) or erythromycin lactobionate (p.270·1).
Bacterial eye infections.

Eritroped *Abbott, Venez.†.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eritropharma *Alpharma, Mex.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eritropiu *Uno, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of the iron.
Iron-deficiency anaemia.

Eritroquim *Quimica y Farmacia, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrosif *Yeni, Turk.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrosol *Solfran, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrovac *Corsalud, Venez.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritroveinte *Medinova, Spain.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Eritrovier *Tecnofarma, Mex.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Eritrovit *Vitapan, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Eritrovit B12 *Lisapharma, Ital.†.*
Cyanocobalamin (p.1980·2).
Anaemia; neuritis.

Eritrowel *Ivax, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Eriwest *Bruluagsa, Mex.*
Erythromycin stearate (p.270·1); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Erjean *Erjean, Fr.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Erka *Aflofarm, Pol.*
Aspirin (p.20·3); ethenzamide (p.51·3); caffeine (p.1116·3).
Pain.

Erkaltungsbalsam *Sanofi Synthelabo, Austria.*
Eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); pine silvestris oil (p.2368·2); camphor (p.2273·2); menthol (p.2340·1).
Cold symptoms.

Erkaltungsbalsam-ratiopharm E Salbe *Ratiopharm, Ger.†.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); turpentine oil (p.2406·3).
Cold symptoms.

Erkaltungstee *Abtswinder, Cz.†.*
Salix (p.121·3); sambucus (p.2383·1); thyme (p.2401·1); fennel (p.2302·3); liquorice (p.1740·3); mallow flower (p.2337·2).
Cold and influenza symptoms.

Erladexone *Malaysia Chemist, Singapore†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Erlan *Landsteiner, Mex.*
⊗ Erythropoetin (p.1061·1).
Anaemias; autologous blood transfusion.

Erlecit *Doctum, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Erlicon *Polychronus, Gr.*
Citalopram (p.385·3).
Depression.

Erliten *Malaysia Chemist, Singapore†.*
Ketotifen fumarate (p.582·2).
Allergic bronchitis; allergic conjunctivitis; allergic rhinitis; allergic skin disorders; asthma; hay fever.

Erlmetin *Malaysia Chemist, Singapore†.*
Cimetidine (p.1716·2).
Acid aspiration; adjunct in pancreatic insufficiency; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Erloric *Malaysia Chemist, Singapore†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Erlvirax *Malaysia Chemist, Singapore†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ermm-1 *CIS, Cz.*
Erbium-169 citrate (p.2053·3).
Joint disorders.

Ermofan *Chrispa (Χρισπα), Gr.*
Ofloxacin (p.310·2).
Bacterial infections.

Ermolax *Chrispa (Χρισπα), Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Ermsech *Pharmacia, Ger.†.*
Calcium lactate (p.1676·1); echinacea (p.2298·1).
Hypersensitivity disorders; increase of immune capacity.

Ermycin *Remedica, Singapore†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Ermysin *Orion, Fin.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Ernex *Casasco, Arg.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders; vulvovaginal disorders.

Ernex Duo *Casasco, Arg.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Ernodasa *Ern, Spain.*
Streptodornase (p.2393·1); streptokinase (p.1402·3).
Inflammation; soft-tissue damage; ulcers.

ERO *Scherer, USA.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Erocap *Lilly, Austral.†.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Erocef *Ethica, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Erodium *Ivax, Arg.*
Bromperidol (p.965·1).
Psychoses.

Erogran *Hovid, Malaysia†.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections; protozoal infections.

Erole Forte *Orion, Fin.†.*
d-Alpha tocopherol; selenium yeast (p.1922·1).
Dietary supplement.

Erole-C *Orion, Fin.†.*
Capsules, *d*-alpha tocopherol; selenium yeast; tablets, ascorbic acid (p.1922·1).
Dietary supplement.

Erolin *Egis, Cz.; Egis, Hong Kong; EGIS, Hung.; Egis, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin reactions; pruritus; urticaria.

Eromel *Aspen, S.Afr.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eromycin *Julphar, UAE.*
Erythromycin (p.269·2), erythromycin ethyl succinate (p.269·3), or erythromycin stearate (p.270·1).
Bacterial infections.

Erosfil *Andromaco, Chile.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Erosil *Pharmanel, Gr.*
Ambroxol (p.1550·3).
Mucolytic.

Erotab *Hovid, Malaysia†; Hovid, Singapore.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Eroxade *Osoth, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Erpaclovir *Med-One, Gr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Erpalfa *INTES, Ital.*
Cytarabine (p.705·1).
Viral keratitis.

Erpecalm *Prisfar, Port.*
Thyme oil (p.2401·2); soapwort (p.2388·2); melissa (p.2339·3); lavender (p.2331·1); lemon (p.2332·3); chamomile (p.2279·3); plantain (p.2369·3).
Herpes labialis.

Erphadrox *Erlimpex, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Erphamol *Erlimpex, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Erphamoxy *Erlimpex, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Erphathrocin *Erlimpex, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erphatrim *Erlimpex, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Erpimycin *Farmedia, Gr.*
Vidarabine (p.912·2).
Herpesvirus eye infections.

Erpizon *Demo, Gr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Erradic *Libbs, Braz.*
Capsules, amoxicillin (p.202·2); tablets, clarithromycin (p.248·2); capsules, omeprazole (p.1753·1).
Peptic ulcer.

Erreclor *Errekappa, Ital.†.*
Cefaclor (p.217·2).
Bacterial infections.

Erreflog *Errekappa, Ital.*
Nimesulide (p.95·3).
Mouth and throat disorders; peri-articular pain.

Errekam *TAD, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Erremox *Errekappa, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Errolon *Sandoz, Arg.*
⊗ Furosemide (p.1292·1).
Hypertension.

Errolon A *Sandoz, Arg.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).

Erser *Serral, Mex.*
Aciclovir (p.862·3).
Viral infections.

Ersilan *Ivax, Cz.*
Etofylline (p.1121·1); dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders.

Ersylan *Kimia, Indon.*
⊗ Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); ephedrine hydrochloride (p.1558·2).
Cough.

Ertaczo *Neutrogena Dermatologicals, USA.*
Sertaconazole nitrate (p.546·1).
Tinea pedis.

Ervemin *Ivax, Arg.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Ervevax *GSK, Austral.; GSK, Austria; GSK, Cz.†; GSK, Irl.†; GSK, Ital.†; GSK, Malaysia†; GSK, Mex.; GSK, NZ; GSK, Rus.; SmithKline Beecham, Switz.†.*
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Ervossil *Natiris, Venez.*
Ginger (p.1732·3); chamomile (p.2279·3); micromeria brownei; star anise (p.2392·1).
Digestive disorders; dyspepsia.

Ervostal *Inter, Venez.*
Ergotamine tartrate (p.620·1); crataegus (p.2289·1); belladonna (p.2263·3); phenobarbital (p.492·2).

Erwinase *Speywood, Cz.†; Ipsen, Denm.†; Ipsen, Fin.†; Ipsen, Ger.†; Ipsen, Gr.; Ipsen, Irl.; Beaufour-Ipsen, Malaysia†; Emerging Pharma, Malaysia†; NZ Medical & Scientific, NZ; OPi, Neth.; EUSA, Port.; Beaufour-Ipsen, Singapore†; Ipsen, Swed.; Beaufour-Ipsen, Thai.†; OPi, UK.*
Crisantaspase (asparaginase) (p.682·2).
Acute lymphocytic leukaemia.

Erxetilan *Leovan, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ery
Bouchara-Recordati, Fr.
Erythromycin ethyl succinate (p.269·3) or erythromycin propionate (p.270·1).
Bacterial infections.

1A, Ger.
Erythromycin stearate (p.270·1).
Bacterial infections.

Eryacne *Galderma, Arg.; Galderma, Austral.; Galderma, Fr.; Laviphar m, Gr.; Galderma, Hong Kong†; Galderma, Ital.; Galderma, NZ; Galderma, Neth.; Galderma, Singapore; Galderma, Thai.; Liba, Turk.; Galderma, Venez.*
Erythromycin (p.269·2).
Acne.

Eryacnen *Galderma, Braz.; Galderma, Chile; Galderma, Mex.*
Erythromycin (p.269·2).
Acne.

Eryaknen *AB-Consult, Austria; Galderma, Ger.; Galderma, Switz.*
Erythromycin (p.269·2).
Acne.

Eryange *Klorane, Fr.†.*
Zinc oxide (p.1621·2); glycerol (p.2314·2); talc (p.1615·2); calendula (p.2273·1).
Skin irritation.

Eryase *Ducray, Fr.*
Avena (p.2262·1); zinc oxide (p.1621·2); copper sulfate (p.1935·3).
Nappy rash.

Erybesan *Sandoz, Austria.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erybeta *Betapharm, Ger.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erybid *Abbott, Canad.*
Erythromycin (p.269·2).
Bacterial infections.

Erybros *Bros, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Eryc
Mayne, Austral.; Pfizer, Canad.; Biogal-Teva, Hung.; Taro, Israel†; Parke, Davis, Neth.†; Warner Chilcott, USA†.
Erythromycin (p.269·2).
Bacterial infections.

Mayne, Port.†.
Erythromycin lactobionate (p.270·1).
Bacterial infections.

Erycar *Ace, Philipp.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erycette *Janssen-Cilag, S.Afr.; Ortho Dermatological, USA.*
Erythromycin (p.269·2).
Acne.

Erycin
Nycomed, Denm.
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Cipla, India.
Erythromycin (p.269·2) or erythromycin estolate (p.269·3).
Bacterial infections.

YSP, Malaysia; Atlantic, Thai.
Erythromycin stearate (p.270·1).
Bacterial infections.

Erycinum *CytoChemia, Ger.*
Erythromycin lactobionate (p.270·1).
Bacterial infections.

Erycip *Cipla, India.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Erycoat *Nufarindo, Indon.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Erycon *TO-Chemicals, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erycream *Faran, Gr.†.*
Erythromycin (p.269·2).

Erycytol *Lannacher, Austria.*
Hydroxocobalamin (p.1980·3).
Herpes zoster infections; liver disorders; macrocytic anaemias; neuralgia; neuritis; tobacco amblyopia; vitamin B deficiency.

Eryderm *Abbott, Belg.†; Abbott, Indon.; Abbott, Israel†; Abbott, Malaysia; Abbott, Mex.; Abbott, Neth.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Switz.; Abbott, USA.*
Erythromycin (p.269·2).
Acne.

Erydermec *Riemser, Ger.*
Erythromycin (p.269·2).
Acne.

Ery-Diolan *Meda, Ger.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eryfer *Cassella-med, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemias.

Eryfer comp *Cassella-med, Ger.*
Ferrous sulfate (p.1939·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Iron and vitamin deficiency.

Eryfluid *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Port.*
Erythromycin (p.269·2).
Acne.

Erygel *Kleva, Gr.; Merz, USA.*
Erythromycin (p.269·2).
Acne; skin infections.

Erygine *Germandre, Fr.*
Enoxolone (p.50·1); allantoin (p.1588·1); mallow (p.2337·2).
Skin irritation in the genital area.

Eryhexal
Hexal, Austral.; Hexal, Austria.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Hexal, Ger.
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erylar *Arlex, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Erylik *D & M, Chile; Biorga, Fr.; Biorga, Hong Kong.*
Erythromycin (p.269·2); tretinoin (p.1618·1).
Acne.

Erymax *Mayne, Irl.; Cephalon, UK; Allergan, USA†.*
Erythromycin (p.269·2).
Acne; bacterial infections.

Ery-Max *AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Swed.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erymed *Surya Dermato, Indon.*
Erythromycin (p.269·2).
Acne.

Erymin *Milano, Thai.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Erymycin *Triomed, S.Afr.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erypark *Pfizer, Chile.*
Erythromycin (p.269·2).
Bacterial infections.

Eryped *Abbott, Malaysia; Abbott, Singapore; Abbott, USA.*
Erythromycin ethyl succinate (p.269·3).
Amoebiasis; bacterial infections.

Eryplast *Reckitt Benckiser, Fr.*
Barrier cream.
Nappy rash.

Erypo *Janssen-Cilag, Austria; Janssen-Cilag, Ger.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Erysafe *USV, India.*
Erythromycin (p.269·2).
Bacterial infections.

Erysanbe *Sanbe, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erysec *Lindopharm, Ger.*
Erythromycin stinoprate (p.272·3).
Bacterial infections.

Ery-Set *Ebewe, Austria.*
Sodium chloride (p.1686·1).
Diluent for concentrated erythrocyte suspensions.

Erysidoron 1 *Weleda, Ger.; Weleda, S.Afr.; Weleda, UK.*
Homoeopathic preparation.

Erysidoron 2 *Weleda, Ger.; Weleda, S.Afr.; Weleda, UK.*
Homoeopathic preparation.

Erysidoron Nr 1 *Weleda, Austria.*
Homoeopathic preparation.

Erysidoron Nr 2 *Weleda, Austria.*
Homoeopathic preparation.

Erysil *Silom, Thai.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Erysol
Stiefel, Canad.
Erythromycin (p.269·2).
Acne.

Xepa-Soul Pattinson, Singapore†.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eryson
CCM, Malaysia.
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Beacons, Singapore.
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erystad *Stada, Austria.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Erystamine-K *Biostam (Βιοσταμ), Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Erystat *Medpro, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Ery-Tab *Abbott, Thai.; Abbott, USA.*
Erythromycin (p.269·2).
Bacterial infections.

Eryteal *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre, Fr.†.*
Cod-liver oil (p.1935·2); halibut-liver oil (p.1948·1); zinc oxide (p.1621·2); cetrimonium bromide (p.1635·1).
Burns; nappy rash.

Eryth-mycin *Pond's, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erythrin *Interbat, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erythro *CT, Ger.; DHA, Hong Kong.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erythrocin
Abbott, Austral.; Abbott, Canad.†; Abbott, Cz.; Abbott, Israel; Abbott, Malaysia; Abbott, NZ; Abbott, S.Afr.; Abbott, Singapore†.
Erythromycin lactobionate (p.270·1).
Bacterial infections.

Abbott, Austria; Abbott, Thai.
Erythromycin ethyl succinate (p.269·3), erythromycin lactobionate (p.270·1), or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Ger.
Erythromycin ethyl succinate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial infections.

Abbott, Gr.; Abbott, Indon.; Abbott, Philipp.
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Hong Kong; Abfar, Turk.
Erythromycin (p.269·2).
Bacterial infections.

Pfizer, India.
Erythromycin (p.269·2) or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Irl.; Abbott, USA.
Erythromycin lactobionate (p.270·1) or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, UK.
Erythromycin stearate (p.270·1).
Bacterial infections.

Erythrocine
Abbott, Belg.; Abbott, Fr.; Abbott, Switz.
Erythromycin ethyl succinate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial infections.

Abbott, Neth.
Erythromycin ethyl succinate (p.269·3), erythromycin lactobionate (p.270·1), or erythromycin stearate (p.270·1).
Bacterial infections.

Erythroforte *Abbott, Belg.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erythrogel *Biorga, Fr.; Biospray, Gr.†.*
Erythromycin (p.269·2).
Acne.

Erythrogenat *Azupharma, Ger.†.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Erythrogram *Pharma 2000, Fr.†.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erythro-Hefa *Sanavita, Ger.†; Wernigerode, Ger.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Erythroped *Abbott, Irl.; Abbott, Israel†; Abbott, S.Afr.†; Abbott, UK.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Erythroskid *Lichtenstein, Cz.†.*
Erythromycin (p.269·2).
Acne.

Erythrostim *Microgen, Rus.*
⊗ Epoetin beta (p.1061·1).
Anaemias.

Erythro-Teva *Teva, Israel.*
Erythromycin ethyl succinate (p.269·3), or erythromycin stearate (p.270·1).
Bacterial infections.

Erythrotrop *Biogal-Teva, Hung.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Erytral *Medikon, Indon.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Erytrociclin *Lisapharma, Ital.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Erytrolyve *Ethypharm, Neth.*
Erythromycin (p.269·2).
Bacterial infections.

Eryval *Gebro, Austria.*
Absinthium (p.2244·1); centaury (p.2279·1); St John's wort (p.422·3); peppermint leaf (p.1761·2); valerian (p.2410·1).
Gastrointestinal disorders.

Eryzole *Alra, USA†.*
Erythromycin ethyl succinate (p.269·3); acetyl sulfafurazole (p.338·3).
Otitis media.

Esacinone *Lisapharma, Ital.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Esafosfina *Biomedica, Hong Kong; Biomedica, Ital.; Biomedica, Thai.*
Fosfructose trisodium (p.2307·1).
Heart failure; hypophosphataemia; ischaemia of lower limbs; myocardial infarction; obstructive airways disease; phosphate deficiency; regional ischaemia; shock.

Esafosfina Glutammica *Biomedica, Hong Kong.*
Fosfructose calcium (p.2307·1); vitamin B substances (p.1922·1); glutamine (p.1947·2).
Metabolic disorders.

Esaglut *Biomedica, Ital.†.*
Glutamine (p.1947·2); fosfructose calcium (p.2307·1); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); calcium pantothenate (p.1959·3).
Asthenia; mental function impairment; tonic.

Esaldox *Gynopharm, Chile.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Esalfon *Recalcine, Chile.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Esalfon-D *Recalcine, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Esametone *Lisapharma, Ital.†.*
⊗ Methylprednisolone (p.1538·1).
Oral corticosteroid.

Esanic *Merck, Arg.*
Idebenone (p.367·1).
Dementia.

Esapent *Pharmacia, Ital.*
Omega-3 triglycerides (p.1362·1).
Hypertriglyceridaemia.

Esarondil *Terapeutico, Ital.*
Methacycline hydrochloride (p.298·2).
Bacterial infections.

Esavir *Boniscontro & Gazzone, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Esbelcaps *Medix, Mex.*
⊗ Fenproporex hydrochloride (p.2157·1); diazepam (p.986·3).
Obesity.

Esbeltex *Medix, Mex.*
Glucomannan (p.2312·3).
Hyperglycaemia; hyperlipidaemias; obesity.

Esbericard novo *Schaper & Brummer, Ger.*
Crataegus (p.2289·1).
Heart failure.

Esbericum *Europharm, Austria; Schaper & Brummer, Cz.†; Schaper & Brummer, Ger.*
St John's wort (p.422·3).
Anxiety; depression.

Esberitop
Note. This name is used for preparations of different composition.
Zeller, Switz.†.
Oral drops: Thuja (p.2400·3); echinacea (p.2298·1); baptisia tinctoria.
Cold symptoms.

Zeller, Switz.
Tablets: Thuja (p.2400·3); echinacea (p.2298·1); baptisia tinctoria; vitamin C (p.1983·3).
Cold symptoms.

Esberitox *Schaper & Brummer, Austria.*
Thuja (p.2400·3); baptisia tinctoria; echinacea (p.2298·1).
Infections.

Esberitox mono *Schaper & Brummer, Ger.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Esberitox N *Schaper & Brummer, Ger.; Schaper & Brummer, Malaysia; Schaper & Brummer, Pol.*
Thuja (p.2400·3); baptisia tinctoria; echinacea purpurea et pallida (p.2298·1).
Respiratory-tract and skin infections; tonic.

Esberiven
Note. This name is used for preparations of different composition.
Abbott, Fr.
Melilot (p.2339·2); heparin sodium (p.1301·2).
Peripheral vascular disorders.

Iquinosa, Spain.
Troxerutin (p.2305·1).
Formerly contained melilot and troxerutin.
Peripheral vascular disorders.

Craveri, Arg.
Tablets: Coumarin (p.2288·2); troxerutin (p.2305·1).
Venous insufficiency.

Craveri, Arg.
Topical application: Coumarin (p.2288·2).
Soft-tissue disorders.

Esberiven Fort *Abbott, Fr.*
Melilot (p.2339·2); rutoside (p.2305·1).
Haemorrhoids; venous insufficiency.

Esboxyl *Filadams, Philipp.*
Carbocisteine (p.1553·2).
Cough.

Escabron *Hebron, Braz.†.*
Lindane (p.2045·3).
Pediculosis; scabies.

Escalar *Hasco-Lek, Pol.*
Aesculus (p.2248·2); arnica (p.2260·2); calendula (p.2273·1).
Oedema; soft-tissue injury; venous insufficiency.

Escalgin sans codeine *Streuli, Switz.†.*
Salicylamide (p.121·2); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Escamox *Streuli, Switz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Escancil *Grunenthal, Chile†.*
⊗ Metamfetamine hydrochloride (p.2158·1).
Attention-deficit hyperactivity disorder; obesity.

Escandar *San Marino, Philipp.*
Mefenamic acid (p.80·1).
Osteoarthritis; pain; rheumatoid arthritis.

Escandine *Zambon, Braz.†; Pharmazam, Spain†.*
⊗ Ibopamine hydrochloride (p.1312·1).
Heart failure.

Escapelle *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Richter, Pol.; Gedeon Richter, Rus.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Escapin-N *Streger, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Escar T *Prater, Chile.*
Centella (p.1592·3).

Escar T-Neomicina *Prater, Chile.*
Neomycin (p.305·1); centella (p.1592·3).

Escarine *Rivadis, Fr.†.*
Barrier preparation.

Escarol *Muller Goppingen, Ger.†.*
Asarabacca (p.2261·3).
Respiratory-tract disorders.

Escatitona *Madaus, Austria.*
Homoeopathic preparation.

Esceven *Herbapol Poznan, Pol.*
Aesculus (p.2248·2).
Oedema; venous insufficiency.

Escina Forte *Omega, Arg.*
Aescin (p.2248·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Escina Omega *Omega, Arg.*
Aescin (p.2248·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Escinogel *Bouchara-Recordati, Fr.†.*
Bamethan sulfate (p.1222·3); aescin (p.2248·2).
Peripheral vascular disorders.

Esclama *Pharmacia, Ger.†.*
Nimorazole (p.842·2).
Protozoal infections.

Esclebin *Alacan, Spain.*
Norfloxacin (p.309·2).
Bacterial infections.

Esclerobion *Merck, Port.*
Vitamin A acetate (p.1973·1); pyridoxine hydrochloride (p.1978·2); *dl*-alpha tocoferil acetate (p.1992·3).
Atherosclerosis; vascular disorders.

Esclerovitan *Merck, Braz.; Merck, Mex.†.*
Vitamins A, B , and E (p.1922·1).

Esclerovitan Antioxidante *Merck, Arg.*
Multivitamin and mineral preparation (p.1922·1).

Esclerovitan E *Merck, Arg.*
Vitamin A palmitate; pyridoxine hydrochloride; alpha tocoferil acetate (p.1922·1).

Esclim *Women First, USA.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Esclima *Fournier, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Escodarone *Streuli, Switz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Escodyn *Streuli, Switz.*
Multivitamin and mineral preparation (p.1922·1).

Escogripp sans codeine *Streuli, Switz.*
Propyphenazone (p.119·3); salicylamide (p.121·2); caffeine (p.1116·3); ascorbic acid (p.1983·3); mepyramine maleate (p.585·2).
Cold and influenza symptoms.

Esconitro *Streuli, Switz.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Escophylline *Streuli, Switz.†.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Escoprim *Streuli, Switz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Escor *Merck, Cz.; Orion, Fin.; Trommsdorff, Ger.*
Nilvadipine (p.1357·1).
Hypertension.

Escoretic *Streuli, Switz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Escotussin *Streuli, Switz.*
Dihydrocodeine thiocyanate (p.48·3); belladonna (p.2263·3); drosera (p.2297·3); guaifenesin (p.1561·3).
Coughs.

Escozem *Streuli, Switz.†.*
Diltiazem hydrochloride (p.1265·1).
Hypertension; ischaemic heart disease.

Escudo *Lampugnani, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Esculape *Omega, Fr.*
Eucalyptus oil; rosemary oil; melaleuca oil; lavander oil; rosewood oil; laurus nobilis oil; clove oil; cinnamon oil; dementholised mint oil.
Cold symptoms.

Esculeol P
Note. This name is used for preparations of different composition.
Medical, Arg.
Ointment: Benzocaine (p.1854·1); hamamelis (p.2318·2); camphor (p.2273·2); rhatany (p.2378·3).
Haemorrhoids.

HMA, Arg.
Oral drops: Aesculus (p.2248·2); rutoside (p.2305·1).
Haemorrhoids; venous insufficiency.

Escumycin *Orion, Denm.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

ESE *Amdipharm, Port.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Eselan
Anfarm, Gr.
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Anfarm, Thai.; TTN, Thai.
Omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eselin *Sifarma, Ital.*
Etamsylate (p.1064·3).
Haemorrhage; vascular disorders.

Esertia *Almirall, Spain.*
Escitalopram (p.391·1).
Anxiety; depression; social phobia.

Esforza *Normon, Spain†.*
Ginseng (p.2312·1); Siberian ginseng (p.2386·3).
Tonic.

Esgic *Forest Pharmaceuticals, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Esgic-Plus *Forest Pharmaceuticals, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Esgipyrin *Sarabhai Piramal, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Esgipyrin DS *Sarabhai Piramal, India.*
Diclofenac sodium (p.44·3).
Pain.

Esidrex *Novartis, Austria; Novartis, Fr.; Novartis, India†; Novartis, Ital.; Novartis, Norw.; Sandoz, Spain; Novartis, Swed.; Novartis, Switz.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; heart failure; hypercalcaemia; hypercalciuria; hypertension; lactation inhibition; Ménière's disease; oedema; renal calculi.

Esidrix *Novartis, Ger.; Ciba, USA†.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Esilgan *Takeda, Indon.; Takeda, Ital.; Takeda, Philipp.*
Estazolam (p.995·1).
Insomnia.

Esimil *Novartis, Ger.†; Ciba, USA.*
⊗ Guanethidine monosulfate (p.1300·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Esine *Minerva (Μινερβα), Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Esinol *Pharmacore, Indon.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Esipram *CNS, Austral.*
Escitalopram oxalate (p.391·1).
Anxiety; depression; social phobia.

Eskacef *Julphar, UAE.*
Cefradine (p.233·1).
Also known as Julphacef.
Bacterial infections.

Eskaflam *GSK, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain; peri-articular and soft-tissue disorders.

Eskalit *GSK, Arg.*
Lithium carbonate (p.401·3).
Mania.

Eskalith *GSK, USA†.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Eskamel *Dermatech, Austral.; Group, S.Afr.; Goldshield, UK.*
Resorcinol (p.1612·1); sulfur (p.1614·1).
Acne.

Eskapar *Armstrong, Mex.*
Nifuroxazide (p.307·2).
Diarrhoea.

Eskapar Compuesto *Armstrong, Mex.*
Nifuroxazide (p.307·2); metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis.

Eskazine *Goldshield, Spain.*
Trifluoperazine hydrochloride (p.1034·2).
Anxiety; psychoses.

Eskazole *GSK, Austral.; GSK, Austria; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Israel; Armstrong, Mex.; GSK, Neth.; Morrith, Spain.*
Albendazole (p.139·2).
Capillariasis; cestode infections; cysticercosis; echinococcosis; giardiasis; intestinal nematode infections; neurocysticercosis; strongyloidiasis; trichinosis.

Eskim *Sigma-Tau, Ital.*
Omega-3 triglycerides (p.1362·1).
Hypertriglyceridaemia.

Eskold *GSK, India†.*
Phenylpropanolamine hydrochloride (p.1569·3); diphenylpyraline hydrochloride (p.578·2).
Cold symptoms; hypersensitivity reactions; nasal congestion; rhinitis.

Eskold Expectorant *GSK, India†.*
Phenylpropanolamine hydrochloride (p.1569·3); diphenylpyraline hydrochloride (p.578·2); guaifenesin (p.1561·3).
Cold symptoms; hypersensitivity reactions; nasal congestion; rhinitis.

Eskornade *SmithKline Beecham, S.Afr.*
Phenylpropanolamine hydrochloride (p.1569·3); diphenylpyraline hydrochloride (p.578·2).
Upper respiratory-tract disorders.

Eslax *Organon, Jpn.*
Rocuronium bromide (p.1908·3).
Competitive neuromuscular blocker.

Eslofen *Essenpharma, Philipp.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Esmacen *Smaller, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Esmalorid *Merck, Ger.†.*
⊗ Trichlormethiazide (p.1418·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Esme Topico *Esme, Arg.*
Strontium chloride (p.2393·1); lidocaine hydrochloride (p.1862·3).
Hypersensitive teeth.

Esmedent Dientes Sens Blanq + Ctrol Sarro *Esme, Arg.*
⊗ Potassium nitrate (p.1658·3); potassium pyrophosphate (p.2390·3).
Sensitive teeth.

Esmedent Dientes Sensibles *Esme, Arg.*
⊗ Potassium nitrate (p.1658·3); triclosan (p.1665·2).

Esmedent con Fluor *Esme, Arg.*
Triclosan (p.1665·2); sodium fluoride (p.1962·2); benzocaine (p.1854·1); allantoin (p.1588·1).
Dental hygiene; sensitive teeth.

Esmeron *Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Sanofi Synthelabo, S.Afr.; Organon, Singapore; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, Venez.*
Rocuronium bromide (p.1908·3).
Competitive neuromuscular blockade.

Esmon *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Desmopressin (p.2185·2).
Diabetes insipidus; haemorrhagic disorders.

Esnicol *Essenpharma, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Eso 70 *Esoform, Ital.*
Paraformaldehyde (p.1655·2); hydrogen peroxide 40/45 (p.1647·3).
Room disinfection.

Eso Cem *Esoform, Ital.*
Glutaral (p.1645·2).
Instrument disinfection.

Eso Deterferri *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection.

Eso Din *Esoform, Ital.*
Glutaral (p.1645·2); phenol (p.1656·1).
Instrument disinfection.

Eso Ferri *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection.

Eso Ferri Alcolico *Esoform, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Instrument disinfection.

Eso Ferri Alcolico Plus *Esoform, Ital.*
Benzalkonium chloride (p.1629·1); isopropyl alcohol (p.1650·3).
Instrument disinfection.

Eso Ferri Plus *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Instrument disinfection and storage.

Eso H1, HP, and HP1 *Esoform, Ital.*
Glutaral (p.1645·2).
Instrument disinfection.

Eso S 80 *Esoform, Ital.*
Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Instrument disinfection.

Eso Zim *Esoform, Ital.*
Proteolytic enzymes; sodium laurilsulfate (p.2138·3); cocoamidopropylbetaine.
Instrument disinfection.

Esoalcolico Incolore *Esoform, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Skin, hand, burn, and wound disinfection.

Esocetic *Esoform, Ital.†.*
Peracetic acid (p.1655·2); isopropyl alcohol (p.1650·3).
Instrument disinfection.

Esocetic Plus *Esoform, Ital.*
Isopropyl alcohol (p.1650·3); peracetic acid (p.1655·2).
Instrument disinfection.

Esodar *Cassara, Arg.*
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3).
Infected eye and ear disorders.

Esodrox *Esoform, Ital.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Esofenol 60 *Esoform, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Waste disinfection.

Esofenol Ferri *Esoform, Ital.*
Orthobenzyl parachlorophenol (p.1655·2); orthophenylphenol (p.1655·1).
Instrument disinfection.

Esofex *Leiras, Fin.†.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; heartburn; peptic ulcer.

Esoform 92 *Esoform, Ital.*
Benzalkonium chloride (p.1629·1); glutaral (p.1645·2); alkylphenoxypolyglycol ether.
Surface disinfection.

Esoform Alcolico *Esoform, Ital.*
⊗ Benzalkonium chloride (p.1629·1); methyl salicylate; camphor; thyme oil; alcohol (p.1625·2); acetone; chloroform.
Skin disinfection.

Esoform Jod 25 *Esoform, Ital.†.*
Alkylphenoxypolyglycol-iodine-ether complex.
Room and surface disinfection.

Esoform Jod 35 and 75 *Esoform, Ital.*
Povidone-iodine (p.1659·2).
Skin, wound, and hand disinfection.

Esoform Jod 20 and 50 *Esoform, Ital.*
Iodine (p.2169·2); potassium iodide (p.2169·2); alcohol; chloroform; isopropyl alcohol.
Skin and hand disinfection.

Esoform Mani *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol; alcohol.
Skin and hand disinfection.

Esoform 7 mc *Esoform, Ital.*
Paraformaldehyde (p.1655·2); hydrogen peroxide (40-45 volume) (p.1647·3).
Surface and room disinfection.

Esoform 70 mc *Esoform, Ital.*
Paraformaldehyde (p.1655·2); hydrogen peroxide (40-45 volume) (p.1647·3).
Room disinfection.

Eso-Jod *Esoform, Ital.*
Povidone-iodine (p.1659·2).
Wound disinfection.

Esoklin *Esoform, Ital.*
Diethyltoluamide (p.2041·1); lemon oil (p.2332·3); thyme oil (p.2401·2); chamomile oil (p.2279·3).
Insect repellent.

Esol *Leiras, Fin.†.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Esolut *Angelini, Ital.*
Progesterone (p.2125·1).
Luteal insufficiency.

E-Solve *Syosset, USA.*
Vehicle for topical preparations.

Esomac *Cipla, India.*
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Esomax *Quesada, Arg.*
Esomeprazole (p.1729·3).

Esomed *Medibrands, Israel.*
Hydroquinone (p.1598·2).

Esonide *Kleva, Gr.; Kleva, Singapore.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps; rhinitis; skin disorders.

Esopral *Bracco, Ital.; Euro Registratie, Neth.*
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Esopraz *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Esorid *Sun, Thai.†.*
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders.

Esosan Casa *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Esosan Gel *Esoform, Ital.*
Denatured ethanol (p.1652·3).
Hand disinfection.

Esosan Pronto *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Disinfection.

Esosan Soap *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Skin and surface disinfection.

Esoterica *Medicis, Canad.*
Hydroquinone (p.1598·2); oxybenzone (p.1608·3); padimate O (p.1609·1).
Skin pigmentation disorders.

Esoterica Facial and Sunscreen *Medicis, USA.*
Hydroquinone (p.1598·2); padimate O (p.1609·1); oxybenzone (p.1608·3).
Hyperpigmentation.

Esoterica Regular *Medicis, Canad.; Medicis, USA.*
Hydroquinone (p.1598·2).
Hyperpigmentation; skin pigmentation disorders.

Esoterica Unscented *Medicis, Canad.*
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Esoxid *Esoform, Ital.*
Glutaral (p.1645·2).
Instrument disinfection.

Esoz
Glenmark, India.
Esomeprazole (p.1729·3) or esomeprazole sodium (p.1729·2).
Gastro-oesophageal reflux; heartburn; peptic ulcer.

Galeno, Venez.
Esomeprazole (p.1729·3).
Gastro-oesophageal reflux; peptic ulcer.

Esoz-D *Glenmark, India.*
Esomeprazole (p.1729·3); domperidone (p.1726·2).
Dyspepsia; flatulence; gastro-oesophageal reflux; nausea and vomiting.

Espabion *Degorts, Mex.*
Trimebutine (p.2404·3).
Gastrointestinal motility disorders.

Espacil *Valeant, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Espacil Compuesto *Valeant, Mex.*
Hyoscine butylbromide (p.1734·1); clonixin lysine (p.37·1).
Smooth muscle pain and spasm.

Espadol *Reckitt & Colman, Arg.†.*
Chloroxylenol (p.1640·2).
Disinfection.

espa-dorm *Esparma, Ger.†.*
Zopiclone (p.1039·1).
Sleep disorders.

espadox *Esparma, Ger.†.*
Doxepin hydrochloride (p.389·1).
Anxiety disorders; depression; withdrawal syndromes.

espa-formin *Esparma, Ger.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

espa-lepsin *Esparma, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

espa-lipon *Esparma, Ger.†.*
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Espa-Lipon *Esparma, Rus.*
Thioctic acid (p.2400·2).
Alcoholic polyneuropathy; diabetic polyneuropathy.

espa-moxin *Esparma, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Espar *Greater Pharma, Thai.*
Aspartame (p.1930·1).
Sugar substitute.

Esparflin *Roemmers Rowe, Venez.*
Desloratadine (p.576·1).
Hypersensitivity reactions.

Espasal *Offenbach, Mex.*
Simeticone (p.1770·2); pipenzolate bromide (p.1762·2).
Smooth muscle spasm.

Espasevit *Richmond, Arg.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Espasin *Diba, Mex.†.*
Pipenzolate bromide (p.1762·2); simeticone (p.1770·2).

Espasmacid *Gemballa, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Espasmalgon *Dovalle, Braz.†.*
Papaverine hydrochloride (p.2191·3); phenobarbital (p.492·2); homatropine methylbromide (p.1881·3); phenazone (p.116·1); hyoscyamus (p.2323·3).
Smooth muscle spasm.

Espasmo Biotenk *Biotenk, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Painful smooth muscle spasm.

Espasmo Canulase *Novartis Consumer, Port.*
Cellulase (p.2279·1); dimeticone (p.1770·2); glutamic acid hydrochloride (p.1947·1); metixene hydrochloride (p.811·3); pancreatin (p.2360·1); pepsin (p.2365·1); sodium dehydrocholate (p.2292·2).

Espasmo Cibalena
Note. This name is used for preparations of different composition.
Novartis, Arg.†.
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3).

Novartis, Arg.
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3); codeine phosphate (p.37·2).

Espasmo Cibalgina *Novartis, Chile; Sandoz, Mex.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3).
Smooth muscle pain and spasm; smooth muscle spasm and pain.

Espasmo Cibalgina Compuesta *Novartis, Chile.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3); codeine phosphate (p.37·2).
Smooth muscle spasm and pain.

Espasmo Colic *Makros, Braz.†.*
Homatropine methylbromide (p.1881·3); dimeticone (p.1770·2).
Smooth muscle spasm.

Espasmo Dioxadol *Bago, Arg.*
Octatropine methylbromide (p.1752·1); dipyrone (p.49·2).
Painful smooth muscle spasm.

Espasmo Dolex *Ivax, Arg.*
Clonixin lysine (p.37·1); pargeverine (p.1761·1).
Smooth muscle spasm.

Espasmo Flatol *Legrand, Braz.*
Simeticone (p.1770·2); homatropine methylbromide (p.1881·3).

Espasmo Ibupirac *Pharmacia, Arg.†.*
Ibuprofen (p.64·2); homatropine methylbromide (p.1881·3).
Painful smooth muscle spasm.

Espasmo Luftal *BMS, Braz.*
Homatropine methylbromide (p.1881·3); dimeticone (p.1770·2).
Smooth muscle spasm.

Espasmo Motrax *Labinca, Arg.†.*
Ciclonium bromide (p.1716·2); ibuprofen (p.64·2).
Painful smooth muscle spasm.

Espasmo Silidron *GSK, Braz.*
Dimeticone (p.1770·2); camylofin hydrochloride (p.2274·1).
Smooth muscle spasm.

Espasmocron *Delta, Braz.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3); thiamine hydrochloride (p.1976·1); dipyrone (p.49·2).
Smooth muscle spasm.

Espasmodid Composto *Uniao Quimica, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Espasmofin *Oriental, Arg.*
Homatropine (p.1881·2); ibuprofen (p.64·2).
Painful smooth muscle spasm.

Espasmogress *Parggon, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Espasmotropin *Sintesina, Arg.*
Homatropine (p.1881·2).
Smooth muscle spasm.

Espauz *Glenmark, India.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Espa-Valept *Esparma, Ger.†.*
Sodium valproate (p.508·2).
Epilepsy.

Espaven
Note. This name is used for preparations of different composition.
Gezzi, Arg.
Ranitidine (p.1766·1).
Gastric hyperacidity.

Valeant, Mex.
Dimeticone (p.1770·2); calcium pantothenate (p.1959·3).
Gastrointestinal disorders.

Espaven Alcalino *Valeant, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastrointestinal hyperacidity.

Espaven Antigas *Gezzi, Arg.*
Simeticone (p.1770·2).
Flatulence.

Espaven Enzimatico *Valeant, Mex.*
Pancreatin (p.2360·1); dimeticone (p.1770·2); ox bile (p.2266·3); *Aspergillus niger* cellulase (p.2279·1).
Gastrointestinal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Espaven MD *Valeant, Mex.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2).
Gastrointestinal disorders.

Espaven Pediatrico *Valeant, Mex.*
Dimeticone (p.1770·2).
Dyspepsia; flatulence; meteorism.

Especlor *Darya-Varia, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

Espectocural *Raymos, Arg.*
Bromhexine (p.1552·2); benzydamine (p.27·3).
Coughs.

Espectral *Centrum, Spain†.*
Ampicillin trihydrate (p.204·2); muramidase hydrochloride (p.2348·1).
Bacterial infections.

Espectrin *GSK, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Espectroprima *Prati-Donaduzzi, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Espectrosira *Clariana, Spain†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Espeden *Lesvi, Spain.*
Norfloxacin (p.309·2).
Bacterial infections.

Esperal *Sanofi-Aventis, Fr.; Torrent, India; Sanofi Winthrop, Rus.*
Disulfiram (p.2296·2).
Chronic alcoholism.

Esperan *Taisho, Jpn.*
Oxapium iodide (p.1759·1).
Gastrointestinal spasm; renal calculi.

Espercil *Grunenthal, Chile.*
Tranexamic acid (p.1080·3).
Haemorrhage; hyperfibrinolysis.

Esperson *Sanofi-Aventis, Braz.; Sanofi-Aventis, Indon.; Aventis, Thai.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Esperson N *Sanofi-Aventis, Braz.*
⊗ Desoximetasone (p.1525·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Espesan *Nutricia-Bago, Arg.*
Preparation for enteral nutrition (p.1922·1).
Dysphagia.

Espesil *Orion, Fin.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Espidifen *Zambon, Spain.*
Ibuprofen arginine (p.65·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Espimax *Klonal, Arg.*
⊗ Spironolactone (p.1400·1).
Hypertension.

Espin *Taejoon, Singapore.*
Dosulepin hydrochloride (p.388·2).
Depression.

Espinal *Intermed, Gr.*
Citalopram (p.385·3).
Depression.

Espiride *Pharmacare, S.Afr.*
Sulpiride (p.1028·3).
Behaviour disorders; depression; peptic ulcer; psychoses; vertigo.

Espirolona *Cazi, Braz.*
⊗ Spironolactone (p.1400·1).
Hypertension.

Espledol *Bial, Spain.*
Acemetacin (p.15·1).
Musculoskeletal and joint disorders; peri-articular disorders.

Espo *Kirin, Jpn.*
⊗ Epoetin alfa (p.1061·1).
Anaemia; autologous blood transfusion.

Espogen *LG Life Sciences, Thai.*
⊗ Epoetin alfa (p.1061·1).
Anaemias.

Espol *Nizpharm, Rus.*
Coriander oil (p.2288·1); lavender oil (p.2331·2); capsicum (p.2276·2); dimethyl sulfoxide (p.2022·1); chloroform (p.1781·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Espontal *Panalab, Arg.*
Tamsulosin hydrochloride (p.2197·1).

Espraden *Degorts, Mex.*
Metoclopramide hydrochloride (p.1747·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastrointestinal disorders.

Esprasone *Seid, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Esprenit *Hennig, Ger.*
Ibuprofen (p.64·2) or ibuprofen sodium (p.65·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Esprit *Bayer, Austral.*
Test for glucose in blood (p.2314·1).

Esprit Sensor *Bayer Diagnostics, Irl.*
Test for glucose in blood.
For use with Esprit Glucometer.

Esprital *Zentiva, Cz.; Zentiva, Pol.*
Mirtazapine (p.409·2).
Depression.

Espritin *Petrasch, Austria.*
Lactic acid (p.2329·3).
Psoriasis.

Esprocy *Nufarindo, Indon.*
Cyproheptadine (p.575·2).
Allergic disorders.

Espumisan *Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Berlin-Chemie, Pol.; Berlin-Chemie, Rus.*
Simeticone (p.1770·2).
Acute poisoning; aerophagia; defoaming agent in radiography and endoscopy of the gastrointestinal tract; detergent poisoning; dyspepsia; excess gastrointestinal gas; flatulence; infant colic; meteorism; preparation for gastrointestinal investigation.

Esputicon *Synteza, Pol.*
Dimeticone (p.1770·2).
Excess gastrointestinal gas; gastrointestinal investigation.

Esracain *Rafa, Israel.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia; regional anaesthesia.

Esradin *Sigma-Tau, Ital.*
Isradipine (p.1319·2).
Hypertension.

Essaven
Note. This name is used for preparations of different composition.
Aventis, Thai.
Aescin (p.2248·2); rutoside (p.2305·1); essential phospholipids.
Haemorrhoids; varicose veins.

Cassella-med, Ger.
Capsules: Aesculus (p.2248·2).
Inflammation; venous insufficiency.

Sanofi-Aventis, Ital.
Capsules: Aescin (p.2248·2); phosphatidyl choline (p.2367·1).
Venous insufficiency.

Aventis, S.Afr.†.
Capsules: Aescin (p.2248·2); rutoside (p.2305·1); essential phospholipids.
Vascular disorders.

Nattermann, Ger.†; Aventis, S.Afr.†.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); essential phospholipids.
Soft-tissue disorders; soft-tissue trauma; superficial vascular disorders; vascular disorders.

Sanofi-Aventis, Ital.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); phosphatidyl choline (p.2367·1).
Venous insufficiency.

Essaven 60 000 *Cassella-med, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue disorders; superficial vascular disorders.

Essaven N *Nattermann, Ger.†.*
Aesculus (p.2248·2); trimethylhesperidin chalcone (p.2305·2).
Soft-tissue disorders; vascular disorders.

Essaven Neu *Cassella-med, Ger.*
Aescin (p.2248·2).
Soft-tissue injuries.

Essaven Sport *Nattermann, Ger.†.*
Glycol salicylate (p.62·3); arnica tincture (p.2260·2).
Sports injuries.

Essaven Tri-Complex *Nattermann, Ger.†.*
Heparin sodium (p.1301·2); allantoin (p.1588·1); dexpanthenol (p.2362·1).
Soft-tissue disorders; superficial vascular disorders.

Essaven ultra *Nattermann, Ger.†.*
Aesculus (p.2248·2); trimethylhesperidin chalcone (p.2305·2); essential phospholipids.
Soft-tissue injury; vascular disorders.

Essavenon *Sanofi-Aventis, Spain.*
Aescin (p.2248·2); phospholipids; heparin sodium (p.1301·2).
Peripheral vascular disorders; soft-tissue disorders.

Essedin *Legrand, Braz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Influenza symptoms.

Esseldon *Anfarm, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Esseliv *Aflofarm, Pol.*
Soya phospholipids (p.1922·1).
Liver and biliary-tract disorders.

Essen *Farmasa, Braz.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2); dehydrocholic acid (p.2292·2); cellulase (p.2279·1); pepsin (p.2365·1); lipase (p.2360·3); amylase (p.2256·3); pancreatin (p.2360·1).
Digestive-system disorders.

Essen Enzimatico *EG, Ital.†.*
Pepsin (p.2365·1); amylase (p.2256·3); lipase (p.2360·3); trypsin (p.2405·3); chymotrypsin (p.2281·3); cellulase (p.2279·1).
Digestive disorders.

Essence Algerienne *Toulade, Fr.*
Cineole (p.2282·3); menthol (p.2340·1); guaiacol (p.1561·2).
Upper respiratory-tract congestion.

Essenfer *Essenpharma, Philipp.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3); cobalt sulfate; vitamin B (p.1980·2); vitamin C; vitamin E (p.1922·1).
Anaemias.

Essenmox *Essenpharma, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Essens Amara of Groen Amara *Lennon, S.Afr.*
Cnicus benedictus (p.2285·2); quassia (p.2377·1).
Appetite loss.

Essential 50+ *Pharmavite, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Essential B *General Nutrition, Canad.†.*
Vitamin B substances (p.1922·1).

Essential Balance *Pharmavite, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Essential ProPlus *Nutrisoy, USA.*
Preparation for enteral nutrition (p.1922·1).

Essentiale
Note. This name is used for preparations of different composition.
Cassella-med, Ger.
Essential phospholipids.
Gallstones; liver disorders; psoriasis; radiation trauma.

Aventis, Hong Kong; Sanofi-Aventis, Malaysia; Natrapharm, Philipp.; Nattermann, Pol.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Thai.
Essential phospholipids and multivitamins (p.1922·1).
Liver and biliary-tract disorders; liver disorders; vitamin supplement.

Aventis, Ital.†.
Phosphatidyl choline (p.2367·1).
Liver disorders.

Gerot, Austria.
Capsules: Essential phospholipids (p.1922·1).
Liver disorders.

Gerot, Austria.
Injection: Essential phospholipids and multivitamins (p.1922·1).
Liver disorders.

Essentiale Forte *Aventis, Cz.†.*
Essential phospholipids; vitamins (p.1922·1).
Liver disorders.

Essentiale Forte N *Sanofi-Aventis, Cz.*
Essential phospholipids (p.1922·1).
Liver disorders.

Essentiale N
Note. This name is used for preparations of different composition.
Aventis, Cz.†.
Lecithin (soya) (p.2332·2).
Liver disorders.

Aventis, Rus.
Essential phospholipids (p.1922·1).
Liver disorders; psoriasis.

Essentiale-L *Nicholas Piramal, India.*
Lecithin (p.2332·2).
Liver disorders.

Essentials *Usana, Singapore.*
Mega Antioxidant tablets, vitamins; olive extract; bioflavonoids; inositol; choline bitartrate; bromelain; thioctic acid; ubidecarenone; glutathione; turmeric; lutein; Chelated Mineral tablets, minerals (p.1922·1).

Essentielle Aminosauren *Fresenius Kabi, Ger.†.*
Amino-acid preparation (p.1922·1).
Dietary supplement in renal failure.

Essex *Schering-Plough, Denm.; Schering-Plough, Fin.; Essex, Ger.; Essex, Switz.*
Emollient.
Skin disorders.

Essigsaure Tonerde-Salbe *Michallik, Ger.*
Aluminium acetotartrate (p.2255·1).
Soft-tissue disorders.

Essitol *Athenstaedt, Ger.*
Aluminium acetotartrate (p.2255·1).
Hyperhidrosis; soft-tissue injury.

Essliver Forte *Nabros, Rus.*
Essential phospholipids; thiamine mononitrate; riboflavin; pyridoxine hydrochloride; cyanocobalamin; nicotinamide; tocopherol acetate (p.1922·1).
Disorders of lipid metabolism.

Essventia *CORNE, Mex.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

EST *Rosch & Handel, Austria.*
Alum (p.2254·1); calcium acetate (p.1675·2); calcium carbonate (p.1714·1).
Bruises; insect bites; sprains; swelling.

Establix *BA Farma, Port.†.*
Buspirone hydrochloride (p.965·3).
Anxiety; insomnia.

Estac *Gross, Braz.†.*
Metoclopramide hydrochloride (p.1747·3); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Estafiloide *IQB, Braz.*
A staphylococcal vaccine (toxoid) (p.2239·3).
Active immunisation.

Estalis *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Fin.; Novartis, Gr.; Novartis, Irl.; Altana, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estalis Continuous *Novartis, Austral.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estalis Sekvens *Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estalis Sequens *Novartis, Austria.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estalis Sequi *Novartis, Arg.; Novartis, Austral.; Novartis, Canad.; Novartis, Cz.; Novartis, Ger.; Novartis, Irl.; Novartis, Ital.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Switz.*
Patch I, estradiol (p.2097·2); patch II, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estalis SQ *Novartis, Braz.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estamin *Biolink, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Estandron P *Organon, Braz.*
⊗ Estradiol benzoate (p.2097·2); estradiol phenylpropionate (p.2097·3); testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1).
Menopausal disorders.

Estandron Prolongado *Organon, Chile.*
⊗ Estradiol benzoate (p.2097·2); estradiol phenylpropionate (p.2097·3); testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1).
Menopausal disorders.

Estandron Prolongatum *Organon, Neth.; Organon, Turk.*
⊗ Estradiol benzoate (p.2097·2); estradiol phenylpropionate (p.2097·3); testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1).
Menopausal disorders; osteoporosis.

Estanolin *Minerva (Μινερβα), Gr.†.*
⊗ Atenolol (p.1217·3).

Estaprol *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Chile.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Estar *Westwood-Squibb, Canad.†; Westwood-Squibb, USA†.*
Coal tar (p.1616·2).
Psoriasis.

Estavam *Precimex, Mex.*
Vancomycin hydrochloride (p.358·3).
Staphylococcal infections.

Estazor *Fahrenheit, Indon.*
Ursodeoxycholic acid (p.2408·1).
Gallstones.

Estecina
Normon, Port.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Normon, Spain.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Esteclin *Syntex, Mex.*
Erdosteine (p.1560·1).
Respiratory-tract disorders with viscous mucus.

Esteclin Bac *Syntex, Mex.*
Amoxicillin trihydrate (p.202·2); erdosteine (p.1560·1).
Respiratory-tract infections.

Estelle *Douglas, Austral.; Taro, Israel; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore.*
21 Tablets, cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
The 28-day pack also contains 7 inert tablets.
Androgen-dependent acne, alopecia, and hirsutism in women; combined oral contraceptive in women with androgenic symptoms; polycystic ovary syndrome.

Esteprim *Solfran, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Ester Aces *Sisu, Canad.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

Ester C EVC *Sisu, Canad.*
Vitamins A, B, and C with zinc (p.1922·1).

Ester Vit *Bilim, Turk.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Esterasine *Baxter, Fr.†.*
Complement C1 esterase inhibitor (p.2287·1).
Hereditary angioedema.

Ester-C *Accurex, Canad.; Holista, Canad.; Natural Factors, Canad.; Pharmetics, Canad.; Quest, Canad.; Regime, Canad.; Sisu, Canad.; Super Nutrition, Canad.; Swiss Herbal, Canad.; WN, Canad.*
Calcium ascorbate (p.1984·1).

Ester-C Plus *Solgar, USA.*
Vitamin C (p.1983·3); citrus bioflavonoids complex (p.2304·1); acerola; rose hips (p.2381·2); rutoside (p.2305·1); calcium (p.1675·2).
Capillary bleeding.

Ester-C Plus Multi-Mineral *Solgar, USA.*
Vitamin C (p.1983·3); citrus bioflavonoids complex (p.2304·1); acerola; rose hips (p.2381·2); rutoside (p.2305·1); calcium; magnesium; potassium; zinc (p.1667·1).
Capillary bleeding.

Estericlean *Braun, Port.†.*
Water for injection (p.2414·3).

Esterinor *Polinac, Venez.†.*
Co-tetroxazine (p.257·3).
Bacterial infections.

Esterofundina *Braun, Port.*
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Esterol *Laborest, Ital.*
Rice oil; vitamin E; oleic acid; linoleic acid; linolenic acid; gamma-orizanol (p.1922·1).
Nutritional supplement.

Esterol Plus *Laborest, Ital.*
Rice oil; vitamin E; Policosanol; vitamin B substances (p.1922·1).
Dyslipidaemias.

Esteronide *Galderma, Arg.†.*
⊗ Desonide (p.1525·1).
Skin disorders.

Estesia *Pharmacore, Indon.*
Prilocaine (p.1868·2); lidocaine (p.1862·3).
Local anaesthesia.

Estibal *Liferpal, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Esticia *Hermal, Ger.*
Chlormadinone acetate (p.2084·3); mestranol (p.2116·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Estilomicin *Beta, Arg.*
Metronidazole (p.837·1); spiramycin (p.333·1).
Mouth infections.

Estilsona *Ern, Spain.*
⊗ Prednisolone steaglate (p.1541·2).
Corticosteroid.

Estima
Note. This name is used for preparations of different composition.
Effik, Fr.
Progesterone (p.2125·1).
Female infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Geofman, Philipp.
Oxytocin (p.2015·2).
Labour induction; lactation promotion; postpartum haemorrhage.

Estimoral *Farmalab, Braz.*
Lysate of: *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus mitis*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Estimul *Nordin, Mex.*
Arnica (p.2260·2).
Musculoskeletal pain.

Estin *Gracia, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Estinette *Effik, Port.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Estinyl *Schering-Plough, S.Afr.†; Schering, USA.*
Ethinylestradiol (p.2101·3).
Breast cancer; female hypogonadism; functional uterine bleeding; menopausal disorders; prostatic cancer.

Estiranox *Greenpharma, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Estival *Specifar (Σπεσιφαρ), Gr.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Estivan *Almirall, Belg.; Almirall, Port.*
Ebastine (p.579·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Esto *Angelini, Ital.*
Alfoscerate olamine.
Anxiety disorders.

esto-gast *Feldhoff, Ger.*
Citronella oil (p.2284·2); nutmeg oil (p.2355·3); cinnamon oil (p.2283·2); clove oil (p.2285·1).
Digestive disorders.

Estomacurol *Alternavida, Mex.*
Bismuth citrate (p.1710·3); sodium bicarbonate (p.1673·2); aluminium hydroxide (p.1706·2).
Antacid.

Estomafitino *Jofadel, Braz.†.*
Chamomile (p.2279·3); condurango (p.2287·1); gentian (p.2310·3); glycerol (p.2314·2); nux vomica (p.2355·3); senna (p.1769·2).
Constipation.

Estomagel
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Neo Quimica, Braz.
Tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Estomepe *Bunker, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Estomil *Merck, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Estomina *Fabra, Arg.*
Bromazepam (p.964·3).
Anxiety.

Estomycin *Columbia, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Estopause *Faran, Gr.*
Estradiol (p.2097·2); medroxyprogesterone (p.2113·3).
Hormone replacement therapy.

Estopein *Diba, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Estovyn-T *Grossman, Mex.*
Tinidazole (p.848·3).

Estrabeta *Betapharm, Ger.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estrace *Shire, Canad.; Shire, Cz.†; BMS, USA.*
Estradiol (p.2097·2).
Breast cancer; female hypogonadism; menopausal disorders; osteoporosis; primary ovarian failure; prostatic cancer; vulval and vaginal atrophy.

Estrace Plus *Shire, Cz.†.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estrace-C *Shire, Cz.†.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders.

Estracomb *Novartis, Arg.; Novartis, Austria; Novartis, Braz.†; Novartis, Canad.; Novartis, Chile; Novartis, Cz.†; Novartis, Denm.; Novartis, Fin.†; Novartis, Ger.†; Novartis, Hong Kong; Novartis, Hung.; Novartis, Ital.; Altana, Mex.; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.†; Novartis, Switz.; Novartis, Venez.†.*
4 Patches, estradiol (p.2097·2) (Estraderm TTS); 4 patches, estradiol; norethisterone acetate (p.2119·3) (Estragest TTS).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estracomb TTS *Novartis, Gr.*
Estradiol (p.2097·2); norethisterone (p.2119·3).
Hormone replacement therapy.

Estracombi *Novartis, Austral.; Novartis, Belg.; Novartis, Irl.; Novartis, S.Afr.; Novartis, Turk.; Novartis, UK.*
4 Patches, estradiol (p.2097·2) (Estraderm); 4 patches, estradiol; norethisterone acetate (p.2119·3) (Estragest).
Menopausal disorders; osteoporosis.

Estracutan *Hexal, Austria.*
Estradiol (p.2097·2).
Menopausal disorders.

Estracyt
Pfizer, Arg.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, Israel; Pfizer, Malaysia†; Pfizer, Singapore.
Estramustine phosphate (p.717·3).
Prostatic cancer.

Pfizer, Austria; Pfizer, Belg.; Pfizer, Cz.; Pfizer, Hung.; Pfizer, Neth.; Pharmacia, Pol.; Pfizer, Spain; Pfizer, Switz.
Estramustine phosphate (p.717·3) or estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Pfizer, Chile; Pfizer, Denm.; Pfizer, Fr.; Pharmacia, Irl.; Pharmacia, Ital.; Shinyaku, Jpn; Pfizer, Norw.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Swed.; Pfizer, Turk.; Pharmacia, UK.
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Pharmacia, Ger.
Estramustine meglumine phosphate (p.717·3) or estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Pfizer, Venez.
Estramustine (p.717·3).
Prostatic cancer.

Estradelle *Sigma, Braz.*
Estradiol (p.2097·2).
Menopausal disorders.

Estraderm *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.†; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.†; Novartis, Fin.†; Novartis, Fr.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India†; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Altana, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.†; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.†; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.†.*
Estradiol (p.2097·2).
Female hypogonadism; menopausal disorders; oestrogen deficiency; osteoporosis; primary ovarian failure; vulval and vaginal atrophy.

Estraderm TTS *Novartis, Gr.†.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency.

Estradot *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.†; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, UK; Novartis, Venez.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estradurin *Pfizer, Austria; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.†; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Rus.†; Pfizer, Swed.; Pfizer, Switz.*
Polyestradiol phosphate (p.2124·1).
Mepivacaine hydrochloride (p.1866·3) may be included in this preparation to alleviate the pain of injection.
Amenorrhoea; breast cancer; menopausal disorders; prostatic cancer.

Estradurine *Pfizer, Belg.*
Polyestradiol phosphate (p.2124·1).
Mepivacaine hydrochloride (p.1866·3) is included in this preparation to alleviate the pain of injection.
Prostatic cancer.

Estrafemol *Sanofi Synthelabo, Ger.*
12 Capsules, estradiol valerate (p.2097·3); 14 capsules, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Estragest *Novartis, Arg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.†; Novartis, Ger.; Novartis, Hung.; Novartis, Switz.; Novartis, Venez.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estrahexal *Hexal, Cz.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estramon *Hexal, Austria; Hexal, Ger.; Hexal, Gr.; Sandoz, Hung.; Hexal, Mex.; Ecosol, Switz.; Ilsan, Turk.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estranova CC *Silesia, Chile.*
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Estranova E *Silesia, Chile.*
Estradiol valerate (p.2097·3).
Menopausal disorders.

Estranova 30 Simple *Silesia, Chile.*
13 Tablets, estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1); 17 tablets, estradiol valerate.
Menopausal disorders.

Estrapak *Novartis, Irl.†; Novartis, NZ†; Novartis, UK†.*
Transdermal patches, estradiol (p.2097·2); tablets, norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Estrapatch *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Port.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency.

Estrarona *Silesia, Chile.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis; prostatic cancer.

Estrasorb *Esprit, USA.*
Estradiol (p.2097·2).
Menopausal vasomotor disorders.

Estratab *Solvay, USA.*
Esterified oestrogens (p.2097·1).
Breast cancer; menopausal vasomotor symptoms; oestrogen deficiency; osteoporosis; prostatic cancer; vulval and vaginal atrophy.

Estratest *Solvay, USA.*
⊗ Esterified oestrogens (p.2097·1); methyltestosterone (p.2117·1).
Menopausal disorders.

Estrefen *Solfran, Mex.*
Dihydrostreptomycin (p.266·1); sulfadiazine (p.336·2).
Diarrhoea.

Estrena *Merck, Fin.*
Estradiol (p.2097·2).
Menopausal disorders.

Estreptobroncol *Atral, Port.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Bacterial infections.

Estreptocarbocaftiazol
Note. This name is used for preparations of different composition.
Bago, Arg.
Oral suspension: Phthalylsulfathiazole (p.315·1); streptomycin sulfate (p.333·3); charcoal (p.1435·2); menadione (p.1995·2).
Diarrhoea; flatulence.

Bago, Arg.
Tablets: Phthalylsulfathiazole (p.315·1); streptomycin sulfate (p.333·3); charcoal (p.1435·2); simeticone (p.1770·2); menadione (p.1995·2).
Diarrhoea; flatulence.

Estreptoenterol *Juste, Spain†.*
Dihydrostreptomycin sulfate (p.266·1); phthalylsulfathiazole (p.315·1); pectin (p.2145·2).
Gastrointestinal infections.

Estreptopal *Reuffer, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Estreva *Merck, Arg.†; Merck, Belg.; Merck, Braz.; Merck, Chile; Theramex, Cz.†; Solvay, Ger.; Merck, Hong Kong; Merck, Indon.; Merck, Mex.; Merck, Neth.; Theramex, Pol.; Theramex, Port.; Merck, Singapore; Eumedica, Switz.†; Merck, Turk.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estrex *Lake, USA.*
Homoeopathic preparation.

Estri-Atlas *Atlas, Arg.*
Rose oil (p.2381·2); hyaluronic acid (p.2320·1); centella (p.1592·3); vitamin E (p.1992·2); elastin (p.2286·1).

Estriel *Mochida, Jpn.*
Estriol (p.2101·1).
Menopausal disorders; osteoporosis.

Estrifam *Novo Nordisk, Ger.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estrimax *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Estrin
Note. This name is used for preparations of different composition.
Cipla, India.
Conjugated oestrogens (p.2087·2).

Loeffler, Mex.
Glycerol (p.2314·2).
Constipation.

Estring *Pharmacia, Arg.†; Pfizer, Austria; Paladin, Canad.; Pharmacia, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pharmacia-Upjohn, Gr.†; Pfizer, Norw.; Pharmacia, S.Afr.; Pfizer, Switz.; Pharmacia, UK; Pharmacia Upjohn, USA.*
Estradiol (p.2097·2).
Menopausal disorders; postmenopausal atrophy of the vagina or lower urinary tact.

Estriopax *Neo Quimica, Braz.*
Estriol (p.2101·1).
Oestrogen deficiency.

Estroact *Kee, India.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Estrocare *Pharmanex, USA.*
Cordyceps sinensis; cimicifuga (p.2282·1).
Menopausal disorders.

Estroclim *Sigma-Tau, Ital.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estrocur *Sigma, Braz.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Estrodose *Wyeth Lederle, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Estrofem
Note. This name is used for preparations of different composition.
Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Gr.†; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia†; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Thai.
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Novo Nordisk, Turk.
Estriol (p.2101·1).
Menopausal disorders.

Estrofem N *Novo Nordisk, Switz.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estroffik *Effik, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estrofort *Rottapharm, Fr.*
Soya isoflavones (p.2391·2); *lactobacillus sporogenes* (p.2372·3); calcium (p.1675·2); colecalciferol (p.1986·2).
Menopausal disorders.

Estrogel *Viatris, Austria; Schering, Canad.; Leiras, Denm.; Leiras, Fin.; Faran, Gr.; Ascend, USA; Biopas, Venez.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estrogenon *Sanval, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Estrokad *Kade, Hung.*
Estriol (p.2101·1).
Menopausal vulvovaginal disorders.

Estro-Logic *Quest, Canad.†.*
Astragalus; black cohosh; chastetree berry; motherwort; sage; soy bean; vervain; wild yam (p.1922·1).

Estromon *Standard Chem & Pharm, Thai.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Estronar *Menarini, Port.†.*
Estradiol (p.2097·2).
Menopausal disorders; prostatic cancer.

Estronorm *Jenapharm, Ger.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estro-Pause *Adcock Ingram, S.Afr.*
Estradiol valerate (p.2097·3).
Menopausal disorders.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Estro-Pause N *Adcock Ingram, S.Afr.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; norethisterone (p.2119·3).
Menopausal disorders.

Estroplast *Adamed, Pol.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Estroplus *Solvay, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Estroquin *Richmond, Arg.*
Calcium folinate (p.1943·3).

Estrostep *Warner Chilcott, USA†.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Estrostep Fe *Warner Chilcott, USA.*
21 Tablets, norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
Triphasic oral contraceptive.

Estulic *Novartis, Belg.; Egis, Cz.†; Novartis, Fr.; EGIS, Hung.; Mochida, Jpn†; Viatris, Neth.†; Egis, Rus.*
Guanfacine hydrochloride (p.1301·1).
Hypertension.

Esucos *UCB, Austria; UCB, Fin.; SIT, Ital.; UCB, Norw.; UCB, Swed.*
Dixyrazine (p.994·3).
Alcohol withdrawal syndrome; anxiety; depression; dysphoria; nervous disorders; premedication; senile agitation; sleep disorders; vomiting.

Esvat *Ferron, Indon.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Esvical *More, Philipp.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); simeticone (p.1770·2).
Calcium supplement; gastric hyperacidity.

Esvicee *More, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Esvimin *Medichem, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Esvit C *Laboratorios Chile, Chile.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Esvorin *Opus Materia, Gr.*
Calcium levofolinate (p.1943·3).
Antidote to folic acid antagonists.

Eta Biocortilen *SIFI, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Eta Biocortilen VC *SIFI, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); gramicidin (p.286·1); tetryzoline hydrochloride (p.1574·1).
Infected eye disorders.

E-Tabs *Sigma, Braz.*
dl-Alpha tocoferil acetate (p.1992·3).

Etabus *Ferring, Mex.*
Disulfiram (p.2296·2).

Etacin *Ethica, Indon.*
Ciprofloxacin (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Etaconil *Tecnofarma, Chile; Nolver, Venez.*
Flutamide (p.725·1).
Benign prostatic hyperplasia; prostatic cancer.

Etacortilen *SIFI, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Etacril *Beta, Arg.†.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux.

Etagerin *Biofarma, Mex.*
Milk thistle (p.1452·1).
Hepatitis.

Etalpha *Leo, Austria; Pentafarma, Chile; Leo, Denm.; Leo, Fin.; Leo, Neth.; Leo, Norw.; Leo, Port.; Leo, Rus.; Leo, Spain; Leo, Swed.*
Alfacalcidol (p.1986·1).
Calcium metabolic disorders; hyperparathyroidism in renal failure; hypocalcaemia; hypoparathyroidism; hypophosphataemic osteodystrophy; osteomalacia; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency; vitamin D supplement.

Etamucin *Etapharm, Austria.*
Sodium hyaluronate (p.2320·1).
Adjunct in ophthalmic surgery.

Etanicozid B6 *Piam, Ital.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Etaphylline *Corsa, Indon.; Sanofi Synthelabo, Indon.*
Acefylline piperazine (p.1114·1).
Asthma; dyspnoea; emphysema.

Etapiam *Piam, Ital.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Etaretin *Etapharm, Austria.*
Retinal phosphatides; sodium bicarbonate (p.1673·2).
Eye disorders.

Etasisen *Rafarm, Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Etason *Otto, Indon.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Etaverol *Dinafarma, Braz.†.*
Homatropine (p.1881·2); belladonna (p.2263·3).
Smooth muscle spasm.

Etaxene
Wassermann, Ital.
Somatostatin (p.1809·1).
Gastrointestinal haemorrhage.

Alfa Wassermann, Thai.
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Etazim *Benedetti, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

ETDR *SIFI, Ital.*
Vitamin C; vitamin E; rutoside; sambucus (p.1922·1).
Nutritional supplement.

Etec *Raffo, Arg.; Tecnofarma, Chile.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Etermol Antitusivo *Quimpe, Spain.*
Benzydamine hydrochloride (p.27·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2).
Coughs.

Eternex *Dabur, India.*
Melatonin (p.2338·3); vitamin B (p.1979·1).
Circadian rhythm disorders; jet lag; sleep disorders.

Etfariol *Vilco, Gr.*
Ticlopidine (p.1412·1).
Thromboembolic disorders.

ETH Ciba *Sandoz, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Ethacid *Stadmed, India.*
Etamsylate (p.1064·3).
Menorrhagia; periventricular haemorrhage.

Etham *Pond's, Thai.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Ethambusin *Synthesis, Rus.†.*
Ethambutol hydrochloride (p.274·1).

Ethamcip *Cipla, India.*
Etamsylate (p.1064·3).

Ethamizid *Medichem, Philipp.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Pyridoxine (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Ethamolin *Farmoquimica, Braz.; Questcor, USA.*
Monoethanolamine oleate (p.2346·2).
Oesophageal varices.

Ethasyl *FDC, India.*
Etamsylate (p.1064·3).
Haemorrhage; menorrhagia.

Ethatyl *Aventis, S.Afr.*
Ethionamide (p.275·3).
Tuberculosis.

Ethbutol *Pharmasant, Thai.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

EtheDent *Ethex, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Ethezyme *Ethex, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).
Debridement of wounds and ulcers.

Ethi 400 *Dynamic, Philipp.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Pyridoxine (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Ethibloc *Ethicon, Ger.*
Sodium amidotrizoate (p.1475·3).
Packing the residual pancreatic duct after partial resection of the pancreas; pre-operative vascular embolisation for renal tumours.

Ethicef *Ethica, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Ethicholine *Baxter, NZ†; DBL, NZ†; Mayne, Singapore.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Ethiclaf *Ethica, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ethicol *Ethica, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Ethicoline *Hospira, Malaysia.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Ethidan *Ethica, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Ethide *Lupin, India.*
Ethionamide (p.275·3).
Tuberculosis.

Ethidol *Ethica, Indon.*
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

Ethiferan *Ethica, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; gastroparesis; nausea and vomiting.

Ethifix *Ethica, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Ethiflox *Ethica, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Ethigent *Ethica, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Ethigobal *Guardian, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Ethilin *Ethica, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Ethimox *Ethica, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ethiodol *Savage, USA.*
Iodised oil (p.1482·1).
Contrast medium for hysterosalpingography and lymphography.

Ethipramine *Pharmacare, S.Afr.*
Imipramine hydrochloride (p.400·3).
Alcohol withdrawal syndrome; behaviour disorders; depression; parkinsonism.

Ethiprid *Ethica, Indon.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Ethirfin *Ethypharm, Port.*
⊗ Morphine sulfate (p.86·3).
Pain.

Ethirov *Ethica, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Ethisolvan *Ethica, Indon.; Soho, Indon.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Ethmozine *Roberts, USA†.*
Moracizine hydrochloride (p.1344·2).
Ventricular arrhythmias.

Ethopil *Ethica, Indon.*
Piracetam (p.368·2).
Alcoholism; behavioural disorders in children; cerebral trauma; mental function impairment.

ETH-Oxydose *Ethex, USA.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Ethrane *Abbott, Austral.†; Abbott, Austria; Abbott, Ger.†; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.†; Abbott, Mex.; Abbott, NZ†; Abbott, Neth.†; Abbott, Philipp.; Abbott, Rus.†; Abbott, S.Afr.; Abbott, Switz.†; Abbott, Turk.; Baxter, USA; Abbott, Venez.*
Enflurane (p.1782·2).
Anaesthesia and analgesia in obstetrics; general anaesthesia.

Ethyfen *Medicus, Gr.†.*
Nabumetone (p.91·2).
Inflammatory disorders; pain.

Ethylex *Orpha-Devel, Austria.*
Naltrexone hydrochloride (p.1455·2).
Alcoholism.

Ethymal *Katwijk, Neth.*
Ethosuximide (p.479·3).
Absence seizures.

Ethyol *Essex, Arg.†; Schering-Plough, Austral.; Schering-Plough, Belg.; Mantecorp, Braz.; Schering-Plough, Chile; Schering-Plough, Cz.; Medimmune, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong†; Schering-Plough, Hung.†; Teva, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia†; Schering-Plough, Mex.; Schering-Plough, NZ; MedImmune, Neth.; Schering-Plough, Philipp.; USB, Pol.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Er-Kim, Turk.; Schering-Plough, UK†; Alza, USA; US Bioscience, USA; Schering-Plough, Venez.*
Amifostine (p.1436·3).
Radiotherapy-induced xerostomia; reduction of neutropenia and renal toxicity due to cyclophosphamide and platinum-containing cytotoxics.

Etiaxil
Cooper, Fr.
Aluminium chloride (p.1588·2) and/or aluminium lactate (p.2255·1).
Hyperhidrosis.

Interdelta, Switz.
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Etibi *Gerot, Austria; Valeant, Canad.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Etideme *Montefarmaco, Ital.*
Cimetidine (p.1716·2).
Gastric hyperacidity.

Etidine *EMS, Braz.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Etidrate *Pacific, NZ.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of the bone.

Etidrel *Hexal, Swed.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Etidrel Kit *Hexal, Swed.*
14 Tablets, etidronate disodium (p.1097·1); 74 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Etidron *Hexal, Ger.; Pharmanel, Gr.; Abiogen, Ital.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Etidron Kombi *Hexal, Ger.*
14 Tablets, etidronate disodium (p.1097·1); 76 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Etil *CT, Ger.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Etil Adrianol *Klonal, Arg.†.*
⊗ Etilefrine (p.1284·1).
Hypotension.

Etildopanan *Neo Quimica, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Etilefril *Uniao Quimica, Braz.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Etiles *Microsules Bernabo, Arg.†.*
Tiapride hydrochloride (p.1032·1).

Etiltox *AFOM, Ital.*
Disulfiram (p.2296·2).
Alcoholism.

Etimex *Etifar, Venez.†.*
Pyrantel (p.155·2).
Worm infections.

Etindrax *Valdecasas, Mex.*
Allopurinol (p.552·2).
Calcium oxalate calculi; hyperuricaemia.

Etinoline *Ethypharm, Cz.†.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma.

Etinox *Ivax, Arg.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Arthroses.

Etioven *Sanofi-Aventis, Fr.*
Naftazone (p.1074·2).
Peripheral vascular disorders.

Etiplus *Biospray, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Eti-Puren *Alpharma-Isis, Ger.†.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Etisux *Fabop, Arg.*
Erythromycin (p.269·2).
Bacterial infections.

Etiyodix *Etifar, Venez.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Etizem *Ethypharm, Cz.†; Ethypharm, Port.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Etizil *Etifar, Venez.†.*
Meclozine (p.585·1); pyridoxine (p.1979·1).

Etnoderm *Koni-Cofarm, Chile.*
Hydroquinone (p.1598·2).

ETO CS *Pharmacia, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Etobion *Medicus, Gr.*
Etoposide (p.718·1).
Malignant neoplasms.

Eto-cell *Cell Pharm, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Etocomed *Richter, Austria.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Etocris *LKM, Arg.*
Etoposide (p.718·1).
Malignant neoplasms.

Etodin *Ulkar, Turk.*
Etodolac (p.52·2).
Osteoarthritis; rheumatoid arthritis.

Etofen *Ecosol, Switz.†.*
Etofenamate (p.53·1).
Musculoskeletal, joint, and soft-tissue disorders.

Etofenol *Medichrom, Gr.*
Etofenamate (p.53·1).
Inflammatory disorders; pain.

Etogel *KRKA, Cz.†.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Eto-Gry *Gry, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Etoina *Klonal, Arg.*
Phenytoin (p.495·2).
Arrhythmias; epilepsy.

Etol *Nobel, Turk.*
Etodolac (p.52·2).
Osteoarthritis; rheumatoid arthritis.

Etomar *Marcmed, Pol.*
Aspirin (p.20·3); ethenzamide (p.51·3); caffeine (p.1116·3).
Pain.

Etomedac *Medac, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Etomine *Novartis, S.Afr.*
Clotiapine (p.980·2).
Agitation; anxiety; depression; psychoses.

Eton *Umeda, Thai.*
Ethionamide (p.275·3).
Tuberculosis.

Etonco *Armstrong, Mex.*
Etoposide (p.718·1).
Malignant neoplasms.

E-Tonil *APS, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Etono *Chefaro, Fin.*
Tripelennamine hydrochloride (p.592·2).
Insect stings and bites.

Etonolver *Nolver, Venez.*
Etoposide (p.718·1).
Malignant neoplasms.

Etonox *Charoen, Thai.*
Etodolac (p.52·2).
Musculoskeletal and joint disorders; pain.

Etopan *Taro, Israel; Winthrop, UK.*
Etodolac (p.52·2).
Osteoarthritis; pain; rheumatoid arthritis.

Etophylate *Martin & Harris, India†.*
Acefylline piperazine (p.1114·1).
Bronchitis; bronchospasm.

Etopiryna *Polpharma, Pol.*
Aspirin (p.20·3); ethenzamide (p.51·3); caffeine (p.1116·3).
Pain.

Etopofos *BMS, Arg.†; BMS, Austria; BMS, Denm.; BMS, Fin.; BMS, Norw.; BMS, Swed.*
Etoposide phosphate (p.718·2).
Malignant neoplasms.

Etopophos *BMS, Austral.; BMS, Belg.†; BMS, Cz.†; BMS, Fr.; BMS, Ger.; BMS, Irl.†; BMS, Israel†; BMS, NZ; BMS, S.Afr.; BMS, Switz.; BMS, UK; BMS Oncology, USA.*
Etoposide phosphate (p.718·2).
Malignant neoplasms.

Etopos *Eurofarma, Braz.†; Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.*
Etoposide (p.718·1).
Malignant neoplasms.

Etopoxan *Baxter, Philipp.*
Etoposide (p.718·1).
Small-cell lung cancer; testicular cancer.

Etopul *BPL-Meizler, Braz.†; Korea United, Philipp.*
Etoposide (p.718·1).
Malignant neoplasms.

Etosid *Cipla, India; Cipla, Venez.*
Etoposide (p.718·1).
Malignant neoplasms.

Etosin *Asta Oncologia, Braz.*
Etoposide (p.718·1).
Malignant neoplasms.

Etoxib *Unichem, India.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Etoxisclerol *Bama, Spain; Flupal, Venez.*
Lauromacrogol 400 (p.1916·1).
Varices.

Etoxisklerol *IFET (ΙΦΕΤ), Gr.*
Lauromacrogol 400 (p.1916·1).
Varices.

Etozox *Cipla, India.*
Etoricoxib (p.53·1).

Etrafon *Schering-Plough, S.Afr.†; Schering, USA.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Mixed anxiety depressive states.

Etrafonil *Doctum, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Etrane *Abbott, Braz.*
Enflurane (p.1782·2).
General anaesthesia.

Etrat
Note. This name is used for preparations of different composition.
Fujisawa, Austria.
Heparin sodium (p.1301·2); menthol (p.2340·1); glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Gemballa, Braz.†.
A heparinoid (p.1305·2); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Soft-tissue injury.

Etrat Sportgel *Fujisawa, Ger.†.*
Heparin sodium (p.1301·2); menthol (p.2340·1); glycol salicylate (p.62·3).
Sports injuries.

Etrat Sportgel HES *Klinge, Ger.*
Glycol salicylate (p.62·3).
Soft-tissue disorders; sports injuries.

Etrat Sportsalbe MPS *Klinge, Ger.†.*
A heparinoid (p.1305·2).
Soft-tissue injury; superficial vascular disorders.

Etrel *Pharmex (Φαρμεξ), Gr.*
Itraconazole (p.536·3).
Fungal infections.

Etrivex *Galderma, Port.; Galderma, UK.*
⊗ Clobetasol propionate (p.1522·2).
Psoriasis; skin disorders.

E-Trocima-P *Keyerson, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Etrogran *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Etrola *Pharmasant, Thai.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Etrolate *Pharmasant, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Etronil *Klonal, Arg.*
Metronidazole (p.837·1).

Etrosteron *Elea, Arg.*
Estradiol undecylate (p.2098·3).
Menopausal disorders.

Etrotab *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Etumina *Novartis, Arg.; Novartis, Spain.*
Clotiapine (p.980·2).
Alcohol withdrawal syndrome; anxiety; bipolar disorder; insomnia; psychoses; schizophrenia.

Etumine *Novartis, Belg.*
Clotiapine (p.980·2).
Agitation; psychoses.

Etyofil *FDC, India†.*
Theophylline (p.1140·1); etofylline (p.1121·1).
Cardiac disorders; cerebrovascular disorders.

Etyomid *Kocak, Turk.*
Ethionamide (p.275·3).
Tuberculosis.

Etyzem *Caber, Ital.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension.

EU 2000 *Union Drug, Thai.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Eubetal Antibiotico
Note. This name is used for preparations of different composition.
SIFI, Ital.
Eye drops: ⊗ Betamethasone sodium phosphate (p.1518·3); rolitetracycline (p.330·3); chloramphenicol (p.239·3); colistimethate sodium (p.256·3).
Eye disorders.

SIFI, Ital.
Eye ointment: ⊗ Betamethasone sodium phosphate (p.1518·3); tetracycline (p.347·1); chloramphenicol (p.239·3); colistimethate sodium (p.256·3).
Eye disorders.

Eubetal Biotic *Craveri, Arg.†.*
⊗ Betamethasone sodium phosphate (p.1518·3); rolitetracycline (p.330·3) or tetracycline (p.347·1); chloramphenicol (p.239·3); colistimethate sodium (p.256·3).
Eye disorders.

Eubine *Chiesi, Fr.†.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Eubiol *Chephasaar, Ger.†.*
Arginine aspartate (p.1928·2).
Liver disorders.

Eubiolac *Verla, Ger.*
Calcium lactate (p.1676·1).
Restoration of normal vaginal flora; vaginal infections.

Euboral *Reig Jofre, Spain.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Eubos *Hobein, Hong Kong; Eubos, Malaysia; Hobein, Malaysia.*
Skin cleanser.
Skin care.

Eubos Feminin *Hobein, Hong Kong.*
Chamomile (p.2279·3); hydrolysed milk and wheat protein; lactic acid (p.2329·3).
Personal hygiene.

Eubucal *Sanopharm, Switz.†.*
Chlorhexidine gluconate (p.1635·3); myrrh (p.2349·2); chamomile (p.2279·3); arnica (p.2260·2); rhatany (p.2378·3); menthol (p.2340·1).
Mouth disorders.

Eucabal *Esparma, Ger.†; Esparma, Rus.*
Ribwort plantain (p.2379·1); thyme (p.2401·1).
Catarrh.

Eucabal-Balsam S *Esparma, Ger.†.*
Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2).
Respiratory-tract disorders.

Eucabal-S *Esparma, Rus.*
Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2).
Respiratory-tract disorders.

Eucalcic *Altana, Fr.*
Calcium carbonate (p.1714·1).
Renal osteodystrophy.

Eucalin *Farcoral, Mex.†.*
Guaiacol (p.1561·2); cineole (p.2282·3).
Respiratory-tract disorders.

Eucaliptan *Bunker, Braz.†.*
Ampoule A, cineole (p.2282·3); guaifenesin (p.1561·3); dipyrone (p.49·2); terpineol (p.2396·1); chlorophyll (p.1471·1); ampoule B, chlorphenamine maleate (p.571·3); vitamin C (p.1983·3).
Influenza symptoms.

Eucaliptine
Note. This name is used for preparations of different composition.
Rudefsa, Mex.
Injection: Guaiacol (p.1561·2).
Upper respiratory-tract infections.

Rudefsa, Mex.
Syrup: Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2).
Coughs.

Eucalipto Composto *Dynacren, Ital.†.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); levomenthol; thymol (p.1664·3).
Nasal congestion.

Eucalyptamint *Ciba, USA.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).

Eucalyptine
Note. This name is used for preparations of different composition.
McNeil, Fr.
Adult suppositories: Cineole (p.2282·3); guaifenesin (p.1561·3); camphor (p.2273·2).
Respiratory-tract disorders.

McNeil, Fr.
Infant suppositories: Cineole (p.2282·3); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Medgenix, Belg.
Suppositories for adults and children: Codeine phosphate (p.37·2); cineole (p.2282·3).
Coughs.

Medgenix, Belg.
Suppositories for infants: Camphor (p.2273·2); cineole (p.2282·3); guaiacol (p.1561·2).
Respiratory disorders.

Medgenix, Belg.
Syrup: Codeine (p.37·2); cineole (p.2282·3).
Coughs.

Eucalyptine Le Brun
Note. This name is used for preparations of different composition.
Medgenix, Belg.†.
Capsules: Cineole (p.2282·3); codeine (p.37·2).
Coughs.

McNeil, Fr.
Infant suppositories: Cineole (p.2282·3); sulfogaiacol (p.1573·2).
Respiratory-tract disorders.

McNeil, Fr.
Syrup: Cineole (p.2282·3); codeine (p.37·2).
Coughs.

Eucalyptine Pholcodine *Medgenix, Belg.*
Cineole (p.2282·3); camphor (p.2273·2); phenol (p.1656·1); guaiacol (p.1561·2); pholcodine (p.1570·2).
Respiratory disorders.

Eucalyptine Pholcodine Le Brun *Medgenix, Belg.†.*
Sulfogaiacol (p.1573·2); sodium camsilate (p.2388·3); sodium phenolsulfonate; pholcodine (p.1570·2); belladonna (p.2263·3); aconite (p.2246·1); cineole (p.2282·3).
Respiratory disorders.

Eucalyptospirine *Pfizer Consumer, Spain†.*
Aspirin (p.20·3); cineole (p.2282·3); guaiacol (p.1561·2).
Influenza and cold symptoms.

Eucalytux *Tilman, Belg.*
Codeine (p.37·2); sulfogaiacol (p.1573·2).
Formerly contained codeine, sulfogaiacol, eucalyptus oil, and pumilio pine oil.
Coughs.

Eucanol
Note. This name is used for preparations of different composition.
Pharma Nord, UK.
Cream: Eucalyptus oil (p.2301·2); lavender oil (p.2331·2); calendula oil (p.2273·1).
Insect bites; skin irritation.

Pharma Nord, UK.
Topical rub; topical spray: Eucalyptus oil (p.2301·2); lavender oil (p.2331·2); sweet birch oil (p.86·2).
Musculoskeletal and joint pain.

Eucapinol *Streuli, Switz.*
Camphor (p.2273·2); menthol (p.2340·1); cypress oil (p.2291·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); thyme oil (p.2401·2).
Cold symptoms.

Eucar *Salus, Ital.*
Levocarnitine hydrochloride (p.1932·3).
Carnitine deficiency.

Eucarbon
Note. This name is used for preparations of different composition.
Trenka, Austria; Santa, Turk.
Senna (p.1769·2); rhubarb (p.1768·3); vegetable charcoal (p.1435·3); sublimed sulfur (p.1614·1); peppermint oil (p.1761·2); fennel oil (p.2303·1).
Constipation.

Trenka, Israel; Giuliani, Ital.
Senna (p.1769·2); rhubarb (p.1768·3); vegetable charcoal (p.1435·3); sulfur (p.1614·1).
Constipation; meteorism.

Trenka, Malaysia†.
Senna (p.1769·2); rhubarb (p.1768·3); charcoal (p.1435·3); sulfur (p.1614·1); mint oil (p.2345·2); fennel oil (p.2303·1).
Bowel evacuation; constipation; flatulence.

Eucarbon Herbal *Trenka, Austria.*
Senna (p.1769·2); rhubarb (p.1768·3); vegetable charcoal (p.1435·3).
Constipation.

Eucardic *Roche, Irl.; Roche, Neth.; Roche, UK.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Eucardina *Italmex, Mex.†.*
Tripsepar.
Thromboembolic disorders.

Eucarnil *Boniscontro & Gazzone, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Eucerin
Note. This name is used for preparations of different composition.
Beiersdorf, Austral.†; Beiersdorf, Irl.; Beiersdorf, Thai.; Beiersdorf, UK; Beiersdorf, USA.
Emollient.
Dry skin; ointment basis.

Beiersdorf, Chile.
Cream-gel: Lactic acid (p.2329·3); sodium lactate (p.1673·3).
Acne.

Beiersdorf, Chile†.
SPF 15: Enzacamene (p.1597·1); octil triazone (p.1608·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, USA.
SPF 25: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Dry skin; sunscreen.

Beiersdorf, Chile†.
SPF 25 cream: Enzacamene (p.1597·1); titanium dioxide (p.1617·3); octil triazone (p.1608·1); avobenzone (p.1589·3).
Sunscreen.

Eucerin Baby & Mom *Beiersdorf, Chile.*
A range of skin cleansing and emollient preparations.

Eucerin Dry Skin Care Daily Facial *Beiersdorf, USA.*
SPF 20: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); ensulizole (p.1597·1); octisalate (p.1608·2).
Sunscreen.

Eucerin Emulsion *Beiersdorf, Chile.*
Hyaluronic acid (p.2320·1).
Soap substitute.

Eucerin Itch-Relief *Beiersdorf, USA.*
Menthol (p.2340·1); evening primrose oil (p.2302·1).
Pruritus.

Eucerin Omega Olbad *Beiersdorf, Ger.†.*
Soya oil (p.1965·3).
Formerly known as Eucerin Omega Fettsauren Olbad.
Bath additive; dry skin.

Eucerin peau seche *Beiersdorf, Switz.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Eucerin Pele Seca *Beiersdorf, Port.†.*
⊗ Urea (p.1620·2).
Dry skin.

Eucerin Pele Sensivel *Beiersdorf, Port.†.*
A range of soap substitutes and moisturisers.

Eucerin Pele com tendencia para o acne *Beiersdorf, Port.†.*
A range of cleansing and moisturising preparations.
Acne.

Eucerin pH5 *Beiersdorf, Arg.*
A range of skin cleansing and emollient preparations.

Eucerin Piel *Beiersdorf, Arg.*
A range of skin cleansing and moisturising preparations.

Eucerin Piel Grasa
Note. This name is used for preparations of different composition.
Beiersdorf, Chile.
Cream: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3) panthenol (p.2362·1); levomenol (p.2333·3); diazolidinyl urea; phenoxyethanol (p.1657·1).
Acne.

Beiersdorf, Chile.
Cream-gel: Lactic acid (p.2329·3); titanium dioxide (p.1617·3); phenoxyethanol (p.1657·1).
Acne.

Beiersdorf, Chile.
Topical gel: Salicylic acid (p.1612·2).
Acne.

Eucerin Piel Seca *Beiersdorf, Chile.*
A range of emollient and moisturising preparations.

Eucerin Piel Seca/Reseca *BDF, Mex.†.*
⊗ Urea (p.1620·2); sodium lactate (p.1673·3).
Dry skin disorders.

Eucerin Piel Sensible al Sol *BDF, Mex.†.*
SPF 20; SPF 25; SPF 35: Titanium dioxide (p.1617·3); octil triazone (p.1608·1); zinc oxide (p.1621·2); avobenzone (p.1589·3).
Sunscreen.

Eucerin Piel con Tendencia Acneica *BDF, Mex.†.*
Lactic acid (p.2329·3).
Acne.

Eucerin Plus *Beiersdorf, USA.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Dry skin; sunscreen.

Eucerin Salbe *Beiersdorf, Ger.†.*
⊗ Urea (p.1620·2).
Dry skin.

Eucerin Shampoo Anticaspa *Beiersdorf, Chile.*
Climbazole (p.529·3); piroctone olamine (p.1610·1); sodium salicylate (p.124·2).
Dandruff.

Eucerin Solar
Note. This name is used for preparations of different composition.
Beiersdorf, Chile†.
Cream SPF 15: Titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile†.
Cream SPF 20: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile.
Gel SPF 25: Enzacamene (p.1597·1); titanium dioxide (p.1617·3); octil triazone (p.1608·1); avobenzone (p.1589·3).
Sunscreen.

Beiersdorf, Chile.
Infant lotion SPF 25: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Beiersdorf, Chile.
Infant topical spray SPF 30: Octil triazone (p.1608·1); enzacamene (p.1597·1); iscotrizinol (p.1599·2); ensulizole (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile.
SPF 35: Enzacamene (p.1597·1); titanium dioxide (p.1617·3); octil triazone (p.1608·1); avobenzone (p.1589·3).
Sunscreen.

Beiersdorf, Chile.
SPF 25 pigmented cream: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile.
SPF 50 Plus: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); octil triazone (p.1608·1); bemotrizinol (p.1590·2); ensulizole (p.1597·1).
Sunscreen.

Beiersdorf, Chile.
Spray SPF 20: Enzacamene (p.1597·1); octil triazone (p.1608·1); avobenzone (p.1589·3); dicaprylyl ether; diethylhexyl butamido triazone; ensulizole (p.1597·1).
Sunscreen.

Beiersdorf, Chile†.
Stick SPF 25: Enzacamene (p.1597·1); octylmethoxyferyl acetate; avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile.
Topical spray SPF 30: Octil triazone (p.1608·1); enzacamene (p.1597·1); iscotrizinol (p.1599·2); ensulizole (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Eucerin Sun Sensitive Skin
Note. This name is used for preparations of different composition.
Beiersdorf, Thai.
Face and Body Cream SPF 60: Avobenzone (p.1589·3); octil triazone (p.1608·1); ensulizole (p.1597·1); iscotrizinol (p.1599·2); bemotrizinol (p.1590·2).
Sunscreen.

Beiersdorf, Thai.
Face Cream SPF 25: Avobenzone (p.1589·3); titanium dioxide (p.1617·3); octocrilene (p.1608·3); octinoxate (p.1608·2); iscotrizinol (p.1599·2); bemotrizinol (p.1590·2).
Sunscreen.

Beiersdorf, Thai.
Gel SPF 25: Avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3); octil triazone (p.1608·1).
Sunscreen.

Beiersdorf, Thai.
Lotion SPF 40: Avobenzone (p.1589·3); titanium dioxide (p.1617·3); iscotrizinol (p.1599·2); bemotrizinol (p.1590·2).
Sunscreen.

Eucerinum *Beiersdorf, Chile†.*
Dry skin; pharmaceutical base.

Euceta *Novartis Consumer, Switz.*
Aluminium acetotartrate (p.2255·1).
Skin disorders.

Euceta avec camomille et arnica *Novartis Consumer, Switz.*
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3); arnica (p.2260·2).
Skin disorders.

Euceta mit Kamille *Novartis Consumer, Austria.*
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3).
Skin disorders.

Euceta Pic *Novartis Consumer, Switz.*
Aluminium acetotartrate (p.2255·1); mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3).
Insect stings.

Euchessina CM *Antonetto, Ital.*
Sodium picosulfate (p.1771·1).
Constipation.

Eucid *Greater Pharma, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux, Zollinger-Ellison syndrome; peptic ulcer.

Eucil *Farmasa, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Eucillin *Petrasch, Austria.*
Bacitracin (p.210·3); dequalinium chloride (p.1641·3); diphenylpyraline hydrochloride (p.578·2).
Infected skin disorders.

Euciton *Roux-Ocefa, Arg.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Euciton Complex *Roux-Ocefa, Arg.*
Domperidone (p.1726·2); dipotassium clorazepate (p.980·1).
Gastrointestinal disorders.

Euciton Reflux *Roux-Ocefa, Arg.*
Domperidone (p.1726·2); ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer.

Euciton Stress *Roux-Ocefa, Arg.*
Domperidone (p.1726·2); alprazolam (p.960·1); simeticone (p.1770·2).
Gastrointestinal motility disorders.

Euclamin *Polpharma, Pol.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Euclivir *TAD, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Euclorina *Bracco, Ital.*
Tosylchloramide sodium (p.1665·1).
Skin, wound, and genital disinfection.

Eucol *Tradiphar, Fr.*
⊗ Arginine oxoglurate (p.1928·3).
Tonic.

Eucoprost *Frosst, Spain.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Eucor *Greater Pharma, Thai.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Eucos-L *Talcris, Arg.†.*
Betaine (p.2265·2); trolamine (p.2405·1).

Eucotol *Bio-Diät, Ger.†.*
Eucalyptus oil (p.2301·2).
Cold symptoms; rheumatism.

Eucreas *Novartis, Cz.; Novartis, Fr.; Novartis, UK.*
Vildagliptin (p.463·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Eucycline *Demo, Gr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Eudal-SR *UAD, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Eudarona *Troika, Venez.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Eudemine *IFET (ΙΦΕΤ), Gr.; Goldshield, UK; UCB, UK.*
Diazoxide (p.1257·3).
Hypertensive crises; hypoglycaemia.

Eudent con Glysan *Kemiprogress, Ital.†.*
Glysan (enoxolone (p.50·1); sanguinaria (p.2383·2)); sodium monofluorophosphate (p.1964·3) or sodium fluoride (p.1962·2).
Gum disorders; oral hygiene.

Euderm *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore†.*
⊗ Urea (p.1620·2).
Pruritus; skin disorders.

Eudermico *Novogaleno, Ital.†.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin disorders.

Eudextran *Medacta, Ital.*
⊗ Dextran 40 (p.1059·1) in sodium chloride or glucose.
Plasma volume expansion; thromboembolic disorders.

Eudiges
Note. This name is used for preparations of different composition.
Liferpal, Mex.
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders.

Lesvi, Spain.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eudigestio *Ogna, Ital.†.*
Pancreatin (p.2360·1); pepsin (p.2365·1).
Dyspepsia.

Eudigox *Teofarma, Ital.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Eudipar *CT, Ital.†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Eudolene *Savio, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Eudon
Note. This name is used for preparations of different composition.
Baliarda, Arg.
Bromazepam (p.964·3); clebopride malate (p.1722·1); simeticone (p.1770·2).
Gastrointestinal disorders.

Eurofarmaco, Ital.†.
Glutathione (p.1448·1).
Drug and alcohol intoxication; reduction of radiation-induced damage.

Eudorlin
Note. This name is used for preparations of different composition.
Berlin-Chemie, Ger.
Tablets: Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Berlin-Chemie, Ger.†.
Tablets: Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Eudorlin Extra *Berlin-Chemie, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Eudorlin Migrane *Berlin-Chemie, Ger.*
Ibuprofen (p.64·2).
Migraine and other headaches.

Eudyna *Abbott, Austria; German Remedies, India; Tunggal Idaman, Indon.*
Tretinoin (p.1618·1).
Acne.

Eufans *Sigma-Tau, Ital.*
Amtolmetin guacil (p.19·2).
Musculoskeletal and joint disorders; pain.

Eufatin *Euromex, Mex.†.*
Famotidine (p.1730·1).
Peptic ulcer.

Eufenil *Gelcaps, Mex.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Eufermen *Sankyo, Braz.†.*
Enzymes from *Aspergillus oryzae*; ethaverine hydrochloride (p.2299·3); dimeticone (p.1770·2).
Digestive-system disorders.

Eufibron *Berlin-Chemie, Ger.†.*
Propyphenazone (p.119·3).
Fever; pain.

Eufilina *Altana, Port.; Altana, Spain.*
Theophylline (p.1140·1).
Cor pulmonale; obstructive airways disease.

Eufimenth-Balsam N *Lichtenstein, Ger.†.*
Cineole (p.2282·3); Norway spruce oil; menthol (p.2340·1).
Respiratory-tract disorders.

Euflat I *Stegropharm, Ger.†.*
Dimethicone (p.1770·2); caraway oil (p.2277·1); fennel oil (p.2303·1).
Digestive system disorders.

Euflat-E *Sudmedica, Ger.†.*
Pancreatin (p.2360·1).
Digestive system disorders.

Euflex *Schering, Canad.*
Flutamide (p.725·1).
Prostatic cancer.

Euflexxa *Ferring, UK; Ferring, USA.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis of the knee.

Eufloxin *Euromex, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Euflux *Sudmedica, Ger.*
Pumilio pine oil (p.2376·3); camphor (p.2273·2).
Catarrh.

Eufor *Farmasa, Braz.*
Fluoxetine (p.397·3).
Depression; obsessive-compulsive disorder.

Euform *Hovid, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Eufusin *Medacta, Ital.*
⊗ Succinylated gelatin (p.1072·1).
Hypovolaemia.

Eufytose *Roche, Venez.†.*
Crataegus (p.2289·1); passion flower (p.2363·2); valerian (p.2410·1); marrubium nigrum; guarana (p.2416·1); kola (p.2416·1).
Anxiety.

Eugalac *Topfer, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Eugalan Topfer *Topfer, Ger.*
Bifidum bacteria; lactulose (p.1738·2).
Cirrhosis; gastrointestinal disorders.

Eugastrim *Grunenthal, Port.*
Omeprazole (p.1753·1).
Gastric hyperacidity.

Eugastrin *Slovakofarma, Cz.†.*
St John's wort (p.422·3); absinthium (p.2244·1); melissa (p.2339·3); calamus (p.2271·3); agrimony (p.2249·2).
Digestive-system disorders.

Eugenol-Guaiacolo Composto *Ogna, Ital.*
Eugenol (p.2301·2); guaiacol (p.1561·2); lidocaine hydrochloride (p.1862·3); thymol (p.1664·3).
Dental extraction pain.

Eugerial *Bago, Arg.; Merck, Braz.*
Nimodipine (p.1357·2).
Cerebrovascular disorders; hypertension; mental function impairment.

Eugerminol *Medix, Mex.†.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Euglamin *Ratiopharm, Fin.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Euglim *Zydus, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Euglo Plus *Roche, Philipp.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Euglucan *Roche, Fr.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Euglucon *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, Braz.; Pharmascience, Canad.; Roche, Fin.; Roche, Hong Kong; Nicholas Piramal, India; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, Philipp.; Roche, Port.; Roche, S.Afr.†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Sanofi-Aventis, UK†; Roche, Venez.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Euglucon N *Aventis, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Euglusid *Roche, Chile.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Eugune *Palmares, Ital.*
Magnesium; bioflavonoids; proline oxide; lupulus; hydroxyapatite (p.1922·1).
Menopausal disorders.

Eugusal *Nutricia-Bago, Arg.†.*
Potassium chloride; potassium tartrate; ammonium chloride; citric acid; calcium phosphate (p.1667·1).
Salt substitute.

Eugynon *Schering, Hong Kong; Schering, Ital.†.*
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Eugynon 30 *Schering, UK†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Eugynon 250 *Schering, Thai.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Euhypnos *Sigma, Austral.†; Pharmacia, Belg.†; Pfizer, Irl.†; Healthcare Logistics, NZ; Pfizer, Thai.*
Temazepam (p.1030·1).
Insomnia; premedication.

Euipnos *Teva, Ital.*
Temazepam (p.1030·1).
Insomnia.

Euka *Pharmonta, Austria.*
Fennel (p.2302·3); aniseed (p.2258·2); rosemary (p.2381·2); eucalyptus oil (p.2301·2); lavender flowers (p.2331·1); laurel leaves; camphor (p.2273·2); peppermint oil (p.1761·2); spearmint oil (p.2391·3).
Gastrointestinal disorders.

Eukadar *Darier, Mex.*
Calcipotriol (p.1591·3).
Psoriasis.

Eukaliptiss *Theiss Naturwaren, Pol.*
Eucalyptus oil (p.2301·2); pine oil (p.2368·2); camphor (p.2273·2).
Musculoskeletal pain; neuralgia; respiratory-tract disorders.

Eukalisan N *Steigerwald, Ger.*
⊗ Cyanocobalamin (p.1980·2); nicotinamide (p.1957·3); rutoside sodium sulfate (p.2305·2). Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Liver disorders; neuralgia; peripheral vascular disorders; tonic.

Eukamillat *Biocur, Ger.†.*
Chamomile (p.2279·3).
Gastrointestinal, anogenital, mouth, respiratory-tract, and skin disorders.

Eukavan *Duopharm, Ger.†.*
Kava (p.2328·3).
Anxiety disorders.

Euketos *CT, Ital.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; phlebitis; thrombophlebitis.

Euky Bear Cough Syrup *Felton, Austral.*
Chlorphenamine (p.572·2); dextromethorphan (p.1555·2); sodium citrate (p.1673·3).
Coughs and cold symptoms.

Euky Bear Eu-Clear Inhalant *Felton, Austral.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Cold symptoms; respiratory-tract congestion.

Euky Bearub *Felton, Austral.*
Eucalyptus oil (p.2301·2); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2); rosemary oil (p.2381·3).
Cold and influenza symptoms; insect bites; muscular aches and pains; nasal congestion.

Eulactol Antifungal *Eulactol, Austral.†.*
Miconazole (p.541·2).
Formerly known as Leuko Fungex Antifungal.
Fungal skin infections.

Eulanta *Europharm, Hong Kong.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Dyspepsia; flatulence; heartburn.

Eulatin N *Riemser, Ger.*
Lidocaine (p.1862·3); bismuth subgallate (p.1711·1).
Anorectal disorders.

Eulatin NN *Riemser, Ger.*
Hamamelis (p.2318·2); bismuth subgallate (p.1711·1); benzocaine (p.1854·1).
Anorectal disorders.

Eulexin *Essex, Arg.†; Schering-Plough, Austral.; Schering-Plough, Belg.; Mantecorp, Braz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Mex.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Spain; Schering-Plough, Swed.; Schering-Plough, Turk.; Schering, USA†; Schering-Plough, Venez.*
Flutamide (p.725·1).
Prostatic cancer.

Eulexine *Schering-Plough, Fr.*
Flutamide (p.725·1).
Prostatic cancer.

Eulitop *Roche, Belg.; Roche, Spain.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Eulux *Mediwhite, Ital.*
Chamomile (p.2279·3); euphrasia (p.2301·3); centaurea cyanus; hamamelis (p.2318·2).
Eye irritation.

Eulyptan *Labima, Belg.†.*
Codeine (p.37·2).
Coughs.

Eu-Med *Gebro, Austria.*
Paracetamol (p.108·1); caffeine (p.1116·3); propyphenazone (p.119·3).
Fever; pain.

Eu-Med Neu *Gebro, Austria.*
Dexibuprofen (p.39·2).
Pain.

Eumetic *Pharmacia, Arg.†.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Eumicel *Cassara, Arg.*
Ketoconazole (p.539·1).
Scalp disorders.

Eumidral *Roemmers Osmoph, Venez.*
Atropine methonitrate (p.1219·3); secbutabarbital sodium (p.1027·2).
Infantile spasm.

Euminz *Lichtwer, Ger.*
Peppermint oil (p.1761·2).
Tension-type headache.

Eumitan *Menarini, Austria.*
Frovatriptan succinate (p.622·3).
Migraine.

Eumol *Arlex, Mex.*
Oxolamine (p.1567·1).
Cough.

Eumosone *GSK, India.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Eumosone-G *GSK, India.*
⊗ Clobetasone butyrate (p.1522·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Eumosone-M *GSK, India.*
⊗ Clobetasone butyrate (p.1522·3); miconazole nitrate (p.541·3).
Infected skin disorders.

Eumotil *Baliarda, Arg.*
Trimebutine maleate (p.2404·3).
Smooth-muscle spasm.

Eumotil-T *Baliarda, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).
Smooth muscle spasm.

Eumovate *Investi, Arg.; GSK, Belg.; Farmoquimica, Braz.; GSK Consumer, Canad.; GSK, Chile†; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; Sekpharma, S.Afr.; GSK, Singapore; GSK, Thai.†; GSK, Turk.; GSK Consumer, UK; GSK, Venez.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

EuMunil *Madaus, Ital.*
Echinacea (p.2298·1).
Immunostimulant; respiratory-tract infections.

Eunades *Pfizer, Braz.*
Etoposide (p.718·1).
Malignant neoplasms.

Eunalgit *Leciva, Cz.†.*
Aminophenazone (p.19·1); allobarbital (p.959·3).
Pain.

Eundin *Novopharm, Philipp.; Pascual, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Eunerpan *Abbott, Ger.*
Melperone hydrochloride (p.1006·2).
Psychiatric disorders; sleep disorders.

Eunice 35-ED *Darier, Mex.*
21 Tablets, cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Androgen-dependent acne, alopecia, and hirsutism in women; oral contraception in women with androgenic symptoms.

Eunoctin *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Nitrazepam (p.1011·2).
Epilepsy; sleep disorders.

Eunova *GSK Consumer, Ger.†.*
Multivitamin and mineral preparation (p.1922·1).

Eupantol *Altana, Fr.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eupatal *Madaus, Ger.†.*
Thyme (p.2401·1); star anise oil (p.2392·2).
Cold symptoms.

Eupatol *Donini, Ital.*
Cascara (p.1715·2); boldo (p.2267·2); rhubarb (p.1768·3).
Constipation.

Eupatorium Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Eupeclanic *Uriach, Spain†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Eupen
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Uriach, Spain.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Eupen Bronquial *Uriach, Spain.*
Amoxicillin trihydrate (p.202·2); brovanexine hydrochloride (p.1553·1).
Respiratory-tract infections.

Eupept *Cifarma, Braz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eupeptina *Almirall, Spain.*
Dibasic sodium phosphate (p.1682·3); magnesium carbonate (p.1743·1); magnesium phosphate (p.1679·2); magnesium oxide (p.1744·1); pepsin carbonate.
Constipation; dyspepsia.

Euphon
Note. This name is used for preparations of different composition.
ACP, Belg.; Mayoly-Spindler, Singapore.
Erysimum.
Formerly contained codeine, aconite, sodium formate, erysimum, and elecampane in *Belg.*
Catarrh; cough; throat disorders.

Mayoly-Spindler, Malaysia.
Erysimum; menthol (p.2340·1).
Sore throat.

Mayoly-Spindler, Fr.
Capsules; syrup: Erysimin; codeine (p.37·2).
Coughs.

Mayoly-Spindler, Fr.
Pastilles: Erysimin.
Mouth and throat disorders.

Jaba, Port.
Pastilles: Erysimum.
Coughs; throat disorders.

Jaba, Port.
Syrup: Codeine (p.37·2); erysimum.
Coughs.

Euphon N *Mayoly-Spindler, Switz.; Uhlmann-Eyraud, Switz.*
Codeine (p.37·2); tolu balsam (p.1574·2).
Coughs and associated respiratory-tract disorders.

Euphorbia Complex *Blackmores, Austral.*
Passion flower (p.2363·2); thyme (p.2401·1); grindelia (p.2317·2); euphorbia (p.2301·3); vitamins (p.1922·1).
Asthma; bronchitis; catarrh.

Euphorbium comp SN *Heel, Ger.*
Homoeopathic preparation.

Euphorbium Complexe no 88 *Lehning, Fr.*
Homoeopathic preparation.

Euphorbium Compositum *Peithner, Austria; Heel, Cz.*
Homoeopathic preparation.

Euphorbium Compositum S *Heel, S.Afr.*
Homoeopathic preparation.

Euphrasia Complex *Mediherb, Austral.*
Euphrasia (p.2301·3); solidago (p.2391·1); echinacea (p.2298·1); hydrastis (p.2321·3); capsicum (p.2276·2).
Catarrh; hayfever; sinusitis.

Euphrasia Complexe no 115 *Lehning, Fr.*
Homoeopathic preparation.

Euphrasia Compound *Phytomedicine, Austral.*
Euphrasia (p.2301·3); solidago (p.2391·1); albizia lebbeck; skullcap (p.2388·2); capsicum (p.2276·2).
Sinusitis.

Euphyllin
Altana, Austria.
Aminophylline hydrate (p.1114·3) or theophylline (p.1140·1).
Central respiratory disorders; cor pulmonale; heart failure; obstructive airways disease.

Altana, Belg.; Byk, Cz.; Meda, Fin.†; Pharos, Indon.; Altana, Pol.; Altana Madaus, S.Afr.; Altana, Switz.
Theophylline (p.1140·1).
Obstructive airways disease.

Byk, Neth.†.
Aminophylline hydrate (p.1114·3).
Obstructive airways disease.

Euphyllina *Altana, Ital.*
Theophylline (p.1140·1).
Obstructive airways disease.

Euphylline *Altana, Fr.*
Theophylline (p.1140·1).
Obstructive airways disease.

Euphylong *Byk, Cz.†; Altana, Ger.; Altana, Hong Kong; Altana, Hung.; Altana, Neth.; Swedish Orphan, Swed.†.*
Theophylline (p.1140·1).
Central respiratory disorders; obstructive airways disease.

Euphytose *Bayer, Fr.*
Crataegus (p.2289·1); passion flower (p.2363·2); valerian (p.2410·1); ballota.
Insomnia; nervous disorders.

Euplix *Desitin, Ger.; Desitin, Swed.†.*
Paroxetine mesilate (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Eupnase *Bilim, Turk.*
⊗ Guaifenesin (p.1561·3); ephedrine hydrochloride (p.1558·2).
Respiratory-tract congestion.

Eupneron *Lyocentre, Fr.†.*
Eprozinol hydrochloride (p.1560·1).
Obstructive airways disease.

Eupnol *Rottapharm, Spain.*
Benzethonium chloride (p.1630·1); cineole (p.2282·3); cherry-laurel; procaine hydrochloride (p.1869·1); terpineol (p.2396·1); menthol (p.2340·1).
Mouth and throat disorders.

Eupres *ICN, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Eupressin *Biosintetica, Braz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Eupressin H *Biosintetica, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Eupressyl *Altana, Fr.*
Urapidil (p.1419·3) or urapidil hydrochloride (p.1419·3).
Controlled hypotension during anaesthesia; hypertension.

Euproct *Andromaco, Chile†.*
Tribenoside (p.2403·3); lidocaine (p.1862·3).
Anorectal disorders.

Euproctol *Sanopharm, Switz.*
⊗ Resorcinol (p.1612·1); ephedrine hydrochloride (p.1558·2); lidocaine (p.1862·3); menthol (p.2340·1).
Anorectal disorders.

Euproctol N *Sanopharm, Switz.*
⊗ Bismuth oxychloride (p.1712·1); ethacridine lactate (p.1625·1); zinc oxide (p.1621·2); menthol (p.2340·1); lidocaine hydrochloride (p.1862·3); ephedrine hydrochloride (p.1558·2); hamamelis (p.2318·2); peru balsam (p.2365·3).
Anorectal disorders.

Euprostatin *Sigma, Braz.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Euprotin *Prasfarma, Spain.*
Lenograstim (p.1073·1).
Mobilisation of autologous peripheral blood progenitor cells; reduction of neutropenia associated with cancer chemotherapy.

Euradal *Lacer, Spain.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Euralben *Reuffer, Mex.*
Albendazole (p.139·2).

Eu-Ran *EuroHealth, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Eurax *Novartis Consumer, Austral.; Novartis Consumer, Austria; Novartis Consumer, Belg.; Columbia, Canad.; Novartis, Chile; Novartis Sante, Fr.; Novartis Consumer, Hong Kong; Novartis Consumer, Irl.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Norw.; Novartis, Philipp.; Novartis Consumer, Port.; Novartis Consumer, S.Afr.; Novartis OTC, Singapore; Novartis Consumer, Switz.; Novartis Consumer, UK; Westwood-Squibb, USA.*
Crotamiton (p.1593·2).
Insect stings; pediculosis; pruritus; scabies.

Eurax-Hydrocortisone *Novartis Consumer, Irl.; Novartis Consumer, UK.*
⊗ Crotamiton (p.1593·2); hydrocortisone (p.1535·2).
Pruritic skin disorders.

Euraxil *Novartis Consumer, Spain.*
Crotamiton (p.1593·2).
Pediculosis; pruritus; scabies.

Euraxsepti *Novartis Sante, Fr.*
Chlorhexidine gluconate (p.1635·3).
Formerly known as Merfene.
Wound disinfection.

Eurelix *Sanofi-Aventis, Fr.*
⊗ Piretanide (p.1372·3).
Hypertension.

Eurespal *Servier, Pol.; Servier, Rus.*
Fenspiride hydrochloride (p.1122·1).
Otitis media; respiratory-tract disorders.

Euretico *Casasco, Arg.*
⊗ Chlortalidone (p.1243·3).
Diabetes insipidus; heart failure; hypertension; oedema.

Euretin *Eupharmed, Ital.*
Omega-3 fatty acids; astaxanthin; myrtillus; vitamin E (p.1922·1).
Dietary supplement.

Eurifam *Euromex, Mex.*
Rifampicin (p.325·3).
Tuberculosis.

Euritmin *Rhein, Mex.†.*
Verapamil (p.1423·2).

Euritsin *Sanofi Synthelabo, Arg.†.*
Adenosine (p.1202·1).
Supraventricular tachycardia.

Eurivit *Am-Europharma, Philipp.*
Vitamin preparation with or without minerals (p.1922·1).

Eurixor *Richter, Austria; Biosyn, Ger.; Loges, Ger.*
Mistletoe (p.2345·3).
Joint disorders; malignant neoplasms.

Euro A & C *Institute of Immunology, Philipp.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Eurobetsol *Europharm, Hong Kong.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Eurobiol *Mayoly-Spindler, Fr.*
Pancreas (porcine) (p.2337·3).
Pancreatic insufficiency.

Eurocal D3 *Procter & Gamble, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Eurocefix *Uno, Ital.†.*
Cefaclor (p.217·2).
Bacterial infections.

Euro-Cid *Euro-Med, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; peptic ulcer.

Eurocilana *Europharm, Hong Kong.*
Cocillana (p.1554·3); senega (p.1572·3); squill (p.1573·1).
Bronchitis; coughs.

Eurocin *EuroHealth, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Euroclear *Euroderm, Arg.*
Sodium laurilsulfate (p.2138·3).
Skin cleansing preparation.

Euroclovir *Europharm, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Eurocoal *Euroderm, Arg.*
Salicylic acid (p.1612·2); benzalkonium chloride (p.1629·1); coal tar (p.1616·2).
Dandruff; seborrhoea.

Eurocof *Am-Europharma, Philipp.*
Guaifenesin (p.1561·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Euro-Collins *Fresenius Hemocare, Thai.*
Glucose (p.1945·3); electrolytes (p.1667·1).
Preservation of donor kidney in transplantation.

Eurocolor
Note. This name is used for preparations of different composition.
Euroderm, Arg.†.
SPF 4: Benzophenone.
Sunscreen.

Euroderm, Arg.
SPF 15; SPF 34; SPF 45: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); vitamin E.
SPF 15 formerly contained titanium dioxide. SPF 34 and SPF 45 formerly contained titanium dioxide and zinc oxide.
Sunscreen.

Eurocolor Bronceador *Euroderm, Arg.*
Oxybenzone (p.1608·3); vitamin E (p.1992·2); octinoxate (p.1608·2).
Sunscreen.

Eurocolor Post Solar *Euroderm, Arg.*
Aloe vera (p.1588·2); calendula (p.2273·1).
Emollient.

Eurocolor Sin Sol *Euroderm, Arg.*
Dihydroxyacetone (p.1594·1).
Tanning agent.

Eurocor *EuroHealth, Philipp.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Eurocoxin *Am-Europharma, Philipp.*
Isoniazid (p.288·1).

Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Euroderm *Euromex, Mex.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Euroderm-A *Euroderm, Arg.*
Vitamin A; vitamin E; vitamin D; allantoin (p.1588·1).
Moisturiser.

Eurodin *Takeda, Jpn.*
Estazolam (p.995·1).
Insomnia; premedication.

Eurodron *Europharm, Hong Kong.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Bacterial eye infections with inflammation.

Eurofenac *Europharm, Hong Kong.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Eurofer
Note. This name is used for preparations of different composition.
Euroderm, Arg.
Ferrous sulfate (p.1939·3).
Iron supplement.

Eurodrug, Hong Kong; Eurodrug, Philipp.; Eurodrug, Singapore; Eurodrug, Thai.
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron-deficiency anaemia.

Euroflash *Lifescan, Fr.; Lifescan, Ital.; Lifescan, Port.†.*
Test for glucose in blood (p.2314·1).

Euroflex *Saval, Chile.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Euroflox *EuroHealth, Philipp.*
Norfloxacin (p.309·2).
Bacterial infections.

Euroflu *Euro-Pharma, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis; asthma; bronchitis.

Eurogel *Cielle, Ital.*
Royal jelly (p.2382·1); dried yeast (p.1998·3); vitamin E (p.1992·2).
Nutritional supplement.

Eurogesic *Saval, Chile.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Eurohair *Euroderm, Arg.*
Collagen (p.2286·1).
Hair disorders.

Euro-Ion in D5 *Euro-Med, Philipp.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Eurolase *Europharm, Hong Kong.*
Papain (p.2362·3).
Inflammation; oedema.

Eurolat *Euromex, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Eurolol *Euromex, Mex.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Euromicina *Saval, Chile.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Euromucil *Saval, Chile.*
Psyllium (p.1737·1).
Constipation.

Euronal *Euromex, Mex.*
Enalapril (p.1276·1).
Hypertension.

Europain *Europharm, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Europave *Euromex, Mex.*
Verapamil (p.1423·2).
Arrhythmias; hypertension.

Europhenicol *Europharm, Hong Kong.*
Chloramphenicol (p.239·3).
Eye infections.

Europiel *Euroderm, Arg.*
Silicone oil (p.2032·1).
Barrier preparation.

Europrotec P *Euroderm, Arg.†.*
SPF 15: Titanium dioxide (p.1617·3).
Sunscreen.

Europrotec Post Solar *Euroderm, Arg.†.*
Aloe vera (p.1588·2); calendula (p.2273·1).
Emollient.

Europrotec Ultra *Euroderm, Arg.†.*
SPF 34: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Eurosan *Mepha, Switz.†.*
Clotrimazole (p.530·1).
Fungal skin and nail infections.

Eurosef *EuroHealth, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Eurosin *Jean-Marie, Hong Kong.*
Crotamiton (p.1593·2).
Pruritus.

Eurosol *Euro-Med, Philipp.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Eurostan *Am-Europharma, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Eurotapp *Europharm, Hong Kong.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Eurotofi *Euromex, Mex.*
Pentoxifylline (p.1367·2).

Euroton *Cielle, Ital.*
Withania somnifera; maca; muira puama; ginseng; damiana; rhodiola.

Eurotretin *Euroderm, Arg.*
Tretinoin (p.1618·1).
Acne.

Eurovan *Europharm, Hong Kong.*
Zopiclone (p.1039·1).
Insomnia.

Eurovir *Saval, Chile.*
Aciclovir (p.862·3).
Herpesvirus infections.

Eurovit *Teva, Hung.*
A range of vitamin preparations with or without minerals (p.1922·1).

Euroxi *Copernico, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Euroxol *Euromex, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Eurozyme *Europharm, Hong Kong.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; inflammation; upper respiratory-tract disorders.

Eurythmic *Troikaa, India.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Eusaprim *GSK, Austria; GSK, Belg.; GSK, Fr.†; GSK, Ger.; GSK, Ital.; GSK, Neth.†; GSK, Swed.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Eusedon mono *Krewel, Ger.†.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; nausea; nervous disorders; sleep disorders; vomiting.

Euserpina Cellulite *Biogena, Ital.*
Aristolochia (p.2260·1).
Cellulite.

Eusilen *Cofasa, Venez.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Euskin *Sankyo, Spain.*
Erythromycin (p.269·2).
Acne.

Eusovit *Strathmann, Ger.*
d-Alpha tocopherol (p.1992·2) or *d*-alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Euspirax *Asche, Ger.†.*
Choline theophyllinate (p.1119·3).
Obstructive airways disease.

Eustidil *Vitoria, Port.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Eutears *Eupharmed, Ital.*
Omega-6 and omega-3 fatty acids; lactoferrin; vitamins; zinc; astragalus membranaceus (p.1922·1).
Dietary supplement.

Eutebrol *Tecnofarma, Chile; Asofarma, Mex.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease; cerebral trauma; dementia; parkinsonism.

Eutecaina *Andromaco, Chile.*
Lidocaine hydrochloride (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Euthyral *Merck-Lipha, Fr.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Hypothyroidism.

Euthyrox *Merck, Arg.; Merck, Austria; Merck, Belg.; Merck, Braz.; Genpharm, Canad.; Merck, Cz.; Merck, Ger.; Merck, Hung.; Merck, Indon.; Merck, Neth.; Merck, Philipp.; Merck, Pol.; Merck, Rus.; Merck, Singapore; Merck, Swed.; Merck, Switz.; Merck, Thai.; Merck, Venez.*
Levothyroxine sodium (p.2171·2).
Adjuvant in obesity; goitre; hypothyroidism; thyroid cancer.

Eutimil *Valda, Ital.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Eutirox *Merck, Chile; Bracco, Ital.; Merck, Mex.; Merck, Port.; Merck, Spain.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Eutiz *Merck, Arg.†.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Eutocol *Gador, Arg.*
Estradiol hemisuccinate (p.2098·3).
Labour induction.

Eutonis *Eurofarma, Braz.*
Cloxazolam (p.981·1).
Anxiety.

Eutopic *Farmacologico Milanese, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Eutrim *Euromex, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Eutrodin *GD, Ital.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Barrier cream.

Eutrofic *Dermoteca, Port.†.*
A range of moisturisers.

Eutroid *Elea, Arg.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Hypothyroidism.

Eutropin *Cristalia, Braz.; Novell, Indon.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Eutroxsig *Fawns & McAllan, Austral.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Euvaderm *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Euvasten *Primera, Philipp.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Euvax B *Sanofi Pasteur, Indon.; Sanofi Pasteur, Malaysia; LG, Pol.; LG Chem, Thai.; Berk, Turk.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Separate preparations are available for adults and for children.
Active immunisation.

Euvaxon *Teva Tuteur, Arg.*
Etoposide (p.718·1).
Malignant neoplasms.

Euvegal *Schwabe, Ger.*
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia; nervous disorders.

Euvegal Balance *Schwabe, Ger.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Euvegal Entspannungs- und Einschlafdragees *Schwabe, Ger.†.*
Valerian (p.2410·1); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Euvegal Entspannungs- und Einschlaftropfen *Schwabe, Ger.*
Valerian (p.2410·1); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Euvekan *Austroplant, Austria; Schwabe, Cz.; Schwabe, Hung.; Stetifarm, Venez.*
Valerian (p.2410·1); melissa (p.2339·3).
Anxiety; nervous disorders; sleep disorders.

Euvifor *Vedim, Port.†.*
Piracetam (p.368·2); codergocrine mesilate (p.363·3).
Cerebrovascular disorders; mental function disorders; vestibular disorders.

Eu-Visus *Cielle, Ital.*
Myrtillus; yeast; carrot; wheat-germ oil; soya phospholipid (p.1922·1).
Dietary supplement.

Euvitol *Bracco, Ital.*
Vitamin A palmitate (p.1973·1).
Skin disorders.

Euxat *PHT, Ital.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Euzymina Lisina I *Menarini, Spain.*
Lysine hydrochloride (p.1955·1); nicotinic acid (p.1957·3); pepsin (p.2365·1); bitter orange (p.2357·1); lactic acid (p.2329·3).
Digestive enzyme deficiency.

Euzymina Lisina II *Menarini, Spain.*
Lysine hydrochloride (p.1955·1); nicotinic acid (p.1957·3); pepsin (p.2365·1); bitter orange (p.2357·1).
Digestive disorders.

Eva Povi *Unipharma, Gr.†.*
Povidone-iodine (p.1659·2).
Antisepsis.

Evac-Q-Mag *Savage, USA.*
Magnesium citrate (p.1743·2).

Evac-Q-Tabs *Savage, USA.*
Bisacodyl (p.1710·1).
Formerly contained phenolphthalein.

Evacream *Gambar, Ital.*
Sodium carboxymethyl betaglucan.
Stretch marks.

Evacrine *Motima, Fr.*
Wild cherry (p.1472·2); ginger (p.1732·3); viola tricolor (p.2415·2).
Gastrointestinal disorders.

Evacuante *Bohm, Spain; Lainco, Spain.*
Macrogol (p.2336·1); electrolytes (p.1667·1).
Bowel evacuation.

Evac-U-Gen *Lee, USA.*
Sennosides (p.1769·3).
Constipation.

Evacuol *Almirall, Spain.*
Sodium picosulfate (p.1771·1).
Constipation.

Evadol
Note. This name is used for preparations of different composition.
Andromaco, Chile.
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm.

Degorts, Mex.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Evafer *Gambar, Ital.*
Iron (p.1949·1); folic acid (p.1940·1).
Anaemia during pregnancy.

Evafilm *Laphal, Fr.†.*
Estradiol (p.2097·2).
Menopausal disorders.

Evagelin *Help, Gr.*
Bromazepam (p.964·3).
Anxiety disorders.

Evagrip *Temis, Arg.†; Kite (Κιτε), Gr.; UCB, Spain.*
An influenza vaccine (p.2218·2).
Active immunisation.

Evalen *Ferron, Indon.*
Adapalene (p.1587·1).
Acne.

Evalgan *Smith & Nephew, Austria.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Skin disorders.

Evalin *Queisser, Ger.†.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Evalon *Organon, India.*
Estriol (p.2101·1).
Adjunct in vaginal operations; menopausal disorders; vulvovaginal disorders.

Evamilk *Gambar, Ital.*
Fennel (p.2302·3); myrtillus (p.2349·3); wild carrot (p.2415·2).
Lactation stimulation.

Evamist *Ther-Rx, USA.*
Estradiol (p.2097·2).
Menopausal disorders.

Evana *Bionorica, Cz.†.*
Agnus castus (p.2249·1).
Menstrual disorders.

Evangio *Rafarm, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Evanol *GSK, Arg.*
Pregnancy test (p.2372·1).

Evanor *Wyeth, Braz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Evanor-D *Wyeth Lederle, Ital.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Evapause *Zambon, Fr.†.*
Progesterone (p.2125·1).
Female infertility; menopausal disorders; menstrual disorders; threatened or habitual miscarriage.

Evaplan *Elea, Arg.*
Fertility test (p.2372·1).

Evarose *Bailly, Fr.*
Arnica (p.2260·2); hamamelis (p.2318·2); melilot (p.2339·2); aesculus (p.2248·2); butcher's broom (p.2270·3).
Skin redness.

Evasen Crema *Gambar, Ital.*
Vitamin E (p.1992·2).
Cracked nipples.

Evasen Dischetti *Gambar, Ital.*
Potassium sorbate (p.1662·2); glycerol (p.2314·2).
Cracked nipples.

Evasen Liquido *Gambar, Ital.*
Potassium sorbate (p.1662·2); glycerol (p.2314·2).
Nipple care during lactation.

Evastel *Almirall, Mex.*
Ebastine (p.579·1).
Allergic rhinitis; allergic skin disorders.

Evastel-D *Almirall, Mex.*
Ebastine (p.579·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; cold symptoms.

Evatest *Elea, Arg.*
Pregnancy test (p.2372·1).

Evaton-B12 *Demo, Gr.*
Vitamin B substances (p.1922·1).

Evaton-D *Demo, Gr.*
Vitamin preparation (p.1922·1).

Evaton-T *Demo, Gr.*
A multivitamin preparation (p.1922·1).

Evavit *Gambar, Ital.*
Multivitamin preparation containing folic acid (p.1922·1).
Nutritional supplement during pregnancy.

Evazol *Petrasch, Austria; Ravensberg, Ger.*
Dequalinium chloride (p.1641·3).
Infected wounds; skin infections.

EVC *Sisu, Canad.*
Vitamin and mineral preparation (p.1922·1).

Eve *Grunenthal, Ger.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Combined oral contraceptive.

Eve 500 *Biofarma, Venez.*
Evening primrose oil (p.2302·1).
Eczema; hypercholesterolaemia; premenstrual syndrome.

Evelea *Elea, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Evening Gold *Larkhall Laboratories, UK.*
Evening primrose oil (p.2302·1).

Eventin *Svizera, India.*
⊗ Menotrophin (p.2109·3).
In-vitro fertilisation.

Evepar *Merck Generiques, Fr.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne in women.

Eveprim *Metro, Philipp.*
Evening primrose oil (p.2302·1).
Cervical ripening; menopausal disorders; premenstrual disorders.

Ever Ce *Konimex, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Ever E *Konimex, Indon.*
Vitamin E; selenium; vitamin B (p.1922·1).
Premature skin ageing.

Ever Ost *Konimex, Indon.*
Calcium; magnesium; vitamin D; zinc (p.1922·1).
Nutritional supplement.

Evercid *Boniscontro & Gazzone, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Evercil *Ivax, Cz.†.*
Phenylephrine hydrochloride (p.1568·1); esculoside (p.2248·2).
Allergic and inflammatory eye disorders.

Everfem *Omega, Arg.*
⊗ Pamabrom (p.1365·3); paracetamol (p.108·1); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Ever-Fit Cardio *Prisfar, Port.*
Multivitamin and mineral preparation (p.1922·1).

Ever-Fit Plus *Prisfar, Port.*
Vitamin and mineral preparation (p.1922·1).

Everiden *Zentiva, Cz.; SL-Farma, Hung.†.*
Sodium valproate (p.508·2).
Epilepsy; mania; migraine.

Evertine *Farmoz, Port.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Everyday Face Sunscreen *Hamilton, Austral.*
SPF 30+: Octocrilene (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Evestrel *Theramex, Ital.*
Phytoestrogens (genistein, daidzein) (p.2391·2) (p.2391·2).
Menopausal disorders.

Eviantrina *Korhispana, Spain.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Evicap *Kocak, Turk.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Evicer *Sanofi Synthelabo, Port.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

E-Vicotrat *Heyl, Ger.; IFET (ΙΦΕΤ), Gr.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Evicyl *Sanofi Synthelabo, Arg.†.*
Inositol nicotinate (p.1316·1).
Hyperlipidaemias; peripheral vascular disorders.

E-vidon *Abigo, Swed.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Evigen *Aksu, Turk.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Evilin *Merck, Chile.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, and hirsutism in women.

Eviline *Kotra, Malaysia.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastritis; heartburn; oesophagitis; peptic ulcer.

Evimal *Andromaco, Chile.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

E-vimin *AstraZeneca, Swed.*
dl-Alpha-tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Evina
Note. This name is used for preparations of different composition.
Klonal, Arg.
Ergometrine (p.2009·3).
Rodisma, Ger.
d-Alpha tocopherol with ascorbic acid (p.1922·1).
Vitamin E and C deficiency.

Evinopon *Bros, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain; prevention of miosis in ophthalmic surgery.

Eviol *Gap, Gr.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Eviol-A *Gap, Gr.*
dl-Alpha tocoferil acetate (p.1992·3); vitamin A acetate (p.1973·1).
Vitamin A and E deficiency.

Evion
Merck, Arg.; Merck, Ger.; Merck, Indon.; Bracco, Ital.; Merck, Philipp.
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency; vitamin E supplement.
Merck, India.
Vitamin E (p.1992·2).
Abetalipoproteinaemia; fibrocystic breast disease; vitamin E deficiency.

Evipon *Armoxindo, Indon.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Evipress *Senosiain, Mex.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Eviprostat
Note. This name is used for preparations of different composition.
Eversil, Braz.†.
Manganese amino acid chelate (p.1956·3); populus tremula (p.2371·1); pulsatilla (p.2376·3); salicylic acid (p.1612·2); kaolin (p.1738·1).
Prostatic disorders.
Evers, Indon.; Pharos, Indon.
Chimaphila umbellata; equisetum (p.2299·3); manganese chloride (p.1956·1); populus tremula (p.2371·1); pulsatilla (p.2376·3); sodium taurocholate (p.2266·3); wheat-germ oil (p.2415·1).
Benign prostatic hyperplasia.
Shinyaku, Jpn.
Wheat-germ oil (p.2415·1); chimaphila umbellata; populus tremula (p.2371·1); pulsatilla (p.2376·3); equisetum (p.2299·3).
Benign prostatic hyperplasia.
Shinyaku, Singapore.
Wheat-germ oil (p.2415·1); chimaphila umbellata; populus tremula (p.2371·1); pulsatilla (p.2376·3); equisetum (p.2299·3); choleinic sodium; manganese chloride (p.1956·1).
Benign prostatic hyperplasia.

Eviprostat N *Evers, Ger.*
Chimaphila umbellata; populus tremula (p.2371·1); pulsatilla (p.2376·3); equisetum (p.2299·3).
Prostatic hyperplasia.

Eviprostat-S *Evers, Ger.*
Saw palmetto (p.2192·3).
Micturition disorders associated with benign prostatic hyperplasia.

Evisco Mistel Urtinktur *Evisco, Ger.*
Homoeopathic preparation.

Evisco Misteltropfen N *Evisco, Ger.*
Homoeopathic preparation.

Evista *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Chugai, Jpn; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
⊗ Raloxifene hydrochloride (p.2128·1).
Breast cancer; osteoporosis.

Evit *Scherer, Cz.†; Vita Health, Switz.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Evitam *Cipla, India.*
Vitamin E (p.1992·2).

Evitam Natural Plus *Cipla, India.*
Vitamin E; vitamin C (p.1922·1).

Evitex
Note. This name is used for preparations of different composition.
Manon, Israel.
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.
Alcon, Ital.
Vitamin A (p.1971·2); tocoferil nicotinate (p.1415·1).
Vitamin A and E deficiency.

Evitex A E Fuerte *Alcon Cusi, Spain.*
Vitamin A palmitate (p.1973·1); tocoferil nicotinate (p.1415·1).
Deficiency of vitamins A and E; eye disorders; infertility; recurrent miscarriage; skin disorders.

Evithrom *Johnson & Johnson, USA.*
Thrombin (p.1080·1).
Haemorrhage.

Evitocor *Apogepha, Ger.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; cardiovascular disorders; hypertension.

Evitol *Lannacher, Austria; Teva, Israel; KRKA, Rus.*
Alpha tocoferil acetate (p.1992·3).
Haemolytic anaemia; retrolenticular fibroplasia in premature neonates; vitamin E deficiency; vitamin E supplement.

E-Vitum *Merck, Ital.*
d-Alpha tocoferil acetate (p.1992·3).
Haemolytic anaemia; intermittent claudication; vitamin E deficiency.

Evocanil *Zodiac, Braz.*
Progesterone (p.2125·1).

Evocarb *Sinterapico, Braz.†.*
Carboplatin (p.693·1).
Malignant neoplasms.

Evoclin *Connetics, USA.*
Clindamycin (p.251·1).
Acne.

Evo-Conti *Janssen-Cilag, Denm.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Evolis *Solvay, Fr.†.*
Betahistine hydrochloride (p.2265·1).
Vestibular disorders.

Evolith DS *Evaux, Fr.*
Piroctone olamine (p.1610·1).
Seborrhoea.

Evoltra *Bioenvision, Cz.; Novex, Fr.; Bioenvision, Port.; Bioenvision, UK.*
Clofarabine (p.701·3).
Acute lymphoblastic leukaemia.

Evon *Bilim, Turk.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Evopad *Janssen-Cilag, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Evoposdo *Sinterapico, Braz.†.*
Etoposide (p.718·1).
Malignant neoplasms.

Evoprim *Bioceuticals, UK.*
Evening primrose oil (p.2302·1).

Evoquin *Ivax, Arg.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; rheumatoid arthritis.

Evorel *Janssen-Cilag, Arg.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Ger.†; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Norw.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, UK.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Evorel Conti *Janssen-Cilag, Arg.; Janssen-Cilag, Fin.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Hormone replacement therapy; menopausal disorders; osteoporosis.

Evorel Micronor *Janssen-Cilag, Swed.*
Patches, estradiol (p.2097·2); tablets, norethisterone (p.2119·3).
Oestrogen deficiency; osteoporosis.

Evorel Pak *Janssen-Cilag, UK†.*
Transdermal patches, estradiol (p.2097·2); tablets, norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

Evorel Sequi *Janssen-Cilag, Arg.; Janssen-Cilag, Fin.; Janssen-Cilag, Israel; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK.*
4 Patches, estradiol (p.2097·2) (Evorel); 4 patches, estradiol; norethisterone acetate (p.2119·3) (Evorel Conti).
Hormone replacement therapy; menopausal disorders; osteoporosis.

Evosebor Li-Zn *Evaux, Fr.*
Zinc gluconate (p.1999·2); chamomile (p.2279·3).
Seborrhoea.

Evo-Sequi *Janssen-Cilag, Denm.*
Patch I, estradiol (p.2097·2); patch II, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Evothyl *Guardian, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Evotrox *Kappin, UK.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; non-toxic goitre; thyroid cancer.

Evoxac *Daiichi, USA.*
Cevimeline hydrochloride (p.2279·2).
Dry mouth associated with Sjögren's syndrome.

Evoxali *Sinterapico, Braz.†.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Evra *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Norelgestromin (p.2119·2); ethinylestradiol (p.2101·3).
Combined transdermal contraceptive.

Ewadyl *Masa, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; hypersensitivity reactions.

Ewofex *Ewopharma, Cz.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis.

Exabet *Fahrenheit, Indon.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Exabetin *Fahrenheit, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Exabrol *Pharmacos, Mex.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Exacol *Pharmacos, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Exacor *Pfizer, Fr.*
Cibenzoline succinate (p.1244·2).
Arrhythmias.

ExacTech *Medisense, Austral.†; Medisense, UK.*
Test for glucose in blood (p.2314·1).

Exacyl *Eumedica, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhagic; haemorrhagic disorders.

Exafenil *Grin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Exafil *Degorts, Mex.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; bronchitis; emphysema.

Exaflam *Guardian, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Exail *Sigma, Arg.*
Garlic (p.2309·2); vitamin P (p.2304·1).
Hypertension; venous disorders.

Exaler *Pharmacos, Mex.†.*
Sodium cromoglicate (p.1136·3).
Inflammatory eye disorders.

Exalgin *Sons, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Exaliver *Pharmacos, Mex.†.*
Aciclovir (p.862·3).
Herpesvirus infections of the eye.

Exalver *Maver, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough; upper respiratory-tract congestion.

Examel *Alet, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Examida *Pharmacos, Mex.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Examolin *Pharmacos, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Examsa *Antibioticos, Mex.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Examycin *Pharmacos, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Exangina *Apotheke Roten Krebs, Austria.*
Homoeopathic preparation.

Exangina N *Muller Goppingen, Ger.*
Homoeopathic preparation.

Exanta
AstraZeneca, Arg.†; AstraZeneca, Austria†.
Melagatran (p.1332·2) or ximelagatran (p.1332·2).
Thromboembolism prophylaxis following orthopaedic surgery.
AstraZeneca, Denm.†; AstraZeneca, Fin.†; AstraZeneca, Fr.†; AstraZeneca, Ger.†; AstraZeneca, Neth.†; AstraZeneca, Norw.†.
Ximelagatran (p.1332·2).
Thromboembolism prophylaxis following orthopaedic surgery.

Exarex *MZ, S.Afr.†.*
Coal tar (p.1616·2).
Eczema.

Exarta *AstraZeneca, Swed.†.*
Ximelagatran (p.1332·2).
Thromboembolism prophylaxis following knee or hip replacement.

Exastrin *Pharmacos, Mex.*
Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Exaverm *Pharmacos, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

Exavir *UCI, Braz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Exavit *Pharmacos, Mex.*
Vitamin and mineral preparation (p.1922·1).

Exazen *Vocate, Gr.*
Azelaic acid (p.1589·3).
Acne.

Exbenzol *Sons, Mex.*
Mebendazole (p.148·3).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Exbequil *Liferpal, Mex.*
Dextromethorphan (p.1555·2); chlorphenamine (p.572·2); ammonium chloride (p.1551·3).
Respiratory-tract disorders.

Excedrin
Note. This name is used for preparations of different composition.
BMS, Braz.; Novartis, Braz.; BMS, Canad.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Novartis, USA.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Excedrin Back & Body Extra Strength *Novartis Consumer, USA.*
Paracetamol (p.108·1); buffered aspirin (p.20·3).
Pain.

Excedrin Migraine *Novartis, USA.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Migraine.

Excedrin PM *Novartis, USA.*
Paracetamol (p.108·1); diphenhydramine citrate (p.577·2) or diphenhydramine hydrochloride (p.577·2).
Pain associated with sleeplessness.

Excedrin QuickTabs *BMS, USA†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Excedrin Sinus Headache Aspirin Free *Novartis, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Excedrin Tension Headache *Novartis, USA.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Headache.

Excegran *Dainippon, Jpn.*
Zonisamide (p.515·2).
Epilepsy.

Excelase-E *Meiji, Indon.*
Amylase (p.2256·3); sanactase; protease; lipase; meicelase; pancreatin (p.2360·1).
Pancreatic enzyme deficiency.

Excelcur MF1 *Maeil, Hong Kong.*
Preparation for enteral nutrition (p.1922·1).
Gastro-enteritis.

Excelgrow *Maeil, Hong Kong.*
Preparation for enteral nutrition (p.1922·1).

Excelkid *Maeil, Hong Kong.*
Preparation for enteral nutrition (p.1922·1).

Excelox *Sydenham, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Excelsior
Note. This name is used for preparations of different composition.
Grisi, Mex.†.
Ointment: Salicylic acid (p.1612·2).
Warts.

Grisi, Mex.†.
Topical solution: Tolnaftate (p.548·3).
Fungal skin infections.

Excess *Neo-Farmaceutica, Port.†.*
Ispaghula (p.1737·1); glucomannan (p.2312·3).
Obesity.

Excillin *Sandoz, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Exciol *Sandoz, Austria.*
Cefixime (p.224·3).
Bacterial infections.

Excipial
Note. This name is used for preparations of different composition.
Spirig, Cz.; Spirig, Singapore; Spirig, Switz.
Emollient.
Skin disorders.

Karrer, Ger.
Almond oil (p.2252·2); liquid paraffin (p.2030·3).
Bath additive; emollient.

Orva, Turk.
⊗ Urea (p.1620·2).
Dry skin disorders.

Excipial U *Spirig, Cz.; Spirig, Singapore; Spirig, Switz.*
⊗ Urea (p.1620·2).
Skin disorders.

Excivit *Gallia, Braz.†.*
Multivitamin and mineral preparation (p.1922·1).

Exclefin *Biomep, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Excosine-S *Sons, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Excough *Fortune, Hong Kong†.*
Guaifenesin (p.1561·3).
Coughs.

Exdol *Pendopharm, Canad.*
Paracetamol (p.108·1); caffeine citrate (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

Exe-Cort *Pinewood, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Executive B *Cenovis, Austral.; Vitelle, Austral.*
Vitamins and minerals (p.1922·1); valerian (p.2410·1); passion flower (p.2363·2).
Stress; vitamin and mineral deficiencies.

Executive B Stress Formula *Blackmores, Austral.*
Vitamins; minerals; passion flower; avena (p.1922·1).
Nutritional supplement; stress.

Exedexe *Julphar, UAE.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

ExeFen-PD *Larken, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Exel *Senosiain, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Exelderm *Bioglan, Irl.†; Abdi, Turk.; Centrapharm, UK; Westwood-Squibb, USA.*
Sulconazole nitrate (p.546·2).
Fungal skin infections.

Exelmin *UCI, Braz.†.*
Cambendazole (p.142·2); mebendazole (p.148·3).
Worm infections.

Exelon *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Rivastigmine hydrogen tartrate (p.369·2).
Alzheimer's disease; dementia in parkinsonism.

Exempla *Fada, Arg.*
Ceftriaxone (p.238·1).
Bacterial infections.

Exen *Sanovel, Turk.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Exepime *Ferron, Indon.*
Cefepime (p.224·1).
Bacterial infections.

Exergin *Guardian, Indon.*
Codergocrine mesilate (p.363·3).
Mental function impairment.

Exermet *Cipla, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Exermet GM *Cipla, India.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Exermet GZ *Cipla, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Exermet P *Cipla, India.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Exertial *Baliarda, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Exetin-A *Pisa, Mex.*
⊗ Epoetin (p.1061·1).
Anaemias.

Exeton *Andromaco, Venez.†.*
Oxolamine phosphate (p.1567·1).
Cough.

Exeu *Hexal, Ger.*
Eucalyptus oil (p.2301·2).
Cold symptoms.

Exflam *Mepro, Chile.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Exflem *Stada, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Exfoliac
Note. This name is used for preparations of different composition.
Merck Medication Familiale, Fr.; Merck, Malaysia.
A range of skin-care preparations.
Acne; seborrhoea.

Merck, Indon.
Cream: Glycolic acid (p.1598·1).
Acne.

Merck, Indon.
Facial scrub: Glycolic acid (p.1598·1); ammonium lactate (p.1589·2); lactic acid (p.2329·3).
Acne.

Merck, Indon.
Foaming gel; tinted cream: Alpha hydroxy acids.
Acne.

Exfoliac Sunblock *Merck, Malaysia.*
SPF 25: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); alpha hydroxy acids.
Sunscreen for oily skin.

Exfoliderm *Albephar, Venez.*
Polyethylene (p.1585·3); triclosan (p.1665·2); imidazolidinyl urea.

Exfolium *Wyeth, Arg.†.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Exforge *Novartis, Cz.; Novartis, Gr.; Novartis, UK; Novartis, USA.*
Amlodipine besilate (p.1214·1); valsartan (p.1420·2).
Hypertension.

Exhantil *Sons, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Dyspepsia; gastritis; peptic ulcer.

Exhidrol *Sons, Mex.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastrointestinal motility disorders.

Exhirud *Sanofi Synthelabo, Austria; Lichtenstein, Ger.†.*
Leech extract (p.1305·3).
Frostbite; haematoma; inflammation; insect bites; scar pain; soft-tissue disorders; superficial phlebitis; superficial thrombosis; superficial vascular disorders.

Exhirud Heparin *Winthrop, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Ex-Histine *WE, USA.*
Phenylephrine (p.1568·1); chlorphenamine (p.572·2); hyoscine (p.1733·3).
Upper respiratory-tract disorders.

Exiadol *Continentales, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Exibral *Bago, Arg.*
Valproic acid (p.508·2) or magnesium valproate (p.511·3).
Bipolar disorder; epilepsy; migraine.

Exidine *Baxter, USA.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Exido *Prater, Chile.*
Lidocaine hydrochloride (p.1862·3).
Erectile dysfunction.

Exidol *Galephar, Fr.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Exifine
Reddy's, India; Reddy, Malaysia; Reddy, Rus.
Terbinafine hydrochloride (p.546·3).
Fungal infections; fungal skin and nail infections.

Biofarma, Venez.†.
Terbinafine (p.546·3).
Fungal skin and nail infections.

Exil *Esoform, Ital.*
Cetylpyridinium chloride (p.1635·1).
Genital hygiene.

Eximius *Duncan, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Exinol *Sankyo, Venez.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Exipan *Agis, Israel.*
Piroxicam (p.117·3).
Inflammation; pain.

Exiplon *Khandelwal, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Exirel *Altana, Austria†.*
⊗ Pirbuterol acetate (p.1130·1).
Obstructive airways disease.

Exit
Note. This name is used for preparations of different composition.
Farmasa, Braz.
Cinnarizine (p.573·1); piracetam (p.368·2).
Cerebral and peripheral vascular disorders; impaired mental function.

Stadmed, India.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Exitop *Baxter, Fin.†; Baxter, Ger.; Baxter, Swed.†.*
Etoposide (p.718·1).
Malignant neoplasms.

Exjade *Novartis, Arg.; Novartis, Austral.; Novartis, Chile; Novartis, Cz.; Novartis, Fr.; Novartis, Gr.; Novartis, Hung.; Novartis, Indon.; Novartis, Malaysia; Novartis, NZ; Novartis, UK; Novartis, USA.*
Deferasirox (p.1438·3).
Iron overload.

Ex-Lax
Note. This name is used for preparations of different composition.
Novartis Consumer, Canad.; Novartis Consumer, Israel.
Sennosides (p.1769·3).
Constipation.

Novartis Consumer, UK; Novartis Consumer, USA.
Senna (p.1769·2).
Constipation.

Ex-Lax Gentle Strength *Novartis, USA.*
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Constipation.

Ex-Lax Stool Softener *Novartis Consumer, Canad.†; Novartis Consumer, USA.*
Docusate sodium (p.1725·1).
Constipation.

Ex-Lax Ultra *Novartis Consumer, USA.*
Bisacodyl (p.1710·1).
Constipation.

Exlutena *Organon, Swed.*
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Exluton *Organon, Arg.; Organon, Braz.; Organon, Chile; Organon, Cz.†; Organon, Fin.†; Organon, Indon.; Organon, Mex.; Organon, Neth.; Organon, Philipp.; Organon, Port.†; Organon, Rus.; Organon, S.Afr.†; Organon, Thai.; Organon, Venez.*
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Exlutona *Organon, Norw.†.*
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Exmykehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Exna *Robins, USA†.*
⊗ Benzthiazide (p.1225·1).
Hypertension; oedema.

Exocaine *Commerce, USA†; Del, USA†.*
Methyl salicylate (p.85·3).
Muscle and joint pain.

Exocin *Allergan, Denm.; Allergan, Fin.; Alvia (Αλβια), Gr.; Allergan, Irl.; Allergan, Ital.; Allergan, Port.; Allergan, S.Afr.; Allergan, Spain; Abdi, Turk.; Allergan, UK.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Exocine *Allergan, Fr.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Exodalina *Sons, Mex.*
Metamizole magnesium (p.49·3).
Fever; pain.

Exoderil *Sandoz, Austria; Sandoz, Cz.; Rentschler, Ger.; Biochemie, Hong Kong; Sandoz, Hung.; Sandoz, Indon.; Merck, Israel; Sandoz, Malaysia; Sandoz, Pol.; Sandoz, Rus.; Biochemie, Singapore†; Eczacibasi, Turk.*
Naftifine hydrochloride (p.542·3).
Fungal and bacterial skin and nail infections.

Exodren *Arkochim, Spain.*
Black currant (p.2267·1); tea (p.2416·1).
Fluid retention.

Exofat *Roehr, Philipp.*
Liphosan; oligofructose; calcium carbonate; magnesium stearate; ascorbic acid (p.1922·1).
Obesity.

Exo'Fat *Sidus, Arg.†.*
Poliglusam (p.2370·1); oligofructose; calcium carbonate (p.1922·1).
Obesity.

Exofil *Loeffler, Mex.*
Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2).
Coughs.

Exofur *Sons, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Exogran *Sandoz, Austria; Sandoz, Neth.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Exolit *Medochemie, Hong Kong; Medochemie, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Exolpen *Integrated Pharmaceutical, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Exolyt *Nevada, Swed.*
Chlorcyclizine hydrochloride (p.571·2); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Coughs.

Exomega *Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.*
Avena (p.2262·1); omega-6 fatty acids (p.2308·2).
Skin disorders.

Exomuc *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Bouchara, Rus.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Exoquin *Sons, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis; infectious diarrhoea.

Exorex *Trans Dermal, Austral.†; Cybermed, Austria; Lavipharm, Gr.; Forest, Irl.; Fagron, Neth.; Forest Laboratories, UK.*
Coal tar (p.1616·2).
Psoriasis.

Exorol *Offenbach, Mex.*
Ketorolac (p.75·2).
Inflammation; pain.

Exortin *Sons, Mex.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Fever; nasal congestion; pain.

Exorvit *Sons, Mex.*
Cyanocobalamin (p.1980·2).
Anaemias; neuritis.

Exorvit VM *Sons, Mex.*
Vitamin and mineral preparation (p.1922·1).

Exoseptoplix *Tonipharm, Fr.†.*
Chlorhexidine gluconate (p.1635·3).
Superficial wounds.

Exostrept *Biomedica-Chemica, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Exosurf *GSK, Arg.†; GSK, Austral.; GSK, Austria; GSK, Braz.†; GSK, Canad.†; GSK, Chile†; GSK, Cz.†; Glaxo Wellcome, Gr.†; GSK, Hong Kong†; Wellcome, Irl.†; Wellcome, Israel†; GSK, Ital.†; GSK, Mex.; GSK, Neth.†; GSK, USA†.*
Colfosceril palmitate (p.2376·1).
Neonatal respiratory distress syndrome.

Exotoux *Bouchara-Recordati, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Exova *Montebello, Fr.†.*
Sorbitol (p.1965·1); xylitol (p.1998·2).
Halitosis.

Exovir *Pharmacia, Arg.†.*
Zidovudine (p.913·3).
HIV infection.

Exovon *Bernofarm, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Expafusin *Fresenius Kabi, Austria; Baxter, Ger.; Kalbe, Indon.*
⊗ An etherified starch (p.1065·1) with electrolytes.
Plasma volume expansion; vascular disorders.

Expahes *Fresenius Kabi, Austria; Fresenius Kabi, Switz.†; Eczacibasi-Baxter, Turk.*
⊗ Hetastarch (p.1065·1) with or without sodium chloride.
Haemodilution; plasma volume expansion.

Expal
Note. This name is used for preparations of different composition.
Bago, Arg.
⊗ Spironolactone (p.1400·1).
Hepatic cirrhosis with ascites; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Sons, Mex.
Pipenzolate bromide (p.1762·2).
Gastrointestinal disorders.

Expal Compuesto *Sons, Mex.*
Pipenzolate bromide (p.1762·2); dimeticone (p.1770·2).
Gastrointestinal disorders.

Expanden *Andromaco, Chile.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); bornyl acetate (p.2269·1); eucalyptus oil (p.2301·2).
Nasal congestion.

Expandox *Expanpharm, Fr.*
Paracetamol (p.108·1).
Formerly known as Expandol.
Fever; pain.

Expanfen *Expanpharm, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Expec *Legrand, Braz.*
Oxomemazine hydrochloride (p.587·1); potassium iodide (p.2169·2); sodium benzoate (p.1630·2); guaifenesin (p.1561·3); ipecacuanha (p.1562·3).
Respiratory-tract congestion.

Expecdilat *Sigma, Braz.*
Ambroxol acefyllinate (p.1114·2).

Expecmin *Parggon, Mex.*
Oxolamine (p.1567·1).
Coughs.

Expectal N *Biocur, Ger.†.*
Thyme (p.2401·1).
Catarrh; coughs.

Expectal-Balsam *Kolassa, Austria.*
Pumilio pine oil (p.2376·3); camphor (p.2273·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); thyme oil (p.2401·2); benzyl nicotinate (p.28·1).
Respiratory-tract disorders.

Expectalin *Pfizer Consumer, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Expectalin with Codeine *Pfizer Consumer, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); codeine phosphate (p.37·2).
Coughs.

Expectal-Tropfen *Kolassa, Austria.*
Codeine (p.37·2); thyme extract (p.2401·1); orange extract (p.2357·2); anise oil (p.2258·2).
Respiratory-tract disorders.

Expectamin *Legrand, Braz.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2); guaifenesin (p.1561·3).
Respiratory-tract disorders.

Expectamin F *Legrand, Braz.*
Dexchlorpheniramine maleate (p.572·1).

Expectein *Farmedia, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Expectil *Bunker, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3).
Respiratory-tract congestion.

Expectobron *Hebron, Braz.†.*
⊗ Guaifenesin (p.1561·3); sodium benzoate (p.1630·2); potassium iodide (p.2169·2); lobelia (p.2157·2).
Coughs.

Expectocilin *EMS, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

Expectol *Teuto, Braz.†.*
⊗ Lobelia (p.2157·2); erysimum; stramonium (p.2392·3).
Coughs.

Expectomel *Cazi, Braz.*
Rorippa nasturtium aquaticum; aconite (p.2246·1); ipecacuanha (p.1562·3); senega (p.1572·3); tolu balsam (p.1574·2); honey (p.1948·2); guaco.
Respiratory-tract congestion.

Expectoral *Hebron, Braz.†.*
Bromelains (p.2269·1); invertase; glucose oxidase (p.2313·3); ribonuclease (p.2378·3).
Coughs.

Expectoran *Grossmann, Switz.†.*
Thyme (p.2401·1); senega (p.1572·3); quillaia (p.1920·1).
Coughs.

Expectoran Codein *Grossmann, Switz.†.*
Codeine phosphate (p.37·2); thyme (p.2401·1); senega (p.1572·3); quillaia (p.1920·1).
Adjuvant in bronchitis; coughs.

Expectorant *Trillium, Canad.*
Guaifenesin (p.1561·3).
Coughs.

Expectorant Cough Formula *Tanta, Canad.*
Guaifenesin (p.1561·3).

Expectorant Cough Syrup *DC Labs, Canad.†; Technilab, Canad.†; AAH, UK.*
Guaifenesin (p.1561·3).
Coughs.

Expectorant and Decongestant Cough Syrup *AAH, UK.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Expectorant Syrup *Rougier, Canad.*
Guaifenesin (p.1561·3).

Expectosan Extra Forte *Excelentia, Arg.*
Bromhexine (p.1552·2).
Cough.

Expectosan Hierbas y Miel
Note. This name is used for preparations of different composition.
Excelentia, Arg.
Adult syrup: Grindelia (p.2317·2); greater burnet saxifrage (p.2270·3); cowslip (p.2372·2); rosa gallica (p.1472·3); thyme (p.2401·1).
Coughs.

Excelentia, Arg.
Paediatric syrup: Ivy (p.2328·1); honey (p.1948·2); vitamin C (p.1983·3); sodium benzoate (p.1630·2).
Cough.

Expectotussin C *Adcock Ingram, S.Afr.†.*
Mepyramine maleate (p.585·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Coughs.

Expectovac *Nikkho, Braz.†.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1); aminocaproic acid (p.1053·2); bacterial antigens.
Bacterial infections.

Expectuss *EMS, Braz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Expectussin *Dinafarma, Braz.†.*
Noscapine (p.1566·2); mepyramine maleate (p.585·2).
Coughs.

Expectysat N *Ysatfabrik, Ger.*
Primula root (p.2372·2); thyme (p.2401·1).
Cold symptoms.

Expeflen *Diba, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Expel *Medichem, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Expelinct *Adcock Ingram, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Expergesic *Win-Medicare, India.*
⊗ Paracetamol (p.108·1); pentazocine hydrochloride (p.112·2).
Pain.

Experience *Awareness, Canad.*
Senna (p.1769·2).
Constipation.

Expicin *Sons, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Expigen *ACO Hud, Fin.; Adcock Ingram, S.Afr.*
Polysorbate 20 (p.1919·1); ammonium chloride (p.1551·3).
Coughs.

Expigment *Orva, Turk.*
Hydroquinone (p.1598·2).
Hyperpigmentation disorders.

Expirobacter *Maffioli, Ital.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for gastroduodenal Helicobacter pylori infection.

Expit
Note. This name is used for preparations of different composition.
Lazar, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Ritsert, Ger.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Explaner *Casasco, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders; subarachnoid haemorrhage; vestibular disorders.

Expogin *LBS, Thai.*
Methylergometrine maleate (p.2011·1).
Management of second and third stage of labour; postpartum haemorrhage; postpartum uterine atony.

Exposis *Osler, Fr.†.*
SPF 20; SPF 30: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Exprep *Mundipharma, Fin.*
Senna (p.1769·2).
Bowel evacuation.

Expril *Collins, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Expron *Lilly, Gr.†.*
Fenoprofen calcium (p.55·2).
Inflammation; musculoskeletal and joint disorders; pain.

Expros *Orion, Fin.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Expulin *Shire, Irl.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

Expulin Childrens Cough *Shire, Irl.; Monmouth, UK†.*
Pholcodine (p.1570·2); chlorphenamine maleate (p.571·3).
Coughs.

Expulin Dry Cough *Shire, Irl.*
Pholcodine (p.1570·2).
Coughs.

Expuryl *Codifra, Fr.*
Cynara; taraxacum; black currant; turmeric; green tea (p.1922·1).
Tonic.

Exputex *Shire, Irl.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excessive or viscous mucus.

Exratuss *Midlothian, USA.*
Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

exrheudon OPT *Optimed, Ger.*
Phenylbutazone (p.117·1).
Acute ankylosing spondylitis; gout; rheumatism.

Exsel *Allergan, USA†.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Exsepta *Tentan, Switz.*
Homoeopathic preparation.

Exten *Zynova, Philipp.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Extencilline *Sanofi-Aventis, Fr.; Sanofi-Aventis, Rus.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Extendryl *Auriga, USA.*
Phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; respiratory congestion; urticaria and angioedema.

Extendryl DM
Note. This name is used for preparations of different composition.
Blooming Fields, Philipp.
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Auriga, USA.
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Extendryl G *Auriga, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Extendryl GCP *Auriga, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Extendryl PEM *Auriga, USA.*
Hyoscine methonitrate (p.1734·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Exteny *IQFA, Mex.*
Mebendazole (p.148·3).
Worm infections.

Exterol *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Extimon *Interbat, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Extin N *Opfermann, Ger.*
Ammonium chloride (p.1551·3).
Urinary-tract infections.

Extina *Stiefel, USA.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Extine *Arrow, Austral.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic distress disorder; social phobia.

Extiser-Q *Serral, Mex.†.*
Praziquantel (p.153·3).
Cysticercosis.

Extosen *Sanitas, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs.

Extovyl *Dexo, Fr.*
Betahistine mesilate (p.2265·1).
Vertigo.

Extra Action Cough *Rugby, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Extra Once A Day *Quest, Canad.*
Multivitamin, mineral, and trace element preparation (p.1922·1).

Extra Power Pain Reliever *AAH, UK.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Extra Strength Alenic Alka *Rugby, USA†.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Hyperacidity.

Extra Strength Alka-Seltzer Effervescent Tablets *Bayer, USA.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); aspirin (p.20·3).
Hyperacidity.

Extra Strength Allergy Sinus *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Extra Strength Analgesic *Prodemdis, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Extra Strength Bayer Plus *Sterling Health, USA.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1), magnesium carbonate (p.1743·1), and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Extra Strength Cold Medication Daytime Relief *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Extra Strength Cold Medication Nightime *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Extra Strength Cold Medication Nighttime Relief *WestCan, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Extra Strength Cough Syrup Expectorant *Stanley, Canad.†.*
Guaifenesin (p.1561·3).
Coughs.

Extra Strength Doans PM *Novartis Consumer, USA.*
Magnesium salicylate (p.79·2); diphenhydramine hydrochloride (p.577·2).

Extra Strength Genaton *Goldline, USA.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Hyperacidity.

Extra Strength Maalox Antacid/Anti-Gas *Novartis Consumer, USA†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Extra Strength Mintox Plus *Major, USA.*
Simeticone (p.1770·2).

Extra Strength Multi-Symptom PMS Relief *Stanley, Canad.†.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).

Extra Strength Pain Reliever PM *Magno-Humphries, USA.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Insomnia.

Extra Strength Sinus and Congestion Relief *WestCan, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Extra Strength Sinus Medication *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Extra Strength Vicks Cough Drops *Procter & Gamble, USA.*
Menthol (p.2340·1).

Extra Strong Formula 12 *Hilarys, Canad.†.*
Aloes (p.1705·2); bisacodyl (p.1710·1); cascara (p.1715·2); frangula (p.1732·2); rhubarb (p.1768·3); senna (p.1769·2).
Constipation.

Extraboline *Genepharm, Gr.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic.

Extracaine *Ethica, Indon.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Extrace *Ethica, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Extracort Tinktur *Galderma, Ger.†.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Extrafer *SoSe, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias.

Extra-Flu *Berlico Mulia, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Extrafoam *Pharmatrix, Arg.*
Range of soap substitutes.

Extraleci *Gezzi, Arg.*
Povidone-iodine (p.1659·2).
Skin disinfection; wounds.

Extralife Arthri-Care *Felton, Austral.*
Turmeric (p.1473·2); ginger (p.1732·3); feverfew (p.622·2); devil's claw root (p.39·1); lecithin (p.2332·2).
Musculoskeletal and joint disorders.

Extralife Extra-Brite *Felton, Austral.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1); lecithin (p.2332·2).
Alzheimer's disease; mental function disorders.

Extralife Eye-Care *Felton, Austral.*
Myrtillus (p.2349·3); ginkgo biloba (p.2311·1); big marigold; riboflavin (p.1977·2); zinc gluconate (p.1999·2).
Eye disorders.

Extralife Flow-Care *Felton, Austral.*
Saw palmetto (p.2192·3); urtica (p.2409·3); pyridoxine hydrochloride (p.1978·2); zinc gluconate (p.1999·2).
Benign prostatic hyperplasia; micturition disorders in men.

Extralife Fluid-Care *Felton, Austral.*
Taraxacum (p.2395·1); equisetum (p.2299·3); parsley (p.2363·2); bearberry (p.2263·3); solidago virgaurea (p.2391·1); pyridoxine hydrochloride (p.1978·2).
Fluid retention.

Extralife Leg-Care *Felton, Austral.*
Aesculus (p.2248·2); butcher's broom (p.2270·3); centella (p.1592·3); ginkgo biloba (p.2311·1); myrtillus (p.2349·3); hesperidin (p.2304·3); rutoside (p.2305·1); ascorbic acid (p.1983·3).
Varicose veins.

Extralife Liva-Care *Felton, Austral.*
Milk thistle (p.1452·1); greater celandine (p.2317·1); cynara (p.2291·2); turmeric (p.1473·2); astragalus; taraxacum (p.2395·1); lecithin (p.2332·2).
Acne; gastrointestinal disorders; halitosis; hyperlipidaemias; hypersensitivity disorders; hypoglycaemia; menopausal disorders; migraine; obesity; premenstrual syndrome.

Extralife Meno-Care *Felton, Austral.*
Soya bean (p.1965·3); cimicifuga (p.2282·1); chaste tree; dong quai (p.2297·3); calcium phosphate (p.1676·2).
Menopausal disorders; osteoporosis.

Extralife Migrai-Care *Felton, Austral.*
Feverfew (p.622·2); salix (p.121·3); magnesium phosphate (p.1679·2).
Migraine and other headaches.

Extralife PMS-Care *Felton, Austral.*
Salix (p.121·3); chaste tree; cimicifuga (p.2282·1); viburnum opulus; bearberry (p.2263·3); pyridoxine hydrochloride (p.1978·2); ferrous fumarate (p.1938·3).
Premenstrual syndrome.

Extralife Sleep-Care *Felton, Austral.*
Valerian (p.2410·1); passion flower (p.2363·2); gentian (p.2310·3); lupulus (p.2335·2); magnesium phosphate (p.1679·2); calcium phosphate (p.1676·2).
Nervous disorders; sleep disorders.

Extralife Uri-Care *Felton, Austral.*
Cranberry (p.2289·1); bearberry (p.2263·3); buchu (p.2269·3); pyridoxine hydrochloride (p.1978·2); ascorbic acid (p.1983·3); potassium sulfate (p.1684·3).
Cystitis.

Extranase *Rottapharm, Fr.*
Bromelains (p.2269·1).
Post-traumatic and postoperative oedema.

Extraneal *Baxter, Austral.; Baxter, Austria; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Hung.; Baxter, Ital.; Baxter, NZ; Baxter, Neth.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, USA.*
Icodextrin; electrolytes (p.1670·3).
Peritoneal dialysis.

Extrapan *Qualiphar, Belg.*
Ibuprofen (p.64·2).
Peri-articular and soft-tissue disorders.

Extraplus *Pierre Fabre, Spain.*
Ketoprofen (p.73·1).
Musculoskeletal, joint disorders, peri-articular, and soft-tissue disorders.

Extrastatin *SJA, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Extrato Hepatico Composto *Delta, Braz.*
Methionine (p.1450·1); choline (p.1934·2); liver extract (p.2337·3).
Liver disorders.

Extrato Hepatico Vitaminado *Granado, Braz.†.*
Methionine (p.1450·1); liver extract (p.2337·3); choline (p.1934·2).
Liver disorders.

Extregen *Diba, Mex.†.*
Vitamin and mineral preparation (p.1922·1).

Extreme Sun *Darier, Mex.*
SPF 85: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); oxybenzone (p.1608·3); octisalate (p.1608·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Extropect *Guardian, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Extur *Normon, Spain.*
⊗ Indapamide (p.1314·1).
Hypertension; oedema.

Extuss *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Exubera *Pfizer, Braz.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Port.; Pfizer, UK†; Pfizer, USA.*
⊗ Insulin (human) for inhalation (p.443·2).
Diabetes mellitus.

Exudrol con Dexametasona *Lafedar, Arg.*
⊗ Dexamethasone (p.1526·1); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Respiratory-tract disorders.

Exuracid *Rosch & Handel, Austria.*
Tisopurine (p.560·1).
Gout; hyperuricaemia; urinary calculi.

Exviral *Kwizda, Austria.*
Aciclovir (p.862·3).
Herpes labialis.

Exxiv *Bial, Port.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Eye Block *Avon, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Eye Dew *Crookes Healthcare, UK.*
⊗ Hamamelis (p.2318·2); naphazoline hydrochloride (p.1565·2).
Formerly known as Optrex Eye Dew.
Eye irritation.

Eye Drops *Zee, Canad.†; Reese, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Eye Formula Euphr L115 *Homeocan, Canad.†.*
Homoeopathic preparation.

Eye Glo Moist *CCM, Hong Kong; CCM, Malaysia.*
Hypromellose (p.2144·2).
Dry eyes.

Eye Glo Plus *CCM, Hong Kong.*
Borax (p.2268·1); boric acid (p.2268·1); hamamelis (p.2318·2).
Eye irritation.

Eye Glo Regular *CCM, Hong Kong.*
Borax (p.2268·1); boric acid (p.2268·1).
Eye irritation.

Eye Glo Relief *CCM, Hong Kong.*
Zinc sulfate (p.1999·2).
Eye irritation.

Eye Health Herbal Plus Formula 4 *Vitelle, Austral.*
Euphrasia (p.2301·3); ginkgo biloba (p.2311·1); betacarotene (p.1930·3); *d*-alpha tocoferil acid succinate (p.1993·1); ascorbic acid (p.1983·3); rutoside (p.2305·1); hesperidin (p.2304·3).
Eye strain.

Eye Mo *GSK, Singapore†; GSK, Thai.*
Boric acid (p.2268·1); borax (p.2268·1).
Eye irritation.

Eye Mo Moist *GSK, Singapore†.*
Hypromellose (p.2144·2).
Dry eyes.

Eye Q *Equazen, Hong Kong.*
Docosahexaenoic acid (p.1362·1); eicosapentaenoic acid (p.1362·1); gamolenic acid (p.2308·2); vitamin E (p.1992·2).
Dietary supplement.

Eye Scrub *Novartis Ophthalmics, USA.*
Eyelid cleanser.

Eye Vites *Natural Life, Arg.†.*
Vitamin and mineral preparation (p.1922·1).

Eye Wash
Note. This name is used for preparations of different composition.
Canadian Custom Packaging, Canad.; Niagara, Canad.
Boric acid (p.2268·1).

Zee, Canad.
Electrolytes (p.1667·1).
Eye irrigation.

Bausch & Lomb, Hong Kong.
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irrigation.

Eyebrex *Alvia (Αλβια), Gr.; Allergan, Mex.*
Tobramycin (p.354·1).
Bacterial eye infections.

Eyebrex-Dexa *Genepharm, Gr.†.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Eye infections.

Eyebright Plus *Swiss Bio, Malaysia†.*
Carrot (p.2415·2); chlorella herb; euphrasia (p.2301·3); fennel (p.2302·3); spirulina (p.2392·1).
Minor eye disorders.

Eyeclof *Genepharm, Gr.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Eyecon *Excelvision, Israel.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Eyedex *Siam Bheasach, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Eye-Gene *IDS, Thai.*
Phenylephrine hydrochloride (p.1568·1); boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation.

Eye-Gene Soft *IDS, Thai.*
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation.

Eyegold *Darya-Varia, Indon.*
Mixed carotenoids.
Antioxidant to reduce cataracts and age-related macular degeneration risk.

Eyelube *Sandoz, Canad.*
Hypromellose (p.2144·2).
Dry eyes.

Eye-Lube-A *Optopics, USA.*
Glycerol (p.2314·2).
Dry eyes.

Eye-Mo *GSK, Mex.; GSK, Philipp.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Eyesalt *Cooper (Κοπερ), Gr.†.*
Sodium chloride (p.1686·1); sodium acetate (p.1673·2).
Cataract surgery.

Eyestil *Ophtapharma, Canad.†.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Eye-Stream *Alcon, Austral.; Alcon, Canad.; Alcon, Hong Kong†; Alcon, Malaysia†; Alcon, NZ; Alcon, Singapore; Alcon Cusi, Spain†; Alcon, USA.*
Electrolyte preparation (p.1667·1).
Eye irrigation.

Eyetobrin *Cooper (Κοπερ), Gr.*
Tobramycin (p.354·1).
Eye infections.

Eye-Visol *Bilim, Turk.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Eyevit *Lapi, Indon.*
Myrtillus (p.2349·3); vitamin A; betacarotene; vitamin E; lutein (p.1954·3); zeaxanthin (p.1999·1); selenium; zinc (p.1922·1).
Nutritional supplement for the eyes.

EyeVit *HealthAid, UK.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Eyevite *Allergan, Austral.; Allergan, NZ†.*
Vitamin and mineral preparation (p.1922·1).
Eye disorders.

Eyewash *Sabex, Canad.*
Electrolyte solution (p.1667·1).
Eye irrigation.

Eyezep *Douglas, NZ.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

Eye-Zine *Ocumed, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Eykosacol *Knop, Chile.*
Fish oil (p.1362·2).
Hyperlipidaemias; hypertension.

Eyrasil *Diba, Mex.*
⊗ Naphazoline (p.1565·1); pheniramine (p.587·2).
Eye disorders.

EZ Detect *Step, Arg.†; Marco, Austral.†; Biomerica, USA.*
Test for occult blood in faeces.

EZ HP *Marco, Austral.†.*
Test for *Helicobacter pylori* antibodies in blood, serum or plasma.

EZ Smart *Exxe, Ital.*
Test for glucose in blood (p.2314·1).

E-Z-Cat *Temis, Arg.; E-Z-EM, Cz.; E-Z-EM, Hung.; E-Z-EM, Israel; E-Z-EM, Port.; E-Z-EM, UK.*
Barium sulfate (p.1477·2).
Contrast medium for computerised axial tomography of the gastrointestinal tract.

Eze *Gap, Gr.†.*
Serrapeptase (p.2385·3).
Inflammatory disorders.

Ezede *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Ezee *Hovid, Malaysia.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Dyspepsia.

Ezerra *Hoe, Malaysia.*
Emollient.
Eczema.

EzeShield *Hoe, Malaysia.*
Emollient.
Dry skin; skin irritation.

Ezetib *Unichem, India.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Ezetrol *MSD, Arg.; MSD, Austral.; Aesca, Austria; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; Schering, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Schering-Plough, Hong Kong; MSD, Hung.; Schering-Plough, Indon.; MSD, Irl.; MSD, Israel; MSD, Malaysia; Schering-Plough, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; Schering-Plough, Philipp.; MSD, Port.; Schering-Plough, Rus.; MSD, S.Afr.; MSD, Singapore; Schering-Plough, Singapore; MSD, Spain; MSD, Swed.; Schering-Plough, Swed.; MSD, Switz.; Schering-Plough, Thai.; MSD, UK; MSD, Venez.*
Ezetimibe (p.1284·3).
Atherosclerosis; hypercholesterolaemia.

EZFE *McNeil, USA.*
Iron (p.1949·1).
Iron supplement.

E-Z-Gas
Note. This name is used for preparations of different composition.
E-Z-EM, Cz.†.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); simeticone (p.1770·2).
Production of CO in double contrast radiography of the gastrointestinal tract.

IFET (ΙΦΕΤ), Gr.; E-Z-EM, Hung.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Production of CO in double contrast radiography of the gastrointestinal tract.

E-Z-Gas II
Note. This name is used for preparations of different composition.
Therapex, Canad.†.
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); simeticone (p.1770·2).
Production of CO in double contrast radiography of the gastrointestinal tract.

E-Z-EM, Israel.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Production of CO in double contrast radiography of the gastrointestinal tract.

Bracco, Switz.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); simeticone (p.1770·2).
Production of CO in double contrast radiography of the gastrointestinal tract.

Ez-HBT *Metabolic Solutions, USA.*
⊗ Carbon-13 (p.2277·1) labelled urea (Helicosol); test meal (Ensure).
Diagnosis of Helicobacter pylori infection.

E-Z-HD *E-Z-EM, Cz.; E-Z-EM, Hung.; E-Z-EM, Israel; E-Z-EM, Neth.; E-Z-EM, Port.; E-Z-EM, UK.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Ezipol *Kleva, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ezon-T
Note. This name is used for preparations of different composition.
Unison, Thai.
Ointment: Tolnaftate (p.548·3).
Fungal skin infections.

Unison, Thai.
Topical solution: Tolnaftate (p.548·3); triacetin (p.549·1).
Fungal skin infections.

Ezopen *Teuto, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ezopta *Biomedica-Chemica, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Ezor *Lainco, Spain.*
Sodium picosulfate (p.1771·1).
Constipation.

Ezosina *Fournier, Ital.*
Terazosin hydrochloride (p.1410·2).
Hypertension.

E-Z-Paque *Infarmed, Belg.; E-Z-EM, Cz.†; E-Z-EM, Israel; E-Z-EM, UK.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Ezulen Biosintetica, Braz.
Oxaliplatin (p.757·3).
Malignant neoplasms.

Ezumycin Rafarm, Gr.
Clarithromycin (p.248·2).
Bacterial infections.

Ezzicad Glenmark, India†.
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

I + I-F Dunhall, USA.
⊗ Hydrocortisone (p.1535·2); clioquinol (p.254·1); pramocaine (p.1868·2).
Skin disorders.

F9 Loren, Mex.†.
Loperamide (p.1741·3).
Diarrhoea.

FAB Medical Research, Austral.
Iron and vitamin B substances (p.1922·1).

FAB Co Medical Research, Austral.
Iron, vitamin B substances, and vitamin C (p.1922·1).

FAB Tri-Cal Medical Research, Austral.
Calcium hydrogen phosphate (p.1676·1); calcium carbonate (p.1714·1); calcium gluconate (p.1675·3); zinc oxide (p.1621·2); magnesium oxide (p.1744·1); colecalciferol (p.1986·2).
Nutritional supplement.

Fabahistin Bayer, S.Afr.
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Fabamox Fabop, Arg.
Amoxicillin (p.202·2).
Bacterial infections.

Faberdin Bernofarm, Indon.
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Faboacid Fabop, Arg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Faboacid-R Fabop, Arg.
Ranitidine (p.1766·1).
Gastric hyperacidity; peptic ulcer.

Faboflem Fabop, Arg.
Diclofenac (p.44·2).

Fabofurox Fabop, Arg.
⊗ Furosemide (p.1292·1).

Fabogesic Fabop, Arg.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Fabolergic Fabop, Arg.
Diphenhydramine (p.577·1).
Hypersensitivity reactions.

Fabomicina Fabop, Arg.
Vancomycin (p.358·3).
Bacterial infections.

Fabopcilina Fabop, Arg.
Ampicillin (p.204·1).
Bacterial infections.

Fabopxicam Fabop, Arg.
Piroxicam (p.117·3).
Fever; inflammation; pain.

Fabotenol Fabop, Arg.
⊗ Atenolol (p.1217·3).

Fabotensil Fabop, Arg.
Enalapril (p.1276·1).
Hypertension.

Fabotensil D Fabop, Arg.
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Fabotop Fabop, Arg.
Cefalexin (p.218·2).
Bacterial infections.

Fabotranil Fabop, Arg.
Diazepam (p.986·3).

Faboxetina Fabop, Arg.
Fluoxetine (p.397·3).
Depression.

Fabozepam Fabop, Arg.
Bromazepam (p.964·3).
Anxiety.

Fabracin Fabra, Arg.
Cinnarizine (p.573·1).
Cerebrovascular disorders.

Fabralgina Fabra, Arg.
Naproxen (p.92·3).
Inflammation; pain.

Fabramicina Fabra, Arg.
Azithromycin (p.207·1).
Bacterial infections.

Fabrapride Fabra, Arg.
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Fabrazol Fabra, Arg.
Omeprazole (p.1753·1).

Fabrazyme Genzyme, Belg.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.†; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hung.; Genzyme, Israel; Genzyme, Ital.; Genzyme, Jpn; Healthcare Logistics, NZ; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Genzyme, Switz.; Genzyme, UK; Genzyme, USA.
Agalsidase beta (p.2252·3).
Fabry disease.

Fabroven
Note.This name is used for preparations of different composition.
Pierre Fabre, Mex.
⊗ Ascorbic acid (p.1983·3); hesperidin methyl chalcone (p.2305·2); butcher's broom (p.2270·3).
Haemorrhoids; metrorrhagia; peripheral vascular disorders.

Pierre Fabre, Spain.
Capsules: ⊗ Ascorbic acid (p.1983·3); hesperidin methyl chalcone (p.2305·2); butcher's broom (p.2270·3).
Peripheral vascular disorders.

Pierre Fabre, Spain.
Cream: Melilot (p.2339·2); butcher's broom (p.2270·3).
Peripheral vascular disorders.

Fabubac Brunel, S.Afr.†.
Co-trimoxazole (p.258·1).
Bacterial infections.

Fabudol Volta, Chile.
Piroxicam (p.117·3).

Fabulaxol Andromaco, Chile.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Constipation.

Fabutin Pharmacos Abug, Mex.
Famotidine (p.1730·1).
Gastric hyperacidity; peptic ulcer.

Face Zone Clinique, Canad.
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Facelit Collins, Mex.
Cefalexin hydrochloride (p.218·3).
Bacterial infections.

Faces Only Schering-Plough, USA.
SPF 15; SPF 6: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Facetin-D Ifusa, Mex.
Diiodohydroxyquinoline (p.832·1); phthalylsulfacetamide (p.315·1); homatropine (p.1881·2); kaolin (p.1738·1); pectin (p.2145·2).
Amoebiasis.

Facicam Senosiain, Mex.
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, peri-articular and soft-tissue disorders.

Facid Kalbe, Indon.
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Facidex Total Liomont, Mex.
Famotidine (p.1730·1); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Facidmol Liomont, Mex.
Bismuth salicylate (p.1711·1).
Diarrhoea; gastric hyperacidity.

Facilgest Raffo, Arg.†.
Metoclopramide (p.1747·3); pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders; flatulence; gastrointestinal motility disorders.

Facilit Fides Ecopharma, Spain†.
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Facimin Mintlab, Chile.
⊗ Oxymetazoline (p.1567·2).

Facitor Mintlab, Chile.
Aspirin (p.20·3); chlorphenamine (p.572·2); caffeine (p.1116·3).
Cold and influenza symptoms.

Faclor Novartis, Braz.†.
Cefaclor (p.217·2).
Bacterial infections.

Facomed Eupharmed, Ital.
Cucumis melo; bioflavonoids; mirtillo nero; vitamins (p.1922·1).
Dietary supplement.

Facort Biolab, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Facoserina Amnol, Ital.†.
Amino acids; phosphatidyl serine; minerals; vitamin A palmitate (p.1922·1).
Nutritional supplement.

Facosmina Amnol, Ital.
Diosmin (p.2304·2); hesperidin (p.2304·3); melilot (p.2339·2); vitamins (p.1922·1).
Circulatory disorders.

Facovit Teofarma, Ital.
⊗ Testosterone propionate (p.2130·1); rubidium iodide (p.2382·2); potassium iodide (p.2169·2); riboflavin (p.1977·2).
Cataract; vitreous turbidity.

Fact Plus Unipath, Canad.; Advanced Care, USA.
Pregnancy test (p.2372·1).

Factane CAF-DCF, Belg.; Lab Francais du Fractionnement, Fr.; LFB, Port.; Er-Kim, Turk.
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Faction Maigal, Arg.
Ketoconazole (p.539·1).
Fungal infections.

Factioneye Maigal, Arg.
⊗ Naphazoline (p.1565·1); neomycin (p.305·1); dexamethasone (p.1526·1).
Eye disorders.

Factiv Veropharm, Rus.
Gemifloxacin mesilate (p.281·3).
Bacterial infections of the respiratory tract.

Factive Ache, Braz.; Pharmacare, S.Afr.; Oscient, USA.
Gemifloxacin mesilate (p.281·3).
Bacterial infections.

Factodin Faran, Gr.
Clotrimazole (p.530·1).
Fungal skin infections.

Factofer Raymos, Arg.
Ferrous sulfate (p.1939·3).
Anaemias.

Factofer B12 Raymos, Arg.
Vitamin B (p.1980·2); folic acid (p.1940·1); ferrous sulfate (p.1939·3).
Anaemias.

Factopan Liade, Spain.
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Factor AF2 Biosyn, Ger.
Liver (p.2337·3) and spleen (p.2337·3) extract.
Supportive tumour therapy.

Factor AG Casasco, Arg.
Simeticone (p.1770·2).
Gastrointestinal disorders with excess gas; preparation for gastrointestinal procedures.

Factor AG Antiacido Casasco, Arg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Factor AG Antiespasmodico Casasco, Arg.
Simeticone (p.1770·2); homatropine methylbromide (p.1881·3).
Gastrointestinal spasm.

Factor Antigripal Inmunolab, Arg.
Pseudoephedrine (p.1571·2); paracetamol (p.108·1); chlorphenamine (p.572·2); bromhexine (p.1552·2).
Formerly contained astemizole, paracetamol, and phenylephrine.
Influenza symptoms.

Factor Bioenterico Inmunolab, Arg.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus casei* (p.2372·3); *Enterococcus faecium* (p.2372·3); simeticone (p.1770·2).
Restoration of gastrointestinal flora.

Factor Dermico Casasco, Arg.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Factor Laxante Inmunolab, Arg.
Sodium picosulfate (p.1771·1).
Constipation.

Factor Vit AE Casasco, Arg.
Vitamin A (p.1971·2); alpha tocopherol (p.1992·2); allantoin (p.1588·1).
Skin disorders.

Factorine Casasco, Arg.
Metoclopramide (p.1747·3); simeticone (p.1770·2).
Dyspepsia; flatulence; nausea and vomiting.

Factoss Laboratorios Chile, Chile†.
Noscapine hydrochloride (p.1566·3).
Coughs.

Factrel Wyeth-Ayerst, USA.
⊗ Gonadorelin hydrochloride (p.2106·2).
Diagnostic evaluation of anterior pituitary function.

Factus
Note.This name is used for preparations of different composition.
Roux-Ocefa, Arg.
Oral drops; oral solution: Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly contained phenylpropanolamine hydrochloride and chlorphenamine maleate.
Allergic rhinitis; cold and influenza symptoms.

Roux-Ocefa, Arg.
Tablets: Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); dexbrompheniramine maleate (p.569·2); vitamin C (p.1983·3).
Formerly contained phenylpropanolamine, paracetamol, moroxydine, dexbrompheniramine, vitamin C, and muramidase.
Influenza symptoms.

Facyl Medley, Braz.
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Facyl M Medley, Braz.
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

FAD Ophthalmic Soln Santen, Hong Kong.
Flavine adenine dinucleotide disodium (p.1978·1).
Blepharitis; keratitis.

Fadacaina Fada, Arg.
Procaine (p.1869·2).
Local anaesthesia.

Fadaespasmol Fada, Arg.†.
Isoxsuprine (p.2327·3).

Fadafilina Fada, Arg.
Aminophylline (p.1114·2).
Obstructive airways disease.

Fadaflumaz Fada, Arg.
Flumazenil (p.1445·2).

Fadagrip Fada, Arg.
Paracetamol (p.108·1); dipyrone (p.49·2); diphenhydramine (p.577·1).
Allergic respiratory-tract disorders.

Fadalefrina Fada, Arg.
Phenylephrine (p.1568·1).

Fadalivio Fada, Arg.
Naproxen (p.92·3).
Fever; pain.

Fadametasona Fada, Arg.†.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Fadamine Fada, Arg.
⊗ Metaraminol (p.1333·2).

Fadanasal Fada, Arg.
⊗ Naphazoline (p.1565·1); nitrofurazone (p.309·1); mepyramine (p.585·1).
Nasal congestion.

Fadastigmina Fada, Arg.
Neostigmine (p.631·2).

Fadatos Fada, Arg.
⊗ Diphenhydramine (p.577·1); guaifenesin (p.1561·3); ephedrine (p.1558·1).
Cold and influenza symptoms; rhinitis.

Fade Cream Cosmofarma, Port.†.
Kojic acid (p.1603·3); achillea (p.2245·2); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Skin pigmentation disorders.

Fadiamone CS, Fr.
Phytoestrogens; centella (p.1592·3).
Skin ageing.

Fadig Arrow, Braz.
Amino acids and vitamin B substances (p.1922·1).

Fadina Cantabria, Spain†.
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Fadine Biolab, Hong Kong; Aristo, India; Biolab, Malaysia†; Biolab, Thai.†.
Famotidine (p.1730·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fadipina Rowe-Fleming, Venez.†.
Famotidine (p.1730·1).
Peptic ulcer.

Fadol Lemery, Mex.
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Fadul Hexal, Ger.
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Faelac Inmunolab, Arg.†.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus casei* (p.2372·3); *Enterococcus faecium* (p.2372·3); simeticone (p.1770·2).
Restoration of normal gastrointestinal flora.

Fagastril Quimifar, Spain.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fagatrim Collins, Mex.†.
Famotidine (p.1730·1).
Peptic ulcer.

Fagifor Biogal-Teva, Hung.†.
Cinnamon oil (p.2283·2); peppermint oil (p.1761·2); menthol (p.2340·1); creosote (p.1555·1); ferrous lactate (p.1939·2); calcium acetate (p.1675·2).
Bronchitis.

Fagizol Continentales, Mex.
Metronidazole (p.837·1).
Amoebiasis; worm infections.

Fagolip Plus Cetus, Arg.
⊗ Mazindol (p.2157·3).
Obesity.

Fagolipo Libbs, Braz.
⊗ Mazindol (p.2157·3).
Obesity.

Fagorutin Buchweizen
Note.This name is used for preparations of different composition.
GSK Consumer, Ger.
Tablets: Buckwheat (p.2270·1); troxerutin (p.2305·1).
Venous insufficiency.

GSK Consumer, Ger.
Tea: Buckwheat (p.2270·1).
Venous insufficiency.

Fagorutin Rosskastanien-Balsam N GSK Consumer, Ger.
⊗ Aesculus (p.2248·2); rutoside sodium sulfate (p.2305·2); menthol (p.2340·1).
Venous insufficiency.

Fagorutin Ruscus GSK Consumer, Ger.
Butcher's broom (p.2270·3).
Chronic venous insufficiency; haemorrhoids.

Fagus GSK, Spain.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fagusan Medphano, Ger.
Guaifenesin (p.1561·3).
Coughs and related respiratory-tract disorders.

Fahifem Farmaceutica H, Mex.
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Faifloc TS, Ital.
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Fairgenol *FDC, India†.*
Dichloroxylenol (p.1642·2); terpineol (p.2396·1).
Skin disinfection.

Fairy ADE *YSP, Malaysia.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); vitamin E (p.1992·2).
Dry skin.

Faktu *Nycomed, Cz.; Meda, Fin.†; Altana, Ger.; Altana, Hong Kong; Altana, Indon.; Pharos, Indon.; Altana, Philipp.; Altana, Port.; Byk Gulden, Singapore†; Altana, Switz.*
Policresulen (p.1077·2); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Faktu akut *Altana, Ger.*
Bufexamac (p.28·3); bismuth subgallate (p.1711·1); titanium dioxide (p.1617·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Falacid *Collins, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Falcigo *Cadila, India.*
Artesunate (p.598·2).
Malaria.

Falcinil *Cipla, India.*
Artesunate (p.598·2).
Malaria.

Falcol *Farma Lepori, Spain.*
Aceclofenac (p.14·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Falergi *Fahrenheit, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Falernol *Liferpal, Mex.*
Miconazole (p.541·2).
Fungal skin infections.

Falexin *HB, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Falexol *Protein, Mex.†.*
Cefalexin (p.218·2).
Bacterial infections.

Falgos *Gramon, Arg.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; hangover; pain.

Falic *TRB, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Falicard *AWD, Ger.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension; ischaemic heart disease.

Falimint *Berlin-Chemie, Ger.†; Berlin-Chemie, Rus.*
Acetylaminonitropropoxybenzene.
Mouth and throat disorders.

Falithrom *Hexal, Ger.*
Phenprocoumon (p.1370·2).
Thromboembolism prophylaxis.

Falitonsin *AWD, Ger.†.*
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension; ischaemic heart disease.

Falkamin
Note.This name is used for preparations of different composition.
Falk, Ger.; Abbott, Ital.†.
Leucine (p.1954·3); valine (p.1971·1); isoleucine (p.1954·1).
Hepatic failure; liver disorders.

Falk, Hong Kong; Darya-Varia, Indon.; Falk, Indon.; Falk, Malaysia; Falk, Philipp.; Pharmalink, Philipp.; Falk, Singapore.
Amino-acid, vitamin and trace element preparation (p.1922·1).
Hepatic failure; nutritional supplement in liver disorders.

Falmonox *Sanofi-Aventis, Braz.; Sanofi-Aventis, Venez.*
Teclozan (p.848·1).
Intestinal amoebiasis.

Falot *Pisa, Mex.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Falquigut *Falqui, Ital.*
Sodium picosulfate (p.1771·1).
Constipation.

Falquilax *Falqui, Ital.*
Senna (p.1769·2).
Constipation.

Falvin *Theramex, Ital.*
Fenticonazole nitrate (p.531·3).
Dermatological and gynaecological fungal infections.

Falvit *Jelfa, Pol.*
Vitamin and mineral preparation (p.1922·1).

Famec *Mecom, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famel
Note.This name is used for preparations of different composition.
Boots Healthcare, Ital.†.
⊗ Lactocreosote (p.1555·1); calcium lactophosphate (p.1677·1); ephedrine hydrochloride (p.1558·2).
Bronchial catarrh.

Boots Healthcare, Switz.
Lactocreosote (p.1555·1); calcium lactophosphate (p.1677·1); codeine (p.37·2); drosera (p.2297·3); grindelia (p.2317·2).
Catarrh; cold symptoms; coughs.

Famel Broomhexine *Boots Healthcare, Neth.†.*
Bromhexine hydrochloride (p.1552·2).
Coughs.

Famel cum Codein *Brady, Austria.*
Lactocreosote (p.1555·1); calcium lactophosphate (p.1677·1); codeine hydrochloride (p.37·2).
Asthma; bronchitis; catarrh; cold symptoms.

Famel cum Ephedrin *Brady, Austria.*
⊗ Lactocreosote (p.1555·1); calcium lactophosphate (p.1677·1); ephedrine hydrochloride (p.1558·2).
Asthma; bronchitis; catarrh; cold symptoms.

Famel Original *SSL, UK.*
Creosote (p.1555·1); codeine phosphate (p.37·2).
Coughs.

Famidal *Andromaco, Chile.*
Miconazole (p.541·2); tinidazole (p.848·3).
Balanitis; vulvovaginal infections.

Famidal Ad *Andromaco, Chile†.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Balanitis; vulvovaginal infections.

Famidyna *Jelfa, Pol.*
Famotidine (p.1730·1).
Dyspepsia; gastric hyperacidity; heartburn.

Family Medic First Aid Treatment *Tender, Canad.*
Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).

Famine *APT, Hong Kong.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Fam-Lax *Torbet Laboratories, UK.*
Yellow phenolphthalein (p.1762·1); rhubarb (p.1768·3).
Constipation.

Fam-Lax Senna *Torbet Laboratories, UK.*
Turkey rhubarb (p.1768·3); senna leaf (p.1769·2); carrageenan (p.2142·3).
Constipation.

Famo *ABZ, Ger.; CTI, Israel; Ulkar, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famobeta *Betapharm, Ger.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famoc *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famocid *Synco, Hong Kong; Sanbe, Indon.; Sun, Rus.; Sun, Thai.†.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer; Zollinger-Ellison syndrome.

Famodil *Sigma-Tau, Ital.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famodin *Cadila, India; Ilsan, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famodine *Farmasa, Braz.†; Duopharma, Hong Kong.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famogast *Polpharma, Pol.; Saba, Turk.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famogel *Vivax, Venez.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famohexal *Hexal, Austral.; Hexal, Austria.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famokey *Inkeysa, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famolta *Jean-Marie, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famonerton *Dolorgiet, Ger.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famonit *Cadila, Rus.*
Famotidine (p.1730·1).

Famonite *Zydus, India.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famonor *Labesfal, Port.*
Amlodipine besilate (p.1214·1).
Angina pectoris.

Famonox *Charoen, Thai.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famopril *BPRL, Singapore.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famopsin *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Singapore†; Remedica, Thai.*
Famotidine (p.1730·1).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Famorila *Glenmark, Philipp.*
Famotidine (p.1730·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famosan *ProMed, Cz.; Promed, Rus.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; pancreatitis; peptic ulcer; Zollinger-Ellison syndrome.

Famoser *Biofarma, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famoset *Solvay, Braz.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famosia *Asian Pharm, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famosin *Lannacher, Austria.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotab *Bangkok Lab & Cosmetic, Thai.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Famotal *Alpharma, Norw.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotec *Julphar, UAE.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotep *Yeni, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotid *Neo Quimica, Braz.*
Famotidine (p.1730·1).
Peptic ulcer.

Famotil *Farmion, Braz.†.*
Famotidine (p.1730·1).
Peptic ulcer.

Famotin *DHA, Hong Kong; DHA, Singapore; LSP, Thai.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famotsan *Drogsan, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famowal *Wallace, India.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famox *Ache, Braz.; Pacific, Hong Kong; Pacific, NZ; Merck, Singapore†; Pacific, Singapore†.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famoxal *Silanes, Mex.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famoxil *Hebron, Braz.†.*
Famotidine (p.1730·1).
Peptic ulcer.

Fampisec *San Marino, Philipp.*
Rifampicin (p.325·3).
Mycobacterial infections.

Fampiz *Spefar, Venez.†.*
Rifampicin (p.325·3).
Bacterial meningitis prophylaxis; tuberculosis.

Famri *Pyridam, Indon.*
Rifampicin (p.325·3).
Tuberculosis.

Famtac *Nicholas Piramal, India.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famtine *Shin Poong, Philipp.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Famtrex *Cipla, India.*
Famciclovir (p.876·1).
Herpesvirus infections.

Famtuss *Genpharm, S.Afr.†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Famucaps *Brunel, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3); caffeine (p.1116·3); paracetamol (p.108·1); atropine sulfate (p.1219·3).
Upper respiratory-tract disorders.

Famulan *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Famulcer *Inkeysa, Spain; Plusandex, Venez.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Famvir
Note.This name is used for preparations of different composition.
Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Irl.; Novartis, Israel†; Novartis, Ital.; Novartis, NZ†; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; SmithKline Beecham, USA.
Famciclovir (p.876·1).
Herpesvirus infections.

Novartis, Austria.
Famciclovir (p.876·1), penciclovir (p.901·2), or penciclovir sodium (p.901·3).
Herpesvirus infections.

Novartis, Neth.; Novartis, Switz.
Cream: Penciclovir (p.901·2).
Herpes labialis.

Novartis, Neth.
Injection: Penciclovir sodium (p.901·3).
Herpesvirus infections.

Novartis, Neth.; Novartis, Switz.
Tablets: Famciclovir (p.876·1).
Herpesvirus infections.

Fanaletas *Lazar, Arg.*
Benzocaine (p.1854·1); tyrothricin (p.358·2); chlorophyllin (p.1471·1); hexylresorcinol (p.1647·1).
Mouth and throat infections.

Fanalgin *Weifa, Norw.*
Phenazone (p.116·1); caffeine (p.1116·3).
Pain.

Fanasal *Quim-Far, Venez.†.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Fanaxal *Esteve, Spain.*
⊗ Alfentanil hydrochloride (p.16·2).
General anaesthesia.

Fanciadazol *Novag, Mex.*
Mebendazole (p.148·3).
Worm infections.

Fanclomax *Blausiegel, Braz.*
Famciclovir (p.876·1).

Fandall *Maver, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Fandhi *Pharmakin, Venez.*
A factor VIII preparation (p.1067·1).
Haemophilia A.

Fangan *Lazar, Arg.*
Ketoconazole (p.539·1).
Vulvovaginal candidiasis.

Fango Cream *Bangkok Lab & Cosmetic, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Fango-B *Bangkok Lab & Cosmetic, Thai.*
⊗ Betamethasone valerate (p.1519·1); clotrimazole (p.530·1).
Infected skin disorders.

Fango-Rubriment *Riemser, Ger.*
Silicic acid; sulfur (p.1614·1).
Musculoskeletal and joint disorders.

Fangotherm *Eifelfango, Ger.*
Medicinal mud.
Gastrointestinal and urogenital disorders; musculoskeletal and joint disorders; neuralgia.

Fanhdi *Grifols, Arg.; Grifols, Chile; Grifols, Cz.; Grifols, Ger.; Demo, Gr.; Grifols, Hung.; Grifols, Israel; Grifols, Ital.; Grifols, Malaysia; Grifols, Port.; Grifols, Singapore; Grifols, Spain; Grifols, Thai.; Dem, Turk.; Grifols, UK.*
A factor VIII preparation (p.1067·1).
Haemophilia A.

Fanolyte *Tonipharm, Fr.*
Glucose; sodium chloride; potassium citrate; citric acid (p.1672·2).
Diarrhoea; oral rehydration therapy.

Fanosin *Abello, Spain†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fanox *Lesvi, Spain†.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fansamac *Farmigea, Ital.*
Bufexamac (p.28·3).
Pruritus; skin disorders; sunburn.

Fansia *Eurodrug, Mex.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Fansidar *Roche, Austral.; Roche, Braz.; Roche, Canad.†; Roche, Denm.†; Roche, Fr.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Malaysia; Roche, Philipp.; Roche, S.Afr.; Roche, Switz.; IDIS, UK; Roche, USA.*
Sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria; pneumocystis pneumonia; toxoplasmosis.

Fansidol *NCSN, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Fansimef *Roche, Switz.†.*
Mefloquine hydrochloride (p.605·3); sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Fansulide *Sofar, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Fantersol *Proel, Gr.*
Miconazole (p.541·2).
Fungal skin infections.

Fantomalt *Nutricia, Cz.†; Nutricia, Fin.; Nutricia, Indon.; Nutricia, Ital.; Nutricia, Pol.; Nutricia, Port.†; Nutricia, Venez.; Roemmers-Klinos, Venez.*
Maltodextrin (p.1955·3).
Dietary supplement; enteral nutrition.

Fantrodol *Farmaco, Mex.†.*
Ambroxol (p.1550·3).
Respiratory-tract disorders.

Faradil *Sidus, Arg.*
Metoclopramide (p.1747·3); diazepam (p.986·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Faradil Enzimatico *Sidus, Arg.*
Metoclopramide (p.1747·3); pancreatin (p.2360·1); simeticone (p.1770·2).
Gastrointestinal disorders.

Faradil Novo *Sidus, Arg.*
Bromazepam (p.964·3); domperidone (p.1726·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Faragel-Forte *Faran, Gr.*
⊗ Camphor (p.2273·2); alcohol (p.1625·2); cineole (p.2282·3); menthol (p.2340·1); methyl nicotinate (p.85·3); turpentine oil (p.2406·3).
Topical analgesia.

Farakil *Chew, Thai.*
⊗ Prednisolone (p.1540·3); neomycin (p.305·1).
Infected skin disorders.

Farapon *Fahrenheit, Indon.*
Paracetamol (p.108·1); ethenzamide (p.51·3); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; cough.

Faraxen *Randall, Mex.*
Naproxen (p.92·3).
Inflammation.

Farbee with Vitamin C *Major, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Farbion *Fahrenheit, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; cervical syndrome; chronic rheumatism; diabetic polyneuropathy; facial paresis; herpes zoster; hyperemesis gravidarum; ischialgia; neuralgia; neuritis; peripheral circulatory disorders.

Farbovil *Pharmathen, Gr.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal and joint disorders; pain.

Farbutin *IFA, Mex.*
Trimebutine (p.2404·3).

Farcef *Faran, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Farcolan *Farcoral, Mex.*
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Dyspepsia; flatulence; gastritis; meteorism; peptic ulcer.

Farco-Tril *Farco, Ger.†.*
⊗ Oxytetracycline calcium (p.312·3); polymyxin B sulfate (p.317·3); hydrocortisone (p.1535·2).
Genito-urinary-tract disorders.

Farco-Uromycin *Farco, Ger.†.*
Neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Urinary-tract infections.

Farcovit Plus *Farcoral, Mex.*
Vitamins; minerals; vegetable extracts (p.1922·1).

Farcyclin *Faran, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Fardixon *Farcoral, Mex.†.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Fardolpin *Farcoral, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Farecef *Lafare, Ital.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Farecillin *Lafare, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Fareclox *Lafare, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Faremicin *Lafare, Ital.†.*
Fosfomycin calcium (p.278·2).
Bacterial infections.

Faremid *Lafare, Ital.*
Pipemidic acid (p.315·1).
Bacterial infections.

Fareston *Essex, Arg.†; Schering-Plough, Austral.; Orion, Austria; Baxter, Belg.; Orion, Cz.; Orion, Fin.; HRA, Fr.; Baxter, Ger.; Schering-Plough, Gr.; Orion, Hung.; Orion, Irl.; Schering-Plough, Ital.; Schering-Plough, Mex.; Schering-Plough, NZ; Orion, Neth.; Orion, Port.; Orion, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Spain; Orion, Swed.; Orion, Switz.; Schering-Plough, Thai.; Abdi, Turk.; Orion, UK; Orion, USA.*
⊗ Toremifene citrate (p.781·1).
Breast cancer.

Faretrizin *Lafare, Ital.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Fargan *Carlo Erba OTC, Ital.*
Promethazine (p.588·2).
Skin irritation.

Farganesse *Pharmacia, Ital.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; premedication.

Fargem *MJ Biopharm, Thai.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Fargoxin *Fahrenheit, Indon.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Farial *Galen, Ger.; Abbott, Turk.*
⊗ Indanazoline hydrochloride (p.1562·2).
Nasal congestion.

Faribrox *Loeffler, Mex.*
Ambroxol hydrochloride (p.1550·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; respiratory-tract congestion.

Farin Gola *Montefarmaco, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

Faringenilo *Diafarm, Spain.*
Benzocaine (p.1854·1); potassium chlorate (p.2371·3).
Mouth and throat disorders.

Faringesic *Diafarm, Spain.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Faringina *SIT, Ital.*
Dequalinium chloride (p.1641·3).
Mouth disinfection.

Faringosept *Terapia, Cz.†; Terapia, Hung.†; SC Terapia, Pol.; Terapia, Rus.*
Ambazone (p.1628·3).
Mouth and throat infections.

Faringotricina *SIT, Ital.*
Tyrothricin (p.358·2).
Stomatitis.

Farizym *Organon, India.*
Lipase (p.2360·3); protease; amylase (p.2256·3); cellulase (p.2279·1); bile extract (p.2266·2).
Fermentative dyspepsia; pancreatic deficiency; phytobezoar.

Farlac *Farmasa, Braz.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Farlev *Fahrenheit, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Farlidone *Farmilia, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Farlin *Continentales, Mex.*
Dipyrone (p.49·2).
Pain.

Farlipid *Farmedia, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Farludiol *Pfizer, Arg.*
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Farludiol Ciclo *Pfizer, Arg.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Farlupost *Pfizer, Chile.*
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).

Farlutal *Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.†; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Carlo Erba OTC, Ital.; Pharmacia, Malaysia†; Pfizer, Mex.†; Pharmacia, NZ†; Pfizer, Neth.†; Pfizer, Norw.; Pfizer, Singapore†; Kenfarma, Spain; Pharmacia, Swed.†; Pfizer, Switz.; Pfizer, Thai.; Deva, Turk.; Pfizer, UK†; Pharmacia, Venez.†.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; breast cancer; cachexia in HIV-positive patients; cancer associated cachexia; dysfunctional uterine bleeding; dysmenorrhoea; endometrial cancer; endometriosis; female infertility; functional uterine bleeding; hormone-dependent malignant neoplasms; menometrorrhagia; menopausal disorders; metrorrhagia; progestogen-only injectable contraceptive; secondary amenorrhoea; uterine cancer.

Farlutal Estrogeno *Pfizer, Chile†.*
11 Tablets, ethinylestradiol (p.2101·3); 10 tablets, ethinylestradiol; medroxyprogesterone acetate (p.2113·1).

Farlutale *Pfizer, Arg.*
Medroxyprogesterone acetate (p.2113·1).
Adenosis; malignant neoplasms; mastodynia; menopausal disorders; metrorrhagia; secondary amenorrhoea.

Farlutes *Pfizer, Chile.*
18 Tablets, estradiol valerate (p.2097·3); 13 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).

Farmabep *Farmaceutica H, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Farmabes *Fahrenheit, Indon.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Farmabex C *Fahrenheit, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C deficiency.

Farmacaina *Farma, Venez.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Farmacef *Farmaline, Thai.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Farmaciclin *Uno, Ital.*
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis.

Farmacne *OTC, Spain.*
Isotretinoin (p.1599·2).
Acne.

Farmacorti *Parggon, Mex.*
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Farmacorti YC *Parggon, Mex.*
⊗ Fluocinolone (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Farmacrol
Note.This name is used for preparations of different composition.
Fahrenheit, Indon.
Oral suspension: Aluminium hydroxide (p.1706·2); simeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity; gastritis; oesophagitis; peptic ulcer.

Fahrenheit, Indon.
Tablets: Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Flatulence; gastric hyperacidity; gastritis; oesophagitis; peptic ulcer.

Farmacrom *Alcon Cusi, Spain.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis; hay fever.

Farmadol *Fahrenheit, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Farmadral *Fahrenheit, Indon.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma.

Farmaflebon *Farmasa, Mex.*
Hydroxypolyethoxydodecanol (p.1916·1).
Oesophageal varices; telangiectasias.

Farmagola *Ribex, Ital.†.*
Cetylpyridinium chloride (p.1635·1); dichlorobenzyl alcohol (p.1642·1).
Mouth and throat irritation; mouth disinfection.

Farmakava *Farmaervas, Braz.†.*
Kava (p.2328·3).
Anxiety.

Farmalat *Fahrenheit, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Farmalcohol *Cinfa, Spain.*
⊗ Alcohol (p.1625·2); cetylpyridinium chloride (p.1635·1).
Disinfection.

Farmalex *Farmaline, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Farmalor *Farmaceutica H, Mex.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Allergic disorders.

Farmapram *IFA, Mex.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Farmaproina *Reig Jofre, Spain.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Farmasal *Fahrenheit, Indon.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Farmasept *Farmec, Ital.*
Didecyldimethylammonium chloride (p.1642·2).
Skin and wound disinfection.

Farmavon *Fahrenheit, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Farmaxetina *IFA, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Farmazol *Pharlab, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Farmeban *Farmasa, Mex.*
Diiodohydroxyquinoline (p.832·1); dimeticone (p.1770·2).
Amoebiasis.

Farmelox *Farmedia, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Farmiblastina *Kenfarma, Spain.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Farmicalcine *Farmilia, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Farmicam *Continentales, Mex.†.*
Piroxicam (p.117·3).

Farmicetina *Rontag, Arg.; Darrow, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections; bacterial infections.

Farmidal S *Continentales, Mex.*
Astemizole (p.567·2).

Farmidil *Relyo, Gr.†.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Farmifeno *Pharmacia, Arg.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Farmigras *Bajer, Arg.*
Sulfur (p.1614·1); resorcinol (p.1612·1).
Skin cleanser.

Farmin *Fahrenheit, Indon.*
⊗ Albumin (p.1052·1).
Hypoproteinaemia; plasma volume expansion.

Farmino *Bajer, Arg.*
Soap substitute.

Farmistin *Pharmacia, Ger.†.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Farmitrexat *Pharmacia, Ger.†.*
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis.

Farmocefe *Farmoz, Port.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Farmorol *Farmoz, Port.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Farmorrubicina *Pfizer, Chile.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Farmorubicin
Pfizer, Arg.; Pfizer, Austria; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hung.; Pharmacia, Israel; Kyowa, Jpn; Pfizer, Mex.; Pfizer, Norw.; Pharmacia, Pol.; Pharmacia Upjohn, Rus.; Pharmacia, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Carlo Erba, Turk.; Deva, Turk.; Pfizer, Venez.
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Pharmacia, Cz.
Epirubicin (p.716·2) or epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Farmorubicina *Pfizer, Braz.; Pharmacia, Ital.; Pfizer, Port.; Kenfarma, Spain.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Farmorubicine *Pfizer, Belg.; Pfizer, Fr.; Pfizer, Neth.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Farmotal *Pharmacia, Ital.*
Thiopental sodium (p.1795·2).
General anaesthesia.

Farmoten *Fahrenheit, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Farmoxicam *Pharlab, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Farmoxil *Elofar, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Farmoxyl *Fahrenheit, Indon.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Farm-X *Bajer, Arg.*
Zinc undecenoate (p.549·3); zinc oxide (p.1621·2); salicylic acid (p.1612·2); sodium propionate (p.545·3); coal tar (Alcoderm) (p.1616·2).
Burns; fungal skin infections; skin disorders; wounds.

Farm-X Duo *Bajer, Arg.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

Farm-X Ginecologico *Bajer, Arg.*
Metronidazole (p.837·1); neomycin sulfate (p.305·1).
Vaginal infections.

Farna FDG *Molypharma, Spain.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide for detection of malignant neoplasms by positron-emission tomography.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Farnat *Fahrenheit, Indon.*
Metronidazole (p.837·1).
Anaerobic infections.

Farnerate *Kuraray, Jpn.*
⊗ Prednisolone farnesil (p.1542·1).
Skin disorders.

Farnezone *Taiho, Jpn.*
⊗ Prednisolone farnesil (p.1542·1).
Skin disorders.

Farnitin *Lafare, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Farnitran *Fariberica, Port.*
Nitrendipine (p.1358·2).
Hypertension.

Farnormin *Fahrenheit, Indon.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Farocid *Faromed, Austria†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Farom *Asubio, Jpn.*
Faropenem sodium (p.276·2).
Bacterial infections.

Faros *Lichtwer, Ger.; Vifor, Switz.*
Crataegus (p.2289·1).
Cardiac disorders; heart failure.

Farpectol *Farcoral, Mex.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Farpik *Farcoral, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Farpresse *Pharmout, Port.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Farsix *Fahrenheit, Indon.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Farsorbid *Fahrenheit, Indon.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Fartadin *Farcoral, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Fartolin *Fahrenheit, Indon.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Fartolin Expectorant *Fahrenheit, Indon.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Fartoxol *Farcoral, Mex.†.*
Oxolamine citrate (p.1567·1).
Coughs.

Fartricon *Farcoral, Mex.*
Metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Fartropin *Continentales, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Fartussin *Farmaline, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Farvicett *Farmec, Ital.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin, wound, burn, and mucous membrane disinfection.

Farviran *Farmigea, Ital.†.*
Inosine pranobex (p.884·2).
Viral gynaecological infections.

Farviron *Mediapharm, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Farxen *Farcoral, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Inflammation; pain.

Fasarax *Prater, Chile.*
Hydroxyzine (p.581·2).

Fascar *Unison, Thai.*
Clarithromycin (p.248·2).
Bacterial infections.

Faselut *ICN, Arg.†.*
Progesterone (p.2125·1).

Fasiclor *Maver, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Fasidine *Siam Medicare, Thai.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Fasigin *Pfizer, Ital.*
Tinidazole (p.848·3).
Trichomoniasis.

Fasigin N *Pfizer, Ital.*
Tinidazole (p.848·3); nystatin (p.543·2).
Vulvovaginal trichomoniasis and candidiasis.

Fasigyn *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer, Israel; Pfizer, Malaysia†; Pfizer, Mex.; Pfizer, Neth.†; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, UK; Pfizer, Venez.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infection; giardiasis; trichomoniasis; ulcerative gingivitis.

Fasigyn Nistatina *Pfizer, Arg.*
Tinidazole (p.848·3); nystatin (p.543·2).
Vaginal trichomoniasis and candidiasis.

Fasigyn VT *Pfizer, Mex.*
Tinidazole (p.848·3); tioconazole (p.548·2).
Vaginal fungal and bacterial infections.

Fasigyne *Teofarma, Fr.; Pfizer, Switz.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Fasigyn-Nystatin *Pfizer, Indon.*
Tinidazole (p.848·3); nystatin (p.543·2).
Vaginal infections.

Faslodex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Fulvestrant (p.726·3).
Breast cancer.

Fasolan *Janssen-Cilag, Mex.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; migraine; vertigo.

Fasolon *Coronet, Indon.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Skin disorders.

Faspic
Zambon, Ital.; Sermmitr, Thai.; Zambon, Thai.
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Zambon, Port.
Ibuprofen arginine (p.65·2).
Fever; pain.

Fast *Perrigo, Israel.*
Calcium carbonate (p.1714·1).
Antacid; calcium supplement.

Fast Powder *Medochemie, Singapore.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial skin infections.

Fast-Acting Mylanta
Note.This name is used for preparations of different composition.
J&J-Merck, USA†.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; hyperacidity.

J&J-Merck, USA†.
Tablets: Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Hyperacidity.

Fastenyl *Viatris, Fr.*
Arginine aspartate (p.1928·2); vitamin C (p.1983·3).
Tonic.

Fastfen *Cristalia, Braz.*
⊗ Sufentanil citrate (p.125·1).
Pain.

Fastjekt
Allergopharma, Ger.; Allergopharma, Pol.
⊗ Adrenaline hydrochloride (p.1203·3).
Anaphylaxis.

Merck, Ital.
⊗ Adrenaline (p.1203·2).
Anaphylactic shock.

Fastjel *UFSA, Turk.*
Ketoprofen (p.73·1).
Musculoskeletal and joint pain.

Fastum *Menarini, Belg.; Raffo, Chile; Menarini, Cz.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Menarini, Irl.; Menarini, Ital.; Menarini, Malaysia; Berlin-Chemie, Pol.; Menarini, Port.; Menarini, Rus.; Adcock Ingram, S.Afr.; Menarini, Singapore; Guidotti, Spain; Menarini, Switz.; Menarini, Thai.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; thrombophlebitis.

Fasturtec *Sanofi Synthelabo, Austral.; Sanofi-Aventis, Belg.; Sanofi Synthelabo, Braz.; Sanofi Synthelabo, Canad.; Sanofi Synthelabo, Chile†; Sanofi Synthelabo, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi Synthelabo, Ital.; Sanofi-Aventis, NZ; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
Rasburicase (p.560·2).
Hyperuricaemia.

Fasulide *Bunker, Braz.*
Nimesulide (p.95·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fate Low Protein *Fate, UK.*
A range of low-protein foods for special diets (p.1922·1).

Fatec *Pharmahof, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic skin disorders; hypersensitivity reactions; rhinitis.

Father John's Medicine Plus *Oakhurst, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); guaifenesin (p.1561·3).
Coughs.

Fatidin *Cipan, Port.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fatigan Bronquial *Phoenix, Arg.†.*
⊗ Salbutamol sulfate (p.1131·3); theophylline (p.1140·1); ketotifen fumarate (p.582·2).
Obstructive airways disease.

Fatigon *Dankos, Indon.*
Vitamin B ; vitamin B ; vitamin B ; vitamin E; potassium aspartate; magnesium aspartate (p.1922·1).
Nutritional supplement.

Fatigue L5 *Homeocan, Canad.†.*
Homoeopathic preparation.

Fatigue Relief *Homeocan, Canad.*
Homoeopathic preparation.

Fatori 8Y *BPL-Meizler, Braz.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Fatoril *Farmaco, Mex.†.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fatral *Fahrenheit, Indon.*
Sertraline hydrochloride (p.421·3).
Depression.

Faulcris *Faulding, Port.†.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Faulcurium *Mayne, Port.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Fauldetic *Hospira, Port.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Fauldexato *Hospira, Port.*
Methotrexate (p.745·2).
Graft-versus-host disease; malignant neoplasms; psoriasis; rheumatoid arthritis.

Fauldoxo *Mayne, Port.*
Doxorubicin hydrochloride (p.712·2).

Faulplatin *Hospira, Port.*
Cisplatin (p.698·2).
Malignant neoplasms.

Faultenocan *Hospira, Port.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Faulviral *Hospira, Port.*
Aciclovir sodium (p.862·3).

Faustan *Temmler, Ger.*
Diazepam (p.986·3).
Anxiety disorders; premedication; skeletal muscle spasm; status epilepticus.

Fave di Fuca *Bayer, Ital.*
Bladderwrack (p.2384·2); cascara (p.1715·2); frangula (p.1732·2).
Constipation.

Faverin *Arrow, Austral.; Solvay, Hong Kong; Solvay, Irl.; Solvay, Philipp.; Solvay, S.Afr.; Solvay, Singapore; Solvay, Thai.; Eczacibasi, Turk.; Solvay, UK.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Favirab *Sanofi Pasteur, Cz.; Aventis Pasteur, Philipp.; Aventis Pasteur, Thai.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Favistan *Biochemie, Austria†; Asta Medica, Cz.†; Temmler, Ger.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Favorat *Aledicine, Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Favorex *TAD, Ger.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Favoxil *Agis, Israel.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Fawodin *Carbel, Mex.†.*
Famotidine (p.1730·1).
Peptic ulcer.

Faxet *Volta, Chile.*
Lidocaine hydrochloride (p.1862·3); methylrosanilinium chloride (p.1653·1).
Antiseptic.

Faxiden *Ifars, Indon.*
Piroxicam (p.117·3).
Osteoarthritis; rheumatoid arthritis.

Faximin *Sandoz, Mex.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Faxine *Wyeth Lederle, Ital.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression.

Faxiprol *Liconsa, Cz.*
Venlafaxine hydrochloride (p.427·3).
Depression; panic disorder.

Fayerex *Lafayette, Philipp.*
Carbocisteine (p.1553·2).
Cough.

FazaClo *Azur, USA.*
Clozapine (p.981·1).
Schizophrenia.

Fazalco *Alamo, USA†.*
Clozapine (p.981·1).
Schizophrenia.

Fazebit *Ultra, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Fazol
Note.This name is used for preparations of different composition.
CS, Fr.
Isoconazole nitrate (p.536·2).
Fungal skin infections.

Aurobindo, Philipp.
Cefazolin sodium (p.222·1).
Bacterial infections.

Dollder, Venez.
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Fazol G *CS, Fr.*
Isoconazole nitrate (p.536·2).
Vaginal candidiasis.

Fazolan *Etifar, Venez.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Fazolin
Note.This name is used for preparations of different composition.
Collins, Mex.
⊗ Naphazoline (p.1565·1).
Eye congestion.

Siam Bheasach, Thai.
Cefazolin (p.222·1).
Bacterial infections.

Fazolon *Ariston, Braz.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Fazonil *Corsalud, Venez.†.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Fazoplex *Inkeysa, Spain.*
Cefazolin sodium (p.222·1).
Bacterial infections.

FB Fer *Pharmasant, Thai.*
Ferrous fumarate (p.1938·3); vitamins; calcium; phosphorus (p.1922·1).
Iron-deficiency anaemia; vitamin and mineral supplement.

FBC *Ranbaxy, Thai.*
Ferrous fumarate (p.1938·3); vitamins; calcium phosphate (p.1922·1).
Anaemias.

FBC Plus *Ranbaxy, Thai.*
Ferrous fumarate (p.1938·3); vitamins; calcium phosphate; sodium fluoride (p.1922·1).
Iron-deficiency anaemia; vitamin and mineral supplement.

FBIC *Pond's, Thai.†.*
Ferrous fumarate (p.1938·3); vitamins; calcium phosphate (p.1922·1).
Anaemia.

FCE *Bago, Chile.*
Urogastrone (p.1778·1); sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

18F-FDG *BSM, Austria.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Assessment of regional glucose metabolism.

FDG Scan *Mallinckrodt, Cz.; Tyco, Spain.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Detection of malignant neoplasms; radionuclide diagnostic aid.

F-Din *Medimar, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

FDP *Fisiopharma, Ital.*
Fosfructose trisodium (p.2307·1).
Hypophosphataemia; ischaemic heart disease.

Fe^{50} *UCB, USA.*
Dried ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

FE Aspartate *Miller, USA.*
Ferrous aspartate (p.1938·2).
Iron supplement.

Feacef *Bros, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Fealin *Bros, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Febichol *Noventis, Cz.; Medphano, Ger.*
Fenipentol (p.2302·3).
Biliary-tract disorders.

Febiotec *Biofarma, Braz.†.*
⊗ Fenoterol hydrobromide (p.1121·1).
Asthma.

Febira *Zentiva, Cz.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Febmil *Milte, Ital.†.*
Dietary fibre supplement with vitamins (p.1922·1).
Fever; nutritional supplement.

Febralgin *Boehringer Ingelheim, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Febran *Columbia, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Febratic *Roemmers, Arg.; Rhein, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Febrax *Syntex, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Febrectal *Almirall, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Febrectol
Note. This name is used for preparations of different composition.
Winthrop, Fr.
Suppositories: Paracetamol (p.108·1); pine needle oil (p.2368·2).
Fever; pain.
Winthrop, Fr.†.
Tablets: Paracetamol (p.108·1).
Fever; pain.

Febricod *Douglas, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Febricol *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly contained chlorphenamine maleate, paracetamol, and phenylpropanolamine hydrochloride.
Allergic rhinitis; catarrh; cold and influenza symptoms.

Febridol *Douglas, Austral.; Cipla, India.*
Paracetamol (p.108·1).
Fever; pain.

Febrigrip *Monserrat, Arg.*
Paracetamol (p.108·1); butetamate citrate (p.1553·1); pseudoephedrine (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold and influenza symptoms.

Febrilin *Beres, Hung.*
Paracetamol (p.108·1).
Fever; pain.

Febrilite *Eulite, Neth.*
Homoeopathic preparation.

Febrimicina *Lazar, Arg.†.*
Tetracycline (p.347·1); dipyrone (p.49·2).
Bacterial infections.

Febrinil *Svizera, India; Oboi, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Febrisan *Nycomed, Cz.; Altana, Pol.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Febro-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Febrofen *Medana, Pol.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Febrofid *Medana, Rus.*
Ketoprofen lysine (p.73·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Febryn *Sunthi Sepuri, Indon.*
Ibuprofen (p.64·2).
Osteoarthritis; pain; rheumatoid arthritis.

Febs *Boots, Singapore.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; fever; pain; sinus congestion.

Febupen *EMS, Braz.*
Oxyphenbutazone (p.107·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Fecinole *Dosa, Arg.*
⊗ Letrozole (p.740·2).

Fecol
Note. This name is used for preparations of different composition.
Nakornpatana, Thai.
Syrup: Paracetamol (p.108·1); salicylamide (p.121·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; nasal congestion.
Nakornpatana, Thai.
Tablets: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; nasal congestion.

Fecontin-F *Modi-Mundipharma, India.*
Ferrous glycine sulfate (p.1939·1); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Fecontin-Z *Modi-Mundipharma, India.*
Ferrous glycine sulfate (p.1939·1); zinc sulfate (p.1999·2); folic acid (p.1940·1).
Iron, zinc, and folic acid deficiency in pregnancy.

Fectri *Parggon, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Fectrim *DDSA Pharmaceuticals, UK.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Fectrin *Bajamed, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Fedac *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; cold symptoms; sinusitis; upper respiratory-tract congestion.

Fedac Compound *DHA, Hong Kong; DHA, Singapore.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3); codeine phosphate (p.37·2).
Coughs; nasal congestion; upper respiratory-tract congestion.

Fedilex *Biotech, Venez.†.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; myocardial infarction.

Fedimed *Largen, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Fedin *Sandoz, Mex.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Fedip *Gebro, Austria.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Fedipin *Medikon, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction.

Fedolen *Viofar, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Fedra *Schering, Ital.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Fedra-Gel-S *Marching, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Fedral *Nycomed, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Fedratal *Etifar, Venez.†.*
⊗ Ephedrine hydrochloride (p.1558·2); aminophylline (p.1114·2); phenobarbital sodium (p.492·2); sodium benzoate (p.1630·2); sodium iodide (p.2169·2); chlorphenamine maleate (p.571·3).
Asthma.

Fedyclar *Schering-Plough, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Feel Chill *Cadila, India.*
Zinc oxide (p.1621·2); alum (p.2254·1); maize starch (p.1968·1); boric acid (p.2268·1); salicylic acid (p.1612·2); menthol (p.2340·1).
Prickly heat.

Feel Naturale *L'Oreal, Canad.*
SPF 15: Octinoxate (p.1608·2).
Sunscreen.

Feels *Laboratorios Chile, Chile.*
Carbomer (p.2141·3).
Vaginal lubricant.

Feen-A-Mint
Note. This name is used for preparations of different composition.
Interbelle, Arg.
Sodium picosulfate (p.1771·1).
Constipation.
Schering-Plough, Canad.†; Schering-Plough, USA.
Bisacodyl (p.1710·1).
Constipation.

Fefluzin *Biogal-Teva, Hung.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fefol
Note. This name is used for preparations of different composition.
Schering-Plough, Arg.; Pfizer Consumer, Austral.; GSK, India; Intrapharm, Irl.; SmithKline Beecham, S.Afr.; Intrapharm, UK.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.
Dollder, Venez.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Fefol-Vit *SmithKline Beecham, S.Afr.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances; vitamin C (p.1922·1).
Iron, folic acid, and vitamin deficiency in pregnancy.

Fefol-Z *GSK, India.*
Dried ferrous sulfate (p.1939·3); zinc sulfate (p.1999·2); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy and lactation.

FegaCoren *Vitorgan, Ger.†.*
Protein extracts from hepar, pancreas, thymus, lien, cor, ren, aorta, gland. suprarenal., mucosa intest., amnion, testes, gland. thyreoidea, diencephalon.
Cardiovascular and liver disorders.

FegaCoren N *Vitorgan, Ger.†.*
Protein extracts from hepar, pancreas, thymus, lien, cor, ren, aorta, gland. suprarenal., mucosa intest., amnion, testes, gland. thyreoidea, diencephalon; metenolone acetate; prednisolone acetate; liothyronine hydrochloride; deslanoside; alpha-tocoferil acetate; cyanocobalamin; pyridoxine hydrochloride.
Cardiovascular and liver disorders.

Fegenor *Leurquin, Fr.; Leurquin, Hong Kong.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fegran *Dovalle, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Feiba *Baxter Immuno, Arg.; Baxter, Austria; Baxter, Belg.; Immuno, Braz.†; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Immuno, Hong Kong†; Baxter, Hung.; Immuno, Israel; Baxter, Ital.; Baxter, Malaysia; Baxter, Mex.†; Baxter, NZ; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Adcock Ingram Critical Care, S.Afr.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.; Baxter BioScience, UK; Immuno, USA.*
A factor VIII inhibitor bypassing fraction (p.1068·2).
Haemorrhagic disorders.

Feisclin *Arlex, Mex.*
Clindamycin (p.251·1).
Acne.

Feklon *Klonal, Arg.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Felanor *LKM, Arg.*
Clonazepam (p.478·2).
Anxiety; epilepsy.

Felaxen *Labomed, Chile†.*
Aloin (p.1705·3); belladonna (p.2263·3); phenolphthalein (p.1762·1).
Constipation.

Felbamyl *Schering-Plough, Arg.*
Felbamate (p.481·1).
Epilepsy.

Felbatol *Wallace, USA.*
Felbamate (p.481·1).
Epilepsy.

Felcam *Mugi, Indon.; Asian Pharm, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Feldanax *Geolab, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Feldegel *Pfizer Consumer, Spain.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Felden *Pfizer, Austria; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pfizer, Norw.; Pfizer, Swed.†; Pfizer, Switz.; Pfizer, Turk.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Feldene *Pfizer, Arg.†; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.†; Pfizer, Chile; Pfizer, Cz.†; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, S.Afr.†; Pfizer, Singapore; Nefox, Spain; Pfizer, Thai.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Piroxicam (p.117·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Feldenedi *Pfizer, Venez.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Feldixid *Galenium, Indon.*
Benzoyl peroxide (p.1590·2); sulfur (p.1614·1).
Acne.

Feldox *Farmion, Braz.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Feldran *Vitapan, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Felexin *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Singapore†; Remedica, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Felfar *Faran, Gr.*
Magaldrate (p.1742·3).
Antacid.

Feliberal *Silanes, Mex.*
Enalapril maleate (p.1276·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Felicium *Stada, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Feliden *Rowe-Fleming, Venez.†.*
Ceftriaxone (p.238·1).
Bacterial infections.

Felim *Sandoz, Philipp.; Sandoz, Thai.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felina *Naturale, Philipp.*
Vaginal lubricant.
Vaginal dryness and pain.

Felipram *Crinos, Ital.*
Citalopram hydrobromide (p.385·3).
Anxiety disorders; depression.

Felis *Hexal, Arg.†; Hexal, Austria†; Hexal, Ger.; Ilsan, Turk.*
St John's wort (p.422·3).
Anxiety; depression; nervous disorders.

Feliselin *Rafarm, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Felisep *Rowe-Fleming, Venez.†.*
Clindamycin (p.251·1).
Bacterial infections.

Felisio *Sandoz, Cz.*
St John's wort (p.422·3).
Depression.

Felison *Bayer, Ital.*
Flurazepam monohydrochloride (p.999·1).
Insomnia.

Felix *Elpen (Ελπεν), Gr.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Felixene *Quimifar, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Feliximir *Krugher, Ital.*
Citalopram hydrobromide (p.385·3).
Anxiety disorders; depression.

Felixina *Lamsa, Arg.*
Fluoxetine (p.397·3).
Depression.

Felixsan *Stada, Austria.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Fellafit *Sahabat, Indon.*
Shark cartilage (p.2277·3).
Joint disorders.

Feller *Makros, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Felo *Pacific, NZ.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felobeta *Betapharm, Ger.*
Felodipine (p.1285·3).
Hypertension.

Felobits *Duncan, Arg.*
⊗ Atenolol (p.1217·3).
Hypertension.

Felocor *Hexal, Cz.; Hexal, Ger.*
Felodipine (p.1285·3).
Hypertension.

Feloday *AstraZeneca, Ital.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felodil *Ecosol, Switz.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felodin *Pharmacodane, Denm.*
Felodipine (p.1285·3).
Hypertension.

Felodip *Ivax, Rus.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felodistad *Stada, Austria.*
Felodipine (p.1285·3).
Hypertension.

Felodur *Alphapharm, Austral.*
Felodipine (p.1285·3).
Hypertension.

Felogamma *Worwag, Ger.*
Felodipine (p.1285·3).
Hypertension.

Felogard *Cipla, India.*
Felodipine (p.1285·3).
Hypertension.

Felogel *Sopharma, Pol.*
Diclofenac (p.44·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Felohexal *Hexal, Pol.; Sandoz, Thai.*
Felodipine (p.1285·3).
Hypertension.

Felop *Shou Chan, Philipp.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felo-Puren *Alpharma-Isis, Ger.*
Felodipine (p.1285·3).
Hypertension.

Feloran *Pharmacia, Cz.†; Pharmachim, Rus.†; Sopharma, Rus.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Felosma *Bernofarm, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Feloten *Biolab, Thai.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Felotens *Genus, UK.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Felrox *Seng, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Felsol *Pasteur, Chile.*
Fluconazole (p.532·1).
Fungal infections.

Felxicam *Hovid, Hong Kong†; Hovid, Malaysia†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Fem-I *BDI, USA†.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).
Pain.

Fem 7 *Merck, Arg.†; Merck, Braz.; Merck, Chile; Merck, Cz.†; Solvay, Ger.; Merck, Hong Kong†; Merck, Indon.; Merck, Mex.; Merck, Neth.; Richter, Pol.; Merck, Singapore†; Vifor, Switz.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Fem 7 Combi *Merck, Arg.†; Merck, Chile; Solvay, Ger.; Richter, Pol.; Vifor, Switz.*
Phase I patch, estradiol (p.2097·2); phase II patch, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Fem Ducha *Arex, Venez.*
Acetic acid (p.2244·2).
Maintenance of vaginal pH.

Fem pH *Pharmics, USA.*
Glacial acetic acid (p.2244·2); hydroxyquinoline sulfate (p.2323·1).
Vaginal disorders.

Fem 7 Sequi *Merck, Neth.*
Patch I, estradiol (p.2097·2); patch II, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Femafit *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement for women.

Femalon *Silesia, Chile.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femanest *Sandoz, Denm.; AstraZeneca, Swed.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Femanor *Sandoz, Denm.; AstraZeneca, Swed.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Femapak *Solvay, UK.*
Combination pack: Patches, estradiol (p.2097·2) (Fematrix); tablets, dydrogesterone (p.2096·2) (Duphaston).
Menopausal disorders; osteoporosis.

Femapirin *Chefaro, Neth.*
Ibuprofen (p.64·2).
Dysmenorrhoea.

Femaplus N Dr Hagedorn *Naturarzneimittel, Ger.*
Homoeopathic preparation.

Femar *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
⊗ Letrozole (p.740·2).
Breast cancer.

Femara *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Chugai, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
⊗ Letrozole (p.740·2).
Breast cancer.

Femarate *Pharmasant, Thai.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Femasekvens *Sandoz, Denm.; AstraZeneca, Swed.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Femaston *Solvay, Gr.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Hormone replacement therapy.

Fematab *Solvay, Irl.*
Estradiol (p.2097·2).
Menopausal disorders.

Fematrix *Solvay, UK.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femavit *Pharmacia, Ger.†.*
21 Tablets, conjugated oestrogens (p.2087·2); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Femcon Fe *Warner Chilcott, USA.*
21 Tablets, ethinylestradiol (p.2101·3); norethisterone (p.2119·3); 7 tablets, ferrous fumarate (p.1938·3).
Formerly known as Ovcon 35 Fe.
Combined oral contraceptive.

Femease *Robinson, UK.*
Self-heating adhesive pad.
Dysmenorrhoea.

Femelle *Gynopharm, Chile.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Femen *Osotspa, Thai.*
Mefenamic acid (p.80·1).
Pain.

femena *Hexal, Ger.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Femenal *Wyeth, Philipp.*
Ethinylestradiol (p.2101·3); norgestrel (p.2121·2).
Combined oral contraceptive; dysfunctional uterine bleeding; endometriosis.

Femendol *Biotech Naturis, Venez.*
Chamomile (p.2279·3); piscidia (p.2328·1); valerian (p.2410·1).
Vaginal inflammation.

Femerital *Interlogim, Neth.*
Ambucetamide (p.2255·2); paracetamol (p.108·1); caffeine hydrate (p.1117·1).
Dysmenorrhoea.

Femex *Roche, Neth.†.*
Naproxen sodium (p.92·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Femexin *Elea, Arg.; Elea, Mex.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

FemHRT *Pfizer, Austria†; Galen, Canad.; Warner Chilcott, USA.*
Ethinylestradiol (p.2101·3); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Femi *Sanol, Ger.; Schwarz, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Femiane *Schering, Arg.; Schering, Braz.; Schering, Venez.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Femibel *Silesia, Chile.*
Esterified oestrogens (p.2097·1).
Menopausal disorders; osteoporosis.

Femibion *Merck, Chile†.*
Vitamin and mineral preparation (p.1922·1).

Femicaps *Zuoz, Venez.*
Ibuprofen (p.64·2).
Inflammation; pain.

Femicine *Vifor, Switz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Femicur N *Schaper & Brummer, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Femi-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Femiderm *Novartis, Chile.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femidot *Novartis, Chile.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femigel *Medi Challenge, S.Afr.*
Estradiol (p.2097·2).
Menopausal disorders.

Femigestrol *Bergamo, Braz.*
Megestrol acetate (p.2114·3).

Femigoa *Wyeth, Ger.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Femihexal *Hexal, Cz.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

Femikliman uno *Hexal, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Femilar *Schering, Fin.*
Cyproterone acetate (p.2088·2); estradiol valerate (p.2097·3).
Biphasic oral contraceptive.

Femilla N *Steigerwald, Ger.†.*
Cimicifuga (p.2282·1).
Dysmenorrhoea.

Femilon *Organon, India.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Femilyane *Biorga, Fr.*
Soap substitute.
Personal hygiene.

Femina
Note.This name is used for preparations of different composition.
Ache, Braz.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

General Drug, Philipp.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Folate deficiency; iron-deficiency anaemia.

Feminac *Spirig, Switz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent alopecia, hirsutism, and seborrhoea in women.

Feminalin *Farma Lepori, Spain.*
Ibuprofen (p.64·2).
Fever; pain.

Feminax
Note.This name is used for preparations of different composition.
Konimex, Indon.
Paracetamol (p.108·1); hyoscyamine (p.1736·1).
Pain.

Bayer, Irl.; Roche Consumer, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); hyoscine hydrobromide (p.1734·1).
Dysmenorrhoea.

Feminax Ultra *Bayer, UK.*
Naproxen (p.92·3).
Dysmenorrhoea.

Femin-Do *Grasler, Ger.*
Homoeopathic preparation.

Feminease *Parnell, USA.*
Vaginal moisturising and lubricating cream with eriodictyon (p.1560·2).

Feminella *Viofar, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Infected skin disorders.

Femineo *Ducto, Braz.†.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Injectable contraceptive.

Feminesse *Anglian, UK.*
Sorbic acid; glycerol; liquid paraffin; polycarbophil.
Vaginal odour.

Feminet *Dexxon, Israel.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Feminex *Sante Naturelle, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Feminil *Durascan, Denm.*
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Combined oral contraceptive in women with androgenic symptoms.

Feminine Herbal Complex *GNLD, Austral.*
Wild yam root; red sage (p.2382·3); St John's wort (p.422·3); vitex agnus castus (p.2249·1); alchemilla vulgaris; dong quai (p.2297·3); skullcap (p.2388·2); ginger (p.1732·3); taraxacum (p.2395·1); liquorice (p.1740·3).
Menstrual disorders.

Feminique *QHP, USA.*
Vinegar (p.2244·2).
Vaginal disorders.

Feminoflex *Help, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Feminol *Laboratorios Chile, Chile.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Feminon *Cesra, Cz.†.*
Homoeopathic preparation.

Feminon A *Cesra, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Feminon C *Cesra, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Feminon N *Cesra, Ger.*
Homoeopathic preparation.

Feminosan *Pasteur, Chile†.*
Propyphenazone (p.119·3); caffeine (p.1116·3).
Dysmenorrhoea.

Feminova *Merck, Belg.; Theramex, Port.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Feminova Plus *Merck, Belg.*
Phase I patch, estradiol (p.2097·2); phase II patch, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Feminova-T *Silesia, Chile.*
⊗ Esterified oestrogens (p.2097·1); methyltestosterone (p.2117·1).
Menopausal disorders; osteoporosis.

Feminvit *Ativus, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Femipak *Sanova, Austria.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Femiplante *Farmasierra, Spain.*
Agnus castus (p.2249·1).
Menstrual disorders.

Femiplus *Quesada, Arg.†.*
Vitamin E; vitamin B ; vitamin A (p.1922·1).

Femipres *Schwarz, Ital.*
Moexipril hydrochloride (p.1343·2).
Hypertension.

Femipres Plus *Schwarz, Ital.*
⊗ Moexipril hydrochloride (p.1343·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Femiprim *Armstrong, Mex.*
Ascorbic acid (p.1983·3).
Bacterial vaginosis; maintenance of vaginal flora and pH.

Femiron *Menley & James, USA.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Femiron Multi-Vitamins and Iron *Menley & James, USA†.*
Multivitamin preparation with iron and folic acid (p.1922·1).

Femisan *Grossman, Mex.*
Ketoconazole (p.539·1); clindamycin phosphate (p.251·2).
Vaginitis.

Femisana *Riemser, Ger.†.*
Agnus castus (p.2249·1); greater celandine (p.2317·1); cimicifuga (p.2282·1); phosphorus.
Gynaecological disorders.

Femisana gyn *Cheplapharm, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Femisana H *Cheplapharm, Ger.*
Homoeopathic preparation.

Femisana mens *Cheplapharm, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Femisic *Caprifarmindo, Indon.; Sanbe, Indon.*
Mefenamic acid (p.80·1).
Pain.

Femitan *Schwabe, Hung.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Femitres *Silesia, Chile.*
84 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, placebo.
Combined oral contraceptive; menstrual disorders.

Femity *Theramex, Ital.*
Estradiol (p.2097·2); levonorgestrel (p.2121·2).
Menopausal disorders.

Femixol *Omega, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Femizol *Douglas, Austral.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Femizol-M *Lake, USA.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Femme *Ache, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Femme Free *Douglas, Austral.*
Naproxen (p.92·3).
Dysmenorrhoea.

FemmeVit *Pharmadass, UK.*
Vitamin, mineral, and nutritional preparation (p.1922·1).
Premenstrual syndrome.

Femmex Plus *Konsuma, Venez.*
Ibuprofen (p.64·2).
Dysmenorrhoea.

Femmexultra *Konsuma, Venez.*
Ibuprofen (p.64·2); caffeine (p.1116·3).
Inflammation; pain.

Fem-Mono *Merck, Denm.; Scand Pharm, Swed.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Femnet *Inibsa, Port.†.*
Genistein (p.2391·2); daidzein (p.2391·2).
Menopausal disorders.

Femodeen *Schering, Neth.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Femoden *Schering, Cz.; Schering, Fin.; Schering, Hung.; Schering, Pol.; Schering, Rus.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Femoden ED *Schering, Austral.*
21 Tablets, ethinylestradiol (p.2101·3); gestodene (p.2105·2); 7 tablets, inert.
Combined oral contraceptive.

Femodene *Schering, Belg.; Schering, Irl.†; Schering, NZ; Bayer, UK.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Femodene ED *Schering, S.Afr.*
21 Tablets, ethinylestradiol (p.2101·3); gestodene (p.2105·2); 7 tablets, inert.
Combined oral contraceptive.

Femodette *Bayer, UK.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Femogyn *Pelpharma, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, and hirsutism in women; oral contraceptive in women with androgenic symptoms.

Femolin PMS *Tribest, S.Afr.*
Evening primrose oil (p.2302·1); vitamins; minerals (p.1922·1).
Dietary supplement.

Femorel *Elea, Arg.*
Ibandronate sodium (p.1098·3).
Osteoporosis.

Femorel Max *Elea, Arg.*
1 tablet, ibandronate sodium (p.1098·3); 30 tablets, calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Femosa *Pyridam, Indon.*
Cimicifuga (p.2282·1); red clover (p.2285·1); isoflavone (p.2391·2); tyrosine; folic acid; vitamin B ; vitamin B ; calcium; vitamin D (p.1922·1).
Hypercholesterolaemia; menopausal disorders; osteoporosis.

Femoston *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Solvay, Braz.; Grunenthal, Chile; Solvay, Cz.; Solvay, Fin.; Solvay, Ger.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Irl.; Solvay, Ital.; Solvay, Malaysia; Solvay, Neth.; Solvay, Philipp.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Solvay, Singapore; Solvay, Switz.; Solvay, UK; Zuoz Solvay, Venez.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; dydrogesterone (p.2096·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Femoston 1/5 *Solvay, Port.; Solvay, Rus.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Femoston 1/10 *Solvay, Thai.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Femoston Conti *Solvay, Austria; Solvay, Belg.; Solvay, Braz.; Grunenthal, Chile; Solvay, Cz.; Solvay, Fin.; Solvay, Ger.; Solvay, Irl.; Solvay, Ital.; Solvay, Malaysia; Solvay, Pol.; Solvay, S.Afr.; Solvay, Singapore; Solvay, Switz.; Solvay, Thai.; Solvay, UK; Zuoz Solvay, Venez.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Femoston Continu *Solvay, Neth.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Femoston mono *Solvay, Ger.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femovan *Schering, Ger.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Fempack *Pfizer, Arg.*
Tablets, estradiol valerate (p.2097·3); capsules, progesterone (p.2125·1).
Menopausal disorders; osteoporosis.

FemPatch *Parke, Davis, USA.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency.

Femphascyl
Note. This name is used for preparations of different composition.
Solvay, Austria.
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Solvay, Port.†.
Ethinylestradiol (p.2101·3); dydrogesterone (p.2096·2).
Menopausal disorders.

Femphascyl conti *Solvay, Austria.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Femphascyl Continu *Solvay, Neth.*
Estradiol (p.2097·2); dydrogesterone (p.2096·2).
Menopausal disorders; osteoporosis.

Fempress *Gebro, Austria; Alpharma-Isis, Ger.*
Moexipril hydrochloride (p.1343·2).
Hypertension.

Fempress Plus *Gebro, Austria; Alpharma-Isis, Ger.*
⊗ Moexipril hydrochloride (p.1343·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Fempro *Cipla, India.*
⊗ Letrozole (p.740·2).
Breast cancer.

Femranette mikro *Wyeth, Ger.†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Femring *Galen, Neth.†; Galen, Port.; Warner Chilcott, USA.*
Estradiol acetate (p.2097·2).
Menopausal disorders.

Femsedin Kutz *Quimica y Farmacia, Mex.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Femsel *Elmor, Venez.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Femsept *Theramex, Mon.*
Estradiol (p.2097·2).
Menopausal disorders.

FemseptCombi *Theramex, Mon.*
Patch 1, estradiol (p.2097·2); patch 2, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Femsete *Theramex, Port.*
Estradiol (p.2097·2).
Menopausal disorders.

Femsete Combi *Theramex, Port.*
Phase 1 patch, estradiol (p.2097·2); phase 2 patch, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Femsete Evo *Theramex, Port.*
Estradiol (p.2097·2); levonorgestrel (p.2121·2).
Menopausal disorders.

FemSeven *Merck, Austria; Merck, Fin.; Gedeon Richter, Hung.; Bracco, Ital.; Merck, Swed.; Golaz, Switz.†; Merck, UK; Merck, Venez.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

FemSeven Combi *Merck, Austria; Merck, Fin.; Gedeon Richter, Hung.*
Phase 1 patch, estradiol (p.2097·2); phase 2 patch, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

FemSeven Conti *Merck, UK.*
Estradiol (p.2097·2); levonorgestrel (p.2121·2).
Menopausal disorders.

FemSeven Sequi *Merck, UK.*
Phase 1, estradiol (p.2097·2); phase 2, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

FemSieben *Merck, Austria.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

FemTab *Merck, UK†.*
Estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

FemTab Continuous *Merck, UK†.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

FemTab Sequi *Merck, UK†.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Femtrace *Warner Chilcott, USA.*
Estradiol acetate (p.2097·2).
Menopausal disorders.

Femtran *3M, Austral.; 3M, NZ.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Femulen *Searle, Cz.†; Pharmacia, Israel†; Pharmacia, NZ; Pharmacia, UK.*
Etynodiol diacetate (p.2103·2).
Progestogen-only oral contraceptive.

Fenabbott *Armstrong, Mex.*
Phenobarbital (p.492·2).
Epilepsy.

Fenac
Alphapharm, Austral.; LBS, Malaysia; LBS, Thai.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Neves, Port.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fenactil *Jelfa, Pol.; Polfa Warszawa, Pol.; Unia, Pol.*
Chlorpromazine hydrochloride (p.969·2).
Extrapyramidal disorders; hiccup; nausea and vomiting; porphyria; premedication; psychoses; withdrawal syndromes.

Fenactol *Discovery, UK.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenadef *Dong Wha, Philipp.; Unimex, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Fenadium *Sunward, Malaysia†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal and biliary colic.

Fenadol *Proge, Ital.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Fenafex *Sriprasit, Thai.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fenaflan *Teuto, Braz.*
Diclofenac diethylamine (p.44·3) or diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fenagel
Euromex, Mex.
Diclofenac (p.44·2).
Inflammation.

SM, Thai.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Fenahex *Hexal, Philipp.; Salutas, Philipp.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Fen-Alcon *Alcon, Philipp.*
Chloramphenicol (p.239·3).
Eye infections.

Fenalgin *Tocogino, Mex.*
Diclofenac (p.44·2).
Inflammation; pain.

Fenam *Lamda (Λαμδα), Gr.†.*
Etofenamate (p.53·1).
Anti-inflammatory; pain.

Fenamic
Note. This name is used for preparations of different composition.
Enila, Braz.†.
Tolfenamic acid (p.130·1).
Inflammation.

Siam Bheasach, Thai.
Mefenamic acid (p.80·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenamide *Farmigea, Ital.*
⊗ Diclofenamide (p.1880·2).
Glaucoma.

Fenamin *Pharmacare, S.Afr.*
Mefenamic acid (p.80·1).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Fenamine *Fawns & McAllan, Austral.†.*
Pheniramine maleate (p.587·3).
Hypersensitivity reactions; motion sickness; vestibular disorders.

Fenamon *Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; myocardial infarction; pulmonary hypertension.

Fenantoin *Recip, Swed.*
Phenytoin (p.495·2).
Epilepsy.

Fenapaed *AFT, NZ.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenaplus *Modi-Mundipharma, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Inflammation; musculoskeletal and joint disorders; pain.

Fenaplus-MR *Modi-Mundipharma, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Painful muscle spasm; premenstrual syndrome.

Fenardin *Schwarz, Pol.*
Fenofibrate (p.1286·2).
Hypercholesterolaemia.

Fenaren
Mundipharma, Austria; Bernofarm, Indon.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Uniao Quimica, Braz.
Diclofenac diethylamine (p.44·3), diclofenac sodium (p.44·3), or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fenarol-S *Sanofi Synthelabo, Chile†.*
Chlorzoxazone (p.1894·3).
Musculoskeletal spasm.

Fenason *Unison, Hong Kong†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; asthma.

Fenaspec *Pharmaspec, Philipp.*
Diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Fenatrop *Gador, Arg.*
Trimebutine maleate (p.2404·3).
Gastrointestinal spasm.

Fenatrop-A *Gador, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).
Gastrointestinal disorders.

Fenavel *Novell, Indon.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; postoperative pain.

Fenax *Andromaco, Chile.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis.

Fenazid *Pharmsintez, Rus.*
Isoniazid ferrous sulfate dihydrate complex.
Tuberculosis.

Fenazil *Sella, Ital.*
Promethazine hydrochloride (p.588·2).
Allergic skin reactions.

Fenazin *Synco, Hong Kong.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; nausea and vomiting; sedative.

Fenbid *Goldshield, UK.*
Ibuprofen (p.64·2).
Inflammation; pain.

Fenburil *De Mayo, Braz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fendazol *Lepori, Port.†.*
Ditazole (p.1271·2).
Thromboembolic disorders.

Fender *Krugher, Ital.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Fendibina *Northia, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Fendin *Ranbaxy, S.Afr.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Fendiprazol *Northia, Arg.*
Omeprazole (p.1753·1).
Peptic ulcer.

Fendrix *GSK, Belg.; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Neth.; GSK, Norw.; GSK, UK.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Fendyl *Jean-Marie, Hong Kong.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Cold symptoms; coughs.

Fenemal *Nycomed, Denm.; SAD, Denm.; Nycomed, Norw.; Recip, Swed.*
Phenobarbital (p.492·2).
Epilepsy; pre-eclampsia; withdrawal syndromes.

Fenergan
Aventis, Arg.; Vitoria, Port.; Aventis, Venez.†.
Promethazine hydrochloride (p.588·2).
Cough; hypersensitivity reactions; insomnia; motion sickness; parkinsonism; urticaria.

Sanofi-Aventis, Braz.
Promethazine (p.588·2) or promethazine hydrochloride (p.588·2).
Adjunct to analgesia and anaesthesia; hypersensitivity reactions; insomnia; nausea and vomiting; sedative.

Fenergan Expectorante *Sanofi-Aventis, Braz.; Teofarma, Spain.*
Promethazine hydrochloride (p.588·2); sulfogaiacol (p.1573·2); ipecacuanha (p.1562·3).
Upper-respiratory-tract disorders.

Fenergan Topico *Teofarma, Spain.*
Promethazine (p.588·2).
Cutaneous hypersensitivity reactions.

Fenesin *DJ, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Fenesin DM *Pharma Medica, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Fenfedrin *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Fengam *Pharmasant, Thai.*
Tiaprofenic acid (p.129·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Feniclor *Luper, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Fenicloran *Neckerman, Braz.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Fenicol *Armoxindo, Indon.; Offenbach, Mex.; Pharmasant, Thai.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Fenicort *Jelfa, Pol.*
⊗ Prednisolone sodium tetrahydrophthalate (p.1542·1).
Corticosteroid.

Fenidantoin S *Altana, Mex.*
Phenytoin sodium (p.495·2).
Epilepsy.

Fenidex *Allergan, Braz.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3); tetryzoline hydrochloride (p.1574·1).
Infected eye disorders.

Fenidin *Merkez, Turk.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Respiratory-tract congestion.

Fenidina *Boniscontro & Gazzone, Ital.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Feniffler *Loeffler, Mex.*
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Epilepsy.

Fenigramon *Gramon, Arg.*
Phenytoin sodium (p.495·2).
Epilepsy.

Fenil-Livre *Mead Johnson, Port.†.*
Preparation for enteral nutrition (p.1922·1).
Phenylketonuria.

Fenilona *Rowe-Fleming, Venez.†.*
⊗ Magnesium pemoline (p.2161·3).

Fenil-V *Vitoria, Port.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis; pain.

Feninox *Gunsa, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Fenint *Pharmacia, Ger.†.*
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Fenipred *Atlas, Arg.*
⊗ Prednisolone sodium phosphate (p.1541·2); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Fenisal *Macrophar, Thai.*
Baclofen (p.1888·1).
Skeletal muscle spasticity.

Fenisol *Reuffer, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Fenisona *Phoenix, Arg.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Fenistil
Note.This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis Consumer, Cz.; Novartis, Gr.; Novartis Consumer, Hung.; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis, Norw.†; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Spain; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Venez.†.
Dimetindene maleate (p.576·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions; insect bites; premedication; pruritus; skin irritation; sunburn; urticaria.

Novartis Consumer, UK.
Penciclovir (p.901·2).
Herpes labialis.

Novartis Consumer, Ger.†.
Cream: Tripelennamine hydrochloride (p.592·2).
Pruritic skin disorders.

Novartis Consumer, Ger.
Delayed-release capsules; injection; nasal spray; oral drops; syrup; tablets; topical gel: Dimetindene maleate (p.576·3).
Hypersensitivity reactions; pruritic skin disorders.

Novartis Consumer, Ger.†.
Eye drops: Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Fenistil Hydrocort *Novartis Consumer, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Fenistil Pencivir *Novartis Consumer, Ger.; Novartis Consumer, Rus.*
Penciclovir (p.901·2).
Herpes labialis.

Fenit *Antibioticos, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Fenital *Cristalia, Braz.*
Phenytoin (p.495·2).
Epilepsy.

Fenitan *Pharmis, Port.*
Phenytoin sodium (p.495·2).
Arrhythmias associated with digitalis toxicity; epilepsy.

Fenitenk *Biotenk, Arg.*
Phenytoin sodium (p.495·2).
Epilepsy.

Fenitina *Leovan, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Feniton *Teuto, Braz.*
Phenytoin (p.495·2).
Epilepsy.

Fenitron *Psicofarma, Mex.*
Phenytoin sodium (p.495·2).
Epilepsy.

Fenivir *Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Port.*
Penciclovir (p.901·2).
Herpes labialis.

Fenizolan *Organon, Ger.*
Fenticonazole nitrate (p.531·3).
Vulvovaginal candidiasis.

Fenizzard *Pizzard, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Fenlodac *Ipca, India†.*
Diclofenac (p.44·2).
Fever; inflammation; pain.

Fenn *Sriprasit, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Fennings Childrens Cooling Powders *Anglian, UK.*
Paracetamol (p.108·1).
Fever; pain.

Fennings Little Healers *Anglian, UK.*
Ipecacuanha (p.1562·3).
Formerly known as Jacksons Little Healers.
Coughs.

Feno *YSP, Malaysia.*
⊗ Fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Fenobest *Best, Mex.*
⊗ Tamoxifen (p.775·1).
Breast cancer; endometrial cancer.

Fenobeta *Betapharm, Ger.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenobrat *BMS, Hung.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenobrate *Sanofi Synthelabo, Arg.*
Fenofibrate (p.1286·2).
Atherosclerosis; hyperlipidaemias.

Fenocin *Actavis, Indon.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Fenoclof *Pharmanel, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Fenocris *Cristalia, Braz.*
Phenobarbital (p.492·2).
Anxiety; epilepsy; hyperbilirubinaemia; insomnia; premedication; sedation.

Fenodid *Pisa, Mex.*
⊗ Fentanyl citrate (p.55·3).
General anaesthesia; neuroleptanalgesia.

Fenofanton *Juta, Ger.; Q-Pharm, Ger.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenofitop *Topgen, Belg.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenofix *Ingers, Cz.*
Fenofibrate (p.1286·2).
Hypercholesterolaemia.

Fenogal *SMB, Belg.; Genus, UK.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenogal Lidose *SMB, Singapore.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenogar *Ibefar, Braz.†.*
Agar (p.2140·3); dantron (p.1722·2); phenolphthalein (p.1762·1); liquid paraffin (p.2030·3).
Constipation.

Fenogel *Basi, Port.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Fenokodin
Note.This name is used for preparations of different composition.
Adeka, Turk.
Syrup: ⊗ Codeine (p.37·2); ephedrine hydrochloride (p.1558·2); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3).
Respiratory-tract congestion.

Adeka, Turk.
Tablets: Codeine (p.37·2); ethylmorphine (p.52·2).
Respiratory-tract congestion.

Fenokomp 39 *Knop, Chile.*
Phenolphthalein (p.1762·1); citric acid (p.2284·1); nux vomica (p.2355·3); belladonna (p.2263·3).
Constipation.

Fenolax *ICN, Cz.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Fenolftaleina Compuesta *Hochstetter, Chile†.*
Phenolphthalein (p.1762·1); belladonna (p.2263·3); nux vomica (p.2355·3).
Constipation.

Fenolip
Note.This name is used for preparations of different composition.
Hexal, Arg.†; Lannacher, Austria; Cipla, India.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lepori, Port.
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Feno-Micro *Apotex, Hung.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenopine *Pinewood, Irl.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fenopol *Gache, Venez.†.*
Hyoscine hydrobromide (p.1734·1); atropine sulfate (p.1219·3); phenobarbital (p.492·2).
Abdominal pain; sedative.

Fenopron *Aspen, S.Afr.†; Typharm, UK; Lilly, Venez.†.*
Fenoprofen calcium (p.55·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Fenoptic *Allergan, Port.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Fenoratio *Ratiopharm, Pol.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fenorin *Lek, Cz.; Lek, Hung.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Fenorit *Scharper, Ital.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Fenotral *Munir, Turk.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; motion sickness; vertigo.

Fenotricin *Dinafarma, Braz.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Fenovent *Cipla, India.*
⊗ Fenoterol (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Fenox
Note.This name is used for preparations of different composition.
Knoll, India.
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline nitrate (p.1565·2).
Nasal congestion.

Fournier, Thai.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Thornton & Ross, UK.
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Fenoxene *Samarth, India.*
Phenoxybenzamine hydrochloride (p.1369·3).
Neuropathic bladder; phaeochromocytoma.

Fenoxil *Biomep, Mex.*
Nimesulide (p.95·3).
Pain.

Fenozan *Zambon, Braz.*
⊗ Fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Fenpaed *Pinewood, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Fenpic *Andromaco, Chile†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Fenris *Interbat, Indon.*
Ibuprofen (p.64·2).
Fever; pain.

Fensaide *Nicholas Piramal, India†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Fensaide-P *Nicholas Piramal, India†.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Fensartan *Elea, Arg.*
Losartan potassium (p.1326·1).
Hypertension.

Fensartan D *Elea, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Fensedyl *Bernabo, Arg.*
Oxatomide (p.587·1).
Hypersensitivity reactions.

Fensel *Pharmacia, Spain.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Fensik *Mugi, Indon.*
Mefenamic acid (p.80·1).
Pain.

Fensipros *Pharos, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Fenspin *Basi, Port.†.*
Fenspiride hydrochloride (p.1122·1).

Fensum *Merckle, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Fentabbott *Abbott, Braz.*
⊗ Fentanyl citrate (p.55·3).
Anaesthesia.

Fentadur *Lavipharm, Gr.*
⊗ Fentanyl (p.55·3).
Pain.

Fentagesic *Pliva, Cz.*
⊗ Fentanyl (p.55·3).
Pain.

Fenta-Hameln *Astrapin, Ger.†; Curasan, Ger.†; Hameln, Ger.†.*
⊗ Fentanyl citrate (p.55·3).
Analgesia during anaesthesia; general anaesthesia; neuroleptanalgesia; premedication.

Fentahexal *Hexal, Cz.; Hexal, Pol.*
⊗ Fentanyl (p.55·3).
Pain.

Fental
Note.This name is used for preparations of different composition.
Alvia (Αλβια), Gr.
Ketotifen (p.582·2).
Allergic eye disorders.

Rowex, Irl.
⊗ Fentanyl (p.55·3).
Pain.

Fentalim *Angelini, Ital.*
⊗ Alfentanil hydrochloride (p.16·2).
General anaesthesia; neuroleptanalgesia.

Fentalis *Sandoz, Cz.; Sandoz, UK.*
⊗ Fentanyl (p.55·3).
Pain.

Fentanest
Cristalia, Braz.; Pharmacia, Ital.; Janssen-Cilag, Mex.; Janssen, Port.
⊗ Fentanyl citrate (p.55·3).
Analgesia during anaesthesia; general anaesthesia; neuroleptanalgesia.

Kern, Spain.
⊗ Fentanyl (p.55·3).
Analgesia during anaesthesia; premedication.

Fentatienil *Angelini, Ital.*
⊗ Sufentanil citrate (p.125·1).
General anaesthesia; neuroleptanalgesia.

Fentatil *Janssen-Cilag, Braz.*
⊗ Fentanyl (p.55·3).
Analgesia during anaesthesia; neuroleptanalgesia.

Fentax *Richmond, Arg.*
⊗ Fentanyl citrate (p.55·3).
Pain.

Fentazin *Goldshield, UK.*
Perphenazine (p.1017·1).
Anxiety; nausea; psychoses; vomiting.

Fentiderm *Pharmarecord, Ital.†.*
Fenticonazole nitrate (p.531·3).
Fungal skin and anogenital infections.

Fentigyn *Novartis, Ital.†.*
Fenticonazole nitrate (p.531·3).
Fungal vulvovaginal infections.

Fentina *LKM, Arg.*
Memantine (p.367·2).

Fentizol *Ache, Braz.*
Fenticonazole nitrate (p.531·3).
Fungal infections.

Fentoinal *Roemmers Rowe, Venez.*
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Epilepsy.

Fentora *Cephalon, USA.*
⊗ Fentanyl citrate (p.55·3).
Pain.

Fentos *Sanofi-Aventis, Chile†.*
Codeine phosphate (p.37·2); caffeine (p.1116·3); chlorphenamine (p.572·2).
Coughs.

Fentrinol *Fresenius Kabi, Austria.*
⊗ Amidefrine mesilate (p.1551·2).
Rhinitis.

Fentul *Ivax, Arg.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Fenugrene *Legras, Fr.*
Fenugreek (p.2303·3).
Appetite stimulant.

Fenules *Ranbaxy, Rus.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Fenuril *ACO Hud, Fin.; ACO Hud, Swed.*
⊗ Urea (p.1620·2).
Dry skin; dry skin disorders.

Fenuril-Hydrokortison *ACO Hud, Swed.*
⊗ Urea (p.1620·2); hydrocortisone (p.1535·2).
Eczema.

Fenyklovy Caj *Megafyt-R, Cz.*
Fennel (p.2302·3).
Catarrh; gastrointestinal disorders.

Fen-y-Tos *Nordin, Mex.*
Drosera (p.2297·3); tolu balsam (p.1574·2).
Coughs.

Feocyte *Dunhall, USA.*
Iron (p.1949·1); liver extracts (p.2337·3); folic acid (p.1940·1); vitamin B substances (p.1922·1); copper.
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Feofol *Vianex (Βιανεξ), Gr.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

FeoGen *Rising Pharmaceuticals, USA.*
Iron (p.1949·1); vitamin B (p.1980·2); stomach extract (p.2337·3).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

FeoGen FA *Rising Pharmaceuticals, USA.*
Iron; vitamin B ; vitamin C; folic acid (p.1922·1).
Anaemias.

Feosol *Valeant, Philipp.; SmithKline Beecham Consumer, USA.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Feospan *ICN, Hong Kong†; Intrapharm, Irl.; ICN, Malaysia†; ICN, Singapore†; Intrapharm, UK.*
Dried ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Feostat *Forest Pharmaceuticals, USA†.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemias.

Feovit *Dynamic, Philipp.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Feparil
Note.This name is used for preparations of different composition.
Phoenix, Arg.†.
Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Soft-tissue injury; venous disorders.

Madaus, Spain.
Diethylamine salicylate (p.47·2); aescin (p.2248·2); sodium aescin polysulfate (p.2248·2).
Peripheral vascular disorders.

Fepiram *Ferron, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Feprapax *Ashbourne, UK†.*
Lofepramine hydrochloride (p.407·1).
Depression.

Feprax *Ferron, Indon.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Feprorex *Medix, Mex.*
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Fer-200 *Hua, Thai.*
Ferrous fumarate (p.1938·3); vitamins; calcium phosphate (p.1922·1).
Anaemias.

Fer UCB *UCB, Fr.*
Ferrous chloride (p.1938·2).
Iron deficiency; iron-deficiency anaemia.

Feraken *Kendrick, Mex.*
Moclobemide (p.411·1).
Depression.

Ferane 35 *Cifarma, Braz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Ferasul *APT, Hong Kong.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Feratab *Upsher-Smith, USA.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemias.

Ferbeaplex *Beacons, Singapore.*
Dried ferrous sulfate (p.1939·3); thiamine hydrochloride; riboflavin; nicotinamide (p.1922·1).
Iron deficiency; iron-deficiency anaemia.

Ferbisol *Vegal, Spain.*
Ferrous glycine sulfate (p.1939·1).
Iron-deficiency anaemia.

Fercayl *Sterop, Belg.*
Iron dextran (p.1951·1).
Iron-deficiency anaemia.

Fercee *Armoxindo, Indon.*
Ferrous fumarate (p.1938·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p.1725·1) is included to reduce the constipating effects of iron.
Iron-deficiency anaemia.

Fercobre *Andromaco, Venez.†.*
Ferric ammonium citrate (p.1938·1); copper gluconate (p.1935·3).
Anaemias.

Fercobre B-12 *Andromaco, Venez.†.*
Ferric ammonium citrate (p.1938·1); vitamin B (p.1980·2).
Anaemias.

Fercor *Corsalud, Venez.†.*
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Fercovit *Andromaco, Chile†.*
Ferrous fumarate; calcium carbonate; magnesium oxide; vitamins (p.1922·1).
Dietary supplement.

Ferdek *Ranbaxy, Thai.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Ferdromaco *Andromaco, Arg.*
Ferrous succinate (p.1939·2).
Succinic acid is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferganic *Roemmers Osmoph, Venez.*
Iron protein.
Anaemias.

Ferganic Folic *Roemmers Osmoph, Venez.*
Iron protein; folic acid (p.1940·1).
Anaemia in pregnancy and lactation.

Fer-gen-sol *Goldline, USA.*
Ferrous sulfate (p.1939·3).
Iron deficiency anaemia.

Fergesol *IAE, Philipp.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron or folic acid deficiency.

Ferglobin *Pharmacare, Philipp.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Fergon *Sanofi Synthelabo, Austral.†; ICN, NZ†; Winthrop Consumer, USA.*
Ferrous gluconate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Fericip
Note. This name is used for preparations of different composition.
Cipla, India.
Capsules; chewable tablets: Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Cipla, India.
Oral drops; syrup: Iron polymaltose (p.1953·1).
Iron deficiency.

Ferid *Uniao Quimica, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Feridex *Temis, Arg.†; Advanced Magnetics, Israel†; Eiken, Jpn; Berlex, USA.*
Ferumoxides (p.1478·1).
Contrast medium for magnetic resonance imaging of the liver.

Ferifer *Streger, Mex.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferig *CT, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferin *Collins, Mex.†.*
Vitamin preparation with iron (p.1922·1).

Ferinject *Vifor, Cz.; Vifor, Switz.; Syner-Med, UK.*
Ferric carboxymaltose (p.1938·1).
Iron deficiency.

Fer-In-Sol *BMS, Arg.; Mead Johnson, Braz.; Mead Johnson Nutritionals, Canad.; BMS, Gr.†; BMS, Irl.; Mead Johnson, Ital.; BMS, Mex.; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, USA; BMS, Venez.*
Ferrous sulfate (p.1939·3).
Formerly known as Enfalac Fer-In-Sol in *Canad.*
Iron deficiency; iron supplement; iron-deficiency anaemia.

Ferinsol *Mead Johnson, Chile.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Fer-Iron *Rugby, USA†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemias.

Feritrin *Dexa, Indon.*
Iron polymaltose (p.1953·1); vitamin B substances; vitamin D; calcium lactate; copper sulfate; potassium iodide (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia; nutritional supplement.

Ferium *Pasteur, Chile.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Feriv *GES, Spain.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Ferlactis *AGIPS, Ital.†.*
Lactococcus lactis (p.2372·3).
Gastrointestinal disorders.

Ferlatum *Lifepharma, Ital.; Italfarmaco, Rus.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Ferlea *Elea, Arg.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferlette *Essenpharma, Philipp.*
Buclizine hydrochloride (p.570·1); ferrous fumarate; lysine hydrochloride; vitamin B substances (p.1922·1).
Appetite stimulant; tonic.

Ferlex *Arlex, Mex.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Ferli-6 *Continental Pharma, Thai.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2).
Anaemia; vitamin and iron supplement.

Ferlin
Note. This name is used for preparations of different composition.
Medifarma, Indon.; Pediatrica, Indon.
Iron (p.1949·1); vitamin B substances (p.1922·1).
Nutritional supplement.

Pediatrica, Philipp.
Oral drops: Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Iron-deficiency anaemia.

Pediatrica, Philipp.
Syrup: Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Iron-deficiency anaemia.

Ferlixir *Aspen, S.Afr.†.*
Multivitamin and mineral preparation (p.1922·1).

Ferlixit *Sanofi-Aventis, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias; iron deficiency.

Ferlor AF *Loren, Mex.†.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Folic-acid deficiency; iron deficiency.

Fermalac Vaginal
Note. This name is used for preparations of different composition.
Rosell, Canad.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Streptococcus lactis* (p.2372·3).
Adjunct in treatment of vaginal infections.

Rosell, Cz.
Lactobacillus rhamnosus (p.2372·3); *Lactobacillus delbrueckii* subs. *bulgaricus* (p.2372·3); *Streptococcus salivarius* subs. *thermophilus* (p.2372·3).
Maintenance of normal vaginal flora.

Fermasian *Asian Pharm, Thai.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Fermate *Kenyaku, Thai.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Fermathron *Biomet, Austral.†; UCB, Ger.; Biomet Merck, UK.*
Sodium hyaluronate (p.2320·1).
Degenerative disorders of the knee and other joints.

Fermavisc *OmniVision, Switz.*
Sodium hyaluronate (p.2320·1) (p.1622·2).
Contact lens lubricant.

Fermed *Bajamed, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Fermento duodenal
Note. This name is used for preparations of different composition.
Hommel, Ger.
Pancreatin (p.2360·1).
Formerly contained pancreatin and dimethicone.
Digestive enzyme deficiency disorders.

Pfizer, Switz.†.
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive disorders.

Fermentol *Church & Dwight, Canad.*
Pepsin (p.2365·1).
Dyspepsia without hyperacidity; oral vehicle.

Fermenturto-Lio *Teknofarma, Ital.*
Lactobacillus bulgaricus (p.2372·3); *Lactobacillus casei* (p.2372·3).
Gastrointestinal disorders.

Fermetone Composto *Lepori, Port.*
Bile extract (p.2266·2); simeticone (p.1770·2); hemicellulase (p.2279·1); pancreatin (p.2360·1).
Digestive disorders.

Fermil *Arrow, Austral.*
⊗ Clomifene citrate (p.2086·1).
Female infertility.

Fernadin *Liferpal, Mex.*
Ferrous fumarate (p.1938·3).
Anaemias.

Ferodan *Odan, Canad.*
Ferrous sulfate (p.1939·3).
Anaemias.

Ferofate *Jaapharm, Canad.*
Ferrous sulfate (p.1939·3).

Fero-Folic *Teofarma, Gr.; Adcock Ingram, S.Afr.; Abbott, Switz.; Abbott, USA.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1) may be included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Ferofort *Kalbe, Indon.*
Iron carbonyl (p.1950·3); vitamin B substances; zinc; lysine hydrochloride (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Feroglobin
Vitabiotics, Hong Kong.
Iron, vitamin B, and mineral preparation (p.1922·1).
Anaemias.

Vitabiotics, UK.
Capsules: Vitamin B substances; folic acid; iron; copper; zinc (p.1922·1).

Vitabiotics, UK.
Oral liquid: Vitamin B substances; vitamin C; minerals; honey; malt; lysine (p.1922·1).

Feroglobin B_{12} *Vitabiotics, Cz.*
Vitamin B substances; iron; copper; zinc (p.1922·1).

Feroglobin-B12 *Vitabiotics, Hung.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Anaemias.

Fero-Grad *Pharma Logistics, Belg.; Abbott, Canad.; Adcock Ingram, S.Afr.; Abbott, USA.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Fero-Grad vitamine C *Teofarma, Fr.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Fero-Gradumet
Pharma Logistics, Belg.; Abbott, Spain.
Ferrous sulfate (p.1939·3).
Anaemias; iron deficiency.

Abbott, Neth.
Dried ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferol *Ronava, Venez.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Feromiel *Herbaxt, Fr.*
Honey (p.1948·2); iron pidolate.
Nutritional supplement.

Feron *Toray, Jpn.*
Interferon beta (p.891·2).
Hepatitis; malignant neoplasms.

Ferona *Sidus, Arg.*
⊗ Fluoxymesterone (p.2103·3); yohimbine hydrochloride (p.2200·2); caffeine (p.1116·3); lysine hydrochloride; vitamins; minerals.
Male impotence.

Ferosal
Note. This name is used for preparations of different composition.
Ad-Drugstel, Philipp.
Capsules: Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Iron deficiency; iron-deficiency anaemia.

Ad-Drugstel, Philipp.
oral drops: Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ad-Drugstel, Philipp.
Syrup: Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron deficiency; iron-deficiency anaemia.

Ferosix *Pharmasant, Thai.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2).
Iron-deficiency anaemia.

Ferotrinsic *Rugby, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); intrinsic factor (p.2326·3); vitamin B substances (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferplex *Bago, Arg.; Italfarmaco, Cz.; Italfarmaco, Ital.; Italfarmaco, Pol.; Italfarmaco, Spain; Abdi, Turk.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Ferplex Fol *Abdi, Turk.*
Iron succinyl-protein complex (p.1953·2); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Ferplus-B *Chew, Thai.*
Ferrous fumarate (p.1938·3); vitamins; minerals (p.1922·1).
Iron-deficiency anaemia; vitamin deficiency.

Ferquifa B_{12} *Merck, Port.†.*
Ferrous citrate; copper sulfate; liver extract; folic acid; cyanocobalamin (p.1922·1).
Anaemias.

Ferradol *Pfizer, India.*
Ferric ammonium citrate (p.1938·1); vitamins (p.1922·1).
Tonic.

Ferralet Plus *Mission Pharmacal, USA†.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); vitamin B substances (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Ferranem *Chemopharma, Chile.*
Ferrous sulfate (p.1939·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability or iron.
Iron-deficiency anaemia.

Ferranim *Sanitas, Chile.*
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability or iron.
Iron deficiency; iron-deficiency anaemia.

Ferranin *Altana, Arg.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferranin Complex *Altana, Arg.*
Iron polymaltose (p.1953·1); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3); folic acid (p.1940·1).
Anaemias.

Ferranina *Altana, Mex.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Ferranina Complex *Altana, Mex.*
Iron polymaltose (p.1953·1); vitamin B substances; vitamin C (p.1922·1).
Anaemias; nutritional supplement.

Ferranina Fol *Altana, Mex.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron-deficiency anaemias.

Ferrascorbin
Note. This name is used for preparations of different composition.
Streuli, Switz.
Oral drops: Ferrous chloride (p.1938·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Streuli, Switz.
Tablets: Ferrous chloride (p.1938·2); ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferremon *San Carlo, Ital.†.*
Iron succinyl-protein complex (p.1953·2).
Anaemias; iron deficiency.

Ferretab *Lannacher, Austria.*
Ferrous fumarate (p.1938·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency anaemias.

Ferretab Comp
Lannacher, Austria.
Ferrous fumarate (p.1938·3); sodium folate (p.1941·2).
Iron and folic acid deficiency.

Lannacher, Rus.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron-deficiency anaemia.

Ferretab Compositum *Lannacher, Cz.*
Ferrous fumarate (p.1938·3); sodium folate (p.1941·2).
Iron deficiency; iron-deficiency anaemia.

Ferretab Compuesto *Biol, Arg.*
Ferrous fumarate (p.1938·3); sodium folate (p.1941·2).
Iron and folic acid deficiency.

Ferretts *Pharmics, USA.*
Ferrous fumarate (p.1938·3).

Ferrex *Breckenridge, USA.*
Polysaccharide-iron complex (p.1960·2).
Iron-deficiency anaemia.

Ferrex Forte *Breckenridge, USA.*
Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Iron-deficiency anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ferrex Forte Plus *Breckenridge, USA†.*
Iron (p.1960·2); vitamin B (p.1980·2); folic acid (p.1940·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrex PC *Breckenridge, USA.*
Multivitamin and mineral preparation with polysaccharide-iron complex (p.1960·2) (p.1922·1).
Nutritional supplement.

Ferrex Plus *Breckenridge, USA.*
Iron (p.1960·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency.

Ferricol
Note.This name is used for preparations of different composition.
Richmond, Arg.
Ferrous sulfate (p.1939·3).

Columbia, Mex.
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1).
Iron supplement; iron-deficiency anaemia.

Ferricrine *Bioprofarma, Arg.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Ferricure *Trenker, Belg.*
Polysaccharide-iron complex (p.1960·2).
Iron-deficiency anaemia.

Ferridal *Parggon, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Ferri-Emina *Lafare, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias; iron deficiency.

Ferrifol *CTI, Israel.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias.

Ferrigot *Pasteur, Chile.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferrimed
Note.This name is used for preparations of different composition.
Altana Madaus, S.Afr.
Capsules: Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron deficiency; iron-deficiency anaemia.

Altana Madaus, S.Afr.
Injection; syrup: Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Ferrimed DS *Altana Madaus, S.Afr.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Ferrini *Ativus, Braz.*
Iron amino acid chelate (p.1950·3).
Iron-deficiency anaemia.

Ferrini Folico *Ativus, Braz.*
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Feripel *CTI, Israel.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferriprox *Purissimus, Arg.; Orphan, Austral.; Pharma Logistics, Belg.; Farmalab, Braz.; Apotex, Cz.; Apotex, Denm.; Orphan, Fin.; Chiesi, Fr.; Orphan, Ger.; Demo, Gr.; Apotex, Hong Kong; Swedish Orphan, Irl.†; Chiesi, Ital.; Apotex, Malaysia; Apotex, Neth.; Swedish Orphan, Port.; Chiesi, Spain; Swedish Orphan, Swed.; PFC, Switz.; Cankat, Turk.; Swedish Orphan, UK.*
Deferiprone (p.1439·1).
Iron overload.

Ferriseltz *Gerolimatos (Γερολυματος), Gr.†; Rovi, Spain.*
Ferric ammonium citrate (p.1938·1).
Contrast medium for magnetic resonance imaging.

FerriSeltz *Bracco, Neth.*
Ferric ammonium citrate (p.1938·1).
Contrast medium for magnetic resonance imaging.

Ferriseptil *Gedis, Ital.*
Glutaral (p.1645·2).
Disinfection.

Ferrison *Vitapan, Braz.†.*
Ferrous sulfate (p.1939·3).

Ferrister *Gedis, Ital.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Ferritamin *Abigo, Swed.*
Multivitamin preparation with iron and caffeine (p.1922·1).

Ferritin Complex *ABC, Ital.*
Sodium ferric gluconate complex (p.1962·2); calcium folinate (p.1943·3).
Anaemias.

Ferritin Oti *ABC, Ital.; ABC, Port.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias; iron deficiency.

Ferrivax *Ivax, Mex.*
Ferritin (p.1938·1).
Iron deficiency; iron-deficiency anaemia.

Ferrlecit *Sanofi-Aventis, Cz.; Aventis, Ger.; Sanofi-Aventis, Hung.; Aventis, Israel; Watson, USA.*
Sodium ferric gluconate complex (p.1962·2).
Iron deficiency; iron-deficiency anaemia.

Ferrlecit 2 *Aventis, Ger.*
Ferrous succinate (p.1939·2).
Iron deficiency; iron-deficiency anaemia.

Ferro
Note.This name is used for preparations of different composition.
AstraZeneca, Denm.
Ferrous sulfate (p.1939·3).
Iron deficiency.

Sam-On, Israel.
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Aroma, Turk.
Ferric ammonium citrate (p.1938·1).
Iron deficiency; iron-deficiency anaemia.

Ferro Complex *Pharmafar, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in some dosage forms to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferro Drops L *Pharmacare, S.Afr.*
Ferrous lactate (p.1939·2).
Iron-deficiency anaemias.

Ferro F-500 Gradumet *Abbott, Chile†.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability or iron.
Iron and folate deficiency.

Ferro Folic *Abbott, Arg.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Ferro Folico *Armstrong, Mex.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Ferro Grin *Grin, Mex.*
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Anaemias.

Ferro Sanol *Sanol, Ger.; Specifar, Gr.; CEPA, Spain; Adeka, Turk.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Ferro Sanol B *Adeka, Turk.*
Ferrous glycine sulfate (p.1939·1); vitamin B substances (p.1922·1).
Iron deficiency; iron-deficiency anaemia.

Ferro sanol comp *Sanol, Ger.*
Ferrous glycine sulfate (p.1939·1); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Iron and vitamin B deficiency; iron-deficiency anaemia.

Ferro sanol duodenal *Sanol, Ger.; Schwarz, Ger.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Ferro sanol gyn *Sanol, Ger.; Schwarz, Ger.*
Ferrous glycine sulfate (p.1939·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Ferro Vitaminico *Laboratorios Chile, Chile.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability or iron.
Iron-deficiency anaemia.

Ferroben *Teuto, Braz.†.*
Ferric ammonium citrate (p.1938·1); vitamin B substances; copper sulfate (p.1922·1).
Iron deficiency; iron-deficiency anaemia.

Ferro-Be-Sian *Asian Pharm, Thai.*
Ferrous gluconate (p.1939·1); vitamins (p.1922·1).
Iron-deficiency anaemia.

Ferrobest *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferrobet *Montavit, Austria.*
Ferrous fumarate (p.1938·3).
Iron deficiency anaemias.

Ferrocal *Rekah, Israel.*
Calcium ferrous citrate (p.1932·1).
Iron-deficiency anaemia.

Ferrocap F *Consolidated Chemicals, Irl.†.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemia during pregnancy.

Ferro-C-Calcium *Cheplapharm, Ger.*
Ferrous gluconate (p.1939·1); calcium gluconate (p.1675·3); ascorbic acid (p.1983·3).
Iron and calcium deficiency.

Ferroce *Alian, Venez.*
Ferrous fumarate (p.1938·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferroce con B12 *Alian, Venez.*
Ferrous sulfate (p.1939·3); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrocebrina
Note.This name is used for preparations of different composition.
Bajer, Arg.
Capsules: Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Bajer, Arg.
Oral solution; syrup: Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferrocel *Marcel, Mex.*
Iron dextran (p.1951·1).
Iron-deficiency anaemia.

Ferrochelate *David, India.*
Ferric ammonium citrate (p.1938·1); vitamin B (p.1980·2); folic acid (p.1940·1); lysine hydrochloride (p.1955·1).
Anaemias.

Ferrochelate-Z *David, India.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1); zinc (p.1999·1).
Anaemias.

Ferrocoban B12 *Bohm, Spain.*
Cyanocobalamin; dexpanthenol; ferrous gluconate; thiamine hydrochloride (p.1922·1).
Tonic; vitamin B deficiency.

Ferrocomplex *Farmalab, Braz.*
Ferrous sulfate (p.1939·3); vitamin B substances; panthenol; liver extract (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferrocur *Schering, Spain.*
Iron succinyl-protein complex (p.1953·2).
Iron-deficiency anaemia.

Ferrocutid *Labocor, Port.†.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Ferrocyte *Eisai, Malaysia; Eisai, Singapore; Eisai, Thai.*
Ferrous sodium citrate (p.1950·3).
Iron-deficiency anaemia.

Ferrodix *Duopharm, Ger.†.*
Ferrous fumarate (p.1938·3); ferric sodium citrate (p.1950·3); ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Ferro-Dok *Major, USA.*
Ferrous fumarate (p.1938·3).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Iron-deficiency anaemias.

Ferro-Folgamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Rus.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and vitamin deficiency.

Ferro-Folic *Abbott, Venez.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrofolin *Schering, Ital.*
Iron succinyl-protein complex (p.1953·2); calcium folinate (p.1943·3).
Anaemias; folic acid deficiency; iron deficiency.

Ferro-Folsan *Desma, Ger.; Solvay, Port.†.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Ferro-Folsan Plus *Solvay, Philipp.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Anaemias; iron deficiency.

Ferrogamma *Worwag, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Ferrogels Forte *Cypress, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folate deficiency.

Ferrograd
Abbott, Irl.; Teofarma, UK.
Dried ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Teofarma, Ital.; EU, Neth.; Eureco, Neth.; Euro Registratie, Neth.
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferrograd C
Abbott, Austral.; Abbott, Austria; Abbott, Irl.; Teofarma, UK.
Dried ferrous sulfate (p.1939·3).
Sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron supplement; iron-deficiency anaemia.

Teofarma, Ital.; Abbott, NZ.
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferrograd Fol *Abbott, Austria.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Ferrograd Folic *Abbott, Cz.†; Teofarma, Hung.; Abbott, Irl.; Abbott, Israel; Teofarma, Ital.; Abbott, NZ; Abbott, Pol.; Teofarma, UK.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and folic acid deficiency in pregnancy.

Ferrograd Folico *Teofarma, Port.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Ferro-Gradumet
Abbott, Austral.; Teofarma, Hung.; Abbott, Israel; Abbott, NZ.
Dried ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Abbott, Austria; ICN, Cz.†; Abbott, Pol.; Teofarma, Port.; Abbott, Rus.; Abbott, Switz.
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferrogyn *SoSe, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Ferroin *Pisa, Mex.†.*
Iron dextran (p.1951·1).
Anaemias.

FERROinfant N *Rubiepharm, Ger.†.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemias.

FERROinfant Neu *Rubiepharm, Ger.†.*
Iron sucrose (p.1953·2).
Iron deficiency; iron-deficiency anaemias.

Ferrokapsul *Strathmann, Ger.†.*
Ferrous fumarate (p.1938·3).
Iron deficiency; iron-deficiency anaemias.

Ferrokatabios *SIT, Ital.†.*
Multivitamin preparation with iron (p.1922·1).

Ferroklinge *Ariston, Braz.†.*
Ferrous fumarate (p.1938·3).
Succinic acid is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferrol-Cal *YSP, Malaysia†.*
Ascorbic acid; calcium carbonate; ferrous fumarate; magnesium carbonate; vitamin E (p.1922·1).
Vitamin and mineral supplement.

Ferroliver *SM, Venez.*
Ferrous fumarate (p.1938·3); vitamin B ; vitamin B ; copper sulfate (p.1922·1).
Iron-deficiency anaemia.

Ferrologic *Fresenius Medical, Cz.*
Iron sucrose (p.1953·2).
Iron deficiency.

Ferromalt *Knop, Chile.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferromas *Mertens, Arg.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferromax *Weifa, Norw.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Ferrometion *Northia, Arg.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Ferromia *Eisai, Indon.; Eisai, Jpn.*
Ferrous sodium citrate (p.1950·3).
Iron-deficiency anaemia.

Ferromina *Provita, Ital.†.*
Ferrous gluconate; vitamin C; magnesium stearate; folic acid; vitamin B (p.1922·1).
Nutritional supplement.

Ferromyn S *AstraZeneca, Swed.*
Ferrous succinate (p.1939·2).
Iron deficiency; iron-deficiency anaemia.

Ferronal *CTS, Rus.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Ferronat *Ivax, Cz.; Zentiva, Cz.*
Ferrous fumarate (p.1938·3).
Iron deficiency; iron-deficiency anaemia.

Ferro-Nes *Nes, Israel.*
Ferrous gluconate (p.1939·1).
Iron deficiency.

Ferronil *Teuto, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferronorm *Medifarm, Venez.*
Ferrous fumarate (p.1938·3); vitamin B substances; zinc; copper (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferroper *Organifar, Venez.†.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Ferroplex
Note.This name is used for preparations of different composition.
Cimed, Braz.
Ferrous sulfate (p.1939·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

JRalph, Philipp.
Ferrous fumarate (p.1938·3); vitamin B substances; cobalt sulfate; calcium gluconate (p.1922·1).
Anaemias; vitamin B deficiency.

Biogal, Rus.
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Ferroplex-frangula *ERA, Denm.*
Ferrous tartrate (p.1940·1); frangula bark (p.1732·2).
Iron deficiency.

Ferropro *Medicine Products, Thai.*
Ferrous fumarate (p.1938·3); vitamins; calcium phosphate (p.1922·1).
Iron-deficiency anaemia.

Ferroprol *Proel, Gr.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Ferroprotina *Faes, Spain.*
Ferritin (p.1938·1).
Iron-deficiency anaemia.

Ferrosanol duodenal *Schwarz, Switz.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Ferrosig *Sigma, Austral.; Zuellig, NZ.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferrosmate *Blue Sky, Philipp.*
Sodium feredetate (p.1962·1).
Iron supplement.

Ferrosol *Prodotti, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferrosprint *Pharmacia, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias.

Ferrostrane *Teofarma, Fr.*
Sodium feredetate (p.1962·1).
Iron deficiency; iron-deficiency anaemia.

Ferrotab *Antigen, Irl.†.*
Dried ferrous sulfate (p.1939·3); copper sulfate (p.1935·3); manganese sulfate (p.1956·2).
Iron-deficiency anaemia.

Ferrotabs *Thaipharmed, Thai.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferrotemp *Medix, Mex.*
Ferrous fumarate (p.1938·3); thiamine hydrochloride (p.1976·1).
Iron-deficiency anaemia.

Ferro-Terapina *Degorts, Mex.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Ferrotonico *Neo Quimica, Braz.†.*
Ferrous sulfate (p.1939·3); phosphoric acid; aloes; myrrh; cinnamon; nutmeg.
Tonic.

Ferrotonico B12
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.†.
Oral solution: Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Neo Quimica, Braz.†.
Tablets: Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Ferrototal *Sanval, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ferrotrat *Medley, Braz.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Iron deficiency; iron-deficiency anaemia.

Ferrotrat B12 *Medley, Braz.†.*
Ferric ammonium citrate (p.1938·1); vitamin B ; liver extract; stomach extract; carnitine hydrochloride; lysine; sodium glycerophosphate; manganese sulfate; copper sulfate (p.1922·1).
Anaemias.

Ferrotrat B12 Plus *Medley, Braz.*
Ferric ammonium citrate (p.1938·1); cyanocobalamin; carnitine hydrochloride; lysine hydrochloride; manganese sulfate; copper sulfate; sodium hypophosphite (p.1922·1).
Iron-deficiency anaemia; reduced appetite.

Ferro-Tre *Mediolanum, Ital.*
Iron acetyltransferrin.
Iron-deficiency anaemias.

Ferrotron
Note. This name is used for preparations of different composition.
Ariston, Braz.†.
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

VAAS, Ital.
Amino-acid preparation with vitamins and minerals (p.1922·1).
Nutritional supplement.

Ferrous Sulphate Compound *Pharmacare, S.Afr.; Pharmagen, S.Afr.*
Ferrous sulfate (p.1939·3); manganese sulfate (p.1956·2); copper sulfate (p.1935·3).
Iron-deficiency anaemia.

Ferrovin *Rafarm, Gr.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Ferrovin-Chinaeisenwein *Pharmonta, Austria.*
Ferric ammonium citrate (p.1938·1); manganese hypophosphite; cinchona bark (p.2282·3); citrus aurantium (p.2357·1).
Anaemias; iron deficiency; tonic.

Ferrovir *Technomedservis, Rus.*
Sodium deoxyribonucleate-iron complex.
HIV infection.

Ferrovit *Mega Lifesciences, Malaysia.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Anaemias.

Ferro-Vital *Eczacibasi, Turk.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Ferrum
Lek, Cz.
Iron polymaltose (p.1953·1) or iron sucrose (p.1953·2).
Iron deficiency.

Hausmann, Irl.
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferrum Complexe no 29 *Lehning, Fr.*
Homoeopathic preparation.

Ferrum Fol *Ferraz, Lynce, Port.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Ferrum Fol Hausmann *Nycomed, Gr.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Ferrum Fort Hausmann *Abdi, Turk.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Ferrum H *Baxter, Austral.; Aspen, NZ.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ferrum Hausmann
Note. This name is used for preparations of different composition.
Richter, Austria; Nycomed, Gr.; Vifor, Hong Kong; Ferraz, Lynce, Port.; Vifor, Singapore; Abdi, Turk.
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Astellas, Ger.
Ferrous fumarate (p.1938·3) or iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Geymonat, Ital.
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Vifor International, Switz.
Ferrous fumarate (p.1938·3) or iron dextran (p.1951·1).
Iron deficiency; iron-deficiency anaemia.

Ferrum Homaccord *Heel, Cz.*
Homoeopathic preparation.

Ferrum Lek *Lek, Pol.; Lek, Rus.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron supplement; iron-deficiency anaemia.

Ferrum Phos Comp *Weleda, S.Afr.*
Homoeopathic preparation.

Ferrum phosphoricum comp *Weleda, Ger.*
Homoeopathic preparation.

Ferrum Sandoz *Novartis Consumer, Spain.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Ferrum Verla *Verla, Ger.*
Ferrous gluconate (p.1939·1).
Iron deficiency.

Ferrum-Quarz *Weleda, Austria.*
Ferrous sulfate (p.1939·3); quartz.
Migraine and related vascular headaches; tonic.

Ferrumvit *Vitermat, Braz.†.*
Iron chelate (p.1949·1); folic acid (p.1940·1).
Anaemias.

Fersaday *Goldshield, UK.*
Ferrous fumarate (p.1938·3).
Iron deficiency.

Fersamal *Goldshield, UK.*
Ferrous fumarate (p.1938·3).
Iron deficiency.

Fertell *Genosis, UK.*
Fertility test (p.2372·1).

Fertifol *Lifepharma, Ital.*
Folic acid (p.1940·1).
Prevention of neural-tube defects.

Fertilan *Codal Synto, Hong Kong.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Fertilin *Unipharm, Turk.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Fertility Day *Blausiegel, Braz.; Maver, Mex.*
Pregnancy test (p.2372·1).

Fertilix *Fortbenton, Arg.*
Acetylcarnitine hydrochloride (p.1932·2); levocarnitine (p.1932·2).

Fertilphen *Landson, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Fertin *Interbat, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Fertinex *Serono, USA.*
⊗ Urofollitropin (p.2136·3).
Female infertility.

Fertinorm *Serono, Canad.†.*
⊗ Urofollitropin (p.2136·3).
Anovulatory infertility.

Fertnon *Cifarma, Braz.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Fertodur *Schering, Mex.†; Schering, Turk.*
⊗ Cyclofenil (p.2088·1).
Anovulatory infertility.

Fertomcidina-U *Theriaca, Ital.*
Magnesium glycerophosphate (p.1679·2); salicylic acid (p.1612·2); sodium iodide (p.2169·2); ammonium bromide (p.2269·2).
Wound disinfection.

Fertomid *Cipla, India; Cipla-Medpro, S.Afr.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Ferval *Valdecasas, Mex.*
Ferrous fumarate (p.1938·3).
Iron supplement; iron-deficiency anaemia.

Fervex
Note. This name is used for preparations of different composition.
Hertz, Braz.
Paracetamol (p.108·1).
Fever; pain.

UPSA Conseil, Fr.; BMS, Hung.; BMS, Pol.
Pheniramine maleate (p.587·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms; upper respiratory-tract disorders.

Andromaco, Mex.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pharmavit, Cz.†.
Effervescent tablets; tablets: Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

BMS, Cz.
Granules: Paracetamol (p.108·1); pheniramine maleate (p.587·3); ascorbic acid (p.1983·3).
Upper respiratory-tract disorders.

Fervical *Garant, Ital.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Fervit
Note. This name is used for preparations of different composition.
Bushnell, India†.
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); folic acid (p.1940·1); vitamin C (p.1983·3).
Anaemias.

Vitoria, Port.
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemias.

Ferxal *Silanes, Mex.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Ferybar *Pinewood, Irl.*
Liver extract; vitamin B substances; minerals (p.1922·1).
Vitamin and mineral supplement.

Ferzobat *Interbat, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Fesanol *Organifar, Venez.†.*
⊗ Naphazoline nitrate (p.1565·2); mepyramine maleate (p.585·2).

Fesema *Etex, Chile.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Fesofor *SmithKline Beecham, S.Afr.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemias.

Fesovit
Note. This name is used for preparations of different composition.
GSK, India.
Capsules: Folic acid (p.1940·1); vitamin B substances (p.1922·1); dried ferrous sulfate (p.1939·3).
Iron-deficiency anaemia; tonic.

GSK, India.
Elixir: Vitamin B substances (p.1922·1); dried ferrous sulfate (p.1939·3).
Nutritional supplement.

Fess *Paedpharm, Austral.*
Sodium chloride (p.1686·1).
Nasal congestion; sinusitis.

Festal *Aventis, Rus.*
Pancreatin (p.2360·1); bovine bile (p.2266·3); hemicellulase (p.2279·1).
Pancreatic insufficiency.

Festal N *Aventis, India; Aventis, Turk.*
Pancreatin (p.2360·1).
Digestive disorders.

Festal Reformulado *Sanofi-Aventis, Venez.*
Lipase; amylase (p.2256·3); protease.
Digestive disorders.

Festone *Novartis, Braz.*
⊗ Tamoxifen citrate (p.772·3).

Fetik *Interbat, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Fe-Tinic *Ethex, USA.*
Polysaccharide-iron complex (p.1960·2).
Iron-deficiency anaemia.

Fe-Tinic Forte *Ethex, USA.*
Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); vitamin B (p.1980·2).
Iron-deficiency anaemia.

Fetinor *Otto, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Feto-Longoral *Artesan, Ger.†; Cassella-med, Ger.†.*
Multivitamin and mineral preparation (p.1922·1).

Fetrin *Lunsco, USA.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); intrinsic factor (p.2326·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Fetrival *Almirall, Port.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Fetusin *EuroHealth, Philipp.*
Oxytocin (p.2015·2).
Labour induction.

Fetylan *Farmamust, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Feudoftal *Bausch & Lomb, Arg.*
Ascorbic acid; alpha tocoferil acetate; vitamin A palmitate (p.1922·1).
Antoxidant preparation.

Feuille de Saule *Gilbert, Fr.*
Salicylic acid (p.1612·2).
Callus; corns; verrucas.

Fevamol *Garec, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Fevapar
Note. This name is used for preparations of different composition.
Xeragen, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Xeragen, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain with tension.

Fevarin *Solvay, Cz.; Solvay, Denm.; Solvay, Fin.; Solvay, Ger.; Solvay, Hung.; Solvay, Ital.; Solvay, Neth.; Solvay, Norw.; Solvay, Pol.; Solvay, Rus.; Solvay, Swed.*
Fluvoxamine maleate (p.399·3).
Bipolar disorder; depression; obsessive-compulsive disorder; panic disorder.

Fever & Inflammation Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Feverall *Alpharma, USA.*
Paracetamol (p.108·1).
Fever; pain.

Feverfen *Wise, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Fevital Simplex *Prospa, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Iron deficiency; iron-deficiency anaemia.

Fevrin *Armoxindo, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Fexadin *Ranbaxy, Rus.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fexadyne *Ali, Turk.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fexazol *Molex Ayus, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Fexicam *Technilab, Canad.†.*
Piroxicam (p.117·3).
Fever; inflammation; pain.

Fexidine *Biofarma, Venez.*
Fexofenadine hydrochloride (p.579·3).
Hypersensitivity reactions.

Fexid-Z *Overseas, India.*
Iron carbonyl (p.1950·3); vitamin B ; folic acid; sodium selenate; vitamin E; zinc sulfate (p.1922·1).
Iron-deficiency anaemia.

Fexigra *Cipla, India.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fexin *Aspen, S.Afr.†.*
Cefalexin (p.218·2).
Bacterial infections.

Fexiron *Rivero, Arg.*
Iron dextran (p.1951·1).
Iron-deficiency anaemia.

Fexmid *Victory, USA.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Fexofen *Elvetium, Arg.†; Aristo, India; Sanovel, Turk.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fexoril *Leti, Venez.*
Fexofenadine hydrochloride (p.579·3).
Hypersensitivity reactions.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Fexotabs *Aventis, Austral.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Fexova *Ipca, India.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; allergic skin disorders.

Fezef *Tai Yu, Philipp.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Fezona *Diba, Mex.†.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders; pain.

FG Ointment *Meiji, Indon.*
Neomycin sulfate (p.305·1); gramicidin S hydrochloride (p.286·2); benzocaine (p.1854·1); chlorphenamine maleate (p.571·3); mafenide (p.296·2).
Skin infections.

FG Troches *Meiji, Indon.*
Neomycin sulfate (p.305·1); gramicidin S hydrochloride (p.286·2).
Mouth and throat infections.

FGF Tabs *Abbott, Austral.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folate deficiency; iron-deficiency anaemia; megaloblastic anaemia.

Fhbc *Baxter, Ital.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Fiacin *Biosarto, Spain.*
⊗ Indometacin (p.66·3); prednisone (p.1542·3).
Musculoskeletal, joint, and peri-articular disorders.

Fiagra *Ultratech, India†.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Fialetta Odontalgica Dr Knapp *Montefarmaco, Ital.*
Benzocaine (p.1854·1); chlorobutanol (p.1639·2); clove oil (p.2285·1); colophony (p.2286·2).
Toothache.

Fiamelis *Teclapharm, Ger.†.*
Hamamelis (p.2318·2).
Skin disorders.

Fibalip *Pacific, NZ.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Fiber Basics *Hormel, Hong Kong.*
Soluble maltodextrin fibre (p.1955·3).
Dietary fibre supplement.

Fiberall *Ciba Consumer, USA.*
Psyllium hydrophilic mucilloid (p.1737·1).
Constipation; stool softener in haemorrhoids.

Fibercon *Wyeth-Whitehall, Arg.†; Wyeth Lederle, Austria†; Wyeth, Gr.†; Lederle, Israel†; Wyeth Consumer, Mex.†; Wyeth Consumer, Neth.†; Whitehall, Thai.†; Lederle, USA.*
Polycarbophil calcium (p.1763·3).
Constipation; stool softener.

Fiberform *Solvay, Neth.; Recip, Swed.*
Wheat bran (p.1712·3).
Constipation.

Fiberform Mix *Recip, Swed.*
Wheat bran (p.1712·3).
Constipation.

Fiberfull *Ponce, Venez.*
Ispaghula (p.1737·1); avena (p.2262·1).
Constipation.

Fibergy *Usana, Hong Kong†.*
Preparation for enteral nutrition (p.1922·1).

Fiberlan *Galagen, USA.*
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Fiber-Lax *Rugby, USA.*
Polycarbophil calcium (p.1763·3).
Constipation; diarrhoea.

Fibermate
Note. This name is used for preparations of different composition.
Westmont, Hong Kong.
Ispaghula (p.1737·1).
Dietary fibre supplement.

United Laboratories, Philipp.
Psyllium (p.1737·1).
Constipation; dietary fibre supplement; hypercholesterolaemia.

FiberNorm *G & W, USA.*
Polycarbophil calcium (p.1763·3).
Constipation.

Fibersource *Novartis, Arg.†; Novartis Consumer, Austral.†; Novartis, Braz.; Novartis Nutrition, Singapore.*
Preparation for enteral nutrition with fibre (p.1922·1).

Fibion *Asta Medica, Switz.†.*
Soya bran (p.1712·3).
Constipation.

Fiblaferon *Biosyn, Ger.*
Interferon beta (human) (p.891·2).
Viral infections.

Fiblast
Note. This name is used for preparations of different composition.
Rontag, Arg.
⊗ Ascorbic acid (p.1983·3); hesperidin methyl chalcone (p.2305·2); butcher's broom (p.2270·3).
Haemorrhoids; metrorrhagia; venous insufficiency.

Kaken, Jpn.
Trafermin (p.1618·1).
Skin ulcer.

Fibonel *Pharma Investi, Chile†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Fiboran *Christiaens, Belg.†; Nycomed, Fr.†; Nycomed, Neth.*
Aprindine hydrochloride (p.1216·2).
Arrhythmias.

Fibra Light *Farmalight, Port.†.*
Fibre; arabinogalactan.
Formerly contained fibre and guar gum.
Dietary fibre supplement.

Fibra Line *Investigacion, Mex.*
A range of dietary fibre supplements (p.1922·1).
Gastrointestinal disorders; obesity.

Fibrabene *Legrand, Braz.*
Dornase alfa (p.1557·1); fibrinolysin (bovine) (p.1287·3).
Wounds.

Fibracap *Hebron, Braz.†.*
Dietary fibre preparation (p.1712·3).
Constipation; fibre supplement.

Fibracare *Herbarium, Braz.*
Ispaghula (p.1737·1).

Fibracol Plus *Johnson & Johnson Medical, Arg.*
Collagen (p.2286·1); calcium alginate (p.1058·1).

Fibrafen *Patriot, Philipp.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fibraguar *Fardi, Spain.*
Guar gum (p.442·3).
Diabetes mellitus.

Fibral *Aliud, Austria.*
Aciclovir (p.862·3).
Herpes labialis.

Fibralax *Ponce, Venez.†.*
Ispaghula (p.1737·1); avena (p.2262·1); senna (p.1769·2).
Constipation.

Fibralime *Bio2, Fr.†.*
Dietary fibre supplement (p.1922·1).
Obesity.

Fibralip *Tunggal Idaman, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Fibramox *Leti, Venez.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Fibranin *Winthrop, Port.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Fibrapen *Leti, Venez.†.*
Ampicillin (p.204·1).
Bacterial infections.

Fibrasan *Errekappa, Ital.*
Cellulose (p.2143·1).
Gastrointestinal disorders.

Fibrase
Note. This name is used for preparations of different composition.
Pfizer, Braz.; Pfizer, Mex.
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1); chloramphenicol (p.239·3).
Infected burns, ulcers, and wounds; skin infections.

Teofarma, Ital.
Pentosan polysulfate sodium (p.1367·1).
Peripheral vascular disorders; soft-tissue disorders; thrombosis prophylaxis.

Fibrase SA *Pfizer, Mex.*
Fibrinolysin (bovine) (p.1287·3); dornase alfa (p.1557·1).
Burns; ulcers; wounds.

Fibrasol *Maver, Chile.*
Psyllium hydrophillic mucilloid (p.1737·1).
Constipation.

Fibrazate *Sandoz, UK.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Fibre Dophilus *Pharmadass, UK.*
Lactobacillus acidophilus (p.2372·3); Acidophilus bifidus; ispaghula (p.1737·1).
Fibre supplement; maintenance of gastrointestinal flora.

Fibre Plus *Pharmadass, UK.*
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation; fibre supplement.

Fibrelief *Manx, UK.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement.

Fibreline *DHN, Fr.*
Dietary fibre supplement (p.1922·1).
Gastrointestinal disorders.

Fibresource *Novartis Nutrition, Hong Kong.*
Preparation for enteral nutrition (p.1922·1).

Fibrex Hot Drink *Berlin-Chemie, Ger.†.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; inflammation; pain.

Fibrex Tabletten *Berlin-Chemie, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1).
Pain.

Fibrexin *Menarini, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Fibrezym *Bene, Ger.*
Pentosan polysulfate sodium (p.1367·1).
Thrombosis prophylaxis.

Fibrimol *Andromaco, Chile†.*
Paracetamol (p.108·1).
Fever; pain.

Fibrin Glue *National Blood Centre, Thai.†.*
Thrombin (p.1080·1); fibrinogen (p.1070·1).
Haemostatic.

Fibrinase c/Cloranfenicol *Cristalia, Braz.*
Dornase alfa (p.1557·1); fibrinolysin (p.1287·3); chloramphenicol (p.239·3).
Infected wounds.

Fibrinon *Jean-Marie, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Fibrocard *Vitoria, Port.; Galepharma, Turk.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Fibrocide *Neo-Farmaceutica, Port.*
Pentosan polysulfate sodium (p.1367·1).
Thromboembolic disorders.

Fibrocit *CT, Ital.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Fibrogammin *ZLB, Austria; ZLB, Belg.; CSL, Braz.; ZLB, Ger.; ZLB, Switz.*
A factor XIII preparation (p.1069·2).
Factor XIII deficiency; haemorrhagic disorders.

Fibrogammin P
Note. This name is used for preparations of different composition.
Aventis Behring, Arg.; Centeon, Cz.†; Aventis Behring, Hong Kong; Aventis Behring, Israel; Aventis Behring, UK.
A factor XIII preparation (p.1069·2).
Factor XIII deficiency; haemorrhagic disorders.

IFET (ΙΦΕΤ), Gr.
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Fibrokinase *Otsira, India.*
Streptokinase (p.1402·3).

Fibrol *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Fibrolan
Note. This name is used for preparations of different composition.
Pfizer, Austria; Pfizer, Cz.; Parke, Davis, Ger.†; Pfizer, Ger.†; Pfizer, Hung.; Parke, Davis, Pol.; Pfizer, Switz.
Fibrinolysin (bovine) (p.1287·3); deoxyribonuclease (p.1557·1).
Burns; gynaecological surgery; skin infections; ulcers; wounds.

Olan-Kemed, Thai.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fibrolax *Giuliani, Ital.*
Ispaghula (p.1737·1).
Constipation.

Fibrolax Complex *Giuliani, Ital.*
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation.

Fibrolip *Anfarm, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Fibromucil *Collins, Mex.*
Ispaghula (p.1737·1).
Constipation; hypercholesterolaemia.

Fibronevrina *Ceccarelli, Ital.*
Thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2).
Vitamin B and B deficiency.

Fibroquel *Ozaki, Mex.*
Collagen (p.2286·1).
Burns; haemorrhage; ulcers; wounds.

Fibroraas *Shanghai RAAS, Thai.*
Fibrinogen (p.1070·1).
Hypofibrinogenaemia.

Fibrorelax *Andromaco, Chile.*
Chlormezanone (p.968·3); paracetamol (p.108·1); glucametacin (p.62·2).
Musculoskeletal, joint, and soft-tissue disorders.

Fibrosan *Biogalenic, Venez.*
Enalapril (p.1276·1).
Hypertension.

Fibrosine
Wyeth Consumer, Malaysia†; Wyeth Consumer, Singapore.
Dietary fibre preparation (p.1712·3).

Wyeth, Philipp.
Dietary fibre preparation from corn starch (p.1922·1).
Constipation; fibre supplement.

Fibrospes *Specifar (Σπεσιφαρ), Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Fibrotina *Buxton, Arg.*
Fluoxetine (p.397·3).
Fibromyalgia.

Fibro-Vein *Craveri, Arg.; Australasian Medical, Austral.†; STD, Cz.†; STD, Hung.; STD, Irl.; Mac, Ital.; NZ Medical & Scientific, NZ; STD Pharmaceutical Products, UK.*
Sodium tetradecyl sulfate (p.2139·2).
Varices; varicose veins.

Fibrovein *Omnimed, S.Afr.*
Sodium tetradecyl sulfate (p.2139·2).
Varicose veins.

Fibroxyn *Garec, S.Afr.†.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Fibrum *Nutricia-Bago, Arg.*
Preparation for enteral nutrition with fibre (p.1922·1).

Fibs *OCFZP, Pol.*
Myrtillus (p.2349·3).
Bacterial infections; eye inflammation.

Fibsol *Arrow, Austral.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Fica-F *Farmamust, Gr.*
Cefatrizine (p.221·3).
Bacterial infections.

Fichtensirup N *Jukunda, Ger.†.*
Spruce needles; thyme (p.2401·1); sage (p.2382·3); liquorice (p.1740·3); thyme oil (p.2401·2); sage oil (p.2382·3).
Respiratory-tract disorders; tonic.

Ficonax *Pisa, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Ficor *Otto, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction.

Ficortril
Mann, Ger.
⊗ Hydrocortisone acetate (p.1535·2).
Eye disorders.

Pfizer, Swed.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Anogenital pruritus; eczema; inflammatory eye disorders.

Fidagenbeta *Fidia, Ital.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Fidato *Fidia, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Fidecaina *Fidex, Arg.*
Lidocaine (p.1862·3).
Local anaesthesia.

Fideine *Bergamo, Braz.*
Bisacodyl (p.1710·1).
Constipation.

FideSan *Heel, Ger.*
Homoeopathic preparation.

Fidium *Rottapharm, Spain.*
Betahistine hydrochloride (p.2265·1).
Vertigo.

Fidoin-Q *Quimpharma, Mex.*
Ibuprofen (p.64·2).
Fever; pain.

Fiebrol *Fabop, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Fiebrolito *Fabop, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Fiedosin *Nupel, Spain.*
Ibuprofen sodium (p.65·2).
Fever; inflammation; pain.

Fienamina *Recordati, Ital.*
⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Hypersensitivity reactions.

Fiery Jack
Note. This name is used for preparations of different composition.
Pickles, UK.
Cream: Glycol salicylate (p.62·3); diethylamine salicylate (p.47·2); capsicum oleoresin (p.2276·2); methyl nicotinate (p.85·3).
Musculoskeletal and joint disorders.

Ransom, UK.
Ointment: Capsicum oleoresin (p.2276·2).
Musculoskeletal and joint disorders.

Figalol *Biomedica-Chemica, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Figatil *Catarinense, Braz.*
Cynara (p.2291·2); boldo (p.2267·2); ox bile (p.2266·3).
Liver disorders.

Figen *ERA, Denm.; SAD, Denm.*
Senna (p.1769·2); fig (p.1731·3).
Constipation.

Figothrom *Chrispa (Χρισπα), Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Figozant *Chrispa (Χρισπα), Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Figrel *Biomedica-Chemica, Gr.†.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Figur-Verlan *Verla, Ger.*
Guar gum (p.442·3).
Obesity.

FIII Hc *Baxter, Ital.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Fijacid *Bajer, Arg.*
Coal tar (Alcoderm) (p.1616·2).
Scalp disorders.

Fil Olor *Andromaco, Arg.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Filabac *Filaxis, Arg.*
Abacavir (p.861·3).
HIV infection.

Filair *3M, Chile; Medsan, Turk.; 3M, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

Filanc *Continentales, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Filartros *Ivax, Arg.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Filatil *Probiomed, Mex.*
Filgrastim (p.1070·1).
Neutropenia.

Filazem *Filadams, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Filcrin *Filaxis, Arg.*
Vinorelbine tartrate (p.789·1).
Malignant neoplasms.

Fildrocin *Lloyd, Philipp.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

File *Bouzen, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Fileen *Sriprasit, Thai.†*
Aminophylline (p.1114·2).
Asthma.

Filena *Organon, Austria†; Organon, Ital.*
11 White tablets, estradiol valerate (p.2097·3); 10 blue tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Filgen *Bioprofarma, Arg.*
Filgrastim (p.1070·1).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Filginase *Filaxis, Arg.*
Efavirenz (p.872·3).
HIV infection.

Filgrastine *Blausiegel, Braz.*
Filgrastim (p.1070·1).
Neutropenia associated with cancer chemotherapy.

Filibon *Wyeth, India; Pharmacare, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).
Supplement for pregnant or lactating women.

Filicine *Adelco, Gr.*
Folic acid (p.1940·1).
Megaloblastic anaemia; neural tube defects.

Filide *Filaxis, Arg.*
Nevirapine (p.899·1).
HIV infection.

Filigel *Codifra, Fr.*
Ispaghula (p.1737·1); glucomannan (p.2312·3); fructose (p.1945·1); guarana (p.2416·1).
Obesity.

Filinar *Eurofarma, Braz.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Filmabak *Farmila, Ital.*
Povidone (p.2146·1); electrolytes.
Dry eyes.

Filmcel *Allergan, Braz.*
Hypromellose (p.2144·2).
Dry eyes.

Filmexil *Pharmacos, Mex.†*
Hypromellose (p.2144·2).
Dry eyes.

Filmogen Same *Savoma, Ital.*
Barrier cream.

Filnarine *Approved Prescription Services, UK; Berk, UK.*
⊗ Morphine sulfate (p.86·3).
Pain.

Filocot *Sanofi-Aventis, Gr.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Filoderma *Ivax, Arg.*
⊗ Diflorasone diacetate (p.1529·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Filoderma Plus *Ivax, Arg.*
⊗ Diflorasone diacetate (p.1529·1); gentamicin sulfate (p.282·1); econazole nitrate (p.531·1).
Infected skin disorders.

Filogaster *Climax, Braz.†*
Amylase (p.2256·3); papain (p.2362·3); pepsin (p.2365·1); homocysteine thiolactone (p.2320·1); pancreatin (p.2360·1); sodium dehydrocholate (p.2292·2); vitamin B substances (p.1922·1); magnesium chloride.
Digestive-system disorders.

Filoklin *Generfarma, Spain†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Filomag B_6 *Filofarm, Pol.*
Magnesium aspartate (p.1679·1); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Filorga Soin Ecran Solaire *Filorga, Fr.*
SPF 30: Zinc oxide (p.1621·2).
Sunscreen.

Filosfil *Filaxis, Arg.*
Nelfinavir (p.899·1).
HIV infection.

Filotempo *Meda, Port.*
Aminophylline (p.1114·2).
Asthma; obstructive airways disease.

Filotricin A *Dupomar, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Filpril *Alphapharm, Austral.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Filten *Gador, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Filter Oil Free
Note.This name is used for preparations of different composition.
Dermoteca, Port.†
SPF 16: Amiloxate (p.1589·1); zinc oxide (p.1621·2).
Sunscreen.

Dermoteca, Port.†
SPF 30: Amiloxate (p.1589·1); zinc oxide (p.1621·2); titanium dioxide (p.1617·3); ferric oxide (p.1471·3).
Sunscreen.

Filter OTC
Note.This name is used for preparations of different composition.
Dermoteca, Port.†
SPF 20; Topical emulsion SPF 15: Amiloxate (p.1589·1); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Dermoteca, Port.†
SPF 40: Amiloxate (p.1589·1); padimate (p.1609·1); enzacamene (p.1597·1); zinc oxide (p.1621·2).
Sunscreen.

Dermoteca, Port.†
Topical spray SPF 15: Amiloxate (p.1589·1); zinc oxide (p.1621·2).
Sunscreen.

Filtrax *Ipso, Ital.†*
Pipemidic acid (p.315·1).
Bacterial urinary-tract infections.

Filtrosol
Note.This name is used for preparations of different composition.
Medihealth, Mex.
Octinoxate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1).
Sunscreen.

Roemmers Medihe, Venez.
Octinoxate (p.1608·2); oxybenzone (p.1608·3); enzacamene (p.1597·1); ensulizole (p.1597·1).
Sunscreen.

Filtrum *Leksir, Rus.*
Lignin.
Acute poisoning; gastrointestinal disorders.

Filtrum HT *Libbs, Braz.*
SPF 20: Sunscreen.

Filup *Union Drug, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal pain.

Filxine *Mertens, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Fima HES *Kalbe, Indon.*
⊗ An etherified starch (p.1065·1) with electrolytes.
Plasma volume expansion.

Fimalbumin *Hexpharm, Indon.*
⊗ Albumin (p.1052·1).
Hypoproteinaemia; neonatal hyperbilirubinaemia; plasma volume expansion.

Fimoplas *Blue Sky, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage; hereditary angioedema.

Finaband *Microsules, Arg.*
Bicalutamide (p.686·2).
Prostatic cancer.

Finaber *Microsules, Arg.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Finaburg *MR Pharma, Neth.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finac *C & M, USA.*
Sulfur (p.1614·1); methylbenzethonium chloride (p.1653·1).
Acne.

Finacea *Schering, Austral.; Intendis, Denm.; Intendis, Fr.; Intendis, Ital.; Intendis, Mex.; Intendis, Norw.; Intendis, Port.; Intendis, Spain; Schering, Swed.; Schering, UK; Berlex, USA.*
Azelaic acid (p.1589·3).
Acne; rosacea.

Finacilen *Microsules, Arg.*
Nimodipine (p.1357·2).
Ischaemic neurological deficit following subarachnoid haemorrhage.

Finagrip *Finadiet, Arg.†*
Paracetamol (p.108·1); salicylamide (p.121·2); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Influenza symptoms.

Finagrip Forte *Finadiet, Arg.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); bromhexine hydrochloride (p.1552·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Finajelf *Jelfa, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finalax *Liferpal, Mex.*
Ispaghula (p.1737·1).
Constipation.

Finalgel *Boehringer Ingelheim, Rus.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Finalgon *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Canad.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, NZ†; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Spain.*
Nonivamide (p.96·2); nicoboxil (p.95·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis; peripheral vascular disorders.

Finalop *Libbs, Braz.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Finamicina *Ivax, Mex.*
Rifampicin (p.325·3).
Tuberculosis.

Finan *Solfran, Mex.†*
Multivitamin and mineral preparation (p.1922·1).

Finanidda *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Finanorm *Valeant, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finap *Raffo, Chile.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder.

Finaplac *Epicaris, Arg.*
Chlorhexidine gluconate (p.1635·3).
Dental hygiene.

Finard *Ardez, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finarid *Nobel, Turk.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finaride *Hexal, Pol.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finartrit *Garden House, Arg.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Finasept *Microsules, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Finast *Reddy, Rus.; Biofarma, Venez.†*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finastec *Neo Quimica, Braz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finaster *Lek-Am, Pol.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finasterin *Finadiet, Arg.*
⊗ Finasteride (p.2188·3).

Finastid *Neopharmed, Ital.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finastil *Sigma, Braz.*
⊗ Finasteride (p.2188·3).

Finaten *Microsules, Arg.*
Bromazepam (p.964·3).
Alcohol withdrawal syndrome; anxiety; panic disorder; post-traumatic stress disorder.

Finater *Ivax, Mex.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Finateramida *Ivax, Mex.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Finatres *Finadiet, Arg.†*
Azithromycin (p.207·1).
Bacterial infections.

Finatux *Jaba, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Finavita *Perivita, Neth.†*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Finaxal *Sandoz, Indon.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Fincar *Cipla, India.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Findaler *Medipharm, Chile.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Findaler-D *Medipharm, Chile.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Findeclin *Finadiet, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Findeclin Combi *Finadiet, Arg.*
4 tablets, alendronate sodium (p.1088·1); 30 tablets, calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Findedol *Recalcine, Chile†.*
Ketorolac trometamol (p.74·2).
Pain.

Findol
Note.This name is used for preparations of different composition.
Temis, Arg.
Glucosamine sulfate (p.2313·2).
Joint disorders.

Senosiain, Mex.†
Ketorolac trometamol (p.74·2).
Pain.

Findol N *Mundipharma, Ger.†*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Findol Plus *Temis, Arg.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3).

Findor *Climax, Braz.†*
Dipyrone (p.49·2).
Fever; pain.

Finecil *LKM, Arg.*
Abacavir (p.861·3).
HIV infection.

Finelium *PP Lab, Thai.†*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; vestibular disorders.

Finescar *Biol, Arg.*
Silicone oil (p.2032·1).
Barrier preparation; decubitus ulcers.

Finevin *Berlex, USA.*
Azelaic acid (p.1589·3).
Acne.

Finex
Note.This name is used for preparations of different composition.
Sintofarma, Braz.†
Terbinafine hydrochloride (p.546·3).
Fungal infections.

Saval, Chile.
Terbinafine (p.546·3).
Fungal skin and nail infections.

Hexal, Cz.
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Fingras
Note.This name is used for preparations of different composition.
Dexter, Arg.†
Carnitine; chromium tripicolinate (p.1922·1).
Dietary supplement.

Phoenix, Arg.
Orlistat (p.2358·1).
Obesity.

Finibax *Shionogi, Jpn.*
Doripenem (p.266·3).
Bacterial infections.

Finicort *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Finidol *Novartis, Fr.†*
Aspirin (p.20·3); caffeine (p.1116·3).
Colloidal aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Finigas *Apsen, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Finil *Coradol, Ger.†*
Homoeopathic preparation.

Finimal *Bayer, Neth.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Finimal C *Bayer, Neth.*
Caffeine (p.1116·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Finimal Junior *Roche, Neth.†*
Paracetamol (p.108·1).
Fever; pain.

Finish *Kowa, Jpn.*
Povidone-iodine (p.1659·2).

Finitor *Confar, Port.*
Selenium sulfide (p.1613·1).
Fungal scalp infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Finlac *Sons, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Finlepsin *AWD, Ger.; Pliva, Hung.†; AWD, Pol.; AWD, Rus.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgia.

Finlipol *Microsules, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Finn *Boehringer Ingelheim, Braz.*
Aspartame (p.1930·1).
Sugar substitute.

Finn Cristal *Boehringer Ingelheim, Braz.*
Saccharin sodium (p.1960·3); sodium cyclamate (p.1936·3).
Sugar substitute.

Finnferon-Alpha *Veripalvelu, Fin.†.*
Interferon alfa (p.885·1).
Malignant neoplasms.

Finoptin *Orion, Rus.*
Verapamil hydrochloride (p.1421·1).

Finormet *Tiefenbacher, Neth.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Finox *Solvang, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Finoxi *Finadiet, Arg.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Finpecia *Cipla, India.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finpro *Interbat, Indon.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finprob *Farcoral, Mex.*
Pipenzolate bromide (p.1762·2); dimeticone (p.1770·2).
Gastrointestinal disorders.

Finpros *KRKA, Cz.; KRKA, Hung.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Finprostat *LKM, Arg.*
⊗ Finasteride (p.2188·3).

Finrexin *Leiras, Fin.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Fever; pain.

Fintal *Nicholas Piramal, India†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma; vernal keratoconjunctivitis.

Fintaxim *Swedpharm, Chile.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Fintop *Glenmark, India.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Finuret *Bernabo, Arg.*
Pipemidic acid (p.315·1).
Bacterial infections of the urinary tract.

Fiometil *Etifar, Venez.†.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); chloroform (p.1781·1); balsam fioraventi.

Fioricet *Watson, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Fioricet with Codeine *Novartis, USA.*
Codeine phosphate (p.37·2); butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Fiorinal
Note. This name is used for preparations of different composition.
Novartis Consumer, Austral.
Codeine phosphate (p.37·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Pain.

Novartis, Canad.; Novartis, USA.
Aspirin (p.20·3); butalbital (p.967·2); caffeine (p.1116·3).
Pain; vascular or tension headaches.

Fiorinal C *Novartis, Canad.*
Butalbital (p.967·2); caffeine (p.1116·3); aspirin (p.20·3); codeine phosphate (p.37·2).
Anxiety; pain; tension.

Fiorinal Codeina *Novartis, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Fiorinal with Codeine *Novartis, USA.*
Aspirin (p.20·3); butalbital (p.967·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Tension headache.

Fioritina *Fada, Arg.*
⊗ Noradrenaline (p.1360·1).

Fiormil *Inpharzam, Switz.†.*
Enterococcus faecium (p.2372·3).
Restoration of normal gastrointestinal flora.

Fiosen Plus *Frasca, Arg.†.*
Alpha tocoferol; vitamin A; pyridoxine (p.1922·1).
Vitamin supplement.

Fiosen-A *Medica, Arg.†.*
Vitamin A (p.1971·2).
Skin disorders.

Fiotan *Nycomed, Braz.*
St John's wort (p.422·3).
Depression.

Fioton *Phoenix, Arg.*
Ginkgo biloba; vitamin E (p.1922·1).
Tonic.

Fipexiam
Note. This name is used for preparations of different composition.
Leti, Venez.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Leti, Venez.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

FiProFLAX *Arkopharma, UK.*
Flax oil; fibre; protein; carbohydrate; lignans (p.1922·1).
Dietary supplement.

Firac *Grossman, Mex.*
Clonixin lysine (p.37·1).
Pain.

Firac Plus *Grossman, Mex.*
Clonixin lysine (p.37·1); pargeverine hydrochloride (p.1761·1).
Smooth muscle pain and spasm.

Firex *Grin, Mex.*
Aciclovir (p.862·3).
Herpes labialis.

Firide *Siam Bheasach, Thai.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Firin *Schwarz, Ger.*
Norfloxacin (p.309·2).
Bacterial infections.

Firmel *Craveri, Arg.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Firon *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Fironetta *Schering, Denm.†.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Triphasic oral contraceptive.

First Choice *Polymer Technology, USA.*
Test for glucose in blood (p.2314·1).

First Defence *Procter & Gamble, Austral.; Procter & Gamble, UK.*
Viscous nasal gel.
Cold prophylaxis.

First Response *Church & Dwight, Canad.; Carter-Wallace, UK; Carter-Wallace, USA.*
Pregnancy or fertility test (p.2372·1).

Firstcin *Takeda, Jpn.*
Cefozopran hydrochloride (p.231·1).
Bacterial infections.

Fisamox *Aspen, Austral.*
Amoxicillin sodium (p.202·2).
Bacterial infections.

Fish Factor *Farmila, Ital.*
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias.

Fishaphos *Felton, Austral.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Fisherman's Friend *Lofthouse of Fleetwood, Canad.*
Menthol (p.2340·1).
Coughs; sore throat.

Fisherman's Friend Original *Lofthouse of Fleetwood, Canad.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold symptoms.

Fishogar *Self-Care Products, UK.*
Fish oil; garlic (p.2309·2).

Fisifax *Reig Jofre, Spain†.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders; vascular headache.

Fisiobil *Salvat, Spain.*
Dimecrotic acid, magnesium salt (p.2294·1).
Hepatobiliary disorders.

Fisiocap *Pasteur, Chile.*
Nutritional supplement (p.1922·1).
Hair and nail disorders.

Fisiodar *Abiogen, Ital.*
Diacerein (p.41·3).
Osteoarthritis.

Fisioderm *Dermofarma, Ital.*
Soap substitute.

Fisiofer *Eurofarma, Braz.†; Labomed, Chile.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Fisiogastrol *Salvat, Spain†.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastroparesis.

Fisiogel *Stiefel, Arg.; Stiefel, Braz.; Stiefel, Chile.*
A range of moisturisers.
Dry skin.

Fisiogen *Zambon, Braz.*
Soya bean (p.1965·3).
Menopausal symptoms.

Fisiolax *Sanfer, Mex.†.*
Natural fibre (p.1712·3).
Constipation.

Fisiolimp *Pasteur, Chile.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene.

Fisiolin *Oftalmi, Venez.*
Sodium chloride (p.1686·1); monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Nasal cleansing; nasal congestion.

Fisiologica *Fardi, Spain.*
Sodium chloride (p.1686·1).
Nasal congestion.

Fisiologico *Betamadrileno, Spain; Neusc, Spain; Perez Gimenez, Spain.*
Sodium chloride (p.1686·1).
Nasal congestion.

Fisiologico Bieffe M *Baxter, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Fisiologico Braun *Braun, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Fisiologico Farmacelsia *Farmacelsia, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Fisiologico Isoton *Braun, Spain†.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Fisiologico Mein *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Fisiologico Serra Pamies *Serra Pamies, Spain.*
Sodium chloride (p.1686·1).
Diluent for parenterally administered drugs.

Fisiologico Vitulia *Ern, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Fisioren *Ducto, Braz.*
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).

Fisioreve *Laborest, Ital.*
Tryptophan (p.427·1); magnesium (p.1678·3); nicotinic acid (p.1957·3).
Depression; insomnia.

Fisiotens *Solvay, Gr.; Solvay, Ital.*
Moxonidine (p.1345·1).
Hypertension.

Fisohex *GSK, Braz.†.*
Triclosan (p.1665·2).
Skin disinfection.

Fisohex II *Farmasa, Braz.*
Triclosan (p.1665·2); pyrithione zinc (p.1611·2).
Skin disinfection.

Fisol *Nature's Way, Philipp.*
Omega-3 fish oil (p.1362·2).
Dietary supplement.

Fisomed *SM, Venez.*
Soap substitute.

Fisopred *Aventis, Mex.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Fissan
Note. This name is used for preparations of different composition.
Cana, Gr.†.
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin disorders.

Group, S.Afr.†.
Lactic protein hydrolysate; zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Uhlmann-Eyraud, Switz.†.
Casein hydrolysate (p.1934·1); bismuth subnitrate (p.1711·2); kaolin (p.1738·1); silica clay (p.2146·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Skin irritation.

Fissan-Pate *Cana, Gr.†.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2); rapeseed oil (p.2378·1); kaolin (p.1738·1); wool fat (p.2033·2).
Skin disorders.

Fissan-Silberpuder *Biovicent, Ger.*
Methenamine silver nitrate compound.
Umbilical cord care.

Fissan-Zinkschuttelmixtur *Salitine, Ger.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Fit Form 3 *Neves, Port.†.*
NeOpuntia; garcinia cambogia (p.2309·2); phaseolamin.
Hyperlipidaemias; obesity.

Fitacnol *Arkomedika, Fr.†.*
Lappa (p.2330·3); viola tricolor (p.2415·2); urtica (p.2409·3).
Seborrhoea.

Fitbon *Soho, Indon.*
Glucosamine hydrochloride (p.2313·2); manganese (p.1956·1).
Joint disorders.

Fitbon Plus *Soho, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); manganese (p.1956·1).
Joint disorders.

Fit-C *Soho, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Fitina *Vargas, Venez.*
Pyritinol (p.369·2).

Fitness *Cipla, India.*
Spirulina (p.2392·1).

Fitness Iper K *Scaglietti, Ital.*
Emollient.

Fitness Perle di Karite *Scaglietti, Ital.*
Emollient.

Fito *Tripharma, Turk.*
Wheat germ (p.2415·1).
Skin disorders.

Fito Stomygen *Stomygen, Ital.*
Mallow; hamamelis; chamomile; sage; calendula.
Herbal toothpaste.

Fitocalmin *Hochstetter, Chile†.*
Homoeopathic preparation.

Fitocassol *Kimia, Indon.*
Centella (p.1592·3).
Keloid scars.

Fitocreme *Fariberica, Port.*
Wheat germ (p.2415·1); phenoxyethanol.
Burns; ulcers; wounds.

Fitocyd *Unipharm, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Fitoderme *Hebron, Braz.†.*
Erigeron bonariensis.
Fungal infections.

Fitodiar *Kimia, Indon.*
Attapulgite (p.1709·1); psidium guajava; turmeric (p.1473·2).
Diarrhoea.

Fitoestimulina *Grossman, Mex.*
Wheat germ (p.2415·1); phenoxyethanol (p.1657·1).
Burns; ulcers; vaginal lesions; wounds.

Fitogen *Bergamon, Ital.*
Soya oil (p.1965·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Menopausal disorders; nutritional supplement.

Fitogen Plus *Bergamon, Ital.*
Nutritional supplement (p.1922·1).

Fitogenase *Bergamon, Ital.*
Soya isoflavones (p.2391·2); Indian frankincense (p.2307·1); glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); ananas sativus; omega-3 (p.1362·1).
Menopausal disorders.

Fitogenos *Framingham, Arg.*
Isoflavones; vitamin D; *d*-alpha tocopherol (p.1922·1).
Dietary supplement.

Fitogyn *Gynea, Spain.*
Soya (p.1965·3); red clover (p.2285·1).
Menopausal disorders.

Fitokey Eleuterococo *Inkeysa, Spain.*
Siberian ginseng (p.2386·3).
Tonic.

Fitokey Ginkgo *Inkeysa, Spain.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral circulatory disorders.

Fitokey Harpagophytum *Inkeysa, Spain.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Fitoladius *Rovi, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Fitolax *IMA, Braz.*
Senna (p.1769·2); cassia pulp (p.1715·3); tamarind (p.1775·3); coriander (p.2288·1).
Constipation.

Fitonal *Andromaco, Arg.*
Ketoconazole (p.539·1).
Fungal infections.

Fitoprost *Hasco-Lek, Pol.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Fitoquinona *Sanderson, Chile†.*
Phytomenadione (p.1995·3).

Fitosonno *Pharbenia, Ital.*
Eschscholtzia californica; passion flower (p.2363·2); valerian (p.2410·1).
Insomnia.

Fitostimoline
Note. This name is used for preparations of different composition.
Damor, Ital.
Cream; medicated dressing; pessaries; vaginal wash: Wheat germ (p.2415·1); phenoxyethanol (p.1657·1).
Burns; skin disorders; vaginal disorders; vascular disorders; wounds.

Damor, Ital.
Injection: Wheat germ (p.2415·1).
Burns; skin disorders; vascular disorders; wounds.

Fitosvelt *Arkochim, Spain†.*
Black currant (p.2267·1); tea (p.2416·1).
Diuretic.

Fitotos *Koni-Cofarm, Chile.*
Tolu balsam (p.1574·2); drosera (p.2297·3); quillaia (p.1920·1).
Coughs.

Fitoven *Herbapol Pruszkow, Pol.*
Aesculus (p.2248·2); crataegus (p.2289·1); solidago (p.2391·1); tilia (p.2402·2); buckwheat (p.2270·1); scoparium (p.2384·2); root beet.
Oedema; phlebitis; venous thrombosis.

Fitovit *Unique, Rus.*
Withania somnifera; emblica officinalis; asparagus; tinospora cordifolia; tribulus terrestris (p.2404·1); picrorhiza kurroa; cyerus scariosus; becopa monnieri; terminalia chebula; piper longum; nutmeg (p.2355·2).

Fitovital *Catarinense, Braz.*
St John's wort (p.422·3).
Depression.

Fitrum *Herbs & Nature, Philipp.*
Green tea extract (p.2416·1); levocarnitine (p.1932·2).
Dietary supplement.

Fittig *Andromaco, Chile.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); hexylresorcinol (p.1647·1); calcium propionate (p.545·3) or sodium propionate (p.545·3).
Fungal skin infections.

Fitzecalm *Julphar, UAE.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Fivasa *Norgine, Fr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Fivefluro *GSK, India.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Fiverdol *Maver, Mex.*
Paracetamol (p.108·1); naproxen (p.92·3).
Inflammation; pain.

Fivoflu *Dabur, Philipp.; Dabur, Thai.; Biogalenic, Venez.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Fixacep *Fahrenheit, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Fixateur phospho-calcique *Bichsel, Switz.*
Calcium carbonate (p.1714·1).
Hyperphosphataemia.

Fixca *Lesvi, Spain†.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Fixcanat *Pisa, Mex.*
Cysteine hydrochloride (p.1936·3).
Cysteine deficiency.

Fixcom 3 *Natrapharm, Philipp.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol (p.275·2).
Tuberculosis.

Fixcom 4 *Natrapharm, Philipp.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol (p.275·2).
Tuberculosis.

Fixef *Kalbe, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Fixical *Expanscience, Fr.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Fixical Vitamine D_3 *Expanscience, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Fixim *Astellas, Neth.*
Cefixime (p.224·3).
Bacterial infections.

Fixime *Merck, S.Afr.*
Cefixime (p.224·3).
Bacterial infections.

Fixiphar *Pharos, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Fixo *Scholl, Canad.†.*
Salicylic acid (p.1612·2).
Corns.

Fixocal *IBSA, Cz.†.*
Calcitonin (salmon) (p.1093·1).
Bone pain due to malignant neoplasms; hypercalcaemia; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Fixon *Novag, Mex.*
Imipramine (p.400·2).
Depression.

Fixopan *Farma, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fixoten *Cryopharma, Mex.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Fixx *Unichem, India.*
Cefixime (p.224·3).
Bacterial infections.

Fizoil *Behrens, Venez.*
Fish oil (p.1362·2).
Hypercholesterolaemia.

Fizyolen *Toprak, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Fizyosol *Oro, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Fizziclean *Bausch & Lomb, Braz.†.*
Subtilisin A (p.2393·3)(p.1622·2).
Cleansing of contact lenses.

FKD *Pasteur, Chile.*
Sodium bicarbonate (p.1673·2); sodium fluoride (p.1962·2); sodium pyrophosphate (p.2390·3).
Dental caries prophylaxis; dental whitener.

Flacar *Schwabe, Ger.*
⊗ Betaine dihydrogen citrate (p.2265·2); sorbitol (p.1965·1); mannitol (p.1330·2).
Liver disorders.

Flacerant *Lloyd, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; peptic ulcer.

Fladalgin *Proel, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Fladex *Dexa, Indon.; Dexa, Singapore.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Fladolef-B *Proel, Gr.†.*
Flurbiprofen (p.61·2).
Inflammatory disorders; pain.

Fladon *Daudt, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Fladystin *Dexa, Indon.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

Flagass *Ache, Braz.*
Simeticone (p.1770·2).
Flatulence.

Flagass Baby *Ache, Braz.*
Simeticone (p.1770·2); homatropine methylbromide (p.1881·3).
Flatulence.

Flagenase *Liomont, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Flagenase 400 *Liomont, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Flagenol *Allen, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Flagentyl *Aventis, Arg.; Aventis, Philipp.; Vitoria, Port.; Eczacibasi, Turk.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Flagepat *Parggon, Mex.*
Metronidazole (p.837·1).
Amoebiasis.

Flagocil *Collins, Mex.*
Diiodohydroxyquinoline (p.832·1); metronidazole (p.837·1).
Protozoal infections.

Flagolin *Farmedia, Gr.*
Metronidazole (p.837·1).

Flagyl
Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Fin.; Aventis, Ger.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Indon.; Aventis, Israel; Zambon, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, Philipp.; Vitoria, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Switz.; Eczacibasi, Turk.
Metronidazole (p.837·1).
Anaerobic bacterial infections; Crohn's disease; protozoal infections.

Aventis, Austral.; Sanofi-Aventis, Chile; Aventis, Denm.; Sanofi-Aventis, Fr.; Nicholas Piramal, India; Sanofi-Aventis, Irl.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Thai.; Winthrop, UK.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; Crohn's disease; protozoal infections.

SCS, USA; Searle, USA.
Metronidazole (p.837·1) or metronidazole hydrochloride (p.837·2).
Anaerobic bacterial infections; protozoal infections.

Flagyl Comp *Sanofi-Aventis, Fin.*
Metronidazole (p.837·1); nystatin (p.543·2).
Bacterial vaginosis; vaginal trichomoniasis.

Flagyl Nistatina *Sanofi-Aventis, Braz.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vulvovaginal candidiasis and trichomoniasis.

Flagyl-F *Nicholas Piramal, India†.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1); furazolidone (p.834·3).
Amoebiasis.

Flagystatin *Aventis, Arg.; Aventis, Canad.; Sanofi-Aventis, Indon.; Aventis, Philipp.; Sanofi-Aventis, Singapore.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vulvovaginal infections.

Flagystatin V *Aventis, Mex.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal trichomoniasis and candidiasis.

Flamador *Sigma, Braz.*
Ketoprofen (p.73·1).

Flamalgen *Vitapan, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flamalit *Vivax, Venez.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders; pain.

Flamanan *Legrand, Braz.*
Paracetamol (p.108·1); oxyphenbutazone (p.107·3).
Fever; inflammation; pain.

Flamar
Note. This name is used for preparations of different composition.
Indoco, India.
Methyl nicotinate (p.85·3); methyl salicylate (p.85·3); mephenesin (p.1897·2); menthol (p.2340·1).
Musculoskeletal, joint and soft-tissue disorders.

Sanbe, Indon.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Nabiqasim, Philipp.
Celecoxib (p.34·2).
Osteoarthritis; pain; rheumatoid arthritis.

Flamaret *Xixia, S.Afr.*
Indometacin (p.66·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Flamar-MX *Indoco, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Painful skeletal muscle spasm.

Flamatak *Alpharma, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Flamatec *Uniao Quimica, Braz.*
Meloxicam (p.80·3).

Flamatrol *Teva, Hong Kong†.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Flamazine *Smith & Nephew, Canad.; Smith & Nephew, Denm.; Smith & Nephew, Fin.; Smith & Nephew, Hong Kong; Smith & Nephew, Irl.; Smith & Nephew, Norw.; Smith & Nephew, S.Afr.; Smith & Nephew, Singapore†; Smith & Nephew, Thai.; Smith & Nephew Healthcare, UK.*
Sulfadiazine silver (p.337·2).
Burns; skin infections; ulcers; wounds.

Flamazine C *Smith & Nephew, Canad.†.*
Sulfadiazine silver (p.337·2); chlorhexidine gluconate (p.1635·3).
Burns; ulcers; wounds.

Flamebin *Offenbach, Mex.*
⊗ Ambroxol (p.1550·3); salbutamol (p.1131·2).
Respiratory-tract disorders.

Flamecid *Adcock Ingram, S.Afr.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Flamenac *Hexpharm, Indon.*
Diclofenac potassium (p.44·3).
Gout; musculoskeletal and joint disorders.

Flamergi *Sanbe, Indon.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic eye disorders; eye irritation.

Flameril
Novartis, Hung.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Biochemie, NZ; Novartis, NZ.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Normal, Port.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Flamesul *Intas, Philipp.*
Nimesulide (p.95·3).
Inflammation; pain.

Flametia *Tunggal Idaman, Indon.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Flamexin *Chiesi, Cz.; Chiesi, Hung.; Polfa Kutno, Pol.*
Piroxicam betadex (p.117·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flamic *Siam Bheasach, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flamicina *Ivax, Mex.*
Ampicillin (p.204·1), ampicillin sodium (p.204·1), or ampicillin trihydrate (p.204·2).
Bacterial infections.

Flamicort *Dexa, Indon.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Flamide *Rayere, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Flamin *Loren, Mex.†.*
Metronidazole (p.837·1).
Amoebiasis.

Flaminal *Intendis, Ital.*
Alginate dressing (p.2140·3).
Wounds.

Flaminase *Formenti, Ital.*
Promelase (p.2373·3).
Respiratory-tract disorders.

Flamints *Nicholas, Indon.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis.

Flamirex *Sanofi Synthelabo, Arg.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Flammacerium *Solvay, Belg.; Solvay, Cz.†; Solvay, Fr.; Solvay, Gr.; Solvay, Neth.; Solvay, Philipp.; Solvay, Pol.; Solvay, UK.*
Sulfadiazine silver (p.337·2); cerous nitrate (p.1593·1).
Available on a named patient basis in the UK.
Infected burns; infected wounds; skin infections.

Flammazine *Solvay, Austria; Solvay, Belg.; Solvay, Cz.†; Solvay, Fr.; Solvay, Ger.; IFET (ΙΦΕΤ), Gr.; Solvay, Neth.; Solvay, Philipp.; Solvay, Port.; Solvay, Spain; Solvay, Switz.*
Sulfadiazine silver (p.337·2).
Infected burns; infected wounds; skin infections; ulcers.

Flamon *Mepha, Switz.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension; ischaemic heart disease.

Flamostat *Cimed, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Flamoxi *Solas, Indon.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Flamozin *Loeffler, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Flamrase *Berk, UK.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Flamydol *Unipharm, Mex.*
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flamygel *Unipharm, Mex.*
Diclofenac diethylamine (p.44·3).

Flanakin *Kinder, Braz.*
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Inflammation; pain.

Flanamox *Wolff, Ger.*
Amoxicillin trihydrate (p.202·2); flucloxacillin sodium (p.277·1).
Bacterial infections.

Flanaren *Teuto, Braz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flanax *Bayer, Braz.; Roche, Braz.; Bayer Consumer, Mex.; Roche, Philipp.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Flancox *Apsen, Braz.*
Etodolac (p.52·2).

Flanders Buttocks *Flanders, USA.*
Zinc oxide (p.1621·2); peru balsam (p.2365·3).
Nappy rash.

Flanid *Pierre Fabre, Fr.*
Tiaprofenic acid (p.129·2).
Musculoskeletal and joint disorders; pain.

Flanil *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Insect bites; musculoskeletal pain; pruritus.

Flanizol *Delta, Braz.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Vaginal infections.

Flankol *Pharmacos, Mex.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Flanoquin *Liomont, Mex.†.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Flantadin *Teofarma, Ital.; Aventis, Turk.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Flanzen *Svizera, India.*
Serrapeptase (p.2385·3).
Hyphaema; inflammation or oedema associated with infection or trauma; respiratory-tract congestion; subconjunctival bleeding.

Flanzen-D *Svizera, India.*
Serrapeptase (p.2385·3); diclofenac sodium (p.44·3).
Inflammation.

Flapex *Silesia, Chile.*
Simeticone (p.1770·2).
Adjunct in gastrointestinal radiography; gastrointestinal disorders with excess gas.

Flapex E *Silesia, Chile.*
Simeticone (p.1770·2); pancreatin (p.2360·1); pepsin (p.2365·1); amylase (p.2256·3); bile (p.2266·2).
Digestive disorders; flatulence.

Flarex Alcon, Arg.; Alcon, Austral.; Alcon, Austria†; Alcon, Canad.; Alcon, Cz.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Pacific, NZ†; Alcon, Neth.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, Thai.; Alcon, Turk.; Alcon, USA.
⊗ Fluorometholone acetate (p.1533·1).
Inflammatory eye disorders.

Flash Vent-3, Arg.
Paracetamol (p.108·1).
Fever; pain.

Flashemel Ratiopharm, Cz.
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Flason Ikapharmindo, Indon.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Flaspas Daito, Jpn†.
Aranidipine (p.1216·3).
Hypertension.

Flatex Farmasa, Braz.
Dimeticone (p.1770·2).
Flatulence.

Flatezol Keyerson, Mex.†.
Albendazole (p.139·2).
Worm infections.

Flatin Prafa, Indon.
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Flatmed Bajamed, Mex.
Ranitidine (p.1766·1).
Peptic ulcer.

Flatol Legrand, Braz.
Dimeticone (p.1770·2).
Flatulence.

Flaton Bilim, Turk.
Pancreatin (p.2360·1); hemicellulase (p.2279·1); bile extract (p.2266·2); simeticone (p.1770·2).

Flatoril
Note.This name is used for preparations of different composition.
Almirall, Spain.
Clebopride malate (p.1722·1); simeticone (p.1770·2).
Dyspepsia; gastro-oesophageal reflux; hiatus hernia.

Elmor, Venez.
Simeticone (p.1770·2).
Digestive disorders; flatulence.

Flatucid Soho, Indon.
Aluminium magnesium silicate (p.2141·2); simeticone (p.1770·2).
Dyspepsia; gastritis; peptic ulcer.

Flatulence Greater Pharma, Thai.
Cascara (p.1715·2); capsicum (p.2276·2); amylase (p.2256·3); ginger (p.1732·3); nux vomica (p.2355·3); asafetida (p.2261·3).
Formerly known as Flatulence Gastulence.
Constipation; flatulence.

Flatulex
Note.This name is used for preparations of different composition.
Bayer, Switz.
Chewable tablets: Simeticone (p.1770·2); caraway oil (p.2277·1); fennel oil (p.2303·1); peppermint oil (p.1761·2).
Detergent poisoning; excess gastrointestinal gas; preparation for gastrointestinal examination.

Bayer, Switz.; Dayton, USA.
Oral drops: Simeticone (p.1770·2).
Detergent poisoning; excess gastrointestinal gas; flatulence; preparation for gastrointestinal examination.

Dayton, USA.
Tablets: Simeticone (p.1770·2); activated charcoal (p.1435·2).
Flatulence.

Flatunic Nicholas, Indon.
Simeticone (p.1770·2).
Abdominal distension; defoaming agent in radiography; dyspepsia; flatulence.

Flaval Cetus, Arg.
Bamethan (p.1222·3); diclofenac (p.44·2); esculoside (p.2248·2).

Flavamed
Berlin-Chemie, Cz.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Berlin-Chemie, Pol.
Ambroxol (p.1550·3) or ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Flavamed Halstabletten Berlin-Chemie, Ger.†.
Benzocaine (p.1854·1).
Sore throat.

Flavan Dexo, Fr.
Leucocianidol (p.2304·3).
Capillary fragility; haemorrhoids; venous insufficiency.

Flavangin Streuli, Switz.†.
Ethacridine lactate (p.1625·1); cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Mouth and throat disorders.

Flavate Overseas, India.
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Flavedon Serdia, India.
Trimetazidine hydrochloride (p.1419·2).
Ischaemic heart disease.

Flaveric Pfizer, Jpn.
Benproperine phosphate (p.1552·1).
Coughs.

Flavettes CCM, Hong Kong; Upha, Indon.; Upha, Singapore.
Vitamin C (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Flavettes Cal D3 CCM, Hong Kong.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Flavettes Neuroforte CCM, Malaysia.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgias; neuritis; neuropathy; vitamin B supplement.

Flaviastase Iphym, Fr.
Amylase (p.2256·3); protease.
Digestive disorders.

Flavicina Pharmacia, Arg.†.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Flavin Landson, Indon.
Echinacea (p.2298·1); serrapeptase (p.2385·3).
Inflammation.

Flavinol Chew, Thai.
Acriflavinium monochloride (p.1625·1); thymol (p.1664·3).
Burns; wounds.

Flavion
Note.This name is used for preparations of different composition.
Terapeutico, Ital.
Tablets: Aesculus; centella; lemon; red vine (p.1922·1).
Nutritional supplement.

Terapeutico, Ital.
Topical gel: Aesculus (p.2248·2); catechu (p.2278·2); solidago virgaurea (p.2391·1).
Peripheral vascular disorders.

Flavit Hormona, Mex.
Bioflavonoids (p.2304·1); ascorbic acid (p.1983·3).
Capillary fragility.

Flavit AV Hormona, Mex.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Hypersensitivity; nasal congestion; pain.

Flavix Wockhardt, India.
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression.

Flavobion Zentiva, Cz.
Silymarin (p.1452·2).
Liver disorders.

Flavobion-C Farmanic, Gr.
Calcium glycerophosphate (p.1676·1); vitamin C (p.1983·3); ergocalciferol (p.1987·1).
Breast-feeding; osteoporosis; pregnancy.

Flavo-C Auriga, Hong Kong.
Vitamin C (p.1983·3); ginkgo biloba (p.2311·1).
Skin ageing; skin hyperpigmentation.

Flavodrei Chiesi, Spain.
Soya bean (p.1965·3).
Menopausal disorders.

Flavogin Baif, Ital.
Ginkgo biloba; bioflavonoids; dog rose; myrtillus; vitamin C (p.1922·1).
Tonic.

Flavol Ronava, Venez.
Troxerutin (p.2305·1).
Haemorrhoids; phlebitis; varices.

Flavon
Note.This name is used for preparations of different composition.
Norma (Νορμα), Gr.†.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

General Drugs, Thai.
Flavonoids (p.2304·1).
Haemorrhoids; vascular insufficiency.

Flavonex Auriga, Fr.
Soya isoflavones (p.2391·2).
Menopausal disorders.

Flavonid Neo Quimica, Braz.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Capillary leakage; venous insufficiency.

Flavonil Kinder, Braz.
Soya isoflavones (p.2391·2).
Dietary supplement.

Flavonoid Complex GNLD, Austral.
Cranberry; kale; green tea; red beetroot; mixed berries; oregon grape; grape; orange extract; lemon extract; grapefruit (p.2304·1).
Flavonoid supplement.

Flavons
Note.This name is used for preparations of different composition.
Eagle, Austral.
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); calcium ascorbate (p.1984·1); hesperidin (p.2304·3); bioflavonoids (p.2304·1); rutoside (p.2305·1); rose fruit (p.2381·2); boneset (p.2267·3); echinacea (p.2298·1); achillea (p.2245·2).
Minor wounds; tonic.

Freeda, USA.
Citrus bioflavonoids complex (p.2304·1); hesperidin (p.2304·3).
Capillary bleeding.

Flavoquine Sanofi-Aventis, Fr.
Amodiaquine hydrochloride (p.597·2).
Malaria.

Flavorin TO-Chemicals, Thai.
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Flavo-Spa Utopian, Thai.
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Flavostat Lafedar, Arg.†.
Vitamin A (p.1971·2).
Vitamin supplement.

Flavoton GD, Ital.
Bioflavonoids; calcium; magnesium; colecalciferol (p.1922·1).
Nutritional supplement.

Flavourpac Vitaflo, Irl.
Range of flavours for use with unflavoured protein substitutes (p.1922·1).

Flavovenyl
Note.This name is used for preparations of different composition.
Plan, Switz.
Capsules; oral drops: ⊗ Bioflavonoids (p.2304·1); hesperidin methyl chalcone (p.2305·2); esculoside (p.2248·2).
Haemorrhoids; venous insufficiency.

Plan, Switz.
Ointment: ⊗ Bioflavonoids (p.2304·1); hesperidin methyl chalcone (p.2305·2); esculoside (p.2248·2); menthol (p.2340·1).
Haemorrhoids; venous insufficiency.

Flavoxen Alpharma, Mex.
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flavo-Zinc Solgar, UK.
Zinc gluconate (p.1999·2); zinc citrate (p.1999·2).
Dietary supplement.

Flaxedil Concord, UK†.
Gallamine triethiodide (p.1906·2).
Competitive neuromuscular blocker.

Flaxendol Vitae, Mex.
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Flaxin Merck, Braz.
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Flaxine IAE, Philipp.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Flaxtec Tecnofarma, Mex.
Metronidazole (p.837·1).
Amoebiasis.

Flaxvan Rontag, Arg.
Naproxen (p.92·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flazal Neo Quimica, Braz.
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Flaz-Cort Cazi, Braz.
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Flebeside Jorba, Spain†.
Carbazochrome (p.1058·2); troxerutin (p.2305·1).
Vascular disorders.

Flebil Plus Bracco, Ital.
Troxerutin (p.2305·1); pycnogenol (p.2368·1).
Nutritional supplement.

Flebior Therasophia, Fr.
Myrtillus (p.2349·3); buckwheat (p.2270·1); red vine (p.2316·3); vitamin E; vitamin C (p.1922·1).
Capillary disorders; nutritional supplement.

Flebitol Phoenix, Arg.
⊗ Ginkgo biloba (p.2311·1); heptaminol hydrochloride (p.2319·1); troxerutin (p.2305·1).
Phlebitis; premenstrual disorders; venous insufficiency.

Flebo Ikatral Baliarda, Arg.
OPC.
Fragile capillaries; haemorrhagic disorders; haemorrhoids; maculopathy; oedema; post-thrombotic syndrome; retinopathy; venous insufficiency.

Flebobag Fisio Grifols, Spain.
Sodium chloride infusion (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Flebobag Glucosa Grifols, Spain.
Glucose infusion (p.1945·3).
Parenteral nutrition.

Flebobag Glucosalina Grifols, Spain.
Sodium chloride infusion (p.1686·1) with glucose (p.1945·3).
Fluid and electrolyte depletion; hypovolaemia.

Flebobag Ring Lact Grifols, Spain.
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Flebocortid Lepetit, Ital.; Janssen-Cilag, Mex.
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Floboderma Sandoz, Arg.
A heparinoid (p.1305·2).
Haemorrhoids; phlebitis; soft-tissue disorders; thrombophlebitis.

Flebodolor Spedrog, Arg.
Ruscogenin (p.2382·2).
Peripheral vascular disorders; soft-tissue disorders.

Fleboflex Glucosa Grifols, Spain.
Glucose infusion (p.1945·3).
Fluid disorders; parenteral nutrition.

Fleboflex Salina Fisio Grifols, Spain.
Sodium chloride infusion (p.1686·1).
Fluid and electrolyte disorders.

Flebofort
Note.This name is used for preparations of different composition.
KG, Ital.
Tablets: Fruit bioflavonoids (p.2304·1); centella (p.1592·3); myrtillus (p.2349·3); melilot (p.2339·2); ananas gambo.
Circulatory disorders.

KG, Ital.
Topical gel: Menthol (p.2340·1); myrtillus (p.2349·3); centella (p.1592·3); ananas sativus; bioflavonoids (p.2304·1).
Circulatory disorders.

Flebogamma Grifols, Arg.; Grifols, Chile; Grifols, Cz.; Grifols, Ger.; Demo, Gr.; Grifols, Hong Kong; Grifols, Israel; Grifols, Ital.; Grifols, Malaysia; Grifols, Neth.; Grifols, Port.; Grifols, Singapore; Grifols, Spain; Grifols, Thai.; Dem, Turk.; Grifols, UK; Grifols, USA; Pharmakin, Venez.
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency disorders; Kawasaki disease; passive immunisation.

Flebolider Amnol, Ital.
Aescin (p.2248·2); caffeine (p.1116·3); diosmin (p.2304·2); coumarin (p.2288·2); butcher's broom (p.2270·3); centella (p.1592·3); arnica (p.2260·2); ivy (p.2328·1); zinc oxide (p.1621·2).
Inflammation.

Flebon Ivax, Arg.
Diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

Flebopex Bago, Chile.
Rutoside (p.2305·1).
Haemorrhoids; metrorrhagia; retinal haemorrhage; venous insufficiency.

Feboplast Fisio Grifols, Spain.
Sodium chloride infusion (p.1686·1).
Fluid and electrolyte depletion; hypovolaemia.

Feboplast Glucosa Grifols, Spain.
Glucose infusion (p.1945·3).
Parenteral nutrition.

Feboplast Glucosalina Grifols, Spain.
Sodium chloride infusion (p.1686·1) with glucose (p.1945·3).
Fluid and electrolyte depletion; hypovolaemia.

Feboplast Plurisal Grifols, Spain.
Electrolyte infusion (p.1667·1) with sodium lactate (p.1673·3).
Fluid and electrolyte depletion; hypovolaemia.

Flebopom Typen, Arg.†.
Ruscogenin (p.2382·2).
Inflammation; phlebitis.

Flebo-Si SIFFRA, Ital.
Centella (p.1592·3); aesculus (p.2248·2); melilot (p.2339·2); myrtillus (p.2349·3); rutoside (p.2305·1).
Circulatory disorders.

Feboside Pharmafar, Ital.
Troxerutin (p.2305·1); carbazochrome (p.1058·2).
Capillary fragility; venous insufficiency.

Febosmil Socopharm, Fr.
Diosmin (p.2304·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Flebostasin
Note.This name is used for preparations of different composition.
Sankyo, Ital.
Aesculus (p.2248·2).
Capillary fragility; chronic venous insufficiency.

Sankyo, Spain.
Aescin (p.2248·2).
Oedema; peripheral vascular disorders.

Flebotrat Neckerman, Braz.†.
Coumarin (p.2288·2); troxerutin (p.2305·1).
Varices.

Flebotropin
Note.This name is used for preparations of different composition.
Bago, Arg.†.
Cream: Flavonoids (p.2304·1); benzocaine (p.1854·1).
Haemorrhoids; venous insufficiency.

Bago, Arg.
Tablets: Flavonoids (p.2304·1).
Haemorrhoids; venous insufficiency.

Flebovis Amnol, Ital.
Soya oil; centella; melilot; cumin; *dl*-alpha tocoferil acetate; rutoside; triglycerides (p.1922·1).
Circulatory disorders; haemorrhoids; nutritional supplement; oedema.

Flebozin Depofarma, Ital.
Melilot; aesculus; centella (p.1922·1).
Nutritional supplement.

Flebs Pierre Fabre, Ital.
Heparin sodium (p.1301·2); a heparinoid (p.1305·2).
Haemorrhoids; phlebitis; soft-tissue injury; thrombophlebitis.

Flebutol Rowe-Fleming, Venez.†.
⊗ Acebutolol (p.1200·1).
Arrhythmias; hypertension.

flecadura Merck dura, Ger.
Flecainide acetate (p.1288·1).
Arrhythmias.

Flecaine 3M, Fr.
Flecainide acetate (p.1288·1).
Arrhythmias.

Flecatab *Alphapharm, Austral.*
Flecainide acetate (p.1288·1).
Arrhythmias.

Flecor-N *Biospray, Gr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Flectadol
Note.This name is used for preparations of different composition.
Recalcine, Chile.
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Musculoskeletal, joint, and peri-articular disorders; tension headache.

Sanofi-Aventis, Ital.
Lysine aspirin (p.79·1).
Musculoskeletal and joint disorders; pain.

Flectar *Biomedica-Chemica, Gr.†.*
Nizatidine (p.1751·2).
Peptic ulcer.

Flector
Sanova, Austria; Therabel, Belg.; Labomed, Chile; IBSA, Cz.; IBSA, Denm.; Meda, Fin.; IBSA, Hong Kong; IBSA, Hung.; Bayer, Ital.; Delta, Port.; Meda, Swed.; Alpharma, USA.
Diclofenac epolamine (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Genevrier, Fr.; IBSA, Switz.
Diclofenac epolamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain.

Fleet *De Witt, Denm.; De Witt, Irl.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Accu-Prep *Fleet, USA.*
Fleet Phospho-Soda; Fleet Relief anorectal wipes.
Bowel evacuation.

Fleet Adulto *Consupharma, Mex.*
Glycerol (p.2314·2).
Bowel evacuation.

Fleet Babylax *Rider, Chile; Fleet, Hong Kong; Fleet, Malaysia; Fleet, Singapore†; Fleet, USA; Zuoz, Venez.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Fleet Bagenema *Fleet, USA.*
Water (p.2414·3).
Formerly contained liquid castile soap.

Fleet Bisacodyl *Fleet, USA.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Fleet Enema *Raymos, Arg.†; Wolfs, Belg.; Wyeth Consumer, Braz.; Johnson & Johnson, Canad.; Rider, Chile; Pharmakochimiki (Φαρμακοχημική), Gr.; Fleet, Hong Kong; Combiphar, Indon.; Dexxon, Israel; Fleet, Malaysia; Fleet, Philipp.; De Witt, Port.; Fleet, Singapore†; Kozmed, Turk.; Fleet, USA; Zuoz, Venez.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Enema Fosf-Sodio *Consupharma, Mex.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Enema Mineral Oil *Johnson & Johnson, Canad.*
Liquid paraffin (p.2030·3).
Bowel evacuation; constipation.

Fleet Fosfo Soda *Kozmed, Turk.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fleet Fosfosoda
Rider, Chile.
Monobasic sodium phosphate (p.1682·3); tribasic sodium phosphate (p.1683·1).
Bowel evacuation; constipation.

Zuoz, Venez.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fleet Gebruiksklaar Klysma *De Witt, Neth.*
Monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Infantil *Consupharma, Mex.*
Glycerol (p.2314·2).
Bowel evacuation.

Fleet Laxative *Baxter, NZ; Fleet, NZ; Fleet, USA.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Fleet Medicated Pads *Fleet, USA†.*
Hamamelis water (p.2318·2); alcohol; glycerol.
Anorectal disorders.

Fleet Micro *Ferring, Swed.†.*
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3).
Constipation.

Fleet Micro-Enema
Note.This name is used for preparations of different composition.
Fleet, Austral.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Fleet-Dewitt, Hong Kong†; Baxter, NZ†; Fleet, NZ†; De Witt, Port.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3).
Bowel evacuation; constipation.

Fleet Mineral Enema *Baxter, NZ†; Fleet, NZ†.*
Liquid paraffin (p.2030·3).
Bowel evacuation; constipation.

Fleet Pain Relief *Fleet, USA.*
Pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Fleet Pedialax *Consupharma, Mex.*
Glycerol (p.2314·2).
Bowel evacuation.

Fleet Phosphate Enema *Baxter, NZ; Fleet, NZ.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Phospho-Soda
Note.This name is used for preparations of different composition.
Fleet, Austral.; De Witt, Austria; Wolfs, Belg.; Johnson & Johnson, Canad.; Ferring, Fr.; Ferring, Ger.; Fleet, Hong Kong; De Witt, Hung.; Fleet, Malaysia; Baxter, NZ; De Witt, Pol.; De Witt, Port.; Fleet, Singapore†; De Witt, UK; Fleet, USA.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Pharmakochimiki (Φαρμακοχημική), Gr.
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.1922·1).
Laxative.

Fleet Phosposoda *Combiphar, Indon.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fleet Prep Kit No. 1 *Fleet, USA.*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p.1710·1), 4 tablets; Fleet Bisacodyl Suppositories, 1 suppository.
Bowel evacuation.

Fleet Prep Kit No. 2 *Fleet, USA.*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p.1710·1), 4 tablets; Fleet Bagenema, 1 enema.
Bowel evacuation.

Fleet Prep Kit No. 3 *Fleet, USA.*
Combination pack: Fleet Phospho-Soda; Fleet Bisacodyl Tablets (p.1710·1), 4 tablets; Fleet Bisacodyl Enema.
Bowel evacuation.

Fleet PS *Consupharma, Mex.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fleet Ready-to-Use *Fleet, Austral.; De Witt, UK.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Flefarmin *Biospray, Gr.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Flegamin *Pliva, Rus.*
Bromhexine hydrochloride (p.1552·2).

Flegamina *Pliva, Cz.†; Pliva Krakow, Pol.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Flegatussin *Herbapol Lublin, Pol.*
Bromhexine hydrochloride (p.1552·2); ribwort plantain (p.2379·1); verbascum (p.2413·3).
Cough; respiratory-tract congestion.

Flegyl *Sanofi-Aventis, Venez.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Flemagon *Coup, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).

Flemdazole *Rowe-Fleming, Venez.†.*
Mebendazole (p.148·3).
Worm infections.

Flemex
Note.This name is used for preparations of different composition.
Precimex, Mex.
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Pfizer Consumer, S.Afr.; Gemardi, Thai.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Flemex Jat *Recalcine, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); tolu (p.1574·2); herbs.
Coughs.

Flemex-AC *Gemardi, Thai.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Flemeze *Pfizer Consumer, S.Afr.*
⊗ Orciprenaline sulfate (p.1129·1); bromhexine hydrochloride (p.1552·2).
Coughs.

Flemgo *Alliance, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased or viscous mucus.

Flemibar *Roemmers Rowe, Venez.*
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Muscle spasm; pain.

Flemicaine *Roemmers Rowe, Venez.*
Lidocaine hydrochloride (p.1862·3); eugenol (p.2301·2).
Toothache.

Flemina *Precimex, Mex.†.*
Dopamine hydrochloride (p.1273·2).

Fleminate *Novo Pharm, Philipp.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Fleming *Medreich, Hong Kong.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Fleminosan *Pharmathen, Hong Kong†.*
Clindamycin phosphate (p.251·2).
Acne.

Flemizyme *Pascual, Hong Kong.*
Muramidase hydrochloride (p.2348·1).
Adjunct in antibacterial therapy; haemorrhage; respiratory-tract congestion; sinusitis.

Flemlite *Garec, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased or viscous mucus.

Flemmi-Ped *SA Druggists Self Med, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Flemoclav *Astellas, Rus.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Flemoxin
Astellas, Belg.; Yamanouchi, Denm.; Yamanouchi, Fin.†; East India Pharma, India; Astellas, Neth.; Astellas, Port.; Astellas, Rus.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Gerolymatos, Gr.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

CSL, NZ; Yamanouchi, Switz.†.
Amoxicillin (p.202·2).
Bacterial infections.

Flemoxine *Astellas, Fr.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Flemoxon *Eurolab, Arg.; Merck, Braz.†; Merck, Mex.; Merck, Venez.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Flemun *Intermuti, Ger.†.*
Sitosterol (p.1373·2).
Rheumatic disorders.

Flemycin *Elpen (Ελπεν), Gr.*
Cefotaxime (p.229·1).
Bacterial infections.

Flenazole *Target, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Flenid *Merckle, Ger.†.*
Sodium cromoglicate (p.1136·3).
Hypersensitivity reactions.

Flenin *Schuck, Ger.*
Homoeopathic preparation.

Flepin X-3 *Farcoral, Mex.†.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2); moroxydine hydrochloride (p.898·2).
Cold symptoms.

Flerox
Note.This name is used for preparations of different composition.
Pharmacia, Arg.†.
Leucocianidol (p.2304·3).
Capillary disorders; haemorrhoids; venous insufficiency.

Sanitas, Chile.
Flunarizine (p.580·3).
Mental function impairment; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Flerudin *Janssen-Cilag, Spain.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Flespan *Vargas, Venez.*
Panpurol.

Fletanol *Sante Naturelle, Canad.†.*
Vitamin A and vitamin D (p.1922·1).

Fletcher's Arachis Oil *Pharmax, Irl.*
Arachis oil (p.2259·1).
Faecal impaction.

Fletchers Arachis Oil Retention Enema *Forest Laboratories, UK†.*
Arachis oil (p.2259·1).
Constipation.

Fletchers Castoria *Mentholatum, USA.*
Senna (p.1769·2).
Constipation.

Fletchers Enemette *Forest Laboratories, UK†.*
Docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Fletchers Phosphate Enema *Forest, Irl.; Pharmax, Irl.; Forest Laboratories, UK†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fletchers Sore Mouth Medicine *Nasmark, Canad.*
Alum (p.2254·1); potassium chlorate (p.2371·3).
Canker sores; denture irritation; herpes labialis.

Flevic *Bernabo, Arg.*
Enterococcus faecium (p.2372·3).
Maintenance of normal gastrointestinal flora.

Flevion *Medicus, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Flevostol *Bros, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Flex Metak *Kener, Mex.*
Dextromethorphan (p.1555·2).
Cough.

Flexafen *Diba, Mex.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flexagen *Lennon, S.Afr.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flexagil *Kern, Spain†.*
Carisoprodol (p.1894·1); propyphenazone (p.119·3).
Musculoskeletal spasms.

Flexal Brennessel *Hexal, Ger.*
Urtica (p.2409·3).
Rheumatic pain.

Flexal Vitamin E *Hexal, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Flexalgex *Geolab, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine (p.1116·3).

Flexalgin *Geolab, Braz.*
Paracetamol (p.108·1); diclofenac (p.44·2); carisoprodol (p.1894·1).

Flex-All *Martin, Arg.; Chattem, Canad.*
Menthol (p.2340·1).
Muscle and joint pain.

Flex-all 454 *Chattem, USA.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal pain and stiffness.

Flexamina *Climax, Braz.†.*
Diclofenac sodium (p.44·3).

Flexamol *Diba, Mex.*
Meloxicam (p.80·3); methocarbamol (p.1897·3).
Formerly contained salicylamide and methocarbamol.
Painful skeletal muscle spasm.

Flexaphen *Trimen, USA.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Musculoskeletal pain.

Flexar *Menarini, Port.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Flexase *TAD, Ger.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Flexasur
Note.This name is used for preparations of different composition.
Kalbe, Indon.
Capsules: Cetyl myristoleate; eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Inflammation; joint disorders.

Kalbe, Indon.
Cream: Cetyl myristoleate; methyl salicylate (p.85·3); menthol (p.2340·1).
Inflammation; musculoskeletal and joint pain.

Flexbumin *Baxter, Cz.; Baxter, Port.*
⊗ Albumin (p.1052·1).
Hypovolaemia; plasma volume expansion.

Flex-Care *Alcon, Mex.; Alcon, USA.*
Solution for complete care of soft contact lenses (p.1622·2).

Flexdor *Bunker, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine (p.1116·3).
Skeletal muscle spasm.

Flexelite *Bros, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Flexen
Note.This name is used for preparations of different composition.
Italfarmaco, Ital.
Ketoprofen (p.73·1) or ketoprofen sodium (p.73·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rayere, Mex.†.
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders.

Italfarmaco, Rus.
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flexeril *Janssen-Ortho, Canad.†; McNeil, USA.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Flexeze
Note.This name is used for preparations of different composition.
Goldshield, Singapore†.
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C (p.1983·3); calcium (p.1675·2).
Maintenance of joint and connective tissue function.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Goldshield, UK.
Capsules: Glucosamine sulfate (p.2313·2); chondroitin (p.2280·3).
Osteoarthritis.

Goldshield, UK.
Topical gel: Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Flexfree *Omega, Belg.*
Felbinac (p.54·3).
Soft-tissue, peri-articular, and joint pain and inflammation.

Flexiban *SIT, Ital.; Valeant, Port.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Flexicamin *Sidus, Arg.*
Piroxicam (p.117·3); carisoprodol (p.1894·1).
Musculoskeletal, joint, and peri-articular disorders.

Flexicamin A *Sidus, Arg.*
Piroxicam (p.117·3); carisoprodol (p.1894·1); dipyrone (p.49·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flexicamin B12
Note.This name is used for preparations of different composition.
Sidus, Arg.
Injection: ⊗ Piroxicam (p.117·3); pyridoxine (p.1979·1); dexamethasone (p.1526·1); hydroxocobalamin (p.1980·3).
Musculoskeletal, joint, peri-articular, and soft tissue disorders; neuritis.

Sidus, Arg.
Tablets: ⊗ Piroxicam (p.117·3); carisoprodol (p.1894·1); dexamethasone (p.1526·1); pyridoxine (p.1979·1); hydroxocobalamin (p.1980·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis.

Flexicamin Crema *Sidus, Arg.†.*
Piroxicam (p.117·3); myrtecaine (p.1867·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flexid *Hoe, Philipp.*
Sodium fusidate (p.279·3).
Bacterial skin infections.

Flexiderm *Herbapol Poznan, Pol.*
Silymarin phospholipids (p.1452·2).
Skin disorders.

Flexidin *Mundipharma, Austria.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Flexidol
Note.This name is used for preparations of different composition.
Raffo, Arg.
Meloxicam (p.80·3).
Inflammation; pain.

Almirall, Spain†.
Fepradinol hydrochloride (p.60·2).
Peri-articular disorders; soft-tissue disorders.

Flexidol Relax *Raffo, Arg.*
Meloxicam (p.80·3); pridinol (p.1898·2).
Inflammation; pain.

Flexidon *Cosmopharm, Gr.†.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux disease; peptic ulcer.

Flexidone *Organifar, Venez.†.*
Carisoprodol (p.1894·1); aminophenazone (p.19·1).
Musculoskeletal and joint disorders.

Flexifer *Pulitzer, Ital.†.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Flexigesic *Medi-Rx, Philipp.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Flexiherb *MedicHerb, UK.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

flexi-loges *Loges, Ger.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Fleximin *Merck, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Flexi-muv
Note.This name is used for preparations of different composition.
Cadila, India.
Oil: Indian bdellium; vitex negundo; cissus quadrangularis; costus speciosus; melia azadirachta (p.2262·2); emblica officinalis; terminalia chebula; terminalia bellirica; camphor (p.2273·2); pinus longifolia; celery (p.2278·3); cedrus deodara; eucalyptus oil (p.2301·2); cajuput oil (p.2271·2).

Cadila, India.
Ointment: Turpentine oil (p.2406·3); sweet birch oil (p.86·2); camphor (p.2273·2); menthol (p.2340·1); capsicum (p.2276·2).
Musculoskeletal pain.

Flexin
Note.This name is used for preparations of different composition.
Sidus, Arg.
Diclofenac sodium (p.44·3).

Taro, Israel.
Orphenadrine citrate (p.812·1).
Skeletal muscle spasm.

Flexin Continus *Napp, Irl.; Napp, UK†.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flexinol *Cipla, India.*
Methocarbamol (p.1897·3); paracetamol (p.108·1).

Flexiplen *Vitarum, Arg.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal and joint disorders; pain.

Flexi-T *Prosan, Hong Kong; Family Planning Sales, UK.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Flexital *Sun, Rus.; Sun, Thai.*
Pentoxifylline (p.1367·2).
Cerebral, ocular, and peripheral vascular disorders.

Flexitec *Technilab, Canad.†.*
Cyclobenzaprine hydrochloride (p.1895·2).

Flexium
Note.This name is used for preparations of different composition.
Sidus, Arg.
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders; pain.

Melisana, Belg.
Etofenamate (p.53·1).
Lumbar spondylosis; peri-articular disorders; soft-tissue injury.

Flexiver *Maver, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flexivit *Eadriex, Philipp.*
Vitamins; lysine; chlorella; taurine (p.1922·1).
Nutritional supplement.

Flexo *Santa, Turk.*
Etofenamate (p.53·1).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Flexocam *Pharma Dynamics, S.Afr.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis; sciatica.

Flexogan *Advance, Singapore.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint pain.

Flexol *Unipharm, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flexon
Note.This name is used for preparations of different composition.
Aristo, India.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; pain.

Keene, USA.
Orphenadrine citrate (p.812·1).
Musculoskeletal pain.

Flexon-MR *Aristo, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1); chlorzoxazone (p.1894·3).

Flexono *Sanitas, Chile.*
Indometacin (p.66·3).
Aluminium glycinate (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; pain.

Flexor *Dexa, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3).
Degenerative joint disorders.

Flexove *Navamedic, Cz.*
Glucosamine hydrochloride (p.2313·2).
Osteoarthritis of the knee.

Flex-Power Performance Sports *Flex-Power, USA.*
Trolamine salicylate (p.132·3).
Musculoskeletal and joint disorders.

Flexresan *Centrum, Spain.*
Isotretinoin (p.1599·2).
Acne.

Flexsa *Mega Lifesciences, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Flextinol *Vitae, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Flextoss *Teuto, Braz.*
Dropropizine (p.1557·3).
Coughs.

Flextra *Poly, USA.*
Paracetamol (p.108·1); phenyltoloxamine citrate (p.588·1).
Pain.

Flexurat *Naturissima, Venez.*
Glucosamine (p.2313·2); chondroitin.
Arthrosis.

Flexure *Mepro, Chile.*
Glucosamine sulfate sodium chloride (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.

Flexxbon *Meyers, Philipp.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Flexy *TP, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal and joint pain and inflammation.

Flezol *Ferrer, Spain†.*
Zolmitriptan (p.628·1).
Migraine.

Flicazen *Med-One, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis; allergic skin disorders.

Flicum *Distriquimica, Spain.*
Flubendazole (p.145·1).
Ascariasis; enterobiasis; hookworm infections; trichuriasis.

Flidaphen *Zwitter, Gr.*
Ketoconazole (p.539·1).
Fungal scalp disorders.

Flihaler *Biospray, Gr.*
⊗ Fluticasone (p.1533·2).
Obstructive airways disease.

Flimutal *Cryopharma, Mex.*
Flutamide (p.725·1).
Prostatic cancer.

Flindix *Vitoria, Port.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

flint *Togal, Ger.*
Poly(butylmethacrylate, methylmethacrylate) (p.2343·3).
Wounds.

Flintstones *Bayer Consumer, Canad.; Bayer, Philipp.; Bayer, Singapore†; Miles Consumer Healthcare, USA.*
Multivitamins or multivitamins and minerals (p.1922·1).

Flipal *Royal, Chile.*
Mefenamic acid (p.80·1).
Pain.

Flisint *Sanofi-Aventis, Fr.*
Fumagillin (p.834·2).
Microsporidiosis.

Flitrion *Iator, Gr.*
Isotretinoin (p.1599·2).
Acne.

Flivas *Asahi, Jpn.*
Naftopidil (p.2190·2).

Flix *Dinctas, Turk.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flixid *Novofarm (Νοβοφαρμ), Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Flixocort *Verisfield, Gr.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Flixoderm *Verisfield, Gr.; GSK, Ital.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Flixonase *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; Allen, Gr.†; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; Allen & Hanburys, Irl.; GSK Consumer, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, Turk.; GSK Consumer, UK; GSK, Venez.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; nasal polyps.

Flixotaide *Glaxo Wellcome, Port.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Flixotide
GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; Allen & Hanburys, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; GSK, Venez.
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; asthma; obstructive airways disease.

GSK, Gr.
Cream; ointment: ⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

GSK, Gr.
Inhaler; nasal spray: ⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; asthma.

Flixovate *GSK, Fr.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Flobacin *Sigma-Tau, Ital.*
Ofloxacin (p.310·2).
Bacterial infections.

Flocadep *Natiris, Venez.*
Smilax officinalis (p.2383·3); taraxacum (p.2395·1); rosemary (p.2381·2).

Flocet *Collins, Mex.*
Fluoxetine (p.397·3).
Depression.

Flociprin
Phoinix Pharm (Φοινιξ Φαρμ), Gr.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

IBI, Ital.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Flo-Coat *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Flocur *Beta, Arg.; Pfizer, Mex.†.*
Tolfenamic acid (p.130·1).
Migraine; pain; rheumatism.

Flodemex *Pasteur, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Flodeneu *Remedina, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flodermol *Juventus, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Flodil
Note.This name is used for preparations of different composition.
AstraZeneca, Fr.
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Minerva (Μινερβα), Gr.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Flodin Duo *Zodiac, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Flodol *Uno, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Flodolor *Alta Care, Ital.*
Polygonatum officinale; meadowsweet (p.2338·1); aesculus (p.2248·2); arnica (p.2260·2); liquorice (p.1740·3); devil's claw root (p.39·1); ananas; papaya; peppermint oil (p.1761·2); juniper oil (p.2328·3).
Muscle and joint pain.

Flodont *Roemmers Rowe, Venez.*
Benzydamine hydrochloride (p.27·3).
Inflammation; mouth and throat disorders.

Flogan *Merck, Braz.*
Diclofenac (p.44·2), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flogaren *Ronava, Venez.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Flogecyl *Wild, Switz.*
Aescin beta (p.2248·2); carrageenan (p.2142·3).
Mouth disorders.

Flogen *Ivax, Mex.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Flogenac *Raffo, Arg.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Flogencyl *Expanpharm, Fr.*
Aescin (p.2248·2).
Mouth ulcers.

Flogene *Ache, Braz.*
Piroxicam betadex (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Flogesic *Klinger, Braz.†.*
Diclofenac sodium (p.44·3).

Flogiatrin *Sanofi Synthelabo, Arg.*
Carisoprodol (p.1894·1); piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Flogiatrin B12 *Sanofi Synthelabo, Arg.*
⊗ Carisoprodol (p.1894·1); piroxicam (p.117·3); dexamethasone (p.1526·1); pyridoxine (p.1979·1); hydroxocobalamin (p.1980·3).
Musculoskeletal, joint, and soft-tissue disorders; neuritis.

Flogiftalmina *Davi, Port.†.*
⊗ Phenylephrine hydrochloride (p.1568·1); prednisolone metasulfobenzoate sodium (p.1541·1).
Eye disorders.

Flogilid *Luper, Braz.†.*
Nimesulide (p.95·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Floginax *Teofarma, Ital.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders; pain.

Flogin-Ped *Stiefel, Braz.†.*
Benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Flogiren *Sanval, Braz.*
Diclofenac (p.44·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flogmed *Farmedia, Gr.*
Nabumetone (p.91·2).
Inflammatory disorders.

Flogo Rosa *Ache, Braz.*
Benzydamine hydrochloride (p.27·3).
Vaginal irritation.

Flogocan *Azevedos, Port.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Flogocefal *Lacefa, Arg.†.*
Naproxen (p.92·3).
Fever; inflammation; pain.

Flogocort *Bago, Chile.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Flogodisten *Omicron, Arg.*
Niflumic acid (p.95·2); orphenadrine citrate (p.812·1).
Formerly contained niflumic acid, orphenadrine citrate, and aluminium hydroxide.

Flogofenac
Ecobi, Hong Kong.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Ecobi, Ital.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Flogofin *Laboratorios Chile, Chile.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Flogofort *Amnol, Ital.*
Maritime pine (p.2368·1); aesculus (p.2248·2); bromelains (p.2269·1); vitamin B substances (p.1922·1).
Inflammation; oedema.

Flogogin *Angelini, Ital.†.*
Naproxen sodium (p.92·3).
Lidocaine hydrochloride (p.1862·3) and lidocaine (p.1862·3) are included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders; pain.

Flogojet *Andromaco, Chile.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Flogoken *Kener, Mex.*
Diclofenac (p.44·2).
Rheumatic disorders.

Flogol *Lazar, Arg.*
Etofenamate (p.53·1).
Musculoskeletal, joint, and soft-tissue disorders.

Flogolab *Multilab, Braz.*
Benzydamine hydrochloride (p.27·3).
Inflammation.

Flogolisin *Lazar, Arg.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Flogonac *Haller, Braz.†.*
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Fever; inflammation; pain.

Flogoprofen *Chiesi, Hong Kong; Chiesi, Spain.*
Etofenamate (p.53·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Flogoral *Ache, Braz.; Lepori, Port.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders.

Flogosan *Liomont, Mex.†.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders; pain.

Flogosine *Ahimsa, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Flogostop
Note. This name is used for preparations of different composition.
Ivax, Arg.
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Biospray, Gr.
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Flogoter *Estedi, Spain.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flogovis *Amnol, Ital.*
Aesculus; bromelains; pineapple; zinc sulfate; copper sulfate (p.1922·1).
Inflammation; nutritional supplement; oedema.

Flogovis IdroGel *Amnol, Ital.*
Aescin (p.2248·2); bromelains (p.2269·1).
Inflammation; oedema.

Flogovital *Bago, Arg.*
Niflumic acid (p.95·2).
Inflammation.

Flogovital NF *Bago, Arg.*
Nimesulide (p.95·3).
Inflammation.

Flogoxen *Medley, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Flogozyme *Norma (Νορμα), Gr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Flohale *Cipla, India.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Flohale DP *Cipla-Medpro, S.Afr.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Floksid *Promed, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Floksin *Sanli, Turk.*
Flucloxacillin (p.277·1).
Bacterial infections.

Flolan *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fr.; IFET (ΙΦΕΤ), Gr.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, UK; Gilead, USA.*
Epoprostenol sodium (p.1279·3).
Pulmonary hypertension; thrombosis prophylaxis during haemodialysis.

Flolid *CT, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Floltec *Greenpharma, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Flomax
Note. This name is used for preparations of different composition.
CSL, Austral.; Boehringer Ingelheim, Canad.; CSL, NZ; Astellas, S.Afr.; Boehringer Ingelheim, Turk.; Yamanouchi, UK†; Abbott, USA.
Tamsulosin hydrochloride (p.2197·1).
Formerly known as Omnic in *NZ.*
Benign prostatic hyperplasia.

Chiesi, Ital.
Morniflumate (p.86·2).
Fever; inflammation; pain.

Flomaxtra *CSL, Austral.; CSL, NZ; Astellas, UK.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Flomed *Boniscontro & Gazzone, Ital.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Flomex *Cipla, India.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flomex N *Cipla, India.*
⊗ Fluorometholone (p.1532·3); neomycin (p.305·1).
Infected eye disorders.

Flomicin *Neo Quimica, Braz.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Flomin *Astellas, Neth.; Astellas, Port.*
Solifenacin succinate (p.2196·1).
Bladder instability.

Flomist *Cipla, India; Cipla-Medpro, S.Afr.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Flomox *Shionogi, Jpn.*
Cefcapene pivoxil hydrochloride (p.223·1).
Bacterial infections.

Flonacin *Ares, Mex.*
Ofloxacin (p.310·2).
Bacterial infections.

Flonase *GSK, Canad.; GSK, Jpn; Glaxo Wellcome, USA.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Flonidan *Sandoz, Cz.; Teva, Hung.; Lek, Pol.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; hypersensitivity reactions; urticaria.

Flonital *Anfarm, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Flonivin *ICN, Cz.†.*
Bacillus subtilis.
Diarrhoea; dyspepsia; flatulence; meteorism; restoration of intestinal flora.

Flonorm *Schering-Plough, Mex.; BioSaude, Port.*
Rifaximin (p.330·1).
Bacterial infections of the gastro-intestinal tract; diarrhoea; diverticular disease; hyperammonaemia secondary to hepatic encephalopathy.

Flopen *CSL, Austral.*
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Gram-positive coccal infections.

Flo-Pred *Taro, USA.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

florabio Manna-Feigen *Schoenenberger, Ger.*
Manna (p.1744·2); fig (p.1731·3).
Constipation.

florabio Mann-Feigen-Sirup mit Senna *Florabio, Ger.†.*
Fig (p.1731·3); cassia; manna (p.1744·2).
Constipation.

florabio naturreiner Heilpflanzensaft *Schoenenberger, Ger.*
A range of plant extracts.

Florac *Cadila, India.*
Fluorouracil (p.722·2).

Floradix Krauterblut
Note. This name is used for preparations of different composition.
Salushaus, Ger.
Oral liquid: Ferrous gluconate (p.1939·1); thiamine hydrochloride; riboflavin sodium phosphate; pyridoxine hydrochloride; cyanocobalamin (p.1922·1).
Iron deficiency; tonic.

Salushaus, Ger.
Tablets: Ferrous gluconate; folic acid; thiamine hydrochloride; riboflavin; nicotinamide (p.1922·1).
Tonic.

Floradix Multipretten N *Salushaus, Ger.*
Caraway (p.2276·3); caraway oil (p.2277·1); fennel (p.2302·3); fennel oil (p.2303·1); aniseed (p.2258·2) anise oil (p.2258·2); coriander (p.2288·1); coriander oil (p.2288·1); peppermint leaf (p.1761·2); peppermint oil (p.1761·2); absinthium (p.2244·1); achillea (p.2245·2).
Gastrointestinal disorders.

Floragermina 6 *Montefarmaco, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins; lactoferrin; inulin (p.1922·1).

Floral Pas *Gache, Venez.*
Valerian (p.2410·1); passion flower (p.2363·2).
Insomnia; nervous disorders.

Floranex *Rising Pharmaceuticals, USA.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3).
Dietary supplement.

Floraquin *Ali, Turk.*
Diiodohydroxyquinoline (p.832·1).
Vaginal infections.

Florastor *Biocodex, USA.*
Saccharomyces boulardii (p.2372·3).

Florate *Alcon, Braz.*
⊗ Fluorometholone acetate (p.1533·1).
Eye disorders.

Floratil *Merck, Arg.; Merck, Braz.; Merck, Mex.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Florax *Hebron, Braz.†.*
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea; restoration of gastrointestinal flora.

Floraxina *Amhof, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Florazole *Ferring, Canad.*
Metronidazole (p.837·1).
Bacterial vaginosis.

Florbiox *Crinos, Ital.†.*
Multivitamin and mineral preparation with *Lactobacillus acidophilus* (p.1922·1)(p.2372·3).
Maintenance of gastrointestinal flora.

Florcidin *Biotech, Venez.*
Lactobacillus acidophilus (p.2372·3).
Restoration of gastrointestinal flora.

Florelax *Sanofi-Aventis OTC, Ital.*
Dried yeast (p.1998·3); lactic-acid-producing organisms (p.2372·3); chamomile (p.2279·3); angelica (p.2258·1); valerian (p.2410·1); peppermint leaf (p.1761·2); caraway (p.2276·3); vitamin B substances (p.1922·1).
Gastrointestinal disorders.

Florelax Stomaco *Sanofi Synthelabo, Ital.†.*
Pineapple stem; rice starch; dog rose; green tea (p.1922·1).
Gastrointestinal disorders.

Floren
Note. This name is used for preparations of different composition.
Ativus, Braz.
Lactobacillus acidophilus (p.2372·3).

KG, Ital.
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium bifidum* (p.2372·3).
Restoration of gastrointestinal flora.

Florent *Cifarma, Braz.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Floresse *Roche Consumer, UK.*
Borage oil (p.2267·3) with or without vitamins.

Florestor *Merck, Venez.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Florexal *Silanes, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Florgynal *IPRAD, Fr.*
Estriol (p.2101·1); progesterone (p.2125·1); *Lactobacillus casei* var. *Rhamnosus* (p.2372·3).
Adjunct in gynaecological surgery during menopause; vulvovaginitis.

Florical *Mericon, USA.*
Calcium carbonate (p.1714·1); sodium fluoride (p.1962·2).
Dietary supplement.

Florid *Mochida, Jpn.*
Miconazole (p.541·2).
Fungal infections.

Floridine *DHN, Fr.*
Preparation for enteral nutrition (p.1922·1).

Floridral *Dicofarm, Ital.*
Glucose; sodium citrate; potassium chloride; sodium chloride; aspartame; *Lactobacillus* (p.1672·2)(p.2372·3).
Diarrhoea; disturbances of the gastrointestinal microbial flora; oral rehydration therapy.

Florilax
Note. This name is used for preparations of different composition.
Floris, Israel.
Senna (p.1769·2).
Constipation.

Confar, Port.†.
Glucomannan (p.2312·3).
Constipation; hyperlipidaemias; obesity.

Florimix *DHN, Fr.†.*
Preparation for enteral nutrition (p.1922·1).

Florinef *BMS, Austral.; Shire, Canad.; BMS, Chile; BMS, Denm.; BMS, Fin.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Irl.; BMS, Israel†; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, UK; Monarch, USA.*
Fludrocortisone acetate (p.1530·1).
Adrenocortical insufficiency; congenital adrenal hyperplasia.

Florinefe *BMS, Braz.; BMS, Venez.†.*
Fludrocortisone acetate (p.1530·1).
Adrenocortical insufficiency; congenital adrenal hyperplasia; orthostatic hypotension.

Floriny *Ativus, Braz.*
Passion flower (p.2363·2); crataegus (p.2289·1); salix (p.121·3).
Anxiety disorders.

Florisan *Boehringer Ingelheim, Gr.*
Docusate sodium (p.1725·1); bisacodyl (p.1710·1).
Constipation.

Florisan N *Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.*
Bisacodyl (p.1710·1).
Constipation.

Florisene *Lamberts Healthcare, UK.*
Ferrous glycine sulfate; vitamin C; vitamin B ; lysine (p.1922·1).
Hair loss in women.

Florissamin *Andrae, Austria†.*
Urtica (p.2409·3); aniseed (p.2258·2).
Diuretic.

Florissamol *Andrae, Austria†.*
Urtica (p.2409·3); camphor (p.2273·2).
Chilblains; muscle and joint pain; scalp disorders; soft-tissue disorders.

Florlax *Cazi, Braz.*
Senna (p.1769·2); tamarind (p.1775·3); coriander (p.2288·1); cassia pulp (p.1715·3).
Constipation.

Floroc *Sandoz, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Florone *Galderma, Ger.; Dermik, USA.*
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Florosan *Ecosol, Switz.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Florsalmin *Zentiva, Cz.*
Sage (p.2382·3).
Halitosis; hyperhidrosis; mouth and throat inflammation.

Florvis GG *Novartis Consumer, Ital.*
Preparation for enteral nutrition (p.1922·1) containing *Lactobacillus* GG (p.2372·3).

Flosa *Merckle, Ger.*
Ispaghula (p.1737·1).
Constipation; stool softener.

Flosef *Milmet, India.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flosep *Euromex, Mex.*
Ofloxacin (p.310·2).
Bacterial infections.

Flosine *Bittermedizin, Ger.*
Ispaghula (p.1737·1).
Constipation; stool softener.

Flossac *Caber, Ital.*
Norfloxacin (p.309·2).
Bacterial urinary-tract infections.

Flotac *Novartis, Arg.†; Novartis, Braz.; Novartis, Chile; Novartis, Mex.; Novartis, Venez.*
Diclofenac colestyramine (p.46·1).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Flotavid *Mersifarma, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Flotina *Lampugnani, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Flotiran *Schering-Plough, Port.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Infected skin disorders.

Flotral *Ranbaxy, India.*
Alfuzosin (p.2183·1).
Benign prostatic hyperplasia.

Flotrin *Mibe, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Flovacil *Pharmabiotics, Chile.*
Moxifloxacin (p.302·2).
Bacterial infections.

Flovent *GSK, Canad.; GSK, USA.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Flovid *Hovid, Hong Kong; Hovid, Malaysia†; Hovid, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Flox *Hexal, Braz.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxacin *Stada, Austria; MSD, Braz.; Medix, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxacipron *BA Farma, Port.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Floxager *Streger, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Floxal *Riel, Austria; Mann, Cz.; Mann, Ger.; Mann, Hung.; Mann, Pol.; Mann, Rus.; Bausch & Lomb, Switz.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Floxalin *Bioprogress, Ital.*
Naproxen sodium (p.92·3).
Musculoskeletal and joint disorders; pain.

Floxamicin *Biotenk, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxan
Note. This name is used for preparations of different composition.
Prodotti, Braz.
Ciprofloxacin (p.243·3).
Bacterial infections.

Sandoz, Indon.
Ofloxacin (p.310·2).
Bacterial infections.

Floxanor *Delta, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxantina *Degorts, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Floxapen
GSK, Austral.; GSK, Irl.; GSK, NZ; GSK, Neth.; GSK, UK.
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Bacterial infections.

GSK, Austria; GSK, Belg.; GSK, Indon.; GSK, Mex.; Beecham, Port.; GSK, S.Afr.; SmithKline Beecham, Switz.; GSK, Venez.
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Ipca, India†.
Flucloxacillin (p.277·1).
Bacterial infections.

Floxaquil *Decomed, Port.†.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Floxatom *Tomnus, Braz.†.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Floxatral *LA, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxatrat *Luper, Braz.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxbio *Sandoz, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Floxedol *Edol, Port.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Floxel *Medichem, Philipp.*
Levofloxacin (p.292·2).
Bacterial infections.

Floxelena *Pharmacos Abug, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Floxen *Raza, Hong Kong; Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxet *Egis, Cz.; EGIS, Hung.*
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorders; premenstrual dysphoric disorder.

Flox-ex *Ecosol, Switz.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Floxicam *Neo Quimica, Braz.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Floxid *Solvay, Braz.*
Roxithromycin (p.331·1).
Bacterial infections.

Floxigra *Graha, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Floxika *Ikapharmindo, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Floxil
Note. This name is used for preparations of different composition.
Janssen-Cilag, Arg.; Janssen-Cilag, Mex.
Ofloxacin (p.310·2).
Bacterial infections.

Tecnimede, Port.†.
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Floxilin *HB, Braz.†.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Floxin
Note. This name is used for preparations of different composition.
Janssen-Ortho, Canad.; Ortho McNeil, USA.
Ofloxacin (p.310·2).
Bacterial infections.

Korea United, Philipp.
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Be-Tabs, S.Afr.
Norfloxacin (p.309·2).
Bacterial urinary-tract infections.

Sriprasit, Thai.
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders.

Floxin Otic *Daiichi, USA.*
Ofloxacin (p.310·2).
Bacterial ear infections.

Floxina *Cazi, Braz.*
Ofloxacin (p.310·2).
Bacterial infections.

Floxinol *Millet Roux, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Floxinon *Ariston, Braz.†.*
Pefloxacin (p.313·3).
Bacterial infections.

Floxitul *Randall, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Floxlevo *Biotenk, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

Floxsig *Sigma, Austral.*
Flucloxacillin sodium (p.277·1).
Gram-positive coccal infections.

Floxstat *Janssen-Cilag, Braz.; Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Ofloxacin (p.310·2).
Bacterial infections.

Floxur *Merind, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Floxy *Millimed, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Floxyfral *Solvay, Austria; Solvay, Belg.; Solvay, Fr.; Solvay, Switz.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Flozepan *Lazar, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Flozul *Farlab, Port.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Flu-21 *Uno, Ital.†.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Flu, Cold & Cough Medicine *Major, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Flu Oph *Seng, Thai.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flu Stop *GMP, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Fluacort *Meda, Belg.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluad *Temis, Arg.; Grunenthal, Austria; Novartis, Cz.; Chiron Vaccines, Ger.; Chiron Vaccines, Hong Kong; Chiron Vaccines, Ital.; Chiron Vaccines, Philipp.; Novartis Vaccines, Port.; Novartis Vaccines, Singapore; Chiron, Swed.; Meda, Swed.; Chiron Vaccines, Thai.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Fluagel *EMS, Braz.†.*
Aluminium hydroxide (p.1706·2).
Gastrointestinal hyperacidity.

Fluanxol
Lundbeck, Austral.; Lundbeck, Hung.; Healthcare Logistics, NZ.
Flupentixol decanoate (p.997·1).
Psychoses.

Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Canad.; Silesia, Chile; Lundbeck, Cz.; Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Fr.; Bayer, Ger.; Lundbeck, Hong Kong; Lundbeck, India; Lundbeck, Israel; Lundbeck, Mex.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Philipp.; Lundbeck, Pol.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Swed.; Lundbeck, Switz.; Lundbeck, Thai.; Lundbeck, Turk.
Flupentixol decanoate (p.997·1) or flupentixol dihydrochloride (p.997·2).
Alcohol or opioid withdrawal syndromes; anxiety; depression; mixed anxiety depressive states; nervous disorders; neuroses; psychoses; schizophrenia.

Lundbeck, Irl.; Lundbeck, UK.
Flupentixol hydrochloride (p.997·2).
Depression; mixed anxiety depressive states.

Lundbeck, Malaysia.
Flupentixol (p.997·1), flupentixol decanoate (p.997·1), or flupentixol hydrochloride (p.997·2).
Anxiety; depression; psychoses.

Lundbeck, Singapore.
Flupentixol (p.997·1) or flupentixol decanoate (p.997·1).
Anxiety; depression; psychoses; psychosomatic disorders.

Fluarix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Braz.†; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; Novolog, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.†; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, USA; GSK, Venez.*
An inactivated influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Fluaton *Tubilux, Ital.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flubason *Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Flubest *Ali, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Flubiclox *Douglas, Austral.*
Flucloxacillin sodium (p.277·1).
Gram-positive coccal infections.

Flubilar *Madaus, Fr.*
Sodium methylcamphorate.
Constipation; dyspepsia.

Flubiotic NF *Pharmazam, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Flubir *Norma (Νορμα), Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Fluc *Hexal, Ger.†.*
Fluconazole (p.532·1).
Fungal infections.

Flucacid *Euro-Pharma, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flucadex *Graha, Indon.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Flucalin *Ariston, Arg.*
Calcium gluceptate (p.1675·3); calcium gluconate (p.1675·3); vitamin C (p.1983·3).
Nutritional supplement.

Flucam *Pfizer, Jpn†.*
Ampiroxicam (p.19·2).
The name FluCam has been used to identify a combination regimen of fludarabine with alemtuzumab.
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flucan *Pfizer, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Flucandid *Ivax, Irl.*
Fluconazole (p.532·1).
Fungal infections.

Flucanil *Geolab, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Flucanol *Zeus, Braz.†; Rafa, Israel.*
Fluconazole (p.532·1).
Fungal infections.

Flucaps *Biotech Naturis, Venez.*
Echinacea angustifolia (p.2298·1).
Cold and influenza.

Flucazol *Cristalia, Braz.; Spirig, Switz.*
Fluconazole (p.532·1).
Fungal infections.

Flucazole *Pacific, NZ.*
Fluconazole (p.532·1).
Vaginal candidiasis.

Fluccil *Ducto, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Fluccinol C *Arlex, Mex.†.*
⊗ Fluocinolone (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Fluccinol N *Arlex, Mex.*
⊗ Fluocinolone (p.1531·3); neomycin (p.305·1).
Infected skin disorders.

Flucef *Max Farma, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flucess *Sandoz, Indon.; Sandoz, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Fluciderm *Shiwa, Thai.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluciderm-N *Shiwa, Thai.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Flucil
Note. This name is used for preparations of different composition.
Aspen, Austral.
Flucloxacillin sodium (p.277·1).
Gram-positive coccal infections.

Masa, Thai.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Flucillin *Pinewood, Irl.*
Flucloxacillin sodium (p.277·1).
Gram-positive bacterial infections.

Flucinal *Selvi, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flucinar *Jelfa, Cz.; Medphano, Ger.; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flucinar N
Jelfa, Hung.; Jelfa, Pol.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Jelfa, Rus.
⊗ Fluocinolone acetonide (p.1531·3); neomycin (p.305·1).
Infected skin disorders.

Flucinom *Schering-Plough, Cz.; Schering-Plough, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Flucinome *Essex, Switz.*
Flutamide (p.725·1).
Prostatic cancer.

Flucirac *Natiris, Venez.*
Hamamelis (p.2318·2); calendula (p.2273·1); phyllantus niruri; aloe vera (p.1588·2).
Haemorrhoids; phlebitis; varices.

Flucis *AB-Consult, Austria; Schering, Neth.; CIS, Port.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide for detection of malignant neoplasms by positron-emission tomography.

Flucistein *Uniao Quimica, Braz.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Fluclomix *Ashbourne, UK.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Fluclon *Clonmel, Irl.*
Flucloxacillin sodium (p.277·1).
Gram-positive bacterial infections.

Fluclox *Carinopharm, Ger.; Uno, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flucloxa *Astrapin, Ger.†; Hameln, Ger.†.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Flucloxil *Duopharma, Hong Kong.*
Flucloxacillin (p.277·1).
Bacterial infections.

Flucloxin *Douglas, NZ.*
Flucloxacillin sodium (p.277·1).
Gram-positive bacterial infections.

Fluco *Sandoz, Cz.*
Fluconazole (p.532·1).
Fungal infections.

Flucobeta *Betapharm, Ger.*
Fluconazole (p.532·1).
Fungal infections.

Flucocaps *AG Therapy, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Flucoccinum *Knop, Chile.*
Homoeopathic preparation.

Flucodan *Arrow, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Flucoderm *Dermapharm, Ger.*
Fluconazole (p.532·1).
Fungal infections.

Flucodrug *Med-One, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Flucofast *Medana, Pol.*
Fluconazole (p.532·1).
Fungal infections.

Flucohexal *Sandoz, Hung.*
Fluconazole (p.532·1).
Fungal infections.

Flucol
Note. This name is used for preparations of different composition.
Rowex, Irl.
Fluconazole (p.532·1).
Fungal infections.

Degorts, Mex.
Naproxen (p.92·3); pseudoephedrine hydrochloride (p.1571·2).
Influenza; rhinitis; sinusitis; upper respiratory-tract congestion.

Acupharm, S.Afr.; Garec, S.Afr.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; sinusitis.

FlucoLich *Winthrop, Ger.*
Fluconazole (p.532·1).
Fungal infections.

Flucoltrix *Gallia, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Flucomed *Cimed, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Flucon
Note. This name is used for preparations of different composition.
Alcon, Austral.; Alcon, Belg.; Alcon, Cz.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, NZ; Alcon, Pol.; Alcon, S.Afr.; Alcon, Thai.
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Roemmers Osmoph, Venez.
Fluconazole (p.532·1).
Fungal infections.

Fluconabene *AB-Consult, Austria.*
Fluconazole (p.532·1).
Fungal infections.

Fluconal *Libbs, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Fluconapen *Elpen (Ελπεν), Gr.*
Fluconazole (p.532·1).
Fungal infections.

Fluconax *Ariston, Braz.†; Drossapharm, Switz.*
Fluconazole (p.532·1).
Fungal infections.

Fluconeo *Neo Quimica, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Fluconovag *Gobbi, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Flucor Day *Hovid, Malaysia.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Flucor Night *Hovid, Malaysia.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Flucoral *Kalbe, Indon.*
Fluconazole (p.532·1).
Fungal infections.

Flucoric *Ranbaxy, Hong Kong; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, S.Afr.*
Fluconazole (p.532·1).
Fungal infections.

Flucort *Glenmark, India.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flu-Cortanest *Piam, Ital.*
⊗ Diflucortolone valerate (p.1529·2).
Burns; insect stings; skin disorders.

Flucort-C *Glenmark, India.*
⊗ Fluocinolone acetonide (p.1531·3); ciclopirox olamine (p.529·2).
Infected skin disorders.

Flucort-H *Glenmark, India.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flucortis *Verisfield, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis.

Flucort-MZ *Glenmark, India.*
⊗ Miconazole nitrate (p.541·3); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Flucort-N *Glenmark, India.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Flucosept *Kwizda, Austria.*
Fluconazole (p.532·1).
Fungal infections.

Flucostat *Dalkhimfarm, Rus.; Masterlek, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Flucoxan *Sanitas, Chile; Pisa, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Flucozal *Faromed, Austria; Aegis, Hong Kong.*
Fluconazole (p.532·1).
Fungal infections.

Flucozan *Veropharm, Rus.†.*
Fluconazole (p.532·1).
Fungal infections.

Flucozen *Cazi, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Flucozix *Luper, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Flucozole *Siam Bheasach, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Flucreme NM *Concept, India.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Fluctin
Note. This name is used for preparations of different composition.
Gynopharm, Chile.
Fluconazole (p.532·1).
Fungal infections.

Lilly, Ger.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluctine *Lilly, Austria; Alpharma, Mex.; Lilly, Switz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Flucur *Shigaken, Singapore†.*
⊗ Chlorphenamine maleate (p.571·3); naphazoline hydrochloride (p.1565·2).
Cold symptoms; rhinitis; sinusitis.

Flucyl *Bode, Indon.; Tempo Scan Pacific, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Fludac *Cadila Pharma, India.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fludactil *Garec, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Fludactil Co *Garec, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Fludactil Expectorant *Garec, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Fludakebir *Aspen, Arg.*
Fludarabine (p.722·1).

Fludan
Biolab, Hong Kong; Biolab, Malaysia.
Flunarizine hydrochloride (p.580·2).
Migraine; peripheral vascular disorders; vestibular disorders.

Biolab, Thai.
Flunarizine (p.580·3).
Cerebrovascular disorders; migraine.

Fludan Codeina *Faes, Spain.*
Codeine phosphate (p.37·2).
Cough.

Fludane *Armoxindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Influenza symptoms.

Fludane Plus *Armoxindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Cough; influenza symptoms.

Fludapamide *Spirig, Switz.*
⊗ Indapamide (p.1314·1).
Hypertension.

Fludara
Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Schering, Hung.; German Remedies, India; Schering, Indon.; Schering, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Lusalfarma, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Singapore; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Bayer, UK; Bayer, USA; Schering, Venez.
Fludarabine phosphate (p.721·1).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Berlex, Canad.
Fludarabine phosphate sodium (p.722·1).
Chronic lymphocytic leukaemia; non-Hodgkin's lymphoma.

Fludarene *Thea, Ital.*
Chromocarb diethylamine (p.2281·1).
Capillary fragility.

Fludecan *Svizera, India.*
Fluphenazine decanoate (p.998·1).
Schizophrenia.

Fludecate *Unipharm, Israel; Intramed, S.Afr.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Fluden *Rekah, Israel.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fludent *Alpharma, Fin.; Alpharma, Swed.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fludep Plus *Cipla, India.*
Fluoxetine hydrochloride (p.391·2); alprazolam (p.960·1).

Fludestrin *BMS, Ger.†.*
⊗ Testolactone (p.778·2).
Breast cancer.

Fludeten
Note. This name is used for preparations of different composition.
Alodial, Port.†.
Paracetamol (p.108·1).
Fever; pain.

Alter, Port.†; Alter, Spain.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Fludex *Servier, Austria; Servier, Belg.; Servier, Denm.†; Eutherapie, Fr.; Servier, Gr.; Servier, Neth.; Servier, Port.; Servier, Switz.; Servier, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Fludexin
Note. This name is used for preparations of different composition.
Dexa, Indon.
Syrup: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); promethazine hydrochloride (p.588·2); sulfogaiacol (p.1573·2).
Allergic rhinitis; cold and influenza symptoms; cough; sinusitis.

Dexa, Indon.
Tablets: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Allergic rhinitis; cold and influenza symptoms; cough; sinusitis.

Fludexol-CL *Vitae, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Fludicon *Quality, Hong Kong.*
Fluconazole (p.532·1).
Fungal infections.

Fludil *Galeno, Venez.*
Flunarizine hydrochloride (p.580·2).
Migraine; peripheral vascular disorders; vestibular disorders.

Fludilat *Organon, Braz.; UCB, Ger.; Organon, Indon.; Organon, Port.†; Organon, Thai.; Organon, Venez.*
Bencyclane fumarate (p.1224·1).
Cerebral and peripheral vascular disorders.

Fludin *Saba, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Fludisol *Merck, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Fluditec *Innotech, Fr.; Innotech, Rus.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Fluditec toux seche *Innotech, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Fludizol *M & H, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Fludocel *CPH, Port.*
Fluconazole (p.532·1).
Fungal infections.

Fludren *Diafarm, Spain.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Fludronef *Iquinosa, Spain.*
Fludrocortisone acetate (p.1530·1); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Eye disorders.

Fludrop *Andromaco, Chile†.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene.

Fluental *Sanofi-Aventis, Ital.*
Sobrerol (p.1572·3); paracetamol (p.108·1).
Respiratory-tract disorders.

Fluesco *Streuli, Switz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Flufenal *Roux-Ocefa, Arg.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders.

Flufenan *Cristalia, Braz.*
Fluphenazine enantate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Fluforte *Allergan, Chile; Allergan, Mex.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluforte N *Allergan, Chile†; Allergan, Mex.*
⊗ Fluorometholone (p.1532·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Flufran *Unique, India†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Flugal *Square, Malaysia.*
Fluconazole (p.532·1).
Fungal infections.

Flugalin *Knoll, Cz.†; Abbott, Hung.; Abbott, Pol.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Flugen *Novartis, Spain.*
⊗ Fluorometholone (p.1532·3); gentamicin sulfate (p.282·1).
Ocular inflammation following cataract surgery.

Flugeral *Italfarmaco, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Flugesic *Ikapharmindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Influenza symptoms.

Fluhalt *Ranbaxy, Malaysia.*
Oseltamivir phosphate (p.900·2).
Influenza.

Fluhexal *Hexal, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Flui-Amoxicillin *Zambon, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Fluibron *Farmalab, Braz.; Andromaco, Chile; Chiesi, Ital.; Chiesi, Switz.†; Santa, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Fluibrox *Medichrom, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Fluicor *Maver, Chile.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Fluid Loss *Vitaplex, Austral.†.*
Celery (p.2278·3); buchu (p.2269·3); taraxacum (p.2395·1); bearberry (p.2263·3).
Fluid retention.

Fluidabak *Thea, Fr.*
Povidone (p.2146·1).
Dry eyes.

Fluidamin *Behrens, Venez.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Fluidamin Plus *Behrens, Venez.*
Amino acid infusion (p.1922·1).
Parenteral nutrition.

Fluidasa
Note. This name is used for preparations of different composition.
Montpellier, Arg.
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Abbott, Mex.
Theophylline (p.1140·1).
Obstructive airways disease.

Bioresearch, Spain.
Mepyramine acefyllinate (p.585·2).
Obstructive airways disease.

Fluide Desalterant Multi-Hydratant *Clarins, Canad.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fluide Hydratant Quotidien *L'Oreal, Canad.*
SPF 15: Octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Fluide Multi-Confort *Clarins, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Fluide Multi-Regenerant Lift Jour *Clarins, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Fluide Protecteur Jeunesse des Mains *Clarins, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fluidema *Baldacci, Port.*
⊗ Indapamide (p.1314·1).
Hypertension.

Fluidin *Ativus, Braz.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Fluidin Mucolitico *Faes, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Flui-DNCG *Zambon, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Fluido *Spineda, Arg.*
Camphor (p.2273·2); turpentine oil (p.2406·3); arnica (p.2260·2).
Musculoskeletal and joint pain.

Fluidox *Baldacci, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Fluidrenol *Sofex, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Fluifort *Eurodrug, Hong Kong; Dompe, Ital.; Eurodrug, Malaysia; Dompe, Rus.; Eurodrug, Thai.*
Carbocisteine lysine (p.1553·3).
Respiratory-tract congestion.

Fluilast *Boniscontro & Gazzone, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Fluimare *Zambon, Braz.; Zambon, Switz.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal irrigation.

Fluimucil
Kirby, Arg.†; Zambon, Austria; Zambon, Braz.; Zambon, Cz.; Zambon, Fr.; Zambon, Ger.; Zambon, Hong Kong; Zambon, Hung.; Zambon, Indon.; Zambon, Ital.; Zambon, Malaysia; Zambon, Philipp.; Zambon,

Pol.; Zambon, Port.; Zambon, Rus.; Zambon, Singapore†; Zambon, Spain; Zambon, Switz.; Sermmitr, Thai.; Zambon, Thai.
Acetylcysteine (p.1548·2).
Haemorrhagic cystitis; poisoning with paracetamol, acrylonitrile, methacrynitrile, or methyl bromide; respiratory-tract congestion; urotoxicity caused by ifosfamide and cyclophosphamide.

Zambon, Neth.
Acetylcysteine (p.1548·2) or acetylcysteine sodium (p.1548·2).
Paracetamol poisoning; respiratory-tract disorders.

Fluimucil Antibiotic
Note.This name is used for preparations of different composition.
Zambon, Belg.; Zambon, Rus.
Thiamphenicol glycinate acetylcysteinate (p.351·2).
Bacterial infections of the respiratory tract associated with increased or viscous mucus.

Sermmitr, Thai.; Zambon, Thai.
Thiamphenicol (p.351·1); acetylcysteine (p.1548·2).
Respiratory-tract infections associated with increased or viscous mucus.

Fluimucil Antibiotico *Zambon, Ital.; Zambon, Spain†.*
Thiamphenicol glycinate acetylcysteinate (p.351·2).
Respiratory-tract infections.

Fluimucil Biotic *Kirby, Arg.†.*
Amoxicillin trihydrate (p.202·2); acetylcysteine (p.1548·2).
Respiratory-tract infections.

Fluimucil Solucao Nasal *Zambon, Braz.*
Acetylcysteine (p.1548·2); benzalkonium chloride (p.1629·1); sodium chloride (p.1686·1).
Nasal congestion.

Fluinol *Almirall, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Nasal polyps; rhinitis.

Fluir *Mantecorp, Braz.; Valmor, Venez.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Fluirespir *Zambon, Ital.†.*
Cineole (p.2282·3).
Formerly contained cineole and camphor.
Nasal congestion.

Fluisedal *Elerte, Fr.*
Meglumine benzoate; polysorbate 20 (p.1919·1); promethazine hydrochloride (p.588·2).
Coughs.

Fluisedal sans promethazine *Elerte, Fr.*
Meglumine benzoate; polysorbate 20 (p.1919·1).
Respiratory-tract congestion.

Fluitoss *Teuto, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Fluixol *Cristalfarma, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Fluizan *Klinger, Braz.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Fluken *Kendrick, Mex.†.*
Flutamide (p.725·1).
Prostatic cancer.

Flukezol *Kener, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Flukit
Note.This name is used for preparations of different composition.
Julphar, UAE.
Syrup: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Julphar, UAE.
Tablets: Paracetamol (p.108·1); salicylamide (p.121·2); promethazine hydrochloride (p.588·2); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; rhinitis.

Fluktan *Tunggal Idaman, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

FluLaval *GSK, USA.*
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Flulem *Laboratorios Chile, Chile; Lemery, Mex.; Lemery, Thai.*
Flutamide (p.725·1).
Prostatic cancer.

Flulium
Note.This name is used for preparations of different composition.
Pharmasant, Thai.
Dipotassium clorazepate (p.980·1).
Anxiety; depression; dystonias.

Utopian, Thai.
Flunarizine (p.580·3).
Cerebrovascular disorders.

Flulon *Santen, Philipp.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flulone *Panalab, Arg.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flulox *Medicine Products, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states.

Flumach *Mayoly-Spindler, Fr.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; myasthenia gravis; oedema.

Flumadine *Forest Pharmaceuticals, USA.*
Rimantadine hydrochloride (p.904·2).
Influenza A.

Flumage *Gemepe, Arg.*
Flumazenil (p.1445·2).

Flumanovag *Gobbi, Arg.*
Flumazenil (p.1445·2).

Flumarc *Raffo, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Flumarin
Note.This name is used for preparations of different composition.
Caber, Ital.
Morniflumate (p.86·2).
Fever; pain.

Shionogi, Jpn.
Flomoxef sodium (p.276·3).
Bacterial infections.

Flumark *Dainippon, Jpn.*
Enoxacin (p.268·3).
Bacterial infections.

Flumasalen *TO-Chemicals, Thai.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders.

Flumates *Mintlab, Chile.*
⊗ Beclometasone dipropionate (p.1516·2).

Flumazen *Scott-Cassara, Arg.; Uniao Quimica, Braz.*
Flumazenil (p.1445·2).
Benzodiazepine antagonist.

Flumazil *Cristalia, Braz.*
Flumazenil (p.1445·2).
Reversal of sedative effects of benzodiazepines.

Flumeciclina *Farmila, Ital.*
⊗ Solution A, tetracycline (p.347·1); solution B, fluorometholone (p.1532·3).
Infected eye disorders.

Flumed
Note.This name is used for preparations of different composition.
Andromaco, Chile.
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Medicom, Cz.
Flutamide (p.725·1).
Prostatic cancer.

Medifive, Thai.
Fluoxetine (p.397·3).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Flumejoralito Gripe *GSK, Mex.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Hay fever; rhinitis.

Flumetholon *Santen, Hong Kong; Ferron, Indon.; Santen, Indon.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flumetol
Note.This name is used for preparations of different composition.
Faran, Gr.†.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Farmila, Ital.
⊗ Fluorometholone (p.1532·3).
Formerly contained fluorometholone and tetryzoline hydrochloride.
Inflammatory eye disorders.

Interko, Turk.
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Inflammatory eye disorders.

Elmor, Venez.
⊗ Fluorometholone acetate (p.1533·1).
Inflammatory eye disorders.

Flumetol Antibiotico *Farmila, Ital.†.*
⊗ Fluorometholone (p.1532·3); tetracycline (p.347·1).
Infected eye disorders.

Flumetol NF *Sophia, Mex.*
⊗ Fluorometholone acetate (p.1533·1).
Inflammatory eye disorders.

Flumetol S *Farmila, Cz.†.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flumetol Semplice *Farmila, Ital.†.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flumex *Allergan, Braz.*
⊗ Fluorometholone (p.1532·3).
Eye disorders.

Flumex N *Allergan, Braz.*
⊗ Neomycin sulfate (p.305·1); fluorometholone (p.1532·3).
Infected eye disorders.

Flumexate *Specifar, Gr.*
Flumazenil (p.1445·2).
Benzodiazepine overdosage.

Flumezina *Farmila, Ital.*
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Inflammatory eye disorders.

Flumicin
Note.This name is used for preparations of different composition.
Hovid, Malaysia.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Collins, Mex.
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Flumicon *Farmstandart, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Flumid *Hexal, Ger.*
Flutamide (p.725·1).
Prostatic cancer.

Flumidon *Medicus, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Flumil
Note.This name is used for preparations of different composition.
Senosiain, Mex.
⊗ Aminophenazone (p.19·1); buphenine hydrochloride (p.2270·2); diphenylpyraline hydrochloride (p.578·2).
Rhinitis; sinusitis.

Zambon, Port.; Pharmazam, Spain.
Acetylcysteine (p.1548·2).
Respiratory-tract congestion; respiratory-tract disorders associated with excessive or viscous mucus.

Flumil Antibiotico *Pharmazam, Spain.*
Acetylcysteine (p.1548·2); thiamphenicol (p.351·1).
Respiratory-tract infections.

Flumil Antidoto *IFET (ΙΦΕΤ), Gr.; Pharmazam, Spain.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning.

Fluminex *Fournier, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Flumirex *Winthrop, Cz.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; premenstrual dysphoric disorder.

FluMist *Medimmune, USA; Wyeth-Ayerst, USA.*
A live influenza vaccine (p.2218·2).
Active immunisation.

Flumonac *Zambon, Spain.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucous.

Flumoxal *Janssen-Cilag, Arg.*
Flubendazole (p.145·1).
Worm infections.

Flumyc *Ipca, India†.*
Fluconazole (p.532·1).
Fungal infections.

Flumycon *Pliva Krakow, Pol.*
Fluconazole (p.532·1).
Fungal infections.

Flunadin *Ifars, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); noscapine (p.1566·2).
Influenza symptoms.

Flunagen *Visufarma, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Flunal
Note.This name is used for preparations of different composition.
Biofarma, Braz.†; Alian, Venez.
Fluconazole (p.532·1).
Fungal infections.

Rayere, Mex.†.
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Flunal-Neo *Rayere, Mex.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin (p.305·1).
Infected skin disorders.

Flunarimed *Ethimed, Belg.*
Flunarizine hydrochloride (p.580·2).
Migraine.

Flunarin *Ache, Braz.*
Flunarizine hydrochloride (p.580·2).
Hemiplegia; migraine and other vascular headaches; subarachnoid haemorrhage.

Flunarium *Pharmaselect, Austria; Greater Pharma, Thai.*
Flunarizine hydrochloride (p.580·2).
Cerebrovascular disorders; migraine; motion sickness; vertigo.

Flunatop *Topgen, Belg.*
Flunarizine hydrochloride (p.580·2).
Migraine.

Flunavert *Hennig, Ger.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Flunax *Graha, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Flunaza *Pharmaland, Thai.†.*
Flunarizine (p.580·3).
Cerebrovascular disorders.

Flunazine *Shiwa, Thai.†.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Flunazol *Sintofarma, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Flunazul *Pfleger, Ger.*
Fluconazole (p.532·1).
Fungal infections.

Flunco *TO-Chemicals, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Fluneurin *Hexal, Ger.; Sandoz, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Fluni *1A, Ger.†.*
Flunitrazepam (p.996·2).
Sleep disorders.

Flunibeta *Betapharm, Ger.*
Flunitrazepam (p.996·2).
Sleep disorders.

Flunidor *Chibret, Port.†.*
Diflunisal (p.47·2).
Inflammation; pain.

Flunigar *Farminvest, Ital.†.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis allergic rhinitis.

Fluniget *MSD, Austria.*
Diflunisal (p.47·2).
Musculoskeletal and joint disorders; pain.

Flunimerck *Merck dura, Ger.†.*
Flunitrazepam (p.996·2).
Insomnia.

Fluninoc *Hexal, Ger.*
Flunitrazepam (p.996·2).
Insomnia.

Flunipam *Alpharma, Denm.; Alpharma, Norw.*
Flunitrazepam (p.996·2).
Insomnia; premedication.

Fluniprol *Proel, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin disorders.

Flunir *UPSA Conseil, Fr.†.*
Niflumic acid (p.95·2).
Post-sclerotherapy inflammation; sprains.

Flunita *Jean-Marie, Hong Kong.*
Flunitrazepam (p.996·2).
Insomnia.

Flunitec *Boehringer Ingelheim, Arg.†.*
⊗ Flunisolide (p.1531·1).
Asthma.

Flunitop *Pierre Fabre, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma, bronchitis; rhinitis.

Flunizol *Ecosol, Switz.*
Fluconazole (p.532·1).
Fungal infections.

Flunol *Farmanic, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Flunolone *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Flunolone-V *Atlantic, Hong Kong†; Atlantic, Singapore; Atlantic, Thai.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flunovon *Novofarm (Νοβοφαρμ), Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin disorders.

Flunox *Roche, Ital.*
Flurazepam monohydrochloride (p.999·1).
Insomnia.

Fluo Fenic *Novartis, Spain.*
⊗ Chloramphenicol (p.239·3); fluocinolone acetonide (p.1531·3).
Infected eye disorders.

Fluo Grin *Grin, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Fluo-calc *Pharmacia, Switz.†.*
Sodium monofluorophosphate (p.1964·3); calcium carbonate (p.1714·1).
Osteoporosis.

Fluocalcic *Raffo, Arg.†; Viatris, Austria; Yamanouchi, Belg.†; Asta Medica, Cz.†.*
Sodium monofluorophosphate (p.1964·3); calcium carbonate (p.1714·1).
Osteoporosis.

Fluocalm *Kleva, Gr.*
Fluoxetine (p.397·3).
Depression.

Fluocaril
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Belg.
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; dental hygiene.

Sanofi Synthelabo, Cz.†; Sanofi Synthelabo, Switz.†.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Procter & Gamble, Ital.
⊗ Potassium fluoride (p.1963·3); potassium nitrate (p.1658·3); enoxolone (p.50·1).
Gum hypersensitivity and pain.

Fluocaril Bi-Fluore *Rider, Chile; Sanofi Synthelabo, Cz.†; Procter & Gamble, Fr.; Sanofi-Aventis OTC, Ital.; Procter & Gamble, Port.; Sanofi Synthelabo, Switz.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluocaril Bi-Fluore Vitamin E *Sanofi Synthelabo, Cz.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2); *dl*-alpha tocopherol (p.1992·2).
Dental caries prophylaxis.

Fluocaril blancheur *Procter & Gamble, Fr.*
Calcium carbonate (p.1714·1); sodium benzoate (p.1630·2); sodium monofluorophosphate (p.1964·3).
Dental discoloration.

Fluocaril dents sensibles *Procter & Gamble, Fr.*
⊗ Potassium fluoride (p.1963·3); potassium nitrate (p.1658·3); enoxolone (p.50·1).
Sensitive teeth.

Fluocaril Junior and Fluocaril Kids *Procter & Gamble, Fr.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluocid Forte *Inkeysa, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluocim *Siegfried, Cz.†; Cimex, Switz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; premenstrual dysphoric disorder.

Fluocit *Pharma 2000, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluoderm *Taro, Canad.†; SA Druggists, S.Afr.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluodermo Fuerte *Septa, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluodont *Gebro, Austria.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluodontyl *Sanofi Synthelabo, Belg.†; Procter & Gamble, Fr.; Sanofi-Aventis, Spain.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; dental hypersensitivity.

Fluodos *Complutense, Spain.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Flu-Off *Europharm, Hong Kong†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Flugal *Siegfried, Cz.†.*
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder.

Flugel *Procter & Gamble, Fr.*
Sodium fluoride (p.1962·2); ammonium difluoride (p.1963·3).
Dental caries prophylaxis.

Flugum *Procter & Gamble, Fr.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluohexal *Hexal, Austral.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Fluomex *Precimex, Mex.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluomint *Daudt, Braz.*
Sodium monofluorophosphate (p.1964·3); cineole (p.2282·3); thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Dental caries prophylaxis; oral hygiene.

Fluomit *Laboratorios Chile, Chile.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Fluomix Same *Savoma, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluomizin *Medinova, Switz.*
Dequalinium chloride (p.1641·3).
Vaginal infections.

Fluomycin N *Organon, Ger.*
Dequalinium chloride (p.1641·3).
Vaginal infections.

Fluon *Dissolvurol, Mon.*
Metesculetol sodium (p.2343·2); hamamelis (p.2318·2); aesculus (p.2248·2); viburnum (p.2267·1).
Capillary fragility; haemorrhoids; venous insufficiency.

Fluonid *Allergan, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluonid-N *Biolab, Hong Kong; Biolab, Malaysia†; Biolab, Thai.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Fluopiram *Ariston, Arg.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoplexe *Lehning, Fr.*
Sodium fluoride (p.1962·2).
Peri-articular disorders.

Fluor *Or-Dov, Austral.†; SMB, Belg.; Kin, Spain; Lacer, Spain.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluor Microsol *Herbaxt, Fr.†.*
Sodium fluoride (p.1962·2).
Peri-articular disorders.

Fluor Verde *Angelini, Ital.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluoracaine *Akorn, Canad.†; Dioptic, Canad.†; Akorn, USA.*
Fluorescein sodium (p.2306·1); proxymetacaine hydrochloride (p.1870·1).
Aid to eye examination; local anaesthesia.

Fluoracilo *Pfizer, Chile.*
Fluorouracil (p.722·2).

Fluor-A-Day *Pharmascience, Canad.; Dental Health Products, UK.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluoralfa *INTES, Ital.*
Fluorescein sodium (p.2306·1).
Diagnosis of eye disorders.

Fluordent *Bernabo, Arg.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluordent PX
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Mouthwash: Sodium fluoride (p.1962·2); sodium pyrophosphate (p.2390·3).
Dental caries prophylaxis; periodontal disease.

Bernabo, Arg.
Toothpaste: Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis; periodontal disease.

Fluore Stain Strips *Bell, India.*
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Fluorescite *Alcon, Arg.; Alcon, Austral.; Alcon, Canad.; Alcon, Cz.; Alcon, Hong Kong†; Alcon, Malaysia; Alcon, NZ; Alcon, Pol.; Alcon, Port.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, USA.*
Fluorescein sodium (p.2306·1).
Diagnosis of circulatory disorders; eye examination.

Fluorets *Smith & Nephew, Austral.; Novartis Ophthalmics, Canad.†; Bausch & Lomb, Hong Kong; Chauvin, Hong Kong; Chauvin, Irl.; Bausch & Lomb, Malaysia; Chauvin, Malaysia; Smith & Nephew, NZ; SofLens, S.Afr.; Bausch & Lomb, Singapore; Chauvin, Singapore; Bausch & Lomb, UK; Akorn, USA.*
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Fluorette *Fertin, Denm.; Fertin, Norw.; Meda, Swed.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluoretten *Aventis, Ger.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorex *Crinex, Fr.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorex Plus *Gerot, Austria.*
⊗ Tetracycline hydrochloride (p.347·2); dequalinium chloride (p.1641·3); prednisone (p.1542·3).
Colpitis.

Fluorexidina *Defuen, Arg.†.*
Sodium fluoride (p.1962·2); chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis.

Fluoridex Daily Defense Sensitivity Relief *Discus, USA.*
⊗ Sodium fluoride (p.1962·2); potassium nitrate (p.1658·3).
Dental caries prophylaxis; sensitive teeth.

Fluoridrops *WestCan, Canad.†.*
Sodium fluoride (p.1962·2).
Fluoride supplement.

Fluorigard *Colgate-Palmolive, UK; Colgate-Palmolive, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorigard Gel-Kam *Colgate-Palmolive, Ital.; Colgate-Palmolive, UK.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Fluoril *Novartis, Ger.*
Sodium monofluorophosphate (p.1964·3); calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Osteoporosis.

Fluorilette *Leiras, Fin.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluori-Methane *Gebauer, USA†.*
Dichlorodifluoromethane (p.1689·1); trichlorofluoromethane (p.1689·1).
Local anaesthesia.

Fluor-In *Procter & Gamble, Ital.; Procter & Gamble, Port.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; fluoride supplement.

Fluorinse *Oral-B, Canad.; Oral-B, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluor-I-Strip *Bausch & Lomb, USA.*
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Fluoritab *Fluoritab, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluoritabs *WestCan, Canad.†.*
Sodium fluoride (p.1962·2).
Fluoride supplement.

Fluormex
Note. This name is used for preparations of different composition.
Chema-Elektromet, Pol.
Dental gel: Olaflur (p.1959·2); sodium fluoride (p.1962·2).
Dental caries prophylaxis; dental disorders.

Chema-Elektromet, Pol.
Dental liquid: Olaflur (p.1959·2).
Dental caries prophylaxis; dental disorders.

Fluornatrium *Odontomed, Braz.†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorocaine *Medical Ophthalmics, USA.*
Fluorescein sodium (p.2306·1); proxymetacaine hydrochloride (p.1870·1).

Fluorocare *Colgate Oral Care, Austral.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis; sensitive teeth.

Fluorogel *Naf, Arg.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorogel 2001 *Naf, Arg.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluorogel 2001 Chiquitos *Naf, Arg.*
Sodium fluoride (p.1962·2); xylitol (p.1998·2).
Dental caries prophylaxis.

Fluorogel 2001 para Dientes Sensibles *Naf, Arg.*
⊗ Sodium fluoride (p.1962·2); xylitol (p.1998·2); potassium nitrate (p.1658·3).
Dental caries prophylaxis.

Fluorometil *Alcon, Mex.*
⊗ Fluorometholone (p.1532·3); tetryzoline (p.1574·1).
Eye disorders.

Fluoro-Ophtal *Winzer, Ger.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluor-Op *Novartis Ophthalmics, USA†.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluoroplat *Naf, Arg.*
Diamino silver fluoride (p.1963·3).
Dental caries prophylaxis.

Fluoroplex *Allergan, USA.*
Fluorouracil (p.722·2).
Actinic keratoses.

Fluoropoen *Poen, Arg.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3); phenylephrine (p.1568·1).
Conjunctivitis.

Fluoropos *Ursapharm, Cz.; Ursapharm, Ger.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluororinil *Farmila, Ital.*
⊗ Betamethasone (p.1518·2); chlorphenamine maleate (p.571·3).
Rhinitis.

Fluoros *Jenapharm, Ger.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Fluorox *Medical Ophthalmics, USA.*
Fluorescein sodium (p.2306·1); oxybuprocaine (p.1868·1).

Fluoro-zel *Farmapol, Pol.*
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Dental caries.

Fluorscan *Molypharma, Spain.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Fluorvas *Llorens, Spain.*
⊗ Fluorometholone (p.1532·3); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Fluor-Vigantoletten *Merck, Ger.*
Colecalciferol (p.1986·2); sodium fluoride (p.1962·2).
Dental caries prophylaxis; rickets; vitamin D deficiency.

Fluoscin *Biospray, Gr.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Topical corticosteroid with antibacterial.

Fluoselgine *Teofarma, Fr.*
Domiphen bromide (p.1643·1); sodium fluoride (p.1962·2).
Dental hygiene; gingivitis.

Fluossen *ICN, Cz.†; ICN, Pol.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Fluosterol *Crinex, Fr.*
Sodium fluoride (p.1962·2); colecalciferol (p.1986·2).
Dental caries prophylaxis; vitamin D deficiency.

Fluotest *Alcon, Port.; Alcon Cusi, Spain.*
Fluorescein sodium (p.2306·1); oxybuprocaine hydrochloride (p.1867·3).
Aid to eye examination.

Fluothane *AstraZeneca, Austral.; AstraZeneca, Austria†; AstraZeneca, Braz.; AstraZeneca, Chile†; AstraZeneca, Fr.†; AstraZeneca, Ger.†; AstraZeneca, Gr.†; Nicholas Piramal, India; AstraZeneca, Indon.; Zeneca, Israel†; AstraZeneca, Malaysia†; AstraZeneca, NZ; AstraZeneca, S.Afr.†; AstraZeneca, Spain; AstraZeneca, Swed.†; AstraZeneca, Turk.; Wyeth-Ayerst, USA†.*
Halothane (p.1784·2).
General anaesthesia.

Fluotic *Aventis, Canad.*
Sodium fluoride (p.1962·2).
Otospongiosis.

Fluotracer *Complutense, Spain.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Contrast agent for detection of malignant neoplasms by positron-emission tomography.

Fluotrat *Biolab Sanus, Braz.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluo-Vaso *Allergan, Braz.*
⊗ Fluocinolone acetonide (p.1531·3); naphazoline hydrochloride (p.1565·2); neomycin sulfate (p.305·1); zinc sulfate (p.1999·2).
Infected eye disorders.

Fluovitef *Teofarma, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluox *Socobom, Belg.; Soma, Braz.; ABZ, Ger.; Basics, Ger.; Pacific, NZ.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Fluoxa *1A, Ger.†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxac *Psicofarma, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder.

Fluoxal *Alpharma, Fin.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression.

Fluoxan *Baxter, Philipp.*
Fluorouracil (p.722·2).
Malignant neoplasms.

fluox-basan *Schonenberger, Switz.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Fluoxebell *Bellwether, Austral.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

FluoxeLich *Winthrop, Ger.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxemed *Ethimed, Belg.*
Fluoxetine (p.397·3).
Depression.

Fluoxemerck *Merck dura, Ger.†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxenorm *Genericon, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluoxe-Q *Juta, Ger.; Q-Pharm, Ger.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxeren *Menarini, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluoxgamma *Worwag, Ger.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxibene *Ratiopharm, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluoxifar *Siphar, Switz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Fluoxin *Hexal, Cz.; Ibirn, Ital.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Flu-Oxinate *Pasadena, USA†.*
Fluorescein sodium (p.2306·1); oxybuprocaine hydrochloride (p.1867·3).

Fluoxine *TO-Chemicals, Thai.*
Fluoxetine (p.397·3).
Mixed anxiety depressive states.

Fluoxistad *Stada, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive compulsive disorder.

Fluoxityrol *Tyrol, Austria†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxone *SMB, Belg.*
Fluoxetine (p.397·3).
Depression.

Fluox-Puren *Alpharma-Isis, Ger.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fluoxstad *Stada, Neth.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluoxytil
Note. This name is used for preparations of different composition.
UCB, Turk.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

GSK, Mex.
Dental gel: Sodium monofluorophosphate (p.1964·3); calcium glycerophosphate (p.1676·1).
Dental caries prophylaxis.

GSK, Mex.
Oral drops: Sodium fluoride (p.1962·2); xylitol (p.1998·2).
Dental caries prophylaxis.

Fluozoid *Valdecasas, Mex.*
Ethosuximide (p.479·3).
Epilepsy.

Flupamid *Sanovel, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Flupar *Orion, Fin.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Flupazine *Psicofarma, Mex.*
Trifluoperazine hydrochloride (p.1034·2).
Nausea and vomiting; psychoses.

Flupendura *Merck dura, Ger.*
Flupentixol decanoate (p.997·1).
Schizophrenia.

Flupid *Damor, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Flupidol *Janssen-Cilag, Gr.*
Penfluridol (p.1015·3).
Psychoses.

Fluprosin *Pharmacodane, Denm.*
Flutamide (p.725·1).
Prostatic cancer.

Fluprost *Lisapharma, Hung.; Lisapharma, Ital.*
Flutamide (p.725·1).
Prostatic cancer.

Fluquinol *Rowe-Fleming, Venez.†.*
⊗ Fluocinolone acetonide (p.1531·3); hydroxyquinoline iodochloride (p.2323·2).
Infected skin disorders.

Fluquinol Simple *Rowe-Fleming, Venez.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flura *Kirkman, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Flurablastin
Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.
Fluorouracil (p.722·2).
Malignant neoplasms.

Pfizer, Swed.
Fluorouracil sodium (p.723·3).
Malignant neoplasms.

Fluracedyl
Teva, Belg.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Pharmachemie, Thai.†; Teva, Thai.†.
Fluorouracil (p.722·2).
Keratoses; malignant neoplasms; skin cancer.

Pharmachemie, Neth.; Nycomed, Swed.†.
Fluorouracil sodium (p.723·3).
Malignant neoplasms.

Fluracil *Biochem, India.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Fluradosa *Dosa, Arg.*
Fludarabine (p.722·1).
Malignant neoplasms.

Fluralema *Biotech, Venez.*
Flurazepam dihydrochloride (p.999·1).
Sleep disorders.

Fluralex
Note. This name is used for preparations of different composition.
Arlex, Mex.
Fluoxetine (p.397·3).
Depression.

Lafayette, Philipp.
Carbocisteine (p.1553·2).
Cough.

Fluran *Ranbaxy, Malaysia.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Flurate *Bausch & Lomb, USA.*
Fluorescein sodium (p.2306·1); oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Fluraz *Brown & Burk, India.*
Flurazepam dihydrochloride (p.999·1).
Anxiety; insomnia.

Flurben *Boehringer Ingelheim, Venez.†.*
Flurbiprofen (p.61·2).
Inflammation; pain.

Flurbic *Klonal, Arg.*
Flurbiprofen (p.61·2).

Flurbid *Klonal, Arg.†.*
Flurbiprofen (p.61·2).
Inflammation; pain.

Flurekain *Croma, Austria.*
Oxybuprocaine hydrochloride (p.1867·3); fluorescein sodium (p.2306·1).
Local anaesthesia.

Fluress *AMO, Austral.; Barnes Hind, NZ†; Abigo, Swed.; Akorn, USA.*
Fluorescein sodium (p.2306·1); oxybuprocaine hydrochloride (p.1867·3).
Aid to eye examination; local anaesthesia.

Flurets *Oral-B, Austral.*
Sodium fluoride (p.1962·2).
Prevention of tooth decay.

Fluricin *Seng, Thai.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; vestibular disorders.

Flurin *Yarindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Influenza symptoms.

Flurin Dmp *Yarindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough; influenza symptoms.

Flurinol
Boehringer Ingelheim, Arg.
Epinastine (p.579·3) or epinastine hydrochloride (p.579·3).
Allergic rhinitis; asthma; pruritus.

Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.
Epinastine hydrochloride (p.579·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity.

Flurinol D
Boehringer Ingelheim, Arg.
Epinastine hydrochloride (p.579·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Boehringer Ingelheim Promeco, Mex.
Epinastine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Flurizic *Pantafarm, Ital.*
Flurithromycin ethyl succinate (p.278·1).
Bacterial infections.

Fluroblastin *Pfizer, Philipp.; Pharmacia, S.Afr.; Pfizer, Venez.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Fluroblastine *Pfizer, Belg.*
Fluorouracil sodium (p.723·3).
Malignant neoplasms.

Fluro-Ethyl *Gebauer, USA.*
Ethyl chloride (p.1861·2); cryofluorane (p.1689·1).
Topical anaesthesia.

Flurofen *Abbott, Denm.; Vianex (Βιανεξ), Gr.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal and joint disorders; pain.

Flurolon *Allergan, Denm.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Flurop *Davi, Port.*
⊗ Fluorometholone (p.1532·3).
Eye disorders.

Fluroptic *Cooper (Κοπερ), Gr.*
Flurbiprofen sodium (p.61·2).
Prevention of miosis in ophthalmic surgery.

Flurosyn *Rugby, USA†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flurox
Note. This name is used for preparations of different composition.
Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.
Fluorouracil (p.722·2).
Malignant neoplasms.

Ocusoft, USA.
Fluorescein sodium (p.2306·1); oxybuprocaine hydrochloride (p.1867·3).

Flurozin *Remedica, Thai.*
Flurbiprofen (p.61·2).
Musculoskeletal and joint disorders.

Flurpax *Teofarma, Spain.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Flusac *Sriprasit, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states.

Flusan *Novag, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Fluscand *Teva, Swed.*
Flunitrazepam (p.996·2).
Premedication; sleep disorders.

Flusemide *Q Pharma, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebral vasospasm; hypertension.

Fluseminal *Anfarm, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Flusenil *Anfarm, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Flusin
Note. This name is used for preparations of different composition.
Aspen Consumer, S.Afr.
Capsules: Chlorphenamine maleate (p.571·3) pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Aspen Consumer, S.Afr.
Tablets: ⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Flusin C *Aspen Consumer, S.Afr.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); vitamin C (p.1983·3).
Cold and influenza symptoms.

Flusin DM *Aspen Consumer, S.Afr.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); ascorbic acid (p.1983·3).
Coughs; upper respiratory-tract congestion.

Flusin S *Aspen Consumer, S.Afr.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); vitamin C (p.1983·3).
Cold and influenza symptoms.

Flusin Sinus *Pharmacare, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Nasal and sinus congestion.

Flusol *Ecosol, Switz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Flusolgen *Geni, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Flusolv *Ecobi, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Flusona *Mediderm, Chile; Pediapharm, Chile; Pharmabiotics, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Asthma; skin disorders.

Flusonal *Almirall, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Fluspi *Hexal, Ger.*
Fluspirilene (p.999·2).
Schizophrenia.

Fluspiral *Menarini, Ital.*
⊗ Fluticasone propionate (p.1533·2).
Obstructive airways disease.

Flusporan *Menarini, Arg.†; Menarini, Spain.*
Flutrimazole (p.535·2).
Fungal skin and nail infections.

Fluss 40 *Scharper, Ital.*
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Ascites; hyperaldosteronism; hypertension; oedema.

Flussorex *Lampugnani, Ital.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; mental function disorders; parkinsonism.

Flustad *Stada, Neth.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Flustaren *Chrispa (Χρισπα), Gr.†.*
Acetylcysteine (p.1548·2).
Mucolytic.

Flu-Stat
Note. This name is used for preparations of different composition.
Be-Tabs, S.Afr.
Capsules: Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Be-Tabs, S.Afr.
Syrup: Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Flusten *Eurofarma, Braz.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Flusterix *Farmanic, Gr.*
Fusidic acid (p.279·3).
Bacterial skin infection.

Fluta *Cell Pharm, Ger.; Gry, Ger.*
Flutamide (p.725·1).
Prostatic cancer.

Flu-Tab *Guardian, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Flutabene *Ratiopharm, Austria.*
Flutamide (p.725·1).
Prostatic cancer.

Flutabs *Farmstandart, Rus.*
Paracetamol (p.108·1).
Fever; pain.

Flutacan *Leiras, Cz.†; Leiras, Denm.†; Ferring, Swed.†.*
Flutamide (p.725·1).
Prostatic cancer.

Flutahexal *Hexal, Austria; Hexal, S.Afr.*
Flutamide (p.725·1).
Prostatic cancer.

Flutaide *Alenfarma, Port.*
⊗ Fluticasone propionate (p.1533·2).
Rhinitis.

Flutalon *Organifar, Venez.†.*
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Flutam *Ratiopharm, Hung.*
Flutamide (p.725·1).
Prostatic cancer.

Flutamid *Anpharm, Rus.*
Flutamide (p.725·1).
Prostatic cancer.

Flutamin *Alphapharm, Austral.; Pacific, NZ.*
Flutamide (p.725·1).
Prostatic cancer.

Flutamol
Note. This name is used for preparations of different composition.
Pyridam, Indon.
Capsules: Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Allergy; cough; fever; headache; nasal congestion.

Pyridam, Indon.
Syrup: Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Allergy; cough; fever; headache; nasal congestion.

Flutamol-P *Pyridam, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Allergy; cough; fever; headache; nasal congestion.

Flutan *Medochemie, Hong Kong†; Medochemie, Malaysia†; Medochemie, Singapore; Medochemie, Thai.*
Flutamide (p.725·1).
Prostatic cancer.

Flutandrona *Stada, Spain.*
Flutamide (p.725·1).
Prostatic cancer.

Flutans *Drogsan, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Flutaplex *Teva Tuteur, Arg.; Teva, Belg.; Teva, Cz.; Detsaves (Νετσαβες), Gr.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Neth.; Teva, Rus.; Pharmachemie, S.Afr.; Tedec Meiji, Spain†; Pharmachemie, Thai.; Teva, Thai.*
Flutamide (p.725·1).
Prostatic cancer.

Flutasin *Sindan, Hung.*
Flutamide (p.725·1).
Prostatic cancer.

Flutastad *Stada, Austria.*
Flutamide (p.725·1).
Prostatic cancer.

Flutax *Hexal, Arg.†.*
Flutamide (p.725·1).
Prostatic cancer.

Flutec *Hexal, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Flutenal *Recordati, Spain.*
⊗ Flupamesone (p.1545·1).
Skin disorders.

Flutenal Gentamicina *Recordati, Spain.*
⊗ Flupamesone (p.1545·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Flutenal Sali *Recordati, Spain.*
⊗ Flupamesone (p.1545·1); salicylic acid (p.1612·2).
Skin disorders.

Flutepan *Sandoz, Arg.*
Flutamide (p.725·1).
Prostatic cancer.

Flutex
Note. This name is used for preparations of different composition.
Syosset, USA.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Pharmacare, S.Afr.
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Flutex Co Linctus *Aspen Consumer, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Flutex Cold and Flu
Note. This name is used for preparations of different composition.
Pharmacare, S.Afr.
Capsules: Ascorbic acid (p.1983·3); salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Aspen Consumer, S.Afr.
Syrup: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Flutex Decon-S *Aspen Consumer, S.Afr.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Flutexin *Juta, Ger.†; Q-Pharm, Ger.†.*
Flutamide (p.725·1).
Prostatic cancer.

Flutiamik *Microsules, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Fluticaps *Biosintetica, Braz.*
⊗ Fluticasone propionate (p.1533·2).
Obstructive airways disease.

Fluticort *Cassara, Arg.; Biogalenic, Venez.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Flutide *GSK, Ger.; Medcor, Neth.; GSK, Norw.; GSK, Swed.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; asthma; nasal polyps; obstructive airways disease.

Fluti-K *Raffo, Arg.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Flutin *Orion, Denm.; Julphar, UAE.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Flutinasal *Farmanic, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis.

Flutinase *GSK, Switz.*
⊗ Fluticasone propionate (p.1533·2).
Nasal polyps; rhinitis.

Flutinax *Ivax, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Flutine *Teva, Israel; Pharmasant, Thai.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Flutinol *Latinofarma, Braz.*
⊗ Fluorometholone acetate (p.1533·1).
Inflammatory eye disorders.

Flutirin *Teva, Hung.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Flutivate *GSK, Braz.; GSK, Chile; GSK, Ger.; GSK, Norw.; GSK, Swed.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Flutivent *Cassara, Arg.*
⊗ Fluticasone propionate (p.1533·2); salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Flutizal *Polychronus, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis.

Flutol *Douglas, NZ†.*
Flutamide (p.725·1).

Flutox *Pharmazam, Spain.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Flutrax *Bioprofarma, Arg.*
Flutamide (p.725·1).
Prostatic cancer.

Flutrim *Interbial, Port.*
Flutrimazole (p.535·2).
Fungal skin infections.

Flutrop *Tropica Mas, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic disorders; cold symptoms; sinusitis.

Fluvaccinol *Stada, Austria.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Fluval
Note. This name is used for preparations of different composition.
KRKA, Cz.†; Lek, Cz.†; KRKA, Rus.
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder.

Omninvest, Hung.
An inactivated influenza vaccine (whole virion) (p.2218·2).
Active immunisation.

Valmor, Venez.
Fluconazole (p.532·1).
Fungal infections.

Fluvax *CSL, Austral.; Commonwealth Serum, Hong Kong; CSL, Malaysia; CSL, NZ; Iscotec, Neth.*
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Fluvean *Formenti, Ital.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fluvermal *McNeil, Fr.; Janssen-Cilag, Port.*
Flubendazole (p.145·1).
Veterinary names include Flubenol.
Worm infections.

Flivermox *Janssen-Cilag, Venez.*
Flubendazole (p.145·1).
Worm infections.

Fluvert *Medley, Braz.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; vestibular disorders.

Fluvet *Vianex (Βιανέξ), Gr.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Fluviatol *Boehringer Ingelheim Promeco, Mex.*
Amantadine hydrochloride (p.792·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; cold and influenza symptoms.

Fluviatol NF *Boehringer Ingelheim Promeco, Mex.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; hay fever.

Fluvic *Pierre Fabre Sante, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Fluvicil *Degorts, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol sulfate (p.1131·3).
Bronchospasm; respiratory-tract congestion.

Fluviral *ID Biomedical, Canad.*
An inactivated influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Fluvirin *Celltech, Belg.†; Medeva, Cz.†; Evans, Fin.†; Evans, Irl.†; Evans, Israel; Chiron Vaccines, Neth.; Evans, Norw.†; Angelini, Port.; Medpro, S.Afr.; SBL, Swed.†; Chiron Vaccines, UK; Novartis Vaccines, USA.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Fluvirine *Celltech, Fr.†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Fluvium *Rekah, Israel.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Fluvohexal *Hexal, Ger.*
Fluvoxamine maleate (p.399·3).
Depression.

Fluvosol *Berner, Fin.†.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Fluvoxadura *Merck dura, Ger.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Fluvoxin *Sun, India; Sun, Thai.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

FluWinox *Zentiva, Hung.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Flux
Note. This name is used for preparations of different composition.
Hexal, Austria.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Alpharma, Norw.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Fluxacil *Uno, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Fluxacina *Laboratorios Chile, Chile.*
Flucloxacillin (p.277·1).
Staphylococcal infections.

Fluxadir *Antor, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Fluxal *Pfizer Consumer, Spain†.*
Lysine aspirin (p.79·1); calcium ascorbate (p.1984·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Influenza and cold symptoms.

Fluxantin *Gea, Denm.†; Gea, Fin.†; Gea, Swed.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Fluxarten *GSK, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Fluxedan *AF, Mex.*
Bromhexine hydrochloride (p.1552·2); oxeladin citrate (p.1567·1).
Respiratory-tract disorders with viscous mucus.

Fluxema *Zimaia, Port.†.*
Bencyclane fumarate (p.1224·1).

Fluxene *Eurofarma, Braz.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Fluxes *Sandoz, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Fluxet *Krewel, Ger.; SM, Venez.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Fluxetil *Unison, Malaysia; Unison, Singapore†; Unison, Thai.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Fluxetin *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states.

Fluxibit *Euromex, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Fluxicap *Arlex, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Fluxidin *Epifarma, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Fluxifarm *Richmond, Arg.*
Flumazenil (p.1445·2).

Fluxil
Note. This name is used for preparations of different composition.
UCB, Austria; Aegis, Hong Kong; Aegis, Singapore.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Teuto, Braz.
⊗ Furosemide (p.1292·1).

Fluxinam *Vilco, Gr.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Fluxol
Note. This name is used for preparations of different composition.
UCI, Braz.†.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Maver, Mex.
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3).
Asthma; bronchitis; respiratory-tract congestion.

FluxoMed *S Med, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fluxon *Neo Quimica, Braz.*
Cinnarizine (p.573·1).
Vertigo.

Fluxonil *Orion, Cz.†.*
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder.

Fluxpiren *Ariston, Arg.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Fluxum *Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; Wassermann, Ital.; Armstrong, Mex.; Alfa Wassermann, Pol.; BioSaude, Port.; Gurel, Turk.*
Parnaparin sodium (p.1366·1).
Thromboembolic disorders.

Fluxus *Tecnofarma, Chile.*
Flunarizine (p.580·3).
Mental function impairment; peripheral vascular disorders; vestibular disorders.

Fluzac *LBS, Thai.; Flupal, Venez.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Fluzak *SVUS, Cz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; premenstrual dysphoric disorder.

Fluzal *Julphar, UAE†.*
Carbinoxamine maleate (p.570·2); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract disorders.

Flu-Zep
Note. A similar name is used for preparations of different composition (see below).
Marching, Hong Kong.
Dexchlorpheniramine maleate (p.572·1); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); salicylamide (p.121·2); caffeine (p.1116·3).
Cold and influenza symptoms.

Fluzep
Note. A similar name is used for preparations of different composition (see above).
Otto, Indon.
Phenylpropanolamine hydrochloride (p.1569·3); dexchlorpheniramine maleate (p.572·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Cough; influenza symptoms.

Fluzerit *De Salute, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Fluzine *PP Lab, Thai.†.*
Fluphenazine hydrochloride (p.998·1).
Anxiety; schizophrenia.

Fluzix *Cazi, Braz.*
Flunarizine hydrochloride (p.580·2).

Fluzol *LKM, Arg.; Hexal, S.Afr.*
Fluconazole (p.532·1).
Fungal infections.

Fluzole *Arrow, Austral.; Biofarma, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Fluzon *Cadila, India.*
Fluconazole (p.532·1).
Fungal infections.

Fluzone *Aventis, Arg.†; Aventis Pasteur, Braz.†; Aventis Pasteur, Canad.†; Sanofi Pasteur, Mex.; Sanofi Pasteur, Thai.; Sanofi Pasteur, USA.*
An inactivated influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Fluzor *Collins, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Fluzoral *APT, Hong Kong.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Flynoken A *Kendrick, Mex.†.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity.

FM7 E *Rubiepharm, Ger.†.*
Vitamins; minerals; caffeine; cinchona; rutoside sodium sulfate; spigelia; fructose; glucose; honey (p.1922·1).
Tonic.

FML *Allergan, Arg.; Allergan, Austral.; Allergan, Belg.; Allergan, Canad.; Allergan, Fin.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Israel; Allergan, Malaysia†; Allergan, NZ; Allergan, Neth.; Allergan, Philipp.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

FML Neo *Allergan, Arg.; Alvia (Αλβια), Gr.; Allergan, Port.; Allergan, S.Afr.; Allergan, Switz.; Allergan, Thai.†.*
⊗ Fluorometholone (p.1532·3); neomycin sulfate (p.305·1).
Inflammatory eye infections.

FML-S *Allergan, USA.*
⊗ Fluorometholone (p.1532·3); sulfacetamide sodium (p.335·3).
Inflammatory eye infections.

FMP *Nakorn, Thai.†.*
21 Tablets, norgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

FN-T-Tus *Cadila, India.*
Terminalia bellirica; liquorice (p.1740·3); adhatoda vasica; ocimum sanctum; turmeric (p.1473·2); galanga; eucalyptus oil (p.2301·2).
Coughs.

Foamicon *Invamed, USA.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2); alginic acid (p.2140·3).
Hyperacidity.

Foban
Hoe, Malaysia; Hoe, Singapore.
Fusidic acid (p.279·3).
Staphylococcal skin infections; streptococcal skin infections.

AFT, NZ; Hoe, Thai.
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Staphylococcal skin infections; streptococcal skin infections.

Fobancort
Note. This name is used for preparations of different composition.
Hoe, Malaysia.
⊗ Sodium fusidate (p.279·3); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Hoe, Singapore.
⊗ Fusidic acid (p.279·3) or sodium fusidate (p.279·3); betamethasone dipropionate (p.1518·3).
Skin disorders infected with staphylococci or streptococci.

Foban-Hydro *Hoe, Malaysia.*
⊗ Sodium fusidate (p.279·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Fobidon *IBN, Ital.†.*
Domperidone (p.1726·2).
Gastric discomfort; nausea; vomiting.

Focalin *Novartis, USA.*
⊗ Dexmethylphenidate hydrochloride (p.2154·2).
Attention-deficit hyperactivity disorder.

Focam *YSP, Malaysia†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Focetria *Novartis Vaccines, Cz.; Novartis Vaccines, Port.*
An influenza vaccine (H5N1) (p.2218·2).
Active immunisation; pandemic influenza prophylaxis.

Focus *Swiss Herbal, Canad.*
Linoleic acid; gamolenic acid; vitamin E (p.1922·1).

Focus 425 *Ocean Nutrition, Canad.*
Docosahexaenoic acid (p.1362·1).

Focus Care All-in-One *Ciba Vision, Austral.; Ciba Vision, NZ†.*
Cleaning, rinsing, disinfecting, and storage solution for soft contact lenses (p.1622·2).

Focus Care One Step *Ciba Vision, Austral.; Ciba Vision, NZ†.*
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfection, neutralisation, and storage of contact lenses.

Focusvax *Berna, Ital.†.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Fodiclo *Interbat, Indon.*
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

Fohnetten N *Ziethen, Ger.†.*
Benzyl mandelate (p.2264·3); caffeine (p.1116·3); paracetamol (p.108·1).
Migraine; pain.

Foille
Note. This name is used for preparations of different composition.
Rider, Chile.
Benzocaine (p.1854·1).
Skin irritation.

Blistex, USA.
Benzocaine (p.1854·1); chloroxylenol (p.1640·2).
Local anaesthesia.

Foille Insetti *Sanofi-Aventis OTC, Ital.*
⊗ Hydrocortisone (p.1535·2).
Insect stings; skin irritation.

Foille Scottature *Sanofi-Aventis OTC, Ital.*
Benzocaine (p.1854·1); benzyl alcohol (p.1631·3); chloroxylenol (p.1640·2).
Burns; skin irritation; wounds.

Foille Sole *Sanofi-Aventis OTC, Ital.*
Benzocaine (p.1854·1); benzyl alcohol (p.1631·3); chloroxylenol (p.1640·2).
Burns; skin irritation; wounds.

Foipan *Ono, Jpn.*
Camostat mesilate (p.2273·2).
Gastro-oesophageal reflux; pancreatitis.

Fokalepsin *Lundbeck, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgias.

Fokeston *Rafarm, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Fokusin *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Fol Sang *IQB, Braz.*
Cyanocobalamin (p.1980·2); hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); folic acid (p.1940·1) liver extract (p.2337·3).
Megaloblastic anaemia.

Folac *Otto, Indon.; Ronava, Venez.*
Folic acid (p.1940·1).
Anaemia; folic acid supplement.

Folacid *ITF, Chile; Synteza, Pol.*
Folic acid (p.1940·1).
Anaemias; prevention of neural tube defects in pregnancy; raised plasma homocysteine.

Folacin
Note. This name is used for preparations of different composition.
Jadran, Rus.; Pfizer, Swed.
Folic acid (p.1940·1).
Folate deficiency; megaloblastic anaemia.

Ativus, Braz.
Oral drops; oral solution: Folic acid (p.1940·1); ascorbic acid (p.1983·3).
Folic acid deficiency; megaloblastic anaemia.

Ativus, Braz.
Tablets: Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Folacite *Erlimpex, Indon.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Folacom *Combiphar, Indon.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Folamil *Dexa, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Folanemin *Schering, Ital.*
Calcium levofolinate (p.1943·3).
Folate deficiency.

Folaplus *Meprofarm, Indon.*
Folic acid (p.1940·1); vitamin B ; vitamin B (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Folaport *Richmond, Arg.*
Folic acid (p.1940·1).

Folarell *Sanorell, Ger.*
Folic acid (p.1940·1).
Antidote to treatment with folic acid antagonists; folate deficiency; megaloblastic anaemia.

Folaren *Ist. Chim. Inter., Ital.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folas *Landson, Indon.*
Folic acid (p.1940·1).
Coronary heart disease; megaloblastic anaemia; prevention of neural tube defects.

Fol-Asmedic *Dyckerhoff, Ger.†.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Folavit *Wolfs, Belg.; Sanbe, Indon.*
Folic acid (p.1940·1).
Anaemias; folic acid deficiency; prevention of neural tube defects in pregnancy; supplement in pregnancy and lactation.

Folaxin
Note. This name is used for preparations of different composition.
Berlico Mulia, Indon.
Folic acid (p.1940·1).
Supplement in pregnancy and lactation.

Zambon, Spain.
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; antidote to folic acid antagonists; reduction of methotrexate toxicity.

Folbiol *Ulagay, Turk.*
Folic acid (p.1940·1).
Megaloblastic anaemia.

Folcodal *Ivax, Arg.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders.

Folcofen *Alliance, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); pholcodine (p.1570·2); guaifenesin (p.1561·3).
Coughs.

Folcres
Note. This name is used for preparations of different composition.
Panalab, Arg.
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Grisi, Mex.†.
Minoxidil (p.1342·1).
Alopecia.

Folcur *1A, Ger.*
Folic acid (p.1940·1).
Folic acid deficiency.

Foldan *Andromaco, Arg.; Uniao Quimica, Braz.*
Tiabendazole (p.156·2).
Worm infections.

Folderm Pomada *Kinder, Braz.*
Tiabendazole (p.156·2); neomycin sulfate (p.305·1).
Scabies.

Foldox
Note. A similar name is used for preparations of different composition (see below).
Roerig, Chile.
Piroxicam (p.117·3).
Inflammation; pain.

Foldoxx
Note. A similar name is used for preparations of different composition (see above).
Sidus, Arg.†.
Rofecoxib (p.121·1).
Osteoarthritis; pain.

Folepar B12 *Lisapharma, Ital.*
Folic acid (p.1940·1); nicotinamide (p.1957·3); thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2).
Deficiency states; macrocytic anaemia.

Folergot-DF *Marnel, USA.*
Phenobarbital (p.492·2); ergotamine tartrate (p.620·1); belladonna (p.2263·3).
Gastrointestinal disorders.

Folerin *Novell, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Folet *Centaur, India.*
Folic acid (p.1940·1).
Megaloblastic anaemia.

Folex
Note. This name is used for preparations of different composition.
Qualiphar, Belg.†.
⊗ Pholcodine (p.1570·2); ephedrine hydrochloride (p.1558·2); sodium citrate (p.1673·3).
Bronchitis; coughs; laryngitis.

Pharmateam, Israel.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Dietary supplement during pregnancy; iron-deficiency anaemia.

Folgamma *Worwag, Ger.*
Cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Vitamin B and folic acid deficiency.

Folgamma Mono *Worwag, Ger.*
Folic acid (p.1940·1).
Antidote to treatment with folic acid antagonists; folic acid deficiency; megaloblastic anaemia.

Folgard *Upsher-Smith, USA.*
Folic acid; cyanocobalamin; pyridoxine hydrochloride; riboflavin (p.1922·1).
Dietary supplement.

Foli Doce *ITF, Chile; Italfarmaco, Spain.*
Folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Prevention of neural-tube defects.

Foliagen *Roux-Ocefa, Arg.*
Folic acid (p.1940·1).
Megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Foliamin *Takeda, Thai.*
Folic acid (p.1940·1).
Anaemias.

Foliben *Shire, Ital.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folic Acid Plus *Cenovis, Austral.; Vitelle, Austral.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).

Folic Plus *Assos, Turk.*
Folic acid (p.1940·1); calcium (p.1675·2); vitamin D (p.1986·1).

Folical *Proel, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency.

Folicalgyn *Amsa, Ital.†.*
Calcium folinate (p.1943·3).
Folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folicare *Rosemont, Thai.; Rosemont, UK.*
Folic acid (p.1940·1).
Folic acid supplement.

FOLI-Cell *Stada, Austria; Cell Pharm, Ger.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; antidote to treatment with folic acid antagonists.

Folicil *Bialport, Port.*
Folic acid (p.1940·1).
Folic acid deficiency; prevention of neural tube defects.

Folicombin *Jenapharm, Ger.*
Ammonium iron sulfate (p.1950·3); folic acid (p.1940·1).
Iron and folate deficiency.

Folicorin *Uniao Quimica, Braz.*
Calcium folinate (p.1943·3).

Folicron *Julphar, UAE.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Folicum *Julphar, UAE.*
Folic acid (p.1940·1).
Folate deficiency.

Folidan *Prasfarma, Spain.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; megaloblastic anaemia; methotrexate poisoning.

Folidar *Italfarmaco, Ital.*
Calcium folinate (p.1943·3).
Folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folidex *Italfarmaco, Ital.*
Folic acid (p.1940·1).
Prevention of neural-tube defects.

Folifem *Biofarm, Pol.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Folifemin *Maver, Chile.*
Folic acid (p.1940·1).

Folifer
Note. This name is used for preparations of different composition.
Ativus, Braz.
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1).
Anaemias.

Rider, Chile.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and folic acid deficiency.

Bialport, Port.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Folifer B-12 *Ronava, Venez.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2); copper sulfate (p.1935·3).
Anaemias.

Foliferron *Teofarma, Spain.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3).
Iron and folic acid deficiency.

Foligan *Desma, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Foliglobin *Pharmaceutical Enterprises, S.Afr.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron deficiency.

Folik *Polfa Grodzisk, Pol.*
Folic acid (p.1940·1).
Prevention of neural tube defects.

Folimax *Panalab, Arg.*
Folic acid (p.1940·1).
Anaemias; folic acid supplement.

Folimax B *Panalab, Arg.*
Folic acid (p.1940·1); biotin (p.1931·3).
Anaemias; folic acid and biotin supplement.

Foliment *Sanofarm, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folimet *Nycomed, Denm.*
Folic acid (p.1940·1).
Folate deficiency.

Folimin *Polfa Lodz, Pol.*
Folic acid (p.1940·1).
Anaemias; prevention of neural tube defects.

Folin *Geyer, Braz.†.*
Folic acid (p.1940·1).

Folina
Note. This name is used for preparations of different composition.
Schwarz, Ital.
Folic acid (p.1940·1) or sodium folate (p.1941·2).
Folate deficiency.

American Taiwan, Thai.
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; antidote to folic acid antagonists; folic acid deficiency.

Folinac *Bioprogress, Ital.†.*
Calcium folinate (p.1943·3).
Antidote to overdosage with folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folina-Cell *Eurogenerics, Belg.*
Folinic acid (p.1943·3).
Adjunct in colorectal cancer; antidote to folic acid antagonists.

Folinato *Faran, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folinemic *Bago, Arg.*
Folic acid (p.1940·1).
Folic acid supplement.

Folinemic Ferro *FIRMA, Ital.†.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemias.

Folinfabra *Fabra, Arg.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists.

Folingrav *Amnol, Ital.*
Folic acid (p.1940·1).
Folic acid supplement.

Folinoral *Therabel, Fr.*
Calcium folinate (p.1943·3).
Drug-induced megaloblastic anaemia; methotrexate toxicity.

Folinovo *Hospira, Port.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; reduction of folic acid antagonist toxicity.

Folinoxan *Baxter, Philipp.*
Calcium folinate (p.1943·3).
Antidote to cytostatic folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity.

Folinvit *Garant, Ital.†.*
Calcium folinate (p.1943·3).
Anaemias; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Folio *SteriPharm, Fr.*
Folic acid (p.1940·1); potassium iodide (p.2169·2).
Nutritional supplement in pregnancy.

Foliplus *Sanofi Synthelabo, Ital.†.*
Calcium folinate (p.1943·3).
Anaemias; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Foli-Rivo *Rivopharm, Switz.†.*
Folic acid (p.1940·1).
Megaloblastic anaemias.

Folisanin *Sanitas, Chile.*
Folic acid (p.1940·1).
Folic acid deficiency.

Folital *Sanval, Braz.*
Folic acid (p.1940·1).
Folic acid supplement.

Folium *Defuen, Arg.*
Vaginal lubricant.

Folium OB *Prosel, Philipp.*
Vitamin preparation with zinc sulfate (p.1922·1).

Folivirin *Biotika, Cz.*
⊗ Estradiol benzoate (p.2097·2); testosterone isobutyrate (p.2131·3).
Menopausal disorders; osteoporosis.

Folivit *Siam Bheasach, Thai.*
Folic acid (p.1940·1).
Anaemias.

Folivital *Silanes, Mex.*
Folic acid (p.1940·1).
Folate supplement; prevention of neural tube defects in pregnancy.

Folivoran *Vocate, Gr.*
Calcium levofolinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency.

Folix-Mater *IQB, Braz.*
Ascorbic acid; folic acid; cyanocobalamin; ferrous fumarate (p.1922·1).

Folizol *Pharmacodane, Denm.*
Fluoxetine (p.397·3).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Follimin *Wyeth Lederle, Norw.†; Wyeth, Swed.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; dysmenorrhoea.

Follimon *LG Pharm, Hong Kong†; LG Life Sciences, Thai.*
⊗ Urofollitropin (p.2136·3).
Female infertility.

Follinett *Wyeth, Swed.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Follistim *Organon, USA.*
⊗ Follitropin beta (p.2104·1).
Male and female infertility.

Follistrel *Wyeth, Swed.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Follitrin *Ferring, Arg.; Ferring, Chile.*
⊗ Urofollitropin (p.2136·3).
Male and female infertility.

Folmigor *Medinova (Μεντινοβα), Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Folovit *Polfarmex, Pol.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Folpace Alaven, USA.
Vitamin B ; vitamin B ; folic acid; vitamin E; magnesium (p.1922·1).

Folsan Solvay, Austria; Solvay, Ger.
Folic acid (p.1940·1).
Folic acid deficiency; prevention of neural tube defects in pregnancy.

Folsav Valeant, Hung.
Folic acid (p.1940·1).
Folic acid deficiency.

Foltene Silesia, Chile.
Tricosaccharides.
Alopecia.

Foltene Research Anticaspa Silesia, Chile.
Tricosaccharides; piroctone olamine (p.1610·1); pantothenic acid (p.1959·3); salicylic acid (p.1612·2).
Dandruff.

Foltran Ivax, Arg.
Zopiclone (p.1039·1).
Insomnia.

FOLTX Pan American, USA.
Folic acid (p.1940·1); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2).
Homocysteinaemia; homocystinuria; nutritional supplement.

Folverlan Verla, Ger.
Folic acid (p.1940·1).
Folic acid deficiency; prophylaxis of neural tube defects.

Folvite
Note. This name is used for preparations of different composition.
Meda, Fin.; Wyeth, India; Valeant, Switz.
Folic acid (p.1940·1).
Folate deficiency; megaloblastic anaemia.

Lederle, USA.
Folic acid (p.1940·1) or sodium folate (p.1941·2).
Megaloblastic anaemias.

Fomagrippin N Michallik, Ger.†.
⊗ Propyphenazone (p.119·3); ephedrine hydrochloride (p.1558·2); ascorbic acid (p.1983·3).
Cold symptoms.

Fomarex PannonPharma, Hung.†.
Dimeticone (p.2032·1).
Skin disorders.

Fomene
Note. This name is used for preparations of different composition.
Almirall, Spain.
Tetridamine maleate (p.129·1).
Vaginitis.

Leti, Venez.
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Fomentil SIT, Ital.
Eucalyptus oil (p.2301·2); menthol (p.2340·1); thyme oil (p.2401·2); peru balsam (p.2365·3); benzoin (p.2394·2).
Laryngitis; respiratory congestion; rhinitis; sore throat.

Fomepikehl Sanum-Kehlbeck, Ger.
Homoeopathic preparation.

Fon Wan Eleuthero Giuliani, Ital.†.
Honey (p.1948·2); siberian ginseng (p.2386·3).
Nervous tension.

Fon Wan Energy Giuliani, Ital.†.
Multivitamin and mineral preparation with ginseng (p.1922·1).
Nutritional supplement.

Fon Wan Ginsenergy
Note. This name is used for preparations of different composition.
Giuliani, Ital.
Ginseng (p.2312·1).
Nutritional supplement.

Giuliani, Ital.
Honey (p.1948·2); royal jelly (p.2382·1); ginseng (p.2312·1).
Nutritional supplement.

Fon Wan Memory Giuliani, Ital.
Multivitamin preparation with eleutherococcus and ginkgo biloba (p.1922·1).
Mental function disorders; nutritional supplement.

Fonarin B Mayo, Mex.
Vitamin B substances (p.1922·1).

Fonderyl Raymos, Arg.
Metoclopramide (p.1747·3).
Nausea and vomiting.

Fondril Procter & Gamble, Ger.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Fondril HCT Procter & Gamble, Ger.
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Fondur Durascan, Denm.†.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fonergin Farmasa, Braz.
⊗ Prednisolone (p.1540·3); framycetin sulfate (p.279·1); gramicidin (p.286·1); amylocaine hydrochloride (p.1853·3); procaine hydrochloride (p.1869·1).
Mouth disorders.

Fonergine Benitol, Arg.
Benzocaine (p.1854·1); tyrothricin (p.358·2); bithionol (p.142·2).
Mouth and throat disorders.

Fonergoral Ducto, Braz.
Benzydamine hydrochloride (p.27·3).

Fonexel Francia, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Fongamil Biorga, Fr.; Remek, Gr.; Saninter, Port.
Omoconazole nitrate (p.544·1).
Fungal infections.

Fongarex Besins, Fr.
Omoconazole nitrate (p.544·1).
Vaginal candidiasis.

Fongeryl Aclae, Fr.
Econazole nitrate (p.531·1).
Fungal skin infections.

Fongitar Stiefel, Austral.; Stiefel, Hong Kong; Stiefel, NZ†; Stiefel, Philipp.; Stiefel, Port.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.
Pyrithione zinc (p.1611·2); tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2).
Scalp disorders; tinea versicolor.

Fonicef Errekappa, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Fonicid Lafare, Ital.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Fonigen Opco, Denm.†.
Fluoxetine (p.397·3).
Bulimia nervosa; depression.

Fonisal Salus, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Fonlipol Cephalon, Fr.
Tiadenol (p.1411·1).
Hypercholesterolaemia.

Fontax Unison, Thai.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Fontex Lilly, Belg.; Lilly, Denm.; Lilly, Fin.†; Lilly, Norw.; Lilly, Swed.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fontol
Note. This name is used for preparations of different composition.
Duncan, Arg.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Nycomed, Braz.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Fontolax Fontovit, Braz.
Cassia (p.1715·3); coriander (p.2288·1); senna (p.1769·2); liquorice (p.1740·3); tamarind (p.1775·3).
Constipation.

Fonto-Vit B6 Fontovit, Braz.
Pyridoxine hydrochloride (p.1978·2).

Fonto-Vit C Fontovit, Braz.
Ascorbic acid (p.1983·3).

Fonto-Vit E Fontovit, Braz.
Vitamin E (p.1992·2).

Fontula Bernofarm, Indon.
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Fonvicol Panpharma, Philipp.
Cefazolin sodium (p.222·1).
Bacterial infections.

Fonx Astellas, Fr.
Oxiconazole nitrate (p.544·2).
Fungal skin infections.

Fonzac Gemelli, Denm.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fonzylane Cephalon, Fr.; Lafon, Hong Kong.
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders; cochlear-vestibular disorders; intermittent claudication; ischaemia; Raynaud's syndrome.

Foot Zeta Zeta, Ital.
Undecenoic acid (p.549·2); usnic acid (p.2409·3).
Burns; fungal skin infections; wounds.

Foothy Otto, Indon.
⊗ Urea (p.1620·2); fructan; portulaca; vitamin E.
Dry skin.

Footworks Avon, Canad.
Tolnaftate (p.548·3).
Fungal skin infections.

Foprin Plus H Teva, Cz.
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

For Gas Uniao Quimica, Braz.
Dimeticone (p.1770·2).
Flatulence.

For Peripheral Circulation Herbal Plus Formula 5 Vitelle, Austral.
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); zanthoxylum (p.2417·1); capsicum (p.2276·2); rutoside (p.2305·1); hesperidin (p.2304·3).
Peripheral vascular disorders.

For Women Active Woman Formula Blackmores, Austral.
Eleutherococcus senticosis; damiana; avena; centella; minerals; vitamin C (p.1922·1).
Dietary supplement.

For Women Multi Plus EPO Blackmores, Austral.
Evening primrose oil (p.2302·1); vitamins; minerals; choline bitartrate; bioflavonoids; rutoside (p.1922·1).
Dietary supplement.

Foracet Solus, India.
⊗ Pentazocine hydrochloride (p.112·2); paracetamol (p.108·1).
Pain.

Foracort
Cipla, India.
⊗ Formoterol (p.1122·3); budesonide (p.1520·1).
Asthma.

Cipla, Malaysia.
⊗ Formoterol fumarate (p.1122·1); budesonide (p.1520·1).
Asthma.

Foradil Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia†; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Schering, USA; Novartis, Venez.
⊗ Formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Foradile Novartis, Austral.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Foragin Mugi, Indon.
Dipyrone (p.49·2).
Fever; pain.

Forair
Note. This name is used for preparations of different composition.
Chiesi, Cz.; Asche Chiesi, Ger.; Chiesi, Gr.; Chiesi, Port.
⊗ Formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

German Remedies, India.
⊗ Salmeterol (p.1135·3); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Foral Grossmann, Switz.†.
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); ivy (p.2328·1); senega (p.1572·3); liquorice (p.1740·3); star anise oil (p.2392·2).
Coughs.

Foralivit Am-Europharma, Philipp.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Iron deficiency; iron-deficiency anaemia; vitamin B deficiency.

Foramefer Foramen, Philipp.
Folic acid (p.1940·1); ferrous fumarate (p.1938·3); vitamin B ; vitamin B (p.1922·1).
Anaemias.

Forane Abbott, Arg.; Abbott, Austria; Abbott, Braz.; Baxter, Canad.; Abbott, Cz.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.; Abbott, Rus.†; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Thai.; Abbott, Turk.; Baxter, USA.
Isoflurane (p.1785·3).
General anaesthesia.

Foraneural Mugi, Indon.
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Forapin Mack, Switz.†.
Bee venom (p.2258·3); benzyl nicotinate (p.28·1); bornyl salicylate (p.28·2); nonivamide (p.96·2).
Musculoskeletal, joint, and peri-articular pain.

Forapin E
Note. This name is used for preparations of different composition.
Mack, Illert., Ger.†.
Liniment: Bee venom (p.2251·1); bornyl salicylate (p.28·2); methyl nicotinate (p.85·3).
Cold damage; musculoskeletal and joint disorders; sports injuries.

Mack, Illert., Ger.†.
Ointment: Bee venom (p.2251·1); benzyl nicotinate (p.28·1); bornyl salicylate (p.28·2).
Cold damage; musculoskeletal and joint disorders; sports injuries.

Foraseq Novartis, Braz.; Novartis, Venez.
⊗ Treatment 1, formoterol fumarate (p.1122·1); treatment 2, budesonide (p.1520·1).
Asthma.

Forasma Guardian, Indon.
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Forastmin Schwarz, Pol.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Forastrol Foramen, Philipp.
Chloramphenicol (p.239·3).
Bacterial infections.

Foratec Cipla, India; Caps, S.Afr.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Forbetes Menarini, Indon.; Sanbe, Indon.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Forbiotic Blackmores, Austral.
Lactobacillus reuteri (p.2372·3).
Restoration of normal gastrointestinal flora.

Forbrand Uragme, Ital.
⊗ Zinc chloride (p.1999·1); alcohol (p.1625·2).
Mouth hygiene.

Forcad Corbridge, Philipp.
Simvastatin (p.1390·2).
Hypercholesterolaemia; ischaemic heart disease.

Forcadion Nutrisante, Fr.
Protein, lipid, and vitamin preparation (p.1922·1).
Tonic.

Forcaltonin Unigene, Port.
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Forcan Cipla, Cz.; Cipla, Hong Kong; Cipla, India.
Fluconazole (p.532·1).
Fungal infections.

Forcan TZ Cipla, India.
Fluconazole (p.532·1); tinidazole (p.848·3).
Trichomoniasis; vulvovaginal candidiasis.

Forcanox Guardian, Indon.
Itraconazole (p.536·3).
Fungal infections.

Forcap Kleva, Gr.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Forcapil Arkopharma, Fr.
Calcium pantothenate; biotin; pyridoxine; folic acid; colecalciferol; zinc pidolate; cystine; methionine (p.1922·1).
Hair and nail tonic.

Forcef Aristo, India.
Cefuroxime axetil (p.238·2).
Bacterial infections.

Forcemil Normon, Spain.
Multivitamin and mineral preparation with ginseng (p.1922·1).

Forceval Unigreg, Irl.; Alliance, UK.
Multivitamin and mineral preparation (p.1922·1).

Forceval Protein Alliance, UK†.
Lactose- and gluten-free nutritional preparation (p.1922·1).
Hypoproteinaemia; malabsorption states; nutritional supplement.

Forcicline Tocogino, Mex.†.
Tetracycline (p.347·1).
Bacterial infections.

Forcid Astellas, Cz.; Astellas, Fin.; Astellas, Gr.; Yamanouchi, Hung.; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Astellas, S.Afr.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Forcil Continentales, Mex.
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Forcilen Specifar (Σπεσιφαρ), Gr.†.
Azelaic acid (p.1589·3).
Acne.

Forcilin LKM, Arg.
⊗ Modafinil (p.2160·3).

Forclina LKM, Arg.
Fludarabine (p.722·1).
Malignant neoplasms.

Forcremol Ifusa, Mex.
Borax (p.2268·1); phenol (p.1656·1); alum (p.2254·1); potassium (p.1684·2).

Forcrim Biotech, Venez.
Co-trimoxazole (p.258·1).
Bacterial infections.

Ford Fibre Vitelle, Austral.
Ispaghula (p.1737·1).
Constipation; digestive disorders.

Ford Pills Faulding, Austral.
Aloin (p.1705·3); phenolphthalein (p.1762·1).
Constipation.

Forderm Ferron, Indon.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Fordesia Kalbe, Indon.
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Fordex Leti, Venez.
Omeprazole (p.1753·1).
Peptic ulcer.

Fordilen Novartis, Arg.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Fordin Promed, Indon.
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Fordiuran Leo, Spain.
⊗ Bumetanide (p.1237·1).
Hypertension; oedema.

Fordrim *Montpellier, Arg.†.*
Flurazepam hydrochloride (p.999·1).
Hypnotic.

Fordtran *Streuli, Switz.*
Macrogol 4000 (p.2336·3) with electrolytes.
Bowel evacuation.

Forelax *Guardian, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Forene *Abbott, Belg.†; Abbott, Chile; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Abbott, Neth.; Abbott, Norw.; Abbott, Port.; Abbott, Swed.; Abbott, Switz.; Abbott, Venez.*
Isoflurane (p.1785·3).
General anaesthesia; sedation in mechanically ventilated patients.

Forenium *Abbott, Gr.*
Isoflurane (p.1785·3).
General anaesthesia.

Foresight *Cantassium Co., UK.*
Multivitamin preparation (p.1922·1).

Foresight Iron Formula *Cantassium Co., UK.*
Ferrous gluconate (p.1939·1); copper gluconate (p.1935·3).

Forexin *Pharmaland, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Forexine *GX, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Forgenac *Formenti, Ital.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; oedema.

Forgesic *Bernofarm, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Forgram *Biomedis, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Forgrip *Ortoquimica, Braz.†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine (p.1568·1); cinnarizine (p.573·1).
Cold and influenza symptoms.

Foric *Sam-On, Israel.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemias; folic acid supplement.

Foricef *Promed, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Forifek *Caprifarmindo, Indon.; Sanbe, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

Forilin *Novo Nordisk, Denm.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Forimycin *Durascan, Denm.*
Roxithromycin (p.331·1).
Bacterial infections.

Forinfec *Lapi, Indon.*
Povidone-iodine (p.1659·2).
Mouth and throat disorders.

Foristal *Novartis, India.*
Dimetindene maleate (p.576·3).
Allergic eye disorders; allergic skin disorders; pruritus.

Forken *Kendrick, Mex.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Forknow *YSP, Malaysia; Yung Shin, Singapore.*
Flunarizine hydrochloride (p.580·2).
Migraine; peripheral vascular disease.

Forlax
Note. This name is used for preparations of different composition.
Ipsen, Belg.; Beaufour-Ipsen, Cz.; Beaufour, Fr.; Intersan, Ger.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Ipsen, Neth.; Beaufour Ipsen, Pol.; Ipsen, Port.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Selena, Swed.; Ipsen, Thai.
Macrogol 4000 (p.2336·3).
Constipation.

IMA, Braz.
Sodium picosulfate (p.1771·1); cassia (p.1715·3).
Constipation.

Forli *Filaxis, Arg.*
Indinavir (p.884·2).
HIV infection.

Forlion *Farmedia, Gr.*
⊗ Triamcinolone (p.1544·2).
Allergic rhinitis.

Forlucyl *Ultra, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Formadon *Gordon, USA.*
Formaldehyde (p.1644·2).
Hyperhidrosis.

Formalaz *Rivers Edge, USA.*
Formaldehyde (p.1644·1).
Drying agent in wart removal.

Formalin *Concept, Israel.*
Paraformaldehyde (p.1655·2).
Instrument disinfection.

Formalyde *Pedinol, USA.*
Formaldehyde (p.1644·2).
Drying agent in surgical removal of warts; hyperhidrosis and offensive odour of the feet.

Formance *Abbott, Hong Kong; Abbott, Irl.†; Abbott, Mex.†; Abbott, Turk.; Abbott Nutrition, UK†.*
Preparation for enteral nutrition (p.1922·1).
Pregnancy and lactation.

Formano *Temapharm, Cz.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formasan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Format *Northia, Arg.*
Metronidazole (p.837·1).

Formatris *Viatris, Ger.*
⊗ Formoterol fumarate (p.1122·1).
Asthma.

Formaxa *SMB, Port.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formedico *Uragme, Ital.*
⊗ Zinc chloride (p.1999·1); alcohol (p.1625·2); sodium monofluorophosphate (p.1964·3).
Mouth disorders.

Formell *Actavis, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Formet *Cellofarm, Braz.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Formicain *DHU, Ger.†.*
Homoeopathic preparation.

Formicina *Roemmers Rowe, Venez.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Formidium *DHU, Ger.*
Homoeopathic preparation.

Formin *Stadmed, India†; Pliva, Rus.; Pharmaland, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Formisoton *Staufen, Ger.*
Homoeopathic preparation.

Formistin *Lusofarmaco, Ital.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Formitrol *Mipharm, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Formocaps *Biosintetica, Braz.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formocarbine *GSK Sante, Fr.*
Activated charcoal (p.1435·2).
Gastrointestinal disorders.

Formo-Cresol Mitis *Colgate Oral Care, Austral.*
Formaldehyde (p.1644·2); cresol (p.1641·1).
Endodontics.

Formodual *Torrex Chiesi, Cz.; Chiesi, Port.*
⊗ Beclometasone dipropionate (p.1516·2); formoterol fumarate (p.1122·1).
Asthma.

Formoftil *Farmigea, Ital.*
⊗ Formocortal (p.1534·3).
Inflammatory eye disorders.

Formol *Plata, Arg.*
Formaldehyde (p.1644·1).

FormoLich *Winthrop, Ger.*
⊗ Formoterol fumarate (p.1122·1).
Asthma.

Formoline L112 *SSL, UK.*
Poliglusam (p.2370·1).
Slimming aid.

Formom *Pyridam, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Formomicin *Farmigea, Ital.*
⊗ Formocortal (p.1534·3); gentamicin sulfate (p.282·1).
Infected inflammatory eye disorders.

Formopen *Elpen (Ελπεν), Gr.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formotec *Cipla, Venez.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formotil *Genepharm, Gr.*
⊗ Formoterol (p.1122·3).
Obstructive airways disease.

Formotop *Astellas, Ger.*
⊗ Formoterol fumarate (p.1122·1).
Asthma.

Formovent *Italchimici, Cz.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Formoxol *YSP, Malaysia.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Formula 2 *Probifasa, Mex.†.*
Preparation for enteral nutrition (p.1922·1).

Formula IV *GNLD, Austral.*
Nutritional supplement with vitamins and minerals (p.1922·1).

Formula 405 *Doak, USA.*
Skin cleanser.

Formula B Plus *Major, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Formula Dermica *Darier, Mex.*
Yellow soft paraffin (p.2031·3).
Ointment basis; skin disorders.

Formula EM *Major, USA.*
Glucose (p.1945·3); fructose (p.1945·1); phosphoric acid (p.2367·1).
Nausea and vomiting.

Formula II Especial *Knop, Chile.*
Homoeopathic preparation.

Formula Forte Seniors *Pharmetics, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Formula HSN *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Formula O *General Nutrition, Canad.†.*
Multivitamin preparation with zinc (p.1922·1).

Formula VM *Solgar, USA.*
A range of vitamin preparations (p.1922·1).

Formula VM-75 *Solgar, UK.*
Multivitamin and mineral preparation (p.1922·1).

Formulaexpec *Procter & Gamble, Spain.*
Guaifenesin (p.1561·3).
Coughs.

Formulat Biosoya *Dicofarm, Ital.*
Infant feed (p.1922·1).
Cow's milk intolerance; lactose intolerance.

Formulat Pregel *Dicofarm, Ital.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Formulation R *G & W, USA.*
Glycerol (p.2314·2); soft paraffin (p.2031·2); phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Formulatus *Procter & Gamble, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Formule A-C-E & Selenium *Sante Naturelle, Canad.*
Vitamin C; vitamin E; betacarotene; selenium (p.1922·1).

Formule de l'Abbe Chaupitre *Arkopharma, Fr.*
A range of homoeopathic preparations.

Formule Stress *Sante Naturelle, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Formule W *Wyeth Consumer, Neth.*
Salicylic acid (p.1612·2).
Corns; warts.

Formulex *ICN, Canad.†.*
Dicycloverine hydrochloride (p.1722·3).
Antispasmodic.

Formuly-Piel *Assistance, Arg.*
Vitamins; minerals; cystine (p.1922·1).
Nutritional supplement.

Formyco *Sanbe, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Formyn *Multilab, Braz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Formyxan *Pisa, Mex.*
Mitoxantrone hydrochloride (p.754·1).
Breast cancer; non-Hodgkin's lymphoma; non-lymphoblastic leukaemia.

Forneuro *Dankos, Indon.*
Vitamin B ; vitamin B ; vitamin B ; vitamin E; folic acid (p.1922·1).
Megaloblastic anaemia; vitamin B and E deficiency.

Fornidd *Boots, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Forpar *Cipla, India.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Forpyn *Rolab, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); doxylamine succinate (p.578·2).
Pain and associated tension.

Forres *Kalbe, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Forsef *Bilim, Turk.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Forsteo *Lilly, Belg.; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hung.; Lilly, Irl.; Lilly, Ital.; Lilly, Norw.; Lilly, Port.; Elanco, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, UK.*
Teriparatide (p.1105·1).
Osteoporosis.

Forsuderm *Sudo, Singapore.*
Sodium fusidate (p.279·3).
Skin infections.

Fort E *Cazi, Braz.*
dl-Alpha tocoferil acetate (p.1992·3).

Forta
Note. This name is used for preparations of different composition.
Nordin, Mex.
Folic acid (p.1940·1); iron (p.1949·1).

Ross, USA.
A range of nutritional supplement preparations (p.1922·1).

Forta B *Pharmacia, Belg.†.*
Hydroxocobalamin acetate (p.1980·3).
Megaloblastic anaemia; neuralgia; vitamin B deficiency.

Forta Shake *Abbott, Israel; Ross, Israel.*
Preparation for enteral nutrition (p.1922·1).

Fortacet *Interdelta, Switz.*
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3); arnica (p.2260·2).
Insect bites; skin irritation; soft-tissue injuries.

Fortacil *Manuell, Mex.*
Amino-acid and mineral preparation (p.1922·1).
Anaemias; tonic.

Fortadim *Umeda, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Fortaflu *Soho, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Allergic disorders; cold and influenza symptoms.

Fortagesic *Sanofi Synthelabo, Irl.†.*
⊗ Pentazocine hydrochloride (p.112·2); paracetamol (p.108·1).
Musculoskeletal pain.

Fortagyl *Prafa, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Fortakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Fortal
Sanofi-Aventis, Belg.; Sanofi Synthelabo, Fr.†.
⊗ Pentazocine (p.112·2).
Pain.

IFET (ΙΦΕΤ), Gr.
⊗ Pentazocine hydrochloride (p.112·2) or pentazocine lactate (p.112·3).
Pain.

Fortal Vision *Prisfar, Port.*
Lutein; fish oil; betacarotene; selenium; vitamin C; vitamin E; zinc (p.1922·1).
Eye disorders.

Fortalgesic *Sanofi Synthelabo, Switz.†.*
⊗ Pentazocine hydrochloride (p.112·2) or pentazocine lactate (p.112·3).
Neuroleptanalgesia; pain; premedication.

Fortalis *Interdelta, Switz.*
⊗ Methyl salicylate (p.85·3); salicylic acid (p.1612·2); formic acid (p.2306·3); camphor (p.2273·2); spike lavender oil (p.2392·1).
Musculoskeletal and joint pain.

Fortam *GSK, Spain; GSK, Switz.*
Ceftazidime (p.234·1).
Bacterial infections.

Fortamet *First Horizon, USA.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Fortamin *Hexpharm, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Fortamol *Nordic Drugs, Denm.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Fortanest *Kalbe, Indon.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedation.

Fortaneurin *Continental Pharma, Belg.†.*
Vitamin B substances (p.1922·1).
Alcohol withdrawal syndrome; chronic alcoholism; vitamin B deficiency.

Fortapal *GSK, Chile.*
Ibuprofen (p.64·2).
Fever; pain.

Fortasec *Esteve, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Fortathrine *Gap, Gr.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Fortavil *Sanitas, Chile.*
Vitamins; minerals; ginseng; rutin; deanol tartrate (p.1922·1).
Tonic.

Fortax *Dankos, Thai.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Fortaz *GSK, Braz.; GSK, Canad.; Glaxo Wellcome, USA.*
Ceftazidime (p.234·1).
Bacterial infections.

Fortcinolona *Fortbenton, Arg.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Fortecortin
Merck, Austria; Merck, Cz.; Merck, Ger.; Merck, Spain; Merck, Switz.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Merck, Indon.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Fortedol *Teva, Hung.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Fortefog *Agropharm, UK.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1). Formerly contained cypermethrin (Fortemethrin), piperonyl butoxide, bioallethrin, and *N*-octylbicycloheptene dicarboximide.
Insecticide.

Fortel *Marco, Austral.†; Biomerica, USA.*
Pregnancy or fertility test (p.2372·1).

Fortelysin *Prafa, Indon.*
Vitamins; lysine hydrochloride; glutamic acid; calcium gluconate (p.1922·1).
Reduced appetite; vitamin supplement.

Forten
Note. This name is used for preparations of different composition.
Farmalab, Braz.
Amino-acid preparation with hydroxocobalamin (p.1922·1).
Nutritional supplement.

Hexpharm, Indon.
Captopril (p.1239·2).
Heart failure; hypertension.

Fortenac *Interdelta, Switz.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Forteo *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Hong Kong; Lilly, Israel; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Philipp.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, USA; Lilly, Venez.*
Teriparatide (p.1105·1).
Osteoporosis.

Fortepen *Sandoz, Austria.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Forteprim *Medi-Rx, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Forterra *Help, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Fortestomachicae *Herbapol Krakow, Pol.*
St John's wort (p.422·3); peppermint leaf (p.1761·2); papaverine hydrochloride (p.2191·3); valerian (p.2410·1).
Dyspepsia; gastrointestinal spasm; reduced appetite.

Fortevita *Mintlab, Chile.*
A multivitamin preparation (p.1922·1).

Fortevital *Tentan, Switz.*
Multivitamin and mineral preparation with caffeine, ginseng, and ginkgo biloba (p.1922·1).
Tonic.

Fortfen *Pharmacare, S.Afr.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Forthane *Abbott, Austral.*
Isoflurane (p.1785·3).
General anaesthesia.

Fortica *ST, Thai.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; hypocalcaemia; osteoporosis; rickets.

Fortical
Note. This name is used for preparations of different composition.
Serral, Mex.
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgias; neuritis; neuropathy.

Rubio, Spain†.
Calcium carbonate (p.1714·1).
Hypocalcaemia; osteoporosis.

Upsher-Smith, USA.
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Forticare *Nutricia, Fr.; Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).

FortiCare *Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Forticeporina *Cipan, Port.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Forticine *Wolfs, Belg.*
Nutritional supplement (p.1922·1).

Forticol *Medinfar, Port.*
⊗ Deanol acetoglutamate (p.2152·3); heptaminol hydrochloride (p.2319·1).
Mental function disorders.

Forticreme *Nutricia, Austral.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Forticrin *Panzera, Ital.*
Vitamin B substances (p.1922·1); vitamin E (p.1992·2); achillea (p.2245·2); ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Hair loss.

Fortidrink *Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Fortifer *United American, Hong Kong; United American, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B substances; liver (p.1922·1).
Anaemias; iron deficiency; iron-deficiency anaemia.

Fortifer FA *United American, Philipp.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Folate deficiency; iron-deficiency anaemia; prevention of neural tube defects.

Fortifresh *Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Fortify *Nutricia, Cz.†.*
Preparation for enteral nutrition (p.1922·1).

Fortify Complete *Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).

Fortijuce *Nutricia, Fr.; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Fortijuice *Nutricia, Austral.†; Nutricia, Irl.; Nutricia, NZ; Nutricia, NZ.*
Preparation for enteral nutrition (p.1922·1).

Fortilan *Ativus, Braz.*
Ginseng (p.2312·1).
Asthenia.

Fortilut *Gap, Gr.*
Norethisterone (p.2119·3).
Breast or endometrial cancer; endometriosis; hormone replacement therapy; secondary amenorrhoea.

Fortimax *Medico Uno, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fortimel *Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, NZ; Nutricia, NZ; Nutricia, Port.; Nutricia Clinical, UK.*
High-protein preparation for enteral nutrition (p.1922·1).

Fortimicin *Kyowa, Jpn.*
Astromicin sulfate (p.206·2).
Bacterial infections.

Fortimin *Vitae, Mex.*
Vitamin and mineral preparation (p.1922·1).

Fortini *Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, NZ; Nutricia, NZ; Nutricia, Port.; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Fortini Multi Fiber *Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Fortini Multi Fibre *Nutricia, Austral.†.*
Preparation for enteral nutrition (p.1922·1).

Fortinol *Pharmanel, Gr.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; raised intra-ocular pressure.

Fortipine *Goldshield, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Fortiplex *Sante Naturelle, Canad.†.*
Vitamin B (p.1980·2); ferrous fumarate (p.1938·3).

Fortisip *Nutricia-Bago, Arg.; Nutricia, Austral.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, NZ; Nutricia, NZ; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Fortison *Roemmers-Klinos, Venez.†.*
Preparation for enteral nutrition (p.1922·1).

Fortistress *Sante Naturelle, Canad.†.*
Vitamin B substances and vitamin C (p.1922·1).

Fortium *KG, Ital.*
A range of amino-acid and vitamin preparations with creatine (p.2289·2) (p.1922·1).
Nutritional supplement.

Fortofan *Gedeon Richter, Hung.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Fortolin *Fortune, Hong Kong†.*
Paracetamol (p.108·1).
Fever; pain.

Fortonol *Microsules, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Fortovase *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.†; Roche, Braz.; Roche, Canad.; Roche, Chile†; Roche, Cz.†; Roche, Denm.; Roche, Fin.†; Roche, Fr.; Roche, Ger.†; Roche, Gr.; Roche, Hong Kong†; Roche, Irl.†; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Port.†; Roche, S.Afr.†; Roche, Spain; Roche, Swed.†; Roche, Switz.†; Roche, Thai.; Roche, UK†; Roche, USA†; Roche, Venez.*
Saquinavir (p.906·1).
HIV infection.

Fortradol *Formenti, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Fortral
Sanofi Synthelabo, Austral.†; Aventis, NZ†; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, UK.
⊗ Pentazocine hydrochloride (p.112·2) or pentazocine lactate (p.112·3).
Pain.

Sanofi Synthelabo, Austria.
⊗ Pentazocine (p.112·2).
Pain.

KRKA, Cz.
⊗ Pentazocine (p.112·2) or pentazocine hydrochloride (p.112·2).
Pain.

Sanofi Synthelabo, Denm.†; Sanofi Synthelabo, Ger.
⊗ Pentazocine (p.112·2), pentazocine hydrochloride (p.112·2), or pentazocine lactate (p.112·3).
Pain.

Fortralin *Sanofi Synthelabo, Norw.†.*
⊗ Pentazocine (p.112·2), pentazocine hydrochloride (p.112·2), or pentazocine lactate (p.112·3).
Pain.

Fortrans *Beaufour-Ipsen, Cz.; Beaufour, Fr.; Ipsen, Gr.; Beaufour-Ipsen, Malaysia; Beaufour Ipsen, Pol.; Beaufour Ipsen, Port.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Emerging Pharma, Singapore.*
Macrogol 4000 (p.2336·3); sodium sulfate; sodium bicarbonate; sodium chloride; potassium chloride (p.1667·1).
Bowel evacuation; constipation.

Fortum *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Rus.; Sekpharma, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
Ceftazidime (p.234·1).
Bacterial infections.

Fortumset *GSK, Fr.*
Ceftazidime (p.234·1).
Bacterial infections.

Fortusin *Solas, Indon.*
Diphenhydramine hydrochloride (p.577·2); bromhexine hydrochloride (p.1552·2); phenylephrine hydrochloride (p.1568·1); sodium citrate (p.1673·3); ammonium chloride (p.1551·3); liquorice (p.1740·3).
Cough.

Fortwin *Ranbaxy, India; Ranbaxy, Thai.†.*
⊗ Pentazocine lactate (p.112·3).
Pain; premedication.

Fortzaar *MSD, Denm.; MSD-Chibret, Fr.; MSD Chibropharm, Ger.; MSD, Malaysia; MSD, Neth.; MSD, Port.; MSD, S.Afr.; MSD, Spain; MSD, Thai.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Forum C *Strathmann, Ger.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Forumen *Sanbe, Indon.*
Docusate sodium (p.1725·1).
Ear wax removal.

Forverm *Elofar, Braz.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Forvey *Menarini, Spain.*
Frovatriptan succinate (p.622·3).
Migraine.

Forvin *Sons, Mex.*
Hydroxocobalamin acetate (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Anaemias; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Forvit *Yarindo, Indon.*
Amino acids; vitamins; calcium gluconate (p.1922·1).
Nutritional supplement.

Forvite *Lennon, S.Afr.*
Vitamin B substances (p.1922·1).
Tonic.

Forza *Ali, Turk.*
Paracetamol (p.108·1); oxolamine citrate (p.1567·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Forzaar *MSD, Ital.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Forzest *Ranbaxy, India.*
Tadalafil (p.2196·2).
Erectile dysfunction.

Forzid *Kalbe, Philipp.; Atlantic, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Fosagen *Merck, S.Afr.*
Alendronic acid (p.1088·1).
Osteoporosis.

Fosalan *MSD, Israel.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fosalen *Genepharm, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fosamax *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Fosamax Plus *MSD, Arg.; MSD, Austral.; MSD, Hong Kong; MSD, Indon.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Singapore; Merck, USA.*
Alendronate sodium (p.1088·1); colecalciferol (p.1986·2).
Osteoporosis.

Fosavance
MSD, Belg.; MSD, Cz.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hung.; MSD, Irl.; MSD, Ital.; MSD, Philipp.; MSD, Port.; MSD, Spain.
Alendronate sodium (p.1088·1); colecalciferol (p.1986·2).
Osteoporosis.

MSD, UK.
Alendronic acid (p.1088·1); colecalciferol (p.1986·2).
Osteoporosis.

Fosazom *Vocate, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Foscald3 *FIRMA, Ital.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Foscalvit *Zuoz, Venez.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Foscan *Biolitec, Belg.; Biolitec, Cz.; Biolitec, Denm.; Biolitec, Ger.; Genesis, Gr.; Medison, Israel; Biolitec, Neth.; Biolitec, Port.; Biolitec, UK.*
Temoporfin (p.776·2).
Photodynamic therapy of head and neck cancer.

Foscavir *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Cz.†; AstraZeneca, Fr.; AstraZeneca, Ger.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hung.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Port.; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK; Astra, USA.*
Foscarnet sodium (p.877·3).
Cytomegalovirus infections; herpes infections of the skin and mucous membranes.

Fosemyk *Dekaz, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Infected skin disorders.

Fosen *Fahrenheit, Indon.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fosfacid *Collins, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fosfacol *Sanitas, Arg.*
Sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fosfafarma *Varifarma, Arg.*
Dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fosfalugel *Astellas, Ital.*
Aluminium phosphate (p.1707·3).
Gastric hyperacidity.

Fosfarsile Forte
Note. This name is used for preparations of different composition.
Fitobucaneve, Ital.
Oral liquid: Royal jelly (p.2382·1); propolis (p.2373·3); selenium (p.1961·1); ginseng (p.2312·1).
Nutritional supplement.

Fitobucaneve, Ital.
Tablets: Glucose (p.1945·3); royal jelly (p.2382·1); ginseng (p.2312·1).
Nutritional supplement.

Fosfarsile Junior *Fitobucaneve, Ital.*
Royal jelly (p.2382·1); vitamins (p.1922·1); phosphorus proteinate; cod-liver oil (p.1935·2).
Nutritional supplement.

Fosfaserin *Amnol, Ital.*
Phosphatidylserine; glutamine; vitamin B substances; lecithin; caffeine; ginseng; ginkgo biloba (p.1922·1).
Mental function disorders; nutritional supplement.

Fosfaseron *Itaca, Braz.†.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Fosfatan *Farmavy, Braz.†.*
Thiamine hydrochloride; magnesium glycerophosphate; calcium glycerophosphate; sodium glycerophosphate; guarana; kola; cinchona bark; nux vomica (p.1922·1).
Tonic.

Fosfitone *Fada, Arg.*
Suxamethonium (p.1912·1).
Depolarising neuromuscular blocker.

Fosfo Plus *FAMA, Ital.*
Glutamine (p.1947·2); -phosphoserine (p.2367·1); cyanocobalamin (p.1980·2).
Tonic.

Fosfo-Acutil *Montpellier, Arg.†.*
-Asparagine; glutamine or -acetyl- -glutamine; pyridoxine hydrochloride; -phosphorylserine (p.1922·1).
Tonic.

Fosfoadital *Gobbi, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fosfobarigraf *Justesa Imagen, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fosfobion *Sicomed, Rus.†.*
Adenosine triphosphate sodium (p.2247·3).

Fosfocaps *Sigma, Braz.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Fosfocil *Senosiain, Mex.*
Fosfomycin calcium (p.278·2) or fosfomycin sodium (p.278·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fosfocin *Crinos, Ital.*
Fosfomycin calcium (p.278·2) or fosfomycin sodium (p.278·2).
Bacterial infections.

Fosfocina *Ern, Spain.*
Fosfomycin calcium (p.278·2) or fosfomycin disodium (p.278·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fosfocine *Sanofi-Aventis, Fr.*
Fosfomycin sodium (p.278·2).
Bacterial infections.

Fosfocrisolo *Zambon, Ital.*
Sodium aurotiosulfate (p.124·2).
Rheumatoid arthritis.

Fosfo-Dom *Dominguez, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Fosfoevac *Bohm, Spain.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fosfoglutina B6 *Baldacci, Port.†.*
Calcium pidolate; glutamine; tetraethylamonium phosphate; pyridoxine hydrochloride (p.1922·1).
Mental function impairment.

Fosfoguaiacol *Ogna, Ital.*
Guaiacol (p.1561·2); eucalyptus (p.2301·2).
Respiratory congestion.

Fosfokalsiyum *Munir, Turk.*
Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Fosfolax *Coup, Gr.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Laxative.

Fosfomik *Finadiet, Arg.*
Terazosin (p.1410·3).
Benign prostatic hyperplasia; hypertension.

Fosfor *Consolidated Chemicals, Irl.; Ayrton, UK.*
Phosphorylcolamine.
Nutritional supplement; tonic.

Fosforal *Etifar, Venez.*
Vitamin preparation (p.1922·1).

Fosforilasi *Polifarma, Ital.*
Cocarboxylase (p.1975·2); riboflavin sodium phosphate (p.1977·3); pyridoxal phosphate (p.1978·2); nicotinamide (p.1957·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Neuritis; toxicosis.

Fosfosoda *Casen Fleet, Spain.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fosfo-Soda Fleet *Bergamon, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Constipation.

Fosfostilben *Labinca, Arg.†.*
Fosfestrol (p.2104·3).

Fosfoutipi Vitaminico *Terapeutico, Ital.†.*
Uridine triphosphate (p.2408·1); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1).
Peripheral neuropathies.

Fosfovita *Temis, Arg.*
Lecithin; phenylalanine; vitamin B substances (p.1922·1).
Nutritional supplement.

Fosfree *Mission Pharmacal, USA.*
Multivitamin preparation with iron and calcium (p.1922·1).
Calcium supplement; nocturnal leg cramping.

Fosgluten Reforzado *Alter, Spain.*
Calcium magnesium fytate; vitamin B substances; glutamine (p.1922·1).
Tonic.

Fosgluten Super Reforcado *Alter, Port.*
Glutamine; vitamin B substances (p.1922·1).
Tonic.

Fosicard *Actavis, Rus.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fosicard H *Actavis, Rus.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fosicomb *BMS, Austria.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fosicombi *Menarini, Ital.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fosicomp *BMS, Switz.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Foside *Solvay, Belg.†.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fosinil *Solvay, Belg.; Squibb, Spain†.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fosinogen *Generics, Cz.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fosinorm *BMS, Ger.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fosinorm comp *BMS, Ger.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fosipres *Menarini, Ital.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fosipril *Arrow, Austral.; Julphar, UAE.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fositen *BMS, Port.; BMS, Switz.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fositen Plus *BMS, Port.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).

Fositens *BMS, Austria; BMS, Spain.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fositens Plus *BMS, Spain.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Foskina *Glenmark, Philipp.*
Mupirocin (p.302·3).
Bacterial skin infections.

Foslainco *Lainco, Spain.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Fosmicin *Meiji, Indon.; Meiji, Thai.*
Fosfomycin sodium (p.278·2).
Bacterial infections.

Fosmicin-S *Meiji, Jpn.*
Fosfomycin sodium (p.278·2).
Bacterial infections.

Fosmidex *Dexa, Indon.*
Fosfomycin sodium (p.278·2).
Bacterial infections.

Fospartan Ginseng *Craveri, Arg.*
Ginseng; magnesium aspartate; potassium aspartate; adenosine triphosphate; vitamin B substances (p.1922·1).
Tonic.

Fosquival *Valmor, Venez.†.*
Calcium glycerophosphate; potassium glycerophosphate; vitamin B substances; sorbitol; phosphoric acid; quinine (p.1922·1).
Tonic.

Fosrenol *Orphan, Austral.; Shire, Cz.; Shire, Fr.; Genesis, Gr.; Shire, Port.; Swedish Orphan, Swed.; Shire, UK; Shire, USA.*
Lanthanum carbonate (p.1449·1).
Hyperphosphataemia.

Fossyol *Merckle, Ger.†.*
Metronidazole (p.837·1).
Trichomoniasis.

Fostair *Trinity, UK.*
⊗ Beclometasone dipropionate (p.1516·2); formoterol fumarate (p.1122·1).
Asthma.

Fosteofos *Arrow, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Foster *Chiesi, Port.*
⊗ Beclometasone dipropionate (p.1516·2); formoterol fumarate (p.1122·1).
Asthma.

Fosteum *Primus, USA.*
Genistein (p.2391·2); zinc amino acid chelate (p.2000·1); colecalciferol (p.1986·2).
Osteopenia; osteoporosis.

Fostex *Westwood, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Fostex Acne Medication Cleansing *Bristol-Myers Products, USA.*
Salicylic acid (p.1612·2).
Acne; hyperkeratosis.

Fostex Medicated *Westwood-Squibb, USA.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne.

Fostimon *Pfizer, Arg.; IBSA, Cz.; Genevrier, Fr.; IBSA, Hong Kong; IBSA, Hung.; IBSA, Ital.; CORNE, Mex.; Lepori, Port.; IBSA, Switz.; Pharmasure, UK.*
⊗ Urofollitropin (p.2136·3).
Female and male infertility.

Fostril *Westwood, USA†.*
Sulfur (p.1614·1); zinc oxide (p.1621·2).
Acne.

Fosular *Novell, Indon.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Fosval *Saval, Chile.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Fosvital *IMA, Braz.*
Vitamin B substances; amino acids; minerals (p.1922·1).
Tonic.

Fotadex *Phoenix, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Fot-Amsa *Antibioticos, Mex.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fotaram *Sanbe, Indon.*
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

Fotax *Neo Quimica, Braz.†; M & H, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Fotex *Phoenix, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Fotexina *Pisa, Mex.*
Cefotaxime sodium (p.228·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Fotil *Croma, Austria; Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Ger.; Amvis, Gr.†; Santen, Hung.; Santen, Neth.; Santen, Norw.; Santen, Philipp.; Santen, Pol.; Santen, Port.; Santen, Rus.; Santen, Swed.; Novartis, Switz.†; Santen, Thai.†.*
⊗ Pilocarpine hydrochloride (p.1884·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Fotobloc *Panalab, Arg.*
SPF 20; SPF 25: Melanin (p.1604·2).
Sunscreen.

Fotocollyre *Rafarm, Gr.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye infections.

Fotocrem *Valeant, Arg.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Fotocrem P
Note. This name is used for preparations of different composition.
ITF, Chile.
Titanium dioxide (p.1617·3).
Sunscreen.

ICN, Arg.†.
SPF 24: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

ICN, Arg.
SPF 34: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Fotocrem Ultra *ICN, Arg.*
SPF 42: Octinoxate (p.1608·2); meradimate (p.1604·2); avobenzone (p.1589·3); melanin (p.1604·2); titanium dioxide (p.1617·3).
Sunscreen.

Fotofil *INTES, Ital.*
⊗ Sodium aminobenzoate (p.2388·3); actinoquinol (p.2246·3); naphazoline nitrate (p.1565·2); borax (p.2268·1).
Blepharitis; conjunctivitis; corneal damage.

Fotoprotector
Note. This name is used for preparations of different composition.
Isdin, Arg.
SPF 15: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Isdin, Arg.
SPF 25: Octinoxate (p.1608·2); amiloxate (p.1589·1); enzacamene (p.1597·1); octil triazone (p.1608·1); octocrilene (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Extrem
Note. This name is used for preparations of different composition.
Ingens, Arg.†.
Cream: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

Isdin, Arg.
Gel SPF 26: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); bisoctrizole (p.1591·2).
Sunscreen.

Isdin, Arg.
Lotion SPF 36: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

Fotoprotector Isdin-25 *Andromaco, Chile†.*
SPF 25: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin-50 *Isdin, Chile.*
SPF 50: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); enzacamene (p.1597·1); zinc oxide (p.1621·2).
Sunscreen.

Fotoprotector Isdin Dry Oil *Isdin, Chile.*
Octinoxate (p.1608·2); octisalate (p.1608·2); enzacamene (p.1597·1); dioctylbutamidotriazone; avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin Extrem
Note. This name is used for preparations of different composition.
Isdin, Chile.
Gel-cream: Octinoxate (p.1608·2); enzacamene (p.1597·1); isopropyl palmitate (p.2030·1); avobenzone (p.1589·3).
Sunscreen.

Isdin, Chile.
Lotion: Octinoxate (p.1608·2); enzacamene (p.1597·1); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin Extrem Pediatrics *Isdin, Chile.*
Octinoxate (p.1608·2); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3); enzacamene (p.1597·1); bemotrizinol (p.1590·2); octil triazone (p.1608·1).
Sunscreen.

Fotoprotector Isdin Extrem Plus *Isdin, Chile.*
Octinoxate (p.1608·2); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin F-15
Note. This name is used for preparations of different composition.
Isdin, Chile.
Stick SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Isdin, Chile.
Topical gel: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin-25 Pediatrics
Note. This name is used for preparations of different composition.
Isdin, Chile.
Lotion SPF 25: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3); enzacamene (p.1597·1); ensulizole (p.1597·1).
Sunscreen.

Isdin, Chile.
Topical spray SPF 25: Octinoxate (p.1608·2); amiloxate (p.1589·1); enzacamene (p.1597·1); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Fotoprotector Isdin Ultra 65 *Isdin, Chile.*
Titanium dioxide (p.1617·3); octinoxate (p.1608·2); bisoctrizole (p.1591·2); enzacamene (p.1597·1); ensulizole (p.1597·1); bemotrizinol (p.1590·2).
Sunscreen.

Fotoprotector Isdin Ultra 90 *Isdin, Chile.*
Titanium dioxide (p.1617·3); octinoxate (p.1608·2); bisoctrizole (p.1591·2); enzacamene (p.1597·1); ensulizole (p.1597·1); bemotrizinol (p.1590·2).
Sunscreen.

Fotoprotector Ultra *Isdin, Arg.*
SPF 65; SPF 90: Bisoctrizole (p.1591·2); bemotrizinol (p.1590·2); octinoxate (p.1608·2); ensulizole (p.1597·1); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Fotoprotectores
Note. This name is used for preparations of different composition.
Silesia, Chile.
Cream SPF 20: MPI; cinnamate.
Sunscreen.

Silesia, Chile.
Cream SPF 50: MPI.
Sunscreen.

Silesia, Chile.
Milk: Dihydroxyacetone (p.1594·1).
Tanning aid.

Isdin, Port.
SPF 15; SPF 20; SPF 25; SPF 50: A range of sunscreen preparations.

Silesia, Chile.
Stick SPF 20: Titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Fotoprotetor Isdin *Medley, Braz.*
SPF 50: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); enzacamene (p.1597·1); zinc oxide (p.1621·2).
Sunscreen.

Fotoprotetor Isdin Extrem
Note. This name is used for preparations of different composition.
Medley, Braz.
Lotion SPF 25: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

Medley, Braz.
Topical gel/cream SPF 25: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2).
Formerly contained octinoxate, enzacamene, bisoctrizole, and avobenzone.
Sunscreen.

Fotoprotetor Isdin Extrem Infantil *Medley, Braz.*
Titanium dioxide (p.1617·3); octinoxate (p.1608·2); enzacamene (p.1597·1).
Sunscreen.

Fotoprotetor Isdin Extrem UVA *Medley, Braz.*
Gel: Bisoctrizole (p.1591·2); enzacamene (p.1597·1); octinoxate (p.1608·2).
Sunscreen.

Fotoprotetor Isdin Infantil *Medley, Braz.*
Titanium dioxide (p.1617·3); enzacamene (p.1597·1).
Sunscreen.

Fotoprotetor Spray Isdin *Medley, Braz.*
SPF 25: Octinoxate (p.1608·2); amiloxate (p.1589·1); enzacamene (p.1597·1); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Fotoral *ICN, Arg.†; Valeant, Mex.*
Vitamin E; vitamin C; betacarotene; zinc; selenium (p.1922·1).
Antoxidant.

Fotorretin
Poen, Arg.
Phenylephrine (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis.

Roemmers Poen, Venez.
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Fotosol *Cassara, Arg.*
SPF 19: Octinoxate (p.1608·2); bisoctrizole (p.1591·2).
Sunscreen.

Fotosol Cassara *D & M, Chile.*
SPF 19: Bisoctrizole (p.1591·2); octinoxate (p.1608·2).
Sunscreen.

Fotosol Ultra
Note. This name is used for preparations of different composition.
Cassara, Arg.
SPF 19: Octinoxate (p.1608·2); bisoctrizole (p.1591·2).
Formerly contained octinoxate.
Sunscreen.

D & M, Chile.
SPF 32: Octinoxate (p.1608·2); bisoctrizole (p.1591·2).
Sunscreen.

Fotosol Ultra Autobronceante *Cassara, Arg.*
SPF 32: Dihydroxyacetone (p.1594·1); octinoxate (p.1608·2); bisoctrizole (p.1591·2).
Sunscreen; tanning aid.

Fototar *ICN, USA.*
Coal tar (p.1616·2).
Psoriasis; seborrhoeic dermatitis.

Fotrec DHA *Visufarma, Ital.*
Docosahexaenoic acid (p.1362·1); omega-3 triglycerides (p.1362·1).
Nutritional supplement.

Foucacillin *Coup, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Fouch *Rafarm, Gr.*
Clindamycin (p.251·1).
Bacterial skin and vaginal infections.

Foudaril *Gap, Gr.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Fourderm *Cipla, India.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Fourderm AF *Cipla, India.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2); clotrimazole (p.530·1).
Infected skin disorders.

Fournox *Charoen, Thai.†*
Ceftazidime (p.234·1).
Bacterial infections.

Four-Ton *Body Spring, Ital.*
Guarana (p.2416·1); damiana (p.2292·1); ginseng (p.2312·1); royal jelly (p.2382·1).
Nutritional supplement.

Fovas *Cadila Pharma, India.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Fovysat *Ysatfabrik, Ger.†*
Crataegus (p.2289·1); ginger (p.1732·3).
Dystonias; neuroses.

Fowlers *Columbia, Canad.*
Attapulgite (p.1709·1).
Diarrhoea.

Foxetin *Gador, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Foxgoria *Nida, Singapore.*
Norfloxacin (p.309·2).
Gonorrhoea; urogenital infections.

Foxil *Ibirn, Ital.*
Cefadroxil (p.218·1).
Bacterial infections.

Foxim *Kalbe, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Foxin *Pharmaland, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Foxinon *M & H, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Foxolin *Gap, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Foxtil *Uniao Quimica, Braz.†*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Foxtin *IPCA, Singapore.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Foy *Lepetit, Ital.; Ono, Jpn.*
Gabexate mesilate (p.2307·3).
Disseminated intravascular coagulation; pancreatitis.

Fozide
BMS, Gr.
⊗ Fosinopril (p.1292·1); hydrochlorothiazide (p.1307·3).
Hypertension.

BMS, Rus.
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Foziretic *Merck-Lipha, Fr.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Fozitec *Merck-Lipha, Fr.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Foznol *Shire, Irl.*
Lanthanum carbonate (p.1449·1).
Hyperphosphataemia in renal failure.

FP 20 *Pisa, Mex.†*
Electrolyte infusion (p.1667·1).

FP Tab *Fujimoto, Jpn.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

F-Psorin *Mediapharm, Gr.*
Calcipotriol (p.1591·3).
Psoriasis.

Fracidin *Rayere, Mex.†*
⊗ Oxymetazoline (p.1567·2).
Nasal congestion.

Fractal *Pierre Fabre, Fr.*
Fluvastatin sodium (p.1290·2).
Cardiovascular risk reduction following coronary angioplasty; hypercholesterolaemia.

Frademicina
Janssen-Cilag, Arg.
Lincomycin (p.293·1).
Respiratory-tract infections.

Pfizer, Braz.
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Fradilen *Thea, Port.*
Chromocarb diethylamine (p.2281·1).
Capillary fragility.

Frador
Note. This name is used for preparations of different composition.
Wilson, NZ.
Menthol (p.2340·1); chlorobutanol (p.1639·2); storax (p.2392·3).
Mouth ulcers.

Trinity, UK.
Menthol (p.2340·1); chlorobutanol (p.1639·2); storax (p.2392·3); benzoin (p.2394·2).
Mouth ulcers.

Fragador
Note. This name is used for preparations of different composition.
Weleda, S.Afr.
Cochlearia officinalis; conchae; fragaria vesca; glycogenum; levisticum root; sodium carbonate; aniseed; sage; urtica; triticum vulgaris; vivianit.
Nervous disorders.

Weleda, UK.
Homoeopathic preparation.

Fragmin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.†; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Dalteparin sodium (p.1255·1).
Myocardial infarction; prevention of clotting in extracorporeal circuits; thromboembolic disorders; unstable angina.

Fragmine *Pfizer, Fr.*
Dalteparin sodium (p.1255·1).
Myocardial infarction; prevention of clotting during haemodialysis; thromboembolic disorders; unstable angina.

Frakas *Arrow, Austral.*
Doxycycline (p.267·1).
Amoebiasis; bacterial infections; malaria.

Frakidex *Chauvin, Belg.; Chauvin, Fr.; Bausch & Lomb, Hong Kong; Chauvin, Hong Kong; Bausch & Lomb, Port.; Chauvin, Singapore†; Bausch & Lomb, Switz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); framycetin sulfate (p.279·1).
Infected inflammatory eye disorders.

Frakitacine *Bausch & Lomb, Switz.†*
Framycetin sulfate (p.279·1).
Bacterial eye infections.

Framacin *Medic+Aid, Philipp.*
Rifampicin (p.325·3).
Nasopharyngeal carriers of Neisseria meningitidis; tuberculosis.

Framecef *Levofarma, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Framex *Gedeon Richter, Cz.†; Gedeon Richter, Rus.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Framicin *Pharlab, Braz.†*
Lincomycin (p.293·1).
Gram-positive bacterial infections.

Framykoin *Biomedica, Cz.; Zentiva, Cz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Infected skin disorders; ulcers; wounds.

Framyxone *Jolly-Jatel, Fr.*
⊗ Dexamethasone sodium phosphate (p.1526·2); framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3).
Ear and nose infections.

Francetin *Mochida, Jpn.*
Neomycin sulfate (p.305·1).
Bacterial infections.

Francital *Francia, Ital.†*
Fosfomycin calcium (p.278·2).
Bacterial infections.

Frangulina *Ottolenghi, Ital.†*
Frangula (p.1732·2); boldo (p.2267·2).
Constipation.

Franol
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
⊗ Ephedrine sulfate (p.1558·2); theophylline (p.1140·1).
Bronchospasm.

Sanofi Synthelabo, Thai.
Theophylline (p.1140·1).
Obstructive airways disease.

Sanofi-Aventis, UK†.
⊗ Ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1).
Obstructive airways disease.

Franol Expectorant *Sanofi Synthelabo, Irl.†*
Theophylline hydrate (p.1140·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Franol Plus *Sanofi-Aventis, UK†.*
⊗ Ephedrine sulfate (p.1558·2); theophylline (p.1140·1).
Obstructive airways disease.

Franzbranns *Hilarys, Canad.†*
⊗ Menthol (p.2340·1); alcohol (p.1625·2); eucalyptus oil (p.2301·2); salol (p.122·1).

Franzbranntwein *Klosterfrau, Ger.*
Camphor (p.2273·2); pumilio pine oil (p.2376·3).
Musculoskeletal and joint pain; soft-tissue disorders.

Franzbranntwein mit Fichtennadelol *Hetterich, Ger.†*
⊗ Camphor (p.2273·2); alcohol (p.1625·2); Norway spruce oil.
Musculoskeletal and joint pain; soft-tissue disorders.

Frauentropfen Nr 18 *Doskar, Austria.*
Homoeopathic preparation.

Fraurs *Francia, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders; gallstones.

Fravit *Degorts, Mex.*
Vitamin A; vitamin D (p.1922·1).
Vitamin deficiency.

Fravitan *Degorts, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Fraxidol *Edmond Pharma, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Fraxiforte *Sanofi Synthelabo, Switz.*
Nadroparin calcium (p.1346·1).
Deep-vein thrombosis.

Fraxiparin *GSK, Austria; GSK, Ger.*
Nadroparin calcium (p.1346·1).
Prevention of clotting during haemodialysis and haemofiltration; thromboembolic disorders.

Fraxiparina *Sanofi-Aventis, Braz.; GSK, Ital.; GSK, Port.; GSK, Spain; GSK, Venez.*
Nadroparin calcium (p.1346·1).
Prevention of clotting during haemodialysis; thromboembolic disorders; unstable angina.

Fraxiparine *GSK, Arg.; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; Sanofi Synthelabo, Israel; GSK, Malaysia; Sanofi Synthelabo, Mex.; GSK, NZ†; GSK, Neth.; Sanofi Synthelabo, Norw.†; GSK, Philipp.; GSK, Pol.; GSK, Rus.; Sanofi Synthelabo, S.Afr.; Sanofi Synthelabo, Singapore; Sanofi Synthelabo, Swed.†; GSK, Switz.; GSK, Thai.; GSK, Turk.*
Nadroparin calcium (p.1346·1).
Myocardial infarction; prevention of clotting in extracorporeal circuits; thromboembolic disorders; unstable angina.

Fraxodi *GSK, Belg.; GSK, Fr.; GSK, Ger.; GSK, Hung.; GSK, Ital.; Sanofi Synthelabo, Mex.; GSK, Neth.; GSK, Pol.; GSK, Port.; GSK, Turk.*
Nadroparin calcium (p.1346·1).
Thromboembolic disorders.

Fraxone *Ranbaxy, S.Afr.†*
Ceftriaxone (p.238·1).
Bacterial infections.

Fray Romano *Ximena Polanco, Chile.*
Honey (p.1948·2); aloe vera (p.1588·2).
Tonic.

Frazim *Francia, Ital.†*
Pirenzepine hydrochloride (p.1762·3).
Peptic ulcer.

Frazoline *Bouchara-Recordati, Hong Kong.*
⊗ Framycetin sulfate (p.279·1); naphazoline nitrate (p.1565·2); amylocaine hydrochloride (p.1853·3).
Nasal infection and congestion.

Frazon *Ferron, Indon.*
Ondansetron (p.1756·3).
Nausea and vomiting.

FreAmine *Eczacibasi-Baxter, Turk.; Victus, Venez.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

FreAmine III *Baxter, Ital.; Braun, USA.*
Amino-acid and electrolyte infusions (p.1922·1).
Parenteral nutrition.

FreAmine HBC *McGaw, USA.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in hepatic encephalopathy.

Freathe *Altana, Gr.*
⊗ Ciclesonide (p.1521·3).
Obstructive airways disease.

Frebac *Macrophar, Thai.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection of skin, wounds, and instruments.

Frebini *Fresenius Kabi, Fin.; Fresenius Kabi, Irl.; Fresenius Kabi, Turk.; Fresenius Kabi, UK.*
A range of preparations for enteral nutrition in children (p.1922·1).

Fre-bre *Self-Care Products, UK.*
Parsley seed (p.2363·2); peppermint oil (p.1761·2); spearmint oil (p.2391·3).

Frecuental *Lacefa, Arg.†*
⊗ Furosemide (p.1292·1).

Fredam *Novell, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Fredol *Medipharm, Chile.*
Ergotamine tartrate (p.620·1); dipyrone (p.49·2); caffeine (p.1116·3); chlorphenamine (p.572·2).
Vascular headache.

Fredyr *Rafarm, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Fredyren *Rafarm, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Free & Clear *Pharmaceutical Specialties, USA.*
Skin cleanser.

Freecad *Wockhardt, India.*
Betacarotene; vitamin E; vitamin C; zinc; copper; manganese; selenium (p.1922·1).
Ischaemic heart disease; prevention of cataract and macular degeneration; skin disorders.

Freedavite *Freeda, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Freederm *Dendron, UK.*
Nicotinamide (p.1957·3).
Acne.

Freederm Tar *Schering-Plough, Pol.; Schering-Plough, Rus.*
Coal tar (p.1616·2).
Scalp psoriasis; seborrhoeic dermatitis.

Freederm Zinc *Schering-Plough, Rus.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Freedox *Pharmacia, Austria†; Pharmacia, Belg.†; Pharmacia, S.Afr.†; Pharmacia, Switz.†*
Tirilazad mesilate (p.1414·1).
Subarachnoid haemorrhage.

Freeflex Cloruro Sodico *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Freeflex Glucosa *Fresenius Kabi, Spain.*
Glucose infusion (p.1945·3).
Fluid disorders; parenteral nutrition.

Freeflex Glucosalina *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1); glucose (p.1945·3).
Carbohydrate source; fluid and electrolyte disorders.

Freeflex Ringer Lactato *Fresenius Kabi, Spain.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Freegas *Prati-Donaduzzi, Braz.†*
Dimeticone (p.1770·2).
Dyspepsia; flatulence.

Freenal *Ache, Braz.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Freesept *Rider, Chile.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat hygiene.

Freestyle *Abbott, Irl.; Abbott Diabetes Care, UK.*
Test for glucose in blood (p.2314·1).

Freestyle Papillon *Abbott Diagnostics, Ital.*
Test for glucose in blood (p.2314·1).

Freetop *Janssen-Cilag, Venez.*
Ketoconazole (p.539·1).
Scalp disorders.

Freeze *SSL, Fr.*
Dimethyl ether (p.1689·2); propane (p.1691·3); isobutane (p.1690·1).
Warts.

Freezone *Medtech, Canad.; SA Druggists Self Med, S.Afr.; Whitehall, USA.*
Salicylic acid (p.1612·2).
Calluses; corns; hyperkeratosis.

Frego *Kalbe, Indon.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; migraine.

Freimax *Caldeira & Marques, Port.†.*
Methyl salicylate (p.85·3); turpentine oil (p.2406·3); camphor (p.2273·2); thymol (p.1664·3); pine oil (p.2368·2).
Inflammation; musculoskeletal and joint disorders.

Freka-cid *Stada, Ger.; Stada, Hong Kong; Stada, Malaysia; Stada, Thai.*
Povidone-iodine (p.1659·2).
Burns; skin disinfection; skin infections; ulcers; wounds.

Freka-Clyss *Fresenius Kabi, Switz.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Freka-Derm *Fresenius Kabi, Ger.*
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1); clorophene (p.1641·1).
Skin disinfection.

Frekaderm *Fresenius Kabi, Switz.†.*
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1); clorophene (p.1641·1).
Skin disinfection.

Freka-Drainjet *Fresenius Kabi, Ger.*
Sodium chloride (p.1686·1).
Irrigation fluid.

Freka-Drainjet Purisole *Fresenius Kabi, Ger.*
⊗ Sorbitol (p.1965·1); mannitol (p.1330·2).
Bladder irrigation.

Freka-Nol *Fresenius Kabi, Ger.*
⊗ Alcohol (p.1625·2); glyoxal (p.1646·1); didecyldimethylammonium chloride (p.1642·2).
Surface and instrument disinfection.

Freka-Sept 80 *Fresenius Kabi, Ger.*
⊗ Alcohol (p.1625·2); orthophenylphenol (p.1655·1); clorophene (p.1641·1); benzalkonium chloride (p.1629·1).
Hand disinfection.

Freka-Steril *Fresenius Kabi, Ger.*
Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3).
Hand disinfection; skin disinfection.

FrekaVit *Fresenius Kabi, Ger.*
Multivitamin infusion (p.1922·1).
Parenteral nutrition.

Fremet *Recordati, Spain.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Fremid *Euro-Med, Philipp.*
⊗ Furosemide (p.1292·1).
Heart failure; hypertension; liver cirrhosis; nephrotic syndrome; oedema.

Fremomet *Frezyderm, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Frenacil *McNeil, Spain.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous mucous.

Frenacol *Sanofi Synthelabo, Chile†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms; nasal congestion; sinusitis.

Frenactil *Janssen-Cilag, Belg.; Janssen-Cilag, Neth.*
Benperidol (p.964·1).
Agitation; delirium; hallucinations; nausea and vomiting; psychoses; sexually deviant behaviour.

Frenadol *McNeil, Spain.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; fever; influenza and cold symptoms; pain.

Frenadol Complex *McNeil, Spain.*
Ascorbic acid (p.1983·3); caffeine citrate (p.1116·3); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms; coughs; fever; pain.

Frenadol PS *McNeil, Spain.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; coughs; fever; pain.

Frenador *Ibfarma, Braz.†.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Frenal *Pharmacia, Ital.†; Sigma-Tau, Spain.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchospasm.

Frenal Compositum *Sigma-Tau, Spain.*
⊗ Sodium cromoglicate (p.1136·3); isoprenaline sulfate (p.1316·3).
Allergic bronchitis; asthma.

Frenaler
Note. This name is used for preparations of different composition.
Roemmers, Arg.
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Laboratorios Chile, Chile.
Loratadine (p.583·3).
Hypersensitivity reactions.

Frenaler-D *Laboratorios Chile, Chile.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2) or pseudoephedrine sulfate (p.1571·2).
Nasal congestion; rhinitis; sinusitis.

Frenaseltz *McNeil, Spain†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, chlorphenamine maleate, and phenylpropanolamine hydrochloride.
Cold and influenza symptoms.

Frenasma *Faran, Gr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Frenatermin *McNeil, Spain.*
Ibuprofen sodium (p.65·2).
Fever; inflammation; pain.

Frenatus *McNeil, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Frenidor *Confar, Port.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

frenopect *Riemser, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Frenotos
Note. This name is used for preparations of different composition.
Columbia, Arg.
Oxeladin citrate (p.1567·1).
Coughs.

Recalcine, Chile.
Zipeprol hydrochloride (p.1575·3).
Coughs.

Frenotos Muc *Columbia, Arg.*
Oxeladin citrate (p.1567·1); bromhexine hydrochloride (p.1552·2).
Coughs; respiratory-tract congestion.

Frenotosse *Cimed, Braz.*
Bromoform (p.2269·3); tolu balsam (p.1574·2); sodium benzoate (p.1630·2).
Coughs.

Frenotossil *Infabra, Braz.†.*
Potassium iodide (p.2169·2); sulfogaiacol (p.1573·2); tolu balsam (p.1574·2).
Respiratory-tract congestion.

Frenurin *UCI, Braz.†.*
Oxybutynin hydrochloride (p.2190·3).
Urinary-tract disorders.

Frerichs Maldifassi *Pharbenia, Ital.†.*
Aloes (p.1705·2); rhubarb (p.1768·3); calamus (p.2271·3); gentian (p.2310·3).
Constipation.

Frescansol *Volta, Chile.*
Borax (p.2268·1); sodium bicarbonate (p.1673·2); boric acid (p.2268·1).
Hyperhidrosis.

Fresco *Rekah, Israel.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1).
Gastrointestinal hyperacidity; peptic ulcer.

Freselamin *Biosel, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Fresenizol *Fresenius Kabi, Mex.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Fresh Tears *Allergan, Braz.*
Carmellose sodium (p.2142·1).
Dry eyes.

Freshburst Listerine *Pfizer Consumer, S.Afr.*
Thymol (p.1664·3).
Mouth and throat disorders.

Freshmel *Laboratorios Chile, Chile.*
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat infections.

Freshmel Tos *Laboratorios Chile, Chile.*
Chlorhexidine hydrochloride (p.1635·3); noscapine (p.1566·2).
Coughs; mouth and throat infections.

Fresh-N-Free *Geritrex, USA.*
Chlorhexidine (p.1635·2); chlorophyll complex (p.1471·1).
Oral hygiene.

Fresofol *Fresenius Kabi, Arg.; Fresenius Kabi, Indon.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Pharmaco, NZ; Fresenius Kabi, Philipp.; Fresenius Kabi, Thai.*
Propofol (p.1791·1).
General anaesthesia; sedation in ventilated patients.

Fresomega *Fresenius Kabi, Mex.*
Omega-3 marine triglycerides (p.1362·2).
Parenteral nutrition.

Fresubin *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Cz.†; Fresenius Kabi, Fin.; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Mex.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Switz.†; Fresenius Kabi, Thai.†; Fresenius Kabi, Turk.; Fresenius Kabi, UK.*
A range of preparations for enteral nutrition (p.1922·1).

Fretic *Vendiz, Philipp.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Freudal *Ifusa, Mex.†.*
Diazepam (p.986·3).

Frevag *Organifar, Venez.†.*
Homatropine methylbromide (p.1881·3); phenobarbital sodium (p.492·2).

Frexocel *Normal, Port.†.*
Lumiracoxib (p.78·1).
Osteoarthritis.

Frezylin *Frezyderm, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Frialgina *Uriach, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

Fribat *Epifarma, Ital.*
Ceftazidime (p.234·1).
Bacterial infections.

Friccion Aromatica *Gache, Venez.*
Methyl salicylate (p.85·3); camphor (p.2273·2); turpentine oil (p.2406·3); lavender oil (p.2331·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Friccion Don Juan *Sophia, Mex.*
Methyl salicylate (p.85·3).
Musculoskeletal pain.

Fricsol *Konsuma, Venez.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Fricsolgel *Konsuma, Venez.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Musculoskeletal and joint disorders.

Fridalit *Fada, Arg.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Fridep *Mersifarma, Indon.*
Sertraline hydrochloride (p.421·3).
Depression.

Frigol *Brady, Austria.*
Xantinol nicotinate (p.1433·1).
Cerebral and peripheral vascular disorders.

Frigoplasma *Kropf, Switz.†.*
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3); hamamelis (p.2318·2); camphor (p.2273·2); cajuput oil (p.2271·2); rosemary oil (p.2381·3); thyme oil (p.2401·2).
Phlebitis; soft-tissue and peri-articular disorders.

Frigrip *Otto, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Cough; influenza symptoms.

Frilen *Offenbach, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Friliver *Bracco, Ital.*
Amino-acid preparations (p.1922·1).
Hepatic failure; tonic.

Frilix *Pharos, Indon.*
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders.

Frimaind *SoSe, Ital.*
Citalopram hydrobromide (p.385·3).
Anxiety disorders; depression.

Frimania *Mersifarma, Indon.*
Lithium carbonate (p.401·3).
Aggression; bipolar depression; self-harm.

Frineg *Epifarma, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Frinova *Sanofi-Aventis, Spain.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

Friobax *Degorts, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Rhinitis; upper respiratory-tract congestion.

Friocal *Columbia, Mex.†.*
Menthol (p.2340·1).

Frionex *Wierhom, Arg.*
Pentane (p.2026·1); butane (p.1688·2).
Pain.

Frionex Plus *Wierhom, Arg.†.*
Menthol (p.2340·1); camphor (p.2273·2).
Inflammation; pain.

Friorub *Hofmann, Chile.*
Menthol (p.2340·1).
Musculoskeletal and soft-tissue injury.

Friosmin N *Michallik, Ger.†.*
Bismuth subgallate (p.1711·1); emplastrum lithargyri.
Burns; wounds.

Fripi *Monserrat, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Fripos *Nufarindo, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); ascorbic acid; magnesium; zinc; manganese (p.1922·1).
Joint disorders.

Friral *Farcoral, Mex.†.*
Moroxydine hydrochloride (p.898·2); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Cold symptoms.

Frisin *Aventis, Chile†.*
Clobazam (p.477·2).
Anxiety; epilepsy.

Frisium *Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Ovation, Canad.; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sandoz, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Pol.; Sanofi-Aventis, Singapore†; Aventis, Thai.; Aventis, UK; Sanofi-Aventis, Venez.*
Clobazam (p.477·2).
Anxiety; epilepsy; insomnia; psychosomatic disorders.

Frisogrow *Friesland, Singapore†.*
Nutritional supplement (p.1922·1).

Frisol *BA Farma, Port.†.*
Ketoconazole (p.539·1).

Frisolac *BA Farma, Port.*
Ketoconazole (p.539·1).
Fungal infections.

Frisolona *Allergan, Port.*
⊗ Prednisolone acetate (p.1541·1).
Eye disorders.

Frisomum *Frisocare, Hong Kong; Friesland, Singapore.*
Preparation for enteral nutrition (p.1922·1).
Pregnancy and lactation.

Frisosoy *Frisocare, Hong Kong; Friesland, Singapore.*
Infant feed (p.1922·1).
Cow's milk protein allergy; lactose intolerance.

Frisovom *Friesland, Hong Kong†; Friesland, Malaysia†; Friesland, Singapore.*
Infant feed (p.1922·1).
Colic; constipation; vomiting.

Fristamin *FIRMA, Ital.*
Loratadine (p.583·3).
Allergic rhinitis; hypersensitivity reactions.

Fristens *Kalbe, Indon.*
Irbesartan (p.1316·1).
Hypertension.

Frivent *Dompe, Ital.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

Frixio *Laboratorios Chile, Chile.*
Methyl salicylate (p.85·3); methyl nicotinate (p.85·3).
Musculoskeletal and joint disorders.

Frixitas *Novell, Indon.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorder.

Frixodon *Brasmedica, Braz.†.*
Methacholine hydrochloride (p.2343·2); thymol (p.1664·3); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Frixo-Dragon Vert *DP-Medica, Switz.†.*
Ethyl nicotinate (p.52·1); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); juniper oil (p.2328·3); nutmeg oil (p.2355·3); pine silvestris oil (p.2368·2); rosemary oil (p.2381·3); sage oil (p.2382·3); wild thyme oil (p.2415·3); thyme oil (p.2401·2); turpentine oil (p.2406·3).
Cold symptoms.

Frixonil *Vincenti, Venez.*
⊗ Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); alcohol (p.1625·2).
Muscle and joint pain.

Frixopel *EMS, Braz.*
Turpentine oil (p.2406·3); methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Froben *Abbott, Austria; Abbott, Belg.; Abbott, Canad.; Knoll, India; Abbott, Irl.; Abbott, Ital.; Abbott, NZ†; Abbott, Neth.; Abbott, Port.; Knoll, S.Afr.; Abbott, Spain; Abbott, Switz.; Abbott, UK.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Froidir *Orion, Fin.*
Clozapine (p.981·1).
Schizophrenia.

Frolicin *ITF, Gr.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Fromen *Menarini, Cz.*
Frovatriptan succinate (p.622·3).
Migraine.

Fromentyl *Medinova (Μεντινοβα), Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Fromil *Valmor, Venez.†.*
⊗ Furosemide (p.1292·1).

Fromilid *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Clarithromycin (p.248·2).
Bacterial infections.

Fromirex *Menarini, Neth.*
Frovatriptan succinate (p.622·3).
Migraine.

Frontal *Pfizer, Braz.; Solvay, Ital.*
Alprazolam (p.960·1).
Anxiety disorders; insomnia; panic disorders; tremor.

Frontin *Egis, Cz.; EGIS, Hung.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorders.

Froop *Ashbourne, UK.*
⊗ Furosemide (p.1292·1).
Oedema; oliguria.

Froop Co *Ashbourne, UK†.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Ascites with cirrhosis; oedema.

Frosinor *Novartis, Spain.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; post-traumatic stress disorder; social phobia.

Frost Cream *Weleda, UK.*
Homoeopathic preparation.

Frostsalbe *Weleda, Austria.*
Homoeopathic preparation.

Frotin *YSP, Malaysia.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Frova *Elan, USA.*
Frovatriptan (p.622·3).
Migraine.

Frovex *Menarini, Irl.*
Frovatriptan succinate (p.622·3).
Migraine.

Froxal *Probiomed, Mex.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Frubiase Calcium forte 500 *Boehringer Ingelheim, Ger.*
Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); ergocalciferol (p.1987·1).
Osteomalacia; osteoporosis.

Frubiase Calcium T *Boehringer Ingelheim, Ger.*
Calcium gluconate (p.1675·3); calcium lactate (p.1676·1).
Calcium deficiency.

Frubienzym *Boehringer Ingelheim, Ger.*
Muramidase (p.2348·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Frubilurgyl *Boehringer Ingelheim, Ger.†.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Frubiose Vitamine D *Boehringer Ingelheim, Fr.†.*
Ergocalciferol (p.1987·1); calcium gluconate (p.1675·3); calcium lactate (p.1676·1).
Vitamin D and calcium deficiency.

Frubiose-N *Galenica, Gr.†.*
Calcium gluconate (p.1675·3); calcium lactate (p.1676·1); phosphoric acid; vitamin C; ergocalciferol (p.1922·1).
Calcium deficiency.

Frubizin akut *Boehringer Ingelheim, Ger.*
Ambroxol hydrochloride (p.1550·3).
Sore throat.

Frubizin Forte *Boehringer Ingelheim, Ger.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Fru-Co *Ivax, Irl.; Ivax, UK.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Ascites; heart failure; nephrotic syndrome; oedema.

Fructal *Bieffe, Ital.†.*
Fructose (p.1945·1).
Diabetes; liver disorders; post-operative care.

Fructan *Skills, Ital.*
Fructose (p.1945·1).
Sugar substitute.

Fructines
Note. This name is used for preparations of different composition.
Fucus, Arg.
Phenolphthalein (p.1762·1).
Constipation.

Pharmethic, Belg.; DB, Fr.; Ferel, Port.; DB, Switz.
Sodium picosulfate (p.1771·1).
Constipation.

Fructofin *Also, Ital.*
Fructose (p.1945·1).
Sugar substitute.

Fructogenase *Luper, Braz.†.*
Fructose; vitamins (p.1922·1).
Vitamin supplement.

Fructopiran *Monico, Ital.†.*
Fructose (p.1945·1).
Cardiac disorders; kidney disorders; liver disorders.

Fructosil *Volchem, Ital.*
Fructose (p.1945·1).
Supplementation of glycogen reserves.

Fructosol *Teva, Hung.*
Fructose (p.1945·1).
Fluid replacement; parenteral nutrition.

Fructosol E *Human, Hung.†.*
⊗ Fructose (p.1945·1); alcohol (p.1625·2).
Carbohydrate source; fluid replacement.

Frugelletten *Bregenzer, Austria.*
Fig (p.1731·3); senna (p.1769·2); tamarind (p.1775·3).
Constipation.

Fruit of the Earth Block-Up Baby Sunblock
Fruit of the Earth, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth Block-Up Kids
Note. This name is used for preparations of different composition.
Fruit of the Earth, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth, Canad.†.
SPF 45: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth Block-Up Regular *Fruit of the Earth, Canad.*
SPF 45: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth Block-Up Regular Sunblock *Fruit of the Earth, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth Block-Up Sport
Note. This name is used for preparations of different composition.
Fruit of the Earth, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth Block-Up Sunblock *Fruit of the Earth, Canad.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruitatives *Rogers, Canad.†.*
Bisacodyl (p.1710·1); docusate sodium (p.1725·1); prune (p.1765·1).
Constipation.

Fruity Chews *Goldline, USA.*
A range of vitamin preparations (p.1922·1).

Frumeron *Remedica, Hong Kong; Remedica, Thai.*
⊗ Indapamide (p.1314·1).
Hypertension.

Frumil *Sanofi-Aventis, Gr.; Geno, India; Aventis, Irl.; Sanofi-Aventis, NZ; Aventis, Switz.†; Helios, UK.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Ascites; heart failure; hypertension; oedema.

Frunalia *Pasteur, Chile.*
Tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2).
Antacid; constipation.

Frusamil *Sanofi-Aventis, Belg.; Aventis, Denm.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Frusehexal *Hexal, Austral.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Frusema *Imperial, Philipp.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Frusemix *Cipla, India.*
⊗ Furosemide (p.1292·1).

Frusene *Orion, UK.*
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Ascites; heart failure; oedema.

Frusenex *Geno, India.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Frusid *Douglas, Austral.; Douglas, NZ; Douglas, Thai.†; TTN, Thai.†; DDSA Pharmaceuticals, UK.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema; renal failure.

Fruside *Pinewood, Irl.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; pulmonary oedema.

Frusix *Cipla, India.*
⊗ Furosemide (p.1292·1).

Frusol *Rosemont, UK.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Frut *Infosint, Ital.†.*
Fosfructose trisodium (p.2307·1).
Hypophosphataemia; ischaemic heart disease.

Frutacid *Calox, Venez.*
Calcium carbonate (p.1714·1).
Antacid; calcium supplement.

Frutalax *Hexal, Braz.†.*
Senna (p.1769·2); cassia pulp (p.1715·3); tamarind (p.1775·3); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Frutasal Knop *Knop, Chile.*
Tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2).
Antacid.

Frutenor *Rafarm, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

FrutiCal *Jelfa, Pol.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Frutin *Prisfar, Port.*
Natural dolomite (p.2297·3).
Gastric hyperacidity.

Frutoplex *Marjan, Braz.*
Fructose; ascorbic acid; riboflavin; pyridoxine hydrochloride; nicotinamide (p.1922·1).
Vitamin supplement.

Frutovena *Farmalab, Braz.*
Fructose; riboflavin sodium phosphate; pyridoxine hydrochloride; ascorbic acid; nicotinamide (p.1922·1).
Vitamin supplement.

Frutovitam *Cristalia, Braz.*
Multivitamin preparation (p.1922·1).

Fruttasan *Graf Fruttasan, Switz.*
Senna (p.1769·2); fig (p.1731·3).
Constipation.

Fruver *EG, Ital.*
Multivitamin preparation (p.1922·1).

F-Slim *Kalbe, Indon.*
Phaseolus vulgaris; green tea (p.2416·1); chromium polynicotinate.
Obesity.

FSME-Bulin *Baxter, Austria†; Baxter, Cz.†; Baxter, Ger.†.*
A tick-borne encephalitis immunoglobulin (p.2241·1).
Passive immunisation.

FSME-Immun *Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Ger.; Baxter, Hung.; Baxter, Pol.; Baxter, Swed.; Baxter, Switz.*
A tick-borne encephalitis vaccine (p.2241·1).
Separate preparations are available for infants and children and for adults.
Active immunisation.

F-Tab *Medicine Products, Thai.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Ftazidime *Lilly, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

FTDA *Cassara, Arg.†.*
Flutamide (p.725·1).

Ftonavil *Vianex (Βιανέξ), Gr.†.*
Captopril (p.1239·2).
Hypertension.

Ftorafur *Grindex, Cz.; Grindex, Hung.; Grindex, Rus.*
Tegafur (p.776·1).
Malignant neoplasms.

Ftorocort *Gedeon Richter, Hung.; Gedeon Richter, Rus.; Gedeon Richter, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Fubaxyn *IAE, Philipp.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Fubecot *Target, Gr.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Fuca *Melisana, Belg.*
Senna (p.1769·2).
Constipation.

Fuca N *Melisana, Switz.*
Senna (p.1769·2).
Constipation.

Fucerox *Pisa, Mex.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Fucibet *Leo, Irl.; Leo, Spain; Leo, UK.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Fucicort *Andromaco, Arg.; Leo, Austria; Leo, Belg.; Andromaco, Chile; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Ger.; Leo (Λεω), Gr.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; Valeant, Mex.; CSL, NZ; Leo, NZ; Leo, Philipp.; Leo, Port.; Leo, Rus.; Leo, Singapore; Leo, Switz.; Leo, Thai.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Fucicream *AG Therapy, Gr.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Fucidin
Andromaco, Arg.; CSL, Austral.; Leo, Austria; Leo, Belg.; Leo, Canad.; Andromaco, Chile; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo (Λεω), Gr.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Leo, Malaysia; Valeant, Mex.; CSL, NZ; Leo, NZ; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Leo, Pol.; Leo, Rus.; Adcock Ingram, S.Afr.; Leo, Singapore; Leo, Swed.; Leo, Switz.; Leo, Thai.; Abdi, Turk.; Leo, UK.
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Gram-positive bacterial infections.

Formenti, Ital.
Fusidic acid (p.279·3).
Bacterial skin infections.

Fucidin H
Leo, Canad.; Andromaco, Chile; Leo, Cz.; Leo (Λεω), Gr.; Leo, Hong Kong; Leo, Hung.; Discotrade, Israel†; Formenti, Ital.; Leo, Malaysia; Leo, Philipp.; Leo, Rus.; Leo, Singapore; Leo, Switz.; Leo, Thai.
⊗ Fusidic acid (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Leo, Irl.; Leo, UK.
⊗ Fusidic acid (p.279·3) or sodium fusidate (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Adcock Ingram, S.Afr.
⊗ Sodium fusidate (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Fucidin Hydrocortisone *Leo, Belg.*
⊗ Fusidic acid (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Fucidine *Leo, Fr.; Leo, Ger.; Leo, Port.; Leo, Spain.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Bacterial infections.

Fucidine H *Leo, Port.; Leo, Spain.*
⊗ Fusidic acid (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Fucidine plus *Boehringer Ingelheim, Ger.†.*
⊗ Sodium fusidate (p.279·3); hydrocortisone butyrate (p.1535·3).
Infected skin disorders.

Fucidin-Hydrocortison
Leo, Denm.; Leo, Swed.
⊗ Fusidic acid (p.279·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Leo, Fin.; Leo, Norw.
⊗ Fusidic acid (p.279·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Fucilex *Molex Ayus, Indon.*
Sodium fusidate (p.279·3).
Skin infections.

Fucithalmic *Andromaco, Arg.; Leo, Austria; Leo, Belg.; Leo, Canad.; Andromaco, Chile; Leo, Cz.; Leo, Denm.; Leo, Fin.; Leo, Fr.; Leo, Ger.; Leo, Hong Kong; Leo, Hung.; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Formenti, Ital.; Leo, Malaysia; CSL, NZ; Leo, NZ; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Leo, Port.; Leo, Rus.; Adcock Ingram, S.Afr.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Switz.; Leo, Thai.; Abdi, Turk.; Leo, UK.*
Fusidic acid (p.279·3).
Bacterial eye infections.

Fuclode *Bioprogress, Ital.†.*
Cefaclor (p.217·2).
Bacterial infections.

Fucoderm *IQFA, Mex.*
Miconazole (p.541·2).
Fungal skin infections.

Fucon *YSP, Malaysia; Yung Shin, Singapore.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Fucsina Fenica *AFOM, Ital.; Marco Viti, Ital.; NewFaDem, Ital.; Nova Argentia, Ital.; Ramini, Ital.; Sella, Ital.; Zeta, Ital.*
Boric acid (p.2268·1); phenol (p.1656·1); magenta (p.1651·3); resorcinol (p.1612·1).
Fungal skin infections.

Fucus Complexe no 111 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 111.

Fucus Compuesto *Hochstetter, Chile†.*
Bladderwrack (p.2384·2); marrubium (p.1564·1); alfalfa (p.2249·2); avena (p.2262·1); carica papaya.
Obesity.

Fucus Especial *Knop, Chile.*
Homoeopathic preparation.

Fucus L111 *Homeocan, Canad.*
Homoeopathic preparation.

Fucusor *Soria Natural, Spain†.*
Bladderwrack (p.2384·2); laminaria (p.2330·2).
Dietary supplement; slimming aid.

Fudermex *Prater, Chile.*
Lansoprazole (p.1739·2).

Fudikin *Samjin, Singapore.*
Sodium fusidate (p.279·3).
Bacterial skin infections.

Fudirine *PP Lab, Thai.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Fudone *Wockhardt, India.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

FUDR *Roche, USA.*
Floxuridine (p.720·3).
Gastrointestinal adenocarcinoma metastatic to the liver.

Fuera Bicho *Biosintex, Arg.*
Quassia (p.2377·1); acetic acid (p.2244·2).
Pediculosis.

Fugacar Janssen-Cilag, Thai.
Mebendazole (p.148·3).
Worm infections.

Fugafebril Northia, Arg.
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine (p.1568·1); butetamate citrate (p.1553·1).

Fuganol Galenica, Gr.†.
Sertaconazole (p.546·1).
Fungal infections.

Fugaten Lysoform, Ger.
⊗ Alcohol (p.1625·2).
Surface disinfection.

Fugentin Elpen (Ελπεν), Gr.; Elpen, Singapore.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Fugerel Essex, Austral.†; Aesca, Austria; Essex, Ger.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Singapore†; Schering-Plough, Thai.
Flutamide (p.725·1).
Prostatic cancer.

Fugin Cofasa, Venez.
Fluconazole (p.532·1).
Fungal infections.

Fugisept Lysoform, Ger.†.
Didecyldimethylammonium chloride (p.1642·2); glyoxal (p.1646·1).
Skin disinfection.

Fugolin Vincenti, Venez.
Clotrimazole (p.530·1).
Fungal infections.

Fugras Biotecnoquimica, Venez.
Fucus (p.2384·2); magnesium sulfate (p.1679·3).
Slimming aid.

Fukole YSP, Malaysia.
Fluconazole (p.532·1).
Fungal infections.

Fukricin Sanbe, Indon.
Natamycin (p.543·1).
Fungal eye infections.

Fuladic Guardian, Indon.
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Skin infections.

Fulcalrex Confar, Port.
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Fulcin AstraZeneca, Braz.; AstraZeneca, Indon.; AstraZeneca, Irl.†; SIT, Ital.; Darier, Mex.; Zeneca, Port.†; Teofarma, Spain.
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Fulcin S AstraZeneca, Ger.†.
Griseofulvin (microfine) (p.535·2).
Fungal skin, hair, and nail infections.

Fulcro Fournier, Ital.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Fulgium Teofarma, Spain.
Benzydamine salicylate (p.27·3).
Peri-articular and soft-tissue disorders.

Ful-Glo Allergan, Austral.†; Akorn, USA.
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Fulgram
Note. This name is used for preparations of different composition.
Labomed, Chile; ABC, Ital.†.
Norfloxacin (p.309·2).
Bacterial infections; urinary-tract infections.

Megat, Venez.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Full Calcio Lafedar, Arg.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Dietary supplement.

Full Marks SSL, NZ; SSL, UK.
Phenothrin (p.2048·3).
Pediculosis.

Full Marks Solution SSL, UK.
Cyclomethicone (p.2032·1); isopropyl myristate (p.2029·3).
Pediculosis.

Full Spectrum B National Vitamin, USA.
Vitamin B substances (p.1922·1).

Fullcilina Elea, Arg.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Fullcilina Duo Elea, Arg.†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Fullcilina Plus Elea, Arg.†.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Fullgrip Elea, Arg.
Levophenylephrine (p.1568·3) or levophenylephrine hydrochloride (p.1568·3); paracetamol (p.108·1); vitamin C (p.1983·3).
Influenza symptoms.

Fulone Osoth, Thai.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Fulsac Biofarma, Turk.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Fulsed
Ranbaxy, Cz.; Ranbaxy, Malaysia†; Ranbaxy, Singapore.
Midazolam (p.1007·3).
General anaesthesia; induction of anaesthesia; premedication; sedative.

Ranbaxy, India.
Midazolam hydrochloride (p.1007·3).
Induction of anaesthesia; premedication; sedative.

Fulsivin Collins, Mex.
Griseofulvin (p.535·2).
Fungal infections.

Fultac Euromex, Mex.
⊗ Ambroxol (p.1550·3); salbutamol (p.1131·2).
Respiratory-tract disorders.

Fulvicin Schering, Canad.†.
Griseofulvin (p.535·2).
Fungal infections.

Fulvin Organifar, Venez.†.
Griseofulvin (p.535·2).
Fungal infections.

Fulvina Schering-Plough, Mex.†.
Griseofulvin (p.535·2).
Fungal infections.

Fulvistatin P/G Essex, Chile†.
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Fulzoltec Tecnofarma, Mex.†.
Itraconazole (p.536·3).
Fungal infections.

Fumaderm Fumedica, Ger.; Hermal, Ger.
Dimethyl fumarate (p.1597·3); calcium monoethyl fumarate (p.1597·3); magnesium monoethyl fumarate (p.1597·3); zinc monoethyl fumarate (p.1597·3).
Psoriasis.

Fumafer Sanofi-Aventis, Fr.; Etifar, Venez.†.
Ferrous fumarate (p.1938·3).
Iron deficiency; iron-deficiency anaemia.

Fumarol Offenbach, Mex.
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Fumasil Sidepal, Braz.†.
Homoeopathic preparation.

Fumatinic Laser, USA.
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Fumavit IQFA, Mex.
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Fumicon Leovan, Gr.
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Fumiron + B Scherer, Philipp.
Ferrous fumarate (p.1938·3); vitamin B substances; ascorbic acid; citrus bioflavonoids (p.1922·1).
Iron deficiency; iron-deficiency anaemia; tonic.

Funa LBS, Thai.
Fluconazole (p.532·1).
Fungal infections.

Funadel Delegant, Gr.
Fluconazole (p.532·1).
Fungal infections.

Funazole Khandelwal, India.
Ketoconazole (p.539·1).
Fungal infections.

Funcenal Farma Lepori, Spain.
Flutrimazole (p.535·2).
Fungal skin and nail infections.

Funcid BioFemme, Philipp.
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Funciobron Northia, Arg.
Noscapine (p.1566·2); chlorphenamine (p.572·2); phenylephrine (p.1568·1).

Funciobron B Northia, Arg.
Bromhexine (p.1552·2).

Funciogrip Northia, Arg.
Salicylamide (p.121·2); pyribenzamine; phenylephrine (p.1568·1).
Cold and influenza symptoms.

Funcort TNP, Thai.†.
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Fundamin Biomedis, Hong Kong†; Biomedis, Malaysia†; Biomedis, Singapore.
Vitamin B substances (p.1922·1).
Nausea and vomiting; neuritis; tonic.

Fundamin-E
Biomedis, Hong Kong; Biomedis, Singapore; Biomedis, Thai.; Great Eastern, Thai.
Vitamin B substances; vitamin E (p.1922·1).
Vitamin supplement.

Medifarma, Indon.; UAP, Indon.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Isoniazid-induced neuritis; nausea and vomiting in pregnancy; neurasthenia; radiation sickness; reduced appetite.

Biomedis, Malaysia.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1922·1).
Nausea and vomiting; neuritis; tonic.

Fundan Ipex, Swed.
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Funduscein Iolab, USA.
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Funet Fahrenheit, Indon.
Ketoconazole (p.539·1).
Fungal infections.

Funga Vida, Hong Kong.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Fungafine Ivax, Irl.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Fungal Durascan, Denm.†.
Fluconazole (p.532·1).
Fungal infections.

Fungan Ulagay, Turk.
Fluconazole (p.532·1).
Fungal infections.

Funganiline BMS, Spain†.
Amphotericin B (p.523·2).
Oropharyngeal candidiasis.

Fungares Guardian, Indon.
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Fungarest Janssen-Cilag, Chile; Janssen-Cilag, Spain.
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Fungasil Clonmel, Irl.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Fungasol Guardian, Indon.
Ketoconazole (p.539·1).
Fungal infections.

Fungata Pfizer, Austria; Pfizer, Ger.
Fluconazole (p.532·1).
Vaginal candidiasis.

Fungatin Ferron, Indon.
Nystatin (p.543·2).
Candidiasis.

Fungazol Biolab, Hong Kong; Biolab, Malaysia; Biolab, Thai.
Ketoconazole (p.539·1).
Fungal infections.

Fungecyl Gunsa, Turk.
Undecenoic acid (p.549·2); calcium lactate (p.1676·1); zinc undecenoate (p.549·3).
Fungal skin and nail infections.

Fungederm Nucare, UK.
Clotrimazole (p.530·1).
Fungal skin infections.

Fungex
Note. This name is used for preparations of different composition.
Streuli, Switz.
Ointment: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Streuli, Switz.
Topical powder: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); aluminium acetotartrate (p.2255·1); calcium lactate (p.1676·1).
Fungal skin infections.

Fungi B Eurofarma, Braz.
Amphotericin B (p.523·2).
Fungal infections.

Fungicida Lauria, Arg.†.
Zinc undecenoate (p.549·3); calcium propionate (p.545·3); sodium propionate (p.545·3); hexylresorcinol (p.1647·1); salicylic acid (p.1612·2); benzoic acid (p.1630·2); thymol (p.1664·3).
Fungal infections.

Fungicide Torrent, India.
Ketoconazole (p.539·1).
Fungal infections.

Fungicidin Zentiva, Cz.
Nystatin (p.543·2).
Candidiasis.

Fungicil Sandoz, Arg.†.
Ketoconazole (p.539·1).
Fungal infections.

Fungicip Cipla, Malaysia.
Clotrimazole (p.530·1).
Vaginal infections.

Fungicon
Note. This name is used for preparations of different composition.
Continental Pharma, Thai.
Cream: Clotrimazole (p.530·1); melaleuca oil (p.2338·2).
Fungal skin infections.

Continental Pharma, Thai.
Vaginal tablets: Clotrimazole (p.530·1).
Trichomoniasis; vaginal candidiasis.

Fungicrem Andromaco, Mex.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Fungiderm
Note. This name is used for preparations of different composition.
Nycomed, Austria†; Biospray, Gr.
Bifonazole (p.527·3).
Fungal skin and nail infections.

Terra-Bio, Ger.; Konimex, Indon.; Greater Pharma, Thai.
Clotrimazole (p.530·1).
Fungal skin and vaginal infections; trichomoniasis.

Rafa, Israel.
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Fungiderm comp Nycomed, Austria†.
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Fungiderm-B Greater Pharma, Thai.
⊗ Clotrimazole (p.530·1); betamethasone (p.1518·2).
Fungal skin infections.

Fungiderm-K Greater Pharma, Thai.
Ketoconazole (p.539·1).
Fungal infections; pityriasis versicolor; seborrhoeic dermatitis.

Fungidermo Cinfa, Spain.
Clotrimazole (p.530·1).
Fungal skin infections.

Fungidexan Hermal, Ger.
⊗ Clotrimazole (p.530·1); urea (p.1620·2).
Fungal and bacterial skin infections.

Fungifax
Note. This name is used for preparations of different composition.
Medipharma, Hong Kong†.
Zinc undecenoate (p.549·3); undecenoic acid (p.549·2); benzoic acid (p.1630·2); camphor (p.2273·2); methyl salicylate (p.85·3); chlorobutanol (p.1639·2).
Fungal skin infections.

Medipharma, Hong Kong†.
IMP Cream: Zinc undecenoate (p.549·3); undecenoic acid (p.549·2).
Fungal skin infections.

Fungifos Combustin, Ger.†.
Tolciclate (p.548·3).
Fungal skin infections.

Fungilin BMS, Austral.; BMS, Denm.†; BMS, Israel†; BMS, Ital.; BMS, NZ; BMS, UK.
Amphotericin B (p.523·2).
Fungal infections.

Fungi-M Nakornpatana, Thai.
Miconazole nitrate (p.541·3).
Fungal skin, nail, and hair infections.

Fungimax
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
Metronidazole (p.837·1); nystatin (p.543·2).
Vulvovaginal infections.

Ventaglio, Chile.
Fluconazole (p.532·1).
Fungal infections.

Fungimed 3DDD, Belg.
Fluconazole (p.532·1).
Fungal infections.

Fungimon Trima, Israel.
Zinc undecenoate (p.549·3); undecenoic acid (p.549·2); aluminium chlorohydrate (p.1588·3).
Fungal skin infections.

Fungi-Nail Kramer, USA.
Resorcinol (p.1612·1); salicylic acid (p.1612·2); chloroxylenol (p.1640·2); benzocaine (p.1854·1); isopropyl alcohol (p.1650·3).
Fungal and bacterial skin infections; fungal nail infections.

Funginox Charoen Bhaesaj, Malaysia; Charoen, Thai.
Ketoconazole (p.539·1).
Fungal infections.

Fungipar Parggon, Mex.
Ketoconazole (p.539·1).
Fungal infections.

Fungiquim Quimica y Farmacia, Mex.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin and nail infections.

Fungireduct Azupharma, Ger.†.
Nystatin (p.543·2).
Candidiasis.

Fungirox UCI, Braz.†.
Ciclopirox (p.529·2).
Fungal vaginal infections.

Fungisdin Isdin, Spain.
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections.

Fungisept Lysoform, Ger.
Didecyldimethylammonium chloride (p.1642·2).
Surface and fabric disinfection.

Fungisil Silom, Thai.
Miconazole nitrate (p.541·3).
Fungal infections of the skin, nails, and mucous membranes.

Fungisil-T Silom, Thai.
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3).
Fungal infections of the skin, nails, and mucous membranes.

Fungispor *Caps, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Fungistat *Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Terconazole (p.548·1).
Vaginal fungal infections.

Fungistop *Bernofarm, Indon.*
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Fungitherapy *AG Therapy, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Fungitif *Tiefenbacher, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Fungitrazol *Ikapharmindo, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Fungium *Saval, Chile.*
Ketoconazole (p.539·1).
Fungal infections.

Fungizid *Ratiopharm, Ger.; Ratiopharm, Hong Kong†.*
Clotrimazole (p.530·1).
Fungal and bacterial vaginal infections; fungal skin infections.

Fungizon *BMS, Braz.; BMS, Chile.*
Amphotericin B (p.523·2).
Fungal infections.

Fungizona *BMS, Spain.*
Amphotericin B (p.523·2).
Fungal infections.

Fungizone *BMS, Austral.; BMS, Belg.; BMS, Canad.; BMS, Denm.; BMS, Fin.; BMS, Fr.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Hung.; Sarabhai Piramal, India; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Malaysia; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Philipp.; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; Apothecon, USA†; BMS, Venez.*
Amphotericin B (p.523·2).
Fungal infections; leishmaniasis.

Fungnon *Ariston, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Fungo
Note.This name is used for preparations of different composition.
Verisfield, Gr.
Fluconazole (p.532·1).
Fungal infections.

Ego, Hong Kong†; Ego, Malaysia†; Douglas, NZ; Ego, Singapore†.
Miconazole nitrate (p.541·3).
Fungal skin infections; vulvovaginal candidiasis.

Fungo Farmasierra *Farmasierra, Spain.*
Ketoconazole (p.539·1).
Formerly known as Fungo Hubber.
Fungal infections.

Fungo Soothing Balm *Ego, Hong Kong.*
Miconazole nitrate (p.541·3); bufexamac (p.28·3).
Infected skin disorders.

Fungo Zeus *Zeus, Spain.*
Ketoconazole (p.539·1).
Fungal infections.

Fungocina *Lazar, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Fungocop *Fecofar, Arg.*
Boric acid (p.2268·1); undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal infections.

Fungocort *Douglas, NZ†.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Fungoid *Pedinol, USA.*
Miconazole nitrate (p.541·3).
Fungal nail infections.

Fungoid HC *Pedinol, USA.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Bacterial and fungal skin infections.

Fungolab *Multilab, Braz.*
Iodine (p.2169·2); benzoic acid (p.1630·2).
Fungal skin infections.

Fungolon *Balkanpharma, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Fungomax *Behrens, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Fungonax *Teuto, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Fungopirox *Royal, Chile.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Fungoral *Janssen-Cilag, Austria; Farmion, Braz.†; Janssen-Cilag, Gr.; Kimia, Indon.; Janssen-Cilag, Mex.; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.; Ilsan, Turk.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Fungores *ICN, Pol.*
Ketoconazole (p.539·1).
Fungal infections.

Fungos *Pasteur, Chile†.*
Miconazole nitrate (p.541·3).
Fungal balanitis; fungal vulvovaginal infections.

Fungosin *Dollder, Venez.*
Itraconazole (p.536·3).
Fungal infections.

Fungosine *Sanofi Synthelabo, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Fungostatin *Nobel, Turk.*
Nystatin (p.543·2).
Candidiasis.

Fungosten *Mulda, Turk.*
Clotrimazole (p.530·1).
Fungal skin infections.

Fungoterbine *Nizpharm, Rus.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Fungototal *TRB, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Fungotox *Mepha, Switz.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Fungowas *Chiesi, Spain.*
Ciclopirox olamine (p.529·2).
Cutaneous, mucosal and nail fungal infections.

Fungtopic *Vendiz, Philipp.*
Miconazole nitrate (p.541·3).
Fungal infections of the skin and nails.

Funguard *Astellas, Jpn.*
Micafungin sodium (p.541·1).
Aspergillosis; candidiasis.

Fungucit *Ilsan, Turk.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Fungueal *Lazar, Arg.*
Terbinafine hydrochloride (p.546·3).
Fungal skin, scalp, and nail infections.

Fungur M *Hexal, Ger.*
Miconazole nitrate (p.541·3).
Fungal skin and vaginal infections.

Fungusol *Bayer, Spain.*
Boric acid (p.2268·1); zinc oxide (p.1621·2).
Fungal skin infections; intertrigo.

Fungustatin *Pfizer, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Fungusteril *Biospray, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Funida *Nakornpatana, Thai.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Funit *Nobel, Turk.*
Itraconazole (p.536·3).
Fungal infections.

Funizol *Megat, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Funser *Serral, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Funtopic *Arex, Venez.†.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Funtyl *Cristalia, Braz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Funzal *Gynopharm, Chile.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Funzela *BioFemme, Philipp.*
Fluconazole (p.532·1).
Fungal infections.

Funzole *Bosnalijek, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Furabid *Goldshield, Neth.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furacin *Schering-Plough, Arg.; Mantecorp, Braz.; Boehringer Ingelheim, Chile; GSK, India; Rhein, Mex.; Boehringer Ingelheim, Philipp.; GSK, S.Afr.; Seid, Spain; Eczacibasi, Turk.; Procter & Gamble, USA†; Roberts, USA†; Farma, Venez.*
Nitrofurazone (p.309·1).
Bacterial infections; bladder irrigation; burns; skin grafts; skin infections; ulcers; wounds.

Furacine *Norgine, Belg.; Norgine, Neth.*
Nitrofurazone (p.309·1).
Infected skin disorders; infected wounds and burns; infection prophylaxis for skin grafts.

Furacin-S *GSK, India.*
⊗ Nitrofurazone (p.309·1); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Furacin-Sol *Riemser, Ger.*
Nitrofurazone (p.309·1).
Skin infections; wounds.

Furadantin *Pfizer, Austral.; Procter & Gamble, Austria; Goldshield, Ger.; GSK, India; Goldshield, Irl.; Formenti, Ital.; Pharmacia, NZ; Recip, Norw.; GSK, S.Afr.; Recip, Swed.; Goldshield, UK; Sciele, USA.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furadantina *Schering-Plough, Arg.; Boehringer Ingelheim Promeco, Mex.; Goldshield, Port.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furadantine *Pharma Logistics, Belg.; Merck-Lipha, Fr.; Vifor, Switz.*
Nitrofurantoin (p.308·1).
Cystitis; urinary-tract infections.

Furadantine MC *Goldshield, Neth.*
Nitrofurantoin (macrocrystalline) (p.308·1).
Urinary-tract infections.

Furaderm *Toprak, Turk.*
Nitrofurazone (p.309·1).
Skin infections.

Furadina *Boehringer Ingelheim, Venez.†.*
Nitrofurantoin (p.308·1).
Bacterial urinary-tract infections.

Furadoine *Merck-Lipha, Fr.*
Nitrofurantoin (p.308·1).
Cystitis; urinary-tract infections.

Furaginum *Adamed, Pol.; Polfa Kutno, Pol.*
Furazidin (p.279·2).
Bacterial infections of the urinary tract.

Furagrand *Ahimsa, Arg.*
⊗ Furosemide (p.1292·1).

Fural *Aliud, Austria.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furanthril *Pharmachim, Cz.†; Medphano, Ger.*
⊗ Furosemide (p.1292·1).
Forced diuresis; heart failure; hypertension; oedema; oliguria.

Furantoin *Zentiva, Cz.†.*
Nitrofurantoin (p.308·1).
Bacterial infections of the genito-urinary tract.

Furantoina *Uriach, Spain.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furanton *Randall, Mex.†.*
Nitrofurantoin (p.308·1); methenamine mandelate (p.298·3).
Urinary-tract infections.

Furasian
Note.This name is used for preparations of different composition.
Asian Pharm, Thai.
Syrup: Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea; enteritis.

Asian Pharm, Thai.
Tablets: Furazolidone (p.834·3).
Diarrhoea; enteritis.

Furaxetil *Farmoz, Port.†.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Furaxil *Remedina, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Furazol *Akdeniz, Turk.*
Nitrofurazone (p.309·1).
Bacterial ear infections.

Furazolidona *Laboratorios Chile, Chile.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Bacterial gastrointestinal infections; giardiasis.

Furdiuren *BMS, Arg.†; Chemopharma, Chile; Dollder, Venez.*
⊗ Furosemide (p.1292·1); amiloride (p.1210·1).
Heart failure; hepatic cirrhosis with ascites; hypertension; oedema.

Furedan *Scharper, Ital.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furese *Sandoz, Denm.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furesin *Prodotti, Braz.*
⊗ Furosemide (p.1292·1).
Hypertension.

Furesis *Orion, Fin.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; renal failure.

Furesis comp *Orion, Fin.*
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Oedema.

Furetic *Siam Bheasach, Thai.*
⊗ Furosemide (p.1292·1).
Ascites; barbiturate poisoning; eclampsia; oedema.

Furex *Aspen, S.Afr.*
Nitrofurazone (p.309·1).
Burns; skin infections; ulcers; wounds.

Furfuril *Roemmers-Klinos, Venez.*
Nitrofurazone (p.309·1).
Burns; skin infections; vaginal infections; wounds.

Furide *Polipharm, Thai.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema.

Furil
Note.This name is used for preparations of different composition.
OFF, Ital.
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Berko, Turk.
Nifuroxazide (p.307·2).
Gastro-enteritis.

Furine *Medicine Products, Thai.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furion *Chew, Thai.*
Furazolidone (p.834·3).
Diarrhoea; enteritis.

Furital *Rivero, Arg.*
⊗ Furosemide (p.1292·1).
Heart failure; oedema.

Furitex *Arlex, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furix *Investi, Arg.; Nycomed, Denm.; Nycomed, Norw.; Nycomed, Swed.*
⊗ Furosemide (p.1292·1).
Forced diuresis; hypertension; nephrotic syndrome; oedema; renal failure.

Furmide *CCM, Malaysia†; Beacons, Singapore.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema.

Furo *ABZ, Ger.; CT, Ger.*
⊗ Furosemide (p.1292·1) or furosemide sodium (p.1294·1).
Ascites; hypertension; oedema; oliguria.

Furo-Aldopur *Kwizda, Austria; Kwizda, Ger.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Ascites; oedema.

Furobactina *Dexter, Spain.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

furo-basan *Schonenberger, Switz.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furobeta *Betapharm, Ger.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; oliguria.

Furocef *Taiwan Biotech, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Furocem *Rotexmedica, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Furocombin *Streuli, Switz.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; oedema.

Furodermal *Streuli, Switz.*
Camphor (p.2273·2); ichthammol (p.1599·1); bismuth oxyiodogallate (p.1712·1); thymol (p.1664·3).
Skin infections.

Furodrix *Streuli, Switz.*
⊗ Furosemide (p.1292·1) or furosemide sodium (p.1294·1).
Forced diuresis; heart failure; hypertension; oedema; oliguria in pregnancy; renal failure.

Furogamma *Worwag, Ger.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema; oliguria.

Furohexal *Hexal, Austria.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furoic *Pharmacia, Ital.*
Calcium mefolinate pentahydrate (p.1932·2).
Antidote in overdosage with folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Furolacton *Lannacher, Austria.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Oedema.

Furolin *Farmanic, Gr.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Furolnok *Medikon, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Furomed *Wolff, Ger.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furomid *Deva, Turk.*
⊗ Furosemide (p.1292·1).
Oedema.

Furomil *Euromex, Mex.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furomin *Ratiopharm, Fin.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furon
Ratiopharm, Austria; Ratiopharm, Hung.
⊗ Furosemide (p.1292·1) or furosemide sodium (p.1294·1).
Forced diuresis; heart failure; hypercalcaemic crisis; hypertension; oedema; renal failure.

Ratiopharm, Cz.
⊗ Furosemide (p.1292·1).
Hypercalcaemia; hypertension; oedema.

Furopectin *PP Lab, Thai.†.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Bacterial diarrhoea; enteritis.

Furo-Puren *Alpharma-Isis, Ger.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema; oliguria.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Furorese *Hexal, Cz.; Hexal, Ger.*
⊗ Furosemide (p.1292·1) or furosemide sodium (p.1294·1).
Ascites; forced diuresis; hypertension; oedema; oliguria.

Furorese Comp *Hexal, Ger.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Ascites; oedema.

Furosal *TAD, Ger.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema; oliguria.

Furosan *Sanval, Braz.; Ivax, Mex.*
⊗ Furosemide (p.1292·1).

Furoscan *Scanpharm, Philipp.*
⊗ Furosemide (p.1292·1).
Heart failure; hypertension; liver cirrhosis with ascites; oedema.

Furosecord *Globo, Braz.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furosem *Medley, Braz.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furosemide Composto *Medley, Braz.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).

Furosen *Pharlab, Braz.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furosetron *Ariston, Braz.*
⊗ Furosemide (p.1292·1).

Furosifar *Siphar, Switz.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; renal failure.

Furosix *Delta, Braz.; Landson, Indon.*
⊗ Furosemide (p.1292·1).
Hepatic cirrhosis; hypertension; oedema.

Furospir *Mepha, Switz.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Oedema.

Furo-Spirobene *Ratiopharm, Austria.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Aldosteronism; oedema.

Furostad *Stada, Austria.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furoter *Protein, Mex.†.*
⊗ Furosemide (p.1292·1).

Furotop *Topgen, Belg.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furotricina *Finderm, Ital.*
Tyrothricin (p.358·2); nitrofurazone (p.309·1).
Gynaecological infections.

Furoxil *Vincenti, Venez.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Furoxim *Lannacher, Austria.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Furoxime
Siam Bheasach, Malaysia.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Siam Bheasach, Thai.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Furoxona *Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Furazolidone (p.834·3).
Gastrointestinal bacterial and protozoal infections.

Furoxona CP *Boehringer Ingelheim Promeco, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal infections.

Furoxone *GSK, India; Boehringer Ingelheim, Philipp.; Roberts, USA†.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Furoxy *Bosch, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Furozix *Bunker, Braz.*
⊗ Furosemide (p.1292·1).

Fursemida *Fabra, Arg.; Northia, Arg.; Sintesina, Arg.; Veinfar, Arg.; Legrand, Braz.*
⊗ Furosemide (p.1292·1).
Hypercalcaemia; hypertension; oedema.

Fursol *Ecosol, Switz.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furtenk *Biotenk, Arg.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Furtulon *Roche, Jpn.*
Doxifluridine (p.712·1).
Malignant neoplasms.

Furunkulosin *Merckle, Ger.†.*
Yeast (p.1998·3).
Furunculosis.

Fusalar *Ivax, Mex.*
⊗ Fluocinolone (p.1531·3).
Skin disorders.

Fusaloyos *Danval, Spain.*
Fusafungine (p.279·2).
Upper respiratory-tract infections and inflammation.

Fusepina *Ivax, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Fuseride *Pharmasant, Thai.*
⊗ Furosemide (p.1292·1).
Oedema.

Fusextrine *Sofex, Port.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Bacterial skin infections.

Fusibact *Cipla, India.*
Fusidic acid (p.279·3).
Skin infections.

Fusibet *Farmedia, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Fusid
Note. This name is used for preparations of different composition.
Gry, Ger.; Teva, Israel.
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema; oliguria; renal failure.

Chew, Thai.
Fusidic acid (p.279·3).
Bacterial skin infections.

Fusidate *Aristopharma, Hong Kong.*
Sodium fusidate (p.279·3).
Gram-positive bacterial skin infections.

Fusidic B *Pharmaniaga, Malaysia.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Formerly called Germacort.
Infected skin disorders.

Fusimed *Cassara, Arg.*
Fusidic acid (p.279·3).
Burns; skin infections; ulcers; wounds.

Fusimed B *Cassara, Arg.*
⊗ Fusidic acid (p.279·3); betamethasone (p.1518·2).
Infected skin, ear, and nose disorders.

Fusimex *SM, Philipp.*
⊗ Furosemide (p.1292·1).
Hypertension; liver cirrhosis; oedema.

Fusitop *HLB, Arg.*
Fusidic acid (p.279·3).
Skin infections; ulcers; wounds.

Fusiwal *Wallace, India.*
Sodium fusidate (p.279·3).
Bacterial skin infections.

Fuson *Pyridam, Indon.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Skin infections.

Fustaren *Ivax, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Fustermicina *Ivax, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Fustermizol *Ivax, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Fuston *YSP, Malaysia†.*
Guaifenesin (p.1561·3).
Coughs.

Fusycom *Combiphar, Indon.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Skin infections.

Futaderm *Interbat, Indon.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Skin infections.

Futaline *Merck, Mex.*
⊗ Metoprolol (p.1338·1).

Futasole *Julphar, UAE.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Bacterial skin infections.

Futasone *Julphar, UAE.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Futraful *Otsuka, Hong Kong; Otsuka, Indon.; Taiho, Jpn.*
Tegafur (p.776·1).
Breast cancer; colorectal cancer; gastric cancer.

Futroken *Kener, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Futura *Marano, Ital.*
Aspartame (p.1930·1).
Sugar substitute.

Futuran *Faes, Spain.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Futuran Plus *Faes, Spain.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Future E *L'Oreal, Canad.*
SPF 15: Ensulizole (p.1597·1); octocrilene (p.1608·3).
Sunscreen.

Fuviron *Proge, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Fuxal *Cafar, Venez.*
Nitrofurazone (p.309·1).
Bacterial skin and vaginal infections.

Fuxaten *Inquifave, Venez.†.*
Naftidrofuryl (p.1346·3).
Cerebral and peripheral vascular disorders.

Fuxen *Ivax, Mex.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Fuxilidin *Viofar, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Fuxol *Ferring, Mex.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Fuzeon *Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Pol.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Roche, USA.*
Enfuvirtide (p.874·2).
HIV infection.

Fuzide *Otto, Indon.*
Nifuroxazide (p.307·2).
Diarrhoea.

Fuzoltec *Tecnofarma, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Fuzotyl *Rayere, Mex.†.*
Furazolidone (p.834·3); homatropine (p.1881·2); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal disorders.

F-Vial *Frankin, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

FX Passage *Phoenix, Austria; Worwag, Ger.*
Magnesium sulfate (p.1679·3).
Constipation; stool softener.

FXT *Oryx, Canad.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Fybogel *Reckitt Benckiser, Austral.; Reckitt & Colman, Belg.†; Reckitt Benckiser, Hong Kong†; Reckitt Benckiser, Irl.; Reckitt Benckiser, Malaysia; Schering-Plough, Mex.; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Reckitt Benckiser, Thai.; Reckitt Benckiser, UK.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement; diverticular disease; haemorrhoids; inflammatory bowel disease; irritable bowel syndrome; ostomy management; spastic colon.

Fybogel Mebeverine *Reckitt Benckiser, Hong Kong†; Reckitt Benckiser, Irl.; Reckitt Benckiser, UK.*
Ispaghula (p.1737·1); mebeverine hydrochloride (p.1744·2).
Gastrointestinal disorders; irritable bowel syndrome.

Fymnal *Farmasa, Braz.†.*
⊗ Ibuprofen (p.64·2); fenoterol hydrobromide (p.1121·1).
Dysmenorrhoea.

Fysiofer *ITF, Gr.*
Iron succinyl-protein complex (p.1953·2).
Iron-deficiency anaemia.

Fysiofol *ITF, Gr.*
Iron succinyl-protein complex (p.1953·2); calcium folinate (p.1943·3).
Prevention of pregnancy-induced anaemia.

Fysionorm *Pharmaselect, Ger.†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Fyterdin *Unipharm, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Fyterol *Slovakofarma, Cz.†.*
Chamomile oil (p.2279·3); levomenol (p.2333·3).
Burns; gastrointestinal inflammation; inflammatory disorders of the skin and mucous membranes; respiratory-tract inflammation; wounds.

Fytokliman Planta *Leros, Cz.*
St John's wort (p.422·3); parsley piert (p.2363·2); origanum (p.2357·3); melissa (p.2339·3); lupulus (p.2335·2); crataegus (p.2289·1); birch leaf (p.2266·3).
Menopausal disorders.

Fyton *Izotop, Hung.*
Sodium fytate (p.1464·2).
For the preparation of technetium-99m sodium fytate for liver scintigraphy.

Fytosid *Dabur, Philipp.; Dabur, Thai.; Biogalenic, Venez.*
Etoposide (p.718·1).
Malignant neoplasms.

G-80 *Kee, India†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

G-204 *Teva, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis.

G-248 *Teva, Israel.*
Electrolyte solution (p.1670·3).
Haemodialysis.

GA *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Glutaric acidaemia.

Gaap Ofteno *Sophia, Mex.; Elmor, Venez.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Gaax *Laboratorios Chile, Chile.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Gaax T *Laboratorios Chile, Chile.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Gab *Gufic, India.*
Lindane (p.2045·3).
Pediculosis; scabies.

Gaba *Nikkho, Braz.†.*
Gamma-aminobutyric acid (p.2308·1); papaverine hydrochloride (p.2191·3); nicotinic acid (p.1957·3); calcium pantothenate (p.1959·3).
Impaired mental function.

Gabacet *Sanofi-Aventis, Fr.*
Piracetam (p.368·2).
Dyslexia in children; mental function disorders; vertigo.

Gabagamma *Worwag, Cz.; Worwag, Ger.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabalept *Pliva, Cz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

GabaLich *Winthrop, Ger.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gaballon *Nikkho, Braz.*
Gamma-aminobutyric acid; lysine hydrochloride; thiamine hydrochloride; pyridoxine hydrochloride; calcium pantothenate (p.1922·1).
Nutritional supplement.

Gabamerck *Merck, Spain.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabamox *Pentafarma, Port.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabaneurin *Sigma, Braz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabanox *Stichting, Cz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabantin *Farmanic, Gr.; Sun, Mex.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabaran *Ranbaxy, Austral.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabarex *Torrex, Austria.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabarone *Ivax, USA.*
Gabapentin (p.482·3).
Epilepsy; postherpetic neuralgia.

Gabatal *Kwizda, Austria.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabator *Torrex Chiesi, Cz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabatril *Abbott, Mex.†.*
Tiagabine hydrochloride (p.505·1).
Epilepsy.

Gabatur *Cantabria, Spain.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabax
Note. This name is used for preparations of different composition.
Nikkho, Braz.
Gamma-aminobutyric acid (p.2308·1); pyridoxine hydrochloride (p.1978·2).
Impaired mental function.

Temmler, Ger.; Norton, Pol.
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabbroral *Pharmacia, Belg.; Pfizer, Ital.*
Paromomycin sulfate (p.843·3).
Amoebiasis; bacterial intestinal infections; bowel sterilisation; giardiasis; hepatic coma.

Gabbryl *Kalbe, Indon.*
Paromomycin sulfate (p.843·3).
Amoebiasis; hepatic coma.

Gabecon M *Dovalle, Braz.†.*
⊗ Methyltestosterone (p.2117·1); vitamin E.

Gabenta *Stichting, Cz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabental *Pharmanel, Gr.*
Gabapentin (p.482·3).
Epilepsy.

Gabex *Andromaco, Chile.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabexal *Sandoz, Indon.*
Gabapentin (p.482·3).
Epilepsy.

Gabictal *Tecnofarma, Chile.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabimex *Sanofi Synthelabo, Arg.*
4-Amino-3-hydroxybutyric acid (p.471·2).
Behaviour disorders; mental function impairment.

Gabimex Plus *Sanofi Synthelabo, Arg.*
4-Amino-3-hydroxybutyric acid (p.471·2); pyritinol (p.369·2).
Mental function impairment.

Gabirol *Chinoin, Mex.*
Rimantadine hydrochloride (p.904·2).
Influenza A.

Gabisedil *Seber, Port.†.*
Amino-hydroxybutyric acid (p.471·2); valerian (p.2410·1); passion flower (p.2363·2); chamomile (p.2279·3); crataegus (p.2289·1).
Anxiety; excitability; infantile convulsions; insomnia.

Gabiten *Ifars, Indon.*
Mebhydrolin (p.584·3).
Allergic disorders.

Gabitran *Solfran, Mex.†.*
Multivitamin preparation (p.1922·1).

Gabitril *Mayne, Austral.; Cephalon, Austria; Lafon, Belg.; Torrex Chiesi, Cz.; Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Fin.†; Cephalon, Fr.; Cephalon, Ger.; Gerolymatos, Gr.; Chiesi, Hung.; Cephalon, Irl.; Chiesi, Ital.; Sanofi-Aventis, Pol.; Cephalon, Port.; Noventure, Spain; Cephalon, Switz.; Cephalon, UK; Cephalon, USA.*
Tiagabine hydrochloride (p.505·1).
Epilepsy.

Gabomade *Esfar, Port.*
4-Amino-3-hydroxybutyric acid (p.471·2).
Convulsions; headache; mental function disorders; nocturnal enuresis.

Gabox *Ronava, Venez.†.*
Carbamazepine (p.471·3).
Epilepsy.

Gabrilen *Mibe, Ger.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Gabrion *Orion, Fin.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabture *Gerard, Irl.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gabunat *Strathmann, Ger.*
Biotin (p.1931·3).
Biotin deficiency.

Gacida *Aventis, Thai.*
Magnesium trisilicate (p.1744·1); dried aluminium hydroxide gel (p.1706·2).
Gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Gadinor *Liferpal, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gadofem *Gador, Arg.*
Drospirenone (p.2095·2); estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Gadograf *Juste, Spain.*
Gadobutrol (p.1478·3).
Contrast medium for magnetic resonance imaging.

Gadol *Ronava, Venez.*
Cimetidine (p.1716·2).
Peptic ulcer.

Gadolax *Gador, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Gadopril *Gador, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Gadopril D *Gador, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Gadovist *Bayer, Austral.; Schering, Austria; Schering, Belg.; Berlex, Canad.; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Ger.; Schering, Gr.; Schering, Hung.; Schering, Ital.; Schering, NZ; Schering, Neth.; Schering, Norw.; Lusal, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Spain; Schering, Swed.; Schering, Switz.; Bayer, UK.*
Gadobutrol (p.1478·3).
Contrast medium for magnetic resonance imaging.

Gadral *GiEnne, Ital.*
Magaldrate (p.1742·3).
Gastro-oesophageal reflux; peptic ulcer.

Gaduol *Climax, Braz.†.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin supplement.

Gain Plus *Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).

Gal *Lennon, S.Afr.*
Senna (p.1769·2).
Constipation.

Galacordin *Biomo, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Potassium and magnesium deficiency.

Galactogil *IPRAD, Fr.*
Galega; calcium phosphate (p.1676·2); malt extract (p.1955·2).
Lactation insufficiency.

Galactomin *SHS, Fr.; Scientific Hospital Supplies, Irl.; SHS, Israel; Nutricia, Ital.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Diarrhoea; lactose, glucose, or galactose intolerance.

Galamed *Ratiopharm, Cz.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Galamila *Doetsch, Grether, Switz.*
Dexpanthenol (p.2362·1); chlorhexidine gluconate (p.1635·3) or chlorhexidine hydrochloride (p.1635·3).
Nipple care during breastfeeding.

Galantase *Mitsubishi, Jpn†.*
Tilactase (p.2402·1).
Lactose intolerance.

Galaren *Fada, Arg.*
Vecuronium (p.1913·2).
Competitive neuromuscular blocker.

Galavit *CMM Medicor, Rus.*
5-amino-1,2,3,4-tetrahydrophthalazin-1,4-dione sodium salt dihydrate.
Immunodeficiency.

Galaxdar *Lacer, Spain.*
Diacerein (p.41·3).
Osteoarthritis.

Galciclina *Sant Gall, Arg.†.*
Ampicillin (p.204·1).
Bacterial infections.

Galcin *Gabriel, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Galcodine *Thornton & Ross, UK.*
Codeine phosphate (p.37·2).
Dry coughs.

Galebiron *Biomedica-Chemica, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Galecin *Probiomed, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Galedol *Probiomed, Mex.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Galemin *Pharmanel, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Galenamet *Galen, Irl.; Galen, UK.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Galenamox *Galen, Irl.†; Galen, UK.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Galenat Kamill N *Hetterich, Ger.†.*
Chamomile (p.2279·3).
Gastrointestinal disorders; inflammatory disorders of skin and mucous membranes.

Galenavowen *Weber & Weber, Ger.†.*
Homoeopathic preparation.
Formerly contained ammi visnaga, boldo, curcuma long., cynara scolymus, frangula, and syzygium cumini.

Galenic Restaurador Capilar *Neo Dermos, Arg.*
Collagen (p.2286·1); ginseng (p.2312·1); aloe vera (p.1588·2).
Alopecia.

Galenol *Elter, Venez.†.*
⊗ Propranolol (p.1381·1).
Angina pectoris; hypertension.

Galenphol *Thornton & Ross, UK.*
Pholcodine (p.1570·2).
Coughs.

Galfer *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Galfer FA *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Galflux *Guardian, Indon.*
Domperidone (p.1726·2).
Dyspepsia; epigastric and abdominal fullness; nausea and vomiting.

Galfol *Sant Gall, Arg.*
Folic acid (p.1940·1).

Galidrin *Probiomed, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Galinocort *Vilco, Gr.*
⊗ Betamethasone valerate (p.1519·1).
Topical corticosteroid.

Galirene *Zydus, Fr.†.*
Calcium bromide (p.2269·3); calcium lactate (p.1676·1).
Insomnia; nervous disorders.

Galium *Heel, Cz.*
Homoeopathic preparation.

Galium Complex *Blackmores, Austral.†.*
Clivers (p.2284·3); echinacea angustifolia (p.2298·1); calendula (p.2273·1); baptisia tinctoria; vitamins (p.1922·1); zinc amino acid chelate (p.2000·1).
Tonic.

Galle-Donau *Sanova, Austria.*
p,α-Dimethylbenzyl alcohol nicotinate (p.2294·2); α-naphthylacetic acid (p.2350·2).
Biliary-tract disorders.

Gallemolan forte *Cesra, Ger.*
Greater celandine (p.2317·1); absinthium (p.2244·1); taraxacum (p.2395·1).
Biliary-tract disorders; dyspepsia.

Gallemolan G *Cesra, Ger.†.*
Absinthium (p.2244·1); boldo leaves (p.2267·2); chamomile flowers (p.2279·3); greater celandine (p.2317·1); taraxacum (p.2395·1).
Biliary-tract disorders; dyspepsia.

Gallen- und Lebertee St Severin *Smetana, Austria.*
Agrimony herb (p.2249·2); marrubium vulgare (p.1564·1); peppermint leaf (p.1761·2); achillea (p.2245·2); taraxacum (p.2395·1).
Biliary-tract disorders.

Gallenja *OTW, Ger.†.*
Homoeopathic preparation.

Gallentee *Abtswinder, Cz.†.*
Peppermint leaf (p.1761·2); taraxacum (p.2395·1); achillea (p.2245·2); curcumae xanthorrhizae (p.2406·3); liquorice (p.1740·3); fennel (p.2302·3); calendula (p.2273·1).
Biliary-tract disorders.

Gallesyn
Note. This name is used for preparations of different composition.
Wenig, Austria.
Oral drops: Frangula (p.1732·2); herba teucrii; peppermint oil (p.1761·2).
Biliary-tract disorders.

Wenig, Austria.
Tablets: Frangula (p.1732·2); herba teucrii; menthol (p.2340·1).
Biliary-tract disorders.

Gallexier
Note. This name is used for preparations of different composition.
Salus, Fr.†.
Cynara (p.2291·2).
Gastrointestinal and liver disorders.

Salushaus, Ger.
Oral liquid: Cynara (p.2291·2); Javanese turmeric (p.2406·3); gentian (p.2310·3); ginger (p.1732·3); cnicus benedictus (p.2285·2); menyanthes (p.2340·3); absinthium (p.2244·1); fennel (p.2302·3); cardamom (p.2277·1); bitter-orange peel (p.2357·1); chamomile (p.2279·3); achillea (p.2245·2); taraxacum (p.2395·1).
Gastrointestinal disorders.

Salushaus, Ger.
Tablets: Javanese turmeric (p.2406·3); cynara (p.2291·2); milk thistle (p.1452·1); taraxacum (p.2395·1); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Biliary disorders.

Gallia Anti-regurgitations *Gallia, Fr.*
Infant feed (p.1922·1).
Regurgitation.

Gallia Calisma *Gallia, Fr.*
Infant feed with *Bifidobacterium breve* and *Streptococcus thermophilus* (p.1922·1).
Maintenance of gastrointestinal flora.

Gallia digest *Gallia, Fr.*
Infant feed with bifidobacteria (p.1922·1).
Digestive disorders.

Gallia HA *Gallia, Fr.*
Infant feed (p.1922·1).
Milk-protein intolerance.

Gallia Lactofidus *Gallia, Fr.*
Infant feed (p.1922·1).
Gastrointestinal disorders.

Gallia Soja *Gallia, Fr.*
Infant feed (p.1922·1).
Cows' milk intolerance; diarrhoea.

Galliagene *Gallia, Fr.*
Infant feed (p.1922·1).
Diarrhoea; malabsorption syndromes; milk-protein intolerance.

Gallifugo *Mediplants, Gr.†.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Gallith *Evers, Ger.*
Ivy (p.2328·1).
Cholesterol gallstones.

Gallo Merz N *Merz, Ger.†.*
Dimethicone (p.1770·2); turmeric (p.1473·2).
Biliary-tract disorders.

Gallo Merz Spasmo *Merz, Ger.†.*
Hymecromone (p.2323·2).
Biliary-tract spasm.

Gallobeta *Betapharm, Ger.*
Gallopamil hydrochloride (p.1295·3).
Angina pectoris; arrhythmias; hypertension.

Gallopas *Pascoe, Ger.†.*
Greater celandine (p.2317·1).
Gastrointestinal and biliary-tract spasm.

Galloselect *Dreluso, Ger.*
Homoeopathic preparation.

Galloselect M *Dreluso, Ger.†.*
Greater celandine (p.2317·1); taraxacum (p.2395·1); milk thistle (p.1452·1); cynara (p.2291·2); chamomile (p.2279·3); peppermint oil (p.1761·2); caraway oil (p.2277·1).
Biliary-tract disorders.

Galloway's Cough Syrup *Chefaro, UK.*
Ipecacuanha liquid extract (p.1562·3); squill vinegar (p.1573·1).
Coughs.

Galmax *Max Farma, Ital.†.*
Sodium succinate ursodeoxycholate (p.2408·2).
Biliary disorders; gallstones.

Galocard *Galenus, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Galol *Elpen (Ελπεν), Gr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Galomega *Gal, Pol.†.*
Omega-3 marine triglycerides (p.1362·2).
Atherosclerosis; degenerative joint disorders; rheumatoid arthritis.

Galopran *Bernabo, Arg.*
Mosapride citrate (p.1750·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting.

Galospa *Galenus, Pol.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Galoxiway *Boots Healthcare, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Galpamol *Galpharm, UK.*
Paracetamol (p.108·1).
Pain.

Galpharm Flu Relief *Galpharm, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Galprofen *Galpharm, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Galpseud Plus *Thornton & Ross, UK.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis.

Galstena *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Galsud *Thornton & Ross, UK.*
Pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Galpseud.
Respiratory-tract congestion.

Galtamicina *Northia, Arg.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Galtes *Boniscontro & Gazzone, Ital.*
Gliclazide (p.440·3).
Diabetes mellitus.

Galusan *Almirall, Spain.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Galutec *Master, Chile†.*
Salol (p.122·1); menthol (p.2340·1); thymol (p.1664·3).
Mouth and throat disorders.

Gal-Vit *Gal, Pol.†.*
Maize oil (p.1955·2).
Benign prostatic hyperplasia.

Galvus *Novartis, Cz.; Novartis, Fr.; Novartis, Port.; Novartis, UK.*
Vildagliptin (p.463·3).
Diabetes mellitus.

Galzin *Teva Tuteur, Arg.; Gate, USA.*
Zinc acetate (p.1999·1).
Wilson's disease.

Gama Venina *CSL, Braz.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; chronic demyelinated polyneuropathy; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; lymphocytic leukaemia; passive immunisation.

Gamacef *Bergamo, Braz.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Gamactrin *Delta, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Gamafine *Haffkine, India.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Gamaflex *Abdi, Turk.*
Phenprobamate (p.1018·1).
Skeletal muscle spasm.

Gamakuil *Embil, Turk.*
Phenprobamate (p.1018·1).
Skeletal muscle spasm.

Gamalate B6
Andromaco, Chile.
Gamma-aminobutyric acid (p.2308·1); gamma-amino beta hydroxybutyric acid; magnesium glutamate hydrobromide (p.2337·1); pyridoxine hydrochloride (p.1978·2).
Mental function impairment.

Novag, Spain.
Gamma-aminobutyric acid (p.2308·1); aminohydroxybutyric acid (p.471·2); magnesium glutamate hydrobromide (p.2337·1); pyridoxine (p.1979·1).
Mental function impairment; senility.

Gamaline-V *Herbarium, Braz.*
Borage oil (p.2267·3); wheat-germ oil (p.2415·1).
Essential fatty acid deficiency.

Gamanil *Merck, Irl.; Merck, UK†.*
Lofepramine hydrochloride (p.407·1).
Depression; mixed anxiety depressive states; panic disorder.

Gamasol
Note. This name is used for preparations of different composition.
Organifar, Venez.†.
Ointment: Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus (p.2301·2).
Organifar, Venez.†.
Topical solution: Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); chloroform (p.1781·1); fioraventi balsam.

Gamastan *Bayer, Canad.; Talecris, Canad.; Talecris, USA.*
A normal immunoglobulin (p.2225·3).
Formerly known as BayGam in the *USA*.
Immunoglobulin deficiency; passive immunisation.

Gamatol *LED, Fr.†.*
Borage oil (p.2267·3).
Dry skin disorders.

Gamavate *Julphar, UAE.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Gamax *Hebron, Braz.†.*
Linoleic acid; linolenic acid; fatty acids (p.1922·1).
Nutritional supplement.

Gambex *Pharmacare, S.Afr.*
Lindane (p.2045·3).
Pediculosis.

Gambrosol *Gambro, Cz.; Gambro, Denm.; Gambro, Fin.; Gambro, Hung.; Gambro, Neth.; Gambro, Port.; Gambro, Spain; Gambro, Swed.*
Sodium chloride; magnesium chloride; calcium chloride; sodium lactate; glucose (p.1670·3).
Peritoneal dialysis.

Gameral *Gache, Venez.*
Sabila; cascara (p.1715·2).
Constipation.

Gamespir *Cosmopharm, Gr.†.*
Acemetacin (p.15·1).
Gout; inflammation; musculoskeletal disorders; pain; spondyloarthritis.

Gamibetal *Dansk-Flama, Braz.†; SIT, Ital.; Italmex, Mex.; Seber, Port.†.*
Aminohydroxybutyric acid (p.471·2).
Behaviour disorders; epilepsy; impaired mental function; infantile convulsions; neurosis; premenstrual syndrome.

Gamibetal Complex
Dansk-Flama, Braz.†; Italmex, Mex.
Aminohydroxybutyric acid (p.471·2); phenobarbital (p.492·2); phenytoin (p.495·2).
Epilepsy.
SIT, Ital.
Aminohydroxybutyric acid (p.471·2); phenobarbital (p.492·2); phenytoin sodium (p.495·2).
Epilepsy.

Gamibetal Compositum *Seber, Port.†.*
4-Amino-3-hydroxybutyric acid (p.471·2); diazepam (p.986·3).
Epilepsy; excitability.

Gamibetal Plus *SIT, Ital.*
Aminohydroxybutyric acid (p.471·2); diazepam (p.986·3).
Childhood behaviour disorders; epilepsy.

Gamikal *Probiomed, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Gamimune *Gador, Arg.†; Sintofarma, Braz.†.*
A normal immunoglobulin (p.2225·3).
Idiopathic thrombocytopenic purpura; immunodeficiency; passive immunisation.

Gamimune N *Bayer, Canad.†; Bayer, Chile†; Bayer, Cz.†; Dipa, Indon.; Bayer, Philipp.; GenAsia, Philipp.; Talecris, Rus.; Biem, Turk.; Bayer, USA†.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; bone-marrow transplantation; graft-versus-host disease; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Gamma Anti D *Grifols, Spain.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Gamma Antihepatitis B *Grifols, Spain.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Gamma Antitetanos *Grifols, Spain.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Gamma Anty D *Biomed Lublin, Pol.*
An anti-D immunoglobulin (p.2204·2).
Prevention of Rhesus sensitisation.

Gamma Anty HBs *Biomed Lublin, Pol.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Gammabulin *Baxter, Austria; Baxter BioScience, UK†.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; hypogammaglobulinaemia; passive immunisation.

Gammacur *Hexal, Ger.*
Evening primrose oil (p.2302·1).
Eczema.

Gammadin *OFF, Ital.*
Povidone-iodine (p.1659·2).
Skin, wound, and mucous membrane disinfection.

Gammadol *Schering-Plough, Mex.*
Ketorolac trometamol (p.74·2); tramadol hydrochloride (p.130·3).
Pain.

Gammagard *Baxter, Austria; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Israel†; Baxter, Ital.; Baxter, Malaysia†; Baxter, Mex.†; Baxter, Neth.; Bioscience, Philipp.; Baxter, Pol.; Baxter, Port.; Baxter, Singapore†; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; auto-immune disorders; bone-marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency disorders; Kawasaki disease; nephrotic syndrome; organ transplantation; passive immunisation.

Gammagard SD *Baxter, Belg.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Gammaglob Antihepatitis BP *ZLB, Spain.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Gammaglobulin *Octapharma, Denm.†; Veripalvelu, Fin.†; Biovitrum, Norw.†.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Gammaglobulina *Hemoderivados, Arg.; Grifols, Spain.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Gamma-Globulina *Biomed Lublin, Pol.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Gammakine *Dompe Biotec, Ital.†.*
Interferon gamma-1b (p.893·3).
Chronic granulomatous disease.

Gammalon *Daiichi, Hong Kong; Daiichi, Thai.*
Gamma-aminobutyric acid (p.2308·1).
Amnesia; cerebrovascular disorders; head injury; hypertension; mental function impairment; palsy; speech disorders.

Gammanorm *Octapharma, Austria; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Ger.; Octapharma, Hung.; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Swed.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; immunodeficiency disorders; passive immunisation.

Gammanova *Ivax, Arg.†.*
Immunoglobulin A-11-S; muramidase hydrochloride (p.2348·1).
Aphthous ulcers.

Gamma-OH *SERB, Fr.*
Sodium oxybate (p.1794·2).
General anaesthesia; sedative.

Gammaplus *Fidia, Ital.*
Omega-3 triglycerides (p.1362·1); omega-6 triglycerides.
Nutritional supplement.

GammaQuin *Sanquin, Neth.*
A normal immunoglobulin (p.2225·3).
Immunodeficiency disorders; passive immunisation.

Gammar
Note. This name is used for preparations of different composition.
Nikkho, Braz.
Gamma-aminobutyric acid (p.2308·1).
Impaired mental function.
Farma-Tek, Turk.
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation.

Gammaraas *Combiphar, Indon.; Shanghai RAAS, Thai.*
A normal immunoglobulin (p.2225·3).
Bone marrow transplant; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease.

Gammar-P *Centeon, USA†.*
A normal immunoglobulin (p.2225·3).
Immunoglobulin deficiency; passive immunisation.

Gamma-Scab
Note. This name is used for preparations of different composition.
Lafedar, Arg.
Lotion: Lindane (p.2045·3); lidocaine hydrochloride (p.1862·3).
Pediculosis; scabies.
Lafedar, Arg.
Shampoo: Lindane (p.2045·3).
Pediculosis.

Gammatet *Gador, Arg.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Gamma-Tet P *ZLB, Ital.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Gammatetanos *Lab Francais du Fractionnement, Fr.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Gamma-Venin *Aventis Behring, Austria†; Centeon, Cz.†; Aventis Behring, Ger.†.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Gamma-Venin P *ZLB, Gr.; Aventis Behring, Ital.†; ZLB Behring, Mex.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation.

Gammonativ *Biovitrum, Denm.†; Pharmacia, Ger.†; Octapharma, Swed.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki syndrome.

Gamonil *Merck, Ger.†; Merck, Switz.†.*
Lofepramine hydrochloride (p.407·1).
Depression.

Gamophen
Note. This name is used for preparations of different composition.
Johnson & Johnson, Austral.; Johnson & Johnson Medical, UK.
Triclosan (p.1665·2).
Acne; skin cleanser; soap substitute.
Aledicine, Gr.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Gamunex *Bayer, Canad.; Talecris, Canad.; Bayer, Cz.; Bayer, Ger.; Bayer, Port.; Bayer, USA.*
A normal immunoglobulin (p.2225·3).
Bone-marrow transplantation; graft-versus-host disease; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Ganaprofene *Ganassini, Ital.†.*
Ibuprofen sodium (p.65·2).
Fever; influenza symptoms; pain.

Ganaton *Abbott, Cz.; Abbott, Jpn; Fujisawa, Jpn; Abbott, Malaysia.*
Itopride hydrochloride (p.1737·3).
Dyspepsia; gastrointestinal motility disorders; gastrointestinal symptoms of chronic gastritis.

Ganavax *Rontag, Arg.*
Venlafaxine hydrochloride (p.427·3).
Depression; mixed anxiety-depressive states.

Ganazolo *Ganassini, Ital.*
Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal and Gram-positive bacterial infections.

Gancivir *Eurofarma, Braz.†.*
Ganciclovir sodium (p.879·2).
Viral infections.

Ganda *Chauvin, Irl.*
⊗ Guanethidine monosulfate (p.1300·2); adrenaline (p.1203·2).
Glaucoma.

Gandhour *Dermoteca, Port.*
A range of soap substitutes and moisturisers.

Gandin *Polipharm, Thai.*
Mefenamic acid (p.80·1).
Pain.

Ganfort *Allergan, Cz.; Alvia (Αλβια), Gr.; Allergan, Port.; Allergan, UK.*
⊗ Bimatoprost (p.1878·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ganidin NR *Cypress, USA.*
Guaifenesin (p.1561·3).

Ganin *Ferron, Indon.*
Gabapentin (p.482·3).
Epilepsy.

Ganite *Genta, USA.*
Gallium nitrate (p.1098·2).
Hypercalcaemia of malignancy.

Gani-Tuss NR *Cypress, USA.*
Guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Gani-Tuss-DM NR *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Gansol *Sanovel, Turk.*
Sulfafurazole diolamine (p.338·3).
Bacterial eye infections.

Ganticol *Oftalmi, Venez.*
Sulfafurazole (p.338·3).
Bacterial eye infections.

Gantil *Elpen (Ελπεν), Gr.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Gantin *Arrow, Austral.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gantrim *Geymonat, Ital.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Gantrimex *Geymonat, Ital.†.*
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Respiratory-tract disorders.

Gantrisin *Roche, USA†.*
Acetyl sulfafurazole (p.338·3) or sulfafurazole diolamine (p.338·3).
Bacterial eye infections; urinary-tract infections.

Ganvirax *Blausiegel, Braz.*
Ganciclovir sodium (p.879·2).
Cytomegalovirus infections.

Ganvirel *Ivax, Arg.*
Lamivudine (p.895·1).
HIV infection.

Ganvirel Duo *Ivax, Arg.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Gapentek *Actavis, Rus.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gapridol *Psicofarma, Mex.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gaproxen *Gap, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Garabet *Oftalmi, Venez.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye disorders.

Garabiotic *Bernofarm, Indon.*
Gentamicin sulfate (p.282·1).
Skin infections.

Garacin *Delta, Braz.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Garacol *Schering-Plough, Neth.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Garacoll *Schering-Plough, Mex.; Schering-Plough, S.Afr.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections of bone and soft tissue.

Garakacin *Offenbach, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Garalen *Probiomed, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Garalone *Schering-Plough, Port.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Garamat *Schering-Plough, Gr.*
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin (p.284·2).
Eye and ear inflammation and infection.

Garamicina *Mantecorp, Braz.; Schering-Plough, Mex.*
Gentamicin (p.284·2) or gentamicin sulfate (p.282·1).
Bacterial infections.

Garamicina-V *Schering-Plough, Mex.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Garamin *Prodotti, Braz.*
Gentamicin (p.284·2).
Bacterial infections.

Garamycin
Aesca, Austria†; Schering, Canad.; Innocoll, Cz.; Schering-Plough, Denm.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Innocoll, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Neth.; Schering-Plough, Norw.; Essex, Philipp.; Schering-Plough, Pol.; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.†; Schering-Plough, UK†; Schering, USA.
Gentamicin sulfate (p.282·1).
Bacterial infections.
Fulford, India.
Gentamicin (p.284·2) or gentamicin sulfate (p.282·1).
Bacterial infections.

Garan *Inter, Venez.†.*
Pyritinol (p.369·2).
Mental function disorders.

Garanil *Zambon, Spain.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Garapepsin *Medichrom, Gr.*
Trimebutine (p.2404·3).
Gastrointestinal and gallbladder pain.

Garapon *Armoxindo, Indon.*
Gentamicin sulfate (p.282·1).
Skin infections.

Garasone *Schering-Plough, Belg.†; Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Cz.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, Philipp.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore; Schering-Plough, Venez.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye and ear disorders.

Garatec *Technilab, Canad.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Garbital *Neo Quimica, Braz.*
Phenobarbital (p.492·2).

Garceptol *Grunenthal, Chile.*
Dimeticone (p.1770·2); metoclopramide (p.1747·3); chlordiazepoxide (p.968·1).
Gastrointestinal disorders.

Garcinia Cambogia Compuesta *Lafarmen, Arg.*
Garcinia cambogia (p.2309·2); chromium tripicolinate (p.1934·3).
Nutritional supplement.

Garcinol Max
Note. This name is used for preparations of different composition.
Garden House, Arg.
Tablets: Centella (p.1592·3); carnitine (p.1932·2); garcinia cambogia (p.2309·2).
Cellulite; dietary supplement; slimming aid.

Garden House, Arg.†.
Topical gel: Centella (p.1592·3); ginkgo biloba (p.2311·1); ivy (p.2328·1).
Cellulite.

Garcol *Christo, Hong Kong.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vestibular disorders.

Gardan *Sanofi Synthelabo, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Gardan P *Polfa Pabianice, Pol.*
Dipyrone (p.49·2); propyphenazone (p.119·3).
Pain.

Gardasil *MSD, Arg.; CSL, Austral.; Sanofi Pasteur, Belg.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; MSD, Malaysia; CSL, NZ; Sanofi Pasteur, Port.; Sanofi Pasteur, UK; Merck, USA.*
A human papillomavirus vaccine (types 6, 11, 16, and 18) (p.2217·3).
Active immunisation.

Gardenal
Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Gr.; Nicholas Piramal, India.
Phenobarbital (p.492·2).
Epilepsy; febrile convulsions; hyperbilirubinaemia; insomnia; sedative.

Aventis, Cz.†; Aventis, NZ†; Aventis, S.Afr.†; Sanofi-Aventis, Spain; Aventis, Thai.; Concord, UK†.
Phenobarbital sodium (p.492·2).
Agitation; convulsive disorders; eclampsia; epilepsy; insomnia; premedication; smooth muscle spasm; tetanus.

Sanofi-Aventis, Fr.; Sanofi-Aventis, Venez.
Phenobarbital (p.492·2) or phenobarbital sodium (p.492·2).
Epilepsy.

Gardenale *Sanofi-Aventis, Ital.*
Phenobarbital (p.492·2).
Epilepsy; insomnia; sedative.

Gardex *Nordic Drugs, Denm.; Nordic Drugs, Fin.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Gardoton
Note.This name is used for preparations of different composition.
Raffo, Arg.
Glibenclamide (p.440·1).
Diabetes mellitus.

Raffo, Chile.
Ondansetron (p.1756·3).
Nausea and vomiting.

Garexin *GMP, Indon.*
Gentamicin sulfate (p.282·1).
Eye infections.

Garfield *Whitehall-Robins, Canad.†; Menley & James, USA.*
Multivitamins with or without minerals (p.1922·1).

Gargaletas *Monserrat, Arg.*
Gramicidin (p.286·1); neomycin sulfate (p.305·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Gargaril *Puerto Galiano, Spain.*
Chlorhexidine (p.1635·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Gargarin *Aflofarm, Pol.*
Borax (p.2268·1); sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1); sodium benzoate; menthol (p.2340·1).
Mouth and throat disorders.

Gargarisma zum Gurgeln *Krewel, Ger.*
Aluminium chloride (p.1588·2).
Mouth inflammation.

Gargarol *Boiron, Canad.†.*
Homoeopathic preparation.

Gargilon *Vemedia, Neth.*
Dequalinium chloride (p.1641·3).
Sore throat.

Gargocetil *Bunker, Braz.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Gargol *Rekah, Israel.*
Boric acid (p.2268·1); thymol (p.1664·3); menthol (p.2340·1); terpineol (p.2396·1); cineole (p.2282·3); methyl salicylate (p.85·3); chloroxylenol (p.1640·2).
Mouth and throat disorders.

Gargotan *Ibefar, Braz.†.*
Tyrothricin (p.358·2); sulfanilamide (p.343·1); thymol (p.1664·3); cineole (p.2282·3); menthol (p.2340·1); benzocaine (p.1854·1).

Garia *Sankyo, Spain.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Garianes *Nufarindo, Indon.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Garlic Allium Complex *GNLD, Austral.*
Garlic (p.2309·2); onion (p.2356·3); chive; leek; rosemary (p.2381·2).
Upper respiratory-tract congestion.

Garlic, Horseradish, A & C Capsules *Vitaplex, Austral.†.*
Garlic oil (p.2309·2); horseradish (p.2320·1); ascorbic acid (p.1983·3); vitamin A palmitate (p.1973·1).
Excess body fluids; excess mucus formation.

Garlic and Horseradish + C Complex *Cenovis, Austral.*
Horseradish (p.2320·1); garlic (p.2309·2); sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3); fenugreek (p.2303·3); althaea (p.2253·3).
Upper respiratory-tract symptoms.

Garlic-Plus *Ikapharmindo, Indon.*
Garlic (p.2309·2); vitamin E (p.1992·2).
Circulation disorders; hyperlipidaemias; hypertension.

Garlimega *Cantassium Co., UK.*
Garlic (p.2309·2).

Garlix *Blackmores, Austral.*
Garlic (p.2309·2).
Cold and influenza symptoms.

Garmastan *Austroplant, Austria; Protina, Cz.†; Med, Turk.*
Guaiazulene (p.2317·3).
Mastitis prophylaxis; skin disorders.

Garoin *Nicholas Piramal, India.*
Phenytoin sodium (p.495·2); phenobarbital sodium (p.492·2).
Epilepsy.

Garonsept
Note.This name is used for preparations of different composition.
Master, Chile.
Chlorhexidine gluconate (p.1635·3).
Mouth and throat infections.

Sam-On, Israel.
Benzalkonium chloride (p.1629·1); menthol (p.2340·1); thymol (p.1664·3); lemon oil (p.2332·3).
Mouth and throat infections.

Gartech *Eagle, Austral.*
Andrographis; astragalus; echinacea purpurea (p.2298·1); garlic (p.2309·2); berberis vulgaris; fucus vesiculosus (p.2384·2); origanum oil (p.2358·1); wild thyme oil (p.2415·3); garlic oil (p.2309·2); anise oil (p.2258·2); savory oil (p.2394·3); cinnamon oil (p.2283·2).
Cold and influenza symptoms.

Gartricin *Cantabria, Spain†.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

Gartun *Lusomedicamenta, Port.*
Benzydamine hydrochloride (p.27·3); aluminium lactate (p.2255·1).
Mouth and throat disorders.

Garydol *Cinfa, Spain.*
Chlorhexidine gluconate (p.1635·3); benzocaine (p.1854·1).
Sore throat.

Gas Ban *Roberts, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Flatulence.

Gas Ban DS *Roberts, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence.

Gas Relief *Rugby, USA.*
Simeticone (p.1770·2).
Flatulence.

Gascoal *YSP, Malaysia; Yung Shin, Singapore.*
Simeticone (p.1770·2).
Flatulence; preparation for gastrointestinal examination.

Gascol *Lafit, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).

Gascon *Kissei, Hong Kong.*
Dimeticone (p.1770·2).
Flatulence; preparation for gastrointestinal investigations.

Gascop *Valdecasas, Mex.*
Albendazole (p.139·2).
Worm infections.

Gasdol *Bago, Chile.*
Domperidone (p.1726·2).
Dyspepsia; nausea; pyrosis; reflux; vomiting.

Gasea *Sevapharma, Cz.†.*
Gas-gangrene antitoxins (p.2213·1).
Gas gangrene.

Gasec *Mepha, Braz.; Mepha, Cz.; Mepha, Malaysia; Mepha, Pol.; Mepha, Port.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gaseofin *Andromaco, Chile†.*
Metoclopramide hydrochloride (p.1747·3); chlordiazepoxide hydrochloride (p.968·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Gasfamin *Meprofarm, Indon.*
Famotidine (p.1730·1).
Gastric hypersecretion; peptic ulcer.

Gaslon N *Shinyaku, Jpn.*
Irsogladine maleate (p.1736·3).
Gastritis; peptic ulcer.

Gasmilen *Ivax, Arg.*
Ganciclovir (p.879·1).
Viral infections.

Gas-MM *Milano, Thai.*
Simeticone (p.1770·2).
Flatulence; preparation for gastrointestinal examination.

Gasmol *Richmond, Arg.*
Bromazepam (p.964·3).
Anxiety.

Gasmotin *Dainippon, Jpn.*
Mosapride citrate (p.1750·3).
Gastritis.

Gas-Nep *Sriprasit, Thai.*
Cataria; sodium bicarbonate (p.1673·2); caraway oil (p.2277·1); fennel oil (p.2303·1); cardamom oil (p.2277·2); anise oil (p.2258·2).
Flatulence; gastrointestinal disorders.

Gasoff *Maver, Chile.*
Simeticone (p.1770·2).
Flatulence; infant colic; meteorism.

Gasopax *Prater, Chile.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid; flatulence.

Gasorbol
Note.This name is used for preparations of different composition.
Andromaco, Chile.
Oral drops: Simeticone (p.1770·2); pipenzolate bromide (p.1762·2).
Aerophagia; infant colic.

Andromaco, Chile†.
Tablets: Simeticone (p.1770·2).
Abdominal distension; aerophagia; meteorism.

Gasorbol Plus *Andromaco, Chile†.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders.

Gaspiren *Biolab Sanus, Braz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Gasprid *Polfa Kutno, Pol.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux.

Gassi *Medicine Products, Thai.*
Simeticone (p.1770·2).
Flatulence.

Gastab
Note.This name is used for preparations of different composition.
APT, Hong Kong.
Cimetidine (p.1716·2).
Dyspepsia; peptic ulcer.

Greater Pharma, Thai.
Sodium bicarbonate (p.1673·2); cataria.
Flatulence.

Gastac *Giempi, Venez.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastric hyperacidity.

Gastal
Note.This name is used for preparations of different composition.
Pliva, Cz.
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); magnesium hydroxide (p.1743·2).
Dyspepsia; gastrointestinal hyperacidity; peptic ulcer.

Pliva, Rus.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Epigastric pain; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Pliva Krakow, Pol.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Pliva Krakow, Pol.
Tablets: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Gastec *Bernabo, Arg.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gasteel *Fuso, Hong Kong.*
Dimethicone (p.1770·2).
Flatulence.

Gastenin *Perez Gimenez, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gaster
Note.This name is used for preparations of different composition.
Astellas, Indon.; Astellas, Jpn.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; pathological hypersecretory disorders; peptic ulcer; premedication; Zollinger-Ellison syndrome.

Unison, Thai.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gasterin *Slovakofarma, Cz.†.*
Aluminium phosphate (p.1707·3).
Diarrhoea; dyspepsia; gastritis; hiatus hernia; peptic ulcer.

Gasterogen *Faran, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Gasterol *Terra, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastidin *Neckerman, Braz.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Gastidine *Vida, Hong Kong.*
Cimetidine (p.1716·2).
Peptic ulcer.

Gastifam *Munir, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastop *Bajer, Arg.*
Simeticone (p.1770·2); bismuth carbonate (p.1711·1).
Gastrointestinal disorders.

Gastopride *Solvay, Port.†.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Gastracid *AWD, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastracol *Streuli, Switz.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Gastral *Novag, Spain.*
Sucralfate (p.1772·2).
Gastrointestinal haemorrhage; peptic ulcer.

Gastralgin *De Angeli, Ital.*
Roxatidine acetate hydrochloride (p.1769·1).
Gastro-oesophageal reflux; peptic ulcer.

Gastralon N *Cesra, Ger.†.*
Chamomile (p.2279·3); gentian (p.2310·3); absinthium (p.2244·1).
Gastrointestinal disorders.

Gastran
Note.This name is used for preparations of different composition.
Socobom, Belg.; Delta, Singapore†.
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer.

Johnson & Johnson, Braz.
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastrointestinal hyperacidity.

Medifarma, Indon.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2).
Bloating; flatulence; gastric hyperacidity; gastric pain; gastritis; heartburn; nausea; peptic ulcer.

Gastranil *Lafage, Arg.†.*
Bismuth hydroxide (p.1712·1); papaverine (p.2191·3); kaolin (p.1738·1); magnesium trisilicate (p.1744·1); titanium dioxide (p.1617·3).
Gastrointestinal disorders.

Gastranin Zdrovit *Natur Produkt, Pol.*
Ranitidine (p.1766·1).
Dyspepsia.

Gastrarctin N *Serum-Werk Bernburg, Ger.*
Colloidal silver (p.2387·3); chamomile flowers (p.2279·3); peppermint leaf (p.1761·2).
Gastrointestinal disorders.

Gastrat *Ibfarma, Braz.†.*
Ranitidine (p.1766·1).
Peptic ulcer.

Gastrax *Asche, Ger.†.*
Nizatidine (p.1751·2).
Peptic ulcer.

Gastrazol *Megat, Venez.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Gastrec *Tecnofarma, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Gastrex
Note.This name is used for preparations of different composition.
Simoes, Braz.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

OM, Port.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrial *Sanofi Synthelabo, Arg.*
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Gastrib *Ibfarma, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Gastribien *Cinfa, Spain†.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; peptic ulcer.

Gastricalm *OJG, Belg.*
Magaldrate (p.1742·3).
Gastrointestinal disorders associated with hyperacidity.

Gastricard
Note.This name is used for preparations of different composition.
Ysatfabrik, Ger.†.
Oral drops: Ginger oil (p.1732·3); fennel oil (p.2303·1); peppermint oil (p.1761·2); caraway oil (p.2277·1); coriander oil (p.2288·1).
Gastrointestinal disorders.

Ysatfabrik, Ger.†.
Tablets: Peppermint oil (p.1761·2); caraway oil (p.2277·1); fennel oil (p.2303·1); coriander oil (p.2288·1).
Gastrointestinal disorders.

Gastricholan-L *Sudmedica, Ger.*
Chamomile flowers (p.2279·3); peppermint leaf (p.1761·2); fennel (p.2302·3).
Gastrointestinal disorders.

Gastricumeel *Peithner, Austria.*
Homoeopathic preparation.

Gastricur
Note. This name is used for preparations of different composition.
Bioquimico, Arg.
Bismuth subnitrate (p.1711·2); magnesium carbonate (p.1743·1).
Gastrointestinal disorders.

Heumann, Ger.†.
Pirenzepine hydrochloride (p.1762·3).
Dyspepsia; gastritis; peptic ulcer.

Gastride
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Standard, Philipp.
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm; vomiting.

Gastridin
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Clebopride (p.1722·1).

Interbat, Indon.; Hexal, Mex.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

MSD, Ital.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastridina *Medibial, Port.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastridin-E *Bernabo, Arg.*
Gastric capsules, clebopride malate (p.1722·1); pepsin (p.2365·1); simeticone (p.1770·2); enteric capsules, pancreatin (p.2360·1); amylase (p.2256·3); lipase (p.2360·3); cellulase (p.2279·1).
Gastrointestinal disorders.

Gastridol *Medichrom, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Gastrifam *Helsinn, Port.†.*
Famotidine (p.1730·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrifom *Tanta, Canad.*
Aluminium hydroxide (p.1706·2); alginic acid (p.2140·3).

Gastril *Duopharma, Hong Kong†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastrointestinal haemorrhage; peptic ulcer.

Gastriloc *Verheilen, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

gastri-loges *Loges, Ger.*
Homoeopathic preparation.
Formerly known as gastri-L 90 N.

Gastrimet *Raffo, Arg.†.*
Mosapride (p.1750·3); cisapride (p.1720·3); dimeticone (p.1770·2).
Gastrointestinal disorders.

Gastrimet Enzimatico *Raffo, Arg.†.*
Cisapride (p.1720·3); simeticone (p.1770·2); pancreatin (p.2360·1).
Gastrointestinal disorders.

Gastrimut *Normon, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrinal
Note. This name is used for preparations of different composition.
Meprofarm, Indon.
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Lek, Pol.
Dihydroxyaluminum sodium carbonate (p.1723·3).
Gastric hyperacidity; gastritis; peptic ulcer.

Gastrin-Do *Grasler, Ger.*
Homoeopathic preparation.

Gastrion *Lesvi, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastripan
Note. This name is used for preparations of different composition.
Ratiopharm, Austria.
Aluminium glycinate (p.1706·2); almasilate (p.1705·1); liquorice (p.1740·3); ethaverine hydrochloride (p.2299·3).
Gastrointestinal disorders.

Merckle, Ger.
Magaldrate (p.1742·3).
Gastric hyperacidity; heartburn; peptic ulcer.

Gastriphar *Teva, Belg.*
Sodium alginate (p.2141·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Gastriselect N *Dreluso, Ger.*
Homoeopathic preparation.
Gastriselect formerly contained nux. vom., alumina, aescul., plumb. acet., and colocynt.

Gastritol *Klein, Ger.*
Potentilla anserina; absinthium (p.2244·1); cnicus benedictus (p.2285·2); liquorice (p.1740·3); angelica (p.2258·1); chamomile (p.2279·3); St John's wort (p.422·3).
Gastrointestinal disorders.

Gastrium
Note. This name is used for preparations of different composition.
Ache, Braz.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Saval, Chile.
Famotidine (p.1730·1).
Acid aspiration; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Gastriveran *Finadiet, Arg.*
Alizapride (p.1705·1).
Nausea and vomiting.

Gastri-Vyr *Cazi, Braz.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Gastrix *Axcan, Cz.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Gastro
Note. This name is used for preparations of different composition.
Cipla, India.
Cisapride (p.1720·3).
Gastrointestinal disorders.

Unipharm, Israel.
Famotidine (p.1730·1).
Gastrointestinal hyperacidity; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Unia, Pol.
Calamus (p.2271·3); bismuth subnitrate (p.1711·2); frangula (p.1732·2); magnesium carbonate (p.1743·1); liquorice (p.1740·3).
Gastric hyperacidity; heartburn; hiatus hernia; peptic ulcer.

Gastro MPS *Cipla, India.*
Cisapride (p.1720·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Gastro-Ad *Dexa, Indon.*
Lactobacillus delbrueckii (p.2372·3); fructose (p.1945·1).
Maintenance of normal gastrointestinal function.

Gastro'Aid *Carrare, Fr.*
Soya protein (p.1965·3).
Gastric hyperacidity.

Gastroalgine *Novag, Spain.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2); enoxolone aluminium (p.1729·1); magnesium hydroxide (p.1743·2).
Dyspepsia; flatulence; gastritis; gastrointestinal hyperacidity.

Gastrobario *Bial, Port.*
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Gastrobene
Note. This name is used for preparations of different composition.
Legrand, Braz.
Oral powder: Calcium carbonate (p.1714·1); belladonna (p.2263·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); dimeticone (p.1770·2); kaolin (p.1738·1).
Gastric hyperacidity.

Legrand, Braz.
Tablets: Calcium carbonate (p.1714·1); belladonna (p.2263·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); dimeticone (p.1770·2).
Gastric hyperacidity.

Gastrobid Continus *Napp, Irl.; Napp, UK†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; nausea and vomiting.

Gastrobion *Galenogal, Braz.†.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Gastro-Bismol *Farmaline, Thai.*
Bismuth salicylate (p.1711·1).
Diarrhoea; dyspepsia; gastrointestinal spasm; nausea; peptic ulcer.

Gastrobonisol *Bonimed, Pol.*
Achillea (p.2245·2); artemisia abrotanum; St John's wort (p.422·3); peppermint (p.1761·2); milk thistle (p.1452·1); taraxacum (p.2395·1).
Gastrointestinal disorders.

Gastrobul *Guerbet, Fr.†; Guerbet, Hung.†; Guerbet, Neth.*
Betaine hydrochloride (p.2265·2); sodium bicarbonate (p.1673·2); dimeticone (p.1770·2).
Gas production for double-contrast radiography.

Gastrocaine *Europharm, Hong Kong.*
Oxetacaine (p.1867·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Gastrocalm
Note. This name is used for preparations of different composition.
Bio-Sante, Canad.
Chewable tablets: Calcium carbonate (p.1714·1); simeticone (p.1770·2).

Bio-Sante, Canad.
Oral liquid: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2).

Gastroccult *SmithKline Diagnostics, USA.*
Test for occult blood in gastric contents.

Gastrocol *Almirall, Chile†.*
Sucralfate (p.1772·2).
Peptic ulcer.

Gastrocote *Thornton & Ross, UK.*
Alginic acid (p.2140·3) or sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Gastrocrom *Celltech, USA.*
Sodium cromoglicate (p.1136·3).
Mastocytosis.

Gastrocure *McNeil, Neth.*
Domperidone maleate (p.1726·3).
Gastrointestinal disorders.

Gastrocynesine *Boiron, Cz.; Boiron, Fr.; Boiron, Neth.; Boiron, Port.*
Homoeopathic preparation.

Gastrodenol *Astellas, Spain.*
Tripotassium dicitratobismuthate (p.1711·2).
Gastritis; peptic ulcer.

Gastrodin *Shiwa, Thai.†.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Gastrodina *Degorts, Mex.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer.

Gastrodine *Medipharm, Chile.*
Rabeprazole sodium (p.1765·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrodomina *Almirall, Hong Kong; Almirall, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrodue *MDM, Ital.†.*
Oxetacaine (p.1867·2); aluminium oxide (p.1585·3); magnesium carbonate (p.1743·1) or magnesium oxide (p.1744·1).
Gastric hyperacidity.

Gastrodyn comp *Leiras, Fin.*
Glycopyrronium bromide (p.2315·3); diazepam (p.986·3).
Gastrointestinal disorders.

Gastroenterol *Dermofarma, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins; minerals; plant extracts (p.1922·1).
Nutritional supplement.

Gastrofam *Atabay, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrofan *Polfa Grodzisk, Pol.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Gastrofilm *Will-Pharma, Belg.†.*
Algeldrate (p.1706·2); magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); bismuth subnitrate (p.1711·2); belladonna (p.2263·3).
Dyspepsia; gastric hyperacidity.

Gastroflat *Bunker, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Gastrofloral *Silesia, Chile.*
Enterococcus faecium (p.2372·3).
Diarrhoea.

Gastroflux *Ashbourne, UK†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Gastrofrenal *Pharmacia, Ital.; Sigma-Tau, Spain.*
Sodium cromoglicate (p.1136·3).
Food hypersensitivity; inflammatory bowel disease.

Gastrogas *E-Z-EM, Neth.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Double-contrast radiography of the gastrointestinal tract.

Gastroge *Klonal, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity.

Gastrogel
Note. This name is used for preparations of different composition.
Zentiva, Cz.
Magnesium aluminate.
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; pancreatitis; peptic ulcer.

Giuliani, Ital.
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sigma, Austral.; Sigma, Hong Kong.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); magnesium hydroxide (p.1743·2).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Fawns & McAllan, Austral.†; Sigma, Hong Kong.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastric hyperacidity; heartburn; peptic ulcer.

Gastrogenol *Profarb, Braz.†.*
Guarana (p.2416·1); kola (p.2416·1); cinchona bark (p.2282·3).

Gastroglutal *Tedec Meiji, Spain†.*
Magnesium oxide (p.1744·1); glutamine (p.1947·2); aluminium glycinate (p.1706·2).
Gastrointestinal hyperacidity.

Gastrografin *Bayer, Austral.; Schering, Austria; Schering, Belg.; Schering, Fin.; Schering, Ger.; Schering, Gr.; Bayer Schering, Hung.; Schering, Ital.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, S.Afr.; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, UK; Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for gastrointestinal radiography; meconium ileus.

Gastrografina *Bayer, Port.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for gastrointestinal radiography.

Gastrografine *Schering, Fr.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for gastrointestinal radiography.

Gastroidam *Tecnifar, Port.*
Idanpramine sulfate (p.2324·2).

Gastrokin *Sanitas, Chile†.*
Cisapride (p.1720·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis; irritable colon; postoperative ileus.

Gastrol *Luper, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Gastrol S *Fides, Ger.†.*
Gentian (p.2310·3); chamomile (p.2279·3); melissa (p.2339·3); caraway (p.2276·3); fennel (p.2302·3); coriander (p.2288·1); sweet basil (p.2263·2); absinthium (p.2244·1); St John's wort (p.422·3); cinchona bark (p.2282·3); juniper (p.2328·2); calamus (p.2271·3); turmeric (p.1473·2).
Gastrointestinal disorders.

Gastrol TC *Luper, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity.

Gastrolan *Gracia, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Gastrolanzo *Biaro, Port.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Gastrolav *Vitoria, Port.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrolen *Chemopharma, Chile.*
Clidinium bromide (p.1722·1); chlordiazepoxide (p.968·1).
Gastrointestinal pain; genitourinary disorders; irritable colon.

Gastrolene *Faran, Gr.†.*
Cimetidine (p.1716·2).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Gastrolets *Hexa, Arg.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Gastroliber *Pentafarma, Port.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrolina Compuesta *Microsules, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Gastrolit *Polfa Kutno, Pol.*
Chamomile (p.2279·3); glucose; potassium chloride; sodium chloride; sodium bicarbonate (p.1672·2).
Diarrhoea; oral rehydration.

Gastroliv *Cifarma, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Gastrolux *Sanochemia, Ger.*
Sodium amidotrizoate (p.1475·3); meglumine amidotrizoate (p.1475·3) or lysine amidotrizoate (p.1477·1).
Contrast medium for gastrointestinal radiography.

Gastrolyte
Aventis, Canad.; Aventis, NZ; Zedchem, S.Afr.
Sodium chloride; sodium acid citrate; potassium chloride; glucose monohydrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Sanofi-Aventis, Austral.
Effervescent tablet: Sodium chloride; potassium chloride; anhydrous citric acid; glucose; sodium bicarbonate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Sanofi-Aventis, Austral.
Oral solution; powder for oral solution: Sodium chloride; potassium chloride; sodium acid citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Gastrolyte-R *Sanofi-Aventis, Austral.*
Rice powder; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Gastrom *Tanabe, Jpn.*
Ecabet sodium (p.1728·3).
Gastritis; peptic ulcer.

Gastromal *Polon, Pol.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Gastromark *Mallinckrodt, USA.*
Ferumoxsil (p.1478·1).
Contrast medium for magnetic resonance imaging of the gastrointestinal tract.

Gastromax
Note. This name is used for preparations of different composition.
Gador, Arg.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Cifarma, Braz.
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Gastromet
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Cisapride (p.1720·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis; irritable colon; postoperative ileus.

Malayan, Singapore†.
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Gastromine *Vida, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; gastric hyperacidity; heartburn; peptic ulcer.

Gastromins *Bros, Gr.†.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Gastromiro *Bracco, Austria; Bracco, Cz.†; Bracco, Hung.†; Merck, Irl.†; Bracco, Israel†; Bracco, Ital.; Bracco, Neth.; Bracco, Port.; Bracco, UK.*
Iopamidol (p.1483·3).
Contrast medium for gastrointestinal radiography.

Gastromol *Cantabria, Spain.*
Magaldrate (p.1742·3).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Gastron *Pharmacare, S.Afr.*
Loperamide hydrochloride (p.1741·1).
Colostomies; diarrhoea; ileostomies.

Gastron Fuerte *Sanofi Synthelabo, Arg.†.*
Pancreatin (p.2360·1); hemicellulase (p.2279·1); ox bile (p.2266·2); simeticone (p.1770·2).
Dyspepsia.

Gastronax *Galena, Pol.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Gastronerton
Sanova, Austria.
Metoclopramide dihydrochloride (p.1749·2).
Gastrointestinal motility disorders; nausea and vomiting.

Dolorgiet, Ger.
Metoclopramide (p.1747·3), metoclopramide dihydrochloride (p.1749·2), or metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Gastronol
Note. This name is used for preparations of different composition.
Bioforce, Switz.
Homoeopathic preparation.

Elmor, Venez.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastronorm *Janssen-Cilag, Ital.*
Domperidone (p.1726·2).
Dyspepsia; nausea.

Gastropan *Neo Quimica, Braz.*
Pantoprazole sodium (p.1760·1).
Peptic ulcer.

Gastropaque *Temis, Arg.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Gastro-Pasc *Pascoe, Ger.†.*
Homoeopathic preparation.

Gastropax *Lehning, Fr.*
Kaolin (p.1738·1); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); magnesium carbonate (p.1743·1); calcium phosphate (p.1676·2); sodium bicarbonate (p.1673·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Gastropeache Susp *Italfarmaco, Spain.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastrointestinal hyperacidity; peptic ulcer.

Gastropect *Pharmacare, S.Afr.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Gastropen *I Farmacologia, Spain†.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastropensan *Zeler, Port.*
Basic aluminium carbonate (p.1706·2); sodium carbonate (p.2389·1); dimeticone (p.1770·2).
Dyspepsia.

Gastro-Pepsin *Ceccarelli, Ital.*
Pepsin (p.2365·1); gastric mucosa (p.2337·3); hydrochloric acid (p.2322·1); lactic acid (p.2329·3); bitter orange (p.2357·1).
Dyspepsia; hypoacidity.

Gastropharm *Plastchim, Rus.*
Lactobacillus bulgaricus strain 51 (LB-51) (p.2372·3).
Gastritis; heartburn; peptic ulcer; protection of the gastrointestinal mucosa from irritants.

Gastropiren *AGIPS, Ital.*
Pirenzepine hydrochloride (p.1762·3).
Gastrointestinal disorders.

Gastroplant *DHU, Ger.*
Homoeopathic preparation.

Gastroplus *Hexal, Braz.†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Gastroprazol *Lamsa, Arg.; Streuli, Switz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastroprotect *Riemser, Ger.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastropulgite *Beaufour, Fr.; Beaufour-Ipsen, Switz.†.*
Activated attapulgite (p.1709·1); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastrointestinal disorders.

Gastrosan *Bioforce, Switz.*
Achillea (p.2245·2); taraxacum (p.2395·1); melissa (p.2339·3); gentian (p.2310·3); cnicus benedictus (p.2285·2); angelica (p.2258·1); centaury (p.2279·1).
Digestive disorders.

Gastrosecur *Duopharm, Ger.†.*
Chirata; gentian (p.2310·3); ginger (p.1732·3); cinnamon (p.2283·1); dried bitter-orange peel (p.2357·1); caraway (p.2276·3).
Gastrointestinal disorders.

Gastrosed *Roberts, USA.*
Hyoscyamine sulfate (p.1736·1).

Gastrosedol *Nova Argentia, Arg.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; pathological gastric hypersecretion; peptic ulcer.

Gastrosidin *Eczacibasi, Rus.; Eczacibasi, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrosil
Note. This name is used for preparations of different composition.
Pfizer, Austria; Heumann, Ger.†.
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; gastrointestinal motility disorders; vomiting.

ICN, Pol.
Simeticone (p.1770·2).
Excess gastrointestinal gas; gastrointestinal procedures.

Heumann, Switz.
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal examination; gastrointestinal disorders.

Gastrosine *Boiron, Canad.*
Homoeopathic preparation.

Gastro-Soothe *AFT, NZ.*
Hyoscine butylbromide (p.1734·1).
Gastro-intestinal spasm.

Gastrosorb *Synco, Hong Kong.*
Attapulgite (p.1709·1).
Diarrhoea.

Gastrostad *Stada, Ger.†.*
Magaldrate (p.1742·3).
Gastrointestinal disorders associated with hyperacidity.

Gastro-Stop *Aspen, Austral.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Gastrotem *Temis, Arg.*
Omeprazole (p.1753·1).

Gastro-Timelets *Sanova, Austria; Temmler, Denm.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; gastrointestinal motility disorders; vomiting.

Gastrotranquil *Azupharma, Ger.†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Gastrotrombina *Biomed Lublin, Pol.*
Thrombin (p.1080·1).
Gastrointestinal haemorrhage.

Gastrotuss *DMG, Ital.*
Magnesium alginate (p.2141·1); simeticone (p.1770·2); dexpanthenol (p.2362·1); althaea (p.2253·3); red-poppy (p.1472·3); zinc oxide (p.1621·2); sodium carbonate (p.2389·1).
Gastro-oesophageal reflux.

Gastrovegetalin *Verla, Ger.*
Melissa (p.2339·3).
Gastrointestinal disorders; sleep disorders.

Gastrovison *Shepa, Gr.†.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); colloidal silicon dioxide (p.2146·2); hypromellose; dimeticone (p.1770·2).
Gas production for double-contrast radiography.

Gastrox *Greenpharma, Braz.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Gastrozac *Klonal, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Gastrozepin *Boehringer Ingelheim, Austria; Slovakofarma, Cz.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.†; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Neth.†; Boehringer Ingelheim, Rus.*
Pirenzepine hydrochloride (p.1762·3).
Duodenitis; gastric hypersecretion; gastritis; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Gastrozepina *Boehringer Ingelheim, Port.†.*
Pirenzepine hydrochloride (p.1762·3).

Gastrozol *Delta, Braz.; Farmstandart, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrucid *Nufarindo, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer; pyrosis.

Gastrul *Fahrenheit, Indon.*
Misoprostol (p.2013·2).
NSAID-induced gastric ulcer.

Gastrulcer *Fariberica, Port.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gastrysat
Note. This name is used for preparations of different composition.
Ysatfabrik, Ger.
Chewable tablet: Fennel oil (p.2303·1); coriander oil (p.2288·1); caraway oil (p.2277·1); peppermint oil (p.1761·2).
Gastrointestinal disorders.

Ysatfabrik, Ger.
Oral liquid: Fennel oil (p.2303·1); ginger oil (p.1732·3); coriander oil (p.2288·1); caraway oil (p.2277·1); peppermint oil (p.1761·2).
Gastrointestinal disorders.

Gastyl *ANB, Malaysia; ANB, Thai.*
Simeticone (p.1770·2).
Abdominal distension; excess gastrointestinal gas; flatulence.

Gasulsol *Herbes Universelles, Canad.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).

Gas-X *Novartis Consumer, Canad.; General Drugs, Thai.; Novartis Consumer, USA.*
Simeticone (p.1770·2).
Excess gastrointestinal gas; flatulence.

Gas-X with Maalox *Novartis, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Antacid; flatulence.

Gasyran *Loren, Mex.†.*
Ranitidine (p.1766·1).
Peptic ulcer.

Gaszym *Ranbaxy, Thai.*
Simeticone (p.1770·2); pancreatin (p.2360·1).
Digestive system disorders; flatulence.

Gaticin *Aristo, India; Fahrenheit, Indon.*
Gatifloxacin (p.281·1).
Bacterial infections.

Gatif *Poen, Arg.*
Gatifloxacin (p.281·1).
Bacterial eye infections.

Gatiflo *Kyorin, Jpn; Senju, Jpn.*
Gatifloxacin (p.281·1).
Bacterial infections.

Gatimax *Pharos, Indon.*
Gatifloxacin (p.281·1).
Bacterial infections.

Gatinar *Melisana, Switz.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Gatiquin *Cipla, India.*
Gatifloxacin (p.281·1).
Bacterial infections.

Gatiquin Oz Kit *Cipla, India.*
Tablets, gatifloxacin (p.281·1); tablets, ornidazole (p.843·1).

Gatt *Cadila, India.*
Gatifloxacin (p.281·1).
Bacterial infections.

Gaudil *Craveri, Arg.*
Rosiglitazone (p.459·3).
Diabetes mellitus.

Gaveril *Bevo, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Gavicid *Grisi, Mex.†.*
Aluminium (p.2254·1); magnesium (p.1678·3).
Gastric hyperacidity.

Gavilast *Reckitt Benckiser, UK.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; heartburn.

Gaviscon
Note. This name is used for preparations of different composition.
Key, Arg.†.
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Nicholas Piramal, India.
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2).
Formerly contained alginic acid, magnesium trisilicate, aluminium hydroxide, and sodium bicarbonate.
Gastro-oesophageal reflux; hiatus hernia.

Reckitt Benckiser, Belg.
Chewable tablets: Sodium alginate (p.2141·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Nordic Drugs, Fin.; Nordic, Swed.; Novartis Consumer, Switz.†.
Chewable tablets: Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Abdominal distension; gastric hyperacidity; gastro-oesophageal reflux; heartburn; hiatus hernia.

SmithKline Beecham Consumer, USA.
Chewable tablets: Dried aluminium hydroxide gel (p.1706·2); magnesium trisilicate (p.1744·1); alginic acid (p.2140·3); sodium bicarbonate (p.1673·2).
Heartburn.

Reckitt Benckiser, Fr.
Chewable tablets; oral suspension: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Reckitt Benckiser, NZ.
Infant oral powder: Magnesium alginate (p.2141·1); sodium alginate (p.2141·1).
Gastro-oesophageal reflux.

Nordic, Swed.
Mixture: Sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Reckitt Benckiser, Austral.; Ali, Turk.
Oral liquid: Sodium alginate (p.2141·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux.

Reckitt Benckiser, Hong Kong.
Oral liquid: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2).
Flatulence; gastro-oesophageal reflux; heartburn; hiatus hernia.

Nordic Drugs, Norw.
Oral liquid: Sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus insufficiency; regurgitation.

Reckitt Benckiser, NZ.
Oral liquid: Sodium alginate (p.2141·1); calcium carbonate (p.1714·1); potassium bicarbonate (p.1673·1) or sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux.

SmithKline Beecham Consumer, USA.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); sodium alginate (p.2141·1).
Dyspepsia.

Reckitt Benckiser, S.Afr.
Oral liquid (aniseed): Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Reckitt Benckiser, S.Afr.
Oral liquid (peppermint): Sodium alginate (p.2141·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Novartis Consumer, Belg.
Oral powder: Alginic acid (p.2140·3); algeldrate (p.1706·2); sodium bicarbonate (p.1673·2).
Formerly contained alginic acid, aluminium hydroxide, magnesium trisilicate, and sodium bicarbonate.
Gastro-oesophageal reflux.

Novartis Consumer, Belg.; Reckitt Benckiser, Cz.
Oral suspension: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2).
Formerly contained sodium alginate, calcium carbonate, and sodium bicarbonate in *Belg.*
Gastro-oesophageal reflux; heartburn.

Essex, Chile; Reckitt Benckiser, Irl.; Novartis Consumer, Ital.; Reckitt Benckiser, Malaysia; Medcor, Neth.; Reckitt Benckiser, Singapore; Reckitt Benckiser, UK†.
Oral suspension: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Dyspepsia; gastro-oesophageal reflux; heartburn; hiatus hernia.

Nordic Drugs, Denm.; Nordic Drugs, Fin.
Oral suspension: Sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Novartis Consumer, Switz.†.
Oral suspension: Sodium alginate (p.2141·1); potassium bicarbonate (p.1673·1); calcium carbonate (p.1714·1).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Reckitt Benckiser, Austral.; Reckitt & Colman, Cz.†; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Irl.; Novartis Consumer, Ital.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Singapore; Ali, Turk.; Reckitt Benckiser, UK†.
Tablets: Alginic acid (p.2140·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Dyspepsia; flatulence; gastro-oesophageal reflux; heartburn; hiatus hernia.

Essex, Chile; Medcor, Neth.
Tablets: Alginic acid (p.2140·3); sodium bicarbonate (p.1673·2); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Nordic Drugs, Denm.; Nordic Drugs, Norw.
Tablets: Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux; heartburn; hiatus hernia; regurgitation.

GSK, Fr.†.
Tablets: Alginic acid (p.2140·3); sodium alginate (p.2141·1); dried colloidal aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2); magnesium trisilicate (p.1744·1).
Gastro-oesophageal reflux.

Pohl, Ger.
Tablets: Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2).
Gastro-oesophageal reflux; heartburn.

Gaviscon Advance
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.; Pohl, Ger.; Reckitt Benckiser, Irl.; Novartis Consumer, Ital.; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore; Reckitt Benckiser, UK.
Sodium alginate (p.2141·1); potassium bicarbonate (p.1673·1).
Dyspepsia; gastro-oesophageal reflux; heartburn; hiatus hernia.

Reckitt Benckiser, S.Afr.
Sodium alginate (p.2141·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Gaviscon Cool *Reckitt Benckiser, UK.*
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Heartburn.

Gaviscon Double Action *Reckitt Benckiser, UK.*
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastric hyperacidity; gastro-oesophageal reflux.

Gaviscon Double Strength *Reckitt Benckiser, Austral.*
Sodium alginate (p.2141·1); potassium bicarbonate (p.1673·1); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Gaviscon Extra Strength *GSK Consumer, USA.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Dyspepsia.

Gaviscon Extra Strength Relief Formula
SmithKline Beecham Consumer, USA.
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); simeticone (p.1770·2).
Hyperacidity.

Gaviscon Heartburn Relief
Note. This name is used for preparations of different composition.
GSK Consumer, Canad.
Oral liquid: Sodium alginate (p.2141·1); aluminium hydroxide (p.1706·2).
Gastro-oesophageal reflux; heartburn.

GSK Consumer, Canad.
Tablets: Alginic acid (p.2140·3); magnesium carbonate (p.1743·1).
Gastro-oesophageal reflux; heartburn.

Gaviscon Infant *Reckitt Benckiser, Irl.; Reckitt Benckiser, UK.*
Magnesium alginate (p.2141·1); sodium alginate (p.2141·1).
Formerly known as Infant Gaviscon and contained aluminium hydroxide, magnesium alginate, and sodium alginate.
NOTE. In view of its high sodium content this preparation should not be used in premature infants or in situations where excess water-loss is likely, such as fever or high room-temperature; some sources have recommended that it should be avoided altogether in children less than 6 months of age.
Gastro-oesophageal reflux.

Gaviscon Lemon *Reckitt Benckiser, Irl.*
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn.

Gaviscon Prevent *GSK Consumer, Canad.†.*
Cimetidine (p.1716·2).

Gavisconell
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Fr.
Chewable tablets: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Reckitt Benckiser, Fr.
Oral suspension: Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux.

Gavistal *Meprofarm, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Gaviz
Note. This name is used for preparations of different composition.
Uniao Quimica, Braz.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Uniao Quimica, Braz.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Gastric hyperacidity.

Gavox *Guardian, Indon.*
Mebendazole (p.148·3).
Worm infections.

Gayabeksin *Casel, Turk.*
Sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Gayaben *Bilim, Turk.*
Sulfogaiacol (p.1573·2); guaifenesin (p.1561·3); diphenhydramine hydrochloride (p.577·2); pentoxyverine citrate (p.1567·3).
Respiratory-tract congestion.

Gaz Away *Swiss Herbal, Canad.*
Alpha galactosidase A (p.2252·3).

Gazim X *CTI, Israel.*
Simeticone (p.1770·2).
Flatulence.

Gazyme *Cifarma, Braz.*
Dimeticone (p.1770·2).
Flatulence.

GB 100 *Sigma, Arg.*
Ginkgo biloba (p.2311·1); choline bitartrate (p.1934·2); glycoside flavonoids (p.2304·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

GB Tablets *Potter's, UK.*
Leptandra virginica; euonymus (p.1730·1); lappa root (p.2330·3).
Abdominal discomfort; gall bladder disorders.

GBN *Malaysia Chemist, Singapore†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

G-Dil *Gap, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

GDP-Ex *Cypress, USA†.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

GE *Thai Otsuka, Thai.*
A range of carbohydrate and electrolyte infusions (p.1922·1).
Parenteral nutrition.

Geabatan *Gea, Fin.†.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Gealcid *GSK, Pol.*
Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

Geangin *Gea, Denm.; Hexal, Neth.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; obstructive cardiomyopathy.

Geasalol *Gea, Denm.†.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Geavir *Hexal, Denm.; Gea, Fin.†; Hexal, Swed.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Gebauers Spray & Stretch *Gebauer, USA.*
Tetrafluoroethane (p.1689·3); pentafluoropropane.
Muscle spasm; myofascial pain; sports injury.

Gebrozil *Cooper (Κοπερ), Gr.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Geclicin *IQFA, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Gedizil *Bevo, Gr.*
Gemfibrozil (p.1295·3).

Gedol *Lafi, Chile†.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Gedun *Duncan, Arg.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Geeox *Cadila, India.*
Doxycycline (p.267·1).
Bacterial infections.

Geepenil *Orion, Fin.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Geffer *Bayer, Ital.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2); potassium citrate (p.1673·2); citric acid (p.2284·1); tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2).
Gastrointestinal disorders associated with hyperacidity.

Gefilus PeptidiTutteli *Valio, Fin.†.*
Infant feed (p.1922·1).
Cow's milk and soya protein allergy.

Gefin *Genericon, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Gefina *Sandoz, Fin.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Geftinat *Natco, India.*
Gefitinib (p.727·1).
Non-small cell lung cancer.

Gefulvin *Sanofi Synthelabo, Turk.*
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Gegorvit *Fher, Ital.*
Multivitamin and mineral preparation with ginseng (p.1922·1).
Nutritional supplement.

Gegrip *Gemballa, Braz.†.*
Paracetamol (p.108·1); pentoxyverine (p.1567·3); phenylephrine (p.1568·1); carbinoxamine (p.570·2).
Cold and influenza symptoms.

Gehwol Fungizid
Note. This name is used for preparations of different composition.
Gerlach, Ger.†.
Cream: Undecenoic acid monoethanolamide (p.549·3); chloroxylenol (p.1640·2); tetrabromocresol (p.1663·3).
Fungal foot infections.

Gerlach, Ger.†.
Topical liquid: Undecenoic acid monoethanolamide (p.549·3); chloroxylenol (p.1640·2); tetrabromocresol (p.1663·3); copper-trolamine complex.
Fungal foot infections.

Gerlach, Ger.†.
Topical powder: Bromosalicylic acid (p.1612·3); undecenoic acid monoethanolamide (p.549·3); chloroxylenol (p.1640·2); tetrabromocresol (p.1663·3).
Fungal foot infections.

Gehwol Huhneraugen Pflaster *Gerlach, Ger.†.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Callouses; corns.

Gehwol Huhneraugen-Pflaster extra stark
Gerlach, Ger.
Salicylic acid (p.1612·2).
Calluses; corns.

Gehwol Huhneraugen-Tinktur *Gerlach, Ger.*
Salicylic acid (p.1612·2); glacial acetic acid (p.2244·2).
Callouses; corns.

Gehwol Nagelpilz *Gerlach, Ger.†.*
Zinc chloride (p.1999·1); bromosalicylic acid (p.1612·3); salicylic acid (p.1612·2); undecenoic acid monoethanolamide (p.549·3).
Fungal nail infections.

Gehwol Schalpaste *Gerlach, Ger.*
Salicylic acid (p.1612·2).
Callouses; corns.

Geklimon *Gea, Denm.†; Gea, Fin.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Gel 4000 *Bruschettini, Ital.*
Hypromellose (p.2144·2).
Aid in ophthalmic procedures.

Gel a la consoude *Phytomed, Switz.*
Comfrey (p.2286·3); calendula (p.2273·1); St John's wort (p.422·3); echinacea (p.2298·1); mint (p.2391·3).
Soft-tissue injuries.

Gel a l'Acetotartrate d'Alumine Defresne *Sanofi-Aventis, Fr.†.*
⊗ Hesperidin methyl chalcone (p.2305·2); aluminium acetotartrate (p.2255·1).
Soft-tissue injury; venous insufficiency.

Gel Antiinflamatorio *Sertex, Arg.†.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.

Gel de Calamine *Bailleul, Fr.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Skin irritation.

Gel Carpina *Alcon, Arg.†.*
Pilocarpine hydrochloride (p.1884·3).
Production of miosis.

Gel Creme Protector *Vichy, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3) ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Gel Kam *Scherer, USA.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Gel Rubefiant *Ducray, Fr.*
Methyl nicotinate (p.85·3); essential oils.
Scalp disorders.

Gel Secante *Johnson & Johnson, Venez.†.*
Isopropyl alcohol (p.1650·3).
Seborrhoea.

Gela *Febena, Ger.†.*
Silicon dioxide (p.2146·2).
Nail and hair disorders.

Gelacet *Hermal, Austria; Boots Healthcare, Switz.†.*
⊗ Vitamin A acetate (p.1973·1); cystine (p.1937·1); gelatin (p.1072·1).
Hair and nail disorders.

Gelacet N *Hermal, Ger.†.*
⊗ Vitamin A acetate (p.1973·1); cystine (p.1937·1); gelatin (p.1072·1).
Hair and nail disorders.

Gelacid
Note. This name is used for preparations of different composition.
Xeragen, S.Afr.
Oral suspension: Sodium bicarbonate (p.1673·2); sodium alginate (p.2141·1); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Xeragen, S.Afr.
Tablets: Alginic acid (p.2140·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Gelafundin *Braun, Arg.; Braun, Ger.; Braun, Indon.; Buminusantara, Indon.; Pisa, Mex.; Braun, Thai.*
⊗ Gelatin polysuccinate (p.1072·1) with electrolytes.
Extracorporeal circulation; haemodilution; hypotension; hypovolaemia; plasma volume expansion.

Gelafundina *Braun, Port.*
⊗ Modified gelatin (p.1072·1) with electrolytes.
Extracorporeal circulation; hypovolaemia.

Gelafusal *Serum-Werk Bernburg, Ger.*
⊗ Gelatin polysuccinate (p.1072·1) in electrolytes.
Hypovolaemia; pre-operative haemodilution.

Gelamel *Morado, Ital.†.*
Royal jelly (p.2382·1).
Nutritional supplement.

Gelan Plus *Chinoin, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Gelar *Arlex, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastric hyperacidity.

Gelargin *Zentiva, Cz.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Gelasim *Berman, Mex.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastric hyperacidity.

Gelaspon *Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.†.*
⊗ Gelatin (p.1072·1).
Haemorrhage; haemostatic.

Gelastypt *Aventis, Ger.*
⊗ Gelatin (p.1072·1).
Haemorrhage.

Gelax *Sidus, Arg.*
Psyllium (p.1737·1); senna (p.1769·2); bran (p.1712·3).
Constipation.

Gelbag *Ioltech, Ger.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Gelbiotic *LKM, Arg.*
Fusidic acid (p.279·3).
Bacterial skin infections.

Gelbiotic Plus *LKM, Arg.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Bacterial skin infections.

Gelcain *Valma, Chile.*
Lidocaine (p.1862·3).
Local anaesthesia.

Gelcavit *Gelcaps, Mex.*
A range of vitamin and mineral preparations (p.1922·1).

Gelcen *Intramed, Gr.; Centrum, Spain.*
Capsaicin (p.32·3).
Muscle and joint pain.

Gelclair *Trima, Israel†; Sinclair, UK; EKR, USA.*
Enoxolone (p.50·1); povidone (p.2146·1); sodium hyaluronate (p.2320·1).
Painful mouth lesions.

Gelconordin *Nordin, Mex.*
Lamium album; aloe vera (p.1588·2).
Abdominal inflammation.

Gelcotar
Note. This name is used for preparations of different composition.
Quinoderm, Irl.†.
Shampoo: Coal tar (p.1616·2); cade oil (p.1616·1).
Scalp disorders.

Quinoderm, Irl.†.
Topical gel: Coal tar (p.1616·2); tar (p.1616·2).
Dermatitis; psoriasis.

Geldako *Gelpharma, Mex.*
Ketorolac (p.75·2).
Pain.

Geldene *Pfizer, Fr.*
Piroxicam (p.117·3).
Soft-tissue disorders; tendinitis.

Geldex *Gelpharma, Mex.*
Calcitriol (p.1986·2).

Geldrox *Pharmacos, Mex.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Geldrox Plus *Pharmacos, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastric hyperacidity.

Gelee Solaire Haute Protection *Clarins, Canad.†.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1).
Sunscreen.

Gelenkja *OTW, Ger.†.*
Homoeopathic preparation.

Gelerit *Koni-Cofarm, Chile.*
Erythromycin (p.269·2).
Acne.

Gelestra *Abiogen, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Gelfilm *Pharmacia, Austral.†; Pfizer, Canad.; Pharmacia, NZ; Pharmacia, Neth.†; Upjohn, USA.*
⊗ Gelatin (p.1072·1).
Haemostatic dressing; prevention of surgical adhesions.

Gelfix *Bros, Gr.*
Collagen type 1 lyophilised (p.2286·1).
Topical haemostatic.

Gelflex *Bunker, Braz.*
Turpentine oil (p.2406·3); methyl salicylate (p.85·3); camphor (p.2273·2); mustard oil (p.2349·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Gelfoam *Pfizer, Austral.; Pharmacia, Belg.†; Pharmacia, Braz.; Pfizer, Canad.; Pfizer, Chile; Pharmacia, Hong Kong†; Pharmacia, Israel; Pfizer, Malaysia; Pharmacia, NZ; Pharmacia, Neth.†; Pfizer, Philipp.; Pfizer, Singapore; Upjohn, USA; Pfizer, Venez.*
⊗ Gelatin (p.1072·1).
Haemorrhage; haemostatic; minor bleeding during surgery; skin ulcers; wounds.

Gelhist *Econolab, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Nasal congestion; rhinitis.

Gelicain *DeltaSelect, Ger.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Gelictar *Nigy, Fr.†.*
Ichthammol (p.1599·1).
Seborrhoeic dermatitis.

Gelictar Fort *Nigy, Fr.*
Ichthammol (p.1599·1); salicylic acid (p.1612·2); resorcinol (p.1612·1).
Keratinisation disorders; seborrhoeic dermatitis.

Gelidina *Astellas, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Gelidol *Gelpharma, Mex.*
Ibuprofen (p.64·2).
Fever; pain.

Gelidral *Spefar, Venez.†.*
Aluminium hydroxide (p.1706·2).
Antacid.

Gelifundol *Biogam, Arg.†; Biotest, Austria; Biotest, Cz.†; Biotest, Ger.†; Biotest, Hong Kong†; Human, Hung.†; Mednostica, S.Afr.†; Biotest, Thai.*
⊗ Oxypolygelatin (p.1075·2).
Hypovolaemia; resuspension of concentrated erythrocytes; shock; thrombosis prophylaxis.

Gelilact *Lagepha, Belg.*
Carmellose sodium (p.2142·1).
Vomiting in infants.

Geliofil *Effik, Fr.; Effik, Ital.*
Lactic acid (p.2329·3); glycogen.
Vaginal disorders; vaginal hygiene.

Geliperm *Geistlich, UK.*
Hydrogel dressing.
Burns; ulcers; wounds.

Gelipur *Curasan, Ger.*
Benzyl alcohol (p.1631·3); hypromellose (p.2144·2).
Instrument lubricant in diagnostic procedures.

Gel-Kam *Colgate-Palmolive, Ital.†; Colgate-Palmolive, USA.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis; sensitive gums.

Gel-Larmes *Thea, Fr.*
Carbomer 974 P (p.2141·3).
Dry eyes.

Gel-Lido *Apsen, Braz.*
Lidocaine (p.1862·3).
Local anaesthesia.

Gel-Malicid *Am-Europharma, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Gelmax *EMS, Braz.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Gelmicin *Collins, Mex.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Gelminthic *Vonnace, Philipp.*
Pyrantel embonate (p.155·1).
Worm infections.

Geloalumin *Gelos, Spain.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity and flatulence.

GeloBacin *Pohl, Ger.*
1,3-Butanediol; glycerol (p.2314·2); dimethyl sulfoxide (p.2022·1); dexpanthenol (p.2362·1).
Ear disorders.

Geloboll *Sinterapico, Braz.†.*
Turpentine; methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Gelobronchial *Pohl, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh.

Gelocaps *Biofarma, Turk.*
Capsicum oleoresin (p.2276·2); camphor (p.2273·2); cineole (p.2282·3); menthol (p.2340·1); turpentine oil (p.2406·3).
Musculoskeletal and joint pain.

Gelocast *BSN, Ital.*
Zinc oxide (p.1621·2).
Medicated dressing.

Gelocatil *Gelos, Cz.†; Gelos, Port.; Gelos, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Gelocatil Codeina *Gelos, Spain.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Geloderm *SMB, Chile.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; malodorous wounds; rosacea.

Gelodiet *DHN, Fr.*
⊗ Gelatin (p.1072·1); sucrose (p.1969·2).
Dehydration.

Gelodrox *Gelos, Spain.*
Dried aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1).
Gastrointestinal hyperacidity.

Gelodual *Gelos, Spain†.*
Dried aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1).
Gastrointestinal hyperacidity.

Gelodurat
Note. This name is used for preparations of different composition.
Pohl, Neth.
Myrtol (p.2349·3).
Bronchitis.

Pohl, Ger.
Ointment: Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Bronchitis; cold symptoms.

Pohl, Ger.†.
Oral drops: Eucalyptus oil (p.2301·2).
Bronchitis; cold symptoms.

Gelofeno *Gelos, Spain.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Geloforte *Forder, Arg.†.*
Glycolic acid (p.1598·1).

Gelofrix *Delta, Braz.*
Turpentine oil (p.2406·3); methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Gelofusin *Braun, Austria; Braun, Turk.*
⊗ Gelatin (p.1072·1) with electrolytes.
Haemodilution; hypovolaemia; plasma volume expansion.

Gelofusine *Braun, Austral.; Braun, Belg.†; Braun, Chile; Braun, Cz.; Braun, Fin.; Braun, Fr.†; Bioser (Βιοσερ), Gr.; Braun, Hong Kong; Braun, Hung.; Braun, Ital.; Biomed, NZ; Braun, Neth.; Braun, Pol.; Braun, Port.; Braun, S.Afr.; Braun, Singapore†; Braun, Thai.; Braun, UK; Behrens, Venez.*
⊗ Succinylated gelatin (p.1072·1) in sodium chloride.
Extracorporeal circulation; haemodilution; hypotension; hypovolaemia; leucapheresis; plasma volume expansion; shock.

Gelogrip *Gelos, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

Gelol *DM, Braz.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); turpentine oil (p.2406·3); mustard oil (p.2349·2); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Musculoskeletal and joint disorders.

Gelolagar *Fada, Arg.*
Atracurium (p.1905·3).
Competitive neuromuscular blocker.

Gelomyrtol *Sanova, Austria; Pohl, Ger.; Lavipharm, Gr.; Pohl, Hong Kong; Pohl, Thai.*
Myrtol (p.2349·3).
Bronchitis; cough; respiratory-tract disorders; sinusitis.

Gelonasal *Pohl, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Gelonevral *Teuto, Braz.†.*
Turpentine oil (p.2406·3); methyl salicylate (p.85·3); camphor (p.2273·2); mustard oil (p.2349·2); menthol (p.2340·1); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Musculoskeletal and joint disorders.

Gelonic *Dermoteca, Port.*
Amino-acid and mineral preparation (p.1922·1).
Hair and nail disorders.

Gelonida *Godecke, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Gelonida NA
Note. This name is used for preparations of different composition.
Godecke, Ger.†.
Oral liquid: Sodium salicylate (p.124·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Cold symptoms; fever; neuralgia; neuritis; pain.

Godecke, Ger.†.
Suppositories: Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Gelopectose *DB, Fr.*
Pectin (p.2145·2); microcrystalline cellulose (p.2143·1); hydrated colloidal silicon dioxide (p.2146·3).
Regurgitation in infants.

Geloplasma *Fresenius Kabi, Arg.; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Neth.; Fresenius Kabi, UK.*
⊗ Gelatin (p.1072·1).
Hypovolaemia; hypovolaemic shock; plasma volume expansion; shock.

Gelora *Reckitt Benckiser, India.*
Choline salicylate (p.36·3).
Cold sores; denture irritation; mouth ulcers.

GeloSitin *Pohl, Ger.*
Sesame oil (p.2386·1); Cetiol CC; orange oil (p.2357·2); lemon oil (p.2332·3).
Nasal congestion.

Gelostretch *BSN, Ital.*
Zinc oxide (p.1621·2).
Medicated dressing.

Gelotralib *Gelos, Port.*
Tramadol hydrochloride (p.130·3).
Pain.

Gelotricar *Gelos, Spain.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastrointestinal hyperacidity.

Gelotrisin *Gelos, Spain.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; gastrointestinal hyperacidity; peptic ulcer.

Gelovis *Amnol, Ital.*
Centella (p.1592·3); capsicum (p.2276·2); menthol (p.2340·1).
Lymphoedema; venous insufficiency.

Gelovital *Pohl, Ger.*
Cod-liver oil (p.1935·2).
Tonic.

Gelox *Beaufour, Fr.*
Montmorillonite; aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Gelpan *Neckerman, Braz.†.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Gelparine *Streuli, Switz.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial inflammation and thrombosis.

Gelpex
Note. This name is used for preparations of different composition.
Parggon, Mex.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Parggon, Mex.
Tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Gel-Phan *Pierre Fabre, Fr.*
⊗ Gelatin (p.1072·1).
Fragile hair or nails.

Gelplex *Fresenius Kabi, Ital.*
⊗ Polygeline (p.1077·2) with electrolytes.
Plasma volume expansion.

Gelprim *Gelpharma, Mex.*
Nifedipine (p.1350·1).
Hypertension.

Gelsem *Medinteg, Venez.*
Aloe vera (p.1588·2); arnica (p.2260·2); aesculus (p.2248·2); chamomile (p.2279·3); calendula (p.2273·1).

Gelsemium Comp *Hevert, Ger.*
Homoeopathic preparation.

Gelsemium Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Gelsemium-Homaccord *Heel, Cz.*
Homoeopathic preparation.

Gelsica *Resinag, Switz.*
Aluminium chlorohydrate (p.1588·3).
Burns; ulcers; wounds.

Gelsolets *SMB, Chile.*
⊗ Carbomer (p.2141·3); mannitol (p.1330·2).
Dry eyes.

Gel-Stat *Geritrex, USA.*
⊗ Alcohol (p.1625·2).
Hand cleanser.

Geltazine *Cardinal, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastritis; heartburn; gastro-oesophagitis; peptic ulcer.

GelTears *Chauvin, Irl.; Bausch & Lomb, UK.*
Carbomer 980 (p.2141·3).
Dry eyes.

Gel-Tin *Young, USA.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Gelucystine *Jolly-Jatel, Fr.*
Cystine (p.1937·1).
Fragile nails and hair.

Gelufene *Cooperation Pharmaceutique, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Gelum
Note. This name is used for preparations of different composition.
Dreluso, Ger.
Oral drops; topical gel: Potassium-iron (III)-citrate-phosphate complex.
Liver disorders; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Dreluso, Ger.†.
Suppositories: Potassium-iron (III)-citrate-phosphate complex; benzocaine (p.1854·1).
Anorectal disorders.

Gelumag *Synco, Hong Kong.*
Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2).
Gastrointestinal hyperacidity; peptic ulcer.

Gelumaline *Solvay, Fr.†.*
Belladonna (p.2263·3); codeine (p.37·2); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Gelumen *Medpro, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); dried aluminium hydroxide gel (p.1706·2); light magnesium oxide (p.1744·1).
Gastric hyperacidity.

Gelumina
Note. This name is used for preparations of different composition.
Sanitas, Port.†.
Oral liquid: Aluminium hydroxide (p.1706·2).
Gastrointestinal disorders.

Menarini, Port.
Tablets: Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1).
Gastrointestinal disorders.

Geluprane *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Gelusil
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.†; Uniao Quimica, Braz.; Parke, Davis, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux.

Pfizer, Austria†; Pfizer Consumer, Ger.
Almasilate (p.1705·1).
Gastrointestinal disorders.

Pfizer Consumer, Canad.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Parke, Davis, Cz.†; Hemofarm, Rus.
Silodrate.
Dyspepsia; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Pfizer Sante, Fr.†; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia†; Pharma Dynamics, S.Afr.; Pfizer Consumer, Singapore; Pfizer, Thai.
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Gelusil Forte *Pfizer, Malaysia†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Gelusil MPS *Parke, Davis, India†; Pfizer, Indon.; Pfizer, Thai.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Bloating; dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Gelusil N *Pfizer Consumer, Switz.*
Almasilate (p.1705·1); milk powder.
Formerly known as Gelusil-Lac.
Gastrointestinal disorders.

Gelusil Plus *Pfizer, Hong Kong; Pfizer, Malaysia†; Pfizer Consumer, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Gelusil S *Pfizer Consumer, S.Afr.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn.

Gelusil Simethicone *Pfizer Consumer, Belg.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal disorders associated with hyperacidity.

Gelusil-Lac *Pfizer Consumer, Ger.*
Almasilate (p.1705·1); fat-free milk powder.
Gastrointestinal disorders.

Gely *Ipsen, Spain.*
Glycerol (p.2314·2).
Barrier preparation; lubricant.

Gem
Note.This name is used for preparations of different composition.
Nycomed, Norw.
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Iromedica, Switz.
Lozenges: Lidocaine hydrochloride (p.1862·3); tyrothricin (p.358·2); muramidase (p.2348·1); cetrimide (p.1634·1).
Mouth and throat disorders.

Iromedica, Switz.
Pastilles: Anise oil (p.2258·2); eucalyptus oil (p.2301·2); solidago root (p.2391·1); menthol (p.2340·1); liquorice (p.1740·3); benzoic acid (p.1630·2).
Coughs.

GEM 21S *Osteohealth, USA.*
Becaplermin (p.1590·1); calcium phosphate (p.1676·2).
Periodontal disease.

Gem Voyage Dragees contre les maux de voyage *Iromedica, Switz.*
Dimenhydrinate (p.576·2); caffeine (p.1116·3).
Formerly known as Dragées contre les maux de voyage formule 537.
Motion sickness.

Gemcite *Lilly, India.*
Gemcitabine hydrochloride (p.727·3).
Bladder cancer; non-small-cell lung cancer; pancreatic cancer.

Gemd *Yung Shin, Singapore†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemfi *1A, Ger.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemfibril *Siam Bheasach, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemfolid *Genepharm, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemhexal *Hexal, Austral.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemicina *Gastroenterologicos, Mex.†.*
Neomycin (p.305·1).
Gastrointestinal infections.

Gemiderma *Gemi, Pol.*
Boric acid (p.2268·1).
Skin disorders.

Gemini *Adcock Ingram, S.Afr.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Eye irritation; inflammatory eye disorders.

Gemiol Plus *SIFFRA, Ital.*
Birch leaf; abies pectinata; black currant; rose fruit; oligosaccharides; zinc gluconate (p.1922·1).
Nutritional supplement.

Gemipasmol *Geminis, Arg.†.*
Dihydrostreptomycin (p.266·1); phthalylsulfathiazole (p.315·1).
Gastrointestinal infections.

Gemistatin *Geminis, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Gemitin *SMB, Chile.*
Chloramphenicol (p.239·3).
Bacterial eye and skin infections.

Gemitin con Prednisolona *SMB, Chile.*
⊗ Chloramphenicol (p.239·3); prednisolone acetate (p.1541·1).
Bacterial skin infections; otitis externa.

Gemizol *Pacific, NZ†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemlipid *Medichrom, Gr.; FIRMA, Ital.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gemtro *Lilly, Arg.*
Gemcitabine hydrochloride (p.727·3).
Bladder cancer; breast cancer; non-small cell lung cancer; ovarian cancer; pancreatic cancer.

Gemzar *Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Spaly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Gemcitabine hydrochloride (p.727·3).
Bladder cancer; breast cancer; non-small cell lung cancer; ovarian cancer; pancreatic cancer.

Gemzil
Note.This name is used for preparations of different composition.
APT, Hong Kong.
Gemfibrozil (p.1295·3).
Cardiovascular risk reduction; hyperlipidaemias.

Pharmasant, Thai.
Captopril (p.1239·2).
Heart failure; hypertension.

Gen H-B-Vax *Aventis Pasteur, Ger.†; Chiron Behring, Ger.†; Sanofi Pasteur, Switz.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Separate preparations are available for children, for adults, and for adult dialysis patients.
Active immunisation.

Genac
Note.This name is used for preparations of different composition.
Genevrier, Fr.
Acetylcysteine (p.1548·2).
Corneal ulceration.

Goldline, USA.
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Genacol *Goldline, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Genahist *Goldline, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia; motion sickness; parkinsonism.

Genalen *Gentili, Ital.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Genalfa *INTES, Ital.*
⊗ Gentamicin sulfate (p.282·1); naphazoline nitrate (p.1565·2).
Eye infections.

Genalgen *Farmaco, Mex.†.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Genalin *BioFemme, Philipp.; Great Eastern, Thai.; Therapharma, Thai.*
Vitamin and mineral preparation (p.1922·1).

Genalmen *Gentek, Venez.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Genam *Genericon, Cz.*
Amlodipine mesilate (p.1214·2).
Angina pectoris; hypertension.

Gen-Amilazide *Genpharm, Canad.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Genapap *Goldline, USA.*
Paracetamol (p.108·1).
Fever; pain.

Genaphed *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Genaplex *Biotecnoquimica, Venez.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Genaprost *Gentili, Ital.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Genasal *Goldline, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Genasma *Alliance, S.Afr.*
⊗ Aminophylline (p.1114·2); ephedrine hydrochloride (p.1558·2).
Asthma.

Genasoft Plus Softgels *Goldline, USA†.*
Docusate sodium (p.1725·1); casanthranol (p.1715·1).
Constipation.

Genaspor *Goldline, USA.*
Tolnaftate (p.548·3).
Fungal skin infections.

Genaton
Note.This name is used for preparations of different composition.
Goldline, USA.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1).
Hyperacidity.

Goldline, USA.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2); alginic acid (p.2140·3).
Hyperacidity.

Genatrop *INTES, Ital.*
Gentamicin sulfate (p.282·1); atropine sulfate (p.1219·3).
Bacterial eye infections.

Genatuss DM *Goldline, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Genavit *General Drugs, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemia; beri-beri; nausea and vomiting during pregnancy; vitamin B deficiency.

Gen-Beclo *Genpharm, Canad.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Genbeclo *Merck, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Nasal congestion.

Gen-bee with C *Goldline, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Gencef *Genepharm, Gr.*
Cefepime (p.224·1).
Bacterial infections.

Gencefal *Llorente, Spain†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Gencin *DeltaSelect, Ger.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gencivol Compuesto *Vincenti, Venez.*
Benzydamine hydrochloride (p.27·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Gencolax *General Drugs, Thai.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Gen-Cromolyn *Genpharm, Canad.†.*
Sodium cromoglicate (p.1136·3).

Gencydo
Note.This name is used for preparations of different composition.
Weleda, Austria; Weleda, Ger.; Weleda, Switz.
Lemon (p.2332·3); cydonia.
Allergic respiratory-tract disorders; hypersensitivity reactions.

Weleda, UK.
Homoeopathic preparation.

Gendazel *General Drugs, Thai.*
Albendazole (p.139·2).
Worm infections.

Gendecon *Goldline, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Gendol *Dynamic, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Gendron *Bentley, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Genebs *Goldline, USA.*
Paracetamol (p.108·1).
Fever; pain.

Genecalcin *Genepharm, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Genecar *Genesis, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Genefacort *Genepharm, Gr.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Infected skin disorders.

Genefadrone *Genepharm, Gr.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Genefilus F19 *SIFFRA, Ital.*
Lactobacillus paracasei (p.2372·3); glucosaccharides; vitamin B substances (p.1922·1).
Nutritional supplement.

Genemicin *Diba, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genephoxal *Genepharm, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Generaid *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, UK.*
Amino-acid and protein preparation (p.1922·1).
Nutritional supplement in liver disease; porto-hepatic encephalopathy.

Generaid Plus *Scientific Hospital Supplies, Irl.*
Amino-acid, carbohydrate, and lipid preparation with vitamins and minerals (p.1922·1).
Liver disorders.

Genercin *General Drugs, Thai.*
Chloramphenicol (p.239·3).
Bacterial infections.

Generet *Goldline, USA.*
Ferrous sulfate (p.1939·3); vitamin B substances with vitamin C (p.1922·1).
Iron-deficiency anaemias.

Genergin *General Drugs, Thai.*
Dipyrone (p.49·2).
Fever; pain.

Generix-T *Goldline, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Generlog *General Drugs, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Generman *Altana, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).

Genes Vit *Wassen, Ital.†.*
A range of vitamin and mineral preparations (p.1922·1).

Genesa *Gensia, USA†.*
⊗ Arbutamine hydrochloride (p.1216·3).
Pharmacological cardiac stress test.

Geneserine *Eisai, Fr.*
Eseridine salicylate (p.1729·1).
Dyspepsia.

Genevac-B *Serum Institute, India.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Genevis *Andromaco, Chile†.*
Ergocalciferol (p.1987·1).
Osteomalacia; rickets; vitamin D deficiency.

Genevis D2 *Andromaco, Chile†.*
Ergocalciferol (p.1987·1).
Osteomalacia; rickets; vitamin D deficiency.

Genexin *Genedec, Port.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Genexol *Pezomed, Hung.; Samyang, Singapore.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Geneye Extra *Goldline, USA†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

GenFlex *Inogen, Austral.*
Glucosamine hydrochloride (p.2313·2).
Osteoarthritis.

GenFlex 3 *Inogen, Austral.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); neptune krill oil.
Osteoarthritis; rheumatoid arthritis.

GenFlex Plus *Inogen, Austral.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Genflox *Cadila, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Genflox TZ *Cadila, India.*
Ofloxacin (p.310·2); tinidazole (p.848·3).
Bacterial infections; protozoal infections.

Genfol *Cadila, India.*
Ferric ammonium citrate (p.1938·1); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Tonic.

Gen-Formula *Thai Otsuka, Thai.*
Preparation for enteral nutrition (p.1922·1).

Gengigel
Esme, Arg.; Qualiphar, Belg.; Ricerfarma, Malaysia; Oraldent, UK.
Hyaluronic acid (p.2320·1).
Mouth lesions.

Abbott, Port.†.
Sodium hyaluronate (p.2320·1).
Mouth lesions.

Gengisyl *Master, Chile.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Gengivario *Ogna, Ital.†.*
Myrrh (p.2349·2); rhatany root (p.2378·3).
Astringent.

Gen-Glybe *Genpharm, Canad.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gengraf *Abbott, Arg.†; Abbott, Braz.; Abbott, Chile; Abbott, Hong Kong; Abbott, Malaysia; Abbott, NZ; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott, USA.*
Ciclosporin (p.1822·2).
Atopic eczema; endogenous uveitis; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection.

GenHeal *Pediatrica, Philipp.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Prader-Willi syndrome; Turner's syndrome.

GenHevac B *Sanofi Pasteur, Fr.; Aventis Pasteur, Turk.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

Geniad *TS, Ital.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Geniceral *Casasco, Arg.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Geniclor *Boniscontro & Gazzone, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Genicol *Guardian, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Genimox *Ecobi, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Genin *General Drugs, Thai.*
Quinine sulfate (p.612·3).
Malaria.

Geniol *GSK, Arg.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Geniol AP *GSK, Arg.†.*
Aspirin (p.20·3).
Pain.

Geniol Flex *GSK, Arg.†.*
Trolamine salicylate (p.132·3).
Musculoskeletal, joint, and peri-articular disorders.

Geniol Prevencion *GSK, Arg.*
Aspirin (p.20·3).
Fever; pain; thromboembolic disorders.

Geniol SC sin Cafeina *GSK, Arg.*
Aspirin (p.20·3).
Fever; pain.

Geniolito *GSK, Arg.†.*
Aspirin (p.20·3).
Fever; pain.

Geniol-P *Mintlab, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Genisol *Teofarma, Ital.*
Piroctone olamine (p.1610·1); disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3).
Seborrhoeic dermatitis.

Genite *Goldline, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Genitoflox *IQB, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Gen-K *Goldline, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Genkova *Sons, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genlac *Arrow, Austral.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Gen-Lac *Genpharm, Canad.*
Lactulose (p.1738·2).
Constipation.

Genlip *Teofarma, Ital.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Gen-Medroxy *Genpharm, Canad.*
Medroxyprogesterone acetate (p.2113·1).

Genmisin *Tum, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genmox *Cadila, India.*
Amoxicillin (p.202·2).
Bacterial infections.

Gen-Nitro *Genpharm, Canad.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Genocin *General Drugs, Thai.*
Chloroquine phosphate (p.599·3).
Amoebiasis; malaria.

Genoclom *Lapi, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Genocolan *Craveri, Arg.*
Lactulose (p.1738·2).
Constipation; gastrointestinal infections; hepatic encephalopathy.

Genofort *Tocogino, Mex.*
Progesterone (p.2125·1); estradiol (p.2097·2).

Genogris *Labesfal, Port.*
Nimodipine (p.1357·2).

Genolaxante *Craveri, Arg.*
Phenolphthalein (p.1762·1); aloes (p.1705·2); simeticone (p.1770·2).
Constipation.

Genolon *Guardian, Indon.*
⊗ Gentamicin sulfate (p.282·1); fluocinolone acetonide (p.1531·3).
Skin disorders.

Genoptic *Allergan, Austral.; Allergan, Hong Kong; Allergan, NZ; Allergan, S.Afr.†; Allergan, Singapore; Allergan, USA.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Genoral *Pfizer, Austral.*
Estropipate (p.2101·2).
Menopausal disorders; oestrogen deficiency.

Genotonorm *Pfizer, Belg.; Pfizer, Chile; Pfizer, Fr.; Pfizer, Spain.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Prader-Willi syndrome; Turner's syndrome.

Genotropin *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pharmacia, UK; Pharmacia, USA; Pfizer, Venez.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; idiopathic short stature; Prader-Willi syndrome; short children born small for gestational age; Turner's syndrome.

Genovox *Kleva, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Genox *Alphapharm, Austral.; Alphapharm, Malaysia; Pacific, NZ.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Genoxacin *Genom, Braz.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Genoxal *Kampel Martian, Arg.†; Baxter, Mex.†; Baxter, Spain.*
Cyclophosphamide (p.702·1).
Auto-immune disorders; malignant neoplasms; transplant rejection.

Genoxal Trofosfamida *Baxter, Spain.*
Trofosfamide (p.783·3).
Malignant neoplasms.

Genozil *Boniscontro & Gazzone, Ital.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Genozym *BMS, Arg.*
⊗ Clomifene citrate (p.2086·1).
Endometrial cancer; endometriosis; female infertility; uterine fibroids.

Gen-Payne *Adcock Ingram, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Genphenil *Generics Pharmacal, Philipp.*
Chloramphenicol (p.239·3).
Bacterial infections.

Genpril *Goldline, USA†.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Genprin *Goldline, USA.*
Aspirin (p.20·3).
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Genprol *Sandoz, Spain.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder.

Genprot *Cadila, India.*
Protein hydrolysate; nicotinamide; minerals (p.1922·1).
Tonic.

Genquin *Seng, Thai.*
Gentamicin sulfate (p.282·1); bacitracin (p.210·3); clioquinol (p.254·1); glycine; threonine; cystine.
Infected skin disorders.

Genrex *Rayere, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genser *Serral, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genser Sweet *Genser, Arg.*
Aspartame (p.1930·1); acesulfame potassium (p.1928·1).
Sugar substitute.

Gensil *General Drugs, Thai.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Genspir *Vocate, Gr.†.*
Paracetamol (p.108·1).
Fever; pain.

Gensulin M10, M20, M30, M40, or M50 *Bioton, Pol.*
⊗ Mixtures of soluble neutral insulin (human) 10%, 20%, 30%, 40%, or 50% and isophane insulin (human) 90%, 80%, 70%, 60%, or 50% (p.443·2).
Diabetes mellitus.

Gensulin N *Bioton, Pol.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Gensulin R *Bioton, Pol.*
⊗ Neutral insulin (human) (p.443·2).
Diabetes mellitus.

Gensumycin *Sanofi-Aventis, Fin.; Aventis, Norw.; Aventis, Swed.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gensyn *Ipca, India†.*
Gentamicin (p.284·2).
Bacterial infections.

Genta *CT, Ger.; Grin, Mex.; M & H, Thai.; Umeda, Thai.; Ulagay, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genta Gobens *Normon, Port.; Normon, Spain.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentac *Sanval, Braz.†; Samakeephaesaj, Thai.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentacid *Vonnace, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Gentacidin *Novartis Ophthalmics, USA.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentacin *Church, Mex.†; Olan-Kemed, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentacip *Cipla, India.*
Gentamicin (p.284·2).
Bacterial eye infections.

Gentacip D *Cipla, India.*
⊗ Gentamicin (p.284·2); dexamethasone (p.1526·1).
Infected eye disorders.

Gentacler *Monserrat, Arg.*
⊗ Gentamicin sulfate (p.282·1); hydrocortisone acetate (p.1535·2); ketoconazole (p.539·1).
Infected skin disorders.

Gentacoll *Schering-Plough, Denm.; Schering-Plough, Fin.*
Gentamicin sulfate (p.282·1).
Bone infections.

Gentacort
Note. This name is used for preparations of different composition.
Allergan, Braz.
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye disorders.

Novartis, Ital.
⊗ Gentamicin sulfate (p.282·1); fluorometholone (p.1532·3).
Infected eye disorders.

Gentacortin *Merck, Indon.*
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Gentacream *Epifarma, Ital.*
Gentamicin sulfate (p.282·1).
Infected skin disorders.

Gentacyl *Darya-Varia, Indon.*
Gentamicin sulfate (p.282·1).
Eye infections.

Gentaderm *Cassara, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Gentadex *Farmex, Gr.*
⊗ Dexamethasone (p.1526·1); gentamicin (p.284·2).
Eye infections.

Gentadexa *Alcon Cusi, Malaysia; Alcon, Port.; Alcon Cusi, Spain.*
⊗ Gentamicin sulfate (p.282·1); dexamethasone sodium phosphate (p.1526·2); tetryzoline hydrochloride (p.1574·1).
Infected eye and ear disorders with inflammation.

Gentagram *Legrand, Braz.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentagut *Bilim, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial eye and ear infections.

Gentak *Akorn, USA.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gental *General Drugs, Thai.; Julphar, UAE.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gental-F *General Drugs, Thai.*
⊗ Gentamicin sulfate (p.282·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Gentalin *Labesfal, Port.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentalline *Schering-Plough, Fr.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentalyn *Schering-Plough, Chile; Schering-Plough, Ital.; Schering-Plough, Venez.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentalyn Beta *Schering-Plough, Ital.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Gentamed
Medochemie, Malaysia†.
Gentamicin (p.284·2).
Bacterial infections.

Kocak, Turk.
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamedical *Medical, Spain†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamen *Fournier, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamerck *Merck, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamicil
Greenpharma, Braz.
Gentamicin (p.284·2).
Bacterial infections.

Behrens, Venez.†.
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genta-Micron *Alcon, Mex.*
Gentamicin (p.284·2).
Bacterial eye infections.

Gentamil *Ducto, Braz.; Bruluart, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamilan *Meyer, Venez.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamina *Schering-Plough, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamisin *Tunggal Idaman, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamival *Mayne, Spain.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentamytrex *Mann, Ger.; Mann, Malaysia†; Tramedico, Neth.; Bausch & Lomb, Philipp.; Mann, Pol.†; Mann, Singapore.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentanacin *Loren, Mex.†.*
Gentamicin (p.284·2).
Bacterial infections.

Genta-Oph *Seng, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentapat *Parggon, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Gentapharma *Fada, Arg.*
Gentamicin (p.284·2).
Bacterial infections.

Gentaplex *Liptis, USA.*
Lyophilised fish roe; ginkgo biloba (p.2311·1).
Decreased libido in men.

Gentaren *Andromaco, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Gentarim *Rimsa, Mex.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentaron *Ariston, Braz.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentasol
Note. This name is used for preparations of different composition.
Monserrat, Arg.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Ocusoft, USA.
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentasolon *Ikapharmindo, Indon.*
⊗ Fluocinolone acetonide (p.1531·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Gentason *Wagner, Hung.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye disorders.

Gentasone *Schering-Plough, Chile.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Bacterial eye infections; infected external ear disorders.

Gentasporin *Pharmaceutical Co, India.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentatenk *Biotenk, Arg.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentatrim *Trima, Israel.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Gentax *Agepha, Austria; Luper, Braz.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentazaf Z *Zafiro, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentazol *Unipharm, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Genteal
Note. This name is used for preparations of different composition.
Novartis Ophthalmics, Arg.; Novartis, Braz.; Novartis Ophthalmics, Canad.; Novartis, Chile; Novartis, Hong Kong; Novartis, Israel; Novartis, Mex.; Novartis, NZ; Novartis, Philipp.; Novartis Ophthalmics, Singapore; Novartis, Thai.; Novartis Ophthalmics, USA.
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Novartis, Ger.; Novartis, Ital.
Hypromellose (p.2144·2) (p.1622·2).
Dry eyes; wetting solution for contact lenses.

Novartis, Indon.; Novartis, Venez.
Eye drops: Hypromellose (p.2144·2).
Dry eyes.

Novartis, Indon.; Novartis, Venez.
Eye gel: Hypromellose (p.2144·2); carbomer 980 (p.2141·3).
Dry eyes.

Genteal Lubricant *Novartis, Austral.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Genteal Moisturising *Novartis, Austral.*
Hypromellose (p.2144·2); carbomer (p.2141·3).
Dry eyes; eye irritation.

Genthaver *Biosel, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentiabron *BMS, Arg.†.*
Clofedanol hydrochloride (p.1554·2); ambroxol hydrochloride (p.1550·3); pseudoephedrine sulfate (p.1571·2); astemizole (p.567·2).
Respiratory-tract disorders with increased or viscous mucus.

Gentialoquin *Collins, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Gentibioptal *Farmila, Ital.†.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Genticin *Roche, Irl.; Roche, UK.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genticina *Pharmacia, Spain†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genticol *Craveri, Arg.†; SIFI, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Genticyn *Nicholas Piramal, India.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Genticyn B Eye/Ear *Nicholas Piramal, India†.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Allergic and inflammatory eye and ear disorders.

Genticyn Eye/Ear *Nicholas Piramal, India†.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections; ear infections; earache.

Genticyn HC *Nicholas Piramal, India†.*
⊗ Gentamicin sulfate (p.282·1); hydrocortisone acetate (p.1535·2).
Allergic and inflammatory eye and ear disorders.

Gentidexa
Note.This name is used for preparations of different composition.
Leti, Venez.
Eye drops: ⊗ Gentamicin sulfate (p.282·1); dexamethasone sodium phosphate (p.1526·2); tetryzoline hydrochloride (p.1574·1).
Inflammatory eye disorders with infection.

Leti, Venez.
Eye ointment: ⊗ Gentamicin sulfate (p.282·1); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Gen-Timolol *Pacific, NZ†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Gentipress *Gentili, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Gentiran *Vocate, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Gentisalyl *Maigal, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation.

Gentisone HC *Roche, Irl.; Roche, UK.*
⊗ Gentamicin sulfate (p.282·1); hydrocortisone acetate (p.1535·2).
Bacterial ear infections; otitis.

Gentisor *Cusi, Venez.†; Megat, Venez.†.*
⊗ Gentamicin (p.284·2); tetryzoline (p.1574·1).
Infected eye disorders.

Gentisul *Megat, Venez.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gentlax *Purdue, Canad.; Purdue Frederick, USA.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Gentlax S *Purdue, Canad.*
Bisacodyl (p.1710·1); docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Gentle C with Bioflavonoids *Cenovis, Austral.†.*
Calcium ascorbate (p.1984·1); lemon bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3).
Capillary disorders; cold and influenza symptoms; wounds.

Gentle Cream *Geritrex, USA.*
Emollient.
Skin disorders.

Gentle Iron *Nature's Bounty, USA.*
Ferrous bisglycinate (p.1939·1).
Iron supplement.

Gentle Tears *Euro-Med, Philipp.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Gentlees *Delamac, Austral.*
Hamamelis water (p.2318·2); glycerol; cetylpyridinium chloride (p.1635·1).
Anogenital wounds; anorectal disorders; nappy rash; nipple care.

Gent-L-Tip *Chester, Canad.†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Gentocelina *Roux-Ocefa, Arg.†.*
Metampicillin (p.298·2); gentamicin (p.284·2).
Bacterial infections.

Gentocil *Edol, Port.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentoler *Lersan, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentomil *Mayne, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gent-Ophtal *Winzer, Ger.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gentos
Note.This name is used for preparations of different composition.
Bittner, Austria; Bittner, Rus.
Homoeopathic preparation:.

Llorente, Spain†.
Clofedanol hydrochloride (p.1554·2).
Coughs.

Gentran 40 *Baxter, Canad.; Baxter, UK; Baxter, USA.*
⊗ Dextran 40 (p.1059·1) in glucose or sodium chloride.
Extracorporeal circulation; plasma volume expansion; thromboembolism prophylaxis.

Gentran 70 *Baxter, Canad.; Baxter, UK; Baxter, USA.*
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Plasma volume expansion.

Gentreks *Bilim, Turk.*
Gentamicin (p.284·2).
Bacterial infections.

Gentriderm *Seoul Pharma, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Gentrisil *Alliance, S.Afr.*
Magnesium trisilicate (p.1744·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity.

Gentrisone *Shin Poong, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Gentussin *General Drugs, Thai.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Genu-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Genuine Australian Eucalyptus Drops *Felton, Austral.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); lemon oil (p.2332·3).
Cough; nasal congestion; sore throat.

Genurat *Soria Natural, Spain.*
Bearberry (p.2263·3); betula alba (p.2266·3); pine silvestris oil (p.2368·2); calluna vulgaris.
Urinary-tract infections.

Genurin *Recordati, Hong Kong†; Recordati, Ital.; Recordati, Singapore†; Elmor, Venez.*
Flavoxate hydrochloride (p.2190·1).
Genito-urinary spasms; genito-urinary tract disorders.

Genurin-S *Sanofi-Aventis, Braz.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract spasm.

Genuxal *Asta Oncologia, Braz.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Gen-Xene *Alra, USA†.*
Dipotassium clorazepate (p.980·1).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Genziana (Specie Composta) *Dynacren, Ital.†.*
Gentian (p.2310·3); bitter orange (p.2357·1); absinthium (p.2244·1); centaury (p.2279·1).
Appetite loss.

Genzosin *Genovate, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Geo Vit H3 *Sedabel, Braz.†.*
Vitamin preparation (p.1922·1).

Geocillin *Pfizer, USA†.*
Carindacillin sodium (p.217·1).
Bacterial infections.

Geodon
Pfizer, Braz.; Pfizer, Mex.; Pfizer, S.Afr.
Ziprasidone hydrochloride (p.1036·2) or ziprasidone mesilate (p.1036·2).
Bipolar disorder; schizophrenia.

Pfizer, Gr.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Spain; Pfizer, USA.
Ziprasidone hydrochloride (p.1036·2).
Mania; schizophrenia.

Pfizer, Venez.
Ziprasidone (p.1036·2) or ziprasidone mesilate (p.1036·2).
Schizophrenia.

Geo-magnit *Biomo, Ger.†.*
Magnesium hydrogen glutamate (p.1680·1); dibasic magnesium phosphate (p.1680·1).
Magnesium deficiency.

Geomicina *Atral, Port.†.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Geomycine *Schering-Plough, Belg.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Geophagol *Sanval, Braz.*
Mebendazole (p.148·3).
Worm infections.

Ge-Oral *Kansuk, Turk.*
Sodium chloride; sodium citrate; potassium chloride; anhydrous glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Geotril *Ulagay, Turk.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Gepacod *Sanofi-Aventis, Fin.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Gepan *Pharmapol, Ger.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; coronary spasm; heart failure; myocardial infarction.

Gepeprostin *Sandoz, Arg.; Novartis, Braz.*
Bicalutamide (p.686·2).
Prostatic cancer.

Gepromi *Ivax, Mex.*
Progesterone (p.2125·1).
Female infertility; menopausal disorders; threatened miscarriage.

Geracin *Reuffer, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Gerafen *Genesis, Philipp.*
Chloramphenicol (p.239·3).
Bacterial infections.

Gerakon *Munir, Turk.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Geralen
Note.This name is used for preparations of different composition.
Gerot, Austria.
5-Methoxypsoralen (p.1607·2).
Psoriasis.

Gerot, Pol.
Methoxsalen (p.1605·1).
Mycosis fungoides; psoriasis; skin pigmentation disorders.

Geralgine
Note.This name is used for preparations of different composition.
Munir, Turk.
Injection; syrup: Dipyrone (p.49·2).
Fever; pain.

Munir, Turk.
K Tablets: Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

Munir, Turk.
P Tablets: Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Munir, Turk.
Paediatric elixir: Paracetamol (p.108·1).
Fever; pain.

Geram *Vedim, Fr.†.*
Piracetam (p.368·2).
Cerebrovascular disorders; dyslexia in children; mental function disorders in the elderly; myoclonus; vertigo.

Geramet *Gerard, Irl.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Geramox *Gerard, Irl.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Geranil *Neuropharma, Arg.†.*
Pergolide (p.813·1).
Parkinsonism.

Geranium Complexe no 108 *Lehning, Fr.*
Homoeopathic preparation.

Gerard House Reumalex *Chefaro, UK.*
Guaiacum resin (p.2317·3); cimicifuga (p.2282·1); salix (p.121·3); sarsaparilla (p.2383·3); poplar bark (p.2371·1).
Musculoskeletal and joint disorders.

Gerard House Serenity *Chefaro, UK.*
Lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Irritability; stress.

Gerard House Skin *Chefaro, UK.*
Lappa (p.2330·3); wild pansy (p.2415·2).
Eczema; skin blemishes.

Gerard House Somnus *Chefaro, UK.*
Valerian (p.2410·1); lupulus (p.2335·2); wild lettuce (p.2415·2).
Insomnia.

Gerard House Water Relief Tablets *Chefaro, UK.*
Bladderwrack (p.2384·2); clivers (p.2284·3); ground ivy (p.2317·2); lappa (p.2330·3).
Premenstrual water retention.

Geratam *UCB, Belg.; UCB, Cz.*
Piracetam (p.368·2).
Alcohol withdrawal syndrome; cerebrovascular disorders; mental function impairment; myoclonus.

Geratar *UCB, S.Afr.*
Inositol nicotinate (p.1316·1); vitamins (p.1922·1); meclozine hydrochloride (p.584·3); hydroxyzine hydrochloride (p.581·2).
Cerebrovascular disorders; nocturnal leg cramps; vertigo.

Geravim *Major, USA.*
Vitamin B substances with minerals (p.1922·1).

Geravitine *Dinafarma, Braz.†.*
Erythroxylon catuaba; muira-puama; vitamin E; vitamin B substances (p.1922·1); yohimbine hydrochloride (p.2200·2).

Gerax *Gerard, Irl.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety disorders; depression; mixed anxiety-depressive states; panic attacks; phobias.

Gerber for Moms *Novartis, Philipp.*
Nutritional supplement for pregnancy and breast feeding (p.1922·1).

Gerbin *Valeant, Spain.*
Aceclofenac (p.14·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Gercid forte *Henkel, Ger.†.*
Didecyldimethylammonium chloride (p.1642·2); isopropyl alcohol (p.1650·3).
Fungal foot infections; surface disinfection.

Gerdex *Lemery, Mex.*
Omeprazole (p.1753·1).
Acid aspiration; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gerdilium *Otto, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Geref
Serono, Austria; Serono, Gr.; Serono, Irl.; Serono, Port.†; Serono, Switz.†; Serono, UK†; Serono, USA.
⊗ Sermorelin acetate (p.1808·3).
Test for growth hormone secretion; test of pituitary function.

Serono, Fin.; Serono, Hong Kong†; Serono, Ital.; Serono, Norw.; Serono, Spain; Serono, Swed.†.
⊗ Sermorelin (p.1808·3).
Test for growth hormone secretion.

Gerelax *Gerard, Irl.; Gerard, Israel.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Geri *Gisand, Switz.*
Vitamin, mineral, and amino-acid preparation (p.1922·1) with ginseng (p.2312·1).
Formerly known as Biorganic Geri.
Dietary supplement; tonic.

Geri SS *Geritrex, USA.*
Emollient.
Dry skin disorders.

Geriacaps *Herbapol Krakow, Pol.*
Garlic (p.2309·2); ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Geriaforce
Note.This name is used for preparations of different composition.
Bioforce, Ger.
Homoeopathic preparation.

Bioforce, Switz.
Ginkgo biloba (p.2311·1).
Atherosclerosis.

Gerial B12 *Allen, Mex.*
Amino-acids and vitamin B substances with iron (p.1922·1).

Geriaplasma *Ardeypharm, Ger.†.*
Bovine heart extract (p.2337·3); bovine liver extract (p.2337·3); bovine spleen extract (p.2337·3).
Tonic.

Geriaton *Ache, Braz.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Geriatric *Herbes Universelles, Canad.; Boehringer Ingelheim, Gr.*
Multivitamin and mineral preparation (p.1922·1).
Cachexia.

Geriatric Pharmaton *Boehringer Ingelheim, Austria; Pharmaton, Israel; Boehringer Ingelheim, Thai.*
Ginseng; vitamins; minerals; lecithin (p.1922·1).
Tonic; vitamin and mineral deficiency.

Geriatrie-Mulsin *Mucos, Ger.†.*
Multivitamin preparation (p.1922·1).

Geriatrix *Natur Produkt, Pol.*
Caffeine (p.1116·3); ginseng; vitamins; minerals (p.1922·1).
Tonic.

Geriavit *Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Pol.; Pharmaton, Rus.; Pharmaton, Switz.*
Deanol tartrate; ginseng; vitamins; rutoside; minerals; lecithin (p.1922·1).
Tonic.

Geriavite *Solvay, Braz.*
Multivitamins with ginseng, inositol, and rutoside (p.1922·1).

Geribion *Soma, Braz.*
Vitamin and mineral preparation (p.1922·1).

Gericaps *Pharmadass, UK.*
Multivitamin and mineral preparation (p.1922·1).

Gericarb *Gerard, Irl.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; epilepsy; pain.

Gericin *Seid, Spain.*
Nitrendipine (p.1358·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Gericomplex *Boehringer Ingelheim, S.Afr.*
Multivitamins; minerals; dimethylaminoethanol bitartrate; ginseng (p.1922·1).
Tonic.

Geri-Dyne *Geritrex, USA.*
Iodine (p.2169·2).
Disinfectant.

Geriflox *Gerard, Irl.*
Flucloxacillin sodium (p.277·1).
Gram-positive bacterial infections.

Geri-Hydrolac *Geritrex, USA.*
Ammonium lactate (p.1589·2).
Skin disorders.

Geri-Lav Free *Geritrex, USA.*
Aloe vera (p.1588·2); chloroxylenol (p.1640·2); sodium laurilsulfate (p.2138·3).
Perineal cleanser.

Gerilide *CPH, Port.*
Nimesulide (p.95·3).
Fever; pain.

Gerilon *Cifarma, Braz.*
Vitamins; minerals; ginseng; rutoside (p.1922·1).

Gerimal *Rugby, USA.*
Codergocrine mesilate (p.363·3).
Senile dementia.

Gerimax *Dansk Droge, Rus.*
Vitamins; minerals; ginseng (p.1922·1).
Tonic.

Gerimax adultes *Merck Medication Familiale, Fr.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Gerimax enfants *Merck Medication Familiale, Fr.*
Multivitamin and mineral preparation (p.1922·1).

Gerimax Ginseng *Dansk Droge, Rus.*
Ginseng (p.2312·1).
Tonic.

Gerimax Junior *Dansk, Israel.*
Multivitamin and mineral preparation (p.1922·1).

Gerimax NF *Dansk, Israel.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Gerimax Plus *Nycomed, Austria.*
A multivitamin preparation (p.1922·1) with ginseng (p.2312·1).
Tonic.

Gerimax Tonique *Merck Medication Familiale, Fr.*
Ginseng (p.2312·1).
Tonic.

Gerimed *Fielding, USA.*
Multivitamin and mineral preparation (p.1922·1).
Osteoporosis.

Gerin *Legrand, Braz.*
Amino acids; minerals; vitamins (p.1922·1); ginseng (p.2312·1).
Tonic.

Gerinap *Gerard, Irl.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Geriot *Goldline, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Geriplen *Diba, Mex.†*
Vitamin and mineral preparation (p.1922·1).

Geri-Plus *Herbes Universelles, Canad.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

Geriprost *Ivax, Arg.*
Terazosin hydrochloride (p.1410·2).

Geri-Protect *Geritrex, USA.*
Perineal barrier ointment.

Geri-Silk *Geritrex, USA.*
Liquid paraffin (p.2030·3); lanolin oil (p.2033·2).
Bath additive; dry skin disorders.

Geriso *Sidefarma, Port.*
Linoleic acid (p.2308·2); vitamin A; vitamin E; pyridoxine; lecithin (p.1922·1).
Atherosclerosis; hypercholesterolaemia; vascular disorders.

Geri-Soft *Geritrex, USA.*
Emollient.
Skin disorders.

Geritol *SmithKline Beecham Consumer, USA.*
Ferric ammonium citrate (p.1938·1); vitamin B substances with methionine (p.1922·1).
Iron-deficiency anaemias.

Geritol Complete *SmithKline Beecham Consumer, USA.*
Iron (p.1949·1); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Geritol Extend *SmithKline Beecham Consumer, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Geriton *Gerbex, Canad.*
Vitamin B substances, calcium, and iron (p.1922·1).

Geritonic *Geriatric Pharm. Corp., USA.*
Ferric ammonium citrate (p.1938·1); liver fraction (p.2337·3); vitamin B substances and minerals (p.1922·1).
Iron-deficiency anaemias.

Gerivent *Gerard, Irl.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Gerivite *Goldline, USA.*
Multivitamin and mineral preparation (p.1922·1).

Gerivites *Rugby, USA†.*
Ferrous sulfate (p.1939·3); vitamin B substances with vitamin C (p.1922·1).
Iron-deficiency anaemia.

Gerivix *Neo Quimica, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Gerlecit *Iromedica, Switz.†*
Vitamin and mineral preparation with pollen extracts and lecithin (p.1922·1).
Tonic.

Germacid *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Sodium fusidate (p.279·3).
Bacterial skin infections.

Germanin *Bayer, Ger.*
Suramin sodium (p.847·1).
Onchocerciasis; trypanosomiasis.

Germentin *Gerard, Irl.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Germex *Lennon, S.Afr.*
Nitrofurazone (p.309·1).
Bacterial skin infections; burns; ulcers; wounds.

Germic *Finadiet, Arg.†*
Rimantadine (p.904·3) or rimantadine hydrochloride (p.904·2).
Influenza A.

Germicid *EGIS, Hung.†*
Aminophenazone (p.19·1); hydroxyquinoline sulfate (p.2323·1).
Cold and influenza symptoms.

Germicid-C *EGIS, Hung.*
Aminophenazone (p.19·1); phenobarbital (p.492·2).
Fever; pain.

Germicidin *IMS, Ital.*
Benzalkonium chloride (p.1629·1).
Surface and instrument disinfection.

Germisdin Antiseptico *Isdin, Port.*
Antiseptic cleanser for skin and hair.

Germisdin Higiene Intima *Isdin, Port.*
Preparation for vaginal hygiene.

Germolene
Note. This name is used for preparations of different composition.
Bayer Consumer, UK.
Cream: Chlorhexidine gluconate (p.1635·3); phenol (p.1656·1).
Burns; skin irritation; wounds.

Group, S.Afr.
Ointment: Zinc oxide (p.1621·2); methyl salicylate (p.85·3); phenol (p.1656·1); menthol (p.2340·1); octafonium chloride (p.1654·2).
Burns; skin irritation; wounds.

Bayer Consumer, UK.
Ointment: Zinc oxide (p.1621·2); methyl salicylate (p.85·3); octafonium chloride (p.1654·2); phenol (p.1656·1).
Burns; skin irritation; wounds.

Group, S.Afr.
Topical liquid: Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Burns; wounds.

Bayer Consumer, UK.
Topical spray: Chlorhexidine gluconate (p.1635·3); phenol (p.1656·1).
Formerly contained triclosan and dichlorophen.
Burns; skin irritation; wounds.

Bayer Consumer, UK†.
Topical wipes: Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Germoloids
Note. This name is used for preparations of different composition.
Bayer Consumer, UK.
Cream; ointment; suppositories: Lidocaine hydrochloride (p.1862·3); zinc oxide (p.1621·2).
Haemorrhoids.

Bayer Consumer, UK†.
Topical wipes: Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); menthol (p.2340·1).
Haemorrhoids.

Germoloids HC *Bayer Consumer, UK.*
⊗ Hydrocortisone (p.1535·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Germose *Besins, Fr.†*
Sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); grindelia (p.2317·2); crataegus (p.2289·1); peppermint (p.1761·2); thyme (p.2401·1).
Respiratory-tract congestion.

Germosept *Medipharm, Chile.*
Benzalkonium chloride (p.1629·1).
Disinfection of instruments and skin.

Germozero Clean *Chefaro, Ital.*
Benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1).
Skin disinfection.

Germozero Dermo *Chefaro, Ital.*
Benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1); alkyl isoquinoline bromide.
Wound disinfection.

Germozero Plus *Chefaro, Ital.*
Benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1).
Wounds disinfection.

Gernebcin *Infectopharm, Ger.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Gernel *Gerbex, Canad.*
Cresol (p.1641·1); zinc oxide (p.1621·2).

Gero H3 *Sedabel, Braz.†*
Multivitamins, amino acids, and minerals with erythroxylon catuaba and adenosine (p.1922·1).

Gero H3 Aslan *Phoenix, Arg.†; Chefaro, Ger.*
Procaine hydrochloride (p.1869·1); benzoic acid; potassium disulfite; sodium phosphate (p.1922·1).
Tonic.

Geroaslan H3 *Sanova, Austria.*
Procaine hydrochloride (p.1869·1).
Tonic.

Geroderm *Sinclair, Ital.*
Triclosan (p.1665·2).
Skin cleansing.

Geroderm Zolfo *Avantgarde, Ital.†*
Sulfur (p.1614·1); lactic acid (p.2329·3); triclosan (p.1665·2).
Skin cleansing in acne.

Gerodorm *Gerot, Austria; Gerot, Cz.; Gerot, Hung.*
Cinolazepam (p.977·3).
Sleep disorders.

Gerodyl *Hexal, Neth.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; rheumatoid arthritis; Wilson's disease.

Gerofen *Munir, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Geroforte *IMA, Braz.*
Multivitamins with guarana and erythroxylon catuaba (p.1922·1).

Gerogelat *Metochem, Austria.*
Vitamin A palmitate (p.1973·1); tocoferil acetate (p.1992·3).
Hearing loss; mucous membrane disorders; tinnitus; vitamin A and E deficiency.

Gerolamic *Gerot, Austria.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Gerolin *CT, Ital.*
Citicoline sodium (p.2283·3).
Parkinsonism.

Geromycin *Gerolymatos, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Geronpol *Hasco-Lek, Pol.*
Ginseng; troxerutin; deanol tartrate; vitamins; minerals (p.1922·1).
Tonic.

Gerontex *Marjan, Braz.†*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Gerontin *Pharmonta, Austria.*
Procaine hydrochloride (p.1869·1); caffeine (p.1116·3).
Tonic.

Geroplus *Recalcine, Chile†.*
Codergocrine mesilate (p.363·3).
Mental function impairment.

Gerosim *Gerot, Austria.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Geroten *Gerard, Irl.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Gerotralin *Gerot, Hung.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Gerotrex H3 *Bunker, Braz.*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Gerovit *EGIS, Hung.*
Multivitamin preparation (p.1922·1).

Gerovital *EMS, Braz.*
Ginseng; rutoside; vitamins; minerals (p.1922·1).
Nutritional supplement.

Gerovital H3 *Sanova, Austria; Sicomed, Hong Kong.*
Procaine hydrochloride (p.1869·1).
Tonic.

Gerovital Zdrovit *Natur Produkt, Pol.*
Crataegus; motherwort; vitamins; minerals (p.1922·1).
Tonic.

Geroxalen *Galderma, Denm.†; Gerot, Hung.†; Sanofi Synthelabo, Neth.; Galderma, Norw.†; Liba, Turk.*
Methoxsalen (p.1605·1).
Eczema; mycosis fungoides; psoriasis; vitiligo.

Gerozac *Gerard, Irl.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Gerskin *YSP, Malaysia; Yung Shin, Singapore.*
Magnesium oxide (p.1744·1); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Gertac *Gerard, Irl.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gertalgin *Faran, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Gertemycin *Faran, Gr.*
Cefatrizine (p.221·3) or cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Gertges Pain Powders *Technikon, S.Afr.*
Aspirin (p.20·3); caffeine citrate (p.1116·3).
Fever; pain.

Gertocalm *Faran, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Gertotus *Faran, Gr.*
Butamirate (p.1553·1).
Cough.

Gervaken *Kendrick, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Gerviton *Welti, Switz.†*
Multivitamin and mineral preparation (p.1922·1).

Gerxidin *Rowe-Fleming, Venez.†*
Ciprofloxacin (p.243·3).
Bacterial infections.

GES 45 *Diele, Fr.; Milupa, Switz.*
Glucose; sucrose; potassium chloride; sodium citrate; sodium chloride (p.1672·2).
Diarrhoea; gastro-enteritis; oral rehydration therapy.

Gesamtnahrlosung *Fresenius Kabi, Austria.*
A range of amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusions (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Gesica *Unison, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint inflammation; pain.

Gesicain *Sarabhai Piramal, India.*
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Gesidine *Lilly, Gr.; Stada, Port.*
Vindesine sulfate (p.788·2).
Malignant neoplasms.

Gesiprox *Kalbe, Singapore†.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Geslutin *Asofarma, Mex.*
Progesterone (p.2125·1).
Benign breast disorders; dysfunctional uterine haemorrhage; female infertility; habitual or threatened miscarriage; menopausal disorders.

Gestabil *Combiphar, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Gestadinona *Schering, Braz.*
Hydroxyprogesterone caproate (p.2110·3); estradiol valerate (p.2097·3).
Endometriosis; menopausal disorders; menstrual disorders.

Gestaferron *Arlex, Mex.*
Ferrous fumarate (p.1938·3).
Anaemias.

Gestafortin *Merck, Ger.†*
Chlormadinone acetate (p.2084·3).
Endometriosis; menstrual disorders.

Gestageno
Note. This name is used for preparations of different composition.
Elea, Arg.
Hydroxyprogesterone acetate (p.2110·3).
Female infertility; hypertrichosis; menstrual disorders; premature labour; threatened or recurrent miscarriage.

Elea, Mex.
Progesterone (p.2125·1).
Benign breast disorders; female infertility; menopausal disorders; threatened miscarriage.

Gestakadin *Kade, Ger.*
Norethisterone acetate (p.2119·3).
Menopausal disorders; menstrual disorders.

Gestamag *Metiska, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Duodenitis; dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Gestamater *Wyeth, Spain†.*
Multivitamin and mineral preparation (p.1922·1).

Gestamestrol N *Hermal, Ger.†*
Chlormadinone acetate (p.2084·3); mestranol (p.2116·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women.

Gestapuran *Leo, Fin.; Leo, Swed.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menopausal disorders; menstrual disorders.

Gestar *Polfa Pabianice, Pol.*
Megestrol acetate (p.2114·3).
Breast cancer; uterine cancer.

Gestarelle *IPRAD-Sante, Fr.*
A range of multivitamin and mineral preparations (p.1922·1).

Gestatest *Polychaco, Arg.†*
Pregnancy test (p.2372·1).

Gestavit *Recalcine, Chile.*
Multivitamin and mineral preparation (p.1922·1).

Gester *Merck, Arg.*
Progesterone (p.2125·1).
Benign breast disorders; female infertility; menopausal disorders; menstrual disorders; threatened or recurrent miscarriage.

Gestid
Note. This name is used for preparations of different composition.
Ranbaxy, Rus.
Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Antacid; flatulence.

Ranbaxy, Singapore†.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Ranbaxy, Singapore†.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Gestiferrol *Kela, Belg.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemias; dietary supplement during pregnancy and lactation.

Gestinol *Libbs, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Gestocal *Gache, Venez.†.*
Ferrous gluconate (p.1939·1); calcium phosphate (p.1676·2); vitamins (p.1922·1).
Dietary supplement in pregnancy and lactation.

Gestodelle *Mithra, Belg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Gestofam *Otto, Indon.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Gestofeme *Mithra, Belg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Gestomikron *Adamed, Pol.*
Medroxyprogesterone acetate (p.2113·1).
Female infertility; menopausal disorders; metrorrhagia.

Gestone *Ferring, Israel; NZ Medical & Scientific, NZ; Paines & Byrne, Thai.†; Nordic, UK.*
Progesterone (p.2125·1).
Adjunct in infertility disorders; dysfunctional uterine bleeding; threatened or recurrent miscarriage.

Gestonette *Sandoz, Denm.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Gestoral *Novartis, Fr.†; IFET (ΙΦΕΤ), Gr.†.*
Medroxyprogesterone acetate (p.2113·1).
Cancer of breast, kidney, and endometrium; contraception; endometriosis; menopausal disorders.

Gestradiol *Neo Quimica, Braz.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Gestrelan *Biolab Sanus, Braz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Gestrocon *Neo Quimica, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Get In *Cinetic, Arg.*
Lubricating gel.

Getamisin *Deva, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Getasin *Gunsa, Turk.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Gets-It
Note. This name is used for preparations of different composition.
Schering-Plough, Braz.†.
Salicylic acid (p.1612·2); fir balsam Oregon; betacarotene; acetone.
Keratinisation disorders.

Oakhurst, USA.
Salicylic acid (p.1612·2); zinc chloride (p.1999·1).
Hyperkeratosis.

Getup *Rafarm, Gr.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Gevatran *Merck-Lipha, Fr.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral and cerebral vascular disorders.

Gevilon *Pfizer, Austria; Parke, Davis, Cz.†; Orion, Fin.; Parke, Davis, Ger.; Pfizer, Switz.*
Gemfibrozil (p.1295·3).
Cardiovascular risk reduction; hyperlipidaemias.

Gevirol *Gerbex, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Gevrabon *Lederle, USA.*
Vitamin B substances with minerals (p.1922·1).

Gevral *Wyeth Consumer, Braz.; Lederle, USA.*
Multivitamin and mineral preparation (p.1922·1).

Gevral Instant Protein *Whitehall, Irl.†; Whitehall-Robins, Switz.†.*
Multivitamin, mineral, and protein preparation (p.1922·1).
Tonic.

Gevral Protein *Lederle, USA.*
Dietary protein supplement (p.1922·1).

Gevral Proteina *Wyeth, Mex.†; Wyeth, Venez.†.*
Vitamin, mineral, and protein supplement (p.1922·1).
Nutritional supplement.

Gevral T *Lederle, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Gevramycin *Schering-Plough, Spain.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Gevramycin Topica *Schering-Plough, Spain.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections; ulcers.

Gewacalm *Nycomed, Austria.*
Diazepam (p.986·3).
Anxiety disorders; eclampsia; neuroses; panic attacks; phobias; premedication; skeletal muscle spasm; sleep disorders; status epilepticus.

Gewadal *Nycomed, Austria; Nycomed, Rus.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Gewamol *Nycomed, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Gewapurol *Pharmaselect, Austria.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Gewodine *Geistlich, Switz.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); propyphenazone (p.119·3).
Fever; pain.

Gexcil *Genesis, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Geyer Complexo B *Geyer, Braz.†.*
Vitamin B substances (p.1922·1).

Geyfritz *Geymonat, Ital.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Cold symptoms; pain.

Geypirina *Proel, Gr.*
Chloramphenicol (p.239·3); sulfadiazine (p.336·2).
Bacterial eye infections.

Gezt *Richmond, Arg.*
Gemcitabine hydrochloride (p.727·3).
Bladder cancer; non small-cell lung cancer; pancreatic cancer.

G-Farlutal *Pharmacia, Ger.†.*
Medroxyprogesterone acetate (p.2113·1).
Menstrual disorders; test of ovarian function.

GFB *Umeda, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

G-Fen *General Drugs, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

GFN Phenylephrine *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs; rhinitis; sinusitis.

GFN PSE DM *Cypress, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

GFN/DM *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

GFN/DM/PE *Cypress, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

GFN/PSE *Cypress, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

GHRH *Ferring, Belg.; Ferring, Ger.; Ferring, Ital.; Ferring, Neth.; Ferring, Switz.; Ferring, UK.*
⊗ Somatorelin acetate (p.1808·3).
Diagnosis of growth hormone deficiency.

G-I *Provit, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Giamebil *Hebron, Braz.†.*
Spearmint (p.2391·3).
Smooth muscle spasm.

Gianda *Grunenthal, Ger.*
12 Capsules, estradiol valerate (p.2097·3); 14 capsules, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Giarcid *Teuto, Braz.†.*
Furazolidone (p.834·3).

Giardil *Phoenix, Arg.*
Furazolidone (p.834·3).
Giardiasis.

Giardyl *Ipca, India†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Giarlam *UCI, Braz.†.*
Furazolidone (p.834·3).
Cholera; diarrhoea; giardiasis.

Gibac *Tocogino, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Gibiflu *Metapharma, Ital.*
⊗ Flunisolide (p.1531·1).
Rhinitis.

Gibilon *Delta, Braz.*
Ginkgo biloba (p.2311·1).

Gibixen *Metapharma, Ital.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders; pain.

Gichtex *Gerot, Austria.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Gichtex plus *Gerot, Austria.*
Allopurinol (p.552·2); benzbromarone (p.555·2).
Gout; hyperuricaemia.

Gidroxyurea *Pliva, Rus.*
Hydroxycarbamide (p.729·1).

Gifaril P *Wander, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Giflorex *Errekappa, Ital.*
Lactobacillus casei var *rhamnosus* (p.2372·3); maltodextrin (p.1955·3); fructose (p.1945·1); vitamin B substances (p.1922·1).
Maintenance of gastrointestinal flora.

Gigasept Med *Schulke & Mayr, Ger.†.*
Didecyldimethylammonium chloride (p.1642·2); phenoxypropanol (p.1657·2); aminoalkylglycine.
Instrument disinfection.

Gigatrom *Medilusa, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Gigemet *Loeffler, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Gilax *Mergers Drugfil, Philipp.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders; nausea; vomiting.

Gilemal *Enzypharm, Austria; Zentiva, Hung.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gilex *Rekah, Israel.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; mixed anxiety depressive states.

Giloba *Mega Lifesciences, Malaysia.*
Ginkgo biloba (p.2311·1).
Circulatory disorders.

Gilphex TR *Gil, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Gilt *Lacoer, Ger.*
Clotrimazole (p.530·1).
Fungal skin infections.

Giltuss TR *Gil, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Gilucor *Solvay, Ger.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Giludop *Solvay, Denm.; Solvay, Gr.; Solvay, Swed.*
Dopamine hydrochloride (p.1273·2).
Shock.

Gilurytmal *Solvay, Austria; Solvay, Cz.†; Solvay, Ger.*
Ajmaline (p.1206·2).
Arrhythmias.

Gilutens *Solvay, Belg.†.*
Moxonidine (p.1345·1).
Hypertension.

Gimabrol *Collins, Mex.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Gimalxina *Collins, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ginacol *Arex, Venez.*
Benzydamine (p.27·3).
Vaginal inflammation.

Ginaikos *Solvay, Ital.*
Estradiol (p.2097·2).
Oestrogen deficiency.

Ginal Cent *Beta, Arg.*
Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); centella (p.1592·3); polymyxin B sulfate (p.317·3).
Vulvovaginal infections.

Ginal Gel *Beta, Arg.†.*
Vaginal moisturiser.
Vaginal dryness.

Ginarsan *Ivax, Arg.*
⊗ Tamoxifen citrate (p.772·3).

Ginatex *Baliarda, Arg.*
Estradiol (p.2097·2).
Menopausal disorders.

Ginazol *Gelcaps, Mex.*
Miconazole nitrate (p.541·3).
Fungal or Gram-positive bacterial vulvovaginal infections.

Ginbiloba *Bunker, Braz.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Gincaps *Medix, Mex.†.*
Ginseng (p.2312·1).
Tonic.

Gincare *YSP, Malaysia; Yung Shin, Singapore.*
Ginkgo biloba (p.2311·1).
Circulation disorders; peripheral vascular disorders.

Gincobem *Cifarma, Braz.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function disorders.

Gincoben *Ipsen, Port.*
Ginkgo biloba (p.2311·1).
Dementia.

Gincolin *Teuto, Braz.*
Ginkgo biloba (p.2311·1).

Ginconazol *Hebron, Braz.†.*
Terconazole (p.548·1).
Fungal vaginal infections.

Gincosan *Boehringer Ingelheim, Chile; Pharmaton, Cz.; Pharmaton, Switz.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Mental function impairment.

Gincuran *Bioplanta, Ger.†.*
Ginkgo biloba (p.2311·1).
Intermittent claudication; mental function disorders; tinnitus; vertigo.

Gine Canesten *Bayer, Spain.*
Clotrimazole (p.530·1).
Balanitis; vulvovaginal candidiasis.

Gine Heyden *Squibb, Spain†.*
Amphotericin B (p.523·2); tetracycline hydrochloride (p.347·2).
Vulvovaginal infections.

Gine Zalain *Cantabria, Spain.*
Sertaconazole nitrate (p.546·1).
Vulvovaginal candidiasis.

Gineane *Teuto, Braz.*
Norethisterone acetate (p.2119·3); estradiol (p.2097·2).
Menopausal disorders.

Gineburno *Dovalle, Braz.†.*
Estrone (p.2101·2); aminophenazone (p.19·1); black haw (p.2267·1).
Dysmenorrhoea.

Ginec *Klinger, Braz.†.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); nystatin (p.543·2); tinidazole (p.848·3).

Ginecopast *Pasteur, Chile.*
Miconazole nitrate (p.541·3); tinidazole (p.848·3).
Fungal balanitis; vulvovaginal infections.

Ginecopast Dual *Pasteur, Chile.*
Miconazole nitrate (p.541·3); tinidazole (p.848·3).
Balanitis; vulvovaginal candidiasis.

Ginecosid
Note. This name is used for preparations of different composition.
Vargas, Venez.
Injection: Progesterone (p.2125·1); estradiol (p.2097·2).
Amenorrhoea.

Vargas, Venez.
Tablets: ⊗ Normethandrone (p.2123·1); methyloestradiol (p.2098·3).
Amenorrhoea.

Ginecoside
Note. This name is used for preparations of different composition.
Darrow, Braz.†.
Injection: Progesterone (p.2125·1); estradiol (p.2097·2).
Menopausal disorders.

Darrow, Braz.†.
Tablets: ⊗ Normethandrone (p.2123·1); methyloestradiol (p.2098·3).
Menopausal disorders.

Ginecrin *Abbott, Spain.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroma.

Ginedak *Organon, Braz.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

Ginedazol *Laboratorios Chile, Chile.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Ginedazol Dual *Laboratorios Chile, Chile.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Ginedermofix *Ferrer, Spain.*
Sertaconazole nitrate (p.546·1).
Vulvovaginal candidiasis.

Ginediol *Elea, Arg.*
Norethisterone enantate (p.2120·1); estradiol valerate (p.2097·3).
Combined injectable contraceptive.

Ginedisc *Schering, Braz.†; Schering, Mex.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Ginedisc 50 Plus *Schering, Braz.†.*
Patch 1, estradiol (p.2097·2); patch 2, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders.

Gineflor *Medestea, Ital.*
Ibuprofen isobutanolammonium (p.65·2).
Gynaecological disorders.

Ginefolin *Gynopharm, Chile.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Ginejuvent *Juventus, Spain.*
Benzalkonium chloride (p.1629·1); calcium lactate (p.1676·1); lactic acid (p.2329·3); chamomile (p.2279·3).
Vulvovaginal candidiasis; vulvovaginal trichomoniasis.

Ginelea *Elea, Arg.; Elea, Mex.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ginelea T *Elea, Arg.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Ginemaxim *Knop, Chile.*
Cimicifuga (p.2282·1).
Menopausal disorders; menstrual disorders; osteoporosis.

Ginenorm *Aesculapius, Ital.*
Ibuprofen isobutanolammonium (p.65·2).
Gynaecological inflammatory disorders.

Ginera *Schering, Turk.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ginesal *Farmigea, Ital.*
Benzydamine hydrochloride (p.27·3).
Gynaecological disorders; vaginal hygiene.

Gineseptina *Lafage, Arg.†.*
Zinc phenolsulfonate (p.1621·3); tyrothricin (p.358·2); borax (p.2268·1); aluminium sulfate (p.2255·1).

Gineservice *Effik, Fr.†.*
A multivitamin and mineral preparation (p.1922·1).
Supplement for pregnancy.

Ginesse *Farmoquimica, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ginestatin *Organon, Braz.*
Metronidazole (p.837·1); nystatin (p.543·2); benzalkonium chloride (p.1629·1).
Vulvovaginal infections.

Gineton *Med-One, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Ginetris *Pharmacia, Hong Kong†.*
Chloramphenicol (p.239·3); myralact (p.1654·1); cloponone (p.1640·3).
Vaginal disorders.

Ginette *Cipla, India; Cipla-Medpro, S.Afr.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne and hirsutism in females; combined oral contraceptive.

Ginevit *Gambar, Ital.*
Vitamin and mineral preparations (p.1922·1).
Menopausal disorders; menstrual disorders.

Ginex *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Ginexin-F *SK, Singapore†.*
Ginkgo biloba (p.2311·1).
Organic brain disorders; peripheral vascular disorders; tinnitus; vertigo.

Gingeron *Baliarda, Arg.*
Ginseng; magnesium glycerophosphate; procaine hydrochloride (p.1869·1); zinc; copper; cobalt; manganese (p.1922·1).
Tonic.

Gingicain D *Aventis, Ger.*
Tetracaine (p.1871·2); benzalkonium chloride (p.1629·1).
Local anaesthesia; skin disinfection.

Gingilacer
Note. This name is used for preparations of different composition.
Andromaco, Chile†.
Mouthwash: Triclosan (p.1665·2); zinc chloride (p.1999·1).
Dental caries prophylaxis; dental hygiene.

Andromaco, Chile†.
Toothpaste: Triclosan (p.1665·2); zinc citrate (p.1999·2); enoxolone (p.50·1); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Gingiloba *1A, Ger.*
Ginkgo biloba (p.2311·1).
Dizziness; mental function disorders; peripheral vascular disorders; tinnitus.

Gingilone
Note. This name is used for preparations of different composition.
Farmasa, Braz.
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); troxerutin (p.2305·1); ascorbic acid (p.1983·3); benzocaine (p.1854·1).
Mouth disorders.

Teofarma, Spain.
⊗ Ascorbic acid (p.1983·3); cortisone acetate (p.1524·2); neomycin sulfate (p.305·1); rutoside (p.2305·1).
Bleeding gums; mouth ulcers; stomatitis.

Gingio *Sandoz, Cz.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; tinnitus.

Gingisan
Note. This name is used for preparations of different composition.
Teva, Israel.
Mouthwash: Chamomile (p.2279·3); eucalyptus (p.2301·2); liquorice (p.1740·3).
Mouth disorders.

Teva, Israel.
Ointment: Chamomile (p.2279·3); eucalyptus (p.2301·2); liquorice (p.1740·3); benzocaine (p.1854·1).
Mouth disorders.

Gingium *Salutas, Cz.†; Hexal, Ger.; Sandoz, Hung.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; dizziness; headache; intermittent claudication; mental function disorders; tinnitus.

Gingivan *Provita, Austria.*
Tyrothricin (p.358·2); thymol (p.1664·3); pancreatin (p.2360·1) lauromacrogol 400 (p.1916·1).
Mouth disorders.

Gingivitol N *Hennig, Ger.*
Hydrastis (p.2321·3).
Inflammatory disorders of the mouth.

Gingkan *Medikon, Indon.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Gingo A *Eagle, Austral.†.*
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); eleutherococcus senticosis (p.2386·3); liquorice (p.1740·3); choline bitartrate (p.1934·2); cayenne (p.2276·2); nicotinic acid (p.1957·3); potassium phosphate (p.1682·2).

Gingobeta *Betapharm, Ger.*
Ginkgo biloba (p.2311·1).
Dizziness; headache; mental function disorders; peripheral vascular disorders; tinnitus.

Gingobil *Tripharma, Turk.*
Ginkgo biloba (p.2311·1).
Dementia; peripheral vascular disorders.

Gingohexal *Hexal, Austria.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; cervical syndrome.

Gingol *Kwizda, Austria.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; cervical syndrome.

Gingopret *Bionorica, Ger.*
Ginkgo biloba (p.2311·1).
Headache; mental function disorders; peripheral vascular disorders; tinnitus; vertigo.

Gingosol *Ecosol, Switz.*
Ginkgo biloba (p.2311·1).
Mental function impairment.

Gingo-Ther *Laboratorios Chile, Chile†.*
Ginkgo biloba (p.2311·1); siberian ginseng (p.2386·3); myrtillus (p.2349·3).
Cerebral and peripheral vascular disorders.

Gingviton *Sam Chun Dang, Singapore.*
Multivitamin and mineral preparation with ginseng and lecithin (p.1922·1).

Ginil
Note. This name is used for preparations of different composition.
Marfarma, Ital.
Topical liquid: Soya (p.1965·3); mimosa tenuiflora.

Marfarma, Ital.
Vaginal tablets: Lactobacillus acidophilus (p.2372·3); lactic acid (p.2329·3).

Ginjal *Cowik, Pol.*
Hippocampus coronatus; methylthioninium chloride (p.1450·3); Java tea (p.2328·2); ginseng (p.2312·1); sonchus arvensis; strobilanthus deyerianus.
Renal calculi.

Ginkan
Note. This name is used for preparations of different composition.
Baliarda, Arg.
Pessaries: Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); centella (p.1592·3).
Vaginal infections.

Baliarda, Arg.
Tablets: Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Ginkapran *Yungjin, Singapore.*
Ginkgo biloba (p.2311·1).
Cerebral disorders; peripheral vascular disorders.

Ginkgo biloba comp *Hevert, Ger.*
Homoeopathic preparation.

Ginkgo Biloba Forte *Lafarmen, Arg.*
Ginkgo biloba (p.2311·1); thiamine; zinc (p.1922·1).
Dietary supplement; mental function disorders.

Ginkgo Biloba Memo Diates *Provefarma, Arg.*
Ginkgo biloba (p.2311·1); guarana (p.2416·1); thiamine (p.1922·1).
Dietary supplement.

Ginkgo Biloba Plus *Eagle, Austral.†.*
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); eleutherococcus senticosis (p.2386·3); ginseng (p.2312·1).
Peripheral circulatory disorders; tinnitus.

Ginkgo Complex *Blackmores, Austral.†.*
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); ginseng (p.2312·1); *d*-alpha tocoferil acid succinate (p.1993·1).
Cerebral and peripheral vascular disorders.

Ginkgo Forte *ISA, Arg.*
Ginkgo biloba (p.2311·1); vitamin B substances (p.1922·1).
Dietary supplement.

Ginkgo Plus Herbal Plus Formula 10 *Vitelle, Austral.†.*
Ginkgo biloba (p.2311·1); ginger (p.1732·3); potassium phosphate (p.1682·2); magnesium oxide (p.1744·1).
Peripheral vascular disorders.

Ginkgo Plus Vivo-Livo *Panpharma, Hong Kong†.*
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); garlic (p.2309·2).
Peripheral and cerebral circulatory disorders.

Ginkgobakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Ginkgocard *Phytofarm Kleka, Pol.*
Crataegus (p.2289·1); ginkgo biloba (p.2311·1).
Fatigue; peripheral vascular disorders.

Ginkgoforce
Note. This name is used for preparations of different composition.
Weber & Weber, Ger.†.
Homoeopathic preparation.

Ikapharmindo, Indon.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Ginkgold *Schwabe, Hung.*
Ginkgo biloba (p.2311·1).
Dizziness; headache; intermittent claudication; mental function disorders; tinnitus.

Ginkgomax *Dansk Droge, Pol.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Ginkgo-PS *Usana, Hong Kong†; Usana, Singapore.*
Ginkgo biloba (p.2311·1); lecithin (p.2332·2).
Dietary supplement; mental function disorders.

Ginkgorell *Sanorell, Ger.*
Homoeopathic preparation.

Ginkoba
Note. This name is used for preparations of different composition.
Nikkho, Braz.; Fher, Ital.
Ginkgo biloba (p.2311·1).
Mental function disorders; vascular disorders.

Quest, Canad.†.
Ginseng (p.2312·1); ginkgo biloba (p.2311·1).

Ginkoba Active *Fher, Ital.*
Ginkgo biloba (p.2311·1); guarana (p.2416·1).
Tonic.

Ginkobil *Infabra, Braz.†; Ratiopharm, Ger.*
Ginkgo biloba (p.2311·1).
Headache; mental function disorders; peripheral vascular disorders; tinnitus; vascular disorders; vertigo.

Ginkocer *Ranbaxy, Malaysia†; Ranbaxy, Philipp.*
Ginkgo biloba (p.2311·1).
Cerebral insufficiency; peripheral circulation disorders; vertigo.

Ginkodilat *Sandoz, Ger.*
Ginkgo biloba (p.2311·1).
Headache; intermittent claudication; mental function disorders; tinnitus; vertigo.

Ginkofar *Biofarm, Pol.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Ginkofarma *Farmaervas, Braz.†.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Ginkoftal
Note. This name is used for preparations of different composition.
Tubilux, Ital.
Bioflavonoids (p.2304·1); ginkgo biloba (p.2311·1).
Eye disorders; nutritional supplement.

Tubilux, Port.†.
Ginkgo biloba (p.2311·1).
Circulatory disorders.

Ginkogink *Beaufour, Fr.*
Ginkgo biloba (p.2311·1).
Mental function impairment in the elderly.

Ginkogreen *Greenpharma, Braz.*
Ginkgo biloba (p.2311·1).

Ginkokan *Farmasan, Ger.†.*
Ginkgo biloba (p.2311·1).
Intermittent claudication; mental function disorders; tinnitus; vertigo.

Ginkolab *Multilab, Braz.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Ginkolin *Duopharma, Hong Kong.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral circulatory disorders.

Ginkomed *Cimed, Braz.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Ginkona *Teguhsindo, Indon.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Ginkoplus *Fontovit, Braz.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Ginkopur *Spitzner, Ger.*
Ginkgo biloba (p.2311·1).
Dizziness; headache; intermittent claudication; mental function disorders; tinnitus.

Ginkor *Beaufour, Fr.*
Ginkgo biloba (p.2311·1); troxerutin (p.2305·1).
Peripheral vascular disorders.

Ginkor Fort *Beaufour-Ipsen, Cz.; Beaufour, Fr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Beaufour-Ipsen, Rus.; Ipsen, Thai.*
⊗ Ginkgo biloba (p.2311·1); heptaminol hydrochloride (p.2319·1); troxerutin (p.2305·1).
Haemorrhoids; peripheral vascular disorders; venous insufficiency.

Ginkor Gel *Beaufour-Ipsen, Rus.*
Ginkgo biloba (p.2311·1); troxerutin (p.2305·1).
Superficial phlebitis; venous insufficiency.

Ginkoret *Tubilux, Ital.*
Ginkgo biloba (p.2311·1); vitamins; lutein (p.1922·1).
Circulatory disorders.

Ginkosen *Tai Guk, Singapore.*
Ginkgo biloba (p.2311·1).
Circulatory disorders.

Ginkovital *Pharmadass, UK.*
Ginkgo biloba (p.2311·1).

Gino Ciriax *Investi, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Genito-urinary tract infections.

Gino Conazol *Kinder, Braz.*
Tioconazole (p.548·2).
Fungal vaginal infections.

Gino Dermazine *Silvestre, Braz.*
Sulfadiazine silver (p.337·2).
Trichomoniasis; vaginal bacterial infections; vaginal candidiasis.

Gino Loprox *Sanofi-Aventis, Braz.*
Ciclopirox olamine (p.529·2).
Vulvovaginal candidiasis.

Gino Monipax *Haller, Braz.†.*
Isoconazole nitrate (p.536·2).
Vaginal infections.

Gino Pletil *Pfizer, Braz.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Gino Tralen *Pfizer, Braz.*
Tioconazole (p.548·2).
Vulvovaginal candidiasis.

Gino-Canesten *Bayer, Braz.; Bayer, Port.*
Clotrimazole (p.530·1).
Fungal vaginal infections; vaginal infections.

Gino-Cauterex *Ache, Braz.*
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1); gentamicin sulfate (p.282·1).
Vulvovaginal infections.

Gino-Clotrimix *Medley, Braz.*
Clotrimazole (p.530·1).
Vaginal infections.

Gino-Daczol *Cifarma, Braz.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

Ginoden *Schering, Ital.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ginoderm *Gynopharm, Chile.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Gino-Fibrase *Pfizer, Braz.*
Fibrinolysin (p.1287·3); dornase alfa (p.1557·1); chloramphenicol (p.239·3).
Vulvovaginal infections.

Ginoflorax *Hebron, Braz.†.*
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea; restoration of gastrointestinal flora.

Gino-Isomax *Prodotti, Braz.*
Isoconazole nitrate (p.536·2).
Vaginal infections.

Ginokan *Medikon, Indon.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Cerebral and peripheral vascular disorders; tonic.

Ginol *Tocogino, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Gino-Lotremine *Schering-Plough, Port.*
Clotrimazole (p.530·1).
Fungal vulvovaginal infections.

Ginolotricomb *Schering-Plough, Venez.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Ginometrim Oral *Nikkho, Braz.†.*
Tinidazole (p.848·3); mepyramine maleate (p.585·2).
Protozoal infections.

Ginomizol *Tocogino, Mex.†.*
Astemizole (p.567·2).

Ginoplan *Carnot, Mex.†.*
Algestone (p.2082·2); estradiol (p.2097·2).
Injectable contraceptive.

Ginorectol *Kleva, Gr.; Kleva, Singapore.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ginos *Veropharm, Rus.*
Ginkgo biloba (p.2311·1).
Vascular disorders; vestibular disorders.

Ginoseptil *Azevedos, Port.*
Povidone-iodine (p.1659·2).

Ginosutin *Organon, Braz.*
Tinidazole (p.848·3).
Vulvovaginal infections.

Ginosutin M *Organon, Braz.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Ginotarin *Bunker, Braz.*
Miconazole nitrate (p.541·3).
Fungal skin and vaginal infections.

Gino-Teracin *Neo Quimica, Braz.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).
Vaginal infections.

Gino-Tralen *Pfizer, Venez.*
Tioconazole (p.548·2).
Fungal vaginal infections.

Gino-Travogen *Bayer, Port.*
Isoconazole nitrate (p.536·2).
Fungal vulvovaginal infections.

Ginotrax *Ativus, Braz.*
Isoconazole nitrate (p.536·2).
Vaginal infections.

Gino-Trosyd *Pfizer Consumer, Ital.†; Pfizer, Port.*
Tioconazole (p.548·2).
Fungal and Gram-positive bacterial vulvovaginal infections.

Ginoxil *Euroderm-RDC, Ital.*
Urea hydrogen peroxide (p.1666·2).
Vaginal disorders; vaginal hygiene.

Ginoxil Ecoschiuma *Euroderm-RDC, Ital.*
Hamamelis (p.2318·2); aloe vera (p.1588·2); allantoin (p.1588·1).
Personal hygiene.

Ginsactiv *Azevedos, Port.†.*
Nutritional supplement (p.1922·1).

Ginsana *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim Consumer, Canad.†; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Fr.†; Boehringer Ingelheim, Ger.; Fher, Ital.; Pharmaton, Malaysia; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Pharmaton, Rus.; Pharmaton, Singapore; Fher, Spain†; GPL, Switz.; Boehringer Ingelheim, Thai.*
Ginseng (p.2312·1).
Asthenia; fatigue; tonic.

Ginsana Ton *Fher, Ital.*
Ginseng (p.2312·1); zinc (p.1999·1).
Tonic.

Ginsavit *Julphar, UAE.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Ginsavita *Bioforce, Switz.†.*
Ginseng (p.2312·1).
Tonic.

Ginseng Bioplus Diates *Provefarma, Arg.*
Ginseng (p.2312·1); thiamine (p.1922·1).
Dietary supplement.

Ginseng Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Ginseng-Complex "Schuh" *Coradol, Ger.†.*
Panax ginseng (p.2312·1); chlorophyllin (p.1471·1); crataegus (p.2289·1).
Tonic.

GinsengSure *Abbott, Hong Kong†.*
Preparation for enteral nutrition with ginseng (p.2312·1) (p.1922·1).

Ginsenol *Herbapol Krakow, Pol.*
Ginseng (p.2312·1).
Tonic.

Ginsex *Delta, Braz.*
Ginseng (p.2312·1).
Tonic.

Ginsomin *Mega Lifesciences, Malaysia; Mega Lifesciences, Philipp.*
Ginseng (p.2312·1); vitamins; minerals (p.1922·1).
Tonic.

Ginsroy *Schumit, Thai.*
Ginseng (p.2312·1).
Tonic.

Gintonal *Biocom, Fr.†.*
Ginseng (p.2312·1); royal jelly (p.2382·1).
Tonic.

Ginurovac *Nikkho, Braz.†.*
Ampoule 1, procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1); ampoule 2, aminocaproic acid (p.1053·2); antigens from *Neisseria gonorrhoeae*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*.
Bacterial infections.

Ginvapast
Note. This name is used for preparations of different composition.
Ogna, Ital.
Calcium gluconate (p.1675·3); procaine hydrochloride (p.1869·1); cetylpyridinium chloride (p.1635·1).
Gum disorders; skin ulcers.

Wild, Switz.
Calcium gluconate (p.1675·3); procaine hydrochloride (p.1869·1); vitamins A and D (p.1922·1).
Gum disorders.

Gin-Vita *Shin Poong, Singapore.*
Ginseng (p.2312·1); oryzanol (p.2358·3); ascorbic acid; tocopherol acetate; fursultiamine; pyridoxine hydrochloride; riboflavin tetrabutyrate (p.1922·1).
Musculoskeletal pain; peripheral vascular disorders; vitamin E supplement.

Giona *Orion, Cz.; Meda, Denm.; Orion, Malaysia; Meda, Norw.; Orion, Singapore; Meda, Swed.; Orion, Thai.*
⊗ Budesonide (p.1520·1).
Asthma.

Giovax *Ivax, Cz.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Giovax plus H *Teva, Cz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Gioxyson *Akrikhin, Rus.; Nizhpharm, Rus.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Giparlix *Loeffler, Mex.*
Triprolidine (p.593·1); phenylephrine (p.1568·1).
Allergic rhinitis.

Gipzide *Sriprasit, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Girabloc *Hexpharm, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Girasid *Abfar, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

Girha "Schuh" *Coradol, Ger.†.*
Homoeopathic preparation.

Girheulit HM *Pfluger, Ger.*
Homoeopathic preparation.

Giro *Panacea, India.*
Ornidazole (p.843·1).
Amoebiasis; giardiasis.

Giroflox *Tecnimede, Port.; Tecnimede, Spain.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Gi-Sen *Giuliani, Ital.†.*
Ginseng (p.2312·1).

Gisfen *More, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Gisistin *Best, Mex.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Gissicor *Innopharm, Singapore.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1); vitamin B substances (p.1922·1).
Dietary supplement.

GI-Tak *Be-Tabs, S.Afr.†.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; heartburn.

Gitako *Daehan, Singapore.*
Ginkgo biloba (p.2311·1).
Cerebral function disorders; peripheral vascular disorders.

Gitaramin *Nufarindo, Indon.*
Mefenamic acid (p.80·1).
Menorrhagia; pain.

Gitas *Interbat, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Gitas Plus *Interbat, Indon.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle pain or spasm.

Gittalun *Boehringer Ingelheim, Ger.*
Doxylamine succinate (p.578·2).
Sleep disorders.

Gityl *Krewel, Ger.*
Bromazepam (p.964·3).
Anxiety; sleep disorders.

Givair *Epifarma, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Givalex *Norgine, Belg.; Norgine, Fr.; Norgine, Ger.†.*
Hexetidine (p.1647·1); choline salicylate (p.36·3); chlorobutanol (p.1639·2).
Mouth and throat disorders.

Givitol *Galen, Irl.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B substances; sodium ascorbate (p.1922·1).
Iron and folic acid deficiency in pregnancy.

Gixaderm *Mergers Drugfil, Philipp.*
Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

GLA *Synergia, Fr.*
Evening primrose oil (p.2302·1); fish oil; vitamin C; vitamin E; zinc citrate (p.1922·1).
Premenstrual syndrome; skin and mucous membrane disorders.

Glacout *Ingens, Arg.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Gladase *Glades, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).
Debridement of necrotic tissue.

Gladase-C *Smith & Nephew, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2); chlorophyllin copper complex sodium (p.1471·1).
Ulcers; wounds.

Gladem *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Switz.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Gladio *Abiogen, Ital.*
Aceclofenac (p.14·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Gladius *Pharmanel, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Gladixol *Kolassa, Austria.*
β-Acetyldigoxin (p.1201·2); potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Arrhythmias; heart failure.

Glafemak *Genepharm, Gr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Glafornil *Merck, Chile; Biotech, Venez.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glakay *Eisai, Jpn; Eisai, Thai.*
Menatetrenone (p.1995·3).
Osteoporosis.

Glamarol *Guardian, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glamaryl *Aventis, S.Afr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glamidolo *Faran, Gr.; Angelini, Israel†; Angelini, Ital.*
Dapiprazole hydrochloride (p.2292·2).
Glaucoma; reversal of mydriasis.

Glamin *Fresenius Medical, Austral.; Fresenius Kabi, Cz.; Baxter, Ger.; Fresenius Kabi, Hong Kong†; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Baxter, NZ; Fresenius Kabi, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore†; Fresenius Kabi, Spain; Fresenius Kabi, Switz.; Fresenius Kabi, UK; Diamedica, Venez.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Glandicin *Degorts, Mex.*
Piroxicam (p.117·3).
Inflammation; pain.

Glandomed *Cell Pharm, Ger.*
Macrogol (p.2336·1).
Mouth disorders.

Glandosane
Note. This name is used for preparations of different composition.
Stada, Austria; Cell Pharm, Ger.; Stada, Hong Kong; Fresenius Kabi, Port.; Helvepharm, Switz.; Fresenius Kabi, Thai.†; Fresenius Kabi, UK.
Carmellose sodium (p.2142·1); sorbitol (p.1965·1); electrolytes (p.1667·1).
Dry mouth; saliva substitute.

Stada, Malaysia.
Electrolytes (p.1667·1).
Dry mouth; saliva replacement.

Glandulae-F-Gastreu R20 *Reckeweg, Ger.*
Homoeopathic preparation.

Glanique *Asofarma, Mex.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Glanos *GSK, Indon.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

GLA-Plus Vitamin E *Shaklee, Canad.*
Essential fatty acids with vitamin E (p.1922·1).
Nutritional supplement.

Glartin *Biomedica-Chemica, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Glatim *Amhof, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaucocare *Thea, Neth.†.*
Aceclidine hydrochloride (p.1875·1).
Glaucoma.

Glaucocarpine *Taro, Israel.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Glaucocin *Klonal, Arg.†.*
⊗ Pilocarpine (p.1884·3); timolol (p.1413·1).
Glaucoma.

Glaucodose *Faran, Gr.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Glaucon *Alcon, Cz.†; Alcon, USA†.*
⊗ Adrenaline hydrochloride (p.1203·3).
Glaucoma.

Glauconex *Alcon, Austria†.*
⊗ Befunolol hydrochloride (p.1878·2).
Glaucoma.

Glauconide *Llorens, Spain.*
⊗ Diclofenamide (p.1880·2).
Glaucoma.

Glauco-Oph *Seng, Hong Kong†; Seng, Thai.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaucoprost *Poen, Arg.*
Travoprost (p.1886·1).
Glaucoma; ocular hypertension.

Glaucosan *Hexal, S.Afr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaucostat
Note. This name is used for preparations of different composition.
Valeant, Arg.
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

IFET (ΙΦΕΤ), Gr.†; Chibret, Port.†.
Aceclidine hydrochloride (p.1875·1).
Glaucoma.

Glauco-Stulln *Stulln, Ger.*
⊗ Pindolol (p.1372·1).
Glaucoma.

Glaucotensil
Note. This name is used for preparations of different composition.
Poen, Arg.
⊗ Pilocarpine hydrochloride (p.1884·3); timolol maleate (p.1412·3).
Glaucoma.

Poen, Chile.
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Glaucotensil D *Roemmers Poen, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Glaucotensil T *Poen, Chile; Roemmers Poen, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaucotensil TD *Poen, Arg.*
⊗ Dorzolamide (p.1880·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaucothil *Alcon, Austria†; Alcon, Ger.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Glaucotrat *Genom, Braz.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

GlaucTabs *Akorn, USA†.*
⊗ Methazolamide (p.1883·1).
Glaucoma.

Glaudrops *Alcon Cusi, Spain†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Glauko Biciron *S & K, Cz.†; S & K, Ger.*
Pilocarpine hydrochloride (p.1884·3); phenylephrine hydrochloride (p.1568·1).
Glaucoma.

Glaumetax *Novartis Ophthalmics, Arg.†.*
⊗ Methazolamide (p.1883·1).

Glaumid *SIFI, Ital.†.*
⊗ Diclofenamide (p.1880·2).
Glaucoma.

Glaunorm *IFET (ΙΦΕΤ), Gr.; Farmigea, Ital.*
Aceclidine hydrochloride (p.1875·1).
Glaucoma.

Glau-opt *Trinity, UK†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glaupax *OmniVision, Ger.; Novartis, Neth.†; OmniVision, Switz.*
⊗ Acetazolamide (p.1875·1).
Glaucoma; oedema.

Glausolets *SMB, Chile.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glausolets Plus *SMB, Chile.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glautarakt *Pekana, Ger.†.*
Homoeopathic preparation.

Glauteolol *Valeant, Arg.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Glautimol
Note. This name is used for preparations of different composition.
Alcon, Braz.
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Farmigea, Ital.
⊗ Aceclidine hydrochloride (p.1875·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glauvent *Sopharma, Rus.†.*
Glaucine phosphate (p.1561·1).

Glavamin *Fresenius Kabi, Austria; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Glaveral *Help, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Glavit *Fontovit, Braz.*
Gamolenic acid (p.2308·2); linolenic acid (p.1362·1); oleic acid (p.2030·1).
Premenstrual syndrome.

Glaxal Base *Wellspring, Canad.*
Emollient.
Dermatological base; dry skin.

Glaxenna *GSK, Rus.*
Calcium sennosides (p.1770·1).
Constipation.

Glaxopar *GSK, Austria.*
Paroxetine (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social-anxiety disorder.

Glaxoprin *GSK, Austria.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Glaxoprost *GSK, Austria.*
Epoprostenol sodium (p.1279·3).
Pulmonary hypertension; thrombosis prophylaxis during haemodialysis.

Glaxosetron *GSK, Austria.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxic chemotherapy; postoperative nausea and vomiting.

Glaxotriptan *GSK, Austria.*
Sumatriptan succinate (p.625·2).
Migraine.

Glazid *Fako, Turk.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glazide *Galena, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glazidim *GSK, Belg.; GSK, Fin.; GSK, Ital.*
Ceftazidime (p.234·1).
Bacterial infections.

Gleevec *Novartis, Canad.; Novartis, S.Afr.; Novartis, USA.*
Imatinib mesilate (p.733·1).
Chronic myeloid leukaemia; gastrointestinal stromal tumours.

Glefos *Grunenthal, Spain†.*
Misoprostol (p.2013·2).
Peptic ulcer.

Gleitgelen
Note. This name is used for preparations of different composition.
Wolff, Ger.
Liquid paraffin (p.2030·3); medium-chain triglycerides (p.1956·3).
Vaginal dryness.

Taymed, Turk.
Hyetellose (p.2143·3); glycerol (p.2314·2); chlorhexidine hydrochloride (p.1635·3).
Atrophic vaginitis.

Gleitmittel *Bichsel, Switz.†.*
Chlorhexidine gluconate (p.1635·3); macrogol (p.2336·3).
Lubrication before catheterisation or endoscopy.

Glemaz *Montpellier, Arg.; Bago, Chile; Montpellier, Rus.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glemicid *Collins, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glemid *Egis, Cz.; Egis, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glempid *EGIS, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glencamide *Pond's, Thai.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

G-Lenk *Mezina, Fin.*
Glucosamine sulfate potassium chloride (p.2313·2).
Joint disorders.

Glenol *Alpes Chemie, Chile†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Glentor *Medipharma, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glevate *Glenmark, Philipp.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Glevo *Glenmark, India†; Glenmark, Malaysia.*
Levofloxacin (p.292·2).
Bacterial infections.

Glevomicina *Bago, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Glez *Otsira, India.*
Glipizide (p.441·3).
Diabetes mellitus.

Gliadel *Orphan, Austral.; Aventis, Chile†; Link, Fr.; Genesis, Gr.; Guilford, Israel; Dompe Biotec, Ital.; MGI, Malaysia; Guildford Pharmaceuticals, Neth.; Esteva, Port.; Pharmaplan, S.Afr.; Pensa, Spain; Link, UK; MGI, USA.*
Carmustine (p.694·3).
Glioblastoma multiforme; malignant glioma.

Glianimon *Bayer, Ger.; Menarini, Gr.*
Benperidol (p.964·1).
Psychoses.

Gliatilin *Montpellier, Arg.†; Italfarmaco, Cz.†; ITF, Gr.; Italfarmaco, Ital.; Italfarmaco, Pol.; Italfarmaco, Rus.*
Choline alfoscerate (p.363·3).
Cerebrovascular disorders; head trauma; mental function impairment.

Glib *ABZ, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibamide *CTS, Rus.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

gli-basan *Schonenberger, Switz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibediab *Hexal, Arg.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibemid *Malayan, Singapore†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibemida *Temis, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliben *Cristalia, Braz.†; CT, Ger.; Winthrop, Ger.; Biolab, Hong Kong; Abiogen, Ital.; Biolab, Malaysia; Pacific, NZ; Biolab, Thai.†; Nobel, Turk.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliben F *Abiogen, Ital.*
Glibenclamide (p.440·1); phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Gliben-Azu *Azupharma, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenbeta *Betapharm, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenclamon *Sanval, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibendiab *Sigma, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibendoc *Docpharm, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenese *Pfizer, Austria; Pfizer, Belg.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Neth.†; Pfizer, Pol.; Pfizer, Rus.; Pfizer, Spain†; Pfizer, Switz.; Pfizer, UK.*
Glipizide (p.441·3).
Diabetes mellitus.

Glibenhexal *Hexal, Cz.†; Hexal, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenil *Cryopharma, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenorme *Streuli, Switz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliben-Puren N *Alpharma-Isis, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibenval *Valdecasas, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibesifar *Siphar, Switz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibesyn *Medochemie, Malaysia; Medochemie, Singapore.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibetic
Note. This name is used for preparations of different composition.
Teva, Israel; The Forty-Two, Thai.
Glibenclamide (p.440·1).
Diabetes mellitus.

Polpharma, Pol.
Glimepiride (p.441·1).
Diabetes mellitus.

Glibex *Biopharm, Rus.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibexil *Royton, Braz.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibezid *Jelfa, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glibic *Medicine Products, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glibomet *Guidotti, Cz.; Guidotti, Ital.; Guidotti, Rus.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gliboral *Menarini, Hong Kong; Guidotti, Ital.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glib-ratiopharm *Ratiopharm, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glicab *Tempo Scan Pacific, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glicalox *Dominguez, Arg.†.*
Alginic acid (p.2140·3); sodium alginate (p.2141·1); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Glicamin
Note. This name is used for preparations of different composition.
Geolab, Braz.
Glibenclamide (p.440·1).
Diabetes mellitus.

Lafare, Ital.†.
A heparinoid (p.1305·2).
Thrombosis prophylaxis.

Glicaron *Cifarma, Braz.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glicavin *Quimica y Farmacia, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glicefor *Geolab, Braz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glicel *Brasterapica, Braz.†.*
Glycerol (p.2314·2).
Constipation.

Glicenex *Bago, Chile.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gliceramin *Behrens, Venez.*
Amino-acid and electrolyte infusion (p.1922·1).

Glicerolax *Dynacren, Ital.*
Glycerol (p.2314·2); mallow (p.2337·2) (p.2337·2).
Constipation.

Glicerolo microclismi *Mediplants, Gr.†.*
Glycerol (p.2314·2).
Bowel evacuation.

Glicerotens *Llorens, Spain.*
Glycerol (p.2314·2).
Glaucoma; ocular surgery.

Glicero-Valerovit *Teofarma, Ital.*
Sodium glycerophosphate (p.2315·2); valerian (p.2410·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Hyperexcitability; tonic.

Gliceroviton *Organifar, Venez.†.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Glicima *Atlantis, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Glicinal *Ogera, Switz.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Gliciron *Roemmers, Venez.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliclamet *Biochem, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glicobase *Bayer, Ital.*
Acarbose (p.436·2).
Diabetes mellitus.

Glicoben *Cazi, Braz.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Glicocef *Bergamo, Braz.*
Ceftriaxone (p.238·1).
Bacterial infections.

Glicoderm *Remexa, Mex.*
Glycolic acid (p.1598·1).
Dry skin disorders.

Glicodril *Reuffer, Mex.*
Diphenhydramine (p.577·1).
Hypersensitivity.

Glicofisiologica *Aster, Braz.†.*
Sodium chloride (p.1686·1); glucose (p.1945·3).
Fluid and electrolyte disorders.

Glico-Fita *Lilly, Braz.*
Test for glucose in urine (p.2314·1).

Glicoisdin *Isdin, Arg.*
Glycolic acid (p.1598·1).
Skin disorders.

Glicolic *Medihealth, Mex.*
Glycolic acid (p.1598·1).
Dry skin disorders; light-induced skin damage.

Gliconorm *Abiogen, Ital.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glicorest *Fournier, Ital.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glicorp *Neo Quimica, Braz.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Glicoxem *Kener, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glicron *Siam Medicare, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glidabet *Hexpharm, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glidan *Roemmers Rowe, Venez.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glidanil
Note. This name is used for preparations of different composition.
Montpellier, Arg.; Mersifarma, Indon.; Montpellier, Rus.
Glibenclamide (p.440·1).
Diabetes mellitus.

Medipharm, Chile.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glide *Franco-Indian, India.*
Glipizide (p.441·3).
Diabetes mellitus.

Glidiamid *ICN, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glifage *Merck, Braz.*
Metformin (p.453·3).
Diabetes mellitus.

Glifapen *Ronnet, Arg.*
Amoxicillin (p.202·2); diclofenac sodium (p.44·3).
Bacterial infections with inflammation.

Glifarcal *Farcoral, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glifor *Bilim, Turk.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gliformin
Note. This name is used for preparations of different composition.
Tempo Scan Pacific, Indon.; Akrikhin, Rus.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Guidotti, Ital.
Glibenclamide (p.440·1); phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Glifortex *Andromaco, Chile.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glifortex-G *Andromaco, Chile.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Gligel *LDA, Arg.*
Glycolic acid (p.1598·1).

Glihexal *Hexal, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glikeyer *Keyerson, Mex.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glimaryl *Hovid, Malaysia.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimax *Ali, Turk.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimbal *CSC, Austria.*
⊗ Clocortolone pivalate (p.1523·1).
Skin disorders.

Glimbax *ITF, Gr.*
Prulifloxacin (p.320·1).
Bacterial infections.

Glimcip *Cipla, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimegamma *Worwag, Ger.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimehexal *Hexal, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimel *Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Indon.; Alphapharm, Singapore; Merck, Singapore.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glimepibal *Baldacci, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimepil *Farmoquimica, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimepiron *AG Therapy, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimeprid *Hexal, Braz.†.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimeran *Neo Quimica, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimerid *Wolff, Ger.; Galeno, Venez.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimesan *Sandoz, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimesec *Marjan, Braz.†.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimespes *Santa, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimet *Mepro, Chile.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Glimetal *Silanes, Mex.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

GlimeWin *Zentiva, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimexal *Sandoz, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimexin *Minerva (Μινερβα), Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimial *Neves, Port.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimicron *Hovid, Hong Kong; Hovid, Malaysia; Hovid, Singapore.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glimide
Note. This name is used for preparations of different composition.
Beta, Arg.
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

CCM, Malaysia; Beacons, Singapore.
Glibenclamide (p.440·1).
Diabetes mellitus.

Glimidstada *Stada, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glimin *Taiwan Biotech, Malaysia.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimiprex *Otsira, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimiprex MF *Otsira, India.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glimitab *Centaur, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimiton *Mead Johnson, Braz.†.*
Mineral preparation with vitamin B substances (p.1922·1).

GlimTek *Ratiopharm, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimulin *Glenmark, India; Glenmark, Malaysia.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glimulin-MF *Glenmark, India†.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glinate *Glenmark, India.*
Nateglinide (p.455·2).
Diabetes mellitus.

Glindia *Gedeon Richter, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glineon *Dovalle, Braz.†.*
Potassium aspartate; magnesium aspartate; fructose; ascorbic acid (p.1922·1).

Glinil *Cipla, India.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glinil M *Cipla, India.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glinor *Ratiopharm, Fin.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Glinorboral *Silanes, Mex.*
Glibenclamide (p.440·1); phenformin (p.437·2).
Diabetes mellitus.

Glinormax *Polfa Kutno, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glinux 70/30 *Probiomed, Mex.*
⊗ Human insulin (p.443·2).
Diabetes mellitus.

Glinux-N *Probiomed, Mex.*
⊗ Human insulin (p.443·2).
Diabetes mellitus.

Gliolan *Medac, Port.*
Aminolevulinic acid hydrochloride (p.679·2).
Location of malignant glioma.

Glionil *Neo Quimica, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliosartan *Bago, Arg.*
Telmisartan (p.1409·2).
Hypertension.

Gliosartan Plus *Bago, Arg.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Glioten *Bago, Arg.; Bago, Braz.; Bago, Chile; Armstrong, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Gliotenzide *Bago, Arg.; Bago, Braz.; Armstrong, Mex.; Bago, Singapore.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Glipal *Farmanic, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Glipar *Degorts, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glipep *Hospira, Port.*
Vancomycin hydrochloride (p.358·3).
Pseudomembranous colitis associated with antibiotics; staphylococcal infections.

Gliperin *Lyofin, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glipgen *Teuto, Braz.†.*
Glipizide (p.441·3).
Diabetes mellitus.

Glipicontin *Modi-Mundipharma, India†.*
Glipizide (p.441·3).
Diabetes mellitus.

Glipid
Note. This name is used for preparations of different composition.
Pacific, NZ†.
Glipizide (p.441·3).
Diabetes mellitus.

Genexo, Pol.
Glimepiride (p.441·1).
Diabetes mellitus.

Glipimed *Medicine Products, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Glipiscand *Scand Pharm, Swed.†.*
Glipizide (p.441·3).
Diabetes mellitus.

Gliplex *Farmasa, Braz.*
Vitamin B substances; vitamin C (p.1922·1).

Glipressina *Ferring, Ital.*
Terlipressin acetate (p.2395·3).
Haemorrhage from oesophageal varices.

Gliprex *Medico Uno, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Gliptid *Merck, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gliptide *Crinos, Ital.*
Sulglicotide (p.1775·3).
Gastrointestinal disorders; peptic ulcer.

Glisend *Konimex, Indon.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Glisodin *Kalbe, Indon.*
Superoxide dismutase (melon) (p.127·3); gliodin.
Antoxidant.

Glisuret *Pisa, Mex.†.*
Glycine (p.1947·3).
Transurethral irrigation.

Glita *Stadmed, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Glitisol
Note. This name is used for preparations of different composition.
Zambon, Braz.
Thiamphenicol (p.351·1).
Bacterial infections.

Remedica, Hong Kong.
Glibenclamide (p.440·1).
Diabetes mellitus.

Zambon, Ital.
Thiamphenicol glycinate hydrochloride (p.351·1).
Bacterial infections.

Glitosslab *Multilab, Braz.*
Potassium iodide (p.2169·2).
Cough.

Glitral *LA, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glivec *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Imatinib mesilate (p.733·1).
Acute lymphoblastic leukaemia; aggressive systemic mastocytosis; chronic myeloid leukaemia; dermatofibrosarcoma protuberans; gastrointestinal stromal tumours; hypereosinophilic syndrome; myelodysplastic syndromes.

Glix *YSP, Malaysia; Yung Shin, Philipp.*
Glipizide (p.441·3).
Diabetes mellitus.

Gliximina *Denver, Arg.*
Rosiglitazone (p.459·3).
Diabetes mellitus.

Gliza *Stadmed, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glizid *Panacea, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glizide
Note. This name is used for preparations of different composition.
Daehan, Singapore.
Gliclazide (p.440·3).
Diabetes mellitus.

Pharmahof, Thai.
Glipizide (p.441·3).
Diabetes mellitus.

Glizid-M *Panacea, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glizigen *SM, Venez.*
Phenoxyethanol (p.1657·1); hydroxybenzoates (p.1648·3).
Herpesvirus skin infections.

Glizolan *Madaus, Spain.*
Diacerein (p.41·3).
Osteoarthritis.

Glizon *Douglas, NZ.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glizone *Zydus, India.*
Pioglitazone (p.456·3).
Diabetes mellitus.

Globac-Z *Zydus, India.*
Ferric ammonium citrate (p.1938·1) or ferrous fumarate (p.1938·3); zinc sulfate (p.1999·2); vitamin B (p.1980·2); folic acid (p.1940·1).
Iron-deficiency anaemia.

Globamox *One Pharma, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Globapen *GX, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Globaxol *GX, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Globenicol *Yamanouchi, Neth.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Globifer *Medi-Rx, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Iron-deficiency anaemia.

Globitan *Vivax, Venez.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Globocef *Roche, Braz.†; Roche, Ger.†; Roche, Hong Kong†; Roche, Ital.†; Roche, Port.†; Roche, Switz.†.*
Cefetamet pivoxil hydrochloride (p.224·2).
Bacterial infections.

Globoid *Nycomed, Norw.*
Aspirin (p.20·3).
Fever; pain; rheumatic disorders.

Globovit *Andromaco, Chile†.*
Multivitamin and mineral preparation (p.1922·1).

Globuce *Sigma-Tau, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Globuli gegen Fieber und Grippe Nr 1 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Fieber und Grippe Nr 2 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Gelenkschmerzen *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Grippe *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Halsweh Nr 1 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Halsweh Nr 2 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Hautausschlage *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Heiserkeit *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Husten Nr 1 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Husten Nr 2 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Husten Nr 3 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Kopfschmerzen *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Schlafstorungen *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 1 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 2 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Schnupfen Nr 3 *Jacoby, Austria.*
Homoeopathic preparation.

Globuli gegen Sonnenallergie *Jacoby, Austria.*
Homoeopathic preparation.

Globuman *Berna, Hong Kong†; Berna, Ital.†; Berna, Malaysia†; Berna, Port.†; Berna, Spain†; Berna, Switz.; Berna, Thai.†; Berna, Turk.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immune deficiency; Kawasaki disease; passive immunisation.

Globuman Hepatite A *Berna, Port.†.*
A hepatitis A immunoglobulin (p.2214·1).
Passive immunisation.

Globuren *Dompe Biotec, Ital.†.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusions.

Gloceda *Medgenix, Belg.†.*
Codeine (p.37·2).
Formerly contained erysimin, aconite, belladonna, euphorbia, drosera, cherry-laurel, and codeine phosphate.
Coughs.

Glocure-Opta *Pascual, Philipp.*
⊗ Timolol maleate (p.1412·3).
Ocular hypertension and glaucoma following cataract surgery.

Glocyp *GMP, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic disorders.

Glofil *Cypros, USA.*
Iodine-125 (p.2054·2) as sodium iotalamate.
Evaluation of glomerular filtration rate.

Glomethyl *Lucas Djaja, Indon.*
Methylergometrine maleate (p.2011·1).
Uterine haemorrhage.

Glonoin Complex N *Coradol, Ger.†.*
Homoeopathic preparation.
Glonoin formerly contained glonoinum, nux. vom., aconitum, arnica, ambra, sumbulus mosch., latrodect. mact., convallaria maj., ignatia, chlorophyllin, fruct. crataeg., and flor. cacti grandiflor.

Glonoinum *Boiron, Cz.*
Homoeopathic preparation.

Glopir *Gap, Gr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Glorixone *Medicus, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Gloros *New Research, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Gloryskin *Medimar, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Glossaliv *Sigma, Braz.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); zinc oxide (p.1621·2); dogfish liver oil.
Skin disorders.

Glossderm
Note. This name is used for preparations of different composition.
Columbia, Arg.†.
Vitamin A (p.1971·2); vitamin D (p.1986·1); allantoin (p.1588·1).

Columbia, Mex.
Cod-liver oil (p.1935·2); benzalkonium chloride (p.1629·1); zinc oxide (p.1621·2); allantoin (p.1588·1).
Nappy rash.

Glossithiase *Jolly-Jatel, Fr.*
Thenoate monoethanolamine (p.351·1); muramidase hydrochloride (p.2348·1).
Infections of the mouth and throat.

Glossyfin *Doctum, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Glotone *Lesvi, Spain.*
Cyproheptadine hydrochloride (p.575·1); arginine hydrochloride; carnitine; cyanocobalamin (p.1922·1).
Tonic.

Glottyl *Meda, Belg.*
Syrup: Codeine phosphate (p.37·2).
Coughs.

Glovan *Teva, Israel.*
Nonoxinol 9 (p.1917·2); ricinoleic acid (p.2379·2).
Contraceptive.

Glovax *BB-NCIPD, Philipp.*
A BCG vaccine (p.2205·3).
Active immunisation.

Gluban *Vendiz, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gluben *Dexcel, Israel.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glubitor *Imperial, Philipp.*
Gliclazide (p.440·3).
Diabetes mellitus.

Gluborid *Grunenthal, Ger.†; Grunenthal, Switz.†.*
Glibornuride (p.440·3).
Diabetes mellitus.

Glubose *Otsira, India.*
Acarbose (p.436·2).
Diabetes mellitus.

Glubrava *Takeda, Cz.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucadol *Leiras, Fin.; Nycomed, Neth.*
Glucosamine sulfate potassium chloride (p.2313·2).
Joint disorders; osteoarthritis of the knee.

GlucaGen *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Abbott, India; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Switz.; Novo Nordisk, Turk.; Novo Nordisk, UK; Bedford, USA.*
Glucagon hydrochloride (p.1447·2).
Aid in gastrointestinal examination; assessment of beta-cell secretion; beta-blocker poisoning; hypoglycaemia.

Glucal
Note. This name is used for preparations of different composition.
Probiomed, Mex.
Glibenclamide (p.440·1).
Diabetes mellitus.

SA Druggists Self Med, S.Afr.
Calcium gluconate (p.1675·3).
Calcium deficiency; calcium supplement.

Glucal B12 *Arrow, Braz.*
Cyanocobalamin; colecalciferol; minerals; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Glucalbott Rth *Abbott, Chile.*
Preparation for enteral nutrition in diabetes mellitus (p.1922·1).

Glucaminol *Roche, Arg.; Roche, Venez.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucanet
Note. This name is used for preparations of different composition.
Noos, Ital.
Glucan.
Nasal cleansing.

Farmalight, Port.†.
Sodium chloride (p.1686·1); carboxymethyl-β-glucan.
Nasal congestion; rhinitis.

Glucanoos *DMG, Ital.†.*
Glucan; vitamins; zinc oxide (p.1922·1).

Glucantim *Aventis, Ital.†.*
Meglumine antimonate (p.828·2).
Leishmaniasis.

Glucantime *Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Meglumine antimonate (p.828·2).
Leishmaniasis.

Glucar *Glenmark, India; Glenmark, Malaysia.*
Acarbose (p.436·2).
Diabetes mellitus.

Glucardiamid *GSK, Pol.*
⊗ Glucose (p.1945·3); nikethamide (p.2161·2).
Hypotension; tonic.

Glucare *IAE, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluceride *Klonal, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glucerna *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.†; Abbott, Fin.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott, USA; Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).
Glucose intolerance.

Glucidoral *Servier, Fr.*
Carbutamide (p.438·3).
Diabetes mellitus.

Glucitol *Flupal, Venez.*
Loperamide (p.1741·3).
Diarrhoea.

Gluco *Masa, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluco Arrumalon *Sidus, Arg.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Joint disorders.

Gluco Arrumalon Duo *Sidus, Arg.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Musculoskeletal, joint, and peri-articular disorders.

Glucobay *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Asche, Ger.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, India; Bayer, Indon.; Bayer, Irl.; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Norw.; Bayer, Philipp.; Bayer, Pol.; Centrofarma, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, Venez.*
Acarbose (p.436·2).
Diabetes mellitus.

Glucobefol *Biotenk, Arg.*
Glucosamine sulfate (p.2313·2); boswellia (p.2307·1); zinc; copper; manganese (p.1922·1).
Joint disorders.

Glucobene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucobloc *Epifarma, Ital.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glucobon *Biomo, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucocal *Beacons, Singapore.*
Glucosamine sulfate (p.2313·2); calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Gluco-Calcium
Note. A similar name is used for preparations of different composition (see below).
Lilly, Hong Kong†.
Calcium (p.1675·2).
Alkalosis; hypocalcaemia; parathyroid deficiency; vitamin D deficiency.

Lilly, Thai.
Calcium (p.1675·2); glucose (p.1945·3).
Hypocalcaemia.

Glucocalcium
Note. A similar name is used for preparations of different composition (see above).
Streuli, Switz.
Calcium gluconate (p.1675·3); calcium saccharate (p.2272·3).
Hypocalcaemia; poisoning.

Glucocard *Menarini, Ital.; NZ Medical & Scientific, NZ†; Menarini Diagnostics, Port.*
Test for glucose in blood (p.2314·1).

Glucocartiflex *ISA, Arg.*
Glucosamine sulfate (p.2313·2).
Joint disorders.

Gluco-Cinta *Lilly, Mex.†.*
Test for glucose in urine (p.2314·1).

Glucocron *Farmaline, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glucodex
Note. This name is used for preparations of different composition.
Rougier, Canad.†.
Glucose (p.1945·3).
Oral glucose tolerance test.

Dexa, Indon.
Gliclazide (p.440·3).
Diabetes mellitus.

Glucodiab *Bangkok Lab & Cosmetic, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Glucodisk *Bayer, Port.*
Test for glucose in blood (p.2314·1).

Glucofage *Merck, Venez.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucoferro *Guidotti, Ital.*
Ferrous gluconate (p.1939·1).
Iron deficiency; iron-deficiency anaemias.

Glucoferro K *Knop, Chile.*
Ferrous gluconate (p.1939·1).
Iron deficiency; iron deficiency anaemia.

Glucofilm *Bayer Diagnostici, Ital.†; Bayer, USA.*
Test for glucose in blood (p.2314·1).

Glucofisiologica *Behrens, Venez.†.*
Sodium chloride infusion (p.1686·1) with glucose (p.1945·3).
Carbohydrate source; fluid and electrolyte disorders.

Glucoflex-R *Technostic, Austral.†.*
Test for glucose in blood (p.2314·1).

Glucofor *Soho, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucoform *Vendiz, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucoformin *Biobras, Braz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucofree *Farmasyn, Gr.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

GlucoGel *BBI, UK.*
Glucose (p.1945·3).
Formerly known as HypoStop.
Hypoglycaemia.

Glucogood *Denver, Arg.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucohex *Eurofarma, Braz.†.*
Chlorhexidine gluconate (p.1635·3).
Antiseptic.

Glucohexal *Hexal, Austral.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluco-K *Lafedar, Arg.*
Potassium gluconate (p.1684·3).
Potassium supplement.

Glucoles-500 *T Man, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucolin *GSK, Arg.*
Glucose monohydrate (p.1945·3).
Dietary supplement.

Glucolip *Wallace, India.*
Glipizide (p.441·3).
Diabetes mellitus.

Glucolon *Generfarma, Spain.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucolyte
Note. This name is used for preparations of different composition.
Pascual, Philipp.
Sodium chloride; sodium citrate; potassium chloride; magnesium gluconate; glucose (p.1672·2).
Diarrhoea; oral rehydration.

Thai Otsuka, Thai.
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

TO-Chemicals, Thai.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucoman *Volchem, Ital.*
Dietary fibre supplement containing glucomannan (p.2312·3), galactomannan, and minerals (p.1922·1).
Disorders of carbohydrate and lipid metabolism; gastrointestinal disorders; obesity.

Glucomed
Note. This name is used for preparations of different composition.
Medlink, Philipp.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Navamedic, Port.; Meda, Swed.
Glucosamine hydrochloride (p.2313·2).
Osteoarthritis; osteoarthritis of the knee.

Adcock Ingram, S.Afr.
Gliclazide (p.440·3).
Diabetes mellitus.

Glucomen *Menarini Diagnostics, Fr.; Menarini, Irl.; Menarini Diagnostics, UK.*
Test system for measuring glucose in blood (p.2314·1).

Glucomerck *Merck, Cz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucomet
Note. This name is used for preparations of different composition.
Douglas, Austral.; Aristopharma, Hong Kong; YSP, Malaysia; Douglas, NZ; Hua, Thai.†.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Chemopharma, Chile.
Glimepiride (p.441·1).
Diabetes mellitus.

Glucometer *Bayer, Austral.†; Bayer Diagnostici, Ital.†.*
Test for glucose in blood (p.2314·1).
For use with Glucometer Elite blood glucose meter.

Glucometer Elite *Bayer Diagnostics, Irl.; Bayer, NZ†.*
Test for glucose in blood (p.2314·1).
For use with Glucometer Elite blood glucose meter.

Glucometer Esprit *Bayer, NZ†.*
Test for glucose in blood (p.2314·1).
For use with Glucometer Esprit blood glucose meter.

Glucomide *Merck, Ital.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Glucomin *Stada, Austria; Dexcel, Israel.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucomol *Allergan, India.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Glucomore *Hayes, Israel.*
Glucose polymers (p.1922·1).
High-calorie supplement.

Gluconase *Therapharma, Philipp.*
Acarbose (p.436·2).
Diabetes mellitus.

Gluconeodesum *Biokhimik, Rus.*
Povidone (p.2146·1); glucose (p.1945·3).
Gastrointestinal infections; liver disorders.

Gluconic *Nicholas, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gluconil
Note. This name is used for preparations of different composition.
Biolab, Philipp.
Gliclazide (p.440·3).
Diabetes mellitus.

Utopian, Thai.
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucono *Pharmahof, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluconol *Biopharm, Chile.*
Nateglinide (p.455·2).
Diabetes mellitus.

Gluconorm *Roche, Braz.; Novo Nordisk, Canad.*
Repaglinide (p.457·2).
Diabetes mellitus.

Gluconormine *Streuli, Switz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucophage *Merck, Arg.; Alphapharm, Austral.; Merck, Austria; Merck, Belg.; Aventis, Canad.; Roche, Chile; Merck, Cz.; Merck Sante, Denm.; Merck, Fin.; Merck-Lipha, Fr.; Merck, Ger.; Petsiavas (Πετσιαβας), Gr.; Merck, Hong Kong; Merck, Indon.; Merck, Irl.; Abic, Israel; Merck, Ital.; Merck, Malaysia; Roche, Mex.; Pacific, NZ†; Merck, Neth.; Merck, Norw.; Merck, Philipp.; Merck Sante, Pol.†; Merck, Port.; Nycomed, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Swed.; Merck, Switz.; Merck, Thai.; Merck, Turk.; Merck, UK; BMS, USA.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucopirida *Biotenk, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glucoplasmal *Braun, Austria; Braun, Ger.; Braun, Hung.†; Braun, Spain.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Glucoplurisalina *Fresenius Kabi, Spain.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte depletion.

Glucopolielectrol *Baxter, Spain.*
Electrolyte infusion with glucose (p.1922·1).
Fluid and electrolyte depletion.

Glucopotasico *Bieffe, Spain.*
Potassium chloride infusion (p.1684·3) with glucose (p.1945·3).
Fluid and electrolyte depletion.

Glucoprime *Interhealthcare, Philipp.; Sunward, Philipp.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glucor *Bayer, Fr.*
Acarbose (p.436·2).
Diabetes mellitus.

Glucored *Coronet, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glucoremed *Lichtenstein, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucoreumin *Zambon, Braz.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Gluco-Rite *Agis, Israel.*
Glipizide (p.441·3).
Diabetes mellitus.

Gluco-S *MD, Singapore†; Standard Chem & Pharm, Thai.*
Glucosamine sulfate (p.2313·2).
Joint and cartilage disorders.

Glucosa *Bangkok Lab & Cosmetic, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Glucosada *Grifols, Port.*
Glucose (p.1945·3).
Carbohydrate source; fluid depletion.

Glucosado *Braun, Port.*
Glucose (p.1945·3).
Carbohydrate source; fluid depletion.

Glucosalin *Baxter, Switz.; Bioren, Switz.*
Anhydrous glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Glucosalina *Braun, Spain; Fresenius Kabi, Spain; Grifols, Spain.*
Sodium chloride infusion (p.1686·1) with glucose (p.1945·3).
Fluid and electrolyte depletion.

Glucosaline *ACS Dobfar, Switz.; Braun, Switz.*
Anhydrous glucose (p.1945·3) or glucose monohydrate (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Glucosalino *Braun, Port.; Baxter, Spain; Bieffe, Spain; Braun, Spain; Ern, Spain.*
Sodium chloride infusion (p.1686·1) with glucose (p.1945·3).
Fluid and electrolyte depletion.

Gluco-Salzlosung *Baxter, Austria.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

GlucOsamax *Health Perception, UK.*
Tablet 1, dimethyl sulfone (p.2294·1); rose fruit (p.2381·2); omega-3 (p.1362·1); tablet 2, glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Glucosamil *Verisfield, Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Glucosamine Joint & Muscle Cream with MSM *Nutravite, Canad.†.*
Evening primrose oil (p.2302·1); glucosamine sulfate (p.2313·2); grape seed oil (p.2316·3); methylsulfonylmethane (p.2294·1).

Glucosan *Ortho, Ital.†.*
Test for glucose in blood (p.2314·1).

GlucoSelene *Wassen, UK.*
Glucosamine sulfate; selenium; vitamins (p.1922·1).

Glucoseral *Streuli, Switz.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders; parenteral nutrition.

Glucosine *Recip, Port.; Recip, Swed.*
Glucosamine sulfate sodium chloride (p.2313·2).
Osteoarthritis.

Glucosmon *Altana, Spain.*
Glucose (p.1945·3).
Carbohydrate source; hypoglycaemia.

Glucost *Pascual, Philipp.*
Sodium; potassium; chloride; citrate; glucose (p.1672·2).
Oral rehydration.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Glucostabil *Gedeon Richter, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glucostad *Stada, Austria.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucosteril
Fresenius Kabi, Austria.
Glucose (p.1945·3).
Carbohydrate source; fluid depletion.

Baxter, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.
Glucose monohydrate (p.1945·3).
Carbohydrate source; fluid depletion; hypoglycaemia.

Glucostix *Bayer, Arg.; Bayer, Austral.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.†; Bayer Diagnostics, Mex.†; Bayer, NZ†; Bayer, Port.; Bayer Diagnostics, UK†; Bayer, USA.*
Test for glucose in blood (p.2314·1).

Glucotec *Maver, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Glucotem *Temis, Arg.*
Glucose monohydrate (p.1945·3).
Hypoglycaemia.

Glucotide *Bayer, Arg.†; Bayer Diagnostics, Fr.†; Bayer Diagnostics, Irl.; Bayer Diagnostics, Mex.†; Bayer Diagnostics, UK†.*
Test for glucose in blood (p.2314·1).

Glucotika *Ikapharmindo, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucotim *Centaur, India.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Glucotouch *Lifescan, Port.†.*
Test for glucose in blood (p.2314·1).

Glucotrace *MDS, Neth.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Contrast agent for positron-emission tomography.

Glucotrend *Roche, Arg.†; Roche Diagnostics, Fr.†; Roche Diagnostics, Ital.†.*
Test for glucose in blood (p.2314·1).

Glucotrin VL *Altana, Arg.*
Chondroitin sulfate sodium (p.2280·3); glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Glucotrol *Pfizer, Cz.†; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Turk.; Pfizer, USA.*
Glipizide (p.441·3).
Diabetes mellitus.

Glucovance *Merck, Arg.; Alphapharm, Austral.; Merck, Belg.; Merck, Braz.; Merck, Chile; Merck, Cz.; Merck-Lipha, Fr.; Merck, Hong Kong; Merck, Indon.; Merck, Malaysia; Merck, Mex.; Merck, Neth.; Merck, Philipp.; Merck, Port.; Nycomed, Rus.; Merck, S.Afr.; Merck, Singapore; Merck, Switz.; BMS, USA; Merck, Venez.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glucoven
Note. A similar name is used for preparations of different composition (see below).
Chinoin, Mex.
Glibenclamide (p.440·1).
Diabetes mellitus.

Glucoven infant
Note. A similar name is used for preparations of different composition (see above).
Fresenius Kabi, Ger.
Carbohydrate and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Glucovitan Ginseng *Elvetium, Arg.†.*
Ginseng; thiamine hydrochloride; pyridoxine hydrochloride; cyanocobalamin; magnesium glycerophosphate (p.1922·1).
Tonic.

Glucozide *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Gluctam *EGIS, Hung.*
Gliclazide (p.440·3).
Diabetes mellitus.

Gludepatic *Fahrenheit, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gludex *Montpellier, Arg.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Gludex Plus *Montpellier, Arg.*
Rosiglitazone maleate (p.458·2); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gludiase *Kyowa, Jpn.*
Glybuzole (p.442·3).
Diabetes mellitus.

Gludon *Merck, Port.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glufan *Rovi, Port.; Rovi, Spain.*
Glucosamine hydrochloride (p.2313·2).
Arthroses; osteoarthritis.

Glufer-C *Nakornpatana, Thai.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Glufor *Pyridam, Indon.; CTI, Israel.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluformin *Pliva, Cz.; Pliva, Hung.; Pliva Krakow, Pol.; Condrugs, Thai.; Biotek, Turk.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glukacel *Braun, Norw.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Glukaut *Sanitas, Chile.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Glukenil *Lazar, Arg.*
Repaglinide (p.457·2).
Diabetes mellitus.

Gluketur *Nicholas Piramal, India†.*
Test for glucose and ketones in urine.

Gluketurtest *Roche Diagnostics, Ital.†.*
Test for glucose and ketone bodies in urine.

Glukofen *Ilsan, Turk.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glukolos *Sanbe, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glukolyt *Kohler, Ger.†.*
Carbohydrate and electrolyte infusion (p.1922·1).
Carbohydrate source; fluid depletion.

Glukoreduct *Sanofi Synthelabo, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glukos-El *Braun, Swed.*
Carbohydrate and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Glukotest *Roche, Arg.†; Roche, Chile†.*
Test for glucose in urine (p.2314·1).

Glukovital *Wolff, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glukurtest *Roche Diagnostics, Ital.†.*
Test for glucose in urine (p.2314·1).

Glulo *Eisai, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glumal *Kyowa, Jpn.*
Aceglutamide aluminium (p.1704·1).
Peptic ulcer.

Glumeff *Tiefenbacher, Neth.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glumet *Raza, Hong Kong; Cipla, India; Pharmaniaga, Malaysia; Imperial, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glumetsan *ProMed, Cz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glumetza *Biovail, Canad.; Depomed, USA.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glumida *Pensa, Spain.*
Acarbose (p.436·2).
Diabetes mellitus.

Glumikron *Santa, Turk.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glumin *Ferron, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glunovag *Novag, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glu-Phos *SPA, Ital.*
Disodium glucose-1-phosphate.
Glucose deficiency.

Glupitel *Lilly, Mex.†.*
Glipizide (p.441·3).
Diabetes mellitus.

Glupozide *APT, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glupropan *Pisa, Mex.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glurenor *Guidotti, Ital.; Boehringer Ingelheim, Port.†; Astellas, Spain; Menarini, Thai.*
Gliquidone (p.442·1).
Diabetes mellitus.

Glurenorm *Boehringer Ingelheim, Austria; Menarini, Belg.; Zentiva, Cz.; Astellas, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Rus.; Eczacibasi, Turk.; Sanofi Synthelabo, UK†.*
Gliquidone (p.442·1).
Diabetes mellitus.

Glusa *Sriprasit, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Glusamine *Meiji, Thai.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Glusamon *Mediapharm, Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Glustar *Galeno, Venez.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Glustin *Takeda, Cz.; Takeda, Neth.; Takeda, Port.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Glustress *Pond's, Thai.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gluta Complex *UCB, Ital.†.*
Cobamamide (p.1980·2); amino acids (p.1922·1).
Tonic.

Glutabasal *Leti, Venez.*
Amino acids; vitamin B substances; minerals; glucose (p.1922·1).
Tonic.

Glutabloc *Umeda, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glutacalcio *Biofarma, Mex.*
Glutamic acid; calcium; thiamine (p.1922·1).
Dietary supplement.

Gluta-calcium *Medichrom, Gr.†.*
Calcium carbonate (p.1714·1); calcium lactate (p.1676·1); vitamin C (p.1983·3).
Breast-feeding; osteoporosis; pregnancy.

Glutacerebro *AFOM, Ital.†.*
Glutamine (p.1947·2).
Mental function impairment.

Glutacyl Vitaminado *Sanitas, Chile.*
Monosodium glutamate (p.2347·3); pyridoxine hydrochloride (p.1978·2); glutamic acid (p.1947·1).
Mental function impairment.

Glutaferro *Medix, Spain.*
Ferrous glycine sulfate (p.1939·1).
Anaemias.

Glutafin *Nutricia, Irl.; Nutricia, Ital.; Nutricia Dietary, UK.*
A range of gluten-free foods (p.1922·1).
Gluten-sensitive enteropathy.

Glutafos C *Carnot, Mex.*
Vitamin and mineral preparation (p.1922·1).

Glutallen *Allen, Mex.*
Vitamin and mineral preparation (p.1922·1).

Glutamin *Verla, Ger.*
Glutamic acid (p.1947·1).
Tonic.

Glutamin Fosforo *SIT, Ital.*
Glutamine (p.1947·2); -phosphoserine (p.2367·1); cyanocobalamin (p.1980·2).
Mental function impairment.

Glutanil *Bioprogress, Ital.†.*
Reduced glutathione sodium (p.1448·1).
Alcohol and drug poisoning; radiation trauma.

Glutapak *Victus, Venez.*
Glutamine (p.1947·2); maltodextrin (p.1955·3).
Glutamine supplement.

Glutapak-R *Victus, Venez.*
Glutamine (p.1947·2); maltodextrin (p.1955·3); *Lactobacillus reuteri* (p.2372·3).
Diarrhoea; malabsorption.

Glutaphos *Pascual, Philipp.*
Calcium hydrogen phosphate (p.1676·1); glutamic acid (p.1947·1); thiamine hydrochloride (p.1976·1); vitamin B (p.1980·2).
Mental function stimulant.

Glutarex *Ross, USA.*
A range of lysine- and tryptophan-free preparations for enteral nutrition including an infant feed (p.1922·1).
Glutaric aciduria type I.

Glutargin *Terapeutico, Ital.†.*
Arginine glutamate (p.1928·2); arginine aspartate (p.1928·2).
Liver disorders.

Glutaridon XLYS, Try *SHS, Fr.*
Food for special diets (p.1922·1).
Glutaric aciduria.

Glutarol *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Glutaral (p.1645·2).
Warts.

Glutarsin E
Note.This name is used for preparations of different composition.
Berlin-Chemie, Ger.†.
Glutamic acid (p.1947·1); arginine hydrochloride (p.1928·2); potassium hydroxide (p.2371·3); sodium hydroxide (p.2389·3).
Hyperammonaemia.

Berlin-Chemie, Hung.
Glutamic acid (p.1947·1); arginine hydrochloride (p.1928·2) with electrolytes.
Hyperammonaemia.

Glutasedan *Northia, Arg.†.*
Diazepam (p.986·3).
Anxiety; muscle spasm.

Glutasey *Alacan, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias; secondary prophylaxis of ischaemic heart disease.

Glutasorb *Hormel, Hong Kong.*
A glutamine-rich preparation for enteral nutrition (p.1922·1).

Glutathin *Mochida, Jpn.*
Glutathione (p.1448·1).
Liver disorders.

Glu-tathion *Toyo, Hong Kong.*
Glutathione (p.1448·1).
Drug poisoning; dyspepsia in children; hypersensitivity reactions; hypertension of pregnancy; leucopenia; liver disorders; skin pigmentation disorders.

Glutaven *Teofarma, Ital.*
Glutamine (p.1947·2).
Mental function impairment.

Glutavigon *Delta, Braz.*
Calcium phosphate; calcium glycerophosphate; glutamic acid; vitamin B substances (p.1922·1).

Gluthion *CT, Ital.*
Reduced glutathione sodium (p.1448·1).
Chemotherapy-induced neuropathy.

Gluti-Agil mono *Riemser, Ger.*
Glutamic acid (p.1947·1).
Tonic.

Glutilage *Beacons, Singapore.*
Glucosamine sulfate (p.2313·2).
Joint and cartilage disorders.

Glutilage Plus *Beacons, Singapore.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Joint and cartilage disorders.

Glutisal *Ravensberg, Ger.†.*
Salicylamide (p.121·2); ethenzamide (p.51·3).
Fever; gout; pain.

Glutofac *Kenwood, Hong Kong; Kenwood, USA.*
Multivitamin and mineral preparation (p.1922·1).

Glutose *Paddock, USA.*
Glucose (p.1945·3).
Hypoglycaemia.

Glutoxim *HPB, Rus.*
Glutathione disodium (p.1448·1).
Hepatitis B and C; immunodeficiency; ionising radiation trauma; tuberculosis; urinary-tract disorders; viral infections.

Glutrex *Cipla, India†.*
Glutaral (p.1645·2).
Disinfection.

Glutril *ICN, Austria; CSP, Fr.; ICN, Ger.†; Valeant, Switz.; Onko, Turk.*
Glibornuride (p.440·3).
Diabetes mellitus.

Gluvas *Dexa, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Gluxine *Recip, Norw.*
Glucosamine sulfate sodium chloride (p.2313·2).
Osteoarthritis.

Gluzo *Pharmasant, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gluzolyte *Pharmasant, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gly Derm Super Sunblock *ICN, Canad.†.*
Meradimate (p.1604·2); octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Gly Thymol *DHA, Hong Kong.*
Glycerol (p.2314·2); methyl salicylate (p.85·3); thymol (p.1664·3); menthol (p.2340·1); borax (p.2268·1); sodium salicylate (p.124·2); sodium benzoate (p.1630·2).
Aphthous ulcer; oral hygiene; sore throat.

Glyade *Alphapharm, Austral.; Alphapharm, Malaysia.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glyamid *Actavis, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glybofen *Liptis, USA.*
Glibenclamide (p.440·1); metformin (p.453·3).
Diabetes mellitus.

Glybovin *Otsira, India.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glycafor *Actavis, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glycare
Note.This name is used for preparations of different composition.
Kafetzis, Gr.
Glycerol (p.2314·2).
Bowel evacuation.

Roi Surya, Indon.
Glycolic acid (p.1598·1).
Skin ageing.

Glycelax *Casen Fleet, Port.*
Glycerol (p.2314·2).
Constipation.

Glycemin *Siam Bheasach, Thai.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Glyceol *Chugai, Hong Kong; Chugai, Jpn; Siam Bheasach, Thai.*
Glycerol (p.2314·2) with fructose and sodium chloride.
Cerebral oedema; ocular hypertension; raised intracranial pressure.

Glycerosteril *Fresenius Kabi, Ger.; Fresenius Kabi, Thai.†.*
Glycerol (p.2314·2).
Cerebral oedema.

Glyceryl-T *Rugby, USA.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Bronchospasm.

Glycifer *Nycomed, Denm.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency.

Glycigon *Aristo, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glycigon-M *Aristo, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glycilax *Engelhard, Ger.*
Glycerol (p.2314·2).
Constipation.

Glycinorm *Ipca, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glycinorm M *Ipca, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glyciphage *Franco-Indian, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glyco-A *Roemmers-Klinos, Venez.†.*
Glycolic acid (p.1598·1).
Sunlight-induced skin damage.

Glycocortison *Novartis Ophthalmics, Ger.†.*
⊗ Hydrocortisone acetate (p.1535·2).
Eye disorders.

Glycocortisone H *Ciba Vision, Switz.†.*
⊗ Hydrocortisone acetate (p.1535·2) in glucose.
Corneal disorders.

Glycodin *Alembic, Rus.*
Dextromethorphan hydrobromide (p.1555·2); terpin hydrate (p.1573·3); levomenthol.
Respiratory-tract disorders with cough.

Glycofed *Pal-Pak, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

glycolande N *Sanofi Synthelabo, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glycolate *Pharmasant, Thai.*
Guaifenesin (p.1561·3).
Coughs.

GlycoLax *Kremers-Urban, USA.*
Macrogol 3350 (p.2336·3).
Bowel evacuation.

Glycomet *USV, Singapore.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glycomin *Pharmacare, S.Afr.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glycon
Note. This name is used for preparations of different composition.
Farmalab, Braz.
Potassium iodide (p.2169·2); ammonium benzoate; tolu balsam (p.1574·2).
Respiratory-tract congestion.

ICN, Canad.†.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Siam Bheasach, Thai.
Gliclazide (p.440·3).
Diabetes mellitus.

Glycophos *Fresenius Kabi, Austria; Fresenius Kabi, Fin.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Malaysia; Pharmaco, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, UK.*
Sodium glycerophosphate (p.2315·2).
Phosphate supplement for parenteral nutrition.

Glycoplex *Vitaplex, Austral.†.*
Vitamins, minerals, and amino acids (p.1922·1); liquorice (p.1740·3); taraxacum (p.2395·1).
Dietary supplement.

Glycoprep *Pharmatel, Austral.; Bamford, NZ†.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Glycoprep-C *Pharmatel, Austral.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1); ascorbic acid (p.1983·3).
Bowel evacuation.

Gly-Coramin *Novartis Consumer, Switz.*
⊗ Nikethamide (p.2161·2); glucose and other reduced sugars (p.1945·3).
Tonic.

Glycoran *Shinyaku, Jpn; Shinyaku, Singapore†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glycosept *Teva, Hung.*
Acriflavinium chloride (p.1625·1); menthol (p.2340·1); sodium benzoate (p.1630·2); resorcinol (p.1612·1).
Mouth and throat disorders.

Glycostigmin *Leiras, Fin.*
Neostigmine metilsulfate (p.631·3).
Glycopyrronium bromide (p.2315·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Glycotuss *Pal-Pak, USA.*
Guaifenesin (p.1561·3).
Coughs.

Glycotuss-dM *Pal-Pak, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Glycovit *Vivipharma, Ital.*
Amino-acid, multivitamin, and mineral preparation (p.1922·1).
Nutritional supplement.

Glycron *Pharmacare, S.Afr.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glycylpressin *Ferring, Arg.; Ferring, Austria; Ferring, Ger.*
Terlipressin acetate (p.2395·3).
Haemorrhagic gastritis; variceal haemorrhage.

Glycyrrhiza Complex *Blackmores, Austral.†.*
Liquorice (p.1740·3); avena (p.2262·1); rose fruit (p.2381·2); vitamins (p.1922·1); ginseng (p.2312·1).
Tonic.

Glyderm *Valeant, Hong Kong; ICN, Malaysia†; Valeant, Singapore.*
Esterified glycolic acid (p.1598·1).
Dry skin disorders.

Glydiab *Akrikhin, Rus.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glyflucan *Legrand, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Glyformin *Remedica, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glygard *Cipla, India; Cipla-Medpro, S.Afr.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glygard M *Cipla, India.*
Gliclazide (p.440·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glygen *General Drugs, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Glykola *Durbin, UK.*
Calcium glycerophosphate (p.1676·1); caffeine (p.1116·3); kola liquid extract (p.2416·1); ferric chloride (p.2303·3).
Tonic.

Glymexan *Jelfa, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glymod *Sandoz, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Glymol *Biopharm, Rus.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Glynase
Note. This name is used for preparations of different composition.
USV, India.
Glipizide (p.441·3).
Diabetes mellitus.

Julphar, UAE; Pharmacia Upjohn, USA.
Glibenclamide (p.440·1).
Diabetes mellitus.

Glynose *Abdi, Turk.*
Acarbose (p.436·2).
Diabetes mellitus.

Glyoktyl *Medic, Denm.; SAD, Denm.*
Docusate sodium (p.1725·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Gly-Oxide *SmithKline Beecham Consumer, USA.*
Urea hydrogen peroxide (p.1666·2).
Oral hygiene; oral inflammation.

Glyphyllin *Rekah, Israel.*
Theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Glypressin
Ferring, Belg.; Ferring, Braz.†; Leciva, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Gr.; Ferring, Hung.; Ferring, Irl.; Ferring, Neth.; Ferring, Spain; Er-Kim, Turk.; Ferring, UK.
Terlipressin acetate (p.2395·3).
Variceal haemorrhage.

Ferring, Hong Kong; Ferring, Malaysia; Ferring, Singapore; Ferring, Thai.
Terlipressin (p.2395·3).
Variceal haemorrhage.

Glypressine *Ferring, Fr.; Ferring, Switz.*
Terlipressin acetate (p.2395·3).
Hepatorenal syndrome; variceal haemorrhage.

Glyprin *CCM, Hong Kong; CCM, Malaysia; Upha, Singapore.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Thromboembolism prophylaxis; thrombosis prophylaxis.

Glyquin
Note. This name is used for preparations of different composition.
Valeant, Braz.; Valeant, Singapore.
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Hyperpigmented skin disorders.

Valeant, Hong Kong.
Hydroquinone (p.1598·2); padimate O (p.1609·1); oxybenzone (p.1608·3); octinoxate (p.1608·2); glycolic acid (p.1598·1).
Hyperpigmented skin disorders.

Glyquin XM
Note. This name is used for preparations of different composition.
Valeant, Canad.; ICN, USA.
Hydroquinone (p.1598·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); avobenzone (p.1589·3); glycolic acid (p.1598·1).
Hyperpigmented skin disorders.

Valeant, Singapore.
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Hyperpigmented skin disorders.

Glyree *Ipca, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Glyree M *Ipca, India.*
Glimepiride (p.441·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Glyroz *Aristo, India.*
Gliclazide (p.440·3); rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Glyryl *Pharmasant, Thai.*
Guaifenesin (p.1561·3).
Coughs.

Glysan *Riemser, Ger.*
Magaldrate (p.1742·3).
Gastric hyperacidity; heartburn; peptic ulcer.

Glysennid *Columbia, Canad.†.*
Sennosides (p.1769·3).
Constipation.

Glyset *Bayer, USA.*
Miglitol (p.454·3).
Diabetes mellitus.

Glyteol Balsamico *Hertz, Braz.*
Guaifenesin (p.1561·3); potassium iodide (p.2169·2); menthol (p.2340·1).
Coughs.

Glytop *Pharmatrix, Arg.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Glytrin *Ayrton, Denm.; Sanofi-Aventis, Irl.; Bioglan, Malaysia†; AFT, NZ; Ayrton, Neth.; Sanofi-Aventis, Port.; Pharmasol, Singapore†; Bioglan, Swed.; Hua, Thai.; Sanofi Synthelabo, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Glyvenol *Novartis, Belg.; Novartis, Braz.; Novartis, Cz.; Novartis, Gr.†; Novartis, Mex.; Novartis, Philipp.; Novartis, Rus.; Novartis, Venez.*
Tribenoside (p.2403·3).
Haemorrhoids; phlebitis; varices; vascular disorders; venous insufficiency.

Glyverase *Ferring, Mex.*
Terlipressin acetate (p.2395·3).
Variceal haemorrhage.

Glyzid *Sunthi Sepuri, Indon.*
Glipizide (p.441·3).
Diabetes mellitus.

Glyzide *Julphar, UAE.*
Gliclazide (p.440·3).
Diabetes mellitus.

Glyzip *Stadmed, India.*
Glipizide (p.441·3).
Diabetes mellitus.

Glyzyl *Medreich, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

GNC *General Nutrition, Canad.*
Range of vitamin and mineral preparations (p.1922·1).

GNC Herbal Laxative *General Nutrition, Canad.†.*
Senna (p.1769·2).
Constipation.

GNO *Arion, Arg.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

GNO CP *Arion, Arg.†.*
Paracetamol (p.108·1); codeine (p.37·2).
Fever; pain.

Gnostocardin *Bros, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Gnostol *Bros, Gr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Gnostoval *Bros, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Go Kit *Pharmatel, Austral.*
3 Tablets, bisacodyl (p.1710·1); 1 sachet, magnesium citrate (p.1743·2).
Bowel evacuation.

Go Kit Plus *Pharmatel, Austral.†.*
3 Tablets, bisacodyl (p.1710·1); 1 suppository, bisacodyl (p.1710·1); 1 sachet, magnesium citrate (p.1743·2).
Bowel evacuation.

Goanna Analgesic Ice *Herron, Austral.†.*
Glycol salicylate (p.62·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Goanna Arthritis Cream *Herron, Austral.*
Trolamine salicylate (p.132·3).
Musculoskeletal and joint pain.

Goanna Heat Cream *Herron, Austral.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); peppermint oil (p.1761·2); cajuput oil (p.2271·2); capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, and soft-tissue pain.

Goanna Salve *Herron, Austral.*
Eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); peppermint oil (p.1761·2); camphor (p.2273·2); methyl salicylate (p.85·3); menthol (p.2340·1); turpentine oil (p.2406·3).
Musculoskeletal and joint pain.

Gobanal *Normon, Spain.*
Diazepam (p.986·3).
Contains pyridoxine hydrochloride.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Gobbicaina *Gobbi, Arg.*
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Gobbicalm *Gobbi, Arg.*
Dipyrone (p.49·2); dextropropoxyphene (p.40·1).
Pain.

Gobbicuronio *Gobbi, Arg.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Gobbidona *Gobbi, Arg.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome; pain.

Gobbifol *Gobbi, Arg.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Gobbigesic *Gobbi, Arg.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Gobbinal *Gobbi, Arg.*
Nalbuphine hydrochloride (p.91·3).
Pain.

Gobbizolam *Gobbi, Arg.*
Midazolam (p.1007·3).
General anaesthesia; sedative.

Gobemicina *Normon, Spain.*
Ampicillin trihydrate (p.204·2) or ampicillin sodium (p.204·1).
Bacterial infections.

Gobemicina Retard *Normon, Spain.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Gobens Trim *Normon, Spain.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Gobrosan *Protein, Mex.*
Ibuprofen (p.64·2).
Rheumatism.

Gocce Lassative Aicardi *SIT, Ital.*
Sodium picosulfate (p.1771·1).
Constipation.

Goccemed *Iodosan, Ital.*
Iodine (p.2169·2).
Oral hygiene.

Goclid *Guardian, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Gocold *Cipla, India.*
⊗ Guaifenesin (p.1561·3); bromhexine (p.1552·2); chlorphenamine (p.572·2); ephedrine (p.1558·1); paracetamol (p.108·1).
Cold symptoms.

Gocox-3 *Ipca, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Gocox-4 *Ipca, India†.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol hydrochloride (p.274·1); vitamin B (p.1979·1).
Tuberculosis.

Gocox Compound *Ipca, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Godabion B6 *Merck, Spain†.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B6 deficiency.

Godal *Merck, Spain.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Godamed *Pfleger, Ger.; Pfleger, Israel.*
Aspirin (p.20·3).
Glycine (p.1947·3) may be included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain; thromboembolic disorders.

Godasal *Pfleger, Cz.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain; thromboembolic disorders.

Goddards Embrocation *Thornton & Ross, UK.*
Turpentine oil (p.2406·3); dilute acetic acid (p.2244·2); dilute ammonia solution (p.2256·1).
Musculoskeletal and soft-tissue disorders.

Godek *Grin, Mex.*
Ketorolac (p.75·2).
Pain.

Godex
Note. This name is used for preparations of different composition.
Mergers Drugfil, Philipp.
Capsules: Carnitine orotate (p.2358·3); liver extract (p.2337·3); adenine hydrochloride (p.2247·2); pyridoxine hydrochloride (p.1978·2); riboflavin (p.1977·2); cyanocobalamin (p.1980·2).
Liver disorders.

Mergers Drugfil, Philipp.
Injection: Carnitine orotate (p.2358·3); carnitine hydrochloride (p.1933·1); liver extract (p.2337·3); adenosine (p.1202·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Liver disorders.

Goflex *Guardian, Indon.*
Nabumetone (p.91·2).
Musculoskeletal and joint disorders.

Goforan *Guardian, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Gokoto *Tsumura, Jpn.*
Gypsum; apricot kernel; ephedra; mulberry bark; liquorice.
Traditional Kampo medicine.

Gola Action *Iodosan, Ital.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Golacetin *Vaillant, Ital.*
Cetylpyridinium chloride (p.1635·1).
Oral disinfection.

Goladin *Sofar, Ital.*
Dequalinium chloride (p.1641·3).
Oral disinfection.

Golafair *Iodosan, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

Golamed *Iodosan, Ital.†*
Cicliomenol (p.1640·3).
Mouth and throat disinfection.

Golamed Due *Iodosan, Ital.†*
Cicliomenol (p.1640·3); hexylresorcinol (p.1647·1).
Mouth and throat disinfection; sore throat.

Golamixin *Teofarma, Ital.*
Tyrothricin (p.358·2); cetrimonium bromide (p.1635·1); benzocaine (p.1854·1).
Bacterial stomatitis.

Golapiol *Antipiol, Ital.*
Propolis (p.2373·3).

Golapiol C *Antipiol, Ital.*
Propolis (p.2373·3); rose fruit (p.2381·2).

Golasan *Dynacren, Ital.*
Chlorhexidine gluconate (p.1635·3) or chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disinfection; oral hygiene.

Golasept *Zeta, Ital.*
Povidone-iodine (p.1659·2).
Oral disinfection.

Golaseptine *SMB, Belg.*
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

Golatux *Antipiol, Ital.*
Ivy (p.2328·1); echinacea (p.2298·1).

Golaval *Carlo Erba OTC, Ital.†*
Cetrimonium tosilate (p.1635·1).
Mouth and throat disinfection.

Gold Alka-Seltzer *Bayer, USA.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); potassium bicarbonate (p.1673·1).
Hyperacidity.

Gold Bond Medicated Triple Action Relief *Chattem, USA.*
Dimeticone (p.2032·1); menthol (p.2340·1); aloe (p.1588·2).
Emollient.

Gold Cross Antihistamine Elixir *Biotech, Austral.†*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; insomnia; motion sickness.

Gold Cross BOZ Ointment *Biotech, Austral.†*
Boric acid (p.2268·1); olive oil (p.2356·2); zinc oxide (p.1621·2).
Eczema; psoriasis.

Gold Cross Cough Medicine *Biotech, Austral.†*
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1); sodium citrate (p.1673·3).
Coughs.

Gold Cross Gluco-lyte *Biotech, Austral.†*
Glucose; sucrose; sodium chloride; potassium chloride; sodium citrate; citric acid (p.1672·2).
Diarrhoea; oral rehydration.

Gold Cross Skin Basics Zinc Cream *Biotech, Austral.†*
SPF 15+: Arachis oil (p.2259·1); white soft paraffin (p.2031·2); zinc oxide (p.1621·2).
Skin disorders.

Gold Cross Vaporiser Fluid *Biotech, Austral.†*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Nasal congestion.

Goldamit *Linker, Gr.*
Citalopram (p.385·3).
Depression.

Goldamycin *Linker, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Goldar
Note. This name is used for preparations of different composition.
Zydus, India.
Auranofin (p.25·3).
Rheumatoid arthritis.

Pentafarma, Port.
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Goldastatin *Leovan, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Goldcare *Vitabiotics, UK.*
Multivitamin and mineral preparation with ginkgo biloba and bioflavonoids (p.1922·1).

Golden Eye *Typharm, UK.*
Chloramphenicol (p.239·3).
Bacterial conjunctivitis.

Golden Eye Drops *Typharm, UK.*
Propamidine isetionate (p.1660·1).
Eye infections.

Golden Eye Ointment
Note. This name is used for preparations of different composition.
Sigma, Austral.†
Yellow mercuric oxide (p.2341·2).
Bacterial eye infections.

Typharm, UK.
Dibrompropamidine isetionate (p.1642·1).
Eye infections.

Goldgeist *Gerlach, Ger.*
Pyrethrum (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Goldgesic *Ranbaxy, S.Afr.†*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Gold-Komplex *Steigerwald, Ger.*
Homoeopathic preparation.

Goldtropfen S *DHU, Ger.*
Homoeopathic preparation.

Golysine *Maigal, Arg.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

GoLytely *Braintree, Canad.; Kloster, S.Afr.; Braintree, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Gomas Garde B *Grisi, Mex.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

Gomas Garde G *Grisi, Mex.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Gomec *General Drugs, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux, Zollinger-Ellison syndrome; peptic ulcer.

Gomenol *Gomenol, Fr.*
Niaouli oil (p.2351·3).
Respiratory-tract congestion.

Gomenoleo *Gomenol, Fr.*
Niaouli oil (p.2351·3).
Instrument lubrication; rhinitis; wounds.

GON *Sanitas, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Gonablok *Win-Medicare, India.*
⊗ Danazol (p.2090·2).
Endometriosis; fibrocystic breast disease.

Gonacor *Ferring, Arg.; Ferring, Chile.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; female infertility; hypogonadism; male hypogonadism.

Gonadoryl *Mochida, Jpn.*
⊗ Menotrophin (p.2109·3).

Gonadotropyl C *Aventis, Mex.†*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; hypogonadism; male and female infertility.

Gonak *Akorn, USA.*
Hypromellose (p.2144·2).
Gonioscopic examination.

Gonakor *Sanfer, Mex.*
⊗ Chorionic gonadotrophin (p.2085·1); hydroxocobalamin (p.1980·3).
Erectile dysfunction; hypogonadism; oligospermia.

Gonal-F *Serono, Arg.; Serono, Austral.; Serono, Austria; Serono, Belg.; Serono, Braz.; Serono, Canad.; Novartis, Chile†; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Hung.; Serum Institute, India; DKSH, Indon.; Serono, Irl.; Serono, Israel; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Douglas, NZ; Serono, Neth.; Serono, Norw.; Serono, Philipp.; Serono, Pol.; Serono, Port.; Serono, Rus.; Serono, S.Afr.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
⊗ Follitropin alfa (p.2104·1).
Controlled ovarian stimulation; male and female infertility.

Gonapeptyl
Ferring, Arg.; Ferring, Fr.; Ferring, Irl.; Ferring, Ital.; Ferring, Neth.; Ferring, Spain.
⊗ Triptorelin acetate (p.2135·3).
Endometriosis; female infertility; pre-operative myoma reduction; precocious puberty; prostatic cancer; uterine fibroids.

Ferring, Gr.; Ferring, UK.
⊗ Triptorelin (p.2135·2).
Endometriosis; infertility; precocious puberty; prostatic cancer; uterine fibroids.

Gonaphene *Organon, Turk.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Gonasi HP *Amsa, Ital.*
⊗ Chorionic gonadotrophin (p.2085·1).
Amenorrhoea; cryptorchidism; hypogonadism; infertility; threatened or recurrent miscarriage.

Gonavislide *Mochida, Jpn.*
Pregnancy test (p.2372·1).

Gonaxine *Motima, Fr.*
Parsley piert (p.2363·2); sage (p.2382·3); achillea (p.2245·2); alfalfa (p.2249·2); avena (p.2262·1).
Tonic for females.

Gondofil *Aurora, Gr.†*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Gondonar *Teva Tuteur, Arg.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Gonic *Hauck, USA.*
⊗ Chorionic gonadotrophin (p.2085·1).
Male and female infertility; male hypogonadism; prepubertal cryptorchidism.

Gonif *Kleva, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Gonioscopic *Alcon, USA.*
Hyetellose (p.2143·3).
Gonioscopic examination.

Goniosoft *Ocusoft, USA.*
Hypromellose (p.2144·2).

Goniosol *Novartis Ophthalmics, USA.*
Hypromellose (p.2144·2).
Gonioscopic examination.

Gonne Balm *Lane, UK.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Joint and muscular pain.

Gonning *HPP, Hong Kong.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Gonoform *Merckle, Cz.†*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Gonol *Neo Quimica, Braz.*
⊗ Ampicillin (p.204·1).
Probenecid (p.558·2) is included in this preparation to reduce renal tubular excretion of the antibiotic.
Bacterial infections.

Gonorcin *General Drugs, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Gonotrop F *Win-Medicare, India.*
⊗ Urofollitropin (p.2136·3).
Stimulation of ovulation.

Goodnight Formula *Vitaplex, Austral.†*
Valerian (p.2410·1); chamomile (p.2279·3); passion flower (p.2363·2); skullcap (p.2388·2); vitamin B substances (p.1922·1); zinc sulfate (p.1999·2).
Insomnia.

Goodnight StopSnore *Swisshealth, UK.*
Sunflower oil (p.1970·3); peppermint oil (p.1761·2); sesame oil (p.2386·1); vitamins B , C, and E (p.1922·1).
Snoring.

Goodypops *Health Imports, UK.*
Echinacea (p.2298·1); vitamin C (p.1983·3); pectin (p.2145·2).
Sore throat.

Goodys Extra Strength *Goodys, USA.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Goody's Headache Powders *GSK Consumer, USA.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).

Goodys PM *GSK Consumer, USA.*
Diphenhydramine citrate (p.577·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Gool
Note. This name is used for preparations of different composition.
Medicom, Cz.
Sodium glucosamine sulfate complex (p.2313·2).
Osteoarthritis.

CSC, Hung.
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Go-On *Opfermann, Ger.; Rotta, Hong Kong; Rottapharm, Ital.; Rotta, Malaysia.*
Sodium hyaluronate (p.2320·1).
Joint disorders; osteoarthritis; synovial fluid replacement.

Go-Pain
Note. This name is used for preparations of different composition.
MDI, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

MDI, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain with tension.

Go-Pain P *MDI, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Gopten *Abbott, Austral.; Abbott, Austria; Abbott, Braz.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.†; Abbott, Fr.†; Abbott, Ger.†; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Ital.; Knoll, Mex.†; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Knoll, S.Afr.†; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Turk.; Abbott, UK.*
Trandolapril (p.1416·2).
Heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Goralgin *Guardian, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Gordius *Gedeon Richter, Hung.*
Gabapentin (p.482·3).
Epilepsy.

Gordobalm *Gordon, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Gordochom *Gordon, USA.*
Undecenoic acid (p.549·2); chloroxylenol (p.1640·2).
Fungal skin infections.

Gordofilm *Gordon, USA.*
Salicylic acid (p.1612·2).
Verrucas.

Gordogesic *Gordon, USA.*
Methyl salicylate (p.85·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Gordox *Gedeon Richter, Cz.†; Gedeon Richter, Hung.†; Gedeon Richter, Rus.*
Aprotinin (p.1055·1).
Fibrinolytic haemorrhage; pancreatitis; reduction of blood loss during open-heart surgery; shock.

Gorei-san *Tsumura, Jpn.*
Alisma rhizome; atractylodes lancea rhizome; polyporus sclerotium; poria sclerotium; cinnamon bark.
Traditional Kampo medicine.

Gorgonium *Drossapharm, Switz.*
Heparin (p.1301·2); allantoin (p.1588·1); dexpanthenol (p.2362·1); collagen (p.2286·1).
Scars.

Gorin-san *Tsumura, Jpn.*
Poria sclerotium; scutellaria root; liquorice; rehmannia root; plantago seed; alisma rhizome; Japanese angelica root; akebia stem; gardenia fruit; peony root; talc.
Traditional Kampo medicine.

Gormel *Gordon, USA.*
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Gosha-jinki-gan *Tsumura, Jpn.*
Rehmannia root; achyranthes root; cornus fruit; dioscorea rhizome; plantago seed; alisma rhizome; poria sclerotium; moutan bark; cinnamon bark; aconite tuber.
Traditional Kampo medicine.

Goshakusan *Tsumura, Jpn.*
Atracylodes lancea rhizome; citrus unshiu peel; Japanese angelica root; pinellia tuber; poria sclerotium; liquorice; platycodon root; immature orange; cinnamon bark; magnolia bark; peony root; ginger; cnidium rhizome; jujube; angelica dahurica root; ephedra.
Traditional Kampo medicine.

Gota Cebrina *Irisfarma, Spain†.*
Multivitamin preparation (p.1922·1).

Gotabiotic *Poen, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Gotabiotic D *Poen, Arg.*
⊗ Tobramycin (p.354·1); naphazoline hydrochloride (p.1565·2); dexamethasone phosphate (p.1526·2).
Conjunctivitis.

Gotabiotic F *Poen, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Gotadex *Collins, Mex.†*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Infected eye disorders.

Gotafer *Spefar, Venez.†*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Gotalax *Mertens, Arg.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Gotal-Be *Galeno, Venez.*
Vitamin B substances (p.1922·1).
Dietary supplement.

Gotalgic *Laboratorios Chile, Chile.*
⊗ Polymyxin B (p.318·2); neomycin (p.305·1); betamethasone phosphate (p.1519·1); lidocaine hydrochloride (p.1862·3).
Otitis externa; otitis media.

Gotas Binelli *Daudt, Braz.*
Fedrilate (p.1560·3).
Coughs.

Gotas Digestivas *Bunker, Braz.*
Chamomile (p.2279·3); gentian (p.2310·3); nux vomica (p.2355·3); boldo (p.2267·2).
Liver disorders.

Gotas Nican
Note.This name is used for preparations of different composition.
Prima, Braz.†.
Belladonna (p.2263·3); grindelia (p.2317·2); aconite (p.2246·1); bromoform (p.2269·3); sodium dibunate (p.1573·1); passion flower (p.2363·2); sodium benzoate (p.1630·2).
Coughs.

Andromaco, Chile†.
Codeine (p.37·2); bromoform (p.2269·3); aconite (p.2246·1); belladonna (p.2263·3); grindelia (p.2317·2); drosera (p.2297·3); sodium benzoate (p.1630·2); cherry-laurel water.
Coughs.

Gotas Otologicas
Drag, Chile†.
Lidocaine (p.1862·3); sulfathiazole (p.343·2).
Bacterial ear infections.

Volta, Chile.
Lidocaine (p.1862·3); sulfathiazole sodium (p.343·3).
Bacterial ear infections.

Gotavit *Berman, Mex.*
Multivitamin preparation (p.1922·1).

Goteborg *Driburg, Arg.*
Magnesium; riboflavin (p.1922·1).
Dietary supplement.

Gotely *Tecnofarma, Chile.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Gothaplast Capsicum-Warmepflaster *Gothaplast, Ger.*
Nonivamide (p.96·2).
Musculoskeletal and joint disorders.

Gothaplast Rheumamed AC *Gothaplast, Ger.*
Capsicum (p.2276·2); arnica (p.2260·2).
Musculoskeletal and joint disorders.

Gotinal *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
⊗ Naphazoline hydrochloride (p.1565·2).
Allergic rhinitis; cold and influenza symptoms; nasal congestion; sinusitis.

Gotir *Hexal, Arg.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Gotropil *Guardian, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Gotu Kola *Natural Life, Arg.†.*
Centella (p.1592·3).
Dietary supplement.

Goutichine *Farmaline, Thai.*
Colchicine (p.556·1).
Gout.

Goutnil *Inga, India; Inga, Malaysia†.*
Colchicine (p.556·1).
Gout.

Gouttes aux Essences *Plantes et Medecines, Fr.*
Peppermint oil (p.1761·2); clove oil (p.2285·1); thyme oil (p.2401·2); cinnamon oil (p.2283·2); lavender oil (p.2331·2).
Respiratory-tract disorders.

Gouttes contre le rhume des foins *Phytomed, Switz.*
Homoeopathic preparation.

Gouttes contre la toux "S" *Hanseler, Switz.*
Codeine phosphate (p.37·2); aromatic tincture; hyoscyamus (p.2323·3); ipecacuanha (p.1562·3); drosera (p.2297·3); ribwort plantain (p.2379·1).
Coughs.

Gouttes d'Or *UB, Switz.*
Homoeopathic preparation.

Gouttes nasales *Spirig, Switz.†.*
Phenylephrine (p.1568·1).
Nasal congestion; rhinitis; sinusitis.

Gouttes nasales N *Spirig, Switz.†.*
⊗ Naphazoline nitrate (p.1565·2); phenylephrine (p.1568·1).
Nasal congestion; rhinitis; sinusitis.

Gouttes pour le coeur et les nerfs Concentrees *Zeller, Switz.†.*
Crataegus (p.2289·1); passion flower (p.2363·2).
Cardiac disorders; nervous disorders.

Goval *Pharma Investi, Chile.*
Risperidone (p.1024·2).
Psychoses.

Govazol *Guardian, Indon.*
Fluconazole (p.532·1).
Fungal infections.

Govotil *Guardian, Indon.*
Haloperidol (p.1000·2).
Anxiety; psychoses.

Goxil *Pharmacia, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Goxyral *Eriochem, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Gozid *General Drugs, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

GP *Cypress, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

G-Press *Gap, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

GP-Zide *Millimed, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Gracetam *Graha, Indon.*
Piracetam (p.368·2).
Cerebral infarction.

Gracevit *Daiichi Sankyo, Jpn.*
Sitafloxacin (p.332·1).
Bacterial infections.

Gracial *Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Ital.; Organon, Neth.; Organon, Philipp.; Organon, Port.; Organon, Spain; Organon, Switz.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Acne; biphasic oral contraceptive.

Gracil *Peithner, Austria.*
Homoeopathic preparation.

Gradiab *Coronet, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Gradient *Polifarma, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Gradin Del D Andreu *Roche, Spain†.*
Benzalkonium chloride (p.1629·1); benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Grafadon *Graha, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Grafic Forte *Bernabo, Arg.*
Aescin (p.2248·2); bamethan (p.1222·3).
Peripheral vascular disorders.

Grafic Retard *Bernabo, Arg.*
Aesculus (p.2248·2).
Haemorrhoids; venous insufficiency.

Grafin *IQFA, Mex.*
Butylhyoscine (p.1735·1).

Grahabion *Graha, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Grains de Vals
Note.This name is used for preparations of different composition.
Qualiphar, Belg.
Aloes (p.1705·2); belladonna (p.2263·3); cascara (p.1715·2); frangula bark (p.1732·2); intestinal mucosa extract (p.2337·3); ox bile extract (p.2266·3); phenolphthalein (p.1762·1).
Constipation.

Nogues, Fr.
Boldo (p.2267·2); cascara (p.1715·2); senna (p.1769·2).
Constipation.

Grains de Vals Nouvelle formule *Nogues, Switz.*
Senna (p.1769·2).
Constipation.

Gralddep *Continentales, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic skin disorders; respiratory-tract disorders.

Gramagen *Sandoz, Arg.*
Gemcitabine hydrochloride (p.727·3).
Malignant neoplasms.

Gramal *Probiomed, Mex.*
Molgramostim (p.1073·3).
Reduction of neutropenia associated with cytotoxic therapy or bone marrow transplants.

Gramalil *Astellas, Jpn.*
Tiapride hydrochloride (p.1032·1).
Behaviour disorders associated with stroke; dyskinesias.

Gramaxin *Antibioticos, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Gramcep *Vitalink, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Gramcil *Pharmawealth, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Gramcilina *Medley, Braz.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Gramenox *Verisfield, Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Gramibiotic *Cordoba, Arg.†.*
Neomycin (p.305·1); gramicidin (p.286·1).
Mouth and throat infections.

Gramicortil *Allergan, Arg.†.*
⊗ Neomycin sulfate (p.305·1); hydrocortisone (p.1535·2); naphazoline hydrochloride (p.1565·2).
Eye infections.

Gramidil *Dexo, Fr.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Gramigna (Specie Composta) *Dynacren, Ital.†.*
Couch-grass (p.2288·2); birch leaf (p.2266·3); solidago (p.2391·1); ononis (p.2357·1); liquorice (p.1740·3).
Urinary-tract disorders.

Graminflor *Adroka, Switz.†.*
Bath additive: Hay flower.
Musculoskeletal and joint disorders; wounds.

Gramipan *Mayoly-Spindler, Switz.†.*
Dequalinium chloride (p.1641·3); ascorbic acid (p.1983·3).
Mouth and throat infections.

Gramipen-F *Loeffler, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Gramium *Verisfield, Gr.*
Cefprozil (p.232·2).
Bacterial infections.

Grammicin *Siam Bheasach, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Grammidin *Domestic, Rus.*
Gramicidin S (p.286·2).
Mouth and throat infections.

Grammixin *Siam Bheasach, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Gramoce A *Vir, Spain.*
Ascorbic acid (p.1983·3); vitamin A (p.1971·2).
Deficiency of vitamins A and C.

Gramokil *Santa, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Gramoneg *Ranbaxy, India.*
Nalidixic acid (p.303·3).
Diarrhoea; urinary-tract infections.

Gramostim *Cristalia, Braz.†.*
Molgramostim (p.1073·3).

Grampenil *BMS, Arg.†.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Grampenil Bronquial *BMS, Arg.†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Respiratory-tract infections.

Gramplus *Chiesi, Ital.*
Clofoctol (p.255·3).
Bacterial infections of the respiratory tract.

Gramuno *Graha, Indon.*
Phyllanthi; curcuma longa; javanese turmeric (p.2406·3).
Liver disorders.

Gran *Kirin, Jpn.*
Filgrastim (p.1070·1).
Mobilisation of autologous peripheral progenitor cells; neutropenia.

Granamon *Norgine, Ger.†.*
Sterculia (p.1772·1).
Constipation.

Grandaxin *Egis, Cz.; EGIS, Hung.; Mochida, Jpn; Egis, Rus.; Egis, Thai.*
Tofisopam (p.1033·1).
Alcohol withdrawal syndrome; anxiety; autonomic dystonia; depression; fatigue; menopausal disorders; myasthenia; myopathy; post-traumatic stress disorder; premenstrual syndrome; psychiatric disorders.

Grand-Pa Headache *Group, S.Afr.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Grandpherol *Ilsan, Turk.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Graneodin
Note.This name is used for preparations of different composition.
BMS, Arg.
Gramicidin (p.286·1); neomycin sulfate (p.305·1); benzocaine (p.1854·1).
Mouth and throat disorders.

BMS, Chile.
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat infections.

BMS, Irl.; BMS, UK†.
Neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial infections of the skin and ear.

Graneodin B *BMS, Mex.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

Graneodin D Mentol *BMS, Mex.*
Phenylephrine (p.1568·1); phenylpropanolamine (p.1569·2); benzocaine (p.1854·1).
Nasal congestion.

Graneodin Expectorante *BMS, Arg.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Graneodin N
Note.This name is used for preparations of different composition.
BMS, Arg.
Gramicidin (p.286·1); neomycin sulfate (p.305·1); benzocaine (p.1854·1); noscapine (p.1566·2).
Coughs; mouth and throat disorders.

BMS, Chile†.
Chlorhexidine hydrochloride (p.1635·3); noscapine (p.1566·2).
Coughs; mouth and throat infections.

Graneodin-Tos *BMS, Chile.*
Noscapine (p.1566·2); chlorhexidine hydrochloride (p.1635·3).
Coughs; mouth and throat infections.

Grani di Vals *Geymonat, Ital.*
Cascara (p.1715·2); aloes (p.1705·2); aloin (p.1705·3).
Constipation.

Granicip
Cipla, India.
Granisetron (p.1733·1).
Nausea and vomiting induced by cytotoxics; postoperative nausea and vomiting.

Cipla, Venez.
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Granigen *Generics, Hung.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Granisol *Hawthorn, USA.*
Granisetron (p.1733·1).
Nausea and vomiting.

Granitron *Richmond, Arg.; Medicus, Gr.*
Granisetron (p.1733·1).
Nausea and vomiting.

Granocol *Schering, Austral.†; Schering, NZ.*
Sterculia (p.1772·1); frangula bark (p.1732·2).
Constipation.

Granocyte *Aventis, Arg.†; Mayne, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Aventis, Cz.†; Chugai, Denm.; Sanofi-Aventis, Fin.; Chugai, Fr.; Chugai, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; CSL, NZ; Aventis, Neth.; Chugai, Norw.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Chugai, Thai.; Aventis, UK; Sanofi-Aventis, Venez.*
Lenograstim (p.1073·1).
Mobilisation of autologous peripheral blood progenitor cells; reduction of neutropenia associated with bone marrow transplantation or cytotoxic therapy.

Granoleina *SIFI, Ital.†.*
dl-Alpha tocoferil acetate (p.1992·3); linoleic acid (p.2308·2); vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).
Vitamin deficiencies.

Granon *Nycomed, Denm.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Grans Remedy *Grans Remedy, NZ.*
Zinc oxide (p.1621·2); zinc undecenoate (p.549·3); alum (p.2254·1); talc (p.1615·2).
Foot odour.

Granu Fink Durchspulungs *GSK Consumer, Ger.†.*
Solidago virgaurea (p.2391·1).
Renal calculi; urinary-tract disorders.

Granu Fink Kurbiskern *GSK Consumer, Ger.*
Cucurbita (p.2290·2).
Urinary-tract disorders.

Granu Fink Kurbiskern N *GSK Consumer, Ger.*
Cucurbita (p.2290·2); cucurbita oil (p.2290·2).
Urinary-tract disorders.

Granu Fink Prosta *GSK Consumer, Ger.; GSK Consumer, Switz.*
Cucurbita (p.2290·2); cucurbita oil (p.2290·2); saw palmetto (p.2192·3).
Benign prostatic hyperplasia; urinary-tract disorders.

Granudoxy *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre, Fr.*
Doxycycline (p.267·1).
Bacterial infections; rosacea.

Granuflex
Note.This name is used for preparations of different composition.
Convatec, Israel; Convatec, UK.
Hydrocolloid dressing.
Burns; ulcers; wounds.

BMS, S.Afr.
⊗ Gelatin (p.1072·1); pectin (p.2145·2); carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Granugel
Note.This name is used for preparations of different composition.
Convatec, Israel.
Hydrocolloid gel.
Skin ulcers; wounds.

BMS, S.Afr.
Pectin (p.2145·2); carmellose sodium (p.2142·1).
Wounds.

Granugen *Abbott, Austral.*
Paraffin oil (p.2030·3); zinc oxide (p.1621·2); titanium dioxide (p.1617·3); paraffin viscous; ethyl vanillin; soft paraffin.
Minor wounds and ulcers; nappy rash.

Granulax *Lacefa, Arg.†.*
Sodium picosulfate (p.1771·1).
Constipation.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Granulderm *Copley, USA.*
Trypsin (p.2405·3); peru balsam (p.2365·3); castor oil (p.2278·1).
Wounds.

Granulen *Eurofarma, Braz.*
Filgrastim (p.1070·1).
Neutropenia.

Granules Boripharm *Dolisos, Fr.*
A range of homoeopathic preparations.

Granulex *Bertek, USA.*
Trypsin (p.2405·3); peru balsam (p.2365·3); castor oil (p.2278·1).
Wound dressing.

Granulokine *Roche, Braz.; Genesis, Gr.; Amgen, Ital.; Roche, Philipp.*
Filgrastim (p.1070·1).
Bone marrow transplantation; mobilisation of autologous peripheral blood progenitor cells; neutropenia.

GranuMed *Rugby, USA.*
Trypsin (p.2405·3); peru balsam (p.2365·3); castor oil (p.2278·1).
Wounds.

Gran-Verm *Brasmedica, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Granvit *Plants, Ital.*
Royal jelly (p.2382·1) with wheat-germ oil, carrot oil, and soya lecithin (p.1922·1).
Nutritional supplement.

Grassolind Neutral *Hartmann, Fr.*
White soft paraffin (p.2031·2); wool fat (p.2033·2); hard paraffin (p.2030·3).
Burns; ulcers; wounds.

Graten *Pisa, Mex.*
⊗ Morphine sulfate (p.86·3).
Pain.

Gratiella *3DDD, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Gratusminal *Almirall, Spain.*
Phenobarbital diethylamine (p.494·1).
Agitation; convulsive disorders; insomnia; smooth muscle spasm.

Grausin *Rowe-Fleming, Venez.†.*
Vitamin B substances (p.1922·1).

Gravergol *Carter Horner, Canad.†; Carter Horner, Hong Kong†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dimenhydrinate (p.576·2).
Migraine and other vascular headaches.

Gravibinan *Schering, Ital.†.*
Hydroxyprogesterone caproate (p.2110·3); estradiol valerate (p.2097·3).
Threatened or recurrent miscarriage.

Gravibinon *Schering, Ger.†.*
Hydroxyprogesterone caproate (p.2110·3); estradiol valerate (p.2097·3).
Threatened or recurrent miscarriage.

Gravida *Beres, Hung.*
Vitamin and mineral preparation (p.1922·1).

Gravidinona *Schering, Chile†; Schering, Mex.*
Hydroxyprogesterone caproate (p.2110·3); estradiol valerate (p.2097·3).
Recurrent miscarriage; threatened and recurrent miscarriage.

Gravi-Fol *Asconex, Ger.*
Folic acid (p.1940·1).
Folic acid deficiency.

Gravigard *SPA, Ital.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Gravigen Plus *Altana, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).

Gravigil DHA *Ganassini, Fr.*
Vitamin, mineral, and fatty acid preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Gravimin DHA *Ethica, Indon.*
Vitamins; minerals; docosahexaenoic acid (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Gravindex *Ortho, Israel†.*
Pregnancy test (p.2372·1).

Gravistat *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Pol.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Gravitest *Scidia, Arg.†.*
Pregnancy test (p.2372·1).

Gravitest Crual *Cruciani, Ital.*
Pregnancy test (p.2372·1).

Gravol *Church & Dwight, Canad.; Carter Horner, Hong Kong; Wallace, India; Carter-Horner, Philipp.; Carter Horner, Thai.*
Dimenhydrinate (p.576·2).
Ménière's disease; motion sickness; nausea; radiation sickness; vertigo; vomiting.

Gravol Natural Source *Church & Dwight, Canad.*
Ginger (p.1732·3).
Nausea and vomiting.

Gravynon *Kimia, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Gray-F *Gray, Arg.*
⊗ Fentanyl citrate (p.55·3).
Pain.

Grayxona *Gray, Arg.*
Naloxone (p.1454·1).

Grazax *ALK, Cz.; ALK, Port.; ALK, UK.*
Grass pollen extracts (*Phleum pratense*) (p.2370·2) (p.2250·2).
Allergen immunotherapy.

GRD *Cadila, India.*
Dietary supplement (p.1922·1).

Greatbloc *Creative Brands, Austral.†.*
SPF 15; SPF 30+: Padimate O (p.1609·1); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Greater-Gloxa *Greater Pharma, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Greatofen *Greater Pharma, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Green Antiseptic Mouthwash & Gargle *Lee-Adams, Canad.*
⊗ Alcohol (p.1625·2); cetylpyridinium chloride (p.1635·1).

Green Diet *Garden House, Arg.*
Glucomanan; seaweed extract (p.1922·1).
Dietary supplement.

Green Throat Spray *Clay Park, USA.*
Phenol (p.1656·1).
Sore throat.

Greenpearl *Ipca, India†.*
d-Alpha Tocopherol (p.1992·2).
Vitamin E deficiency.

Grefen *Doetsch, Grether, Switz.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Gregoderm *Alliance, UK†.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); hydrocortisone (p.1535·2); nystatin (p.543·2).
Infected skin disorders.

Greini *Fada, Arg.*
Amikacin (p.200·2).
Bacterial infections.

Grenfung *Cevallos, Arg.*
Ketoconazole (p.539·1).
Fungal infections.

Grenin *YSP, Malaysia†.*
Theophylline sodium glycinate (p.1146·3); guaifenesin (p.1561·3).
Asthma; bronchitis.

Grenis *Genepharm, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Grenis-cipro *Genepharm, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Grenis-Oflo *Genepharm, Gr.*
Ofloxacin (p.310·2).
Bacterial infections.

Grenovix *Genepharm, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Greosin *GSK, Spain†.*
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Grepiflox *Rivero, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

G-Revm *Gap, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Grexin *Pharmasant, Thai.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Gribex Hot *Ulkar, Turk.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); pseudoephedrine (p.1571·2).
Fever; pain.

Gricin *Riemser, Ger.*
Griseofulvin (p.535·2).
Fungal skin, hair, and nail infections.

Grietalgen *Uriach Aquilea OTC, Spain.*
Peru balsam (p.2365·3); bismuth subnitrate (p.1711·2); ergocalciferol (p.1987·1); estrone (p.2101·2); benzocaine (p.1854·1); vitamin A (p.1971·2).
Cracked nipples; mastitis.

Grietalgen Hidrocort *Diviser Aquilea, Spain†.*
⊗ Bismuth subnitrate (p.1711·2); colecalciferol (p.1986·2); estrone (p.2101·2); benzocaine (p.1854·1); vitamin A (p.1971·2); hydrocortisone glycyrrhetinate (p.1536·2); neomycin sulfate (p.305·1).
Burns; cracked nipples; mastitis; skin disorders; wounds.

Grifed *Bayer Consumer, Mex.*
Naproxen sodium (p.92·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; rhinitis; sinusitis.

Grifoalpram *Laboratorios Chile, Chile.*
Alprazolam (p.960·1).
Anxiety; panic attacks.

Grifobutol *Laboratorios Chile, Chile.*
⊗ Acebutolol (p.1200·1).
Angina pectoris; arrhythmias; hypertension.

Grifociprox *Laboratorios Chile, Chile.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Grifoclobam *Laboratorios Chile, Chile.*
Clobazam (p.477·2).
Anxiety; epilepsy.

Grifocriptina *Laboratorios Chile, Chile.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation suppression; mastodynia; parkinsonism; prolactinoma.

Grifodilzem *Laboratorios Chile, Chile.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Grifoftal
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile†.
Eye drops: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Laboratorios Chile, Chile†.
Eye ointment: Polymyxin B (p.318·2); neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial eye infections.

Grifoftal-D *Laboratorios Chile, Chile.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1); polymyxin B (p.318·2).
Bacterial eye infections with inflammation.

Grifogemzilo *Laboratorios Chile, Chile.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Grifonimod *Laboratorios Chile, Chile.*
Nimodipine (p.1357·2).
Ischaemic neurological deficit following cerebral vasospasm.

Grifonitren *Laboratorios Chile, Chile.*
Nitrendipine (p.1358·2).
Hypertension.

Grifoparkin *Laboratorios Chile, Chile.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Grifopril *Laboratorios Chile, Chile.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Grifopril-D *Laboratorios Chile, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Grifotaxima *Laboratorios Chile, Chile†.*
Cefotaxime (p.229·1).
Bacterial infections.

Grifotenol *Laboratorios Chile, Chile.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Grifotriaxona *Laboratorios Chile, Chile.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Grifulin *Teva, Israel.*
Griseofulvin (p.535·2).
Fungal skin infections.

Grifulvin *General Drugs, Thai.*
Griseofulvin (p.535·2).
Fungal skin, hair, and nail infections.

Grilinctus
Note. This name is used for preparations of different composition.
Franco-Indian, India.
Capsules: Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Coughs.

Franco-Indian, India.
Syrup: Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Coughs.

Grilinctus-BM *Franco-Indian, India.*
⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2).
Asthma; bronchitis; respiratory-tract disorders associated with increased or viscous mucus.

Grimal *Grin, Mex.*
⊗ Sodium hyaluronate (p.2320·1); oxymetazoline (p.1567·2).
Dry eyes; eye congestion.

Grimeral *Biomep, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Grindocin *Grin, Mex.†.*
Indometacin (p.66·3).
Anterior eye inflammation following laser treatment or surgery; cystoid macular oedema following cataract surgery; intra-operative miosis.

Grinevel *Filaxis, Arg.*
Ganciclovir sodium (p.879·2).
Viral infections.

Grinflux *Selvi, Ital.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Grinsil *Nova Argentia, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Grinsil Clavulanico *Nova Argentia, Arg.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Grinsil Duo *Nova Argentia, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Grinsil Respiratorio *Nova Argentia, Arg.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Gripakin *Almi, Spain.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Gripaleta *Naturex, Mex.†.*
Echinacea (p.2298·1); zinc (p.1999·1); ascorbic acid (p.1983·3).
Influenza.

Gripanil
Note. This name is used for preparations of different composition.
Ducto, Braz.†.
Injection: Ampoule A, dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); ampoule B, ascorbic acid (p.1983·3); mepyramine maleate (p.585·2). Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Influenza symptoms.

Ducto, Braz.†.
Tablets: Green tablets, dipyrone (p.49·2); camphor (p.2273·2); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); white tablets, ascorbic acid (p.1983·3); mepyramine maleate (p.585·2).
Influenza symptoms.

Gripanil C *Ahimsa, Arg.*
Paracetamol (p.108·1); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Fever; pain.

Gripasan Compuesto *Laboratorios Chile, Chile.*
Paracetamol (p.108·1); propyphenazone (p.119·3); pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Formerly contained paracetamol, propyphenazone, phenylpropanolamine hydrochloride, chlorphenamine maleate, and caffeine.
Cold and influenza symptoms.

Gripasan Nueva Formula *Laboratorios Chile, Chile.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Gripavac *Sanofi Pasteur, Spain.*
An influenza vaccine (p.2218·2).
Active immunisation.

Gripcaps C *Infabra, Braz.†.*
Phenylephrine (p.1568·1); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Gripe Mixture *British Dispensary, Thai.*
Sodium bicarbonate (p.1673·2); dill oil (p.2293·3); caraway oil (p.2277·1); peppermint oil (p.1761·2).
Flatulence; infant colic.

Gripe Water *Beacons, Singapore†.*
Sodium bicarbonate (p.1673·2).
Flatulence; gastric hyperacidity.

Gripen *EMS, Braz.*
Dimetindene maleate (p.576·3); rutoside (p.2305·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Gripen F *EMS, Braz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).

Gripeol *Cifarma, Braz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Gripeonil *Faria, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Gripetral *Atral, Port.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Gripex *US Pharmacia, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Gripex Noc *US Pharmacia, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Gripexin Limonada Caliente *Labomed, Chile.*
Paracetamol (p.108·1); sodium ascorbate (p.1984·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Gripexin Nueva Formula Compuesto *Labomed, Chile†.*
Paracetamol (p.108·1); sodium ascorbate (p.1984·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Gripexin Nueva Formula C/Pseudoefedrina *Labomed, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Gripguard *Socopharm, Fr.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Gripidor *Gestafarma, Port.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Gripin *Gripin, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Gripin Kase *Gripin, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Gripion *Makros, Braz.†.*
Diphenhydramine hydrochloride (p.577·2); dipyrone (p.49·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Gripomatine
Note. This name is used for preparations of different composition.
Hexal, Braz.†.
Syrup: Dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); vitamin C (p.1983·3).
Cold and influenza symptoms.

Hexal, Braz.†.
Tablets: Green tablets, dipyrone (p.49·2); guaifenesin (p.1561·3); orange tablets, ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Griponal *Merck, Port.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Griponia *Bunker, Braz.†.*
Green tablets or ampoule 1, dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); yellow tablets or ampoule 2, ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Gripotermon *Prodotti, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Gripp Heel *Peithner, Austria; Heel, Cz.*
Homoeopathic preparation.

Grippakit *Ximena Polanco, Chile.*
Homoeopathic preparation.

Grippal *Bayer, Spain.*
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); phenylephrine (p.1568·1).
Formerly contained aspirin, chlorphenamine maleate, and phenylpropanolamine.
Influenza and cold symptoms; nasal congestion.

Grippalgine N *DP-Medica, Switz.†.*
Paracetamol (p.108·1); salicylamide (p.121·2); caffeine (p.1116·3).
Cold and influenza symptoms.

Grippalin *Multi-Pro, Canad.†.*
⊗ Ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1).

Grippalin & C *Multi-Pro, Canad.†.*
⊗ Ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1).

Grippe-Gastreu S R6 *Reckeweg, Ger.*
Homoeopathic preparation.

Grippetee St Severin *Smetana, Austria.*
Sambucus flower (p.2383·1); tilia flower (p.2402·2); ribwort plantain (p.2379·1).
Cold symptoms.

Grippetropfen Nr 20 *Doskar, Austria.*
Homoeopathic preparation.

Grippex *Unipharm, Rus.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract disorders with congestion.

Gripp-Heel *Heel, Ger.; Heel, S.Afr.*
Homoeopathic preparation.

Grippinon *Nycomed, Austria.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms.

Grippol *Microgen, Rus.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Grippon
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Capsules: Paracetamol (p.108·1); caffeine (p.1116·3); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Adcock Ingram, S.Afr.
Syrup: ⊗ Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); ephedrine (p.1558·1).
Cold and influenza symptoms.

Grippostad
Note. This name is used for preparations of different composition.
Stada, Austria; Stada, Hung.; Stada, Pol.
Paracetamol (p.108·1).
Fever; pain.

Stada, Rus.
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Grippostad C
Note. This name is used for preparations of different composition.
Stada, Austria; Stada, Cz.; Stada, Ger.; Stada, Hung.; Stada, Pol.; Stada, Rus.
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Medika, Switz.†.
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Grippostad Gute Nacht-Saft *Stada, Ger.†.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Grippostad Heissgetrank *Stada, Ger.†.*
Paracetamol (p.108·1).
Fever; pain.

Grippostad Horky Napoj *Stada, Cz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Grippostad Rhino *Stada, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Gripps *Pascoe, Ger.†.*
Homoeopathic preparation.

Gripsay *Delta, Braz.*
Ampoule A, dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); ampoule B, mepyramine maleate (p.585·2); ascorbic acid (p.1983·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Cold and influenza symptoms.

Gripson *Sons, Mex.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Influenza symptoms.

Griptol *Brasmedica, Braz.†.*
Aspirin (p.20·3); caffeine (p.1116·3); vitamin C (p.1983·3).
Fever; pain.

Grisactin *CFL, India.*
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Grisefuline *Sanofi-Aventis, Fr.*
Griseofulvin (p.535·2).
Fungal infections.

Griseo *CT, Ger.*
Griseofulvin (p.535·2).
Fungal skin infections.

Griseocrem *Ivax, Arg.*
⊗ Diflorasone diacetate (p.1529·1); econazole nitrate (p.531·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Griseofort *Schering-Plough, Indon.*
Griseofulvin (ultramicronized) (p.535·2).
Fungal infections of the skin, hair, and nails.

Griseomed *Sanochemia, Austria†.*
Griseofulvin (p.535·2).
Superficial fungal infections.

Griseoplus *Ivax, Arg.*
⊗ Griseofulvin (p.535·2); econazole nitrate (p.531·1); hydrocortisone (p.1535·2); salicylic acid (p.1612·2); neomycin undecenoate (p.305·2); boric acid (p.2268·1).
Infected skin disorders.

Griseostatin *Schering-Plough, Austral.†.*
Griseofulvin (p.535·2).
Fungal infections of the skin and nails.

Grisetin *Ipsen, Spain.*
Flutamide (p.725·1).
Prostatic cancer.

Grisetin Con Carnitina *Andromaco, Chile†.*
Cyproheptadine hydrochloride (p.575·1); carnitine hydrochloride (p.1933·1).
Reduced appetite.

Grisflavin *Asian Pharm, Thai.*
Griseofulvin (p.535·2).
Fungal skin, hair, and nail infections.

Grisical *Grisi, Mex.†.*
Calcium carbonate (p.1714·1).

Grisol *Gebro, Switz.†; Transdermal, UK.*
Griseofulvin (p.535·2).
Tinea pedis.

Grisomicon *Sanitas, Port.†.*
Griseofulvin (p.535·2).
Fungal infections.

Grisovin *Medac, Arg.; Sigma, Austral.; GSK, Austria; GSK, Mex.; GSK, Philipp.; Glaxo Wellcome, Port.; GSK, Turk.; GSK, UK†; GSK, Venez.*
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Grisovina FP *Teofarma, Ital.*
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Gris-PEG *Pedinol, USA.*
Griseofulvin (ultramicrosize) (p.535·2).
Fungal skin, hair, and nail infections.

Grisuvin *DHA, Malaysia.*
Griseofulvin (p.535·2).
Fungal skin, hair, and nail infections.

Grisux Dia y Noche *Prater, Chile.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); chlorphenamine (p.572·2).

Grivin *Atlantic, Malaysia; Atlantic, Singapore†; Atlantic, Thai.*
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Grizol *Grisi, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Grodurex *Grossmann, Switz.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Grofenac *Grossmann, Hong Kong; Grossmann, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Grofibrat *Polfa, Cz.†; Polfa Grodzisk, Pol.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Gromazol *Grossmann, Switz.*
Clotrimazole (p.530·1).
Fungal foot infections.

Groprim *Grossmann, Switz.*
Co-trimoxazole (p.258·1).
Bacterial infections; blastomycosis; pneumocystis pneumonia.

Groprinosin *Polfa Grodzisk, Pol.*
Inosine pranobex (p.884·2).
Herpesvirus infections.

Groseptol *Polfa Grodzisk, Pol.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Groven *Filaxis, Arg.*
Aripiprazole (p.962·3).
Schizophrenia.

Growart *Iapharm, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Growee *Pediatrica, Indon.*
Calcium gluconate; vitamins; lysine hydrochloride; taurine; glutamic acid (p.1922·1).
Nutritional supplement.

Growee with Chlorella *Pediatrica, Philipp.*
Vitamins; amino acids; chlorella growth factor (p.1922·1).

Growell *ICM, Singapore.*
Minoxidil (p.1342·1).
Alopecia.

Growgen-GM *Bioprofarma, Arg.*
Molgramostim (p.1073·3).
Neutropenia.

Growject *Sumitomo, Jpn.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Gruben *Pasteur, Chile.*
Codeine phosphate (p.37·2); bromoform (p.2269·3); sodium camsilate (p.2388·3); belladonna (p.2263·3); sodium benzoate (p.1630·2).
Coughs.

Grumivit *Piemont, Ital.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Grunamox *Grunenthal, Cz.†; Grunenthal, Pol.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Gruncef *Grunenthal, Ger.*
Cefadroxil (p.218·1).
Bacterial infections.

Grunicef *Grunenthal, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Grunicina *Grunenthal, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Gruntin Tropfen *Grunenthal, Ger.†.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Grupozil *Velka, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Grypolek *Kato, Pol.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough and cold symptoms.

Grypostop *Omega Rex, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Grypostop Mix *Omega Rex, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

G-Tase *Unichem, India.*
Pioglitazone (p.456·3).
Diabetes mellitus.

G.Test *Sabiluc, Fr.†.*
Pregnancy test (p.2372·1).

GTO Oil *Nutricia, Ital.*
Glyceryl trioleate (p.2334·3).
Adrenoleucodystrophy.

GU Eau *Knobel, Switz.†.*
Arnica (p.2260·2); rhatany root (p.2378·3); myrrh (p.2349·2); salol (p.122·1); anethole (p.2258·1); menthol (p.2340·1); poppy-seed oil (p.2371·1); mint oil (p.2345·2); thymol (p.1664·3).
Mouth and throat disorders.

Guadal *Rafarm, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Guadex *Hoe, Malaysia.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Guaiacalcium Complex *SIT, Ital.*
Dropropizine (p.1557·3); sulfogaiacol (p.1573·2).
Coughs.

Guaiacol *Vitamed, Israel.*
Sulfogaiacol (p.1573·2).
Coughs.

Guaiacum Complex *Mediherb, Austral.†.*
Guaiacum resin (p.2317·3); celery (p.2278·3); feverfew (p.622·2); birch leaf (p.2266·3); devil's claw root (p.39·1); salix (p.121·3).
Arthritis and rheumatic pain.

GUAI/DM *Brighton, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Guaifed *Verum, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Formerly contained pseudoephedrine hydrochloride and guaifenesin.
Coughs; nasal congestion.

Guaifed-PD *Verum, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Formerly contained pseudoephedrine hydrochloride and guaifenesin.
Coughs; nasal congestion.

Guaifen *Cassara, Arg.*
Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Guaifenesin DAC *Cypress, USA.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.

Guaifenesin DM *Prasco, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Guaifenesin PSE *Cypress, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Guaifenex LA *Ethex, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Guaifenex DM *Ethex, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Guaifenex G *Ethex, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Guaifenex PSE *Ethex, Hong Kong; Ethex, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Guaifenex Rx *Ethex, USA†.*
AM tablets, guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); PM tablets, guaifenesin.
Coughs.

Guaifenex Rx DM *Ethex, USA†.*
AM tablets, guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); PM tablets, guaifenesin; dextromethorphan hydrobromide (p.1555·2).
Coughs.

Guaimax-D *Schwarz, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Guais *Medic+Aid, Philipp.*
Guaifenesin (p.1561·3).
Cough.

Guaitab *Muro, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Guaivent *Ethex, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Guai-Vent/PSE *Dura, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Guajacuran *Zentiva, Cz.*
Guaifenesin (p.1561·3).
Anxiety disorders; depression; pain; skeletal muscle spasm.

Guajanal *Leciva, Cz.†.*
Paracetamol (p.108·1); guaifenesin (p.1561·3).
Musculoskeletal pain; neuralgia.

Guajazyl *Espefa, Pol.*
Guaifenesin (p.1561·3).
Cough.

Guamet *Medreich, Hong Kong.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Guanicar *Biotech, Venez.*
Succinylsulfathiazole (p.334·3); activated charcoal (p.1435·2).
Gastrointestinal infections.

Guaphenyl II *Rivers Edge, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Guar Verlan *Verla, Ger.*
Guar gum (p.442·3).
Diabetes mellitus; hyperlipidaemias.

Guarafort *Fontovit, Braz.*
Guarana (p.2416·1).

Guarana *Natufarma, Arg.*
Caffeine (p.1116·3).
Fatigue.

Guarana Diates *Provefarma, Arg.*
Guarana (p.2416·1); calcium pantothenate (p.1959·3).
Dietary supplement.

Guaranace *Tecnonat, Arg.†.*
Ascorbic acid; magnesium; guarana (p.1922·1).
Tonic.

Guarcol *Orion, NZ.*
Food thickener (p.442·3).
Dysphagia.

Guarem *Orion, Fin.; Shire, Hong Kong†; Rybar, Irl.†.*
Guar gum (p.442·3).
Diabetes mellitus; dumping syndrome; hyperlipidaemias.

Guarposid *Guardian, Indon.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Guastil *Uriach, Spain.*
Sulpiride (p.1028·3).
Anxiety; psychoses; vertigo.

Guayalin *Farcoral, Mex.*
Cineole (p.2282·3); guaiacol (p.1561·2).
Coughs.

Guayalin-Plus *Farcoral, Mex.†.*
Guaiacol (p.1561·2); gordolobo; cineole (p.2282·3); honey (p.1948·2); vitamin C (p.1983·3).
Respiratory-tract disorders.

Guayaprin *Liferpal, Mex.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Guayaten *Flupal, Venez.*
Minoxidil (p.1342·1).
Hypertension.

Guemusin *Fada, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Guep'Away *Clement, Fr.†.*
Ethyl butylacetylaminopropionate (p.2043·1); Frepylate.
Insect repellent.

Guethural *Elerte, Fr.*
Guaietolin (p.1561·2).
Respiratory-tract congestion.

Gufensin *Christo, Hong Kong.*
Guaifenesin (p.1561·3).
Coughs.

Gugecin *Lilly, Mex.†.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Gug/X *Ximena Polanco, Chile.*
Homoeopathic preparation.

Guiatex PSE *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Guiatuss *Goldline, USA.*
Guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Guiatuss PE *Barre-National, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Guiatussin with Codeine Expectorant *Rugby, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Guiatussin DAC *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Guiatussin with Dextromethorphan *Rugby, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Guigoz Hypoallergenique *Guigoz, Fr.*
Infant feed (p.1922·1).
Milk-protein allergy.

Guigoz Soja *Guigoz, Fr.†.*
Infant feed (p.1922·1).
Lactose intolerance.

Guigoz Transit *Guigoz, Fr.*
Infant feed (p.1922·1).
Gastrointestinal disorders.

Gulamyl *Elpen (Ελπεν), Gr.*
Guaiacol (p.1561·2); theophylline (p.1140·1).
Bronchodilator.

Gulaper *Roemmers Osmoph, Venez.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Gum PerioBalance *Sunstar, UK.*
Lactobacillus reuteri prodentis (p.2372·3).
Gum disorders.

Gumbaral *AWD, Ger.*
Ademetionine sulfate tosilate (p.2247·1).
Degenerative joint disorders.

Gumbix *Solvay, Austria†; Solvay, Cz.†; Riemser, Ger.*
Aminomethylbenzoic acid (p.1054·1).
Haemorrhage.

Gum-Ese *McGloin, Austral.†.*
Lidocaine hydrochloride (p.1862·3); benzalkonium chloride (p.1629·1).
Mouth ulcers.

Gumilk *Gallia, Fr.*
Ceratonia (p.2143·2); maltodextrin (p.1955·3).
Regurgitation in infants.

Gunabion *Sunthi Sepuri, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1975·1).
Lumbago; migraine; neuralgia; neuritis; neuropathy; tonic; vomiting of pregnancy.

Gunaceta *Sunthi Sepuri, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Gunacold *Sunthi Sepuri, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Allergy; cold symptoms; cough.

Gunapect *Sunthi Sepuri, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Gunevax *Chiron Vaccines, Ital.†; Chiron Behring, Malaysia†; Fustery, Mex.†; Chiron, Thai.†.*
A rubella vaccine (Wistar RAA 27/3 strain) (p.2236·3).
Active immunisation.

Gupisone *Julphar, UAE.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Gurfi Fibras *Gurfi, Arg.†.*
Bran (p.1712·3); wheat; glucose.
Fibre supplement.

Gurfix *Novartis Consumer, Austria.*
Hexetidine (p.1647·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat inflammation.

Gurgellosung Chauvin *Chauvin ankerpharm, Ger.†.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Gurgellosung-ratiopharm *Ratiopharm, Ger.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Guronsan
Note. This name is used for preparations of different composition.
Exel, Belg.; Organon, Fr.; Jaba Recordati, Port.
Glucuronamide (p.2314·2); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Asthenia; tonic.

Inibsa, Spain.
Glucuronamide (p.2314·2); ascorbic acid (p.1983·3).
Tonic.

Chugai, Hong Kong†.
Injection: Glucuronic acid (p.2314·1).
Tonic.

Chugai, Hong Kong†.
Oral liquid: Vitamin B ; vitamin B ; glucurolactone; vitamin B (p.1922·1).
Tonic.

Chugai, Hong Kong†.
Tablets: Glucurolactone; glucuronamide; vitamin C; thiamine disulfide (p.1922·1).
Tonic.

Guronsan C *Pharmacare, S.Afr.*
Glucurolactone; glucuronamide; ascorbic acid; caffeine (p.1922·1).
Tonic.

Gustamax *Alodial, Port.†.*
Levosulpiride (p.1028·3).
Gastrointestinal motility disorders.

Gutalax *Boehringer Ingelheim, Spain.*
Sodium picosulfate (p.1771·1).
Constipation.

Gutman *Rafarm, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).

Gutnacht
Note. This name is used for preparations of different composition.
Salushaus, Ger.†.
Oral liquid: Valerian (p.2410·1); passion flower (p.2363·2); St John's wort (p.422·3); melissa (p.2339·3); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Insomnia; nervous disorders.

Salushaus, Ger.†.
Tablets: Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2); melissa (p.2339·3).
Nervousness; sleep disorders.

Gutron *Nycomed, Austria; Silesia, Chile; Nycomed, Cz.; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Hong Kong; Nycomed, Hung.; Nycomed, Israel; Lusofarmaco, Ital.; Douglas, NZ; Nycomed, Neth.; Nycomed, Pol.; Nostrum, Port.; Nycomed, Rus.; Nycomed, Singapore; Nycomed, Switz.; Nycomed, Thai.†.*
⊗ Midodrine hydrochloride (p.1341·1).
Circulatory disorders; ejaculation disorders; hypotension; orthostatic hypotension; urinary incontinence.

Guttae Stomachicae *Prolab, Pol.*
St John's wort (p.422·3); peppermint leaf (p.1761·2); bitter tincture; valerian (p.2410·1).
Gastric disorders.

Guttalax *Boehringer Ingelheim, Austria; Wolfs, Belg.†; Boehringer Ingelheim, Braz.; Silesia, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation; stool softener.

Guttanotte *Sigmapharm, Austria.*
Flunitrazepam (p.996·2).
Insomnia.

Guttaplast *Beiersdorf, Ger.†.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Guven *Megat, Venez.†.*
Sulpiride (p.1028·3).

Gwajatussin *Herbapol Lublin, Pol.*
Sulfogaiacol (p.1573·2); ribwort plantain (p.2379·1); verbascum (p.2413·3).
Cough; respiratory-tract congestion.

GX *Braun, Ger.; DeltaSelect, Ger.; Serum-Werk Bernburg, Ger.*
Glucose and xylitol infusion (p.1922·1).
Parenteral nutrition.

GXE *Braun, Ger.*
Glucose, xylitol, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Gyalme *Biocom, Fr.†.*
Sodium laurilsulfate (p.2138·3).
Genito-urinary cleansing.

Gydrelle *IPRAD, Fr.*
Estriol (p.2101·1).
Menopausal disorders.

Gydrelle Phyto *IPRAD-Sante, Fr.*
Soya bean (p.1965·3).

Gygel *Marlborough Pharmaceuticals, UK.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Gymiso *HRA, Fr.*
Misoprostol (p.2013·2).
Termination of pregnancy.

Gynae-CVP *Sterling, India.*
Citrus bioflavonoids (p.2304·1); vitamin C (p.1983·3); vitamin K (p.1995·2); ferrous gluconate (p.1939·1); calcium lactate (p.1676·1).
Gynaecological haemorrhage.

Gynaelite *Eulite, Neth.*
Homoeopathic preparation.

Gynaemine *Sriprasit, Thai.*
Ergotamine tartrate (p.620·1); ergometrine maleate (p.2009·2).
Oxytocic.

Gynafem *Rimsa, Mex.*
Butoconazole nitrate (p.528·1).
Vaginal infections.

Gynalgin *ICN, Pol.; Valeant, Rus.*
Chlorquinaldol (p.242·3); metronidazole (p.837·1).
Vaginal infections.

Gynalpha *CCD, Fr.*
Soya bean (p.1965·3).
Menopausal disorders.

Gynalpha Plus *CCD, Fr.*
Soya isoflavones (p.2391·2); chromium; selenium (p.1922·1).
Dietary supplement.

Gynamon *Jenapharm, Ger.*
Orange tablets, estradiol (p.2097·2); grey tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Gynasan *Bastian, Ger.†.*
Estriol (p.2101·1).
Menopausal disorders.

Gynastan *Slovakofarma, Cz.†.*
Lamium album; parsley piert (p.2363·2); potentilla anserina; peppermint leaf (p.1761·2).
Menstrual disorders.

Gynatam *Dabur, Philipp.; Dabur, Thai.; Biogalenic, Venez.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Gynatren *Strathmann, Ger.*
A trichomonal vaccine (p.2241·2).

Gynatrol *Wyeth Lederle, Denm.†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Gynax-N *Ativus, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); nystatin (p.543·2); neomycin sulfate (p.305·1); tyrothricin (p.358·2); sodium propionate (p.545·3); boric acid (p.2268·1).
Vulvovaginal disorders.

Gynazol *Gedeon Richter, Hung.; Richter, Pol.*
Butoconazole nitrate (p.528·1).
Vulvovaginal candidiasis.

Gynazole *Arrow, Austral.; Sigma, Braz.; Ferring, Canad.; Ther-Rx, USA.*
Butoconazole nitrate (p.528·1).
Vulvovaginal candidiasis.

Gyncobem *Cifarma, Braz.*
Ginkgo biloba (p.2311·1).

Gyndelta *CCD, Fr.*
Cranberry (p.2289·1).
Urinary-tract disorders.

Gynebo *Chew, Thai.*
Clotrimazole (p.530·1).
Trichomoniasis; vaginal fungal infections.

Gynecon *Continental Pharma, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1).
Fungal, trichomonal and bacterial vaginitis.

Gynecon-T *Continental Pharma, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1); melaleuca oil (p.2338·2).
Fungal, trichomonal and bacterial vaginitis.

Gynecort *Combe, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Gynecure *Pfizer Consumer, Canad.†.*
Tioconazole (p.548·2).
Vulvovaginal candidiasis.

Gynefam *Effik, Fr.*
Multivitamin and mineral preparation with omega-3 triglycerides (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Gynefix
Note. This name is used for preparations of different composition.
Ivax, Arg.
Ascorbic acid (p.1983·3).
Bacterial vaginosis.

Rottapharm, Ital.; Family Planning Sales, UK.
Copper-wound polypropylene thread (p.1935·2).
Intra-uterine contraceptive device.

Gynegella P *Rottapharm, Ital.†.*
Loosestrife (p.2334·3); α-ketoglutaric acid.
Vaginal douche.

Gyneiod *Wockhardt, Hung.†.*
Povidone-iodine (p.1659·2).
Vaginitis.

Gynelle 375 *CCD, Fr.*
Copper-wound polyethylene (p.1935·2).
Intra-uterine contraceptive device.

Gyne-Lotremin *Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Singapore†.*
Clotrimazole (p.530·1).
Vaginitis; vulvovaginal candidiasis.

Gyne-Lotrimin *Schering-Plough, Austral.†; Schering-Plough, USA.*
Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

Gyne-Moistrin *Schering-Plough, Canad.†.*
Polyglyceryl methacrylate; propylene glycol (p.2374·1).
Vaginal dryness.

Gynera *Schering, Braz.; Schering, Chile; Schering, Denm.; Schering, Gr.; Schering, Hong Kong; Schering, Indon.; Schering, Israel; Bayer Schering, Malaysia; Schering, Philipp.; Bayer, Port.; Schering, Singapore; Schering, Switz.; Schering, Thai.; Schering, Venez.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Gynergen Comp *Novartis, Denm.*
Belladonna (p.2263·3); butalbital (p.967·2); caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Migraine.

Gynergene Cafeine *Novartis, Fr.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Gynerium *Ivax, Arg.*
Ketoconazole (p.539·1); secnidazole (p.846·3).
Bacterial infections; candidiasis; trichomoniasis.

Gynerium UD *Ivax, Arg.*
1 Capsule, fluconazole (p.532·1); 4 tablets, secnidazole (p.846·3).
Trichomoniasis; urogenital candidiasis.

Gynesol *Biolab, Philipp.*
Clotrimazole (p.530·1).
Fungal skin infections.

Gynesten-B *Bangkok Lab & Cosmetic, Thai.*
⊗ Clotrimazole (p.530·1); betamethasone (p.1518·2).
Infected skin disorders.

Gynestin *Kenyaku, Thai.*
⊗ Clotrimazole (p.530·1); urea (p.1620·2).
Trichomoniasis.

Gynestrel *Recordati, Ital.*
Naproxen sodium (p.92·3).
Gynaecological disorders.

Gyne-T *Janssen-Ortho, Canad.†.*
Copper-wound polyethylene (p.1935·2).
Intra-uterine contraceptive device.

Gynevac *Vakcina, Hung.*
Lactobacillus acidophilus (p.2372·3).
Maintenance of vaginal flora.

Gynezol *Sagmel, Rus.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Gyn-Hydralin *Bayer, Fr.; Roche Nicholas, Hong Kong.*
Glycine (p.1947·3).
Formerly known as Hydralin in *Hong Kong.*
Pruritus; soap substitute.

Gynipral *Nycomed, Austria; Silesia, Chile†; Nycomed, Cz.; Nycomed, Hung.†; Nycomed, Rus.; Nycomed, Switz.*
⊗ Hexoprenaline sulfate (p.1123·2).
Premature labour.

Gyno Canesten *Bayer, Venez.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Gyno Icaden *Schering, Braz.*
Isoconazole nitrate (p.536·2).
Vulvovaginal candidiasis.

Gyno Iruxol *Abbott, Braz.*
Chloramphenicol (p.239·3); collagenase (p.2286·2).
Vulvovaginal infections.

Gyno Zalain *Pharmacia, Braz.*
Sertaconazole nitrate (p.546·1).
Fungal vaginal infections.

Gynocanesten *Bayer, Chile.*
Clotrimazole (p.530·1).
Vaginal infections.

Gyno-Canesten *Bayer, Ger.†; Bayer, Ital.; Bayer, Turk.*
Clotrimazole (p.530·1).
Balanitis; fungal vulvovaginal infections.

Gyno-Canestene *Bayer, Belg.†; Bayer, Switz.*
Clotrimazole (p.530·1).
Fungal vulvovaginal infections.

Gynocastus *Zilly, Ger.*
Vitex agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Gynoclin-V *Janssen-Cilag, Mex.*
⊗ Clindamycin (p.251·1); ketoconazole (p.539·1); fluocinolone (p.1531·3).
Vaginal infections.

Gynoco *TO-Chemicals, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1).
Trichomoniasis; vaginal fungal infections.

Gyno-Daktar *Janssen-Cilag, Ger.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Gyno-Daktarin *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen, Hong Kong†; Ethnor, India; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Miconazole nitrate (p.541·3).
Balanitis; vulvovaginal fungal and Gram-positive bacterial infections.

Gynodal *Asta Oncologia, Braz.*
Megestrol acetate (p.2114·3).
Malignant neoplasms.

Gynodel *Il-ko, Turk.*
Bromocriptine (p.800·3).
Acromegaly; benign breast disorders; female infertility; hyperprolactinaemia; lactation inhibition; menstrual disorders; parkinsonism; prolactinoma.

Gynoderain *Leti, Venez.*
Triticum aestivum (p.2415·1).
Vaginal disorders.

Gynodian Depot *Schering, Arg.; Schering, Austria; Schering, Chile; Schering, Cz.; Schering, Ger.; Schering, Ital.; Schering, Pol.; Schering, Rus.; Schering, Switz.; Schering, Venez.*
⊗ Estradiol valerate (p.2097·3); prasterone enantate (p.2124·2).
Menopausal disorders; osteoporosis.

Gynodiol *Fielding, USA.*
Estradiol (p.2097·2).
Breast cancer; menopausal disorders; oestrogen deficiency; osteoporosis; prostatic cancer.

Gyno-Femidazol *Polfa Grodzisk, Pol.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial vaginal infections.

Gynofen 35 *Schering, Gr.*
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Androgen-related disorders in women; male-pattern alopecia.

Gynoferon *Kocak, Turk.*
Ferrous sulfate (p.1939·3); mucoproteose; folic acid (p.1940·1).
Iron and folic acid deficiency.

Gynoflor *Pfizer, Austria; Grunenthal, Belg.; Vivax, Cz.; Organon, Ger.; Medico Uno, Hung.; Jaba Recordati, Port.; Medinova, Switz.; Abdi, Turk.*
Lactobacillus acidophilus (p.2372·3); estriol (p.2101·1).
Restoration of vaginal flora; vaginal disorders.

Gynofort *KV, Malaysia; Gedeon Richter, Rus.; KV, Singapore.*
Butoconazole nitrate (p.528·1).
Vulvovaginal candidiasis.

Gynofug *Wolff, Ger.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Gyno-Fungix *Janssen-Cilag, Braz.*
Terconazole (p.548·1).
Vulvovaginal candidiasis.

Gynokadin *Besins, Ger.; Kade, Ger.*
Estradiol (p.2097·2) or estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

Gynol II *Johnson & Johnson, Canad.†; Janssen-Cilag, Irl.†; Johnson & Johnson, S.Afr.; Janssen-Cilag, UK†; Advanced Care, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Gyno-Liderman *Jacoby, Austria.*
Oxiconazole nitrate (p.544·2).
Fungal and Gram-positive vaginal infections.

Gyno-Lomexin *Organon, Turk.*
Fenticonazole nitrate (p.531·3).
Vulvovaginal candidiasis.

Gynol-Plus *Janssen-Cilag, Swed.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Gynomax *Farmoquimica, Braz.*
Tioconazole (p.548·2); tinidazole (p.848·3).
Fungal infections.

Gynomiconax *Meyer, Venez.†.*
Econazole (p.531·1).
Fungal vaginal infections.

Gyno-Mikozal *Julphar, UAE.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

Gyno-Mycel *Biolab Sanus, Braz.†.*
Isoconazole nitrate (p.536·2).
Vaginal candidiasis.

Gyno-Myfungar *Leciva, Cz.†; Rhein, Mex.†.*
Oxiconazole nitrate (p.544·2).
Fungal and Gram-positive vulvovaginal infections.

Gynomyk *Will-Pharma, Belg.; Jolly-Jatel, Fr.; Will-Pharma, Neth.*
Butoconazole nitrate (p.528·1).
Fungal vulvovaginal infections.

Gyno-Mykotral *Rosen, Ger.*
Miconazole nitrate (p.541·3).
Fungal genital infections.

Gyno-Neuralgin *Pfleger, Ger.*
Ibuprofen (p.64·2).
Dysmenorrhoea.

Gynopac *Farmoquimica, Braz.*
Cream, tioconazole (p.548·2); tinidazole (p.848·3); tablets, secnidazole (p.846·3).
Vulvovaginal infections.

Gyno-Pevaryl *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Codepharma, Fr.; Janssen-Cilag, Ger.; Cilag, Hong Kong†; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia; ICN, NZ†; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Pensa, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Econazole nitrate (p.531·1).
Balanitis; fungal and Gram-positive vulvovaginal infections.

Gynophilus *IPRAD-Sante, Fr.*
Lactobacillus casei rhamnosus (p.2372·3).
Restoration of vaginal flora.

Gynoplix *Bouchara-Recordati, Hong Kong.*
Metronidazole (p.837·1).
Vaginal infections.

Gynoplus
Note. A similar name is used for preparations of different composition (see below).
Gallia, Braz.†.
Isoconazole nitrate (p.536·2).
Fungal vaginal infections.

Gyno-Plus
Note. A similar name is used for preparations of different composition (see above).
Jin Yang, Malaysia.
Cimicifuga (p.2282·1); St John's wort (p.422·3).
Menopausal disorders; menstrual disorders.

Gynormal
Note.This name is used for preparations of different composition.
Andromaco, Arg.
Cream; pessaries: Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vaginal infections.

Andromaco, Arg.
Tablets: Tinidazole (p.848·3).
Anaerobic bacterial infections of the vagina; protozoal vaginal infections.

Gynosant *Gerolymatos, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Gynosoja *Codifra, Fr.*
Soya bean (p.1965·3); alfalfa (p.2249·2); folic acid (p.1940·1).
Menopausal disorders.

Gynosoya *Arkopharma, Belg.*
Soya (p.1965·3).
Menopausal disorders.

Gynospor *Garec, S.Afr.*
Miconazole nitrate (p.541·3).
Vaginal fungal infections.

Gynostat *Laboratorios Chile, Chile.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Gynostatum *Ranbaxy, Malaysia†.*
Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

Gyno-Tardyferon *Pharmafabre (Φαρμαφαμπρ), Gr.; Pierre Fabre, Rus.; Robapharm, Switz.; Pierre Fabre, Turk.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Gyno-Terazol *Janssen-Cilag, Belg.†; Janssen-Cilag, Switz.*
Terconazole (p.548·1).
Fungal vulvovaginal infections.

Gynotocin *Svizera, India.*
Oxytocin (p.2015·2).
Incomplete abortion; labour induction; postpartum haemorrhage.

Gynotran
Schering, Arg.
Metronidazole (p.837·1); miconazole nitrate (p.541·3).
Bacterial vaginosis; trichomoniasis; vaginal candidiasis.

Schering, Mex.
Metronidazole (p.837·1); miconazole (p.541·2).
Vaginal infections.

Gyno-Travogen *Schering, Austria; Schering, Hong Kong†; Schering, Pol.; Schering, Rus.; Schering, Singapore; Schering, Switz.; Schering, Turk.*
Isoconazole nitrate (p.536·2).
Fungal and Gram-positive bacterial vaginal infections.

Gyno-Trimaze *Garec, S.Afr.†.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Gyno-Trosyd *Pfizer, Fin.; Teofarma, Fr.; Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, NZ†; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Turk.*
Tioconazole (p.548·2).
Fungal vulvovaginal infections.

Gynova *Milano, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1).
Fungal, trichomonal and bacterial vaginitis.

Gynovin *Schering, Arg.; Schering, Austria; Schering, Mex.; Schering, Spain.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Gynovit *Vargas, Venez.*
Acetic acid (p.2244·2); benzalkonium chloride (p.1629·1).
Vaginal douche.

Gynovite Plus *Optimox, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Gynoxa *Kalbe, Indon.*
Nimorazole (p.842·2); chloramphenicol (p.239·3); nystatin (p.543·2).
Vaginal infections.

Gynoxin *Fournier, Hung.; Organon, Neth.; Recordati, Pol.*
Fenticonazole nitrate (p.531·3).
Fungal vulvovaginal infections.

GynPolar *Orion, Ger.*
Estradiol (p.2097·2).
Menopausal disorders.

Gyrablock *Medochemie, Cz.; Medochemie, Rus.; Medochemie, Singapore.*
Norfloxacin (p.309·2).
Bacterial infections.

Gyracip *Gry, Ger.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Gyracon *Pond's, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1).
Fungal, trichomonal and bacterial vaginitis.

Gyraxen *Korea United, Philipp.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Gyroflox *Gry, Ger.*
Ofloxacin (p.310·2).
Bacterial infections.

Gyrol *Brasmedica, Braz.†.*
Tyrothricin (p.358·2); thymol (p.1664·3); boric acid (p.2268·1).
Vulvovaginal infections.

Gyros *Hexal, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Gyrosan *CMS, Switz.†.*
Heavy kaolin (p.1738·1); silver (p.2387·1).
Burns; wounds.

H2 Bloc *Biomedis, Philipp.*
Famotidine (p.1730·1).
Dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

H 2 Blocker *Ratiopharm, Ger.*
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; hypersensitivity reactions; peptic ulcer; Zollinger-Ellison syndrome.

H Tussan *Inibsa, Spain.*
Anise oil (p.2258·2); ivy (p.2328·1); thyme oil (p.2401·2).
Coughs.

Haarlemensis *Lennon, S.Afr.*
Precipitated sulfur (p.1614·1); arachis oil (p.2259·1); tar (p.1616·2); turpentine oil (p.2406·3).
Upper urinary-tract disorders.

Habebion *Medikon, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; vitamin B with intrinsic factor; folic acid (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; nutritional supplement.

Habitek *SJA, Gr.*
Cetirizine (p.571·1).
Allergic disorders.

Habitrol
Novartis Consumer, Canad.; Novartis Consumer, USA.
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Novartis Consumer, NZ.
Nicotine resin (p.2352·2) or nicotine (p.2352·2).
Aid to smoking withdrawal.

Habstal-Cor N *Steierl, Ger.*
Homoeopathic preparation.

Habstal-Nerv N *Steierl, Ger.†.*
Passion flower (p.2363·2); valerian root (p.2410·1).
Insomnia; nervous disorders.

Habstal-Pulm N *Steierl, Ger.*
Homoeopathic preparation.

HAC *Molnlycke, Belg.*
Cetrimonium bromide (p.1635·1); chlorhexidine gluconate (p.1635·3).
Burns; disinfection of skin, instruments, textiles, and surfaces; wounds.

Hacdil-S *Molnlycke, Belg.*
Cetrimonium bromide (p.1635·1); chlorhexidine gluconate (p.1635·3).
Disinfection of wounds and instruments.

Hachemina Fuerte *Medea, Spain.*
Aminobenzoic acid (p.1589·1).
Alopecia; eye and skin disorders; leucopenia.

Hachimi-jio-gan *Tsumura, Jpn.*
Rehmannia root; cornus fruit; dioscorea rhizome; alisma rhizome; poria sclerotium; moutan bark; cinnamon bark; aconite tuber.
Traditional Kampo medicine.

Hacks *Ernest Jackson, UK.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2); vitamin C (p.1983·3).
Cold symptoms; coughs.

Hacks Blackcurrant *Ernest Jackson, UK.*
Menthol (p.2340·1); vitamin C (p.1983·3).
Cold symptoms; coughs.

Hactos *Hubert, UK.*
Capsicum (p.2276·2); peppermint oil (p.1761·2); anise oil (p.2258·2); clove oil (p.2285·1).
Catarrh; cold symptoms; coughs.

Hadarax *Greater Pharma, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Pruritus.

Hadensa
Note.This name is used for preparations of different composition.
Ferrer, Spain.
Chlorocarvacrol (p.1639·3); ichthammol (p.1599·1); menthol (p.2340·1).
Anorectal disorders.

Kolassa, Austria; Leiras, Fin.
Ointment: Monochlorocarvacrol (p.1639·3); ichthammol (p.1599·1); menthol (p.2340·1).
Anorectal disorders.

Kolassa, Austria; Leiras, Fin.
Suppositories: Monochlorocarvacrol (p.1639·3); ichthammol (p.1599·1); chamomile oil (p.2279·3); menthol (p.2340·1).
Anorectal disorders.

Hadiel *Piam, Ital.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Hadlinol *Medicus, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Haelan *Typharm, UK.*
⊗ Fludroxycortide (p.1530·3).
Skin disorders.

Haem Up *Cadila Pharma, India.*
⊗ Glycerinated haemoglobin (p.1072·3); copper sulfate; manganese sulfate; zinc sulfate (p.1922·1); ferric ammonium citrate (p.1938·1).
Anaemia of pregnancy.

Haemaccel *Aventis, Arg.†; AFT, Austral.; Aventis, Austria; Aventis, Belg.†; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile†; Aventis, Cz.†; DeltaSelect, Ger.; Hoechst Marion Roussel, Gr.†; Aventis, Hong Kong†; Nicholas Piramal, India; Dexa, Indon.; Aventis, Irl.†; Aventis, Israel†; Aventis, Malaysia†; Antibioticos, Mex.; AFT, NZ; Aventis, Neth.; Aventis, Norw.†; TheraSelect, Port.; Mednostica, S.Afr.; DeltaSelect, Singapore; Aventis, Switz.†; Aventis, Thai.; Beacon, UK.*
⊗ Polygeline (p.1077·2) with electrolytes.
Extracorporeal circulation; haemodialysis; hypovolaemia; organ perfusion; plasma exchange; plasma volume expansion; shock; suspending agent.

Haemanal *Sigmapharm, Austria.*
Hydrastinine hydrochloride (p.2321·2); chlorocarvacrol (p.1639·3); zinc oxide (p.1621·2); tannic acid (p.2394·3); menthol (p.2340·1).
Anorectal disorders.

Haemate *Aventis Behring, Arg.; ZLB, Austria; ZLB, Belg.; CSL, Braz.; CSL, Cz.; ZLB, Denm.; ZLB, Ger.; ZLB Behring, Hong Kong; CSL, Hung.; Aventis Behring, Irl.†; Aventis Behring, Israel; ZLB, Ital.; ZLB, Neth.; CSL, Port.; ZLB, Spain; ZLB, Swed.; ZLB, Switz.; Farma-Tek, Turk.; Aventis Behring, UK.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemorrhagic disorders.

Haemiton *AWD, Ger.†; AWD, Rus.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Haemiton compositum *AWD, Ger.†.*
⊗ Clonidine hydrochloride (p.1247·1); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Haemo Duoform *Mauermann, Ger.†.*
Hamamelis leaves (p.2318·2).
Haemorrhoids.

Haemocaine *Galenium, Indon.*
⊗ Lidocaine hydrochloride (p.1862·3); aluminium subacetate (p.2255·1); hydrocortisone acetate (p.1535·2); zinc oxide (p.1621·2).
Haemorrhoids.

Haemocomplettan *ZLB, Austria; CSL, Cz.; ZLB, Ger.; IFET (ΙΦΕΤ), Gr.; CSL, Hung.; ZLB, Neth.; CSL, Port.; ZLB, Switz.*
Fibrinogen (p.1070·1).
Haemorrhagic disorders associated with hypofibrinogenaemia.

Haemocortin
Note. This name is used for preparations of different composition.
Streuli, Switz.
Ointment: ⊗ Hydrocortisone acetate (p.1535·2); bismuth oxychloride (p.1712·1); lidocaine hydrochloride (p.1862·3); zinc oxide (p.1621·2).
Anorectal disorders.

Streuli, Switz.
Suppositories: ⊗ Hydrocortisone acetate (p.1535·2); bismuth oxychloride (p.1712·1); lidocaine hydrochloride (p.1862·3); zinc oxide (p.1621·2); ethacridine lactate (p.1625·1); menthol (p.2340·1); adrenaline hydrochloride (p.1203·3); hamamelis (p.2318·2); peru balsam (p.2365·3).
Anorectal disorders.

Haemoctin *Biotest, Gr.; Biotest, Pol.*
A factor VIII preparation (p.1067·1).
Haemophilia A; haemorrhagic disorders.

Haemoctin SDH *Biogam, Arg.; Biotest, Austria; Biotest, Cz.; Biotest, Ger.; Biotest, Hung.; Biotest, Israel; Boehringer Ingelheim, Port.; Biotest, Singapore; Biotest, Thai.; Kansuk, Turk.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Haemodez-N *Biokhimik, Rus.*
Povidone (p.2146·1); sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium bicarbonate (p.1667·1).
Infections; liver disorders.

Haemodyn *Fujisawa, Austria.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Haemoetin *Biotest, Turk.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Haemo-Exhirud *Lichtenstein, Ger.†.*
Leech extract (p.1305·3); allantoin (p.1588·1); lauromacrogol 400 (p.1916·1).
Anorectal disorders; urogenital venous disorders.

Haemo-Exhirud Bufexamac *Winthrop, Ger.*
Bufexamac (p.28·3); bismuth subgallate (p.1711·1); titanium dioxide (p.1617·3); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Haemofusin *Baxter, Ger.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Plasma volume expansion.

Haemo-Glukotest *Roche Diagnostics, Braz.*
Test for glucose in blood (p.2314·1).

Haemo-Glukotest 20-800 *Roche, Arg.†; Roche Diagnostics, Mex.*
Test for glucose in blood (p.2314·1).

Haemoglukotest 20-800 *Roche Diagnostics, Ital.†.*
Test for glucose in blood (p.2314·1).

Haemolan
Note. This name is used for preparations of different composition.
Streuli, Switz.
Ointment: Lidocaine hydrochloride (p.1862·3); bismuth oxychloride (p.1712·1); zinc oxide (p.1621·2); menthol (p.2340·1); peru balsam (p.2365·3).
Anorectal disorders.

Streuli, Switz.
Suppositories: ⊗ Lidocaine hydrochloride (p.1862·3); bismuth oxychloride (p.1712·1); zinc oxide (p.1621·2); menthol (p.2340·1); peru balsam (p.2365·3); ethacridine lactate (p.1625·1); ephedrine hydrochloride (p.1558·2); hamamelis (p.2318·2).
Anorectal disorders.

Haemopressin *Torrex, Austria; Curatis, Ger.; Meduna, Ger.*
Terlipressin acetate (p.2395·3).
Gastric haemorrhage; variceal haemorrhage.

Haemoproct *Julphar, UAE.*
Tribenoside (p.2403·3); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Haemoprotect *Betapharm, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Haemoral
Note. This name is used for preparations of different composition.
Ritter, Hong Kong.
Ointment: Hydroxypolyethoxydodecane (p.1916·1); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); peru balsam (p.2365·3).
Anorectal disorders.

Ritter, Hong Kong.
Suppository: Aluminium acetotartrate (p.2255·1); trichloro-i-butylester of salicylic acid; sodium acetate (p.1673·2).
Anorectal disorders.

Haemo-Red Formula *Eagle, Austral.*
Vitamins; minerals (p.1922·1) yellow dock (p.2416·3); urtica (p.2409·3).

Haemorrhoid Cream *Nelson, UK.*
Homoeopathic preparation.

Haemosolvate *NBI, S.Afr.*
Factor VIII (p.1067·1).
Factor VIII deficiency.

Haemosolvex *NBI, S.Afr.*
Factor IX (p.1068·3).
Coagulation disorders.

Haemovex 4 *Gambro, Swed.†.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration.

Haemovex 8 *Gambro, Swed.†.*
Sodium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration.

Haemovital *Pharmadass, UK.*
Vitamin, mineral, and nutritional preparation (p.1922·1).
Tonic.

Haenal *Strathmann, Ger.*
Quinisocaine hydrochloride (p.1870·3).
Anorectal disorders; insect stings.

HAES Esteril *Fresenius Kabi, Spain.*
⊗ Pentastarch (p.1065·1).
Plasma volume expansion.

HAES-Rheopond *Serag-Wiessner, Ger.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Hypovolaemia; shock.

HAES-steril *Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.†; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Singapore; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Diamedica, Venez.†.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Haemodilution; hypovolaemic shock; microcirculatory disorders; plasma volume expansion; shock.

HAES-sterile *Fresenius, Israel.*
⊗ Pentastarch (p.1065·1).
Plasma volume expansion; shock.

Hafif *Teva, Israel.*
Carbaryl (p.2037·1).
Pediculosis.

Hagevir *Cosmopharm, Gr.*
Aciclovir (p.862·3).
Herpes simplex infections.

Haimabig *Nuovo ISM, Ital.†.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Haima-D *Nuovo ISM, Ital.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Haimaferone *Schiapparelli, Ital.†.*
Interferon alfa (p.885·1).
Malignant neoplasms; viral infections.

Haimaserum *Hardis, Ital.†.*
⊗ Plasma protein fraction (p.1076·2).
Hypoproteinaemia; hypovolaemia.

Haimaven *Hardis, Ital.†.*
A normal immunoglobulin (p.2225·3).
Guillain Barré syndrome; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Haiprex *3M, Denm.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

4 Hair *Marlyn, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Hair Booster *Nature's Bounty, USA.*
Vitamin B substances with minerals, iron, and folic acid (p.1922·1).

Hair Nutrition *Cantassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Hair & Scalp *ICN, Canad.†.*
Pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Hair and Skin Formula *Vitaplex, Austral.†.*
Calcium pantothenate (p.1959·3); inositol (p.2325·2); aminobenzoic acid (p.1589·1); ascorbic acid (p.1983·3); *dl*-alpha tocoferil acetate (p.1992·3).
Multivitamin preparation.

Hair Stabil *Polinac, Venez.†.*
Piroctone olamine (p.1610·1).
Dandruff.

Hairclin *Galderma, Arg.†.*
Permethrin (p.2048·2).
Pediculosis.

Hairgaine *Agis, Israel.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Hairgrow *Dar Al Dawa, Hong Kong.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Hairplus
Note. This name is used for preparations of different composition.
Euroderm, Arg.
Lotion: Salicylic acid (p.1612·2); calcium pantothenate; tricopeptides; collagen; urea.
Dandruff; seborrhoeic dermatitis.

Euroderm, Arg.
Shampoo: Pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Hairscience *Ego, Singapore†.*
Miconazole nitrate (p.541·3).
Formerly contained miconazole nitrate and salicylic acid.
Dandruff; seborrhoeic dermatitis.

Hairscience Anti-Dandruff *Ego, Austral.*
Miconazole (p.541·2).
Scalp disorders.

Hairscience Antidandruff *Ego, NZ†.*
Miconazole nitrate (p.541·3).
Dandruff; seborrhoeic dermatitis.

Hairscience Conditioner *Ego, NZ†.*
Cetrimide (p.1634·1); lipids; cationic polymer.
Scalp disorders.

Hairscience Shampoo *Ego, NZ†.*
Sodium salicylate (p.124·2).
Dandruff.

Hairtene *Labesfal, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Hair-Treat *Rekah, Israel.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

HairVit *Pharmadass, UK.*
Multivitamin, mineral, and trace element preparation (p.1922·1).

Hairway *Med-One, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Hairy Lemon *Douglas, Austral.*
Vitamin B substances; vitamin C; guarana; ginseng (p.1922·1).
Tonic.

H-AL *Sevapharma, Cz.*
A range of allergen extracts (p.2250·2).
Hyposensitisation.

Halamid *Viatris, Ger.†.*
Nedocromil sodium (p.1127·3).
Obstructive airways disease.

Halazolin *Warsaw-Polfa, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Otitis media; rhinitis; sinusitis.

Halbmond *Whitehall-Much, Ger.†.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Halcepin *Vamsler, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Halcicomb *BMS, Venez.*
⊗ Halcinonide (p.1535·1); nystatin (p.543·2).
Infected skin disorders.

Halciderm
Note. This name is used for preparations of different composition.
BMS, UK†.
⊗ Halcinonide (p.1535·1).
Skin disorders.

Rottapharm, Ital.
Cream: ⊗ Halcinonide (p.1535·1).
Skin disorders.

Rottapharm, Ital.
Tincture: ⊗ Halcinonide (p.1535·1); salicylic acid (p.1612·2).
Skin disorders.

Halciderm Combi *Rottapharm, Ital.*
⊗ Halcinonide (p.1535·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Halcion *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pharmacia, Braz.†; Pfizer, Canad.; Pharmacia, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.†; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.; Pharmacia, NZ; Pharmacia, Neth.†; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia Upjohn, USA.*
Triazolam (p.1033·2).
Insomnia.

Haldid *Janssen-Cilag, Denm.*
⊗ Fentanyl citrate (p.55·3).
Analgesia in anaesthesia.

Haldol
Janssen-Cilag, Austral.; Janssen-Cilag, Irl.; Janssen-Cilag, NZ; Ortho McNeil, USA.
Haloperidol decanoate (p.1000·2).
Behaviour disorders in children; motor tics; psychoses; Tourette syndrome.

Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Janssen-Cilag, Venez.
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Agitation; alcohol withdrawal syndrome; anxiety; behaviour disorders; bipolar disorder; chorea; extrapyramidal disorders; gastrointestinal disorders; hiccup; hyperkinesias; mania; motor tics; nausea and vomiting; pain; psychoses; psychosomatic disorders; stutter; Tourette syndrome.

Janssen-Ortho, Canad.†.
Haloperidol lactate (p.1001·1).
Aggression; agitation; psychoses; Tourette syndrome.

Halenol *Halsey, USA.*
Paracetamol (p.108·1).
Fever; pain.

Haley's M-O *Sterling Health, USA.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Half Beta-Prograne *Tillomed, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; essential tremor; hyperthyroidism; migraine; prophylaxis of gastrointestinal bleeding.

Half Capozide *BMS, Irl.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Half Inderal *AstraZeneca, Irl.; AstraZeneca, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; hypertension; hyperthyroidism; migraine; myocardial infarction; tremor; variceal haemorrhage.

Half Securon *Abbott, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension; myocardial infarction.

Half Sinemet *Du Pont, Irl.; BMS, UK.*
Carbidopa (p.803·1); levodopa (p.804·3).
These ingredients can be described by the British Approved Name Co-careldopa.
Parkinsonism.

Halfan *GSK, Belg.†; GSK, Fr.; GSK, Ger.†; Smith Kline & French, Port.; GSK, S.Afr.; SmithKline, Spain; SmithKline Beecham, Switz.†.*
Halofantrine hydrochloride (p.603·3).
Malaria.

HalfLytely *Braintree, USA.*
Powder for oral solution, macrogol 3350 (p.2336·3); electrolytes (p.1667·1); delayed release tablets, bisacodyl (p.1710·1).
Bowel evacuation.

Halfprin *Kramer, USA.*
Aspirin (p.20·3).
Myocardial infarction.

Haliborange
Eurospital, Ital.; Boots Healthcare, NZ; Inibsa, Spain†; Seven Seas, UK.
Vitamins A, C, and D (p.1922·1).
Vitamin A and D supplement.

GSK, Venez.†.
Halibut liver oil; calciferol (p.1922·1).
Vitamin A and D supplement.

Haliborange Calcium Plus Vitamin D *Seven Seas, UK.*
Calcium (p.1675·2); vitamin D (p.1986·1).

Haliborange Halibonbons *Seven Seas, UK.*
Vitamin C (p.1983·3).

Haliborange High Strength Vitamin C *Seven Seas, UK.*
Vitamin C with or without vitamin E and bioflavonoids (p.1922·1).

Haliborange Multivitamins *Seven Seas, UK.*
Multivitamins with or without calcium and iron (p.1922·1).

Halibut
Note. This name is used for preparations of different composition.
Grunenthal, Port.
Halibut oil (p.1948·1); zinc oxide (p.1621·2).
Burns; skin disorders; ulcers; wounds.

Novartis Consumer, Spain.
Benzethonium chloride (p.1630·1); vitamin A (p.1971·2); zinc oxide (p.1621·2).
Burns; cracked nipples; skin irritation; ulcers; wounds.

Merz, Switz.
Halibut-liver oil (p.1948·1).
Tonic; vitamin A and D deficiency.

Halibut Hidrocortisona *Novartis Consumer, Spain.*
⊗ Hydrocortisone acetate (p.1535·2); vitamin A (p.1971·2); zinc oxide (p.1621·2); benzethonium chloride (p.1630·1).
Insect bites; skin disorders.

Halibut plus *Merz, Switz.*
Halibut-liver oil with multivitamins (p.1922·1).
Formerly known as Halibut Multivit.
Vitamin deficiency.

Halicar *Peithner, Austria; Peithner, Cz; DHU, Ger.*
Homoeopathic preparation.

Halidor *EGIS, Hung.; Egis, Pol.; Egis, Rus.*
Bencyclane fumarate (p.1224·1).
Cerebral and peripheral vascular disorders; gastrointestinal and urinary-tract disorders; renal calculi; urinary-tract spasm; vascular eye disorders.

Halita *Dentaid, Chile.*
Zinc lactate; chlorhexidine gluconate (p.1635·3); cetylpyridinium chloride (p.1635·1).
Halitosis.

Halitol *Caldeira & Marques, Port.†.*
Salicylic acid (p.1612·2); benzocaine (p.1854·1); lactic acid (p.2329·3).
Formerly contained salicylic acid, benzocaine, and cineole.
Mouth disorders.

Halitran *Roche Consumer, Neth.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Vitamin A and D deficiency.

Haliver *Velka, Gr.*
Thiocolchicoside (p.1898·2).
Muscle relaxant.

Halivite *Whitehall, Fr.†.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin disorders.

Halixol *Egis, Cz.; EGIS, Hung.; Egis, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders; respiratory-tract disorders with viscous mucus.

Halloo-Wach N *Altana, Ger.*
Caffeine (p.1116·3); glucose monohydrate.
Fatigue.

Halls *Adams, Canad.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Coughs; nasal congestion.

Halls Mentholyptus *Adams Confectionery, UK.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Cold symptoms; nasal congestion; sore throat.

Halls Soothers Triple Action *Ernest Jackson, UK.*
Hexylresorcinol (p.1647·1).
Sore throat.

Halls Sugar Free Mentho-Lyptus *Warner-Lambert, USA.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Sore throats.

Halls Zinc Defense *Warner-Lambert, USA.*
Zinc acetate (p.1999·1).
Zinc supplement.

Halls-Plus Maximum Strength *Warner-Lambert, USA.*
Menthol (p.2340·1).

Halmezin *Coronet, Indon.*
Dextromethorphan hydrobromide (p.1555·2); promethazine hydrochloride (p.588·2); bromhexine hydrochloride (p.1552·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough.

Halo *Cristalia, Braz.*
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Psychoses.

Halocef *Otsira, India.*
Cefaclor (p.217·2).
Bacterial infections.

Halodin *TO-Chemicals, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Halofed *Halsey, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Halog
Note.This name is used for preparations of different composition.
BMS, Austria; BMS, Braz.; Westwood-Squibb, Canad.; BMS, Ger.†; BMS, Hong Kong; BMS, Indon.; BMS, Spain; Princeton, USA.
⊗ Halcinonide (p.1535·1).
Skin disorders.

BMS, Venez.
Cream: ⊗ Halcinonide (p.1535·1).
Skin disorders.

BMS, Venez.
Topical solution: ⊗ Halcinonide (p.1535·1); salicylic acid (p.1612·2).

Halog Tri *BMS, Ger.†.*
⊗ Halcinonide (p.1535·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Halogedol *Fardi, Spain†.*
Camphor (p.2273·2); methyl salicylate (p.85·3).
Muscle and joint pain.

Halomed *Medifive, Thai.*
Haloperidol (p.1000·2).
Alcohol withdrawal syndrome; anxiety; psychomotor agitation.

Halomycetin *Kwizda, Austria.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Haloneural *Hexal, Ger.†.*
Haloperidol (p.1000·2).
Psychoses.

Halonix *Cadila Pharma, India.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis of the knee.

Halo-P *PP Lab, Thai.†.*
Haloperidol (p.1000·2).
Anxiety; psychomotor agitation.

Haloper *Teuto, Braz.; CT, Ger.; CTI, Israel; CTS, Rus.†.*
Haloperidol (p.1000·2).
Extrapyramidal disorders; hiccups; pain; psychoses; Tourette syndrome; vomiting.

Haloperil *Psicofarma, Mex.*
Haloperidol (p.1000·2).
Movement disorders; psychoses.

Halopidol *Janssen-Cilag, Arg.*
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Behaviour disorders; psychoses.

Halopol *General Drugs, Thai.*
Haloperidol (p.1000·2).
Alcohol withdrawal syndrome; anxiety; behaviour disorders in children; psychomotor agitation.

Halotestin *Pharmacia, Hong Kong†; Pfizer, Thai.†.*
⊗ Fluoxymesterone (p.2103·3).
Breast cancer; delayed puberty; lactation control; male hypogonadism; osteoporosis.

Halotussin *Halsey, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Halotussin-DM *Halsey, USA†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Halozen *Bouzen, Arg.*
Haloperidol (p.1000·2).

Halset *Novartis Consumer, Austria; Gebro, Cz.; Gebro, Hung.; Biofarm, Pol.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Halstabletten akute *Ratiopharm, Ger.*
Cetylpyridinium chloride (p.1635·1).
Inflammatory disorders of the mouth and throat.

Halstropfen Nr 21 *Doskar, Austria.*
Homoeopathic preparation.

Haltran *Roberts, USA†.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Halycitrol *Tamar, Israel; Laboratories for Applied Biology, UK.*
Vitamin A; vitamin D (p.1922·1).
Vitamin A and D deficiency; vitamin A and D supplement.

Hamadin N *Schwabe, Ger.*
Saccharomyces cerevisiae (p.1998·3).
Hamadin formerly contained *Saccharomyces boulardii.*
Acne; diarrhoea.

Hamamelis Comp *Weleda, S.Afr.*
Homoeopathic preparation.

Hamamelis Compose *Boiron, Fr.†.*
Homoeopathic preparation.

Hamamelis-Homaccord *Peithner, Austria.*
Homoeopathic preparation.

Hamamilla *Pharmasette, Ital.†.*
Benzalkonium chloride (p.1629·1); hamamelis (p.2318·2); chamomile (p.2279·3); hypromellose (p.2144·2).
Eye disinfection; eye irritation.

Hamasana *Robugen, Ger.†.*
Hamamelis (p.2318·2).
Burns; haemorrhoids; skin disorders; varicose veins; wounds.

Hamatopan *Wolff, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Hamatopan F *Wolff, Ger.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Hamburg Tea *SA Druggists Self Med, S.Afr.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Hametan *Abdi, Turk.*
Hamamelis (p.2318·2).
Haemorrhoids; skin disorders.

Hametol *Schwabe, Spain.*
Hamamelis (p.2318·2).
Skin irritation.

Hametum *Peithner, Austria; Schwabe, Ger.; Spitzner, Ger.*
Hamamelis (p.2318·2).
Gingivitis; haemorrhoids; skin disorders.

Hametum-N *Schwabe, Ger.†; Spitzner, Ger.†.*
Hamamelis (p.2318·2); aesculus (p.2248·2).
Anorectal disorders; haemorrhoids.

HAMFL *Fresenius Medical, Austria.*
A range of electrolyte infusions with or without glucose (p.1670·3).
Haemofiltration.

Hamilton Body Lotion *Hamilton, Austral.†.*
Chlorhexidine gluconate (p.1635·3); glycerol (p.2314·2); liquid paraffin (p.2030·3).
Emollient.

Hamilton Body Wash *Hamilton, Hong Kong.*
Light liquid paraffin (p.2031·1); cocoamphodiacetate.
Skin disorders.

Hamilton Cleansing Lotion *Hamilton, Austral.†.*
Glycerol (p.2314·2); liquid paraffin (p.2030·3); chlorhexidine gluconate (p.1635·3).
Skin cleansing; skin disorders.

Hamilton Dry Skin
Note.This name is used for preparations of different composition.
Hamilton, Austral.
Bath oil: Light liquid paraffin (p.2031·1).
Bath additive; dry skin; eczema; psoriasis.

Hamilton, Austral.
Lotion: Liquid paraffin (p.2030·3); glycerol (p.2314·2).
Dry skin.

Hamilton Family Sunscreen *Hamilton, Austral.*
Lotion spray SPF 30: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Hamilton Lip Balm *Hamilton, Austral.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Dry chapped lips; sunscreen.

Hamilton Pine Tar with Menthol *Hamilton, Austral.*
Menthol (p.2340·1); cetrimide (p.1634·1); dimeticone (p.2032·1); pine tar (p.1616·2).
Skin disorders.

Hamilton Sensitive *Hamilton, Austral.*
SPF 30+: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton Sensitive Broad Spectrum Milk
Note.This name is used for preparations of different composition.
Hamilton, Austral.†.
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton, Austral.†.
SPF 30+: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Hamilton Skin Repair *Hamilton, Austral.†; Hamilton, Hong Kong.*
Dimeticone (p.2032·1); cetrimide (p.1634·1).
Dermatitis; dry skin; skin disorders.

Hamilton Skin Therapy
Note.This name is used for preparations of different composition.
Hamilton, Austral.
Cream: ⊗ Urea (p.1620·2).
Dry skin.

Hamilton, Austral.
Wash: Light liquid paraffin (p.2031·1); disodium cocamphodiacetate.
Dry skin.

Hamilton Solastick *Hamilton, Austral.*
SPF 30+: Avobenzone (p.1589·3); enzacamene (p.1597·1); octocrilene (p.1608·3).
Formerly contained octinoxate, avobenzone, oxybenzone, and titanium dioxide.
Sunscreen.

Hamilton Solastick Broad Spectrum *Hamilton, Austral.†.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Hamilton Sportblock Broad Spectrum Milk *Hamilton, Austral.*
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton Sunscreen
Note.This name is used for preparations of different composition.
Intercare, NZ.
Cream; Solastick; Sunstick: Octinoxate (p.1608·2); octisalate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Intercare, NZ.
Kidscreen; Low Allergy Milk: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Intercare, NZ.
Quadblock Cream SPF 40: Octinoxate (p.1608·2); oxybenzone (p.1608·3); padimate O (p.1609·1); titanium dioxide (p.1617·3).
Sunscreen.

Intercare, NZ.
Quadblock Milk; Water Resistant Milk: Octinoxate (p.1608·2); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Intercare, NZ.
Quadblock Stick; Sunsport Lotion: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Hamilton Sunscreen Clear Lotion Broad Spectrum *Hamilton, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Hamilton Sunscreen Cream Broad Spectrum
Note.This name is used for preparations of different composition.
Hamilton, Austral.†.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Hamilton, Austral.†.
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton Sunscreen Milk Broad Spectrum
Note.This name is used for preparations of different composition.
Hamilton, Austral.†.
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Hamilton, Austral.†.
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton Sunscreen *Intercare, NZ.*
Clear Lotion: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Hamilton Superblock Broad Spectrum Milk *Hamilton, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton Toddler
Note.This name is used for preparations of different composition.
Hamilton, Austral.
Milk SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Hamilton, Austral.
Roll-on SPF 30+: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Hamilton Watersport Broad Spectrum Milk *Hamilton, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Hamiltosin *Rafarm, Gr.*
Cetirizine (p.571·1).
Allergic disorders.

Hamitan *Safire, Hong Kong.*
Mefenamic acid (p.80·1).
Menorrhagia; pain.

Hamoagil plus *Chefaro, Ger.*
Bufexamac (p.28·3); lidocaine hydrochloride (p.1862·3); bismuth subgallate (p.1711·1); titanium dioxide (p.1617·3).
Haemorrhoids.

Hamo-ratiopharm N *Ratiopharm, Ger.*
Bufexamac (p.28·3); bismuth subgallate (p.1711·1); lidocaine hydrochloride (p.1862·3); titanium dioxide (p.1617·3).
Anal fissure; haemorrhoids.

Hamorrhoidal-Zapfchen *Weleda, Austria.*
Antimony.
Anorectal disorders.

Hamos N *Dr Janssen, Ger.†.*
Menthol (p.2340·1); aesculus (p.2248·2).
Haemorrhoids.

Hamos-Tropfen-S *Dr Janssen, Ger.†.*
Aesculus (p.2248·2).
Thrombophlebitis; venous insufficiency.

Hamovannad *Bastian, Ger.†.*
Inositol nicotinate (p.1316·1).
Haemorrhoids; peripheral vascular disorders.

Hamo-Vibolex *Chephasaar, Ger.†.*
Cyanocobalamin (p.1980·2).
Hyperchromic anaemia.

Hamoxillin *Safire, Hong Kong.*
Amoxicillin (p.202·2).
Bacterial infections.

Hand Joy *Unison, Thai.*
⊗ Alcohol (p.1625·2); triclosan (p.1665·2).
Skin disinfection.

Handexin *Teleflex, Ital.*
Chlorhexidine gluconate (p.1635·3); aminoxide.
Hand disinfection.

Handscrub *Paracelsia, Port.*
Chlorhexidine gluconate (p.1635·3).
Hand disinfection; wound disinfection.

Handy Clean *Kalbe, Indon.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Hangekobokuto *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; magnolia bark; perilla herb; ginger.
Traditional Kampo medicine.

Hangeshashinto *Tsumura, Jpn.*
Pinellia tuber; scutellaria root; ginger; liquorice; jujube; ginseng; coptis rhizome.
Traditional Kampo medicine.

Hangover Relief *Brauer, Austral.*
Homoeopathic preparation.

HanoCor *Hanosan, Ger.*
Homoeopathic preparation.

HanoFemin *Hanosan, Ger.*
Homoeopathic preparation.

HanoHepar *Hanosan, Ger.*
Homoeopathic preparation.

Hanotoxin M *Hanosan, Ger.*
Homoeopathic preparation.

Hanotoxin N *Hanosan, Ger.†.*
Homoeopathic preparation.

Hanp *Asubio, Jpn.*
⊗ Carperitide (p.1241·1).
Heart failure.

Hansamed Spray *Beiersdorf, Ger.†.*
Chlorhexidine gluconate (p.1635·3).
Wound disinfection.

Hansamedic *Beiersdorf, Belg.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hansamedic Warmtepleister *Beiersdorf, Belg.*
Capsaicin (p.32·3).
Neuropathic pain.

Hansaplast *Beiersdorf, Hung.*
Salicylic acid (p.1612·2).
Callosities.

Hansaplast ABC Warme-Pflaster *Beiersdorf, Ger.†.*
Cayenne pepper (p.2276·2).
Musculoskeletal and joint pain.

Hansaplast ABC Warme-Pflaster Sensitive *Beiersdorf, Ger.†.*
Nonivamide (p.96·2).
Musculoskeletal and joint pain.

Hansaplast Antimicotico *Beiersdorf, Chile.*
Triclosan (p.1665·2); dichlorobenzyl alcohol (p.1642·1).

Hansaplast Callous *Beiersdorf, Gr.*
Salicylic acid (p.1612·2).
Calluses.

Hansaplast Descongestionante *Beiersdorf, Chile.*
Menthol (p.2340·1); camphor (p.2273·2); thymol (p.1664·3); pine oil (p.2368·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); anfocerina K.
Respiratory-tract congestion.

Hansaplast Emplastro Termico *Beiersdorf, Port.*
Capsaicin (p.32·3).
Inflammation.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hansaplast Footcare
Note. This name is used for preparations of different composition.
Beiersdorf, Chile.
Cream; topical spray: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis of feet.
Beiersdorf, Chile†.
Powder spray: Purified talc (p.1615·2); camphor (p.2273·2); menthol (p.2340·1); undecenoic acid (p.549·2).
Hyperhidrosis of feet.
Beiersdorf, Chile.
Topical powder: Triclosan (p.1665·2); aluminium stearate; camphor (p.2273·2); menthol (p.2340·1); purified talc (p.1615·2).
Hyperhidrosis of feet.

Hansaplast Herbal Heat Plaster *Beiersdorf, UK.*
Capsicum (p.2276·2); arnica (p.2260·2).
Musculoskeletal and joint pain.

Hansaplast Hornhaut-Pflaster *Beiersdorf, Ger.†.*
Salicylic acid (p.1612·2).
Keratinisation disorders.

Hansaplast Huhneraugen-Pflaster *Beiersdorf, Ger.†.*
Salicylic acid (p.1612·2).
Corns.

Hansaterm *Beiersdorf, Port.; Beiersdorf, Spain.*
Capsaicin (p.32·3).
Musculoskeletal and joint pain.

Hansepran *Sarabhai Piramal, India.*
Clofazimine (p.254·2).
Lepra reactions; leprosy.

Hantina *Apsen, Braz.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Hapase *Kowa, Jpn.*
Tisokinase.
Myocardial infarction.

Hapilux
Sandoz, Gr.
Fluoxetine (p.397·3).
Depression.
Biochemie, Thai.†; Novartis, Thai.†.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression.

Hapisor *Eisai, Indon.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; myocardial infarction.

Happinose *Dendron, UK.*
Menthol (p.2340·1).
Nasal congestion.

Happy'tizer *Cadila, India.*
Asparagus racemosus; ginger (p.1732·3); piper longum; black pepper (p.2364·3); embelia ribes (p.144·2); embelica officinalis; fenugreek (p.2303·3); cuminum cyminum.
Reduced appetite.

Hapsen *Pharos, Indon.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Harbamind *Bajamed, Mex.*
Metformin (p.453·3).
Diabetes mellitus.

Hard Nails *Mericon, USA.*
Biotin (p.1931·3).

Haricon *Condrugs, Thai.*
Haloperidol (p.1000·2).
Alcohol withdrawal syndrome; anxiety; psychomotor agitation.

Haridol *Atlantic, Thai.*
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Anxiety; behaviour disorders in children; nausea and vomiting; psychoses; psychosomatic disorders.

Harifin *TO-Chemicals, Thai.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica; benign prostatic hyperplasia.

Harmogen *Abbott, Irl.†; Pharmacia, UK.*
Estropipate (p.2101·2).
Menopausal disorders; osteoporosis.

Harmomed *Kwizda, Austria.*
Dosulepin hydrochloride (p.388·2); diazepam (p.986·3).
Depression.

Harmonet *Wyeth, Arg.; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Hong Kong; Wyeth, Hung.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Neth.†; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Spain; Wyeth, Switz.; Wyeth, Venez.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Harmonette *Wyeth Lederle, Austria; Wyeth, Gr.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Harmonise *Hamilton, Austral.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Harmosin *Temmler, Ger.*
Melperone hydrochloride (p.1006·2).
Disturbed behaviour; psychoses; sleep disorders.

Harnal *Yamanouchi, Hong Kong; Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Harnsauretropfen F *Syxyl, Ger.*
Homoeopathic preparation.

Harntee 400 N *TAD, Ger.*
Birch leaf (p.2266·3); java tea (p.2328·2); solidago (p.2391·1).
Harntee 400 formerly contained birch leaf, equisetum, and ononis.
Urinary-tract infections.

Harntee STADA *Stada, Ger.*
Bearberry (p.2263·3); birch leaf (p.2266·3); fructus phaseoli; solidago virgaurea (p.2391·1); java tea (p.2328·2); equisetum (p.2299·3).
Urinary-tract disorders.

Harntee-Steiner *Steiner, Ger.*
Silver birch (p.2266·3); java tea (p.2328·2); solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Harongan *Schwabe, Ger.*
Haronga.
Dyspepsia.

Harpadol *Arkopharma, Fr.*
Devil's claw root (p.39·1).
Joint pain.

Harpagin *Merz, Ger.; Merz, Hung.†; Merz, Malaysia†.*
Benzbromarone (p.555·2); allopurinol (p.552·2).
Gout; hyperuricaemia.

Harpagocid *Phytomedica, Fr.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Harpagofito Orto *Normon, Spain.*
Devil's claw root (p.39·1).
Rheumatic and joint pain.

Harpagoforte *Dyckerhoff, Ger.*
Devil's claw root (p.39·1).
Gastrointestinal disorders; musculoskeletal and joint disorders.

HarpagoMega *Twardy, Ger.†.*
Devil's claw root (p.39·1).
Degenerative joint disorders; dyspepsia.

Harpagosan *Hagen, Ger.†.*
Devil's claw root (p.39·1).
Gastrointestinal disorders; musculoskeletal and joint disorders.

Hart *Ivax, Arg.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; heart failure; hypertension.

Hartil *Egis, Cz.; EGIS, Hung.; Actavis, Rus.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Hartil HCT *EGIS, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hartil-H *Egis, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hartmannsche *Enzypharm, Austria.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Hartsorb *Siam Bheasach, Thai.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Hartylox *Integrated Pharmaceutical, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Harvellin *Wescrib, Philipp.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Harvifer *Wescrib, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); folic acid (p.1940·1).
Iron-deficiency anaemia.

Harzer Hustenloser *Wernigerode, Ger.†.*
Thyme (p.2401·1); primula root (p.2372·2).
Cold symptoms.

Harzol *Europharm, Austria; Schwarz, Ger.*
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Hasceral *Hasco-Lek, Pol.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2).
Skin disorders.

Hascoderm *Hasco-Lek, Pol.*
Azelaic acid (p.1589·3).
Acne; hyperpigmented skin disorders.

Hascofungin *Hasco-Lek, Pol.*
Ciclopirox olamine (p.529·2).
Fungal skin and nail infections.

Hascosept *Hasco-Lek, Pol.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders.

Hascovir *Hasco-Lek, Pol.*
Aciclovir (p.862·3).
Herpes simplex infections of the face and lips.

Hassapirin Puro *Mintlab, Chile.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Hastel *Viofar, Gr.*
Indometacin (p.66·3).
Inflammatory disorders.

Hastilan *Continentales, Mex.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

HA-Tabletten N *Boehringer Ingelheim, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Hatial *Medipha, Fr.†.*
Pentoxifylline (p.1367·2).
Intermittent claudication; mental function impairment in the elderly.

Hautfunktionstabletten N *Heel, Ger.*
Homoeopathic preparation.

Hautfunktionstropfen N *Heel, Ger.*
Homoeopathic preparation.

Hautfunktionstropfen S *Cosmochema, Ger.†.*
Homoeopathic preparation.

Hautplus N Dr Hagedorn *Naturarzneimittel, Ger.*
Homoeopathic preparation.

Havlane *Sanofi-Aventis, Fr.*
Loprazolam mesilate (p.1003·3).
Insomnia.

Havpur *Chiron Behring, Ger.*
A hepatitis A vaccine (p.2214·2).
Active immunisation.

Havrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; SmithKline Beecham, USA; GSK, Venez.*
An adsorbed inactivated hepatitis A vaccine (HM 175 strain) (p.2214·2).
Separate preparations are available for children and for adults.
Active immunisation.

Hawaiian Tropic
Note. This name is used for preparations of different composition.
Tanning Research, USA.
Gel SPF 15+: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); meradimate (p.1604·2).
Sunscreen.
Tanning Research, USA.
Lotion SPF 15+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); meradimate (p.1604·2).
Sunscreen.
Solpro, Mex.†.
SPF 2: Octinoxate (p.1608·2).
Sunscreen.
Solpro, Mex.†.
SPF 4: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.
Solpro, Mex.
SPF 10: Octinoxate (p.1608·2).
Sunscreen.
Tanning Research, USA.
SPF 10+; SPF 8+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); meradimate (p.1604·2).
Sunscreen.
Solpro, Mex.
SPF 15+: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.
Tanning Research, USA.
SPF 30+: Octinoxate (p.1608·2); meradimate (p.1604·2); oxybenzone (p.1608·3); octisalate (p.1608·2); homosalate (p.1598·1).
Sunscreen.
Tanning Research, USA.
SPF 45+: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.
Tanning Research, USA.
SPF 45+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3); meradimate (p.1604·2).
Sunscreen.

Hawaiian Tropic Baby Faces
Note. This name is used for preparations of different composition.
Tanning Research, USA.
SPF 20: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); meradimate (p.1604·2).
Sunscreen.
Tanning Research, USA.
SPF 35; SPF 50: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.
Tanning Research, Canad.
SPF 50: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Hawaiian Tropic Cool Aloe with I.C.E. *Tanning Research, USA.*
Lidocaine (p.1862·3); menthol (p.2340·1); aloe vera (p.1588·2).

Hawaiian Tropic Dark Tanning
Note. This name is used for preparations of different composition.
Tanning Research, USA.
Gel SPF 2; gel SPF 4: Ensulizole (p.1597·1).
Sunscreen.
Tanning Research, Canad.
Lotion SPF 4: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.
Tanning Research, USA.
Oil SPF 2; oil SPF 4: Octinoxate (p.1608·2); padimate O (p.1609·1).
Sunscreen.
Tanning Research, Canad.
Oil SPF 4: Octinoxate (p.1608·2).
Sunscreen.

Hawaiian Tropic Dark Tanning Oil with Extra Sunscreen *Tanning Research, Canad.†.*
Oil SPF 4: Octinoxate (p.1608·2); padimate O (p.1609·1).
Sunscreen.

Hawaiian Tropic Herbal
Note. This name is used for preparations of different composition.
Tanning Research, Canad.†.
SPF 4: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.
Tanning Research, Canad.†.
SPF 15; SPF 2: Ensulizole (p.1597·1); sulisobenzone (p.1614·3).
Sunscreen.

Hawaiian Tropic Just For Kids
Note. This name is used for preparations of different composition.
Tanning Research, USA.
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); homosalate (p.1598·1).
Sunscreen.
Tanning Research, USA.
SPF 45: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Hawaiian Tropic Plus *Tanning Research, Canad.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Hawaiian Tropic Protective Tanning
Note. This name is used for preparations of different composition.
Tanning Research, Canad.
Dry oil SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.
Tanning Research, Canad.
Lotion SPF 8: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.
Tanning Research, Canad.†.
Oil spray SPF 12: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.
Tanning Research, USA.
SPF 6: Titanium dioxide (p.1617·3).
Sunscreen.

Hawaiian Tropic Protective Tanning Dry
Note. This name is used for preparations of different composition.
Tanning Research, USA.
Gel SPF 6: Ensulizole (p.1597·1); sulisobenzone (p.1614·3).
Sunscreen.
Tanning Research, USA.
Oil SPF 6: Octinoxate (p.1608·2); homosalate (p.1598·1); meradimate (p.1604·2).
Sunscreen.

Hawaiian Tropic Self Tanning Sunblock *Tanning Research, USA.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Hawaiian Tropic Shimmering *Tanning Research, Canad.†.*
SPF 6: Ensulizole (p.1597·1).
Sunscreen.

Hawaiian Tropic Splash for Kids *Tanning Research, Canad.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

Hawaiian Tropic Sport
Note. This name is used for preparations of different composition.
Tanning Research, USA.
SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.
Tanning Research, Canad.†.
SPF 15; SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.
Tanning Research, USA.
SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Hawaiian Tropic Sport Sunblock *Tanning Research, Canad.*
SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2); oxybenzone.
Sunscreen.

Hawkmide *LBS, Thai.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Hawkperan *LBS, Thai.†.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Haxifal *Erempharma, Fr.*
Cefaclor (p.217·2).
Bacterial infections.

Hay Fever *Brauer, Austral.*
Homoeopathic preparation.

Hay Fever Relief *Homeocan, Canad.*
Homoeopathic preparation.

Hay Fever & Sinus Relief *Herbal Concepts, UK.*
Echinacea (p.2298·1); sambucus (p.2383·1); garlic (p.2309·2).
Catarrh; hay fever; sinus congestion.

Hay-Crom *Galena, Cz.†; Ivax, Irl.; Norton, Rus.; Ivax, UK.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic eye disorders.

Hayfebrol *Scot-Tussin, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Hayfever *Hylands, Canad.*
Homoeopathic preparation.

Hayfever & Allergy Relief *Galpharm, UK.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Hayfever Eye Drops *Pliva, UK.*
Sodium cromoglicate (p.1136·3).
Ocular symptoms of hay fever.

Hayfever Relief
Note.This name is used for preparations of different composition.
Peach, UK.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis.

Thornton & Ross, UK.
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Head & Sinus Relief *Herbal Concepts, UK.*
Echinacea (p.2298·1); sambucus (p.2383·1); garlic (p.2309·2).
Catarrh; hay fever; sinus congestion.

Hayleve *Chatfield Laboratories, UK.*
Chlorphenamine (p.572·2).
Hypersensitivity reactions.

Haymine *Forest Laboratories, UK.*
⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2).
Hypersensitivity reactions.

Hazmolin *Munir, Turk.*
Pancreatin (p.2360·1); simeticone (p.1770·2).

HB Vac *Cadila, India.*
An adsorbed hepatitis B vaccine (surface antigen) (p.2215·2).
Active immunisation.

H-Bacter *Cifarma, Braz.*
Capsules, lansoprazole (p.1739·2); tablets, clarithromycin (p.248·2); capsules, amoxicillin trihydrate (p.202·2).
Helicobacter pylori-associated peptic ulcer.

H-B-Vax *Aventis Pasteur, Denm.†.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

H-B-Vax II *MSD, Arg.†; CSL, Austral.; MSD, Cz.†; MSD, Hong Kong; MSD, Indon.; Aventis Pasteur, Irl.†; MSD, Malaysia†; MSD, Mex.; MSD, NZ; MSD, Rus.; MSD, S.Afr.; MSD, Singapore†; MSD, Thai.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Separate preparations are available for children and for adults.
Active immunisation.

HB-Vax-DNA *Aventis Pasteur, Fr.†; MSD, Neth.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

HBVaxPro *MSD, Arg.; Sanofi Pasteur, Belg.; Aventis Pasteur, Cz.; Sanofi Pasteur, Fin.; Aventis Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; MSD, Malaysia; MSD, NZ; Aventis Pasteur, Neth.; MSD, Pol.; MSD, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; MSD, Thai.; MSD, Turk.; Aventis Pasteur, UK.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Hc45 *Boots Healthcare, Irl.; Crookes Healthcare, UK.*
⊗ Hydrocortisone acetate (p.1535·2).
Eczema; insect bites.

HC Bidex *Collins, Mex.†.*
Vitamin preparation (p.1922·1).

HC Derma-Pax *Recsei, USA.*
⊗ Hydrocortisone acetate (p.1535·2); mepyramine maleate (p.585·2); chlorphenamine maleate (p.571·3).
Skin disorders.

HC Pramoxine *Veracity, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

H-Cort *Hoe, Malaysia.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

HCQS *Ipca, India.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; rheumatoid arthritis.

HCT *1A, Ger.; CT, Ger.; Hexal, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Kimia, Indon.*
⊗ Hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

HCTad *TAD, Ger.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

HCT-Beta *Betapharm, Ger.*
⊗ Hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

HCT-gamma *Worwag, Ger.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

HCT-ISIS *Alpharma-Isis, Ger.*
⊗ Hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

HCU *Scientific Hospital Supplies, Irl.; Vitaflo, Irl.; Medifood, Ital.*
Food for special diets (p.1922·1).
Homocystinuria.

HCY *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Homocystinuria.

HD 85 *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

HD 200 Plus *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

HDCV *Sanofi Pasteur, Braz.; Aventis Pasteur, Turk.*
A rabies vaccine (p.2234·1).
Active immunisation.

HDG *Sigma, Arg.*
Cynara (p.2291·2); carqueja; quercetin (p.2305·1); cynarine (p.2291·2).
Gastrointestinal disorders; hepatic disorders.

4Head *Diomed, UK.*
Levomenthol.
Headache.

Head & Shoulders *Procter & Gamble, Canad.; Procter & Gamble, USA.*
Pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Head & Shoulders Intensive Treatment *Procter & Gamble, Canad.; Procter & Gamble, USA.*
Selenium sulfide (p.1613·1).
Dandruff; seborrhoeic dermatitis.

Headache & Migraine L77 *Homeocan, Canad.*
Homoeopathic preparation.

Headache & Migraine Relief *Homeocan, Canad.*
Homoeopathic preparation.

Headache Pads *3-OL, Israel.*
Eucalyptus oil (p.2301·2); lavender oil (p.2331·2); menthol (p.2340·1).
Headache.

Headache Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Headgen *YSP, Malaysia; Yung Shin, Singapore.*
Codergocrine mesilate (p.363·3).
Dementia; mental function disorders in the elderly.

Headmaster *SSL, Irl.*
Phenothrin (p.2048·3).
Pediculosis.

Head-O *Otto, Indon.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Headrin Extra Strength *Reese, USA.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).

Heads Shampoo *Hamilton, Hong Kong.*
Econazole nitrate (p.531·1).
Dandruff; seborrhoeic dermatitis.

Headway *Pacific, Hong Kong; Alphapharm, Malaysia; Pacific, NZ.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Heafusine *Braun, Fr.†.*
⊗ Pentastarch (p.1065·1).
Haemodilution; shock.

Heal Aid Plus *Reese, USA.*
Resorcinol (p.1612·1); phenol (p.1656·1).

Healex *Shreya, India.*
Polyvinyl polymer; benzocaine (p.1854·1).
Wound dressing.

Healing Cream *Nelson, UK.*
Homoeopathic preparation.

Healip *Jenson, Gr.; ACO Hud, Swed.*
Docosanol (p.872·2).
Herpes labialis.

Healon *AMO, Austral.; Pharmacia, Belg.†; Pfizer, Braz.; Pfizer, Canad.†; Pfizer, Chile; Kabi Pharmacia, Cz.†; Pfizer, Fin.†; Pharmacia, Ger.†; Pfizer, Hong Kong; Pharmacia, Hung.†; Tradis-Gat, Israel; Pharmacia, Malaysia†; Pharmacia, NZ; Pharmacia, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore†; Pharmacia Upjohn, Switz.†; Pfizer, Thai.†; Optik, Turk.; Pharmacia Upjohn, USA; Pharmacia, Venez.†.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery; corneal burns; dry eyes.

Healon Yellow *Kabi Pharmacia, USA.*
Sodium hyaluronate (p.2320·1); fluorescein sodium (p.2306·1).
Adjunct in eye surgery.

Healonid *Pharmacia, UK†.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Healox *Cipla, Malaysia.*
Ofloxacin (p.310·2).
Bacterial infections.

HealthAid Boldo-Plus *Pharmadass, UK.*
Boldo (p.2267·2); taraxacum (p.2395·1); bladderwrack (p.2384·2); clivers (p.2284·3); bearberry (p.2263·3); juniper oil (p.2328·3); vitamin B (p.1978·2).
Formerly known as HealthAid AquaFall.
Water retention.

Healtheries Musseltone *Optima, UK.*
Green-lipped mussel (p.2317·2).
Musculoskeletal and joint disorders.

Healtheries Musseltone & Glucosamine *Optima, UK.*
Green-lipped mussel (p.2317·2); glucosamine (p.2313·2).
Musculoskeletal and joint disorders.

Healthy Feet *Pickles, UK.*
Undecenoic acid (p.549·2); dibrompropamidine isetionate (p.1642·1).
Fungal skin infections.

Heartburn Relief
Note.This name is used for preparations of different composition.
Sandoz, Austral.†.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux.

Stanley, Canad.†.
Aluminium hydroxide (p.1706·2); alginic acid (p.2140·3).

AAH, UK; Numark, UK; Thornton & Ross, UK.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux.

Heartfelt *Panacea, India†.*
Sucrose polyesters (p.1970·2).
Hypercholesterolaemia.

Heat Cream *General Drugs, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Muscle pain; sprains.

Heat Rub *Stanley, Canad.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Hebagam IM *NBI, S.Afr.*
Hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Heberbiovac HB *Enila, Braz.†; Bago, Chile; Ivax, Mex.; Biovac, S.Afr.; Heber, Thai.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

Hebermin *Bago, Chile†.*
Urogastrone (p.1778·1); sulfadiazine silver (p.337·2).
Burns; ulcers.

Hebert Caramelos *Fecofar, Arg.*
Guaifenesin (p.1561·3); senega (p.1572·3).
Formerly contained cineole, guaifenesin, and senega.
Respiratory-tract congestion.

Heblopin *Manix, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Hebrin *Uniao Quimica, Braz.*
Iodine (p.2169·2); cade oil (p.1616·1); salicylic acid (p.1612·2).
Fungal skin infections.

Hebsbulin-IH *Mitsubishi, Jpn.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hebucol *Will-Pharma, Belg.*
Cynara (p.2291·2).
Biliary-tract disorders.

HEC
Note.This name is used for preparations of different composition.
Chauvin, Fr.; Bausch & Lomb, Singapore†; Chauvin, Singapore†.
Tannic acid (p.2394·3); hamamelis (p.2318·2); phenazone (p.116·1).
Burns; haemorrhoids; nose bleeds; wounds.

Bausch & Lomb, Switz.
Tannin (p.2394·3); pectin (p.2145·2); peru balsam (p.2365·3); hamamelis (p.2318·2).
Mucous membrane disorders of the nose.

Heclivir *Neo Quimica, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Hecobac *Nufarindo, Indon.*
Clarithromycin (p.248·2).
Bacterial infections.

Hecrosine B12 *Ortoquimica, Braz.†.*
Methionine (p.1450·1); choline (p.1934·2); inositol (p.2325·2); liver extract (p.2337·3); cynara (p.2291·2); solanum paniculatum.
Liver disorders.

Hectonona *Milo, Spain.*
Dried aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Gastric hyperacidity.

Hectorol *Shire, Canad.; Genzyme, USA.*
Doxercalciferol (p.1987·1).
Hyperparathyroidism.

Hedazol *Arlex, Mex.*
Mebendazole (p.148·3).

Hedelicum *Natur Produkt, Pol.*
Liquorice (p.1740·3); ivy (p.2328·1); thyme (p.2401·1).
Cough; respiratory-tract congestion.

Hedelix *Krewel Meuselbach, Cz.; Krewel, Ger.; Krewel Meuselbach, Pol.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Hedensa *Santa, Turk.*
Monochlorocarvacrol (p.1639·3); chamomile oil (p.2279·3); menthol (p.2340·1); ichthammol (p.1599·1).
Haemorrhoids.

Hederasal *Herbapol Wroclaw, Pol.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Hederix
Note.This name is used for preparations of different composition.
SIT, Ital.
Codeine hydrobromide (p.38·3); ivy (p.2328·1).
Coughs.

Plan, Switz.
Noscapine hydrochloride (p.1566·3); ivy (p.2328·1); senega (p.1572·3); helenium (p.1558·1); orris; marrubium (p.1564·1).
Coughs.

Hederoin *Herbapol Wroclaw, Pol.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Hedex *GSK Consumer, Irl.; GSK Consumer, Neth.; GSK Consumer, UK.*
Paracetamol (p.108·1).
Fever; pain.

Hedex Extra *GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Hedex Ibuprofen *GSK Consumer, UK.*
Ibuprofen (p.64·2).
Cold and influenza symptoms; fever; pain.

Hedilar *Andromaco, Chile.*
Ivy (p.2328·1).

Hedix *Sandoz, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Hedonin *Gerot, Austria.*
Phenylpropanol (p.2366·2); moxaverine hydrochloride (p.2347·3).
Biliary-tract disorders; gastrointestinal disorders.

Hedrin *Thornton & Ross, UK.*
Dimeticone (p.2032·1).
Pediculosis.

Heduline *Costec, Arg.*
Salicylic acid (p.1612·2); triclosan (Irgasan DP-300) (p.1665·2); dexpanthenol (p.2362·1).
Seborrhoeic dermatitis.

Heemex *Lane, UK.*
Hamamelis (p.2318·2); compound benzoin tincture; zinc oxide (p.1621·2).
Haemorrhoids.

Heer-More *Eagle, Austral.†.*
Homoeopathic preparation.

Heet *Medtech, Canad.; Whitehall, USA.*
Methyl salicylate (p.85·3); camphor (p.2273·2); capsaicin (p.32·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Hefaclor *Sanavita, Ger.†; Wernigerode, Ger.†.*
Cefaclor (p.217·2).
Bacterial infections.

hefasolon *Sanavita, Ger.*
⊗ Prednisolone (p.1540·3) or prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Hegon *Beta, Arg.*
Zaleplon (p.1035·3).
Insomnia.

Hegor *Procter & Gamble, Austria.*
Shampoo.
Scalp and hair disorders.

Hegrimarin *Strathmann, Ger.; Strathmann, Hung.*
Milk thistle (p.1452·1).
Liver disorders.

Heidi *Siam Bheasach, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Heilsalbe *Weleda, S.Afr.*
Calendula (p.2273·1); mercurialis perennis; stibium met; peru balsam (p.2365·3); resina laricis.
Skin lesions; wounds.

Heinix *Verman, Fin.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Heitrin *Abbott, Ger.*
Terazosin hydrochloride (p.1410·2).
Hypertension.

Hekabetol *Fortbenton, Arg.*
Triclosan (Irgasan) (p.1665·2); betanaphthol (p.142·1).
Seborrhoeic dermatitis.

Heksa *Polifarma, Turk.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Heksavit *Leiras, Fin.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Heksoral *Mega, Turk.*
Hexetidine (p.1647·1).
Oral hygiene.

Hekzoton *Drogsan, Turk.*
Hexetidine (p.1647·1).
Oral hygiene.

Helago-Pflege-Oel *Helago, Ger.†.*
Chamomile (p.2279·3); sage (p.2382·3).
Formerly known as Helago-oel N.
Mouth and throat inflammation.

Helal *Roemmers, Venez.*
Albendazole (p.139·2).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Helarium *Austroplant, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Hung.; Bionorica, Rus.*
St John's wort (p.422·3).
Depression; neuroses; sleep disorders.

Helason *Jelfa, Pol.*
A heparinoid (p.1305·2); hyaluronidase (p.2321·1).
Soft-tissue injury; venous thrombosis.

Helastop *Hamilton, Austral.†*
Propolis (p.2373·3).
Herpes labialis.

Helcon *Polipharm, Thai.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Helen *Masa, Thai.†*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Oral contraceptive in women with androgenic symptoms.

Helenil *Roux-Ocefa, Arg.*
Ketoprofen (p.73·1).
Inflammation; pain.

Helex *KRKA, Cz.; KRKA, Rus.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety disorders; depression; mixed anxiety-depressive states; panic disorder.

Helfergin *Lundbeck, Ger.†; Promonta, Hung.†*
⊗ Meclofenoxate hydrochloride (p.2338·1).
Cerebrovascular disorders.

Helianthus comp *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Helical *Medana, Pol.*
Ivy (p.2328·1).
Respiratory-tract disorders.

HeliCap *Kibion, Cz.; Noster, Neth.; Noster, Port.*
⊗ Carbon-14 (p.2053·1) urea.
Diagnosis of Helicobacter pylori infection.

Helicid
Zentiva, Cz.; Zentiva, Pol.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zentiva, Rus.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Heliclar *Abbott, Belg.*
Clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Heliclear *Wyeth, UK†.*
Capsules, lansoprazole (Zoton) (p.1739·2); tablets, clarithromycin (Klaricid) (p.248·2); capsules, amoxicillin (p.202·2).
Helicobacter pylori-associated duodenal ulcer.

Helico State *Simac, Neth.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Helicobacter *Faran, Gr.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for Helicobacter pylori infection.

Helicobacter Test *Utandningstester, Denm.; Medicaland, Port.; Utandningstester, Swed.; INFAI, Switz.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Test for Helicobacter pylori infection.

Helicocid Triplice *Sigma, Braz.†.*
Capsules, omeprazole (p.1753·1); tablets, clarithromycin (p.248·2); capsules, amoxicillin (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Helicocin *Sandoz, Austria.*
Oval tablet, amoxicillin trihydrate (p.202·2); round tablet, metronidazole (p.837·1).
Helicobacter pylori infection.

Helicokit *Italchimici, Ital.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Helicol *Eczacibasi, Rus.; Eczacibasi, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Helicopac *Sigma, Braz.*
Capsules, lansoprazole (p.1739·2); tablets, clarithromycin (p.248·2); tablets, amoxicillin (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Helicostad *Stada, Austria.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Helico-teste *Isomed, Port.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Test for Helicobacter pylori infection.

Helidac *Procter & Gamble, USA.*
Pink tablets, bismuth salicylate (p.1711·1); white tablets, metronidazole (p.837·1); orange/white capsules, tetracycline hydrochloride (p.347·2).
Duodenal ulcer.

Helifenicol *Ariston, Braz.†.*
Dextromethorphan hydrobromide (p.1555·2); helicin.
Coughs.

Heli-Kit *Mayoly-Spindler, Fr.*
⊗ Carbon-13 labelled urea (p.2277·1).
Detection of Helicobacter pylori infection.

Heliklar *Abbott, Arg.†; Abbott, Braz.*
Tablets, clarithromycin (Klaricid) (p.248·2); capsules, amoxicillin (p.202·2); capsules, lansoprazole (Ogasto) (p.1739·2).
Helicobacter pylori-associated peptic ulcer.

HeliMet *Wyeth, UK†.*
Capsules, lansoprazole (Zoton) (p.1739·2); tablets, clarithromycin (Klaricid) (p.248·2); tablets, metronidazole (p.837·1).
Peptic ulcer.

Helioban *Galderma, Mex.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Helioblock
Note. This name is used for preparations of different composition.
Roche-Posay, Braz.
SPF 20; SPF 40; SPF 50; SPF 60: Drometrizole trisiloxane (p.1596·1); ecamsule (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Roche-Posay, Braz.
SPF 30: Drometrizole trisiloxane (p.1596·1); avobenzone (p.1589·3); octocrilene (p.1608·3); titanium dioxide (p.1617·3); octil triazone (p.1608·1).
Sunscreen.

Heliocare *Labomed, Chile; Serral, Mex.†.*
A range of sunscreens containing polypodium leucotomos.
Prevention of sun-induced skin damage.

Heliofilm *Szama, Arg.†.*
Benzophenone; enzacamene (p.1597·1).
Sunscreen.

Heliopar *Orion, Fin.*
Chloroquine phosphate (p.599·3).
Amoebiasis; light-sensitive skin disorders; lupus erythematosus; malaria; musculoskeletal and joint disorders.

Helioperl IP 20 *Oenobiol, Fr.†.*
Helioperl; octinoxate (p.1608·2); bisoctrizole (p.1591·2).
Sunscreen.

Helipac
Note. This name is used for preparations of different composition.
Altana, Austria.
Beige tablets, pantoprazole sodium (p.1760·1); white tablets, amoxicillin trihydrate (p.202·2); yellow tablets, clarithromycin (p.248·2).
Helicobacter pylori infection.

Cipla, India.
Amoxicillin (p.202·2); tinidazole (p.848·3); omeprazole (p.1753·1).
Peptic ulcer.

Helipak *Fako, Turk.*
Capsules, lansoprazole (p.1739·2); tablets, clarithromycin (p.248·2); tablets, amoxicillin (p.202·2).
Peptic ulcer.

Helipak A *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Lanzo) (p.1739·2); tablets, amoxicillin (Amorion) (p.202·2); tablets, metronidazole (Trikozol) (p.837·1).
Peptic ulcer.

Helipak K *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Lanzo) (p.1739·2); tablets, clarithromycin (Zeclar) (p.248·2); tablets, amoxicillin (Amorion) (p.202·2).
Peptic ulcer.

Helipak T *Orion, Fin.*
Enteric-coated capsules, lansoprazole (Lanzo) (p.1739·2); tablets, tetracycline (Oricyclin) (p.347·1); tablets, metronidazole (Trikozol) (p.837·1).
Peptic ulcer.

Heliphenicol *Ariston, Arg.*
Butetamate citrate (p.1553·1).
Coughs.

Helipur *Braun, Ger.; Braun, Ital.*
Chlorocresol (p.1640·1); clorophene (p.1641·1); orthophenylphenol (p.1655·1).
Surface and instrument disinfection.

Helipur H plus N *Braun, Ger.*
Glutaral (p.1645·2); isopropyl alcohol (p.1650·3); ethylhexanal (p.1644·1).
Instrument disinfection.

Helirad *Allen, Austria.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Helis *Bifarma, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection.

Helisal *Cortecs, Irl.*
Test for *Helicobacter pylori* infection.

Heliton
Note. This name is used for preparations of different composition.
Columbia, Arg.†.
Nitazoxanide (p.842·3).
Protozoal infections; worm infections.

Columbia, Mex.
Nitazoxanide (p.842·3); tripotassium dicitratobismuthate (p.1711·2).
Peptic ulcer.

Helix I *Braun, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Instrument disinfection.

Helixate *Bayer, Austria; ZLB, Belg.; CSL Behring, Canad.; Bayer, Cz.; Bayer, Denm.; ZLB, Fr.; ZLB, Ger.; Gerolymatos, Gr.; ZLB, Ital.; Bayer, Neth.; ZLB, Norw.; Bayer, Port.; ZLB, Spain; ZLB, Swed.; ZLB, Switz.; Aventis Behring, UK; Centeon, USA.*
Octocog alfa (p.1067·2).
Haemophilia A.

Helixderm *Gerolymatos, Gr.*
Alkanna tinctoria oily extract.
Skin healing aid.

Helixir *Hexal, Cz.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Helixor *Germania, Austria; Helixor, Ger.*
Mistletoe (p.2345·3) from fir trees, pine trees, or apple trees.
Malignant neoplasms.

Helmazan *Noel, India†.*
Diethylcarbamazine citrate (p.143·1); piperazine citrate (p.152·3).
Worm infections.

Helmex *Infectopharm, Ger.*
Pyrantel embonate (p.155·1).
Worm infections.

Helmib *Ibfarma, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Helmiben *Eurofarma, Braz.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Helmicide *Atabay, Turk.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Helmicin *Sanval, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Helmidrax *Haller, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Helmifar *Farcoral, Mex.†.*
Piperazine citrate (p.152·3).
Worm infections.

Helmint *Lafedar, Arg.*
Mebendazole (p.148·3).
Worm infections.

Helmint Compuesto *Lafedar, Arg.*
Mebendazole (p.148·3); tinidazole (p.848·3).
Worm infections.

Helmintox *Innotech, Fr.; Innotech, Rus.*
Pyrantel embonate (p.155·1).
Intestinal nematode infections; worm infections.

Helminzole *Randall, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

Helmipar *Saba, Turk.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Helmi-Ped *Stiefel, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Helmisons *Sons, Mex.*
Albendazole (p.139·2).
Worm infections.

Helmizol *Teuto, Braz.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).

Helmobleu *Ilsan, Turk.*
Methenamine (p.298·3); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

Helmontskruie *Lennon, S.Afr.*
Aloes (p.1705·2); camphor (p.2273·2); potassium carbonate; rhubarb (p.1768·3); gentian (p.2310·3); valerian (p.2410·1); ginger (p.1732·3); cardamom fruit (p.2277·1); myrrh (p.2349·2); clove oil (p.2285·1).
Constipation; dyspepsia.

Helo-acid *Rosch & Handel, Austria.*
Citric acid (p.2284·1); tartaric acid (p.2395·2); lactic acid (p.2329·3); pepsin (p.2365·1).
Digestive disorders.

Helol *Sri Jay, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Helopanflat *Rosch & Handel, Austria; Abbott, Port.; Knoll, Switz.†.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive system disorders; flatulence; preparation for gastrointestinal radiography; Roemheld syndrome.

Helopanzym *Rosch & Handel, Austria.*
Pepsin (p.2365·1); pancreatin (p.2360·1); porcine bile (p.2266·2).
Digestive system disorders.

Helopyrin *Rosch & Handel, Austria.*
⊗ Ethenzamide (p.51·3); ascorbic acid (p.1983·3); flavonoids (p.2304·1); rutoside (p.2305·1); ephedrine hydrochloride (p.1558·2).
Cold symptoms.

Helpa *Adeka, Turk.*
Methenamine anhydromethylenecitrate (p.299·1).
Urinary-tract infections.

Helpin *Megahealth, Chile.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Helporigin *Help, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Helposol *Help, Gr.*
Aciclovir (p.862·3).
Herpes simplex infections.

Helposper *Help, Gr.*
Risperidone (p.1024·2).
Psychoses.

Helposteol *Help, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Helpovion *Medicus, Gr.†.*
Bifonazole (p.527·3).
Fungal skin infections.

Helpp *ISA, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Heltine Plus *Wescrib, Philipp.*
Vitamins; lysine hydrochloride; lecithin (p.1922·1).

Heltiskin *Konimex, Indon.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections.

Helvedoclyn *Helvepharm, Cz.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Helvedstensstifter *Braun, Denm.†.*
Silver nitrate (p.2387·2).
Hyperkeratosis.

Helvegeron *Helvepharm, Switz.†.*
Amino-acid, multivitamin and mineral preparation with ginseng and lecithin (p.1922·1).
Tonic.

Helver Sal *Bauxili, Spain†.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Helvevir *Helvepharm, Switz.*
Aciclovir (p.862·3).
Herpes labialis.

Hem Anth *Llorens, Spain.*
⊗ Chlorphenamine maleate (p.571·3); dexamethasone phosphate (p.1526·2).
Eye disorders.

Hem Fe *Wakefield, USA.*
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); desiccated gastric substance.
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Iron deficiency anaemias.

Hemabate *Pfizer, Canad.; Pharmacia, UK; Upjohn, USA.*
Carboprost trometamol (p.2006·1).
Postpartum haemorrhage; termination of pregnancy.

Hema-Chek *Bayer Diagnostics, UK; Bayer, USA.*
Test for blood in faeces.

Hema-Combistix *Bayer, Austral.†; Bayer Diagnostics, Irl.; Bayer Diagnostics, UK.*
Test for pH, protein, glucose, and blood in urine.

Hemadone *Oboi, Philipp.*
Menadione sodium bisulfite (p.1995·3).
Vitamin K deficiency.

Hemafer *Unipharma, Gr.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Hemafer fol *Unipharma, Gr.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy.

Hemagene Tailleur *Elerte, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Hema-K *Taiwan Biotech, Philipp.*
Phytomenadione (p.1995·3).
Anticoagulant-induced prothrombin deficiency; haemorrhagic disease of the newborn; hypoprothrombinaemia.

Hemamina *Byk Gulden, Mex.†.*
Vitamin preparation (p.1922·1).

Hemapep *SA Druggists Self Med, S.Afr.*
Potassium chloride; sodium chloride; calcium carbonate; glucose (p.1672·2).
Oral rehydration therapy.

Hemapo *Kalbe, Indon.*
⊗ Epoetin alfa (p.1061·1).
Anaemia in renal failure.

Hemarate *BioFemme, Philipp.; Biomedis, Thai.; Great Eastern, Thai.*
Ferrous fumarate (p.1938·3); vitamins (p.1922·1).
Iron-deficiency anaemia; vitamin B deficiency.

Hemarate CE *Biomedis, Indon.; Medifarma, Indon.*
Ferrous fumarate (p.1938·3); vitamin B substances; vitamin E (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; vitamin B deficiency.

Hemarexin *Sabex, Canad.; Sandoz, Canad.*
Vitamin B substances; sodium glycerophosphate (p.1922·1).

Hemarexin + C *Sandoz, Canad.*
Vitamin preparation (p.1922·1).

Hemaspan *Sanofi Winthrop, USA†.*
Ferrous fumarate (p.1938·3).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Iron-deficiency anaemias.

Hemastix *Bayer, Austral.†; Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, UK; Bayer, USA.*
Test for blood in urine.

Hematest *Bayer, Austral.†; Bayer Diagnostics, Mex.†; Bayer, USA.*
Test for occult blood in faeces.

Hematiase B12 *Gross, Braz.*
Liver extract (p.2337·3); gastric mucosa extract (p.2337·3); ferric ammonium citrate (p.1938·1); cyanocobalamin (p.1980·2).
Anaemias; iron-deficiency.

Hematinic
Note. This name is used for preparations of different composition.
Solgar, UK.
Liver (desiccated) (p.2337·3); vitamin B (p.1980·2); iron (p.1949·1); calcium ascorbate (p.1984·1); folic acid (p.1940·1).
Dietary supplement.

Cypress, USA.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemias.

Hematinic Plus *Cypress, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B substances; minerals (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hematiron *Ibefar, Braz.†.*
Lysine hydrochloride; vitamin B substances; ferric ammonium citrate; copper sulfate; liver extract; gastric mucosa extract (p.1922·1).
Nutritional supplement.

Hematofer *Prati-Donaduzzi, Braz.†.*
Ferrous sulfate (p.1939·3).

Hematon *Defuen, Arg.†.*
Ferrous fumarate (p.1938·3); copper; vitamin B substances; intrinsic factor; liver extract (p.1922·1).
Anaemias.

Hematrine *Novartis, India.*
Ferrous succinate (p.1939·2); vitamins (p.1922·1).
Anaemias; nutritional supplement; tonic.

Hemaviton Brain Nutrient *Bode, Indon.; Tempo Scan Pacific, Indon.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1); vitamins A, C, and E; zinc; selenium (p.1922·1).
Tonic.

Hemaviton Energy Drink *Bode, Indon.; Tempo Scan Pacific, Indon.*
Taurine; nicotinamide; caffeine; ginseng (p.2312·1); royal jelly (p.2382·1)(p.1922·1).
Dietary supplement.

Hemaviton Jreng *Bode, Indon.; Tempo Scan Pacific, Indon.*
Taurine; nicotinamide; caffeine; ginseng (p.2312·1); royal jelly (p.2382·1)(p.1922·1).
Dietary supplement.

Hemax
Sidus, Arg.
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood transfusion.

Bio Sidus, Thai.
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Hemax-Eritron *Biosintetica, Braz.*
⊗ Epoetin (p.1061·1).
Anaemias.

Hemcort HC *Technilab, Hong Kong†; Technilab, Pol.*
⊗ Hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2).
Anorectal disorders.

Hemeran *Novartis, Arg.†; Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Gr.; Novartis Consumer, Port.; Novartis Consumer, Switz.*
A heparinoid (p.1305·2).
Haematoma; phlebitis; thrombophlebitis; venous insufficiency.

Hemerven *Interdelta, Switz.*
Diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

HemeSelect *SmithKline Diagnostics, USA.*
Test for occult blood in faeces.

Hemestal *Silanes, Mex.*
Metronidazole hydrogen succinate (p.839·3).
Anaerobic bacterial infections; protozoal infections.

Hemetiken *Kener, Mex.*
Difenidol (p.1723·2).
Nausea and vomiting; vertigo.

Hemibe *Rider, Chile.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; gastrointestinal radiography.

Hemicraneal *Abbott, Spain.*
Caffeine (p.1116·3); ergotamine tartrate (p.620·1); paracetamol (p.108·1).
Headache; migraine.

Hemi-Daonil *Sanofi-Aventis, Fr.; Aventis, Neth.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Hemifol *Solfran, Mex.*
Vitamin B substances (p.1922·1).

Hemigoxine Nativelle *Procter & Gamble, Fr.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Hemineurin *AstraZeneca, Austral.*
Clomethiazole (p.978·1).
Agitation; alcohol withdrawal syndrome.

Heminevrin
AstraZeneca, Cz.; AstraZeneca, Irl.; AstraZeneca, Swed.; AstraZeneca, UK.
Clomethiazole (p.978·1) or clomethiazole edisilate (p.978·1).
Alcohol withdrawal syndrome; anxiety; behaviour disorders in the elderly; eclampsia; pre-eclamptic toxaemia; psychomotor agitation; psychoses; sedative; sleep disorders; status epilepticus.

AstraZeneca, Denm.; AstraZeneca, Fin.†; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hung.; AstraZeneca, Norw.; AstraZeneca, Pol.
Clomethiazole edisilate (p.978·1).
Alcohol withdrawal syndrome; behaviour disorders in the elderly; eclampsia; psychomotor agitation; sleep disorders in the elderly; status epilepticus.

AstraZeneca, Hong Kong†.
Clomethiazole (p.978·1).
Alcohol withdrawal syndrome; insomnia; psychomotor agitation; sedative.

Hemiphos *Wyeth, India.*
Vitamin B substances; minerals (p.1922·1).

Hemipralon *Beaufour, Fr.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Cardiovascular disorders; migraine.

Hemo
Note. This name is used for preparations of different composition.
Rekah, Israel.
Ointment: Bismuth subgallate (p.1711·1); benzocaine (p.1854·1); zinc oxide (p.1621·2); chloroxylenol (p.1640·2); zinc sulfate (p.1999·2).
Anorectal disorders.

Rekah, Israel.
Suppositories: Bismuth subgallate (p.1711·1); benzocaine (p.1854·1); zinc oxide (p.1621·2); peru balsam (p.2365·3).
Anorectal disorders.

Hemo 141 *Esteve, Spain.*
Etamsylate (p.1064·3).
Haemorrhage.

Hemo Derminiol *DHU, Spain.*
Hamamelis (p.2318·2).
Haemorrhoids.

Hemo Rid *CCM, Hong Kong.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Hemoal *Combe, Spain.*
⊗ Ephedrine (p.1558·1); benzocaine (p.1854·1).
Anorectal disorders.

Hemobion
Note. This name is used for preparations of different composition.
Merck, Indon.; Merck, Philipp.
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B ; calcium carbonate; colecalciferol (p.1922·1).
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Anaemias; nutritional supplement; prevention of neural-tube defects in pregnancy.

Merck, Mex.
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Hemoblock *Sigma, Braz.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Hemocalcin *Vinas, Spain†.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolytic bone metastases.

Hemocane
Note. This name is used for preparations of different composition.
Key, Austral.
Lidocaine (p.1862·3); allantoin (p.1588·1); hamamelis (p.2318·2); zinc oxide (p.1621·2); chlorhexidine acetate (p.1635·2).
Anal pruritus; haemorrhoids.

LPC, UK.
Lidocaine hydrochloride (p.1862·3); zinc oxide (p.1621·2); bismuth oxide (p.1710·3); benzoic acid (p.1630·2); cinnamic acid (p.1640·3).
Haemorrhoids.

Hemoccult *Beckman, Canad.; Prevention et Biologie, Fr.†; SmithKline Diagnostics, USA.*
Test for occult blood in faeces.

Hemocheck *Preventys, Fr.*
Test for blood in faeces.

Hemocid *GSK, India.*
Aminocaproic acid (p.1053·2).
Haemorrhage.

Hemoclar *Sanofi-Aventis, Fr.*
Pentosan polysulfate (p.1367·1).
Soft-tissue disorders; superficial vascular disorders.

Hemoclot *Solvang, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Hemocol *MBP, Ger.*
Collagen (porcine) (p.2286·1).
Haemorrhage.

Hemocromo *Francia, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Iron-deficiency anaemia.

Hemocyte *US Pharmaceutical, USA.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemias.

Hemocyte Plus *US Pharmaceutical, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); sodium ascorbate (p.1984·1); vitamin B substances and minerals (p.1922·1).
Iron-deficiency anaemias.

Hemocyte-F
Note. This name is used for preparations of different composition.
US Pharmaceutical, USA.
Elixir: Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); vitamin B (p.1980·2).
Anaemias.

US Pharmaceutical, USA.
Tablets: Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron-deficiency anaemias.

Hemo-Cyto-Serum *Hua, Thai.*
⊗ Monosodium glutamate (p.2347·3); strychnine sulfate (p.2393·2); iron (p.1949·1).
Anaemias; tonic.

Hemodotti *Prodotti, Braz.*
⊗ Rutoside (p.2305·1); naphazoline hydrochloride (p.1565·2); hydrocortisone acetate (p.1535·2); hamamelis (p.2318·2); amylocaine hydrochloride (p.1853·3).
Haemorrhoids.

Hemodren *Llorens, Spain.*
⊗ Hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Hemodren Compuesto *Llorens, Spain†.*
⊗ Bismuth subgallate (p.1711·1); aesculus (p.2248·2); hamamelis (p.2318·2); hydrocortisone acetate (p.1535·2); ruscogenin (p.2382·2); tyrothricin (p.358·2); amylocaine hydrochloride (p.1853·3); benzocaine (p.1854·1).
Anorectal disorders.

Hemo-Fec *Roche Diagnostics, Fr.*
Test for blood in faeces.

Hemofer
Note. This name is used for preparations of different composition.
Profarb, Braz.†.
Iron (p.1949·1); intrinsic factor (p.2326·3); liver extract (p.2337·3); vitamins (p.1922·1).
Iron deficiency; iron-deficiency anaemias.

Pangaoshou, Philipp.
Angelica (p.2258·1); sichuan rhizome; astragalus root; asiabell root; indian bread; rahmania root; liquorice (p.1740·3).
Dietary supplement.

GSK, Pol.; Medana, Pol.
Ferrous chloride (p.1938·2) or ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

GSK, Rus.; Medana, Rus.
Ferrous sulfate (p.1939·3) or ferric chloride (p.2303·3).
Iron deficiency; iron-deficiency anaemia.

Hemofer F *GSK, Pol.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Anaemias.

Hemoferrol *Sintesina, Arg.*
Ferrous sulfate (p.1939·3).
Anaemias; iron supplement.

Hemofil *Baxter, Ger.†; Baxter, Malaysia; Baxter, Neth.; Baxter, Pol.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Hemofil M *Baxter Immuno, Arg.; Baxter, Cz.†; Baxter, Fr.†; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter, Mex.†; Bioscience, Philipp.; Baxter, Singapore†; Baxter, Spain; Baxter, Swed.†; Eczacibasi-Baxter, Turk.; Baxter BioScience, UK†; Baxter, USA; Baxter, Venez.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Hemofiltracion E2 and E3 *Baxter, Spain.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration solution.

Hemofiltracion E4 and E5 *Baxter, Spain.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate (p.1670·3).
Haemofiltration solution.

Hemofiltracion HF 01 *Fresenius Medical, Spain†.*
Sodium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration solution.

Hemofiltracion HF 02 *Fresenius Medical, Spain†.*
Sodium chloride; calcium chloride; magnesium chloride; sodium acetate (p.1670·3).
Haemofiltration solution.

Hemofiltracion HF 11 and HF 23 *Fresenius Medical, Spain†.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemofiltration solution.

Hemofiltrasol *Gambro, Swed.†.*
Anhydrous glucose; electrolytes (p.1670·3).
Haemofiltration.

Hemofiltrationslosning 401 *Baxter, Swed.†.*
Anhydrous glucose; sodium chloride; sodium lactate; calcium chloride; magnesium chloride; potassium chloride (p.1670·3).
Haemofiltration.

Hemofissural *Baldacci, Port.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3); hamamelis (p.2318·2); tetracaine hydrochloride (p.1871·3).
Anorectal disorders.

Hemofluss *Fonten, Ital.†.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Hemogenin *Sanofi-Aventis, Braz.*
⊗ Oxymetholone (p.2123·3).
Anaemias; growth retardation; hereditary angioedema.

Hemohes *Braun, Arg.†; Braun, Chile; Braun, Cz.; Braun, Fin.; Braun, Ger.; Bioser (Βιοσερ), Gr.; Braun, Hung.; Braun, Indon.; Biomed, NZ; Braun, Neth.; Braun, Norw.; Braun, Pol.; Braun, Port.; Braun, Singapore†; Braun, Spain; Braun, Swed.†; Braun, Switz.; Braun, Thai.; Braun, Turk.; Braun, UK.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Extracorporeal circulation; haemodilution; hypotension; leucapheresis; plasma volume expansion; shock.

Hemo-Ice *Key, Israel.*
Freezable solution in plastic applicator.
Haemorrhoids.

Hemoinfant *Nucitec, Mex.*
Vitamin B substances; vitamin C; ferrous sulfate; zinc sulfate (p.1922·1).

Hemo-K *Am-Europharma, Philipp.*
Menadione sodium bisulfite (p.1995·3).
Haemorrhagic disease; vitamin K deficiency.

Hemolactol *Gambro, Port.; Gambro, Swed.*
Potassium chloride; glucose; sodium chloride; magnesium chloride; calcium chloride; sodium lactate (p.1670·3).
Haemodialysis; haemofiltration.

Hemolax *Hua, Thai.*
Ferrous fumarate (p.1938·3); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); cascara (p.1715·2).
Beri-beri; constipation; iron-deficiency anaemia; vitamin B deficiency.

Hemoleven *Lab Francais du Fractionnement, Fr.*
A factor XI preparation (p.1069·2).
Factor XI deficiency.

Hemolok *Dexa, Indon.*
Feracrylum.
Burns; haemorrhage; skin disinfection; wounds.

Hemomycin *Hemofarm, Rus.*
Azithromycin (p.207·1).
Bacterial infections; peptic ulcer.

Hemon *Norma (Νορμα), Gr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Hemonet *Diafarm, Spain.*
Tetracaine hydrochloride (p.1871·3).
Haemorrhoids.

Hemoplex *Recalcine, Chile†.*
Citrobioflavonoides (p.2304·1); ascorbic acid (p.1983·3).
Haemorrhage; haemorrhoids; venous insufficiency.

Hemoprex *Bergamo, Braz.*
⊗ Epoetin (p.1061·1).
Anaemias.

Hemopure *Tshepo, S.Afr.*
⊗ Polymerised hemoglobin (bovine) (p.1072·3).
Anaemia.

Hemoraas *Shanghai RAAS, Thai.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemophilia A.

Hemoral *Slovakofarma, Cz.†.*
Oak bark (p.2355·3); chamomile (p.2279·3); agrimony (p.2249·2); peppermint leaf (p.1761·2); achillea (p.2245·2).
Haemorrhoids.

Hemoralgine *Atabay, Turk.*
⊗ Chlorhexidine hydrochloride (p.1635·3); menthol (p.2340·1); aluminium acetotartrate (p.2255·1); ephedrine hydrochloride (p.1558·2); bismuth subgallate (p.1711·1); tetracaine hydrochloride (p.1871·3); zinc oxide (p.1621·2).
Haemorrhoids.

Hemoray *Varifarma, Arg.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Hemorectal *GSK, Pol.*
Bismuth oxide (p.1710·3); bismuth subgallate (p.1711·1); bismuth oxyiodogallate (p.1712·1); boric acid (p.2268·1); Peru balsam (p.2365·3); resorcinol (p.1612·1); zinc oxide (p.1621·2).
Anorectal disorders.

Hemorhin *Hua, Thai.*
Docusate sodium (p.1725·1); spermaceti.
Haemorrhoids.

Hemorhinol *Chauvin, Belg.*
Hamamelis (p.2318·2); phenazone (p.116·1); tannic acid (p.2394·3).
Skin irritation.

Hemorid
Note. This name is used for preparations of different composition.
Pfizer, Israel.
Phenylephrine hydrochloride (p.1568·1); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

CCM, Malaysia.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Wagner, Hung.
Rectal ointment: ⊗ Camphor (p.2273·2); menthol (p.2340·1); achillea oil (p.2245·2); procaine hydrochloride (p.1869·1); ephedrine hydrochloride (p.1558·2).
Anorectal disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pharmamagist, Hung.
Suppositories: ⊗ Camphor (p.2273·2); menthol (p.2340·1); achillea oil (p.2245·2); adrenaline hydrochloride (p.1203·3); procaine hydrochloride (p.1869·1); ephedrine hydrochloride (p.1558·2).
Anorectal disorders.

Hemorid For Women
Note. This name is used for preparations of different composition.
Thompson, USA.
Cream: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); pramocaine hydrochloride (p.1868·1); phenylephrine hydrochloride (p.1568·1); aloe vera (p.1588·2).
Anorectal disorders.
Thompson, USA.
Lotion: Liquid paraffin (p.2030·3); yellow soft paraffin (p.2031·3); glycerol (p.2314·2).
Anorectal disorders.
Thompson, USA.
Suppositories: Zinc oxide (p.1621·2); phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Hemorigen *Herbapol Wroclaw, Pol.*
Erigeron canadensis.
Haemorrhage.

Hemorol *Herbapol Wroclaw, Pol.*
Achillea (p.2245·2); aesculus (p.2248·2); belladonna (p.2263·3); benzocaine (p.1854·1); chamomile (p.2279·3); tormentil (p.2403·2); janowca.
Anorectal disorders.

Hemorrane *Altana, Spain.*
⊗ Hydrocortisone acetate (p.1535·2).
Haemorrhoids.

Hemorrhoid Ointment *Jamp, Canad.*
Pramocaine hydrochloride (p.1868·1); zinc sulfate (p.1999·2).
Haemorrhoids.

Hemorrogel *Arkopharma, Fr.*
Pilewort (p.2368·1); aesculus (p.2248·2); calendula (p.2273·1).
Haemorrhoids.

Hemorroidex *Medic, Braz.†.*
Rutoside (p.2305·1); hamamelis (p.2318·2); aesculus (p.2248·2).
Haemorrhoids.

Hemorrol *Hochstetter, Chile†.*
Aescin (p.2248·2); hamamelis (p.2318·2); rhatany (p.2378·3).
Haemorrhoids.

Hemorrolite *Eulite, Neth.*
Homoeopathic preparation.

Hemosedan *Centrapharm, Belg.*
⊗ Prednisolone acetate (p.1541·1); lidocaine hydrochloride (p.1862·3).
Formerly contained prednisolone, hexachlorophene, cinchocaine hydrochloride, and belladonna.
Haemorrhoids.

Hemosin-K *Hormona, Mex.*
Carbazochrome sodium sulfonate (p.1058·2); vitamin K (p.1995·2).
Haemorrhage.

Hemosol *Gambro, Cz.; Teva, Israel†; Gambro, Neth.; Gambro, Port.; Hospal, Spain; Gambro, Swed.*
Calcium chloride; magnesium chloride; lactic acid; sodium bicarbonate; sodium chloride (p.1670·3).
Haemodialysis; haemofiltration.

Hemosol Bicar *Gambro, Denm.*
Calcium chloride; magnesium chloride; sodium chloride; sodium bicarbonate; sodium lactate (p.1670·3).
Haemodialysis; haemofiltration.

Hemostan *Biomedis, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Hemotene *Astra, USA†.*
Absorbable collagen (p.2286·1).
Haemostatic.

Hemototal *Grunenthal, Port.*
Ferrous gluconate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Hemotrex *Foramen, Philipp.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage; hereditary angioedema.

Hemovas *Robert, Spain.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Hemovasal *Manetti Roberts, Ital.*
Suleparoid (p.1406·3).
Soft-tissue disorders; superficial vascular disorders; thrombosis prophylaxis.

Hemovit *Dayton, USA.*
Vitamin B substances; vitamin C (p.1922·1).

Hem-Prep *G & W, USA.*
Shark-liver oil (p.2386·1); phenylmercuric nitrate (p.1657·3); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); benzocaine (p.1854·1).
Anorectal disorders.

Hemril *Upsher-Smith, USA.*
Bismuth subgallate (p.1711·1); bismuth resorcinol compound (p.1712·1); benzyl benzoate (p.2036·1); peru balsam (p.2365·3); zinc oxide (p.1621·2).

Hemril-HC *Upsher-Smith, USA.*
⊗ Hydrocortisone acetate (p.1535·2).

Hemsi *Serum Institute, India.*
Ferrous fumarate (p.1938·3); lysine hydrochloride; vitamins; minerals (p.1922·1).
Iron-deficiency anaemia.

Hemsyl *Indoco, India.*
Etamsylate (p.1064·3).
Haemorrhage; menorrhagia.

Henafurine *Delattre-Hemapurine, Belg.*
Bisacodyl (p.1710·1).
Constipation.

Henetix *Guerbet, Braz.†.*
Iobitridol (p.1481·2).
Contrast media for angiography.

Henexal *Pisa, Mex.*
⊗ Furosemide (p.1292·1).

Henovic *Vargas, Venez.*
Ascorbic acid; vitamin A; ergocalciferol (p.1922·1).

Hep Lok *IFET (ΙΦΕΤ), Gr.†.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Hepa *Kolassa, Austria.*
Ornithine aspartate (p.1959·2).
Hyperammonaemia associated with liver disorders.

Hepa Factor *Sigma-Tau, Spain.*
Folic acid (p.1940·1); cobamamide (p.1980·2).
Folic acid deficiency; liver disorders.

Hepabene *Ratiopharm, Austria; Merckle, Cz.†; Ratiopharm, Hung.; Merckle, Rus.*
Fumitory (p.2307·2); milk thistle (p.1452·1).
Biliary-tract and liver disorders.

HepaBesch *Strathmann, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Hepabig *Green Cross, Malaysia; Green Cross, Philipp.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepabil *Sanitas, Chile.*
Bile extract (p.2266·2); choline dihydrogen citrate (p.1934·2); inositol (p.2325·2); boldo (p.2267·2); vitamin K (p.1995·2); pancreatin (p.2360·1).
Digestive disorders.

Hepabion *Merck, Indon.*
Essential phospholipids; choline; soya oil (p.1965·3); mono and diglycerides; medium-chain triglycerides (p.1922·1).
Dietary supplement to support liver function.

Hepabionta *Merck, S.Afr.*
Vitamin B substances (p.1922·1); orotic acid (p.2358·3); folic acid (p.1940·1).
Liver disorders.

Hepabuzone *Spirig, Switz.*
Heparin sodium (p.1301·2); phenylbutazone (p.117·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; peripheral vascular disease; thrombophlebitis.

Hepacaf *CAF-DCF, Belg.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepacalmina *Prisfar, Port.*
Bioflavonoids (p.2304·1).
Liver disorders.

Hepacap *Medicap, Thai.*
Essential phospholipids and multivitamins (p.1922·1).
Liver disorders.

Hepacare *Jean-Marie, Hong Kong.*
A heparinoid (p.1305·2).
Haematomas; hard scars; thrombophlebitis; varicose veins.

Hepaccine-B *Biovac, S.Afr.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Hepacell *Medikon, Indon.*
Schisandra (p.2384·2); javanese turmeric (p.2406·3); vitamin B substances; vitamin E (p.1922·1).
Liver disorders.

Hepachol *Landson, Indon.*
Lecithin (p.2332·2); vitamin B substances; vitamin E; selenium; zinc (p.1922·1).
Dietary supplement.

Hepacholine *Sanofi-Aventis, Fr.†.*
Choline citrate (p.1934·2); sorbitol (p.1965·1).
Constipation; dyspepsia.

Hepacitron *Ibefar, Braz.†.*
Adenosine (p.1202·1); betaine (p.2265·2); methionine (p.1450·1); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2).
Liver disorders.

Hepaclem *Clement Thionville, Fr.*
Cynara (p.2291·2); boldo (p.2267·2); kinkeliba (p.2329·2); Javanese turmeric (p.2406·3).
Digestive-system disorders; renal disorders.

Hepacom *Sanofi-Aventis, Pol.*
Timonacic (p.2402·2).
Liver disorders.

Hepacomplet B12 Triple *Reig Jofre, Spain†.*
Vitamin B substances (p.1922·1); liver (p.2337·3); amino acids.
Anaemias; tonic.

Hepacur *Medical, Arg.*
Boldo (p.2267·2); carqueja; cynara (p.2291·2); hyoscyamus (p.2323·3); belladonna (p.2263·3).
Gastrointestinal disorders.

Hepacynar *Europlant Phytofarm, Pol.*
Cynara (p.2291·2).
Dyspepsia; hyperlipidaemias.

Hepa-Desicol *Elmor, Venez.*
Pig bile (Desicol) (p.2266·2).
Digestive disorders.

Hepadial *Biocodex, Fr.*
Dimecrotic acid, magnesium salt (p.2294·1).
Dyspepsia.

Hepadif
Note. This name is used for preparations of different composition.
Reig Jofre, Spain.
Oral solution: Carnitine orotate (p.2358·3); carnitine (p.1932·2); vitamin B substances (p.1922·1); liver extract (p.2337·3).
Acetonaemia; hepatitis.
Reig Jofre, Spain.
Tablets: Carnitine orotate (p.2358·3); vitamin B substances (p.1922·1); liver extract (p.2337·3); adenine hydrochloride (p.2247·2).
Acetonaemia; hepatitis.

Hepadigenor *Baliarda, Arg.†.*
Silymarin (p.1452·2); dehydrocholic acid (p.2292·2); pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders; liver disorders.

Hepadoddi *Merck, Port.*
Dimecrotic acid, magnesium salt (p.2294·1).
Biliary-tract disorders.

Hepaduran V *OTW, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Hepa-Factor *Max Farma, Ital.*
Folinic acid (p.1943·3); hydroxocobalamin (p.1980·3).
Hyperchromic anaemia; liver disorders.

Hepaflex *Baxter, Fin.*
Heparin sodium (p.1301·2).
Thrombosis prophylaxis.

Hepafol *Meyer, Venez.*
Iron citrate; vitamin B (p.1980·2).
Anaemias.

Hepafol con B-12 *Meyer, Venez.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1); copper sulfate (p.1935·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Hepafol-F *Farcoral, Mex.*
Multivitamin and mineral preparation with garlic and royal jelly (p.1922·1).

Hepagallin N *Pfluger, Ger.*
Cynara (p.2291·2).
Dyspepsia.

HepaGam B *Apotex, USA.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepa-Gastreu R7 *Reckeweg, Neth.*
Homoeopathic preparation.

Hepa-Gastreu S R7 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Hepa-Gel *Lichtenstein, Cz.†; Winthrop, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

HepaGel *Spirig, Switz.*
Heparin sodium (p.1301·2).
Peripheral vascular disease; soft-tissue disorders.

Hepagrisevit Forte-N
Note. This name is used for preparations of different composition.
Pharmacia, Ger.†.
Injection: Cyanocobalamin (p.1980·2); folic acid (p.1940·1); nicotinamide (p.1957·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Liver disorders.
Pharmacia, Ger.†.
Tablets: Cyanocobalamin (p.1980·2); folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2).
Liver disorders.

Hepagrume *EG, Fr.*
Arginine (p.1928·2); betaine (p.2265·2); choline dihydrogen citrate (p.1934·2); inositol (p.2325·2); sorbitol (p.1965·1).
Constipation; dyspepsia.

Hepakur *Mediquest, Singapore.*
Phosphatidyl choline (p.2367·1) with other phospholipids.
Hyperlipidaemias; liver disorders.

Hepalac *Berlin Pharm, Thai.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Hepalean *Organon, Canad.*
Heparin sodium (p.1301·2).
Thromboembolic disorders; thrombosis prophylaxis.

Hepalean-Lok *Organon, Canad.*
Heparin sodium (p.1301·2).
To maintain patency of intravenous injection devices.

Hepalin *Bergamo, Braz.*
Methionine (p.1450·1); betaine (p.2265·2); choline citrate (p.1934·2); sorbitol (p.1965·1).
Liver disorders.

Hepalite *Eulite, Neth.*
Homoeopathic preparation.

Hepa-Loges
Note. This name is used for preparations of different composition.
Loges, Ger.
Capsules: Milk thistle (p.1452·1).
Liver disorders.
Loges, Ger.
Injection: Homoeopathic preparation.
Formerly known as Hepa-L 90 N.

Hepamax *Dankos, Indon.*
PPC; silymarin phytosome (p.1452·2); schisandra (p.2384·2); *d*-alpha tocopherol (p.1992·2).
Liver disorders.

Hepa-Merz
Note. This name is used for preparations of different composition.
Grunenthal, Chile†; Merz, Cz.†; Merz, Hong Kong; Merz, Hung.; Combiphar, Indon.; Merz, Indon.; Merz, Mex.; Merz, Philipp.
Ornithine aspartate (p.1959·2).
Hepatic encephalopathy; hyperammonaemia; liver disorders.
Merz, Pol.
Ornithine aspartate (p.1959·2); pancreatin (p.2360·1).
Digestive disorders.
Merz, Ger.; Win-Medicare, India.
Injection; oral granules: Ornithine aspartate (p.1959·2).
Hyperammonaemia in hepatic encephalopathy; liver disorders.
Win-Medicare, India.
Syrup: Ornithine aspartate (p.1959·2); nicotinamide (p.1957·3); vitamin B (p.1977·2).
Liver disorders.
Win-Medicare, India.
Tablets: Ornithine aspartate (p.1959·2); pancreatin (p.2360·1).
Liver disorders.

Hepa-Merz KT *Merz, Ger.*
Ornithine aspartate (p.1959·2).
Liver disorders.

Hepa-Merz Lact *Merz, Ger.†.*
Lactulose (p.1738·2).
Constipation; liver disorders; salmonella enteritis.

Hepa-Merz Sil *Merz, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Hepanephrol *Zambon, Fr.; Knoll, Port.†.*
Cynara (p.2291·2).
Dyspepsia; fluid retention.

Hepanutrin *JP, Braz.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Hepaplus *Hexal, Ger.†.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Hepa-Q *Pyridam, Indon.*
Schisandra (p.2384·2); milk thistle (p.1452·1); Javanese turmeric (p.2406·3).
Dietary supplement.

Hepaquifa *Angelini, Port.*
Dimecrotic acid (p.2294·1).
Biliary-tract disorders.

Hepar 10% *Baxter, Ger.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in liver disorders.

Hepar HM *Pfluger, Ger.†.*
Homoeopathic preparation.

Hepar 202 N *Staufen, Ger.†.*
Homoeopathic preparation.

Hepar SL *Lichtwer, Ger.*
Cynara (p.2291·2).
Dyspepsia.

Heparanox *Pfluger, Ger.*
Homoeopathic preparation.

Heparegen *Jelfa, Pol.; Drossapharm, Switz.†.*
Timonacic (p.2402·2).
Liver disorders.

Heparfelien *Streuli, Switz.*
Boldo (p.2267·2); buchu (p.2269·3); cynara (p.2291·2); taraxacum (p.2395·1); juniper (p.2328·2).
Digestive disorders.

Hepargitol *Elerte, Fr.*
Arginine hydrochloride (p.1928·2); sorbitol (p.1965·1); anhydrous sodium sulfate (p.1771·3); sodium phosphate (p.1682·3); citric acid (p.2284·1).
Constipation; dyspepsia.

Hepar-Hevert *Hevert, Ger.*
Homoeopathic preparation.

Heparibene *Ratiopharm, Hung.*
Heparin calcium (p.1301·2) or heparin sodium (p.1301·2).
Thromboembolic disorders.

Heparin Comp *Sanidom, Austria; CT, Ger.†.*
Heparin sodium (p.1301·2); arnica (p.2260·2); aesculus (p.2248·2).
Soft-tissue injury; superficial vascular disorders.

Heparin Kombi-Gel *Ratiopharm, Ger.†.*
Heparin sodium (p.1301·2); arnica (p.2260·2); aesculus (p.2248·2).
Soft-tissue injury; superficial vascular disorders.

Heparin Ointment *Akrikhin, Rus.; Nizpharm, Rus.*
Heparin sodium (p.1301·2); benzocaine (p.1854·1); benzyl nicotinate (p.28·1).
Superficial vascular disorders.

Heparin Plus *Heumann, Ger.†.*
Heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Soft-tissue injury.

Heparin-Gel *Funcke, Cz.†.*
Heparin sodium (p.1301·2); arnica (p.2260·2); aesculus (p.2248·2).
Soft-tissue injury; thrombophlebitis.

Heparinol *Streuli, Switz.*
Heparin sodium (p.1301·2); thymol.
Haematomas; thrombophlebitis; varices.

Heparizen Ziaja, Pol.
Heparin sodium (p.1301·2).
Keloids; scars; soft-tissue injury; superficial vascular disorders.

Heparmin Tentan, Switz.†.
Homoeopathic preparation.

Heparoid Zentiva, Cz.; Leciva, Rus.
A heparinoid (p.1305·2).
Soft-tissue injury; superficial vascular disorders.

Heparon Nutricia, Ital.
Preparation for enteral nutrition in liver disorders (p.1922·1).

Hepar-Pasc Pascoe, Ger.
Milk thistle (p.1452·1).
Liver disorders.

Hepar-POS Croma, Austria; Ursapharm, Ger.
Cynara (p.2291·2).
Digestive disorders; dyspepsia; lipid metabolism disorders.

Heparstad Stada, Ger.†.
Cynara (p.2291·2).
Biliary-tract disorders.

Heparsyx N Syxyl, Ger.†.
Milk thistle (p.1452·1).
Liver disorders.

Heparviton Bode, Indon.; Tempo Scan Pacific, Indon.
Essential phospholipids; curcuminoid (p.1473·2); silymarin (p.1452·2).
Gallstones; liver disorders.

Heparviton NF Tempo Scan Pacific, Indon.
Essential phospholipids; curcuminoid (p.1473·2); oleum xanthorrhizae (p.1473·2); vitamin E; selenium; zinc (p.1922·1).
Supplement to maintain healthy liver function.

Hepa-S Vifor, Switz.
Cynara (p.2291·2).
Digestive disorders.

Hepa-Salbe Lichtenstein, Cz.†; Winthrop, Ger.
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Hepaselamin Biosel, Turk.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Hepasil
Note. This name is used for preparations of different composition.
Kalbe, Indon.
Silymarin (p.1452·2); oleum xanthorrhizae (p.1473·2); turmeric (p.1473·2); echinacea (p.2298·1).
Liver disorders.

Lapreven, Venez.
Lecithin; inositol; choline; silymarin; vitamin B substances; calcium carbonate; magnesium oxide (p.1922·1).
Dietary supplement.

Hepasil DTX Usana, Singapore.
Milk thistle; green tea; turmeric; broccoli; cysteine hydrochloride; olive oil; soya lecithin (p.1922·1).
Dietary supplement.

Hepasol Pfizer, Austral.
Vitamin and mineral preparation with liver extract (p.1922·1).
Tonic.

Hepasol A Hemofarm, Rus.
Amino-acid, sorbitol, malic acid, electrolyte, and vitamin infusion (p.1922·1).
Parenteral nutrition in liver disorders.

Hepasol Lipogel Ecosol, Switz.
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial thrombosis.

HepaSpray Spirig, Switz.†.
Heparin sodium (p.1301·2).
Cicatrisation; soft-tissue injury; venous insufficiency.

Hepasules Biological E, India.
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); folic acid (p.1940·1); docusate sodium (p.1725·1); vitamin C (p.1983·3).
Anaemia.

Hepasulfol Franco-Indian, India.
Anethole trithione (p.2258·1).
Liver and biliary disorders.

Hepasulfol-AA Franco-Indian, India.
Anethole trithione (p.2258·1); chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Hepatalgina
Note. This name is used for preparations of different composition.
Altana, Arg.
Oral drops: Cynara (p.2291·2); boldo (p.2267·2); wild carrot (p.2415·2); menthol (p.2340·1).
Dyspepsia.

Altana, Arg.
Tablets: Cynara (p.2291·2); boldine (p.2267·3); wild carrot (p.2415·2); menthol (p.2340·1); dehydrocholic acid (p.2292·2); deoxycholic acid (p.2266·3).
Dyspepsia.

Hepatamine
Scientific Hospital Supplies, Austral.; Nutricia, Ital.; SHS, Singapore†.
Amino-acid preparation (p.1922·1).
Nutritional supplement in liver disorders.

Braun, Hong Kong†; McGaw, USA.
Amino-acid infusion (p.1922·1).
Parenteral nutrition in hepatic encephalopathy.

HepatAmine Eczacibasi-Baxter, Turk.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Hepatect Biotest, Austria; Biotest, Cz.†; Biotest, Ger.; Biotest, Hong Kong†; Biotest, Hung.; Intra Pharma, Irl.; Biotest, Israel; Biotest, Neth.; Biotest, Pol.; Biotest, Port.; Biotest, Switz.; Kansuk, Turk.
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepathromb Riemser, Ger.
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Hepathrombin Teofarma, Ger.
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Hepathrombine Lyron, Switz.†.
Heparin sodium (p.1301·2); allantoin (p.1588·1); dexpanthenol (p.2362·1).
Scars; soft-tissue injury; venous insufficiency.

Hepatic-Aid II McGaw, USA.
Preparation for enteral nutrition (p.1922·1).
Liver disease.

Hepatical Nutricia, Ital.
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement in liver disorders.

Hepaticum novo Pascoe, Ger.†.
Javanese turmeric (p.2406·3); peppermint leaf (p.1761·2); absinthium (p.2244·1).
Biliary disorders.

Hepaticum-Lac-Medice Medice, Ger.†.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Hepaticum-Medice H Medice, Ger.†.
Cinchona bark (p.2282·3); milk thistle (p.1452·1); greater celandine (p.2317·1); gentian (p.2310·3); turmeric (p.1473·2).
Adjunct in skin disorders; constipation; liver and biliary disorders.

Hepatil Pliva Krakow, Pol.
Ornithine aspartate (p.1959·2).
Liver disorders.

Hepatin Lapi, Indon.
Curcuminoid (p.1473·2); silymarin (p.1452·2); echinacea (p.2298·1); choline bitartrate (p.1934·2); vitamin B (p.1922·1).
Liver disorders.

Hepatitis B Ig-P Farma-Tek, Turk.
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepativax Sanofi Pasteur, Arg.
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

Hepato Diet Support, Braz.†.
Preparation for enteral nutrition (p.1922·1).
Liver disorders.

Hepato Fardi Fardi, Spain†.
Choline orotate (p.2358·3); almond milk.
Liver disorders.

Hepatobe Sinterapico, Braz.†.
Adenosine (p.1202·1); betaine (p.2265·2); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2); sorbitol (p.1965·1).
Digestive disorders.

Hepatodirectol Sanitas, Arg.
Homatropine methylbromide (p.1881·3); papaverine hydrochloride (p.2191·3); boldo (p.2267·2); carqueja; cynara (p.2291·2); crataegus (p.2289·1); bitter orange peel (p.2357·1); belladonna (p.2263·3).
Gastrointestinal spasm; liver and biliary-tract disorders.

Hepatodoron Weleda, Austria; Weleda, Ger.; Weleda, S.Afr.
Fragaria vesca; vitis vinifera (p.2316·3).
Constipation; eczema; liver disorders.

Hepatodrainol Boiron, Neth.
Homoeopathic preparation.

Hepatofalk Falk, Hong Kong.
Choline orotate (p.2358·3); cysteine hydrochloride (p.1936·3); vitamin B substances (p.1922·1); folic acid (p.1940·1); ox bile (p.2266·3); greater celandine (p.2317·1); Javanese turmeric (p.2406·3); cynara (p.2291·2); taraxacum (p.2395·1); frangula (p.1732·2); rhubarb (p.1768·3).
Liver disorders.

Hepatofalk Planta
Note. This name is used for preparations of different composition.
Falk, Hong Kong.
Silymarin (p.1452·2); turmeric (p.1473·2); greater celandine (p.2317·1).
Liver disorders.

Darya-Varia, Indon.; Falk, Indon.
Silymarin (p.1452·2); chelidonine; javanese turmeric (p.2406·3).
Colic; dyspepsia; liver disorders.

Falk, Singapore.
Milk thistle (p.1452·1); Javanese turmeric (p.2406·3); greater celandine (p.2317·1).
Colic; dyspepsia; liver disorders.

Hepatogenol Profarb, Braz.†.
Inositol (p.2325·2); acetylmethionine (p.1450·2); vitamin B (p.1922·1).
Liver disorders.

Hepatoglobine
Note. This name is used for preparations of different composition.
Raptakos, India.
Capsules: Vitamin B (p.1980·2); peptone; ferrous fumarate (p.1938·3); copper sulfate (p.1935·3); folic acid (p.1940·1).
Anaemias.

Raptakos, India.
Oral drops: Vitamin B (p.1980·2); peptone; ferric ammonium citrate (p.1938·1); folic acid (p.1940·1).
Anaemias.

Raptakos, India.
Oral liquid: Liver extract (proteolysed) (p.2337·3); peptone; ferric ammonium citrate (p.1938·1); folic acid (p.1940·1).
Anaemias.

Hepatoregius Dovalle, Braz.†.
Pepsin (p.2365·1); pancreatin (p.2360·1); boldo (p.2267·2); cynara (p.2291·2).
Digestive-system disorders.

Hepatorell H Leber-Spezifikum Sanorell, Ger.
Homoeopathic preparation.

Hepatos
Note. This name is used for preparations of different composition.
Hevert, Ger.
Milk thistle (p.1452·1).
Liver disorders.

Teofarma, Ital.
Cascara (p.1715·2); boldo (p.2267·2).
Constipation.

Hepatos B12 Teofarma, Ital.
Cascara (p.1715·2); boldo (p.2267·2); inositol (p.2325·2); cyanocobalamin (p.1980·2).
Constipation.

Hepatosol Kalbe, Indon.; Sanghiang, Indon.
Preparation for enteral nutrition (p.1922·1).
Hepatic insufficiency.

Hepatotal Family Excelentia, Arg.†.
Boldo (p.2267·2); chamomile (p.2279·3).
Digestive disorders.

Hepatotris Medic, Braz.†.
Methionine (p.1450·1); vitamin B (p.1980·2); choline (p.1934·2).
Liver disorders.

Hepatoum Hepatoum, Fr.
Pulsatilla (p.2376·3); turmeric (p.1473·2); peppermint oil (p.1761·2); alverine citrate (p.1708·1).
Formerly contained pulsatilla, turmeric, and peppermint oil.
Gastrointestinal disorders.

Hepatox Cifarma, Braz.
Adenosine (p.1202·1); -methionine (p.1450·2); betaine (p.2265·2); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2); sorbitol (p.1965·1).
Liver disorders.

Hepatrombin Hemofarm, Rus.
Allantoin (p.1588·1); dexpanthenol (p.2362·1); heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Hepatrombin H Hemofarm, Rus.
⊗ Heparin sodium (p.1301·2); prednisolone (p.1540·3); lauromacrogol 400 (p.1916·1).
Anorectal disorders.

Hepatron C Schering-Plough, Mex.
Capsules, ribavirin (p.902·3); injection, interferon alfa-2b (p.885·1).
Chronic hepatitis C.

Hepatyrix GSK, Austria; GSK, Ger.; GSK, Irl.; GSK, Israel; GSK, NZ; GSK, UK.
A hepatitis A and typhoid vaccine (HM175 and Ty2 strains respectively) (p.2217·2).
Active immunisation.

Hepavax Berna, Indon.
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Hepavax-Gene Biosano, Chile; Berna, Malaysia; Green Cross, Philipp.; Berna, Pol.; Berna, Thai.; Kocsel, Turk.
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Hepa-Vibolex Rosen, Ger.
Ornithine aspartate (p.1959·2).
Hepatic encephalopathy.

Hepavit
Note. This name is used for preparations of different composition.
Fresenius Kabi, Austria.
Hydroxocobalamin acetate (p.1980·3).
Anaemias; liver disorders; neurologic disorders.

Littman, Philipp.
Silymarin (p.1452·2).
Nutritional supplement for liver function.

General Drugs, Thai.
Liver extract (p.2337·3).
Anaemias.

Hepavite
Note. This name is used for preparations of different composition.
YSP, Malaysia; Yung Shin, Singapore.
Silymarin (p.1452·2); vitamin B substances (p.1975·1).
Formerly known as Luckyhepa in *Malaysia*.
Liver disorders; vitamin B supplement.

Adcock Ingram, S.Afr.
Choline bitartrate (p.1934·2); inositol (p.2325·2); methionine (p.1450·1); vitamin B substances; bioflavonoids; magnesium sulfate; zinc sulfate; potassium chloride (p.1922·1).
Liver disorders; vitamin deficiency.

Hepavitose Climax, Braz.†.
Ferric ammonium citrate (p.1938·1); vitamin B substances; manganese hypophosphite; copper chloride (p.1922·1); liver extract; gastric mucosa extract.
Iron deficiency; iron-deficiency anaemias.

Hepax Tradiphar, Fr.
Cynara (p.2291·2); kinkeliba (p.2329·2); boldo (p.2267·2); rosemary (p.2381·2).
Digestive disorders.

HepBQuin Sanquin, Neth.
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepdine Pharmasant, Thai.
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; hypersensitivity reactions; urticaria.

Hepedren Parggon, Mex.
Magnesium sulfate (p.1679·3); cynara (p.2291·2); boldo (p.2267·2).
Biliary-tract disorders.

Hepeel Heel, Cz.
Homoeopathic preparation.

Hepeel H Heel, Neth.
Homoeopathic preparation.

Hepflush American Pharmaceutical, USA.
Heparin sodium (p.1301·2).
To maintain patency of indwelling intravenous catheters.

Hep-Forte Marlyn, USA.
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Hepimun Landson, Indon.
Phyllanthus niruri; javanese turmeric (p.2406·3).
Immunostimulant; liver disorders; tonic.

Hepirax CCM, Malaysia.
Aciclovir (p.862·3).
Herpesvirus infections.

Heplant Spitzner, Ger.
Milk thistle (p.1452·1).
Liver disorders.

Hepliv Bharat, Philipp.
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Hep-Lock Elkins-Sinn, USA.
Heparin sodium (p.1301·2).
To maintain patency of in-dwelling intravenous lines.

Heplok Leo, Irl.†.
Heparin sodium (p.1301·2).
To maintain patency of in-dwelling intravenous lines.

Hepofer Cipla, India.
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Hepon Immapharma, Rus.
Synthetic peptide composed of 14 amino-acid residues.
Immunodeficiency; infections.

Hepothesan Bock, Ger.†.
Homoeopathic preparation.

Heprecomb Berna, Switz.
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

Hep-Rinse Leo, Irl.†.
Heparin sodium (p.1301·2).
To maintain patency of intravenous lines.

Hepro Casen Fleet, Spain.
⊗ Allantoin (p.1588·1); aminoacridine hydrochloride (p.1625·1); hydrocortisone hydrogen succinate (p.1535·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Hepsal IFET (ΙΦΕΤ), Gr.; Technopharm, Irl.; CP Pharmaceuticals, UK.
Heparin sodium (p.1301·2).
Anticoagulant; thromboembolic disorders; to maintain patency of in-dwelling intravenous lines.

Hepsera GSK, Arg.; Gilead, Austral.; UCB, Belg.; GSK, Chile; Gilead, Cz.; Gilead, Denm.; Orphan, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; GSK, Hong Kong; Gilead, Hung.; GSK, Indon.; Gilead, Irl.; GSK, Israel; Gilead, Ital.; GSK, Malaysia; GSK, Mex.; Muir Hutchinson, NZ; Gilead, Neth.; Gilead, Norw.; GSK, Philipp.; Gilead, Pol.; Gilead, Port.; GSK, Singapore; Gilead, Spain; Swedish Orphan, Swed.; Chemedica, Switz.; GSK, Thai.; Er-Kim, Turk.; Gilead, UK; Gilead, USA; GSK, Venez.
Adefovir dipivoxil (p.865·1).
Chronic hepatitis B.

Heptadon Ebewe, Austria.
⊗ Methadone hydrochloride (p.82·3).
Pain.

Hept-A-Myl Sanofi-Aventis, Fr.
⊗ Heptaminol hydrochloride (p.2319·1).
Hypotension.

Hept-a-myl Corsa, Indon.; Sanofi Synthelabo, Indon.
⊗ Heptaminol hydrochloride (p.2319·1).
Fatigue; hypotension; resuscitation in neonates.

Heptan Aguettant, Fr.†.
Minerals and trace element preparation (p.1922·1).
Parenteral nutrition.

Heptar Eurofarma, Braz.
Heparin sodium (p.1301·2).

Heptasan Sanbe, Indon.
Cyproheptadine hydrochloride (p.575·1).
Pruritus; rhinitis; urticaria.

Hep-Tec Tecnofarma, Mex.
Heparin (p.1301·2).

Heptodine GSK, Arg.; GSK, Venez.†.
Lamivudine (p.895·1).
Chronic hepatitis B.

Heptor Veropharm, Rus.
Ademetionine (p.2247·1).
Liver disorders.

Heptovir GSK, Canad.
Lamivudine (p.895·1).
Hepatitis B.

Heptral Hospira, Rus.
Ademetionine butanedisulfonate (p.2247·1).
Alcohol withdrawal syndrome; cirrhosis; depression; hepatic cholestasis; hepatic encephalopathy.

Hepuman *Berna, Hong Kong†; Berna, Spain; Berna, Switz.†; Berna, Turk.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Hepuman B *Berna, Ital.†.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Her Soy Plus *Taiwan Biotech, Philipp.*
Calcium lactate (p.1676·1); soya bean (p.1965·3); colecalciferol (p.1986·2).
Menopausal symptoms; osteoporosis.

Heracillin
AstraZeneca, Denm.
Flucloxacillin sodium (p.277·1).
Staphylococcal infections.

AstraZeneca, Swed.
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Bacterial infections.

Heraclene *Natrapharm, Philipp.*
Cobamamide (p.1980·2).
Appetite stimulant; tonic.

Herax *Novell, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herb and Honey Cough Elixir *Weleda, UK.*
Honey (p.1948·2); althaea (p.2253·3); Iceland moss (p.2324·1); marrubium (p.1564·1); aniseed (p.2258·2); sambucus (p.2383·1); thyme (p.2401·1).
Coughs.

Herbabiloba *Herbapol Poznan, Pol.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Herbaccion Antioxidante *ISA, Arg.*
Vitamin C; bearberry; betacarotene; vitamin E; selenium; zinc (p.1922·1).

Herbaccion Bioenergizante *ISA, Arg.*
Ginseng (p.2312·1).
Tonic.

Herbaccion Celfin *ISA, Arg.*
Centella (p.1592·3); bladderwrack (p.2384·2); ginkgo biloba (p.2311·1); vitamin B .
Dietary supplement.

Herbaccion Cerebral *ISA, Arg.†.*
Ginkgo biloba (p.2311·1).

Herbaccion Circumax *ISA, Arg.†.*
Selenium; garlic (p.1922·1).
Dietary supplement.

Herbaccion Desinflamante *ISA, Arg.†.*
Arnica (p.2260·2).

Herbaccion Diet *ISA, Arg.*
Chromium (p.1934·3); carnitine (p.1932·2); bladderwrack (p.2384·2).
Obesity.

Herbaccion Dig Fresh *ISA, Arg.†.*
Boldo (p.2267·2); cynara (p.2291·2); carqueja.
Liver and biliary-tract disorders.

Herbaccion Digestivo *ISA, Arg.†.*
Cynara (p.2291·2); boldo (p.2267·2); carqueja.

Herbaccion Flex *ISA, Arg.†.*
Devil's claw root (p.39·1).
Joint disorders.

Herbaccion Ginseng Y Magnesio *ISA, Arg.*
Magnesium; ginseng (p.2312·1).
Tonic.

Herbaccion Laxante *ISA, Arg.†.*
Ispaghula (p.1737·1).
Constipation.

Herbaccion Lecitina *ISA, Arg.*
Lecithin (p.2332·2).
Nutritional supplement.

Herbaccion Memory *ISA, Arg.*
Ginkgo biloba (p.2311·1); vitamin B ; vitamin B ; soya lecithin (p.2332·2).

Herbaccion Menopausia *ISA, Arg.†.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Herbaccion Motivante *ISA, Arg.†.*
St John's wort (p.422·3).
Depression.

Herbaccion Nutriderm *ISA, Arg.†.*
Vitamin A (p.1971·2); aloe vera (p.1588·2).
Skin disorders.

Herbaccion Prostatico *ISA, Arg.†.*
Saw palmetto (p.2192·3).
Prostate disorders.

Herbaccion Sedante *ISA, Arg.†.*
Tilia (p.2402·2); passion flower (p.2363·2); valerian (p.2410·1).
Anxiety; sedative.

Herbaccion Venotonico *ISA, Arg.*
Aesculus (p.2248·2).
Vascular disorders.

Herbadent *Aura, Cz.*
Herbarum extract; salicylic acid (p.1612·2); boric acid (p.2268·1); citric acid (p.2284·1); benzocaine (p.1854·1); peppermint oil (p.1761·2); clove oil (p.2285·1); fennel oil (p.2303·1).
Mouth inflammation; oral lesions.

Herbadon *Mavena, Ger.†.*
Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Herbal *Rider, Chile.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Herbal Anxiety Formula *Faulding, Austral.†.*
Passion flower (p.2363·2); chamomile (p.2279·3).
Anxiety; nervous tension.

Herbal Arthritis Formula *Faulding, Austral.†.*
Ginkgo biloba (p.2311·1); devil's claw root (p.39·1).
Arthritis; rheumatism.

Herbal Booster *Pharmadass, UK.*
Herbal preparation with vitamins (p.1922·1).
Tonic.

Herbal Capillary Care *Faulding, Austral.†.*
Ginkgo biloba (p.2311·1); aesculus (p.2248·2).
Nocturnal leg cramps; tinnitus; tired legs and feet.

Herbal Cleanse *Vitaplex, Austral.†.*
Aloes (p.1705·2); taraxacum (p.2395·1); ispaghula (p.1737·1); yellow dock (p.2416·3); sarsaparilla (p.2383·3); lappa (p.2330·3); clivers (p.2284·3); hydrastis (p.2321·3); slippery elm (p.2388·2); echinacea purpurea (p.2298·1); ginger (p.1732·3); milk thistle (p.1452·1).
Constipation; liver disorders.

Herbal Cold & Flu Relief *Faulding, Austral.†.*
Echinacea angustifolia (p.2298·1); liquorice (p.1740·3); garlic (p.2309·2).
Catarrh; cold and influenza symptoms.

Herbal Cold Relief *Jamieson, Canad.†.*
⊗ Ephedra (p.1558·1); eucalyptus oil (p.2301·2); grindelia (p.2317·2).

Herbal Digestive Formula *Faulding, Austral.†.*
Liquorice (p.1740·3); turmeric (p.1473·2); ginger (p.1732·3).
Dyspepsia; flatulence.

Herbal Diuretic
Note. This name is used for preparations of different composition.
Purity Life, Canad.; Swiss Herbal, Canad.
Buchu (p.2269·3); celery seed (p.2278·3); parsley (p.2363·2); bearberry (p.2263·3); juniper (p.2328·2).

Vita Health, Canad.
Batilol; bearberry (p.2263·3); buchu (p.2269·3); juniper (p.2328·2); parsley (p.2363·2).

Herbal Diuretic Formula *Faulding, Austral.†.*
Taraxacum (p.2395·1); bearberry (p.2263·3).
Fluid retention.

Herbal Essences Anti-Dandruff *Clairol, Canad.*
Salicylic acid (p.1612·2).
Dandruff.

Herbal Eye Care Formula *Faulding, Austral.†.*
Myrtillus (p.2349·3).
Eye disorders.

Herbal Headache Relief *Faulding, Austral.†.*
Feverfew (p.622·2).
Headache.

Herbal Indigestion Naturtabs *Cantassium Co., UK.*
Skullcap (p.2388·2); valerian (p.2410·1); fennel (p.2302·3); myrrh (p.2349·2); papain (p.2362·3); capsicum oleoresin (p.2276·2).

Herbal Laxative
Note. This name is used for preparations of different composition.
Blackhawk, Canad.
Aniseed (p.2258·2); cascara (p.1715·2); dioscorea villosa; fennel (p.2302·3); gentian (p.2310·3); jalap (p.1737·3); lappa (p.2330·3); liquorice (p.1740·3); senna (p.1769·2).

Li Chung Yun, Canad.
Cascara (p.1715·2); frangula (p.1732·2); liquorice (p.1740·3); rhubarb (p.1768·3); senna (p.1769·2).

Nutricorp, Canad.
Cascara (p.1715·2); senna (p.1769·2).

Quest, Canad.†.
Cascara (p.1715·2); rhubarb (p.1768·3).

Shaklee, Canad.
Senna (p.1769·2).
Constipation.

Swiss Herbal, Canad.
Senna leaves (p.1769·2); cascara (p.1715·2); rhubarb root (p.1768·3); gentian root (p.2310·3).
Constipation.

WN, Canad.
Cascara (p.1715·2); liquorice (p.1740·3); rhubarb (p.1768·3); senna (p.1769·2).

Herbal Laxative plus Yogurt *Trophic, Canad.*
Buchu (p.2269·3); cascara (p.1715·2); fennel (p.2302·3); gentian (p.2310·3); juniper (p.2328·2); leptandra virginica; liquorice (p.1740·3); senna (p.1769·2); yogurt.

Herbal Liver Formula *Faulding, Austral.†.*
Milk thistle (p.1452·1).
Digestive disorders; liver disorders.

Herbal Nerve
Note. This name is used for preparations of different composition.
Purity Life, Canad.
Lupulus (p.2335·2); skullcap (p.2388·2); valerian (p.2410·1).

Swiss Herbal, Canad.
Valerian root (p.2410·1); skullcap (p.2388·2).

Herbal Pain Relief *Cantassium Co., UK.*
Salix bark (p.121·3); passion flower (p.2363·2); valerian (p.2410·1).
Pain.

Herbal PMS Formula *Faulding, Austral.†.*
Myrtillus (p.2349·3); liquorice (p.1740·3); cimicifuga (p.2282·1).
Menstrual disorders.

Herbal Premens *Swisshealth, UK.*
Agnus castus (p.2249·1).
Premenstrual syndrome.

Herbal Sleep Formula *Faulding, Austral.†.*
Valerian (p.2410·1).
Insomnia.

Herbal Sleep Well *Swiss Herbal, Canad.†.*
Valerian root (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2); melissa (p.2339·3); tilia (p.2402·2).
Insomnia due to fatigue.

Herbal Stress Relief *Faulding, Austral.†.*
Ginseng (p.2312·1).
Stress.

Herbal Support for Active Lifestyles *Nutravite, Canad.†.*
Bee pollen; guarana; ginseng; royal jelly; ginseng (p.1922·1).

Herbal Support for Men Over 45 *Nutravite, Canad.†.*
Cayenne; chamomile; taraxacum; kelp; pygeum; saw palmetto berries skullcap; tribulus terrestris; yellow dock (p.1922·1).

Herbal Support for Stressful Lifestyles *Nutravite, Canad.†.*
Ginger root; lupulus; kava; passion flower; hypericum; skullcap; valerian root; wood betony (p.1922·1).

Herbal Support for Women Over 45 *Nutravite, Canad.†.*
Black cohosh; dong quai; passion flower; red clover; raspberry leaves; squaw vine; wild yam; agnus castus (p.1922·1).

Herbal Throat *Jamieson, Canad.†.*
Camphor (p.2273·2); elm bark (p.2388·2); marrubium (p.1564·1); menthol (p.2340·1); parsley (p.2363·2); thyme (p.2401·1).

Herbalacta *Phyto Kemo, Indon.*
Vitex trifolia; agnus castus (p.2249·1).
Aid in lactation.

Herbalax *Sante Naturelle, Canad.†.*
Cascara (p.1715·2); frangula (p.1732·2); rhubarb (p.1768·3); senna (p.1769·2); bile salts (p.2266·2).

HerbAllerg *Herbamed, Switz.*
Homoeopathic preparation.

Herbaneurin *Mavena, Ger.†.*
St John's wort (p.422·3).
Depression.

Herbapect *Aflofarm, Pol.*
Primula root (p.2372·2); sulfogaiacol (p.1573·2); thyme (p.2401·1).
Respiratory-tract disorders.

Herbapharm Rical *Mavena, Switz.†.*
Castor oil (p.2278·1).
Constipation.

Herbaton *Herbapol Poznan, Pol.*
Birch leaf (p.2266·3); crataegus (p.2289·1); fucus vesiculosus (p.2384·2); urtica (p.2409·3); condurango bark (p.2287·1); bitter orange (p.2357·1).
Digestive disorders; obesity.

Herba-Vision Augenbad *OmniVision, Ger.*
Chamomile (p.2279·3); euphrasia (p.2301·3).
Tired eyes.

Herbe *Recordati, Ital.†.*
Benzalkonium chloride (p.1629·1); hamamelis (p.2318·2).
Eye disinfection.

Herbelax *Sanochemia, Austria.*
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1); bran (p.1712·3); fig (p.1731·3).
Bowel evacuation; constipation; stool softener.

Herbelix *Lane, UK.*
⊗ Lobelia (p.2157·2); tolu solution; sodium bicarbonate (p.1673·2).
Nasal congestion.

Herbesan
Note. This name is used for preparations of different composition.
Omega, Fr.
Senna (p.1769·2); aniseed (p.2258·2); peppermint leaf (p.1761·2); couch-grass (p.2288·2).
Constipation.

Nycomed, Neth.
Tritici rhiz; cynodon dactylon rhizome; frangula bark; peppermint; caraway; fennel; melissa; hyssop; aniseed; greater celandine; meadowsweet; mallow flower; calendula; senna; coriander.
Constipation.

Herbesan Instantane *Pfizer Sante, Fr.†.*
Sennosides B (p.1769·3).
Constipation.

Herbesser *Tanabe, Hong Kong; Tanabe, Indon.; Tanabe, Jpn; Tanabe, Malaysia; Delta, Port.; Solvay, Singapore; Tanabe, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; blood pressure control during surgery; hypertension.

Herb-Fibe *Shaklee, Canad.*
Fibre.
Constipation.

Herbheal Ointment *Potter's, UK.*
Colophony (p.2286·2); starch (p.1968·1); sublimed sulfur (p.1614·1); zinc oxide (p.1621·2); althaea root (p.2253·3); stellaria media.
Skin irritation.

Herbion Drops for the Gallbladder *KRKA, Rus.*
Peppermint (p.1761·2); agrimony (p.2249·2); chamomile (p.2279·3); caraway (p.2276·3); cynara (p.2291·2).

Herbion Drops for the Heart *KRKA, Rus.*
Crataegus (p.2289·1); mistletoe (p.2345·3); valerian (p.2410·1).

Herbion Drops for the Stomach *KRKA, Rus.*
Gentian (p.2310·3); centaury (p.2279·1); chamomile (p.2279·3); caraway (p.2276·3).

Herbion Plantain Syrup *KRKA, Rus.*
Ribwort plantain (p.2379·1); mallow flower (p.2337·2); ascorbic acid (p.1983·3).

Herbion Urological Drops *KRKA, Rus.*
Parsley root (p.2363·2); equisetum (p.2299·3); bearberry (p.2263·3); green birch (p.2266·3); ononis (p.2357·1).
Cystitis; pyelonephritis.

Herbion Urtica *KRKA, Rus.*
Urtica (p.2409·3); sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Herbogastrin *Herbapol Pruszkow, Pol.*
Chamomile (p.2279·3); liquorice (p.1740·3); St John's wort (p.422·3); peppermint leaf (p.1761·2); sage (p.2382·3).
Digestive disorders.

Herbogesic *Seroyal, Canad.*
Magnesium salicylate (p.79·2).

Herbolax *Seroyal, Canad.*
Cascara (p.1715·2); rhubarb (p.1768·3); senna (p.1769·2); liquorice (p.1740·3).

Herbolen *Herbapol Poznan, Pol.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); majoram oil (p.2358·1); pine oil (p.2368·2); turpentine oil (p.2406·3).
Respiratory-tract congestion.

Herbolen D *Herbapol Poznan, Pol.*
Anise oil (p.2258·2); eucalyptus oil (p.2301·2); majoram oil (p.2358·1); pine oil (p.2368·2).
Respiratory-tract congestion.

Herbopyrine *Herbes Universelles, Canad.*
Aspirin (p.20·3); caffeine citrate (p.1116·3).

Herborex *Rolmex, Canad.*
Cascara (p.1715·2); yellow dock (p.2416·3).
Constipation.

Herbulax *Chefaro, UK.*
Frangula bark (p.1732·2); taraxacum (p.2395·1).
Constipation.

Hercap *Ativus, Braz.*
Capsicum oleoresin (p.2276·2).

Herceptin *Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Genentech, USA; Roche, Venez.*
Trastuzumab (p.782·2).
Breast cancer.

Hercivir *Diba, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herclov *Sanbe, Indon.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Herden *Remedica, Thai.†.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Herivyl *Libbs, Braz.*
Phentolamine mesilate (p.1370·2).
Erectile dysfunction.

Herklin
Note. This name is used for preparations of different composition.
Armstrong, Mex.
Lotion: Lindane (p.2045·3); lidocaine (p.1862·3).
Pediculosis; scabies.

Armstrong, Mex.
Shampoo: Lindane (p.2045·3).
Pediculosis; scabies.

Herklin NF
Note. This name is used for preparations of different composition.
Armstrong, Mex.
Lotion: Phenothrin (p.2048·3); lidocaine (p.1862·3).
Pediculosis.

Armstrong, Mex.
Shampoo: Phenothrin (p.2048·3).
Pediculosis.

Hermalind *Hermal, Ger.†.*
Dexpanthenol (p.2362·1); chlorhexidine gluconate (p.1635·3).
Burns; wounds.

Hermankovy *Megafyt-R, Cz.*
Chamomile (p.2279·3).
Gastrointestinal disorders; inflammation of the skin and mucous membranes.

Hermes Cevitt *Hermes, Ger.; Hermes, Hung.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Hermesetas *Sifar, Turk.; Polinac, Venez.*
Saccharin sodium (p.1960·3).
Sugar substitute.

Hermesetas Gold
Note. This name is used for preparations of different composition.
Sifar, Turk.
Aspartame (p.1930·1).
Sugar substitute.

Polinac, Venez.
Granules: Aspartame (p.1930·1); acesulfame potassium (p.1928·1); maltodextrin (p.1955·3).
Sugar substitute.

Polinac, Venez.
Powder; tablets: Aspartame (p.1930·1).
Sugar substitute.

Hermin *Alembic, India.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Hermix-Sofex *Sofex, Port.*
Aciclovir (p.862·3).
Herpes simplex infections.

Hermocil *Oftalder, Port.†.*
Aciclovir (p.862·3).
Herpes simplex keratitis.

Hermolepsin *Orion, Swed.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; epilepsy; trigeminal neuralgia.

Hernidisc *Eagle, Austral.*
Vitamins; minerals; bromelains; rutoside; equisetum; bioflavonoids; ruta graveolens; arnica; rhus tox; ferrous phosphate; hypericum perforatum.

Hernovir *Nobel, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Heroid *Chew, Thai.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; phlebitis; varicose veins; venous insufficiency.

Herolan Aerosol *Laboratorios Chile, Chile.*
⊗ Beclometasone (p.1517·2); salbutamol (p.1131·2).
Obstructive airways disease.

Herpavir *TAD, Denm.*
Aciclovir (p.862·3).
Herpes simplex infections.

Herpecin-L *Chattem, USA.*
Dimeticone (p.2032·1); meradimate (p.1604·2); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Formerly contained allantoin and padimate O.
Chapped lips; sunscreen.

Herpeks *Bio-Sen, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herpenon *Polipharm, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections of the skin and mucous membranes.

Herpes Soothing Cream *Homeocan, Canad.*
Homoeopathic preparation.

Herpesan *Rowa, Hong Kong; Rowa, Malaysia; Rowa, Singapore.*
Carbenoxolone sodium (p.1714·3).
Mouth ulcers; orofacial lesions.

Herpes-Gastreu R68 *Reckeweg, Ger.*
Homoeopathic preparation.

Herpesil *Hexal, Braz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herpesin
Pliva, Cz.; Pliva, Hung.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Pliva Lachema, Pol.
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Lachema, Rus.
Aciclovir (p.862·3).
Herpesvirus infections.

Herpesine *Nikkho, Braz.*
Idoxuridine (p.881·2).
Herpesvirus skin infections.

Herpesnil *Sofar, Ital.*
Aciclovir (p.862·3).
Herpes simplex infections.

Herpetad *TAD, Ger.; Boehringer Ingelheim, UK.*
Aciclovir (p.862·3).
Herpes simplex infections.

Herpetrol *Alva, USA.*
Multivitamin preparation with zinc and lysine (p.1922·1).

Herpex
Note. This name is used for preparations of different composition.
Uniao Quimica, Braz.
Tromantadine hydrochloride (p.911·1).
Viral skin infections.

Torrent, India; Metropolitan, Philipp.; Hexal, Pol.; Edol, Port.
Aciclovir (p.862·3).
Herpesvirus infections.

Herphonal *Temmler, Ger.*
Trimipramine maleate (p.426·3).
Depression; pain.

Herpiclof *Nufarindo, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herpiclor *Behrens, Venez.†.*
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Herpid *Astellas, UK.*
Idoxuridine (p.881·2) in dimethyl sulfoxide.
Herpesvirus skin infections.

Herpidum *Farma, Venez.†.*
Idoxuridine (p.881·2).
Herpesvirus skin infections.

Herpilem *Lemery, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herpin *Cafar, Venez.*
Aciclovir (p.862·3).

Herpirax *Pond's, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections of skin and mucous membranes.

Herplex *Allergan, Canad.*
Idoxuridine (p.881·2).
Herpes simplex infections.

Herplex-D *Allergan, Austral.†.*
Idoxuridine (p.881·2).
Herpes simplex skin infections.

Herpolips *Berner, Fin.; Stada, Neth.*
Aciclovir (p.862·3).
Herpes labialis.

Herpomed *S Med, Austria.*
Aciclovir (p.862·3).
Herpes labialis.

Herposicc *Pharmaselect, Austria.*
Benzocaine (p.1854·1); sulfur (p.1614·1); zinc oxide (p.1621·2); talc (p.1615·2); phenol (p.1656·1).
Herpes labialis.

Herpotern *Rentschler, Cz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herron Baby Teething Gel *Herron, Austral.*
Choline salicylate (p.36·3).
Sore gums; teething pain.

Herronduo *Farma, Venez.*
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Herrongyn *Farma, Venez.*
Ferrous glycine sulfate (p.1939·1); folic acid (p.1940·1).
Iron and folic acid supplement.

Herten *Vir, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Hertz- und Kreislauftee *Abtswinder, Cz.†.*
Crataegus (p.2289·1); rosemary (p.2381·2); raspberry leaf (p.2378·2); spearmint (p.2391·3); coriander (p.2288·1); melissa (p.2339·3); valerian (p.2410·1); achillea (p.2245·2); calendula (p.2273·1); centaurea cyanus.
Cardiac disorders; circulatory disorders; hypertension.

Hervirax *Pharlab, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Herviros *Hermal, Austria; Hermal, Ger.†.*
Tetracaine hydrochloride (p.1871·3); aminoquinuride hydrochloride (p.1628·3).
Mouth disorders.

Herz ASS *Gerot, Austria.*
Aspirin (p.20·3).
Ischaemic heart disease; myocardial infarction; thromboembolism prophylaxis.

HerzASS *Ratiopharm, Ger.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Herzkur *Chrispa (Χρισπα), Gr.*
Aciclovir (p.862·3).
Herpes simplex infections.

Herzschutz ASS *Ratiopharm, Austria.*
Aspirin (p.20·3).
Formerly known as Corsalbene.
Migraine; myocardial infarction; thrombosis prophylaxis.

Herz-Starkung N *Jukunda, Ger.†.*
Crataegus (p.2289·1); lycopus virg.; cactus; kalmia latifolia; camphora.
Cardiac disorders.

Herztropfen CM *Cosmochema, Ger.†.*
Homoeopathic preparation.

Herztropfen N Cosmochema *Heel, Ger.*
Homoeopathic preparation.

Hes Grifols *Grifols, Spain.*
⊗ An etherified starch (p.1065·1).
Plasma volume expansion.

Hespan *Braun, USA.*
⊗ Hetastarch (p.1065·1) in sodium chloride.
Plasma volume expansion.

Hespander *Kyorin, Jpn; Kyorin, Thai.†.*
⊗ Hetastarch (p.1065·1) in glucose with electrolytes.
Haemodiluent; haemorrhage; plasma volume expansion.

Hespercorbin *Zambon, Spain.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Hessico *Rivero, Arg.*
⊗ An etherified starch (p.1065·1).
Plasma volume expansion.

Hestar *Pisa, Mex.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Plasma volume expansion; shock.

Hesteril *Fresenius Kabi, Fr.; Fresenius Kabi, Spain.*
⊗ Pentastarch (p.1065·1).
Haemodilution; plasma volume expansion.

Hetaclox *Faran, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Hetacloxacin *Faran, Gr.†.*
Ofloxacin (p.310·2).
Bacterial infections.

Heteroid *Chew, Thai.*
Diosmin (p.2304·2).
Haemorrhoids; phlebitis; varicose veins; venous insufficiency.

Hetrazan *IFET (ΙΦΕΤ), Gr.†; Wyeth, India.*
Diethylcarbamazine citrate (p.143·1).
Eosinophilia; filariasis.

Hettral N *Hetterich, Ger.†.*
Pepsin (pork) (p.2365·1).
Gastrointestinal disorders.

Hettytropin *Elvetium, Arg.†.*
Dopamine hydrochloride (p.1273·2).
Heart failure.

Heumann Abfurhtee Solubilax N *Sanofi Synthelabo, Ger.†.*
Senna (p.1769·2); frangula bark (p.1732·2).
Constipation.

Heumann Beruhigungstee Tenerval *Winthrop, Ger.*
Valerian root (p.2410·1); melissa (p.2339·3); valerian oil (p.2410·1).
Nervous disorders.

Heumann Blasen- und Nierentee Solubitrat S *Sanofi Synthelabo, Ger.†.*
Java tea (p.2328·2); solidago virgaurea (p.2391·1); birch leaf (p.2266·3).
Urinary-tract disorders.

Heumann Blasen- und Nierentee Solubitrat uro *Winthrop, Ger.*
Birch leaf (p.2266·3); solidaga virgaurea (p.2391·1).
Urinary-tract disorders.

Heumann Bronchialtee Solubifix T *Winthrop, Ger.*
Althaea (p.2253·3); liquorice (p.1740·3); primula root (p.2372·2); anise oil (p.2258·2); thyme oil (p.2401·2).
Respiratory-tract disorders.

Heumann Leber- und Gallentee Solu-Hepar S *Sanofi Synthelabo, Ger.†.*
Boldo (p.2267·2); milk thistle (p.1452·1); peppermint oil (p.1761·2).
Digestive disorders.

Heumann Magentee Solu-Vetan *Winthrop, Ger.*
Liquorice root (p.1740·3); peppermint leaf (p.1761·2); peppermint oil (p.1761·2).
Gastrointestinal disorders.

Heumann Verdauungstee Solu-Lipar *Winthrop, Ger.*
Boldo (p.2267·2); milk thistle (p.1452·1); peppermint oil (p.1761·2).
Digestive disorders.

Heumann's Blasen- und Nierentee *Sanova, Austria.*
Birch leaf (p.2266·3); solidago (p.2391·1).
Bladder and urinary-tract disorders.

Heumann's Bronchialtee *Sanova, Austria.*
Althaea (p.2253·3); liquorice (p.1740·3); cowslip root (p.2372·2); anise oil (p.2258·2); thyme oil (p.2401·2).
Bronchitis; catarrh; coughs.

Heuschnupfenmittel *DHU, Ger.; Dreluso, Ger.*
Homoeopathic preparation.

Heuschnupfenmittel DHU *Peithner, Austria.*
Homoeopathic preparation.

Heusin *Riemser, Ger.†.*
Aesculus (p.2248·2); mistletoe (p.2345·3); crataegus (p.2289·1); hamamelis (p.2318·2); arnica (p.2260·2); milk thistle (p.1452·1).
Peripheral vascular disorders.

Hevert-Aktivon Mono *Hevert, Ger.†.*
Ginseng (p.2312·1).
Tonic.

Hevert-Blasen-Nieren-Tee N *Hevert, Ger.*
Java tea (p.2328·2); birch leaf (p.2266·3); equisetum (p.2299·3); ononis (p.2357·1); couch-grass (p.2288·2); gartebohnenhulsen.
Urinary-tract disorders.

Hevert-Dorm *Hevert, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Hevert-Enzym Comp *Hevert, Ger.*
Dimeticone (p.1770·2); pancreas extract (p.2337·3).
Formerly Hevert-Enzym Plus.
Digestive disorders.

Hevertigon *Hevert, Ger.†.*
Homoeopathic preparation.

Hevertigon SL *Hevert, Ger.†.*
Homoeopathic preparation.

Hevert-Mag *Hevert, Ger.*
Magaldrate (p.1742·3).
Gastric hyperacidity; heartburn; peptic ulcer.

Hevert-Migrane *Hevert, Ger.*
Homoeopathic preparation.

Hevert-Migrane N *Hevert, Ger.*
Homoeopathic preparation.

Hevertnier Complex *Hevert, Ger.†.*
Homoeopathic preparation.

Hevertnier Complex N *Hevert, Ger.*
Homoeopathic preparation.

Heverto *Hevert, Ger.†.*
Senna (p.1769·2).
Constipation.

Hevertogyn *Hevert, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Hevertolax duo *Hevert, Ger.†.*
Frangula bark (p.1732·2); senna (p.1769·2).
Constipation.

Hevertopect *Hevert, Ger.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); turpentine oil (p.2406·3).
Respiratory-tract congestion.

Hevertopect N *Hevert, Ger.†.*
Anise oil (p.2258·2); eucalyptus oil (p.2301·2); fennel oil (p.2303·1); peppermint oil (p.1761·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); eucalyptus (p.2301·2); thyme (p.2401·1); verbascum (p.2413·3).
Respiratory-tract disorders.

Hevertotox N *Hevert, Ger.*
Homoeopathic preparation.

Hevertoval bei Nervositat *Hevert, Ger.*
Homoeopathic preparation.
Formerly known as Hevertoval mono.

Hevertozym *Hevert, Ger.†.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Heviran *Polpharma, Pol.*
Aciclovir (p.862·3).
Herpesvirus infections.

Hevizos *Teva, Hung.*
Epervudine.
Herpesvirus infections.

Hevronaz *Rafarm, Gr.*
Mupirocin (p.302·3).
Skin infections.

Hevtin *Pharos, Indon.; Scherer, Indon.*
Ornithine aspartate (p.1959·2).
Dietary supplement; liver disorders.

Hewallergia Complex *Hevert, Ger.*
Homoeopathic preparation.

Heweberberol *Hevert, Ger.*
Homoeopathic preparation.

Heweberberol-Tee *Hevert, Ger.*
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1); ononis (p.2357·1); java tea (p.2328·2); pterocarpus santalinus; liquorice root (p.1740·3).
Urinary-tract disorders.

Hewechol Artischockendragees *Hevert, Ger.*
Cynara (p.2291·2).
Dyspepsia.

Hewedolor N *Hevert, Ger.*
Methyl salicylate (p.85·3).
Neuromuscular disorders; peri-articular and soft-tissue disorders.

Hewedolor neuro *Hevert, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Formerly contained thiamine hydrochloride, pyridoxine hydrochloride, and lidocaine hydrochloride.
Nerve pain.

Hewedolor plus Coffein *Hevert, Ger.*
Procaine hydrochloride (p.1869·1); caffeine (p.1116·3).
Nerve pain.

Hewedolor Procain *Hevert, Ger.*
Procaine hydrochloride (p.1869·1).
Pain.

Hewedolor propy *Hevert, Ger.†.*
Propyphenazone (p.119·3).
Fever; pain.

Hewedormir doxyl intens *Hevert, Ger.†.*
Doxylamine succinate (p.578·2).
Anxiety; hypersensitivity reactions; sleep disorders.

Heweformica *Hevert, Ger.*
Homoeopathic preparation.

Heweginkgo *Hevert, Ger.†.*
Homoeopathic preparation.

Hewekliman *Hevert, Ger.†.*
Homoeopathic preparation.

Hewekzem novo N *Hevert, Ger.*
Chamomile oil (p.2279·3); dexpanthenol (p.2362·1); vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Skin disorders.

Hewelymphon N *Hevert, Ger.*
Homoeopathic preparation.

Hewenephron duo *Hevert, Ger.†.*
Solidago virgaurea (p.2391·1); echinacea (p.2298·1).
Renal calculi.

Heweneural *Hevert, Ger.*
Lidocaine hydrochloride (p.1862·3).
Migraine; neuromuscular disorders.

Hewepsychon duo *Hevert, Ger.†.*
Kava (p.2328·3); St John's wort (p.422·3).
Depression; dystonias; hypertension; menopausal disorders; migraine; nocturnal enuresis; tonic.

Hewepsychon Mono *Hevert, Ger.*
Homoeopathic preparation.

Hewepsychon uno *Hevert, Ger.*
St John's wort (p.422·3).
Depression.

Hewerheum N *Hevert, Ger.*
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hewesabal comp *Hevert, Ger.†*
Homoeopathic preparation.

Hewesabal mono *Hevert, Ger.*
Homoeopathic preparation.

Heweselen *Hevert, Ger.*
Homoeopathic preparation.

Hewethyreon *Hevert, Ger.*
Homoeopathic preparation.

Hewetraumen *Hevert, Ger.†*
Homoeopathic preparation.

Heweurat *Hevert, Ger.*
Homoeopathic preparation.

Heweven Phyto *Hevert, Ger.*
Aesculus (p.2248·2).
Haemorrhoids; venous insufficiency.

Hewletts *Kestrel, UK.*
Zinc oxide (p.1621·2); hydrous wool fat (p.2033·3); arachis oil (p.2259·1); white soft paraffin (p.2031·2).
Dry skin; nappy rash.

Hexabencil *Sandoz, Arg.*
Permethrin (p.2048·2); benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Hexa-Blok *Hexal, S.Afr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Hexabotin *Sandoz, Denm.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Hexabrix *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Codali, Belg.; Guerbet, Braz.†; Tyco, Canad.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.; Guerbet, Israel; Guerbet, Ital.; Biotek, NZ; Guerbet, Neth.; Guerbet, Norw.; Martins & Fernandes, Port.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; May & Baker, UK; Mallinckrodt, USA; Quifoven, Venez.*
Meglumine ioxaglate (p.1486·3); sodium ioxaglate (p.1486·3).
Radiographic contrast medium.

Hexacorton *Orva, Turk.*
⊗ Prednisolone acetate (p.1541·1).
Skin disorders.

Hexacortone *Spirig, Switz.*
⊗ Prednisolone acetate (p.1541·1).
Skin disorders.

Hexacroman *Durascan, Denm.†*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Hexacyl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Hexadecyl *Galena, Cz.†*
Hexachlorophene (p.1646·1); undecenoic acid monoethanolamide (p.549·3).
Fungal skin infections.

Hexa-Defital
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Lotion: Lindane (p.2045·3); benzocaine (p.1854·1).
Pediculosis; scabies.

Sandoz, Arg.
Shampoo: Lindane (p.2045·3).
Pediculosis.

Hexa-Defital Crema Enjuague *Sandoz, Arg.*
Acetic acid (p.2244·2).
Pediculosis.

Hexa-Defital NF *Sandoz, Arg.*
Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis.

Hexa-Defital Plus *Sandoz, Arg.*
Acetic acid (p.2244·2); permethrin (p.2048·2).
Pediculosis.

Hexadilat *Sandoz, Denm.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Hexadol *Otto, Indon.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Hexadrol *Organon Teknika, Canad.†; Organon, USA.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Hexafen *EMS, Braz.†*
Deltamethrin (p.2040·1).
Scabies.

Hexagastron *Durascan, Denm.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Hexaglucon *Sandoz, Denm.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Hexagon *Omega, Irl.*
Test for detection of antibodies to *Helicobacter pylori* in blood, serum, or plasma.

Hexakapron *Teva, Israel.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Hexal Comfarol Plus *Hexal, Austral.†*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Hexal Compufen *Hexal, Austral.†*
Ibuprofen (p.64·2).

Hexal Konazol Shampoo *Hexal, Austral.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Hexalacton *Sandoz, Denm.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Hexalectol *Rider, Chile.*
Glutamic acid (p.1947·1); pyridoxine (p.1979·1).
Mental function impairment.

Hexalen
Note. This name is used for preparations of different composition.
Mayne, Austral.; Mayne, NZ†; IDIS, Neth.; Medimmune, Norw.†; Teva, Rus.; Swedish Orphan, Swed.†; American Taiwan, Thai.; MGI, USA.
Altretamine (p.678·2).
Ovarian cancer.

Pfizer, Gr.
Hexetidine (p.1647·1).
Mouth infections.

Hexalense *Ioltech, Fr.†*
Aminocaproic acid (p.1053·2).
Eye irritation.

Hexaler *Investi, Arg.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Hexalid *Sandoz, Denm.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; spasticity.

Hexalyse *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Bouchara, Rus.*
Biclotymol (p.1632·1); muramidase hydrochloride (p.2348·1); enoxolone (p.50·1).
Mouth and throat disorders.

Hexamet *Hexal, S.Afr.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hexamidin *Akrikhin, Rus.*
Primidone (p.503·2).
Epilepsy.

Hexamon *Schoning-Berlin, Ger.*
Hexylresorcinol (p.1647·1); lauromacrogol 400 (p.1916·1).
Anorectal disorders.

Hexamycin *Sandoz, Denm.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Hexanios G+R *Anios, Fr.*
Polihexanide (p.1658·2); didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Hexanitrat *Hexal, Austria.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Hexanurat *Sandoz, Denm.*
Allopurinol (p.552·2).
Gout.

Hexapindol *Sandoz, Denm.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Hexapneumine
Note. This name is used for preparations of different composition.
Bouchara-Recordati, Fr.
Adult suppositories; paediatric suppositories: Biclotymol (p.1632·1); cineole (p.2282·3); pholcodine (p.1570·2).
Coughs.

Bouchara-Recordati, Fr.
Adult syrup; paediatric syrup: Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); pholcodine (p.1570·2).
Formerly contained biclotymol, chlorphenamine maleate, guaifenesin, and pholcodine.
Coughs.

Bouchara-Recordati, Hong Kong.
Adult syrup; paediatric syrup: Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); pholcodine (p.1570·2).
Coughs.

Bouchara-Recordati, Fr.
Infant suppositories: Biclotymol (p.1632·1); cineole (p.2282·3).
Respiratory-tract disorders.

Bouchara-Recordati, Fr.
Infant syrup: Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); tolu balsam (p.1574·2).
Coughs.

Bouchara-Recordati, Hong Kong.
Infant syrup: Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); paracetamol (p.108·1); tolu balsam (p.1574·2).
Coughs; fever.

Bouchara-Recordati, Hong Kong.
Tablets: Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Hexaporine *Texinfine, Fr.*
Pomegranate bark (p.153·3).
Fluid and electrolyte imbalance.

Hexapress *Durascan, Denm.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Hexaquart L *Braun, Ger.†*
Didecyldimethylammonium chloride (p.1642·2); benzalkonium chloride (p.1629·1).
Surface disinfection.

Hexaquart plus *Braun, Ger.*
Didecyldimethylammonium chloride (p.1642·2); lauryldipropylene triamine; biguanidinium acetate.
Surface and instrument disinfection.

Hexaquart S *Braun, Ger.*
Didecyldimethylammonium chloride (p.1642·2); benzalkonium chloride (p.1629·1).
Fungal skin infection prophylaxis; surface disinfection.

Hexaquine *Gomenol, Fr.*
Quinine benzoate (p.614·3); thiamine hydrochloride (p.1976·1); niaouli oil (p.2351·3).
Muscle cramps.

Hexaretic *Hexal, S.Afr.*
⊗ Amiloride (p.1210·1); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hexarhume *Bouchara-Recordati, Fr.*
Biclotymol (p.1632·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Formerly known as Hexapneumine.
Nasal congestion.

Hexarone *Hexal, S.Afr.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Hexaseptine *Gifrer Barbezat, Fr.*
Hexamidine isetionate (p.1646·3).
Bacterial skin infections; skin and mucous membrane disinfection.

Hexasoptin *Sandoz, Denm.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Hexaspray *Doms-Adrian, Cz.†; Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Decafarma, Port.; Bouchara, Rus.*
Biclotymol (p.1632·1).
Mouth and throat disorders.

Hexatrione *Sankyo, Fr.*
⊗ Triamcinolone hexacetonide (p.1544·3).
Musculoskeletal and joint disorders.

Hexatron *Hexal, Denm.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Hexavac *Sanofi Pasteur, Arg.†; Aventis Pasteur, Austria†; Aventis Pasteur, Braz.†; Sanofi Pasteur, Chile; Aventis Pasteur, Fr.†; Aventis Pasteur, Ger.†; Vianex (Βιανέξ), Gr.†; Sanofi Pasteur, Hung.; Aventis Pasteur, Ital.†; Aventis Pasteur, Mex.†; Aventis Pasteur, Pol.†; Sanofi Pasteur, Spain†; Sanofi Pasteur, Swed.†; Sanofi Pasteur, Switz.*
A diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Hexavitamin *Upsher-Smith, USA.*
Multivitamin preparation (p.1922·1).

Hexavitamins *Novopharm, Canad.*
Multivitamin preparation (p.1922·1).

Hexazide *Hexal, S.Afr.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hexbio *YSP, Malaysia.*
Lactobacillus acidophilus; Lactobacillus casei; Lactobacillus lactis; Bifidobacterium bifidum; Bifidobacterium longum; Bifidobacterium infantis (p.2372·3).
Dietary supplement.

Hexene *Osoth, Thai.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hexer *Kalbe, Indon.*
Ranitidine hydrochloride (p.1766·1).
Duodenitis; gastric hyperacidity; gastritis; gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Hexiben *Sidus, Arg.*
Calcium peroxide (p.1633·3); sodium monofluorophosphate (p.1964·3).
Dental whitener.

Hexiben Plus *Sidus, Arg.†*
Urea hydrogen peroxide (p.1666·2); sodium monofluorophosphate (p.1964·3).
Dental whitener.

Hexicon *Nizpharm, Rus.*
Chlorhexidine gluconate (p.1635·3).
Skin and mucous membrane infections.

Hexide *Milano, Thai.*
Chlorhexidine gluconate (p.1635·3).
Antiseptic lubricant for vaginal examination.

Hexident *Ipex, Swed.*
Chlorhexidine gluconate (p.1635·3).
Mouth disinfection; oral hygiene.

Hexidin
Barnes Hind, Arg.
Chlorhexidine gluconate (p.1635·3) (p.1622·2).
Disinfecting solution for soft contact lenses.

Zedchem, S.Afr.
Chlorhexidine gluconate (p.1635·3).
Lubricant for gynaecological examinations.

Hexil *Inmunolab, Arg.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Hexil Antiseptico *Inmunolab, Arg.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).

Hexilium *Pharmasant, Thai.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Hexilon *Kalbe, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Hexil-P *Inmunolab, Arg.*
Chlorhexidine (p.1635·2).
Skin disinfection.

Hexit *Odan, Canad.*
Lindane (p.2045·3).
Pediculosis; scabies.

Hexobion *Merck, Ger.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Hexodane Handrub *ICM, Singapore.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Hand and skin disinfection.

Hexodane Mouthwash *ICM, Singapore.*
Chlorhexidine gluconate (p.1635·3).
Dental plaque prevention; mouth disorders; oral hygiene.

Hexogen *Antigen, Irl.†*
Inositol nicotinate (p.1316·1).
Peripheral and cerebral vascular disorders.

Hexokain *Nycomed, Denm.*
Benzocaine (p.1854·1); chlorhexidine hydrochloride (p.1635·3).
Mouth disorders; oral hygiene.

Hexol *Sigma, Austral.†; Sigma, Hong Kong†; Pharmaland, Thai.†*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Hexolvon *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Bromhexine hydrochloride (p.1552·2).
Coughs.

Hexomedin *Sanofi-Aventis, Spain.*
Hexamidine isetionate (p.1646·3).
Burns; skin infections; wounds.

Hexomedin N *Nattermann, Ger.†*
Hexamidine isetionate (p.1646·3).
Acne; paronychia.

Hexomedine
Note. This name is used for preparations of different composition.
Melisana, Belg.; Sanofi-Aventis, Venez.
Hexamidine isetionate (p.1646·3).
Mouth and throat disorders; skin infections.

Sanofi-Aventis, Braz.
Hexamidine isetionate (p.1646·3); tetracaine hydrochloride (p.1871·3).
Mouth disorders.

Theraplix, Fr.†
Throat spray: Hexamidine isetionate (p.1646·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Sanofi-Aventis, Fr.
topical gel; Topical solution: Hexamidine isetionate (p.1646·3).
Bacterial skin infections.

Hexon *GMP, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with viscous mucus.

Hexopal *Clonmel, Irl.; Genus, UK.*
Inositol nicotinate (p.1316·1).
Intermittent claudication; peripheral vascular disorders; Raynaud's syndrome.

Hexoral
Note. This name is used for preparations of different composition.
Pfizer, Austria; Pfizer Consumer, Ger.; Pfizer, Rus.
Hexetidine (p.1647·1).
Mouth and throat disorders.

McNeil, Cz.
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Hexoraletten N *McNeil, Cz.; Pfizer Consumer, Ger.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Hexoscrub *ICM, Singapore.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hextend *Biotime, Canad.*
⊗ Hetastarch (p.1065·1) in electrolytes.
Plasma volume expansion.

Hextrate *Hexal, Philipp.; Salutas, Philipp.*
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis.

Hextril *Pfizer Consumer, Belg.; Pfizer Sante, Fr.; Pfizer Consumer, Neth.; Janssen-Cilag, Port.; Pfizer Consumer, Spain; Pfizer Consumer, Switz.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Hextriletten *Pfizer Consumer, Switz.*
Cetylpyridinium chloride (p.1635·1); dichlorobenzyl alcohol (p.1642·1); lidocaine hydrochloride (p.1862·3).
Mouth inflammation; sore throat.

Hextrimint *Pfizer Consumer, Switz.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Mouth and throat disorders.

Hexvix *GE, Cz.; Photocure, Fin.; GE, Gr.; GE Healthcare, Neth.; Photocure, Norw.; Satis, Port.; Photocure, Swed.*
Hexaminolevulinate hydrochloride (p.679·3).
Diagnosis of bladder cancer.

Hexymer *Mersifarma, Indon.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

HF *Fresenius Medical, Hung.; Fresenius Medical, Switz.*
Glucose; sodium chloride; sodium lactate; potasssium chloride; calcium chloride; magnesium chloride (p.1670·3).
Haemofiltration.

HF-BIC35+HF-EL010 *Dicamed, Swed.†.*
Sodium chloride; sodium bicarbonate; calcium chloride; magnesium chloride; glucose (p.1670·3).
Haemofiltration.

HF-BIC35+HF-EL210 *Dicamed, Swed.†.*
Sodium chloride; sodium bicarbonate; calcium chloride; magnesium chloride; potassium chloride; glucose (p.1670·3).
Haemofiltration.

HHT *Sidus, Arg.; Biolatina, Chile; Landsteiner, Mex.*
⊗ Somatropin (p.1799·3).
Cachexia; growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Hi Potency B Compound *Trophic, Canad.*
Vitamin B substances (p.1922·1).

Hi Potency Cal *Swiss Herbal, Canad.*
Calcium carbonate (p.1714·1).

Hi Potency Multi-Mineral *Swiss Herbal, Canad.†.*
Mineral and trace element preparation (p.1922·1).

Hi Potency Stress B with C *Lee-Adams, Canad.*
Vitamin B substances; vitamin C (p.1922·1).

Hialid *Santen, Hong Kong; Ferron, Indon.; Santen, Indon.; Santen, Philipp.; Santen, Singapore; Santen, Thai.*
Sodium hyaluronate (p.2320·1).
Dry eyes; keratoconjunctival injury.

Hialudorf *Pharmadorf, Arg.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Hibadren *Stada, Austria.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Hiberix *GSK, Austral.; GSK, Belg.†; GSK, Braz.†; GSK, Cz.; GSK, Fin.†; GSK, Gr.; GSK, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p.2213·2).
Active immunisation.

Hibernal *EGIS, Hung.; Aventis, Swed.*
Chlorpromazine hydrochloride (p.969·2).
Nausea and vomiting; pain; premedication; psychoses.

Hi-Beston *Tanabe, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Hibicet *Cana, Gr.; SSL, Irl.; SSL, Malaysia†; AstraZeneca, S.Afr.†; SSL, Thai.†; SSL, UK†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection of skin, wounds, and burns.

Hibicet concentraat *SSL, Neth.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Hibicet Hospital Concentrate *AstraZeneca, Cz.†; SSL, Hong Kong†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Hibicet verdunning *SSL, Neth.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Hibiclens *Regent, USA.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hibicrick *Master, Chile†.*
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat infections.

Hibida *Rez, Cz.*
Technetium-99m (p.2055·3) mebrofenin.
Radionuclide imaging of the liver and biliary tract.

Hibidil *Molnlycke, Belg.; Regent, Canad.; CSP, Fr.; Zeneca, S.Afr.†; Regent, Switz.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of burns, wounds, skin, mucous membrane, and instruments.

Hibiguard *Molnlycke, Belg.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of hands and skin.

Hibimax *Mab, Spain.*
Chlorhexidine gluconate (p.1635·3).
Burns; instrument disinfection; skin disinfection; skin disorders; wounds.

Hibiron *Otto, Indon.*
Iron dextran (p.1951·1).
Iron deficiency.

Hibiscrub *Scott-Cassara, Arg.; Molnlycke, Belg.; AstraZeneca, Chile†; AstraZeneca, Cz.†; CSP, Fr.; SSL, Hong Kong†; SSL, Irl.; SSL, Malaysia†; Zeneca, Mex.†; SSL, Neth.; Regent Medical, Norw.; AstraZeneca, S.Afr.; Mab, Spain; Regent Medical, Swed.; Regent, Switz.; SSL, Thai.†; Regent Medical, UK.*
Chlorhexidine gluconate (p.1635·3).
Skin and hand disinfection.

Hibisol
Note. This name is used for preparations of different composition.
SSL, Hong Kong†; SSL, Irl.; SSL, Neth.; Regent Medical, UK.
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin and hand disinfection.

SSL, Malaysia†.
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hibisprint *CSP, Fr.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hibistat *Zeneca, USA.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Hibital *Regent, Switz.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin and hand disinfection.

Hibitane
Note. This name is used for preparations of different composition.
AstraZeneca, Braz.; Wyeth, Canad.; Bioglan, Denm.; CSP, Fr.; Cana, Gr.; SSL, Hong Kong†; SSL, Irl.; SSL, Malaysia†; AstraZeneca, NZ; Bouwer Bartlett, S.Afr.; Bioglan, Swed.; Regent, Switz.; SSL, Thai.†; Centrapharm, UK.
Chlorhexidine gluconate (p.1635·3).
Antiseptic; disinfection; lubricant in obstetrics; mouth infections.

GSK Consumer, Neth.
Chlorhexidine hydrochloride (p.1635·3).
Mouth infections.

Tramedico, Belg.; CS, Port.
Cream: Chlorhexidine gluconate (p.1635·3).
Gynaecological and obstetric lubricant and disinfectant; skin disinfection.

Bioglan, Norw.
Obstetric cream: Chlorhexidine gluconate (p.1635·3).
Disinfectant in obstetrics and gynaecology.

GSK Consumer, Belg.
Pastilles: Chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

GSK Consumer, Port.†; GSK Consumer, Spain.
Pastilles: Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Molnlycke, Belg.
Solution; tincture: Chlorhexidine gluconate (p.1635·3).
Disinfection.

Hibitane Menta *GSK Consumer, Port.†.*
Benzocaine (p.1854·1); chlorhexidine hydrochloride (p.1635·3); menthol (p.2340·1).
Mouth and throat disorders.

Hibitane Teinture *Regent, Switz.*
Chlorhexidine gluconate (p.1635·3); isopropyl alcohol (p.1650·3).
Skin disinfection.

Hibizene *SSL, Ital.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Disinfection of burns, wounds, and external genitalia.

Hiblok *Nufarindo, Indon.*
⊗ Atenolol (p.1217·3).
Hypertension.

Hibon *Mitsubishi-Tokyo, Hong Kong.*
Riboflavin tetrabutyrate (p.1978·1).
Vitamin B deficiency.

Hi-Bone *Otto, Indon.*
Genistein (p.2391·2); calcium phosphate (p.1676·2); phytomenadione (p.1995·3); colecalciferol (p.1986·2).
Osteoporosis.

Hiboquad *Eczane, Arg.†.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Hibor *Rovi, Spain.*
Bemiparin sodium (p.1223·1).
Thromboembolism prophylaxis.

HibTITER *Wyeth, Austral.†; Wyeth Lederle, Austria; Wyeth Lederle, Belg.†; Wyeth, Cz.†; Wyeth Lederle, Denm.†; Wyeth Lederle, Fin.†; Wyeth, Ger.†; Lilly, Gr.†; Wyeth, Irl.†; Lederle, Israel†; Wyeth Lederle, Ital.†; Wyeth, Mex.†; Lederle, NZ†; Wyeth, Pol.; Wyeth Lederle, Port.†; Wyeth, Spain; Wyeth Lederle, Swed.†; Lederle, USA.*
A haemophilus influenzae conjugate vaccine (diphtheria CRM protein conjugate) (p.2213·2).
Active immunisation.

Hi-Bumin *Plasti-Esteril, Mex.†.*
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; hypovolaemia.

Hical *Meprofarm, Indon.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide; zinc sulfate; sodium fluoride (p.1922·1).
Calcium and vitamin D deficiency.

Hicaryl *Eadriex, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol (p.1131·2).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Hicee *Takeda, Jpn; Takeda, Thai.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Hicomp *GHP, Thai.†.*
Vitamin B substances with glucose (p.1922·1).
Nutritional supplement.

Hicon *Draximage, USA.*
Iodine-131 (p.2054·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Hiconcil *BMS, Belg.; BMS, Braz.; BMS, Fr.; BMS, Israel†; KRKA, Pol.; KRKA, Rus.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hiconcil-NS *BMS, S.Afr.*
Amoxicillin trihydrate (p.202·2); nystatin (p.543·2).
Bacterial infections; candidiasis.

Hi-Cor *C & M, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hicoseen *Iromedica, Switz.*
Butamirate citrate (p.1553·1); dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Hicoton *Medika, Ger.†.*
Ferric saccharose complex (p.1953·2); calcium glycerophosphate (p.1676·1); rhus toxicodendron (p.2378·3); lupulus (p.2335·2); cinchona bark (p.2282·3); lecithin (p.2332·2); camphor monobromide.
Urinary-tract disorders.

Hidalone *Schering-Plough, Port.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hidantal *Sanofi-Aventis, Braz.*
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; neuralgia; skeletal muscle spasm.

Hidantin *Yeni, Turk.*
Phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia.

Hidantina *Vitoria, Port.*
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy.

Hidantina Composta *Vitoria, Port.†.*
Phenytoin sodium (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Hidantoina *Rudefsa, Mex.*
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Epilepsy.

Hidex *BMS, Mex.*
Iron dextran (p.1951·1).
Anaemias.

Hidil *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Hidine *PD, Thai.†.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

Hidomin *Yung Shin, Singapore†.*
Hydroxocobalamin (p.1980·3).
Anaemias.

Hidonac *Zambon, Hong Kong; Zambon, Indon.; Zambon, Ital.; Zambon, Malaysia; Zambon, Philipp.; Zambon, Thai.*
Acetylcysteine (p.1548·2).
Cyclophosphamide-induced haemorrhagic cystitis; paracetamol, carbon tetrachloride, arsenic, metallic mercury, and yellow phosphorus poisoning.

Hidra Plus *Luper, Braz.†.*
Oral rehydration solution (p.1672·2).

Hidrabene *Legrand, Braz.*
Sodium chloride; potassium chloride; sodium citrate; anhydrous glucose (p.1672·2).
Oral rehydration therapy.

Hidrafil
Note. This name is used for preparations of different composition.
Stiefel, Arg.
Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Barrier preparation with sunscreens.

Stiefel, Braz.
Lotion: Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Stiefel, Chile; Stiefel, Mex.
SPF 14: Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Stiefel, Chile.
SPF 20: Sulisobenzone (p.1614·3); ensulizole (p.1597·1).
Sunscreen.

Hidrafix *Nycomed, Braz.*
Sodium citrate; sodium chloride; potassium chloride; glucose (p.1672·2).
Oral rehydration therapy.

Hidrafix 90 *Nycomed, Braz.*
Potassium citrate; sodium citrate; sodium chloride; glucose (p.1672·2).
Oral rehydration therapy.

Hidral *Biocontrol, Arg.*
Hydralazine (p.1307·2).
Hypertension.

Hidramilac *Pharmacia, Venez.†.*
Electrolytes (p.1672·2).
Oral rehydration.

Hidramines *Pharmacia, Venez.†.*
Electrolytes (p.1672·2).
Oral rehydration.

Hidramox *Church, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hidramox-M *Church, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Hidrapel *Stiefel, Braz.*
Moisturiser.

Hidrapel Plus *Stiefel, Braz.*
⊗ Urea (p.1620·2).
Skin disorders.

Hidraplus *Baxter, Mex.†; Farma, Venez.*
Sodium chloride; potassium chloride; sodium citrate; glucose; anhydrous citric acid (p.1672·2).
Oral rehydration; oral rehydration therapy.

Hidrasec *Galenica, Gr.; GSK, Indon.; Ferrer-Novag, Mex.; GSK, Thai.†; Leti, Venez.*
Racecadotril (p.1765·2).
Diarrhoea.

Hidrasix *Serral, Mex.*
Isoniazid (p.288·1).
Tuberculosis.

Hidratacion Total (Linear Blistex) *Rider, Chile.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Hidratagel *Barnes Hind, Arg.*
Hyetellose (p.2143·3); non-ionic surfactants (p.1622·2).
Cleansing and wetting solution for soft contact lenses.

Hidratant *Maurino, Arg.*
Benzalkonium chloride (p.1629·1) (p.1622·2).
Cleansing solution for soft contact lenses.

Hidratante Enriquecida *Silesia, Chile.*
Emollient.
Dry skin.

Hidratante Ligera *Silesia, Chile.*
Emollient.
Dry skin.

Hidratante VG *Isdin, Port.*
Polyglycerylmethacrylate; glycerol (p.2314·2); carbomer (p.2141·3).
Vaginal lubricant.

Hidratante VV *Isdin, Port.*
Polyglycerylmethacrylate; lauromacrogol (p.1916·1); borage oil (p.2267·3); levomenol (p.2333·3).
Vulval lubricant.

Hidratarvin *Arex, Venez.*
Sodium chloride; sodium citrate; potassium chloride; glucose (p.1672·2).
Oral rehydration.

Hidratil *Ducto, Braz.*
Sodium chloride; potassium citrate; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

Hidratoderme *Sofex, Port.†.*
⊗ Urea (p.1620·2); allantoin (p.1588·1).
Skin disorders.

Hidratoil Free *Dermoteca, Port.†.*
A range of moisturisers and skin cleansers.

Hidrazida *Merck, Port.; Zimaia, Port.*
Isoniazid (p.288·1).
Tuberculosis.

Hidrenox A *Ivax, Arg.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Hidribet *Medihealth, Mex.†; Roemmers Medihe, Venez.*
⊗ Urea (p.1620·2); dimeticone (p.2032·1).
Barrier preparation; dry skin disorders.

Hidribet 5 *Medihealth, Mex.†.*
⊗ Urea (p.1620·2); octinoxate (p.1608·2); avobenzone (p.1589·3).
Dry skin; sunscreen.

Hidribet 5/5 *Roemmers Medihe, Venez.*
⊗ Urea (p.1620·2); octinoxate (p.1608·2); avobenzone (p.1589·3).
Dry skin; sunscreen.

Hidrion *Gross, Braz.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).
Hypertension; oedema.

Hidrium *Saval, Chile.*
⊗ Furosemide (p.1292·1); amiloride (p.1210·1).
Heart failure; hepatic cirrhosis; hypertension.

Hidroaltesona *Alter, Spain.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Hidrocil *Edol, Port.†.*
Hypromellose (p.2144·2).
Dry eyes.

Hidrocilina *Grossman, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Hidrocin *Asta Medica, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Hidrocisdin *Isdin, Spain.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hidroclorana *Pharlab, Braz.†.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hidroclorozil *IMA, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hidrocort *Behrens, Venez.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Hidrocorte *Legrand, Braz.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Skin disorders.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hidrocortex *Bergamo, Braz.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Hidrocortin *Alcon, Arg.†.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Hidro-Doce *Meyer, Venez.*
Hydroxocobalamin (p.1980·3).
Neuralgia; neuritis.

Hidrofall *Sanval, Braz.†.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hidrofan
Note. This name is used for preparations of different composition.
Corsalud, Venez.†.
Oral drops: Dextromethorphan hydrobromide (p.1555·2).
Cough.
Corsalud, Venez.†.
Syrup: Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3).
Cough.

Hidrofenil *Grin, Mex.*
⊗ Hydrocortisone (p.1535·2); phenylephrine (p.1568·1).
Eye disorders.

Hidroferol *Faes, Spain.*
Calcifediol (p.1986·1).
Hypoparathyroidism; hypophosphataemia; osteodystrophy; osteomalacia; rickets.

Hidrofosmin *Sanfer, Mex.*
Cyclophosphamide (p.702·1).
Auto-immune disorders; malignant neoplasms.

Hidrofrut *Lagos, Arg.*
Alpha hydroxy acids.

Hidrofugal
Note. This name is used for preparations of different composition.
Beiersdorf, Chile.
Cream; roll-on: Aluminium chlorohydrate (p.1588·3); aluminium chloride (p.1588·2).
Hyperhidrosis.
Beiersdorf, Chile.
Stick; topical spray: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Hidrofugal Forte *Beiersdorf, Chile.*
Aluminium chlorohydrate (p.1588·3); aluminium chloride (p.1588·2).
Hyperhidrosis.

Hidrogel
Note. This name is used for preparations of different composition.
Omega, Arg.
Vaginal lubricant.
Vaginal dryness.
Roi Surya, Indon.
Hydroquinone (p.1598·2); kojic acid; gluconolactone.
Hyperpigmented skin; melasma.

Hidrolac *Lagos, Arg.*
⊗ Lactic acid (p.2329·3); urea (p.1620·2).
Skin disorders.

Hidrolan *Geolab, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hidromagma *Medifarma, Mex.†.*
Kaolin (p.1738·1); pectin (p.2145·2); neomycin (p.305·1).
Gastrointestinal infections.

Hidromed *Cimed, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).

Hidromens *Dumont, Arg.†.*
⊗ Bendroflumethiazide (p.1224·1); chlorphenamine maleate (p.571·3); meprobamate (p.1006·2); potassium dihydrocholate.
Premenstrual syndrome.

Hidrona *Ivax, Mex.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Hidroneo *Luper, Braz.†.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Hidronovag Complex *Gobbi, Arg.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Hidropharm *Alpharma, Mex.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Hidropid *Recalcine, Chile.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Heart failure; hypertension; oedema.

Hidroplus *Lagos, Arg.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Hidroplus CL *Lagos, Arg.*
Collagen (p.2286·1).
Skin disorders.

Hidroplus Nieve *Lagos, Arg.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); collagen (p.2286·1).
Sunscreen.

Hidropolicin *Grin, Mex.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2).
Infected eye disorders.

Hidropolivit *Menarini, Spain.*
Multivitamin preparation (p.1922·1).

Hidropolivit Mineral *Menarini, Spain.*
Multivitamins and minerals (p.1922·1); orotic acid; hesperidin.
Tonic.

Hidropril *Neo Quimica, Braz.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Hidroquilaude *Dermofarm, Spain.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Hidroquin *Remexa, Mex.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Hidroral *JP, Braz.†.*
Sodium chloride; potassium chloride; sodium lactate; glucose (p.1672·2).
Oral rehydration therapy.

Hidroronol *Labomed, Chile.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hidroronol T *Labomed, Chile.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Heart failure; hepatic cirrhosis; hypertension; nephrotic syndrome; oedema.

Hidrosaluretil *Chiesi, Spain.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema; renal calculi.

Hidrosam *Szama, Arg.*
Collagen (p.2286·1); elastin; reticulin.
Skin disorders.

Hidrosam T *Szama, Arg.*
Tretinoin (p.1618·1); collagen (p.2286·1); elastin; reticulin.
Acne; photoageing; skin pigmentation disorders.

Hidroskin *Lagos, Arg.*
A range of moisturisers containing glycolic acid (p.1598·1).

Hidrosol *Pacific, NZ.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Hidrotiazida *Globo, Braz.†.*
Nystatin (p.543·2).
Candidiasis.

Hidrotisona *Aventis, Arg.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Hidroxialiv *Globo, Braz.†.*
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Hidroxil B12 B6 B1 *Almirall, Spain.*
Hydroxocobalamin (p.1980·3); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Hidroxina *ICN, Arg.†.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions; sedative.

Hidroxogel *Delta, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Hidroxovit *Degorts, Mex.†.*
Hydroxocobalamin (p.1980·3).
Anaemias; neuritis.

Hidrozona *SM, Venez.*
⊗ Hydrocortisone hydrogen succinate (p.1535·3).
Corticosteroid.

Hidyn H *Ativus, Braz.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hielorub *Maver, Chile.*
Menthol (p.2340·1).
Sports injuries.

Hierbal *Kener, Mex.*
Chlorphenamine (p.572·2).
Hypersensitivity.

Hierco *Ern, Spain†.*
Ferritin (p.1938·1).
Iron-deficiency anaemia.

Hierro Dupofol *Dupomar, Arg.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias.

Hierro Folico *Columbia, Arg.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and vitamin supplement.

Hierro Plus *Plata, Arg.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; dietary supplement.

Hierrocal Z-Plus *Farcoral, Mex.*
Calcium; iron; zinc (p.1922·1).

Hierroquick *Purissimus, Arg.*
Iron (p.1949·1); folic acid (p.1940·1).
Anaemias.

Hifamonil *Raymos, Arg.*
Sodium perborate (p.1662·1).

Hifamonil Crema *Raymos, Arg.*
⊗ Miconazole (p.541·2); betamethasone valerate (p.1519·1); gentamicin (p.284·2).
Skin infections.

Higan *Unison, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Higesan *Esoform, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Surface disinfection.

High Energy *Lafarmen, Arg.*
Glucose (p.1945·3); fructose (p.1945·1).

High Potency Cal-Mag Plus *Quest, Canad.*
Calcium; magnesium; zinc; vitamin D (p.1922·1).

High Potency N-Vites *Nion, USA.*
Vitamin B substances with vitamin C (p.1922·1).

High-C *Beacons, Singapore.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Highmix *Domestic, Rus.*
An amino-acid and sorbitol preparation (p.1922·1).
Parenteral nutrition.

Higicler *Latinofarma, Braz.*
Benzalkonium chloride (p.1629·1); boric acid (p.2268·1); hamamelis (p.2318·2); chamomile (p.2279·3); borax (p.2268·1).
Eye irritation.

Higlucem *Lazar, Arg.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Higrotensin *Visfarm, Spain.*
⊗ Chlortalidone (p.1243·3); metoprolol tartrate (p.1338·1).
Hypertension.

Higroton *Novartis, Braz.; Sandoz, Mex.; Novartis, Venez.†.*
⊗ Chlortalidone (p.1243·3).
Ascites; heart failure; hypertension; oedema; renal calculi.

Higroton Reserpina *Novartis, Braz.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Higrotona *Novartis, Spain.*
⊗ Chlortalidone (p.1243·3).
Diabetes insipidus; hypertension; oedema.

Higrotona Reserpina *Novartis, Spain†.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Higroton-Res *Sandoz, Mex.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Hijuven *Eisai, Hong Kong; Eisai, Malaysia; Eisai, Philipp.*
dl-Alpha tocoferil nicotinate (p.1415·1).
Arteriosclerosis obliterans; cerebral and peripheral vascular disorders; hyperlipidaemias.

Hill's Balsam Chesty Cough *LPC, UK.*
Guaifenesin (p.1561·3).
Coughs.

Hill's Balsam Chesty Cough for Children *LPC, UK.*
Citric acid (p.2284·1); ipecacuanha (p.1562·3).
Coughs.

Hill's Balsam Chesty Cough Pastilles *LPC, UK.*
Compound benzoin tincture; peppermint oil (p.1761·2); ipecacuanha (p.1562·3); menthol (p.2340·1).
Cough and cold symptoms.

Hill's Balsam Dry Cough *LPC, UK.*
Pholcodine (p.1570·2).
Coughs.

Hill's Balsam Extra Strong *LPC, UK.*
Compound benzoin tincture; peppermint oil (p.1761·2); ipecacuanha (p.1562·3); menthol (p.2340·1).
Coughs and cold symptoms.

Hill's Balsam Nasal Congestion Pastilles *LPC, UK.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).
Nasal congestion.

Hima-Pasta *Mundipharma, Switz.*
Zinc sulfate (p.1999·2); zinc oxide (p.1621·2).
Herpes labialis.

Himcolin *Himalaya, Rus.*
Celastrus paniculatus; hibiscus abelmoschus; prunus dulcis; vitex negundo; cotton root bark; pistacia vera; nutmeg (p.2355·2); mace (p.2336·1); syzygium aromaticum; cinnamon (p.2283·1).
Erectile dysfunction.

Himega *Sigma, Austral.†; Sigma, Hong Kong†.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Dietary supplement.

Himelan *Soria Natural, Spain†.*
Fennel (p.2302·3); burnet saxifrage (p.2270·3); angelica (p.2258·1); melissa (p.2339·3).
Aerophagia; dyspepsia; meteorism.

Himetin *Dong, Singapore.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer.

Himox *Westmont, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hincomox *Teuto, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hingfong-Essenz Hofmanns *Hofmann & Sommer, Ger.*
Valerian (p.2410·1); peppermint oil (p.1761·2); rosemary oil (p.2381·3); camphor (p.2273·2).
Circulatory disorders; nervous disorders.

Hinox *Hebron, Braz.†.*
Multivitamin and mineral preparation (p.1922·1).

Hinuron-E *Icon, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Chronic hepatitis; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Hioariston *Ariston, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Hiocin *Biofarma, Venez.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hioscinol Compuesto *Etifar, Venez.†.*
Hyoscine (p.1733·3); dipyrone (p.49·2).
Muscle spasm; pain.

Hiosinotil *Loren, Mex.†.*
Hyoscine butylbromide (p.1734·1).

Hiosinotil Compuesto *Loren, Mex.†.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Hiospan *Teuto, Braz.*
Hyoscine butylbromide (p.1734·1).
Skeletal muscle spasm.

Hiospan Composto *Teuto, Braz.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Pain; skeletal muscle spasm.

Hiosultrina *Ultra, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hiosultrina-F *Ultra, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Hioxyl *Quinoderm, Irl.; Ferndale, UK†.*
Hydrogen peroxide (p.1647·3).
Pressure sores; skin infections; skin ulcers; wounds.

Hipalen *Braun, Chile.*
Preparation for enteral nutrition (p.1922·1).

Hipax *Baliarda, Arg.*
St John's wort (p.422·3).
Depression.

Hipecor *BMS, Chile.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Hipeksal *Leiras, Fin.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Hipen *Cadila, India.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hipenox *Cadila, India.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Hiper Diet *Support, Braz.†.*
A range of preparations for enteral nutrition (p.1922·1).

Hiperbiotico *Atral, Port.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Hiperbiotico Retard *Atral, Port.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Bacterial infections.

Hipercol *Angelini, Port.*
Citicoline (p.2283·3).
Cerebrovascular disorders; cranial trauma.

Hiperdipina *Tecnimede, Port.*
Nitrendipine (p.1358·2).
Angina pectoris; hypertension.

Hiperex *Eurofarma, Braz.*
St John's wort (p.422·3).
Depression.

Hiperflex *Lafi, Chile; Recalcine, Chile.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Hipericin *Herbarium, Braz.*
St John's wort (p.422·3).
Depression.

Hiperico *Herbarium, Braz.; Natysal, Spain; Uriach, Spain.*
St John's wort (p.422·3).
Depression; sleep disorders; tonic.

Hiperifarma *Farmaervas, Braz.†.*
St John's wort (p.422·3).
Depression.

Hiperikan *Farmasa, Mex.*
St John's wort (p.422·3).
Depression.

Hiperil *Teuto, Braz.†.*
St John's wort (p.422·3).
Depression.

Hiperinat *Natufarma, Arg.*
St John's wort (p.422·3).
Depression.

Hiperlex *Cantabria, Spain.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Hiperlex Plus *Cantabria, Spain.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hiperlipen *Sanofi-Aventis, Venez.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Hipermessel *Biomep, Mex.*
Methyldopa (p.1334·1).
Hypertension.

Hipernolol *Neo Quimica, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Hiperogyn *Madaus, Ital.*
Magnesium (p.1678·3); cimicifuga (p.2282·1); St John's wort (p.422·3).
Insomnia; menopausal disorders; menstrual disorders.

Hiperpril *Cafar, Venez.*
Enalapril maleate (p.1276·1).
Hypertension.

Hipersac *Bunker, Braz.*
St John's wort (p.422·3).
Depression.

Hipersex *Medical, Port.†.*
⊗ Testis; pituitary; fitine; zinc phosphate; strychnine sulfate (p.2393·2); adonis vernalis; boldo (p.1922·1).
Tonic.

Hiperson *Medipharm, Chile.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Hiperson-D *Medipharm, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Hipertal *Samjin, Philipp.; Unimex, Philipp.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Hipertan *Gramon, Arg.*
Enalapril maleate (p.1276·1).
Hypertension.

Hipertene *Bial, Spain.*
Imidapril hydrochloride (p.1313·3).
Hypertension.

Hipertenol *Sanofi Synthelabo, Port.†.*
Nitrendipine (p.1358·2).

Hipertensal *Finadiet, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Hipertensal Combi *Finadiet, Arg.*
Tablets, amlodipine besilate (p.1214·1); tablets, atorvastatin calcium (p.1218·3).
Angina pectoris; hypercholesterolaemia; hypertension.

Hipertex *Rayere, Mex.*
Captopril (p.1239·2).
Diabetic neuropathy; heart failure; hypertension; myocardial infarction.

Hipertil
Note.This name is used for preparations of different composition.
Farmalab, Braz.
Delapril hydrochloride (p.1256·2); manidipine hydrochloride (p.1330·2).
Hypertension.

Normal, Port.
Captopril (p.1239·2).
Diabetic nephropathy; diabetic retinopathy; heart failure; hypertension; myocardial infarction.

Hipertin *Luper, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Hiperton *Grin, Mex.*
Sodium chloride (p.1686·1).
Corneal oedema.

Hipfix *SNBTS, UK†.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Hipnazolam *Sigma, Braz.*
Midazolam hydrochloride (p.1007·3) or midazolam maleate (p.1007·3).
Insomnia; premedication.

Hipnodem *Ivax, Arg.*
Zaleplon (p.1035·3).
Insomnia.

Hipnopento *Gray, Arg.*
Thiopental sodium (p.1795·2).
General anaesthesia; hypnotic.

Hipnosedon *Roche, Gr.*
Flunitrazepam (p.996·2).
Insomnia.

Hipo Femme *Andromaco, Mex.*
Miconazole nitrate (p.541·3).
Vulvovaginal infections.

Hipo Sport *Andromaco, Mex.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal and joint disorders.

Hipoartel *Andromaco, Chile†; Faes, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Hipoartel H *Andromaco, Chile†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Hipoartel Plus *Faes, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Hipobar *Cipan, Port.*
Enalapril maleate (p.1276·1).

Hipocol *Valdecasas, Mex.*
Nicotinic acid (p.1957·3).
Hypercholesterolaemia; pellagra.

Hipoden *Andromaco, Mex.*
Lidocaine hydrochloride (p.1862·3).
Teething pain.

Hipoderme *Teuto, Braz.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Barrier preparation.

Hipodermon *Neo Quimica, Braz.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); boric acid (p.2268·1); zinc oxide (p.1621·2).
Barrier preparation; emollient.

Hipodex *Bunker, Braz.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); neomycin sulfate (p.305·1); benzethonium chloride (p.1630·1).
Barrier preparation; infected skin disorders.

Hipodor *Angelini, Port.†.*
Hexyl nicotinate (p.63·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders; neuritis; soft-tissue disorders.

Hipofagin S *Sigma, Braz.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Hipofisina *Biol, Arg.*
Oxytocin (p.2015·2).
Labour induction; postpartum haemorrhage; postpartum uterine atony.

Hipoge *SMB, Chile.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hipoglos
Note.This name is used for preparations of different composition.
Andromaco, Arg.
Vitamin A (p.1971·2); zinc oxide (p.1621·2).
Nappy rash; nipple care.

Procter & Gamble, Braz.
Vitamin A (p.1971·2); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Skin disorders.

Andromaco, Chile.
Halibut-liver oil (p.1948·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Burns; skin disorders; ulcers; wounds.

Andromaco, Mex.
Vitamin A (p.1971·2); zinc oxide (p.1621·2); allantoin (p.1588·1); boric acid (p.2268·1); talc (p.1615·2).
Skin disorders.

Andromaco, Venez.†.
Boric acid (p.2268·1); zinc oxide (p.1621·2); talc (p.1615·2); vitamin A (p.1971·2); vitamin D (p.1986·1).
Skin disorders.

Hipoglos Cicatrizante *Andromaco, Arg.*
Zinc undecenoate (p.549·3); sodium propionate (p.545·3); diiodohydroxyquinoline (p.832·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Wounds.

Hipoglos Cremoso *Andromaco, Mex.*
Zinc oxide (p.1621·2); vitamin A (p.1971·2); vitamin E (p.1992·2); allantoin (p.1588·1); aloe vera (p.1588·2).
Nappy rash.

Hipoglos con Hidrocortisona
Note.This name is used for preparations of different composition.
Andromaco, Arg.
⊗ Hydrocortisone (p.1535·2); vitamin A (p.1971·2); cod-liver oil (p.1935·2); boric acid (p.2268·1).
Skin disorders.

Andromaco, Venez.†.
⊗ Hydrocortisone (p.1535·2); zinc oxide (p.1621·2); talc (p.1615·2).
Skin disorders.

Hipoglucin *Laboratorios Chile, Chile.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Hipoglucin DA *Laboratorios Chile, Chile.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Hipokinon *Psicofarma, Mex.*
Trihexyphenidyl hydrochloride (p.820·2).
Extrapyramidal disorders; parkinsonism.

Hipokort *Orva, Turk.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hipolixan
Note.This name is used for preparations of different composition.
Bago, Arg.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Pasteur, Chile.
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Hipomeril *Teuto, Braz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Hiposan *Sanval, Braz.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Barrier preparation; skin disorders.

Hiposcler *Basi, Port.†.*
Clofibrate nicotinyl alcohol.

Hiposterol *Laboratorios Chile, Chile.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Hipotears Plus *Novartis, Venez.†.*
Povidone (p.2146·1).
Dry eyes.

Hipoten
Note.This name is used for preparations of different composition.
Klonal, Arg.
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Sanval, Braz.
Captopril (p.1239·2).
Hypertension.

Hipotensil *Medinfar, Port.*
Captopril (p.1239·2).
Diabetic nephropathy; diabetic retinopathy; heart failure; hypertension; myocardial infarction.

Hipotermal *Sanval, Braz.*
Aspirin (p.20·3).
Fever; pain.

Hipotest *Marlop, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Hipotosse *Labesfal, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Hipovastin *Gador, Arg.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Hipover *Biopharm, Chile.*
Repaglinide (p.457·2).
Diabetes mellitus.

Hi-Po-Vites *Hudson, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Hippophan *Weleda, Fr.†.*
Sea buckthorn (p.2384·2).
Tonic.

Hippramine *3M, S.Afr.†.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Hippuran
Note.This name is used for preparations of different composition.
Mallinckrodt, Cz.
Iodine-123 (p.2054·2) or iodine-131 (p.2054·3) as sodium iodohippurate.
Radionuclide imaging of the kidneys.

Mallinckrodt, Neth.
Iodine-123 (p.2054·2) as sodium iodohippurate.
Radionuclide investigation of renal function.

Hippurin *Yeni, Turk.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Hipres
Note.This name is used for preparations of different composition.
KRKA, Cz.
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Cipla, India.
⊗ Atenolol (p.1217·3).
Hypertension.

Hipres-D *Cipla, India.*
⊗ Atenolol (p.1217·3); hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Hiprex *3M, Austral.; Sanova, Austria; 3M, Belg.†; 3M, Canad.; 3M, Fin.; 3M, Irl.†; 3M, Israel; 3M, NZ; 3M, Norw.; 3M, Philipp.; 3M, Swed.; 3M, UK; Sanofi-Aventis, USA.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Hipten *Farmorcore, Port.†.*
Enalapril maleate (p.1276·1).

Hiremon *Demo, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Hirox *Vargas, Venez.*
Heparin sodium (p.1301·2).
Phlebitis.

Hirtonin *Takeda, Jpn.*
Protirelin tartrate (p.2176·2).
Prolonged disturbance of consciousness; spinocerebellar degeneration.

Hirucreme *Bayer, Fr.*
Hirudin (p.1305·3).
Peripheral vascular disorders.

Hirudex *Pharmafar, Ital.†.*
Leech extract (p.1305·3); esculoside (p.2248·2).
Bruises; inflammation; oedema; phlebitis; varices.

Hirudoid *Ivax, Arg.; Sankyo, Austral.; Sankyo, Austria; Will-Pharma, Belg.; Sankyo, Braz.; Silesia, Chile; Stada, Cz.; Sankyo, Denm.; Sankyo, Fin.; Sankyo, Ger.; Medinova, Hong Kong; Sankyo, Hung.; CFL, India; Medinova, Indon.; Sankyo, Ital.; Wilson, NZ; Will-Pharma, Neth.; Sankyo, Norw.; Medinova, Philipp.; Sankyo, Pol.; Ciclum, Port.; Medinova, Singapore; Sankyo, Spain; Selena, Swed.; Medinova, Switz.; Medinova, Thai.; Santa, Turk.; Genus, UK; Sankyo, Venez.*
A heparinoid (p.1305·2).
Bruising; burns; haematoma; haemorrhoids; ichthyosis; inflammation; oedema; phlebitis; prevention of extravasation during parenteral administration; scars; soft-tissue injury; sunburn; thrombophlebitis; variceal ulcers; venous insufficiency; wounds.

Hirzia *Wander, Port.†.*
Lumiracoxib (p.78·1).
Osteoarthritis of the knee.

Hiscifed *Greater Pharma, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms; hypersensitivity reactions; nasal congestion; otitis media; rhinitis.

Hiscolgen *Greater Pharma, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Hisdane *Duopharma, Hong Kong†.*
Terfenadine (p.590·3).
Allergic rhinitis.

Hisdec *Essenpharma, Philipp.*
Brompheniramine maleate (p.569·2); phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Hisfedin *Wolff, Ger.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Hislorex *Konimex, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Hismanal *Janssen-Cilag, Cz.†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Hispadol *Farmaceutica H, Mex.*
Haloperidol (p.1000·2).
Movement disorders; psychoses.

Hispatrel *Farmaceutica H, Mex.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Hispen *Genesis, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Hisplenil *Biotech, Venez.†.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Hisplex *Biotenk, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions; urticaria.

Hisracon *Condrugs, Thai.*
Loratadine (p.583·3).
Allergic skin disorders; asthma; hay fever.

Hista *Pharmasant, Thai.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Skin irritation.

Hista-Bloc *Intas, Philipp.; Standard, Philipp.*
Famotidine (p.1730·1).
Dyspepsia; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Histac *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatitis; peptic ulcer; short bowel syndrome; Zollinger-Ellison syndrome.

Histacet *Medreich, Hong Kong.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Histaclar *Gerard, Irl.*
Loratadine (p.583·3).
Allergic rhinitis; idiopathic chronic urticaria.

Histacol DM *Breckenridge, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Histacon *Aspen, S.Afr.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Allergic rhinitis; cold symptoms; sinusitis.

Histacort
Note.This name is used for preparations of different composition.
BioFemme, Philipp.
Cream: ⊗ Prednisolone (p.1540·3).
Skin disorders.

BioFemme, Philipp.
Tablets: ⊗ Chlorphenamine maleate (p.571·3); prednisolone (p.1540·3).
Skin disorders.

Histacyl Compositum *Streuli, Switz.†.*
Diphenhydramine hydrochloride (p.577·2); mepyramine maleate (p.585·2).
Hypersensitivity reactions.

Histacyl Cutane N *Streuli, Switz.*
Diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); menthol (p.2340·1).
Skin disorders.

Histacylettes *Streuli, Switz.†.*
Diphenhydramine hydrochloride (p.577·2); mepyramine hydrochloride (p.585·2); caffeine (p.1116·3).
Hypersensitivity reactions.

Histadestal *Bioimmun, Ger.*
A normal immunoglobulin (p.2225·3); histamine hydrochloride (p.2319·2).
Hypersensitivity reactions.

Histadex *Vitamed, Israel.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine hydrochloride (p.1571·2).
Hypersensitivity reactions; respiratory-tract congestion.

Histadin *Uniao Quimica, Braz.; Azevedos, Port.; Nobel, Turk.*
Loratadine (p.583·3).
Allergic rhinitis; hypersensitivity reactions; urticaria.

Histadin D *Uniao Quimica, Braz.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Histadryl
Note. This name is used for preparations of different composition.
Parggon, Mex.
Syrup: Diphenhydramine (p.577·1).
Hypersensitivity.

Parggon, Mex.
Tablets: Chlorphenamine (p.572·2).
Hypersensitivity.

Histafed *Trima, Israel.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Hypersensitivity reactions; respiratory-tract congestion.

Histafed Comp *Trima, Israel.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs; upper respiratory-tract infections.

Histafed Expectorant *Trima, Israel.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Histafen
Note. This name is used for preparations of different composition.
Xepa-Soul Pattinson, Hong Kong.
Terfenadine (p.590·3).
Allergic rhinitis; allergic skin reactions.

Douglas, NZ.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Histafilin *Estedi, Spain.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Histafren *Unipharma, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Histagesic Modified *Jones, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Histaglobin *Sidus, Arg.; Germania, Austria; Biobasal, Cz.†; Mirren, S.Afr.*
A normal immunoglobulin (p.2225·3); histamine hydrochloride (p.2319·2).
Hypersensitivity reactions.

Histaglobulin *Serum Institute, India.*
A normal immunoglobulin (p.2225·3); histamine hydrochloride (p.2319·2).
Allergic skin disorders; asthma; migraine.

Histaglobulina *Biomed Lublin, Pol.*
Normal immunoglobulin (p.2225·3); histamine hydrochloride (p.2319·2).
Hypersensitivity reactions.

Histagrip para adultos *Calox, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine (p.572·2).
Influenza symptoms.

Histagrip pediatrico *Calox, Venez.*
Paracetamol (p.108·1); chlorphenamine (p.572·2).
Influenza symptoms.

Histak *Ranbaxy, S.Afr.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Histalen *Andromaco, Chile.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Histalen D *Andromaco, Chile.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Histaler *Duncan, Arg.*
Diphenhydramine (p.577·1).
Hypersensitivity reactions; sedative; vomiting.

Histalet *Numark, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Histalet X *Numark, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Histalgan Balsamo *Silva, Venez.†.*
Histamine (p.2319·2).
Diagnostic agent.

Histalgane *Spirig, Switz.*
Nonivamide (p.96·2); benzyl nicotinate (p.28·1); glycol salicylate (p.62·3); dimethyl sulfoxide (p.2022·1).
Musculoskeletal, joint, and peri-articular pain.

Histalgane mite *Spirig, Switz.*
Glycol salicylate (p.62·3); dimethyl sulfoxide (p.2022·1).
Musculoskeletal, joint, and peri-articular pain.

Histalino *Arlex, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Histalix
Note. This name is used for preparations of different composition.
Roche Consumer, S.Afr.†.
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2).
Coughs; nasal congestion; rhinitis.

Wallace Mfg Chem., UK.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Histaloc *Julphar, UAE.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity; motion sickness.

Histalong *Biofarma, Venez.†.*
Astemizole (p.567·2).
Allergic rhinitis; allergic skin disorders; pruritus; sinusitis; urticaria.

Histalor *Reddy, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Histamed
Note. This name is used for preparations of different composition.
Cimed, Braz.
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).

Premier, S.Afr.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2); benzocaine (p.1854·1).
Skin irritation.

Histamed Compound *Adcock Ingram, S.Afr.*
Chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3); salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Histamin *Neo Quimica, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Histamino Corteroid L *Montpellier, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Hypersensitivity reactions.

Histamix *Hebron, Braz.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Histan *Siam Bheasach, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions.

Histantil *Pharmascience, Canad.*
Promethazine hydrochloride (p.588·2).
Antihistamine.

Histaoph *Seng, Thai.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic eye disorders; conjunctivitis.

Histapan *Sanbe, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders.

Histaplus *Pasteur, Chile†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Histaril *Aldril, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Histaritin *Medikon, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Histaser *Serral, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Histasona *Valmor, Venez.†.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Histastop *Pyridam, Indon.*
Terfenadine (p.590·3).
Allergic disorders.

Histatab *Pharmasant, Thai.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Histatab D *Breckenridge, USA.*
Dexchlorpheniramine maleate (p.572·1); hyoscine methonitrate (p.1734·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Histatab Plus *Century, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Histatapp *Pharmasant, Thai.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Histatec *Streuli, Switz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Histatex *Medix, Mex.†.*
Pheniramine (p.587·2).
Hypersensitivity.

Hista-tussin *Pharmasant, Thai.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; nasal congestion.

Hista-Vent DA *Ethex, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).

Histaverin *Estedi, Spain.*
Codeine phosphate (p.37·2).
Cough.

Histax *Recalcine, Chile.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Histaxin *Viatris, Austria.*
Diphenhydramine hydrochloride (p.577·2).
Allergic skin disorders.

Histazine
Trima, Hong Kong.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Trima, Israel.
Cetirizine (p.571·1).
Allergic rhinitis.

Histec *Orion, Fin.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Histek *Helsinn Birex, Irl.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Histenol Cold *Zee, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Histenol-Forte *Zee, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Histergan *Norma, UK.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Histex *Teamm, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Histex CT *Teamm, USA.*
Carbinoxamine maleate (p.570·2).
Hypersensitivity reactions.

Histex I/E *Teamm, USA.*
Carbinoxamine maleate (p.570·2).
Allergic rhinitis.

Histex HC *Teamm, USA.*
Pseudoephedrine hydrochloride (p.1571·2); hydrocodone tartrate (p.63·1); carbinoxamine hydrochloride (p.570·2) or carbinoxamine maleate (p.570·2).
Coughs; respiratory-tract congestion; rhinitis.

Histex PD *Teamm, USA.*
Carbinoxamine (p.570·2).
Allergic rhinitis.

Histex SR *Teamm, USA.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Allergic rhinitis; cold symptoms; sinusitis.

Histiacil G *Sanofi Synthelabo, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Histiacil NF *Sanofi Synthelabo, Mex.*
Dextromethorphan hydrobromide (p.1555·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Histiacil T *Sanofi Synthelabo, Mex.*
Chlorphenamine (p.572·2); paracetamol (p.108·1); pseudoephedrine (p.1571·2).

Histiacil Tex *Sanofi Synthelabo, Mex.*
Chlorphenamine (p.572·2); paracetamol (p.108·1); pseudoephedrine (p.1571·2).

Histica *M & H, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Histidanol *Geminis, Arg.†.*
Boric acid (p.2268·1); bismuth salicylate (p.1711·1); diphenhydramine (p.577·1); resorcinol (p.1612·1).
Skin disorders.

Histimed *3DDD, Belg.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity disorders.

Histimerck *Generics, Pol.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Histimet *Janssen-Cilag, Arg.*
Levocabastine (p.583·1).
Allergic conjunctivitis; allergic rhinitis.

Histin *Kenyaku, Thai.*
Carbinoxamine maleate (p.570·2).
Allergic rhinitis; allergic skin disorders.

Histina *Solara, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Histinex D *Ethex, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Histinex HC *Ethex, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs.

Histinex PV *Ethex, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cough and cold symptoms.

Histoacryl *Braun, UK.*
Enbucrilate (p.2290·2).
Tissue adhesive for closure of minor wounds.

Histodil *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Cimetidine (p.1716·2).
Acid aspiration; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Histodor
Note. This name is used for preparations of different composition.
Aspen, S.Afr.
Cream: Mepyramine maleate (p.585·2); diphenhydramine hydrochloride (p.577·2).
Insect bites; skin disorders.

Aspen, S.Afr.
Tablets: Mepyramine maleate (p.585·2); promethazine hydrochloride (p.588·2); caffeine (p.1116·3).
Hypersensitivity reactions.

Histodor Expectorant *Aspen, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Histodryl
Note. This name is used for preparations of different composition.
Biolab, Malaysia†.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Bronchitis; cold symptoms; coughs.

Biolab, Thai.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cold symptoms; coughs.

Histo-Fluine P *Richard, Fr.*
Aesculus (p.2248·2); hamamelis (p.2318·2); shepherd's purse (p.2386·2); pulsatilla (p.2376·3); esculoside (p.2248·2).
Peripheral vascular disorders.

Histofreezer
Note. This name is used for preparations of different composition.
Hamilton, Austral.†; koGen, UK.
Dimethyl ether (p.1689·2); propane (p.1691·3); isobutane (p.1690·1).
Warts.

Braun, Fr.†.
Dimethyl ether (p.1689·2); propane (p.1691·3).
Warts.

Histogenol *Biofarma, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Histol *Julphar, UAE.*
Pheniramine maleate (p.587·3).
Hypersensitivity.

Histol Exp *Julphar, UAE.*
Pheniramine maleate (p.587·3); ammonium chloride (p.1551·3).
Cough.

Histolyn-CYL *ALK, USA.*
Histoplasmin (p.2319·3).
Diagnostic test.

Histop *Salvat, Spain.*
Simvastatin (p.1390·2).
Atherosclerosis; hyperlipidaemias.

Histopen *Bernabo, Arg.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Histophtal *Metochem, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2); antazoline hydrochloride (p.567·1).
Eye disorders.

Histor-D *Roberts, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Histor-D Timecelles *Roberts, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

Histox *Mavi, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Histrine *Ferron, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Histussin D *Sanofi Winthrop, USA†.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract congestion.

Histussin HC *Victory, USA.*
Dexbrompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); hydrocodone tartrate (p.63·1).

Formerly contained chlorphenamine maleate, phenylephrine hydrochloride, and hydrocodone tartrate.
Coughs and cold symptoms.

Hitocobamin *Hishiyama, Thai.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Hitrizin *Deva, Turk.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Hivalase *Atral, Port.*
Zidovudine (p.913·3).
HIV infection.

Hi-Vegi-Lip *Freeda, USA.*
Pancreatin (p.2360·1); pancrelipase (p.2360·1).
Deficiency of digestive enzymes.

Hivent *Euro-Med, Indon.; Euro-Med, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Hivernum *Arkopharma, Fr.*
Homoeopathic preparation.
Formerly known as Formule de l'Abbé Chaupitre no 5.

Hives *Hylands, Canad.*
Homoeopathic preparation.

Hivid *Roche, Arg.†; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.†; Roche, Canad.; Roche, Chile†; Roche, Cz.†; Roche, Denm.†; Roche, Fin.; Roche, Fr.†; Roche, Ger.; Roche, Gr.; Roche, Hong Kong†; Roche, Irl.†; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, Neth.; Roche, Port.†; Roche, S.Afr.†; Roche, Singapore†; Roche, Spain; Roche, Swed.†; Roche, Switz.†; Roche, Thai.; Roche, Turk.; Roche, UK†; Roche, USA†; Roche, Venez.*
Zalcitabine (p.912·3).
HIV infection.

Hivirux *Labinca, Arg.†.*
Lamivudine (p.895·1).
HIV infection.

Hivirux Complex *Labinca, Arg.†.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Hivit *Behrens, Venez.*
Ginseng (p.2312·1); vitamins; minerals (p.1922·1).
Tonic.

Hivita *Mega Vitamin, Austral.†.*
A range of multivitamin and mineral preparations (p.1922·1).

Hivita Childvita *Mega Vitamin, Austral.†.*
Multivitamin and mineral preparation with enzymes (p.1922·1).

Hivita Liquivita *Mega Vitamin, Austral.†.*
Multivitamin and mineral preparation with plant extracts (p.1922·1).

Hivotex *Kleva, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Hixizine *Theraskin, Braz.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions.

Hizaar *MSD, Ital.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Hizest *Ivax, Pol.†.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Hizin *Unichem, Singapore; Ranbaxy, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions; nausea and vomiting; pruritus.

Hjerdyl *Sandoz, Denm.*
Aspirin (p.20·3).
Ischaemic heart disease.

Hjertemagnyl *Nycomed, Denm.*
Aspirin (p.20·3).
Ischaemic heart disease.

Hloh *Kneipp, Cz.*
Crataegus (p.2289·1).
Cardiac disorders; hypertension.

HMG *Farma Lepori, Spain.*
⊗ Menotrophin (p.2109·3).
Female infertility; male infertility.

HMG Ferring *Ferring, Arg.*
⊗ Menotrophin (p.2109·3).
Formerly known as HMG Massone.
Male and female infertility.

H-Mide *LBS, Thai.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

HM-PAO Kit *Rez, Cz.*
Technetium-99m (p.2055·3) exametazime.
Radionuclide imaging of the brain.

HMS *Allergan, Austral.†; Allergan, USA†.*
⊗ Medrysone (p.1537·3).
Inflammatory eye disorders.

HN 25 *Milupa, Fr.; Milupa, Irl.†; Milupa, Port.*
Infant feed (p.1922·1).
Diarrhoea; gastro-enteritis in infants and children.

HN RL *Milupa, Fr.†.*
Lactose-free infant feed (p.1922·1).
Diarrhoea.

Hobaticam *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Hobatolex *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Hobatstress *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Hochu-ekki-to *Tsumura, Jpn.*
Astragalus root; atractylodes lancea rhizome; ginseng; angelica acutiloba root; bupleurum root; jujube; citrus unshiu peel; liquorice; cimicifuga rhizome; ginger.
Traditional Kampo medicine.

Hocimin *Durascan, Denm.†.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hodernal *Rottapharm, Spain.*
Liquid paraffin (p.2030·3).
Constipation.

Hoebedic *Hoe, Philipp.*
⊗ Fusidic acid (p.279·3); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Hoemal *Hoe, Malaysia.*
Paracetamol (p.108·1).
Fever; pain.

Hoepixin Bad N *Hoernecke, Ger.†.*
Coal tar (p.1616·2).
Bath additive; pruritic skin disorders.

Hoevenol *Hoernecke, Ger.*
Capsules: Aesculus (p.2248·2).
Soft-tissue injury; venous insufficiency.

Hofcomant
Kolassa, Austria.
Amantadine sulfate (p.793·1).
Drug-induced extrapyramidal disorders; herpes zoster; parkinsonism.

Sevens, Gr.†.
Amantadine hydrochloride (p.792·3).
Parkinsonism.

Hoffmannstropfen *Hofmann & Sommer, Ger.*
Ether; alcohol.
Tonic.

Hoffmans Druppels *Lennon, S.Afr.*
Anaesthetic ether (p.1783·2).
Colic; flatulence.

Hoggar Balance *Stada, Ger.*
Passion flower (p.2363·2).
Nervous disorders.

Hoggar N *Stada, Cz.†.*
Doxylamine succinate (p.578·2).
Sleep disorders.

Hoggar Night *Stada, Ger.*
Doxylamine succinate (p.578·2).
Formerly known as Hoggar N.
Sleep disorders.

Hokunalin *Abbott, Jpn.*
⊗ Tulobuterol (p.1150·1).
Obstructive airways disease.

Holadren *Laboratorios Chile, Chile.*
Alendronate sodium (p.1088·1).
Bone metastases; hypercalcaemia; osteoporosis; Paget's disease of bone.

Hold DM *Ascher, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Holetar *KRKA, Cz.; KRKA, Rus.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Holfungin *Hollborn, Ger.†.*
Clotrimazole (p.530·1).
Fungal and bacterial skin infections.

Holgyeme *Effik, Fr.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Acne in women.

Holisten *Demo, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Holofusine *Braun, Switz.*
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Holomagnesio *Phoenix, Arg.*
Magnesium citrate (p.1743·2).
Asthenia; dystonias; magnesium deficiency.

Holomagnesio Antioxidante *Phoenix, Arg.*
Magnesium lactate; vitamin E (p.1922·1).

Holomagnesio B6 *Phoenix, Arg.*
Magnesium citrate (p.1743·2); pyridoxine hydrochloride (p.1978·2).
Atherosclerosis; muscular disorders.

Holomagnesio Ginseng *Phoenix, Arg.†.*
Magnesium lactate; ginseng (p.1922·1).
Tonic.

Holomagnesio Vital *Phoenix, Arg.*
⊗ Ginseng (p.2312·1); arginine N-acetylasparaginate (p.1928·3); magnesium carbonate; magnesium stearate (p.1922·1).
Tonic.

Holoxan *Kampel Martian, Arg.†; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Chile; Baxter, Cz.; Baxter, Denm.†; Baxter, Fin.; Baxter Oncology, Fr.; Baxter Oncology, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Indon.; Baxter, Ital.; Baxter Oncology, Malaysia†; Baxter, NZ; Baxter, Neth.; Baxter Oncology, Norw.; Baxter, Philipp.; Baxter Oncology, Pol.; Baxter, Port.; Aventis, S.Afr.; Baxter Oncology, Singapore; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Holoxan Uromitexan *German Remedies, India.*
Ifosfamide (p.731·3); mesna (p.1449·2).
Malignant neoplasms.

Holoxane *Asta Oncologia, Braz.*
Ifosfamide (p.731·3).
Malignant neoplasms.

HOM *Nutricia-Bago, Arg.*
Food for special diets (p.1922·1).
Homocystinuria.

Homa *Upha, Malaysia†.*
Homatropine hydrobromide (p.1881·3).
Production of mydriasis.

Homasedin *Medifarma, Mex.†.*
Homatropine methylbromide (p.1881·3).

Homatrop *Llorens, Spain.*
Homatropine hydrobromide (p.1881·3).
Production of mydriasis and cycloplegia; uveitis.

Homeoaftyl *Boiron, Fr.*
Homoeopathic preparation.

Homeocare *Timm, Neth.*
A range of homoeopathic preparations.

Homeocoksinum *Homeocan, Canad.*
Homoeopathic preparation.

Homeodent *Boiron, Canad.†; Boiron, Port.*
Homoeopathic preparation.

Homeodose *Dolisos, Fr.; Dolisos, Canad.†.*
A range of homoeopathic preparations.

Homeofortil *Dolisos, Fr.*
Homoeopathic preparation.

Homeofortin III *Hochstetter, Chile†.*
Phosphoric acid (p.2367·1); avena (p.2262·1); strychnos ignatii (p.2355·3).
Depression.

Homeogene 9 *Boiron, Cz.; Boiron, Fr.; Boiron, Neth.; Boiron, Port.*
Homoeopathic preparation.

Homeogene 46 *Boiron, Canad.; Boiron, Fr.*
Homoeopathic preparation.

Homeogrippe *Boiron, Fr.*
Homoeopathic preparation.

Homeomunil *Dolisos, Fr.†.*
Homoeopathic preparation.

Homeoplasmina *Hochstetter, Chile†.*
Boric acid (p.2268·1); pokeroot (p.2370·1); calendula (p.2273·1).

Homeoplasmine
Note. This name is used for preparations of different composition.
Boiron, Fr.
Calendula (p.2273·1); pokeroot (p.2370·1); bryonia (p.2269·3); Siam benzoin (p.2386·2); boric acid (p.2268·1).
Skin irritation.

Boiron, Port.
Homoeopathic preparation.

Homeoptic *Boiron, Fr.*
Homoeopathic preparation.

Homeovox
Note. This name is used for preparations of different composition.
Boiron, Canad.; Boiron, Neth.; Boiron, Port.
Homoeopathic preparation.

Boiron, Cz.
Aconitum napellus (p.2246·1); arum triphyllum; ferri phosphas (p.1950·3); calendula officinalis (p.2273·1); euspongia officinalis; belladonna (p.2263·3); hydrargyri aminochloridum (p.1604·3); calcii sulfidum (p.1614·3); kalii dichromas; populus candicans (p.2371·1); bryonia (p.2269·3).
Homeopathic preparation.

Hominex *Ross, USA.*
A range of methionine-free preparations for enteral nutrition including an infant feed (p.1922·1).
Vitamin B -nonresponsive homocystinuria or hypermethioninaemia.

Homocalmefyba *Northia, Arg.*
Piroxicam (p.117·3).
Inflammation.

Homocisteon Compuesto *Purissimus, Arg.*
Amylase (p.2256·3); papain (p.2362·3); pancrelipase (p.2360·1); cysteine; vitamin B substances.
Gastrointestinal disorders; pancreatic insufficiency.

Homoclomin *Eisai, Hong Kong; Eisai, Indon.; Eisai, Jpn; Eisai, Thai.*
Homochlorcyclizine hydrochloride (p.581·1).
Allergic rhinitis; pruritus; urticaria.

Homoderma *Brauer, Austral.*
Homoeopathic preparation.

Homogrin *Grin, Mex.*
Homatropine hydrobromide (p.1881·3).
Production of mydriasis.

Homopafen *Bioresearch, Mex.†.*
Propafenone (p.1380·2).
Arrhythmias.

Homopan *Collins, Mex.†.*
Multivitamin preparation (p.1922·1).

Homosismin *Pharmavite, Canad.†.*
Multivitamin preparation with selenium (p.1922·1).

Homoxid *Anglo-French Drugs, India.*
Vitamin preparation with selenium (p.1922·1).

Homtamin-G Plus *Korea United, Philipp.; Pharmatrix, Philipp.*
Vitamins; minerals; ginseng (p.2312·1); aloe; lecithin (p.1922·1).
Tonic.

Honey & Molasses *Lane, UK.*
Ipecacuanha liquid extract (p.1562·3); marrubium (p.1564·1); squill vinegar (p.1573·1); capsicum (p.2276·2); peppermint oil (p.1761·2); tolu solution; honey (p.1948·2); molasses (p.1969·3); glycerol (p.2314·2); liquorice (p.1740·3); anise oil (p.2258·2).
Coughs.

Honeycold *Wyeth Consumer, Ital.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Honeyflu *Wyeth Consumer, Ital.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2).
Cough; fever.

Honeygola *Wyeth Consumer, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth infections.

Honeytuss *Wyeth Consumer, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Hongal *Ahimsa, Arg.*
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Fungal skin infections.

Hongosan *Medea, Spain.*
⊗ Acedoben (p.2244·2); aluminium chlorohydrate (p.1588·3); cetrimonium bromide (p.1635·1); dexamethasone (p.1526·1); salicylic acid (p.1612·2).
Fungal skin infections.

Hongoseril *Isdin, Spain.*
Itraconazole (p.536·3).
Fungal infections.

Honguil *Raymos, Arg.*
Tioconazole (p.548·2).
Fungal vaginal infections.

Honguil Plus *Raymos, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Honsa *M & H, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Honvan *Kampel Martian, Arg.†; Baxter, Austria; Baxter, Belg.†; Baxter Oncology, Ger.†; IFET (ΙΦΕΤ), Gr.; Baxter, Hong Kong†; German Remedies, India; Sanfer, Mex.†; Viatris, Neth.†; Baxter, Port.†; Prasfarma, Spain†; Asta Medica, Switz.†.*
Fosfestrol sodium (p.2105·1).
Prostatic cancer.

Honvol *Baxter, Canad.*
Fosfestrol sodium (p.2105·1).
Prostatic cancer.

Honzil *Arlex, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Hopacem *Hommel, Ger.†.*
Mianserin hydrochloride (p.408·1).
Depression.

Hopaq *Hoe, Philipp.*
Fusidic acid (p.279·3).
Skin infections.

Hopecard *Aristo, India.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Hopram
Note. This name is used for preparations of different composition.
Arlex, Mex.
Metoclopramide (p.1747·3).
Nausea and vomiting.

IQFA, Mex.†.
Omeprazole (p.1753·1).
Peptic ulcer.

Hopranolol *Hovid, Hong Kong†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic subaortic stenosis; migraine; phaeochromocytoma; tremor.

Horacort *Ifarm, Pol.*
⊗ Budesonide (p.1520·1).
Asthma.

Horehound and Aniseed Cough Mixture *Potter's, UK.*
⊗ Pleurisy root (p.2370·1); elecampane (p.1558·1); horehound (p.1564·1); skunk cabbage (p.2388·2); lobelia (p.2157·2).
Coughs.

Horestyl *Kleva, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Horex *Pharmacos, Mex.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Horf *YSP, Malaysia.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Hormeel S *Heel, Cz.*
Homoeopathic preparation.

Hormo Hepatico *Iodo Suma, Braz.†.*
Adenosine (p.1202·1); methionine (p.1450·1); betaine hydrochloride (p.2265·2); choline citrate (p.1934·2); inositol (p.2325·2); pyridoxine hydrochloride

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

(p.1978·2); liver extract (p.2337·3); sorbitol (p.1965·1).
Liver disorders.

Hormocervix *Millet Roux, Braz.*
Estriol (p.2101·1).
Vulvovaginal disorders.

Hormodausse *Sandoz, Canad.*
Vitamin B substances; iron (p.1922·1).

Hormodiol *Omega, Arg.*
Estradiol (p.2097·2).
Menopausal disorders.

Hormodose *Farmasa, Braz.*
Estradiol (p.2097·2).
Menopausal disorders.

Hormolax *Hormona, Mex.*
Ispaghula (p.1737·1).
Constipation.

Hormone Multicap *Scherer, Thai.†*
⊗ Methyltestosterone (p.2117·1); ethinylestradiol (p.2101·3); vitamins; rutoside; inositol; methionine; choline bitartrate (p.1922·1).
Nutritional supplement.

Hormonin *Shire, Hong Kong; Amdipharm, UK.*
Estriol (p.2101·1); estradiol (p.2097·2); estrone (p.2101·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Hormoniol *Teuto, Braz.*
Estriol (p.2101·1).
Menopausal disorders.

Hormoral *Silesia, Chile.*
Progesterone (p.2125·1).
Benign breast disorders; menopausal disorders; menstrual disorders.

Hormotrop *Bergamo, Braz.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Hornel *Taisho, Jpn.*
Falecalcitriol (p.1987·1).
Hyperparathyroidism; osteomalacia; rickets.

Horon *Scherer, Thai.†*
⊗ Methyltestosterone (p.2117·1); ethinylestradiol (p.2101·3); vitamins; minerals; inositol; methionine; choline bitartrate (p.1922·1).
Nutritional supplement.

Horseradish Plus *Swiss Bio, Malaysia†.*
Althaea (p.2253·3); eucalyptus oil (p.2301·2); fenugreek (p.2303·3); garlic (p.2309·2); horseradish (p.2320·1); liquorice (p.1740·3).
Upper respiratory-tract congestion.

Horsulin *Terramedic, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Horvilan N *Schoning-Berlin, Ger.*
Turmeric (p.1473·2); peppermint oil (p.1761·2); greater celandine (p.2317·1).
Biliary-tract disorders.

Hosboral *Quimifar, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hosedyl DM *Hovid, Malaysia.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms; cough.

Hosolvan DM *Hovid, Malaysia.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2).
Cough.

Hospasol
Gambro, Neth.; Gambro, Port.
Sodium bicarbonate (p.1673·2).
Haemofiltration.

Gambro, Spain.
Sodium bicarbonate (p.1673·2) (p.1670·3).
Haemodialysis.

Hospidermin *Lysoform, Ger.*
⊗ Alcohol (p.1625·2); potassium thiocyanate; 5-chloro-2-hydroxybenzoic acid.
Skin disinfection.

Hospisept *Lysoform, Ger.*
⊗ Propyl alcohol (p.1660·2); alcohol (p.1625·2).
Hand disinfection; skin disinfection.

Hostacyclin *Sanofi-Aventis, Gr.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Hostacycline *Aventis, India.*
Tetracycline (p.347·1).
Bacterial infections.

Hostan *Hovid, Hong Kong.*
Mefenamic acid (p.80·1).
Musculoskeletal and joint disorders; pain.

Hosterona *Gador, Arg.*
Progesterone (p.2125·1); estradiol hemisuccinate (p.2098·3).
Menstrual disorders.

Hot Coldrex *GSK Consumer, Neth.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Hot Ize *ANB, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2); cineole (p.2282·3); cajuput oil (p.2271·2); peppermint oil (p.1761·2).
Musculoskeletal, joint, and soft-tissue disorders.

Hot Lemon *Prodemdis, Canad.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).

Hot Lemon Cough and Colds Relief DM *Jamp, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).

Hot Lemon Relief *Apotex, Canad.; Jamp, Canad.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).

Hot Lemon Relief for Cough and Cold *Pharmetics, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).

Hot Lemon Relief for Symptoms of Cough, Cold & Flu *Pharmetics, Canad.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).

Hot Thermo *Merck dura, Ger.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; superficial vascular disorders.

Hotemin *Egis, Cz.; Egis, Hong Kong†; EGIS, Hung.; Egis, Pol.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

12 Hour Antihistamine Nasal Decongestant *URL, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

12 Hour Cold *Goldline, USA.*
Pseudoephedrine sulfate (p.1571·2); dexbrompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Hova *Novartis Consumer, Austria; Gebro, Cz.; Gebro, Hung.; Biofarm, Pol.; Gebro, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety disorders; nervous disorders; sleep disorders.

Hova Expectorant *Hovid, Hong Kong†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs; respiratory-tract congestion.

Hovalin *AstraZeneca, Gr.*
Fluvastatin (p.1290·3).
Hypercholesterolaemia.

Hovid Omega-3 *Hovid, Malaysia†.*
Omega-3 fatty acids (p.1362·1).
Dietary supplement.

Hovid Q10 Plus *Hovid, Malaysia.*
Vitamins; ubidecarenone (p.1922·1).

Hovite *Raptakos, India.*
A range of vitamin preparations with or without minerals (p.1922·1).

Hovizol *Hovid, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hox Alpha *Strathmann, Ger.*
Urtica (p.2409·3).
Rheumatic disorders.

HPB *Panalab, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

H-Peran *LBS, Thai.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

HPMC-Ophtal *Winzer, Ger.†.*
Hypromellose (p.2144·2).
Adjunct in ophthalmic surgery.

Hp-Pac *TAP, Canad.*
Capsules, lansoprazole (Prevacid) (p.1739·2); tablets, clarithromycin (Biaxin) (p.248·2); capsules, amoxicillin trihydrate (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Hpvir *Geolab, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

H-R Lubricating Jelly *Wallace, USA.*
Vaginal lubricant.

HRF
Tramedico, Belg.; Intrapharm, Irl.; Wyeth, NZ†; Tramedico, Neth.; Intrapharm, UK.
⊗ Gonadorelin hydrochloride (p.2106·2).
Anovulatory infertility; anterior pituitary function test; cryptorchidism; sterility or delayed puberty due to hypogonadotrophic hypogonadism; test of hypothalamic function.

Akromed, S.Afr.
⊗ Gonadorelin (p.2106·2).
Anovulatory infertility; diagnostic aid.

HRI Calm Life *Jessup, UK.*
Jamaica dogwood (p.2328·1); lupulus (p.2335·2); skullcap (p.2388·2); chamomile (p.2279·3); valerian (p.2410·1).
Irritability; restlessness.

HRI Clear Complexion *Jessup, UK.*
Sarsaparilla (p.2383·3); iris versicolor (p.2327·1); lappa (p.2330·3).
Skin disorders.

HRI Golden Seal Digestive *Jessup, UK.*
Ginger (p.1732·3); myrrh (p.2349·2); hydrastis (p.2321·3); rhubarb (p.1768·3); valerian (p.2410·1).
Dyspepsia; flatulence.

HRI Night *Jessup, UK.*
Valerian (p.2410·1); passion flower (p.2363·2); wild lettuce (p.2415·2); vervain (p.2413·3); lupulus (p.2335·2).
Insomnia.

HRI Water Balance *Jessup, UK.*
Taraxacum (p.2395·1); buchu (p.2269·3); parsley piert (p.2363·2); bearberry (p.2263·3).
Water retention.

H-Tab *Pharmaland, Thai.*
Haloperidol (p.1000·2).
Hypomania; mania; psychoses.

H-Tronin *Aventis, Ger.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

H-Tuss-D *Cypress, USA†.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Huberdoxina *Ferrer, Spain.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Hubergrip
Note.This name is used for preparations of different composition.
ICN, Spain†.
Suppositories: Caffeine (p.1116·3); calcium pantothenate (p.1959·3); citiolone (p.2283·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); vitamin A (p.1971·2).
Influenza and cold symptoms.

Valeant, Spain†.
Tablets: Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); propyphenazone (p.119·3); salicylamide (p.121·2).
Influenza and cold symptoms.

Hubermizol *Eight, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Huberplex *Teofarma, Spain.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety; insomnia; skeletal muscle spasm.

Huile analgesique "Temple of Heaven" contre les maux de tete *Panax, Switz.†.*
Mint oil (p.2345·2); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); thymol (p.1664·3).
Headache.

Huile de Bain Therapeutique *Atlas, Canad.*
Wool fat (p.2033·2); liquid paraffin (p.2030·3).
Skin disorders.

Huile Gomenolee *Gomenol, Fr.*
Niaouli oil (p.2351·3).
Rhinitis.

Huile de millepertuis A. Vogel (huile de St. Jean) *Bioforce, Switz.*
St John's wort (p.422·3); sunflower oil (p.1970·3).
Superficial burns and wounds.

Huile Po-Ho A. Vogel *Bioforce, Switz.*
Peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); juniper oil (p.2328·3); caraway oil (p.2277·1); fennel oil (p.2303·1).
Cold symptoms; headache; muscular tension.

Huma-Atenol *Humanpharma, Hung.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Humacain *Teva, Hung.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Huma-Captoril *Humanpharma, Hung.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Humacarpin *Teva, Hung.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Humacart 3/7 *Lilly, Jpn.*
⊗ A mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Huma-Col-Asa *Teva, Hung.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Huma-Difenac *Humanpharma, Hung.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Huma-Doxylin *Teva, Hung.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Humafactor-8 *Teva, Hung.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemophilia A.

Humafactor-9 *Teva, Hung.*
A factor IX preparation (p.1068·3).
Factor IX deficiency; haemophilia B.

Huma-Folacid *Teva, Hung.*
Folic acid (p.1940·1).
Folic acid deficiency.

Humaglobin *Teva, Hung.; HSPMM, Rus.†.*
A normal immunoglobulin (p.2225·3).
Auto-immune disorders; Guillain-Barré syndrome; hypogammaglobulinaemia; hypoproteinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; juvenile rheumatoid arthritis; Kawasaki disease; passive immunisation.

Humaject 30/70 *Lilly, Belg.†.*
⊗ Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Humaject M3 (30/70) *Lilly, Pol.†.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Humaject NPH *Lilly, Belg.†.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Humaject R *Lilly, Pol.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Humaject Regular *Lilly, Belg.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Humaject S *Lilly, UK†.*
⊗ Injection device containing Humulin S (p.443·2).
Diabetes mellitus.

Humal *Rosch & Handel, Austria.*
Humic acid (p.2389·3); salicylic acid (p.1612·2).
Rheumatism.

Humalac A and C *Teva, Hung.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Humalac B *Teva, Hung.*
Hypromellose (p.2144·2).
Dry eyes.

Humalog *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
⊗ Insulin lispro (p.449·3).
Diabetes mellitus.

Humalog Mix 25 *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Indon.; Lilly, Israel; Lilly, Mex.; Lilly, Norw.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, Venez.*
⊗ Mixture of insulin lispro 25% and protamine insulin lispro 75% (p.449·3).
Diabetes mellitus.

Humalog Mix 25 and 50 *Lilly, Austria; Lilly, Belg.; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Irl.; Lilly, Ital.; Lilly, NZ; Lilly, Neth.; Lilly, Pol.; Lilly, Spain; Lilly, Swed.; Lilly, Turk.; Lilly, UK.*
⊗ Mixtures of insulin lispro 25% and 50% and isophane insulin lispro 75% and 50% respectively (p.449·3).
Diabetes mellitus.

Humalog Mix 75/25 and 50/50 *Lilly, USA.*
⊗ Mixtures of isophane insulin lispro 75% and 50% and insulin lispro 25% and 50% respectively (p.449·3).
Diabetes mellitus.

Humalog Mix25 and Mix50 *Lilly, Hung.*
⊗ Mixtures of insulin lispro 25% and 50% and isophane insulin lispro 75% and 50% respectively (p.449·3).
Diabetes mellitus.

Humalog NPL *Lilly, Cz.; Lilly, Gr.; Lilly, Neth.; Lilly, Spain.*
⊗ Isophane insulin lispro (p.449·3).
Diabetes mellitus.

Humamet *Lilly, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Huma-Metoprol *Humanpharma, Hung.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Humamoxin *Human, Hung.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Human Actrapid *Abbott, India.*
⊗ Neutral insulin injection (human) (p.443·2).
Diabetes mellitus.

Human Insultard *Abbott, India.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Human Mixtard 30 and 50 *Abbott, India.*
⊗ Mixture of neutral insulin injection (human) 30 or 50% and isophane insulin injection (human) 70 or 50%, respectively (p.443·2).
Diabetes mellitus.

Human Monotard *Abbott, India.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humana AR *Humana, Ital.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux; regurgitation.

Humana HA *Humana, Ital.*
Infant feed (p.1922·1).
Food intolerance.

Humana Sinelac *Humana, Ital.*
Infant feed (p.1922·1).
Milk intolerance.

Humana SL *Humana, Pol.*
Infant feed (p.1922·1).
Cows' milk allergy; lactose and sucrose intolerance.

Humana z MCT *Humana, Pol.*
Preparation for enteral nutrition (p.1922·1).

Humanalbin *ZLB, Ger.*
⊗ Albumin (p.1052·1).
Hypovolaemia.

Humanilusin *Cryopharma, Mex.*
⊗ Human insulin (p.443·2).
Diabetes mellitus.

Humapent *Teva, Hung.*
Cyclopentolate hydrochloride (p.1879·3).
Production of cycloplegia and mydriasis.

Huma-Pirocam *Teva, Hung.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders.

Humaplus 30/70 *Lilly, Spain†.*
⊗ Mixtures of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Humaplus NPH *Lilly, Spain†.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Humaplus Regular *Lilly, Spain†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Huma-Prazin *Humanpharma, Hung.†.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Huma-Profen *Teva, Hung.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Huma-Pronol *Teva, Hung.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; essential tremor; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma; tachycardia.

Humaqua *Teva, Hung.*
Water for injections (p.2414·3).

Huma-Ranidine *Humanpharma, Hung.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Huma-Salmol *Humanpharma, Hung.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Huma-Semide *Humanpharma, Hung.†.*
⊗ Furosemide (p.1292·1).
Heart failure; hypertension; liver cirrhosis; oedema.

Huma-Spiroton *Teva, Hung.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; liver cirrhosis; nephrotic syndrome; oedema.

Humate-P *CSL Behring, Canad.; Aventis, USA.*
A factor VIII preparation (p.1067·1).
Haemophilia A; von Willebrand's disease.

Humatin *Pfizer, Austria; Erfa, Canad.; Parke, Davis, Ger.; Pfizer, Ital.; Parke, Davis, Spain; Pfizer, Switz.; Parke, Davis, USA.*
Paromomycin sulfate (p.843·3).
Amoebiasis; dysentery; gastrointestinal bacterial infections; hepatic coma; hepatic encephalopathy; preoperative bowel decontamination; taeniasis.

Humatrope *Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Ital.; Lilly, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore†; Irisfarma, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; idiopathic short stature; Prader-Willi syndrome; short children born small for gestational age; SHOX deficiency; Turner's syndrome.

Humatro-Pen *Aza, Austral.†.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency.

Humavent *WE, USA.*
Guaifenesin (p.1561·3).

Huma-Zolamide *Teva, Hung.*
⊗ Acetazolamide (p.1875·1).
Altitude sickness; epilepsy; glaucoma; oedema.

Humectante *Alcon Cusi, Spain.*
Hypromellose (p.2144·2); sodium chloride (p.1686·1).
Formerly contained methylcellulose and sodium chloride.
Dry eyes in contact lens wearers.

Humectante Bucal *Pharmatrix, Arg.*
Carmellose sodium (p.2142·1); sorbitol (p.1965·1); electrolytes (p.1667·1).
Artificial saliva.

Humedia *Mauermann, Cz.†; Insurrir, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Humegon *Organon, Austral.; Organon, Canad.†; Organon, Cz.†; Organon, Ger.†; Organon, Irl.; Organon, Israel†; Organon, Ital.†; Organon, Mex.†; Organon, Neth.; Organon, Port.†; Donmed, S.Afr.†; Organon, USA.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Humektan *Orion, Fin.*
Moisturiser; vehicle for topical drugs.

Humex
Note. This name is used for preparations of different composition.
Urgo, Belg.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Urgo, Fr.
Adult syrup: Pholcodine (p.1570·2).
Formerly contained ethylmorphine hydrochloride, squill, ipecacuanha, and belladonna.
Coughs.

Urgo, Fr.†.
Lozenges: Ethylmorphine hydrochloride (p.52·2); ipecacuanha (p.1562·3); belladonna (p.2263·3).
Coughs.

Urgo, Fr.
Nasal solution: Benzalkonium chloride (p.1629·1).
Nasal infections.

Urgo, Fr.
Paediatric syrup: Pholcodine (p.1570·2).
Coughs.

Urgo, Fr.
Pastilles: Biclotymol (p.1632·1).
Mouth and throat disorders.

Urgo, Fr.†.
Throat spray: Benzalkonium chloride (p.1629·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Humex Cold *Urgo, Cz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Humex Expectorant
Note. This name is used for preparations of different composition.
Urgo, Fr.
Lozenges: Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Urgo, Fr.
Syrup: Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Humex Mal de Gorge sans sucre *Urgo, Fr.*
Dequalinium chloride (p.1641·3); ascorbic acid (p.1983·3).
Formerly known as Humex Kinaldine.
Mouth and throat disorders.

Humex Nosni *Urgo, Cz.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Humex Pro Deti *Urgo, Cz.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Humex Rhinite Allergique
Note. This name is used for preparations of different composition.
Urgo, Fr.
Day tablets, pseudoephedrine (p.1571·2); night tablets, cetirizine (p.571·1).
Allergic rhinitis.

999908-n4584-yUrgo, Fr.†.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Humex Rhume *Urgo, Fr.*
Tablets (daytime), paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); capsules (evening), paracetamol; chlorphenamine maleate (p.571·3).
Cold symptoms.

Humex Rhume des Foins *Urgo, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Humex Toux Seche Dextromethorphane *Urgo, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly known as Akindex.
Coughs.

Humibid *Carolina, USA.*
Guaifenesin (p.1561·3); sulfogaiacol (p.1573·2).
Formerly contained guaifenesin.
Coughs.

Humibid DM *Carolina, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sulfogaiacol (p.1573·2).
Formerly contained dextromethorphan hydrobromide and guaifenesin.
Coughs.

Humibid Maximum Strength *Adams, USA.*
Guaifenesin (p.1561·3).
Cough.

Humiderm *Szama, Arg.*
Emollient.

Humiderma *Darier, Mex.*
Emollient (Higroplex).
Dry skin disorders.

Huminsulin Basal *Lilly, Austria; Lilly, Ger.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Huminsulin Basal (NPH) *Lilly, Switz.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Huminsulin Long *Lilly, Austria; Lilly, Switz.*
⊗ Insulin zinc suspension (crystalline 70%) (human, prb) (p.443·2).
Diabetes mellitus.

Huminsulin Normal *Lilly, Austria; Lilly, Ger.; Lilly, Switz.*
⊗ Neutral insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Huminsulin Profil II and III *Lilly, Austria.*
⊗ Mixtures of neutral insulin injection (human, prb) 20% and 30% and isophane insulin injection (human, prb) 80% and 70% respectively (p.443·2).
Diabetes mellitus.

Huminsulin Profil III *Lilly, Ger.; Lilly, Switz.*
⊗ Mixture of neutral insulin injection (human, prb) 30% and isophane insulin injection (human, prb) 70% (p.443·2).
Diabetes mellitus.

Huminsulin Ultralong *Lilly, Austria; Lilly, Switz.*
⊗ Insulin zinc suspension (crystalline) (human, prb) (p.443·2).
Diabetes mellitus.

Humira *Abbott, Arg.; Abbott, Austral.; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Adalimumab (p.15·2).
Ankylosing spondylitis; Crohn's disease; juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis.

HuMist Nasal Mist *Scherer, USA.*
Sodium chloride (p.1686·1).
Nasal irritation.

Humoferon *Sigma-Tau, Ital.†.*
Interferon alfa-n1 (p.885·1).
Chronic hepatitis; leukaemias.

Humopin N *Schoning-Berlin, Ger.†.*
Salicylic acid (p.1612·2).
Bath additive; musculoskeletal and joint disorders.

Humorap *Bago, Arg.*
Citalopram hydrobromide (p.385·3).
Depression.

Humorsol *Merck, USA†.*
Demecarium bromide (p.1880·2).
Open-angle glaucoma; strabismus.

Humulin I *Lilly, Irl.; Lilly, Ital.; Lilly, UK.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Humulin 20/80, 30/70 *Lilly, Canad.*
⊗ Mixtures of insulin injection (human, prb) and isophane insulin injection (human, prb) (p.443·2) respectively in the proportions indicated.
Diabetes mellitus.

Humulin 30/70 *Lilly, Austral.; Lilly, Indon.; Lilly, Malaysia; Lilly, S.Afr.; Lilly, Singapore.*
⊗ A mixture of insulin injection (human, prb) 30% and isophane insulin (human, prb) 70% (p.443·2).
Diabetes mellitus.

Humulin 30/70 and 50/50 *Lilly, Ital.*
⊗ Mixtures of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Humulin 70/30 *Lilly, Arg.; Lilly, Braz.; Lilly, Chile†; Lilly, Hong Kong; Lilly, Israel; Lilly, NZ; Lilly, Philipp.; Lilly, Thai.; Lilly, Venez.*
⊗ A mixture of isophane insulin injection (human) 70% and insulin injection (human) 30% (p.443·2).
Diabetes mellitus.

Humulin 70/30, 50/50 *Lilly, USA.*
⊗ Mixture of isophane insulin suspension (human, crb) and insulin injection (human, crb) in the proportions indicated (p.443·2).
Diabetes mellitus.

Humulin 70/30, 80/20 *Lilly, Mex.*
⊗ Mixtures of isophane insulin injection (human) and insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Humulin L *Lilly, Arg.†; Lilly, Austral.†; Lilly, Canad.; Lilly, Chile†; Lilly, Cz.†; Lilly, Hong Kong; Lilly, Hung.†; Lilly, Ital.†; Lilly, Malaysia†; Lilly, Mex.; Lilly, NZ†; Lilly, S.Afr.†; Lilly, Singapore†; Lilly, USA†; Lilly, Venez.†.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humulin Lenta *Lilly, Braz.; Lilly, Port.†.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humulin Lente *Lilly, Gr.; Lilly, Irl.†; Lilly, UK†.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humulin M3 *Lilly, Cz.; Lilly, Hung.; Lilly, Irl.; Lilly, Port.; Lilly, Rus.; Lilly, UK.*
⊗ Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70%, respectively (p.443·2).
Diabetes mellitus.

Humulin M3 (30/70) *Lilly, Pol.*
⊗ A mixture of soluble insulin (human) 30% and isophane insulin 70% (p.443·2).
Diabetes mellitus.

Humulin M 70/30 and 80/20 *Lilly, Turk.*
⊗ Mixtures of isophane insulin injection (human) and insulin injection (human) in th proportions indicated (p.443·2).
Diabetes mellitus.

Humulin M2, M3 *Lilly, Gr.*
⊗ Mixtures of insulin injection (human) 20% and 30% and isophane insulin injection (human) 80% and 70%, respectively (p.443·2).
Diabetes mellitus.

Humulin Mix 30/70 *Lilly, Denm.; Lilly, Swed.*
⊗ Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Humulin N *Lilly, Canad.; Lilly, Chile†; Lilly, Cz.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Israel; Lilly, Malaysia; Lilly, Mex.; Lilly, Pol.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, Turk.; Lilly, USA; Lilly, Venez.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Humulin N (NPH) *Lilly, Philipp.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Humulin NPH *Lilly, Arg.; Lilly, Austral.; Lilly, Braz.; Lilly, Denm.; Lilly, Fin.; Lilly, Gr.; Lilly, NZ; Lilly, Norw.; Lilly, Port.; Lilly, Rus.; Lilly, Swed.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Humulin R *Lilly, Arg.; Lilly, Austral.; Lilly, Canad.; Lilly, Chile†; Lilly, Cz.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Pol.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, Turk.; Lilly, USA; Lilly, Venez.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Humulin R (Regular) *Lilly, Philipp.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Humulin Regular *Lilly, Braz.; Lilly, Denm.; Lilly, Fin.; Lilly, Gr.; Lilly, Port.; Lilly, Rus.; Lilly, Swed.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Humulin S *Lilly, Irl.; Lilly, UK.*
⊗ Insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Humulin U *Lilly, Arg.†; Lilly, Canad.; Lilly, Cz.†; Lilly, Hung.†; Lilly, Israel†; Lilly, Ital.†; Lilly, NZ†.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humulin U Ultralente *Lilly, USA†.*
⊗ Insulin zinc suspension, extended (human, crb) (p.443·2).
Diabetes mellitus.

Humulin UL *Lilly, Austral.†.*
⊗ Insulin zinc suspension (crystalline) (human, prb) (p.443·2).
Diabetes mellitus.

Humulin Ultralenta *Lilly, Port.†.*
⊗ Insulin zinc suspension (crystalline) (human) (p.443·2).
Diabetes mellitus.

Humulin Utralente *Lilly, Gr.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humulin Zn *Lilly, Irl.†; Lilly, UK†.*
⊗ Insulin zinc suspension (human, prb) (p.443·2).
Diabetes mellitus.

Humulina 30:70 *Lilly, Spain.*
⊗ Mixture of insulin injection (human, prb) and isophane insulin injection (human, prb) (p.443·2) respectively in the proportions indicated.
Diabetes mellitus.

Humulina Lenta *Lilly, Spain†.*
⊗ Insulin zinc suspension (crystalline 70%, amorphous 30%) (human) (p.443·2).
Diabetes mellitus.

Humulina NPH *Lilly, Spain.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Humulina Regular *Lilly, Spain.*
⊗ Insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Humulina Ultralenta *Lilly, Spain†.*
⊗ Insulin zinc suspension (human) (p.443·2).
Diabetes mellitus.

Humuline *Lilly, Neth.*
⊗ Neutral insulin injection (human) (p.443·2).
Diabetes mellitus.

Humuline 30/70 *Lilly, Neth.*
⊗ Mixtures of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Humuline 30/70, 50/50 *Lilly, Belg.*
⊗ Mixtures of neutral insulin injection (human, biosynthetic) and isophane insulin injection (human, biosynthetic) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Humuline Long *Lilly, Belg.†.*
⊗ Insulin zinc suspension (30 amorphous, 70% crystalline) (p.443·2).
Diabetes mellitus.

Humuline NPH *Lilly, Belg.; Lilly, Neth.*
⊗ Isophane insulin injection (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Humuline Regular *Lilly, Belg.*
⊗ Neutral insulin injection (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Humuline Ultralong *Lilly, Belg.†.*
⊗ Insulin zinc suspension (crystalline) (human, biosynthetic) (p.443·2).
Diabetes mellitus.

Humulus Compound *Phytomedicine, Austral.*
Lupulus (p.2335·2); valerian (p.2410·1); passion flower (p.2363·2); withania somnifera.
Insomnia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Humutard *Lilly, Fin.†.*
⊗ Insulin zinc suspension (human) (amorphous 30%, crystalline 70%) (p.443·2).
Diabetes mellitus.

Hunperdal *Gedeon Richter, Hung.*
Risperidone (p.1024·2).

Huperloid *Rafarm, Gr.†.*
Codergocrine (p.364·1).
Peripheral vascular disorders.

Hurplex *Alpharma, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Hurricaine *Clarben, Spain; Beutlich, USA.*
Benzocaine (p.1854·1).
Local anaesthesia; mouth pain.

Hustadin *Guardian, Indon.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Hustagil
Note. This name is used for preparations of different composition.
Master, Chile†.
Ointment: Thyme oil (p.2401·2); eterea; pine oil (p.2368·2); eucalyptus oil (p.2301·2) clove oil (p.2285·1).
Respiratory-tract congestion.

Master, Chile†.
Syrup: Thyme (p.2401·1).
Respiratory-tract disorders.

Hustagil Erkaltungsbalsam *Dentinox, Ger.†.*
Thyme oil (p.2401·2); pine silvestris oil (p.2368·2); eucalyptus oil (p.2301·2); clove oil (p.2285·1).
Coughs and associated respiratory-tract disorders.

Hustagil Thymian-Hustensaft *Dentinox, Ger.*
Thyme (p.2401·1).
Coughs and associated respiratory-tract disorders.

Hustagil Thymiantropfen *Dentinox, Ger.*
Thyme (p.2401·1).
Coughs and associated respiratory-tract disorders.

Hustazol *Mitsubishi, Jpn.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Hustazol-C *Takeda, Thai.†.*
⊗ Cloperastine hydrochloride (p.1554·3); sulfogaiacol (p.1573·2); *dl*-methylephedrine hydrochloride (p.1564·3).
Coughs.

Husten ACC *Hexal, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with viscous secretions.

Hustenloser *1A, Austria.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Hustensaft Weleda *Weleda, Austria.*
Herbal and homoeopathic preparation.

Hustenstiller
Note. This name is used for preparations of different composition.
Ratiopharm, Ger.†.
Clobutinol hydrochloride (p.1554·1).
Coughs.

Ratiopharm, Ger.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Hustentabs *Ratiopharm, Ger.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Hustentropfen Nr 24 *Doskar, Austria.*
Homoeopathic preparation.

Husties *Eu Rho, Ger.†.*
Thyme (p.2401·1).
Catarrh; coughs.

Hustosol *Pharmeso, Switz.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Hutrope *Lilly, Arg.; Lilly, Chile.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Hvit *D & M, Chile.*
Biotin (p.1931·3).
Dietary supplement.

HVM *Scherer, Singapore†.*
Multivitamin and mineral preparation (p.1922·1).

Hyabak
Thea, Fr.; Farmila, Ital.; Spectrum, UK..
Sodium hyaluronate (p.2320·1) (p.1622·2).
Contact lens care; contact lens lubricant; dry eyes; eye irritation.

Hya-ject *Ormed, Ger.*
Sodium hyaluronate (p.2320·1).
Joint disorders.

Hyal *LG Life Sciences, Malaysia; Shin Poong, Malaysia.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye procedures; osteoarthritis of the knee; shoulder periarthritis.

Hyalart *TRB, Arg.†; Tropon, Ger.; Faran, Gr.; SPA, Ital.; Grunenthal, Port.; Chiesi, Spain.*
Sodium hyaluronate (p.2320·1).
Joint disorders; osteoarthritis.

Hyalase *Sanofi-Aventis, Austral.; IFET (ΙΦΕΤ), Gr.; CP, Israel; Artex, NZ; Xixia, S.Afr.; CP Pharmaceuticals, UK.*
Hyaluronidase (p.2321·1).
Enhancement of absorption of intramuscular and subcutaneous injections; enhancement of local anaesthesia; extravasation; haematoma; hypodermoclysis; oedema; promote tissue fluid and blood resorption.

Hyalcrom *Biocumed, Arg.*
⊗ Sodium cromoglicate (p.1136·3); naphazoline hydrochloride (p.1565·2); hyaluronic acid (p.2320·1).
Eye disorders.

Hyalcrom NF
Biocumed, Arg.
Ketotifen (p.582·2); hyaluronic acid (p.2320·1).
Eye disorders.

Bausch & Lomb, Mex.
Ketotifen fumarate (p.582·2); sodium hyaluronate (p.2320·1).
Allergic conjunctivitis.

Hyal-Drop *Chauvin, Fr.; Bausch & Lomb, Switz.*
Sodium hyaluronate (p.2320·1) (p.1622·2).
Contact lens lubrication; dry eyes.

Hyalein *Santen, Jpn.*
Sodium hyaluronate (p.2320·1).
Keratoconjunctival disorders.

Hyalgan *Kolassa, Austria; Wolfs, Belg.; Medexus, Canad.; Silesia, Chile; Fidia, Cz.; Nycomed, Denm.; Leiras, Fin.; Expanscience, Fr.; Fidia, Hong Kong; CSC, Hung.; Combiphar, Indon.; Fidia, Indon.; Shire, Irl.; Fidia, Ital.; Fidia, Malaysia; Fidia, Pol.; TRB, Singapore; Bioiberica, Spain; Nycomed, Swed.; Chemedica, Thai.; Fidia, Thai.; Bilim, Turk.; Shire, UK; Sanofi Winthrop, USA; Leti, Venez.*
Sodium hyaluronate (p.2320·1).
Orthopaedic surgery; osteoarthritis and other degenerative joint disorders.

Hyalistil *SIFI, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Hyalix *Roemmers Medihe, Venez.*
Moisturiser.

Hyalofemme *Bivea, Fr.*
Hyaluronic acid (p.2320·1).
Vaginal dryness.

Hyalofill
Convatec, Canad.†.
Hyaluronic acid (p.2320·1).
Wounds.

Convatec, Fr.; Convatec, Port.†; Convatec, UK.
Hyaff (p.2320·2).
Ulcers; wounds.

Hyalogran *Convatec, Fr.*
Sodium alginate (p.2141·1); Hyaff (p.2320·2).
Ulcers; wounds.

Hyalox *Sophia, Mex.*
⊗ Oxymetazoline hydrochloride (p.1567·2); sodium hyaluronate (p.2320·1).
Eye irritation.

Hyalozima *Apsen, Braz.*
Hyaluronidase (p.2321·1).
Enhancement of absorption of intramuscular and subcutaneous injections; reduction of extravasation.

Hyal-System *Merz, Ger.†.*
Sodium hyaluronate (p.2320·1).
Skin regeneration.

Hyalubrix *Tropon, Ger.*
Sodium hyaluronate (p.2320·1).
Synovial fluid replacement.

Hyaludermin *TRB, Braz.*
Sodium hyaluronate (p.2320·1).
Ulcers; wounds.

Hyalugel *Expanscience, Fr.*
Hyaluronic acid (p.2320·1).
Gum inflammation or injury.

Hyaluron *Maigal, Arg.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); boric acid (p.2268·1).
Scalp disorders.

Hyanac *Biocumed, Arg.†.*
Diclofenac sodium (p.44·3); sodium hyaluronate (p.2320·1).
Eye disorders.

Hyanit N *Strathmann, Ger.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Hya-Ophtal *Winzer, Ger.†.*
Sodium hyaluronate (p.2320·1).
Aid in eye surgery.

Hyarhinol *Chauvin, Fr.*
Sodium hyaluronate (p.2320·1); electrolytes.
Nasal dryness.

Hyasa *Sevapharma, Cz.†.*
Hyaluronidase (p.2321·1).
Adjuvant in local anaesthesia; adjuvant to increase absorption and dispersion of drugs; haematoma; oedema; reduction of extravasation.

Hyase *Human, Hung.†.*
Hyaluronidase (p.2321·1).
Enhancement of local anaesthesia injections; haematoma; hypodermoclysis; oedema.

Hyasol *Biocumed, Arg.; Bausch & Lomb, Mex.*
Sodium hyaluronate (p.2320·1).
Dry eyes; eye irritation.

Hyason *Organon, Neth.*
Hyaluronidase (p.2321·1).
Adjunct to local anaesthesia of the eye.

Hyate:C *Porton, Israel; Ipsen, UK; Speywood, USA†.*
A porcine factor VIII:C preparation (p.1067·1).
Haemophilia in patients with antibodies to human factor VIII.

Hybloc *Pacific, NZ.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Hybolin *Hyrex, USA.*
⊗ Nandrolone phenylpropionate (p.2118·3) or nandrolone decanoate (p.2118·2).
Anaemia in renal disease; breast cancer.

Hybridil *Roche, Austria.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Hybutin *Jean-Marie, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Hybutyl *Pharmaland, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hycamptin *GSK, Turk.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer.

Hycamtin *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, USA; GSK, Venez.†.*
Topotecan hydrochloride (p.780·1).
Cervical cancer; ovarian cancer; small-cell lung cancer.

Hycemia *Guardian, Indon.*
Allopurinol (p.552·2).
Gout.

Hyceral *Condrugs, Thai.*
Codergocrine mesilate (p.363·3).
Mental function impairment; peripheral vascular disorders.

Hycet *Xanodyne, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Hychlozide *Pharmasant, Thai.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hycibex *Pharmed, India.*
Vitamin B substances (p.1975·1).
Vitamin B deficiency.

Hycocin *Rekah, Israel.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected eye, ear, and nose disorders.

HycoClear Tuss *Ethex, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Hycodan
Note. This name is used for preparations of different composition.
BMS, Canad.
Hydrocodone tartrate (p.63·1).
Coughs.

Endo, USA.
Hydrocodone tartrate (p.63·1); homatropine methylbromide (p.1881·3).
Coughs.

Hycolloid Ultra Thin *Geritrex, USA.*
Hydrocolloid dressing.
Wounds.

Hycomine *BMS, Canad.*
Hydrocodone tartrate (p.63·1); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3).
Coughs; upper respiratory-tract congestion.

Hycomine Compound *Endo, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); caffeine (p.1116·3).
Coughs and cold symptoms.

Hycomycin *Teva, Israel.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Hycor *Sigma, Austral.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Inflammatory eye disorders.

Hycort *Valeant, Canad.*
⊗ Hydrocortisone (p.1535·2).
Inflammatory diseases of the gastrointestinal tract.

Hycortil *Rotexmedica, Philipp.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Hycortin *Medipharma, Hong Kong†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hycosan *Bausch & Lomb, UK.*
Hyaluronic acid (p.2320·1).
Dry eyes.

HycoSan5 *Pharma Medica, Switz.*
Sodium hyaluronate (p.2320·1) (p.1622·2).
Contact lens lubrication.

Hycotuss *Endo, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Hydab *Dabur, India; Dabur, Philipp.*
Hydroxycarbamide (p.729·1).
Beta-thalassaemia; malignant neoplasms; psoriasis; radiosensitiser; sickle cell disease.

Hydac *Aventis, Denm.†; Sanofi-Aventis, Fin.*
Felodipine (p.1285·3).
Hypertension.

Hydal *Mundipharma, Austria.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Hydantin *Orion, Fin.*
Phenytoin (p.495·2).
Epilepsy.

Hydase *PrimaPharm, USA.*
Hyaluronidase (p.2321·1).
Adjunct in urography; hypodermoclysis; to increase the absorption and dispersion of injected drugs.

Hydeltrasol *MSD, USA†.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Hyderan *Organifar, Venez.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; mental function impairment.

Hyderax *HLB, Arg.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; premedication; pruritus.

Hydergin *Novartis, Austria; Novartis, Fin.; Novartis, Ger.; Novartis, Indon.; Novartis, Swed.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; cervical syndrome; hypertension; mental function impairment; migraine and other vascular headache; shock.

Hydergina *Novartis, Arg.; Novartis, Chile†; Novartis, Ital.; Novartis, Mex.; Novartis, Spain; Novartis, Venez.†.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; hypertension; mental function impairment; migraine and other vascular headache; vascular disorders.

Hydergine *Novartis, Belg.; Novartis, Braz.; SteriMax, Canad.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Israel; Novartis, Malaysia; Novartis, Philipp.; Novartis, Port.; Novartis, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, UK†; Sandoz, USA.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; dementia; hypertension; mental function impairment; migraine and other vascular headache; senile dementia; vascular eye disorders.

Hyderm
Note. This name is used for preparations of different composition.
Taro, Canad.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Labomed, Chile.
⊗ Urea (p.1620·2).
Skin disorders.

Hydex PD *Cypress, USA.*
Hydrocodone tartrate (p.63·1); dexchlorpheniramine maleate (p.572·1); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; coughs; nasal congestion.

Hydiphen *Dresden, Cz.†; Dresden, Ger.†; AWD, Pol.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; nocturnal enuresis; obsessive-compulsive disorder; pain; panic disorder; psychoses; sleep disorders.

Hydoftal *Agepha, Austria.*
⊗ Hydrocortisone (p.1535·2); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Inflammatory eye disorders.

Hydoftal sine neomycino *Agepha, Austria.*
⊗ Hydrocortisone (p.1535·2); hydrocortisone acetate (p.1535·2).
Inflammatory eye disorders.

Hydopa *Alphapharm, Austral.*
Methyldopa (p.1334·1).
Hypertension.

Hydra *Otsuka, Jpn.*
Isoniazid (p.288·1).
Tuberculosis.

Hydra Firm Day *New Vision, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Hydrabak *Farmila, Ital.*
Sodium chloride (p.1686·1) (p.1622·2).
Comfort drops for contact lenses.

Hydrabis *Bioderma, Venez.*
Barrier preparation.

Hydracort *Galderma, Fr.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydracuivre *SVR, Fr.*
Zinc pidolate (p.1614·1); copper pidolate (p.1614·1); sodium pidolate (p.1614·1); allantoin (p.1588·1).
Dry skin; skin irritation.

Hydracur *Lero, Fr.*
Black currant (p.2267·1); taraxacum (p.2395·1); cynorrhodon; hibiscus (p.2319·2).
Diuretic.

Hydraderm *Sigma, Austral.*
Moisturiser.

Hydrafuca *Fuca, Fr.†.*
Pentaerythritol (p.1761·1).
Formerly known as Combeylax.
Constipation.

Hydragel *Bayer, Fr.*
Vaginal lubricant.

Hydragenic *Forder, Arg.†.*
Glycolic acid (p.1598·1); triclosan (Irgasan) (p.1665·2).
Skin hygiene.

Hydralift Day *Avon, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Hydralin
Note.This name is used for preparations of different composition.
Roche Nicholas, Hong Kong.
Sodium perborate (p.1662·1); borax (p.2268·1); sodium bicarbonate (p.1673·2); sodium carbonate anhydrous (p.2389·1).
Genital pruritus.

Bayer, Fr.
Powder for topical solution: Sodium perborate (p.1662·1); borax (p.2268·1); sodium bicarbonate (p.1673·2); sodium carbonate anhydrous (p.2389·1).
Skin cleansing in gynaecological care.

Bayer, Fr.
Soap: Borax (p.2268·1).
Skin cleansing in gynaecological care.

Hydralyte *River Foods, Austral.; Hydration, Singapore.*
Oral rehydration solution (p.1672·2).
Diarrhoea; oral rehydration therapy; vomiting.

Hydramine Cream *Medipharma, Hong Kong†.*
Diphenhydramine hydrochloride (p.577·2).

Hydramine Expectorant *Medipharma, Hong Kong†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold and influenza symptoms; coughs.

Hydramox *Caber, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Hydran
Note.This name is used for preparations of different composition.
Orion, Fin.
Vehicle for topical preparations.

Teva, Israel.
Sodium chloride; anhydrous trisodium citrate; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Hydranorme *Roche-Posay, Braz.; Roche-Posay, Irl.*
Emollient.
Dry skin; psoriasis.

Hydrap-ES *Parmed, USA†.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Hydraphase *Roche-Posay, Braz.*
Emollient.

Hydrapres *Omedir, Arg.; Rubio, Spain.*
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension.

Hydrares *Pharmasant, Thai.*
⊗ Reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hydrasense *Schering, Canad.*
Isotonic desalinated sea water.
Nasal congestion; nasal dryness.

Hydrasor *Novag, Mex.†.*
Oral rehydration therapy (p.1672·2).

Hydrastis Complex *Blackmores, Austral.†.*
Liquorice (p.1740·3); althaea (p.2253·3); chamomile (p.2279·3); hydrastis (p.2321·3); vitamin A acetate (p.1973·1).
Gastrointestinal disorders.

Hydrastis Salbe N *Steigerwald, Ger.*
Homoeopathic preparation.

Hydrate *Hyrex, USA†.*
Dimenhydrinate (p.576·2).
Motion sickness.

Hydrating B5 Gel *Dispolab, Chile.*
Sodium hyaluronate (p.2320·1); pantothenic acid (p.1959·3).
Skin disorders.

Hydratone *Forder, Arg.†.*
Hyaluronic acid (p.2320·1); panthenol (p.2362·1).

Hydrax *Klinger, Braz.†.*
Oral rehydration solution (p.1672·2).

Hydrazide
Note.This name is used for preparations of different composition.
Cipla, India.
⊗ Hydrochlorothiazide (p.1307·3).
Oedema.

Otsuka, Jpn.
Isoniazid (p.288·1).
Tuberculosis.

Hydra-zide
Note. A similar name is used for preparations of different composition (see above).
Par, USA.
⊗ Hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).

Hydrea *BMS, Arg.†; BMS, Austral.; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Denm.; BMS, Fin.; BMS, Fr.; IFET (ΙΦΕΤ), Gr.†; BMS, Hong Kong; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Port.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms; polycythaemia vera; sickle-cell anaemia; thrombocythaemia; thrombocytosis.

Hydrene *Alphapharm, Austral.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hydrex
Note.This name is used for preparations of different composition.
Orion, Fin.
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema.

Adams, Hong Kong; Ecolab, Neth.; Adams, Thai.; Adams, UK.
Chlorhexidine gluconate (p.1635·3).
Hand disinfection; skin disinfection.

Hydrigoz *Guigoz, Fr.*
Maltodextrin; sucrose; sodium chloride; citric acid; potassium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Hydrinate *CCM, Malaysia.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Hydrine
Note.This name is used for preparations of different composition.
BPL-Meizler, Braz.†.
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

TO-Chemicals, Thai.
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; mental function impairment.

Hydrisalic *Pedinol, USA.*
Salicylic acid (p.1612·2).
Hyperkeratotic skin.

Hydrisea *Pedinol, USA.*
Emollient and moisturiser.

Hydrisinol *Pedinol, USA.*
Emollient and moisturiser.

Hydrite *Westmont, Philipp.*
Sodium chloride; sodium bicarbonate; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration.

Hydro 40 *Quinnova, USA.*
⊗ Urea (p.1620·2).
Dry skin.

Hydro Cobex *Pasadena, USA.*
Hydroxocobalamin (p.1980·3).
Schilling test; vitamin B deficiency.

Hydro Cordes *Ichthyol, Ger.*
Allantoin (p.1588·1); dexpanthenol (p.2362·1); ethyl linoleate (p.2308·2).
Skin disorders.

Hydro DP *Cypress, USA.*
Hydrocodone tartrate (p.63·1); diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1).
Coughs; upper respiratory-tract congestion.

Hydro PC *Cypress, USA†.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs; upper respiratory-tract congestion.

Hydroagisten *Agis, Israel.*
⊗ Hydrocortisone acetate (p.1535·2); clotrimazole (p.530·1).
Infected skin disorders.

Hydrocare *Visiontech, Arg.; Allergan, Braz.†; Allergan, USA.*
Prolase (p.1622·2).
Protein remover for soft contact lenses.

Hydrocare Enzymatic Protein Remover *Allergan, Austral.†.*
Papain (p.2362·3) (p.1622·2).
Cleanser for soft and gas permeable contact lenses.

Hydro-Cebral *Ratiopharm, Ger.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Hydrocerin
Note.This name is used for preparations of different composition.
Geritrex, USA.
Cream: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Product basis.

Geritrex, USA.
Lotion: Liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Product basis.

Hydrocerin Plus *Geritrex, USA.*
⊗ Alpha hydroxy; urea (p.1620·2).
Dry skin.

Hydrocet *Carnrick, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Hydrocil Instant *Numark, USA.*
Psyllium hydrophilic mucilloid (p.1737·1).
Constipation.

Hydroclean *Hartmann, Fr.*
Sodium polyacrylate; cellulose (p.2143·1).
Burns; ulcers; wounds.

Hydroclonazone *DB, Fr.*
Tosylchloramide sodium (p.1665·1).
Water purification.

Hydrocobamine *Altana, Neth.*
Hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; vitamin B deficiency.

Hydrocodeinon *Streuli, Switz.*
Hydrocodone hydrochloride (p.63·1).
Coughs.

Hydrocodin *Valeant, Hung.*
Dihydrocodeine tartrate (p.48·1).
Coughs; pain.

Hydrocodone CP *Morton Grove, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Hydrocodone GF *Morton Grove, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Upper respiratory-tract symptoms.

Hydrocodone HD *Morton Grove, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Hydrocoll *Hartmann, Fr.*
⊗ Carmellose sodium (p.2142·1); pectin (p.2145·2); gelatin (p.1072·1).
Burns; ulcers; wounds.

Hydrocort *CT, Ger.†; YSP, Malaysia; Yung Shin, Singapore.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hydrocortancyl *Sanofi-Aventis, Fr.*
⊗ Prednisolone (p.1540·3) or prednisolone acetate (p.1541·1).
Corticosteroid.

Hydrocortimycin *Kolassa, Austria.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Inflammatory eye disorders.

Hydrocortison med Terramycin *Pfizer, Denm.*
⊗ Hydrocortisone (p.1535·2); oxytetracycline hydrochloride (p.312·3).
Skin infections.

Hydrocortison med Terramycin og Polymyxin-B *Pfizer, Denm.*
⊗ Hydrocortisone (p.1535·2); oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Infected ear or eye disorders.

Hydrocortisone compositum *Streuli, Switz.*
⊗ Hydrocortisone acetate (p.1535·2); zinc stearate (p.2139·3).
Skin disorders.

Hydrocortistab *Sovereign, UK.*
⊗ Hydrocortisone acetate (p.1535·2).
Corticosteroid.

Hydrocortisyl *Sanofi-Aventis, Irl.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydrocortone
MSD, Austria; MSD, Irl.; MSD, Switz.; Auden McKenzie, UK.
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

MSD, Port.
⊗ Hydrocortisone acetate (p.1535·2).
Corticosteroid.

Merck, USA.
⊗ Hydrocortisone (p.1535·2), hydrocortisone acetate (p.1535·2), or hydrocortisone sodium phosphate (p.1535·3).
Corticosteroid.

Hydrocream *Paddock, USA.*
Vehicle for topical preparations.

Hydro-Crysti-12 *Hauck, USA; Roberts, USA.*
Hydroxocobalamin (p.1980·3).
Schilling test; vitamin B deficiency.

Hydrocutan *Dermapharm, Ger.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Corticosteroid.

Hydrocutan mild *Dermapharm, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydroderm
Note.This name is used for preparations of different composition.
Aesca, Austria.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Pacific, NZ.
Dewaxed oil-soluble lanolin fraction (p.2033·2); liquid paraffin (p.2030·3).
Dry skin disorders; pruritus.

ICM, Singapore.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hydroderm HC *Karrer, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydroderm-C *ICM, Singapore.*
⊗ Hydrocortisone acetate (p.1535·2); clioquinol (p.254·1).
Infected skin disorders.

Hydrodermed *Karrer, Ger.*
Erythromycin (p.269·2).
Acne.

Hydrodexan *Hermal, Ger.*
⊗ Hydrocortisone (p.1535·2); urea (p.1620·2).
Skin and scalp disorders.

HydroDiuril *Merck Frosst, Canad.†; Merck, USA.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Hydrofer-3 *Mediapharm, Gr.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Hydrofluoric Acid Antidote *Malaysia Chemist, Singapore†.*
Calcium gluconate (p.1675·3).
Hydrofluoric acid burns.

Hydroflux *Unipharma, Gr.*
⊗ Furosemide (p.1292·1).
Heart failure; hypertension; oedema; oliguria due to renal failure.

Hydroform *Stiefel, Austral.*
⊗ Hydrocortisone (p.1535·2); clioquinol (p.254·1).
Skin disorders.

Hydro-Funga *Vida, Hong Kong.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal skin infections with inflammation.

Hydrofusin *Remek, Gr.*
⊗ Fusidic acid (p.279·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Hydrogalen *Galen, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydrogesic *Edwards, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Hydro-GP *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Allergic rhinitis; cold symptoms; coughs.

Hydrol *Janssen-Cilag, S.Afr.*
Potassium chloride; sodium chloride; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

Hydrolac *Milk Industries, Israel.*
Protein hydrolysate (p.1922·1).
Nutritional supplement.

Hydrolan *Orion, Fin.*
Emollient.
Dry skin disorders.

Hydro-Less *Aspen, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Hydrolipidique *Uriage, Fr.†.*
Emollient.
Dry skin.

Hydro-long *Lichtenstein, Ger.†.*
⊗ Chlortalidone (p.1243·3).
Diabetes insipidus; hypertension; oedema.

Hydrolotion *Pacific Biosciences, Singapore†; Spirig, Singapore†.*
Emollient and moisturiser.

Hydromax *Forder, Arg.†.*
Moisturiser.

Hydromedin *MSD, Ger.†.*
⊗ Sodium etacrynate (p.1283·2).
Ascites; oedema.

Hydromet
Note.This name is used for preparations of different composition.
MSD, Braz.; Vianex (Βιανέξ), Gr.†.
⊗ Hydrochlorothiazide (p.1307·3); methyldopa (p.1334·1).
Hypertension.

Barre-National, USA.
Hydrocodone tartrate (p.63·1); homatropine methylbromide (p.1881·3).
Coughs.

Hydromol
Note.This name is used for preparations of different composition.
Quinoderm, Irl.†.
Cream: Sodium pidolate (p.1614·1); arachis oil (p.2259·1); isopropyl myristate (p.2029·3); liquid paraffin (p.2030·3); sodium lactate (p.1673·3).
Dry skin.

Alliance, UK.
Cream: Isopropyl myristate (p.2029·3); liquid paraffin (p.2030·3); sodium pidolate (p.1614·1); sodium lactate (p.1673·3).
Dry skin conditions.

Quinoderm, Hong Kong†; Alliance, UK.
Emollient: Light liquid paraffin (p.2031·1); isopropyl myristate (p.2029·3).
Dry skin; dry skin conditions.

Alliance, UK.
Ointment: Yellow soft paraffin (p.2031·3); emulsifying wax (p.2029·2).
Dry skin; soap substitute.

Quinoderm, Irl.†.
Topical solution: Light liquid paraffin (p.2031·1); isopropyl myristate (p.2029·3).
Dry skin.

Hydromorph *Purdue, Canad.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Hydromycin *PP Lab, Thai.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Hydron CP *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms; coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hydron EX *Cypress, USA.*
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Hydron KGS *Cypress, USA.*
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Hydron PSC *Cypress, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs; hay fever; respiratory-tract congestion.

Hy-Drop *Bausch & Lomb, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Hydropane *Halsey, USA.*
Hydrocodone tartrate (p.63·1); homatropine methylbromide (p.1881·3).
Coughs.

Hydropel *C & M, USA.*
Topical barrier preparation.

Hydrophed *Rugby, USA.*
⊗ Theophylline (p.1140·1); ephedrine sulfate (p.1558·2); hydroxyzine hydrochloride (p.581·2).
Bronchospasm.

Hydrophil *Omega, Canad.*
⊗ Urea (p.1620·2); white soft paraffin (p.2031·2).
Dry skin.

Hydrophilic *Rugby, USA.*
Vehicle for topical preparations.

Hydropres *Merck, USA.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Hydroquin *Sun, Thai.*
Hydroxychloroquine sulfate (p.604·2).
Juvenile arthritis; lupus erythematosus; rheumatoid arthritis.

Hydros G *Chaix et du Marais, Fr.†.*
Glucose, sodium chloride, and potassium chloride infusion (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Hydrosan *Wabosan, Austria.*
⊗ Chlortalidone (p.1243·3).
Heart failure; hypertension; oedema.

Hydro-Serp *Rugby, USA†.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Hydroserpine *Rugby, USA†.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Hydrosil *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Singapore†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastro-oesophageal reflux; heartburn; meteorism; peptic ulcer.

HydroSkin *Rugby, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydrosol Polyvitamine *Pharmadeveloppement, Fr.*
Multivitamin preparation (p.1922·1).

Hydrosol Polyvitamine BON *Bouchara-Recordati, Fr.†.*
Multivitamin preparation (p.1922·1).

Hydrosone
Rougier, Canad.
⊗ Hydrocortisone (p.1535·2).

Christo, Hong Kong.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Hydrospor *Vendiz, Philipp.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Ear infections.

Hydrotab *Actavis, UK.*
Malic acid (p.2337·1); sodium fluoride (p.1962·2).
Dry mouth.

Hydrotopic *Vendiz, Philipp.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Hydrotricine *Sanofi-Aventis, Ital.; Vitoria, Port.; Unipharm, Turk.*
Tyrothricin (p.358·2).
Bacterial stomatitis; mouth and throat infections.

Hydrotrix *Kolassa, Austria; Medice, Ger.*
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Heart failure; hypertension; oedema.

Hydro-Tussin DM *Ethex, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Hydro-Tussin HD *Ethex, USA.*
Guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Hydro-Tussin HG *Ethex, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Cough.

HydroVal *Taro, Canad.*
⊗ Hydrocortisone valerate (p.1536·1).
Skin disorders.

Hydro-Wolff *Wolff, Ger.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hydroxin *Shiwa, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions.

Hydroxy-Cal *Sisu, Canad.†.*
Vitamin C and minerals (p.1922·1).

Hydrozide *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
⊗ Hydrochlorothiazide (p.1307·3).
Diuretic; hypertension; oedema.

Hydrozide Plus *Progress, Thai.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hepatic cirrhosis with ascites; hypertension; oedema.

Hydrozole *Stiefel, Austral.*
⊗ Hydrocortisone (p.1535·2); clotrimazole (p.530·1).
Skin disorders.

Hydryllin *Ali, Turk.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Respiratory-tract congestion.

Hyfac soin keratolytique *Biorga, Fr.†.*
Glycolic acid (p.1598·1); alpha hydroxy acid ester; piroctone olamine (p.1610·1).
Skin disorders.

Hyflex
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Breckenridge, USA.
Paracetamol (p.108·1); phenyltoloxamine citrate (p.588·1).
Pain.

Hyflon *Elmor, Venez.*
⊗ Hidrosmin (p.2305·2).
Venous insufficiency.

Hyflox *Masa, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Hy-GAG *Curasan, Ger.*
Sodium hyaluronate (p.2320·1).
Degenerative joint disorders.

Hygeol *Pendopharm, Canad.*
Sodium hypochlorite (p.1661·1).
Disinfection; wound cleansing.

Hygienist *Bayer, Ital.†.*
Chlorocresol (preventol CMK) (p.1640·1); clorophene (preventol BP) (p.1641·1); orthophenylphenol (preventol extra) (p.1655·1).
Surface disinfection.

Hygienist Pavimenti e Piastrelle *Bayer, Ital.†.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Hygine *Soma, Braz.*
Triclosan (p.1665·2).
Soap substitute.

Hygiodermil *Vifor, Switz.*
Bornyl salicylate (p.28·2); neroli oil (p.2351·1); lavender oil (p.2331·2); menthol (p.2340·1).
Skin disorders.

Hygroton *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Mibe, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Sandoz, Hung.; Novartis, Indon.; Novartis, Malaysia†; Novartis, NZ; Novartis, Neth.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Switz.; Novartis, Turk.; Alliance, UK; Rhone-Poulenc Rorer, USA.*
⊗ Chlortalidone (p.1243·3).
Diabetes insipidus; heart failure; hypercalciuria; hypertension; liver cirrhosis with ascites; oedema; renal calculi.

Hygroton-Reserpina *Novartis, Arg.†.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Hygroton-Reserpine *Novartis, Gr.; Novartis, S.Afr.†; Novartis, Switz.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Hy-KXP *Cypress, USA.*
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Hylaform *Collagen, Ger.†; McGhan, Ger.†; Collagen Aesthetics, NZ; Inamed, Singapore; Inamed, USA.*
Sodium hyaluronate (p.2320·1).
Facial wrinkles; skin contour defects.

Hylak *Ratiopharm, Austria.*
Metabolic products of lactic-acid producing organisms (p.2372·3); lactic acid (p.2329·3); amino acids.
Gastrointestinal disorders; liver disorders; skin disorders.

Hylak Forte
Note. This name is used for preparations of different composition.
Ratiopharm, Austria.
Metabolic products of lactic-acid producing organisms (p.2372·3); metabolic products of Gram-positive and Gram-negative intestinal flora; lactic acid (p.2329·3); amino acids.
Gastrointestinal disorders; liver disorders; skin disorders.

Ratiopharm, Cz.; Merckle, Rus.
Metabolic products of: *Escherichia coli*; *Enterococcus faecalis* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus helveticus* (p.2372·3).
Gastrointestinal disorders; restoration of gastrointestinal flora; skin disorders.

Hylak N *Merckle, Ger.*
Metabolic products of *Lactobacillus helveticus* (p.2372·3).
Gastrointestinal disorders.

Hylak Plus *Merckle, Ger.*
Metabolic products of *Lactobacillus helveticus* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3).
Gastrointestinal disorders.

Hylan *Stulln, Ger.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Hylands Cough *Hylands, Canad.*
Homoeopathic preparation.

Hylands Flu *Hylands, Canad.*
Homoeopathic preparation.

Hylands Gas *Hylands, Canad.*
Homoeopathic preparation.

Hylands Headache *Hylands, Canad.*
Homoeopathic preparation.

Hylands Hemorrhoids *Hylands, Canad.*
Homoeopathic preparation.

Hylands Insomnia *Hylands, Canad.*
Homoeopathic preparation.

Hylands Leg Cramps *Hylands, Canad.*
Homoeopathic preparation.

Hylands Low Back Pain *Hylands, Canad.†.*
Homoeopathic preparation.

Hylands Menstrual Cramps *Hylands, Canad.*
Homoeopathic preparation.

Hylands Motion Sickness *Hylands, Canad.*
Homoeopathic preparation.

Hylands PMS *Hylands, Canad.*
Homoeopathic preparation.

Hylands Sinus *Hylands, Canad.*
Homoeopathic preparation.

Hylands Sore Throat *Hylands, Canad.*
Homoeopathic preparation.

Hylands Upset Stomach *Hylands, Canad.*
Homoeopathic preparation.

Hylands Vaginitis *Hylands, Canad.*
Homoeopathic preparation.

Hylase *Dessau, Cz.; Riemser, Ger.*
Hyaluronidase (p.2321·1).
Adjunct in ocular surgery; adjuvant in local anaesthesia; adjuvant to increase absorption and dispersion of drugs; haematoma; inflammation; myocardial infarction; oedema; orthopaedic surgery; urological procedures.

Hylenex *Baxter, USA.*
Hyaluronidase (p.2321·1).
Hypodermoclysis; to increase the absorption and dispersion of injected drugs.

Hyles *Berlin Pharm, Thai.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; ascites; hypertension; oedema.

Hylira *Hawthorn, USA.*
Sodium hyaluronate (p.2320·1).
Xerosis.

Hylo-Care *Ursapharm, Ger.*
Sodium hyaluronate (p.2320·1); dexpanthenol (p.2362·1).
Dry eyes.

Hylo-COMOD *Ioltech, Fr.; Ursapharm, Ger.; Ursapharm, Israel; Visufarma, Ital.; OM, Port.†; Ursapharm, Rus.; Pharma Medica, Switz.*
Sodium hyaluronate (p.2320·1).
Dry eyes; eye irritation.

Hylo-Vision *OmniVision, Ger.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Hylozar-COMOD *Ursapharm, Rus.*
Sodium hyaluronate (p.2320·1); dexpanthenol (p.2362·1).
Dry eyes.

Hyluprotect *Thea, Fr.; Thea, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes; eye irritation.

Hylutin *Hyrex, USA†.*
Hydroxyprogesterone caproate (p.2110·3).
Abnormal uterine bleeding; amenorrhoea; metrorrhagia.

Hymed *Medifive, Thai.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; mental function impairment.

Hyneurin *Korhispana, Spain.*
St John's wort (p.422·3).
Asthenia.

Hynidase *Shreya, India.*
Hyaluronidase (p.2321·1).
Enhancement of absorption of intramuscular and subcutaneous injections; reduction of extravasation.

Hyomide *CCM, Malaysia; Beacons, Singapore.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hyoscal *Steierl, Ger.†.*
Scopolia carniolica root.
Smooth muscle spasm.

Hyosmed *Medifive, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal motility disorders; smooth muscle spasm.

Hyosophen *Rugby, USA.*
Atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); hyoscyamine hydrobromide (p.1736·1) or hyoscyamine sulfate (p.1736·1); phenobarbital (p.492·2).
Gastrointestinal disorders.

Hyospan *Cipla, India; Polipharm, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastroduodenitis; peptic ulcer; postoperative nausea and vomiting; smooth muscle spasm.

Hyospasmol *Pharmacare, S.Afr.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm.

Hyostan *Pharmaland, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastro-duodenitis; nausea and vomiting; peptic ulcer; smooth muscle spasm.

Hyozin *Samakeephaesaj, Thai.†.*
Hyoscine butylbromide (p.1734·1).
Nausea and vomiting; peptic ulcer; smooth muscle spasm.

Hypace *Pascual, Philipp.; Alchemy, S.Afr.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Hypadil *Kowa, Jpn.*
⊗ Nipradilol (p.1883·2).
Glaucoma; ocular hypertension.

Hypam *Pacific, NZ.*
Triazolam (p.1033·2).
Insomnia.

Hypan *Sandipro, Belg.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Hypaque
Sanofi Synthelabo, Braz.; Intrapharm, UK.
Sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Nycomed Imaging, Canad.†; Abbott, Rus.†; Nycomed, USA.
Meglumine amidotrizoate (p.1475·3) or sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Hypaque 60% *Nycomed, Arg.†; Sanofi Synthelabo, Chile†.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Hypaque 76% *Nycomed, Arg.†; Sanofi Synthelabo, Chile†.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Hypaque-M
Sanofi Synthelabo, Braz.; Nycomed Imaging, Canad.†.
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Sanofi Synthelabo, Venez.†.
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Hypaque-M, Hypaque-76 *Nycomed, USA.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Hypen *Shinyaku, Jpn.*
Etodolac (p.52·2).
Inflammation; musculoskeletal and joint disorders; pain.

Hyper Sensitive *Grimberg, Arg.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2); xylitol (p.1998·2).
Dental caries prophylaxis; sensitive teeth.

Hyperamine *Braun, Fr.†; Braun, UK.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Hypercal *Nelson, UK.*
Homoeopathic preparation.

Hypercalcio *Luper, Braz.†.*
Calcium, vitamin D, vitamin B , and fluoride supplement (p.1922·1).

Hyperchol *Ikapharmindo, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Hypercircin *Cheplapharm, Ger.*
Mistletoe (p.2345·3); olive (p.2356·2).
Cardiac disorders.

Hypercrit *Delta, Arg.; Biolatina, Chile; Landsteiner, Mex.; Biogalenic, Venez.*
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood transfusion.

Hyperdine *Masa, Thai.†.*
⊗ Clopamide (p.1250·1); dihydroergocristine mesilate (p.364·2); reserpine (p.1387·3).
Hypertension.

Hyperdix *Servier, Philipp.; Servier, Thai.*
Rilmenidine phosphate (p.1388·3).
Hypertension.

Hyperesa *Dolorgiet, Ger.*
Valerian (p.2410·1); St John's wort (p.422·3).
Insomnia; nervous disorders.

Hyperforat *Klein, Ger.; Pharmacie du College, Switz.†.*
St John's wort (p.422·3).
Depression; insomnia; nervous disorders.

Hyperforat-forte *Klein, Ger.†.*
St John's wort (p.422·3); rauwolfia vomitoria (p.1387·1).
Anxiety disorders.

Hypergel *Molnlycke, Austral.; Molnlycke, Canad.; Molnlycke, Fr.*
Hypertonic saline debriding agent (p.1686·1).
Ulcers; wounds.

HyperHAES *Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Ger.; Fresenius Kabi, Hung.; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, UK.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Hypovolaemia; plasma volume expansion; shock.

HyperHep B *Bayer, Canad.; Talecris, Canad.; Dipa, Indon.; Bayer, NZ; Bayer, USA.*
A hepatitis B immunoglobulin (p.2214·3).
Formerly known as BayHep B in some countries.
Passive immunisation.

Hyperherba *Labofarm, Pol.*
St John's wort (p.422·3).
Depression.

Hyperhes *Fresenius Kabi, Austria; Fresenius Kabi, Fr.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Plasma volume expansion; shock.

HyperiCalm *MedicHerb, UK.*
St John's wort (p.422·3).
Anxiety; depression.

Hypericaps *Duopharm, Ger.†.*
St John's wort (p.422·3).
Anxiety.

Hypericettes *Kneipp, Switz.†.*
St John's wort (p.422·3).
Depression; sleep disorders.

Hyperico *Viternat, Braz.†.*
St John's wort (p.422·3).
Depression.

Hyperiforce *Bio-Garten, Austria; Bioforce, Switz.*
St John's wort (p.422·3).
Anxiety; depression; nervous disorders; sleep disorders.

Hyperiforce comp *Bioforce, Switz.*
St John's wort (p.422·3); melissa (p.2339·3); lupulus (p.2335·2).
Depression; nervous disorders; sleep disorders.

Hyperiforte *Blackmores, Austral.†.*
St John's wort (p.422·3).
Anxiety; depression; nervous disorders.

Hyperigreen *Greenpharma, Braz.*
St John's wort (p.422·3).

Hyperikan *Schwabe, Cz.; Schwabe, Hung.; Stetifarm, Venez.*
St John's wort (p.422·3).
Depression.

Hyperil *Ferron, Indon.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Hyperilite *Eulite, Neth.*
Homoeopathic preparation.

HyperiMed *Bioforce, Switz.*
St John's wort (p.422·3).
Depression; nervous disorders; sleep disorders.

Hyperimerck *Merck dura, Ger.*
St John's wort (p.422·3).
Depression.

Hyperiplant *VSM, Belg.; Schwabe, Switz.*
St John's wort (p.422·3).
Depression; insomnia; nervous disorders.

Hyperium *Servier, Arg.; Servier, Braz.; Biopharma, Fr.; Servier, Port.; Servier, Turk.; Servier, Venez.*
Rilmenidine phosphate (p.1388·3).
Hypertension.

Hyperlex *Servier, Hung.*
Rilmenidine phosphate (p.1388·3).
Hypertension.

Hyperlipen *Sanofi-Aventis, Belg.; Sanofi-Aventis, Neth.; Sanofi Synthelabo, Switz.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Hyperlite *Braun, Spain.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte depletion.

Hyperliz *Remedina, Gr.*
Lisinopril (p.1325·2).
Hypertension.

Hyperlyte *McGaw, USA.*
A range of electrolyte preparations (p.1667·1).
Fluid and electrolyte disorders.

Hypermol *Pacific, NZ.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Hypermycin *Prafa, Indon.*
Spiramycin (p.333·1).
Bacterial infections; toxoplasmosis.

Hypernol *DHA, Hong Kong; DHA, Singapore.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Hyperol *Meditop, Hung.*
Urea hydrogen peroxide (p.1666·2).
Skin and mucous membrane infections.

Hyperosedat *Gal, Pol.*
St John's wort (p.422·3).
Depression.

Hyperphen *Pharmacare, S.Afr.*
Hydralazine hydrochloride (p.1305·3).
Hypertension.

Hyperprost *Makiz-Pharma, Rus.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Hyperprost Uno *Robugen, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Hyperprotidine *NPC, Fr.*
Preparation for enteral nutrition (p.1922·1).

Hyperpur *Alpharma-Isis, Ger.*
St John's wort (p.422·3).
Depression.

Hyperrab *Bayer, Canad.; Talecris, Canad.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

HyperRab *Talecris, USA.*
A rabies immunoglobulin (p.2233·3).
Formerly known as BayRab.
Passive immunisation.

Hyperretic *Pharmasant, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Hyperrho S/D *Bayer, Canad.; Talecris, Canad.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

HyperRho S/D *Dipa, Indon.; Talecris, USA.*
An anti-D immunoglobulin (p.2204·2).
Formerly known as BayRho-D in the *USA.*
Prevention of rhesus sensitisation.

HyperRHO S/D *Talecris, Rus.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Hypersol *Cassara, Arg.*
Sodium chloride (p.1686·1).
Nasal dryness.

Hypersol B *Cassara, Arg.*
⊗ Budesonide (p.1520·1).

Hyperstat *Schering, Canad.†; IFET (ΙΦΕΤ), Gr.†; Schering-Plough, Ital.†; Schering-Plough, Mex.†; Schering-Plough, Swed.†; Schering, USA.*
Diazoxide (p.1257·3).
Hypertension; hypoglycaemia.

Hypertel *Polychronus, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Hypertet *Bayer, Canad.; Talecris, Canad.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Hypertonalum *Essex, Ger.†.*
Diazoxide (p.1257·3).
Hypertension.

Hyperval *Sidroga, Switz.*
St John's wort (p.422·3).
Depression; insomnia; nervous disorders.

Hypery *Pond's, Thai.†.*
⊗ Reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hyphed *Cypress, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cough.

Hy-Phen *Ascher, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).

Hyphoral
Note. This name is used for preparations of different composition.
Ipca, India.
Lotion: Ketoconazole (p.539·1); pyrithione zinc (p.1611·2).
Dandruff.

Ipca, India.
Tablets: Ketoconazole (p.539·1).
Fungal infections.

Hypnasmine *Elerte, Fr.†.*
Butobarbital (p.967·2); theophylline (p.1140·1).
Respiratory-tract disorders.

Hypnodorm *Alphapharm, Austral.; Teva, Israel.*
Flunitrazepam (p.996·2).
Insomnia.

Hypnoforin *Unipharma, Gr.*
Zolpidem (p.1038·2).

Hypnogen *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Leciva, Rus.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Hypnomidate *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile†; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Spain; Janssen-Cilag, Turk.; Janssen-Cilag, UK.*
Etomidate (p.1783·3).
General anaesthesia.

Hypnomidato *Janssen, Port.*
Etomidate (p.1783·3).
General anaesthesia.

Hypnor *Rolab, S.Afr.†.*
Flunitrazepam (p.996·2).
Insomnia.

Hypnorex *Sanofi Synthelabo, Ger.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Hypnotex *Pharmaceutical Co, India.*
Nitrazepam (p.1011·2).
Insomnia.

Hypnovel
Roche, Austral.; Roche, Fr.; Roche, Irl.; Roche, UK.
Midazolam hydrochloride (p.1007·3).
General anaesthesia; induction of anaesthesia; premedication; sedative.

Roche, NZ.
Midazolam hydrochloride (p.1007·3) or midazolam maleate (p.1007·3).
General anaesthesia; insomnia; premedication; sedative.

Hypo Tears *Novartis, Spain.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Hypoca *Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Hypochylin *Recip, Fin.; Recip, Swed.*
Glutamic acid hydrochloride (p.1947·1).
Hypochylia.

Hypocol *Wearnes, Malaysia; Steward Cross, Singapore.*
Red yeast rice.
Hypercholesterolaemia.

Hypodine *Pharmasant, Thai.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Hypodol *Ivax, Arg.*
Lornoxicam (p.77·3).
Musculoskeletal and joint disorders; pain.

Hypodyn *Novartis, Austria.*
⊗ Dihydroergotamine mesilate (p.618·2); etilefrine hydrochloride (p.1284·1).
Hypotension.

Hypofil *Sanbe, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Hypoguard *Hypoguard, Irl.†.*
Test for glucose in blood (p.2314·1).

Hypoguard Supreme Plus *Hypoguard, UK.*
Test for glucose in blood (p.2314·1).

Hypol
Note. This name is used for preparations of different composition.
Felton, Austral.†.
Capsules: Cod-liver oil (p.1935·2).
Arthritis; cardiovascular disorders; cold and influenza symptoms; dietary supplement; inflammatory disorders.

Felton, Austral.
Oral emulsion: Cod-liver oil (p.1935·2); soya oil (p.1965·3); calcium hypophosphite; sodium hypophosphite.
Arthritis; cardiovascular disorders; cold and influenza symptoms; dietary supplement; inflammatory disorders.

Felton, Austral.†.
Tablets: Vitamin A; colecalciferol; vitamin C; calcium dihydrogen phosphate (p.1922·1).
Vitamin and calcium supplement.

Hypolac *Noos, Ital.*
Infant feed (p.1922·1).
Food intolerance.

Hypolar Retard *Sandoz, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Hypolip
Note. This name is used for preparations of different composition.
Pharmavit, Cz.†.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

PharmaConsult, Hung.
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Hypoloc *Menarini, Neth.; Menarini, Port.*
⊗ Nebivolol hydrochloride (p.1347·1).
Heart failure; hypertension.

Hypomide *Pharmacare, S.Afr.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Hyposedon N *Harras-Curarina, Ger.†.*
Kava (p.2328·3); passion flower (p.2363·2).
Agitation; sleep disorders.

Hypostamin *Novartis Consumer, Austria.*
Tritoqualine (p.593·3).
Hypersensitivity reactions.

Hypostamine *Chiesi, Fr.*
Tritoqualine (p.593·3).
Hypersensitivity reactions.

Hypotears
Note. This name is used for preparations of different composition.
Novartis, Cz.
Vitamin A palmitate (p.1973·1); carbomer 940 (p.2141·3).
Dry eyes.

Novartis, Ital.; Novartis, Switz.
Polyvinyl alcohol (p.2145·3); macrogol 400 (p.2336·3).
Dry eyes; eye irritation.

Novartis, Malaysia.
Polyvinyl alcohol (p.2145·3); macrogol (p.2336·1).
Dry eyes.

Novartis, Philipp.
Vitamin A palmitate (p.1973·1).
Dry eyes.

Adcock Ingram, S.Afr.
Povidone (p.2146·1).
Contact lens lubricant; dry eyes.

Novartis Ophthalmics, Singapore.
Polyvinyl alcohol (p.2145·3).
Dry eyes; eye irritation.

Novartis, UK†.
Polyvinyl alcohol (p.2145·3); macrogol 8000 (p.2336·3).
Dry eyes.

Novartis Ophthalmics, Canad.; Novartis, Israel†.
Eye drops: Polyvinyl alcohol (p.2145·3).
Dry eyes.

Novartis, Hong Kong; Novartis Ophthalmics, USA.
Eye drops: Polyvinyl alcohol (p.2145·3); macrogol 400 (p.2336·3).
Dry eyes.

Novartis Ophthalmics, Hong Kong†.
Eye gel: Vitamin A palmitate (p.1973·1); carbomer (p.2141·3).
Dry eyes.

Novartis Ophthalmics, Canad.; Novartis Ophthalmics, USA.
Eye ointment: White soft paraffin (p.2031·2); light liquid paraffin (p.2031·1).
Dry eyes.

Hypotears E *Novartis, Israel.*
Povidone (p.2146·1).
Dry eyes.

Hypotears Plus *Novartis Ophthalmics, Arg.; Novartis, Braz.; Novartis, Cz.; Novartis, Hong Kong; Novartis, Mex.; Novartis, Thai.; Novartis, Venez.*
Povidone (p.2146·1).
Dry eyes; lubricant for contact lenses.

Hypoten
Note. This name is used for preparations of different composition.
Hikma, Rus.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Adcock Ingram, S.Afr.
Sodium nitroprusside (p.1397·1).
Hypertension.

Hypotens *Dexxon, Israel.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; hypertension.

Hypotensor *Faran, Gr.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Hypothiazid *Sanofi-Aventis, Hung.; Chinoin, Rus.*
⊗ Hydrochlorothiazide (p.1307·3).
Diabetes insipidus; hypertension; oedema.

Hy-Po-Tone *Pharmacare, S.Afr.*
Methyldopa (p.1334·1).
Hypertension.

Hypotonicka *Megafyt-R, Cz.*
Crataegus (p.2289·1); mistletoe (p.2345·3); polygonum avicularis; raspberry leaf (p.2378·2); melissa (p.2339·3).
Hypertension.

Hypotonie-Gastreu R44 *Reckeweg, Ger.*
Homoeopathic preparation.

Hypotylin *Zentiva, Cz.*
⊗ Metipamide (p.1336·3).
Hypertension.

Hypovase *Pfizer, Irl.; Pfizer, UK.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Hypozar *Verisfield, Gr.*
Losartan (p.1327·2).
Hypertension.

Hypren *AstraZeneca, Austria.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction; nephropathy.

Hypren plus *AstraZeneca, Austria.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hyprosia *Asian Pharm, Thai.*
⊗ Etilefrine (p.1284·1).
Hypotension.

Hyprosin *Pacific, NZ.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's disease.

Hyprosol *Dzwon, India.*
Hypromellose (p.2144·2).
Dry eyes.

Hypurin 30/70 *Wockhardt, UK.*
⊗ Mixture of neutral insulin injection (porcine, highly purified) 30% and isophane insulin injection (porcine, highly purified) 70% (p.443·2).
Diabetes mellitus.

Hypurin Bovine Isophane *CP, Cz.†.*
⊗ Isophane insulin injection (bovine, monocomponent) (p.443·2).
Diabetes mellitus.

Hypurin Bovine Protamin Zink Sulfat *CP, Cz.†.*
⊗ Protamine zinc insulin injection (bovine, monocomponent) (p.443·2).
Diabetes mellitus.

Hypurin Isophane *Aspen, Austral.; CP Pharma, Switz.; Wockhardt, UK.*
⊗ Isophane insulin injection (bovine, highly purified) (p.443·2).
Diabetes mellitus.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hypurin Lente *Wockhardt, UK.*
⊗ Insulin zinc suspension (30% amorphous, 70% crystalline) (bovine, highly purified) (p.443·2).
Diabetes mellitus.

Hypurin 30/70 Mix *CP Pharma, Switz.*
⊗ A mixture of insulin injection (porcine) and isophane insulin injection (porcine) respectively in the proportion indicated (p.443·2).
Diabetes mellitus.

Hypurin Neutral *Aspen, Austral.; CP Pharma, Switz.; Wockhardt, UK.*
⊗ Neutral insulin injection (bovine, highly purified) (p.443·2).
Diabetes mellitus.

Hypurin NPH *Nucro-Technics, Canad.*
⊗ Isophane insulin (porcine) (p.443·2).
Diabetes mellitus.

Hypurin Porcin Neutral *CP, Cz.†.*
⊗ Neutral insulin injection (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Hypurin Protamine Zinc *Wockhardt, UK.*
⊗ Protamine zinc insulin injection (bovine, highly purified) (p.443·2).
Diabetes mellitus.

Hypurin Regular *Nucro-Technics, Canad.*
⊗ Soluble insulin (porcine) (p.443·2).
Diabetes mellitus.

Hyric *Interbat, Indon.*
Syzygium polyanthum; physalis angulata (p.2367·3); sonchus arvensis; plantain (p.2369·3).
Hyperuricaemia.

Hyrin *Merckle, Ger.†.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea; vomiting.

Hyron *Gedeon Richter, Hung.†.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Hyruan *LG Pharm, Hong Kong; LG Life Sciences, Malaysia; LG Life Sciences, Thai.*
Sodium hyaluronate (p.2320·1).
Adjunct in orthopaedic surgery; degenerative joint disorders.

Hysan *Ursapharm, Ger.; Kivema, Israel; Pharma Medica, Switz.*
Sodium hyaluronate (p.2320·1).
Nasal dryness.

Hyscopan *Armoxindo, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hyseke *Biorga, Fr.*
Sodium pidolate (p.1614·1); zinc pidolate (p.1614·1); enoxolone (p.50·1).
Dry skin.

Hyseke Solaire *Biorga, Fr.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3); enoxolone (p.50·1).
Sunscreen.

Hyskon *Dermatech, Austral.; Pharmacia, USA.*
⊗ Dextran 70 (p.1059·3) in glucose.
Aid to hysteroscopy.

Hysone
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Roberts, USA.
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Inflammatory skin disorders.

Hysopan *Denk, Hong Kong.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hy-Spa *Medicine Products, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastroduodenitis; peptic ulcer; smooth muscle spasm.

Hysron *Kyowa, Jpn.*
Medroxyprogesterone acetate (p.2113·1).

Hysticlar *Mintlab, Chile.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Hystin *Geolab, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Hystolan *Dexa, Indon.*
Isoxsuprine hydrochloride (p.2327·3).
Peripheral vascular disorders; uterine relaxant.

Hytacand *AstraZeneca, Fr.; AstraZeneca, Port.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Hytakerol *Sanofi Synthelabo, Canad.†; Sanofi Winthrop, USA†.*
Dihydrotachysterol (p.1986·3).
Hypoparathyroidism; tetany.

HyTan *Prasco, USA.*
Hydrocodone tannate (p.63·2); chlorphenamine tannate (p.572·2).
Cough.

Hythalton *Sarabhai Piramal, India†.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema; premenstrual syndrome.

Hytic *Seng, Thai.†.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Hytinic
Note. This name is used for preparations of different composition.
Hyrex, USA†.
Capsules: Polysaccharide-iron complex (p.1960·2).
Iron-deficiency anaemias.

Hyrex, USA†.
Injection: Ferrous gluconate (p.1939·1); vitamin B substances (p.1922·1).
Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Iron-deficiency anaemias.

Hytisone
Atlantic, Hong Kong.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Atlantic, Thai.
⊗ Hydrocortisone acetate (p.1535·2).
Inflammatory skin disorders.

Hytone *Dermik, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Hytos Plus *Uniao Quimica, Braz.*
Clobutinol hydrochloride (p.1554·1); doxylamine succinate (p.578·2).
Coughs.

Hytrin *Abbott, Austral.; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Amdipharm, Cz.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, India; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Philipp.; Abbott, Pol.; Amdipharm, Port.; Abbott, Rus.†; Abbott, S.Afr.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Amdipharm, UK; Abbott, USA; Wellcome, USA; Abbott, Venez.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Hytrin BPH *Abbott, Switz.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Hytrine *Abbott, Fr.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Hytrinex *Abbott, Swed.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Hytuss *Hyrex, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Hyzaar
Note. This name is used for preparations of different composition.
MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.†; MSD-Chibret, Fr.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Philipp.; MSD, Pol.; MSD, Rus.; MSD, Singapore; MSD, Thai.; MSD, Turk.; Merck, USA.
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension; left-ventricular hypertrophy; stroke prophylaxis.

MSD, Venez.
Losartan potassium (p.1326·1).
Hypertension.

Hyzaar Plus *MSD, Venez.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Hyzan *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Hyzum N *Merckle, Ger.†.*
Arnica (p.2260·2).
Inflammation; muscle and joint pain; soft-tissue injury.

Ial *Fidia, Hung.†; Bausch & Lomb, Ital.; Chemedica, Switz.; Chemedica, Thai.; Fidia, Thai.; Interko, Turk.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Ialect *Fidia, Ital.†.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Ialex *Aspen, Austral.*
Cefalexin (p.218·2).
Bacterial infections.

Ialugen *IBSA, Switz.*
Sodium hyaluronate (p.2320·1).
Burns; ulcers; wounds.

Ialugen Plus *IBSA, Cz.; IBSA, Hung.; IBSA, Switz.*
Sodium hyaluronate (p.2320·1); sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Ialum *Bausch & Lomb, Ital.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Ialurex *Bausch & Lomb, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Ialuset *Genevrier, Fr.*
Sodium hyaluronate (p.2320·1).
Skin ulceration.

Ialuset Plus *Genevrier, Fr.*
Sodium hyaluronate (p.2320·1); sulfadiazine silver (p.337·2).
Burns; wounds.

Ialutim *Bausch & Lomb, Ital.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Iamacalcin *Iamatica, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Iamastatin *Iamatica, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Iamaxicam *Iamatica, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Iamin *Merck, Mex.*
Prezatide copper acetate (p.1611·2).
Burns; ulcers; wounds.

Iamin Hydrating Gel *Procyte, USA.*
Prezatide copper acetate (p.1611·2).
Burns; ulcers; wounds.

Iasvest *Iapharm, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Iaten *Iapharm, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Ibalgin *Zentiva, Cz.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibalgin Sport *Zentiva, Pol.*
Ibuprofen (p.64·2); a heparinoid (p.1305·2).
Musculoskeletal, joint, and soft-tissue disorders; superficial vascular disorders.

Ibamoxil *Ibfarma, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Ibaril *Aventis, Denm.; Sanofi-Aventis, Fin.; Bipharma, Neth.; Aventis, Norw.; Aventis, Swed.†.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Ibaril med salicylsyra *Aventis, Swed.†.*
⊗ Desoximetasone (p.1525·2); salicylic acid (p.1612·2).
Skin disorders.

Ibaril med salicylsyre *Aventis, Denm.†; Aventis, Norw.†.*
⊗ Desoximetasone (p.1525·2); salicylic acid (p.1612·2).
Skin disorders.

Ibarin *Laboratorios Chile, Chile.*
Fluconazole (p.532·1).
Fungal infections.

Ibax *Sandoz, Mex.*
Omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

IBC *Pacific, Philipp.*
Vitamin B substances (p.1975·1); ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and vitamin supplement for pregnancy; iron-deficiency anaemia.

Ibdazol *Ibfarma, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Ibedox *Polinac, Venez.*
Hydroxocobalamin (p.1980·3).
Neurological disorders.

Ibercal *BOI, Spain.*
Calcium pidolate (p.1676·3).
Hypocalcaemia; osteoporosis.

Ibercal D *BOI, Spain.*
Calcium pidolate (p.1676·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Iberet *Abbott, Canad.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Malaysia†; Armstrong, Mex.; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.†; Abbott, USA†.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron and vitamin B deficiency.

Iberet-Folic *Abbott, Hong Kong; Abbott, Indon.; Abbott, Malaysia; Abbott, Philipp.; Abbott, Singapore; Abbott, USA†.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Anaemias; folic acid deficiency; iron and vitamin B deficiency.

Iberin Folico *Abbott, Braz.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Iberis HM *Pfluger, Ger.†.*
Homoeopathic preparation.

Iberogast
Note. This name is used for preparations of different composition.
Steigerwald, Cz.; Steigerwald, Ger.
Iberis; angelica (p.2258·1); chamomile (p.2279·3); caraway (p.2276·3); milk thistle (p.1452·1); melissa (p.2339·3); peppermint leaf (p.1761·2); greater celandine (p.2317·1); liquorice (p.1740·3).
Gastrointestinal disorders.

Steigerwald, Switz.
Iberis amara; angelica (p.2258·1); milk thistle (p.1452·1); cuminum cyminum; chamomile (p.2279·3); greater celandine (p.2317·1); liquorice (p.1740·3); melissa (p.2339·3); peppermint leaf (p.1761·2).
Digestive disorders.

Iberol
Note. This name is used for preparations of different composition.
Abbott, Chile; Armstrong, Mex.
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia; vitamin B deficiency.

Abbott, Arg.; Abbott, Braz.
Oral drops: Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Pharmacia, India.
Oral liquid: Ferrous sulfate (p.1939·3); vitamins (p.1922·1).
Anaemias.

Abbott, Braz.
Oral liquid; tablets: Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Abbott, Arg.
Syrup; tablets: Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability or iron.
Iron deficiency.

Pharmacia, India.
Tablets: Ferrous sulfate (p.1939·3); desiccated liver (p.2337·3); vitamins (p.1922·1).
Anaemias.

Iberol C *Abbott, Venez.*
Ferrous sulfate; vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Iberol Folico *Abbott, Chile.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folate deficiency; iron-deficiency anaemia.

Iberol Simple *Abbott, Chile†.*
Ferrous sulfate (p.1939·3).
Iron deficiency.

Ibexone *Sandipro, Belg.*
Codergocrine mesilate (p.363·3).
Mental function impairment.

Ibiamox
Douglas, Austral.; IBI, Ital.†; Douglas, NZ.
Amoxicillin sodium (p.202·2).
Bacterial infections.

Siam Bheasach, Thai.
Amoxicillin (p.202·2).
Bacterial infections.

Ibifen *IBI, Ital.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibilex *Alphapharm, Austral.; Siam Bheasach, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Ibimicyn *Douglas, Austral.; IBI, Ital.†.*
Injection: Ampicillin sodium (p.204·1).
Bacterial infections.

Ibiprovir *IBI, Ital.†.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Ibis *Pharmaland, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Ibition *Genepharm, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Ibixetin *IBI, Ital.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Ibizolam *IBI, Ital.†.*
Alprazolam (p.960·1).
Anxiety disorders; panic disorder.

Iboflam *MDI, S.Afr.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Ibosure *Sandoz, Neth.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders.

Ibotec *Fariberica, Port.*
Amlodipine besilate (p.1214·1).
Angina pectoris.

Ib-Profeno *Ibfarma, Braz.†.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Ibrofen *TO-Chemicals, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Ibrufhalal *Halal, UK.*
Ibuprofen (p.64·2).
Inflammation; pain.

IBS Eze *Brauer, Austral.*
Homoeopathic preparation.

IBS Relief *Thornton & Ross, UK†.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

IB-Stat *Inkine, USA.*
Hyoscyamine sulfate (p.1736·1).

Ibu
ISA, Arg.; Ratiopharm, Austria; Master, Chile; 1A, Ger.; Euro OTC, Ger.; Kade, Ger.; Pose, Thai.; Boots, USA.
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.
Hemopharm, Ger.
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; pain.

Ibu-4 *Master, Chile†.*
Ibuprofen (p.64·2).

Ibu-6 *Master, Chile†.*
Ibuprofen (p.64·2).

Ibu-600 *Yeni, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibu-4, -6, -8 *Truxton, USA.*
Ibuprofen (p.64·2).

Ibu Benuron *Novartis Consumer, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Ibu Evanol *GSK, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Ibu Evanol Plus *GSK, Arg.*
Ibuprofen (p.64·2); caffeine (p.1116·3).
Fever; pain.

Ibualgic *EG, Fr.†.*
Ibuprofen (p.64·2).
Pain.

ibu-Attritin *Tussin, Ger.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibubenitol *Benitol, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibubeta *Betapharm, Ger.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibubex *Bexal, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ibu-Buscapina *Boehringer Ingelheim, Arg.†.*
Ibuprofen (p.64·2); hyoscine butylbromide (p.1734·1).
Pain with muscle spasm.

Ibucalmin *Tetrafarm, Arg.*
Ibuprofen (p.64·2).
Inflammation; pain.

Ibucaps *Zuoz, Venez.*
Ibuprofen (p.64·2).
Inflammation; pain.

Ibucare *PSM, NZ.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibucler *Monserrat, Arg.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Ibuclin *Reddy, Rus.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Ibucod *Pharmacare, S.Afr.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Inflammation; pain.

Ibucoden *Farma, Venez.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Pain.

Ibudol *Sanova, Austria.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ibudolofrix *Penn, Arg.*
Ibuprofen (p.64·2); codeine (p.37·2).
Pain.

Ibudolor *Stada, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Ibudone *Proethic, USA.*
Hydrocodone tartrate (p.63·1); ibuprofen (p.64·2).
Pain.

Ibudristan *Wyeth Consumer, Arg.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Fever; nasal congestion; pain.

Ibudros *Manetti Roberts, Ital.†.*
Ibuproxam (p.66·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; phlebitis; superficial thrombophlebitis.

Ibufabra *Fabra, Arg.*
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; inflammation; pain.

Ibufac *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibufein *Slovakofarma, Cz.†.*
Ibuprofen (p.64·2); caffeine (p.1116·3).
Fever; pain.

Ibufem *Sanova, Austria; Galpharm, UK.*
Ibuprofen (p.64·2).
Dysmenorrhoea; pain.

Ibufen *Dexxon, Israel; CCM, Malaysia†; Medana, Pol.; Medana, Rus.; Beacons, Singapore; Cinfa, Spain; Abbott, Turk.; Vargas, Venez.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain; soft-tissue injury.

Ibufenac *Ronava, Venez.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Ibufen-L
Note. This name is used for preparations of different composition.
Amino, Switz.
Suppositories: Ibuprofen lysine (p.64·2); lidocaine hydrochloride (p.1862·3).
Gout; musculoskeletal, joint, and peri-articular disorders.
Amino, Switz.
Tablets: Ibuprofen lysine (p.64·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Ibufix *Investi, Arg.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibuflam *Lichtenstein, Ger.; 3M, Mex.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibuflamar-P *Indoco, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Ibuflex *Rayere, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Ibufran *Neo Quimica, Braz.*
Ibuprofen (p.64·2).

Ibugan *Aventis, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Ibugel *Abbott, Austria; Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Ibugesic *Cipla, India; Cipla-Medpro, S.Afr.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ibugesic Plus *Cipla, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Musculoskeletal and joint disorders; pain.

Ibugesic-M *Cipla, India.*
Methocarbamol (p.1897·3); ibuprofen (p.64·2).
Skeletal muscle spasm.

Ibu-Hepa *Zentiva, Cz.*
Ibuprofen (p.64·2); a heparinoid (p.1305·2).
Inflammation; soft-tissue disorders; venous insufficiency.

Ibuhexal *Hexal, Ger.*
Ibuprofen (p.64·2) or ibuprofen sodium (p.65·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibu-Lady *Microsules Bernabo, Arg.†.*
Ibuprofen (p.64·2).
Fever; pain.

Ibulam *Lamsa, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibulan *Olan-Kemed, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ibuleve *Dermal, Israel; Pharmacia, S.Afr.; Dendron, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ibulgan *Logap, Neth.†.*
Ibuprofen (p.64·2).
Fever; pain.

Ibuloid *Reddy, Singapore†.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; pain.

Ibulos *Vomelin, Hung.†.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Ibum *Hasco-Lek, Pol.*
Ibuprofen (p.64·2).
Fever; pain.

Ibumac *Belmac, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ibumar *Mar, Arg.*
Ibuprofen (p.64·2).
Inflammation; pain.

Ibumar Migra *Mar, Arg.†.*
Ibuprofen (p.64·2); caffeine (p.1116·3); ergotamine (p.621·3).
Migraine.

Ibumax *Vitabalans, Cz.; Vitabalans, Fin.; Vitabalans, Hung.; Xeragen, S.Afr.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibumed *Pharmethic, Belg.; Group, S.Afr.*
Ibuprofen (p.64·2).
Fever; pain.

Ibumerck *Merck dura, Ger.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibumetin *Nycomed, Austria; Nycomed, Denm.; United Nordic, Denm.; Leiras, Fin.; Nycomed, Norw.; Nycomed, Swed.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibumol *Pharmacare, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; pain.

Ibumousse *Dermal Laboratories, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Ibumultin *Lazar, Arg.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Ibunastizol *Bago, Arg.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Cold and influenza symptoms.

Ibu-Novalgina *Aventis, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibup *Bouzen, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibupain *Sandoz, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Ibupain Forte *Sandoz, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Ibupal *Jagson, India.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; pain.

Ibupar *Polfa Pabianice, Pol.*
Ibuprofen (p.64·2).
Fever; pain.

Ibupax *Alter, Port.†.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibupen *APT, Hong Kong.*
Ibuprofen (p.64·2).
Fever; pain.

Ibuphlogont *Azupharma, Ger.†.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibupirac
Pfizer, Arg.
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.
Chemopharma, Chile.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibupirac Compuesto *Chemopharma, Chile.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Ibupirac Fem *Pfizer, Arg.*
Ibuprofen (p.64·2); homatropine methylbromide (p.1881·3).
Pain with muscle spasm.

Ibupirac Flex *Pfizer, Arg.*
Ibuprofen (p.64·2); chlorzoxazone (p.1894·3).
Musculoskeletal and joint disorders; pain.

Ibupirac Flu *Chemopharma, Chile.*
Ibuprofen (p.64·2); pseudoephedrine (p.1571·2).
Cold and influenza symptoms; nasal congestion.

Ibupirac Migra *Pfizer, Arg.*
Ibuprofen (p.64·2); caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Migraine.

Ibupiretas *Pfizer, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Ibupril *Teuto, Braz.*
Ibuprofen (p.64·2).

Ibuprin *Vivax, Venez.*
Ibuprofen (p.64·2).
Fever; pain.

Ibuproct *Olvos, Gr.*
Trimebutine (p.2404·3); ruscogenin (p.2382·2).
Rectal disorders.

Ibuprof *CT, Ger.†.*
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibuprofan *Bunker, Braz.*
Ibuprofen (p.64·2).

Ibuprofenix *Phoenix, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Ibuprofex *Sertex, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibuprom *US Pharmacia, Pol.*
Ibuprofen (p.64·2).
Fever; pain.

Ibuprom Zatoki *US Pharmacia, Pol.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Ibupron *Ratiopharm, Austria.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ibuprox *Ratiopharm, Norw.; Ferrer, Spain; Elmor, Venez.†.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal and joint disorders; musculoskeletal, joint, and peri-articular disorders; pain.

Ibu-Proxyvon *Wockhardt, India.*
Ibuprofen (p.64·2); dextropropoxyphene hydrochloride (p.40·1).
Musculoskeletal and joint disorders; pain.

Ibu-ratiopharm *Ratiopharm, Ger.*
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Iburem *Sanova, Austria†.*
Ibuprofen (p.64·2).
Pain.

Iburen *Hua, Thai.†.*
Ibuprofen (p.64·2).
Gout; musculoskeletal and joint disorders.

Ibureumin *Durascan, Denm.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Ibusal *Orion, Fin.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Ibusi *Mertens, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibusifar *Siphar, Switz.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibu-Slow *Therabel, Belg.†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ibusol *Cassara, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibuspray *Dermal Laboratories, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Ibustrin
Pfizer, Austria; Pfizer, Cz.; Pfizer, Mex.; Pharmacia, Pol.; Pfizer, Port.; Pfizer, Venez.
Indobufen (p.1315·1).
Thromboembolic disorders.
Pfizer, Ital.
Indobufen (p.1315·1) or indobufen sodium (p.1315·1).
Thrombosis prophylaxis.

Ibusumal *Purissimus, Arg.*
Ibuprofen (p.64·2).
Pain.

Ibu-Tab *Alra, USA.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Ibutab *Zee, USA.*
Ibuprofen (p.64·2).
Fever; pain.

Ibutad *TAD, Ger.*
Ibuprofen (p.64·2) or ibuprofen sodium (p.65·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibutan *Meyer, Venez.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibutenk *Biotenk, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Ibu-Tetralgin *Craveri, Arg.*
Ibuprofen (p.64·2); ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Ibutin *Galenica, Gr.*
Trimebutine (p.2404·3).
Gastrointestinal and gallbladder pain.

Ibutop *Sanova, Austria; Omega, Belg.; Dolorgiet, Denm.; Omega, Fr.; Chefaro, Ger.; Dolorgiet, Hung.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ibutop Cuprofen *SSL, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ibutop Ralgex *SSL, UK.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal pain.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ibux *Weifa, Norw.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Ibuxim *Vitarum, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ibuxin *Ratiopharm, Fin.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Ibuzidine *Hexa, Arg.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

IC Green *Akorn, Israel; Akorn, USA.*
Indocyanine green (p.2324·3).
Determination of cardiac output and liver blood flow; ophthalmic angiography.

Icaden *Intendis, Braz.; Intendis, Mex.; Schering, Mex.; Schering, Venez.*
Isoconazole (p.536·2) or isoconazole nitrate (p.536·2).
Fungal and Gram-positive vulvovaginal infections; fungal skin infections.

Icaps
Alcon, Canad.; Alcon, Chile; Ciba Vision, USA.
Multivitamin and mineral preparation (p.1922·1).

Alcon, Singapore; Alcon, UK.
Vitamins; minerals; lutein; zeaxanthin (p.1922·1).
Nutritional supplement.

Alcon, Hong Kong; Alcon, Thai.; Alcon, Venez.†.
Vitamins; minerals; lutein (p.1922·1).
Dietary supplement.

Icaps Lutein and Zeaxanthin *Alcon, Canad.*
Vitamin and mineral preparation with lutein and zeaxanthin (p.1922·1).

Icaps Plus *Alcon, Arg.*
Vitamins; minerals; cysteine (p.1922·1).

Icar *Hawthorn, USA.*
Carbonyl iron (p.1949·1).
Iron deficiency; iron supplement.

Icar Prenatal *Hawthorn, USA.*
Tablets, vitamins; minerals; chewable tablets, calcium carbonate; soft gel capsules, omega-3 marine triglycerides (p.1922·1).
Nutritional supplement during pregnancy and lactation.

Icar-C Plus *Hawthorn, USA.*
Carbonyl iron (p.1949·1); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Folate deficiency; iron-deficiency anaemia.

Icavex *Viatris, Fr.†.*
Moxisylyte hydrochloride (p.1344·3).
Erectile dysfunction.

Icaz *Sankyo, Fr.; Wander, Philipp.*
Isradipine (p.1319·2).
Hypertension.

Ice Cool *Hovid, Malaysia.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Musculoskeletal pain.

Ice Cool Stress & Tension Relief *Amirose, UK.*
Menthol (p.2340·1).
Headache; tension.

Ice Gel *Mentholatum, Austral.; Hyde, Canad.†.*
Menthol (p.2340·1).
Muscular aches and pains.

Ice Gel Therapy *Sutton, Canad.*
Menthol (p.2340·1).

Ice Lipbalm *Mentholatum, Canad.†.*
SPF 12: Padimate O (p.1609·1).
Sunscreen.

Icetazol *IQFA, Mex.*
Paracetamol (p.108·1).
Fever; pain.

ICG-Pulsion *Pulsion, Ger.; IFET (ΙΦΕΤ), Gr.; Pulsion, Israel; Pulsion, Neth.*
Indocyanine green (p.2324·3).
Diagnostic agent.

Ichthalgan *Ichthyol, Ger.†.*
Heparin sodium (p.1301·2); ictasol (p.1599·1).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Ichthalgan forte *Ichthyol, Austria.*
Heparin sodium (p.1301·2); ictasol (p.1599·1).
Musculoskeletal, joint, and peri-articular disorders.

Ichtho-Bad *Ichthyol, Austria; Ichthyol, Ger.; Ichthyol, Switz.*
Ichthammol (p.1599·1).
Bath additive; genito-urinary disorders; hyperhidrosis; musculoskeletal and joint disorders; neuralgia; skin disorders; superficial circulatory disorders; wounds.

Ichtho-Bellol *Ichthyol, Austria; Ichthyol, Ger.†.*
Ictasol (p.1599·1); atropine sulfate (p.1219·3).
Anogenital disorders; pelvic disorders; urogenital disorders.

Ichtho-Bellol compositum S *Ichthyol, Ger.†.*
Ictasol (p.1599·1); atropine sulfate (p.1219·3); propyphenazone (p.119·3).
Pelvic disorders.

Ichtho-Cortin *Ichthyol, Austria.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2); ictasol (p.1599·1).
Skin disorders.

Ichthocortin *Ichthyol, Ger.*
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2); ictasol (p.1599·1).
Skin disorders.

Ichthoderm *Ichthyol, Ger.*
Ictasol (p.1599·1).
Scalp disorders.

Ichth-Oestren *Ichthyol, Austria.*
⊗ Estradiol benzoate (p.2097·2); light ammonium bituminosulfonate (p.1599·1); urea (p.1620·2); lactose (p.1954·1).
Vaginal disorders.

Ichtholan *Ichthyol, Austria; Ichthyol, Ger.; Ichthyol, Switz.*
Ichthammol (p.1599·1).
Musculoskeletal, joint, and peri-articular disorders; pyoderma; skin disorders; sports injuries; thrombophlebitis.

Ichtholan spezial *Ichthyol, Ger.*
Ichthammol (p.1599·1).
Musculoskeletal and joint disorders.

Ichtholan T *Ichthyol, Ger.*
Ictasol (p.1599·1).
Skin disorders.

Ichthopaste *Smith & Nephew, Ital.; Smith & Nephew, UK.*
Ichthammol (p.1599·1); zinc oxide (p.1621·2).
Medicated bandage; skin disorders.

Ichthoseptal *Ichthyol, Ger.*
Chloramphenicol (p.239·3); ictasol (p.1599·1).
Infected skin disorders.

Ichthosin *Ichthyol, Ger.*
Ictasol (p.1599·1).
Skin disorders.

Ichthraletten *Ichthyol, Austria; Ichthyol, Ger.*
Sodium bituminosulfonate (p.1599·1).
Acne; chilblains; seborrhoea; skin disorders.

Ichthyol *Ichthyol, Ger.*
Ichthammol (p.1599·1).
Skin disorders.

Ichtopur *Ichthyol, Austria.*
Ichthammol (p.1599·1).
Urogenital disorders.

Ichtoxyl *Herbacos, Cz.*
Ichthammol (p.1599·1).
Skin disorders.

Ichtyosoft
Note. This name is used for preparations of different composition.
Fouchard, Chile†.
Ictasol (p.1599·1); ammonium lactate (p.1589·2); salicylic acid (p.1612·2).
Seborrhoea.

LED, Fr.†.
Cream: Ictasol (p.1599·1); ammonium lactate (p.1589·2).
Skin disorders.

LED, Fr.†.
Shampoo: Ictasol (p.1599·1); ammonium lactate (p.1589·2); salicylic acid (p.1612·2).
Scalp disorders.

I-Clom *Yung Shin, Philipp.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Iclopid *Polfa Pabianice, Pol.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Iclox *Ipca, India†.*
Cloxacillin (p.256·1).
Bacterial infections.

Icodial *Bieffe, Ital.†; ML, Neth.; Baxter, Spain†.*
Icodextrin; sodium chloride; sodium lactate; calcium chloride; magnesium chloride (p.1670·3).
Peritoneal dialysis.

I-Cof *TC Pharma-Chem, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Icol *Alcon Cusi, Spain.*
⊗ Chloramphenicol (p.239·3) or chloramphenicol succinate (p.241·3); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Icolid *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Icolid CPM *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Coughs.

Icolid Plus *Greater Pharma, Thai.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold symptoms; coughs.

Icona *Farmaline, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Iconal *Anpharm (Ανφαρμ), Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Icoplax *Richmond, Arg.*
Vancomycin (p.358·3).
Bacterial infections.

Icoran *Biomedica-Chemica, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Icorsan *Tocogino, Mex.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Ictage 6 *Q-Med, Ital.†.*
Gamolenic acid (p.2308·2).
Skin disorders.

Icthaband *SSL, Austral.†; Medlock Medical, UK.*
Ichthammol (p.1599·1); zinc oxide (p.1621·2).
Eczema; leg ulcers; medicated bandage.

Ictiomen *Casen Fleet, Spain.*
Ichthammol (p.1599·1); talc (p.1615·2); menthol (p.2340·1).
Skin disorders.

Ictom 3 *Q-Med, Ital.†.*
Omega-3 triglycerides (p.1362·1); vitamin E (p.1992·2).
Dry skin.

Ictotest *Bayer, Austral.; Bayer Diagnostici, Ital.†; Bayer Diagnostics, Mex.†; Bayer Diagnostics, UK; Bayer, USA.*
Test for bilirubin in urine.

Ictus *Biolab Sanus, Braz.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Ictyane
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
A range of moisturisers and soap substitutes.

Ducray, Fr.
Glycerol (p.2314·2); white soft paraffin (p.2031·2).
Dry skin disorders.

Ictyane HD *Ducray, Fr.*
Hydroxydecine; white soft paraffin (p.2031·2); glycerol (p.2314·2); karite.
Dry skin disorders.

Ictyoderm *Bioderma, Fr.†.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin; keratinisation disorders.

Icy Hot *Pharmacia, S.Afr.; Chattem, Singapore; Chattem, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Icy Hot Back Pain Relief *Chattem, USA.*
Menthol (p.2340·1).

Icy Hot Pop & Peel *Chattem, USA.*
Menthol (p.2340·1).

Icy Hot Pro-Therapy *Chattem, USA.*
Menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue pain.

Icy Rub *Kato, Pol.*
Benzocaine (p.1854·1); menthol (p.2340·1); thymol (p.1664·3).
Musculoskeletal, joint, and soft-tissue pain.

Id Sedin *Nikkho, Braz.†.*
Gamma-aminobutyric acid (p.2308·1); reserpine (p.1387·3).
Cerebral disorders.

Ida *The Forty-Two, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Ida-D *The Forty-Two, Thai.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Idalprem *Novartis Consumer, Spain.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; nausea and vomiting.

Idamycin *Pfizer, Canad.; Pfizer, Mex.; Pharmacia Upjohn, USA.*
Idarubicin hydrochloride (p.731·1).
Breast cancer; leukaemias.

Idaptan *Danval, Spain.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; neurosensorial ischaemia; retinal ischaemia; vestibular disorders.

Idarac *Sanofi Synthelabo, Canad.†; Sanofi-Aventis, Fr.; Aventis, Irl.†; Aventis, Thai.*
Floctafenine (p.60·3).
Inflammation; pain.

Idaralem *Lemery, Mex.; Lemery, Thai.*
Idarubicin hydrochloride (p.731·1).
Acute leukaemias; breast cancer.

Idarrux *Richmond, Arg.†.*
Idarubicin (p.731·2).
Malignant neoplasms.

Idasal *Chefaro, Spain.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; sinusitis.

Idasal Nebulizador *Pfizer Lambert, Spain†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Idazole *Chew, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; necrotising ulcerative gingivitis; trichomoniasis.

Idc *Pharmaland, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Idealid
Note. This name is used for preparations of different composition.
Alterna, Ital.
Nimesulide (p.95·3).
Fever; inflammation; pain.

AF, Mex.†.
Lidamidine (p.1740·2).
Diarrhoea; irritable bowel syndrome.

Idealite *Rafarm, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Idecortex *Pentafarma, Port.*
Idebenone (p.367·1).
Mental function disorders.

Idena *Raffo, Arg.*
Ibandronate (p.1098·3).

Idenona *Andromaco, Arg.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Ideogrip *Bioquimico, Arg.*
Loratadine (p.583·3); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Formerly contained astemizole, paracetamol, and phenylephrine.
Cold and influenza symptoms.

Ideolaxyl *GSK Sante, Fr.*
Aloes (p.1705·2); senna (p.1769·2).
Constipation.

Ideos *Innotech, Cz.; Innotech, Denm.†; Meda, Fin.; Innotech, Fr.; Sanofi Synthelabo, Ger.; Winthrop, Ger.; Vianex (Βιανεξ), Gr.; Innotech, Hung.; Helsinn Birex, Irl.; Madaus, Ital.; Innotech, Neth.; Innotech, Norw.; Innothera, Pol.; Innotech, Port.; Innotech, Rus.; Vita, Spain; Meda, Swed.; Zuoz, Venez.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium supplement; hyperparathyroidism; osteoporosis.

Iderpes *Pierre Fabre, Switz.†.*
Idoxuridine (p.881·2).

Idesole *Phoenix, Arg.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Idesole Plus *Phoenix, Arg.*
Idebenone (p.367·1); nimodipine (p.1357·2).
Cerebrovascular disorders.

Idicin *Indian Drugs, India†.*
Indometacin (p.66·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Idina *Grin, Mex.†.*
Idoxuridine (p.881·2).
Herpes simplex eye infections.

Idle *Klonal, Arg.†.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Ido-C *Abigo, Swed.*
Ascorbic acid (p.1983·3).
Some tablets also contain sodium ascorbate.
Vitamin C deficiency.

Ido-E *Pfizer, Fin.; Pfizer, Norw.; ACO, Swed.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Idom *Biokanol, Ger.*
Dosulepin hydrochloride (p.388·2).
Depression.

Idomethine *Kowa, Jpn.*
Indometacin (p.66·3).
Inflammation; oedema; pain.

Idon *Saval, Chile.*
Domperidone (p.1726·2).
Gastrointestinal disorders; gastrointestinal investigations; parkinsonism.

Idotrim *Abigo, Swed.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Idotyl *Ferrosan, Denm.*
Aspirin (p.20·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Idovit *Vitamed, Israel.*
Povidone-iodine (p.1659·2).
Bacterial and fungal skin infections; burns; skin disinfection; wounds.

Idoxen *Dollder, Venez.*
Venlafaxine (p.430·1).
Anxiety; depression.

IDR *Sidefarma, Port.†.*
Fentiazac (p.60·1).
Inflammation; pain.

Idracal *Bruno, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; rickets.

Idracemi
Note. This name is used for preparations of different composition.
Farmigea, Ital.
Eye drops: ⊗ Hydrocortisone sodium phosphate (p.1535·3).
Eye disorders.

Farmigea, Ital.
Eye ointment: ⊗ Hydrocortisone hydrogen succinate (p.1535·3); neomycin sulfate (p.305·1); chloramphenicol (p.239·3).
Eye disorders.

Idracemi Eparina *Farmigea, Ital.*
⊗ Hydrocortisone sodium phosphate (p.1535·3); heparin sodium (p.1301·2).
Eye disorders.

Idranox *Gap, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Idril N sine *Winzer, Ger.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye disorders.

Idro P2 *Sanofi Synthelabo, Ital.†.*
Sulmarin sodium; ascorbic acid (p.1983·3).
Capillary disorders; haemorrhage.

Idrocet *Lusofarmaco, Ital.†.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Inflammatory eye and ear disorders.

Idrolax *Schwarz, UK†.*
Macrogol 4000 (p.2336·3).
Constipation.

Idrolone *Sanofi-Aventis, Ital.*
⊗ Fenquizone potassium (p.1287·3).
Hypertension; oedema.

Idroneomicil *Pharmacia, Ital.†.*
⊗ Neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2); naphazoline nitrate (p.1565·2).
Infection and inflammation of the eye, nose, and ear.

Idropan B *Lisapharma, Ital.†.*
Vitamin B substances (p.1922·1); calcium folinate (p.1943·3).
Deficiency states; megaloblastic anaemia.

Idroplurivit *Menarini, Ital.*
Multivitamin preparation (p.1922·1).

Idroquark *Polifarma, Ital.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Idroskin *Mavi, Ital.*
Collagen (p.2286·1).
Dry skin.

Idroskin C *Mavi, Ital.*
Hyaluronic acid (p.2320·1); vitamin C (p.1983·3).
Dry skin.

Idrostamin *Gap, Gr.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Idrovel *Savoma, Ital.*
Emollient.

Idroxocobalamina *IFET (IΦET), Gr.†.*
Vitamin B (p.1980·2).
Megaloblastic anaemia.

Iducher *Farmigea, Ital.*
Idoxuridine (p.881·2).
Herpesvirus infections of the eye.

Idulamine *Schering-Plough, Mex.†.*
Azatadine maleate (p.568·1).
Allergic skin reactions; rhinitis.

Idulanex *Schering-Plough, Spain.*
Azatadine maleate (p.568·1); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Idulea *Elea, Arg.*
Idoxuridine (p.881·2).
Herpesvirus infections of the eye, face, lips, and genitals.

Idustatin *Sanofi-Aventis OTC, Ital.*
Idoxuridine (p.881·2).
Herpes simplex infections of the skin and mucous membranes.

Iduvo *Dosa, Arg.†.*
Zidovudine (p.913·3).
HIV infection.

Idyl *Multicare, Philipp.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Iecatec *Tedec Meiji, Spain; Meiji, Thai.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Iecilline *Ulagay, Turk.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Iesef *Ulagay, Turk.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Iesetum *Ulagay, Turk.*
Ceftazidime (p.234·1).
Bacterial infections.

Iespor *Ulagay, Turk.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ietepar *Rottapharm, Ital.†.*
Betaine glucuronate (p.2265·2); diolamine glucuronate (p.2314·2); nicotinamide ascorbate (p.1957·2).
Liver disorders; poisoning.

Ifa Acxion *Investigacion, Mex.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Ifa Kafen *Investigacion, Mex.†.*
Caffeine (p.1116·3).
Fatigue.

Ifa Lose *Investigacion, Mex.*
⊗ Mazindol (p.2157·3).
Obesity.

Ifa Norex *Investigacion, Mex.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Ifa Reduccing *Investigacion, Mex.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Ifa Slim *Investigacion, Mex.†.*
Chromium (p.1934·3).
Prevention of hypoglycaemia.

Ifabla *Andromaco, Mex.†.*
Vinblastine (p.786·3).
Malignant neoplasms.

Ifacap *Mayne, Mex.*
Carboplatin (p.693·1).
Ovarian cancer.

Ifa-Certez *Investigacion, Mex.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Ifacil *Andromaco, Mex.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Ifacur *Andromaco, Mex.†.*
Atracurium besilate (p.1902·1).

Ifadac *Mayne, Mex.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Ifa-Diety *Investigacion, Mex.*
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Ifadox *Mayne, Mex.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Ifa-Fonal *Investigacion, Mex.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm; spasticity.

Ifamet *Mayne, Mex.*
Methotrexate (p.745·2).
Malignant neoplasms.

Ifamit *Andromaco, Mex.†.*
Mitomycin (p.752·1).
Malignant neoplasms.

Ifamul *Guardian, Indon.*
Famotidine (p.1730·1).
Endocrine adenoma; peptic ulcer; Zollinger-Ellison syndrome.

Ifapidin *Anpharm, Pol.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Ifarab *Mayne, Mex.*
Cytarabine (p.705·1).
Malignant neoplasms.

Ifavac *Mayne, Mex.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Ifavin *Andromaco, Mex.†.*
Vincristine (p.788·1).
Malignant neoplasms.

Ifavor *Mayne, Mex.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy in colorectal cancer; antidote to folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity.

Ifaxol *Mayne, Mex.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Ifemed *Medifive, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Ifenec
Italfarmaco, Ital.
Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal infections; Gram-positive bacterial infections.

Italfarmaco, Rus.
Econazole nitrate (p.531·1).
Fungal skin and vaginal infections.

Ifentil *Biomep, Mex.*
Ibuprofen (p.64·2).
Pain.

Ifex *Baxter, Canad.; BMS Oncology, USA.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifex-M *Biochem, India.*
Ifosfamide (p.731·3); mesna (p.1449·2).
Malignant neoplasms.

Ificef *Unique, Rus.*
Ceftriaxone (p.238·1).
Bacterial infections.

Ificipro
Unique, India†.
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Unique, Rus.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ifipef *Unique, India†.*
Pefloxacin (p.313·3).
Gram-positive bacterial infections.

Ifiral *Unique, Rus.*
Sodium cromoglicate (p.1136·3).

Ifistatin *Unique, Singapore.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Ifizol *Unique, Rus.*
Cefazolin (p.222·1).
Bacterial infections.

IFO-cell *Cell Pharm, Ger.; Cell-Pharm, Thai.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifocid *Richmond, Arg.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Ifocris *LKM, Arg.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifolem *Laboratorios Chile, Chile; Lemery, Mex.; Lemery, Thai.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifomida *Asofarma, Mex.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifor *Medix, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Ifos
Note. This name is used for preparations of different composition.
Tecnofarma, Chile†.
Ofloxacin (p.310·2).
Bacterial infections.

Cipla, India.
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifosmixan *Richmond, Arg.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifoxan *Baxter Oncology, Israel; Baxter, Mex.†.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ifuchol *Ifusa, Mex.*
Cynara (p.2291·2); boldo (p.2267·2); turmeric (p.1473·2).
Digestive disorders.

Ifumelus *Ifusa, Mex.†.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Ifupasil *Ifusa, Mex.*
Passion flower (p.2363·2); salix (p.121·3); crataegus (p.2289·1).
Nervous disorders.

Ifupeptol Magnesiado *Ifusa, Mex.*
Magnesium sulfate (p.1679·3).
Hypersensitivity.

Ifutemp *Ifusa, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

IFX *Pfizer, Arg.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ig Gamma *Nuovo ISM, Ital.†.*
A normal immunoglobulin (p.2225·3).
Immune deficiency; passive immunisation.

Ig Tetano *Nuovo ISM, Ital.†.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Ig Vena *Kedrion, Ital.; Kedrion, Port.; Kedrion, Thai.*
A normal immunoglobulin (p.2225·3).
Bone-marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Ig Vena N *Biosano, Chile.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; immunodeficiency disorders.

IG Vena NIV *Onko, Turk.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation.

Igamad *Grifols, Chile; Grifols, Cz.; Grifols, Ital.; Grifols, Thai.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Igantet *Grifols, Arg.; Grifols, Chile; Grifols, Ital.; Grifols, Malaysia; Grifols, Singapore.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Igantibe *Grifols, Arg.; Grifols, Chile; Grifols, Ital.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Igantid *Grifols, Arg.; Grifols, Port.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Igastrum Plus *Pharos, Indon.*
Bovine colostrum; vitamins (p.1922·1).
Nutritional supplement.

IgeE *Grands Espaces, Fr.*
Black currant (p.2267·1); raspberry (p.1472·2).
Cold symptoms.

I-Gesic *Centaur, India.*
Diclofenac sodium (p.44·3).
Allergic conjunctivitis; eye inflammation and pain; inhibition of miosis in cataract surgery.

IgG *Purissimus, Arg.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Igir *Velka, Gr.*
Loratadine (p.583·3).

Igitur-antirheumatische *Apomedica, Austria.*
Diethylamine salicylate (p.47·2); salicylic acid (p.1612·2); benzyl nicotinate (p.28·1); camphor (p.2273·2).
Musculoskeletal, joint, and peri-articular disorders.

Igitur-Rheumafluid *Apomedica, Austria.*
Diethylamine salicylate (p.47·2); salicylic acid (p.1612·2); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); camphor (p.2273·2).
Musculoskeletal and joint disorders; peripheral vascular disorders.

I-Glo *Aspen, S.Afr.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Iglodine *Fecofar, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.

Iglodine Flex *Fecofar, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Inflammation; musculoskeletal disorders; pain.

Iglu *Dendron, UK.*
Aminoacridine hydrochloride (p.1625·1); lidocaine hydrochloride (p.1862·3).
Mouth ulcers, sore gums.

Ignatia-Homaccord *Peithner, Austria.*
Homoeopathic preparation.

Igroseles *Schwarz, Ital.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Igroton *Novartis, Ital.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Igroton-Lopresor *Sankyo, Ital.*
⊗ Chlortalidone (p.1243·3); metoprolol tartrate (p.1338·1).
Hypertension.

Igroton-Reserpina *Novartis, Ital.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Iguassina *Zambon, Braz.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

IHD *Stadmed, India.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Ihtiyol *Cagdas, Turk.; Oro, Turk.*
Ichthammol (p.1599·1).
Eczema.

Ika Sariawan *Ikapharmindo, Indon.*
Abrus precatorius (p.2244·1); betel; liquorice (p.1740·3); peppermint oil (p.1761·2).
Mouth hygiene; mouth ulcers.

Ikaclomin *Teva, Israel.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; oligospermia.

Ikacor *Teva, Israel.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Ikacycline *Ikapharmindo, Indon.*
Tetracycline hydrochloride (p.347·2).
Skin infections.

Ikaderm *Ikapharmindo, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Ikadryl *Ikapharmindo, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Ikadryl DMP
Note. This name is used for preparations of different composition.
Ikapharmindo, Indon.
Syrup: Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough.

Ikapharmindo, Indon.
Tablets: Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cough.

Ikaflux *Cifarma, Braz.*
Potassium iodide (p.2169·2); guaifenesin (p.1561·3).
Coughs.

Ikagen *Ikapharmindo, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Ikamicetin *Ikapharmindo, Indon.*
Chloramphenicol (p.239·3).
Skin infections eye infections.

Ikamoxyl *Ikapharmindo, Indon.*
Amoxicillin (p.202·2).
Bacterial infections.

Ikaneuron *Ikapharmindo, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Migraine; neuralgia; neuritis; neuropathy; paraesthesia; vitamin B deficiency; vomiting of pregnancy.

Ikaneuron Plus *Ikapharmindo, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ikaphen *Ikapharmindo, Indon.*
Phenytoin sodium (p.495·2).
Epilepsy.

Ikapress *Teva, Israel.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Ikaprim *Ikapharmindo, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections; toxoplasmosis.

Ikaran *Pierre Fabre, Fr.; Formenti, Ital.; Robapharm, Switz.†.*
Dihydroergotamine mesilate (p.618·2).
Hypotension;migraine and vascular headache; venous insufficiency; vertigo.

Ikatin *Pisa, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Ikatral *Baliarda, Arg.*
OPC.
Varices; venous disorders.

Ikatral Periferico *Baliarda, Arg.*
OPC; pentoxifylline (p.1367·2).
Vascular disorders.

Ikeriane *Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.*
Guanidine glycolate.
Dry skin disorders.

Ikestatina *Crinos, Ital.; Neopharma, Venez.*
Somatostatin acetate (p.1809·2).
Diabetic ketoacidosis; gastrointestinal haemorrhage; gastrointestinal radiography; prevention of complications following pancreatic surgery.

Ikobel *Rafarm, Gr.*
Tobramycin (p.354·1).
Eye infections.

Ikolan *Hexal, Arg.†.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Ikoplex *Knop, Chile.*
A range of homoeopathic preparations.

Ikorel *Aventis, Austral.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Aventis, Neth.; Aventis, UK.*
Nicorandil (p.1349·1).
Angina pectoris.

Iktorivil *Roche, Swed.*
Clonazepam (p.478·2).
Epilepsy.

Ikx Autobronceante *Ikx, Arg.*
Dihydroxyacetone (p.1594·1).
Tanning aid.

Ikx Gel Reductor *Ikx, Arg.*
Phosphatidyl choline (p.2367·1); caffeine (p.1116·3); guarana (p.2416·1).

IL-33 *Istanbul, Turk.*
Trichloroacetic acid (p.1620·1); monochloroacetic acid (p.1608·1); dichloroacetic acid.
Warts.

IL HWA *Allcura, Ger.*
Ginseng (p.2312·1).
Tonic.

Ila-med m *Paesel, Ger.*
Pipenzolate bromide (p.1762·2).
Gastrointestinal disorders.

Ilaten *Lamsa, Arg.*
⊗ Atenolol (p.1217·3).
Hypertension.

Ildamen *Viatris, Austria; AWD, Ger.†; Zydus, India; Transfarma, Philipp.; Sidefarma, Port.*
Oxyfedrine hydrochloride (p.1365·2).
Angina pectoris; arrhythmias; heart failure; myocardial infarction.

Ilduc *Baliarda, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Ilduc Duo *Baliarda, Arg.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Ilefrin *GMP, Indon.*
Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Iletin II Pork Lente *Lilly, Canad.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Iletin II Pork NPH *Lilly, Canad.*
⊗ Isophane insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Iletin II Pork Regular *Lilly, Canad.*
⊗ Neutral insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Ilezol *Medimport, Mex.*
⊗ Mazindol (p.2157·3).
Obesity.

Ilgem *Rafarm, Gr.*
Ketoconazole (p.539·1).
Fungal infections.

Ilgen *Bioprofarma, Arg.*
Interleukin-2 (p.735·1).
Metastatic melanoma; renal cancer.

Iliaclor *Depofarma, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Iliadin *Merck, Chile; Merck, Denm.; Merck, Hong Kong; Merck, Indon.; Merck, Malaysia; Merck, Mex.; Merck, Norw.; Merck, S.Afr.; Merck, Singapore; Merck, Swed.; Merck, Thai.; Santa, Turk.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; cold symptoms; conjunctivitis; ear disorders; laryngitis; nasal congestion; otitis media; pharyngitis; rhinitis; sinusitis; syringitis.

Iliaxone *Farmaurino, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Iliocin *Offenbach, Mex.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Ilio-Funkton *Robugen, Ger.*
Dimethicone (p.1770·2).
Reduction of gastrointestinal gas.

Ilja Rogoff *Bayer, Ger.*
Garlic (p.2309·2); mistletoe (p.2345·3); crataegus (p.2289·1); sophora japonica; lupulus (p.2335·2).
Vascular disorders.

Ilja Rogoff Forte *Roche Consumer, Ger.†.*
Garlic (p.2309·2).
Hyperlipidaemia; vascular disorders.

Illa *Pietrasanta, Ital.*
Pregnancy test (p.2372·1).

Illings Bozner Maycur-Tee *Esplanade, Austria†.*
Senna (p.1769·2); magnesium sulfate (p.1679·3); chamomile (p.2279·3); fennel (p.2302·3).

Illument *Pliva, Hung.*
Sumatriptan succinate (p.625·2).
Migraine.

Illumina *InterMed, Philipp.; TMCi, Philipp.*
Glutathione (p.1448·1); thioctic acid (p.2400·2).
Nutritional supplement; premature skin ageing; uV-induced skin damage.

Ilman *Demo, Gr.*
Flunitrazepam (p.996·2).
Insomnia.

Iloban *Merck, Braz.*
Cyanocobalamin (p.1980·2); ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron deficiency.

Iloc *Sophia, Mex.*
Acetylcholine (p.1877·2).
Production of miosis.

Ilocin *Haller, Braz.†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Ilocit *Juste, Spain.*
Iloprost trometamol (p.1313·1).
Peripheral vascular disorders; thromboangitis obliterans.

Ilomedin *Schering, Austria; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Bayer Schering, Hung.; Agis, Israel; Bayer Schering, Malaysia†; Bayer, NZ; Schering, Norw.; Schering, Pol.; Berlimed, Port.; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.*
Iloprost trometamol (p.1313·1).
Peripheral vascular disorders; pulmonary hypertension; Raynaud's syndrome; thromboangiitis obliterans.

Ilomedine *Schering, Arg.†; Schering, Fr.; Schering, Neth.*
Iloprost trometamol (p.1313·1).
Peripheral vascular disorders; Raynaud's syndrome; thromboangiitis obliterans.

Ilon Abszess
Caesaro, Austria.
Venice turpentine; turpentine oil (p.2406·3).
Abscess; furunculosis; paranitium.

Cesra, Cz.; Cesra, Ger.
Turpentine; turpentine oil (p.2406·3).
Infected skin disorders; skin disorders.

Ilopan *Savage, USA.*
Dexpanthenol (p.2362·1).
Intestinal atony; paralytic ileus.

Ilopar *Pharmanel, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemia.

Ilosin *Collins, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Ilosone
Lilly, Arg.†; Lilly, Mex.; GSK, Philipp.; Aspen, S.Afr.; Lilly, Thai.; Dista, USA†; Farma, Venez.
Erythromycin estolate (p.269·3).
Bacterial infections.

ICN, Braz.; Lilly, Braz.
Erythromycin (p.269·2) or erythromycin estolate (p.269·3).
Bacterial infections.

Ilostal *Merck, Chile.*
Cilostazol (p.1245·2).
Intermittent claudication.

Iloticina *Medac, Arg.†; Lilly, Venez.†.*
Erythromycin (p.269·2).
Acne; bacterial infections.

Ilotycin *Dista, USA†.*
Erythromycin (p.269·2).
Bacterial eye infections.

Ilotycin TS *Pharmacare, S.Afr.*
Erythromycin (p.269·2).
Acne.

Ilotycin-A *Pharmacare, S.Afr.*
Tretinoin (p.1618·1).
Acne.

Ilozef *Shenzhen, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Ilsatec *Boehringer Ingelheim, Arg.†; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.†.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

I-Lube
Note. A similar name is used for preparations of different composition (see below).
FDC, India.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Ilube
Note. A similar name is used for preparations of different composition (see above).
Alcon, Irl.; Alcon, UK.
Acetylcysteine (p.1548·2); hypromellose (p.2144·2).
Dry eye syndromes.

Iluminoderm *Hautel, Arg.†.*
Padimate O (p.1609·1).
Sunscreen.

Iluminoderm Lips *Hautel, Arg.†.*
Homosalate (p.1598·1); titanium dioxide (p.1617·3).
Sunscreen.

Iluminoderm Plus *Hautel, Arg.†.*
Homosalate (p.1598·1); titanium dioxide (p.1617·3).
Sunscreen.

Ilvico
Note.This name is used for preparations of different composition.
Merck, Spain.
Brompheniramine maleate (p.569·2); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; nasal congestion; pain.

Merck, Venez.
Oral granules; tablets: Brompheniramine maleate (Ilvin) (p.569·2); paracetamol (p.108·1); caffeine (p.1116·3).
The tablets formerly contained brompheniramine, codeine, and paracetamol.
Influenza symptoms.

Merck, S.Afr.
Syrup: ⊗ Brompheniramine maleate (p.569·2); sodium ascorbate (p.1984·1); methylephedrine hydrochloride (p.1564·3); phenazone (p.116·1); sodium salicylate (p.124·2); codeine phosphate (p.37·2).
Allergic rhinitis; cold and influenza symptoms; sinusitis.

Merck, Venez.
Syrup: ⊗ Brompheniramine maleate (p.569·2); methylephedrine hydrochloride (p.1564·3); codeine phosphate (p.37·2).
Formerly contained brompheniramine, codeine, and paracetamol.
Coughs.

Merck, S.Afr.
Tablets: Brompheniramine maleate (p.569·2); calcium ascorbate (p.1984·1); propyphenazone (p.119·3); salicylamide (p.121·2); quinine hydrochloride (p.612·3); caffeine (p.1116·3).
Allergic rhinitis; cold and influenza symptoms; sinusitis.

Ilvico grippal *Merck, Ger.†.*
Ibuprofen (p.64·2).
Fever; pain.

Ilvico N *Merck, Port.*
Brompheniramine maleate (p.569·2); calcium ascorbate (p.1984·1); caffeine (p.1116·3); paracetamol (p.108·1).
Cold symptoms; fever; pain.

Ilvinax *Merck, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Ilvitus *Merck, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

I-L-X *Kenwood, USA.*
A range of preparations containing iron (p.1949·1), liver extracts (p.2337·3), and vitamin B substances (p.1922·1).
Vitamin C (p.1983·3) is included in some preparations to increase the absorption and availability of iron.
Iron-deficiency anaemias.

I-L-X B_{12} *Kenwood, USA.*
Iron preparation with multivitamins (p.1922·1).

IM 75 *Montpellier, Arg.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Imacillin
AstraZeneca, Denm.
Amoxicillin (p.202·2).
Bacterial infections.

AstraZeneca, Norw.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

AstraZeneca, Swed.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Imacort *Spirig, Cz.; Spirig, Switz.*
⊗ Clotrimazole (p.530·1); hexamidine isetionate (p.1646·3); prednisolone acetate (p.1541·1).
Infected skin disorders.

Imadrax *Sandoz, Denm.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Imagenil *Kyowa, Jpn.*
Ioxilan (p.1487·1).
Radiographic contrast agent.

Imagent *Alliance, USA.*
Perflexane lipid microspheres (p.1488·2).
Contrast medium for echocardiography.

Imagent GI *Alliance, USA.*
⊗ Perflubron (p.2365·1).
Adjunct to magnetic resonance imaging of the gastrointestinal tract.

Imagopaque *Amersham, Austria; Amersham Buchler, Ger.; Nycomed, Gr.; Amersham, Ital.; Amersham, Spain†; Amersham, Switz.†.*
Iopentol (p.1484·2).
Radiographic contrast medium.

Imalet *Best, Mex.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Imanance *Lancome, Canad.†.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Imanol *Biosintex, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.

Imap *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.†; Janssen-Cilag, Ger.; Janssen-Cilag, Neth.*
Fluspirilene (p.999·2).
Anxiety; insomnia; psychoses; schizophrenia.

Imatib *Cipla, India.*
Imatinib mesilate (p.733·1).
Chronic myeloid leukaemia.

Imavermil *IMA, Braz.*
Albendazole (p.139·2).
Worm infections.

Imax
Note. A similar name is used for preparations of different composition (see below).
Otsira, India.
Iron carbonyl (p.1950·3); vitamin B ; folic acid; vitamin C; zinc (p.1922·1).

I-Max
Note. A similar name is used for preparations of different composition (see above).
Patriot, Philipp.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Imazin *Napp, UK†.*
Aspirin (p.20·3); isosorbide mononitrate (p.1318·3).
Angina pectoris; myocardial infarction.

Imazol
Note.This name is used for preparations of different composition.
Spirig, Cz.; Meyer, Venez.
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Ivax, Mex.
Itraconazole (p.536·3).
Fungal infections.

Orva, Turk.
Clotrimazole (p.530·1); hexamidine isetionate (p.1646·3).
Fungal skin infections.

Karrer, Ger.; Spirig, Switz.
Cream: Clotrimazole (p.530·1); hexamidine isetionate (p.1646·3).
Fungal skin infections.

Karrer, Ger.
Paste: Clotrimazole (p.530·1); phenethyl alcohol (p.1655·3).
Fungal skin infections.

Spirig, Switz.
Paste: Clotrimazole (p.530·1).
Skin disorders.

Imazol comp *Karrer, Ger.*
⊗ Clotrimazole (p.530·1); hexamidine isetionate (p.1646·3); prednisolone acetate (p.1541·1).
Fungal skin infections.

Imazol Plus *Spirig, Cz.*
Clotrimazole (p.530·1); hexamidine isetionate (p.1646·3).
Fungal skin infections.

Imbibe *Ipca, India.*
Ezetimibe (p.1284·3).
Hyperlipidaemias.

Imbistad *Bajamed, Mex.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Imboost *Soho, Indon.*
Echinacea (p.2298·1); zinc picolinate (p.2001·1).
Immunostimulant.

Imboost Force *Soho, Indon.*
Echinacea purpurea (p.2298·1); black elderberry (p.2383·1); zinc picolinate (p.2001·1).
Immunostimulant.

Imbun
Ratiopharm, Austria.
Ibuprofen lysine (p.64·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Merckle, Ger.
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

IMD *Malaysia Chemist, Singapore†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imda *Dosa, Arg.†.*
Bicalutamide (p.686·2).

Imdex *CCM, Hong Kong; CCM, Malaysia; CCM, Singapore; CCM, Thai.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Imdur *AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK; Key, USA.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Imecol *Andromaco, Chile.*
Phthalylsulfathiazole (p.315·1); nifuroxazide (p.307·2).
Diarrhoea.

Imedeen *Gobbi, Arg.*
Marine proteins; ascorbic acid; zinc gluconate (p.1922·1).
Dietary supplement.

Imedeen Prime Renewal *Ferrosan, Fr.*
Soya isoflavones; marine proteins; white tea; vitamin C; tomato; grape seed; vitamin E; zinc; chamomile (p.1922·1).
Dietary supplement for protection against skin ageing.

Imedeen Tan Optimizer *Ferrosan, Fr.*
Tomato; betacarotene; vitamin C; vitamin E (p.1922·1).
Dietary supplement for promotion of safe tanning.

Imedeen Time Perfection *Ferrosan, Fr.*
Marine proteins; acerola; tomato; grape seed (p.1922·1).
Dietary supplement for protection against skin ageing.

Imediat N *Gador, Arg.†.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Imefer *Jumont, Philipp.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron, vitamin B, and folic acid deficiency.

Imegul *Arkomedika, Fr.†.*
Cascara (p.1715·2); ispaghula (p.1737·1).
Constipation.

Imelde *Frasca, Arg.; Medica, Arg.*
Barrier preparation.

Imerid *Hizon, Philipp.; Pharmatrix, Philipp.*
Glimepiride (p.441·1).
Diabetes mellitus.

Imeron *Altana, Ger.*
Iomeprol (p.1483·2).
Radiographic contrast medium.

Imeson *Taurus, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Imet *FIRMA, Ital.†.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Imex *Merz, Ger.; Pharmacare, Gr.; Assos, Turk.*
Tetracycline hydrochloride (p.347·2).
Acne; bacterial skin infections.

Imferon *Shreya, India; Llorente, Spain†.*
Iron dextran (p.1951·1).
Iron-deficiency anaemia.

Imflac *Douglas, Austral.*
Diclofenac sodium (p.44·3).
Inflammation; pain; peri-articular and soft-tissue disorders.

Imgalt *Jaldes, Fr.*
Bifidobacterium bifidum (p.2372·3); *Bifidobacterium longum* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus casei* (p.2372·3).
Skin and mucous membrane disorders.

Imidazyl *Recordati, Ital.*
⊗ Naphazoline nitrate (p.1565·2).
Conjunctivitis.

Imidazyl Antistaminico *Recordati, Ital.*
⊗ Naphazoline nitrate (p.1565·2); thonzylamine hydrochloride (p.592·1).
Conjunctivitis.

Imidex *Medix, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Imidil *Hetero, India.*
Clotrimazole (p.530·1).
Balanitis; fungal skin and vulvovaginal infections.

Imidin K *Wernigerode, Ger.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Imidin N *Wernigerode, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Imigran
GSK, Arg.; GSK, Braz.; GSK, Hong Kong; GSK, Malaysia; GSK, NZ; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Thai.; GSK, Venez.
Sumatriptan succinate (p.625·2).
Cluster headache; migraine.

GSK, Austral.; GSK, Austria; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Norw.; GSK, Swed.; GSK, Switz.; GSK, UK.
Sumatriptan (p.625·2) or sumatriptan succinate (p.625·2).
Cluster headache; migraine.

GSK, Mex.
Sumatriptan hemisulfate (p.627·1) or sumatriptan succinate (p.625·2).
Migraine.

GSK, Neth.
Sumatriptan (p.625·2), sumatriptan hemisulfate (p.627·1), or sumatriptan succinate (p.625·2).
Cluster headache; migraine.

GSK, Turk.
Sumatriptan (p.625·2).
Cluster headache; migraine.

Imigrane *GSK, Fr.*
Sumatriptan (p.625·2) or sumatriptan succinate (p.625·2).
Migraine; vascular facial pain.

Imiject *GSK, Fr.*
Sumatriptan succinate (p.625·2).
Vascular facial pain.

Imimor *Royal, Chile.*
Imiquimod (p.881·3).
Anogenital warts.

Imimore *Panalab, Arg.*
Imiquimod (p.881·3).
Anogenital warts.

Imin *Yung Shin, Singapore.*
Inosine pranobex (p.884·2).
Herpes zoster; measles.

Iminen *Ivax, Mex.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Imipecil *Northia, Arg.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Imipem *Neopharmed, Ital.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Imipra *Cristalia, Braz.*
Imipramine hydrochloride (p.400·3).
Depression.

Imistatin *Richmond, Arg.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Imitrex
GSK, Arg.†.
Sumatriptan (p.625·2).
Migraine.

GSK, Belg.; GSK, USA.
Sumatriptan (p.625·2) or sumatriptan succinate (p.625·2).
Cluster headache; migraine.

GSK, Canad.
Sumatriptan hemisulfate (p.627·1) or sumatriptan succinate (p.625·2).
Migraine.

GSK, Indon.; GSK, Israel.
Sumatriptan succinate (p.625·2).
Cluster headache; migraine.

Immediat *Volta, Chile†.*
Propyphenazone (p.119·3); adiphenine hydrochloride (p.2248·1); phenobarbital (p.492·2).

Immodin *Sevapharma, Cz.*
Leucocytes (p.1073·2).
Immune-system disorders.

Immubron *Bruschettini, Ital.*
Lysates of: *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Haemophilus influenzae*; *Moraxella catarrhalis*; strains of *Streptococcus pneumoniae*.
Respiratory-tract infections.

Immucothel *Richter, Austria; Biosyn, Neth.*
Immunocyanin.
Bladder cancer.

ImmuCyst *Aventis Pasteur, Arg.†; Aventis, Austral.; Aventis Pasteur, Austria; SGS Biopharma, Belg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; CytoChemia, Ger.; Gerolymatos, Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Aventis Pasteur, Israel; Wassermann, Ital.; Sanofi Pasteur, Malaysia; Aventis, NZ; Inibsa, Port.; Sanofi Pasteur, Singapore; Inibsa, Spain; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.; Cambridge, UK; Zuoz, Venez.†.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Immucytal *Pierre Fabre, Ital.*
Ribosomal fractions of *Klebsiella pneumoniae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Haemophilus influenzae*; membrane fraction of *Klebsiella pneumoniae*.
Bronchial infections; otorhinolaryngeal infections.

Immudynal *Ardeypharm, Ger.*
Homoeopathic preparation.

Immugrip *Pierre Fabre, Fr.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Immukin *Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, UK.*
Interferon gamma-1b (recombinant) (p.893·3).
Infections in chronic granulomatous disease and malignant osteopetrosis.

Immukine *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Neth.*
Interferon gamma-1b (recombinant) (p.893·3).
Infections in chronic granulomatous disease.

Immulem *Lemery, Mex.*
Ciclosporin (p.1822·2).
Transplant rejection.

Immumil *Milte, Ital.†.*
Propolis (p.2373·3); echinacea (p.2298·1); thyme (p.2401·1).
Cold symptoms.

Immumil Plus *Milte, Ital.*
Propolis (p.2373·3); echinacea (p.2298·1); thyme (p.2401·1); acerola.
Cold symptoms.

Immunace *Vitabiotics, UK.*
Multivitamin, mineral, and bioflavonoid preparation (p.1922·1).

Immun-Aid *Pisa, Mex.†; McGaw, USA.*
Preparation for enteral nutrition (p.1922·1).
Immunosuppression.

Immunal *Lek, Cz.; Lek, Pol.; Lek, Rus.*
Echinacea (p.2298·1).
Respiratory-tract infections.

Immunate *Baxter Immuno, Arg.; Baxter, Austria; Immuno, Braz.†; Baxter, Cz.; Baxter BioScience, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Ital.; Plasti-Esteril, Mex.†; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.; Baxter, Venez.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Immune BCG Pasteur F *Pasteur Merieux, Israel.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Immune Boost *Johnson & Johnson, Austral.*
Lactoferrin (bovine) (p.2330·1).
Immune system tonic.

Immune Formula *Nutravite, Canad.*
Astragalus; black seed; echinacea; grape seed (p.1922·1).

Immunex CRP *Wampole, USA.*
Test for C-reactive protein in serum.

Immunine *Baxter Immuno, Arg.; Baxter, Austria; Immuno, Braz.†; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.†; Baxter BioScience, Ger.; Baxter, Hung.; Baxter, Ital.; Plasti-Esteril, Mex.†; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Eczacibasi-Baxter, Turk.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Immunja *OTW, Ger.†.*
Homoeopathic preparation.

Immunocal *Immunotec, USA.*
Preparation for enteral nutrition (p.1922·1).

ImmunoDefence *Blackmores, Austral.*
Lactoferrin (p.2330·1).
Tonic.

Immunoendocig *Nuovo ISM, Ital.†.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Immunofort *Leki Natury, Pol.*
Lappa (p.2330·3); aronia melanocarpa; chamomile (p.2279·3); echinacea purpurea (p.2298·1); urtica (p.2409·3).
Upper respiratory-tract infections; wounds.

ImmunoHBs *Kedrion, Ital.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Immunokine *Oxo, Thai.*
Tetrachlorodecaoxide (p.2396·3).
Post-radiation-therapy syndromes.

Immunomaxe *Immapharma, Rus.*
Acid peptidoglycans.
Bacterial and viral infections.

Immunomega *Larkhall Laboratories, UK.*
Multivitamin and mineral preparation (p.1922·1).

Immunonine *Baxter, Neth.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Immunoprin *Ebewe, Cz.; Ashbourne, UK†.*
Azathioprine (p.1818·2).
Auto-immune disorders; inflammatory disorders; transplant rejection.

Immunorho *Kedrion, Arg.; Biosano, Chile; Kedrion, Ital.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Immunorm *Merckle, Rus.*
Echinacea (p.2298·1).
Infections of the respiratory and urinary-tract.

Immunosin *Westmont, Philipp.*
Inosine pranobex (p.884·2).
Viral infections.

Immunosporin *Novartis, Ger.*
Ciclosporin (p.1822·2).
Atopic dermatitis; psoriasis; rheumatoid arthritis; uveitis.

Immunostim *Herbapol Lublin, Pol.*
Siberian ginseng (p.2386·3).
Atherosclerosis; tonic.

Immunotetan *Kedrion, Ital.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Immunotrofina *DMG, Ital.*
A range of vitamin and mineral supplements (p.1922·1).

Immunovac *Artu, Neth.†.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Immunovenin *Microgen, Rus.†.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; immunodeficiency; passive immunisation.

Immunovir *PRC, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Immunozig *Interko, Turk.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Immunozima *Valens, Ital.†.*
Muramidase hydrochloride (p.2348·1).
Viral infections.

Immun-up *Dicofarm, Ital.*
Echinacea (p.2298·1); betaglucan.
Immunostimulant.

Immutone *Pharmadass, UK.*
Shark-liver oil (p.2386·1).

Immuvac *Cadila, India.*
A leprosy vaccine (p.2220·3).
Active immunisation.

Immuvit *Pascual, Philipp.; Rueckert, Philipp.*
Vitamins; minerals; ginseng (p.2312·1); Siberian ginseng (p.2386·3); ubidecarenone (p.2407·2).
Tonic.

Immuvital *Rueckert, Singapore.*
Vitamin and mineral preparation with ginseng (p.2312·1)(p.1922·1).

Immuwash *DMG, Ital.*
Glucan.
Nasal cleansing.

Immuzinc *Medlink, Philipp.*
Zinc sulfate (p.1999·2).
Nutritional supplement.

Imocap *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Imoclone *Orion, Denm.*
Zopiclone (p.1039·1).
Insomnia.

Imocur
Note. This name is used for preparations of different composition.
Merck, Fin.
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Zambon, Fr.†.
Bacterial fractions of *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Klebsiella ozaenae*; *Klebsiella pneumoniae*; *Staphylococcus aureus*; *Streptococcus viridans*; *Streptococcus pyogenes*; *Moraxella catarrhalis*.
Prevention of upper respiratory-tract infection.

Imodium *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; McNeil Consumer, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Orion, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; McNeil, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; McNeil, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; McNeil, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; McNeil, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Janssen, USA; McNeil Consumer, USA; Janssen-Cilag, Venez.*
Loperamide hydrochloride (p.1741·1).
Colostomy and ileostomy management; control of intestinal transit time; diarrhoea.

Imodium Advanced *Janssen-Cilag, Austral.; McNeil Consumer, Canad.; Janssen-Cilag, NZ; McNeil Consumer, USA.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Abdominal discomfort; diarrhoea; excess gastrointestinal gas; flatulence.

Imodium Komplett *Janssen-Cilag, Hung.†.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Diarrhoea; excess gastrointestinal gas.

Imodium med Simethicon *Janssen-Cilag, Denm.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Diarrhoea.

Imodium Plus *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.†; Janssen-Cilag, Cz.; McNeil, Ger.; Janssen, Hong Kong; Janssen-Cilag, Mex.; Janssen-Cilag, Pol.; Janssen, Port.; Janssen-Cilag, S.Afr.; McNeil, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Johnson & Johnson MSD Consumer, UK.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Abdominal discomfort; diarrhoea; diarrhoea with excess gastrointestinal gas; flatulence.

Imodiumduo *McNeil, Fr.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Formerly known as Imosselduo.
Diarrhoea; flatulence.

Imodiumlingual *McNeil, Fr.*
Loperamide hydrochloride (p.1741·1).
Formerly known as Imossellingual.
Diarrhoea.

Imodonl *Christo, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Imoflora *McNeil, Ger.*
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea.

Imogam *Aventis Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Indon.; Aventis Pasteur, Turk.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Imogam Rabia *Sanofi Pasteur, Arg.; Sanofi Pasteur, Spain.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Imogam Rabies *Aventis Pasteur, Cz.†; Pasteur Merieux, Israel; Sanofi Pasteur, Thai.; Sanofi Pasteur, USA.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Imogam Rage *Sanofi Pasteur, Fr.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Imogan Rabia *Zuoz, Venez.†.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Imogas *McNeil, Ger.; Janssen-Cilag, Port.*
Simeticone (p.1770·2).
Flatulence; preparation for gastrointestinal investigations; reduction of gastrointestinal gas.

Imomed *Medikon, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imore *Soho, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imosa *Corsa, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imosec *Janssen-Cilag, Braz.; Abello, Spain†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imossel *McNeil, Fr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Imot *Sophia, Mex.; Elmor, Venez.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Imotab *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Imotec *Rafarm, Gr.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Imotest Tuberculin *Vianex (Βιανέξ), Gr.*
Tuberculin PPD (p.2405·3).
Tuberculosis diagnosis.

Imotest Tuberculina *Zuoz, Venez.†.*
Tuberculin (p.2405·3).
Tuberculosis diagnosis.

Imotoran *Rayere, Mex.*
Enalapril (p.1276·1).
Hypertension.

Imovane *Aventis, Arg.; Sanofi-Aventis, Austral.; Tramedico, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Pol.; Sanofi-Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Meda, Swed.; Aventis, Switz.; Eczacibasi, Turk.; Aventis, Venez.†.*
Zopiclone (p.1039·1).
Insomnia.

Imovax BCG *Aventis Pasteur, Ital.†.*
A BCG vaccine (p.2205·3).
Active immunisation.

Imovax DT *Sanofi Pasteur, Arg.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Imovax Gripe *Aventis, Arg.†; Zuoz, Venez.†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Imovax Meningo A & C *Aventis, S.Afr.*
A meningococcal vaccine (p.2224·1).
Active immunisation.

Imovax Meningo A+C *Aventis Pasteur, Turk.; Zuoz, Venez.†.*
A meningococcal vaccine (p.2224·1).
Active immunisation.

Imovax Mumps *Aventis Pasteur, Braz.†.*
A mumps vaccine (p.2225·1).
Active immunisation.

Imovax Neumo 23 *Zuoz, Venez.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Imovax Parotiditis *Aventis Pasteur, Arg.†; Zuoz, Venez.†.*
A mumps vaccine (Urabe Am 9 strain) (p.2225·1).
Active immunisation.

Imovax Pneumo *Aventis, Arg.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Imovax Pneumo 23 *Aventis, S.Afr.*
A pneumococcal vaccine (p.2231·2).
Active immunisation.

Imovax Polio *Sanofi Pasteur, Arg.; Sanofi Pasteur, Belg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; IFET (ΙΦΕΤ), Gr.†; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Pasteur Merieux, Israel; Sanofi Pasteur, Ital.; Aventis, NZ; Sanofi Pasteur, Norw.; Aventis Pasteur, Pol.; Sanofi Pasteur, Singapore†; Sanofi Pasteur, Swed.; Zuoz, Venez.†.*
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

Imovax Rabbia *Sanofi Pasteur, Ital.*
A rabies vaccine (p.2234·1).
Active immunisation.

Imovax Rabies *Sanofi Pasteur, Canad.; Sanofi Pasteur, USA.*
An inactivated rabies vaccine (human diploid cell) (p.2234·1).
Active immunisation.

Imovax Rubeola *Sanofi Pasteur, Arg.†; Zuoz, Venez.†.*
A rubella vaccine (Wistar RA 27/3-M strain) (p.2236·3).
Active immunisation.

Imovax Sarampion *Zuoz, Venez.†.*
A measles vaccine (p.2221·3).
Active immunisation.

Imovax Tetano *Sanofi Pasteur, Ital.*
A tetanus vaccine (p.2240·1).
Active immunisation.

Imovexil *Aledicine, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Imoviral *Cristalfarma, Ital.*
Catechu; shiitake; betaglucan; black currant (p.1922·1).
Nutritional supplement.

Imox *Ipca, India.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Imox-Clo *Ipca, India.*
Amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Imox-Clo LB *Ipca, India.*
Amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1); lactobacillus (p.2372·3).
Bacterial infections.

Imozop *Sandoz, Denm.*
Zopiclone (p.1039·1).
Insomnia.

Impact *Novartis, Arg.†; Novartis Consumer, Austral.†; Novartis, Braz.; Novartis, Fin.†; Novartis Nutrition, Hong Kong†; Novartis Consumer, Ital.; Novartis Consumer, Port.†; Novartis Nutrition, Singapore†; Novartis, Turk.; Novartis Consumer, UK; Novartis Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).

Impalamycin *Bros, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Impavido *Zentaris, Ger.*
Miltefosine (p.751·1).
Leishmaniasis.

Impedil *Phoenix, Arg.*
Etamsylate (p.1064·3).
Haemorrhage.

Impelium *TO-Chemicals, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Impetex *Teofarma, Ital.; Roche, Turk.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Impidol *Andromaco, Chile.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Implanon *Organon, Arg.†; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.†; Organon, Hung.; Organon, Indon.; Organon, Irl.; Organon, Ital.†; Organon, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; Organon, Port.; Organon, Singapore; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, USA; Organon, Venez.*
Etonogestrel (p.2103·1).
Progestogen-only implantable contraceptive.

Implementor *Pentafarma, Port.*
Pirlindole hydrochloride (p.420·2).
Depression.

Implicane *Tecnofarma, Chile.*
Sertraline (p.422·1).
Depression.

Importal *Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis Consumer, Cz.†; Novartis, Denm.; Novartis Sante, Fr.; Novartis Consumer, Ger.; Novartis, Gr.; Novartis Consumer, Israel†; Novartis, NZ; Novartis Consumer, Neth.; Novartis, Norw.†; Novartis Consumer, Port.; Novartis, Swed.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.*
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

Imposergon *Rafarm, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Impregon *Fleming, USA.*
Tetrachlorosalicylanilide.
Napkin disinfection.

Impresial *Zambon, Indon.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Impresso *Alpharma-Isis, Ger.†.*
⊗ Oxprenolol hydrochloride (p.1365·1); hydralazine hydrochloride (p.1305·3); chlortalidone (p.1243·3).
Hypertension.

Imprida *Novartis, Cz.; Novartis, Port.*
Amlodipine besilate (p.1214·1); valsartan (p.1420·2).
Hypertension.

Impromen
Janssen-Cilag, Belg.; Janssen-Cilag, Neth.
Bromperidol (p.965·1) or bromperidol decanoate (p.965·1).
Psychoses; schizophrenia.

Janssen-Cilag, Ger.
Bromperidol lactate (p.965·2).
Schizophrenia.

Formenti, Ital.; Janssen, Port.†; Janssen, Thai.†.
Bromperidol (p.965·1).
Psychoses.

Improntal *Rottapharm, Spain.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Improved Analgesic *Rugby, USA†.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Improved Once A Day *Quest, UK.*
Multivitamin and mineral preparation (p.1922·1).

Improvil *Pfizer, Austral.*
21 Tablets, norethisterone (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Improvox *Tempo Scan Pacific, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Impugan *Actavis, Indon.; Alpharma, Swed.; Alpharma, Switz.†; Dumex-Alpharma, Thai.†.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; nephrotic syndrome; oedema; renal insufficiency.

Imrest *Alphapharm, Austral.*
Zopiclone (p.1039·1).
Insomnia.

Imtrate *Douglas, Austral.; Douglas, NZ.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Imucell WGP *Biopolymer, Philipp.*
WGP beta 1,3/1,6 glucan.
Dietary supplement.

Imudator *Pyridam, Indon.*
Echinacea (p.2298·1); zinc picolinate (p.2001·1); phyllanthus niruri; ganoderma lucidum.
Antioxidant; immunostimulant; liver disorders; renal calculi; wound healing.

Imuderm
Note. This name is used for preparations of different composition.
Goldshield, UK.
Cream: White soft paraffin (p.2031·2); fractionated coconut oil (p.1956·3); glycerol (p.2314·2).
Skin disorders.

Goldshield, UK†.
Hand & face wash; shower gel: Soap substitute.
Dry skin disorders.

Goldshield, UK.
Oil: Light liquid paraffin (p.2031·1); almond oil (p.2252·2).
Dry skin disorders.

Imudon
Note. This name is used for preparations of different composition.
Solvay, Cz.; Solvay, Fr.†.
Lysates of *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus helveticus* (p.2372·3); *Lactobacillus lactis* (p.2372·3); *Lactobacillus fermentum* (p.2372·3); *Streptococcus pyogenes*; *Enterococcus faecium* (p.2372·3); *Enterococcus faecalis* (p.2372·3); *Streptococcus sanguis*; *Staphylococcus aureus*; *Klebsiella pneumoniae*; *Corynebacterium pseudodiphtheriae*; *Fusobacterium nucleatum*; *Candida albicans*.
Mouth disorders.

Solvay, Rus.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus fermentum* (p.2372·3); *Lactobacillus helveticus* (p.2372·3); *Lactobacillus debrulcki* subsp. lactis; *Streptococcus pyogenes* group A; *Enterococcus faecalis* (p.2372·3); *Enterococcus faecium* (p.2372·3); *Streptococcus sangius*; *Staphylococcus aureus*; *Klebsiella pneumoniae*; *Corynebacterium pseudodiphtheriticum*; *Fusobacterium nucleatum*; *Candida albicans*.
Mouth and throat disorders.

Imufor *Boehringer Ingelheim, Arg.†.*
Interferon gamma-1b (p.893·3).

Imuger *Gerard, Irl.*
Azathioprine (p.1818·2).
Immunosuppressant.

Imugins *Schumit, Thai.*
Ginseng (p.2312·1); multivitamins and minerals (p.1922·1).
Tonic.

Imukin *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.*
Interferon gamma-1b (rbe) (p.893·3).
Infections in chronic granulomatous disease; infections in malignant osteopetrosis.

Imulan *Soho, Indon.*
Phyllanthus niruri; curcuma longa; selenium (p.1961·1).
Immunostimulant.

Imunace *Shionogi, Jpn.*
Teceleukin (p.735·1).
Recombinant interleukin-2. Anticancer.

Imunen *Cristalia, Braz.*
Azathioprine (p.1818·2).
Immunosuppressant.

Imuneprim *IQB, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Imunex *Galenium, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Imunnal *Herbarium, Braz.*
Echinacea (p.2298·1).
Cold symptoms.

Imuno Max *Herbarium, Braz.*
Urtica (p.2409·3).

Imuno Max-gel *Herbarium, Braz.†.*
Plant alkaloids.
Genital herpes; herpes labialis.

Imunocel *Teuto, Braz.†.*
Echinacea (p.2298·1).
Cold symptoms.

Imunoest *Sanofi Pasteur, Braz.*
A BCG vaccine (p.2205·3).
Active immunisation.

Imunoferon *Fariberica, Port.*
Glicofosfopeptical (p.2312·3).
Immunodeficiency.

Imunogreen *Greenpharma, Braz.*
Echinacea (p.2298·1).

Imunonutril *Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Imunor *Imunomedica, Cz.*
Transfer factor (p.2403·3).
Immune-system disorders.

Imunoskintest *Sevapharma, Cz.†.*
Tuberculin (p.2405·3); *Candida albicans* antigen; diphtheria toxin; tetanus toxoid.
Test for immunity.

Imunovir *Rivex, Canad.; Newport, Irl.; NZ Medical & Scientific, NZ; Ardern, UK.*
Inosine pranobex (p.884·2).
Subacute sclerosing panencephalitis; viral infections.

Imunoxa *Gador, Arg.*
Lamivudine (p.895·1).
HIV infection.

Imunoxa Complex *Gador, Arg.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Imuprel *Adcock Ingram, S.Afr.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Bronchospasm; heart block; shock.

Imuprin *Pfizer, Fin.†.*
Azathioprine (p.1818·2).
Auto-immune disorders; lupus erythematosus; rheumatoid arthritis; transplant rejection.

Imuran
GSK, Arg.; GSK, Austral.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; Wellcome, Israel; GSK, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.†; GSK, S.Afr.; GSK, Singapore; GSK, Thai.; GSK, Turk.
Azathioprine (p.1818·2).
Auto-immune disorders; haemolytic anaemia; hepatitis; idiopathic thrombocytopenic purpura; lupus erythematosus; rheumatoid arthritis; thrombocytopenic purpura; transplant rejection.

GSK, Belg.; GSK, Canad.; Wellcome, Irl.; GSK, NZ; GSK, Neth.; GSK, UK; Prometheus, USA.
Azathioprine (p.1818·2) or azathioprine sodium (p.1820·1).
Auto-immune disorders; Crohn's disease; haemolytic anaemia; hepatitis; rheumatoid arthritis; skin disorders; systemic lupus erythematosus; thrombocytopenic purpura; transplant rejection.

Glaxo Wellcome, Gr.†.
Azathioprine sodium (p.1820·1).
Transplant rejection.

Imurek *GSK, Austria; GSK, Ger.; GSK, Switz.*
Azathioprine (p.1818·2) or azathioprine sodium (p.1820·1).
Auto-immune disorders; auto-immune haemolytic anaemia; hepatitis; idiopathic thrombocytopenic purpura; rheumatoid arthritis; skin disorders; systemic lupus erythematosus; transplant rejection.

Imurel *GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Norw.; UCB, Spain; GSK, Swed.*
Azathioprine (p.1818·2).
Auto-immune disorders; immunosuppressant; rheumatoid arthritis; systemic lupus erythematosus; transplant rejection.

Imusporin *Cipla, India; Cipla, Venez.*
Ciclosporin (p.1822·2).
Atopic dermatitis; graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection.

Imustrum *Erlimpex, Indon.*
Prebiotic; bovine colostrum; curcuminoid; docosahexaenoic acid; lysine hydrochloride; vitamin B substances; vitamin A; vitamin D; zinc sulfate (p.1922·1).
Nutritional supplement.

Imutrex *Cipla, India.*
Methotrexate (p.745·2).
Malignant neoplasms; rheumatoid arthritis.

Imuvac *Solvay, Spain†; Masta, UK; Solvay, UK.*
An influenza vaccine (p.2218·2).
Active immunisation.

Imuvit *Rueckert, Malaysia; Boots Healthcare, Switz.; Rueckert, Thai.*
Ginseng (p.2312·1); vitamins; minerals (p.1922·1).
Tonic; vitamin and mineral deficiency.

Imuvital *Vita Health, Switz.*
Multivitamin and mineral preparation with ginseng (p.1922·1).
Tonic.

Imuxgen *Bioprofarma, Arg.*
Mycophenolate mofetil (p.1836·2).
Prevention of renal, cardiac, and hepatic transplant rejection.

In A Wink
Note. This name is used for preparations of different composition.
Ciba Vision, Austral.†.
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Conjunctivitis; eye irritation.

Ciba Vision, Canad.†.
A range of solutions for contact lenses (p.1622·2).

In A Wink Allergy *Ciba Vision, Austral.†.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic conjunctivitis; hay fever.

In A Wink Moisturing *Ciba Vision, Austral.†.*
Povidone (p.2146·1).
Dry eyes.

Inabutol Forte *Themis Chemicals, India.*
Isoniazid (p.288·1); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Inac *Recon, Singapore.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Inacid *MSD, Spain; McNeil, Spain.*
Indometacin (p.66·3) or indometacin sodium (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; patent ductus arteriosus.

Inadine *Johnson & Johnson, Ger.†; Johnson & Johnson, Irl.; Johnson & Johnson, Ital.; Johnson & Johnson Medical, UK.*
Povidone-iodine (p.1659·2).
Burns; skin infections; skin ulcers; wounds.

Inadol *Pharmagenus, Spain†.*
Ibuprofen (p.64·2).
Musculoskeletal pain and inflammation.

Inadryl *Interbat, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); menthol (p.2340·1); alcohol (p.1625·2).
Cough; nasal congestion.

Inadryl Plus *Interbat, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); menthol (p.2340·1); alcohol (p.1625·2); sodium citrate (p.1673·3).
Cough; nasal congestion; sneezing.

Inalacor *Faes, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Inaladuo *Faes, Spain.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma.

Inalar *Montefarmaco, Ital.*
⊗ Xylometazoline hydrochloride (p.1575·1); domiphen bromide (p.1643·1).
Nasal congestion.

Inalcort *Caber, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Inalgon Neu *Fresenius Kabi, Austria.*
Dipyrone (p.49·2).
Fever; pain.

Inalpin *Qualiphar, Belg.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Inamid *Nufarindo, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Inamide *Gerard, Irl.†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Inapas *Neo-Pharma, India.*
Sodium aminosalicylate (p.201·2); isoniazid (p.288·1).
Tuberculosis.

Inapsine *Akorn, USA.*
Droperidol (p.994·3).
Nausea and vomiting in surgical and diagnostic procedures; neuroleptanalgesia; premedication.

Inaspir *Almirall, Spain.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Inastmol *Phoenix, Arg.†.*
Theophylline (p.1140·1); ketotifen (p.582·2).
Asthma.

Inazid *Rekah, Israel.*
Isoniazid (p.288·1).
Tuberculosis.

Inbion *Interbat, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid; vitamin B with intrinsic factor (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Incad *Bushnell, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement.

Incaico Serenidad *Incaico, Arg.*
Valerian (p.2410·1); tilia (p.2402·2); peppermint (p.1761·2); chamomile (p.2279·3).

Incardel *Pisa, Mex.*
Acarbose (p.436·2).
Diabetes mellitus.

Inca's Gold *Larkhall Laboratories, UK.*
Jojoba oil.

Incee-Vit *Interhealthcare, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Incel *Darrow, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Incena *Bittner, Austria.*
Homoeopathic preparation.

Incid *Verheilen, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Incidal-OD *Bayer, Indon.; Bayer, Thai.†.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; rhinitis; urticaria.

Incidin
Note. This name is used for preparations of different composition.
Ecolab, Ger.
Foam: ⊗ Propyl alcohol (p.1660·2); alcohol (p.1625·2); benzalkonium chloride (p.1629·1); glucoprotamine (p.1645·2).
Equipment disinfection.

Ecolab, Ger.
Liquid: Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2).
Equipment disinfection.

Incidin Extra *Henkel, Ger.†.*
Benzalkonium chloride (p.1629·1); oligo(di(iminoimidocarbonyl)iminohexamethylene); orthophenylphenol (p.1655·1).
Surface disinfection.

Incidin extra N *Ecolab, Ger.*
Glucoprotamine (p.1645·2); benzalkonium chloride (p.1629·1).
Surface disinfection.

Incidin M Spray Extra *Henkel, Ger.†.*
Tributyltin benzoate; isopropyl alcohol (p.1650·3).
Skin disinfection.

Incidin perfekt *Ecolab, Ger.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); benzalkonium chloride (p.1629·1); oligo(di(iminoimidocarbonyl)iminohexamethylene).
Surface disinfection.

Incidin Plus *Ecolab, Ger.*
Glucoprotamine (p.1645·2).
Surface disinfection.

Incidin Spezial
Note. This name is used for preparations of different composition.
Henkel, Ger.
⊗ Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); alcohol (p.1625·2).
Surface disinfection.

Ecolab, Ital.
⊗ Alcohol (p.1625·2); glyoxal (p.1646·1); glutaral (p.1645·2); benzalkonium chloride (p.1629·1).
Surface disinfection.

Incidine *Paragerm, Fr.†.*
Glutaral (p.1645·2); formaldehyde (p.1644·2); glyoxal (p.1646·1).
Surface and instrument disinfection.

Incidur *Ecolab, Ger.*
Glutaral (p.1645·2); glyoxal (p.1646·1).
Surface disinfection.

Incidur Spray
Note. This name is used for preparations of different composition.
Henkel, Ger.†.
⊗ Glutaral (p.1645·2); benzalkonium chloride (p.1629·1); 5-bromo-5-nitro-1,3-dioxacyclohexane; alcohol (p.1625·2); propyl alcohol (p.1660·2).
Surface disinfection.

Ecolab, Ital.
⊗ Alcohol (p.1625·2); benzalkonium chloride (p.1629·1); 5-bromo-5-nitro-1,3-dioxacyclohexane.
Disinfection of surfaces and instruments.

Incil *Alliance, S.Afr.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Incitin *Bernofarm, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders.

Inclarin *Interbat, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Inclens *Cofasa, Venez.*
⊗ Furosemide (p.1292·1).
Diuretic.

Incontinol *Millet Roux, Braz.*
Oxybutynin hydrochloride (p.2190·3).
Urinary-tract disorders.

Inconturina *OTW, Ger.†.*
Solidago virgaurea (p.2391·1); clove (p.2284·3).
Urinary-tract disorders.

Inconturina mono *OTW, Ger.*
Homoeopathic preparation.

Incoril *Bago, Arg.; Bago, Braz.; Bago, Chile.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Increlex *Beaufour, Fr.; Beaufour-Ipsen, Cz.; Ipsen, UK; Tercica, USA.*
⊗ Mecasermin (p.1807·3).
Growth failure in children and adolescents.

Incremin
Note. This name is used for preparations of different composition.
Wyeth Consumer, Chile†.
Lysine hydrochloride; vitamin B substances; ferric pyrophosphate (p.1938·1) (p.1922·1).
Iron-deficiency anaemia; reduced appetite.

Wyeth, Mex.†.
Lysine hydrochloride; vitamin B substances (p.1922·1).
Nutritional supplement.

Wyeth, Philipp.
Iron (p.1949·1); lysine hydrochloride; vitamin B substances (p.1922·1).
Iron-deficiency anaemia; nutritional supplement.

Wyeth Lederle, Port.†.
Lysine (p.1955·1).

Incremin Con Hierro *Wyeth, Mex.*
Ferric pyrophosphate (p.1938·1); vitamin B substances; lysine hydrochloride (p.1922·1).
Iron and vitamin B deficiency; iron-deficiency anaemia.

Incremin Iron *Wyeth Consumer, Austral.*
Ferric pyrophosphate (p.1938·1); vitamin B substances (p.1922·1); lysine hydrochloride.
Dietary supplement.

Incremin with Iron *Lederle, Indon.; Wyeth Consumer, NZ.*
Iron (p.1949·1); lysine hydrochloride; vitamin B substances (p.1922·1).
Dietary supplement; iron deficiency; iron-deficiency anaemia.

Incremin with Vitamin C *Whitehall, Austral.†.*
Vitamin B substances; lysine hydrochloride; vitamin C (p.1922·1).
Dietary supplement.

Incresil *Permatec, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Indacar *Pharmacodane, Denm.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indaco *Eupharmed, Ital.*
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Indaflex
Note. This name is used for preparations of different composition.
Lampugnani, Ital.
⊗ Indapamide (p.1314·1).
Hypertension.

Andromaco, Mex.
Indometacin (p.66·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Indahexal *Hexal, Austral.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indal *Andromaco, Venez.†.*
⊗ Propranolol (p.1381·1).
Hypertension.

Indalgin *Orion, Fin.*
Indometacin (p.66·3); ethylmorphine hydrochloride (p.52·2).
Pain.

Indalix *Duopharma, Hong Kong; Quality, Hong Kong; Triomed, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indamid
Note. This name is used for preparations of different composition.
Pisa, Mex.
Clindamycin (p.251·1).
Bacterial infections.

Ilsan, Turk.
⊗ Indapamide (p.1314·1).
Hypertension.

Indamix DM *Centurion, USA.*
Dexchlorpheniramine tannate (p.572·2); dextromethorphan tannate (p.1556·1); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Indamol *Teofarma, Ital.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indanorm *Julphar, UAE.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indanox *Guardian, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Indap *ProMed, Cz.; Pro.Med, Rus.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indapen *Torrent, Braz.; Polpharma, Pol.; Biofarma, Turk.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indapres *Polfa Grodzisk, Pol.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indapress *Labomed, Chile.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indapsan *Sanofi-Aventis, Pol.*
⊗ Indapamide (p.1314·1).
Hypertension.

Inda-Puren *Alpharma-Isis, Ger.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indarzona-N *Streger, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Inderal *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; Wyeth, Canad.; AstraZeneca, Denm.†; AstraZeneca, Fin.†; Cana, Gr.; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Hong Kong; Nicholas Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; Zeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, NZ; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; Wyeth-Ayerst, USA; AstraZeneca, Venez.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; fallot's tetralogy; glaucoma; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; hypertrophic subaortic stenosis; migraine; myocardial infarction; phaeochromocytoma; prevention of gastrointestinal haemorrhage; thyrotoxic crisis; tremor; variceal haemorrhage.

Inderalici *AstraZeneca, Mex.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; glaucoma; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma; variceal haemorrhage.

Inderetic *AstraZeneca, Austria†; AstraZeneca, Belg.†; AstraZeneca, Neth.; AstraZeneca, S.Afr.†; AstraZeneca, Switz.†; AstraZeneca, UK†.*
⊗ Propranolol hydrochloride (p.1380·3); bendroflumethiazide (p.1224·1).
Hypertension.

Inderex *AstraZeneca, UK†.*
⊗ Propranolol hydrochloride (p.1380·3); bendroflumethiazide (p.1224·1).
Hypertension.

Inderide *Wyeth-Ayerst, USA†.*
⊗ Propranolol hydrochloride (p.1380·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Inderm *Will-Pharma, Belg.; Dermapharm, Ger.; Will-Pharma, Neth.; Sankyo, Switz.†; Sankyo, Venez.*
Erythromycin (p.269·2).
Acne.

Indermil *Tyco, UK.*
Enbucrilate (p.2290·2).
Wound closure.

Indexon *Interbat, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Indian Brandee
Note. This name is used for preparations of different composition.
OTC Concepts, UK.
Capsicum (p.2276·2); compound cardamom tincture (p.2277·1).
Dyspepsia; flatulence.

Potter's, UK.
Capsicum (p.2276·2); ginger (p.1732·3); compound rhubarb tincture (p.1768·3).
Colic; dyspepsia.

Indianische Frauenwurzel *NAM, Ger.†.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Indiaral *Gifrer Barbezat, Fr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Indican *Sidus, Arg.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Indicatest *Polidis, Fr.†.*
Pregnancy test (p.2372·1).

Indicontin *Modi-Mundipharma, India.*
⊗ Indapamide (p.1314·1).
Hypertension.

Indigestion *Homeocan, Canad.; Hylands, Canad.*
Homoeopathic preparation.

Indigestion and Flatulence *Cantassium Co., UK.*
Capsicum oleoresin (p.2276·2); valerian (p.2410·1); fennel (p.2302·3); myrrh (p.2349·2); papain (p.2362·3).

Indigestion Mixture Potter's, UK.
Meadowsweet (p.2338·1); gentian (p.2310·3); euonymus (p.1730·1).
Dyspepsia; flatulence; heartburn.

Indigestion Relief Herbal Concepts, UK.
Leptandra virginica; capsicum (p.2276·2); fringetree bark; ginger (p.1732·3).
Colic; dyspepsia; nausea.

Indigestion Tablets Brauer, Austral.†.
Homoeopathic preparation.

Indigon IQFA, Mex.
Dipyrone (p.49·2).
Fever; inflammation; muscle spasm; pain.

Indilan Landsteiner, Mex.
Indinavir sulfate (p.882·2).
HIV infection.

Indilea Elea, Arg.
Indinavir (p.884·2).
HIV infection.

Indinax Eurofarma, Braz.
Indinavir (p.884·2).
HIV infection.

Inditor Ipca, India.
⊗ Indapamide (p.1314·1).
Hypertension.

Indiur Gedeon Richter, Rus.
⊗ Indapamide (p.1314·1).
Hypertension.

Indivan Cipla, India; Cipla, Venez.
Indinavir sulfate (p.882·2).
HIV infection.

Indivina Orion, Cz.; Orion, Denm.; Orion, Fin.; Orion, Ger.; Orion, Hung.; Orion, Irl.; Orion, Norw.; Orion, Pol.; Orion, Rus.; Orion, Swed.; Orion, Switz.; Orion, Thai.; Orion, UK.
Estradiol valerate (p.2097·3); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Indix Pliva Krakow, Pol.
⊗ Indapamide (p.1314·1).
Hypertension.

Indo Agepha, Austria; CT, Ger.; CCM, Malaysia; Beacons, Singapore.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain.

Indo Top Ratiopharm, Ger.
Indometacin (p.66·3).
Peri-articular and soft-tissue disorders.

Indobene Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.
Indometacin (p.66·3).
Aluminium glycinate (p.1706·2) may be included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Indobiotic Chauvin, Fr.; Bausch & Lomb, Port.; Bausch & Lomb, Switz.†; Abdi, Turk.
Indometacin (p.66·3); gentamicin sulfate (p.282·1).
Inflammation and bacterial eye infections following surgery.

Indo-bros Bros, Gr.
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Indocaf Reig Jofre, Spain.
Indometacin (p.66·3).
Peri-articular and soft-tissue pain and inflammation.

Indocalm Koni-Cofarm, Chile.
Lidocaine (p.1862·3); sulfathiazole (p.343·2).
Ear infections.

Indocap Jagson, India.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders; pain.

Indocarsil Solfran, Mex.
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Indocid
MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.†; MSD, Denm.†; MSD, Fin.; MSD-Chibret, Fr.; MSD, Hong Kong; Cipla, India; MSD, Irl.†; McNeil, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Port.; MSD, S.Afr.; MSD, Switz.; M & H, Thai.; MSD, UK†; MSD, Venez.
Indometacin (p.66·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; prevention of oedema and miosis during cataract extraction.

MSD, Belg.; IFET (ΙΦΕΤ), Gr.
Indometacin (p.66·3) or indometacin sodium (p.66·3).
Closure of patent ductus arteriosus in premature neonates; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain; prevention of miosis during cataract extraction; trismus.

Indocid Colirio MSD, Braz.†.
Indometacin (p.66·3).
Prevention of miosis and inflammation during ocular surgery.

Indocid PDA MSD, Austral.; Merck Frosst, Canad.; MSD, Irl.; MSD, NZ; MSD, Neth.; IDIS, UK.
Indometacin sodium (p.66·3).
Closure of patent ductus arteriosus.

Indocin
Pharmasant, Thai.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

MSD, USA.
Injection: Indometacin sodium (p.66·3).
Closure of patent ductus arteriosus.

Forte, USA; Merck, USA.
Oral suspension; sustained-release capsules: Indometacin (p.66·3).
Acute gouty arthritis; ankylosing spondylitis; bursitis; osteoarthritis; rheumatoid arthritis; tendinitis.

Indocin PDA MSD, Hong Kong.
Indometacin sodium (p.66·3).
Formerly called Indocid PDA.
Closure of patent ductus arteriosus.

Indocolir Chauvin ankerpharm, Ger.; Abdi, Turk.
Indometacin (p.66·3).
Inflammation following eye surgery; prevention of miosis during eye surgery.

Indocollirio Bausch & Lomb, Ital.
Indometacin (p.66·3).
Prevention of miosis and inflammation during cataract surgery.

Indocollyre Germania, Austria; Chauvin, Belg.; Chauvin, Cz.; Chauvin, Fr.; Bausch & Lomb, Hong Kong; Chauvin, Hong Kong; Chauvin, Hung.; Chauvin, Israel; Chauvin, Neth.; Chauvin, Pol.; Bausch & Lomb, Port.; Bausch & Lomb, Singapore; Chauvin, Singapore; Chauvin, Thai.
Indometacin (p.66·3).
Cystoid macular oedema; eye inflammation and pain; prevention of intra-operative miosis.

Indocontin Mundipharma, Ger.†.
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Indocort Biospray, Gr.†.
⊗ Fluorometholone (p.1532·3); neomycin (p.305·1).
Inflammatory disorders.

Indocycline Nufarindo, Indon.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Indofeno Fada, Arg.†.
Diclofenac (p.44·2).
Inflammation; pain.

Indofrin Darya-Varia, Indon.
Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Indofrin-A Darya-Varia, Indon.
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Allergic eye disorders; conjunctivitis.

Indogel Farmoz, Port.
Indometacin (p.66·3).
Musculoskeletal pain; soft-tissue injury.

Indogesic Dar Al Dawa, Hong Kong†.
Indometacin (p.66·3).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Indohexal Hexal, Austria.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Indolar SR Sandoz, UK.
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Indolgina Uriach, Spain.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Indolin Benedetti, Ital.†.
⊗ Indapamide (p.1314·1).
Hypertension.

Indom INTES, Ital.
Indometacin (p.66·3).
Prevention of miosis and inflammation during cataract surgery.

Indoman Berman, Mex.
Indometacin (p.66·3).
Inflammation; musculoskeletal and joint disorders.

Indomax Ashbourne, UK†.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Indomed MSD, Israel; Greater Pharma, Thai.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; musculoskeletal, joint, peri-articular, and soft-tissue disorders gout; primary dysmenorrhoea; rheumatic fever.

Indomee MSD, Swed.
Indometacin (p.66·3).
Gout; musculoskeletal, joint and peri-articular disorders.

Indomelan Lannacher, Austria.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Indomen YSP, Malaysia; Yung Shin, Singapore.
Indometacin (p.66·3).
Inflammation; musculoskeletal and joint disorders.

Indo-Mepha Mepha, Switz.†.
Indometacin (p.66·3).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Indomet Heumann, Ger.†; Ratiopharm, Hong Kong†.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Indomethol Specifar (Σπεσιφαρ), Gr.
Indometacin (p.66·3).
Inflammatory disorders.

Indometin Orion, Fin.
Indometacin (p.66·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Indomet-ratiopharm Ratiopharm, Ger.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Indomet-ratiopharm m Ratiopharm, Ger.†.
Indometacin (p.66·3).
Aluminium glycinate (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Indomin Hikma, Rus.
Indometacin (p.66·3).

Indomisal Riemser, Ger.†.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Indomod Pharmacia, UK†.
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Indon YSP, Malaysia†.
⊗ Propranolol (p.1381·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic obstructive cardiomyopathy; phaeochromocytoma.

Indonilo Sigma-Tau, Spain.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Indono Milano, Thai.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders; rheumatic fever.

Indop Fahrenheit, Indon.
Dopamine hydrochloride (p.1273·2).
Heart failure; shock.

Indo-paed 1A, Ger.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Indo-Phlogont Azupharma, Ger.†.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Indophtal Bausch & Lomb, Switz.
Indometacin (p.66·3).
Inflammatory eye disorders; prevention of cystoid macular oedema after cataract surgery; prevention of intra-operative miosis.

Indoprex Demo, Gr.†.
Sodium cromoglicate (p.1136·3).
Allergy.

Indoptic MSD, Israel†.
Indometacin (p.66·3).
Prevention of cystoid macular oedema after cataract surgery.

Indoptol MSD, Austria; MSD, Neth.†.
Indometacin (p.66·3).
Inhibition of intra-operative miosis; prevention of cystoid macular oedema after cataract surgery.

Indoson Nufarindo, Indon.
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Indospray Farmoz, Port.
Indometacin (p.66·3).
Musculoskeletal and joint pain; soft-tissue injury.

Indotard CTI, Israel; CTS, Rus.†.
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Indotec Technilab, Canad.†.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders; ovarian hyperstimulation syndrome; pain; renal calculi; renal colic.

Indotex Rontag, Arg.
Indometacin (p.66·3).
Musculoskeletal and joint disorders; pain.

Indotrin Liferpal, Mex.
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Indovasin Balkanpharma, Rus.
Indometacin (p.66·3); troxerutin (p.2305·1).
Haematoma; musculoskeletal, joint, and peri-articular disorders; venous insufficiency.

Indovis CTI, Israel; CTS, Rus.†.
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Indoxen Sigma-Tau, Ital.
Indometacin (p.66·3).
Musculoskeletal disorders.

Indoxyl Stiefel, Chile; Gabriel, Gr.; Stiefel, Mex.
Clindamycin phosphate (p.251·2); benzoyl peroxide (p.1590·2).
Acne.

Indozul Degorts, Mex.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Inducmina Gray, Arg.
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Inductal Roemmers, Arg.
Eszopiclone (p.995·2).
Insomnia.

InductOs Wyeth, Belg.; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Gr.; Wyeth, Irl.; Wyeth, Norw.; Wyeth, Spain; Wyeth, Swed.; Wyeth, UK.
Dibotermin alfa (p.1092·3).
Anterior lumbar spine fusion; degenerative disc disease; tibia fracture.

Indufol Lemery, Mex.
Propofol (p.1791·1).
General anaesthesia.

Induken Kendrick, Mex.†.
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Indulfan Ecolab, Ital.
Glyoxal (p.1646·1); benzalkonium chloride (p.1629·1).
Surface disinfection.

Indumir Gelcaps, Mex.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Indurgan Shire, Spain.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Indurin Terra, Turk.
⊗ Indapamide (p.1314·1).
Hypertension.

Indusil Recordati, Ital.
Cobamamide (p.1980·2).
Vitamin B deficiency.

Indux Sigma, Braz.
⊗ Clomifene citrate (p.2086·1).
Female infertility.

Induxin Kalbe, Indon.
Oxytocin (p.2015·2).
Incomplete abortion; labour induction; postpartum uterine bleeding.

Induzepam Finadiet, Arg.
Clonazepam (p.478·2).
Panic disorder.

Inegy MSD, Austria; MSD, Cz.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hung.; Schering-Plough, Hung.; MSD, Irl.; MSD, Ital.; MSD, Neth.; Schering-Plough, Neth.; MSD, Norw.; MSD, Port.; MSD, UK.
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Ineltano Richmond, Arg.
Halothane (p.1784·2).
General anaesthesia.

Inem Laboratorios Chile, Chile.
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Inerson Interbat, Indon.
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Inespecin Biol, Arg.
Salmonella typhi glycolipids.
Infection prophylaxis.

Inesprin Prisfar, Port.
Lysine aspirin (p.79·1).
Fever; pain.

Inestom Medicus, Gr.
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Inexbron Inexfa, Spain†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Inexium AstraZeneca, Fr.
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

INF Bioprofarma, Arg.
Interferon alfa-2b (p.885·1).
Anogenital warts; hepatitis B and C; malignant neoplasms.

Infacet Protea, S.Afr.
Promethazine hydrochloride (p.588·2); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; nasal congestion; pain.

Infacol Nice Pak, Austral.; Pfizer, Hong Kong; Rosken, Hong Kong; Forest, Hung.; Forest, Irl.; Pfizer, NZ; Forest Laboratories, Pol.; Pfizer Consumer, Singapore†; Forest Laboratories, UK.
Simeticone (p.1770·2).
Colic; flatulence; meteorism.

Infacol Probiotic Forest Laboratories, UK.
Lactobacillus reuteri (p.2372·3).
Maintenance of healthy gastrointestinal flora.

Infacolic Medihelm, Gr.
Dimeticone (p.1770·2).
Infant colic.

Infaderm Goldshield, UK.
Light liquid paraffin (p.2031·1); almond oil (p.2252·2).
Dry skin disorders.

Infadin Zentiva, Cz.
Ergocalciferol (p.1987·1).
Hypocalcaemia; hypoparathyroidism; hypophosphataemia; osteomalacia; osteoporosis; tetany; vitamin D deficiency.

Infadolan *Herbacos, Cz.*
Vitamin A acetate (p.1973·1); ergocalciferol (p.1987·1).
Burns; skin disorders; ulcers; wounds.

Infadrops *Goldshield, UK.*
Paracetamol (p.108·1).
Fever; pain.

Infaflor *Pediapharma, Philipp.*
Fluoride (p.1962·2).
Dental caries prophylaxis.

Infafren Compuesto *Pisa, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).

Infafren Simple *Pisa, Mex.*
Homatropine (p.1881·2).

Infalgina *Pisa, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Infalyte *Mead Johnson Nutritionals, USA.*
Electrolytes and rice syrup solids (p.1672·2).
Formerly known as Ricelyte.
Oral rehydration therapy.

Infanolyte *GHP, Thai.†.*
Calcium chloride; glucose; magnesium chloride; potassium chloride; sodium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Infanrix *GSK, Austral.; GSK, Austria; GSK, Belg.†; GSK, Braz.†; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Indon.; GSK, Irl.†; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Philipp.; Smith Kline & French, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, UK†; SmithKline Beecham, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Infanrix DTPa *GSK, Pol.; GSK, S.Afr.; GSK, Switz.†; GSK, Turk.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Infanrix DTPa-Hib *SmithKline Beecham, Switz.†.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Infanrix DTPa-IPV *GSK, Switz.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Infanrix DTPa-IPV+Hib *GSK, Switz.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Infanrix HB *GSK, S.Afr.†.*
A diphtheria, tetanus, acellular pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Infanrix HepB *GSK, Austral.; GSK, Cz.†; GSK, Fin.†; GSK, Gr.; GSK, Ital.†; GSK, NZ; GSK, Spain†; GSK, Swed.†.*
A diphtheria, tetanus, acellular pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Infanrix Hexa *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Venez.*
A diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Infanrix Hib *GSK, Austral.; GSK, Cz.; GSK, Indon.; GSK, Israel; GSK, Malaysia; GSK, NZ; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, UK†.*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Infanrix + Hib *GSK, Belg.†; GSK, Ger.†.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation; active immunization.

Infanrix IPV *GSK, Austral.; GSK, Belg.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, UK.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Infanrix IPV + Hib *GSK, Austria; GSK, Belg.†; GSK, Braz.†; GSK, Cz.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Thai.; GSK, UK; GSK, Venez.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Infanrix IPV-HIB *GSK, Turk.*
An adsorbed diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Infanrix Penta *GSK, Austral.; GSK, Cz.; GSK, Gr.; GSK, Ital.; GSK, NZ; GSK, Neth.; GSK, Port.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and hepatitis B vaccine (p.2212·2).
Active immunisation.

Infanrix Polio *GSK, Cz.; GSK, Fin.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Infanrix Polio + Hib *GSK, Fin.; GSK, Norw.; GSK, Swed.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Infanrix Polio IPV - Hib *GSK, Israel.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Infanrix Tetra *GSK, Gr.; GSK, Port.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Infanrix-Hep *SmithKline Beecham, Gr.†.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Infanrix-HepB/HI *SmithKline Beecham, Gr.†.*
A diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Infanrixhexa *GSK, Fr.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Infanrixquinta *GSK, Fr.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Formerly known as Infanrix Polio-Hib.
Active immunisation.

Infanrixtetra *GSK, Fr.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Formerly known as Infanrix Polio.
Active immunisation.

Infant Gaviscon
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Austral.
Magnesium alginate (p.2141·1); sodium alginate (p.2141·1).
Gastro-oesophageal reflux.

Reckitt Benckiser, S.Afr.
Alginic acid (p.2140·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux.

Infant Multiple Vitamin *Stanley, Canad.†.*
Vitamins A, C, and D (p.1922·1).

Infant Tonic *Brauer, Austral.†.*
Angelica (p.2258·1); ascorbic acid (p.1983·3); kola (p.2416·1); St John's wort (p.422·3); ginseng (p.2312·1); urtica (p.2409·3); aurum mur.; calc. phos.; ferrum met.; ferrum phos.; kali phos.; mag. phos.; phosphoricum acidum.
Tonic.

Infantaire *Altaire, USA.*
Paracetamol (p.108·1).
Fever; pain.

Infantol *Church & Dwight, Canad.*
Multivitamin preparation (p.1922·1).
Dietary supplement.

Infantoss *Herbarium, Braz.†.*
Grindelia (p.2317·2); guaco; tolu balsam (p.1574·2); propolis (p.2373·3); echinacea (p.2298·1); horseradish (p.2320·1).

Infant's Tylenol *Johnson & Johnson, Hong Kong†.*
Paracetamol (p.108·1).
Fever; pain.

Infapain *Alliance, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Infapain Forte *Alliance, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Infasoy *Cow & Gate, Irl.; Nucitec, Mex.; Wyeth, NZ; Cow & Gate, UK.*
Infant feed (p.1922·1).
Formerly known as Nutrilon Soya in the *UK*.
Cow's milk intolerance; galactosaemia; gluten intolerance; lactase deficiency; lactose intolerance.

Infasurf *Ony, Israel; Forest Pharmaceuticals, USA.*
Calfactant (p.2375·3).
Neonatal respiratory distress syndrome.

Infa-Tardyferon *Germania, Austria.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Infatrim *Molex Ayus, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections; toxoplasmosis.

Infatrini *Nutricia, Austral.†; Nutricia, Fin.; Nutricia, Irl.; Nutricia Clinical, UK.*
Infant feed (p.1922·1).
Disease-related malnutrition.

Infazinc *Atlas, Canad.*
Zinc oxide (p.1621·2).
Nappy rash.

Infectina *Verisfield, Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

InfectoBicillin *Infectopharm, Ger.*
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

InfectoBicillin H *Infectopharm, Ger.*
Azidocillin sodium (p.206·3).
Bacterial infections.

InfectoCef *Infectopharm, Ger.*
Cefaclor (p.217·2).
Bacterial infections.

InfectoCillin *Infectopharm, Cz.†; Infectopharm, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Infectoclont *Infectopharm, Ger.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Infectocortikrupp *Infectopharm, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Infectodiarrstop *Infectopharm, Ger.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration.

Infectodiarrstop GG *Infectopharm, Ger.†.*
Lactic-acid-producing organisms (p.2372·3).
Gastrointestinal disorders.

InfectoDiarrstop LGG *Infectopharm, Ger.*
Lactobacillus rhamnosus (p.2372·3); electrolytes (p.1667·1); glucose (p.1672·2).
Diarrhoea.

Infectoflam *Novartis, Belg.; Ciba Vision, Cz.†; Novartis, Malaysia†; Novartis, Philipp.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.*
⊗ Fluorometholone (p.1532·3); gentamicin sulfate (p.282·1).
Infected and inflammatory eye disorders.

InfectoFlu *Infectopharm, Ger.*
Amantadine hydrochloride (p.792·3).
Influenza A.

InfectoFos *Infectopharm, Ger.*
Fosfomycin sodium (p.278·2).
Bacterial infections.

InfectoKrupp *Infectopharm, Ger.*
⊗ Adrenaline acid tartrate (p.1203·2).
Obstructive airways disease.

InfectoMox
Biochemie, Cz.†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Infectopharm, Ger.
Amoxicillin (p.202·2).
Bacterial infections.

InfectoMycin *Infectopharm, Ger.*
Erythromycin estolate (p.269·3) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

InfectoOpticef *Infectopharm, Ger.*
Cefixime (p.224·3).
Bacterial infections.

InfectoPedicul
Note. This name is used for preparations of different composition.
Infectopharm, Ger.
Lotion: Permethrin (p.2048·2).
Pediculosis.

Infectopharm, Ger.
Topical gel: Lindane (p.2045·3).
Pediculosis.

InfectoPyoderm *Infectopharm, Ger.*
Mupirocin (p.302·3).
Bacterial skin infections.

Infectoroxit *Infectopharm, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Infectoscab *Infectopharm, Cz.; Infectopharm, Ger.*
Permethrin (p.2048·2).
Scabies.

InfectoSoor
Note. This name is used for preparations of different composition.
Infectopharm, Ger.
Ointment: Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Napkin rash.

Infectopharm, Ger.
Oral gel: Miconazole (p.541·2).
Mouth and throat candidiasis.

InfectoStaph *Infectopharm, Ger.*
Dicloxacillin sodium (p.265·2) or oxacillin sodium (p.311·3).
Staphylococcal infections.

InfectoTrimet *Azupharma, Cz.†; Infectopharm, Ger.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Infectovac Flu *Infectopharm, Ger.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

InfectoZidim *Infectopharm, Ger.*
Ceftazidime (p.234·1).
Bacterial infections.

Infectrin *Boehringer Ingelheim, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

INFeD *Schein, USA.*
Iron dextran (p.1951·1).
Iron deficiency.

Infekor *Korea United, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Infekt-Komplex L Ho-Fu-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Infeld *Interbat, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Infelon *Sanbe, Indon.*
⊗ Mesterolone (p.2116·1).
Male hypogonadism; male infertility.

Inferax *Astellas, Ger.*
Interferon alfacon-1 (p.888·3).
Hepatitis C.

Infergen *Yamanouchi, Belg.†; Valeant, Canad.; Yamanouchi, Cz.†; Chiesi, Fr.; Gerolymatos, Gr.; Yamanouchi, Hung.†; Astellas, Ital.; Astellas, Neth.; Three Rivers, USA.*
Interferon alfacon-1 (p.888·3).
Chronic hepatitis C.

Inferil *Recofarma, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Iron-deficiency anaemia.

Inferoxin *Farmoz, Port.*
Roxithromycin (p.331·1).
Bacterial infections.

Infesol E *Berlin-Chemie, Ger.*
An amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Infesol XE *Berlin-Chemie, Ger.*
Amino-acid, electrolyte, and xylitol infusion (p.1922·1).
Parenteral nutrition.

Infex
Note. This name is used for preparations of different composition.
Elofar, Braz.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Pediapharm, Chile; Pharmabiotics, Chile.
Clarithromycin (p.248·2).
Bacterial infections.

Merz, Ger.
Amantadine sulfate (p.793·1).
Influenza A.

Infexin *Solvang, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Infezol *Berlin-Chemie, Rus.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Infibran *CS, Port.*
Wheat bran (p.1712·3).
Constipation.

Infi-Camphora *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infi-China *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infidyston *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infi-Echinacea *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infifer *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infigripp *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infihepan *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infi-Lymphect *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infiossan *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infi-Symphytum *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Infi-tract
Note. This name is used for preparations of different composition.
Infirmarius-Rovit, Ger.
Capsules: Javanese turmeric (p.2406·3).
Dyspepsia.

Infirmarius-Rovit, Ger.†.
Oral drops: Scopolia carniolica; Javanese turmeric (p.2406·3); greater celandine (p.2317·1); gentian (p.2310·3); angelica (p.2258·1); manna (p.1744·2); saffron (p.1472·3); zedoary; myrrh (p.2349·2).
Biliary disorders; digestive disorders; gastrointestinal spasm.

Infla-Ban *Triomed, S.Afr.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders.

Inflabion *Help, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Inflaced *Dexo, Fr.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Inflacor *Pharmachemie, S.Afr.†; Rolab, S.Afr.†.*
⊗ Budesonide (p.1520·1).
Asthma.

Inflacort *Bilim, Turk.*
⊗ Budesonide (p.1520·1).
Asthma.

Infladase *Centaur, India.*
Serrapeptase (p.2385·3); traces of cobalt, manganese, and zinc.
Alveolar abscess; breast engorgement; inflammation; pain; pericoronitis.

Infladoren *Hexal, Braz.†.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Inflaflur *Faran, Gr.*
Flurbiprofen sodium (p.61·2).
Inhibition of intraoperative miosis.

Inflagel *EMS, Braz.*
Tenoxicam (p.128·2).

Inflalid *Legrand, Braz.*
Nimesulide (p.95·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Inflam
Note.This name is used for preparations of different composition.
Lichtenstein, Ger.†.
Ointment: Indometacin (p.66·3); lauromacrogol 400 (p.1916·1).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.
Winthrop, Ger.
Topical spray: Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Inflamac
Spirig, Cz.†.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Spirig, Switz.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Inflamase
Note.This name is used for preparations of different composition.
Novartis Ophthalmics, Canad.†; Novartis Ophthalmics, USA†.
⊗ Prednisolone sodium phosphate (p.1541·2).
Inflammatory eye disorders.
Amnol, Ital.
Aesculus (p.2248·2); bromelain (p.2269·1); zinc sulfate (p.1999·2); copper sulfate (p.1935·3).
Inflammation; oedema.

Inflamase IdroGel *Amnol, Ital.*
Aescin (p.2248·2); bromelains (p.2269·1).
Inflammation; oedema.

Inflamate *TO-Chemicals, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders; rheumatic fever.

Inflamax *Elofar, Braz.*
Diclofenac sodium (p.44·3).

Inflamene *Farmalab, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Inflamex *Biofarma, Turk.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Inflammide *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Thai.†.*
⊗ Budesonide (p.1520·1).
Asthma; rhinitis.

Inflanac *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders.

Inflanan *Marjan, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Inflanaze *Boehringer Ingelheim, S.Afr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Inflanefran *Allergan, Cz.†; Allergan, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Eye disorders.

Inflanegent *Allergan, Ger.*
⊗ Prednisolone acetate (p.1541·1); gentamicin sulfate (p.282·1).
Infected eye disorders.

Inflanox
Note.This name is used for preparations of different composition.
Farmoquimica, Braz.†.
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.
Euromex, Mex.
Naproxen (p.92·3).
Fever; inflammation; pain.

Inflased *Bilim, Turk.*
Diclofenac sodium (p.44·3).
Allergic conjunctivitis; postoperative eye inflammation; prevention of miosis during cataract surgery.

Inflasic *Blue Sky, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Inflason *Berlico Mulia, Indon.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Inflastat *Sensomed, Philipp.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Inflax *Ativus, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Inflazone
Note.This name is used for preparations of different composition.
Centaur, India.
Diclofenac diethylamine (p.44·3); methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); mephenesin (p.1897·2); capsicum oleoresin (p.2276·2).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.
Aspen, S.Afr.
Phenylbutazone (p.117·1).
Ankylosing spondylitis.

Inflexal *Scott-Cassara, Arg.; Kwizda, Austria; Biosano, Chile; Berna, Cz.; Baxter BioScience, Ger.; Berna, Hong Kong; Berna, Ital.; Berna, Malaysia; Berna, Neth.; Berna, Philipp.; Berna, Pol.; Berna, Port.; Berna, Switz.; Berna, Turk.; Sanofi Pasteur, UK†.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Infliplus *HLB, Arg.*
⊗ Budesonide (p.1520·1).

Infloc *SFD, Port.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Bacterial skin infections.

Infloran
Note.This name is used for preparations of different composition.
Kwizda, Austria; Berna, Hong Kong; One Pharma, Philipp.; Vieira, Port.†; Desma, Switz.; Berna, Thai.
Bifidobacterium infantis (p.2372·3); *Lactobacillus acidophilus* (p.2372·3).
Constipation; diarrhoea; digestive disorders in infants on artificial diets; dyspepsia; enterocolitis; gastrointestinal disorders; restoration of gastrointestinal flora.
SIT, Ital.; Desma, Spain.
Bifidobacterium bifidum (p.2372·3); *Lactobacillus acidophilus* (p.2372·3).
Diarrhoea; gastrointestinal disorders; restoration of gastrointestinal flora.

Infloran Bio *SIT, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins (p.1922·1).
Dietary supplement.

Infloxa *Alpharma, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Influ-A *Trima, Israel†.*
Amantadine hydrochloride (p.792·3).
Influenza A.

Influaforce *Bioforce, Switz.*
Homoeopathic preparation.

Influbene *Ratiopharm, Austria.*
⊗ Paracetamol (p.108·1); etilefrine hydrochloride (p.1284·1); butetamate citrate (p.1553·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Influbene C *Mepha, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Influbene N *Mepha, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Influcid *DHU, Rus.*
Homoeopathic preparation.

Infludo *Weleda, Austria; Weleda, Fr.; Weleda, Ger.; Weleda, Neth; Weleda, S.Afr.; Weleda, UK.*
Homoeopathic preparation.

Influenzine *Hochstetter, Chile†.*
Influenzinum.
Cold and influenza prophylaxis.

Influex *Steigerwald, Ger.*
oral tincture; Tablets: Homoeopathic preparation.

Influject *Baxter, Neth.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Influk *Knop, Chile.*
Homoeopathic preparation.

Influpiol C *Antipiol, Ital.*
Vitamin C; propolis; salix; dog rose (p.1922·1).

Influpozzi *IVP, Ital.*
An influenza vaccine (p.2218·2).
Active immunisation.

Influrem *Edmond Pharma, Ital.†.*
Propyphenazone (p.119·3); caffeine (p.1116·3); paracetamol (p.108·1).
Cold symptoms; pain.

Influsplit *Valda, Ital.†.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Influsplit SSW *GSK, Ger.*
An influenza vaccine (p.2218·2).
Active immunisation.

Influtruw *Truw, Ger.†.*
Homoeopathic preparation.

Influtux *Antipiol, Ital.*
Hedera; propolis; dog rose; echinacea (p.1922·1).

Influvac *Raffo, Arg.; Solvay, Austral.; Solvay, Austria; Grunenthal, Chile; Solvay, Cz.; Solvay, Denm.; Solvay, Fin.; Solvay, Fr.; Solvay, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Irl.; Solvay, Israel; Landsteiner, Mex.†; Healthcare Logistics, NZ; Solvay, Neth.; Solvay, Norw.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Solvay, Singapore; Solvay, Spain; Solvay, Swed.; Solvay, Switz.; Solvay, UK.*
An inactivated influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Influvac S *Solvay, Belg.; Solvay, Ital.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Influvirus *Hardis, Ital.*
An influenza vaccine (p.2218·2).
Active immunisation.

Influvit
Note.This name is used for preparations of different composition.
DHU, Ger.
Homoeopathic preparation.
Recordati, Ital.
Paracetamol (p.108·1); ascorbic acid (p.1983·3); propyphenazone (p.119·3).
Fever; pain.

Influ-Zinc *Marfarma, Ital.*
Zinc gluconate (p.1999·2); vitamin C (p.1983·3); selenium (p.1961·1); echinacea (p.2298·1); salix (p.121·3).

Influ-Zinc Gola *Marfarma, Ital.*
Zinc acetate (p.1999·1); zinc citrate (p.1999·2); liquorice (p.1740·3).

Infomel *Bevo, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Inf-Oph *Seng, Thai.*
⊗ Prednisolone acetate (p.1541·1).
Conjunctivitis.

Infor *Prater, Chile.*
A range of vitamin and mineral preparations (p.1922·1).

Informin *Gap, Gr.*
Phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Infortin *Prater, Chile.*
Vitamin preparation (p.1922·1).

Infostat *Bioprofarma, Arg.*
Interferon alfa-2a (p.885·1).
Hepatitis C; malignant neoplasms.

Infracyanine *SERB, Fr.*
Indocyanine green (p.2324·3).
Diagnostic aid.

Inframin *Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Infrarub *Wyeth-Whitehall, Arg.†; SA Druggists Self Med, S.Afr.*
Glycol salicylate (p.62·3); methyl nicotinate (p.85·3); histamine hydrochloride (p.2319·2); capsicum oleoresin (p.2276·2).
Musculoskeletal and joint disorders.

Infree *Eisai, Jpn; Eisai, Philipp.*
Indometacin farnesil (p.68·1).
Musculoskeletal, joint, and peri-articular disorders.

Infrotto Ultra *Cassella-med, Ger.†.*
Glycol salicylate (p.62·3); nonivamide (p.96·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Infufer *Sandoz, Canad.*
Iron dextran (p.1951·1).
Iron deficiency.

Infukoll
Note.This name is used for preparations of different composition.
Gobbi, Arg.
⊗ Succinylated gelatin (p.1072·1) with electrolytes.
Plasma volume expansion.
Beacon, UK.
⊗ Pentastarch (p.1065·1) in sodium chloride.
Plasma volume expansion.

Infukoll HES *Gobbi, Arg.; Schwarz, Ger.; Serum-Werk Bernburg, Ger.; Serum-Werk Bernburg, Rus.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Haemodilution; hypovolaemia; microcirculatory disorders; shock.

Infukoll M 40 *Serum-Werk Bernburg, Ger.†.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Hypovolaemia; thrombosis prophylaxis.

Infumorph *Elkins-Sinn, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Infusamin *Teva, Hung.*
A range of amino-acid infusions with or without carbohydrate and electrolytes (p.1922·1).
Parenteral nutrition.

Infuse Bone Graft *Medtronic, USA.*
Dibotermin alfa (p.1092·3).
Maxillofacial and dental bone grafting.

Infuvite *Baxter, USA.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Ingafol *Inga, India.*
Folic acid (p.1940·1).
Folic acid supplement; megaloblastic anaemia.

Ingagen-M *Inga, India.*
Methylergometrine maleate (p.2011·1).
Uterine atony; uterine haemorrhage.

Ingastri *Ipsen, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ingatol *Nufarindo, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1); vinca minor.
Circulation disorders; vitamin B supplement.

Ingebrax *Ingens, Arg.*
Tobramycin (p.354·1); diclofenac sodium (p.44·3); sodium hyaluronate (p.2320·1).
Eye disorders.

Ingebut *Ingens, Arg.*
Butenafine (p.528·1).
Fungal skin infections.

Ingeclof *Ingens, Arg.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Ingedex *Ingens, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Ingeflox *Ingens, Arg.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Ingelan
Note.This name is used for preparations of different composition.
Germania, Austria; Boehringer Ingelheim, Ger.†.
Topical gel: ⊗ Isoprenaline sulfate (p.1316·3).
Pruritus; skin disorders.
Germania, Austria; Boehringer Ingelheim, Ger.†.
Topical powder: ⊗ Isoprenaline sulfate (p.1316·3); salicylic acid (p.1612·2).
Skin disorders.

Ingelets *Ingens, Arg.*
Erythromycin (p.269·2).
Bacterial eye infections.

Ingemet *Ingens, Arg.*
⊗ Betamethasone valerate (p.1519·1); salicylic acid (p.1612·2); coal tar (p.1616·2).
Skin disorders.

Ingepsor *Ingens, Arg.*
Fumaric acid esters (p.1597·3).
Psoriasis.

Ingeshamp *Ingens, Arg.*
Coal tar (p.1616·2).
Seborrhoeic dermatitis.

Ingetim *Ingens, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

INH *Kocak, Turk.*
Isoniazid (p.288·1).
Tuberculosis.

INHA *Mersifarma, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inhacort *Boehringer Ingelheim, Ger.†.*
⊗ Flunisolide (p.1531·1).
Asthma.

Inhadrina *Ibefar, Braz.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2); menthol (p.2340·1); cineole (p.2282·3); sumatra benzoin (p.2394·2).
Respiratory-tract congestion.

Inhalador Medex *Sidus, Arg.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pine oil (p.2368·2); sassafras oil (p.2383·3).
Respiratory-tract congestion.

Inhalante Yatropan *Sanofi-Aventis, Braz.*
⊗ Ephedrine (p.1558·1); menthol (p.2340·1); cineole (p.2282·3); tolu (p.1574·2); lavender oil (p.2331·2); benzoin (p.2394·2); sodium guaiacol sulfanilamide.
Respiratory-tract congestion.

Inhalene *Sanofi Synthelabo, Belg.†.*
Menthol (p.2340·1); cineole (p.2282·3).
Cold symptoms; laryngitis; sinusitis.

Inhalex
Note.This name is used for preparations of different composition.
Cipla, India.
Ambroxol (p.1550·3).
Respiratory-tract disorders.
Silom, Thai.
⊗ Ipratropium bromide (p.1124·1); fenoterol hydrobromide (p.1121·1).
Obstructive airways disease.

Inhalo Rhinathiol *Sanofi-Aventis, Belg.*
Menthol (p.2340·1); cineole (p.2282·3).
Upper respiratory-tract disorders.

Inhalol *Profarm, Pol.*
Pine oil (p.2368·2); thyme oil (p.2401·2); peppermint oil (p.1761·2); turpentine oil (p.2406·3).
Upper respiratory-tract congestion.

INH-Ciba *Sandoz, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in the 400mg tablets for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inhelthran *Abbott, Arg.†.*
Enflurane (p.1782·2).
General anaesthesia.

Inhepar *Pisa, Mex.†.*
Heparin sodium (p.1301·2).

Inhibac *Pharmaland, Thai.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Inhibace
Note.This name is used for preparations of different composition.
Merck, Austria; Roche, Austria; Roche, Belg.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Hong Kong; Roche, Hung.; Chugai, Jpn; Syntex, Mex.†; Roche, NZ; Roche, Pol.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Venez.
Cilazapril (p.1244·3).
Heart failure; hypertension.

BMS, Israel†.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Inhibace comp *Roche, Swed.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Inhibace Plus *Merck, Austria; Roche, Austria; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Hung.; Roche, NZ; Roche, Pol.; Roche, S.Afr.; Roche, Spain; Roche, Switz.; Roche, Turk.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Inhibin *Viatris, Neth.*
Hydroquinine hydrobromide (p.2322·3).
Nocturnal muscle cramps.

Inhibisam *Richmond, Arg.*
Indinavir (p.884·2).
HIV infection.

Inhibitron *Liomont, Mex.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Inhibostamin *Novartis Consumer, Ger.†.*
Tritoqualine (p.593·3).
Hypersensitivity reactions; pruritus.

Inhiplex *Remedina, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Inhipraz *Bernofarm, Indon.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Inhiston *Biomedica, Ital.†.*
Pheniramine maleate (p.587·3).
Hypersensitivity reactions.

Inibace *Roche, Ital.; Roche, Port.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Inibace Plus *Roche, Ital.; Roche, Port.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Inib-Dor *Ibfarma, Braz.†.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Inibex S *Medley, Braz.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Inibina *Apsen, Braz.*
Isoxsuprine (p.2327·3) or isoxsuprine hydrochloride (p.2327·3).
Premature labour.

Inicox *Farmoquimica, Braz.*
Meloxicam (p.80·3).
Dysmenorrhoea; musculoskeletal and joint disorders.

Inigrin *Grin, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Inim *Sandoz, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Inimur *Taurus, Ger.*
Nifuratel (p.841·3).
Bacterial infections; fungal infections; trichomoniasis.

Inimur Myko *Taurus, Ger.*
Ciclopirox olamine (p.529·2).
Fungal vaginal infections.

Inipomp *Sanofi-Aventis, Fr.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Inistolin Antitusivo Ped *Pfizer Consumer, Spain.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Inistolin Expectoran Ped *Pfizer Consumer, Spain.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Iniston Antitusivo *Pfizer Consumer, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly contained dextromethorphan hydrobromide, pseudoephedrine hydrochloride, and triprolidine hydrochloride.
Coughs.

Iniston Antitusivo y Descongestivo *Pfizer Consumer, Spain.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Coughs; nasal congestion.

Iniston Descongestivo *Pfizer Consumer, Spain.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Formerly known as Iniston.
Cold symptoms; nasal congestion.

Iniston Expectorante y Descongestivo *Pfizer Consumer, Spain.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Formerly known as Iniston Expectorante.
Coughs; nasal congestion.

Iniston Mucolitico *Pfizer Consumer, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Initiss *Crinos, Ital.*
Cilazapril (p.1244·3).
Hypertension.

Initiss Plus *Crinos, Ital.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Injectrax *Blausiegel, Braz.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Injeflex *Zodiac, Braz.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Joint disorders.

Inkodiet *Nutrichem Diat, Cz.†.*
Preparation for enteral nutrition (p.1922·1).

Inkontan *Montavit, Austria.*
Trospium chloride (p.2198·3).
Bladder instability.

Inkopeptid *Nutrichem Diat, Cz.†.*
Preparation for enteral nutrition (p.1922·1).

Inkurin *Interbat, Indon.*
Cucurbita (p.2290·2).
Urinary incontinence.

Inmatrol *Interbat, Indon.*
⊗ Dexamethasone (p.1526·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Eye disorders with infection.

Inmune Booster *Solara, Mex.†.*
Echinacea (p.2298·1).
Immunostimulant.

Inmunex Plus *Victus, Venez.*
Preparation for enteral nutrition (p.1922·1).

Inmunine *Baxter, Venez.†.*
A factor IX preparation (p.1068·3).
Haemophilia.

Inmunoartro *Beta, Arg.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Inmunobalt *Rudefsa, Mex.†.*
Tablets: A lysate of *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Streptococcus haemolyticus*; *Staphylococcus aureus*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Inmunoferon *Cantabria, Spain.*
Glicofosfopeptical (p.2312·3).
Immunotherapy.

Inmunogrip *Gezzi, Arg.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).

Inmunogrip C *Gezzi, Arg.*
Phenylephrine (p.1568·1); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain; upper respiratory-tract congestion.

Inmunogrip T Caliente *Gezzi, Arg.*
Paracetamol (p.108·1).
Cold symptoms.

Inmunol *Andromaco, Mex.*
Glicofosfopeptical (p.2312·3).
Immunostimulant.

Inmunoprin *Asofarma, Mex.*
Thalidomide (p.2397·1).
Behcet's syndrome; erythema nodosum leprosum; malignant neoplasms.

Inmupen *Llorente, Spain†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Inmutag *Pharmacia, Arg.†.*
Interferon alfa (p.885·1).
Anogenital warts; hepatitis B and C; malignant neoplasms.

Innersource *Quest, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Innobion *Farmaceutica H, Mex.*
⊗ Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); dexamethasone sodium phosphate (p.1526·2); lidocaine hydrochloride (p.1862·3).
Musculoskeletal and joint disorders; neuralgia; neuritis.

Innobloc *Innoderm, Philipp.*
SPF 24: Titanium dioxide (p.1617·3).
Sunscreen.

Innobranduo *Lab Francais du Fractionnement, Fr.†.*
A complex of factor VIII and von Willebrand's factor (p.1067·1).
Formerly known as Innobrand.
Von Willebrand's disease.

Innogem *Egis, Cz.†; EGIS, Hung.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Innohep *Purissimus, Arg.†; Leo, Belg.; Leo, Canad.; Leo, Denm.; Leo, Fin.†; Leo, Fr.; Leo, Ger.; ZLB, Ger.; Leo (Λεο), Gr.; Leo, Hong Kong; Leo, Irl.; Leo, Israel†; Leo, Malaysia; CSL, NZ; Leo, NZ; Leo, Neth.; Leo, Norw.; Leo, Philipp.; Leo, Port.; Leo, Singapore; Leo, Spain; Leo, Swed.; Leo, Thai.; Abdi, Turk.; Leo, UK; Pharmion, USA.*
Tinzaparin sodium (p.1413·2).
Prevention of clotting during haemodialysis or extracorporeal circulation; thromboembolic disorders; unstable angina.

InnoLet N *Novo Nordisk, Jpn.*
⊗ Isophane insulin injection (human, recombinant) (p.443·2).
Diabetes mellitus.

InnoLet R *Novo Nordisk, Jpn.*
⊗ Insulin injection (human, recombinant) (p.443·2).
Diabetes mellitus.

InnoLet 10R, 20R, 30R, 40R, and 50R *Novo Nordisk, Jpn.*
⊗ Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40% and 50% and isophane insulin (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Diabetes mellitus.

Innomel *Clonmel, Irl.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

InnoPran *GSK, USA.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Innosensitive *Faran, Gr.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Innosfen *Bergamo, Braz.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Innova Cd *Laboratorios Chile, Chile.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Innovace *MSD, Irl.; MSD, UK.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Innovair *Chiesi, Fr.*
⊗ Beclometasone dipropionate (p.1516·2); formoterol fumarate (p.1122·1).
Asthma.

Innoxiderm *Innoderm, Philipp.*
Sulfadiazine silver (p.337·2).
Burns.

Innozide *MSD, Irl.; MSD, UK.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Inobes *Prafa, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Inocar *Solvay, Spain.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Inocar Plus *Solvay, Spain.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Inoclear *Tubilux, Port.†.*
Cleansing and wetting solution for contact lenses (p.1622·2).

Inoclim *Innotech, Fr.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Inocor
Sanofi Winthrop, Israel; Sanofi Synthelabo, Malaysia†; Sanofi Synthelabo, Port.†; Sanofi Winthrop, USA.
Amrinone lactate (p.1215·1).
Heart failure.

Sanofi Synthelabo, Ital.†; Sanofi Synthelabo, Mex.
Amrinone (p.1215·1).
Heart failure.

Inoderm *Meprofarm, Indon.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Inoflox *Biomedis, Malaysia; Biomedis, Philipp.; Biomedis, Singapore.*
Ofloxacin (p.310·2).
Bacterial infections.

Inofungin *Bergamo, Braz.*
Nystatin (p.543·2).
Vaginal candidiasis.

Inokain *Promed, Rus.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Inolaxine *Fournier, Fr.†; Fournier, Switz.*
Sterculia (p.1772·1).
Constipation.

Inolaxol *Selena, Swed.*
Sterculia (p.1772·1).
Adjunct in treatment of diarrhoea; constipation.

Inolin *Tanabe, Indon.; Tanabe, Jpn†.*
⊗ Tretoquinol hydrochloride (p.1149·3).
Obstructive airways disease.

INOmax *INO Therapeutics, Cz.; AGA, Denm.; AGA, Gr.; INO Therapeutics, Neth.; INO Therapeutics, Pol.; INO Therapeutics, Port.; INO Therapeutics, Spain; Trimedal, Switz.; INO Therapeutics, USA.*
Nitric oxide (p.1358·3).
Neonatal respiratory distress syndrome.

Inomet *Ulkar, Turk.*
Indometacin (p.66·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Inongan *Fumouze, Fr.*
Menthol (p.2340·1); methyl salicylate (p.85·3); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Muscle pain.

Inopamil *Zambon, Neth.*
⊗ Ibopamine hydrochloride (p.1312·1).
Heart failure.

Inopectol *Christiaens, Belg.*
Camphor (p.2273·2); cineole (p.2282·3); guaiacol (p.1561·2); menthol (p.2340·1); pine oil (p.2368·2).
Rhinitis; sinusitis.

Inopin *Siam Bheasach, Thai.*
Dopamine hydrochloride (p.1273·2).
Shock.

Inosert *Ipca, India.*
Sertraline hydrochloride (p.421·3).
Depression.

Inositech *Bio-Tech, USA.*
Inositol (p.2325·2).

Inotop *Torrex, Austria.*
Dobutamine hydrochloride (p.1271·2).
Cardiac stress testing; heart failure; shock.

Inotrex *Lilly, Gr.; Ferraz, Lynce, Port.*
Dobutamine hydrochloride (p.1271·2).
Cardiac surgery; cardiomyopathy; heart failure; myocardial infarction; shock.

Inotrin *Medicus, Gr.*
Isotretinoin (p.1599·2).
Acne.

Inotrop
Note. This name is used for preparations of different composition.
Fahrenheit, Indon.
Dobutamine hydrochloride (p.1271·2).
Arrhythmias; heart failure.

Samarth, Philipp.
⊗ Noradrenaline acid tartrate (p.1360·1).
Cardiac arrest; hypotension.

Inotropin *Bago, Arg.*
Dopamine hydrochloride (p.1273·2).
Heart failure; shock.

Inotropisa *Pisa, Mex.*
Dopamine hydrochloride (p.1273·2).
Cardiac surgery; hypovolaemia; shock.

Inotyol
Note. This name is used for preparations of different composition.
Selena Fournier, Denm.; Selena Fournier, Norw.; Selena, Swed.
Ichthammol (p.1599·1); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Eczema; psoriasis; skin disorders.

Urgo, Israel.
Ichthammol (p.1599·1); hamamelis (p.2318·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3); siam benzoin (p.2386·2).
Burns; skin disorders; wounds.

Brady, Austria; Aventis, Ital.†.
Ointment: Ichthammol (p.1599·1); hamamelis (p.2318·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Burns; skin disorders; skin irritation; wounds.

Urgo, Belg.
Ointment: Ichthammol (p.1599·1); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Skin disorders; superficial wounds and burns.

Fournier, Fr.†.
Ointment: Ichthammol (p.1599·1); hamamelis (p.2318·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3); siam benzoin (p.2386·2).
Skin disorders.

Brady, Austria.
Topical powder: Ichthammol (p.1599·1); hamamelis (p.2318·2); zinc oxide (p.1621·2); calcium carbonate (p.1714·1).
Skin disorders.

Inova *Inova, Ger.†.*
Dialkyldimethylammonium chloride (p.1642·2); alkyldimethylbenzylammonium chloride (p.1629·1); alkyldimethylethylbenzylammonium chloride.
Surface disinfection.

Inovan *Kyowa, Jpn.*
Dopamine hydrochloride (p.1273·2).
Anuria; oliguria; shock.

Inovelon *Eisai, Cz.; Eisai, Port.; Eisai, UK.*
Rufinamide (p.504·1).
Lennox-Gastaut syndrome.

Inovic *Ferraz, Lynce, Port.*
⊗ Eplerenone (p.1279·2).
Heart failure following myocardial infarction.

Inox *Hovid, Malaysia.*
Itraconazole (p.536·3).
Fungal infections.

Inoxin *Dexa, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Inoxitan *Galena, Cz.†; Ivax, Cz.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Inpained *Bajamed, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Inpamide *Pharmasant, Thai.*
⊗ Indapamide (p.1314·1).
Hypertension.

Inpanol *DHA, Hong Kong; DHA, Singapore.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Inpepsa *Fahrenheit, Indon.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Inprax *Degorts, Mex.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Inpront *Laboratorios Chile, Chile.*
Moclobemide (p.411·1).
Depression.

Inprosyn-HP *Wescrib, Philipp.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Inquifric *Inquifave, Venez.†.*
Menthol (p.2340·1).

Inquilim *Inquifave, Venez.†.*
Sodium salicylate (p.124·2); chlorphenamine (p.572·2).
Influenza symptoms.

Inquiper *Drovepat, Venez.†.*
Piperazine citrate (p.152·3).
Worm infections.

Inquiramin *Drovepat, Venez.†.*
Dexchlorpheniramine maleate (p.572·1).

Inquixol *Inquifave, Venez.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Insaar *Interbat, Indon.*
Losartan potassium (p.1326·1).
Hypertension.

Insadol *Expanpharm, Fr.; Expanpharm, Switz.*
Maize (p.2288·1).
Dental disorders; mouth disorders.

Insect Ecran
Note.This name is used for preparations of different composition.
Cooper, Fr.
Paediatric spray; special tropical spray: Icaridin.
Insect repellent.

Cooper, Fr.
Solution; spray: Permethrin (p.2048·2).
Insect repellent for clothing and bedding.

Cooper, Fr.
Spray: Diethyltoluamide (p.2041·1).
Insect repellent.

Insegar *Laus, Spain.*
⊗ Letrozole (p.740·2).
Breast cancer.

Insensye *MSD, Austral.*
Norfloxacin (p.309·2).
Bacterial infections.

Insertec *Baliarda, Arg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Inside *Antula, Swed.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Inside Brus *Antula, Fin.; Antula, Norw.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Insidon *Novartis, Austria; Novartis, Ger.; Novartis, Switz.; Novartis, Turk.*
Opipramol hydrochloride (p.414·1).
Anxiety; depression; non-psychotic mental disorders; psychosomatic symptoms; sleep disorders.

Insig *Sigma, Austral.*
⊗ Indapamide (p.1314·1).
Hypertension.

Insocaps *Infinity, Venez.*
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders.

Insogen *Altana, Mex.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Insogen Plus *Altana, Mex.*
Metformin hydrochloride (p.453·2); chlorpropamide (p.438·3).
Diabetes mellitus.

Insol *Pharmaspec, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Insom *Lennon, S.Afr.*
Flunitrazepam (p.996·2).
Insomnia.

Insoma *Pacific, NZ.*
Nitrazepam (p.1011·2).
Insomnia.

Insomin
Note.This name is used for preparations of different composition.
Orion, Fin.
Nitrazepam (p.1011·2).
Epilepsy; insomnia; premedication.

Abdi, Turk.
Opipramol hydrochloride (p.414·1).
Depression.

Insomnal
Note.This name is used for preparations of different composition.
Northia, Arg.†.
Passion flower (p.2363·2); valerian (p.2410·1); tilia (p.2402·2).
Insomnia.

Rougier, Canad.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Insomn-Eze *Aventis, Austral.†.*
Promethazine hydrochloride (p.588·2).
Insomnia.

Insomnia Passiflora *Homeocan, Canad.*
Homoeopathic preparation.

Insomnia Relief *Homeocan, Canad.*
Homoeopathic preparation.

Insomniger *Gerard, Irl.*
Temazepam (p.1030·1).
Insomnia; premedication.

Insomnium *Gador, Arg.*
Zopiclone (p.1039·1).
Insomnia.

Inspirol Halsschmerztabletten *Riemser, Ger.†.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); dequalinium chloride (p.1641·3).
Mouth and throat infections.

Inspirol Heilpflanzenol *Riemser, Ger.*
Peppermint oil (p.1761·2).
Cold symptoms; gastrointestinal disorders.

Inspirol P *Riemser, Ger.*
Myrrh (p.2349·2).
Mouth and throat inflammation.

Inspra *Pfizer, Austral.; Pfizer, Austria; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.; Pfizer, UK; Pfizer, USA.*
⊗ Eplerenone (p.1279·2).
Heart failure following myocardial infarction; hypertension.

Instacare *Ciba Vision, Austral.; Ciba Vision, NZ†.*
Cleaning and disinfectant solutions for soft contact lenses (p.1622·2).

Instacyl *Streuli, Switz.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold symptoms.

Insta-Glucose *ICN, Austral.†.*
Glucose (p.1945·3).
Hypoglycaemia.

Instalax *Knop, Chile.*
Senna (p.1769·2); linseed (p.2333·3); fennel (p.2302·3); liquorice (p.1740·3).
Constipation.

Instana *Cantabria, Spain.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Instant Hand Sanitizer *Scott, Canad.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Instantine *Bayer Consumer, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; headache; pain.

Instaret *Unipharma, Gr.*
Acetic acid (p.2244·2).
Mild bacterial or fungal infections of the outer ear.

Instenon *Nycomed, Austria; Nycomed, Hong Kong; Nycomed, Rus.; Nycomed, Thai.†.*
⊗ Hexobendine hydrochloride (p.1305·2); etofylline (p.1121·1); etamivan (p.2156·1).
Cerebrovascular disorders.

Insti *Herbion, Rus.*
Ivy (p.2328·1); adhatoda; viola odorata; liquorice (p.1740·3); chinese tea (p.2416·1); fennel (p.2302·3); eucalyptus (p.2301·2); valerian (p.2410·1).
Symptomatic treatment of respiratory-tract infections.

Instillagel *Raffo, Arg.; Solco, Austria; Melisana, Belg.; Farco, Cz.; Farco, Denm.; Fuca, Fr.; Farco, Ger.; Alfin, Gr.; Farco, Hong Kong; Farco, Hung.; Farco, Irl.; Farco, Israel†; Asofarma, Mex.†; Farco, Neth.; Farco, Port.; Selena, Swed.; CliniMed, UK.*
Lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Catheterisation; cystoscopy; endoscopy; urethroscopy.

Instink *Sunthi Sepuri, Indon.*
Tribulus terrestris (p.2404·1); saw palmetto (p.2192·3); damiana (p.2292·1); ginseng (p.2312·1); muira-puama; sarsaparilla (p.2383·3).
Dietary supplement for men.

Insto *Sterling, Indon.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Instrunet *Inibsa, Port.*
A range of solutions for skin and instrument disinfection.

Instru-Safe *Eagle, Austral.†.*
Silicone (p.2032·1).
Instrument lubrication.

Insucar *Apotex, Mex.*
Isosorbide dinitrate (p.1317·3).

Insuflen *Fada, Arg.†.*
Ranitidine (p.1766·1).

Insulatard *Novo Nordisk, Belg.; Pentafarma, Chile†; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Malaysia; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK.*
⊗ Isophane insulin injection (human, monocomponent) (p.443·2).
Formerly known as Human Insulatard in the *UK*.
Diabetes mellitus.

Insulatard HM *Novo Nordisk, Arg.; Novo Nordisk, Austria; Novo Nordisk, Chile; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Philipp.; Novo Nordisk, Singapore; Novo Nordisk, Switz.*
⊗ Isophane insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Insulatard Human *Novo Nordisk, Ger.†.*
⊗ Isophane insulin injection (human, ge) (p.443·2).
Diabetes mellitus.

Insulatard MC *Novo Nordisk, Arg.†; Novo Nordisk, Hong Kong†; Novo Nordisk, NZ; Novo Nordisk, Switz.*
⊗ Isophane insulin injection (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Insulatard NPH *Novo Nordisk, Spain†.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Insulex *Pisa, Mex.*
⊗ Insulin (human) (p.443·2).
Diabetes mellitus.

Insulidd L *Marvel, Rus.*
⊗ Insulin zinc suspension (crytalline 70%, amorphous 30%) (human) (p.443·2).
Diabetes mellitus.

Insulidd N *Marvel, Rus.†.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Insulidd R *Marvel, Rus.†.*
⊗ Soluble insulin (human) (p.443·2).
Diabetes mellitus.

Insulin Basal *Braun, Ger.; Ratiopharm, Ger.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Insulin Comb 30/70 *Braun, Ger.; Ratiopharm, Ger.*
⊗ Mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Insulin Lt *Tarchomin, Rus.*
⊗ Insulin zinc suspension (crystalline 70%, amorphous 30%) (porcine) (p.443·2).
Diabetes mellitus.

Insulin Lyhyt *Orion, Fin.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Insulin Maxirapid *Tarchomin, Rus.*
⊗ Neutral insulin (porcine) (p.443·2).
Diabetes mellitus.

Insulin Monotard *Novo Nordisk, Hung.†.*
⊗ Insulin zinc suspension (30% amorphous, 70% crystalline) (human) (p.443·2).
Diabetes mellitus.

Insulin Monotard HM *Novo Nordisk, Ger.†.*
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (human) (p.443·2).
Diabetes mellitus.

Insulin Novo Semilente MC *Novo Nordisk, Ger.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Insulin Pitka *Orion, Fin.†.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Insulin Rapid *Braun, Ger.; Ratiopharm, Ger.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Insulin Reaction *Sherwood, USA.*
Glucose (p.1945·3).
Hypoglycaemia.

Insulin S *Berlin-Chemie, Ger.†; Hoechst, Ger.†.*
⊗ Insulin injection (pork) (p.443·2).
Diabetes mellitus.

Insulin Semilente *Novo Nordisk, Hung.†.*
⊗ Insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Insulin SNC *Berlin-Chemie, Ger.†.*
⊗ Insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Insulin Ultratard *Novo Nordisk, Hung.†.*
⊗ Insulin zinc suspension (crystalline) (human) (p.443·2).
Diabetes mellitus.

Insulinum Lente *Polfa Tarchomin, Pol.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Insulinum Maxirapid *Polfa Tarchomin, Pol.*
⊗ Insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Insulinum Semilente *Polfa Tarchomin, Pol.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Insulinum Ultralente *Polfa Tarchomin, Pol.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Insuman 25/75 and 50/50 *Aventis, India.*
⊗ Mixtures of neutral insulin injection (human) 25% or 50% and isophane insulin injection (human) 75% or 50%, respectively (p.443·2).
Diabetes mellitus.

Insuman Basal *Aventis, Austria; Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Irl.; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Aventis, Swed.; Aventis, Switz.; Aventis, UK.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Insuman Comb 15, 25, and 50 *Aventis, Austria; Aventis, Cz.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Irl.; Aventis, Neth.; Aventis, UK.*
⊗ Mixtures of soluble insulin injection (human) 15%, 25%, and 50% and isophane insulin injection (human) 85%, 75%, and 50% respectively (p.443·2).
Diabetes mellitus.

Insuman Comb 25 *Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Aventis, Swed.; Aventis, Switz.*
⊗ Mixture of soluble insulin (human) 25% and isophane insulin (human) 75% (p.443·2).
Diabetes mellitus.

Insuman Comb 85N/15R and 75N/25R *Sanofi-Aventis, Braz.*
⊗ Mixtures of isophane insulin injection (human) 85% and 75% and soluble insulin injection (human) 15% and 25% respectively (p.443·2).
Diabetes mellitus.

Insuman Infusat *Aventis, Austria; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Aventis, Neth.; Aventis, Norw.; Aventis, Swed.; Aventis, Switz.*
⊗ Soluble insulin injection (human) (p.443·2).
Diabetes mellitus.

Insuman N *Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Venez.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Insuman 15R/85N, 25R/75N, and 50R/50N *Aventis, Mex.*
⊗ Mixtures of soluble insulin injection (human) 15%, 25%, and 50% and isophane insulin injection (human) 85%, 75%, and 50%, respectively (p.443·2).
Diabetes mellitus.

Insuman 100N *Aventis, Mex.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Insuman R *Aventis, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Aventis, Mex.; Sanofi-Aventis, Venez.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Insuman Rapid *Aventis, Austria; Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Aventis, India; Sanofi-Aventis, Irl.; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Aventis, Swed.; Aventis, Switz.; Aventis, UK.*
⊗ Soluble insulin injection (human) (p.443·2).
Diabetes mellitus.

Insumet *Cadila, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Insunex *Medopharm, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Insup *Alacan, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Insuplant *ProStrakan, Fr.*
⊗ Insulin (human) (p.443·2).
Diabetes mellitus.

Insusym *Ultra, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Insusym-Forte *Ultra, Mex.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Insuven *Almirall, Chile.*
Diosmin (p.2304·2).
Capillary fragility; venous insufficiency.

Intafer
Note.This name is used for preparations of different composition.
Zuoz, Venez.
Oral drops; tablets: Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Zuoz, Venez.
Syrup: Iron polymaltose (p.1953·1); cyanocobalamin (p.1980·2).
Iron-deficiency anaemia.

Intaferfol *Zuoz, Venez.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias.

Intal *Phoenix, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.; Aventis, Cz.†; Aventis, Ger.; Aventis, Hong Kong†; Teva, Hung.; Sanofi-Aventis, Irl.; Astellas, Jpn; Aventis, Malaysia†; Aventis, Mex.; Douglas, NZ; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Aventis, Spain†; Aventis, Thai.; Eczacibasi, Turk.; Aventis, UK; King, USA.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma; bronchitis; bronchospasm; food allergy.

Intal Plus *Aventis, Cz.†.*
⊗ Sodium cromoglicate (p.1136·3); salbutamol sulfate (p.1131·3).
Asthma.

Intapan *Duopharma, Hong Kong.*
Nalbuphine hydrochloride (p.91·3).
Adjunct in general anaesthesia; pain.

Intard *Julphar, UAE.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Intaxel *Dabur, Hung.; Dabur, India; Dabur, Philipp.; Dabur, Thai.; Biogalenic, Venez.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Inteflora *Adcock Ingram, S.Afr.*
Saccharomyces boulardii (p.2372·3).
Gastrointestinal disorders.

Integra
Note.This name is used for preparations of different composition.
Johnson & Johnson, Ger.†.
Collagen (p.2286·1); chondroitin sulfate (p.2280·3).
Skin defects.

Quimica y Farmacia, Mex.
A range of vitamin and mineral preparations (p.1922·1).

Integral *Merck, Pol.†.*
A vitamin and mineral preparation (p.1922·1).

Integrilin *Schering-Plough, Austral.; Schering-Plough, Belg.; Schering, Canad.; Essex, Chile†; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; Schering-Plough, Hong Kong; GSK, Hung.; GSK, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, NZ; GSK, Neth.; GSK, Norw.; Schering-Plough, Philipp.; GSK, Pol.; GSK, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; GSK, Spain; Schering-Plough, Swed.; GSK, Switz.; Schering-Plough, Thai.; GSK, UK; Schering, USA.*
Eptifibatide (p.1281·3).
Myocardial infarction; prevention of ischaemic cardiac complications in coronary angioplasty or atherectomy; unstable angina.

Integrobe *Northia, Arg.*
Dipyrone (p.49·2).
Inflammation; pain.

Integrobe Plus *Northia, Arg.*
Dipyrone (p.49·2); ergotamine (p.621·3); caffeine (p.1116·3).

Integrovin *Liferpal, Mex.*
Vitamin B substances with lysine (p.1922·1).

Intelec *Buxton, Arg.*
Galantamine (p.366·2).
Alzheimer's disease.

Intelecta *Unipharma, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Intelektan *Biofarm, Pol.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Fatigue; mental function impairment.

Intelence *Tibotec, USA.*
Etravirine (p.875·3).
HIV infection.

Inteligen *Phoenix, Arg.†.*
⊗ Arginine acetylasparaginate (p.1928·3).
Fatigue.

Inteligen Ginseng *Phoenix, Arg.†.*
⊗ Arginine acetylasparaginate (p.1928·3); ginseng (p.2312·1).
Asthenia.

Intemipril *Sandoz, Mex.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction.

Inter 2-B *Delta, Arg.*
Interferon alfa-2b (p.885·1).
Anogenital warts; chronic hepatitis B and C; malignant neoplasms.

Interal *HPB, Rus.*
Interferon alfa-2b (p.885·1).
Infections; malignant neoplasms.

Interbi *Interbat, Indon.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Interbion *Biospray, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Intercon *Interbat, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Intercron *Zambon, Fr.*
Sodium cromoglicate (p.1136·3).
Food hypersensitivity.

Intercyton *UCB, Fr.*
Flavodate sodium (p.2304·2).
Capillary fragility; circulatory eye disorders; haemorrhoids; menometrorrhagia associated with intra-uterine devices; venous insufficiency.

Interderm *Interpharma, Spain.*
⊗ Gentamicin sulfate (p.282·1); nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Interdoxin *Interbat, Indon.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Interfam *Interbat, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Interferon Alfanative *Rentschler, Cz.†; BioNative, Indon.; Fahrenheit, Indon.*
Interferon alfa (p.885·1).
Chronic myeloid leukaemia; hairy-cell leukaemia.

Interflox *Interbat, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Interhistin *Interbat, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders.

Intermax-Alpha *Raffo, Chile.*
Interferon alfa (p.885·1).
Hepatitis B; hepatitis C; malignant neoplasms.

Intermic *Interbat, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Intermoxil *Interbat, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Internase *Quality, Hong Kong.*
Bromelains (p.2269·1).
Soft-tissue inflammation and oedema.

Internolol *Interbat, Indon.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Interpec *Interbat, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Interpril *Interbat, Indon.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Interquin *Interbat, Indon.*
Hydroquinone (p.1598·2); sunscreen.
Skin hyperpigmentation.

Interquin Plus *Interbat, Indon.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Skin hyperpigmentation.

Intersept *Interdelta, Switz.*
Povidone-iodine (p.1659·2).
Burns; skin disinfection; wounds.

Intersun
Note.This name is used for preparations of different composition.
Interbat, Indon.
Cream SPF 35: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Interbat, Indon.
Lotion SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Intervein *Gerolymatos, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Intervit *San Marino, Philipp.*
Calcium lactate; vitamins A, B, and D (p.1922·1).
Nutritional supplement.

Interzol *Interbat, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Intestamin *Fresenius Kabi, Ger.†; Fresenius Kabi, Port.†.*
Preparation for enteral nutrition (p.1922·1).

Intestinex *Marin, USA.*
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

Intestinol
Note.This name is used for preparations of different composition.
Rosch & Handel, Austria.
Pancreatin (p.2360·1); sodium cholate (p.2266·3); duodenum extract (p.2337·3); charcoal (p.1435·2).
Gastrointestinal disorders.

Kocak, Turk.
Pancreatin (p.2360·1); ox bile (p.2266·3); medicinal charcoal (p.1435·2).

Intesul *Beta, Arg.*
Mosapride citrate (p.1750·3).
Gastritis; gastro-oesophageal reflux; gastroparesis.

Intetrix *Beaufour, Fr.; Beaufour-Ipsen, Rus.*
Tiliquinol (p.848·2); tiliquinol lauril sulfate (p.848·2); tilbroquinol (p.848·2).
Intestinal amoebiasis.

Inthacine *The Forty-Two, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Inthesa-5 *Fahrenheit, Indon.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Intidrol *Interbat, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Intifen *Interbat, Indon.*
Ketotifen fumarate (p.582·2).
Asthma.

Intim
Note.This name is used for preparations of different composition.
ICIM, Ital.
Hamamelis (p.2318·2); levomenol (p.2333·3).
Personal hygiene.

Biogen, Rus.†.
Chlorhexidine (p.1635·2).
Disinfection of mucous membranes, skin, and equipment.

Intima *Pascual, Philipp.*
Lactic acid (p.2329·3); chamomile (p.2279·3); aloe vera (p.1588·2); sodium lactate (p.1673·3).
Feminine hygiene.

Intimide *Novag, Mex.†.*
Pregnancy test (p.2372·1).

Intocel *Sidus, Arg.*
Cladribine (p.701·1).
Hairy-cell leukaemia.

Intra *Eurofarma, Braz.*
Lubricating gel.

Intracef
Note.This name is used for preparations of different composition.
Bergamo, Braz.
Ceftazidime (p.234·1).
Bacterial infections.

Pharmacare, S.Afr.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Intradermi *Eberth, Ger.*
Troxerutin (p.2305·1); aesculus (p.2248·2).
Venous insufficiency.

Intradermo Cort Ant Fung *Cederroth, Spain†.*
⊗ Fluocinolone acetonide (p.1531·3); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Intradermo Corticosteroi *Cederroth, Spain†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Intradine *Intra, Venez.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Intradyn *Intra, Venez.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Intrafat *Nihon, Jpn†.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intrafer
Note.This name is used for preparations of different composition.
Geymonat, Ital.
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Unipharm, Mex.
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1).
Anaemias.

Intrafer F-800 *Unipharm, Mex.*
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Folate deficiency; iron deficiency; iron-deficiency anaemia.

Intrafer TF *Unipharm, Mex.*
Iron amino acid chelate (p.1950·3); folic acid (p.1940·1).
Anaemias.

Intrafusin *Fresenius Kabi, Austria; Baxter, Ger.; Fresenius Kabi, UK.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Intrafusin E *Baxter, Ger.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Intrafusin SX-E *Kalbe, Indon.*
Amino-acid, sorbitol, xylitol, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Intragam *CSL, Austral.; CSL, NZ; NBI, S.Afr.*
A normal immunoglobulin (p.2225·3).
Bone marrow transplantation; Guillain-Barré syndrome; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Intraglobin *MDA, Austral.†; Biotest, Austria; Biotest, Ger.†; Intra Pharma, Irl.; Biotest, Ital.; Biotest, Thai.; Kansuk, Turk.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation; thrombocytopenic purpura; Wiskott-Aldrich syndrome.

Intraglobin F *Biotest, Cz.†; Ionios (Ιονιος), Gr.; Biotest, Hong Kong; Biotest, Israel; Biotest, Malaysia†; Biotest, Pol.; Mednostica, S.Afr.; Biotest, Singapore; Biotest, Switz.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; auto-immune disorders; bone marrow transplantation; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Intrait de Marron d'Inde P *Aerocid, Fr.*
Aesculus (p.2248·2); metesculetol sodium (p.2343·2).
Haemorrhoids.

Intralgin *3M, UK†.*
Benzocaine (p.1854·1); salicylamide (p.121·2).
Musculoskeletal pain.

Intralgis *Urgo, Fr.*
Ibuprofen (p.64·2).
Peri-articular and soft-tissue disorders.

Intralipid *Baxter, Austral.; Fresenius Kabi, Austria; Baxter, Canad.; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Baxter, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Pharmacia, Irl.; Pharmacia Upjohn, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Baxter, USA; Diamedica, Venez.†.*
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Intralipide *Fresenius Kabi, Fr.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intralipos *Tempo Scan Pacific, Indon.; Green Cross, Malaysia†; Grifols, Malaysia†; Green Cross Guangzhou, Singapore; Green Cross, Thai.†.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Intralon *Darier, Mex.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Intramin *Baxter, Ger.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Intramin G *Fresenius Kabi, Austria.*
Amino-acid, electrolyte, and glucose infusion (p.1922·1).
Parenteral nutrition.

Intrapen *Intra, Venez.†.*
Ampicillin (p.204·1).
Bacterial infections.

Intrasept *Farmo Quimica, Chile.*
Thiomersal (p.1663·3).
Skin and wound disinfection.

Intrasite
Note.This name is used for preparations of different composition.
Smith & Nephew, Austral.; Smith & Nephew, S.Afr.
Crilanomer (p.1593·1).
Wound dressing; wounds.

Smith & Nephew, Fr.
Carmellose sodium (p.2142·1); propylene glycol (p.2374·1).
Wounds.

Smith & Nephew, Irl.; Smith & Nephew, Ital.
Hydrogel starch copolymer.
Ulcers; wounds.

Smith & Nephew Healthcare, UK.
Carmellose (p.2142·1).
Formerly known as Scherisorb. Formerly contained hydrogel starch copolymer.
Wound dressing.

Intraspir *Tecnifar, Port.*
Lysine aspirin (p.79·1).
Fever; pain.

Intrastigmina *Lusofarmaco, Ital.; Lusofarmaco, Port.*
Neostigmine metilsulfate (p.631·3).
Abdominal distension; myasthenia gravis; post-operative intestinal atony; urinary retention.

Intrataxime *LDP, Rus.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Intratect *Biotest, Ger.; Biotest, Hung.; Biotest, Pol.*
A normal immunoglobulin (p.2225·3).
Bone-marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Intraval *Aventis, NZ.*
Thiopental sodium (p.1795·2).
General anaesthesia.

Intraval Sodium *Aventis, Irl.†.*
Thiopental sodium (p.1795·2).
Convulsive states; general anaesthesia.

Intra-Vite *Roche, Austral.*
Vitamin B substances with vitamin C (p.1922·1).
Formerly known as Intra-Vite B Group plus Ascorbic Acid.
Vitamin deficiencies; vitamin supplement.

Intrazolina *Torlan, Spain.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Intrazoline *LDP, Rus.*
Cefazolin (p.222·1).
Bacterial infections.

Intrenon *Spofa, Cz.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Intricon *Great Eastern, Thai.; United American, Thai.*
Ferrous fumarate (p.1938·3); vitamin B substances; vitamin C; liver (p.1922·1).
Anaemias.

Intrinsa *Procter & Gamble, Cz.; Procter & Gamble, Fr.; Procter & Gamble, Port.; Procter & Gamble, UK.*
⊗ Testosterone (p.2129·3).
Sexual hypoactivity following oophorectomy or hysterectomy.

Intrix *Pharos, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Introcin *Andromaco, Chile†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Introlan *Galagen, USA.*
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Introlite *Abbott Nutrition, UK; Ross, USA.*
Preparation for enteral nutrition (p.1922·1).

Intron *Schering-Plough, Venez.*
Interferon alfa-2b (p.885·1).
Chronic hepatitis; malignant neoplasms.

Intron A *Schering-Plough, Arg.†; Schering-Plough, Austral.; Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Chile†; Schering-Plough, Cz.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Israel; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, NZ; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering, USA; Schering-Plough, Venez.*
Interferon alfa-2b (rbe) (p.885·1).
Anogenital warts; chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Intron A Peg *Schering-Plough, Arg.†.*
Peginterferon alfa-2b (rbe) (p.888·3).
Chronic hepatitis C.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Intron A/Rebetol *Essex, Switz.†.*
Capsules, ribavirin (Rebetol) (p.902·3); injection, interferon alfa-2b (p.885·1).
Hepatitis C.

IntronA *Aesca, Austria; Schering-Plough, Belg.; Schering-Plough, Chile; SP, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Ital.; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Swed.; Schering-Plough, UK.*
Interferon alfa-2b (p.885·1).
Formerly known as Intron A.
Anogenital warts; carcinoid syndrome; chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Intropaste *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Intropin *BMS, Canad.†; Boots, Hong Kong†; Du Pont, Hong Kong†; Sanofi Synthelabo, S.Afr.; BMS, Swed.†; Du Pont, USA†.*
Dopamine hydrochloride (p.1273·2).
Heart failure; shock.

Intrum Plus *Interbat, Indon.*
Bovine colostrum; vitamins; docosahexaenoic acid (p.1922·1).
Nutritional supplement.

Intunal *Meprofarm, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dexchlorpheniramine maleate (p.572·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Influenza symptoms.

Inulac *Corypharma, Ital.*
Lactic-acid-producing organisms (p.2372·3).
Maintenance of normal gastrointestinal flora.

Inutest *Fresenius Kabi, Austria; Fresenius Kabi, Cz.†.*
Polyfructosan (Sinistrin) (p.2326·3).
Determination of glomerular filtration rate.

Inuvic *Leti, Venez.*
Montelukast (p.1126·3).
Asthma.

Invanz *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.†; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, NZ; MSD, Neth.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Thai.; MSD, UK; Merck, USA; MSD, Venez.*
Ertapenem sodium (p.269·1).
Bacterial infections.

Invega *Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Port.; Janssen-Cilag, UK; Janssen, USA.*
Paliperidone (p.1015·1).
Schizophrenia.

Inveoxel *Drag, Chile†.*
Naproxen (p.92·3).

Invernosan *Excelentia, Arg.†.*
Paracetamol (p.108·1).

Inversine *Layton, USA.*
Mecamylamine hydrochloride (p.1331·3).
Hypertension.

Invex *Solvay, Braz.*
⊗ Prednicarbate (p.1540·2).
Corticosteroid.

Inviclot *Fahrenheit, Indon.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Invicorp *Douglas, NZ.*
Aviptadil (p.2411·2); phentolamine mesilate (p.1370·2).
Erectile dysfunction.

Invigan
Note.This name is used for preparations of different composition.
Bago, Chile.
Ornidazole (p.843·1).
Anaerobic bacterial infections; dracunculiasis; protozoal infections.

Almi, Spain.
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Invirase *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, UK; Roche, USA.*
Saquinavir mesilate (p.906·1).
HIV infection.

Invivac *Solvay, Austria; Solvay, Ger.; Solvay, Neth.; Solvay, Norw.; Solvay, UK.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Invoigin *Chew, Thai.*
Dipyrone (p.49·2).
Fever; pain.

Invomit *Interbat, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Invoril *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; ischaemic heart disease.

Invozide *Ranbaxy, India.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Inxibir *Pharmacia, Arg.†.*
Zalcitabine (p.912·3).
HIV infection.

Inyesprin *Grunenthal, Spain.*
Lysine aspirin (p.79·1).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Inza
Note.This name is used for preparations of different composition.
Alphapharm, Austral.; Alphapharm, Hong Kong; Alphapharm, Malaysia†; Merck, Malaysia†; Alphapharm, Singapore.
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; musculoskeletal, joint, and soft-tissue disorders; pain.

Konimex, Indon.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Pharmacare, S.Afr.
Ibuprofen (p.64·2).
Gout; musculoskeletal and joint disorders.

Inzana *Konimex, Indon.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Inzelloval *Kohler-Pharma, Ger.*
Mineral preparation (p.1922·1).

Inzeton *Ilsan, Turk.*
Opipramol hydrochloride (p.414·1).
Depression.

Inzitan *Kern, Spain.*
⊗ Cyanocobalamin (p.1980·2); dexamethasone (p.1526·1); thiamine hydrochloride (p.1976·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Myalgia; neuralgia; neuritis.

Inzolen *Kohler, Ger.*
A range of electrolyte (p.1667·1) and trace element (p.1922·1) infusions.
Electrolyte disorders; metabolic disorders.

Iobid DM *Iomed, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Iobrim *FDC, India.*
Brimonidine tartrate (p.1878·3).
Glaucoma; ocular hypertension.

Iocare *Ciba Vision, Ital.*
Electrolytes (p.1667·1).
Eye irrigation.

Iocare Balanced Salt Solution *Iocom, UK; Novartis Ophthalmics, USA.*
Electrolytes (p.1667·1).
Eye irrigation.

Iocare BSS *Ioltech, Ger.*
Electrolytes (p.1667·1).
Eye irrigation.

Iodal *Iomed, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Iodalg *Thalgo, Fr.*
Marine algae.
Dietary supplement.

Iodarsolo B12 *Medifarma, Mex.†.*
Iodine (p.2169·2); potassium iodide (p.2169·2); sodium arsenate (p.2388·3); vitamin B (p.1980·2).

Iodax *Rekah, Israel.*
Iodine (p.2169·2); potassium iodide (p.2169·2).
Disinfection of minor cuts and bruises.

Iode *Atlas, Canad.*
Iodine (p.2169·2); potassium iodide (p.2169·2).

Iodep *Novara, Arg.*
Povidone-iodine (p.1659·2).
Disinfection.

Iodepol *Ache, Braz.†.*
Potassium iodide (p.2169·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Iodesin *EMS, Braz.*
Oxomemazine hydrochloride (p.587·1); potassium iodide (p.2169·2); sodium benzoate (p.1630·2); guaifenesin (p.1561·3); ipecacuanha (p.1562·3).
Respiratory-tract congestion.

Iodetal *Sanval, Braz.*
Sulfogaiacol (p.1573·2); potassium iodide (p.2169·2); tolu balsam (p.1574·2).
Respiratory-tract congestion.

Iodeto de Potassio
Note.This name is used for preparations of different composition.
Delta, Braz.†.
⊗ Potassium iodide (p.2169·2); belladonna (p.2263·3); lobelia (p.2157·2); diphenhydramine hydrochloride (p.577·2).
Coughs.

Sedar, Braz.†.
⊗ Potassium iodide (p.2169·2); lobelia (p.2157·2); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Coughs.

Iodeto de Potassio Composto *Delta, Braz.†.*
Potassium iodide (p.2169·2); guaifenesin (p.1561·3); carbinoxamine (p.570·2).
Respiratory-tract congestion.

Iodeto de Potassium Composto *Farmedica, Braz.†.*
Potassium iodide (p.2169·2); oxomemazine (p.587·1).
Respiratory-tract congestion.

Iodeton *Cazi, Braz.*
Potassium iodide (p.2169·2).
Coughs.

Iodetoss *Ducto, Braz.*
Potassium iodide (p.2169·2).
Coughs.

Iodex
Note.This name is used for preparations of different composition.
Qualiphar, Belg.; Lee, USA.
Povidone-iodine (p.1659·2).
Disinfection of skin, burns, wounds, and instruments; infected skin, mouth, and throat disorders.

EMS, Braz.
Iodine (p.2169·2).
Skin infections.

Polinac, Venez.†.
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); chloroform (p.1781·1); balsam fioraventi.
Musculoskeletal and joint disorders.

Iodex Clasico *GSK, Mex.*
Iodine (p.2169·2); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Iodex Cristal *GSK, Mex.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); cineole (p.2282·3).
Cold symptoms; musculoskeletal pain.

Iodex with Methyl Salicylate *Lee, USA.*
Iodine (p.2169·2); methyl salicylate (p.85·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Iodex com Salicilato de Metila *EMS, Braz.*
Iodine (p.2169·2); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Iodex con Salicilato de Metilo *Polinac, Venez.*
Iodine (p.2169·2); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Iodiflor *Floris, Israel.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Iodina *Orravan, Spain.*
Povidone-iodine (p.1659·2).
Skin, wound, and burn disinfection.

Iodisis *Prisfar, Port.†.*
Iodine (p.2169·2).
Mouth and throat infections and inflammation.

Iodispray *Floris, Israel.*
Povidone-iodine (p.1659·2).
Burn and wound disinfection.

Iodoasept *ICN, Arg.†.*
Povidone-iodine (p.1659·2).
Eye disinfection.

Iodocaine *Sedabel, Braz.†.*
Lidocaine hydrochloride (p.1862·3); povidone (p.1659·2).
Skin infections.

Iodocollyre *Cooper (Κοπερ), Gr.*
Sodium iodide (p.2169·2); calcium chloride (p.1675·2).
Glaucoma.

Iodoflex *Smith & Nephew, Irl.; Smith & Nephew, Singapore; Smith & Nephew Healthcare, UK.*
Cadexomer-iodine (p.1633·3).
Ulcers; wounds.

Iodolab *Labesfal, Port.*
Povidone-iodine (p.1659·2).
Disinfection.

Iodomarin *Berlin-Chemie, Rus.*
Potassium iodide (p.2169·2).
Iodine-deficiency disorders.

Iodomax *Lafedar, Arg.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Iodomine *Lacefa, Arg.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Iodopen *American Pharmaceutical, USA.*
Sodium iodide (p.2169·2).
Additive for intravenous total parenteral nutrition solutions.

Iodophil Viscous *FDC, India†.*
Sodium acetrizoate.
Hysterosalpingography.

Iodopulmin *Neckerman, Braz.†.*
Potassium iodide (p.2169·2); pepilamine maleate; ipecacuanha (p.1562·3); sodium benzoate (p.1630·2); guaifenesin (p.1561·3).
Coughs.

Iodosan Clorexidina *GSK Consumer, Ital.*
Chlorhexidine gluconate (p.1635·3).
Dental hygiene.

Iodosorb *Smith & Nephew, Austral.†; Lannacher, Austria; Smith & Nephew, Canad.; Smith & Nephew, Denm.; Smith & Nephew, Fin.; Smith & Nephew, Fr.†; Smith & Nephew, Ger.†; Organon (Οργανον), Gr.; Smith & Nephew, Ital.; Smith & Nephew, Neth.; Smith & Nephew, Singapore; Smith & Nephew, Spain†; Smith & Nephew, Swed.; Smith & Nephew, Switz.; Smith & Nephew Healthcare, UK.*
Cadexomer-iodine (p.1633·3).
Ulcers; wounds.

Iodosteril *IMS, Ital.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Iodoten *Sanitas, Ital.*
Povidone-iodine (p.1659·2).
Wound disinfection.

Iodotiazol *Ferro, Arg.†.*
Sulfathiazole sodium (p.343·3); sulfanilamide (p.343·1) benzocaine (p.1854·1); iodine (p.2169·2); potassium iodide (p.2169·2).
Mouth and throat disorders.

Iodotope *Squibb Diagnostics, USA.*
Iodine-131 (p.2054·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Iodo-Vit *Vitamed, Israel.*
Povidone-iodine (p.1659·2).
Skin and wound disinfection.

Iodoxyd *Nizpharm, Rus.*
Povidone-iodine (p.1659·2).
Vaginal infections.

Iofed *Iomed, USA.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Ioiro *Regional Health, NZ.*
Ioidol.
Radiographic contrast medium.

Iol *Quimioterapica, Braz.†.*
⊗ Potassium iodide (p.2169·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2); lobelia (p.2157·2).
Coughs.

Iolin *Quimioterapica, Braz.†.*
⊗ Potassium iodide (p.2169·2); lobelia (p.2157·2).
Coughs.

Iomeron *Regional Health, Austral.; Bracco, Austria; Altana, Belg.; Bracco, Cz.; Bracco, Denm.; Astra Tech, Fin.; Altana, Fr.; Gerolymatos, Gr.; Bracco, Hung.; Merck, Irl.†; Bracco, Israel; Bracco, Ital.; Eisai, Jpn; Regional Health, NZ; Altana, Neth.; Bracco, Norw.; Bracco, Port.; Rovi, Spain; Astra Tech, Swed.; Bracco, Switz.; Bracco, UK.*
Iomeprol (p.1483·2).
Radiographic contrast medium.

Ionamin *Aventis, Canad.; Pfizer, Malaysia†; Pfizer, Singapore†; Celltech, USA.*
⊗ Phentermine (as an ion-exchange resin complex) (p.2162·2).
Obesity.

Ionamine *Celltech, Switz.†.*
⊗ Phentermine (as an ion-exchange resin complex) (p.2162·2).
Obesity.

Ionarthrol *Picot, Fr.†.*
Copper gluconate (p.1935·3).
Joint disorders; viral infections.

Ionax Astringent *Healthpoint, USA.*
Salicylic acid (p.1612·2); allantoin (p.1588·1).
Acne.

Ionax Foam *Healthpoint, USA.*
Skin cleanser.

Ionax P *Galderma, Fr.; Galderma, Spain†.*
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2).
Dandruff; scalp disorders.

Ionax Scrub *Galderma, Arg.; Galderma, Austral.†; Galderma, Braz.; Galderma, Chile; Galderma, Fr.; Galderma, Hong Kong†; Galderma, Irl.†; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Healthpoint, USA; Galderma, Venez.*
Polyethylene granules (abrasive) (p.1585·3).
Acne; seborrhoea; skin cleanser.

Ionax T *Galderma, India.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Scalp disorders.

Ionet *Cetus, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Ionik *Obolenskoe, Rus.*
⊗ Indapamide (p.1314·1).
Hypertension.

Ionil
Note.This name is used for preparations of different composition.
Galderma, Austral.; Biosintetica, Braz.; Galderma, Mex.†; Galderma, Philipp.; Healthpoint, USA.
Salicylic acid (p.1612·2).
Dandruff; scalp disorders; seborrhoea; seborrheic dermatitis.

Lavipharm, Gr.
Coal tar (p.1616·2).
Chronic eczema; psoriasis; seborrhoeic dermatitis.

Galderma, Spain†.
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Scalp disorders.

Ionil Champu *Galderma, Spain.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Scalp disorders.

Ionil P *Galderma, Port.†.*
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2).
Scalp disorders.

Ionil Plus *Galderma, Mex.; Healthpoint, USA.*
Salicylic acid (p.1612·2).
Dandruff; scalp psoriasis; seborrhoeic dermatitis.

Ionil Rinse *Galderma, Austral.; Galderma, NZ†.*
Hydrolised collagen proteins (p.2286·1).
Dry brittle hair.

Ionil-T *Galderma, Arg.; Galderma, Austral.; Biosintetica, Braz.; Galderma, Chile; Galderma, Hong Kong; Galderma, Irl.†; Galderma, Mex.;*

Galderma, NZ; Galderma, Philipp.; Galderma, Singapore; Galderma, Thai.†; Healthpoint, USA.
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Dandruff; psoriasis; scalp disorders; seborrhoeic dermatitis.

Ionil-T Plus *Galderma, Arg.†; Galderma, Austral.†; Biosintetica, Braz.†; Galderma, Mex.; Healthpoint, USA.*
Coal tar (Owentar II) (p.1616·2).
Scalp disorders; scalp psoriasis; seborrhoeic dermatitis.

Ionimag *Madaus, Fr.†.*
Magnesium lactate (p.1679·2).
Magnesium deficiency.

Ionitan *Aguettant, Fr.†.*
Electrolyte infusion (p.1667·1).
Parenteral nutrition.

Ionosol-T *Hospira, USA.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Ionosteril *Fresenius Kabi, Port.; Fresenius Kabi, Rus.*
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders; plasma substitute.

Ion-O-Trate *Abbott, Philipp.*
Potassium chloride (p.1684·3).
Potassium supplement.

Ion-Sol *Berman, Mex.†.*
Electrolytes (p.1667·1).
Electrolyte imbalance.

Ionsys *Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Port.; Janssen-Cilag, UK; Ortho McNeil, USA.*
⊗ Fentanyl hydrochloride (p.56·1).
Pain.

Ionyl *Pharmadeveloppement, Fr.*
Phosphoric acid (p.2367·1); sodium glycerophosphate (p.2315·2); magnesium glycerophosphate (p.1679·2); manganese glycerophosphate (p.2315·2).
Tonic.

Iopamiro *Bracco, Cz.†; Bracco, Denm.; Gerolymatos, Gr.; Bracco, Hung.; Bracco, Israel; Bracco, Ital.; Regional Health, NZ; Dagra, Neth.; Bracco, Norw.; Rovi, Port.; Rovi, Spain; Astra Tech, Swed.; Bracco, Switz.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Iopamiron *Schering, Arg.; Schering, Braz.; Schering, Fr.; Schering, Venez.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Iopanchol *Genepharm, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Iopasen *Senese, Ital.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Iophen *Rugby, USA.*
Iodinated glycerol (p.1562·2).
Coughs.

Iopidine *Alcon, Arg.†; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.†; Alcon, Canad.; Alcon, Chile†; Alcon, Cz.†; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Jpn†; Alcon, Malaysia†; Alcon, Mex.; Alcon, NZ†; Alcon, Neth.; Alcon, Norw.; Alcon, Port.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.†.*
Apraclonidine hydrochloride (p.1877·3).
Control of intra-ocular pressure following eye surgery; glaucoma; ocular hypertension.

Iopimax *Alcon Cusi, Spain.*
Apraclonidine hydrochloride (p.1877·3).
Glaucoma; prevention of ocular hypertension in laser surgery.

Iopotoss *Globo, Braz.†.*
Potassium iodide (p.2169·2).

Iopovidona *SM, Venez.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Iopox *Denver, Arg.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Ior T3 *Bago, Chile†.*
Muromonab-CD3 (p.1835·2).
Renal transplant rejection.

Ior-T3 *Pisa, Mex.*
Muromonab-CD3 (p.1835·2).
Renal transplant rejection.

Iosal II *Iomed, USA.*
Pseudoephedrine (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Iosalide *Astellas, Ital.*
Josamycin (p.291·1) or josamycin propionate (p.291·1).
Bacterial infections.

Iosopan *Goldline, USA.*
Magaldrate (p.1742·3).
Hyperacidity.

Iosopan Plus *Goldline, USA.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Hyperacidity.

Iotussin HC *Iomed, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

IP-6 *Sigma, Arg.*
Nicotinamide (p.1957·3); chromium (p.1934·3); picolinic acid; vitamin C (p.1983·3).
Hyperglycaemia; hyperlipidaemias; vascular occlusive disorders.

Ipacef *IPA, Ital.†.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Ipacid *IPA, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Ipacillin *Ipca, India†.*
Ampicillin (p.204·1).
Bacterial infections.

Ipagastril *IPA, Ital.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ipalat *Cofasa, Venez.*
Clotrimazole (p.530·1).
Fungal skin infections.

Ipamicina *IPA, Ital.†.*
Tablets: Fosfomycin calcium (p.278·2).
Bacterial infections.

Ipamide *Dabur, India.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ipamide with Mesna *Dabur, India.*
Ifosfamide (p.731·3); mesna (p.1449·2).
Malignant neoplasms.

Ipamix *Visufarma, Ital.*
⊗ Indapamide (p.1314·1).
Hypertension.

Ipasin *Vifor, Switz.*
Crataegus (p.2289·1); aesculus (p.2248·2).
Cardiac disorders.

Ipaton *Egis, Cz.; EGIS, Hung.*
Ticlopidine hydrochloride (p.1411·2).
Maintenance of extracorporeal circulation; stroke prophylaxis; thromboembolism prophylaxis.

Ipatox *IPA, Ital.†.*
Reduced glutathione sodium (p.1448·1).
Alcohol and drug poisoning; radiation trauma.

Ipatrizina *IPA, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Ipaviran *NCSN, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ipavit *IPA, Ital.†.*
Vitamin B substances with calcium folinate (p.1922·1)(p.1943·3).

Ipazone *IPA, Ital.†.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Ipcacin Kid *Ipca, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Ipcamox *Nat Druggists, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ipcaquin *Ipca, India†.*
Amodiaquine (p.597·2).
Malaria.

Ipcavite *Ipca, India†.*
Multivitamin preparation (p.1922·1).

Ipcazide *Ipca, India.*
Isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

IPD *Taiho, Jpn.*
Suplatast tosilate (p.1138·2).
Allergic rhinitis; asthma; atopic eczema.

Ipeca
Note. This name is used for preparations of different composition.
Orion, Fin.†.
Ipecacuanha (p.1562·3).
Poisoning.

Amino, Switz.†.
⊗ Emetine hydrochloride (p.833·3); ethylmorphine hydrochloride (p.52·2); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2); cherry-laurel water; tolu balsam (p.1574·2).
Respiratory-tract disorders.

Ipecarin *Galena, Cz.†; Ivax, Cz.†.*
⊗ Codeine hydrochloride (p.37·2); emetine hydrochloride (p.833·3); ephedrine hydrochloride (p.1558·2); liquorice (p.1740·3); pilocarpine hydrochloride (p.1884·3).
Coughs; respiratory-tract disorders.

Ipecavom *Elpen (Ελπεν), Gr.*
Ipecacuanha (p.1562·3).
Induction of vomiting in poisoning.

Ipecol *Simoes, Braz.†.*
Noscapine (p.1566·2); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); tolu balsam (p.1574·2); ipecacuanha (p.1562·3).
Coughs.

Ipental *Ipca, India†; Ipca, Rus.*
Pancreatin (p.2360·1); ox bile (p.2266·2); hemicellulase (p.2279·1).
Pancreatic insufficiency.

Ipenxin *Farmaceutica H, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

IperClean *UCB, Ital.*
Sodium chloride (p.1686·1); sodium bicarbonate (p.1673·2); monobasic sodium phosphate (p.1682·3).
Nasal hygiene.

Ipercortis *AGIPS, Ital.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Iperdix *Servier, Hong Kong.*
Rilmenidine phosphate (p.1388·3).
Hypertension.

Iperisan *Marjan, Braz.*
St John's wort (p.422·3).
Depression.

Iperplasin *CSC, Austria; Medinfar, Port.*
Mepartricin (p.541·1).
Benign prostatic hyperplasia.

Iperten *Torrex, Austria; Chiesi, Fr.; Chiesi, Ital.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Iperton *Kleva, Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Ipertrofan *SPA, Cz.; SPA, Ital.; Pascual, Philipp.; SPA, Philipp.; SPA, Pol.; Prospa, Port.*
Mepartricin (p.541·1).
Benign prostatic hyperplasia; oral candidiasis.

Ipesandrine *Novartis Consumer, Port.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Iphox *Korea United, Philipp.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Ipibiofen *IPI, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Ipirasa *Esteve, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Iplex *Insmed, USA†.*
⊗ Mecasermin rinfabate (p.1807·3).
Growth failure in children.

Ipnolor *Krugher, Ital.*
Lormetazepam (p.1005·2).
Insomnia.

Ipnopen *Recalcine, Chile.*
Flunitrazepam (p.996·2).
Insomnia.

Ipnovel *Roche, Ital.*
Midazolam hydrochloride (p.1007·3).
General anaesthesia; premedication; sedative.

Ipoazotal *SIT, Ital.†.*
Arginine hydrochloride (p.1928·2); ornithine hydrochloride (p.1959·2); citrulline (p.1935·1).
Hyperammonaemia.

Ipoazotal Complex *SIT, Ital.*
Arginine hydrochloride (p.1928·2); ornithine hydrochloride (p.1959·2); citrulline (p.1935·1); acetylaspartic acid; aceglumic acid; calcium oxoglurate.
Hyperammonaemia.

Ipocalcin *Salus, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Ipocol
Note. This name is used for preparations of different composition.
Lagap, Switz.
Colestyramine (p.1252·3).
Biliary-tract disorders; hypercholesterolaemia.

Sandoz, UK.
Mesalazine (p.1745·1).
Ulcerative colitis.

Ipogras *Laboratorios Chile, Chile.*
⊗ Sibutramine (p.2164·1).
Obesity.

Ipol *Aventis Pasteur, Austral.; MSD, NZ; Sanofi Pasteur, USA.*
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

Ipolab *Benedetti, Ital.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Ipolipid *Medochemie, Cz.†; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Ipomex *Ivax, Arg.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Iporel *Jelfa, Pol.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Ippi Verde *Ecolab, Ital.*
Triclosan (Irgasan DP 300) (p.1665·2).
Skin and hand disinfection.

Ipra *Pacific, NZ†.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Iprabon *Zambon, Braz.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Iprabron *Prieto, Arg.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Ipradol
Nycomed, Austria.
⊗ Hexoprenaline hydrochloride (p.1123·2) or hexoprenaline sulfate (p.1123·2).
Obstructive airways disease.

Nycomed, Hong Kong.
⊗ Hexoprenaline (p.1123·2).
Obstructive airways disease.

Nycomed, Hung.†; Intramed, S.Afr.; Nycomed, Thai.†.
⊗ Hexoprenaline sulfate (p.1123·2).
Obstructive airways disease; premature labour; prevention of uterine contractions.

Ipradual *Prieto, Arg.*
⊗ Ipratropium bromide (p.1124·1); fenoterol (p.1121·1).
Obstructive airways disease.

Iprafen *Chiesi, Ital.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Ipragocce *Proge, Ital.†.*
Benzalkonium chloride (p.1629·1); hypromellose (p.2144·2).
Eye disinfection; eye irritation.

Ipral *BMS, Irl.†.*
Trimethoprim (p.355·2).
Bacterial urinary- and respiratory-tract infections.

Ipralin *Biogalenic, Venez.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ipramid *Farmedia, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Ipramol *Ivax, Irl.; Ivax, Malaysia; Ivax, UK.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ipran *Drugtech, Chile.*
Escitalopram (p.391·1).
Depression.

Ipranase *Cipla, India.*
Ipratropium bromide (p.1124·1).
Nasal congestion.

Ipraneo *Neo Quimica, Braz.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Iprasalb *Prieto, Arg.*
⊗ Ipratropium bromide (p.1124·1); salbutamol (p.1131·2).
Obstructive airways disease.

Ipratrin *Alphapharm, Austral.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Ipravent *Pfizer, Austral.; Apotex, Hong Kong†; Cipla, India.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Ipraxa *Ivax, Neth.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Ipren *Nycomed, Denm.; Pfizer, Swed.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Ipres *Schwarz, Pol.*
⊗ Indapamide (p.1314·1).
Hypertension.

Ipri V *Vannier, Arg.*
Vitamin E acetate; vitamin C; betacarotene (p.1922·1).
Antoxidant preparation.

Ipriosten *Pharmacia, Arg.†.*
Ipriflavone (p.1100·1).
Osteoporosis.

Iprivask *Aventis, USA.*
Desirudin (p.1257·1).
Deep-vein thrombosis prophylaxis following hip replacement.

Iproben *Mepha, Switz.*
Ibuprofen (p.64·2).
Fever; pain.

Iprogel *Mepha, Switz.†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular and soft-tissue pain and inflammation.

Iprolan *Hexal, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ipromax *Ildong, Philipp.; Integra, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Iprosten *Takeda, Ital.†.*
Ipriflavone (p.1100·1).
Osteoporosis.

Iprox *Novell, Indon.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Iproxin *Plusandex, Venez.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ipsatol *Orion, Fin.*
Biperiden hydrochloride (p.797·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Ipsilon *Nova Argentia, Arg.; Nikkho, Braz.*
Aminocaproic acid (p.1053·2).
Fibrinolytic haemorrhage.

Ipso Urea *Difa, Ital.*
⊗ Urea (p.1620·2); ammonium lactate (p.1589·2); lactic acid (p.2329·3).
Dry skin conditions.

Ipsoflog *Epifarma, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ipson *Saval, Chile.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ipson-D *Saval, Chile.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; nasal congestion.

Ipsovir *Ipso, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ipstyl
Ipsen, Denm.; Ipsen, Norw.
Lanreotide acetate (p.1803·1).
Acromegaly; carcinoid tumours.

Ipsen, Ital.
Lanreotide (p.1803·1) or lanreotide acetate (p.1803·1).
Acromegaly; carcinoid tumour.

Ipsumor *TAD, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

IPV
Note. This name is used for preparations of different composition.
Plata, Arg.†.
Povidone-iodine (p.1659·2).
Skin disinfection.

Sanofi Pasteur, Braz.
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

IPV Merieux *Sanofi Pasteur, Ger.*
An inactivated poliomyelitis vaccine (type 1, 2, and 3) (p.2232·1).
Active immunisation.

Ipvent *Cipla-Medpro, S.Afr.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

IPV-Virelon *Novartis Vaccines, Cz.; Chiron Vaccines, Ger.*
An inactivated poliomyelitis vaccine (trivalent) (p.2232·1).
Active immunisation.

Iqcona *IQFA, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Iqfacilina *IQFA, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Iqfadina *IQFA, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Iqfamicina *IQFA, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Iqfasol *IQFA, Mex.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders.

Iquinol *Integra, Philipp.; Medica Korea, Philipp.*
Ofloxacin hydrochloride (p.310·2).
Bacterial infections.

Iquix *Vistakon, USA.*
Levofloxacin (p.292·2).
Bacterial eye infections.

Ira *Cassara, Arg.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Irahex *Hexal, Philipp.*
Piracetam (p.368·2).
Cerebrovascular disorders; dyslexia; myoclonus; vertigo.

Iralgesic *Darou Pakhsh, Rus.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Irazem *Roemmers, Arg.*
Aripiprazole (p.962·3).
Bipolar disorder; schizophrenia.

Irban *BMS, Israel†.*
Irbesartan (p.1316·1).
Diabetic nephropathy; hypertension.

Irban Plus *BMS, Israel†.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Diabetic nephropathy; hypertension.

Irbosyd *Fahrenheit, Indon.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Ircon *Kenwood, USA.*
Iron carbonyl (p.1950·3).
Formerly contained ferrous fumarate.
Iron-deficiency anaemias.

Ircon-FA *Kenwood, USA†.*
Iron carbonyl (p.1950·3); folic acid (p.1940·1).
Iron-deficiency anaemias.

Iremax *Guardian, Indon.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Iremofar *Unipharma, Gr.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions.

Irenat *Kolassa, Austria; Bayer, Cz.; Bayer, Ger.; Bayer, Pol.*
Sodium perchlorate (p.2174·3).
Adjunct in radionuclide brain scanning; hyperthyroidism; thyroid block during radio-imaging of other organs.

Irenax *Sandoz, Arg.; Novartis, Braz.*
Irinotecan hydrochloride (p.737·1).
Malignant neoplasms.

Irenor *Juste, Spain.*
Reboxetine mesilate (p.420·3).
Depression.

Iressa *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Fr.†; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Rus.; AstraZeneca, Singapore; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Gefitinib (p.727·1).
Non-small cell lung cancer.

Iretensa *Fahrenheit, Indon.*
Irbesartan (p.1316·1).
Hypertension.

Irfen *Mepha, Cz.†; Mepha, Switz.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; musculoskeletal, joint, and peri-articular disorders; pain.

Irgaman *Teleflex, Ital.*
Triclosan (Irgasan DP 300) (p.1665·2).
Skin disinfection.

Irgamid *Novartis, Denm.†; Novartis, Fin.†; Novartis Ophthalmics, Hung.†; Novartis, Switz.*
Sulfadicramide (p.337·3).
Bacterial eye infections.

Irgapan *Dexa, Indon.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders; thrombophlebitis.

Iricalcin *Vocate, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Iricar *DHU, Rus.*
Homoeopathic preparation.

Iricil *Cantabria, Spain.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Iricil Plus *Cantabria, Spain.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Iridil *Montefarmaco, Ital.*
Hamamelis (p.2318·2); chamomile (p.2279·3); euphrasia (p.2301·3); mallow (p.2337·2).
Eye irritation.

Iridina Due *Montefarmaco, Ital.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Iridina Light *Montefarmaco, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection; eye irritation.

Iridus
Aventis, Arg.†; Aventis, Mex.
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders.

Sanofi-Aventis, Venez.
Naftidrofuryl (p.1346·3).
Cerebral and peripheral vascular disorders.

Iridux *Sanofi-Aventis, Braz.*
Naftidrofuryl oxalate (p.1346·2).
Vascular disorders.

Irifrin *Promed, Rus.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Irigal *Gobbi, Arg.*
⊗ Neomycin sulfate (p.305·1); hydrocortisone (p.1535·2); lidocaine (p.1862·3); boric acid (p.2268·1); zinc oxide (p.1621·2).
Wounds.

Irilens *Montefarmaco, Ital.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Irin *Biomedica-Chemica, Gr.*
Hexetidine (p.1647·1).
Oral hygiene.

Iriniozol *Rafarm, Gr.*
⊗ Dexamethasone dipropionate (p.1526·3).
Allergic rhinitis.

Irinogen *Bioprofarma, Arg.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Irinotel
Dabur, India.
Irinotecan (p.738·1).
Colorectal cancer.

Dabur, Thai.
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Iris Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Iri-Sol *Ocumed, USA.*
Eye irrigation.

Irisol *Corsalud, Venez.†.*
Berberine chloride (p.2264·3).
Eye irritation.

Iristamina *Montefarmaco, Ital.*
⊗ Thonzylamine hydrochloride (p.592·1); naphazoline nitrate (p.1565·2).
Conjunctivitis; eye irritation.

Iriten *Veropharm, Rus.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Irix *Gramon, Arg.*
⊗ Ephedrine (p.1558·1); phenazone (p.116·1).
Eye disorders.

Irix Biotic *Gramon, Arg.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Eye infections with congestion.

Irix Lagrimas *Gramon, Arg.*
Macrogol 400 (p.2336·3); hypromellose (p.2144·2); glycerol (p.2314·2).
Dry eyes.

Irix Solution Multiproposito *Gramon, Arg.*
Protein removal, wetting, and disinfecting solution for contact lenses (p.1622·2).

Irizz *Probiomed, Mex.*
Alprazolam (p.960·1).
Anxiety.

Irnocam *Reddy, Rus.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Irobon *Roddensers, Philipp.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Iron-deficiency anaemia; vitamin B supplement.

Irocopar c C *Schmidgall, Austria.*
Carbasalate calcium (p.33·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Irocophan *Schmidgall, Austria.*
Carbasalate calcium (p.33·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Irolax *Iromedica, Switz.†.*
Senna (p.1769·2).
Constipation.

Irolen *Etifar, Venez.†.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Iromin *Schmidgall, Austria.*
Carbasalate calcium (p.33·3).
Cold symptoms; fever; pain.

Iromin-Chinin-C *Schmidgall, Austria.*
Carbasalate calcium (p.33·3); quinine hydrochloride (p.612·3); calcium ascorbate (p.1984·1).
Cold symptoms; fever; pain.

Iromin-G *Mission Pharmacal, USA.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Iron-200 *Christo, Hong Kong.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Iron Beacons *Beacons, Singapore.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Iron Compound *Blackmores, Austral.†.*
Sodium sulfate (p.1771·3); ferrous phosphate (p.1950·3); potassium chloride (p.1684·3).
Iron deficiency.

Iron Melts *Douglas, Singapore.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Vitamin and iron supplement.

Iron Plus *Cenovis, Austral.†; Vitelle, Austral.†; Swiss Herbal, Canad.*
Multivitamin preparation with iron (p.1922·1).
Tonic; vitamin and iron supplement.

Ironcor *Corsalud, Venez.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Irondex *Tocogino, Mex.*
Iron dextran (p.1951·1).

Ironfer *Uniao Quimica, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Ironfol *Alpharma, Mex.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias.

Ironorm
Note. This name is used for preparations of different composition.
Wallace Mfg Chem., UK.
Capsules: Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances; vitamin C (p.1922·1).
Iron deficiency.

Wallace Mfg Chem., UK.
Oral drops: Ferrous sulfate (p.1939·3).
Iron deficiency.

Wallace Mfg Chem., UK.
Syrup: Ferric ammonium citrate (p.1938·1); vitamin B substances; minerals (p.1922·1).
Iron deficiency.

Irontona *Brauer, Austral.*
Angelica (p.2258·1); ascorbic acid (p.1983·3); kola (p.2416·1); ferrous sulfate (p.1939·3); alfalfa (p.2249·2); ginseng (p.2312·1); urtica (p.2409·3); aurum muriaticum; calcarea phosphorica; ferrum metallicum; ferrum phosphoricum; hypericum perforatum; kali phosphoricum; magnesia phosphorica; phosphoricum acidum.
Tonic.

Iroplex
Note. This name is used for preparations of different composition.
Bioquimica, Arg.†.
Cinnarizine (p.573·1).
Vertigo.

Wellhealth, Philipp.
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Iron-deficiency anaemia.

Irospan *Fielding, USA.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Irovel *Sun, India.*
Irbesartan (p.1316·1).
Hypertension.

Iroviton *Iromedica, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Iroviton Multivitamin *Schmidgall, Austria.*
A multivitamin preparation (p.1922·1) with hesperidin (p.2304·3).

Iroviton Vitamin C *Schmidgall, Austria.*
Sodium ascorbate (p.1984·1).
Vitamin C supplement.

Iroviton-Irocovit-C *Schmidgall, Austria†.*
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1).
Vitamin C supplement.

Irpax *Anpharm, Pol.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Irradial *Ivax, Arg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Irriclens *Convatec, Fr.; Convatec, UK.*
Sodium chloride (p.1686·1).
Wound cleansing and irrigation.

Irricutan *Biosintex, Arg.*
Calamine (p.1591·2); diphenhydramine (p.577·1).

Irrigacion CLNA *Bieffe, Spain†.*
Sodium chloride (p.1686·1).
Bladder irrigation.

Irrigor *Andromaco, Chile.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Irripod *Pharmachem, UK.*
Sodium chloride (p.1686·1).
Eye irrigation; irrigation and cleansing of wounds and burns.

Irrisol *Baxter, Neth.*
Chlorhexidine gluconate (p.1635·3).
Catheter disinfection.

Irritos *Faes, Spain.*
Phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Irritren *Altana, Austria†.*
Lonazolac calcium (p.77·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Irrodan *Nikolakopoulos (Νικολακοπουλος), Gr.†; Biomedica, Hong Kong; Biomedica, Ital.; Biomedica, Thai.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

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Note. This name is used for preparations of different composition.
Solvay, Cz.†.
Lysates of *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus dysgalacta*; *Enterococcus faecium* (p.2372·3); *Enterococcus faecalis* (p.2372·3); *Streptococcus* group G; *Staphylococcus aureus*; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Neisseria subflava*; *Klebsiella pneumoniae*; *Acinetobacter calcoaceticus baumanii*.
Respiratory-tract infections.

Solvay, Fr.†.
Lysates of *Streptococcus pneumoniae*; *Streptococcus* group G; *Streptococcus pyogenes*; *Staphylococcus aureus*; *Acinetobacter calcoaceticus*; *Neisseria subflava*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*; *Streptococcus dysgalactiae*; *Enterococcus faecium*; *Enterococcus faecalis* (p.2372·3).
Respiratory-tract disorders.

Sanavita, Ger.; Solvay, Pol.
Lysate of: *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus dysgalactiae*; *Enterococcus faecium* (p.2372·3); *Streptococcus* Group G; *Enterococcus faecalis* (p.2372·3); *Staphylococcus aureus*; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Neis-*

seria flava; *Neisseria perflava*; *Klebsiella pneumoniae*; *Acinetobacter calcoaceticus*.
Respiratory-tract infections.

Solvay, Rus.
Lysates of *Streptococcus pneumoniae*; *Haemophilus influenzae* type B; *Klebsiella pneumoniae*; *Staphylococcus aureus*; Acinetobacter calcoaceticus; *Moraxella catarrhalis*; *Neisseria subflava*; Streptococcus groups A, C, G; *Enterococcus faecium* (p.2372·3); *Enterococcus faecalis* (p.2372·3).
Respiratory-tract infections.

Irtan Aventis, Ger.; Allergan, Mex.
Nedocromil sodium (p.1127·3).
Allergic conjunctivitis; allergic rhinitis.

Irtan Plus Ikapharmindo, Indon.
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Irtonin Takeda, Ital.†.
Protirelin tartrate (p.2176·2).
Mental function disorders.

Irtopan Biotech, Venez.
Metoclopramide (p.1747·3).
Aid in gastrointestinal investigations; gastrointestinal disorders.

Irumed Belupo, Cz.†; Belupo, Rus.
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Irunine Veropharm, Rus.
Itraconazole (p.536·3).
Fungal infections.

Iruxol Abbott, Arg.; Abbott, Braz.; Smith & Nephew, Fin.; Smith & Nephew, Ital.; Pliva, Rus.
Collagenase (p.2286·2); chloramphenicol (p.239·3).
Burns; debridement of wounds; skin infections; ulcers; wounds.

Iruxol Mono Smith & Nephew, Belg.; Abbott, Braz.; Aura, Cz.; Smith & Nephew, Fin.; Farmalex, Gr.; Smith & Nephew, Hong Kong; Smith, Hung.; Smith & Nephew, Irl.; Smith & Nephew, Malaysia; Smith & Nephew, S.Afr.; Smith & Nephew, Singapore; Smith & Nephew, Spain; Smith & Nephew, Switz.
Collagenase (p.2286·2).
Burns; debridement of ulcers and wounds; necrotic ulcers; wounds.

Iruxol N
Note.This name is used for preparations of different composition.
Knoll, Ger.†.
Collagenase (p.2286·2); proteases.
Skin ulcers.

Smith & Nephew, Ger.†.
Enzymes from *Clostridium histolyticum* (proteases).
Skin ulcers and wounds.

Iruxol Neo Smith & Nephew, Spain.
Collagenase (p.2286·2); neomycin sulfate (p.305·1).
Burns; ulcers; wounds.

Iruxol Simplex Abbott, Venez.
Collagenase (p.2286·2).
Ulcers; wounds.

Iruxolum mono Ebewe, Austria.
Enzymes from *Clostridium histolyticum*.
Necrotic ulcers; wounds.

Iruzid Belupo, Rus.
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Irvell Novell, Indon.
Irbesartan (p.1316·1).
Hypertension.

IS 5 Mono Ratiopharm, Ger.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Isacol Organifar, Venez.†.
Sodium benzoate (p.1630·2); ammonium acetate (p.1551·2); polygala (p.1572·3); Desessartz syrup; potion de Todd.
Cough.

Isaflavon ISA, Arg.
Calcium (p.1675·2); soya isoflavones (p.2391·2).
Menopausal disorders.

Isaflex ISA, Arg.
Vitamin D; magnesium; calcium (p.1922·1).
Tonic.

Isairon Pfizer, Ital.
Chondroitin sulfate–iron complex (p.1934·2).
Iron deficiency; iron-deficiency anaemias.

Isalax Fibras ISA, Arg.
Vitamin C (p.1983·3); ispaghula (p.1737·1).
Dietary supplement.

Isangina Schwarz, Fin.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Isaplic Novartis, Spain.
Pimecrolimus (p.1609·1).
Atopic eczema.

Isaprandil Uniform, Ital.
Metoclopramide hydrochloride (p.1747·3).
Gastric motility disorders; nausea.

Isaprid Vargas, Venez.†.
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Isatol Bausch & Lomb, USA.
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Isavir Pisa, Mex.
Aciclovir sodium (p.862·3).
Cytomegalovirus infections; herpesvirus infections.

Isaxion Ferring, Port.†.
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Iscador Weleda, Austria; Weleda, Ger.; Weleda, Switz.
Mistletoe (p.2345·3) from apple trees, pine trees, or oak trees.
Malignant neoplasms.

Iscaten Rowe-Fleming, Venez.†.
Cimetidine (p.1716·2).
Peptic ulcer.

Ischelium Polifarma, Ital.†.
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders.

Ischemol A Farmila, Ital.
⊗ Tetryzoline hydrochloride (p.1574·1); chlorphenamine maleate (p.571·3).
Eye disorders.

Iscover BMS, Arg.; BMS, Austral.; BMS, Braz.; BMS, Cz.; BMS, Ger.; BMS, Gr.; BMS, Ital.†; BMS, Mex.; BMS, Neth.; BMS, Port.†; BMS, Spain.
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis; ischaemic stroke; myocardial infarction; peripheral vascular disease; thromboembolism prophylaxis; unstable angina.

Isdiben Isdin, Port.; Isdin, Spain.
Isotretinoin (p.1599·2).
Acne.

Isdibudol Isdin, Spain†.
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Isdin Infantil Medley, Braz.†.
SPF 40: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); enzacamene (p.1597·1); ensulizole (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Isdinex Isdin, Spain†.
Benzethonium chloride (p.1630·1); diphenhydramine hydrochloride (p.577·2).
Pruritus.

Isdinium Isdin, Spain.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone buteprate (p.1535·2).
Skin disorders.

Isdol Isdin, Spain†.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Iselpin Wyeth, Philipp.
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

I-Sense Akorn, USA.
Multivitamin preparation (p.1922·1).

Isentress MSD, Cz.; MSD-Chibret, Fr.; MSD, UK; Merck, USA.
Raltegravir potassium (p.902·2).
HIV infection.

Isepacin Calea, Austria†; Schering-Plough, Cz.†; Schering-Plough, Ital.†; Schering-Plough, Mex.†.
Isepamicin sulfate (p.288·1).
Bacterial infections.

Isepacine Schering-Plough, Belg.†; Schering-Plough, Turk.
Isepamicin sulfate (p.288·1).
Bacterial infections.

Isepalline Schering-Plough, Fr.†.
Isepamicin sulfate (p.288·1).
Bacterial infections.

Isephca S Iso, Ger.
Thyme (p.2401·1).
Coughs.

Iset Casasco, Arg.
Clarithromycin (p.248·2).
Bacterial infections.

ISF 09338 ISF, Ital.†.
Temocillin sodium (p.347·1).
Gram-negative bacterial infections.

Isib Ashbourne, UK.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isicom Desitin, Cz.; Desitin, Ger.
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Isiferone Kedrion, Ital.†.
Interferon alfa (p.885·1).
Malignant neoplasms; viral infections.

Isiflu Medifarm, Venez.
An influenza vaccine (p.2218·2).
Active immunisation.

Isiflu V Berna, Ital.
An influenza vaccine (p.2218·2).
Active immunisation.

Isiflu Zonale Scott-Cassara, Arg.†.
An influenza vaccine (p.2218·2).
Active immunisation.

Isifluor Rottapharm, Ital.
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Isigrip Zonale Kedrion, Ital.
An influenza vaccine (p.2218·2).
Active immunisation.

Isilax Cifarma, Braz.
Bisacodyl (p.1710·1).
Constipation.

Isilung Exel, Belg.
Eprazinone hydrochloride (p.1559·3).
Respiratory-tract disorders.

Isimet Abbott, Ital.†.
Ademetionine busilate (p.2247·1).
Depression.

Isimoxin Kedrion, Ital.†.
Amoxicillin (p.202·2).
Bacterial infections.

ISINO Sifauman, Port.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Isipredon Heremco, Gr.
Risperidone (p.1024·2).
Psychoses.

Isis Investi, Arg.
21 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Isis Fe Investi, Arg.
21 Tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); 7 tablets, iron polymaltose (p.1953·1).
Combined oral contraceptive.

Isiven Scott-Cassara, Arg.†; Kedrion, Ital.; Serono, Mex.†; Interko, Turk.
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency disorders; Kawasaki disease; passive immunisation.

Iskedyl Pierre Fabre, Fr.
Dihydroergocristine mesilate (p.364·2); raubasine (p.1386·3).
Mental function disorders of the elderly; vascular eye disorders.

Iskemil Ache, Braz.
Dihydroergocristine mesilate (p.364·2).
Impaired mental function.

Isketam Ache, Braz.
Piracetam (p.368·2); dihydroergocristine mesilate (p.364·2).
Impaired mental function.

Iskevert Eversil, Braz.†.
Dihydroergocristine mesilate (p.364·2).
Impaired mental function.

Iski Stadmed, India.
Diltiazem (p.1267·1).
Angina pectoris.

Iskimil Royal, Chile.
Clopidogrel (p.1251·1).
Atherosclerosis.

Isla-Mint Engelhard, Ger.†; Engelhard, Hong Kong†.
Iceland moss (p.2324·1).
Catarrh; coughs; respiratory-tract disorders; sore throat.

Isla-Mint Herbal Engelhard, Singapore†.
Iceland moss (p.2324·1).
Catarrh; coughs; sore throat.

Isla-Moos Engelhard, Ger.†; Engelhard, Hong Kong†.
Iceland moss (p.2324·1).
Catarrh; coughs; respiratory-tract disorders; sore throat.

Isloglib Craveri, Arg.
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Islopir Craveri, Arg.
Glimepiride (p.441·1).
Diabetes mellitus.

Islotin Craveri, Arg.
Metformin (p.453·3) or metformin hydrochloride (p.453·2).
Diabetes mellitus.

Isly Alcon, Arg.†; Alcon, Chile†.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Dry eyes; eye congestion.

Ismacrol IPI, Indon.
Spiramycin (p.333·1).
Bacterial infections.

Ismanton Juta, Ger.; Q-Pharm, Ger.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Ismelin Novartis, Austral.; IFET (ΙΦΕΤ), Gr.; Amdipharm, UK; Ciba, USA†.
Guanethidine monosulfate (p.1300·2).
Hypertension; hypertensive crisis; regional nerve blocks.

Ismexin Ratiopharm, Fin.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Ismigen Zambon, Ital.
Lysates of: *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Streptococcus pneumoniae*.
Respiratory-tract infections.

Ismin Aliud, Cz.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Ismo Roche, Chile; Roche, Ger.; Roche, Hong Kong†; Nicholas Piramal, India; Roche, Ital.; Roche, Malaysia; Roche, NZ; Roche, Norw.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Swed.; Roche, Switz.†; Roche, Thai.; Roche, UK; Reddy, USA; Roche, Venez.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction; pulmonary hypertension.

Ismotic Alcon, USA.
⊗ Isosorbide (p.1317·2).
Raised intra-ocular pressure.

Ismox Roche, Fin.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Iso Lacer, Spain.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Iso Estedi Estedi, Spain†.
Isotretinoin (p.1599·2).
Acne.

Iso Mack Pfizer, Austria; Mack, Cz.; Mack, Denm.†; Mack, Illert., Ger.†; Mack, Hong Kong†; Mack, Hung.†; Mack, Singapore†; Pfizer, Switz.; Mack, Thai.†.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension; pulmonary oedema.

Isoacne Schering-Plough, Braz.†.
Isotretinoin (p.1599·2).
Acne.

ISO-Augentropfen C Iso, Ger.
Homoeopathic preparation.

Iso-B Tyson, USA.
Multivitamin preparation (p.1922·1).

Isobar
Note.This name is used for preparations of different composition.
Chiesi, Fr.
⊗ Methyclothiazide (p.1334·1); triamterene (p.1417·2).
Hypertension.

Jean-Marie, Philipp.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Iso-Betadine Viatris, Belg.
Povidone-iodine (p.1659·2).
Burns; disinfection of the skin and mucous membranes; mouth and throat infections; skin infections; ulcers; vulvovaginal infections; wounds.

Isobin Korea United, Singapore†.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isobinate General Drugs, Thai.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isobloc Casasco, Arg.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Isobranch Bieffe, Ital.
-Isoleucine (p.1954·1); -leucine (p.1954·3); -valine (p.1971·1).
Hepatic encephalopathy; post-trauma disorders.

Isobutil Chinoin, Mex.†.
⊗ Isoprenaline (p.1316·3); aminophylline (p.1114·2); bromhexine (p.1552·2).
Respiratory-tract congestion.

Isocaine Novocol, USA.
⊗ Mepivacaine hydrochloride (p.1866·3).
Corbadrine (p.2287·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Isocal Mead Johnson, Austral.†; Mead Johnson Nutritionals, Canad.†; Novartis Nutrition, Hong Kong; Mead Johnson, Israel; Mead Johnson, Malaysia†; Mead Johnson, Philipp.; Novartis Nutrition, Singapore; Novartis, Thai.; Mead Johnson Nutritionals, USA.
A range of preparations for enteral nutrition (p.1922·1).

Isocar Offenbach, Mex.
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Isocard Schwarz, Fr.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isocardide Sam-On, Israel.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isocaren Pharmanel, Gr.
Ketotifen (p.582·2).
Allergic eye disorders.

Isocef Recordati, Ital.
Ceftibuten (p.235·3).
Bacterial infections.

IsoCell Antonetto, Ital.
Multivitamin and mineral preparation with plant extracts (p.1922·1).

Isochinol Schwarzhaupt, Ger.†; Vifor, Switz.
Quinisocaine hydrochloride (p.1870·3).
Burns; haemorrhoids; pruritus; skin disorders; wounds.

Isochol Zentiva, Cz.
Hymecromone (p.2323·2).
Biliary-tract disorders.

Isochron Forest Pharmaceuticals, USA.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isocillin Aventis, Ger.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Isoclar Boniscontro & Gazzone, Ital.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Isocolan Giuliani, Ital.; Sanofi Synthelabo, Switz.
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; colonic lavage; constipation.

Isocomb *Akrikhin, Rus.*
Isoniazid (p.288·1); rifampicin (p.325·3); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1). Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isocord *Asta Medica, Braz.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isocort *Pharma Clal, Israel.*
⊗ Isoconazole nitrate (p.536·2); diflucortolone valerate (p.1529·2).
Fungal skin infections.

IsoCrom *Pari, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Isocutan *Hexal, Austria†.*
Isotretinoin (p.1599·2).
Acne.

Isodeksol *Ulagay, Turk.*
Sodium chloride (p.1686·1) infusion with glucose.
Carbohydrate source; fluid and electrolyte disorders.

Isoderm
Note. This name is used for preparations of different composition.
Dermapharm, Ger.
Isotretinoin (p.1599·2).
Acne.
Alkapharm, Singapore.
Skin cleanser.

Isodermal *Kleva, Gr.*
Isotretinoin (p.1599·2).
Acne.

Isodex *Teva, Hung.*
Glucose monohydrate infusion (p.1945·3).

Isodexam *Sensomed, Philipp.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Isodexid *Medi-Rx, Philipp.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isodilan *Klonal, Arg.*
Isoxsuprine (p.2327·3).

Isodine *Faulding, Austral.†; Mahakam Beta, Indon.; Mundipharma, Indon.; Boehringer Ingelheim Promeco, Mex.; Meda, Port.; Meiji, Thai.*
Povidone-iodine (p.1659·2).
Burns; mouth and throat disorders; oral hygiene; skin infections; skin, mucous membrane, and instrument disinfection; ulcers; vaginitis; wounds.

Isodiur *Italfarmaco, Spain.*
⊗ Torasemide sodium (p.1416·1).
Hypertension; oedema.

Isodol *Magis, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Isodonna *Madaus, Spain.*
Soya bean (p.1965·3).
Menopausal disorders.

Isodrink *Volchem, Ital.*
Isotonic rehydration solution (p.1922·1).

Isodur *Sandoz, Denm.; AstraZeneca, Swed.; Galen, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Iso-Eremfat *Fatol, Ger.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Isoess *Bieffe, Ital.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Isoface *Valeant, Braz.; Valeant, Mex.; Vivax Gynopharm, Venez.*
Isotretinoin (p.1599·2).
Acne; rosacea; seborrhoea.

Isofarma *Farmaervas, Braz.†.*
Soya (p.1965·3).
Hypercholesterolaemia.

Isofem *Meprofarm, Indon.*
Isoflavone (p.2391·2); vitamin C; vitamin D; vitamin E; calcium; zinc (p.1922·1).
Menopausal disorders; osteoporosis.

Isofenal *SoSe, Ital.*
Ketoprofen (p.73·1).
Inflammation; pain.

Isoflavine *Herbarium, Braz.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Isoflon *Proel, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Isoforine *Cristalia, Braz.*
Isoflurane (p.1785·3).
General anaesthesia.

Isofort *Bieffe, Ital.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Isofra *Bouchara, Rus.*
Framycetin sulfate (p.279·1).
Bacterial infections of the upper respiratory tract.

I-Soft
Note. This name is used for preparations of different composition.
LED, Fr.†.
Cream: Ictasol (p.1599·1); ammonium lactate (p.1589·2).
Hyperkeratotic skin disorders.
LED, Fr.†.
Shampoo: Ictasol (p.1599·1); ammonium lactate (p.1589·2); salicylic acid (p.1612·2).
Dandruff.

Isoftal *Agepha, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2).
Conjunctivitis.

Isofundin *Braun, Port.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte imbalance.

Isogaine *Clarben, Port.; Clarben, Spain.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Isogel *GSK, India; GSK, NZ; Potter's, UK.*
Ispaghula (p.1737·1).
Colostomy management; constipation; diarrhoea; irritable bowel syndrome.

Isogen *Pharma Clal, Israel.*
Isoconazole nitrate (p.536·2).
Fungal skin infections.

Isogeril *Gerolimatos (Γερολυματος), Gr.†.*
Isotretinoin (p.1599·2).
Acne.

Isoginkgo *Merck dura, Ger.*
Ginkgo biloba (p.2311·1).
Intermittent claudication; mental function impairment; tinnitus; vertigo.

Isoglaucon *Agepha, Austria; Alcon, Ger.; Alcon, Ital.; Alcon Cusi, Spain.*
Clonidine hydrochloride (p.1247·1).
Glaucoma.

Isogrow *Bieffe, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in neonates.

Isogutt *Winzer, Ger.†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Ocular burns.

Isogutt akut *Winzer, Ger.*
Sodium chloride (p.1686·1).
Eye injuries and burns.

Isogyn
Note. This name is used for preparations of different composition.
Finderm, Ital.
Isoconazole nitrate (p.536·2).
Fungal vulvovaginal infections.
BioSaude, Port.†.
Soya isoflavones (p.2391·2).
Menopausal disorders.

Isohes *Fresenius Kabi, Austria; Fresenius Kabi, Hung.†; Fresenius Kabi, Switz.†; Eczacibasi-Baxter, Turk.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Haemodilution; hypovolaemic shock; plasma volume expansion.

Isohexal *Hexal, Austral.*
Isotretinoin (p.1599·2).
Acne.

Isoket *Sidus, Arg.; Gebro, Austria; Schwarz, Cz.; Sanol, Ger.; Schwarz, Ger.; Schwarz, Hong Kong; Schwarz, Hung.†; Pharos, Indon.; Schwarz, Irl.; Schwarz, Israel; Schwarz, Malaysia; Abbott, Mex.; Schwarz, Philipp.; Schwarz, Pol.; Neo-Farmaceutica, Port.; Schwarz, Rus.; Omnimed, S.Afr.; Schwarz, Singapore; Schwarz, Switz.; Schwarz, Thai.; UCB, UK; Farma, Venez.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; cor pulmonale; coronary circulatory disorders; coronary spasm; heart failure; myocardial infarction; prolongation of ischaemia tolerance during angioplasty; pulmonary hypertension.

Isokin *Pfizer, India.*
Isoniazid (p.288·1).
Tuberculosis.

Isokin-300 *Pfizer, India.*
Isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Isokin-T Forte *Pfizer, India.*
Isoniazid (p.288·1); thioacetazone (p.351·2).
Tuberculosis.

Isolan
Note. This name is used for preparations of different composition.
Hexal, Arg.†.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.
Galagen, USA.
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Isolin *Samarth, India.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Bradycardia; shock; Stokes-Adams attacks.

Isolipan *Servier, Cz.†; Servier, Hung.†.*
⊗ Dexfenfluramine hydrochloride (p.2154·1).
Obesity.

Isolong *CTI, Israel; CTS, Rus.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isolyte *Baxter, Ital.; Baxter, Turk.; McGaw, USA.*
Electrolyte infusion with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Isomack *Zuoz, Venez.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; myocardial infarction.

Isomax *Prodotti, Braz.*
Isoconazole nitrate (p.536·2).
Fungal skin infections.

Isomel *Clonmel, Irl.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isomerine *Key, Arg.†.*
Chlorphenamine (p.572·2).

Isomerine N *Schering-Plough, Arg.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2); guaifenesin (p.1561·3).
Coughs; rhinitis.

Isomet *M & H, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Isomicot *Prieto, Arg.*
Isoconazole (p.536·2).
Fungal skin and vaginal infections.

Isomil *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Israel; Ordesa, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, Philipp.; Abbott, Pol.; Abbott, Singapore; Abbott, Thai.; Abbott Nutrition, UK; Ross, USA; Abbott, Venez.*
Lactose-free soy protein infant feed (p.1922·1).
Cows' milk intolerance; diarrhoea; enteral nutrition; galactosaemia; gluten intolerance; lactase deficiency; lactose intolerance.

Isomil DF *Abbott, NZ†; Ross, USA.*
Infant feed (p.1922·1).
Diarrhoea.

Isomin *Cipla, India.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isomina *Megat, Venez.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; pyrosis; Zollinger-Ellison syndrome.

Isomol *Sanol, Ger.; Schwarz, Ger.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Constipation.

Isomon *Roche, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Isomonat *Roche, Austria.*
Isosorbide mononitrate (p.1318·3).
Heart failure; ischaemic heart disease; pulmonary hypertension.

Isomonit *Hexal, Austral.; Hexal, Ger.; Sandoz, Indon.; Rowex, Irl.; Hexal, Philipp.; Hexal, Pol.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Isomyrtine *Schwarz, Fr.†.*
Pholcodine (p.1570·2); isomyrtol.
Coughs.

IsonaRif *Versapharm, USA.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Isonefrine *Tubilux, Ital.*
Phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

Isonep *Sensomed, Philipp.*
Neomycin (p.305·1); polymyxin B sulfate (p.317·3).
Eye infections.

Isonep H *Sensomed, Philipp.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye disorders; eye infections.

Isonex *Pfizer, India.*
Isoniazid (p.288·1).
Tuberculosis.

Isoniac *Klonal, Arg.*
Isoniazid (p.288·1).
Tuberculosis.

Isoniaton *Sanval, Braz.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Isonicid *PannonPharma, Hung.*
Isoniazid (p.288·1).
Tuberculosis.

Isonid *Arlex, Mex.†.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Isonitril *Rubio, Spain.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isontyn *Abbott, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Isopamil *General Drugs, Thai.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Isopaque Cysto *Nycomed Amersham, UK†.*
Calcium metrizoate (p.1488·1); magnesium metrizoate (p.1488·1); meglumine metrizoate (p.1488·1); sodium metrizoate (p.1488·1).
Radiographic contrast medium.

Isopelet *Zentiva, Cz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isopen *Siam Bheasach, Thai.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Isoplasmal G *Braun, Spain.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Isoporum *Diba, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Isoprinosin *Gerot, Austria.*
Inosine pranobex (p.884·2).
Viral infections.

Isoprinosine *Sanofi-Aventis, Belg.; Andromaco, Chile; Ewopharma, Cz.; Sanofi-Aventis, Fr.; Riemser, Ger.; Unipharma, Gr.; Ewopharma, Hung.; Newport, Irl.; Armstrong, Mex.; Newport, Philipp.; Biogal, Rus.*
Inosine pranobex (p.884·2).
Viral infections.

Isoprochin P *Merckle, Ger.†.*
Propyphenazone (p.119·3).
Fever; pain.

Isoprodian *Fatol, Austria; Fatol, Ger.†.*
Isoniazid (p.288·1); protionamide (p.320·1); dapsone (p.261·2).
Buruli ulcer; leprosy; mycobacterial infections; tuberculosis.

Isopront *Ferraz, Lynce, Port.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary oedema.

Isoprotil *Azevedos, Port.*
Isotretinoin (p.1599·2).
Acne.

Isoproxal *Lazar, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Isoptin *Abbott, Austral.; Abbott, Austria; Abbott, Canad.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Vianex (Βιανεξ), Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Neth.; Abbott, Norw.; Abbott, NZ; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, USA.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; cardiomyopathy; coronary spasm; heart failure; hypertension; hypertrophic obstructive cardiomyopathy; myocardial infarction.

Isoptin plus *Abbott, Ger.*
⊗ Verapamil hydrochloride (p.1421·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Isoptina *Abbott, Chile.*
Verapamil (p.1423·2).
Angina pectoris; arrhythmias; hypertension.

Isoptine *Abbott, Belg.; Abbott, Fr.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Isoptino *Abbott, Arg.*
Verapamil (p.1423·2) or verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Isopto Alkaline *Alcon, Fin.; Alcon, Irl.; Alcon, UK.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Isopto B 12 *Alcon Cusi, Spain.*
Cyanocobalamin (p.1980·2).
Corneal damage.

Isopto Biotic *Alcon, Swed.†.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Isopto Carpina *Alcon, Arg.; Alcon Cusi, Spain; Alcon, Venez.†.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension; production of miosis; reversal of mydriasis.

Isopto Carpine *Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Fin.; Alcon, Gr.; Alcon, Hong Kong†; Alcon, Irl.†; Alcon, Malaysia; Alcon, NZ†; Alcon, Neth.†; Alcon, Norw.; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension; production of miosis; production of mydriasis; raised intra-ocular pressure; reversal of mydriasis.

Isopto Cetamide *Alcon, USA.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Isopto Cetapred *Alcon, Braz.; Alcon, Cz.†; Alcon, Gr.; Alcon, Mex.; Alcon, Philipp.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Infected eye disorders; inflammatory eye disorders.

Isopto Dex *Alcon, Ger.*
⊗ Dexamethasone (p.1526·1).
Eye disorders.

Isopto Fenicol *Alcon, Arg.; Alcon, Belg.; Alcon, NZ†; Alcon, Singapore.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Isopto Flucon *Alcon, Ger.†; Alcon Cusi, Spain.*
⊗ Fluorometholone (p.1532·3).
Eye disorders.

Isopto Frin *Alcon, Austral.†; Alcon, Irl.†; Alcon, Malaysia†; Alcon, NZ†; Alcon, Singapore†.*
Phenylephrine hydrochloride (p.1568·1).
Dry eyes; eye fatigue; eye irritation; wetting agent for hard contact lenses.

Isopto Karbakolin *Alcon, Swed.*
Carbachol (p.1879·2).
Glaucoma.

Isopto Max *Alcon, Ger.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Isopto Maxidex *Alcon, Arg.; Alcon, Norw.; Alcon, Swed.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Isopto Maxitrol *Alcon, Gr.*
⊗ Dexamethasone (p.1526·1); polymyxin B (p.318·2); neomycin (p.305·1).
Inflammation and allergy of the eye.

Isopto Naturale *Alcon, Ger.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Isopto Plain *Alcon, Fin.; Alcon, Irl.; Alcon, Swed.; Alcon, UK; Alcon, USA.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Isopto Tears *Alcon, Austral.†; Alcon, Belg.; Alcon, Canad.; Alcon, Cz.†; Alcon, Hong Kong; Alcon, Switz.; Alcon, Thai.; Alcon, USA.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation; keratitis.

Isoptomax *Alcon, Arg.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Isopuramin *Bieffe, Ital.*
A range of amino-acid infusions (p.1922·1).
Parenteral nutrition.

Iso-Puren *Alpharma-Isis, Ger.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isoradin *YSP, Malaysia.*
⊗ Isoconazole nitrate (p.536·2); diflucortolone valerate (p.1529·2).
Fungal skin infections with inflammation.

Isoram *Bieffe, Ital.*
-Arginine (p.1928·2); -isoleucine (p.1954·1); -leucine (p.1954·3); -valine (p.1971·1).
Hepatic encephalopathy; post-trauma disorders.

Isorat *Munir, Turk.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Isorbid *Teuto, Braz.†; Armstrong, Mex.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isordil *Wyeth, Arg.; Sigma, Austral.; Wyeth Lederle, Belg.†; Sigma, Braz.; Wyeth, Hong Kong†; Ipca, India; Sunthi Sepuri, Indon.; Wyeth, Indon.; Shire, Irl.†; Wyeth, Malaysia†; Teofarma, Neth.; Wyeth, Philipp.; Akromed, S.Afr.; Wyeth, Singapore†; Inibsa, Spain†; Wyeth-Ayerst, Thai.; Fako, Turk.; Biovail, USA; Wyeth, Venez.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction.

Isorel *Novipharm, Austria.*
Mistletoe (p.2345·3) from fir trees, apple trees or pine trees.
Malignant neoplasms.

Isorem *Remedica, Hong Kong; Remedica, Thai.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isoren *Bieffe, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Isoric *Interbat, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Isorifam *Biochem, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Isoritmon *Basi, Port.†.*
Chloroprocainamide.
Arrhythmias.

Isorythm *Merck-Lipha, Fr.*
Disopyramide (p.1269·1) or disopyramide phosphate (p.1269·2).
Arrhythmias.

Isoselect *Bieffe, Ital.*
Amino-acid infusion (p.1922·1).
Hepatic encephalopathy; parenteral nutrition.

Isosifar *Siphar, Switz.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Isoskin *Biospray, Gr.*
Isotretinoin (p.1599·2).
Acne.

Isosol
Note. This name is used for preparations of different composition.
Sanova, Austria.
Isotretinoin (p.1599·2).
Acne.

Merkez, Turk.
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection; skin disorders; vaginal infections.

Ulagay, Turk.
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Isosor *Vitabalans, Fin.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Isosource *Novartis, Arg.†; Novartis Consumer, Austral.†; Novartis, Braz.; Novartis Nutrition, Cz.†; Novartis, Fin.; Novartis Nutrition, Fr.; Novartis Nutrition, Hong Kong; Novartis Consumer, Ital.; Novartis Consumer, Port.†; Novartis Nutrition, Singapore; Novartis, Turk.; Sandoz Nutrition, USA.*
A range of preparations for enteral nutrition (p.1922·1).

Isospan *PannonPharma, Hung.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isospray *Biotech, Venez.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Isostenase *Azupharma, Ger.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Isosteril *Fresenius Kabi, Switz.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Isosupra Lidose *SMB, Belg.*
Isotretinoin (p.1599·2).
Acne.

Isotamine *Valeant, Canad.*
Isoniazid (p.288·1).
Tuberculosis.

Isotane *Pacific, NZ; Shanghai Yanan, Thai.*
Isotretinoin (p.1599·2).
Acne.

Isotard
Note. This name is used for preparations of different composition.
CTI, Israel†.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

ProStrakan, UK.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isotein HN *Sandoz Nutrition, USA.*
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Isoten *Wyeth, Belg.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; cardiac hyperkinetic syndrome; heart failure; hypertension.

Isotenk *Biotenk, Arg.*
Isoxsuprine hydrochloride (p.2327·3).
Dysmenorrhoea; peripheral vascular disorders; premature labour; threatened miscarriage.

Isothane *Baxter, Braz.†.*
Isoflurane (p.1785·3).
General anaesthesia.

Isotic Adretor *Fahrenheit, Indon.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Isotic Azora *Fahrenheit, Indon.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic or inflammatory eye disorders.

Isotic Betaracin *Fahrenheit, Indon.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye disorders.

Isotic Cetride *Fahrenheit, Indon.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Isotic Clearin *Fahrenheit, Indon.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Isotic Cycloma *Fahrenheit, Indon.*
Atropine sulfate (p.1219·3).
Production of cycloplegia; uveitis.

Isotic Engigi *Fahrenheit, Indon.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Eye infections.

Isotic Frizin *Fahrenheit, Indon.*
Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Isotic Ixodine *Fahrenheit, Indon.*
Idoxuridine (p.881·2).
Viral keratitis.

Isotic Neolyson *Fahrenheit, Indon.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Isotic Nepafrin *Fahrenheit, Indon.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); phenylephrine hydrochloride (p.1568·1).
Eye infections.

Isotic Renator *Fahrenheit, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Eye infections.

Isotic Salmicol *Fahrenheit, Indon.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Isotic Tearin *Fahrenheit, Indon.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3); glycerol (p.2314·2).
Dry eyes; eye irritation.

Isotic Timact *Fahrenheit, Indon.*
Gentamicin sulfate (p.282·1).
Eye infections.

Isotic Tobrizon *Fahrenheit, Indon.*
⊗ Dexamethasone (p.1526·1); tobramycin (p.354·1).
Infected eye disorders.

Isotic Tobryne *Fahrenheit, Indon.*
Tobramycin (p.354·1).
Bacterial eye infections.

Isotol *Diaco, Ital.*
⊗ Mannitol (p.1330·2).
Raised intra-ocular pressure; raised intracranial pressure.

Isotone Kochsalz *Baxter, Ger.; Braun, Ger.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Isotonic *Ratiopharm, Ger.†.*
Sodium chloride; sodium citrate; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration solution.

Isotonische Kochsalzlosung *Eifelfango, Ger.; Fresenius Kabi, Ger.; Serum-Werk Bernburg, Ger.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders; respiratory-tract disorders.

Isotrate
Note. This name is used for preparations of different composition.
Berlin Pharm, Thai.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Bioglan, UK†.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Isotret *Hexal, Ger.*
Isotretinoin (p.1599·2).
Acne.

Isotretin *Sandoz, Cz.*
Isotretinoin (p.1599·2).
Acne.

Isotrex *Stiefel, Arg.; Stiefel, Austral.; Sanova, Austria; Stiefel, Braz.; Stiefel, Canad.†; Stiefel, Chile; Stiefel, Cz.†; Stiefel, Denm.; Stiefel, Ger.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Irl.; Stiefel, Israel; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Port.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Spain; Stiefel, Thai.; Stiefel, UK; Stiefel, Venez.†.*
Isotretinoin (p.1599·2).
Acne.

Isotrex Eritromicina *Stiefel, Spain.*
Isotretinoin (p.1599·2); erythromycin (p.269·2).
Acne.

Isotrexin *Sanova, Austria; Stiefel, Braz.; Stiefel, Cz.; Stiefel, Ger.; Stiefel, Hung.; Stiefel, Irl.; Stiefel, Ital.; Stiefel, Pol.; Stiefel, Port.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK.*
Isotretinoin (p.1599·2); erythromycin (p.269·2).
Acne.

Isotrexol *Stiefel, Braz.*
Isotretinoin (p.1599·2); ensulizole (p.1597·1); avobenzone (p.1589·3); octinoxate (p.1608·2).

Iso-Triraupin *Roche, Thai.†.*
⊗ Butizide (p.1238·1); reserpine (p.1387·3); rescinnamine (p.1387·2); raubasine (p.1386·3).
Hypertension.

Isotroin *Farmanic, Gr.; Cipla, India.*
Isotretinoin (p.1599·2).
Acne.

Isovir *Sanofi-Aventis, Port.*
Inosine pranobex (p.884·2).
Subacute sclerosing panencephalitis.

Isovist *Schering, Austral.†; Schering, Austria; Schering, Cz.†; Schering, Denm.; Schering, Fin.†; Schering, Ger.; Schering, Hung.; Schering, NZ; Schering, Neth.; Schering, S.Afr.; Schering, Switz.; Bayer, UK.*
Iotrolan (p.1486·1).
Radiographic contrast medium.

Isovit *Deva, Turk.*
Isoniazid (p.288·1).
Vitamin B (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isovon *Alembic, Singapore.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Isovorin *Wyeth Lederle, Austria; Wyeth, Braz.†; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Gr.; Wyeth, Irl.†; Wyeth, Norw.; Interfarma, Port.; Wyeth, S.Afr.; Wyeth, Spain; Wyeth, Swed.; Wyeth, UK.*
Calcium levofolinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; methanol poisoning; reduction of folic acid antagonist toxicity; reduction of high dose methotrexate toxicity.

Isovue *Regional Health, Austral.; Regional Health, NZ; Squibb Diagnostics, USA.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Isox
Note. This name is used for preparations of different composition.
Saval, Chile.
Meloxicam (p.80·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Senosiain, Mex.
Itraconazole (p.536·3).
Fungal infections.

Isoxan *NHS, Fr.*
Multivitamin and mineral preparation (p.1922·1).

Isoxilan *BioFemme, Philipp.*
Isoxsuprine hydrochloride (p.2327·3).
Dysmenorrhoea; peripheral vascular disorders; premature labour; threatened abortion.

Isoxin *Pascual, Philipp.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for prophylaxis of peripheral neuropathy.
Tuberculosis.

I-Soyalac *Nutricia-Loma Lindar, USA.*
Corn- and lactose-free soy protein infant feed (p.1922·1).

Isozid *Fatol, Ger.; IFET (ΙΦΕΤ), Gr.†.*
Isoniazid (p.288·1).
Tuberculosis.

Isozid comp N *Fatol, Ger.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Isozid-H *Gebro, Austria.*
Hexetidine (p.1647·1).
Skin disinfection.

Ispagel *LPC, UK.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; irritable bowel syndrome.

Ispenoral *Rosen, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Isprinol *Novell, Indon.*
Inosine pranobex (p.884·2).
Viral infections.

Isquelium *Rider, Chile.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Issium *Lifepharma, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Istalol *Bausch & Lomb, USA.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Istamex *Adelco, Gr.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Istan *Elin, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Istantal *Unifarm, Ital.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Istasol *Grin, Mex.*
⊗ Naphazoline (p.1565·1); pheniramine (p.587·2).
Eye disorders.

Isteropac *Bracco, Switz.†.*
Iodamide (p.1481·3).
Contrast medium for hysterosalpingography.

Isteropac ER *Bracco, Ital.*
Meglumine iodamide (p.1481·3).
Contrast medium for hysterosalpingography.

Isticilline *Norma (Νορμα), Gr.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Istin *Pfizer, Irl.; Pfizer, UK.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Istivac *Sanofi Pasteur, Arg.; Sanofi Pasteur, Port.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Istix *Sons, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Istopirin *Biogal-Teva, Hung.†.*
Aspirin (p.20·3).
Fever; pain.

Istopril *Codal Synto, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Istotosal *Biospray, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Isuhuman Basal *Sanofi-Aventis, Port.†.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Isuhuman Comb 25 *Sanofi-Aventis, Port.†.*
⊗ Mixture of insulin injection (human) 25% and isophane insulin injection (human) 75% (p.443·2).
Diabetes mellitus.

Isuhuman Infusat *Hoechst Marion Roussel, Neth.†.*
⊗ Neutral insulin injection (human) (p.443·2).
Diabetes mellitus.

Isuhuman Rapid *Sanofi-Aventis, Port.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Isuprel *Abbott, Austral.; Abbott, Belg.; Abbott, Cz.; Abbott, Fr.; Abbott, Gr.†; Abbott, Hung.†; Abbott, Indon.; Abbott, Israel; InterMed, NZ; Abbott, Singapore†; Abbott, Thai.; Sanofi Winthrop, USA.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Arrhythmias; bronchospasm; cardiac arrest; carotid sinus hypersensitivity; heart block; heart failure; hypoperfusion syndrome; overdose of beta blockers or

calcium channel blockers; pulmonary hypertension; shock; Stokes-Adams attacks.

IT SD-T Purissimus, Arg.
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

I-Tab Pascual, Philipp.
Vitamin and mineral preparation (p.1922·1).

Itagil Actavis, Port.
Buspirone hydrochloride (p.965·3).
Anxiety.

Itaiflex Ortoquimica, Braz.†.
Orphenadrine (p.812·2); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Itaka Roemmers, Venez.
Sildenafil (p.2195·1).
Erectile dysfunction.

Italdermol Italmex, Mex.
Wheat germ (p.2415·1); phenoxyethanol (p.1657·1).
Burns; ulcers; wounds.

Italker Italmex, Mex.
Ketorolac trometamol (p.74·2).
Pain.

Italnik Italmex, Mex.
Ciprofloxacin (p.243·3).
Bacterial infections.

Italon Offenbach, Mex.
Indometacin (p.66·3).
Inflammation.

Italprid Teofarma, Ital.
Tiapride hydrochloride (p.1032·1).
Alcohol withdrawal syndrome; behaviour disorders; gastrointestinal motility disorders; headache; movement disorders.

Ital-Ultra Italmex, Mex.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Italviron Italmex, Mex.
Asparagine; acetylglutamine; pyridoxine; phosphorylserine (p.1922·1).
Memory disorders.

Itami
Fidia, Ital.
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Fidia, Neth.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Itamol
Note. This name is used for preparations of different composition.
Berlico Mulia, Indon.
Paracetamol (p.108·1).
Fever; pain.

Euromex, Mex.
Bismuth salicylate (p.1711·1).
Diarrhoea; peptic ulcer.

Itan Saval, Chile.
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Itane Pharmasant, Thai.
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Itapredin Rafarm, Gr.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Itax Pierre Fabre Dermo-Cosmetique, Rus.
Phenothrin (p.2048·3).
Pediculosis.

Itax Antipoux Pierre Fabre, Fr.
Shampoo: Phenothrin (p.2048·3).
Pediculosis.

ITC Giscard, Arg.†.
Itraconazole (p.536·3).
Fungal infections.

Itch Care Kiwi, Neth.
Homoeopathic preparation.

Itch-X Ascher, USA.
Pramocaine hydrochloride (p.1868·1); benzyl alcohol (p.1631·3).
Local anaesthesia.

ITE B12 Forte Purissimus, Arg.
Cyanocobalamin (p.1980·2); folic acid (p.1940·1); ferric ammonium citrate (p.1938·1); liver extract (p.2337·3).
Anaemias.

Itedal Dicofar, Arg.
Paracetamol (p.108·1).
Fever; pain.

Itedal Plus Dicofar, Arg.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Fever; influenza symptoms; nasal congestion; pain.

Item Alphacade Gandhour, Fr.
Alpha hydroxy acids; salicylic acid (p.1612·2); cedar oil (p.2400·3); cade oil (p.1616·1).
Dandruff; scalp psoriasis.

Item Alphakeptol Gandhour, Fr.
Glycolic acid (p.1598·1); salicylic acid (p.1612·2); pyrithione zinc (p.1611·2); piroctone olamine (p.1610·1).
Dandruff.

Item Alphazole Gandhour, Fr.
Climbazole (p.529·3); glycine (p.1947·3); salicylic acid (p.1612·2); alpha hydroxy acids; cedar oil (p.2400·3).
Seborrhoeic dermatitis.

Item Antipoux
Note. This name is used for preparations of different composition.
Gandhour, Fr.
Lotion; shampoo: Phenothrin (p.2048·3).
Pediculosis.

Gandhour, Fr.
Topical spray: Diethyltoluamide (p.2041·1).
Head lice repellent.

Item Lentes Gandhour, Fr.
Eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); rosemary oil (p.2381·3); sage oil (p.2382·3); artemisia oil; saffron oil; hyssop oil (p.2323·3); cedar leaf oil (p.2400·3); myrtillus oil; persic oil (p.2365·3).
Pediculosis.

Iteol-3 AstraZeneca, India.
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin disinfection.

Iterax UCB, Indon.; UCB, Philipp.
Hydroxyzine hydrochloride (p.581·2).
Anxiety; premedication; pruritus.

Iterium Servier, Austria.
Rilmenidine phosphate (p.1388·3).
Hypertension.

Itinerol B_6 Vifor, Switz.
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2); caffeine (p.1116·3).
Motion sickness; nausea and vomiting.

Itisona Galeno, Venez.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Itodal Laboratorios Chile, Chile.
Itraconazole (p.536·3).
Fungal infections.

Itoprid Cipla, India.
Itopride hydrochloride (p.1737·3).

Itorex Pharma Italia, Ital.
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Itoxaril LKM, Arg.
Irinotecan (p.738·1).
Malignant neoplasms.

Itra Macrophar, Thai.
Itraconazole (p.536·3).
Fungal infections.

Itrabene Ratiopharm, Austria.
Itraconazole (p.536·3).
Fungal infections.

Itrabest Phoinix Pharm (Φοινιξ Φαρμ), Gr.
Itraconazole (p.536·3).
Fungal infections.

Itrac Cassara, Arg.
Itraconazole (p.536·3).
Fungal infections.

Itracan Cipla, India.
Itraconazole (p.536·3).
Fungal infections.

Itracol Hexal, Ger.
Itraconazole (p.536·3).
Fungal infections.

Itracon Med-One, Gr.; Unison, Thai.
Itraconazole (p.536·3).
Fungal infections.

Itraconal Polychronus, Gr.
Itraconazole (p.536·3).
Fungal infections.

Itracotan Royton, Braz.
Itraconazole (p.536·3).
Fungal infections.

Itrahexal Hexal, Braz.†.
Itraconazole (p.536·3).
Fungal infections.

Itralfa Chrispa (Χρισπα), Gr.
Itraconazole (p.536·3).
Fungal infections.

Itranax Janssen-Cilag, Braz.†; Janssen-Cilag, Mex.
Itraconazole (p.536·3).
Fungal infections.

Itranol Rafa, Israel.
Itraconazole (p.536·3).
Fungal infections.

Itraspor Sigma, Braz.; Eczacibasi, Turk.
Itraconazole (p.536·3).
Fungal infections.

Itravil Investigacion, Mex.
⊗ Clobenzorex hydrochloride (p.2152·3).
Obesity.

Itraviron Farmedia, Gr.
Itraconazole (p.536·3).
Fungal infections.

Itrazol Biolab Sanus, Braz.; Verisfield, Gr.
Itraconazole (p.536·3).
Fungal infections.

Itrin Keryos, Ital.
Terazosin hydrochloride (p.1410·2).
Hypertension.

Itrizole Kyowa, Jpn.
Itraconazole (p.536·3).
Fungal infections.

Itro Elea, Arg.†.
⊗ Idoxuridine (p.881·2); neomycin sulfate (p.305·1); prednisolone sodium phosphate (p.1541·2).
Eye infections.

Itrop Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Ger.
Ipratropium bromide (p.1124·1).
Arrhythmias; bradycardia; heart block.

Itrop Plus Cipla, India.
Tropicamide (p.1886·2); phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

Itzol Lapi, Indon.
Itraconazole (p.536·3).
Fungal infections.

Iuronico Biotic Paylos, Arg.
Sodium hyaluronate (p.2320·1); sulfadiazine silver (p.337·2).
Bacterial skin infections.

Iuronicoderm Paylos, Arg.
Hyaluronic acid (p.2320·1).
Skin disorders.

Iuvacor Sanofi-Aventis, Ital.
Ubidecarenone (p.2407·2).
Co-enzyme Q deficiency.

Ivacin Wyeth Lederle, Denm.†.
Piperacillin sodium (p.315·2).
Bacterial infections.

Ivadal Sanofi Synthelabo, Austria.
Zolpidem tartrate (p.1037·3).
Insomnia.

Ivagan Arex, Venez.
Dihydroergotamine mesilate (p.618·2); paracetamol (p.108·1); caffeine (p.1116·3).
Headache.

I-Valex Ross, USA.
A range of leucine-free preparations for enteral nutrition including an infant feed (p.1922·1).
Leucine catabolism disorders.

Ivaliten Lavipharm, Gr.
Phenothrin (p.2048·3).
Head, body, and crab lice.

Ivamix Fresenius Kabi, Norw.†.
Amino-acid and lipid (from soya oil (p.1965·3)) infusion (p.1922·1).
Parenteral nutrition.

Ivanes Ikapharmindo, Indon.
Ketamine hydrochloride (p.1787·1).
Anaesthesia; analgesia in obstetrics.

Ivarest Rider, Chile; Blistex, USA.
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Formerly contained calamine and benzocaine.
Allergic skin reactions; minor skin irritation; pruritus.

Ivast Integra, Philipp.; Medica Korea, Philipp.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Ivatrim Sydenham, Philipp.
Co-trimoxazole (p.258·1).
Bacterial infections.

Ivedal Sanofi Synthelabo, S.Afr.
Zolpidem tartrate (p.1037·3).
Insomnia.

Iveegam Baxter, Canad.; Immuno, USA†.
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; immunodeficiency; Kawasaki syndrome; passive immunisation.

Ivegam Sanquin, Neth.
A normal immunoglobulin (p.2225·3).
Idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki syndrome; transplant rejection.

Ivegam-CMV CAF-DCF, Belg.
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Ivel Abbott, Mex.
Lupulus (p.2335·2); valerian (p.2410·1).
Anxiety; insomnia.

Ivelip Baxter, Arg.; Baxter, Austral.†; Clintec, Cz.†; Baxter, Fr.; Kalbe, Indon.; Clintec, Israel; Baxter, Ital.†; Baxter, Mex.†; Baxter, NZ; Baxter, Pol.; Baxter, Spain; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK; Baxter, Venez.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Ivemend MSD, Cz.; MSD, Port.; MSD, UK.
Fosaprepitant meglumine (p.1732·1).
Nausea and vomiting associated with cancer chemotherapy.

Ivepaque Amersham, Fr.
Iopentol (p.1484·2).
Radiographic contrast medium.

Ivermec UCI, Braz.†.
Ivermectin (p.145·2).
Onchocerciasis.

Iversal Athenstaedt, Cz.†.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Ivexterm Valeant, Mex.
Ivermectin (p.145·2).
Worm infections.

IVF-C LG Life Sciences, Thai.
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; hypogonadotrophic hypogonadism; male and female infertility; menstrual disorders; threatened or recurrent miscarriage.

IVF-M LG Life Sciences, Thai.
⊗ Menotrophin (p.2109·3).
Male and female infertility.

IV-Globulin Green Cross, Malaysia.
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

IV-Globulin S Green Cross, Philipp.
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease.

Ivhebex Lab Francais du Fractionnement, Fr.; IFET (ΙΦΕΤ), Gr.
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Ividol Rafarm, Gr.
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

I-Vite Yu Sheng, Singapore.
Vitamins; minerals; lutein (p.1922·1).
Nutritional supplement.

i-Vitein Indrugco, Singapore.
Vitamins; minerals; lutein (p.1922·1).
Dietary supplement.

Ivix
Note. This name is used for preparations of different composition.
Cinetic, Arg.
Capsules: Amino acids; vitamins; minerals; ginkgo biloba; soya protein (p.1922·1).
Dietary supplement.

Cinetic, Arg.
Topical solution: Minoxidil (p.1342·1).
Alopecia.

Ivofol Juste, Spain.
Propofol (p.1791·1).
General anaesthesia; sedative.

Ivor Vianex (Βιανεξ), Gr.; Sigma-Tau, Ital.; Rovi, Port.
Bemiparin sodium (p.1223·1).
Thromboembolic disorders.

Ivoran Pilot Eczane, Arg.†.
Nitrofurazone (p.309·1).
Bacterial infections.

Ivormax Vianex (Βιανεξ), Gr.
Bemiparin sodium (p.1223·1).
Thromboembolic disorders.

Ivracain Sintetica, Switz.
Chloroprocaine hydrochloride (p.1857·1).
Local anaesthesia.

Ivumir Dicofarm, Ital.
Cranberry (p.2289·1).
Urinary-tract disorders.

Ivy Block Enviroderm, USA.
Bentoquatam (p.1590·2).
Prophylaxis against poison ivy-, oak-, or sumac-induced contact dermatitis.

Ivy Dry Ivy Corp, USA.
Zinc acetate (p.1999·1).
Minor skin irritation.

Iwamet Masa, Thai.
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; systemic mastocytosis; Zollinger-Ellison syndrome.

Iwazin Masa, Thai.
Tyrothricin (p.358·2); benzethonium chloride (p.1630·1); benzocaine (p.1854·1).
Mouth and throat infections.

Ixacor Roemmers, Arg.
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Ixana
Note. This name is used for preparations of different composition.
Medical, Arg.
Lozenges: Hexylresorcinol (p.1647·1) sodium benzoate (p.1630·2); senega (p.1572·3); ambay.
Mouth and throat disorders.

Medical, Arg.
Syrup: Guaifenesin (p.1561·3); sodium benzoate (p.1630·2); senega (p.1572·3); aescin (p.2248·2); ambay.
Coughs.

Ixel Pierre Fabre, Arg.; Pierre Fabre, Austria; Roche, Braz.; Silesia, Chile; Pierre Fabre, Cz.; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Israel; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Turk.
Milnacipran hydrochloride (p.409·2).
Depression.

Ixempra BMS, USA.
Ixabepilone (p.738·3).
Breast cancer.

Ixense Takeda, Austria†; Takeda, Fr.†; Takeda, Ger.†; Takeda, Ital.†; Takeda, Jpn; Takeda, Thai.†.
Apomorphine hydrochloride (p.795·1).
Erectile dysfunction.

Ixia Menarini, Spain.
Olmesartan medoxomil (p.1361·1).
Hypertension.

Ixopolet Best, Mex.
dl-Alpha tocoferil acetate (p.1992·3).
Antoxidant.

Ixor
Note. This name is used for preparations of different composition.
Phoinix Pharm (Φοινιξ Φαρμ), Gr.
⊗ Budesonide (p.1520·1).
Also known as Ιχωρ (Ichor).
Allergic rhinitis; skin disorders.

Soho, Indon.
Roxithromycin (p.331·1).
Bacterial infections.

Ixoten *Baxter, Austria; Baxter, Ger.*
Trofosfamide (p.783·3).
Malignant neoplasms.

Ixprim *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1); tramadol hydrochloride (p.130·3).
Pain.

Iyafin
Note.This name is used for preparations of different composition.
TNP, Thai.†.
Junior syrup: Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Coughs.
TNP, Thai.†.
Syrup: Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.
TNP, Thai.†.
Tablets: Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Formerly contained dextromethorphan hydrobromide, phenylpropanolamine hydrochloride, chlorphenamine maleate, and guaifenesin.
Coughs.

Izac *TNP, Thai.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth infections.

Izacef *Intramed, S.Afr.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Izadima *Pisa, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Izatax *Sandoz, Denm.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Izerin *Rafarm, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Izetafin *Rafarm, Gr.*
Macrogol 400 (p.2336·3); potassium chloride; sodium chloride; sodium bicarbonate; sodium sulfate (p.1667·1).
Bowel evacuation.

Izilox *Bayer, Fr.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections of the respiratory tract.

Izo *Pond's, Thai.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Izodeks *Eczacibasi-Baxter, Turk.*
Sodium chloride (p.1686·1) infusion with glucose.
Carbohydrate source; fluid and electrolyte disorders.

Izofran *GSK, Chile.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Izolen *Polifarma, Turk.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Izonit *Lek, Pol.*
Isosorbide mononitrate (p.1318·3).
Ischaemic heart disease.

Izotek *Blau, Pol.*
Isotretinoin (p.1599·2).
Acne.

Jaa Pyral *Jaapharm, Canad.*
Pyrantel embonate (p.155·1).

Jaaps Health Salt *Askit, UK.*
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); potassium sodium tartrate (p.1764·1).
Constipation; dyspepsia; heartburn.

Jaba B_{12} *Jaba Recordati, Port.*
Cobamamide (p.1980·2).
Neuralgia; neuritis; vitamin B deficiency.

Jabastatina *Jaba Recordati, Port.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hyperlipidaemias.

Jabasulide *Jaba Recordati, Port.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Jabobip *Billiet, Arg.†.*
Triclocarban (p.1665·2).
Skin disinfection.

Jabodine *Drovepat, Venez.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Jabolac *Roemmers-Klinos, Venez.†.*
Lactic acid (p.2329·3).
Skin disinfection.

Jabon del Tio Nacho *Bustillos, Mex.*
Tar (p.1616·2); resorcinol (p.1612·1); sulfur (p.1614·1).
Scalp disorders; skin disorders.

Jabonacid *Bajer, Arg.*
Chloroxylenol (p.1640·2); cetrimide (p.1634·1); bornyl acetate (p.2269·1).
Skin cleanser.

Jabonoil *Panalab, Arg.*
Trichlorosalicylanilide.
Emollient.

Jack and Jill *Buckley, Canad.*
Guaifenesin (p.1561·3); mepyramine maleate (p.585·2).
Cold symptoms; coughs.

Jack & Jill Bedtime *Buckley, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Jack & Jill Children's Formula Cough Liquid *Buckley, Canad.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Formerly known as Jack & Jill DM.
Cold symptoms; coughs.

Jack & Jill Cough & Cold *Buckley, Canad.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Jack & Jill Cough Cold & Flu *Buckley, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms; coughs.

Jack & Jill Thin Strips Cough *Buckley, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Jack & Jill Thin Strips Cough & Cold *Buckley, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Jackson's All Fours *Anglian, UK.*
Guaifenesin (p.1561·3).
Coughs.

Jackson's Bronchial Balsam *Anglian, UK.*
Guaifenesin (p.1561·3).
Coughs.

Jacksons Herbal Laxative *Anglian, UK.*
Cascara (p.1715·2); rhubarb (p.1768·3); senna (p.1769·2).
Constipation.

Jackson's Lemon Linctus *Anglian, UK.*
Glycerol (p.2314·2); honey (p.1948·2).
Coughs; sore throat.

Jacksons Mentholated Balm *Anglian, UK.*
Eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); camphor (p.2273·2); terpineol (p.2396·1); menthol (p.2340·1).
Musculoskeletal pain; respiratory-tract congestion.

Jackson's Pain & Fever *Anglian, UK.*
Sodium salicylate (p.124·2).
Formerly known as Jacksons Febrifuge.
Cold and influenza symptoms; musculoskeletal, joint, and soft-tissue disorders.

Jackson's Troublesome Coughs *Anglian, UK.*
Ipecacuanha (p.1562·3); glycerol (p.2314·2); honey (p.1948·2).
Coughs.

Jactuss *Coup, Gr.†.*
Zipeprol hydrochloride (p.1575·3).
Cough.

Jacutin *Hermal, Austria; Hermal, Cz.†; Hermal, Ger.; Hermal, Hung.; Hermal, Malaysia; Herrmann, Pol.; Hermal, Singapore; Boots Healthcare, Switz.; Boots, Thai.; Hermal, Thai.*
Lindane (p.2045·3).
Pediculosis; scabies.

Jacutin N *Hermal, Ger.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Jadelle *Schering, Fin.; Bayer, Neth.; Schering, Norw.; Bayer Schering, Port.; Schering, Spain; Schering, Swed.; Schering, Thai.; Schering, Venez.*
Levonorgestrel (p.2121·2).
Progestogen-only contraceptive implant.

Jaga *Aldril, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Joint pain; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Jagaplex
Aldril, Philipp.
Oral drops: Vitamin preparation (p.1922·1).
Aldril, Philipp.
syrup; Tablets: Vitamin and mineral preparation with lysine hydrochloride (p.1922·1).

Jagcin *Jagson, India.*
Paracetamol (p.108·1).
Fever; pain.

Jaikal *S & K, Ger.†.*
Sodium thiosulfate (p.1466·1); salicylic acid (p.1612·2); resorcinol (p.1612·1).
Acne.

Jaikin N *Galderma, Ger.†.*
Dimethicone (p.2032·1).
Acne.

Jalapa comp *Pfluger, Ger.†.*
Homoeopathic preparation.

Jalapa Composta *Granado, Braz.†.*
Jalap (p.1737·3); escamonea.

Jaluran *Pfizer, Ital.†.*
Hyaluronidase (p.2321·1).
Facilitates subcutaneous absorption of drugs.

Jalvase *MSD, Neth.*
Losartan potassium (p.1326·1).
Cardiovascular risk reduction; diabetic nephropathy; hypertension.

Jamaican Sarsaparilla *Potter's, UK.*
Sarsaparilla root (p.2383·3); capsicum (p.2276·2); liquorice (p.1740·3); peppermint oil (p.1761·2).
Skin disorders.

Jamax-S *SJA, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Jamieson Total Energy *Jamieson, Philipp.*
Siberian ginseng (p.2386·3); bee pollen (p.2370·2); royal jelly (p.2382·1); kola nut (p.2416·1); wheat grass.
Nutritional supplement.

Jamylene *Expanpharm, Fr.*
Docusate sodium (p.1725·1).
Constipation.

Janacin *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Jantoven *Upsher-Smith, USA.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Janumet *Merck, USA.*
Sitagliptin phosphate (p.460·2); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Januvia *MSD, Austral.; MSD, Braz.; MSD, Cz.; MSD-Chibret, Fr.; Vianex (Βιανεξ), Gr.; MSD, Malaysia; MSD, Mex.; MSD, Port.; MSD, UK; Merck, USA.*
Sitagliptin phosphate (p.460·2).
Diabetes mellitus.

Japan Freeze-Dried Tuberculin *Vaccina, S.Afr.*
Tuberculin purified protein derivative (p.2405·3).
Tuberculosis test.

Japanol *Liebermann, Ger.*
Mint oil (p.2345·2).
Cold symptoms; dyspepsia; myalgia.

Jaquedryl *Elea, Arg.†; Pfizer, Chile.*
Ergotamine tartrate (p.620·1); caffeine citrate (p.1116·3); diphenhydramine hydrochloride (p.577·2).
Migraine and other vascular headache.

Jaquesor *Soria Natural, Spain†.*
Salix (p.121·3); bitter orange (p.2357·1); melissa (p.2339·3); achillea (p.2245·2); tilia (p.2402·2).
Migraine.

Jarabe Bago *Bago, Arg.†.*
Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3).
Coughs.

Jarabe de Capulin *Nordin, Mex.*
⊗ Ammonium chloride (p.1551·3); ephedrine (p.1558·1).
Coughs.

Jarabe Garde *Grisi, Mex.; Grisi, Mex.*
Dextromethorphan (p.1555·2).
Cough; coughs.

Jarabe Manceau *Alcor, Spain.*
Senna (p.1769·2); coriander (p.2288·1); pyrus malus.
Constipation.

Jarabe de Manzanas *Ifusa, Mex.*
⊗ Mannitol (p.1330·2); senna (p.1769·2).
Constipation.

Jarabe Medex *Sidus, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with viscous mucus.

Jarabe Palto Compuesto con Miel Adulto *Maver, Chile.*
Avocado leaf (p.2262·2); eucalyptus oil (p.2301·2); tolu balsam (p.1574·2); honey (p.1948·2).
Coughs.

Jarabe Palto Compuesto con Miel Infantil *Maver, Chile.*
Avocado (p.2262·2); honey (p.1948·2).
Coughs.

Jarsin *Kwizda, Austria; Biosintetica, Braz.†; Cassella-med, Cz.; Lichtwer, Ger.; Vifor, Switz.*
St John's wort (p.422·3).
Anxiety; depression; insomnia.

Jasimenth CN *Bolder, Ger.*
Dequalinium chloride (p.1641·3); ascorbic acid (p.1983·3).
Mouth and throat disorders.

Jasmine *Schering, Fr.*
Ethinylestradiol (p.2101·3); drospirenone (p.2095·2).
Combined oral contraceptive.

Jasminelle *Schering, Fr.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Jatamansin *BMS, Arg.†.*
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

Jatrosom N *Esparma, Ger.*
Tranylcypromine sulfate (p.424·1).
Depression.

Jatrox *Procter & Gamble, Cz.†.*
Bismuth salicylate (p.1711·1).
Diarrhoea; gastritis; peptic ulcer.

Jayacin *Danpac, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Jay-Phyl *Jaymac, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Jeanine *Schering, Austria; Jenapharm, Cz.; Schering, Pol.; Lusal, Port.; Jenapharm, Rus.*
Ethinylestradiol (p.2101·3); dienogest (p.2094·1).
Combined oral contraceptive.

Jecopeptol *Zydus, Fr.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); sodium bicarbonate (p.1673·2); boldo (p.2267·2); kinkeliba (p.2329·2); euonymus (p.1730·1).
Digestive disorders.

Jectocos *CFL, India.*
Iron sorbitol (p.1953·1).
Iron-deficiency anaemia.

Jectocos Plus *CFL, India.*
Iron sorbitol (p.1953·1); folic acid (p.1940·1); vitamin B (p.1980·2).
Iron-deficiency anaemia.

Jectofer *AstraZeneca, Canad.†; AstraZeneca, Ger.†; AstraZeneca, Irl.†; AstraZeneca, Norw.†; Eczacibasi, Turk.*
Iron sorbitol (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Jedipin *Jenapharm, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Jekovit *Orion, Fin.*
Ergocalciferol (p.1987·1).
Vitamin D deficiency.

Jellin *Grunenthal, Ger.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Jellin Basis *Grunenthal, Ger.*
Emollient.
Skin disorders.

Jellin polyvalent *Grunenthal, Ger.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Jellin-Neomycin *Grunenthal, Ger.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Jelliproct *Grunenthal, Ger.*
⊗ Fluocinonide (p.1532·1); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Jellisoft *Grunenthal, Ger.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Jelonet *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Smith & Nephew, Ital.; Smith & Nephew, S.Afr.; Smith & Nephew Healthcare, UK.*
Soft paraffin (p.2031·3).
Burns; wound dressing.

Jemalt 13+13 *Wander Health Care, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Jemizym *Jean-Marie, Hong Kong†.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; respiratory-tract disorders.

Jenabroxol comp *Jenapharm, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Jenacard *Jenapharm, Ger.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Jenacillin V *Jenapharm, Ger.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Jenacillin A *Jenapharm, Ger.†.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Jenacillin O *Jenapharm, Ger.†.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Jenacyclin *Jenapharm, Ger.†.*
Doxycycline (p.267·1).
Bacterial infections.

Jenafenac *Jenapharm, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Jenamazol *Quintesence, Cz.; Jenapharm, Ger.†.*
Clotrimazole (p.530·1).
Corynebacterium infections; fungal infections; vulvovaginal infections.

Jenapamil *Jenapharm, Ger.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension; tachycardia.

Jenapirox *Jenapharm, Ger.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Jenaprofen *Jenapharm, Ger.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Jenaprogon *Jenapharm, Malaysia†.*
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; female infertility; threatened or recurrent miscarriage.

Jenapurinol *Jenapharm, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Jenaspiron *Jenapharm, Ger.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Jenasteron *Jenapharm, Malaysia†.*
⊗ Testosterone enantate (p.2130·1).
Aplastic anaemia; breast cancer; delayed puberty and hypogonadism in males.

Jenatenol *Jenapharm, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Jenateren comp *Jenapharm, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Jenetten *Jenapharm, Cz.†.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Jengimiel
Note. This name is used for preparations of different composition.
Jengimiel, Venez.
Adult syrup: Ginger (p.1732·3); honey (p.1948·2).
Throat disorders.

Jengimiel, Venez.
Paediatric syrup: Ginger (p.1732·3); honey (p.1948·2); aloe vera (p.1588·2).
Throat disorders.

Jengimiel Sabila *Jengimiel, Venez.*
Ginger (p.1732·3); aloe vera (p.1588·2); honey (p.1948·2).
Cough and cold symptoms.

Jenoquine *Julphar, UAE.*
Levofloxacin (p.292·2).
Bacterial infections.

Jenoverine *Boiron, Neth.*
Homoeopathic preparation.

Jenoxifen *Jenapharm, Ger.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Jeny-FMP *TNP, Thai.†.*
21 Tablets, norgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Jephagynon *Jenapharm, Ger.†.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Amenorrhoea.

Jeprolol *Jenapharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; migraine; myocardial infarction.

Jeracin *Nufarindo, Indon.*
Erythromycin (p.269·2).
Acne.

Jeraklin *Darya-Varia, Indon.*
Tretinoin (p.1618·1).
Acne.

Jersin *Andromaco, Mex.*
Aciclovir (p.862·3).
Herpes labialis.

Jertz *Diba, Mex.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Jesscool *Konimex, Indon.*
Thyme (p.2401·1); bitter-orange peel (p.2357·1); cichorium root.
Constipation; cracked lips; scurvy; sore throat.

Jestryl *Ankerpharm, Cz.†; Chauvin ankerpharm, Ger.†.*
Carbachol (p.1879·2).
Adjunct in herpesvirus corneal infections; glaucoma; production of miosis.

Jet Lag Relief *Homeocan, Canad.*
Homoeopathic preparation.

Jetepar
Rotta, Hong Kong; Rotta, Malaysia; Rotta, Singapore.
Betaine glucuronate (p.2265·2); diolamine glucuronate (p.2314·2); nicotinamide ascorbate (p.1957·2).
Biliary-tract disorders; liver disorders.

Pharmalink, Philipp.; Rotta, Philipp.
Betaine glucuronate (p.2265·2); diolamine glucuronate (p.2314·2); nicotinamide (p.1957·3) or nicotinamide ascorbate (p.1957·2).
Liver disorders.

Jetokain *Adeka, Turk.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Jetomisol-P *Ethnor, India.*
Tetramisole (p.156·2); phenolphthalein (p.1762·1).
Worm infections.

Jetosel *Biosel, Turk.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Jets *Freeda, USA.*
Multivitamin preparation with lysine (p.1922·1).

Jetsan *Inter, Venez.†.*
Piperazine adipate (p.152·3).
Worm infections.

JE-Vaccine *Kaketsuken, Thai.*
An inactivated Japanese encephalitis vaccine, Beijing strain (p.2219·3).
Active immunisation.

JE-Vax *Aventis Pasteur, Austral.; Sanofi Pasteur, Canad.; Osaka University, Cz.†; Sanofi Pasteur, USA.*
An inactivated Japanese encephalitis vaccine (p.2219·3).
Active immunisation.

Jevity *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.†; Abbott, Chile; Abbott, Fin.; Abbott, Fr.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott Nutrition, UK; Ross, USA; Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).

Jezil *Alphapharm, Austral.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

JF Sulfur *Galenium, Indon.; Galenium, Malaysia.*
A range of preparations containing precipitated sulfur (p.1614·1).
Acne; fungal skin infections; seborrhoea; skin disorders.

JHP Rodler *McNeil, Ger.*
Mint oil (p.2345·2).
Cold symptoms; gastrointestinal disorders; headache.

Jiffy Medi+ Plus *Brovar, S.Afr.*
Salicylic acid (p.1612·2).
Calluses.

Jinda *Kwizda, Austria; Riemser, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders; premenstrual syndrome.

Jinsoin *Tsumura, Jpn.*
Pinellia tuber; poria sclerotium; pueraria root; platycodon root; citrus unshiu peel; jujube; ginseng; liquorice; immature orange; perilla; ginger; peucedanum root.
Traditional Kampo medicine.

Jitrocel v Nalevovych *Leros, Cz.†.*
Plantaginis (p.2379·1).
Respiratory-tract disorders; skin disorders; wounds.

Jitrocelovy *Megafyt-R, Cz.*
Plantaginis (p.2379·1).
Respiratory-tract disorders; skin disorders; wounds.

J-Max *Jaymac, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

J.Navit *Pharmasant, Thai.*
Vitamin preparation (p.1922·1).

Jobenguaan *CIS, Neth.*
Iodine-131 (p.2054·3) iobenguane.
Radioimaging of malignant neoplasms.

Jod beta *Betapharm, Ger.*
Potassium iodide (p.2169·2).
Goitre; iodine deficiency.

Jod plus *Selenium Pharma, Hung.*
Potassium iodide (p.2169·2).
Iodine deficiency; iodine supplement.

Jodbalance *Merck, Rus.*
Potassium iodide (p.2169·2).
Goitre.

Jodetten *Henning, Ger.; Sanofi Synthelabo, Ger.*
Potassium iodide (p.2169·2).
Iodine-deficiency disorders.

Jodgamma *Worwag, Ger.*
Potassium iodide (p.2169·2).
Iodine-deficiency disorders.

Jodi *Gemi, Pol.*
Povidone-iodine (p.1659·2).
Disinfection of skin and wounds.

Jodid *Merck, Austria; CT, Ger.; Hexal, Ger.; Merck, Ger.; Merck dura, Ger.; Ratiopharm, Ger.; Verla, Ger.; Merck, Hung.; Merck, Philipp.; Merck, Pol.; Merck, Rus.*
Potassium iodide (p.2169·2).
Goitre; iodine-deficiency disorders.

Jodieci *Esoform, Ital.*
⊗ Povidone-iodine (p.1659·2); alcohol (p.1625·2).
Disinfection of skin and superficial wounds; infected skin disorders.

Jodisol *Spofa, Cz.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, and mucous membranes.

Jodix *Orion, Fin.*
Potassium iodide (p.2169·2).
Protection of the thyroid from radio-iodine.

Jodlauge, Tolzer *Jodquellen, Ger.*
Anions: chloride, bromide, iodide, bicarbonate; cations: sodium, magnesium, potassium, calcium.
Circulatory disorders.

Jodo Calcio Vitaminico *Bruschettini, Ital.*
Sodium iodide (p.2169·2); potassium iodide (p.2169·2); rubidium iodide (p.2382·2); calcium gluconate (p.1675·3); ascorbic acid (p.1983·3).
Cataracts.

Jodobac *Beiersdorf, Cz.†; Bode, Ger.†.*
Povidone-iodine (p.1659·2).
Catheter care; disinfection of skin, wounds, and mucous membranes.

Jodocur *Farmacologico Milanese, Ital.†.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, and burns; mouth and throat infections; vaginal hygiene.

Jodoform *Lohmann, Ger.†.*
Iodoform (p.1650·2).
Wounds.

Jodogard *Gedis, Ital.*
Povidone-iodine (p.1659·2).
Skin, hand, and surface disinfection.

Jodomax *Selenium Pharma, Hung.*
Potassium iodate (p.2169·2).
Hyperthyroidism; protection of the thyroid from radio-iodine.

Jodoplex *Streuli, Switz.*
Povidone-iodine (p.1659·2).
Burns; infected skin disorders; skin, hand, and mucous-membrane disinfection; ulcers; wounds.

Jodosan *Brenntag, Norw.*
Iodine (p.2169·2).
Disinfection of skin and wounds.

Jodox *Berlin-Chemie, Pol.†.*
Potassium iodide (p.2169·2).
Iodine-deficiency states.

Jodthyrox *Merck, Austria; Merck, Cz.; Merck, Ger.; Merck, Pol.; Merck, Rus.*
Levothyroxine sodium (p.2171·2); potassium iodide (p.2169·2).
Goitre; hypothyroidism; iodine-deficiency disorders.

Jofen *Lamda (Λαμδα), Gr.†.*
Baclofen (p.1888·1).
Muscle relaxant.

Jogen *General Drugs House, Philipp.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Johanicum *Apomedica, Austria.*
St John's wort (p.422·3).
Depression.

John Plunketts Protective Day Cream *Sunspot, Austral.*
SPF 25: Elastin (p.2286·1); collagen (p.2286·1); vitamin A (p.1971·2); Dermasome SOD; Dermasome E; Megasol Complex; oxybenzone (p.1608·3); octinoxate (p.1608·2).
Emollient; sunscreen.

John Plunketts Sunspot Cream *Sunspot, Austral.*
Salicylic acid (p.1612·2).
Actinic keratosis; hard dry skin.

John Plunketts Super Wrinkle Cream *Sunspot, Austral.*
Active soluble elastin (p.2286·1); active soluble collagen (p.2286·1).
Dry skin; wrinkles.

Johni *Interpharm, Austria.*
St John's wort (p.422·3).
Nervous disorders.

Johnson & Johnson First Aid Ointment *Johnson & Johnson, Canad.†.*
Bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).

Johnson's Antiseptic Powder *Pharmedica, S.Afr.*
Benzethonium chloride (p.1630·1).
Skin disorders.

Johnsons Baby *Johnson & Johnson, Canad.†.*
SPF 15: Meradimate (p.1604·2); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnson's Baby Clear *Johnson & Johnson, Thai.†.*
Ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Johnson's Baby Creme Contra Assaduras *Johnson & Johnson, Braz.*
Barrier cream.
Nappy rash.

Johnson's Baby Double Protection Powder *Johnson & Johnson, Philipp.*
Talc (p.1615·2); magnesium stearate (p.2138·2); zinc oxide (p.1621·2).
Nappy rash.

Johnson's Baby Locao Anti-Mosquito *Johnson & Johnson, Braz.*
Ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Johnson's Baby Nappy Rash Ointment *Pharmedica, S.Afr.*
Zinc oxide (p.1621·2).
Napkin rash; skin irritation.

Johnson's Baby Prickly Heat Powder *Johnson & Johnson, Thai.†.*
Eucalyptus oil (p.2301·2); zinc oxide (p.1621·2); chloroxylenol (p.1640·2).
Heat rash.

Johnson's Baby Sorbolene *Johnson & Johnson, Philipp.*
Soap substitute.

Johnson's Baby Sunblock
Note. This name is used for preparations of different composition.
Johnson & Johnson, USA.
SPF 15: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnson & Johnson, USA.
SPF 30: Oxybenzone (p.1608·3); octinoxate (p.1608·2) octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnsons Clean & Clear Daily Facial Moisturiser *Johnson & Johnson, Austral.†.*
SPF 15: Salicylic acid (p.1612·2); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Moisturiser; sunscreen.

Johnsons Clean & Clear Dual Action Moisturizer *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Johnsons Clean & Clear Facial Cleansing Bar *Johnson & Johnson, Austral.†.*
Triclosan (p.1665·2).
Acne; soap substitute.

Johnsons Clean & Clear Foaming Facial Wash *Johnson & Johnson, Austral.*
Triclosan (p.1665·2).
Acne; soap substitute.

Johnsons Clean & Clear Invisible Blemish Treatment *Johnson & Johnson, Austral.†.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Johnsons Clean & Clear Oil Controlling Toner *Johnson & Johnson, Austral.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Johnsons Clean & Clear Pore Prep *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Johnsons Clean & Clear Skin Balancing Moisturiser *Johnson & Johnson, Austral.*
Salicylic acid (p.1612·2).
Acne.

Johnson's Diaper Rash *Johnson & Johnson, Canad.*
Zinc oxide (p.1621·2).
Nappy rash.

Johnson's Medicated *Johnson & Johnson, Canad.†.*
Zinc oxide (p.1621·2).
Nappy rash.

Johnson's Sabonete Liquido Anti-Septico *Johnson & Johnson, Braz.*
Triclosan (p.1665·2).
Soap substitute.

Joint *Pharmacia, Arg.†.*
Oxaceprol (p.2359·1).
Musculoskeletal and joint disorders.

Joint Action *Lifeplan, UK.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese (p.1922·1).
Musculoskeletal and joint disorders.

Joint Care *Tempo Scan Pacific, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; vitamin E; manganese; magnesium; zinc; selenium (p.1922·1).
Joint disorders.

Joint & Muscle Cream *Brauer, Austral.*
Arnica (p.2260·2); bellis perennis; bryonia (p.2269·3); St John's wort (p.422·3); kalmia latifolia; ledum palustre; rue (p.2382·2); ranunculus bulbosus; rhus toxicodendron (p.2378·3); apis mel.; belladonna; camphora; strontium carb.; symphytum.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Joint & Muscle Oral Spray *Brauer, Austral.*
Homoeopathic preparation.

Joint Support *Eurosup, Ital.*
Glucosamine sulfate (p.2313·2); acetyl glucosamine (p.2313·2); chondroitin sulfate (p.2280·3).
Cartilage disorders.

Jointace
Note. This name is used for preparations of different composition.
Vitabiotics, UK.
Capsules: Glucosamine; omega-3 fish oil; cod-liver oil; vitamins; trace elements (p.1922·1).
Nutritional supplement.

Vitabiotics, UK.
Effervescent tablets: Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; magnesium (p.1922·1).
Nutritional supplement.

Vitabiotics, UK.
Tablets: Collagen (p.2286·1); glucosamine (p.2313·2); chondroitin; vitamins; ginger; minerals (p.1922·1).
Dietary supplement.

Vitabiotics, UK.
Topical gel: Glucosamine (p.2313·2); chondroitin.
Musculoskeletal and joint disorders.

JointCare Max *Seven Seas, UK.*
Glucosamine sulfate (p.2313·2); cod-liver oil (p.1935·2); marine collagen (p.2286·1).
Joint disorders.

Joint-e-Licious *Naturopathica, UK.*
Glucosamine hydrochloride (p.2313·2).
Joint pain.

Jointfit
Note. This name is used for preparations of different composition.
Combiphar, Indon.
Cream: Glucosamine hydrochloride (p.2313·2); glucosamine sulfate (p.2313·2).
Joint disorders.

Combiphar, Indon.
Powder of oral solution: Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); colecalciferol (p.1986·2); collagen (p.2286·1); vitamin C (p.1983·3); calcium lactate gluconate (p.1676·2).
Bone and joint disorders.

Combiphar, Indon.
Topical gel: *N*-Acetyl glucosamine (p.2313·2); aloe vera (p.1588·2); vitamin E (p.1992·2).
Joint disorders.

Jointfit Cream *Combiphar, Indon.*
Glucosamine sulfate (p.2313·2); glucosamine hydrochloride (p.2313·2).
Joint disorders.

Jolessa *Barr, USA.*
84 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Jolivette *Watson, USA.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Jomax *Taurus, Ger.*
Bufexamac (p.28·3).
Skin disorders.

Jonac *German Remedies, India.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Jonctum *CS, Fr.*
Oxaceprol (p.2359·1).
Burns; rheumatic disorders.

Jonosteril *Fresenius Kabi, Ger.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Jonosteril Basic z Glukoza *Fresenius Kabi, Pol.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Jopamiro *Bracco, Austria.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Jo-Sabona *Sabona, Ger.†.*
St John's wort (p.422·3).
Depression.

Josacine *Bayer, Fr.*
Josamycin (p.291·1) or josamycin propionate (p.291·1).
Bacterial infections.

Josalid *Sandoz, Austria.*
Josamycin (p.291·1).
Bacterial infections; toxoplasmosis.

Josamina *Novag, Spain.*
Josamycin propionate (p.291·1).
Bacterial infections.

Josamy *Yamanouchi, Jpn.*
Josamycin propionate (p.291·1).
Bacterial infections.

Josaxin *UCB, Ital.†.*
Josamycin (p.291·1) or josamycin propionate (p.291·1).
Bacterial infections.

Josilvite + Calcium *Pharmacare, Philipp.*
Calcium lactate; vitamins (p.1922·1).
Nutritional supplement.

Josir *Boehringer Ingelheim, Fr.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Josken *Kendrick, Mex.†.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hyperlipidaemias.

Josverm *Josper, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Jouvence *Aroli-Aromes, Fr.*
Calophyllum oil; beeswax.
Dry skin disorders; scars.

Jouvence de l'Abbe Soury
Note. This name is used for preparations of different composition.
Omega, Fr.
Oral solution; tablets: Hamamelis (p.2318·2); calamus (p.2271·3); piscidia (p.2328·1); viburnum (p.2267·1).
Peripheral vascular disorders.

Chefaro Ardeval, Fr.†.
Tea: Red vine leaves (p.2316·3); hamamelis (p.2318·2).
Haemorrhoids; venous insufficiency.

Omega, Fr.
Topical gel: Hamamelis (p.2318·2); viburnum (p.2267·1).
Capillary fragility; venous insufficiency.

Jox *Ivax, Cz.; Ivax, Hung.†; Ivax, Rus.*
Povidone-iodine (p.1659·2); allantoin (p.1588·1).
Mouth and throat disorders.

Joy-Rides *GSK Consumer, UK.*
Hyoscine hydrobromide (p.1734·1).
Motion sickness.

Joysun *YSP, Malaysia.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Infected eye and ear disorders.

Joyzol *Wockhardt, India.*
Olanzapine (p.1012·1).
Bipolar disorder; psychoses.

JP Tone *Jagson, India.*
Ferrous gluconate (p.1939·1); vitamin B substances (p.1975·1).
Anaemias; tonic.

JP Tone-TR *Jagson, India.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1); zinc sulfate (p.1999·2).
Anaemias; tonic.

Jsoskleran *Iso, Ger.*
Homoeopathic preparation.

Jsostoma S *Iso, Ger.*
Homoeopathic preparation.

J-Tan *Jaymac, USA.*
Brompheniramine tannate (p.569·3).
Hypersensitivity reactions.

Juan *Cadila, India.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

JuBronchan C *Jukunda, Ger.†.*
Homoeopathic preparation.

Jucapt *Juta, Ger.; Q-Pharm, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Jucolon *Anpharm, Pol.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

JuCor *Jukunda, Ger.*
Homoeopathic preparation.

Jucurba
Note. This name is used for preparations of different composition.
Strathmann, Ger.
Tablets: Devil's claw root (p.39·1).
Musculoskeletal and joint disorders.

Strathmann, Ger.
Topical emulsion: Capsicum (p.2276·2).
Diabetic neuropathy; musculoskeletal and joint pain; neuralgia.

JuCystan S *Jukunda, Ger.†.*
Homoeopathic preparation.

JuDorm *Jukunda, Ger.†.*
Lupulus (p.2335·2); melissa (p.2339·3); valerian (p.2410·1); St John's wort (p.422·3).
Insomnia; stress.

Juformin *Juta, Ger.; Q-Pharm, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Jufurix *Juta, Ger.; Q-Pharm, Ger.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

JuGrippan S *Jukunda, Ger.*
Homoeopathic preparation.

JuHepan *Jukunda, Ger.†.*
Homoeopathic preparation.

Jukunda Melissen-Krautergeist N *Jukunda, Ger.†.*
Melissa (p.2339·3); melissa oil; rosemary oil; lavender oil; pimentol; cinnamon oil; clove oil (p.1922·1).
Jukunda Melissen-Krautergeist formerly contained melissa, sloe, ginger, melissa oil, rosemary oil, lavender oil, pimentol, cinnamon oil,and clove oil.
Gastrointestinal disorders; nervous disorders.

Julab *Biolab, Hong Kong; Biolab, Thai.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

JuLax *Shreya, India.*
Bisacodyl (p.1710·1).
Constipation.

JuLax-M *Shreya, India†.*
Bisacodyl (p.1710·1).
Constipation.

Juliet *Schering, Austral.†.*
21 Tablets, cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3); 7 tablets, inert.

Juliette *Merck dura, Ger.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne and hirsutism in women; oral contraceptive in women with androgenic symptoms.

Julmentin *Julphar, UAE.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Julphacef *Julphar, UAE.*
Cefradine (p.233·1).
Also known as Eskacef.
Bacterial infections.

Julphamox *Julphar, UAE.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Julphapen *Julphar, UAE.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

JuMenstran *Jukunda, Ger.†.*
Homoeopathic preparation.

Jumex *Ivax, Arg.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Dexxon, Israel; Chiesi, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.; Chinoin, Pol.; Novartis, Port.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.; Sanofi-Aventis, Venez.*
⊗ Selegiline hydrochloride (p.817·1).
Alzheimer's disease; dementia; parkinsonism.

Jumexal *Sanofi Synthelabo, Switz.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Jumexil *Farmalab, Braz.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Jumihaidokuto *Tsumura, Jpn.*
Platycodon root; bupleurum root; cnidium rhizome; poria sclerotium; saposhnikovia root; liquorice; schizonepeta spike; ginger; oak bark; udo rhizome.
Traditional Kampo medicine.

Junamac *Cantassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Junel Fe *Barr, USA.*
21 Tablets, norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
Combined oral contraceptive.

Jungborn
Note. This name is used for preparations of different composition.
Taro, Israel.
Oral granules: Senna (p.1769·2).
Constipation.

Taro, Israel.
Teabags: Senna (p.1769·2); tilia (p.2402·2); caraway (p.2276·3); aniseed (p.2258·2); fennel (p.2302·3); bearberry (p.2263·3); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Constipation.

Jungle *Sagmel, Rus.*
Multivitamin preparation with or without minerals (p.1922·1).

Jungle Formula Insect Repellent *Chefaro, UK.*
Diethyltoluamide (p.2041·1).

Junifen *Boots Healthcare, Belg.; Reckitt Benckiser, Port.; Boots Healthcare, Spain; Boots, Thai.†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Junik *Astellas, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Junior Citrex *Pharmaniaga, Malaysia.*
Vitamin preparations with omega-3 marine triglycerides or lysine (p.1922·1).
Nutritional supplement.

Junior Citrex Cal-Mag-D3 *Pharmaniaga, Malaysia.*
Calcium (p.1675·2); magnesium (p.1678·3); colecalciferol (p.1986·2).

Junior Disprin *Reckitt Benckiser, S.Afr.†.*
Paracetamol (p.108·1).
Fever; pain.

Junior Ideal Quota *Cantassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Junior Kao-C *Torbet Laboratories, UK.*
Calcium carbonate (p.1714·1); light kaolin (p.1738·1).
Diarrhoea.

Junior Strength Cold DM *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Junior Strength Tylenol *McNeil, Hong Kong†.*
Paracetamol (p.108·1).
Fever; pain.

Junior Time C *Vitaplex, Austral.†.*
Vitamin C substances (p.1922·1).

Juniorvit *Pharmadass, UK.*
Multivitamin and mineral preparation (p.1922·1).

Junisana *Riemser, Ger.†.*
Althaea (p.2253·3); thyme (p.2401·1); guaiacum; liquorice (p.1740·3); iron(III)-sucrose-complex (p.1953·2); juniper (p.2328·2); calcium lactate (p.1676·1).
Bronchitis; catarrh; coughs.

Junivite *Boots, Thai.†.*
Multivitamin preparation (p.1922·1).

Junizac *Juta, Ger.; Q-Pharm, Ger.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Juno *ICN, Arg.†.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Juridin *Togal, Switz.*
Aspirin (p.20·3).
Fever; pain.

Jurnista *Janssen-Cilag, Cz.; Janssen-Cilag, Port.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Jurubileno *Ibefar, Braz.†.*
Solanum paniculatum; boldo (p.2267·2); cascara (p.1715·2); cynara (p.2291·2); choline citrate (p.1934·2); sodium glycolate (p.2266·2).
Liver disorders.

Jusline 70/30 *Julphar, UAE.*
⊗ A mixture of isophane insulin (human) 70% and insulin injection (human) 30% (p.443·2).
Diabetes mellitus.

Jusline N *Julphar, UAE.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Jusline R *Julphar, UAE.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Jusprin *Julphar, UAE.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolism prophylaxis.

Just For Kids *Tanning Research, Canad.†.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Justar *Ipsen, Ger.*
⊗ Cicletanine hydrochloride (p.1244·3).
Hypertension.

Justebarin *Juste, Spain†.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Justegas *Schering, Chile†; Juste, Spain.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Gastrointestinal hyperacidity.

Justelax *Juste, Spain.*
Sennosides A and B (p.1769·3).
Bowel evacuation.

Justor *Chiesi, Fr.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Justum *Sandoz, Arg.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Jutabis *Juta, Ger.; Q-Pharm, Ger.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Jutabloc *Juta, Ger.; Q-Pharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; migraine; myocardial infarction.

Jutaclin *Juta, Ger.; Q-Pharm, Ger.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Jutacor comp *Juta, Ger.; Q-Pharm, Ger.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Jutadilat *Juta, Ger.; Q-Pharm, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Jutadol *Juta, Ger.; Q-Pharm, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Jutafenac *Juta, Ger.; Q-Pharm, Ger.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Jutagilin *Juta, Ger.; Q-Pharm, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Jutaglucon *Juta, Ger.†; Q-Pharm, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Jutalar *Juta, Ger.; Q-Pharm, Ger.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Jutalex *Juta, Ger.; Q-Pharm, Ger.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Jutamox *Juta, Ger.; Q-Pharm, Ger.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Jutanorm *Juta, Ger.†; Q-Pharm, Ger.†.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Jutapress *Juta, Ger.; Q-Pharm, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Jutaxan *Juta, Ger.; Q-Pharm, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Juthiac *Juta, Ger.†; Q-Pharm, Ger.†.*
Thioctic acid (p.2400·2).
Diabetic polyneuropathy.

Jutussin *Reckeweg, Ger.*
Homoeopathic preparation.

Jutussin N R8 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Jutussin R9 *Reckeweg, Neth.*
Homoeopathic preparation.

Juvederm *Inamed, USA.*
Hyaluronic acid (p.2320·1).
Facial wrinkles and folds.

Juvela
Note. This name is used for preparations of different composition.
Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.
Food for special diets (p.1922·1).
Gluten-sensitive enteropathies.

Eisai, Jpn.
Tocoferil nicotinate (p.1415·1).
Hyperlipidaemias; hypertension; peripheral circulatory disorders.

Eisai, Malaysia†.
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Juvelon B *Eisai, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Juvelon E+ *Eisai, Philipp.*
Multivitamin preparation (p.1922·1).

Juvelon-C *Eisai, Indon.*
Ascorbic acid (p.1983·3); *dl*-alpha tocoferil acetate (p.1992·3).
Nutritional supplement.

Juvenit *Andromaco, Chile†.*
Grape (p.2316·3).

Juvental *Hennig, Ger.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Juvigor *Roux-Ocefa, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Juviral *Juta, Ger.†; Q-Pharm, Ger.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Juvit Hasco-Lek, Pol.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Juvit D_3 Hasco-Lek, Pol.
Colecalciferol (p.1986·2).
Osteomalacia; rickets; vitamin D deficiency.

Juvit Multi Hasco-Lek, Pol.
Vitamin preparation (p.1922·1).

Juvitan Elea, Arg.†.
Ginsenosides (p.2312·1).
Tonic.

JuViton Jukunda, Ger.†.
Crataegus (p.2289·1); rosemary (p.2381·2); St John's wort (p.422·3); primrose flower (p.2372·2); ginger (p.1732·3); primula veris; kola; cactus; kalmia; lilium tigrinum; ambra; aurum colloidale; lycopus virg.
Cardiovascular disorders.

Juzen-taiho-to Tsumura, Jpn.
Astragalus root; cinnamon bark; rehmannia root; peony root; cnidium rhizome; atractylodes lancea rhizome; Japanese angelica root; ginseng; poria sclerotium; liquorice.
Traditional Kampo medicine.

K1 Sivaderm, Arg.
Phytomenadione (p.1995·3).

K-10 GSK, Canad.
Potassium chloride (p.1684·3).
Potassium depletion.

K-50 Valeant, Mex.
Menadione sodium bisulfite (p.1995·3).
Haemorrhagic disorders.

K + 8 Alra, USA†.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

K + 10 Edwards, USA.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

K + Care Alra, USA†.
Potassium bicarbonate (p.1673·1).
Hypokalaemia; potassium depletion.

K5 Hair Tincture German Remedies, India†.
Benzyl nicotinate (p.28·1); vitamin K (p.1995·2); salicylic acid (p.1612·2).
Scalp disorders.

K 1000 T Hanosan, Ger.†.
Homoeopathic preparation.

K Thrombin Fawns & McAllan, Austral.†.
Menadione sodium bisulfite (p.1995·3).
Prothrombin deficiency.

K-A Plus Diamond, Philipp.
Vitamins; minerals; ginseng (p.2312·1); deanol; inositol; choline chloride; linoleic acid; lysine hydrochloride (p.1922·1).
Tonic.

Kaarmepakkaus Lyocentre, Fin.
⊗ Dexamethasone (p.1526·1).
Bee and wasp stings; snake bites.

Kaban Asche, Ger.
⊗ Clocortolone pivalate (p.1523·1); clocortolone caproate (p.1523·1).
Skin disorders.

Kabanimat Asche, Ger.
⊗ Clocortolone pivalate (p.1523·1); clocortolone caproate (p.1523·1).
Skin disorders.

Kabikinase Pharmacia, Braz.†; Pharmacia, Cz.†; Pharmacia Upjohn, Israel; Pharmacia, Norw.†; Pharmacia, Spain†.
Streptokinase (p.1402·3).
Thromboembolic disorders.

KabiMix Fresenius Kabi, Austria; Fresenius Kabi, Fr.†; Pharmacia Upjohn, Ital.†; Fresenius Kabi, Neth.†; Fresenius Kabi, Norw.†; Fresenius Kabi, Port.; Fresenius Kabi, Spain†; Fresenius Kabi, Swed.†.
Amino-acid, carbohydrate, and lipid (from soya oil (p.1965·3)) infusion with or without electrolytes (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Kabiven Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Pharmaco, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK.
Amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusion with or without electrolytes (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Kabizol Fresenius Kabi, Chile.
Metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Kacerutin Purissimus, Arg.
Vitamin K (p.1995·2); rutoside (p.2305·1); vitamin C (p.1983·3).
Capillary haemorrhage.

KA-Cilone SM, Thai.
⊗ Triamcinolone acetonide (p.1544·3); kanamycin sulfate (p.291·2).
Infected skin disorders.

Kacinth-A Intramed, S.Afr.
Amikacin sulfate (p.200·3).
Bacterial infections.

Kadaleks Eczacibasi-Baxter, Turk.
Potassium chloride (p.1684·3) in glucose.
Hypokalaemia.

Kadalex Diaco, Ital.
Potassium chloride (p.1684·3).
Hypokalaemia.

KadeFungin Kade, Ger.
Clotrimazole (p.530·1).
Fungal and bacterial infections of the vagina.

Kadeks Eczacibasi-Baxter, Turk.
Potassium chloride (p.1684·3); sodium chloride (p.1686·1) in glucose.
Carbohydrate source; fluid and electrolyte disorders.

Kadian Abbott, Canad.; Alpharma, USA.
⊗ Morphine sulfate (p.86·3).
Pain.

Kadiflam Metiska, Indon.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Kadiur GiEnne, Ital.
⊗ Potassium canrenoate (p.1374·1); butizide (p.1238·1).
Hyperaldosteronism.

Kadol Teofarma, Ital.
Phenylbutazone (p.117·1).
Musculoskeletal and soft-tissue disorders; skin irritation.

Kadolax Hua, Thai.
Bisacodyl (p.1710·1).
Constipation.

Kadolin Dermadolin, Turk.
Cade oil (p.1616·1); salicylic acid (p.1612·2).
Scalp disorders.

Kaergona Hidrosoluble Ern, Spain.
Menadione (p.1995·2).
Hypoprothrombinaemia.

Kafa Vifor, Switz.
Paracetamol (p.108·1).
Formerly contained propyphenazone, paracetamol, and caffeine.
Fever; pain.

Kafa plus cafeine Vifor, Switz.
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Kafalgin Sanli, Turk.
Dipyrone (p.49·2).
Fever; pain.

Kafen Investigacion, Mex.†.
Caffeine (p.1116·3).
Fatigue.

Kafenac Almirall, Ital.
Aceclofenac (p.14·3).
Musculoskeletal and joint disorders; pain.

Kaflam Kalbe, Indon.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Kafran Solfran, Mex.
Amikacin (p.200·2).
Bacterial infections.

Kafsir Sandoz, Indon.
⊗ Ammonium chloride (p.1551·3); paracetamol (p.108·1); ephedrine hydrochloride (p.1558·2); liquorice (p.1740·3); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Cough; fever; headache; nasal congestion.

Kaftrim Kimia, Indon.
Co-trimoxazole (p.258·1).
Bacterial infections.

Kaidor Krugher, Ital.
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Kailasa Duncan, Arg.
Clarithromycin (p.248·2).
Bacterial infections.

Kaimil Lisapharma, Ital.
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Kainever Seber, Port.
Estazolam (p.995·1).
Insomnia; premedication.

Kaion Retard Andromaco, Chile.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kaizem Wockhardt, India.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Kajos AstraZeneca, Norw.; AstraZeneca, Swed.
Potassium citrate (p.1673·2).
Hypokalaemia; potassium supplement.

Kakkon-to Tsumura, Jpn.
Pueraria root; jujube; ephedra herb; liquorice; cinnamon bark; peony root; ginger.
Traditional Kampo medicine.

Kakkontokasenkyushin'i Tsumura, Jpn.
Pueraria root; jujube; ephedra; liquorice; cinnamon; peony root; magnolia flowe; cnidium rhizome; ginger.
Traditional Kampo medicine.

Kala
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Freeda, USA.
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

Kalamin Ilsan, Turk.
Oxolamine (p.1567·1).
Coughs.

Kalaz D3 Savio, Ital.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Kalbamin Kalbe, Indon.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Kalbeten Sam-On, Israel.
Bismuth salicylate (p.1711·1).
Abdominal cramps; diarrhoea; dyspepsia; flatulence; nausea.

Kal-Cee Hua, Thai.
Vitamins; calcium carbonate (p.1922·1).

Kalcef Kalbe, Indon.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Kalcidon Verman, Fin.; Abigo, Swed.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; hyperphosphataemia; osteoporosis.

Kalcikidz Diepharmex, Fr.†.
Calcium phosphate (p.1676·2).
Calcium supplement.

Kalcinol-N Kalbe, Indon.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Kalcinova KRKA, Rus.
Vitamin and mineral preparation (p.1922·1).

Kalcipos Recip, Fin.; Recip, Swed.
Calcium carbonate (p.1714·1).
Calcium deficiency; hyperphosphataemia; osteoporosis.

Kalcipos-D Recip, Fin.; Recip, Swed.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Kalcitena ACO, Swed.
Calcium carbonate (p.1714·1).
Calcium deficiency; hyperphosphataemia; osteoporosis.

Kalcytriol Ifarm, Pol.
Calcitriol (p.1986·2).
Hypoparathyroidism; osteomalacia; renal osteodystrophy; rickets.

Kaldil Diet Higate, Arg.
Sodium cyclamate (p.1936·3).
Sugar substitute.

Kaldor Finn Vita, Chile†.
Opuntia streptacantha lemaire.
Dietary fibre supplement.

Kaldyum Egis, Cz.; EGIS, Hung.; Egis, Pol.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium deficiency.

Kaleorid Leo, Denm.; Leo, Fr.; Leo, Norw.; Leo, Swed.†.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Kaletra Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Abbott, USA; Abbott, Venez.
Lopinavir (p.896·3); ritonavir (p.905·1).
HIV infection.

Kalferon Kalbe, Indon.
Interferon alfa-2b (p.885·1).
Chronic hepatitis.

Kal-Forte Hua, Thai.
Calcium carbonate (p.1714·1); calcium gluconate (p.1675·3); calcium lactate (p.1676·1).
Calcium deficiency.

Kalfoxim Kalbe, Indon.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Kalgaron Rafa, Israel.
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Kalgut Tanabe, Jpn.
Denopamine (p.1256·3).
Heart failure.

Kali Mag Vitaplex, Austral.†.
Potassium amino acid chelate (p.1685·1); magnesium amino acid chelate (p.1680·1).
Potassium and magnesium supplement.

Kali Phos Complexe no 100 Lehning, Fr.
Homoeopathic preparation.

Kaliale Effik, Fr.
Cyproterone acetate (p.2088·2).
Hirsutism in females; prostatic cancer.

Kalibex Konimex, Indon.
Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); chlorphenamine maleate (p.571·3).
Allergic disorders; cough; nasal congestion.

Kalicet Rhone-Poulenc Aventis, Ital.†.
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Kalicor Lek, Cz.
Piracetam (p.368·2).
Cerebral disorders; dementia; memory function impairment; vertigo.

Kalidren Fako, Turk.
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Kaliglutol Streuli, Switz.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kaliject Pharmadica, Thai.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kalijev Lek, Cz.
Potassium iodide (p.2169·2).
Prevention of contamination with radioactive iodine.

Kalima Theraskin, Braz.
Soap: Dry skin disorders.

Kalimat Lek, Pol.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalimate Nikken, Jpn; Nikken, Malaysia; DeGa, Philipp.; Nikken, Thai.
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Kalinor Desma, Ger.; Abbott, Turk.
Potassium citrate (p.1673·2); potassium bicarbonate (p.1673·1).
Hyperchloraemic acidosis; potassium deficiency, particularly in association with metabolic acidosis; urinary alkalinisation; urinary-tract infections.

Kalinorm Leiras, Fin.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Kalinor-retard P Desma, Ger.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalinox Air Liquide, Fr.
Nitrous oxide (p.1789·3); oxygen (p.1690·2).
Analgesia in anaesthesia and painful procedures.

Kaliolite Merck, Mex.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kalioral Fresenius Kabi, Austria.
Anhydrous potassium citrate (p.1673·2); potassium bicarbonate (p.1673·1); citric acid (p.2284·1).
Oedema; potassium deficiency.

Kalipoz GSK, Pol.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalisol Orion, Fin.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kalisteril Orion, Fin.†.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kali-Sterop Sterop, Belg.†.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kalitabs Leo, Swed.
Potassium chloride (p.1684·3).
Potassium deficiency; potassium supplement.

Kalitake Dipa, Indon.
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Kalitrans Stada, Ger.
Potassium bicarbonate (p.1673·1).
Potassium deficiency.

Kalium
Apogepha, Ger.†.
Potassium adipate (p.1685·1).
Potassium deficiency.

Verla, Ger.
Potassium citrate (p.1673·2).
Hypokalaemia.

Vifor, Hong Kong†; AstraZeneca, Philipp.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium deficiency; potassium supplement.

Kalium Duretter Hassle, Swed.†.
Potassium chloride (p.1684·3).
Potassium deficiency; potassium supplement.

Kalium Durettes AstraZeneca, Belg.†; AstraZeneca, Neth.†.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Kalium Durules Biogal-Teva, Hung.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalium Phos Comp Weleda, S.Afr.
Homoeopathic preparation.

Kalium Retard Nycomed, Swed.
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Kalium-Can Ratiopharm, Ger.
⊗ Potassium canrenoate (p.1374·1).
Ascites; hyperaldosteronism; oedema.

Kalium-Duriles AstraZeneca, Ger.†.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalium-Magnesium Apogepha, Ger.†.
Potassium adipate (p.1685·1); magnesium adipate (p.1680·1).
Potassium and magnesium deficiency.

Kalium-Magnesium-Asparaginat Berlin-Chemie, Ger.†.
Potassium hydroxide (p.2371·3); magnesium oxide (p.1744·1); -aspartic acid; xylitol (p.1998·2).
Cardiac disorders.

Kalium-R Valeant, Hung.
Potassium chloride (p.1684·3).
Potassium deficiency.

Kalixocin Alphapharm, Austral.
Clarithromycin (p.248·2).
Bacterial infections.

Kalkurenal Darya-Varia, Indon.; Muller Goppingen, Indon.
Berberis; rubia tinctorum; saxifraga granulata; lithium hydrochloride; magnesium borocitrate; sodium phosphate (p.1682·3).
Renal calculi.

Kalkurenal Goldrute Muller Goppingen, Ger.
Solidago virgaurea (p.2391·1).
Renal calculi.

Kalloplast DM, Braz.†.
Salicylic acid (p.1612·2); zinc chloride (p.1999·1).
Keratinisation disorders.

Kalma
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
Alprazolam (p.960·1).
Anxiety; panic disorders.

Stada, Austria; Stada, Ger.
Tryptophan (p.427·1).
Depression; sleep disorders.

Kalmafta Silesia, Chile.
Benzocaine (p.1854·1).
Local anaesthesia.

Kalmalin Bago, Arg.
Lorazepam (p.1004·1).
Anxiety.

Kalmaline-AC Coup, Gr.
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Kalm-B Cantassium Co., UK.
Multivitamin and mineral preparation (p.1922·1).

Kalmeco Kalbe, Indon.
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Kalmethasone Kalbe, Indon.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Kalmicetine Kalbe, Indon.
Chloramphenicol (p.239·3).
Bacterial infections.

Kalmiren Aegis, Hong Kong.
Buspirone hydrochloride (p.965·3).
Anxiety.

Kalmocaps Medix, Mex.†.
Chlordiazepoxide (p.968·1).
Skeletal muscle spasm.

Kalmol Extra Specifar (Σπεσιφαρ), Gr.
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Kalmopyrin Gedeon Richter, Hung.
Aspirin (p.20·3).
Calcium carbonate (p.1714·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Kalmosan Kurtsan, Turk.
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2); camphor (p.2273·2); glycerol (p.2314·2).
Pruritus.

Kalmoxillin Kalbe, Indon.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Kalms Lane, Pol.; Lane, UK.
Lupulus (p.2335·2); valerian (p.2410·1); gentian (p.2310·3).
Menopausal disorders; nervous disorders; sleep disorders; stresses and strains.

Kalms Sleep Lane, UK.
Passion flower (p.2363·2); lupulus (p.2335·2); valerian (p.2410·1); vervain (p.2413·3); wild lettuce (p.2415·2).
Insomnia.

Kalnex Kalbe, Indon.
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Kalnormin ICN, Cz.
Potassium chloride (p.1684·3).
Hypokalaemia.

Kaloba Nycomed, Braz.; Schwabe, UK; Roemmers, Venez.
Pelargonium sidoides (p.2311·1).
Respiratory-tract disorders; upper respiratory-tract infections.

Kalopsis Roux-Ocefa, Arg.
⊗ Ephedrine (p.1558·1); phenazone (p.116·1).
Eye disorders.

Kalopsis Lagrimas Roux-Ocefa, Arg.
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Kalostop Hexal, Braz.†.
Salicylic acid (p.1612·2); lactic acid (p.2329·3); acetic acid (p.2244·2).
Keratinisation disorders.

Kalovowen Weber & Weber, Ger.†.
Homoeopathic preparation.

Kalpanax Kalbe, Indon.
Salicylic acid (p.1612·2); benzoic acid (p.1630·2); povidone-iodine (p.1659·2).
Fungal skin infections.

Kalpastic BDH, India.
Rutoside (p.2305·1); vitamin C (p.1983·3); acetomenaphthone (p.1995·2); calcium gluconate (p.1675·3).
Capillary fragility.

Kalpicilin Hexpharm, Indon.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Kalpiren Medochemie, Rus.
Enalapril maleate (p.1276·1).

Kalpress Lacer, Spain.
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Kalpress Plus Lacer, Spain.
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Kalsifluor Ilsan, Turk.
Sodium fluoride (p.1962·2); calcium phosphate (p.1676·2); calcium gluconate (p.1675·3); ergocalciferol (p.1987·1).

Kalsis SM, Venez.
Calcium carbonate (p.1714·1); magnesium chloride (p.1679·1); vitamin C (p.1983·3); vitamin E (p.1992·2); sodium selenite (p.1961·1).
Osteoporosis.

Kalspare DHP, UK.
⊗ Chlortalidone (p.1243·3); triamterene (p.1417·2).
Ascites; hypertension; oedema.

Kalten AstraZeneca, Belg.†; Teofarma, Spain; AstraZeneca, Switz.; BPC, UK.
⊗ Atenolol (p.1217·3); amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Kalter Phoenix, Arg.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Kaltiazem Fabra, Arg.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Kalticol Kalbe, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Kaltin MF Pharmacia, India.
Metronidazole (p.837·1); furazolidone (p.834·3).
Gastrointestinal infections.

Kaltocarb Convatec, Israel.
Calcium alginate (p.1058·1); sodium alginate (p.2141·1); activated charcoal (p.1435·2).
Malodorous wounds.

Kaltostat
Convatec, Arg.; Convatec, UK.
Calcium alginate (p.1058·1).
Absorbable haemostatic wound dressing.

Convatec, Austral.†; Convatec, Canad.; Convatec, Irl.; Convatec, Israel; Convatec, Ital.; Convatec, Port.; BMS, S.Afr.
Calcium alginate (p.1058·1); sodium alginate (p.2141·1).
Haemostatic wound dressing; skin ulceration; wounds.

Kaltrim Offenbach, Mex.
Co-trimoxazole (p.258·1).
Bacterial infections.

Kaltrofen Kalbe, Indon.
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Kaluril
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
⊗ Amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Teva, Israel.
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Kalxetin Kalbe, Indon.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Kalyamon B12 Janssen-Cilag, Braz.
Minerals; vitamin B ; vitamin D (p.1922·1).

Kalymin Temmler, Ger.; Pliva, Rus.
Pyridostigmine bromide (p.633·3).
Antimuscarinic toxicity; bladder atony; gastrointestinal atony; myasthenia gravis; reversal of competitive neuromuscular blockade; smooth muscle atony.

Kalzana German Remedies, India.
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium supplement.

Kam Rho-D Teva Tuteur, Arg.
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Kamacaine Kamada, Israel.
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Kamadol Kimia, Indon.
Tramadol hydrochloride (p.130·3).
Pain.

Kamaflam Kimia, Indon.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Kamagel KRKA, Pol.
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3).
Skin irritation; soft-tissue injury.

Kaman Savio, Ital.
Paromomycin sulfate (p.843·3).
Gastro-enteritis; gastrointestinal sterilisation; hepatic coma; intestinal amoebiasis.

Kamapharm Kamada, Hong Kong.
⊗ Albumin (p.1052·1).
Burns; erythroblastosis fetalis; hepatic cirrhosis; hyperbilirubinaemia; hypoproteinaemia; nephrosis; shock.

Kambakutaisoto Tsumura, Jpn.
Jujube; liquorice; common wheat seed.
Traditional Kampo medicine.

Kamelyn Krugher, Ital.
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Kamfeine Wolfs, Belg.†.
⊗ Sodium camsilate (p.2388·3); ephedrine hydrochloride (p.1558·2); lobelia (p.2157·2); sodium benzoate (p.1630·2).
Convalescence after influenza; dyspnoea.

Kamfolin Munir, Turk.
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Kamicin Christo, Hong Kong.
Clotrimazole (p.530·1).
Vaginitis.

Kamikihito Tsumura, Jpn.
Astralagus root; bupleurum root; jujube seed; atractylodes lancea rhizome; ginseng; poria sclerotium; polygala root; gardenia fruit; jujube; japanese angelica root; liquorice; ginger; saussurea root; longan fruit.
Traditional Kampo medicine.

Kamil Blue
Note. This name is used for preparations of different composition.
Fischer, Israel.
Liquid soap: Azulene (p.2262·3); chamomile (p.2279·3).
Skin cleansing; skin disorders.

Fischer, Israel.
Lotion: Azulene (p.2262·3); glycerol (p.2314·2); silicone (p.2032·1); panthenol (p.2362·1).
Barrier preparation; skin disorders.

Fischer, Israel.
Ointment: Chamomile (p.2279·3); panthenol (p.2362·1); wool fat (p.2033·2); white soft paraffin (p.2031·2); silicone (p.2032·1); zinc oxide (p.1621·2).
Barrier preparation; skin disorders.

Fischer, Israel.
Topical oil: Azulene (p.2262·3).
Barrier preparation; skin disorders.

Kamillan Plus Wernigerode, Cz.†; Wernigerode, Ger.†.
Chamomile (p.2279·3); achillea (p.2245·2).
Burns; gastrointestinal disorders; inflammation of mucous membranes; ulcers; wounds.

Kamillan supra Wernigerode, Ger.
Chamomile (p.2279·3).
Gastrointestinal disorders; inflammation and infections of the skin and mucous membranes; respiratory-tract disorders.

Kamille Madaus, Ger.†.
Chamomile (p.2279·3).
Gastrointestinal disorders; skin and mucous membrane disorders.

Kamille N Spitzner, Ger.†.
Chamomile (p.2279·3).
Gastrointestinal disorders; inflammation of skin and mucous membranes; upper respiratory-tract inflammation.

Kamillen Robugen, Ger.†; Biotecnoquimica, Venez.
Chamomile (p.2279·3).
Skin disorders.

Kamillen-Bad Iromedica, Switz.†.
Chamomile flowers (p.2279·3).
Skin disorders.

Kamillenbad Intradermi Eberth, Ger.
Chamomile oil (p.2279·3).
Anogenital disorders; bath additive; skin and mucous membrane disorders.

Kamillen-Bad N Ritsert Ritsert, Ger.
Chamomile oil (p.2279·3).
Anorectal disorders; bath additive; inflammation of skin and mucous membranes.

Kamillen-Bad-Robugen Robugen, Ger.†.
Chamomile (p.2279·3).
Anogenital disorders; bath additive; skin and mucous membrane disorders; wounds.

Kamillencreme N Ratiopharm, Ger.†.
Chamomile (p.2279·3).
Skin disorders; wounds.

Kamillenextract Steierl, Ger.†.
Chamomile (p.2279·3).
Anogenital disorders; gastrointestinal disorders; respiratory-tract disorders; skin and mucous membrane disorders.

Kamillen-Heel Peithner, Austria†.
Homoeopathic preparation.

Kamillex Streuli, Switz.
Chamomile (p.2279·3).
Burns; mouth and throat inflammation; skin disorders; wounds.

Kamillin Robugen, Ger.
Chamomile (p.2279·3).
Gastrointestinal disorders; skin and mucous membrane disorders.

Kamillin Medipharm Iromedica, Switz.
Chamomile (p.2279·3).
Inflammation of skin and mucous membranes.

Kamilloderm Serum-Werk Bernburg, Ger.†.
Chamomile (p.2279·3).
Burns; skin irritation; wounds.

Kamillofluid Amino, Switz.
Chamomile (p.2279·3).
Mouth and throat disorders; skin disorders.

Kamillopur Steierl, Ger.
Chamomile (p.2279·3).
Gastrointestinal disorders; respiratory-tract disorders; skin and mucous membrane disorders.

Kamillosan
Note. This name is used for preparations of different composition.
Viatris, Belg.; Ache, Braz.; Grunenthal, Chile†; Viatris, Ger.; German Remedies, India; Asta Medica, Indon.; Goldshield, Irl.; Sanfer, Mex.; CSL, NZ†; Pharmafrica, S.Afr.; Goldshield, UK.
Chamomile (p.2279·3).
Burns; chapped skin; cracked feet; digestive disorders; gastrointestinal spasm; inflammation of mucous membranes; irritable bowel disorders; mouth and throat disorders; nappy rash; respiratory-tract disorders; skin irritation; sore nipples; vulvovaginal irritation; wounds.

Asta Medica, Hong Kong†; Transfarma, Thai.†.
Chamazulene (p.2279·3); levomenol (p.2333·3).
Burns; minor cuts and abrasions; mucous membrane disorders; nappy rash; skin irritation.

Zuoz, Venez.
Chamomile (p.2279·3); levomenol (p.2333·3); essential oils.
Inflammatory skin disorders.

Viatris, Cz.
Buccal spray: Chamomile (p.2279·3).
Formerly contained chamomile, peppermint oil, and anise oil.
Mouth and throat disorders.

Meda, Switz.
Buccal spray: Chamomile (p.2279·3); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth and throat disorders.

Meda, Switz.
Cream; liquid; ointment: Chamomile (p.2279·3).
Mouth and throat disorders; skin disorders.

Viatris, Austria.
Drops; ointment: Chamomile oil (p.2279·3).
Anal disorders; gastrointestinal disorders; mouth and throat disorders; respiratory-tract disorders; skin disorders; vulvovaginal disorders.

Viatris, Austria.
Mouth spray: Chamomile oil (p.2279·3); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth and throat disorders.

Viatris, Cz.
Ointment: Chamomile (p.2279·3).
Burns; inflammation of mucous membranes; skin disorders; ulcers.

Kamillosan M
Note. This name is used for preparations of different composition.
Transfarma, Philipp.
Anise oil (p.2258·2); bergamot oil (p.2265·1); chamomile (p.2279·3); cineole (p.2282·3); methyl salicylate (p.85·3); peppermint oil (p.1761·2); pine-needle oil (p.2368·2); sage oil (p.2382·3).
Mouth and throat disorders.

Meda, Thai.; Pharmalink, Thai.
Chamomile (p.2279·3); chamazulene (p.2279·3); essential oil.
Mouth and throat disorders.

Kamillosan Mundspray Viatris, Ger.
Chamomile (p.2279·3); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth and throat disorders.

Kamillosan Ocean Viatris, Fr.; Viatris, Ital.
Sea water (p.1686·1); chamomile (p.2279·3).
Nasal dryness; nasal hygiene.

Kamillosan-N German Remedies, India.
Chamomile (p.2279·3); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth and throat disorders.

Kamiloderm Remexa, Mex.
Chamomile (p.2279·3); vitamin A (p.1971·2).
Skin disorders.

Kamilon Offenbach, Mex.
Nalidixic acid (p.303·3).
Urinary-tract disorders.

Kamilosan Meda, Port.
Chamomile (p.2279·3).
Burns; gastrointestinal disorders; haemorrhoids; nasal congestion; oropharyngeal hygiene; skin disorders; vaginal hygiene; varicose veins; wounds.

Kamilotract Tamar, Israel.
Chamomile (p.2279·3); sage (p.2382·3).
Mucous membrane inflammation.

Kamin Bosch, Philipp.
Amikacin sulfate (p.200·3).
Bacterial infections.

Kamina *Hikma, Port.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Kamiren *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Kami-shoyo-san *Tsumura, Jpn.*
Bupleurum root; peony root; atractylodes lancea rhizome; angelica acutiloba root; poria sclerotium; gardenia fruit; moutan bark; liquorice; ginger; mentha herb.
Traditional Kampo medicine.

Kamistad
Note. This name is used for preparations of different composition.
Stada, Cz.; Stada, Rus.
Lidocaine hydrochloride (p.1862·3); chamomile (p.2279·3).
Inflammatory disorders of the mouth.
Stada, Hong Kong; Stada, Singapore; Stada, Thai.
Lidocaine hydrochloride (p.1862·3); thymol (p.1664·3); chamomile (p.2279·3).
Inflammatory disorders of the mouth.

Kamistad Gel N *Stada, Thai.*
Lidocaine hydrochloride (p.1862·3); chamomile (p.2279·3).
Inflammatory disorders of the mouth.

Kamistad N *Stada, Ger.*
Lidocaine hydrochloride (p.1862·3); chamomile (p.2279·3).
Mouth disorders.

Kamol *Whitehall, Fr.†.*
Capsicum oleoresin (p.2276·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); camphor (p.2273·2); methyl salicylate (p.85·3).
Muscle and joint pain.

Kamoxin *Chew, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Kamrab *Landsteiner, Mex.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

KamRho-D *Kamada, Israel.*
An anti-D immunoglobulin (p.2204·2).
Immune thrombocytopenic purpura; prevention of rhesus sensitisation.

Kamu Jay *Jamieson, Canad.†.*
Ascorbic acid (p.1983·3).
Vitamin supplement.

Kana *Maver, Mex.*
Amikacin (p.200·2).
Bacterial infections.

Kanabiotic *Bernofarm, Indon.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kanacil *Collins, Mex.†.*
Kanamycin (p.291·3).
Bacterial infections.

Kanacitrin *Rider, Chile.*
Potassium citrate (p.1673·2); citric acid monohydrate (p.2284·1).
Metabolic acidosis; urinary alkalinisation.

Kanacyl
Note. This name is used for preparations of different composition.
Edol, Port.†.
Bekanamycin sulfate (p.211·3).
Bacterial eye infections.
Leti, Venez.†.
Kanamycin (p.291·3).
Bacterial infections.

Kanadrex *Collins, Mex.†.*
Kanamycin (p.291·3).
Bacterial infections.

Kanafosal *Medical, Spain.*
⊗ Ephedrine hydrochloride (p.1558·2); kanamycin sulfate (p.291·2); naphazoline hydrochloride (p.1565·2); procaine hydrochloride (p.1869·1); sulfanilamide sodium mesilate (p.343·1).
Nasal congestion and infection.

Kanafosal Predni *Medical, Spain.*
⊗ Ephedrine hydrochloride (p.1558·2); kanamycin sulfate (p.291·2); naphazoline hydrochloride (p.1565·2); prednisone (p.1542·3); procaine hydrochloride (p.1869·1); sulfanilamide sodium mesilate (p.343·1).
Nasal congestion and infection.

Kanakion *Roche, Braz.; Roche, Port.*
Phytomenadione (p.1995·3).
Haemorrhagic disorders; vitamin K deficiency.

Kanamytrex *Alcon, Ger.*
Kanamycin sulfate (p.291·2).
Bacterial eye infections.

Kanapat *Parggon, Mex.*
Kanamycin (p.291·3).
Bacterial infections.

Kanapomada *Medical, Spain.*
⊗ Kanamycin sulfate (p.291·2); prednisolone (p.1540·3); trypsin (p.2405·3); urea (p.1620·2); lidocaine (p.1862·3).
Infected skin disorders.

Kanarco *Armoxindo, Indon.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kanasone *Leti, Venez.†.*
⊗ Kanamycin (p.291·3); dexamethasone (p.1526·1).
Infected eye disorders.

Kana-Stulln *Stulln, Ger.*
Kanamycin sulfate (p.291·2).
Bacterial eye infections.

Kanavit *BB, Cz.; Zentiva, Cz.; Medphano, Ger.*
Phytomenadione (p.1995·3).
Haemorrhagic disorders; vitamin K deficiency.

Kanazima *Kinder, Braz.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Kanbine *Mayne, Spain.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Kancin
Alembic, India.
Kanamycin (p.291·3).
Bacterial infections.
Atlantic, Malaysia; Atlantic, Singapore†; Atlantic, Thai.
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kancin-Gap *Gap, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Kancin-L *Atlantic, Singapore.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kandicin *Bernabo, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Kandistat *Kinder, Braz.*
Nystatin (p.543·2).
Fungal infections.

Kandistatin *Metiska, Indon.*
Nystatin (p.543·2).
Candidiasis.

Kandizol *Nobel, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Kandril *Kinder, Braz.*
Sodium citrate (p.1673·3); ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2).

Kanegan *Pharmasant, Thai.*
Pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Irritable bowel syndrome.

Kaneuron *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Phenobarbital (p.492·2).
Epilepsy.

Kanezin *Swiss Pharm, Thai.*
Clotrimazole (p.530·1).
Trichomoniasis; vaginal candidiasis.

Kangen *General Drugs, Thai.*
Kanamycin acid sulfate (p.291·2).
Bacterial infections.

Kanin *LBS, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastro-duodenitis; nausea and vomiting; peptic ulcer; smooth muscle spasm.

Kank-A
Note. This name is used for preparations of different composition.
Blistex, Canad.
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Canker sores; mouth irritation.
Blistex, Israel.
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1); benzoin tincture (p.2394·2).
Mouth irritation.
Blistex, USA.
Benzocaine (p.1854·1); compound benzoin tincture.
Mouth disorders.

Kank-Eze *Rider, Chile.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth disorders.

Kan-Mycin *Olan-Kemed, Thai.†.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kanolone *LBS, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Musculoskeletal and joint disorders; skin and mouth disorders.

Kan-Ophtal *Winzer, Ger.*
Kanamycin sulfate (p.291·2).
Bacterial eye infections.

Kanormal *German Remedies, India.*
Sterculia (p.1772·1); frangula bark (p.1732·2).
Constipation.

Kanoxin *Actavis, Indon.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kanrenol *Abbott, Ital.*
⊗ Potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypertension.

Kansilak *Kansuk, Turk.*
Sorbitol (p.1965·1); Tween 80 (p.1919·2); sodium citrate (p.1673·3); glycerol (p.2314·2).

Kantol *Quim-Far, Venez.†.*
Sodium benzoate (p.1630·2); ammonium acetate (p.1551·2).
Cough.

Kantrenol *Medinova (Μεντινοβα), Gr.*
Acetylcysteine (p.1548·2).
Mucolytic.

Kantrex
BMS, Mex.
Kanamycin (p.291·3).
Bacterial infections.
Bristol-Myers, Spain†; Apothecon, USA; BMS, Venez.
Kanamycin sulfate (p.291·2).
Bacterial infections.

Kantrexil *Opus, S.Afr.*
Kanamycin sulfate (p.291·2); dimevamide (p.2294·2); pectin (p.2145·2); bismuth subcarbonate (p.1711·1); activated attapulgite (p.1709·1).
Gastro-enteritis.

Kanzuk *Kansuk, Turk.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Mouth and throat disorders.

Kao *Covan, S.Afr.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaobrol *GSK Sante, Fr.†.*
Magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); heavy kaolin (p.1738·1).
Gastrointestinal disorders.

Kaodene *Sovereign, UK†.*
Codeine phosphate (p.37·2); light kaolin (p.1738·1).
Diarrhoea.

Kaodene Non-Narcotic *Pfeiffer, USA.*
Kaolin (p.1738·1); pectin (p.2145·2); bismuth salicylate (p.1711·1).
Diarrhoea.

Kaodin *Nordin, Mex.*
Furazolidone (p.834·3).
Diarrhoea.

Kaogel *Sedabel, Braz.†.*
Aluminium hydroxide (p.1706·2); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaologeais *Chiesi, Fr.*
Magnesium oxide (p.1744·1); meprobamate (p.1006·2); magnesium sulfate (p.1679·3); kaolin (p.1738·1); sterculia (p.1772·1).
Gastrointestinal disorders.

Kaomagma
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.†.
Kaolin (p.1738·1); aluminium hydroxide (p.1706·2).
Diarrhoea.
Sigma, Braz.
Kaolin (p.1738·1); aluminium hydroxide (p.1706·2); pectin (p.2145·2).
Diarrhoea.

Kaomagma with Pectin *Wyeth Consumer, Austral.†.*
Kaolin (p.1738·1); aluminium hydroxide (p.1706·2); pectin (p.2145·2).
Diarrhoea.

Kaomix *ICM, Singapore.*
Light kaolin (p.1738·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Diarrhoea.

Kaomuth *Bailly, Fr.*
Kaolin (p.1738·1); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Kaomycin *Armstrong, Mex.*
Neomycin sulfate (p.305·1); kaolin (p.1738·1); pectin (p.2145·2).
Gastro-enteritis.

Kaon *Montpellier, Arg.; Pharmacia, Canad.†; Savage, USA; Andromaco, Venez.†.*
Potassium gluconate (p.1684·3).
Hypokalaemia; potassium depletion; potassium supplement.

Kaon-Cl *Savage, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Kao-Paverin
Note. This name is used for preparations of different composition.
Reese, USA.
Capsules: Loperamide hydrochloride (p.1741·1).
Reese, USA.
Oral liquid: Kaolin (p.1738·1); pectin (p.2145·2); bismuth salicylate (p.1711·1).

Kaopecon *Pharmacia, Venez.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaopectal *Silom, Thai.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea; dysentery; food poisoning.

Kaopectate
Note. This name is used for preparations of different composition.
Johnson & Johnson, Canad.
Attapulgite (p.1709·1).
Cramps; diarrhoea.
Pharmacia-Upjohn, Gr.†; Pfizer, Indon.; Pharmacia, Irl.†; Pharmacia, Malaysia†; Pfizer Consumer, Mex.; Pharmacia, Singapore†; Pharmacia, Venez.†.
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.
Pfizer Consumer, USA.
Bismuth salicylate (p.1711·1).
Gastrointestinal disorders.

Kaopectate II *Upjohn, USA†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Kaopectate Advanced Formula *Upjohn, USA†.*
Attapulgite (p.1709·1).
Diarrhoea.

Kaopectate Maximum Strength *Upjohn, USA.*
Attapulgite (p.1709·1).
Diarrhoea.

Kaopectin *Dinafarma, Braz.†; Vitamed, Israel; Adcock Ingram, S.Afr.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaoprompt-H *Pfizer Consumer, Ger.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kao-Spen *Century, USA.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaostatex *Garec, S.Afr.*
Kaolin (p.1738·1); pectin (p.2145·2); sodium lactate; potassium chloride; sodium chloride (p.1672·2).
Diarrhoea.

Kaosyl *Anfarm, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Kaotate *Pfizer, Indon.*
Activated attapulgite (p.1709·1).
Diarrhoea.

Kao-Tin *Major, USA.*
Bismuth salicylate (p.1711·1).
Gastrointestinal disorders.

Kapabloc *Allen, Austria.*
⊗ Morphine sulfate (p.86·3).
Opioid withdrawal syndrome.

Kapake *Galen, Irl.; Galen, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

Kapanol *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Fr.; GSK, Ger.; GSK, Israel†; GSK, NZ; GSK, Neth.; GSK, Switz.*
⊗ Morphine sulfate (p.86·3).
Opioid withdrawal syndrome; pain.

Kaparlon-S *Anfarm, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Kapecfuran *Novag, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kapectin Forte *Taro, Israel†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kapectolin *United Research, USA.*
Bismuth salicylate (p.1711·1).
Diarrhoea.

Kaplon *Approved Prescription Services, UK.*
Captopril (p.1239·2).
Heart failure; hypertension.

Kaplus *K2 Pharmacare, Chile.*
Calcium citrate (p.1675·3); calcium carbonate (p.1714·1).
Calcium supplement; hypocalcaemia; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Kaplus-D *K2 Pharmacare, Chile.*
Calcium citrate (p.1675·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; hypocalcaemia; hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Kapnax *Kozmed, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Kaposalt *Tecnofarma, Mex.*
Potassium bicarbonate (p.1673·1); potassium tartrate (p.1684·3); citric acid (p.2284·1).
Hypokalaemia.

Kappacef *Errekappa, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Kapril *Nevzat, Turk.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Kaprin *Unipharma, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Kaprofen *Siam Bheasach, Thai.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Kaprogest *Jelfa, Pol.*
Hydroxyprogesterone caproate (p.2110·3).
Endometriosis; female infertility; menstrual disorders; threatened or recurrent miscarriage.

Kapsiplast *3M, Pol.*
Belladonna (p.2263·3); capsicum (p.2276·2).
Neuromuscular pain.

Kaptin *Julphar, UAE.*
Light kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kaptin II *Julphar, UAE.*
Activated attapulgite (p.1709·1).
Diarrhoea.

Kaptoril *Deva, Turk.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Kara *Polipharm, Thai.†.*
Ketoconazole (p.539·1).
Scalp disorders.

Karayal *Chiesi, Fr.*
Magnesium oxide (p.1744·1); magnesium sulfate (p.1679·3); kaolin (p.1738·1); sterculia (p.1772·1).
Gastrointestinal disorders.

Karazepin *Terra, Turk.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Karbaderm *NM, Swed.†.*
⊗ Urea (p.1620·2).
Dry skin.

Karbalex *Liba, Turk.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Karbasal *CCS, Swed.*
⊗ Urea (p.1620·2).
Dry skin.

Karbasalin *Laboratorios Chile, Chile†.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Streptococcal sore throat.

Karbasif *Yeni, Turk.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Karberol *Munir, Turk.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Karbolytt *Fresenius Kabi, Norw.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Karbonetas *Argenfarma, Arg.*
Yeast (p.1998·3); activated charcoal (p.1435·2).
Formerly contained yeast.
Dietary supplement.

Karbons *Eagle, Austral.†.*
Activated charcoal (p.1435·2).
Digestive system disorders.

Karboseptin *Hakay, Turk.*
Vegetable charcoal (p.1435·3); sulfur (p.1614·1); senna (p.1769·2); rhubarb (p.1768·3); phenolphthalein (p.1762·1).

Kardegic *Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi Synthelabo, Mex.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Switz.*
Lysine aspirin (p.79·1).
Myocardial infarction; thrombosis prophylaxis; unstable angina.

Karden *Novartis, Austria.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Kardiket *Schwarz, Rus.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Kardil *Atabay, Turk.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Kardilat *Fako, Turk.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Kardion *Lemery, Mex.†.*
Dobutamine (p.1272·1).

Kardioplex *SAD, Denm.*
Electrolytes (p.1667·1); procaine hydrochloride (p.1869·1).
Cardioplegia in open heart surgery.

Kardiren *Sanofi Synthelabo, Hung.†.*
Lysine aspirin (p.79·1).
Fever; pain; thromboembolism prophylaxis.

Kardisentin *Ilsan, Turk.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Kardopal *Orion, Fin.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Karex *Wolff, Ger.†; Medika, Switz.†.*
Erythromycin stinoprate (p.272·3).
Bacterial infections.

Kariax *Koni-Cofarm, Chile†.*
Triclosan (p.1665·2); sodium fluoride (p.1962·2).
Caries prophylaxis; oral hygiene.

Karicare AR *Nutricia, Austral.; Nutricia, NZ.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Karicare Barrier Cream *Nutricia, NZ†.*
Dimeticone (p.2032·1); cetrimide (p.1634·1).
Nappy rash; skin irritation.

Karicare Breast and Body Cream *Nutricia, NZ†.*
Glycerol (p.2314·2); light liquid paraffin (p.2031·1).
This preparation was formerly marketed as Karicare Breast Care.
Moisturiser; nipple care during pregnancy and lactation.

Karicare De Lact Infant *Nutricia, NZ.*
Infant feed (p.1922·1).
Lactose intolerance.

Karicare Food Thickener *Nutricia, Austral.; Nutricia, NZ.*
Pregelatinised maize starch (p.1968·1).
Dysphagia; gastro-oesophageal reflux in infants.

Karicare Goat Milk *Nutricia, Austral.; Nutricia, NZ.*
Infant feed (p.1922·1).
Cow's milk intolerance.

Karicare Ointment *Nutricia, NZ†.*
Zinc oxide (p.1621·2); glycerol (p.2314·2).
Nappy rash; skin irritation.

Karicare Soy *Nutricia, Austral.*
Infant feed (p.1922·1).
Cow's milk or lactose intolerance.

Karicare Soya *Nutricia, NZ.*
Infant feed (p.1922·1).
Cow's milk intolerance; galactosaemia; lactose intolerance.

Karidium
Note. This name is used for preparations of different composition.
Aventis, Arg.
Clobazam (p.477·2).
Anxiety; epilepsy.
Lorvic, Canad.†; Lorvic, USA.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Karigel *Lorvic, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Karigel-N *Lorvic, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Karil *Novartis, Ger.*
Calcitonin (salmon) (p.1093·1) or calcitonin (salmon) acetate (p.1094·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Karile *Phoenix, Arg.*
Nortriptyline hydrochloride (p.413·2); perphenazine (p.1017·1).
Depression.

Karilex *Arlex, Mex.*
Cinnarizine (p.573·1).

Karin *Unipharm, Israel.*
Clarithromycin (p.248·2).
Bacterial infections.

Karison *Dermapharm, Ger.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Kariva *Barr, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 5 tablets, ethinylestradiol; 2 tablets, inert.
Sequential-type oral contraceptive.

Karlit *Biotenk, Arg.*
Lithium carbonate (p.401·3).
Bipolar disorder; schizophrenia.

Karlor *Aspen, Austral.*
Cefaclor (p.217·2).
Bacterial infections.

Karmelitos *Cadila, India.*
Glimepiride (p.441·1).
Diabetes mellitus.

Karmikin *Bruluart, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Karmosan *Darier, Mex.*
⊗ Urea (p.1620·2).
Skin disorders; wounds.

Karoksen *Munir, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Karon *Zentiva, Cz.*
Alprostadil (p.2183·2).
Erectile dysfunction.

Karrer *Lisapharma, Ital.†.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Kartal *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Karvea *Sanofi-Aventis, Austral.; BMS, Cz.; BMS, Ger.; BMS, Gr.; BMS, Ital.; Sanofi-Aventis, NZ; BMS, Neth.; BMS, Port.; BMS, Spain; Sanofi Synthelabo, Turk.*
Irbesartan (p.1316·1).
Diabetic nephropathy; hypertension.

Karvezide *Sanofi-Aventis, Austral.; BMS, Cz.; BMS, Ger.; BMS, Gr.; BMS, Ital.; Sanofi-Aventis, NZ; BMS, Neth.; BMS, Port.; BMS, Spain; Sanofi Synthelabo, Turk.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Karvil *Torrent, Braz.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Karvol
Note. This name is used for preparations of different composition.
Boots, Austral.†.
Menthol (p.2340·1); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); terpineol (p.2396·1).
Nasal congestion.
Boots Healthcare, Irl.; Crookes Healthcare, UK.
Chlorobutanol (p.1639·2); menthol (p.2340·1); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); terpineol (p.2396·1); thymol (p.1664·3).
Cold symptoms; respiratory-tract congestion.
Boots, Israel.
Menthol (p.2340·1); cinnamon oil (p.2283·2); terpineol (p.2396·1); chlorobutanol (p.1639·2); pine silvestris oil (p.2368·2); thymol (p.1664·3); pumilio pine oil (p.2376·3).
Cold symptoms.
Boots Healthcare, NZ.
Menthol (p.2340·1); pine oil (p.2368·2); cinnamon oil (p.2283·2).
Nasal congestion.
Permark, S.Afr.; Boots, Singapore.
Chlorobutanol (p.1639·2); menthol (p.2340·1); cinnamon oil (p.2283·2); pine oil (p.2368·2); terpineol (p.2396·1); thymol (p.1664·3).
Upper respiratory-tract congestion.

Karvol Plus *Solvay, India.*
Menthol (p.2340·1); terpineol (p.2396·1); chlorothymol (p.1640·1); camphor (p.2273·2); cineole (p.2282·3).
Cold symptoms; nasal congestion.

Kary Uni *Santen, Hong Kong; Ferron, Indon.; Santen, Indon.; Santen, Philipp.; Santen, Singapore; Santen, Thai.*
Pirenoxine (p.2369·1).
Cataract.

Kas *Nutricia-Bago, Arg.*
Preparation for enteral nutrition (p.1922·1).
Cow's milk protein allergy; diarrhoea; pancreatic insufficiency; soya allergy.

Ka-Sabona *Sabona, Ger.†.*
Kava (p.2328·3).
Anxiety disorders.

Kas-Bah *Potter's, UK.*
Buchu (p.2269·3); clivers (p.2284·3); couch-grass (p.2288·2); equisetum (p.2299·3); bearberry (p.2263·3); senna (p.1769·2).
Urinary and bladder discomfort.

Kasele *Baxter, Mex.†.*
Potassium chloride (p.1684·3).

Kaskadil *Lab Francais du Fractionnement, Fr.; Er-Kim, Turk.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Kasmal *Silanes, Mex.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; atopic eczema; bronchitis; urticaria.

Kassemox *Square, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Kastipron *YSP, Malaysia.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased mucus.

Kata *Ibirn, Ital.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Katabexin *Medichrom, Gr.†.*
Betahistine hydrochloride (p.2265·1).
Vertigo.

Katabios *SIT, Ital.*
Multivitamin preparation (p.1922·1).

Katadolon
Ache, Braz.; AWD, Rus.
Flupirtine maleate (p.61·1).
Pain.
AWD, Ger.; Grunenthal, Ger.
Flupirtine gluconate (p.61·1) or flupirtine maleate (p.61·1).
Pain.

Katagrip *Lepori, Port.*
Paracetamol (p.108·1).
Formerly contained ethenzamide and paracetamol.
Cold symptoms.

Katalem *Lemery, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Kataljin *Sanli, Turk.*
Camphor (p.2273·2); thymol (p.1664·3); benzocaine (p.1854·1); menthol (p.2340·1); coconut oil (p.2029·2); cedar leaf oil (p.2400·3); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2).
Musculoskeletal and joint pain.

Kataljin-P *Sanli, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Katapekt *Vitabalans, Fin.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); thyme (p.2401·1).
Coughs.

Katarin *Biofarma, Turk.*
Paracetamol (p.108·1); oxolamine citrate (p.1567·1); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Katarin Forte *Biofarma, Turk.*
Paracetamol (p.108·1); oxolamine citrate (p.1567·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Katasma *Bruschettini, Ital.*
Diprophylline (p.1120·2).
Obstructive airways disease.

Kataval *Farmigea, Ital.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Anorectal disorders; otitis externa; skin disorders.

Katen *Zentiva, Cz.*
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Kathargon *Farmedia, Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).
Bowel evacuation.

Kathricol *Mediapharm, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Katifen *General Drugs, Thai.*
Ketotifen (p.582·2).
Asthma; hypersensitivity reactions.

Katin *Sanitas, Chile.*
Menadione (p.1995·2); bile salts (p.2266·2).
Biliary-tract and liver disorders; coumarin anticoagulant overdosage; hypoprothrombinaemia.

Kationen *Fresenius Kabi, Austria.*
A trace element preparation (p.1922·1).
Parenteral nutrition.

Kativil *Cofasa, Venez.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Katoderm *Deverge, Ital.*
Emollient.
Skin irritation.

Katogel *Deverge, Ital.*
Emollient.
Dry skin; skin irritation.

Katomed *Deverge, Ital.*
Silver (p.2387·1).
Burns; skin ulcers; wounds.

Kato-Nasal *Kato, Pol.*
Mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; sinusitis.

Katopil *ICN, Cz.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Katosilver *Deverge, Ital.*
Silver sucralfate.
Prevention of decubitus ulcers; skin irritation.

Katoxyn *Deverge, Ital.*
Silver (p.2387·1); benzoyl peroxide (p.1590·2); kaolin (p.1738·1); calcium gluconate (p.1675·3).
Disinfection of wounds and burns; skin irritation.

Katrasic *Kalbe, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Katrax *Hua, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Katrum *Smaller, Spain.*
Capsaicin (p.32·3).
Muscle and joint pain.

Katsin *M & H, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Kattwicor *Kattwiga, Ger.*
Homoeopathic preparation.

Kattwiderm *Kattwiga, Ger.†.*
Homoeopathic preparation.

Kattwigast *Kattwiga, Ger.†.*
Homoeopathic preparation.

Kattwigripp *Kattwiga, Ger.*
Homoeopathic preparation.

Kattwilact *Kattwiga, Ger.†.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Katulcin-R *Kattwiga, Ger.†.*
Bismuth salicylate (p.1711·1).
Gastritis; peptic ulcer.

Katya *Stragen, Cz.; Stragen, UK.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Kavaderm *Relyo, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Kavain Harras N *Harras-Curarina, Ger.†.*
Kava (p.2328·3).
Anxiety disorders.

Kavakan *Ativus, Braz.*
Kava (p.2328·3).
Anxiety; insomnia; tension.

Kavalac *Fontovit, Braz.†.*
Kava (p.2328·3).
Anxiety.

Kavamed *Cimed, Braz.*
Kava (p.2328·3).
Anxiety.

Kava-Phyton *Merckle, Ger.†.*
Kava (p.2328·3).
Anxiety disorders.

Kavasedon *Sigma, Braz.; Harras-Curarina, Cz.†; Harras-Curarina, Ger.†; HPC, Switz.†; Cofasa, Venez.†.*
Kava (p.2328·3).
Anxiety.

Kavelor *Megat, Venez.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Kavepenin *AstraZeneca, Norw.†; AstraZeneca, Swed.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Kaveri *Lichtwer, Ger.*
Ginkgo biloba leaf (p.2311·1).
Headache; intermittent claudication; mental function impairment; vestibular disorders.

Kavipen *Maver, Mex.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Kavit *Cristalia, Braz.*
Phytomenadione (p.1995·3).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Kavitol *Lannacher, Austria.*
Menadione sodium bisulfite (p.1995·3).
Haemorrhage; overdosage with coumarin anticoagulants.

Kavosan *Oral-B, Ital.†.*
Sodium perborate (p.1662·1).
Oral hygiene.

Kavosporal comp *Muller Goppingen, Ger.†.*
Kava (p.2328·3); valerian (p.2410·1).
Anxiety disorders.

Kavosporal forte *Muller Goppingen, Ger.†.*
Kava (p.2328·3).
Anxiety disorders.

Kawaform *Klinge, Switz.†.*
Kawain (p.2328·3); magnesium orotate (p.2358·3); vitis vinifera (p.2316·3).
Insomnia; tension; tonic.

Kay Ciel *Forest Pharmaceuticals, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Kay-Cee-L *Geistlich, Irl.; Geistlich, UK.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium deficiency; potassium depletion.

Kaycin *Cadila, India.*
Kanamycin (p.291·3).
Bacterial infections.

Kayexalate
Sanofi-Aventis, Belg.
Calcium polystyrene sulfonate (p.1438·2) or sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Sanofi Synthelabo, Canad.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi Winthrop, Israel; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Thai.; Sanofi Winthrop, USA; Sanofi-Aventis, Venez.
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Kayivis *Vincenti, Venez.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3); acetic acid (p.2244·2); collodion.

Kaytwo *Eisai, Jpn.*
Menatetrenone (p.1995·3).
Vitamin K deficiency.

Kazepin *Gunsa, Turk.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Kazinal *Asian Pharm, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

K-C *Century, USA.*
Kaolin (p.1738·1); pectin (p.2145·2); bismuth subcarbonate (p.1711·1).
Diarrhoea.

K-Cil *TP, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

K-Citra *Seaford, Canad.*
Potassium citrate (p.1673·2).
Potassium supplement.

KCl-retard *Novartis Consumer, Austria; Novartis, Ger.*
Potassium chloride (p.1684·3).
Hypokalaemia.

K.C.M.C *Knop, Chile.*
Carmellose (p.2142·1); marine algae; cholic acid (p.2266·3).
Obesity.

Kdiron *Julphar, UAE.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

K-Drops *Faran, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

K-Dur *Key, Canad.; Schering-Plough, Mex.; Key, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Keal *EG, Fr.*
Sucralfate (p.1772·2).
Peptic ulcer.

Kebir *Aspen, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Kebirtecan *Aspen, Arg.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Kebirterona *Aspen, Arg.*
Cyproterone (p.2089·2).

Kebirzol *Aspen, Arg.*
⊗ Letrozole (p.740·2).

Keciflox *Pfleger, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Kecnitril *Proula, Venez.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Kedacillin *Takeda, Indon.; Hormona, Mex.; Takeda, Philipp.*
Sulbenicillin sodium (p.335·2).
Lidocaine hydrochloride (p.1862·3) may be included in this preparation to alleviate the pain of injection.
Bacterial infections.

Kediar *Kener, Mex.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kedrop *Grin, Mex.*
Ketotifen (p.582·2).
Allergic eye disorders.

Keduo *LKM, Arg.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Keduril *Aventis, Mex.†.*
Ketoprofen sodium (p.73·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Keefloxin *Angenerico, Port.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Keep Alert *Reese, USA.*
Caffeine (p.1116·3).

Kefaclor *LSP, Thai.†.*
Cefaclor (p.217·2).
Bacterial infections.

Kefadim *Lilly, Belg.†; Lilly, Braz.; Lilly, Cz.†; Lilly, UK.*
Ceftazidime (p.234·1).
Bacterial infections.

Kefadol *Lilly, Irl.†.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Kefalex *Ratiopharm, Fin.*
Cefalexin (p.218·2).
Bacterial infections.

Kefalexin *Royton, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Kefalgin *Extractum, Hung.*
Ergotamine tartrate (p.620·1); belladonna (p.2263·3); caffeine (p.1116·3); aminophenazone (p.19·1).
Migraine.

Kefalotin *Biochimico, Braz.†.*
Cefalotin (p.220·2).
Bacterial infections.

Kefamin *Biomed, Spain.*
Ceftazidime (p.234·1).
Bacterial infections.

Kefazim *Astro, Austria.*
Ceftazidime (p.234·1).
Bacterial infections.

Kefazin *Vitamed, Israel.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Kefazol *ABL, Braz.; Lilly, Braz.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Kefdole *Aspen, S.Afr.†.*
Cefamandole nafate (p.220·3).
Bacterial infections.

Kefentech *JE IL, Singapore.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Kefexin *Orion, Fin.; Orion, Irl.†; Orion, Malaysia†.*
Cefalexin (p.218·2).
Bacterial infections.

Keflaxina *Hexal, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Keflex *Aspen, Austral.; Arcana, Austria; Lilly, Braz.; Lilly, Denm.; Lilly, Hong Kong†; Lilly, Hung.†; Flynn, Irl.; Lilly, Israel†; Lilly, Mex.; Lilly, NZ†; EuroCept, Norw.; Duncan, Philipp.; Actavis, Pol.; Lilly, Port.†; Aspen, S.Afr.; Meda, Swed.; Lilly, Thai.; Flynn, UK; Advancis, USA.*
Cefalexin (p.218·2).
Bacterial infections.

Keflin *Ivax, Arg.; ABL, Braz.; Lilly, Braz.; Lilly, Denm.†; Lilly, Fin.†; Lilly, Israel†; Lilly, Ital.†; Sandoz, Mex.; EuroCept, Neth.; EuroCept, Norw.; Aspen, S.Afr.†; Lilly, Thai.†; Lilly, Venez.†.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Keflin Neutral *Lilly, Austral.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Keflor *Alphapharm, Austral.; Lilly, Chile†; Ranbaxy, India.*
Cefaclor (p.217·2).
Bacterial infections.

Kefloridina *Ciclum, Spain; Stada, Spain.*
Cefalexin (p.218·2).
Bacterial infections.

Kefloxin *Ranbaxy, Malaysia.*
Cefadroxil (p.218·1).
Bacterial infections.

Kefnir *Glenmark, India†.*
Cefdinir (p.223·1).
Bacterial infections.

Kefol *Irisfarma, Spain†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Kefolor *Actavis, Fin.*
Cefaclor (p.217·2).
Bacterial infections.

Keforal *Ivax, Arg.; EuroCept, Belg.; ABL, Braz.; Sciencex, Fr.; Crinos, Ital.; EuroCept, Neth.; Farma, Venez.*
Cefalexin (p.218·2).
Bacterial infections.

Kefotax *Sandoz, S.Afr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Kefox *CT, Ital.†; CT, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Kefoxin *Biochimico, Braz.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Kefpod *Glenmark, India.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Kefsid *Fako, Turk.*
Cefaclor (p.217·2).
Bacterial infections.

Kefstar *Wockhardt, Rus.*
Cefuroxime (p.238·2).
Bacterial infections.

Keftab *Biovail, USA†.*
Cefalexin hydrochloride (p.218·3).
Bacterial infections.

Keftid *Galen, Irl.; Galen, UK.*
Cefaclor (p.217·2).
Bacterial infections.

Keftil *Zynova, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Keftragard *Ipca, India.*
Ceftriaxone sodium (p.237·1); sulbactam sodium (p.335·1).
Bacterial infections.

Keftriaxon *Vitamed, Israel.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Kefurim *Vitamed, Israel.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Kefurox *Lilly, Belg.†; Lilly, Canad.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Kefzim *Lilly, Chile†; Lilly, S.Afr.†.*
Ceftazidime (p.234·1).
Bacterial infections.

Kefzol *Lilly, Austral.; Astro, Austria; Lilly, Belg.†; Lilly, Canad.†; Lilly, Chile†; Lilly, Cz.†; Lilly, Israel†; Lilly, NZ†; EuroCept, Neth.; Lilly, Rus.; Sandoz, S.Afr.; Lilly, Switz.; Lilly, Venez.†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) may be included in the solvent for intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Keigairengyoto *Tsumura, Jpn.*
Scutellaria root; phellodendron bark; coptis rhizome; platycodon root; immature orange; schizonepeta spike; bupleurum root; gardenia fruit; rehmannia root; peony root; cnidium rhizome; Japanese angelica root; mentha herb; angelica dahurica root; saposhnikovia root; forsythia fruit; liquorice.
Traditional Kampo medicine.

Keimax *Essex, Ger.*
Ceftibuten (p.235·3).
Bacterial infections.

Keimicina *Zambon, Ital.*
Kanamycin sulfate (p.291·2).
Vulvovaginal bacterial infections.

Keiran *Pharmakin, Venez.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Keishi-bukuryo-gan *Tsumura, Jpn.*
Cinnamon bark; peony root; peach kernel; poria sclerotium; moutan bark.
Traditional Kampo medicine.

Keishikajutsubuto *Tsumura, Jpn.*
Cinnamon bark; peony root; atractylodes lancea rhizome; jujube; liquorice; ginger; aconite root.
Traditional Kampo medicine.

Keishikaryukotsuboreito *Tsumura, Jpn.*
Cinnamon bark; peony root; jujube; oyster shell; longgu; liquorice; ginger.
Traditional Kampo medicine.

Keishikashakuyakudaioto *Tsumura, Jpn.*
Peony root; cinnamon bark; jujube; liquorice; rhubarb; ginger.
Traditional Kampo medicine.

Keishikashakuyakuto *Tsumura, Jpn.*
Cinnamon bark; peony root; jujube; liquorice; ginger.
Traditional Kampo medicine.

Keishito *Tsumura, Jpn.*
Cinnamon bark; peony root; jujube; liquorice; ginger.
Traditional Kampo medicine.

Kela *TO-Chemicals, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Kelac
Richmond, Arg.
Ketorolac (p.75·2).
Inflammation; pain.

Giempi, Venez.
Ketorolac trometamol (p.74·2).
Pain.

Keladormet *Kela, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Kelalexan *Kela, Belg.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Kelamigra *Kela, Belg.*
Flunarizine hydrochloride (p.580·2).
Migraine.

Kelaplus *TO-Chemicals, Thai.*
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3).
Fungal skin infections.

Kelatin *Yamanouchi, Belg.†.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; rheumatoid arthritis; Wilson's disease.

Kelatine *Medirex, Port.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; rheumatoid arthritis; Wilson's disease.

Kelbium *Sankyo, Spain.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Kelefusin *Pisa, Mex.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Kelfen *Roemmers Osmoph, Venez.*
Ketoprofen (p.73·1).
Inflammation; pain.

Kelfer *Vianex (Βιανέξ), Gr.; Cipla, India; Cipla, Malaysia.*
Deferiprone (p.1439·1).
Iron overload.

Kelfex *Combiphar, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Kelfiprim *Pfizer, Mex.†.*
Trimethoprim (p.355·2); sulfametopyrazine (p.342·2).
Bacterial infections.

Kelicardina *Herbapol Wroclaw, Pol.*
Ammi visnaga (p.2256·1); convallaria (p.2287·3); crataegus (p.2289·1); rutoside (p.2305·1).
Circulatory disorders.

Keli-med *Permamed, Switz.*
Garlic (p.2309·2); hyoscyamus (p.2323·3); allantoin (p.1588·1); heparin sodium (p.1301·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Scars.

Kelly *Sigma, Braz.*
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Kelnac *Sankyo, Jpn; Sankyo, Thai.*
Purified plau-noi extract (plaunotol) (p.1763·2).
Gastric ulcer; gastritis; peptic ulcer.

Kelnor *Barr, USA.*
Ethinylestradiol (p.2101·3); etynodiol diacetate (p.2103·2).
Combined oral contraceptive.

Keloc *Approved Prescription Services, UK.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Kelo-Cote *Advanced Biotechnologies, Israel.*
Polysiloxane (p.2032·1); silicon dioxide (p.2146·2).
Aid in skin healing; scar prevention.

Kelocyanor *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Dicobalt edetate (p.1443·2).
Cyanide poisoning.

Kelofibrase *Azupharma, Ger.†.*
⊗ Urea (p.1620·2); heparin sodium (p.1301·2); camphor (p.2273·2).
Keloids; scars.

Kelomedil *Kela, Belg.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Kelosal *Quimifar, Spain†.*
Cisapride (p.1720·3).
Gastroparesis.

Kelosoft *Chemomedica, Austria; Geistlich, Switz.*
Hyoscyamus oil (p.2323·3).
Nasal disorders; scars.

Kelp B_6 Cider Vinegar *Adams, Canad.*
Vitamin B ; kelp (p.2384·2); lecithin; vinegar (p.1922·1).

Kelp Plus 3 *Larkhall Laboratories, UK.*
Kelp (p.2384·2); vitamin B (p.1978·2); soya lecithin (p.2332·2); cider vinegar.

Kelsef *Zydus, Fr.†.*
Cefradine (p.233·1).
Bacterial infections.

Kelsopen *Reig Jofre, Spain.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Keltican N *Trommsdorff, Ger.*
Disodium uridine phosphate (p.2296·1); disodium cytidine phosphate (p.2291·3).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Formerly contained trisodium uridine triphosphate, disodium uridine diphosphate, disodium uridine phosphate, and disodium cytidine phosphate.
Neuralgia; neuritis; neuropathy.

Keltrina *Multilab, Braz.*
Permethrin (p.2048·2).
Pediculosis.

Kelual *Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.*
Keluamid (p.1603·2).
Seborrhoeic dermatitis.

Kelual DS
Note.This name is used for preparations of different composition.
Ducray, Fr.
Cream: Glycolic acid (p.1598·1); guanidine carbonate; crotamiton (p.1593·2); saw palmetto (p.2192·3); keluamid (p.1603·2); piroctone olamine (p.1610·1).
Irritative and oily skin conditions.

Ducray, Fr.
Shampoo: Piroctone olamine (p.1610·1); pyrithione zinc (p.1611·2); keluamid (p.1603·2).
Receding hair.

Kelual Zinc Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.
Keluamid (p.1603·2); zinc sulfate (p.1999·2).
Seborrhoeic dermatitis; skin disorders.

Kemadren GSK, Spain.
Procyclidine hydrochloride (p.814·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Kemadrin GSK, Austria; GSK, Belg.; GSK, Canad.†; GSK, Cz.; GSK, Denm.; GSK, Hung.; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.†; GSK, Malaysia†; GSK, NZ; GSK, Switz.; Auden McKenzie, UK; GSK, UK; Glaxo Wellcome, USA.
Procyclidine hydrochloride (p.814·3).
Cardiac disorders; drug-induced extrapyramidal disorders; hypertension; mental function impairment; parkinsonism; peptic ulcer.

Kemanat Microsules, Arg.
Ketorolac trometamol (p.74·2).
Pain.

Kemeol Interdelta, Switz.
⊗ Ephedrine (p.1558·1); neroli oil (p.2351·1); eucalyptus oil (p.2301·2).
Rhinitis.

Kemerhinose Interdelta, Switz.
Sodium chloride (p.1686·1); benzododecinium bromide (p.1631·2).
Nasal congestion.

Kemial Janssen-Cilag, Arg.
Vaginal and rectal lubricant.

Kemicetin Sanochemia, Austria.
Chloramphenicol (p.239·3).
Bacterial eye infections.

Kemicetina Pharmacia, Belg.†.
Chloramphenicol (p.239·3).
Bacterial infections.

Kemicetine
Pfizer, Hong Kong; Kalbe, Indon.; Carlo Erba, Turk.
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Mac, India†; Pfizer, Philipp.; Pfizer, Thai.†.
Chloramphenicol (p.239·3).
Bacterial infections.

Pfizer, Singapore; Pharmacia, UK.
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Kemicetine Antiozena Mac, India.
Chloramphenicol (p.239·3); estradiol dipropionate (p.2097·3); colecalciferol (p.1986·2).
Rhinitis; rhinopharyngitis.

Kemicetine Otological
Note.This name is used for preparations of different composition.
Mac, India†.
Ear drops (1%): Chloramphenicol (p.239·3).
Ear infections.

Mac, India†.
Ear drops (5%): Chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Ear infections.

Kemiderm Berlico Mulia, Indon.
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Kemocarb Dabur, India; Alternavida, Mex.; Dabur, Philipp.; Dabur, Thai.
Carboplatin (p.693·1).
Malignant neoplasms.

Kemodyn Esseti, Ital.†.
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; parkinsonism.

Kemoplat Dabur, India; Dabur, Philipp.; Dabur, Thai.
Cisplatin (p.698·2).
Malignant neoplasms.

Kemoprim Ulagay, Turk.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Kemphor Salusif, Port.
Zinc chloride (p.1999·1); methyl salicylate (p.85·3); menthol (p.2340·1).
Formerly contained zinc chloride, sumatra benzoin, gaultheria oil, and menthol.
Mouth disorders.

Kempi Pfizer, Spain.
Spectinomycin hydrochloride (p.332·3).
Gonorrhoea.

Kemsol Carter Horner, Canad.†.
Dimethyl sulfoxide (p.2022·1).
Scleroderma.

Kemstro Schwarz, USA.
Baclofen (p.1888·1).
Skeletal muscle spasm and spasticity.

Kemudin FHC, Port.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Kemzid Unison, Hong Kong†; Unison, Singapore†; Unison, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Skin and scalp disorders.

Kenacef Medikon, Indon.
Cefuroxime axetil (p.238·2).
Bacterial infections.

Kenacomb
Note.This name is used for preparations of different composition.
BMS, Arg.; BMS, Austral.; Westwood-Squibb, Canad.†; BMS, Gr.; BMS, Hong Kong; Sarabhai Piramal, India; BMS, Irl.; BMS, Israel†; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Philipp.; BMS, Port.; BMS, S.Afr.; BMS, Singapore†; BMS, Thai.
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1); nystatin (p.543·2).
Infected ear disorders; infected skin disorders; otitis externa.

BMS, Venez.
⊗ Triamcinolone acetonide (p.1544·3); gramicidin (p.286·1); nystatin (p.543·2).
Infected skin disorders.

Kenacombin Novum BMS, Swed.
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Fungal skin infections.

Kenacort
BMS, Arg.; BMS, Mex.; Dermapharm, Switz.
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

BMS, Belg.†; BMS, Fr.; Sarabhai Piramal, India; BMS, Ital.; BMS, Philipp.; BMS, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

BMS, Indon.
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Corticosteroid.

BMS, Venez.
⊗ Triamcinolone (p.1544·2), trimacinolone acetonide (p.1544·3), or trimacinolone diacetate (p.1544·3).
Corticosteroid.

Kenacort-A
Note.This name is used for preparations of different composition.
BMS, Arg.; BMS, Austral.; BMS, Belg.; BMS, Chile; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Indon.; BMS, Malaysia†; BMS, NZ; BMS, Neth.; BMS, Philipp.; BMS, Singapore; BMS, Turk.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Dermapharm, Switz.
Injection; oral paste: ⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Dermapharm, Switz.
Tincture: ⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Kenacort-A Solubile BMS, Switz.
⊗ Triamcinolone acetonide dipotassium phosphate (p.1545·1).
Corticosteroid.

Kenacort-T BMS, Fin.; BMS, Norw.; BMS, Swed.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Kenacort-T comp BMS, Norw.; BMS, Swed.
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Otitis externa; skin disorders.

Kenacutan BMS, Denm.; BMS, Norw.; BMS, Swed.
⊗ Triamcinolone acetonide (p.1544·3); halquinol (p.286·2).
Infected skin disorders.

Kenaderm Pharmaniaga, Malaysia†; Raza, Malaysia†.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Kenadion Samarth, India.
Phytomenadione (p.1995·3).
Antidote to coumarin anticoagulants in hypoprothrombinaemia.

Kenalcol BMS, Fr.
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2); benzalkonium chloride (p.1629·1).
Skin disorders.

Kenalin Kendrick, Mex.
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Kena-Lite Nupharma, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Kenalog
Note.This name is used for preparations of different composition.
Westwood-Squibb, Canad.; Leciva, Cz.†; BMS, Denm.; BMS, Ger.†; KRKA, Hung.; BMS, Irl.; BMS, Israel†; BMS, UK; Westwood-Squibb, USA.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

BMS, Rus.; KRKA, Rus.
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).

BMS, Venez.
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Psoriasis.

Kenalog Comp med Mycostatin BMS, Denm.
⊗ Triamcinolone acetonide (p.1544·3); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Kenalog Dental BMS, Mex.
⊗ Triamcinolone (p.1544·2).
Mouth disorders.

Kenalog med Salicylsyre BMS, Denm.
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Kenalog in Orabase BMS, Austral.; BMS, Canad.; BMS, Hong Kong; BMS, Indon.; BMS, Israel†; BMS, Malaysia; BMS, NZ; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Thai.; Apothecon, USA.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Kenalog-S Sarabhai Piramal, India.
⊗ Triamcinolone acetonide (p.1544·3); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Inflammatory eye disorders.

Kenalyn Silom, Thai.
Ketoconazole (p.539·1).
Fungal scalp infections.

Kenantist BMS, Indon.
⊗ Triamcinolone (p.1544·2); carbinoxamine maleate (p.570·2).
Allergic disorders.

Kenapril Kener, Mex.†.
Captopril (p.1239·2).
Hypertension.

Kenaprol Kener, Mex.
⊗ Metoprolol tartrate (p.1338·1).
Hypertension.

Kenaprox Kener, Mex.†.
Naproxen (p.92·3).

Kenazol
Note.This name is used for preparations of different composition.
Kendrick, Mex.
Etoposide (p.718·1).
Malignant neoplasms.

Pharmasant, Thai.; Roemmers Osmoph, Venez.
Ketoconazole (p.539·1).
Fungal infections.

Kenazole Greater Pharma, Thai.†.
Ketoconazole (p.539·1).
Fungal infections.

Kenbrid Kendrick, Mex.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Kenciclen Kener, Mex.
Doxycycline hyclate (p.267·1).
Amoebiasis; bacterial infections; malaria.

Kendaron Darya-Varia, Indon.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Kendazol Kener, Mex.†.
⊗ Danazol (p.2090·2).

Kendix EG, Fr.
Aciclovir (p.862·3).
Herpesvirus infections.

Kendolit Kendrick, Mex.
Ketorolac (p.75·2) or ketorolac trometamol (p.74·2).
Pain.

Kendural Abbott, Switz.
Ferrous sulfate (p.1939·3).
Sodium ascorbate (p.1984·1) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Kendural C Teofarma, Ger.
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Kendural-Fol-500 Teofarma, Ger.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemias.

Kenedril Biospray, Gr.
Azelaic acid (p.1589·3).
Acne.

Kenefen Pharmasant, Thai.
Ketotifen fumarate (p.582·2).
Asthma; bronchitis; hypersensitivity reactions.

Kenergon Magistra, Switz.
Lidocaine (p.1862·3).
Premature ejaculation.

Kenesil Cantabria, Spain.
Nimodipine (p.1357·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Kenetrol
Note.This name is used for preparations of different composition.
Darya-Varia, Indon.
Eye drops: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Darya-Varia, Indon.
Eye ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Kenhancer Sang-A, Malaysia; Sang-A Pharm, Singapore.
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Kenicef Taiho, Jpn.
Cefodizime sodium (p.226·1).
Bacterial infections.

Kenicet Kendrick, Mex.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Keno TO-Chemicals, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Kenoket Kendrick, Mex.
Clonazepam (p.478·2).
Epilepsy.

Kenolan Kendrick, Mex.
Captopril (p.1239·2).
Heart failure; hypertension.

Kenonel Marnel, USA.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Kenopril Kendrick, Mex.†.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Kenoral General Drugs, Thai.
Ketoconazole (p.539·1).
Fungal infections.

Kenrovir Darya-Varia, Indon.
Aciclovir (p.862·3).
Herpesvirus infections.

Kensedal Precimex, Mex.
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; pain.

Kensodic Kendrick, Mex.
Roxithromycin (p.331·1).
Bacterial infections.

Kenspa Kenyaku, Thai.
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal disorders; smooth muscle spasm.

Kenstatin Kendrick, Mex.
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Kentacef BMS, Gr.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Kentadin Kendrick, Mex.
Pentoxifylline (p.1367·2).
Vascular disorders.

Kentamol Ivax, UK†.
⊗ Salbutamol (p.1131·2).
Asthma.

Kentera UCB, Cz.; Nicobrand, Denm.; UCB, Fin.; UCB, Gr.; UCB, Irl.; Nicobrand, Neth.; Nicobrand, Norw.; UCB, Port.; UCB, Swed.; Recordati, UK.
Oxybutynin (p.2190·3).
Bladder instability; urinary incontinence.

Kentimol Darya-Varia, Indon.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Kentosanil Kener, Mex.†.
Oxolamine citrate (p.1567·1).
Respiratory-tract congestion.

Kentovase Kent, UK†.
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension.

Kenvastin Kener, Mex.
Pravastatin sodium (p.1374·3).
Hyperlipidaemias.

Kenwood Therapeutic Liquid Kenwood, USA.
Multivitamin and mineral preparation (p.1922·1).

Kenyamine Kenyaku, Hong Kong.
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Kenya-Mox Kenyaku, Thai.†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Kenyna Kendrick, Mex.
Pancreatin (p.2360·1).
Pancreatic insufficiency; steatorrhoea.

Kenzen Takeda, Fr.
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension.

Kenzoflex Collins, Mex.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Kenzolol Kendrick, Mex.
Nimodipine (p.1357·2).
Mental function disorders; neurological deficit following subarachnoid haemorrhage; vestibular disorders.

Kenzomyl Kendrick, Mex.†.
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Kephalodoron
Note.This name is used for preparations of different composition.
Weleda, Austria.
Ferrous sulfate (p.1939·3); silicon dioxide (p.2146·2).
Migraine; nervous disorders; vasomotor headache.

Weleda, S.Afr.
Homoeopathic preparation.

Kepinol Pfleger, Ger.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Kepivance Amgen, Austral.; Amgen, Cz.; Amgen, Fin.; Amgen, Fr.; Genesis, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Neth.; Amgen, Pol.; Amgen, Port.; Amgen, Swed.; Amgen, UK; Amgen, USA.
Palifermin (p.2359·3).
Oral mucositis associated with myelotoxic chemotherapy.

Keplat Hisamitsu, Cz.; Sigma-Tau, Ital.; Hisamitsu, Port.
Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue disorders; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Keppra *Rontag, Arg.; UCB, Austral.; UCB, Belg.; Lundbeck, Canad.; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; UCB, Gr.; UCB, Hong Kong; UCB, Hung.; UCB, Indon.; UCB, Irl.; CTS, Israel; UCB, Ital.; UCB, Malaysia; UCB, Mex.; UCB, NZ; UCB, Neth.; UCB, Norw.; UCB, Philipp.; UCB, Pol.; UCB, Port.; UCB, Rus.; UCB, S.Afr.; UCB, Singapore; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, Thai.; UCB, Turk.; UCB, UK; UCB, USA.*
Levetiracetam (p.488·2).
Epilepsy.

Keppur
Note.This name is used for preparations of different composition.
Drossapharm, Switz.
Cream: Heparin sodium (p.1301·2); comfrey (p.2286·3); St John's wort oil (p.423·2); calendula oil (p.2273·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; venous insufficiency.
Drossapharm, Switz.
Topical gel: Heparin sodium (p.1301·2); comfrey (p.2286·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; venous insufficiency.

Keprobiozol *Columbia, Mex.†.*
Ketoconazole (p.539·1).
Fungal infections.

Keprodol *Ratiopharm, Austria†.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal and joint disorders; pain.

Kepsidol *Kener, Mex.*
Haloperidol (p.1000·2).

Keptan Compuesto *Sanofi Synthelabo, Arg.†.*
Trospium chloride (p.2198·3); dipyrone (p.49·2).
Muscle spasm; pain.

Keptrix *Biolab, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Keracnyl
Note.This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
Cream: Saw palmetto (p.2192·3); zinc salicylate (p.1612·3); glycolic acid (p.1598·1); salicylic acid (p.1612·2); lactic acid (p.2329·3); levomenol (p.2333·3); stearyl glycyrrhetinate.
Acne.
Ducray, Fr.
Cream: Salicylic acid (p.1612·2); glycolic acid (p.1598·1); lactic acid (p.2329·3); saw palmetto (p.2192·3); zinc salicylate (p.1612·3); levomenol (p.2333·3); saw palmetto (p.2192·3).
Acne; seborrhoea.
Ducray, Fr.
Face mask: Glycolic acid (p.1598·1); zinc salicylate (p.1612·3); kaolin (p.1738·1).
Seborrhoea.
Pierre Fabre Dermo-Cosmetique, Arg.
Topical gel: Saw palmetto (p.2192·3); zinc salicylate (p.1612·3); glycerol (p.2314·2); glycolic acid (p.1598·1).
Skin cleansing.
Ducray, Fr.
Topical mousse: Poly hydroxy acids; glycolic acid (p.1598·1); saw palmetto (p.2192·3); zinc salicylate (p.1612·3).
Seborrhoea.

Keracnyl eau nettoyante *Ducray, Fr.*
Salicylic acid (p.1612·2); glycolic acid (p.1598·1); levomenol (p.2333·3); hamamelis (p.2318·2).
Skin cleanser for oily skin.

Keracnyl stop bouton *Ducray, Fr.*
Ammonium glycyrrhizate (p.2316·1); lactamide; glycolic acid (p.1598·1); salicylic acid (p.1612·2); hamamelis (p.2318·2).
Acne.

Keraffler *Loeffler, Mex.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; atopic eczema; urticaria.

Kerafilm *Pierre Fabre, Fr.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; verrucae.

Kerafilmver *Pierre Fabre, Ital.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Hyperkeratosis; verrucas.

Keraflex *Pergam, Ital.*
⊗ Carbocisteine (p.1553·2); malic acid (p.2337·1); mucopolysaccharides; urea (p.1620·2); allantoin (p.1588·1).
Cicatrisation.

Keraflox *Angelini, Ital.; ACRAF, Port.*
Prulifloxacin (p.320·1).
Bacterial infections.

Kerafoam *Onset, USA.*
⊗ Urea (p.1620·2).
Dry skin.

Keral *Menarini, Irl.; Menarini, UK.*
Dexketoprofen trometamol (p.73·1).
Pain.

Keralac *Doak, USA.*
⊗ Urea (p.1620·2).
Skin and nail disorders.

Keralac Plus *LED, Fr.†.*
Ammonium lactate (p.1589·2); salicylic acid (p.1612·2); zinc gluconate (p.1999·2).
Acne.

Keralin *East India Pharma, India.*
⊗ Hydrocortisone acetate (p.1535·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Corns.

Keralyt *Summers, USA.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Keranin *Quimifar, Spain.*
Acetic acid (p.2244·2); flexible collodion; lactic acid (p.2329·3); castor oil; salicylic acid (p.1612·2).
Warts.

Keranon *Pentamedical, Ital.*
Salicylic acid (p.1612·2).
Keratinisation disorders.

Kerapil *Fouchard, Chile†; LED, Fr.†.*
Ammonium lactate (p.1589·2).
Keratinisation disorders.

Kerarer *LKM, Arg.*
Ketorolac trometamol (p.74·2).
Pain.

Kerasal *Alterna, Canad.; Spirig, Cz.; Spirig, Switz.; Orva, Turk.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2).
Skin and scalp disorders.

Kerasal AL *Taro Consumer, USA.*
Ammonium lactate (p.1589·2).
Emollient.

Kerastil *Loeffler, Mex.*
Aciclovir (p.862·3).
Herpes simplex infections of the lips and face.

Keratinamin *Kowa, Jpn.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Keratisdin *Isdin, Spain.*
Lactic acid (p.2329·3).
Skin disorders.

Kerato Biciron *S & K, Ger.*
Calcium pantothenate (p.1959·3).
Corneal injury.

Keratolip *Qualifarma, Ital.*
Betacarotene (p.1930·3); propolis (p.2373·3).
Emollient for lips.

Keratolit *ICN, Pol.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2).
Skin disorders.

Keratolysin *RiC, Pol.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Corns.

Keratopic *Cassara, Arg.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Keratosane *Uriage, Fr.*
A range of emollients.
Dry skin disorders hyperkeratotic skin disorders.

Keratosis *Widmer, Austria.*
⊗ Urea (p.1620·2); dexpanthenol (p.2362·1).
Hyperkeratotic skin disorders.

Keratosis forte *Widmer, Austria.*
⊗ Urea (p.1620·2); dexpanthenol (p.2362·1); tretinoin (p.1618·1).
Skin disorders.

Keratospor *Agis, Israel.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Keratyl *Sidus, Arg.†; Chauvin Ankerpharm, Cz.†; Chauvin, Fr.†; Chauvin ankerpharm, Ger.†; Bausch & Lomb, Switz.; Chauvin, Thai.*
⊗ Nandrolone sodium sulfate (p.2118·3).
Corneal lesions.

Keri
Note.This name is used for preparations of different composition.
BMS, Canad.†; Novartis Consumer, USA.
A range of emollient and moisturiser preparations.
Dry skin.
BMS, Hong Kong; Novartis, UK.
Liquid paraffin (p.2030·3).
Dry skin.

Keri Lotion UVB/A *BMS, Canad.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Keri Silky Smooth *Mentholatum, Austral.*
Emollient.
Dry skin disorders; pruritus; skin irritation.

Keri Skin Renewal *BMS, Canad.†.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Keri Vit E *BMS, Hong Kong.*
Vitamin E (p.1992·2).
Facial wrinkles; scars.

Keritmon *Best, Mex.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Keritrina *Keryos, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Kerium Intensive *Roche-Posay, Fr.*
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1).
Dandruff.

Kerlofin *Chrispa (Χρισπα), Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kerlon *Lorex, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Neth.; Pharmacia, Swed.†; Synthelabo, Switz.†.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris; hypertension.

Kerlone *Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi Synthelabo, Fr.; Sanofi Synthelabo, Ger.; Lavipharm, Gr.; Synthelabo, Israel; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Singapore; Sanofi, USA.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris; hypertension.

Kerlong *Mitsubishi, Jpn.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris.

Kerniox *Kern, Spain.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Kernit *CT, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Kernosan Elixir *Kern, Switz.*
Aniseed (p.2258·2); horseradish (p.2320·1); calamus (p.2271·3); fennel (p.2302·3); ivy (p.2328·1); imperatoria root; Iceland moss (p.2324·1); pimpinella root (p.2270·3); plantain seed (p.2369·3); oak bark (p.2355·3); primula root (p.2372·2); liquorice (p.1740·3).
Bronchitis; catarrh; coughs.

Kernosan Heidelberger Poudre *Kern, Switz.*
Absinthium (p.2244·1); aniseed (p.2258·2); caraway (p.2276·3); fennel (p.2302·3); juniper (p.2328·2); achillea (p.2245·2); pimpinella root (p.2270·3).
Digestive system disorders.

Kernosan Huile de Massage *Kern, Switz.*
Eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); sweet birch oil (p.86·2); camphor (p.2273·2).
Formerly contained plum oil, camphor, methyl salicylate, eucalyptus oil, lavender oil, mint oil, rosemary oil, sage oil, thyme oil, turpentine oil, and hyoscyamus oil.
Musculoskeletal, joint, and peri-articular pain.

Keroderm *Turimed, Switz.†.*
Linoleic acid ethyl ester (p.2308·2); triclosan (p.1665·2); cholesterol; cod-liver oil (p.1935·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Eczema; inflammation; minor skin lesions.

Kerodex *Miba, Ital.; Whitehall, USA.*
Barrier cream.

Kerol *Doak, USA.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Keromask *Network Health & Beauty, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Kerpet *Roux-Ocefa, Arg.†.*
⊗ Budesonide (p.1520·1).

Kertyol *Medifarm Ducray, Venez.*
Salicylic acid (p.1612·2); benzyl benzoate (p.2036·1); cetrimonium chloride (p.1635·1); crotamiton (p.1593·2); piroctone olamine (p.1610·1).
Dandruff.

Kertyol PFDC *Pierre Fabre Dermo-Cosmetique, Arg.*
Kertyol; salicylic acid (p.1612·2).
Dandruff.

Kertyol S
Note. A similar name is used for preparations of different composition (see below).
Pierre Fabre Dermo-Cosmetique, Arg.
Kertyol; salicylic acid (p.1612·2); zinc salicylate (p.1612·3).
Dandruff.

Kertyol-S
Note.This name is used for preparations of different composition.
Ducray, Fr.
Cream: Kertyol; glycolic acid (p.1598·1); glycerol (p.2314·2); keluamid (p.1603·2).
Seborrhoeic dermatitis.
Ducray, Fr.
Shampoo: Kertyol; salicylic acid (p.1612·2); glycolic acid (p.1598·1).
Scalp disorders.

Kertyol Shampooing *Ducray, Fr.*
Kertyol; salicylic acid (p.1612·2).
Dandruff.

Kesan *Baliarda, Arg.†.*
Ibuprofen (p.64·2).
Pain.

Kesint *Copernico, Ital.*
Cefuroxime sodium (p.238·2).
Gram-negative bacterial infections.

Kesol *DMG, Ital.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Kess *Filaxis, Arg.*
Lamivudine (p.895·1).
HIV infection.

Kess Complex *Filaxis, Arg.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Kessar *Pfizer, Austria; Pharmacia, Braz.; Pfizer, Chile; Pfizer, Fr.; Pharmacia, Ger.†; Pfizer, Gr.; Pfizer, Ital.; Pfizer, Mex.†; Pfizer, Philipp.; Pharmacia, S.Afr.; Pfizer, Switz.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Kest *Torbet Laboratories, UK.*
Magnesium sulfate (p.1679·3).
Formerly contained magnesium sulfate and phenolphthalein.
Constipation.

Kesterina *Rowe-Fleming, Venez.†.*
Ceftazidime (p.234·1).
Bacterial infections.

Kestin *Almirall, Fr.*
Ebastine (p.579·1).
Allergic rhinitis; urticaria.

Kestine *Aventis, Cz.†; Nycomed, Denm.; Leiras, Fin.; Novis, Gr.; Eisai, Hong Kong; Almirall, Ital.; Almirall, Neth.; Almirall, Norw.; Almirall, Port.; Aventis, Rus.; Pharmacare, S.Afr.; Almirall, Singapore; Nycomed, Swed.*
Ebastine (p.579·1).
Allergic conjunctivitis; allergic rhinitis; hypersensitivity reactions; pruritus; urticaria.

Kestomatine *Sanofi-Aventis, Belg.*
Algeldrate (p.1706·2); simeticone (p.1770·2).
Drug-induced gastric irritation; flatulence; gastric hyperacidity.

Kestomatine Baby *Sanofi Synthelabo, Belg.†.*
Simeticone (p.1770·2); ceratonia (p.2143·2).
Abdominal distension; flatulence; vomiting.

Kestomatine Bebe *Sanofi Synthelabo, Switz.†.*
Simeticone (p.1770·2); carob fruit and seed (p.2143·2).
Gastrointestinal disorders.

Kestomicol *Farmaco, Mex.†.*
Ketoconazole (p.539·1).
Fungal infections.

Kestrone *Hyrex, USA.*
Estrone (p.2101·2).
Abnormal uterine bleeding; breast cancer; female castration; female hypogonadism; menopausal vulval and vaginal atrophy; primary ovarian failure; prostatic cancer.

Keta *DeltaSelect, Ger.†.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia; status asthmaticus.

Keta-Hameln *Hameln, Thai.†; TTN, Thai.†.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketaject *Astrapin, Philipp.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketalar *Elea, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Erfa, Canad.; Pfizer, Chile†; Pfizer, Denm.†; Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.†; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Parke, Davis, Israel; Pfizer, NZ; Pfizer, Norw.; Pfizer, Port.; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; JHP, USA.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketalgin *Farmstandart, Rus.*
Ketorolac trometamol (p.74·2).
Pain.

Ketalgine *Amino, Switz.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome; pain.

Ketalin *Probiomed, Mex.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketamax *Rotexmedica, Philipp.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketanest
Note.This name is used for preparations of different composition.
Scott-Cassara, Arg.; Parke, Davis, Pol.
Ketamine hydrochloride (p.1787·1).
General anaesthesia.
Pfizer, Austria; Pfizer, Fin.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Neth.
Esketamine hydrochloride (p.1787·1).
Formerly contained ketamine hydrochloride in *Ger.*
Analgesia in anaesthesia; general anaesthesia; regional anaesthesia; status asthmaticus.

Ketanine *Korea United, Singapore†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Ketanov *Ranbaxy, India; Ranbaxy, Malaysia†; Ranbaxy, Philipp.; Ranbaxy, Rus.*
Ketorolac trometamol (p.74·2).
Pain; postoperative eye inflammation.

Ketartrium *Esseti, Ital.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Ketas *Kyorin, Jpn.*
Ibudilast (p.1123·3).
Asthma; cerebrovascular disorders.

Ketasma *Sun, India; Vita, Spain†.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma.

Ketava *Atlantic, Malaysia.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketaxal *Hexal, Mex.†.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; atopic eczema; urticaria.

Ketazol
Note.This name is used for preparations of different composition.
Korea United, Philipp.
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Pharmacare, S.Afr.; Shiwa, Thai.†; Vargas, Venez.
Ketoconazole (p.539·1).
Fungal infections.

Ketazon
Note. This name is used for preparations of different composition.
BMS, Arg.†.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Gerot, Austria†; Leciva, Cz.†.
Kebuzone (p.72·3).
Trimecaine (p.1872·3) may be included in the injection to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis; pain; thrombophlebitis.

Siam Bheasach, Thai.
Ketoconazole (p.539·1).
Fungal infections.

Ketazon Compositum *Leciva, Cz.†.*
Kebuzone (p.72·3); a heparinoid (p.1305·2).
Musculoskeletal disorders; thrombophlebitis.

Ketazon Flex *BMS, Arg.†.*
Piroxicam (p.117·3); carisoprodol (p.1894·1).
Musculoskeletal and joint disorders with muscle spasm.

Ketek *Aventis, Arg.†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile†; Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Aventis, Ital.; Astellas, Jpn; Aventis, Mex.; Aventis, Neth.; Aventis, Norw.; Aventis, Pol.; Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Aventis, USA; Sanofi-Aventis, Venez.*
Telithromycin (p.345·3).
Bacterial infections of the respiratory tract.

Keten *Siam Bheasach, Thai.*
Ketotifen (p.582·2).
Asthma; hypersensitivity reactions.

Ketensin *Janssen-Cilag, Neth.*
Ketanserin tartrate (p.1320·2).
Hypertension.

Ketesgel *Rovi, Spain.*
Dexketoprofen trometamol (p.73·1).
Musculoskeletal and joint disorders.

Ketesse *Menarini, Cz.; Ferron, Indon.; Lusofarmaco, Ital.; Menarini, Port.; Rovi, Spain; Menarini, Switz.*
Dexketoprofen trometamol (p.73·1).
Pain.

Ketidin *Montpellier, Arg.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Ketifen *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Thai.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; bronchitis; hypersensitivity reactions.

Ketilept *Egis, Cz.; EGIS, Hung.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; psychoses; schizophrenia.

Ketlur *Milmet, India.*
Ketorolac trometamol (p.74·2).
Allergic conjunctivitis.

Ketmin *Themis Chemicals, India.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Keto
Note. This name is used for preparations of different composition.
Vitabalans, Fin.; Ilsan, Turk.; Valmor, Venez.
Ketoprofen (p.73·1).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Yung Shin, Hong Kong; YSP, Malaysia; Yung Shin, Singapore†.
Ketorolac trometamol (p.74·2).
Pain.

Cipla, India.
Ketoconazole (p.539·1).
Fungal infections.

Masa, Thai.
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Keto Plus *Glenmark, Rus.*
Ketoconazole (p.539·1); pyrithione zinc (p.1611·2).
Dandruff; pityriasis; seborrhoeic dermatitis.

Keto Z *Alta Care, Ital.*
Ketoconazole (p.539·1); dexpanthenol (p.2362·1); pyrithione zinc (p.1611·2); vitamin E.
Dandruff.

Ketobene *Merckle, Cz.†.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Ketocal *Scientific Hospital Supplies, Irl.; Nutricia, Ital.*
Food for ketogenic diet (p.1922·1).
Epilepsy.

Ketocef *Pliva, Rus.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Ketocev *Cevallos, Arg.*
Ketotifen (p.582·2).

Ketocid *Trinity, UK.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ketocine *Medicine Products, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Ketocoval *Valmor, Venez.†.*
Ketoconazole (p.539·1).
Fungal infections.

Keto-Cure *OTC, Spain.*
Ketoconazole (p.539·1).
Fungal skin and nail infections.

Ketoderm *Taro, Canad.; Janssen-Cilag, Fr.*
Ketoconazole (p.539·1).
Fungal skin infections.

Ketoderma *Cantabria, Spain.*
Ketoconazole (p.539·1).
Fungal skin and nail infections.

Ketodex *Berlin-Chemie, Hung.; Menarini, Hung.*
Dexketoprofen trometamol (p.73·1).
Pain.

Keto-Diabur *Roche Diagnostics, Braz.*
Test for glucose and ketones in urine.

Keto-Diabur Test *Roche Diagnostics, Irl.*
Test for glucose and ketones in urine.

Keto-Diabur Test 5000 *Roche, Arg.; Roche Diagnostics, Austral.; Roche Diagnostics, Fr.; Roche Diagnostics, Mex.; Roche Diagnostics, NZ; Roche Diagnostics, UK.*
Test for glucose and ketones in urine.

Ketodiaburtest 5000 *Roche, Chile; Roche Diagnostics, Ital.*
Test for glucose and ketones in urine.

Keto-Diastix *Bayer, Arg.; Bayer, Austral.; Bayer, Canad.; Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, Mex.†; Bayer, NZ; Bayer Diagnostics, UK; Bayer, USA.*
Test for glucose and ketones in urine.

Ketodiastix *Bayer, Port.*
Test for glucose and ketones in urine.

Ketodol *Wassermann, Ital.*
Ketoprofen (p.73·1).
Sucralfate (p.1772·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Ketodrops *Cipla, India.*
Ketorolac trometamol (p.74·2).

Ketodur
Note. This name is used for preparations of different composition.
Pfizer, Denm.†; Pharmacia, Norw.†; Pharmacia, Swed.†.
Ketobemidone hydrochloride (p.73·1).
Pain.

Biospray, Gr.†.
Ketoprofen (p.73·1).
Inflammatory disorders.

Ketof *Hexal, Cz.; Hexal, Ger.*
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Ketofar *Farcoral, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Ketofarm *Madaus, Ital.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketofen
Note. This name is used for preparations of different composition.
Asian Pharm, Thai.
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Nobel, Turk.
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Ketofene *Alter, Port.†.*
Ketoprofen (p.73·1).

Ketoflam *Adcock Ingram, S.Afr.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ketoflex *Merck, Mex.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Ketoftil *Farmigea, Ital.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis.

Ketogan *Pfizer, Denm.; Pfizer, Norw.; Pfizer, Swed.*
Ketobemidone hydrochloride (p.73·1); 3-dimethylamino-1,1-diphenylbuten-(1)hydrochloride.
Pain.

Ketogan Novum *Pfizer, Swed.*
Ketobemidone hydrochloride (p.73·1).
Adjunct in regional anaesthesia; pain.

Ketogel *Stiefel, Arg.†.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Ketohair *Euroderm, Arg.†.*
Ketoconazole (p.539·1); collagen; coconut oil.
Dandruff.

Ketohexal *Hexal, S.Afr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma.

Ketoisdin *Isdin, Spain.*
Ketoconazole (p.539·1).
Fungal infections.

Ketokid *Hexal, Arg.†.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma; bronchospasm.

Ketolan *Olan-Kemed, Thai.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Ketolar *Parke, Davis, Spain.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Ketolef *Biosintex, Arg.*
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Ketolist *Thiemann, Ger.†.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Ketolium *McNeil, Fr.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Ketomed
Note. This name is used for preparations of different composition.
Surya Dermato, Indon.; Medihealth, Mex.; Rhein, Mex.; Medifive, Thai.; Roemmers Medihe, Venez.
Ketoconazole (p.539·1).
Fungal infections; scalp disorders.

Medhaus, Philipp.
Ketorolac trometamol (p.74·2).
Pain.

Ketomex *Ratiopharm, Fin.*
Ketoprofen (p.73·1).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Ketomicol *Luper, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Ketomizol *Reuffer, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Ketomousse *Mipharm, Ital.*
Ketoconazole (p.539·1); pyrithione zinc (p.1611·2); salicylic acid (p.1612·2).
Dandruff.

Ketonal *Lek, Cz.; Agis, Israel†; Lek, Pol.; Lek, Rus.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ketonan *Marjan, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Ketonazol *Lafedar, Arg.; Bunker, Braz.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Ketonazole *Polipharm, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Ketonex *Abbott, Austral.†; Ross, USA.*
Isoleucine, leucine, and valine free preparation for enteral nutrition (p.1922·1).
Beta-ketothiolase deficiency; maple syrup urine disease.

Ketonic *Nicholas Piramal, India†.*
Ketorolac trometamol (p.74·2).
Pain.

Ketonil *Grunenthal, Chile†.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Ketop *Biobras, Braz.†.*
Ketoprofen (p.73·1).

Ketopain *Soho, Indon.*
Ketorolac trometamol (p.74·2).
Postoperative pain.

Ketopharm *Valeant, Arg.*
Ketorolac trometamol (p.74·2).
Allergic conjunctivitis; postoperative eye inflammation.

Ketopine *AFT, NZ.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Ketoplus
Note. This name is used for preparations of different composition.
Pantafarm, Ital.
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; phlebitis.

Glenmark, Malaysia.
Ketoconazole (p.539·1); pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Ketoprom *GSK, Pol.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular pain.

Ketopronil *Unia, Pol.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketoptic *Oftalmi, Venez.*
Ketotifen (p.582·2).
Allergic conjunctivitis.

Ketoral *Community Pharmacy, Thai.†; Bilim, Turk.*
Ketoconazole (p.539·1).
Fungal infections.

Ketorax *Pfizer, Norw.*
Ketobemidone hydrochloride (p.73·1).
Pain.

Ketorel *Leti, Venez.†.*
Ketorolac trometamol (p.74·2).
Inflammation; pain.

Ketores *ICN, Pol.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders.

Ketoril *Vitae, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Ketorin *Orion, Fin.*
Ketoprofen (p.73·1).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Ketorol *Reddy, Rus.; Biofarma, Venez.†.*
Ketorolac trometamol (p.74·2).
Pain.

Ketoselect *Menarini, Ital.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; thrombophlebitis.

Ketosil *Silom, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Ketosolan *Spyfarma, Spain.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Ketoson *CCS, Swed.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Ketospor *AC Helcor, Hung.*
Ketoconazole (p.539·1).
Fungal infections.

Ketospray *CSC, Hung.; Medicom, Pol.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketosteril *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Ger.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Diamedica, Venez.†.*
Amino-acid preparation (p.1922·1).
Nutritional supplement in renal failure.

Ketostix *Bayer, Austral.; Bayer, Canad.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer, NZ; Bayer Diagnostics, UK; Bayer, USA.*
Test for ketones in urine.

Ketotisan *Wabosan, Austria.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Ketotisin
Chemopharma, Chile.
Ketotifen (p.582·2).
Hypersensitivity reactions.

Dollder, Venez.
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Ketotop *Pacific, Malaysia†; Pacific, Philipp.; Unimex, Philipp.; Pacific, Singapore†.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Ketovail *Approved Prescription Services, UK.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal and joint disorders; pain.

Ketovid *Hovid, Philipp.*
Ketoconazole (p.539·1).
Fungal infections.

Ketovite
IFET (ΙΦΕΤ), Gr.; Paines & Byrne, NZ; Paines & Byrne, UK.
Multivitamin preparation (p.1922·1).

Paines & Byrne, Irl.
Oral liquid: Vitamin A, choline chloride, ergocalciferol, and cyanocobalamin (p.1922·1).
Dietary supplement.

Paines & Byrne, Irl.
Tablets: Multivitamin preparation (p.1922·1).
Dietary supplement.

Ketozal *Pond's, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Ketozip *Ashbourne, UK†.*
Ketoprofen (p.73·1).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders; sciatica.

Ketozol *Galderma, Arg.†; Christo, Hong Kong; Mepha, Switz.*
Ketoconazole (p.539·1).
Fungal infections.

Ketozole *DHA, Hong Kong; DHA, Malaysia†; DHA, Singapore.*
Ketoconazole (p.539·1).
Fungal infections.

Ketrax *AstraZeneca, Irl.†; IDIS, UK†.*
Levamisole hydrochloride (p.147·2).
Worm infections.

Ketrel
Note. This name is used for preparations of different composition.
Biorga, Fr.; Saninter, Port.
Tretinoin (p.1618·1).
Acne; psoriasis.

Celon, Pol.
Quetiapine fumarate (p.1022·2).
Schizophrenia.

Ketricin *Ferron, Indon.*
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Corticosteroid.

Ketrizin *Esseti, Ital.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ketros *Pharos, Indon.*
Ketoprofen (p.73·1).
Gout; musculoskeletal and joint disorders.

Ketum *Menarini, Fr.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ketur-Test *Roche Diagnostics, Irl.; Roche Diagnostics, Ital.; Roche Diagnostics, NZ; Roche Diagnostics, UK.*
Test for ketones in urine.

Keunmixin *Keun Wha, Philipp.; Unimex, Philipp.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Keunzef *Keun Wha, Philipp.; Unimex, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Keval *Pharmacos Abug, Mex.*
Lansoprazole (p.1739·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kevatril *Roche, Ger.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Kevis *Pfizer Consumer, Ital.*
Pyrithione magnesium (p.1611·2); iceland moss (p.2324·1).
Seborrhoeic dermatitis.

Kexelate *Adcock Ingram Critical Care, S.Afr.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Kexidil *Kener, Mex.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

K-Exit *Omega, Canad.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Keydol *Roemmers-Klinos, Venez.*
Ketoprofen (p.73·1).
Inflammation; pain.

Keyerpril *Keyerson, Mex.†.*
Captopril (p.1239·2).
Hypertension.

Keylyte *Wallace, India.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Key-Plex *Hyrex, USA†.*
Vitamin B substances and vitamin C (p.1922·1).
Parenteral nutrition.

Key-Pred *Hyrex, USA†.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Key-Pred-SP *Hyrex, USA.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Kez *Pharma Dynamics, S.Afr.*
Ketoconazole (p.539·1).
Fungal infections.

Kezon *Osoth, Thai.*
Ketoconazole (p.539·1).
Fungal skin infections.

Kezoral *Sandoz, Denm.; Upha, Malaysia; Upha, Singapore.*
Ketoconazole (p.539·1).
Fungal infections; pityriasis versicolor; seborrhoeic dermatitis.

K-Fenac *Cipla, India.*
Diclofenac potassium (p.44·3).

K-Fenak *Cipla-Medpro, S.Afr.*
Diclofenac potassium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

K-Flebo *Hardis, Ital.*
Potassium aspartate (p.1684·2).
Hyperammonaemia; hypokalaemia.

K-Fosfosteril *Orion, Fin.†.*
Dibasic potassium phosphate (p.1682·2).
Potassium deficiency.

K-G Elixir *Geneva, USA.*
Potassium gluconate (p.1684·3).
Hypokalaemia; potassium depletion.

KGS-PE *Cypress, USA.*
Phenylephrine hydrochloride (p.1568·1); sulfogaiacol (p.1573·2).
Coughs; upper respiratory-tract congestion.

KH3
Note.This name is used for preparations of different composition.
Raffo, Arg.
Procaine; ginseng; alfa tocoferol (p.1922·1).
Tonic.

Schwarzhaupt, Austria; Schwarzhaupt, Ger.†; Schwarzhaupt, Thai.
Procaine hydrochloride (p.1869·1); haematoporphyrin (p.2318·1).
Reduced physical and mental capacity in the elderly; tonic.

Deutsche, Chile†.
Procaine (p.1869·2); haematoporphyrin (p.2318·1).
Tonic.

Bipharma, Hong Kong.
Procaine hydrochloride (p.1869·1); haematoporphyrin (p.2318·1); electrolytes (p.1667·1).
Tonic.

Bamford, NZ.
Procaine hydrochloride (p.1869·1); haematoporphyrin (p.2318·1); magnesium carbonate; magnesium phosphate; potassium chloride; sodium phosphate (p.1922·1).
Tonic.

Khellangan N *Ardeypharm, Ger.†.*
Ammi visnaga fruit (p.2256·1).
Cardiac disorders; obstructive airways disease.

KH3-Vit *Deutsche, Chile†.*
Procaine hydrochloride (p.1869·1); haematoporphyrin (p.2318·1); vitamins (p.1922·1).
Tonic.

Kiadon *Merck, Braz.†; Mepro, Chile; Merck, Venez.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; ear disorders; eye disorders; tonic; vestibular disorders.

Kiatrium *Gross, Braz.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Kid Kare Childrens Cough/Cold *Rugby, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Kid Kare Pediatric Nasal Decongestant *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Kidbar *Piam, Ital.*
Food for special diets (p.1922·1).
Phenylketonuria.

Kidcal *Farma, Venez.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Calcium supplement.

Kiddi *Boehringer Ingelheim, Arg.; Pharmaton, Israel; Pharmaton, S.Afr.†; Pharmaton, Switz.*
Lysine hydrochloride; vitamins; minerals (p.1922·1).
Nutritional supplement; tonic.

Kiddi Choo *Boehringer Ingelheim, S.Afr.†.*
Multivitamin and mineral preparation (p.1922·1).

Kiddi Pharmaton *Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Pharmaton, Indon.; Boehringer Ingelheim, Irl.; Pharmaton, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Philipp.; Pharmaton, Singapore; Boehringer Ingelheim, Thai.*
Multivitamin and mineral preparation with lysine (p.1922·1).
Nutritional supplement; tonic.

Kiddie Estamin *Biolink, Philipp.*
Vitamins; lysine; taurine; chlorella (p.1922·1).

Kiddie Prime *Primera, Philipp.*
Vitamins; minerals; amino acids; chlorella growth factor (p.1922·1).

Kiddie Vite *Covan, S.Afr.†.*
Ferrous gluconate (p.1939·1); vitamin B (p.1976·3).
Iron-deficiency anaemia.

Kiddigum *Adco, S.Afr.*
Benzocaine (p.1854·1).
Aphthous ulcers; teething.

Kiddirel *Metz, Philipp.*
Vitamin; lysine; taurine; chlorella growth factor (p.1922·1).

Kiddyflu *Caps, S.Afr.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Kid-Eeze *Pharmachoice, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Kidmin *Otsuka, Indon.; Otsuka, Jpn; Thai Otsuka, Thai.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Kidonax *Unipharm, Mex.*
Nitazoxanide (p.842·3).
Protozoal infections; worm infections.

Kidrolase *Bioprofarma, Arg.; OPi, Canad.; OPi, Cz.; Orphan, Fr.; CTS, Israel.*
Asparaginase (p.682·1).
Malignant neoplasms.

Kids *IQFA, Mex.*
Vitamin preparation (p.1922·1).

Kid's Bumps *Homeocan, Canad.†.*
Homoeopathic preparation.

Kid's Chewable Cal-Mag *Quixtar, Canad.†.*
Calcium (p.1675·2); magnesium carbonate (p.1743·1).

Kid's Colic *Homeocan, Canad.*
Homoeopathic preparation.

Kids' Earache *Homeocan, Canad.*
Homoeopathic preparation.

Kids Sunblock *Tanning Research, Canad.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Kids' Teething *Homeocan, Canad.*
Homoeopathic preparation.

Kidz Kit 2 *Natrapharm, Philipp.*
Oral suspension, rifampicin (p.325·3) (Natricin Forte); syrup, isoniazid (p.288·1) (Curazid Forte).
Pyridoxine hydrochloride (p.1978·2) is included in the Curazid Forte syrup for prophylaxis of peripheral neuropathy.
Tuberculosis.

Kidz Kit 3 *Natrapharm, Philipp.*
Oral suspension, pyrazinamide (p.320·2) (Zcure); oral suspension, rifampicin (p.325·3) (Natricin Forte); syrup, isoniazid (p.288·1) (Curazid Forte).
Pyridoxine hydrochloride (p.1978·2) is included in the Curazid Forte syrup for prophylaxis of peripheral neuropathy.
Tuberculosis.

KIE *Laser, USA.*
⊗ Ephedrine hydrochloride (p.1558·2); potassium iodide (p.2169·2).
Coughs.

KI-Expectorante *Cimed, Braz.*
Oxomemazine hydrochloride (p.587·1); potassium iodide (p.2169·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2); ipecacuanha (p.1562·3).
Respiratory-tract congestion.

Kifadene *Kimia, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Kifarol *Pharmanik (Φαρμανικ), Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Kifarox *Kimia, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Kiflexin *Balldarassi, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Kikelaio EF 3 *Norma (Νορμα), Gr.†.*
Castor oil (p.2278·1).
Bowel evacuation.

Kilios
Note.This name is used for preparations of different composition.
Pfizer, Chile.
18 Tablets, estradiol (p.2097·2); 13 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Pharmacia, Ital.†.
Aspirin (p.20·3).
Fever; pain.

Kilkof *Bell, UK.*
Cetylpyridinium chloride (p.1635·1); benzoin tincture (p.2394·2); ipecacuanha tincture (p.1562·3); capsicum tincture (p.2276·2).
Cold symptoms; coughs; sore throat.

Killavon *Lysoform, Ger.*
Benzalkonium chloride (p.1629·1).
Fungal skin infections; surface disinfection.

Killgrip
Note.This name is used for preparations of different composition.
Sedabel, Braz.†.
Injection: Dipyrone (p.49·2); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); ascorbic acid (p.1983·3); mepyramine maleate (p.585·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Cold and influenza symptoms.

Sedabel, Braz.†.
Tablets: Green tablets, dipyrone (p.49·2); guaifenesin (p.1561·3); white tablets, ascorbic acid (p.1983·3); mepyramine maleate (p.585·2).
Cold and influenza symptoms.

Killit *Biosintetica, Braz.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Kilmicen *Pfizer, Mex.†.*
Tolciclate (p.548·3).
Fungal skin infections.

Kilnits *Andromaco, Chile.*
Permethrin (p.2048·2).
Pediculosis.

Kilonum *Frik, Turk.*
Lithium carbonate (p.401·3).
Behaviour disorders; bipolar disorder; depression; mania.

Kilor *Guidotti, Spain.*
Ferritin (p.1938·1).
Iron-deficiency anaemia.

Kilovit *Italmex, Mex.*
Vitamin and mineral preparation (p.1922·1).

Kilpane *GSK, India.*
Eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal disorders.

Kilsol *Biomedica-Chemica, Gr.*
Cetirizine (p.571·1).
Allergic disorders.

Kimafan *Duopharma, Hong Kong.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Ki-Min-To *Aventis, Cz.†.*
Peppermint oil (p.1761·2).
Catarrh; gastrointestinal disorders; headache; myalgia; neuralgia.

Kimotab *Mochida, Jpn.*
Bromelains (p.2269·1); trypsin (p.2405·3).
Inflammation.

Kimoxil *Kimia, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Kin *Andromaco, Chile.*
Ibuprofen (p.64·2).
Inflammation; pain.

Kin Soff *Kanion, Israel.*
Pyrethrum (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Kinabide *Bago, Arg.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Kinasten *Kinder, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Kincinat *Inquifave, Venez.†.*
Gentamicin (p.284·2).
Bacterial infections.

Kindaren *Kinder, Braz.*
Diclofenac sodium (p.44·3).

Kindcalcio *Kinder, Braz.*
Calcium phosphate; cyanocobalamin; ergocalciferol; sodium fluoride (p.1922·1).

Kindcetin *Kinder, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).

Kindelmin *Kinder, Braz.*
Mebendazole (p.148·3).
Worm infections.

Kinder Biovital *Roche Consumer, Hung.†; Bayer, Pol.; Nattermann, Rus.*
Vitamins; manganese; molybdenum; lecithin (p.1922·1).
Iron deficiency; tonic.

Kinder Em-eukal Hustensaft *Soldan, Ger.†.*
Thyme (p.2401·1); primula root (p.2372·2).
Catarrh; respiratory-tract congestion.

Kinder Finimal *Roche, Neth.†.*
Paracetamol (p.108·1).
Fever; pain.

Kinder Luuf *Apomedica, Austria.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); thymol (p.1664·3).
Catarrh; coughs and cold symptoms.

Kindercal *Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).

Kindergen *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Scientific Hospital Supplies, UK.*
Preparation for enteral nutrition in infants and children (p.1922·1).
Renal failure.

Kinderval *Omicron, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Kindigest *VSM, Neth.*
Homoeopathic preparation.

Kinditherm *VSM, Neth.*
Homoeopathic preparation.

Kindival *VSM, Neth.*
Homoeopathic preparation.

Kindomet *Kinder, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Kindpasm *Kinder, Braz.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Pain; skeletal muscle spasm.

Kinectine *Anglo-French Drugs, India.*
Aceclofenac (p.14·3).
Formerly contained valdecoxib and tizanidine hydrochloride.
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Kinectine P *Anglo-French Drugs, India.*
Aceclofenac (p.14·3); paracetamol (p.108·1).
Fever; pain.

Kinectine-MR *Anglo-French Drugs, India.*
Aceclofenac (p.14·3); paracetamol (p.108·1); tizanidine (p.1899·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Kinedak *Ono, Jpn.*
Epalrestat (p.439·1).
Diabetic neuropathy.

Kinedryl *Noventis, Cz.*
Moxastine teoclate (p.586·2); caffeine (p.1116·3).
Ménière's disease; motion sickness; vestibular disorders.

Kinerase *ICN, Arg.†; Valeant, Braz.; Valeant, Hong Kong; ICN, Malaysia†; Valeant, Mex.; Valeant, Singapore; Valeant, USA.*
Kinetin (p.1603·2).
Emollient; photodamaged skin; skin hyperpigmentation.

Kineret *Amgen, Austral.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Genesis, Gr.; Amgen, Irl.; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, UK; Amgen, USA.*
Anakinra (p.19·3).
Rheumatoid arthritis.

Kinerton *Vivax, Venez.*
Ginseng; vitamins; minerals (p.1922·1).
Tonic.

Kinestase *Liomont, Mex.*
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastroparesis; impaired gastric motility.

Kinestrel *Psicofarma, Mex.*
Amantadine hydrochloride (p.792·3).
Parkinsonism.

Kinetal *Cipla, India.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Kinetizine *Cetus, Arg.†.*
Cisapride (p.1720·3).

Kineto *Systopic, India.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; inflammation; pain; pericoronitis.

Kinetone *Abbott, India.*
Multivitamin and mineral preparation (p.1922·1).

Kinevac *Bracco, Canad.†; Bracco, USA.*
Sincalide (p.2388·1).
Diagnosis of biliary-tract and pancreatic disorders.

Kinex *Psicofarma, Mex.*
Biperiden hydrochloride (p.797·2).
Extrapyramidal disorders; parkinsonism.

Kinfil *Nova Argentia, Arg.*
Enalapril (p.1276·1).
Heart failure; hypertension.

Kinfil D *Nova Argentia, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Kinidin *AstraZeneca, Austral.; AstraZeneca, Cz.†; Durascan, Denm.; AstraZeneca, Hong Kong†; AstraZeneca, Irl.; AstraZeneca, Philipp.; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK†.*
Quinidine bisulfate (p.1383·1).
Arrhythmias.

Kinidine
AstraZeneca, Belg.†; AstraZeneca, Neth.†.
Quinidine bisulfate (p.1383·1).
Arrhythmias.

IFET (ΙΦΕΤ), Gr.
Quinidine (p.1383·1).
Arrhythmias.

Kiniduron *Orion, Fin.*
Quinidine bisulfate (p.1383·1).
Arrhythmias.

Kinin *Nycomed, Denm.; SAD, Denm.; IFET (ΙΦΕΤ), Gr.†; Recip, Swed.*
Quinine hydrochloride (p.612·3).
Malaria; myotonia; night cramps.

Kinline *Siam Bheasach, Thai.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Kinnoferon 2A *Bergamo, Braz.*
Interferon alfa-2a (p.885·1).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Kinogen *Geymonat, Ital.*
⊗ Tyrothricin (p.358·2); hydrocortisone sodium succinate (p.1536·1).
Vulvovaginal infections.

Kinolymphat *PGM, Ger.*
Homoeopathic preparation.

Kinor *Medihealth, Mex.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; hyperkeratosis; warts.

Kinoves *Samjin, Philipp.; Unimex, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Kinson *Alphapharm, Austral.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Kintal *Pharmasant, Thai.†.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; soft-tissue pain.

Kintavit *Synthelabo, Switz.†.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

KintaVital *Sanofi-Aventis, Switz.*
Ginseng (p.2312·1).
Tonic.

Kinurea H *Neitum, Fr.*
Quinine and urea hydrochloride (p.2377·2).
Anorectal disorders.

Kinussen *Kleva, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Kinzal *Bayer, Switz.*
Telmisartan (p.1409·2).
Hypertension.

Kinzalkomb *Bayer, Belg.; Bayer, Cz.; Bayer, Denm.†; Bayer, Fin.; Bayer, Ger.; Bayer, Neth.; Bayer, Port.; Bayer, Swed.†.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Kinzalmono *Bayer, Belg.; Bayer, Cz.; Bayer, Denm.†; Bayer, Fin.; Bayer, Ger.; Bayer, Neth.; Bayer, Port.; Bayer, Swed.†.*
Telmisartan (p.1409·2).
Hypertension.

Kinzalplus *Bayer, Switz.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Kionex *Paddock, USA.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Kiovig *Baxter, Cz.; Baxter, Gr.; Baxter, Pol.; Baxter, UK.*
A normal immunoglobulin (p.2225·3).
Bone marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Kiper *Monserrat, Arg.*
Paracetamol (p.108·1); butetamate citrate (p.1553·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Kipres *Kyorin, Jpn.*
Montelukast sodium (p.1126·2).
Asthma.

Kira *Kwizda, Austria; Lichtwer, Canad.; Lichtwer, Cz.†; Riemser, Ger.; Lichtwer, UK; Konsuma, Venez.†.*
St John's wort (p.422·3).
Anxiety; depression; nervous disorders.

Kiri *Lampugnani, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamin B substances (p.1922·1).
Disturbances of the gastrointestinal flora.

kirim *Hormosan, Ger.*
Bromocriptine mesilate (p.798·1).
Parkinsonism.

kirim gyn *Taurus, Ger.*
Bromocriptine mesilate (p.798·1).
Hyperprolactinaemia; lactation inhibition.

Kirin *Medochemie, Hong Kong; Medochemie, Malaysia†; Medochemie, Rus.*
Spectinomycin hydrochloride (p.332·3).
Gonorrhoea.

Kiro Rub *Prodemdis, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Kirom *Eurofarma, Braz.*
Teicoplanin (p.344·3).
Bacterial infections.

Kirsan *Ativus, Braz.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Kirumelle *Raffo, Arg.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Kisolv *Ecupharma, Ital.†.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Kissimin *Argenfarma, Arg.*
Glucose (p.1945·3).
Dietary supplement.

Kit *Continental Pharma, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Kitacne *Fortbenton, Arg.*
Erythromycin (p.269·2).
Acne.

Kitacne AR *Fortbenton, Arg.†.*
Erythromycin (p.269·2); tretinoin (p.1618·1).
Acne.

Kitacne PB *Fortbenton, Arg.†.*
Erythromycin (p.269·2); benzoyl peroxide (p.1590·2).
Acne.

Kitadol *Laboratorios Chile, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Kitadol Flu *Laboratorios Chile, Chile†.*
Paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); sodium ascorbate (p.1984·1).
Cold and influenza symptoms.

Kitadol Flu Noche *Laboratorios Chile, Chile†.*
Paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); sodium ascorbate (p.1984·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold and influenza symptoms.

Kitadol Max *Laboratorios Chile, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Kitadol Periodo Menstrual *Laboratorios Chile, Chile.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine (p.585·1).
Menstrual disorders.

Kitnos *Pfizer, Braz.; Pfizer, Mex.; Pfizer, Philipp.*
Etofamide (p.834·2).
Amoebiasis; protozoal infections.

Kitoles *Soho, Indon.*
Poliglusam (p.2370·1); nicotinamide (p.1957·3); chromium tripicolinate (p.1934·3).
Hyperlipidaemias; to increase weight loss.

Kiton *Pulitzer, Ital.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; cardiac stenosis; heart failure; myocardial infarction.

kivat *Hormosan, Ger.†.*
Fluspirilene (p.999·2).
Anxiety disorders.

Kivexa
GSK, Arg.; GSK, Austral.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Spain; GSK, Swed.
Abacavir sulfate (p.861·3); lamivudine (p.895·1).
HIV infection.

GSK, Belg.; GSK, Chile; GSK, Gr.; GSK, UK.
Abacavir (p.861·3); lamivudine (p.895·1).
HIV infection.

Klabax *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Pol.; Ranbaxy, Rus.*
Clarithromycin (p.248·2).
Bacterial infections.

Klabet *Wermar, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Klabion *Bioton, Pol.*
Clarithromycin (p.248·2).
Bacterial infections.

Klacid
Abbott, Austral.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Thai.; Abbott, Turk.
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Abbott, Austria; Abbott, Hung.; Abbott, Pol.; Abbott, Switz.
Clarithromycin (p.248·2) or clarithromycin lactobionate (p.249·3).
Bacterial infections.

Klacid HP 7
Note. This name is used for preparations of different composition.
Abbott, Austral.; Abbott, NZ†.
Capsules, omeprazole (Probitor) (p.1753·1); capsules, amoxicillin trihydrate (p.202·2); tablets, clarithromycin (Klacid) (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Abbott, Malaysia; Altana, Malaysia; Sandoz, Malaysia.
Tablets, pantoprazole sodium (Controloc) (p.1760·1); tablets, amoxicillin (Ospamox) (p.202·2); tablets, clarithromycin (Klacid) (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Klaciped *Abbott, Switz.*
Clarithromycin (p.248·2).
Bacterial infections.

Klafenac *Galeno, Venez.*
Diclofenac (p.44·2) or diclofenac potassium (p.44·3).
Ankylosing spondylitis; inflammation; osteoarthritis; pain; rheumatoid arthritis.

Klafotaxim *Be-Tabs, S.Afr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Klallergine *Obolenskoe, Rus.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Klamacin *Hua, Thai.*
Clotrimazole (p.530·1).
Trichomoniasis.

Klamiran *Gedeon Richter, Hung.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Klamoks *Bilim, Thai.; TTN, Thai.; Bilim, Turk.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Klamoxin *Salutas, Cz.†.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Klaretop *Santa, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarfast *Cadila, Rus.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Klari *Abbott, Hung.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaricid
Abbott, Arg.; Abbott, Mex.; Abbott, UK.
Clarithromycin (p.248·2) or clarithromycin lactobionate (p.249·3).
Bacterial infections.

Abbott, Braz.; Abbott, Chile; Abbott, Gr.; Fisher, Neth.; Abbott, Philipp.; Abbott, Venez.
Clarithromycin (p.248·2).
Adjunct in Helicobacter pylori eradication; bacterial infections.

Klariderm *Clariana, Spain†.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Klaridex *Dexcel, Israel.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaridol *Shreya, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Klarifar *Farmedia, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarifect *Minerva (Μινέρβα), Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarigen *Generics, Hung.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarithran *Ranbaxy, S.Afr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarithrin *Iapharm, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaritril *Pharlab, Braz.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarivitina *Clariana, Spain†.*
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; reduced appetite; urticaria.

Klarix *Maver, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarmin *ICN, Pol.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Klarmyn *Sandoz, Mex.; Sandoz, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarolid *Ilsan, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaromin *Eczacibasi, Rus.; Eczacibasi, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaron *Dermik, Israel; Dermik, USA.*
Sulfacetamide sodium (p.335·3).
Acne.

Klaroxin *Farmanic, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Klarpharma *Alpharma, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaryl *Labocean, Fr.†.*
Sambucus; black currant; cynara; spiraea ulmaria; bladderwrack (p.1922·1).
Tonic.

Klaryne *Hua, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Klas *Elmor, Venez.*
Ambroxol theophyllinate.
Cough.

Klavic *Karnataka, Philipp.*
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Klavunat *Atabay, Turk.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Klavupen *Toprak, Turk.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Klax *Toprak, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Klaz *United Laboratories, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Klazidem *Demo, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

KLB6 *Nature's Bounty, USA.*
Pyridoxine hydrochloride (p.1978·2); soya lecithin (p.2332·2); kelp (p.2384·2); cider vinegar.

KLB6 Fruit Diet *Natural Life, Arg.*
Kelp (p.2384·2); lecithin (p.2332·2); vitamin B (p.1979·1); glucomannan (p.2312·3); grapefruit; bearberry (p.2263·3); cider vinegar; phenylalanine (p.1960·1).
Obesity.

Klean-Prep *Norgine, Austria; Norgine, Belg.; Rivex, Canad.; Norgine, Denm.†; Sabora, Fin.; Norgine, Fr.; Norgine, Ger.; Kite (Κιτε), Gr.; Norgine, Hong Kong; Helsinn Birex, Irl.; Norgine, Ital.; Healthcare Logistics, NZ; Norgine, Neth.; Norgine, Norw.; Helsinn, Port.; Norgine, S.Afr.; Norgine, Singapore; UCB, Spain; Biolac, Swed.†; Norgine, Switz.; Norgine, UK.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

K-Lease *Adria, USA†.*
Potassium chloride (p.1684·3).
Potassium deficiency.

Klebicil *Greenpharma, Braz.*
Amikacin (p.200·2).
Bacterial infections.

Kleen-Handz *American Medical, USA†.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Klenac *Klonal, Arg.*
Ketorolac (p.75·2).
Eye disorders.

Klenyl
Note. This name is used for preparations of different composition.
Medipharm, Venez.
Soap: Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne; seborrhoea.

Medipharm, Venez.
Topical gel: Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne; seborrhoea.

Klenzit *Glenmark, Philipp.*
Adapalene (p.1587·1).
Acne.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Kleotrat *Kleva, Gr.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Kleren *Rowe-Fleming, Venez.†.*
Nimodipine (p.1357·2).
Ischaemia following subarachnoid haemorrhage.

Klerimed *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Klerist-D *Nutripharm, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Klesidren *Chrispa (Χρισπα), Gr.*
Thiocolchicoside (p.1898·2).
Muscle relaxant.

Klestran *Rayere, Mex.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Klevasin *Kleva, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Klevistamin *Kleva, Gr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Klexane *Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Norw.; Sanofi-Aventis, Port.; Aventis, Swed.*
Enoxaparin sodium (p.1277·2).
Thromboembolic disorders.

Kliacef *SoSe, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Kliane *Schering, Cz.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Klicina *Roemmers-Klinos, Venez.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Klidibrax *Sandoz, Indon.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal hypermotility.

Klifem *Pekana, Ger.†.*
Homoeopathic preparation.

Klimadynon *Austroplant, Austria; Bionorica, Ger.; Bionorica, Hong Kong; Bionorica, Hung.; Bionorica, Indon.; Darya-Varia, Indon.; Bionorica, Rus.; Bionorica, Singapore.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Klimaktolan *VSM, Neth.*
Homoeopathic preparation.

Klimaktoplan *DHU, Rus.*
Homoeopathic preparation.

Klimaktoplant *Peithner, Austria; Omida, Switz.†.*
Homoeopathic preparation.

Klimaktoplant H *DHU, Ger.*
Homoeopathic preparation.

Klimaktosin *Meckel, Ger.*
Homoeopathic preparation.

Klimalet *Organon, Denm.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Klimapur
Note.This name is used for preparations of different composition.
Kwizda, Austria.
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Medico Uno, Hung.
Cimicifuga (p.2282·1).
Menopausal disorders.

Klimareduct *Solvay, Austria.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Klimasol *Phytofarm Kleka, Pol.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Klimasyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Klimater *Cifarma, Braz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Klimax *Herbapol Krakow, Pol.†.*
Shepherd's purse (p.2386·2); cimicifuga (p.2282·1); lupulus (p.2335·2); motherwort (p.2347·3); melissa (p.2339·3).
Menopausal disorders.

Klimax-Gastreu R10 *Reckeweg, Neth.*
Homoeopathic preparation.

Klimax-Gastreu S R10 *Reckeweg, Ger.*
Homoeopathic preparation.

Klimaxil *Leo, Denm.†.*
12 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Klimicin
Lek, Cz.; Lek, Hung.; Lek, Pol.; Sandoz, Thai.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Lek, Rus.
Clindamycin (p.251·1).

Klimodien *Schering, Cz.; Schering, Hung.†.*
Estradiol valerate (p.2097·3); dienogest (p.2094·1).
Menopausal disorders.

Klimonorm *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Hong Kong†; Jenapharm, Hung.; Jenapharm, Malaysia†; Jenapharm, Pol.; Jenapharm, Rus.; Jenapharm, Thai.*
9 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Klina *Royal, Chile.*
Clindamycin (p.251·1); benzoyl peroxide (p.1590·2).
Acne.

Klincosal *Roemmers, Venez.*
Bismuth subcarbonate (p.1711·1); calcium carbonate (p.1714·1); kaolin (p.1738·1); pectin (p.2145·2); carmellose (p.2142·1).
Gastrointestinal disorders.

Klindacin T *Polfa Tarchomin, Pol.*
Clindamycin phosphate (p.251·2).
Acne; bacterial skin infections.

Klindagol *Algol, Fin.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Klindan
Idol, Thai.; TTN, Thai.
Clindamycin phosphate (p.251·2).
Bacterial infections.

Bilim, Turk.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Klindaver *Biosel, Turk.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Klinna *Greater Pharma, Thai.*
Clindamycin phosphate (p.251·2).
Acne.

Klinoc *Wyeth Lederle, Austria†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Klinoksin *Deva, Turk.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Klinomel *Roemmers-Klinos, Venez.†.*
Dipyrone (p.49·2).
Fever; pain.

Klinomycin *Valeant, Ger.*
Minocycline hydrochloride (p.300·3).
Acne.

Klinotab *PSI, Belg.*
Minocycline hydrochloride (p.300·3).
Acne.

Klinotal *Roemmers-Klinos, Venez.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Klinoxid *Valeant, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Klinset *Bernofarm, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Kliofem *Novo Nordisk, UK.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Oestrogen deficiency; postmenopausal osteoporosis.

Kliogest *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia†; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Swed.; Novo Nordisk, Turk.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Hormone replacement therapy; menopausal disorders; oestrogen deficiency; osteoporosis.

Kliogest N *Novo Nordisk, Ger.; Novo Nordisk, Switz.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Klion *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Pharmamagist, Hung.; Gedeon Richter, Rus.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; peptic ulcer; protozoal infections; rosacea.

Klion-D *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Metronidazole (p.837·1); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Kliotex *Solvay, Rus.*
White soft paraffin (p.2031·2).
Burns; ulcers; wounds.

Kliovance *Novo Nordisk, Austral.; Novo Nordisk, NZ; Novo Nordisk, UK.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Klipaks *Ulagay, Turk.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Alcohol withdrawal syndrome; anxiety.

Klipal *Pharmacia, Arg.†.*
Paracetamol (p.108·1); codeine (p.37·2).
Pain.

Klipal Codeine *Pierre Fabre, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Klismacort *Bene, Ger.; Novartis Consumer, Ger.; Bene, Hung.†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Klispel *Ativus, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Klistier *Fresenius Kabi, Ger.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Klitopsin *Toprak, Turk.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Klizin *Cimed, Braz.*
Buclizine (p.570·1); vitamin B substances (p.1922·1).
Reduced appetite; tonic.

KLN *Roche Consumer, UK.*
Kaolin (p.1738·1); pectin (p.2145·2); sodium citrate (p.1673·3); peppermint oil (p.1761·2).
Diarrhoea.

Kloderma *Surya Dermato, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Klodin *Savio, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Klodipin *APS, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Klomazole *Klonal, Arg.*
Clotrimazole (p.530·1).
Fungal infections.

Klomen *Kocak, Turk.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Klomeprax *Klonal, Arg.*
Omeprazole (p.1753·1).
Peptic ulcer.

Klomicina *Klonal, Arg.*
Roxithromycin (p.331·1).
Bacterial infections.

Klonacid *Klonal, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Klonadroxil *Klonal, Arg.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Klonadryl *Klonal, Arg.*
Diphenhydramine (p.577·1).

Klonadryl Antitusivo *Klonal, Arg.†.*
Diphenhydramine (p.577·1); ammonium chloride (p.1551·3).
Coughs.

Klonafenac *Klonal, Arg.*
Diclofenac (p.44·2).
Inflammation; pain.

Klonalcrom *Klonal, Arg.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Klonalfenicol *Klonal, Arg.*
Chloramphenicol (p.239·3).
Bacterial infections.

Klonalflox *Klonal, Arg.*
Ofloxacin (p.310·2).
Bacterial infections.

Klonalmox *Klonal, Arg.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Klonalol *Klonal, Arg.*
⊗ Timolol (p.1413·1).
Ocular hypertension.

Klonam *Klonal, Arg.†.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Klonametacina *Klonal, Arg.*
Indometacin (p.66·3).
Inflammation; pain.

Klonamicin *Klonal, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Klonamicin Compuesto *Klonal, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Klonaprost *Klonal, Arg.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Klonastin *Klonal, Arg.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Klonat *Sandoz, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Klonatropina *Klonal, Arg.*
Atropine (p.1219·2).
Production of mydriasis.

Klonaza *Atlantis, Mex.*
Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3); clonixin lysine (p.37·1).
Smooth muscle spasm.

Klonazol *Klonal, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Klonocarpina *Klonal, Arg.†.*
Pilocarpine (p.1884·3).
Glaucoma.

Klonopin *Roche, USA.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Klonovan *Klonal, Arg.*
Chloramphenicol (p.239·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Klopoxid *Nycomed, Denm.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety.

K-Lor *Abbott, Canad.†; Abbott, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Kloracef *Bioton, Pol.†.*
Cefaclor (p.217·2).
Bacterial infections.

Kloramin *Hua, Thai.*
Chlorphenamine maleate (p.571·3).
Allergic skin disorders; hypersensitivity reactions; insect bites.

Kloramixin *Armoxindo, Indon.*
Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3).
Eye infections.

Kloramixin D *Armoxindo, Indon.*
⊗ Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2).
Bacterial eye infections.

Klorane Bebe Eryteal *Pierre Fabre Dermo-Cosmetique, Arg.*
Cod-liver oil (p.1935·2); halibut-liver oil (p.1948·1); zinc oxide (p.1621·2); cetrimonium bromide (p.1635·1).

Klorane Shampooing Antipelliculaire *Klorane, Fr.*
Myrtillus (p.2349·3); brevete; pyrithione zinc (p.1611·2).
Dandruff.

Klorasuksinat *Ulagay, Turk.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Klor-Con *Upsher-Smith, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Klor-Con/EF *Upsher-Smith, USA.*
Potassium bicarbonate (p.1673·1); potassium citrate (p.1673·2).
Hypokalaemia.

Klor-De *Medentech, Israel.*
Troclosene sodium (p.1665·3).
Surface and instrument disinfection.

Kloref
Note.This name is used for preparations of different composition.
Adelco, Gr.
Betaine hydrochloride (p.2265·2); potassium bicarbonate (p.1673·1).
Hypokalaemia; potassium depletion.

Abbott, S.Afr.; Alpharma, UK.
Betaine hydrochloride (p.2265·2); potassium bicarbonate (p.1673·1); potassium chloride (p.1684·3); potassium benzoate (p.1685·1).
Hypokalaemia; potassium depletion.

Klorfen *Karnataka, Philipp.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Klorfeson *Molex Ayus, Indon.*
⊗ Chloramphenicol (p.239·3); prednisolone (p.1540·3).
Infected skin disorders.

Klorheksol *Merkez, Turk.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Klorhex *Drogsan, Turk.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene; skin disinfection.

Klorhexol *Leiras, Fin.*
Chlorhexidine gluconate (p.1635·3).
Hand and skin disinfection.

Kloroben *Drogsan, Turk.*
Chlorhexidine gluconate (p.1635·3); benzydamine hydrochloride (p.27·3).
Oral hygiene.

Klorpo
Upha, Malaysia†.
Chlordiazepoxide (p.968·1).
Anxiety disorders.

Beacons, Singapore.
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety; skeletal muscle spasm.

Klorproman *Orion, Fin.*
Chlorpromazine hydrochloride (p.969·2).
Alcohol withdrawal syndrome; nausea and vomiting; pain; psychoses; sedative.

Klorsept *Medentech, Israel.*
Troclosene sodium (p.1665·3).
Skin and wound disinfection.

Klorvess
Note. This name is used for preparations of different composition.
Novartis, USA.
Effervescent tablets: Potassium chloride (p.1684·3); potassium bicarbonate (p.1673·1); lysine hydrochloride (p.1955·1).
Hypokalaemic-hypochloraemic alkalosis; potassium depletion.
Novartis, USA.
Oral effervescent granules: Potassium chloride (p.1684·3); potassium bicarbonate (p.1673·1); potassium citrate (p.1673·2); lysine hydrochloride (p.1955·1).
Hypokalaemic-hypochloraemic alkalosis; potassium depletion.
Novartis, USA.
Oral liquid: Potassium chloride (p.1684·3).
Hypokalaemic-hypochloraemic alkalosis; potassium depletion.

Klosartan *Klonal, Arg.*
Losartan (p.1327·2).
Hypertension.

Klosartan D *Klonal, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Klosidol *Bago, Arg.*
Dextropropoxyphene hydrochloride (p.40·1) or dextropropoxyphene napsilate (p.40·1); dipyrone (p.49·2).
Pain.

Klosidol B1 B6 B12 *Bago, Arg.*
Dextropropoxyphene hydrochloride (p.40·1) or dextropropoxyphene napsilate (p.40·1); dipyrone (p.49·2); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Joint pain; neuralgia.

Klostenal *Bracco, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Ulcerative colitis.

Klosterfrau Aktiv *Klosterfrau, Ger.; Klosterfrau, Pol.*
Garlic; vitamin A; alpha tocoferil acetate (p.1922·1).
Tonic.

Klosterfrau Aktiv V *Klosterfrau, Cz.†.*
Garlic; St John's wort; *dl*-alpha tocoferil acetate; vitamin A (p.1922·1).
Tonic.

Klosterfrau Beruhigungs Forte *Klosterfrau, Cz.†.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety; sleep disorders.

Klosterfrau Franzbranntwein *Klosterfrau, Ger.*
⊗ Menthol (p.2340·1); camphor (p.2273·2); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau Franzbranntwein Latschenkiefer
Klosterfrau, Ger.
Topical gel: ⊗ Camphor (p.2273·2); pumilio pine oil (p.2376·3); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue disorders.
Klosterfrau, Ger.
Topical lotion: ⊗ Camphor (p.2273·2); pumilio pine oil (p.2376·3); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau Franzbranntwein Menthol *Klosterfrau, Ger.*
⊗ Menthol (p.2340·1); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue disorders.

Klosterfrau Melisana *Klosterfrau, Cz.*
Melissa (p.2339·3); elecampane (p.1558·1); angelica (p.2258·1); ginger (p.1732·3); clove (p.2284·3); galanga; black pepper (p.2364·3); gentian (p.2310·3); nutmeg (p.2355·2); dried bitter-orange peel (p.2357·1); cinnamon (p.2283·1); cassiae floris; cardamom (p.2277·1).
Gastrointestinal disorders; pain; respiratory-tract disorders.

Klosterfrau Melissengeist *Klosterfrau, Austria; Klosterfrau, Ger.*
Melissa; elecampane; gentian; dried bitter-orange peel; angelica; ginger; clove; galganga; cinnamon; nutmeg; black pepper; cardamom.
Tonic.

Klosterfrau Nervenruh Dragees *Melisana, Switz.*
Lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Klosterfrau Sedinal *Klosterfrau, Hung.*
St John's wort (p.422·3).
Depression.

Klotaren *Kimia, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Klotriptyl *Orion, Fin.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Depression; insomnia.

Klotrix *Apothecon, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Klout *Pediamed, USA.*
Acetic acid (p.2244·2); isopropyl alcohol (p.1650·3); sodium laurilsulfate (p.2138·3).
Pediculosis.

Klovir *Biofarma, Venez.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Klovireks-L *Nevzat, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Klozapol *Anpharm, Pol.*
Clozapine (p.981·1).
Psychoses.

Klozivex *Torrent, Philipp.*
Aciclovir (p.862·3).
Herpesvirus infections.

Klyndaken *Kendrick, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Klysma Salinisch *Baxter, Ger.†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Klysma Sorbit *Baxter, Ger.*
Sorbitol (p.1965·1); potassium sorbate (p.1662·2).
Bowel evacuation; constipation.

Klysmol *Demo, Gr.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

K-Lyte
Wellspring, Canad.
Potassium citrate (p.1673·2).
Potassium depletion.
Apothecon, USA.
Potassium bicarbonate (p.1673·1).
Potassium deficiency.

K-Lyte DS *Apothecon, USA.*
Potassium bicarbonate (p.1673·1); potassium citrate (p.1673·2).
Potassium deficiency.

K-Lyte/Cl
Note. This name is used for preparations of different composition.
Wellspring, Canad.
Potassium chloride (p.1684·3).
Potassium depletion.
Apothecon, USA.
Effervescent powder: Potassium chloride (p.1684·3).
Potassium deficiency.
Apothecon, USA.
Effervescent tablets: Potassium chloride (p.1684·3); potassium bicarbonate (p.1673·1).
Potassium deficiency.

Klyx *Ferring, Denm.; Ferring, Fin.; Pharmachemie, Neth.; Ferring, Norw.; Ferring, Swed.*
Docusate sodium (p.1725·1); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Klyx Magnum *Ferring, Switz.*
⊗ Docusate sodium (p.1725·1); dried magnesium sulfate (p.1680·1); urea (p.1620·2).
Bowel evacuation; constipation.

K-Mag *Vitaglow, Austral.†.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Potassium and magnesium supplement.

KMH *M & H, Thai.*
Kanamycin sulfate (p.291·2).
Bacterial infections.

K-Mizol *Arlex, Mex.*
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections.

KN Solution *Otsuka, Jpn.*
A range of electrolyte infusions with glucose (p.1667·1).
Fluid and electrolyte disorders.

Kneipp Beruhigungs-Bad spezial *Kneipp, Ger.*
Citronella oil (p.2284·2).
Anxiety; bath additive; tension.

Kneipp Erkaltungsbad Spezial *Kneipp, Ger.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2).
Bath additive; catarrh.

Kneipp Gute Nacht *Kneipp, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Sleep disorders.

Kneipp Husten- und Bronchial-Tee *Kneipp, Ger.*
Fennel (p.2302·3); cowslip flowers and calyx (p.2372·2); thyme (p.2401·1); ribwort plantain (p.2379·1).
Respiratory-tract congestion.

Kneipp Pflanzen-Dragees Weissdorn *Kneipp, Cz.†.*
Crataegus leaves, flowers, and fruit (p.2289·1).
Cardiac disorders.

Kneipp Rheumabad *Kneipp, Ger.*
Juniper oil (p.2328·3); sweet birch oil (p.86·2).
Bath additive; rheumatism and spinal disorders.

Kneipp Woerisetten S *Kneipp, Switz.†.*
Senna (p.1769·2).
Constipation.

Knobel Huile N *Streuli, Switz.*
Ethyl nicotinate (p.52·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); volatile mustard oil (p.2349·2).
Musculoskeletal and joint disorders.

Kno-Paine *Continental Pharma, Thai.*
Dipyrone (p.49·2).
Pain.

K-Norm *Fisons, USA†.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Knowful *YSP, Malaysia.*
Piracetam (p.368·2).
Mental function disorders.

Koal *Ethicus, Arg.*
Salicylic acid (p.1612·2).
Scalp disorders.

Koate *Sintofarma, Braz.†; Bayer, Hung.†; Dipa, Indon.; Bayer, Israel; Talecris, Rus.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Koate-DVI *Gador, Arg.†; Bayer, Chile; Bayer Biological, Hong Kong; Bayer Schering, Malaysia†; Octafarma, Mex.†; Bayer, Philipp.; GenAsia, Philipp.; Bayer, Singapore†; Biem, Turk.; Bayer, USA.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Ko-Cap *Sriprasit, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Kocefan *Mediolanum, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Kochsalz mit Glucose *Braun, Ger.*
Sodium chloride (p.1686·1); glucose (p.1945·3).
Carbohydrate source; fluid and electrolyte disorders.

Kodakon *Loren, Mex.†.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Bacterial eye infections.

Kodamid *Nycomed, Denm.*
Codeine phosphate (p.37·2); caffeine (p.1116·3); propyphenazone (p.119·3); salicylamide (p.121·2).
Magnesium hydroxide (p.1743·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Kodan *Schulke & Mayr, Austria.*
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); orthophenylphenol (p.1655·1); hydrogen peroxide solution 30% (p.1648·1).
Skin disinfection.

Kodan Teinture forte *Schulke & Mayr, Switz.*
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); orthophenylphenol (p.1655·1).
Skin disinfection.

Kodan Tinktur Forte *Schulke & Mayr, Ger.†.*
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); orthophenylphenol (p.1655·1).
Skin disinfection.

Kodel *Columbia, Mex.*
Bromhexine hydrochloride (p.1552·2); codeine phosphate (p.37·2).
Cough; respiratory-tract congestion.

Kodimagnyl *Nycomed, Denm.; SAD, Denm.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Magnesium hydroxide (p.1743·2) is included in some dosage forms in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Kodipar *Nycomed, Denm.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Kodynal *Slovakofarma, Cz.†.*
⊗ Emetine hydrochloride (p.833·3); ephedrine hydrochloride (p.1558·2); codeine hydrochloride (p.37·2).
Coughs.

Kofan *Bosnalek, Rus.*
Caffeine (p.1116·3); paracetamol (p.108·1); propyphenazone (p.119·3).
Pain.

Kofarest *Centaur, India.*
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3); guaifenesin (p.1561·3); menthol (p.2340·1).
Respiratory-tract disorders.

Kofemin *Robugen, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Kofepar *Pliva Krakow, Pol.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Kofevit *Polfa Lodz, Pol.*
Caffeine (p.1116·3); levocarnitine; vitamins; calcium lactogluconate; magnesium hydroaspartate (p.1922·1).
Tonic.

Kofex *GSK, Pol.*
Caffeine and sodium benzoate (p.1118·2).
Fatigue.

Kof-Eze *Roberts, USA.*
Menthol (p.2340·1).
Coughs; sore throats.

Koffazon *Recip, Swed.*
Caffeine (p.1116·3); phenazone (p.116·1).
Pain.

Koffex *Actavis, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1); alcohol (p.1625·2).
Cough.

Koffex for Children *Actavis, Indon.*
⊗ Ephedrine hydrochloride (p.1558·2); ipecacuanha (p.1562·3); ammonium chloride (p.1551·3); citric acid (p.2284·1); tolu syrup.
Cough.

Koffex DM *Rougier, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Koffex DM-D *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Koffex DM-E *Technilab, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Koffex Expectorant *Technilab, Canad.†.*
Guaifenesin (p.1561·3).

Koffisal *Nycomed, Denm.*
Caffeine (p.1116·3); phenazone salicylate (p.116·1); salicylamide (p.121·2).
Pain.

Kofron *Guidotti, Spain.*
Clarithromycin (p.248·2).
Bacterial infections.

Kogenate
Bayer, Austral.; Bayer, Austria; Bayer, Canad.; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Irl.; Bayer, Ital.; Bayer, Neth.; Bayer, Norw.; Bayer, Port.; Bayer, Swed.; Bayer, Switz.; Bayer, UK.
Octocog alfa (p.1067·2).
Haemorrhagic disorders.
Bayer, Belg.; Bayer, Hung.; Bayer, NZ; Bayer, Spain; Bayer, USA.
A factor VIII preparation (recombinant) (p.1067·1).
Haemorrhagic disorders.

Kohle-Compretten *Merck, Ger.; Merck, Norw.*
Activated charcoal (p.1435·2).
Acute poisoning; diarrhoea.

Kohle-Hevert *Hevert, Ger.*
Activated charcoal (p.1435·2).
Acute poisoning; diarrhoea.

Kohlensaurebad Bastian *Bastian, Ger.*
Sodium bicarbonate (p.1673·2).
Bath additive; cardiac and circulatory disorders.

Kohle-Pulvis *Kohler, Ger.*
Activated charcoal (p.1435·2).
Acute poisoning; diarrhoea.

Kohle-Tabletten *Cheplapharm, Ger.*
Activated charcoal (p.1435·2).
Acute poisoning; diarrhoea.

Kohrsolin *Bode, Ger.*
Glutaral (p.1645·2); 1,6-dihydroxy-2,5-dioxahexane (p.1642·3); polymethylolurea derivative.
Surface and instrument disinfection.

Kohrsolin FF *Bode, Ger.*
Glutaral (p.1645·2); benzalkonium chloride (p.1629·1); didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Koide *Eurofarma, Braz.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Koide D *Eurofarma, Braz.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).

Ko-Kure *Sriprasit, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Kola Fosfatada Soel *Regius, Braz.†.*
Kola (p.2416·1); nux vomica (p.2355·3); sodium glycerophosphate; calcium glycerophosphate (p.1922·1).
Tonic.

Kolampept *Teuto, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Kolanticon *Peckforton, UK.*
Aluminium hydroxide (p.1706·2); dicycloverine hydrochloride (p.1722·3); light magnesium oxide (p.1744·1); simeticone (p.1770·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Kolantyl
Note. This name is used for preparations of different composition.
Medley, Braz.
Chewable tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); methylcellulose (p.2145·1); magnesium trisilicate (p.1744·1).
Gastric hyperacidity.
Adcock Ingram, S.Afr.
Oral gel: Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); methylcellulose (p.2145·1).
Gastrointestinal disorders.
Medley, Braz.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); methylcellulose (p.2145·1).
Gastric hyperacidity.
Adcock Ingram, S.Afr.
Wafers: Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); methylcellulose (p.2145·1); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders.

Kolantyl DMP *Medley, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); methylcellulose (p.2145·1); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Kolephrin *Pfeiffer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Kolephrin GG/DM *Pfeiffer, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Kolephrin/DM *Pfeiffer, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Koleskol *Metiska, Indon.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Kolestop *Omni, UK.*
Sitosterol (p.1373·2); beta sitostanol (p.1373·2).
Nutritional supplement to reduce serum cholesterol.

Kolestor *Eczacibasi, Turk.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Kolestran *Ilsan, Turk.*
Colestyramine (p.1252·3).
Diarrhoea; hypercholesterolaemia; pruritus.

Kolexan *Biomep, Mex.*
Albendazole (p.139·2).

Kolibel *Sanitas, Chile.*
Clofedanol hydrochloride (p.1554·2); pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; coughs.

Kolikoject *Syxyl, Ger.†.*
Homoeopathic preparation.

Kolkin *Duncan, Arg.*
⊗ Furosemide (p.1292·1).
Hypertension.

Kollagenase *Cristalia, Braz.*
Collagenase (p.2286·2).
Skin ulcers; wounds.

Kollagenase com cloranfenicol *Cristalia, Braz.*
Collagenase (p.2286·2); chloramphenicol (p.239·3).
Skin ulcers; wounds.

Kollaps-Gastreu N R67 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Kollateral *Ursapharm, Ger.*
Moxaverine hydrochloride (p.2347·3).
Cerebral, coronary, and peripheral vascular disorders.

Kollosteril *Lafedar, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Kolob *Unipharm, Mex.†.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders.

Kolpazol *Globo, Braz.†.*
Nystatin (p.543·2).
Candidiasis.

Kolplex *Collins, Mex.*
Multivitamin preparation (p.1922·1).

Kolpovent *Grunenthal, Chile†.*
⊗ Salmeterol xinafoate (p.1135·1).
Asthma.

Kolsan *Bittner, Austria.*
Homoeopathic preparation.

Kolsin *Ulagay, Turk.*
Colchicine (p.556·1).
Gout.

Kolsuspension *Abigo, Swed.*
Activated charcoal (p.1435·2).
Diarrhoea; poisoning.

Kolton grippale N *Byk Gulden, Ger.†.*
Piprinhydrinate (p.588·2); paracetamol (p.108·1); ethenzamide (p.51·3).
Cold and influenza symptoms.

Komasin *Medinova (Μεντινοβα), Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Kombetin *Pharmafar, Ital.*
Strophanthin-K (p.1406·3).
Cardiac disorders.

Kombevit-C *Deva, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Kombi-Kalz *Viatris, Austria; Meda, Cz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium metabolic disorders with vitamin D deficiency; osteoporosis.

Komb-Insulin *Aventis, Ger.†.*
⊗ Insulin (chromatographically purified, bovine), comprising a mixture of Insulin and Depot-Insulin *(Hoechst, Ger.)* (p.443·2).
Diabetes mellitus.

Komb-Insulin S *Aventis, Ger.†.*
⊗ Insulin (chromatographically purified, porcine), comprising a mixture of Insulin S and Depot-Insulin S *(Hoechst, Ger.)* (p.443·2).
Diabetes mellitus.

Kombi-Stulln N *Stulln, Ger.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Eye infections.

Kombivit *Streuli, Switz.*
Multivitamin preparation (p.1922·1).

Komil *Goldshield, UK.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Liver cirrhosis with ascites; oedema.

K-Omistron *Mayo, Mex.*
Neomycin (p.305·1); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Kompensan *Pfizer, Ger.; Janssen-Cilag, Port.; Pfizer Consumer, Switz.; Pfizer, Turk.*
Dihydroxyaluminum sodium carbonate (p.1723·3).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Kompensan Dimeticon *Pfizer, Ger.*
Dimeticone 350 (p.1770·2).
Adjunct in gastrointestinal radiography; gastrointestinal disorders with excess gas.

Kompensan-S *Pfizer, Ger.†; Janssen-Cilag, Port.*
Dihydroxyaluminum sodium carbonate (hydrated) (p.1723·3); dimethicone (p.1770·2).
Gastrointestinal disorders.

Kona *M & H, Thai.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; coughs; nasal congestion.

Konaderm *Valeant, Mex.*
Ketoconazole (p.539·1).
Fungal skin infections.

Konakion *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Chile; Roche, Denm.; Roche, Fin.; Roche, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK.*
Phytomenadione (p.1995·3).
Anticoagulant antidote; anticoagulant overdose; haemorrhagic disease of the newborn; hypoprothrombinaemia; phenylbutazone overdose; salicylate overdose; vitamin K deficiency; vitamin K deficiency bleeding.

Konakion MM *Roche, Turk.*
Phytomenadione (p.1995·3).
Vitamin K deficiency; vitamin K deficiency bleeding.

Konat *Drovepat, Venez.†.*
Potassium gluconate (p.1684·3).
Potassium supplement.

Konaturil *IQFA, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Konazal *Alpharma, Norw.*
Ketoconazole (p.539·1).
Seborrhoeic dermatitis.

Konazol *PP Lab, Thai.†; Kurtsan, Turk.*
Ketoconazole (p.539·1).
Fungal infections.

Kondon's Nasal *Kondon, USA.*
⊗ Ephedrine (p.1558·1).
Nasal congestion.

Kondremul *Fisons, USA.*
Liquid paraffin (p.2030·3).
Constipation.

Kondro *Panacea, India.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).
Osteoarthritis.

Kongest *Eczacibasi, Turk.*
Paracetamol (p.108·1); chlorphenamine (p.572·2).
Respiratory-tract congestion.

Konibalm *Konimex, Indon.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Konicortil *Koni-Cofarm, Chile.*
⊗ Betamethasone (p.1518·2).
Skin disorders.

Koniderm *Koni-Cofarm, Chile.*
⊗ Clobetasol (p.1522·2).
Skin disorders.

Konidin *Konimex, Indon.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Konifungil *Koni-Cofarm, Chile.*
Clotrimazole (p.530·1).
Fungal skin infections.

Konigen *Konimex, Indon.*
Gentamicin sulfate (p.282·1).
Skin infections.

Konirub *Mepro, Chile.*
Methyl nicotinate (p.85·3); methyl salicylate (p.85·3); benzocaine (p.1854·1).
Musculoskeletal and joint disorders.

Konjunktival *Alcon, Hong Kong†.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Conjunctivitis.

Konjunktival Thilo *Alcon, Ger.†.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye disorders.

Konk *Air Guard Control, Canad.†.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Konlax *Shinyaku, Hong Kong†.*
Pridinol mesilate (p.1898·1).
Skeletal muscle spasm.

Konor *Italzama, Ital.*
Tar (p.1616·2).
Seborrhoeic dermatitis.

Konor Fluid *Italzama, Ital.*
Barrier cream.

Konorderm *Italzama, Ital.*
Inositol; nicotinamide; vitamin E; betacarotene; selenium; -cystine (p.1922·1).
Antoxidant nutritional supplement.

Konovid *TO-Chemicals, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Konstitutin *CytoChemia, Ger.*
Siberian ginseng (p.2386·3).
Tonic.

Konsyl *GSK, Arg.; Konsyl, Israel; Glaxo Wellcome, Mex.†; Eastern Pharmaceuticals, UK†; Konsyl, USA.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; irritable bowel syndrome.

Konsyl-D *Konsyl, USA.*
Psyllium hydrophilic mucilloid (p.1737·1).
Constipation.

Kontagripp *Sandoz, Ger.*
Ibuprofen (p.64·2).
Formerly known as Kontagripp Mono.
Fever; pain.

Kontakto Derm *Combe, Ger.†.*
Benzocaine (p.1854·1).
Eczema; pruritus.

Kontal *Pharmia, Fin.*
Niclosamide (p.151·1).
Worm infections.

Kontexin *Pfizer, Switz.†.*
Phenylpropanolamine hydrochloride (p.1569·3).
Urinary incontinence.

Kontic *Coup, Gr.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Kontil *Bilim, Turk.*
Pyrantel embonate (p.155·1).
Ascariasis; oxyuriasis.

Kontrabat *Bernofarm, Indon.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cough and cold symptoms.

Kontryhelova Nat *Megafyt-R, Cz.*
Parsley piert (p.2363·2).
Diarrhoea; inflammation of skin and mucous membranes; menopausal disorders; menstrual disorders; wounds.

Konveril *Nobel, Turk.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Konveril Plus *Nobel, Turk.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Konvermex *Konimex, Indon.*
Pyrantel embonate (p.155·1).
Worm infections.

Konyne *Octafarma, Mex.†; Biem, Turk.*
Factor IX complex (p.1068·3).
Haemophilia B.

Kopamex *Konimex, Indon.*
Povidone-iodine (p.1659·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Fungal skin infections.

Kopen *Athlone, Irl.*
Phenoxymethylpenicillin (p.314·1).
Gram-positive bacterial infections.

Kopodex *Drugtech, Chile.*
Levetiracetam (p.488·2).
Epilepsy.

Koprak *Tocogino, Mex.*
Ketorolac (p.75·2).
Pain.

Koprivovy Caj, Koprivova Nat *Megafyt-R, Cz.*
Urtica (p.2409·3).
Rheumatic disorders; urinary-tract disorders.

Koptilan *Coup, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Koptin *Chinoin, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Korandil *Remedica, Singapore; Remedica, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Kordinol Compuesto *Laboratorios Chile, Chile†.*
Diiodohydroxyquinoline (p.832·1); phthalylsulfacetamide (p.315·1); vegetable carbon (p.1473·3); hyoscine butylbromide (p.1734·1).
Diarrhoea.

Kordobis *Pliva, Cz.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Korec *Sanofi-Aventis, Fr.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Koren Kozliku Lekarskeho *Leros, Cz.†.*
Valerian (p.2410·1).
Anxiety; gastrointestinal spasm; sleep disorders.

Koren Puskvorce *Leros, Cz.*
Calamus (p.2271·3).
Anorexia; diarrhoea; dyspepsia; gastrointestinal spasm; inflammation of the mouth and throat.

Koretic *Sanofi-Aventis, Fr.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Korgivit-E *Diamond, Philipp.*
Vitamin E; bee pollen (p.2370·2); ginseng (p.2312·1); lecithin (p.2332·2); calcium pantothenate (p.1922·1).
Tonic.

Korifen *Collins, Mex.*
Dipyrone (p.49·2); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Formerly contained citric acid and dipyrone.
Cold and influenza symptoms.

Kormakin *Korea United, Philipp.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Kornam *Lek, Cz.; Lek, Hung.†; Lek, Pol.; Lek, Rus.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Koro *M & H, Thai.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Korodin *Robugen, Ger.*
Camphor (p.2273·2); crataegus (p.2289·1).
Cardiac disorders; circulatory disorders.

Koro-Nyhadin *Robugen, Ger.*
Crataegus (p.2289·1).
Heart failure.

Korseng *Self-Care Products, UK.*
Ginseng (p.2312·1).

Korsolex AF *Bode, Ger.*
Laurylpropylenediamine; dodecylbispropylenetriamine.
Instrument disinfection.

Korsolex basic *Bode, Ger.*
Glutaral (p.1645·2); dihydroxydioxahexane (p.1642·3).
Instrument disinfection.

Korsolex Extra *Bode, Ger.*
Dihydroxydioxahexane (p.1642·3); glutaral (p.1645·2); benzalkonium chloride (p.1629·1); didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Korsolex FF *Bode, Ger.*
Glutaral (p.1645·2); benzalkonium chloride (p.1629·1); didecyldimethylammonium chloride (p.1642·2).
Instrument disinfection.

Korsolex Plus *Bode, Ger.*
Dodecylbispropylenetriamine; didecyldimethylammonium chloride (p.1642·2).
Instrument infection.

Korsolex-Endo-Disinfectant *Bode, Ger.*
Glutaral (p.1645·2).
Disinfection of endoscopes.

Kortezor *Biomedis, Philipp.*
Ketorolac trometamol (p.74·2).
Pain.

Kortikoid-ratiopharm *Ratiopharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Kortos
Note.This name is used for preparations of different composition.
Embil, Turk.
Cream: ⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); bismuth subgallate (p.1711·1).
Haemorrhoids.

Embil, Turk.
Suppositories: ⊗ Hydrocortisone acetate (p.1535·2); lauromacrogol 400 (p.1916·1).
Haemorrhoids.

Korylan *Zentiva, Cz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Korynase *Kyorin, Thai.†.*
Promelase (p.2373·3).
Inflammation; oedema.

Korzen *Korean Drug, Singapore†.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Kososan *Tsumura, Jpn.*
Cyperus rhizome; perilla; citrus unshiu peel; liquorice; ginger.
Traditional Kampo medicine.

Kostal *Royal, Chile.*
Cilostazol (p.1245·2).
Intermittent claudication.

Kosteo *Arrow, Austral.*
Calcitriol (p.1986·2).
Hypocalcaemia; osteoporosis.

Kotor Articulations *Kotor, Fr.*
Javanese turmeric; vitamin E; vitamin C; perslane oil (p.1922·1).
Dietary supplement for joint disorders.

Kotor Meno *Kotor, Fr.*
Soya; vitamin E; vitamin C; perslane oil (p.1922·1).
Dietary supplement for menopausal disorders.

Kovan *Laboratorios Chile, Chile.*
Vancomycin (p.358·3).
Gram-positive bacterial infections.

Kovia *Stratus, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).

Kovilen *Mediolanum, Ital.*
Nedocromil sodium (p.1127·3).
Ocular hypersensitivity reactions.

Kovinal *Mediolanum, Ital.*
Nedocromil sodium (p.1127·3).
Allergic rhinitis.

Kozlik *Kneipp, Cz.*
Valerian (p.2410·1).
Nervous disorders.

KP *PP Lab, Thai.†.*
Phytomenadione (p.1995·3).
Haemorrhagic disorders.

K-Pek *Rugby, USA†.*
Bismuth salicylate (p.1711·1).
Formerly contained attapulgite.
Diarrhoea.

K-Pek II *Rugby, USA.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

K-Phos MF *Beach, USA.*
Monobasic potassium phosphate (p.1682·2); monobasic sodium phosphate (p.1682·3).
Urinary acidification.

K-Phos Neutral *Beach, USA.*
Dibasic sodium phosphate (p.1682·3); monobasic potassium phosphate (p.1682·2); monobasic sodium phosphate (p.1682·3).
Phosphorus supplement.

K-Phos No.2 *Beach, USA.*
Monobasic potassium phosphate (p.1682·2); monobasic sodium phosphate (p.1682·3).
Urinary acidification.

K-Phos Original *Beach, USA.*
Monobasic potassium phosphate (p.1682·2).
Urinary acidification.

KPL *Fouchard, Chile†.*
Ketoconazole (p.539·1); piroctone (p.1610·1); ammonium lactate (p.1589·2).
Dandruff; seborrhoeic dermatitis.

KPN *Freeda, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

KPP *Novartis Consumer, S.Afr.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine citrate (p.1116·3); caffeine (p.1116·3).

K-Profen *Medix, Mex.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders.

Krabinex *Korea United, Philipp.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Kraftol *Profarb, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Krallendorn *Immodal, Austria.*
Uncaria tomentosa.
Rheumatoid arthritis.

Krama
Note. This name is used for preparations of different composition.
Duncan, Arg.
Alprazolam (p.960·1).
Anxiety.
Miba, Ital.†.
Barrier cream.

Kramollex *Kramer, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Kramon *Kramer, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Krampdruppels *Lennon, S.Afr.*
Valerian (p.2410·1); lavender (p.2331·1); solvent ether (p.2023·2).
Colic; flatulence; nervous disorders.

Kranit Nova *Codali, Belg.†.*
Caffeine (p.1116·3); paracetamol (p.108·1); propyphenazone (p.119·3).
Headache.

Kranos *Nufarindo, Indon.*
Clotrimazole (p.530·1).
Fungal skin infections.

Kratalgin *Kwizda, Austria.*
Ibuprofen (p.64·2).
Pain.

Kratium *Medochemie, Hong Kong.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; febrile convulsions; premedication; skeletal muscle spasm; sleep disorders; spasticity; status epilepticus.

Kratofin simplex *Kwizda, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Krauter Hustensaft *Apomedica, Austria.*
Thyme (p.2401·1); ononis (p.2357·1); cowslip root (p.2372·2); liquorice (p.1740·3); castanea vulgaris; sambucus (p.2383·1).
Catarrh; coughs.

Krauterlax *Dolorgiet, Ger.*
Aloes (p.1705·2).
Formerly known as Kräuterlax A.
Constipation.

Krautin *Pharmanel, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Krebs *Sigma, Arg.*
Vitamin C; vitamin E; betacarotene (p.1922·1).
Nutritional supplement.

Krebs Plus *Sigma, Arg.*
Vitamin and mineral preparation (p.1922·1).
Macular degeneration; tonic.

Krebs-E *Sigma, Arg.*
Vitamin A; vitamin E; vitamin B (p.1922·1).

Krebsilasi *Wyeth Lederle, Ital.†.*
Pancrelipase (p.2360·1).
Cystic fibrosis; malabsorption syndromes.

Kredex *Roche, Austral.; Roche, Belg.; Roche, Fr.; Roche, Norw.; Roche, Swed.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Kreislaufja *OTW, Ger.†.*
Homoeopathic preparation.

Kremezin *Daiichi Sankyo, Jpn.*
AST-120 (p.1438·1).
Renal failure.

Kremil *Great Eastern, Thai.; Therapharma, Thai.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2).
Gastrointestinal hyperacidity; peptic ulcer.

Kremil-S
Note. This name is used for preparations of different composition.
United Laboratories, Philipp.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.
Great Eastern, Thai.; Therapharma, Thai.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2); dicycloverine hydrochloride (p.1722·3).
Gastrointestinal disorders.

Krenosin *Sanofi-Aventis, Fr.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Mex.*
Adenosine (p.1202·1).
Diagnosis of arrhythmias; paroxysmal supraventricular tachycardia.

Krenosine *Sanofi Synthelabo, Switz.*
Adenosine (p.1202·1).
Supraventricular tachycardia.

Kreon *Solvay, Austria; Solvay, Cz.; Solvay, Ger.; Solvay, Hung.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, Spain; Frik, Turk.*
Pancreatin (p.2360·1).
Digestive system disorders; pancreatic insufficiency.

Kreosotum Complexe no 62 *Lehning, Fr.*
Homoeopathic preparation.

Krestin *Daiichi Sankyo, Jpn.*
Polysaccharide-K (p.2370·3).
Malignant neoplasms.

Kretos *Glenmark, India†.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; pain; rheumatoid arthritis.

Kreuzlinger Klosterliniment *Luond, Switz.†.*
Salicylic acid (p.1612·2); camphor (p.2273·2); plant extracts.
Musculoskeletal, joint, and soft-tissue disorders.

Kreval *Frik, Turk.*
Butamirate (p.1553·1).
Coughs.

Kriadex *Psicofarma, Mex.*
Clonazepam (p.478·2).
Alcohol withdrawal syndrome; anxiety; epilepsy; mania; obsessive-compulsive disorder; panic disorder.

Krimbeson *Nufarindo, Indon.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Krinuven *Fresenius Kabi, Ital.*
Amino-acid, glucose, and lipid infusion with or without electrolytes (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Kriolen *Rafarm, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Kriptiser *Serral, Mex.*
Bromocriptine (p.800·3).

Kripton *Alphapharm, Austral.*
Bromocriptine mesilate (p.798·1).
Acromegaly; hyperprolactinaemia; lactation inhibition; parkinsonism.

Kriptonal *Chemopharma, Chile.*
Bromocriptine (p.800·3).
Acromegaly; benign breast disorders; female infertility; hyperprolactinaemia; lactation inhibition; menstrual disorders; parkinsonism; prolactinomas.

Krisovin *CCM, Malaysia; Beacons, Singapore.*
Griseofulvin (p.535·2).
Fungal skin, hair, and nail infections.

Kristalose *Bertek, USA.*
Lactulose (p.1738·2).
Constipation.

Kristapen *Deva, Turk.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Kristasil *Bilim, Turk.*
Benzylpenicillin (p.213·1).
Bacterial infections.

Krisxon *Sons, Mex.*
Trimebutine (p.2404·3).
Gastrointestinal motility disorders.

Kritel *Monserrat, Arg.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Kritel Enema *Monserrat, Arg.*
Sodium phosphate (p.1682·3).
Bowel evacuation.

Krobicin *Euromex, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Kroko *Lennon, S.Afr.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; warts.

Krol *Benitol, Arg.†.*
Ketoconazole (p.539·1).
Dandruff; fungal skin infections.

Kronel *Hebron, Braz.†.*
Pistacia lentiscus.
Wounds.

Kronofed-A *Ferndale, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Kronolax *Altana, Arg.†.*
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation.

Kropanol *Sintez, Rus.*
Pantogematogen (deer antler velvet).
Asthenia; tonic.

Krophan N *Repha, Ger.†.*
Bladderwrack (p.2384·2); potassium iodide (p.2169·2); thyreoidinum.
Iodine-deficiency disorders.

Krople Zoladkowe
Note. This name is used for preparations of different composition.
Aflofarm, Pol.; Hasco-Lek, Pol.; Herbapol Krakow, Pol.
St John's wort (p.422·3); peppermint leaf (p.1761·2); tinctura amara; valerian (p.2410·1).
Digestive disorders.
Farmina, Pol.
St John's wort (p.422·3); peppermint leaf (p.1761·2); tinctura amara (absinthium (p.2244·1), menyanthes (p.2340·3), bitter orange (p.2357·1), calamus (p.2271·3)); valerian (p.2410·1); propyphenazone (p.119·3); allobarbital (p.959·3).
Digestive disorders.
Herbapol Lublin, Pol.
St John's wort (p.422·3); peppermint leaf (p.1761·2); tinctura amara (absinthium (p.2244·1), menyanthes (p.2340·3), bitter orange (p.2357·1), calamus (p.2271·3)); valerian (p.2410·1); propyphenazone (p.119·3).
Gastrointestinal disorders.

Krucef *Krugher, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Kruidvat *Pharmethica, Neth.*
Caffeine (p.1116·3); paracetamol (p.108·1); propyphenazone (p.119·3).
Fever; pain.

Kruidvat Antischimmelcreme *Marel, Neth.*
Miconazole nitrate (p.541·3).
Candidiasis of the skin and nails.

Kruidvat Anti-worm *Marel, Neth.*
Mebendazole (p.148·3).
Worm infections.

Kruidvat APC *Marel, Neth.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Kruidvat Diarreeremmer *Marel, Neth.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Kruidvat Hoestelixer *Pharmethica, Neth.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Kruidvat Hoesttabletten *Marel, Neth.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Kruidvat Homeopathie Neusspray *Schwabe, Neth.*
Homoeopathic preparation.

Kruidvat Hooikoortstabletten *Marel, Neth.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Kruidvat Koortslipcreme *Pharmethica, Neth.*
Aciclovir (p.862·3).
Herpes labialis.

Kruidvat Laxeertabletten *Marel, Neth.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Kruidvat Neusdruppels *Pharmethica, Neth.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Kruidvat Neusspray *Pharmethica, Neth.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Kruidvat Reistabletten *Pharmethica, Neth.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea and vomiting.

Kruidvat Spierbalsem *Pharmethica, Neth.*
Capsicum (p.2276·2); glycol salicylate (p.62·3); histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3).
Musculoskeletal and joint pain.

Kruses Fluid Magnesia *Felton, Austral.*
Magnesium bicarbonate.
Gastrointestinal hyperacidity.

Kryobulin *Immuno, Braz.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Kryptocur
Aventis, Austria; Aventis, Ger.; Sanofi-Aventis, Ital.
⊗ Gonadorelin (p.2106·2).
Cryptorchidism.
Aventis, Switz.
⊗ Gonadorelin acetate (p.2106·2).
Cryptorchidism.

KryptoScan *Mallinckrodt, Cz.; Mallinckrodt, Neth.*
Krypton-81m (p.2055·1).
Diagnosis of pulmonary embolism; radionuclide lung studies.

K-Sein *Nucitec, Mex.*
Calcium caseinate (p.1934·1).
Dietary supplement.

Ksenakvin *Promed, Rus.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Ksilidin *Biosel, Turk.*
Lidocaine (p.1862·3).
Local anaesthesia.

KSR *Alphapharm, Austral.†; Alphapharm, Hong Kong; Alphapharm, Malaysia†; Merck, Malaysia†; Alphapharm, Singapore†; Merck, Singapore†.*
Potassium chloride (p.1684·3).
Hypokalaemia.

K-SR *Pacific, NZ†.*
Potassium chloride (p.1684·3).
Potassium supplement.

K-Tab *Abbott, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

K-Thrombin *Sigma, NZ.*
Menadione sodium bisulfite (p.1995·3).
Prothrombin deficiency; vitamin K deficiency.

KTM *Guardian, Indon.*
Ketamine (p.1788·1).
General anaesthesia; pain.

Kudeq *Pfizer, Neth.†.*
Valdecoxib (p.132·3).
Dysmenorrhoea; osteoarthritis; rheumatoid arthritis.

Kudona *Synmosa, Singapore†.*
Glucosamine sulfate (p.2313·2).
Maintenance of healthy joints and cartilage.

Kudrox Double Strength *Schwarz, USA†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Kufro *Andromaco, Mex.*
Nitrofurazone (p.309·1).
Cervicitis; vaginitis.

Kuhlprednon *Gerot, Austria.*
⊗ Prednisolone (p.1540·3).
Skin disorders.

Kuiflex *Abdi, Turk.*
Phenprobamate (p.1018·1); paracetamol (p.108·1).
Skeletal muscle spasm.

Kuilil *Embil, Turk.*
Phenprobamate (p.1018·1); paracetamol (p.108·1).
Skeletal muscle spasm.

Kupa *M & H, Thai.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Kuracid *Gea, Denm.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Kurapel *Ivax, Arg.*
Silicone oil (p.2032·1).
Barrier preparation.

Kurgan *Normon, Port.; Normon, Spain.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Kurom *Grunenthal, Chile†.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs; nasal congestion.

Kuroment *Ratiopharm, Cz.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Kursept *Orva, Turk.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Kusuk *Andromaco, Venez.†.*
Vitamins; malt; sucrose (p.1922·1).
Dietary supplement.

Kutapressin *Schwarz, USA†.*
Liver-derivative complex (p.2337·3).
Skin disorders.

Kuterid *Lek, Cz.; Lek, Pol.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Kutesan *Plurisystem, Ital.*
Emollient.

Kutoin *Mersifarma, Indon.*
Phenytoin sodium (p.495·2).
Epilepsy.

Kutrase *Schwarz, USA.*
Lipase; amylase (p.2256·3); protease.
Formerly contained lipase, amylase, protease, cellulase, hyoscyamine sulfate, and phenyltoloxamine citrate.
Functional dyspepsia devoid of organic pathology (nervous dyspepsia).

Kuvan *BioMarin, USA.*
Sapropterin hydrochloride (p.2383·2).
Hyperphenylalaninaemia.

Ku-Zyme *Schwarz, USA.*
Lipase; amylase (p.2256·3); protease.
Functional dyspepsia due to enzyme deficiency or imbalance.

Ku-Zyme HP *Schwarz, USA.*
Pancrelipase (p.2360·1).
Pancreatic insufficiency.

Kventiax *KRKA, Cz.*
Quetiapine fumarate (p.1022·2).
Mania; schizophrenia.

Kvet Bazy Ciernej *Slovakofarma, Cz.†.*
Sambucus (p.2383·1).
Cold symptoms; fever.

Kvet Lipy *Slovakofarma, Cz.†.*
Tilia (p.2402·2).
Cold symptoms; fever.

Kvilla *ACO Hud, Fin.*
Quillaia (p.1920·1); ammonium chloride (p.1551·3).
Coughs.

KW *Lagos, Arg.*
Aloe vera (p.1588·2); camphor (p.2273·2); mallow (p.2337·2); chamomile (p.2279·3); ethyl linoleate (p.2308·2).
Pruritus.

Kwai *Kwizda, Austria; Lichtwer, Canad.†; Lichtwer, Cz.†; Lichtwer, Ger.; Solvay, Ital.; Lichtwer, Switz.†; Lichtwer, UK; Konsuma, Venez.†.*
Garlic (p.2309·2).
Atherosclerosis; dietary supplement; hyperlipidaemias; memory impairment.

Kwan Loong Oil *Haw Par, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Kwelcof *Ascher, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Kwell
Note. A similar name is used for preparations of different composition (see below).
GSK, Arg.; GSK, Braz.
Permethrin (p.2048·2).
Pediculosis.

Kwell Reformulated *GSK, Philipp.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Kwellada *Ali, Turk.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Kwellada-P *GSK Consumer, Canad.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Kwell-P *Ali, Turk.*
Pyrethrin (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Kwells
Note. A similar name is used for preparations of different composition (see above).
Bayer Consumer, Austral.; Bayer, Irl.; Bayer, UK.
Hyoscine hydrobromide (p.1734·1).
Motion sickness.

Kwicap *Cevallos, Arg.†.*
Cefaclor (p.217·2).
Bacterial infections.

Kwim *Duopharm, Ger.†.*
Vitamin A palmitate (p.1973·1); riboflavin sodium phosphate (p.1977·3).
Eye disorders.

K-Y *Polive, Fr.; Ethnor, India; Johnson & Johnson, Israel; Johnson & Johnson, Ital.; Johnson & Johnson, NZ; Johnson & Johnson, UK; Johnson & Johnson, USA.*
Lubricating gel.
Aid in ultrasound scanning; catheterisation; endoscopy; lubrication of mucous membranes and instruments; rectal and vaginal lubrication.

K-Y Plus Spermicidal Lubricant *Johnson & Johnson, Canad.*
Nonoxinol 9 (p.1917·2).
Contraceptive; vaginal lubricant.

Kybernin *ZLB, Ger.; ZLB, Switz.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Kybernin P *Aventis Behring, Arg.; ZLB, Austria; CSL, Braz.; CSL, Cz.; ZLB, Gr.; CSL, Hung.; Dexa, Indon.; ZLB, Indon.; ZLB, Ital.; ZLB, Spain; Farma-Tek, Turk.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency; congenital deficiency of antithrombin III; disseminated intravascular coagulation.

Kymazol *Rafarm, Gr.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Kyolarte *Kyorin, Thai.†.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Kyolic *Quest, Canad.†; Quest, Malaysia; Quest, UK.*
Garlic (p.2309·2).
Dietary supplement.

Kyolic 101 *Quest, Canad.*
Garlic (p.2309·2); brewers yeast; kelp.

Kyolic 102 *Quest, Canad.*
Garlic (p.2309·2); enzyme complex; rice protein complex.

Kyolic 103 *Quest, Canad.†.*
Garlic (p.2309·2); vitamin C; astragulus (p.1922·1).

Kyolic 104 *Quest, Canad.†.*
Garlic (p.2309·2); lecithin (p.2332·2).

Kyolic 106 *Quest, Canad.†.*
Garlic (p.2309·2); vitamin E; crataegus; cayenne (p.1922·1).

Kyolic Formula 103 *Purity Health, Canad.*
Calcium ascorbate (p.1984·1).
Dietary supplement.

Kyolic Formula 106 *Purity Health, Canad.*
d-Alpha tocoferil acid succinate (p.1993·1).

Kyolic Super Formula *Primula, Arg.†.*
Garlic (p.2309·2).
Hyperlipidaemias; hypertension.

Kyrin *Silom, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Kytinon ABC *Asmopul, Arg.†.*
Lidocaine (p.1862·3); porcine skin (p.1613·3); polysaccharides.
Mouth disorders.

Kytinon ARHI *Asmopul, Arg.†.*
Porcine skin (p.1613·3); mucopolysaccharides.

Kytinon ATM *Asmopul, Arg.†.*
Porcine skin (p.1613·3); mucopolysaccharides; chloroxylenol (p.1640·2).
Wounds.

Kytinon Lamina *Asmopul, Arg.†.*
Porcine skin (p.1613·3).
Burns.

Kytinon Membrana *Asmopul, Arg.†.*
Porcine skin (p.1613·3).

Kytril *Roche, Arg.†; Mayne, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; GSK, NZ; Roche, Neth.; Roche, Norw.†; Roche, Philipp.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Kytta *Merck, Ger.†.*
Glycol salicylate (p.62·3).
Inflammation; pain; superficial vascular disorders.

Kytta Baume *Iromedica, Switz.*
Comfrey (p.2286·3); methyl nicotinate (p.85·3).
Musculoskeletal pain.

Kytta Gel *Melisana, Switz.†.*
Comfrey (p.2286·3); St John's wort (p.422·3); calendula (p.2273·1); peppermint leaf (p.1761·2); echinacea (p.2298·1).
Soft-tissue disorders.

Kytta Pommade *Iromedica, Switz.*
Comfrey (p.2286·3).
Musculoskeletal pain; soft-tissue injury; wounds.

Kytta-Balsam f *Merck, Ger.*
Comfrey (p.2286·3); methyl nicotinate (p.85·3).
Local circulatory disorders; musculoskeletal, joint, and soft-tissue disorders.

Kytta-Cor *Merck, Ger.*
Crataegus (p.2289·1).
Heart failure.

Kytta-Femin *Merck, Ger.†.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Kytta-Modal *Merck, Ger.†.*
St John's wort (p.422·3).
Depression.

Kytta-Plasma f *Merck, Ger.*
Comfrey (p.2286·3).
Soft-tissue disorders.

Kytta-Rheumabad N *Merck, Ger.†.*
Norway spruce oil.
Bath additive; rheumatism.

Kytta-Salbe f *Merck, Ger.*
Comfrey (p.2286·3).
Soft-tissue disorders.

Kytta-Sedativum
Note.This name is used for preparations of different composition.
Merck, Ger.
Oral drops: Valerian (p.2410·1).
Agitation; sleep disorders.

Merck, Ger.
Tablets: Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Agitation; sleep disorders.

Kytta-Sedativum fur den Tag *Merck Selbstmedikation, Ger.*
Passion flower (p.2363·2).
Nervous disorders.

Kytta-Thermopack *Merck, Ger.*
Peat; medicinal mud.
Musculoskeletal, joint, and soft-tissue disorders.

Kyypakkaus *Orion, Fin.*
⊗ Hydrocortisone (p.1535·2).
Bee and wasp stings; snake bites.

L107 *Lehning, Fr.*
Homoeopathic preparation.

L 25 *Lehning, Fr.*
Homoeopathic preparation.

L 28 *Lehning, Fr.*
Homoeopathic preparation.

L 52 *Lehning, Fr.*
Homoeopathic preparation.

L 72 *Lehning, Fr.*
Homoeopathic preparation.

L 114 *Lehning, Fr.*
Homoeopathic preparation.

LA-12 *Hyrex, USA†.*
Hydroxocobalamin (p.1980·3).
Schilling test; vitamin B deficiency.

La Edad De Oro *Cinetic, Arg.*
Evening primrose oil; borage oil; soya isoflavones; vitamin E (p.1922·1).
Dietary supplement.

LA Morph *Douglas, NZ.*
⊗ Morphine sulfate (p.86·3).
Pain.

La pommade du Dr Brand *Baren-Apotheke, Switz.*
Zinc oxide (p.1621·2); bismuth subnitrate (p.1711·2).
Burns; skin irritation; wounds.

La Tez *Nicholas Piramal, India.*
Tazarotene (p.1617·1).
Psoriasis.

Lab/A *Tosi, Ital.†.*
Lactobacillus (p.2372·3).
Vulvovaginal candidiasis.

Labdiazina *Zimaia, Port.*
Sulfadiazine (p.336·2).
Bacterial infections.

Label *Ache, Braz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Labello UV *Beiersdorf, Canad.†.*
SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Labelphen *Chrispa (Χρισπα), Gr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Labenda *Medicine Products, Thai.*
Albendazole (p.139·2).
Worm infections.

Labentrol *Chrispa (Χρισπα), Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Laberitin *Pharlab, Braz.†.*
Cinnarizine (p.573·1).
Vestibular disorders.

Labigeron *Teuto, Braz.*
Cinnarizine (p.573·1).

Labileno *Faes, Spain.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Labilex *Pharmathen, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Labimion *Sandoz, Arg.†.*
Etoposide (p.718·1).
Malignant neoplasms.

Labimiq *Labomed, Chile.*
Imiquimod (p.881·3).
Actinic keratoses; anogenital warts; basal cell carcinoma.

Labioline Plus *Qualiphar, Belg.*
SPF 15: Eusolex; titanium dioxide (p.1617·3).
Chapped lips; sunscreen.

Labiosan *Schoenenberger, Ger.*
Zinc oxide (p.1621·2).
Lip disorders.

Labirin *Apsen, Braz.*
Betahistine hydrochloride (p.2265·1).
Vestibular disorders.

Labistatin *Sandoz, Arg.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Labistatin Duo *Sandoz, Arg.*
Simvastatin (p.1390·2); ezetimibe (p.1284·3).
Hyperlipidaemias.

Labiton *Laboratories for Applied Biology, UK†.*
Thiamine (p.1976·3); caffeine (p.1116·3); kola nuts (p.2416·1); alcohol.
Tonic.

Labocaina *Combe, Ital.*
Benzocaine (p.1854·1); resorcinol (p.1612·1); chlorothymol (p.1640·1).
Pruritus.

Labocane *Combe, Ger.*
Benzocaine (p.1854·1).
Eczema; pruritus.

Labocne *Labomed, Chile.*
Erythromycin (p.269·2).
Acne.

Labocton *Viofar, Gr.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Labodrex *Padro, Spain.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Labopal *GSK, Spain.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension; renal failure.

Labopurinol *Sinterapico, Braz.†.*
Allopurinol (p.552·2).
Gout.

Laboriodine *Biosintetica, Braz.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Labosalic *Labomed, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Labosept *Laboratories for Applied Biology, UK.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Labosona *Labomed, Chile.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Labosona G *Labomed, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Labosona N *Labomed, Chile†.*
⊗ Betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Labotensil *Labomed, Chile.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Laboterol *Labomed, Chile†.*
Clotrimazole (p.530·1).
Fungal skin and nail infections.

Laboxantryl *Chrispa (Χρισπα), Gr.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Labstix *Siemens, Canad.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, UK; Bayer, USA.*
Test for pH, protein, glucose, ketones, and blood in urine.

Labstix SG *Bayer Diagnostics, Irl.; Bayer Diagnostics, UK.*
Test for pH, protein, glucose, ketones, blood, and specific gravity in urine.

Laburide *Wolfs, Belg.*
Pheneturide (p.492·1).
Epilepsy.

Labymetacyn *Arlex, Mex.†.*
Indometacin (p.66·3).
Inflammation; rheumatism.

Lac Stop *Rontag, Arg.*
Cabergoline (p.802·1).
Hyperprolactinaemias; inhibition of lactation.

Lacalut *Naturwaren, Ital.*
Aluminium lactate (p.2255·1); aluminium fluoride (p.1963·3); aluminium hydroxide (p.1706·2); silicon dioxide (p.2146·2).
Gum disorders; oral hygiene; sensitive teeth.

Lacbon
Note.This name is used for preparations of different composition.
Kimia, Indon.
Lactobacillus sporogenes (p.2372·3).
Gastrointestinal disorders; skin disorders.

Sankyo, Thai.†.
Lactobacillus spp. (p.2372·3).
Constipation; restoration of intestinal flora.

Laccoderme a l'huile de cade *Pierre Fabre, Fr.*
Rectified cade oil (p.1616·1); hyoscyamus oil (p.2323·3); salicylic acid (p.1612·2).
Psoriasis; seborrhoeic dermatitis.

Lacdigest *Italchimici, Ital.; Grogg, Switz.*
Tilactase (p.2402·1).
Lactase deficiency.

Lac-Dol
Note. A similar name is used for preparations of different composition (see below).
Douglas, Austral.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lacdol
Note. A similar name is used for preparations of different composition (see above).
Wermar, Mex.
Ketorolac trometamol (p.74·2).
Pain.

Lacedim *Lapi, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Lacefal *Lacefa, Arg.†.*
Aspirin (p.20·3).

Laceran Piel Seca *Beiersdorf, Chile†.*
A range of emollients.
Dry skin.

Lacerdermol *Lacer, Spain.*
Biotin (p.1931·3); calcium pantothenate (p.1959·3); vitamin A (p.1971·2).
Blepharitis; fragile nails; glossitis; skin disorders.

Lacerdermol Complex *Lacer, Spain.*
Vitamin B substances (p.1922·1); vitamin A (p.1971·2).
Seborrhoeic blepharitis; skin disorders.

Lacerol *Lacer, Port.†; Lacer, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Lacetilina *Pentafarma, Port.*
Acetylcarnitine hydrochloride (p.1932·2).
Mental function disorders.

Lacgel *Hetero, India.*
Lactic acid (p.2329·3); glycogen.
Vaginal disorders.

Lachemistol *Richter, Austria†; Wiedemann, Ger.*
Homoeopathic preparation.

Lachess *Knop, Chile.*
Homoeopathic preparation.

Lac-Hydrin *BMS, Braz.; Westwood-Squibb, Canad.; BMS, Mex.; BMS, NZ; BMS, Singapore; Westwood-Squibb, USA.*
Ammonium lactate (p.1589·2).
Dry skin disorders; ichthyosis vulgaris; pruritus; xerosis.

Lacidofil *Rosell, Canad.; Rosell, Cz.; Dexa, Indon.; Lallemand, Pol.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3).
Diarrhoea; maintenance of normal gastrointestinal function; restoration of gastrointestinal flora.

Laciken *Kendrick, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Lacimen *Menarini, Spain.*
Lacidipine (p.1322·2).
Hypertension.

Lacin *Atlantic, Thai.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Lacipil *GSK, Arg.†; GSK, Braz.; GSK, Cz.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Turk.; GSK, Venez.*
Lacidipine (p.1322·2).
Hypertension.

Lacirex *Guidotti, Ital.*
Lacidipine (p.1322·2).
Hypertension.

Lacitens *Lavipharm, Gr.*
Lacidipine (p.1322·2).
Hypertension.

Laclorene *Spedrog, Arg.*
Arginine aspartate (p.1928·2).
Tonic.

Laclorhex *Sertex, Arg.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

LAC-Lotion *Paddock, USA.*
Ammonium lactate (p.1589·2).
Emollient.

Lacoerdin Mg Plus *Weber & Weber, Ger.†.*
Crataegus (p.2289·1); magnesium aspartate (p.1679·1); magnesium phosphate (p.1679·2); magnesium sulfate (p.1679·3).
Cardiovascular disorders.

Lacoldin *Lapi, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold and influenza symptoms.

Lacomin *Best, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Lac-Oph *Seng, Hong Kong; Seng, Thai.*
Hypromellose (p.2144·2) (p.1622·2).
Dry eyes; wetting solution for contact lenses.

Lacophen *Lapi, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Lacophtal *Winzer, Ger.*
Povidone (p.2146·1).
Dry eye disorders.

Lacovin *Galderma, Spain.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Lacribase *Tubilux, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection.

Lacribell *Latinofarma, Braz.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Lacridos *Oftalmi, Venez.*
⊗ Dextran 70 (p.1059·3).
Dry eyes.

Lacrifilm *Genom, Braz.*
Carmellose sodium (p.2142·1).
Dry eyes.

Lacrigel
Note.This name is used for preparations of different composition.
Winzer, Ger.
Hyetellose (p.2143·3).
Dry eyes.

Farmigea, Ital.
Carbomer (p.2141·3).
Dry eyes; eye disinfection.

Lacri-Gel
Note. A similar name is used for preparations of different composition (see above).
Medical Ophthalmics, USA.
Soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Lacrigel A *Novartis Ophthalmics, Braz.*
Vitamin A (p.1971·2).
Dry eyes.

Lacril
Note.This name is used for preparations of different composition.
Allergan, Braz.; Allergan, Denm.; Allergan, Venez.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Allergan, Canad.; Allergan, USA.
Hypromellose (p.2144·2).
Dry eyes.

Lacrilens *Tubilux, Ital.*
Carmellose (p.2142·1) (p.1622·2).
Contact lens care.

Lacri-Lube
Note.This name is used for preparations of different composition.
Allergan, Austral.; Allergan, Chile; Allergan, USA.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Allergan, Fin.; Allergan, UK.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Dry eyes.

Allergan, Irl.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); hydrous wool fat (p.2033·3).
Corneal protection; dry eyes.

Lacrilube
Note.This name is used for preparations of different composition.
Allergan, Ital.; Allergan, NZ.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Dry eyes.

Allergan, Malaysia†; Allergan, Singapore.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); non-ionic lanolin derivatives (p.2033·2).
Dry eyes.

Allergan, Spain.
Soft paraffin (p.2031·2).
Dry eyes.

Lacrilux *Tubilux, Ital.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lacrima *Alcon, Braz.†.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Lacrima Plus *Alcon, Braz.; Alcon, Mex.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Lacrimal *Allergan, Ger.†; Polfa Warszawa, Pol.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lacrimal OK *Allergan, Ger.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Lacrimalfa *INTES, Ital.*
Sodium chloride; sodium bicarbonate; sodium acid phosphate; magnesium sulfate.
Dry eyes.

Lacrimart
Note.This name is used for preparations of different composition.
Baif, Ital.
Methylcellulose (p.2145·1).
Dry eyes; eye disinfection.

Oftalmi, Venez.
Eye drops: ⊗ Dextran 70 (p.1059·3).
Dry eyes.

Oftalmi, Venez.†.
Eye ointment: white soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Lacrimax *Ingens, Arg.*
Chondroitin sulfate (p.2280·3); aprotinin (p.1055·1); sodium hyaluronate (p.2320·1).
Dry eyes; eye disorders.

Lacrimill *Ottolenghi, Ital.†.*
Hypromellose (p.2144·2).
Dry eyes; eye disinfection; eye irritation.

Lacrimol
Note.This name is used for preparations of different composition.
Fischer, Israel.
Eye drops: Povidone (p.2146·1).
Dry eyes.

Fischer, Israel.
Eye ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Lacrinorm *Chauvin, Belg.; Ophtapharma, Canad.†; Chauvin, Fr.; Farmigea, Ital.; Chauvin, Neth.; Bausch & Lomb, Switz.*
Carbomer (p.2141·3).
Dry eyes; eye disinfection.

Lacripharma *ICN, Arg.†.*
Sodium hyaluronate (p.2320·1).
Dry eyes; keratitis.

Lacrisert *Sigma, Austral.†; Merck Frosst, Canad.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Neth.; MSD, Norw.†; MSD, Swed.; Aton, USA.*
Hyprolose (p.2144·1).
Decreased corneal sensitivity; dry eyes; exposure keratitis; Sjögren's syndrome.

Lacrisic *Alcon, Austria; Alcon, Ger.*
Hypromellose (p.2144·2); povidone (p.2146·1); glycerol (p.2314·2).
Dry eyes.

Lacrisifi *Craveri, Arg.†; SIFI, Ital.; SIFI, Rus.; SIFI, Singapore†; Teka, Turk.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Lacrisol *Bruschettini, Ital.*
Hypromellose (p.2144·2).
Dry eyes; eye disinfection.

Lacri-Stulln *Stulln, Ger.*
Povidone (p.2146·1).
Dry eyes.

Lacrisyn *Galena, Cz.†; Ivax, Cz.†; Ivax, Hung.†; Galena, Rus.*
Hypromellose (p.2144·2).
Aid in gonioscopy; corneal epithelial disorders; dry eyes.

Lacri-Tears *Medical Ophthalmics, USA.*
⊗ Hypromellose (p.2144·2); dextran (p.1059·3).
Dry eyes.

Lacromycin *Fischer, Israel.*
Gentamicin sulfate (p.282·1).
Eye infections.

Lacry+ *Europhta, Mon.*
Vitamins; minerals; plant extracts (p.1922·1).
Dietary supplement for dry eye disorders.

Lacrycon *Thea, Switz.*
Sodium hyaluronate (p.2320·1); carbomer 981 (p.2141·3); glycerol (p.2314·2).
Dry eyes.

Lacrypos *Alcon, Belg.; Alcon, Fr.*
Chondroitin sulfate sodium (p.2280·3).
Dry eyes; eye disorders.

Lacrystat *Meda, Belg.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Lacrytube *Meda, Belg.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2); wool fat (p.2033·2).
Corneal protection in comatose or anaesthetised patients; keratoconjunctivitis sicca.

Lacryvisc *Alcon, Arg.†; Alcon, Chile; Alcon, Cz.†; Alcon, Fr.; Alcon, Hong Kong; Alcon, Mex.; Alcon, Philipp.; Alcon, Port.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, Venez.*
Carbomer (p.2141·3).
Dry eyes; eye irritation.

Lacson *Pharmacare, S.Afr.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lacspan *Kissei, Hong Kong.*
Lysates of *Lactobacillus acidophilus* (p.2372·3); *Bifidobacterium infantis* (p.2372·3); *Enterococcus faecalis* (p.2372·3).
Restoration of gastrointestinal flora.

Lactacin *Solas, Indon.*
Sauropus androgynus; thiamine hydrochloride; pyridoxine hydrochloride; cyanocobalamin; ferrous fumarate; folic acid; zinc sulphate (p.1922·1).
Nutritional supplement in lactation.

Lactacyd *Rider, Chile; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.; GSK Consumer, Port.†; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.*
Milk serum; lactic acid (p.2329·3).
Skin cleanser; skin disorders; vulvovaginal disorders; vulvovaginal hygiene.

Lactacyd Antibatterico *GSK Consumer, Ital.*
Triclosan (p.1665·2).
Skin disinfection.

Lactacyd Derma *GSK Sante, Fr.; GSK Consumer, Ital.*
Milk serum; lactic acid (p.2329·3).
Acne; skin disorders; soap substitute.

Lactacyd Femina
GSK Sante, Fr.
Topical emulsion: Milk serum; lactic acid (p.2329·3).
Genital hygiene in females.

GSK Sante, Fr.
Wipes: Lactic acid (p.2329·3).
Genital hygiene in females.

Lactacyd Intimo *GSK Consumer, Ital.*
Milk serum; lactic acid (p.2329·3).
Genital hygiene.

Lactacyd VG *Sanofi Synthelabo, Philipp.*
Lactic acid (p.2329·3).
Genital hygiene in females.

Lactaderm *Sanofi Synthelabo, Philipp.*
Calendula (p.2273·1); glycerol (p.2314·2); amino acids.
Infant skin cleanser.

Lactagard *Ipca, India.*
Cefoperazone sodium (p.227·1); sulbactam sodium (p.335·1).
Bacterial infections.

Lacta-Gynecogel *Medgenix, Belg.*
Lactic acid (p.2329·3).
Anogenital infections.

Lactaid *Sunrise, Austral.†; McNeil Consumer, Canad.; McNeil Consumer, USA.*
Tilactase (p.2402·1).
Lactase insufficiency; lactose intolerance.

Lactaide *YSP, Malaysia†.*
Tilactase (p.2402·1).
Lactose intolerance.

Lactamax *Beta, Arg.*
Cabergoline (p.802·1).
Hyperprolactinaemia; lactation inhibition; prolactinomas.

Lactamil *Sari Husada, Indon.*
Preparation for enteral nutrition (p.1922·1).

Lac-Tas *Dominguez, Arg.*
Tilactase (p.2402·1).
Lactose intolerance.

Lactasol *Gambro, Denm.; Gambro, Port.; Gambro, Swed.*
Calcium chloride; magnesium chloride; sodium chloride; sodium lactate (p.1670·3).
Haemodialysis; haemofiltration.

Lact-Easy *Sunrise, Austral.†.*
Tilactase (p.2402·1).
Lactose intolerance.

Lactec *Otsuka, Jpn.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Lactec D *Otsuka, Jpn.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Lactec G *Otsuka, Jpn.*
Electrolyte infusion with d-sorbitol (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Lactecon *Solvay, Cz.; Solvay, Port.†.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lacteol *Menarini, Belg.; Axcan, Fr.; Pohl, Ger.; Axcan, Hong Kong; Bruschettini, Ital.; BioSaude, Port.; Amsco, Singapore; Axcan, Singapore; Ramon Sala, Spain; Lacteol, Switz.†; Axcan, Thai.†; Biopas, Venez.*
Metabolic products of *Lactobacillus acidophilus* (p.2372·3).
Colopathy; diarrhoea; enterocolitis; restoration of the gastrointestinal flora.

Lacteol Fort *Carnot, Mex.*
Lactobacillus acidophilus (Boucardii) (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Lacteol Forte *Master, Chile†.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea.

Lactibon *Medihealth, Mex.; Roemmers Medihe, Venez.*
Lactic acid (p.2329·3).
Skin cleansing; soap substitute.

Lacticare
Note.This name is used for preparations of different composition.
Stiefel, Arg.; Stiefel, Braz.; Stiefel, Chile†; Stiefel, Fr.; Stiefel, Hong Kong†; Stiefel, Indon.; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK†.
Lactic acid (p.2329·3); sodium pidolate (p.1614·1).
Dry skin disorders.

Stiefel, USA.
Lactic acid (p.2329·3); liquid paraffin (p.2030·3).
Emollient and moisturiser.

Lacticare-HC *Stiefel, Chile†; Stiefel, Hong Kong†; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, USA; Stiefel, Venez.†.*
⊗ Hydrocortisone (p.1535·2).
Humectant; skin disorders.

Lactid HC *Cassara, Arg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Lactiderm *Cassara, Arg.*
⊗ Ammonium lactate (p.1589·2); urea (p.1620·2).
Dry skin.

Lactiderm HC *Cassara, Arg.†.*
⊗ Hydrocortisone (p.1535·2); ammonium lactate (p.1589·2); urea (p.1620·2).
Skin disorders.

Lactidorm *Galactopharm, Ger.†.*
Lupulus (p.2335·2).
Anxiety.

Lactigriet *Isdin, Port.*
Dexpanthenol (p.2362·1); chlorhexidine (p.1635·2).
Sore nipples.

Lactil *Laboratorios Chile, Chile.*
Lactobacillus rhamnosus (p.2372·3).
Diarrhoea.

Lactinex
Note.This name is used for preparations of different composition.
Omega, Arg.
Lactobacillus acidophilus (p.2372·3).
Restoration of vaginal flora.

Becton Dickinson, USA.
Lactobacillus acidophilus (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3).
Dietary supplement.

Lactinol *Pedinol, USA.*
Lactic acid (p.2329·3).
Dry skin.

Lactinol-E *Pedinol, USA.*
Lactic acid (p.2329·3); vitamin E (p.1992·2).
Dry skin.

Lactipan
Note.This name is used for preparations of different composition.
Sigma, Braz.
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

IBI, Ital.
Lactococcus lactis (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3).
Gastrointestinal disorders.

Italmex, Mex.
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of intestinal flora.

Lactisan *Galactopharm, Ger.*
Sour milk whey concentrate (p.2329·3).
Vaginal disorders.

Lactisol *Galactopharm, Ger.*
Lactic acid (p.2329·3).
Gastrointestinal disorders; skin disorders.

Lactisona *Stiefel, Port.; Stiefel, Spain.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Lactisporin *Medisint, Ital.*
Lactic-acid-producing organisms (p.2372·3); dried yeast (p.1998·3); vitamin B substances (p.1922·1).
Restoration of normal gastrointestinal flora.

Lactisyn *Franco-Indian, India.*
Lactobacillus lactis (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3); *Lactococcus lactis* (p.2372·3).
Aphthous stomatitis; diarrhoea; infections.

Lactivis
Note.This name is used for preparations of different composition.
Fitobucaneve, Ital.
Capsules: Vitamins (p.1922·1); *Lactobacillus acidophilus* (p.2372·3); dried yeast (p.1998·3); dried yogurt.
Nutritional supplement.

Fitobucaneve, Ital.
Powder for oral liquid: Vitamins (p.1922·1); lactic-acid-producing organisms (p.2372·3).
Nutritional supplement.

Lacto Calamine
Note.This name is used for preparations of different composition.
CSL, NZ†.
Calamine (p.1591·2); hamamelis (p.2318·2).
Insect bites; sunburn.

Rolfe, S.Afr.†.
Calamine (p.1591·2); hamamelis water (p.2318·2); phenol (p.1656·1); zinc oxide (p.1621·2).
Skin disorders.

Schering-Plough, UK.
Cream: Calamine (p.1591·2); zinc oxide (p.1621·2); hamamelis (p.2318·2).
Dry skin; sunburn.

Schering-Plough, UK.
Lotion: Calamine (p.1591·2); zinc oxide (p.1621·2); hamamelis (p.2318·2); phenol (p.1656·1).
Skin irritation; sunburn.

Lacto Calcium *Innopharm, Singapore†.*
Calcium (p.1675·2); phosphorus (p.2367·2).
Calcium supplement; osteoporosis.

Lacto Pregomine *Milupa, Fr.†.*
Infant feed (p.1922·1).
Cow's milk intolerance.

Lacto Vagin *UCI, Braz.†.*
Tyrothricin (p.358·2); hydroxyquinoline (p.2323·2); tannic acid (p.2394·3); lactic acid (p.2329·3); acetic acid (p.2244·2); camphor (p.2273·2).
Vulvovaginal disorders.

Lacto-B *Novell, Indon.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium longum* (p.2372·3); *Enterococcus faecium* (p.2372·3); vitamins.
Diarrhoea.

Lactobacilos *Biotech Naturis, Venez.*
Lactobacillus acidophilus (p.2372·3).
Restoration of gastrointestinal flora.

Lactocal-F *Laser, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Supplement for pregnant or lactating women.

Lactocef *Cadila, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Lacto-Cev *Cevallos, Arg.*
Ammonium lactate (p.1589·2).

Lacto-Cev Zn *Cevallos, Arg.*
Ammonium lactate (p.1589·2); zinc gluconate (p.1999·2).
Skin disorders.

Lactocil *Gelcaps, Mex.*
Lactobacillus acidophilus (p.2372·3).
Restoration of intestinal flora.

Lactocol *Ogna, Ital.*
Guaiacol (p.1561·2); lactic acid (p.2329·3); calcium phosphate (p.1676·2); calcium lactate (p.1676·1); codeine hydrochloride (p.37·2); aconite (p.2246·1).
Coughs.

Lactocom Forte *Cadila, India.*
Lactic-acid producing organisms; vitamin B substances; vitamin C (p.1922·1).

Lactocrem *Giscard, Arg.*
⊗ Urea (p.1620·2) alfa hydroxyacids.
Dry skin.

Lactocrem Bebe *Giscard, Arg.*
Allantoin (p.1588·1); zinc (p.1999·1); vegetable extracts.
Barrier preparation.

Lactocur *Sandoz, Austral.; Hexal, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactoferment *Gebro, Switz.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Lactoferrina *Chiesi, Spain.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency anaemia.

Lactofilus *Juventus, Spain.*
Lactobacillus acidophilus (p.2372·3).
Restoration of the gastrointestinal flora.

Lactofit *Germania, Austria.*
Lactobacillus rhamnosus (p.2372·3).
Diarrhoea.

Lactofree *Mead Johnson Nutritionals, USA.*
Lactose-free infant feed (p.1922·1).

Lactoger *Schwarz, Ital.†.*
Lactulose (p.1738·2).
Hepatic cirrhosis; hepatic encephalopathy.

Lactogermine *Humana, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins (p.1922·1).
Nutritional supplement.

Lacto-Key *Key, USA.*
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

Lactolas *Infosint, Ital.*
Lactulose (p.1738·2); inulin (p.2326·3); rhubarb (p.1768·3); frangula (p.1732·2); senna (p.1769·2); vitamin B substances (p.1922·1).
Nutritional supplement.

Lactolavol *Rosch & Handel, Austria.*
Calcium lactate (p.1676·1); tartaric acid (p.2395·2); atropine sulfate (p.1219·3).
Vaginal disorders.

Lactolife *Fitolife, Ital.*
Dried yeast (p.1998·3); lactic-acid-producing organisms (p.2372·3).
Gastrointestinal disorders; nutritional supplement.

Lactomannan *CaDiGroup, Ital.*
Glucomannan (p.2312·3); lactulose (p.1738·2).
Constipation; obesity.

Lactomina *Ibefar, Braz.†.*
Calcium lactophosphate; manganese hypophosphite; vitamin B substances (p.1922·1).
Nutritional supplement.

Lactonico *Dermoteca, Port.†.*
Ammonium lactate (p.1589·2); squalane (p.2032·3); levomenol (p.2333·3); vitamin E.
Barrier preparation; dry skin disorders.

Lactonorm *Geymonat, Ital.*
Lactobacillus acidophilus (p.2372·3).
Disturbances in vaginal flora.

Lactopan *Forder, Arg.†.*
Cetyl alcohol (p.2028·3).
Skin cleanser.

Lactopectin *Sanofi Synthelabo, Mex.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Lactophilus *Lyocentre, Fin.*
Lactobacillus rhamnosus (p.2372·3).
Restoration of gastrointestinal flora.

Lactopregomine *Milupa, Fr.†.*
Infant feed (p.1922·1).
Milk protein intolerance.

Lactopurum *Pfluger, Ger.*
Homoeopathic preparation.

Lactosec *Pharmacare, S.Afr.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin deficiency.

Lactovaginal *Biomed Krakow, Pol.*
Lactobacillus rhamnosus (p.2372·3).
Restoration of vaginal flora.

Lactovita *Sanofi Synthelabo, Mex.*
Lactobacillus acidophilus (p.2372·3).
Restoration of intestinal flora.

Lactrase *Rivex, Canad.†; Schwarz, USA.*
Tilactase (p.2402·1).
Lactase insufficiency; lactose intolerance.

Lactrex
Note.This name is used for preparations of different composition.
Galderma, Arg.
Ammonium lactate (p.1589·2).
Dry skin disorders.

Galderma, Braz.; Galderma, Chile†; Galderma, Mex.; Galderma, Venez.
Allantoin (p.1588·1); ammonium lactate (p.1589·2).
Cicatrisation; dry skin.

SDR, USA.
Lactic acid (p.2329·3).
Emollient.

Lactrime *Forder, Arg.†.*
Glycolic acid (p.1598·1).
Moisturiser.

Lactucol *Distrifarma, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Lactuflor *Rosen, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactugal *Intrapharm, UK.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactul *YSP, Malaysia.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactulac *Kocak, Turk.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactulax *Fresenius Kabi, Indon.; Sam-On, Israel; Senosiain, Mex.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactulol *Hasco-Lek, Pol.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactulon *Lazar, Arg.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactulona *Sankyo, Braz.; Sankyo, Venez.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactumed *Medochemie, Malaysia†.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactus *ICM, Singapore.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lactuverlan *Verla, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Ladar *Millimed, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Ladazol *Adcock Ingram, S.Afr.*
⊗ Danazol (p.2090·2).
Endometriosis; hereditary angioedema; mastalgia.

Laderm *Galderma, Braz.*
Almond oil (p.2252·2).
Dry skin disorders; soap substitute.

Ladinin *Pharmathen, Gr.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Ladip *Valda, Ital.*
Lacidipine (p.1322·2).
Hypertension.

Ladiwin *Zydus, India.*
Lamivudine (p.895·1).
HIV infection.

Ladocort *LBS, Thai.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Ladogal *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.; Sanofi-Aventis, Venez.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; gynaecomastia; hereditary angioedema; mastalgia; menorrhagia; precocious puberty.

Ladose *Lilly, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Ladropen *Berk, UK.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Lady *Pond's, Philipp.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Lady-35 *Masa, Thai.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Oral contraceptive in women with androgenic symptoms.

Lady Fittig *Andromaco, Chile†.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); hexylresorcinol (p.1647·1); aluminium chlorohydrate (p.1588·3).
Fungal skin infections.

Ladybon *Zentiva, Cz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Ladylen *Mertens, Arg.*
Miconazole nitrate (p.541·3); tinidazole (p.848·3).
Vaginal infections.

Ladylen Duo *Mertens, Arg.*
Tinidazole (p.848·3).
Bacterial infections; candidiasis; trichomoniasis.

Ladymega *Contassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Lady-Ten 35 *Laboratorios Chile, Chile.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, hirsutism, and menstrual disorders.

Ladytone *Vitabiotics, UK.*
Multivitamin and mineral preparation (p.1922·1).

Ladyvital *Pharmadass, UK.*
Multivitamin, mineral, and nutritional preparation (p.1922·1).

Laevadosin
Note.This name is used for preparations of different composition.
Ebewe, Cz.†.
Injection: Adenosine (p.1202·1); inosine (p.2325·2); adenosine triphosphate sodium (p.2247·3); adenosine phosphate disodium (p.2247·3); disodium guanylate (p.2296·1); guanosine (p.2318·1); uridine (p.2407·3).
Myopathies; peripheral and cerebral vascular disorders.

Ebewe, Cz.†.
Tablets: Adenosine phosphate disodium (p.2247·3); disodium cytidine monophosphate (p.2291·3); disodium guanylate (p.2296·1); disodium uridine monophosphate (p.2296·1); adenosine (p.1202·1); guanosine (p.2318·1).
Myopathies; peripheral and cerebral vascular disorders.

Laevilac S *Fresenius Kabi, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laevofusin Isoton *Fresenius Kabi, Austria.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Laevolac *Fresenius Kabi, Austria; Fresenius Medical, Cz.†; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius, Israel; Roche, Ital.; Douglas, NZ; Ferraz, Lynce, Port.; Fresenius Kabi, Thai.†; Ulagay, Turk.*
Lactulose (p.1738·2).
Constipation; disturbances of gastrointestinal flora; gum disorders; hepatic cirrhosis; hepatic encephalopathy; hyperammonaemia; salmonella enteritis.

Laevosan *Roche, Ital.†.*
Fructose (p.1945·1).
Asthenia; cardiac disorders; diabetes; liver disorders; poisoning.

Laevovit D_3 *Fresenius Kabi, Austria; Fresenius Kabi, Hung.†.*
Colecalciferol (p.1986·2).
Osteomalacia; rickets; vitamin D supplementation.

Lafalos *Sanbe, Indon.*
Menthol (p.2340·1); eugenol (p.2301·2); methyl salicylate (p.85·3).
Headache; musculoskeletal pain.

Lafamme *Schering, Austria; Jenapharm, Ger.; Schering, Neth.; Lusal, Port.*
Estradiol valerate (p.2097·3); dienogest (p.2094·1).
Menopausal disorders.

LAfamo *Cipla, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lafarcaina *Elmor, Venez.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1); thymol (p.1664·3).
Sore throat.

Lafarclor *Lafare, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Lafarin *Lafare, Ital.*
Cefalexin (p.218·2).
Bacterial infections.

Lafaxon *Ingers, Cz.*
Venlafaxine hydrochloride (p.427·3).
Anxiety disorders; depression; panic disorder.

Lafeaspirina *Lafedar, Arg.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Lafedam *Elvetium, Arg.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Lafedoxin *Lafedar, Arg.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Lafelax *Lafedar, Arg.*
Lactulose (p.1738·2).
Constipation.

Lafevir *Lafedar, Arg.*
Aciclovir (p.862·3).

Laffed *Lafayette, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Lafigesic *Recalcine, Chile.*
Clonixin lysine (p.37·1).
Inflammation; pain.

Lafigin *Drugtech, Chile; Recalcine, Chile.*
Lamotrigine (p.485·1).
Epilepsy.

Lafin *Loeffler, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Laflanac *Lapi, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Lafol *Valeant, Ger.*
Folic acid (p.1940·1).
Folic acid supplement.

La-Fu *Pliva, Cz.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Lafurex *Lafare, Ital.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Lagalgin *Lagap, Neth.†.*
Paracetamol (p.108·1).
Fever; pain.

Lagarmicin *Medicalia, Spain.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Lagatrim *Alliance, S.Afr.; Lagap, Switz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Lagenbach *Remexa, Mex.*
Senna (p.1769·2).
Constipation.

Lagesic *Laser, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Pain.

Lagesil *Lapi, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Excess gastrointestinal gas; gastric hyperacidity; peptic ulcer.

Lagin *Epifarma, Ital.†.*
Benzydamine hydrochloride (p.27·3).
Gynaecological disorders.

Lagosa
Note.This name is used for preparations of different composition.
Worwag, Cz.; Worwag, Ger.
Milk thistle (p.1452·1).
Liver disorders.

Worwag, Pol.
Silymarin (p.1452·2).
Liver disorders.

Lagotran Beta, Arg.
Lamotrigine (p.485·1).
Epilepsy.

Lagricel Sophia, Mex.
Sodium hyaluronate (p.2320·1).
Dry eyes.

Lagricel Ofteno Volta, Chile; Elmor, Venez.
Sodium hyaluronate (p.2320·1).
Dry eyes; eye irritation.

Lagrifilm Plus Allergan, Mex.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Lagrima Artificial Poen, Arg.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lagrima Dorf Pharmadorf, Arg.
Hypromellose (p.2144·2).
Dry eyes.

Lagrima Humectante Inmunolab, Arg.†.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lagrimas Artificiales
Note.This name is used for preparations of different composition.
Andromaco, Chile.
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Laboratorios Chile, Chile.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Alcon, Venez.; Oftalmi, Venez.
⊗ Dextran 70 (p.1059·3).
Dry eyes.

Lagrimas de Santa Lucia
Note.This name is used for preparations of different composition.
Ferro, Arg.†.
Eye drops: Zinc sulfate (p.1999·2); boric acid (p.2268·1); methylthioninium chloride (p.1450·3).
Dry eyes.

Ferro, Arg.†.
Powder: Mercuric oxycyanide (p.2342·2).
Dry eyes.

Lagun Orion, Fin.†.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Lagylan Arlex, Mex.
Metronidazole (p.837·1).
Amoebiasis.

Laidor Esseti, Ital.†.
Nimesulide (p.95·3).
Fever; inflammation; pain.

Laif Steigerwald, Cz.; Steigerwald, Ger.
St John's wort (p.422·3).
Depression; nervous disorders.

Laikan 100 Grunenthal, Chile†.
Kava (p.2328·3).
Anxiety.

Laiken Farmasa, Mex.
Kava extract (p.2328·3).
Anxiety.

Laimolin Flupal, Venez.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Laimoqualin Vargas, Venez.
Dequalinium chloride (p.1641·3); lidocaine (p.1862·3).
Mouth and throat disorders.

Lais Lofarma, Hung.
A range of allergen preparations (p.2250·2).
Hyposensitisation.

Lait Auto-Bronzant Clarins, Canad.
SPF 6: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Lait Ecran Total Intolerance Vichy, Canad.
SPF 30: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Lait Solaire Ecran Total Lancome, Canad.†.
SPF 25: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Lait Solaire Haute Protection Lancome, Canad.†.
SPF 15: Avobenzone (p.1589·3); enzacamene (p.1597·1); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Laitan Nycomed, Braz.; Schwabe, Ger.†; Spitzner, Ger.†.
Kava (p.2328·3).
Anxiety; tension.

Laitun Pasteur, Philipp.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Lakcid Biomed Lublin, Pol.†.
Lactobacillus rhamnosus (p.2372·3).
Maintenance of gastrointestinal flora.

Lake Faes, Spain.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lakea Lek, Cz.; Lek, Pol.
Losartan potassium (p.1326·1).
Hypertension.

Lakinal Slovakofarma, Cz.†.
Melissa (p.2339·3).
Herpes simplex infections.

Lakrima Bittner, Austria.
Homoeopathic preparation.

Lakriment Neu Dolorgiet, Ger.†.
Liquorice (p.1740·3).
Catarrh.

Laksafenol Liba, Turk.
Phenolphthalein (p.1762·1).

LaktaFit Dexa, Indon.
Placenta extract (p.2337·3); vitamin B (p.1980·2); calcium hydrogen phosphate (p.1676·1).
Lactation insufficiency.

Laktipex Selena, Swed.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laktobion Sanghiang, Indon.
Lactoferrin (p.2330·1); lactulose (p.1738·2); bifidobacteria (p.2372·3).
Immunomodulator; restoration of gastrointestinal flora.

Laktol Sanofi Synthelabo, Turk.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laktomag Chance, Pol.
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Laktomag B_6 Chance, Pol.
Magnesium aspartate (p.1679·1).
Pyridoxine (p.1979·1) is included in this preparation to increase the absorption of magnesium.
Magnesium deficiency.

Lalax Orion, Fin.
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

Lalide Pharmacypria, Gr.
Nimesulide (p.95·3).
Inflammatory disorders.

Lama
Note.This name is used for preparations of different composition.
Stadmed, India.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Pharmaland, Thai.
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Lamafer Bros, Gr.†.
Cisapride (p.1720·3).
Gastric motility disorders.

Lamaline Solvay, Fr.
Paracetamol (p.108·1); opium (p.105·1); caffeine (p.1116·3).
Pain.

Lambda
Note.This name is used for preparations of different composition.
Isdin, Port.
Cream: Triclosan (p.1665·2); aluminium hydroxide (p.1706·2).
Hyperhidrosis.

Isdin, Port.
Roll-on: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Lambeta Farmedia, Gr.
Cetirizine (p.571·1).
Hypersensitivity disorders.

Lambipol GSK, Belg.
Lamotrigine (p.485·1).
Epilepsy.

Lambliquin Novag, Mex.
Metronidazole (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Lamblit Novag, Mex.
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Lambucid Hexpharm, Indon.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; epigastric pain; gastric pain.

Lambutol Atlantic, Thai.
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Lamcoin Pond's, Thai.
Clofazimine (p.254·2).
Leprosy.

Lamda Cadila, India.
Lamivudine (p.895·1).
HIV infection.

Lamda-Z Cadila, India.
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Lamdra Bioquimed, Mex.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamepil Ipca, India.
Lamotrigine (p.485·1).
Epilepsy.

Lameson Lapi, Indon.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Lametec Cipla, India.
Lamotrigine (p.485·1).
Epilepsy.

Lameton Sandoz, Cz.
Lamotrigine (p.485·1).
Epilepsy.

Lametta Vipharm, Pol.
⊗ Letrozole (p.740·2).
Breast cancer.

Lami Cristalia, Braz.
Lamivudine (p.895·1).
HIV infection.

Lamia Genexo, Pol.
Lamotrigine (p.485·1).
Epilepsy.

Lamibergen Paylos, Arg.
Lamivudine (p.895·1).
HIV infection.

Lamican Kanonfarma, Rus.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Lamicosil Novartis Consumer, Spain.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Lamicstart GSK, Fr.
Lamotrigine (p.485·1).
Epilepsy.

Lamictal GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; Wellcome, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamictin GSK, S.Afr.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamidac Zydus, India.
Lamivudine (p.895·1).
Chronic hepatitis B.

Lamiderm Gifrer Barbezat, Fr.
Trolamine (p.2405·1).

Lamidus Ranbaxy, Austral.
Lamotrigine (p.485·1).
Epilepsy.

Lamifen Wander, Philipp.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Lamigen Alvia (Αλβια), Gr.
Terbinafine (p.546·3).
Fungal skin infections.

Lamiger MH Consulting, Cz.
Lamotrigine (p.485·1).
Epilepsy.

Lamilea Elea, Arg.
Lamivudine (p.895·1).
HIV infection.

Lamilept Ivax, Pol.
Lamotrigine (p.485·1).
Epilepsy.

Lamioflur Heel, Cz.
Homoeopathic preparation.

Lamirax Elea, Arg.
Lamotrigine (p.485·1).
Epilepsy.

Lamirex Ipca, India†.
Lamivudine (p.895·1).
HIV infection.

Lamisil
Novartis, Arg.; Novartis, Austral.; Novartis Consumer, Austral.; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Hong Kong; Novartis, India†; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, NZ†; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, S.Afr.; Novartis, Spain; Novartis, Thai.; Novartis, Turk.; Novartis, UK.
Terbinafine hydrochloride (p.546·3).
Fungal infections of the skin, hair, scalp, and nails.

Novartis, Austria; Novartis, Braz.; Novartis, Chile; Novartis, Ger.; Novartis, Hung.; Novartis Consumer, Hung.; Novartis, Malaysia; Novartis Consumer, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, Rus.; Novartis OTC, Singapore; Novartis, Swed.; Novartis, Switz.; Novartis, USA; Novartis, Venez.
Terbinafine (p.546·3) or terbinafine hydrochloride (p.546·3).
Fungal infections of the skin, hair, and nails.

Novartis, Gr.
Terbinafine (p.546·3).
Fungal skin infections.

Lamisil AF Defense Novartis Consumer, USA.
Tolnaftate (p.548·3).
Fungal skin infections.

Lamisil Odor Eze Novartis, NZ.
Aloe vera (p.1588·2); aluminium starch octenylsuccinate; corn starch (p.1968·1); silicon dioxide (p.2146·2); talc (p.1615·2).
Foot odour.

Lamisilate Novartis Sante, Fr.
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Lamisilatt Novartis Consumer, Pol.
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

LamisilDermgel Novartis Sante, Fr.
Terbinafine (p.546·3).
Fungal skin infections.

Lamitor Torrent, Braz.; Torrent, Neth.; Torrent, Rus.; Reddy, S.Afr.
Lamotrigine (p.485·1).
Epilepsy.

Lamitrin Hexal, Austral.; GSK, Hung.; GSK, Pol.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamivir Cipla, India; Cipla, Venez.
Lamivudine (p.895·1).
HIV infection.

Lamivir S Cipla, India.
Lamivudine (p.895·1); stavudine (p.907·1).
HIV infection.

Lamnotyl Farmasur, Spain†.
Boric acid (p.2268·1); hamamelis (p.2318·2); ichthammol (p.1599·1); zinc oxide (p.1621·2).
Burns; grazes; skin disorders.

Lamo TAD, Ger.
Lamotrigine (p.485·1).
Epilepsy.

Lamochem Tiefenbacher, Neth.†.
Lamotrigine (p.485·1).
Epilepsy.

Lamodex
Note.This name is used for preparations of different composition.
Guardian, Indon.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dexcel, Israel.
Lamotrigine (p.485·1).
Epilepsy.

Lamogine Alphapharm, Austral.; Montrose, Cz.; Trima, Israel.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamolep Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamomont Tiefenbacher, Neth.
Lamotrigine (p.485·1).
Epilepsy.

Lamotax Ranbaxy, Cz.
Lamotrigine (p.485·1).
Epilepsy.

Lamotifi Tiefenbacher, Neth.
Lamotrigine (p.485·1).
Epilepsy.

Lamotri Hexal, Cz.
Lamotrigine (p.485·1).
Epilepsy.

Lamotriax Temmler, Ger.
Lamotrigine (p.485·1).
Epilepsy.

Lamotrig Alpharma-Isis, Ger.
Lamotrigine (p.485·1).
Epilepsy.

Lamotriglax GSK, Austria.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lamotrihexal Hexal, Pol.
Lamotrigine (p.485·1).
Epilepsy.

Lamotril Omedir, Arg.
Lamotrigine (p.485·1).
Epilepsy.

Lamotrix Medochemie, Cz.; Pharmacypria, Gr.; Medochemie, Malaysia; Biovena, Pol.
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Lampicin Grunenthal, Mex.
Ampicillin (p.204·1), ampicillin sodium (p.204·1), or ampicillin trihydrate (p.204·2).
Bacterial infections.

Lampocef Lampugnani, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Lampoflex Lampugnani, Ital.
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Lampomandol AGIPS, Ital.
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Lampopram Lampugnani, Ital.
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Lampral Biotech, Venez.
Thiocolchicoside (p.1898·2).
Muscle spasm.

Lampren Novartis, Jpn; Novartis, Neth.; Padro, Spain.
Clofazimine (p.254·2).
Leprosy.

Lamprene Novartis, Austral.; Scanpharm, Cz.; Novartis, Fr.; IFET (ΙΦΕΤ), Gr.; Novartis, Hong Kong†; Novartis, Malaysia†; Novartis, NZ; Novartis, S.Afr.†; Novartis, Switz.†; Alliance, UK†; Novartis, USA.
Clofazimine (p.254·2).

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Available from WHO for the treatment of leprosy.
Leprosy.

Lamra *Merckle, Ger.*
Diazepam (p.986·3).
Anxiety; premedication; skeletal muscle spasm.

Lamuna *Hexal, Ger.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lamuran *SIT, Ital.*
Raubasine (p.1386·3).
Peripheral circulatory disorders.

Lamuzid *Zydus, India.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Lamzid *Pharmacare, S.Afr.*
Zidovudine (p.913·3); lamivudine (p.895·1).
HIV infection.

Lanabiotic *Combe, USA†.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin (p.210·3); lidocaine (p.1862·3).
Bacterial skin infections.

Lanacaina *Combe, Arg.†.*
Benzocaine (p.1854·1).
Pruritus.

Lanacane
Note.This name is used for preparations of different composition.
Combe, Israel; Combe, Spain; Combe, UK; Combe, USA.
Benzocaine (p.1854·1).
Local anaesthesia; skin disorders; skin irritation.

Formula, NZ.
Benzocaine (p.1854·1); resorcinol (p.1612·1).
Skin irritation.

Lanacane Medicated Cream *Combe, Canad.*
Benzocaine (p.1854·1); resorcinol (p.1612·1).
Skin disorders.

Lanacane Medicated Powder *Combe, UK.*
Menthol (p.2340·1); zinc oxide (p.1621·2).
Skin irritation.

Lanacef *Lannacher, Austria†.*
Cefaclor (p.217·2).
Bacterial infections.

Lanacetine *Landson, Indon.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Lanacine *Lannacher, Austria.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Lanacol *Landson, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Lanacordin *Kern, Spain.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Lanacort *Combe, Israel; Combe, Ital.; Combe, UK; Combe, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Lanacrist *AstraZeneca, Swed.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Lanadexon *Landson, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Lanafine *Niche, Irl.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Lanaginkola *Landson, Indon.*
Ginkgo biloba (p.2311·1).
Vascular dementia.

Lanagogum *Landson, Indon.*
Greater celandine (p.2317·1); turmeric (p.1473·2); spinaceae; lecithin (p.2332·2); peppermint oil (p.1761·2); turmeric oil (p.1473·2).
Digestive disorders.

Lanakeloid *Landson, Indon.; Landson, Malaysia.*
Centella (p.1592·3).
Burns; circulatory disorders; wounds.

Lanakeloid-E *Landson, Indon.*
Centella (p.1592·3); vitamin E (p.1992·2).
Burns; wounds.

Lanalget *Lannacher, Austria.*
Tramadol hydrochloride (p.130·3).
Pain.

Lanamol *Landson, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Lanamont *SJA, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Lanaphilic
Note.This name is used for preparations of different composition.
Medco, USA.
Vehicle for topical preparations.

Medco, USA.
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Lanaprost *Landson, Indon.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Lanareuma *Landson, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Lanarif *Landson, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Lanate *Douglas, Malaysia; Douglas, NZ; Douglas, Singapore.*
Ammonium lactate (p.1589·2).
Dry skin disorders.

Lanatilin *Wabosan, Austria.*
α-Acetyldigoxin (p.1201·2).
Heart failure.

Lanatin *Nycomed, Denm.†.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lanaven *Landson, Indon.*
Soya bean (p.1965·3); aesculus (p.2248·2); citrus complex.
Venous disorders.

Lanaven Plus *Landson, Indon.*
Aesculus (p.2248·2); citrus complex; lecithin (p.2332·2); grape seed (p.2316·3).
Venous disorders.

Lanavision
Note.This name is used for preparations of different composition.
Landson, Indon.
Capsules: Myrtillus (p.2349·3).
Circulatory eye disorders.

Landson, Indon.
Syrup: Myrtillus (p.2349·3); betacarotene; vitamin A; vitamin E; vitamin B substances (p.1922·1).
Circulatory eye disorders.

Lanavision Plus *Landson, Indon.*
Myrtillus (p.2349·3); betacarotene; vitamin A; pyridoxine hydrochloride; tocopherol acetate; chromium; zinc; selenium; taurine; glutamine; cysteine hydrochloride; lecithin (p.1922·1).
Circulatory eye disorders.

Lanazapin *Lannacher, Austria.*
Mirtazapine (p.409·2).
Depression.

Lanbica *Lannacher, Cz.*
Bicalutamide (p.686·2).
Prostatic cancer.

Lancap *Pharma Dynamics, S.Afr.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Lancef *Landson, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Lancetan *Prolab, Pol.*
Ribwort plantain (p.2379·1).
Respiratory-tract congestion.

Lanceticum *Theiss Naturwaren, Pol.*
Ribwort plantain (p.2379·1).
Catarrh; cough.

Lancid *Kalbe, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lanciprol *Med-One, Gr.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Lancolin *Landson, Indon.*
Citicoline sodium (p.2283·3).
Head injury; hemiplegia; mental function impairment.

Lancome-Gelee Fraicheur *Lancome, Canad.†.*
SPF 8: Enzacamene (p.1597·1); octinoxate (p.1608·2); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Formerly known as Lancome-Creme Gelee.
Sunscreen.

Lancus *Cadila, India.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Landel *Shionogi, Jpn.*
Efonidipine hydrochloride (p.1276·1).
Hypertension.

Lander Dandruff Control *Lander, Canad.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Lando *Pyridam, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Landolaxin *Faran, Gr.†.*
Lisinopril (p.1325·2).
Hypertension.

Landrolen *Landsteiner, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Landstav *Landsteiner, Mex.*
Stavudine (p.907·1).
HIV infection.

Lanex *Lavipharm, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanexat *Roche, Arg.†; Roche, Braz.; Roche, Chile; Roche, Denm.; Roche, Fin.; Roche, Mex.; Roche, Swed.; Roche, Venez.*
Flumazenil (p.1445·2).
Benzodiazepine overdose; reversal of benzodiazepine-induced sedation.

Lanfast *Julphar, UAE.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanfix *Landson, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Lanfluzol *Landsteiner, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Langerin *Zentiva, Cz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Langoran *Sanofi-Aventis, Fr.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Laniazid *Lannett, USA.*
Isoniazid (p.288·1).
Tuberculosis.

Lanicor *Roche, Arg.; Roche, Austria; Teofarma, Ger.; Vargas, Venez.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Lanirapid *Chugai, Jpn; Kern, Spain.*
Metildigoxin (p.1336·2).
Arrhythmias; heart failure.

Lanitop *Roche, Austria; Roche, Belg.; Sinterapico, Braz.†; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Ital.; Roche, Port.; Roche, Switz.†; Vargas, Venez.*
Metildigoxin (p.1336·2).
Arrhythmias; heart failure.

Lannapril *Lannacher, Austria.*
Ramipril (p.1385·3).
Hypertension.

Lannapril plus *Lannacher, Austria.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Lannatam *Lannacher, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Lanoc *Lannacher, Austria.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Lanocardique *Faran, Gr.†.*
Nitrendipine (p.1358·2).
Hypertension.

Lanoclav *Lannacher, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Lanodil *Landson, Indon.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Lanodizol *Diba, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanogastro *Teuto, Braz.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Lanol *Nakornpatana, Thai.*
Calamine (p.1591·2); zinc oxide (p.1621·2); phenol (p.1656·1); camphor (p.2273·2); menthol (p.2340·1).
Skin disorders.

Lanolept *Lannacher, Austria.*
Clozapine (p.981·1).
Schizophrenia.

Lanolor *Squibb, USA.*
Emollient and moisturiser.

Lanol-Zinc *Valmor, Venez.*
Zinc oxide (p.1621·2).
Skin disorders.

Lanomycin *Pharmathen, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Lanoxicaps *Cardinal Health, USA†.*
Digoxin (p.1259·3).
Atrial fibrillation; heart failure.

Lanoxin *Roemmers, Arg.; Sigma, Austral.; GSK, Belg.; GSK, Braz.†; Virco, Canad.; Sigma, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; Wellcome, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Thai.; GSK, UK; Glaxo Wellcome, USA.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Lanpirome *Landson, Indon.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Lansacid *Keri, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansazol *Ilsan, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansek A *Investi, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lansenol *Landsteiner, Mex.*
Difenidol hydrochloride (p.1723·2).
Nausea and vomiting; vertigo.

Lansiclav *Landson, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Lansinoh *Key, Austral.†; Hollister, Canad.†; Ameda, Port.*
Wool fat (p.2033·2).
Nipple care.

Lanso *Farmanic, Gr.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Lansobene *Ratiopharm, Austria.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansodom *Medley, Braz.*
Lansoprazole (p.1739·2); domperidone (p.1726·2).
Dyspepsia; gastro-oesophageal reflux.

Lansogen *Generics, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

LansoLek *Lek, Pol.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoloc *Cipla, S.Afr.*
Lansoprazole (p.1739·2).
Gastric hyperacidity; heartburn.

Lansone *Gedeon Richter, Cz.†; Gedeon Richter, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Lansoprid *Medley, Braz.*
Lansoprazole (p.1739·2); bromopride (p.1713·3).
Dyspepsia; gastro-oesophageal reflux.

Lansoprol *Genericon, Cz.; Nobel, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoptol *KRKA, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansor *Sanovel, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansovax *Vivax, Venez.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansox *Takeda, Ital.; Fariberica, Port.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lansoyl *Ivax, Arg.; Pfizer Consumer, Belg.; Aurium, Canad.; Pfizer Sante, Fr.; Parke, Davis, Switz.*
Liquid paraffin (p.2030·3).
Constipation.

Lantacid *Christo, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Lantanon *Organon, Ital.; Donmed, S.Afr.; Organon, Spain.*
Mianserin hydrochloride (p.408·1).
Depression.

Lantarel *Wyeth, Ger.*
Methotrexate sodium (p.745·2).
Juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis.

Lanterbine *Ethypharm, Hong Kong.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Lantiflam *Landson, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Lantigen B *Bruschettini, Ital.; Seber, Port.*
Antigen extracts of: *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Moraxella catarrhalis*; *Staphylococcus aureus*; *Klebsiella pneumoniae*; *Haemophilus influenzae* type b.
Respiratory-tract disorders; upper respiratory-tract infections.

Lantipain *Landson, Indon.*
Ketorolac trometamol (p.74·2).
Postoperative pain.

Lanton *Rafa, Israel.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lantulos *Landson, Indon.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lanturol *Landson, Indon.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Lantus *Aventis, Arg.; Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Aventis, USA; Sanofi-Aventis, Venez.*
⊗ Insulin glargine (p.449·3).
Diabetes mellitus.

Lanuretic *Lannacher, Austria.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Lanvis *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Fr.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Pol.; GSK, S.Afr.; GSK, Singapore†; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK.*
Tioguanine (p.779·1).
Leukaemias; polycythaemia vera.

Lanx *Elea, Arg.*
⊗ Spironolactone (p.1400·1).
Cirrhosis; heart failure; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Lanz *Sigma, Braz.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Lanzacor *Neo Quimica, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Lanzap *Reddy, Rus.; Biofarma, Venez.†.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzedin *Biofarma, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanziop *Ivax, Irl.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzo *Wyeth, Denm.; Wyeth, Fin.; Wyeth, Norw.; Wyeth, Swed.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzogastro *BioSaude, Port.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Lanzohex *Hexal, Philipp.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lanzol *Ache, Braz.; Cipla, India; Rowex, Irl.; Belmac, Spain; Dollder, Venez.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzopept *Geolab, Braz.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzopral *Roemmers, Arg.; Pharma Investi, Chile; Roemmers, Venez.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzor *Sanofi-Aventis, Fr.; Aventis, Ger.; Aventis, S.Afr.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Lanzostad *Steigerwald, Pol.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lanzox *Kalbe, Indon.*
Botulinum A toxin (p.1890·1).
Blepharospasm; hemifacial spasm; strabismus.

Lanzul *KRKA, Cz.; KRKA, Pol.*
Lansoprazole (p.1739·2).
Gastric hypersecretion; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Lapase *Cypress, USA.*
Pancreatin (p.2360·1).
Digestive enzyme deficiency.

Lapenax *Novartis, Arg.*
Clozapine (p.981·1).
Schizophrenia.

Lapibal *Lapi, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy; tinnitus; vertigo; vitamin B deficiency.

Lapibion *Lapi, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Asthenia; morning sickness; neuralgia; neuritis; neuropathy.

Lapibroz *Lapi, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lapicef *Lapi, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Lapices Epiderm Metadier *Prats, Spain.*
Dithranol (p.1595·2); salicylic acid (p.1612·2).
Skin disorders.

Lapidar 4 *Kunzle, Switz.*
Rutoside (p.2305·1); aescin (p.2248·2).
Haemorrhoids; venous insufficiency.

Lapidar 10 *Kunzle, Switz.*
Frangula bark (p.1732·2); senna (p.1769·2); liquorice (p.1740·3).
Constipation.

Lapifed *Lapi, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic disorders; cold symptoms; sinusitis.

Lapifed DM *Lapi, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough; nasal congestion; rhinitis.

Lapifed Expectorant *Lapi, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Cold symptoms; cough.

Lapiflox *Lapi, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Lapikot *Lapi, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Lapimox *Lapi, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Lapimuc *Lapi, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Lapis *SAD, Denm.*
Silver nitrate (p.2387·2).
Wound infections.

Lapisiv
Note. This name is used for preparations of different composition.
Lapi, Indon.
Syrup: Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); ammonium chloride (p.1551·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cold symptoms; cough.

Lapi, Indon.
Tablets: Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2).
Cold symptoms; cough.

Lapistan *Lapi, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Lapixime *Lapi, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Lapiz Gras *Quimifar, Spain†.*
Theobroma oil (p.2033·1).
Dietary supplement.

Lapol *Sofex, Port.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lapraz *Sanbe, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Laprazol *Vianex (Βιανέξ), Gr.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lapril *Jean-Marie, Hong Kong; Pharmasant, Thai.; Rowe-Fleming, Venez.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Laprilen *Baldacci, Port.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Laprost *Oftalmi, Venez.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Laproton *Tempo Scan Pacific, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lapsus *Klonal, Arg.*
Fluoxetine (p.397·3).
Depression.

Lara
Note. This name is used for preparations of different composition.
Alkem, India.
Losartan potassium (p.1326·1).
Hypertension.

Ipca, India†.
Leflunomide (p.75·3).
Rheumatoid arthritis.

Laracit *Laboratorios Chile, Chile; Lemery, Mex.*
Cytarabine (p.705·1).
Leukaemias; lymphomas.

Laractyl *Patriot, Philipp.*
Chlorpromazine hydrochloride (p.969·2).
Anxiety; hiccup; nausea and vomiting; psychoses.

Larafen *Sandoz, UK.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders; pain.

Laragon *Roemmers, Arg.*
Silymarin (p.1452·2).
Liver disorders.

Larapam *Sandoz, UK.*
Tramadol (p.132·1).
Pain.

Larch Resin comp. *Weleda, UK.*
Ananassa fruit; lavender oil (p.2331·2); larch resin.
Sore eyes.

Larcooral *Columbia, Arg.*
Staphylococcus; Micrococcus; Pneumococcus; Streptococcus; Klebsiella; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Laremid *Polfa Warszawa, Pol.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Largactil
Aventis, Austral.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong†; Aventis, Irl.†; Teofarma, Ital.; Aventis, Norw.; Vitoria, Port.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Eczacibasi, Turk.
Chlorpromazine hydrochloride (p.969·2).
Agitation; alcohol or opioid withdrawal syndrome; anxiety; behaviour disorders; bipolar disorder; controlled hypotension; depression; eclampsia; hiccup; induction of hypothermia; nausea and vomiting; neuroses; pain; pre-eclampsia; premedication; psychoses; schizophrenia; sedative; sleep disorders.

Aventis, Mex.; Aventis, Venez.†.
Chlorpromazine (p.969·1).
Alcohol withdrawal syndrome; behaviour disorders; eclampsia; hiccups; nausea and vomiting; premedication; psychoses.

Aventis, Neth.
Chlorpromazine (p.969·1) or chlorpromazine hydrochloride (p.969·2).
Agitation; hiccup; nausea and vomiting; pain; psychoses.

Sanofi-Aventis, NZ; Hawgreen, UK.
Chlorpromazine embonate (p.969·2) or chlorpromazine hydrochloride (p.969·2).
Agitation; anxiety; autism; hiccups; induction of hypothermia; nausea and vomiting; psychoses.

Largatrex
Note. This name is used for preparations of different composition.
Vitoria, Port.
Chlorpromazine hydrochloride (p.969·2).

Sanofi-Aventis, Spain†.
⊗ Chlorpromazine (p.969·1); heptaminol (p.2319·1); trihexyphenidyl (p.820·3).
Aggression; anxiety; psychoses.

Largo *Beacons, Singapore.*
Chlorpromazine hydrochloride (p.969·2).
Nausea and vomiting; premedication; psychoses; sedative.

Largopen *Bilim, Turk.*
Amoxicillin (p.202·2) or amoxicillin sodium (p.202·2).
Bacterial infections.

Lariago *Ipca, India.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Lariam *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, S.Afr.; Roche, Singapore; Roche, Swed.; Roche, Switz.; Roche, UK; Roche, USA.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Laricid *Biofarma, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Laridox *Ipca, India.*
Sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Larifikehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Larig *Rowex, Irl.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Larimal *Ipca, India†.*
Amodiaquine (p.597·2); artesunate (p.598·2).
Malaria.

Larimef *Ipca, India.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Larinate *Ipca, India.*
Artesunate (p.598·2).
Malaria.

Laringex *Cazi, Braz.*
Cetylpyridinium chloride (p.1635·1).
Formerly contained tyrothricin, cetrimonium bromide, and lidocaine.
Mouth and throat disorders.

Larintil *Brasmedica, Braz.†.*
Tyrothricin (p.358·2); neomycin sulfate (p.305·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Larither *Ipca, India.*
Artemether (p.598·1).
Malaria.

Larithro *Verisfield, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Laritol *Maver, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Laritol D *Maver, Mex.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).

Laritol Ex *Maver, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Laritol G *Maver, Mex.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); loratadine (p.583·3).

Larixin *Taisho, Jpn.*
Cefalexin (p.218·2).
Bacterial infections.

Larizin *Hizon, Philipp.; Pharmatrix, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Larjancaina *Veinfar, Arg.*
⊗ Lidocaine (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Larjanfilina *Veinfar, Arg.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Larmabak *Sidus, Arg.; Pfizer, Chile; Thea, Fr.; Pharmex (Φαρμεξ), Gr.†; Thea, Hong Kong; Thea, Philipp.; Pfizer, Singapore; Pfizer, Venez.*
Sodium chloride (p.1686·1).
Dry eyes; eye wash.

Larmadex *Schering, Arg.*
⊗ Goserelin acetate (p.2108·2).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids.

Larmax *Andromaco, Chile†.*
Loratadine (p.583·3).
Allergic skin disorders; rhinitis.

Larmax D *Andromaco, Chile.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Larmecran *Thea, Fr.*
Povidone (p.2146·1) (p.1622·2).
Contact lens lubricant; dry eyes.

Larmes Artificielles *Tonipharm, Fr.†.*
Sodium chloride (p.1686·1).
Dry eyes.

Larodopa *Roche, USA†.*
Levodopa (p.804·3).
Parkinsonism.

Laromin *Kleva, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Laroscorbine *Bayer, Fr.*
Ascorbic acid (p.1983·3).
Asthenia; vitamin C deficiency.

Larotabe *Bayer Consumer, Arg.; Bayer, Chile.*
Betacarotene; vitamin C; vitamin E; minerals (p.1922·1).
Antoxidant preparation.

Laroxyl *Roche, Fr.; Roche, Ital.; Roche, Turk.*
Amitriptyline hydrochloride (p.376·1).
Depression; headache; migraine; nocturnal enuresis; pain.

Larpose *Cipla, India.*
Lorazepam (p.1004·1).
Anxiety; insomnia; premedication.

Larry *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Ketoconazole (p.539·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Lars *Duncan, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Larsen *Hexa, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Larsimal *Poen, Arg.*
⊗ Fluorometholone (p.1532·3); tetryzoline (p.1574·1).
Inflammatory eye disorders.

LarvE *SMTL, UK.*
Sterile larvae of *Lucilia sericata* (p.1604·1).
Infected or necrotic wounds.

Larvitan *Cimed, Braz.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Larydol *Dolisos, Canad.*
Homoeopathic preparation.

Larylin *Andromaco, Chile†.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Larylin Husten-Loser Pastillen *Cheplapharm, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscid or excessive mucus.

Larylin Husten-Loser Saft *Merck, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscid or excessive mucus.

Larylin Husten-Stiller *Cheplapharm, Ger.*
Dropropizine (p.1557·3).
Coughs.

Laryngarsol *Sanofi-Aventis, Belg.*
Lozenges: Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Laryng-O-Jet *Celltech, UK.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Laryngomedin N *Artegodan, Ger.*
Hexamidine isetionate (p.1646·3).
Mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Laryngsan *Opfermann, Ger.*
Camphor (p.2273·2); peppermint oil (p.1761·2).
Cold and influenza symptoms; laryngitis; pharyngitis.

Lary-Phary *Dr P, Ger.*
Carmellose (p.2142·1); sodium chloride; magnesium chloride (p.1667·1).
Dry mouth; mouth and throat lubricant.

Larypront *Mack, Cz.†.*
Muramidase hydrochloride (p.2348·1); dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Lasa *Grunenthal, Port.*
Famotidine (p.1730·1).
Gastric hyperacidity.

Lasa Con Codeina *Ipsen, Spain.*
Chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Lasain *Inibsa, Spain.*
Metamizole magnesium (p.49·3).
Fever; pain.

Lasal *Lapi, Indon.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Lasal Expectorant *Lapi, Indon.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Lasalar-Y *Alpharma, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Lasalar-Y Simple *Alpharma, Mex.*
Clioquinol (p.254·1).
Skin infections.

Lasapride *ITF, Gr.†.*
Cisapride (p.1720·3).
Gastric motility disorders.

Lasazin *Leovan, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Laser *Princeps, Ital.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; neuralgia.

Laservis *Chemedica, Ger.; Chemedica, Malaysia†; Chemedica, Switz.*
Sodium hyaluronate (p.2320·1).
Adjunct in ocular procedures.

Lasgan *Lapi, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lasikal *Borg, UK.*
⊗ Furosemide (p.1292·1); potassium chloride (p.1684·3).
Oedema.

Lasilacton *Aventis, Arg.; Aventis, Austria; Aventis, Mex.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Lasilactona *Sanofi-Aventis, Braz.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Hypertension; oedema.

Lasilactone *Aventis, India; Aventis, Switz.; Borg, UK.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Ascites; hypertension; oedema.

Lasiletten *Aventis, Neth.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Lasilix *Sanofi-Aventis, Fr.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Lasiride *Aventis, Arg.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Lasitace *Aventis, Austria.*
⊗ Furosemide (p.1292·1); ramipril (p.1385·3).
Heart failure.

Lasitone *Sanofi-Aventis, Ital.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Oedema.

Lasiven *Umeda, Thai.*
⊗ Furosemide (p.1292·1).
Forced diuresis; heart failure; oedema; renal failure.

Lasix
Aventis, Arg.; Aventis, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Aventis, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel†; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Swed.; Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Aventis, USA; Sanofi-Aventis, Venez.
⊗ Furosemide (p.1292·1).
Barbiturate poisoning; cirrhosis with ascites; forced diuresis; heart failure; hypertension; nephrotic syndrome; oedema; oliguria; renal insufficiency.

Aventis, Austria; Aventis, Chile†; Aventis, Ger.; Sanofi-Aventis, Ital.; Aventis, Neth.; Aventis, Switz.
⊗ Furosemide (p.1292·1) or furosemide sodium (p.1294·1).
Forced diuresis; heart failure; hypertension; nephrotic syndrome; oedema; oliguria; renal failure.

Lasmalin *Lapi, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Lasoberon *Boehringer Ingelheim, Venez.*
Sodium picosulfate (p.1771·1).
Constipation.

Lasolvan *Boehringer Ingelheim, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Lasonil
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Ital.†; Bayer, NZ; Bayer, Neth.; Bayer, Port.; Bayer, Turk.; Bayer Consumer, UK†.
A heparinoid (p.1305·2).
Formerly contained a heparinoid and hyaluronidase.
Bruising; ecchymoses; haematoma; soft-tissue injury; sports injuries; sprains; thrombophlebitis; varicose ulcers; venous disorders.

Bayer, Spain†.
A heparinoid (p.1305·2); hyaluronidase (p.2321·1).
Soft-tissue disorders; thrombophlebitis; varicose veins.

Lasonil CM *Bayer, Ital.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue pain and inflammation.

Lasonil N *Bayer, Ger.†; Bayer, Gr.*
A heparinoid (p.1305·2).
Soft-tissue injury; superficial venous disorders.

Lasoride *Aventis, Irl.†; Sanofi-Aventis, UK†.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
These ingredients can be described by the British Approved Name Co-amilofruse.
Oedema.

Lasoven *Bayer, Ital.†.*
A heparinoid (p.1305·2).
Venous insufficiency.

L-Asp *Pharmacia, Arg.†.*
Asparaginase (p.682·1).
Acute leukaemias.

Laspal *Sanofi-Aventis, Pol.*
Lysine aspirin (p.79·1).
Fever; pain.

Laspar *Bodene, S.Afr.*
Asparaginase (p.682·1).
Lymphoblastic leukaemias.

LAsprin *Cipla, Hong Kong.*
Aspirin (p.20·3).
Thromboembolic disorders.

Lassadermil *Edol, Port.*
Zinc oxide (p.1621·2).
Minor burns and wounds; skin disorders.

Lassatina *Kedrion, Ital.†.*
Senna (p.1769·2); cascara (p.1715·2); rhubarb (p.1768·3); liquorice (p.1740·3); belladonna (p.2263·3); nux vomica (p.2355·3); aniseed (p.2258·2).
Constipation.

Lassativi Vegetali *AFOM, Ital.; Ogna, Ital.*
Aloes (p.1705·2); rhubarb (p.1768·3).
Constipation.

Lassen *Farmanic, Gr.*
Risperidone (p.1024·2).
Psychoses.

Lassifar *Lafare, Ital.†.*
Lactulose (p.1738·2).
Disturbance of gastrointestinal bacterial flora; hyperammonaemia.

Lastet *Pfizer, Chile†; Kayaku, Cz.; Kayaku, Hung.; Khandelwal, India†; Pharmacia, Ital.; Kayaku, Jpn; Kayaku, Malaysia; Sanfer, Mex.†; Kayaku, Philipp.; Euro Nippon Kayaku, Pol.; Probios, Port.; Kayaku, Singapore; Prasfarma, Spain; Kayaku, Thai.; Onko, Turk.*
Etoposide (p.718·1).
Malignant neoplasms.

Lasticom *Viatris, Austria; Asta Medica, Ital.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; asthma; bronchitis.

Lastin *Santen, Fin.; Viatris, Norw.; Santen, Swed.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Lastrim *Chew, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Lastuss *FDC, India.*
Dextromethorphan (p.1555·2) or dextromethorphan hydrobromide (p.1555·2).
Cough.

LAtac *Cipla, Hong Kong.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Latanoflax *Sidus, Arg.*
Latanoprost (p.1882·1).
Glaucoma.

Latanopress *Roemmers Poen, Venez.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Latensin *Sanum-Kehlbeck, Ger.*
Bacillus cereus.
Immunotherapy.

Latesil *CS, Port.*
Flufenamic acid (p.60·3); myrtecaine (p.1867·2); diethylamine salicylate (p.47·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Latesyl *Roth, Austria.*
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Laticort *Jelfa, Cz.†; Hermal, Ger.; Medphano, Ger.; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
⊗ Hydrocortisone butyrate (p.1535·3).
Skin disorders.

Laticort-CH *Jelfa, Pol.*
⊗ Hydrocortisone butyrate (p.1535·3); chlorquinaldol (p.242·3).
Infected skin disorders.

Latisona B *Biotenk, Arg.*
⊗ Meprednisone (p.1538·1) or meprednisone hemisuccinate (p.1538·1).
Corticosteroid.

LAtiwen *Cipla, Hong Kong.*
Lorazepam (p.1004·1).
Anxiety; insomnia; premedication.

Latlas *Atlas, Arg.*
Carbomer 974P (p.2141·3); polyvinyl alcohol (p.2145·3); lysine (p.1955·1).
Dry eyes.

Latof *Saval, Chile.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Latof-T *Saval, Chile.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Latonid *Anasco, Fin.; Abbott, Swed.†.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders; osteoarthritis.

Latonina *Faran, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Latoren *Anfarm, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Latotryd *Atlantis, Mex.*
Erythromycin (p.269·2) or erythromycin stearate (p.270·1).
Bacterial infections.

Latrigil *Stada, Cz.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Latrigin *Baliarda, Arg.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Latrimet *Lamda (Λαμδα), Gr.†.*
Trimetazidine (p.1419·2).
Angina pectoris.

Latropil *Lapi, Indon.*
Piracetam (p.368·2).
Alcoholism; behaviour disorders in children; cerebral trauma; mental function impairment.

Latsol *Antibioticos, Mex.*
Latanoprost (p.1882·1).
Glaucoma.

Lattubio *Bioprogress, Ital.†.*
Lactulose (p.1738·2).
Constipation.

Lattulac *Sofar, Ital.*
Lactulose (p.1738·2).
Cirrhosis; constipation; hepatic encephalopathy.

Latusin *Sano, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); codeine (p.37·2).
Respiratory-tract congestion.

Latycin *Boucher & Muir, Austral.; Sandoz, Austria.*
Tetracycline hydrochloride (p.347·2).
Bacterial eye infections.

Latycyn *Biochemie, Malaysia†.*
Tetracycline hydrochloride (p.347·2).
Bacterial eye infections.

Latys *Leovan, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Laubeel *Desitin, Ger.*
Lorazepam (p.1004·1).
Anxiety disorders.

Laudamonium *Ecolab, Ger.*
Benzalkonium chloride (p.1629·1).
Skin and surface disinfection.

Laudil *Recalcine, Chile†.*
Pinaverium bromide (p.2368·1).

Launol *Laboratorios Chile, Chile.*
Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis; scabies.

Laur *Sons, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Laura *Ranbaxy, S.Afr.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lauracalm *Socobom, Belg.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Laurak *Vita, Spain.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Lauricin *Sons, Mex.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Laurimic *Effik, Spain.*
Fenticonazole nitrate (p.531·3).
Fungal skin and nail infections; vulvovaginal candidiasis.

Laurimicina
Mavi, Mex.
Erythromycin (p.269·2).
Bacterial infections.

Organifar, Venez.†.
Erythromycin estolate (p.269·3).
Bacterial infections.

Laurina *Organon, Austria; Organon, Cz.; Organon (Οργανον), Gr.; Organon, Port.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Laurinol Plus *Szama, Arg.*
Undecenoic acid diethanolamide (p.549·3); cade oil (p.1616·1); vitamin B .
Psoriasis; scalp disorders.

Lauritran *Chinoin, Mex.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Lauroderme *Baldacci, Port.*
Salicylic acid (p.1612·2); zinc oxide (p.1621·2).
Skin inflammation and irritation.

Lauroderme Po *Baldacci, Port.*
Salicylic acid (p.1612·2); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Skin disorders.

Lauromentol *Angelini, Port.†.*
Menthol (p.2340·1); methyl salicylate (p.85·3); salicylic acid (p.1612·2); laurel oil; turpentine oil (p.2406·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lauromicina
Note. This name is used for preparations of different composition.
Lafare, Ital.
Ointment: ⊗ Fluocinolone acetonide (p.1531·3); erythromycin stearate (p.270·1).
Infected skin disorders.

Lafare, Ital.
Tablets: Laurilsulfate salt of erythromycin stearate (p.270·1).
Bacterial infections.

Lav Ofteno *Sophia, Mex.*
Boric acid (p.2268·1); borax (p.2268·1).
Eye disorders.

Lavagin *Mayrhofer, Austria.*
Lactic acid (p.2329·3); sodium lactate (p.1673·3).
Vaginal disorders.

Lavanda Sofar *Sofar, Ital.*
Anhydrous citric acid (p.2284·1); sodium citrate (p.1673·3); alum (p.2254·1); phenol (p.1656·1).
Vaginal disinfection.

Lavandula Oligoplex *Madaus, Arg.*
Lavender (p.2331·1); calendula (p.2273·1); hamamelis (p.2318·2).

Lavasept
Note. This name is used for preparations of different composition.
Farmo Quimica, Chile.
Triclosan (p.1665·2).
Hand disinfection; skin infections.

Fresenius Kabi, Rus.; Fresenius Kabi, Switz.
Polihexanide (p.1658·2).
Bone and soft-tissue infections; burns; skin and instrument disinfection; skin infections; wounds.

Lavement au Phosphate *Norgine, Belg.†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Laver *Neopharm, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Laveran
Note. This name is used for preparations of different composition.
Brasmedica, Braz.†.
Cimetidine (p.1716·2).
Gastro-intestinal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Unicure, India.
Proguanil hydrochloride (p.609·2).
Malaria.

Laverio *Elpen (Ελπεν), Gr.*
Itraconazole (p.536·3).
Fungal infections.

Lavestra *KRKA, Hung.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Lavichthol *Ichthyol, Austria.*
Ictasol (p.1599·1).
Skin disorders.

Laviest *Franco-Indian, India.*
Saccharomyces cerevisiae (p.1998·3).
Moniliasis after antibiotic therapy; vitamin B deficiency.

Lavisa *Gynea, Spain.*
Fluconazole (p.532·1).
Fungal infections.

Lavolen *Lacer, Spain.*
Trisodium polysaccharide sulfate; a nonoxinol (p.1917·1).
Contraceptive.

Lavolho *Regius, Braz.†.*
Boric acid (p.2268·1); chlorobutanol (p.1639·2).
Eye disorders.

Lavomax *Nizpharm, Rus.*
Tilorone.
Viral infections.

Lavoptik *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Lawarin *Pliva, Cz.*
Warfarin sodium clathrate (p.1425·3).
Thromboembolic disorders.

Lawefluor N *Dental-Kosmetik, Ger.†.*
Olaflur (p.1959·2); dectaflur (p.1937·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth.

Lawenol *Prolab, Pol.*
Lavender oil (p.2331·2).
Musculoskeletal and joint pain; neuralgia; skin disinfection.

Lax Ewe Jalea *Sanitas, Arg.*
Liquid paraffin (p.2030·3).
Bowel evacuation.

Lax Pills *G & W, USA.*
Sennosides (p.1769·3).
Constipation.

Laxabene *Alter, Spain.*
Ispaghula (p.1737·1).
Constipation; diarrhoea.

Laxabon *AstraZeneca, Norw.; AstraZeneca, Swed.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Laxacaps *Gelcaps, Mex.*
Senna (p.1769·2); prune (p.1765·1).
Bowel evacuation; constipation.

Laxaco *Jamieson, Canad.*
Cascara (p.1715·2); senna (p.1769·2).
Constipation.

Laxacod *Galenium, Indon.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Laxadilac *Galenium, Indon.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laxadin *Teva, Israel.*
Bisacodyl (p.1710·1).
Constipation.

Laxadine *Galenium, Indon.*
Phenolphthalein (p.1762·1); liquid paraffin (p.2030·3); glycerol (p.2314·2).
Bowel evacuation; constipation.

Laxador *SA Druggists Self Med, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Laxadoron *Weleda, UK.*
Homoeopathic preparation.

Laxagetten *CT, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Laxal *Julphar, UAE.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Laxalpin *Kwizda, Austria.*
Senna (p.1769·2); frangula bark (p.1732·2); fennel (p.2302·3); chamomile (p.2279·3); guaiacum wood; liquorice (p.1740·3); sambucus (p.2383·1); adiantum capillus veneris; potassium sodium tartrate (p.1764·1).
Constipation.

Laxamalt *Bouchara-Recordati, Fr.†; Bouchara, Switz.*
Liquid paraffin (p.2030·3).
Constipation.

Laxamex *Konimex, Indon.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Laxamin
Note. This name is used for preparations of different composition.
Temis, Arg.
Oral drops: Sodium picosulfate (p.1771·1).
Constipation.

Temis, Arg.
Tablets: Bisacodyl (p.1710·1).
Constipation.

Laxamix *Agropharm, Pol.*
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation.

Laxamucil *Orion, Fin.*
Ispaghula (p.1737·1).
Constipation.

Laxan *Chew, Thai.*
Methocarbamol (p.1897·3).
Musculoskeletal pain.

Laxanin N *Schwarzhaupt, Ger.†.*
Bisacodyl (p.1710·1).
Constipation.

Laxans *Schulke & Mayr, Austria.*
Ispaghula (p.1737·1).
Constipation.

Laxans-ratiopharm *Ratiopharm, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Laxans-ratiopharm Pico *Ratiopharm, Ger.*
Sodium picosulfate (p.1771·1).
Constipation.

Laxante Arceli *Gezzi, Arg.*
Liquid paraffin (p.2030·3).

Laxante Bescansa Aloico *Bescansa, Spain.*
Aloin (p.1705·3); belladonna (p.2263·3); phenolphthalein (p.1762·1); rhubarb (p.1768·3).
Constipation.

Laxante Bescansa Normal *Bescansa, Spain.*
Senna (p.1769·2).
Constipation.

Laxante Olan *Puerto Galiano, Spain.*
Senna (p.1769·2).
Constipation.

Laxante Salud *Boots Healthcare, Spain.*
Senna (p.1769·2).
Constipation.

Laxante Sanatorium *Santiveri, Spain.*
Aloes (p.1705·2); aniseed (p.2258·2); sulfur (p.1614·1); senna (p.1769·2); chamomile (p.2279·3).
Constipation.

Laxantil *Chemopharma, Chile.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Laxantol *Herbapol Krakow, Pol.*
Couch-grass (p.2288·2); caraway (p.2276·3); frangula (p.1732·2); linseed (p.2333·3); rhubarb (p.1768·3).
Constipation; meteorism.

Laxarec *Galenium, Indon.*
Sodium laurilsulfate (p.2138·3); macrogol 400 (p.2336·3); sodium citrate (p.1673·3); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Laxarine
Note. This name is used for preparations of different composition.
Farmion, Braz.†.
Senna (p.1769·2); cassia pulp (p.1715·3); tamarind (p.1775·3); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Fuca, Fr.
Prune (p.1765·1); tamarind (p.1775·3).
Constipation.

Laxarol *ICM, Singapore.*
Liquid paraffin (p.2030·3).
Constipation.

Laxaron
Note. This name is used for preparations of different composition.
Merck Medication Familiale, Fr.
Lactulose (p.1738·2).
Constipation.

Strand, Malaysia†.
Liquid paraffin (p.2030·3).
Constipation.

Laxasan
Note. This name is used for preparations of different composition.
Gebro, Austria.
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Gebro, Switz.
Sodium picosulfate (p.1771·1); fennel oil (p.2303·1); peppermint oil (p.1761·2).
Constipation.

Laxasium *Fahrenheit, Indon.*
Magnesium hydroxide (p.1743·2).
Constipation; indigestion.

Laxat *Medinfar, Port.*
Ispaghula (p.1737·1).
Constipation; hypercholesterolaemia; irritable bowel syndrome; ostomy regulation.

Laxative
Note. This name is used for preparations of different composition.
Lalco, Canad.†.
Aloes (p.1705·2); cascara (p.1715·2); bile salts (p.2266·2).
Constipation.

Trima, Israel.
Aloin (p.1705·3); phenolphthalein (p.1762·1); belladonna (p.2263·3).
Constipation.

Laxative Comp *Teva, Israel.*
Aloin (p.1705·3); phenolphthalein (p.1762·1); aloes (p.1705·2); ipecacuanha (p.1562·3); belladonna (p.2263·3).
Constipation.

Laxative Pills *Tanta, Canad.*
Sennosides (p.1769·3).

Laxative & Stool Softener *Rugby, USA.*
Docusate sodium (p.1725·1); casanthranol (p.1715·1).
Constipation.

Laxative Tablets *Herbal Concepts, UK.*
Aloes (p.1705·2); cascara (p.1715·2); senna (p.1769·2); valerian (p.2410·1).
Constipation.

Laxatol *Omega, Gr.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Laxavit *Kela, Belg.*
Docusate sodium (p.1725·1); glycerol (p.2314·2).
Constipation.

Laxbene
Note. This name is used for preparations of different composition.
Merckle, Ger.†.
Bisacodyl (p.1710·1).
Constipation.

Ratiopharm, Hung.
Bisacodyl (p.1710·1); simeticone (p.1770·2).
Constipation.

Ratiopharm, Austria.
Suppositories: Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Ratiopharm, Austria.
Tablets: Bisacodyl (p.1710·1); dimeticone (p.1770·2).
Bowel evacuation; constipation.

Laxcodyl *Tanta, Canad.†; Pharmasant, Thai.*
Bisacodyl (p.1710·1).
Constipation.

Laxeersiroop *SAN, Neth.*
Lactulose (p.1738·2).
Constipation.

Laxene *Pharmador, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Laxette *Medpro, S.Afr.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laxettes
Note. This name is used for preparations of different composition.
Mentholatum, Austral.
Chocolate: Sennosides (p.1769·3).
Formerly contained phenolphthalein.
Constipation.

Mentholatum, Austral.
Tablets: Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Constipation.

Laxicaps P *Propan, S.Afr.†.*
Phenolphthalein (p.1762·1).
Constipation.

Laxicon *Stadmed, India.*
Docusate sodium (p.1725·1).
Constipation.

Laxicona *Baliarda, Arg.*
Bisacodyl (p.1710·1); simeticone (p.1770·2).
Constipation; flatulence.

Laxido *Galen, UK.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Constipation.

Laxifos *Itaca, Braz.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Laxikal Forte *Teva, Israel.*
Senna (p.1769·2).
Constipation.

Laxilose *Technilab, Canad.†.*
Lactulose (p.1738·2).
Constipation.

Laxinat *Alkem, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Laxiplant Soft *Schwabe, Ger.†; Schwabe, Switz.*
Ispaghula (p.1737·1).
Constipation; diarrhoea.

Laxiruela *Garden House, Arg.*
Senna (p.1769·2).
Constipation.

Laxiruela Ciruela Fibra *Garden House, Arg.*
Senna (p.1769·2).
Constipation.

Laxisoft *Schwabe, Spain†.*
Ispaghula (p.1737·1).
Constipation; diarrhoea.

Laxitab
Note. This name is used for preparations of different composition.
Biofarm, Pol.
Rhubarb (p.1768·3).
Constipation.

Ranbaxy, Thai.
Bisacodyl (p.1710·1).
Constipation.

Laxoberal *Boehringer Ingelheim, Chile; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim Self Medication, UK.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Laxoberal Bisa *Boehringer Ingelheim, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Laxoberon *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Indon.; Teijin, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Switz.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Laxocodyl *Julphar, UAE.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Laxodal *Baldacci, Port.*
Sodium picosulfate (p.1771·1).
Constipation.

Laxofalk *Falk, Ger.*
Macrogol 4000 (p.2336·3).
Constipation.

Laxogeno *Grunenthal, Chile.*
Oral solution, magnesium citrate (p.1743·2); oral powder, sodium bicarbonate (p.1673·2); tablets, bisacodyl (p.1710·1); suppositories, bisacodyl.
Bowel evacuation.

Laxol
Note. This name is used for preparations of different composition.
Daudt, Braz.
Castor oil (p.2278·1).
Constipation.

Herbapol Wroclaw, Pol.
Docusate sodium (p.1725·1).
Constipation.

Laxolen *Basi, Port.†.*
Cascara (p.1715·2).
Constipation.

Laxolind *Metochem, Austria.*
Senna (p.1769·2); frangula (p.1732·2); chamomile (p.2279·3).
Bowel regulation.

Laxolyne *Julphar, UAE.*
Glycerol (p.2314·2).
Constipation.

Laxomax *Soria Natural, Spain†.*
Senna (p.1769·2); peppermint leaf (p.1761·2); liquorice (p.1740·3); aniseed (p.2258·2).
Constipation.

Laxonarol *Farmo Quimica, Chile.*
Liquid paraffin (p.2030·3).
Constipation.

Laxopol
Note. This name is used for preparations of different composition.
Pohl, Ger.; Pohl, Israel.
Castor oil (p.2278·1).
Constipation.

Unia, Pol.
Docusate sodium (p.1725·1).
Constipation.

Laxose *Pinewood, Irl.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Laxovar *Infinity, Venez.*
Sennosides A and B (p.1769·3).
Constipation.

Laxsol *Sigma, NZ.*
Docusate sodium (p.1725·1); sennosides (p.1769·3).
Constipation.

Laxsotrin *Catarinense, Braz.*
Cascara (p.1715·2).
Constipation.

Laxtam *Merck, Braz.*
Senna (p.1769·2); cassia pulp (p.1715·3); tamarind (p.1775·3); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Laxuave Enteral *Elea, Arg.*
Liquid paraffin (p.2030·3).
Constipation.

Laxuave Jalea *Elea, Arg.*
Liquid paraffin (p.2030·3).
Constipation.

Laxuave Sen *Elea, Arg.*
Senna (p.1769·2).
Constipation.

Laxucil *Novopharm, Canad.*
Ispaghula (p.1737·1).
Constipation.

Laxvital *Maxfarma, Spain.*
Carmellose (p.2142·1); docusate sodium (p.1725·1); casanthranol (p.1715·1).
Constipation.

Laxygal *Ivax, Cz.; Ivax, Hung.; Galena, Rus.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Laxyl *Solfran, Mex.*
Diazepam (p.986·3).

Laxysat Burger *Ysatfabrik, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Laz *Dexa, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lazafin *Novell, Indon.*
Sulfasalazine (p.1773·2).
Crohn's disease; rheumatoid arthritis; ulcerative colitis.

Lazar-Cort *Lazar, Arg.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Lazar-Cort Complex *Lazar, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Lazercreme *Pedinol, USA.*
Vitamin E (p.1992·2); vitamin A (p.1971·2).
Minor skin irritation.

Lazerformaldehyde *Pedinol, USA.*
Formaldehyde (p.1644·2).
Bromhidrosis (feet); hyperhidrosis; warts.

LazerSporin-C *Pedinol, USA.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); hydrocortisone (p.1535·2).
Bacterial ear infections.

Lazitrom *Azevedos, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Laztie *Bioprofarma, Arg.*
Ribavirin (p.902·3).
Chronic hepatitis C.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

LB Jabon con Purcelin *Billiet, Arg.†.*
Triclocarban (p.1665·2); purcelin oil (p.549·3).
Skin cleansing.

LC-65 *AMO, Austral.†; Allergan, Canad.†; Advanced Medical Optics, NZ†; Allergan, USA.*
Solutions for contact lens care (p.1622·2).

L-Carn *Sigma-Tau, Ger.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

L-Cetridoc *Glenmark, India†.*
Levocetirizine (p.583·2).
Bronchitis; rhinitis; urticaria.

L-Cimexyl *Cimex, Cz.†; Cimex, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

L-Combur-5-Test *Roche Diagnostics, Austral.†.*
Test for pH, protein, glucose, ketones, and blood in urine.

LCP *Nutricia, Ital.*
Fish oil; borage oil; vegetable oil; vitamin E (p.1922·1).
Amino-acid disorders; phenylketonuria.

LD-Caine *Millimed, Thai.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Le Face Protection *Creative Brands, Austral.†.*
SPF 15+: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Le Fibre *Or-Dov, Austral.†.*
Wheat fibre.
Dietary fibre supplement; obesity.

Le Pont Tratamiento Ungueal Formula 405 *Dermaclin, Mex.†.*
Phospholipids; vitamin A; vitamin E (p.1922·1).
Nail disorders.

Le Tan Fast Extra Dark *Creative Brands, Austral.†.*
Dihydroxyacetone (p.1594·1).
Artificial suntan.

Le Tan Fast Plus *Creative Brands, Austral.†.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3); dihydroxyacetone (p.1594·1).
Artificial suntan; sunscreen.

Le Tan Fast Self Tan *Creative Brands, Austral.†.*
Dihydroxyacetone (p.1594·1).
Artificial suntan.

Le Tan Gel
Note. This name is used for preparations of different composition.
Creative Brands, Austral.†.
SPF 8: Octinoxate (p.1608·2); benzophenone.
Sunscreen.

Creative Brands, Austral.†.
SPF 15: Octinoxate (p.1608·2); benzophenone; avobenzone (p.1589·3).
Sunscreen.

Le Tan Natural *Creative Brands, Austral.†.*
SPF 15: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Le Tan Roll On Lotion *Creative Brands, Austral.†.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Le Tan Sensitive *Creative Brands, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); amiloxate (p.1589·1); octisalate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Le Tan Sport Dry Lotion *Creative Brands, Austral.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Le Tan Sport & Surf *Creative Brands, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); amiloxate (p.1589·1); octisalate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Le Tan Sunblock Stick *Creative Brands, Austral.†.*
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Le Tan Sunscreen Lotion
Note. This name is used for preparations of different composition.
Creative Brands, Austral.†.
SPF 4; SPF 8: Octinoxate (p.1608·2).
Sunscreen.

Creative Brands, Austral.†.
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Creative Brands, Austral.
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Le Tan Sunscreen Lotion Broad Spectrum *Creative Brands, Austral.†.*
SPF 15+: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Le Tan Ultimate
Note. This name is used for preparations of different composition.
Creative Brands, Austral.†.
SPF 8: Octinoxate (p.1608·2); benzophenone.
Sunscreen.

Creative Brands, Austral.†.
SPF 15+: Octinoxate (p.1608·2); avobenzone (p.1589·3); benzophenone.
Sunscreen.

Le Thermogene *Tradiphar, Fr.†.*
Capsicum oleoresin (p.2276·2); glycol salicylate (p.62·3).
Musculoskeletal and peri-articular pain; respiratory-tract congestion.

Le Trim-BM *Or-Dov, Austral.†.*
Benzocaine (p.1854·1); methylcellulose (p.2145·1); ferrous gluconate; vitamins (p.1922·1).
Obesity.

LEAN Formula w/ Advantra *Usana, Hong Kong†.*
Sour orange (p.2357·1); green tea (p.2416·1); guarana (p.2416·1); cayenne (p.2276·2).
Obesity.

Leanor *Aspen Consumer, S.Afr.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Leaton
Note. This name is used for preparations of different composition.
Pharmacia, Hung.†.
Adult solution: Multivitamin preparation with caffeine (p.1116·3) (p.1922·1).
Tonic.

Pharmacia, Hung.†.
Paediatric solution: Multivitamin preparation (p.1922·1).
Tonic.

Leaton fur Erwachsene *Kwizda, Austria.*
Multivitamins (p.1922·1) with caffeine (p.1116·3).
Tonic.

Leaton fur Kinder *Kwizda, Austria.*
Multivitamins (p.1922·1).
Tonic.

Lebensart *Bioquimed, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety-depressive disorders; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder.

Lebensenergie-Kapseln *Twardy, Ger.†.*
Siberian ginseng (p.2386·3).
Tonic.

Leberetic *Ern, Spain.*
Potassium sulfate (p.1684·3); sodium bicarbonate (p.1673·2); sodium sulfate (p.1771·3).
Liver disorders.

Leber-Galletropfen *Heel, Ger.*
Homoeopathic preparation.

Leber-Galle-Tropfen 83 *Bio-Diat, Ger.†.*
Sage (p.2382·3); absinthium (p.2244·1); gentian (p.2310·3); fennel (p.2302·3); centaury (p.2279·1); elecampane (p.1558·1); anise oil (p.2258·2); peppermint oil (p.1761·2); calamus oil; lavender oil (p.2331·2).
Biliary disorders; dyspepsia.

Leberinfusion *Fresenius Kabi, Austria.*
Arginine (p.1928·2); malic acid (p.2337·1); sodium hydroxide (p.2389·3); potassium hydroxide (p.2371·3).
Liver disorders.

Lebersal *Ern, Spain.*
Magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2); dibasic sodium phosphate (p.1682·3); sodium sulfate (p.1771·3).
Gastrointestinal disorders; hepatic insufficiency.

Lebic *Alpharma-Isis, Ger.*
Baclofen (p.1888·1).
Skeletal muscle spasm or spasticity.

Lebilon *Pharmathen, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Lebocar *Pfizer, Arg.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Lebopride *Spyfarma, Spain.*
Sulpiride (p.1028·3).
Anxiety disorders; psychoses; vertigo.

Lebrocetin *Liferpal, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Lecardop *Teva, Cz.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Lecarge *Klonal, Arg.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Leche Autobronceadora *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Dihydroxyacetone (p.1594·1).
Artificial tanning.

Leche Autobronceadora Cara Y Cuerpo *Silesia, Chile.*
Dihydroxyacetone (p.1594·1).
Artificial suntan.

Leche de Magnesia Normex *Quimica y Farmacia, Mex.*
Magnesium hydroxide (p.1743·2).
Constipation; gastric hyperacidity.

Leche de Magnesia Phillips *GSK, Arg.; GSK, Chile.*
Magnesium hydroxide (p.1743·2).
Antacid; constipation.

Leche de Proteccion Total *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Lecia *Caldeira & Marques, Port.†.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2); collodion.
Formerly contained ortho-oxybenzoic acid, lactic acid, phenol, glacial acetic acid, and turpentine oil.
Corns; verrucas.

Lecibis *Andromaco, Venez.†.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Lecibral *Desma, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Lecicarbon
Note. This name is used for preparations of different composition.
Brady, Austria.
Sodium bicarbonate (p.1673·2); potassium acid tartrate (p.1764·1).
Constipation.

Athenstaedt, Ger.; Athenstaedt, Switz.
Sodium bicarbonate (p.1673·2); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Leciderm *Darier, Mex.*
Lecithin (p.2332·2).
Dry skin disorders.

Lecifar-K *Farcoral, Mex.†.*
Lecithin (p.2332·2); kelp (p.2384·2); vitamin B (p.1979·1); apple.
Obesity.

Lecigal *Gal, Pol.†.*
Soya oil (p.1965·3); lecithin (p.2332·2).
Atherosclerosis; hypercholesterolaemia.

Lecikur *Agepha, Austria.*
Lecithin (p.2332·2); caffeine (p.1116·3).
Tonic.

Lecimar *Spyfarma, Spain.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; mixed anxiety depressive disorder; obsessive-compulsive disorder.

Lecinova *Novartis Consumer, Ital.†.*
Nutritional supplement containing phospholipids and vitamins (p.1922·1).

Leciplus *Nutrition & Sante, Ital.*
Nutritional supplement containing phospholipids and vitamins (p.1922·1).

Lecitan *Pliva Krakow, Pol.*
Soya lecithin (p.2332·2).
Hypercholesterolaemia; tonic.

Lecithin ACE *YSP, Malaysia†.*
Lecithin; vitamin A; vitamin C; vitamin E (p.1922·1).
Dietary supplement.

Lecithin AE *YSP, Malaysia†.*
Lecithin; vitamin A; vitamin E (p.1922·1).
Dietary supplement.

Lecitone *Nutrisante, Fr.; Yves Ponroy, Singapore.*
A range of nutritional supplements containing phospholipids (p.1922·1).
Tonic.

Lecivar *Infinity, Venez.*
Soya lecithin (p.2332·2).
Hyperlipidaemias.

Lecivar Plus *Infinity, Venez.*
Soya lecithin (p.2332·2); vitamin B (p.1979·1); kelp (p.2384·2); malic acid (p.2337·1).
Slimming aid.

Leclor A *Provit, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Leclyte
Note. This name is used for preparations of different composition.
David, India.
Calcium lactate; potassium chloride; magnesium sulfate; sodium chloride; sodium acid phosphate; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

David, India.
A range of electrolyte infusions with glucose (p.1667·1).
Fluid and electrolyte imbalance.

Lecrolyn *Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Hung.; Santen, Norw.; Santen, Philipp.; Santen, Pol.; Santen, Rus.; Santen, Swed.; Santen, Thai.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Lectan *Diba, Mex.*
⊗ Meprednisone (p.1538·1).
Corticosteroid.

Lectil *Bouchara-Recordati, Fr.*
Betahistine hydrochloride (p.2265·1).
Vertigo.

Lectopam *Roche, Canad.*
Bromazepam (p.964·3).
Anxiety; sedative.

Lectozim *Leti, Venez.†.*
Tilactase (p.2402·1).

Lectrum *Sandoz, Arg.; Novartis, Braz.; Sandoz, Indon.; Sandoz, Mex.*
⊗ Leuprorelin acetate (p.2111·1).
Anaemia associated with uterine fibroids; breast cancer; endometriosis; precocious puberty; prostatic cancer; uterine fibroids.

Lecur *Dexa, Indon.*
Essential phospholipids; turmeric (p.1473·2); vitamin E (p.1922·1).
Liver function aid.

Lecytyna E *KRKA, Pol.*
Lecithin (p.2332·2); vitamin E (p.1992·2).
Tonic.

Ledamin *Pharma Nord, Denm.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Leda-Rix *Proula, Venez.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Ledclair *IFET (ΙΦΕΤ), Gr.; Sinclair, Irl.; Durbin, UK.*
Sodium calcium edetate (p.1462·2).
Heavy metal poisoning; hypercalcaemia.

Ledercort
Wyeth, Arg.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Wyeth, India.
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Corticosteroid.

Wyeth Lederle, Ital.†.
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Wyeth Lederle, Belg.†; ICN, Switz.†.
⊗ Triamcinolone (p.1544·2) or triamcinolone diacetate (p.1544·3).
Corticosteroid.

Ledercort con Neomicina *Wyeth, Arg.†.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Ledercort-N *Wyeth, India.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Lederderm *Lederle, Ger.†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Lederfen *Wyeth Lederle, Austria†; Wyeth, Irl.; Goldshield, UK.*
Fenbufen (p.54·3).
Musculoskeletal and joint disorders.

Lederfolat *Teofarma, Ger.*
Calcium folinate (p.1943·3).
Folate deficiency.

Lederfolin *Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, Spain; Wyeth, UK†.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; folic acid deficiency; megaloblastic anaemia; methotrexate toxicity; reduction of folic acid antagonist toxicity.

Lederfoline *Wyeth, Fr.; Teofarma, Port.*
Calcium folinate (p.1943·3).
Drug-induced megaloblastic anaemia; folic acid deficiency; megaloblastic anaemia; prevention of methotrexate toxicity; reduction of folic acid antagonist toxicity.

Lederlind *Riemser, Ger.*
Nystatin (p.543·2).
Fungal infections of the skin and mucous membranes.

Lederlon *Riemser, Ger.*
⊗ Triamcinolone hexacetonide (p.1544·3).
Parenteral corticosteroid.

Ledermix
Note. This name is used for preparations of different composition.
ICN, Austria; Riemser, Ger.; Globopharm, Switz.; Blackwell, UK.
⊗ Paste, triamcinolone acetonide (p.1544·3); demeclocycline calcium (p.265·1); cement, triamcinolone acetonide; demeclocycline hydrochloride (p.264·3); solution, eugenol (p.2301·2).
Bacterial infection and inflammatory disorders in dentistry.

Wyeth Lederle, Denm.†.
⊗ Paste, triamcinolone acetonide (p.1544·3); demeclocycline calcium (p.265·1); cement, triamcinolone acetonide; demeclocycline calcium; hardener N, macrogol 400 (p.2336·3); hardener S, eugenol (p.2301·2).
Bacterial infection and inflammatory disorders in dentistry.

Neopharm, Israel.
⊗ Triamcinolone acetonide (p.1544·3); demeclocycline calcium (p.265·1).
Bacterial infection and inflammatory disorders in dentistry.

Ledermycin *Wyeth, Austral.†; Wyeth, India; EuroCept, Neth.; Goldshield, UK.*
Demeclocycline hydrochloride (p.264·3).
Bacterial infections; hyponatraemia; intestinal amoebiasis.

Ledermycine *Genopharm, Fr.*
Demeclocycline hydrochloride (p.264·3).
Syndrome of inappropriate ADH secretion.

Lederpax *Wyeth, Arg.†; Wyeth, Mex.†; Wyeth, Spain.*
Erythromycin (p.269·2).
Acne.

Lederplatin *Pharmachemie, Denm.*
Cisplatin (p.698·2).
Malignant neoplasms.

Lederspan *Meda, Denm.; Meda, Fin.; Meda, Norw.; Meda, Swed.*
⊗ Triamcinolone hexacetonide (p.1544·3).
Corticosteroid.

Ledertam *Wyeth Lederle, Ital.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Ledertepa *IFET (ΙΦΕΤ), Gr.†; EuroCept, Neth.*
Thiotepa (p.778·3).
Bladder cancer; breast cancer; ovarian cancer.

Ledertrexate
Wyeth, Austral.; Wyeth Lederle, Fr.†; Wyeth, NZ†.
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.
Wyeth, Belg.; Wyeth, Mex.; Wyeth, Neth.†.
Methotrexate sodium (p.745·2).
Malignant neoplasms; mycosis fungoides; psoriasis; rheumatoid arthritis.

Ledervorin *Wyeth, Belg.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; adjunct to high-dose methotrexate therapy; overdosage with folic acid antagonists.

Ledflex *Velin, Denm.†.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Ledion *Help, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Ledocar *Unison, Philipp.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Ledolid *Pulitzer, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Ledopsan *Teva, Port.; BMS, Spain.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Ledoren *Boniscontro & Gazzone, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Ledox *Weifa, Norw.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Ledoxan *Dabur, Philipp.; Dabur, Thai.*
Cyclophosphamide (p.702·1).
Auto-immune disorders; malignant neoplasms.

Ledoxina *Laboratorios Chile, Chile; Lemery, Mex.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Ledum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Leeflox *Centaur, India.*
Levofloxacin (p.292·2).
Bacterial eye infections.

Leena *Watson, USA.*
21 Tablets, norethisterone (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Lefa Enteril *Fecofar, Arg.†.*
Neomycin (p.305·1); activated charcoal (p.1435·2); phthalylsulfathiazole (p.315·1).
Diarrhoea.

Lefa Enteril L *Fecofar, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Lefax *Bayer, Cz.; Bayer, Ger.; Hanseler, Switz.*
Simeticone (p.1770·2).
Aid in gastrointestinal examination; anti-foaming agent in radiography of the gastrointestinal tract; detergent intoxication; flatulence; gastrointestinal disorders associated with excess gas; meteorism.

Lefaxin *Bayer, Austria.*
Simeticone (p.1770·2).
Flatulence.

Lefcar *GSK, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Leferdivin *Asconex, Ger.*
Vitamin B substances; phosphatidyl choline; ferrous citrate; glutamic acid (p.1922·1).
Tonic.

Lefkacid *Knop, Chile.*
Calcium carbonate (p.1714·1); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Lefkaflam *Knop, Chile.*
Arnica (p.2260·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3).
Musculoskeletal, joint, and peri-articular disorders; oedema.

Lefkur *Knop, Chile.*
Cucurbita oil (p.2290·2).
Benign prostatic hyperplasia.

Leflokin *PharmaConsult, Hung.*
Levofloxacin (p.292·2).
Bacterial infections.

Lefloxin *Siam Bheasach, Thai.*
Levofloxacin (p.292·2).
Bacterial infections.

Lefluar *Rontag, Arg.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Leflumax *Elea, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

Lefos *Guardian, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Lefoxin *Shreya, Rus.*
Levofloxacin (p.292·2).
Bacterial infections.

Lefrine *Grin, Mex.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Leftose *Shinyaku, Hong Kong; Shinyaku, Jpn; Shinyaku, Malaysia†; Shinyaku, Singapore; Shinyaku, Thai.*
Muramidase hydrochloride (p.2348·1).
Adjunct in antibiotic therapy; allergic rhinitis; haemorrhage; infections; inflammation; sinusitis.

Lefumide *Cipla, India.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Leg Cramps with Quinine *Hylands, Canad.*
Homoeopathic preparation.

Legalon
Note. This name is used for preparations of different composition.
Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Madaus, Cz.; Madaus, Fr.; Madaus, Ger.; Madaus, Hung.; Madaus, Ital.; Neo-Farmaceutica, Port.; Madaus, Switz.
Milk thistle (p.1452·1).
Liver disorders; poisoning with alcohol and drugs.
Bayer, Chile; Madaus, Hong Kong; Altana, Mex.; Madaus, Philipp.; Pharmalink, Philipp.; Madaus, Pol.; Altana Madaus, S.Afr.; Madaus, Spain; Madaus, Thai.; Zuoz, Venez.
Silymarin (p.1452·2).
Amanita phalloides poisoning; alcohol-induced hepatic disorders; liver disorders.
IFET (ΙΦΕΤ), Gr.
Silibinin (p.1452·1).
Mushroom poisoning.

Legalon SIL
Note. This name is used for preparations of different composition.
Madaus, Belg.; Madaus, Ger.; Madaus, Hung.; Neo-Farmaceutica, Port.; Madaus, Switz.
Disodium silibinin dihemisuccinate (p.1452·2).
Amanita phalloides poisoning.
Madaus, Spain.
Silibinin dihemisuccinate (p.1452·2).
Amanita phalloides poisoning.

Legapas *Pascoe, Ger.*
Cascara (p.1715·2).
Constipation.

Legatrin PM *Columbia, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia.

Legatrin Rub *Columbia, USA.*
Menthol (p.2340·1); benzocaine (p.1854·1).

Legederm *Schering-Plough, Denm.†; Schering-Plough, Fin.†; Schering-Plough, Ital.; Schering-Plough, Swed.†.*
⊗ Alclometasone dipropionate (p.1516·1).
Eczema; skin disorders.

Legendal *Zambon, Neth.; Zambon, Switz.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Legifol CS *Pfizer, Braz.*
Calcium folinate (p.1943·3).

Legil *Galenus, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Leginsol OB *Cardinal, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Leginsol Vita *Cardinal, Philipp.*
Vitamins; lysine hydrochloride (p.1922·1).

Leginsol-E *Cardinal, Philipp.*
Vitamins; minerals; Siberian ginseng; lecithin; choline bitartrate (p.1922·1).
Tonic.

Legis *Boehringer Ingelheim, Spain†.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Legius *Benefoot, UK.*
Activated charcoal (p.1435·2).
Wounds.

Legofer *ITF, Chile; Elpen (Ελπεν), Gr.; Asta Medica, Ital.†; ITF, Port.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Legres *Soho, Indon.*
Leucoselect phytosome; lycopene (p.2335·2).
Antoxidant.

Legreskin *Soho, Indon.*
Marine protein extract; collagen (p.2286·1); vitamin E (p.1992·2); leucoselect phytosome; lycopene (p.2335·2).
Antoxidant.

Lehnigrip *Lehning, Cz.*
Homoeopathic preparation.

Lehning Toothpaste *Homeocan, Canad.†.*
Homoeopathic preparation.

Lehydan *Nevada, Swed.*
Phenytoin (p.495·2).
Epilepsy.

Leiba *Uniao Quimica, Braz.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of intestinal flora.

Leicester *Polifarma, Ital.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Leiguar *Labatec, Switz.*
Guar gum (p.442·3).
Diabetes mellitus; hyperlipidaemias.

Leikan *Schwabe, Cz.†.*
Kava (p.2328·3).
Anxiety.

Leioderm *Riemser, Ger.*
Hydroxyquinoline sulfate (p.2323·1).
Impetigo.

Leioderm P *Riemser, Ger.*
⊗ Hydroxyquinoline sulfate (p.2323·1); prednisolone (p.1540·3).
Infected skin disorders.

Leios *Wyeth, Ger.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Leite de Magnesia *Hertz, Braz.†.*
Magnesium hydroxide (p.1743·2).
Constipation.

Leite de Magnesia de Phillips *GSK, Braz.*
Magnesium hydroxide (p.1743·2).
Constipation.

Leite Magnesia Phillips *GSK Consumer, Port.*
Magnesium hydroxide (p.1743·2).
Antacid.

Lekamoxiclav *LEK, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Lekoklar *Hexal, Cz.; Lek, Hung.; Lek, Pol.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Lekoprost *Gedeon Richter, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Lekoptin *Lek, Cz.; Lek, Pol.; Lek, Rus.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; migraine; obstructive cardiomyopathy; peripheral vascular disorders.

Lekosen *Lek, Pol.*
Lupulus (p.2335·2); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Lektinol *Madaus, Ger.*
Mistletoe (p.2345·3).
Malignant neoplasms.

Lelco *Defuen, Arg.*
SPF 20: Amiloxate (p.1589·1); bisoctrizole (p.1591·2); avobenzone (p.1589·3); oxybenzone (p.1608·3); octisalate (p.1608·2); imidazolidinyl urea.
Sunscreen.

Lelco 23 *Defuen, Arg.†.*
SPF 23: Amiloxate (p.1589·1); titanium dioxide (p.1617·3).
Sunscreen.

Lelco Bebe *Defuen, Arg.†.*
SPF 15: Titanium dioxide (p.1617·3).
Sunscreen.

Lelco Labial *Defuen, Arg.*
Amiloxate (p.1589·1); titanium dioxide (p.1617·3).
Formerly contained *p*-methoxycinnamate and titanium dioxide.
Sunscreen for lips.

Lelco Locion Bronceadora *Defuen, Arg.†.*
Avobenzone (p.1589·3); amiloxate (p.1589·1); octocrilene (p.1608·3).
Sunscreen.

Lelco P *Defuen, Arg.†.*
p-Methoxycinnamate; titanium dioxide (p.1617·3).
Sunscreen.

Lelco P Ultra *Defuen, Arg.*
SPF 34: Amiloxate (p.1589·1); oxybenzone (p.1608·3); avobenzone (p.1589·3); titanium dioxide (p.1617·3); octocrilene (p.1608·3); ensulizole (p.1597·1).
Formerly contained*p*-methoxycinnamate, octisalate, oxybenzone, avobenzone, and titanium dioxide.
Sunscreen.

Lelco sin Sol *Defuen, Arg.*
Dihydroxyacetone (p.1594·1).
Artificial tanning.

Lelco Spray *Defuen, Arg.*
SPF 15: Amiloxate (p.1589·1); avobenzone (p.1589·3); octocrilene (p.1608·3).
Formerly contained amiloxate and avobenzone.
Sunscreen.

Lelco Ultrablock *Defuen, Arg.*
SPF 65: Amiloxate (p.1589·1); ensulizole (p.1597·1); titanium dioxide (p.1617·3); avobenzone (p.1589·3); octocrilene (p.1608·3); bisoctrizole (p.1591·2); ethylhexyl triazone (p.1608·1).
Formerly contained amiloxate, ensulizole, titanium dioxide, avobenzone, oxybenzone, and octocrilene.
Sunscreen.

Lelong Contusions *Zambon, Fr.†.*
Arnica (p.2260·2); tamus communis.
Soft-tissue disorders.

Lem *Obolenskoe, Rus.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Lema C *Ern, Spain.*
Ascorbic acid (p.1983·3); sodium perborate (p.1662·1).
Halitosis; mouth and throat inflammation; pyorrhoea.

Lemazol
Note. This name is used for preparations of different composition.
Petrasch, Austria.
Ascorbic acid (p.1983·3); potassium orotate (p.2358·3); inositol (p.2325·2); sorbitol (p.1965·1).
Liver disorders.
Vargas, Venez.
Diethylamine salicylate (p.47·2); myrtecaine (p.1867·2).
Musculoskeletal and joint disorders.

Lemblastine *Laboratorios Chile, Chile; Lemery, Mex.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Lembrol *Sanofi Synthelabo, Arg.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; muscle spasm.

Lemdopa *Lemery, Mex.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

L-Emental *Hormel, Israel.*
Preparation for enteral nutrition (p.1922·1).

Lemeron *Lemery, Mex.*
Interferon alfa-2b (p.885·1).
Hepatitis B; hepatitis C; malignant neoplasms.

Lemesil *Anfarm, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Lemil *Fecofar, Arg.*
Bismuth salicylate (p.1711·1); bismuth subgallate (p.1711·1); boric acid (p.2268·1).

Lemlax *Co-Pharma, UK.*
Lactulose (p.1738·2).
Constipation.

Lemnis Fatty Cream *CSL, NZ.*
Emollient.
Barrier cream; emollient.

Lemnis Fatty Cream HC *CSL, NZ.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Lemocin
Note. This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Belg.
Tyrothricin (p.358·2); cetrimide (p.1634·1); lidocaine (p.1862·3).
Mouth and throat disorders.
Novartis Consumer, Ger.; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Switz.
Tyrothricin (p.358·2); cetrimonium bromide (p.1635·1); lidocaine (p.1862·3).
Mouth and throat disorders.

Lemocin CX *Novartis Consumer, Ger.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Lemon Coldrex *GSK Consumer, Hung.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemophar *Alpharma, Mex.*
Hyoscine butylbromide (p.1734·1).

Lemorcan *Leovan, Gr.*
Norfloxacin (p.309·2).
Bacterial infections.

Lemotussin-DM *Seneca, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sulfogaiacol (p.1573·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).

Lemoxin *Lemery, Mex.†.*
Cefuroxime (p.238·2).
Bacterial infections.

Lemoxol *Demo, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Lemsip
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Austral.; Reckitt Benckiser, Belg.
Paracetamol (p.108·1).
Cold and influenza symptoms; fever; pain.
Reckitt Benckiser, Hong Kong†.
Paracetamol (p.108·1); sodium citrate (p.1673·3); vitamin C (p.1983·3).
Cold and influenza symptoms.

Lemsip Chesty Cough *Reckitt Benckiser, NZ†.*
Guaifenesin (p.1561·3).
Coughs.

Lemsip Children's Cold Relief *Reckitt Benckiser, Irl.*
Paracetamol (p.108·1).
Cold and influenza symptoms.

Lemsip Childrens Six+ Cold & Flu Relief
Reckitt Benckiser, UK.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Lemsip Cold & Flu
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Singapore.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.
Reckitt Benckiser, Irl.
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Breathe Easy *Reckitt Benckiser, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Headcold *Reckitt Benckiser, NZ.*
Paracetamol (p.108·1); menthol (p.2340·1).
Cold and influenza symptoms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lemsip Cold & Flu Max Strength *Reckitt Benckiser, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Max Strength Capsules *Reckitt Benckiser, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Lemsip Cold & Flu Original *Reckitt Benckiser, UK.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Lemsip Cold & Flu Original, Cold & Flu Max *Reckitt Benckiser, NZ.*
Paracetamol (p.108·1).
Cold and influenza symptoms.

Lemsip Cough & Cold Chesty Cough *Reckitt Benckiser, UK.*
Guaifenesin (p.1561·3).
Coughs.

Lemsip Cough & Cold Dry Cough *Reckitt Benckiser, UK.*
Honey (p.1948·2); terpeneless lemon oil (p.2332·3); glycerol (p.2314·2); citric acid (p.2284·1).
Coughs; sore throat.

Lemsip Dry Cough *Reckitt Benckiser, NZ†.*
Citric acid (p.2284·1); glycerol (p.2314·2); honey (p.1948·2); lemon oil (p.2332·3).
Coughs.

Lemsip Flu 12Hr *Reckitt Benckiser, UK.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Lemsip Flu Nightime *Reckitt Benckiser, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; coughs.

Lemsip Flu Strength *Reckitt Benckiser, NZ.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Lozenges *Reckitt Benckiser, Austral.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Lemsip Max Day & Night *Reckitt Benckiser, NZ†.*
Day, dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night, dextromethorphan hydrobromide; paracetamol; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Lemsip Max Decongestant *Reckitt Benckiser, Austral.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Lemsip Max Relief Capsules *Reckitt Benckiser, Irl.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Lemsip Max Sinus & Flu *Reckitt Benckiser, Irl.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Lemsip Max Strength Sinus Relief *Reckitt Benckiser, UK.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold symptoms; sinusitis.

Lemsip Non-Decongestant *Reckitt Benckiser, UK†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Pharmacy Flu Strength
Note. This name is used for preparations of different composition.
Reckitt Benckiser, Irl.
Ascorbic acid (p.1983·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Reckitt Benckiser, UK.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; sinusitis.

Lemsip Pharmacy Flu Strength Daytime *Reckitt Benckiser, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Lemsip Pharmacy Flu Strength Nightime *Reckitt Benckiser, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Lemsip Pharmacy with Phenylephrine *Reckitt Benckiser, Irl.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Lemsip Pharmacy Powercaps *Reckitt Benckiser, UK.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Lemsip Sore Throat *Reckitt Benckiser, UK.*
Hexylresorcinol (p.1647·1).
Sore throat.

Lemsip Throat Lozenges *Reckitt Benckiser, NZ.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Lemsip Vapo-Patches *Reckitt Benckiser, UK.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2).
Respiratory-tract congestion.

Lemtosid *Lemery, Mex.*
Benzonatate (p.1552·1).
Coughs.

Lemuval *Bayer, Austria.*
A heparinoid (p.1305·2); hyaluronidase (p.2321·1); vitamin A palmitate (p.1973·1); calcium pantothenate (p.1959·3); menthol (p.2340·1).
Anorectal disorders.

Lemyflox *Lemery, Mex.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Lemyken *Euromex, Mex.†.*
Ketoconazole (p.539·1).
Scalp disorders.

Lemytriol *Lemery, Mex.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Len B Co *SA Druggists Self Med, S.Afr.*
Vitamin B substances (p.1922·1).

Len V.K. *Pharmacare, S.Afr.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Lenadol *Pharmacare, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3).
Fever; pain and associated tension.

Lenafen *Aspen, S.Afr.†.*
Ibuprofen (p.64·2).
Fever; pain.

Lenaken *Serral, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Lenamet *Pharmacare, S.Afr.*
Cimetidine (p.1716·2).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lenapain *Pharmacare, S.Afr.*
Doxylamine succinate (p.578·2); codeine phosphate (p.37·2); caffeine (p.1116·3); paracetamol (p.108·1).
Pain and associated tension.

Lenar *Biomedica-Chemica, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lenasone *Pharmacare, S.Afr.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Lenazine *Pharmacare, S.Afr.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions.

Lenazine Forte *Pharmacare, S.Afr.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Lendacin *Lek, Cz.; Biogal-Teva, Hung.; Lek, Pol.; Lek, Rus.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Lenditro *Pharmacare, S.Afr.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; nocturnal enuresis.

Lendorm *Boehringer Ingelheim, Austria; Roche, Denm.†.*
Brotizolam (p.965·2).
Sleep disorders.

Lendormin *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Neth.; Unilfarma, Port.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Venez.*
Brotizolam (p.965·2).
Anxiety; premedication; sleep disorders.

Lendormine *Boehringer Ingelheim, Switz.†.*
Brotizolam (p.965·2).
Sleep disorders.

Lendrex *Sidepal, Braz.†.*
Permethrin (p.2048·2).
Pediculosis.

Lendronal *Lafedar, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Lengout *Aspen, Austral.*
Colchicine (p.556·1).
Gout.

Lenicalm *Dolisos, Fr.†; Dolisos, Ital.*
Asperula odorata; crataegus (p.2289·1); tilia (p.2402·2).
Nervous disorders; sleep disorders.

Lenicet *Athenstaedt, Ger.*
Aluminium diacetate hydroxide; aluminium hydroxide (p.1706·2).
Skin disorders.

Lenident *Zeta, Ital.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Leniderm *Inpharzam, Switz.†.*
Vitamin A (p.1971·2); alpha tocopherol (p.1992·2); dexpanthenol (p.2362·1); allantoin (p.1588·1); titanium dioxide (p.1617·3).
Burns; skin disorders; wounds.

Lenide-T *Pharmacare, S.Afr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Lenidolor *Menarini, Ital.*
Meclofenamic acid (p.79·3) or meclofenamate sodium (p.79·3).
Musculoskeletal and joint disorders; pain.

Lenidor *Simoes, Braz.†.*
Thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint disorders.

Lenifren *DermoDuemila, Ital.*
Magnesium; melissa; St John's wort; rhodiola; vitamins (p.1922·1).
Nutritional supplement.

Lenil *Zeta, Ital.*
Chlorhexidine hydrochloride (p.1635·3).
Disinfection of wounds and burns.

Lenipasta *Novogaleno, Ital.†.*
Zinc oxide (p.1621·2); rice starch (p.1968·1); enoxolone (p.50·1).
Skin irritation; wounds.

Lenirit *EG, Ital.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Lenirose *Novogaleno, Ital.†.*
Sulfur (p.1614·1); titanium dioxide (p.1617·3); panthenol (p.2362·1); rusco; calendula (p.2273·1); oryzanol (p.2358·3); enoxolone (p.50·1).
Rosacea; seborrhoeic dermatitis; skin irritation.

Lenisan *Bittner, Austria.*
Homoeopathic preparation.

Lenisolone *Pharmacare, S.Afr.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Lenistar *Boniscontro & Gazzone, Ital.*
Butamirate citrate (p.1553·1).
Coughs.

Lenitil *Mertens, Arg.†.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Lenitin *Teva, Israel.*
Bromazepam (p.964·3).
Anxiety; premedication; sedative.

Lenitral *Besins, Fr.†; Besins, Hong Kong†; Organon, Neth.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; pulmonary oedema.

Lennacol *Intramed, S.Afr.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Lennamine *Lennon, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Lenobio *Delta, Arg.*
Lenograstim (p.1073·1).
Neutropenia.

Lenocef *Pharmacare, S.Afr.*
Cefalexin (p.218·2).
Bacterial infections.

Lenocin *General Drugs, Thai.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Lenolax *Pharmacare, S.Afr.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Lenoprel *Intramed, S.Afr.†.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Bronchospasm; cardiac arrest; shock.

Lenovate *Pharmacare, S.Afr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Lenovor *Itaca, Braz.†.*
Folinic acid (p.1943·3).

Lenoxe *Air Liquide, Port.*
Xenon (p.1797·3).
General anaesthesia.

Lenoxin *GSK, Ger.*
Digoxin (p.1259·3).
Heart failure; tachycardia.

Lenpryl *Probiomed, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension.

Lens Lubricant *Bausch & Lomb, USA.*
Wetting solution for hard contact lenses (p.1622·2).

Lens Plus
Note. This name is used for preparations of different composition.
AMO, Austral.
Sodium chloride (p.1686·1)(p.1622·2).
Rinsing, cleaning, and storage of soft and gas permeable contact lenses.

Advanced Medical Optics, NZ; Allergan, USA.
Rinsing solutions for contact lenses (p.1622·2).

Lens Plus Buffered Saline Solution *Allergan, Canad.†.*
Buffered sodium chloride (p.1686·1)(p.1622·2).
Rinsing solution for contact lenses.

Lenta *Pentafarma, Chile†.*
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (bovine and porcine) (p.443·2).
Diabetes mellitus.

Lentard *Abbott, India.*
⊗ Insulin zinc suspension (porcine, highly purified) (amorphous 30%, crystalline 70%) (p.443·2).
Diabetes mellitus.

Lentare *Novartis, S.Afr.†.*
⊗ Formestane (p.726·1).
Breast cancer.

Lentaron *Novartis, Arg.†; Novartis, Austria; Novartis, Braz.†; Novartis, Chile†; Novartis, Cz.†; Novartis, Denm.†; Novartis, Ger.†; Novartis, Gr.†; Novartis, Hong Kong†; Novartis, Ital.†; Novartis, Malaysia†; Novartis, Spain†; Novartis, Turk.*
⊗ Formestane (p.726·1).
Breast cancer; prostatic cancer.

Lente *Novo Nordisk, USA.*
⊗ Insulin zinc suspension (bovine or porcine) (p.443·2).
Diabetes mellitus.

Lente Iletin II *Lilly, USA.*
⊗ Insulin zinc suspension (porcine) (p.443·2).
Diabetes mellitus.

Lente MC *Novo Nordisk, Switz.†.*
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (bovine with porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Lenteclin *Aristo, India.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Lentermina Complex *Biotech, Venez.*
Hydroxocobalamin (p.1980·3); pyridoxine hydrochloride (p.1978·2); thiamine phosphate chloride.
Neurological disorders.

Lentisol *Barnes Hind, Arg.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Wetting solution for hard contact lenses.

Lentizol *Pfizer, Irl.†.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Lento Nit K *Optima, Ger.*
Potassium iodide; calcium chloride; sodium thiosulfate (p.1667·1).
Eye care.

Lentocilin *Atral, Port.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Lentocilin S *Atral, Port.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Lentogesic
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Capsules: Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1); glutamine (p.1947·2). Formerly contained dextropropoxyphene hydrochloride, paracetamol, pemoline, and glutamine.
Pain.

Adcock Ingram, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Lentogest *Amsa, Ital.*
Hydroxyprogesterone caproate (p.2110·3).
Infertility; menstrual and menopausal disorders; threatened or recurrent miscarriage.

Lento-Kalium *Teofarma, Ital.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Lentolith *Adcock Ingram, S.Afr.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression.

Lentopenil *Grossman, Mex.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Lentoquine *Sanofi-Aventis, Spain.*
Hydroquinidine hydrochloride (p.1312·1).
Arrhythmias.

Lentorsil *Italfarmaco, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders; cholesterol gallstones.

Lentostamin *Italmex, Mex.*
Carbinoxamine (p.570·2); phenylpropanolamine (p.1569·2); mepyramine (p.585·1).

Lentrin *Metiska, Indon.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Lentusin *Chobet, Arg.*
Dihydrocodeine resinate (p.48·3); phenyltoloxamine resinate.
Cough.

Lenurex-K *Lennon, S.Afr.*
⊗ Cyclopenthiazide (p.1254·1); potassium chloride (p.1684·3).
Diabetes insipidus; hypertension; oedema.

Leo-400 *Charoen, Thai.*
Albendazole (p.139·2).
Worm infections.

Leo-Doce *Solfran, Mex.*
Hydroxocobalamin (p.1980·3).
Anaemias; neuritis.

Leodrin *Gynopharm, Chile.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Leogumil *Leovan, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Leomoxyl *Guardian, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Leonitren *Medinova (Μεντινοβα), Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Leopin *Purity Life, Canad.*
Vitamin B substances (p.1922·1).
Dietary supplement.

Leoron *CNN, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Leovinezal *Medinova (Μεντινοβα), Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Lepan *Yes, Neth.*
Lidocaine hydrochloride (p.1862·3).
Sore throat.

Leparan *Italfarmaco, Ital.†.*
Suleparoid (p.1406·3).
Thrombosis prophylaxis.

Leparson *Dexa, Indon.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Lepex *SMB, Chile.*
Povidone (p.2146·1).
Dry eyes.

Lepexal *Biotech, Venez.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; musculoskeletal and joint disorders.

Lepheton *Ipex, Swed.*
⊗ Ethylmorphine hydrochloride (p.52·2); ephedrine hydrochloride (p.1558·2).
Bronchitis; coughs.

Lephin *Pharmadica, Thai.†.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Lepicortinolo *Decomed, Port.*
⊗ Prednisolone (p.1540·3) or prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Lepisor *Soria Natural, Spain†.*
Lepidium latifolium; java tea (p.2328·2).
Prostatitis; renal calculi.

Lepobron *Lepori, Port.†.*
Theophylline (p.1140·1).
Asthma.

Leponex *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, Venez.*
Clozapine (p.981·1).
Parkinsonism-associated psychoses; schizophrenia.

Lepravir *Virgo, Philipp.*
Dapsone (p.261·2).
Leprosy.

Leprofen *LKM, Arg.*
⊗ Anastrozole (p.681·2).

Leptanal *Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
⊗ Fentanyl citrate (p.55·3).
Adjunct in neuroleptanalgesia; pain.

Leptazine *Roemmers Rowe, Venez.*
Trifluoperazine hydrochloride (p.1034·2).
Anxiety.

Leptic *Chobet, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Lepticur *Sanofi-Aventis, Fr.*
Tropatepine hydrochloride (p.821·3).
Extrapyramidal disorders; parkinsonism.

Leptilan *Novartis, Chile†; Dolorgiet, Ger.; Novartis, Mex.*
Sodium valproate (p.508·2).
Epilepsy; febrile convulsions.

Leptofen *Pharmacia, Ital.*
⊗ Fentanyl (p.55·3); droperidol (p.994·3).
Neuroleptanalgesia; premedication.

Leptopsique *Psicofarma, Mex.*
Perphenazine (p.1017·1).
Anxiety disorders; nausea and vomiting; pain; psychoses.

Lepur *Elpen (Ελπεν), Gr.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Lercadip *Gador, Arg.; Recordati, Gr.; Innova, Ital.; Biohorm, Spain; Fako, Turk.; Zuoz, Venez.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lercan *Pierre Fabre, Fr.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lercaton *Berlin-Chemie, Hung.; Menarini, Hung.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lerdip *Zambon, Neth.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lerez *Glenmark, India.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lerez-AT *Glenmark, India†.*
⊗ Lercanidipine hydrochloride (p.1324·2); atenolol (p.1217·3).
Hypertension.

Lerfimin *Mintlab, Chile.*
Benzocaine (p.1854·1); benzethonium chloride (p.1630·1); alcohol.

Lergan *Viofor, Gr.†.*
Serrapeptase (p.2385·3).
Inflammatory disorders.

Lergia *Mecosin, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lergicyl *Eurowest, Philipp.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Lergigan *Recip, Swed.*
Promethazine hydrochloride (p.588·2).
Alcoholism; anxiety; croup; hypersensitivity reactions; nausea; premedication; sedative; sleep disorders; tension; vertigo.

Lergigan comp *Recip, Swed.*
⊗ Promethazine hydrochloride (p.588·2); caffeine (p.1116·3); ephedrine sulfate (p.1558·2).
Alcoholism; anxiety; croup; hypersensitivity reactions; nausea; premedication; sedative; sleep disorders; tension; vertigo.

Lergilite *Eulite, Neth.*
Homoeopathic preparation.

Lergocil *Juste, Spain.*
Azatadine maleate (p.568·1).
Hypersensitivity reactions.

Lergosin *Degorts, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Lergosin A *Degorts, Mex.*
⊗ Dexamethasone (p.1526·1); chlorphenamine (p.572·2).

Lerin *Allergan, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc phenolsulfonate (p.1621·3).
Ocular congestion.

Lerivon *Organon, Arg.; Organon, Belg.; Organon, Cz.; Organon, Pol.; Organon, Rus.*
Mianserin hydrochloride (p.408·1).
Depression.

Lermex *Sriprasit, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Lero *Lero, Fr.*
A range of vitamin, mineral, and fish oil preparations (p.1922·1).

Lerogin *Recalcine, Chile.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal disorders; urinary-tract disorders.

Leroid *Geminis, Arg.†.*
Phenazone (p.116·1); benzocaine (p.1854·1); sulfathiazole (p.343·2).
Ear disorders.

Lerpin *Berlin-Chemie, Cz.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lersan *Lersan, Arg.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lerskin *Nufarindo, Indon.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Lertamine
Note.This name is used for preparations of different composition.
White, Arg.†; Schering-Plough, Mex.
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Schering-Plough, Chile.
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Lertamine D *White, Arg.†; Schering-Plough, Mex.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; nasal congestion.

Lertamine Extra *Schering-Plough, Chile.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Lertus
Tecnofarma, Chile.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Asofarma, Mex.
Diclofenac colestyramine (p.46·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lertus Biotic *Ivax, Arg.†.*
Diclofenac potassium (p.44·3); amoxicillin trihydrate (p.202·2).
Respiratory-tract infections.

Lertus CD *Asofarma, Mex.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Leruze *Rafarm, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lerzam *Rottapharm, Spain.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Lesaclor *Euromex, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Lesbest *Best, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Lescol *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ†; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.†.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; cardiovascular risk reduction; coronary heart disease; hypercholesterolaemia; prevention of coronary events following percutaneous coronary intervention.

Leset *Ipca, India.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; allergic skin disorders.

Lesflam *Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Diclofenac potassium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Leshcutan *Teva, Israel.*
Paromomycin (p.843·3); methylbenzethonium chloride (p.1653·1).
Cutaneous leishmaniasis.

Lesichol *Landson, Indon.*
Lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1).
Supplement for supporting liver function.

Lesidas *Kalbe, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lesiden *Euromex, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Lesifit *Sandoz, Indon.*
Lecithin; vitamin B substances (p.1975·1); vitamin E (p.1992·2); betacarotene (p.1930·3).
Vitamins A, B, and E deficiency.

Lesil *Farmatrading, Port.*
Tolu balsam (p.1574·2); sulfogaiacol (p.1573·2); pine oil (p.2368·2).
Coughs.

Lespenefril *Produfarma, Port.†.*
Lespedeza capitata.
Diuretic.

Lespenephryl *UCB, Austria; UCB, Fr.†.*
Lespedeza capitata.
Diuresis; renal disorders.

Lessfat *Ximena Polanco, Chile.*
Homoeopathic preparation.

Lessina *Barr, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Lessmusec *Brunel, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased or viscous mucus.

Lesspain *Adcock Ingram, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Lestamil *Teuto, Braz.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).

Lestid *Pfizer, Denm.; Pfizer, Fin.; Pharmacia-Upjohn, Gr.†; Pfizer, Norw.; Pharmacia, Swed.*
Colestipol hydrochloride (p.1252·2).
Hypercholesterolaemia.

Lestric *Ranbaxy, Malaysia.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lestrin *Cedar Health, UK.*
Sitosterol (p.1373·2); beta sitostanol (p.1373·2).
Food supplement.

Lestron *Bernofarm, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Letairis *Gilead, USA.*
Ambrisentan (p.1209·1).
Pulmonary hypertension.

Letansil *IQB, Braz.*
Diazepam (p.986·3).
Anxiety.

Letequatro *Upsifarma, Port.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Lethyl *Pharmacare, S.Afr.*
Phenobarbital (p.492·2).
Anxiety; insomnia; migraine.

Letigen *Nycomed, Denm.†.*
⊗ Caffeine (p.1116·3); ephedrine hydrochloride (p.1558·2).
Obesity.

Letinnov *Farmaceutica H, Mex.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Letin-Tran *Sanofi-Aventis, Pol.*
Cod-liver oil (p.1935·2).
Dietary supplement.

Letisan *Leti, Venez.*
Ascorbic acid; citrus bioflavonoids (p.1922·1).

Letizen *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Let-Nasal *Sertex, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Letonal *Otto, Indon.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; hepatic cirrhosis; hypertension; hypokalaemia; oedema.

Letondal *Finadiet, Arg.*
Ambroxol hydrochloride (p.1550·3); paracetamol (p.108·1); oxatomide (p.587·1).
Allergic rhinitis; influenza symptoms.

Letrox *Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Berlin-Chemie, Pol.*
Levothyroxine sodium (p.2171·2).
Goitre; hypothyroidism; thyroid cancer.

Letter *Sanofi-Aventis, Port.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Letus *Unison, Hong Kong; Unison, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Letydol *Leti, Venez.*
Paracetamol (p.108·1); dihydroergotamine mesilate (p.618·2); caffeine (p.1116·3).

Letynol *Norma (Νορμα), Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Leucen *Tentan, Switz.*
Lauric acid; benzalkonium chloride (p.1629·1); peru balsam (p.2365·3); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); cod-liver oil (p.1935·2); colophony (p.2286·2); camphor (p.2273·2); aluminium acetate (p.2255·1); ichthammol (p.1599·1).
Skin lesions.

Leucin *Bergamo, Braz.*
Filgrastim (p.1070·1).
Neutropenia induced by cytotoxic agents.

Leuco-4 *Expanscience, Fr.*
Adenine (p.2247·2).
Asthenia.

Leuco Hubber *Aventis, Port.†; Teofarma, Spain.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Vulvovaginal disorders.

Leucobasal *Germania, Austria.*
Mequinol (p.1604·2).
Hyperpigmentation.

Leucocalcin *LKM, Arg.*
Calcium levofolinate (p.1943·3).

Leucocida *Simoes, Braz.†.*
Hydroxyquinoline sulfate (p.2323·1); borax (p.2268·1); cetrimonium bromide (p.1635·1).
Vulvovaginal disorders.

Leucocitim *Blausiegel, Braz.*
Molgramostim (p.1073·3).
Neutropenia.

Leucodin *Darrow, Braz.*
Mequinol (p.1604·2).
Vitiligo.

Leucodinine B *DB, Fr.*
Mequinol (p.1604·2).
Hyperpigmentation.

Leucodinine-M *Unipharma, Gr.*
Mequinol (p.1604·2).
Hyperpigmentation.

Leucogen *Ache, Braz.*
Thymomodulin (p.2401·3).
Immunodeficiencies; leucopenia.

Leucomax *Essex, Arg.†; Aesca, Austria†; Novartis, Austria†; Novartis, Belg.†; Novartis, Braz.†; Schering-Plough, Chile†; Novartis, Cz.†; Novartis, Denm.†; Schering-Plough, Denm.†; Novartis, Fin.†; Schering-Plough, Fin.†; Essex, Ger.†; Novartis, Ger.†; Novartis, Gr.; Novartis, Hong Kong†; Schering-Plough, Hong Kong†; Novartis, Hung.†; Novartis, India; Schering-Plough, Irl.; Novartis, Israel; Novartis, Ital.†; Novartis, Malaysia†; Schering-Plough, Malaysia†; Novartis, Mex.†; Schering-Plough, NZ; Schering-Plough, Neth.†; Schering-Plough, Norw.†; Schering-Plough, S.Afr.†; Schering-Plough, Spain†; Novartis, Swed.†; Schering-Plough, Swed.†; Essex, Switz.†; Novartis, Switz.†; Novartis, Thai.†; Schering-Plough, Thai.†; Schering-Plough, UK†; Schering-Plough, Venez.†.*
Molgramostim (p.1073·3).
Aplastic anaemia; myelodysplastic syndromes; neutropenia induced by cytotoxic therapy, bone marrow transplantation, or ganciclovir.

Leuconolver *Nolver, Venez.*
Folinic acid (p.1943·3).
Megaloblastic anaemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Leuco-Scint *Medi-Radiopharma, Cz.*
Technetium-99m (p.2055·3) exametazime.
Localisation of infection and inflammation.

Leucotrofina *Bago, Arg.*
Thymomodulin (p.2401·3).
Leucopenia.

Leucyt *Dabur, Philipp.*
Cytarabine (p.705·1).
Leukaemias.

Leukase *Merck, Austria.*
Framycetin sulfate (p.279·1); trypsin (p.2405·3).
Infected burns and wounds; infected skin disorders.

Leukase N
Note. This name is used for preparations of different composition.
Dermapharm, Ger.
ointment; Topical powder: Framycetin sulfate (p.279·1).
Infected skin disorders; infected wounds.

Dermapharm, Ger.
Topical gel: Framycetin sulfate (p.279·1); lidocaine hydrochloride (p.1862·3).
Infected skin disorders; infected wounds.

Leukase-Kegel *Merck, Austria.*
Framycetin sulfate (p.279·1); trypsin (p.2405·3); lidocaine hydrochloride (p.1862·3).
Infected skin and mouth disorders.

Leukast *Andromaco, Chile†.*
Montelukast sodium (p.1126·2).
Asthma.

Leukeran *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; Wellcome, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK.*
Chlorambucil (p.696·3).
Malignant neoplasms; nephrotic syndrome; polycythaemia vera.

Leukichtan
Note. This name is used for preparations of different composition.
Ichthyol, Austria.
Ictasol (p.1599·1); cod-liver oil (p.1935·2).
Burns; skin disorders; wounds.

Ichthyol, Ger.
Ictasol (p.1599·1).
Ulcers; wounds.

Leukine *Berlex, USA.*
Sargramostim (p.1079·2).
Mobilisation of autologous peripheral blood progenitor cells; neutropenia.

leukominerase *Biosyn, Ger.†.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Leukona-Aktiv-Rheumabad *Atzinger, Ger.†.*
Benzyl nicotinate (p.28·1).
Bath additive; peripheral vascular disorders; rheumatism.

Leukona-Beruhigungsbad *Atzinger, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2).
Bath additive; nervous disorders.

Leukona-Eukalpin-Bad *Atzinger, Ger.†.*
Norway spruce oil; eucalyptus oil (p.2301·2).
Bath additive; respiratory-tract disorders.

Leukona-Jod-Bad *Richter, Austria†; Atzinger, Ger.†.*
Iodine (p.2169·2).
Atherosclerosis; bath additive; circulatory disorders; iodine-deficiency goitre; neuralgia; spinal disorders.

Leukona-Kreislauf-Bad *Atzinger, Ger.†.*
Rosemary oil (p.2381·3); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Bath additive; circulatory disorders.

Leukona-Rheuma-Bad *Richter, Austria.*
Pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Leukona-Rheuma-Bad N *Atzinger, Ger.†.*
Methyl salicylate (p.85·3); turpentine oil (p.2406·3); Norway spruce oil.
Bath additive; rheumatic disorders.

Leukona-Rheumasalbe *Atzinger, Ger.†.*
Camphor (p.2273·2); turpentine oil (p.2406·3); rosemary oil (p.2381·3).
Cold symptoms; frostbite; rheumatism; soft-tissue injury.

Leukona-Stoffwechsel-Bad *Atzinger, Ger.†.*
Juniper oil (p.2328·3).
Allergic skin disorders; bath additive; metabolic disorders.

Leukona-Sulfomoor-Bad *Richter, Austria†.*
Sulfurated potash (p.1614·3); colloidal sulfur (p.1614·1); sodium humate (p.2389·3); peat.
Musculoskeletal and joint disorders; skin disorders.

Leukona-Sulfomoor-Bad F *Atzinger, Ger.†.*
Sodium humate (p.2389·3).
Bath additive; musculoskeletal and joint disorders.

Leukona-Wundsalbe *Atzinger, Ger.†.*
Cod-liver oil (p.1935·2); hamamelis water (p.2318·2); allantoin (p.1588·1).
Wounds.

LeukoNorm *CytoChemia, Ger.*
Leucocytes (p.1073·2).
Immunological disorders.

Leukoprol *Kyowa, Jpn.*
Mirimostim (p.1073·3).
Neutropenia.

LeukoScan *Immunomedics, Cz.; Altana, Ital.; Immunomedics, Neth.; Immunomedics, Port.*
Technetium-99m (p.2055·3) sulesomab.
Bone scanning in osteomyelitis.

Leulin *Baxter, Mex.†.*
Methotrexate sodium (p.745·2).
Malignant neoplasms.

Leumostin *Pharmacia, Arg.†.*
Lenograstim (p.1073·1).
Neutropenia.

Leunase *Aventis, Austral.; Kyowa, Hong Kong; Biochem, India; Indra Sakti, Indon.; Kyowa, Jpn; Kyowa, Malaysia; Sanfer, Mex.; Aventis, NZ; Kyowa Hakko, Philipp.; Kyowa, Singapore; Kyowa, Thai.; Onko, Turk.*
Asparaginase (colaspase) (p.682·1).
Acute leukaemias; malignant lymphomas.

Leuplin *Takeda, Jpn.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; precocious puberty; prostatic cancer; uterine myoma.

Leuprol *Zaraco, Gr.*
⊗ Leuprorelin (p.2111·1).
Endometriosis; prostatic cancer; uterine fibroids.

Leustat *Janssen-Cilag, Arg.; Janssen-Cilag, UK.*
Cladribine (p.701·1).
Chronic lymphocytic leukaemia; hairy-cell leukaemia; lymphoma.

Leustatin *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Cilag, Hong Kong; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.†; Ortho Biotech, USA; Janssen-Cilag, Venez.*
Cladribine (p.701·1).
Chronic lymphocytic leukaemia; hairy-cell leukaemia; non-Hodgkins lymphoma.

Leustatine *Janssen-Cilag, Fr.*
Cladribine (p.701·1).
Hairy-cell leukaemia.

Leutrol *Abbott, Braz.; Caber, Ital.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Levacet *Pharmakon, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1); salicylamide (p.121·2); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Levadol *Italfar, Ital.*
Paracetamol (p.108·1).
Fever; pain.

Levalastine *Biomedica-Chemica, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Levall *Auriga, USA.*
Phenylephrine hydrochloride (p.1568·1); pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Formerly contained phenylephrine hydrochloride, hydrocodone tartrate, and guaifenesin.
Coughs.

Levall 5.0 *Auriga, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Levall 12 *Auriga, USA.*
Pentoxyverine tannate (p.1567·3); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Levam *Lafedar, Arg.*
Levamisole hydrochloride (p.147·2).

Levamin
Note. This name is used for preparations of different composition.
Genepharm, Gr.
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Pisa, Mex.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Levant *Focus, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Levantol Procaina *Mertens, Arg.*
Calcium phosphate; methionine; pyritinol hydrochloride; procaine hydrochloride; vitamin B substances (p.1922·1).
Asthenia; mental function impairment.

Levanxol *Strallhofer, Austria.*
Temazepam (p.1030·1).
Anxiety disorders; sleep disorders.

Levaquin *Janssen-Cilag, Arg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Ortho McNeil, USA; Janssen-Cilag, Venez.*
Levofloxacin (p.292·2).
Bacterial infections.

Levars *Arsmedendi, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Levatol *Schwarz, USA.*
⊗ Penbutolol sulfate (p.1366·2).
Hypertension.

Levaxin *Nycomed, Norw.; Nycomed, Swed.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; thyroid cancer.

Levazide *Pyridam, Indon.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Levbid *Alaven, USA.*
Hyoscyamine sulfate (p.1736·1).
Biliary and renal colic; gastrointestinal disorders; parkinsonism; rhinitis; urinary-tract disorders.

Levedad *Valeant, Arg.*
Diclofenac sodium (p.44·3).
Postoperative eye inflammation.

Levedo *Fontovit, Braz.*
Brewer's yeast (p.1998·3).

Leveglutan *Bunker, Braz.*
Dried yeast; vitamin B substances (p.1922·1).
Dietary supplement.

Level *Biolab Sanus, Braz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Level Up *Garden House, Arg.*
Ginseng; minerals (p.1922·1).
Dietary supplement.

Levelina *Ern, Spain.*
Bifonazole (p.527·3).
Fungal skin and nail infections.

Levemir *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, UK; Novo Nordisk, USA.*
⊗ Insulin detemir (p.449·3).
Diabetes mellitus.

Leverctin *Sigma, Braz.*
Ivermectin (p.145·2).

Leveron *Vesco, Thai.*
Silymarin (p.1452·2).
Liver disorders.

Leviax *Aventis, Norw.†.*
Telithromycin (p.345·3).
Bacterial infections.

Levicor *IFET (ΙΦΕΤ), Gr.†.*
⊗ Metaraminol tartrate (p.1333·2).
Hypotension.

Leviden *Toho, Hong Kong.*
Liver hydrolysate (p.2337·3).
Liver disorders.

Levifusa *Ifusa, Mex.*
Yeast (p.1998·3).
Dietary supplement.

Levinan *Link, UK.*
Levomepromazine maleate (p.1003·1).
Nausea and vomiting.

Leviogel *Chefaro, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Levistan *Giempi, Venez.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Levital Plus *SIFFRA, Ital.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3); centella (p.1592·3); melilot (p.2339·2); aesculus (p.2248·2); ananas sativus; myrtillus (p.2349·3).
Circulatory disorders.

Levitra *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; GSK, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Norw.; GSK, Norw.; Bayer, Philipp.; Bayer, Pol.; Bayer, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; GSK, USA; Schering-Plough, USA; Bayer, Venez.*
Vardenafil hydrochloride (p.2199·3).
Erectile dysfunction.

Levium *Hexal, Ger.*
Levomepromazine maleate (p.1003·1).
Pain; psychoses.

Levlen *Berlipharm, Neth.†; Berlex, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Levlen ED *Schering, Austral.; Bayer, NZ.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Levlite *Berlex, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Levo *Unipharm, Israel.*
Levofloxacin (p.292·2).
Bacterial infections.

Levobens *Viatris, Austria.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Levobeta C *Betapharm, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levobren *GiEnne, Ital.*
Levosulpiride (p.1028·3).
Gastrointestinal disorders; headache; migraine; nausea and vomiting; vertigo.

Levo-C *Aliud, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levocar *Stada, Austria.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levocarb *Biolab Sanus, Braz.; Teva, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levocarnil *Sigma-Tau, Fr.; Biospray, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Levocarnin *Sintofarma, Braz.†.*
Carnitine (p.1932·2).
Nutritional supplement.

Levocarvit *Mitim, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Levocide *Cadila, India.*
Levofloxacin (p.292·2).
Bacterial infections.

Levocin *Sanbe, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Levocina *Cryopharma, Mex.*
Levomepromazine maleate (p.1003·1).
Psychoses.

Levocof *Valeant, Mex.*
Levodropropizine (p.1557·3).
Coughs.

Levocomp *Hexal, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levodex *Dexxon, Israel.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris.

Levodexan *Grin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Infected eye disorders.

Levodop *Neuraxpharm, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levodopa Comp *ABZ, Ger.; CT, Ger.; Ratiopharm, Ger.; TAD, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levodopa comp B *Stada, Ger.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Levodopa comp C *Stada, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levodopa-Carbi *Azupharma, Ger.†.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levo-Dromoran *ICN, USA†.*
Levorphanol tartrate (p.77·2).
Pain.

Levofamil *Andromaco, Chile†.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levofenil *Grin, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3); phenylephrine hydrochloride (p.1568·1).
Inflammatory eye infections.

Levoff *Biochem, India.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoflox *Cipla, India.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoflox Oz Kit *Cipla, India.*
Levofloxacin (p.292·2); ornidazole (p.843·1).
Bacterial infections.

Levofolene *Schering, Ital.*
Calcium levofolinate (p.1943·3).
Antidote to folic acid antagonists; folate deficiency anaemia.

Levofolic *Medac, Cz.*
Sodium levofolinate (p.1944·1).
Adjunct to fluorouracil therapy; reduction of folate antagonist toxicity.

Levogastrol *Salvat, Spain.*
Levosulpiride (p.1028·3).
Dyspepsia.

Levoglutil Vitaminado *Spedrog, Arg.*
Glutamine; vitamin B ; vitamin B ; calcium lactate; magnesium gluconate (p.1922·1).
Dietary supplement.

Levograf *Schering, Spain.*
Galactose (p.1481·1).
Ultrasound contrast medium.

Levogynon *Schering, Ger.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Levolac *Leiras, Fin.; Fresenius Kabi, Norw.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Levolam *Lamsa, Arg.*
Levomepromazine (p.1002·3).
Psychoses.

Levolin *Cipla, India.*
⊗ Levosalbutamol hydrochloride (p.1125·3).
Asthma; bronchospasm.

Levomecol *Akrikhin, Rus.; Nizhpharm, Rus.*
Chloramphenicol (p.239·3); methyluracil.
Bacterial skin infections.

Levomed *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Thai.†.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levomet
Note.This name is used for preparations of different composition.
Unison, Hong Kong; Unison, Singapore; Unison, Thai.
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Chiesi, Ital.†.
Melevodopa hydrochloride (p.808·3).
Parkinsonism.

Levomine *Cinetic, Arg.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; allergic skin disorders; pruritus.

Levomol *Cipla, India.*
Levamisole (p.147·2).
Worm infections.

Levomycetin *Chew, Thai.*
Chloramphenicol (p.239·3).
Bacterial infections.

Levonelle *Berlipharm, Irl.; Schering, Ital.; Bayer, NZ; Medimpex, Port.; Schering, UK.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Levonis *TS, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Levonor *Polfa Warszawa, Pol.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Circulatory failure; shock; vasoconstrictor in local anaesthesia.

Levonova *Schering, Denm.; Leiras, Fin.†; Schering, Norw.; Schering, Swed.*
Levonorgestrel (p.2121·2).
Menorrhagia; menstrual disorders; progestogen-releasing intra-uterine contraceptive device.

Levopa *Wallace, India†.*
Levodopa (p.804·3).
Parkinsonism.

Levopa-C *Wallace, India†.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Levopar
Hexal, Ger.
Levodopa (p.804·3); benserazide (p.796·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Meprofarm, Indon.
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Levopar Plus *Teva, Israel.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Levophed *Abbott, Austral.; Abbott, Belg.; Abbott, Braz.; Hospira, Canad.; IFET (ΙΦΕΤ), Gr.; Abbott, Hong Kong†; Abbott, Indon.; Hospira, Irl.; Abbott, Israel; Abbott, Malaysia; InterMed, NZ; Abbott, Philipp.; Abbott, Singapore†; Abbott, Thai.; Hospira, USA.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Cardiac arrest; hypotension; shock.

Levophta *Chauvin, Fr.; Novartis Ophthalmics, Ger.†; Winzer, Ger.†.*
Levocabastine hydrochloride (p.583·1).
Allergic conjunctivitis.

Levoplus *Montefarmaco, Ital.*
⊗ Dietary fibre (p.1712·3); lactulose (p.1738·2); lactitol (p.1738·2); mannitol (p.1330·2).

Levopraid *Therabel, Belg.; Abbott, Ital.*
Levosulpiride (p.1028·3).
Depression; gastrointestinal disorders; headache; psychoses; psychosomatic syndromes; vertigo.

Levopront *Dompe, Cz.; Dompe, Hung.; Combiphar, Indon.; Dompe, Philipp.; Dompe, Pol.; Mack, Singapore†; Mack, Thai.; Abdi, Turk.; Zuoz, Venez.*
Levodropropizine (p.1557·3).
Cough.

Levoptin *Archifar, Thai.*
⊗ Chloramphenicol (p.239·3); prednisolone sodium phosphate (p.1541·2); naphazoline hydrochloride (p.1565·2).
Eye disorders.

Levora *Watson, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Levordiol *Sigma, Braz.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); pyridoxine hydrochloride (p.1978·2); 7 tablets, pyridoxine hydrochloride.
Triphasic oral contraceptive.

Levores *Novell, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Levorid *Cipla, India.*
Levocetirizine (p.583·2).
Allergic rhinitis; urticaria.

Levorid D *Cipla, India.*
Levocetirizine (p.583·2); pseudoephedrine (p.1571·2).
Allergic rhinitis.

Levorin *Blausiegel, Braz.*
Calcium levofolinate (p.1943·3).
Anaemias; antidote to folic acid antagonists.

Levosan *Sanus, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Levosin *Nizhpharm, Rus.*
Chloramphenicol (p.239·3); sulfadimethoxine (p.337·3); methyluracil; trimecaine (p.1872·3).
Skin infections.

Levostab *Formenti, Ital.*
Levocabastine hydrochloride (p.583·1).
Allergic conjunctivitis; allergic rhinitis.

Levotac *Cristalia, Braz.*
Levofloxacin (p.292·2).
Bacterial infections.

Levothroid *IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Spain; Forest Laboratories, USA.*
Levothyroxine sodium (p.2171·2).
Hypercholesterolaemia; hypothyroidism; TSH suppression.

Levothym *Lundbeck, Ger.†.*
Oxitriptan (p.414·1).
Neurological disorders.

Levothyrox *Merck-Lipha, Fr.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Levotiron *Abdi, Turk.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Levotonine *Panpharma, Fr.*
Oxitriptan (p.414·1).
Myoclonus.

Levotrin *GSK, Arg.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Hypothyroidism.

Levotuss *Therabel, Belg.; Arriani, Gr.; Dompe, Ital.; Dompe, Neth.; Neo-Farmaceutica, Port.; Stada, Spain.*
Levodropropizine (p.1557·3).
Cough.

Levovanox *Levofarma, Ital.*
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis.

Levovid *Bernofarm, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Levovist *Schering, Arg.†; Bayer, Austral.; Schering, Austria†; Berlex, Canad.†; Schering, Cz.†; Schering, Denm.†; Schering, Fin.†; Schering, Fr.; Schering, Ger.; Schering, Ital.; Schering, NZ; Schering, Neth.; Schering, Norw.†; Bayer, Port.; Schering, Spain; Schering, Swed.†; Schering, Switz.; Schering, UK†.*
Galactose (p.1481·1).
Contrast medium for echocardiography; Doppler sonography contrast medium; ultrasound contrast medium.

Levox *Westmont, Philipp.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoxacin *GSK, Ital.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoxal *Sandoz, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoxin *Apsen, Braz.*
Levofloxacin (p.292·2).
Bacterial infections.

Levoxyl *Jones, USA.*
Levothyroxine sodium (p.2171·2).
Formerly known as Levoxine.
Hypothyroidism; TSH suppression.

Levozin *Orion, Fin.*
Levomepromazine maleate (p.1003·1).
Agitation; insomnia; pain; psychoses.

Levozine *Cristalia, Braz.*
Levomepromazine maleate (p.1003·1).
Adjunct in general anaesthesia; pain in obstetrics; premedication; psychoses.

Levrix *Tecnifar, Port.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; urticaria.

Levron *Rontag, Arg.*
Levetiracetam (p.488·2).
Epilepsy.

Levroxa *Solus, India.*
Levetiracetam (p.488·2).
Epilepsy.

Levsin *Rivex, Canad.†; Schwarz, Hong Kong; Schwarz, USA.*
Hyoscyamine sulfate (p.1736·1).
Adjunct to hypotonic duodenography; anticholinesterase poisoning; biliary and renal colic; gastrointestinal and renal disorders associated with smooth muscle spasm; heart block; improvement of radiological visibility of the kidneys; neurogenic bladder; pancreatitis; parkinsonism; premedication; rhinitis.

Levsinex *Schwarz, USA.*
Hyoscyamine sulfate (p.1736·1).
Biliary and renal colic; gastrointestinal disorders; parkinsonism; rhinitis; urinary-tract disorders.

Levucal *Pasteur, Chile.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteomalacia; osteoporosis; rickets; tetany.

Levucal D *Pasteur, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Levudin *GD, Ital.†.*
Yeast (p.1998·3); betacarotene (p.1930·3).

Levulan Kerastick *DUSA, USA.*
Aminolevulinic acid hydrochloride (p.679·2).
Actinic keratoses.

Levulin L *Marvel, Rus.*
⊗ Insulin zinc suspension (crystalline 70%, amorphous 30%) (porcine) (p.443·2).
Diabetes mellitus.

Levulin N *Marvel, Rus.†.*
⊗ Isophane insulin (porcine) (p.443·2).
Diabetes mellitus.

Levulin R *Marvel, Rus.†.*
⊗ Neutral insulin (porcine) (p.443·2).
Diabetes mellitus.

Levulosado *Baxter, Spain†; Bieffe, Spain†.*
Fructose (p.1945·1).
Fluid and electrolyte disorders; liver disorders.

Levunolol *Luar, Arg.*
⊗ Levobunolol (p.1883·1).
Ocular hypertension.

Levure Or *Grimberg, Fr.*
Potassium bromoaurate; dried yeast (p.1998·3).
Rheumatic disorders.

Levurinetten *Novartis Consumer, Austria.*
Dried yeast (p.1998·3); vitamin B substances (p.1922·1).
Skin disorders.

Levurinetten N *Teofarma, Ger.†.*
Dried yeast (p.1998·3).
Appetite loss; skin disorders.

Levusid *Quesada, Arg.*
Mosapride citrate (p.1750·3).
Gastrointestinal motility disorders.

Levviax *Aventis, Cz.†; Aventis, Neth.†; Aventis, Port.†; Aventis, Spain†.*
Telithromycin (p.345·3).
Bacterial infections of the respiratory tract.

Lewensessens *Lennon, S.Afr.*
Aloes (p.1705·2); ginger (p.1732·3); rhubarb (p.1768·3); gentian (p.2310·3); myrrh (p.2349·2); galanga; turmeric (p.1473·2).
Constipation; gastric disorders.

Lewimycin *Lewison, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Lewinex *Lewison, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Lewixin *Lewison, Philipp.*
Amoxicillin (p.202·2).
Bacterial infections.

Lexa *Landson, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Lexacorton *Molex Ayus, Indon.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Lexacrol
Note.This name is used for preparations of different composition.
Molex Ayus, Indon.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; flatulence; gastric hyperacidity; peptic ulcer.

Molex Ayus, Indon.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Bloating; flatulence; gastric hyperacidity; peptic ulcer.

Lexadium *Molex Ayus, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lexahist *Molex Ayus, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic disorders; pruritus.

Lexalgin *Danlex, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Lexapram *Molex Ayus, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Lexapro *Lundbeck, Arg.; Lundbeck, Austral.; Lundbeck, Braz.; Lundbeck, Chile; Lundbeck, Hong Kong; Lundbeck, Irl.; Lundbeck, Malaysia; Lundbeck, Mex.; Healthcare Logistics, NZ; Lundbeck, Neth.; Lundbeck, Philipp.; Lundbeck, Pol.; Lundbeck, Singapore; Lundbeck, Thai.; Forest Pharmaceuticals, USA; Abbott, Venez.*
Escitalopram oxalate (p.391·1).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Lexaprofen *Molex Ayus, Indon.*
Ibuprofen (p.64·2).
Fever; pain; rheumatoid arthritis.

Lexat *Eagle, Austral.†.*
Bile salts (p.2266·2); pancreatin (p.2360·1); boldo (p.2267·2); greater celandine (p.2317·1); aloes (p.1705·2); agar (p.2140·3); sanguinaria (p.2383·2).
Constipation; digestive system disorders.

Lexatin *Roche, Spain.*
Bromazepam (p.964·3).
Anxiety.

Lexaurin *KRKA, Cz.*
Bromazepam (p.964·3).
Anxiety disorders; depression; insomnia.

Lexavit *Molex Ayus, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Lexavite *Bajer, Arg.†.*
Liquid paraffin (p.2030·3).
Bowel evacuation.

Lexavon *Molex Ayus, Indon.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Lexcof
Note.This name is used for preparations of different composition.
Cipla, India.
Lozenges: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Cipla, India.
Syrup: Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine (p.1569·2); chlorphenamine maleate (p.571·3).
Coughs.

Lexcomet *Molex Ayus, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Lexemin *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lexet *Lemery, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Lexfor *TNP, Thai.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Lexifal *Inquifave, Venez.†.*
⊗ Flumetasone (p.1531·1).
Eczema.

Lexiflox *Duopharma, Hong Kong.*
Norfloxacin (p.309·2).
Bacterial infections.

Lexil *Roche, Ital.*
Bromazepam (p.964·3); propantheline bromide (p.1764·3).
Gastrointestinal disorders.

Lexilium *Remedica, Hong Kong.*
Bromazepam (p.964·3).
Anxiety.

Lexin *Biotenk, Arg.; Teuto, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Lexincef *Serra Pamies, Spain.*
Cefalexin (p.218·2).
Bacterial infections.

Lexinor *AstraZeneca, Fin.†; AstraZeneca, Hong Kong†; AstraZeneca, Malaysia†; AstraZeneca, Philipp.; AstraZeneca, Swed.; AstraZeneca, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Lexipad *Korea United, Philipp.*
Cefadroxil (p.218·1).
Bacterial infections.

Lexis *Mintlab, Chile†.*
Clindamycin phosphate (p.251·2).
Bacterial skin infections.

Lexiscan *Astellas, USA.*
Regadenoson (p.1387·1).
Coronary vasodilator during radionuclide myocardial perfusion imaging.

Lexiva *GSK, Israel; GSK, USA.*
Fosamprenavir calcium (p.877·1).
HIV infection.

Lexivit *Lewison, Philipp.*
Vitamins; taurine; lysine (p.1922·1).

Lexmodine *Molex Ayus, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Lexo *Flupal, Venez.*
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Cough.

Lexobene *Merckle, Ger.†.*
Diclofenac sodium (p.44·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis; pain.

Lexomil *Roche, Fr.*
Bromazepam (p.964·3).
Alcohol withdrawal syndrome; anxiety.

Lexosedin *Union Health, Ital.*
Butamirate citrate (p.1553·1).
Coughs.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lexostad Stada, Ger.
Bromazepam (p.964·3).
Anxiety disorders; insomnia.

Lexotan Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Denm.; Roche, Hong Kong; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Thai.
Bromazepam (p.964·3).
Anxiety; insomnia; obsessive-compulsive disorders; phobias; psychosomatic disorders.

Lexotanil Roche, Arg.; Roche, Austria; Roche, Chile; Roche, Ger.; Roche, Gr.; Roche, Neth.; Roche, Switz.; Roche, Venez.
Bromazepam (p.964·3).
Anxiety; insomnia; psychosomatic disorders.

Lexpec Rosemont, UK.
Folic acid (p.1940·1).
Anaemias.

Lexpec with Iron Rosemont, UK†.
Ferric ammonium citrate (p.1938·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Lexpec with Iron-M Rosemont, UK†.
Ferric ammonium citrate (p.1938·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Lexpram Arlex, Mex.
Meloxicam (p.80·3).
Inflammation.

Lextarol Pharmacypria, Gr.
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Lextor Casasco, Arg.
Escitalopram oxalate (p.391·1).
Depression.

Lextrasa Maffioli, Ital.
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Lexum Westmont, Philipp.
Cefalexin (p.218·2).
Bacterial infections.

Lexxel Astra, USA.
Enalapril maleate (p.1276·1); felodipine (p.1285·3).
Hypertension.

Lexxema Italfarmaco, Spain.
⊗ Methylprednisolone aceponate (p.1539·1).
Skin disorders.

Lezepan Neo Quimica, Braz.
Bromazepam (p.964·3).
Epilepsy; sedative; skeletal muscle spasm.

Lezidim Lemery, Mex.†.
Ceftazidime (p.234·1).
Bacterial infections.

Lezole Kampel Martian, Arg.†.
⊗ Anastrozole (p.681·2).
Malignant neoplasms.

Lezpain YSP, Malaysia.
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

LF 100 Dicofarm, Ital.
Nutritional supplement (p.1922·1).

L-G Vita Mertens, Arg.†.
Calcium phosphate; methionine; pyritinol hydrochloride; vitamin B substances (p.1922·1).
Asthenia; mental function impairment.

L-Gel Medical Industries, Austral.†.
Lubricating gel.

Lghyal LG Life Sciences, India.
Sodium hyaluronate (p.2320·1).
Adjunct in cataract surgery.

LGNil Cadila, India.
Cetirizine (p.571·1).

LH Predict Aptus, NZ†.
Fertility test (p.2372·1).

Li 450 Ziethen, Ger.†.
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Liaderyl Kleva, Gr.
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Lialda Shire, USA.
Mesalazine (p.1745·1).
Ulcerative colitis.

Liamycin Coup, Gr.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Liatriz Solfran, Mex.
Meclozine (p.585·1); pyridoxine (p.1979·1).
Nausea and vomiting.

Libalaks Liba, Turk.
Sorbitol (p.1965·1); Tween 80 (p.1919·2); sodium citrate (p.1673·3); glycerol (p.2314·2).
Constipation.

Libamic Zafiro, Mex.
Amikacin sulfate (p.200·3).
Bacterial infections.

Libavit B_6 Liba, Turk.
Pyridoxine hydrochloride (p.1978·2).
Idiopathic sideroblastic anaemia; isoniazid neuropathy; premenstrual syndrome; vitamin B deficiency.

Libavit K Liba, Turk.
Menadione sodium bisulfite (p.1995·3).
Vitamin K deficiency.

Libeeda for Men Nutravite, Canad.
Bee pollen; damiana; ginseng; tribulus terrestris (p.1922·1).

Libeeda for Women Nutravite, Canad.
Damiana; ginkgo biloba; red clover; tribulus terrestris; wild yam (p.1922·1).

Libefor Quim-Far, Venez.
Vitamin B substances (p.1922·1).

Libeli Grunenthal, Port.
Ethinylestradiol (p.2101·3); chlormadinone acetate (p.2084·3).
Combined oral contraceptive.

Libenar GSK Consumer, Ital.; GSK Consumer, Port.†.
Sodium chloride (p.1686·1).
Nasal dryness; nasal hygiene.

Libenta Liba, Turk.
Sodium calcium edetate (p.1462·2).
Heavy metal poisoning.

Libeprosta Pharmafabre (Φαρμαφαμπρ), Gr.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Liberal Asian Pharm, Thai.
Flunarizine hydrochloride (p.580·2).
Cerebrovascular disorders; vestibular disorders.

Liberan
Note. This name is used for preparations of different composition.
Apsen, Braz.
Bethanechol (p.2266·1).
Urinary retention.

AF, Mex.
Simeticone (p.1770·2).
Flatulence.

Liberate Biem, Turk.; SNBTS, UK†.
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Liberato Schering, Canad.
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Formerly known as Claritin Liberator.
Allergic rhinitis.

Liberaxim Pisa, Mex.
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Liberel Kwizda, Austria.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Liberen Lisapharma, Ital.†.
Dextropropoxyphene hydrochloride (p.40·1).
Pain; renal and hepatic colic.

Liberim T SNBTS, UK†.
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Liberol Baby N Doetsch, Grether, Switz.
Eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); star anise oil (p.2392·2); juniper oil (p.2328·3).
Cold symptoms.

Liberol Bain Mavena, Switz.†.
Thyme oil (p.2401·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); niaouli oil (p.2351·3).
Coughs and cold symptoms.

Liberol Dragees contre la toux Mavena, Switz.†.
Thyme (p.2401·1); ivy (p.2328·1).
Coughs.

Liberol N Doetsch, Grether, Switz.
Camphor (p.2273·2); pumilio pine oil (p.2376·3); thyme oil (p.2401·2); eucalyptus oil (p.2301·2).
Cold symptoms.

Liberol Pastilles contre la toux Mavena, Switz.†.
Thyme (p.2401·1); senega root (p.1572·3).
Coughs.

Liberol Sirop contre la toux Mavena, Switz.†.
Thyme (p.2401·1); ivy (p.2328·1); senega root (p.1572·3); liquorice (p.1740·3).
Coughs.

Liberprost LKM, Arg.
Bicalutamide (p.686·2).

Libertin Robugen, Ger.†; Iromedica, Switz.†.
St John's wort (p.422·3).
Anxiety; depression.

Libertrim AF, Mex.
Trimebutine (p.2404·3) or trimebutine maleate (p.2404·3).
Gastrointestinal motility disorders; irritable bowel syndrome.

Libertrim SDP AF, Mex.
Trimebutine (p.2404·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Libexin Chinoin, Cz.†; Sanofi-Aventis, Hung.; Khandelwal, India; Chinoin, Rus.
Prenoxdiazine hydrochloride (p.1571·1).
Cough.

Libexin Mucolitico Teofarma, Ital.
Prenoxdiazine hibenzate (p.1571·1); carbocisteine (p.1553·2).
Coughs.

Libiam Libbs, Braz.
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Libidomega Cantassium Co., UK.
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Libiocid Rayere, Mex.
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Libiplus Delta, Braz.
Vitamins; yohimbine hydrochloride (p.2200·2); glutamic acid; calcium magnesium fytate (p.1922·1).
Tonic.

Libkol Saba, Turk.
Chlordiazepoxide hydrochloride (p.968·2); pipenzolate bromide (p.1762·2).
Alcohol withdrawal syndrome; anxiety.

Liblan YSP, Malaysia.
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Enterocolitis; irritable bowel syndrome; peptic ulcer.

Libolar Quim-Far, Venez.
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Libracor Merck, Port.
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Libradin Sigma-Tau, Ital.; Astellas, Neth.; Astellas, Port.; Andromaco, Spain.
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Librax
Valeant, Canad.; Valeant, USA.
Chlordiazepoxide hydrochloride (p.968·2); clidinium bromide (p.1722·1).
Formerly contained chlordiazepoxide hydrochloride and hyoscine methonitrate in the *USA*.
Gastrointestinal disorders associated with anxiety; irritable bowel syndrome; peptic ulcer (adjunct).

ICN, Fin.; CSP, Fr.; IFET (ΙΦΕΤ), Gr.; Lapapharm (Λαπαφαρμ), Gr.; Valeant, Hong Kong; Combiphar, Indon.; Valeant, Indon.; ICN, Ital.; Valeant, Port.; Pharmaco, S.Afr.; Valeant, Singapore; Valeant, Switz.; ICN, Thai.; Onko, Turk.; Farma, Venez.
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Alcohol withdrawal syndrome; anxiety; autonomic symptoms of anxiety and tension; biliary dyskinesia; dysmenorrhoea; dyspepsia; gastrointestinal spasm; irritable bowel syndrome; irritable colon; nocturnal enuresis; peptic ulcer; smooth muscle spasm; ureteric spasm.

Libraxin Valeant, Arg.; Raffo, Chile.
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Formerly known as Librax in *Arg.*
Colitis; gastrointestinal and genitourinary disorders associated with anxiety; irritable colon; nocturnal enuresis; peptic ulcer; smooth muscle spasm.

Librentin
Westmont, Indon.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Westmont, Philipp.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Libritabs Roche Products, USA†.
Chlordiazepoxide (p.968·1).
Anxiety.

Librium
Valeant, Ger.; Valeant, Hong Kong; Teva, Hung.; Piramal, India; Combiphar, Indon.; Valeant, Indon.; Valeant, Irl.; Pharmaco, S.Afr.
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety; insomnia; skeletal muscle spasm.

ICN, Ital.; ICN, UK; ICN, USA.
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety; insomnia; premedication; skeletal muscle spasm.

Librocef Hexpharm, Indon.
Cefadroxil (p.218·1).
Bacterial infections.

Librocol Lagap, Switz.
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Dysmenorrhoea; nocturnal enuresis; smooth muscle spasm.

Librodan Hexpharm, Indon.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Librofem LPC, UK.
Ibuprofen (p.64·2).
Fever; pain.

Libroman Dekaz, Gr.
Ketoconazole (p.539·1).
Fungal scalp disorders.

Libronil Hexpharm, Indon.
Glibenclamide (p.440·1).
Diabetes mellitus.

Libronil-R Coup, Gr.
Bromazepam (p.964·3).
Anxiety disorders.

Librozym Hexpharm, Indon.
Amylase (p.2256·3); pancreatin (p.2360·1); pepsin (p.2365·1); Javanese turmeric (p.2406·3).
Digestive disorders.

Librozym Plus Hexpharm, Indon.
Amylase (p.2256·3); pancreatin (p.2360·1); pepsin (p.2365·1); simeticone (p.1770·2).
Digestive disorders.

Lic Polvo Rowe-Fleming, Venez.†.
Macrogol (p.2336·1); electrolytes (p.1667·1).
Bowel evacuation.

Licab Torrent, India.
Lithium carbonate (p.401·3).
Bipolar disorder; hypomania; mania.

Licain DeltaSelect, Ger.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Licarb RX, Thai.
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Licarbium Rekah, Israel.
Lithium carbonate (p.401·3).
Bipolar disorder.

Lice Blaster Douglas, NZ.
Adhatoda vasica; echinacea (p.2298·1); melaleuca oil (p.2338·2); stemona sessifolia root.
Pediculosis.

Lice Care ICM, Singapore.
Malathion (p.2046·1).
Pediculosis; scabies.

Lice Rid Florafaun, Austral.†.
Malathion (Maldison) (p.2046·1).
Pediculosis.

Licetrol Stanley, Canad.†.
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Lichtena UCB, Singapore†.
Emollient.
Dry skin.

Licide Reese, USA.
Pyrethrum (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Licilon Sanval, Braz.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Licla Daewon, Hong Kong.
Gliclazide (p.440·3).
Diabetes mellitus.

Licobevit Berlico Mulia, Indon.
Thiamine nitrate (p.1976·2).
Vitamin B deficiency.

Licobion Berlico Mulia, Indon.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Peripheral nervous system disorders; vitamin B deficiency.

Licodexon Berlico Mulia, Indon.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Licodril Berlico Mulia, Indon.
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Cough.

Licodril DMP Berlico Mulia, Indon.
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough.

Licofel Berlico Mulia, Indon.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Licoften Remedica, Malaysia.
Ketotifen fumarate (p.582·2).
Allergic disorders; asthma.

Licogenta Berlico Mulia, Indon.
Gentamicin sulfate (p.282·1).
Skin infections.

Licogin Berlico Mulia, Indon.
Dipyrone (p.49·2).
Pain.

Licokalk Berlico Mulia, Indon.
Calcium lactate (p.1676·1).
Calcium deficiency.

Licokalk Plus Berlico Mulia, Indon.
Calcium lactate (p.1676·1); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Licoklin Berlico Mulia, Indon.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Licoklor Berlico Mulia, Indon.
Chloramphenicol (p.239·3).
Bacterial infections.

Licomet Berlico Mulia, Indon.
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Liconam Berlico Mulia, Indon.
Pyridoxine hydrochloride (p.1978·2).
Isoniazid-induced peripheral neuritis; vitamin B deficiency.

Liconar Biolab, Singapore; Biolab, Thai.†.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Licopec Berlico Mulia, Indon.
Activated attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Licopene Herbarium, Braz.
Lycopene; vitamin E; betacarotene (p.1922·1).
Dietary supplement.

Licopenox Sigma, Arg.
Lycopene (p.2335·2).
Antoxidant.

Licopid Peptek, Rus.
GMDP (p.2316·2).
Secondary immunodeficiency.

Licoplex Berlico Mulia, Indon.
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Licoprima Berlico Mulia, Indon.
Co-trimoxazole (p.258·1).
Bacterial infections; toxoplasmosis.

Licoprox Berlico Mulia, Indon.
Ciprofloxacin (p.243·3).
Bacterial infections.

Licoric Berlico Mulia, Indon.
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Licosolon Berlico Mulia, Indon.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Licostan Berlico Mulia, Indon.
Mefenamic acid (p.80·1).
Pain.

Licostrata Cantabria, Spain.
Hydroquinone (p.1598·2).
Hyperpigmentation.

Licovit Ativus, Braz.
Vitamin A (p.1971·2); vitamin E (p.1992·2); lycopene (p.2335·2).
Skin disorders.

Licrease Zambon, Fr.†.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Lictora Tolmann, Philipp.
Co-trimoxazole (p.258·1).
Bacterial infections.

Lictyn Sandoz, Austria; Sandoz, Mex.
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Licuagen Elea, Arg.
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Licuamon Merck, Arg.
Aspirin (p.20·3); dipyridamole (p.1268·1).
Atherosclerosis; thromboembolic disorders.

Lidaltrin Lacer, Spain.
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Lidaltrin Diu Lacer, Spain.
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

LidaMantle Doak, USA.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

LidaMantle HC Doak, USA.
⊗ Lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2).
Skin disorders.

Lidanil Novartis, Turk.
Mesoridazine (p.1007·1).
Agitation; anxiety; behaviour disorders.

Lidaprim Nycomed, Austria; Nycomed, Gr.; Nycomed, Hong Kong; Lisapharma, Ital.†; Nycomed, Rus.; Nycomed, Thai.†.
Sulfametrole (p.342·2); trimethoprim (p.355·2).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Lidatrim Nycomed, Neth.
Sulfametrole sodium (p.342·3); trimethoprim (p.355·2).
Bacterial infections.

Lidazon Vifor, Switz.
Cetylpyridinium chloride (p.1635·1); dichlorobenzyl alcohol (p.1642·1); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Lid-Care Novartis Ophthalmics, Austral.; Novartis, Canad.; Novartis, NZ; Novartis Ophthalmics, UK.
Eyelid cleanser.

Lidemol Medicis, Canad.; Stiefel, Philipp.
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Lidene Cooperation Pharmaceutique, Fr.
Doxylamine succinate (p.578·2).
Insomnia.

Lidenix Nobel, Ital.†.
Nimesulide (p.95·3).
Fever; inflammation; pain.

Lident Adrenalina Cosmo, Ital.†.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Lident Andrenor Cosmo, Ital.†.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) and noradrenaline acid tartrate (p.1360·1) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Liderclox Ecobi, Ital.
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Liderma Medika, Switz.
Isotretinoin (p.1599·2).
Acne.

Liderman Jacoby, Austria.
Oxiconazole nitrate (p.544·2).
Fungal and Gram-positive bacterial skin infections.

Lidersoft Higate, Arg.†.
Marine algae; centella (p.1592·3).

Lidesthesin Ritsert, Ger.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidevine AJC, Rus.
Disulfiram (p.2296·2); adenine (p.2247·2); nicotinamide (p.1957·3).
Chronic alcoholism.

Lidex Yamanouchi, Belg.†; Medicis, Canad.; Minerva (Μινερβα), Gr.; Stiefel, Philipp.; MD, Singapore†; Medicis, USA.
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Lidex NGN Stiefel, Philipp.
⊗ Fluocinonide (p.1532·1); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Lidial Bunker, Braz.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidil Roemmers, Arg.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis; nasal congestion.

Lidil Cort Roemmers, Arg.
⊗ Fluticasone propionate (p.1533·2).
Nasal polyps; rhinitis.

Lido Spray Ritter, Thai.†.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lido Tea Trima, Israel.
Senna (p.1769·2); caraway (p.2276·3); liquorice (p.1740·3); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Constipation.

Lidobag Eczacibasi-Baxter, Turk.
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Lidocabbott Abbott, Braz.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Arrhythmias; local anaesthesia.

Lidocadren Teva, Israel†.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidocaina Spray Ogna, Ital.
Lidocaine (p.1862·3); cetrimide (p.1634·1).
Local anaesthesia and disinfection in dentistry.

Lidocalm Teuto, Braz.†.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidocard Orion, Fin.; Braun, Ger.
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; ventricular tachycardia.

Lidocation Weimer, Thai.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidocaton Weimer, Thai.†.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidochlor Unique, Rus.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidocorit Gebro, Austria.
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Lidocort Proct Northia, Arg.
⊗ Hydrocortisone (p.1535·2); lidocaine (p.1862·3).

Lidodan Odan, Canad.
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidodent Marmir, Pol.
Lidocaine hydrochloride (p.1862·3); cetylpyridinium chloride (p.1635·1).
Gingivitis; teething pain.

Lidoderm IFET (ΙΦΕΤ), Gr.; Endo, USA.
Lidocaine (p.1862·3).
Local anaesthesia; postherpetic neuralgia.

Lidodex Bernofarm, Indon.
Lidocaine hydrochloride (p.1862·3).
Subarachnoid anaesthesia.

Lidofast Angelini, Ital.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidogel Neo Quimica, Braz.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidogeyer Geyer, Braz.†.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidohex Bichsel, Switz.†.
Lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Catheterisation; endoscopy.

Lido-Hyal Ogna, Ital.; Wild, Switz.
Hyaluronidase (p.2321·1); lidocaine hydrochloride (p.1862·3).
Local anaesthesia; prophylaxis of soft-tissue disorders.

Lidoject Hexal, Ger.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidojet Uniao Quimica, Braz.†.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidomex Kowa, Jpn.
⊗ Prednisolone valeroacetate (p.1542·1).
Skin disorders.

Lidomol Molteni, Ital.†.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidomyxin Sandoz, Canad.
Polymyxin B sulfate (p.317·3); lidocaine hydrochloride (p.1862·3).
Ear infections, pain, and pruritus.

Lidonest AstraZeneca, Indon.
Lidocaine (p.1862·3).
Local anaesthesia.

Lidonostrum Nostrum, Port.
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Catheterisation; endoscopy; local anaesthesia; tracheal intubation.

LidoPen Meridian, Israel; Survival Technology, USA.
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Lidoposterin Kade, Pol.
Lidocaine (p.1862·3).
Anorectal disorders.

LidoPosterine Kade, Ger.
Lidocaine (p.1862·3).
Anorectal disorders.

Lidosel Biosel, Turk.
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Lidosen Senese, Ital.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidosense Rivers Edge, USA†.
Lidocaine (p.1862·3).
Local anaesthesia.

Lidosite Braun, USA.
Lidocaine hydrochloride (p.1862·3).
Adrenaline is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lidosporin
Farmoquimica, Braz.
Polymyxin B sulfate (p.317·3); lidocaine (p.1862·3).
Ear infections.

Pfizer Consumer, Canad.
Polymyxin B sulfate (p.317·3); lidocaine hydrochloride (p.1862·3).
Ear infections.

Lidospray Apsen, Braz.
Lidocaine (p.1862·3).
Local anaesthesia.

Lidoston Ariston, Braz.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lidoxin Unison, Hong Kong; Unison, Singapore; Unison, Thai.
Cloxacillin sodium (p.256·1).
Bacterial infections.

Lidrian Baxter, Ital.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Lievitosohn Antonetto, Ital.
Saccharomyces cerevisiae (p.1998·3); vitamin B substances (p.1922·1).
Restoration of normal gastrointestinal flora.

Lievitovit Nutrition & Sante, Ital.
Dried yeast (p.1998·3); vitamin B substances (p.1922·1).
Restoration of normal gastrointestinal flora.

Liexina Megat, Venez.†.
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Lifacilina LIFAERP, Braz.†.
Ampicillin (p.204·1).
Bacterial infections.

Lifactrin LIFAERP, Braz.†.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Lifalexin LIFAERP, Braz.†.
Cefalexin (p.218·2).
Bacterial infections.

Lifamox LIFAERP, Braz.†.
Amoxicillin (p.202·2).
Bacterial infections.

Lifar Grunenthal, Chile†.
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Lifaren LIFAERP, Braz.†.
Diclofenac (p.44·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Life Brand Soothing Bath Treatment McCaughey, Canad.
Avena (p.2262·1).
Dry skin.

Life Brand Sunblock Tanning Research, Canad.†.
SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2); oxybenzone (p.1608·3).
Formerly contained octinoxate, avobenzone, and homosalate.
Sunscreen.

Life Drops Potter's, UK.
Capsicum (p.2276·2); sambucus (p.2383·1); peppermint oil (p.1761·2).
Cold symptoms; sore throat.

Lifecell Pfizer, Arg.
⊗ Human menopausal gonadotrophins (p.2109·3).
Female and male infertility.

Lifechange Circulation Aid Cenovis, Austral.†.
Fish oil (p.1362·2); *dl*-alpha tocoferil acetate (p.1992·3); ginkgo biloba (p.2311·1); crataegus (p.2289·1).
Peripheral circulatory disorders; wounds.

Lifechange Menopause Formula Cenovis, Austral.†.
Soya bean (p.1965·3); red clover (p.2285·1).
Menopausal disorders.

Lifechange Mens Complex with Saw Palmetto Cenovis, Austral.†.
Zinc amino acid chelate (p.2000·1); cucurbita (p.2290·2); saw palmetto (p.2192·3).
Tonic.

Lifechange Multi Plus Antioxidant Cenovis, Austral.†.
Vitamins and minerals (p.1922·1); vitis vinifera (p.2316·3); ginkgo biloba (p.2311·1).
Peripheral circulatory disorders; vitamin and mineral deficiencies.

Lifegram Liferpal, Mex.
Gentamicin (p.284·2).
Bacterial infections.

Lifenac Liferpal, Mex.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Liferamin Liferpal, Mex.
Loratadine (p.583·3).
Hypersensitivity.

Lifercal Leovan, Gr.
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Lifermycin Leovan, Gr.
Amikacin sulfate (p.200·3).
Bacterial infections.

Liferol Master Pharma, Ital.
⊗ Formoterol fumarate (p.1122·1).
Bronchospasm.

Liferost Biostam (Βιοσταμ), Gr.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Liferxina Liferpal, Mex.
Ciprofloxacin (p.243·3).
Bacterial infections.

Liferzit Medinova (Μεντινοβα), Gr.
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Liferzol Liferpal, Mex.
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Lifestyles Ansell, Canad.; Ansell, NZ.
Nonoxinol 9 (p.1917·2).
Contraceptive.

Lifesystem Herbal Formula 1 Arthritic Aid Cenovis, Austral.†.
Celery (p.2278·3); juniper (p.2328·2); devil's claw root (p.39·1); salix (p.121·3).
Arthritic and rheumatic pain.

Lifesystem Herbal Formula 7 Liver Tonic Cenovis, Austral.†.
Milk thistle (p.1452·1); taraxacum (p.2395·1); cynara (p.2291·2); garlic (p.2309·2).
Digestive disorders; liver tonic.

Lifesystem Herbal Formula 6 For Peripheral Circulation Cenovis, Austral.†.
Ginkgo biloba (p.2311·1); crataegus (p.2289·1); zanthoxylum (p.2417·1); capsicum (p.2276·2); rutoside (p.2305·1); hesperidin (p.2304·3).
Peripheral circulatory disorders.

Lifesystem Herbal Formula 4 Women's Formula Cenovis, Austral.†.
Angelica (p.2258·1); cimicifuga (p.2282·1); blue cohosh (p.2267·2); pulsatilla (p.2376·3); agnus castus (p.2249·1).
Menstrual disorders.

Lifesystem Herbal Plus Formula 8 Echinacea Cenovis, Austral.†.
Echinacea (p.2298·1); *d*-alpha tocoferil acid succinate (p.1993·1); betacarotene (p.1930·3); ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1); zinc amino acid chelate (p.2000·1).
Minor upper respiratory-tract disorders; skin disorders; wounds.

Lifesystem Herbal Plus Formula 5 Eye Relief Cenovis, Austral.†.
Euphrasia officinalis (p.2301·3); ginkgo biloba (p.2311·1); betacarotene (p.1930·3); *d*-alpha tocoferil acid succinate (p.1993·1); ascorbic acid (p.1983·3); rutoside (p.2305·1); hesperidin (p.2304·3).
Eye strain; tired eyes.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lifesystem Herbal Plus Formula 11 Ginkgo *Cenovis, Austral.†.*
Ginkgo biloba (p.2311·1); ginger (p.1732·3); dibasic potassium phosphate (p.1682·2); magnesium oxide (p.1744·1).
Peripheral circulatory disorders; tonic.

Lifesystem Herbal Plus Formula 3 Male Formula *Cenovis, Austral.†.*
Eleutherococcus senticosis; equisetum; sarsaparilla; liquorice; damiana; zinc amino acid chelate; betacarotene; pyridoxine hydrochloride; *d*-alpha tocoferil acid succinate; magnesium oxide (p.1922·1).
Tonic.

Lifesystem Herbal Plus Formula 2 Valerian *Cenovis, Austral.†.*
Valerian (p.2410·1); passion flower (p.2363·2); dibasic potassium phosphate (p.1682·2); magnesium oxide (p.1744·1).
Nervous tension; sleep disorders.

Lifezar *Therapharma, Philipp.*
Losartan potassium (p.1326·1).
Hypertension.

Lifibron *Metiska, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lifin *Farmacom, Pol.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Lifo-Scrub *Braun, Neth.; Braun, Port.; Braun, Switz.*
Chlorhexidine gluconate (p.1635·3).
Skin and hand disinfection.

Lifter *Saval, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Lifurom *Lilly, S.Afr.†.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Lifurox
Note.This name is used for preparations of different composition.
Lilly, Cz.†; Elanco, Spain†.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Proula, Venez.
⊗ Furosemide (p.1292·1).
Forced diuresis; heart failure; hypertension; oedema.

Ligeral *Boehringer Ingelheim, Venez.†.*
Pirenzepine (p.1763·1).

Lightening *Mac, Ital.*
Glycolic acid (p.1598·1); fytic acid (p.1464·2).
Hyperpigmentation disorders.

Lightning Cough Remedy *Potter's, UK.*
Liquorice (p.1740·3); anise oil (p.2258·2).
Coughs.

Lignospan *Dentsply, Austral.†; Pharmodontal, Neth.; Septodont, Switz.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lignospan Special *Dental Warehouse, S.Afr.†.*
⊗ Lidocaine (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lignostab-A *Dentsply, UK†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ligofragmin *Pfizer, Arg.*
Dalteparin sodium (p.1255·1).
Thromboembolic disorders.

Ligramex *Fada, Arg.†.*
Cefuroxime (p.238·2).
Bacterial infections.

Likacin
Kleva, Gr.
Amikacin (p.200·2).
Bacterial infections.

Lisapharma, Hung.; Lisapharma, Ital.; Medifarm, Venez.
Amikacin sulfate (p.200·3).
Bacterial infections.

Likenil *Antibioticos, Spain.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Likuden M *Aventis, Ger.*
Griseofulvin (microfine) (p.535·2).
Fungal infections.

Likurmin *Kalbe, Indon.*
Curcuminoid; lysine hydrochloride; vitamin B substances (p.1922·1).
Nutritional supplement in children.

Lilac *Getz, Philipp.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Lilacillin *Takeda, Jpn†.*
Sulbenicillin sodium (p.335·2).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Liliam *Columbia, Mex.†.*
Hyoscine butylbromide (p.1734·1).

Li-Liquid *Rosemont, UK.*
Lithium citrate (p.401·3).
Depression; mania; psychoses.

Lilium Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Lillypen Rapide *Lilly, Fr.†.*
⊗ Insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Lima C *Cazi, Braz.*
Siparuna apiosyce; cetylpyridinium chloride (p.1635·1); ascorbic acid (p.1983·3).
Cold symptoms.

Limao Bravo
Note.This name is used for preparations of different composition.
Catarinense, Braz.†.
Siparuna guyanensis; aconite (p.2246·1); grindelia (p.2317·2); senega (p.1572·3); sodium benzoate (p.1630·2).
Respiratory-tract congestion.

Simoes, Braz.†.
Siparuna apiosyce; ascorbic acid (p.1983·3); cetylpyridinium chloride (p.1635·1).

Limao Bravo com Vitamina C *Cazi, Braz.†.*
Cetylpyridinium chloride (p.1635·1); vitamin C (p.1983·3); siparuna guyanensis.
Mouth and throat disorders.

Limarcan *Sanofi-Aventis, Port.*
Miglitol (p.454·3).
Diabetes mellitus.

Limarin *Serum Institute, India.*
Silymarin (p.1452·2).
Liver disorders.

Limas *Taisho, Jpn.*
Lithium carbonate (p.401·3).
Mania.

Limasip *Berlico Mulia, Indon.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Pain.

Limatic *Arlex, Mex.*
Lamotrigine (p.485·1).
Epilepsy.

Limbatrilin *Raffo, Chile.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Anxiety; depression.

Limbial *Chiesi, Ital.*
Oxazepam (p.1014·2).
Anxiety; insomnia; nervous disorders.

Limbitrol *ICN, Austria; Valeant, Braz.; ICN, Fin.; Pharmaco, S.Afr.; Valeant, Switz.; Valeant, USA.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Depression; insomnia; mixed anxiety depressive states.

Limbitryl *ICN, Ital.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide (p.968·1).
Mixed anxiety depressive states.

Limbrel *Primus, USA.*
Flavocoxid (p.2304·1).
Osteoarthritis.

Limbritol *Combiphar, Indon.; Valeant, Indon.*
Chlordiazepoxide (p.968·1); amitriptyline (p.376·1).
Mixed anxiety depressive states.

Limcee *Sarabhai Piramal, India.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Limclair *Sinclair, Irl.; Durbin, UK†.*
Trisodium edetate (p.1463·3).
Corneal opacities; hypercalcaemia; parathyroidism.

Limectant *Maurino, Arg.*
Sodium laurilsulfate (p.2138·3)(p.1622·2).
Cleansing solution for soft contact lenses.

Limed *Medifive, Thai.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Limeral *Actavis, Hung.; Actavis, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Limerix *Ivax, Arg.*
Haloperidol (p.1000·2).
Psychoses.

Limethason *Mitsubishi, Jpn; Mitsubishi, Malaysia†; Welfide, Singapore†; Mitsubishi, Thai.†.*
⊗ Dexamethasone palmitate (p.1526·3).
Rheumatoid arthritis.

Limexx *Kwizda, Austria.*
Tyrothricin (p.358·2); benzalkonium chloride (p.1629·1).
Mouth and throat disorders.

Limican *Pharmafar, Ital.*
Alizapride hydrochloride (p.1704·3).
Nausea and vomiting.

Limidrax *Serral, Mex.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Limifen *Janssen-Cilag, Spain.*
⊗ Alfentanil hydrochloride (p.16·2).
General anaesthesia.

Liminos *Glaxo Wellcome, Mex.†.*
Alosetron hydrochloride (p.1705·3).
Irritable bowel syndrome.

Limiprol *Sons, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Limit-X *UB, Switz.†.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Limonada Roge *Plata, Arg.*
Magnesium citrate (p.1743·2).
Constipation.

Limonade Asepta *Rougier, Canad.*
Sodium tartrate (p.1772·1).
Constipation.

Limonata Citromagnes *Mediplants, Gr.*
Magnesium carbonate (p.1743·1).
Dyspepsia.

Limone *CliniMed, UK.*
A deodorant spray for stoma care.

Limorid *Mepha, Cz.†.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; liver cirrhosis; oedema.

Limovan *Sanofi-Aventis, Spain.*
Zopiclone (p.1039·1).
Insomnia.

Limox *Biomedica-Chemica, Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Limoxin *Liferpal, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Limpacid *Bajer, Arg.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Limpidex *Sigma-Tau, Ital.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Limptar *Aventis, Austria; Cassella-med, Ger.†.*
Quinine sulfate (p.612·3); aminophylline (p.1114·2).
Leg cramp; night cramp.

Limptar N *Cassella-med, Ger.*
Quinine sulfate (p.612·3).
Night cramp.

Limustin *Landsteiner, Mex.*
Tacrolimus (p.1843·1).
Kidney or liver transplant rejection.

Linac *Ethica, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Linamin Plus *Seber, Port.†.*
Fursultiamine (p.1975·3); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3); pyridoxine hydrochloride (p.1978·2).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Neuralgia; neuritis; neuropathy; rheumatoid arthritis.

Linamon *KRKA, Cz.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Lin-Amox *Linson, Canad.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Linatecan *Tecnofarma, Chile.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Linatil *Sandoz, Fin.; Gea, Norw.†; Hexal, Swed.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Linatil Comp *Sandoz, Fin.; Hexal, Swed.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Linatron *Ariston, Braz.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Linazine *Asian Pharm, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Linbac *Hexal, Mex.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincaina *Braun, Port.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Lincil *Almirall, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Linco
Medikon, Indon.; ANB, Thai.; General Drugs, Thai.
Lincomycin (p.293·1).
Gram-positive bacterial infections.

Atlantic, Malaysia.
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lincocilin *Vesco, Thai.*
Lincomycin (p.293·1).
Gram-positive bacterial infections.

Lincocin *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pharmacia, Cz.†; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pharmacia, Ital.; Pfizer, Mex.; Pfizer, Philipp.; Pfizer, Pol.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Thai.; Eczacibasi, Turk.; Pharmacia Upjohn, USA; Pfizer, Venez.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincocina *Pfizer, Port.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincocine *Pfizer, Fr.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincoflan *Bunker, Braz.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincogin *Samakeephaesaj, Thai.†.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lincolan *Olan-Kemed, Thai.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lincomax *Millimed, Thai.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lincomed *Kocak, Turk.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincomiral *Ducto, Braz.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincomy *TNP, Thai.†.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lincomyn *Teuto, Braz.†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincono *Milano, Thai.*
Lincomycin (p.293·1).
Bacterial infections.

Lincopat *Parggon, Mex.*
Lincomycin (p.293·1).
Bacterial infections.

Lincophar *Pharos, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincoplax *Royton, Braz.†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincorex *Hyrex, USA†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincosa *LBS, Malaysia.*
Lincomycin hydrochloride (p.293·2).

Lincotax *Luper, Braz.†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lincovax *Delta, Braz.*
Lincomycin (p.293·1).
Gram-positive bacterial infections.

Lincover *Maver, Mex.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Linctifed *GSK, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Linctodyl *Pharmaceutical Enterprises, S.Afr.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); ammonium chloride (p.1551·3).
Coughs.

Linctosan *Garec, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Linctus Tussi Infans *Adcock Ingram, S.Afr.*
Ipecacuanha (p.1562·3); squill (p.1573·1); tolu (p.1574·2).
Coughs.

Lincyn
Note.This name is used for preparations of different composition.
Promed, Indon.
Lincomycin (p.293·1).
Bacterial infections.

Samjin, Philipp.; Unimex, Philipp.
Clindamycin phosphate (p.251·2).
Bacterial infections.

Lindacil *Sandoz, Mex.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Lindacyn *Coronet, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Lindan *Corsa, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Lindasol *Kleva, Gr.†.*
Clindamycin phosphate (p.251·2).
Acne.

Lindaxa *Zentiva, Cz.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Lindemicina *Greenpharma, Braz.*
Lincomycin (p.293·1).
Gram-positive bacterial infections.

Lindemil *Abbott, Spain.*
Alum (p.2254·1); benzalkonium chloride (p.1629·1).
Vaginal antiseptic; vulvovaginal trichomoniasis (adjuvant).

Lindigoa S *Riemser, Ger.†.*
Aesculus (p.2248·2); troxerutin (p.2305·1).
Haemorrhoids; thrombophlebitis; venous insufficiency.

Lindilan *Sanofi-Aventis, Venez.*
Ketoprofen (p.73·1).
Pain.

Lindilane *Grunenthal, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Lindine *Pharmaland, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Lindiol *Organon, Arg.†.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lindisc *Schering, Arg.; Schering, Braz.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Lindisc Duo *Berlimed, Braz.†.*
Patch 1, estradiol (p.2097·2); patch 2, estradiol; levonorgestrel (p.2121·2).

Lindofluid N *Lindopharm, Ger.*
Bornyl acetate (p.2269·1); α-pinene (p.2368·3); arnica (p.2260·2); melissa (p.2339·3).
Musculoskeletal, joint, and soft-tissue disorders.

Lindormin *Boehringer Ingelheim Promeco, Mex.*
Brotizolam (p.965·2).
Insomnia.

Lindoxyl *Meda, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Lindron *KRKA, Cz.; KRKA, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Lindynette *Gedeon Richter, Cz.; Sandoz, Denm.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Rus.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Linea F *Angelini, Ital.*
Benzalkonium chloride (p.1629·1); benzydamine hydrochloride (p.27·3).
Disinfection of wounds and burns.

Linervidol *Interdelta, Switz.†.*
Paracetamol (p.108·1); pyridoxine hydrochloride (p.1978·2); promethazine hydrochloride (p.588·2).
Agitation; fever; pain.

Linex *Lek, Rus.*
Lysates of *Lactobacillus acidophilus* (p.2372·3); *Bifidobacterium infantis* v.liberorum (p.2372·3); *Enterococcus faecium* (p.2372·3).
Restoration of gastrointestinal flora.

Linfarden *Continentales, Mex.*
Ambroxol hydrochloride (p.1550·3); loratadine (p.583·3).
Respiratory-tract disorders.

Linfocilin *Climax, Braz.†.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Linfoderm *Vargas, Venez.*
Conium maculatum; colchicum (p.558·1); digitalis (p.1258·3); podophyllum (p.1610·2); hyoscyamus (p.2323·3); calendula (p.2273·1).
Inflammation.

Linfogex *Climax, Braz.†.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Linfoglobulina *Genzyme, Arg.; Sanofi Pasteur, Chile; Genzyme, Spain; Zuoz, Venez.†.*
Antilymphocyte immunoglobulin (horse) (p.1817·3).
Aplastic anaemia; graft-versus-host disease; transplant rejection.

Linfoiodine *Noos, Ital.*
Arginine (p.1928·2); vitamin B substances (p.1922·1); potassium iodide (p.2169·2).

Linfol
Note. This name is used for preparations of different composition.
Omega, Arg.
Pessaries: ⊗ Metronidazole (p.837·1); nystatin (p.543·2); neomycin sulfate (p.305·1); dexamethasone (p.1526·1); lidocaine (p.1862·3).
Vulvovaginal infections.

Omega, Arg.
Tablets: Metronidazole (p.837·1); nystatin (p.543·2).
Anaerobic bacterial infections; protozoal infections.

Linfol Cicatrizante *Omega, Arg.*
Metronidazole (p.837·1); centella (p.1592·3); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Vulvovaginal infections.

Linfol Dermico *Omega, Arg.*
⊗ Ketoconazole (p.539·1); hydrocortisone (p.1535·2); gentamicin (p.284·2).
Bacterial and fungal skin infections.

Linfovenodren *Amnol, Ital.*
Coumarin (p.2288·2).
Circulatory disorders.

Ling Zhi PsP *Sahabat, Indon.*
Polysaccharide peptide from *Ganoderma lucidum.*
Immunomodulator.

Lingo *Siam Bheasach, Thai.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lingopen *Viofar, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Liniderm *Remexa, Mex.*
Almond oil (p.2252·2); calcium hydroxide (p.2272·2).
Burns; skin disorders.

Linimento Klari *Clariana, Spain†.*
Camphor (p.2273·2); amyl salicylate (p.19·3); rosemary oil (p.2381·3); sassafras oil (p.2383·3); turpentine oil (p.2406·3).
Rheumatic and muscle pain.

Linimento Naion *Puerto Galiano, Spain.*
⊗ Camphor (p.2273·2); alcohol (p.1625·2); salicylic acid (p.1612·2); turpentine; menthol (p.2340·1); soft soap (p.2139·2); capsicum (p.2276·2); methyl salicylate (p.85·3); rosemary (p.2381·2); lavender (p.2331·1).
Rheumatic and muscle pain.

Liniplant *Spitzner, Ger.*
Eucalyptus oil (p.2301·2); cajuput oil (p.2271·2).
Upper respiratory-tract disorders.

Linisol *Braun, Belg.†.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Linitul *Bama, Spain.*
Peru balsam (p.2365·3); castor oil.
Burns; wounds.

Link
Note. This name is used for preparations of different composition.
Alpharma, Denm.; Alpharma, Fin.; Alpharma, Norw.; Alpharma, Swed.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Savio, Ital.†.
Citicoline sodium (p.2283·3).
Parkinsonism.

Linkoles *Aroma, Turk.*
Lincomycin (p.293·1).
Bacterial infections.

Linkosol *Biosel, Turk.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Links-Glaukosan *Teclapharm, Ger.†.*
⊗ Adrenaline acid tartrate (p.1203·2); adrenalone hydrochloride (p.2248·2).
Glaucoma; inflammatory eye disorders.

Linkus *Herbion, Rus.*
Adhatoda vasica; liquorice (p.1740·3); piper longum; viola odorata; hyssop (p.2323·3); tormentil (p.2403·2); cordia latifolia; zizyphus jujuba; althaea (p.2253·3); onosma bracteatum.
Respiratory-tract disorders.

Linkus Lor *Herbion, Rus.*
Adhatoda vasica; liquorice (p.1740·3); piper longum; viola odorata; hyssop (p.2323·3); galanga.
Respiratory-tract disorders.

Linmycin *Atlantic, Thai.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Linna-Oil *Knop, Chile.*
Linseed oil (p.2334·1).
Essential fatty acid supplement.

Linodiab *Pyridam, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Linoeparol *Agropharm, Pol.*
Evening primrose oil (p.2302·1).
Skin disorders.

Linoforce *Bioforce, Switz.*
Linseed (p.2333·3); senna (p.1769·2); frangula bark (p.1732·2).
Constipation.

Linola *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.; Wolff, Pol.; Medika, Switz.*
Linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Skin disorders.

Linola Cort Beta *Wolff, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Linola Cort Hydro *Wolff, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Linola Cort Triam *Wolff, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Linola gamma *Wolff, Ger.*
Evening primrose oil (p.2302·1).
Skin disorders.

Linola Gamma *Linderma, UK.*
Evening primrose oil (p.2302·1).
Formerly known as Gammaderm.
Dry skin disorders.

Linola gras *Medika, Switz.*
Linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Skin disorders.

Linola mi-gras *Medika, Switz.*
Linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Skin disorders.

Linola Urea *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Linola Uree *Medika, Switz.*
⊗ Urea (p.1620·2).
Skin disorders.

Linoladiol
Note. This name is used for preparations of different composition.
Montavit, Austria.
Estradiol (p.2097·2).
Vaginal disorders.

Medika, Switz.†.
Estradiol (p.2097·2); linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Vulvovaginal disorders.

Linoladiol N *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
Estradiol (p.2097·2).
Oestrogen deficiency; skin disorders; vaginal disorders.

Linoladiol-H N *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.†.*
⊗ Estradiol (p.2097·2); prednisolone (p.1540·3).
Acne; ulcus cruris; vaginal disorders.

Linola-Fett
Note. This name is used for preparations of different composition.
Montavit, Austria.
Fatty acids, betacarotene, and vitamin E (p.1922·1).
Skin disorders.

Wolff, Cz.; Wolff, Ger.
Linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Skin disorders.

Linola-Fett 2000 *Wolff, Ger.†.*
Linoleic acid (p.2308·2).
Skin disorders.

Linola-Fett Furdoolaj *Wolff, Hung.*
Bath additive; emollient.

Linola-Fett N *Wolff, Hung.†.*
Linoleic acid (p.2308·2); 9,11-octadecadienoic acid (p.2308·2).
Skin disorders.

Linola-Fett Olbad *Wolff, Cz.*
Bath additive; emollient.

Linola-Fett-N Olbad *Wolff, Ger.*
Bath additive; emollient.

Linola-H N *Wolff, Cz.†; Wolff, Ger.; Wolff, Hung.*
⊗ Prednisolone (p.1540·3).
Skin disorders.

Linola-H-compositum N *Wolff, Cz.†; Wolff, Ger.†.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1).
Burns; infected skin disorders; skin ulcers.

Linola-H-Fett N *Wolff, Cz.; Wolff, Ger.; Wolff, Hung.*
⊗ Prednisolone (p.1540·3).
Skin disorders.

Linola-sept *Wolff, Ger.; Wolff, Hung.†.*
Clioquinol (p.254·1).
Infected skin disorders.

Linomag *Ziololek, Pol.*
Vitamin F (p.2308·2).
Skin disorders.

LinoMed *Bioforce, Switz.*
Linseed (p.2333·3); senna (p.1769·2); frangula bark (p.1732·2).
Constipation.

Linoril *Stadmed, India.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension.

Linosin *Deva, Turk.*
Lincomycin (p.293·1).
Bacterial infections.

Linospan *Cipla, India.*
Linezolid (p.293·3).
Bacterial infections.

Linospril *Kendrick, Mex.*
Lisinopril (p.1325·2).
Hypertension.

Linosun *Silesia, Chile.*
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Linotar *EpiPharm, Austral.; MZ, S.Afr.*
Coal tar (p.1616·2).
Skin and scalp disorders.

Linoten *Mayne, Spain.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolytic lesions in multiple myeloma and bone metastases associated with breast cancer; Paget's disease of bone.

Linox *Unichem, India.*
Linezolid (p.293·3).
Bacterial infections.

Linoxal *Sandoz, Indon.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Linsal *Sigma, Austral.†.*
Methyl salicylate (p.85·3).
Rubefacient and topical analgesic.

Lintia *Protina, Ger.†.*
Salix (p.121·3).
Fever; headache; rheumatic disorders.

Lintos *Wassermann, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Lintropsin *Tropica Mas, Indon.*
Lincomycin (p.293·1).
Bacterial infections.

Linurin *Dovalle, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Linvas *Cadila Pharma, India.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension.

Liobac *Sriprasit, Thai.*
Baclofen (p.1888·1).
Muscle spasticity.

Liobifar *Italfarmaco, Ital.†.*
Lactic acid producing organisms; vitamin B substances (p.1922·1).

Liocort *Ronava, Venez.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Liofindol *ICN, Mex.†.*
⊗ Mazindol (p.2157·3).
Obesity.

Liofora *Schering, Neth.*
Drospirenone (p.2095·2); ethinylestradiol betadex.
Combined oral contraceptive.

Liolactil *Ivax, Mex.; Elmor, Venez.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Lio-Levedura *Vitoria, Port.†.*
Saccharomyces cerevisiae (p.1998·3).

Liomagen *Chrispa (Χρισπα), Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Liometacen *Gerot, Austria; Promedica, Ital.; Chiesi, Thai.*
Meglumine indometacin (p.68·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain; renal and biliary colic; thrombophlebitis.

Lion *Filaxis, Arg.*
Stavudine (p.907·1).
Viral infections.

Lion Cleansing Herbs *Potter's, UK.*
Buckthorn (p.1713·3); psyllium seed (p.1737·1); senna (p.1769·2); sambucus (p.2383·1); fennel (p.2302·3); maté (p.2416·1).
Constipation.

Lioram *Mantecorp, Braz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Lioresal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; IFET (ΙΦΕΤ), Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore†; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Geigy, USA; Novartis, Venez.*
Baclofen (p.1888·1).
Skeletal muscle spasm; spasticity; trigeminal neuralgia.

Lioresyl *Novartis, Chile.*
Baclofen (p.1888·1).
Skeletal muscle spasm or spasticity.

Liotec *Technilab, Canad.†.*
Baclofen (p.1888·1).

Liotixil *Boniscontro & Gazzone, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Lioton *Menarini, Cz.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Sanofi-Aventis, Ital.; Berlin-Chemie, Pol.; Menarini, Rus.; Menarini, Switz.*
Heparin sodium (p.1301·2).
Keloids; oedema; peripheral vascular disorders; scars; soft-tissue disorders; superficial vascular disorders; venous insufficiency.

Liotrex
Note. This name is used for preparations of different composition.
Raffo, Chile†.
Sumatriptan succinate (p.625·2).
Migraine.

Investigacion, Mex.
Liothyronine sodium (p.2174·1).
Hypothyroidism.

Lioxam *Grunenthal, Pol.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Liozim *Farmanova, Ital.*
Fructose (p.1945·1); acacia honey (p.1948·2); lactic-acid-producing organisms (p.2372·3).
Nutritional supplement.

Lip Block Sunscreen *Norwood, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Lip Infusion *Rider, Chile.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lip Medex
Note. This name is used for preparations of different composition.
Blistex, Canad.†.
Camphor (p.2273·2); phenol (p.1656·1); menthol (p.2340·1).
Dry, cracked lips; herpes labialis.

Blistex, USA.
Camphor (p.2273·2); phenol (p.1656·1).
Oral lesions.

Lip Tone
Note. This name is used for preparations of different composition.
Rider, Chile†.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Blistex, USA.
SPF 15: Octinoxate (p.1608·2); meradimate (p.1604·2).
Sunscreen.

Lip Treatment *Shaklee, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lipactin *Widmer, Austria; Widmer, Belg.; Novartis Consumer, Canad.; Widmer, Fin.; Widmer, Ger.; Widmer, Switz.*
Heparin sodium (p.1301·2); zinc sulfate (p.1999·2).
Herpes simplex infections of the lips and orofacial area.

Lipagent *Fahrenheit, Indon.*
Methionine (p.1450·1); choline bitartrate (p.1934·2); vitamin B substances; vitamin E (p.1922·1).
Liver disorders; vitamin and amino acid deficiency.

Lipancrea *Polfa Warszawa, Pol.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Lipanon *Farmasa, Braz.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipanor *Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; CTI, Israel; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Lipanthyl *Solvay, Belg.; Fournier, Cz.; Leiras, Fin.; Fournier, Fr.; Fournier, Ger.; Solvay, Gr.; Fournier, Hong Kong; Gedeon Richter, Hung.†; Fournier, Indon.; Formenti, Ital.†; Fournier, Malaysia; Fournier, Philipp.; Fournier, Pol.; Solvay, Port.; Fournier, Rus.; Solvay, Singapore; Selena, Swed.; Fournier, Switz.; Fournier, Thai.; Fournier, Turk.*
Fenofibrate (p.1286·2).
Atherosclerosis; hyperlipidaemias.

Lipantil *Fournier, Irl.; Fournier, UK.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Liparex *Finadiet, Arg.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Liparex Duo *Finadiet, Arg.*
Tablets, atorvastatin calcium (p.1218·3); tablets, ezetimibe (p.1284·3).
Hypercholesterolaemia.

Liparison *Novartis, Spain.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipascor
Note. This name is used for preparations of different composition.
Wearnes, Malaysia; Steward Cross, Singapore.
Red yeast.
Hyperlipidaemias.

Servier, Venez.
Benfluorex hydrochloride (p.1224·3).
Hyperglycaemia; hyperlipidaemias.

Lipaven *Sogefin, Ital.*
Lespedeza; java tea (p.2328·2); birch (p.2266·3); myrtillus (p.2349·3); melilot (p.2339·2); ascorbic acid (p.1983·3).
Nutritional supplement.

Lipaxan *Italfarmaco, Ital.*
Fluvastatin sodium (p.1290·2).
Hypercholesterolaemia.

Lipaz *Daquimed, Port.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lipazil *Douglas, Austral.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipazym *Bittermedizin, Ger.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Lipbalm with Sunscreen *Hyde, Canad.†.*
Padimate O (p.1609·1).
Sunscreen.

Lipcor
Note. This name is used for preparations of different composition.
Nycomed, Austria.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Pharmacia, Braz.†.
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias; nutritional supplement.

Lipcut *Sandoz, Fin.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Lipdaune *Sofex, Port.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lip-Down *Veltipharm, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lipei *Steiner, Ger.*
Cynara (p.2291·2).
Dyspepsia.

Lipemia *Verisfield, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Lipemol *BMS, Spain.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Lipenan *Klinger, Braz.†.*
Poliglusam (p.2370·1).
Obesity.

Liperol
Note. This name is used for preparations of different composition.
Spirig, Fr.
⊗ Urea (p.1620·2); piroctone olamine (p.1610·1).
Scalp disorders.

Rayere, Mex.
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lipex
Note. This name is used for preparations of different composition.
Elea, Arg.
Policosanol (p.1373·3).
Hypercholesterolaemia.

MSD, Austral.; MSD, NZ.
Simvastatin (p.1390·2).
Coronary atherosclerosis; hypercholesterolaemia.

Lip-Eze *GSK Consumer, Austral.*
SPF 15+: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Dry, cracked, and chapped lips; sunscreen.

Lipibec *Ivax, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Lipibec Duo *Ivax, Arg.*
Tablets, atorvastatin calcium (p.1218·3); tablets, ezetimibe (p.1284·3).
Hypercholesterolaemia.

Lipicard *USV, India.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipidal *BMS, Israel†.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia; myocardial infarction; stroke prophylaxis.

Lipidavit *Rodisma, Ger.*
Garlic (p.2309·2); alpha tocoferil acetate (p.1992·3); lecithin (p.2332·2).
Hyperlipidaemias.

Lipidem *Braun, UK.*
Omega-3 triglycerides (p.1362·1); soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Lipid infusion for parenteral nutrition.

Lipiderm *Chauvin, Fr.*
Moisturiser.
Dry skin disorders.

Lipidex *Hexal, S.Afr.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Lipidil *Craveri, Arg.†; Fournier, Austral.; Farmalab, Braz.; Fournier, Canad.; Andromaco, Chile; Fournier, Ger.; Solvay, Gr.; Fournier, Hung.; Schering-Plough, Mex.†.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipidless *Faran, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lipidos *Abbott, Arg.†.*
Cartamo oil (p.1960·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipidys *Medifive, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipifen *Raffo, Arg.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Lipiforce *Forder, Arg.†.*
Phospholipids; ceramide.

Lipigan *Alvia (Αλβια), Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipigem *Littman, Philipp.*
Gemfibrozil (p.1295·3).
Coronary heart disease; hyperlipidaemias.

Lipikar *Roche-Posay, Arg.†; Roche-Posay, Braz.; Roche-Posay, Fr.; Roche-Posay, Irl.*
Emollient.
Dry skin disorders; psoriasis.

Lipilim *Atlantic, Hong Kong.*
Clofibrate (p.1246·2).
Hyperlipidaemias.

Lipimibe *Penn, Arg.*
Simvastatin (p.1390·2); ezetimibe (p.1284·3).
Hypercholesterolaemia.

Lipinorm *Dankos, Indon.*
Simvastatin (p.1390·2).
Coronary heart disease; hyperlipidaemias.

Lipiocis *CIS, Cz.†.*
Iodine-131 (p.2054·3) in iodised oil.
Liver cancer.

Lipiodol *Temis, Arg.; Aspen, Austral.; Guerbet, Austria; Codali, Belg.; Guerbet, Braz.†; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fr.; Guerbet, Ger.; IFET (ΙΦΕΤ), Gr.; R+N, Gr.; Guerbet, Hung.; Guerbet, Israel; Guerbet, Ital.; Obex, NZ; Guerbet, Neth.; Guerbet, Norw.†; Martins & Fernandes, Port.; Guerbet, Switz.; May & Baker, UK; Quifoven, Venez.*
Iodised oil (p.1482·1).
Contrast medium for hysterosalpingography and lymphography; iodine deficiency.

Lipira *Combiphar, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipirex *Sanofi-Aventis, Cz.; Winthrop, Fr.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipiscor *Sanum-Kehlbeck, Ger.*
Marine fish oil (p.1362·2).
Hyperlipidaemias.

Lipison *Unison, Hong Kong; Unison, Philipp.; Unison, Singapore†; Unison, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias; ischaemic heart disease.

Lipisorb *Mead Johnson, Austral.†; Mead Johnson Nutritionals, USA.*
Food for special diets (p.1922·1).
Fat malabsorption.

Lipistat *Knop, Chile.*
Yeast extract from Monascus purpureus.
Hypercholesterolaemia.

Lipistorol *Hovid, Hong Kong; Hovid, Malaysia†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipitaksin *Fako, Turk.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Lipitifi *Tiefenbacher, Neth.*
Pravastatin sodium (p.1374·3).
Hyperlipidaemias; reduction of cardiovascular risk.

Lipitor *Elea, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Parke, Davis, Israel; Warner-Lambert, Ital.†; Astellas, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Atorvastatin calcium (p.1218·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Lipitrol *Julphar, UAE.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Lipitrop *Tropica Mas, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipivas *Nabiqasim, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lipizem *Verisfield, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipizile *Integrated Pharmaceutical, Philipp.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias; ischaemic heart disease.

Liplat *Esteve, Spain.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Liple *Mitsubishi, Jpn.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus; mesenteric arterial portography; peripheral vascular disorders; skin ulcers.

Lipless *Biolab Sanus, Braz.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Lipmagik *Reese, USA.*
⊗ Benzocaine (p.1854·1); phenol (p.1656·1); alcohol (p.1625·2).

Lipo Cordes *Ichthyol, Ger.*
Allantoin (p.1588·1); dexpanthenol (p.2362·1); ethyl linoleate (p.2308·2).
Skin disorders.

Lipo E *Seviton, Switz.†.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Lipo Slim N *Investigacion, Mex.†.*
Chromium (p.1934·3); citric acid (p.2284·1); nopal.
Obesity.

Lipo Sol *Widmer, Cz.†; Widmer, Philipp.; Widmer, Switz.*
Triclosan (p.1665·2).
Acne; seborrhoea.

Lipoabsorver *Neves, Port.†.*
Poliglusam (p.2370·1); vitamin C.
Hypercholesterolaemia; slimming aid.

Lipoacid *Dermoteca, Port.*
Thioctic acid (p.2400·2); tocoferil acetate; acetyl glucosamine; glucuronic acid; hyaluronic acid; saccharide isomerate; panthenol.
Skin ageing.

Lipoacid Combi
Note. This name is used for preparations of different composition.
General Topics, Ital.
Thioctic acid (p.2400·2); cysteine; vitamin E; eicosapentaenoic acid (p.1922·1).
Nutritional supplement.

Dermoteca, Port.†.
Thioctic acid (p.2400·2); cysteine; vitamin C; vitamin E; eicosapentaenoic acid.
Skin ageing and photo-damaged skin.

Lipoarteriosan *Bernabo, Arg.*
Atorvastatin (p.1219·1); amlodipine (p.1214·2).
Angina pectoris; hyperlipidaemias; hypertension.

Lipobalsamo *Teofarma, Ital.*
Cineole (p.2282·3); guaiacol (p.1561·2).
Respiratory-tract disorders.

Lipobase *Astellas, Cz.; Yamanouchi, Hung.†; Yamanouchi, Irl.†; CSL, NZ; Yamanouchi, NZ; Astellas, UK.*
Emollient.
Diluent for Locoid Lipocream; dry skin; pruritus; skin disorders.

LIPObind
Note. This name is used for preparations of different composition.
Goldshield, Austral.
Opuntia ficus-indica.
Slimming aid.

Goldshield, UK.
Fibre complex from cactus leaves.
Aid to weight control.

Lipocambi *Bernabo, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Lipochol *Takeda, Hong Kong; Takeda, Thai.*
Orotic acid (p.2358·3); thioctic acid amide (p.2400·2); methionine (p.1450·1); vitamin B substances; vitamin C (p.1922·1); inositol (p.2325·2).
Liver disorders.

Lipociden *Vita, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias; secondary prophylaxis of ischaemic heart disease.

Lipocin *Kener, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Lipocinetic *Investigacion, Mex.*
Citric acid (p.2284·1).
Hypercholesterolaemia.

Lipoclin
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
Lovastatin (p.1328·2).
Hyperlipidaemias.

Sumitomo, Jpn.
Clinofibrate (p.1246·2).
Hyperlipidaemias.

Lipocol *Merz, Ger.*
Colestyramine (p.1252·3).
Diarrhoea; hypercholesterolaemia; pruritus associated with biliary obstruction.

Lipocort *CSL, NZ.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Lipoderm *Pacific, Singapore; Spirig, Singapore.*
SPF 16; SPF 20; SPF 25: Bemotrizinol (p.1590·2); octisalate (p.1608·2); octinoxate (p.1608·2).
Sunscreen.

Lipodial *Adipharm, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipo-Dox *American Taiwan, Thai.*
Liposomal doxorubicin hydrochloride (p.712·2) (p.712·2).
Kaposi's sarcoma; ovarian cancer.

Lipoenergy *Farma Energy, Ital.*
Choline; inositol; methionine; carnitine; vitamin B (p.1922·1).
Nutritional supplement.

Lipofacton *Organon, Braz.*
Clofibrate (p.1246·2); nicotinyl alcohol tartrate (p.1349·3).
Hyperlipidaemias.

Lipofen *Vitoria, Port.; Nobel, Turk.; Proethic, USA.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipofene *Teofarma, Ital.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipofin *Fabop, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Lipoflavonoid *Numark, USA.*
Multivitamin preparation with lemon bioflavonoids (p.2304·1)(p.1922·1).

Lipofor *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Singapore.*
Gemfibrozil (p.1295·3).
Cardiovascular risk reduction; hyperlipidaemias.

Lipoforte *Neves, Port.†.*
Poliglusam (p.2370·1); ascorbic acid (p.1983·3); green tea (p.2416·1).
Obesity.

Lipofren *Abello, Spain†.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lipofundin *Braun, Chile; Braun, Hung.; Braun, UK.*
Soya oil (p.1965·3).

Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin MCT Braun, Ger.; Braun, Hung.; Braun, Ital.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipofundin MCT/LCT Braun, Arg.†; Braun, Chile; Braun, Cz.; Bioser (Βιοσερ), Gr.; Braun, Hong Kong; Braun, Indon.; Braun, Israel; Pisa, Mex.; Braun, Neth.; Braun, Pol.; Braun, S.Afr.; Braun, Singapore†; Braun, Switz.; Braun, Thai.; Braun, Turk.; Braun, UK; Behrens, Venez.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipofundin MCT/LCT-E Braun, Arg.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3); alpha-tocopherol (p.1992·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipofundin mit MCT Braun, Austria.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg phospholipid.
Lipid infusion for parenteral nutrition.

Lipofundin N Braun, Arg.; Braun, Cz.†; Braun, Ger.; Braun, Hong Kong; Pisa, Mex.; Braun, Pol.; Braun, Thai.; Behrens, Venez.†.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipofundin S Braun, Ital.; Braun, Thai.
Soya oil (p.1965·3).
Lipid infusion for parenteral nutrition.

Lipofundina MCT/LCT Braun, Port.; Braun, Spain.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipogen
Note. This name is used for preparations of different composition.
Biores, Ital.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.
Goldline, USA.
Vitamin B substances (p.1922·1).
It may also contain vitamin C.

Lipograsil Uriach, Spain.
Cynara (p.2291·2); cascara (p.1715·2); bladderwrack (p.2384·2).
Obesity.

Lipohep CSC, Austria; Medicom, Cz.†; Medicom, Pol.
Heparin sodium (p.1301·2).
Peripheral vascular disorders; soft-tissue disorders; superficial vascular disorders; thrombophlebitis.

Lipohexal Hexal, Cz.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipoicin Takeda, Thai.†.
Thioctic acid (p.2400·2).
Liver disorders.

Lipoite Angenerico, Port.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipolac Bausch & Lomb, Mex.; Farma Lepori, Spain.
Carbomer (p.2141·3).
Dry eyes; eye irritation.

Lipolan Orion, Fin.
Emollient.
Dry skin disorders.

Lipoleum SFD, Port.†.
Emollient.
Barrier preparation; skin disorders.

Lipolin Bausch & Lomb, Philipp.
Carbomer (p.2141·3).
Dry eyes.

Lipolo Macrophar, Thai.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipolotion Pacific Biosciences, Singapore†; Spirig, Singapore†.
Emollient and moisturiser.
Dry skin disorders.

Lipomal Aflofarm, Pol.
Tilia (p.2402·2).
Fever.

Lipomax
Note. This name is used for preparations of different composition.
Forder, Arg.†.
Glycolic acid (p.1598·1).
Makros, Braz.†.
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Lipomega Nutri-Well, Hong Kong.
Omega-3 marine triglycerides (p.1362·2).
Hypercholesterolaemia.

Lipo-Merz Kolassa, Austria; Grunenthal, Chile†; Merz, Ger.; Merz, Hong Kong; Merz, Malaysia†; Medinfar, Port.; Merz, Singapore†; Merz, Switz.
Etofibrate (p.1284·2).
Hyperlipidaemias.

Lipomin Alvia (Αλβια), Gr.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lipomul Roberts, USA.
High calorie preparation containing maize oil for enteral nutrition (p.1922·1)(p.1955·2).

Liponet Vedim, Spain†.
Pantethine (p.1365·3).
Hyperlipidaemias.

Liponol Rugby, USA.
Vitamin B substances with methionine (p.1922·1).

Liponorm
Note. This name is used for preparations of different composition.
Lazar, Arg.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.
Gentili, Ital.
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Liponorm Duo Lazar, Arg.
Tablets, atorvastatin calcium (p.1218·3); tablets, ezetimibe (p.1284·3).
Hypercholesterolaemia.

Lipontal Alian, Venez.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipopharm Medphano, Ger.
Soya phospholipid (p.1965·3).
Hypercholesterolaemia.

Lipophoral Servier, Gr.
Benfluorex (p.1224·3).
Hyperlipidaemias.

Lipoplasmin Elvetium, Arg.†.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipoplus Braun, Cz.; Braun, Fin.; Braun, Neth.; Braun, Port.; Braun, Swed.
Medium-chain triglycerides (p.1956·3); soya oil (p.1965·3); omega-3 triglycerides (p.1362·1).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipoprav Biospray, Gr.
Pravastatin (p.1375·1).
Hyperlipidaemias.

Lipopress Remedina, Gr.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Liporegul Lero, Fr.
Fish oil; nicotinamide; vitamin E; selenium yeast; chromium yeast (p.1922·1).
Nutritional supplement.

Liporest Centaur, India.
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Liporex Genepharm, Gr.
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Liporon General Drugs, Thai.
Choline bitartrate (p.1934·2); inositol (p.2325·2); methionine (p.1450·1); vitamin B substances (p.1922·1).
Liver disorders.

Liposcler CEPA, Spain.
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Liposel Wassen, Ital.†.
Vitamin A; vitamin C; vitamin E; selenium; lipoic acid; astaxanthin (p.1922·1).
Nutritional supplement.

Liposerin Landson, Indon.
Phosphatidyl serine (p.2367·1); phosphatidyl choline (p.2367·1).
Memory function adjuvant.

Liposic Bausch & Lomb, Arg.; Riel, Austria; Tramedico, Belg.; Chauvin, Fr.; Mann, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Hong Kong; Mann, Irl.; Tramedico, Neth.; Bausch & Lomb, Port.; Bausch & Lomb, UK.
Carbomer (p.2141·3).
Dry eyes.

Liposit Ferrer, Spain.
Fluvastatin sodium (p.1290·2).
Atherosclerosis; cardiovascular risk reduction; hyperlipidaemias.

Liposom Fidia, Ital.
Hypothalamic phospholipids (p.2337·3).
Neuroendocrine disorders.

Liposomas Stiefel, Arg.
Cholesterol (p.2029·1); oxybenzone (p.1608·3); octinoxate (p.1608·2); soya oil (p.1965·3); vitamin E (p.1992·2).
Sun-induced skin disorders; sunscreen.

Liposorb Metro, Philipp.
Liphosan; ascorbic acid (p.1983·3); chromium tripicolinate (p.1934·3).
Obesity.

Lipostabil
Note. This name is used for preparations of different composition.
Nattermann, Ger.
Soya phospholipids (p.1965·3).
Fat emboli; hypercholesterolaemia.
Aventis, Ital.†.
Phosphatidyl choline (p.2367·1).
Fat emboli; hyperlipidaemias.
Aventis, S.Afr.†.
Essential phospholipids; multivitamins (p.1922·1); adenosine phosphate (p.2247·2).
Atherosclerosis; diabetic angiopathies; hyperlipidaemias; thromboembolism prophylaxis.

Lipostabil N Aventis, Cz.†.
Essential phospholipids (p.1922·1).
Thromboembolic disorders.

Lipostat Arrow, Austral.; BMS, Cz.†; BMS, Irl.; BMS, NZ; BMS, Philipp.; BMS, UK.
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia; myocardial infarction; stroke prophylaxis.

Lipostatin Remedina, Gr.
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipostop Denver, Arg.
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Liposyn Abbott, Chile†; Abbott, Denm.†; Abbott, Fin.†; Abbott, Israel; Abbott, Ital.†; Abbott, Mex.; Abbott, Swed.†; Abbott, Turk.
Safflower oil (p.1960·3); soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Liposyn II Hospira, USA.
Safflower oil (p.1960·3); soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Liposyn III Hospira, USA.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipotalon Merckle, Ger.
⊗ Dexamethasone palmitate (p.1526·3).
Rheumatic disorders.

Lipotex Medley, Braz.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lipoton Basi, Port.†.
Choline; inositol; methionine (p.1922·1).

Lipotop Spirig, Fr.
A range of skin care and barrier preparations.

Lipotrend Cholesterol Roche Diagnostics, Ital.†.
Test for cholesterol in blood.

Lipotriad Numark, USA.
Multivitamin and mineral preparation (p.1922·1).

Lipotril Sanitas, Chile.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipotropic Drugtech, Chile.
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Lipotropic Factors Solgar, UK.
Choline bitartrate (p.1934·2); inositol (p.2325·2); methionine (p.1450·1).
Dietary supplement.

Lipovas
Note. This name is used for preparations of different composition.
Tempo Scan Pacific, Indon.
Lovastatin (p.1328·2).
Hypercholesterolaemia.
Ilsan, Turk.
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Lipovast Anpharm (Ανφαρμ), Gr.
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipovastinklonal Klonal, Arg.
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lipovenoes Fresenius Kabi, Cz.; Bioser (Βιοσερ), Gr.†; Fresenius Kabi, Indon.; Fresenius Kabi, Mex.; Fresenius Kabi, Port.; Fresenius Kabi, Thai.†.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipovenoes MCT Fresenius Kabi, Mex.†.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenos Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Ger.; Fresenius Kabi, Hung.†; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.†; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Lipovenos MCT Fresenius Kabi, Ger.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg phospholipid.
Lipid infusion for parenteral nutrition.

Lipovenos MCT/LCT
Fresenius Kabi, Arg.
A lipid infusion (p.1922·1).
Parenteral nutrition.
Fresenius Kabi, Chile.
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovenos PLR Fresenius Kabi, Hung.†.
Soya oil (p.1965·3); esential fatty acids (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Lipovisc Bausch & Lomb, Ital.
Carbomer (p.2141·3).
Dry eyes.

Lipovitan Leciva, Cz.†; Medphano, Ger.†.
Choline bitartrate (p.1934·2); methionine (p.1450·1); inositol (p.2325·2); alpha tocoferil acetate (p.1992·3); vitamin B substances (p.1922·1); dexpanthenol (p.2362·1).
Liver disorders.

Lipovitasi-Or Atlantis, Mex.
Carnitine orotate (p.2358·3); thiamine nitrate (p.1976·2); DL-methionine (p.1450·1).
Chronic fatigue syndrome; hyperammonaemia; liver disorders.

Lipovy Megafyt-R, Cz.
Tilia (p.2402·2).
Catarrh; cold symptoms; coughs.

Lipox
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Atorvastatin (p.1219·1).
Hypercholesterolaemia.
TAD, Ger.
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Lipox Gemfi TAD, Ger.†.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipozid
Note. This name is used for preparations of different composition.
MTF, Gr.
Simvastatin (p.1390·2).
Hyperlipidaemias.
Pharmacia, Ital.; Pharma Nutria, Philipp.
Gemfibrozil (p.1295·3).
Hyperlipidaemias; ischaemic heart disease.

Lipozil M & H, Thai.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Liprace Douglas, Austral.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lipraken Kener, Mex.
Enalapril (p.1276·1).
Hypertension.

Lipram Global, USA.
Pancrelipase (p.2360·1).
Pancreatic insufficiency.

Lipratif Tiefenbacher, Neth.
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Lipreren Labomed, Chile.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lipribela Belupo, Cz.
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lipribela plus H Belupo, Cz.
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lipril Lupin, India; Merck, Port.
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension.

Liprimar Pfizer, Hung.; Goedecke, Rus.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Liprocil Nestle, Fr.
Medium-chain triglycerides (p.1956·3); vitamins (p.1922·1).
Nutritional supplement.

Liprolog Lilly, Cz.; Berlin-Chemie, Ger.; Lilly, Neth.; Lilly, Port.
⊗ Insulin lispro (p.449·3).
Diabetes mellitus.

Liprolog Mix 25 and 50 Lilly, Cz.; Berlin-Chemie, Ger.; Lilly, Neth.; Lilly, Port.
⊗ Mixtures of insulin lispro 25% or 50% and isophane insulin lispro 75% or 50%, respectively (p.449·3).
Diabetes mellitus.

Liprox Biofarm, Pol.
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Liproxal Biofarm, Pol.
Cynara (p.2291·2).
Digestive disorders; hypercholesterolaemia.

Lip-Sed Pfizer Consumer, Austral.†; Pfizer, NZ.
Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Chapped, cracked, or blistered lips; sunscreen.

Lipshield Lipbalm Mentholatum, Canad.†.
SPF 21: Padimate O (p.1609·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lipsin Nycomed, Austria; Caber, Ital.; Aventis, S.Afr.†.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipsorex Canderm, Canad.†.
Benzethonium chloride (p.1630·1); menthol (p.2340·1); thymol (p.1664·3).

Lipsorex Plus Canderm, Canad.
Lidocaine (p.1862·3); benzethonium chloride (p.1630·1); menthol (p.2340·1); thymol (p.1664·3).

Liptonorm Biopharm, Rus.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Liptrat Uniao Quimica, Braz.
Simvastatin (p.1390·2).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lipur *Pfizer, Fr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lipus *BA Farma, Port.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lipway *Cathay, Philipp.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Lipz Lip Balm *Hamilton, Austral.*
SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Lipz Lip Ointment *Hamilton, Austral.*
SP 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); avobenzone (p.1589·3); menthol (p.2340·1); aloe vera (p.1588·2).
Sunscreen.

Liquemin
Roche, Austria.
Heparin (p.1301·2).
Thromboembolic disorders.

Roche, Ital.†.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Liquemin N *Roche, Ger.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Liquemine *Roche, Belg.†; Roche, Braz.; Roche, Switz.; Roche, Turk.; Roche, Venez.†.*
Heparin sodium (p.1301·2).
Hyperlipidaemias; thromboembolic disorders.

Liqufruta Garlic Cough Medicine *Chefaro, UK.*
Garlic oil (p.2309·2); guaifenesin (p.1561·3).
Coughs.

LiquiBand *Medlogic, UK.*
Enbucrilate (p.2290·2).
Tissue adhesive for wound closure.

Liquibid *Capellon, USA.*
Guaifenesin (p.1561·3).

Liquibid-D *Capellon, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract symptoms.

Liquibid-PD *Capellon, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Liquicet *Mallinckrodt, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Liqui-Char *Jones, USA.*
Activated charcoal (p.1435·2).
Emergency treatment of poisoning.

Liqui-Coat HD *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Liquicough DM *Breckenridge, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Liquid Antacid *Pennex, Israel†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Gastrointestinal hyperacidity; heartburn.

Liquid Antacid Plus Simethicon *Pennex, Israel†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity; heartburn.

Liquid Cal-Mag plus Vitamin D and Phosphorus *Swiss Herbal, Canad.*
Vitamin D; calcium; magnesium; phosphate (p.1922·1).

Liquid Polibar Plus *E-Z-EM, Israel.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Liquid Pred *Muro, USA.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Liquid Soap Pre-Op *Orion, Austral.†; Orion, NZ.*
Triclosan (p.1665·2).
Skin cleansing.

Liquidepur *Woelm, Ger.†.*
Senna (p.1769·2).
Constipation.

Liquidepur mit Natriumpicosulfat *Woelm, Ger.*
Sodium picosulfate (p.1771·1).
Constipation.

Liquido de Dakin *Granado, Braz.†.*
Sodium hypochlorite (p.1661·1).
Disinfection.

Liquidorm N *Hanosan, Ger.*
Homoeopathic preparation.

Liqui-Doss *Ferndale, USA.*
Liquid paraffin (p.2030·3).
Constipation.

Liquifer *Abbott, Austria†; Abbott, Ital.†.*
Iron polystyrene sulfonate (p.1950·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Liquifilm *Allergan, Austral.; Allergan, Belg.; Allergan, Canad.; Allergan, Cz.†; Allergan, Fin.; Allergan, Ger.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Malaysia†; Allergan, NZ; Allergan, Port.; Allergan, Switz.†; Abdi, Turk.; Allergan, USA.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Dry eyes; eye irritation; wetting solution for contact lenses.

Liquifilm Lagrimas *Allergan, Arg.†; Allergan, Chile†; Allergan, Spain.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Dry eyes; lubricating solution for contact lenses.

Liquifilm OK *Allergan, Ger.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Liquifilm Tears *Alvia (Αλβια), Gr.; Allergan, Israel; Allergan, S.Afr.; Allergan, Singapore; Allergan, Thai.; Allergan, UK.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Dry eyes; lubricant for hard contact lenses.

Liquifilm Wetting *Allergan, USA.*
Wetting solution for hard contact lenses (p.1622·2).

Liquifresh *Allergan, Spain.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1) (p.1622·2).
Contact lens discomfort; dry eyes.

Liquigel *Allergan, Ger.*
Carbomer 974P (p.2141·3).
Dry eyes.

Liquigen *Scientific Hospital Supplies, Austral.; Nutricia, Fin.; SHS, Fr.; Scientific Hospital Supplies, Irl.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Scientific Hospital Supplies, UK.*
Medium-chain triglycerides (p.1956·3).
Enteral nutrition; food for special diets.

Liquigesic Co *Paedpharm, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Liquimat *Summers, USA.*
Sulfur (p.1614·1).
Acne; oily skin.

Liquipake *Lafayette, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Liquipom Dexa Antib *Iquinosa, Spain.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye and ear disorders.

Liquipred *Transfarma, Philipp.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Liquiprin
Note.This name is used for preparations of different composition.
Ingens, Arg.
Chondroitin sulfate (p.2280·3).
Dry eyes.

Menley & James, USA.
Paracetamol (p.108·1).
Fever; pain.

Liquirit *Loges, Ger.*
Algeldrate (p.1706·2); magnesium carbonate (p.1743·1); liquorice (p.1740·3).
Gastrointestinal disorders.

Liquitears *Allergan, Switz.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Contact lens discomfort; dry eyes.

LiquiVent *Alliance, USA.*
⊗ Perflubron (p.2365·1).
Acute respiratory distress syndrome.

Liquivisc *Allergan, Irl.; Allergan, UK.*
Carbomer 974P (p.2141·3).
Dry eyes.

Liracol
Note.This name is used for preparations of different composition.
Medipharm, Chile.
Oral suspension: Nifuroxazide (p.307·2); activated attapulgite (p.1709·1).
Bacterial gastrointestinal infections.

Medipharm, Chile.
Tablets: Nifuroxazide (p.307·2); phthalylsulfathiazole (p.315·1).
Gastrointestinal infections.

Liramin *Proula, Venez.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Lirebin *Help, Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Lirex *Silesia, Chile.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Lirgosin *Fidia, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Liroken *Kendrick, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Liroken I *Kendrick, Mex.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Lironex *Master, Chile†.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).

Lirpan *Casasco, Arg.*
Donepezil (p.365·2).
Alzheimer's disease.

Lirugen *Sanofi Pasteur, Arg.†.*
A measles vaccine (Schwarz strain) (p.2221·3).
Active immunisation.

Lis *Lisapharma, Ital.†.*
Lactulose (p.1738·2).
Constipation; disturbances of the gastrointestinal flora; hepatic cirrhosis; hepatic encephalopathy.

Lisa *Lisapharma, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Lisac *Bernabo, Arg.*
Simvastatin (p.1390·2).
Coronary insufficiency; hypercholesterolaemia.

Lisacef *Lisapharma, Ital.*
Cefradine (p.233·1).
Bacterial infections.

Lisacne *Andromaco, Chile†.*
Isotretinoin (p.1599·2).
Acne.

Lisacol *Hebron, Braz.†.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Lisador *Farmasa, Braz.*
Dipyrone (p.49·2); promethazine hydrochloride (p.588·2); adiphenine hydrochloride (p.2248·1).
Smooth muscle spasm.

Lisaglucon *Farmasa, Braz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Lisaler *Fortbenton, Arg.*
Loratadine (p.583·3).

Lisaler Beta *Fortbenton, Arg.*
⊗ Loratadine (p.583·3); betamethasone valerate (p.1519·1).

Lisalgil *Boehringer Ingelheim, Arg.*
Metamizole magnesium (p.49·3).
Pain.

Lisalgil Compuesto *Boehringer Ingelheim, Arg.*
Metamizole magnesium (p.49·3); hyoscine butylbromide (p.1734·1).
Painful gastrointestinal spasm.

Lisan *Hebron, Braz.†.*
Liver extract (p.2337·3); vitamin B (p.1975·2); vitamin B (p.1980·2).
Anaemias.

Lisanirc *Lisapharma, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Lisapres *Libbs, Braz.*
Guanabenz acetate (p.1299·3).
Hypertension.

Lisaspin *Grunenthal, Port.*
Lysine aspirin (p.79·1).
Fever; pain.

Lisba *Rafarm, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Lisbak *Savio, Ital.†.*
A *Bacillus subtilis* preparation.
Gastrointestinal disorders.

Lisdene *Sandoz, Hung.; Sandoz, Pol.; Sandoz, Singapore; Sandoz, Thai.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lisedema *Climax, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Lisefor *Vocate, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Lisenteral *Lisapharma, Ital.*
Lysates of various *Escherichia coli* strains and other coliform bacteria.
Colibacilliary gastrointestinal and genito-urinary infections.

Liserdol *Teofarma, Ger.; Pharmacia, Hong Kong†; Teofarma, Ital.; Pharmacia, Singapore†; Wyeth, Switz.†.*
Metergoline (p.2343·1).
Dumping syndrome; galactorrhoea; gastric motility disorders; hyperprolactinaemia; hyperprolactinaemic amenorrhoea; intestinal chromaffinomas; lactation inhibition; menstrual disorders; migraine and other vascular headaches.

Liseta *Organon, Austria†.*
12 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; desogestrel (p.2093·2); 4 tablets, inert.
Menopausal disorders; osteoporosis.

Lisi *ABZ, Ger.; Hennig, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisi Lich *Lichtenstein, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisian *Iodo Suma, Braz.†.*
Methylthioninium chloride (p.1450·3); avocado (p.2262·2); bearberry (p.2263·3); phyllanthus niruri; mikania hirsutissima.

Lisibac *Degorts, Mex.†.*
Gentamicin (p.284·2).
Bacterial infections.

Lisibal *Proula, Venez.*
Vitamin B substances (p.1922·1).

Lisibeta *Betapharm, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisibeta comp *Betapharm, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisicostad *Genus, UK.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisidigal HCT *Mibe, Neth.*
⊗ Hydrochlorothiazide (p.1307·3); lisinopril (p.1325·2).
Hypertension.

Lisidoc *Docpharm, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisiflen *De Salute, Ital.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Lisigamma *Worwag, Cz.; Worwag, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisigamma HCT *Worwag, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisihexal *Hexal, Austria; Hexal, Ger.; Hexal, Pol.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lisihexal comb *Hexal, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisiken *Kendrick, Mex.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Lisilet *Megat, Venez.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisiletic *Megat, Venez.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

LisiLich comp *Winthrop, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisim *Sunward, Malaysia.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Lisin Sorb *Nikkho, Braz.†.*
Lysine hydrochloride; vitamin B substances; gastric mucosa extract (p.1922·1).
Tonic.

Lisinal *Beta, Arg.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisinfos *Fabra, Arg.*
Vitamin B substances (p.1922·1).

Lisino *Essex, Ger.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lisinobell *Bellwether, Austral.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisinocomp *Genericon, Austria.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisinogen *Generics, Denm.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisinol *Cipan, Port.*
Lisinopril (p.1325·2).

Lisinoplus *Pharmacodane, Denm.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisinopril comp *Arcana, Austria; ABZ, Ger.; CT, Ger.; Ratiopharm, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisinopril HCT *AWD, Ger.; Sandoz, Ger.; TAD, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisinoratio *Ratiopharm, Pol.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisinoretic *Hexal, Braz.†.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisinospes *Alet, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisinostad *Stada, Austria.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lisinoton *Actavis, Rus.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisinotyrol *Tyrol, Austria†.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisipin *Cofasa, Venez.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Lisiplus *Aliud, Ger.; Stada, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisipril *Hexal, Cz.; Orion, Fin.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisipril Comp *Orion, Fin.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisiprol *Polfa Grodzisk, Pol.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisi-Puren *Alpharma-Isis, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisi-Puren comp *Alpharma-Isis, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisi-Tos *Vannier, Arg.*
Bromhexine (p.1552·2).
Cough.

Lisitril *Ecosol, Switz.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisitril comp *Ecosol, Switz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Liskantin *Desitin, Cz.; Desitin, Ger.*
Primidone (p.503·2).
Epilepsy.

Liskonum *GSK, UK.*
Lithium carbonate (p.401·3).
Bipolar disorder; mania.

Lismol *Lesvi, Spain†.*
Colestyramine (p.1252·3).
Hyperlipidaemias.

Lisobac *Hexal, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Lisobron *Unipharma, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Lisoclor *Neo Quimica, Braz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisoder *Laboratorios Chile, Chile.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Lisoderma *Ivax, Arg.*
Sodium acexamate (p.2245·2); gentamicin sulfate (p.282·1).
Burns; ulcers; wounds.

Lisodinol *Med-One, Gr.*
Lisinopril (p.1325·2).
Hypertension.

Lisodren *BMS, Braz.*
Mitotane (p.753·2).
Adrenal cortex cancer; Cushing's syndrome.

Lisodur *Alphapharm, Austral.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisodura *Merck dura, Ger.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisodura plus *Merck dura, Ger.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisolac *Tecnimede, Port.*
Tilactase (p.2402·1).
Lactose intolerance.

Lisolip *Gap, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lisomucil *Sanofi-Aventis OTC, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Lisomucil Gola *Sanofi-Aventis OTC, Ital.*
Dequalinium chloride (p.1641·3); enoxolone (p.50·1).
Mouth and throat disorders.

Lisomucil Tosse Sedativo *Sanofi-Aventis OTC, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Lisomucin *Cipan, Port.; Polinac, Venez.*
Bromhexine hydrochloride (p.1552·2).
Cough; respiratory-tract disorders associated with increased or viscous mucus.

Lisoneurin B12 *Dupomar, Arg.*
Hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; peripheral neuropathy.

Lisonid *Actavis, Pol.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Lisonin *Sons, Mex.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lisonorm *Gedeon Richter, Hung.*
Amlodipine besilate (p.1214·1); lisinopril (p.1325·2).
Hypertension.

Lisonotec *Teuto, Braz.†.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisoplus *Vida, Port.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisopress *Gedeon Richter, Hung.; Niche, Irl.; Medimpex, Port.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lisopride *Sanofi Synthelabo, Port.†.*
Sulpiride (p.1028·3).

Lisopril *Neo Quimica, Braz.; Spirig, Switz.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Lisopril plus *Spirig, Switz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisopulm *Esseti, Ital.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Lisorane *Baxter, Mex.†.*
Isoflurane (p.1785·3).
General anaesthesia.

Lisoretic *Ipca, Rus.; Pharma Dynamics, S.Afr.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisoril *Ipca, India; Ipca, Rus.; IPCA, Singapore.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension.

Lisoril-5HT *Ipca, India.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lisosterol *Sanigen, Port.*
Probucol (p.1377·1).
Hyperlipidaemias.

Lisotec *Julphar, UAE.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lisotox *Cifarma, Braz.*
Acetylmethionine (p.1450·2); cynara (p.2291·2); liver extract (p.2337·3); choline citrate (p.1934·2); cyanocobalamin (p.1980·2).
Liver disorders.

Lisotran *Dovalle, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Lisotrex *Profarb, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Lisovyr *Elea, Arg.; Mintlab, Chile.*
Aciclovir (p.862·3).
Herpesvirus infections.

Lispor *Medipharm, Chile.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lispril *Rowex, Irl.; Siam Bheasach, Thai.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Lispril-hydrochlorothiazide *Rowex, Irl.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

List Medvedice Lecive *Leros, Cz.†.*
Bearberry (p.2263·3).
Urinary-tract disorders.

List Senny *Leros, Cz.*
Senna (p.1769·2).
Constipation.

List Vachty Trojliste *Leros, Cz.†.*
Menyanthes (p.2340·3).
Digestive disorders; liver and biliary disorders.

Listaflex *Finadiet, Arg.*
Carisoprodol (p.1894·1).
Muscle spasm.

Listerfluor *Pfizer Consumer, S.Afr.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Listerine
Note. This name is used for preparations of different composition.
Pfizer, Chile; Pfizer, Hong Kong.
⊗ Alcohol (p.1625·2); thymol (p.1664·3); cineole (p.2282·3); methyl salicylate (p.85·3); menthol (p.2340·1); benzoic acid (p.1630·2).
Dental plaque; gingivitis; halitosis; oral hygiene.

Pfizer Sante, Fr.
Benzoic acid (p.1630·2); cineole (p.2282·3); methyl salicylate (p.85·3); thymol (p.1664·3); menthol (p.2340·1).
Dental plaque prophylaxis; oral hygiene.

Pfizer, Indon.
⊗ Thymol (p.1664·3); cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); alcohol (p.1625·2).
Oral hygiene.

Pfizer, Malaysia†; Pfizer Consumer, Mex.; Pfizer Consumer, Port.†; Pfizer Consumer, USA.
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Minor mouth and throat irritation; oral hygiene.

Johnson & Johnson, NZ.
Benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3).
Oral hygiene.

Pfizer Consumer, Singapore.
⊗ Alcohol (p.1625·2); benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Gingivitis; oral hygiene.

Pfizer Consumer, Canad.
Cineole (p.2282·3); thymol (p.1664·3); menthol (p.2340·1).
Dental plaque prophylaxis; oral hygiene.

Listerine Antiseptic *Pfizer Consumer, S.Afr.*
⊗ Thymol (p.1664·3); alcohol (p.1625·2).
Dental plaque prophylaxis; gingivitis; mouth and throat infections.

Listerine Antiseptic Mouthwash *Pfizer Consumer, UK.*
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Oral hygiene.

Listerine Antiseptic Tartar Control *Pfizer Consumer, Canad.*
Cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3); zinc chloride (p.1999·1).
Dental plaque; oral hygiene.

Listerine Clasico *Interbelle, Arg.*
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Oral hygiene.

Listerine Cool Mint
Note. This name is used for preparations of different composition.
Interbelle, Arg.
Thymol (p.1664·3); cineole (p.2282·3); methyl salicylate (p.85·3).
Oral hygiene.

Pfizer Consumer, Singapore.
⊗ Alcohol (p.1625·2); benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1); sodium benzoate (p.1630·2); propyl alcohol (p.1660·2).
Gingivitis; oral hygiene.

Listerine Coolmint
Note. This name is used for preparations of different composition.
Pfizer, Indon.
⊗ Thymol (p.1664·3); cineole (p.2282·3); methyl salicylate (p.85·3); alcohol (p.1625·2); anethole (p.2258·1); pluronic; benzoic acid (p.1630·2); peppermint oil (p.1761·2); spearmint oil (p.2391·3).
Oral hygiene.

Pfizer, Philipp.
⊗ Benzoic acid (p.1630·2); alcohol (p.1625·2); cineole (p.2282·3); thymol (p.1664·3); anethole (p.2258·1); peppermint oil (p.1761·2); spearmint oil (p.2391·3).
Mouth disorders; oral hygiene.

Listerine Difesa *Pfizer Consumer, Ital.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Listerine Fresh Burst
Note. This name is used for preparations of different composition.
Interbelle, Arg.
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Oral hygiene.

Pfizer Consumer, Singapore.
⊗ Alcohol (p.1625·2); propyl alcohol (p.1660·2); benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Gingivitis; oral hygiene.

Listerine Fresh Citrus
Note. This name is used for preparations of different composition.
Pfizer Consumer, Ital.
Mint oil (p.2345·2); thymol (p.1664·3); cineole (p.2282·3); birch oil (p.2266·3).
Oral hygiene.

Pfizer, Philipp.
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Mouth disorders; oral hygiene.

Listerine Freshburst *Pfizer, Philipp.*
Benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3).
Mouth disorders; oral hygiene.

Listerine Original *Pfizer, Philipp.*
⊗ Benzoic acid (p.1630·2); alcohol (p.1625·2); cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3).
Mouth disorders; oral hygiene.

Listerine protection dents et gencives *Pfizer Sante, Fr.*
Cineole (p.2282·3); methyl salicylate (p.85·3); thymol (p.1664·3); menthol (p.2340·1); sodium fluoride (p.1962·2).
Oral hygiene.

Listerine Tartar Control
Note. This name is used for preparations of different composition.
Pfizer, Hong Kong.
⊗ Alcohol (p.1625·2); methyl salicylate (p.85·3); benzoic acid (p.1630·2); thymol (p.1664·3); cineole (p.2282·3); menthol (p.2340·1); zinc chloride (p.1999·1).
Dental plaque; dental tartar; gingivitis; halitosis.

Pfizer Consumer, Ital.
Mint oil (p.2345·2); thymol (p.1664·3); cineole (p.2282·3); birch tar oil (p.2266·3); zinc chloride (p.1999·1).
Oral hygiene.

Johnson & Johnson, NZ.
Benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); zinc chloride (p.1999·1).
Oral hygiene.

Pfizer, Philipp.
Cineole (p.2282·3); menthol (p.2340·1); methyl salicylate (p.85·3); thymol (p.1664·3); zinc chloride (p.1999·1).
Mouth disorders; oral hygiene.

Pfizer Consumer, Singapore.
⊗ Alcohol (p.1625·2); propyl alcohol (p.1660·2); benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); methyl salicylate (p.85·3); menthol (p.2340·1); zinc chloride (p.1999·1).
Gingivitis; oral hygiene.

Listerine Teeth and Gum Defence *Pfizer, Hong Kong.*
Methyl salicylate (p.85·3); benzoic acid (p.1630·2); thymol (p.1664·3); cineole (p.2282·3); menthol (p.2340·1); sodium fluoride (p.1962·2).
Dental caries; dental plaque; gingivitis; halitosis.

Listerine Teeth & Gum Defense *Pfizer, Philipp.*
Benzoic acid (p.1630·2); cineole (p.2282·3); thymol (p.1664·3); sodium fluoride (p.1962·2).
Mouth disorders; oral hygiene.

Listerine Tooth Defense *Pfizer Consumer, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Listermint
Note. This name is used for preparations of different composition.
Pfizer, Indon.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; oral hygiene.

Pfizer Consumer, UK.
Cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Listermint Arctic Fresh *Pfizer, Indon.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Oral hygiene.

Listermint Arctic Mint Mouthwash *Warner-Wellcome, USA.*
Glycerol (p.2314·2).

Listermint Con Fluor *Pfizer, Chile.*
⊗ Sodium fluoride (p.1962·2); alcohol (p.1625·2); thymol (p.1664·3); methyl salicylate (p.85·3); eugenol (p.2301·2).
Dental caries prophylaxis; oral hygiene.

Listermint with Fluoride *Pfizer Consumer, UK.*
Sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Listover *Biosynthesis, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Listran *Uriach, Spain.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Listril *Torrent, Braz.; Torrent, Cz.†; Torrent, Rus.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Lisvifar *Farcoral, Mex.†.*
Multivitamin preparation (p.1922·1).

Lit-300 *Hua, Thai.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Litacor *Korea United, Philipp.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; colorectal cancer; rescue after high-dose methotrexate.

Litak *Orphan, Austral.; Lipomed, Cz.; Lipomed, Denm.; Medifront, Fin.; Lipomed, Fr.; Lipomed, Ger.; Haupt, Israel; Lipomed, Neth.; Lipomed, Port.; Lipomed, Switz.; Lipomed, UK.*
Cladribine (p.701·1).
Chronic lymphocytic leukaemia; hairy-cell leukaemia; lymphoplasmacytic lymphoma; lymphoproliferative disorders; non-Hodgkin's lymphoma.

Litalgin *Leiras, Fin.*
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).
Gastrointestinal, biliary, and renal colic.

Litalir *BMS, Austria; BMS, Cz.; BMS, Ger.; BMS, Hung.; BMS, Philipp.; BMS, Switz.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms; myeloproliferative disorders; polycythaemia vera; psoriasis; thrombocythaemia.

Litarex *Alpharma, Denm.; Alpharma, Neth.; Team Medica, Switz.*
Lithium citrate (p.401·3).
Bipolar disorder; depression; mania.

Litec *Novartis, Philipp.*
Pizotifen malate (p.624·2).
Anorexia; depression.

Liten *Bosnalijek, Rus.*
Lisinopril (p.1325·2).

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lithane *Erfa, Canad.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Litheum *Valdecasas, Mex.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Lithias-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Lithicarb *Aspen, Austral.; Pacific, Hong Kong; Pacific, NZ.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania; schizophrenia.

Lithimole *Cooper (Κοπερ), Gr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Lithioderm *Labcatal, Fr.*
Lithium gluconate (p.406·1).
Seborrhoeic dermatitis.

Lithiofalk *Galenica, Gr.†.*
Ursodeoxycholic acid (p.2408·1); chenodeoxycholic acid (p.2280·1).

Lithiofor *Nikolakopoulos (Νικολακοπουλος), Gr.; Vifor, Hong Kong; Vifor, Switz.*
Lithium sulfate (p.406·1).
Bipolar disorder; depression; mania; premenstrual syndrome; psychoses.

Lithionit *AstraZeneca, Norw.; AstraZeneca, Swed.*
Lithium sulfate (p.406·1).
Bipolar disorder; mania.

Lithiorsan *Plata, Arg.*
Thiomersal (p.1663·3).
Antiseptic.

Lithiun *Elisium, Arg.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Lithobid *Solvay, USA.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Lithofalk *Merck, Austria†; Falk, Ger.*
Chenodeoxycholic acid (p.2280·1); ursodeoxycholic acid (p.2408·1).
Adjunct to lithotripsy; cholesterol gallstones.

Lithonate *Approved Prescription Services, UK.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Lithostat *Mission Pharmacal, USA.*
Acetohydroxamic acid (p.2245·1).
Adjunct in urinary-tract infection with urea-splitting organisms.

Lithurex S *Phonix, Ger.†.*
Magnesium citrate (p.1743·2); citric acid (p.2284·1); sodium citrate (p.1673·3); potassium citrate (p.1673·2).
Urinary-tract disorders.

Lithuril *Kocak, Turk.*
Lithium carbonate (p.401·3).
Behaviour disorders; bipolar disorder; depression; mania.

Litiax *Novag, Spain.*
Gall (p.2307·3).
Renal calculi.

Litican *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Neth.*
Alizapride hydrochloride (p.1704·3).
Nausea; vomiting.

Liticarb *Parma, Hung.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Litiocar *Biosintetica, Braz.†.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; migraine and other vascular headaches; neutropenia; schizophrenia.

Litiofarm *ICN, Arg.†.*
Lithium succinate (p.1604·1); zinc sulfate (p.1999·2).
Seborrhoeic dermatitis.

Litiset *Diba, Mex.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium subacetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

Lito *Orion, Fin.*
Lithium carbonate (p.401·3).
Bipolar disorder.

Litocid *Labor, Pol.*
Potassium citrate (p.1673·2).
Urinary alkalinisation.

Litocit *Apsen, Braz.*
Potassium citrate (p.1673·2).
Renal calculi.

Litoff *Caber, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Litonate *Biotech, Venez.*
Centella (p.1592·3).

LitoZin *Lane, UK.*
Rose fruit extract (p.2381·2).
Joint disorders.

Litropina *Quim-Far, Venez.*
Homatropine methylbromide (p.1881·3).
Smooth muscle spasm.

Little Colds Cough Formula *Vetco, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Little Tummys Laxative *Vetco, USA.*
Sennosides (p.1769·3).
Constipation.

Littmox *Littman, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Litursol *Crinos, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Litusix *Dollder, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Litusix Compositum *Dollder, Venez.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol (p.1120·1).
Respiratory-tract congestion.

Liv 52
Note. This name is used for preparations of different composition.
Himalaya Drug, Pol.
Achillea (p.2245·2); capparis spinosa; cassia occidentalis; cichorium intybus; mandur bhasma calx; solanum nigrum (p.2267·1); tamarix gallica; terminalia arjuna.
Liver poisoning; tonic.

Ebi, Switz.
Capparis spinosa; cichorium intybus; solanum nigrum; cassia occidentalis; terminalia arjuna; achillea millefolium; tamarix gallica; ferrum bhasma.
Gastrointestinal disorders; tonic.

Himalaya, Rus.
Oral drops: Caparis sinosa; cichorium intybus; black nightshade (p.2267·1); senna occidentalis; arjuna; cassia occidentalis; achillea (p.2245·2); tamarix gallica.
Liver disorders.

Himalaya, Rus.
Tablets: Caparis sinosa; cichorium intybus; black nightshade (p.2267·1); arjuna; cassia occidentalis; achillea (p.2245·2); tamarix gallica; ferrum bhasma.
Liver disorders.

Livadex *Restan, S.Afr.†.*
Vitamin B substances; liver extracts; caffeine (p.1922·1).
Tonic.

Livage *Aristo, India.*
Lecithin (p.2332·2); phosphatidyl choline (p.2367·1); phosphatidyl ethanolamine; phosphatidyl serine (p.2367·1); phosphatidyl inositol.

Livalo *Kowa, Jpn.*
Pitavastatin calcium (p.1373·1).
Hypercholesterolaemia.

Livamine *Bioceuticals, UK.*
Multivitamin and mineral preparation (p.1922·1).

Livari *Diba, Mex.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Livarole *Nizpharm, Rus.*
Ketoconazole (p.539·1).
Fungal vaginal infections.

Liv-Detox *Blackmores, Austral.†.*
-Methionine (p.1450·2); choline bitartrate (p.1934·2); inositol (p.2325·2); glutamine (p.1947·2); pyridoxine hydrochloride (p.1978·2); riboflavin (p.1977·2); sodium sulfate (p.1771·3).
Liver disorders.

Livensa *Procter & Gamble, Cz.; Procter & Gamble, Port.*
⊗ Testosterone (p.2129·3).
Sexual hypoactivity following oophorectomy and hysterectomy.

Liver Tonic Herbal Formula 6 *Vitelle, Austral.†.*
Milk thistle (p.1452·1); taraxacum (p.2395·1); cynara (p.2291·2); garlic (p.2309·2).
Digestive disorders; liver tonic.

Liveraide *Herbs & Nature, Philipp.*
Silymarin (p.1452·2).
Nutritional supplement.

Liverall *Sankyo, Hong Kong†.*
Di-isopropylammonium dichloroacetate (p.1265·1); calcium gluconate (p.1675·3).
Liver disorders.

Liverasi *Francia, Ital.†.*
Cogalactoisomerase sodium (p.2285·3).
Liver disorders.

Livergen F *Degorts, Mex.†.*
Vitamin preparation (p.1922·1).

Liverine *Cardinal, Philipp.*
Silymarin (p.1452·2); vitamin B substances (p.1922·1); lecithin (p.2332·2).
Liver disorders.

Livermin *Korean Ginseng, Philipp.*
Silymarin (p.1452·2); vitamin B substances; palm oil; beeswax; soybean oil (p.1922·1).
Liver disorders.

Liverton *SIFFRA, Ital.*
Vitamins; minerals; lactoferrin (p.2330·1); desmodium adscendens; milk thistle (p.1452·1); *Lactobacillus paracasei* (p.2372·3).
Liver disorders.

Livguard *CCM, Malaysia.*
Soya lecithin (p.2332·2); vitamin B substances; vitamin E (p.1922·1).
Dietary supplement.

Livial *Organon, Austral.; Organon, Belg.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, India; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Organon, Singapore; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, Venez.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Livianne *Bago, Arg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Liviel *Organon, Austria.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Liviella *Organon, Ger.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Livifem *Donmed, S.Afr.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Livifol *Biosintex, Arg.*
Folic acid (p.1940·1).
Anaemias.

Livimex *Kowa, Jpn.*
⊗ Prednisolone valeroacetate (p.1542·1).
Skin disorders.

Liviton *Adcock Ingram, S.Afr.*
Vitamins; minerals; caffeine; liver extract (p.1922·1).
Tonic.

Livitrinsic-f *Goldline, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); intrinsic factor (p.2326·3); vitamin B substances (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Livocab *McNeil, Ger.; Janssen-Cilag, Ital.; Janssen-Cilag, Neth.; Janssen-Cilag, Spain.*
Levocabastine hydrochloride (p.583·1).
Allergic conjunctivitis; allergic rhinitis.

Livocip *Cipla, India.*
Tricholine citrate (p.1934·2); sorbitol (p.1965·1).

Livogen
Note. This name is used for preparations of different composition.
Merck, India†.
Capsules: Liver (p.2337·3); dried yeast (p.1998·3); vitamin B substances (p.1975·1); folic acid (p.1940·1); vitamin C (p.1983·3); ferrous fumarate (p.1938·3).
Anaemias.

Merck, India†.
Oral liquid: Liver; dried yeast; vitamin B ; nicotinic acid (p.1922·1).
Tonic.

Livogen Captab *Merck, India.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Anaemias.

Livogen Hemtonic *Merck, India.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1).
Anaemias.

Livogen-Z *Merck, India.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); zinc sulfate (p.1999·2).
Anaemias.

Livolin *Mega Lifesciences, Malaysia; Medicap, Rus.*
Essential phospholipids; vitamin B substances; vitamin E (p.1922·1).
Liver disorders.

Livolon *Biolab Sanus, Braz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Livoluk *Panacea, India.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Livomarin *Varifarma, Arg.*
Conjugated oestrogens (p.2087·2).

Livomedrox *Varifarma, Arg.*
Medroxyprogesterone (p.2113·3).

Livomonil *Varifarma, Arg.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Livoncel *Scherer, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Livosil-B *Centaur, India.*
Silymarin (p.1452·2); thiamine; riboflavin; pyridoxine; nicotinamide; pantothenic acid; vitamin B (p.1922·1).
Liver disorders.

Livostin *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Novartis Ophthalmics, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Gr.; KRKA, Hung.†; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Shinyaku, Jpn; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Norw.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen, Thai.†; Janssen-Cilag, Thai.†; Novartis, Turk.; Janssen-Cilag, UK; Novartis Ophthalmics, USA†; Janssen-Cilag, Venez.*
Levocabastine hydrochloride (p.583·1).
Allergic conjunctivitis; allergic rhinitis.

Livotab *Woelm, Ger.†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Livovid *Hovid, Malaysia.*
Lecithin; vitamin B substances; vitamin E (p.1922·1).
Dietary supplement in liver disorders.

Livstim *Mediherb, Austral.†.*
Greater celandine (p.2317·1); chionanthus virginica; cynara (p.2291·2); milk thistle (p.1452·1); taraxacum (p.2395·1).
Liver disorders.

Livten *Ativus, Braz.*
Polyunsaturated fatty acids.
Dietary supplement.

Livten Vit *Ativus, Braz.*
Vitamin B ; betacarotene; vitamin C; magnesium; borage oil (p.2267·3) (p.1922·1).

Livton Complex *Mediherb, Austral.†.*
Milk thistle (p.1452·1); taraxacum (p.2395·1); cynara (p.2291·2); greater celandine (p.2317·1); chionanthus virginica.
Liver disorders.

Lixacol *Faes, Spain.*
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Lixamide *Xeragen, S.Afr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Lixi *Biotech, Venez.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Lixidol *Roche, Ital.*
Ketorolac trometamol (p.74·2).
Pain.

Lixin *Henning, Ger.; Sanofi Synthelabo, Ger.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Lixir *Abigo, Swed.*
Multivitamins (p.1922·1); caffeine.

Lixocam *Med-One, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Lixogan *Tocogino, Mex.†.*
Naproxen (p.92·3).
Inflammation; pain.

Lixtress *Pharmacare, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Vitamin B deficiency.

Lizan *Nobel, Turk.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; muscle spasm; premedication; status epilepticus.

Lizarona *Northia, Arg.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Lizepat *Cosmopharm, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Lizik *Aksu, Turk.*
⊗ Furosemide (p.1292·1).
Oedema.

Lizipaina *Boehringer Ingelheim, Spain.*
Bacitracin (p.210·3); muramidase (p.2348·1); papain (p.2362·3).
Mouth and throat inflammation.

Lizocalcio *SJA, Gr.*
Calcium folinate (p.1943·3).
Reduction of folic acid antagonist toxicity.

Lizolid *Glenmark, India.*
Linezolid (p.293·3).
Bacterial infections.

Lizor *Pharos, Indon.*
Cefprozil (p.232·2).
Bacterial infections.

Lizovag *Novag, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Lizul *Baldacci, Port.†.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Llanol *Medifarma, Indon.; Therapharma, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Llanten *Ximena Polanco, Chile.*
Homoeopathic preparation.

Llantusil *Soria Natural, Spain†.*
Eucalyptus (p.2301·2); satureja montana; wild thyme (p.2415·3); althaea (p.2253·3); coltsfoot (p.1555·1); ribwort plantain (p.2379·1).
Respiratory-tract infections.

Lloyd's Cream *Thornton & Ross, UK.*
Diethylamine salicylate (p.47·2).
Musculoskeletal and soft-tissue disorders.

LM6
Note. This name is used for preparations of different composition.
AF, Mex.
Oral solution: Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Fever; hypersensitivity; pain.

AF, Mex.
Tablets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, mepyramine maleate, phenylephrine hydrochloride, and caffeine.
Cold symptoms.

LM Dextran *Euro-Med, Philipp.*
⊗ Dextran 40 (p.1059·1).
Shock; thromboembolism prophylaxis.

LMD *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Disorders of leucine metabolism.

LMX *Cadila, India.*
Amoxicillin trihydrate (p.202·2); *Lactobacillus sporogenes* (p.2372·3).
Bacterial infections.

L-M-X4 *Ferndale, USA.*
Lidocaine (p.1862·3).
Formerly known as ELA-Max.
Anorectal disorders; topical anaesthesia.

Lo-Acid *Be-Tabs, S.Afr.*
Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Antacid; flatulence.

Lobac *Seatrace, USA.*
Salicylamide (p.121·2); phenyltoloxamine (p.588·1); paracetamol (p.108·1).
Musculoskeletal pain.

Lobafen *IAE, Philipp.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Lobamine-Cysteine *Pierre Fabre, Fr.*
Methionine (p.1450·1); cysteine hydrochloride (p.1936·3).
Alopecia.

Lobana *Ulmer, USA.*
Soap-free skin cleanser.

Lobana Body *Ulmer, USA.*
Emollient and moisturiser.

Lobana Derm-Aide *Ulmer, USA.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); vitamin E (p.1992·2).
Skin disorders.

Lobana Peri-Garde *Ulmer, USA.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); vitamin E (p.1992·2); chloroxylenol (p.1640·2).
Skin disorders.

Lobate *Nicholas Piramal, India.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Lobate-G *Nicholas Piramal, India.*
⊗ Clobetasol propionate (p.1522·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Lobate-GM *Nicholas Piramal, India.*
⊗ Clobetasol propionate (p.1522·2); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Lobate-M *Nicholas Piramal, India.*
⊗ Clobetasol propionate (p.1522·2); miconazole nitrate (p.541·3).
Infected skin disorders.

Lobelia Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Lobelo *Rafarm, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Lobem *Eczacibasi, Turk.*
Moclobemide (p.411·1).
Depression; social phobia.

Lobesol *Sunward, Malaysia†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Lobeta *Betapharm, Ger.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lobevat *Stiefel, Chile†; Stiefel, Mex.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Lobivon *Menarini, Gr.; Menarini, Ital.; Menarini, Neth.; Menarini, Spain.*
⊗ Nebivolol hydrochloride (p.1347·1).
Hypertension.

Lobu *Ohara, Jpn.*
Loxoprofen sodium (p.78·1).
Inflammation; pain.

Locabase *Pierre Fabre, Fr.*
Basis for topical preparations.

Locabiosol *Servier, Austria; Servier, Chile†; Servier, Ger.; Servier, Port.*
Fusafungine (p.279·2).
Upper respiratory-tract infection and inflammation.

Locabiotal
Note.This name is used for preparations of different composition.
Servier, Belg.; Servier, Braz.; Servier, Gr.; Servier, Hong Kong†; Servier, Irl.; Stroder, Ital.; Servier, Malaysia; Servier, Philipp.; Servier, S.Afr.; Servier, Switz.; Servier, Turk.; Servier, UK†.
Fusafungine (p.279·2).
Upper respiratory-tract infection and inflammation.

Ardix, Fr.
Peppermint oil (p.1761·2).
Formerly contained fusafungine.
Upper respiratory-tract infections.

Locacid *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre, Cz.; Pierre Fabre, Fr.; Primal, Hong Kong†; Pierre Fabre, Israel; Pierre Fabre Dermatologie, Pol.; Pierre Fabre, Port.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders; psoriasis.

Locacorten *Riemser, Ger.; Amdipharm, Neth.; Novartis, Switz.*
⊗ Flumetasone pivalate (p.1531·1).
Skin disorders.

Locacorten mit Neomycin *Novartis, Austria.*
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Locacorten Neomycin *Novartis, Gr.†.*
⊗ Flumetasone (p.1531·1); neomycin (p.305·1).
Topical corticosteroid with antimicrobial.

Locacorten with Neomycin *Novartis, Israel†.*
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Skin disorders.

Locacorten Tar *Novartis, Austria; Novartis, Cz.†; Novartis, Hong Kong†.*
⊗ Flumetasone pivalate (p.1531·1); coal tar (p.1616·2); salicylic acid (p.1612·2).
Skin disorders.

Locacorten Vioform *Novartis, Austral.; Novartis, Austria; Paladin, Canad.; Amdipharm, Denm.; Amdipharm, Fin.; Riemser, Ger.; Amdipharm, Neth.; Novartis, S.Afr.; Novartis, Swed.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected ear disorders; infected skin disorders.

Locacortene
Note.This name is used for preparations of different composition.
Novartis Consumer, Belg.
⊗ Flumetasone pivalate (p.1531·1).
Skin disorders.

Genopharm, Fr.†.
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Locacortene Tar *Novartis Consumer, Belg.†.*
⊗ Flumetasone pivalate (p.1531·1); coal tar (p.1616·2); salicylic acid (p.1612·2).
Skin disorders.

Locacortene Vioform *Novartis, Turk.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected skin disorders.

Locacortene Vioforme *Novartis Consumer, Belg.†; Genopharm, Fr.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
External ear disorders; infected skin disorders.

Localin *Fischer, Israel.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Localone *Pierre Fabre, Fr.; Pierre Fabre, Port.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Localyn
Note.This name is used for preparations of different composition.
Recordati, Ital.
Ear drops: ⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Ear disorders.

Recordati, Ital.
Lotion; ointment; topical solution: ⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Recordati, Ital.
Nasal spray: ⊗ Fluocinolone acetonide (p.1531·3); clonazoline hydrochloride (p.1554·2).
Nasal inflammation and hypersensitivity.

Localyn SV *Recordati, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Nasal inflammation and hypersensitivity.

Localyn-Neomicina *Recordati, Ital.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Locap *Sandoz, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Locapred *Pierre Fabre, Fr.; Pierre Fabre, Port.; Pierre Fabre, Switz.*
⊗ Desonide (p.1525·1).
Skin disorders.

Locarp *Cadila, India.*
Pilocarpine nitrate (p.1884·3).
Production of miosis.

Locasalen *Novartis, Austria; Novartis Consumer, Belg.; Riemser, Ger.; Novartis, Hong Kong; Novartis, Indon.; Amdipharm, Neth.; Sandoz, Philipp.; Novartis, Switz.; Novartis, Thai.; Novartis, Venez.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Pruritus; scalp disorders; skin disorders.

Locasalene *Genopharm, Fr.; Novartis, Gr.; Novartis, Turk.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders.

Locaseptil-Neo *Drossapharm, Switz.*
⊗ Prednisolone acetate (p.1541·1); cinchocaine (p.1857·2).
Nasal and buccal lesions.

Locasol *Nutricia, Austral.; Scientific Hospital Supplies, Irl.; Baxter, NZ; Nutricia, NZ; Scientific Hospital Supplies, UK.*
Low-calcium infant feed (p.1922·1).
Calcium and vitamin D restriction; calcium intolerance; hypercalcaemia.

Locason *Proel, Gr.†.*
⊗ Betamethasone valerate (p.1519·1).
Topical corticosteroid.

Locason-N *Proel, Gr.*
⊗ Betamethasone valerate (p.1519·1).
Inflammatory skin conditions.

Locasyn *Roche, Denm.†.*
⊗ Flunisolide (p.1531·1).
Rhinitis.

Locatop *Pierre Fabre Dermo-Cosmetique, Arg.; Pierre Fabre Dermatologie, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Israel; Pierre Fabre Dermatologie, Pol.; Pierre Fabre, Switz.*
⊗ Desonide (p.1525·1).
Skin disorders.

L'Oceane *Thalgo, Fr.*
Sea water (p.1686·1).
Tonic.

Locemix *Euroderm, Arg.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Loceryl *Galderma, Arg.; Galderma, Austral.; AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Chile; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Ger.; Lavipharm, Gr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Malaysia; Galderma, Mex.; Galderma, NZ; Galderma, Norw.; Galderma, Pol.; Roche, Rus.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Swed.; Galderma, Switz.; Galderma, UK; Galderma, Venez.*
Amorolfine hydrochloride (p.523·1).
Fungal skin and nail infections.

Locetar *Galderma, Arg.†; Galderma, Ital.; Galderma, Philipp.; Galderma, Port.; Galderma, Spain.*
Amorolfine hydrochloride (p.523·1).
Fungal skin and nail infections.

Lochol
Note.This name is used for preparations of different composition.
Novartis, Hung.; Tanabe, Jpn.
Fluvastatin sodium (p.1290·2).
Atherosclerosis; hypercholesterolaemia.

Siam Bheasach, Thai.
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Locholes *TO-Chemicals, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Locholest *Warner Chilcott, USA.*
Colestyramine (p.1252·3).
Hypercholesterolaemia; pruritus associated with biliary obstruction.

Lociherp *Maigal, Arg.*
⊗ Urea (p.1620·2).
Skin disorders.

Lociherp Liposomas Antiage *Maigal, Arg.*
Collagen (p.2286·1); centella (p.1592·3).
Skin disorders.

Lociherp Liposomas Vitaminado *Maigal, Arg.*
Centella (p.1592·3); collagen (p.2286·1); vitamin A; vitamin E; vitamin C (p.1922·1); panthenol (p.2362·1); allantoin (p.1588·1).
Skin disorders.

Locilan *Pfizer, Austral.*
Norethisterone (p.2119·3).
Progestogen-only contraceptive.

Locion Axel *Grisi, Mex.†.*
Sulfur (p.1614·1); sulfacetamide (p.335·3).
Acne.

Locion Corporal Suavizante AHA Formula 405 *Dermaclin, Mex.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Skin disorders; sunscreen.

Locion Humectante *Johnson & Johnson, Venez.†.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Locion Limpiadora AHA Formula 405 *Dermaclin, Mex.†.*
Soap substitute.
Acne; xerosis.

Lock-2 *Cadila, Cz.†.*
Cimetidine (p.1716·2).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatitis; peptic ulcer; Zollinger-Ellison syndrome.

Lockesol *Dzwon, India.*
Solution 1, sodium chloride; potassium chloride; sodium phosphate; sodium bicarbonate; solution 2, calcium chloride; magnesium chloride; glucose; glutathione disulfate (p.1667·1).
Eye irrigation.

Lockets *Mars, UK.*
Menthol (p.2340·1); cineole (p.2282·3); honey (p.1948·2); glycerol (p.2314·2).
Nasal congestion; sore throat.

Lockets Medicated Linctus *Thornton & Ross, UK.*
Ipecacuanha (p.1562·3); honey (p.1948·2); glucose (p.1945·3); glycerol (p.2314·2); menthol (p.2340·1).
Coughs; sore throats.

Locobase *Astellas, Fin.; Astellas, Ital.; Astellas, Swed.; Fujisawa, Switz.*
Vehicle for topical preparations.

Locoid *Eurolab, Arg.; Astellas, Belg.; Eurofarma, Braz.; Labomed, Chile; Astellas, Cz.; Yamanouchi, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Hung.; Astellas, Indon.; Astellas, Irl.; Liomont, Mex.; CSL, NZ; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; Astellas, Port.; Yamanouchi, Rus.; Astellas, S.Afr.; Astellas, Swed.; Fujisawa, Switz.; Santa, Turk.; Astellas, UK; Ferndale, USA.*
⊗ Hydrocortisone butyrate (p.1535·3).
Eczema; psoriasis; scalp disorders; skin disorders.

Locoid C *Astellas, Irl.; CSL, NZ; Yabrofarma, Port.†; Astellas, UK.*
⊗ Hydrocortisone butyrate (p.1535·3); chlorquinaldol (p.242·3).
Infected skin disorders.

Locoidol *Yamanouchi, Denm.; Yamanouchi, Fin.†; Astellas, Norw.*
⊗ Hydrocortisone butyrate (p.1535·3); chlorquinaldol (p.242·3).
Infected skin disorders.

Locoidon *Zak, Austria; Astellas, Ital.*
⊗ Hydrocortisone butyrate (p.1535·3).
Skin disorders.

LOCOL *Novartis, Ger.*
Fluvastatin sodium (p.1290·2).
Hypercholesterolaemia.

Locomin *UCB, Switz.†.*
Aceclofenac (p.14·3).
Musculoskeletal and joint disorders.

Locomucil *Pharmazam, Spain†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Locorten
Note.This name is used for preparations of different composition.
Novartis, Braz.†.
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Formerly known as Locorten Neomicina.
Skin disorders.

Novartis, Venez.†.
⊗ Flumetasone pivalate (p.1531·1).
Skin disorders.

Novartis, Ital.
Cream; ointment: ⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Otitis externa; skin disorders.

Novartis, Ital.
Ear drops; oral drops: ⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Gingivitis; oral inflammatory lesions; otitis.

Novartis, Ital.†.
Lotion: ⊗ Flumetasone pivalate (p.1531·1).
Otitis externa; skin disorders.

Locorten Vioform *AFT, NZ; Amdipharm, UK.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected ear disorders.

Locorten Vioformio *Novartis, Braz.; Novartis, Ital.; Novartis Consumer, Port.†.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected skin disorders; otitis externa.

Locorten Vioformo *Novartis, Arg.†; Novartis, Venez.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected ear disorders; infected skin disorders.

Locose *T Man, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Locrim *Pharma Investi, Chile.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections with inflammation.

Loctenk *Biotenk, Arg.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Loctenk D *Biotenk, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Locula *East India Pharma, India.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Lodales *Sanofi-Aventis, Fr.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Lodecon *Solas, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Allergic disorders; cold and influenza symptoms.

Lodep *Sunthi Sepuri, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Lodeprem *Velka, Gr.*
Citalopram (p.385·3).
Depression.

Loderm *Vinas, Spain.*
Erythromycin laurilsulfate (p.272·3).
Acne.

Loderm Retinoico *Vinas, Spain.*
Erythromycin laurilsulfate (p.272·3); tretinoin (p.1618·1).
Acne.

Lodia *Sanbe, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lodimol *Kener, Mex.*
Dipyridamole (p.1268·1).

Lodine *Wyeth Lederle, Austria†; Algol, Fin.; Sankyo, Fr.; Wyeth, Hong Kong; Wyeth Lederle, Ital.†; Wyeth, Mex.†; Wyeth Lederle, Port.†; Sigma-Tau, Switz.; Wyeth, Turk.; Shire, UK; Wyeth-Ayerst, USA†; Wyeth, Venez.†.*
Etodolac (p.52·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lodipen *Royton, Braz.†.*
Amlodipine besilate (p.1214·1).
Hypertension.

Lodipil *Geolab, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Lodipin *Farmanic, Gr.; Roemmers, Venez.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Lodipres *Laboratorios Chile, Chile.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Lodistad *Stada, Philipp.*
Felodipine (p.1285·3).
Hypertension.

Lodixal *Abbott, Belg.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Lodoc *Columbia, Arg.*
Benzocaine (p.1854·1).
Obesity.

Lodomer *Mersifarma, Indon.*
Haloperidol (p.1000·2).
Behaviour disorders; psychoses.

Lodopin *Kalbe, Indon.; Astellas, Jpn.*
Zotepine (p.1040·1).
Schizophrenia.

Lodosyn *BMS, USA.*
Carbidopa (p.803·1).
Parkinsonism.

Lodot *BA Farma, Port.†.*
Etodolac (p.52·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Lodoz *Merck, Belg.; Merck, Cz.; Merck-Lipha, Fr.; Merck, Hong Kong; Merck, Hung.; Merck, India; Merck, Indon.; Merck, Ital.; Merck, Norw.; Merck, Singapore; Merck, Switz.; Merck, Thai.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lodrane *ECR, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Allergic rhinitis; nasal congestion.

Lodrane 12 *ECR, USA.*
Brompheniramine maleate (p.569·2).
Formerly known as Lodrane Allergy.
Allergic rhinitis.

Lodrane 24 *ECR, USA.*
Brompheniramine maleate (p.569·2).
Allergic rhinitis.

Lodrane D *ECR, USA.*
Pseudoephedrine tannate (p.1572·1); brompheniramine tannate (p.569·3).
Upper respiratory-tract disorders.

Lodrane 12D *ECR, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Allergic rhinitis; nasal congestion.

Lodronat *Roche, Austria; Roche, Chile†; Roche Diagnostics, Cz.; Roche, Hung.†.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolysis of malignancy; osteoporosis; Paget's disease of bone; sympathetic pain syndromes.

Lodulce *Littman, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Lodyfen *Grin, Mex.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders; prevention of miosis and cystoid macular oedema in ocular surgery.

Loesfer *Pharmacia, Switz.†.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Loestrin *Galen, UK; Warner Chilcott, USA.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Loestrin 1.5/30 *Warner Chilcott, Canad.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs contain 7 inert tablets.
Combined oral contraceptive.

Loestrin Fe *Warner Chilcott, USA.*
21 Tablets, norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
Loestrin Fe 24 contains 24 tablets and 4 tablets, respectively.
Combined oral contraceptive.

Loette *Wyeth, Arg.; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth, Chile†; Wyeth, Cz.; Wyeth, Gr.; Wyeth, Hung.; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, NZ; Wyeth, Norw.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain.*
21 Tablets levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Acne in females; combined oral contraceptive.

Loexom *IQFA, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Loexom FC *IQFA, Mex.*
Ambroxol (p.1550·3); amoxicillin (p.202·2).
Respiratory-tract congestion.

Loexom FS *IQFA, Mex.*
Ambroxol (p.1550·3); amoxicillin (p.202·2).
Respiratory-tract congestion.

Lofacol *Dexa, Hong Kong†; Ferron, Indon.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lofenac *Chew, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Lofenalac *Mead Johnson, Austral.†; Mead Johnson Nutritionals, Canad.†; Mead Johnson, Fr.†; Mead Johnson, Irl.†; Mead Johnson, Israel; Mead Johnson, Ital.†; Mead Johnson Nutritionals, Thai.†.*
Food for special diets (p.1922·1).
Phenylketonuria.

Lofenax *Geofman, Philipp.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; renal colic.

Lofenin *Solvang, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders congestion.

Lofenoxal *Pfizer Consumer, Austral.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Lofensaid *Trinity, UK†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lofibra *Gate, USA.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Loflox *Meyer, Venez.*
Lomefloxacin (p.295·3).
Bacterial infections.

Lofostin *Farmedia, Gr.*
Levocarnitine (p.1932·2).
Myocardial ischaemia.

Lofoto *Rafarm, Gr.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections with inflammation.

Loftan *GSK, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Lofton *Abbott, Arg.; Abbott, Spain.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Loftyl *Abbott, Austria; Abbott, Belg.; Abbott, Chile†; Abbott, Fr.†; Abbott, Gr.; Abbott, Indon.; Abbott, Ital.; Abbott, Mex.†; Abbott, Neth.; Abbott, Port.; Abbott, S.Afr.; Abbott, Switz.; Abbott, Venez.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Logafox *Meprofarm, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Logan *Ist. Chim. Inter., Ital.*
Citicoline sodium (p.2283·3).
Parkinsonism.

Loganil *Arex, Venez.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Logascid *AstraZeneca, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal hyperacidity; peptic ulcer.

Logastin *Osoth, Thai.*
Simeticone (p.1770·2).
Flatulence; meteorism.

Logastric *Biothera, Belg.*
Omeprazole magnesium (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Logat *Libbs, Braz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Logazil *Loeffler, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Logen *Goldline, USA.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Logesic *Church, Mex.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Logest *Schering, Cz.; Schering, Pol.; Schering, Rus.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Logical
Note.This name is used for preparations of different composition.
Ivax, Arg.
Magnesium valproate (p.511·3) or sodium valproate (p.508·2).
Epilepsy.

Recalcine, Chile.
Vitamin E; ascorbic acid; ubidecarenone (p.1922·1).
Antoxidant preparation.

Serum Institute, India.
Calcium carbonate (p.1714·1); lysine hydrochloride (p.1955·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Armstrong, Mex.
Crospovidone (p.2146·1).
Diarrhoea.

Logican *Win-Medicare, India.*
Fluconazole (p.532·1).
Fungal infections.

Logicin Chest Rub *Sigma, Austral.†.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Nasal congestion.

Logicin Cough & Cold *Sigma, Austral.†.*
Codeine phosphate (p.37·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Logicin Cough Mixture for Congested Chesty Coughs *Sigma, Austral.†; Sigma, Hong Kong†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Logicin Cough Mixture for Dry Coughs *Sigma, Austral.†; Sigma, Hong Kong†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Logicin Cough Suppressant *Sigma, Austral.†.*
Pholcodine (p.1570·2).
Coughs.

Logicin Expectorant *Sigma, Austral.†.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Logicin Flu Strength *Sigma, Austral.†; Sigma, Hong Kong†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Logicin Flu Strength Day & Night *Sigma, Austral.; Sigma, Hong Kong.*
Daytime tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); night-time tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Logicin Hay Fever *Sigma, Austral.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Hay fever.

Logicin Junior Childrens Cough Mixture *Sigma, Austral.†; Sigma, Hong Kong†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Logicin Natural Lozenges *Sigma, Austral.†.*
Zinc gluconate (p.1999·2); echinacea (p.2298·1); vitamin C (p.1983·3); honey (p.1948·2).

Logicin Rapid Relief
Note.This name is used for preparations of different composition.
Sigma, Austral.; Sigma, Hong Kong.
Lozenges: Lidocaine hydrochloride (p.1862·3); benzydamine hydrochloride (p.27·3); dichlorobenzyl alcohol (p.1642·1).
Mouth and throat disorders; sore throat.

Sigma, Austral.; Sigma, Hong Kong.
Nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Logicin Sinus *Sigma, Austral.; Sigma, Hong Kong.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Logicin Sore Throat *Sigma, Austral.†.*
Povidone-iodine (p.1659·2).
Sore throat.

Logiflox *Biocodex, Fr.*
Lomefloxacin hydrochloride (p.295·2).
Cystitis in women.

Logimat *AstraZeneca, Belg.*
⊗ Felodipine (p.1285·3); metoprolol succinate (p.1338·1).
Hypertension.

Logimax
AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Israel; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Philipp.; AstraZeneca, Rus.; Astra, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.
⊗ Felodipine (p.1285·3); metoprolol succinate (p.1338·1).
Angina pectoris; hypertension.

AstraZeneca, Hong Kong.
⊗ Felodipine (p.1285·3); metoprolol tartrate (p.1338·1).
Hypertension.

Logirene *Pfizer, Fr.*
⊗ Furosemide (p.1292·1); amiloride hydrochloride (p.1209·2).
Heart failure.

Logistic *Craveri, Arg.*
Gabapentin (p.482·3).
Epilepsy; peripheral neuropathy; postherpetic neuralgia.

Logoderm *Schering-Plough, Austral.†; Essex, Chile†; Schering-Plough, Mex.; Schering-Plough, NZ†.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Logrosal *Silesia, Chile†.*
Triflusal (p.1418·3).
Thromboembolic disorders.

Logroton *Sankyo, Belg.; Sankyo, Fr.; Novartis, Malaysia; Sankyo, Switz.*
⊗ Metoprolol tartrate (p.1338·1); chlortalidone (p.1243·3).
Hypertension.

Logynon *Schering, Irl.; Schering, Israel†; Berlipharm, Neth.; Schering, Philipp.; Bayer, UK.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Logynon ED *Schering, Austral.; Schering, S.Afr.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Menstrual disorders; triphasic oral contraceptive.

Lohp *HLB, Arg.*
Cystine (p.1937·1); pyridoxine hydrochloride (p.1978·2).
Skin, nail, and eye disorders.

Loisan *Baliarda, Arg.*
Loratadine (p.583·3).
Allergic disorders of the respiratory tract; allergic skin disorders; conjunctivitis.

Loisan-D *Baliarda, Arg.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Conjunctivitis; respiratory-tract disorders.

Loitin *Lesvi, Spain.*
Fluconazole (p.532·1).
Fungal infections.

Lo-Kal *Cipla, India†.*
Aspartame (p.1930·1).

Lokalen *Toprak, Turk.*
Lidocaine (p.1862·3).
Local anaesthesia.

Lokalison-antimikrobiell Creme N *Dermapharm, Ger.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

LoKara *PharmaDerm, USA.*
⊗ Desonide (p.1525·1).
Skin disorders.

Lokarin *Biotech, Venez.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Lokilan *Ivax, Norw.*
⊗ Flunisolide (p.1531·1).
Rhinitis.

Loklor *Medikon, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lokman Kase *Lokman, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Lokoles *Corsa, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lokren *Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.*
⊗ Betaxolol hydrochloride (p.1231·2).
Angina pectoris; hypertension; ischaemic heart disease.

Loksetin *Nobel, Turk.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Lolergi *Mugi, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lolita *Unison, Thai.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lomabronchin N *Lomapharm, Ger.*
Homoeopathic preparation.

Lomac *Cipla, Cz.; Cipla, India; Cipla, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lomacard *Lomapharm, Ger.†.*
Crataegus (p.2289·1).
Arrhythmias; heart failure.

Lomacholan *Lomapharm, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Lomacin *Novartis, Mex.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye infections.

Lomaday *Reddy, Malaysia†; Biofarma, Venez.†.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Lomadryl *SJA, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Lomaherpan *Madaus, Austria; Lomapharm, Cz.†; Lomapharm, Ger.*
Melissa (p.2339·3).
Herpes simplex infections of the skin and mucous membranes.

Lomahypericum *Lomapharm, Ger.†.*
St John's wort (p.422·3).
Anxiety; depression.

Lomal *Lomapharm, Ger.†.*
Thyme (p.2401·1); drosera (p.2297·3).
Coughs and cold symptoms.

Lomar *Aegis, Hong Kong.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lomaren *Lomapharm, Ger.*
Equisetum (p.2299·3).
Urinary-tract disorders.

Lomarheumin N *Lomapharm, Ger.†.*
Homoeopathic preparation.

Lomarin
Note. This name is used for preparations of different composition.
Medipharm, Chile.
Lamotrigine (p.485·1).
Bipolar disorder.

Geymonat, Ital.
Dimenhydrinate (p.576·2).
Nausea; vertigo; vomiting.

Lomasleep *Lomapharm, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2).
Agitation; sleep disorders.

Lomatol
Note. This name is used for preparations of different composition.
Lomapharm, Ger.†.
Oral drops: Peppermint leaf (p.1761·2); fennel (p.2302·3); caraway (p.2276·3); absinthium (p.2244·1).
Gastrointestinal disorders.

Lomapharm, Ger.†.
Tablets: Absinthium (p.2244·1); caraway (p.2276·3); peppermint leaf (p.1761·2); caraway oil (p.2277·1); peppermint oil (p.1761·2).
Gastrointestinal disorders.

Lomatuell H *Lohmann, Ital.*
White soft paraffin (p.2031·2).
Wound dressing.

Lomavital *Lomapharm, Ger.*
Siberian ginseng (p.2386·3).
Tonic.

Lomax *Julphar, UAE.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Lomazell forte N *Lomapharm, Ger.†.*
Benzyl nicotinate (p.28·1); nonivamide (p.96·2); bovine placental extract (p.2337·3).
Circulatory disorders of the skin.

Lombalgina *Neo Quimica, Braz.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Lombocid *Proel, Gr.†.*
Povidone-iodine (p.1659·2).
Antiseptic.

Lombriareu *Areu, Spain.*
Pyrantel embonate (p.155·1).
Worm infections.

Lombrimade *Esfar, Port.†.*
Piperazine (p.152·3).

L-Ombrix *Liomont, Mex.*
Mebendazole (p.148·3).
Worm infections.

Lomebact *Medivis, Ital.*
Lomefloxacin (p.295·3).
Eye infections.

Lomecan V *Liferpal, Mex.*
Clotrimazole (p.530·1).
Fungal vaginal infections.

Lomecomb *Akrikhin, Rus.*
Isoniazid (p.288·1); lomefloxacin hydrochloride (p.295·2); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Lomef *Torrent, India.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Lomeflon *Senju, Jpn.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye and ear infections.

Lomeflox *Aristopharma, Hong Kong.*
Lomefloxacin (p.295·3).
Bacterial eye infections.

Lomepral *Pharmacia, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Lomesone *Schering-Plough, Gr.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Lomet *Microsules, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Lomex
Note. This name is used for preparations of different composition.
Saval, Chile.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Oftalmi, Venez.
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye infections.

Lomexin *Elea, Arg.†; Gerot, Austria; Nycomed, Braz.; Recordati, Cz.; Effik, Fr.; S & K, Ger.; Galenica, Gr.; Recordati, Ital.; Altana, Mex.; Jaba Recordati, Port.; Aspen, S.Afr.†; MD, Singapore†; Recordati, Spain; Akita, UK†.*
Fenticonazole nitrate (p.531·3).
Fungal and Gram-positive bacterial nail, skin, and vulvovaginal infections; fungal ear infections; vulvovaginal trichomoniasis.

Lomezec *Pharma Line, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Lomfer *Osorio de Moraes, Braz.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Lomflox
Ipca, India; IPCA, Singapore.
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Ipca, Rus.
Lomefloxacin (p.295·3).
Bacterial infections.

Lomide
Note. This name is used for preparations of different composition.
Alcon, Austral.; Alcon, NZ.
Lodoxamide trometamol (p.2334·2).
Allergic conjunctivitis; vernal keratoconjunctivitis.

Siam Bheasach, Thai.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lomilan *Lek, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.

Lomine *Riva, Canad.*
Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Lomir *Novartis, Austria; Sankyo, Belg.; Novartis, Braz.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Sankyo, Ital.; Novartis, Neth.; Novartis, Norw.; Novartis, Pol.; Daiichi Sankyo, Port.; Novartis, Rus.; Mizar, Spain; Novartis, Swed.; Novartis, Switz.*
Isradipine (p.1319·2).
Angina pectoris; hypertension.

Lomofen *RPG, India.*
Diphenoxylate hydrochloride (p.1724·1); furazolidone (p.834·3).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Bacterial diarrhoea.

Lomont *Rosemont, UK.*
Lofepramine hydrochloride (p.407·1).
Depression.

Lomotil
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Hong Kong; RPG, India; Goldshield, Irl.; Pharmacia, Malaysia†; Pharmacia, NZ†; Monsanto, Port.†; Pharmacia, S.Afr.; Pfizer Consumer, Singapore; Pfizer, Thai.; Ali, Turk.; Goldshield, UK; Searle, USA; Pharmacia, Venez.†.
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in the tablets to discourage abuse.
These ingredients can be described by the British Approved Name Co-phenotrope.
Diarrhoea; ostomy management; ulcerative colitis.

Pfizer Consumer, Mex.
Loperamide hydrochloride (p.1741·1).
Diarrhoea; regulation of intestinal transit time in patients with ileostomy or colostomy.

Lomper *Esteve, Spain.*
Mebendazole (p.148·3).
Worm infections.

Lomprax *Mintlab, Chile.*
Dimeticone (p.2032·1).
Flatulence.

Lomudal *Sanofi-Aventis, Belg.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Neth.; Aventis, Norw.; Aventis, Swed.; Aventis, Switz.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma; bronchial hypersensitivity; bronchitis; food hypersensitivity.

Lomupren *Aventis, Ger.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Lomupren compositum *Aventis, Ger.†.*
⊗ Sodium cromoglicate (p.1136·3); xylometazoline hydrochloride (p.1575·1).
Allergic rhinitis.

Lomusol *Sigmapharm, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Aventis, Neth.; Sanofi-Aventis, Switz.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Lomusol-X *Aventis, Switz.†.*
⊗ Sodium cromoglicate (p.1136·3); xylometazoline hydrochloride (p.1575·1).
Allergic rhinitis; nasal congestion.

Lomuspray *Aventis, Ital.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Lomvit *Osorio de Moraes, Braz.†.*
Yeast (p.1998·3).

Lomy *Masa, Thai.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lonactene *Ferring, Mex.*
Carbetocin (p.2005·3).
Postpartum haemorrhage; uterine atony.

Lonaflam *Merck, Braz.†.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders; pain.

Lonalac *Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).

Lonalgal *Boehringer Ingelheim, Gr.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Lonarel *Tolmann, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Lonarid *Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Ital.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Lonarid Aplo *Boehringer Ingelheim, Gr.*
Paracetamol (p.108·1).
Fever; pain.

Lonarid N
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Belg.
Paracetamol (p.108·1); caffeine (p.1116·3).
Formerly contained paracetamol, caffeine, and codeine phosphate.
Fever; pain.

Boehringer Ingelheim, Gr.
Codeine phosphate (p.37·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Lonasen *Dainippon, Jpn.*
Blonanserin (p.964·2).
Schizophrenia.

Lonason *Alpharma, Mex.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Lonatec *Arlex, Mex.*
Diclofenac (p.44·2).
Inflammation; pain.

Lonavar *Biotechnology, Israel.*
⊗ Oxandrolone (p.2123·2).
Growth failure in boys.

Loncord *Diffucap, Braz.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Londerm-N *Kinder, Braz.*
⊗ Triamcinolone acetonide (p.1544·3); gramicidin (p.286·1); nystatin (p.543·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Londoman *Panvifarm, Gr.†.*
Pefloxacin (p.313·3).
Bacterial infections.

Londopon *Panvifarm, Gr.†.*
Nimesulide (p.95·3).
Inflammatory disorders.

Lonene *Sunthi Sepuri, Indon.*
Etodolac (p.52·2).
Osteoarthritis; pain; rheumatoid arthritis.

Lonestin *Rayere, Mex.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Lonevit *Gastroenterologicos, Mex.†.*
Vitamin preparation (p.1922·1).

Long Lasting Decongestant Nasal Mist *Confab, Hong Kong.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Long Lasting Nasal Mist *Jamp, Canad.; Pharmascience, Canad.*
⊗ Oxymetazoline hydrochloride (p.1567·2).

Longacef
Note. A similar name is used for preparations of different composition (see below).
Leti, Venez.
Cefixime (p.224·3).
Bacterial infections.

Longaceph
Note. A similar name is used for preparations of different composition (see above).
ICN, Cz.†.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Longachin *Teofarma, Ital.*
Quinidine arabogalactane sulfate (p.1385·1).
Arrhythmias.

Longacilin *Biolab Sanus, Braz.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Longacor *Rovi, Spain†; Elaiapharm, Switz.†; Adilna, Turk.*
Quinidine arabogalactane sulfate (p.1385·1).
Arrhythmias.

Longactil *Cristalia, Braz.*
Chlorpromazine hydrochloride (p.969·2).
Psychoses.

Longaplex *Wyeth, Spain.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Longastatina *Italfarmaco, Ital.*
Octreotide (p.1804·1) or octreotide acetate (p.1803·2).
Acromegaly; diarrhoea associated with immunodeficiency; gastrointestinal endocrine tumours; gastrointestinal haemorrhage; pancreatic disorders.

Longasteril 40 *Fresenius Kabi, Ger.†.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Plasma volume expansion; thrombosis prophylaxis; vascular disorders.

Longasteril 70 *Fresenius Kabi, Ger.†.*
⊗ Dextran 70 (p.1059·3) with electrolytes.
Plasma volume expansion; thrombosis prophylaxis.

Longatin *Actavis, Indon.*
Noscapine (p.1566·2).
Respiratory-tract disorders.

Longazem *Difass, Ital.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Longbalsem *Wolfs, Belg.*
Ethylmorphine hydrochloride (p.52·2); guaifenesin (p.1561·3).
Coughs.

Longcef *Kalbe, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Longes *Shionogi, Jpn.*
Lisinopril (p.1325·2).

Longevit *Hexal, Braz.†.*
Vitamin B substances; vitamin E; arginine aspartate (p.1922·1).

Longevit Plus *Hexal, Braz.†.*
Ginseng; erythroxylon catuaba; ptychopetalum uncinatum; vitamins (p.1922·1).

Longevital
Note. This name is used for preparations of different composition.
Bogo, Arg.
Procaine; vitamin B substances; prasterone (p.1922·1).
Mental function impairment.

Sanitalia, Ital.
Pollen (p.2370·2); royal jelly (p.2382·1); rose fruit (p.2381·2); selenium (p.1961·1).
Nutritional supplement.

Longifene *UCB, Belg.; UCB, Hong Kong†; UCB, India; UCB, Malaysia†; Adcock Ingram, S.Afr.; UCB, Singapore†; UCB, Turk.*
Buclizine hydrochloride (p.570·1).
Hay fever; hypersensitivity reactions; motion sickness; nausea and vomiting; pruritus; reduced appetite; urticaria; vertigo; vestibular disorders.

Longimin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Buclizine hydrochloride (p.570·1).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

Longtussin Duplex Tag und Nacht N *Tussin, Ger.*
Day capsules, guaifenesin (p.1561·3); night capsules, codeine (p.37·2).
Bronchitis; coughs.

Longum *Pharmacia, Ger.†.*
Sulfametopyrazine (p.342·2).
Malaria.

Lonikan *Merck, Arg.*
Fludrocortisone (p.1530·1).
Corticosteroid.

Lonine *Wyeth, Gr.*
Etodolac (p.52·2).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Lonipril *Geolab, Braz.*
Lisinopril (p.1325·2).
Hypertension.

Lonipril-H *Geolab, Braz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Loniten *Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Canad.; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pharmacia, Ital.; Pfizer, Port.†; Pharmacia, S.Afr.; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Upjohn, USA†.*
Minoxidil (p.1342·1).
Alopecia androgenetica; hypertension.

Lonium *Apsen, Braz.*
Otilonium bromide (p.2359·1).

Lonixer *Serral, Mex.*
Clonixin lysine (p.37·1).
Pain.

Lonnoten *Pfizer, Neth.*
Minoxidil (p.1342·1).
Hypertension.

Lonol
Note. This name is used for preparations of different composition.
Khandelwal, India.
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Boehringer Ingelheim Promeco, Mex.
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders; musculoskeletal, joint and peri-articular disorders.

Garec, S.Afr.
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Lonol Sport *Boehringer Ingelheim Promeco, Mex.*
Benzydamine hydrochloride (p.27·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Lonolox *Pfizer, Ger.; Pharmacia, Ger.*
Minoxidil (p.1342·1).
Hypertension.

Lonoten *Pfizer, Fr.*
Minoxidil (p.1342·1).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lonox *Sandoz, USA.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Lonseren *Sanofi-Aventis, Spain.*
Pipotiazine palmitate (p.1019·2).
Anxiety; psychoses.

Lontadex *Recalcine, Chile.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Lontadex D *Recalcine, Chile†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion; otitis media.

Lontax *Fidia, Neth.*
Citalopram hydrobromide (p.385·3).
Depression.

Lontermin *Lek, Cz.; Lek, Hung.†.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Lonza *Medicine Products, Thai.*
Lorazepam (p.1004·1).
Anxiety.

Loortan *Therabel, Belg.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Loortan Plus *Therabel, Belg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lo-Ovral *Wyeth, Turk.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lo/Ovral *Wyeth-Ayerst, USA.*
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Lop *Sons, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopalind *Lindopharm, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopamide *Torrent, India.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopamine *Shiwa, Thai.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lo-P-Caps *ST, Thai.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Lop-Dia *Philopharm, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopecian *Cinetic, Arg.*
Amino acids; vitamins; minerals; ginkgo biloba; soya protein (p.1922·1).
Dietary supplement.

Lopediar *Pasteur, Chile.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopedium *Gebro, Austria; Hexal, Ger.; Sandoz, Hung.; Hexal, Rus.; Hexal, S.Afr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Lopela *Pharmasant, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopemid *Visufarma, Ital.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Lopepham *Phamos, Ger.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loper *Quality, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopera akut *Basics, Ger.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperacap *Valeant, Canad.; ICN, Hung.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Loperam *Vargas, Venez.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperamil *DHA, Hong Kong; DHA, Singapore.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperan *Chiesi, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperastat *Be-Tabs, S.Afr.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Loperax *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopercin *Polipharm, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperdium *General Drugs, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperhoe *Betapharm, Ger.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperia *Great Eastern, Thai.; Therapharma, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy and colostomy management.

Loperid *Vitamed, Israel.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperidol *Medley, Braz.*
Haloperidol (p.1000·2).
Autism; Huntington's chorea; nausea and vomiting; psychoses; Tourette's syndrome.

Loperin *Teuto, Braz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperium *Remedica, Hong Kong; Pharbita, Israel; Remedica, Malaysia.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperkey *Inkeysa, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopermid *Saba, Turk.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopermide *Atlantic, Hong Kong†; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loperon *Hexal, Cz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Lopex *Leiras, Fin.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Lophakomp-B 12 *Lomapharm, Ger.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Lophakomp-B 12 Depot *Lomapharm, Ger.*
Hydroxocobalamin acetate (p.1980·3).
Vitamin B deficiency.

Lophakomp-Procain *Lomapharm, Ger.*
Procaine hydrochloride (p.1869·1).
Nervous system disorders.

Lophlex *Scientific Hospital Supplies, Irl.; Nutricia, Ital.*
Food for special diets (p.1922·1).
Phenylketonuria.

Lopid *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Malaysia†; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore†; Parke, Davis, Spain; Pfizer, Swed.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Parke, Davis, USA; Pfizer, Venez.*
Gemfibrozil (p.1295·3).
Cardiovascular risk reduction; hyperlipidaemias.

Lopimed *Sandoz, Switz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Lopiretic *BMS, Port.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lopirin *BMS, Austria; BMS, Ger.; BMS, Switz.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Loplac *Casasco, Arg.*
Losartan potassium (p.1326·1).
Hypertension.

Loplac-D *Casasco, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Loporic *M & H, Thai.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Lopracil *Medicus, Gr.*
Citalopram (p.385·3).
Depression.

Lopram *Liferpal, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Lopratin *Sandoz, Neth.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Lopraxer *Help, Gr.*
Citalopram (p.385·3).
Depression.

Lopraz *Ivax, Irl.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Loprazol *Teuto, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Lopred *Phoenix, Arg.*
⊗ Loteprednol etabonate (p.1537·3).
Inflammatory eye disorders.

Lopresor
Novartis, Arg.; Novartis, Austral.; Sankyo, Belg.; Novartis, Canad.; Novartis, Ger.; Novartis, Gr.; Novartis, Indon.; Novartis, Irl.; Sankyo, Ital.; Novartis, NZ; Sankyo, Port.; Novartis, S.Afr.; Novartis, Spain; Novartis, Turk.; Novartis, UK; Novartis, Venez.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; ischaemic heart disease; migraine; myocardial infarction; phaeochromocytoma.

Novartis, Israel; Novartis, Neth.; Sankyo, Switz.
⊗ Metoprolol fumarate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Sandoz, Mex.
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Lopress *Siam Bheasach, Thai.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Lopressor *Novartis, Braz.; Sankyo, Fr.; Novartis, USA.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; cardiomyopathies; hypertension; migraine and other vascular headache; myocardial infarction; neuroleptic-induced akathisia; prolapsed mitral valve; tremor.

Lopressor HCT *Novartis, USA.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Loprex *Medirex, Port.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loprezol *Kimia, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Lopric *Integrated Pharmaceutical, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Lopril
Note. This name is used for preparations of different composition.
BMS, Braz.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Orion, Fin.; BMS, Fr.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Loproc *Norma (Νορμα), Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Loprofin *SHS, Fr.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, UK.*
A range of foods for special diets (p.1922·1).
Disorders of amino-acid metabolism; liver disorders; phenylketonuria; protein restriction; renal failure.

Loprolol *Ikapharmindo, Indon.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Loprox
Aventis, Arg.; Sanofi-Aventis, Braz.; Aventis, Mex.; Medicis, USA.
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin and nail infections.

Dermik, Canad.; Bipharma, Neth.; Aventis, Thai.
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Sanofi-Aventis, Indon.
Ciclopirox (p.529·2).
Fungal nail infections.

Loptomit *Bournonville, Neth.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; raised intra-ocular pressure.

Lopurax *Sanval, Braz.*
Allopurinol (p.552·2).
Gout.

Lora
Note. This name is used for preparations of different composition.
Basics, Ger.; Phoinix Pharm (Φοινιξ Φαρμ), Gr.
Loratadine (p.583·3).
Allergic rhinitis; pruritus; urticaria.

Atlantic, Thai.; PP Lab, Thai.
Lorazepam (p.1004·1).
Anxiety; insomnia.

Lorabenz *Ivax, Denm.*
Lorazepam (p.1004·1).
Anxiety.

Lorabid *Lilly, Mex.†; Lilly, S.Afr.; Actavis, Swed.; Lilly, Turk.; Monarch, USA†.*
Loracarbef (p.295·3).
Bacterial infections.

Loracert *Galeno, Venez.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Loracine *Medicine Products, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Loraclar *Krewel, Ger.†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Loraderm *Dermapharm, Ger.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loradex *Essex, Philipp.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Loradif *Sanofi Synthelabo, Turk.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loradin *Aristopharma, Hong Kong; Rowe-Fleming, Venez.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loradine *Teuto, Braz.; YSP, Malaysia; Greater Pharma, Thai.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Loradur *Ratiopharm, Austria; Ratiopharm, Cz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites; hypertension; oedema.

Lorafem *Zambon, Ger.*
Loracarbef (p.295·3).
Bacterial infections.

Lorafen *Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Lorazepam (p.1004·1).
Anxiety; nausea and vomiting during chemotherapy; premedication; sleep disorders.

Loraga
Note. This name is used for preparations of different composition.
Pfizer, Braz.†.
Psyllium (p.1737·1).
Constipation.

Pfizer, Fin.†; Pfizer, Swed.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Loragalen *Galen, Ger.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lorahexal *Hexal, Pol.; Hexal, Rus.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; hypersensitivity reactions; urticaria.

Lorahist *Unison, Philipp.; Adcock Ingram, S.Afr.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Loralerg *Farmasa, Braz.; AWD, Ger.†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Loralerg-D *Farmasa, Braz.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Lora-Lich *Winthrop, Ger.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Loralin *Boniscontro & Gazzone, Ital.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Loram
Note. This name is used for preparations of different composition.
Lek, Cz.†.
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; premedication; psychoses.

Hexal, Pol.
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Loramed *Medifive, Thai.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Loramet *Wyeth, Belg.; Wyeth, Gr.; Wyeth, Hong Kong†; Wyeth, Neth.†; Akromed, S.Afr.; Wyeth, Singapore; Wyeth, Spain; Valeant, Switz.; Wyeth-Ayerst, Thai.†.*
Lormetazepam (p.1005·2).
Hypnotic; premedication; sedative; sleep disorders.

Loramide *YSP, Malaysia; Yung Shin, Singapore†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loramyc *SpePharm, UK.*
Miconazole (p.541·2).
Oropharyngeal candidiasis.

Loran *Guardian, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loranil *Libbs, Braz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Loranil D *Libbs, Braz.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Nasal congestion.

Loranka *SMB, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Lorano *Hexal, Austral.; Hexal, Austria; Hexal, Ger.; Sandoz, Hung.; Hexal, Philipp.; Hexal, S.Afr.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Loranol *Hexal, Cz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Loranox *Charoen, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Lorans *Medochemie, Hong Kong; Schwarz, Ital.; Medochemie, Malaysia; Medochemie, Singapore.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Loransil *Pentafarma, Port.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Lorantis *Yeni, Turk.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lorapam *Pacific, NZ†; Siam Bheasach, Thai.*
Lorazepam (p.1004·1).
Anxiety; insomnia; neuroses; premedication.

Lorapan *Neo Quimica, Braz.*
Lorazepam (p.1004·1).

Lorapharm *Actavis, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lora-Puren *Alpharma-Isis, Ger.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Lorasc *Vitapan, Braz.†*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lorasifar *Siphar, Switz.*
Lorazepam (p.1004·1).
Anxiety; sedative; sleep disorders.

Lorasil Feminine Hygeine *Vita Health, Malaysia†.*
Aloe (p.1588·2); glycerol (p.2314·2); lactic acid (p.2329·3); sodium lactate (p.1673·3); sodium laurilsulfate (p.2138·3).
Feminine hygiene.

Lorastad *Stada, Neth.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lorastine *Schering-Plough, Israel.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lorastyne *Schering-Plough, Austral.†; Schering-Plough, Malaysia†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lorat *Oftalmi, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Loratab *Biospray, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Lora-Tabs *Pacific, NZ.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Loratadura *Merck dura, Ger.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; urticaria.

Loratagamma *Worwag, Ger.*
Loratadine (p.583·3).
Formerly known as Loragamma.
Allergic conjunctivitis; allergic rhinitis; urticaria.

Loratamed *Cimed, Braz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Loratan *Hasco-Lek, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loratex *Litex, Arg.†.*
Loratadine (p.583·3).

Loratin *Cipla, India; Julphar, UAE.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Loratin D *Cipla, India.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Allergic rhinitis.

Loratine *Investi, Arg.; Medana, Pol.; Polpharma, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loraton *Quality, Hong Kong.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Loratrim *Trima, Israel.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loratyn *Aesca, Austria; Hovid, Malaysia†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Loratyne *Hua Shin, Philipp.; Schering-Plough, S.Afr.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loraval *Valmor, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Loravis *Lindopharm, Ger.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Lorax *Wyeth, Braz.*
Lorazepam (p.1004·1).
Anxiety; premedication.

Loraxone *Exir, Rus.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Lorazefast *Sigma, Braz.*
Lorazepam (p.1004·1).
Anxiety; premedication.

Lorazemed *Ethimed, Belg.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Lorazene *Berlin Pharm, Thai.†.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; muscle relaxation.

Lorazep *Asian Pharm, Thai.*
Lorazepam (p.1004·1).
Anxiety.

Lorazepan *Dovalle, Braz.†.*
Lorazepam (p.1004·1).
Anxiety.

Lorazetop *Topgen, Belg.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Lorazidime *Exir, Rus.*
Ceftazidime (p.234·1).
Bacterial infections.

Lorbef *Lilly, Gr.*
Loracarbef (p.295·3).
Bacterial infections.

Lorbi *Bioquimico, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Lorbi-Bis *Bioquimico, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Lorbicefax *Bioquimico, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Lorbifenac *Bioquimico, Arg.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Lorbifloxacina *Bioquimico, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Lorbihepatic *Bioquimico, Arg.*
Cynara (p.2291·2); dehydrocholic acid (p.2292·2).
Liver disorders.

Lorbinafil *Bioquimico, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Lorbitidina *Bioquimico, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Lorcam *Taisho, Jpn.*
Lornoxicam (p.77·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Lorcamin *Coup, Gr.*
Norfloxacin (p.309·2).
Bacterial infections.

Lorcef *Metz, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Lorcet 10/650 *Forest Pharmaceuticals, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Lorcet Plus *Forest Pharmaceuticals, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Lorcet-HD *Forest Pharmaceuticals, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Lordam *Surge, Philipp.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lordane *Kalbe, Philipp.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Lordin
Note. This name is used for preparations of different composition.
Vianex (Βιανέξ), Gr.
Omeprazole (p.1753·1).
Peptic ulcer.

Masa, Thai.
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Lorelin *Bergamo, Braz.; Dong Kook, Hong Kong; Cryopharma, Mex.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; precocious puberty; prostatic cancer; uterine fibroids.

Loremex Antialergico *Phoenix, Arg.*
Loratadine (p.583·3).
Allergic eye disorders; allergic rhinitis; allergic skin disorders.

Loremex Descongestivo *Phoenix, Arg.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2) or pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms; otitis.

Loremid *Meprofarm, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loremix *Ativus, Braz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Loremix D *Ativus, Braz.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Nasal congestion.

Lorenin *Wyeth Lederle, Port.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; insomnia; premedication.

Lorentin *Hexal, Austral.†.*
⊗ Methylphenidate hydrochloride (p.2159·2).

Lorenzol *Rafarm, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Loretam *Valeant, Ger.*
Lormetazepam (p.1005·2).
Insomnia; premedication.

Loretsin *Best, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hyperlipidaemias.

Lorex *Dollder, Venez.*
Loratadine (p.583·3).
Allergic eye disorders; allergic rhinitis; allergic skin disorders.

Lorexen *Loren, Mex.†.*
Naproxen (p.92·3).
Fever; inflammation; pain.

Lorexil M *Mayo, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Lorezan *Klonal, Arg.*
Lorazepam (p.1004·1).
Anxiety.

Lorfast
Note. This name is used for preparations of different composition.
Suan, Gr.
Losartan (p.1327·2).
Hypertension.

Cadila Pharma, India; Cadila, Singapore.
Loratadine (p.583·3).
Allergic rhinitis; hypersensitivity reactions; urticaria.

Lorfast-D *Cadila, India.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).

Lorfenil *Loren, Mex.†.*
Phenylbutazone (p.117·1).
Inflammation.

Loricid *Littman, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Loricin *Sigma-Tau, Ital.*
Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Lorid *Unique, Rus.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Loride *Medinfar, Port.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Loridem *Sandipro, Belg.*
Lorazepam (p.1004·1).
Anxiety; insomnia; premedication.

Loriden *Giempi, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Loriderm *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Loridin *Cadila, India; Cadila, Rus.; Zydus Cadila, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; hypersensitivity reactions; urticaria.

Loridin-D *Cadila, India.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Allergic rhinitis.

Lorien *Pharmacare, S.Afr.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Lorihis *Erlimpex, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Loriken *Kendrick, Mex.†.*
Cefalotin sodium (p.219·2).
Bacterial infections.

Lorin *Stadmed, India; Great Eastern, Thai.; United American, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Lorinden *Jelfa, Pol.*
⊗ Flumetasone pivalate (p.1531·1).
Skin disorders.

Lorinden A *Jelfa, Cz.†; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders; warts.

Lorinden C *Jelfa, Cz.†; Jelfa, Hung.; Jelfa, Pol.; Jelfa, Rus.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected skin disorders.

Lorinden N *Jelfa, Pol.*
⊗ Flumetasone pivalate (p.1531·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Lorinden T *Medphano, Ger.†.*
⊗ Flumetasone pivalate (p.1531·1); coal tar (p.1616·2); salicylic acid (p.1612·2).
Skin disorders.

Lorinden Teersalbe *Medphano, Ger.*
Coal tar (p.1616·2).
Skin disorders.

Lorinid *Actavis, Indon.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis; hypertension; oedema.

Lorista *KRKA, Cz.; KRKA, Pol.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Lorista H *KRKA, Cz.; KRKA, Pol.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lorita *Farmaline, Thai.*
Loratadine (p.583·3).
Allergic skin disorders.

Loriter *Elvetium, Arg.†.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Loritil *Geolab, Braz.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Loritin *Actavis, Denm.*
Loratadine (p.583·3).
Allergic rhinitis; hay fever; urticaria.

Loritine *Ilsan, Turk.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lorityne *LSP, Thai.†.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Lorivan *Remedica, Hong Kong; Dexxon, Israel.*
Lorazepam (p.1004·1).
Anxiety; mixed anxiety depressive states; obsessive-compulsive disorder; psychosomatic disorders.

Lormed *ProMed, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; degenerative joint disorders; rheumatoid arthritis.

Lormetamed *Ethimed, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Lormide *Westmont, Philipp.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Lormine *Northia, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Lormyx *Alfa Wassermann, Gr.*
Rifaximin (p.330·1).
Gastrointestinal infections.

Lornazol *Loren, Mex.†.*
Ketoconazole (p.539·1).
Fungal infections.

Lornox *Nycomed, Austria.*
Lornoxicam (p.77·3).
Inflammation; pain.

Loron *Roche, Irl.; Roche, UK.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; tumour-induced osteolysis and bone pain.

Lorophyn *Schering-Plough, Arg.; Columbia, Mex.; Eczacibasi, Turk.*
Nonoxinol 9 (p.1917·2).
Contraception.

Lorotec *Maver, Mex.*
Ketorolac (p.75·2).
Pain.

Lorpa *Beacons, Singapore.*
Loperamide (p.1741·3).
Diarrhoea.

Lorsacor *Hexal, Braz.†.*
Losartan potassium (p.1326·1).
Hypertension.

Lorsar + HCT *Hexal, Braz.†.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lorsedal *Prospa, Port.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; insomnia; premedication.

Lorsedin *Siam Bheasach, Thai.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Lorson *IPI, Indon.*
⊗ Dexchlorpheniramine maleate (p.572·1); dexamethasone (p.1526·1).
Allergic disorders.

Lortaan *MSD, Ital.; Medinfar, Port.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Lortaan Plus *Medinfar, Port.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lortab *UCB, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Lortab ASA *UCB, USA.*
Hydrocodone tartrate (p.63·1); aspirin (p.20·3).
Pain.

Lortadine *Olan-Kemed, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Lortuss DM *Proethic, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Lortuss HC *Proethic, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Lorvas *Torrent, India.*
⊗ Indapamide (p.1314·1).
Hypertension.

Lorvaten *Pharmex (Φαρμεξ), Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Lorzaar *MSD Chibropharm, Ger.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Lorzaar plus *MSD Chibropharm, Ger.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Losacar *Zydus, India.*
Losartan potassium (p.1326·1).
Hypertension.

Losacar-H *Zydus, India.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Losacor *Roemmers, Arg.; Biofarm, Pol.*
Losartan potassium (p.1326·1).
Hypertension.

Losacor D *Roemmers, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Losalen *Novartis, Braz.; Novartis, Ital.; Novartis Consumer, Port.†; Sandoz, Spain.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders.

Losamel *Clonmel, Irl.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Losanorm *Ipca, India†.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; hypertension.

Losapan *Duopharm, Ger.†.*
Cynara (p.2291·2).
Dyspepsia.

Losapres *Pharma Investi, Chile.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Losapres-D *Pharma Investi, Chile.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Losaprex *Sigma-Tau, Ital.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Losaprol *Luper, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Losar *Aurantis, Braz.†; Biochimico, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Losaratio Plus H *Ratiopharm, Cz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Losargal *Sant Gall, Arg.*
Losartan (p.1327·2).
Hypertension.

Losarlan *Lanpharm, Arg.*
Losartan (p.1327·2).
Hypertension.

Losartec *Marjan, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Losartic *Pliva, Cz.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Losatal *Hebron, Braz.†.*
Losartan potassium (p.1326·1).
Hypertension.

Losazid *Sigma-Tau, Ital.; Euro Registratie, Neth.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Loscalcon *Lilly, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Loscon *Galderma, Ger.†.*
Tincture: Tioxolone (p.1617·3); benzoxonium chloride (p.1631·2).
Scalp disorders.

Losec
AstraZeneca, Arg.; AstraZeneca, Austria; AstraZeneca, Neth.; AstraZeneca, UK.
Omeprazole (p.1753·1), omeprazole magnesium (p.1753·1), or omeprazole sodium (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Chile; Mepro, Chile; AstraZeneca, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Norw.; AstraZeneca, Singapore; Tau, Spain; AstraZeneca, Swed.
Omeprazole magnesium (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Canad.; AstraZeneca, Rus.; AstraZeneca, Thai.; AstraZeneca, Venez.
Omeprazole (p.1753·1) or omeprazole magnesium (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Hung.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Port.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Gr.; AstraZeneca, Indon.; Abic, Israel; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, S.Afr.; AstraZeneca, Turk.
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Losec 1-2-3 A *AstraZeneca, Canad.*
Omeprazole magnesium (p.1753·1); amoxicillin (p.202·2); clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Losec Helira *AstraZeneca, Fin.†.*
Tablets I, metronidazole (p.837·1); tablets II, omeprazole magnesium (Losec) (p.1753·1); tablets III, amoxicillin trihydrate (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Losec Hp 7
AstraZeneca, Austral.
Tablets, omeprazole magnesium (Losec) (p.1753·1); capsules, amoxicillin trihydrate (Amoxil) (p.202·2); tablets, clarithromycin (Klacid) (p.248·2).
Helicobacter pylori-associated peptic ulcer.

AstraZeneca, NZ.
Capsules, omeprazole (p.1753·1); capsules, amoxicillin trihydrate (p.202·2); tablets, clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Losec 1-2-3 M *AstraZeneca, Canad.*
Omeprazole magnesium (p.1753·1); metronidazole (p.837·1); clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Losec 20 Triple *AstraZeneca, S.Afr.†.*
Capsules, omeprazole (Losec) (p.1753·1); tablets, clarithromycin (Klacid) (p.248·2); capsules, amoxicillin (Moxan) (p.202·2).
Peptic ulcer associated with Helicobacter pylori infection.

Losefan *Proel, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Losefar *Eczacibasi, Turk.*
Cefaclor (p.217·2).
Bacterial infections.

Losepine *Pinewood, Irl.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Loseprazol *ProMed, Cz.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Losertrin *Serral, Mex.*
Clindamycin (p.251·1).
Bacterial infections.

Losferron *Viatris, Austria; Grunenthal, Belg.; Meda, Cz.; Lilly, Ger.; SPA, Ital.; Grunenthal, Neth.; Prospa, Port.†; Andromaco, Spain; Ulagay, Turk.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Losferron-Fol *Viatris, Austria.*
Ferrous gluconate (p.1939·1); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency anaemias.

Losil-T *Ares, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Losium *Cadila, India.*
Losartan potassium (p.1326·1).
Hypertension.

Losnesium *Lilly, Ger.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Magnesium deficiency.

Losopil *Medipharm, Chile.*
Zopiclone (p.1039·1).
Insomnia.

Lostad *Stada, Austria.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lostam *Temis, Arg.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Lostamucil *Temis, Arg.*
Ispaghula (p.1737·1).
Constipation; irritable bowel syndrome.

Lostapres *Temis, Arg.*
Ramipril (p.1385·3).
Hypertension.

Lostapride *Temis, Arg.*
Mosapride citrate (p.1750·3).
Dyspepsia; gastritis.

Lostaprolol *Temis, Arg.*
⊗ Bisoprolol fumarate (p.1234·1).
Hypertension.

Lostatin *Reddy, Malaysia; Reddy, Singapore; Biofarma, Venez.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lostin *Pharmathen, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lostradyl *Chrispa (Χρισπα), Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Lotadine *Jean-Marie, Hong Kong; Yung Shin, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Lotal *Alian, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Lotan *Hexal, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Lotanax *Leciva, Cz.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Lotasbat *Interbat, Indon.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Loteflam *Cipla, India.*
⊗ Loteprednol etabonate (p.1537·3).
Allergic conjunctivitis.

Lotem *Adcock Ingram, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Lotemax *Bausch & Lomb, Arg.; Mann, Ger.; Kite (Κιτε), Gr.; Bausch & Lomb, Hong Kong; Bausch & Lomb, Ital.; Bausch & Lomb, Singapore; Bausch & Lomb, UK; Bausch & Lomb, USA.*
⊗ Loteprednol etabonate (p.1537·3).
Inflammatory eye disorders.

Lotemicin *Poen, Arg.*
⊗ Loteprednol etabonate (p.1537·3); tobramycin (p.354·1).
Inflammatory eye infections.

Lotemp *Biolab, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Lo-Ten *Pacific, Hong Kong; Pacific, NZ.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Loten *Alphapharm, Malaysia.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Lotencin *Pasteur, Philipp.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Lotensin
Note. This name is used for preparations of different composition.
Novartis, Braz.; Novartis, Canad.; Meda, Hung.; Novartis, Mex.; Meda, Pol.; Novartis, Rus.; Novartis, USA; Novartis, Venez.†.
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension; renal failure.

Kimia, Indon.
Captopril (p.1239·2).
Heart failure; hypertension.

Lotensin H *Novartis, Braz.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Lotensin HCT *Meda, Hung.; Novartis, Pol.; Novartis, USA.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Loterex *Bausch & Lomb, Mex.*
⊗ Loteprednol etabonate (p.1537·3).
Inflammatory eye disorders.

Lotesoft *Poen, Arg.; Roemmers Poen, Venez.*
⊗ Loteprednol etabonate (p.1537·3).
Inflammatory eye disorders.

Lotharson *Nufarindo, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Lotil *Fenton, UK.*
Emollient.
Dry skin.

Lotin
Note. This name is used for preparations of different composition.
Medreich, Hong Kong.
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Ivax, Mex.
Cefalotin (p.220·2).
Bacterial infections.

Lotio decapans *Widmer, Switz.*
Resorcinol (p.1612·1); salicylic acid (p.1612·2).
Scalp disorders.

Lotio Pruni Comp cum Cupro *Weleda, S.Afr.*
Arnica (p.2260·2); citron fruit; copper sulfate (p.1935·3); hamamelis (p.2318·2); iris germanica; lappa major (p.2330·3); silicea (p.2146·2); blackthorn (p.2267·2).
Varicose veins.

Lotio Zinc *Sam-On, Israel.*
Zinc oxide (p.1621·2).
Skin irritation.

Lotio Zinci *Floris, Israel.*
Zinc oxide (p.1621·2).
Skin irritation.

Lotioblanc *Panalab, Arg.*
Tretinoin (p.1618·1).
Dry skin.

Lotion Ecran Solaire Extreme *Prodemdis, Canad.*
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Lotion pour Feux Sauvages
Note. This name is used for preparations of different composition.
Atlas, Canad.
Camphor (p.2273·2); zinc salicylate (p.1612·3).

Sabex, Canad.†.
Benzoin (p.2394·2); camphor (p.2273·2); menthol (p.2340·1); myrrh (p.2349·2).

Lotion Solaire *Rolmex, Canad.*
SPF 15: Oxybenzone (p.1608·3); padimate O (p.1609·1).
Sunscreen.

Lotoquis *Beta, Arg.*
Phenytoin calcium (p.501·1); phenobarbital (p.492·2).
Epilepsy.

Lotoquis Simple *Beta, Arg.*
Phenytoin calcium (p.501·1) or phenytoin sodium (p.495·2).
Epilepsy.

Lotorin *Unipharma, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Lotrel *Novartis, USA.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Lotremin *Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Singapore†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Lotremine *Plough, Port.*
Clotrimazole (p.530·1).
Fungal skin infections.

Lotrial
Roemmers, Arg.
Enalapril (p.1276·1) or enalaprilat (p.1276·2).
Heart failure; hypertension.

Pharma Investi, Chile.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Lotrial D *Roemmers, Arg.; Pharma Investi, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lotricomb *Schering-Plough, Arg.; Essex, Ger.; Schering-Plough, NZ†; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Skin disorders with fungal infection.

Lotriderm
Schering-Plough, Belg.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.†; Pliva, Irl.; Schering-Plough, Pol.; Schering-Plough, S.Afr.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Skin disorders with fungal infections.

Schering-Plough, Indon.
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1).
Fungal skin infections.

Lotrimin *Schering-Plough, Mex.; Schering, USA.*
Clotrimazole (p.530·1).
Fungal skin infections.

Lotrimin AF
Note. This name is used for preparations of different composition.
Schering-Plough, Mex.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Schering-Plough, USA.
Cream; lotion; topical solution: Clotrimazole (p.530·1).
Fungal skin infections.

Schering-Plough, USA.
Powder; spray: Miconazole nitrate (p.541·3).

Lotrimin Ultra *Schering-Plough, USA.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Lotrisone *Schering, USA; Schering-Plough, Venez.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Skin disorders with fungal infection.

Lotrix *Roemmers, Arg.†.*
Enalapril maleate (p.1276·1); diltiazem hydrochloride (p.1265·1).
Hypertension.

Lotronex *GSK, Arg.†; Prometheus, USA.*
Alosetron hydrochloride (p.1705·3).
Irritable bowel syndrome in women.

Lotussin *Pharmacia, S.Afr.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

Lotussin Expectorant *Pharmacia, S.Afr.†.*
Diphenhydramine (p.577·1); aminophylline (p.1114·2); ammonium chloride (p.1551·3).
Coughs.

Lotyn *Interbat, Indon.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Louten *Poen, Arg.; Poen, Chile.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Louten T *Poen, Arg.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Lova *TAD, Ger.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovabeta *Betapharm, Ger.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovacard *Leciva, Cz.†; Cipla, India.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lovachol *Pharmacare, S.Afr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovacodan *Stada, Denm.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovacol *Saval, Chile; Orion, Fin.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovacor *Farmasa, Braz.†.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lovadrug *Med-One, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovadura *Merck dura, Ger.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovagamma *Worwag, Ger.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovahexal *Hexal, Ger.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovalip *MSD, Israel†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovamine *Nuvia, Fr.*
Nutritional supplement (p.1922·1).

Lovan *Alphapharm, Austral.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Lovanil *Flupal, Venez.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovapen *Elpen (Ελπεν), Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovarem *Remedica, Malaysia.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovarin *Collins, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Lovarin P *Collins, Mex.†.*
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Hypersensitivity; nasal congestion.

Lovas
Note.This name is used for preparations of different composition.
Millimed, Thai.
Amlodipine besilate (p.1214·1).
Hypertension; ischaemic heart disease.

Roemmers-Klinos, Venez.†.
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovasa *Reliant, USA.*
Omega-3 triglycerides (p.1362·1).
Dietary supplement.

Lovast *Teuto, Braz.†.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovasten *Vocate, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovasterol *Polpharma, Pol.; Polpharma, Rus.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Lovastin *YSP, Malaysia; Polfa Grodzisk, Pol.; Yung Shin, Singapore.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovatex *Gap, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovaton *Royton, Braz.†.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Lovatop *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovatrol *Fahrenheit, Indon.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovax *Cellofarm, Braz.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovaza *GSK, USA.*
Omega-3-acid ethyl esters (p.1362·1).
Formerly known as Omacor.
Hypertriglyceridaemia.

Lovecef *Medikon, Indon.*
Cefradine (p.233·1).
Bacterial infections.

Lovelle
Note.This name is used for preparations of different composition.
Biolab Sanus, Braz.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Organon, Ger.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lovenox *Aventis, Austria; Aventis, Canad.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Port.; Aventis, USA.*
Enoxaparin sodium (p.1277·2).
Myocardial infarction; prevention of coagulation during haemodialysis; thromboembolic disorders; unstable angina.

Lovequin *Kimia, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Loveral *Rayere, Mex.*
Albendazole (p.139·2).
Worm infections.

Lovette *Wyeth, Neth.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lovilia *ICN, Arg.†.*
Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Lovinacor *Rottapharm, Ital.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lovinda *Andromaco, Chile.*
Chlormadinone acetate (p.2084·3); ethinylestradiol (p.2101·3).
Androgen-induced acne; combined oral contraceptive.

Lovir
Douglas, Austral.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Ranbaxy, Hong Kong; Ranbaxy, Malaysia; Douglas, NZ; Ranbaxy, Rus.; Ranbaxy, Singapore.
Aciclovir (p.862·3).
Herpesvirus infections.

Lovire *Ranbaxy, S.Afr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Lovirem *Farmamust, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Loviscol *Wyeth, Philipp.; Wyeth, Venez.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Lovorin *Biomedis, Philipp.*
Calcium folinate (p.1943·3).
Adjunct to high-dose methotrexate therapy; methotrexate overdosage.

Lovrak *Julphar, UAE.*
Aciclovir (p.862·3).
Herpes simplex skin and mucous membrane infections; varicella-zoster skin infections.

Low Centyl K *Leo, Irl.*
⊗ Bendroflumethiazide (p.1224·1); potassium chloride (p.1684·3).
Hypertension.

Lowasa *Mayne, Irl.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Low-Cal *Cipla, India†.*
Aspartame (p.1930·1).

Lowcholid *Biomedica-Chemica, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lowden *Saval, Chile.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Lowe-Komplex *Infirmarius-Rovit, Ger.*
A range of homoeopathic preparations.

Lowette *Wyeth, Belg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Acne; combined oral contraceptive.

Lowfin *Mintlab, Chile.*
Sertraline hydrochloride (p.421·3).
Depression.

Lowila *BMS, Mex.*
⊗ Boric acid (p.2268·1); urea (p.1620·2).
Skin cleansing.

Lowila Cake
Note.This name is used for preparations of different composition.
BMS, Hong Kong.
Sodium lauril sulfoacetate (p.2138·3).
Soap substitute.

Westwood-Squibb, USA.
Skin cleanser.

Lowin *Duopharma, Hong Kong.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lowlip *Medikon, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lowlipid *Biomedica-Chemica, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Lowpres
Note. A similar name is used for preparations of different composition (see below).
Behrens, Venez.
Clonidine hydrochloride (p.1247·1).
Hypertension.

Lowpress
Note. A similar name is used for preparations of different composition (see above).
Sanval, Braz.†.
Enalapril maleate (p.1276·1).
Hypertension.

Lowsium Plus *Rugby, USA.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Hyperacidity.

Loxam *Neo Quimica, Braz.; Merck, Mex.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Loxamine *Pacific, NZ.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Loxapac
Sandoz, Canad.
Loxapine hydrochloride (p.1005·3).
Psychoses.

Eisai, Fr.
Loxapine (p.1005·2) or loxapine succinate (p.1005·3).
Psychoses.

Wyeth, Gr.†; Wyeth, UK†.
Loxapine succinate (p.1005·3).
Psychoses.

Wyeth, India.
Loxapine hydrochloride (p.1005·3) or loxapine succinate (p.1005·3).
Psychoses.

Loxapin *Norma (Νορμα), Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Loxasid *Toprak, Turk.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Loxatrel *Manix, Philipp.; Tolmann, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Loxavit *Vitamed, Israel.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Loxazol *Chefaro, Neth.; GSK, Neth.; Interdelta, Switz.*
Permethrin (p.2048·2).
Pediculosis.

Loxen *Novartis, Fr.; Novartis, Turk.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; controlled hypotension during anaesthesia; hypertension.

Loxetine *March, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states.

Loxibach *Offenbach, Mex.*
Meloxicam (p.80·3).

Loxibest *Best, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; pain.

Loxibrin *Merck, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Loxidil *LDA, Arg.*
Glycolic acid (p.1598·1).

Loxifen *Gador, Arg.†.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Loxiflam *Aspen, S.Afr.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Loxiflan *Farmasa, Braz.*
Meloxicam (p.80·3).
Inflammation; pain.

Loxin *Mann, Ger.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

Loxina *Neves, Port.†.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Loxinic *Nicholas, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Loxinter *Interbat, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Loxitan *Vianex (Βιανεξ), Gr.*
Meloxicam (p.80·3).
Ankylosing spondylitis; inflammation; osteoarthritis; pain; rheumatoid arthritis.

Loxitane *Watson, USA.*
Loxapine succinate (p.1005·3).
Psychoses.

Loxitenk *Biotenk, Arg.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Loxof *Ranbaxy, Malaysia.*
Levofloxacin (p.292·2).
Bacterial infections.

Loxon *Sanofi-Aventis, Pol.*
Minoxidil (p.1342·1).
Alopecia.

Loxone *Micro, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Loxonin *Sankyo, Braz.; Sankyo, Jpn; Rhein, Mex.; Sankyo, Philipp.; Sankyo, Thai.; Sankyo, Venez.*
Loxoprofen sodium (p.78·1).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Loxorol *Best, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Loxyn *Anglo-French Drugs, India.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Loxzalin *Pond's, Thai.*
Cloxacillin (p.256·1).
Gram-positive bacterial infections.

Lozad *Wermar, Mex.*
Metronidazole (p.837·1).
Amoebiasis.

Lozan *Teuto, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Lozap
Note.This name is used for preparations of different composition.
Farmoquimica, Braz.†.
Omeprazole (p.1753·1).
Peptic ulcer.

Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Lozap H *Zentiva, Cz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lozap Plus *Zentiva, Rus.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Lozapin *Torrent, India.*
Clozapine (p.981·1).
Psychoses associated with parkinsonism; schizophrenia.

Lozapine *Taro, Israel.*
Clozapine (p.981·1).
Schizophrenia.

Lozaprin *Coup, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lozartil *Novag, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Lozeprel *Multilab, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Lozide *Servier, Canad.*
⊗ Indapamide (p.1314·1).
Hypertension.

Lozil *Neo Quimica, Braz.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Lozima *Bioresearch, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Lozione Same Urto *Savoma, Ital.*
Coltsfoot (p.1555·1); achillea (p.2245·2); china; ginger oil (p.1732·3).
Hair loss.

Lozione Vittoria *Polifarma, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of burns, skin, and wounds.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Lozitan *Wockhardt, India.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; hypertension; stroke prophylaxis.

Lozix *Cellofarm, Braz.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lozol *Rhone-Poulenc Rorer, USA.*
⊗ Indapamide (p.1314·1).
Heart failure; hypertension.

Lozopin *Merck, Hong Kong.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); neomycin sulfate (p.305·1).
Infected skin disorders.

LP Drink *Nutricia-Bago, Arg.; Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).
Phenylketonuria and other disorders of protein metabolism.

LP Mix *Braun, Fr.†.*
Amino-acid and lipid infusion (p.1922·1).
Parenteral nutrition.

L-Polamidon *Aventis, Ger.*
⊗ Levomethadone hydrochloride (p.77·2).
Opioid withdrawal syndrome; pain.

LPV *Aspen, Austral.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

LQ10 *SHS Nutricia, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

LTA *Hospira, USA.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

L-Thyrox *Hexal, Ger.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

L-Thyrox Jod *Hexal, Ger.*
Levothyroxine sodium (p.2171·2); potassium iodide (p.2169·2).
Iodine-deficiency disorders.

L-Tine *Orchid, India†.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

LTK250 *Sigma, Arg.*
Potassium citrate (p.1673·2).
Renal calculi; urinary alkalinisation.

Luan *Molteni, Ital.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Luar-G *Klonal, Arg.*
Hyoscine butylbromide (p.1734·1).

Luar-G Compositum *Klonal, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Luarprofeno *Luar, Arg.*
Flurbiprofen (p.61·2).
Eye disorders.

Luase *Sankyo, Spain.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain; renal colic.

Lubafax *Douglas, Austral.*
Lubricant for skin or for medical instruments.

Lubalix *Drossapharm, Switz.†.*
Cloxazolam (p.981·1).
Anxiety disorders; insomnia.

Lubarol *Biovital, Austral.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Lubentyl *Sanofi-Aventis, Fr.*
Liquid paraffin (p.2030·3).
Constipation.

Lubentyl a la Magnesie *Sanofi-Aventis, Fr.*
Liquid paraffin (p.2030·3); magnesium hydroxide (p.1743·2).
Constipation.

Lubex *Phoenix, Hung.; Permamed, Switz.*
Disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3).
Skin disorders.

Lubexyl *Phoenix, Hung.; Permamed, Pol.; Permamed, Switz.*
Benzoyl peroxide (p.1590·2).
Acne.

Lubical *Lisapharma, Ital.*
Calcium carbonate (p.1714·1).
Formerly known as Calciomed.
Calcium deficiency; calcium supplement.

Luborant *Antigen, UK.*
Electrolytes (p.1667·1); carmellose sodium (p.2142·1); sorbitol (p.1965·1).
Saliva substitute.

Lubovnik *Slovakofarma, Cz.†.*
St John's wort (p.422·3).
Anxiety; menopausal disorders.

Lubricans *Vitamed, Israel.*
Emollient.
Dry skin.

Lubricante Urol *Organon, Spain.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Lubrictin *Klonal, Arg.*
Chondroitin sulfate (p.2280·3).
Dry eyes.

Lubriderm
Note.This name is used for preparations of different composition.
Fortbenton, Arg.
Vitamin A; progesterone (p.2125·1); estradiol (p.2097·2).
Skin disorders.

Pfizer Consumer, Canad.†.
Wool fat (p.2033·2); liquid paraffin (p.2030·3).
Skin disorders.

Pfizer, Chile; Warner-Lambert, USA.
A range of emollients.
Dry skin.

Lubriderm Advanced Moisture *Pfizer Consumer, Canad.†.*
Glycerol (p.2314·2); liquid paraffin (p.2030·3); vitamin E (p.1992·2); vitamin A (p.1971·2).
Dry skin.

Lubriderm AHA *Pfizer Consumer, Canad.†.*
Lactic acid (p.2329·3).

Lubriderm Daily *Pfizer Consumer, USA.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Dry skin; sunscreen.

Lubriderm Seriously Sensitive *Pfizer Consumer, Canad.†.*
Emollient.
Dry skin.

Lubriderm UV *Pfizer Consumer, Canad.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lubriderm UV 15 *Pfizer, Chile.*
Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lubrificante Anestesico *Braun, Port.*
Tetracaine hydrochloride (p.1871·3); glycerol (p.2314·2); chlorhexidine gluconate (p.1635·3).
Local anaesthesia and lubricant for catheterisation and endoscopy.

Lubrifilm *Alcon Cusi, Spain.*
Soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Eye irritation.

LubriFresh PM *Major, USA.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); lanolin oil (p.2033·2).
Dry eyes.

Lubrik
Note.This name is used for preparations of different composition.
Alcon, Braz.†.
Hypromellose (p.2144·2).
Eye irritation.

Grin, Mex.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Lubrikano *Farco, Ger.*
Glycerol (p.2314·2); hyetellose (p.2143·3).
Adjunct in radiography; catheterisation; endoscopy.

Lubrilac *Zwitter, Gr.*
Hypromellose (p.2144·2).
Dry eyes.

Lubrilax *Normon, Spain.*
Sodium picosulfate (p.1771·1).
Constipation.

Lubrilin *Grin, Mex.*
White soft paraffin (p.2031·2).

Lubrin *Aurora, Austral.; Upsher Smith, Israel; Torbet Laboratories, UK†; Kenwood, USA.*
Vaginal lubricant.

Lubrisec *Poen, Arg.†.*
Acetylcysteine (p.1548·2).
Eye disorders.

Lubriskin *Geritrex, USA.*
Emollient.
Skin disorders.

Lubri-Tears *Alcon, UK.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2); wool fat (p.2033·2).
Eye lubrication and protection.

LubriTears
Note.This name is used for preparations of different composition.
Bausch & Lomb, USA.
Eye drops: ⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Bausch & Lomb, USA.
Eye ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Lubritina Franklin *Millet-Franklin, Arg.*
Liquid paraffin (p.2030·3).
Constipation.

Lubrizal *Columbia, Mex.†.*
Benzalkonium chloride (p.1629·1).
Vaginal lubricant.

Lucebanol *Hormona, Mex.*
Idebenone (p.367·1).
Cerebrovascular disorders; mental function disorders.

Lucen *Malesci, Ital.*
Esomeprazole magnesium (p.1729·2) or esomeprazole sodium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Lucenfal *Farma Lepori, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Lucentis *Novartis, Austral.; Novartis, Cz.; Novartis, Fr.; Novartis, Gr.; Novartis, Indon.; Novartis, Malaysia; Novartis, Port.; Novartis, UK; Genentech, USA.*
Ranibizumab (p.2377·3).
Neovascular (wet) age-related macular degeneration.

Lucetam *EGIS, Hung.; Egis, Pol.; Egis, Rus.*
Piracetam (p.368·2).
Alcoholism; cerebrovascular disorders; cranial trauma; dementia; dyslexia; learning disorders in children; mental function impairment; myoclonus; vertigo.

Luci *Rexcel, India.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Lucidex
Note.This name is used for preparations of different composition.
Bago, Arg.
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Xanodyne, USA.
Caffeine (p.1116·3).

Lucidril *Kolassa, Austria.*
⊗ Meclofenoxate hydrochloride (p.2338·1).
Cerebral function disorders.

Lucilium *Ecosol, Switz.*
St John's wort (p.422·3).
Anxiety; depression; insomnia.

Luci-N *Rexcel, India.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Lucipral *Balu, Gr.*
Risperidone (p.1024·2).
Psychoses.

Lucon *Medreich, Hong Kong.*
Fluconazole (p.532·1).
Fungal infections.

Luco-Oph *Seng, Thai.†.*
Sulfamethizole (p.339·3).
Eye and ear infections.

Lucosil *Rosco, Denm.; Rosco, Norw.†.*
Sulfamethizole (p.339·3).
Bacterial infections; urinary-tract infections.

Lucretin *Farmasa, Braz.*
Boric acid (p.2268·1); salicylic acid (p.1612·2); ammonium alum (p.2254·1).
Vulvovaginal disorders.

Lucrin
Abbott, Austral.; Abbott, Belg.; Abbott, Cz.; Abbott, Hung.; Abbott, Israel; Takeda, Israel; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Port.; Abbott, Rus.; Abbott, Singapore; Abbott, Switz.; Abbott, Turk.
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; menopausal disorders; precocious puberty; prostatic cancer; uterine fibroids.

Abbott, Fr.†; Abbott, Hong Kong†.
⊗ Leuprorelin (p.2111·1).
Prostatic cancer.

Abbott, S.Afr.
⊗ Leuprorelin (p.2111·1) or leuprorelin acetate (p.2111·1).
Endometriosis; prostatic cancer.

Lucrin Depot *Abbott, Pol.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; premature puberty; prostatic cancer; uterine fibroids.

Ludeal *Pierre Fabre Sante, Fr.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ludex *Grisi, Mex.*
Famotidine (p.1730·1).
Peptic ulcer.

Ludilat *Organon, Austria.*
Bencyclane fumarate (p.1224·1).
Peripheral and cerebral vascular disorders.

Ludiomil
Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Cz.; Dolorgiet, Ger.; Novartis, Hung.; Novartis, Switz.; Novartis, Turk.
Maprotiline hydrochloride (p.407·2) or maprotiline mesilate (p.407·3).
Depression.

Novartis, Canad.†; Novartis, Denm.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Indon.; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore†; Novartis, Spain; Novartis, Swed.; Novartis, Thai.; Novartis, UK†; Novartis, Venez.
Maprotiline hydrochloride (p.407·2).
Depression.

Novartis, Pol.
Maprotiline (p.407·2).
Depression.

Ludios *Soho, Indon.*
Maprotiline hydrochloride (p.407·2).
Depression.

Luditec *Collins, Mex.*
Glipizide (p.441·3).
Diabetes mellitus.

Lufac-Z *Zafiro, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Lufer *Drossapharm, Switz.*
Ferrous fumarate (p.1938·3); ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Luffa compositum-Heel *Peithner, Austria.*
Homoeopathic preparation.

Luffa Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Luffa Nasentropfen *DHU, Ger.*
Homoeopathic preparation.

Luffanil *VSM, Neth.*
Homoeopathic preparation.

Luffasan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Luffeel *Heel, Cz.*
Homoeopathic preparation.

Luffeel Comp *Heel, Ger.*
Homoeopathic preparation.

Luffeel H *Heel, Neth.*
Homoeopathic preparation.

Lufi *Ipca, India.*
Levofloxacin (p.292·2).
Bacterial infections.

Luforan *Serono, Spain†.*
⊗ Gonadorelin (p.2106·2).
Hypothalamic-pituitary dysfunction.

Luftal *BMS, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Luftrin *Vitapan, Braz.†.*
Dimeticone (p.1770·2).
Dyspepsia; flatulence.

Lufyllin *Medpointe, USA.*
Diprophylline (p.1120·2).
Asthma; reversible bronchospasm.

Lufyllin-EPG *Wallace, USA†.*
⊗ Diprophylline (p.1120·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); phenobarbital (p.492·2).
Bronchospasm.

Lufyllin-GG *Medpointe, USA.*
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Asthma; reversible bronchospasm.

Lugaxil *Bruluagsa, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Lugesteron *Leiras, Fin.*
Progesterone (p.2125·1).
Female infertility; menstrual and menopausal disorders; progesterone deficiency.

Luiflex *Sankyo, Austria; Will-Pharma, Belg.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders; peri-articular and soft-tissue disorders.

Luitase *Euderma, Ital.†.*
Pancrelipase (p.2360·1).
Cystic fibrosis; malabsorption.

Luivac *Rontag, Arg.; Sankyo, Austria; Sankyo, Cz.; Sankyo, Ger.; Altana, Mex.; Sankyo, Pol.; Daiichi Sankyo, Port.; Sankyo, Switz.; Sankyo, Venez.*
Lysates of *Staphylococcus aureus*; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Ear infections; respiratory-tract infections.

Lukadin *San Carlo, Ital.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Lukair *Sidus, Arg.†; Farmasix, Port.*
Montelukast sodium (p.1126·2).
Allergic rhinitis; asthma.

Lukasm *Addenda, Ital.*
Montelukast sodium (p.1126·2).
Asthma.

Lullan *Sumitomo, Jpn.*
Perospirone hydrochloride (p.1017·1).
Schizophrenia.

Lumalia *Pierre Fabre, Fr.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne in women.

Lumaren *Elpen (Ελπεν), Gr.; Elpen, Singapore.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hypersecretion including Zollinger-Ellison syndrome; gastro-oesophageal reflux; peptic ulcer.

Lumat *Casasco, Arg.†.*
Permethrin (p.2048·2).
Pediculosis.

Lumbago-Gastreu S R11 *Reckeweg, Ger.*
Homoeopathic preparation.

Lumbalgine *Cooperation Pharmaceutique, Fr.*
Glycol salicylate (p.62·3); menthol (p.2340·1); camphor (p.2273·2); turpentine oil (p.2406·3); benzyl nicotinate (p.28·1).
Muscular disorders.

Lumbax *Vargas, Venez.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Lumbicid *Offenbach, Mex.*
Mebendazole (p.148·3).
Amoebiasis.

Lumbinon *Lichtenstein, Cz.†; Lichtenstein, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lumbinon Thermo *Lichtenstein, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; superficial vascular disorders.

Lumbolin *Jelfa, Pol.*
Benzyl nicotinate (p.28·1); glycol salicylate (p.62·3); heparinoids (p.1305·2).
Musculoskeletal, joint, and peri-articular disorders; neuralgia.

Lumen *Nevzat, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Lumeran *Aristopharma, Hong Kong.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lumewal *Prolab, Pol.*
Lupulus (p.2335·2); lavender (p.2331·1); motherwort (p.2347·3); melissa (p.2339·3); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Lumiclar *Valeant, Arg.*
Disodium inosinate (p.2296·1).
Eye disorders.

Lumidrops *Unipharma, Gr.†.*
Phenobarbital (p.492·2).
Epilepsy.

Lumifurex *Winthrop, Fr.*
Nifuroxazide (p.307·2).
Diarrhoea.

Lumigan *Allergan, Arg.; Allergan, Austral.; Allergan, Austria; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hong Kong; Allergan, Hung.; Allergan, India; Allergan, Irl.; Allergan, Israel; Allergan, Ital.; Allergan, Malaysia†; Allergan, Mex.; Allergan, NZ; Allergan, Neth.; Allergan, Norw.; Allergan, Philipp.; Allergan, Pol.; Allergan, Port.; Allergan, S.Afr.; Allergan, Singapore; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA; Allergan, Venez.*
Bimatoprost (p.1878·2).
Glaucoma; ocular hypertension.

Lumin *Alphapharm, Austral.*
Mianserin hydrochloride (p.408·1).
Depression.

Luminal
Bayer, Arg.; Bayer, India; Bayer, Port.; Kern, Spain; Merck, Switz.; Bayer, Turk.
Phenobarbital (p.492·2).
Adjunct in the treatment of poisoning; agitation; anxiety; convulsions; epilepsy; excitation; insomnia; premedication; sedative; smooth muscle spasm.
Desitin, Cz.; Abbott, Israel†; Abbott, Philipp.; Hospira, USA.
Phenobarbital sodium (p.492·2).
Anxiety; eclampsia; epilepsy; insomnia; premedication; sedative; tetanus.
Desitin, Ger.
Phenobarbital (p.492·2) or phenobarbital sodium (p.492·2).
Epilepsy; premedication.

Luminale *Bracco, Ital.*
Phenobarbital (p.492·2) or phenobarbital sodium (p.492·2).
Barbiturate withdrawal; epilepsy; sedative.

Luminaletas *Bayer, Arg.; Bayer, Port.; Kern, Spain.*
Phenobarbital (p.492·2).
Anxiety; convulsions; epilepsy; hypnotic; insomnia; sedative; smooth muscle spasm.

Luminalette *Bracco, Ital.*
Phenobarbital (p.492·2).
Barbiturate withdrawal; epilepsy; sedative.

Luminaletten *Desitin, Ger.; Bayer, Turk.*
Phenobarbital (p.492·2).
Epilepsy.

Luminalettes *Bayer, India†.*
Phenobarbital (p.492·2).
Epilepsy; sedative.

Luminalum *Galenus, Pol.*
Phenobarbital (p.492·2).
Epilepsy; premedication; sedative.

Luminity *BMS, Cz.; BMS, Fr.; BMS, Port.; BMS, UK.*
Perflutren (p.1488·2).
Ultrasound contrast medium for echocardiography.

Luminovag *Novag, Mex.*
Quinfamide (p.846·2).
Formerly contained ketoconazole.
Amoebiasis.

Lumirelax *Zydus, Fr.*
Methocarbamol (p.1897·3).
Musculoskeletal and joint disorders.

Lumirem *Sanova, Austria; Guerbet, Braz.†; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Ital.; Guerbet, Neth.; Martins & Fernandes, Port.; Gothia, Swed.*
Ferumoxsil (p.1478·1).
Contrast medium for magnetic resonance imaging of the gastrointestinal tract.

Lumitens *Solvay, Fr.†.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Lumix *Bago, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Lumox *IQFA, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Lumoxbron S *IQFA, Mex.*
Amoxicillin (p.202·2); bromhexine (p.1552·2).
Bacterial infections.

Lunadon *Vifor, Switz.*
Tolazoline hydrochloride (p.1415·2); drofenine hydrochloride (p.1727·3); diphenhydramine hydrochloride (p.577·2).
Nervous disorders; sleep disorders.

Lunafem *Bayer Schering, Cz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lunare *Interpharm, Austria.*
St John's wort (p.422·3).
Depression.

Lundiran *Vir, Spain.*
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Lunelax *Recip, Norw.; AstraZeneca, Swed.*
Ispaghula (p.1737·1).
Adjunct in treatment of diarrhoea; bowel evacuation; constipation; irritable bowel syndrome.

Lunelle *Pharmacia, USA†.*
Medroxyprogesterone acetate (p.2113·1); estradiol cipionate (p.2097·2).
Injectable contraceptive.

Lunesta *Sepracor, USA.*
Eszopiclone (p.995·2).
Insomnia.

Lunex *Lucas Djaja, Indon.*
Tranexamic acid (p.1080·3).
Haemorrhage; hereditary angioedema.

Lunibron *Valeas, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis; obstructive airways disease.

Lunis *Valeas, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis.

Luparen *Luper, Braz.†.*
Diclofenac sodium (p.44·3).

Lupassin *Elmor, Venez.*
Passion flower (p.2363·2); valerian (p.2410·1); lupulus (p.2335·2).

Lupectrim *Luper, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Lu-Peracina *Reuffer, Mex.*
Piperazine (p.152·3).

Lupex *Yung Shin, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Lupidon *Seid, Spain.*
Calcium pantothenate (p.1959·3); dimeticone (p.1770·2); magnesium polygalacturonate.
Flatulence.

Lupidon G *Bruschettini, Ital.*
A herpes simplex type 2 vaccine (p.2217·2).
Active immunisation.

Lupidon H *Bruschettini, Ital.*
A herpes simplex type 1 vaccine (p.2217·2).
Active immunisation.

Lupihist *Lupin, India.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough; hypersensitivity reactions.

Lupizyme *Lupin, India.*
Pepsin (p.2365·1); amylase (p.2256·3); vitamin B substances (p.1975·1).
Dyspepsia; flatulence.

Luprac *Toyama, Jpn.*
⊗ Torasemide (p.1415·3).
Oedema.

Lupram *Lundbeck, Philipp.*
Citalopram (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Lupride *Sun, India.*
⊗ Leuprorelin acetate (p.2111·1).
Prostatic cancer.

Luprolex *Takeda, Philipp.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids; uterine myoma.

Lupron
Abbott, Arg.; Abbott, Braz.; TAP, Canad.; Takeda, Jpn; TAP, USA; Abbott, Venez.
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; gynaecological disorders; infertility; precocious puberty; prostatic cancer; uterine fibroids.
Abbott, Chile.
⊗ Leuprorelin (p.2111·1) or leuprorelin acetate (p.2111·1).
Endometriosis; prostatic cancer; uterine fibroids.

Luramon *Vir, Spain.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Lurantal *Schering, Austria; Intendis, Braz.*
Isotretinoin (p.1599·2).
Acne.

Lurdex *Liferpal, Mex.*
Albendazole (p.139·2).
Worm infections.

Luride *Colgate Oral, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Lurispan *Romsa, Mex.*
Diphenhydramine (p.577·1).
Insomnia.

Lurline PMS *Fielding, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); pyridoxine (p.1979·1).
Premenstrual syndrome.

Lurselle *Mer-National, S.Afr.†; Aventis, Thai.†.*
Probucol (p.1377·1).
Hypercholesterolaemia.

Lusanoc *Meprofarm, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Lusap *Interdelta, Switz.†.*
Malathion (p.2046·1).
Pediculosis.

Lusedan *Leti, Venez.*
Sertraline hydrochloride (p.421·3).
Depression.

Lusemin *Best, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Lusert *Pinewood, Irl.*
Sertraline hydrochloride (p.421·3).
Depression.

Lusimva *Balu, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Lusocef *Medilusa, Port.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Lusonal *WraSer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Lusopress *Lusofarmaco, Cz.*
Nitrendipine (p.1358·2).
Hypertension.

Lustra *Taro, Canad.; Medicis, USA.*
Hydroquinone (p.1598·2).
Hyperpigmentation.

Lustra-AF *Taro, Canad.*
Hydroquinone (p.1598·2); octinoxate (p.1608·2); avobenzone (p.1589·3).
Hyperpigmentation.

Lustral *Pfizer, Irl.; Pfizer, Israel; Pfizer, Turk.; Pfizer, UK.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic attack; post-traumatic stress disorder.

Lustys Herbalene *Lane, UK.*
Senna leaf (p.1769·2); frangula bark (p.1732·2); sambucus (p.2383·1); fennel (p.2302·3).
Constipation.

Lutalmin *Offenbach, Mex.*
Dydrogesterone (p.2096·2); estradiol (p.2097·2).
Injectable contraceptive.

Lutamidal *Zodiac, Braz.; Tecnofarma, Chile.*
Bicalutamide (p.686·2).
Prostatic cancer.

Lutebiol *Biophytarom, Fr.*
Lutein (p.1954·3).
Prevention of eye disorders.

Luteina *Adamed, Pol.*
Progesterone (p.2125·1).
Endometriosis; female infertility; menopausal disorders; menstrual disorders; threatened and recurrent miscarriage.

Lutene *Herbarium, Braz.*
Agnus castus (p.2249·1).
Female infertility; hyperprolactinaemia; mastodynia; menstrual disorders.

Lutenil *Merck, Braz.*
Nomegestrol acetate (p.2119·1).
Menstrual disorders.

Lutenyl *Merck, Arg.; Merck, Belg.; Merck, Chile; Theramex, Cz.†; Merck, Hong Kong; Merck, Indon.; Theramex, Ital.; Theramex, Mon.; Theramex, Pol.; Theramex, Port.; Merck, Turk.; Gentek, Venez.†.*
Nomegestrol acetate (p.2119·1).
Dysfunctional uterine bleeding; dysmenorrhoea; endometriosis; female infertility; fibromas; hormone replacement therapy; menopausal disorders; menstrual disorders; progesterone deficiency; recurrent miscarriage.

Luteoliberina *Elea, Arg.*
⊗ Gonadorelin (p.2106·2).
Amenorrhoea; male and female infertility.

Lutera *Watson, USA.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Luteran *Sanofi-Aventis, Fr.*
Chlormadinone acetate (p.2084·3).
Endometriosis; fibromas; menstrual disorders.

Lutevision *Ikapharmindo, Indon.*
Myrtillus (p.2349·3); lutein (p.1954·3).
Antioxidant; dietary supplement.

Lutevision Extra *Ikapharmindo, Indon.*
Myrtillus (p.2349·3); lutein (p.1954·3); vitamin A; vitamin E; zinc; selenium (p.1922·1).
Antioxidant; dietary supplement.

Lutevit *Otto, Indon.*
Lutein (p.1954·3); zeaxanthin; vitamin C; vitamin E; betacarotene; zinc (p.1922·1).
Dietary supplement for eye health.

Lutogin *Farmigea, Ital.†.*
Progesterone (p.2125·1).
Female infertility; menopausal disorders; menstrual disorders; threatened or habitual miscarriage.

Lutoginestryl F *Aventis, Mex.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Lutogynestryl *Aventis, Arg.*
Ethisterone; ethinylestradiol (p.2101·3).
Amenorrhoea.

Lutopolar *Orion, Fin.†.*
Medroxyprogesterone acetate (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; malignant neoplasms; menstrual disorders.

Lutoral *Pfizer, Mex.*
Chlormadinone acetate (p.2084·3).
Menstrual disorders; uterine cancer; uterine fibroids.

Lutoral-E *Pfizer, Mex.*
Chlormadinone acetate (p.2084·3); mestranol (p.2116·2).
Endometriosis; menstrual disorders.

Lutrax *Alcon, Mex.*
Azapentacene (p.2262·2).
Cataracts.

Lutrelef *Ferring, Austria; Ferring, Fr.; Ferring, Ger.; Ferring, Israel†; Ferring, Ital.; Ferring, Neth.; Ferring, Swed.; Ferring, Switz.*
⊗ Gonadorelin acetate (p.2106·2).
Amenorrhoea; delayed puberty; hypogonadal hypogonadism; investigation of hypothalamic-pituitary function; male and female infertility; menstrual disorders; polycystic ovary syndrome.

Lutrepulse *Ferring, Canad.*
⊗ Gonadorelin acetate (p.2106·2).
Infertility.

Lutrotam *Danpac, Indon.*
Piracetam (p.368·2).
Cerebral infarction.

Lutsimed *Reckitt Benckiser, Port.*
Benzoyl peroxide (p.1590·2).

Luuf Balsam *Apomedica, Austria.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); pumilio pine oil (p.2376·3); pine silvestris oil (p.2368·2); thymol (p.1664·3).
Respiratory-tract disorders.

Luuf Verkoudheidsbalsem *Nycomed, Neth.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); pumilio pine oil (p.2376·3); pine silvestris oil (p.2368·2); turpentine oil (p.2406·3).

Luuf Verkoudheidsbalsem (voor babies) *Nycomed, Neth.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); majoranae oil (p.2337·3); turpentine oil (p.2406·3).

Luuf Verkoudheidsbalsem (voor Kinderen) *Nycomed, Neth.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); turpentine oil (p.2406·3).

Luuf-Hustentee *Apomedica, Austria.*
Thyme (p.2401·1); guaifenesin (p.1561·3); menthol (p.2340·1); camphor (p.2273·2); fennel oil (p.2303·1); anise oil (p.2258·2); eucalyptus oil (p.2301·2); thyme oil (p.2401·2).
Coughs and cold symptoms.

Luuf-Nasenspray *Apomedica, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2).
Colds; hay fever; sinusitis.

Luva Invisivel *Dermoteca, Port.*
Barrier preparation.

Luvased *Hexal, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Luvased mono *Hexal, Ger.*
Valerian (p.2410·1).
Anxiety disorders; sleep disorders.

Luvatren *Yamanouchi, Jpn.*
Moperone hydrochloride (p.1010·3).

Luvenyl *Merck, Mex.*
Nomegestrol acetate (p.2119·1).
Endometriosis; menopausal disorders; menstrual disorders.

Luveris *Serono, Arg.; Serono, Austral.; Serono, Belg.†; Serono, Braz.; Novartis, Chile†; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Hung.; DKSH, Indon.; Serono, Indon.; Serono, Irl.; Serono, Israel; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Douglas, NZ; Serono, Neth.; Serono, Norw.; Serono, Philipp.; Serono, Pol.; Serono, Port.; Serono, Rus.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
⊗ Lutropin alfa (p.2112·2).
Female infertility.

Luvier *Casasco, Arg.*
Ranitidine (p.1766·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Luvion *GiEnne, Ital.*
⊗ Canrenone (p.1239·2) or potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypertension.

Luvistar *Diba, Mex.*
Hypromellose (p.2144·2).
Contact lens lubricant; dry eyes; eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Luvos *Dunner, Switz.; Duomed, Switz.*
Clay loam.
Gastrointestinal disorders; skin disorders.

Luvox *Pharmacia, Arg.†; Solvay, Austral.; Solvay, Braz.; Solvay, Canad.; Royal, Chile; Solvay, Indon.; Astellas, Jpn; Solvay, Malaysia; Italmex, Mex.; Schering, S.Afr.; Jazz, USA; Zuoz, Venez.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder; social phobia.

Luxazone *Allergan, Ital.*
⊗ Dexamethasone (p.1526·1).
Eye disorders.

Luxazone Eparina *Tubilux, Ital.*
⊗ Dexamethasone (p.1526·1); heparin sodium (p.1301·2).
Eye disorders.

Luxeta *Pliva Krakow, Pol.*
Sertraline hydrochloride (p.421·3).
Depression.

Luxiq *Connetics, USA.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Luxiva Changing *Norman, Canad.*
SPF 15: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Luxiva Preventage Firming *Norman, Canad.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Luxofont *Solfran, Mex.*
Vitamin B substances (p.1922·1).
Anaemias; neuritis.

Luxomicina *Tubilux, Ital.*
Micronomicin sulfate (p.300·2).
Eye infections.

Luzin *Theodoridis, Gr.*
⊗ Fluorometholone (p.1532·3); gentamicin (p.284·2).
Inflammatory eye disorders.

Luzolona Simple *IQFA, Mex.*
Clioquinol (p.254·1).

Luzolona Y *IQFA, Mex.*
⊗ Clioquinol (p.254·1); fluocinolone (p.1531·3).
Infected skin disorders.

Luzone *Sigma-Tau, Spain.*
Sulodexide (p.1406·3).
Atherosclerosis; hyperlipidaemias; thromboembolic disorders.

Luzul *Baldacci, Ital.*
Lormetazepam (p.1005·2).
Insomnia.

L-Vist *Schering, Gr.*
Palmitic acid; galactose (p.1481·1).
Adjunct to ultrasound.

LX-30 *Sigma, Arg.*
Senna (p.1769·2); rhubarb (p.1768·3); magnesium oxide (p.1744·1).
Constipation.

Lybex *Armoxindo, Indon.*
Vitamin B substances; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Lybrel *Wyeth, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Lycalin *Pharmedia (Φαρμεντια), Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Lycazid *Jagson, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Lyceft *Hetero, India.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Lyceplix *Pharmacare, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Lycia Luminique *Artsana, Ital.*
Benzalkonium chloride (p.1629·1); hamamelis (p.2318·2); chamomile (p.2279·3).
Eye disinfection; eye irritation.

Lycinate *Fawns & McAllan, Austral.; Healthcare Logistics, NZ.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Lycitrope *Cooper (Κοπερ), Gr.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Lyclear *Pfizer Consumer, Austral.; GSK, Irl.; Pfizer Consumer, Irl.; GSK, Israel; GSK, S.Afr.; Chefaro, UK.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Lycoaktin *Steigerwald, Ger.*
Homoeopathic preparation.

Lycobeta-G *Loyal Advance, Hong Kong.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Inflammation and infection of the eye, ear, or nose.

Lycobiol *Biophytarom, Fr.*
Tomato extract.
Antioxidant dietary supplement.

Lycoq *Meprofarm, Indon.*
Lycopene (p.2335·2); ubidecarenone (p.2407·2); grape seed (p.2316·3); green tea (p.2416·1); vitamin E (p.1992·2).
Antoxidant.

Lycored *Jagson, India.*
Lycopene (p.2335·2); vitamins; minerals (p.1922·1).
Antoxidant dietary supplement.

Lycovowen-N *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Lydenal *Biomedica-Chemica, Gr.†.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Lyderm
Note. This name is used for preparations of different composition.
Taro, Canad.
⊗ Fluocinonide (p.1532·1).
Skin disorders.

PSM, NZ.
Permethrin (p.2048·2).
Scabies.

Lydonide *Technilab, Canad.†.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Lydroxil *Hetero, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Lyflex *Chemidex, UK.*
Baclofen (p.1888·1).
Spasticity.

Lyforan *Hetero, India.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Lygal E Tinktur *Taurus, Ger.†.*
⊗ Betamethasone benzoate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Lygal Kopfsalbe N *Taurus, Ger.*
Salicylic acid (p.1612·2).
Scalp disorders.

Lygal Kopftinktur N *Taurus, Ger.*
⊗ Prednisolone (p.1540·3).
Scalp disorders.

Lygnonex *Medopharm, Philipp.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Lykocin *Lyka, Rus.*
Capreomycin sulfate (p.215·3).
Tuberculosis.

Lyman *Drossapharm, Switz.*
cream; Topical gel: Heparin sodium (p.1301·2); allantoin (p.1588·1); dexpanthenol (p.2362·1).
Soft-tissue disorders; venous insufficiency.

Lymetel *Libropharm, Spain.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; hyperlipidaemias.

Lymium *Ativus, Braz.*
Vitamin C; vitamin E; lycopene; selenium (p.1922·1).

Lymphaden Complex *Hevert, Ger.*
Homoeopathic preparation.

Lymphaden Lymphdrusentabletten *Hevert, Ger.*
Homoeopathic preparation.

Lymphaden N *Hevert, Ger.†.*
Homoeopathic preparation.

Lymphaden PE *Hevert, Ger.*
Homoeopathic preparation.

Lymphadenomtropfen N *Syxyl, Ger.†.*
Homoeopathic preparation.

Lymphazurin *Tyco, Canad.; US Surgical, USA.*
Sulphan blue (p.2394·2).
Adjunct in lymphography.

Lymphdiaral *Pascoe, Neth.; Pascoe, Ger.*
Homoeopathic preparation.

Lymphdiaral Aktiv *Pascoe, Ger.*
Homoeopathic preparation.

Lymphdiaral sensitiv *Pascoe, Ger.*
Homoeopathic preparation.

Lymphoglobulin *Genzyme, Ger.*
An antilymphocyte immunoglobulin (horse) (p.1817·3).
Aplastic anaemia; graft-versus-host disease; transplant rejection.

Lymphoglobuline *Aventis Pasteur, Braz.†; Imtix, Cz.†; Genzyme, Fr.; Gerolymatos, Gr.; IFET (ΙΦΕΤ), Gr.; Sangstat, Hong Kong†; Imtix Sangstat, Israel; Imtix, Ital.; Sangstat, Malaysia†; Genzyme, Neth.; Genzyme, Pol.; Aventis, S.Afr.; Pacific Biosciences, Singapore†; Sangstat, Singapore†; Genzyme, Switz.; Aventis Pasteur, Thai.†; Aventis Pasteur, Turk.*
An antilymphocyte immunoglobulin (p.1817·3).
Aplastic anaemia; graft-versus-host disease; immunosuppressant; medullary aplasia; transplant rejection.

Lymphomyosot *Peithner, Austria; Heel, Cz.; Heel, Ger.; Heel, Neth.; Heel, S.Afr.; Biotecnoquimica, Venez.†.*
Homoeopathic preparation.

Lymphomyosot N *Heel, Ger.*
Homoeopathic preparation.

Lymphoscint *Nycomed, Cz.†.*
Technetium-99m (p.2055·3) stannous sulfide.
Radionuclide imaging of the lymphatic system.

Lymphozil
Note. This name is used for preparations of different composition.
Cesra, Cz.
Thiamine hydrochloride; echinacea; fucus vesiculosus; lachesis mutus; silicii dioxidum; calcii carbonas; faex desenzymata (p.1922·1).
Tonic.

Cesra, Ger.; Cesra, Pol.
Echinaceae pallida (p.2298·1).
Tonic; upper respiratory-tract infection.

Lymphtropfen S *Cosmochema, Ger.†.*
Homoeopathic preparation.

Lyndan *LA, Arg.*
Lindane (p.2045·3); benzocaine (p.1854·1).

Lyndavel *Umeda, Philipp.*
Medroxyprogesterone acetate (p.2113·1).
Adjunct in hormone replacement therapy; endometriosis; menstrual disorders; progestogen-only injectable contraceptive.

Lyndiol *Organon, Neth.†; Organon, Thai.†.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Lynoral *Organon, India; Organon, Indon.; Organon, Neth.*
Ethinylestradiol (p.2101·3).
Breast cancer; lactation inhibition; male hypersexuality; menopausal disorders; menstrual disorders; oestrogen deficiency; prostatic cancer.

Lyn-ratiopharm-Sequenz *Ratiopharm, Ger.*
7 Capsules, ethinylestradiol (p.2101·3); 15 capsules, lynestrenol (p.2112·3); ethinylestradiol.
Sequential-type oral contraceptive.

Lynx *Wallace, India.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lyo-Bifidus *Zydus, Fr.*
Bifidobacterium bifidus (*Bacillus bifidus*) (p.2372·3).
Diarrhoea.

Lyoclar *Lyofin, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Lyo-Cortin *Vianex (Βιανεξ), Gr.†.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Lyoderm *Proel, Gr.*
⊗ Chlorocresol (p.1640·1); urea (p.1620·2).
Keratolytic.

Lyo-drol *Vianex (Βιανεξ), Gr.†.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Lyofoam *Medlock Medical, UK.*
Polyurethane foam dressing (p.1611·1).
Ulcers; wounds.

Lyofoam C *Medlock Medical, UK.*
Activated charcoal (p.1435·2).
Malodorous wounds.

Lyogen *Lundbeck, Ger.*
Fluphenazine decanoate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Lyomer *Jaba, Port.†; Abdi, Turk.*
Sea water (p.1686·1).
Nasal congestion; nasal hygiene.

Lyomer Plus *Qualiphar, Belg.*
Sterile hypertonic sea water (p.1686·1).
Nasal congestion.

Lyoprovir *Biomedica-Chemica, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Lyorodin *Rodleben, Ger.; UCB, Ger.*
Fluphenazine decanoate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Lyotret *Biomedica-Chemica, Gr.*
Isotretinoin (p.1599·2).
Acne.

Lyovac Cosmegen *MSD, Belg.; MSD, Ger.; MSD, Neth.; MSD, Thai.*
Dactinomycin (p.707·2).
Malignant neoplasms.

Lyphocin *APP, Hong Kong; American Pharmaceutical, USA.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Lypholyte *American Pharmaceutical, USA.*
A range of electrolyte preparations (p.1667·1).
Fluid and electrolyte disorders.

Lyprinol *Blackmores, Austral.; Life Plus, UK.*
Green-lipped mussel extract (p.2317·2).
Inflammation.

Lypsyl Cold Sore Gel *Novartis Consumer, UK.*
Lidocaine hydrochloride (p.1862·3); zinc sulfate (p.1999·2); cetrimide (p.1634·1).
Herpes labialis.

Lyrica *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Pregabalin (p.502·2).
Anxiety; epilepsy; fibromyalgia; generalised anxiety disorder; neuropathic pain; postherpetic neuralgia.

Lyrinel *Janssen-Cilag, Austria; Janssen-Cilag, Ger.; Medac, Ger.; IFET (ΙΦΕΤ), Gr.; Janssen-Cilag, Mex.; Janssen-Cilag, Port.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Lyrinel XL *Janssen-Cilag, Irl.; Janssen-Cilag, UK.*
Oxybutynin hydrochloride (p.2190·3).
Formerly known as Ditropan XL in the *UK.*
Urinary incontinence.

Lyrsedin *Sons, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

LYS *Nutricia-Bago, Arg.*
Food for special diets (p.1922·1).
Hyperlysinaemia.

Lysadam *Filadams, Philipp.*
Vitamins; calcium lactate; lecithin; lysine hydrochloride (p.1922·1).

Lysagor *Kalbe, Indon.*
Pizotifen (p.624·2).
Vascular headache.

Lysalgo *SIT, Ital.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Lysantin *Medic, Denm.*
Orphenadrine hydrochloride (p.812·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Lysanxia *Pfizer, Belg.; Lynapharm, Fr.*
Prazepam (p.1019·3).
Alcohol withdrawal syndrome; anxiety.

Lysbex *Provita, Austria.*
Bibenzonium bromide (p.1552·2).
Coughs.

Lysedil *Vifor, Switz.*
Promethazine hydrochloride (p.588·2); belladonna (p.2263·3).
Coughs; gastrointestinal disorders; hypersensitivity reactions; sedative.

Lyseen
Note. This name is used for preparations of different composition.
Strathmann, Ger.
Lactic-acid-producing organisms (p.2372·3).
Vaginal infections.

Novartis Consumer, Ital.
Pridinol mesilate (p.1898·1).
Skeletal muscle spasm.

Lysetol FF *Schulke & Mayr, Ger.†.*
Glutaral (p.1645·2); ethylhexanal (p.1644·1).
Instrument disinfection.

Lysetol Med *Schulke & Mayr, Ger.†.*
Cocospropylendiguanidinacetat; phenoxypropanol (p.1657·2); benzalkonium chloride (p.1629·1).
Instrument disinfection.

Lysinotol *Viatris, Spain†.*
Lysine aspirin (p.79·1).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Lyso-6 *UCB, Fr.; Galenica, Gr.; UCB, Switz.†.*
Muramidase hydrochloride (p.2348·1); pyridoxine hydrochloride (p.1978·2).
Mouth and throat disorders.

Lysobact *Bosnalijek, Rus.*
Muramidase hydrochloride (p.2348·1); pyridoxine hydrochloride (p.1978·2).
Mouth disorders.

Lysocalmspray *UCB, Fr.*
Cetrimide (p.1634·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Lysocline *Teofarma, Fr.*
Methacycline hydrochloride (p.298·2).
Bacterial infections.

Lysodren *BMS, Canad.; HRA, Cz.; HRA, Denm.; HRA, Fin.; HRA, Fr.; HRA, Ger.; Arriani, Gr.; BMS, Hong Kong; HRA, Neth.; HRA, Pol.; HRA, Spain; HRA, UK; BMS Oncology, USA.*
Mitotane (p.753·2).
Adrenocortical cancer.

Lysodrop *Viatris, Belg.†.*
Acetylcysteine (p.1548·2).
Dry eyes.

Lysoform *Lysoform, Ger.*
Formaldehyde (p.1644·2).
Surface and linen disinfection.

Lysoform Killavon *Lysoform, Ger.†.*
Benzalkonium chloride (p.1629·1).
Disinfection of skin, mucous membranes, and surfaces; skin disorders.

Lysoformin *Lysoform, Ger.*
Formaldehyde (p.1644·2); glutaral (p.1645·2).
Surface disinfection.

Lysoformin 3000 *Lysoform, Ger.*
Glyoxal (p.1646·1); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Disinfection of instruments and surfaces.

Lysoformin spezial *Lysoform, Ger.*
Guanidine derivative; didecyldimethylammonium chloride (p.1642·2).
Disinfection of surfaces.

Lysomucil *Zambon, Belg.*
Acetylcysteine (p.1548·2).
Paracetamol overdose; respiratory-tract disorders associated with viscous mucus.

Lysopadol *Boehringer Ingelheim, Fr.*
Ambroxol hydrochloride (p.1550·3).
Sore throat.

Lysopaine
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Fr.
Muramidase hydrochloride (p.2348·1); cetylpyridinium chloride (p.1635·1).
Formerly contained muramidase hydrochloride, papaya sap, and bacitracin.
Mouth and throat infections.

Olvos, Gr.; Boehringer Ingelheim, Switz.
Muramidase hydrochloride (p.2348·1); papain (p.2362·3); bacitracin (p.210·3).
Mouth and throat disorders.

Lysoplac *Pierre Fabre, Rus.*
Chlorhexidine gluconate (p.1635·3); sodium citrate (p.1673·3); borax (p.2268·1).

Lysoprin *Rafa, Israel†.*
Lysine aspirin (p.79·1).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Lysosmin *Seiko Eiyo, Hong Kong.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; respiratory-tract congestion; sinusitis.

Lysotossil *Zambon, Belg.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Lysovir *Alliance, UK.*
Amantadine hydrochloride (p.792·3).
Influenza A.

Lysox *Menarini, Belg.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous secretions.

Lyssavac N *Berna, Ital.†; Berna, Switz.†; Berna, Thai.*
A rabies vaccine (duck embryo) (p.2234·1).
Active immunisation.

Lysthenon *Nycomed, Austria; Nycomed, Ger.; Nycomed, Rus.; Unique, Rus.; Nycomed, Switz.; Fako, Turk.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Lystin *Biolab, Hong Kong; Biolab, Thai.†.*
Nystatin (p.543·2).
Fungal infections; vaginal candidiasis.

Lytacur *Dexa, Indon.*
Lysine hydrochloride; vitamins; curcuminoid (p.1922·1).
Nutritional supplement.

Lyteers *Fischer, Israel.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Eye irritation.

Lyteprep *E-Z-EM, Canad.†.*
Electrolyte solution (p.1667·1).
Gastrointestinal lavage.

Lytos *Roche, Fr.*
Clodronate disodium (p.1095·3).
Malignant hypercalcaemia; malignant osteolysis.

Lytren *Mead Johnson Nutritionals, Canad.†; Mead Johnson, Fr.†.*
Glucose; potassium citrate; sodium chloride; sodium citrate; citric acid (p.1672·2).
Diarrhoea; oral rehydration therapy.

Lyzyme *Shin Poong, Singapore.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; respiratory-tract congestion; sinusitis.

M & M *Malam, UK.*
Dressing: Cod-liver oil (p.1935·2); purified honey (p.1948·2).

Maalox
Note. This name is used for preparations of different composition.
Raffo, Arg.†; Gerot, Austria; Sanofi-Aventis, Belg.; Novartis Consumer, Canad.†; Sanofi-Aventis, Chile†; Sanofi-Aventis, Fr.; Cassella-med, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong†; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Neth.; Aventis, Philipp.; Rhone-Poulenc Rorer, Pol.; Sanofi-Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Aventis, UK; Novartis Consumer, USA†; Sanofi-Aventis, Venez.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
These ingredients can be described by the British Approved Name Co-magaldrox.
Antacid; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Sanofi-Aventis, Cz.
Oral suspension: Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Sanofi-Aventis, Cz.
Tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Maalox Antacid with Anti-gas *Novartis Consumer, Canad.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Maalox Antacid/Calcium *Novartis, USA†.*
Calcium carbonate (p.1714·1).
Calcium supplement; hyperacidity.

Maalox Anti-Gas *Novartis, USA†.*
Simeticone (p.1770·2).
Excess gastrointestinal gas.

Maalox Anti-Gas Extra Strength *Novartis, USA†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Maalox Ballonnements *Sanofi-Aventis, Fr.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Maalox Childrens *Novartis Consumer, USA.*
Calcium carbonate (p.1714·1).
Antacid.

Maalox Extra Strength *Novartis Consumer, Canad.*
Calcium carbonate (p.1714·1).

Maalox Extra Strength with Anti-gas *Novartis Consumer, Canad.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).

Maalox H_2 Acid Controller *Apotex, Canad.*
Famotidine (p.1730·1).
Gastric hyperacidity.

Maalox HRF *Novartis Consumer, Canad.*
Calcium carbonate (p.1714·1); sodium alginate (p.2141·1); magnesium carbonate (p.1743·1).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Maalox Max *Novartis, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Antacid; flatulence.

Maalox Maximum Strength Multi-Symptom *Novartis Consumer, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Maalox Multi-action *Novartis Consumer, Canad.*
Bismuth salicylate (p.1711·1).

Maalox Plus *Sanofi-Aventis, Braz.; Novartis Consumer, Canad.†; Sanofi-Aventis, Chile†; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Neth.; Aventis, Philipp.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Aventis, UK; Rhone-Poulenc Rorer, USA†; Sanofi-Aventis, Venez.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Maalox Plus Antacid Junior *Novartis Consumer, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Antacid; flatulence.

Maalox Quick Dissolve *Novartis Consumer, Canad.†; Novartis, USA†.*
Calcium carbonate (p.1714·1).
Antacid; gastric hyperacidity.

Maalox Quick Dissolve with Antigas *Novartis Consumer, Canad.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Antacid; flatulence.

Maalox Regular Strength
Note. This name is used for preparations of different composition.
Novartis Consumer, Canad.
Calcium carbonate (p.1714·1).

Novartis, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Maalox TC *Novartis Consumer, Canad.†; Sanofi-Aventis, Ital.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders associated with hyperacidity; gastrointestinal haemorrhage.

Maalox Total Stomach Relief *Novartis, USA.*
Bismuth salicylate (p.1711·1).
Antacid.

Maaloxan *Cassella-med, Ger.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity; peptic ulcer.

Maalucol *Labormed, Rus.*
Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Maasol *GE Healthcare, Neth.*
⊗ Technetium-99m (p.2055·3) albumin macroaggregates (Macrosalb).
Radionuclide lung scanning; venography.

Mab *Wyeth, Fr.†.*
Magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastrointestinal disorders.

MabCampath *Ilex, Austria; Schering, Belg.; Genzyme, Cz.; Ilex, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Genzyme, Gr.; Schering, Gr.; Genzyme, Hung.; Schering, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Genzyme, Neth.; Ilex, Norw.; Genzyme, Pol.; Genzyme, Port.; Schering, S.Afr.; Bayer, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, UK.*
Alemtuzumab (p.677·2).
Chronic lymphocytic leukaemia.

Mabex *Cofasa, Venez.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal disorders.

Mabicrol *Boehringer Ingelheim Promeco, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Mabis *Lafedar, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); bismuth subnitrate (p.1711·2).
Gastrointestinal hyperacidity.

Mabogastrol *Merck, Spain.*
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity.

Mabron *Medochemie, Cz.; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.†; Morningside, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

MabThera *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.*
Rituximab (p.767·1).
Chronic lymphocytic leukaemia; follicular lymphoma; non-Hodgkin's lymphoma; rheumatoid arthritis.

Mabuson *Polfa Pabianice, Pol.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Mac Azi *Sigma, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Macaine *Adcock Ingram, S.Afr.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Macalvit
Note. This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis, Swed.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Calcium and vitamin C deficiency.

Novartis, India.
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2); colecalciferol (p.1986·2); vitamin B (p.1980·2).
Calcium supplement; tonic.

Novartis Consumer, Ger.
Ascorbic acid (p.1983·3).
Formerly contained ascorbic acid, calcium lactate gluconate, and calcium phosphinate.
Vitamin C deficiency.

Macbirs *Maigal, Arg.*
Sulfur (p.1614·1).
Seborrhoeic dermatitis.

Macbirs Minoxidil *Maigal, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Macbirs Sulphur *Maigal, Arg.*
Sulfur (p.1614·1).
Seborrhoea.

Maccrol *Pharmasant, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Macdafen *Ifarm, Pol.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Macgel *YSP, Malaysia; Yung Shin, Singapore.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Mach-2 *Tocogino, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Machlor *Eagle, Austral.*
Magnesium chloride (p.1679·1); magnesium oxide (p.1744·1); magnesium amino acid chelate (p.1680·1); pyridoxine hydrochloride.
Magnesium supplement.

Machto
Note. This name is used for preparations of different composition.
Nakornpatana, Thai.
Oral gel: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Nakornpatana, Thai.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); magnesium hydroxide (p.1743·2); peppermint oil (p.1761·2).
Flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Mackenzies Smelling Salts *Actavis, UK.*
Ammonia (p.2256·1); eucalyptus oil (p.2301·2).
Catarrh; nasal congestion.

Macladin *Target, Gr.; Guidotti, Ital.*
Clarithromycin (p.248·2).
Bacterial infections.

Maclar *Abbott, Austria; Abbott, Belg.; Glenmark, India; Glenmark, Malaysia.*
Clarithromycin (p.248·2).
Bacterial infections; Helicobacter pylori eradication.

Macleans Mouthguard *GSK Consumer, UK.*
Cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).
Oral hygiene.

Macleans Sensitive *GSK Consumer, Austral.*
Sodium fluoride (p.1962·2); strontium acetate.
Dental caries prophylaxis; pain associated with sensitive teeth.

Maclorex *Alpharma, Mex.*
Chloroquine (p.599·2).
Malaria.

Maclov *Mavi, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Macmiror *Sanova, Austria; Poli, Cz.; Polichem, Hong Kong; World Pioneer, Hong Kong; Pharmacia, Ital.; Italmex, Mex.; Poli, Pol.; Poli, Rus.*
Nifuratel (p.841·3).
Amoebiasis; genito-urinary tract infections; giardiasis; Helicobacter pylori infections; vulvovaginal infection.

Macmiror Complex *Poli, Cz.; Polichem, Hong Kong; World Pioneer, Hong Kong; Pharmacia, Ital.; Poli, Pol.; Poli, Rus.*
Nifuratel (p.841·3); nystatin (p.543·2).
Vulvovaginal infections.

Macmiror Complex V *Italmex, Mex.*
Nifuratel (p.841·3); nystatin (p.543·2).
Vulvovaginal infections.

Macobal *Gramon, Arg.*
Nimodipine (p.1357·2).
Cerebrovascular disorders; mental function impairment.

Macoderm
Note. This name is used for preparations of different composition.
Valuge, Arg.
Zinc oxide (p.1621·2); acetylated wool alcohols (p.2033·2).
Skin disorders.

Farmachimici, Ital.
Soap substitute.

Macodin *Parggon, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Macorel *Elpen (Ελπεν), Gr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Macovan *Depofarma, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Macril *Andromaco, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Macro Antioxidant *Whitehall, Austral.†.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Macro Anti-Stress *Whitehall, Austral.†.*
Vitamin B substances, ascorbic acid, and valerian (p.2410·1)(p.1922·1).
Dietary supplement; stress.

Macro B *Wyeth Consumer, Austral.†.*
Vitamin B substances and ascorbic acid (p.1922·1).
Dietary supplement.

Macro C *Wyeth Consumer, Austral.†.*
Ascorbic acid (p.1983·3); calcium ascorbate (p.1984·1); citrus bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3).
Vitamin C supplement.

Macro E *Wyeth Consumer, Austral.†.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Macro Garlic *Wyeth Consumer, Austral.†.*
Odourless Arizona garlic (p.2309·2).
Cold and influenza symptoms.

Macro M *Wyeth Consumer, Austral.†.*
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement.

Macro Maxepa *Wyeth Consumer, Austral.†.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1); *d*-alpha tocoferil acetate.
Omega-3 fatty acid supplement.

Macro Natural Vitamin E Cream *Wyeth Consumer, Austral.*
d-Alpha tocoferil acetate (p.1992·3); vitamin A palmitate (p.1973·1); panthenol (p.2362·1); allantoin (p.1588·1); avocado oil.
Dry skin; minor skin disorders.

Macro-Albumon *Medi-Radiopharma, Cz.*
⊗ Technetium-99m (p.2055·3) labelled human albumin macroaggregate.
Diagnosis of lung disorders; radionuclide imaging of veins.

Macrobee with Iron *Pharma Nutria, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B substances; manganese sulfate; copper sulfate (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Macrobee with Lysine *Pharma Nutria, Philipp.*
Lysine hydrochloride; vitamins (p.1922·1).
Nutritional supplement; tonic.

Macrobid *Procter & Gamble, Canad.; Goldshield, Irl.; Goldshield, UK; Procter & Gamble, USA.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Macrocal-D *Ventaglio, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteoporosis.

Macrodantin *Pfizer, Austral.; Alza, Canad.†; Goldshield, Irl.; Procter & Gamble, Israel†; Geymonat, Ital.; Boehringer Ingelheim, Philipp.; GSK, S.Afr.; Goldshield, UK; Procter & Gamble, USA.*
Nitrofurantoin (macrocrystalline) (p.308·1).
Urinary-tract infections.

Macrodantina *Mantecorp, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Farma, Venez.*
Nitrofurantoin (p.308·1).
Bacterial infections of the urinary tract.

Macrodex
Note. This name is used for preparations of different composition.
Torrex, Austria; Pharmalink, Ger.†; Meda, Hung.
⊗ Dextran 60 (p.1059·3) in sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Meda, Denm.; Pharmacia Upjohn, Israel; Pisa, Mex.†; Meda, Norw.; Alliance, S.Afr.; Meda, Swed.; Braun, Switz.†; Eczacibasi-Baxter, Turk.; Pharmacia, USA.
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Hypovolaemic shock; plasma volume expansion; shock; thromboembolism prophylaxis.

Macrodoxine *Lagamed, S.Afr.†.*
Vitamin B substances with vitamin C (p.1922·1).

Macrofurin *Mavi, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Macrol
Note. This name is used for preparations of different composition.
United American, Philipp.
Roxithromycin (p.331·1).
Bacterial infections; meningococcal meningitis prophylaxis.

Sanovel, Turk.
Clarithromycin (p.248·2).
Bacterial infections.

Macrolax *Chefaro, Ital.*
Docusate sodium (p.1725·1); sorbitol (p.1965·1).
Constipation.

Macrolid-S *SJA, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Macromax *Valeant, Arg.; ICN, Pol.*
Azithromycin (p.207·1).
Bacterial infections.

Macromed *MedGen, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Macromicina *Frasca, Arg.*
Clarithromycin (p.248·2).
Bacterial infections.

Macromin *Macrophar, Thai.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Macro-P *Promefarm, Ital.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Macropen
Note. This name is used for preparations of different composition.
Menarini, Port.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

KRKA, Rus.
Midecamycin (p.300·2).
Bacterial infections.

Xixia, S.Afr.
Amoxicillin trihydrate (p.202·2); flucloxacillin sodium (p.277·1).
Bacterial infections.

Macroral *Malesci, Ital.*
Midecamycin (p.300·2).
Bacterial infections.

Macrosan *Sanitas, Chile.*
Nitrofurantoin (p.308·1).
Bacterial urinary-tract infections.

Macrosil *Faes, Spain.*
Roxithromycin (p.331·1).
Bacterial infections.

Macrotec *GE, Cz.; GE, Port.; Amersham, Spain.*
⊗ Technetium-99m (p.2055·3) labelled human albumin macroaggregate.
Diagnostic agent; lung scintigraphy; radionuclide imaging of veins.

Macrox-5 *Liferpal, Mex.*
Thiamine (p.1976·3); vitamin B (p.1980·2); pyridoxine (p.1979·1).
Anaemias; neuritis.

Macroxam *Macropharma, Philipp.; SK, Philipp.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Macrozit *Liomont, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Macsoralen *Mac, India†.*
Methoxsalen (p.1605·1).
Vitiligo.

Mactex *Gynopharm, Chile.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Macugen *Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Singapore; Pfizer, UK; Eyetech, USA.*
Pegaptanib sodium (p.2364·1).
Neovascular (wet) age-related macular degeneration.

Macvit *Baif, Ital.*
Vitamin and mineral preparation (p.1922·1).

Madar *Teofarma, Ital.*
Nordazepam (p.1012·1).
Sleep disorders.

Madecassol *Bayer, Austria; Bayer, Belg.; Bayer, Chile; Bayer, Fr.; Nikolakopoulos (Νικολακόπουλος), Gr.; Roche Nicholas, Hong Kong; Corsa, Indon.; Roche Nicholas, Indon.; Serdex, Indon.; Sanofi Synthelabo, Mex.; Confar, Port.; Serdex, Thai.†; Roche, Turk.; Polinac, Venez.*
Centella (p.1592·3).
Burns; cicatrisation; haemorrhoids; keloids; phlebitis; scars; ulcers; venous insufficiency; wounds.

Madecassol C *Sanofi Synthelabo, Mex.*
Centella (p.1592·3); metronidazole (p.837·1); nitrofurazone (p.309·1).
Bacterial vaginosis; trichomoniasis.

Madecassol N *Sanofi Synthelabo, Mex.*
Centella (p.1592·3); nitrofurazone (p.309·1).
Vaginosis.

Madecassol Neomicina *Roche, Chile†.*
Centella (p.1592·3); neomycin sulfate (p.305·1).
Infected skin disorders; wounds.

Madecassol Neomycine Hydrocortisone *Bayer, Fr.†.*
⊗ Centella (p.1592·3); neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Madexin *Medic+Aid, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Madicure *McNeil, Neth.*
Mebendazole (p.148·3).
Enterobiasis.

Madiplot *Takeda, Thai.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Madiprazole *Pharmadica, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Maditez *Medipharma, Arg.*
Terbinafine (p.546·3) or terbinafine hydrochloride (p.546·3).
Fungal infections.

Madlexin *Meiji, Indon.*
Cefalexin (p.218·2).
Bacterial infections.

Madol *Masa, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Madola *Pharmaland, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Madomine *Atlantic, Malaysia; Atlantic, Singapore†.*
Sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Madonella *Kwizda, Austria.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Madonna *Biolab, Malaysia; Biolab, Thai.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Madopar
Note. This name is used for preparations of different composition.
Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
These ingredients can be described by the British Approved Name Co-beneldopa.
Parkinsonism; restless legs syndrome.

Madopark *Roche, Swed.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Madoxy *Pharmadica, Thai.*
Doxycycline (p.267·1).
Bacterial infections.

Madrox *Konimex, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; epigastric pain; flatulence; gastric hyperacidity; gastric pain; nausea; peptic ulcer.

Maelenoxyl *Foramen, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mafel *Raymos, Arg.*
Progesterone (p.2125·1).

Mafena *Maver, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Maflurell *Sanorell, Ger.*
Homoeopathic preparation.

Maforan *Sriprasit, Thai.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Maformin *Sanofi Synthelabo, Hung.†; Pharmadica, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mafusol *Biosynthesis, Rus.*
Sodium fumarate; sodium chloride; potassium chloride; magnesium chloride (p.1667·1).
Hypovolaemia; plasma substitute.

Mag *Cipla, India.*
Magnesium chloride (p.1679·1).

Mag-200 *Optimox, USA.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Mag 2
Cooperation Pharmaceutique, Fr.
Magnesium carbonate (p.1743·1) or magnesium pidolate (p.1679·3).
Magnesium deficiency.

Galenica, Gr.; Sanofi-Aventis OTC, Ital.; Aventis, Switz.
Magnesium pidolate (p.1679·3).
Eclampsia; magnesium deficiency; magnesium supplement; muscular cramp; nervous disorders.

Mag 3 *Rez, Cz.*
Technetium-99m (p.2055·3) betiatide.
Kidney scintigraphy.

Mag 50 *Vitaplex, Austral.†.*
Magnesium amino acid chelate (p.1680·1).
Magnesium supplement.

Mag 77 *Osotspa, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Mag Cit Prep *Medefield, Austral.†.*
Magnesium citrate (p.1743·2).
Bowel evacuation.

Mag 2 Junior *Cooperation Pharmaceutique, Fr.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Magnesium supplement.

Mag Kottas Krauterexpress Abfuhrtee *Kottas-Heldenberg, Austria.*
Frangula (p.1732·2); senna (p.1769·2); peppermint leaf (p.1761·2); fennel (p.2302·3); caraway (p.2276·3).
Constipation.

Mag Kottas May-Cur-Tee *Kottas-Heldenberg, Austria.*
Frangula bark (p.1732·2); senna (p.1769·2); fennel (p.2302·3); chamomile (p.2279·3); magnesium sulfate (p.1679·3).
Bowel evacuation; constipation.

Magalat *Ferron, Indon.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Gastric hyperacidity.

Magalite *Codifra, Fr.*
Cod-liver oil (p.1935·2); minerals; vitamins (p.1922·1).
Nutritional supplement.

Magalphil *Philopharm, Rus.*
Magaldrate (p.1742·3).
Gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Magaltop *Therabel, Ital.*
Magaldrate (p.1742·3).
Gastro-oesophageal reflux; hyperacidity; peptic ulcer.

Magan *Savage, USA.*
Magnesium salicylate (p.79·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Maganol *Guardian, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Magasida *Kimia, Indon.*
Aluminium magnesium hydroxide; simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Magastron *1A, Ger.*
Magaldrate (p.1742·3).
Gastric hyperacidity; peptic ulcer.

Mag-Cal Mega *Freeda, USA.*
Magnesium (p.1678·3); calcium (p.1675·2).
Dietary supplement.

Mag-Caps *Genesis, USA.*
Magnesium oxide (p.1744·1).
Antacid; magnesium supplement.

Mag-Carb *R&D, USA.*
Magnesium carbonate (p.1743·1).
Nutritional supplement.

Mag-CE *Asofarma, Arg.*
Magnesium; ascorbic acid (p.1922·1).
Dietary supplement.

Magcine *Berko, Turk.*
Magnesium hydroxide (p.1743·2).

Mag-Citrate *Tanta, Canad.*
Magnesium citrate (p.1743·2).
Bowel lavage.

Magcol *Pharmasant, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Magen-700 *Marfarma, Ital.*
Magnesium; potassium; sodium; taurine (p.1922·1).
Dietary supplement.

Magen- und Darmtee N *Abtswinder, Cz.†.*
Chamomile (p.2279·3); peppermint leaf (p.1761·2); liquorice (p.1740·3); mallow flower (p.2337·2); cinnamon (p.2283·1).
Indigestion.

Magen-Darmtropfen N *Heel, Ger.*
Homoeopathic preparation.

Magenpulver Hafter *Streuli, Switz.†.*
Bismuth subnitrate (p.1711·2); calcium carbonate (p.1714·1); magnesium peroxide (p.1651·3).
Gastric hyperacidity.

Magentabletten Hafter *Streuli, Switz.†.*
Bismuth subnitrate (p.1711·2); calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Magentee St Severin *Smetana, Austria.*
Absinthium (p.2244·1); centaury (p.2279·1); taraxacum (p.2395·1); sweet orange peel (p.2357·2); St John's wort (p.422·3).
Gastrointestinal disorders.

Magesto
Note. This name is used for preparations of different composition.
Takeda, Hong Kong.
Calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); amylase (p.2256·3); thiamine (p.1976·3); scopolia; clove oil (p.2285·1); fennel oil (p.2303·1); ginger oil (p.1732·3); cinnamon oil (p.2283·2); orange oil (p.2357·2); aluminium hydroxide (p.1706·2); menthol (p.2340·1); calcium hydrogen phosphate (p.1676·1).
Digestive-system disorders.

Takeda, Thai.
Mamylase; amylase (p.2256·3); vitamin B ; scopolia; sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); cinnamon oil (p.2283·2); clove oil (p.2285·1); fennel oil (p.2303·1); ginger oil (p.1732·3); orange peel oil (p.2357·2); menthol (p.2340·1); aluminium hydroxide gel (p.1706·2).
Gastrointestinal tract disorders.

Mag-G *Cypress, USA.*
Magnesium gluconate (p.1679·2).
Dietary supplement.

Maghora *Grands Espaces, Fr.*
Olive oil (p.2356·2); lavender oil (p.2331·2); pine oil (p.2368·2); rosemary oil (p.2381·3).
Skin irritation.

Magic Mix *DHN, Fr.*
Maize starch (p.1968·1).
Dietary aid; gastro-oesophageal reflux in infants.

Magicul *Alphapharm, Austral.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Magion *Ern, Spain.*
Magaldrate (p.1742·3).
Gastric hyperacidity.

Magisbile *Magis, Ital.†.*
Fencibutirol (p.2302·3); boldo (p.2267·2); rhubarb (p.1768·3); cascara (p.1715·2); sorbitol (p.1965·1).
Constipation.

Magium
Hexal, Austria.
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Hexal, Ger.
Magnesium aspartate (p.1679·1) or magnesium oxide (p.1744·1).
Magnesium deficiency.

Magium K *Hexal, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Potassium and magnesium deficiency.

Maglek B_6 *Lek-Am, Pol.*
Magnesium lactate (p.1679·2); pyridoxine hydrochloride (p.1978·2).
Magnesium and vitamin B deficiency.

Maglid
Note. This name is used for preparations of different composition.
Melisana, Belg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders associated with hyperacidity.

Overseas, India.
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Maglucate *Pharmascience, Canad.*
Magnesium gluconate (p.1679·2).
Hypomagnesaemia.

Magluphen *Tyrol, Austria†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain; renal and biliary colic.

Maglut *Magis, Ital.†.*
Glutathione (p.1448·1).
Alcohol and drug poisoning; radiation trauma.

Magmin *Blackmores, Austral.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Mag-Min *Selmag, Switz.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Magnacal *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Magnacet *Mallinckrodt, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Magnalum *Protein, Mex.†.*
Aluminium hydroxide (p.1706·2).
Flatulence; gastric hyperacidity.

Magnamycin *Pfizer, India.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Magnapen
Note. This name is used for preparations of different composition.
CP Pharmaceuticals, UK.
Capsules: Ampicillin trihydrate (p.204·2); flucloxacillin sodium (p.277·1) (p.205·1).
These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.

CP Pharmaceuticals, UK.
Injection: Ampicillin sodium (p.204·1); flucloxacillin sodium (p.277·1) (p.205·1).
These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.

CP Pharmaceuticals, UK.
Syrup: Ampicillin trihydrate (p.204·2); flucloxacillin magnesium (p.277·1) (p.205·1).

These ingredients can be described by the British Approved Name Co-fluampicil.
Bacterial infections.

Magnaprin *Rugby, USA†.*
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2), calcium carbonate (p.1714·1), and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Magnaspart *Rosen, Ger.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Magnaspor *Ranbaxy, Mex.; Ranbaxy, Thai.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Magnatil *Tecnofarma, Chile.*
Magnesium; vitamin C (p.1922·1).
Dietary supplement.

Magnatil Calcico *Tecnofarma, Chile.*
Ascorbic acid; magnesium; calcium (p.1922·1).
Dietary supplement.

Magne B6
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Rus.
Oral solution: Magnesium lactate (p.1679·2); magnesium pidolate (p.1679·3); pyridoxine hydrochloride (p.1978·2).
Asthenia; magnesium deficiency.

Sanofi-Aventis, Rus.
Tablets: Magnesium lactate (p.1679·2); pyridoxine hydrochloride (p.1978·2).
Asthenia; magnesium deficiency.

Magne-B$_6$
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Pol.
Magnesium lactate (p.1679·2); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.†; Sanofi-Aventis, Hung.
Oral solution: Magnesium lactate (p.1679·2); magnesium pidolate (p.1679·3); pyridoxine hydrochloride (p.1978·2).
Magnesium deficiency.

Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.
Tablets: Magnesium lactate (p.1679·2); pyridoxine hydrochloride (p.1978·2).
Magnesium deficiency.

Sanofi-Aventis, Fr.
Tablets: Magnesium citrate (p.1743·2) or magnesium lactate (p.1679·2); pyridoxine hydrochloride (p.1978·2).
Magnesium deficiency.

Magne-Balans Plus *Aflofarm, Pol.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Magnesium and potassium deficiency.

Magnebe
Note.This name is used for preparations of different composition.
Dominguez, Arg.
Injection: Magnesium pidolate (p.1679·3).
Magnesium supplement.

Dominguez, Arg.
Tablets: Magnesium citrate (p.1743·2); pyridoxine hydrochloride (p.1978·2).
Magnesium supplement.

MagneBind *Nephro-Tech, USA.*
Magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1).
Dietary phosphate binder.

Magnecyl *Pfizer, Swed.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Magnecyl-koffein *Pfizer, Swed.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Magnefar *Biofarm, Pol.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Magnefar B$_6$ *Biofarm, Pol.*
Magnesium aspartate (p.1679·1); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Magneforte *Hexal, Arg.†.*
Magnesium oxide (p.1744·1).
Magnesium supplement.

Magnefusin *Pisa, Mex.†.*
Magnesium sulfate (p.1679·3).

Magneginseng *Omega, Fr.*
Magnesium lactate; ginseng; soy lethicin (p.1922·1).
Tonic.

Magnegita *Curagita, Cz.*
Meglumine gadopentetate (p.1479·2).
Contrast agent for magnetic resonance imaging.

Magnegon *Nycomed, Switz.*
Magnesium lactate (p.1679·2); magnesium citrate (p.1743·2).
Magnesium deficiency; magnesium supplement.

Magnerot
Worwag, Cz.; Worwag, Hung.; Worwag, Rus.
Magnesium orotate (p.2358·3).
Atherosclerosis; heart failure; hyperlipidaemias; magnesium deficiency; magnesium-dependent arrhythmias; myocardial infarction.

Worwag, Ger.
Magnesium gluconate (p.1679·2).
Magnesium deficiency.

Magnerot A *Worwag, Ger.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

magnerot Classic *Worwag, Ger.*
Magnesium orotate (p.2358·3).
Magnesium deficiency.

Magnerot N *Worwag, Ger.*
Magnesium phosphate (p.1679·2); magnesium citrate (p.1743·2).
Magnesium deficiency.

Magnesia *Medic, Denm.; Nycomed, Denm.; Cinfa, Spain.*
Magnesium hydroxide (p.1743·2).
Constipation; dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Magnesia Bisurada *Wyeth Consumer, Braz.*
Magnesium carbonate (p.1743·1); bismuth subcarbonate (p.1711·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity.

Magnesia Bisurata Aromatic *Wyeth Lederle, Ital.*
Magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastrointestinal hyperacidity.

Magnesia Effervescente Sella *Sella, Ital.*
Magnesium hydroxide (p.1743·2); tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2).
Constipation; gastrointestinal hyperacidity.

Magnesia Pasteur *Pasteur, Chile.*
Magnesium hydroxide (p.1743·2).
Antacid; constipation.

Magnesia Phosphorica I Oligoplex *Madaus, Arg.*
Magnesium phosphate (p.1679·2); sodium sulfate (p.1771·3); lycopodium.
Biliary-tract disorders.

Magnesia S Pellegrino *Saprochi, Israel; Sanofi-Aventis OTC, Ital.; Saprochi, Switz.*
Magnesium hydroxide (p.1743·2).
Constipation; gastrointestinal hyperacidity; heartburn.

Magnesia San Pellegrino *Welt, Arg.; Upsifarma, Port.; Seid, Spain; Arex, Venez.*
Magnesium hydroxide (p.1743·2).
Antacid; constipation; dyspepsia; hyperacidity.

Magnesia Volta *Edmond Pharma, Ital.†.*
Magnesium hydroxide (p.1743·2).
Constipation; gastrointestinal hyperacidity.

Magnesiamaito *Orion, Fin.*
Magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Magnesie Calcinee *Carlo Erba, Turk.*
Magnesium hydroxide (p.1743·2).
Constipation; dyspepsia.

Magnesie Plus *Omega, Belg.*
Magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastrointestinal disorders associated with hyperacidity.

Magnesie S Pellegrino *Zambon, Fr.†.*
Magnesium hydroxide (p.1743·2).
Constipation.

Magnesin *Neckerman, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Magnesio + C/Mag-CE *Asofarma, Arg.†.*
Magnesium; ascorbic acid (p.1922·1).
Dietary supplement.

Magnesio Incaico *Incaico, Arg.*
Magnesium (p.1678·3); calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium, magnesium and vitamin D supplement; osteoporosis.

Magnesio 102 Plus *ISA, Arg.*
Magnesium; iron; zinc; selenium; ginseng (p.1922·1).
Dietary supplement.

Magnesioboi *BOI, Spain.*
Magnesium lactate (p.1679·2).
Magnesium depletion.

Magnesiocard *Verla, Ger.; Verla, Hung.; Tecnimede, Port.; Verla, Switz.*
Magnesium aspartate hydrochloride (p.1680·1).
Magnesium deficiency; magnesium supplement.

Magnesiokatabios *SIT, Ital.*
Vitamins; magnesium (p.1922·1).
Nutritional supplement.

Magnesiol *Teuto, Braz.†.*
Magnesium hydroxide (p.1743·2).
Antacid.

Magnesit *Altana Madaus, S.Afr.*
Magnesium l-aspartate hydrochloride (p.1680·1).
Hypomagnesaemia.

Magnesium Biomed
Note.This name is used for preparations of different composition.
Verla, Switz.
Effervescent tablets; granules for oral liquid: Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Verla, Switz.
Lozenges; tablets: Magnesium hydrogen glutamate (p.1680·1); magnesium citrate (p.1743·2).
Magnesium deficiency; magnesium supplement.

Magnesium Complexe *Vifor, Switz.*
Magnesium chloride (p.1679·1); magnesium hydrogen glutamate (p.1680·1); magnesium glycerophosphate (p.1679·2); magnesium orotate (p.2358·3); magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Magnesium compositum *OPW, Ger.†.*
Magnesium adipate (p.1680·1); magnesium nicotinate.
Circulatory disorders.

Magnesium Diasporal
Austroplant, Austria; Nycomed, Austria.
Magnesium citrate (p.1743·2), magnesium levulinate (p.1680·1); or magnesium sulfate (p.1679·3).
Magnesium deficiency.

Protina, Cz.†.
Magnesium citrate (p.1743·2) or magnesium sulfate (p.1679·3).
Magnesium deficiency.

Protina, Ger.
Magnesium citrate (p.1743·2), magnesium oxide (p.1744·1), or magnesium sulfate (p.1679·3).
Magnesium deficiency.

Protina, Hung.†; Protina, Switz.
Magnesium citrate (p.1743·2).
Magnesium deficiency; magnesium supplement.

Magnesium Naneli Lafar *Saba, Turk.*
Magnesium hydroxide (p.1743·2).

Magnesium Nutrimed *Nutrimed, Switz.*
Magnesium carbonate (p.1743·1).
Magnesium deficiency; magnesium supplement.

Magnesium Pharmavit *BMS, Cz.*
Magnesium oxide (p.1744·1); ascorbic acid (p.1983·3).
Magnesium deficiency.

Magnesium Plus *Cenovis, Austral.†; Vitelle, Austral.†.*
Magnesium orotate (p.2358·3); magnesium oxide (p.1744·1); magnesium amino acid chelate (p.1680·1); monobasic potassium phosphate (p.1682·2); calcium hydrogen phosphate (p.1676·1).
Mineral supplement.

Magnesium Pyre *Salvat, Spain.*
Magnesium bromide (p.1680·1); magnesium chloride (p.1679·1); magnesium fluoride (p.1955·2); magnesium iodide (p.1680·1).
Magnesium depletion.

Magnesium Sandoz *Novartis, Gr.*
Magnesium aspartate (p.1679·1); magnesium citrate (p.1743·2).
Magnesium deficiency.

Magnesium Tonil *APS, Ger.*
Capsules: Heavy magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnesium Tonil mit Vitamin E *APS, Ger.*
Heavy magnesium oxide (p.1744·1); *dl*-alpha tocoferil acetate (p.1992·3).
Magnesium or vitamin E deficiency.

Magnesium Verla
Rowa, Irl.
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Verla, Ger.
Chewable tablets: Magnesium aspartate tetrahydrate (p.1679·1).
Magnesium deficiency.

Verla, Ger.
Effervescent tablets: Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Verla, Ger.
Injection: Magnesium hydrogen glutamate (p.1680·1) or magnesium sulfate heptahydrate (p.1679·3).
Magnesium deficiency.

Magnesium Verla N
Verla, Ger.
Powder for oral solution: Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Verla, Ger.
Tablets: Magnesium hydrogen glutamate (p.1680·1); magnesium citrate (p.1743·2).
Magnesium deficiency.

Magnesium Vital *Vifor, Switz.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Magnesium-B *Angelini, Port.†; Wassen, UK.*
Magnesium; vitamin B substances; vitamin C; betaine hydrochloride (p.1922·1).
Nutritional supplement.

Magnesium-OK
Note.This name is used for preparations of different composition.
Angelini, Ital.; Angelini, Port.†.
Magnesium; vitamins; minerals (p.1922·1).
Nutritional supplement.

Wassen, UK.
Magnesium oxide (p.1744·1); minerals; multivitamins (p.1922·1).

Magnesium-Plus-Hevert *Hevert, Ger.*
Magnesium oxide (p.1744·1); *d*-alpha tocopherol (p.1992·2).
Magnesium or vitamin E deficiency.

Magnesium-Sandoz *Sandoz, Switz.*
Magnesium aspartate (p.1679·1); magnesium citrate (p.1743·2).
Magnesium deficiency; magnesium supplement.

Magnesoide *Argenfarma, Arg.†.*
Magnesium (p.1678·3).
Magnesium supplement.

Magnesol *KRKA, Cz.†; KRKA, Pol.*
Magnesium citrate (p.1743·2).
Magnesium deficiency.

Magnesona *Vitoria, Port.*
Magnesium pidolate (p.1679·3).
Magnesium deficiency.

Magnesorot *Worwag, Ger.*
Magnesium orotate (p.2358·3).
Magnesium deficiency.

Magnespasmil *Grunenthal, Port.*
Magnesium lactate (p.1679·2).
Magnesium deficiency.

Magnespasmyl *Meuse, Belg.; Dexo, Fr.; Sanofi Synthelabo, Switz.†.*
Magnesium lactate (p.1679·2).
Magnesium deficiency; magnesium supplement.

Magnesulf *Austroplant, Austria.*
Magnesium sulfate (p.1679·3).
Arrhythmias; eclampsia; magnesium deficiency.

Magnetop *Grunenthal, Belg.†.*
Magnesium citrate (p.1743·2).

Magnetrans extra *Stada, Ger.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnetrans forte *Stada, Ger.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnevist *Schering, Arg.; Bayer, Austral.; Schering, Austria; Schering, Belg.; Berlex, Canad.; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Bayer Schering, Hung.; Schering, Ital.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Spain; Schering, Swed.; Schering, Switz.; Bayer, UK; Hospira, USA.*
Meglumine gadopentetate (p.1479·2).
Contrast medium for magnetic resonance imaging.

Magnevistan *Schering, Braz.; Schering, Chile; Schering, Venez.*
Meglumine gadopentetate (p.1479·2).
Contrast medium for magnetic resonance imaging.

Magnevital *Bioextra, Hung.*
Magnesium oxide (p.1744·1); *d* tocopherol (p.1992·2).
Magnesium and vitamin E deficiency.

Magnezi Kalsine *Istanbul, Turk.*
Magnesium oxide (p.1744·1).
Dyspepsia.

Magnezin *Polfa Grodzisk, Pol.*
Magnesium carbonate (p.1743·1).
Arrhythmias; magnesium deficiency; tonic.

Magnezium *BMS, Hung.†.*
Magnesium oxide (p.1744·1); ascorbic acid (p.1983·3).
Magnesium deficiency.

Magnezytki *Sanofi-Aventis, Pol.*
Magnesium lactate (p.1679·2); wheat bran (p.1712·3).
Constipation; obesity.

Magnidicon *Tunggal Idaman, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; epigastric pain; flatulence; gastritis; peptic ulcer.

Magnidol *Streger, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Magnidol-Plus *Streger, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Magniferron *Filadams, Philipp.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Magnil *Sons, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Magniton-R *Coup, Gr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Magno Sanol *Sanol, Ger.; Schwarz, Ger.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnocor *Viatris, Austria.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Coronary heart disease; magnesium deficiency.

Magnodor *Teuto, Braz.†.*
Metamizole magnesium (p.49·3).
Fever; pain.

Magnofit
Viatris, Ital.
Magnesium carbonate (p.1743·1).
Magnesium deficiency.

Viatris, Austria.
Magnesium citrate (p.1743·2); magnesium carbonate (p.1743·1).
Magnesium deficiency.

Magnogen *Baliarda, Arg.†.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Magnogene
Note.This name is used for preparations of different composition.
Novartis Sante, Fr.; Interdelta, Switz.
Magnesium chloride (p.1679·1).
Magnesium deficiency; magnesium supplement.

Uriach, Spain.
Magnesium bromide (p.1680·1); magnesium fluoride (p.1955·2); magnesium hydroxide (p.1743·2).
Magnesium depletion.

Magnograf *Schering, Spain.*
Meglumine gadopentetate (p.1479·2).
Contrast medium for magnetic resonance imaging.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Magnokal
Note. This name is used for preparations of different composition.
Polfa Kutno, Pol.
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Magnesium and potassium deficiency.

Saba, Turk.
Magnesium hydroxide (p.1743·2).

Magnol *Atlantis, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Magnolat *Daudt, Braz.†.*
Magnesium pidolate (p.1679·3).
Magnesium supplement.

Magnolax *Pendopharm, Canad.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Magnolex *Sante Naturelle, Canad.*
Magnesium chloride (p.1679·1) or magnesium glucep-tate (p.1679·1).

Magnolonas *Technobio, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Magnonorm *Generic on, Austria.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnoplasm *Mayne, Austral.*
Glycerol (p.2314·2); magnesium sulfate (p.1679·3).
Poultice for abscesses, boils, and carbuncles.

Magnopyrol *Farmasa, Braz.; Rhein, Mex.*
Metamizole magnesium (p.49·3).
Fever; pain.

Magnoral *Medinfar, Port.*
Magnesium chloride (p.1679·1).
Magnesium deficiency.

Magnorol *Rolmex, Canad.*
Magnesium gluceptate (p.1679·1).

Magnosol *Viatris, Ital.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1); potassium bicarbonate (p.1673·1).
Magnesium and potassium deficiency.

Magnosolv
Meda, Cz.; Meda, Hung.
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Magnesium deficiency.

Viatris, Austria.
Chewable tablets: Magnesium citrate (p.1743·2); magnesium carbonate (p.1743·1).
Magnesium deficiency.

Viatris, Austria.
Oral granules: Precipitated magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnostase *Neo Quimica, Braz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Magnoston *Ariston, Braz.*
Magnesium sulfate (p.1679·3).

Magnotab *Genericon, Austria.*
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Magnox *Lennod, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Hyperacidity.

Magnurol *Esteve, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Magnus *Sidus, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Magnyl *Nycomed, Denm.; SAD, Denm.*
Aspirin (p.20·3).
Magnesium hydroxide (p.1743·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; ischaemic heart disease; pain; thromboembolism prophylaxis.

Magocean *Proceane, Fr.*
Magnesium oxide (p.1744·1).
Magnesium supplement.

Magonate *Fleming, USA.*
Magnesium gluconate (p.1679·2); calcium hydrogen phosphate (p.1676·1).
Formerly contained magnesium gluconate.
Dietary supplement.

Magoral *ST, Thai.*
Magnesium oxide (p.1744·1).
Gastric hyperacidity; magnesium deficiency.

Mag-Oro *Eagle, Austral.*
Magnesium orotate (p.2358·3); magnesium aspartate (p.1679·1); magnesium amino acid chelate (p.1680·1); potassium aspartate (p.1684·2); pyridoxine hydrochloride (p.1978·2).
Magnesium, potassium, and vitamin B supplement.

Mag-Ox *Blaine, USA.*
Magnesium oxide (p.1744·1).
Hyperacidity; magnesium deficiency.

Magralibi *IBI, Ital.*
Magaldrate (p.1742·3).
Gastritis; gastro-oesophageal reflux; gastroduodenitis; peptic ulcer.

Magrilan *Medochemie, Cz.; Medochemie, Hong Kong†; Medochemie, Singapore; Medochemie, Thai.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Magrix *Ativus, Braz.*
Poliglusam (p.2370·1).
Hypercholesterolaemia; slimming aid.

Magsil *Fortune, Hong Kong†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimethicone (p.1770·2).
Gastrointestinal hyperacidity; meteorism.

Magsolvit B_6 *Galenus, Pol.*
Magnesium gluconate (p.1679·2); magnesium lactate (p.1679·2); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Magsons *Sons, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Mag-SR *Cypress, USA.*
Magnesium chloride (p.1679·1).
Magnesium supplement.

Mag-SR plus Calcium *Cypress, USA.*
Magnesium chloride (p.1679·1); calcium carbonate (p.1714·1).
Magnesium and calcium supplement.

Mag-Tab
Note. This name is used for preparations of different composition.
Sigma, Braz.
Magnesium amino acid chelate (p.1680·1).
Magnesium supplement.

Rider, Chile; Niche, USA.
Magnesium lactate (p.1679·2).
Magnesium deficiency; magnesium supplement.

Magtacid *Prafa, Indon.*
Aluminium magnesium hydroxide; simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Magtasil *ICM, Singapore.*
Magnesium trisilicate (p.1744·1); light magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastric hyperacidity.

Magto *Polipharm, Thai.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity.

Magtral *Otto, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Magtrate *Mission Pharmacal, USA.*
Magnesium gluconate (p.1679·2).
Dietary supplement.

Maguran *Pharmacypria, Gr.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Magurlit *Sanofi Synthelabo, Hung.†.*
Potassium citrate (p.1673·2); sodium citrate (p.1673·3); citric acid monohydrate (p.2284·1); magnesium citrate (p.1743·2); pyridoxine hydrochloride (p.1978·2).
Renal calculi; urinary alkalinisation.

Magurol
Medochemie, Malaysia.
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Medochemie, Rus.
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Magvit B_6 *GSK, Pol.*
Magnesium lactate (p.1679·2); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Magvital *Panderma, Austria.*
Magnesium hydrogen aspartate (p.1679·1) or magnesium sulfate (p.1679·3).
Arrhythmias; eclampsia; magnesium deficiency; premature labour.

Magytax *Hungaro-Gen, Hung.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Mahiou *Vectem, Spain†.*
Phenolphthalein (p.1762·1); vitamin F (p.2308·2).
Chilblains; haematomas; haemorrhoids; insect bites and stings; varices.

Mailen
Note. This name is used for preparations of different composition.
Investi, Arg.
Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); centella (p.1592·3).
Vaginal infections.

Roemmers, Chile; Roemmers, Venez.
Desloratadine (p.576·1).
Hypersensitivity reactions.

Mainnox *Charoen, Thai.*
Mefenamic acid (p.80·1); dicycloverine hydrochloride (p.1722·3).
Pain; smooth muscle spasm.

Maintain
Note. A similar name is used for preparations of different composition (see below).
Durex, Canad.; Schmid, Israel.
Benzocaine (p.1854·1).
Premature ejaculation.

Maintane
Note. This name is used for preparations of different composition.
Jagson, India.
Injection: Hydroxyprogesterone caproate (p.2110·3).
Threatened or habitual miscarriage.

Jagson, India.
Tablets: Allylestrenol (p.2082·2).
Premature labour; threatened miscarriage.

Maintate
Tanabe, Indon.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; heart failure; hypertension.

Tanabe, Jpn.
⊗ Bisoprolol (p.1234·2).
Angina pectoris; hypertension.

Maiorad *Rotta, Ital.; Delta, Port.; Rotta, Thai.*
Tiropramide hydrochloride (p.2403·1).
Smooth muscle spasm.

Maizar *Vitoria, Port.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma; obstructive airways disease.

Majamil *Polpharma, Pol.*
Diclofenac (p.44·2).
Inflammation; musculoskeletal and joint disorders; neuralgia; pain.

Majeptil *Erfa, Canad.; IFET (ΙΦΕΤ), Gr.; Aventis, Mex.†; Sanofi-Aventis, Rus.; Sanofi-Aventis, Spain; Aventis, Venez.†.*
Thioproperazine mesilate (p.1031·1).
Anxiety; mania; psychoses; schizophrenia.

Majezik *Sanovel, Turk.*
Flurbiprofen (p.61·2).
Musculoskeletal and joint disorders; pain.

Majocarmin forte *Hevert, Ger.†.*
Caraway oil (p.2277·1); fennel oil (p.2303·1); peppermint oil (p.1761·2); absinthium (p.2244·1); cinnamon (p.2283·1); gentian (p.2310·3); burnet saxifrage (p.2270·3); ginger (p.1732·3); sweet orange (p.2357·2); cinchona bark (p.2282·3); condurango (p.2287·1).
Gastrointestinal disorders.

Majocarmin mite *Hevert, Ger.†.*
Absinthium (p.2244·1); calamus (p.2271·3); cinchona bark (p.2282·3); gentian (p.2310·3); valerian (p.2410·1); peppermint leaf (p.1761·2).
Dyspepsia; hypochlorhydria; loss of appetite.

Majocarmin-Tee *Hevert, Ger.*
Aniseed (p.2258·2); fennel (p.2302·3); caraway (p.2276·3); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Gastrointestinal disorders.

Majolat *Fujisawa, Austria.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Major-Con *Major, USA.*
Simeticone (p.1770·2).
Flatulence.

Majorem *Sanofi Synthelabo, Austria.*
Amisulpride (p.961·1).
Schizophrenia.

Major-gesic *Major, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Majorpen *Ipso, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Makaphyt Baume *Gebro, Switz.†.*
Camphor (p.2273·2); menthol (p.2340·1); cypress oil (p.2291·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); pine-needle oil (p.2368·2); turpentine oil (p.2406·3); thyme oil (p.2401·2).
Respiratory-tract disorders.

Makaphyt Gouttes antitussives *Gebro, Switz.*
Drosera (p.2297·3); liquorice (p.1740·3); pimpinella (p.2270·3); senega root (p.1572·3); thyme (p.2401·1); camphor (p.2273·2); menthol (p.2340·1); anise oil (p.2258·2); eucalyptus oil (p.2301·2).
Coughs.

Makaphyt Sirop *Gebro, Switz.*
Drosera (p.2297·3); liquorice (p.1740·3); senega root (p.1572·3); thyme (p.2401·1).
Respiratory-tract disorders.

Ma-Ka-Ta *Lokman, Turk.*
⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1); hydrastis (p.2321·3).
Haemorrhoids.

Makatussin Codein *Altana, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Makatussin Comp *Gebro, Switz.*
Dihydrocodeine hydrochloride (p.48·3); diphenhydramine hydrochloride (p.577·2).
Respiratory-tract disorders.

Makatussin nouvelle formule *Gebro, Switz.*
Codeine phosphate (p.37·2).
Coughs.

Makatussin Saft *Altana, Ger.†.*
Thyme (p.2401·1).
Bronchitis; catarrh.

Makatussin Saft Drosera *Altana, Ger.†.*
Drosera (p.2297·3).
Coughs.

Makatussin Tropfen *Altana, Ger.*
Thyme (p.2401·1); star anise oil (p.2392·2).
Respiratory-tract congestion.

Makatussin Tropfen Drosera *Altana, Ger.†.*
Drosera (p.2297·3).
Coughs.

Makatussin Tropfen forte *Altana, Ger.†.*
Dihydrocodeine hydrochloride (p.48·3); drosera (p.2297·3).
Coughs.

Makatussin-Hustentropfen *Gebro, Austria.*
Codeine phosphate (p.37·2).
Coughs.

Makiren *Rafarm, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Makovan *Medimar, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Makro B *Tunggal Idaman, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Makrovit *KRKA, Rus.*
Vitamin preparation (p.1922·1).

Maksipor *Fako, Turk.*
Cefalexin (p.218·2).
Bacterial infections.

Maksiporin *Fako, Turk.*
Cefazolin (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Maladin *Unicure, India.*
Mepacrine hydrochloride (p.836·2).
Malaria.

Malafene *Abbott, Belg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Malandil *Bohm, Spain.*
Carnitine hydrochloride (p.1933·1); cobamamide (p.1980·2); lysine hydrochloride (p.1955·1).
Anaemias; tonic.

Malanil *GSK, S.Afr.*
Atovaquone (p.829·2); proguanil hydrochloride (p.609·2).
Malaria.

Malarex *Alpharma, Denm.; Actavis, Indon.*
Chloroquine phosphate (p.599·3).
Amoebiasis; lupus erythematosus; malaria; photosensitivity; rheumatoid arthritis.

Malarivon *Wallace Mfg Chem., UK.*
Chloroquine phosphate (p.599·3).
Malaria.

Malarone *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK; Glaxo Wellcome, USA.*
Atovaquone (p.829·2); proguanil hydrochloride (p.609·2).
Malaria.

Malastop *Sterop, Belg.†.*
Pyrimethamine (p.610·2); sulfadoxine (p.338·1).
Malaria.

Malaviron *Wallace Mfg Chem., UK.*
Chloroquine phosphate (p.599·3).
Malaria.

Male + *Homeocan, Canad.*
Homoeopathic preparation.

Male Formula Herbal Plus Formula 2 *Vitelle, Austral.†.*
Eleutherococcus senticosis; equisetum; sarsaparilla; liquorice; damiana; zinc amino acid chelate; betacarotene; pyridoxine hydrochloride; *d*-alpha tocoferil acid succinate; magnesium oxide (p.1922·1).
Tonic.

Maleapril *Gallia, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Maledrol *Chrispa (Χρισπα), Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Malen *BA Farma, Port.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Malena *Juste, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Malena HCT *Sigma, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Malex *Ecosol, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Malgacid *Ziololek, Pol.*
Hydrotalcite (p.1733·3).
Gastric hyperacidity; gastritis; peptic ulcer.

Maliago *Cipla, India.*
Chloroquine (p.599·2).
Malaria.

Maliaquine *Sriprasit, Thai.*
Chloroquine phosphate (p.599·3).
Malaria; rheumatoid arthritis.

Maliasin *Abbott, Austria; Knoll, Braz.; Pharmalex (Φαρμαλέξ), Gr.; Abbott, Ital.; Abbott, Switz.; Abbott, Turk.*
Barbexaclone (p.471·2).
Epilepsy.

Malicon Norma (Νορμα), Gr.
Citalopram (p.385·3).
Depression.

Malidens Nicholas Piramal, India.
Paracetamol (p.108·1).
Fever; pain.

Malimed Ecosol, Switz.†.
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Malipuran Pfizer Consumer, Ger.
Bufexamac (p.28·3).
Skin disorders.

Malirid Ipca, India.
Primaquine phosphate (p.608·1).
Malaria.

Malival Silanes, Mex.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint and periarticular disorders; pain.

Malival Compuesto Silanes, Mex.
Methocarbamol (p.1897·3); indometacin (p.66·3).
Inflammation; musculoskeletal, joint and periarticular disorders; pain; skeletal muscle spasm.

Mallamint Roberts, USA.
Calcium carbonate (p.1714·1).
Hyperacidity.

Mallazine Hauck, USA†; Roberts, USA†.
⊗ Tetryzoline hydrochloride (p.1574·1).
Minor eye irritation.

Mallebrin Krewel, Ger.
Hexaurea aluminium chloride.
Mouth and throat disorders.

Mallebrin Konzentrat Krewel, Ger.
Aluminium chloride (p.1588·2).
Mouth and throat inflammation.

Mallorol Novartis, Swed.†.
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Pain; psychoses.

Malocef Pharmanel, Gr.
Ceftazidime (p.234·1).
Bacterial infections.

Malocide Sanofi-Aventis, Fr.
Pyrimethamine (p.610·2).
Toxoplasmosis.

Malocin M & H, Thai.
Erythromycin stearate (p.270·1).
Bacterial infections.

Malonetta Sandoz, Denm.
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Maloprim GSK, Austral.; Wellcome, Irl.†; GSK, S.Afr.†.
Pyrimethamine (p.610·2); dapsone (p.261·2).
Malaria.

Malortil Alet, Gr.
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Maltan Masters, Pol.
Glucose (p.1945·3).
Nipple care.

Maltin Reccius, Chile.
Malt extract (p.1955·2).
Nutritional supplement.

Maltiron Meprofarm, Indon.
Vitamin B substances (p.1922·1); ferrous gluconate (p.1939·1).
Nutritional supplement.

Maltiron Plus Meprofarm, Indon.
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Maltlevol Church & Dwight, Canad.
Multivitamin preparation (p.1922·1) with ferric ammonium citrate (p.1938·1).
Food supplement; iron-deficiency anaemia.

Maltlevol-M Carter Horner, Canad.†.
Multivitamin and mineral preparation (p.1922·1).

Maltocalcine Etifar, Venez.
Calcium gluconate (p.1675·3); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Maltofer
Note. This name is used for preparations of different composition.
Bago, Arg.; Andromaco, Chile; Vifor, Cz.; Meda, Fin.; Therabel, Fr.†; Sanofi-Aventis, Hung.; Combiphar, Indon.; Vifor, Port.; Vifor International, Switz.; Abdi, Turk.; Zuoz, Venez.
Iron polymaltose (p.1953·1).
Iron deficiency; iron supplement; iron-deficiency anaemia.

Vifor, Malaysia.
Chewable tablets: Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron deficiency; iron-deficiency anaemia.

Vifor, Malaysia.
Syrup: Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Maltofer Fol Quesada, Arg.†; Andromaco, Chile; Vifor, Cz.; Sanofi-Aventis, Hung.; Combiphar, Indon.; Vifor International, Switz.; Abdi, Turk.
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Maltofer Vitaminado Andromaco, Chile.
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement.

Maltoferfol Vifor, Port.; Zuoz, Venez.
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Anaemias; iron deficiency.

Malton E Riemser, Ger.
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Maltovis Volchem, Ital.
Maltodextrin (p.1955·3).
Carbohydrate source.

Maltsupex Wallace, USA.
Malt extract (p.1955·2).
Constipation.

Maltyl Merckle, Ger.†.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Malu Sigma, Braz.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Maludil Sandoz, Denm.
Maprotiline hydrochloride (p.407·2).
Depression.

Malugastrin Polfa Lodz, Pol.
Magaldrate (p.1742·3).
Gastric hyperacidity; peptic ulcer.

Malugel Charoen, Thai.
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Malvaliz Soria Natural, Spain†.
Althaea (p.2253·3); liquorice (p.1740·3); clay.
Gastrointestinal disorders.

Malvatricin Daudt, Braz.
Sodium fluoride (p.1962·2); tyrothricin (p.358·2).
Dental caries prophylaxis.

Malvatricin Antiplaca Daudt, Braz.
Sodium monofluorophosphate (p.1964·3); potassium pyrophosphate (p.2390·3); triclosan (p.1665·2).
Mouth disorders.

Malvatricin Antitartaro Daudt, Braz.
Sodium monofluorophosphate (p.1964·3); tetrapotassium pyrophosphate.
Dental caries prophylaxis.

Malvatricin Branqueador Daudt, Braz.
Sodium fluoride (p.1962·2) or sodium monofluorophosphate (p.1964·3); sodium perborate (p.1662·1); hydrogen peroxide (p.1647·3); triclosan (p.1665·2).
Dental caries prophylaxis; dental whitener.

Malvatricin Dentes Sensiveis Daudt, Braz.
⊗ Sodium monofluorophosphate (p.1964·3); potassium nitrate (p.1658·3); tetrapotassium pyrophosphate; triclosan (p.1665·2).
Dental caries prophylaxis; sensitive teeth.

Malvatricin Ginecologico Daudt, Braz.
Tyrothricin (p.358·2); quinosol (p.2323·1).
Vaginal disorders.

Malvatricin Natural Daudt, Braz.
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3); calendula (p.2273·1); echinacea (p.2298·1); guaco.
Dental caries prophylaxis.

Malvatricin Natural Organic Daudt, Braz.
Sodium monofluorophosphate (p.1964·3); echinacea (p.2298·1); propolis (p.2373·3); rhatany (p.2378·3); with or without hamamelis (p.2318·2).
Dental caries prophylaxis.

Malvatricin Natural Soft Daudt, Braz.
Sodium monofluorophosphate (p.1964·3); echinacea (p.2298·1); chamomile (p.2279·3); aloe vera (p.1588·2); mallow (p.2337·2).
Dental caries prophylaxis.

Malvatricin Pastilhas Daudt, Braz.
Quinosol (p.2323·1); tyrothricin (p.358·2); benzocaine (p.1854·1); mallow (p.2337·2).
Mouth disorders.

Malvatricin Plus Daudt, Braz.
Sodium monofluorophosphate (p.1964·3); triclosan (p.1665·2).
Mouth disorders.

Malvatricin Pronto Daudt, Braz.
Quinosol (p.2323·1); tyrothricin (p.358·2); mallow (p.2337·2).
Mouth disorders.

Malvatricin Solucao para diluir Daudt, Braz.
Quinosol (p.2323·1); tyrothricin (p.358·2); mallow (p.2337·2).
Mouth disorders.

Malvatricin Spray Daudt, Braz.
Quinosol (p.2323·1); tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3); mallow (p.2337·2).
Mouth disorders.

Malvedrin
Note. This name is used for preparations of different composition.
Merz, Switz.
Ointment: Mallow leaves (p.2337·2); vitamin A (p.1971·2); vitamin D (p.1986·1); chamomile oil (p.2279·3); St John's wort oil (p.423·2); linseed oil (p.2334·1).
Skin irritation; superficial wounds.

Merz, Switz.
Topical liquid: Mallow leaves (p.2337·2).
Mouth and throat disorders; superficial wounds.

Malveol Magistra, Switz.
Althaea leaves (p.2253·3); mallow leaves (p.2337·2); salicylic acid (p.1612·2); mint oil (p.2345·2).
Mouth and throat disorders.

Malvitona Leo, Fin.; Leo, Swed.
Vitamin B substances (p.1922·1); caffeine (p.1116·3).
Tonic.

Malvodon IMA, Braz.
Mallow (p.2337·2); poppy (p.1571·1).
Mouth disorders.

Malvona
Note. This name is used for preparations of different composition.
Prima, Braz.†.
Mouthwash; pastilles: Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1); borax (p.2268·1).
Mouth and throat disorders.

Prima, Braz.†.
Toothpaste: Borax (p.2268·1); sodium chloride (p.1686·1); benzocaine (p.1854·1).

Mama Wyeth, Hong Kong.
Preparation for enteral nutrition during pregnancy and lactation (p.1922·1).

Mama with DHA Wyeth, Malaysia.
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Mamacare Mead Johnson, Philipp.
Nutritional supplement for pregnant and breast feeding women (p.1922·1).

Mama's Best Abbott, Indon.; Abbott, Philipp.
Preparation for enteral nutrition (p.1922·1).
Nutritional supplement in pregnancy and breast feeding.

Mama-Whiz Sydenham, Philipp.
Multivitamin and mineral preparation (p.1922·1).

Mamellin Fresenius Kabi, Austria.
Vitamin F (p.2308·2); peru balsam (p.2365·3); alpha tocoferil acetate (p.1992·3).
Skin damage.

Mamex LF Dumex, Singapore.
Infant feed (p.1922·1).
Lactose intolerance.

Mammol Abbott, USA.
Bismuth subnitrate (p.1711·2); castor oil (p.2278·1); peru balsam (p.2365·3).
Nipple care.

Mamofen Khandelwal, India.
⊗ Tamoxifen (p.775·1).
Breast cancer.

Mamograf Temis, Arg.
Activated charcoal (p.1435·2).
Adjunct in breast examination.

Mamomit Pliva, Rus.
⊗ Aminoglutethimide (p.679·1).

Man Formula Avon, Canad.†.
Multivitamin and mineral preparation (p.1922·1).

Manace Duopharma, Malaysia.
Haloperidol (p.1000·2).
Alcoholism; mania; nausea and vomiting; neuroleptanalgesia; psychoses; Tourette syndrome.

Manacon Mavi, Mex.
Diclofenac (p.44·2).
Inflammation; pain.

Manaderm Wyeth, India.
Psoralen (p.1606·1).
Leukoderma; psoriasis; vitiligo.

Mancef Lafare, Ital.
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Mandafen Pharmachem, UK.
Ibuprofen (p.64·2).
Cold and influenza symptoms; fever; pain.

Mandalyn Expectorant Pharmachem, UK.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs and cold symptoms.

Mandalyn Paediatric Pharmachem, UK.
Diphenhydramine hydrochloride (p.577·2).
Coughs and cold symptoms.

Mandanol Pharmachem, UK.
Paracetamol (p.108·1).
Fever; pain.

Mandarine Boiron, Canad.†.
Homoeopathic preparation.

Mandelamine Erfa, Canad.; Aspen, S.Afr.†; Warner Chilcott, USA; Pfizer, Venez.
Methenamine mandelate (p.298·3).
Bacterial infections of the urinary tract.

ManDelay Majestic, Canad.
Benzocaine (p.1854·1).
Premature ejaculation.

Mandelip Dermoteca, Port.†.
Mandelic acid (p.296·3) with sunscreens.
Chapped lips.

Mandelo-katt Kattwiga, Ger.†.
Homoeopathic preparation.

Mandofen Juta, Ger.; Q-Pharm, Ger.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Mandokef Astro, Austria; Lilly, Gr.; Lilly, Hung.†; Lilly, Ital.†; Lilly, Port.†; Aspen, S.Afr.; Lilly, Switz.
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mandol Lilly, Austral.; EuroCept, Belg.; Lilly, Cz.†; Lilly, Hong Kong†; Lilly, NZ; EuroCept, Neth.; Lilly, Rus.; Lilly, Thai.†.
Cefamandole nafate (p.220·3).
Bacterial infections.

Mandolgin Sandoz, Denm.
Tramadol hydrochloride (p.130·3).
Pain.

Mandolsan San Carlo, Ital.†.
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mandragora comp Weleda, Ger.
Homoeopathic preparation.

Mandragora Med Complex Dynamit, Austria.
Homoeopathic preparation.

Manerix Roche, Canad.; Roche, Irl.; Roche, Spain; Roche, UK.
Moclobemide (p.411·1).
Depression.

Manevac Galen, UK.
Ispaghula (p.1737·1); senna fruit (p.1769·2).
A similar product was formerly marketed in the *UK* under the name Agiolax.
Bowel evacuation; constipation.

Mangaplexe Lehning, Fr.†.
Manganese gluconate (p.1956·2).
Hypersensitivity.

Manhae Nutrisante, Fr.
Nutritional supplement (p.1922·1).
Menopausal disorders.

Manibee-C Aventis, Mex.†.
Vitamin B substances; vitamin C (p.1922·1).

Manic Medifive, Thai.
Mefenamic acid (p.80·1).
Pain.

Manidon Abbott, Spain; Abbott, Venez.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Maninil Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Berlin-Chemie, Rus.
Glibenclamide (p.440·1).
Diabetes mellitus.

Maniprex Wolfs, Belg.
Lithium carbonate (p.401·3).
Bipolar disorder; depression.

Maniton Kyorin, Thai.†.
⊗ Mannitol (p.1330·2).
Anuria; oliguria; raised intracranial pressure.

Manivasc Farmalab, Braz.
Manidipine hydrochloride (p.1330·2).
Hypertension.

Manmox T Man, Thai.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mann SMB, Belg.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Mannex Bioceuticals, UK.
Multivitamin and mineral preparation (p.1922·1).

Mannisol Human, Cz.; Teva, Hung.
⊗ Mannitol (p.1330·2).
Cranial and ocular hypertension; forced diuresis; oedema; oliguria; renal failure.

Mannistol Bieffe, Ital.†.
⊗ Mannitol (p.1330·2).
Cranial and ocular hypertension.

Mannite Saprochi, Switz.
⊗ Mannitol (p.1330·2).
Constipation.

Mannit-Losung Serag-Wiessner, Ger.
⊗ Mannitol (p.1330·2).
Forced diuresis; oedema; renal failure.

Mano
Note. This name is used for preparations of different composition.
March, Thai.
⊗ Tetryzoline hydrochloride (p.1574·1); boric acid (p.2268·1); sodium chloride (p.1686·1).
Allergic eye disorders.

Milano, Thai.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; heartburn; oesophagitis; peptic ulcer.

Manoane March, Thai.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Oral contraceptive in women with androgenic symptoms.

Mano-Ap-Es Lam Thong, Thai.
⊗ Reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Manobaxine March, Thai.
Methocarbamol (p.1897·3).
Peri-articular disorders; skeletal muscle spasm.

Manobrozil March, Thai.
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Mano-Bruzone *March, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; pain; rheumatoid arthritis.

Manocidal *March, Thai.*
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Manodepo *March, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; menstrual disorders; pregnancy test; threatened or recurrent miscarriage.

Manodextro *March, Thai.*
Dextromethorphan (p.1555·2).
Coughs.

Manodiol *March, Thai.*
Ethinylestradiol (p.2101·3).
Menstrual disorders.

Manoeidai *March, Thai.*
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Manoflox *March, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Manoglucon *March, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Manoketo *March, Thai.*
Ketoconazole (p.539·1).
Scalp disorders.

Manol *Sanitas, Chile.*
Tramadol hydrochloride (p.130·3).
Pain.

Manolio *Brasmedica, Braz.†.*
Hamamelis (p.2318·2); yeast (p.1998·3); rutoside (p.2305·1); phenolphthalein (p.1762·1).

Manolone *Lam Thong, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Manomazole *March, Thai.*
Clotrimazole (p.530·1).
Fungal and trichomonal vaginitis.

Manomet *March, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Manomic *March, Thai.*
Mefenamic acid (p.80·1).
Pain.

Manorfen *Manor, UK.*
Ibuprofen (p.64·2).

Manorifcin *March, Thai.*
Rifampicin (p.325·3).
Gonorrhoea; tuberculosis.

Manoron *March, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Manotran *March, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Mano-Trim *Lam Thong, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Manoverm *March, Thai.*
Albendazole (p.139·2).
Worm infections.

Manovon *March, Thai.*
Bromhexine hydrochloride (p.1552·2).
Obstructive airways disease.

Manoxicam *Lam Thong, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Manoxidil *March, Thai.*
Minoxidil (p.1342·1).
Heart failure; hypertension.

Manozide *March, Thai.*
Niclosamide (p.151·1).
Cestode infections.

Mansal *Vita, Spain†.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; short-bowel syndrome; Zollinger-Ellison syndrome.

Mansil *Pfizer, Braz.*
Oxamniquine (p.151·3).
Schistosomiasis.

Mantadan *Boehringer Ingelheim, Ital.*
Amantadine hydrochloride (p.792·3).
Influenza A; mental function impairment; parkinsonism.

Mantadix *BMS, Fr.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Mantai *Pentafarma, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Manti *US Pharmacia, Pol.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastric hyperacidity; hiatus hernia; peptic ulcer.

Manti Gastop *US Pharmacia, Pol.*
Simeticone (p.1770·2).
Excess gastrointestinal gas; gastrointestinal procedures.

Mantidan *Eurofarma, Braz.*
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; fatigue associated with multiple sclerosis; influenza A; parkinsonism.

Mantus *Sandoz, Arg.*
⊗ A heparinoid (p.1305·2); triamcinolone acetonide (p.1544·3); hexetidine (p.1647·1); lidocaine (p.1862·3).
Haemorrhoids.

Manugel *Anios, Fr.*
Isopropyl alcohol (p.1650·3); phenoxyethanol (p.1657·1).
Skin disinfection.

Manuprin *Yeni, Turk.*
Methenamine mandelate (p.298·3).
Urinary-tract infections.

Manusept
Note. This name is used for preparations of different composition.
Beiersdorf, Switz.†.
Orthophenylphenol (p.1655·1).
Hand disinfection.

Medlock Medical, UK.
Triclosan (p.1665·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Manusept HD *Bode, Ger.†.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Manyper *Asche Chiesi, Ger.; Chiesi, Gr.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Manzan *Gezzi, Arg.*
Camphor (p.2273·2); phenol (p.1656·1); thymol (p.1664·3); hamamelis (p.2318·2); eucalyptus oil (p.2301·2).
Haemorrhoids.

Manzan Plus *Gezzi, Arg.*
Zinc oxide (p.1621·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Maolate *Upjohn, USA†.*
Chlorphenesin carbamate (p.1894·3).
Musculoskeletal pain.

Maoni *Lichtwer, Ger.†.*
Kava (p.2328·3).
Nervous disorders.

Maorex *Torrex Chiesi, Hung.*
Moclobemide (p.411·1).
Depression; social phobia.

Maosig *Sigma, Austral.*
Moclobemide (p.411·1).
Depression.

MAOtil *Acis, Ger.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Maox *Manne, USA.*
Magnesium oxide (p.1744·1).
Hyperacidity.

Map An *Pfizer, Arg.*
Medroxyprogesterone acetate (p.2113·1).
Malignant neoplasms.

Mapap *Major, USA.*
Paracetamol (p.108·1).
Fever; pain.

Mapap Cold Formula *Major, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Mapap Sinus Congestion & Pain *Major, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Mapelor *Boehringer Ingelheim, Neth.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Mapezine *Siam Bheasach, Thai.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Mapin *Duopharma, Hong Kong; Duopharma, Malaysia.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Maple Melts *Green Turtle Bay Vitamin Co., USA.*
Vitamin and mineral preparation (p.1922·1).
Tonic.

Mapleflex *Scientific Hospital Supplies, Irl.; SHS, UK.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

Mapluxin *Novartis, Mex.*
Digoxin (p.1259·3).
Heart failure; paroxysmal supraventricular tachycardia.

Mapox *Stada, Ger.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Maprilex *Liferpal, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Maprolu *Hexal, Ger.; Hexal, Hung.†.*
Maprotiline hydrochloride (p.407·2).
Depression.

Mapromil *Farmo Quimica, Chile.*
Maprotiline hydrochloride (p.407·2).
Depression.

Maprotibene *Ratiopharm, Cz.*
Maprotiline hydrochloride (p.407·2).
Anxiety disorders; depression.

Maprotil *Terra, Turk.*
Maprotiline hydrochloride (p.407·2).
Depression.

Mapryl
Note. This name is used for preparations of different composition.
Ikapharmindo, Indon.
Glimepiride (p.441·1).
Diabetes mellitus.

Polfa Warszawa, Pol.
Enalapril maleate (p.1276·1).
Diabetic nephropathy; heart failure; hypertension.

Mapurit *Sanum-Kehlbeck, Ger.*
dl-Alpha tocoferil acetate (p.1992·3); magnesium oxide (p.1744·1).
Magnesium or vitamin E deficiency.

Maqui-Libre *Lancome, Canad.†.*
SPF 15: Octinoxate (p.1608·2).
Sunscreen.

Mar *Masa, Thai.†.*
Dried aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; peptic ulcer.

Mar Plus
Stada, Ger.†.
Dexpanthenol (p.2362·1); sodium chloride (p.1686·1).
Nasal congestion.

Stada, Hong Kong; Stada, Malaysia; Stada, Thai.
Dexpanthenol (p.2362·1); sea water.
Nasal congestion; nasal hygiene; rhinitis.

Mar Rhino *Stada, Cz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

Maradex *Oftalmi, Venez.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Marament-N *Amino, Switz.*
Camphor (p.2273·2); methyl salicylate (p.85·3); benzyl nicotinate (p.28·1); pine silvestris oil (p.2368·2).
Musculoskeletal, joint, and soft-tissue disorders.

Maranon H *Henkel, Ger.†.*
Sodium hypochlorite (p.1661·1).
Instrument disinfection.

Maranox *Dent, USA.*
Paracetamol (p.108·1).
Fever; pain.

Maraslavin *Sopharma, Rus.*
Absinthium (p.2244·1); clove flowers (p.2284·3); black pepper (p.2364·3); ginger (p.1732·3); thyme (p.2401·1).
Periodontitis.

Marathon *Ivax, Arg.; Laboratorios Chile, Chile.*
Ubidecarenone; ginseng; vitamins; minerals; trace elements (p.1922·1).
Dietary supplement; tonic.

Marathon Antioxidante *Ivax, Arg.*
Ubidecarenone; vitamin E; betacarotene; selenium (p.1922·1).
Antoxidant preparation.

Marax
Note. This name is used for preparations of different composition.
Pfizer, Braz.; Pfizer, USA; Pfizer, Venez.†.
⊗ Hydroxyzine hydrochloride (p.581·2); ephedrine sulfate (p.1558·2); theophylline (p.1140·1).
Bronchospasm; obstructive airways disease.

Asche, Cz.†; Asche, Ger.
Magaldrate (p.1742·3).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Marching, Hong Kong.
Crotamiton (p.1593·2).
Pediculosis; pruritus; scabies.

Unimed, India.
⊗ Hydroxyzine hydrochloride (p.581·2); ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1).
Asthma; bronchospasm.

Marblen *Fleming, USA.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Hyperacidity.

Marbroxol *Marching, Hong Kong.*
Ambroxol hydrochloride (p.1550·3).
Cough.

Marbrozil *Marching, Hong Kong.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease in men.

Marcain *AstraZeneca, Austral.; Dentsply, Austral.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; Sarabhai Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, NZ; AstraZeneca, Norw.; AstraZeneca, Rus.; AstraZeneca, Singapore; AstraZeneca, Swed.; AstraZeneca, Thai.; AstraZeneca, UK.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

Marcain with Fentanyl *AstraZeneca, Austral.; AstraZeneca, NZ.*
⊗ Bupivacaine hydrochloride (p.1854·3); fentanyl citrate (p.55·3).
Epidural analgesia.

Marcain with Pethidine *AstraZeneca, Austral.†.*
⊗ Bupivacaine hydrochloride (p.1854·3); pethidine hydrochloride (p.113·2).
Epidural analgesia.

Marcaina *AstraZeneca, Braz.; AstraZeneca, Ital.; Astra, Port.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Marcaine *AstraZeneca, Belg.; Hospira, Canad.; AstraZeneca, Cz.; AstraZeneca, Fr.†; IFET (ΙΦΕΤ), Gr.; AstraZeneca, Israel; AstraZeneca, Neth.; AstraZeneca, Pol.; AstraZeneca, Turk.; Hospira, USA.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Analgesia; local anaesthesia; pain.

Marcelle Moisture Eye Cream *Marcelle, Canad.*
SPF 15: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Marcelle Multi-Defense *Marcelle, Canad.*
SPF 15: Meradimate (p.1604·2); octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Marcelle Protective Block
Note. This name is used for preparations of different composition.
Prof. Pharm. Corp., Canad.†.
SPF 15: Titanium dioxide (p.1617·3).
Sunscreen.

Prof. Pharm. Corp., Canad.†.
SPF 25: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Marcelle Sheer Tint *Marcelle, Canad.*
SPF 15: Octinoxate (p.1608·2).
Sunscreen.

Marcelle Sunblock
Note. This name is used for preparations of different composition.
Prof. Pharm. Corp., Canad.†.
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Prof. Pharm. Corp., Canad.†.
SPF 15; SPF 20: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Marcelle True Radiance *Marcelle, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Marcen *Pharmacia, Spain.*
Ketazolam (p.1002·2).
Anxiety; insomnia; skeletal muscle spasm.

Marcholax *Marching, Hong Kong.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Marclazide *Marching, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Marclorhex *Cristalia, Braz.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Marco Sweet Light *Laboratorios Chile, Chile.*
Aspartame (p.1930·1); acesulfame potassium (p.1928·1).
Sugar substitute.

Marco Sweett *Laboratorios Chile, Chile†.*
Aspartame (p.1930·1).
Sugar substitute.

Marcocid *Willvonseder, Austria.*
Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Marcodine *Cristalia, Braz.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Marcof *Marnel, USA.*
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Marcoumar *Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Denm.; Roche, Neth.; Roche, Switz.*
Phenprocoumon (p.1370·2).
Thromboembolic disorders.

Marcumar *Roche, Ger.*
Phenprocoumon (p.1370·2).
Thromboembolic disorders.

marcuphen *CT, Ger.*
Phenprocoumon (p.1370·2).
Thromboembolic disorders.

Marduk *S & K, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Mareamin *Volta, Chile.*
Dimenhydrinate (p.576·2).
Motion sickness.

Mareen *Krewel, Ger.*
Doxepin hydrochloride (p.389·1).
Anxiety disorders; depression; sleep disorders; withdrawal syndromes.

Marenin *Berman, Mex.*
Meclozine (p.585·1).
Vertigo.

Marespin *Abiogen, Ital.†.*
Sulfamazone sodium (p.339·2).
Respiratory-tract infections.

Marevan *Sigma, Austral.; Therabel, Belg.; Farmoquimica, Braz.; Nycomed, Denm.; Orion, Fin.; IFET (ΙΦΕΤ), Gr.; GSK, NZ; Nycomed, Norw.; GSK, Singapore; Goldshield, UK.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Marezine *Himmel, USA.*
Cyclizine hydrochloride (p.574·2).
Motion sickness.

Marfarin *Generics, Hung.*
Warfarin sodium clathrate (p.1425·3).
Thromboembolic disorders.

Marfloxacin *Marching, Hong Kong.*
Ofloxacin (p.310·2).
Bacterial infections.

Marflu-X *Marching, Hong Kong.*
Paracetamol (p.108·1); pentoxyverine citrate (p.1567·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3); guaifenesin (p.1561·3).
Cold symptoms.

Margel *Millimed, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; peptic ulcer.

Margesic *Marnel, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Margesic H *Marnel, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Marglucon *Marching, Hong Kong.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Marianon *Klein, Ger.†.*
Milk thistle (p.1452·1); greater celandine (p.2317·1); achillea (p.2245·2); absinthium (p.2244·1); St John's wort (p.422·3).
Biliary disorders.

Mariazeller *Apotheke Gnadenmutter, Austria.*
Cinnamon (p.2283·1); cinchona bark (p.2282·3); dried bitter-orange peel (p.2357·1); clove (p.2284·3); flos aurantii (p.2357·2); chamomile (p.2279·3); folium aurantium; melissa (p.2339·3); menyanthes (p.2340·3); cardamom fruit (p.2277·1); fructus aurantii immat; coriander (p.2288·1); absinthium (p.2244·1); cnicus benedictus (p.2285·2); centaury (p.2279·1); achillea moschata; achillea (p.2245·2); guaiacum wood; juniper (p.2328·2); galanga; gentian (p.2310·3); ginger (p.1732·3); nutmeg (p.2355·2).
Gastrointestinal disorders.

Maridin *Pliva, Cz.*
Rimantadine hydrochloride (p.904·2).
Influenza A infection.

Marienbader Pillen N *Cheplapharm, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Mariendistel Curarina *Harras-Curarina, Ger.*
Homoeopathic preparation.

Maril *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in duodenal intubation; adjunct in gastrointestinal radiography; gastrointestinal motility disorders; nausea and vomiting.

Marimer *Gilbert, Fr.*
Sea water.
Nasal hygiene.

Marina
Note. This name is used for preparations of different composition.
T Man, Thai.
Silymarin (p.1452·2).
Liver disorders.

Biofarma, Venez.
Omega-3 marine triglycerides (p.1362·2).
Hypercholesterolaemia; rheumatoid arthritis.

Marincap *Kocak, Turk.*
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias; ischaemic heart disease.

Marine *Hexal, Arg.†.*
Dimenhydrinate (p.576·2).
Motion sickness.

Marine Lipid Concentrate *Vitaline, USA.*
Omega-3 marine triglycerides with vitamin E (p.1362·2).
Dietary supplement.

MarinEx *Beacons, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Marinol
Note. This name is used for preparations of different composition.
Solvay, Canad.; Solvay, USA.
⊗ Dronabinol (p.1728·1).
AIDS related anorexia; appetite stimulant; nausea and vomiting associated with cancer chemotherapy.

Pharmadeveloppement, Fr.
Bladderwrack (p.2384·2); laminaria (p.2330·2); calcium carbonate (p.1714·1); phosphoric acid (p.2367·1); sea water.
Tonic.

Marching, Hong Kong.
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Mariomigran *Phytofarm Kleka, Pol.*
Chrysanthemum parthenium.
Migraine.

Maripen *Teva, Hung.*
Penamecillin.
Bacterial infections.

Mariston *Codal Synto, Malaysia†; Codal Synto, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Maritidine *Marching, Hong Kong.*
Cimetidine (p.1716·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Marizine *Marching, Hong Kong.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Markalakt *Pascoe, Ger.†.*
Chamomile (p.2279·3).
Allergic disorders; gastrointestinal disorders; skin disorders.

Marlex *Neves, Port.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Marlin Salt System *Marlin, USA.*
Sodium chloride (p.1686·1)(p.1622·2).
Rinsing and storage solution for soft contact lenses.

Mar-Loper *Marching, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Marlora *Marching, Hong Kong.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Marlyn Formula 50 *Marlyn, USA.*
Amino acids; pyridoxine hydrochloride (p.1978·2).
Nail disorders; postnatal hair-loss.

Marmodine *Marching, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Marnatal-F *Marnel, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Marolderm *Dermapharm, Ger.*
Dexpanthenol (p.2362·1).
Skin disorders.

Maronil *Unipharm, Israel.*
Clomipramine hydrochloride (p.386·3).
Depression; obsessive-compulsive disorder.

Marovil *Medipharm, Chile†.*
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal pseudo-obstruction; gastroparesis.

Marovilina *Atlantis, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Marphazole *Marching, Hong Kong.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Marplan *Royal, Chile†; Medilink, Denm.; Validus, USA.*
Isocarboxazid (p.401·2).
Depression.

Marpram *Marvecs, Ital.*
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Marpres *Marnel, USA.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Marsedyl
Note. This name is used for preparations of different composition.
Marching, Hong Kong.
Syrup: ⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); promethazine hydrochloride (p.588·2).
Cough; upper respiratory-tract congestion.

Marching, Hong Kong.
Tablets: ⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); promethazine hydrochloride (p.588·2).
Cough; upper respiratory-tract congestion.

Marsilid *Laphal, Fr.†.*
Iproniazid phosphate (p.401·2).
Depression.

Marsonil *Makros, Braz.†.*
⊗ Ephedrine hydrochloride (p.1558·2); homatropine methylbromide (p.1881·3).
Obstructive airways disease.

Mar-Spas *Marnel, USA.*
Hyoscyamine sulfate (p.1736·1).

Marsthine *Towa, Philipp.*
Clemastine fumarate (p.573·2).
Allergic disorders.

Martenol *Marching, Hong Kong.*
⊗ Atenolol (p.1217·3).
Alcohol withdrawal; angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Marten-Tab *Marnel, USA.*
Butalbital (p.967·2); paracetamol (p.108·1).
Tension headache.

Martham *Vamsler, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Marthritic *Marnel, USA.*
Salsalate (p.122·1).

Martigene *Novartis, Fr.†.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Allergic conjunctivitis.

Martindale Methadone Mixture DTF *Martindale Pharmaceuticals, UK.*
⊗ Methadone hydrochloride (p.82·3).
It contains hydroxybenzoate esters as preservatives. . There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Opioid withdrawal.

Martispasmol *Martin & Harris, India†.*
Cyclandelate (p.1254·1).
Peripheral vascular disorders.

Martomide *Marching, Hong Kong.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal procedures; gastrointestinal motility disorders; nausea and vomiting.

Martos *Otsuka, Indon.; Otsuka, Jpn.*
Maltose (p.1956·1).
Carbohydrate source; diabetes mellitus.

Martulose *Marching, Hong Kong.*
Lactulose (p.1738·2).
Constipation; hepatic coma; hepatic encephalopathy.

Marulide *Pasteur, Philipp.*
Roxithromycin (p.331·1).
Bacterial infections.

Mar-V *Dupomar, Arg.*
Electrolytes (p.1667·1).
Respiratory-tract congestion.

Marvelon *Organon, Arg.; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Canad.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Donmed, S.Afr.; Organon, Singapore; Organon, Switz.; Organon, Thai.; Organon, UK; Organon, Venez.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Androgen-associated skin disorders in women; combined oral contraceptive.

Marvil *Elisium, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Marviol *Organon, Irl.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Marvir *Lam Thong, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Marzine *Pfizer, Denm.; Pfizer, Fin.; GSK, Hong Kong†; Pfizer, NZ; Pfizer, Norw.; GSK, Singapore†; GSK, Swed.†; Pfizer Consumer, Switz.*
Cyclizine hydrochloride (p.574·2).
Ménière's disease; motion sickness; nausea; vertigo; vestibular disorders; vomiting.

Marzolam *March, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Masa 3B *Masa, Thai.†.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Masabalm *Masa, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal and joint pain.

Masafen *Masa, Thai.*
Mefenamic acid (p.80·1).
Pain.

Masaga *Nakornpatana, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); clove oil (p.2285·1).
Musculoskeletal pain; neuralgia; sciatica.

Masagil
Note. This name is used for preparations of different composition.
Perez Gimenez, Spain.
Liniment: Camphor (p.2273·2); ammonia (p.2256·1); methyl salicylate (p.85·3); rosemary oil (p.2381·3); turpentine oil (p.2406·3).
Rheumatic and muscle pain.

Perez Gimenez, Spain.
Topical Spray: Camphor (p.2273·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3); menthol (p.2340·1).
Rheumatic and muscle pain.

Masapara w/ Codeine *Masa, Thai.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Masarax *Masa, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions; sedative.

Masaren *Masa, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Masarol *Masa, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Masaworm *Masa, Thai.†.*
Albendazole (p.139·2).
Worm infections.

Masaworm-1 *Masa, Thai.*
Mebendazole (p.148·3).
Worm infections.

Masc na Odciski
Note. This name is used for preparations of different composition.
Aflofarm, Pol.; Hasco-Lek, Pol.
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Corns.

Gemi, Pol.
Melilotus emplastrum; salicylic acid (p.1612·2).
Corns.

Masc Ochronna z Witamina A *Hasco-Lek, Pol.*
Vitamin A palmitate (p.1973·1).
Skin disorders.

Masc przeciw Odciskom i Zgrubieniom Skory *Farmal, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns.

Masc Tranowa *Farmina, Pol.*
Cod-liver oil (p.1935·2).
Skin disorders.

Masc Witaminowa Ochronna *Homeofarm, Pol.*
Vitamin A (p.1971·2).
Skin disorders.

Masculine Herbal Complex *GNLD, Austral.*
Saw palmetto; avena; celery; damiana; achillea; St John's wort; skullcap; astragalus; chillies.
Tonic.

Masdil *Esteve, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Masern-Impfstoff Merieux *Sanofi Pasteur, Ger.*
A live measles vaccine (attenuated Schwarz strain) (p.2221·3).
Active immunisation.

Masferol *Quimica y Farmacia, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Masflex *Abbott, Mex.†.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Masivol *Valeant, Arg.*
Vitamin A (p.1971·2).
Skin disorders.

Masivol Urea *Valeant, Arg.*
⊗ Hydrocortisone acetate (p.1535·2); vitamin A palmitate (p.1973·1); urea (p.1620·2).
Skin disorders.

Massage Balm with Calendula *Weleda, UK.*
Calendula (p.2273·1); betula alba (p.2266·3); lavender oil (p.2331·2).
Muscle tension.

Massageol *Neo Quimica, Braz.*
Camphor (p.2273·2); turpentine oil (p.2406·3); menthol (p.2340·1); methyl salicylate (p.85·3).
Formerly contained camphor, turpentine oil, menthol, methyl salicylate, and chlorophyll.
Musculoskeletal and joint disorders.

Massagim *Vitoria, Port.*
Diethylamine salicylate (p.47·2).

Masse
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.; Janssen-Cilag, Chile†; Janssen-Cilag, S.Afr.; Advanced Care, USA.
Emollient.
Dry skin; nipple care.

Ethnor, India.
Allantoin (p.1588·1).
Nipple disorders.

Massengill *SmithKline Beecham Consumer, USA.*
Ammonium alum (p.2254·1); phenol (p.1656·1); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); sodium chloride (p.1686·1).
Vaginal disorders.

Massengill Disposable *SmithKline Beecham Consumer, USA.*
Vinegar (p.2244·2).
Vaginal disorders.

Massengill Feminine Cleansing Wash *SmithKline Beecham Consumer, USA.*
Vaginal cleanser.

Massengill Medicated
Note. This name is used for preparations of different composition.
SmithKline Beecham, Israel†.
Povidone-iodine (p.1659·2).
Vaginal irritation.

SmithKline Beecham Consumer, USA.
Soft cloth towelette: ⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

SmithKline Beecham Consumer, USA.
Vaginal douche: Povidone-iodine (p.1659·2).
Vaginal disorders.

Massidron *PharmaConsult, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Massorax *RTA, Switz.†.*
Methyl salicylate (p.85·3); isopropyl nicotinate; capsicum (p.2276·2); camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); lavender oil (p.2331·2).
Musculoskeletal, joint, and soft-tissue disorders.

Mastaflu *Solvay, UK.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Master-Aid *Pietrasanta, Ital.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin, burns, and wounds.

Masterelax *Master, Chile†.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Master-Gel *Master, Chile†.*
Etofenamate (p.53·1).
Inflammation.

Mastical *Altana, Spain.*
Calcium carbonate (p.1714·1).
Hypocalcaemia; osteoporosis.

Mastical D *Altana, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Masticalcio *Garden House, Arg.†.*
Calcium; vitamin D (p.1922·1).
Dietary supplement.

Mastika *Goldshield, UK.*
Mastic gum (p.2338·1).
Peptic ulcer.

Mastiol *Reig Jofre, Spain.*
Chlorhexidine acetate (p.1635·2); benzocaine (p.1854·1); vitamin A (p.1971·2).
Mastitis.

Mastodanatrol *Sanofi Synthelabo, Port.†.*
⊗ Danazol (p.2090·2).
Benign breast disorders.

Mastodynon *Bionorica, Cz.; Bionorica, Ger.; Bionorica, Rus.; Bionorica, Thai.*
Homoeopathic preparation.

Mastofen *Pentafarma, Port.*
⊗ Tamoxifen citrate (p.772·3).

Mastroson *Darya-Varia, Indon.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2).
Skin disorders with bacterial infection.

Mastu S *Stada, Cz.; Stada, Ger.; Stada, Hong Kong; Stada, Hung.; Stada, Thai.*
Bufexamac (p.28·3); bismuth subgallate (p.1711·1); titanium dioxide (p.1617·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders; haemorrhoids.

Masvitalin Ginseng *Higate, Arg.*
Ginseng; magnesium glycerophosphate; vitamins (p.1922·1).
Tonic.

Maswin *Masa, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Mata Pieporna *Slovakofarma, Cz.†.*
Peppermint leaf (p.1761·2).
Gastrointestinal spasm.

Matai *Engelhard, Ger.†.*
Devil's claw root (p.39·1).
Degenerative joint disorders.

Matase *Nufarindo, Indon.*
Myrtillus (p.2349·3); betacarotene (p.1930·3); ascorbic acid (p.1983·3); vitamin B (p.1977·2).
Dietary supplement.

Matcine *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorpromazine hydrochloride (p.969·2).
Affective disorders; controlled hypotension; induction of hypothermia; nausea and vomiting; premedication; psychoses; schizophrenia; sedative.

Matenol *Unison, Thai.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris.

Mater Test *Biosintex, Arg.*
Pregnancy test (p.2372·1).

Materfol *Biofarma, Mex.*
Folic acid (p.1940·1).
Prevention of neonatal lip and palate defects; prevention of neural tube defects.

Materfolic *Farmoquimica, Braz.*
Folic acid (p.1940·1).

Matergam *CSL, Braz.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Matergam-P *Zydus, India.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Materlac *Andromaco, Chile†.*
⊗ Ritodrine hydrochloride (p.2017·2).
Fetal distress; premature labour; threatened abortion.

Materna *Wyeth, Braz.; Wyeth Consumer, Canad.; Wyeth, Chile†; Lederle, Cz.†; Wyeth, Hong Kong; Wyeth, Hung.†; Wyeth-Ayerst, Israel; Wyeth, Mex.; Wyeth, Turk.; Wyeth, Venez.*
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement.

Materna Nova *Lederle, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Materna Tsimchit *Maabarot, Israel.*
Infant feed (p.1922·1).
Milk intolerance.

MaternAid *Gerber, Mex.†.*
Preparation for enteral nutrition (p.1922·1).
Pregnancy and lactation.

Maternavit *Medifarm, Venez.*
Vitamins; minerals; omega-3 marine triglycerides; soya oil (p.1922·1).
Dietary supplement.

Maternity One *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Matersupre *Teuto, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Matervit *Farmoquimica, Braz.; RPF, Ital.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy.

Matico Compuesto *Knop, Chile.*
Homoeopathic preparation.

Matidan *Mintlab, Chile.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Matigel *Oftalmi, Venez.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Matikomp *Knop, Chile.*
Matico; calendula (p.2273·1); arnica (p.2260·2).
Soft-tissue injury; ulcers; wounds.

Matilol *Oftalmi, Venez.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Matinor *Farmo Quimica, Chile.*
Phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1); carbinoxamine maleate (p.570·2).
Cold and influenza symptoms; otitis media; rhinitis; sinusitis.

Matmille
Note.This name is used for preparations of different composition.
Ritsert, Ger.†.
Bath additive: Chamomile (p.2279·3); chamomile oil (p.2279·3).
Skin and mucous-membrane disorders.

Ritsert, Ger.
Oral liquid: Chamomile (p.2279·3).
Gastrointestinal disorders.

Matmille N *Ritsert, Ger.*
Chamomile (p.2279·3); chamomile oil (p.2279·3).
Gingivitis; skin and mucous membrane disorders.

Mato *Hevert, Ger.*
Homoeopathic preparation.

Matovit *Soho, Indon.*
Betacarotene (p.1930·3); myrtillus (p.2349·3); vitamin A; vitamin E.
Eye disorders.

Matovit Fifty *Soho, Indon.*
Myrtillus (p.2349·3); lutein (p.1954·3); zeaxanthin (p.1999·1); vitamin E.
Eye disorders.

Matovy *Megafyt-R, Cz.*
Peppermint leaf (p.1761·2).
Digestive-system disorders.

Matricaria C/Vit AED2 Composta *Arrow, Braz.†.*
Vitamin A; ergocalciferol; matricaria; calcium lactate; tribasic calcium phosphate (p.1922·1).

Matricur *Sandoz, Ger.*
Lyophilised collagen (p.2286·1).
Obesity.

Matrifen *Nycomed, Cz.; Nycomed, Gr.; Nycomed, Hung.; Nycomed, Swed.; Nycomed, UK.*
⊗ Fentanyl (p.55·3).
Pain.

Matrifolin *Orion, Fin.*
Ferrous fumarate (p.1938·3); vitamin B substances; alfa tocoferil acetate (p.1922·1).
Iron-deficiency anaemia; vitamin supplement.

Matrix
Note.This name is used for preparations of different composition.
TRB, Arg.
Ibuprofen (p.64·2).
Formerly contained diacerein.
Fever; musculoskeletal and joint disorders; pain.

Wyeth Lederle, Ital.
A heparinoid (p.1305·2).
Osteoarthritis.

Matrovir *Konimex, Indon.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin.

Matsunaflam *Nufarindo, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Matulane *Sigma-Tau, Canad.; Roche, USA.*
Procarbazine hydrochloride (p.765·2).
Malignant neoplasms.

Maturity Test *Blausiegel, Braz.*
Test for the menopause.

Mavena Anal-Gen *Psorimed, Switz.*
Hamamelis (p.2318·2).
Anorectal disorders.

Mavena C-Tron Calcium *Psorimed, Switz.*
Vitamin C; colecalciferol; calcium phosphate (p.1922·1).
Cold symptoms; tonic.

Mavena Proctal-Gen *Psorimed, Switz.*
Hamamelis (p.2318·2); diethylamine salicylate (p.47·2).
Formerly known as Proctalgen.
Anorectal disorders.

Maveral *Schering, Ital.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Maverex *Veropharm, Rus.*
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small-cell lung cancer.

Mavicam *Mavi, Mex.*
Meloxicam (p.80·3).
Inflammation; pain.

Mavid *Abbott, Ger.*
Clarithromycin (p.248·2).
Mycobacterial infections.

Mavidol *Mavi, Mex.*
Ketorolac (p.75·2).
Inflammation; pain.

Maviflox *Mavi, Mex.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Mavigen Sebo *Mavi, Ital.*
Cystine (p.1937·1).
Seborrhoea.

Maviglin *Mavi, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Mavik *Abbott, Canad.; Abbott, S.Afr.; Abbott, USA.*
Trandolapril (p.1416·2).
Heart failure following myocardial infarction; hypertension; myocardial infarction.

Mavilan *Mavi, Mex.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Mavipiu *Mavi, Ital.†.*
Calamine (p.1591·2); zinc oxide (p.1621·2); oryzanol (p.2358·3).
Barrier preparation; nappy rash.

Mavisid *Mavi, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Mavitalon *Help, Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Mavitina *Mavi, Mex.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Mavixan *Pharmaten (Φαρματεν), Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Max
Note.This name is used for preparations of different composition.
Unison, Hong Kong; Unison, Singapore; Unison, Thai.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Valmor, Venez.
Ibuprofen (p.64·2).
Fever; pain.

Max Uric *Labinca, Arg.†.*
Benzbromarone (p.555·2).
Hyperuricaemia.

Maxadol *Restan, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Maxair *3M, Fr.; 3M, Switz.†; Graceway, USA.*
⊗ Pirbuterol acetate (p.1130·1).
Obstructive airways disease.

Maxalt *MSD, Arg.†; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.†; MSD, Denm.; MSD, Fin.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hung.†; MSD, Ital.; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, UK; Merck, USA; MSD, Venez.*
Rizatriptan benzoate (p.625·1).
Migraine.

Maxamaid MSUD *SHS, Fr.*
Food for special diets (p.1922·1).
Leucinosis.

Maxamaid XLEU *SHS, Fr.*
Food for special diets (p.1922·1).
Isovaleric acidaemia.

Maxamaid XLYS *SHS, Fr.*
Food for special diets (p.1922·1).
Hyperlysinaemia.

Maxamaid XLYS, Low Try *SHS, Fr.*
Food for special diets (p.1922·1).
Glutaric aciduria.

Maxamaid XMET *SHS, Fr.*
Food for special diets (p.1922·1).
Homocystinuria.

Maxamaid XMET, Cys *SHS, Fr.*
Food for special diets (p.1922·1).
Sulfite oxidase deficiency.

Maxamaid XMTVI *SHS, Fr.*
Food for special diets (p.1922·1).
Methylmalonic or propionic acidaemia.

Maxamaid XMTVIL *SHS, Fr.*
Food for special diets (p.1922·1).
Methylmalonic or propionic acidaemia.

Maxamaid XP *Nutricia, Ital.; Scientific Hospital Supplies, NZ.*
Food for special diets (p.1922·1).
Phenylketonuria.

Maxamaid XPHEN, Tyr *SHS, Fr.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Maxamaid XPTM *SHS, Fr.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Maxamox *Sandoz, Austral.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Maxamum MSUD *SHS, Fr.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, NZ.*
Food for special diets (p.1922·1).
Leucinosis; maple syrup urine disease.

Maxamum XLYS, Low Try *SHS, Fr.*
Food for special diets (p.1922·1).
Glutaric aciduria.

Maxamum XMET *SHS, Fr.*
Food for special diets (p.1922·1).
Homocystinuria.

Maxamum XMTVI *SHS, Fr.*
Food for special diets (p.1922·1).
Methylmalonic or propionic acidaemia.

Maxamum XP *Nutricia, Ital.; Scientific Hospital Supplies, NZ.*
Food for special diets (p.1922·1).
Phenylketonuria.

Maxamum XPhen, Tyr *SHS, Fr.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Maxaquin *Pfizer, Braz.; Searle, Cz.†; Pfizer, Hong Kong; ICN, Ital.; Pfizer, Mex.; Pfizer, Port.; Searle, Rus.†; Pharmacare, S.Afr.; Pfizer, Switz.; Pfizer, Thai.†; Searle, USA; Pfizer, Venez.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Maxbon *Gynea, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Maxcef *BMS, Arg.; BMS, Braz.; BMS, Israel†.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Maxcep *Danlex, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Maxcil *Triomed, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Maxdosa *Dosa, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Maxen *Baliarda, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Maxen D *Baliarda, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Maxepa
Cenovis, Austral.†; Vitelle, Austral.†; Pierre Fabre, Fr.; Novartis Consumer, Ital.; Seven Seas, UK; Solgar, USA.
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement; hyperlipidaemias.

Cana, Gr.; Merck, India; Seven Seas, Irl.; Merck, Venez.
Omega-3 fatty acids (p.1362·1).
Dietary supplement; hyperlipidaemias.

Maxepa & EPO *Vitaplex, Austral.†.*
Marine fish oil (p.1362·2); evening primrose oil (p.2302·1).
Dietary supplement.

Maxeron *Wallace, India.*
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; gastritis; gastro-oesophageal reflux; nausea and vomiting; postoperative gastric hypotonia.

Maxflin *Labesfal, Port.*
Fluconazole (p.532·1).
Fungal infections.

MaxFlu *Pliva Krakow, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Maxfluor *Labesfal, Port.*
Sodium fluoride (p.1962·2).

Maxi Force Energy Cocktail *Homeocan, Canad.†.*
Homoeopathic preparation.

Maxibell *Latinofarma, Braz.*
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Maxibiloba *Biofarma, Mex.*
Ginkgo biloba (p.2311·1); vitamin B substances; minerals (p.2314·2).
Mental function impairment; vitamin and mineral supplement.

Maxibol *Aventis, Mex.; Sanofi-Aventis, Venez.*
Cobamamide (p.1980·2).
Tonic.

Maxibone *Unipharm, Israel.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Maxibral *Demo, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Maxical *Leti, Venez.*
Calcium pidolate (p.1676·3).

Maxicalc *Ache, Braz.*
Calcium carbonate (p.1714·1).

Maxi-calc *Pharmacia, Switz.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Maxicalc-D *Ache, Braz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).

Maxicam *Hexpharm, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Maxicardil *Northia, Arg.*
Dipyridamole (p.1268·1).

Maxicef *Pharos, Indon.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Maxicilina *Reig Jofre, Spain.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Bacterial infections.

Maxicold *Farmstandart, Rus.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Maxicort *Oftalmi, Venez.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Maxicrom *Alcon, Braz.; Alcon, Mex.; Alcon, Venez.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Maxid *SoSe, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Maxidauno *Varifarma, Arg.*
Daunorubicin (p.709·3).
Malignant neoplasms.

Maxidex
Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Denm.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Philipp.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Alcon, Turk.; Alcon, UK.
⊗ Dexamethasone (p.1526·1).
Inflammatory external ear disorders; inflammatory eye disorders.

Alcon, USA.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Maxidone *Watson, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Maxidraine *Bio2, Fr.†.*
Black currant (p.2267·1); taraxacum (p.2395·1); bladderwrack (p.2384·2); green tea (p.2416·1).
Water retention.

Maxidrat *Defuen, Arg.*
A range of moisturisers.

Maxidrate *Libbs, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Maxidrin *Hertz, Braz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Maxidrol *Alcon, Fr.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Maxifed *MCR, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Maxifed DM *MCR, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Maxifed DMX *MCR, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract congestion.

Maxifed G *MCR, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Maxifem *Ecosol, Switz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Maxifen *Unipharm, Mex.*
Ibuprofen (p.64·2).
Inflammation.

Maxiferon *Cipla, India.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); copper sulfate; manganese sulfate (p.1922·1).

Maxiflor
Note. A similar name is used for preparations of different composition (see below).
Allergan, USA.
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Maxi-Flore
Note. A similar name is used for preparations of different composition (see above).
Synergia, Fr.
Fibre (p.1712·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Bifidobacterium longum* (p.2372·3); *Bifidobacterium breve* (p.2372·3).
Restoration of intestinal flora.

Maxiflox *Latinofarma, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Maxiflox D *Latinofarma, Braz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Maxigan *Unichem, Rus.*
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Pain; smooth muscle spasm.

Maxijul
Note.This name is used for preparations of different composition.
Scientific Hospital Supplies, Austral.
Maltodextrin (p.1955·3).
Carbohydrate food supplement.

SHS, Fr.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.
Food for special diets (p.1922·1).

Maxi-Kalz
Note.This name is used for preparations of different composition.
Viatris, Austria.
Calcium monocitrate (p.1675·3); calcium dicitrate (p.1675·3).
Calcium supplementation.

Meda, Cz.
Calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; renal osteodystrophy.

Maxi-Kalz Vit D3 *Viatris, Austria.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Maxil *Haller, Braz.†.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Maxilac *Ingens, Arg.*
Povidone (p.2146·1); sodium hyaluronate (p.2320·1).
Dry eyes.

Maxilase *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Alpha-amylase (p.2256·3).
Oedema; upper respiratory-tract congestion.

Maxilene *Andromaco, Mex.*
Glycerol oxyester; silicon.
Alopecia.

Maxilerg *Latinofarma, Braz.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Maxilief *Clonmel, Irl.*
Caffeine (p.1116·3); codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Maxilin *Anpharm (Ανφαρμ), Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Maxiliv *Ache, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Maxilube *Mission Pharmacal, USA.*
Dimethicone (p.2032·1); glycerol (p.2314·2); carbomer 934 (p.2141·3); trolamine (p.2405·1); sodium laurilsulfate (p.2138·3).
Vaginal lubricant.

Maxiluz *Valeant, Arg.*
Soap substitute.

Maxim Hp *Dabur, India†.*
Preparation for enteral nutrition (p.1922·1).

Maxima *Bago, Arg.*
Yellow tablets, drospirenone (p.2095·2); ethinylestradiol (p.2101·3); red tablets, inert.
Combined oral contraceptive.

Maximin *Anglo-French Drugs, India.*
Range of multivitamin preparations with or without minerals (p.1922·1).

Maximiton *Varifarma, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Maximo *Savant, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Maximum Blue Label *Vitaline, USA.*
Multivitamin and mineral preparation (p.1922·1).

Maximum D3 *Propharma, USA.*
Colecalciferol (p.1986·2).
Vitamin D supplement.

Maximum Green Label *Vitaline, USA.*
Multivitamin and mineral preparation (p.1922·1).

Maximum Once A Day *Quest, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Maximum Potential for Men *Natural Life, Arg.†.*
Vitamins; minerals; royal jelly; pollen; ginseng; kola; saw palmetto; damiana (p.1922·1).

Maximum Red Label *Vitaline, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Maximum Relief Ex-Lax *Novartis Consumer, USA.*
Senna (p.1769·2).
Constipation.

Maximum Strength Allergy Drops *Bausch & Lomb, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); hypromellose (p.2144·2).
Minor eye irritation.

Maximum Strength Anbesol *Whitehall, USA.*
⊗ Benzocaine (p.1854·1); alcohol (p.1625·2).
Local anaesthesia.

Maximum Strength Aqua-Ban *Thompson, USA.*
⊗ Pamabrom (p.1365·3).
Premenstrual water retention.

Maximum Strength Desenex Antifungal *Novartis Consumer, USA†.*
Miconazole nitrate (p.541·3).

Maximum Strength Dristan Cold *Whitehall, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Cold symptoms; nasal congestion.

Maximum Strength Flexall 454 *Chattem, USA.*
Menthol (p.2340·1); aloe vera (p.1588·2); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); thyme oil (p.2401·2).
Musculoskeletal disorders; pain.

Maximum Strength Ornex *Menley & James, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Maximum Strength Sine-Aid *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Maximum Strength Sleepinal *Thompson, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Maximum Strength Sudogest Sinus *Major, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Maximum Strength Unisom SleepGels *Pfizer Consumer, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Maxinject *Suan, Gr.*
Cefepime (p.224·1).
Bacterial infections.

Maxint *Bajamed, Mex.†.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Maxiostenil *TRB, Arg.*
Sodium hyaluronate (p.2320·1).
Joint disorders; synovial fluid replacement.

Maxiphen DM *MCR, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Maxiphen-G DM *AMBI, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Maxipime *BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.†; BMS, Fin.; BMS, Ger.; Vianex (Βιανεξ), Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.†; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, USA; BMS, Venez.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Maxipiro *Gache, Venez.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders; pain.

Maxipril *Boniscontro & Gazzone, Ital.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Maxipro *Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Hypoproteinaemia.

Maxiquin *Sterop, Belg.†.*
Quinine-resorcinol.
Malaria.

Maxirap *Sensomed, Philipp.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
External ear disorders with infection; infected eye disorders.

Maxirex *Interbat, Indon.*
Tribulus terrestris (p.2404·1); arginine hydrochloride; muira-puama; damiana (p.2292·1); ginseng (p.2312·1); yohimbe; zinc; vitamin E; saw palmetto (p.2192·3) (p.1922·1).
Tonic.

Maxirich *Cipla, India.*
Multivitamin and mineral preparation (p.1922·1).

Maxisalic *Valeant, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Maxisona *ICN, Arg.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Maxisorb *Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).

Maxisteril *Germo, Ital.*
Benzalkonium chloride (p.1629·1).
Skin and instrument disinfection.

Maxitone *Brunel, S.Afr.†.*
Haematoporphyrin; cyanocobalamin; caffeine; rose hip; yeast (p.1922·1).
Tonic.

Maxitratobes *Columbia, Arg.*
⊗ Mazindol (p.2157·3); dipotassium clorazepate (p.980·1).
Obesity.

Maxitrin *Dipa, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); fish oil (p.1362·2); dimethyl sulfone (p.2294·1); vitamin E; soya oil (p.1965·3).
Maintenance of healthy joint function.

Maxitrol *Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Fin.; Alcon, Hong Kong; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Neth.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, UK; Alcon, USA; Alcon, Venez.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected inflammatory eye disorders.

Maxi-Tuss HCG *MCR, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Maxi-Tuss HCX *MCR, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Maxius *OM, Port.*
Tibezonium iodide (p.2402·1).
Mouth and throat disorders.

Maxivalet *Demo, Gr.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Maxivanil *Max Farma, Ital.*
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis.

Maxivate *Westwood-Squibb, USA.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Maxivision *Medical Ophthalmics, USA.*
Vitamin, mineral, and nutrient preparation (p.1922·1).

Maxivit
Gelcaps, Mex.
Vitamin and mineral preparation with royal jelly (p.1922·1).

Pfizer Consumer, Switz.†.
Multivitamin and mineral preparation (p.1922·1).

Maxi-Vite *Goldline, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Maxoflam *Liferpal, Mex.*
Meloxicam (p.80·3).
Fever; inflammation; pain.

Maxolon
ICN, Austral.; Valeant, Hong Kong; Shire, Irl.; ICN, Malaysia; ICN, Singapore†; Amdipharm, UK; SmithKline Beecham, USA†.
Metoclopramide hydrochloride (p.1747·3).
Adjunct to gastrointestinal procedures; gastro-oesophageal reflux; gastrointestinal motility disorders; migraine; nausea and vomiting; premedication.

Pacific, NZ; Pharmaco, S.Afr.
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal procedures; gastrointestinal motility disorders; hiccup; nausea and vomiting.

Maxomat *Sanofi-Aventis, Fr.*
⊗ Somatropin (p.1799·3).
Growth-hormone deficiency; Turner's syndrome.

Maxoptic *Vendiz, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Inflammatory eye infections.

Maxor *Alphapharm, Austral.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Maxoral *Armstrong, Mex.*
Tibezonium iodide (p.2402·1).
Mouth and throat disorders.

Maxotin *Unison, Thai.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Maxovite *Tyson, USA.*
Multivitamin and mineral preparation (p.1922·1).
Premenstrual syndrome.

Max-Pax *Biolab Sanus, Braz.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; premedication.

Maxpro *Meprofarm, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Maxsoten *Wyeth, Belg.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Maxsulid *Farmasa, Braz.*
Nimesulide betadex (p.95·3).
Musculoskeletal and joint disorders.

Maxtenk *Biotenk, Arg.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism; restless legs syndrome.

Maxtol *Bausch & Lomb, Arg.*
Piroxicam (p.117·3).
Inflammatory eye disorders.

Maxtral *Baliarda, Arg.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Maxtrex *Pharmacia, UK.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Maxtrim *BMS, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Maxudin *Menarini, Gr.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Maxulid *Verheilen, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Maxus
Note.This name is used for preparations of different composition.
Bausch & Lomb, Arg.
Chondroitin sulfate (p.2280·3); aprotinin (p.1055·1); sodium hyaluronate (p.2320·1).
Dry eyes.

Bausch & Lomb, Mex.
Chondroitin sulfate (p.2280·3).
Dry eyes.

Maxzide *Bertek, USA.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Maycardin K *Mayrhofer, Austria.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Digitalis poisoning; potassium and magnesium deficiency.

Maycor *Parke, Davis, Cz.†; Godecke, Ger.†; Parke, Davis, Ger.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Maycor Nitrospray *Parke, Davis, Cz.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Maydol *BMS, Venez.*
Ibuprofen (p.64·2).
Pain.

Mayfung
Note.This name is used for preparations of different composition.
Mayrhofer, Austria.
Bath additive: Disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3).
Fungal infections.

Mayrhofer, Austria.
Topical solution: Undecenoic acid monoethanolamide (p.549·3).
Fungal skin infections.

Mayfusin *Mayrhofer, Austria.*
Amino-acid infusion with or without electrolytes and glucose (p.1922·1).
Parenteral nutrition.

Maygace *BMS, Spain.*
Megestrol acetate (p.2114·3).
Anorexia and cachexia in AIDS and cancer; breast cancer; endometrial cancer.

Maylox *Nicholas Piramal, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Dyspepsia; flatulence; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Maylyt *Mayrhofer, Austria.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Maynar *Novag, Spain.*
Aciclovir (p.862·3).
Herpesvirus infections.

Mayogel *Adcock Ingram, S.Afr.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Dyspepsia; gastric hyperacidity; peptic ulcer.

Mayoprina *Mayo, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Mayozest *Otsira, India.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; heart failure.

Mayul *Q Pharma, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Mazetol *Sarabhai Piramal, India.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Mazitrom *Uniao Quimica, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Mazon Medicated Cream *Nasmark, Canad.*
Coal tar (p.1616·2); resorcinol (p.1612·1); salicylic acid (p.1612·2).
Skin disorders.

Mazon Medicated Shampoo *Nasmark, Canad.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Scalp disorders.

Mazon Medicated Soap *Nasmark, Canad.*
Coal tar (p.1616·2).
Skin disorders.

M&B Cough Syrup *Nicholas Piramal, India†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

MBE *Hasco-Lek, Pol.*
Magnesium oxide (p.1744·1); pyridoxine hydrochloride (p.1978·2); *dl*-alpha tocoferil acetate (p.1992·3).
Atherosclerosis; dietary supplement; ischaemic heart disease.

M-Bentabs *Allen, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

M-beta *Betapharm, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

MC 506 *Medevale, Cz.*
Aminolevulinic acid (p.679·2).

MC Modulo Calorico *Braun, Arg.*
Maltodextrin (p.1955·3).
Nutritional supplement.

M-Caps *Pal-Pak, USA.*
Methionine (p.1450·1).
Odour, dermatitis, and ulceration in incontinent adults.

M-Clear WC *McNeil, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cough.

MCP
Hexal, Cz.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

1A, Ger.; Aliud, Ger.; Alpharma-Isis, Ger.; Betapharm, Ger.; CT, Ger.; Hexal, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Stada, Ger.
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

MCPham *Phamos, Ger.†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders.

MCR
Note. A similar name is used for preparations of different composition (see below).
Rafa, Israel.
⊗ Morphine sulfate (p.86·3).
Pain.

MCR-50
Note. A similar name is used for preparations of different composition (see above).
Pfizer, UK†.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

MCT
Note.This name is used for preparations of different composition.
Mead Johnson, Israel; Milk Industries, Israel; SHS, Israel; Nutricia, Ital.; Mead Johnson, Singapore†; Mead Johnson Nutritionals, USA.
Medium-chain triglycerides (p.1956·3).
Adjunct in the management of disorders of fat absorption and transport; disorders of lymph circulation.

Vitaflo, UK.
Preparation for enteral nutrition (p.1922·1).
Fat malabsorption.

MCT Duocal
Note.This name is used for preparations of different composition.
Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.†.
Medium-chain triglycerides (p.1956·3).
Fat malabsorption; food for special diets.

Scientific Hospital Supplies, UK.
Protein-, lactose-, gluten-, fructose-, and sucrose-free food with medium-chain triglycerides (p.1956·3) (p.1922·1).
Fat malabsorption.

MCT Oil *Mead Johnson, Austral.; Mead Johnson Nutritionals, Canad.†; IFET (ΙΦΕΤ), Gr.; Mead Johnson, Malaysia†; Nutricia, NZ; Mead Johnson, Port.; Nutricia, Port.; Mead Johnson Nutritionals, UK; Scientific Hospital Supplies, UK.*
Medium-chain triglycerides (p.1956·3).
Dietary supplement in disorders of fat absorption and digestion; ketogenic diets.

MCT Oljy *Nutricia, Fin.*
Medium-chain triglycerides (p.1956·3).
Fat malabsorption.

MCT Pepdite *Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Infant feed (p.1922·1).
Bowel disorders; disorders of fat absorption; protein intolerance.

MCT Peptide *Nutricia, NZ†; Scientific Hospital Supplies, NZ†.*
Infant feed (p.1922·1).
Cystic fibrosis; gastrointestinal disorders; lymphatic disorders.

MCXY *Millimed, Thai.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; rhinitis; sinusitis.

M-D *Milano, Thai.*
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2).
Contact dermatitis; urticaria.

MD-60 *Mallinckrodt, Austral.†.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

MD-76 *Mallinckrodt, Arg.; Mallinckrodt, Austral.; Tyco, Canad.; Mallinckrodt, USA.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

MD Complejo *Liferpal, Mex.*
Vitamin B substances (p.1922·1).
Neuritis.

MD-Cal *Combiphar, Indon.*
Calcium carbonate (p.1714·1); magnesium; vitamin D; zinc (p.1922·1).
Osteoporosis.

MD-Gastroview *Mallinckrodt, Arg.; Mallinckrodt, Austral.; Mallinckrodt, USA.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for gastrointestinal radiography.

M-Dolor *Ethypharm, Austria; Hexal, Ger.†; Hexal, Philipp.; Salutas, Philipp.*
⊗ Morphine sulfate (p.86·3).
Pain.

6-MDP, 8-MDP *Rez, Cz.*
Technetium-99m (p.2055·3) medronate.
Bone scanning.

MDR Fitness Tabs *MDR, USA.*
Multivitamin and mineral preparation (p.1922·1).

MDS Quick *MDS Diagnostics, NZ.*
Pregnancy test (p.2372·1).

Mealin *Pharmasant, Thai.*
Mianserin hydrochloride (p.408·1).
Depression.

Mealis *Pharmacypria, Gr.*
Lisinopril (p.1325·2).
Hypertension.

Meaverin
Note.This name is used for preparations of different composition.
DeltaSelect, Ger.
Injection: Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Aventis, Ger.†.
Topical gel: Mepivacaine hydrochloride (p.1866·3); lauromacrogol 400 (p.1916·1).
Catheterisation; intubation; local anaesthesia.

Meba *Polipharm, Thai.†.*
Mebendazole (p.148·3).
Worm infections.

Mebaral *Ovation, USA.*
Methylphenobarbital (p.490·2).
Anxiety; epilepsy.

Mebax *Quim-Far, Venez.†.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Vomiting.

Mebaxol *Richmond, Arg.*
Ornidazole (p.843·1).

Mebeciclol *Sanofi Synthelabo, Mex.*
Mebendazole (p.148·3); tinidazole (p.848·3).
Nematode infections; protozoal infections.

Mebelmin *Jofrain, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebemerck *Merck dura, Ger.*
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Meben *General Drugs, Thai.*
Mebendazole (p.148·3).
Worm infections.

Mebendan *Tedec Meiji, Spain.*
Mebendazole (p.148·3).
Worm infections.

Mebenda-P *PP Lab, Thai.†.*
Mebendazole (p.148·3).
Worm infections.

Mebendicin *Technobio, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebenix *Cimed, Braz.*
Albendazole (p.139·2).
Worm infections.

Mebensole *Sanofi Synthelabo, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebental *Royton, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Mebentiasis *Keton, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebentral *Berman, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebetin *Sam Chun Dang, Malaysia; Sam Chun Dang, Singapore.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm; irritable bowel syndrome.

Mebex *Cipla, India.*
Mebendazole (p.148·3).
Worm infections.

Mebex Plus *Cipla, India.*
Mebendazole (p.148·3); pyrantel embonate (p.155·1).
Worm infections.

Mebiozol *Biofarma, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Mebo *Mebo, Thai.; Julphar, UAE.*
Sitosterol (p.1373·2).
Burns; haemorrhoids; scalds; ulcers; wounds.

Mebocaina *Novartis Consumer, Port.*
Tyrothricin (p.358·2); cetylpyridinium chloride (p.1635·1); oxybuprocaine hydrochloride (p.1867·3).
Mouth and throat disorders.

Mebonat *Roche, Spain†.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolytic bone metastases.

Meborilan *Sofex, Port.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Meb-Overoid *Valdecasas, Mex.*
Mebendazole (p.148·3).
Worm infections.

Mebron *Nikkho, Braz.†; Daiichi, Jpn.*
Epirizole (p.50·2).
Fever; inflammation; pain.

Mebronol *Farmamust, Gr.*
Butamirate (p.1553·1).
Cough.

Mebryl *GSK, India.*
Embramine hydrochloride (p.579·1).
Angioedema; eczema; hypersensitivity reactions; urticaria.

Mebucain
Note.This name is used for preparations of different composition.
Novartis Consumer, Hung.
Lozenges (mint): Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Novartis Consumer, Hung.
Lozenges (orange); pastilles; throat spray: Benzoxonium chloride (p.1631·2); lidocaine hydrochloride (p.1862·3).
Formerly contained cetylpyridinium chloride, oxybuprocaine hydrochloride, and tyrothricin.
Mouth and throat disorders.

Mebucaine *Novartis Consumer, Switz.*
Cetylpyridinium chloride (p.1635·1); oxybuprocaine hydrochloride (p.1867·3); tyrothricin (p.358·2).
Mouth and throat disorders.

Mebucalets f *Novartis Consumer, Switz.*
Benzoxonium chloride (p.1631·2); lidocaine (p.1862·3).
Mouth and throat disorders.

Mebucasol f *Novartis Consumer, Switz.*
Lidocaine hydrochloride (p.1862·3); muramidase hydrochloride (p.2348·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Mebumal *SAD, Denm.*
Pentobarbital sodium (p.1016·1).
Adjuvant in anaesthesia; sedative.

Mebutan *Meda, Neth.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Mebutar *Andromaco, Arg.*
Mebendazole (p.148·3).
Worm infections.

Mebutar Compuesto *Andromaco, Arg.*
Mebendazole (p.148·3); tinidazole (p.848·3).

Mebzol *Julphar, UAE.*
Mebendazole (p.148·3).
Worm infections.

Mecain *DeltaSelect, Ger.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mecalox *Pharmathen, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Mecanyl *Beta, Arg.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Mecanyl Duo *Beta, Arg.*
Glucosamine hydrochloride (p.2313·2) or glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Joint disorders.

Mecaton *Norma (Νορμα), Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Mecca *Mentholatum, Canad.*
Camphor (p.2273·2); phenol (p.1656·1); zinc oxide (p.1621·2).

Mecholyl *Gordon, USA.*
Methacholine chloride (p.2343·2).
Iontophoresis.

Mechovit *Streuli, Switz.*
-methionine (p.1450·2); vitamins (p.1922·1).
Liver disorders.

Mecid A *Lewison, Philipp.*
Mefenamic acid (p.80·1).
Musculoskeletal and joint disorders; pain.

Meclifar *Farcoral, Mex.*
Meclozine (p.585·1); pyridoxine (p.1979·1).
Nausea and vomiting; vertigo.

Meclin *Apsen, Braz.*
Meclozine hydrochloride (p.584·3).

Meclison *Sons, Mex.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Gastrointestinal disorders; nausea and vomiting; vertigo.

Meclivin *Biomedica-Chemica, Gr.†.*
Piracetam (p.368·2).
Mental function disorders.

Mecloderm *Shire, Ital.*
Meclocycline sulfosalicylate (p.297·2).
Bacterial skin infections.

Mecloderm Antiacne *Shire, Ital.*
Meclocycline sulfosalicylate (p.297·2).
Acne; seborrhoeic dermatitis.

Mecloderm F *Shire, Ital.*
⊗ Meclocycline sulfosalicylate (p.297·2); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Mecloderm Ovuli *Shire, Ital.*
Meclocycline sulfosalicylate (p.297·2).
Vulvovaginal and cervical infections.

Mecloderm Polvere Aspersoria *Shire, Ital.†.*
Meclocycline sulfosalicylate (p.297·2).
Bacterial skin infections.

Meclodol *Parke, Davis, Ital.†.*
Meclofenamate sodium (p.79·3).
Musculoskeletal and joint disorders; pain.

Meclomen *Pfizer, Chile; Parke, Davis, Spain†.*
Meclofenamate sodium (p.79·3).
Fever; inflammation; menorrhagia; musculoskeletal, joint, and peri-articular disorders; pain.

Meclomid *Randall, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Meclon *Farmigea, Ital.*
Clotrimazole (p.530·1); metronidazole (p.837·1).
Vulvovaginal and cervical infections.

Meclopin *Spofa, Cz.†.*
Oxyprothepin decanoate or oxyprothepin mesilate.
Schizophrenia.

Meclosil *Sunward, Singapore.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2); dicycloverine hydrochloride (p.1722·3).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Meclosorb *S & K, Ger.*
Meclocycline sulfosalicylate (p.297·2).
Bacterial skin infections.

Meclutin *IBC, Ital.†.*
⊗ Meclocycline sulfosalicylate (p.297·2); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Meclutin Semplice *IBC, Ital.†.*
Meclocycline sulfosalicylate (p.297·2).
Bacterial skin infections.

Mecobal *TO-Chemicals, Thai.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Mecola *Lapi, Indon.*
Thioctic acid (p.2400·2); cyanocobalamin (p.1980·2).
Antoxidant; diabetic neuropathy.

Mecola Forte *Lapi, Indon.*
Thioctic acid (p.2400·2).
Antoxidant; diabetic neuropathy.

Mecolin *Stadmed, India.*
Tricholine citrate (p.1934·2); sorbitol (p.1965·1).
Biliary hypotonia; constipation; fatty infiltration of liver.

Meconeuro *Novell, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Mecortolon *Jelfa, Pol.*
⊗ Prednisolone pivalate (p.1541·1).
Skin disorders.

Mecortolon N *Jelfa, Pol.*
⊗ Prednisolone pivalate (p.1541·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Mecoten *Promeco, Mex.†.*
Dipyrone (p.49·2).
Pain.

Mecovit *Cipla, India; Towa, Philipp.*
Mecobalamin (p.1981·1).
Megaloblastic anaemia; peripheral neuropathy; vitamin B deficiency.

Mecox *Ferron, Indon.; Valmor, Venez.†.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders; pain.

Mectan *Prafa, Indon.*
Mefenamic acid (p.80·1).
Pain.

Mectin *Elea, Arg.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mectizan *MSD-Chibret, Fr.; Merck, USA.*
Ivermectin (p.145·2).
Veterinary names include: Eqvalan; Ivomec; Oramec.
Lymphatic filariasis; onchocerciasis.

Med Pass *Hormel, Hong Kong.*
Preparation for enteral nutrition (p.1922·1).

Meda *Circle, USA†.*
Paracetamol (p.108·1).
Fever; pain.

Medacalm *GSK Consumer, Ger.*
Peppermint oil (p.1761·2).
Gastrointestinal disorders.

Medacinase *Medac, Neth.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Medacter *Faran, Gr.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Med-Actigen *Medical Supply, Thai.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; hay fever; rhinitis; upper respiratory-tract congestion.

Medactin *Medac, Ger.*
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Medafein *Kocak, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Medaflox *Eurolab, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Medalgin *Medical Supply, Thai.†.*
Dipyrone (p.49·2).
Pain.

Medalginan *Medinfar, Port.*
Benzyl nicotinate (p.28·1); capsicum (p.2276·2); camphor (p.2273·2); diethylamine salicylate (p.47·2).
Musculoskeletal and joint disorders; neuritis.

Medalin *Alian, Venez.*
Famotidine (p.1730·1).
Peptic ulcer.

Medamet *Caps, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Medamor *MSD, Fin.†.*
⊗ Amiloride hydrochloride (p.1209·2).
Hypertension; liver cirrhosis with ascites; oedema.

Med-Anspasmic *Medical Supply, Thai.†.*
Mefenamic acid (p.80·1); dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Medaren *Medical Supply, Thai.†.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Medarex *Medipharm, Chile.*
Cyclobenzaprine (p.1895·3).
Skeletal muscle spasm.

Medarum *Obolenskoe, Rus.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; vascular eye disorders; vestibular disorders.

Medaspor *Medpro, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin and vulvovaginal infections.

Medatz *Bajamed, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Medaxime *Specpharm, S.Afr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Medaxone *Pharmacypria, Gr.; Medochemie, Rus.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Medaxonum *Medochemie, Hong Kong.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Medazine
Cipla, India.
Cyclizine (p.574·2).
Medpro, S.Afr.
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Medazol
Note. This name is used for preparations of different composition.
Greenpharma, Braz.
Mebendazole (p.148·3).
Worm infections.
Medipharm, Chile; Belupo, Cz.†; Offenbach, Mex.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; protozoal infections; rosacea.

Medazole
Note. This name is used for preparations of different composition.
Beacons, Singapore.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis.
Asian Pharm, Thai.
Mebendazole (p.148·3).
Worm infections.

Medazyl *M & H, Thai.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Med-Broncodil *Medical Supply, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Med-Broncodil Expectorant *Medical Supply, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Med-C *Millimed, Thai.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Medcef *Bergamo, Braz.*
Cefuroxime (p.238·2).
Bacterial infections.

Medcin *Millimed, Thai.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Med-Circuron *Medical Supply, Thai.†.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Medebar *Mallinckrodt, Austral.; Regional Health, NZ†; Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Medebiotin *Medea, Spain.*
Biotin sodium (p.1931·3).
Biotin deficiency.

Mededoxi *Reig Jofre, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Medefizz *Medefield, Austral.†; Regional Health, NZ†.*
Potassium bicarbonate; citric acid.
Adjunct in gastrointestinal radiography; effervescent system for double-contrast radiography.

Medefoam *Medefield, Austral.†; Regional Health, NZ†.*
Simeticone (p.1770·2).
Adjunct in gastrointestinal radiography; antifoaming agent for barium radiography.

Medemycin *Meiji, Hong Kong; Meiji, Jpn.*
Midecamycin (p.300·2).
Bacterial infections.

Medenorex *Medea, Spain.*
Cyproheptadine hydrochloride (p.575·1); amino acids and vitamins (p.1922·1).
Tonic.

Medent-DM *Stewart Jackson, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Medent-PE *Stewart Jackson, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Mede-Prep *Medefield, Austral.; Regional Health, NZ†.*
⊗ Mannitol (p.1330·2).
Bowel evacuation.

Mederebro *Nupel, Spain.*
Cyanocobalamin (p.1980·2); thiamine (p.1976·3); pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Mederma
Note. This name is used for preparations of different composition.
Aurora, Austral.; Royal, Chile†; Merz, Israel; Merz, Malaysia; Merz, Singapore; Merz, USA.
Onion (p.2356·3).
Scars.
Combiphar, Indon.; Merz, Indon.
Cepalin (p.2356·3); allantoin (p.1588·1).
Keloid scars.
Merz, Mex.
Emollient.
Dry skin disorders.

Mederreumol *Medea, Spain†.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Medescan *Medefield, Austral.; Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Medeserpine Co *Medical Supply, Thai.†.*
⊗ Reserpine (p.1387·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Medeton *TP, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; progestogen-only injectable contraceptive.

Medevac *Medefield, Austral.†; Regional Health, NZ†.*
Arachis oil (p.2259·1); sorbitol (p.1965·1).
Gallbladder evacuant for oral cholecystography.

Medex Rub
Note. This name is used for preparations of different composition.
Sidus, Arg.
Adult rub: Sulfogaiacol (p.1573·2); methyl nicotinate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); pine oil (p.2368·2); eucalyptus oil (p.2301·2).
Catarrh; cold symptoms.
Sidus, Arg.
Infant rub: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); niaouli oil (p.2351·3).
Catarrh; cold symptoms.

Medezol *Medea, Spain.*
Ketoconazole (p.539·1).
Fungal skin and nail infections.

Med-Gastramet *Medical Supply, Thai.†.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Medgenol *MedGen, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Medgesic *Medifive, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal disorders; pain; tension headache.

Medgivit *MedGen, Philipp.*
Vitamins; lysine hydrochloride (p.1922·1).

Med-Glionil *Medical Supply, Thai.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Med-Guaiphan *Medical Supply, Thai.†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Medi Creme *Pfizer Consumer, Austral.*
Chlorhexidine acetate (p.1635·2); cetrimide (p.1634·1); hexamidine isetionate (p.1646·3); allantoin (p.1588·1); lidocaine hydrochloride (p.1862·3).
Abrasions; cuts; insect bites and stings; minor burns; skin irritation.

Medi Pulv *Aspen, Austral.*
Hexamidine isetionate (p.1646·3); chlorhexidine hydrochloride (p.1635·3); allantoin (p.1588·1).
Cuts; minor burns and scalds.

Mediab *Medicom, Cz.†.*
Glipizide (p.441·3).
Diabetes mellitus.

Mediabet *Medice, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Medialipide *Braun, Belg.†; Braun, Fr.*
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Mediamer B6 *Darya-Varia, Indon.*
Parathiazine teoclate; pyridoxine hydrochloride (p.1979·1).
Motion sickness; nausea; vomiting.

Mediamik *Medisint, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Medianox *Grossmann, Switz.*
Cloral hydrate (p.979·1).
Nervousness; sleep disorders.

Medianut *Braun, Fr.†.*
Amino-acid and lipid infusion (p.1922·1).
Parenteral nutrition.

Mediatensyl *Fournier, Fr.*
Urapidil (p.1419·3).
Hypertension.

Mediator *Servier, Fr.; Servier, Port.*
Benfluorex hydrochloride (p.1224·3).
Adjunct in diabetes mellitus; hyperlipidaemias.

Mediaven *Will-Pharma, Belg.; Drossapharm, Switz.*
Naftazone (p.1074·2).
Diabetic retinopathy; venous insufficiency.

Mediaxal *Servier, Hong Kong; Servier, Ital.†; Servier, Malaysia; Servier, Singapore.*
Benfluorex hydrochloride (p.1224·3).
Diabetes mellitus; hyperlipidaemias; lipid and glucose metabolic disorders.

Medibiox *Medipharm, Chile.*
Levofloxacin (p.292·2).
Bacterial infections.

Medibron *Medi-Rx, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Medic *DNR, Arg.†.*
Salicylic acid (p.1612·2); allantoin (p.1588·1); coal tar (p.1616·2).
Skin and scalp disorders.

Medica *Qualiphar, Belg.*
Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3).
Throat disorders.

Medica Junior *Qualiphar, Belg.*
Echinacea (p.2298·1); vitamin C (p.1983·3); menthol (p.2340·1).
Sore throat.

Medicaid *LPC, UK.*
Cetrimide (p.1634·1).
Nappy rash.

Medicament Sinus *Prodemdis, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Medicap *Xepa-Soul Pattinson, Hong Kong.*
Mefenamic acid (p.80·1).
Musculoskeletal disorders; pain; soft-tissue injuries.

Medicated Analgesic Cream *Prodemdis, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Medicated Extract of Rosemary *Potter's, UK.*
Geranium oil (p.2311·1); rosemary oil (p.2381·3); methyl salicylate (p.85·3); bay oil (p.2263·2).
Scalp disorders.

Medicatex *Raymos, Arg.*
Menthol (p.2340·1); sulfur (p.1614·1).
Scalp disorders.

Medichrom *Qualiphar, Belg.*
Merbromin (p.1652·1).
Disinfection of minor wounds.

Medicillin *Ratiopharm, Fin.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Medicinal Gargle *Weleda, UK.*
Homoeopathic preparation.

Medicol *United Laboratories, Philipp.*
Ibuprofen (p.64·2).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Medicold *Kocak, Turk.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Medicomtrin *Medikon, Indon.*
Pyrantel embonate (p.155·1).
Worm infections.

Medicone
Note.This name is used for preparations of different composition.
Dickinson, USA†.
Yeast extract (p.1998·3); shark-liver oil (p.2386·1).

Dickinson, USA.
Ointment: Benzocaine (p.1854·1).
Anorectal disorders.

Dickinson, USA†.
Suppositories: Phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Medicone Derma *Medicone, USA†.*
Benzocaine (p.1854·1); zinc oxide (p.1621·2); hydroxyquinoline sulfate (p.2323·1); ichthammol (p.1599·1); menthol (p.2340·1).
Skin disorders.

Medicort *Surya Dermato, Indon.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Medicreme
Note.This name is used for preparations of different composition.
Bajer, Arg.
Vitamin A palmitate (p.1973·1); collagen (p.2286·1).
Skin disorders.

Pharmacare, Hong Kong.
Chlorhexidine acetate (p.1635·2); cetrimide (p.1634·1); hexamidine isetionate (p.1646·3); lidocaine hydrochloride (p.1862·3).
Burns; cuts and abrasions; insect bites and stings; skin irritation.

Shreya, India.
Methyl nicotinate (p.85·3); mephenesin (p.1897·2); methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Pharmabroker, NZ.
Chlorhexidine acetate (p.1635·2); cetrimide (p.1634·1); hexamidine isetionate (p.1646·3); lidocaine (p.1862·3).
Bites; burns; insect stings; wounds.

Medic-S *DNR, Arg.†.*
Collagen (p.2286·1).
Hair disorders.

Medicyclomine *Brunel, S.Afr.†.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm; urinary-tract spasm.

Medi-Dan *Mahdeen, Canad.*
Coal tar (p.1616·2); benzalkonium chloride (p.1629·1); salicylic acid (p.1612·2).
Dandruff; seborrhoeic dermatitis.

Medident *Medibrands, Israel.*
Chlorhexidine gluconate (p.1635·3).
Mouth disinfection.

Medidos *Medipharm, Chile.*
Miconazole (p.541·2); tinidazole (p.848·3).
Trichomoniasis; vulvovaginal anaerobic and fungal infections.

Medifam *Medichem, Philipp.*
Rifampicin (p.325·3).
Tuberculosis.

Medifed *Medpro, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Medifen
Note.This name is used for preparations of different composition.
Medipharma, Hong Kong†.
Chlorphenamine maleate (p.571·3).

Grisi, Mex.
Ibuprofen (p.64·2).
Inflammation; pain.

Medifer
Cassara, Arg.
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Medimport, Mex.
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemia.

Mediferron-Vita *Medi-Rx, Philipp.*
Ferrous sulfate (p.1939·3); lysine hydrochloride; vitamin B substances (p.1922·1).
Iron-deficiency; iron-deficiency anaemia; tonic.

Medi-First Sinus Decongestant *Textilease, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Mediflex
Note.This name is used for preparations of different composition.
Medicom, Cz.
Glucosamine sulfate sodium (p.2313·2).
Osteoarthritis.

Kalbe, Indon.
Glucosamine sulfate (p.2313·2).
Musculoskeletal and joint pain.

Crown, S.Afr.†.
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Mediflor *Merck, Indon.*
Comfrey (p.2286·3).
Soft-tissue disorders.

Mediflor no 11 Draineur Renal et Digestif *Merck Medication Familiale, Fr.†.*
Boldo (p.2267·2); birch leaf (p.2266·3); black currant (p.2267·1).
Digestive disorders; kidney disorders.

Mediflor Tisane Antirhumatismale No 2 *Merck Medication Familiale, Fr.*
Birch leaf (p.2266·3); ash (p.2262·1); meadowsweet (p.2338·1); strawberry plant; parietaria; couch-grass (p.2288·2); asparagus; juniper (p.2328·2); bearberry (p.2263·3); black currant (p.2267·1); tilia (p.2402·2); frangula bark (p.1732·2).
Muscular pain; rheumatic pain.

Mediflor Tisane Calmante Troubles du Sommeil No 14 *Merck Medication Familiale, Fr.*
Passion flower (p.2363·2); bitter orange (p.2357·1); crataegus (p.2289·1); melissa (p.2339·3); tilia (p.2402·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Mediflor Tisane Circulation du Sang No 12 *Merck Medication Familiale, Fr.*
Aesculus (p.2248·2); red vine (p.2316·3); hyssop (p.2323·3); valerian (p.2410·1); hamamelis (p.2318·2); cypress nut (p.2291·2); mistletoe (p.2345·3); willow leaf (p.121·3); melissa (p.2339·3); crataegus (p.2289·1); frangula bark (p.1732·2).
Peripheral vascular disorders.

Mediflor Tisane Contre la Constipation Passagere No 7 *Merck Medication Familiale, Fr.*
Senna (p.1769·2); ash (p.2262·1); fennel (p.2302·3); liquorice (p.1740·3); rosemary (p.2381·2).
Constipation.

Mediflor Tisane Digestive No 3 *Merck Medication Familiale, Fr.*
Aniseed (p.2258·2); mint (p.2391·3); angelica (p.2258·1); lavender (p.2331·1); orange leaf; rosemary (p.2381·2); elecampane (p.1558·1); fennel (p.2302·3); coriander (p.2288·1); hyssop (p.2323·3).
Digestive disorders.

Mediflor Tisane Hepatique No 5 *Merck Medication Familiale, Fr.*
Boldo (p.2267·2); kinkeliba (p.2329·2); elecampane root (p.1558·1); rosemary (p.2381·2); liquorice (p.1740·3); berberis; mercury herb; mallow leaves (p.2337·2); senna leaves (p.1769·2).
Digestive disorders; liver disorders.

Mediflor Tisane No 4 Diuretique *Merck Medication Familiale, Fr.*
Asparagus; fennel (p.2302·3); couch-grass (p.2288·2); bearberry (p.2263·3); ash (p.2262·1); meadowsweet (p.2338·1); strawberry root; althaea leaf (p.2253·3); liquorice (p.1740·3).
Diuresis; renal calculi.

Medifol *LA, Arg.*
Folic acid (p.1940·1).
Anaemias.

Medifolin *Medinfar, Port.*
Calcium folinate (p.1943·3).
Folate deficiency; megaloblastic anaemia; toxicity due to folic acid antagonists.

Medifome *GE, Ger.*
Collagen (porcine) (p.2286·1).
Haemorrhage.

Medifon *Medinfar, Port.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); dequalinium chloride (p.1641·3); vitamin C (p.1983·3); menthol (p.2340·1).
Mouth and throat disorders.

Medifortan *Medi-Rx, Philipp.*
Vitamin preparation with or without lysine hydrochloride (p.1922·1).

Medifortan-AS *Medi-Rx, Philipp.*
Buclizine hydrochloride (p.570·1); vitamins (p.1922·1).
Reduced appetite; tonic.

Medifungol *Hexa, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Medigel
Note.This name is used for preparations of different composition.
Medice, Ger.†.
⊗ Bamethan sulfate (p.1222·3); ephedrine sulfate (p.1558·2); lauromacrogol 400 (p.1916·1).
Soft-tissue injury; venous insufficiency.

Medifood, Ital.
Nutritional supplement (p.1922·1).
Vomiting.

Adcock Ingram, S.Afr.
Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide gel (p.1706·2); magnesium oxide (p.1744·1); simeticone (p.1770·2); sodium laurilsulfate (p.2138·3); methylcellulose (p.2145·1).
Gastrointestinal disorders.

Medigesic
Note.This name is used for preparations of different composition.
Maver, Chile.
Clonixin lysine (p.37·1).
Pain.

US Pharmaceutical, USA.
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Medigox *Polfa Warszawa, Pol.*
Metildigoxin (p.1336·2).
Heart failure; supraventricular arrhythmias.

Medihaler *3M, Arg.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Medihaler-Iso *3M, USA.*
⊗ Isoprenaline sulfate (p.1316·3).
Bronchospasm.

Medihoney Antibacterial Wound Gel *Miles, UK.*
Honey (p.1948·2).
Burns; ulcers; wounds.

Medijel *Key, Austral.; DDD, Hong Kong; DDD, Israel; DDD, Malaysia; Wilson, NZ; DDD, Singapore; DDD, UK.*
Lidocaine hydrochloride (p.1862·3); aminoacridine hydrochloride (p.1625·1).
Denture irritation; gingivitis; mouth ulcers; oral lesions; sore gums; teething pain.

Medi-Kain *Pfizer Consumer, S.Afr.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Sore throat.

Medi-Keel A
Note.This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Lozenges: Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Sore throat.

Adcock Ingram, S.Afr.
Throat gargle: Cinchocaine hydrochloride (p.1857·3); benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Adcock Ingram, S.Afr.
Throat spray: Phenol (p.1656·1).
Mouth and throat infections.

Medikem *Maver, Chile†.*
Benzocaine (p.1854·1); benzyl alcohol (p.1631·3).

Mediker *SIT, Ital.*
Phenothrin (p.2048·3).
Pediculosis.

Medikinet *Medice, Ger.; Flynn, UK.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder.

Mediklin
Note.This name is used for preparations of different composition.
Maver, Chile.
Salicylic acid (p.1612·2).
Acne.

Surya Dermato, Indon.
Clindamycin phosphate (p.251·2).
Acne.

Medi-Klin TR *Surya Dermato, Indon.*
Clindamycin phosphate (p.251·2); tretinoin (p.1618·1).
Acne.

Medikol *Selena, Swed.*
Activated charcoal (p.1435·2).
Diarrhoea; poisoning.

Medikoncef *Medikon, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

Medilar
Chauvin, Fr.
Omega-3 fatty acids; omega-6 fatty acids; vitamins; zinc sulfate (p.1922·1).
Dietary supplement for healthy eyes.

Bausch & Lomb, Ital.
Multivitamin and mineral preparation with gamolenic acid (p.1922·1).
Nutritional supplement.

Medilax *Medic, Denm.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Medilaxan *Beta, Arg.*
Ispaghula (p.1737·1); sennosides (p.1769·3).
Constipation.

Medilet *Medice, Ger.†.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy; salmonella enteritis.

Medilexin *IAE, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Medilium *Medifive, Thai.*
Flunarizine (p.580·3).
Cerebrovascular disorders; migraine.

Medilyn *Medpro, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Medimix *AGA, Fr.*
Nitrous oxide (p.1789·3); oxygen (p.1690·2).
Pain.

Medimox *Medikon, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Medimoxil *MedGen, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Medimycetin *MedGen, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Medin G *Grisi, Mex.*
Paracetamol (p.108·1); chlorphenamine (p.572·2).
Cold and influenza symptoms.

Medinait *Procter & Gamble, Spain.*
⊗ Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); ephedrine sulfate (p.1558·2); paracetamol (p.108·1).
Cold and influenza symptoms; coughs.

Medinat Esten *Bioglan, Austral.†.*
Vitamins; minerals (p.1922·1); equisetum (p.2299·3); eleutherococcus senticosis (p.2386·3); damiana (p.2292·1); cimicifuga (p.2282·1); angelica (p.2258·1).
Menopausal disorders.

Medinat PMT-Eze *Bioglan, Austral.†.*
Pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ferrous fumarate (p.1938·3); buchu (p.2269·3); bearberry (p.2263·3); parsley (p.2363·2); juniper oil (p.2328·3); evening primrose oil (p.2302·1).
Premenstrual syndrome.

Medinh-OD *Medichem, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Medinol *SSL, UK.*
Paracetamol (p.108·1).
Fever; pain.

Medinor *Solvay, Port.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Mediocin *Medical Supply, Thai.†.*
Diiodohydroxyquinoline (p.832·1); furazolidone (p.834·3); phthalylsulfathiazole (p.315·1).
Diarrhoea; dysentery; food poisoning.

Mediol *Meprofarm, Indon.*
⊗ Normethandrone (p.2123·1); methyloestradiol (p.2098·3).
Amenorrhoea.

Mediolax *Medice, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Mediotic-HC *Dayton, USA.*
⊗ Hydrocortisone (p.1535·2); pramocaine hydrochloride (p.1868·1); chloroxylenol (p.1640·2); benzalkonium chloride (p.1629·1).
Ear infections; pruritus.

Medipam *Ratiopharm, Fin.*
Diazepam (p.986·3).
Anxiety disorders; insomnia; neuroses; pain; premedication; psychosomatic disorders; skeletal muscle spasm.

Medipax *Tecnifar, Port.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Medipekt *Orion, Fin.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Mediphlegm *Medic+Aid, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mediphyllin Chrono *Medicus, Gr.*
Theophylline (p.1140·1).
Bronchodilator.

Medipina *Medinfar, Port.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Medipirol *Medimport, Mex.*
Metamizole magnesium (p.49·3).
Pain.

Mediplast *Beiersdorf, USA.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Mediplaster *Montefarmaco, Ital.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal pain.

Mediplus *Angelini, Ital.*
Benzalkonium chloride (p.1629·1); benzydamine hydrochloride (p.27·3).
Disinfection of skin, wounds, and burns.

Medipo *Mediolanum, Ital.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Medi-Prep *SSL, UK.*
Cetrimide (p.1634·1).
Skin disinfection.

Mediprim
Note.This name is used for preparations of different composition.
Sons, Mex.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Medika, Switz.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Medipulv *Rosken, Hong Kong†; Pharmabroker, NZ.*
Chlorhexidine hydrochloride (p.1635·3); hexamidine isetionate (p.1646·3); allantoin (p.1588·1).
Burns; cuts and abrasions; wounds.

Medipyn
Note.This name is used for preparations of different composition.
Caps, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Caps, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain associated with tension.

Medipyrin *Medicamenta, Cz.*
Paracetamol (p.108·1).
Fever; pain.

Medi-Quik *Mentholatum, USA.*
Lidocaine (p.1862·3); benzalkonium chloride (p.1629·1).
Skin disorders.

Mediquin *Surya Dermato, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Medirif *Medikon, Indon.*
Rifampicin (p.325·3).
Tuberculosis.

Medirov *Medikon, Indon.*
Spiramycin (p.333·1).
Bacterial infections; toxoplasmosis.

Mediscrub *Medikon, Indon.; Medifarm, Turk.*
Chlorhexidine gluconate (p.1635·3).
Hand disinfection; oral hygiene; skin disinfection.

Medised Infant *SSL, UK.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Cold symptoms; fever; pain.

Medisense *Abbott Diabetes Care, Fr.; Abbott, Irl.†; Abbott Diabetes Care, UK.*
Test for glucose in blood (p.2314·1).

MediSense Sof-Tact *Medisense, Austral.†.*
Test for glucose in blood (p.2314·1).

Medisept *Laboratorios Chile, Chile†.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1); benzyl alcohol (p.1631·3).
Burns; disinfection of instruments and skin; wounds.

Medisepta *Medgenix, Belg.*
Chlorhexidine acetate (p.1635·2) or chlorhexidine gluconate (p.1635·3).
Burns; skin disinfection; skin infections; wounds.

Medisol Bi0 *Medites, Cz.*
Sodium chloride; calcium chloride; magnesium chloride; sodium dihydrogen phosphate; sodium bicarbonate; glucose (p.1670·3).
Haemodialysis; haemofiltration.

Medisol Bi4 *Medites, Cz.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium hydrogen phosphate; sodium bicarbonate; glucose (p.1670·3).
Haemodialysis; haemofiltration.

Medisol K *Medites, Cz.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1670·3).
Haemodialysis; haemofiltration.

Medistatin *Medichrom, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Medisten *Medikon, Indon.*
Clotrimazole (p.530·1).
Fungal skin infections.

Medi-Swab *Smith & Nephew, S.Afr.; SSL, UK.*
Isopropyl alcohol (p.1650·3).
Pre-injection swab; skin disinfection.

Medi-Swab H *SSL, UK.*
Isopropyl alcohol (p.1650·3); chlorhexidine acetate (p.1635·2).
Pre-injection swab.

Medisyl *Korea United, Philipp.*
Methylergometrine maleate (p.2011·1).
Labour management; postpartum haemorrhage; puerperal bleeding.

Meditam
Note. A similar name is used for preparations of different composition (see below).
Help, Gr.†.
Piracetam (p.368·2).
Mental function disorders.

Meditam-6
Note. A similar name is used for preparations of different composition (see above).
Medikon, Indon.
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Meditapp *Medifive, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Coughs; hypersensitivity reactions.

Meditapp Expectorant *Medifive, Thai.*
Guaifenesin (p.1561·3); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Coughs; hypersensitivity reactions.

Medi-Test Combi 2 *BHR, UK.*
Test for glucose and protein in urine.

Medi-Test Combi 5 *Dutec, Austral.*
Test for glucose, blood, ascorbic acid, protein, and pH in urine.

Medi-Test Combi 7 *Dutec, Austral.*
Test for glucose, blood, ketones, ascorbic acid, nitrite, protein, and pH in urine.

Medi-Test Combi 9 *Dutec, Austral.; BHR, UK†.*
Test for glucose, ascorbic acid, ketones, blood, protein, nitrite, pH, bilirubin, and urobilinogen in urine.

Medi-Test Combi 3A *Dutec, Austral.*
Test for glucose, protein, pH, and ascorbic acid in urine.

Medi-Test Combi 4A *Dutec, Austral.*
Test for nitrite, blood, protein, pH, and ascorbic acid in urine.

Medi-Test Combi 6A *Dutec, Austral.*
Test for blood, bilirubin, protein, ascorbic acid, glucose, and pH in urine.

Medi-Test Combi 5N *Dutec, Austral.*
Test for pH, glucose, blood, ascorbic acid, protein, and nitrite in urine.

Medi-Test Glucose *Dutec, Austral.; BHR, UK.*
Test for glucose in urine (p.2314·1).

Medi-Test Glucose 2 *Dutec, Austral.*
Test for glucose and ascorbic acid in urine.

Medi-Test Glucose 3 *Dutec, Austral.*
Test for glucose, ketones, and ascorbic acid in urine.

Medi-Test Glycaemie C *BHR, UK†.*
Test for glucose in blood (p.2314·1).

Medi-Test Keton *Dutec, Austral.*
Test for ketones in urine.

Medi-Test Nitrit *Dutec, Austral.*
Test for nitrite in urine.

Medi-Test Protein 2 *Dutec, Austral.*
Test for protein and pH in urine.

Medi-Test Urbi *Dutec, Austral.*
Test for urobilinogen and bilirubin in urine.

Medithane *Wyeth, India.*
⊗ Hydrocortisone acetate (p.1535·2); skin respiratory factor derived from yeast cells (p.1998·3); shark-liver oil (p.2386·1); vitamin A (p.1971·2).
Anorectal disorders.

Meditil *Medikon, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Meditoina *Medipharm, Chile.*
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal spasm.

Meditonsin *Europharm, Austria; Medice, Ger.*
Homoeopathic preparation.

Meditrim *Medikon, Indon.; Impilo, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Meditrol *Mega Lifesciences, Thai.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Medituss *Crown, S.Afr.†.*
⊗ Mepyramine maleate (p.585·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); cetrimide (p.1634·1); menthol (p.2340·1); ephedrine hydrochloride (p.1558·2).
Respiratory-tract congestion.

Mediuresix *Medical Supply, Thai.†.*
⊗ Furosemide (p.1292·1).
Ascites; oedema.

Mediveine *Elerte, Fr.*
Diosmin (p.2304·2).
Haemorrhoids; peripheral vascular disorders.

Medivitan N *Medice, Ger.*
Hydroxocobalamin (p.1980·3); sodium folate (p.1941·2); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Vitamin deficiency.

Medivitan N Neuro *Medice, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Vitamin B and B deficiency.

Medi-Wipe *SSL, UK.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Hard surface disinfection.

Medix *IAE, Philipp.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Medixel *Taro, Israel.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Medixil *Rider, Chile.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Medixin *Merck, Arg.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Medixon *Ferron, Indon.; Dexa, Philipp.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Medizinisches Erkaltungs Bad *Tetesept, Ger.*
Eucalyptus oil (p.2301·2); Norway spruce oil; thyme oil (p.2401·2).
Cold symptoms.

Medizol
Note. This name is used for preparations of different composition.
Ratiopharm, Fin.†.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Medimport, Mex.
Metronidazole (p.837·1).
Trichomoniasis.

Medizyme *Utopian, Thai.†.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Med-Kafuzone *Medical Supply, Thai.†.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Bacterial gastro-enteritis; diarrhoea.

Medkofen *Medifive, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Med-Lemon Cough Syrup *Group, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Med-Lemon Hot Medication with Vitamin C *Group, S.Afr.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3); menthol (p.2340·1).
Cold and influenza symptoms.

Med-Lemon Hot Medication-Lemon Menthol *Group, S.Afr.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3); menthol (p.2340·1).
Cold and influenza symptoms.

Med-Mucolo *Medical Supply, Thai.†.*
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Med-Myolax *Medical Supply, Thai.†.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal and joint pain; neuralgia.

Mednil *Pharmaland, Thai.*
Mefenamic acid (p.80·1).
Pain.

Medobiotin *Apotheke Roten Krebs, Austria; Medopharm, Ger.†.*
Biotin (p.1931·3).
Biotin deficiency; hair and nail disorders.

Medobis *Lazar, Arg.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Medobis G *Lazar, Arg.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Medocalum *Medochemie, Hong Kong†; Medochemie, Singapore.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Gastrointestinal disorders; nocturnal enuresis; smooth muscle spasm.

Medocarnitin *Medosan, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Medocef *Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Thai.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Medociprin *Medochemie, Hong Kong; Medochemie, Rus.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Medoclav *Medochemie, Rus.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Medoclazide *Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Medoclor *Medochemie, Hong Kong.*
Cefaclor (p.217·2).
Bacterial infections.

Medocodene *Schwarz, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Medocor *Roemmers, Arg.*
Isosorbide mononitrate (p.1318·3).
Ischaemic heart disease.

Medocriptine *Medochemie, Cz.; Medochemie, Hong Kong; Medochemie, Malaysia.*
Bromocriptine mesilate (p.798·1).
Acromegaly; benign breast disorders; galactorrhoea; hyperprolactinaemia; hypogonadism; infertility; lactation inhibition; menstrual disorders; parkinsonism; prolactinomas.

Medocycline *Medochemie, Hong Kong.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Medocyl *Westmont, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Medodermone *Medochemie, Hong Kong; Medochemie, Singapore; Medochemie, Thai.†.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Medoenzym *Medicopharm, Austria.*
Mucosal stomach extract (p.2337·3).
Gastrointestinal disorders.

Medofed *Medifive, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Medofloran *Anfarm, Rus.*
Terbinafine (p.546·3).
Fungal skin, mucous membrane, and nail infections.

Medofloxine *Medochemie, Malaysia.*
Ofloxacin (p.310·2).
Bacterial infections.

Medoflucon *Pharmacypria, Gr.; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Fluconazole (p.532·1).
Fungal infections.

Medofulvin *Medochemie, Malaysia†; Medochemie, Singapore†.*
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Medoglycin *Medochemie, Hong Kong†; Medochemie, Malaysia†.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Medolexin *Medochemie, Hong Kong; Medochemie, Malaysia.*
Cefalexin (p.218·2).
Bacterial infections.

Medolin *Medochemie, Singapore.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Medomycin *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Medonol *Medochemie, Hong Kong.*
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Fever; pain.

Medopa
Note. This name is used for preparations of different composition.
Armoxindo, Indon.; Atlantic, Thai.
Methyldopa (p.1334·1).
Hypertension.

Medinfar, Port.
Dopamine hydrochloride (p.1273·2).
Shock.

Medopam *Schwulst, S.Afr.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Medophyll *Li-il, Ger.†.*
Thymol (p.1664·3).
Skin ulceration; superficial skin disorders; wounds.

Medoprazol *Cl, Austria.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Medoprazole *Medochemie, Malaysia.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Medopred *Medochemie, Rus.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Medopren *Malesci, Ital.†.*
Methyldopa (p.1334·1).
Hypertension.

Medoram plus H *Medochemie, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Medoric *Medifive, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Medorisper *Medochemie, Cz.*
Risperidone (p.1024·2).
Bipolar disorder; schizophrenia.

Medostatin *Medochemie, Cz.; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Medotar *Medco, USA.*
Coal tar (p.1616·2); zinc oxide (p.1621·2).
Skin disorders.

Medotifen *Medical Supply, Thai.†.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Medovascin *Pharmacypria, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Medovent *Medochemie, Hong Kong†; Medochemie, Rus.; Medochemie, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Medovir
Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore.
Aciclovir (p.862·3).
Herpesvirus infections.

Medochemie, Rus.
Aciclovir sodium (p.862·3).

Medovka Lekarska *Slovakofarma, Cz.†.*
Melissa (p.2339·3).
Flatulence; gastrointestinal spasm; insomnia; taste disorders.

Medox ABC *Unipharm, Mex.*
Vitamin and mineral preparation with lysine hydrochloride (p.1922·1).

Medox Prenatal *Unipharm, Mex.*
Vitamin and mineral preparation (p.1922·1).

Medoxem *Pharmacypria, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Medoxicam *Pharmacypria, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Medoxin *Milano, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Medoxine *MedGen, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Medozem *Medochemie, Thai.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Medozide *Malesci, Ital.*
⊗ Methyldopa (p.1334·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Medozine *Medochemie, Hong Kong; Medochemie, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine.

Medphlem *Medpro, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract associated with excess and viscous mucus.

Med-Phylline *Medical Supply, Thai.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Medpramol *Schwulst, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Medral *Offenbach, Mex.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Medrate *Pharmacia, Ger.*
⊗ Methylprednisolone (p.1538·1) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Medrin *Zentiva, Cz.*
Embramine teoclate (p.579·2).
Hypersensitivity reactions; nausea and vomiting; vestibular disorders.

Medrisocil *Oftalder, Port.†.*
⊗ Medrysone (p.1537·3).
Eye disorders.

Medrivas *Alcon Cusi, Spain.*
⊗ Medroxyprogesterone acetate (p.2113·1); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Medrivas Antib *Alcon Cusi, Spain.*
⊗ Chloramphenicol succinate (p.241·3); medroxyprogesterone acetate (p.2113·1); tetryzoline hydrochloride (p.1574·1).
Infected eye disorders.

Medrivas Antibiotico *Alcon, Port.*
⊗ Chloramphenicol sodium succinate (p.240·1); medroxyprogesterone acetate (p.2113·1); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Medrocil *Fortbenton, Arg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Medrocis *Schering, UK†.*
Technetium-99m medronate (p.2055·3).
Bone scintigraphy.

Medrol *Pharmacia, Austral.†; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, NZ; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Swed.; Pfizer, Switz.; Pharmacia Upjohn, USA; Pfizer, Venez.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Medrol Acne Lotion *Pfizer, Canad.*
⊗ Methylprednisolone acetate (p.1538·2); aluminium chlorohydrate complex (p.1588·3); sulfur (p.1614·1).
Acne; rosacea; seborrhoeic dermatitis.

Medrol Lozione Antiacne *Pharmacia, Ital.†.*
⊗ Methylprednisolone acetate (p.1538·2); aluminium chlorohydrate (p.1588·3); colloidal sulfur (p.1614·1).
Acne.

Medronal *LKM, Arg.*
Alprazolam (p.960·1).
Anxiety.

Medrone *Pfizer, UK.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Medroplex *Teva, Cz.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer; renal cancer.

Medrosterona *Gador, Arg.*
Medroxyprogesterone acetate (p.2113·1).
Endometrial cancer; renal cancer.

Medroxitest *Delta, Braz.*
Medroxyprogesterone acetate (p.2113·1).

Medroxon *Sanval, Braz.*
Medroxyprogesterone acetate (p.2113·1).

Medroxyhexal *Hexal, Austral.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menopausal disorders; menstrual disorders.

Medroxyurea *Medac, Gr.†.*
Hydroxycarbamide (p.729·1).
Chronic myeloid leukaemia; myelodysplastic syndromes; polycythaemia vera; primary thrombocythaemia.

MED-Rx *Iomed, USA†.*
Blue tablets, pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); white tablets, guaifenesin.
Upper respiratory-tract symptoms.

MED-Rx DM *Iopharm, USA†.*
Blue tablets, pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); green tablets, guaifenesin; dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract symptoms.

Medsara *Asofarma, Mex.*
Cytarabine (p.705·1).
Malignant neoplasms.

Medsatrexate *Asofarma, Mex.*
Methotrexate (p.745·2).
Malignant neoplasms.

Medsavorina *Asofarma, Mex.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia; reduction of methotrexate toxicity.

Med-Spastic *Medical Supply, Thai.†.*
Oxyphencyclimine hydrochloride (p.1759·2).
Gastrointestinal disorders; genito-urinary disorders.

Med-Sultrim *Medical Supply, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Med-Tricocide *Medical Supply, Thai.†.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Med-Tussin *Medical Supply, Thai.†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Medunkovy, Medunkova *Megafyt-R, Cz.*
Melissa (p.2339·3).
Gastrointestinal disorders; nervous disorders; sleep disorders.

Medusit *Grunenthal, Port.†.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Medusyl Adulte *Bioreance, Fr.*
SPF 15: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Medusyl Enfant *Bioreance, Fr.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Medvedice *Leciva, Cz.†.*
Bearberry (p.2263·3).
Urinary-tract disorders.

Medvox *Medhaus, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Medway *Mitsubishi-Tanabe, Jpn.*
⊗ Albumin (recombinant) (p.1052·1).
Hypoalbuminaemia; hypovolaemic shock.

Med-Xyzarax *Medical Supply, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Allergic skin disorders; anxiety.

Medyn *Medice, Ger.*
Pyridoxine hydrochloride (p.1978·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Prevention of elevated homocysteine concentration; vitamin supplement.

ME-F *TNP, Thai.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mefa *Jean-Marie, Hong Kong; Macrophar, Thai.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Mefac *Rowex, Irl.*
Mefenamic acid (p.80·1).
Musculoskeletal and joint disorders; pain.

Mefacap *Malayan, Singapore†.*
Mefenamic acid (p.80·1).
Menstrual disorders; musculoskeletal and joint disorders; pain.

Mefacit *Polfa Pabianice, Pol.; SecFarm, Pol.*
Mefenamic acid (p.80·1).
Pain.

Mefamic *APT, Hong Kong.*
Mefenamic acid (p.80·1).
Pain; peri-articular and soft-tissue disorders.

Mefast *GMP, Indon.*
Mefenamic acid (p.80·1).
Pain.

Mefazil *Mayo, Mex.*
Indometacin (p.66·3).
Inflammation; rheumatism.

mefe-basan *Schonenberger, Switz.†.*
Mefenamic acid (p.80·1).
Fever; pain.

Mefedra-N *Medipharma, Hong Kong†.*
⊗ Noscapine hydrochloride (p.1566·3); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); cocillana (p.1554·3); euphorbia (p.2301·3); adhatoda; senega (p.1572·3); squill (p.1573·1).
Cold and influenza symptoms.

Mefen *Strand, Malaysia†; Milano, Thai.*
Mefenamic acid (p.80·1).
Pain.

Mefenacide *Streuli, Switz.*
Mefenamic acid (p.80·1).
Influenza symptoms; pain.

Mefenan *Greater Pharma, Thai.*
Mefenamic acid (p.80·1).
Pain.

Mefenax *One Pharma, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Mefenix
Note. This name is used for preparations of different composition.
Phoenix, Arg.†.
Tenoxicam (p.128·2).
Inflammation; pain.

Ranbaxy, Singapore.
Mefenamic acid (p.80·1).
Pain.

Mefenix Relax *Phoenix, Arg.†.*
⊗ Tenoxicam (p.128·2); carisoprodol (p.1894·1); dexamethasone (p.1526·1).
Musculoskeletal, joint, and peri-articular disorders; pain.

Mefic *Pfizer, Austral.; Alphapharm, Hong Kong; Alphapharm, Malaysia.*
Mefenamic acid (p.80·1).
Dysmenorrhoea; menorrhagia; pain.

Mefinal *Sanbe, Indon.*
Mefenamic acid (p.80·1).
Pain.

Mefinter *Interbat, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Mefiron *Chew, Thai.*
Metronidazole (p.837·1).
Trichomoniasis.

Mefix *Meprofarm, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Meflen *Diba, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Mefliam *Cipla, India; Cipla-Medpro, S.Afr.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Mefloc *Aristo, India.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Meflosin *Metiska, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Meflotas *Intas, India.*
Mefloquine (p.607·2).
Malaria.

Meflox *Klinger, Braz.†.*
Lomefloxacin (p.295·3).
Bacterial infections.

Meforal *Berlin-Chemie, Hung.; Guidotti, Hung.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Meformed *Medifive, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mefoxa *Metiska, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Mefoxil *Vianex (Βιανέξ), Gr.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Mefoxin *MSD, Arg.†; MSD, Austral.; MSD, Belg.†; MSD, Braz.; Merck Frosst, Canad.†; MSD, Cz.†; MSD, Fin.†; MSD-Chibret, Fr.†; MSD, Hong Kong; Visufarma, Ital.; MSD, NZ; MSD, Neth.†; MSD, Port.†; MSD, S.Afr.; MSD, UK†; Merck, USA.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mefoxitin *MSD, Austria; Infectopharm, Ger.; MSD, Norw.†; MSD, Spain†; MSD, Swed.†; MSD, Switz.†; MSD, Venez.†.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Mefpa *Pharmasant, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Mefren
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.
Pastilles: Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat infections.

Novartis Consumer, Belg.
Topical solution: Chlorhexidine gluconate (p.1635·3).
Disinfection of minor wounds; disinfection of the skin.

Meftal Forte *Blue Cross, India.*
Mefenamic acid (p.80·1); paracetamol (p.108·1).
Pain.

Mefurosan *Sanbe, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Mega AO *Usana, Canad.*
Multivitamin preparation with ubidecarenone (p.2407·2) (p.1922·1).

Mega B
Cenovis, Austral.
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B deficiency.

Gahler, Canad.; Nu-Life, Canad.; Quest, Canad.; Sisu, Canad.; Quest, UK; Arco, USA.
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Mega B Slow Release *Vitaglow, Austral.†.*
Vitamin B substances; ascorbic acid (p.1922·1).
Dietary supplement; premenstrual syndrome.

Mega Balance *Pharmavite, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Mega Cal Calcium *Jamieson, Canad.†.*
Calcium carbonate; calcium citrate; calcium fumarate; calcium glutamate; calcium malate; calcium succinate (p.1675·2); vitamin D (p.1986·1).

Mega E *Cenovis, Austral.†.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Mega Multi *Cenovis, Austral.†.*
Vitamin and mineral preparation (p.1922·1).

Mega Stress Vitamins *Vita Pharm, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Mega Swiss One *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Mega Vim *Jamieson, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Mega VM *Nature's Bounty, USA.*
Multivitamin and mineral preparation (p.1922·1).

Mega-Alpha *Aurora, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Mega-Antioxidant *Usana, Hong Kong†.*
Multivitamin preparation with inositol, rutoside, hesperidin, green tea, bilberry, choline bitartrate, L-cysteine hydrochloride, cabbage, broccoli (p.1922·1).

Megabal *Sanbe, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy; vitamin B deficiency.

Megabrain *Hebron, Braz.†.*
Multivitamin and mineral preparation (p.1922·1).

Megabron *Sidus, Arg.*
Streptococcus pneumoniae; *Staphylococcus aureus*; *Streptococcus viridans*; *Haemophilus influenzae*; *Klebsiella.*
Respiratory-tract infections.

Mega-Cal *Jamieson, Hong Kong.*
Calcium (p.1675·2).
Calcium deficiency; calcium supplement.

Mega-Cal with Vit D *Jamieson, Hong Kong.*
Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Mega-Calcium *Novartis Consumer, Austria; Novartis, Fin.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency.

Mega-calcium *Novartis, Gr.*
Calcium carbonate (p.1714·1); calcium gluconate (p.1675·3); calcium lactate (p.1676·1).
Calcium deficiency.

Megace *BMS, Arg.†; BMS, Austral.; BMS, Austria; BMS, Belg.; Bristol, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, Singapore; BMS, Swed.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA; Par, USA.*
Megestrol acetate (p.2114·3).
Anabolic; anorexia, cachexia, or unexplained significant weight loss in AIDS patients; breast cancer; cancer-associated anorexia and cachexia; endometrial cancer; hormone-dependent cancer; prostatic cancer.

Megacef *Oboi, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Megacid *Fako, Turk.*
Clarithromycin (p.248·2).
Bacterial infections.

Megacillin *Grunenthal, Austria; Grunenthal, Cz.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Megacillin oral *Grunenthal, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Megacilline
Note. This name is used for preparations of different composition.
Grunenthal, Switz.†.
Injection: Clemizole penicillin (p.251·1).
Bacterial infections.

Grunenthal, Switz.†.
Syrup; tablets: Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Megacistin *Valeant, Arg.*
Cystine (p.1937·1); vitamin B (p.1978·2).
Eye disorders; skin, hair, and nail disorders.

Megacistin G *ICN, Arg.†.*
Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Megaclox *Cipla, India.*
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Megaclox LB *Cipla, India.*
Ampicillin (p.204·1); cloxacillin (p.256·1); lactobacillus spores (p.2372·3).
Bacterial infections.

Megacorp *Panalab, Arg.*
Megestrol acetate (p.2114·3).
Breast cancer; endometrial cancer.

Megacort *Uno, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Musculoskeletal and joint disorders.

Megadin *Mecom, Rus.*
Vitamin and mineral preparation (p.1922·1).

Megadose
Note. This name is used for preparations of different composition.
Fada, Arg.
Dopamine (p.1274·1).
Arco, USA.
Multivitamin and mineral preparation (p.1922·1).

Megadoxa *Adcock Ingram, S.Afr.*
Vitamin B substances (p.1922·1).

Megadoxa Forte *Adcock Ingram, S.Afr.*
Vitamin B substances; vitamin C (p.1922·1).

Megadyn *Mecom, Turk.*
A range of vitamin and mineral preparations (p.1922·1).

Megafer *Boniscontro & Gazzone, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Megaflox *Baldacci, Port.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Megafol *Alphapharm, Austral.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia.

Megagrisevit *Pharmacia, Ger.†.*
⊗ Clostebol acetate (p.2087·1).
Anabolic; fractures; osteoporosis.

Megakids *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Megal *Andromaco, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Coughs.

Megal Simple *Andromaco, Mex.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Megalac *Krewel, Ger.*
Almasilate (p.1705·1) or hydrotalcite (p.1733·3).
Gastrointestinal hyperacidity.

Megalat *Agis, Israel†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Megalax *Adcock Ingram, S.Afr.†.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Megalex *Phoenix, Arg.*
Ranitidine hydrochloride (p.1766·1); domperidone (p.1726·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Megalex Antiacido *Phoenix, Arg.*
Famotidine (p.1730·1); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Formerly known as Megalax Novo.
Gastric hyperacidity.

Megalia *Vipharm, Pol.*
Megestrol acetate (p.2114·3).
AIDS-associated or cancer-associated cachexia.

Megalis *Cafar, Venez.†.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Megalocin *Kyorin, Jpn.*
Fleroxacin (p.276·2).
Bacterial infections.

Megalotect *Biogam, Arg.; Biotest, Gr.; Intra Pharma, Irl.†; Biotest, Israel; Biotest, Neth.; Boehringer Ingelheim, Port.; Mednostica, S.Afr.†; Biotest, Singapore; Biotest, Thai.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Megamag *Mayoly-Spindler, Fr.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Megamilbedoce *Andromaco, Spain.*
Hydroxocobalamin (p.1980·3).
Vitamin B12 deficiency.

Megamox
Note. This name is used for preparations of different composition.
Hikma, Cz.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.
Maver, Mex.
Amoxicillin trihydrate (p.202·2); sulbactam sodium (p.335·1).
Bacterial infections.
Dynamic, Philipp.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.
Garec, S.Afr.
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Megamylase *Leurquin, Fr.*
Alpha-amylase (p.2256·3).
Upper respiratory-tract congestion.

Meganerv *More, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Hyperemesis gravidarum; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Meganerv F-A *More, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); folic acid (p.1940·1).
Folic acid deficiency; neuralgia; neuropathy; prevention of neural-tube defects.

Meganerv-E *More, Philipp.*
Vitamins; ferrous sulfate (p.1922·1).
Tonic.

Meganest *Clarben, Port.; Clarben, Spain.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mega-Neubion *Merck, Venez.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Neuralgia; neuritis.

Meganox *Etex, Chile.*
Lamotrigine (p.485·1).
Epilepsy.

Megapen
Note. This name is used for preparations of different composition.
Eurofarma, Braz.†.
Benzylpenicillin potassium (p.213·1).
Bacterial infections.
Aristo, India.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.
Garec, S.Afr.
Amoxicillin trihydrate (p.202·2); flucloxacillin sodium (p.277·1).
Bacterial infections.

Megapenil
Note. This name is used for preparations of different composition.
Grunenthal, Mex.
Injection: Clemizole penicillin (p.251·1).
Bacterial infections.
Lakeside, Mex.†.
Tablets: Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Megapenil Forte *Grunenthal, Mex.*
Clemizole penicillin (p.251·1); benzylpenicillin sodium (p.213·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to reduce the pain of injection.
Bacterial infections.

Megaplatin *Genepharm, Gr.*
Carboplatin (p.693·1).
Ovarian cancer; small-cell lung cancer.

Megaplex *Teva, Cz.; Pharmachemie, Indon.; Teva, Rus.; Pharmachemie, Thai.; Teva, Thai.*
Megestrol acetate (p.2114·3).
AIDS- and cancer-associated cachexia; breast cancer; endometrial cancer.

Megaplus *Valeant, Arg.*
⊗ Cystine (p.1937·1); pyridoxine hydrochloride (p.1978·2); biotin (p.1931·3); calcium pantothenate (p.1959·3); zinc sulfate (p.1999·2); gelatin (p.1072·1).
Hair and nail disorders; seborrhoea.

Megapress *Genepharm, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Mega-Prim *Hua, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Megapyn
Note. This name is used for preparations of different composition.
Pharmacare, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.
Pharmacare, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Megarubicin *Opus Materia, Gr.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Megase *BMS, Venez.*
Megestrol acetate (p.2114·3).

Megasin *Pierre Fabre, Port.*
Ofloxacin (p.310·2).
Bacterial infections.

Megasoft-E *Otsira, India.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).

Megastene *Servier, Arg.*
Sulbutiamine (p.1976·1).
Asthenia.

Megatears *ICN, Arg.†.*
Povidone (p.2146·1).
Dry eyes.

Megaton *Hyrex, USA†.*
Vitamin B substances with minerals (p.1922·1).

Megaval *Recalcine, Chile†.*
⊗ Fenfluramine hydrochloride (p.2156·2).
Obesity.

Megavir *Gador, Arg.†.*
Didanosine (p.870·2).
HIV infection.

Megavis *Volchem, Ital.*
Levocarnitine (p.1932·2).
Asthenia.

Megavit *Laboratorios Chile, Chile†.*
Vitamins; minerals; ginseng; procaine hydrochloride (p.1869·1) (p.1922·1).
Dietary supplement.

Megavit Natal *Laboratorios Chile, Chile†.*
Vitamin and mineral preparation (p.1922·1).

Megavites *ICN, Canad.†.*
Vitamin B substances and vitamin C (p.1922·1).

Megavix *Winthrop, Fr.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Megaxin *Agis, Israel.*
Moxifloxacin (p.302·2).
Bacterial infections.

Megefren *Prasfarma, Spain.*
Megestrol acetate (p.2114·3).
Anorexia and cachexia in AIDS and cancer; breast cancer; endometrial cancer.

Megental *Menarini, Cz.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Megesin *Sindan, Hung.; Sindan, Pol.*
Megestrol acetate (p.2114·3).
Breast cancer; endometrial cancer.

Megestat *BMS, Braz.; BMS, Ger.; BMS, Switz.*
Megestrol acetate (p.2114·3).
AIDS-associated cachexia; benign prostatic hyperplasia; breast cancer; endometrial cancer; endometriosis; ovarian cancer; prostatic cancer; uterine cancer.

Megestil *Crinos, Ital.*
Megestrol acetate (p.2114·3).
AIDS-associated and cancer-associated cachexia; breast cancer; endometrial cancer.

Megestin *Leiras, Fin.†.*
Megestrol acetate (p.2114·3).
Menopausal disorders; menstrual disorders.

Megestran *Sigma, Braz.†.*
21 Tablets, norethisterone (p.2119·3); mestranol (p.2116·2); 7 tablets, pyridoxine hydrochloride (p.1978·2).
Combined oral contraceptive.

Megestrin *Organon, Mex.†.*
Medroxyprogesterone (p.2113·3).
Injectable progestogen-only contraceptive.

Megestron *Organon, Mex.; Organon, Neth.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Meggezones *Schering, Canad.†; Schering-Plough, UK.*
Menthol (p.2340·1).
Catarrh; cough; nasal congestion; sore throat.

Megion *Biochemie, Cz.; Sandoz, Hung.; Sandoz, Mex.; Sandoz, Philipp.; Sandoz, Venez.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Meglimid *KRKA, Hung.*
Glimepiride (p.441·1).

Meglubet *Sandoz, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Meglucon *Pharma & Co, Austria; Hexal, Ger.; Sandoz, Hung.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Meglum *Bago, Arg.*
Levamisole (p.147·2).
Immunostimulant.

Megostat *Squibb, Spain†.*
Megestrol acetate (p.2114·3).
AIDS-associated cachexia.

Meiact *Meiji, Indon.; Meiji, Jpn; Tedec Meiji, Port.; Tedec Meiji, Spain; Meiji, Thai.*
Cefditoren pivoxil (p.223·2).
Bacterial infections.

Meibi *LKM, Arg.*
Minocycline (p.300·3).
Bacterial infections.

Meicelin *Meiji, Jpn; Meiji, Thai.*
Cefminox sodium (p.226·1).
Bacterial infections.

Meiceral *Meiji, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Meiclox *Meiji, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Meilax *Meiji, Jpn.*
Ethyl loflazepate (p.995·3).
Anxiety; sleep disorders.

Meinvenil Fisiologico *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Meinvenil Glucosa *Fresenius Kabi, Spain.*
Glucose infusion (p.1945·3).
Fluid disorders; parenteral nutrition.

Meinvenil Glucosalina *Fresenius Kabi, Spain.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Meipril *Meiji, Indon.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Meisec *Meiji, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Meixam *Meiji, Indon.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Meixil *Meiji, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mejoral
Note. This name is used for preparations of different composition.
Elisium, Arg.
Paracetamol (p.108·1).
Fever; pain.
GSK, Mex.
Paracetamol (p.108·1); caffeine (p.1116·3).
Formerly contained aspirin.
Fever; pain.
SmithKline Beecham, Spain†.
Aspirin (p.20·3).
Fever; musculoskeletal and joint disorders; pain; periarticular disorders; thromboembolism prophylaxis.

Mejoral Acti-Rapido *GSK, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Mejoral Cafeina
Note. This name is used for preparations of different composition.
Elisium, Arg.
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.
GSK Consumer, Spain.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Mejoral Grip *Elisium, Arg.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); butetamate citrate (p.1553·1).
Fever; pain; respiratory-tract congestion.

Mejoral Grip T Descongestivo *Elisium, Arg.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); vitamin C (p.1983·3).
Fever; pain; respiratory-tract congestion.

Mejoral Plus *GSK, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Mejoralito *GSK, Mex.*
Paracetamol (p.108·1).
Fever; pain; post-vaccination reactions.

Mejorultra *GSK, Mex.†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Mekan *Biomedica-Chemica, Gr.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Mekoll *IIP, Port.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mela'aura *CS, Fr.*
Piroctone olamine (p.1610·1); macadamia oil; salicylic acid (p.1612·2); panthenol (p.2362·1).
Dandruff.

Melablock *Forder, Arg.†.*
Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Melabon
Note. This name is used for preparations of different composition.
Provita, Austria.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine citrate (p.1116·3).
Fever; pain.
Lacer, Spain.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.
Merz, Switz.
Ibuprofen (p.64·2).
Fever; pain.

Melabon Infantil *Lacer, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Melabon K *Rentschler, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Melabon N *Adroka, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Melabon plus C *Rentschler, Ger.*
Aspirin (p.20·3); ascorbic acid.
Cold symptoms; fever; pain.

Melac *Collins, Mex.†.*
Multivitamins with folic acid (p.1922·1).

Melacine *Schering, Canad.†.*
Melanoma vaccine (p.742·1).
Malignant melanoma.

Melacler *Forder, Arg.†.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).

Meladinina *Chinoin, Mex.*
Methoxsalen (p.1605·1).
Psoriasis; vitiligo.

Meladinine *DB, Fr.; Galderma, Ger.; Promedica, Malaysia†; Galderma, Neth.; Galderma, Switz.; Promedica, Thai.†.*
Methoxsalen (p.1605·1).
Alopecia; mycosis fungoides; psoriasis; vitiligo.

Melagel *Giscard, Arg.*
Ascorbic acid (p.1983·3); placenta extract (p.2337·3).
Skin disorders.

Melagesic PM *Ascher, USA.*
Paracetamol (p.108·1); melatonin (p.2338·3).
Pain; sleep disorders.

Melagriao *Catarinense, Braz.*
Nasturtium officinale; aconite (p.2246·1); mikania glomerata; ipecacuanha (p.1562·3); senega (p.1572·3); tolu balsam (p.1574·2); honey (p.1948·2).
Respiratory-tract congestion.

Melalite 15 *Nicholas Piramal, India.*
Hydroquinone (p.1598·2); oxybenzone (p.1608·3); octinoxate (p.1608·2).
Skin pigmentation disorders.

Melanasa *Vinas, Spain.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Melanex *Janssen-Cilag, Mex.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Melani-D Maos *Roche-Posay, Braz.*
Kojic acid (p.1603·3); octocrilene (p.1608·3); avobenzone (p.1589·3); ecamsule (p.1596·1); drometrizole trisiloxane (p.1596·1).
Skin hyperpigmentation.

Melanocyl
Note. This name is used for preparations of different composition.
Franco-Indian, India.
Ointment: Methoxsalen (p.1605·1); aminobenzoic acid (p.1589·1).
Psoriasis; skin depigmentation.

Franco-Indian, India.
solution; Tablets: Methoxsalen (p.1605·1).
Psoriasis; skin depigmentation.

Melanox *Surya Dermato, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Melaoline *Unipharma, Gr.*
Methoxsalen (p.1605·1).
Atopic dermatitis; psoriasis; vitiligo.

Melapure *Genzyme, Hong Kong†.*
Melatonin (p.2338·3).
Insomnia associated with melatonin deficiency; jet lag.

Melarthryl *Sons, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Melaskin *Roi Surya, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Melasmax *Dominguez, Arg.*
⊗ Hydroquinone (p.1598·2); tretinoin (p.1618·1); dexamethasone phosphate (p.1526·2).
Skin hyperpigmentation.

Melasoft *Forder, Arg.†.*
Kojic acid (p.1603·3); arbutin (p.1589·2).

Melatol *Elisium, Arg.*
Melatonin (p.2338·3).
Sleep disorders.

Melaton *Slovakofarma, Cz.†.*
Origanum (p.2357·3); melissa (p.2339·3); lavender (p.2331·1).
Nervous disorders; sleep disorders.

Melatouch *Forder, Arg.†.*
Saxifraga sarmentosa; aminoethylphosphinic acid.

Melavir *Australian Bodycare, UK.*
Melaleuca oil (p.2338·2).
Herpes labialis.

Melavita *Galenium, Indon.*
Tretinoin (p.1618·1).
Acne; melasma; photoageing.

Melaxen *Unipharm, Rus.*
Melatonin (p.2338·3).
Circadian rhythm disturbances.

Melaxose *UCB, Fr.; Pharmasearch, Port.*
Lactulose (p.1738·2); liquid paraffin (p.2030·3).
Constipation.

Melbexa *Investigacion, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Melbin *Sumitomo, Hong Kong; Sumitomo, Jpn.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mel-C *Fresenius Kabi, Austria.*
Sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Melcam *Rowex, Irl.; Unison, Thai.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meldopa *Clonmel, Irl.†.*
Methyldopa (p.1334·1).
Hypertension.

Meleril
Novartis, Arg.†.
Thioridazine (p.1031·2).
Antipsychotic; sedative.

Novartis, Chile†.
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Behaviour disorders in children; depression; psychoses; senile dementia.

Novartis, Spain†; Novartis, Venez.†.
Thioridazine hydrochloride (p.1031·2).
Schizophrenia.

Melfen *PannonPharma, Hung.; Clonmel, Irl.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Melferut *Rafarm, Gr.*
Etofenamate (p.53·1).
Inflammatory disorders.

Melfiat *Numark, USA.*
⊗ Phendimetrazine tartrate (p.2162·1).
Obesity.

Melflam *Cipla, Hong Kong; Cipla, India; Hexal, S.Afr.*
Meloxicam (p.80·3).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Melgar *Hexa, Arg.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Melgisorb
Note. This name is used for preparations of different composition.
Molnlycke, Austral.; Molnlycke, Canad.
Calcium alginate (p.1058·1).
Wounds.

Molnlycke, Fr.
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Exudative wounds.

Mel-H *Fresenius Kabi, Austria; Nycomed, Thai.†.*
Multivitamin and amino-acid preparation (p.1922·1).

Melhoral *DM, Braz.†; GSK Consumer, Port.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Melhoral C *DM, Braz.†.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Melhoral Infantil *GSK Consumer, Port.†.*
Aspirin (p.20·3).
Fever; pain.

Meli Rephastasan *Repha, Ger.*
Melilot (p.2339·2).
Haemorrhoids; thrombophlebitis; venous insufficiency.

Meliane *Schering, Austria; Schering, Belg.; Schering, Fin.; Schering, Fr.; Schering, Gr.; Schering, Hong Kong; Bayer Schering, Hung.; Schering, Israel; Bayer Schering, Malaysia; Schering, Neth.; Schering, Philipp.; Bayer, Singapore; Schering, Spain; Schering, Thai.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Melic
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Meloxicam (p.80·3).
Inflammation; pain.

Pharmasant, Thai.
⊗ Methandienone (p.2116·3).
Osteoporosis.

Melican *Ivax, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Melicate *Coup, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Melice *Farmilia, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melicron *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore†.*
Gliclazide (p.440·3).
Diabetes mellitus.

Meliden *Mavi, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Melidox *Meprofarm, Indon.*
Chlordiazepoxide hydrochloride (p.968·2); clidinium bromide (p.1722·1).
Irritable bowel syndrome; peptic ulcer.

Melimont *Antor, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Melinerv *Ximena Polanco, Chile.*
Homoeopathic preparation.

Melior *Etifar, Venez.†.*
Indometacin (p.66·3).
Inflammation; pain.

Melipass *Knop, Chile.*
Melissa (p.2339·3); passiflora coerulea.
Anxiety; gastrointestinal disorders; sedative.

Melipramin *Egis, Cz.; EGIS, Hung.; Egis, Rus.*
Imipramine hydrochloride (p.400·3).
Depression; migraine; nocturnal enuresis; obsessive-compulsive disorder; panic disorder.

Melipramine *Boucher & Muir, Austral.*
Imipramine hydrochloride (p.400·3).
Depression.

Melirgan *Coup, Gr.†.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Melisal *Herbapol Wroclaw, Pol.*
Chamomile (p.2279·3); crataegus (p.2289·1); St John's wort (p.422·3); melissa (p.2339·3); tilia (p.2402·2); angelica (p.2258·1); black currant (p.2267·1).
Nervous disorders; sleep disorders.

Melisana Klosterfrau *Klosterfrau, Pol.*
Angelica (p.2258·1); gentian (p.2310·3); melissa (p.2339·3); phaseolus vulgaris; ginger rhizome (p.1732·3); black pepper (p.2364·3); nutmeg (p.2355·2); cinchona (p.2282·3); senna (p.1769·2); cardamom (p.2277·1).
Gastrointestinal disorders; gingivitis; nervous disorders; neuromuscular pain; sleep disorders.

Meliseptol *Braun, Ger.*
Propyl alcohol (p.1660·2); glyoxal (p.1646·1).
Surface disinfection.

Meliseptol Rapid *Braun, Ger.*
Propyl alcohol (p.1660·2); didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Melissa Comp. *Weleda, UK.*
Angelica root (p.2258·1); cinnamon (p.2283·1); melissa leaf (p.2339·3); nutmeg (p.2355·2); lemon oil (p.2332·3); coriander (p.2288·1); clove (p.2284·3).
Diarrhoea; dyspepsia; nausea; stomach pain.

Melissa (Specie Composta) *Dynacren, Ital.†.*
Valerian (p.2410·1); melissa (p.2339·3); lupulus (p.2335·2); peppermint leaf (p.1761·2).

Melissed *Hasco-Lek, Pol.*
Angelica (p.2258·1); chamomile (p.2279·3); crataegus (p.2289·1); St John's wort (p.422·3); melissa (p.2339·3); tilia (p.2402·2); black currant (p.2267·1).
Insomnia; nervous disorders.

Melissengeist
Note. This name is used for preparations of different composition.
Hofmann & Sommer, Ger.
Melissa (p.2339·3); sage (p.2382·3); rosemary (p.2381·2); thyme (p.2401·1); angelica (p.2258·1); nutmeg (p.2355·2); cinnamon (p.2283·1); clove (p.2284·3); lemon oil (p.2332·3); menthol (p.2340·1); citronella oil (p.2284·2); clove oil (p.2285·1); cinnamon oil (p.2283·2).
Gastrointestinal disorders; superficial circulatory disorders.

Weleda, S.Afr.
Angelica (p.2258·1); coriander (p.2288·1); nutmeg (p.2355·2); clove (p.2284·3); cinnamon (p.2283·1); melissa (p.2339·3); citronella oil (p.2284·2).
Circulatory disorders; dizziness; gastrointestinal disorders; headache; influenza symptoms; migraine; muscle pain; neuralgia; toothache.

Melis-Tonic *Herbapol Krakow, Pol.*
Angelica (p.2258·1); caraway (p.2276·3); chamomile (p.2279·3); crataegus (p.2289·1); honey; peppermint leaf (p.1761·2).
Nervous disorders; sleep disorders.

Melitase *Tecnofarma, Chile.*
Levodopa (p.804·3); benserazide (p.796·2).
Parkinsonism.

Melitrast *Kohler, Austria; Kohler, Ger.*
Iosarcol (p.1485·2).
Radiographic contrast medium.

Melival *Boehringer Ingelheim, Spain.*
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia; nervous disorders.

Melix *Lagap, Switz.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Melizid *Leiras, Fin.*
Glipizide (p.441·3).
Diabetes mellitus.

Melizide *Alphapharm, Austral.; Alphapharm, Malaysia; Alphapharm, Singapore; Merck, Singapore; Merck, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Mellaril *Novartis, USA†.*
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Depression with anxiety; hyperactivity in children; psychoses; severe behavioural problems in children.

Melleretten *AWD, Ger.†.*
Thioridazine hydrochloride (p.1031·2).
Anxiety disorders; psychoses.

Mellerettes *Novartis, Switz.†; Novartis, Turk.†.*
Thioridazine hydrochloride (p.1031·2).
Schizophrenia.

Melleril
Novartis, Austral.†; Novartis, Fr.†; AWD, Ger.†; Novartis, Mex.†; Novartis, UK†.
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Agitation; alcohol withdrawal syndrome; anxiety; behaviour disorders; insomnia; mixed anxiety depressive states; psychoses; schizophrenia.

Novartis, Austria†; Novartis, Belg.†; Novartis, Braz.†; Novartis, Denm.†; Novartis, Fin.†; Novartis, Gr.†; Novartis, Hong Kong†; EGIS, Hung.†; Novartis, Indon.; Novartis, Irl.†; Novartis, Ital.†; Novartis, Malaysia†; Novartis, NZ†; Novartis, Neth.†; Novartis, Norw.†; Novartis, Port.†; Novartis, S.Afr.†; Novartis, Switz.†; Novartis, Turk.†.
Thioridazine hydrochloride (p.1031·2).
Agitation; agitation and insomnia in the elderly; alcohol withdrawal syndrome; anxiety; behavioural disorders; depression; mixed anxiety-depressive states; neuroses; psychoses; schizophrenia.

Mellin AD *Mellin, Ital.*
Infant feed (p.1922·1).
Diarrhoea.

Mellin AR *Mellin, Ital.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Mellin HA *Mellin, Ital.*
Infant feed (p.1922·1).
Food intolerance.

Mellin Polilat *Mellin, Ital.†.*
Infant feed (p.1922·1).
Cow's milk intolerance.

Mellinorm *Hemofarm, Rus.*
Pentoxifylline (p.1367·2).

Mellitron *Janssen-Cilag, Mex.*
Metformin (p.453·3); chlorpropamide (p.438·3).
Diabetes mellitus.

Melneurin *Hexal, Ger.*
Melperone hydrochloride (p.1006·2).
Alcoholism; anxiety disorders; psychoses; sleep disorders.

Melobax *Ranbaxy, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melobic *TO-Chemicals, Thai.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melocalm *Kleva, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melocam *YSP, Malaysia.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melock *Santa, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melocox *Eurofarma, Braz.; Galex, Cz.; Verisfield, Gr.*
Meloxicam (p.80·3).
Ankylosing spondylitis; inflammatory disorders; osteoarthritis; rheumatoid arthritis.

Mel-OD *Cadila, India; Cadila, Malaysia.*
Meloxicam (p.80·3).
Ankylosing spondylitis; juvenile arthritis; osteoarthritis; rheumatoid arthritis.

Meloden *Schering, Denm.; Schering, Switz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Melodene *Schering, NZ; Schering, S.Afr.*
21 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Melodene 15 *Schering, Spain.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Melodia *Schering, Fr.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Melodil *Unipharm, Israel.*
Maprotiline hydrochloride (p.407·2).
Depression; mixed anxiety depressive states.

Melodin *Biostam (Βιοσταμ), Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melodol
Note. This name is used for preparations of different composition.
Raffo, Chile.
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders.

Otsira, India.
Meloxicam (p.80·3); paracetamol (p.108·1).
Musculoskeletal and joint disorders.

Melodyn *Gerot, Austria; Gerot, Hung.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melogen *Generics, Hung.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloids *Boots, Thai.*
Liquorice (p.1740·3); menthol (p.2340·1); cinnamon (p.2283·1); capsicum (p.2276·2).
Throat disorders.

Meloka *Lacer, Spain.*
Benfotiamine (p.1975·2); caffeine (p.1116·3); codeine phosphate (p.37·2); paracetamol (p.108·1); propyphenazone (p.119·3).
Fever; pain.

Melokan *Kanonfarma, Rus.*
Meloxicam (p.80·3).

Meloksam *Polfa Grodzisk, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melokssia *Pliva Krakow, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melol *Pharmasant, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; myocardial infarction.

Melonan *Cifarma, Braz.†.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders.

Melonax *Cellofarm, Braz.†; Biofarma, Venez.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Melopat *Medopharm, Ger.†.*
Betahistine mesilate (p.2265·1).
Ménière's syndrome; vestibular disorders.

Meloprol *Energon, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melora *Zynova, Philipp.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders; pain.

Melorilif *Med-One, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Meloset *Aristo, India.*
Melatonin (p.2338·3).
Sleep disorders.

Melosteral *Silanes, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Melotec *EMS, Braz.; AG Therapy, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders; osteoarthritis; rheumatoid arthritis.

Melotop *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melovax *Vivax, Venez.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders.

Melovis *Keri, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melox *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Siam Bheasach, Thai.; Nobel, Turk.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Melox Plus *Aventis, Mex.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Meloxan *Keri, Hung.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxat *Clonmel, Irl.*
Paroxetine mesilate (p.414·2).
Depression; obsessive-compulsive disorder; panic attacks.

Meloxep *Extractum, Hung.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxic *Polpharma, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxid *Klonal, Arg.†.*
Meloxicam (p.80·3).

Meloxigran *Legrand, Braz.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Meloxil *Ativus, Braz.; Biospray, Gr.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

MeloxiLek *Lek, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxin *Interbat, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Meloxistad *Stada, Austria; Stada, Cz.; Steigerwald, Pol.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Meloxitor *Iator, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Melpax *Orion, Fin.*
Melperone hydrochloride (p.1006·2).
Alcohol withdrawal syndrome; anxiety disorders; pain; psychoses.

Melpaz *Profarb, Braz.†.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Melperomerck *Merck dura, Ger.*
Melperone hydrochloride (p.1006·2).
Alcoholism; anxiety disorders; psychoses; sleep disorders.

Melpor *Neves, Port.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Mel-Puren *Alpharma-Isis, Ger.*
Melperone hydrochloride (p.1006·2).
Alcoholism; anxiety disorders; psychoses; sleep disorders.

Melrose *Roberts & Sheppey, UK.*
Hydrous wool fat (p.2033·3); yellow soft paraffin (p.2031·3); hard paraffin (p.2030·3).
Emollient.

Melrosum *Aventis, Neth.*
Honey (p.1948·2).
Coughs.

Melrosum Codein Hustensirup *Nattermann, Ger.†.*
Codeine phosphate (p.37·2).
Coughs and catarrh.

Melrosum Extra Sterk *Aventis, Neth.*
Codeine phosphate (p.37·2); vegetable extracts.
Coughs.

Melrosum Hustensirup *Cassella-med, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh; cough.

Melrosum Medizinalbad *Nattermann, Ger.†.*
Thyme oil (p.2401·2); pine silvestris oil (p.2368·2).
Bath additive; respiratory-tract disorders.

Melsept *Braun, Ger.†; Braun, Ital.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2).
Surface disinfection.

Melsept SF *Braun, Ger.; Braun, Ital.*
Glutaral (p.1645·2); glyoxal (p.1646·1); didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Melsept Spray *Braun, Ital.*
⊗ Alcohol (p.1625·2); glyoxal (p.1646·1).
Disinfection of minor wounds and surfaces.

Melsitt *Braun, Ger.*
Formaldehyde (p.1644·2); glutaral (p.1645·2); didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Melstar *Ipca, India†.*
Meloxicam (p.80·3).
Osteoarthritis.

Meltika *Ikapharmindo, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Meltonar *Teva Tuteur, Arg.*
Megestrol (p.2115·1).
Breast cancer; endometrial cancer.

Meltus Baby *SSL, UK.*
Dilute acetic acid (p.2244·2).
Coughs.

Meltus Decongestant *Cupal, UK.*
Pseudoephedrine hydrochloride (p.1571·2).
Catarrh; sinusitis.

Meltus Dry Cough *SSL, UK.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Meltus Expectorant *SSL, UK.*
Guaifenesin (p.1561·3); cetylpyridinium chloride (p.1635·1); honey (p.1948·2).
Coughs.

Meltus Expectorant with Decongestant *SSL, UK.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal and sinus congestion.

Meltus Honey & Lemon *SSL, UK.*
Guaifenesin (p.1561·3); honey (p.1948·2); glycerol (p.2314·2); terpeneless lemon oil (p.2332·3).
Coughs.

Meltus Junior Expectorant *SSL, UK.*
Guaifenesin (p.1561·3); cetylpyridinium chloride (p.1635·1).
Catarrh; coughs.

Meltus Junior Night Time *SSL, UK.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3).
Cold symptoms; coughs.

Meltus Night Time *SSL, UK.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; coughs.

Melubrin *Solus, India.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Melur *Medika, Switz.*
Mefenamic acid (p.80·1).
Fever; pain.

Melvit *Beta, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Melxi *Hebron, Braz.†.*
Pineapple; honey (p.1948·2).
Respiratory-tract congestion.

Melyd *Stada, Cz.; Stada, Hung.; Steigerwald, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Melzine *Clonmel, Irl.†.*
Thioridazine hydrochloride (p.1031·2).
Agitation; anxiety disorders; childhood behaviour disorders; psychoses; senile confusion; tension.

Memac *Bracco, Ital.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Memax *Labomed, Chile.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Membracel *Celina, Arg.†.*
Collagen (p.2286·1).
Medicated dressing.

MembraneBlue *DORC, Neth.*
Trypan blue (p.2405·2).
Ophthalmic stain.

Memento *Merck, Arg.*
Pipemidic acid (p.315·1).
Skin infections; urinary-tract infections.

Memento NF *Merck, Arg.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Memfit *Boehringer Ingelheim, Belg.*
Ginkgo biloba (p.2311·1).
Mental function disorders.

Memoactive *Euroderm, Ital.†.*
Omega-3 triglycerides (p.1362·1); phospholipids (p.1922·1); ginkgo biloba (p.2311·1).
Mental function disorders.

Memodrin *Lavipharm, Gr.*
⊗ Aniracetam (p.363·2).
Mental function disorders.

Memokit *Ximena Polanco, Chile.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders; mental function impairment; peripheral vascular disorders.

Memoloba *Goldshield, Singapore†.*
Ginkgo biloba (p.2311·1); vitamin C (p.1983·3); iron (p.1949·1); phosphatidyl choline (p.2367·1).
Maintenance of mental function.

Memonol *Utopian, Thai.*
Pyritinol hydrochloride (p.369·1).
Mental function disorders.

Memoplant *Schwabe, Pol.; Schwabe, Rus.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function disorders; vestibular disorders.

Memo-Puren *Alpharma-Isis, Ger.†.*
Piracetam (p.368·2).
Mental function disorders.

Memorandum *Lampugnani, Ital.*
Ginkgo biloba (p.2311·1); guarana (p.2416·1); levocarnitine (p.1932·2).
Mental function disorders.

Memorex Compuesto *Montpellier, Arg.*
Vitamin B substances; amino acids (p.1922·1).
Tonic.

Memorex Vital *Montpellier, Arg.*
Asparagine; glutamine; pyridoxine hydrochloride; phosphoryl serine (p.1922·1).
Tonic.

Memori Plus *Green Leaf, Philipp.*
Centella (p.1592·3); lecithin (p.2332·2); docosahexaenoic acid (p.1362·1).
Mental function impairment; tonic.

Memoria
Note. This name is used for preparations of different composition.
AM, Arg.
Vitamin B substances; amino acids (p.1922·1).
Dietary supplement.
Bittner, Austria; Bittner, Rus.
Homoeopathic preparation.

Memoril
Note. This name is used for preparations of different composition.
Meditop, Hung.
Piracetam (p.368·2).
Mental function disorders.
Recordati, Ital.†.
Glutamine (p.1947·2).
Mental function impairment.

Memorioglutan *Bunker, Braz.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Memoriol B6 *Baldacci, Braz.*
Glutamine; calcium glutamate; ditetraethylammonium phosphate; pyridoxine hydrochloride (p.1922·1).
Nutritional supplement.

Memorisan *Loprofar, Braz.†.*
Phosphoric acid; saw palmetto; turnera aphrodisiaca; calcium phosphate; selenium (p.1922·1).
Tonic.

Memorit *Unipharm, Israel.*
Donepezil (p.365·2).
Alzheimer's disease.

Memorx IQ Plus *Tynor, Philipp.*
Acetylcarnitine; taurine; lysine hydrochloride; vitamins; zinc (p.1922·1).
Mental function aid; tonic.

Memory Booster *Natural Life, Arg.†.*
Glutamine; ribonucleic acid; phenylalanine; choline; kola; lecithin (p.1922·1).
Tonic.

Memory DD *Green Leaf, Philipp.*
Centella (p.1592·3); lecithin (p.2332·2); camellia sinensis (p.2416·1); becopa; gynostemma pentaphyllum.
Anxiety; mental function impairment; stress.

Memory Plus *Life Essence, UK.*
Becopa.
Memory impairment.

Memosprint *Monsanto, Ital.†.*
Pyridoxine phosphoserinate (p.1979·1).
Mental function impairment; tonic.

Memotil *Genepharm, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Memotropil *Polpharma, Pol.; Polpharma, Rus.*
Piracetam (p.368·2).
Alcohol withdrawal syndrome; behavioural disorders in children; cerebrovascular disorders; cranial trauma; dizziness; dyslexia; mental function impairment; myoclonus; stroke; vertigo.

Memovigor *Euro-Pharma, Ital.*
Multivitamin and mineral preparation with phospholipids, acetylcarnitine, myrtillus, and ginkgo biloba (p.1922·1).
Mental function disorders.

Memovisus *Carlo Erba OTC, Ital.†.*
Myrtillus (p.2349·3); cobamamide (p.1980·2); -phosphoserine (p.2367·1); aceglutamide (p.2244·2).
Tonic.

Memovit B12 *Magis, Ital.*
Glutamine (p.1947·2); -phosphoserine (p.2367·1); cyanocobalamin (p.1980·2).
Tonic.

Memovit-E *Health Saver, Philipp.*
Lecithin; royal jelly; ginseng; rutoside; vitamins; amino acids; minerals (p.1922·1).
Nutritional supplement; tonic.

Memox *Unipharm, Israel.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Mempil *General Drugs, Thai.*
Piracetam (p.368·2).
Cerebrovascular disorders; mental function disorders.

Mempotal *Inquifave, Venez.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Memzotil *Pharmasant, Thai.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Men Hormone *TP, Thai.*
⊗ Methyltestosterone (p.2117·1); vitamin E (p.1992·2).
Hypogonadism.

Menabil Complex *Menarini, Spain†.*
Cynara (p.2291·2); boldine (p.2267·3); cyclobutyrol (p.2290·3); methionine phenylbutyrate; rhubarb (p.1768·3); bile salts (p.2266·2); fenipentol sodium hemisuccinate (p.2302·3); belladonna (p.2263·3); cascara (p.1715·2).
Constipation; hepatobiliary disorders.

Menabol *CFL, India.*
⊗ Stanozolol (p.2129·1).
Anabolic; aplastic anaemia; osteoporosis.

Menactra *Aventis Pasteur, USA.*
A meningococcal vaccine (groups A, C, W , and Y) (p.2224·1).
Active immunisation.

Menaderm
Note. This name is used for preparations of different composition.
Menarini, Ital.
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1).
Infected skin disorders.
Galeno, Venez.
Sulfadiazine silver (p.337·2).
Burns.

Menaderm Clio *Menarini, Spain.*
⊗ Beclometasone dipropionate (p.1516·2); clioquinol (p.254·1).
Infected skin disorders.

Menaderm N *Menarini, Arg.*
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Menaderm Neomicina *Menarini, Spain.*
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Menaderm Otologico *Menarini, Spain.*
⊗ Beclometasone dipropionate (p.1516·2); clioquinol (p.254·1).
External ear disorders.

Menaderm Simple *Menarini, Arg.; Menarini, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Menaderm Simplex *Menarini, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Menadion *Medic, Denm.*
Phytomenadione (p.1995·3).
Anticoagulant antidote; vitamin K deficiency.

Menadol *Rugby, USA.*
Ibuprofen (p.64·2).

Menalation *McGloin, Austral.†.*
Menthol (p.2340·1); pumilio pine oil (p.2376·3).
Cold symptoms.

Menalcol *Orravan, Spain.*
⊗ Alcohol (p.1625·2); chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Menalgil B6 *Menarini, Spain.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1) pyridoxine hydrochloride (p.1978·2).

Formerly contained cyanocobalamin, di-isopropylammonium dichloroacetate, monophosphothiamine, and pyridoxine hydrochloride.
Vitamin B deficiency.

Menalmina *Orravan, Spain.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Menamig *Menarini, Switz.*
Frovatriptan succinate (p.622·3).
Migraine.

Menamin *PP Lab, Thai.†*
Prosultiamine (p.1975·3).
Beri-beri; thiamine deficiency.

Mena-Phase Formula *Nutrifarma, Turk.*
Vitamin and mineral preparation (p.1922·1).

Menaril *Guidotti, Gr.*
Ketoprofen (p.73·1).
Inflammatory disorders.

Menarini-Metforal *EciFarma, Chile†.*
Metformin (p.453·3).
Diabetes mellitus.

Menaven *Menarini, Spain.*
Heparin sodium (p.1301·2).
Peripheral vascular disorders.

Menbel *Geolab, Braz.*
Mebendazole (p.148·3).
Worm infections.

Mencalisvit *Retrain, Spain.*
Calcium lactate (p.1676·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Mencevax *GSK, S.Afr.*
A meningococcal vaccine (groups A, C, W , and Y) (p.2224·1).
Active immunisation.

Mencevax AC *SmithKline Beecham, Israel†; GSK, Norw.; GSK, Spain.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Mencevax ACWY *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Fin.; GSK, Ger.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Rus.; GSK, Singapore; GSK, Switz.; GSK, Venez.†.*
A meningococcal polysaccharide vaccine (groups A, C, W and Y) (p.2224·1).
Active immunisation.

Mencirax *Ativus, Braz.*
Cimicifuga (p.2282·1).
Menopausal disorders; menstrual disorders.

Mencogrin
Note. This name is used for preparations of different composition.
Defuen, Arg.
Cream: ⊗ Coal tar (p.1616·2); allantoin (p.1588·1); betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Defuen, Arg.
Shampoo: Salicylic acid (p.1612·2); climbazole (p.529·3) coconut fatty acids; allantoin (p.1588·1).
Scalp disorders.

Defuen, Arg.†.
Topical gel: Salicylic acid (p.1612·2); allantoin (p.1588·1).
Skin disorders.

Defuen, Arg.
Topical solution: ⊗ Coal tar (p.1616·2); salicylic acid (p.1612·2); betamethasone valerate (p.1519·1).
Skin and scalp disorders.

Mencogrin AP *Defuen, Arg.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); cade oil (p.1616·1); allantoin (p.1588·1).
Scalp disorders.

Mencor *Helm, Port.*
Felodipine (p.1285·3).
Angina pectoris.

M-END WC *McNeil, USA.*
Brompheniramine maleate (p.569·2); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Mendatrex *Liptis, USA.*
Valproate semisodium (p.508·2).

Menefloks *Nevzat, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

Menegradil *Fada, Arg.†.*
⊗ Etilefrine (p.1284·1).
Hypotension.

Meneklin *Tum, Turk.*
Clindamycin phosphate (p.251·2).
Bacterial infections.

Menest *Raffo, Arg.†; Monarch, USA.*
Esterified oestrogens (p.2097·1).
Breast cancer; female castration; female hypogonadism; menopausal disorders; primary ovarian failure; prostatic cancer; vulval and vaginal atrophy.

Menflixil *Solara, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Mengivac (A+C) *Aventis Pasteur, Irl.†; Aventis Pasteur, UK†.*
An inactivated meningococcal vaccine (groups A and C polysaccharide) (p.2224·1).
Active immunisation.

Meni-D *Seatrace, USA.*
Meclozine hydrochloride (p.584·3).
Motion sickness; vertigo.

Meniero *Jean-Marie, Hong Kong.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Meniex *Fortbenton, Arg.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Menin *Novell, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Meningitec *Wyeth, Arg.†; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Canad.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hung.; Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, NZ; Wyeth, Norw.; Wyeth Lederle, Port.; Wyeth, Spain; Wyeth Lederle, Swed.†; Lederle, Switz.; Wyeth, UK.*
A meningococcal C conjugate vaccine (diphtheria CRM protein conjugate) (p.2224·1).
Active immunisation.

Meningo A+C *Sanofi Pasteur, Chile.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Meningococcal A+C *Aventis Pasteur, Hong Kong†; Aventis Pasteur, Thai.†.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Meningokokken-Impfstoff A + C *Sanofi Pasteur, Ger.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Meningovax A+C *Aventis Pasteur, Belg.†; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Swed.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Meninvact *Sanofi Pasteur, Fr.; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Ital.; Aventis Pasteur, Neth.; Sanofi Pasteur, Spain†.*
A meningococcal C conjugate vaccine (diphtheria CRM-197 protein conjugate) (p.2224·1).
Active immunisation.

Menisole *Atlantic, Thai.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Menitorix *GSK, UK.*
A haemophilus influenzae and meningococcal C conjugate vaccine (p.2214·1).
Active immunisation.

Menizol *Valmor, Venez.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Menjugate *Elea, Arg.; CSL, Austral.; Sanofi Pasteur, Belg.; Merck Frosst, Canad.; Novartis Vaccines, Cz.; Chiron Vaccines, Ger.; Gerolymatos, Gr.; Chiron, Hung.; Sanofi Pasteur, Irl.; Chiron, Ital.; Chiron, Neth.; Esteve, Port.; Esteve, Spain; Berna, Switz.; Chiron, UK.*
A meningococcal C conjugate vaccine (diphtheria CRM protein conjugate) (p.2224·1).
Active immunisation.

Menobarb *Milano, Thai.*
Phenobarbital sodium (p.492·2).
Epilepsy; insomnia; sedative.

Menocal *Welfide, Malaysia†; Welfide, Singapore†.*
Calcitonin (salmon) (p.1093·1).
Bone pain due to osteolysis; hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone; pancreatitis.

Menocalm *Bunker, Braz.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Menoceane *Thalgo, Fr.*
Calciomer (marine complex containing calcium and iodine); soya extract; colecalciferol (p.1922·1).
Nutritional supplement.

Menocol *Multilab, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Menoconfort *Yves Ponroy, Fr.†.*
Nutritional supplement (p.1922·1).
Menopausal disorders.

Meno-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Menodoron
Note. This name is used for preparations of different composition.
Weleda, Austria; Weleda, S.Afr.
Shepherd's purse (p.2386·2); majorana fructus (p.2337·3); achillea (p.2245·2); oak bark (p.2355·3); urtica (p.2409·3).
Menstrual disorders.

Weleda, UK.
Homoeopathic preparation.

Menofem *Boehringer Ingelheim, Arg.; Bionorica, Cz.; Boehringer Ingelheim, Pol.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Menoflavon *Cedar Health, UK.*
Red clover (p.2285·1).
Menopausal disorders.

Menoflush *Pharmaceutical Enterprises, S.Afr.*
Ethinylestradiol (p.2101·3); multivitamins (p.1922·1).
Menopausal disorders.

Menogon *Ferring, Braz.†; Ferring, Cz.; Ferring, Denm.†; Ferring, Fin.†; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.†; Ferring, Irl.†; Ferring, Israel; Ferring, Ital.; Ferring, Neth.; Ferring, Rus.; Ferring, Singapore; Ferring, Switz.†; Ferring, Thai.; Er-Kim, Turk.; Ferring, UK†.*
⊗ Gonadotrophin (p.2109·3).
Female and male infertility; hypogonadism.

Menograine *Pharmacare, S.Afr.*
Clonidine hydrochloride (p.1247·1).
Menopausal flushing; migraine.

Menoherb *MedicHerb, UK.*
Cimicifuga (p.2282·1).
Menopausal symptoms.

Meno-Implant *Organon, Belg.; Organon, Neth.*
Estradiol (p.2097·2).
Oestrogen deficiency.

Menolia *Sunthi Sepuri, Indon.*
Avena (p.2262·1); saw palmetto (p.2192·3); damiana (p.2292·1); ginseng (p.2312·1); arginine (p.1922·1).
Nutritional supplement.

Menolistica *Holistica, Fr.*
Borage oil; dioscorea; sunflower oil; fucus; fish oil; sea-lettuce; olive oil beeswax; vitamin E (p.1922·1).
Menopausal disorders.

Menoliv *Teuto, Braz.†.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Meno-MPA *Antigen, Israel†.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Menomune *Aventis Pasteur, Austral.; Aventis Pasteur, Austria; Aventis Pasteur, Canad.; Sanofi Pasteur, Fr.; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Ital.; Aventis Pasteur, Malaysia†; MSD, NZ; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Sanofi Pasteur, USA.*
A meningococcal polysaccharide vaccine (groups A, C, W and Y) (p.2224·1).
Active immunisation.

Meno-Net *Antigen, Israel†.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

Menop *Ativus, Braz.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Menopace *Vitabiotics, Cz.; Vitabiotics, Hong Kong; Vitabiotics, Hung.; Nobel, Turk.; Vitabiotics, UK.*
Multivitamin and mineral preparation (p.1922·1).
Menopausal disorders.

Meno-Patch *Hexal, Israel†.*
Estradiol (p.2097·2).
Menopausal disorders.

Menopause *Homeocan, Canad.*
Homoeopathic preparation.

Menopause L122 *Homeocan, Canad.†.*
Homoeopathic preparation.

Menopause Relief *Herbal Concepts, UK.*
Tilia (p.2402·2); motherwort (p.2347·3); pulsatilla (p.2376·3); valerian (p.2410·1).
Menopausal disorders.

Menopause Test *Electramed, Irl.*
Test for raised FSH in urine.

Menopax *Ache, Braz.*
⊗ Cyclofenil (p.2088·1).
Menopausal disorders.

Menophase *Syntex, Cz.†.*
15 Tablets, mestranol (p.2116·2); 13 tablets, mestranol; norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

Menoprem *Wyeth, Austral.†; Wyeth, NZ†.*
Maroon tablets, conjugated oestrogens (Premarin) (p.2087·2); blue tablets, medroxyprogesterone acetate (Provera) (p.2113·1).
Menopausal disorders; osteoporosis.

Menoprin *Cifarma, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Menopur *Ferring, Arg.; Ferring, Austria; Ferring, Belg.; Ferring, Braz.†; Ferring, Chile; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Irl.; Ferring, Israel; Ferring, Malaysia; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Rus.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, UK; Ferring, USA.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Menorest *Novartis, Austral.; Novartis, Austria; Novartis, Braz.†; Aventis, Cz.†; Novartis, Fin.†; Novartis, Fr.; Novartis, Ger.†; Novartis, Gr.; Novartis, Irl.†; Novartis, Ital.; Novartis, Neth.; Novartis, Port.†; Novartis, Spain†; Novartis, Swed.†; Novartis, Switz.†; Novartis, UK†.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Menoring *Galen, UK†.*
Estradiol acetate (p.2097·2).
Menopausal disorders.

Menosan *Bioforce, Switz.*
Homoeopathic preparation.

Menose *Dankos, Indon.*
Cimicifuga (p.2282·1); lactoval; oxitriptan (p.414·1).
Menopausal disorders; osteoporosis.

Menosedan *Haller, Braz.†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Menosedan Ciclo *Haller, Braz.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Menosedan Fase *Haller, Braz.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Menosedan MPA *Haller, Braz.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Menosor *TP, Thai.*
Mebeverine hydrochloride (p.1744·2).
Smooth muscle spasm.

Menostar *Berlex, USA.*
Estradiol (p.2097·2).
Menopausal disorders.

Menostat *Medifarm, Venez.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Menostress *Arrow, Braz.*
Diazepam (p.986·3).
Anxiety.

Menotensil *Solvay, Braz.*
Chlordiazepoxide (p.968·1); conjugated oestrogens (p.2087·2).
Menopausal disorders.

Menotime *Omega, Fr.*
Test for menopause.

Menovis *Teofarma, Ital.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Menstrual disorders.

Menoxa *Soho, Indon.*
Cimicifuga (p.2282·1); calcium (p.1675·2); colecalciferol (p.1986·2).
Menopausal disorders.

Menoxine *Motima, Fr.*
Alchemilla; sage (p.2382·3); achillea (p.2245·2); alfalfa (p.2249·2); avena (p.2262·1).
Menopausal disorders.

Men-Phor *Geritrex, USA.*
Camphor (p.2273·2); menthol (p.2340·1).
Dry skin; pruritus.

Menpirin *Intra, Venez.†.*
Paracetamol (p.108·1).
Pain.

Menpovax A+C *Chiron, Cz.†.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Menpoz *Jean-Marie, Philipp.*
Conjugated oestrogens (p.2087·2).
Dysfunctional uterine bleeding; female hypogonadism; menopausal symptoms; osteoporosis; prostatic cancer.

Mensalgin *Chobet, Arg.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Pain.

Mensana *Darrow, Braz.†.*
Ginkgo biloba (p.2311·1).
Peripheral vascular disorders.

Mensifem *Boehringer Ingelheim, Chile†; Boehringer Ingelheim Promeco, Mex.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Mensipox *Meprofarm, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Mensiso *Menarini, Ital.†.*
Sisomicin sulfate (p.332·1).
Bacterial infections.

Mensoma *Baldacci, Port.*
Famotidine (p.1730·1).
Gastric hypersecretion; peptic ulcer.

Mensoton *Berlin-Chemie, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Menstrogen *Organon, Arg.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Amenorrhoea.

Menstruasan *Bioforce, Switz.*
Homoeopathic preparation.

Menstrunat *Soria Natural, Spain†.*
Artemisia vulgaris; calendula (p.2273·1); greater celandine (p.2317·1); achillea (p.2245·2); sage (p.2382·3).
Menstrual disorders.

Ment Vital *Andromaco, Chile†.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; cerebral trauma; diabetic retinopathy.

Mentacur *Asche, Ger.†.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome.

Mentaden *Inquifave, Venez.†.*
Loperamide (p.1741·3).
Diarrhoea.

Mental Alertness *Homeocan, Canad.*
Homoeopathic preparation.

Mentalgina *Novartis, Mex.*
Cetylpyridinium chloride (p.1635·1); oxybuprocaine hydrochloride (p.1867·3).
Mouth and throat disorders.

Mentalium *Soho, Indon.*
Diazepam (p.986·3).
Anxiety; psychoses.

Mentalol
Note. This name is used for preparations of different composition.
Neckerman, Braz.†.
Menthol (p.2340·1); terpineol (p.2396·1); camphor (p.2273·2); cineole (p.2282·3); niaouli oil (p.2351·3);

turpentine oil (p.2406·3); lavender oil (p.2331·2); cedar oil (p.2400·3).
Musculoskeletal and joint disorders.

Farmo Quimica, Chile.
Menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion; skin irritation.

Mentamida *Kin, Spain.*
Benzydamine hydrochloride (p.27·3); hexetidine (p.1647·1).
Mouth and throat inflammation.

Mentania *Saval, Chile.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Mental function impairment.

Mentar *Hoe, Malaysia.*
Coal tar (p.1616·2); menthol (p.2340·1).
Scalp disorders.

Mentax *Agis, Israel; Kaken, Jpn; Mylan, USA.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Menthacin *Mentholatum, Canad.; Mentholatum, USA.*
Menthol (p.2340·1); capsaicin (p.32·3).
Arthritis.

Menthodex *Bell, UK.*
Ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Mentholatum Balm *Mentholatum, Israel.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); methyl salicylate (p.85·3).
Cold symptoms; nasal congestion.

Mentholatum Balm NF *Mentholatum, S.Afr.*
Camphor (p.2273·2); menthol (p.2340·1).
Upper respiratory-tract disorders.

Mentholatum Cherry Chest Rub *Mentholatum, USA.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Coughs and cold symptoms.

Mentholatum Cherry Ice *Mentholatum, USA.*
SPF 11: Padimate O (p.1609·1); dimethicone (p.2032·1).
Dry lips; sunscreen.

Mentholatum Cough Drops *Mentholatum, Canad.†.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1).

Mentholatum Ibuprofen *Mentholatum, UK.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders.

Mentholatum Inhalador *Hofmann, Chile.*
Camphor (p.2273·2); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); pine oil (p.2368·2).
Upper respiratory-tract congestion.

Mentholatum Kids *Hofmann, Chile.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Skin irritation; upper respiratory-tract congestion.

Mentholatum Natural Ice *Mentholatum, USA.*
SPF 14: Padimate O (p.1609·1); dimethicone (p.2032·1).
Dry lips; sunscreen.

Mentholatum Natural Ice Lip Protectant *Mentholatum, USA.*
Menthol (p.2340·1); camphor (p.2273·2).
Dry lips.

Mentholatum Ointment
Note. This name is used for preparations of different composition.
Mentholatum, Canad.; Hofmann, Chile; Mentholatum, Singapore†.
Camphor (p.2273·2); menthol (p.2340·1).
Cold symptoms; nasal congestion; skin disorders; skin irritation.

Mentholatum, USA.
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Coughs and cold symptoms.

Mentholatum Patch *Hofmann, Chile.*
Menthol (p.2340·1).
Musculoskeletal pain.

Mentholatum Rub *Mentholatum, UK.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); methyl salicylate (p.85·3).
Catarrh; cold symptoms; hay fever; minor skin disorders; musculoskeletal and joint disorders.

Mentholatum Softlips *Mentholatum, USA.*
Dimeticone (p.2032·1).
Dry lips.

Mentholatum Softlips Lipbalm *Mentholatum, USA.*
Dimethicone (p.2032·1); padimate O (p.1609·1).
Dry lips.

Mentholatum Softlips Lipbalm (UV) *Mentholatum, USA.*
Octinoxate (p.1608·2); padimate O (p.1609·1); oxybenzone (p.1608·3); dimethicone (p.2032·1).
Dry lips; sunscreen.

Mentholatum Vapour Rub *Mentholatum, UK.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain; nasal congestion; skin irritation.

Mentholon Original N *Schoning-Berlin, Ger.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Catarrh.

Menthoneurin
Note. This name is used for preparations of different composition.
Altana, Austria.
Liniment: Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Altana, Austria.
Ointment: Glycol salicylate (p.62·3); menthol (p.2340·1).
Headache; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Menthoneurin-Salbe *Altana, Ger.*
Glycol salicylate (p.62·3); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis.

Mentho-Paraffinol *Aflofarm, Pol.; Farmina, Pol.; Gemi, Pol.; Hasco-Lek, Pol.*
Peppermint oil (p.1761·2); liquid paraffin (p.2030·3).
Constipation.

Menthose *Pasteur, Chile.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); pine oil (p.2368·2); methyl salicylate (p.85·3).
Mucous membrane inflammation; musculoskeletal pain; soft-tissue injury.

Menthosept *Polfa Lodz, Pol.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders; oral hygiene.

Menthymin mono *Chauvin ankerpharm, Ger.†.*
Thyme (p.2401·1).
Bronchitis; catarrh.

Menticol *Proula, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Mentidose *Faran, Gr.†.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Mentimol
Note. This name is used for preparations of different composition.
Olgunsoy, Turk.
Ointment: Menthol (p.2340·1); camphor (p.2273·2); cineole (p.2282·3); thymol (p.1664·3).
Musculoskeletal and joint pain.

Olgunsoy, Turk.
Pastilles: Menthol (p.2340·1); vitamin C (p.1983·3); cineole (p.2282·3).
Mouth and throat disorders; musculoskeletal and joint pain.

Mentis *Tecefarma, Spain.*
Pirisudanol maleate (p.2369·2).
Cerebrovascular impairment; senile dementia.

Mentium *Guidotti, Ital.†.*
Pirisudanol maleate (p.2369·2).
Mental function disorders.

Mentix *Royal, Chile.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome.

Mentobalsam *Farmo Quimica, Chile.*
Methyl salicylate (p.85·3); methyl nicotinate (p.85·3); a macrogol lauril ether (p.1916·1); menthol (p.2340·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal and joint disorders; soft-tissue disorders.

Mentobox *Serra Pamies, Spain.*
Camphor (p.2273·2); Cedrus deodora oil; cineole (p.2282·3); methyl salicylate (p.85·3); thymol (p.1664·3); turpentine; menthol (p.2340·1).
Upper respiratory-tract disorders.

Mentocaina R *Azevedos, Port.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Ment-O-Cap *Rekah, Israel.*
Turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); pine oil (p.2368·2); capsicum (p.2276·2); methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Cold symptoms; musculoskeletal and joint disorders.

Mentodrin *Ibefar, Braz.†.*
⊗ Diphenhydramine hydrochloride (p.577·2); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Mentolin
Note. This name is used for preparations of different composition.
Mento, Turk.
Inhalation; ointment: Menthol (p.2340·1); camphor (p.2273·2); cineole (p.2282·3); thymol (p.1664·3).
Musculoskeletal and joint pain; respiratory-tract disorders.

Mento, Turk.
Pastilles: Menthol (p.2340·1); cineole (p.2282·3); thymol (p.1664·3); capsicum (p.2276·2).
Mouth and throat disorders.

Mentopas *Sin Sin, Philipp.*
Menthol (p.2340·1); methyl salicylate (p.85·3); camphor (p.2273·2); thymol (p.1664·3); borneol (p.2268·3); zinc oxide (p.1621·2).
Musculoskeletal and joint pain.

Mentopin
Note. This name is used for preparations of different composition.
Brady, Austria.
Lavender flower (p.2331·1); sage (p.2382·3); peppermint leaf (p.1761·2); paprika (p.2276·2); urtica (p.2409·3); pine; camphor (p.2273·2); menthol (p.2340·1); pumilio pine oil (p.2376·3); peppermint oil (p.1761·2).
Musculoskeletal and joint disorders; neuralgia.

Vitamed, Turk.
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory disorders with increased mucus.

Mentopin Nasenspray *Hermes, Ger.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; sinusitis.

Mentoseptol *Drogsan, Turk.*
Menthol (p.2340·1); cineole (p.2282·3); peppermint oil (p.1761·2); thyme oil (p.2401·2).
Oral hygiene.

Mentowal *Polpharma, Pol.*
Menthyl isovalerate.
Gastrointestinal disorders; migraine; vertigo.

Mentozil *Ibefar, Braz.†.*
Tyrothricin (p.358·2); sulfathiazole (p.343·2); chlorophyll (p.1471·1); menthol (p.2340·1); benzocaine (p.1854·1).

MeNZB *Medconsult, NZ.*
A meningococcal B (outer membrane vesicle) vaccine (p.2224·1).
Active immunisation.

Menzza *Hoe, Malaysia.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Menzza Ice *Hoe, Malaysia.*
Menthol (p.2340·1).
Musculoskeletal pain.

Meocil *Edol, Port.*
⊗ Prednisolone acetate (p.1541·1); neomycin sulfate (p.305·1); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Meomel *Rafarm, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

282 Mep *Lioh, Canad.†.*
Aspirin (p.20·3); caffeine citrate (p.1116·3); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Anxiety; pain; skeletal muscle spasm.

Mepa *Mega Lifesciences, Malaysia.*
Fish oil (p.1362·2).
Dietary supplement.

Mepadol *Akdeniz, Turk.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle spasm.

Mepagyl *TNP, Thai.†.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; trichomoniasis.

Mepalax *ABC, Ital.*
Boldo (p.2267·2); rhubarb (p.1768·3); cascara (p.1715·2).
Constipation.

Mepastat *Orion, Fin.*
Medroxyprogesterone acetate (p.2113·1).
Malignant neoplasms.

Mepebrox *Medica Pedia, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Meperol *LKM, Arg.*
⊗ Pethidine (p.115·1).
Pain.

Mepha B-1000 *Mepha, Israel.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Mephadolor *Mepha, Switz.*
Mefenamic acid (p.80·1).
Fever; pain.

Mephamesone *Mepha, Switz.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Mephanol *Mepha, Hong Kong†; Mepha, Switz.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Mephaquin *Mepha, Braz.; Mepha, Cz.†; Mepha, Hong Kong; Mepha, Israel; Mepha, Malaysia; Mepha, Port.; Mepha, Singapore; Mepha, Thai.†.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Mephaquine *Mepha, Switz.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Mepharis *Mepha, Pol.*
Risperidone (p.1024·2).
Schizophrenia.

Mephathiol *Mepha, Switz.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased mucus.

Mephenon *Denolin, Belg.*
⊗ Methadone hydrochloride (p.82·3).
Pain.

Mephentine *Wyeth, India.*
⊗ Mephentermine sulfate (p.1332·3).
Shock.

Mephyton *Aton, USA.*
Phytomenadione (p.1995·3).
Coagulation disorders due to faulty formation of factors II, VII, IX, and X.

Mepibil *Mayne, Ital.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mepicain *Monico, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepicaton *Weimer, Thai.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mepident *Cosmo, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Mepiforan *Baxter, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepiform *Molnlycke, Ger.; Molnlycke, Ital.; Molnlycke, UK.*
Silicone (p.2032·1).
Hypertrophic and keloid scars.

Mepigobbi *Gobbi, Arg.*
Mepivacaine (p.1867·1).
Local anaesthesia.

Mepihexal *Hexal, Ger.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mepilex *Molnlycke, Ger.*
Silicone (p.2032·1).
Ulcers; wounds.

Mepi-Mynol *Curaden, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepinaest *Gebro, Austria.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mepirid *Vocate, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Mepisolver *AltaSelect, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Mepitel *Molnlycke, Ger.; Molnlycke, Ital.*
Silicone (p.2032·1).
Burns; ulcers; wounds.

Mepivamol *Molteni, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthetic.

Mepivastesin *Espe, Cz.; 3M Espe, Ger.; 3M, Hong Kong; Machado Malcher, Port.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Mepivirgi *Keryos, Ital.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthetic.

Meplar *Baliarda, Arg.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Mepotin *Mepha, Braz.†.*
⊗ Epoetin (p.1061·1).
Anaemias.

Mepracid *Nabiqasim, Philipp.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mepral *Bracco, Ital.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mepramida *Roemmers Rowe, Venez.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Mepramide *Pyridam, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Meprate *Serum Institute, India.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menstrual disorders.

Mepraz *Baldacci, Port.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Meprazan *Cazi, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Meprazol *Sandoz, Austral.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mepril *Kwizda, Austria.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Meprilon *Mugi, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Meprizina *Pisa, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Mepro *Rekah, Israel.*
Meprobamate (p.1006·2).
Anxiety; insomnia.

Meprodil *Streuli, Switz.*
Meprobamate (p.1006·2).
Anxiety; muscle relaxant; sedative.

Meprofen *AGIPS, Ital.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Meprogesic *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Pain and associated tension.

Meprogest *Infosint, Ital.†.*
Megestrol acetate (p.2114·3).
Breast cancer; endometrial cancer.

Meprolen *Vocate, Gr.*
Omeprazole (p.1753·1).

Meprolol *TAD, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Meprolol Comp *TAD, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Mepromaag *Meprofarm, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; gastritis; gastrointestinal motility disorders; peptic ulcer.

Mepromol
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Adcock Ingram, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Mepron *GSK, Canad.; Glaxo Wellcome, USA.*
Atovaquone (p.829·2).
Pneumocystis pneumonia.

Mepronet *Nycomed, Denm.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Mepronizine *Sanofi-Aventis, Fr.*
Meprobamate (p.1006·2); aceprometazine maleate (p.959·3).
Insomnia.

Meprosetil *Meprofarm, Indon.*
Chlorpromazine hydrochloride (p.969·2).
Convulsions; epilepsy; neuralgia; premedication; pruritus; psychoses; spasmalgia; vomiting.

Meproson *Meprofarm, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Meprosona-F *Sons, Mex.*
⊗ Prednisone (p.1542·3); phenylbutazone (p.117·1).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Meprotrin *Meprofarm, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Meprox *Galeno, Venez.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Meptid *Riemser, Ger.; Shire, Irl.; Monmouth, UK.*
Meptazinol hydrochloride (p.81·3).
Pain.

Meptidol *Wyeth Lederle, Austria†.*
Meptazinol hydrochloride (p.81·3).
Pain.

Meptin *Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Malaysia; Otsuka, Philipp.; Otsuka, Singapore; Otsuka, Thai.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Mepyraderm *Be-Tabs, S.Afr.*
Mepyramine maleate (p.585·2).
Allergic and pruritic skin disorders.

Mepyrimal *Adcock Ingram, S.Afr.*
Mepyramine maleate (p.585·2).
Hypersensitivity reactions.

Mequin *Atlantic, Thai.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Merabin *Daewoo, Thai.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Meracilina *Ache, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Meracote *Sigma, Austral.†.*
Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux; heartburn.

Meralop *Thea, Ital.†; Thea, Spain†.*
Keracyanin (p.2329·1).
Capillary fragility; disorders of vision.

Meralut *Farmila, Ital.*
Vitamin A; anthocyanosides; lutein; zeaxanthin (p.1922·1).
Nutritional supplement.

Meramide *Hua, Thai.†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting; peptic ulcer.

Meramyl *Keri, Hung.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction.

Meramyl HCT *Actavis, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Merankol Pastiglie *Bruno, Ital.*
Dicycloverine hydrochloride (p.1722·3); methylcellulose; sodium laurilsulfate; magnesium hydroxide (p.1743·2); dried aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders.

Meranol *Vargas, Venez.†.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Merapiran *Finadiet, Arg.†.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders.

Merapril *CT, Ital.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Merapur HP *Ferring, Mex.*
⊗ Menotrophin (p.2109·3).
Female infertility.

Merasyn *Adcock Ingram, S.Afr.*
Aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2); methylcellulose (p.2145·1).
Flatulence; hyperchlorhydria.

Merbenloc *Maigal, Arg.*
Sulfur (p.1614·1).
Acne; seborrhoea.

Merbentyl *Sigma, Austral.†; Aventis, Irl.†; Sigma, NZ†; Adcock Ingram, S.Afr.; Florizel, UK.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm.

Merbromin *Biospray, Gr.; Mediplants, Gr.*
Merbromin (p.1652·1).
Antiseptic.

Mercalm *Pfizer Sante, Fr.*
Caffeine (p.1116·3); dimenhydrinate (p.576·2).
Motion sickness.

Mercaptizol *Taro, Israel.*
Thiamazole (p.2176·3).
Hyperthyroidism; toxic adenoma.

Mercaptyl *Abbott, Switz.*
Penicillamine (p.1456·2).
Biliary cirrhosis; cystinuria; heavy-metal poisoning; pulmonary fibrosis; rheumatoid arthritis; scleroderma; Wilson's disease.

Mercazolil *Akrikhin, Rus.*
Thiamazole (p.2176·3).

Merced *Menarini, Belg.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Mercilon *Organon, Arg.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Organon, NZ; Organon, Neth.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Donmed, S.Afr.; Organon, Singapore; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, UK; Organon, Venez.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Mercilon Conti *Organon, Braz.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 5 tablets, ethinylestradiol; 2 inert tablets.
Combined oral contraceptive.

Mercina *Mepro, Chile.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Mercindol *Sanofi-Aventis, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); doxylamine succinate (p.578·2); codeine phosphate (p.37·2).
Fever; pain.

Merckazitro *Merck, Neth.*
Azithromycin ethanolate (p.207·3).
Bacterial infections.

Merck-Co-Bisoprolol *Merck, Belg.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Merck-Co-Lisinopril *Merck, Belg.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Merck-Cough Linctus *Merck, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Merckelisa *Merck, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

Merckenzyme *Merck, India.*
Bromelains (p.2269·1); pancreatin (p.2360·1); ox bile (p.2266·3).
Pancreatic insufficiency.

Merck-Expectorant *Merck, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Merck-Fed *Merck, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Merck-Flu
Note. This name is used for preparations of different composition.
Merck, S.Afr.
Capsules: Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Merck, S.Afr.
Syrup: Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Merckformin *Merck, Hung.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Merck-Gesic *Xixia, S.Afr.†.*
Paracetamol (p.108·1).
Fever; pain.

Merck-P Nasal *Merck, S.Afr.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Adjunct in middle ear infections; nasal congestion.

Merckprareduct *Sankyo, Belg.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Merckrhinobudesonide *Merck, Belg.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Mercol *Pharmacos, Mex.*
Policosanol (p.1373·3).
Hypercholesterolaemia.

Mercotin *Eisai, Indon.*
Noscapine (p.1566·2).
Cough.

Mercromina *Lainco, Spain.*
Merbromin (p.1652·1).
Wound disinfection.

Mercrotona *Orravan, Spain.*
⊗ Merbromin sodium (p.1652·1); alcohol (p.1625·2).
Wound disinfection.

Mercryl *Menarini, Fr.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Bacterial infections of the skin and mucous membranes.

Mercryl Plus *Sanofi-Aventis, Spain.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Burns; skin disinfection; wounds.

Mercrylsoins *NHS, Fr.*
Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Skin cleansing and disinfection.

Mercuchrom *Krewel, Ger.†.*
Merbromin (p.1652·1).
Burns; skin disinfection; skin ulceration; wounds.

Mercuchrom-Jod *Krewel, Ger.*
Povidone-iodine (p.1659·2).
Burns; infected skin disorders; ulcers; wounds.

Mercur Sol Complexe no 39 *Lehning, Fr.†.*
Homoeopathic preparation.
Formerly known as Complexe no 39.

Mercurin *Monik, Spain.*
Merbromin sodium (p.1652·1).
Wound disinfection.

Mercurio Cromo *Phos-Kola, Braz.†.*
Merbromin (p.1652·1).
Skin disinfection.

Mercurobromo *Spyfarma, Spain.*
Merbromin (p.1652·1).
Wound disinfection.

Mercurochrome *Zarbi (Ζαρμπη), Gr.*
Merbromin (p.1652·1).
Antiseptic.

Mercutina Brota *Escaned, Spain.*
Merbromin (p.1652·1).
Wound disinfection.

Mercuval *Biosyn, Ger.*
Unithiol (p.1468·1).
Lead poisoning; mercury poisoning.

Merebral *Altana, Arg.*
Amino acids; cyanocobalamin; ginseng (p.1922·1).
Mental function impairment.

Mereprine
Note. This name is used for preparations of different composition.
Cassella-med, Ger.
Doxylamine succinate (p.578·2).
Allergic disorders; restlessness and excitement in children; sleep disorders.

Inibsa, Port.†.
Captopril (p.1239·2).
Heart failure; hypertension.

Meresa *Sanova, Austria; Dolorgiet, Ger.; Adeka, Turk.*
Sulpiride (p.1028·3).
Depression; Ménière's disease; psychoses; schizophrenia; vestibular disorders.

Meretek UBT *Meretek, USA.*
⊗ Carbon-13 (p.2277·1) labelled urea (Pranactin).
Diagnosis of Helicobacter pylori infection.

Merex *Tentan, Switz.†.*
Phenylpropanolamine hydrochloride (p.1569·3).
Obesity.

Merfen
Novartis Consumer, Israel.
Chlorhexidine gluconate (p.1635·3); benzoxonium chloride (p.1631·2).
Formerly known as Merphen.
Burns; insect bites; wounds.

Novartis Consumer, Switz.
Chlorhexidine gluconate (p.1635·3) or chlorhexidine hydrochloride (p.1635·3); benzoxonium chloride (p.1631·2).
Burns; skin disinfection; wounds.

Merflam *Mersifarma, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Mergexin *Mergers Drugfil, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Mergot *Solvang, Philipp.*
Methylergometrine maleate (p.2011·1).
Postpartum atony; postpartum haemorrhage.

Mergotrex *Rotexmedica, Philipp.*
Methylergometrine maleate (p.2011·1).
Postpartum atony; postpartum haemorrhage.

Mericomb *Novartis, Austria; Novartis, Braz.; Novartis, Fin.; Novartis, Ger.; Pierre Fabre, Ger.; Novartis, Switz.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; norethisterone (p.2119·3).
Hormone replacement therapy; menopausal disorders; osteoporosis.

Meridia *Abbott, Austria; Abbott, Canad.; Abbott, Cz.; Abbott, Pol.; Abbott, Rus.; Abbott, USA.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Meridian *Roemmers, Arg.*
Escitalopram oxalate (p.391·1).
Depression.

Meridol *GABA, Fr.†; Teva, Israel.*
Olaflur (p.1959·2); stannous fluoride (p.1967·3).
Dental caries prophylaxis; gingivitis; plaque prophylaxis.

Meriestra *Novartis, Spain.*
Estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

Merigest *Novartis, Austria; Novartis, Braz.; Novartis, Fin.; Novartis, Ger.; Pierre Fabre, Ger.; Novartis, Spain; Novartis, Switz.*
Estradiol valerate (p.2097·3); norethisterone (p.2119·3).
Hormone replacement therapy; menopausal disorders; osteoporosis.

Merigest Sequi *Novartis, Spain.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; norethisterone (p.2119·3).
Formerly known as Merigest Combi.
Menopausal disorders.

Merimac *Mersifarma, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Merimono *Novartis, Austria; Novartis, Braz.; Novartis, Fin.; Novartis, Ger.; Pierre Fabre, Ger.*
Estradiol valerate (p.2097·3).
Hormone replacement therapy; menopausal disorders.

Merional *IBSA, Cz.; Faran, Gr.; IBSA, Hong Kong; IBSA, Hung.; CORNE, Mex.; IBSA, Switz.; Pharmasure, UK.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Merional-HMG *BPL-Meizler, Braz.†.*
⊗ Gonadotrophin (p.2109·3).
Female infertility.

Merislon *Eisai, Hong Kong; Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo; vestibular disorders.

Meristin
Note. This name is used for preparations of different composition.
Extractum, Hung.†.
Suppositories: Atropine methonitrate (p.1219·3); codeine (p.37·2); phenobarbital (p.492·2); papaverine (p.2191·3); aminophenazone (p.19·1).
Smooth muscle spasm and pain.

Valeant, Hung.
Tablets: Phenobarbital (p.492·2); papaverine hydrochloride (p.2191·3); aminophenazone (p.19·1).
Smooth muscle spasm and pain.

Merital *Roemmers, Arg.*
Memantine (p.367·2).
Alzheimer's disease; spasticity.

Meritene *Novartis, Arg.†; Novartis, Braz.; Novartis Nutrition, Cz.†; Novartis Consumer, Port.†; Novartis Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).

Merlin *TO-Chemicals, Thai.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Merlit
Note. This name is used for preparations of different composition.
Ebewe, Austria.
Lorazepam (p.1004·1).
Anxiety disorders; sleep disorders.

Leovan, Gr.
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Merlopam *Mersifarma, Indon.*
Lorazepam (p.1004·1).
Anxiety.

Mermelax *Argenfarma, Arg.*
Prune (p.1765·1); ispaghula (p.1737·1); garcinia cambogia (p.2309·2).
Constipation.

Mermid *Merck, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Merocaine *SSL, Irl.; SSL, UK.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Adjunct in dental procedures; mouth and throat disorders.

Merocets *SSL, Irl.; SSL, UK.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Merocets Plus *SSL, UK.*
Cetylpyridinium chloride (p.1635·1); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Formerly known as Merothol.
Nasal congestion; sore mouth and throat.

Meroefectil *Northia, Arg.*
Meropenem (p.297·2).
Bacterial infections.

Merofen *Kalbe, Indon.*
Meropenem (p.297·2).
Bacterial infections.

Meroken New *Taro, Israel.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Meromycin
Ratiopharm, Austria.
Erythromycin (p.269·2).
Acne.

Merckle, Cz.†.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Ratiopharm, Hung.
Erythromycin (p.269·2) or erythromycin stearate (p.270·1).
Bacterial infections.

Meronem *AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; Nova, Port.; Sumitomo, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Venez.*
Meropenem (p.297·2).
Bacterial infections.

Meropen *Sumitomo, Jpn.*
Meropenem (p.297·2).
Bacterial infections.

Meropur *Ferring, Ital.*
⊗ Menotrophin (p.2109·3).
Female infertility.

Merotenk *Biotenk, Arg.*
Meropenem (p.297·2).
Bacterial infections.

Meroxan *Merck, Mex.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Meroxil *Haller, Braz.†.*
Meropenem (p.297·2).
Bacterial infections.

Merozen *AstraZeneca, Arg.*
Meropenem (p.297·2).
Bacterial infections.

Merpal *Prater, Chile.*
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Inflammation; pain.

Merpem *Richmond, Arg.*
Meropenem (p.297·2).
Bacterial infections.

Merrem *AstraZeneca, Austral.; AstraZeneca, Canad.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, NZ; Zeneca, USA.*
Meropenem (p.297·2).
Bacterial infections.

Merron *Mersifarma, Indon.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Mersibion *Mersifarma, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1922·1).
Neuritis; vitamin deficiency.

Mersidryl *Mersifarma, Indon.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough; nasal congestion; rhinitis.

Mersikol *Mersifarma, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Mersitropil *Mersifarma, Indon.*
Piracetam (p.368·2).
Alcoholism; behaviour disorders in children; cerebral trauma; mental function impairment.

Mersivas *Mersifarma, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

MerSol *Ratiopharm, Ger.†.*
Nicotinamide (p.1957·3); folic acid (p.1940·1).
Photosensitivity.

Mersol
Note. This name is used for preparations of different composition.
Merkez, Turk.
Merbromin (p.1652·1).
Minor cuts and abrasion.

Century, USA.
Thiomersal (p.1663·3).
Skin disinfection.

Mersyndol *Sanofi-Aventis, Austral.; Sanofi-Aventis, NZ.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Fever; pain; pain with tension.

Mersyndol with Codeine *Aventis, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Cold symptoms; pain.

Mersyndol Daystrength *Sanofi-Aventis, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Mertan *Sigmapharm, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Merthiolate
Note. This name is used for preparations of different composition.
Gramon, Arg.; Lilly, Arg.; Aspen Consumer, S.Afr.; Lilly, Thai.†; Vargas, Venez.
Thiomersal (p.1663·3).
Skin disinfection; wounds.

DM, Braz.†.
Chlorhexidine (p.1635·2).
Skin disinfection.

Lilly, Mex.†.
Benzalkonium chloride (p.1629·1).

Merthiolate Iodopovidona *Gramon, Arg.*
Povidone-iodine (p.1659·2); nonoxinol 9 (p.1917·2).
Burns; skin and mucous membrane disinfection; wounds.

Merthiolate NF *Gramon, Arg.*
Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3).
Skin disinfection; wounds.

Mertigo *Dexa, Indon.*
Betahistine mesilate (p.2265·1).
Ménière's disease.

Mertioscan *Rotop, Port.*
Technetium-99m (p.2055·3) mertiatide.
Diagnosis of urinary-tract disorders.

Meruvax *Aventis Pasteur, Denm.†; Aventis Pasteur, Swed.†; Sanofi Pasteur, Switz.*
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Meruvax II *CSL, Austral.; Merck, USA.*
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Merxil *Merck, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Merz Dragees Speciales *Merz, Switz.*
Multivitamin and mineral preparation with dried yeast (p.1922·1).
Skin, hair, and nail disorders.

Merz Spezial
Medra, Austria.
Multivitamin and mineral preparation (p.1922·1).

Merz, Cz.
Vitamins; dried yeast, cystine, ferrous fumarate (p.1922·1).

Merz, Hong Kong
Vitamin; iron, yeast, cystine (p.1922·1).

Merz, Pol.
Iron, cystine, vitamins (p.1922·1).
Skin, hair, and nail disorders.

Merz Spezial Dragees *Merz, Rus.*
Vitamins; ferrous fumarate; yeast extract; cystine (p.1922·1).

Merz Spezial Dragees N *Merz Consumer, Ger.*
Multivitamin preparation with iron and acetylmethionine (p.1922·1).

Merzbiotin *Medra, Austria.*
Biotin (p.1931·3).
Biotin deficiency; hair and nail disorders.

Merzin *Keri, Hung.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Me-Sabona *Sabona, Ger.*
Melissa (p.2339·3).
Gastrointestinal disorders; sleep disorders.

Me-Sabona plus *Sabona, Ger.†.*
Melissa (p.2339·3); St John's wort (p.422·3).
Nervous disorders; sleep disorders.

Mesacol *Nycomed, Braz.; Sun, India; Sun, Rus.; Sun, Thai.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Mesactol *Sandoz, Arg.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Mesaflor *SoSe, Ital.*
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Mesagin *Kleva, Gr.†.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Mesalt *Molnlycke, Canad.*
Sodium chloride (p.1686·1).
Wounds.

Mesasal *GSK, Austral.; GSK, Canad.; Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Norw.; Pharmacare, S.Afr.; Sanofi Synthelabo, Swed.*
Mesalazine (p.1745·1).
Inflammatory bowel disease; ulcerative colitis; ulcerative proctitis.

Mesatil *Soria Natural, Spain†.*
Melissa (p.2339·3); salix (p.121·3); tilia (p.2402·2); rosemary (p.2381·2).
Migraine.

Mesazine *Vifor, Switz.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Mescolor *Horizon, USA†.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

Mesconcept *Northia, Arg.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Mescorit *Roche, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Mesickovy *Megafyt-R, Cz.*
Calendula (p.2273·1).
Biliary-tract disorders; gastrointestinal disorders; inflammation of the skin and mucous membranes.

Mesigyna *Schering, Arg.; Schering, Braz.; Schering, Chile; Schering, Mex.; Schering, Turk.; Schering, Venez.*
Norethisterone enantate (p.2120·1); estradiol valerate (p.2097·3).
Combined injectable contraceptive.

Mesiken *Kener, Mex.*
Bromocriptine (p.800·3).

Mesin *Unison, Thai.*
Albendazole (p.139·2).
Worm infections.

Mesine *Pinewood, Irl.†*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Mesitran *Medlock Medical, UK.*
Purified honey (p.1948·2).
Burns; ulcers; wounds.

M-Eslon *Aventis, Canad.; Grunenthal, Chile; Ethypharm, Cz.; Ethypharm, Hong Kong; EGIS, Hung.; Multichem, NZ; Nobel, Turk.*
⊗ Morphine sulfate (p.86·3).
Pain.

Mesmerin *Sigma, Braz.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; nausea and vomiting; premedication.

Mesmor *Rafarm, Gr.*
Itraconazole (p.536·3).

Mesnex *Kampel Martian, Arg.†; BMS Oncology, USA.*
Mesna (p.1449·2).
Prevention of oxazaphosphorine-induced urinary-tract toxicity.

Mesnil *Asofarma, Mex.*
Mesna (p.1449·2).
Prevention of urotoxicity due to antineoplastic therapy.

Mesocain
Note. A similar name is used for preparations of different composition (see below).
Zentiva, Cz.
Injection: Trimecaine hydrochloride (p.1872·3).
Arrhythmias; local anaesthesia.

Zentiva, Cz.
Topical gel: Trimecaine hydrochloride (p.1872·3); carbaethopendecinium bromide (p.1633·3).
Aid in urological examination; catheterisation.

Mesocaine
Note. A similar name is used for preparations of different composition (see above).
Pharmy, Fr.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Mesodal *Probiomed, Mex.*
Mesna (p.1449·2).
Prevention of ifosfamide- and cyclophosphamide-induced haemorrhagic cystitis.

Mesofol *Biomet, Ger.*
Lactid-caprolactone copolymer.
Postoperative adhesions.

Mesol *Gracia, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Mesolex *Shiwa, Thai.†.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Mesolona *Laboratorios Chile, Chile†.*
Chlormezanone (p.968·3); diazepam (p.986·3).
Anxiety; insomnia; skeletal muscle spasm.

Mesone *Pharmacore, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Mesonex *Adelco, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Mesonta *Galenium, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Mesopran *Royton, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Mesorfan *Collins, Mex.*
Pseudoephedrine (p.1571·2); chlorphenamine (p.572·2); dextromethorphan (p.1555·2).
Respiratory-tract congestion.

Mesotina *Rivero, Arg.*
Papaverine hydrochloride (p.2191·3).
Vascular spasm.

Mespafin *Merckle, Ger.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Mesporan *Mepha, Braz.*
Ceftriaxone (p.238·1).
Bacterial infections.

Mesporin *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Port.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Mesren *Ivax, UK.*
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Messeldazol *Biomep, Mex.*
Metronidazole (p.837·1).

Messelfenil *Biomep, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Messelxen *Biomep, Mex.*
Naproxen (p.92·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Messelzol *Biomep, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Mestacine *Tonipharm, Fr.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Mestamox *Metiska, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mestian *LKM, Arg.*
Mesna (p.1449·2).

Mestil-Ka *Fada, Arg.*
Menadione (p.1995·2).
Vitamin K supplement.

Mestinon *Valeant, Arg.; Valeant, Austral.; ICN, Austria; Pharma Logistics, Belg.; Valeant, Braz.; Valeant, Canad.; Raffo, Chile; Valeant, Cz.; ICN, Denm.; ICN, Fin.; CSP, Fr.; Valeant, Ger.; IFET (ΙΦΕΤ), Gr.; Lapapharm (Λαπαφαρμ), Gr.; Valeant, Hong Kong; ICN, Hung.; Combiphar, Indon.; Valeant, Indon.; Valeant, Irl.; ICN, Israel; ICN, Ital.; ICN, Malaysia; Valeant, Mex.; Pacific, NZ; Pacific, NZ; ICN, Neth.; ICN, Norw.; Valeant, Philipp.; ICN, Pol.; Codifar, Port.; Pharmaco, S.Afr.; Valeant, Singapore; Valeant, Spain; Medilink, Swed.; Valeant, Switz.; ICN, Thai.; Onko, Turk.; ICN, UK; ICN, USA; Farma, Venez.*
Pyridostigmine bromide (p.633·3).
Atonic constipation; gastrointestinal motility disorders; headache; ileus; meteorism; myasthenia gravis; paraesthesias; postoperative urinary retention; reversal of competitive neuromuscular blockade; tachycardia.

Mesto-Of *Pond's, Thai.*
Amylase (p.2256·3); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); thiamine nitrate (p.1976·2); menthol (p.2340·1); ginger oil (p.1732·3); anise oil (p.2258·2); cinnamon oil (p.2283·2); clove oil (p.2285·1); scopolia.
Dyspepsia; gastritis; gastrointestinal motility disorders; heartburn; hyperacidity.

Mestoranum *Schering, Denm.†.*
⊗ Mesterolone (p.2116·1).
Breast cancer; hypogonadism; metrorrhagia.

Mestral *Meyer Alian, Venez.*
Ibuprofen (p.64·2).
Pain.

Mestrel *Laboratorios Chile, Chile†; Lemery, Mex.; Lemery, Thai.*
Megestrol acetate (p.2114·3).
Breast cancer; endometrial cancer.

Mestrolin *Darya-Varia, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Mesulid
CSC, Austria; Therabel, Belg.; CSC, Cz.; Boehringer Ingelheim, Gr.; Helsinn, Hong Kong; Schering-Plough, Hong Kong; Sanofi-Aventis,

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Hung.; Stadmed, India; Ergha, Irl.†; Rafa, Israel; Roche, Mex.; Schering-Plough, Philipp.; Pfizer, Turk.
Nimesulide (p.95·3).
Cold and influenza symptoms; fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Novartis, Ital.
Nimesulide (p.95·3) or nimesulide betadex (p.95·3).
Fever; inflammation; joint disorders; pain.

Mesupon *Remek, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Mesura *Andromaco, Chile.*
⊗ Sibutramine (p.2164·1).
Obesity.

Met *Betapharm, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Meta *Millimed, Thai.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

metabiarex *Meta Fackler, Ger.*
Homoeopathic preparation.

Metabol *Jagson, India.*
⊗ Nandrolone phenylpropionate (p.2118·3).
Adjuvant to steroid therapy; debility; osteoporosis; uraemia.

Metabolic *Framingham, Arg.*
Carnitine (p.1932·2); chromium tripicolinate (p.1934·3); garcinia cambogia (p.2309·2).
Obesity.

Metabolic Mineral Mixture *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Nutricia, NZ; Scientific Hospital Supplies, UK.*
Mineral and trace element preparation (p.1922·1).
Mineral supplementation for enteral diets.

Metabolite-A *Forder, Arg.†.*
Retinol (p.1971·2).
Skin disorders.

Metabol-Mg *Pentafarma, Port.*
Magnesium aspartate (p.1679·1).

Metacaf *Chong Kun Dang, Ital.†.*
Cefmetazole sodium (p.225·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Metacard *Ipca, India.*
Trimetazidine hydrochloride (p.1419·2).
Ischaemic heart disease.

Metacen *Promedica, Ital.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Metacidil *Teuto, Braz.†.*
Indometacin (p.66·3).

Metacuprol *Lemoine, Fr.*
Copper sulfate (p.1935·3).
Skin and mucous membrane infections.

Metadate *Celltech, Israel; UCB, USA.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Metadec *Jagson, India.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic; anaemia; osteoporosis.

Metadol *Pharmascience, Canad.*
⊗ Methadone hydrochloride (p.82·3).
Opioid dependence.

Metadon *Cristalia, Braz.; Extractum, Hung.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome; pain.

Metadoxil *Silesia, Chile†; Eurodrug, Hung.; Baldacci, Ital.; Baldacci, Port.†; Baldacci, Rus.; Eurodrug, Thai.*
Metadoxine (p.1978·2).
Alcoholic liver disease.

Metafar *Lafare, Ital.*
Cefmetazole sodium (p.225·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Metafen *Polfa Lodz, Pol.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Metafisol *Menarini, Spain.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Metaflam *Jumont, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Metaflex *Montpellier, Arg.†.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Metaflex Gesic *Montpellier, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Metaflex NF *Montpellier, Arg.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Metaflex Plus *Montpellier, Arg.†.*
Nimesulide (p.95·3); orphenadrine citrate (p.812·1).
Musculoskeletal and joint disorders.

Metaflex Plus NF *Montpellier, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint, and peri-articular disorders.

Metagard *Ipca, India; IPCA, Malaysia; IPCA, Singapore.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; ischaemic heart disease.

metaginkgo *Meta Fackler, Ger.*
Homoeopathic preparation.

Metaglez *Otsira, India.*
Glipizide (p.441·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metaglip *BMS, USA.*
Glipizide (p.441·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metagliz *Almirall, Spain†.*
Metoclopramide glycyrrhizate (p.1749·2).
Aid in gastrointestinal examination; gastro-oesophageal reflux; gastroparesis; nausea and vomiting.

Metagyl *Ranbaxy, S.Afr.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metaharonga *Meta Fackler, Ger.*
Homoeopathic preparation.

Metahydrin *Hoechst Marion Roussel, USA†.*
⊗ Trichlormethiazide (p.1418·3).
Hypertension; oedema.

metakaveron *Meta Fackler, Ger.†.*
Homoeopathic preparation.

Metakelfin *Pharmacia, Ital.*
Sulfametopyrazine (p.342·2); pyrimethamine (p.610·2).
Malaria.

Metalax *Leiras, Fin.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Metalcaptase *Heyl, Cz.; Heyl, Ger.; Taisho, Jpn; Abbott, S.Afr.*
Penicillamine (p.1456·2).
Chronic hepatitis; chronic polyarthritis; cystinuria; heavy metal poisoning; rheumatoid arthritis; scleroderma; Wilson's disease.

Metalexina *Rowe-Fleming, Venez.†.*
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Metalgin *Hexal, Ger.†.*
Dipyrone (p.49·2).
Pain.

Metalino *Baxter, Mex.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Metalon *Caps, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; vomiting.

Metalyse *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK.*
Tenecteplase (p.1410·1).
Myocardial infarction.

metamagnesol *Meta Fackler, Ger.†.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Metamar *Mar, Arg.*
⊗ Betamethasone (p.1518·2) or betamethasone acetate (p.1518·2).
Corticosteroid.

Metamide *Pacific, NZ.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal investigations; gastrointestinal motility disorders; nausea and vomiting.

Metamidol *Winthrop, Port.*
Diazepam (p.986·3).
Anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Metamorfoz *Sanli, Turk.*
Hydroquinone (p.1598·2); bismuth subnitrate (p.1711·2); almond oil (p.2252·2); bitter almond oil.
Hyperpigmentation disorders.

Metamucil *Procter & Gamble, Arg.; Procter & Gamble, Austral.; Procter & Gamble, Austria; Procter & Gamble, Braz.; Procter & Gamble, Canad.; K2 Pharmacare, Chile†; Wick, Ger.; Pfizer, Hong Kong; Procter & Gamble, Mex.; Procter & Gamble, NZ; Procter & Gamble, Neth.; Searle, S.Afr.†; Procter & Gamble, Spain; Procter & Gamble, Switz.; Pfizer, Thai.; Procter & Gamble, USA.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement; diverticular disease; haemorrhoids; hypercholesterolaemia; irritable bowel syndrome; ostomy management; stool softener.

Metanabol *Jelfa, Pol.*
⊗ Methandienone (p.2116·3).
Anabolic.

Metanium *Ransom, UK.*
Titanium dioxide (p.1617·3); titanium peroxide (p.1618·1); titanium salicylate (p.1618·1).
Nappy rash.

Metanor *Meda, Port.*
Flupirtine maleate (p.61·1).
Pain.

Metanx *Pamlab, USA.*
Vitamin B (p.1978·2); vitamin B (p.1980·2); calcium mefolinate (p.1932·2).

Metapio *Andromaco, Chile.*
Phenol (p.1656·1).
Disinfection.

Metapirona *Allen, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Metaplatin *Teva Tuteur, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Metaplex *Takeda, Hong Kong†; Takeda, Thai.*
Vitamin B substances (p.1922·1).
Tonic; vitamin deficiency.

Metaplexan *Pierre Fabre, Ger.*
Mequitazine (p.585·3).
Hypersensitivity disorders.

Metaptyl *Elpen (Ελπεν), Gr.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Metargen Pediatrico *Farmaco, Mex.†.*
Vitamin preparation (p.1922·1).

Metasal *Salus, Ital.†.*
Cefmetazole sodium (p.225·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Metasedin *Esteve, Spain.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal; pain.

Metasin *Ivax, Mex.*
Metadoxine (p.1978·2).
Alcohol withdrawal syndrome.

Metaskin-N *Metiska, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

metasolidago S *Meta Fackler, Ger.*
Homoeopathic preparation.

Metason *Fortbenton, Arg.; AG Therapy, Gr.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; skin disorders.

Metaspirine *GSK Sante, Fr.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Metaspray *Cipla, India.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis.

Metastron *Amersham, Austral.; Amersham, Austria; GE, Cz.; Amersham, Fr.; Amersham, Ital.; GE Healthcare, Neth.; Satis, Port.; Amersham, Spain; Amersham, UK; Amersham, USA; Medi-Physics, USA.*
Strontium-89 chloride (p.2055·3).
Metastatic bone pain.

Metatensin *Hoechst Marion Roussel, USA†.*
⊗ Trichlormethiazide (p.1418·3); reserpine (p.1387·3).
Hypertension.

Metatone *Pfizer Consumer, Irl.; Chefaro, UK.*
Calcium glycerophosphate; manganese glycerophosphate; potassium glycerophosphate; sodium glycerophosphate; thiamine hydrochloride (p.1922·1).
Tonic.

Metatop *Topgen, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

metavirulent *Meta Fackler, Ger.*
Homoeopathic preparation.

Metax
Note. This name is used for preparations of different composition.
Kemifar, Ital.
Cefmetazole sodium (p.225·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Sons, Mex.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Metaxol *Adcock Ingram, S.Afr.*
Theophylline (p.1140·1); codeine phosphate (p.37·2); mepyramine maleate (p.585·2).
Coughs.

Metaxon *Ariston, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Metazin *Clintex, Port.†.*
Etodolac (p.52·2).
Gout; musculoskeletal and joint disorders; pain.

Metazol
Note. This name is used for preparations of different composition.
CT, Ital.†.
Cefmetazole sodium (p.225·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Alliance, S.Afr.
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metazydyna *Polfa Pabianice, Pol.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; tinnitus; vascular eye disorders; vertigo.

Metbay *Bayer, Ital.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metblock *Pfizer, Fin.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metcort *Delta, Braz.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Meted *Medicis, Canad.; Alliance, Irl.; Alliance, UK; GenDerm, USA.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Scalp disorders; seborrhoea.

Metenix *IFET (ΙΦΕΤ), Gr.; Borg, UK.*
⊗ Metolazone (p.1337·2).
Ascites; hypertension; oedema.

Meteophyt forte *OTW, Ger.†.*
Pancreatin (p.2360·1).
Pancreatic disorders.

Meteoril *Salvat, Spain.*
Simeticone (p.1770·2); magnesium trisilicate (p.1744·1); aluminium glycinate (p.1706·2).
Flatulence; gastrointestinal hyperacidity.

Meteosan *Novartis Consumer, Ger.†.*
Dimethicone (p.1770·2).
Gastrointestinal disorders associated with excess gas.

Meteosim *IBI, Ital.*
Simeticone (p.1770·2).
Aerophagia; meteorism.

Meteospasmyl *Craveri, Arg.; Mayoly-Spindler, Cz.; Mayoly-Spindler, Fr.; Teva, Hung.; Mayoly-Spindler, Malaysia; Mayoly-Spindler, Mex.; Mayoly Spindler, Pol.; Mayoly-Spindler, Rus.; Mayoly-Spindler, Singapore; Mayoly-Spindler, Thai.; Ali, Turk.*
Alverine citrate (p.1708·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastrointestinal distension; gastrointestinal spasm; irritable bowel syndrome; meteorism.

Meteoxane *IPRAD, Fr.*
Simeticone (p.1770·2); phloroglucinol (p.2366·3).
Gastrointestinal disorders.

Meteozym *Novartis Consumer, Ger.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive-system disorders.

Meterfolic *Durbin, UK.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy; neural tube defect prophylaxis.

Metex *Medac, Ger.*
Methotrexate sodium (p.745·2).
Juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis.

Metfin *Ecosol, Switz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfirex *Sanofi-Aventis, Cz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfodoc *Docpharm, Ger.*
Metformin (p.453·3).
Diabetes mellitus.

Metfogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.; Worwag, Rus.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfonorm *Abiogen, Ital.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfor *Acis, Ger.†; Millimed, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metforal *Menarini, Arg.; Guidotti, Ital.; Adcock Ingram, S.Afr.; Menarini, Singapore.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfordin *Biofarma, Braz.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metforem *Orion, Fin.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metfori *Hexal, Arg.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metforil *Menarini, Gr.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metform *ABZ, Ger.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metformax *Menarini, Belg.; Polfa Kutno, Pol.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metformed *Cimed, Braz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metformin Duo *Temis, Arg.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Metfron *Asian Pharm, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Methaderm *Taiho, Jpn.*
⊗ Dexamethasone propionate (p.1526·3).
Skin disorders.

Methadose *Rosemont, UK; Mallinckrodt, USA.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal; pain.

Methagual *Gordon, USA.*
Methyl salicylate (p.85·3); guaiacol (p.1561·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Methalgen *Alra, USA†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); mustard oil (p.2349·2).
Musculoskeletal and joint pain.

Methaphyllin *Eisai, Indon.*
Chlorophyllin copper complex sodium (p.1471·1); propantheline bromide (p.1764·3); magnesium trisilicate (p.1744·1).
Gastritis; peptic ulcer.

Metharmon-F *Zoki, Thai.*
⊗ Pregnenolone; androstenedione (p.2082·3); androstenediol; testosterone (p.2129·3); estrone (p.2101·2); thyroid (p.2177·1).
Menopausal disorders; ovarian disorders.

Methatabs *PSM, NZ.*
⊗ Methadone hydrochloride (p.82·3).
Coughs; opioid withdrawal syndrome; pain.

Methatropic *Goldline, USA.*
Vitamin B substances with methionine (p.1922·1).

Methazil *Bell, India.*
Methyl alcohol (p.2024·3); salicylic acid (p.1612·2).
Fungal ear infections.

Methergin *Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile†; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Sandoz, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Port.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, Venez.*
Methylergometrine maleate (p.2011·1).
Incomplete abortion; menorrhagia; postpartum haemorrhage; postpartum uterine atony or subinvolution; third-stage labour management.

Methergine *Novartis, USA.*
Methylergometrine maleate (p.2011·1).
Postpartum atony; postpartum haemorrhage.

Metherinal *Landson, Indon.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; third-stage labour management; uterine haemorrhage.

Methiaden Calcium *Leciva, Cz.†.*
Medosulepin hydrochloride; calcium gluceptate (p.1675·3).
Hypersensitivity reactions.

Methicol *Otto, Indon.*
-Methionine (p.1450·2); choline bitartrate (p.1934·2); vitamin B substances; vitamin E (p.1922·1).
Liver disorders.

Methio *TAD, Ger.*
Methionine (p.1450·1).
Acidification of urine; adjunct in antibacterial therapy; phosphate calculi.

Methioson *Soho, Indon.*
Methionine (p.1450·1); choline bitartrate (p.1934·2); vitamin B substances; vitamin E (p.1922·1).
Liver disorders.

Methiotrans *Abbott, Ger.*
Methionine (p.1450·1).
Adjunct in antibacterial therapy; phosphate calculi; urinary acidification.

Methiovit *Polfa Warszawa, Pol.*
Methionine; choline citrate; vitamin B substances; vitamin E (p.1922·1).
Dietary supplement; liver disorders.

Methnine *Medical Research, Austral.*
Methionine (p.1450·1).
Liver disorders; paracetamol overdosage.

Methobax *Baxter, Philipp.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Methobion *Medicus, Gr.*
Methotrexate (p.745·2).
Malignant neoplasms.

Methoblastin
Pfizer, Austral.; Pfizer, NZ.
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Pfizer, Mex.†.
Methotrexate (p.745·2).
Malignant neoplasms.

Methocaps *Caps, S.Afr.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Methocel
Note. This name is used for preparations of different composition.
OmniVision, Ger.; Novartis Ophthalmics, Hong Kong†; Novartis Consumer, Ital.; Restan, S.Afr.; Novartis Ophthalmics, Singapore†; OmniVision, Switz.
Hypromellose (p.2144·2) (p.1622·2).
Aid in eye examination; eye lubrication during contact lens fitting; lubricating and disinfecting drops for use with contact lenses.

Novartis Ophthalmics, Malaysia†.
Methylcellulose (p.2145·1).
Aid in eye examination.

Methocip *Cipla, India.*
Methotrexate (p.745·2).
Malignant neoplasms; rheumatoid arthritis.

Method M *Baxter, Thai.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Methopt *Sigma, Austral.†; Sigma, NZ; Sigma, Philipp.*
Hypromellose (p.2144·2).
Dry eyes.

Methor *Valeant, Hung.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Methor-Co *Marching, Hong Kong.*
⊗ Dextromethorphan hydrobromide (p.1555·2); bromhexine hydrochloride (p.1552·2); ephedrine hydrochloride (p.1558·2); papaverine hydrochloride (p.2191·3); caffeine (p.1116·3).
Coughs; respiratory-tract congestion.

Methorcon *YF Chem, Thai.*
⊗ Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); *dl*-methylephedrine hydrochloride (p.1564·3).
Coughs.

Methormyl *Mugi, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Methorsedyl *Europharm, Hong Kong.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); promethazine hydrochloride (p.588·2).
Cold symptoms; cough.

Methovin *Kimia, Indon.*
Methylergometrine maleate (p.2011·1).
Lochiometra; menorrhagia; metrorrhagia; postpartum haemorrhage; uterine subinvolution.

Methoxacet *Rougier, Canad.*
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Methoxacet-C *Rougier, Canad.*
Methocarbamol (p.1897·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain associated with skeletal muscle spasm.

Methoxisal *Rougier, Canad.*
Methocarbamol (p.1897·3); aspirin (p.20·3).
Pain associated with skeletal muscle spasm.

Methoxisal-C *Rougier, Canad.*
Methocarbamol (p.1897·3); aspirin (p.20·3); codeine phosphate (p.37·2).
Pain associated with skeletal muscle spasm.

Methozane *Taro, Israel.*
Levomepromazine maleate (p.1003·1).
Anxiety; bipolar disorder; pain; premedication; psychoses.

Methpica *Tropica Mas, Indon.*
Metformin (p.453·3).
Diabetes mellitus.

Methycobal *TRB, Arg.†; Eisai, Hong Kong; Wockhardt, India; Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.*
Mecobalamin (p.1981·1).
Megaloblastic anaemia; peripheral neuropathy.

Methyl Salicylate Compound Liniment *McGloin, Austral.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Muscle pain.

Methyl Salicylate Ointment Compound *McGloin, Austral.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3); cajuput oil (p.2271·2).
Muscle pain.

Methylergobrevin *Wernigerode, Ger.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; third-stage labour.

Methylin *Rontag, Arg.; Alliant, USA.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; minimal brain dysfunction; narcoleptic syndrome.

Methylon *Bernofarm, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Methyment *Pharmonta, Austria.*
Aluminium acetotartrate (p.2255·1); aluminium formate (p.1706·2); methylthioninium chloride (p.1450·3).
Inflammation and infection of the mouth and throat.

Metiaben *Ibfarma, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Metibasol *Sanobia, Port.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Meticel
Note. This name is used for preparations of different composition.
Sophia, Mex.
Hypromellose (p.2144·2).
Eye irritation.

GSK, Spain†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Meticil *Ivax, Arg.*
Ampicillin (p.204·1); diclofenac sodium (p.44·3).
Mouth and throat infections.

Meticone *Elofar, Braz.*
Dimeticone (p.1770·2).
Dyspepsia; flatulence.

Meticortelone
Schering-Plough, Ital.†; Schering-Plough, S.Afr.†.
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Schering-Plough, Mex.; Schering-Plough, Venez.
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Meticorten *Schering-Plough, Arg.; Mantecorp, Braz.; Essex, Chile; Schering-Plough, Mex.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering, USA; Schering-Plough, Venez.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Metidisol *Protein, Mex.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Metidrol *Medikon, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Metifer *Ikapharmindo, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Metifex *Cassella-med, Ger.*
Ethacridine lactate (p.1625·1).
Diarrhoea; gastro-enteritis.

Metifor
Note. This name is used for preparations of different composition.
Polfarmex, Pol.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Corsalud, Venez.†.
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and joint disorders; neuralgia.

Metiguanide *Pfizer, Ital.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metilat *Metiska, Indon.*
Methylergometrine maleate (p.2011·1).
Lochiometra; menorrhagia; metrorrhagia; third-stage labour management; uterine bleeding; uterine subinvolution.

Metilbetasone Solubile *SoSe, Ital.*
⊗ Methylprednisolone acetate (p.1538·2).
Injectable corticosteroid.

Metilbio *Biofarma, Braz.†.*
Methyldopa (p.1334·1).
Hypertension.

Metilcanfor *Quim-Far, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Metilcodin *Organifar, Venez.†.*
Codeine (p.37·2); mepyramine maleate (p.585·2).
Cough.

Metilcord *Luper, Braz.†.*
Methyldopa (p.1334·1).
Hypertension.

Metil-DT *Cristalia, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Metilen *Eversil, Braz.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Metilenkek *Pharmamagist, Hung.*
Methylthioninium chloride (p.1450·3).
Methaemoglobinaemia.

Metiler *Adeka, Turk.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage.

Metilfedrin *Organifar, Venez.†.*
⊗ Ephedrine hydrochloride (p.1558·2); theophylline sodium glycinate (p.1146·3); phenobarbital sodium (p.492·2); homatropine methylbromide (p.1881·3); sodium benzoate (p.1630·2); mepyramine maleate (p.585·2).
Asthma.

Metilon *Daiichi, Hong Kong†.*
Dipyrone (p.49·2).
Fever.

Metilpren *Mayne, Port.*
⊗ Methylprednisolone hydrogen succinate (p.1538·2).
Corticosteroid.

Metilpres
Note. A similar name is used for preparations of different composition (see below).
TRB, Arg.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Metilpress
Note. A similar name is used for preparations of different composition (see above).
Sigma, Braz.
Methyldopa (p.1334·1).
Hypertension.

Metilprod *Prodotti, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Metimyd *Schering-Plough, Mex.†; Schering, USA.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Eye inflammation with bacterial infection.

Metina *Fournier, Ital.†.*
Levocarnitine hydrochloride (p.1932·3).
Carnitine deficiency; myocardial ischaemia.

Metinal-Idantoina *Bayer, Ital.*
Phenytoin (p.495·2); methylphenobarbital (p.490·2).
Epilepsy.

Metinal-Idantoina L *Bayer, Ital.*
Phenytoin (p.495·2); methylphenobarbital (p.490·2); phenobarbital (p.492·2).
Epilepsy.

Metindo *Kenyaku, Thai.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis.

Metindol *GSK, Pol.; ICN, Pol.; Polfa Warszawa, Pol.; GSK, Rus.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Metinox *Lennon, S.Afr.*
Tin (p.2402·3); tin oxide (p.2402·3).
Acne; boils.

Metiocolin B12 *Farmasa, Braz.*
Methionine (p.1450·1); choline chloride (p.1934·2); inositol (p.2325·2); vitamin B (p.1980·2).
Liver disorders.

Metiocolin Composto *Farmasa, Braz.*
Methionine (p.1450·1); choline citrate (p.1934·2); betaine (p.2265·2); cyanocobalamin (p.1980·2).
Liver disorders.

Metiogen *Medical, Arg.*
Cynara (p.2291·2); boldo (p.2267·2); wild carrot (p.2415·2); menthol (p.2340·1).
Hepato-biliary disorders.

Metiorisan *Duncan, Arg.*
Simeticone (p.1770·2).
Flatulence.

Metirel *Pfizer, Arg.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; rheumatoid arthritis.

Metis *Gedeon Richter, Cz.*
Glimepiride (p.441·1).
Diabetes mellitus.

Metisol *Hexpharm, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Metison *Unison, Thai.†.*
Cisapride (p.1720·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastroparesis.

Metisona *Precimex, Mex.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Metizol *ICN, Pol.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Metligine *Taisho, Jpn.*
⊗ Midodrine hydrochloride (p.1341·1).
Hypotension.

Metlong *Panacea, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Meto *APS, Ger.; Alpharma-Isis, Ger.; Hennig, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Meto comp *ABZ, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metobeta *Betapharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metobeta comp *Betapharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metoblock *Silom, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Metoc *Oriental, Arg.*
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Metocal *Rottapharm, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Metocal Vitamina D *Rottapharm, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Metocalcium *Rottapharm, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Metocar *Pharmacodane, Denm.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metocard
Polpharma, Pol.
⊗ Metoprolol (p.1338·1).
Arrhythmias; hypertension; hyperthyroidism; ischaemic heart disease; migraine.

Polpharma, Rus.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension.

Metocare *IAE, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metoclan *Medinfar, Port.†.*
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; gastritis; nausea and vomiting.

Metoclor *Pharmaland, Thai.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Metoclosan *Sanval, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Metocontin *Modi-Mundipharma, India.*
Metoclopramide hydrochloride (p.1747·3).
Duodenitis; dyspepsia; gastritis; gastro-oesophageal reflux; nausea and vomiting.

Metocor *Rowex, Irl.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metocyl *Rowa, Hong Kong†; Rowa, Irl.; Rowa, Malaysia†; Rowa, Singapore†.*
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; flatulence; gastrointestinal disorders; heartburn; nausea and vomiting; peptic ulcer.

Metoda M *Baxter, Cz.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Metodine *Pfizer, Mex.*
Diiodohydroxyquinoline (p.832·1); metronidazole benzoate (p.837·1).

Metodoc *Docpharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metodura *Merck dura, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metodura comp *Merck dura, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metofen Forte *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Metogastron *Hexal, Austria.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting; upper gastrointestinal motility disorders.

Metohexal
Hexal, Austral.; Hexal, Austria; Hexal, Cz.†.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Hexal, Ger.; Hexal, Pol.
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; hyperthyroidism; ischaemic heart disease; migraine; myocardial infarction.

Metohexal comp *Hexal, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Meto-Isis comp *Alpharma-Isis, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metoject *Medac, Cz.; Medac, Denm.; Medac, Fin.; Biochem, Gr.; Medac, Hung.; Medac, Neth.; Medac, Norw.; Medac, Port.; Gebro, Spain; Medac, Swed.; Medac, UK.*
Methotrexate sodium (p.745·2).
Juvenile idiopathic arthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis.

Metok *ABZ, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; migraine; myocardial infarction.

Metoklamide *Sanli, Turk.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Metolar *Cipla, India.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; myocardial infarction.

Metolar-H *Cipla, India.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metolate *Santen, Jpn.*
Methotrexate (p.745·2).
Rheumatoid arthritis.

Metole *APT, Hong Kong.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; ulcerative gingivitis.

Metolol *Douglas, Austral.†; Pharmaland, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; migraine; myocardial infarction.

Metolon *Bernofarm, Indon.; Malaysia Chemist, Singapore†.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders; nausea and vomiting.

Metomax *Alphapharm, Austral.*
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

MetoMed *S Med, Austria.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Metomerck *Merck dura, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metomide *Grunenthal, Port.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Metomin *Pacific, NZ.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metomit *Laboratorios Chile, Chile†.*
Mitomycin (p.752·1).
Malignant neoplasms.

Metonate *Otto, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Metop *Gerard, Irl.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metopal *Aliud, Austria†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metophan *ICM, Singapore.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Metopiron *Novartis, Neth.; Novartis, Swed.*
Metyrapone (p.2344·2).
Cushing's syndrome; hyperaldosteronism; oedema; test of pituitary-adrenocortical function.

Metopirone *Novartis, Austral.; Novartis, Cz.†; Novartis, Fr.; IFET (ΙΦΕΤ), Gr.; Novartis, Irl.; Novartis, Israel; Novartis, NZ; Novartis, Switz.; Alliance, UK; Ciba-Geigy, USA.*
Metyrapone (p.2344·2).
Cushing's syndrome; hyperaldosteronism; oedema; testing of hypothalamic-pituitary ACTH function.

Metoplamin *Cifarma, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Metoplex *Jean-Marie, Hong Kong.*
⊗ Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2); bromhexine hydrochloride (p.1552·2); ephedrine hydrochloride (p.1558·2); caffeine (p.1116·3); papaverine hydrochloride (p.2191·3).
Coughs; viscous bronchial secretions.

Metopram *Leiras, Fin.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal investigations; gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting.

Metopresol *Tecnofarma, Mex.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Metopress *Agis, Israel†; Ecosol, Switz.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metopril *Metiska, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Metoprim
Note. This name is used for preparations of different composition.
Primera, Philipp.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension.

Munir, Turk.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Metoprin *Bunker, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Metoprin Balsamico *Bunker, Braz.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Bacterial infections.

Metoprogamma *Worwag, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Metoprolin *Ratiopharm, Fin.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metoprolol comp *ABZ, Ger.; CT, Ger.; Ratiopharm, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metoprolol compositum *Ratiopharm, Austria.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metoral *Unison, Malaysia; Unison, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Mouth disorders; oral inflammation; oral lesions.

Metordex *Etifar, Venez.†.*
Dextromethorphan (p.1555·2).
Cough.

Metorfan *Pliva, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Metorfedrin *Intra, Venez.*
Dextromethorphan hydrobromide (p.1555·2); brompheniramine (p.569·3).
Cough.

Metosan
Note. This name is used for preparations of different composition.
Lannacher, Austria.
Meloxicam (p.80·3).
Formerly contained beclometasone dipropionate.
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Sanfer, Mex.†.
Metronidazole (p.837·1).
Amoebiasis.

Metospec *Pharmaspec, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism.

Metostad *Stada, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Metostad Comp *Stada, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metostadol *Stada, Austria.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Meto-Succinat *Sandoz, Ger.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine.

Metosyn *Bioglan, Denm.; Bioglan, Norw.; GP, UK.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Meto-Tablinen *Winthrop, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

meto-thiazid *CT, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Metothyrin *PannonPharma, Hung.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Metotyrol *Tyrol, Austria†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metovit *Brasmedica, Braz.†.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Metoxifilin *Galeno, Venez.*
⊗ Methoxyphenamine hydrochloride (p.1564·2); theophylline (p.1140·1).
Asthma.

Metoxiprim *Rhein, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Metoz *Centaur, India.*
⊗ Metolazone (p.1337·2).
Formerly known as Metolaz.
Ascites; hypertension; oedema.

Metozoc *Gea, Denm.†; Gea, Fin.†; Gea, Norw.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Metpamid *Yeni, Turk.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Metpata *Pharmasant, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Metphar *Novell, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metracin *Quimica y Farmacia, Mex.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Metrajil *Mulda, Turk.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metral *Cassara, Arg.; LA, Arg.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections; rosacea.

Metram *APT, Hong Kong.*
Metoclopramide hydrochloride (p.1747·3).
Duodenitis; dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; nausea and vomiting; peptic ulcer.

Metrazol *Elpen (Ελπεν), Gr.; Dinctas, Turk.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrazole *MDI, S.Afr.; General Drugs, Thai.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Metrecina *Liferpal, Mex.*
Oxytetracycline (p.312·2).
Bacterial infections.

Metren *Alian, Venez.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrergina *Biol, Arg.*
Ergometrine maleate (p.2009·2).
Postpartum haemorrhage.

Metrexato *Blausiegel, Braz.*
Methotrexate sodium (p.745·2).
Malignant neoplasms; rheumatoid arthritis.

Metricom *Apotex, Mex.*
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Metrigen Fuerte *Organon, Mex.*
Estradiol benzoate (p.2097·2); progesterone (p.2125·1).
Menstrual disorders.

Metrim *Siam Bheasach, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Metrine *TP, Thai.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; postpartum uterine atony or subinvolution.

Metrinox *Euro-Med, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metris *Biogalenic, Venez.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrivin *Biogal-Teva, Hung.†.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metrix *Kalbe, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Metrizol *Cellofarm, Braz.†; Liferpal, Mex.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrobendizol *Technobio, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Metrocev *Cevallos, Arg.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections; rosacea.

Metrocide *Pharmaland, Thai.*
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Metrocream *Galderma, Canad.; Galderma, Chile; Galderma, Mex.; Galderma, USA.*
Metronidazole (p.837·1).
Rosacea.

Metrocreme *Galderma, Ger.*
Metronidazole (p.837·1).
Rosacea.

Metrodal *One Pharma, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrodax *Royton, Braz.†.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).

Metroderme *Galderma, Port.*
Metronidazole (p.837·1).
Rosacea.

Metrodin *Serono, Austral.; Serono, Braz.; Serono, Cz.†; Serono, Gr.†; Serono, Hong Kong†; Serono, Hung.†; Serum Institute, India; Serono, Irl.†; Serono, Israel†; Teva, Israel†; Serono, Ital.†; Serono, Neth.†; Serono, Port.; Serono, Rus.; Serono, S.Afr.†; Serono, Singapore†; Serono, Switz.†; Serono, Turk.; Serono, USA.*
⊗ Urofollitropin (p.2136·3).
Male and female infertility.

Metrodiyod *Serral, Mex.*
Diiodohydroxyquinoline (p.832·1); metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Metrofur *Sanofi Synthelabo, Mex.*
Metronidazole (p.837·1); nystatin (p.543·2).
Trichomoniasis.

Metrofusin *Kalbe, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrogel *Galderma, Canad.; Galderma, Chile; Galderma, Denm.†; Galderma, Ger.; Galderma, Mex.; Galderma, Neth.; Galderma, UK; Galderma, USA.*
Metronidazole (p.837·1).
Fungating malodorous tumours; rosacea.

Metrogel Vaginal *Graceway, USA.*
Metronidazole (p.837·1).
Bacterial vaginosis.

Metrogyl
Alphapharm, Austral.; Hexal, Braz.†; Fresenius Kabi, Gr.; Alphapharm, Hong Kong; Unique, India; Teva, Israel; Unique, Rus.; Unique, Venez.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; bacterial vaginosis; giardiasis; rosacea; trichomoniasis.

JB Chemicals, Thai.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections.

Metrogyl Denta *Unique, Rus.*
Chlorhexidine gluconate (p.1635·3); metronidazole benzoate (p.837·1).
Bacterial mouth infections.

Metrogyl Plus *Unique, Rus.*
Metronidazole (p.837·1); clotrimazole (p.530·1).
Vaginal infections.

Metrogyl-F *Unique, India†.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1); furazolidone (p.834·3).
Amoebiasis; giardiasis.

Metrol *Arrow, Austral.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; migraine; myocardial infarction.

Metrolag *Lagap, Switz.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrolex *Siam Bheasach, Thai.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis; ulcerative gingivitis.

Metrolocal *Paylos, Arg.*
Metronidazole (p.837·1).
Malodorous skin disorders.

Metrolotion *Galderma, Canad.*
Metronidazole (p.837·1).
Rosacea.

Metrolyl *Sandoz, UK.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Metronib *Ibfarma, Braz.†.*
Metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Metronide *Aventis, Austral.; Prodotti, Braz.; Clonmel, Irl.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metronid-Puren *Alpharma-Isis, Ger.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metroniflex *Baxter, Braz.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metronil *Cazi, Braz.*
Metronidazole benzoate (p.837·1).

Metronimerck *Merck dura, Ger.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metronin *Cifarma, Braz.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Protozoal infections.

Metronix *Cristalia, Braz.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metronour *Organon, Ger.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metront *Hexal, Ger.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metropast *Pasteur, Chile.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrophenicol *Virgo, Philipp.*
Chloramphenicol (p.239·3), chloramphenicol palmitate (p.239·3), or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Metrosa *Linderma, UK.*
Metronidazole (p.837·1).
Rosacea.

Metrosel *Biosel, Turk.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrosept *ICN, Pol.*
Metronidazole (p.837·1).
Bacterial skin infections; rosacea.

Metroseptol *Jelfa, Rus.*
Metronidazole (p.837·1).
Bacterial skin infections; rosacea.

Metroson *Sons, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Metrostat *Adcock Ingram, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrotix *Biofarma, Braz.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Metrotop *SSL, Irl.; Medlock Medical, UK.*
Metronidazole (p.837·1).
Malodorous fungating tumours; malodorous skin ulcers; rosacea.

Metroval *Sanval, Braz.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).

Metrovax *Vivax, Venez.*
Metronidazole (p.837·1).
Protozoal infections.

Metrovid *Millimed, Thai.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Metroviform *Pharmacos, Mex.†.*
Metronidazole (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Metrozol
Elofar, Braz.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Bacterial infections; protozoal infections.

Parkfields, UK.
Metronidazole (p.837·1).

Metrozole *Malayan, Singapore†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Met-Rx *Met-Rx, USA.*
Preparations for enteral nutrition (p.1922·1).

Metsal *3M, Austral.; 3M, Hong Kong; 3M, Malaysia; 3M, NZ; 3M, Philipp.; 3M, Singapore.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Metsal AR Analgesic *3M, Austral.; 3M, Singapore.*
Trolamine salicylate (p.132·3).
Musculoskeletal and joint pain.

Metsal AR Heat Rub *3M, Austral.†.*
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Musculoskeletal and joint pain.

Metsal Heat Rub *3M, Austral.; 3M, Singapore.*
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Metsec *TP, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Met-Sil *TP, Thai.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Metsil *Bilim, Turk.*
Simeticone (p.1770·2).

Metsol *Orbis Consumer, UK.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

MetSurrir *Insurrir, Ger.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Metussan *Great Eastern, Thai.; Pediatrica, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Coughs.

Metvell *Novell, Indon.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; third-stage labour management.

Metvix *AB-Consult, Austria; Galderma, Belg.; Galderma, Cz.; Photocure, Denm.; Photocure, Fin.; Galderma, Ger.; Galderma, Ital.; Healthcare Logistics, NZ; Galderma, Neth.; Photocure, Norw.; Galderma, Port.; Galderma, S.Afr.; Galderma, Spain; Photocure, Swed.; Galderma, Switz.; Galderma, UK.*
Methyl aminolevulinate hydrochloride (p.679·3).
Actinic keratoses; basal cell carcinoma.

Metvixia
Galderma, Fr.
Methyl aminolevulinate (p.680·1).
Actinic keratoses; skin cancer.

Photocure, USA.
Methyl aminolevulinate hydrochloride (p.679·3).
Actinic keratosis.

Metxaprim *General Drugs, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Metypred
Orion, Cz.†; Galen, Ger.; Orion, Rus.
⊗ Methylprednisolone (p.1538·1) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Orion, Hung.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Orion, Pol.
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Metypresol *Pharmachemie, Neth.†; Intramed, S.Afr.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Metysolon *Dermapharm, Ger.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Mevachol *Meprofarm, Indon.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Mevacor *MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile†; MSD, Cz.; MSD, Denm.; MSD, Fin.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Malaysia†; MSD, Mex.; MSD, Norw.; MSD, Spain; Merck, USA; MSD, Venez.*
Lovastatin (p.1328·2).
Atherosclerosis; coronary heart disease; hypercholesterolaemia.

Mevalip *Teuto, Braz.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Mevalon *Guidotti, Ital.†.*
Meglutol (p.1332·2).
Hyperlipidaemias.

Mevalotin *Sankyo, Braz.; Sankyo, Ger.; Sankyo, Jpn; Sankyo, Switz.; Sankyo, Thai.; Sankyo, Venez.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Mevamox *Teuto, Braz.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Mevamyst *Chrispa (Χρισπα), Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Mevaren *Juste, Spain.*
Estradiol valerate (p.2097·3); dienogest (p.2094·1).
Menopausal disorders.

Mevasterol *Cantabria, Spain.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Mevastin *Genepharm, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Mevecan *Help, Gr.†.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Mevedal *Help, Gr.*
Nabumetone (p.91·2).
Inflammation; musculoskeletal and joint disorders; pain.

Mevilox *Bernofarm, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Mevinacor *MSD, Ger.; MSD, Port.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Mevinol *Vianex (Βιανέξ), Gr.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Meviton *Meprofarm, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C deficiency; vitamin B and C supplement.

Mevlor *MSD, Arg.; Chibret, Port.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Mevrabal *Medikon, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Mex *Phoenix, Arg.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Mexalen *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Paracetamol (p.108·1).
Fever; pain.

Mexan
Note. This name is used for preparations of different composition.
Mintlab, Chile.
Meloxicam (p.80·3).

Teva, Israel.
Mesna (p.1449·2).
Prevention of ifosfamide or cyclophosphamide urothelial toxicity.

Mexapin *Wandel, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Mexaquin *Konimex, Indon.*
Chloroquine phosphate (p.599·3).
Malaria.

Mexar *Hawthorn, USA.*
Sulfacetamide sodium (p.335·3).
Dandruff; infected skin disorders; seborrhoeic dermatitis.

Mexasone *Malayan, Singapore†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Mexavit *Ratiopharm, Cz.; Merckle, Rus.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Mexa-Vit C *Ratiopharm, Austria.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Mexe N *Merckle, Ger.†.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Mexicor *Moskhimfarm, Rus.*
Emoxypine succinate.
Ischaemic heart disease; myocardial infarction.

Mexicord *Polfa Grodzisk, Pol.*
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Mexidol *Farmasoft, Rus.*
Emoxypine succinate.
Alcohol withdrawal syndrome; anxiety; cerebrovascular disorders; epilepsy; mental function impairment; neuroleptic toxicity.

Mexilal *Sanitas, Chile.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders.

Mexilen *Rafa, Israel.*
Mexiletine hydrochloride (p.1339·2).
Ventricular arrhythmias.

Mexitil *Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.†; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong†; German Remedies, India; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Mex.†; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.†; Boehringer Ingelheim, S.Afr.†; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.†; Boehringer Ingelheim, Thai.†; Eczacibasi, Turk.; Boehringer Ingelheim, UK†; Boehringer Ingelheim, USA.*
Mexiletine hydrochloride (p.1339·2).
Ventricular arrhythmias.

Mexitilen *Boehringer Ingelheim, Arg.*
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Mexobron *Inquifave, Venez.†.*
Dextromethorphan (p.1555·2).
Cough.

Mexochrome *Konimex, Indon.*
Lidocaine hydrochloride (p.1862·3); menthol (p.2340·1); benzalkonium chloride (p.1629·1); isopropyl alcohol (p.1650·3).
Burns; insect bites; local anaesthesia; minor wounds.

Mexpharm *Kalbe, Indon.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Mexsana *Schering-Plough, USA.*
Kaolin (p.1738·1); eucalyptus oil (p.2301·2); camphor (p.2273·2); corn starch (p.1968·1); lemon oil (p.2332·3); zinc oxide (p.1621·2).
Nappy rash.

Mextran *Phoenix, Arg.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mextran Flex *Phoenix, Arg.*
Meloxicam (p.80·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

MEXY *Millimed, Thai.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Hay fever; rhinitis.

Mexylin *Promed, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mexylor *Epifarma, Ital.*
Lormetazepam (p.1005·2).
Insomnia.

Meylon *Otsuka, Jpn.*
Sodium bicarbonate (p.1673·2).
Drug intoxication; metabolic acidosis; nausea; vomiting.

Mezabox *Sriprasit, Thai.*
Dipyrone (p.49·2).
Pain.

Mezalit *Biopharm, Chile.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Mezarid *Genepharm, Gr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Mezatrin *Sanbe, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Mezavant *Shire, UK.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Mezen *Errekappa, Ital.†.*
Promelase (p.2373·3).
Inflammation; oedema.

Mezenol *Aspen, S.Afr.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Mezinc *Abigo, Swed.*
Zinc oxide (p.1621·2); zinc resin (p.1999·1).
Wound dressing.

Mezine *Phoenix, Arg.*
Venlafaxine (p.430·1).
Anxiety; depression; social phobia.

Meziv *Euroderm, Ital.†.*
Methionine (p.1450·1); vitamin B substances (p.1922·1); zinc sulfate (p.1999·2).
Hair loss.

Mezolitan *Dekaz, Gr.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mezym F *Berlin-Chemie, Ger.*
Pancreatin (p.2360·1).
Pancreatic disorders.

Mezym Forte *Berlin-Chemie, Hung.; Berlin-Chemie, Rus.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

M-Flox *Millimed, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

M-Furo *Orva, Turk.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

MG400 *Triton, USA.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Seborrhoea.

MG 50 *Terapeutico, Ital.*
Magnesium proteinate (p.1678·3).
Magnesium deficiency; magnesium supplement.

MG Cold Sore Formula *Outdoor Recreations, USA.*
Menthol (p.2340·1); lidocaine (p.1862·3).

Mg 5-Granoral *Vifor, Switz.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

Mg 5-Granulat *Artesan, Cz.†; Cassella-med, Cz.†; Artesan, Ger.†; Cassella-med, Ger.†.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Mg 5-Longoral *Kolassa, Austria; Artesan, Cz.†; Cassella-med, Cz.†; Artesan, Ger.; Cassella-med, Ger.; Vifor, Switz.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

MG217 Medicated *Triton, USA.*
Coal tar (p.1616·2).
MG217 Medicated shampoo and ointment formerly contained coal tar, salicylic acid, and colloidal sulfur.
Skin disorders.

MG217 Medicated Tar-Free *Triton, USA.*
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Dandruff.

Mg 5-Oraleff *Vifor, Switz.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency; magnesium supplement.

MG217 Sal-Acid *Triton, USA.*
Salicylic acid (p.1612·2).
Psoriasis.

Mg 5-Sulfat *Artesan, Ger.; Cassella-med, Ger.; Vifor, Switz.*
Magnesium sulfate (p.1679·3).
Arrhythmias; eclampsia; fetal hypotrophy; magnesium deficiency; myocardial infarction; pre-eclampsia; premature labour.

Mg-nor *Teofarma, Ger.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

MHP-A *Cypress, USA.*
Hyoscyamine sulfate (p.1736·1); methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); methylthioninium chloride (p.1450·3); benzoic acid (p.1630·2).
Lower urinary-tract disorders.

Miabene *Ratiopharm, Austria†; Ratiopharm, Cz.*
Mianserin hydrochloride (p.408·1).
Depression.

Miacalcic *Novartis, Austral.; Novartis, Austria†; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Israel; LPB, Ital.†; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.†.*
Calcitonin (salmon) (p.1093·1).
Bone pain associated with osteolysis or osteopenia; hypercalcaemia; hyperparathyroidism; neurodystrophies; osteogenesis imperfecta; osteolysis of malignancy; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy; vitamin D intoxication; vitamin D overdose.

Miacalcin *Novartis, Canad.; Novartis, USA.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Mi-Acid *Major, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Mi-Acid Gelcaps *Major, USA.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Hyperacidity.

Miacin *Hikma, Cz.†.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Miadenil *Anfarm, Gr.; Francia, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Mialgex *Cazi, Braz.†.*
Methyl salicylate (p.85·3); turpentine oil (p.2406·3); camphor (p.2273·2); mustard oil (p.2349·2); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Musculoskeletal and joint disorders.

Mialin *Biomedica, Ital.*
Alprazolam (p.960·1).
Anxiety disorders.

Miambutol *Teofarma, Ital.; Kocak, Turk.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Mianeurin *Hexal, Ger.*
Mianserin hydrochloride (p.408·1).
Depression.

Miansemerck *Generics, Pol.*
Mianserin hydrochloride (p.408·1).
Depression.

Miantor *Pfizer, Mex.†.*
Etomidoline.

Miantrex *Pfizer, Braz.*
Methotrexate (p.745·2).
Malignant neoplasms.

Miaryl *Jin Yang, Malaysia.*
Glimepiride (p.441·1).
Diabetes mellitus.

Miaxan *Orion, Fin.*
Mianserin hydrochloride (p.408·1).
Depression; insomnia.

Miazide B6 *Wyeth Lederle, Ital.†.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1); pyridoxine hydrochloride (p.1978·2).
Tuberculosis.

Mibalin *Polfa Warszawa, Pol.*
⊗ Methylthioninium chloride (p.1450·3); naphazoline nitrate (p.1565·2).
Conjunctivitis.

Mibeclag *Bajamed, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Mibesan-S *Alpharma, Mex.*
Nystatin (p.543·2).
Oral candidiasis.

MIBG *Mallinckrodt, Neth.*
Iodine-131 (p.2054·3) iobenguan.
Radioimaging of malignant neoplasms.

Mibiot *Serral, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Mibiron *Faran, Gr.†.*
Astemizole (p.567·2).
Allergic disorders.

Mibloc FT *Andromaco, Chile.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Mibral *Pentafarma, Port.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Miburell *Sanorell, Ger.*
Homoeopathic preparation.

Mica *Epifarma, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Micaden *Teuto, Braz.*
Isoconazole nitrate (p.536·2).
Fungal vaginal infections.

Mical *Sam-On, Israel.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with viscous mucus.

Micalpha *Chrispa (Χρισπα), Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Micane *Edol, Port.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Micanol *Link, Austral.†; Schering, Austria; Tramedica, Belg.†; Canderm, Canad.†; Bioglan, Denm.†; Bioglan, Fin.†; Riemser, Ger.; Bioglan, Hong Kong†; Celltech, Irl.†; Bioglan, Israel; AFT, NZ; Bioglan, Norw.; CS, Port.; Vinas, Spain; Bioglan, Swed.; Bioglan, Thai.†; Bioglan, UK.*
Dithranol (p.1595·2).
Psoriasis.

Micar *Microsules, Arg.*
Piroxicam (p.117·3).
Fever; inflammation; pain.

Micardis *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
Telmisartan (p.1409·2).
Hypertension.

Micardis HCT *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, USA.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Micardis Plus *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, Venez.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

MicardisPlus *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, UK.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Micatex *Andromaco, Arg.†.*
Bifonazole (p.527·3); diphenhydramine hydrochloride (p.577·2).
Fungal skin infections.

Micatin *McNeil Consumer, Canad.; Advanced Care, USA.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micaveen
Note. This name is used for preparations of different composition.
Johnson & Johnson, Ital.
Avena (p.2262·1).
Soap substitute.

Dermoteca, Port.
Avena (p.2262·1); undecenoic acid (p.549·2); benzoic acid (p.1630·2).
Fungal skin infections.

Micazin *Chew, Thai.*
Miconazole (p.541·2).
Fungal skin and nail infections.

Miccil *Senosiain, Mex.*
⊗ Bumetanide (p.1237·1).
Hypertension; oedema.

Micebrina *Sanofi-Aventis, Spain.*
A range of vitamin preparations with or without minerals and ginseng (p.1922·1).

Micelle E *HSL, NZ.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E supplement.

Micerfin *LKM, Arg.*
Lomifylline (p.2334·3); dihydroergocristine (p.364·2).
Cerebrovascular disorders.

Micetal *CSC, Austria; Biosintetica, Braz.; Silesia, Chile; Medicom, Cz.; CSC, Hung.; Scharper, Ital.; Hormona, Mex.; Uriach, Pol.; Uriach, Spain.*
Flutrimazole (p.535·2).
Fungal skin and scalp infections.

Micetinoftalmina *Davi, Port.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Miciclin *Reuffer, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Micifrona *Q Pharma, Spain.*
Lespedeza capitata.
Uraemia.

Micitrex *Bausch & Lomb, Mex.*
Tobramycin (p.354·1).
Bacterial eye infections.

Miclast *Pierre Fabre, Ital.*
Ciclopirox olamine (p.529·2).
Fungal skin and vaginal infections.

Miclobet *Rayere, Mex.*
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1); gentamicin (p.284·2).
Infected skin disorders.

Miclonazol *Cazi, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Micoban *Genepharm, Gr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Micobeta *Betapharm, Ger.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micocert *Sidus, Arg.*
Piroctone olamine (p.1610·1); climbazole (p.529·3).
Scalp disorders.

Micocide *Atlas, Arg.*
Econazole nitrate (p.531·1).
Fungal skin, nail, and vaginal infections.

Micocide A *Atlas, Arg.*
Amorolfine (p.523·1).
Fungal nail infections.

Micoclin *Monserrat, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Micoder *BioSaude, Port.*
Lanoconazole (p.540·3).
Fungal skin infections.

Micodual *Atlas, Arg.*
Climbazole (p.529·3); piroctone (p.1610·1).
Scalp disorders.

Micoespec *Centrum, Spain.*
Econazole nitrate (p.531·1).
Fungal skin and nail infections.

Micoespec K *Euroderm, Arg.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Micofeet *SM, Venez.*
Boric acid (p.2268·1); calamine (p.1591·2); zinc oxide (p.1621·2); salicylic acid (p.1612·2); camphor (p.2273·2); menthol (p.2340·1).
Foot hygiene.

Micoffen *Offenbach, Mex.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micofim *Elofar, Braz.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micofin *Andromaco, Chile†.*
Fluconazole (p.532·1).
Fungal infections.

Micofitex *Pharmacia, Arg.†.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Micoflup *Chrispa (Χρισπα), Gr.*
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Micoflux *Dollder, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Micofoot *Zeta, Ital.*
Undecenoic acid (p.549·2); usnic acid (p.2409·3); salicylic acid (p.1612·2); aluminium acetate (p.2255·1).
Disinfection of skin, burns, and wounds; fungal skin infections.

Micofulvin *Cantabria, Spain.*
Fenticonazole nitrate (p.531·3).
Fungal infections.

Micogel *Cipla, India.*
Miconazole nitrate (p.541·3).
Fungal infections of the skin and nails; Gram-positive bacterial skin infections.

Micogel F *Cipla, India.*
⊗ Miconazole nitrate (p.541·3); fluocinolone acetonide (p.1531·3).
Fungal skin infections.

Micogen *Genepharm, Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections with inflammation.

Micogyn *Elofar, Braz.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

Micoisdin *Isdin, Spain†.*
Tolnaftate (p.548·3).
Fungal skin and nail infections.

Micolamina *Theraskin, Braz.*
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin infections.

Micolette *Pinewood, Irl.; Pinewood, UK.*
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); glycerol (p.2314·2).
Bowel evacuation; constipation.

Micolis *Valeant, Arg.; Pharma Investi, Chile.*
Econazole nitrate (p.531·1).
Fungal infections.

Micolis Novo *Valeant, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Micoliv *Farmalab, Braz.†.*
Ciclopirox olamine (p.529·2).
Fungal vulvovaginal infections.

Micolysin *Labialfarma, Port.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Micomax *Plata, Arg.*
Clotrimazole (p.530·1).
Balanitis; fungal skin infections; vulvitis.

Micomazol *Valeant, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Micomazol B *Valeant, Arg.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Micomazol Deo *Valeant, Arg.*
Clotrimazole (p.530·1).
Bromhidrosis; hyperhidrosis; pityriasis versicolor.

Micomicen *Sanofi-Aventis, Ital.*
Ciclopirox olamine (p.529·2).
Vulvovaginal candidiasis.

Micomisan *Adcock Ingram, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections; vaginal candidiasis.

Micon *Beacons, Singapore.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Miconacina *Grin, Mex.*
Natamycin (p.543·1).
Bacterial eye infections.

Miconal
Ecobi, Ital.
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections; secondary Gram-positive bacterial infections.

Polfa Tarchomin, Pol.
Miconazole (p.541·2).
Fungal skin and nail infections.

Miconan *Ativus, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Miconax *Meyer, Venez.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Miconazole H *Pharmaniaga, Malaysia†.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone acetate (p.1535·2).
Skin disorders with fungal infection.

Micon-H *Beacons, Singapore.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone acetate (p.1535·2).
Fungal skin and nail infections.

Miconol *Lafedar, Arg.*
Miconazole (p.541·2).
Fungal skin infections.

Micopar *Vida, Port.*
Ketoconazole (p.539·1).
Fungal infections.

Micopirox *Cassara, Arg.*
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin infections.

Micoplex *Cazi, Braz.*
Tiabendazole (p.156·2); neomycin sulfate (p.305·1).
Skin infections.

Micoral *Valeant, Arg.; Elofar, Braz.*
Ketoconazole (p.539·1).
Dandruff; fungal infections; seborrhoeic dermatitis.

Micoren *Novartis Consumer, Ital.*
⊗ Prethcamide (p.2162·3).
Respiratory insufficiency.

Micos *AGIPS, Ital.*
Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal infections; Gram-positive bacterial infections.

Micosan *Brasmedica, Braz.†.*
Undecenoic acid (p.549·2); triacetin (p.549·1); hexachlorophene (p.1646·1).
Skin disinfection.

Micosep *Cassara, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Micosep B *Cassara, Arg.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections with inflammation.

Micoser *Serral, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Micoset *Bago, Chile.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Micosil *Teuto, Braz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Micoskin *Corsa, Indon.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Micosol *Cassara, Arg.*
Bifonazole (p.527·3).
Fungal skin infections.

Micosona *Intendis, Spain.*
Naftifine hydrochloride (p.542·3).
Fungal skin and nail infections.

Micosone *Christo, Hong Kong.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone acetate (p.1535·2).
Fungal skin infections with inflammation.

Micostal *Elofar, Braz.*
Nystatin (p.543·2).
Candidiasis.

Micostalab *Multilab, Braz.*
Nystatin (p.543·2).
Candidiasis.

Micostatin *BMS, Arg.; BMS, Braz.; BMS, Chile; BMS, Mex.; BMS, Venez.*
Nystatin (p.543·2).
Candidiasis.

Micostatin Baby *BMS, Mex.*
Nystatin (p.543·2); zinc (p.1999·1).
Fungal skin infections.

Micosten *Hexal, Braz.†.*
Clotrimazole (p.530·1).
Fungal infections.

Micostop *Andromaco, Chile†.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Micostyl *Stiefel, Braz.; Stiefel, Mex.*
Econazole nitrate (p.531·1).
Fungal skin, scalp, and nail infections.

Micotar *Dermapharm, Ger.*
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections of the skin and mucous membranes.

Micotar ZP *Dermapharm, Ger.*
Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Fungal skin infections.

Micotarin *Uniao Quimica, Braz.*
Miconazole (p.541·2).
Fungal infections.

Micotef *Teofarma, Ital.*
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal infections; Gram-positive bacterial infections.

Micotenk *Biotenk, Arg.*
Itraconazole (p.536·3).
Fungal infections.

Micoter *Alcon Cusi, Malaysia†.*
Clotrimazole (p.530·1).
Tinea pedis.

Micotex
Note. This name is used for preparations of different composition.
Sertex, Arg.
Econazole nitrate (p.531·1).
Fungal skin infections.

Altana, Mex.
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3) aluminium zirconium glycine hydroxytetrachloride.
Fungal skin infections.

Micotgez *Gezzi, Arg.*
Miconazole (p.541·2).
Fungal skin infections.

Micotiazol *Cazi, Braz.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2); iodine (p.2169·2).
Fungal skin infections.

Micoticum *Mecosin, Indon.; Lesvi, Spain.*
Ketoconazole (p.539·1).
Fungal infections.

Micotin *Sanval, Braz.*
Oxiconazole nitrate (p.544·2).
Fungal skin infections.

Micotopic *Recalcine, Chile†.*
Bifonazole (p.527·3).
Fungal skin infections.

Micotox *Ibefar, Braz.†.*
Undecenoic acid (p.549·2); sodium propionate (p.545·3); benzoic acid (p.1630·2); copper sulfate (p.1935·3); menthol (p.2340·1); coumarin (p.2288·2).
Disinfection.

Micotral *LA, Arg.*
Miconazole (p.541·2).
Fungal skin infections.

Micotrat *Delta, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Micotrim *Schering-Plough, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Micotrim P *Schering-Plough, Arg.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micotrim S *Key, Arg.†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Micotrizol *Eurofarma, Braz.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Micoxolamina *Mastelli, Ital.*
Ciclopirox olamine (p.529·2).
Fungal infections.

Micoz *Hexal, Braz.†.*
Undecenoic acid (p.549·2); sodium undecenoate (p.549·3); salicylic acid (p.1612·2); benzoic acid (p.1630·2); hexylresorcinol (p.1647·1); sumatra benzoin (p.2394·2).
Skin infections.

Micozen *Teuto, Braz.*
Miconazole nitrate (p.541·3).
Fungal skin and vaginal infections.

Micozol
Note. This name is used for preparations of different composition.
Hexal, Mex.
Ketoconazole (p.539·1).
Fungal infections.

Vivax Gynopharm, Venez.
Clotrimazole (p.530·1).
Genital fungal infections.

Micozol Compuesto *Klonal, Arg.†.*
⊗ Ketoconazole (p.539·1); hydrocortisone (p.1535·2); gentamicin (p.284·2).
Infected skin disorders.

Micozole *Taro, Canad.; AFT, NZ.*
Miconazole nitrate (p.541·3).
Balanitis; vaginal fungal infections.

Micrainin *Wallace, USA†.*
Aspirin (p.20·3); meprobamate (p.1006·2).
Pain.

Micral Test *Roche Diagnostics, Irl.*
Test for microalbuminuria.

Micral Test II *Roche Diagnostics, Austral.†; Roche Diagnostics, Braz.; Roche Diagnostics, Mex.; Roche Diagnostics, UK.*
Test for microalbuminuria in diagnosis of nephropathy.

Micralax *Pfizer Consumer, Spain; UCB, UK.*
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3).
Bowel evacuation; constipation; painful defaecation.

Micraleve *Ivax, Arg.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Micraltest II *Roche, Chile.*
Test for microalbuminuria.

Micranet *Ogna, Ital.†.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Migraine; toothache.

Micranex *Vamsler, Philipp.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Micranil *Phoenix, Arg.*
Sumatriptan succinate (p.625·2).
Migraine.

Micrem *Merck, Indon.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Micreme *Pacific, NZ.*
Miconazole nitrate (p.541·3).
Balanitis; fungal and Gram-positive bacterial vulvovaginal infections.

Micreme H *Pacific, NZ.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Infected skin disorders.

MICRhoGAM *Ortho Diagnostic, USA.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Micro Mox *Micro, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Microalbustix *Bayer Diagnostics, Irl.*
Test for albumin and creatinine in urine.

Microbactim *Pharmacos, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Microbamat *Sanochemia, Austria.*
Meprobamate (p.1006·2).
Anxiety disorders; sleep disorders.

Microbar-HD (E-Z-HD) *Bracco, Switz.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal double-contrast radiography.

Microbiogen *Brasmedica, Braz.†.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Microcel *CPH, Port.*
Glycerol (p.2314·2).
Constipation.

Microcetim *Cipan, Port.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Microcid
Note. This name is used for preparations of different composition.
Bioglan, Denm.; Bioglan, Hung.†; Bioglan, Norw.; Bioglan, Swed.
Hydrogen peroxide (p.1647·3).
Bacterial skin infections; impetigo.

Boniscontro & Gazzone, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Microcidal *Pharmacare, S.Afr.*
Griseofulvin (p.535·2).
Fungal infections of the skin and nails.

Microclismata *Farmakochimiki, Gr.*
Glycerol (p.2314·2).
Bowel evacuation.

Microclismi Marco Viti *Marco Viti, Ital.*
Glycerol (p.2314·2); chamomile (p.2279·3); mallow (p.2337·2).
Bowel evacuation; constipation.

Microclismi Sella *Sella, Ital.*
Glycerol (p.2314·2); chamomile (p.2279·3); mallow (p.2337·2).
Bowel evacuation; constipation.

Microdiol
Note. This name is used for preparations of different composition.
Organon, Braz.; Organon, Israel; Organon, Spain.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Kimia, Indon.
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microdit *Kener, Mex.†.*
Ranitidine hydrochloride (p.1766·1).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Microdoine *Gomenol, Fr.*
Nitrofurantoin (p.308·1).
Cystitis.

Microfem *Lafedar, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microfemin *Grunenthal, Chile†.*
21 Tablets ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, ferrous fumarate (p.1938·3).
Combined oral contraceptive.

Microfer *Vianex (Βιανέξ), Gr.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Microflox *Micro, Thai.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Microfollin *Gedeon Richter, Rus.*
Ethinylestradiol (p.2101·3).

Microgel
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Oral suspension: Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Restan, S.Afr.†.
Tablets: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Gastrointestinal disorders.

Microgen *Silesia, Chile.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Micro-Gesic
Note. This name is used for preparations of different composition.
Micro, S.Afr.
Syrup: Paracetamol (p.108·1).
Fever; pain.

Micro, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain associated with tension.

Microgest
Note. A similar name is used for preparations of different composition (see below).
Schering, Thai.
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Microgeste
Note. A similar name is used for preparations of different composition (see above).
Bayer, Port.
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microginon *Bayer, Port.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microgyn *Schering, Denm.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microgynon *Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Chile; Schering, Cz.; Schering, Fin.; Schering, Ger.; Schering, Hong Kong; Schering, Indon.; Schering, Israel; Schering, Ital.; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Schering, Rus.; Bayer, Singapore; Schering, Spain; Schering, Switz.; Schering, Thai.; Schering, Turk.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Microgynon 30 *Schering, Irl.†; Bayer Schering, Malaysia; Bayer, UK.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Microiodid *Tatkhimfarmpreparaty, Rus.*
Potassium iodide (p.2169·2).
Goitre.

Micro-K *Wyeth, Canad.; Continental Ethicals, S.Afr.; Ther-Rx, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium supplement.

Microka *Valeant, Mex.*
Vitamin A (p.1971·2); phytomenadione (p.1995·3).
Bruising; periorbital hyperpigmentation; petechiae; purpura; telangiectasia.

Micro-Kalium *Lannacher, Austria.*
Potassium chloride (p.1684·3).
Potassium deficiency.

Microklist *Pfizer, Austria; Pfizer Consumer, Ger.; Pfizer Consumer, Switz.*
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Microlax
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer Consumer, Belg.; Pfizer, Canad.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Hong Kong; Pharmacia, Malaysia†; Pharmacia, NZ; Pfizer, Norw.; Pfizer, Rus.; Pharmacia, S.Afr.†; Pfizer, Swed.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Pfizer, Denm.; Pfizer Consumer, Irl.; Pfizer Consumer, Mex.; Jaba Recordati, Port.; Johnson & Johnson, Singapore.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3).
Bowel evacuation; constipation.

Pharos, Indon.
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); sorbitol (p.1965·1); macrogol 400 (p.2336·3).
Bowel evacuation; constipation.

Pfizer Consumer, Neth.
Sodium lauril sulfoacetate (p.2138·3); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Microlenyn *Pond's, Thai.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Microlet *Dexxon, Israel.*
Sodium citrate (p.1673·3); sodium lauril sulfoacetate (p.2138·3); glycerol (p.2314·2).
Constipation.

Microlev *Ido, Fr.†.*
Dried yeast (p.1998·3).
Vitamin B deficiency.

Microlevlen ED *Schering, Austral.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Microlift *Lagos, Arg.*
Marine algae; wheat germ (p.2415·1).
Skin disorders.

Microlipid *Novartis Nutrition, Canad.; Novartis, USA.*
Preparation for enteral nutrition containing safflower oil (p.1960·3) (p.1922·1).

Microlite *Berlipharm, Irl.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Microlut *Schering, Arg.; Schering, Austral.; Schering, Belg.; Schering, Chile†; Schering, Ger.; Schering, Mex.; Bayer, NZ; Schering, Rus.; Schering, Switz.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Microluton *Schering, Denm.; Schering, Fin.; Schering, Norw.†.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Micromex *Recalcine, Chile.*
Omeprazole (p.1753·1).
Gastric hyperacidity.

Micromycin *Darier, Mex.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Micronase *Pharmacia Upjohn, USA.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Micronazol *Pharma Line, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Micron-C *Dynamic, Philipp.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias due to deficiency of iron, folic acid, or vitamin B; vitamin B deficiency.

microNefrin *Bird, USA.*
⊗ Racepinefrine hydrochloride (p.1204·2).
Bronchospasm.

Micronema *Pfizer, Arg.*
Glycerol (p.2314·2); sodium laurilsulfate (p.2138·3); sorbitol (p.1965·1).
Constipation.

Micronoan *Abbott, Ital.*
Diazepam (p.986·3).
Epilepsy; sedative.

Micronor *Janssen-Cilag, Austral.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, UK.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Micronor HRT *Janssen-Cilag, UK†.*
Norethisterone (p.2119·3).
Menopausal disorders.

Micronovag *Novag, Mex.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Micronovum *Janssen-Cilag, Austria; Janssen-Cilag, S.Afr.; Janssen-Cilag, Switz.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Micropakine *Sanofi-Aventis, Fr.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy; febrile convulsions.

Micropaque *Codali, Belg.; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fr.; Guerbet, Ger.; R+N, Gr.; Guerbet, Hung.; Guerbet, Neth.; Martins & Fernandes, Port.; Rovi, Spain†; Guerbet, Switz.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Microphyllin *Aventis, S.Afr.*
Theophylline (p.1140·1).
Obstructive airways disease.

Micropil
Note. This name is used for preparations of different composition.
Sigma, Braz.
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
28-Day packs also contains 7 inert tablets.
Combined oral contraceptive.

Pascual, Philipp.
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Combined oral contraceptive; dysfunctional uterine bleeding.

Micropirin *Dexcel, Israel; Ratiopharm, UK.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Micropur *Voyage, Fr.†.*
Silver chloride complex (p.2387·1).
Water disinfection.

Micropur Forte DCCNa *Katadyn, Fr.*
Troclosene sodium (p.1665·3); silver (p.2387·1).
Water disinfection.

Micropyrin *Nicholas Piramal, India.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; inflammation; pain.

Microret *Royal, Chile; Darier, Mex.*
Vitamin A (p.1971·2).
Skin ageing; skin hyperpigmentation; wrinkles.

Microret K *Royal, Chile; Darier, Mex.*
Vitamin K (p.1995·2); vitamin A (p.1971·2).
Skin ageing; skin hyperpigmentation; wrinkles.

Microrgan *Liomont, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Microsan N *Biosyn, Ger.†.*
Multivitamin and magnesium preparation (p.1922·1).

Microser *Altana, Arg.; Grunenthal, Chile; Formenti, Cz.; Formenti, Hung.; Formenti, Ital.; Formenti, Pol.; Grunenthal, Venez.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; nausea and vomiting; nystagmus; vestibular disorders.

Microshield 2, 4, and 5 *Johnson & Johnson, Austral.*
Chlorhexidine gluconate (p.1635·3).
Skin, wound, and instrument disinfection.

Microshield Antimicrobial Hand Gel *Johnson & Johnson, Austral.*
⊗ Alcohol (p.1625·2).
Skin disinfection.

Microshield Antiseptic *Johnson & Johnson, Austral.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Skin, wound, burn, and instrument disinfection.

Microshield Handrub *Johnson & Johnson, Austral.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Skin disinfection.

Microshield PVP *Johnson & Johnson, Austral.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Microshield PVP-S *Johnson & Johnson, Austral.*
Povidone-iodine (p.1659·2).
Bacterial or fungal skin and mucous membrane infections; skin, wound, and burn disinfection.

Microshield T *Johnson & Johnson, Austral.*
Triclosan (p.1665·2).
Skin disinfection.

Microshield Tincture *Johnson & Johnson, Austral.*
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Skin, surface, and instrument disinfection.

Microsol *Herbaxt, Fr.*
A range of trace element and mineral preparations (p.1922·1).

Microsona *Valeant, Arg.; Valeant, Mex.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Microsona C *Valeant, Arg.*
⊗ Hydrocortisone acetate (p.1535·2); ketoconazole (p.539·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Microsona Otica *Valeant, Arg.*
⊗ Hydrocortisone (p.1535·2); acetic acid (p.2244·2).
Ear disorders.

Microstix-3 *Bayer, USA.*
Test for nitrite in urine and for bacterial growth.

Microsulf *Microsules, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Microsuy *Bernabo, Arg.*
Rutoside (p.2305·1) or troxerutin (p.2305·1); coumarin (p.2288·2).
Haemorrhoids; venous insufficiency.

Microterol *Microsules, Arg.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Microtid *Kener, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Microtina *Pyridam, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Microtrast *Codali, Belg.; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fr.; Guerbet, Ger.; Guerbet, Hung.; Guerbet, Port.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Microtrim *Rosen, Ger.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Microvac *Dupomar, Arg.*
Streptococcus pneumoniae; *Staphylococcus aureus*; *Streptococcus viridans*; *Haemophilus influenzae*; *Klebsiella pneumoniae*.
Respiratory-tract infections.

Microvaccin
Note. A similar name is used for preparations of different composition (see below).
Prater, Chile.
Fluconazole (p.532·1).
Fungal infections.

Microvacin
Note. A similar name is used for preparations of different composition (see above).
Asta Medica, Braz.†.
Bacterial antigens.
Allergen immunotherapy.

Microval *Wyeth, Austral.; Wyeth Lederle, Belg.†; Wyeth, Chile; Wyeth, Fr.; Aspen, NZ†; Akromed, S.Afr.; Wyeth, UK†; Wyeth, Venez.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Microvibrate *Lavipharm, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Microvita *Valeant, Mex.*
Vitamin A (p.1971·2).
Acne; cellulitis; keratinisation disorders; sun-induced skin damage.

Microvlar *Schering, Arg.; Schering, Braz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Microxin *Rayere, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Microzepam *Microsules, Arg.*
Lorazepam (p.1004·1).
Anxiety.

Microzide *Watson, USA.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Mictasol
Note. This name is used for preparations of different composition.
Medgenix, Belg.†.
Camphor monobromide; methenamine (p.298·3); mallow fruit (p.2337·2).
Anorectal disorders; urogenital disorders.

Millet Roux, Braz.
Mallow (p.2337·2).
Urinary-tract infections.

McNeil, Fr.
Mallow (p.2337·2); methenamine (p.298·3).
Urinary-tract disorders.

Asofarma, Mex.
Norfloxacin (p.309·2); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Mictasol Azul *Millet-Franklin, Arg.*
Mallow (p.2337·2); camphor monobromide; methylthioninium chloride (p.1450·3).
Genito-urinary tract disorders.

Mictasol Bleu *Formenti, Ital.†.*
Mallow (p.2337·2); methylthioninium chloride (p.1450·3).
Genito-urinary tract disorders; haemorrhoids.

Mictasol com Sulfa *Millet Roux, Braz.†.*
Mallow (p.2337·2); sulfachlorpyridazine (p.336·1); camphor (p.2273·2).
Urinary-tract infections.

Mictasol-P *Medgenix, Belg.*
Esculoside (p.2248·2); mallow (p.2337·2); methenamine (p.298·3); camphor monobromide; rutoside (p.2305·1).
Vascular disorders.

Mictasone *Formenti, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); tetracycline hydrochloride (p.347·2); mallow (p.2337·2).
Genito-urinary tract infections; haemorrhoids.

Mictonetten *Apogepha, Cz.; Apogepha, Ger.*
Propiverine hydrochloride (p.2192·2).
Bladder disorders; urinary incontinence.

Mictonorm *Apogepha, Cz.; Apogepha, Ger.; Apogepha, Port.; Apogepha, Thai.; Sandoz, Thai.*
Propiverine hydrochloride (p.2192·2).
Bladder instability; neurogenic bladder; urinary incontinence.

Mictral *Sanofi Synthelabo, Irl.†.*
Nalidixic acid (p.303·3); sodium citrate (p.1673·3); anhydrous citric acid (p.2284·1); sodium bicarbonate (p.1673·2).
Cystitis; lower urinary-tract infections.

Mictrin *HB, Braz.†; Econo Med, USA.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Micturol Sedante *Desma, Spain.*
Phenazopyridine hydrochloride (p.116·2); sulfamethizole (p.339·3).
Urinary-tract infections.

Micutrin *Pharmacia, Ital.*
Pyrrolnitrin (p.545·3).
Fungal skin infections.

Micutrin Beta *Pharmacia, Ital.†.*
⊗ Pyrrolnitrin (p.545·3); betamethasone valerate (p.1519·1).
Inflammatory fungal skin infections; onychomycosis.

Micyn-2 *Meyer, Venez.*
Pectin (p.2145·2); activated attapulgite (p.1709·1).
Diarrhoea.

Midacina *Lensa, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); gramicidin (p.286·1); neomycin (p.305·1).
Infected skin disorders.

Midacum *Hexal, S.Afr.*
Midazolam hydrochloride (p.1007·3).
General anaesthesia; premedication; sedative.

Midalet *Silesia, Chile.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Midalgan
Note. This name is used for preparations of different composition.
Welcker-Lyster, Canad.†.
Histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3); glycol salicylate (p.62·3); capsaicin (p.32·3).
Musculoskeletal and joint disorders.

Sanofi Synthelabo, Port.†.
Histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3); glycol salicylate (p.62·3).
Musculoskeletal and joint disorders.

Qualicare, Switz.
Histamine hydrochloride (p.2319·2); methyl nicotinate (p.85·3); glycol salicylate (p.62·3); capsicum (p.2276·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Midamor *MSD, Austral.; MSD, Austria; Orbus, Canad.; MSD, NZ; MSD, Swed.†; MSD, Switz.†; Merck, USA.*
⊗ Amiloride hydrochloride (p.1209·2).
Heart failure; hepatic cirrhosis with ascites; hypertension; hypokalaemia; oedema.

Midane *Pelpharma, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, or hirsutism in women; oral contraceptive in women with androgenic symptoms.

Midanium *Polfa Warszawa, Pol.; Cipla-Medpro, S.Afr.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedative.

Midapharma *Ares, Mex.*
Metformin hydrochloride (p.453·2); glibenclamide (p.440·1).
Diabetes mellitus.

Midarine *GSK, India; GSK, Ital.; GSK, Switz.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Midaselect *Curasan, Ger.†.*
Midazolam hydrochloride (p.1007·3).
Premedication; sedative.

Midatenk *Biotenk, Arg.*
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Midaven *Merck, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Midax *Gador, Arg.*
Olanzapine (p.1012·1).
Bipolar disorder; psychoses.

Midazepin *Behrens, Venez.*
Midazolam (p.1007·3).

Midazol *Taro, Israel; Hameln, Thai.†; TTN, Thai.†.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedative; status epilepticus.

Midazol Ofteno *Sophia, Mex.*
⊗ Naphazoline (p.1565·1); antazoline (p.567·1).

Midecamin *Merck, Mex.†.*
Midecamycin acetate (p.300·2).
Upper respiratory-tract infections.

Midecin *Farmaka, Ital.*
Midecamycin (p.300·2).
Bacterial infections.

Midelin *Quimica y Farmacia, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Miderm *Mendelejeff, Ital.*
Miconazole (p.541·2).
Fungal and Gram-positive bacterial infections.

Midermus
Note. This name is used for preparations of different composition.
Biosintex, Arg.
Range of emollient creams.

Ofar, Arg.†.
Vitamin A (p.1971·2).
Skin disorders.

Midermus Sol *Biosintex, Arg.*
Range of sunscreens.

Midetol *Precimex, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Midexone *SM, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Midium *Teofarma, Ital.*
Vitamin A palmitate (p.1973·1); tocoferil acetate (p.1992·3); pyridoxine hydrochloride (p.1978·2).
Metabolic disorders.

Midol
Note. This name is used for preparations of different composition.
Andromaco, Chile†.
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Valeant, Philipp.
Ibuprofen (p.64·2).
Pain.

Midol C *Hemofarm, Rus.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).

Midol Cramp & Body Aches *Bayer Consumer, USA.*
Ibuprofen (p.64·2).
Dysmenorrhoea; musculoskeletal and joint disorders.

Midol Extra Strength *Bayer Consumer, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3); mepyramine maleate (p.585·2).
Pain.

Midol Maximum Strength Multi-Symptom Menstrual *Sterling Health, USA.*
Paracetamol (p.108·1); mepyramine maleate (p.585·2).
Pain.

Midol PM *Sterling Health, USA.*
Paracetamol (p.108·1); diphenhydramine (p.577·1).

Midol PMS Extra Strength *Bayer Consumer, Canad.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Midol Pre-Menstrual Syndrome *Bayer Consumer, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Menstrual disorders.

Midol Regular *Bayer Consumer, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3).
Dysmenorrhoea.

Midol Teen Formula *Bayer Consumer, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).
Menstrual disorders.

Midol Traditional *Bayer Consumer, Canad.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Dysmenorrhoea.

Midolam Rafa, Israel.
Midazolam (p.1007·3).
General anaesthesia; premedication; status epilepticus.

Midolen Degorts, Mex.
Aspirin (p.20·3).
Fever; pain.

Midon Shire, Irl.
⊗ Midodrine hydrochloride (p.1341·1).
Orthostatic hypotension.

Midonat Aurora, Gr.†.
Nitrendipine (p.1358·2).
Hypertension.

Midotens Boehringer Ingelheim, Arg.†; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim Promeco, Mex.
Lacidipine (p.1322·2).
Hypertension.

Midrat Sandoz, Mex.
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Midriati Llorens, Spain.
Atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); phenylephrine hydrochloride (p.1568·1).
Eye disorders; production of mydriasis.

Midriaticum Allergan, Arg.†.
Tropicamide (p.1886·2).
Production of mydriasis.

Midric Sanbe, Indon.
Tropicamide (p.1886·2).
Production od mydriasis and cycloplegia.

Midrid Shire, Hong Kong†; Manx, UK.
⊗ Isometheptene mucate (p.2327·2); paracetamol (p.108·1).
Migraine and other vascular headaches.

Midrin Women First, USA.
⊗ Isometheptene mucate (p.2327·2); dichloralphenazone (p.994·2); paracetamol (p.108·1).
Tension and vascular headaches.

Midriodavi Davi, Port.
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis.

Midro
Note. This name is used for preparations of different composition.
Wolfs, Belg.†; Midro, Switz.
Senna (p.1769·2).
Constipation.

Vaillant, Ital.
Senna (p.1769·2); liquorice (p.1740·3); peppermint leaf (p.1761·2); caraway (p.2276·3).
Constipation.

Crefar, Port.†.
Senna (p.1769·2); liquorice (p.1740·3); peppermint leaf (p.1761·2); clove (p.2284·3); delphinium consolida; mallow (p.2337·2).
Constipation.

Midro Abfuhr Midro, Ger.
Senna (p.1769·2).
Constipation.

Midro Pico Midro, Ger.†.
Sodium picosulfate (p.1771·1).
Constipation.

Midro Tee
Note. This name is used for preparations of different composition.
Sanova, Austria.
Senna (p.1769·2); peppermint leaf (p.1761·2); caraway (p.2276·3); liquorice (p.1740·3); delphinium consolida; mallow flowers (p.2337·2).
Constipation.

Midro, Ger.
Senna (p.1769·2).
Constipation.

Midro-Tea Midro, Israel.
Senna (p.1769·2); peppermint leaf (p.1761·2); caraway (p.2276·3); liquorice (p.1740·3); delphinium consolida flower; mallow flower (p.2337·2).
Constipation.

Miduret PP Lab, Thai.†.
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Midy Vitamine C GSK Sante, Fr.
Ascorbic acid (p.1983·3).
Asthenia; vitamin C deficiency.

Mielax Valma, Chile.
Senna (p.1769·2); honey (p.1948·2).

Mielito Ximena Polanco, Chile.
Honey (p.1948·2); herbal extract.
Colds and influenza; tonic.

Mielocol Herbes Universelles, Canad.
Guaifenesin (p.1561·3); aralia racemosa; cineole (p.2282·3); honey (p.1948·2); poplar buds (p.2371·1); sanguinaria (p.2383·2); white pine; wild cherry (p.2415·2).

Mielogen Schering-Plough, Gr.; Schering-Plough, Ital.†.
Molgramostim (p.1073·3).
Bone marrow transplantation; neutropenia.

Mielomade Esfar, Port.†.
Gamma-aminobutyric acid (p.2308·1).
Hypertension; mental function disorders.

Mifegest Zydus, India.
Mifepristone (p.2011·2).
Termination of pregnancy.

Mifegyne Pharma Logistics, Belg.; Exelgyn, Denm.; Exelgyn, Fin.; Exelgyn, Fr.; Contragest, Ger.; Exelgyn, Gr.; Exelgyn, Israel; Istar, NZ; Nordic, Neth.; Exelgyn, Norw.; Medirex, Port.; Medi Challenge, S.Afr.; Anroch, Spain; Exelgyn, Swed.; Cosan, Switz.; Exelgyn, UK.
Mifepristone (p.2011·2).
Induction of labour following intra-uterine fetal death; termination of pregnancy.

Mifelar Arlex, Mex.
Metformin (p.453·3).
Diabetes mellitus.

Mifelar-C Arlex, Mex.
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Mifeprex Danco, USA.
Mifepristone (p.2011·2).
Termination of pregnancy.

Miferen Sterling Health, Spain†.
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Miflason Novartis, Cz.†.
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Miflasona Novartis, Braz.
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Miflasone Novartis, Fr.; Novartis, NZ†.
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Mifler Velka, Gr.
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin disorders.

Miflo Promedica, Ital.
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Miflonid Novartis, Cz.; Novartis, Turk.
⊗ Budesonide (p.1520·1).
Asthma.

Miflonide Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Denm.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Switz.; Novartis, Venez.
⊗ Budesonide (p.1520·1).
Asthma; obstructive airways disease.

Miflonil Novartis, Fr.
⊗ Budesonide (p.1520·1).
Asthma.

Miformin Greater Pharma, Thai.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Migard Menarini, Fin.; Menarini, Gr.; Menarini, Neth.; Menarini, Port.; Menarini, UK.
Frovatriptan succinate (p.622·3).
Migraine.

Migarid Cipla, India; Cipla, Malaysia.
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Migea Hexal, Austria; Hexal, Cz.; Hexal, Denm.; Gea, Fin.†; Gea, Norw.†; Gea, Pol.; Gea, Swed.†.
Tolfenamic acid (p.130·1).
Migraine.

Migel Pharma Italia, Ital.
Acetylcysteine (p.1548·2); hyaluronic acid (p.2320·1); vitamin E (p.1992·2).
Nasal congestion.

Migentax Geofman, Philipp.
Gentamicin sulfate (p.282·1).
Bacterial infections.

Miglucan Roche, Fr.
Glibenclamide (p.440·1).
Diabetes mellitus.

Mignar Glenmark, India†.
Miglitol (p.454·3).
Diabetes mellitus.

Migpriv Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.†; Sanofi Winthrop, Denm.†; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Norw.†; Sanofi-Aventis, Pol.; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.
Lysine aspirin (p.79·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migra Dioxadol Bago, Arg.
Metamizole magnesium (p.49·3); ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Migra Dorixina Roemmers, Arg.
Clonixin lysine (p.37·1); ergotamine tartrate (p.620·1).
Migraine.

Migracin Max Farma, Ital.
Amikacin sulfate (p.200·3).
Bacterial infections.

Migradexan Collins, Mex.†.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Migradon Schmidgall, Austria.
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Migradorixina Roemmers, Venez.
Clonixin lysine (p.37·1); ergotamine tartrate (p.620·1).
Migraine.

Migraeflux Hennig, Cz.
Dimenhydrinate (p.576·2); paracetamol (p.108·1).
Migraine.

Migraeflux MCP Hennig, Ger.
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migraeflux N Hennig, Ger.
Orange tablets, dimenhydrinate (p.576·2); paracetamol (p.108·1); green tablets, paracetamol; codeine phosphate (p.37·2).
Migraine and other vascular headaches.

Migraeflux orange N Hennig, Ger.
Dimenhydrinate (p.576·2); paracetamol (p.108·1).
Migraine and other vascular headaches.

Migrafen Chatfield Laboratories, UK.
Ibuprofen (p.64·2).

Migrafin Sanofi Synthelabo, Neth.
Lysine aspirin (p.79·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migragesic Andromaco, Chile.
Ergotamine tartrate (p.620·1); dipyrone (p.49·2); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Migraine and other vascular headaches.

Migraherb MedicHerb, UK.
Feverfew (p.622·2).
Migraine.

Migraine Ice Mentholatum, UK.
Water-based gel compress.
Migraine and other severe headache.

Migraine-Kranit Krewel, Switz.
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Migraine and other vascular headaches.

Migral Montpellier, Arg.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dipyrone (p.49·2).
Cluster headache; migraine; tension headache.

Migral II Montpellier, Arg.
Ibuprofen (p.64·2); caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Cluster headache; migraine; tension headache.

Migral Compositum Montpellier, Arg.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dipyrone (p.49·2); metoclopramide hydrochloride (p.1747·3).
Cluster headache; migraine; tension headache.

Migralave + MCP Temmler, Ger.
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migralave N Temmler, Ger.†.
Buclizine hydrochloride (p.570·1); paracetamol (p.108·1).
Migraine and other vascular headaches.

Migraless Pliva, Ital.
Nimesulide (p.95·3).
Fever; inflammation; pain.

Migraleve
Note. This name is used for preparations of different composition.
Pfizer Consumer, Irl.; Janssen-Cilag, Port.; Unipharma, Switz.; McNeil, UK.
Pink tablets, buclizine hydrochloride (p.570·1); paracetamol (p.108·1); codeine phosphate (p.37·2); yellow tablets, paracetamol; codeine phosphate.
Migraine and other vascular headaches.

Charwell, Israel; Llorens, Spain.
Buclizine hydrochloride (p.570·1); paracetamol (p.108·1); codeine phosphate (p.37·2); docusate sodium (p.1725·1).
Migraine and other vascular headaches.

Migralgine McNeil, Fr.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain.

Migralin Menarini, Gr.
Frovatriptan (p.622·3).
Migraine.

Migraliv Sigma, Braz.
Caffeine (p.1116·3); dipyrone (p.49·2); dihydroergotamine mesilate (p.618·2).
Migraine.

Migramax Cephalon, UK.
Lysine aspirin (p.79·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migran Konimex, Indon.
Paracetamol (p.108·1); propyphenazone (p.119·3).
Pain.

Migranal Novartis, Austria; SteriMax, Canad.; Novartis, Ital.†; Novartis, Swed.†; Valeant, USA.
Dihydroergotamine mesilate (p.618·2).
Migraine.

Migranat Rowa, Irl.
Caffeine (p.1116·3); ergotamine tartrate (p.620·1); pipoxolan hydrochloride (p.2368·3).
Migraine and other vascular headaches.

Migrane Sigma, Braz.
Aspirin (p.20·3); ergotamine tartrate (p.620·1); homatropine methylbromide (p.1881·3); caffeine (p.1116·3).
Migraine.

Migra-Nefersil Pharma Investi, Chile.
Clonixin lysine (p.37·1); ergotamine tartrate (p.620·1).
Migraine and other vascular headaches.

Migrane-Gastreu R16 Reckeweg, Ger.
Homoeopathic preparation.

Migraneitor Driburg, Arg.
Sumatriptan (p.625·2).
Migraine.

Migrane-Kranit Krewel, Ger.
Phenazone (p.116·1).
Formerly known as Migräne-Kranit mono.
Migraine.

Migrane-Kranit Duo Krewel, Ger.†.
Paracetamol (p.108·1); propyphenazone (p.119·3).
Dysmenorrhoea; headache including migraine.

Migrane-Kranit N Krewel, Ger.†.
Paracetamol (p.108·1); propyphenazone (p.119·3); codeine phosphate (p.37·2).
Headache including migraine.

Migrane-Neuridal Krewel, Ger.
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine and other vascular headaches.

Migranerton Dolorgiet, Cz.; Dolorgiet, Ger.
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine and other vascular headaches.

Migranette Sigma, Braz.
⊗ Dipyrone (p.49·2); isometheptene mucate (p.2327·2); caffeine (p.1116·3).
Migraine.

Migranil
Note. This name is used for preparations of different composition.
Inga, India.
Injection: Dihydroergotamine mesilate (p.618·2).
Migraine.

Inga, India.
Tablets: Ergotamine tartrate (p.620·1); caffeine (p.1116·3); belladonna (p.2263·3); paracetamol (p.108·1).
Formerly contained ergotamine tartrate and caffeine.
Migraine.

Migranin Boots Healthcare, Ger.†.
Phenazone (p.116·1); caffeine (p.1116·3).
Migraine; pain.

Migranin Ibuprofen Boots Healthcare, Ger.
Ibuprofen (p.64·2).
Headache including migraine.

Migranol Bago, Chile.
Ergotamine tartrate (p.620·1); dipyrone (p.49·2); caffeine (p.1116·3).
Migraine and other vascular headaches.

Migraprim Sanofi-Aventis, Ital.
Lysine aspirin (p.79·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Migraspirina Bayer, Port.
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Migrastick Arkopharma, UK.
Lavender oil (p.2331·2); peppermint oil (p.1761·2).
Migraine.

Migratam Laboratorios Chile, Chile.
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dipyrone (p.49·2).
Migraine and other vascular headaches.

Migratan S Berlin-Chemie, Ger.†.
Ergotamine tartrate (p.620·1); propyphenazone (p.119·3).
Migraine and other vascular headaches.

Migratapsin Maver, Chile.
Paracetamol (p.108·1); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Migraine.

MigraTen Pharmelle, USA.
⊗ Isometheptene mucate (p.2327·2); caffeine (p.1116·3); paracetamol (p.108·1).
Migraine; tension headache.

Migratine Major, USA†.
⊗ Isometheptene mucate (p.2327·2); dichloralphenazone (p.994·2); paracetamol (p.108·1).
Tension and vascular headaches.

Migraval Giempi, Venez.
Sumatriptan succinate (p.625·2).
Cluster headache; migraine.

Migrax Saval, Chile.
Paracetamol (p.108·1); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Vascular headache.

Migrenol Sanofi-Aventis, Pol.
Camphor (p.2273·2); eucalyptus oil (p.2301·2); mint oil (p.2345·2); menthol (p.2340·1).
Migraine; neuromuscular pain.

Migretil Bial, Port.
Belladonna (p.2263·3); caffeine (p.1116·3); ergotamine tartrate (p.620·1); paracetamol (p.108·1).
Migraine.

Migrexa Lichtenstein, Ger.†.
Ergotamine tartrate (p.620·1).
Cluster headache; migraine.

Migril GSK, Austria; GSK, Hong Kong†; Wellcome, Irl.†; 3M, S.Afr.; CP Pharmaceuticals, UK.
Ergotamine tartrate (p.620·1); cyclizine hydrochloride (p.574·2); caffeine hydrate (p.1117·1).
Migraine.

Migristene Aventis, Indon.; Aventis, Mex.
Dimetotiazine mesilate (p.577·1).
Migraine.

Migrof Chibret, Port.
Rizatriptan benzoate (p.625·1).
Migraine.

Mihexine Milano, Thai.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mijal *Juste, Spain†.*
Butibufen (p.31·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Mijex
Pickles, UK.
Gel: Diethyltoluamide (p.2041·1).
Insect repellent.
Pickles, UK.
Topical liquid; topical spray; topical stick: Diethyltoluamide (p.2041·1).
Insect repellent.

Mijex Extra *Pickles, UK.*
Ethyl butylacetylamino propionate (p.2043·1).
Insect repellent.

Mikacin *Aristo, India; Julphar, UAE.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Mikan *Boniscontro & Gazzone, Ital.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

mikanil *Mickan, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; superficial vascular disorders.

Mikasin *Kalbe, Indon.; Abfar, Turk.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Mikavir *Salus, Ital.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Mikazul *Ederka, Mex.*
Amikacin (p.200·2).
Bacterial infections.

Mikelan *Merck-Lipha, Fr.; Otsuka, Jpn; Otsuka, Philipp.; Noristan, S.Afr.†; Otsuka, Spain.*
⊗ Carteolol hydrochloride (p.1241·1).
Angina pectoris; arrhythmias; glaucoma; hypertension; ocular hypertension.

Mikesan *Baliarda, Arg.*
Ergotamine tartrate (p.620·1); cyproheptadine hydrochloride (p.575·1); clonixin (p.37·1).
Migraine.

Mi-Ke-Sons *Sons, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Mikium *Almirall, Chile†.*
Ciclopirox (p.529·2).
Nail, skin, and vulvovaginal infections.

Miklogen *Klonal, Arg.*
⊗ Miconazole (p.541·2); betamethasone valerate (p.1519·1); gentamicin (p.284·2).
Infected skin disorders.

Mikoderm *Adeka, Turk.*
Tolnaftate (p.548·3).
Fungal skin infections.

Mikogal *Teva, Hung.; Biogal, Rus.*
Omoconazole nitrate (p.544·1).
Fungal and bacterial skin, nail, and vulvovaginal infections.

Miko-Penetran *Embil, Turk.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

Mikorex *Bintang Toedjoe, Indon.*
Menthol (p.2340·1); salicylic acid (p.1612·2); undecenoic acid (p.549·2); benzoic acid (p.1630·2).
Fungal skin infections.

Mikostat *Gulf, Malaysia; Julphar, UAE.*
Nystatin (p.543·2).
Candidiasis.

Mikostat Baby Ointment *Julphar, UAE.*
Nystatin (p.543·2); zinc oxide (p.1621·2).
Fungal skin infections; nappy rash.

Mikostatin *BMS, Turk.*
Nystatin (p.543·2).
Candidiasis.

Mikozal *Julphar, UAE.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mikrazym *Leksir, Rus.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Mikro-30 *Wyeth, Ger.†.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Mikrobac *Bode, Ger.*
Benzalkonium chloride (p.1629·1); dodecylbispropylenetriamine.
Surface disinfection.

Mikrofollin *Gedeon Richter, Hung.†.*
Ethinylestradiol (p.2101·3).
Acne; amenorrhoea; prostatic cancer.

Mikrosid *Gunsa, Turk.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Miktosyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Mikutan N *Streuli, Switz.*
Aluminium acetate (p.2255·1); zinc oxide (p.1621·2).
Burns; skin disorders.

Mila-Asma *Milano, Thai.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Mila-Cono *Milano, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Milador *Hexal, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Milafed *Milano, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Milage *Cadila, India.*
Protein and vitamin preparation (p.1922·1).
Nutritional supplement.

Milagin *Milano, Thai.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Milamet *Milano, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer.

Milamox *Milano, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Milanidazole *Milano, Thai.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Milanolone *Milano, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Mouth disorders.

Mila-Tercon *Milano, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Milavir *Novartis Consumer, Port.; Novartis Consumer, Spain.*
Aciclovir (p.862·3).
Herpes simplex infections.

Milax
Note. This name is used for preparations of different composition.
Josper, Braz.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Berlin-Chemie, Ger.
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Milbeta *Offenbach, Mex.*
Cyanocobalamin (p.1980·2); hydroxocobalamin (p.1980·3).

Milbron *Silesia, Chile†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Milco *Piam, Ital.*
Preparation for enteral nutrition (p.1922·1).
Phenylketonuria.

Milcobalin *Richet, Arg.*
Hydroxocobalamin; thiamine; pyridoxine (p.1922·1).
Formerly known as Mil Cobalin Nueva Formula.
Neuritis; vitamin supplement.

Milcopen *Leiras, Fin.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Milcor *Corsalud, Venez.†.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Mildac *Merck Medication Familiale, Fr.*
St John's wort (p.422·3).
Depression.

Mildex *Parggon, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin (p.305·1).
Infected eye disorders.

Mildin *Copyfarm, Denm.*
Loratadine (p.583·3).
Allergic rhinitis; hay fever; urticaria.

Mildison *Yamanouchi, Denm.; Yamanouchi, Irl.†; CSL, NZ; Yamanouchi, NZ; Astellas, Neth.; Astellas, Norw.; Astellas, Swed.; Astellas, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Mildronate *Grindex, Rus.*
Meldonium dihydrate (p.1332·3).
Alcohol withdrawal syndrome; cerebrovascular disorders; heart failure; ischaemic heart disease; retinal disorders; tonic.

Mildroxyn *Makiz-Pharma, Rus.*
Meldonium dihydrate (p.1332·3).
Alcohol withdrawal syndrome; cerebrovascular disorders; ischaemic heart disease; tonic.

Miles Nervine *Miles, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Mileva *Elea, Arg.; Elea, Mex.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; combined oral contraceptive in women with androgenic symptoms; polycystic ovary syndrome.

Milezin *Leciva, Cz.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive disorders; premenstrual dysphoric disorder.

Milezzol *Randall, Mex.*
Metronidazole (p.837·1).
Trichomoniasis.

Milfarin *Milupa, Port.†.*
Nutritional supplement (p.1922·1).

Milgamma
Note. This name is used for preparations of different composition.
Worwag, Cz.; Worwag, Hung.
Benfotiamine (p.1975·2); cyanocobalamin (p.1980·2).
Neurological symptoms associated with vitamin B deficiency.
Worwag, Ger.; Worwag, Hong Kong.
Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Neurological symptoms associated with vitamin B deficiency.
Worwag, Rus.
Injection: Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine (p.1976·3).
Worwag, Rus.
Lozenges: Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Myalgia; neuralgia; neuritis; neuropathy.

Milgamma mono *Worwag, Ger.*
Benfotiamine (p.1975·2).
Vitamin B deficiency.

Milgamma N
Note. This name is used for preparations of different composition.
Worwag, Ger.
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Myalgia; neuralgia; neuritis; polyneuropathy.
Worwag, Hung.
Pyridoxine hydrochloride (p.1978·2); benfotiamine (p.1975·2) or thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Myalgia; neuralgia; neuritis.
Worwag, Pol.
Thiamine (p.1976·3); pyridoxine (p.1979·1); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to reduce the pain of injection.
Neuralgia; neuritis; neuropathy.
Worwag, Cz.
Capsules: Benfotiamine (p.1975·2); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2).
Neurological symptoms associated with vitamin B deficiency.
Worwag, Cz.
Injection: Thiamine hydrochloride (p.1976·1); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2).
Neurological symptoms associated with vitamin B deficiency.

Milgamma-NA *Worwag, Ger.*
Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Neurological symptoms associated with vitamin B deficiency.

Milgex *Klinger, Braz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Milical
Note. This name is used for preparations of different composition.
Recalcine, Chile; Vivax Gynopharm, Venez.
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.
Glenmark, India; Glenmark, Malaysia.
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium supplement; dietary supplement in pregnancy and lactation; osteoporosis.

Milical-XP *Glenmark, India†.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); magnesium; zinc (p.1922·1).
Mineral and vitamin D supplement.

Milice *Mipharm, Ital.*
Piperonyl butoxide (p.2049·1); pyrethrin (p.2049·3).
Pediculosis.

Milicor *Samarth, India.*
Milrinone (p.1341·2).
Heart failure.

Milid *Sanochemia, Austria; Rottapharm, Ital.†; Delta, Port.†.*
Proglumide (p.1764·2).
Gastrointestinal disorders.

Milidon *Malayan, Singapore†.*
Paracetamol (p.108·1).
Cold and influenza symptoms; fever; pain.

Milidon CF *Malayan, Singapore†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion; rhinitis.

Milithin *Minerva (Μινερβα), Gr.*
Lithium carbonate (p.401·3).
Bipolar disorder; mania.

Milk of Magnesia *Rougier, Canad.; GSK, Gr.; GSK Consumer, Irl.; Droreth, Israel; Pharmasant, Thai.; GSK Consumer, UK; Cypress, USA; Roxane, USA.*
Magnesium hydroxide (p.1743·2).
Antacid; constipation; dyspepsia; heartburn.

Milk Thistle *Nutravite, Canad.*
Cynara flower (p.2291·2); milk thistle (p.1452·1); turmeric rhizome (p.1473·2).

Milk Thistle Extract Formula *Quest, Canad.†.*
Butternut root; taraxacum root (p.2395·1); liquorice root (p.1740·3); milk thistle (p.1452·1); dioscorea villosa root.

Milla *SIT, Ital.*
Chamomile (p.2279·3).

Millerspas *Aspen, S.Afr.*
Hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); phenobarbital (p.492·2).
Peptic ulcer; reduction of respiratory and gastrointestinal secretions; renal and biliary colic.

Millibar *Lisapharma, Hong Kong; Lisapharma, Ital.; Lisapharma, Singapore†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Millicortene *Novartis, Switz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Millicortenol *Novartis, India.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Millicorten-Vioform *Novartis, India.*
⊗ Dexamethasone pivalate (p.1526·3); clioquinol (p.254·1).
Infected skin disorders.

Millidol *Millimed, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Milligest *Gedeon Richter, Cz.; Gedeon Richter, Hung.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Triphasic oral contraceptive.

Milligynon *Schering, Fr.*
Norethisterone acetate (p.2119·3).
Progestogen-only oral contraceptive.

Millipred *Laser, USA.*
Prednisolone (p.1540·3).
Corticosteroid.

Millisrol *Khandelwal, India; Kayaku, Jpn.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension during surgery; maintenance of hypotension during surgery.

Milneuron NA *Worwag, Ger.*
Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Neurological symptoms associated with vitamin B deficiency.

Milocardin *Polpharma, Pol.*
Bromisoval (p.965·1); mint oil (p.2345·2); phenobarbital sodium (p.492·2); lupulus oil.
Gastrointestinal motility disorders; nervous disorders.

Miloderme *Schering-Plough, Port.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Milorex *Remedica, Thai.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Miloride *Merck, Fin.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Miloz *Novell, Indon.*
Midazolam (p.1007·3).
Anaesthesia; premedication; sedative.

Mil-Par *Gramon, Arg.; Merck Consumer, UK; Sanofi-Aventis, Venez.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Milpar *Sanofi Synthelabo, Mex.*
Magnesium hydroxide (p.1743·2); liquid paraffin (p.2030·3).
Constipation.

Milperinol *Pierre Fabre, Belg.*
St John's wort (p.422·3).
Depression.

Milrila *Yamanouchi, Jpn.*
Milrinone (p.1341·2).
Heart failure.

Milrosina *Biogalenica, Spain.*
Resorcinol (p.1612·1); borax (p.2268·1).
Mouth ulcers.

Milrosina Nistatina *Biogalenica, Spain.*
⊗ Hydrocortisone hydrogen succinate (p.1535·3); nystatin (p.543·2).
Oral candidiasis.

Milsan *Merck, Mex.*
Preparation for enteral nutrition (p.1922·1).
Gastro-enteritis.

Milsana *Milte, Ital.*
Zinc oxide (p.1621·2).
Barrier cream; nappy rash.

Miltaun *Altana, Austria.*
Meprobamate (p.1006·2).
Anxiety disorders; premedication; skeletal muscle spasticity; sleep disorders.

Miltex *Baxter, Austria; Asta Oncologia, Braz.; Baxter, Chile†; Asta Medica, Cz.†; Asta Medica, Fin.†; Baxter Oncology, Fr.; Baxter Oncology, Ger.; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter Oncology, Malaysia†; Baxter, Philipp.; Baxter Oncology, Singapore; Prasfarma, Spain; Baxter, Swed.; IDIS, UK.*
Miltefosine (p.751·1).
Skin metastases of breast cancer.

Miltina IPO *Milte, Ital.*
Infant feed (p.1922·1).
Food intolerance.

Milton
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.
Troclosene sodium (p.1665·3) or sodium hypochlorite (p.1661·1).
Disinfection of infant feeding equipment; disinfection of surfaces and equipment.

SIT, Ital.
Sodium hypochlorite (p.1661·1).
Decontamination of fruit and vegetables; sterilisation of feeding bottles; water purification.

Ceuta, UK.
Liquid: Sodium hypochlorite (p.1661·1).
Disinfection.

Ceuta, UK.
Sterilising tablets: Troclosene sodium (p.1665·3).
Disinfection.

Milton Anti-Bacterial *Biotech, Singapore.*
Troclosene sodium (p.1665·3) or sodium hypochlorite (p.1661·1).
Disinfection.

Miltown *Wallace, USA†.*
Meprobamate (p.1006·2).
Anxiety.

Milumel AR *Milupa, Fr.*
Infant feed (p.1922·1).
Regurgitation.

Milumel HA *Milupa, Fr.*
Infant feed (p.1922·1).
Milk-protein allergy.

Milupa Aptamil AR *Milupa, Ital.*
Infant feed (p.1922·1).
Regurgitation.

Milupa Aptamil HA *Milupa, Ital.*
Infant feed (p.1922·1).
Food intolerance.

Milupa Aptamil HN 25 *Milupa, Ital.*
Food for special diets (p.1922·1).
Diarrhoea.

Milupa Aptamil Soya *Milupa, Ital.*
Infant feed (p.1922·1).
Lactose intolerance.

Milupa basic *Milupa, Ital.*
A range of foods for special diets (p.1922·1).

Milupa Biber-C *Milupa, Ital.*
Carbohydrate, amino-acid, lipid, and mineral preparation with vitamin C (p.1922·1).
Nutritional supplement.

Milupa Biberfrutta *Milupa, Ital.*
Carbohydrate, amino-acid, and lipid preparation with vitamin C and iron (p.1922·1).
Nutritional supplement.

Milupa Cystilac *Milupa, Pol.*
Infant feed (p.1922·1).
Cystic fibrosis.

Milupa GES *Milupa, Austria; Milupa, Ital.; Milupa, Switz.*
Potassium chloride; sodium chloride; sodium bicarbonate; anhydrous glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Milupa HN 25 *Altana, Mex.; Milupa, Switz.*
Food for special diets (p.1922·1).
Diarrhoea; gluten intolerance.

Milupa HOM *Milupa, Ital.*
Food for special diets (p.1922·1).
Homocystinuria.

Milupa LP *Milupa, Ital.*
Low protein food for special diets (p.1922·1).

Milupa lpd *Milupa, UK.*
Food for special diets (p.1922·1).
Inherited disorders of amino-acid metabolism in childhood.

Milupa Lpf *Milupa, Ital.*
Food for special diets (p.1922·1).
Protein metabolism disorders; renal impairment.

Milupa LYS *Milupa, Ital.*
Food for special diets (p.1922·1).
Hyperlysinaemia.

Milupa Milumil AR *Milupa, Ital.†.*
Infant feed (p.1922·1).
Gastro-oesophageal disorders.

Milupa MSUD *Milupa, Ital.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

Milupa OS *Milupa, Ital.*
Food for special diets (p.1922·1).
Methylmalonic aciduria; propionic acidaemia.

Milupa PKU *Milupa, Cz.†; Milupa, Ital.; Milupa, Pol.*
Infant feed (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Milupa Pregomin *Milupa, Ital.*
Preparation for enteral nutrition (p.1922·1).
Diarrhoea; disorders of fructose and galactose metabolism; food hypersensitivity; gastrointestinal resection; milk and soya intolerance.

Milupa Som *Milupa, Ital.†.*
Food for special diets (p.1922·1).
Disaccharide deficiency; fructosaemia; galactosaemia; milk intolerance.

Milupa TYR *Milupa, Ital.*
Food for special diets (p.1922·1).
Hypertyrosinaemia.

Milupa UCD *Milupa, Ital.*
Food for special diets (p.1922·1).
Argininosuccinic aciduria; citrullinaemia; hyperammonaemia; hyperargininaemia; ornithinaemia.

Milurit *Egis, Cz.; UCB, Ger.; Egis, Hong Kong; EGIS, Hung.; Egis, Pol.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi; uric acid nephropathy.

Milvane *Schering, Cz.†; Schering, Denm.; Schering, Ital.; Schering, Pol.; Schering, Switz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Milyzer *Mitsui, Jpn†.*
Nateplase (p.1346·3).

Milzimmunosyx *Syxyl, Ger.*
Homoeopathic preparation.

Milzine
Note. This name is used for preparations of different composition.
Vickmans, Hong Kong†.
Oral suspension: Oxetacaine (p.1867·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Vickmans, Hong Kong†.
Tablets: Oxetacaine (p.1867·2); magnesium carbonate (p.1743·1); aluminium hydroxide (p.1706·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Milzone *Rubio, Spain.*
Sodium valproate (p.508·2).
Epilepsy.

Mimedran *Esteve, Spain.*
Piperazine sultamate (p.153·2).
Hyperlipidaemias.

Mimetix *Drugtech, Chile.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Mimixin *Merck, Arg.*
Buflomedil (p.1237·1); diosmin (p.2304·2).
Peripheral vascular disorders; thromboses; venous insufficiency.

Mimpara
Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Genesis, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Amgen, UK.
Cinacalcet hydrochloride (p.1095·1).
Hypercalcaemia in parathyroid cancer; hypercalcaemia in primary hyperparathyroidism; secondary hyperparathyroidism in dialysis patients with end-stage renal failure.

Mimyx *Stiefel, USA.*
Betaine; olive oil; glycerol; pentylene glycol; palm glycerides; vegetable oil; squalane; hyetellose; carbomer; xanthan gum.
Burning and pruritus associated with eczema.

Min Huil *Neo Dermos, Arg.*
Pyrithione zinc (p.1611·2).
Pityriasis.

Min O *Biol, Arg.*
Nystatin (p.543·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Vaginal infections.

Minac 50 *Spirig, Switz.*
Minocycline hydrochloride (p.300·3).
Acne.

Minachlor *Esoform, Ital.*
Tosylchloramide sodium (p.1665·1).
Disinfection of wounds, burns, and external genitalia.

Minadex *Abdi, Turk.; Seven Seas, UK.*
Vitamin preparation (p.1922·1).

Minafen *Drogsan, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Minakne *Galen, Ger.*
Minocycline hydrochloride (p.300·3).
Acne.

Minalerg *Minerva (Μινέρβα), Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Minalfene *Bouchara-Recordati, Fr.*
Alminoprofen (p.18·3).
Inflammation; pain.

Minalgine *Streuli, Switz.*
Dipyrone (p.49·2).
Colic; fever; pain.

Minalka *Cedar Health, UK.*
Mineral preparation with vitamin D (p.1922·1).
Musculoskeletal and joint disorders.

Minamino
MPS, Austral.†.
Vitamins, minerals, and amino acids with liver, spleen, and gastric mucosa (p.1922·1).
Dietary supplement.

Pharmacare, S.Afr.
Amino acids, vitamin B substances, minerals, organ extracts (p.1922·1).
Tonic.

Ayrton, UK.
Vitamin B substances, amino acids, minerals (p.1922·1).

Minaphlex *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; SHS, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

Min-A-Pon *Minerva (Μινέρβα), Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Minard's Joint Relief *Stella, Canad.*
Menthol (p.2340·1); methyl salicylate (p.85·3).

Minard's Liniment *Stella, Canad.*
Camphor (p.2273·2); ammonium hydroxide; turpentine.

Minartine *Minerva (Μινέρβα), Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Minatuss *Minerva (Μινέρβα), Gr.*
Butamirate citrate (p.1553·1).
Cough.

Minax *Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Thai.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; migraine; myocardial infarction.

Minaxen *Aegis, Hong Kong.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minazol
Note. This name is used for preparations of different composition.
Cimed, Braz.
Phenazopyridine (p.116·3); nitroxoline (p.309·2).
Urinary-tract infections.

Camden, Singapore.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mincifit *Arkopharma, Fr.*
Black currant leaves (p.2267·1); green tea (p.2416·1).
Obesity.

Mindac *Eagle, Austral.*
Bacopa monnieri; ginkgo biloba; centella asiatica; withania somnifera; schisandra chinensis; ginger oleoresin; glutamine; magnesium aspartate; potassium aspartate; nux vomica; pyridoxine hydrochloride.
Tonic.

Mindiab *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
Glipizide (p.441·3).
Diabetes mellitus.

Mindol *Pacific, NZ†.*
Mebendazole (p.148·3).
Worm infections.

Mindol-Merck *Bracco, Ital.†.*
Propyphenazone (p.119·3); caffeine (p.1116·3); ethylmorphine hydrochloride (dionina) (p.52·2).
Pain.

Mindosan V *Loren, Mex.†.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Minegyl *Luper, Braz.†.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).

Minegyl C/Nistatina *Luper, Braz.†.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

Minera *Hua, Thai.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Mineral *Volchem, Ital.*
Mineral preparation (p.1922·1).

Mineral Freez Gel *Geritrex, USA.*
Menthol (p.2340·1).

Minerali *CTS, Israel.*
Glucose; sodium chloride; sodium citrate; potassium chloride; citric acid (p.1672·2).
Diarrhoea; oral rehydration therapy.

Mineralin *Doctum, Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).
Constipation.

Minerasol *Pharno-Wedropharm, Ger.*
Emser salts.
Nasal congestion.

Minerbon *Diba, Mex.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Minerovit *Cifarma, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Minerva *Schering, Austria; Bayer Schering, Cz.; Biogaran, Fr.; Schering, Hung.; Schering, S.Afr.; Berlis, Switz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, hirsutism, or seborrhoea in women; oral contraceptive in women with androgenic symptoms.

Minervit *Medisint, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Minervit Plus *Vitemat, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Minesol *Janssen-Cilag, Braz.*
Titanium; zinc; beta glucan; ginkgo biloba (p.1922·1).
Tonic.

Minesol 40 *RoC, Fr.*
SPF 40: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Minesol 60 *RoC, Fr.†.*
Cinoxate (p.1593·1); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Minesol Protect
Note. This name is used for preparations of different composition.
RoC, Fr.
SPF 30: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); bemotrizinol (p.1590·2).
Sunscreen.

Johnson & Johnson Consumer, Fr.
SPF 50+: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); bemotrizinol (p.1590·2); titanium dioxide (p.1617·3).
Sunscreen.

Minesse *Wyeth, Arg.; Wyeth Lederle, Austria; Wyeth, Braz.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Fr.; Wyeth, Hung.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Mex.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Spain; Wyeth, Switz.; Wyeth, Venez.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Minestril *Parke, Davis, Belg.†.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive; gynaecological disorders.

Minestrin *Warner Chilcott, Canad.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Minesulin *Polfa Pabianice, Pol.*
Nimesulide (p.95·3).
Pain.

Minfaden *Mintlab, Chile.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).

Minha *Vifor, Switz.†.*
⊗ Naphazoline nitrate (p.1565·2).
Eye disorders.

Minhavez *Melisana, Belg.*
⊗ Melissa (p.2339·3); naphazoline nitrate (p.1565·2).
Eye irritation.

28 mini *Jenapharm, Ger.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Mini Ovulo Lanzas *Ipsen, Spain.*
Benzalkonium chloride (p.1629·1).
Contraceptive.

Mini Pseudo *BDI, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Mini Thin Pseudo.
Nasal congestion.

Mini Two-Way Action *BDI, USA†.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).

Minian *Libbs, Braz.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Minias *Schering, Ital.*
Lormetazepam (p.1005·2).
Insomnia.

Miniasal *Altana, Ger.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Minibit *Polipharm, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Miniblock *USV, India.*
⊗ Esmolol hydrochloride (p.1282·3).
Arrhythmias; hypertension during surgery.

Minicam *Gramon, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Minicam Carb *Gramon, Arg.*
Activated charcoal (p.1435·2).
Diarrhoea; meteorism.

Miniceronal *Tunggal Idaman, Indon.*
L-Cysteine; choline bitartrate; inositol; vitamin B (p.1922·1).
Vitamin B and cysteine deficiency.

Miniderm *ACO Hud, Swed.*
Glycerol (p.2314·2).
Dry skin.

Minidex *Alcon, Braz.*
⊗ Dexamethasone (p.1526·1).
Eye disorders.

Minidiab *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Carlo Erba, Turk.; Pfizer, Venez.*
Glipizide (p.441·3).
Diabetes mellitus.

Minidine *Sigma, Austral.†.*
Povidone-iodine (p.1659·2).
Herpes labialis; skin disinfection; sore throat; wounds.

Minidol *Andromaco, Chile.*
Tramadol hydrochloride (p.130·3).
Pain.

Minidol Plus *Andromaco, Chile.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Minidril *Wyeth, Fr.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Minidyne *Pedinol, USA.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Miniestrel *Andromaco, Chile.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Minifom *AstraZeneca, Fin.; AstraZeneca, Norw.; AstraZeneca, Swed.*
Dimethicone (p.1770·2).
Adjunct to gastrointestinal endoscopy and radiography; colic; flatulence; meteorism.

Minigest *Andromaco, Chile.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Minigeste *Bayer, Port.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Mini-Glynase *Julphar, UAE.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Minigrip *Kalbe, Indon.*
Aspirin (p.20·3).
Glycine (p.1947·3) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Minigynon *Schering, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Minihep *Leo, Irl.†.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Minilax
Note. This name is used for preparations of different composition.
Eurofarma, Braz.
Sorbitol (p.1965·1).
Constipation.

Sam-On, Israel†.
Glycerol (p.2314·2).
Constipation.

Minilip *Teva, Hung.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Minima *Medley, Braz.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Minims Artificial Tears *Smith & Nephew, Austral.†; Chauvin, Irl.; Bausch & Lomb, UK.*
Hyetellose (p.2143·3); sodium chloride (p.1686·1).
Dry eyes.

Miniostenil *TRB, Arg.*
Sodium hyaluronate (p.2320·1).
Joint disorders.

Mini-Pe *Pfizer, Denm.; Pfizer, Swed.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Miniphase *Schering, Fr.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Minipil
Note. A similar name is used for preparations of different composition (see below).
Sigma, Braz.
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Minipil-2 Post *Sigma, Braz.*
Levonorgestrel (p.2121·2).
Post-coital oral contraceptive.

Mini-Pill
Note. A similar name is used for preparations of different composition (see above).
Pfizer, Fin.
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Minipres *Pfizer, Arg.†; Pfizer, Mex.; Nostrum, Spain.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Minipress *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Erfa, Canad.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Jpn†; Pfizer, Malaysia; Pfizer, S.Afr.†; Pfizer, Singapore; Pfizer, Switz.†; Pfizer, Thai.; Pfizer, USA.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Minique *Wyeth Lederle, Austria†.*
14 Tablets, estradiol hemihydrate (p.2097·2); 14 tablets, estradiol hemihydrate; trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Minirin *Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Canad.; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Israel; Ferring, Malaysia; Ferring, Mex.; Ferring, NZ; Pharmaco, NZ; Ferring, Norw.; Ferring, Philipp.; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, Singapore; Ferring, Swed.; Ferring, Switz.; Ferring, Thai.; Er-Kim, Turk.; Ferring, USA.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemophilia A; nocturia; nocturnal enuresis; polydipsia; polyuria; stimulation of factor VIII activity; test of renal concentrating capacity; von Willebrand's disease.

Minirin/DDAVP *Ferring, Ital.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemophilia A; nocturnal enuresis; polydipsia; polyuria; renal function tests.

Minirinmelt *Ferring, Fr.*
Desmopressin (p.2185·2).
Diabetes insipidus; nocturnal enuresis.

Miniscap *Vifor, Switz.†.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Minisem *Pik, Rus.*
Synthetic polypeptide.
Behaviour disorders in children; mental function impairment; nootropic.

Mini-sintrom *Novartis, Fr.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Minisiston *Jenapharm, Cz.; Jenapharm, Ger.; Jenapharm, Pol.; Jenapharm, Rus.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive; menstrual disorders.

Minison *YSP, Malaysia.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Ministat *Organon, Neth.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Miniten *Utopian, Thai.*
Nitrendipine (p.1358·2).
Hypertension.

Minitran
Note. This name is used for preparations of different composition.
3M, Arg.†; 3M, Austral.; Altana, Austria; 3M, Belg.; 3M, Canad.; 3M, Cz.†; 3M, Fin.; 3M, Ital.; 3M, Mex.; 3M, NZ; 3M, Neth.; 3M, Norw.; 3M, Philipp.; 3M, Spain; 3M, Swed.; 3M, Switz.; 3M, UK; Graceway, USA; Zuoz, Venez.†.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; maintenance of venous patency at peripheral infusion sites.

Adelco, Gr.
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Depression accompanied by psychosis.

MinitranS *3M, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Minit-Rub *Bristol-Myers Products, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Miniversol *Aguettant, UK.*
Sodium chloride (p.1686·1) for irrigation.

Minixime *Brown & Burk, Malaysia.*
Cefixime (p.224·3).
Bacterial infections.

Minizide *Pfizer, USA†.*
⊗ Prazosin hydrochloride (p.1375·2); polythiazide (p.1373·3).
Hypertension.

Mino-50 *PSI, Belg.*
Minocycline hydrochloride (p.300·3).
Acne.

Minoa *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Minocalve *Janssen-Cilag, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Minocin *Wyeth, Arg.; Wyeth Lederle, Austria†; PSI, Belg.; Stiefel, Canad.; Wyeth, Chile†; Teofarma, Gr.; Wyeth, Hong Kong; Lederle, Indon.; Wyeth, Irl.; Lederle, Israel†; Teofarma, Ital.; Wyeth, Malaysia†; Wyeth, Mex.; Wyeth, Neth.; Wyeth, Philipp.; Teofarma, Port.; Wyeth, Singapore†; Teofarma, Spain; Lederle, Switz.; Wyeth-Ayerst, Thai.†; Wyeth, UK; Triax, USA; Wyeth, Venez.†.*
Minocycline hydrochloride (p.300·3).
Acne; bacterial infections; intestinal amoebiasis.

Minoclin *Vitamed, Israel; Ranbaxy, Malaysia.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minoclir *Jenapharm, Ger.*
Minocycline hydrochloride (p.300·3).
Acne.

Minoderm *Stiefel, Braz.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minodiab *Pfizer, Arg.; Pharmacia-Upjohn, Gr.†; Pfizer, Mex.; Kenfarma, Spain; Pharmacia, UK.*
Glipizide (p.441·3).
Diabetes mellitus.

Minodril *Kleva, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Minofen *Epifarma, Ital.; Liomont, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Minoglen *Strides, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Minolis *Expanscience, Fr.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minomax *Wyeth, Braz.†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minomycin *Sigma, Austral.; Zuellig, NZ.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minoplus *Rosen, Ger.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minor *Biosintetica, Braz.†.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Minoral *Liferpal, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Minorplex *Abigo, Swed.*
Multivitamin preparation (p.1922·1).

Minos *Minorock Mandiri, Indon.*
Calamine (p.1591·2); camphor (p.2273·2); magnesium carbonate (p.1743·1); menthol (p.2340·1); talc (p.1615·2); zinc oxide (p.1621·2).
Pruritus; skin irritation.

Minoset *Roche, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Minoset Plus *Roche, Turk.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Minostad *Stada, Austria.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minostoss *Hertz, Braz.†.*
Potassium iodide (p.2169·2).

Minot *Roemmers, Arg.†.*
Sulconazole nitrate (p.546·2).
Fungal skin infections.

Minotab *PSI, Belg.; Wyeth, Neth.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minotabs *Zuellig, NZ; Hexal, S.Afr.*
Minocycline hydrochloride (p.300·3).
Acne; bacterial infections.

Minoton
Note. This name is used for preparations of different composition.
Ariston, Braz.
Aminophylline (p.1114·2).
Obstructive airways disease.

Madaus, Spain.
Magaldrate (p.1742·3).
Gastric hyperacidity.

Minotrex *Medinfar, Port.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minotyrol *Tyrol, Austria†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Minovag *Novag, Mex.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Minovital *Terapeutico, Ital.*
Minoxidil (p.1342·1).
Alopecia.

Min-Ovral *Wyeth, Canad.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Mino-Wolff *Wolff, Ger.†.*
Minocycline hydrochloride (p.300·3).
Acne.

Minox
Note. This name is used for preparations of different composition.
Riva, Canad.†; Edol, Port.
Minoxidil (p.1342·1).
Alopecia.

Rowex, Irl.
Minocycline (p.300·3).
Bacterial infections.

Minoxi *Trima, Hong Kong; Trima, Israel.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Minoxile *Finadiet, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Minoximen *Menarini, Ital.*
Minoxidil (p.1342·1).
Alopecia.

Minoxitrim *Trima, Cz.†; Trima, Singapore; Unipharm, Singapore; Trima, Thai.†.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Minpres *Pfizer, Venez.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hypertrophy; heart failure; hypertension; Raynaud's syndrome.

Minprog *Pfizer, Austria; Pharmacia, Ger.*
Alprostadil (p.2183·2).
Maintenance of ductus arteriosus patency.

Minprostin *Pfizer, Denm.; Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.; Pfizer, Norw.; Pfizer, Swed.*
Dinoprostone (p.2007·1).
Labour induction.

Minprostin E_2 *Pharmacia, Ger.*
Dinoprostone (p.2007·1).
Labour induction; production of cervical dilatation.

Minprostin $F_{2}\alpha$ *Pharmacia, Ger.*
Dinoprost trometamol (p.2006·3).
Uterine bleeding.

Minra *TNP, Thai.†.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Hay fever; rhinitis.

Minrin *Ferring, Neth.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemorrhagic disorders; nocturnal enuresis; polyuria; test of renal concentrating capacity; uraemia.

Minroset *Win-Medicare, India.*
Alfacalcidol (p.1986·1).
Osteoporosis; renal osteodystrophy.

Minroset-C *Win-Medicare, India.*
Alfacalcidol (p.1986·1); calcium carbonate (p.1714·1).
Osteoporosis.

Minsk *Anpharm (Ανφαρμ), Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Min-T *Offenbach, Mex.*
⊗ Atenolol (p.1217·3).
Hypertension.

Mintaglos *Mintlab, Chile.*
Halibut oil (p.1948·1); vitamin A; vitamin D; zinc oxide (p.1621·2).
Skin disorders; wounds.

Mintagras *Mintlab, Chile.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Mintamox *Mintlab, Chile.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Mintavit-C *Mintlab, Chile.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Mintec *Key, Austral.; Wilson, NZ; Monmouth, UK.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome; spastic colon syndrome.

Mintezol *MSD, Austral.; IFET (ΙΦΕΤ), Gr.; Merck, USA.*
Tiabendazole (p.156·2).
Worm infections.

Minthi JHP Huile *Tentan, Switz.*
Japanese mint oil (p.2345·2).
Cold symptoms; flatulence; headache; muscle pain.

Mint-Lysoform *Lysoform, Ger.*
Myrrh tincture (p.2349·2); peppermint oil (p.1761·2).
Mouth and throat disorders.

Mintoil *CaDiGroup, Ital.*
Peppermint oil (p.1761·2).
Gastrointestinal spasm.

Mintop *Reddy's, India.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Mintox *Major, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Hyperacidity.

Mintox Plus *Major, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Minulet *Wyeth, Arg.; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hong Kong†; Wyeth, Hung.; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Singapore; Wyeth, Spain; Wyeth, Switz.; Wyeth-Ayerst, Thai.†; Wyeth, Turk.; Wyeth, UK†; Wyeth, Venez.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Minulette *Wyeth, S.Afr.*
21 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Minuric *Sanofi Synthelabo, S.Afr.†.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia.

Minurin
Euro Registratie, Neth.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; polydipsia; polyuria; test for renal concentrating capacity.

Ferring, Spain.
Desmopressin (p.2185·2) or desmopressin acetate (p.2185·3).
Diabetes insipidus; haemorrhage; nocturnal enuresis; test of renal concentrating capacity.

Minus *Tocogino, Mex.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Minuslip *Ivax, Arg.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Minusorb *UCI, Braz.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Minute-Gel *Oral-B, USA.*
Acidulated phosphate fluoride (p.1962·2).
Dental caries prophylaxis.

Minutil *Henkel, Ger.†.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2).
Surface disinfection.

Minvitin *Wander Health Care, Switz.†.*
Food for special diets (p.1922·1).
Obesity.

Minyak Telon *Minorock Mandiri, Indon.*
Cajuput oil (p.2271·2); coconut oil (p.2029·2); fennel oil (p.2303·1).
Emollient.

Minyak Telon Cap Tiga Anak *Berlico Mulia, Indon.*
Cajuput oil (p.2271·2); coconut oil (p.2029·2); anise oil (p.2258·2).
Muscle and joint stiffness.

Mio Aldoron *Ivax, Arg.*
Nimesulide (p.95·3); orphenadrine citrate (p.812·1).
Musculoskeletal pain and spasm.

Mio Aldoron NF *Ivax, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint, and peri-articular disorders.

Mio D *Kowa, Jpn.*
Vitamin B substances; oxoamidine (p.1922·1).
Tonic.

Mio Relax *Belmac, Spain†.*
Carisoprodol (p.1894·1).
Skeletal muscle spasm.

Mioblock *Organon, Jpn.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Miocacin *Faran, Gr.; Sanofi-Aventis, Port.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Miocalm *Hexa, Arg.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Miocalven *Farmalab, Braz.*
Calcium citrate (p.1675·3).
Calcium supplement.

Miocalven D *Farmalab, Braz.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium deficiency; osteoporosis.

Miocamen *Menarini, Gr.; Menarini, Ital.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Miocamycin *Meiji, Jpn.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Miocap *Arlex, Mex.*
Captopril (p.1239·2).
Hypertension.

Miocardin *Magis, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Miocarpine *Novartis Ophthalmics, Canad.†.*
Pilocarpine hydrochloride (p.1884·3).
Open-angle glaucoma.

Miochol *Novartis, Austral.; Ciba Vision, Canad.†; Novartis, Irl.; Iolab, Israel; Novartis, NZ; Thea, Neth.; Novartis, Port.; Adcock Ingram, S.Afr.; Novartis, Switz.; General Drugs, Thai.†; Novartis, UK; Novartis Ophthalmics, USA.*
Acetylcholine chloride (p.1877·1).
Production of miosis in eye surgery.

Miochole *Eumedica, Belg.; Novartis, Fr.*
Acetylcholine chloride (p.1877·1).
Production of miosis in eye surgery.

Miochol-E *Novartis Ophthalmics, Canad.; Novartis, Chile†; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; OMJ, Hong Kong; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis Ophthalmics, Singapore†; Novartis Ophthalmics, Swed.; Novartis, Turk.*
Acetylcholine chloride (p.1877·1).
Production of miosis in eye surgery.

Miocina *Tecnofarma, Mex.*
Dopamine (p.1274·1).
Cardiovascular disorders.

Mio-Citalgan *Merck, Braz.*
Carisoprodol (p.1894·1); caffeine (p.1116·3); vitamin B substances (p.1922·1); paracetamol (p.108·1).
Skeletal muscle spasm.

Miocor *Ecobi, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Miocoron *Cristalia, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Miocrin *IFET (ΙΦΕΤ), Gr.; Rubio, Singapore; Rubio, Spain.*
Sodium aurothiomalate (p.122·2).
Juvenile idiopathic arthritis; rheumatoid arthritis.

Miocuril *Terapeutico, Ital.†.*
Sodium uridine triphosphate (p.2408·1).
Heart failure; muscular disorders.

Miodarid *Neo Quimica, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Miodaron *Biosintetica, Braz.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Miodarona *Lafedar, Arg.*
Amiodarone (p.1210·2).
Arrhythmias.

Miodene *Bioprogress, Ital.†.*
Ubidecarenone (p.2407·2).
Cardiac disorders.

Miodom *Dominguez, Arg.*
Tolperisone hydrochloride (p.1899·3).
Muscle relaxant.

Miodrina *Apsen, Braz.*
⊗ Ritodrine hydrochloride (p.2017·2).
Premature labour.

Miodrone *Alodial, Port.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Mioflex
Note. This name is used for preparations of different composition.
Farmasa, Braz.
Carisoprodol (p.1894·1); paracetamol (p.108·1); phenylbutazone (p.117·1).
Skeletal muscle spasm.

Braun, Port.; Braun, Spain.
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Mioflex A *Farmasa, Braz.*
Diclofenac sodium (p.44·3); carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Miogesil *GSK, Arg.†.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Miokacin *FIRMA, Ital.*
Midecamycin (p.300·2).
Bacterial infections.

Miol *Robert, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Miolastan *Sanofi Synthelabo, Mex.*
Tetrazepam (p.1031·1).

Miolene *Lusofarmaco, Ital.*
⊗ Ritodrine hydrochloride (p.2017·2).
Premature labour; threatened miscarriage.

Miolox *Baliarda, Arg.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Mionevrasi *Teofarma, Ital.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); cocarboxylase (p.1975·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis; vitamin B deficiencies.

Mionevrix *Ache, Braz.*
Carisoprodol (p.1894·1); dipyrone (p.49·2); vitamin B substances (p.1922·1).
Skeletal muscle spasm.

Miopropan *Bernabo, Arg.*
Trimebutine (p.2404·3) or trimebutine maleate (p.2404·3).
Gastrointestinal spasm.

Miopropan Proctologico *Bernabo, Arg.*
Ruscogenin (p.2382·2); trimebutine (p.2404·3).
Haemorrhoids.

Miopropan-T *Bernabo, Arg.*
Trimebutine maleate (p.2404·3); bromazepam (p.964·3).

Miorel
Note. This name is used for preparations of different composition.
Sankyo, Fr.
Thiocolchicoside (p.1898·2).
Skeletal muscle spasm.

Kleva, Gr.
Baclofen (p.1888·1).
Spasticity.

Miorrelax *Ducto, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Skeletal muscle spasm.

Mios *INTES, Ital.*
Pilocarpine hydrochloride (p.1884·3); carbachol (p.1879·2); paraoxon (p.1883·3); procaine hydrochloride (p.1869·1).
Raised intra-ocular pressure.

Miosan *Apsen, Braz.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Mioser *Help, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Miostat *Alcon, Arg.; Alcon, Austral.; Alcon, Belg.; Alcon, Braz.†; Alcon, Canad.; Alcon, Cz.; Alcon, Hong Kong†; Alcon, Hung.; Alcon, Israel; Alcon, Malaysia; Alcon, Neth.; Alcon, Philipp.; Alcon, Pol.; Alcon, Singapore; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.†.*
Carbachol (p.1879·2).
Production of miosis; reduction of intra-ocular pressure following eye surgery.

Miostenil *Bial, Port.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).

Miosys *Alcon, S.Afr.†.*
Carbachol (p.1879·2).
Production of miosis.

Miotenk *Biotenk, Arg.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Miotens *Dompe, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Mioticol *Farmigea, Ital.*
Carbachol (p.1879·2).
Production of miosis in eye surgery.

Miotin *Meiji, Thai.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Miotonachol *Fortbenton, Arg.*
Bethanechol chloride (p.2265·3).
Prostate disorders.

Miotonal *Caber, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Miotyn *Ibirn, Ital.†.*
Ubidecarenone (p.2407·2).
Cardiac disorders.

Mio-Virobron *Temis, Arg.*
Nimesulide (p.95·3); orphenadrine citrate (p.812·1).
Musculoskeletal inflammation.

Mio-Virobron NF *Temis, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Muscle spasm; musculoskeletal and joint disorders.

Miovisin *Farmigea, Ital.*
Acetylcholine chloride (p.1877·1).
Production of miosis in eye surgery.

Miovit *Cofasa, Venez.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis.

Miozac *Fisiopharma, Ital.*
Dobutamine hydrochloride (p.1271·2).
Cardiac inotropic.

Miozepam
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Clonazepam (p.478·2).
Anxiety; epilepsy.

Jelfa, Pol.
Tetrazepam (p.1031·1).
Painful skeletal muscle spasm.

Miozets *Uriach Aquilea OTC, Spain.*
Benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Miphar *Pharmachemie, Israel.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; renal failure.

Mipil *Grunenthal, Venez.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Mi-Pilo *Fischer, Israel.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.

Mipralin *Lennon, S.Afr.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis.

Mipramid *IQFA, Mex.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Miquimod *Lazar, Arg.*
Imiquimod (p.881·3).
Actinic keratosis; anogenital warts.

MIR *Rafa, Israel.*
⊗ Morphine sulfate (p.86·3).
Pain; premedication.

Mira Klonal *Klonal, Arg.*
⊗ Naphazoline (p.1565·1); pheniramine (p.587·2).
Eye disorders.

Mirabel *Allergan, Braz.*
⊗ Tetryzoline hydrochloride (p.1574·1); zinc sulfate (p.1999·2).
Ocular congestion.

Mirabol *Volchem, Ital.*
Preparations for enteral nutrition (p.1922·1).

Miracef *Tosi, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Miracid *Berlin Pharm, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Miraclar *Iquinosa, Spain.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye disorders.

Miraclid *Mochida, Jpn.*
Ulinastatin (p.2407·2).
Pancreatitis; shock.

Miraclin *Farmacologico Milanese, Ital.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Miracolon *Laborest, Ital.*
Rice oil; cassia (p.1715·3).
Gastrointestinal disorders.

Miradol *Durbin, UK.*
Paracetamol (p.108·1).

Miraflow *Ciba Vision, Austral.; Ciba Vision, Canad.†; Novartis, NZ; Ciba Vision, USA.*
Cleaning solution for contact lenses (p.1622·2).

Miraftil *Zambon, Neth.*
Amlexanox (p.1115·2).
Aphthous ulcers.

Mirafur *Orion, Fin.*
Carmofur (p.694·2).
Breast cancer; ovarian cancer.

Miragran *Royal, Chile.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Miral
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
⊗ Pheniramine maleate (p.587·3); naphazoline hydrochloride (p.1565·2).
Eye disorders.

Leiras, Fin.
Potassium chloride (p.1684·3); magnesium hydroxide (p.1743·2).
Potassium and magnesium deficiency.

MiraLax *Schering-Plough, USA.*
Macrogol 3350 (p.2336·3).
Bowel evacuation.

Miralgin *PannonPharma, Hung.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Miralis *Ativus, Braz.*
Myrtillus (p.2349·3).
Retinopathy.

Miraluma *Du Pont, USA.*
Technetium-99m sestamibi (p.2055·3).
Breast imaging.

Miramycin *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Miranax *Grunenthal, Austria; Roche, Denm.†; Roche, Fin.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Miranova *Schering, Arg.; Schering, Ger.; Schering, Hung.†; Schering, Ital.; Schering, Neth.; Bayer, Port.; Schering, S.Afr.; Schering, Switz.; Schering, Turk.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Mirap *Rowex, Irl.*
Mirtazapine (p.409·2).
Depression.

Mirapex *Pharmacia, Arg.†; Pharmacia, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, USA.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism; restless legs syndrome.

Mirapexin
Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Spain; Pharmacia, Spain.
Pramipexole (p.814·2).
Parkinsonism.

Boehringer Ingelheim, Cz.; Pharmacia, Denm.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, UK.
Pramipexole hydrochloride (p.814·1).
Parkinsonism; restless legs syndrome.

Mirapront N *Mack, Thai.†.*
⊗ Cathine (p.2152·2).
Obesity.

Mirasan *Allergan, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye disorders.

MiraSept *Alcon, USA.*
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting solution for soft contact lenses.

Miraton *Codal Synto, Malaysia†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Mirax
Note. A similar name is used for preparations of different composition (see below).
Berlin Pharm, Singapore.
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Berlin Pharm, Thai.
Domperidone (p.1726·2) or domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea and vomiting.

Miraxx
Note. A similar name is used for preparations of different composition (see above).
Neopharmed, Ital.†.
Rofecoxib (p.121·1).
Pain.

Mirazul *Fardi, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Mircera *Roche, Cz.; Roche, Fr.; Roche, Port.; Roche, UK; Roche, USA.*
⊗ Pegzerepoetin alfa (p.1075·2).
Anaemia in renal failure.

Mircette *Duramed, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 5 tablets, ethinylestradiol; 2 tablets, placebo.
Sequential oral contraceptive.

Mircol *Recalcine, Chile; Medilab, Spain.*
Mequitazine (p.585·3).
Hypersensitivity reactions.

Mirelle *Schering, Arg.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Schering, Cz.; Schering, Fin.; Schering, Pol.; Schering, S.Afr.; Schering, Switz.; Schering, Venez.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Mirena *Schering, Arg.†; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Berlex, Canad.; Schering, Chile; Bayer Scher-*

ing, Cz.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Bayer Schering, Hung.; Schering, Indon.; Berlipharm, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Bayer, Singapore; Schering, Spain; Schering, Switz.; Schering, Thai.; Schering, Turk.; Bayer, UK; Berlex, USA; Schering, Venez.
Levonorgestrel (p.2121·2).
Hormone replacement therapy; hypermenorrhoea; menorrhagia; menstrual disorders; prevention of endometrial hyperplasia in hormone replacement therapy; progestogen-releasing intra-uterine contraceptive device.

Miretic *Utopian, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Miretilan *Slovakofarma, Cz.†.*
Endralazine mesilate (p.1277·2).
Hypertension.

Mirfat *Merckle, Ger.†.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Mirfudorm *Merckle, Ger.*
Oxazepam (p.1014·2).
Anxiety; sleep disorders.

Mirfulan *Ratiopharm, Austria; Merckle, Ger.*
⊗ Cod-liver oil (p.1935·2); zinc oxide (p.1621·2); hamamelis (p.2318·2); urea (p.1620·2).
Skin disorders.

Mirfulan Spray N *Merckle, Ger.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2); levomenol (p.2333·3).
Burns; skin disorders; wounds.

Mirfusot *Merckle, Ger.†.*
Thyme (p.2401·1).
Coughs and associated respiratory-tract disorders.

Miridacin *Taiho, Jpn.*
Proglumetacin maleate (p.119·1).

Miril *Ivax, Cz.*
Ramipril (p.1385·3).
Glomerular nephropathy; heart failure; hypertension; myocardial infarction.

Miril plus H *Teva, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Mirinda *Organifar, Venez.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Mirion *Pfizer, Chile.*
Estradiol valerate (p.2097·3).

Mirlox *Gedeon Richter, Rus.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Miro *Unipharm, Israel.*
Mirtazapine (p.409·2).
Depression.

Mirocef *Pliva Krakow, Pol.*
Ceftazidime sodium (p.235·1).
Bacterial infections.

Mironal *Slovakofarma, Cz.†.*
Aspirin (p.20·3); phenacetin (p.115·3); caffeine (p.1116·3).
Pain.

Mirorroidin *Sedabel, Braz.†.*
Rutoside (p.2305·1); hamamelis (p.2318·2); aesculus (p.2248·2); zinc (p.1999·1); menthol (p.2340·1); benzocaine (p.1854·1).
Haemorrhoids.

Miroton *Abbott, Ger.*
Squill (p.1573·1); convallaria (p.2287·3); oleander (p.2356·2); adonis vernalis (p.2248·1).
Cardiovascular disorders.

Miroton N *Knoll, Ger.†.*
Adonis vernalis (p.2248·1); convallaria (p.2287·3); squill (p.1573·1).
Cardiac disorders.

Mirquin *Mirren, S.Afr.*
Chloroquine sulfate (p.599·3).
Malaria.

Mirta TAD *TAD, Ger.*
Mirtazapine (p.409·2).
Depression.

Mirtabene *Ratiopharm, Austria.*
Mirtazapine (p.409·2).
Depression.

Mirtadepi *Keri, Hung.*
Mirtazapine (p.409·2).
Depression.

MirtaLich *Winthrop, Ger.*
Mirtazapine (p.409·2).
Depression.

Mirtaril *Alternova, Fin.*
Mirtazapine (p.409·2).
Depression.

Mirtaron *Interpharm, Austria.*
Mirtazapine (p.409·2).
Depression.

Mirtastad *Stada, Cz.; Steigerwald, Pol.*
Mirtazapine (p.409·2).
Depression.

Mirtax *Ache, Braz.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Mirtaz *Sun, India.*
Mirtazapine (p.409·2).
Depression.

Mirtazelon *Krewel, Ger.*
Mirtazapine (p.409·2).
Depression.

Mirtazon *Arrow, Austral.; Imi, Denm.; Organon, Fin.; Aacifar, Port.*
Mirtazapine (p.409·2).
Depression.

Mirtazza *Temmler, Ger.*
Mirtazapine (p.409·2).
Depression.

Mirtel *Lannacher, Austria; Gerot, Hung.*
Mirtazapine (p.409·2).
Depression.

Mirtex P *DMG, Ital.*
Vitamin, mineral, and lipid preparation with myrtillus (p.1922·1).
Nutritional supplement.

Mirticam *Kameliya, Rus.*
Homoeopathic preparation.

Mirtilene *SIFI, Ital.*
Myrtillus (p.2349·3); betacarotene (p.1930·3); *dl*-alpha tocoferil acetate (p.1992·3).
Capillary fragility.

Mirtilene Forte *Craveri, Arg.†; SIFI, Ital.; SIFI, Rus.*
Myrtillus (p.2349·3).
Capillary fragility; eye disorders.

Mirtilus *Llorens, Spain.*
Betacarotene (p.1930·3); myrtillus (p.2349·3).
Eye disorders.

Mirtilux
Note. This name is used for preparations of different composition.
Mediwhite, Ital.
Capsules: Vitamins; minerals (p.1922·1); myrtillus (p.2349·3).
Nutritional supplement.

Mediwhite, Ital.
Oral solution: Myrtillus (p.2349·3); vitis vinifera (p.2316·3); magnesium; phosphatidyl serine; phosphatidyl choline; rhodiola rosea (p.1922·1).
Nutritional supplement.

Mirtilvedo C *Fitobucaneve, Ital.*
Vitamin preparation with betacarotene, myrtillus, carrot, and rose fruit (p.1922·1).
Nutritional supplement.

Mirtivit *SIFI, Singapore†.*
Food supplement (p.1922·1).

Mirubal *Zuoz, Venez.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Mirus *Alcon, Arg.; Alcon, Chile†; Alcon, Mex.*
⊗ Pheniramine maleate (p.587·3); naphazoline hydrochloride (p.1565·2).
Eye disorders.

Mirus-S *Alcon, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Mirzalux *Sandoz, Mex.*
Mirtazapine (p.409·2).
Depression.

Mirzaten *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
Mirtazapine (p.409·2).
Depression.

Misaf *Verisfield, Gr.*
Oxaprozin (p.105·3).
Inflammatory disorders.

Miscidon *Torlan, Spain†.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Misodex *Sefarma, Ital.*
Misoprostol (p.2013·2).
NSAID-induced peptic ulcer.

Misodomin *Kleva, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Misofenac *Sefarma, Ital.; Euro Registratie, Neth.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Misone *PD, Thai.†.*
Miconazole nitrate (p.541·3).
Fungal skin, hair, and nail infections.

Misoprost *Cipla, India.*
Misoprostol (p.2013·2).
Peptic ulcer.

Misordil *Wyeth, Arg.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Misostol *Zodiac, Braz.; Nolver, Venez.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Misotrol *Sanofi-Aventis, Chile.*
Misoprostol (p.2013·2).
Peptic ulcer.

Misovan *TO-Chemicals, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Missecap *Galeno, Venez.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Missilor *Pierre Fabre, Fr.*
Spiramycin (p.333·1); metronidazole (p.837·1).
Bacterial infections.

Mission Prenatal *Mission Pharmacal, USA.*
A range of multivitamin and mineral preparations with iron and folic acid (p.1922·1).
Iron-deficiency anaemias; prenatal and postpartum supplement.

Mission Surgical Supplement *Mission Pharmacal, USA†.*
Ferrous gluconate (p.1939·1); multivitamins and minerals (p.1922·1).
Dietary supplement for pre- and postsurgical patients; iron-deficiency anaemias.

Mist Expect Stim *Vida, Hong Kong.*
Ammonium bicarbonate (p.1551·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); squill (p.1573·1); senega (p.1572·3); liquorice (p.1740·3).
Cold symptoms; coughs.

Mistabron *UCB, Austria; UCB, Belg.; UCB, Cz.; UCB, Hong Kong; UCB, Malaysia†; UCB, Neth.; UCB, Philipp.; GSK, Pol.; UCB, S.Afr.; UCB, Singapore; UCB, Switz.†; UCB, Thai.†.*
Mesna (p.1449·2).
Respiratory-tract congestion.

Mistabronco *UCB, Ger.†.*
Mesna (p.1449·2).
Respiratory-tract disorders.

Mistamine *Galderma, Arg.†; Galderma, Belg.†; Galderma, Chile†; Galderma, Irl.†; Galderma, Mex.; Galderma, Port.†; Galderma, Spain†; Galderma, Switz.†.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; allergic rhinoconjunctivitis; urticaria.

Mistel Curarina *Harras-Curarina, Ger.*
Mistletoe (p.2345·3).
Circulatory disorders.

Mistel-Krautertabletten *Salushaus, Ger.*
Mistletoe (p.2345·3).
Circulatory disorders.

Mistelol-Kapseln *Twardy, Ger.†.*
Mistletoe (p.2345·3).
Cardiovascular disorders.

Misteltropfen *Bio-Diat, Ger.†.*
Mistletoe (p.2345·3).
Circulatory disorders.

Misteltropfen Hofmanns *Hofmann & Sommer, Ger.*
Mistletoe (p.2345·3).
Circulatory disorders.

Mistick Verde *Marco Viti, Ital.*
Geranium oil (p.2311·1); citronella oil (p.2284·2); lavender oil (p.2331·2).
Insect repellent.

Mistral *Mediolanum, Ital.*
Dermatan sulfate sodium (p.1256·3).
Thrombosis prophylaxis.

Misubar *Farmachimici, Ital.†.*
Barrier preparation.
Nappy rash.

Misultina *Bernabo, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Misulvan *Plusandex, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Misurid *Farmachimici, Ital.*
Sulfur (p.1614·1).
Skin disorders.

Misurid Plus *Farmachimici, Ital.*
Barrier cream.

Mita-C *Milano, Thai.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Mitafar *Quimpharma, Mex.*
Nitazoxanide (p.842·3).
Anaerobic bacterial infections; protozoal infections; worm infections.

Mitatonin *Toyo, Hong Kong.*
Norfloxacin (p.309·2).
Bacterial eye infections.

Mitaxis *Itaca, Braz.†.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mitayaku *Toyo, Hong Kong.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Mitem *Curasan, Ger.; Schwarz, Ger.*
Mitomycin (p.752·1).
Malignant neoplasms.

Miten *CEPA, Spain.*
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Miten Plus *CEPA, Spain.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Mitex
Note. A similar name is used for preparations of different composition (see below).
Kampel Martian, Arg.†.
Miltefosine (p.751·1).
Skin metastases.

Mite-X
Note. A similar name is used for preparations of different composition (see above).
Fischer, Israel.
Permethrin (p.2048·2).
Scabies.

Mitexan *Asta Oncologia, Braz.*
Mesna (p.1449·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Mithen *Fidia, Ital.*
Amino acids; vitamins; minerals (p.1922·1); St John's wort (p.422·3).
Nutritional supplement.

Mithracin *IFET (ΙΦΕΤ), Gr.†.*
Plicamycin (p.1103·2).
Hypercalcaemia of malignancy; malignant neoplasms.

Miticocan *Ache, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Mitiderma *Milo, Spain†.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); pine silvestris oil (p.2368·2); menthol (p.2340·1).
Coughs; muscular pain; nasal congestion.

Mitil *Pharmacare, S.Afr.*
Prochlorperazine maleate (p.1020·1).
Agitation; anxiety; migraine; nausea and vomiting; vestibular disorders.

Mitilase *Spedrog, Arg.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Mitituss *Magis, Ital.*
Cloperastine fendizoate (p.1554·3).
Coughs.

Mitocin *BMS, Braz.; Cadila, India.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitocin-C *BMS, Mex.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitocor *Zambon, Ital.†.*
Ubidecarenone (p.2407·2).
Cardiac disorders; co-enzyme Q deficiency.

Mitocortyl *Sanofi-Aventis, Fr.*
⊗ Hydrocortisone (p.1535·2).
Insect and nettle stings; sunburn.

Mitocyna *Richmond, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mito-extra *Medac, Ger.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitog *Microsules, Arg.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Mitokebir *Aspen, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitokor *Biotenk, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Mitolem *Lemery, Mex.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mito-medac *Medac, Ger.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitonovag *Gobbi, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitostat *Orion, Fin.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitosyl
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Belg.
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2); methyl salicylate (p.85·3).
Burns; skin disorders; wounds.

Sanofi-Aventis, Fr.
Fish-liver oil; zinc oxide (p.1621·2).
Skin irritation.

Sanofi-Aventis, Port.
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Burns; skin disorders; ulcers; wounds.

Sanofi-Aventis, Spain.
Colecalciferol (p.1986·2); vitamin A (p.1971·2); zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Mitosyl N *Winthrop, Ger.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2); methyl salicylate (p.85·3).
Burns; skin disorders; wounds.

Mitotax *Reddy, Malaysia; Reddy, Rus.*
Paclitaxel (p.759·1).
Breast cancer; non-small-cell lung cancer; ovarian cancer.

Mitotie *Bioprofarma, Arg.; Armstrong, Mex.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mitoxal *Asta Oncologia, Braz.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mitoxan *Adipharm (Αδηφαρμ), Gr.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mitoxana *Asta Medica, Irl.; Baxter Oncology, UK†.*
Ifosfamide (p.731·3).
Now known as Ifosfamide Injection.
Malignant neoplasms.

Mitoxgen *Bioprofarma, Arg.; Armstrong, Mex.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mitoxmar *LKM, Arg.*
Mitoxantrone (p.754·3).
Malignant neoplasms.

Mitozytrex *SuperGen, USA.*
Mitomycin (p.752·1).
Adenocarcinoma of the stomach or pancreas.

Mitran *Hauck, USA†.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety.

Mitranax *Polipharm, Thai.†.*
Alprazolam (p.960·1).
Anxiety.

Mitrip *Polfa Kutno, Pol.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension.

Mitroken *Kendrick, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Mitrotan *Gap, Gr.*
Ergometrine maleate (p.2009·2).
Postpartum haemorrhage.

Mitrotil *Recalcine, Chile.*
Tenoxicam (p.128·2).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders.

Mitroxene *Pharmis, Port.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mitroxone *Columbia, Mex.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Mit's Linctus Codeinae Co *AstraZeneca, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Mittavin *Nicholas Piramal, India†.*
Multivitamin preparation (p.1922·1).

Mittoval *Sanofi-Aventis, Ital.; Euro Registratie, Neth.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Mivacron *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; Abbott, Canad.†; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; Wellcome, Israel†; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Abbott, USA†.*
Mivacurium chloride (p.1906·3).
Competitive neuromuscular blocker.

Mivalen *Ativus, Braz.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

mivitase 2000 *Biosyn, Ger.†.*
Multivitamin and mineral preparation (p.1922·1).

Mixadin *Kalbe, Indon.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Allergic disorders; cold symptoms; cough.

Mixaflu *Kalbe, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.

Mixagel *Naturissima, Venez.†.*
Thyme (p.2401·1); chamomile (p.2279·3); eucalyptus (p.2301·2).
Skin cleansing.

Mixagrip *Kalbe, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.

MixaLax *acaSan, Austria.*
Macrogol 4000 (p.2336·3).
Constipation.

Mix-Alpha 3 *Synergia, Fr.*
Kiwi seed oil; fish oil; vitamin E (p.1922·1).
Nutritional supplement.

Mixandex *Pisa, Mex.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mixange *Tocogino, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Mixavit *Julphar, UAE.*
Multivitamin preparation (p.1922·1).

Mixavit C *Kalbe, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C deficiency; vitamin B and C supplement.

Mixavit-M *Julphar, UAE.*
Multivitamin and mineral preparation (p.1922·1).

Mix-3B *Synergia, Fr.*
Vitamin preparation (p.1922·1).

Mixcilin *Gramon, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Mixed Vegetable Tablets *Dorwest, UK.*
Rorippa nasturtium aquaticum; celery seed and plant (p.2278·3); horseradish (p.2320·1); parsley (p.2363·2).
Cystitis; minor bladder disorders; musculoskeletal and joint disorders.

Mixer *Biomedica, Ital.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Mixgen *Laboratorios Chile, Chile.*
⊗ Betamethasone (p.1518·2) or betamethasone dipropionate (p.1518·3); gentamicin (p.284·2) or gentamicin sulfate (p.282·1).
Infected eye disorders; infected skin disorders.

Mixobar *Astra Tech, Denm.; Astra Tech, Fin.; Byk Gulden, Ital.†; Astra Tech, Norw.; Astra Tech, Swed.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Mixogen
Note. This name is used for preparations of different composition.
Organon, India; Donmed, S.Afr.
Injection: ⊗ Estradiol benzoate (p.2097·2); estradiol phenylpropionate (p.2097·3); testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1).
Menopausal disorders; oestrogen deficiency.

Organon, India.
Tablets: ⊗ Ethinylestradiol (p.2101·3); methyltestosterone (p.2117·1).
Menopausal disorders.

Mixotone *Teofarma, Ital.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone sodium succinate (p.1536·1); lidocaine hydrochloride (p.1862·3).
Bacterial infections of the ear.

Mixtard 10, 20, 30, and 50 *Novo Nordisk, Fin.*
⊗ Mixtures of insulin injection (human) 10%, 20%, 30%, and 50% and isophane insulin injection (human) 90%, 80%, 70%, and 50% respectively (p.443·2).
Diabetes mellitus.

Mixtard 10, 20, 30, 40, and 50 *Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fr.; Novo Nordisk, Gr.; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Novo Nordisk, Swed.; Novo Nordisk, Turk.*
⊗ Mixtures of insulin injection (human, recombinant monocomponent) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, recombinant monocomponent) 90%, 80%, 70%, 60%, and 50%, respectively (p.443·2).
Diabetes mellitus.

Mixtard 10, 20, 30, 40, and 50 HM *Novo Nordisk, Port.*
⊗ Mixtures of insulin injection (human) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Diabetes mellitus.

Mixtard 20/80 *Novo Nordisk, S.Afr.†.*
⊗ A mixture of soluble insulin injection (human) 80% and isophane insulin injection (human) 20% respectively (p.443·2).
Diabetes mellitus.

Mixtard 20/80, 30/70, 50/50 *Novo Nordisk, Austral.*
⊗ Mixtures of neutral insulin injection (human, pyr, monocomponent) and isophane insulin injection (human, pyr, monocomponent) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Mixtard 30 *Novo Nordisk, Spain; Novo Nordisk, UK.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Formerly known as Human Mixtard.
Diabetes mellitus.

Mixtard 30, 50 *Novo Nordisk, Singapore.*
⊗ Mixtures of insulin injection (human, monocomponent) 30% or 50% and isophane insulin injection (human, monocomponent) 70% or 50%, respectively (p.443·2).
Diabetes mellitus.

Mixtard 30/70 *Novo Nordisk, Ger.†; Novo Nordisk, Spain†.*
⊗ Mixture of soluble insulin (human) 30% and isophane insulin (human) 70% (p.443·2).
Diabetes mellitus.

Mixtard HM *Novo Nordisk, Thai.*
⊗ A mixture of insulin injection (human, monocomponent) 30% and isophane insulin injection (human, monocomponent) 70% (p.443·2).
Diabetes mellitus.

Mixtard 30 HM *Novo Nordisk, Arg.; Novo Nordisk, Chile; Novo Nordisk, Hong Kong; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Malaysia; Novo Nordisk, Philipp.; Novo Nordisk, Rus.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70%, respectively (p.443·2).
Diabetes mellitus.

Mixtard HM 10, 20, 30, 40, 50 *Novo Nordisk, Switz.*
⊗ Mixtures of insulin injection (human, monocomponent) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, monocomponent) 90%, 80%, 70%, 60%, and 50%, respectively (p.443·2).
Diabetes mellitus.

Mixtard HM 10/90, 20/80, 30/70, 40/60, and 50/50 *Novo Nordisk, Austria.*
⊗ Mixtures of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Mixtard 30 MC *Novo Nordisk, Switz.*
⊗ Mixture of insulin injection (porcine, monocomponent) 30% and isophane insulin injection (porcine, monocomponent) 70% (p.443·2).
Diabetes mellitus.

Mixtard 30 or 50 *Novo Nordisk, NZ.*
⊗ Mixtures of insulin injection (human) 30% or 50% and isophane insulin (human) 70% or 50% (p.443·2).
Formerly known as Mixtard 30/70 and Mixtard 50/50.
Diabetes mellitus.

Mixtura Pepsini *Pampa, Pol.*
Pepsin (p.2365·1); hydrochloric acid (p.2322·1).
Gastric hypoacidity.

Mixtus *Orion, Fin.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Mixulin *Cadila, India.*
⊗ A mixture of neutral insulin 30% and isophane insulin 70% (p.443·2).
Diabetes mellitus.

Miya-BM *Miyarisan, Jpn†.*
Clostridium butyricum.
Restoration of gastrointestinal flora.

Miyadren *Fako, Turk.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Miyorel *Sanofi Synthelabo, Turk.*
Paracetamol (p.108·1); methocarbamol (p.1897·3).
Skeletal muscle spasm.

Mizac *Labesfal, Port.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Mizapin *Teva, Hung.*
Mirtazapine (p.409·2).
Depression.

Mizar *ICN, Ital.*
Flurithromycin ethyl succinate (p.278·1).
Bacterial infections.

Mizodin *Unia, Pol.*
Primidone (p.503·2).
Epilepsy.

Mizol *Roemmers-Klinos, Venez.†.*
Econazole (p.531·1).
Fungal infections.

Mizolam *CCM, Malaysia.*
Midazolam (p.1007·3).
Insomnia; premedication.

Mizolen *Sanofi-Aventis, Spain.*
Mizolastine (p.586·1).
Allergic rhinitis; urticaria.

Mizollen *Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.†; Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Fin.†; Therabel, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hung.†; Synthelabo, Israel; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Synthelabo, S.Afr.; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Sanofi-Aventis, UK.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; allergic rhinoconjunctivitis; pruritus; urticaria.

Mizoltec *Tecnofarma, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Mizonase *Gynopharm, Chile.*
Miconazole (p.541·2); tinidazole (p.848·3).
Fungal balanitis; trichomoniasis; vulvovaginal infections.

Mizoron *Milano, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Mizosin *Duopharma, Hong Kong.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's disease.

ML 20 *Blackmores, Austral.†.*
Magnesium phosphate (p.1679·2); dibasic potassium phosphate (p.1682·2); dried yeast (p.1998·3); lecithin (p.2332·2); *d*-alpha tocoferil acid succinate (p.1993·1).
Magnesium deficiency.

MLM-Dex *Millimed, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

M-long *Grunenthal, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

MM Expectorante *Farmasa, Braz.*
⊗ Potassium iodide (p.2169·2); lobelia (p.2157·2); hyoscyamus (p.2323·3).
Respiratory-tract congestion.

M-M Vax *Chiron Behring, Ger.†.*
A measles and mumps vaccine (more attenuated Enders' and Jeryl Lynn strains, respectively) (p.2222·3).
Active immunisation.

MMA/PA *Medifood, Ital.*
Food for special diets (p.1922·1).
Methylmalonic aciduria; propionic aciduria.

MMR *Sanofi Pasteur, Denm.*
A measles, mumps, and rubella vaccine (Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

MMR II *MSD, Arg.; CSL, Austral.†; MSD, Braz.†; Merck Frosst, Canad.; MSD, Cz.; Sanofi Pasteur, Fin.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; Sanofi Pasteur, Irl.; MSD, Israel; Sanofi Pasteur, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; Sanofi Pasteur, Norw.; MSD, Pol.; MSD, Rus.; MSD, Singapore; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; MSD, Thai.; MSD, Turk.; Aventis Pasteur, UK; Merck, USA.*
A measles, mumps, and rubella vaccine (Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains respectively) (p.2223·1).
Active immunisation.

MMR Triplovax *Sanofi Pasteur, Ger.*
A measles, mumps, and rubella vaccine (More attenuated Enders', Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

MMR Vax *Sanofi Pasteur, Belg.; Chiron Vaccines, Ger.*
A measles, mumps, and rubella vaccine (Enders' attenuated Edmonston, Jeryl Lynn B, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

MMRVaxPro *Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Sanofi-Aventis, Gr.*
A measles, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

MND *Malaysia Chemist, Singapore†.*
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Mnesis *Takeda, Ital.; Takeda, Switz.*
Idebenone (p.367·1).
Cerebrovascular disorders; friedreich's ataxia.

MN-Fusin *Pisa, Mex.†.*
Manganese sulfate (p.1956·2).

Moapar *Debioclinic, Swed.*
⊗ Triptorelin embonate (p.2135·3).
Deviant sexual behaviour in men.

Moban *Endo, USA.*
Molindone hydrochloride (p.1010·2).
Psychoses.

Mobec *Boehringer Ingelheim, Ger.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobemid *Jelfa, Pol.*
Moclobemide (p.411·1).
Depression; social phobia.

Mobemide *Unipharm, Israel; Trima, Singapore; Unipharm, Singapore.*
Moclobemide (p.411·1).
Depression; social phobia.

Moben *Elofar, Braz.*
Mebendazole (p.148·3).
Worm infections.

Mobex *Boehringer Ingelheim, Chile.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobic *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Abbott, USA; Boehringer Ingelheim, USA; Boehringer Ingelheim, Venez.*
Meloxicam (p.80·3).
Ankylosing spondylitis; inflammation; osteoarthritis; pain; rheumatoid arthritis.

Mobicam DT *Cipla, India.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Mobicox *Boehringer Ingelheim, Canad.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Switz.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Mobidin *Ascher, USA.*
Magnesium salicylate (p.79·2).
Fever; inflammation; pain.

Mobiflex
Note. This name is used for preparations of different composition.
Soho, Indon.
Meloxicam (p.80·3).
Gout; musculoskeletal and joint disorders.

Roche, Irl.†; Roche, UK.
Tenoxicam (p.128·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Mobiforton *Winthrop, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm; spasticity.

Mobigesic *Ascher, USA.*
Magnesium salicylate (p.79·2); phenyltoloxamine citrate (p.588·1).
Pain.

Mobiglan *Niche, Irl.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobilat
Note. This name is used for preparations of different composition.
Sankyo, Austria; Will-Pharma, Belg.; Sankyo, Braz.; Silesia, Chile; Stada, Cz.; Sankyo, Fin.; Sankyo, Ger.†; Sankyo, Hong Kong†; Medinova, Philipp.; Sankyo, Pol.; Sankyo, Singapore†; Medinova, Thai.
⊗ Suprarenal extract (p.1543·3); a heparinoid (p.1305·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Sankyo, Ital.
⊗ Hydrocortisone (p.1535·2); a heparinoid (p.1305·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Altana, Mex.; Will-Pharma, Neth.; Ciclum, Port.
A heparinoid (p.1305·2); salicylic acid (p.1612·2). Formerly contained prednisolone, a heparinoid, and salicylic acid in *Port*.
Peri-articular and soft-tissue disorders.

Mobilat Aktiv *Sankyo, Ger.*
A heparinoid (p.1305·2); salicylic acid (p.1612·2).
Soft-tissue injury.

Mobilat Akut HES *Sankyo, Ger.*
Glycol salicylate (p.62·3).
Soft-tissue injury.

Mobilat Akut Indo *Sankyo, Ger.*
Indometacin (p.66·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Mobilat Akut Piroxicam *Sankyo, Ger.*
Piroxicam (p.117·3).
Soft-tissue injury.

Mobilat N *Sankyo, Hung.; Medinova, Switz.*
A heparinoid (p.1305·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, and soft-tissue disorders.

Mobilis *Alphapharm, Austral.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Mobilisin
Note. This name is used for preparations of different composition.
Sankyo, Austria; Will-Pharma, Belg.; Sankyo, Hung.†; Sankyo, Ital.
Flufenamic acid (p.60·3); glycol salicylate (p.62·3); a heparinoid (p.1305·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Medinova, Switz.
Flufenamic acid (p.60·3); glycol salicylate (p.62·3) or salicylic acid (p.1612·2); a heparinoid (p.1305·2).
Musculoskeletal and joint disorders.

Ciclum, Port.
Cream: Flufenamic acid (p.60·3); a heparinoid (p.1305·2).
Musculoskeletal, joint, and peri-articular disorders.

Ciclum, Port.
Topical gel: Flufenamic acid (p.60·3); salicylic acid (p.1612·2); a heparinoid (p.1305·2).
Musculoskeletal, joint, and peri-articular disorders.

Mobilisin Composto *Sankyo, Braz.*
Flufenamic acid (p.60·3); a heparinoid (p.1305·2); glycol salicylate (p.62·3).
Musculoskeletal and joint disorders.

Mobilisin plus *Sankyo, Austria.*
Flufenamic acid (p.60·3); a heparinoid (p.1305·2); benzyl nicotinate (p.28·1).
Musculoskeletal and joint disorders.

Mobilyzer *Omni, UK.*
Green-lipped mussel (p.2317·2).
Nutritional supplement for joint care.

Mobisyl *Ascher, USA.*
Trolamine salicylate (p.132·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Mobloc *AstraZeneca, Ger.; Promed, Ger.*
⊗ Felodipine (p.1285·3); metoprolol succinate (p.1338·1).
Hypertension.

Mocimed *Bajamed, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Moclamine *Biocodex, Fr.*
Moclobemide (p.411·1).
Depression.

Moclix *Hexal, Ger.†.*
Moclobemide (p.411·1).
Depression.

Moclo A *Ecosol, Switz.*
Moclobemide (p.411·1).
Depression; social phobia.

Moclobeta *Betapharm, Ger.*
Moclobemide (p.411·1).
Depression.

Moclodura *Merck dura, Ger.*
Moclobemide (p.411·1).
Depression.

Moclonorm *Esparma, Ger.†.*
Moclobemide (p.411·1).
Depression.

Moclopharm *Actavis, Hung.*
Moclobemide (p.411·1).
Depression.

Moclostad *Pharmacodane, Denm.*
Moclobemide (p.411·1).
Depression.

Mocloxil *Anpharm, Pol.*
Moclobemide (p.411·1).
Depression; social phobia.

Mocrim *Apotex, Hung.*
Moclobemide (p.411·1).
Depression; social phobia.

Moctanin *Ethitek, USA†.*
Monoctanoin (p.2346·1).
Gallstones.

Mocydone *Pharmasant, Thai.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; nausea and vomiting.

Modaderm *Samik, Singapore.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1); clotrimazole (p.530·1).
Infected skin disorders.

Modafen *Zentiva, Cz.; Zentiva, Pol.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract disorders.

Modal *Rafa, Israel.*
Sulpiride (p.1028·3).
Peptic ulcer; psychoses; vestibular disorders.

Modalim *Sanofi-Aventis, Indon.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, UK.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Modalina *SIT, Ital.*
Trifluoperazine hydrochloride (p.1034·2).
Psychiatric disorders.

Modamide *Substipharm, Fr.*
⊗ Amiloride hydrochloride (p.1209·2).
Ascites; hypertension; oedema.

Modane
Note. This name is used for preparations of different composition.
Bago, Chile.
Dantron (p.1722·2); calcium pantothenate (p.1959·3).
Constipation.

Cooperation Pharmaceutique, Fr.
Calcium pantothenate (p.1959·3); senna (p.1769·2).
Constipation.

Korhispana, Spain.
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Constipation.

Savage, USA.
Bisacodyl (p.1710·1).
Constipation.

Modasomil *Ratiopharm, Austria; Cephalon, Switz.*
⊗ Modafinil (p.2160·3).
Daytime somnolence due to obstructive sleep apnoea; narcoleptic syndrome with or without cataplexy.

Modaton
Note. This name is used for preparations of different composition.
Armstrong, Mex.
Calcium pantothenate (p.1959·3); dantron (p.1722·2).
Constipation.

Montpellier, Arg.
Oral drops: Sodium picosulfate (p.1771·1).
Constipation.

Montpellier, Arg.
Tablets: Bisacodyl (p.1710·1).
Constipation.

Modaton NI *Montpellier, Arg.*
Liquid paraffin (p.2030·3).
Constipation.

Modavigil *CSL, Austral.; CSL, NZ.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome; obstructive sleep apnoea-hypopnoea syndrome; shift work sleep disorder.

Modecate *BMS, Austral.; Squibb, Canad.; BMS, Chile; Sanofi Synthelabo, Fr.; BMS, Hong Kong; BMS, Indon.; BMS, Irl.; BMS, NZ; BMS, S.Afr.; BMS, Singapore; BMS, Spain; Sanofi Synthelabo, UK.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Modekal *Crealko, Arg.†.*
Glucomannan (p.2312·3).
Dietary fibre supplement.

Modellsweet *Mintlab, Chile†.*
Aspartame (p.1930·1).
Sugar substitute.

Modenol *Roche, Ger.†.*
⊗ Butizide (p.1238·1); reserpine (p.1387·3).
Hypertension.

Moderan *Vargas, Venez.*
Lactulose (p.1738·2).
Constipation; liver disorders.

Moderin Acne *Pharmacia, Spain†.*
⊗ Aluminium chlorohydrate (p.1588·3); sulfur (p.1614·1); methylprednisolone acetate (p.1538·2).
Acne.

Moderine *Uniao Quimica, Braz.*
⊗ Mazindol (p.2157·3); diazepam (p.986·3).
Obesity.

Moderlax *Atral, Port.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Modern Herbals Cold & Catarrh *Lane, UK.*
Althaea (p.2253·3); echinacea (p.2298·1); sambucus (p.2383·1).
Catarrh; sinus congestion.

Modern Herbals Cold & Congestion *Lane, UK.*
⊗ Lobelia (p.2157·2); tolu solution (p.1574·2).
Catarrh; cold symptoms; congestion; hay fever; rhinitis.

Modern Herbals Cough Mixture *Lane, UK.*
Ipecacuanha (p.1562·3); marrubium (p.1564·1); squill vinegar (p.1573·1).
Catarrh; cold symptoms; coughs; sore throat.

Modern Herbals Laxative *Lane, UK.*
Senna (p.1769·2); aloin (p.1705·3); cascara (p.1715·2).
Constipation.

Modern Herbals Menopause *Lane, UK.*
Parsley (p.2363·2); vervain (p.2413·3); clivers (p.2284·3); senna (p.1769·2).
Menopausal disorders.

Modern Herbals Muscular Pain *Lane, UK.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Muscle pain.

Modern Herbals Pile
Note. This name is used for preparations of different composition.
Lane, UK.
Ointment: Hamamelis (p.2318·2); compound benzoin tincture; zinc oxide (p.1621·2).
Haemorrhoids.

Lane, UK.
Tablets: Cascara (p.1715·2); slippery elm (p.2388·2).
Haemorrhoids.

Modern Herbals Rheumatic Pain *Lane, UK.*
Celery leaf (p.2278·3); menyanthes (p.2340·3); cimicifuga (p.2282·1).
Musculoskeletal and joint pain.

Modern Herbals Sleep Aid *Lane, UK.*
Passion flower (p.2363·2).
Insomnia.

Modern Herbals Stress *Lane, UK.*
Motherwort (p.2347·3); valerian (p.2410·1); vervain (p.2413·3); passion flower (p.2363·2).
Irritability; stresses and strains.

Modern Herbals Trapped Wind & Indigestion *Lane, UK.*
Activated charcoal (p.1435·2).
Diarrhoea; dyspepsia; flatulence; heartburn.

Modern Herbals Water Retention *Lane, UK.*
Bearberry (p.2263·3); clivers (p.2284·3); lappa (p.2330·3).
Water retention.

Modernel *Phoenix, Arg.†.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Modezine *Atlantic, Philipp.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Modibloq *Zeler, Port.*
Nimodipine (p.1357·2).

Modicef *Ipso, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Modicon *Janssen-Cilag, Neth.; Ortho McNeil, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Modiem *Piam, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Modifast *Wander Health Care, Switz.†.*
Food for special diets (p.1922·1).
Obesity.

Modifenac *Alpharma, Denm.; Alpharma, Norw.; Alpharma, Swed.†.*
Diclofenac sodium (p.44·3).
Dysmenorrhoea; inflammation; musculoskeletal and joint disorders.

Modifical
Note. This name is used for preparations of different composition.
Beta, Arg.
Ibandronate (p.1098·3).
Osteoporosis.

Zodiac, Braz.; Asofarma, Mex.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Modil *General Drugs, Thai.*
Minoxidil (p.1342·1).
Hypertension.

Modilac HA *Sodilac, Fr.*
Infant feed (p.1922·1).
Milk-protein allergy.

Modilac sans Lactose *Sodilac, Fr.*
Infant feed (p.1922·1).
Diarrhoea; lactose intolerance.

Modimet *Ultra, Mex.*
Dipyrone (p.49·2).
Fever; pain.

ModimMunal *Medice, Ger.†.*
Escherichia coli antigens.
Arthritis.

Modina *Pentafarma, Port.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Modinexil *Neiadas (Νεϊαδας), Gr.†.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Modinol *Vianex (Βιανεξ), Gr.†.*
Rizatriptan benzoate (p.625·1).
Migraine.

Modiodal *Cephalon, Denm.; Cephalon, Fr.; Genesis, Gr.; Armstrong, Mex.; Cephalon, Neth.; Organon, Norw.; Cephalon, Port.; Noventure, Spain; Organon, Swed.; Gen, Turk.*
⊗ Modafinil (p.2160·3).
Attention-deficit hyperactivity disorder; hypersomnia; narcoleptic syndrome; sleep apnoea.

Modip *AstraZeneca, Ger.; Promed, Ger.*
Felodipine (p.1285·3).
Hypertension.

Modisal *Sandoz, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Modiscop *Brady, Austria.*
⊗ Morphine hydrochloride (p.86·3); ethylmorphine hydrochloride (p.52·2); hyoscine hydrobromide (p.1734·1).
Pain.

Moditen
Squibb, Canad.†.
Fluphenazine enantate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Biotika, Cz.; KRKA, Hung.; BMS, Ital.; KRKA, Rus.; BMS, Venez.
Fluphenazine decanoate (p.998·1).
Psychoses.

Sanofi-Aventis, Fr.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, UK†.
Fluphenazine hydrochloride (p.998·1).
Anxiety; disturbed behaviour; psychoses.

Modium *Pharmaten (Φαρματεν), Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Modival *Saval, Chile†.*
Dipotassium clorazepate (p.980·1).
Anxiety disorders; insomnia; premedication.

Modivid *Sanofi-Aventis, Ital.; Aventis, Mex.†; Sanofi-Aventis, Port.; Aventis, Turk.*
Cefodizime sodium (p.226·1).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Modjul *Scientific Hospital Supplies, Irl.*
Flavouring for use with unflavoured peptide and amino-acid preparations (p.1922·1).

Modomed *Medifive, Thai.*
Domperidone (p.1726·2).
Digestive disorders; dyspepsia; heartburn; nausea and vomiting.

Modopar *Roche, Fr.; Eureco, Neth.; Euro Registratie, Neth.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Modrasone *Pliva, Irl.; Pliva, UK.*
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Modrenal *Bioenvision, UK.*
Trilostane (p.2404·2).
Breast cancer; Cushing's syndrome; hyperaldosteronism.

Moducal *Mead Johnson Nutritionals, Canad.†; Mead Johnson, NZ; Mead Johnson, Port.†; Mead Johnson Nutritionals, USA.*
Maltodextrin (p.1955·3).
Carbohydrate source; carbohydrate supplement.

Moducren *Sidus, Arg.†; Substipharm, Fr.; MSD, Hong Kong; MSD, Irl.; MSD, Port.†; MSD, S.Afr.; MSD, Switz.; MSD, UK†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3); timolol maleate (p.1412·3).
Hypertension.

Moducrin *MSD, Austria; Teofarma, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3); timolol maleate (p.1412·3).
Hypertension.

Modula *Antonetto, Ital.*
Polycarbophil calcium (p.1763·3).
Constipation; diarrhoea.

Modulactone *Lafedar, Arg.*
⊗ Spironolactone (p.1400·1).

Modul'Aid *Voyage, Fr.†.*
Permethrin (p.2048·2).
Mosquito repellent.

Modulamin *Braun, Switz.*
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Modulan *Macrophar, Thai.†.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Modulanzime *Grunenthal, Port.*
Bromopride (p.1713·3); dimeticone (p.1770·2); pepsin (p.2365·1); amylase (p.2256·3); fungal lipase.
Gastrointestinal disorders.

Modulator *Servier, Spain†.*
Benfluorex hydrochloride (p.1224·3).
Diabetes mellitus; hyperlipidaemias.

Modulen IBD *Nestle, Austral.†; Nestle, Braz.; Nestle, Fin.; Nestle, Fr.; Nestle Clinical, Irl.; Nestle, Israel; Nestle, Ital.*
Preparation for enteral nutrition (p.1922·1).
Inflammatory bowel disease.

Modulo Calorico *Braun, Chile; Behrens, Venez.*
Maltodextrin (p.1955·3).
Nutritional supplement.

Modulon *Axcan, Canad.; Pfizer, Fr.*
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders; irritable bowel syndrome; postoperative paralytic ileus.

Moduret *Prempharm, Canad.; Du Pont, Irl.; MSD, UK.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-amilozide.
Ascites; heart failure; hypertension; oedema.

Moduretic *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Cz.; MSD, Denm.†; MSD, Fin.; BMS, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Ital.; MSD, Malaysia; MSD, Mex.;*

MSD, Neth.; MSD, Norw.; MSD, Port.; MSD, S.Afr.; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; BMS, UK; Merck, USA; MSD, Venez.
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-amilozide.
Heart failure; hepatic cirrhosis with ascites; hypertension; hypokalaemia; oedema.

Moduretik *BMS, Ger.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites; hypertension; oedema.

Modus *Almirall, Spain.*
Nimodipine (p.1357·2).
Mental function impairment; neurological deficit following subarachnoid haemorrhage.

Modusik-A *Volta, Chile; Sophia, Mex.*
Ciclosporin (p.1822·2).
Dry eyes.

Modustatina *Sanofi-Aventis, Ital.*
Somatostatin acetate (p.1809·2).
Adjunct in gastrointestinal radiography; diabetic ketoacidosis; gastrointestinal haemorrhage; pancreatic disorders.

Modustatine *Sanofi Synthelabo, Belg.†; Sanofi-Aventis, Fr.*
Somatostatin acetate (p.1809·2).
Gastrointestinal fistulae; gastrointestinal haemorrhage.

Modutrol *Gynopharm, Chile.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Triphasic oral contraceptive.

Moex *Schwarz, Cz.; Schwarz, Fr.; Schwarz, Hong Kong; Schwarz, Rus.*
Moexipril hydrochloride (p.1343·2).
Hypertension.

Moex Plus *Schwarz, Rus.*
⊗ Moexipril hydrochloride (p.1343·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Mofacort *Surya Dermato, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Mofesal N *Medice, Ger.†.*
Mofebutazone sodium (p.86·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Rheumatism; superficial thrombophlebitis.

Mofulex *Molex Ayus, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Mofur *Gabriel, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Mogadan *Valeant, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Mogadon *Valeant, Austral.; ICN, Austria; ICN, Belg.; Valeant, Canad.; ICN, Denm.; CSP, Fr.; Valeant, Hong Kong; Valeant, Irl.; ICN, Ital.; ICN, Malaysia†; ICN, Neth.; ICN, Norw.; Pharmaco, S.Afr.; Medilink, Swed.; Valeant, Switz.; ICN, UK.*
Nitrazepam (p.1011·2).
Epilepsy; sleep disorders.

Mogasinte *CPH, Port.*
Domperidone (p.1726·2).
Adjunct in gastrointestinal examinations; dyspepsia; nausea and vomiting.

Mogetic *Azupharma, Ger.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

Mogine *Douglas, NZ.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Mohexal *Hexal, Austral.*
Moclobemide (p.411·1).
Depression.

Mohrus *Hisamitsu, Hong Kong; Hisamitsu, Jpn.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Moisderm *Interbat, Indon.*
⊗ Urea (p.1620·2).
Dry skin disorders; hyperkeratotic skin disorders.

Moisol *FDC, India.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Moist Again *Lake, USA.*
Vaginal lubricant.

Moi-Stir
Note. This name is used for preparations of different composition.
Pharmascience, Canad.
Electrolytes (p.1667·1).
Kingswood, USA.
Carmellose sodium (p.2142·1); electrolytes (p.1667·1); sorbitol (p.1965·1).
Dry mouth.

Moisture Drops
Note. This name is used for preparations of different composition.
Bausch & Lomb, Canad.†; Bausch & Lomb, S.Afr.†.
Hypromellose (p.2144·2); glycerol (p.2314·2); povidone (p.2146·1).
Dry eye; eye irritation.
Bausch & Lomb, USA.
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3); glycerol (p.2314·2).
Dry eyes.

Moisture Eyes *Bausch & Lomb, Hong Kong; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.*
Glycerol (p.2314·2); propylene glycol (p.2374·1).
Dry eyes.

Moisture Lift Protective *Avon, Canad.†.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Moisture Shield *Avon, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Moisture Therapy *Avon, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Moisturel
Note. This name is used for preparations of different composition.
Westwood-Squibb, Canad.
White soft paraffin (p.2031·2); dimeticone (p.2032·1).
Dry skin disorders.
Westwood-Squibb, USA.
Emollient.
Dry skin disorders.

Moisturizing All Clear *Bausch & Lomb, Philipp.*
⊗ Macrogol (p.2336·1); naphazoline hydrochloride (p.1565·2).
Eye irritation.

Mokbios *Mersifarma, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Mokcan *Cadila, India.*
Amoxicillin (p.202·2).
Bacterial infections.

Moklar *Biovena, Pol.*
Moclobemide (p.411·1).
Depression; social phobia.

Moksilin *Ilsan, Turk.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Molacort *Molex Ayus, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Moladec *Molex Ayus, Indon.*
Vitamins A, B, C, and D (p.1922·1).
Nutritional supplement.

Moladerm *Molex Ayus, Indon.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Molaflam *Molex Ayus, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Molagar *Finadiet, Arg.†.*
Leflunomide (p.75·3).

Molagit *Molex Ayus, Indon.*
Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Molakrim *Molex Ayus, Indon.*
Menthol (p.2340·1); eugenol (p.2301·2); methyl salicylate (p.85·3).
Headache; musculoskeletal pain; soft-tissue injury.

Molapect *Molex Ayus, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Molasic *Molex Ayus, Indon.*
Mefenamic acid (p.80·1).
Pain.

Molason *Molex Ayus, Indon.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Molavir *Molex Ayus, Indon.*
Aciclovir (p.862·3).
Herpex simplex infections of the skin.

Molax *Siam Bheasach, Thai.*
Domperidone (p.1726·2) or domperidone maleate (p.1726·3).
Gastrointestinal disorders; nausea and vomiting.

Molazol *Molex Ayus, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Molca *Andromaco, Chile.*
Benzethonium chloride (p.1630·1); proflavine hydrochloride (p.1625·2).
Disinfection of instruments, mucous membranes, and skin.

Molcain *Molteni, Ital.†.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Molcass *Varifarma, Arg.*
Molgramostim (p.1073·3).
Neutropenia.

Molcer *Wallace Mfg Chem., UK.*
Docusate sodium (p.1725·1).
Ear wax removal.

Moldina *Juventus, Spain†.*
Bifonazole (p.527·3).
Fungal skin infections.

Molelant *Chrispa (Χρισπα), Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Molevac *Pfizer, Austria; Parke, Davis, Ger.*
Pyrvinium embonate (p.155·3).
Enterobiasis.

Molexdine *Molex Ayus, Indon.*
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection; wounds.

Molexdryl *Molex Ayus, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Molexflu *Molex Ayus, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Molfenac *Amsa, Ital.*
Diclofenac epolamine (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Molipaxin *Sanofi-Aventis, Irl.; Aventis, S.Afr.; Aventis, UK.*
Trazodone hydrochloride (p.424·3).
Depression; mixed anxiety depressive states.

Mol-Iron *Schering-Plough, Venez.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Molit *Adeka, Turk.*
Hyoscine butylbromide (p.1734·1).

Molit Plus *Adeka, Turk.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).

Molival *Temis, Arg.†.*
Bromazepam (p.964·3).
Anxiety.

Molken *Unipharma, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Mollifene *Pfeiffer, USA.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Mollipect *AstraZeneca, Swed.*
⊗ Bromhexine hydrochloride (p.1552·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Mollome *Gedeon Richter, Cz.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Molnia *Maigal, Arg.*
Sulfur (p.1614·1); pyrithione zinc (p.1611·2).
Seborrhoea.

Moloco + B12 *Darya-Varia, Indon.*
Placenta extract (p.2337·3); vitamin B (p.1980·2).
Lactation insufficiency.

Molsi *1A, Ger.†.*
Molsidomine (p.1343·3).
Angina pectoris.

Molsi-Azu *Azupharma, Ger.†.*
Molsidomine (p.1343·3).
Ischaemic heart disease.

Molsibeta *Betapharm, Ger.*
Molsidomine (p.1343·3).
Formerly known as Molsicor.
Angina pectoris.

Molsicor *Investi, Arg.*
Molsidomine (p.1343·3).
Angina pectoris.

Molsidain *Sanofi-Aventis, Spain.*
Molsidomine (p.1343·3).
Angina pectoris.

Molsidaine *Aventis, Arg.*
Molsidomine (p.1343·3).
Angina pectoris.

Molsidolat *Aventis, Austria.*
Molsidomine (p.1343·3).
Angina pectoris.

Molsihexal *Hexal, Austria; Hexal, Cz.; Hexal, Ger.*
Molsidomine (p.1343·3).
Angina pectoris; heart failure; pulmonary hypertension.

Molsiket *Schwarz, Cz.*
Molsidomine (p.1343·3).
Angina pectoris.

molsiket *Schwarz, Ger.*
Molsidomine (p.1343·3).
Ischaemic heart disease.

Molsi-Puren *Alpharma-Isis, Ger.*
Molsidomine (p.1343·3).
Ischaemic heart disease.

Molval *Merck Medication Familiale, Fr.*
Omega-3 fatty acids (p.1362·2).
Hyperlipidaemias.

Molvite with Iron *Pharma Nutria, Philipp.*
Ferrous sulfate (p.1939·3); lysine hydrochloride; vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Nutritional supplement; vitamin and iron deficiency.

Molvite-OB *Pharma Nutria, Philipp.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamins; minerals (p.1922·1).
Nutritional supplement for pregnancy and lactation.

Molybdene Injectable *Aguettant, Fr.*
Ammonium molybdate (p.1957·1).
Parenteral nutrition.

Molypen *American Pharmaceutical, USA.*
Ammonium molybdate (p.1957·1).
Parenteral nutrition.

Molzyme *FDC, India†.*
Papain (p.2362·3); amylase (p.2256·3); cumin oil; ajowan oil; activated charcoal (p.1435·2); simeticone (p.1770·2); belladonna (p.2263·3).
Anorexia; dyspepsia.

Mom *Nestle, Mex.†.*
Nutritional supplement during pregnancy and lactation (p.1922·1).

Mom Gel *Candioli, Ital.*
Phenothrin (p.2048·3).
Pediculosis.

Mom Lozione Preventiva *Candioli, Ital.*
Benzyl benzoate (p.2036·1).
Insect repellent.

Mom Piretro Emulsione *Candioli, Ital.†.*
Tetramethrin (p.2051·1); piperonyl butoxide (p.2049·1).
Pediculosis.

Mom Shampoo Antiparassitario *Candioli, Ital.*
Tetramethrin (p.2051·1); phenothrin (p.2048·3).
Pediculosis.

Mom Shampoo Schiuma *Candioli, Ital.*
Phenothrin (p.2048·3).
Pediculosis.

Momate *Glenmark, India; Glenmark, Malaysia; Glenmark, Philipp.*
⊗ Mometasone furoate (p.1539·3).
Skin and scalp disorders.

Momate-S *Glenmark, India.*
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Psoriasis.

Momecort *Verisfield, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Momelab *Labomed, Chile.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Momen
Note. This name is used for preparations of different composition.
Lepori, Port.
Benzydamine hydrochloride (p.27·3).
Musculoskeletal and joint disorders.
Farma Lepori, Spain.
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Momendol
Note. This name is used for preparations of different composition.
ACRAF, Neth.; Lepori, Port.
Naproxen sodium (p.92·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.
Angelini, Ital.
Oral granules; tablets: Naproxen sodium (p.92·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.
Angelini, Ital.
Topical gel: Naproxen sodium (p.92·3); a heparinoid (p.1305·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Moment
Note. This name is used for preparations of different composition.
Apsen, Braz.
Capsaicin (p.32·3).
Neuralgia.
Angelini, Ital.; Lepori, Port.
Ibuprofen (p.64·2).
Fever; influenza symptoms; pain.

Momento *CSC, Austria.*
Ibuprofen (p.64·2).
Pain.

Momentol *BMS, Spain.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Momentum
Note. This name is used for preparations of different composition.
Montavit, Austria; Wyeth Consumer, Neth.
Paracetamol (p.108·1).
Fever; pain.
Whitehall, USA.
Aspirin (p.20·3); phenyltoloxamine citrate (p.588·1).
Backache.

Momentum Muscular Backache Formula
Whitehall, USA.
Magnesium salicylate (p.79·2).
Pain.

Momeplus *Panalab, Arg.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Momesalic *Schering-Plough, Cz.*
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Psoriasis.

Momet *Erlimpex, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Momicine *Inibsa, Spain.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Monace *Alphapharm, Austral.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Monactil *Gebro, Austria.*
Dexibuprofen (p.39·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Monafed DM *Monarch, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Mona-Lisa *Mona Lisa, Israel.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Monapax *Cassella-med, Ger.*
Homoeopathic preparation.

Monarc-M *Teva Tuteur, Arg.†; Kamada, Israel; Cankat, Turk.; American Red Cross, USA.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Monarit *Rontag, Arg.*
Naproxen sodium (p.92·3).
Pain.

Monasens *Theramex, Mon.*
Nicotinamide (p.1957·3); sodium hyaluronate (p.2320·1).
Vaginal lubricant.

Monaxin *Therabel, Belg.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Monazole *Technilab, Canad.†.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Moncycline *Am-Europharma, Philipp.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Mondeal *Stada, Austria.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Mondrian *Andromaco, Chile†.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Mondus *Sandoz, Arg.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Monecto *Fahrenheit, Indon.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monell *Novell, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Moneva *Schering, Fr.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Monicil *Sanval, Braz.*
Rifampicin (p.325·3).
Tuberculosis.

Monicor *Pierre Fabre, Fr.; Wallace, India.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monigen *Generics, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monilac *Chugai, Jpn.*
Lactulose (p.1738·2).
Constipation; hyperammonaemia.

Monilen *Recip, Swed.*
⊗ Urea (p.1620·2).
Dry skin.

Monipax *Haller, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Moni-Sanorania *Winthrop, Ger.*
Isosorbide mononitrate (p.1318·3).
Formerly known as Moni.
Angina pectoris.

Monisol *Zorka, Rus.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Monistat *Janssen-Cilag, Austral.†; McNeil Consumer, Canad.; Johnson & Johnson, NZ; Janssen, Philipp.; Janssen-Cilag, Switz.; Advanced Care, USA; Personal Products, USA.*
Miconazole nitrate (p.541·3).
Balanitis; fungal skin infections; fungal vulvovaginal infections.

Monit *Sanofi Synthelabo, UK†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monitan *Wyeth, Canad.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; hypertension.

Monit-Puren *Alpharma-Isis, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monizol *Krolton, Arg.*
Miconazole nitrate (p.541·3).
Vaginal candidiasis.

Monizol Cort *Krolton, Arg.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2); metronidazole (p.837·1).
Vulvovaginal infections.

Monizol Cort Crema *Krolton, Arg.*
⊗ Betamethasone valerate (p.1519·1); miconazole (p.541·2); gentamicin sulfate (p.282·1).

Monizole *Pharmaceutical Co, India.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis.

Monnax *Medhaus, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Monnax Plus *Medhaus, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; gastric hyperacidity.

5-Mono *Biochem, India.*
Isosorbide mononitrate (p.1318·3).

Mono Acis *Acis, Ger.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

mono corax *corax, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Mono Demetrin *Parke, Davis, Ger.*
Prazepam (p.1019·3).
Anxiety disorders.

Mono & Disaccharide Free Diet Powder (Product 3232A) *Mead Johnson, Austral.†.*
Preparation for enteral nutrition (p.1922·1).
Impaired glucose transport; intractable diarrhoea; lactase, sucrase, or maltase deficiency; test for fructose utilisation.

Mono Kalz *Viatris, Austria.*
Calcium monocitrate and dicitrate (p.1675·3).
Calcium deficiency; osteoporosis.

Mono Mack *Pfizer, Austria; Bago, Chile†; Mack, Cz.; Pfizer, Ger.; Mack, Hong Kong†; Mack, Hung.; Armstrong, Mex.†; Mack, Pol.; Mack, Thai.†; Zuoz, Venez.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Mono Migranin *Boots, Ger.*
Phenazone (p.116·1).
Fever; pain.

Mono Praecimed *Molimin, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Mono Wolff *Wolff, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Mono-A *Troikaa, India.*
Isosorbide mononitrate (p.1318·3); aspirin (p.20·3).
Angina pectoris; myocardial infarction.

Monobac *BMS, Mex.*
Aztreonam (p.209·2).
Gram-negative bacterial infections.

Monobeta *Betapharm, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monobios *CT, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Monobiotic *Ecobi, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Monobracin *Faran, Gr.†.*
Tobramycin (p.354·1).
Eye infections.

Monocal *Mericon, USA.*
Calcium carbonate (p.1714·1); sodium monofluorophosphate (p.1964·3).
Dietary supplement.

Monocaps *Freeda, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Monocard *Synteza, Pol.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Mono-Cedocard *Altana, Neth.; Cedona, Neth.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monocef
Note. This name is used for preparations of different composition.
Aristo, India.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Goldshield, Israel.
Cefonicid (p.226·3).
Bacterial infections.

Monocef-O *Aristo, India.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Monocetin *Sigma, Braz.*
Tetracycline hydrochloride (p.347·2); bromelains (p.2269·1).
Bacterial infections.

Monocid
Note. This name is used for preparations of different composition.
Abbott, Austria.
Clarithromycin (p.248·2).
Bacterial infections.

GSK, Belg.†; Shire, Ital.†; Decomed, Port.; Rottapharm, Spain; SmithKline Beecham, USA†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Monocide *Fischer, Israel.*
Carbophos; bioallethrin (p.2036·2).
Pediculosis.

Monocinque *Menarini, Hong Kong; Lusofarmaco, Ital.; Berlin-Chemie, Rus.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Monoclair *Hennig, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monoclate-P *Aventis Behring, Arg.; Aventis Behring, Austria†; CSL, Braz.; Centeon, Cz.†; Aventis Behring, Denm.†; Aventis Behring, Fr.†; Aventis Behring, Ger.†; Gerolimatos (Γερολυματος), Gr.†; Aventis Behring, Irl.†; Centeon, Israel; ZLB Behring, Mex.; ZLB, Spain†; Aventis Behring, Swed.†; Aventis Behring, UK; Centeon, USA.*
A factor VIII preparation (p.1067·1).
Factor VIII deficiency; haemophilia A.

Monoclox *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore†.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Monocontin *Win-Medicare, India.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monocor *Biovail, Canad.; Wyeth, UK†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Monocorat *Armstrong, Mex.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monocord *Dexxon, Israel.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monocordil *Baldacci, Braz.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monocrin *Pasteur, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Monocrixo *Therabel, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Monodin *Pfizer, Port.*
Amlodipine besilate (p.1214·1).
Hypertension; ischaemic heart disease.

Monodoks *Deva, Turk.*
Doxycycline (p.267·1).
Bacterial infections; malaria; oral herpes simplex infections.

Monodox *Oclassen, USA.*
Doxycycline (p.267·1).
Bacterial infections; intestinal amoebiasis.

Monodur *PMC, Austral.; AstraZeneca, Turk.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Mono-Embolex *Novartis, Ger.*
Certoparin sodium (p.1242·3).
Depp-vein thrombosis; postoperative thrombosis prophylaxis.

Monofed *Garec, S.Afr.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Monofeme *Wyeth, Austral.; Wyeth, NZ.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Monoferro *Ganassini, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Monofix *CSL, NZ.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Monofix-VF *CSL, Austral.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Monoflam *Winthrop, Cz.; Winthrop, Ger.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Monoflocet *Sanofi-Aventis, Fr.*
Ofloxacin (p.310·2).
Bacterial infections.

Monogen *Scientific Hospital Supplies, Austral.; SHS, Fr.; Scientific Hospital Supplies, Irl.; SHS, Israel; Nutricia, NZ; Scientific Hospital Supplies, NZ; Scientific Hospital Supplies, UK.*
Preparation for enteral nutrition (p.1922·1).
Disorders of lipid metabolism and absorption; lymphatic disorders.

Mono-Gesic *Schwarz, USA†.*
Salsalate (p.122·1).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Monoginal *Sandoz, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Mono-Jod *Philopharm, Ger.*
Potassium iodide (p.2169·2).
Iodine deficiency.

Monoket *Sidus, Arg.; Gebro, Austria; Schwarz, Gr.; Chiesi, Ital.; Schwarz, Norw.; Neo-Farmaceutica, Port.; Pfizer, Swed.; Adeka, Turk.; Schwarz, USA.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Mono-Latex *Wampole, USA.*
Test for infectious mononucleosis.

Monolin *Berlin Pharm, Thai.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monolitum *Lepori, Port.†; Salvat, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Monolong *Alpharma-Isis, Ger.; CTI, Israel; CTS, Rus.†; Ali, Turk.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monomax *Trinity, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monomil *Ivax, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monomycin *Grunenthal, Cz.†; Grunenthal, Ger.†.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Mononaxy *Cephalon, Fr.*
Clarithromycin (p.248·2).
Bacterial infections.

Mononine *Aventis Behring, Arg.; ZLB, Belg.; CSL, Braz.; CSL Behring, Canad.; CSL, Cz.; Aventis Behring, Denm.†; ZLB, Fr.; ZLB, Ger.; ZLB, Gr.; Aventis Behring, Irl.†; ZLB, Ital.; ZLB, Neth.; CSL, Port.; ZLB, Spain; ZLB, Swed.; Aventis Behring, UK; Centeon, USA.*
A factor IX preparation (p.1068·3).
Factor IX deficiency; haemophilia B.

Mononit *Medis, Israel; Sanofi-Aventis, Pol.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Mononitrat *Verla, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Mononitril *Baldacci, Port.*
Isosorbide mononitrate (p.1318·3).
Heart failure; ischaemic heart disease.

Monopack *Bago, Chile.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monoparin
IFET (ΙΦΕΤ), Gr.; CP Pharmaceuticals, Irl.; Artex, NZ†.
Heparin sodium (p.1301·2).
Anticoagulant; thrombosis.

CP Pharmaceuticals, UK.
Heparin calcium (p.1301·2) or heparin sodium (p.1301·2).
Thromboembolic disorders.

Monopina *Pfizer, Ital.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Monoplus *BMS, Austral.; BMS, Braz.; BMS, Gr.†; BMS, Thai.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Monopril *BMS, Austral.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Malaysia†; BMS, Mex.; BMS, Pol.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, Thai.; BMS, Turk.; BMS, USA; BMS, Venez.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Monopril comp *BMS, Swed.†.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Monopril Plus *BMS, Chile; BMS, Turk.; BMS, Venez.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Monopril-HCT *BMS, USA.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Monopront *Ferraz, Lynce, Port.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monopur *Pohl, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monoquin *Zambon, Port.†.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Monorapid *Promedico, Israel.*
Isopropyl alcohol (p.1650·3); 1,3-butanediol.
Skin disinfection.

Monores *Valeas, Ital.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Monorythm *Santa, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monos *Selvi, Ital.*
Rufloxacin hydrochloride (p.331·3).
Bacterial infections.

Monosan ProMed, Cz.; Promed, Rus.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monosol Baxter, Austria.
Glucose; electrolytes (p.1670·3).
Haemodialysis; haemofiltration.

Monosor Vitabalans, Cz.
Isosorbide mononitrate (p.1318·3).
Stenocardia prophylaxis.

Monosorb Amedius, Philipp.; Dexcel, UK.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monosorbitrate Nicholas Piramal, India.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monosordil Elpen (Ελπεν), Gr.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monostenase Azupharma, Ger.†.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

MonoStep Schering, Ger.
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Monosulpa Leti, Venez.
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); kanamycin sulfate (p.291·2).

Monotab Zentiva, Cz.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Monotard Novo Nordisk, Austral.†; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.†; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Irl.†; Novo Nordisk, Ital.; Novo Nordisk, Jpn†; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.†; Novo Nordisk, Port.†; Novo Nordisk, Spain†; Novo Nordisk, Swed.; Novo Nordisk, UK†.
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (human, monocomponent) (p.443·2).
Formerly known as Human Monotard.
Diabetes mellitus.

Monotard HM Novo Nordisk, Arg.†; Novo Nordisk, Austria; Novo Nordisk, Belg.†; Novo Nordisk, Chile†; Novo Nordisk, Cz.†; Novo Nordisk, Hong Kong; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Malaysia†; Novo Nordisk, S.Afr.†; Novo Nordisk, Singapore†; Novo Nordisk, Switz.; Novo Nordisk, Thai.†.
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (human, monocomponent) (p.443·2).
Diabetes mellitus.

Monotard MC Novo Nordisk, Arg.†; Novo Nordisk, Braz.†; Novo Nordisk, Hong Kong†; Human, Hung.†; Novo Nordisk, Rus.
⊗ Insulin zinc suspension (amorphous 30%, crystalline 70%) (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Monotax Biochem, India.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Monotax-O Biochem, India.
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Monotest Aventis Pasteur, Austria; Aventis Pasteur, Fr.†; Aventis Pasteur, Ital.†; CSL, NZ†; Aventis, S.Afr.†; Aventis Pasteur, Swed.†.
Tuberculin PPD (p.2405·3).
Sensitivity test; tuberculosis test.

Mono-Tildiem Sanofi-Aventis, Fr.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Singapore.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Monotobrin Pharmanel, Gr.
Tobramycin (p.354·1).
Eye infections.

Monotrate Sun, India; Sun, Thai.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Monotrean Sankyo, Braz.; Sankyo, Ital.†.
Papaverine (p.2191·3); quinine hydrochloride (p.612·3).
Vertigo.

Monotrean B6 Sankyo, Braz.
Papaverine (p.2191·3); quinine hydrochloride (p.612·3); pyridoxine hydrochloride (p.1978·2).
Vertigo.

Mono-Tridin Opfermann, Ger.
Sodium monofluorophosphate (p.1964·3).
Osteoporosis.

Monotrim Hexal, Denm.; Solvay, Irl.†; Hexal, Neth.; Gea, Switz.†; Chemidex, UK.
Trimethoprim (p.355·2).
Bacterial infections.

Monotrin Bago, Arg.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Monovacc-Test Aventis Pasteur, Belg.†.
Old tuberculin (p.2405·3).
Test for tuberculin sensitivity.

Monovas Nevzat, Turk.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Monovax Sanofi Pasteur, Fr.†.
A BCG vaccine (p.2205·3).
Active immunisation.

Monovent Sandoz, UK†.
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour.

Monovit-3 B Kocak, Turk.
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Monovitan C Pliva Krakow, Pol.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Monowel Biolab, Philipp.
Cefoxitin sodium (p.230·2).
Bacterial infections.

Monox Viatris, Austria.
Moxonidine (p.1345·1).
Hypertension.

Monoxar Proge, Ital.
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Monoxidil Lamda (Λαμδα), Gr.†.
Minoxidil (p.1342·1).
Alopecia androgenetica.

Monozeclar Abbott, Fr.
Clarithromycin (p.248·2).
Bacterial infections.

Monozide BMS, S.Afr.
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Monozol Legrand, Braz.
Albendazole (p.139·2).
Worm infections.

Monphytol Laboratories for Applied Biology, UK†.
Methyl undecenoate (p.549·3); propyl undecenoate (p.549·3); salicylic acid (p.1612·2); methyl salicylate (p.85·3); propyl salicylate (p.1612·3); chlorobutanol (p.1639·2).
Fungal skin and nail infections.

Monsalic Schering-Plough, Cz.†; Schering-Plough, Port.
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Psoriasis; skin disorders.

Montair Cipla, India.
Montelukast sodium (p.1126·2).
Asthma.

Montair Plus Cipla, India.
⊗ Montelukast sodium (p.1126·2); bambuterol hydrochloride (p.1115·3).
Asthma.

Montalen Pharmonta, Austria.
Magnesium trisilicate (p.1744·1); aluminium hydroxide gel (p.1706·2); peppermint oil (p.1761·2).
Gastrointestinal disorders associated with hyperacidity.

Montamed Montavit, Austria.
Salverine hydrochloride (p.2383·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Pain.

Montana Pharmonta, Austria.
Lupulus (p.2335·2); gentian (p.2310·3); cinnamon (p.2283·1); bitter-orange peel (p.2357·1); caraway (p.2276·3); taraxacum (p.2395·1); peppermint oil (p.1761·2); pterocarpus santalinus.
Gastrointestinal disorders.

Montana N Pharmonta, Ger.
Cardamom (p.2277·1); cinnamon (p.2283·1); centaury (p.2279·1); caraway (p.2276·3); bitter-orange peel (p.2357·1); peppermint leaf (p.1761·2); gentian (p.2310·3).
Gastrointestinal disorders.

Montebloc Danlex, Philipp.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Montegen Gentili, Ital.
Montelukast sodium (p.1126·2).
Asthma.

Montelast Cadila, India.
Montelukast (p.1126·3).
Asthma.

Monticina Mintlab, Chile.
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Skin infections.

Montidin Danlex, Philipp.
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Montralex Danlex, Philipp.
Cefalexin (p.218·2).
Bacterial infections.

Montramox Danlex, Philipp.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Montricin Asta Medica, Braz.†.
Mepartricin sodium laurilsulfate (p.541·1).
Vulvovaginal candidiasis and trichomoniasis.

Monukast Galeno, Venez.
Montelukast (p.1126·3).
Asthma.

Monural Zambon, Hung.; Zambon, Pol.; Zambon, Rus.
Fosfomycin trometamol (p.278·2).
Bacterial infections of the urinary tract.

Monuril Zambon, Austria; Zambon, Belg.; Zambon, Braz.; Zambon, Fr.; Apogepha, Ger.; Zambon, Ger.; Zambon, Indon.; Zambon, Ital.; Zambon, Neth.; Zambon, Port.; Zambon, Switz.
Fosfomycin trometamol (p.278·2).
Bacterial infections of the urinary tract.

Monurol Purdue, Canad.; Labomed, Chile; Orion, Fin.†; Gerolimatos (Γερολυματος), Gr.†; Zambon, Hong Kong; Rafa, Israel; Zambon, Malaysia; Sanofi Synthelabo, Mex.; Zambon, Philipp.; Pharmazam, Spain; Orion, Swed.†; Bilim, Turk.; Forest Pharmaceuticals, USA.
Fosfomycin trometamol (p.278·2).
Bacterial infections of the urinary tract.

MoodLift Naturopathica, Austral.†.
Ademetionine (p.2247·1).
Tonic.

Moorland Torbet Laboratories, UK.
Bismuth aluminate (p.1710·3); magnesium trisilicate (p.1744·1); dried aluminium hydroxide gel (p.1706·2); heavy magnesium carbonate (p.1743·1); light kaolin (p.1738·1); calcium carbonate (p.1714·1).
Dyspepsia; flatulence; heartburn.

MOOV Ego, Malaysia.
Melaleuca oil (p.2338·2).
Insect repellent.

Mopasol Sevapharma, Cz.
Monobasic potassium phosphate (p.1682·2); dibasic sodium phosphate (p.1682·3).
Solvent for antiviral vaccines.

Mopavac Sevapharma, Cz.
A measles and mumps vaccine (Schwarz and Jeryl Lynn strains, respectively) (p.2222·3).
Active immunisation.

Mopen FIRMA, Ital.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moperidona Sidus, Arg.
Domperidone (p.1726·2).
Gastrointestinal disorders.

Moperidona AF Sidus, Arg.
Domperidone (p.1726·2); simeticone (p.1770·2).
Gastrointestinal disorders with excess gas.

Moperidona Enzimatica Sidus, Arg.
Domperidone (p.1726·2); pancreatin (p.2360·1); simeticone (p.1770·2).
Gastrointestinal disorders with excess gas; pancreatic insufficiency.

Mopral
AstraZeneca, Fr.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Mex.
Omeprazole magnesium (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Spain†.
Omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Mopsoralen Wolfs, Belg.
Methoxsalen (p.1605·1).
Mycosis fungoides; psoriasis; vitiligo.

Moradol ICN, Cz.†.
Butorphanol tartrate (p.32·1).
Adjunct to anaesthesia; pain; premedication.

Moradorm Bouhon, Ger.
Diphenhydramine hydrochloride (p.577·2).
Formerly contained valerian, passion flower, and diphenhydramine hydrochloride.
Sleep disorders.

Moradorm S Bouhon, Ger.
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Moragel IQFA, Mex.
Vitamin and mineral preparation (p.1922·1).

Moragen Euroderm, Arg.
Centella (p.1592·3); marine algae.

Morapid Mundipharma, Austria.
⊗ Morphine sulfate (p.86·3).
Pain.

Moraten Berna, Switz.
A measles vaccine (attenuated Edmonston-Zagreb strain) (p.2221·3).
Active immunisation.

Moraxine Fahrenheit, Indon.
Cefalotin (p.220·2).
Bacterial infections.

Morbilvax Chiron Vaccines, Ital.†; Biovac, S.Afr.; Chiron, Thai.†.
A measles vaccine (Schwarz strain) (p.2221·3).
Active immunisation.

Morcap Mayne, UK†.
⊗ Morphine sulfate (p.86·3).
Pain.

Morcontin Modi-Mundipharma, India.
⊗ Morphine sulfate (p.86·3).
Pain.

Morde X Vitafarma, Spain.
Sucrose octa-acetate (p.2394·1).
Nail biting deterrent.

Mordek Lloyd, Philipp.; Vitalink, Philipp.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

MorDHA Shield, Irl.
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Docosahexaenoic acid deficiency.

MoreDophilus Freeda, USA.
Acidophilus-carrot derivative (p.2372·3).
Dietary supplement.

Morelac Pharmacare, Philipp.
Moringa oleifera.
Nutritional supplement.

Morelax Loeffler, Mex.
Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3).
Renal calculi; smooth muscle spasm.

Morelin Laboratorios Chile, Chile.
Amitriptyline (p.376·1); chlordiazepoxide (p.968·1).
Mixed anxiety depressive states.

MorEPA Shield, Irl.
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Eicosapentaenoic acid deficiency.

Morera Compuesta Hochstetter, Chile†.
Homoeopathic preparation.

Moretal ICN, Hung.
⊗ Morphine sulfate (p.86·3).
Pain.

Morfex Tecnifar, Port.
Flurazepam hydrochloride (p.999·1).
Insomnia.

Morfozid Kocak, Turk.
Morinamide hydrochloride (p.302·1).
Tuberculosis.

Morgenxil Llorente, Spain†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Morhulin Thornton & Ross, Irl.; Thornton & Ross, UK.
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Nappy rash; skin disorders.

Moriamin Far East, Thai.
Multivitamin and amino-acid preparation (p.1922·1).

Moriamin Forte Morishita, Philipp.
5-Oxyanthranillic acid; vitamins; amino acids (p.1922·1).
Nutritional supplement.

Moriamin S-2 Ajinomoto, Philipp.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Moriavit Tai Yu, Philipp.
Amino-acid injection (p.1922·1).
Parenteral nutrition.

Morlan Andromaco, Mex.
Indometacin (p.66·3); methocarbamol (p.1897·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Morniflu Master Pharma, Ital.
Morniflumate (p.86·2).
Fever; inflammation; pain.

Mornin Sons, Mex.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Moronal Dermapharm, Ger.
Nystatin (p.543·2).
Fungal infections.

Moronal V Dermapharm, Ger.
⊗ Nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Skin disorders with fungal infection.

Morph Sandoz, Ger.
⊗ Morphine sulfate (p.86·3).
Pain.

Morphalgin Fawns & McAllan, Austral.†.
⊗ Morphine hydrochloride (p.86·3); aspirin (p.20·3).
Pain.

Morphanton Juta, Ger.; Q-Pharm, Ger.
⊗ Morphine sulfate (p.86·3).
Pain.

Morphex Lannacher, Israel.
⊗ Morphine hydrochloride (p.86·3).
Pain.

Morphgesic Amdipharm, UK.
⊗ Morphine sulfate (p.86·3).
Pain.

Morphitec Technilab, Canad.†.
⊗ Morphine hydrochloride (p.86·3).
Pain.

Morrhulan Streuli, Switz.
Cod-liver oil (p.1935·2).
Minor skin lesions.

Morstel Clonmel, Irl.†.
⊗ Morphine sulfate (p.86·3).
Pain.

Morton Salt Substitute Morton Salt, USA.
Low sodium dietary salt substitute (p.1922·1).

Morupar Chiron Vaccines, Ital.†; Ivax, Mex.†; Chiron Vaccines, Philipp.†; Biovac, S.Afr.†; Chiron Vaccines, Thai.†.
A measles, mumps, and rubella vaccine (Schwarz, Urabe AM9, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

MoRu-Viraten Biosano, Chile; Berna, Ital.†.
A measles and rubella vaccine (p.2223·1).
Active immunisation.

Moruviraten Carbel, Mex.
A measles and rubella vaccine (p.2223·1).
Active immunisation.

MorZet Apothecon, Neth.
Nicomorphine hydrochloride (p.95·1).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

MOS *Valeant, Canad.*
⊗ Morphine hydrochloride (p.86·3) or morphine sulfate (p.86·3).
Pain.

Mosafe *Glenmark, India.*
Mosapride citrate (p.1750·3).
Diabetic gastropathy; dyspepsia; gastritis; gastro-oesophageal reflux.

Mosalan *Chrispa (Χρισπα), Gr.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Mosapid *Cipla, India.*
Mosapride citrate (p.1750·3).

Mosar *Phoenix, Arg.*
Mosapride citrate (p.1750·3).
Dyspepsia; gastritis.

Mosar Enzimatico *Phoenix, Arg.*
Mosapride citrate (p.1750·3); simeticone (p.1770·2); pancreatin (p.2360·1).
Digestive disorders; dyspepsia.

Mosar Plus *Phoenix, Arg.*
Mosapride citrate (p.1750·3); simeticone (p.1770·2).
Flatulence; gastroparesis; meteorism.

Mosardal *Soho, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Mosart *Cadila, India.*
Mosapride sodium (p.1750·3).

Mosco *Medtech, USA.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Moscontin *Mundipharma, Fr.*
⊗ Morphine sulfate (p.86·3).
Pain.

Mosegor *Novartis, Ger.†; Novartis, Gr.†; Wander, Philipp.; Novartis, Spain; Novartis, Switz.; Novartis, Thai.*
Pizotifen malate (p.624·2).
Anorexia; migraine and other vascular headaches; reduced appetite; tonic.

Mosegor Vita *Wander, Philipp.*
Pizotifen malate (p.624·2); vitamin B substances (p.1922·1).
Reduced appetite.

Moselar *Milano, Thai.*
Pizotifen malate (p.624·2).
Migraine.

Mosether *Cipla, India.*
Alpha-beta arteether (p.598·3).
Malaria.

Mosi-Guard *Mosi-Guard, UK.*
Citriodol.
Insect repellent.

Mosil *Menarini, Fr.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Mostanol *Boehringer Ingelheim, Venez.†.*
Acemetacin (p.15·1).
Fever; inflammation; pain.

Mostardina *Ibefar, Braz.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); salicylic acid (p.1612·2); menthol (p.2340·1); mustard oil (p.2349·2).
Musculoskeletal and joint disorders.

Mostrafin *Pliva, Cz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Mostrelan *Sanofarm, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Mosuolit *Help, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Mosvit *Multicare, Philipp.*
Vitamin and mineral preparation (p.1922·1).

Motaderm *Bernofarm, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Motaxim *Millimed, Thai.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Motens *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Ger.; Glaxo Wellcome, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK.*
Lacidipine (p.1322·2).
Hypertension.

Moteson *Konimex, Indon.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Mother and Child Vitamin Drops *SSL, UK.*
Vitamins A, C, and D (p.1922·1).

Motiax *Neopharmed, Ital.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Moticlod *Lisapharma, Ital.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Moticon *Condrugs, Thai.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Motid *Randril, Philipp.*
Famotidine (p.1730·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Motidin *Valeant, Hung.*
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Motidine *Unison, Hong Kong; Unison, Singapore; Unison, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; multiple endocrine adenoma; peptic ulcer; systemic mastocytosis; Zollinger-Ellison syndrome.

Motidom *TO-Chemicals, Thai.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders; nausea and vomiting.

Motifene *Will-Pharma, Belg.; Sankyo, Fin.; Sankyo, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Motilak *Veropharm, Rus.*
Domperidone (p.1726·2).
Abdominal distension; dyspepsia; gastro-oesophageal reflux; heartburn; meteorism; nausea and vomiting.

Motilar *Rowe-Fleming, Venez.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Motilex
Note. This name is used for preparations of different composition.
Kalbe, Indon.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Almirall, Ital.
Clebopride malate (p.1722·1).
Gastrointestinal disorders.

Motilium
Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Altana, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen, Port.; Janssen, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Turk.
Domperidone (p.1726·2).
Abdominal discomfort; abdominal distension; aid in gastrointestinal examination; delayed gastric emptying; dyspepsia; flatulence; gastro-oesophageal reflux; gastroparesis; heartburn; hiccup; meteorism; nausea and vomiting.

Janssen-Cilag, Belg.; Janssen-Cilag, Denm.; McNeil, Neth.; Janssen, Thai.; McNeil, UK; Winthrop, UK.
Domperidone (p.1726·2) or domperidone maleate (p.1726·3).
Abdominal discomfort; delayed gastric emptying; dyspepsia; gastro-oesophageal reflux; nausea and vomiting; pyrosis.

Janssen-Ortho, Canad.†; Esteve, Spain.
Domperidone maleate (p.1726·3).
Dyspepsia; gastrointestinal motility disorders; gastroparesis; nausea and vomiting.

Motilyo *Janssen-Cilag, Fr.*
Domperidone (p.1726·2).
Abdominal distension; gastro-oesophageal reflux; nausea and vomiting.

Motional *Beta, Arg.*
Ispaghula (p.1737·1).
Constipation; diverticular disease; irritable bowel syndrome.

Motiron *Sandoz, Denm.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Motitrel *BMS, Chile.*
Fluphenazine hydrochloride (p.998·1); nortriptyline hydrochloride (p.413·2).
Mixed anxiety depressive states.

Motival
Note. This name is used for preparations of different composition.
BMS, Indon.; BMS, Irl.; BMS, Mex.; BMS, S.Afr.; Sanofi-Aventis, UK†.
Fluphenazine hydrochloride (p.998·1); nortriptyline hydrochloride (p.413·2).
Mixed anxiety-depressive states.

Biofarma, Turk.
Nimesulide (p.95·3).
Inflammation; musculoskeletal and joint disorders; pain.

Motivan
Note. This name is used for preparations of different composition.
Faes, Spain.
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Union Drug, Thai.
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Motiven *Fontovit, Braz.*
St John's wort (p.422·3).
Depression.

Motofen *Valeant, USA.*
Difenoxin hydrochloride (p.1723·3).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Motonium *Leksir, Rus.*
Domperidone (p.1726·2).
Abdominal distension; dyspepsia; gastro-oesophageal reflux; heartburn; meteorism; nausea and vomiting.

Motosol *Boehringer Ingelheim, Spain.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Motozina *Biomedica, Ital.*
Dimenhydrinate (p.576·2).
Motion sickness.

Motrax *Labinca, Arg.†.*
Ibuprofen (p.64·2).
Inflammation; pain.

Motrim *Lannacher, Austria.*
Trimethoprim (p.355·2).
Bacterial infections.

Motrin *Pfizer, Braz.; McNeil Consumer, Canad.; Pfizer, Chile; Janssen-Cilag, Mex.; Pfizer, Mex.; Pharmacia Upjohn, Port.†; Pfizer, UK†; McNeil Consumer, USA; Pfizer, Venez.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Motrin IB Sinus *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Cold symptoms; sinusitis.

Moultons Herbal Extract *Pharmaceutical Enterprises, S.Afr.*
Aloes (p.1705·2); rhubarb (p.1768·3); cascara (p.1715·2).
Constipation.

Moultons Pain Paint *Pharmaceutical Enterprises, S.Afr.*
Capsicum oleoresin (p.2276·2); menthol (p.2340·1); cassia oil (p.2278·1); solvent ether (p.2023·2); sassafras oil (p.2383·3); clove oil (p.2285·1); methyl salicylate (p.85·3).
Colic; digestive disorders; muscular pain; neuralgia.

Moure-M *Pond's, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites; hypertension; oedema.

Mouskito *Qualiphar, Belg.*
Ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Mouskito Sun
Note. This name is used for preparations of different composition.
Qualiphar, Belg.
Cream SPF 15: Ethyl butylacetylaminopropionate (p.2043·1); avobenzone (p.1589·3); octocrilene (p.1608·3); octinoxate (p.1608·2).
Insect repellent; sunscreen.

Qualiphar, Belg.
Topical spray SPF 20: Diethyltoluamide (p.2041·1); avobenzone (p.1589·3); octocrilene (p.1608·3); octinoxate (p.1608·2).
Insect repellent; sunscreen.

Mouskito Textile *Qualiphar, Belg.*
Permethrin (p.2048·2).
Insect repellent for textiles.

Mouskito Travel Milk *Qualiphar, Belg.*
Diethyltoluamide (p.2041·1); lavender oil (p.2331·2).
Insect repellent.

Mouskito Travel Stick *Qualiphar, Belg.*
Diethyltoluamide (p.2041·1); citronella oil (p.2284·2).
Insect repellent.

Mouskito Tropical *Qualiphar, Belg.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Mousticologne
Note. This name is used for preparations of different composition.
Omega, Fr.
Cream; lotion: Repellent 26/12; ethyl butylacetylaminopropionate (p.2043·1); enoxolone (p.50·1); sunscreen.
Insect repellent.

Omega, Fr.
Cream sensitive skin; lotion sensitive skin: Ethyl butylacetylaminopropionate (p.2043·1); enoxolone (p.50·1).
Insect repellent.

Omega, Fr.
Diffuser: Esdepallethrine (p.2042·3).
Insect repellent.

Omega, Fr.
Gel special; lotion special: Repellent 26/12; diethyltoluamide (p.2041·1); enoxolone (p.50·1); sunscreen.
Insect repellent.

Omega, Fr.
Mosquito net: Permethrin (p.2048·2).
Insect repellent.

Moustidose
Note. This name is used for preparations of different composition.
Gilbert, Fr.
Enoxolone (p.50·1).
Insect bites and stings.

Gilbert, Fr.
Compress: Menthol (p.2340·1); thymol (p.1664·3); lavender oil (p.2331·2).
Insect bites and stings.

Gilbert, Fr.
Fabric spray: Permethrin (p.2048·2).
Insect repellent.

Gilbert, Fr.
Vaporiser: Citronellal; geraniol (p.2310·3).
Insect repellent.

Moustidose Adult et Enfant *Gilbert, Fr.*
Diethyltoluamide (p.2041·1); ethohexadiol (p.2043·1).
Insect repellent.

Moustidose Bebe-Nourrisson
Note. This name is used for preparations of different composition.
Gilbert, Fr.
Cream: Ethyl butylacetylaminopropionate (p.2043·1); enoxolone (p.50·1); lavender oil (p.2331·2); sunscreen.
Insect repellent.

Gilbert, Fr.
Lotion: Ethyl butylacetylaminopropionate (p.2043·1); enoxolone (p.50·1).
Insect repellent.

Mouth Kote *Parnell, Canad.*
Eriodictyon (p.1560·2).
Dry mouth.

MouthKote *Parnell, Irl.; Parnell, USA.*
Artificial saliva.
Dry mouth.

MouthKote F/R *Parnell, USA.*
Sodium fluoride (p.1962·2).

MouthKote O/R
Note. This name is used for preparations of different composition.
Unimed, USA.
Oral rinse: Benzyl alcohol (p.1631·3); menthol (p.2340·1).
Minor mouth or throat irritation.

Unimed, USA.
Topical solution: Cetylpyridinium chloride (p.1635·1); diphenhydramine (p.577·1).
Sore throat.

MouthKote P/R
Note. This name is used for preparations of different composition.
Unimed, USA†.
Ointment: Diphenhydramine hydrochloride (p.577·2).
Oral lesions.

Unimed, USA†.
Topical solution: Diphenhydramine (p.577·1); cetylpyridinium chloride (p.1635·1).
Minor mouth or throat irritation.

Mouthwash *National Care, Canad.†.*
Cetylpyridinium chloride (p.1635·1).

Mouthwash Antiseptic & Gargle *Lander, Canad.†.*
⊗ Alcohol (p.1625·2); cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3).
Oral hygiene.

Mova Nitrat *Lindopharm, Ger.; Polfa Kutno, Pol.*
Silver nitrate (p.2387·2).
Bacterial eye infections in neonates; eye disorders.

Movacox *Hexal, Braz.†.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Movalis *Arrow, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, Spain.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movana *Quest, Canad.†.*
St John's wort (p.422·3).

Movasin *Synthesis, Rus.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movatec *Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Gr.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Movaxin *Genepharm, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Movelat
Note. This name is used for preparations of different composition.
Key, Austral.†; Sankyo, Thai.†; Genus, UK.
A heparinoid (p.1305·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, and soft-tissue disorders; sprains; strains.

Wilson, NZ†.
Adrenal extract (p.2337·3); a heparinoid (p.1305·2); salicylic acid (p.1612·2).
Musculoskeletal and joint disorders.

Movelium *Medicine Products, Thai.*
Domperidone (p.1726·2) or domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea and vomiting.

Movens *Pharmafar, Ital.*
Meclofenamate sodium (p.79·3).
Musculoskeletal and joint disorders; pain.

Movent *Community Pharmacy, Thai.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mover *Mitsubishi, Jpn†.*
Actarit (p.15·2).
Rheumatoid arthritis.

Moverdin *Kocak, Turk.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Movere *Antula, Fin.; Antula, Norw.*
Glucosamine hydrochloride (p.2313·2).
Joint disorders; osteoarthritis.

Movergan *Orion, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Movesan *Farmanic, Gr.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Movex
Note. This name is used for preparations of different composition.
Vitamed, Israel.
Bromhexine hydrochloride (p.1552·2).
Bronchitis.

Rayere, Mex.
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; pain.

Movicard *Ravensberg, Ger.*
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2); troxerutin (p.2305·1).
Cardiac disorders.

Movicol *Norgine, Austral.; Norgine, Austria; Norgine, Belg.; Norgine, Cz.; Norgine, Denm.; Sobora, Fin.; Norgine, Fr.; Norgine, Ger.; Norgine, Hong Kong; Norgine, Irl.; Norgine, Ital.; Norgine, NZ; Norgine, Norw.; Angelini, Port.; Norgine, S.Afr.; Norgine, Singapore; Norgine, Spain; Biolac, Swed.; Norgine, Switz.; PMP, Turk.; Norgine, UK.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation; faecal impaction.

Movicolon *Norgine, Neth.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Constipation.

Movi-Cox *Boehringer Ingelheim, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Movicox *Boehringer Ingelheim, Neth.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movidone *Milano, Thai.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, burns, and umbilicus.

Moviflex
Note. This name is used for preparations of different composition.
Sankyo, Austria; Sankyo, Fin.†.
Phenylephrine hydrochloride (p.1568·1); a heparinoid (p.1305·2); glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Silesia, Chile.
Indometacin (p.66·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Movilat *Sankyo, Spain.*
A heparinoid (p.1305·2); salicylic acid (p.1612·2).
Rheumatic and muscular pain.

Movileps *Dexa, Indon.*
Phenytoin (p.495·2).
Epilepsy.

Movilisin *Sankyo, Spain.*
Flufenamic acid (p.60·3); a heparinoid (p.1305·2); glycol salicylate (p.62·3) or salicylic acid (p.1612·2).
Myalgia; peri-articular disorders; soft-tissue disorders.

Movin *Neo-Farmaceutica, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Moviprep *Norgine, Fr.; Norgine, UK.*
Sachet A, macrogol 3350 (p.2336·3); sodium sulfate; sodium chloride; potassium chloride (p.1667·1); sachet B, ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Bowel evacuation.

MoviPrep *Salix, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Movistal *SMB, Belg.†.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting.

Movithiol *Pharmanik (Φαρμανικ), Gr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Movivac *Sevapharma, Cz.*
An attenuated measles vaccine (Schwarz strain) (p.2221·3).
Active immunisation.

Movix *Lapi, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Movon
Note. This name is used for preparations of different composition.
Ipca, India.
Capsules; dispersible tablets; topical gel: Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and soft-tissue disorders.

Ipca, India.
Tablets: Aceclofenac (p.14·3).
Musculoskeletal and joint disorders.

Movone *Gebro, Austria.*
Dexibuprofen (p.39·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Movon-MR *Ipca, India.*
Aceclofenac (p.14·3); paracetamol (p.108·1); tizanidine hydrochloride (p.1898·2).
Muscle pain and spasm.

Movon-P *Ipca, India†.*
Aceclofenac (p.14·3); paracetamol (p.108·1).
Inflammation; pain.

Movox
Note. This name is used for preparations of different composition.
Alphapharm, Austral.
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Ivax, Irl.
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Movoxicam *Bunker, Braz.*
Meloxicam (p.80·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Mowin *Abbott, Venez.†.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

Mowineuron *Rodisma, Ger.†.*
Vitamin B substances; vitamin E (p.1922·1).
Tonic; vitamin B deficiency.

Mowivit *Rodisma, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Mox *Ranbaxy, India.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxacef *BMS, Belg.†; Mead Johnson, Gr.*
Cefadroxil (p.218·1).
Bacterial infections.

Moxacil *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxacin *Aspen, Austral.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxadden *Roddensers, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Moxadent *Vitoria, Port.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxal *Julphar, UAE.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; heartburn.

Moxal II *Julphar, UAE.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; heartburn.

Moxal Plus *Julphar, UAE.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastro-oesophageal reflux.

Moxalid *Farmanic, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Moxaline *BMS, Belg.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxam *Pharos, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Moxamar *ct, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxan *Garec, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxapen *Olan-Kemed, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxatag *Middlebrook, USA.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxaviv *Sandoz, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxcil *TP, Thai.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxcin *General Drugs, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxic *Otto, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Moxicam
Note. This name is used for preparations of different composition.
Alphapharm, Austral.; Medico Uno, Hung.
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Milano, Thai.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Moxicip *Cipla, India.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Moxiclav *Pharmacypria, Gr.; Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Moxicle *Daewoong, Thai.; TTN, Thai.*
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Moxiclina *Vitae, Mex.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxif *Torrent, India.*
Moxifloxacin (p.302·2).
Bacterial infections.

Moxilanic *Pediapharm, Chile; Pharmabiotics, Chile.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxilcap *Masa, Thai.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxilen *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxilin *The Forty-Two, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxillin *United American, Philipp.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moximed *Unison, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxin *Stada, Austria.*
Moxonidine (p.1345·1).
Hypertension.

Moxina *Richmond, Arg.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis.

Moxipan *TNP, Thai.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxiped *Wescrib, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxipen
Xepa-Soul Pattinson, Malaysia†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sanofi Synthelabo, Port.†; Xepa-Soul Pattinson, Singapore.
Amoxicillin (p.202·2).
Bacterial infections.

Moxiplus *Medley, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxiren *Ist. Chim. Inter., Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxitab *Unison, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxitop *Topgen, Belg.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxitral *LA, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxlin *Pacific, Hong Kong; Merck, Indon.; Merck, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxlin CLV *Merck, Mex.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Moxobeta *Betapharm, Ger.*
Moxonidine (p.1345·1).
Hypertension.

Moxocard *AWD, Ger.*
Moxonidine (p.1345·1).
Hypertension.

moxodura *Merck dura, Ger.*
Moxonidine (p.1345·1).
Hypertension.

Moxogamma *Worwag, Cz.; Worwag, Ger.; Worwag, Hung.; Worwag, Pol.*
Moxonidine (p.1345·1).
Hypertension.

Moxoham *Alpharma, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxon *Solvay, Belg.; Solvay, Port.; Solvay, Spain.*
Moxonidine (p.1345·1).
Hypertension.

Moxonat *Pharmacodane, Denm.*
Moxonidine (p.1345·1).
Hypertension.

Moxonur *Ratiopharm, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxostad *Stada, Cz.; Stada, Hung.*
Moxonidine (p.1345·1).
Hypertension.

Moxotel *Corax, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxovasc *AWD, Neth.*
Moxonidine (p.1345·1).
Hypertension.

Moxtid *Sunthi Sepuri, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxycarb *Nicholas Piramal, India.*
Amoxicillin (p.202·2).
Bacterial infections.

Moxycarb-DT *Nicholas Piramal, India†.*
Amoxicillin (p.202·2); carbocisteine (p.1553·2).
Otitis media; respiratory-tract disorders.

Moxyclav *Group, S.Afr.†.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Moxydar *Grimberg, Fr.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); aluminium phosphate (p.1707·3); guar gum (p.442·3).
Gastrointestinal disorders.

Moxypen *Teva, Israel; Pharmacare, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxyvit *Vitamed, Israel.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Moxzole *Medic+Aid, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Mozartan *Vocate, Gr.*
Losartan (p.1327·2).
Hypertension.

Moz-Away *Hoe, Malaysia.*
Citronella oil (p.2284·2); azadirachta oil (p.2262·2).
Insect repellent.

Moz-Bite *Hoe, Malaysia; Hoe, Singapore.*
Crotamiton (p.1593·2).
Insect bites; stings.

Mozeton *Biomedica-Chemica, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Mozuku *Tropica Mas, Indon.*
Fucoidan (p.2307·2).
Digestive function.

Mozzie Patch *Bioconcepts, UK.*
Citronella oil (p.2284·2).
Insect repellent.

MozzyOff Cocktail *Sommerville, UK.*
Bog myrtle oil (p.2267·2); azadirachta oil (p.2262·2); eucalyptus oil (p.2301·2).
Insect repellent.

MPA *Hexal, Ger.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

MPA Gyn *Hexal, Ger.*
Medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; menstrual disorders.

MPA-beta *Betapharm, Ger.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

MPA-Noury *Nourypharma, Ger.†.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

M-PredniHexal *Hexal, Ger.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Mr. Multy *Ideal Health, UK.*
Multivitamin and mineral preparation (p.1922·1).

Mr Nits *Botanica, NZ.*
Avocado (p.2262·2); azadirachta (p.2262·2); borage (p.2267·3); canola oil (p.2276·1); coconut oil (p.2029·2); evening primrose oil (p.2302·1); geranium oil (p.2311·1); hemp; jojoba oil; melissa (p.2339·3).
Pediculosis.

M-retard *Helvepharm, Switz.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

M-Ron B *Virgo, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Mrs Cullen's Powders *Cullen & Davison, UK.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Mrs Johnsons American Soothing Syrup *Adco, S.Afr.*
Sodium chloride (p.1686·1); chloroform (p.1781·1).
Teething pain.

MRX *Mahdeen, Canad.†.*
⊗ Benzethonium chloride (p.1630·1); camphor (p.2273·2); alcohol (p.1625·2); benzoic acid (p.1630·2).

MS Contin *Mundipharma, Austral.; Mundipharma, Belg.; Purdue, Canad.; Mundipharma, Ital.; Shionogi, Jpn; Mundipharma, Neth.; Purdue Frederick, USA; Nolver, Venez.*
⊗ Morphine sulfate (p.86·3).
Pain.

MS Direct *Mundipharma, Belg.*
⊗ Morphine sulfate (p.86·3).
Pain.

MS Mono *Mundipharma, Austral.*
⊗ Morphine sulfate (p.86·3).
Pain.

MSI *Mundipharma, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

MSIR *Purdue, Canad.; Purdue Frederick, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

MS-Long *Janssen-Cilag, Braz.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

MSP *Rafa, Israel.*
⊗ Morphine sulfate (p.86·3).
Pain; premedication.

MSP-Blu *Cypress, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract disorders.

MSR *Mundipharma, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

MST
Note. This name is used for preparations of different composition.
Mundipharma, Ger.; Mahakam Beta, Indon.; Mundipharma, Indon.; Viatris, Port.
⊗ Morphine sulfate (p.86·3) or morphine polistirex.
Pain.

Cypress, USA.
Magnesium salicylate (p.79·2).
Osteoarthritis; rheumatoid arthritis.

MST Continus *Raffo, Arg.; Asta Medica, Braz.†; Mundipharma, Cz.; Napp, Hong Kong; Extractum, Hung.; Mundipharma, Hung.; Napp, Irl.; Mundipharma, Malaysia; Pharmaco, NZ†; Mundipharma, Philipp.; Norpharma, Pol.; Adcock Ingram, S.Afr.; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Switz.; Napp, UK.*
⊗ Morphine sulfate (p.86·3).
Dyspnoea; pain; premedication.

MST Mono *Pharmaco, NZ†.*
⊗ Morphine sulfate (p.86·3).
Pain.

MST Unicontinus *Mundipharma, Spain.*
⊗ Morphine sulfate (p.86·3).
Dyspnoea; pain; premedication.

MST Uno *Mundipharma, Cz.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

MSTA *Pasteur Merieux, USA†.*
Mumps skin test (p.2348·1).
Assessment of cell-mediated immunity; detection of delayed hypersensitivity to mumps.

M-Stada *Stada, Ger.*
⊗ Morphine hydrochloride (p.86·3) or morphine sulfate (p.86·3).
Pain.

MSUD *Nutricia-Bago, Arg.; Medifood, Ital.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Vitaflo, UK.*
Food for special diets (p.1922·1).
Maple syrup urine disease; metabolic disorders.

MSUD 1 *Support, Braz.†.*
Food for special diets (p.1922·1).

MSUD 2 *Support, Braz.†.*
Food for special diets (p.1922·1).

MSUD III *Scientific Hospital Supplies, Irl.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

MSUD Aid *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Disorders of branched-chain amino acid metabolism; maple syrup urine disease.

MSUD Aid III *SHS, Fr.†.*
Food for special diets (p.1922·1).
Formerly known as Aid III MSUD.
Leucinosis.

MSUD Analog *Scientific Hospital Supplies, Austral.; SHS, Fr.; SHS, Israel.*
Food for special diets (p.1922·1).
Leucinosis; maple syrup urine disease.

MSUD Diet *Mead Johnson, Hong Kong†.*
Food for special diets (p.1922·1).
Disorders of branched-chain amino-acid metabolism; maple syrup urine disease.

MSUD Express *Vitaflo, Irl.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

MSUD Maxamaid *Scientific Hospital Supplies, Austral.; Support, Braz.†; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

MSUD Maxamum *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).
Maple syrup urine disease.

MT Pill *Cipla, India.*
Mifepristone (p.2011·2).
Termination of pregnancy.

MTE *APP, Hong Kong; Baxter, NZ†; American Pharmaceutical, USA.*
Trace-element preparation (p.1922·1).
Additive for intravenous total parenteral nutrition solutions.

M-Trim *Milano, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

MTX *Hexal, Ger.*
Methotrexate sodium (p.745·2).
Arthritis; malignant neoplasms; psoriasis.

MTX-2 Alf *Investigaciones Filosoficas y Cientificas, Mex.*
Thiamine nitrate (p.1976·2).
Gastrointestinal disorders.

Mubonet *Best, Mex.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Mucabrox *Streuli, Switz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucaderma S *Merz Consumer, Ger.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Wounds.

Mucaine
Note. This name is used for preparations of different composition.
Lafedar, Arg.
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1) or magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastrointestinal disorders.

Aurium, Canad.; Wyeth Consumer, Chile†; Wyeth, India; Whitehall, NZ†; Akromed, S.Afr.; Wyeth, Turk.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

Wyeth Consumer, Austral.; Wyeth Consumer, Singapore; Whitehall, Thai.†.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Wyeth, Hong Kong; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.
Tablets: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); oxetacaine (p.1867·2).
Gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

Mucaine 2 in 1 *Whitehall, Austral.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence.

Mucal *OM, Port.†.*
Aluminium silicate (p.1707·3); magnesium silicate (p.2144·3); calcium silicate (p.1676·3).
Gastrointestinal disorders.

Mucalan *Bernabo, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Mucaryl-AX *Glenmark, India†.*
⊗ Ambroxol (p.1550·3); terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Mucasept-A *Merz Consumer, Ger.*
⊗ Isopropyl alcohol (p.1650·3); alcohol (p.1625·2).
Hand disinfection.

Mucedokehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Mucera *Otto, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Muchan *Fada, Arg.*
⊗ Ephedrine (p.1558·1).

Mucibron
Medley, Braz.; Normon, Spain.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Novag, Mex.
Ambroxol (p.1550·3).
Coughs.

Muciclar
Note. This name is used for preparations of different composition.
Pfizer, Fr.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Piam, Ital.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Mucil *TO-Chemicals, Thai.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucilag *Quimica y Farmacia, Mex.*
Ispaghula (p.1737·1).
Constipation.

Mucilar *Spirig, Switz.*
Ispaghula (p.1737·1).
Constipation; obesity.

Mucilar Avena *Spirig, Switz.*
Ispaghula (p.1737·1); avena (p.2262·1).
Constipation; obesity.

Mucilax *Douglas, Austral.†; Douglas, NZ.*
Ispaghula (p.1737·1).
Constipation.

Mucilin *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Ispaghula (p.1737·1).
Constipation; dietary fibre supplement; stool softener.

Mucillium *Pharmascience, Canad.*
Ispaghula (p.1737·1).
Constipation.

Mucine *Silom, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucinex *Adams, USA.*
Guaifenesin (p.1561·3).
Coughs.

Mucinex DM *Adams, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Mucinol *Sanofi Synthelabo, Ger.†.*
Anethole trithione (p.2258·1).
Dry mouth.

Mucinum
Note. This name is used for preparations of different composition.
Pharmethic, Belg.
Bisacodyl (p.1710·1).
Constipation.

Sabex, Canad.†.
Cascara (p.1715·2); senna (p.1769·2).
Constipation.

Confar, Port.
Cascara (p.1715·2); senna (p.1769·2); aniseed (p.2258·2); boldo (p.2267·2).
Formerly contained cascara.
Constipation.

Mucinum a l'Extrait de Cascara *Innotech, Fr.*
Cascara (p.1715·2); senna leaf (p.1769·2); boldo (p.2267·2); aniseed (p.2258·2).
Constipation.

Mucinum Cascara *Innotech, Hong Kong†.*
Senna (p.1769·2); boldo (p.2267·2); cascara (p.1715·2); aniseed (p.2258·2).
Constipation.

Muciplasma *Serra Pamies, Spain.*
Methylcellulose (p.2145·1).
Constipation.

Mucipulgite *Dexo, Fr.; Beaufour, Switz.†.*
Activated attapulgite (p.1709·1); guar gum (p.442·3).
Constipation; gastrointestinal disorders.

Mucisol *Deca, Ital.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Muciteran *Farmasan, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucivital *Arkopharma, Fr.; Arkopharma, Israel†.*
Ispaghula (p.1737·1).
Constipation.

Muco4 *Sanofi-Aventis, Ital.*
Neltenexine (p.1566·1).
Respiratory-tract disorders.

Muco Cortos *Raffo, Arg.†.*
Ambroxol hydrochloride (p.1550·3); astemizole (p.567·2); butetamate citrate (p.1553·1); phenylephrine hydrochloride (p.1568·1).

Muco Dosodos *Beta, Arg.*
Ambroxol hydrochloride (p.1550·3); butamirate citrate (p.1553·1); chlorphenamine maleate (p.571·3).
Coughs.

Muco Dosodos Biotic *Beta, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Formerly contained amoxicillin, ambroxol hydrochloride, butamirate citrate, and chlorphenamine maleate.
Respiratory-tract infections.

Muco Rhinathiol *Sanofi-Aventis, Belg.*
Carbocisteine (p.1553·2).
Formerly known as Rhinathiol Mucolyticum.
Otitis; respiratory-tract disorders associated with abnormal mucus production; sinusitis.

Muco Sanigen *Thiemann, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucoaliv *Cinfa, Spain.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Muco-Anestyl *Preston, Arg.†.*
Lidocaine (p.1862·3); benzocaine (p.1854·1); procaine (p.1869·2).
Local anaesthesia.

Mucoangin *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Venez.*
Ambroxol hydrochloride (p.1550·3).
Cough; sore throat.

Mucoaricodil *Menarini, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Muco-Aspecton *Krewel, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucobase *Defuen, Arg.*
⊗ Benzocaine (p.1854·1); dexpanthenol (p.2362·1); aloe vera (p.1588·2); gelatin (p.1072·1); pectin (p.2145·2); carmellose sodium (p.2142·1); frutilla.
Aphthous ulcers.

Mucobene *Ratiopharm, Austria; Ratiopharm, Cz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous mucus.

Mucobrol
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Bromhexine hydrochloride (p.1552·2); clofedanol hydrochloride (p.1554·2); ammonium citrate (p.2256·3).
Coughs.

Cofasa, Venez.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Mucobron
Note. This name is used for preparations of different composition.
Corsa, Indon.
Bromhexine (p.1552·2).
Cough.

OFF, Ital.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Medi-Rx, Philipp.
Guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Cough.

Mucobron D *Medi-Rx, Philipp.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Cough.

Mucobron Forte *Medi-Rx, Philipp.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3).
Allergic rhinitis; cold and influenza symptoms; cough; nasal congestion; sinusitis.

Mucobroxol *Mundipharma, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucocaps *Roche, S.Afr.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased, viscous mucus.

Mucocedyl *3M, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucocef *Lilly, Mex.*
Cefalexin (p.218·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections with excessive mucus.

Mucocil
Note. This name is used for preparations of different composition.
Prafa, Indon.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Utopian, Thai.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucocis *EMS, Braz.; SoSe, Ital.; Drogsan, Turk.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucocistein *Neo Quimica, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucoclean *Royton, Braz.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Muco-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Muco-Dest *Klus, Switz.†.*
Peppermint oil (p.1761·2); camphor oil (p.2273·3).
Dry nose; nasal cleansing.

Mucodic *Medicine Products, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucodin *Zorka, Rus.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with viscous mucus.

Mucodox *Delta, Port.*
Sobrerol (p.1572·3).
Respiratory-tract congestion.

Mucodrenol *Medinfar, Port.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Muco-DX *Greater Pharma, Thai.*
Dextromethorphan hydrobromide (p.1555·2); terpin hydrate (p.1573·3); chlorphenamine maleate (p.571·3).
Coughs.

Mucodyne *Sanofi-Aventis, Irl.; Kyorin, Jpn; Aventis, Neth.; Beacon, UK.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucoease Plus *Pharmaniaga, Malaysia.*
Carbocisteine (p.1553·2); promethazine hydrochloride (p.588·2).
Cough.

Mucofalk *Cevallos, Arg.; Falk, Ger.; Falk, Hong Kong; Darya-Varia, Indon.; Falk, Indon.; Falk, Malaysia; Tramedico, Neth.; Falk, Philipp.; Pharmalink, Philipp.; Falk, Pol.; Falk, Port.; Falk, Singapore; Falk, Thai.†.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement; diverticular disease; hypercholesterolaemia; inflammatory bowel disease; irritable bowel syndrome; stool softener.

Mucofan *Uniao Quimica, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucofar *Quim-Far, Venez.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Muco-Fen *Ivax, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Muco-Fen DM *Ivax, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Mucofial *Pliva, Ital.*
Acetylcysteine (p.1548·2).
Cyclophosphamide-induced uropathy; paracetamol poisoning; respiratory-tract disorders.

Mucoflem *Xixia, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased, viscous mucus.

Mucofluid
Note. This name is used for preparations of different composition.
Sanofi Pasteur, Chile; UCB, Fr.; UCB, Ital.†; UCB, Pol.; UCB, Spain.
Mesna (p.1449·2).
Respiratory-tract congestion.

Spirig, Switz.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucoflux
Note. This name is used for preparations of different composition.
Merck, Braz.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Rotta, Hong Kong; Rotta, Malaysia; Pharmalink, Philipp.; Rotta, Philipp.; Rotta, Singapore; Rotta, Thai.
Sobrerol (p.1572·3).
Respiratory-tract disorders.

Liomont, Mex.
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Mucofor *Vifor, Switz.*
Erdosteine (p.1560·1).
Respiratory-tract disorders associated with viscous mucus.

Mucofrin *Epifarma, Ital.*
Acetylcysteine (p.1548·2).
Cyclophosphamide-induced uropathy; paracetamol poisoning; respiratory-tract congestion.

Mucogel *Forest Laboratories, UK.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
These ingredients can be described by the British Approved Name Co-magaldrox.
Dyspepsia; gastro-oesophageal reflux; heartburn.

Mucogen *Antigen, Irl.*
Carbocisteine (p.1553·2).
Lower respiratory-tract disorders with excessive or viscous mucus.

Mucogeran *Ogera, Switz.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucogyne *CAG, Fr.*
Mallow (p.2337·2); chamomile (p.2279·3); sodium hyaluronate (p.2320·1).
Menopausal vaginal disorders.

Mucohex *ProMed, Cz.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Mucohexin *Sanbe, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Mucojet *Segix, Ital.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Mucokehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Mucola *Samakeephaesaj, Thai.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucolab *Multilab, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Mucolan *Milano, Thai.*
Ambroxol hydrochloride (p.1550·3).
Asthma; bronchitis.

Mucolase *Lampugnani, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Mucolate *Pharmasant, Thai.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Mucolator *Abbott, Fr.; Abbott, Hong Kong†; Abbott, Malaysia; Abbott, Port.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory-tract congestion.

Mucolavi *Vitoria, Port.†.*
Sobrerol (p.1572·3).

Mucolene *Formenti, Ital.†.*
Mesna (p.1449·2).
Respiratory-tract disorders associated with excess or viscous mucus.

Mucoless *Parke-Med, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased, viscous mucus.

Mucolex
Note. This name is used for preparations of different composition.
Marching, Hong Kong.
Guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Pfizer Consumer, Irl.; Janssen-Cilag, Port.; Fascino, Thai.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucolexin *United Lab, Malaysia; Pediatrica, Singapore.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Coughs.

Mucolibex *Bexal, Spain.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Mucolica *Ikapharmindo, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucolid *Greater Pharma, Thai.*
Ambroxol hydrochloride (p.1550·3).
Asthma; bronchitis.

Mucolin
Note. This name is used for preparations of different composition.
Abbott, Braz.; Cooper (Κοπερ), Gr.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Sanofi Synthelabo, Mex.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Zuoz, Venez.
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Asthma.

Mucolin A *Sanofi Synthelabo, Mex.*
Ampicillin (p.204·1); carbocisteine (p.1553·2).
Respiratory-tract infections.

Mucolinc *Cipla, India.*
⊗ Bromhexine hydrochloride (p.1552·2); salbutamol (p.1131·2).
Obstructive airways disease.

Mucolinct *Adcock Ingram, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucolisil *Sanofi-Aventis, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucolit *CTI, Israel.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with abnormal or viscous mucus.

Mucolitic *Nova Argentia, Arg.; Nycomed, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucolitic Antitusivo *BMS, Arg.†.*
Carbocisteine (p.1553·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Mucolitico *Sanitas, Chile.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Mucolix *Cifarma, Braz.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucolyptus *Medi-Rx, Philipp.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Mucolysin
Note. This name is used for preparations of different composition.
Sandoz, Denm.
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Farmila, Ital.†; Interdelta, Switz.†.
Tiopronin (p.1467·1).
Respiratory-tract disorders.

Mucolyt
Note. A similar name is used for preparations of different composition (see below).
Hamilton, Austral.†.
Sodium chloride (p.1686·1).
Viscous mucus in the throat.

Mucolyte
Note. A similar name is used for preparations of different composition (see above).
Julphar, UAE.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with viscous mucus.

Mucomed
Note. This name is used for preparations of different composition.
Medibrands, Israel.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with viscous mucus.

Medifive, Thai.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Muco-Mepha *Mepha, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucomex
Note. This name is used for preparations of different composition.
Phoenix, Arg.†.
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Greater Pharma, Thai.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucomix *Samarth, India.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory-tract disorders.

Mucomyst
BMS, Austral.; BMS, Neth.; Apothecon, USA.
Acetylcysteine sodium (p.1548·2).
Respiratory-tract congestion.

BMS, Austria; BMS, Belg.; Wellspring, Canad.; AstraZeneca, Denm.; AstraZeneca, Fin.; BMS, Fr.; BMS, Gr.; BMS, Israel†; AstraZeneca, Norw.; AstraZeneca, Swed.
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory complications of thoracic surgery; respiratory-tract congestion; tracheotomy care.

Mucomystendo *BMS, Fr.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion in tracheotomised patients.

Muconasal Plus *Boehringer Ingelheim, Cz.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Muconex *Tripharma, Rus.; Tripharma, Turk.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory disorders with increased mucus.

Muconorm *Prospa, Ital.†.*
Telmesteine (p.1573·3).
Respiratory-tract disorders.

Mucopec *Macrophar, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucopect *Boehringer Ingelheim, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucophlogat *Azupharma, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucophylline *Medi-Rx, Philipp.*
Guaifenesin (p.1561·3); sodium citrate (p.1673·3); theophylline (p.1140·1).
Respiratory-tract disorders.

Mucoplant Eukalyptovy *Naturwaren, Cz.*
Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2); camphor (p.2273·2).
Respiratory-tract disorders.

Mucoplant Jitrocelovy *Naturwaren, Cz.*
Plantaginis (p.2379·1); peppermint oil (p.1761·2).
Respiratory-tract disorders.

Mucoporetta *ACO Hud, Fin.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Mucoprednibron *Pfizer, Arg.*
Ambroxol hydrochloride (p.1550·3); butetamate citrate (p.1553·1).
Formerly contained ambroxol, astemizole, butetamate, and phenylephrine hydrochloride.
Respiratory-tract disorders.

Mucopront
Mack, Cz.†; Mack, Illert., Ger.†; Keri, Hung.
Carbocisteine (p.1553·2) or carbocisteine sodium (p.1553·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mack, Malaysia†; Mack, Singapore†; Mack, Thai.†.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Zuoz, Venez.
Carbocisteine sodium (p.1553·3).
Respiratory-tract congestion.

Mucorama *Zuoz, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucorem *Remek, Gr.†.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Mucorespiral *Sanofi-Aventis, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucorex *Almirall, Spain†.*
Citiolone (p.2283·3).
Respiratory-tract disorders.

Mucorhinathiol Infantil *Sanofi-Aventis, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Mucorhinathiol Mucoral *Sanofi-Aventis, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucorhinyl *Sanofi-Aventis, Neth.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Mucos *Meprofarm, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucosa compositum *Heel, Ger.*
Homoeopathic preparation.

Mucosal *Boehringer Ingelheim, Jpn.*
Ambroxol hydrochloride (p.1550·3).

Mucosan *Boehringer Ingelheim, Spain.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Muco-Sana *Klus, Switz.†.*
Peppermint oil (p.1761·2); camphor oil (p.2273·3); lavender oil (p.2331·2).
Nasal disorders.

Mucoseptal *Actipharm, Switz.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Mucosil *Dey, USA†.*
Acetylcysteine sodium (p.1548·2).
Mucolytic in bronchopulmonary disorders.

Mucosin
Note. This name is used for preparations of different composition.
Zentiva, Cz.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Europharm, Hong Kong.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucosirop *Roche, S.Afr.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased, viscous mucus.

Mucosit *Herbapol Poznan, Pol.*
Allantoin (p.1588·1); calendula (p.2273·1); chamomile oil (p.2279·3); chamomile (p.2279·3); mint oil (p.2345·2); oak bark (p.2355·3); sage (p.2382·3); thyme (p.2401·1); coltsfoot (p.1555·1).
Mouth disorders.

Mucosol
Note. This name is used for preparations of different composition.
AstraZeneca, India.
⊗ Terbutaline sulfate (p.1138·3); bromhexine (p.1552·2).
Coughs associated with obstructive airways disease.

Malaysia Chemist, Singapore†.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucosolin *Terramedic, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Mucosolvan
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Ital.; Teijin, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Unilfarma, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Venez.
Ambroxol hydrochloride (p.1550·3).
Neonatal respiratory distress syndrome; respiratory-tract congestion.

Hexpharm, Indon.
Bromhexine hydrochloride (p.1552·2).
Cough.

Mucosolvan Compositum *Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion.

Mucosolvon *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Switz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucosolvon Compositum *Boehringer Ingelheim, Arg.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion.

Mucospas *Boehringer Ingelheim, Austria; Unilfarma, Port.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Mucospect *Universal, Hong Kong; Triomed, S.Afr.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucospire *Rosa-Phytopharma, Fr.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Mucosta *Otsuka, Indon.; Otsuka, Jpn; Otsuka, Philipp.; Otsuka, Thai.*
Rebamipide (p.1768·2).
Gastric ulcer; gastritis; peptic ulcer.

Mucostar *Krugher, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucostein
Note. A similar name is used for preparations of different composition (see below).
Kleva, Gr.
Carbocisteine (p.1553·2); sobrerol (p.1572·3).

Mucosteine
Note. A similar name is used for preparations of different composition (see above).
Medgenix, Belg.†.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with viscous mucus.

Mucostop *Mepha, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous mucus.

Mucosyt *Bioprogress, Ital.†.*
Tiopronin (p.1467·1).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucothera *Therabel, Belg.†.*
Erdosteine (p.1560·1).
Respiratory-tract disorders.

Mucotherm *Lannacher, Austria.*
Ethyl nicotinate (p.52·1).
Anorectal disorders; prostatitis.

Mucothiol
Note. This name is used for preparations of different composition.
Jolly-Jatel, Fr.; ICN, Hung.†; Geymonat, Ital.
Methyl dacisteine (p.1564·3).
Respiratory-tract congestion.

Sanofi-Aventis, Gr.
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Mucotic *Hua, Thai.*
Acetylcysteine (p.1548·2).
Bronchitis associated with increased or viscous mucus.

Mucotoss
Note. A similar name is used for preparations of different composition (see below).
Sigma, Braz.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mucotosse
Note. A similar name is used for preparations of different composition (see above).
Labialfarma, Port.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucotreis *Ecobi, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Muco-Trin *Klus, Switz.†.*
⊗ Xylometazoline hydrochloride (p.1575·1); peppermint oil (p.1761·2); camphor oil (p.2273·3).
Nasal congestion.

Mucotuss
Note. This name is used for preparations of different composition.
Terramedic, Philipp.
Capsules: Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cough.

Terramedic, Philipp.
Syrup: Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Mucotussan *Medikon, Indon.*
Dextromethorphan (p.1555·2); phenylpropanolamine (p.1569·2); diphenhydramine (p.577·1); bromhexine (p.1552·2).
Cough.

Mucovibrol *Liomont, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucovibrol Amoxi *Liomont, Mex.*
Ambroxol hydrochloride (p.1550·3); amoxicillin trihydrate (p.202·2).
Respiratory-tract infections.

Mucovibrol C *Liomont, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract congestion.

Mucovibrol T *Liomont, Mex.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucovin *Leiras, Fin.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Mucovis *Pharma Nutria, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucovital *Stada, Spain.*
Carbocisteine lysine (p.1553·3).
Respiratory-tract congestion.

Mucovix *Verisfield, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucoxan *IBSA, Ital.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Mucoxin *Pharmasant, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucoxina *Bruluagsa, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Mucoxine-F *Pharmasant, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Mucoxol
Note. This name is used for preparations of different composition.
Montpellier, Arg.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tempo Scan Pacific, Indon.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Serral, Mex.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Mucoxolan *Teuto, Braz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mucoza *Pond's Chemical, Singapore†; Pond's, Thai.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Mucozan *Pond's, Thai.*
Ambroxol hydrochloride (p.1550·3).
Asthma; bronchitis.

Mucozym *Mucos, Ger.*
Bromelains (p.2269·1).
Nasal inflammation.

Mucret *AstraZeneca, Ger.; Stern, Ger.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Muc-Sabona *Sabona, Ger.†.*
Ivy (p.2328·1); liquorice (p.1740·3); thyme (p.2401·1).
Respiratory-tract disorders with viscous mucus.

Mucum *Julphar, UAE.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Mud *Eurofarma, Braz.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1); nystatin (p.543·2).
Infected skin disorders.

Mudagrip *Geminis, Arg.†.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Fever; pain.

Mudantil *Geminis, Arg.†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Mudantos H *Geminis, Arg.†.*
Diphenhydramine (p.577·1).

Mudapenil *Geminis, Arg.†.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Muelita *Cabuchi, Arg.*
Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); peppermint oil (p.1761·2); methylthioninium chloride (p.1450·3).

Muflex *TO-Chemicals, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Muforan *Pfizer, Arg.†.*
Fotemustine (p.726·2).
Cerebral cancer; malignant melanoma.

Mugasin *Apotex, Mex.*
Ispaghula (p.1737·1).
Constipation.

Mugisept *Mugi, Indon.*
Povidone-iodine (p.1659·2).
Wounds.

Mukobron *Polfa Grodzisk, Pol.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Mukolina *Pliva Krakow, Pol.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Mukoliz *Terra, Turk.*
Carbocisteine (p.1553·2).
Respiratory disorders with increased mucus.

Mukoral *Biofarma, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Mukoseptonex *Ivax, Cz.*
Carbaethopendecinium bromide (p.1633·3).
Nose and throat disorders.

Mukoseptonex E *Ivax, Cz.*
⊗ Carbaethopendecinium bromide (p.1633·3); ephedrine hydrochloride (p.1558·2).
Nose and throat disorders.

Mukotik *Kocak, Turk.*
Carbocisteine (p.1553·2).
Respiratory disorders with increased mucus.

Mulade *Sriprasit, Thai.*
Guaifenesin (p.1561·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Mulax *Fahrenheit, Indon.*
Psyllium (p.1737·1).
Constipation; irritable bowel syndrome.

Mulcatel *Maver, Chile.*
Sucralfate (p.1772·2).
Peptic ulcer.

Mulimen *Peithner, Austria; Heel, Ger.*
Homoeopathic preparation.

Mulimen S *Heel, Ger.*
Homoeopathic preparation.

Mulkine *Dexo, Fr.*
Montmorillonite; guar gum (p.442·3).
Constipation.

Mulmicor *Scheffler, Ger.*
Camphor (p.2273·2).
Hypotension.

Mulsal N *Mucos, Ger.†.*
Trypsin (p.2405·3); papain (p.2362·3); bromelains (p.2269·1).
Inflammation; musculoskeletal and joint disorders; oedema.

Multanzim *Fako, Turk.*
Pancreatin (p.2360·1); bile extract (p.2266·2).

Multe-Pak *SoloPak, USA.*
A range of trace element preparations (p.1922·1).
Parenteral nutrition.

Multi *Lafarmen, Arg.*
Vitamin and mineral preparation (p.1922·1).

Multi-12 *Sabex, Canad.; Sandoz, Canad.*
A multivitamin preparation (p.1922·1).
Parenteral nutrition.

Multi II *Solgar, UK.*
Amino-acid, multivitamin, and mineral preparation (p.1922·1).

Multi II IV VI *Sisu, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Multi 75 *Fibertone, USA.*
Multivitamin and mineral preparation (p.1922·1).

Multi AJR *Erjean, Fr.†.*
Vitamins; minerals; ginseng (p.1922·1).
Tonic.

Multi B Complex *Quest, UK.*
Vitamin B and C preparation (p.1922·1).

Multi Forte 29 *Stanley, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Multi + Ginkgo for 55+ *Blackmores, Austral.*
Multivitamin, mineral and ginkgo biloba preparation (p.1922·1).

Multi Mineral *Swiss Herbal, Canad.*
Mineral preparation (p.1922·1).

Multi Mineral Plus *Swiss Herbal, Canad.†.*
Mineral preparation (p.1922·1).

Multi Mineral with Vitamin D *Adams, Canad.*
Mineral preparation with vitamin D (p.1922·1).

Multi Up *Fher, Ital.*
Multivitamin and mineral preparation with ginseng (p.1922·1).
Tonic.

Multi Vit Drops with Iron *Barre-National, USA.*
Multivitamin preparation with iron (p.1922·1).

Multi-Action Actifed *Pfizer Consumer, UK.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Actifed.
Cold and influenza symptoms; rhinitis.

Multi-Action Actifed Chesty Coughs Expectorant *Pfizer Consumer, UK.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly known as Actifed Expectorant.
Coughs; upper respiratory-tract congestion.

Multi-Action Actifed Dry Coughs *Pfizer Consumer, UK.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Actifed Compound.
Coughs; upper respiratory-tract congestion.

Multi-B Forte *Johnson & Johnson, Austral.*
Vitamin B substances and vitamin C (p.1922·1).

Multi-B Strong *Vitabalans, Fin.*
Vitamin B substances (p.1922·1).

Multibay *Bayer, India.*
Multivitamin preparation (p.1922·1).

MultiBic *Fresenius Medical, Cz.*
Glucose monohydrate; sodium chloride; calcium chloride; magnesium chloride; sodium bicarbonate; with or without potassium chloride (p.1670·3).
Haemofiltration.

Multibic *Fresenius Medical, Denm.; Fresenius Medical, Neth.; Fresenius Medical, Port.; Fresenius Medical, Swed.; Fresenius Medical, Switz.*
Glucose; calcium chloride; magnesium chloride; sodium bicarbonate; sodium chloride; with or without potassium chloride (p.1670·3).
Haemodialysis; haemofiltration.

Multibionta
Merck, Austria; Merck, Ger.; Merck, Irl.†; Merck, Spain†; Merck, Switz.†; Seven Seas, UK.
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Merck, Chile†.
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Multibionta complete *Merck, Austria†.*
A multivitamin and mineral preparation (p.1922·1).

Multibionta Complex Ginseng *Merck, Spain.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Multibionta Forte *Merck, Cz.†.*
Multivitamin preparation (p.1922·1).

Multibionta Mineral *Merck, Spain.*
Multivitamin and mineral preparation (p.1922·1).

Multibionta N *Merck, Cz.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Multibionta plus Mineral *Merck, Cz.†; Merck, Ger.*
Multivitamin and mineral preparation (p.1922·1).

Multibionta plus Mineralien und Spurenelemente *Merck, Austria.*
Multivitamin, mineral, and trace element preparation (p.1922·1).

Multibionta pro Infusione *Merck, Cz.†.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Multibionta Probiotic *Seven Seas, Irl.*
Vitamins; minerals; *Lactobacillus acidophilus*; *Bifidobacterium longum* (p.1922·1).

Multibiotic *Chema-Elektromet, Pol.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Multi-Boost *Avon, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Multicap *Sriprasit, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Multicebrina Efevit *Sanofi Synthelabo, Spain†.*
Multivitamin and mineral preparation (p.1922·1).

Multicentrum *Wyeth Consumer, Chile†; Wyeth Consumer, Ital.*
Vitamin and mineral preparations (p.1922·1).
Dietary supplement; nutritional supplement.

Multichew *Chew, Thai.*
Multivitamin preparation (p.1922·1).

Multicor *Multilab, Braz.*
Verapamil hydrochloride (p.1421·1).
Hypertension.

Multicrom *Menarini, Fr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Multi-Day *Nature's Bounty, USA.*
A range of vitamin preparations (p.1922·1).

Multiderm
Note. A similar name is used for preparations of different composition (see below).
Agis, Israel.
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Skin disorders.

Multiderme
Note. A similar name is used for preparations of different composition (see above).
Multilab, Braz.
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Skin disorders.

Multidex *Medifarm, Venez.*
Maltodextrin (p.1955·3); ascorbic acid (p.1983·3).
Burns; wounds.

Multielmin *Osorio de Moraes, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Multifebrin *Bajer, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Multiferon *Key Oncologics, S.Afr.; Viranative, Swed.*
Interferon alfa (leucocyte) (p.885·1).
Formerly known as Interferon Alfanative in *Swed.*
Chronic myeloid leukaemia; hairy-cell leukaemia.

Multifluorid *DMG, Ger.*
Sodium fluoride (p.1962·2); olaflur (p.1959·2); dectaflur (p.1937·1).
Dental caries prophylaxis; hypersensitive teeth.

Multifol *Breckenridge, USA.*
Calcium; ferrous fumarate; vitamins (p.1922·1).

Multiformil *Farmedia, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Multifung *Rider, Chile.*
Bifonazole (p.527·3).
Fungal and Gram-positive bacterial skin infections.

Multifungin
Note. This name is used for preparations of different composition.
Nicholas Piramal, India†.
Cream; topical solution: Bromochlorosalicylanilide (p.527·3); bamipine salicylate (p.568·3).
Fungal skin infections.

Nicholas Piramal, India†.
Topical powder: Bromochlorosalicylanilide (p.527·3); salicylic acid (p.1612·2).
Fungal skin infections.

Multifungin H *Nicholas Piramal, India†.*
⊗ Bromochlorosalicylanilide (p.527·3); bamipine (p.568·3); hydrocortisone acetate (p.1535·2).
Inflamed fungal skin infections.

Multigam *CAF-DCF, Belg.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Multigen *Medhaus, Philipp.*
Vitamin preparation with lysine hydrochloride (p.1922·1).
Nutritional supplement.

Multigen AL *Asta Medica, Braz.†.*
Allergen extracts of house dust (p.2251·1), grass pollen (p.2370·2), *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* (p.2250·2).
Allergen immunotherapy.

Multigen Plus *Medhaus, Philipp.*
Vitamins; amino acids; chlorella (p.1922·1).
Nutritional supplement.

Multi-gesic
Note. A similar name is used for preparations of different composition (see below).
Multi-Pro, Canad.
Paracetamol (p.108·1).
Pain.

Multigesic
Note. A similar name is used for preparations of different composition (see above).
Nicholas Piramal, India†.
Diethylamine salicylate (p.47·2).
Fibrositis; lumbago; sciatica; sprains.

Multigotas *Gobbi, Arg.*
Multivitamin preparation (p.1922·1).

Multigran *Prati-Donaduzzi, Braz.†.*
Tetracycline (p.347·1).
Bacterial infections.

Multigrip *Multilab, Braz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

MultiHance *Gerot, Austria; Altana, Belg.; Bracco, Cz.; Bracco, Denm.; Astra Tech, Fin.; Altana, Fr.; Altana, Ger.; Gerolymatos, Gr.; Bracco, Hung.; Merck, Irl.†; Bracco, Israel; Bracco, Ital.; Regional Health, NZ; Altana, Neth.; Bracco, Norw.; Bracco, Port.; Rovi, Spain; Astra Tech, Swed.; Bracco, Switz.; Bracco, UK; Bracco, USA. .*
Meglumine gadobenate (p.1478·2).
Contrast medium for magnetic resonance imaging of the liver and central nervous system.

Multi-12/K1 *Sandoz, Canad.*
Multivitamin preparation for infusion (p.1922·1).

Multilex *Rugby, USA.*
A range of vitamin preparations (p.1922·1).

Multilim *Atlantic, Hong Kong; Atlantic, Thai.*
Multivitamin preparation (p.1922·1).
Tonic; vitamin supplement.

Multilim RG *Atlantic, Thai.*
Ginseng (p.2312·1); royal jelly (p.2382·1); vitamins; minerals (p.1922·1).

Multilind *BMS, Chile; Stada, Ger.; Dermapharm, Switz.*
Zinc oxide (p.1621·2); nystatin (p.543·2).
Fungal skin infections.

Multiload *Organon, Austral.; Organon, Braz.; Organon, Chile; Organon, Denm.; Organon, Fr.; Organon, Ger.; Organon, Hong Kong; Multilan, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.†; Pharmaco, NZ; Organon, Neth.†; Organon, Port.†; Donmed, S.Afr.†; Organon, Singapore; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, Venez.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Multilyte *American Pharmaceutical, USA.*
A range of electrolyte preparations (p.1667·1).
Fluid and electrolyte disorders.

Multi-Mam Compressas *Farmalight, Port.†.*
Aloe (p.1588·2); glycerol (p.2314·2).
Nipple care during breastfeeding.

Multi-Mam Lanolina *Farmalight, Port.†.*
Wool fat (p.2033·2).
Nipple care during breastfeeding.

Multimax *Unipharm, Rus.†.*
Vitamins; minerals; trace elements (p.1922·1).

Multi-Mega *Natural Life, Arg.*
Multivitamin, mineral, and nutritional preparation (p.1922·1).

Multi-Min *GNLD, Austral.*
Mineral and trace element preparation with vitamin D (p.1922·1).

MultiMineral *Usana, Canad.*
Mineral preparation (p.1922·1).

Multi-Mulsin N *Mucos, Ger.†.*
Multivitamin preparation (p.1922·1).

Multi-Mune *Purity Life, Canad.†.*
Vitamin and mineral preparation (p.1922·1).

Multin *Lazar, Arg.*
Paracetamol (p.108·1); dipyrone (p.49·2).
Fever; pain.

Multiparin *IFET (ΙΦΕΤ), Gr.; Technopharm, Irl.; Artex, NZ; CP Pharmaceuticals, UK.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Multiplex *Pharmasant, Thai.*
Vitamin preparation (p.1922·1).

Multipore *Orion, Fin.*
Multivitamin and mineral preparation (p.1922·1).

Multipressim *Multilab, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Multi-Pro *Alpharma, Malaysia†.*
Multivitamin preparation (p.1922·1).

Multi-Purpose Lens Drops *Bausch & Lomb, Canad.†.*
Wetting solution for contact lenses (p.1622·2).

Multiralgim *Multilab, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Multiron *Vitabiotics, UK.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Multisal *Polfa Kutno, Pol.*
Mineral preparation (p.1922·1).

Multi-Sanasol *Vifor, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Multi-Sanostol
Nycomed, Cz.; Altana, Hung.; Altana, Malaysia†; Altana, Pol.
Vitamin preparation with calcium (p.1922·1).
Tonic.

Altana, Ger.
Vitamin preparation (p.1922·1).

Altana, Mex.
Vitamin preparation with calcium and phosphorus (p.1922·1).

Multi-Sanosvit mit Eisen
Byk, Cz.†.
Multivitamin preparation with calcium and iron (p.1922·1).

Altana, Ger.†.
Vitamin preparation with minerals including iron (p.1922·1).

Multisedil *Andromaco, Chile.*
Diazepam (p.986·3); chlormezanone (p.968·3).
Anxiety; skeletal muscle spasm; sleep disorders.

Multisef *Nevzat, Turk.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Multiselect 29 *Stanley, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Multisoro
Note. This name is used for preparations of different composition.
Multilab, Braz.
Adult: ⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Multilab, Braz.
Infant: Sodium chloride (p.1686·1).
Nasal congestion.

Multisoy *Dieterba, Ital.†.*
Infant feed (p.1922·1).
Milk intolerance.

Multispec-E *Cardinal, Philipp.; Pharmaspec, Philipp.*
Ferrous fumarate (p.1938·3); vitamins (p.1922·1).
Iron-deficiency anaemia; nutritional supplement; vitamin B deficiency.

Multistix *Bayer, Austral.; Bayer Diagnostici, Ital.†; Bayer, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, and pH in urine.

Multistix 2 *Miles, Ital.†; Bayer, USA.*
Test for nitrites and leucocytes in urine.

Multistix 5 *Bayer, Austral.*
Test for glucose, blood, protein, nitrite, and leucocytes in urine.

Multistix 7 *Bayer, USA.*
Test for glucose, protein, blood, ketones, nitrites, leucocytes, and pH in urine.

Multistix 9 *Bayer, Austral.†; Bayer, USA.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, and leucocytes in urine.

Multistix GP *Bayer Diagnostics, Irl.; Bayer Diagnostics, UK.*
Test for pH, protein, glucose, ketones, leucocytes, blood, nitrites, and specific gravity in urine.

Multistix SG *Bayer Diagnostics, Irl.; Bayer Diagnostics, UK; Bayer, USA.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, and specific gravity in urine.

Multistix 8SG *Bayer, Arg.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, and specific gravity in urine.

Multistix 8 SG *Bayer, Austral.; Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, UK; Bayer, USA.*
Test for glucose, protein, blood, ketones, nitrites, leucocytes, pH, and specific gravity in urine.

Multistix 9 SG *Bayer, USA.*
Test for glucose, protein, blood, ketones, bilirubin, nitrites, leucocytes, pH, and specific gravity in urine.

Multistix 10 SG *Bayer, Arg.; Bayer, Austral.; Bayer Diagnostics, Fr.; Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, Mex.†; Bayer, Port.†; Bayer Diagnostics, UK; Bayer, USA.*
Test for pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leucocytes, and specific gravity in urine.

Multi-Symptom Tylenol Cough *McNeil Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Formerly known as Maximum Strength Tylenol Cough.
Coughs.

Multi-Symptom Tylenol Cough with Decongestant *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Formerly known as Maximum Strength Tylenol Cough with Decongestant.
Coughs and cold symptoms.

Multi-Tabs
Ferrosan, Cz.; Ferrosan, Pol.; Ferrosan, Rus.; Nutrifarma, Turk.
A range of multivitamin or multivitamin and mineral preparations (p.1922·1).

EGIS, Hung.†.
Ascorbic acid; colecalciferol; vitamin A palmitate (p.1922·1).

Multi-Tabs B-Complex *Ferrosan, Rus.*
Thiamine nitrate; riboflavin; pyridoxine hydrochloride; cyanocobalamin; nicotinamide; calcium pantothenate; folic acid (p.1922·1).
Neuralgia; neuritis; tonic; vitamin B deficiency.

Multi-Tabs Neo *Ferrosan, Fin.*
Multivitamin and mineral preparation (p.1922·1).

Multi-Tar *Valeant, Hong Kong.*
Pyrithione zinc (p.1611·2); tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2).
Scalp disorders.

Multi-Tar Plus *Valeant, Canad.*
Cade oil (p.1616·1); tar (p.1616·2); coal tar (p.1616·2); pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Multitest *Richter, Austria; Serotherapeutisches, Austria; Biosyn, Ger.†.*
Tetanus toxoid antigen; diphtheria toxoid antigen; streptococcus group C antigen; tuberculin antigen (p.2405·3); candida albicans antigen; tricophyton mentagrophytes antigen; proteus mirabilis antigen.
Assessment of cell-mediated immunity.

Multitest CMI *CSL, Austral.; Pasteur Merieux, Israel; CSL, NZ†; Aventis, S.Afr.†.*
Tetanus toxoid; diphtheria toxoid; streptococcus group C antigen; tuberculin (p.2405·3); candida antigen; trichophyton antigen; proteus antigen.
Assessment of cell-mediated immunity.

Multiton *Biochimici, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Multivac VR *Nikkho, Braz.†.*
Staphylococcus aureus; *Streptococcus pyogenes*; *Streptococcus viridans*; group D Streptococcus; *Moraxella catarrhalis*; *Corynebacterium diphtheroides*; *Streptococcus pneumoniae*; *Listeria monocytogenes*; *Klebsiella pneumoniae*; *Pseudomonas aeruginosa*; *Serratia marcesens* (p.2250·2); *Haemophilus influenzae*; *Candida albicans*; *Penicillium* sp.; *Alternaria* sp.; *Rhodotorula mucilaginosa*; *Mucor racemosus*; *Hormodendrum*; *Aspergillus niger*.
Allergen immunotherapy.

Multi-Vi-Min *Sisu, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Multiviral *Meyer, Venez.*
Vitamin and mineral preparation (p.1922·1).

Multivit *Garden House, Arg.†.*
Multivitamin preparation (p.1922·1).

Multi-Vit *Lafarmen, Arg.*
Multivitamin preparation (p.1922·1).

Multivitamin Cink + Rez Stressz *Humanpharma, Hung.†.*
Multivitamin preparation with zinc and copper (p.1922·1).

Multi-Vitamin Day & Night *Cenovis, Austral.†.*
Day tablets, vitamins and minerals (p.1922·1); night tablets, valerian (p.2410·1); passion flower (p.2363·2); chamomile (p.2279·3); crataegus (p.2289·1); vitamins and minerals.
Dietary supplement; insomnia; tonic.

Multivitamin Phytopharma V *OTW, Ger.†.*
Multivitamin preparation (p.1922·1).

Multivitaminas Isamax *ISA, Arg.*
Vitamins; magnesium; selenium; zinc (p.1922·1).

Multivitamin-Aufbau-Kapseln *Wiedemann, Ger.†.*
Multivitamin and mineral preparation (p.1922·1).

Multivitamines N *Gisand, Switz.†.*
Vitamins; minerals; choline bitartrate; inositol; rutoside; bioflavonoids; hesperidin; betaine; glutamic acid (p.1922·1).
Tonic.

Multivitamol *Natur Produkt, Pol.*
Ferrous lactate; vitamins (p.1922·1).
Tonic.

Multivitaplex *Alpharma, Malaysia†; Alpharma, Singapore†.*
Multivitamin preparation (p.1922·1).

Multivit-B *Lannacher, Austria.*
Vitamin B substances (p.1922·1).

Multivite Six *Boots Healthcare, NZ†.*
Multivitamin preparation (p.1922·1).

Multizol *Multilab, Braz.*
Mebendazole (p.148·3).
Worm infections.

Multodrin *Montavit, Austria.*
⊗ Dexamethasone (p.1526·1); diphenhydramine hydrochloride (p.577·2).
Skin disorders.

Multojod-Gastreu N R12 *Reckeweg, Ger.*
Homoeopathic preparation.

Multosin *Takeda, Ger.*
Estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Multramin *Scherer, Philipp.*
Vitamins; minerals; citrus bioflavonoids; lecithin (p.1922·1).
Nutritional supplement.

Multum
Note. This name is used for preparations of different composition.
Rosen, Ger.
Chlordiazepoxide (p.968·1).
Anxiety disorders; sleep disorders.

Lampugnani, Ital.†.
Benzydamine hydrochloride (p.27·3).
Gynaecological disorders.

Mulvidren-F Softab *Stuart, USA.*
Sodium fluoride (p.1962·2) with multivitamins (p.1922·1).
Dental caries prophylaxis in children.

Mulvitron *Wescrib, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Mumfer
Note. This name is used for preparations of different composition.
Glenmark, India.
Oral drops; syrup: Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Glenmark, India†.
Tablets: Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy; iron-deficiency anaemia.

Mumfer-Z *Glenmark, India†.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1); zinc (p.1999·1).
Iron, zinc and folic acid deficiency in pregnancy; iron-deficiency anaemia.

Mummin *Pharmasant, Thai.*
Vitamin and mineral preparation with iron (p.1922·1).
Nutritional supplement during and after pregnancy.

Mumomega *Equazen, Hong Kong.*
Marine fish oil (p.1362·2); evening primrose oil (p.2302·1).
Dietary supplement.

Mumpsvax *Merck Frosst, Canad.†; Aventis Pasteur, Denm.†; Chiron Behring, Ger.†; Vianex (Βιανέξ), Gr.†; Sanofi Pasteur, Switz.; Merck, USA.*
A live, attenuated mumps vaccine (Jeryl Lynn (B Level) strain) (p.2225·1).
Active immunisation.

Mundbalsam *Wala, Ger.*
Homoeopathic preparation.

Mundidol *Mundipharma, Austria.*
⊗ Morphine sulfate (p.86·3).
Pain.

Mundil *Mundipharma, Ger.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Mundiphyllin *Mundipharma, Austria†.*
Aminophylline (p.1114·2).
Heart failure; oedema; respiratory-tract disorders.

Mundisal *Mundipharma, Austria; Mundipharma, Cz.; Mundipharma, Ger.†; Lavipharm, Gr.; Extractum, Hung.; Mundipharma, Hung.; Mundipharma, Switz.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Mouth and throat disorders.

Municaps *Schwarzhaupt, Ger.†.*
Multivitamin preparation (p.1922·1).
Tonic.

Municor *Heel, Ger.*
Homoeopathic preparation.

Munit-E *Holista, Canad.†.*
Vitamins; echinacea; garlic; ginger; zinc gluconate (p.1922·1).

Munitren *Robugen, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Munleit *Hommel, Ger.†.*
Doxylamine succinate (p.578·2).
Insomnia.

Munobal *Aventis, Arg.; Aventis, Austria; Aventis, Ger.; Aventis, Mex.; Aventis, Switz.†; AstraZeneca, Venez.†.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Munostin *Atlantis, Mex.†.*
Lysates of *Streptococcus pneumoniae*; *Moraxella catarrhalis*; *Streptococcus pyogenes*; *Haemophilus influenzae*; *Staphylococcus aureus*; *Klebsiella pneumoniae*.
Respiratory-tract infections.

Munotras *Monte Verde, Arg.*
Mycophenolate mofetil (p.1836·2).

Muntel *Lacer, Spain.*
Levocetirizine hydrochloride (p.583·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Munti-Vim *Hua, Thai.*
Multivitamin preparation (p.1922·1).

Mupaten *Schering, Arg.*
Isoconazole (p.536·2) or isoconazole nitrate (p.536·2).
Fungal or Gram-positive bacterial vaginal infections; fungal skin infections.

Mupax
Note. This name is used for preparations of different composition.
Lazar, Arg.
Mupirocin (p.302·3) or mupirocin calcium (p.302·3).
Bacterial skin infections; elimination of nasal staphylococci.

Arrow, Fr.
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Antacid.

Muphoran *Servier, Austral.; Servier, Austria; Servier, Belg.; Servier, Braz.; Servier, Fr.; Servier, Gr.; Servier, Israel; Italfarmaco, Ital.; Servier, NZ; Servier, Port.; Servier, Turk.*
Fotemustine (p.726·2).
Cerebral cancer; malignant melanoma.

Mupider *Kleva, Gr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Mupiderm *Almirall, Fr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Mupiran *Vocate, Gr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Mupirox *Fortbenton, Arg.; Blau, Pol.*
Mupirocin (p.302·3).
Bacterial skin infections; elimination of nasal staphylococci.

Mupiskin *Mastelli, Ital.*
Mupirocin (p.302·3).
Bacterial skin infections.

Muporin *TO-Chemicals, Thai.*
Mupirocin (p.302·3).
Bacterial skin infections.

Muprin *Hoe, Malaysia.*
Mupirocin (p.302·3).
Bacterial skin infections.

Muraligne *Shire, Fr.†.*
Glucomannan (p.2312·3).
Obesity.

Muralion *Socofar, Port.*
Flavonoids (p.2304·1).
Vascular disorders.

Muramyl *Master, Chile†.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Murazyme *Grunenthal, Belg.; Asta Medica, Braz.†.*
Muramidase hydrochloride (p.2348·1).
Minor wounds; viral skin infections.

Murelax *Sigma, Austral.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Murhinal *Farmaline, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Muricalm *Novartis, Braz.*
Pimethixene (p.588·1).
Respiratory-tract disorders in children.

Murine
Note. This name is used for preparations of different composition.
Aspen, Austral.
Berberine chloride (p.2264·3).
Eye cleansing; eye irritation.
Prestige, UK.
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.
Prestige, Canad.; Ross, USA.
Ear drops: Urea hydrogen peroxide (p.1666·2).
Ear wax removal.
Prestige, Canad.; Ross, USA.
Eye drops: Povidone (p.2146·1); polyvinyl alcohol (p.2145·3).
Dry eyes.

Murine Clear Eyes *Abbott, S.Afr.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Murine NTF *Abbott, Malaysia†.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Murine Plus
Note. This name is used for preparations of different composition.
Abbott, Chile†.
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.
Abbott, Malaysia†; Ross, USA.
⊗ Polyvinyl alcohol (p.2145·3); povidone (p.2146·1); tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Murine Revital Eyes *Aspen, Austral.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes; eye cleansing; eye irritation.

Murine Sore Eyes *Aspen, Austral.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Murine Supplemental Tears *Abbott, Canad.†.*
Artificial tears.

Murine Tears for Eyes *Aspen, Austral.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes; eye irritation.

Muro 128 *Bausch & Lomb, Arg.; Bausch & Lomb, Canad.†; Bausch & Lomb, Mex.; Bausch & Lomb, USA.*
Sodium chloride (p.1686·1).
Corneal oedema.

Murocel *Bausch & Lomb, USA.*
Methylcellulose (p.2145·1).
Dry eyes.

Murocoll-2 *Bausch & Lomb, USA.*
Hyoscine hydrobromide (p.1734·1); phenylephrine hydrochloride (p.1568·1).
Induction of mydriasis and cycloplegia; uveitis.

Murode *Teofarma, Spain.*
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Muroptic *Optopics, USA.*
Sodium chloride (p.1686·1).
Corneal oedema.

Murri Antidolorifico *Bracco, Ital.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Mus *Grunenthal, Chile†.*
Clarithromycin (p.248·2).
Bacterial infections.

Musaldox *Continentales, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Musalten *Continentales, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Musapam *Krewel, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasm.

Musaril *Sanofi Synthelabo, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Musashi *Sidus, Arg.†.*
Amino-acid preparation (p.1922·1).
Dietary supplement.

Musashi Barras Growling Dog *Sidus, Arg.†.*
Preparation for enteral nutrition (p.1922·1).

Musashi Creatina *Sidus, Arg.†.*
Creatine (p.2289·2).
Muscular fatigue.

Muscadol *Julphar, UAE.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain.

Muscalax *Polipharm, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal and joint pain; sprains; strains.

Muscalm *Kayaku, Jpn.*
Tolperisone hydrochloride (p.1899·3).
Muscle relaxant; muscle tension; spastic paralysis.

Muscarsan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Muscelax *Hua, Thai.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal and joint disorders; skeletal muscle spasm.

Muscinil *Opus, UK†.*
Procyclidine hydrochloride (p.814·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Muscle & Back Pain Relief *Jamp, Canad.; Pharmetics, Canad.; Rougier, Canad.; Vita Health, Canad.*
Paracetamol (p.108·1); methocarbamol (p.1897·3).

Muscle & Back Pain Relief-8 *Pendopharm, Canad.; Rougier, Canad.; Vita Health, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); methocarbamol (p.1897·3).

Muscle & Back Pain Relief Extra Strength *Pendopharm, Canad.*
Aspirin (p.20·3); methocarbamol (p.1897·3).

Muscle Care *Kiwi, Neth.*
Homoeopathic preparation.

Muscle & Joint Cream *Bayer, USA.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Muscle Relaxant and Analgesic *Technilab, Canad.†.*
Aspirin (p.20·3); methocarbamol (p.1897·3).

Muscle Rub *Weleda, S.Afr.*
Copper (p.1935·2); camphor (p.2273·2); capsicum (p.2276·2); arnica (p.2260·2); clove oil (p.2285·1); menthol (p.2340·1); cajuput oil (p.2271·2).
Musculoskeletal pain and stiffness.

Muscoflex *Epifarma, Ital.; Bilim, Turk.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; skeletal muscle spasm; spasticity.

Muscol *Teva, Israel; Teva, Thai.†.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Headache; musculoskeletal and joint disorders; musculoskeletal pain; neuralgia.

Muscoril *Sigma, Braz.; Sanofi Synthelabo, Cz.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Pol.; Sanofi Synthelabo, Turk.*
Thiocolchicoside (p.1898·2).
Dysmenorrhoea; muscle spasticity; neuromuscular pain; oedema; parkinsonism; skeletal muscle spasm; soft-tissue disorders.

Musco-ril *Sanofi-Aventis, Gr.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Muscoril Trauma *Sanofi-Aventis, Ital.*
Thiocolchicoside (p.1898·2); aescin (p.2248·2).
Soft-tissue injury.

Musculare *Eurofarma, Braz.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Musculax *Organon, Jpn.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Muscunor *Fada, Arg.*
Vitamin B substances (p.1922·1).

Muse *Abbott, Austral.†; Abbott, Austria; Abbott, Braz.†; Paladin, Canad.; Meda, Cz.; Meda, Denm.; Meda, Fin.; Meda, Fr.; Meda, Ger.; Meda, Irl.; Janssen-Cilag, Israel†; Janssen-Cilag, Mex.†; Abbott, NZ†; Meda, Neth.; Meda, Port.; Janssen-Cilag, S.Afr.; Alloga, Switz.; Janssen, Thai.†; Meda, UK; Vivus, USA.*
Alprostadil (p.2183·2).
Adjunct to ultrasound examination of penile function; erectile dysfunction.

Musibon *Biotech, Venez.†.*
Ketotifen fumarate (p.582·2).
Allergic respiratory-tract disorders; asthma.

Musilaks *Gunsa, Turk.*
Phenolphthalein (p.1762·1); vanillin (p.2410·3).

Musin *Otto, Indon.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Muskazon *Kurtsan, Turk.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle spasm.

Muskelat *Azupharma, Ger.†.*
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasm.

Muskelax *Medichem, Philipp.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Muskol *Schering-Plough, Canad.†.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Muskol with Sunblock *Schering-Plough, Canad.†.*
SPF 6: Diethyltoluamide (p.2041·1); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Insect repellent; sunscreen.

Muslax *Biological E, India.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Musocalm *Medicine Products, Thai.*
Tolperisone hydrochloride (p.1899·3).
Skeletal muscle spasm.

Musocan *Sripasit, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Musol *Ivax, Mex.*
Diclofenac diethylamine (p.44·3).
Inflammation; pain.

Musside *Cosmofarma, Port.†.*
Lindane (p.2045·3).
Pediculosis.

Mustargen *Merck Frosst, Canad.; MSD, Israel; MSD, Switz.; Merck, USA.*
Chlormethine hydrochloride (p.697·3).
Malignant neoplasms; mycosis fungoides; polycythaemia vera.

Musterole *Schering-Plough, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); methyl nicotinate (p.85·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Musterole Extra *Schering-Plough, USA.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); mustard oil (p.2349·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Mustoforan *Servier, Spain.*
Fotemustine (p.726·2).
Malignant melanoma.

Mustophoran *Servier, Cz.; Servier, Hung.; Servier, Pol.; Servier, Rus.*
Fotemustine (p.726·2).
Brain tumours; malignant melanoma.

Mustopic *Systopic, India.*
Tacrolimus (p.1843·1).
Atopic eczema.

Musvan *Parggon, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Musxan *Pharmasant, Thai.*
Methocarbamol (p.1897·3).
Skeletal muscle spasm.

Mutabase *Schering-Plough, Spain.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Depression.

Mutabon *Schering-Plough, Ital.; Schering-Plough, Port.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Anxiety; mixed anxiety-depressive disorders; psychiatric disorders.

Mutabon D
Kirby, Arg.†.
Perphenazine (p.1017·1); amitriptyline (p.376·1).
Mixed anxiety depressive states.
Essex, Chile†.
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Agitation; anxiety; mixed anxiety depressive states; schizophrenia.

Mutabon-D *Schering-Plough, Indon.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Depression; mixed anxiety-depressive disorders.

Mutabon-M *Schering-Plough, Indon.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Mixed anxiety-depressive states.

Mutacol *Berna, Canad.†.*
A live oral attenuated cholera vaccine (CVD 103-HgR) (p.2208·1).
Active immunisation.

Mutaflor *Emonta, Austria; Ardeypharm, Cz.; Ardeypharm, Ger.; Ardeypharm, Hung.; Emonta, Switz.*
Escherichia coli.
Constipation; diarrhoea; irritable colon; ulcerative colitis.

Mutagrip *Aventis Pasteur, Belg.†; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Sanofi Pasteur, Switz.*
An inactivated influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Mutamso *Europharm, Hong Kong.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous mucus.

Mutamycin *Bristol, Canad.; BMS, Fin.; BMS, Norw.; BMS, Swed.; BMS Oncology, USA.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mutamycine *BMS, Switz.†.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mutan *Lannacher, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Mutellon *Klein, Ger.*
Lycopus europaeus; motherwort (p.2347·3); valerian (p.2410·1).
Hyperthyroidism.

Mutesa *Genopharm, Fr.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); oxetacaine (p.1867·2).
Gastro-oesophageal pain.

Muthesa
Omega, Belg.
Algeldrate (p.1706·2); magnesium carbonate (p.1743·1) or magnesium oxide (p.1744·1); oxetacaine (p.1867·2).
Gastrointestinal disorders.
Valeant, Switz.
Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); oxetacaine (p.1867·2).
Gastrointestinal disorders.

Muthesa Compositum *Galena, Cz.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Gastrointestinal disorders.

Muthesa N
Note. This name is used for preparations of different composition.
Wyeth Consumer, Neth.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.
Wyeth Consumer, Neth.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Mutigan *Andromaco, Venez.†.*
Primidone (p.503·2).
Epilepsy.

Muttifen *Offenbach, Mex.*
Trimebutine (p.2404·3).

Mutum *Raffo, Arg.; Nolver, Venez.*
Fluconazole (p.532·1).
Fungal infections.

Muvar *Pharmatrix, Arg.*
Hyaluronic acid (p.2320·1); lactic acid (p.2329·3).
Hand and foot care.

Muveron *Solas, Indon.*
Vitamins; calcium gluconate; lysine hydrochloride; ferrous gluconate (p.1939·1); zinc sulphate (p.1922·1).
Anaemias; nutritional supplement.

Muvial *AGIPS, Ital.†.*
Timonacic methyl hydrochloride (p.2402·2).
Otorhinolaryngeal disorders; respiratory-tract disorders.

Muvidina *LKM, Arg.*
Zidovudine (p.913·3); lamivudine (p.895·1).
HIV infection.

Muvinlax *Libbs, Braz.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Muvinor *Libbs, Braz.*
Polycarbophil calcium (p.1763·3).
Constipation.

Muvito *Rafarm, Gr.*
Tetracycline hydrochloride (p.347·2).
Acne.

Muxen *Alian, Venez.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Muxol
Note. This name is used for preparations of different composition.
Saval, Chile.
Ambroxol (p.1550·3).
Respiratory-tract disorders.
Leurquin, Fr.; Andromaco, Mex.†.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.
Vifor, Switz.
Bisacodyl (p.1710·1).
Constipation.

Muzoral *Mugi, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

M.V. Poly P *Pharmasant, Thai.*
Vitamin preparation (p.1922·1).

M-Vac *Serum Institute, India.*
A measles vaccine (attenuated Edmonston Zagreb strain) (p.2221·3).
Active immunisation.

MVI *Aventis, Canad.†; USV, India; Grossman, Mex.; Hospira, USA; Mayne, USA.*
Multivitamin infusion (p.1922·1).
Parenteral nutrition.

MVI-12 *ICN, Braz.†.*
Multivitamin preparation (p.1922·1).

MVM *Tyson, USA.*
Multivitamin and mineral preparation (p.1922·1).

MXL *Napp, Irl.; Viatris, Port.†; Napp, UK.*
⊗ Morphine sulfate (p.86·3).
Pain.

My Check *Bergamo, Braz.†.*
Pregnancy test (p.2372·1).

Myacyne *Schur, Ger.*
Neomycin sulfate (p.305·1).
Infected skin disorders; infected wounds.

Myadec *Myadec, Austral.; Parke, Davis, USA.*
Multivitamin and mineral preparation (p.1922·1).

Myalgesic *Pharmanik (Φαρμανικ), Gr.†.*
Salicylamide (p.121·2); benzocaine (p.1854·1).
Topical analgesic.

Myambutol *Sigma, Austral.; Torrex, Austria; PSI, Belg.; Meda, Denm.; Genopharm, Fr.; Riemser, Ger.; Wyeth, Gr.; Wyeth, Hong Kong†; Wyeth, India; Wyeth, Mex.†; Zuellig, NZ; Teofarma, Neth.; Teofarma, Spain; Meda, Swed.; Labatec, Switz.; Lederle, Switz.; Wyeth-Ayerst, Thai.†; X-Gen, USA.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis and other mycobacterial infections.

Myambutol-INH *Torrex, Austria; Riemser, Ger.; Wyeth, Mex.†; Lederle, Switz.†.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Tuberculosis.

Myamolite *Eulite, Neth.*
Homoeopathic preparation.

My-B *Greater Pharma, Thai.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).
Infected skin disorders.

Mybacin *Greater Pharma, Thai.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); amylocaine hydrochloride (p.1853·3).
Mouth and throat disorders.

Mybacin Dermic *Greater Pharma, Thai.*
Bacitracin (p.210·3); neomycin (p.305·1).
Infected skin disorders.

Mybucod *Pharmacare, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Mybulen *Pharmacare, S.Afr.*
Ibuprofen (p.64·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Inflammation; pain.

Mycamine *Astellas, UK; Astellas, USA.*
Micafungin sodium (p.541·1).
Candidiasis; candidiasis prophylaxis in haematopoietic stem cell transplant patients; oesophageal candidiasis; prophylaxis of candidiasis following haematopoietic stem-cell transplantation.

Mycanden *Ronnet, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycarzem *Pharmanel, Gr.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Mycatox *Riemser, Ger.†.*
Dequalinium chloride (p.1641·3); hexylresorcinol (p.1647·1); sage (p.2382·3).
Bath additive; fungal infections.

Mycazole *Verisfield, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Mycel Gyno *Biolab Sanus, Braz.*
Isoconazole nitrate (p.536·2).
Fungal skin infections.

Mycelex *Ortho McNeil, USA.*
Clotrimazole (p.530·1).
Oral candidiasis.

Mycelex-3 *Ortho McNeil, USA.*
Butoconazole nitrate (p.528·1).
Vaginal candidiasis.

Mycelex-7 *Ortho McNeil, USA.*
Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

Mycella *Silom, Thai.*
Ketoconazole (p.539·1).
Fungal infections of the skin, nails, and mucous membranes.

Mycelvan *Liomont, Mex.*
Terbinafine (p.546·3).
Fungal infections.

Mycept *Panacea, India.*
Mycophenolate mofetil (p.1836·2).
Transplant rejection.

Mycetin *Farmigea, Ital.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Mycidex *Mac, India†.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye disorders.

Mycifradin *Upjohn, USA†.*
Neomycin sulfate (p.305·1).
Bacterial infections.

Mycil
Note. This name is used for preparations of different composition.
Wellspring, Canad.†.
Chlorphenesin (p.529·2).
Fungal and bacterial skin infections.

Boots, Hong Kong.
Tolnaftate (p.548·3); benzalkonium chloride (p.1629·1); chlorhexidine hydrochloride (p.1635·3).
Fungal skin infections.

Boots Healthcare, Irl.; Crookes Healthcare, UK.
Ointment: Tolnaftate (p.548·3); benzalkonium chloride (p.1629·1).
Fungal skin infections; prickly heat.

Boots Healthcare, Irl.; Crookes Healthcare, UK.
Topical powder: Tolnaftate (p.548·3); chlorhexidine hydrochloride (p.1635·3).
Fungal skin infections; prickly heat.

Boots Healthcare, Irl.; Crookes Healthcare, UK.
Topical spray: Tolnaftate (p.548·3).
Fungal skin infections; prickly heat.

Mycil Healthy Feet
Note. This name is used for preparations of different composition.
Boots Healthcare, Austral.†.
Cream: Tolnaftate (p.548·3); benzalkonium chloride (p.1629·1).
Fungal skin infections.

Reckitt & Colman, Austral.
Topical powder: Tolnaftate (p.548·3); chlorhexidine hydrochloride (p.1635·3).
Fungal skin infections.

Mycin-2 *Meyer, Venez.†.*
Pectin (p.2145·2); activated attapulgite (p.1709·1).
Diarrhoea.

Mycinette *Pfeiffer, USA.*
Phenol (p.1656·1); alum (p.2254·1).
Sore throat.

Mycinettes *Pfeiffer, USA.*
Benzocaine (p.1854·1).
Sore throat.

Mycinopred *Allergan, Switz.*
⊗ Prednisolone acetate (p.1541·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Myci-Spray *Misemer, USA.*
Phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Nasal congestion.

Mycitracin *Upjohn, USA†.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Myclin *Sanbe, Philipp.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Myclopir *Bevo, Gr.*
Ciclopirox (p.529·2).
Fungal vaginal infections.

Myco *T Man, Thai.*
Ketoconazole (p.539·1).
Scalp disorders.

Myco-Aid *Pharmaniaga, Malaysia.*
Tolnaftate (p.548·3).
Fungal skin infections.

Mycoapaisyl *Merck Medication Familiale, Fr.*
Econazole nitrate (p.531·1).
Formerly known as Furazanol.
Fungal skin infections.

Mycobact *Cipla, India.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Mycobacter *Biospray, Gr.*
Econazole nitrate (p.531·1).
Fungal skin and vaginal infections.

Mycoban
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.†.
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal candidiasis.

ICM, Singapore.
Miconazole nitrate (p.541·3).
Fungal infections of skin, nails, or scalp.

Myco-Biotic II *Moore, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

Mycobutin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pharmacia, Ger.†; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pfizer, Hong Kong; Pharmacia, Israel; Pharmacia, Ital.; Pharmacia, NZ; Pfizer, Neth.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pharmacia Upjohn, USA.*
Rifabutin (p.323·3).
Tuberculosis and other mycobacterial infections.

Mycobutol *Cadila Pharma, India.*
Ethambutol (p.275·2).
Tuberculosis.

Mycochlorin *SM, Thai.; Sermmitr, Thai.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Mycocid *Chemo-Pharma, India.*
Clotrimazole (p.530·1).
Fungal skin and nail infections.

Mycocide NS *Woodward, USA.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Mycocur *Nobel, Turk.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Myco-Decidin *Ivax, Cz.*
2-Aminotridecane undecenoate.
Fungal skin infections.

Mycodecyl
Note. This name is used for preparations of different composition.
Tonipharm, Fr.
Cream: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Tonipharm, Fr.
Topical powder: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); calcium undecenoate (p.549·3).
Fungal skin infections.

Tonipharm, Fr.
Topical solution: Undecenoic acid (p.549·2).
Fungal skin infections.

Mycodekan *Ivax, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Mycoderm
Note. This name is used for preparations of different composition.
FDC, India.
Salicylic acid (p.1612·2); benzoic acid (p.1630·2); menthol (p.2340·1).
Bromhidrosis; fungal skin infections; hyperhidrosis; seborrhoeic dermatitis.

Otto, Indon.
Ketoconazole (p.539·1).
Fungal infections.

Ego, Malaysia.
Salicylic acid (p.1612·2); sodium propionate (p.545·3); butyl hydroxybenzoate (p.1649·1).
Fungal skin infections.

Ego, Austral.†; Ego, Hong Kong†.
Cream: Salicylic acid (p.1612·2); undecenoic acid monoethanolamide (p.549·3); sodium propionate (p.545·3); butyl hydroxybenzoate (p.1649·1).
Fungal and bacterial skin infections.

Ego, Austral.
Dusting powder: Salicylic acid (p.1612·2); sodium propionate (p.545·3); butyl hydroxybenzoate (p.1649·1).
Fungal skin infections.

Ego, Hong Kong.
Dusting powder: Salicylic acid (p.1612·2); sodium propionate (p.545·3).
Fungal skin infections.

Mycoderm-C *FDC, India; FDC, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycodermil *Vifor, Switz.*
Fenticonazole nitrate (p.531·3).
Fungal skin infections.

Mycodib *Diba, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Mycofebrin *Coup, Gr.*
Ketoconazole (p.539·1).
Fungal infections.

Mycofen *Nycomed, Denm.*
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal skin and nail infections.

Mycofentin *Elmor, Venez.*
Fenticonazole nitrate (p.531·3).
Fungal skin and vaginal infections.

Mycoflucan *Reddy, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Myco-flusemidon *Anfarm, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Mycofug *Hermal, Ger.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycogel *Biorga, Fr.; Biorga, Hong Kong.*
Copper pidolate (p.1614·1); zinc pidolate (p.1614·1); melaleuca oil (p.2338·2).
Skin and scalp cleanser; skin and scalp disorders.

Mycogen II *Goldline, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

Myco-Hermal *Hermal, Israel; Hermal, Singapore.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycohexal *Hexal, S.Afr.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Mycol *Greater Pharma, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Mycolog
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Belg.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Switz.†.
⊗ Triamcinolone acetonide (p.1544·3); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

BMS, Fr.†.
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Mycolog N *Sanofi Synthelabo, Switz.*
⊗ Fluocinonide (p.1532·1); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Mycolog-II *Westwood-Squibb, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Cutaneous candidiasis.

Mycomax *Zentiva, Cz.; Zentiva, Pol.; Leciva, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Mycomycen *Verisfield, Gr.*
Ciclopirox (p.529·2).
Fungal nail and vaginal infections.

Myconafine *Actavis, Pol.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Myconel *Marnel, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

Myconex *Cadila Pharma, India.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Tuberculosis.

Myconil *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Griseofulvin (p.535·2).
Fungal skin and nail infections.

Myconip *Uni-Sankyo, India.*
Lactobacillus sporogenes (p.2372·3).
Leucorrhoea; vaginitis.

Myconormin *Hermal, Ger.; Boots Healthcare, Switz.*
Terbinafine hydrochloride (p.546·3).
Fungal nail, scalp, and skin infections.

Mycopol *Nycomed, Austria.*
Undecenoic acid (p.549·2); benzoic acid (p.1630·2); isopropyl alcohol (p.1650·3).
Fungal skin and nail infections.

Mycoral *Kalbe, Indon.; T Man, Thai.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Mycorest *Recon, Singapore.*
Fluconazole (p.532·1).
Fungal infections.

Mycoril *Remedica, Hong Kong; Remedica, Singapore.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycorine *Galenium, Indon.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mycosamthong *Sermmitr, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Mycosid *Meditop, Hung.*
Sodium *p*-chlorobenzoate (p.546·2); zinc oxide (p.1621·2).
Fungal skin infections.

Mycosin *Prodotti, Braz.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mycosolon
Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.
⊗ Mazipredone hydrochloride (p.1537·3); miconazole (p.541·2).
Fungal and Gram-positive skin and nail infections.

Richter, Pol.
⊗ Mazipredone hydrochloride (p.1537·3); miconazole nitrate (p.541·3).
Fungal skin infections.

Mycosoral *Akrikhin, Rus.*
Ketoconazole (p.539·1).
Fungal skin infections.

Mycospor
Note. This name is used for preparations of different composition.
Bayer, Arg.†; Bayer, Austral.; Bayer, Belg.†; Bayer, Braz.; Bayer, Cz.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Mex.; Bayer, Neth.; Bayer, Pol.; Bayer, S.Afr.; Bayhealth, Spain; Bayer, Venez.
Bifonazole (p.527·3).
Corynebacterial erythrasma; dandruff; fungal balanitis; fungal skin and nail infections.

Bayer, Turk.
Cream: Bifonazole (p.527·3).
Fungal skin infections.

Bayer, Port.
Cream; topical spray: Bifonazole (p.527·3).
Fungal skin and nail infections.

Bayer, Rus.
Cream; topical solution: Bifonazole (p.527·3).
Fungal skin infections.

Bayer, Port.†; Bayer, Rus.; Bayer, Turk.
Ointment: ⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycospor Nagelset *Bayer, Ger.†.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycospor Onicoset *Bayer, Mex.; Bayhealth, Spain; Bayer, Venez.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycospor Onychoset *Bayer, Pol.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycospor Onycho-set *Bayer, S.Afr.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycospor Sada na Nehty *Bayer, Cz.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycosporan *Bayer, Chile; Bayer, Swed.*
Bifonazole (p.527·3).
Fungal skin infections.

Mycosporan Onycoset *Bayer, Chile†.*
⊗ Bifonazole (p.527·3); urea (p.1620·2).
Fungal nail infections.

Mycosquam *Pierre Fabre, Fr.*
Ciclopirox olamine (p.529·2).
Scalp disorders.

Mycostatin *BMS, Austral.; Dermapharm, Austria; Convatec, Canad.; Convatec, Canad.; BMS, Denm.; BMS, Fin.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; Sarabhai Piramal, India; BMS, Indon.; BMS, Irl.; BMS, Ital.; BMS, Malaysia; BMS, NZ; BMS, Norw.; BMS, Philipp.; BMS, Port.; BMS, S.Afr.; BMS, Singapore†; BMS, Spain; BMS, Swed.; BMS, Thai.; BMS, USA.*
Nystatin (p.543·2).
Candidiasis.

Mycostatin V *Dermapharm, Austria.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1); nystatin (p.543·2).
Infected skin disorders.

Mycostatine *BMS, Fr.; Sanofi Synthelabo, Switz.*
Nystatin (p.543·2).
Candidiasis.

Mycostatin-Zinkoxid *Dermapharm, Austria.*
Nystatin (p.543·2); zinc oxide (p.1621·2).
Candidiasis.

Mycoster *Pierre Fabre, Fr.; Pierre Fabre, Port.*
Ciclopirox (p.529·2) or ciclopirox olamine (p.529·2).
Fungal and bacterial skin infection; fungal nail infections.

Mycostop *Galenium, Indon.*
Griseofulvin (micronized) (p.535·2).
Fungal infections of the skin, hair, and nails.

Myco-Synalar
Note. This name is used for preparations of different composition.
Minerva (Μινερβα), Gr.
⊗ Fluocinolone (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Grunenthal, Austria; Grunenthal, Switz.†.
Cream: ⊗ Fluocinolone acetonide (p.1531·3); chlormidazole hydrochloride (p.529·1).
Fungal skin infections.

Grunenthal, Austria; Grunenthal, Switz.†.
Topical solution: ⊗ Fluocinolone acetonide (p.1531·3); chlormidazole hydrochloride (p.529·1); salicylic acid (p.1612·2).
Fungal skin infections.

Mycosyst *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Mycota
Note. This name is used for preparations of different composition.
Reckitt Benckiser, S.Afr.; Thornton & Ross, UK.
Cream; topical powder: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Reckitt Benckiser, S.Afr.†; Thornton & Ross, UK.
Topical spray: Undecenoic acid (p.549·2); dichlorophen (p.143·1).
Fungal skin infections.

Mycotel *SM, Thai.*
Albendazole (p.139·2).
Worm infections.

Mycothambin-INH *UAP, Indon.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Myco-Triacet II *Lemmon, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

Mycotricide *SM, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Myco-Z *BMS, Indon.*
Nystatin (p.543·2); zinc oxide (p.1621·2).
Fungal skin infections.

Mycozid *Soho, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Mycozole *Osoth, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Mycurium *Taro, Israel.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Mycutol *Mediapharm, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Myda-B *T Man, Thai.*
⊗ Clotrimazole (p.530·1); betamethasone valerate (p.1519·1).
Fungal skin infections.

Myderison *Meditop, Hung.*
Tolperisone hydrochloride (p.1899·3).
Skeletal muscle spasm.

Mydeton *Gedeon Richter, Hung.*
Tolperisone hydrochloride (p.1899·3).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Skeletal muscle spasm and spasticity.

Mydfrin *Alcon, Arg.†; Alcon, Canad.; Alcon, Chile; Alcon, Hong Kong; Alcon, Malaysia; Alcon, Philipp.; Alcon, Singapore; Alcon, Turk.; Alcon, USA.*
Phenylephrine hydrochloride (p.1568·1).
Funduscopy; open-angle glaucoma; production of mydriasis without cycloplegia; uveitis.

Mydocalm *Nycomed, Austria; Gedeon Richter, Cz.; Strathmann, Ger.; Gedeon Richter, Hong Kong; Richter, Pol.; Gedeon Richter, Rus.; Labatec, Switz.; Gedeon Richter, Thai.*
Tolperisone hydrochloride (p.1899·3).
Lidocaine hydrochloride (p.1862·3) may be included in the injection to reduce the pain of injection
Obliterative vascular disorders; peripheral vascular disease; skeletal muscle spasticity and spasm.

Mydocalm-A *Chinoin, Mex.*
Tolperisone hydrochloride (p.1899·3); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Mydono *Milano, Thai.*
Tolperisone hydrochloride (p.1899·3).
Obliterative vascular diseases; skeletal muscle spasm and spasticity.

Mydosone *Condrugs, Thai.*
Tolperisone hydrochloride (p.1899·3).
Skeletal muscle spasm.

Mydral *Agepha, Austria; Ocusoft, USA.*
Tropicamide (p.1886·2).
Production of mydriasis.

Mydramide *Fischer, Israel.*
Tropicamide (p.1886·2).
Production of mydriasis.

Mydriacil *Alcon, Irl.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Mydriacyl *Alcon, Austral.; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.†; Alcon, Denm.; Alcon, Hong Kong; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Swed.; Alcon, Thai.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Tropicamide (p.1886·2).
Aid in eye examination; production of cycloplegia and mydriasis.

Mydrial-Atropin *Winzer, Ger.†.*
⊗ Tyramine hydrochloride (p.2407·1); atropine borate (p.1220·3); adrenaline acid tartrate (p.1203·2).
Production of mydriasis.

Mydrian *Novartis, Norw.†.*
Tropicamide (p.1886·2).
Production of mydriasis.

Mydriasert *Ioltech, Fr.; Ioltech, Port.*
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis.

Mydriaticum *Agepha, Austria; Thea, Fr.; Stulln, Ger.; Novartis Ophthalmics, Hong Kong†; Restan, S.Afr.; Novartis, Switz.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Mydril *Alcon, Arg.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Mydrilate *Intrapharm, Irl.; Intrapharm, UK.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Mydrin-P *Santen, Hong Kong.*
Tropicamide (p.1886·2); phenylephrine hydrochloride (p.1568·1).
Production of mydriasis and cycloplegia.

Mydrox *Oftalmi, Venez.†.*
Tropicamide (p.1886·2).
Production of cycloplegia and mydriasis.

Mydrum *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.; Chauvin, Rus.*
Tropicamide (p.1886·2).
Aid in eye examination; production of cycloplegia and mydriasis.

Myelobromol *Enzypharm, Austria; Durbin, UK.*
Mitobronitol (p.751·2).
Chronic myeloid leukaemia.

Myelogen *Panacea, India†.*
Mecobalamin (p.1981·1).
Peripheral neuropathy; vitamin B deficiency.

Myelostim *Italfarmaco, Ital.*
Lenograstim (p.1073·1).
Mobilisation of autologous peripheral blood progenitor cells; neutropenia induced by bone-marrow transplantation or cytotoxic chemotherapy.

Myfenax
Note. This name is used for preparations of different composition.
Teva, Cz.
Mycophenolate mofetil (p.1836·2).
Transplant rejection.

Greater Pharma, Thai.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Myfloxin *Greater Pharma, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Myfortic *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Mycophenolate sodium (p.1836·3).
Cardiac, hepatic, and renal transplant rejection.

Myfungar *Zentiva, Cz.; Taurus, Ger.; Rhein, Mex.; Leciva, Rus.*
Oxiconazole nitrate (p.544·2).
Fungal and Gram-positive bacterial infections.

Mygale compositum *Weleda, Austria.*
Homoeopathic preparation.

Mygel *Geneva, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Mygesal *Greater Pharma, Thai.*
Methyl salicylate (p.85·3).
Musculoskeletal and joint pain; sprains; strains.

MyHist-DM *Larken, USA.*
Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

MyHist-PD *Larken, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); mepyramine maleate (p.585·2).
Upper respiratory-tract disorders.

Myk *Jolly-Jatel, Fr.*
Sulconazole nitrate (p.546·2).
Fungal skin infections.

Myk-1 *Will-Pharma, Belg.; Will-Pharma, Neth.*
Sulconazole nitrate (p.546·2).
Fungal skin infections.

Mykantol *Medika, Switz.*
Fluconazole (p.532·1).
Fungal infections.

Myko Cordes
Note. This name is used for preparations of different composition.
Ichthyol, Ger.
Clotrimazole (p.530·1).
Fungal and corynebacterial skin infections.

Ichthyol, Austria.
Cream: Clotrimazole (p.530·1).
Fungal skin infections.

Ichthyol, Austria.
Paste: Clotrimazole (p.530·1); zinc oxide (p.1621·2).
Fungal skin infections.

Myko Cordes Plus *Ichthyol, Ger.*
Clotrimazole (p.530·1); zinc oxide (p.1621·2).
Fungal skin infections.

Mykoderm *Engelhard, Ger.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Mykoderm Heilsalbe *Engelhard, Ger.*
Nystatin (p.543·2).
Fungal skin infections.

Mykoderm Mund-Gel *Engelhard, Ger.*
Miconazole (p.541·2).
Fungal mouth infections.

Mykodermina
Note. This name is used for preparations of different composition.
Pampa, Pol.
Ointment; topical liquid: Undecenoic acid monoethanolamide (p.549·3).
Fungal skin infections.

Pampa, Pol.
Topical powder: Undecenoic acid monoethanolamide (p.549·3); zinc undecenoate (p.549·3).
Fungal skin infections.

Mykofungin *Riemser, Ger.*
Clotrimazole (p.530·1).
Fungal and bacterial infections of skin and genito-urinary tract.

Mykohaug *Betapharm, Ger.*
Clotrimazole (p.530·1).
Fungal and bacterial infections of skin and vagina.

Mykohexal *Hexal, Cz.*
Fluconazole (p.532·1).
Fungal infections.

Mykontral *Riemser, Ger.*
Tioconazole (p.548·2).
Fungal skin infections.

MykoPosterine N *Kade, Ger.†.*
Nystatin (p.543·2).
Anorectal fungal infections.

Mykoproct sine *Stegropharm, Ger.*
⊗ Nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Fungal skin infections.

Mykoseptin *Zentiva, Cz.; Zentiva, Rus.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Mykosert *Pfleger, Ger.*
Sertaconazole (p.546·1) or sertaconazole nitrate (p.546·1).
Fungal skin infections.

Mykotin *Ardeypharm, Ger.*
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal skin and mouth infections.

Mykrox *Celltech, USA.*
⊗ Metolazone (p.1337·2).
Formerly known as Microx.
Hypertension.

Mykundex *Riemser, Ger.*
Nystatin (p.543·2).
Fungal infections.

Mykundex Heilsalbe *Riemser, Ger.*
Nystatin (p.543·2); zinc oxide (p.1621·2).
Fungal skin infections.

Mykundex mono *Riemser, Ger.*
Nystatin (p.543·2).
Fungal skin infections.

Mylagen
Note. This name is used for preparations of different composition.
Goldline, USA.
Capsules: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Hyperacidity.

Goldline, USA.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Mylange Creme *Mylange, Fr.†.*
Zinc oxide (p.1621·2).
Dry skin; nappy rash.

Mylanta
Note. This name is used for preparations of different composition.
Elea, Arg.; Pfizer, Philipp.
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; heartburn.

Johnson & Johnson, Austral.; Pfizer Consumer, Canad.; Pfizer, Chile; Pfizer, Indon.; Johnson & Johnson, NZ; Pfizer, Venez.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

J&J-Merck, USA.
Chewable tablets: Calcium carbonate (p.1714·1).
Hyperacidity.

Johnson & Johnson, Hong Kong†; Janssen-Cilag, Malaysia†; J&J-Merck, USA.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity.

Janssen-Cilag, Singapore†.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; heartburn.

Johnson & Johnson, Hong Kong†; Janssen-Cilag, Malaysia†; Janssen-Cilag, Singapore†.
Tablets: Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Dyspepsia; gastric hyperacidity; heartburn.

Mylanta II *Elea, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Mylanta AR Acid Reducer *J&J-Merck, USA†.*
Famotidine (p.1730·1).
Dyspepsia; heartburn.

Mylanta de Bolso *Pfizer, Braz.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Mylanta DS *Johnson & Johnson, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; heartburn.

Mylanta Effervescent *Pfizer, NZ†.*
Magnesium oxide (p.1744·1).
Antacid.

Mylanta Extra *Elea, Arg.*
Calcium carbonate (p.1714·1); magnesium (p.1678·3); famotidine (p.1730·1).
Gastric hyperacidity.

Mylanta Gas *Elea, Arg.; J&J-Merck, USA.*
Simeticone (p.1770·2).
Flatulence; gastrointestinal disorders with excess gas.

Mylanta Gelcaps *J&J-Merck, USA.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Formerly contained calcium carbonate and magnesium carbonate.
Hyperacidity.

Mylanta Heartburn Relief
Note. This name is used for preparations of different composition.
Johnson & Johnson, NZ.
Alginic acid (p.2140·3); calcium carbonate (p.1714·1); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); sodium bicarbonate (p.1673·2).
Antacid; gastro-oesophageal reflux.

Pfizer Consumer, Austral.†.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); alginic acid (p.2140·3).
Dyspepsia; gastro-oesophageal reflux.

Pfizer Consumer, Austral.†.
Tablets: Magaldrate (p.1742·3); alginic acid (p.2140·3); sodium bicarbonate (p.1673·2).
Dyspepsia; gastro-oesophageal reflux.

Mylanta Max Elea, Arg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Mylanta Natural Fiber J&J-Merck, USA†.
Psyllium hydrophilic mucilloid (p.1737·1).

Mylanta Plain Pfizer Consumer, Canad.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; hiatus hernia; peptic ulcer.

Mylanta Plus
Note. This name is used for preparations of different composition.
Elea, Arg.; Pfizer, Braz.; Pfizer, Mex.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Pfizer, Venez.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); calcium alginate (p.1058·1).
Antacid; gastro-oesophageal reflux.

Mylanta Pocket Parke, Davis, Arg.†.
Calcium carbonate (p.1714·1).
Gastrointestinal hyperacidity.

Mylanta Reflux
Note. This name is used for preparations of different composition.
Elea, Arg.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium alginate (p.1058·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity.

Elea, Arg.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); alginic acid (p.2140·3).
Gastro-oesophageal reflux; gastrointestinal hyperacidity.

Mylanta Rolltabs Pfizer Consumer, Austral.†; Johnson & Johnson, NZ.
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Antacid; dyspepsia.

Mylanta Simple Elea, Arg.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity.

Mylanta Ultra J&J-Merck, USA.
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Antacid.

Mylantados Pfizer, Venez.†.
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Antacid; flatulence.

Mylantamil Pfizer, Venez.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid.

Mylepsinum AWD, Ger.
Primidone (p.503·2).
Epilepsy.

Myleran GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Fr.; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.†; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.
Busulfan (p.690·2).
Chronic myeloid leukaemia; essential thrombocythaemia; haematopoietic stem cell transplantation; myelofibrosis; polycythaemia vera; primary thrombocythaemia.

Myleuca IPRAD, Fr.
Melaleuca oil (p.2338·2).
Adjunct in fungal skin infections; skin cleansing.

Mylicon Janssen-Cilag, Braz.; Pfizer, Denm.; Pfizer Consumer, Ital.; J&J-Merck, USA.
Dimeticone (p.1770·2).
Adjunct in gastrointestinal investigations; aerophagia; dyspepsia; flatulence; infant colic; meteorism.

Mylocel MGI, USA†.
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Mylocort Triomed, S.Afr.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Mylol
Note. This name is used for preparations of different composition.
Rolfe, S.Afr.†.
Topical liquid: Diethyltoluamide (p.2041·1); dimethyl phthalate (p.2041·3); dibutyl phthalate (p.2040·1).
Insect repellent.

Rolfe, S.Afr.†.
Topical spray: Diethyltoluamide (p.2041·1).
Insect repellent.

Mylom Ranbaxy, Thai.
Simeticone (p.1770·2).
Flatulence.

Mylotarg Wyeth, Arg.; Wyeth-Ayerst, USA; Wyeth, Venez.
Gemtuzumab ozogamicin (p.728·3).
Acute myeloid leukaemia.

My-Marvel Herbs & Nature, Philipp.
Taheebo tree bark.
Nutritional supplement.

Mynatal ME Pharmaceuticals, USA.
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Mynate 90 Plus ME Pharmaceuticals, USA.
Multivitamin and mineral preparation (p.1922·1).

Myneocin Greater Pharma, Thai.
Neomycin (p.305·1).
Diarrhoea; gastrointestinal infections.

Mynocine Tonipharm, Fr.
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Myobid Panacea, India.
Ethionamide (p.275·3).
Tuberculosis.

Myobloc
Note. This name is used for preparations of different composition.
Genepharm, Gr.
Diacerein (p.41·3).
Osteoarthritis.

Elan, USA.
Botulinum B toxin (p.1890·1).
Spasmodic torticollis.

Myocalm Taiho, Jpn.
Piracetam (p.368·2).

Myocard Korea United, Philipp.
Dopamine hydrochloride (p.1273·2).
Shock.

Myocardon Altana, Austria.
Aminophylline hydrochloride (p.1114·3); papaverine hydrochloride (p.2191·3); atropine methonitrate (p.1219·3); glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Myocardon mono Altana, Austria.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction.

Myocet
Elan, Austria; Cephalon, Cz.; Zeneus, Irl.; Elan, Neth.; Cephalon, Port.
Liposomal doxorubicin citrate (p.712·2) (p.712·2).
Breast cancer.

Zeneus, Belg.; Sopherion, Canad.; Zeneus, Fr.; Zeneus, Ger.; Wyeth, Gr.; Elan, Hung.; Elan, Ital.; Zeneus, Spain; Cephalon, UK.
Liposomal doxorubicin hydrochloride (p.712·2) (p.712·2).
Breast cancer.

Myocholine Glenwood, Austria; Infarmed, Belg.; Glenwood, Ger.; Vifor, Switz.
Bethanechol chloride (p.2265·3).
Bladder atony; urinary retention.

Myochrysine Aventis, Canad.; Taylor, USA.
Sodium aurothiomalate (p.122·2).
Psoriatic arthritis; rheumatoid arthritis.

Myocin Shiwa, Thai.†.
Methocarbamol (p.1897·3).
Cramps; skeletal muscle spasm.

Myocord Ivax, Arg.
⊗ Atenolol (p.1217·3).
Arrhythmias; hypertension.

Myocrisin Aventis, Austral.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Aventis, NZ; Aventis, Norw.; Aventis, S.Afr.†; Aventis, Swed.; Aventis, Thai.; JHC Healthcare, UK.
Sodium aurothiomalate (p.122·2).
Juvenile idiopathic arthritis; lupus erythematosus; rheumatoid arthritis; Still's disease.

Myocrysine Aventis, Gr.†.
Sodium aurothiomalate (p.122·2).
Rheumatic disorders.

Myodipine Help, Gr.
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Myodrine Charoen, Thai.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Muscle pain; rheumatism; tension headache.

Myodura Wockhardt, India.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Myofedrin Apogepha, Cz.†; Apogepha, Ger.†.
Oxyfedrine hydrochloride (p.1365·2).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction.

Myoflex
Note. This name is used for preparations of different composition.
Bayer Consumer, Canad.; Armstrong, Mex.; Fisons, USA.
Trolamine salicylate (p.132·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Pharmacare, S.Afr.
Paracetamol (p.108·1); chlormezanone (p.968·3).
Pain and associated tension.

Siam Bheasach, Thai.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal and joint pain; neuralgia.

Myoflex Extra Strength Ice Bayer Consumer, Canad.
Trolamine salicylate (p.132·3); menthol (p.2340·1).
Formerly known as Myoflex Ice Plus.
Musculoskeletal and joint pain.

Myoflexin Zentiva, Hung.
Chlorzoxazone (p.1894·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Myogard RPG, India.
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Myogeloticum N Hanosan, Ger.†.
Homoeopathic preparation.

Myogit Pfleger, Cz.; Pfleger, Ger.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Myolastan Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Spain.
Tetrazepam (p.1031·1).
Skeletal muscle spasm; spasticity.

Myolax Siam Bheasach, Thai.†.
Carisoprodol (p.1894·1).
Skeletal muscle spasm.

Myolosyx Syxyl, Ger.†.
Homoeopathic preparation.

Myomergin Ethica, Indon.
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; third-stage labour management.

Myomethol RX, Thai.
Methocarbamol (p.1897·3).
Cramps; skeletal muscle spasm.

Myometril Oriental, Philipp.
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage.

Myonac M & H, Thai.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders.

Myonal Eisai, Indon.; Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore; Eisai, Thai.
Eperisone hydrochloride (p.1897·1).
Myotonias; skeletal muscle spasm; spasticity.

Myonep Lapi, Indon.
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Myonil Ferrosan, Denm.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Myonit Troikaa, India.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; hypertension and controlled hypotension during surgery.

Myopam Chephasaar, Pol.
Tetrazepam (p.1031·1).
Skeletal muscle spasm; spasticity.

Myophen Charoen, Thai.
Carisoprodol (p.1894·1); phenylbutazone (p.117·1).
Musculoskeletal, joint, and peri-articular disorders.

Myoplege Genevrier, Fr.
Thiocolchicoside (p.1898·2).
Skeletal muscle spasm.

Myoplegine Christiaens, Belg.†.
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Myopril Unique, Rus.
Enalapril maleate (p.1276·1).

Myoprin Desatnik, S.Afr.
Aspirin (p.20·3).
Fever; pain; thromboembolism prophylaxis.

Myoqinon Pharma Nord, Hung.
Ubidecarenone (p.2407·2).
Coenzyme deficiency.

Myoquin Fawns & McAllan, Austral.†.
Quinine bisulfate (p.612·2).
Malaria; nocturnal cramps.

Myora Bangkok Lab & Cosmetic, Thai.
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle pain and spasm.

Myores Meprofarm, Indon.
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasm.

Myori Tempo Scan Pacific, Indon.
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Myoril Sanofi-Aventis, India.
Thiocolchicoside (p.1898·2).
Painful skeletal muscle spasm.

Myoscint Mallinckrodt, Cz.†.
Indium-111 imciromab pentetate (p.2054·1).
Localisation of myocardial infarction.

Myoserv Win-Medicare, Thai.†.
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Myosic M & H, Thai.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain.

Myoson Strathmann, Ger.
Pridinol mesilate (p.1898·1).
Skeletal muscle spasm.

Myospa Hua, Thai.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle pain.

Myospasmal TAD, Ger.
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasm.

Myospaz Win-Medicare, India.
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Muscle spasm; pain.

Myospaz Forte Win-Medicare, India.
Diclofenac potassium (p.44·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Muscle spasm; pain.

Myostin Ivax, Irl.
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Myotenlis Pharmacia, Ital.†.
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Myotonachol Glenwood, Canad.†; Glenwood, USA.
Bethanechol chloride (p.2265·3).
Gastro-oesophageal reflux; neurogenic bladder; urinary retention.

Myotonic Meprofarm, Indon.
Methylergometrine maleate (p.2011·1).
Third-stage labour management; uterine bleeding.

Myotonine Glenwood, UK.
Bethanechol chloride (p.2265·3).
Gastro-oesophageal reflux; urinary retention.

Myovek Faran, Gr.†.
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Myoview Amersham, Austral.; Amersham, Austria; GE, Cz.; Amersham, Fr.; Amersham, Ital.; GE Healthcare, Neth.; GE, Port.; Amersham, Spain; Nycomed Amersham, UK.
Technetium-99m tetrofosmin (p.2055·3).
Detection of breast tumours; myocardial perfusion imaging.

Myovin Cadila Pharma, India.
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Myoviton Pharos, Indon.
Pyridoxine hydrochloride (p.1978·2); adenosine triphosphate, disodium salt (p.2247·3).
Muscle weakness.

Myoxam Menarini, Arg.†; Menarini, Spain.
Midecamycin acetate (p.300·2).
Bacterial infections.

Myoxan TO-Chemicals, Thai.
Tolperisone hydrochloride (p.1899·3).
Parkinsonism; skeletal muscle spasm.

Myozyme Genzyme, Cz.; Genzyme, Fr.; Genzyme, Port.; Genzyme, UK; Genzyme, USA.
Alglucosidase alfa (p.2245·3).
Pompe disease.

Mypaid Adcock Ingram, S.Afr.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Mypara Greater Pharma, Thai.
Paracetamol (p.108·1).
Fever; pain.

Myphetane DX Morton Grove, USA.
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Myprodol Adcock Ingram, S.Afr.
Ibuprofen (p.64·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Myproflam Adcock Ingram, S.Afr.
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders.

Myra General Drug, Philipp.
Vitamin E (p.1992·2).

Myra 300-E Myra, Hong Kong; Myra, Singapore.
Vitamin E (p.1992·2).
Vitamin E deficiency.

Myrac Glades, USA.
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Myracof-AF General Drug, Philipp.
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Myracof-T General Drug, Philipp.
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Myrall Stada, Hung.
St John's wort (p.422·3).
Depression.

Myralon Organon, Turk.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Myrazole-B T Man, Thai.
⊗ Betamethasone valerate (p.1519·1); clotrimazole (p.530·1).
Infected skin disorders.

Myriacyl Alcon, Mex.
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Myrin Wyeth, Philipp.; Aspen, S.Afr.†; Wyeth-Ayerst, Thai.†.
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Myrin Plus Wyeth, S.Afr.†.
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1); rifampicin (p.325·3); pyrazinamide (p.320·2).
Tuberculosis.

Myrin-P *Wyeth, Philipp.; Wyeth-Ayerst, Thai.*
Ethambutol hydrochloride (p.274·1); rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Myristoll *Eagle, Austral.†.*
Cetyl myristoleate.
Dietary supplement.

Myroxine *Sandoz, Gr.*
Fluvoxamine maleate (p.399·3).
Depression.

Myrrhinil-Intest *Repha, Ger.*
Myrrh (p.2349·2); carbo coffeae (p.2416·1); chamomile (p.2279·3).
Gastrointestinal disorders.

Myrtaven *IBSA, Switz.*
Myrtillus (p.2349·3).
Capillary fragility; haemorrhoids; venous insufficiency.

Myrtoplex *Darou Pakhsh, Rus.*
Myrrh (p.2349·2).
Herpes simplex infections of skin and mucous membranes.

Mysalfon *Ivax, Cz.†.*
Terguride maleate (p.819·2).
Acromegaly; benign prostatic hyperplasia; drug-induced extrapyramidal disorders; hyperprolactinaemia; parkinsonism; schizophrenia.

Myser *Mitsubishi, Jpn†.*
⊗ Difluprednate (p.1529·3).
Skin disorders.

Myskin *CellTran, UK.*
Bioengineered autologous human skin substitute (p.1613·3).
Burns; diabetic foot ulcers; wounds.

Myslee *Astellas, Jpn.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Mysocort *Greater Pharma, Thai.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Mysoline *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.†; AstraZeneca, Braz.; Draxis, Canad.†; AstraZeneca, Chile†; AstraZeneca, Cz.†; AstraZeneca, Denm.†; AstraZeneca, Fin.†; AstraZeneca, Fr.†; IFET (ΙΦΕΤ), Gr.; Nicholas Piramal, India†; Acorus, Irl.; SIT, Ital.; Columbia, Mex.; Fagron, Neth.; AstraZeneca, Norw.†; Azevedos, Port.; Pharmaplan, S.Afr.; AstraZeneca, Spain; AstraZeneca, Swed.†; AstraZeneca, Switz.; AstraZeneca, Turk.; Acorus, UK; Athena Neurosciences, USA.*
Primidone (p.503·2).
Epilepsy; essential tremor.

Mysolone-N *Greater Pharma, Thai.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1).
Burns; skin disorders; wounds.

Mysoven *Greater Pharma, Thai.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Myspa *Greater Pharma, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm.

Mysteclin
Note. This name is used for preparations of different composition.
Dermapharm, Austria.
Tetracycline (p.347·1); amphotericin B (p.523·2).
Vaginal infections.

Dermapharm, Ger.
Tetracycline (p.347·1); amphotericin B (p.523·2).
Vaginal infections.

Mytaderm *GMP, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Skin disorders with bacterial infection.

Mytancid *Synco, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimethicone (p.1770·2).
Flatulence; gastric hyperacidity.

Mytedom *Cristalia, Braz.*
⊗ Methadone hydrochloride (p.82·3).

Mytelase *Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Pol.; Sanofi Synthelabo, Swed.; Sanofi Winthrop, USA.*
Ambenonium chloride (p.629·3).
Myasthenia gravis; postoperative bladder atony; postoperative ileus.

Mytic 810 *Piam, Ital.*
Medium-chain triglycerides (p.1956·3).
Obesity.

Mytoxid *Korea United, Philipp.*
Mitomycin (p.752·1).
Malignant neoplasms.

Mytrex *Savage, USA†.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

Mytrocin *Greater Pharma, Thai.*
Nitrofurazone (p.309·1).
Bacterial skin and wound infections.

Mytusan DM *Am-Europharma, Philipp.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Mytussin AC *Morton Grove, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Mytussin DAC *Morton Grove, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Mytussin DM *Morton Grove, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Mytussin PE *Morton Grove, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).

My-Vitalife *ME Pharmaceuticals, USA.*
Multivitamin and mineral preparation (p.1922·1).

Myvlar *Schering, Austria.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Myxina *Norma (Νορμα), Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Myxofat *Fatol, Ger.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

MZM *Ciba Vision, USA†.*
⊗ Methazolamide (p.1883·1).

M-Zole *Alpharma, USA.*
Miconazole nitrate (p.541·3).
Vulvovaginal candidiasis.

N D Clear *Seatrace, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Naabak
Pfizer, Arg.; Allergan, Braz.; Thea, Fr.; Pfizer, Singapore; Pfizer, Venez.
Sodium isospaglumate (p.2327·2).
Allergic conjunctivitis.

Thea, Port.
Spaglumic acid (p.2327·2).
Allergic conjunctivitis.

Naaprep *GSK Consumer, Belg.†; GSK Consumer, Switz.*
Sodium chloride (p.1686·1).
Cleansing of of nose and eyelids; nasal disorders; nasal irrigation; rinsing solution for contact lenses.

Naaxia
Allergan, Braz.; Pfizer, Chile; Thea, Fr.; Thea, Spain; Thea, Switz.
Sodium isospaglumate (p.2327·2).
Allergic conjunctivitis; allergic keratoconjunctivitis; blepharoconjunctivitis.

Novartis Ophthalmics, Cz.†; Novartis Ophthalmics, Hung.; Novartis, Turk.
Sodium spaglumate (p.2327·2); sodium isospaglumate (p.2327·2).
Allergic conjunctivitis.

Novartis, Gr.; Restan, S.Afr.†.
Spaglumic acid (p.2327·2); isospaglumate (p.2327·2).
Allergic conjunctivitis.

Thea, Hong Kong; Thea, Philipp.
Isospaglumic acid (p.2327·2).
Allergic conjunctivitis.

Novartis, Ital.
Sodium spaglumate (p.2327·2).
Allergic conjunctivitis.

Novartis, Port.†.
Spaglumic acid (p.2327·2).
Allergic conjunctivitis.

Naaxiafree *Thea, Fr.*
Sodium isospaglumate (p.2327·2).
Allergic conjunctivitis.

Nabesac *Masa, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle pain.

Nabicortin *Help, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Nabi-HB *Nabi, USA.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Nabone *TO-Chemicals, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Nabonet *M & H, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Naborel *Elpen (Ελπεν), Gr.*
Nimodipine (p.1357·2).
Prophylaxis and prevention of ischaemic neurological findings.

Nabratin *Raffo, Arg.*
Clopidogrel bisulfate (p.1250·2).

Nabuco *Trima, Israel.*
Nabumetone (p.91·2).
Musculoskeletal and joint disorders.

Nabucox *Mayoly-Spindler, Fr.*
Nabumetone (p.91·2).
Musculoskeletal and joint disorders.

Nabuflam *Micro, India.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Nabuser *Geymonat, Ital.*
Nabumetone (p.91·2).
Musculoskeletal, joint, and peri-articular disorders.

Nabutil *UPSA Conseil, Fr.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Nabuton *Medichrom, Gr.; ICN, Pol.*
Nabumetone (p.91·2).
Inflammation; musculoskeletal and joint disorders; pain.

Nac
Note. A similar name is used for preparations of different composition (see below).
Klonal, Arg.
Piroxicam (p.117·3).
Inflammation; pain.

NAC
Note. A similar name is used for preparations of different composition (see above).
Nycomed, Austria; Sigma, Braz.; Aliud, Cz.; 1A, Ger.; ABZ, Ger.; Aliud, Ger.; CT, Ger.; Hemopharm, Ger.; Ratiopharm, Ger.; Sandoz, Ger.; Stada, Ger.; Aliud, Hung.; Pharmalink, Thai.; Temmler, Thai.; Basel, Turk.
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory-tract congestion.

Nac
Note. A similar name is used for preparations of different composition (see above).
Systopic, India.
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Nac Gel *Systopic, India.*
Diclofenac diethylamine (p.44·3).
Soft-tissue disorders.

Nacha *Lineafarm, Spain†.*
A nonoxinol (p.1917·1).
Contraceptive.

Naclodin *Valmor, Venez.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Naclof *Novartis Ophthalmics, Cz.†; Novartis, Neth.; Novartis, Pol.; Novartis, Rus.; Novartis, Thai.*
Diclofenac sodium (p.44·3).
Eye inflammation; inhibition of intra-operative miosis; prevention of cystoid macular oedema following eye surgery.

Nacom *BMS, Ger.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Nacomic *Alpharma, Mex.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin and nail infections.

Nacon *Cypress, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2); hyoscine methonitrate (p.1734·2).
Rhinitis.

Nacor *Merck, Spain†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Nacozil *TO-Chemicals, Thai.†.*
Isoconazole nitrate (p.536·2).
Fungal skin infections.

Nacro *Investigaciones Filosoficas y Cientificas, Mex.*
Nicotinamide (p.1957·3).
Neurodermatitis; vitamin B deficiency.

Nactol *Offenbach, Mex.†.*
Benzonatate (p.1552·1).
Coughs.

Nacua *Ronava, Venez.†.*
⊗ Furosemide (p.1292·1).
Hypertension.

Nad *Medical, Spain.*
Nadide (p.2350·1).
Vertigo.

Nadamen *Medochemie, Hong Kong†; Medochemie, Malaysia†; Medochemie, Singapore†; Medochemie, Thai.†.*
Tenoxicam (p.128·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nadem *Ivax, Arg.*
Aesculus (p.2248·2).
Nadem Forte formerly contained bamethan succinate and aesculus.
Haemorrhoids; venous insufficiency.

Naderm *Cristalia, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Nadetos *Raymos, Arg.*
Oxeladin (p.1567·1).
Coughs.

Nadib *Diba, Mex.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Nadib-M *Diba, Mex.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Nadiclox *Medinfar, Port.*
Fusidic acid (p.279·3) or sodium fusidate (p.279·3).
Bacterial skin infections.

Nadifen *GMP, Indon.*
Diclofenac sodium (p.44·3).
Inflammation following cataract surgery; musculoskeletal and joint disorders.

Nadiflox *Cipla, India.*
Nadifloxacin (p.303·2).
Bacterial infections.

Nadinola *Nadinola, Canad.†.*
Hydroquinone (p.1598·2).

Nadione *DMG, Ital.*
Bioflavonoids; vitamin C; phytomenadione (p.1922·1).
Nutritional supplement.

Nadipinia *Cardinal, Hong Kong.*
Nifedipine (p.1350·1).
Heart failure; hypertension.

Naditone *Kleva, Gr.*
Nabumetone (p.91·2).
Inflammation; musculoskeletal and joint disorders; pain.

Nadixa *Pfleger, Ger.; Galenica, Gr.; Galderma, Mex.†; Ferrer, Port.*
Nadifloxacin (p.303·2).
Acne.

Nadona *Medea, Spain.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Nadopen-V *Lioh, Canad.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Nadostine *Nadeau, Canad.†.*
Nystatin (p.543·2).
Candidiasis.

Nadrifor *Kleva, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Naeltjie-Olie *Lennon, S.Afr.*
Clove oil (p.2285·1).
Colic; toothache.

Naemis *Theramex, Ital.; Theramex, Mon.; Merck, Neth.; Theramex, Port.*
10 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; nomegestrol acetate (p.2119·1).
Menopausal disorders.

Naetene *Novartis, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Naf Buches *Naf, Arg.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Nafacil *Tecnofarma, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Nafarin *Medifarma, Indon.; UAP, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic disorders; cold symptoms; nasal congestion; sinusitis.

Nafarin A (Reformulated) *United American, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine (p.572·2) or chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Nafasol *Pharmacare, S.Afr.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Nafavine *Roemmers Osmoph, Venez.*
Sodium chloride (p.1686·1).
Nasal congestion.

Nafazair *Bausch & Lomb, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Minor eye irritation.

Nafazair A *Bausch & Lomb, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye irritation.

Nafazolex *Biosintex, Arg.*
⊗ Naphazoline (p.1565·1).
Nasal congestion.

Nafcon A *Alcon, Ital.†.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Conjunctivitis.

Nafin *Quim-Far, Venez.†.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Nafina *Giempi, Venez.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Nafiset *Pizzard, Mex.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; polydipsia; test of renal function.

Naflam *Collins, Mex.*
Nabumetone (p.91·2).
Musculoskeletal, joint, and soft-tissue disorders.

Naflapen *Collins, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Naflex *Seven Stars, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Nafloxin *Cooper (Κοπερ), Gr.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Nafluor *Naf, Arg.†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Nafluryl *Atlantis, Mex.*
Flunarizine (p.580·3).
Migraine; peripheral vascular disorders.

Nafluvent *Fada, Arg.*
⊗ Fentanyl (p.55·3).
Pain.

Nafordyl *Kleva, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Nafoxal *Sandoz, Indon.*
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders.

NaFril *Merckle, Ger.†.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Nafrine *Schering, Canad.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).

Naftate *Apex, Indon.*
Tolnaftate (p.548·3).
Fungal skin infections.

Naftazolina *Bruschettini, Ital.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye congestion; eye irritation.

Nafti *Alpharma-Isis, Ger.; CT, Ger.; Ratiopharm, Ger.; Sandoz, Ger.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral vascular disorders.

Naftilong *Hexal, Ger.; Sandoz, Hung.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral vascular disorders.

Naftilux *Therabel, Fr.*
Naftidrofuryl oxalate (p.1346·2).
Mental function impairment in the elderly; peripheral vascular and cerebrovascular disorders.

Naftin *Allergan, Canad.; Merz, USA; Merz, USA.*
Naftifine hydrochloride (p.542·3).
Fungal skin infections.

Naftodril *Arcana, Austria.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral and cerebral vascular disorders.

Nagel Batrafen *Aventis, Ger.*
Ciclopirox (p.529·2).
Fungal nail infections.

Nagelin *IAE, Philipp.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; coughs; nasal congestion.

Naglazyme *BioMarin, Cz.; BioMarin, Fr.; BioMarin, Port.; BioMarin, USA.*
Galsulfase (p.2308·1).
Mucopolysaccharidosis type VI.

Nagun *Dosa, Arg.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Nahrkraftquell Irocal *Weleda, S.Afr.†.*
Oats; hazelnut; malt; honey; saccharum levistici; siderit; conchae (p.1922·1).
Dietary supplement; tonic.

Nail Nutrition *Cantassium Co., UK.*
Multivitamins; minerals; amino acids (p.1922·1).

Nailderm *Gerard, Irl.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

4 Nails *Marlyn, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

NailVit *Pharmadass, UK.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Na-Iodina Compuesta *Pulmobronk, Venez.†.*
Sodium iodide (p.2169·2); vitamin B ; vitamin B (p.1922·1).

Nairet *Otto, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Nakaron *Vamsler, Philipp.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3); vitamin B ; vitamin B (p.1922·1).
Iron-deficiency anaemia.

Naklofen
KRKA, Cz.; KRKA, Rus.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
KRKA, Pol.
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naklofen Duo *KRKA, Rus.*
Diclofenac sodium (p.44·3).

Nakom *Lek, Cz.; Lek, Pol.; Lek, Rus.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Naksol *Human, Hung.†.*
Rose oil (p.2381·2).
Minor burns and skin injuries.

Nalabest *Best, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; ischaemic heart disease.

Nal-acid *Pharmanik (Φαρμανικ), Gr.†.*
Nalidixic acid (p.303·3).
For antisepsis of the genito-urinary tract.

Nalador *Schering, Austria; Schering, Fin.†; Schering, Fr.; Schering, Ger.; Schering, Hong Kong; Schering, Hung.†; Schering, Ital.; Schering, Neth.; Bayer, Port.; Schering, Switz.; Schering, Thai.*
Sulprostone (p.2018·1).
Facilitate intra-uterine manipulation; labour induction following fetal death; postpartum haemorrhage; termination of pregnancy.

Nalapres *Mediolanum, Ital.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Nalapril *Klonal, Arg.*
Enalapril (p.1276·1).
Hypertension.

Nalaprix *Royton, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Nalator *Plus, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Nalbix *Azevedos, Port.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Nalcrom *Aventis, Canad.; Italchimici, Cz.; IFET (ΙΦΕΤ), Gr.; Aventis, Irl.; Italchimici, Ital.; Douglas, NZ; Aventis, Neth.; Rhone-Poulenc Rorer, Pol.; Aventis, Switz.; Sanofi-Aventis, UK.*
Sodium cromoglicate (p.1136·3).
Food allergy; inflammatory bowel disease.

Nalcron *Sanofi-Aventis, Fr.†.*
Sodium cromoglicate (p.1136·3).
Food hypersensitivity.

Nalcryn *Cryopharma, Mex.*
Nalbuphine (p.92·2).
Pain.

Naldec *IAE, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Naldecol NF
Note. This name is used for preparations of different composition.
BMS, Chile.
Oral drops; syrup: Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms.
BMS, Chile.
Tablets: Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms.

Naldecol-D *BMS, Chile†.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).

Naldecon
Note. This name is used for preparations of different composition.
BMS, Braz.
Oral solution: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2).
BMS, Braz.
Tablets: Yellow tablets, paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); orange tablets, paracetamol; carbinoxamine maleate (p.570·2).

Naldecon Pediatrico *BMS, Braz.*
Paracetamol (p.108·1); carbinoxamine maleate (p.570·2).

Naldecon Senior EX *Sandoz, USA.*
Guaifenesin (p.1561·3).
Coughs and cold symptoms.

Nalecol *Casasco, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Nalergine *BMS, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Nalerona *Silesia, Chile.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal.

Naletal *Guardian, Indon.*
Cilostazol (p.1245·2).
Arterial occlusion; intermittent claudication.

Nalex *Blansett, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Nalex AC *Great Southern, USA.*
Brompheniramine maleate (p.569·2); codeine phosphate (p.37·2).
Upper respiratory-tract disorders.

Nalex DH *Blansett, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).

Nalex Expectorant *Blansett, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Nalex-A *Blansett, USA.*
Chlorphenamine maleate (p.571·3); phenyltoloxamine citrate (p.588·1); phenylephrine hydrochloride (p.1568·1).

Nalex-A 12 *Blansett, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract disorders.

Nalfon *Lilly, Canad.†; Lilly, Denm.†; Lilly, Mex.†; Pedinol, USA.*
Fenoprofen calcium (p.55·2).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Nalgesic
Note. This name is used for preparations of different composition.
Hexa, Arg.
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.
Sciencex, Fr.
Fenoprofen calcium (p.55·2).
Pain.

Nalgesin *KRKA, Cz.; KRKA, Rus.*
Naproxen sodium (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Nalgestan *Medifarma, Indon.; UAP, Indon.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Nasal congestion; rhinitis; sinusitis.

Nalgiflex *Ronnet, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Nalgiflex Relax *Ronnet, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Nalidin *TAD, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Nalidix *Lacefa, Arg.†.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Nalidixin *NCSN, Ital.†.*
Nalidixic acid (p.303·3).
Gram-negative genito-urinary tract infections.

Naligram *Geymonat, Ital.†.*
Nalidixic acid (p.303·3).
Gram-negative genito-urinary tract infections.

Naline *Pharmaland, Thai.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders.

Nalion
Note. This name is used for preparations of different composition.
Medochemie, Hong Kong.
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.
Sandoz, Spain.
Norfloxacin (p.309·2).
Bacterial infections.

Nalix *Reuffer, Mex.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Nalixone *Sons, Mex.*
Nalidixic acid (p.303·3); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections and pain.

Nalle *Ativus, Braz.*
Vitex agnus castus (p.2249·1).
Menopausal disorders.

Nalone
Note. This name is used for preparations of different composition.
Hexal, Austria†.
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome.
SERB, Fr.†.
Naloxone hydrochloride (p.1453·2).
Diagnosis of opioid dependence; diagnosis of toxic coma; opioid overdosage; opioid-induced respiratory depression.

Nalopril *Siam Bheasach, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Nalorex *BMS, Belg.; Schering-Plough, Fr.; Vianex (Βιανέξ), Gr.; BMS, Irl.; BMS, Ital.; BMS, Neth.; BMS, Port.; BMS, UK.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal.

Naloselect *DeltaSelect, Ger.†.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; opioid-induced respiratory depression.

Nalox *Omega, Arg.*
Metronidazole (p.837·1).
Bacterial infections; trichomoniasis.

Naloxon *Warsaw-Polfa, Rus.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Naltrexin *Orpha-Devel, Austria; Opopharma, Switz.*
Naltrexone hydrochloride (p.1455·2).
Opioid overdosage; opioid withdrawal.

Naltrox *Richmond, Arg.*
Nalbuphine (p.92·2).
Pain.

Naluril *Cazi, Braz.*
Nalidixic acid (p.303·3).
Bacterial infections.

Nalvir *Richmond, Arg.*
Nelfinavir (p.899·1).
HIV infection.

Namedia *Pharmasant, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

Namenda *Forest Laboratories, USA.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Nametone *Pharmasant, Thai.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Namic *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.*
Mefenamic acid (p.80·1).
Fever; pain.

Namifen *Novag, Mex.*
Mefenamic acid (p.80·1).
Pain.

Namir *Duncan, Arg.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Nan *Nestle, Braz.*
A range of infant feeds (p.1922·1).

Nan AR *Nestle, Arg.; Nestle, Mex.; Nestle, Venez.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Nan HA *Nestle, Arg.; Nestle, Hong Kong; Nestle, Indon.; Nestle, Malaysia; Nestle, Mex.; Nestle, Port.; Nestle, Singapore†; Nestle, Thai.*
Infant feed (p.1922·1).
Allergic disorders; cow's milk allergy; soya allergy.

Nan HA with Protect Start *Nestle, Philipp.*
Hypoallergenic infant feed (p.1922·1).

Nan HA/AR *Nestle, Port.†.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Nan Lactose Free *Nestle, Indon.; Nestle, Thai.*
Infant feed (p.1922·1).
Diarrhoea; infant colic; lactose intolerance.

Nan sin Lactosa *Nestle, Arg.; Nestle, Mex.; Nestle, Venez.*
Infant feed (p.1922·1).
Gastro-enteritis; lactose intolerance.

Nan Soy *Nestle, Thai.; Nestle, Venez.*
Infant feed (p.1922·1).
Diarrhoea; galactosaemia; lactose intolerance.

Nan Soya *Nestle, Arg.†; Nestle, Mex.*
Infant feed (p.1922·1).
Cow's milk allergy; lactose intolerance.

Nanafed *PD, Thai.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Nanalan *Merck, Austria.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Nanalan Plus *Merck, Austria.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Nandain *Ciba Vision, Port.†.*
⊗ Nandrolone sodium sulfate (p.2118·3).
Corneal disorders.

Nandrosande *Sanderson, Chile.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic.

Nani Pre Dental *Alter, Spain.*
Benzocaine (p.1854·1).
Formerly contained saffron, guaiazulene, lidocaine hydrochloride, myrrh, and menthol.
Toothache.

Naniprus *Pharmachim, Rus.*
Sodium nitroprusside (p.1397·1).

Nano-Albumon *Medi-Radiopharma, Cz.*
⊗ Technetium-99m (p.2055·3) labelled human albumin macroaggregate.
Imaging of bone marrow and lymphatic system.

Nanocis *CIS, Cz.*
Rhenium-186 (p.2055·2) colloidal sulfide.
Imaging of the lymphatic system.

Nanocoll *GE, Cz.; GE, Port.; Nycomed Amersham, UK.*
⊗ Technetium-99m (p.2055·3) labelled albumin colloid.
Imaging of bone marrow and lymphatic system; scanning for inflammation.

Nanogam *Sanquin, Fin.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki syndrome; passive immunisation.

Nanotiv *Octapharma, Port.; Octapharma, Spain; Octapharma, Swed.*
A factor IX preparation (p.1068·3).
Haemophilia B; haemorrhagic disorders.

Nantarid *Gedeon Richter, Cz.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Naofid *Velka, Gr.*
Nimesulide (p.95·3).

Naox *Eurofarma, Braz.*
Oxytocin (p.2015·2).

Napa *Beximco, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Napacod *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Napamide *Douglas, Austral.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore; Douglas, Thai.; TTN, Thai.*
⊗ Indapamide (p.1314·1).
Hypertension.

Napamol *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Napan *DHA, Hong Kong; DHA, Malaysia.*
Mefenamic acid (p.80·1).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Napflam *Aspen, S.Afr.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Napha A *CCM, Malaysia.*
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2).
Eye irritation.

Napha Forte *Medical Ophthalmics, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).

Naphacel *Sophia, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2); hypromellose (p.2144·2).
Eye irritation.

Naphasal *Sam-On, Israel.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion; rhinitis; sinusitis.

Naphazoline Plus *Parmed, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Minor eye irritation.

Naphcon *Alcon, Austral.; Alcon, Belg.; Pharmex (Φαρμεξ), Gr.; Alcon, Hung.†; Alcon, NZ; Alcon, Thai.; Alcon, USA; Alcon, Venez.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye congestion; eye irritation.

Naphcon Forte *Alcon, Canad.; Alcon, Israel.*
⊗ Naphazoline hydrochloride (p.1565·2).
Conjunctivitis; eye congestion; eye irritation; nasal congestion.

Naphcon-A *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Hong Kong; Alcon, Indon.; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, Singapore; Alcon, Thai.; Alcon, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic and inflammatory eye disorders; eye irritation.

Naphensyl *Adcock Ingram, S.Afr.*
Phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Naphoptic-A *Optopics, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye irritation.

Naphtears
Note. This name is used for preparations of different composition.
Alcon, Chile.
⊗ Naphazoline hydrochloride (p.1565·2); dextran 70 (p.1059·3).
Eye disorders.

Alcon, Mex.
⊗ Naphazoline hydrochloride (p.1565·2); hypromellose (p.2144·2) and dextran 70 (Duasorb) (p.1059·3).
Allergic conjunctivitis; dry eyes; eye irritation.

Naphthyzin *Synthesis, Rus.†.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Napilene *Chinta, Thai.*
Benzalkonium chloride (p.1629·1); cetrimide (p.1634·1).
Minor burns and wounds; napkin rash.

Napitol *ICM, Singapore†.*
Cetrimide (p.1634·1); benzalkonium chloride (p.1629·1).
Minor burns and wounds; nappy rash.

Naplin *Pacific, NZ†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Napmel *PannonPharma, Hung.; Clonmel, Irl.†.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Napolit *Biomedica-Chemica, Gr.†.*
⊗ Carteolol (p.1241·2).
Glaucoma.

Naponal *Munir, Turk.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Napox *Drovepat, Venez.†.*
Ketoconazole (p.539·1).
Fungal skin infections; seborrhoeic dermatitis.

Napoxol *Ultra, Mex.*
Naproxen (p.92·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nappy Rash Relief Cream *Brauer, Austral.*
Calendula (p.2273·1); clematis recta; St John's wort (p.422·3); chamomile (p.2279·3); mezereum.
Nappy rash.

Nappy-Hippo *Sriprasit, Thai.*
Zinc oxide (p.1621·2).
Nappy rash.

Nappy-Mate *Ethicare, Austral.†.*
Aluminium chlorohydrate (p.1588·3); zinc oxide (p.1621·2); benzoin tincture (p.2394·2); silicone (p.2032·1).
Nappy rash.

Napradol *Abfar, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Napratec *Pharmacia, UK.*
Naproxen (p.92·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Napreben *Fulton, Ital.†.*
Naproxen betainate sodium (p.93·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Naprel *Brunel, S.Afr.†.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Naprelan *Elan, Neth.; OEP, Philipp.; Victory, USA.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Napren
Nycomed, Norw.
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Ilsan, Turk.
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Naprex
Note. This name is used for preparations of different composition.
Medifarma, Indon.; Pediatrica, Indon.; Pediatrica, Malaysia†; Pediatrica, Philipp.; Pediatrica, Singapore.
Paracetamol (p.108·1).
Fever; pain.

Pinewood, Irl.†.
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Naprilate *Taiwan Biotech, Philipp.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Naprilene *Sigma-Tau, Ital.; Sigma-Tau, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Naprius *Aesculapius, Ital.*
Naproxen (p.92·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Naprix *Libbs, Braz.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; primary prophylaxis of atherosclerotic complications.

Naprix A *Libbs, Braz.*
Ramipril (p.1385·3); amlodipine besilate (p.1214·1).
Hypertension.

Naprix D *Libbs, Braz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Naprizide *Taro, Israel.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Naprobene *Ratiopharm, Austria; Merckle, Cz.†.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; musculoskeletal, joint, and peri-articular disorders; pain.

Naprocet *Boniscontro & Gazzone, Ital.; Tecnifar, Port.*
Naproxen cetrimonium (p.93·3).
Mouth and throat disorders; vaginal infections.

Naprocoat *Roche, Neth.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders.

Naprodeva *Deva, Turk.*
Naproxen (p.92·3).
Musculoskeletal and joint pain.

Naprodil *Diba, Mex.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naprodil Plus *Diba, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Naprofidex *Fidex, Arg.*
Naproxen (p.92·3).
Inflammation; pain.

Naproflam *Socobom, Belg.*
Naproxen (p.92·3).

Naproflex *Pharmasant, Thai.*
Naproxen sodium (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Naprogen *Klonal, Arg.*
Naproxen (p.92·3).
Fever; pain.

Naprogesic *Bayer Consumer, Austral.; Bayer, Chile; Bayer, NZ.*
Naproxen sodium (p.92·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Naprometin *Roche, Fin.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Napromex *Ratiopharm, Fin.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Napronax *Neo Quimica, Braz.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Naprontag *Rontag, Arg.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naprontag Flex *Rontag, Arg.*
Naproxen (p.92·3); carisoprodol (p.1894·1).
Inflammation; musculoskeletal spasm.

Naprorex
Aegis, Hong Kong.
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Lampugnani, Ital.†.
Naproxen sodium (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Naproscript *Ranbaxy, S.Afr.†.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Naprosian *Asian Pharm, Thai.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Naprosyn
Roche, Austral.; Roche, Canad.; KRKA, Cz.†; Roche, Denm.; Roche, Fin.†; Minerva (Μινερβα), Gr.; Roche, Hong Kong; Valeant, Hung.; RPG, India; Roche, Irl.; Recordati, Ital.; Roche, NZ; Roche, Norw.; Roche, Philipp.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, Switz.†; Roche, Thai.; Abdi, Turk.; Roche, UK; Roche, USA.
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Roche, Braz.
Naproxen sodium (p.92·3).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Roche, S.Afr.†.
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and soft-tissue disorders.

Naprosyne *Roche, Belg.; Grunenthal, Fr.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Naprotab *Sanli, Turk.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Naproval *Reig Jofre, Spain.*
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Naprovite *Roche, Neth.*
Naproxen sodium (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Naprox *Teuto, Braz.*
Naproxen (p.92·3).
Inflammation; pain.

Naproxi *Gerard, Israel.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders; pain.

Naprux *Andromaco, Arg.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Napsen *Sriprasit, Thai.†.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Napsyn *ICN, Cz.†.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Napxen *APT, Hong Kong; Berlin Pharm, Thai.†.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Naqua
Note. This name is used for preparations of different composition.
CNW, Hong Kong; Bial, Port.
⊗ Furosemide (p.1292·1).
Forced diuresis; hypertension; nephrotic syndrome; oedema; renal failure.

Schering, USA†.
⊗ Trichlormethiazide (p.1418·3).
Hypertension; oedema.

Naquinto *Makros, Braz.†.*
Sodium dibunate (p.1573·1); homatropine (p.1881·2); bromoform (p.2269·3).
Coughs.

Naragran *GSK, Denm.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Naramig *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Fin.; GSK, Fr.; GSK, Ger.; Schwarz, Ger.; GSK, Gr.; GSK, Hung.†; GSK, Israel; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.†; GSK, Turk.; GSK, UK.*
Naratriptan hydrochloride (p.623·3).
Migraine.

Naranocor H *Pfluger, Ger.*
Homoeopathic preparation.

Naranocut H *Pfluger, Ger.†.*
Homoeopathic preparation.

Naranofem *Pfluger, Ger.*
Homoeopathic preparation.

Naranopect P *Pfluger, Ger.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Naranotox *Pfluger, Ger.*
Homoeopathic preparation.

Naranotox Plus *Pfluger, Ger.*
Homoeopathic preparation.

Narapril *Julphar, UAE.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Narbalek *Genopharm, Fr.*
Vitamin B substances, iron, and mineral preparation (p.1922·1).
Tonic.

Narben *Wala, Ger.*
Homoeopathic preparation.

Narbon *Buxton, Arg.*
Hydroxychloroquine sulfate (p.604·2).
Juvenile arthritis; rheumatoid arthritis; systemic lupus erythematosus.

Narcan *Reckitt Benckiser, Austral.; BMS, Belg.†; Cristalia, Braz.; BMS, Canad.†; SERB, Fr.†; IFET (ΙΦΕΤ), Gr.; Boots, Hong Kong†; Du Pont, Hong Kong†; BMS, Irl.; BMS, Israel†; Sirton, Ital.; BMS, Malaysia†; AFT, NZ; Vitoria, Port.†; Sanofi Synthelabo, S.Afr.†; BMS, Singapore†; BMS, Switz.; BMS, Thai.; BMS, UK†; Endo, USA†; BMS, Venez.*
Naloxone hydrochloride (p.1453·2).
Diagnosis of opioid dependence; diagnosis of toxic coma; opioid overdosage; opioid-induced respiratory depression; reversal of opioid depression.

Narcanti *AstraZeneca, Arg.; Torrex, Austria; BMS, Cz.†; Du Pont, Cz.†; BMS, Denm.; BMS, Fin.; BMS, Ger.; Torrex, Hung.†; Aventis, Mex.†; BMS, Norw.; BMS, Swed.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Narcaricin *Heumann, Ger.†; Ludwig, Singapore†; Heumann, Thai.†.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia; renal calculi.

Narcaricina *Sinterapico, Braz.†.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia.

Narcof *Cypress, USA.*
Guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Cough.

Narcoral *Sirton, Ital.*
Naltrexone hydrochloride (p.1455·2).
Opioid overdosage; opioid withdrawal.

Narcotan
Note. This name is used for preparations of different composition.
Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.
Halothane (p.1784·2).
General anaesthesia.

Troikaa, India.
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Narcotuss *Legrand, Braz.*
Guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Respiratory-tract disorders.

Narcozep *Roche, Fr.*
Flunitrazepam (p.996·2).
General anaesthesia; premedication.

Nardelzine *Pfizer, Belg.*
Phenelzine sulfate (p.415·2).
Depression.

Nardil *Link, Austral.; Erfa, Canad.; Hansam, Irl.; Link, NZ; Concord, UK; Parke, Davis, USA.*
Phenelzine sulfate (p.415·2).
Depression; mixed anxiety depressive states; phobic states.

Nardyl *Vifor, Switz.*
Promethazine hydrochloride (p.588·2); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1).
Anxiety; nervous disorders; sleep disorders; tension.

Narebox *Zydus, India.*
Reboxetine (p.421·2).
Depression.

Narfen *Alter, Spain.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Narfoz *Pharos, Indon.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Narhinel *Novartis Consumer, Ital.*
Sodium chloride (p.1686·1).
Nasal hygiene.

Narial *Sinterapico, Braz.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Naribel *Sanofi Synthelabo, Ital.†.*
Sodium chloride (p.1686·1).
Nasal disorders.

Naridrin *EMS, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); mepyramine maleate (p.585·2); dexpanthenol (p.2362·1).
Nasal congestion.

Nariflux *Cifarma, Braz.*
⊗ Dexpanthenol (p.2362·1); naphazoline hydrochloride (p.1565·2); mepyramine maleate (p.585·2).
Nasal congestion.

Narifont *Rappai, Switz.*
Electrolytes (p.1667·1).
Nasal dryness; nasal irrigation.

Narifresh *Rappai, Switz.*
Sea salt (p.1686·1); chamomile (p.2279·3).
Nasal disorders.

Narigen *Vocate, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Narine *Schering-Plough, Spain.*
Pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Allergic rhinitis.

Narisoro *Legrand, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Naristar *UCB, Ital.; UCB, Spain†.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Conjunctivitis; rhinitis.

Naritec *TO-Chemicals, Thai.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Narium *Hamilton, Austral.; Hamilton, NZ.*
Sodium chloride (p.1686·1).
Nasal irritation and inflammation.

Narix *Cimed, Braz.*
⊗ Naphazoline (p.1565·1).
Nasal congestion.

Narixan *Wassermann, Ital.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Rhinitis; upper respiratory-tract congestion.

Nariz
Note. This name is used for preparations of different composition.
Tempo Scan Pacific, Indon.
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Hawthorn, USA.
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Nariz HC *Hawthorn, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); hydrocodone tartrate (p.63·1).
Cough.

Narizima *Baldacci, Port.*
Muramidase hydrochloride (p.2348·1); thonzylamine hydrochloride (p.592·1); isobenzidrine iodide.
Rhinitis; sinusitis.

Narizine *Beacons, Singapore†.*
Flunarizine hydrochloride (p.580·2).
Epilepsy; migraine; peripheral vascular disorders; vestibular disorders.

Narkamon *Spofa, Cz.*
Ketamine hydrochloride (p.1787·1).
Bronchospasm; general anaesthesia; pain.

Narlisim *Baldacci, Ital.*
⊗ Muramidase hydrochloride (p.2348·1); phenolpropamine iodide; thonzylamine hydrochloride (p.592·1).
Nasal congestion.

Narobic *Alliance, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Narocin *Teva, Israel.*
Naproxen sodium (p.92·3).
Fever; musculoskeletal and joint disorders; pain.

Narol *Minerva (Μινέρβα), Gr.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Narop *AstraZeneca, Israel; AstraZeneca, Swed.*
Ropivacaine hydrochloride (p.1870·3).
Local anaesthesia; pain.

Naropeine *AstraZeneca, Fr.; Cana, Gr.; AstraZeneca, Port.*
Ropivacaine hydrochloride (p.1870·3).
Local anaesthesia.

Naropin *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Thai.†; AstraZeneca, Turk.; AstraZeneca, UK; Astra, USA; AstraZeneca, Venez.†.*
Ropivacaine hydrochloride (p.1870·3).
Local anaesthesia; pain.

Naropin with Fentanyl *AstraZeneca, Austral.; AstraZeneca, NZ.*
⊗ Ropivacaine hydrochloride (p.1870·3); fentanyl citrate (p.55·3).
Epidural analgesia.

Naropina *AstraZeneca, Ital.*
Ropivacaine hydrochloride (p.1870·3).
Epidural anaesthesia; local anaesthesia; pain.

Nartap *Condrugs, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; rhinitis; upper respiratory-tract congestion.

Narvizol *Narval, Spain†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Narvox *Vindex, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Narxona *Scott-Cassara, Arg.*
Naloxone (p.1454·1).

Narzen *Shiwa, Thai.†.*
Naproxen (p.92·3).
Musculoskeletal and joint disorders.

Nas *Oftalmi, Venez.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Nasa *Millimed, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Nasa Rhinathiol *Sanofi-Aventis, Belg.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasa W/ Codeine *Millimed, Thai.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Nasabid *Jones, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Cough; nasal congestion.

Nasaclear *Pacific, NZ.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Nasacor *Aventis, S.Afr.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Nasacort *Aventis, Arg.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Aventis, Mex.; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Singapore; Italfarmaco, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Nasacort AQ *Sanofi-Aventis, Malaysia.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Nasadec *Medlink, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion; sinusitis.

Nasafed *Medikon, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic disorders; cold symptoms; sinusitis.

Nasafed Plus *Medikon, Indon.*
Triprolidine (p.593·1); paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Cold and influenza symptoms; nasopharyngitis; sinusitis.

Nasaflam *Fahrenheit, Indon.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Nasair *Oftalmi, Venez.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

NaSal *Sterling Health, USA.*
Sodium chloride (p.1686·1).
Nasal congestion.

Nasal Decongestant *Prodemdis, Canad.*
⊗ Xylometazoline hydrochloride (p.1575·1).

Nasal Jelly
Note. This name is used for preparations of different composition.
Thuna, Canad.†.
⊗ Ephedrine hydrochloride (p.1558·2); methyl salicylate (p.85·3); thymol (p.1664·3).

Kondon, USA.
Phenol (p.1656·1); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); lavender oil (p.2331·2).
Nasal congestion.

Nasal Moist *Blairex, USA.*
Sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Nasal Physiologic Solution *Prodemdis, Canad.*
Sodium chloride (p.1686·1).

Nasal Physiological Solution *Confab, Hong Kong.*
Sodium chloride (p.1686·1).
Nasal hygiene.

Nasal Relief *Rugby, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nasal & Sinus Cold Formula *Stanley, Canad.†.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Nasal & Sinus Relief *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2).

Nasal Spray *Reese, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).

Nasalate *Paedpharm, Austral.*
Chlorhexidine (p.1635·2); phenylephrine hydrochloride (p.1568·1).
Epistaxis; nasal surgery; nasal vestibulitis.

Nasal-Bec *Ivax, UK†.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Nasalcrom *Pharmacia, USA.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Nasal-Ease
Note. This name is used for preparations of different composition.
Health Care Products, USA.
Nasal gel: Zinc acetate (p.1999·1); aloe vera (p.1588·2); calendula (p.2273·1).
Inflammation and dryness of nasal membranes.

Health Care Products, USA.
Nasal spray: Zinc gluconate (p.1999·2); sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Nasalex *Fabop, Arg.*
⊗ Naphazoline (p.1565·1).
Nasal congestion.

Nasaleze *Cedar Health, UK.*
Cellulose (p.2143·1).
Allergic rhinitis.

Nasalflu *Berna, Switz.†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Nasalide *Ivax, Fr.; Ivax, USA†.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis.

Nasaliv *Uniao Quimica, Braz.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); carbinoxamine maleate (p.570·2).
Influenza symptoms.

Nasalub *Quimica y Farmacia, Mex.*
Sodium chloride (p.1686·1); glycerol (p.2314·2).
Nasal dryness.

Nasamet *Verisfield, Gr.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis.

Nasamex *Konimex, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms; sinusitis.

Nasamine *Maxi, Thai.†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Nasamol *Nicholas, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Nasan *Hexal, Ger.; Sandoz, Hung.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Nasanal *Brady, Austria.*
Aluminium acetotartrate (p.2255·1); pumilio pine oil (p.2376·3).
Nasal disorders.

Nasaphen *Prohealth, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Nasarel
Note. This name is used for preparations of different composition.
Dabur, India.
⊗ Nafarelin acetate (p.2117·3).
Endometriosis; pituitary desensitisation in controlled ovarian stimulation.

Ivax, USA.
⊗ Flunisolide (p.1531·1).
Rhinitis.

Nasarox *Plough, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nasasinutab *Pfizer Consumer, Belg.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasatab LA *ECR, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Nasatapp *Prohealth, Philipp.*
Brompheniramine maleate (p.569·2); phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Nasathera *Morishita, Philipp.*
Paracetamol (p.108·1); phenylpropanolamine (p.1569·2) or phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; nasal congestion.

Nasathera P *Morishita, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Nasatrim *Verisfield, Gr.*
⊗ Triamcinolone (p.1544·2).
Allergic rhinitis.

Nasben *Democal, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasciodine *Pharmadass, UK.*
Iodine (p.2169·2); menthol (p.2340·1); methyl salicylate (p.85·3); turpentine oil (p.2406·3); rectified camphor oil (p.2273·3).
Musculoskeletal, joint, and soft-tissue disorders.

Nascobal *Nastech, Israel; Questcor, USA.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Nasdro *Adcock Ingram, S.Afr.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline nitrate (p.1565·2).
Nasal congestion.

Nasea *Astellas, Indon.; Astellas, Jpn; Astellas, Philipp.; Astellas, Thai.*
Ramosetron hydrochloride (p.1765·3).
Nausea and vomiting induced by cytotoxic chemotherapy.

Naselin *Cipla, India.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nasen *Polfarmex, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Nasenbalsam *Wala, Ger.*
Peru balsam (p.2365·3); berberis vulgaris; cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); blackthorn (p.2267·2); colloidal silica.
Nasal congestion.

Nasenbalsam fur Kinder *Wala, Ger.*
Peru balsam (p.2365·3); berberis vulgaris; blackthorn (p.2267·2); colloidal silica.
Nasal congestion.

Nasengel *Ratiopharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Catarrh; nasal congestion; sinusitis.

Nasengel AL *Aliud, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Nasenspray *Sandoz, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasenspray AL *Aliud, Cz.; Aliud, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Nasenspray E *Ratiopharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Catarrh; nasal congestion; sinusitis.

Nasenspray K *Ratiopharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Catarrh; nasal congestion; sinusitis.

NasenSpray Panthenol *Ratiopharm, Ger.*
Dexpanthenol (p.2362·1).
Nasal congestion.

Nasenspray-CT *CT, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasentropfen AL *Aliud, Cz.; Aliud, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Nasentropfen E *Ratiopharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasentropfen K *Ratiopharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasentropfen Stada *Stada, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nasentropfen-ratiopharm *Ratiopharm, Ger.†.*
Pine needle oil (p.2368·2); peppermint oil (p.1761·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); thymol (p.1664·3).
Cold symptoms; nasal congestion.

Naseptin *Alliance, Irl.; Bartlett, S.Afr.; Alliance, UK.*
Chlorhexidine hydrochloride (p.1635·3); neomycin sulfate (p.305·1).
Nasal carriage of staphylococci; staphylococcal infections.

Nasex
Note. This name is used for preparations of different composition.
Felton, Austral.
⊗ Oxymetazoline hydrochloride (p.1567·2); cineole (p.2282·3); menthol (p.2340·1).
Nasal congestion.

Janssen-Cilag, Port.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

DP-Medica, Switz.†.
Phenylephrine hydrochloride (p.1568·1); cetylpyridinium chloride (p.1635·1).
Nasal disorders.

Cypress, USA†.
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Nasic *Artesan, Ger.; Cassella-med, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1); dexpanthenol (p.2362·1).
Nasal congestion.

Nasic-cur *Artesan, Ger.; Cassella-med, Ger.*
Dexpanthenol (p.2362·1).
Formerly known as Nasicur.
Rhinitis sicca.

Nasilex *Pediapharm, Chile.*
Pseudoephedrine hydrochloride (p.1571·2) or pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms; hypersensitivity reactions.

Nasin *AstraZeneca, Swed.; Leti, Venez.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinitis; sinusitis.

Nasiral *Istanbul, Turk.*
Salicylic acid (p.1612·2).
Calluses.

Nasivin
Note. This name is used for preparations of different composition.
Merck, Austria; Merck, Braz.; Merck, Cz.; Merck, Ger.; Merck, Hung.; Merck, Israel†; Chugai, Jpn; Merck, Neth.; Merck, Philipp.; Merck, Pol.; Merck, Rus.; Julphar, UAE; Seven Seas, UK.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; cold symptoms; Eustachian tube congestion; nasal congestion; ocular congestion; otitis media; rhinitis; sinusitis.

Merck, Chile.
Sodium chloride (p.1686·1); glycerol (p.2314·2).
Nasal congestion; nasal hygiene.

Nasivin gegen Schnupfen *Merck, Ger.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; otitis media; rhinitis; sinusitis.

Nasivin Sanft *Merck, Ger.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; nasal congestion; otitis media; rhinitis; sinusitis.

Nasivine *Iromedica, Switz.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; rhinitis; sinusitis.

Nasivinetten gegen Schnupfen *Merck, Ger.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; otitis media; rhinitis; sinusitis.

Nasivinettes *Asta Medica, Switz.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; rhinitis; sinusitis.

Nasivion *Merck, India.*
⊗ Oxymetazoline (p.1567·2) or oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

nasmer *Vifor, Switz.*
Dead Sea salt (p.1686·1).
Nasal disorders.

Naso *Ratiopharm, Norw.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

Naso Pekamin *Medical, Spain.*
Phenylephrine hydrochloride (p.1568·1); kanamycin sulfate (p.291·2); trypsin (p.2405·3).
Nose and throat disorders.

Nasobec *Ivax, Cz.; Ivax, Hong Kong; Ivax, Irl.; Norton, Pol.; Galena, Rus.; Ivax, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Nasobol *Sanofi, Switz.†.*
Benzoic acid (p.1630·2); peru balsam (p.2365·3); verbena oil; eucalyptus oil (p.2301·2); lavender oil (p.2331·2); wild thyme oil (p.2415·3).
Respiratory-tract disorders.

Nasobol N *Sanofi, Switz.*
Cineole (p.2282·3); menthol (p.2340·1); rosemary oil (p.2381·3); thyme oil (p.2401·2).
Respiratory-tract disorders.

Nasobol Xylo *Sanofi, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; sinusitis.

Naso-Calma *Salusif, Port.†.*
⊗ Ephedrine hydrochloride (p.1558·2); silver protein (p.2387·3).
Cold and influenza symptoms.

Nasocan *Protein, Mex.†.*
Naproxen sodium (p.92·3).
Inflammation.

Nasoclean *Terme di Tabiano, Ital.*
Thermal water.
Nasal cleansing.

Nasocort *Teva, Israel.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Nasofan *Ivax, Cz.; Ivax, Irl.; Ivax, UK.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Nasofed *Hawthorn, USA.*
Pseudoephedrine tannate (p.1572·1).
Nasal congestion.

Nasofelin *Neo Quimica, Braz.*
⊗ Fenoxazoline hydrochloride (p.1560·3).
Nasal congestion.

Nasoferm *Nordic, Swed.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

Nasogrip *Cazi, Braz.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); mepyramine maleate (p.585·2); caffeine (p.1116·3).
Cold and influenza symptoms.

Nasohist *Hawthorn, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Nasohist-DM *Hawthorn, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; cold symptoms.

Nasojol *Geminis, Arg.†.*
⊗ Naphazoline (p.1565·1); neomycin (p.305·1).
Nasal congestion.

Naso-Josp *Josper, Braz.†.*
⊗ Naphazoline (p.1565·1); diphenhydramine (p.577·1).

Nasolac *Hebron, Braz.†.*
Sodium chloride (p.1686·1).
Nasal congestion.

Nasolin
Note. This name is used for preparations of different composition.
Cifarma, Braz.
Sodium chloride (p.1686·1); benzalkonium chloride (p.1629·1).
Nasal disorders.

Orion, Fin.
⊗ Xylometazoline hydrochloride (p.1575·1).
Allergic rhinitis.

TNP, Thai.†.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Nasolina *Salvat, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nasolver *Mintlab, Chile.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
No indications.

Nasomet *Schering-Plough, Port.*
⊗ Mometasone furoate (p.1539·3).
Nasal polyps; rhinitis.

Nasomicina *Northia, Arg.*
⊗ Naphazoline (p.1565·1); neomycin (p.305·1); gramicidin (p.286·1).
Nasal disorders.

Nasomicina Salina *Northia, Arg.†.*
Sodium chloride (p.1686·1).
Nasal congestion.

Nasomin *Medipharm, Chile.*
⊗ Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); xylometazoline hydrochloride (p.1575·1); antazoline phosphate (p.567·1).
Upper respiratory-tract disorders.

Nasomixin
Note. This name is used for preparations of different composition.
Teofarma, Ital.
⊗ Phenylpropanolamine hydrochloride (p.1569·3); hydrocortisone (p.1535·2).
Cold symptoms; rhinitis; sinusitis.

Aventis, S.Afr.†.
⊗ Phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3); hydrocortisone (p.1535·2); neomycin sulfate (p.305·1).
Rhinitis; sinusitis.

Nasonex *Schering-Plough, Arg.; Schering-Plough, Austral.; Aesca, Austria; Schering-Plough, Belg.; Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; nasal polyps; sinusitis.

Nasop *Hawthorn, USA.*
Phenylephrine hydrochloride (p.1568·1) or phenylephrine tannate (p.1568·3).
Nasal congestion.

Nasopax *Meditop, Hung.*
⊗ Bromhexine hydrochloride (p.1552·2); oxymetazoline hydrochloride (p.1567·2).
Influenza symptoms; rhinitis; sinusitis.

Nasopomada *Medical, Spain.*
⊗ Bismuth subgallate (p.1711·1); prednisolone (p.1540·3); rutoside (p.2305·1); sulfanilamide (p.343·1); tetracycline hydrochloride (p.347·2); urea; benzocaine (p.1854·1).
Nasal polyps; sinusitis.

Naso-Prieulina *Medical, Port.†.*
⊗ Naphazoline hydrochloride (p.1565·2); ephedrine hydrochloride (p.1558·2); mepyramine maleate (p.585·2).
Rhinitis; sinusitis.

Naso-Ratiopharm *Ratiopharm, Fin.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Nasorest
Note. This name is used for preparations of different composition.
Community Pharmacy, Thai.†.
Expectorant: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); bromhexine hydrochloride (p.1552·2).
Coughs; respiratory-tract disorders.

Community Pharmacy, Thai.†.
Syrup; tablets: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Nasorhinathiol *Sanofi-Aventis, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Naspor *Genepharm, Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Naspro *Nicholas, Indon.*
Aspirin (p.20·3).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) are included in Naspro Forte in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Nasterid *Ativus, Braz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Nasterid A *Ativus, Braz.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Nasteril *Asofarma, Arg.*
⊗ Finasteride (p.2188·3).
Prostate disorders.

Nasterol *Nolver, Venez.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Nastifrin *Laboratorios Chile, Chile.*
Chlorphenamine maleate (p.571·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract disorders.

Nastifrin Compuesto *Laboratorios Chile, Chile.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms.

Nastifrin DN Compuesto *Laboratorios Chile, Chile.*
Day tablets, paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Nastil *Best, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Nastilox *Pharmaten (Φαρματεν), Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Nastizol
Note. This name is used for preparations of different composition.
Bago, Chile.
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Rhinitis; upper respiratory-tract disorders.

Bago, Arg.
Nose drops: ⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Bago, Arg.
Oral drops; syrup; tablets: Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Nasal congestion.

Nastizol Antialergico *Bago, Arg.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Nastizol Compositum
Note. This name is used for preparations of different composition.
Bago, Arg.
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3); bromhexine hydrochloride (p.1552·2); paracetamol (p.108·1).
Influenza symptoms.

Bago, Chile.
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Coughs and cold symptoms; rhinitis; sinusitis.

Nastizol Dia-Noche *Bago, Chile.*
Day tablets, paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); night tablets, paracetamol; pseudoephedrine sulfate; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; nasal congestion.

Nastizol Ex *Armstrong, Mex.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Nastizol Expectorante *Bago, Arg.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with excess or viscous mucus.

Nastizol Hidrospray *Bago, Arg.*
⊗ Budesonide (p.1520·1).
Rhinitis.

Nastizol-L *Bago, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Nastoren *Lepetit, Ital.*
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage; prevention of postoperative complications following pancreatic surgery.

Nastul *Chemopharma, Chile.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Nastul Compuesto *Chemopharma, Chile.*
Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Nasulind *Steierl, Ger.*
Peppermint oil (p.1761·2); thyme oil (p.2401·2).
Nasal congestion.

Nat Cubetu Benediktu *Leros, Cz.†.*
Milk thistle (p.1452·1).
Appetite loss; digestive disorders; dyspepsia.

Nat Jmeli *Megafyt-R, Cz.*
Mistletoe (p.2345·3).
Hypertension; presclerotic disorders.

Nat Maty Peprne *Megafyt-R, Cz.*
Peppermint leaf (p.1761·2).
Digestive-system disorders.

Nat Pelynku Praveho *Leros, Cz.*
Absinthium (p.2244·1).
Digestive-system disorders.

Nat Preslicky *Leros, Cz.†.*
Equisetum (p.2299·3).
Epistaxis; urinary-tract disorders; wounds.

Nat Rebricku *Leros, Cz.*
Achillea (p.2245·2).
Dyspepsia; loss of appetite; pelvic pain; wounds.

Nat Repiku Lekarskeho *Leros, Cz.†.*
Agrimony (p.2249·2).
Gastro-enteritis; mouth and throat inflammation; wounds.

Nat Salveje Lekarske *Leros, Cz.*
Sage (p.2382·3).
Diarrhoea; dyspepsia; mouth disorders.

Nat Trezalky *Leros, Cz.*
St John's wort (p.422·3).
Depression.

Nat Zemezluce *Leros, Cz.†.*
Centaury (p.2279·1).
Tonic.

Natabec
Note. This name is used for preparations of different composition.
Pfizer, Austria†; Pfizer, Chile; Pfizer Consumer, Ger.†; Pfizer, Switz.†.
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement.

Pfizer, Turk.
Ferrous sulfate (p.1939·3); calcium carbonate (p.1714·1); vitamins (p.1922·1).

Natabec F *Godecke, Cz.†; Pfizer Consumer, Ger.†.*
Multivitamin and mineral preparation (p.1922·1) with sodium fluoride (p.1962·2).

Natabion *Pyridam, Indon.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B ; calcium carbonate; colecalciferol (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias in pregnancy and lactation.

NataChew *Warner Chilcott, USA.*
A multivitamin preparation with iron (p.1922·1).

Natacyn *Alcon, Arg.; Alcon, Malaysia; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, USA.*
Natamycin (p.543·1).
Fungal eye infections.

Natadrops *Cipla, India.*
Natamycin (p.543·1).
Fungal eye infections.

Natafort *Warner Chilcott, USA.*
Multivitamin and mineral preparation (p.1922·1).

Natafucin *Yamanouchi, Ital.†.*
Natamycin (p.543·1).
Fungal skin infections.

Natal *Diepharmex, Fr.†.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement during pregnancy.

Natal Extra *Cypress, USA†.*
Multivitamin and mineral preparation (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Natalac *Tynor, Philipp.*
Moringa oleifera.
Nutritional supplement for breastfeeding women.

Natalbes *Scherer, Philipp.*
Ferrous fumarate; sodium fluoride; folic acid; vitamins; minerals (p.1922·1).
Nutritional supplement for pre- and post-natal women.

NatalCare *Ethex, USA.*
A range of multivitamin and multivitamin and mineral preparations (p.1922·1).

Natalgen Prenatal *Lapreven, Venez.†.*
Vitamin and mineral preparation (p.1922·1).

Natalience *Lero, Fr.*
Vitamins; minerals; fish oil (p.1922·1).
Nutritional supplement.

Natalin *Mead Johnson Nutritionals, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Dietary supplement during pregnancy and lactation.

Natalins com Fluor *Mead Johnson, Braz.*
Multivitamin and mineral preparation with iron, folic acid, and fluoride (p.1922·1).

Natalins Folico *Mead Johnson, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Natalins-M *Mead Johnson, Philipp.*
Vitamin and mineral preparation with or without fluoride (p.1922·1).
Dietary supplement for pre- and post-natal women.

Natalsid *Nizhpharm, Rus.*
Sodium alginate (p.2141·1).
Anorectal disorders.

Natalwiz *Metro, Philipp.*
Vitamin and mineral preparation with taurine (p.1922·1).
Dietary supplement for pregnant and breast-feeding women.

Nataral *Kenyaku, Thai.*
A range of vitamin and mineral preparations with iron (p.1922·1).
Dietary supplement during pregnancy and lactation.

Natarex Prenatal *Major, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

NataTab *Ethex, USA.*
Multivitamin and mineral preparation (p.1922·1).

Natavite *Schein, Canad.†.*
Multivitamin preparation with iron and folic acid (p.1922·1).

Natberry *Duopharma, Malaysia.*
Myrtillus (p.2349·3).
Tired eyes.

Natberry Extra *Duopharma, Malaysia.*
Myrtillus (p.2349·3); calendula (p.2273·1).
Tired eyes.

Natberry Plus *Duopharma, Malaysia.*
Myrtillus (p.2349·3); wolfberry.
Tired eyes.

Nat-C *Mega Lifesciences, Malaysia.*
Vitamin C (p.1983·3); bioflavonoids (p.2304·1); hesperidin (p.2304·3); rutoside (p.2305·1); acerola; rose fruit (p.2381·2).
Dietary supplement.

Nat-C Medicrafts *Mega Lifesciences, Thai.*
Vitamin C (p.1983·3); bioflavonoids (p.2304·1); hesperidin (p.2304·3); rutoside (p.2305·1); acerola; rose hips (p.2381·2).
Vitamin C deficiency.

Nat-E *Biofarma, Venez.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Natear *Silom, Thai.*
Hypromellose (p.2144·2).
Dry eyes; eye irritation.

Natecal
Note. This name is used for preparations of different composition.
Eurofarma, Braz.†; ITF, Chile; Italfarmaco, Port.; Italfarmaco, Spain.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Italfarmaco, Ital.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Natecal D *Eurofarma, Braz.†; ITF, Chile; Italfarmaco, Port.; Italfarmaco, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; fractures; osteoporosis.

Natecal D3 *ITF, Gr.; Trinity, UK.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Natecal D_3 *Italfarmaco, Rus.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Nateglin *Phoenix, Arg.*
Nateglinide (p.455·2).
Diabetes mellitus.

Natele *Schering, Braz.; Schering, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Natele Easygels *Schering, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Natelle-EZ *Pharmelle, USA.*
Vitamin and mineral preparation (p.1922·1).

Nathergen *PD, Thai.†.*
Methylergometrine maleate (p.2011·1).
Functional uterine bleeding; management of third stage of labour; postpartum haemorrhage; puerperal haemorrhage.

Naticardina *Viatris, Ital.†.*
Quinidine polygalacturonate (p.1383·2).
Arrhythmias.

Natifa *Libbs, Braz.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Natifa Pro *Libbs, Braz.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Natigesta *Farmalab, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Nati-K *DB, Fr.*
Potassium tartrate (p.1684·3).
Hypokalaemia.

Natiken *Kener, Mex.†.*
Ibuprofen (p.64·2).
Inflammation.

Natil *3M, Ger.; Hormosan, Ger.*
Cyclandelate (p.1254·1).
Cerebrovascular disorders; migraine; vestibular disorders.

Natil-N *Hormosan, Ger.*
Flunarizine hydrochloride (p.580·2).
Migraine; vestibular disorders.

Natisedina *Teofarma, Ital.*
Quinidine phenylethylbarbiturate (p.1385·1).
Arrhythmias.

Natisedine *Adilna, Turk.*
Quinidine phenylethylbarbiturate (p.1385·1).
Arrhythmias.

Natispray *Procter & Gamble, Fr.; Teofarma, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; pulmonary oedema.

Nativa *Natural San, Arg.*
A range of herbal preparations and dietary supplements (p.1922·1).

Nativa 2 Bifidus *Guigoz, Ital.†.*
Infant feed (p.1922·1) containing *Bifidobacterium lactis.*
Gastrointestinal disorders.

Nativa HA *Guigoz, Ital.*
Infant feed (p.1922·1).
Milk intolerance.

Nativit *Sigma, Braz.*
Vitamin and mineral preparation with iron (p.1922·1).

Nativit Fluor *Sigma, Braz.*
A vitamin and mineral preparation with fluoride (p.1922·1).

Nativit Minerais *Sigma, Braz.*
A vitamin and mineral preparation (p.1922·1).

Natopherol *Abbott, Hong Kong; Abbott, Indon.; Abbott, Singapore.*
Vitamin E (p.1992·2).
Antoxidant; nutritional supplement.

Abbott, Malaysia.
d-Alpha tocopherol (p.1992·2).
Skin disorders; vitamin E deficiency.

Natopherol Dermal-Day *Scherer, Malaysia†.*
SPF 30: d-Alpha tocopherol (p.1992·2); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Dry skin disorders; sunscreen.

Nat'Os *Monin, Fr.*
Soya; vitamin c; calcium carbonate; selenium (p.1922·1).
Dietary supplement.

Natovit *Bruno, Ital.*
Tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Natracalm *Chefaro, UK.*
Passion flower (p.2363·2).
Tension.

NatraFlex *Nutralife, UK.*
Capsaicin (p.32·3); dimethyl sulfone (p.2294·1); boswellia serrata (p.2307·1).
Joint pain.

Natrapel
Note. This name is used for preparations of different composition.
Tender, Canad.
Citronella oil (p.2284·2); geraniol (p.2310·3).
Insect repellent.

Ardern, UK.
Citronella oil (p.2284·2).
Insect repellent.

Natrasleep *Chefaro, UK.*
Lupulus (p.2335·2); valerian (p.2410·1).
Insomnia.

Natravene *Chefaro, UK.*
Frangula bark (p.1732·2); taraxacum (p.2395·1).
Constipation.

Natravox *Natrapharm, Philipp.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Natrax *Polfa Pabianice, Pol.*
Naproxen (p.92·3).
Fever; pain.

Natrecor *Janssen-Cilag, Arg.; Janssen-Cilag, Indon.; Scios, USA; Janssen-Cilag, Venez.*
⊗ Nesiritide citrate (p.1347·3).
Heart failure.

Natricin *Natrapharm, Philipp.*
Rifampicin (p.325·3).
Leprosy; neisseria meningitidis carriers; tuberculosis.

Natriclo *Sterop, Belg.†.*
Sodium chloride (p.1686·1).
Hyponatraemia.

Natrilix *Servier, Arg.; Servier, Austral.; Servier, Braz.; Grunenthal, Chile; Servier, Denm.; Servier, Fin.; Servier, Ger.; Servier, Hong Kong; Serdia, India; Servier, Indon.; Servier, Irl.; Servier, Ital.; Servier, Malaysia; Servier, Mex.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Singapore; Servier, Thai.; Servier, UK; Servier, Venez.*
⊗ Indapamide (p.1314·1).
Hypertension; oedema.

Natrium-Homaccord *Peithner, Austria†.*
Homoeopathic preparation.

Natrocitral *Tarbis, Spain.*
Oxetacaine (p.1867·2); sodium citrate (p.1673·3); aluminium glycinate (p.1706·2).
Gastrointestinal disorders.

Natropas *Finadiet, Arg.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders.

Natrophylline Compound *Lennon, S.Afr.*
⊗ Aminophylline (p.1114·2); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2).
Obstructive airways disease.

Natrossil *Natiris, Venez.*
Rhubarb (p.1768·3); boldo (p.2267·2); achyranthes aspera; phyllantus niruri.
Liver disorders.

Natrosteril *Baxter, Fin.*
A range of sodium chloride infusions with or without glucose (p.1686·1).
Fluid and electrolyte disorders.

Natsurf *ICN, Arg.†.*
Pulmonary surfactant (p.2375·3).
Neonatal respiratory distress syndrome.

Natterman Streptofree *Novum, Neth.*
Dequalinium chloride (p.1641·3).
Sore throat.

Natubiotin *Rodisma, Ger.*
Biotin (p.1931·3).
Biotin deficiency.

Natubrown *Natufarma, Arg.*
Betacarotene (p.1930·3); lycopene (p.2335·2).
Dietary supplement; tanning aid.

Natucor *Rodisma, Ger.*
Crataegus (p.2289·1).
Heart failure.

Natuderm *Rodisma, Ger.†.*
Biotin (p.1931·3).
Biotin deficiency.

Natudolor *Duopharm, Ger.†.*
Potentilla anserina.
Dysmenorrhoea.

Natudophilus *Cantassium Co., UK.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium bifidum* (p.2372·3).

Natudor
Note. This name is used for preparations of different composition.
Pierre Fabre, Belg.
Valerian (p.2410·1); crataegus (p.2289·1); tilia (p.2402·2).
Anxiety; insomnia.

Plantes et Medecines, Fr.
Crataegus (p.2289·1); passion flower (p.2363·2).
Anxiety; insomnia; palpitations.

Natu-fem *Rodisma, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Natu-Hepa *Rodisma, Ger.; Vita Health, Switz.*
Cynara (p.2291·2).
Biliary-tract disorders; digestive-system disorders; dyspepsia.

Natuimmun *Hevert, Ger.*
Homoeopathic preparation.

Natulan *Link, Austral.; Sigma-Tau, Canad.†; Sigma-Tau, Fr.; Sigma-Tau, Ger.; IFET (ΙΦΕΤ), Gr.; Sigma-Tau, Hung.†; Sigma-Tau, Ital.; AFT, NZ†; Sigma-Tau, Neth.; Sigma-Tau, Rus.; Sigma-Tau, Spain.*
Procarbazine hydrochloride (p.765·2).
Malignant neoplasms.

Natulax *Natufarma, Arg.*
Cascara (p.1715·2).
Constipation.

Natu-lind *Rodisma, Ger.*
Urtica leaf (p.2409·3).
Rheumatism; urinary-tract disorders.

Natu-prosta *Rodisma, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Natura 10 *Maurino, Arg.*
Cleansing, disinfecting, storage, and wetting solution for soft contact lenses (p.1622·2).

Natura Asep *Maurino, Arg.†.*
Solutions for soft contact lens care (p.1622·2).

Natura Clean *Maurino, Arg.*
Cleansing solution for contact lenses (p.1622·2).

Natura Clens *Maurinho, Arg.*
Cleansing, wetting, and protein-removal solution for hard and gas-permeable contact lenses (p.1622·2).

Natura Express *Maurinho, Arg.*
Cleansing and wetting solution for soft contact lenses (p.1622·2).

Natura Fenac *Amhof, Arg.*
Diclofenac sodium (p.44·3).
Eye disorders.

Natura Fresh *Maurino, Arg.*
Carmellose sodium (p.2142·1).
Dry eyes.

Natura Lagrimas *Amhof, Arg.*
Hypromellose (p.2144·2).
Dry eyes.

Natura Perflex *Maurino, Arg.*
Ethoxylated propylene glycol.
Cleansing solution for flexible and gas permeable contact lenses.

Natura Plus *Maurino, Arg.*
Poloxamine (p.1622·2).
Cleansing, disinfecting, storage, and wetting solution for soft contact lenses.

Natura Wet *Maurino, Arg.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Wetting solution for flexible and gas permeable contact lenses.

Natural Deep Sleep *Naturopathica, Austral.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2) melissa (p.2339·3).
Sleep disorders.

Natural Diet *AM, Arg.*
Bladderwrack; centella; equisetum; carnitine; vitamin E (p.1922·1).
Dietary supplement.

Natural E *Nutrifarma, Turk.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Natural Fibre *Cenovis, Austral.†; Vitelle, Austral.†.*
Psyllium seed (p.1737·1).
Constipation; dietary fibre supplement.

Natural Herb Tablets *Dorwest, UK.*
Senna (p.1769·2); aloes (p.1705·2); cascara (p.1715·2); valerian (p.2410·1); taraxacum (p.2395·1).
Constipation.

Natural Horizons Solar Block Extreme *Mentholatum, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Natural Horizons Solar Block Lotion
Note. This name is used for preparations of different composition.
Mentholatum, Austral.†.
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3); octil triazone (p.1608·1); titanium dioxide (p.1617·3).
Sunscreen.

Mentholatum, Austral.†.
SPF 30+: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Natural Horizons Solar Block Toddler *Mentholatum, Austral.†.*
SPF 30+: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Natural HRT *Swiss Herbal, Canad.*
Dong quai (p.2297·3); agnus castus (p.2249·1); cimicifuga (p.2282·1); dioscorea villosa; soya isoflavones (p.2391·2); lappa (p.2330·3).
Menopausal disorders.

Natural HRT Nightime *Swiss Herbal, Canad.*
Cimicifuga (p.2282·1); passion flower (p.2363·2); melissa (p.2339·3).
Sleep disorders associated with the menopause.

Natural Ice Extreme *Mentholatum, Canad.*
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Natural Ice Lipbalm *Mentholatum, Canad.†.*
Ointment: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Natural Ice Lipbalm with Vitamin E & Aloe Vera *Mentholatum, Canad.†.*
SPF 15: Padimate O (p.1609·1).
Sunscreen.

Natural Source Laxative *Adams, Canad.†.*
Ispaghula (p.1737·1).
Constipation; fibre supplementation.

Natural Wealth *Nefa, Turk.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Naturalag *Alcon, Mex.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes; eye irritation.

Naturalass *Naturmed, Ital.*
⊗ Lactulose (p.1738·2); mannitol (p.1330·2); glycerol (p.2314·2); inulin (p.2326·3); plant fibre; minerals (p.1922·1).
Gastrointestinal disorders.

Naturalfit *Medix, Mex.†.*
Glucomannan (p.2312·3).
Constipation; obesity.

Naturalist *Prater, Chile.*
Aspartame (p.1930·1).
Sugar substitute.

Naturalyte *Unico, USA.*
Glucose; electrolytes (p.1672·2).
Diarrhoea; oral rehydration therapy.

Naturapia Calcium Complex *US Pharmacia, Pol.*
Calcium carbonate; magnesium oxide; colecalciferol; ascorbic acid (p.1922·1).
Dietary supplement; osteomalacia; osteoporosis.

Naturapia Menopauza *US Pharmacia, Pol.*
Calcium citrate; calcium phosphate; magnesium oxide; colecalciferol (p.1922·1); cimicifuga (p.2282·1); soya (p.1965·3).
Menopausal disorders.

Naturapia Prostata *US Pharmacia, Pol.*
Alanine; glutamic acid; glycine; pyridoxine; zinc picolinate (p.2001·1); saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Natur-E *Darya-Varia, Indon.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Nature Complex Reduct-Te *Prater, Chile.*
Boldo (p.2267·2); trique; equisetum (p.2299·3); tilia (p.2402·2); stevia rebaudiana (p.1969·1).

Nature Made Oyster Shell Calcium *Abdi, Turk.*
Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Nature Throid *RLC, USA.*
Thyroid (p.2177·1).
Hypothyroidism.

Naturee *Innopharm, Singapore.*
d-alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Nature's Choice *New Vision, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Nature's Tears *Rugby, USA.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Naturest *Lane, UK.*
Passion flower (p.2363·2).
Insomnia.

Naturetin *Apothecon, USA†.*
⊗ Bendroflumethiazide (p.1224·1).
Hypertension; oedema.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Naturetti *Sanofi-Aventis, Braz.; Aventis, Mex.†.*
Senna (p.1769·2); cassia (p.1715·3); tamarind (p.1775·3); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Naturica Artro *Ikapharmindo, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; zinc; manganese; magnesium (p.1922·1).
Joint disorders.

Naturica Artro Plus *Ikapharmindo, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); selenium; vitamin C; zinc; manganese (p.1922·1).
Joint disorders.

Naturica Carniplus *Ikapharmindo, Indon.*
Levocarnitine; choline bitartrate; inositol; methionine; nicotinamide; zinc amino-acid chelate; magnesium amino-acid chelate; manganese amino-acid chelate; vitamin B (p.1922·1).
Obesity.

Naturica DFM *Ikapharmindo, Indon.*
Choline bitartrate (p.1934·2); inositol (p.2325·2); methionine (p.1450·1); vitamin B ; betaine hydrochloride (p.2265·2); taraxacum (p.2395·1); carnitine (p.1932·2); kelp (p.2384·2).
Liver disorders.

Naturident *Memsep, Cz.†.*
St John's wort (p.422·3); plantain (p.2379·1); chamomile oil (p.2279·3); caraway oil (p.2277·1); fennel oil (p.2303·1).
Mouth disorders.

Naturkaps Tran *Hasco-Lek, Pol.*
Cod-liver oil (p.1935·2).
Dietary supplement.

Naturland Grosser Swedenbitter *Naturland, Cz.†.*
Milk thistle (p.1452·1); carlina; chamomile (p.2279·3); gentian (p.2310·3); liquorice (p.1740·3); manna (p.1744·2); peppermint leaf (p.1761·2); nutmeg (p.2355·2); theriaci sine opio (angelica; basil; cardamom; cimicifuga; cinnamon; myrrh; origanum; valerian; zedoary); menyanthes (p.2340·3); zedoary; agrimony (p.2249·2); star anise (p.2392·1); aurantii dulcis pericarpii; clove (p.2284·3); bitter orange (p.2357·1); centaury (p.2279·1); cubeb (p.2290·1); galanga; rosemary (p.2381·2); verbascum (p.2413·3); ginger (p.1732·3); sachari tosti.
Digestive disorders; rheumatic pain.

Naturlax
Note. This name is used for preparations of different composition.
Great Eastern, Hong Kong.
Ispaghula (p.1737·1).
Constipation.

Maver, Chile.
Jelly: Senna (p.1769·2); liquorice (p.1740·3); plum.
Constipation.

Maver, Chile.
Tea: Senna (p.1769·2).
Constipation.

Naturogest *German Remedies, India.*
Progesterone (p.2125·1).
Premenstrual syndrome; puerperal depression.

Naturol *Prafa, Indon.*
d-Alpha tocopherol (p.1992·2).
Vitamin E supplement.

Naturpep-C *Ximena Polanco, Chile.*
Opuntia ficus-indica.
Gastrointestinal disorders.

Naturreiner *Kneipp, Ger.†.*
Cynara (p.2291·2).
Digestive system disorders.

Natursel-C *Ximena Polanco, Chile.*
Rosa mosqueta (p.2381·2); wild carrot (p.2415·2); spirulina (p.2392·1); vitamin E; selenium (p.1961·1).
Antoxidant.

Natur-Zin *Ximena Polanco, Chile.*
Wild carrot (p.2415·2); spirulina (p.2392·1); magnesium; zinc (p.1922·1).
Dietary supplement.

Natus Gerin *Legrand, Braz.*
Multivitamin, mineral, and amino-acid preparation with ginseng (p.1922·1).

Natusan *Johnson & Johnson, Spain.*
Glyceroborate complex; boric acid (p.2268·1); borax (p.2268·1).
Skin irritation.

Natuscap retard *Vifor, Switz.†.*
Chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); phenylephrine hydrochloride (p.1568·1).
Coughs and associated respiratory-tract disorders.

Natu-Seda *Vita Health, Switz.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Natusgel
Note. This name is used for preparations of different composition.
Neovita, Braz.†.
Oral suspension: Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

Neovita, Braz.†.
Tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity.

Natusor Aerofane *Soria Natural, Spain†.*
Burnet saxifrage (p.2270·3); fennel (p.2302·3); peppermint leaf (p.1761·2); caraway (p.2276·3); melissa (p.2339·3).
Aerophagia; gastrointestinal spasm.

Natusor Artilane *Soria Natural, Spain†.*
Ash (p.2262·1); urtica (p.2409·3); solidago (p.2391·1); equisetum (p.2299·3); betula alba (p.2266·3).
Musculoskeletal and joint disorders.

Natusor Asmaten *Soria Natural, Spain†.*
Elecampane (p.1558·1); satureja montana; thyme (p.2401·1); hyssop (p.2323·3); marrubium (p.1564·1).
Asthma.

Natusor Astringel *Soria Natural, Spain†.*
Loosestrife (p.2334·3); summer savory (p.2394·3); oak bark (p.2355·3); agrimony (p.2249·2); burnet saxifrage (p.2270·3); liquorice (p.1740·3).
Diarrhoea.

Natusor Broncopul *Soria Natural, Spain†.*
Eucalyptus (p.2301·2); verbascum flower (p.2413·3); althaea (p.2253·3); elecampane (p.1558·1); marrubium (p.1564·1).
Lower respiratory-tract infections.

Natusor Circusil *Soria Natural, Spain†.*
Cypress (p.2291·2); juglans regia; achillea (p.2245·2).
Haemorrhoids; phlebitis; varices.

Natusor Farinol *Soria Natural, Spain†.*
Agrimony (p.2249·2); althaea (p.2253·3); sage (p.2382·3); thyme (p.2401·1); ribwort plantain (p.2379·1).
Mouth and throat disorders.

Natusor Gastrolen *Soria Natural, Spain†.*
Liquorice (p.1740·3); ribwort plantain (p.2379·1); althaea (p.2253·3); St John's wort (p.422·3); achillea (p.2245·2).
Gastritis; peptic ulcer.

Natusor Gripotul *Soria Natural, Spain†.*
Thyme (p.2401·1); tilia (p.2402·2); eucalyptus (p.2301·2); sambucus (p.2383·1).
Catarrh; influenza symptoms; sore throat.

Natusor Harpagosinol *Soria Natural, Spain†.*
Devil's claw root (p.39·1); salix (p.121·3); equisetum (p.2299·3); meadowsweet (p.2338·1); peppermint flower (p.1761·2).
Musculoskeletal and joint disorders.

Natusor Hepavesical *Soria Natural, Spain†.*
Cichorium intybus; rosemary (p.2381·2); fumitory (p.2307·2); centaury (p.2279·1); boldo (p.2267·2); greater celandine (p.2317·1); peppermint leaf (p.1761·2).
Gallstones; liver disorders.

Natusor High Blood Pressure *Soria Natural, Spain†.*
Olive oil (p.2356·2); betula alba (p.2266·3); crataegus (p.2289·1).
Hypertension.

Natusor Infenol *Soria Natural, Spain†.*
Red-rose petal (p.1472·3); equisetum (p.2299·3); juglans regia; thyme (p.2401·1); ribwort plantain (p.2379·1).
Vaginal irrigation; wounds.

Natusor Jaquesan *Soria Natural, Spain†.*
Salix (p.121·3); bitter orange (p.2357·1); melissa (p.2339·3); achillea (p.2245·2); tilia (p.2402·2).
Headache; migraine.

Natusor Low Blood Pressure *Soria Natural, Spain†.*
Siberian ginseng (p.2386·3); rosemary (p.2381·2); summer savory (p.2394·3); liquorice (p.1740·3); sage (p.2382·3).
Hypotension.

Natusor Malvasen *Soria Natural, Spain†.*
Senna (p.1769·2); althaea (p.2253·3); fennel (p.2302·3).
Constipation.

Natusor Renal *Soria Natural, Spain†.*
Thyme (p.2401·1); meadowsweet (p.2338·1); equisetum (p.2299·3); betula alba (p.2266·3); solidago (p.2391·1); peppermint leaf (p.1761·2).
Urinary-tract infections.

Natusor Sinulan *Soria Natural, Spain†.*
Thyme (p.2401·1); rosemary (p.2381·2); sambucus (p.2383·1); marjoram (p.2337·3); tilia (p.2402·2).
Catarrh.

Natusor Somnisedan *Soria Natural, Spain†.*
Valerian (p.2410·1); St John's wort (p.422·3); tilia (p.2402·2); spike lavender (p.2391·3); crataegus (p.2289·1).
Depression; insomnia; nervous disorders.

Natuzilium *Teuto, Braz.†.*
Kava (p.2328·3).
Anxiety.

Naudicelle *Key, Austral.†; Bio-Oil Research, Irl.*
Evening primrose oil (p.2302·1).
Dietary supplement.

Naudicelle Marine *Key, Austral.†.*
Evening primrose oil (p.2302·1); marine fish oil (p.1362·2).
Dietary supplement.

Nausamine *Sriprasit, Thai.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Nausea Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Nauseatol *Sabex, Canad.*
Dimenhydrinate (p.576·2).
Nausea and vomiting.

Nausedron *Cristalia, Braz.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Nausefe *Inibsa, Port.*
Dicycloverine hydrochloride (p.1722·3); doxylamine succinate (p.578·2); pyridoxine hydrochloride (p.1978·2).
Nausea; vomiting.

Nausetrol *Walsh, USA.*
Glucose (p.1945·3); fructose (p.1945·1); phosphoric acid (p.2367·1).
Nausea and vomiting.

Nausetron *Generix, S.Afr.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Nausetum *Ferrier, Fr.*
Homoeopathic preparation.

Nausex *Viatris, Austria.*
Dimenhydrinate (p.576·2).
Ménière's disease; motion sickness; nausea and vomiting; vestibular disorders.

Nausicalm
Note. This name is used for preparations of different composition.
Uniao Quimica, Braz.
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting; vertigo.

Brothier, Fr.
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

AFT, NZ.
Cyclizine hydrochloride (p.574·2).
Nausea and vomiting; vestibular disorders.

Nausidone *Sofex, Port.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Nausiend *Pharmis, Port.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Nausil
Hertz, Braz.†.
Metoclopramide (p.1747·3).
Nausea and vomiting.

Siam Bheasach, Thai.
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; flatulence; gastro-oesophageal reflux; nausea and vomiting; peptic ulcer.

Nausilon B6 *Cifarma, Braz.*
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting; vertigo.

Nausyn *Weleda, Austria; Weleda, UK.*
Homoeopathic preparation.

Nautamine *Sanofi-Aventis, Fr.*
Diphenhydramine di(acefyllinate) (p.577·2).
Motion sickness.

Nautigo *Bell, India.*
Domperidone (p.1726·2).
Gastro-oesophageal reflux; gastroparesis; meteorism; nausea and vomiting.

Nautisol *Medochemie, Malaysia.*
Prochlorperazine mesilate (p.1020·1).
Anxiety; mania; nausea and vomiting; schizophrenia; vertigo.

Nautrol *Precimex, Mex.*
Difenidol hydrochloride (p.1723·2).
Nausea and vomiting; vertigo.

Nauzelin *Kyowa, Jpn.*
Domperidone (p.1726·2).

Nauzine *Be-Tabs, S.Afr.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Navamin *Greater Pharma, Thai.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting.

Navane
Pfizer, Austral.; Erfa, Canad.; Pfizer, Hong Kong; Pfizer, Neth.†.
Tiotixene (p.1032·3).
Depression; psychoses.

Pfizer, USA.
Tiotixene (p.1032·3) or tiotixene hydrochloride (p.1032·3).
Psychoses.

Navelbin *Pierre Fabre, Hung.*
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Navelbine *Pierre Fabre, Arg.; Pierre Fabre, Austral.; Boehringer Ingelheim, Austria; Pierre Fabre, Belg.; Asta Oncologia, Braz.; Pierre Fabre, Canad.; Baxter, Chile; Pierre Fabre, Cz.; Pierre Fabre, Denm.; Pierre Fabre, Fin.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pierre Fabre, Gr.; Orient, Hong Kong; Pierre Fabre, Hong Kong; Pierre Fabre, Israel; Pierre Fabre, Ital.; Kyowa, Jpn; Pierre Fabre, Malaysia; Pierre Fabre, Mex.; NZ Medical & Scientific, NZ; Pierre Fabre, Neth.; Pierre Fabre, Norw.; Baxter, Philipp.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Tema, S.Afr.; Pierre Fabre, Singapore; Pierre Fabre, Spain; Pierre Fabre, Swed.; Robapharm, Switz.; Baxter, Thai.; Pierre Fabre, Turk.; Pierre Fabre, UK; Pierre Fabre, USA.*
Vinorelbine tartrate (p.789·1).
Breast cancer; malignant lymphoma; non-small cell lung cancer; ovarian cancer; prostatic cancer.

Navicalm
Note. This name is used for preparations of different composition.
UCB, Neth.†.
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus; urticaria.

Cavalheiro, Port.; UCB, Spain†.
Meclozine hydrochloride (p.584·3).
Motion sickness; vestibular disorders.

Navidoxine *UCB, Hong Kong; UCB, Malaysia†; UCB, Singapore†.*
Meclozine hydrochloride (p.584·3); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Navidrex *Novartis, NZ†; Goldshield, UK.*
⊗ Cyclopenthiazide (p.1254·1).
Heart failure; hypertension; oedema.

Naviga *Bittner, Austria.*
Homoeopathic preparation.

Navirel *Medac, Cz.; Medac, Denm.; Medac, Pol.*
Vinorelbine tartrate (p.789·1).
Breast cancer; lung cancer; non small-cell lung cancer.

Navispare *Novartis, Hong Kong; Goldshield, UK.*
⊗ Cyclopenthiazide (p.1254·1); amiloride hydrochloride (p.1209·2).
Hypertension.

Navixen
Note. This name is used for preparations of different composition.
Mavi, Mex.
Naproxen (p.92·3).
Fever; inflammation; pain.

Ferrer, Spain.
Eprosartan mesilate (p.1281·1).
Hypertension.

Navixen Plus *Ferrer, Spain.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Navoban *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Braz.†; Novartis, Chile; Novartis, Cz.†; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel†; Novartis, Ital.; Kyowa, Jpn; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Tropisetron hydrochloride (p.1777·2).
Nausea and vomiting induced by cytotoxic therapy; postoperative nausea and vomiting.

Navotrax *Neo Quimica, Braz.*
Clonazepam (p.478·2).
Epilepsy.

Naxan *Hikma, Port.*
Naloxone hydrochloride (p.1453·2).
Diagnosis of opioid overdosage; reversal of opioid-induced depression.

Naxelan *Labomed, Chile.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome.

Naxen *Altimed, Canad.†; Darya-Varia, Indon.; Syntex, Indon.; Syntex, Mex.; Douglas, NZ.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Naxidin *Zelion, Hung.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Naxilan-Plus *Rayere, Mex.*
Nalidixic acid (p.303·3); phenazopyridine (p.116·3).
Urinary-tract infections.

Naxo *Sons, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Naxo C *Rontag, Arg.*
Fluconazole (p.532·1).
Vaginal candidiasis.

Naxo TV *Rontag, Arg.*
⊗ Metronidazole (p.837·1); nystatin (p.543·2); dexamethasone (p.1526·1); lidocaine (p.1862·3); neomycin sulfate (p.305·1).
Vaginal infections.

Naxocina *Rontag, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Naxoclinda *Rontag, Arg.*
Clindamycin phosphate (p.251·2).
Vaginal infections.

Naxodol *Syntex, Mex.*
Naproxen (p.92·3); carisoprodol (p.1894·1).
Musculoskeletal, joint, and peri-articular disorders.

Naxogin *Rontag, Arg.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile†; Pfizer, Rus.*
Nimorazole (p.842·2).
Acute ulcerative gingivitis; amoebiasis; anaerobic bacterial infections; bacterial vaginosis; giardiasis; trichomoniasis.

Naxogin Complex *Kalbe, Indon.; Pfizer, Indon.*
Nimorazole (p.842·2); chloramphenicol (p.239·3); nystatin (p.543·2).
Vaginal infections.

Naxogin Compositum *Pfizer, Chile.*
Nimorazole (p.842·2); nystatin (p.543·2); chloramphenicol (p.239·3).
Vaginal infections.

Naxogin Composto *Pfizer, Braz.*
Nimorazole (p.842·2); chloramphenicol (p.239·3); nystatin (p.543·2).
Vulvovaginal infections.

Naxogin Dos *Pfizer, Chile†.*
Nimorazole (p.842·2); nystatin (p.543·2).
Vaginal infections.

Naxolan *Hospira, Port.*
Naloxone hydrochloride (p.1453·2).

Naxopaar *Parggon, Mex.*
Naproxen (p.92·3).
Inflammation.

Naxopren *Merck, Fin.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Naxpa *Novag, Spain.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Naxuril *Vianex (Βιανέξ), Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Naxy *Cephalon, Fr.*
Clarithromycin (p.248·2).
Bacterial infections.

Naxyn *Teva, Israel.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Nazalet *Stanley, Israel.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nazalin *Bell, India.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Formerly contained naphazoline hydrochloride, phenylephrine hydrochloride, and sulfacetamide sodium.
Nasal congestion.

Nazamit *Mintlab, Chile.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Nazaren *Weifa, Norw.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Otitis; rhinitis; sinusitis.

Naze *Yenisehir, Turk.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Nazene Z *Adcock Ingram, S.Afr.*
⊗ Oxymetazoline hydrochloride (p.1567·2); zinc sulfate (p.1999·2).
Allergic rhinitis; nasal congestion; sinusitis.

Nazicol *Kinder, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Nazil *Sophia, Mex.*
⊗ Naphazoline (p.1565·1).
Eye congestion.

Nazin *Aristopharma, Hong Kong.*
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Nazinette du Docteur Gilbert *Pharmadeveloppement, Fr.*
Wild thyme oil (p.2415·3); pine silvestris oil (p.2368·2); eucalyptus oil (p.2301·2); myrtle oil (p.2349·3); clove oil (p.2285·1); thyme oil (p.2401·2); terpineol (p.2396·1).
Rhinopharyngeal disorders.

Nazo *Pharma Dynamics, S.Afr.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2).
Nasal congestion.

Nazobel *Sedabel, Braz.†.*
⊗ Naphazoline (p.1565·1); neomycin (p.305·1).
Nasal disorders.

Nazobio *Luper, Braz.†.*
⊗ Naphazoline hydrochloride (p.1565·2); panthenol (p.2362·1).
Nasal congestion.

Nazol *Sagmel, Rus.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nazol Advance *Sagmel, Rus.*
⊗ Oxymetazoline hydrochloride (p.1567·2); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3).
Rhinitis; sinusitis.

Nazol Baby *Sagmel, Rus.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Nazol Kids *Sagmel, Rus.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Nazolfarm *Continentales, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Nazolin *Beximco, Singapore.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nazoltec *Tecnofarma, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Nazosoro *Sedabel, Braz.†.*
Sodium chloride (p.1686·1).
Nasal Congestion.

Nazovell *Novell, Indon.*
Ketoprofen (p.73·1).
Osteoarthritis; pain; rheumatoid arthritis.

Naztril *Quimica y Farmacia, Mex.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

NB-3 *Sigma, Arg.*
Nicotinamide (p.1957·3).
Alcoholism; anxiety; depression; headache; migraine; obesity.

NC-Derm *Kee, India.*
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1); clotrimazole (p.530·1).
Infected skin disorders.

N-Combur Test *Roche Diagnostics, Austral.†.*
Test for nitrite, protein, glucose, and pH in urine.

ND-Gesic *Hyrex, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3); mepyramine maleate (p.585·2).
Upper respiratory-tract symptoms.

Nealorin *Probios, Port.; Prasfarma, Spain.*
Carboplatin (p.693·1).
Malignant neoplasms.

Neat Effect *Neat Feat, NZ.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Neat Feat *Neat Feat, NZ.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Neat One *Neat Feat, NZ.*
Aluminium-zirconium tetrachlorohydrex glycine (p.1588·3).
Hyperhidrosis.

Neat Touch *Neat Feat, NZ.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Neatenol *Rottapharm, Spain.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Neatenol Diu *Rottapharm, Spain.*
⊗ Bendroflumethiazide (p.1224·1); atenolol (p.1217·3).
Hypertension.

Neatenol Diuvas *Rottapharm, Spain.*
⊗ Bendroflumethiazide (p.1224·1); hydralazine hydrochloride (p.1305·3); atenolol (p.1217·3).
Hypertension.

Nebacetin
Sandoz, Austria; Eumedica, Switz.
Neomycin sulfate (p.305·1); bacitracin (p.210·3) or bacitracin zinc (p.210·3).
Bacterial infections.

Nycomed, Braz.; Astellas, Ger.; Nycomed, Gr.; Altana, Hong Kong†; Pharos, Indon.
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial infections; burns; wounds.

Nebacetin N *Yamanouchi, Ger.†.*
Neomycin sulfate (p.305·1).
Burns; skin infections; wounds.

Nebacetina *Altana, Mex.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial skin infections; infected burns, wounds, and ulcers.

Nebacetine *Eumedica, Belg.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Cystitis; eye disorders; otitis externa; rhinitis; skin disorders; surgical wound irrigation.

Nebaciderme *Multilab, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Nebacimed *Cimed, Braz.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Nebacitrin *Neo Quimica, Braz.†.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Skin infections.

Nebactrina *Pharlab, Braz.†.*
Neomycin (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Nebal *Reuffer, Mex.*
Hydroxocobalamin (p.1980·3).
Neuritis.

Nebalgan *Ipca, Rus.*
Fenpiverinium bromide (p.2303·2); dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).

Nebalon *Sinterapico, Braz.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Nebapol B *Galderma, Arg.†.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).
Burns; skin, nose, and ear infections; wounds.

Nebapul *Royal, Chile.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Nebasulf *Omni-Protech, India.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3); sulfacetamide (p.335·3) or sulfacetamide sodium (p.335·3).
Bacterial skin infections.

Nebcin *Aspen, Austral.; Lilly, Canad.†; Lilly, Gr.; Lilly, Hong Kong†; Lilly, Irl.†; Lilly, Israel†; Lilly, NZ; Aspen, S.Afr.; King, UK†; Lilly, USA†.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Nebcina *NordMedica, Denm.; Lilly, Fin.†; Lilly, Norw.†; Meda, Swed.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Nebcine *Erempharma, Fr.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Nebenhohlen-Tropfen Nr 26 *Doskar, Austria.*
Homoeopathic preparation.

Nebicina *Teofarma, Ital.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Nebido
Schering, Arg.; Schering, Austria; Schering, Braz.; Schering, Chile; Bayer Schering, Cz.; Schering, Fin.; Schering, Fr.; Jenapharm, Ger.; Schering, Gr.; Bayer Schering, Hung.; Schering, Indon.; Schering, Irl.; Bayer Schering, Malaysia; Schering, Mex.; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, Swed.; Schering, Switz.; Schering, UK.
⊗ Testosterone undecylate (p.2130·2).
Hypogonadism.

Schering, Denm.
⊗ Testosterone decanoate (p.2130·1).
Male hypogonadism.

Nebilet *Menarini, Arg.; Labomed, Chile; Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.; Menarini, Irl.; Menarini, Neth.; Berlin-Chemie, Pol.; Berlin-Chemie, Port.; Berlin-Chemie, Rus.; Adcock Ingram, S.Afr.; Menarini, Singapore; Retrain, Spain; Menarini, Switz.; Menarini, Thai.; Menarini, UK; Leti, Venez.*
⊗ Nebivolol hydrochloride (p.1347·1).
Heart failure; hypertension; ischaemic heart disease.

Nebiloc *Menarini, Neth.*
⊗ Nebivolol hydrochloride (p.1347·1).
Hypertension.

Nebilox *Negma, Fr.; GSK, Ital.; Guidotti, Spain.*
⊗ Nebivolol hydrochloride (p.1347·1).
Heart failure; hypertension.

Nebiotin *CGM, Ital.*
Biotin (p.1931·3).
Biotin deficiency.

Nebispes *Specifar, Cz.*
⊗ Nebivolol hydrochloride (p.1347·1).
Heart failure; hypertension.

Neblic
Note. A similar name is used for preparations of different composition (see below).
Lazar, Arg.
Azithromycin (p.207·1).
Bacterial infections.

Neblik
Note. A similar name is used for preparations of different composition (see above).
Astellas, Spain.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Nebril *Montpellier, Arg.†.*
Desipramine dibudinate (p.387·3) or desipramine hydrochloride (p.387·3).
Depression; pain.

Nebufur *Fabra, Arg.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Nebulasma *Urbion, Spain.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchospasm.

Nebulcort *Italchimici, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis; asthma; bronchitis.

Nebulcrom *Sanofi-Aventis, Spain.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchospasm.

Nebulex *Laboratorios Chile, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Rhinitis.

Nebulicina
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Arg.
⊗ Fenoxazoline hydrochloride (p.1560·3).
Nasal congestion.

Boehringer Ingelheim, Spain.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

NebuPent *American Pharmaceutical, USA.*
Pentamidine isetionate (p.844·2).
Pneumocystis pneumonia.

Nebutrax *Vannier, Arg.*
⊗ Salbutamol (p.1131·2).

NEC *Piam, Ital.*
Protein-free preparation for enteral nutrition (p.1922·1).
Renal disease.

Necamin *Ache, Braz.*
Mebendazole (p.148·3).
Worm infections.

Neciblok *Kalbe, Indon.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Necid *New Research, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Neck-Fer *Neckerman, Braz.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Necloral *New Research, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Neclovir *New Research, Ital.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Necon 0.5/35, 1/35 *Watson, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Necon 1/50 *Watson, USA.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Necon 10/11 *Watson, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Biphasic oral contraceptive.

Necopen *Esteve, Spain.*
Cefixime (p.224·3).
Bacterial infections.

Necro B-6 *Bunker, Braz.*
Adenosine (p.1202·1); methionine (p.1450·1); betaine (p.2265·2); choline citrate (p.1934·2); pyridoxine hydrochloride (p.1978·2).
Liver disorders.

Necta C *Maver, Chile.*
Sodium ascorbate (p.1984·1).
Vitamin C supplement.

Nectaday *Maver, Chile.*
A range of vitamin and mineral preparations (p.1922·1) with or without ginseng (p.2312·1).
Dietary supplement.

Nectar G *Del Sol, Arg.*
Vitamin E (p.1992·2); vitamin C (p.1983·3); glucosamine (p.2313·2).
Antoxidant; degenerative joint disorders.

Nectarmicin *Lamda (Λαμδα), Gr.†.*
Econazole (p.531·1).
Fungal infections.

Necyrane *UCB, Fr.*
Ritiometan magnesium (p.1660·2).
Nose and throat infections.

Neda Fruchtewurfel
Note. This name is used for preparations of different composition.
Novartis Consumer, Austria.
Senna (p.1769·2); fig (p.1731·3); tamarind (p.1775·3); liquid paraffin (p.2030·3).
Constipation.

Novartis Consumer, Ger.
Senna (p.1769·2).
Constipation.

Neda-Lactitol *Novartis Consumer, Austria.*
Lactitol (p.1738·2).
Constipation.

Nedax *Stiefel, Braz.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Nedax Plus *Stiefel, Braz.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Nedeltran *Aventis, Neth.*
Alimemazine tartrate (p.566·2).
Hypersensitivity reactions.

Nediclon *Bruluart, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nedios *Altana, Neth.*
Acipimox (p.1201·2).
Hyperlipidaemias.

Nedis *Omega, Arg.*
Miconazole nitrate (p.541·3).
Vulvovaginal infections.

Nedolon P *Merck, Cz.†; Merck, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Nedoxal *Quimica y Farmacia, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

NEE 1/35 *Lexis, USA.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Nefadon *Ad-Drugstel, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Nefalox *Lamda (Λαμδα), Gr.†.*
Cefadroxil (p.218·1).
Bacterial infections.

Nefam *Kedrion, Ital.†.*
Nefopam hydrochloride (p.94·2).
Pain.

Nefazan *Phoenix, Arg.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis.

Nefazan Compuesto *Phoenix, Arg.*
Tablets, clopidogrel bisulfate (Nefazan) (p.1250·2); tablets, aspirin (p.20·3).
Thromboembolic disorders.

Nefazol *New Research, Ital.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Nefelid *Farmamust, Gr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nefersil *Pharma Investi, Chile.*
Clonixin lysine (p.37·1).
Pain.

Nefersil B *Pharma Investi, Chile.*
Clonixin lysine (p.37·1); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2) or hydroxocobalamin acetate (p.1980·3).
Musculoskeletal, joint, and peri-articular disorders; neuralgia; neuritis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Nefirel *BMS, Gr.†.*
Nefazodone hydrochloride (p.412·1).
Depression.

Nefius *Grunenthal, Port.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders.

Neflox *Lamsa, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Nefluan *Molteni, Ital.*
⊗ Lidocaine hydrochloride (p.1862·3); neomycin sulfate (p.305·1); fluocinolone acetonide (p.1531·3).
Endoscopy.

Nefoben *Ivax, Arg.*
Theophylline (p.1140·1).
Obstructive airways disease.

Nefrecil *Labor, Pol.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Nefrin
Note. This name is used for preparations of different composition.
Geyer, Braz.†.
⊗ Adrenaline (p.1203·2).

Sophia, Mex.
Phenylephrine (p.1568·1).
Production of mydriasis.

Nefro Diet *Support, Braz.†.*
Preparation for enteral nutrition in renal disease (p.1922·1).

Nefroamino *Braun, Chile.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Nefrobonisol *Bonimed, Pol.*
Achillea (p.2245·2); birch leaf (p.2266·3); equisetum (p.2299·3); solidago (p.2391·1); taraxacum (p.2395·1); urtica (p.2409·3).
Hyperuricaemia; renal calculi.

Nefrocarnit *Medice, Ger.; Medice, Neth.*
Levocarnitine (p.1932·2).
Carnitine deficiency.

Nefrodial *Abbott, Braz.*
Preparation for enteral nutrition in renal disease (p.1922·1).

Nefrol *Herbapol Krakow, Pol.*
Ammi visnaga (p.2256·1); petroselinum sativum; phaseolus vulgaris; solidago (p.2391·1); taraxacum (p.2395·1).
Renal calculi.

Nefrolactona *Vedim, Port.†.*
⊗ Spironolactone (p.1400·1).
Hepatic cirrhosis; hyperaldosteronism; hypertension of pregnancy; hypokalaemia; hypomagnesaemia; oedema.

Nefroplasmal *Braun, Port.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Nefroselamin *Biosel, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Nefrosept *Aflofarm, Pol.*
Bearberry (p.2263·3); solidago (p.2391·1).
Urinary-tract disorders.

Nefrotal *Roemmers Rowe, Venez.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Nefrotal H *Roemmers Rowe, Venez.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Nefro-Zinc *Medice, Ger.*
Zinc chloride (p.1999·1).
Zinc deficiency in dialysis patients.

Nefryl *Armstrong, Mex.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Negaban *Eumedica, Belg.; Eumedica, UK.*
Temocillin sodium (p.347·1).
Gram-negative bacterial infections.

Negacef *Julphar, UAE.*
Ceftazidime (p.234·1).
Bacterial infections.

Negacne *Wierhom, Arg.*
Salicylic acid (p.1612·2); glycolic acid (p.1598·1); zinc sulfate (p.1999·2); coltsfoot (p.1555·1); aloe vera (p.1588·2).
Acne.

Negadix *CFL, India.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Negaflox *Cadila, Rus.*
Norfloxacin (p.309·2).
Bacterial infections.

Negalerg *ICN, Arg.†.*
⊗ Betamethasone (p.1518·2); loratadine (p.583·3).
Hypersensitivity reactions.

Negalerg L *ICN, Arg.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Negaporosis *Bajer, Arg.*
Calcium carbonate (p.1714·1); sodium monofluorophosphate (p.1964·3).
Osteoporosis.

Negatol *Altana, Fr.†; Altana, Ital.; Altana, Switz.*
Policresulen (p.1077·2).
Chilblains; furunculosis; gynaecological disorders; vaginitis; wounds.

Negatol Dental *Wild, Switz.*
Policresulen (p.1077·2).
Aphthous stomatitis; gingival haemorrhage.

Negazole *Julphar, UAE.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; bacterial vaginosis; dracunculiasis; inflammatory bowel disease; protozoal infections.

NegGram *Sanofi Synthelabo, Canad.†; Sanofi Winthrop, Israel†; Sanofi Synthelabo, Ital.†; Sanofi-Aventis, USA.*
Nalidixic acid (p.303·3).
Gram-negative urinary-tract infections.

Negortire *Armstrong, Mex.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion; chronic renal failure.

Negram *Sanofi-Aventis, Fr.†; Sanofi, Irl.; KRKA, Rus.; Sanofi-Aventis, UK†.*
Nalidixic acid (p.303·3).
Gram-negative urinary- and gastrointestinal-tract infections.

Negrustin *Hexal, Rus.*
St John's wort (p.422·3).
Anxiety; depression.

Nehydrin *Sanochemia, Austria.*
Dihydroergocristine mesilate (p.364·2).
Cerebrovascular disorders.

NeisVac *Baxter, Fr.*
A meningococcal group C conjugate vaccine (tetanus toxoid protein conjugate) (p.2224·1).
Active immunisation.

NeisVac-C *Baxter Immuno, Arg.; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; ID Biomedical, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Ital.; Baxter, Neth.; Baxter, Norw.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK.*
A meningococcal group C conjugate vaccine (tetanus toxoid protein conjugate) (p.2224·1).
Active immunisation.

Nekacin *New Research, Ital.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Nektol *Vamsler, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Nelabocin *Pharmathen, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Neladryl DMP *Galenium, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); paracetamol (p.108·1).
Cough; fever; respiratory-tract congestion.

Neladryl Expectorant *Galenium, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Nelapine *Littman, Philipp.; Berlin Pharm, Thai.*
Nifedipine (p.1350·1).
Angina pectoris; cardiac disorders; hypertension; Raynaud's syndrome.

Nelbinex *Pharmaten (Φαρματεν), Gr.†.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Nelconil *SJA, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Neldim *Vilco, Gr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Nelex *Altana, Port.; Byk Madaus, S.Afr.†.*
Policresulen (p.1077·2).
Anogenital warts; cervical erosion; cervicitis; external urethral erosion; vaginal disorders; vaginitis.

Nelfilea *Elea, Arg.*
Nelfinavir (p.899·1).
HIV infection.

Nelicort *GMP, Indon.*
Fludrocortisone acetate (p.1530·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Inflammatory ear disorders; otitis externa.

Nelin *Biolab, Thai.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Neloren
Lek, Cz.
Lincomycin (p.293·1) or lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Lek, Pol.
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Lek, Rus.
Lincomycin (p.293·1).
Bacterial infections.

Nelorpin *Ferrer, Spain.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Nelsons Clikpak Series *Nelson, UK.*
A range of homoeopathic remedies.

Nelvir *Cipla, India; Cipla, Venez.*
Nelfinavir mesilate (p.898·2).
HIV infection.

Nemactil *Sanofi-Aventis, Spain.*
Pericyazine (p.1016·3).
Anxiety; behaviour disorders; psychoses.

Nemagran *Nestmann, Cz.†.*
Homoeopathic preparation.

Nemalin *Valetudo, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Nemapres *Kener, Mex.*
Mebendazole (p.148·3).
Worm infections.

Nemasol *ICN, Canad.†.*
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Nemasole *Janssen-Cilag, Arg.*
Mebendazole (p.148·3).
Worm infections.

Nembutal *Abbott, Canad.†; Abbott, Hong Kong†; Abbott, Thai.†; Ovation, USA.*
Pentobarbital sodium (p.1016·1).
Epilepsy; insomnia; premedication; sedative.

Nemdyn *Hamilton, Austral.*
Neomycin undecenoate (p.305·2); bacitracin zinc (p.210·3).
Fungal or bacterial ear infections.

Nemegel *Medica, Arg.†.*
Sulfur (p.1614·1); resorcinol (p.1612·1); zinc oxide (p.1621·2); vitamin A palmitate (p.1973·1).
Acne.

Nemestran *Aventis, Arg.; Aventis, Cz.†; Aventis, Mex.; Aventis, Neth.; Aventis, Spain†; Aventis, Switz.*
⊗ Gestrinone (p.2106·1).
Endometriosis.

Nemexin *Torrex, Austria; Torrex Chiesi, Cz.; BMS, Ger.; Torrex, Hung.; BMS, Switz.*
Naltrexone hydrochloride (p.1455·2).
Opioid withdrawal.

Nemicina *Bunker, Braz.*
Neomycin sulfate (p.305·1).
Bacterial skin infections.

Nemocebral *Ivax, Arg.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Nemocebral Plus *Ivax, Arg.*
Idebenone (p.367·1); nimodipine (p.1357·2).
Cerebrovascular disorders; mental function impairment.

Nemocid *Mexin, India; Ipca, Rus.*
Pyrantel embonate (p.155·1).
Worm infections.

Nemodine
Note. This name is used for preparations of different composition.
Diffucap, Braz.†.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Kener, Mex.
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Dollder, Venez.
Nimodipine (p.1357·2).
Ischaemic neurological deficit; mental function impairment.

Nemoril *Gelpharma, Mex.*
Ginkgo biloba (p.2311·1).
Dietary supplement.

Nemotan *Medochemie, Rus.*
Nimodipine (p.1357·2).

Nemoxil *Neckerman, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Nemozole *Ipca, India; Ipca, Rus.*
Albendazole (p.139·2).
Hydatid cyst; worm infections.

Nene Dent
Note. A similar name is used for preparations of different composition (see Nenedent, below).
Altana, Arg.
Benzocaine (p.1854·1); ethacridine lactate (p.1625·1); acriflavinium chloride (p.1625·1).
Mouth disorders.

Altana, Mex.
Lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1).
Teething pain.

Nene Dent N *Nycomed, Braz.*
Lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1); chamomile (p.2279·3).
Teething disorders.

Nene Dent NF *Altana, Arg.*
Chamomile (p.2279·3); lidocaine hydrochloride (p.1862·3); lauromacrogol 400 (p.1916·1).
Gingivitis.

Nenedent
Note. A similar name is used for preparations of different composition (see Nene Dent, above).
Zuoz, Venez.
Lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Nenegloss *Maver, Chile.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); vitamin A (p.1971·2); vitamin D (p.1986·1); allantoin (p.1588·1); with or without aloe vera (p.1588·2).
Cicatrisation.

Nenegloss Z *Maver, Chile.*
Zinc oxide (p.1621·2).
Barrier preparation.

Nene-Lax *Dentinox, Ger.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Nenia *IBI, Ital.†.*
Zopiclone (p.1039·1).
Insomnia.

Neo Alertop *Laboratorios Chile, Chile.*
Levocetirizine (p.583·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Neo Analsona *Casen Fleet, Spain.*
⊗ Benzocaine (p.1854·1); fluocinolone acetonide (p.1531·3); neomycin (p.305·1); ruscogenin (p.2382·2).
Anorectal disorders.

Neo Artrol *Abbott, Spain†.*
Flurbiprofen (p.61·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Neo A-V *Neo Dermos, Arg.*
Salicylic acid (p.1612·2).
Astringent.

Neo Axedil *Norma (Νορμα), Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Neo Baby Cream *Neo Laboratories, UK.*
Cetrimide (p.1634·1); benzalkonium chloride (p.1629·1).
Nappy rash; skin irritation.

Neo Baby Gripe Mixture *Neo Laboratories, UK.*
Dill oil (p.2293·3); Strong Ginger Tincture BP (p.1732·3); sodium bicarbonate (p.1673·2).
Infant colic.

Neo Bacitrin
Note. This name is used for preparations of different composition.
Rottapharm, Spain.
Ointment: Bacitracin (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2).
Burns; skin infections; ulcers; wounds.

Rottapharm, Spain†.
Topical powder: Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Burns; skin infections; ulcers; wounds.

Neo Bendazol *Neo Quimica, Braz.*
Albendazole (p.139·2).

Neo Benzil *Neo Quimica, Braz.†.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Neo Borocillina *Wassermann, Ital.*
Dichlorobenzyl alcohol (p.1642·1); sodium benzoate (p.1630·2).
Mouth and throat disinfection.

Neo Borocillina Balsamica *Wassermann, Ital.*
Dichlorobenzyl alcohol (p.1642·1); terpin hydrate (p.1573·3); menglytate (p.1564·2).
Mouth and throat disinfection; respiratory-tract infections.

Neo Borocillina C *Wassermann, Ital.*
Dichlorobenzyl alcohol (p.1642·1); ascorbic acid (p.1983·3).
Mouth and throat disinfection.

Neo Borocillina Collutorio *Wassermann, Ital.*
Dichlorobenzyl alcohol (p.1642·1).
Mouth and throat disinfection.

Neo Borocillina Spray *Wassermann, Ital.*
Dichlorobenzyl alcohol (p.1642·1).
Mouth and throat disinfection.

Neo Borocillina Tosse Compresse *Wassermann, Ital.*
Dextromethorphan hydrobromide (p.1555·2); dichlorobenzyl alcohol (p.1642·1).
Coughs; mouth and throat disinfection.

Neo Borocillina Tosse Sciroppo *Wassermann, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Neo Butartrol *Sanitas, Chile.*
Ibuprofen (p.64·2); dipyrone (p.49·2); chlormezanone (p.968·3).
Headache; musculoskeletal and joint disorders.

Neo Butazol *Neo Quimica, Braz.*
Phenylbutazone calcium (p.117·1).

Neo Cal
Note. This name is used for preparations of different composition.
Golden Neo-Life, Canad.
Vitamin and mineral preparation (p.1922·1).

Neolab, Canad.
Calcium carbonate (p.1714·1).

Neo Cal D *Neolab, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Neo Cardiol *Francia, Ital.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Neo Cebetil *Uniao Quimica, Braz.*
Vitamin B substances with vitamin C and fructose (p.1922·1).

Neo Cefadril *Neo Quimica, Braz.*
Cefadroxil (p.218·1).
Bacterial infections.

Neo Cefix *Neo Quimica, Braz.*
Cefixime (p.224·3).
Bacterial infections.

Neo Ceflex *Neo Quimica, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Neo Cepacol Pastiglie *Sanofi-Aventis, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

Neo Cerinutrina *Prospa, Port.†.*
Nutritional supplement (p.1922·1).

Neo Citran *Novartis, Austria; Novartis Consumer, Canad.†; Novartis Consumer, Hung.*
Paracetamol (p.108·1); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Neo Citran A *Novartis Consumer, Canad.†.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); ascorbic acid (p.1983·3).

Neo Citran Calorie Reduced *Novartis Consumer, Canad.†.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); paracetamol (p.108·1).

Neo Citran Chest Congestion & Cough *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).

Neo Citran Cold & Flu *Novartis Consumer, Canad.†.*
Syrup: Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).

Neo Citran Colds & Flu *Novartis Consumer, Canad.*
Oral powder: Pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Neo Citran Cough *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Neo Citran Cough & Cold *Novartis Consumer, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).

Neo Citran Cough Cold & Flu *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Neo Citran DM *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); dextromethorphan hydrobromide (p.1555·2).

Neo Citran Extra Strength *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); paracetamol (p.108·1).

Neo Citran Extra Strength Cold & Sinus *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Neo Citran Grippe/refroidissement *Novartis Consumer, Switz.*
Paracetamol (p.108·1); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Neo Citran Nighttime Cold & Flu *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).

Neo Citran Nighttime Cough *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Neo Citran Non Drowsy Cold & Flu *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Neo Citran Sinus *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Neo Citran Sore Throat & Cough *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Neo Citran Total *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Neo Clodil *Neo Quimica, Braz.†.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Neo Clotrimazyl *Neo Quimica, Braz.*
Clotrimazole (p.530·1).
Fungal infections.

Neo Coltirot
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.†.
Lozenges: Neomycin sulfate (p.305·1); gramicidin (p.286·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Roux-Ocefa, Arg.
Topical spray: Neomycin sulfate (p.305·1); gramicidin (p.286·1); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Neo Coricidin *Schering-Plough, Ital.†.*
Chlorphenamine maleate (p.571·3); aspirin (p.20·3); caffeine (p.1116·3).
Cold symptoms.

Neo Coricidin Gola *Schering-Plough, Ital.†.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disinfection.

Neo Cortofen *Biodue, Ital.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Eczema; nasal mucosal inflammation; otitis externa; rhinitis.

Neo Davenol *Sunthi Sepuri, Indon.; Wyeth, Indon.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Allergic disorders; cold symptoms; cough.

Neo Decabutin *Inkeysa, Spain.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Neo Decapeptyl *Ache, Braz.*
⊗ Triptorelin embonate (p.2135·3).
Prostatic cancer.

Neo Diaform *Corsa, Indon.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Neo Diastop *Armoxindo, Indon.*
Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Neo DM *Laser, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Cold symptoms; cough.

Neo Doxicilin *Neo Quimica, Braz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Neo Eblimon *Guidotti, Ital.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Neo Emocicatrol *Bouty, Ital.*
Tannic acid (p.2394·3); benzalkonium chloride (p.1629·1).

Neo Emoform *Altana, Ital.†.*
Sodium monofluorophosphate (p.1964·3).
Gingivitis; oral hygiene.

Neo Entrostop *Kalbe, Indon.*
Activated attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Neo Esoformolo *Esoform, Ital.*
Sodium *o*-phenylphenol (p.1655·1).
Disinfection of waste materials.

Neo Fedipina *Neo Quimica, Braz.*
Nifedipine (p.1350·1).
Hypertension.

Neo Fenicol *Neo Quimica, Braz.*
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Neo Fertinorm *Serono, Spain†.*
⊗ Urofollitropin (p.2136·3).
Female infertility; male infertility.

Neo Fluostomygen *Stomygen, Ital.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Neo Folico *Neo Quimica, Braz.*
Folic acid (p.1940·1).
Anaemias.

Neo Formitrol *Mipharm, Ital.*
Cetylpyridinium chloride (p.1635·1).
Mouth disinfection.

Neo Fulvigal *Anfarm, Gr.*
Ticlopidine (p.1412·1).
Thromboembolic disorders.

Neo Furasil *Neo Quimica, Braz.*
Furazolidone (p.834·3).

Neo Gripe Mixture *Neo Laboratories, UK.*
Dill oil (p.2293·3); ginger (p.1732·3); sodium bicarbonate (p.1673·2).
Colic; teething.

Neo H2 *Boniscontro & Gazzone, Ital.*
Roxatidine acetate hydrochloride (p.1769·1).
Gastro-oesophageal reflux; peptic ulcer.

Neo HC *Laser, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; cough.

Neo Hidroclor *Neo Quimica, Braz.*
⊗ Hydrochlorothiazide (p.1307·3).
Diuretic.

Neo Hormoviton *Bode, Indon.; Tempo Scan Pacific, Indon.*
Yohimbe; damiana (p.2292·1); ginseng (p.2312·1); zinc; vitamin B ; royal jelly (p.2382·1) (p.1922·1).
Tonic for males.

Neo Hormoviton Greng *Bode, Indon.; Tempo Scan Pacific, Indon.*
Yohimbe; ginseng (p.2312·1); vitamin B ; royal jelly (p.2382·1) (p.1922·1).
Tonic for males.

Neo Hubber *Teofarma, Spain.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Ear disorders; rhinitis.

Neo Iloticina *Dista, Spain†.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Neo Iodine *Combiphar, Indon.*
Povidone-iodine (p.1659·2).
Mouth and throat disorders; skin disinfection; skin infections; wounds.

Neo Isocaden *Neo Quimica, Braz.*
Isoconazole nitrate (p.536·2).
Vaginal infections.

Neo Itrax *Neo Quimica, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Neo Kaocitin *Erlimpex, Indon.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Neo Kaolana *Sanbe, Indon.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Neo Kaominal *Molex Ayus, Indon.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Neo Kef *Phoenix, Arg.*
Loperamide hydrochloride (p.1741·1); neomycin sulfate (p.305·1).
Diarrhoea.

Neo Kodan *Schulke & Mayr, Ger.†.*
Octenidine hydrochloride (p.1654·3); propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Neo Koniform *Konimex, Indon.*
Activated attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Neo Lactoflorene *Montefarmaco, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins (p.1922·1).
Nutritional supplement.

Neo Larmax *Andromaco, Chile.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Neo Linco *Neo Quimica, Braz.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Neo Loratadin *Neo Quimica, Braz.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Neo Mebend *Neo Quimica, Braz.*
Mebendazole (p.148·3).
Worm infections.

Neo Melubrina *Sanofi-Aventis, Spain.*
Dipyrone (p.49·2).
Fever; pain.

Neo Metrodazol *Neo Quimica, Braz.*
Metronidazole (p.837·1).

Neo Mistatin *Neo Quimica, Braz.*
Nystatin (p.543·2).
Fungal infections.

Neo Moldava *ICN, Arg.†.*
Salicylic acid (p.1612·2); pyrithione zinc (p.1611·2).
Skin disorders.

Neo Mom
Note. This name is used for preparations of different composition.
Candioli, Ital.
Shampoo: Phenothrin (p.2048·3).
Pediculosis.

Candioli, Ital.
Topical powder: Tetramethrin (p.2051·1); phenothrin (p.2048·3).
Pediculosis.

Neo Moxicilin *Neo Quimica, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Neo Multigrin *Grin, Mex.*
Vitamin and mineral preparation (p.1922·1).

Neo Napacin *Konimex, Indon.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2).
Asthma.

Neo Need *Quimica y Farmacia, Mex.†.*
Vitamin and mineral preparation (p.1922·1).

Neo Nifalium *Pharmanik (Φαρμανικ), Gr.*
Flunitrazepam (p.996·2).
Insomnia.

Neo Nisidina-Fher *Boehringer Ingelheim, Ital.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold symptoms; fever; pain.

Neo Novapon *Tanabe, Indon.*
⊗ Paracetamol (p.108·1); tipepidine hibenzate (p.1574·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); alcohol (p.1625·2).
Cold and influenza symptoms; cough; nasal congestion.

Neo Novapon Plus *Tanabe, Indon.*
Paracetamol (p.108·1); ethenzamide (p.51·3); tipepidine hibenzate (p.1574·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; cough; nasal congestion.

neo OPT *Optimed, Ger.*
Bromazepam (p.964·3).
Anxiety; sleep disorders.

Neo Pelvicillin *Temis, Arg.*
⊗ Neomycin undecenoate (p.305·2); neomycin sulfate (p.305·1); gramicidin (p.286·1); hydrocortisone (p.1535·2); nitrofurazone (p.309·1); chlorphenamine maleate (p.571·3).
Vaginal infections.

Neo Perginol *Gambar, Ital.†.*
Chlorhexidine gluconate (p.1635·3).
Genital hygiene.

Neo POM *Uniao Quimica, Braz.†.*
Neomycin sulfate (p.305·1).
Skin infections.

Neo Prodiar *Erlimpex, Indon.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Neo Propranol *Neo Quimica, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Neo Quimica Colirio *Neo Quimica, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc phenolsulfonate (p.1621·3); berberine sulfate (p.2264·3).
Eye congestion.

Neo Resiguard *Nicholas, Indon.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Hand disinfection; skin infections; wounds.

Neo Rheumacyl *Bode, Indon.; Tempo Scan Pacific, Indon.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Neo Rhinovit *Menarini, Gr.*
⊗ Ephedrine hydrochloride (p.1558·2).
Nasal congestion.

Neo Rinactive *Alcon, Port.; M4, Spain.*
⊗ Budesonide (p.1520·1).
Rhinitis.

Neo Rinoleina *Sanofi-Aventis OTC, Ital.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Neo Sampoon *Eisai, Hong Kong; Eisai, Malaysia; Eisai, Philipp.; Eisai, Singapore.*
Menfegol (p.1917·1).
Spermicidal contraceptive.

Neo Sedeks *Ulagay, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); potassium iodide (p.2169·2).
Respiratory-tract congestion.

Neo Strata Astringent Acne Treatment *Canderm, Canad.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Neo Strata Blemish Spot *Canderm, Canad.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Neo Sulfazina *Neo Quimica, Braz.†.*
Sulfadiazine (p.336·2).
Bacterial infections.

Neo Tionazol *Neo Quimica, Braz.*
Tioconazole (p.548·2).
Fungal infections.

Neo Tomizol *Tarbis, Spain.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Neo Triaminic *Novartis, Indon.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Neo Tusilan *Landson, Indon.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Allergic disorders; cold symptoms; cough.

Neo Uniplus *Angelini, Ital.†.*
Aspirin (p.20·3); paracetamol (p.108·1).
Cold symptoms; pain.

Neo Uniplus C *Angelini, Ital.†.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms; pain.

Neo Urgenin *Neo-Farmaceutica, Port.; Madaus, Spain.*
Echinacea angustifolia (p.2298·1); pygeum africanum (p.2192·3); saw palmetto (p.2192·3).
Prostatic disorders.

Neo Verpamil *Neo Quimica, Braz.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension.

Neo-Acarina *Upsifarma, Port.†.*
Benzyl benzoate (p.2036·1).
Pediculosis.

Neo-adlibamin *Norma (Νορμα), Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Neo-Aesculan *Herbapol Poznan, Pol.*
Esculoside (p.2248·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Neoalexil *Diba, Mex.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Neoalexil P *Diba, Mex.†.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Neoamiyu *Ajinomoto, Thai.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Neoampicil *Etifar, Venez.†.*
Ampicillin (p.204·1).
Bacterial infections.

Neo-Ampiplus *Menarini, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Neo-Angin
Note. This name is used for preparations of different composition.
Klosterfrau, Austria; Divapharma, Cz.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1); anise oil (p.2258·2); peppermint oil (p.1761·2).
Mouth and throat disorders.

Divapharma, Ger.; Divapharma, Hung.; Divapharma, Pol.
Dichlorobenzyl alcohol (p.1642·1); menthol (p.2340·1); amylmetacresol (p.1628·3).
Mouth and throat disorders.

Neo-Angin avec vitamin C sans sucre *Doetsch, Grether, Switz.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1); ascorbic acid (p.1983·3).
Sore throat.

Neo-Angin Lido *Doetsch, Grether, Switz.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Mouth and throat disorders.

Neo-Angin au miel et citron *Doetsch, Grether, Switz.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); honey (p.1948·2); lemon oil (p.2332·3); mint oil (p.2345·2).
Sore throat.

Neo-Angin sans sucre *Doetsch, Grether, Switz.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1); anethole (p.2258·1); mint oil (p.2345·2); rectified camphor oil (p.2273·3).
Sore throat.

Neo-antiperstam *Biostam (Βιοσταμ), Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Neo-Anusol *Nizhpharm, Rus.*
Bismuth subnitrate (p.1711·2); zinc oxide (p.1621·2); tannic acid (p.2394·3); resorcinol (p.1612·1); iodine (p.2169·2); methylthioninium chloride (p.1450·3).
Anorectal disorders.

Neoasma *Tarmac, USA.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Neoate *APT, Hong Kong.*
Neomycin sulfate (p.305·1).
Bowel preparation before abdominal surgery.

Neo-Atropan *Quim-Far, Venez.†.*
Papaverine hydrochloride (p.2191·3); belladonna (p.2263·3); hyoscyamus (p.2323·3); aniseed (p.2258·2).

Neoazarina *Herbapol Wroclaw, Pol.*
Greater celandine (p.2317·1); codeine phosphate (p.37·2); thyme (p.2401·1).
Catarrh; cough.

Neo-B12 *Mayne, NZ.*
Hydroxocobalamin chloride (p.1980·3).
Optic neuropathies; vitamin B deficiency anaemias.

Neobac *Dermapharm, Ger.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Burns; skin and nose infections; wounds.

Neobacigrin *Grin, Mex.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).
Infected inflammatory eye disorders.

Neobacina *Hexal, Braz.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Skin infections.

Neobacipan *Royton, Braz.†.*
Neomycin (p.305·1); bacitracin zinc (p.210·3).
Skin infections.

Neobacitracine *Erfa, Belg.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Bacterial eye, ear, and skin infections.

Neo-Ballistol
Note. This name is used for preparations of different composition.
Klever, Ger.†.
Capsules: Potassium oleate (p.2139·1); peppermint oil (p.1761·2); anise oil (p.2258·2); caraway oil (p.2277·1).
Gastrointestinal disorders.

Klever, Ger.†.
Oral liquid: Potassium oleate (p.2139·1); ammonium oleate; peppermint oil (p.1761·2); anise oil (p.2258·2).
Gastrointestinal disorders.

Neobefol *Italfarmaco, Port.*
Folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Folic acid and vitamin B deficiency; prevention of neural tube defects.

NeoBenz *SkinMedica, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Neobes *Medix, Mex.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Neo-Bex *Neolab, Canad.*
Vitamin B substances (p.1922·1).

Neo-Bex Forte *Neolab, Canad.*
Vitamin B substances; vitamin C; zinc sulfate (p.1922·1).

Neo-Bilagit *Sanofi-Aventis, Hung.*
Papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3); dehydrocholic acid (p.2292·2).

Neobitiol *Fortbenton, Arg.*
Aluminium chlorohydrate (p.1588·3); neomycin (p.305·1).
Hyperhidrosis.

Neobloc *Unipharm, Israel; GX, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; migraine; myocardial infarction; reduction of paroxysmal tachycardia before cardiac catheterisation.

Neobol *Unipharm, Mex.*
⊗ Neomycin sulfate (p.305·1); clostebol acetate (p.2087·1).
Infected burns, wounds, and ulcers; infected skin disorders.

Neobonsen *Duopharm, Ger.*
Evening primrose oil (p.2302·1).
Eczema.

Neo-botacreme *Norma (Νορμα), Gr.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Neobradoral *Novartis Consumer, Port.*
Domiphen bromide (p.1643·1).
Mouth and throat infections.

Neo-Bromexan *Medi-Rx, Philipp.*
Chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3).
Cough; nasal congestion.

Neo-Bromexan Forte *Medi-Rx, Philipp.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Fever; nasal congestion; pain.

Neobron *Pfizer, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Neo-Bronchol
Note. This name is used for preparations of different composition.
Divapharma, Cz.; Divapharma, Ger.†.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

DP-Medica, Switz.
Guaifenesin (p.1561·3); cineole (p.2282·3); anise oil (p.2258·2).
Coughs.

Neo-Brontyl *Collins, Mex.*
Guaifenesin (p.1561·3); sodium dibunate (p.1573·1); dipyrone (p.49·2).
Coughs.

NeoBros *Fidia, Ital.*
Phosphatidyl serine (p.2367·1); vitamin E (p.1922·1).
Mental function disorders.

NeoBros 10 *Fidia, Ital.*
Phosphatidyl serine (p.2367·1); vitamins; minerals (p.1922·1).
Mental function disorders.

NeoBros C *Fidia, Ital.*
Phosphatidyl serine (p.2367·1); creatine; vitamins; minerals (p.1922·1).
Nutritional supplement.

Neobrufen *Abbott, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Neo-Bucosin *Hanseler, Switz.†.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Neobutamina *Neo Quimica, Braz.*
Dobutamine hydrochloride (p.1271·2).

Neo-C *GNLD, Austral.*
Ascorbic acid (p.1983·3); Neo-Plex Concentrate (orange juice; orange peel; orange bioflavonoid complex); acerola; rose fruit; rutoside; hesperidin; lemon bioflavonoid complex.
Vitamin C deficiency.

Neocaina *Cristalia, Braz.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Neocalcit *Biospray, Gr.*
Calcium phosphate (p.1676·2).
Prevention and treatment of calcium deficiency.

Neocalmans *Chobet, Arg.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

Neocapil *Spirig, Cz.; Medicine & Business, Hung.; Spirig, Switz.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Neo-Capsiderm *Herbapol Poznan, Pol.*
Camphor (p.2273·2); capsaicin (p.32·3); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Neuromuscular pain.

Neocarbo *Neocorp, Ger.*
Carboplatin (p.693·1).
Malignant neoplasms.

Neocarbon *Galenogal, Braz.†.*
Charcoal (p.1435·2).
Diarrhoea.

Neocardina *Herbapol Wroclaw, Pol.*
Convallaria (p.2287·3); crataegus (p.2289·1); valerian (p.2410·1).
Cardiovascular disorders.

Neocardon *Gap, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Neocate *Scientific Hospital Supplies, Austral.; Support, Braz.†; SHS, Cz.†; Nutricia, Fin.; SHS, Fr.; Nutricia, Hong Kong; Scientific Hospital Supplies, Irl.; SHS, Israel; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Nutricia, Port.; SHS, Singapore†; Scientific Hospital Supplies, UK.*
Infant feed (p.1922·1).
Bowel disorders; cow's milk protein intolerance; elemental diet; malabsorption; protein intolerance.

Neocate Advance *SHS, Israel.*
Preparation for enteral nutrition (p.1922·1).
Food allergy.

Neocate One + *SHS, USA.*
Preparation for enteral nutrition (p.1922·1).

Neocef *Atral, Port.*
Cefixime (p.224·3).
Bacterial infections.

Neoceflex *Neo Quimica, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Neoceftriona *Neo Quimica, Braz.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Neocel *Pharmacia, Arg.†.*
Docetaxel (p.710·3).
Breast cancer; non-small cell lung cancer.

Neo-Cephyl *Boiron, Cz.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Neoceptin-R *Beximco, Singapore.*
Ranitidine (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neocetrin *Bunker, Braz.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Neoceuticals Clear Skin *Q-Med, Ital.*
Salicylic acid (p.1612·2); acetyl mandelic acid (p.296·3).
Acne.

Neoceuticals Clear Skin Solution *Hamilton, Austral.†.*
Salicylic acid (p.1612·2); alpha hydroxy acids.
Oily skin.

Neoceuticals Crema Despigmentante de Dia *Ingens, Arg.†.*
Hydroquinone (p.1598·2); gluconolactone (p.2313·1); sunscreens.
Skin hyperpigmentation.

Neoceuticals Gel de Limpieza Facial *HLB, Arg.*
Gluconolactone (p.2313·1); triclosan (p.1665·2).
Seborrhoea; skin cleanser.

Neoceuticals PDS *Hamilton, Austral.†; Q-Med, Ital.*
Barrier cream.
Dry skin conditions.

Neoceuticals Spot Treatment *Q-Med, Ital.*
Glycolic acid (p.1598·1); acetyl mandelic acid (p.296·3); vitamin A (p.1971·2).
Acne.

Neoceuticals Therapeutic Shampoo *Hamilton, Austral.†.*
Piroctone olamine (p.1610·1).
Dandruff.

Neochinosol *Chinosolfabrik, Ger.*
Ethacridine lactate (p.1625·1).
Mouth and throat disorders.

Neocibalena *Novartis Consumer, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Neo-Cibalgina *Novartis Consumer, Ital.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Neociclina *Upsifarma, Port.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Neo-Cimexon *Cimex, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Neo-Cimexon G *Cimex, Switz.†.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Neocin
Note. This name is used for preparations of different composition.
Fischer, Israel.
Neomycin sulfate (p.305·1).
Bacterial eye infections.

Ocusoft, USA.
Polymyxin B (p.318·2); neomycin (p.305·1); bacitracin (p.210·3).
Bacterial eye infections.

Neocina
Note. This name is used for preparations of different composition.
Elofar, Braz.
Neomycin sulfate (p.305·1).

Hexal, Braz.†.
Neomycin sulfate (p.305·1); zinc oxide (p.1621·2).

Neocinolon *Teuto, Braz.*
⊗ Neomycin sulfate (p.305·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Neocip *Cipla, India.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Neocip FC *Cipla, India.*
⊗ Ciprofloxacin (p.243·3); fluocinolone acetonide (p.1531·3); clotrimazole (p.530·1).
Infected skin disorders.

Neocip M *Cipla, India.*
Ciprofloxacin (p.243·3); metronidazole (p.837·1).

Neocitec *Sandoz, Arg.; Novartis, Braz.*
Vinorelbine tartrate (p.789·1).
Malignant neoplasms.

NeoCitran Antitussif *Novartis Consumer, Switz.*
Butamirate citrate (p.1553·1).
Coughs.

NeoCitran Antitussive *Novartis, Hung.*
Butamirate citrate (p.1553·1).
Cough.

NeoCitran Expectorant
Note. This name is used for preparations of different composition.
Novartis, Hung.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Novartis Consumer, Switz.
Acetylcysteine (p.1548·2).
Coughs.

Neoclaritine *Essex, Chile.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Neoclarityn *Schering-Plough, Cz.; Schering-Plough, Gr.†; Schering-Plough, Irl.; Schering-Plough, Neth.; Schering-Plough, Port.; Schering-Plough, UK.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Neo-Clarosip *Grunenthal, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Neo-Cleanse *GNLD, Austral.*
Senna leaf (p.1769·2); buckthorn bark (p.1713·3); liquorice root (p.1740·3); prune (p.1765·1); alfalfa leaf (p.2249·2); rhubarb root (p.1768·3); leptandra virginica root; blue malva flowers (p.2337·2); asparagus; aniseed (p.2258·2).
Constipation.

Neoclym *Pharmacia, Ital.*
⊗ Cyclofenil (p.2088·1).
Anovulatory infertility; menopausal disorders; menstrual disorders.

Neocodin *Slovakofarma, Cz.†.*
Pholcodine (p.1570·2).
Coughs.

Neo-Codion
Note. This name is used for preparations of different composition.
Bouchara-Recordati, Fr.
Infant syrup: Sodium benzoate (p.1630·2); grindelia (p.2317·2); senega (p.1572·3).
Respiratory-tract congestion.

Bouchara-Recordati, Fr.†.
Paediatric suppositories: Codeine camsilate (p.38·3); cineole (p.2282·3).
Coughs.

Bouchara-Recordati, Fr.
Paediatric syrup: Codeine camsilate (p.38·3); sodium benzoate (p.1630·2).
Coughs.

Bouchara-Recordati, Fr.; Bouchara, Rus.
Syrup: Codeine camsilate (p.38·3).
Cough.

Bouchara-Recordati, Fr.; Bouchara, Rus.
Tablets: Codeine camsilate (p.38·3); sulfogaiacol (p.1573·2); grindelia (p.2317·2).
Cough.

Neo-Codion Babies *Bouchara, Rus.*
Senega root (p.1572·3); grindelia (p.2317·2); sodium benzoate (p.1630·2).
Respiratory-tract disorders with viscous mucus.

Neo-Codion N
Note. This name is used for preparations of different composition.
Bouchara, Switz.
Syrup: Codeine camsilate (p.38·3); ascorbic acid (p.1983·3); ipecacuanha (p.1562·3); tolu balsam (p.1574·2).
Coughs.

Bouchara, Switz.
Tablets: Codeine camsilate (p.38·3); sulfogaiacol (p.1573·2); grindelia (p.2317·2).
Coughs.

Neo-Codion NN *Fatol, Ger.†.*
Codeine camsilate (p.38·3).
Coughs.

Neocof
Note. This name is used for preparations of different composition.
Norma (Νορμα), Gr.
Acetylcysteine (p.1548·2).
Mucolytic.

Masa, Thai.†.
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Neocoflan *Neo Quimica, Braz.*
Diclofenac diethylamine (p.44·3).
Inflammation.

Neocol *Gunsa, Turk.*
Oxytetracycline (p.312·2).
Bacterial skin infections.

Neocolan *Seid, Spain.*
Dicycloverine hydrochloride (p.1722·3); metochalcone (p.2344·2); procaine hydrochloride (p.1869·1).
Hepatobiliary disorders.

Neo-Coldan *Ad-Drugstel, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Neocolpoben *Quesada, Arg.†.*
Metronidazole (p.837·1); nystatin (p.543·2).

Neocon *Janssen-Cilag, Neth.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neocones
Note. This name is used for preparations of different composition.
Schein, Austria.
Tetracaine hydrochloride (p.1871·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); tyrothricin (p.358·2).
Temporary dental filling.

Prats, Spain.
Tetracaine hydrochloride (p.1871·3); neomycin (p.305·1); polymyxin B sulfate (p.317·3); tyrothricin (p.358·2).
Dental disorders.

Septodont, Switz.
Neomycin sulfate (p.305·1); benzocaine (p.1854·1).
Dental disorders.

Neocopan *Ducto, Braz.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Pain; skeletal muscle spasm.

Neocophen *Millimed, Thai.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; cough.

Neo-Cortef *Pharmacia, Canad.†.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin or eye disorders.

Neocorten *Sanli, Turk.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Neocortic *Ferron, Indon.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); dexamethasone sodium sulfate.
Infected eye disorders.

Neocortin *Legrand, Braz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Neocortizul *Lersan, Arg.*
⊗ Chloramphenicol succinate (p.241·3); prednisolone (p.1540·3); phenylephrine hydrochloride (p.1568·1).

Neocristin *GSK, India.*
Vincristine sulfate (p.787·1).
Leukaemias; lymphomas.

Neo-Cromaton Bicomplesso *Menarini, Ital.*
Vitamin B substances (p.1922·1).
Deficiency states; macrocytic anaemias.

Neocrystepin *Zentiva, Cz.*
⊗ Chlortalidone (p.1243·3); dihydroergocristine mesilate (p.364·2); reserpine (p.1387·3).
Hypertension.

Neo-Currino *Fabra, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); neomycin sulfate (p.305·1).
Nasal congestion.

Neocutan *Medibrands, Israel.*
Dexpanthenol (p.2362·1).
Skin irritation.

Neocutan Silver *Medibrands, Israel.*
Dexpanthenol (p.2362·1); chlorhexidine gluconate (p.1635·3); silver chloride (p.2387·1); vitamin a (p.1971·2).
Minor burns.

Neo-Cutigenol *Centrapharm, Belg.*
Chlorhexidine acetate (p.1635·2); vitamin A palmitate (p.1973·1).
Burns; skin disorders; ulcers; wounds.

Neocutis *Pentaderm, Ital.*
Azelaic acid (p.1589·3); jaluramina.
Acne; seborrhoea.

Neo-Cystine *Sofex, Port.*
Cystine; vitamin A acetate (p.1922·1).
Hair and nail disorders.

Neo-Cytamen *Mayne, Austral.; UCB, Irl.; Teofarma, Ital.; GSK, NZ; UCB, UK.*
Hydroxocobalamin (p.1980·3).
Leber's optic atrophy; macrocytic anaemias; neuritis; tobacco amblyopia; vitamin B deficiency.

Neocyte *Biomedis, Philipp.*
Recombinant human granulocyte colony-stimulating factor.
Chemotherapy-induced neutropenia.

Neo-Davisolona *Davi, Port.*
⊗ Neomycin sulfate (p.305·1); prednisolone sodium phosphate (p.1541·2).
Infected eye disorders.

Neodazol *Neo Quimica, Braz.*
Secnidazole (p.846·3).
Amoebiasis; trichomoniasis.

Neo-Deca *CCM, Malaysia.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Allergic and inflammatory eye and ear disorders.

NeoDecadron *Merck, USA†.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye inflammation with bacterial infection; inflammatory skin disorders with secondary infection.

Neo-Decongestine *Sanopharm, Switz.*
Kaolin (p.1738·1); glycerol (p.2314·2); salicylic acid (p.1612·2); methyl salicylate (p.85·3).
Formerly contained kaolin, glycerol, guaiacol salicylate, and methyl salicylate.
Soft-tissue disorders; sore throat.

Neo-Delphicort *Dermapharm, Austria.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Ear or eye infection and inflammation.

Neoderm
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Skin disorders.

Tai Guk, Singapore.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Neoderma 47 *Neovita, Ital.*
Mallow (p.2337·2); vervain (p.2413·3); pansy (p.2415·2).
Barrier preparation.

Neoderm-F *Sons, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Neo-Desogen *Teleflex, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection; skin, burn, and wound disinfection.

Neo-Destomygen *Stomygen, Ital.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Neodetoxergon *Baldacci, Ital.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).
Nutritional supplement.

Neodex
Note. This name is used for preparations of different composition.
Osoth, Thai.
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Neo Quimica, Braz.
Cream: ⊗ Dexamethasone acetate (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Neo Quimica, Braz.
Tablets: ⊗ Dexamethasone acetate (p.1526·1).
Corticosteroid.

Neo-Dex (Improved) *Jean-Marie, Hong Kong.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Inflammatory eye infections.

Neodexa *Llorens, Spain.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Neodexa Plus *Novartis Ophthalmics, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).

Neo-Dexameth *Major, USA†.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Eye inflammation with bacterial infection.

Neodexasone *Medical Ophthalmics, USA.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin (p.305·1).
Infected eye disorders.

Neodextril 40 *Fresenius Kabi, Port.*
⊗ Dextran 40 (p.1059·1) in glucose or sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

Neodextril 70 *Fresenius Kabi, Port.*
⊗ Dextran 70 (p.1059·3) in glucose or sodium chloride.
Plasma volume expansion; thromboembolism prophylaxis.

Neo-Diaral *Roberts, USA.*
Loperamide (p.1741·3).
Diarrhoea.

Neo-Diophen *Hamilton, Austral.†.*
Mepyramine maleate (p.585·2); phenylpropanolamine hydrochloride (p.1569·3); dextromethorphan hydrobromide (p.1555·2); atropine sulfate (p.1219·3).
Asthma; bronchitis; coughs and cold symptoms; hay fever.

Neo-Disterin *Norma (Νορμα), Gr.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Neodol *Diba, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Neo-Dolaren *AF, Mex.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Neodolito *Diba, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Neodolpasse *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Hung.*
Diclofenac sodium (p.44·3); orphenadrine citrate (p.812·1).
Inflammation; musculoskeletal and joint disorders; pain.

Neodor *Neo-Farmaceutica, Port.*
Capsicum oleoresin (p.2276·2).
Joint pain.

Neodox *Rosen, Ger.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Neo-DP *DP-Medica, Switz.†.*
Guaifenesin (p.1561·3); sodium benzoate (p.1630·2); althaea (p.2253·3); tolu balsam (p.1574·2); ribwort plantain (p.2379·1); thyme (p.2401·1); pini turionum; specierum pectoralium.
Coughs.

Neodrea *VHB, India†.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Neodrin *Neo Quimica, Braz.*
Dimenhydrinate (p.576·2).
Nausea and vomiting.

Neoduplamox *Procter & Gamble, Ital.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Neo-Duplofer *Hexal, Braz.†.*
Vitamins; minerals; liver extract; gastric mucosa (p.1922·1).

Neodur *Laborterapia, Port.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Neo-Durabolic *Hauck, USA.*
⊗ Nandrolone decanoate (p.2118·2).
Anaemia in renal disease.

Neodurasina *GSK Consumer, Spain†.*
Pseudoephedrine (p.1571·2).
Nasal congestion.

Neodyn *Carlo Erba OTC, Ital.†.*
Vitamin, mineral, and carbohydrate preparation with creatine (p.1922·1).
Nutritional supplement.

Neoefodil *Lafage, Arg.†.*
⊗ Naphazoline (p.1565·1); sodium citrate (p.1673·3); ephedrine (p.1558·1).
Nasal congestion.

Neo-egmol *Target, Gr.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Neo-Emedyl *Montavit, Austria.*
Dimenhydrinate (p.576·2); caffeine (p.1116·3).
Motion sickness; nausea and vomiting; vestibular disorders.

Neo-endusix *Anfarm, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Neo-Enteroseptol *Specifar (Σπεσιφαρ), Gr.*
Loperamide (p.1741·3).
Diarrhoea.

Neo-Eparbiol *Ecobi, Ital.†.*
Inosine (p.2325·2); cyanocobalamin (p.1980·2).
Anaemias; tonic.

Neo-Eunomin *Grunenthal, Ger.*
Ethinylestradiol (p.2101·3); chlormadinone acetate (p.2084·3).
Acne; alopecia; biphasic oral contraceptive; hirsutism; seborrhoea.

Neofam *Silesia, Chile.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neofarmiz *Neo-Farmaceutica, Port.*
Azithromycin (p.207·1).
Formerly known as Farmiz.
Bacterial infections.

Neofazol *Rubio, Spain†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Neofed *Adcock Ingram, S.Afr.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Neofedrin
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Akdeniz, Turk.
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Neofel *Neolab, UK.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Neofen *Ferron, Indon.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Neofenox *Boots Healthcare, Belg.*
⊗ Phenylephrine hydrochloride (p.1568·1); dichlorobenzyl alcohol (p.1642·1); naphazoline nitrate (p.1565·2).
Adjuvant in sinusitis; nasal congestion.

Neo-Fer *Neolab, Canad.*
Ferrous fumarate (p.1938·3).
Iron deficiency.

Neo-Fer CF *Neolab, Canad.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

NeoFitolizyna *Herbapol Pruszkow, Pol.*
Couch-grass (p.2288·2); birch leaf (p.2266·3); equisetum (p.2299·3); petroselinum sativum; solidago (p.2391·1).
Urinary-tract disorders.

Neoflogin *Neo Quimica, Braz.*
Benzydamine hydrochloride (p.27·3).
Fever; inflammation; pain.

Neoflor *Altana, Mex.*
Enterococcus faecium (p.2372·3).
Diarrhoea; hepatic encephalopathy; irritable bowel syndrome; restoration of intestinal flora.

Neofloxin
Note. This name is used for preparations of different composition.
Neo Quimica, Braz.
Norfloxacin (p.309·2).
Bacterial infections.

Beximco, Singapore.
Ciprofloxacin (p.243·3).
Bacterial infections.

Neoflu *Organifar, Venez.†.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Neoflu con Neomicina *Organifar, Venez.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Neofluor *Neocorp, Ger.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Neofolin
Note. A similar name is used for preparations of different composition (see below).
Neocorp, Ger.
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; folic acid deficiency; prevention of methotrexate toxicity.

Neofollin
Note. A similar name is used for preparations of different composition (see above).
Biotika, Cz.
Estradiol valerate (p.2097·3).
Menopausal disorders; menstrual disorders; oestrogen deficiency.

Neofomiral *Silanes, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Neoform
Note. This name is used for preparations of different composition.
Pietrasanta, Ital.†.
Quercia marina (p.2384·2); frangula (p.1732·2); rhubarb (p.1768·3).
Constipation.

GX, Philipp.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Neo-fradin *Pharma Tek, USA.*
Neomycin sulfate (p.305·1).

Neofrin *Ocusoft, USA.*
Phenylephrine hydrochloride (p.1568·1).

Neoftalm *Valeant, Arg.*
Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3).
Eye infections.

Neoftalm Dexa *Valeant, Arg.*
⊗ Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2).
Eye infections.

Neofulvin *Chew, Thai.*
Griseofulvin (p.535·2).
Fungal infections.

Neo-Furadantin *Formenti, Ital.*
Nitrofurantoin (p.308·1).
Bacterial infections of the genito-urinary tract.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Neogadine *Raptakos, India.*
Iodised peptone; magnesium chloride; manganese sulfate; zinc sulfate; sodium metavanadate; vitamin B ; vitamin B ; nicotinamide (p.1922·1).
Asthenia; tonic.

Neogadine SG *Raptakos, India.*
Iodised peptone; sulfogaiacol (p.1573·2); magnesium chloride; manganese sulfate; zinc sulfate; vitamin B ; vitamin B ; nicotinamide (p.1922·1).
Chronic bronchitis.

neogama *Hormosan, Ger.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vestibular disorders.

neogama D novo *Hormosan, Ger.†.*
Sulpiride (p.1028·3).
Depression.

Neogasol *Recalcine, Chile.*
Dimeticones (p.2032·1).
Aerophagia.

Neogastro *Douglas, Austral.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Neogecim *Gemballa, Braz.†.*
Neomycin (p.305·1).

Neogel *Masa, Thai.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Neogentin *Svizera, India.*
⊗ Urofollitropin (p.2136·3).
Female infertility.

Neogentrol *Wyeth Lederle, Denm.†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Neogest *Schering, UK†.*
Norgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Neo-Gilurythmal *Giulini, Israel†.*
Prajmalium bitartrate (p.1374·2).
Arrhythmias.

Neo-Gilurytmal *Solvay, Austria; Solvay, Cz.; Solvay, Ger.; Solvay, Hung.; Solvay, Indon.*
Prajmalium bitartrate (p.1374·2).
Arrhythmias.

Neoglandyna *Tymofarm, Pol.*
Borage oil (p.2267·3).
Atopic eczema; hepatitis; metabolic disorders; premenstrual syndrome.

Neogobion *Pharos, Indon.; Pharos, Singapore.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate (p.1922·1); folic acid (p.1940·1); vitamin B (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; nutritional supplement.

Neo-Golaseptine *SMB, Belg.*
Chlorhexidine (p.1635·2); benzethonium chloride (p.1630·1).
Mouth and throat disorders.

Negranormon *Teva, Hung.*
Ergocalciferol (p.1987·1); vitamin A (p.1971·2); pancreas extract (p.2337·3); zinc oxide (p.1621·2).
Skin disorders.

Neogrein *Neo Quimica, Braz.*
Paracetamol (p.108·1); ergotamine tartrate (p.620·1); caffeine (p.1116·3); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3).
Migraine.

Neogrip
Note. This name is used for preparations of different composition.
Rider, Chile.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; rhinitis.

Neo-Farmaceutica, Port.
Paracetamol (p.108·1).
Fever; pain.

Neogyn *Ecobi, Ital.*
Lysates of lactobacilli (p.2372·3); chlorhexidine (p.1635·2).
Personal hygiene.

Neogynon *Schering, Arg.; Schering, Austria†; Schering, Belg.†; Schering, Denm.; Schering, Ger.†; Shepa, Gr.†; Schering, Hong Kong†; Schering, Israel†; Schering, Mex.; Schering, Neth.; Schering, Switz.†; Schering, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; endometriosis; menstrual disorders.

Neogynona *Schering, Spain.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Neo-Healar *Arab, Malaysia.*
Lupinus albus; vateria indica; peppermint (p.1761·2); aloe vera (p.1588·2).
Haemorrhoids.

NeoHepatect *Biotest, Cz.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Neohepatect *Biotest, Ital.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Neo-Hesna *Takeda, Thai.*
Carbazochrome sodium sulfonate (p.1058·2).
Haemorrhagic disorders.

Neo-Hydro *Upha, Malaysia†; Beacons, Singapore; Streuli, Switz.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders; inflammation and infection of the eye; otitis externa; rhinitis; sinusitis.

Neohysticlar *Mintlab, Chile.*
Desloratadine (p.576·1).

Neoimmun *Kwizda, Austria.*
Ciclosporin (p.1822·2).
Atopic dermatitis; auto-immune disorders; nephrotic syndrome; rheumatoid arthritis; transplant rejection.

Neointestopan *Novartis, Rus.*
Attapulgite (p.1709·1).
Diarrhoea; food intolerance or poisoning.

Neoiodarsolo *Baldacci, Ital.*
Amino-acid preparation with vitamin B substances (p.1922·1).
Tonic.

Neo-Ipertas *Norma (Νορμα), Gr.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Neo-K *Combiphar, Indon.*
Phytomenadione (p.1995·3).
Haemorrhagic disease of the newborn.

Neokap *Degorts, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Gastrointestinal infections.

Neo-Kiddielets *United Laboratories, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Neolag *Atlas, Arg.*
⊗ Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Neolaikan *Farmasa, Mex.*
Valerian (p.2410·1).
Anxiety; sleep disorders.

Neolapril *Biobras, Braz.†.*
Enalapril maleate (p.1276·1).
Hypertension.

Neo-Laryngobis *Rougier, Canad.*
Bismuth dipropylacetate (p.1712·1).
Sore throat.

Neolasil *Neo Quimica, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Neolecsin *Jumont, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Neolefrin *Neo Quimica, Braz.*
Phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2); paracetamol (p.108·1).

Neolefrin Baby *Neo Quimica, Braz.*
Carbinoxamine maleate (p.570·2); paracetamol (p.108·1).

Neolend *Globo, Braz.†.*
Deltamethrin (p.2040·1).

Neolet
Note. A similar name is used for preparations of different composition (see below).
Eczacibasi, Turk.
Tyrothricin (p.358·2); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2).
Mouth and throat disorders.

Neolette
Note. A similar name is used for preparations of different composition (see above).
Silesia, Chile.
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 5 tablets, ethinylestradiol; 2 tablets, placebo.
Sequential oral contraceptive.

Neo-Lidocaton *Weimer, Thai.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Vasopressin (p.2411·3) and noradrenaline (p.1360·1) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Neolidona *Neo Quimica, Braz.*
⊗ Chlortalidone (p.1243·3).
Hypertension.

Neolipid *Biobras, Braz.†.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Neoloid *Bradley, Canad.†; Kenwood, USA.*
Castor oil (p.2278·1).
Bowel evacuation; constipation; diarrhoea.

Neolon-D *Neo Quimica, Braz.*
⊗ Gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Neo-Lotan *Neopharmed, Ital.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Neo-Lotan Plus *Neopharmed, Ital.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Neolucid *SMB, Chile.*
Soap substitute.

Neolucid-C *SMB, Chile.*
Ascorbyl palmitate (p.1629·1).
Skin ageing; sun-induced skin damage.

Neolucid-pH5 *SMB, Chile.*
A moisturiser.

Neolutin Forte *Spofa, Cz.*
Hydroxyprogesterone caproate (p.2110·3).
Menstrual disorders; progesterone deficiency.

Neom *Globo, Braz.†.*
Neomycin (p.305·1).

Neomagnol *Valeant, Hung.*
Tosylchloramide sodium B (p.1665·1).
Disinfection.

Neomas *Temis, Arg.*
Neomycin sulfate (p.305·1).
Gastrointestinal infections.

Neomas L *Temis, Arg.*
Neomycin sulfate (p.305·1); loperamide hydrochloride (p.1741·1).
Diarrhoea.

Neomed *Cimed, Braz.*
Neomycin (p.305·1).

Neomedil *Farmec, Ital.*
⊗ Benzalkonium chloride (p.1629·1); alcohol (p.1625·2).
Skin and wound disinfection.

Neo-Medrol
Note. This name is used for preparations of different composition.
Pharmacia, Austral.; Pharmacia, Israel; Pharmacia, S.Afr.
⊗ Methylprednisolone acetate (p.1538·2); neomycin sulfate (p.305·1); aluminium chlorohydrate (p.1588·3); colloidal sulfur (p.1614·1).
Acne; infected skin disorders.

Pfizer, Malaysia; Pfizer, Singapore; Pfizer, Thai.
⊗ Methylprednisolone acetate (p.1538·2); neomycin sulfate (p.305·1); alcloxa (p.1587·2); sulfur (p.1614·1).
Acne; rosacea; seborrhoeic dermatitis.

Neo-Medrol Acne *Pfizer, Canad.; Pfizer, Hong Kong.*
⊗ Methylprednisolone acetate (p.1538·2); neomycin sulfate (p.305·1); aluminium chlorohydrate (p.1588·3); colloidal sulfur (p.1614·1).
Acne; seborrhoeic dermatitis.

Neo-Medrol comp *Pfizer, Fin.†.*
⊗ Methylprednisolone acetate (p.1538·2); neomycin sulfate (p.305·1); aluminium chlorohydrate (p.1588·3); sulfur (p.1614·1).
Acne.

Neo-Medrol Veriderm *Pharmacia, Canad.†; Pharmacia, Ital.†.*
⊗ Methylprednisolone acetate (p.1538·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Neomelin *Collins, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Neo-Melubrina *Aventis, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Neo-Mercazole *Link, Austral.; Amdipharm, Denm.; CSP, Fr.; Nicholas Piramal, India; Nicholas, Indon.; Amdipharm, Irl.; AFT, NZ; Amdipharm, Norw.; Roche, Philipp.; Pharmacare, S.Afr.; Pro Concepta, Switz.; Roche, UK.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Neomercurocromo
Note. This name is used for preparations of different composition.
SIT, Ital.
Ointment; topical powder: Chlorhexidine gluconate (p.1635·3).
Wound disinfection.

SIT, Ital.
Topical solution: Chloroxylenol (p.1640·2).
Wound disinfection.

Neomicol *Medix, Mex.*
Miconazole nitrate (p.541·3).
Fungal infections.

Neomicon *Cifarma, Braz.*
Neomycin sulfate (p.305·1).
Bacterial skin infections.

Neomigran *Hexal, Braz.†.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Neomina *Brasterapica, Braz.†.*
Neomycin (p.305·1).
Bacterial skin infections.

Neo-Minophagen C *Dexa, Indon.; Torii, Jpn.*
Ammonium glycyrrhizate (p.2316·1).
Liver disorders; skin disorders.

Neomixen *Pisa, Mex.*
Neomycin (p.305·1).
Bacterial infections.

Neomonovar *Wyeth Lederle, Port.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neomox *Danlex, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Neo-Mudapenil *Geminis, Arg.†.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Neo-Mune *Otsuka, Indon.; Thai Otsuka, Thai.*
Preparation for enteral nutrition (p.1922·1).

Neo-mycodermol *Adelco, Gr.*
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Neo-Mydrial *Winzer, Ger.†.*
Phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

Neomyrt Plus *Baif, Ital.*
Myrtillus (p.2349·3); bioflavonoids (p.2304·1); centella (p.1592·3); selenium (p.1961·1); vitamin C (p.1983·3); rutoside (p.2305·1).
Nutritional supplement.

Neo-NaClex *GSK, NZ; Goldshield, UK.*
⊗ Bendroflumethiazide (p.1224·1).
Hypertension; oedema.

Neo-NaClex-K *Goldshield, UK.*
⊗ Bendroflumethiazide (p.1224·1); potassium chloride (p.1684·3).
Hypertension; oedema.

Neonaxil *Probiomed, Mex.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Neo-Nevral *Bruno, Ital.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Neonutrin *Fresenius Kabi, Cz.*
A range of amino-acid infusions (p.1922·1).
Parenteral nutrition.

Neo-omnipen *Norma (Νορμα), Gr.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Neo-Optal *Olan-Kemed, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Neo-Optalidon *Novartis Consumer, Ital.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

NeoOstrogynal *Schering, Ger.†.*
Estradiol valerate (p.2097·3); estriol (p.2101·1).
Menopausal disorders; oestrogenic.

Neopam *Troikaa, India.*
Pralidoxime iodide (p.1460·2).
Organophosphorus poisoning.

Neopan *Adcock Ingram, S.Afr.*
Neomycin sulfate (p.305·1); sodium propionate (p.545·3).
Ear infections.

Neo-Pancreatinum *Jelfa, Pol.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Neopankreoflat *Grunenthal, Chile.*
Pancreatin (p.2360·1); dimeticones (p.2032·1).
Digestive disorders; flatulence.

Neo-Panlacticos *Italmex, Mex.*
Lactic-acid-producing organisms (p.2372·3); vitamin B substances (p.1922·1).
Restoration of normal gastrointestinal flora.

Neo-Panlacticos Plus *Italmex, Mex.*
Lactic-acid-producing organisms (p.2372·3); vitamin B substances (p.1922·1); dimeticone (p.1770·2).
Flatulence; restoration of normal gastrointestinal flora.

Neo-Panpur *EGIS, Hung.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Neo-Parmecal *Geymonat, Ital.*
Food for special diets (p.1922·1).
Gastrointestinal disorders.

Neo-Pasmonal *Technobio, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Neopecsul *Parggon, Mex.*
Neomycin (p.305·1); homatropine (p.1881·2); sulfaguanidine (p.339·2).

Neopect *Masa, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cold symptoms; coughs.

Neopelle *Also, Ital.†.*
Collagen (p.2286·1).
Wound dressing.

Neo-Penotran *Embil, Malaysia; Embil, Philipp.; Schering, Philipp.; Embil, Rus.; Embil, Singapore; Embil, Turk.*
Metronidazole (p.837·1); miconazole nitrate (p.541·3).
Bacterial vaginosis; vaginal candidiasis; vaginal trichomoniasis.

Neopenyl *Grunenthal, Spain.*
Benzylpenicillin sodium (p.213·1); clemizole penicillin (p.251·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Neopeptine
Note. This name is used for preparations of different composition.
Raptakos, India.
Capsules: Amylase (p.2256·3); papain (p.2362·3); simeticone (p.1770·2).
Anorexia; dyspepsia; flatulence; meteorism.

Raptakos, India.
Oral drops: Amylase (p.2256·3); papain (p.2362·3); dill oil (p.2293·3); anise oil (p.2258·2); caraway oil (p.2277·1).
Anorexia; dyspepsia; flatulence; meteorism.

Raptakos, India.
Oral liquid: Amylase (p.2256·3); papain (p.2362·3).
Anorexia; dyspepsia; flatulence; meteorism.

Neoperazona *Neo Quimica, Braz.†.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Neo-Percodan *Aventis, Mex.*
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Fever; pain.

Neophedan *Bodene, S.Afr.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Neophenicol *Westmont, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Neophyllin *Eisai, Jpn.*
Aminophylline (p.1114·2).
Congestive heart failure; obstructive airways disease.

Neopiridin *Neo Quimica, Braz.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).

Neo-Planotest *Bio Merieux, UK†.*
Pregnancy test (p.2372·1).

Neoplatin *BMS, Spain.*
Cisplatin (p.698·2).
Malignant neoplasms.

Neoplaxol *Richmond, Arg.*
Etoposide (p.718·1).
Malignant neoplasms.

Neoplex *Austroplant, Austria.*
Albumin tannate (p.1704·2); liquorice (p.1740·3); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders.

Neoplex B *Neo Quimica, Braz.†.*
Vitamin B substances (p.1922·1).

Neoplex B+C *Neo Quimica, Braz.†.*
Vitamin B substances; ascorbic acid (p.1922·1).

Neoplus *Terapeutico, Ital.*
Royal jelly (p.2382·1); pollen (p.2370·2); ginseng (p.2312·1).
Nutritional supplement.

Neopoldanen *Herbapol Poznan, Pol.*
Pygeum africanum (p.2192·3); maize (p.2288·1).
Benign prostatic hyperplasia.

Neopolydex *Medical Ophthalmics, USA.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1); polymyxin B (p.318·2).
Infected eye disorders.

Neoposid *Neocorp, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Neoprazol *Neo Quimica, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Neopred *PD, Thai.†.*
⊗ Neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Allergic and inflammatory skin disorders.

Neo-Preocil *Edol, Port.*
⊗ Fluorometholone (p.1532·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Neopress *Neo Quimica, Braz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Neoprex *Sigma-Tau, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Neo-Primovlar *Schering, Fin.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neo-Priphen *Minerva (Μινερβα), Gr.*
⊗ Neomycin (p.305·1); gramicidin (p.286·1); naphazoline (p.1565·1); phenylephrine (p.1568·1).
Decongestant.

Neoprobal *Mayo, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Neoproct *Schering, Fin.*
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

NeoProfen *Ovation, USA.*
Ibuprofen lysine (p.64·2).
Closure of patent ductus arteriosus.

Neoproxil *Lemery, Mex.*
Cyproterone acetate (p.2088·2).
Androgenisation in females; male sexual deviation; precocious puberty; prostatic cancer.

Neo-Pruristam *Biostam (Βιοσταμ), Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Neopulmonier *Quimica y Farmacia, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Formerly contained dextromethorphan hydrobromide.
Coughs.

Neo-Pyodron N *Cassella-med, Ger.*
Zinc oxide (p.1621·2); almasilate (p.1705·1).
Neo-Pyodron formerly contained zinc oxide, almasilate, and dequalinium chloride.
Skin disorders.

Neo-Pyrazol *Bonapace, Thai.*
Phenylbutazone sodium (p.117·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Musculoskeletal, joint, and soft-tissue disorders.

Neo-Pyrazon *United American, Malaysia; United American, Philipp.; United American, Singapore†.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Neopyrin *Riemser, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Neopyrin ASA *Biofarm, Pol.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Neoquin *Cassara, Arg.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1); kojic acid (p.1603·3) titanium dioxide (p.1617·3).
Skin hyperpigmentation.

Neoquin Forte *Cassara, Arg.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Skin hyperpigmentation.

Neoral *Novartis, Austral.; Novartis, Canad.; Novartis, Fr.; Novartis, Irl.; Novartis, NZ; Novartis, Neth.; Novartis, UK; Novartis, USA.*
Ciclosporin (p.1822·2).
Atopic dermatitis; graft-versus-host disease; medullary aplasia; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Neoral-Sandimmun *Novartis, Belg.*
Ciclosporin (p.1822·2).
Atopic eczema; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

NeoRecormon *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche Diagnostics, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Ital.; Roche, Neth.; Roche, Norw.; Roche, Pol.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, Turk.; Roche, UK.*
⊗ Epoetin beta (p.1061·1).
Anaemias; autologous blood transfusion.

Neorinol *Silesia, Chile†.*
Ipratropium bromide (p.1124·1).
Rhinitis; rhinorrhoea.

Neo-Rowachol *Rowa Wagner, Hong Kong.*
Menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); β-pinene (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3).
Biliary disorders; gallstones; liver disorders.

Neo-Rowatinex *Rowa Wagner, Hong Kong.*
Camphene (p.2273·2); borneol (p.2268·3); fenchone (p.2302·3); cineole (p.2282·3); α-pinene (p.2368·3); β-pinene (p.2368·3); anethole (p.2258·1).
Urinary-tract disorders.

Neorpan Plus *Quimica y Farmacia, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Neorutin *Helvepharm, Switz.†.*
Rutoside (p.2305·1).
Venous insufficiency.

neos nitro OPT *Optimed, Ger.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Neo-Sabenyl *Qualiphar, Belg.*
Clorophene (p.1641·1); trolamine laurilsulfate (p.2138·3).
Disinfection of skin, hands, mucous membranes, instruments, and materials; irrigation in ear, nose, and throat procedures; skin disorders; wound irrigation.

Neosac *Neo Quimica, Braz.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Neosaldina *Abbott, Braz.*
⊗ Dipyrone (p.49·2); isometheptene mucate (p.2327·2); caffeine (p.1116·3).
Smooth muscle spasm.

Neosanmag *Sanbe, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastrointestinal motility disorders; peptic ulcer.

Neosanmag Fast *Sanbe, Indon.*
Calcium carbonate (p.1714·1); famotidine (p.1730·1); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Neosar *Gensia, USA.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Neo-Sarkol *Cooper (Κοπερ), Gr.*
Vitamin B substances (p.1922·1).

Neosayomol *Cinfa, Spain.*
Diphenhydramine hydrochloride (p.577·2).
Allergic skin reactions.

Neosec *Masa, Thai.*
Paracetamol (p.108·1); orphenadrine citrate (p.812·1).
Pain.

Neosedal *Loeffler, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Neosemid *Neo Quimica, Braz.*
⊗ Furosemide (p.1292·1).
Hypertension.

Neoseptil *Dinafarma, Braz.†.*
Bismuth subgallate (p.1711·1); zinc oxide (p.1621·2).
Barrier preparation; skin disorders.

Neoseptolete *KRKA, Cz.*
Cetylpyridinium chloride (p.1635·1); menthol (p.2340·1); peppermint oil (p.1761·2).
Mouth and throat disorders.

Neosidantoina *BMS, Spain.*
Phenytoin sodium (p.495·2).
Epilepsy.

Neosilin *Sanli, Turk.*
Ampicillin (p.204·1).
Bacterial infections.

Neo-Sinedol *Wild, Switz.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Neo-Sinefrina *GSK Consumer, Port.*
Phenylephrine hydrochloride (p.1568·1).

Neosinol *Interbat, Indon.*
⊗ Neomycin sulfate (p.305·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Neo-Sintrom *Novartis, Chile.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Neosol *Breckenridge, USA.*
Hyoscyamine sulfate (p.1736·1).

Neosolets *SMB, Chile.*
Glycolic acid (p.1598·1).
Acne; keratinisation disorders.

Neosona *Amhof, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); naphazoline hydrochloride (p.1565·2).

Neosoralen *Mac, India†.*
Trioxysalen (p.1620·1).
Vitiligo.

Neosoro *Neo Quimica, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Neospasmina *Herbapol Lublin, Pol.*
Crataegus (p.2289·1); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Neospasmol *Herbapol Lublin, Pol.*
Crataegus (p.2289·1); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Neospect *CIS, Cz.; Amersham, Ital.; Amersham, Spain.*
Technetium-99m (p.2055·3) depreotide trifluoroacetate.
Radionuclide imaging for pulmonary malignancy.

NeoSpect *GE Healthcare, Neth.; CIS, Port.*
Technetium-99m (p.2055·3) depreotide trifluoroacetate.
Radiographic imaging of suspected lung tumours.

Neosporin
Note. This name is used for preparations of different composition.
GSK, Irl.†; GSK, Philipp.; GSK, Switz.; GSK, Thai.†; GSK, Turk.; Pliva, UK.
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Bacterial eye infections.

GSK, Canad.
Bladder irrigation: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial urinary-tract infections.

GSK, Canad.
Cream; eye and ear drops: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Bacterial eye and ear infections; bacterial skin infections.

Pfizer Consumer, Austral.; GSK, Hong Kong; GSK, India; GSK, Mex.; Glaxo Wellcome, S.Afr.†; Monarch, USA.
Eye drops: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Bacterial eye infections.

GSK, Hong Kong†.
Eye ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Bacterial eye infections.

Monarch, USA†; Warner-Lambert, USA†.
Eye ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin (p.210·3) or bacitracin zinc (p.210·3).
Eye infections.

Pfizer Consumer, Austral.
Eye ointment; ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Eye infections; infected skin disorders.

GSK, Canad.; GSK, Mex.; Pfizer Consumer, S.Afr.†.
Ointment: Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Bacterial skin infections.

GSK, India.
Ointment; topical powder: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Neosporin AF *Pfizer Consumer, USA.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Neosporin GU *Glaxo Wellcome, USA.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Prevention of catheter-associated urinary-tract infections.

Neosporin + Pain Relief
Note. This name is used for preparations of different composition.
Warner-Lambert, USA.
Cream: Neomycin (p.305·1); polymyxin B sulfate (p.317·3); pramocaine hydrochloride (p.1868·1).

Warner-Lambert, USA.
Ointment: Neomycin (p.305·1); polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); pramocaine hydrochloride (p.1868·1).

Neosporin-H
Note. This name is used for preparations of different composition.
GSK, India.
Ear drops: ⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); hydrocortisone (p.1535·2).
Otitis externa.

GSK, India.
Ointment: ⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Neossolvan *Neo Quimica, Braz.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Neostan *Danlex, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Neostatin *Cassara, Arg.; Delta, Braz.*
Nystatin (p.543·2).
Candidiasis.

Neo-Stediril *Wyeth Lederle, Austria; Wyeth Lederle, Belg.†; Wyeth, Ger.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neostesin *Nycomed, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Neostig *Carinopharm, Ger.*
Neostigmine metilsulfate (p.631·3).
Myasthenia gravis; reversal of competitive neuromuscular blockade.

Neostigmine Min-I-Mix *IMS, USA.*
Neostigmine metilsulfate (p.631·3).
Atropine sulfate (p.1219·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Neostil *Novartis Consumer, Port.*
Dimetindene maleate (p.576·3).
Hypersensitivity reactions.

Neostix-N *Bayer, Austral.†.*
Test for protein, glucose, blood, and nitrite in urine.

Neo-Stomygen
Note. This name is used for preparations of different composition.
Stomygen, Ital.
Mouthwash: Chlorhexidine gluconate (p.1635·3); cetylpyridinium chloride (p.1635·1).
Oral disinfection; oral hygiene.

Stomygen, Ital.
Toothpaste: Sodium monofluorophosphate (p.1964·3); propolis (p.2373·3); enoxolone (p.50·1); cetylpyridinium chloride (p.1635·1).
Oral disinfection; oral hygiene.

Neostrata
Note. This name is used for preparations of different composition.
HLB, Arg.; Hamilton, Austral.; Canderm, Canad.; Medstyle, Chile; Q-Med, Ital.
A range of preparations containing glycolic acid (p.1598·1) or gluconolactone (p.2313·1).
Emollient; skin care; skin disorders.

Finn Vita, Chile†.
Cream SPF 15: Glycolic acid (p.1598·1); gluconolactone (p.2313·1); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Finn Vita, Chile†.
Depigmenting cream SPF 15: Octinoxate (p.1608·2); hydroquinone (p.1598·2); titanium dioxide (p.1617·3); gluconolactone (p.2313·1).
Skin pigmentation disorders; sunscreen.

Finn Vita, Chile†.
Depigmenting gel: Glycolic acid (p.1598·1); hydroquinone (p.1598·2).
Skin pigmentation disorders.

Medstyle, Chile.
Depigmenting gel forte: Gluconolactone (p.2313·1); lactobionic acid; kojic acid (p.1603·3); hydroquinone (p.1598·2); liquorice (p.1740·3).
Skin pigmentation disorders.

Finn Vita, Chile†.
Lip conditioner: Glucurolactone (p.2314·2); octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Chapped lips; sunscreen.

Medstyle, Chile.
Shampoo: Gluconolactone (p.2313·1); mandelic acid (p.296·3); piroctone olamine (p.1610·1).
Dandruff.

NeoStrata AHA Light *Canderm, Canad.†.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).

NeoStrata AHA Smoothing and Moisturizing *Canderm, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).

NeoStrata Astringent Acne Treatment *Canderm, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

NeoStrata Blemish Spot Gel *Canderm, Canad.*
Salicylic acid (p.1612·2); glycolic acid (p.1598·1).
Acne.

NeoStrata Canada HQ Plus
Note. This name is used for preparations of different composition.
Canderm, Canad.
Cream: Hydroquinone (p.1598·2); padimate O (p.1609·1); oxybenzone (p.1608·3); octocrilene (p.1608·3).
Canderm, Canad.
Topical gel: Hydroquinone (p.1598·2).

NeoStrata Daytime *Canderm, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); glycolic acid (p.1598·1).

Neostrata Daytime Protection Cream *Hamilton, Austral.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Emollient; sunscreen.

Neostrata Gel Despigmentante *HLB, Arg.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Skin hyperpigmentation.

NeoStrata HQ *Canderm, Canad.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1).
Skin hyperpigmentation.

Neostrata Lip Conditioner *Hamilton, Austral.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2).
Dry lips; sunscreen.

Neostrata Sunblock
Note. This name is used for preparations of different composition.
Canderm, Canad.
Lotion SPF 30: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.
Canderm, Canad.
Spray SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Neosulf *Alphapharm, Austral.; Pacific, NZ†.*
Neomycin sulfate (p.305·1).
Bowel sterilisation before surgery; hepatic encephalopathy.

Neosulfur *Laborest, Ital.*
Dimethyl sulfone (Lignisul) (p.2294·1); zinc; copper; vitis vinifera (p.2316·3); vitamin B substances (p.1922·1).
Musculoskeletal, joint, and peri-articular pain.

Neosulida *Neo Quimica, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Neo-Suxigal *Anfarm, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Neosyd *GMP, Indon.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Eye infections.

Neo-Synalar
Note. This name is used for preparations of different composition.
Stiefel, Philipp.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.
Roche, Venez.†.
Ear drops: ⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected ear disorders.
Roche, Venez.
Ointment: ⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Neo-Synalar con Neomicina *Roche, Venez.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected ear and skin disorders.

Neo-Synalar con Yodoclorohidroxiquina *Roche, Venez.†.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Neo-Synephrine *Hospira, Canad.; Ursapharm, Cz.; Sanofi Winthrop, Israel; Teofarma, Ital.; Bayer, USA; Hospira, USA.*
Phenylephrine hydrochloride (p.1568·1).
Adjunct in spinal or regional anaesthesia; eye congestion; hypotension; maintenance of blood pressure during surgery; nasal congestion; paroxysmal supraventricular tachycardia; production of mydriasis; vascular failure in shock, drug-induced hypotension, or hypersensitivity.
Sanofi Synthelabo, Austral.†.
Eye drops: Phenylephrine hydrochloride (p.1568·1).
Eye congestion; production of mydriasis.
Abbott, Austral.
Injection: Phenylephrine hydrochloride (p.1568·1).
Maintenance of blood pressure during surgery; paroxysmal supraventricular tachycardia; spinal and regional analgesia; vascular failure in shock or drug-induced hypotension or hypersensitivity.

Neosynephrine *AGEPS, Fr.; InterMed, NZ.*
Phenylephrine hydrochloride (p.1568·1).
Hypotension.

Neo-Synephrine 12 Hour *Bayer, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Neosynephrin-POS *Ursapharm, Ger.*
Phenylephrine hydrochloride (p.1568·1).
Production of mydriasis; uveitis.

Neotab *Deva, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neotaflan *Neo Quimica, Braz.*
Diclofenac potassium (p.44·3) or diclofenac resinate (p.46·1).
Inflammation; pain.

Neotalem *Laboratorios Chile, Chile†; Lemery, Mex.; Lemery, Thai.; Atafarm, Turk.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Neotaren *Neo Quimica, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

NeoTaxan *Neocorp, Ger.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.

NeoTect *Diatide, USA.*
Technetium-99m depreotide (p.2055·3).
Scintigraphic imaging for pulmonary malignancy.

Neotenol *Biobras, Braz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Neotensin *CEPA, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Neotensin Diu *CEPA, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); enalapril maleate (p.1276·1).
Hypertension.

Neotetranase *Rottapharm, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Neo-Thyreostat *Herbrand, Ger.†.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Neothyron *Sanofi Synthelabo, Austria.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Neotibi *Pyridam, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Neotica
Note. This name is used for preparations of different composition.
TNP, Thai.†.
Balm: Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); eugenol (p.2301·2).
Insect bites; muscle pain and inflammation; sports injuries; sprains.
TNP, Thai.†.
Capsules: Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Neotigason *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile; Actavis, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong†; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.*
Acitretin (p.1586·1).
Darier's disease; keratinisation disorders; psoriasis.

Neo-Tinic *Neolab, Canad.*
Multivitamins and iron (p.1922·1).

Neo-Tiroimade *Esfar, Port.*
Liothyronine sodium (p.2174·1).
Thyroid disorders.

Neo-Tizide *Pfizer, Austria.*
Methaniazide calcium (p.298·3).
Tuberculosis.

Neotomic *NBZ, India.*
Glycerol (p.2314·2); sodium chloride (p.1686·1).
Bowel evacuation; constipation.

Neoton
Note. This name is used for preparations of different composition.
Alfa Wassermann, Cz.; Pharmacia, Ital.†; Alfa Wassermann, Rus.
Fosfocreatinine sodium (p.2289·3).
Cardiac disorders.
Alfa Wassermann, Pol.
Creatine phosphate (p.2289·3).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Cardiac disorders.

Neotop *Medley, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Bacterial skin infections.

Neotopic *Technilab, Canad.†; Technilab, Pol.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial skin infections; infected wounds.

Neo-Tormentil *Galenowe Olsztyn, Pol.*
Borax (p.2268·1); ichthammol (p.1599·1); tormentil (p.2403·2); zinc oxide (p.1621·2).
Wounds.

Neo-Tosel *Geminis, Arg.†.*
Bromhexine (p.1552·2); clofedanol (p.1554·2).
Coughs.

Neotoss *Neo Quimica, Braz.*
Dropropizine (p.1557·3).
Coughs.

Neotrace *American Pharmaceutical, USA.*
Trace element preparation (p.1922·1).
Additive for intravenous total parenteral nutrition solutions.

Neotracin *Novartis, Switz.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial eye infections.

Neotren *Apotex, UK.*
Pentoxifylline (p.1367·2).
Peripheral vascular disease.

Neotretin *Cassara, Arg.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders.

Neotrex *Serral, Mex.*
Isotretinoin (p.1599·2).
Acne.

Neotrexate *GSK, India.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Neotri *Lilly, Ger.*
⊗ Xipamide (p.1434·1); triamterene (p.1417·2).
Hypertension; oedema.

Neotricin *Legrand, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Eye infections.

Neotricin HC *Bausch & Lomb, USA.*
⊗ Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3); hydrocortisone acetate (p.1535·2).
Eye inflammation with bacterial infection.

Neotrim *Danlex, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Neo-Trim Fibre *GNLD, Austral.†.*
Fibre blend (from oat bran, barley bran, soy bran, orange gibre, acacia, ispaghula husk) (p.1712·3); methylcellulose (p.2145·1).
Obesity.

Neo-Trim Meal Replacement *GNLD, Austral.†.*
Food for special diets (p.1922·1).
Obesity.

Neotrin *Neo Quimica, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Neo-Tuss *Neolab, Canad.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); sodium citrate (p.1673·3); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

NeoTussan *Novartis Consumer, Ger.*
Dextromethorphan polistirex (p.1556·1).
Coughs.

Neo-Ulcoid *Valdecasas, Mex.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Neourizine *Adelco, Gr.*
⊗ Reserpine (p.1387·3); chlorothiazide (p.1243·1).
Hypertension.

Neo-Ustiol *INTES, Ital.*
Sodium citrate (p.1673·3); sodium aminobenzoate (p.2388·3); procaine (p.1869·2); cod-liver oil (p.1935·2).
Ophthalmic burns.

Neovent *Interhealthcare, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders associated with bronchospasm and excessive mucus.

Neovermin *Neo Quimica, Braz.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Neovir *Pharmsintez, Rus.*
Cridanimod.
Candidiasis of the skin and mucous membranes; chlamydial infections; multiple sclerosis; radiation immunodeficiency; venereal lymphogranuloma; viral infections.

Neovis *Pharmacia, Ital.*
Vitamin, carbohydrate, and mineral preparation with creatine (p.1922·1).
Nutritional supplement.

NeoVisc *Stellar, Canad.*
Sodium hyaluronate (p.2320·1).
Replacement of synovial fluid following arthrocentesis.

Neovita
Savoy, Singapore.
Multivitamin and mineral preparation with ginseng (p.1922·1).
Tonic.
Wallace Mfg Chem., UK.
Multivitamin and ginseng preparation with or without minerals and lecithin (p.1922·1).

Neovlar *Schering, Braz.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Neovletta *Schering, Swed.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Neoxane *Asta Oncologia, Braz.†.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Neoxantron *Neocorp, Ger.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Neoxene *Finderm, Ital.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin, wounds, burns, and vagina.

Neoxidil *Galderma, Belg.; Galderma, Braz.†; Galderma, Hong Kong†; Galderma, Israel; Galderma, Port.; Galderma, Singapore†.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Neoxil *Offenbach, Mex.*
Neomycin (p.305·1); kaolin (p.1738·1); pectin (p.2145·2); homatropine (p.1881·2).
Diarrhoea.

Neoxinal *Farmec, Ital.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin, wounds, and burns.

Neo-Xylestesin *Espe, Austria.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Neo-Xylestesin forte *Espe, Austria.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) and noradrenaline hydrochloride (p.1360·2) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

NeOxyn *Richter, Philipp.*
Oxytocin (p.2015·2).
Incomplete abortion; third-stage labour; uterine atony; uterine curettage.

Neoyod *Grunenthal, Chile†.*
Povidone-iodine (p.1659·2).
Disinfection of mucous membranes, skin, and wounds; vaginal infections.

Neozentius *Pharma Investi, Chile.*
Escitalopram (p.391·1).
Depression.

Neozep
Note. This name is used for preparations of different composition.
United American, Hong Kong; Medifarma, Indon.
Phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1); salicylamide (p.121·2); chlorphenamine maleate (p.571·3); vitamin C (p.1983·3).
Cold and influenza symptoms; nasopharyngeal congestion; nasopharyngeal disorders.
Great Eastern, Thai.; Myra, Thai.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms; hay fever; sinusitis.
United Laboratories, Philipp.
Oral drops: Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; nasal congestion.
United Laboratories, Philipp.
Syrup; tablets: Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms; nasal congestion.

Neozep Non-Drowsy *United Laboratories, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cold and influenza symptoms; nasal congestion.

Neozimina *Neo Quimica, Braz.*
Clofazimine (p.254·2).
Leprosy.

Neozine
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Levomepromazine hydrochloride (p.1002·3).
Adjunct in general anaesthesia; pain; premedication; psychoses.
Sanofi Synthelabo, Port.†.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Neozol *Neo Quimica, Braz.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neozolam *Neo Quimica, Braz.*
Alprazolam (p.960·1).
Anxiety.

Neozolone *British Dispensary, Thai.*
⊗ Prednisolone (p.1540·3); neomycin (p.305·1).
Eczema; infected skin disorders; seborrhoeic dermatitis.

Nepatic *Kalbe, Indon.*
Gabapentin (p.482·3).
Epilepsy.

Nepenic *New Research, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Nepenthe *Hexal, Philipp.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Neper *Ivax, Arg.*
Mesna (p.1449·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Neperlan *Terramedic, Philipp.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

NephPlex RX *Nephro-Tech, USA.*
Multivitamin preparation for dialysis patients (p.1922·1).

Nephraamine *Eczacibasi-Baxter, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Nephral *Pfleger, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Nephramine *Fresenius Kabi, Fr.; Braun, Hong Kong†; Pisa, Mex.†; Braun, Spain; R&D, USA.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal impairment.

Nephrisan P *Ziethen, Ger.†.*
Squill (p.1573·1); crataegus (p.2289·1).
Heart failure.

Nephrisol *Kalbe, Indon.; Sanghiang, Indon.*
Preparation for enteral nutrition in renal failure (p.1922·1).

Nephrisol mono *Cesra, Ger.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Nephritin *Tentan, Switz.†.*
Homoeopathic preparation.

Nephro-Calci *R&D, USA.*
Calcium carbonate (p.1714·1).
Calcium deficiency; dietary supplement.

Nephrocaps *Fleming, USA.*
Vitamin B substances with vitamin C (p.1922·1).
Vitamin deficiency in renal dialysis.

Nephrocare *Abbott, Israel; Ross, Israel.*
Preparation for enteral nutrition (p.1922·1).
Complete nutrition or food supplement in renal disease.

Nephro-Fer *Watson, USA.*
Ferrous fumarate (p.1938·3).
Iron-deficiency anaemias.

Nephro-Fer Rx *R&D, USA†.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Iron deficiency.

Nephrogesic *Ethnor, India.*
Phenazopyridine hydrochloride (p.116·2); nitrofurantoin (p.308·1).
Urinary-tract infections.

Nephrolith mono *Biomo, Ger.†.*
Solidago virgaurea (p.2391·1).
Renal calculi.

nephro-loges *Loges, Ger.*
Equisetum (p.2299·3); solidago virgaurea (p.2391·1); ononis (p.2357·1); parsley root (p.2363·2).
Urinary-tract disorders.

Nephron *Nephron, USA.*
⊗ Racepinefrine hydrochloride (p.1204·2).
Bronchospasm.

Nephron FA *Nephro-Tech, USA.*
Multivitamin preparation with iron and folic acid (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Nephronorm med
Note. This name is used for preparations of different composition.
APS, Ger.
Tablets: Java tea (p.2328·2).
Urinary-tract disorders.

Mauermann, Ger.†.
Tea: Silver birch (p.2266·3); solidago virgaurea (p.2391·1); java tea (p.2328·2); ononis (p.2357·1); rose fruit (p.2381·2); centaurea cyanus; calendula (p.2273·1).
Urinary-tract disorders.

Nephro-Pasc *Pascoe, Ger.†.*
Solidago virgaurea (p.2391·1); birch leaf (p.2266·3); java tea (p.2328·2).
Urinary-tract disorders.

Nephropur tri *Repha, Ger.†.*
Solidago virgaurea (p.2391·1); birch leaf (p.2266·3); java tea (p.2328·2).
Urinary-tract disorders.

Nephrosal *Slovakofarma, Cz.†.*
Birch leaf (p.2266·3); phaseolus; equisetum (p.2299·3); ononis (p.2357·1); urtica (p.2409·3).
Urinary-tract disorders.

Nephroselect M *Dreluso, Ger.*
Solidago virgaurea (p.2391·1); equisetum (p.2299·3); birch leaf (p.2266·3); ononis (p.2357·1); lovage (p.2335·1); tropaeolum majus (p.2264·3); saw palmetto (p.2192·3).
Urinary-tract disorders.

Nephrosolid *Bioforce, Switz.*
Solidago virgaurea (p.2391·1); silver birch (p.2266·3); ononis (p.2357·1); equisetum (p.2299·3).
Urinary-tract disorders.

Nephrosteril *Roux-Ocefa, Arg.†; Fresenius Kabi, Hong Kong; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, Neth.; Fresenius Kabi, Philipp.; Fresenius Kabi, Singapore†; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal disease.

Nephrotect *Fresenius Kabi, Cz.; Fresenius Kabi, Ger.; Fresenius Kabi, Hung.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Switz.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal failure.

Nephrotrans *Medice, Ger.; Salmon, Switz.*
Sodium bicarbonate (p.1673·2).
Metabolic acidosis.

Nephro-Vite *R&D, USA.*
Multivitamin preparations (p.1922·1).

Nephro-Vite +Fe *R&D, USA†.*
Multivitamin preparation with iron (p.1922·1).

Nephrox *Fleming, USA.*
Aluminium hydroxide (p.1706·2).
Hyperacidity.

Nephrubin-N
Note. This name is used for preparations of different composition.
Weber & Weber, Ger.†.
Herbal tea: Birch leaf (p.2266·3); ononis (p.2357·1); java tea (p.2328·2); solidago (p.2391·1).
Urinary-tract disorders.

Weber & Weber, Ger.†.
Tablets: Birch leaf (p.2266·3); java tea (p.2328·2).
Urinary-tract disorders.

Nephur 6 *Roche Diagnostics, Austral.†; Roche Diagnostics, Irl.†.*
Test for nitrite, pH, protein, glucose, blood, and leucocytes in urine.

Nephur 7 *Roche Diagnostics, Fr.†; Roche Diagnostics, Irl.†.*
Test for pH, leucocytes, nitrites, proteins, glucose, ketones, and blood in urine.

Nephur-Test + Leucocytes *Roche Diagnostics, Austral.†.*
Test for leucocytes, nitrite, pH, protein, glucose, and blood in urine.

N-Epi *Novell, Indon.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Hypotension.

Nepiros *SIFFRA, Ital.*
Vitamin B substances (p.1922·1); propolis (p.2373·3); *Lactobacillus paracasei* (p.2372·3); acacia honey (p.1948·2); black currant (p.2267·1); lactoferrin (p.2330·1); rose fruit (p.2381·2); echinacea angustifolia (p.2298·1); salix alba (p.121·3).
Fever; inflammation.

Nepituss *Bioindustria, Ital.*
Nepinalone hydrochloride (p.1566·1).
Coughs.

Neplit *Menarini, Hung.; Berlin-Chemie, Pol.*
⊗ Budesonide (p.1520·1).
Asthma.

Nepodex *Latinofarma, Braz.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Nepresol
Note. This name is used for preparations of different composition.
Novartis, Austria; Teofarma, Ger.; IFET (ΙΦΕΤ), Gr.
Dihydralazine mesilate (p.1264·3) or dihydralazine sulfate (p.1264·3).
Eclampsia; heart failure; hypertension.

Novartis, Belg.; Novartis, Hong Kong†; Novartis, India.
Dihydralazine sulfate (p.1264·3).
Hypertension.

Cristalia, Braz.
Hydralazine hydrochloride (p.1305·3).
Heart failure; hypertension.

Novartis, Cz.†; Novartis, Malaysia†; Novartis, S.Afr.†; Novartis, Swed.†; Novartis, Switz.†; Novartis, Thai.
Dihydralazine mesilate (p.1264·3).
Hypertension.

Nepressol *Genopharm, Fr.*
Dihydralazine mesilate (p.1264·3).
Pre-eclampsia.

Nepro *Abbott, Arg.; Abbott, Austral.; Abbott, Chile; Abbott, Cz.†; Abbott, Fin.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Malaysia; Abbott, Mex.†; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.; Abbott Nutrition, UK; Ross, USA.*
Preparation for enteral nutrition in renal failure (p.1922·1).

Neptalip *Rayere, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Neptazane *Wyeth-Ayerst, Canad.†; Lederle, Israel†; Wyeth-Ayerst, Thai.†.*
⊗ Methazolamide (p.1883·1).
Glaucoma.

Neptide *Bangkok Lab & Cosmetic, Thai.*
Nimesulide (p.95·3).
Inflammation; pain.

Neradin *Collins, Mex.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Nerapin *LKM, Arg.*
Nevirapine (p.899·1).
HIV infection.

Nerdipina *OM, Port.; Ferrer, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Nerdipine *Medochemie, Thai.†.*
Nicardipine (p.1348·2).
Angina pectoris; hypertension.

Nereflun *New Research, Ital.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis; asthma; bronchostenosis.

Nerelid *New Research, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nerex *Farmanova, Ital.*
Royal jelly (p.2382·1); honey (p.1948·2); myrtillus (p.2349·3); fructose.
Nutritional supplement.

Nerfalex *Generics Pharmacal, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Nerfeco *Ferron, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Ner-fluid S *Fides, Ger.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3).
Skin disorders.

Nergadan *Uriach, Spain.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Neribas *Schering, Switz.†.*
Emollient.
Skin disorders.

Neribase *Intendis, Denm.; Leiras, Fin.; Intendis, Fr.; Intendis, Ital.; Intendis, Port.*
Emollient.
Dry skin disorders.

Neribax *Baxter, Mex.†.*
Hydroxocobalamin (p.1980·3).

Neriderm *Agis, Israel.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Neriforte *Schering, Austria.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Nerilon *Interbat, Indon.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Neripros *Pharos, Indon.*
Risperidone (p.1024·2).
Psychoses.

Nerisalic *Stiefel, Canad.; Schering, Fr.; Intendis, Ital.*
⊗ Diflucortolone valerate (p.1529·2); salicylic acid (p.1612·2).
Skin disorders.

Nerisona *Schering, Arg.; Schering, Austria; Schering, Belg.; Schering, Braz.; Intendis, Denm.; Schering, Ger.; Schering, Indon.; Intendis, Ital.; Intendis, Mex.; Schering, Neth.; Schering, Philipp.; Intendis, Port.; Schering, Switz.†.*
⊗ Diflucortolone valerate (p.1529·2).
Skin and scalp disorders.

Nerisona C *Schering, Arg.; Asche, Ger.†; Schering, Ger.†; Intendis, Ital.; Intendis, Port.; Schering, Turk.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Nerisona Combi *Schering, Indon.; Schering, Philipp.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Nerisone *Stiefel, Canad.; Intendis, Fr.; Schering, Hong Kong; Bayer Schering, Malaysia†; CSL, NZ; Schering, S.Afr.; Schering, Singapore†; Meadow, UK.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Nerisone C *Intendis, Fr.; Schering, Hong Kong; Schering, NZ; Schering, Singapore†.*
⊗ Diflucortolone valerate (p.1529·2); chlorquinaldol (p.242·3).
Infected skin disorders.

Nerita *Delegant, Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Nerixia *Abiogen, Ital.*
Neridronate sodium (p.1100·2).
Osteogenesis imperfecta; Paget's disease of bone.

Nerizina *Neckerman, Braz.†.*
Cinnarizine (p.573·1).
Vertigo.

Nero *Elea, Arg.*
Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3).
Smooth muscle spasm.

Nerox-B *Abdi, Turk.*
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Nerva Plus *Gracia, Indon.*
Vitamin B; vitamin B; vitamin B; folic acid (p.1922·1).
Vitamin B and folic acid deficiency.

Nervafil *Filadams, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Neurological pain; neuropathies; vitamin B deficiency.

Nervan
Note. This name is used for preparations of different composition.
Rosch & Handel, Austria.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine citrate (p.1116·3).
Fever; pain.

Meyer, Venez.
Bromazepam (p.964·3).
Anxiety.

Nervatona Calm
Note. This name is used for preparations of different composition.
Brauer, Austral.
Oral liquid: Anamirta cocculus; helonias (p.2318·3); passion flower (p.2363·2); ignatia; nux vomica; phosphoricum acidum; sepia; zincum metallicum.
Anxiety.

Brauer, Austral.
Oral spray; tablets: Homoeopathic preparation.

Nervatona Focus
Note. This name is used for preparations of different composition.
Brauer, Austral.
Oral liquid: Anamirta cocculus; helonias (p.2318·3); ginseng (p.2312·1); passion flower (p.2363·2); argentum nitricum; ignatia; kali phosphoricum; magnesia phosphorica; nux vomica; phosphoricum acidum; sepia; valeriana; zincum metallicum.
Formerly known as Nervatona Plus.
Anxiety; stress.

Brauer, Austral.
Oral spray: Homoeopathic preparation.

Nervaxon *Fidia, Ital.*
St John's wort (p.422·3).
Depression.

Nerve *Med-One, Gr.*
Risperidone (p.1024·2).
Psychoses.

Nerve Agent Antidote L4A1 *Ministry of Defence, UK.*
Pralidoxime mesilate (p.1460·2); avizafone (p.963·3); atropine sulfate (p.1219·3).
Nerve agent exposure.

Nerve Agent Pre-Treatment Tablet Set L1A1 *Ministry of Defence, UK.*
Pyridostigmine bromide (p.633·3).
Risk of poisoning by organophosphorus cholinesterase inhibitors.

Nerve Tonic *Hylands, Canad.*
Homoeopathic preparation.

Nervei *Rodisma, Ger.*
St John's wort (p.422·3).
Depression.

Nervencreme S *Fides, Ger.†.*
Peppermint oil (p.1761·2); eucalyptus oil (p.2301·2).
Pain.

Nervendragees *Ratiopharm, Ger.†; Ratiopharm, Pol.*
Valerian root (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Anxiety disorders; insomnia; nervous disorders; sleep disorders.

Nerven-Dragees *Zeller, Israel.*
Crataegus (p.2289·1); passion flower (p.2363·2); lupulus (p.2335·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Nervenja *OTW, Ger.†.*
Homoeopathic preparation.

Nervenkapseln *Ratiopharm, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Nervenruh *Klosterfrau, Austria.*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Anxiety disorders; sleep disorders.

Nerventee St Severin *Smetana, Austria.*
Valerian (p.2410·1); lupulus (p.2335·2); St John's wort (p.422·3); peppermint leaf (p.1761·2); calluna vulgaris; delphinium consolida.
Anxiety disorders; sleep disorders.

Nerventropfen *Jacoby, Austria.*
Homoeopathic preparation.

Nerveplex
IAE, Philipp.
Capsules: Vitamin and mineral preparation with taurine (p.1922·1).
Nutritional supplement.

IAE, Philipp.
Oral drops; syrup: Vitamin and mineral preparation with chlorella, lysine, and taurine (p.1922·1).
Nutritional supplement.

Nervex *Prosel, Philipp.*
Vitamin B substances; vitamin E (p.1922·1).

Nervifene *Interdelta, Switz.*
Cloral hydrate (p.979·1).
Agitation; insomnia.

Nervigenol Magnesio *Labinca, Arg.†.*
Vitamin C (p.1983·3); magnesium aspartate (p.1679·1).
Dietary supplement.

Nervikan *DHU, Spain.*
Valerian (p.2410·1); melissa (p.2339·3).
Anxiety; insomnia.

Nervilan *Jumont, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Encephalopathy; neuralgia; neuritis; neuropathy.

Nervinetas *Novum, Mex.; Grunenthal, Venez.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety; insomnia; sleep disorders.

Nervinetten *Zellaforte, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2).
Agitation; sleep disorders.

Nervinex *Menarini, Spain.*
Brivudine (p.867·3).
Herpes zoster infections.

Nervinfant N *Rubiepharm, Ger.†.*
Lupulus (p.2335·2); passion flower (p.2363·2).
Agitation; sleep disorders.

Nervinolum *Herbapol Krakow, Pol.*
Lupulus (p.2335·2); lavender (p.2331·1); motherwort (p.2347·3); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Nervisatis *Gezzi, Arg.*
Valerian (p.2410·1).

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Nervistop *Lafedar, Arg.*
Lorazepam (p.1004·1).
Anxiety; muscle spasm.

Nervita *Boiron, Canad.*
Homoeopathic preparation.

Nervitone
Note. This name is used for preparations of different composition.
Alembic, India.
Peptone; calcium gluconate; magnesium chloride; manganese sulfate; yeast extract (p.1922·1).
Tonic.

Combiphar, Indon.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Facial paresis; ischialgia; neuralgia; neuritis; vitamin B deficiency.

Nervitone E *Combiphar, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Facial paresis; ischialgia; neuralgia; neuritis; vitamin B deficiency.

Nervium
Note. This name is used for preparations of different composition.
De Mayo, Braz.
Bromazepam (p.964·3).
Anxiety; insomnia.

Saba, Turk.
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; muscle spasm; premedication; status epilepticus.

Nervival *VSM, Neth.*
Homoeopathic preparation.

Nervix *Bago, Chile.*
Venlafaxine hydrochloride (p.427·3).
Depression.

nervo OPT N *Optimed, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Nervobion *Merck, Spain.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2).
Vitamin B deficiency.

Nervobion Fuerte *Merck, Arg.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Nervocaine *Keene, USA.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Nervocalm *Garden House, Arg.*
Passion flower (p.2363·2); melissa (p.2339·3); valerian (p.2410·1); tilia (p.2402·2).
Nervous disorders.

Nervocur *Fabra, Arg.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Nervocuril *Fabra, Arg.*
Flunitrazepam (p.996·2).

Nervogastrol N *Sanofi Synthelabo, Ger.†.*
Bismuth subnitrate (p.1711·2); bismuth subgallate (p.1711·1); heavy magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); greater celandine (p.2317·1); condurango (p.2287·1).
Gastrointestinal disorders.

Nervoheel *Peithner, Austria.*
Homoeopathic preparation.

Nervoid N *Hanosan, Ger.*
Homoeopathic preparation.

Nervoject F *Syxyl, Ger.*
Homoeopathic preparation.

Nervol *Retrain, Spain.*
Brivudine (p.867·3).
Herpes zoster infections.

Nervolta *Volta, Chile.*
Calcium bromolactobionate (p.967·3).
Sedative.

Nervomax TB12 *TRB, Arg.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); thioctic acid (p.2400·2).
Alcoholism; antoxidant; neuritis; tonic.

Nervomix *Agropharm, Pol.*
Lupulus (p.2335·2); St John's wort (p.422·3); melissa (p.2339·3); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Nervonocton N *Pfluger, Ger.†.*
Kava (p.2328·3).
Nervous disorders.

Nervopax *Lehning, Fr.*
Homoeopathic preparation.

Nervoregin comp *Pfluger, Ger.*
Homoeopathic preparation.

Nervoregin forte *Pfluger, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Nervous disorders.

Nervoregin H *Pfluger, Ger.*
Homoeopathic preparation.

Nervoregin phyto *Pfluger, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Nervous disorders.

Nervosal *Neuropharma, Arg.*
Fluoxetine (p.397·3).
Depression.

Nervosan *Farmo Quimica, Chile†.*
Thioridazine (p.1031·2).

Nervosana *Riemser, Ger.†.*
Achillea (p.2245·2); liquorice (p.1740·3); melissa (p.2339·3); peppermint leaf (p.1761·2); rubus fruticosus; chamomile (p.2279·3); tilia (p.2402·2); valerian (p.2410·1); absinthium (p.2244·1).
Nervous disorders; sleep disorders.

Nervosol *Herbapol Wroclaw, Pol.*
Angelica (p.2258·1); lupulus (p.2335·2); melissa (p.2339·3); valerian (p.2410·1); lavender (p.2331·1).
Insomnia; nervous disorders.

Nervostal *Pharmanik (Φαρμανικ), Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Nervoton *Farmo Quimica, Chile.*
Vitamin B substances (p.1922·1).
Tonic.

Nervova Cajova Smes *Megafyt-R, Cz.*
Valerian (p.2410·1); peppermint leaf (p.1761·2); melissa (p.2339·3); fennel (p.2302·3).
Nervous disorders.

Nervpin N *Schoning-Berlin, Ger.*
Menthol (p.2340·1); noble fir oil.
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; superficial vascular disorders.

Nervuton N *Cesra, Ger.†.*
Homoeopathic preparation.

Nerwobonisol *Bonimed, Pol.*
Chamomile (p.2279·3); crataegus (p.2289·1); lupulus (p.2335·2); motherwort (p.2347·3); melissa (p.2339·3); valerian (p.2410·1).
Insomnia; nervous disorders.

Nerwonal *Pampa, Pol.*
Crataegus (p.2289·1); passion flower (p.2363·2).
Arrhythmias; nervous disorders; sleep disorders.

Nesacain *AstraZeneca, Switz.*
Chloroprocaine hydrochloride (p.1857·1).
Local anaesthesia.

Nesacaine *AstraZeneca, Canad.; Astra, USA.*
Chloroprocaine hydrochloride (p.1857·1).
Local anaesthesia.

Nesbiler *Klonal, Arg.†.*
⊗ Fluorometholone (p.1532·3); neomycin (p.305·1).
Infected eye disorders.

Nescon-PD *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Nesfare *Madaus, Spain.*
⊗ Framycetin sulfate (p.279·1); triamcinolone acetonide (p.1544·3); centella (p.1592·3).
Infected skin disorders.

Nesgarin *Yeni, Turk.*
Benzoic acid (p.1630·2); sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1); menthol (p.2340·1); methyl salicylate (p.85·3).
Oral hygiene.

Nesivine *Merck, Belg.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eustachian-tube inflammation; nasal congestion; otitis media; sinusitis.

Nespo *Dompe, Cz.; Dompe Biotec, Ital.; Dompe Biotec, Neth.; Dompe, Port.*
⊗ Darbepoetin alfa (p.1058·2).
Anaemias.

Nestabs *Fielding, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Multivitamin and mineral supplement for pregnancy and lactation.

Nestargel *Nestle, Switz.; Nestle, UK.*
Ceratonia (p.2143·2).
Infant feed thickener; vomiting.

Nesthakchen *Schulke & Mayr, Austria.*
Fennel (p.2302·3); aniseed (p.2258·2); caraway (p.2276·3); chamomile (p.2279·3); liquorice (p.1740·3); fennel oil (p.2303·1); anise oil (p.2258·2); caraway oil (p.2277·1); chamomile oil (p.2279·3).
Gastrointestinal disorders.

Nestic *Asian Pharm, Thai.*
Clotrimazole (p.530·1).
Trichomoniasis; vaginal fungal infections.

Nestle VHC *Nestle, USA.*
Preparation for enteral nutrition (p.1922·1).

Nestosyl
Note. This name is used for preparations of different composition.
Pharmethic, Belg.
Pramocaine hydrochloride (p.1868·1); chlorhexidine hydrochloride (p.1635·3); zinc oxide (p.1621·2).
Minor wounds; skin disorders.

Heca, Neth.
Pramocaine hydrochloride (p.1868·1); zinc oxide (p.1621·2).
Skin disorders.

Zydus, Fr.
Ointment: Benzocaine (p.1854·1); butyl aminobenzoate (p.1857·1); resorcinol (p.1612·1); hydroxyquinoline (p.2323·2); zinc oxide (p.1621·2).
Insect stings.

Zydus, Fr.
Topical solution: Benzocaine (p.1854·1); butyl aminobenzoate (p.1857·1); hydroxyquinoline (p.2323·2).
Catheterisation; local anaesthesia.

Nestrolan *3DDD, Belg.*
Trazodone hydrochloride (p.424·3).
Depression.

Nestum *Nestle, Port.*
Gluten-free food (p.1922·1).

Nesvital *Nestle, Fr.†.*
A range of foods for special diets (p.1922·1).
Obesity.

Netaf *Chemopharma, Chile.*
Ketorolac (p.75·2).
Pain.

Netan *Almirall, Neth.*
Ebastine (p.579·1).
Allergic rhinitis.

Netazon *Neckerman, Braz.†.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Nethaprin Dospan *Adcock Ingram, S.Afr.*
⊗ Bufylline (p.1116·3); doxylamine succinate (p.578·2); etafedrine hydrochloride (p.1560·2); phenylephrine hydrochloride (p.1568·1).
Coughs; obstructive airways disease.

Nethaprin Expectorant *Adcock Ingram, S.Afr.*
⊗ Bufylline (p.1116·3); doxylamine succinate (p.578·2); etafedrine hydrochloride (p.1560·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Neticin *Undra, Mex.†.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netil *Siam Bheasach, Thai.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netildex *SIFI, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2); netilmicin sulfate (p.306·3).
Infected eye disorders.

Netillin *Schering-Plough, Irl.†; Schering-Plough, UK†.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netilyn *Schering-Plough, Denm.†; Schering-Plough, Fin.; Schering-Plough, Norw.; Schering-Plough, Swed.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netira *Craveri, Arg.†; Teka, Turk.*
Netilmicin sulfate (p.306·3).
Bacterial eye infections.

Netocur *Duncan, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Netocur Balsamico *Duncan, Arg.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Formerly contained co-trimoxazole and guaifenesin.
Bacterial infections.

Netra *Sam-On, Israel.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Calcium supplement; gastric hyperacidity; heartburn.

Netracin *Pyridam, Indon.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Skin infections.

Netrocin *Schering-Plough, Spain†.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netromicina *Mantecorp, Braz.; Schering-Plough, Mex.; Schering-Plough, Port.; Schering-Plough, Venez.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netromicine *Schering-Plough, Fr.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netromycin *Schering-Plough, Austral.†; Schering, Canad.†; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Fulford, India; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, NZ†; Schering-Plough, Philipp.; Schering-Plough, S.Afr.; Schering-Plough, Thai.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netromycine *Schering-Plough, Belg.†; Schering-Plough, Cz.; Schering-Plough, Hung.; Schering-Plough, Neth.; Schering-Plough, Pol.; Essex, Switz.; Schering-Plough, Turk.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Netspan *Cipla, India.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Nettacin *SIFI, Cz.; Schering-Plough, Ital.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Nettavisc *SIFI, Ital.*
Netilmicin sulfate (p.306·3).
Bacterial eye infections.

Nettinerv S *Iso, Ger.†.*
Homoeopathic preparation.

Nettle Rash L88 *Homeocan, Canad.†.*
Homoeopathic preparation.

Netunal *Merck, Arg.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Neturone *Liba, Turk.*
Methenamine (p.298·3).
Urinary-tract infections.

Netux *Bayer, Fr.†.*
Codeine (p.37·2); phenyltoloxamine (p.588·1).
Coughs.

Neu Viplex *Siam Bheasach, Thai.*
Vitamin B substances (p.1922·1).
Joint disorders; neurological disorders; pernicious anaemia; vitamin deficiency.

Neuart *Mitsubishi, Jpn.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Neubee *Medifive, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; neuropathy; toxaemia of pregnancy; vitamin B deficiency; vitamin supplement.

Neubion *Merck, Venez.*
Thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B supplement.

Neucare *Hoe, Singapore.*
Topical barrier preparation.

Neucor *CT, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Neuer *Daiichi, Jpn.*
Cetraxate hydrochloride (p.1716·1).
Gastritis; peptic ulcer.

Neufil *Bial, Port.*
Diprophylline (p.1120·2).
Obstructive airways disease.

Neuflo *Yung Shin, Singapore.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; sinusitis.

Neugabin *Mepro, Chile.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Neugal *Diba, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Neugeron *Armstrong, Mex.*
Carbamazepine (p.471·3).
Epilepsy; neuralgias.

Neukan *Apivita, Gr.*
St John's wort (p.422·3).
Depression.

Neukob *Behrens, Venez.*
Ginkgo biloba (p.2311·1).

Neukonigsforder *Desma, Ger.†.*
Mineral preparation (p.1922·1).
Mineral deficiency.

Neulactil *Sanofi-Aventis, Austral.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Hong Kong; Aventis, Irl.†; Sanofi-Aventis, NZ; Aventis, S.Afr.†; JHC Healthcare, UK.*
Pericyazine (p.1016·3).
Aggression; anxiety; behaviour disorders; psychoses; tension.

Neulamin *Sandoz, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Neulasta *Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Genesis, Gr.; Amgen, Hung.; Amgen, Irl.; Amgen, Ital.; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Amgen, UK; Amgen, USA.*
Pegfilgrastim (p.1070·1).
Neutropenia.

Neulastim *Roche, Braz.; Roche, Indon.; Roche, Mex.; Roche, Singapore.*
Pegfilgrastim (p.1070·1).
Neutropenia.

Neuleptil
Aventis, Arg.; Rhone-Poulenc Rorer, Austria; Sanofi-Aventis, Braz.; Erfa, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.†; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Aventis, Israel; Aventis, Neth.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Venez.
Pericyazine (p.1016·3).
Behaviour disorders; psychoses.

Teofarma, Ital.
Pericyazine (p.1016·3) or pericyazine mesilate (p.1016·3).
Psychiatric disorders.

Neulin *Ferron, Indon.*
Citicoline (p.2283·3).
Cerebrovascular disorders; head injury.

Neumak *Biotenk, Arg.†.*
A pneumococcal vaccine (14-valent) (p.2231·2).
Active immunisation.

Neumega *Wyeth, Arg.†; Wyeth, Braz.; Wyeth, Chile†; Wyeth, Mex.†; Genetics Institute, USA; Wyeth, Venez.*
Oprelvekin (p.1074·3).
Thrombocytopenia.

Neumobacticel *Bago, Arg.*
Co-trimoxazole (p.258·1); bromhexine hydrochloride (p.1552·2).
Bacterial infections.

Neumocort *Cassara, Arg.; D & M, Chile.*
⊗ Budesonide (p.1520·1).
Asthma.

Neumopectolina *Inkeysa, Spain†.*
Guaifenesin (p.1561·3); sodium benzoate (p.1630·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Neumoterol *Phoenix, Arg.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma.

Neumotex *Phoenix, Arg.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; obstructive airways disease.

Neumotide *Phoenix, Arg.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Neumyn-AS *Rayere, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol sulfate (p.1131·3).
Asthma; bronchitis.

Neupax
Note. This name is used for preparations of different composition.
Bago, Arg.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; panic attacks.
Armstrong, Mex.
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Neupogen *Roche, Arg.; Amgen, Austral.; Amgen, Austria; Amgen, Belg.; Amgen, Canad.; Roche, Chile; Amgen, Cz.; Amgen, Denm.; Amgen, Fin.; Amgen, Fr.; Amgen, Ger.; Roche, Ger.; Roche, Hong Kong; Amgen, Hung.; Piramal, India; Roche, Indon.; Amgen, Irl.; Roche, Israel; Dompe Biotec, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Amgen, Neth.; Amgen, Norw.; Amgen, Pol.; Amgen, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Amgen, Spain; Amgen, Swed.; Amgen, Switz.; Roche, Thai.; Roche, Turk.; Amgen, UK; Amgen, USA; Roche, Venez.*
Filgrastim (p.1070·1).
Mobilisation of autologous peripheral blood progenitor cells; neutropenia.

Neupopeg *Dompe, Cz.; Dompe Biotec, Ital.; Dompe Biotec, Neth.; Dompe, Port.*
Pegfilgrastim (p.1070·1).
Neutropenia.

Neupram *Neuropharma, Arg.*
Haloperidol (p.1000·2).

Neupramir *Lusofarmaco, Ital.†.*
Pramiracetam sulfate (p.369·1).
Mental function impairment.

Neupro *Schwarz, Cz.; Schwarz, Gr.; Schwarz, Pol.; UCB, Port.; UCB, UK; Schwarz, USA†.*
Rotigotine (p.816·3).
Parkinsonism.

Neuquinon *Eisai, Jpn; Eisai, Malaysia; Eisai, Philipp.*
Ubidecarenone (p.2407·2).
Angina pectoris; heart failure.

Neuraben *Pfizer, Ital.*
Thiamine bezomil (p.1976·3); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuritis.

Neurabol
Note. This name is used for preparations of different composition.
Cadila, India.
Capsules: ⊗ Stanozolol (p.2129·1).
Anabolic; osteoporosis.
Cadila, India.
Injection: ⊗ Nandrolone phenylpropionate (p.2118·3).
Anabolic; osteoporosis.

Neuractin *Drugtech, Chile.*
Valproate semisodium (p.508·2).
Epilepsy; migraine.

Neuragon *Sriprasit, Thai.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Mixed anxiety depressive states.

Neural *Cristalia, Braz.*
Lamotrigine (p.485·1).
Epilepsy.

Neuralfa *Amnol, Ital.*
Thioctic acid (p.2400·2); linoleic acid (p.2308·2); asparagine (p.1929·3); vitamins; minerals.
Nutritional supplement.

Neuralgie-Gastreu R70 *Reckeweg, Ger.*
Homoeopathic preparation.

Neuralgietabletten N *Heel, Ger.*
Homoeopathic preparation.

Neuralgietropfen CM *Heel, Ger.*
Homoeopathic preparation.

Neuralgin
Note. This name is used for preparations of different composition.
Pfleger, Ger.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.
Kalbe, Indon.
Paracetamol (p.108·1); ibuprofen (p.64·2); caffeine (p.1116·3).
Pain.

Neuralgin RX *Kalbe, Indon.*
Dipyrone (p.49·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); caffeine (p.1116·3).
Pain.

Neuralgina *Cifarma, Braz.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).

Neuralin *Chinoin, Mex.*
⊗ 1 Ampoule, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3); 1 ampoule, dexamethasone sodium phosphate (p.1526·2); lidocaine hydrochloride (p.1862·3).
Inflammation; neuralgias; neuritis; rheumatism.

Neuralprona *Bioquimico, Arg.*
Naproxen (p.92·3).
Fever; inflammation; pain.

Neuralta Migren *Alta Care, Ital.*
Ginkgo biloba (p.2311·1); meadowsweet (p.2338·1); feverfew (p.622·2); peppermint oil (p.1761·2); melissa oil (p.2339·3); rosemary oil (p.2381·3).
Headaches; mental function impairment; migraine.

Neuralysan S *Steigerwald, Ger.†.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgia; neuritis.

Neuramate *Halsey, USA†.*
Meprobamate (p.1006·2).
Anxiety.

Neuramide Sherman *Difa, Ital.*
Neuramide.
Herpesvirus infections.

Neuramin *Orion, Fin.*
Thiamine hydrochloride (p.1976·1).
Thiamine deficiency; wernicke-Korsakoff syndrome.

Neuramizone *Sriprasit, Thai.*
Belladonna alkaloids (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).
Menopausal disorders; migraine; sedative.

Neur-Amyl *Sigma, Austral.†.*
Amobarbital (p.961·3).
Hypnotic; sedative.

Neuranidal *Stada, Ger.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Neurapas *Pascoe, Ger.*
St John's wort (p.422·3); valerian (p.2410·1); passion flower (p.2363·2).
Depression; neuropathy; neuroses.

Neurax *Merck, S.Afr.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity disorders.

NeuRecover *NeuroGenesis, USA.*
A range of multivitamin, mineral, and amino-acid preparations (p.1922·1).

Neurex
Note. This name is used for preparations of different composition.
Beta, Arg.
Acetylcarnitine hydrochloride (p.1932·2).
Cerebral vasculopathy; peripheral neuropathy.
Euro-Pharma, Ital.
Citicoline sodium (p.2283·3).
Parkinsonism.
Hexal, Pol.
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Neurexan *Heel, Ger.*
Homoeopathic preparation.

Neuri B6 *Cazi, Braz.*
Pyridoxine hydrochloride (p.1978·2).
Neuritis.

Neuribe *Vivax, Venez.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Vitamin B deficiency neurological disorders.

Neuriberi *Haller, Braz.†.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Neuriclor *Sanofi Synthelabo, Arg.†.*
Citicoline (p.2283·3).
Cerebrovascular disorders.

Neuriclor Vascular *Sanofi Synthelabo, Arg.†.*
Citicoline (p.2283·3); codergocrine mesilate (p.363·3).
Cerebrovascular disorders; neurological disorders.

Neuri-cyl N Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Neuril
Note. This name is used for preparations of different composition.
Sanova, Austria†.
Melperone hydrochloride (p.1006·2).
Anxiety disorders; drug and alcohol withdrawal syndrome; psychoses; senile dementia; sleep disorders.
Alternova, Denm.; Alternova, Fin.
Gabapentin (p.482·3).
Epilepsy; neuralgia; neuropathic pain.

Neurilan *Gross, Braz.*
Bromazepam (p.964·3).
Anxiety.

Neuriplege *Genevrier, Fr.†.*
Chlorproethazine hydrochloride (p.969·1).
Painful skeletal muscle spasm.

Neurium
Note. This name is used for preparations of different composition.
Solvay, Braz.
Lamotrigine (p.485·1).
Epilepsy.
Hexal, Ger.
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Neurivit *Cazi, Braz.*
Thiamine hydrochloride (p.1976·1).

Neuro *Stada, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neuro B *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Diabetic neuropathy; neuralgia; neuritis; vitamin B deficiency.

Neuro B1-6-12 *Jean-Marie, Hong Kong†.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgias; neuritis; vitamin B deficiencies.

Neuro Laz *Lazar, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Neuro Nutrients *Solgar, UK.*
Amino-acid preparation with vitamin B substances, vitamin C, and ginkgo biloba (p.1922·1).

Neuro Panstop *Armoxindo, Indon.*
Dipyrone (p.49·2); thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis.

Neuro uno *Stada, Ger.*
Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neuroactil *Bago, Arg.*
Acetylcarnitine hydrochloride (p.1932·2).

Neuro-AS N *Teva, Ger.†.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

neuro-B forte *Biomo, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neurological system disorders.

Neurobat *Interbat, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Nausea and vomiting of pregnancy; neuralgia; neuritis; tonic; vitamin B deficiency.

Neurobat A *Interbat, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Ischialgia; lumbago; neuralgia; neuritis.

Neurobene *Ratiopharm, Cz.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; neuralgias; neuritis; vitamin B deficiency.

Neuro-Beston *Tanabe, Indon.*
Bisbentiamine (p.1975·2); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; arthralgia; myalgia; neuritis; vitamin B deficiency; vitamin B supplement.

Neurobex *British Dispensary, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neurological disorders.

Neurobexol *EuroHealth, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Encephalopathy; neuralgia; neuritis; neuropathy; vitamin B deficiency; vitamin B supplement.

Neurobiol *Teofarma, Ital.†.*
Phenobarbital (p.492·2).
Epilepsy; insomnia; sedative.

Neurobion
Note. This name is used for preparations of different composition.
Merck, Austria; Merck, Fin.; Merck, Hung.
Thiamine hydrochloride (p.1976·1) or thiamine disulfide (p.1976·3); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.
Merck, Belg.; Merck, Ger.; Galenica, Gr.; Merck, Mex.; Merck, Neth.; Merck, Port.; Merck, Swed.
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Alcoholism; joint disorders; neuralgia; neuritis; neuropathy; vitamin B deficiency.
Merck, Hong Kong; Merck, Malaysia; Merck, S.Afr.; Merck, Singapore; Merck, Thai.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Facial paresis; neuralgia; neuritis; neuropathy; polyneuritis; toxaemia of pregnancy; vitamin B deficiency.
Merck, India.
Vitamin B ; vitamin B ; vitamin B ; nicotinamide; calcium pantothenate (p.1922·1).
Vitamin B deficiency.
Merck, Indon.; Merck, Philipp.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Asthenia; hyperemesis gravidarum; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Neurobion N *Merck, Ger.*
Octotiamine (p.1975·3); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neurobionta *Merck, Chile.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Lidocaine (p.1862·3) is included in some injections to alleviate the pain of injection.
Musculoskeletal and joint pain; neuralgia; neuritis; vitamin B deficiency.

Neurobiovit *Prafa, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Asthenia; neuralgia; neuritis; vitamin B supplement; vomiting of pregnancy.

NeuroBloc *Elan, Austria; Eisai, Cz.; Zeneus, Fr.; Elan, Ger.†; Zeneus, Irl.; Elan, Ital.; Elan, Neth.; Eisai, Port.; Zeneus, Spain; Eisai, UK.*
Botulinum B toxin (p.1890·1).
Spasmodic torticollis.

Neuro-B's *Dynamic, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Neurocalme *Geistlich, Switz.*
Vitamin B substances; calcium carbonate; magnesium glycerophosphate; magnesium oxide (p.1922·1).
Tonic.

Neurocam *Recalcine, Chile.*
Clonixin lysine (p.37·1); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Pain.

Neurocardol *Cavalheiro, Port.†.*
Passion flower (p.2363·2); crataegus (p.2289·1); salix (p.121·3); valerian (p.2410·1).

Neurocatavin Dexa *Llorente, Spain†.*
⊗ Vitamin B substances (p.1922·1); dexamethasone sodium phosphate (p.1526·2); suprarenal cortex (p.1543·3).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Myalgia; neuralgia; neuritis; rheumatism.

Neurocet *Hexpharm, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; mental function impairment.

Neurochol *Landson, Indon.*
Lecithin (p.2332·2).
Brain function supplement.

Neurochol C *Merck, Ger.†.*
Greater celandine (p.2317·1); taraxacum (p.2395·1); absinthium (p.2244·1).
Biliary disorders; dyspepsia.

Neurocil *Bayer, Ger.*
Levomepromazine hydrochloride (p.1002·3) or levomepromazine maleate (p.1003·1).
Bipolar disorder; pain; psychoses.

Neurocine *Ivax, Arg.*
Bifemelane hydrochloride (p.363·2).
Cerebrovascular disorders; mental function impairment.

Neurocynesine *Boiron, Neth.*
Homoeopathic preparation.

Neurodavur *Davur, Spain.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Neurodavur Plus *Davur, Spain.*
⊗ Vitamin B substances (p.1922·1); dexamethasone sodium phosphate (p.1526·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Myalgia; neuralgia; neuritis.

Neurodep
Med. Prod. Panam., USA.
Capsules: Vitamin B substances (p.1922·1).
Med. Prod. Panam., USA.
Injection: Vitamin B substances and vitamin C (p.1922·1).

Neurodex
Note. This name is used for preparations of different composition.
Dexa, Indon.; Dexa, Singapore.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; nausea; neurological disorders; tonic; vitamin B deficiency.

Neurodial *Kimia, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Neuro-Do *Grasler, Ger.*
Homoeopathic preparation.

Neurodol Tissugel *IBSA, Switz.*
Lidocaine (p.1862·3).
Post-herpetic neuralgia.

Neuro-Effekton B *Teofarma, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neurofenac
Note. This name is used for preparations of different composition.
Merck, Austria; Merck, Hong Kong†.
Diclofenac sodium (p.44·3); vitamin B substances (p.1922·1).
Gout; musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis; pain.
Merck, Indon.
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Neuroflax *Aventis, Mex.*
Cobamamide (p.1980·2); thiocolchicoside (p.1898·2).
Musculoskeletal and joint disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Neuroflorine *Fuca, Fr.*
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1).
Anxiety; insomnia; palpitations.

Neurofor *Aventis, Mex.*
Cobamamide (p.1980·2).
Anaemias; neuritis.

Neuroforte *Beacons, Singapore.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Diabetic neuropathy; neuralgia; polyneuritis.

Neuroforte-E *Medi-Rx, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1); vitamin E (p.1992·2).
Degenerative nerve disorders; neuralgia; neuritis.

Neuroftal
Note. This name is used for preparations of different composition.
Lepori, Port.†.
Fructose; fish oil; ginkgo biloba; vitamin B substances; vitamin E; zinc (p.1922·1).
Nutritional supplement.

INTES, Ital.†.
Injection: ⊗ Thiamine hydrochloride (p.1976·1); nicotinamide (p.1957·3); strychnine glycerophosphate.
Procaine hydrochloride (p.1869·1) is included in this preparation to alleviate the pain of injection.
Optic nerve atrophy.

INTES, Ital.†.
Tablets: ⊗ Thiamine hydrochloride (p.1976·1); riboflavin (p.1977·2); nicotinamide (p.1957·3); strychnine nitrate (p.2393·2); sodium glycerophosphate (p.2315·2).
Optic nerve atrophy.

Neurogabaf *Richmond, Arg.*
Phenobarbital (p.492·2).
Epilepsy; insomnia; sedative.

Neurogen *Bernofarm, Indon.*
Dipyrone (p.49·2); chlordiazepoxide (p.968·1); vitamin B (p.1976·3).
Pain.

Neurogen-E *Imperial, Hong Kong; Imperial, Malaysia; Imperial, Singapore.*
Vitamin B ; vitamin B ; vitamin B ; vitamin E (p.1922·1).
Vitamin supplement.

Neurogeron *Andromaco, Chile†.*
Nimodipine (p.1357·2).
Cerebrovascular disorders; migraine; neurological deficit following neurosurgery or subarachnoid haemorrhage.

Neuroglutamin *Pharmonta, Austria.*
Glutamic acid (p.1947·1).
Memory and concentration disorders.

Neurogriseovit *Deva, Turk.*
Ampoule I, vitamin B (p.1980·2); ampoule II, vitamin B (p.1976·3); vitamin B (p.1979·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiency.

Neurohax *Guardian, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Peripheral nervous system disorders; vitamin B deficiency.

Neurol
Note. This name is used for preparations of different composition.
Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.
Alprazolam (p.960·1).
Anxiety; mixed anxiety-depressive states.

SIT, Ital.
Sodium valerate; sodium glycerophosphate (p.2315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Tonic.

Abigo, Swed.
Valerian (p.2410·1).
Insomnia; nervous disorders.

Neurolea *Elea, Arg.†.*
Bifemelane hydrochloride (p.363·2).
Cerebrovascular disorders; mental function impairment.

Neurolep *Hexal, Mex.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias; polydipsia; polyuria.

Neurolepsin *Kwizda, Austria.*
Lithium carbonate (p.401·3).
Depression; mania.

Neuro-Lichtenstein M *Winthrop, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuro-Lichtenstein formerly contained thiamine hydrochloride, pyridoxine hydrochloride, and cyanocobalamin.
Vitamin B deficiency.

Neuro-Lichtenstein N *Winthrop, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neurolil *Sigma, Braz.†.*
Zopiclone (p.1039·1).
Insomnia.

Neurolink *Biolink, Philipp.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neurological disorders; vitamin B deficiency.

Neurolite *BMS, Austral.; BMS, Belg.†; BMS, Cz.; Du Pont, Fr.†; BMS, Ital.; BMS, Neth.; BMS, Port.; BMS, Spain.*
Technetium-99m bicisate (p.2055·3).
Cerebral perfusion imaging.

Neurolithium
Cristalia, Braz.
Lithium carbonate (p.401·3).
Alcoholism; bipolar disorder; depression; headache; mania; psychoses.

Labcatal, Fr.; Pharmafactory, Switz.
Lithium gluconate (p.406·1).
Bipolar disorder; hypomania; mania.

Neuromade *Teofarma, Spain.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Vitamin B deficiency.

Neuromax *Vitabalans, Cz.; Vitabalans, Fin.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Neuromerck *Merck, Austria.*
Thiamine disulfide (p.1976·3) or thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgias; neuritis.

Neuromet *Merck, Thai.*
Mecobalamin (p.1981·1).
Peripheral neuropathies; vitamin B deficiency.

Neuromethyn *Sam Chun Dang, Malaysia; Sam Chun Dang, Singapore.*
Mecobalamin (p.1981·1).
Megaloblastic anaemia; peripheral neuropathy.

Neuromin *Quality, Hong Kong.*
vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Facial paresis; neuralgias; neuritis; neuropathies; vitamin B deficiency.

Neuromins *Andromaco, Chile†.*
Docosahexaenoic acid (p.1362·1).
Dietary supplement.

Neuromultivit *Lannacher, Austria; Lannacher, Cz.; Lannacher, Rus.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy.

Neuron *Uniao Quimica, Braz.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Neuronal Vascular *Elvetium, Arg.†.*
Pyridoxine phosphoserinate (p.1979·1); codergocrine mesilate (p.363·3).
Cerebrovascular disorders.

Neuronika *Fujisawa, Ger.†.*
Kawain (p.2328·3).
Alcohol withdrawal syndrome; psychiatric disorders.

Neurontin *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fin.; Pfizer, Fr.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Parke, Davis, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Parke, Davis, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Parke, Davis, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Gabapentin (p.482·3).
Diabetic neuropathy; epilepsy; neuralgia; neuropathic pain; postherpetic neuralgia.

Neurophil *Ethica, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Circulatory disorders; neuralgia; neuritis; vomiting of pregnancy.

Neurophosphates *GSK, India.*
Vitamin B ; vitamin B ; vitamin B ; vitamin B ; nicotinamide (p.1922·1).
Tonic; vitamin B supplement.

Neuroplant *Schwabe, Ger.*
St John's wort (p.422·3).
Anxiety; depression.

Neuroplus *Baliarda, Arg.*
Memantine (p.367·2).
Mental function impairment; parkinsonism; spasticity.

Neuroptic *Sogefin, Ital.*
Thioctic acid (p.2400·2); vitamins.
Nutritional supplement.

Neuropyramin *Pyridam, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; tonic; vitamin B deficiency.

Neuro-ratiopharm *Ratiopharm, Ger.†.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Nervous-system disorders.

Neuro-ratiopharm N *Ratiopharm, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neurorubin *Mepha, Switz.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgias; neuritis; neuropathy.

Neurorubine *Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Lidocaine hydrochloride (p.1862·3) may be included in the injection to alleviate the pain of injection.
Drug-induced vitamin B deficiency; neuralgia; neuritis; neuropathy; rheumatic pain; toxic lesions of the nervous system.

Neurosanbe *Sanbe, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis; vitamin B deficiency.

Neurosanbe Plus *Sanbe, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Neurosande *Sanderson, Chile.*
Pyridoxine; cyanocobalamin; thiamine (p.1922·1).
Vitamin B supplement.

Neuroscan *Rotop, Cz.*
Technetium-99m (p.2055·3) exametazime.

Neurosedine *Adelco, Gr.*
Sertraline (p.422·1).
Depression.

Neuroselect *Dreluso, Ger.*
Homoeopathic preparation.

NeuroSlim *Matrix, USA; NeuroGenesis, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Neurosporal *Muller Goppingen, Ger.*
St John's wort (p.422·3).
Depression.

Neurosthenol *Richard, Fr.*
Glutamic acid; phosphoric acid; electrolytes (p.1922·1).
Tonic.

Neurostil *Ivax, Irl.*
Gabapentin (p.482·3).
Epilepsy; seizures.

Neurostop *Lacer, Spain.*
Benfotiamine (p.1975·2).
Vitamin B1 deficiency.

Neurostop Complex *Lacer, Spain.*
Benfotiamine (p.1975·2); hydroxocobalamin acetate (p.1980·3); pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Neurotam *Kalbe, Indon.*
Piracetam (p.368·2).
Alcoholism; cerebral trauma; learning difficulties in children; mental function impairment.

Neurotioct *TRB, Arg.*
Thioctic acid (p.2400·2).
Neuropathy.

Neurotol *Orion, Fin.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; trigeminal neuralgia.

Neuroton
Note. This name is used for preparations of different composition.
PGN, Arg.
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).

NCSN, Ital.
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; parkinsonism.

Neurotone *Pharmaceutical Enterprises, S.Afr.*
Cinchona; cardamom; lavender; cnicus benedictus; ammonia; chloroform; lecithin (p.1922·1).
Tonic.

Neurotonico *EMS, Braz.*
Minerals with vitamin B substances (p.1922·1).

Neurotop *Gerot, Austria; Gerot, Cz.; Gerot, Hung.; Gerot, Pol.; Gerot, Singapore; Gerot, Switz.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; dysarthria; epilepsy; glossopharyngeal neuralgia; migraine; nocturia; polydipsia; polyuria; trigeminal neuralgia.

Neurotrat
Note. This name is used for preparations of different composition.
Nordmark, Indon.; Tunggal Idaman, Indon.
Thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Neuralgia; neuritis.

German Remedies, India.
Capsules: Vitamin B ; vitamin B ; vitamin B ; vitamin C; folic acid; nicotinamide; calcium pantothenate; zinc sulfate; chromium tripicolinate (p.1922·1).
Vitamin B and C deficiency.

German Remedies, India.
Injection: 1 Vial, vitamin C; 1 vial, vitamin B ; folic acid; nicotinamide (p.1922·1).
Vitamin B and C deficiency.

Neurotrat S *Abbott, Ger.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

neurotropan *Phonix, Ger.†.*
Choline citrate (p.1934·2).
Liver disorders.

Neurotropic *GMP, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Neurotropic Plus *GMP, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Pain.

Neurotrox *Elea, Arg.*
Paroxetine (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Neurotrypt *Sigma, Braz.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Neuroval *GMP, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Neurovasculaire Serocytol *Serolab, Switz.*
An immunoglobulin (equine).
Circulatory disorders; musculoskeletal, joint and periarticular disorders; skin disorders.

Neurovegetalin *Verla, Ger.*
St John's wort (p.422·3).
Depression.

Neuro-Vibolex *Rosen, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Neurovit
Note. This name is used for preparations of different composition.
Hovid, Malaysia†.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; vitamin B deficiency.

Hovid, Singapore.
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; peripheral neuropathy.

Bilim, Turk.
Thiamine (p.1976·3); pyridoxine (p.1979·1).
Vitamin B deficiency.

Neurovit E *Kimia, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1922·1).
Neuralgia; neuritis; neuropathy; tonic.

Neurovitan
Note. This name is used for preparations of different composition.
Orion, Fin.
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); nicotinamide (p.1957·3); cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Fujisawa, Jpn†.
Octotiamine (p.1975·3); riboflavin (p.1977·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B deficiency; vitamin B supplement.

Neuro-Wied Novo *Wiedemann, Ger.*
Vitamin B substances (p.1922·1).
Neuro-Wied formerly contained vitamin B substances, di-isopropylammonium dichloroacetate, and magnesium orotate.
Tonic.

Neuroxel *DHA, Singapore.*
Thiamine nitrate (p.1976·2); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2).
Neuralgia; neuritis; neuropathy.

Neuroxin *Age D'or, Singapore.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders.

Neurozan *Vitabiotics, UK.*
Phosphatidyl serine; ubidecarenone; glutathione; omega-3 docosahexaenoic acid; arginine; folic acid; vitamin B ; vitamin B (p.1922·1).

Neurozepam *Sandoz, Arg.*
Bromazepam (p.964·3).
Anxiety.

Neuryl *Bago, Arg.; Bago, Chile.*
Clonazepam (p.478·2).
Anxiety; epilepsy; panic attacks.

Neusilin *Soho, Indon.*
Aluminium magnesium silicate (p.2141·2).
Gastric hyperacidity; peptic ulcer.

Neusinol *Labima, Belg.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Neut *Abbott, USA.*
Sodium bicarbonate (p.1673·2).
Neutralising additive solution for acidic intravenous infusions.

Neutar *Johnson & Johnson, Port.*
Coal tar (p.1616·2).
Dandruff; seborrhoeic dermatitis of the scalp.

Neutop *Elea, Arg.*
Topiramate (p.506·2).
Epilepsy.

Neutra-C *Sorgente della Vita, Switz.†.*
Calcium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

Neutracid *Vivax, Venez.*
Famotidine (p.1730·1).
Gastric hyperacidity.

Neutracide *CPH, Port.*
Calcium carbonate (p.1714·1); glycocolic acid.
Gastric hyperacidity.

Neutracol *Beta, Arg.*
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Neutrafluor *Colgate-Palmolive, Austral.*
Sodium fluoride (p.1962·2).
Fluoride supplement; sensitive teeth.

Neutraforte *Ariston, Braz.†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

NeutraGard Advanced *Pascal, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Neutragel-D *Adcock Ingram, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); dried aluminium hydroxide (p.1706·2); light magnesium oxide (p.1744·1).
Gastrointestinal hyperacidity.

Neutrahist *Cypress, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Neutrahist PDX *Cypress, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; upper respiratory-tract symptoms.

Neutral C + Coenzyme Q10 plus Vitamins & Minerals *New Vision, Canad.†.*
Vitamin B substances; vitamin C; minerals; ubidecarenone (p.1922·1).

Neutralice *Key, Austral.*
Melaleuca oil (p.2338·2); lavender oil (p.2331·2).
Pediculosis.

Neutramine *YSP, Malaysia†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Neutran *Prodotti, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal hyperacidity.

Neutra-Phos *Alza, USA.*
Monobasic and dibasic sodium and potassium phosphates (p.1682·3) (p.1682·3) (p.1682·2) (p.1682·2).
Phosphorus supplement.

Neutra-Phos-K *Alza, USA.*
Monobasic and dibasic potassium phosphates (p.1682·2) (p.1682·2).
Phosphorus supplement.

Neutrexin *Schering-Plough, Hong Kong†; Ipsen, Irl.†; Ipsen, Spain†; Schering-Plough, Thai.†; Medimmune, USA†.*
Trimetrexate glucuronate (p.549·1).
Pneumocystis pneumonia.

Neutrobar *Darier, Mex.*
Glycerol (p.2314·2).
Skin disorders; soap substitute.

Neutrodor *ICN, Arg.†.*
Methionine (p.1450·1).
Urinary acidification.

Neutrofer *Sigma, Braz.*
Ferrous glycinate (p.1939·1).
Anaemias.

Neutrofer Folico *Sigma, Braz.*
Ferrous glycinate (p.1939·1); folic acid (p.1940·1).
Anaemias.

Neutrofil *Varifarma, Arg.*
Filgrastim (p.1070·1).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Neutrogena
Note. This name is used for preparations of different composition.
Johnson & Johnson, Arg.; Johnson & Johnson, Braz.; Key, Chile; Johnson & Johnson, NZ; Neutrogena, Philipp.; Neutrogena Dermatologicals, USA; Johnson & Johnson, Venez.
A range of skincare preparations.
Skin disorders.

Johnson & Johnson, Austral.
Trolamine (p.2405·1).
Soap substitute.

Neutrogena, USA.
SPF 8: Octinoxate (p.1608·2); meradimate (p.1604·2); titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena, USA.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); meradimate (p.1604·2); titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena, USA.
SPF 25: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Neutrogena, USA.
SPF 30: Octinoxate (p.1608·2); octocrilene (p.1608·3); meradimate (p.1604·2); zinc oxide (p.1621·2).
Sunscreen.

Neutrogena Acne Mask *Faulding, Austral.†; Johnson & Johnson, Canad.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Neutrogena Acne Skin Cleanser *Johnson & Johnson, Austral.*
Triclosan (p.1665·2).
Acne; oily skin.

Neutrogena Acne Wash *Johnson & Johnson, Canad.*
Salicylic acid (p.1612·2).
Acne.

Neutrogena Acondicionador Neutar Gel *Key, Chile.*
Salicylic acid (p.1612·2).
Scalp disorders.

Neutrogena Antiacne *Johnson & Johnson, Braz.*
Salicylic acid (p.1612·2).
Acne.

Neutrogena Anti-Itch *Johnson & Johnson, Canad.†.*
Camphor (p.2273·2); lidocaine hydrochloride (p.1862·3).
Pruritus.

Neutrogena Antiseptic *Neutrogena, USA.*
Skin cleanser.

Neutrogena Antiseptic Cleanser *Johnson & Johnson, Canad.†.*
Benzethonium chloride (p.1630·1).
Acne.

Neutrogena Anti-Wrinkle *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Neutrogena Barra *Key, Chile.*
SPF 15: Octinoxate (p.1608·2); octyl palmitate; oxybenzone (p.1608·3).
Chapped lips; sunscreen.

Neutrogena Bloqueador Solar *Key, Chile.*
SPF 30; SPF 45: Methoxycinnamic acid esters; benzimidazole; homosalate (p.1598·1).
Sunscreen.

Neutrogena Bloqueador Solar Piel Sensible *Key, Chile.*
SPF 30: Titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena Bronceador *Key, Chile.*
Dihydroxyacetone (p.1594·1).
Suntanning agent.

Neutrogena Chemical-Free *Neutrogena, USA.*
SPF 17: Titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena Clear Pore *Johnson & Johnson, Canad.*
Salicylic acid (p.1612·2).
Acne.

Neutrogena Crema Humectante *Key, Chile.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena Day Moisture *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Neutrogena Drying *Neutrogena Dermatologicals, USA.*
Hamamelis (p.2318·2).

Neutrogena Fairness UV Block *Neutrogena, Philipp.*
SPF 30: Titanium dioxide (p.1617·3); octinoxate (p.1608·2).
Sunscreen.

Neutrogena Gel Control Brillo *Key, Chile.*
Salicylic acid (p.1612·2).
Seborrhoea.

Neutrogena Glow *Neutrogena, USA.*
SPF 8: Octinoxate (p.1608·2).
Sunscreen.

Neutrogena Healthy Scalp Anti-Dandruff *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Scalp disorders.

Neutrogena Healthy Skin
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.; Johnson & Johnson, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Key, Chile.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); glycolic acid (p.1598·1).
Skin pigmentation disorders; sunscreen.

Neutrogena Healthy Skin Anti-rugas *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Neutrogena Intensified *Johnson & Johnson, Canad.†; Neutrogena, USA.*
SPF 15: Octinoxate (p.1608·2); ensulizole (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena Kids Sunblock *Johnson & Johnson, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Limpiadora *Key, Chile.*
Glycolic acid (p.1598·1); salicylic acid (p.1612·2).
Skin cleansing.

Neutrogena Linea Acne *Key, Chile.*
Salicylic acid (p.1612·2).
Acne; seborrhoea.

Neutrogena Lip *Neutrogena, USA.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Lip Moisturizer *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Locion Humectante *Key, Chile.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Moisture
Note. This name is used for preparations of different composition.
Neutrogena, USA.
SPF 5: Octinoxate (p.1608·2).
Sunscreen.

Johnson & Johnson, Canad.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena New Hands *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Norwegian Formula Dermatological Cream *Neutrogena, UK.*
Glycerol (p.2314·2).
Dry skin.

Neutrogena No-Stick *Neutrogena, USA.*
Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Neutrogena Oil-Free Sunblock *Johnson & Johnson, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena Sensitive Skin *Johnson & Johnson, Canad.*
SPF 30: Titanium dioxide (p.1617·3).
Sunscreen.

Neutrogena Shampoo Neutar *Key, Chile.*
Coal tar (p.1616·2).
Scalp disorders.

Neutrogena Skin Cleaning *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Neutrogena Soothing Gel Astringent *Johnson & Johnson, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Neutrogena SPF 15 *Johnson & Johnson, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena SPF 30 *Johnson & Johnson, Canad.*
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena SPF 45 *Johnson & Johnson, Canad.*
SPF 45: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Neutrogena SPF 30 Health Defense *Johnson & Johnson, Canad.*
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Neutrogena SPF 30 Stick *Johnson & Johnson, Canad.*
SPF 30: Avobenzone (p.1589·3); homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Neutrogena On The Spot Acne Treatment *Johnson & Johnson, Canad.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Neutrogena Sunblock
Note. This name is used for preparations of different composition.
Johnson & Johnson, Canad.†.
SPF 20: Homosalate (p.1598·1); meradimate (p.1604·2); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Johnson & Johnson, Canad.†.
SPF 30: Meradimate (p.1604·2); octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Neutrogena T/Gel *Johnson & Johnson, Austral.; Johnson & Johnson, Canad.; Neutrogena, USA.*
Coal tar (p.1616·2).
Scalp disorders.

Neutrogena T/Gel Therapeutic *Johnson & Johnson, Canad.*
Coal tar (p.1616·2).
Formerly contained salicylic acid.
Scalp disorders.

Neutrogena T/Sal *Faulding, Austral.†; Neutrogena Dermatologicals, USA.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Scalp disorders; seborrhoeic dermatitis.

Neutrogena T/Scalp *Neutrogena Dermatologicals, USA.*
⊗ Hydrocortisone (p.1535·2).
Pruritus of the scalp.

Neutrogena Ultra Sheer Dry-Touch Sunblock *Neutrogena, USA.*
SPF 70: Avobenzone (p.1589·3); homosalate (p.1598·1); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Neutrogin *Chugai, Jpn.*
Lenograstim (p.1073·1).
Mobilisation of peripheral blood progenitor cells; neutropenia.

Neutrolac *SIT, Ital.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1).
Gastrointestinal hyperacidity.

Neutromax *Sidus, Arg.; Biolatina, Chile; Bio Sidus, Thai.*
Filgrastim (p.1070·1).
Neutropenia.

Neutromed *Kwizda, Austria.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal erosions; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Neutronorm *Ebewe, Austria.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal erosions; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Neutropain *HPP, Hong Kong.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and peri-articular disorders.

Neutrose S Pellegrino *Sanofi-Aventis OTC, Ital.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); kaolin (p.1738·1); magnesium trisilicate (p.1744·1).
Gastrointestinal hyperacidity.

Neutrosec *Tablets, India.*
-Methionine (p.1450·2); vitamin B substances; vitamin E (p.1922·1).
Liver disorders.

Neutroses *Pharmethic, Belg.; DB, Fr.; DB, Switz.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); kaolin (p.1738·1); magnesium trisilicate (p.1744·1).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; meteorism; peptic ulcer.

Neutrosol *Behrens, Venez.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

NeutroSpec *Mallinckrodt, USA†.*
Technetium-99m fanolesomab (p.2055·3).
Radiolabelling of white blood cells for diagnosis of appendicitis.

Neu-Up *Kyowa, Jpn.*
Nartograstim (p.1074·3).
Neutropenia.

Neuvita *Kobayashi, Jpn.*
Octotiamine (p.1975·3).
Vitamin B deficiency; vitamin B supplement.

Neuvitan *Eczacibasi, Turk.*
Octotiamine (p.1975·3); vitamin B (p.1977·2).
Vitamin B deficiency.

Neuzym *Eisai, Hong Kong; Eisai, Jpn; Eisai, Malaysia.*
Muramidase hydrochloride (p.2348·1).
Chronic sinusitis; haemorrhage; respiratory-tract congestion and inflammation.

Neuzyme *Eisai, Singapore.*
Muramidase hydrochloride (p.2348·1).
Haemorrhage; respiratory-tract congestion and inflammation; sinusitis.

Nevacort *Finderm, Ital.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1).
Bacterial vaginal infections.

Nevakson *Nevzat, Turk.*
Ceftriaxone (p.238·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Nevanac *Alcon, Arg.; Alcon, Chile; Alcon, Cz.; Alcon, Port.; Alcon, USA.*
Nepafenac (p.95·1).
Pain and inflammation associated with cataract surgery.

Nevaton *Mediherb, Austral.*
St John's wort (p.422·3); skullcap (p.2388·2); damiana (p.2292·1); vervain (p.2413·3).
Nervous disorders.

Neve *Cadila, India.*
Nevirapine (p.899·1).
HIV infection.

Nevexitin *Hexal, Philipp.; Salutas, Philipp.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Nevigramon *Sanofi-Aventis, Hung.; Chinoin, Pol.*
Nalidixic acid (p.303·3).
Gram-negative bacterial infections.

Nevimune *Cipla, India; Cipla, Venez.*
Nevirapine (p.899·1).
HIV infection.

Nevipan *Ranbaxy, Malaysia.*
Nevirapine (p.899·1).
HIV infection.

Neviralea *Elea, Arg.†.*
Nevirapine (p.899·1).
HIV infection.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Neviran *SF, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Nevirz *Guardian, Indon.*
Aciclovir (p.862·3).
Herpes virus infections.

Nevofam *Nevzat, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nevparin *Nevzat, Turk.*
Heparin (p.1301·2).
Thromboembolic disorders.

Nevradin
Bernofarm, Indon.
Capsules: Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); adenosine monophosphate.
Megaloblastic anaemia; neuralgia; neuritis.

Bernofarm, Indon.
Injection: Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Megaloblastic anaemia; neuralgia; neuritis.

Nevradin E *Bernofarm, Indon.*
Vitamin B ; vitamin B ; vitamin B ; vitamin E (p.1922·1).
Vitamin B and E deficiency.

Nevralgex *Cimed, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Formerly contained dipyrone and orphenadrine.
Pain; smooth muscle spasm.

Nevramin
Note. This name is used for preparations of different composition.
Takeda, Hong Kong.
Fursultiamine hydrochloride (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis; rheumatic disorders.

Takeda, Indon.; Takeda, Philipp.
Fursultiamine (p.1975·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neural disorders; vitamin B deficiency; vitamin B supplement.

Takeda, Singapore; Takeda, Thai.
Fursultiamine (p.1975·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Anaemias; diabetic neuropathy; neuralgia; neuritis; paresis; polyneuritis.

Takeda, Malaysia†.
Injection: Fursultiamine (p.1975·3); vitamin B (p.1979·1); hydroxocobalamin (p.1980·3).
Mepivacaine hydrochloride (p.1866·3) is included in this injection to alleviate the pain of injection.
Anaemias; neuralgia; rheumatic disorders.

Takeda, Malaysia.
Tablets: Fursultiamine (p.1975·3); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Anaemias; neuralgia; rheumatic disorders.

Nevril *Amnol, Ital.*
Hamamelis (p.2318·2); devil's claw root (p.39·1); chamomile (p.2279·3); mallow (p.2337·2); calendula (p.2273·1); salix (p.121·3); copper; zinc; menthol (p.2340·1).
Musculoskeletal and joint disorders.

Nevril Crono *Amnol, Ital.*
Multivitamin and mineral preparation with plant extracts (p.1922·1).
Musculoskeletal and joint disorders; nutritional supplement.

Nevrine Codeine *Sterop, Belg.*
Paracetamol (p.108·1); caffeine hydrate (p.1117·1); codeine phosphate (p.37·2).
Fever; pain.

Nevrol *Prodotti, Braz.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); turpentine oil (p.2406·3); lavender oil (p.2331·2); rosemary oil (p.2381·3); mustard oil (p.2349·2).
Musculoskeletal and joint disorders.

Nevrorestol *Bros, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Nevrovit *Menarini, Gr.*
Vitamin B substances (p.1922·1).

New B-Cool *Julphar, UAE.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

New Coldin *Medikon, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold and influenza symptoms.

New Daigaku *Santen, Singapore†.*
Boric acid (p.2268·1); d-borneol (p.2268·3); menthol (p.2340·1); zinc sulfate (p.1999·2).
Eye irritation.

New Diatabs *Medifarma, Indon.*
Activated attapulgite (p.1709·1).
Diarrhoea.

New Era Biochemic Tissue Salts *Seven Seas, UK.*
Homoeopathic preparation.

New Era Combination Remedy *Seven Seas, UK.*
Homoeopathic preparation.

New Era Elasto *Seven Seas, UK.*
Homoeopathic preparation.

New Era Nervone *Seven Seas, UK.*
Homoeopathic preparation.

New Eye Lotion *Optrex, India.*
Boric acid (p.2268·1); borax (p.2268·1); allantoin (p.1588·1); salicylic acid (p.1612·2); zinc sulfate (p.1999·2).
Eye irritation; tired eyes.

New Gen *Roche, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement.

New Hands *Johnson & Johnson, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

New Kenacomb *BMS, Indon.*
⊗ Nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Skin disorders with fungal infection.

New Panazox *Cadila, India.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).

New Patecs A *Daiichi, Hong Kong.*
Arnica (p.2260·2); glycol salicylate (p.62·3).
Musculoskeletal and joint disorders.

New Skelan *Medifarma, Indon.*
Phenylbutazone calcium (p.117·1); carisoprodol (p.1894·1).
Musculoskeletal and joint pain and spasm.

New Skin *Beiersdorf, Chile.*
Barrier preparation.

NewAce *BMS, Neth.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Newclar *Valeant, Arg.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis.

Newderm *Wolfs, Belg.†.*
Zinc oxide (p.1621·2); vitamin A (p.1971·2); vitamin D (p.1986·1); cod-liver oil (p.1935·2).
Skin irritation.

New-Fill *Sanofi-Aventis, Fr.*
Poly L-lactic acid.
Lipoatrophy in HIV infection.

Newflox *Valeant, Arg.*
Ofloxacin (p.310·2).
Bacterial eye infections.

New-Nok *Meditrend, Israel.*
Permethrin (p.2048·2).
Pediculosis.

Newrelax *Potter's, UK.*
Lupulus (p.2335·2); skullcap (p.2388·2); valerian (p.2410·1); vervain (p.2413·3).
Tension.

New-Skin *Medtech, USA.*
Topical barrier preparation.

Newspar *Interbat, Indon.*
Sparfloxacin (p.332·1).
Bacterial infections of the respiratory tract.

Nexa *Kalbe, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Nexadron *Klonal, Arg.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Nexadron Compuesto
Note. This name is used for preparations of different composition.
Klonal, Arg.
Eye drops: ⊗ Dexamethasone (p.1526·1); naphazoline (p.1565·1); neomycin (p.305·1).

Klonal, Arg.†.
Syrup; tablets: ⊗ Dexamethasone (p.1526·1); chlorphenamine (p.572·2).

Nexadron Plus *Klonal, Arg.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chlorphenamine maleate (p.571·3); naphazoline hydrochloride (p.1565·2); neomycin sulfate (p.305·1).
Nasal disorders.

Nexavar *Bayer, Arg.; Bayer, Austral.; Bayer, Chile; Bayer, Cz.; Bayer, Fr.; Bayer, Gr.; Bayer, Hung.; Bayer, Indon.; Bayer Schering, Malaysia; Bayer, Mex.; Bayer, NZ; Bayer, Port.; Bayer, UK; Bayer, USA.*
Sorafenib tosilate (p.770·2).
Hepatocellular carcinoma; renal cell carcinoma.

Nexen *Therabel, Fr.*
Nimesulide (p.95·3).
Musculoskeletal and joint disorders; pain.

Nexiam *AstraZeneca, Belg.; AstraZeneca, S.Afr.*
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Nexit *Grunenthal, Chile†.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus; sedative.

Nexium
AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Fin.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Spain; AstraZeneca, Thai.; AstraZeneca, UK.
Esomeprazole magnesium (p.1729·2) or esomeprazole sodium (p.1729·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Denm.; AstraZeneca, Gr.; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Malaysia; AstraZeneca, Rus.; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, USA.
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

AstraZeneca, Philipp.; AstraZeneca, Turk.
Esomeprazole (p.1729·3).
Gastro-oesophageal reflux; peptic ulcer.

AstraZeneca, Singapore; AstraZeneca, Venez.
Esomeprazole (p.1729·3) or esomeprazole sodium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Nexium Hp *AstraZeneca, Austral.; AstraZeneca, Swed.*
Tablets, esomeprazole magnesium (Nexium) (p.1729·2); capsules, amoxicillin trihydrate (Amoxil) (p.202·2); tablets, clarithromycin (Klacid) (p.248·2).
Peptic ulcer.

Nexofil *Nexo, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Nexogrip *Nexo, Arg.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); bromhexine (p.1552·2).
Influenza symptoms.

Nexotensil *Nexo, Arg.*
Amlodipine (p.1214·2).
Hypertension.

Nexproxyn *Medopharm, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Next Step *Omedir, Arg.*
Glimepiride (p.441·1).
Diabetes mellitus.

Nextrim Aktiv *Polpharma, Rus.*
Aspirin (p.20·3); ethenzamide (p.51·3); caffeine (p.1116·3).
Fever; pain.

Nexus *Senosiain, Mex.*
Amlodipine (p.1214·2).
Hypertension.

Nexvep *BMS, Braz.*
Etoposide phosphate (p.718·2).
Malignant neoplasms.

Nexxair *Schwarz, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

NeyArthros Nr 43-Sol *Vitorgan, Ger.*
Homoeopathic preparation.

NeyArthros (Revitorgan-Dilutionen Nr 43) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyArthros-Liposome (Revitorgan Lp Nr 83) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyArthrosome (Revitorgan-Dilution) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyCalm (Revitorgan-Dilutionen Nr 98, Revitorgan-Lingual Nr 98) *Vitorgan, Ger.*
Animal tissue extract: cortex cerebri; diencephalon; epiphysis; placenta mat.
Nervous disorders.

NeyCalm-Solubile *Vitorgan, Ger.†.*
Animal tissue extract: cort. cerebri; diencephalon; epiphysis; placenta mat.
Nervous disorders.

NeyChondrin N (Revitorgan-Dilutionen N Nr 68) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyChondrin Nr 68-Sol *Vitorgan, Ger.*
Homoeopathic preparation.

NeyChondrin (Revitorgan-Dilutionen Nr 68) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyChondrin (Revitorgan-Lingual Nr. 68) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyCorenar (Revitorgan-Dilutionen Nr 6) *Vitorgan, Ger.†.*
Cor fet.
Cardiovascular disorders.

NeyCorenar-Solubile *Vitorgan, Ger.†.*
Cor fet.
Cardiovascular disorders.

NeyDesib (Revitorgan-Dilutionen Nr 78) *Vitorgan, Ger.†.*
Thymus fet.; lien fet.; lymphonodi; gland. suprarenal.
Allergies; auto-immune disorders.

NeyDesib-Solubile *Vitorgan, Ger.†.*
Thymus fet.; lien fet.; lymphonodi; gland. suprarenal.
Allergies; auto-immune disorders.

NeyDil 66N (Revitorgan-Dilutionen Nr. 66 N) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyDil 66 (Revitorgan-Dilutionen Nr. 66) *Vitorgan, Ger.*
Homoeopathic preparation.

Neydin-F *Vitorgan, Ger.*
Homoeopathic preparation.

Neydin-M *Vitorgan, Ger.*
Homoeopathic preparation.

NeyDop N (Revitorgan-Dilutionen N Nr 97) *Vitorgan, Ger.†.*
Cortex cerebri; diencephalon; cerebellum; placenta fet.; ascorbic acid (p.1983·3); lithium chloride (p.406·1); levodopa (p.804·3).
Central nervous system disorders.

NeyDop (Revitorgan-Dilutionen Nr 97) *Vitorgan, Ger.†.*
Cortex cerebri; diencephalon; cerebellum; placenat fet.
Central nervous system disorders.

NeyDop (Revitorgan-Lingual Nr. 97) *Vitorgan, Ger.†.*
Animal tissue extracts (NeyDop N); ascorbic acid; lithium chloride; levodopa.
Central nervous system disorders.

NeyDop-Solubile *Vitorgan, Ger.†.*
Animal tissue extract: cort. cerebri; diencephalon; cerebellum; placenta fet.
Central nervous system disorders.

NeyFaexan (Revitorgan-Dilutionen Nr 55) *Vitorgan, Ger.†.*
Mucosa intestinal.; muc. vesicae urinar.; mucosa vesicae felleae; muc. nasopharyngea.
Gastrointestinal disorders.

NeyFegan (Revitorgan-Dilutionen Nr 26) *Vitorgan, Ger.†.*
Liver extract (p.2337·3).
Liver disorders.

NeyFegan-Solubile *Vitorgan, Ger.†.*
Liver extract (p.2337·3).
Liver disorders.

NeyGeront N (Revitorgan-Dilutionen N Nr 64) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyGeront (Revitorgan-Dilutionen Nr 64) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyGeront (Revitorgan-Lingual Nr 64) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyGeront-Vitalkapseln *Vitorgan, Ger.*
Homoeopathic preparation.

NeyImmun Nr 73-Sol *Vitorgan, Ger.*
Homoeopathic preparation.

NeyImmun (Revitorgan-Dilutionen Nr 73) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyLing (Revitorgan-Lingual Nr.66) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyNormin N (Revitorgan-Dilutionen N Nr 65) *Vitorgan, Ger.†.*
⊗ Animal tissue extracts (NeyNormin); prednisolone acetate (p.1541·1); liothyronine hydrochloride (p.2174·2); estradiol benzoate (p.2097·2); chorionic gonadotrophin (p.2085·1); alpha tocoferil acetate (p.1992·3); cyanocobalamin (p.1980·2).
Allergic diathesis; insufficiency of the diencephalon-pituitary-adrenal system; rheumatism; vegetative dystonias; virus infection.

NeyNormin (Revitorgan-Dilutionen Nr 65) *Vitorgan, Ger.†.*
Thymus fet.; gland. suprarenal.; lymphonodi; gland. parathyreoidea; hepar; ren; pancreas; lien; vasa fet.; funiculus umbilical.; hypophysis; diencephalon; mucosae miscae; cutis; medulla ossium.
Allergic diathesis; insufficiency of the diencephalon-pituitary-adrenal system; rheumatism; vegetative dystonias; virus infection.

NeyNormin (Revitorgan-Lingual Nr 65) *Vitorgan, Ger.†.*
Animal tissue extracts (NeyNormin); prednisolone acetate; liothyronine hydrochloride; estradiol benzoate; chorionic gonadotrophin; alpha tocoferil acetate; cyanocobalamin.
Allergic diathesis; insufficiency of the diencephalon-pituitary-adrenal system; rheumatism; vegetative dystonias; viral infections.

NeyNormin-Solubile *Vitorgan, Ger.†.*
Animal tissue extracts: thymus fet.; gland. suprarenal.; lymphonodi; gland. parathyreoidea; hepar; ren; pancreas; lien; vasa fet.; funiculus umbilical.; hypophysis; diencephalon; mucosa miscae; cutis; medulla ossium.
Allergies; insufficiency of the diencephalons-pituitary-adrenal system; rheumatism; vegetative dystonias; viral infections.

NeyParadent-Liposome *Vitorgan, Ger.†.*
Protein extracts from crista dentalis, placenta, and diencephalon; metenolone acetate; alpha tocoferil acetate; procaine hydrochloride; lipid extract from crista dentalis; sodium salicylate; ascorbic acid; chamomile; arnica; myrrh; sea salt.
Mouth disorders.

NeyPsorin (Revitorgan-Dilutionen Nr 5) *Vitorgan, Ger.†.*
Bovine skin extract (p.2337·3).
Skin disorders.

NeyPsorin-Solubile *Vitorgan, Ger.†.*
Cutis fet.
Skin disorders.

NeyPulpin N (Revitorgan-Dilutionen N Nr 10) *Vitorgan, Ger.†.*
⊗ Crista dentalis; placenta; diencephalon; metenolone acetate (p.2116·3); alpha tocoferil acetate (p.1992·3); ascorbic acid (p.1983·3); procaine hydrochloride (p.1869·1).
Dental disorders.

NeyPulpin (Revitorgan-Dilutionen Nr 10) *Vitorgan, Ger.†.*
Crista dental. fet.; placenta; diencephalon.
Dental disorders.

NeyPulpin-Solubile *Vitorgan, Ger.†.*
Crista dental. fet.; placenta; diencephalon.
Dental disorders.

NeySol L 66 *Vitorgan, Ger.*
Homoeopathic preparation.

Neythymun *Vitorgan, Ger.*
Homoeopathic preparation.

NeyTroph (Revitorgan-Dilutionen Nr 96) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyTroph (Revitorgan-Lingual Nr 96) *Vitorgan, Ger.*
Homoeopathic preparation.

NeyTroph-Solubile *Vitorgan, Ger.*
Homoeopathic preparation.

NeyTumorin N (Revitorgan-Dilutionen N Nr 66) *Vitorgan, Ger.†.*
⊗ Animal tissue extracts (NeyTumorin) (p.2337·3); metenolone acetate (p.2116·3); prednisolone acetate (p.1541·1); liothyronine hydrochloride (p.2174·2); alpha tocoferil acetate (p.1992·3); cyanocobalamin (p.1980·2).
Neoplasms.

NeyTumorin (Revitorgan-Dilutionen Nr 66) *Vitorgan, Ger.†.*
Diencephalon; placenta mat.; funiculus umbilical.; thymus juv.; epiphysis; testes juv.; gland. suprarenal.; gland. thyreoidea; medulla ossium; pulmo; hepar; pancreas; ren; lien; mucosa intestinal.
Neoplasms.

NeyTumorin (Revitorgan-Lingual Nr 66) *Vitorgan, Ger.†.*
Animal tissue extracts (NeyTumorin) (p.2337·3); metenolone acetate; prednisolone acetate; liothyronine hydrochloride; alpha tocoferil acetate; cyanocobalamin.
Neoplasms.

NeyTumorin-Solubile *Vitorgan, Ger.†.*
Animal extracts: diencephalon; placenta matern.; funiculus umbilical.; thymus juvenil; epiphysis; testes juvenil; gland. suprarenal.; gland. thyreoidea; medulla oss.; pulmo; hepar; pancreas; ren; lien; mucosa intestinal.
Malignant neoplasms.

Nezefib *Rafarm, Gr.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Bacterial eye infections with inflammation.

Nezeril *AstraZeneca, Hong Kong†; AstraZeneca, Swed.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinitis; sinusitis.

NF Cough Syrup with Codeine *Technilab, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).

NGT *Geneva, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

NH4 Silhouette *ISA, Arg.*
Chromium (p.1934·3).
Dietary supplement.

Nherea *Zwitter, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Niacef
Note. This name is used for preparations of different composition.
Surya Dermato, Indon.
Nicotinamide (p.1957·3).
Acne.

Cipan, Port.
Cefoxitin sodium (p.230·2).
Bacterial infections.

Niacex *Isdin, Chile.*
Nicotinamide (p.1957·3).
Acne.

Niacifort-6 *Ikapharmindo, Indon.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Nialen *Novag, Spain.*
Ibuproxam (p.66·2).
Peri-articular and soft-tissue disorders.

Nialip *Reddy's, India.*
Nicotinic acid (p.1957·3).
Hyperlipidaemias.

Niar *Abbott, Braz.; Abbott, Cz.; Abbott, Mex.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism; psychiatric disorders.

Niaspan *Merck, Arg.; Oryx, Canad.; Merck, Chile; Merck, Fin.; Merck-Lipha, Fr.; Merck, Ger.; Merck, Hong Kong; Merck, Indon.; Merck, Irl.; Merck, Neth.; Merck, Philipp.; Abbott, Port.; Merck, Singapore; Merck, Swed.; Merck, UK; Abbott, USA; Merck, Venez.*
Nicotinic acid (p.1957·3).
Hyperlipidaemias.

NiaStase *Novo Nordisk, Canad.*
Eptacog alfa (activated) (p.1066·2).
Haemophilia.

Niazitol *GMP, Indon.*
Ethambutol (p.275·2); isoniazid (p.288·1).
Vitamin B_6 (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Niazol *Arex, Venez.*
⊗ Naphazoline nitrate (p.1565·2).
Conjunctivitis; rhinitis; sinusitis.

Nibentan *Experimental Production, Rus.†.*
(RS)-4-Nitro-N-{1-phenyl-5-(diethylamino)pentyl}benzamide hydrochloride.
Arrhythmias.

Niberan *Balu, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Nibiol *Fournier, Fr.†.*
Nitroxoline (p.309·2).
Bacterial infections of the urinary tract.

Nibocin *Antor, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Nibren *Coup, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Nibrevin *Ingers, Cz.*
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Nibulen *Aventis, Turk.*
Ciclopirox olamine (p.529·2).
Fungal skin infections; vaginal candidiasis.

Nica *Yung Shin, Philipp.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Nicabate
GSK Consumer, Austral.
Nicotine (p.2352·2) or nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

GSK, NZ.
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Nicam *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Nicotinamide (p.1957·3).
Acne.

Nican *Uhlmann-Eyraud, Switz.*
Codeine (p.37·2); belladonna (p.2263·3); drosera (p.2297·3); grindelia (p.2317·2); ribwort plantain (p.2379·1); thyme (p.2401·1); sodium benzoate (p.1630·2).
Coughs.

Nicangin *AstraZeneca, Swed.*
Nicotinic acid (p.1957·3).
Hyperlipidaemias.

Nicant *Piam, Ital.†.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Nicaphlogyl *Vifor, Switz.†.*
Propyphenazone (p.119·3); ethenzamide (p.51·3).
Inflammation; pain.

Nicapress *Benedetti, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Nicardal *Italfarmaco, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Nicardia *Unique, India†; Unique, Rus.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nicarpin *San Carlo, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; hypertension.

Nicaven *Uno, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

N'ice
Note. This name is used for preparations of different composition.
SmithKline Beecham Consumer, USA.
Lozenges: Menthol (p.2340·1).
Sore throat.

SmithKline Beecham Consumer, USA.
Throat spray: Menthol (p.2340·1); glycerol (p.2314·2).
Sore throat.

Nice 'n Clear
Note. A similar name is used for preparations of different composition (see below).
Nelson, UK.
Azadirachta oil (p.2262·2).
Pediculosis.

N'ice 'n Clear
Note. A similar name is used for preparations of different composition (see above).
SmithKline Beecham Consumer, USA.
Menthol (p.2340·1).

N'ice Vitamin C *Insight, USA.*
Ascorbic acid (p.1983·3).
Scurvy; vitamin C deficiency.

Nicef *Galen, UK.*
Cefradine (p.233·1).
Bacterial infections.

Nicene N *Adcock Ingram, S.Afr.*
Nitroxoline (p.309·2).
Urinary-tract infections.

Nicer *Ist. Chim. Inter., Ital.†.*
Nicergoline (p.2352·1).
Cerebrovascular disorders.

Nicergin *Madaus, Austria.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders.

Nicergobeta *Betapharm, Ger.*
Nicergoline (p.2352·1).
Mental function disorders.

Nicergolent *Sanofi Synthelabo, Arg.†.*
Nicergoline (p.2352·1).
Vascular disorders.

Nicerin *Biovena, Pol.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders.

Nicerium *Hexal, Ger.*
Nicergoline (p.2352·1).
Mental function impairment.

Nicetal *Sandoz, Philipp.*
Isoniazid (p.288·1).
Vitamin B_6 (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Nicetile *Sigma-Tau, Ital.*
Acetylcarnitine hydrochloride (p.1932·2).
Cerebrovascular disorders; nerve disorders.

Nichobion *Nicholas, Indon.*
Ferrous fumarate (p.1938·3); magnesium sulfate; copper sulfate; folic acid; vitamin B_{12} with intrinsic factor (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Nichodryl *Nicholas, Indon.*
⊗ Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1); alcohol (p.1625·2).
Cough due to allergy.

Nichofed *Nicholas, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine (p.1571·2).
Allergic rhinitis; cold symptoms; sinusitis.

Nichoflam *Nicholas, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Nichogencin *Nicholas, Indon.*
Gentamicin sulfate (p.282·1).
Skin infections.

Nicholin *Takeda, Indon.; Wyeth Lederle, Ital.; Takeda, Jpn; Takeda, Philipp.*
Citicoline (p.2283·3).
Cerebrovascular disorders; head injury; neurological disorders; pancreatitis; parkinsonism.

Nichomedson *Nicholas, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Nichomycin *Nicholas, Indon.*
Lincomycin (p.293·1).
Bacterial infections.

Nichospor *Nicholas, Indon.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Nichostan *Nicholas, Indon.*
Mefenamic acid (p.80·1).
Fever; menorrhagia; pain.

Niciflex-T *Cipla, India.*
Nimesulide (p.95·3); paracetamol (p.108·1); tizanidine hydrochloride (p.1898·2).

Nicip *Cipla, India.*
Nimesulide (p.95·3).
Inflammation; pain.

Nicip Cold *Cipla, India.*
Nimesulide (p.95·3); phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2); caffeine (p.1116·3).
Cold symptoms.

Nicip D *Cipla, India.*
Nimesulide (p.95·3); diclofenac (p.44·2).
Inflammation; pain.

Nicip MR *Cipla, India.*
Nimesulide (p.95·3); paracetamol (p.108·1); chlorzoxazone (p.1894·3).

Nicip Plus *Cipla, India.*
Nimesulide (p.95·3); paracetamol (p.108·1).
Inflammation; pain.

Nicip Super *Cipla, India.*
Nimesulide (p.95·3); methyl salicylate (p.85·3); menthol (p.2340·1); linseed oil (p.2334·1).

Nicip T *Cipla, India.*
Nimesulide (p.95·3); tizanidine hydrochloride (p.1898·2).

Nicispas *Cipla, India.*
Nimesulide (p.95·3); dicycloverine hydrochloride (p.1722·3).

Nicizina *Pharmacia, Ital.*
Isoniazid (p.288·1).
Tuberculosis.

Niclosan *GSK, India; Pharmasant, Thai.†.*
Niclosamide (p.151·1).
Diphyllobothriasis; hymenolepiasis; taeniasis.

Nico Drops *Saval, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2); dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Nico Hepatocyn *Uriach, Spain.*
Cynara (p.2291·2); aloes (p.1705·2); boldo (p.2267·2); cascara (p.1715·2).
Constipation.

Nicobio *Columbia, Mex.†.*
Polymyxin B (p.318·2); neomycin (p.305·1); gramicidin (p.286·1).
Bacterial infections.

Nicobion *AstraZeneca, Fr.; Merck, Ger.*
Nicotinamide (p.1957·3).
Nicotinamide deficiency; pellagra.

NicoBloc *Jaba, Port.†; Galpharm, UK.*
Aid to smoking withdrawal.

Nicobrevin *Pro-Health, NZ; Cedar Health, UK.*
Menthyl valerate; quinine (p.612·2); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Aid to smoking withdrawal.

Nicobrevin N *Tentan, Switz.†.*
Guaifenesin (p.1561·3); thiamine nitrate (p.1976·2); ascorbic acid (p.1983·3); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Aid to smoking withdrawal.

Nicodan *Wernigerode, Ger.†.*
Propyl nicotinate (p.119·2).
Musculoskeletal and joint pain; neuralgia; peripheral vascular disorders.

Nicoderm *Pfizer Consumer, Canad.; SmithKline Beecham Consumer, USA.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Nicoflex *Reanal, Hung.*
Capsaicin (p.32·3); ethyl nicotinate (p.52·1); glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nicogum *Pierre Fabre, Fr.*
Nicotine resin complex (p.2352·2).
Aid to smoking withdrawal.

Nicojuvel *Basi, Port.†.*
Tocoferil nicotinate (p.1415·1).

Nicol *CCM, Malaysia.*
Chloramphenicol (p.239·3).
Bacterial eye and ear infections.

Nicolip *Hennig, Ger.*
Inositol nicotinate (p.1316·1).
Hyperlipidaemias.

Nicolmycetin *Unison, Thai.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Nicolsint *Epifarma, Ital.*
Citicoline (p.2283·3).
Parkinsonism.

Nicomax *Pensa, Spain.*
Nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

Nicomide *Sirius, USA.*
Nicotinamide; zinc oxide; copper oxide; folic acid (p.1922·1).

Nicopass
Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Hung.
Nicotine resinate (p.2352·2).
Aid to smoking withdrawal.

Pharmafabre (Φαρμαφαμπρ), Gr.; Wockhardt, UK.
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Pierre Fabre Dermo-Cosmetique, Port.
Nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

Nicopatch *Pierre Fabre, Cz.; Pierre Fabre Sante, Fr.; Pierre Fabre Dermo-Cosmetique, Port.; Wockhardt, UK.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Nicopaverina *Enila, Braz.†.*
Nicotinic acid (p.1957·3); papaverine hydrochloride (p.2191·3).
Atherosclerosis.

Nicopaverina B6 *Enila, Braz.†.*
Nicotinic acid (p.1957·3); papaverine hydrochloride (p.2191·3); pyridoxine hydrochloride (p.1978·2).
Atherosclerosis.

Nicoprive *DB, Fr.*
Ascorbic acid (p.1983·3); crataegus (p.2289·1); vitamin B substances (p.1922·1).
Aid to smoking withdrawal.

Nicord *Marjan, Braz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Nicorette
Pfizer, Arg.; Pharmacia, S.Afr.; Pfizer Consumer, Spain; Pfizer, Thai.; SmithKline Beecham Consumer, USA.
Nicotine resin (p.2352·2).
Aid to smoking withdrawal.

Pfizer Consumer, Austral.; McNeil, Cz.; Pfizer, Cz.; Pfizer, Hung.; Pfizer, Rus.; Pharmacia, Venez.†.
Nicotine (p.2352·2) or nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

Pfizer, Austria; Pfizer, Fin.
Nicotine (p.2352·2), nicotine betadex (p.2353·2), or nicotine resinate (p.2352·2).
Aid to smoking withdrawal.

Pfizer Consumer, Belg.; Pfizer, Denm.; Pfizer Sante, Fr.; Pfizer, Ger.; Pfizer Consumer, Irl.; Pharmacia, Ital.; Pfizer Consumer, Neth.; Pfizer, Norw.; Pfizer, Swed.; Pfizer Consumer, Switz.; Pfizer Consumer, UK.
Nicotine (p.2352·2), nicotine betadex (p.2353·2), or nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

Pharmacia, Braz.; Pfizer Consumer, Canad.; Pfizer, Chile; Pfizer, Gr.; Pharmacia, Israel; Pfizer, Malaysia; Pharmacia, Pol.; Johnson & Johnson, Singapore.
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Pfizer, Hong Kong.
Nicotine resinate (p.2352·2).
Aid to smoking withdrawal.

Pfizer Consumer, Mex.; Johnson & Johnson, NZ; Janssen-Cilag, Port.
Nicotine (p.2352·2) or nicotine resin complex (p.2352·2).
Aid to smoking withdrawal.

Nicostat *Greenpharma, Braz.*
Nystatin (p.543·2).
Candidiasis.

Nicosyn *Sirius, USA.*
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne.

Nicotabs *Thaipharmed, Thai.*
Nicotinic acid (p.1957·3).
Hyperlipidaemias; nicotinic acid deficiency; vascular disorders.

Nicotears
Note. This name is used for preparations of different composition.
Saval, Chile.
Eye drops: ⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.
Saval, Chile.
Eye gel: Carbomer 940 (p.2141·3).
Dry eyes.

Nicotex *Cipla, India.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Nicotibine *Econophar, Belg.*
Isoniazid (p.288·1).
Tuberculosis.

Nicotinell
Novartis Consumer, Austral.; Novartis, Chile; Novartis Consumer, Cz.; Novartis, Denm.; Novartis Sante, Fr.; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Malaysia; Novartis, Norw.; Novartis Consumer, Pol.; Novartis OTC, Singapore; Novartis, Thai.; Novartis, Turk.
Nicotine (p.2352·2).
Aid to smoking withdrawal.
Novartis Consumer, Austria; Novartis Consumer, NZ.
Nicotine (p.2352·2) or nicotine resinate (p.2352·2).
Aid to smoking withdrawal.
Novartis Consumer, Belg.; Novartis Consumer, Spain.
Nicotine (p.2352·2) or nicotine resin (p.2352·2).
Aid to smoking withdrawal.
Novartis, Fin.; Novartis Consumer, Ger.; Novartis Consumer, Hong Kong; Novartis Consumer, Irl.; Novartis Consumer, Neth.; Novartis, Swed.; Novartis Consumer, Switz.; Novartis Consumer, UK.
Nicotine (p.2352·2), nicotine tartrate (p.2352·2), or nicotine resin (p.2352·2).
Aid to smoking withdrawal.
Novartis Consumer, Ital.
Nicotine (p.2352·2) or nicotine tartrate (p.2352·2).
Aid to smoking withdrawal.

Nicotinell TTS *Novartis Consumer, Arg.; Novartis, Braz.; Novartis, India†; Novartis, Mex.†; Novartis Consumer, Port.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Nicotinex *Fleming, USA†.*
Nicotinic acid (p.1957·3).
Hyperlipidaemia (adjunct); nicotinic acid deficiency; pellagra.

Nicotol *Polfa Pabianice, Pol.†.*
Nicotinyl alcohol tartrate (p.1349·3).
Cerebrovascular disorders; Ménière's disease.

Nicotrol
Pfizer, Austria; McNeil Consumer, Canad.; Pharmacia, Spain†; Pharmacia, USA.
Nicotine (p.2352·2).
Aid to smoking withdrawal.
Pfizer Consumer, NZ.
Nicotine (p.2352·2) or nicotine resin complex (p.2352·2).
Aid to smoking withdrawal.

Nicovitol *Lannacher, Austria.*
Nicotinamide (p.1957·3).
Nicotinamide deficiency.

Nicox *Novell, Indon.*
Nimesulide (p.95·3).
Inflammation; osteoarthritis; pain; peri-articular disorders.

Nicozid *IFET (ΙΦΕΤ), Gr.; Piam, Ital.*
Isoniazid (p.288·1).
Tuberculosis.

Nicozinc
Note. This name is used for preparations of different composition.
Chobet, Arg.
Tablets: Zinc nicotinamide (p.1958·3).
Peripheral vascular disorders.
Chobet, Arg.
Topical solution: Zinc nicotinamide (p.1958·3); lincomycin hydrochloride (p.293·2).
Skin infections.

Nicozone *Nida, Singapore.*
Ketoconazole (p.539·1).
Fungal infections.

NidaGel *3M, Canad.*
Metronidazole (p.837·1).
Bacterial vaginosis.

Nidal AR *Nestle, Fr.*
Infant feed (p.1922·1).
Regurgitation in infants.

Nidal HA *Nestle, Fr.*
Infant feed (p.1922·1).
Potential hypersensitivity to cows milk.

Nidatar *Apotex, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Nidazol *Ulagay, Turk.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Nidazole *Kalbe, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Nidazolin *Bunker, Braz.*
Nystatin (p.543·2).
Fungal infections.

Nidazol-M *Ulagay, Turk.*
Miconazole nitrate (p.541·3); metronidazole (p.837·1).
Vulvovaginal candidiasis.

Nidcor *Pharma Nutria, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Niddafin *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Niddaryl *Dee, UK.*
Glimepiride (p.441·1).
Diabetes mellitus.

Niddavita *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Niddazol *Stada, Denm.*
Itraconazole (p.536·3).
Fungal infections.

Nide *Ibirn, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nidem *Arrow, Austral.; Arrow, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Nidex *Nestle, Braz.; Nestle, Ital.*
Maltodextrin (p.1955·3).
Nutritional supplement.

Nidicard *Kocak, Turk.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nidilat *Sanofi Synthelabo, Turk.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nidina Active Excel *Nestle, Ital.*
Infant feed (p.1922·1).
Lactose intolerance.

Nidina Confort *Nestle, Ital.*
Infant feed (p.1922·1).
Regurgitation.

Nidina HA *Nestle, Ital.†; Nestle, Port.*
Infant feed (p.1922·1).
Food hypersensitivity; protein intolerance.

Nidina probiotico *Nestle, Ital.†.*
Infant feed (p.1922·1).
Gastrointestinal disorders.

Nidol *Eurodrug, Hong Kong; Eurodrug, Hung.; Eurodrug, Malaysia†; Eurodrug, Singapore†; Eurodrug, Thai.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Nidolid *Eurodrug, Philipp.*
Nimesulide (p.95·3).
Cold and influenza symptoms; inflammation; musculoskeletal and joint disorders.

Nidralon-V *Liferpal, Mex.*
Metronidazole (p.837·1).
Vaginal infections.

Nidran *Sankyo, Jpn†.*
Nimustine hydrochloride (p.756·3).
Malignant neoplasms.

Nidrazid *Zentiva, Cz.*
Isoniazid (p.288·1).
Tuberculosis.

Nidrel *Schwarz, Fr.*
Nitrendipine (p.1358·2).
Hypertension.

Nidrozol *Ivax, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Nieral *Schuck, Ger.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Nierano HOM *Pfluger, Ger.*
Homoeopathic preparation.

Nieren-Elixier ST *Cosmochema, Ger.†.*
Homoeopathic preparation.

Nierentee 2000 *Sanofi Synthelabo, Ger.†.*
Birch leaf (p.2266·3); java tea (p.2328·2); juniper berry oil (p.2328·3); fennel oil (p.2303·1).
Urinary-tract disorders.

Nierentee St Severin *Smetana, Austria.*
Ononis (p.2357·1); equisetum (p.2299·3); herb. polygonii.
Urinary-tract disorders.

Nierentropfen Cosmochema *Heel, Ger.*
Homoeopathic preparation.

Niereston *Otsuka, Indon.*
Electrolyte and carbohydrate infusion (p.1667·1).
Renal insufficiency.

Nieron Blasen- und Nieren-Tee VI *Hoyer, Ger.†.*
Birch leaf (p.2266·3); java tea (p.2328·2); solidago virgaurea (p.2391·1); peppermint leaf (p.1761·2); liquorice root (p.1740·3); ononis (p.2357·1).
Urinary-tract disorders.

Nieron E *Schwarz, Ger.*
Equisetum (p.2299·3).
Urinary-tract disorders.

Nieron S *Hoyer, Ger.†.*
Solidago virgaurea (p.2391·1); taraxacum (p.2395·1).
Urinary-tract disorders.

Nieron-Tee N *Hoyer, Ger.†.*
Birch leaf (p.2266·3); equisetum (p.2299·3); taraxacum (p.2395·1); ononis (p.2357·1).
Urinary-tract disorders.

Nieroxin N *Hoyer, Ger.†.*
Maté leaf (p.2416·1); solidago virgaurea (p.2391·1); juniper oil (p.2328·3).
Urinary-tract disorders.

Nifadil *Sanval, Braz.*
Nifedipine (p.1350·1).
Angina pectoris.

Nifal *Aliud, Austria; Meyer, Venez.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifalin *Pharmanik (Φαρμανικ), Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Nifangin *Orion, Fin.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nif-Atenil *Ecosol, Switz.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Nifatenol *Hexal, Ger.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Nifatin *Biofarma, Braz.†.*
Nystatin (p.543·2).
Vaginal candidiasis.

Nifdemin *Ratiopharm, Fin.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nife *ABZ, Ger.; CT, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

nife uno *CT, Ger.†.*
Nifedipine (p.1350·1).
Hypertension.

nife-basan *Schonenberger, Switz.†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease.

Nifebene *Ratiopharm, Austria.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifecard
Note. This name is used for preparations of different composition.
Sigma, Austral.; Lek, Cz.; Lek, Hong Kong; Teva, Hung.; Lek, Rus.; Lek, Singapore†; Lek, Thai.
Nifedipine (p.1350·1).
Angina pectoris; hypertension; migraine; Raynaud's syndrome.
Bros, Gr.
Nitrendipine (p.1358·2).
Hypertension.

Nifecip *Cipla, Malaysia.*
Nifedipine (p.1350·1).
Hypertension.

Nifeclair *Hennig, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifecodan *Pharmacodane, Denm.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifecor *Hexal, Arg.†; Pharmacia, Fin.†; Betapharm, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; hypertrophic cardiomyopathy; Raynaud's syndrome.

Nifed *Rowex, Irl.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifed Sol *Phoenix, Arg.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedalat *Hexal, S.Afr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifedate *Euro-Labor, Port.†; Grunenthal, Port.†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease; Raynaud's syndrome.

Nifedax *Royton, Braz.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedel *Klonal, Arg.*
Nifedipine (p.1350·1).
Angina pectoris.

Nifediac *Teva, USA.*
Nifedipine (p.1350·1).
Hypertension.

Nifedical *Teva, USA.*
Nifedipine (p.1350·1).
Hypertension.

Nifedicard *Kinder, Braz.*
Nifedipine (p.1350·1).
Angina pectoris.

Nifedicor *Nikolakopoulos, Gr.; ICN, Ital.; Streuli, Switz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; ischaemic heart disease; Raynaud's syndrome.

Nifedicron *Pharmacia, Ital.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedi-Denk *Denk, Singapore†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease; Raynaud's syndrome.

Nifedigel *Gelcaps, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedin *Cristalia, Braz.†; Sanbe, Indon.; Benedetti, Ital.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; myocardial infarction; Raynaud's syndrome.

Nifedine *Sarabhai Piramal, India.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedipat *Azupharma, Ger.†; Hexal, Gr.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifedipres *Cryopharma, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension.

Nifedipress *Dexcel, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifehexal *Hexal, Austral.; Hexal, Austria; Hexal, Braz.†; Hexal, Cz.†; Hexal, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifelat
Note. This name is used for preparations of different composition.
Sidus, Arg.†; TAD, Ger.; Cipla, Hong Kong; Cipla, India; Remedica, Singapore†; Remedica, Thai.
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; hypertrophic cardiomyopathy; Raynaud's syndrome.
Biosintetica, Braz.
⊗ Nifedipine (p.1350·1); atenolol (p.1217·3).
Angina pectoris; hypertension.

Nifelease *Pinewood, Irl.†.*
Nifedipine (p.1350·1).
Angina pectoris.

Niferex
Note. This name is used for preparations of different composition.
Raffo, Chile†; Schwarz, Hong Kong; Schwarz, Norw.; Tillomed, UK; Ther-Rx, USA.
Polysaccharide-iron complex (p.1960·2).
Succinic acid and vitamin C (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia; iron-deficiency anaemias.
Schwarz, Denm.; UCB, Port.; Erol, Swed.
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Niferex Forte *Ther-Rx, USA.*
Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; megaloblastic anaemia.

Niferex Prenatal *Raffo, Chile†.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Niferex-PN *Ther-Rx, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Nifesal *Pliva, Ital.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifestad *Stada, Austria; Stada, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifetex *BPRL, Singapore.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifetolol *Anglo-French Drugs, India.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Hypertension.

Nifezzard *Pizzard, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nifical *Winthrop, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifint *Merckle, Ger.†.*
Menthol (p.2340·1).
Upper respiratory-tract catarrh.

Nifiran *Ranbaxy, Thai.†.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; myocardial infarction.

Niflactol *BMS, Spain.*
Morniflumate (p.86·2) or niflumic acid (p.95·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Niflam
Note. This name is used for preparations of different composition.
Roemmers, Arg.†.
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

BMS, Ital.
Capsules; cream; topical gel: Niflumic acid (p.95·2).
Inflammation; pain.

BMS, Ital.
Suppositories: Morniflumate (p.86·2).
Inflammation; pain.

Niflamol *BMS, Gr.*
Niflumic acid (p.95·2).
Inflammatory joint disorders; spondyloarthropathies.

Niflan *Senju, Jpn.*
Pranoprofen (p.119·1).
Inflammatory eye disorders.

Niflec *Meiji, Thai.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Niflucan *Duncan, Arg.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders.

Niflugel *BMS, Belg.; BMS, Cz.; BMS, Fr.*
Niflumic acid (p.95·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Nifluril
Note. This name is used for preparations of different composition.
BMS, Belg.; BMS, Cz.
Niflumic acid (p.95·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

BMS, Fr.; BMS, Port.
Capsules; ointment: Niflumic acid (p.95·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

BMS, Fr.
Suppositories: Morniflumate (p.86·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Niflux *Alter, Port.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Respiratory-tract congestion.

Nifopress *Goldshield, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Niformina *Tiefenbacher, Neth.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Nifostin *Penn, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Nifser *Serral, Mex.*
Nifedipine (p.1350·1).
Hypertension.

Nif-Ten *AstraZeneca, Austria; AstraZeneca, Fin.; AstraZeneca, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; Zeneca, Neth.†; AstraZeneca, Philipp.; AstraZeneca, Singapore; AstraZeneca, Switz.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nifudiar *Meprofarm, Indon.*
Nifuroxazide (p.307·2).
Diarrhoea.

Nifural *Medifarma, Indon.; Pediatrica, Indon.*
Nifuroxazide (p.307·2).
Diarrhoea.

Nifuran
Note. This name is used for preparations of different composition.
Jenapharm, Ger.†.
Furazolidone (p.834·3).
Vaginal infections.

Bamford, NZ.
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Nifurantin *Apogepha, Cz.†; Apogepha, Ger.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Nifurantin B 6 *Apogepha, Ger.*
Nitrofurantoin (p.308·1); pyridoxine hydrochloride (p.1978·2).
Urinary-tract infections.

Nifurat *Bago, Chile†.*
Nifuroxazide (p.307·2); activated attapulgite (p.1709·1).
Diarrhoea.

Nifuretten *Apogepha, Ger.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Nifurol *Reuffer, Mex.*
Nitrofurazone (p.309·1).

Nifurtox *Richmond, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Nifuryl *Gunsa, Turk.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Nigalax
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Arg.
Suppositories: Bisacodyl (p.1710·1); docusate sodium (p.1725·1); sodium lauril sulfoacetate (p.2138·3).
Bowel evacuation.

Sanofi Synthelabo, Arg.
Tablets: Bisacodyl (p.1710·1); docusate sodium (p.1725·1).
Bowel evacuation.

Nigepan *Nizpharm, Rus.*
Benzocaine (p.1854·1); heparin sodium (p.1301·2).
Haemorrhoids.

Nigersan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Night Nurse *GSK Consumer, Irl.; GSK Consumer, UK.*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Night Peel *Lierac, Fr.*
⊗ Salicylic acid (p.1612·2); glycolic acid (p.1598·1); urea (p.1620·2); enoxolone (p.50·1).
Sun-induced skin damage.

Night Time Cold/Flu Relief *Prometic, USA.*
Doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Nightcalm *Galpharm, UK.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Nighttime *Jamp, Canad.; Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Nighttime Cold & Flu *Pharmetics, Canad.; Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Nighttime Pamprin *Chattem, USA.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Insomnia.

Niglinar *Rivero, Arg.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; hypertension; induction of intra-operative hypotension.

Nigroids *Ernest Jackson, UK.*
Liquorice (p.1740·3); menthol (p.2340·1).

Nij-Terol *Deutsche, Chile†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Nikableomicina *Pfizer, Chile.*
Bleomycin hydrochloride (p.688·2).
Malignant neoplasms.

Nikarin *TO-Chemicals, Thai.*
Miconazole nitrate (p.541·3).
Oral candidiasis.

Nikion *Roux-Ocefa, Arg.†.*
Enalapril maleate (p.1276·1); felodipine (p.1285·3).
Hypertension.

Nikkho Vac *Nikkho, Braz.*
Allergen extracts (airborne proteins, food proteins, and respiratory-tract bacterial antigens) (p.2250·2).
Allergen immunotherapy.

Niklod *Savio, Ital.*
Clodronate disodium (p.1095·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

nikofrenon *Riemser, Ger.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Nikolam *Meprofarm, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Nikor *Indeco, Arg.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Nikoril *Medinfar, Port.*
Nicorandil (p.1349·1).
Angina pectoris.

Nikotugg *ACO, Swed.*
Nicotine resin (p.2352·2).
Aid to smoking withdrawal.

Nikron *Zentiva, Hung.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Niksen *Toprak, Turk.*
Permethrin (p.2048·2).
Pediculosis.

Nilacelin *Nicholas, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Nilacid *Zentiva, Hung.*
Magnesium trisilicate (p.1744·1); magnesium oxide (p.1744·1); monobasic sodium phosphate (p.1682·3); bismuth subnitrate (p.1711·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Nilacol *Nicholas, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Niladacin *Nicholas, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Nilaflox *Nicholas, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Nilan *Rowe-Fleming, Venez.†.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Nilandron *Hoechst Marion Roussel, USA.*
Nilutamide (p.756·2).
Prostatic cancer.

Nilapur *Nicholas, Indon.*
Allopurinol (p.552·2).
Hyperuricaemia.

Nilaren *Nicholas, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Nilatika *Nicholas, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Nilcid *Abbott, Mex.†.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Nilcid-MPS *Abbott, Hong Kong†.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity; heartburn.

Nilevar *Pharmion, Fr.*
⊗ Norethandrolone (p.2119·3).
Medullary aplasia.

Nilfene *Pharmis, Port.*
⊗ Fentanyl citrate (p.55·3).
Neuroleptanalagesia; pain.

Nilflux *Biol, Arg.*
Staphylococcus aureus; haemolytic Streptococcus; *Streptococcus pyogenes*; non-haemolytic Streptococcus; *Enterococcus faecalis* (p.2372·3); *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Micrococcus roseus*; *Moraxella catarrhalis*; *Haemophilus influenzae*; hyaluronidase (p.2321·1); ox bile (p.2266·3); ascorbic acid (p.1983·3).
Respiratory-tract infections.

Nilgrip *Biol, Arg.*
An influenza vaccine (p.2218·2).
Active immunisation.

Nilide *Cadila, India; Pharmasant, Thai.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nilium *Help, Gr.†.*
Flunitrazepam (p.996·2).
Hypnotic.

Nilken *Kener, Mex.*
⊗ Buphenine hydrochloride (p.2270·2).

Nilogrin *Polfa, Cz.†; Polfa Pabianice, Pol.; Pabianice, Rus.*
Nicergoline (p.2352·1).
Alzheimer's disease; cerebral and peripheral vascular disorders; circulatory ear disorders; mental function impairment; migraine; retinopathy; vascular eye disorders; vestibular disorders.

Nilperidol *Cristalia, Braz.*
⊗ Fentanyl citrate (p.55·3); droperidol (p.994·3).

Nilson *Pantafarm, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Nilstat *Sigma, Austral.; Teofarma, Belg.; Technilab, Canad.†; Zuellig, NZ; Lederle, USA.*
Nystatin (p.543·2).
Candidiasis.

Niltro *Duncan, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Nilvadis *Eczacibasi, Turk.*
Nilvadipine (p.1357·1).
Hypertension.

Nim *Hexal, Ger.†.*
Nimodipine (p.1357·2).
Cerebral disorders in the elderly; neurological deficit following cerebral vasospasm.

Nimadorm *Sandoz, Denm.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Nimalge *Labesfal, Port.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Nimalgex *Hexal, Braz.†.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nimartin *Vida, Port.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Nimbex *GSK, Arg.†; GSK, Austral.; GSK, Austria; GSK, Belg.; Abbott, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore†; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.*
Cisatracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Nimbisan *Caber, Ital.*
Brotizolam (p.965·2).
Insomnia.

Nimbium *GSK, Arg.; GSK, Braz.*
Cisatracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Nimbola *Kee, India†.*
Azadirachta oil (p.2262·2).
Acne; diabetes mellitus.

Nimbus *Marco, Austral.†; Biomerica, USA.*
Pregnancy test (p.2372·1).

Nimcet *Svizera, India.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimecox *Leti, Venez.*
Nimesulide betadex (p.95·3).
Inflammation; pain.

Nimed *Medicom, Cz.; Aventis, Fin.†; Helsinn Birex, Indon.; Schering-Plough, Indon.; Sanofi-Aventis, Port.*
Nimesulide (p.95·3).
Fever; inflammation; osteoarthritis; pain; peri-articular disorders.

Nimedalin *Biofarma, Braz.†.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nimedex *Italfarmaco, Ital.*
Nimesulide betadex (p.95·3).
Fever; inflammation; pain.

Nimeflan *Infabra, Braz.†.*
Nimesulide (p.95·3).

Nimegel *Lamda (Λαμδα), Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Nimegen *Medica Korea, Malaysia; Medica Korea, Singapore.*
Isotretinoin (p.1599·2).
Acne.

Nimel *Proula, Venez.†.*
Dipyrone (p.49·2).
Fever; pain.

Nimelid *PannonPharma, Hung.; SM, Venez.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimelide *Genepharm, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Nimenol *Krugher, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimepast *Pasteur, Chile.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimepirex *Leti, Venez.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimepis *Pisa, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimes *Stada, Thai.†; Sanovel, Turk.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Nimesil *Guidotti, Cz.; Lusofarmaco, Ital.; Guidotti, Pol.; Menarini, Rus.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimesilam *Sigma, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nimesubal *Baldacci, Braz.*
Nimesulide (p.95·3).

Nimesul *Medichrom, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Nimesulene *Guidotti, Ital.; Menarini, Port.*
Nimesulide (p.95·3).
Fever; inflammation; osteoarthritis; pain.

Nimesulin *Cifarma, Braz.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimesulix *Teuto, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nimesulon *Sanval, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nimesyl *Rider, Chile.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimex *Andromaco, Chile†.*
Nimesulide (p.95·3).
Inflammation; pain.

Nimexan *Angelini, Ital.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimfast *Cadila, India.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Nimica *Ipca, India; Ipca, Rus.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimica Plus *Ipca, India.*
Nimesulide (p.95·3); paracetamol (p.108·1).
Fever, inflammation; pain.

Nimicon *Precimex, Mex.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Nimicor
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Formenti, Ital.
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Nimind *Indoco, Thai.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal and joint disorders; pain.

Nimm *Codal Synto, Hong Kong.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimobal *Baldacci, Braz.*
Nimodipine (p.1357·2).

Nimodil *Remedina, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Nimodilat *Lazar, Arg.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Nimodilat Plus *Lazar, Arg.*
Nimodipine (p.1357·2); citicoline sodium (p.2283·3).
Cerebrovascular disorders.

Nimodol *Aristo, India.*
Nimesulide (p.95·3).
Inflammation; pain.

Nimopax *Cifarma, Braz.*
Nimodipine (p.1357·2).
Mental function disorders; neurological deficit following subarachnoid haemorrhage.

Nimopect *Hevert, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh.

Nimoreagin *Baliarda, Arg.*
Nimodipine (p.1357·2); citicoline (p.2283·3).
Cerebrovascular disorders.

Nimo-Somazina *Temis, Arg.*
Citicoline (p.2283·3); nimodipine (p.1357·2).
Cerebrovascular disorders.

Nimost *Sanbe, Indon.*
Nimesulide (p.95·3).
Osteoarthritis; pain; peri-articular disorders.

Nimotop *Bayer, Arg.; Bayer, Austral.; Bayer, Austria; Bayer, Belg.; Bayer, Braz.; Bayer, Canad.; Bayer, Chile; Bayer, Cz.; Bayer, Denm.; Bayer, Fin.; Bayer, Fr.; Bayer, Ger.; Bayer, Gr.; Bayer, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Irl.; Bayer, Israel; Bayer, Ital.; Bayer Schering, Malaysia†; Bayer, Mex.; Bayer, NZ; Bayer, Neth.; Bayer, Norw.; Bayer, Philipp.; Bayer, Pol.; Bayer, Port.; Bayer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Bayer, Swed.; Bayer, Switz.; Bayer, Thai.; Bayer, Turk.; Bayer, UK; Bayer, USA; Bayer, Venez.*
Nimodipine (p.1357·2).
Cerebrovascular disorders; ischaemic neurological deficit following subarachnoid haemorrhage; mental function impairment; vertigo.

Nimovac-V *Pharmathen, Gr.*
Nimodipine (p.1357·2).
Subarachnoid haemorrhage.

Nimovas *Diffucap, Braz.†.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Nims *Caber, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nimulid *Panacea, India; Biogenetech, Thai.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nimulid MR *Panacea, India.*
Nimesulide (p.95·3); tizanidine hydrochloride (p.1898·2).
Muscle spasm; osteoarthritis; pain.

Nimulid Nugel *Panacea, India.*
Nimesulide (p.95·3); menthol (p.2340·1); methyl salicylate (p.85·3); capsaicin (p.32·3); linseed oil (p.2334·1).
Musculoskeletal, joint, and peri-articular disorders.

Nimulid SP *Panacea, India.*
Nimesulide (p.95·3); serrapeptase (p.2385·3).
Haematoma; inflammation.

Nimus *Tecnofarma, Chile.*
Bezafibrate (p.1232·1).
Atherosclerosis; hyperlipidaemias.

Nimusyp *Centaur, India.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nimutab *Centaur, India.*
Nimesulide (p.95·3).
Dysmenorrhoea; osteoarthritis; pain.

Nimvista *Cadila, India.*
Nimesulide (p.95·3).

Nimvista Plus *Cadila, India.*
Nimesulide (p.95·3); paracetamol (p.108·1).

Nina *Medichemie, Switz.†.*
Paracetamol (p.108·1).
Fever; pain.

Ninazo *Gache, Venez.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Ninazol *TO-Chemicals, Thai.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Nindaxa *Ashbourne, UK†.*
⊗ Indapamide (p.1314·1).

Ninderm *Maigal, Arg.*
Wool fat (p.2033·2); azulene (p.2262·3); zinc (p.1999·1).

Nine Rubbing Oils *Potter's, UK.*
Amber oil; clove oil (p.2285·1); eucalyptus oil (p.2301·2); linseed oil (p.2334·1); methyl salicylate (p.85·3); volatile mustard oil (p.2349·2); turpentine oil (p.2406·3); thyme oil (p.2401·2); peppermint oil (p.1761·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ninfagin *RPF, Ital.*
Grapefruit; lactic-acid-producing organisms (p.2372·3); chlorhexidine gluconate (p.1635·3); mallow (p.2337·2); aloe vera (p.1588·2).
Restoration of vaginal mucosa.

Ninjin-to *Tsumura, Jpn.*
Liquorice; atractylodes lancea rhizome; ginseng; ginger.
Traditional Kampo medicine.

Ninjin-yoei-to *Tsumura, Jpn.*
Ginseng; angelica acutiloba root; peony root; rehmannia root; atractyloides rhizome; poria sclerotium; cinnamon bark; astragalus root; citrus unshiu peel; polygala root; schisandra fruit; liquorice.
Traditional Kampo medicine.

Ninlium *Chinta, Thai.*
Domperidone (p.1726·2).
Delayed gastric emptying; nausea and vomiting.

Nio Marine *Lagos, Arg.*
Rhodysterol; fucus (p.2384·2); centella (p.1592·3); ivy (p.2328·1); caffeine (p.1116·3).
Cellulite.

Niocitran *Novartis Consumer, Belg.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Niofen
Note. This name is used for preparations of different composition.
Megahealth, Chile.
Ibuprofen (p.64·2).
Fever; pain.

Investi, Arg.
Capsules: Fluconazole (p.532·1).
Candidiasis.

Investi, Arg.
Pessaries: Tioconazole (p.548·2).
Vulvovaginal fungal infections.

Niofen Flu *Megahealth, Chile.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Influenza symptoms.

Niopam *Merck, Irl.†; Bracco, UK.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Niosilin *Medigivor, Venez.*
Benzoic acid (p.1630·2); precipitated sulfur (p.1614·1); salicylic acid (p.1612·2); menthol (p.2340·1); titanium dioxide (p.1617·3); kaolin (p.1738·1).
Fungal skin infections.

Niostal *Spefar, Venez.†.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Niotal *Sanofi-Aventis, Ital.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Nioxil *Geolab, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nipas *Galena, Pol.*
Aspirin (p.20·3).
Dental pain.

Nipaxon *Pfizer, Swed.*
Noscapine (p.1566·2).
Coughs.

Nipcan *Ipca, India.*
Fluconazole (p.532·1).
Fungal infections.

Nipe
Note. This name is used for preparations of different composition.
Vargas, Venez.
Capsules; oral powder; syrup: Paracetamol (p.108·1); chlorphenamine (p.572·2); caffeine (p.1116·3).
Influenza symptoms.

Vargas, Venez.
Oral drops; oral powder (sin cafeina): Paracetamol (p.108·1); chlorphenamine (p.572·2).
Influenza symptoms.

Nipent *SuperGen, Canad.†; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Pfizer, Ital.; Eurogen, Neth.; Hospira, Port.; Parke, Davis, Spain; Eurogen, UK; Hospira, USA.*
Pentostatin (p.763·1).
Hairy-cell leukaemia.

Nipidol *Biofarma, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Nipin *Lisapharma, Ital.; Lisapharma, Singapore.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nipiol *Billiet, Arg.†.*
⊗ Cyproheptadine (p.575·2); dexamethasone (p.1526·1).

Nipodur *Anfarm, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Nipogalin *Anfarm, Gr.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Nipolen *Mintlab, Chile.*
Chlorphenamine maleate (p.571·3).

Nipolept *Fujisawa, Austria; Aventis, Ger.*
Zotepine (p.1040·1).
Schizophrenia.

Niponeurin *Lacer, Port.*
⊗ Selegiline hydrochloride (p.817·1).

Nipress *Rider, Chile.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Nipride *Biolab Sanus, Braz.; Mayne, Canad.; Roche, Irl.†.*
Sodium nitroprusside (p.1397·1).
Controlled hypotension; ergot intoxication; heart failure; hypertensive crisis.

Niprina *Pensa, Spain.*
Nitrendipine (p.1358·2).
Angina pectoris; hypertension; Raynaud's syndrome.

Niprolide *Rowe-Fleming, Venez.†.*
Nimesulide (p.95·3).
Inflammation; pain.

Niprusodio *Fada, Arg.*
Sodium nitroprusside (p.1397·1).
Hypertension.

Nipruss *Schwarz, Cz.; Schwarz, Ger.; Schwarz, Israel; Adeka, Turk.*
Sodium nitroprusside (p.1397·1).
Controlled hypotension; heart failure; hypertension; hypertensive crisis.

NiQuitin
GSK Consumer, Belg.; GSK Sante, Fr.; GSK Consumer, Ger.; GSK Consumer, Irl.; GSK Consumer, Neth.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Swed.; GSK Consumer, UK.
Nicotine (p.2352·2) or nicotine polacrilex (p.2352·2).
Aid to smoking withdrawal.

GSK, Braz.; GSK Consumer, Cz.; GSK Consumer, Denm.†; GSK Consumer, Hung.; GSK, Israel; GSK, Mex.; GSK Consumer, Spain.
Nicotine (p.2352·2).
Aid to smoking withdrawal.

GSK Consumer, Ital.
Nicotine (p.2352·2) or nicotine resinate (p.2352·2).
Aid to smoking withdrawal.

Niraben *Samchully, Singapore.*
Nifuroxazide (p.307·2).
Bacterial diarrhoea.

Nirapel *Ivax, Arg.*
Nitrendipine (p.1358·2).
Hypertension.

Nirason N *Ravensberg, Ger.*
Pentaerithrityl tetranitrate (p.1366·3).
Ischaemic heart disease; myocardial infarction.

Niravam *Schwarz, USA.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Nirmadil *Fahrenheit, Indon.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Nirmin *Zorka, Rus.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; myocardial infarction; pulmonary oedema.

Nirolex Chesty Coughs with Decongestant *Boots, UK.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Nirolex Day Cold & Flu *Boots, UK.*
Paracetamol (p.108·1); pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nirolex Dry Cough *Boots, UK.*
Glycerol (p.2314·2).
Coughs.

Nirolex Dry Coughs with Decongestant *Boots, UK.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Nirolex Night Cold & Flu *Boots, UK.*
Paracetamol (p.108·1); pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Nirox *Gabriel, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Nirulid *MSD, Denm.*
⊗ Amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Nirvaxal *Teva, Israel.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Nervous gastrointestinal disorders.

Nisacalm *Mayoly-Spindler, Fr.*
Thymol (p.1664·3); salol (p.122·1); menthol (p.2340·1).
Formerly known as Borostyrol.
Minor burns.

Nisaid
Note. This name is used for preparations of different composition.
Zwitter, Gr.
Oxaprozin (p.105·3).
Inflammatory disorders.

Alliance, S.Afr.
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Nisalgen *UCI, Braz.†.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nisapulvol *Mayoly-Spindler, Fr.; Mayoly-Spindler, Malaysia.*
Benzyl hydroxybenzoate (p.1649·1).
Pruritus.

Nisaseptol *Mayoly-Spindler, Fr.*
Benzyl hydroxybenzoate (p.1649·1).
Pruritus.

Nisasol *Mayoly-Spindler, Fr.*
Benzyl hydroxybenzoate (p.1649·1).
Burn and wound disinfection.

Niscamil *Loeffler, Mex.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Nise *Reddy's, India; Reddy, Rus.; Reddy, Singapore†; Biofarma, Venez.†.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Nisicur *Apomedica, Austria.*
Ethenzamide (p.51·3); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Nisis *Beaufour, Fr.*
Valsartan (p.1420·2).
Hypertension; myocardial infarction.

Nisisco *Beaufour, Fr.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Nisita
Note. This name is used for preparations of different composition.
Engelhard, Ger.†; Engelhardt, Hung.†.
Sodium chloride (p.1686·1); sodium bicarbonate (p.1673·2).
Dry mouth; nasal disorders; nasal dryness.

Engelhard, Hong Kong†.
Sodium iodide; sodium bromide; sodium chloride; lithium chloride; sodium bicarbonate; sodium sulfate; sodium phosphate; potassium sulfate (p.1667·1).
Nasal dryness.

Nislev *Pharos, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Nisodipen *Roemmers, Arg.†.*
Nisoldipine (p.1358·1).
Angina pectoris; hypertension.

Nisoflan *Geolab, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nisolid *Chiesi, Ital.*
⊗ Flunisolide (p.1531·1).
Obstructive airways disease; rhinitis.

Nisoran *Aesculapius, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Nispil *Sons, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Infected eye disorders.

Nistafesa *Organifar, Venez.†.*
Nystatin (p.543·2).
Candidiasis.

Nistagen *Vitapan, Braz.†.*
Nystatin (p.543·2).
Candidiasis.

Nistaglos *Andromaco, Chile.*
Halibut-liver oil (p.1948·1); nystatin (p.543·2); zinc oxide (p.1621·2).
Fungal skin infections; nappy rash.

Nistagrand *Ahimsa, Arg.*
Nystatin (p.543·2).
Fungal infections.

Nistagyn *Medley, Braz.*
Nystatin (p.543·2).
Vaginal candidiasis.

Nistaken *Kendrick, Mex.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Nistamed *Omedir, Arg.*
Nystatin (p.543·2).
Fungal infections.

Nistan *Apotex, Mex.*
Nystatin (p.543·2).
Fungal infections.

Nistanil *Ducto, Braz.†.*
Nystatin (p.543·2).
Fungal infections.

Nistaquim *Quimica y Farmacia, Mex.*
Nystatin (p.543·2).
Fungal infections.

Nistat *Cevallos, Arg.*
Nystatin (p.543·2).
Bacterial and fungal infections.

Nistatin *Prodotti, Braz.*
Nystatin (p.543·2).
Candidiasis.

Nistaval *Sanval, Braz.*
Nystatin (p.543·2).
Fungal infections.

Nistax *Luper, Braz.†.*
Nystatin (p.543·2).
Fungal infections.

Nistazol *Hebron, Braz.†.*
Metronidazole benzoate (p.837·1); nystatin (p.543·2).
Vaginal infections.

Nistinol *Luar, Arg.*
Nystatin (p.543·2); tinidazole (p.848·3).
Vaginal infections.

Nistomic *Cifarma, Braz.*
Nystatin (p.543·2).
Vaginal candidiasis.

Nistoral *Laboratorios Chile, Chile.*
Nystatin (p.543·2).
Candidiasis.

Nisuflex *Cazi, Braz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Nisulid *Ache, Braz.; Grunenthal, Chile; Robapharm, Switz.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nisural *Laboratorios Chile, Chile.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Nisykind *VSM, Neth.*
Homoeopathic preparation.

Nisyleen *VSM, Neth.*
Homoeopathic preparation.

Nisylen *Peithner, Austria; DHU, Ger.*
Homoeopathic preparation.

Nisyspray *VSM, Neth.*
Homoeopathic preparation.

Nitagon *Medpro, S.Afr.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Nitan
Note. This name is used for preparations of different composition.
Rekah, Israel.
⊗ Pemoline (p.2161·2).
Attention deficit hyperactivity disorder; depression; fatigue.
Abbott, Mex.†.
Sodium nitroprusside (p.1397·1).
Controlled hypotension during surgery; heart failure; hypertension.

Nitastin *Novis, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Nitavan *Stadmed, India.*
Nitrazepam (p.1011·2).
Insomnia.

Nite Time Cold Formula *Barre-National, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Nite Time Diet *Natural Life, Arg.†.*
Lysine; ornithine; arginine (p.1922·1).
Slimming aid.

Nitecall *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Niteherb *MedicHerb, UK.*
Valerian (p.2410·1).
Sleep disturbances.

Niteherb Plus *MedicHerb, UK.*
Valerian (p.2410·1); passion flower (p.2363·2).
Sleep disturbances.

Niten *Ivax, Arg.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; hypertension.

Niten D *Ivax, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Nitens *Crinos, Ital.*
Naproxen cetrimonium (p.93·3).
Gynaecological disorders; mouth and throat disorders.

Nitepax *Pharmacare, S.Afr.*
Noscapine resin complex (p.1566·2).
Coughs.

Niterey *Pharmatrix, Arg.*
Tretinoin (p.1618·1).
Light-induced skin damage.

Nitised *Petsiavas (Πετσιαβας), Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Nititom *Tomnus, Braz.†.*
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nitlotion *Shantys, UK.*
Coconut oil (p.2029·2).
Pediculosis.

Nit-N-Mite
Note. This name is used for preparations of different composition.
Ipca, India†.
Cream: Lindane (p.2045·3); benzocaine (p.1854·1).
Pediculosis; scabies.
Ipca, India.
Lotion: Lindane (p.2045·3).
Pediculosis; scabies.

Nitoman *Prestwick, Canad.; Medilink, Denm.; Cambridge, Irl.; UCB, Port.*
Tetrabenazine (p.2396·2).
Chorea; drug-induced extrapyramidal disorders; movement disorders.

Nitopro *Maruishi, Jpn.*
Sodium nitroprusside (p.1397·1).
Hypertension.

Nitorol *Eisai, Jpn; Eisai, Malaysia†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; coronary sclerosis; ischaemic heart disease; myocardial infarction.

Nitossil *Novartis Consumer, Ital.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Nitozol *Korea Pharma, Singapore.*
Ketoconazole (p.539·1).
Dandruff.

Nitracor *Pliva Krakow, Pol.*
Glyceryl trinitrate (p.1296·2).
Controlled hypotension; hypertensive crisis; myocardial infarction; pulmonary oedema; unstable angina.

Nitradisc *Pfizer, Arg.†; Pfizer, Braz.; Pfizer, Mex.; Pfizer, Port.; Pfizer, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrados *Douglas, NZ; Douglas, Singapore; Douglas, Thai.†; TTN, Thai.†.*
Nitrazepam (p.1011·2).
Epilepsy; infantile spasm; insomnia.

Nitraket *Chiesi, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitramin *Coup, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Nitrangin *Isis, Cz.†; Alpharma-Isis, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; coronary spasm; gastrointestinal spasm; heart failure; myocardial infarction.

Nitrangin compositum *Alpharma-Isis, Ger.†.*
Glyceryl trinitrate (p.1296·2); valerian (p.2410·1).
Angina pectoris; myocardial infarction.

Nitrapan *Cristalia, Braz.*
Nitrazepam (p.1011·2).
Insomnia.

Nitravet *Anglo-French Drugs, India.*
Nitrazepam (p.1011·2).
Insomnia.

Nitrazadon *Valeant, Canad.*
Nitrazepam (p.1011·2).

Nitrazepol *Farmasa, Braz.*
Nitrazepam (p.1011·2).
Insomnia.

Nitre *ABZ, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitregamma *Worwag, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrek *Bertek, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitren *1A, Ger.†; Acis, Ger.†.*
Nitrendipine (p.1358·2).
Hypertension.

Nitren Lich *Winthrop, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrencord *Biosintetica, Braz.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrendepat *Azupharma, Ger.†.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrendicor *Labomed, Chile†.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrendidoc *Docpharm, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrendil *Bago, Arg.; Elmor, Venez.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrendimerck *Merck dura, Ger.†.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrensal *TAD, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrepress *Hexal, Cz.; Hexal, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitre-Puren *Alpharma-Isis, Ger.*
Nitrendipine (p.1358·2).
Hypertension.

Nitresan *ProMed, Cz.*
Nitrendipine (p.1358·2).
Hypertension.

Nitrest *Sun, Rus.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Nit-Ret *Zentiva, Cz.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; coronary spasm; heart failure.

Nitrex *Essex, Ital.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Nitriate *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Sodium nitroprusside (p.1397·1).
Controlled hypotension; heart failure; hypertensive crisis.

Nitridazol *HLB, Arg.*
Itraconazole (p.536·3).
Fungal infections.

Nitriderm TTS *Novartis, Fr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrilan *Biomedica-Chemica, Gr.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Nitrileno *Libbs, Braz.*
⊗ Nitrofurazone (p.309·1); naphazoline hydrochloride (p.1565·2).
Nasal disorders.

Nitrilex *Galena, Cz.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Nitro
Note. This name is used for preparations of different composition.
Rontag, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.
Genericon, Austria; Orion, Fin.; Orion, Rus.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension during cardiac surgery; myocardial infarction; prophylaxis of phlebitis and peripheral extravasation.

Nitro Mack *Pfizer, Austria; Mack, Cz.†; Slovakofarma, Cz.†; Mack, Illert., Ger.†; Galenica, Gr.†; Mack, Hong Kong; Mack, Singapore†; Pfizer, Switz.; Mack, Thai.†; Zuoz, Venez.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; coronary spasm; heart failure; hypertension; myocardial infarction; pulmonary hypertension; pulmonary oedema.

Nitro Pohl *Sanova, Austria; Pohl, Cz.; Pohl, Hong Kong†; Pohl-Boskamp, Hung.; Pohl, Neth.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension; hypertensive crisis; myocardial infarction.

Nitro Solvay *Solvay, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Nitro-Bid *Hoechst Marion Roussel, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; perioperative hypertension.

Nitrocard *Chema-Elektromet, Pol.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; peripheral vascular disorders.

Nitrocine *Schwarz, Hong Kong; Pharos, Indon.; Schwarz, Irl.; Medis, Israel; Schwarz, Malaysia; Omnimed, S.Afr.; Schwarz, Singapore; Schwarz, Thai.; UCB, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension; hypertension or myocardial ischaemia during cardiac surgery; hypertensive crisis; pulmonary oedema; unstable angina.

Nitrocod *Adcock Ingram, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Nitrocontin *Modi-Mundipharma, India.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrocor *3M, Chile; Recordati, Ital.; Farmstandart, Rus.; Troika, Venez.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; hypertensive crisis; myocardial infarction.

Nitro-Crataegutt *Schwabe, Ger.†.*
Pentaerithrityl tetranitrate (p.1366·3); crataegus (p.2289·1).
Heart failure.

Nitroder *Keton, Mex.*
Glyceryl trinitrate (p.1296·2).

Nitroderm *Novartis, Austria; Novartis, Belg.; Novartis, Chile; Novartis, Malaysia; Novartis, NZ; Novartis, Pol.; Gervasi, Spain; Novartis, Spain; Novartis, Thai.; Novartis, Venez.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; prophylaxis of phlebitis and extravasation.

Nitro-Derm *Reuabuen, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitroderm TTS *Novartis, Arg.; Novartis, Braz.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Port.; Novartis, Switz.; Novartis, Turk.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; haematomas; heart failure; prophylaxis of phlebitis and extravasation.

Nitrodex *Dexo, Fr.†; Dexo, Switz.†.*
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris; heart failure.

Nitrodisc *Roberts, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrodom *Dominguez, Arg.*
Glyceryl trinitrate (p.1296·2).
Anal fissures.

Nitro-Dur *Schering-Plough, Arg.; Schering-Plough, Austral.; Ebewe, Austria; Key, Canad.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Irl.; Sigma-Tau, Ital.; Schering-Plough, Mex.; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Port.; Schering-Plough, Spain; Essex, Switz.; Schering-Plough, UK; Key, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Nitro-Dyl *Therabel, Belg.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrodyl *Schering-Plough, Gr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Nitrofen *Teuto, Braz.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Nitrofix *Nobel, Turk.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Nitroflu *Beige, S.Afr.†.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Nitrofungin *Galena, Cz.†.*
Chloronitrophenol; triethylene glycol.
Fungal skin infections.

Nitrofur-C *Leiras, Fin.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Nitrogard *Forest Pharmaceuticals, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrogesic *Troikaa, India.*
Glyceryl trinitrate (p.1296·2).
Anal fissures.

Nitroglyn *Kenwood, USA†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrogray *Gray, Arg.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitroina *Teofarma, Spain.*
Acetic acid (p.2244·2); greater celandine (p.2317·1); salicylic acid (p.1612·2); iodine tincture (p.2169·2); thuja (p.2400·3).
Warts.

Nitroject *Omega, Canad.; Sun, Rus.; Sun, Thai.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; cardiac disorders; controlled hypotension; heart failure; hypertension; myocardial infarction; perioperative hypertension.

Nitrokaf *Kimia, Indon.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrokor *Robugen, Ger.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Nitrol
Note. This name is used for preparations of different composition.
Paladin, Canad.
Glyceryl trinitrate (p.1296·2).
Angina pectoris.
GSK Sante, Fr.
Celandine (p.2317·1); thuja (p.2400·3); iodine (p.2169·2); salicylic acid (p.1612·2); glacial acetic acid (p.2244·2).
Warts.

Nitrolerg *Sedabel, Braz.†.*
⊗ Hydrocortisone (p.1535·2); nitrofurazone (p.309·1).
Infected skin disorders.

Nitrolingual *Aventis, Austral.; Sanova, Austria; Tramedico, Belg.; Aventis, Canad.; Pohl, Cz.†; Pohl, Denm.; Pohl, Ger.; Lavipharm, Gr.; Pohl, Hong Kong; Pohl-Boskamp, Hung.; Modi-Mundipharma, India; Merck, Irl.; Pohl, Israel; Douglas, NZ; Pohl, Neth.; Pohl, Norw.; Pohl-Boskamp, Philipp.; Merck, S.Afr.; Pohl-Boskamp, Swed.; Pohl, Switz.; Opokim, Turk.; Merck, UK; Horizon, USA; Rhone-Poulenc Rorer, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; biliary colic; coronary artery spasm; heart failure; hypertensive crisis; ischaemic heart disease; myocardial infarction; pulmonary oedema; smooth muscle spasm.

Nitromed *Omedir, Arg.*
Nitrofurazone (p.309·1).
Bacterial infections.

Nitromex *Alpharma, Denm.; Alpharma, Fin.; Alpharma, Norw.; Alpharma, Swed.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitromidager *Streger, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Nitromin *Servier, Irl.; Egis, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitromint *Egis, Cz.; EGIS, Hung.; Egis, Pol.; Quilaban, Port.; Egis, Rus.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; coronary artery spasm; heart failure; myocardial infarction.

NitroMist *Par, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitronal *Biobras, Braz.†; Royal, Chile†; Merck, Irl.; Pohl, Israel; Douglas, NZ; Pohl-Boskamp, Philipp.; Pohl, Switz.; Merck, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; control of blood pressure during cardiovascular procedures; controlled hypotension; coronary artery spasm; heart failure; hypertensive crisis; increased ischaemia tolerance during angioplasty; myocardial infarction.

Nitrong *Aventis, Canad.†; Lavipharm, Gr.; KRKA, Rus.; Rhone-Poulenc Rorer, USA†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Nitro-Obsidan *Alpharma-Isis, Ger.†.*
⊗ Pentaerithrityl tetranitrate (p.1366·3); propranolol hydrochloride (p.1380·3).
Angina pectoris; hypertension.

Nitropenton *EGIS, Hung.*
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris.

Nitro-Pflaster-ratiopharm TL *Ratiopharm, Ger.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitroplast *Lacer, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitropresabbott *Abbott, Braz.*
Sodium nitroprusside (p.1397·1).
Hypertension.

Nitropress *Hospira, USA.*
Sodium nitroprusside (p.1397·1).
Controlled hypotension; hypertensive crisis.

Nitro-pro *Elan, USA.*
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).
Formerly known as Nitrolan.

Nitroprus *Scott-Cassara, Arg.; Cristalia, Braz.*
Sodium nitroprusside (p.1397·1).
Hypertension.

Nitroprussiat *Rottapharm, Spain.*
Sodium nitroprusside (p.1397·1).
Controlled hypotension; heart failure; hypertension; myocardial infarction; phaeochromocytoma.

NitroQuick *Ethex, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitroretard *Faran, Gr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Nitrosid *Orion, Fin.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

Nitrosorbide *Lusofarmaco, Ital.*
Isosorbide dinitrate (p.1317·3).
Cardiac disorders.

Nitrosorbon *Pohl, Ger.; Pohl-Boskamp, Philipp.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; ischaemic heart disease; myocardial infarction; pulmonary hypertension.

Nitrospray *Farmstandart, Rus.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrostat *Pfizer, Canad.; Pfizer, Philipp.; Parke, Davis, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitrosun *Sun, Rus.*
Nitrazepam (p.1011·2).

Nitrosylon *Lavipharm, Gr.; Abbott, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

NitroTab *Able, USA†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitro-Time *Time-Cap, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Nitroven *Pohl, Norw.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; blood pressure control during cardiac surgery; heart failure.

5-Nitrox *Balkanpharma, Rus.*
Nitroxoline (p.309·2).
Urinary antiseptic.

Nitrumon *Almirall, Belg.†; IFET (ΙΦΕΤ), Gr.†; Cetin, Turk.*
Carmustine (p.694·3).
Malignant neoplasms.

Nitux *Zambon, Switz.*
Morclofone (p.1565·1).
Coughs.

Nivabetol *Zydus, Fr.*
Betaine (p.2265·2); acetylmethionine (p.1450·2); sorbitol (p.1965·1).
Constipation; dyspepsia.

Nivadil *Dolorgiet, Ger.; Astellas, Irl.; Astellas, Jpn; Menarini, Port.; Klinge, Switz.†.*
Nilvadipine (p.1357·1).
Hypertension.

Nivador *Wellcome, Spain.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Nivagin *TP, Thai.*
Dipyrone (p.49·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Fever; pain.

Nivalin *Pharmachim, Hung.†; Sopharma, Pol.; Sopharma, Rus.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease; impotence; muscular dystrophy; myasthenia gravis; neuritis; neuromuscular disorders; poliomyelitis; reversal of competitive neuromuscular blockade; smooth muscle atony.

Nivaquine *Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Aventis, NZ; Aventis, Neth.; Aventis, S.Afr.; Aventis, Switz.; Beacon, UK.*
Chloroquine sulfate (p.599·3).
Amoebiasis; arthritis; giardiasis; light-sensitive skin disorders; lupus; malaria; rheumatoid arthritis.

Nivaquine-P *Nicholas Piramal, India.*
Chloroquine phosphate (p.599·3).
Hepatic amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Nivas
Note. This name is used for preparations of different composition.
Raffo, Arg.
Nimodipine (p.1357·2).
Alzheimer's disease; cerebrovascular disorders; neurological deficit following subarachnoid haemorrhage.

Tecnofarma, Chile.
Nisoldipine (p.1358·1).
Angina pectoris; hypertension.

Nivas Plus *Raffo, Arg.*
Nimodipine (p.1357·2); citicoline (p.2283·3).
Cerebrovascular disorders.

Nivea *Beiersdorf, USA.*
A range of emollient, cleansing, and moisturising preparations.

Nivea Sun *Beiersdorf, USA.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1).
Sunscreen.

Nivea Visage
Note. This name is used for preparations of different composition.
Beiersdorf, Canad.†.
SPF 4: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Beiersdorf, Canad.†.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1).
Sunscreen.

Nivelan *Lacefa, Arg.†.*
Sulpiride (p.1028·3).
Sedative.

Nivelan N *Lafedar, Arg.*
Alprazolam (p.960·1).
Anxiety.

Nivelcor *Bragafarm, Port.†.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Nivelipol *Temis, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Nivelon *Essex, Chile†.*
Diphemanil metilsulfate (p.2295·2).
Peptic ulcer.

Nivemycin *IFET (ΙΦΕΤ), Gr.; Sovereign, UK.*
Neomycin sulfate (p.305·1).
Bacterial infections; bowel preparation; hepatic coma.

Niven *Pulitzer, Ital.†.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Nivetril *Nafar, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Nivitron *Coup, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Nivoflox *Andromaco, Mex.†; Grunenthal, Port.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Nix *Omega, Belg.; GSK Consumer, Canad.; Insight, Canad.; ACO Hud, Denm.; ACO Hud, Fin.; Omega, Fr.; Omega, Gr.; Chefaro, Ital.; ACO Hud, Norw.; Chefaro, Port.; GSK, Rus.; ACO Hud, Swed.; GSK, Swed.; Warner-Lambert, USA.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Nixal *Columbia, Mex.†.*
Naproxen sodium (p.92·3).
Fever; inflammation; pain.

Nixelaf-C *Bruluagsa, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Nixin *Mepha, Braz.; Mepha, Port.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Nixoderm *Nixoderm, Malaysia.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Skin disorders.

Nixol *Filaxis, Arg.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism.

Nixoran *Roemmers, Arg.*
Nitazoxanide (p.842·3).
Protozoal infections; worm infections.

Nixotinex *Homeocan, Canad.*
Homoeopathic preparation.
Formerly known as Nicotinex.

Nixtensyn *Kramer, Philipp.*
Diazepam (p.986·3).
Anxiety; delirium tremens; musculoskeletal spasm; spasticity.

Nixyn
Note. This name is used for preparations of different composition.
Teofarma, Spain.
Capsules; suppositories: Isonixin (p.72·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Teofarma, Spain.
Cream: Isonixin (p.72·3); methyl salicylate (p.85·3).
Peri-articular and soft-tissue disorders.

Niyaplat *Precimex, Mex.†.*
Cisplatin (p.698·2).

Nizac *Aspen, Austral.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Nizacol *PS, Ital.*
Miconazole (p.541·2).
Gastrointestinal candidiasis.

Nizale *Janssen, Port.*
Ketoconazole (p.539·1).
Fungal infections.

Nizamyl *Novag, Mex.*
Pyrazinamide (p.320·2).
Tuberculosis.

Nizax *Actavis, Denm.; Actavis, Fin.; Lilly, Ger.; Teofarma, Ital.; Lilly, Swed.†.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Nizaxid *Recalcine, Chile; Norgine, Fr.; Prospa, Port.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nizcreme *Janssen-Cilag, S.Afr.*
Ketoconazole (p.539·1).
Fungal skin infections.

Nizer *USV, India.*
Nimesulide (p.95·3); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and peri-articular disorders.

Nizin-V *Andromaco, Mex.*
Nystatin (p.543·2).
Fungal vulvovaginal infections.

Niziran *Cardinal, Philipp.*
Cinnarizine (p.573·1).
Atherosclerosis; cerebrovascular disorders; Ménière's disease; motion sickness.

Nizol *Pyridam, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Nizole *Hovid, Singapore.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Nizolex *Yung Shin, Philipp.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Nizoral *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; McNeil Consumer, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Orion, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; McNeil, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen, Port.; Janssen, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Janssen, USA; McNeil Consumer, USA; Janssen-Cilag, Venez.*
Ketoconazole (p.539·1).
Dandruff; fungal infections; pityriasis capitis; pityriasis versicolor; seborrhoeic dermatitis.

Nizorelle *Janssen-Cilag, S.Afr.*
Ketoconazole (p.539·1).
Dandruff.

Nizoretic *Kinder, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Nizovules *Janssen-Cilag, S.Afr.*
Ketoconazole (p.539·1).
Vaginal candidiasis.

Nizshampoo *Janssen-Cilag, S.Afr.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Nizurin *Collins, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

NL-33 *Morinaga, Indon.*
Infant feed (p.1922·1).
Galactosaemia; lactose intolerance.

N-Labstix *Bayer Diagnostics, Irl.; Bayer Diagnostics, UK.*
Test for glucose, protein, pH, ketones, blood, and nitrite in urine.

NM Powder *Cadila, India.*
Norfloxacin (p.309·2); metronidazole (p.837·1).
Bacterial infections; protozoal infections.

N-Multistix *Bayer, USA.*
Test for glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrites, and pH in urine.

N-Multistix SG *Bayer Diagnostics, Irl.; Bayer Diagnostici, Ital.; Bayer Diagnostics, UK; Bayer, USA.*
Test for specific gravity, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and pH in urine.

No 440 *Herbes Universelles, Canad.*
Vitamins A, C, and D (p.1922·1).

No Doz Plus *Key, Austral.*
Caffeine (p.1116·3); vitamin B substances (p.1922·1); glucose (p.1945·3).
Fatigue.

No Drowsiness Sinarest *Ciba, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

No Gas *Key, Austral.†.*
Activated charcoal (p.1435·2); simeticone (p.1770·2).
Diarrhoea; drug poisoning; excess gastrointestinal gas.

No Grip C *Vifor, Switz.†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

No Pain-HP *Young Again Nutrients, USA.*
Capsaicin (p.32·3).
Pain.

Noacid
Note. This name is used for preparations of different composition.
Infabra, Braz.†.
Aluminium hydroxide (p.1706·2).
Gastric hyperacidity.

OBA, Denm.
Dihydroxyaluminum sodium carbonate (p.1723·3).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Noacid Diates *Provefarma, Arg.*
Liquorice (p.1740·3); calcium (p.1675·2); magnesium (p.1678·3).
Dietary supplement.

NO-AD Babies *Solar, Canad.*
SPF 45: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1); zinc oxide (p.1621·2).
Sunscreen.

NO-AD Easy Block *Solar, Canad.†.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

NO-AD Kids *Solar, Canad.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3) with or without zinc oxide (p.1621·2).
Sunscreen.

NO-AD Sport *Solar, Canad.*
SPF 50: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1).
Sunscreen.

NO-AD Sunblock *Solar, Canad.†.*
SPF 15; SPF 30; SPF 45: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

NO-AD Sunscreen *Solar, Canad.†.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Noalgos *Levofarma, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Noameba-DS *Ipca, India.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis.

Noan *Farmasa, Braz.; Teofarma, Ital.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Noax 3 *AF, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Noax Uno *CSC, Cz.*
Tramadol hydrochloride (p.130·3).
Pain.

Nobactam *Microsules, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Nobactam Bronquial *Microsules, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Nobacter *Eucerin, Fr.*
A range of skin cleansers containing triclocarban (p.1665·2) or triclosan (p.1665·2).

Nobateks *Nobel, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Nobec *MDI, S.Afr.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis.

Nobecid
Note. This name is used for preparations of different composition.
Nobel, Turk.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1).

Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Nobel, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Noben Binnofarm, Rus.
Idebenone (p.367·1).
Cerebrovascular disorders; mental function disorders.

Nobese No. 1 Adcock Ingram, S.Afr.
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

No-Bite Brunel, S.Afr.†.
Diethyltoluamide (p.2041·1); citronella oil (p.2284·2).
Mosquito bites.

Nobiten Menarini, Belg.
⊗ Nebivolol hydrochloride (p.1347·1).
Hypertension.

Nobligan Altana, Arg.; Grunenthal, Denm.; Janssen-Cilag, Mex.; Grunenthal, Norw.; Grunenthal, Port.; Meda, Swed.; Grunenthal, UK.
Tramadol hydrochloride (p.130·3).
Pain.

Nobritol Kern, Spain.
Amitriptyline hydrochloride (p.376·1); medazepam (p.1006·1).
Depression.

Nobrium Teva, Hung.
Medazepam (p.1006·1).
Anxiety disorders.

Nobroncit Eurogenerics, Belg.
Sodium dibunate (p.1573·1); sulfogaiacol (p.1573·2).
Respiratory-tract disorders.

Noc Recalcine, Chile.
Apomorphine hydrochloride (p.795·1).

Nocarex Pisa, Mex.
Nalmefene (p.1452·3).
Opioid antagonist.

Nocazin Alpharma, Mex.
Isoconazole nitrate (p.536·2).
Fungal skin and nail infections.

Noceptin Nycomed, Neth.†.
⊗ Morphine sulfate (p.86·3).
Pain.

Nocertone Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Fr.
Oxetorone fumarate (p.624·1).
Cluster headache; migraine.

Nochix Lacefa, Arg.†.
Melatonin (p.2338·3).
Regulation of sleep-wake cycles.

Nociclin EMS, Braz.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Nocid Farmaline, Thai.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nocold
Note. This name is used for preparations of different composition.
Cipla, India.
Oral drops; sustained-release capsules; syrup: Phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2).
Cold symptoms.

Cipla, India.
Tablets: Paracetamol (p.108·1); phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2); caffeine (p.1116·3).
Cold symptoms.

Nocold Plus
Note. This name is used for preparations of different composition.
Cipla, India.
Caplets: Paracetamol (p.108·1); pseudoephedrine (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms.

Cipla, India.
Syrup: Paracetamol (p.108·1); sodium citrate (p.1673·3); chlorphenamine (p.572·2).
Cold symptoms.

Nocpaz Sanitas, Chile.
Doxylamine succinate (p.578·2).
Insomnia.

Nocsin PM Sanfer, Mex.†.
Paracetamol (p.108·1); diphenhydramine (p.577·1).
Pain.

Noctacalm Socobom, Belg.
Lormetazepam (p.1005·2).
Sleep disorders.

Noctal Abbott, Braz.
Estazolam (p.995·1).
Insomnia.

Noctamid Schering, Austria; Schering, Belg.; Asche, Ger.; Schering, Ger.; Schering, Irl.; Bayer, NZ; Schering, Neth.; Schering, Port.†; Schering, S.Afr.; Schering, Spain; Schering, Switz.
Lormetazepam (p.1005·2).
Insomnia; premedication.

Noctamide Schering, Fr.
Lormetazepam (p.1005·2).
Insomnia.

Noctaval Sigma, Braz.
Valerian (p.2410·1).
Anxiety.

Noctazepam Hexal, Ger.†.
Oxazepam (p.1014·2).
Anxiety; sleep disorders.

Nocte Bago, Arg.; Armstrong, Mex.
Zolpidem tartrate (p.1037·3).
Insomnia.

Noctilan Boehringer Ingelheim, Chile.
Brotizolam (p.965·2).
Insomnia.

Noctiplon Medipharm, Chile†.
Zaleplon (p.1035·3).
Insomnia.

Noctis Bouty, Ital.
Valerian (p.2410·1); passion flower (p.2363·2); crataegus (p.2289·1).
Sleep disorders.

Noctium Ferrier, Fr.
Homoeopathic preparation.

Noctofer Polfa Tarchomin, Pol.
Lormetazepam (p.1005·2).
Sleep disorders.

Nocton Saval, Chile.
Lormetazepam (p.1005·2).
Sleep disorders.

Noctor Torrex, Austria.
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; sedative.

Noctran Menarini, Fr.
Dipotassium clorazepate (p.980·1); acepromazine (p.959·2); aceprometazine (p.959·3).
Insomnia.

Noctura
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Midazolam (p.1007·3).
Hypnotic.

Nelson, UK.
Homoeopathic preparation.

Nocturin
Ferring, Austria.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemorrhagic disorders; nocturia; nocturnal enuresis.

Ferring, Spain.
Desmopressin (p.2185·2).
Diabetes insipidus; nocturnal enuresis.

Nocturne Wyeth, Austral.†.
Temazepam (p.1030·1).
Insomnia.

Nocturno Unipharm, Israel.
Zopiclone (p.1039·1).
Insomnia.

Noctyl Merck Medication Familiale, Fr.
Doxylamine succinate (p.578·2).
Insomnia.

Nocutil Gebro, Austria; Gebro, Cz.†; Schwarz, Ger.; Gebro, Hung.; Gebro, Switz.; Norgine, UK†.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; polydipsia; polyuria.

Nocvalene Arkomedika, Fr.†.
Crataegus (p.2289·1); red-poppy petal (p.1472·3); passion flower (p.2363·2).
Insomnia.

Node DS
Note. This name is used for preparations of different composition.
Dispolab, Chile.
Climbazole (p.529·3); salicylic acid (p.1612·2); piroctone olamine (p.1610·1); lactic acid (p.2329·3); pyrithione zinc (p.1611·2); castor oil (p.2278·1).
Dandruff; seborrhoeic dermatitis.

Bioderma, Fr.
Ichthammol (p.1599·1); cade oil (p.1616·1); salicylic acid (p.1612·2); climbazole (p.529·3); pyrithione zinc (p.1611·2); piroctone olamine (p.1610·1).
Scalp disorders.

Bioderma, Venez.
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2); ichthammol (p.1599·1); pyrithione zinc (p.1611·2); climbazole (p.529·3).
Scalp disorders.

Node G Bioderma, Fr.
Sage oil (p.2382·3).
Scalp disorders.

Node K Bioderma, Fr.
Salicylic acid (p.1612·2); cade hydrolate (p.1616·3); zanthoxylum (p.2417·1); coleus barbatus.
Dandruff.

Node P Bioderma, Fr.
Cade oil (p.1616·1); salicylic acid (p.1612·2); climbazole (p.529·3); pyrithione zinc (p.1611·2); piroctone olamine (p.1610·1).
Scalp disorders.

Nodepe Euro-Labor, Port.†; Grunenthal, Port.†; Andromaco, Spain.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Nodex Brothier, Fr.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Nodia
Note. This name is used for preparations of different composition.
Marvecs, Ital.
Diosmectite (p.1771·1).
Gastrointestinal disorders.

Multichem, NZ.
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Nodiamex IQFA, Mex.
Loperamide (p.1741·3).
Diarrhoea.

Nodict Sun, India.
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Nodipir Klonal, Arg.
Paracetamol (p.108·1).
Fever; pain.

Noditran Naturland, Hung.†.
⊗ Achillea (p.2245·2); adrenaline (p.1203·2); menthol (p.2340·1); camphor (p.2273·2); procaine hydrochloride (p.1869·1); ephedrine hydrochloride (p.1558·2); furazolidone (p.834·3).
Anorectal disorders.

Nodoff
Note. This name is used for preparations of different composition.
Potter's, UK.
Oral liquid: Passion flower (p.2363·2); skullcap (p.2388·2); lupulus (p.2335·2); valerian (p.2410·1); Jamaica dogwood (p.2328·1).
Insomnia.

Potter's, UK.
Tablets: Passion flower (p.2363·2).
Insomnia.

Nodolex Bago, Arg.†.
Paracetamol (p.108·1).
Fever; pain.

Nodolfen Lacer, Spain.
Ibuprofen (p.64·2).
Fever; pain.

Nodon Cadila, India.
⊗ Nebivolol (p.1347·1).
Hypertension.

NoDoz Novartis, USA.
Caffeine (p.1116·3).
Fatigue.

Nodrix Biomep, Mex.
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Nodrof Tempo Scan Pacific, Indon.
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

No-Drowsiness Allerest Ciba, USA.
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Nodryl Teva, Israel†.
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2); neomycin sulfate (p.305·1).
Allergic rhinitis; nasal congestion.

Noducil Andromaco, Chile.
⊗ Sibutramine (p.2164·1).
Obesity.

Noell Polfarmex, Pol.
Ketoconazole (p.539·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Noex Eurofarma, Braz.
⊗ Budesonide (p.1520·1).

Nofebrin Legrand, Braz.
Dipyrone (p.49·2).
Fever; pain.

Nofena Konimex, Indon.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Noflam Pacific, NZ.
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Noflamen EGIS, Hung.
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Noflam-N Pacific, Hong Kong; Merck, Singapore†; Pacific, Singapore†.
Naproxen sodium (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Noflexin Novell, Indon.
Pefloxacin (p.313·3).
Bacterial infections.

Noflorox Merck, Mex.
Norfloxacin (p.309·2).
Bacterial infections.

No-Flu Klinge, Switz.†.
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Noflux YSP, Malaysia.
Muramidase hydrochloride (p.2348·1).
Haemorrhage; sinusitis.

Nofoklam Nufarindo, Indon.
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Noforit Kite (Κιτε), Gr.
Piracetam (p.368·2).
Mental function disorders.

Nofung
Note. This name is used for preparations of different composition.
Egis, Hong Kong; EGIS, Hung.
Fluconazole (p.532·1).
Fungal infections.

Nufarindo, Indon.
Ketoconazole (p.539·1).
Fungal skin and scalp infections.

Nogacid Cadila, India.
Omeprazole (p.1753·1).
Peptic ulcer.

Nogacid D Cadila, India.
Omeprazole (p.1753·1); domperidone (p.1726·2).

Nogas
Note. A similar name is used for preparations of different composition (see below).
Lafit, Braz.†.
Dimeticone (p.1770·2).
Dyspepsia; flatulence.

No-Gas
Note. A similar name is used for preparations of different composition (see above).
Giuliani, Ital.
Dimeticone (p.1770·2); activated charcoal (p.1435·2).
Aerophagia; meteorism.

Nogastra
Note. This name is used for preparations of different composition.
Andromaco, Chile.
Oral suspension: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Andromaco, Chile.
Tablets: Simeticone (p.1770·2); magnesium carbonate (p.1743·1); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Flatulence; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Nogesic Kocak, Turk.
Dipyrone (p.49·2).
Fever; pain.

Nogesta Laboratorios Chile, Chile.
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Noginox Galeno, Venez.
Isoconazole nitrate (p.536·2).
Vulvovaginal infections.

No-Gras Higate, Arg.
Centella (p.1592·3); spirulina (p.2392·1); lecithin (p.2332·2).
Slimming aid.

No-Gravid Irmed, Ital.
Copper (p.1935·2).
Intra-uterine contraceptive device.

Nogrimine Eurogenerics, Belg.
Aspirin (p.20·3); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Nogripe Teuto, Braz.
Ascorbic acid (p.1983·3); salicylamide (p.121·2); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

NoHist DMX Larken, USA.
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

NoHist Plus Larken, USA.
Chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Noiafren Sanofi-Aventis, Spain.
Clobazam (p.477·2).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Noitron Help, Gr.
Isotretinoin (p.1599·2).
Acne.

Nok CTS, Israel†.
Permethrin (p.2048·2).
Pediculosis.

5-Nok Lek, Rus.
Nitroxoline (p.309·2).
Urogenital infections.

Nokatar Prater, Chile.
Ginkgo biloba (p.2311·1).

Nokid Benedetti, Ital.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Nokinal Leciva, Cz.†.
Moxastine teoclate (p.586·2); caffeine (p.1116·3).
Ménière's syndrome; nausea and vomiting; tinnitus.

Noklot Zydus, India.
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis; myocardial infarction; peripheral arterial disease.

Nokoba Fahrenheit, Indon.
Naloxone hydrochloride (p.1453·2).
Opioid overdosage.

Nolac Nestle, Ital.
Infant feed (p.1922·1).
Intolerance to cow's milk, soya, egg, and gluten.

Nolahist Carrick, USA.
Phenindamine tartrate (p.587·2).
Allergic rhinitis.

Nolaid Yes, Neth.
Lidocaine hydrochloride (p.1862·3).
Sore throat.

Nolarac Fada, Arg.†.
Ketorolac (p.75·2).
Inflammation; pain.

Nolargin Eurogenerics, Belg.
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

Nolarmin Coup, Gr.
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Nolder Pharmacia, Ital.
Amino-acid, carbohydrate, and phospholipid preparation with vitamins and selenium (p.1922·1).
Nutritional supplement.

Noleptan
Boehringer Ingelheim, Jpn.
Fominoben hydrochloride (p.1561·1).

Boehringer Ingelheim Promeco, Mex.
Fominoben (p.1561·1) or fominoben hydrochloride (p.1561·1).
Coughs.

Nolgen Antigen, Irl.†.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Nolicin KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.
Norfloxacin (p.309·2).
Bacterial infections.

Nolil Offenbach, Mex.
Clioquinol (p.254·1).
Fungal skin infections.

Nolipax Salus, Ital.
Fenofibrate (p.1286·2).
Diabetic retinopathy; hyperlipidaemias; xanthomatosis.

Noliprel Servier, Cz.; Servier, Hung.†; Anpharm, Pol.; Servier, Pol.; Servier, Rus.
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Nolol Pharmaland, Thai.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Nolotil Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain.
Metamizole magnesium (p.49·3).
Fever; pain.

Nolotil Compositum Europharma, Spain†.
Metamizole magnesium (p.49·3); hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm; pain.

Nolpaza KRKA, Cz.; Pharma-Regist, Hung.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nolvac Pharmathen, Gr.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Nolvadex AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Fin.†; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; ICI, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA†; AstraZeneca, Venez.
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer.

Nomafen Fidia, Ital.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Nomexor Menarini, Austria.
⊗ Nebivolol hydrochloride (p.1347·1).
Hypertension.

Nomigrain Torrent, India.
Flunarizine hydrochloride (p.580·2).
Migraine.

Nomokof Cadila, India†.
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Nomokof-B Cadila, India.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Nomon mono Schwarz, Ger.
Cucurbita (p.2290·2).
Urinary-tract disorders.

Nomopain Aventis, S.Afr.
Paracetamol (p.108·1); caffeine (p.1116·3); doxylamine succinate (p.578·2); codeine phosphate (p.37·2).
Pain and associated tension.

Nomotec Tecnofarma, Mex.
Ketotifen (p.582·2).
Asthma; hypersensitivity.

Nonafact Sanquin, Cz.; Sanquin, Fin.; Sanquin, Neth.; Sanquin, Port.
A factor IX preparation (p.1068·3).
Haemophilia B.

Nonak Pentamedical, Ital.
Azeloyl glycinate; sulfosalicylic acid; piroctone olamine (p.1610·1).
Skin disorders.

Nonak Detergente Pentamedical, Ital.
Soap substitute.

Nonalges Tempo Scan Pacific, Indon.
Tramadol (p.132·1).
Pain.

Nonan Aguettant, Fr.
Mineral preparation (p.1922·1).
Parenteral nutrition.

Nonavit De Mayo, Braz.
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Non-Drowsy Allergy Major, USA.
Loratadine (p.583·3).
Allergic rhinitis.

Non-Drowsy Sinutab Pfizer Consumer, Irl.; Pfizer Consumer, UK.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; nasal and sinus congestion with pain; sinusitis.

Non-Drowsy Sudafed Congestion Cold & Flu Pfizer Consumer, UK.
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly known as Sudafed Co.
Cold and influenza symptoms.

Non-Drowsy Sudafed Congestion Relief Pfizer Consumer, UK.
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Non-Drowsy Sudafed Decongestant Pfizer Consumer, UK.
Pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Sudafed.
Cold and influenza symptoms; hay fever.

Non-Drowsy Sudafed Decongestant Nasal Spray Pfizer Consumer, UK.
⊗ Xylometazoline hydrochloride (p.1575·1).
Formerly known as Sudafed Nasal Spray and contained oxymetazoline hydrochloride.
Nasal congestion.

Non-Drowsy Sudafed Dual Relief Pfizer Consumer, UK.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Formerly known as Sudafed Dual Relief.
Cold and influenza symptoms.

Non-Drowsy Sudafed Dual Relief Max Pfizer Consumer, UK.
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion with pain or fever.

Non-Drowsy Sudafed Expectorant Pfizer Consumer, UK.
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly known as Sudafed Expectorant.
Coughs; upper respiratory-tract congestion.

Non-Drowsy Sudafed Linctus Pfizer Consumer, UK.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Sudafed Linctus.
Coughs; upper respiratory-tract congestion.

No-Nerviol Higate, Arg.†.
Chamomile (p.2279·3); tilia (p.2402·2); passion flower (p.2363·2).
Sedative.

Noneston Help, Gr.†.
Sulpiride (p.1028·3).
Antipsychotic.

Nonflamin Takeda, Indon.
Tinoridine hydrochloride.
Inflammation; pain.

Non-Ovlon Jenapharm, Cz.†; Jenapharm, Ger.†; Jenapharm, Rus.
Ethinylestradiol (p.2101·3); norethisterone acetate (p.2119·3).
Combined oral contraceptive; menstrual disorders.

Non-Preg LBS, Malaysia.
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; progestogen-only injectable contraceptive.

Nontoss Verisfield, Gr.
Butamirate citrate (p.1553·1).
Cough.

Nontusyl Slovakofarma, Cz.†.
Thyme (p.2401·1); agrimony (p.2249·2); althaea (p.2253·3); melissa (p.2339·3); tilia (p.2402·2).
Respiratory-tract disorders.

Noocephal Pyridam, Indon.
Piracetam (p.368·2).
Cerebral trauma; learning difficulties in children; mental function impairment.

Noocetam Pharmasant, Thai.
Piracetam (p.368·2).
Cerebral trauma; cerebrovascular disorders; chronic alcoholism; mental function impairment.

Nooclerin Institute for Molecular Genetics, Rus.
⊗ Deanol aceglumate (p.2152·3).
Alcohol withdrawal syndrome; asthenia; cerebrovascular disorders; mental function impairment.

Noodipina Apsen, Braz.
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Noodis UCB, Belg.
Piracetam (p.368·2).
Childhood learning difficulties.

Noostan Rontag, Arg.; UCB, Port.
Piracetam (p.368·2).
Cerebrovascular disorders; dyslexia; mental function disorders; myoclonus; vertigo.

Nootrofic Cristalia, Braz.†.
Piracetam (p.368·2).

Nootron Biosintetica, Braz.
Piracetam (p.368·2).
Cerebrovascular disorders; senile dementia.

Nootrop UCB, Ger.; UCB, Gr.
Piracetam (p.368·2).
Mental function disorders.

Nootropil UCB, Austria; UCB, Belg.; Sanofi-Aventis, Braz.; UCB, Cz.; UCB, Fin.; UCB, Hong Kong; UCB, Hung.; UCB, India; UCB, Indon.; UCB, Ital.; UCB, Jpn; UCB, Malaysia; UCB, Mex.; UCB, Neth.; UCB, Norw.; UCB, Philipp.; Jelfa, Pol.; UCB, Pol.; Vedim, Port.; UCB, Rus.; UCB, S.Afr.; UCB, Singapore; UCB, Spain; UCB, Swed.; UCB, Switz.; UCB, Thai.; UCB, Turk.; UCB, UK; Grunenthal, Venez.†.
Piracetam (p.368·2).
Alcohol withdrawal syndrome; cerebral trauma; cerebrovascular disorders; coma; dementia; dyslexia; improved intellectual performance in children; mental function impairment; myoclonus; senile dementia; vertigo.

Nootropyl Sanofi Pasteur, Chile; UCB, Fr.
Piracetam (p.368·2).
Alcoholism; cerebrovascular disorders; childhood behaviour disorders; dyslexia in children; mental function impairment; myoclonus; senile dementia; vertigo.

Nooxid Garden House, Arg.†.
Multivitamin and mineral preparation (p.1922·1).

Nopain Krewel, Ger.
Dipyrone (p.49·2).
Fever; pain.

Nopain Plus Casel, Turk.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Nopal Eurodrug, Hong Kong; Eurodrug, Singapore.
Opuntia streptacantha; opuntia ficus-indica; opuntia robusta.
Dietary supplement.

Nopan
CTI, Israel.
⊗ Buprenorphine (p.29·1).
Pain.

CTS, Rus.†.
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Nopar
Note. This name is used for preparations of different composition.
Unipharma, Gr.
Homatropine methylbromide (p.1881·3).
Gastrointestinal disorders characterised by smooth muscle spasm.

Lilly, Ital.
Pergolide mesilate (p.812·3).
Parkinsonism.

Nopatic Rayere, Mex.
Gabapentin (p.482·3).
Epilepsy.

Noperten Dexa, Indon.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Nopil Mepha, Cz.†; Mepha, Switz.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Noplak Daudt, Braz.
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Nopremin Minerva (Μινέρβα), Gr.
Calcitonin (p.1093·1).
Osteoporosis.

Nopres
Dexa, Hong Kong.
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Ferron, Indon.
Fluoxetine (p.397·3).
Depression.

Nopretens Valeant, Cz.
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Nopretens Plus H Valeant, Cz.
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Nopriken Kendrick, Mex.†.
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Nopril Kimia, Indon.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Noprilam Bial, Port.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Noprilex Cosmopharm, Gr.
Paroxetine (p.414·2).
Depression.

Nopron Genopharm, Fr.; Sanofi-Aventis, Ital.
Niaprazine (p.586·3).
Insomnia.

Noprop Farmasa, Braz.†.
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Noprostol Novell, Indon.
Misoprostol (p.2013·2).
NSAID-induced peptic ulcer.

Nopucid
Note. This name is used for preparations of different composition.
Interbelle, Arg.
Permethrin (p.2048·2).
Pediculosis.

Dollder, Venez.
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Nopucid Compuesto Interbelle, Arg.
Deltamethrin (p.2040·1); piperonyl butoxide (p.2049·1).
Pediculosis.

Nopucid MC Interbelle, Arg.
Phenothrin (p.2048·3).
Pediculosis.

Nopyn Rolab, S.Afr.†.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain associated with tension.

Noquerat ICN, Arg.†.
Calcium dimethyl fumarate (p.1597·3); calcium ethylfumarate; magnesium ethylfumarate; zinc ethylfumarate (p.1597·3).
Psoriasis.

Nor 2 Raffo, Arg.
Norfloxacin (p.309·2); phenazopyridine (p.116·3).
Urinary-tract infections.

Nor T Cipla, India.
Norfloxacin (p.309·2); tinidazole (p.848·3).

Nora TNP, Thai.†.
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Norabromol N Michallik, Ger.†.
Sodium 3,5-dibromo-4-hydroxybenzenesulphonate.
Wounds.

Norace Hormona, Mex.
14 Tablets, mestranol (p.2116·2); 7 tablets, mestranol; norethisterone (p.2119·3).
Menopausal disorders; menstrual disorders; sequential oral contraceptive.

Noracin Chew, Thai.
Norfloxacin (p.309·2).
Bacterial infections.

Noractin Biotech, Venez.†.
Ketoconazole (p.539·1).
Fungal infections.

Noradran Norma, UK.
⊗ Diphenhydramine hydrochloride (p.577·2); diprophylline (p.1120·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

Noradren IFET (ΙΦΕΤ), Gr.
⊗ Noradrenaline (p.1360·1).

Norages
Note. This name is used for preparations of different composition.
Meprofarm, Indon.
Dipyrone (p.49·2).
Pain.

GES, Spain.
⊗ Noradrenaline acid tartrate (p.1360·1).
Cardiac arrest; hypotension.

Norakin N Hexal, Ger.†.
Biperiden hydrochloride (p.797·2).
Blepharospasm; drug-induced extrapyramidal disorders; dystonias; parkinsonism; torticollis.

Noral Ulagay, Turk.
Paracetamol (p.108·1).
Fever; pain.

Noralget Aspen, S.Afr.†.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Noranat Sandoz, Arg.
⊗ Indapamide (p.1314·1).
Hypertension.

Norapred Bruluart, Mex.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Nora-ratiopharm Ratiopharm, Ger.†.
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Combined oral contraceptive.

Noratak JC Healthcare, Israel; GSK, Switz.
⊗ Nesiritide citrate (p.1347·3).
Heart failure.

Noravid Crinos, Ital.
Defibrotide (p.1256·2).
Thromboembolic disorders.

Norbactin *Solus, India; Ranbaxy, Malaysia†; Ranbaxy, Philipp.; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norbal *Relyo, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Norboral *Silanes, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Norcalcin *Biomedica-Chemica, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Norcin *The Forty-Two, Thai.; Utopian, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norco *Watson, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Norcolut *Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Gedeon Richter, Singapore.*
Norethisterone (p.2119·3).
Benign breast disorders; dysfunctional uterine bleeding; endometriosis; female infertility; lactation inhibition; menopausal disorders; menstrual disorders.

Norcuron *Organon, Arg.†; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Canad.†; Organon, Chile; Organon, Cz.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, India; Organon, Indon.; Organon Teknika, Irl.†; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pisa, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Sanofi Synthelabo, S.Afr.; Organon, Singapore; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, USA; Organon, Venez.†.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Nordapanin N *Michallik, Ger.†.*
Benzocaine (p.1854·1); acriflavinium chloride (p.1625·1).
Mouth and throat disorders.

Nordathricin N *Michallik, Ger.†.*
Tyrothricin (p.358·2); cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Nordaz *Bouchara-Recordati, Fr.; Bouchara, Singapore.*
Nordazepam (p.1012·1).
Alcohol withdrawal syndrome; anxiety.

Nordet *Wyeth, Mex.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Nordette *Wyeth, Arg.; Wyeth, Austral.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Gr.†; Wyeth, Hong Kong; Wyeth, Israel; Wyeth, Malaysia; Wyeth, NZ; Wyeth, Philipp.; Akromed, S.Afr.; Wyeth, Singapore; Wyeth-Ayerst, Thai.; Barr, USA; Duramed, USA; Wyeth, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; dysfunctional uterine bleeding; dysmenorrhoea; endometriosis; menstrual disorders.

Nordex *Alvia (Αλβια), Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Nordimenty *Nordin, Mex.*
St John's wort (p.422·3); melissa (p.2339·3); chamomile (p.2279·3).

Nordinet Adulto *Nordin, Mex.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Nordinet Infantil *Nordin, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Nordiol *Wyeth, Arg.†; Wyeth, Austral.†; Wyeth, Chile; Wyeth, Gr.†; Wyeth, Mex.; Wyeth, NZ†; Wyeth, Philipp.; Akromed, S.Afr.; Wyeth, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; dysfunctional uterine bleeding; dysmenorrhoea; endometriosis; menstrual disorders.

Nordipine *Duopharma, Malaysia.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Norditropin *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Ferron, Indon.; Novo Nordisk, Indon.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, USA; Roemmers-Klinos, Venez.†.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Noonan syndrome; Prader-Willi syndrome; short children born small for gestational age; Turner's syndrome.

Norditropine *Novo Nordisk, Fr.; Novo Nordisk, Switz.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Nordolce *Vegetal, Ital.*
Acero canadese.
Nutritional supplement.

Nordonil *Medinfar, Port.†.*
Domperidone (p.1726·2).
Dyspepsia; nausea; vomiting.

Nordotol *Orion, Denm.†.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; benzodiazepine withdrawal syndrome; diabetes insipidus; epilepsy; neuralgias.

Nordox *Tecnofarma, Chile.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain and irritation.

Nordurine *Ferring, Austria; Ferring, Irl.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemorrhagic disorders; nocturia; nocturnal enuresis.

Nordyl *Rosemont, Thai.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Norebox *Pfizer, Spain.*
Reboxetine mesilate (p.420·3).
Depression.

Norecil *Maver, Mex.*
Metronidazole (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis.

No-Ref *Sanitas, Chile.*
Simeticone (p.1770·2); metoclopramide (p.1747·3); chlordiazepoxide (p.968·1).
Gastrointestinal disorders.

Noregyna *Cifarma, Braz.*
Norethisterone enantate (p.2120·1); estradiol valerate (p.2097·3).
Combined injectable contraceptive.

Norel LA *US Pharmaceutical, USA.*
Phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2).
Upper respiratory-tract disorders.

Norel DM *US Pharmaceutical, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Norel EX *US Pharmaceutical, USA.*
Phenylephrine (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Norel SD *US Pharmaceutical, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Formerly known as Norel DM.

Norelbin *Eurofarma, Braz.*
Vinorelbine tartrate (p.789·1).
Malignant neoplasms.

Norelut *Dexa, Indon.*
Norethisterone (p.2119·3).
Abnormal uterine bleeding; amenorrhoea; endometriosis.

Norephed *Haller, Braz.†.*
⊗ Noradrenaline acid tartrate (p.1360·1).

Norepine *Sterop, Belg.†.*
⊗ Noradrenaline (p.1360·1).

Noreskin *Genepharm, Gr.*
Azelaic acid (p.1589·3).
Acne.

Norestin *Biolab Sanus, Braz.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Norexan *Baxter, Indon.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Norf *Sigma, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfaben M *Pisa, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Norfacin *Shreya, Rus.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfan *Vocate, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Norfcin *SM, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfenazin *Nupel, Spain.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Norfenon *Abbott, Mex.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Norfisar *Typen, Arg.†.*
Chondroitin sulfate A (p.2280·3).

Norflam *Solas, Indon.*
Echinacea (p.2298·1); vitamin B substances (p.1922·1); javanese turmeric (p.2406·3); acacia (p.2140·2).
Inflammation.

Norflam T *3M, S.Afr.*
Ibuprofen (p.64·2).
Fever; pain.

Norflamin *Royton, Braz.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflex *3M, Austral.; 3M, Canad.; 3M, Denm.†; 3M, Fin.; 3M, Ger.; Cana, Gr.; 3M, Malaysia; 3M, Mex.; 3M, NZ; 3M, Port.†; 3M, S.Afr.; 3M, Swed.; 3M, Thai.; 3M, USA; Zuoz, Venez.*
Orphenadrine citrate (p.812·1).
Drug-induced extrapyramidal disorders; hiccups; musculoskeletal pain; parkinsonism; peri-articular and soft-tissue disorders; prolapsed intervertebral disc; skeletal muscle spasm; tension headache; torticollis.

Norflex Co *3M, S.Afr.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Pain; skeletal muscle spasm.

Norflex Plus *3M, Mex.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle spasm.

Norflo *Medifive, Thai.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflocin *Polipharm, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflocine *Mepha, Switz.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflohexal *Hexal, Austral.; Hexal, Ger.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflok *Inkeysa, Spain.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflol *Oriental, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflosal *TAD, Ger.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Norflosan *Gentek, Venez.†.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Norflostad *Stada, Austria.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Norfloval *Valmor, Venez.†.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Norflox
Prodotti, Braz.; 1A, Ger.; CT, Ger.; Sandoz, Ger.; Cipla, India.
Norfloxacin (p.309·2).
Bacterial infections.

Benedetti, Ital.
Norfloxacin pivoxil (p.309·3).
Urinary-tract infections.

Norflox TZ *Cipla, India.*
Norfloxacin (p.309·2); tinidazole (p.848·3).
Gastrointestinal infections.

Norfloxasan *Sanval, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflox-Azu *Azupharma, Ger.†.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Norfloxbeta *Betapharm, Ger.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfloxil *Greenpharma, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfloxin *Cipla, Malaysia; TO-Chemicals, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfloxinor *CCM, Malaysia†.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfloxmed *Cimed, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Norflox-Puren *Alpharma-Isis, Ger.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfloxyl *Bangkok Lab & Cosmetic, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norfluxx *Ruhrpharm, Ger.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Norforms
Note. This name is used for preparations of different composition.
Columbia, Mex.†.
Nonoxinol (p.1917·1); methylbenzethonium chloride (p.1653·1).
Contraceptive; gynaecological disorders.

Fleet, USA.
Pessaries: Vaginal deodorant.

Fleet, USA†.
Topical powder: Corn starch (p.1968·1); zinc oxide (p.1621·2).
Vaginal irritation.

Norgalax *Norgine, Belg.; Norgine, Fr.†; Norgine, Hong Kong†; Norgine, Irl.†; Norgine, Neth.; Angelini, Port.; Norgine, Singapore†; Norgine, Switz.; Norgine, UK.*
Docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Norgalax Miniklistier *Norgine, Ger.*
Docusate sodium (p.1725·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Norgeal *Wyeth, Arg.†.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Norgesic
Note. This name is used for preparations of different composition.
3M, Austral.; Sanova, Austria; 3M, Chile; 3M, Fin.; Cana, Gr.; 3M, Hong Kong; 3M, Irl.†; 3M, Israel; 3M, Malaysia; 3M, NZ; 3M, Philipp.; 3M, Port.†; 3M, Singapore; 3M, Swed.; 3M, Thai.; Zuoz, Venez.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Dysmenorrhoea; headache; musculoskeletal spasm with pain; musculoskeletal, peri-articular, and soft-tissue disorders; pain; prolapsed intervertebral disc; tension headache; torticollis.

3M, Canad.; 3M, USA.
Orphenadrine citrate (p.812·1); aspirin (p.20·3); caffeine (p.1116·3).
Musculoskeletal pain.

Norgesic N *3M, Ger.†.*
Orphenadrine citrate (p.812·1); propyphenazone (p.119·3).
Dysmenorrhoea; headache; musculoskeletal pain.

Norgeston *Schering, UK.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Norgestrel Continuo *Biotenk, Arg.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Norgestrel Max *Biotenk, Arg.*
Levonorgestrel (p.2121·2).
Progestogen-only post-coital oral contraceptive.

Norgestrel Minor *Biotenk, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Norgestrel Plus *Biotenk, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Norgic *Pond's, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle spasm.

Norglicem *Rottapharm, Spain.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Norhitis *Eurogenerics, Belg.*
Pholcodine (p.1570·2); pseudoephedrine (p.1571·2).
Coughs.

Norica
Note. This name is used for preparations of different composition.
Ottolenghi, Ital.†.
Solution: Benzalkonium chloride (p.1629·1).
Room disinfection and deodorization.

Polifarma, Ital.
Spray: Orthophenylphenol (p.1655·1); benzalkonium chloride (p.1629·1).
Surface disinfection.

Noricaven
Note. This name is used for preparations of different composition.
Bionorica, Ger.
Aesculus (p.2248·2).
Venous insufficiency.

Bionorica, Singapore†.
Asperula odorata; milk thistle (p.1452·1); crataegus (p.2289·1); rue (p.2382·2); echinacea (p.2298·1).
Haemorrhoids; venous insufficiency.

Noriday *Pfizer, Austral.; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pharmacia, UK.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Noriderm *EMS, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Norifortan *Hoechst Marion Roussel, S.Afr.†.*
Avapyrazone; dipyrone (p.49·2).
Painful smooth muscle spasm.

Norilet *Reddy, Rus.; Biofarma, Venez.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Noriline *Quatromed, S.Afr.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Norimin *Pfizer, Austral.; Pharmacia, Hong Kong†; Pfizer, NZ; Pharmacia, UK.*
21 Tablets, norethisterone (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Norimode *Aspen, S.Afr.; Tillomed, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Norincol *Volchem, Ital.*
Carbohydrate, lipid, amino-acid, and dietary fibre preparation (p.1922·1).
Nutritional supplement.

Norinyl *Pfizer, Mex.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menopausal disorders.

Norinyl-1 *Pfizer, Austral.; Pfizer, Hong Kong; Pfizer, NZ; Pharmacia, UK.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Norinyl-1/28 *Pharmacia, S.Afr.*
21 Tablets, norethisterone (p.2119·3); mestranol (p.2116·2); 7 tablets, inert.
Combined oral contraceptive.

Norinyl 1 + 35 *Searle, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).

28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Norinyl 1 + 50 *Searle, USA.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Noripam *Brainware, S.Afr.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety disorders.

Noriplex *EGIS, Hung.†.*
⊗ Indapamide (p.1314·1); perindopril erbumine (p.1368·3).
Hypertension.

Noripurum *Nycomed, Braz.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemias.

Noripurum Folico *Nycomed, Braz.*
Folic acid (p.1940·1); iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemias.

Noripurum Vitaminado *Nycomed, Braz.*
Iron polymaltose (p.1953·1); vitamins (p.1922·1).
Iron-deficiency anaemia.

Norisodrine with Calcium Iodide *Abbott, USA.*
⊗ Isoprenaline sulfate (p.1316·3); calcium iodide (p.1553·2).
Coughs.

Noristerat *Schering, Ger.; German Remedies, India; Bayer Schering, Malaysia; Schering, Mex.; Schering, Philipp.; Schering, Singapore†; Schering, Thai.†; Bayer, UK.*
Norethisterone enantate (p.2120·1).
Progestogen-only injectable contraceptive.

Norit *Norit, Austria; Wolfs, Belg.; Norit, Cz.; Farmasyn, Gr.; Norit, Israel; Norit, Neth.; Norit, Port.; Galpharm, UK.*
Activated charcoal (p.1435·2).
Diarrhoea; dyspepsia; flatulence; hypercholesterolaemia; poisoning; porphyria.

Noritate *Ingens, Arg.†; Dermik, Canad.; Finn Vita, Chile†; Dermik, Hong Kong; Pangeo, Israel; Aventis, UK; Dermik, USA.*
Metronidazole (p.837·1).
Acne; rosacea.

Norit-Carbomix *Norit, Austria; Wolfs, Belg.*
Activated charcoal (p.1435·2).
Diarrhoea; treatment of poisoning.

Noritet *Quatromed, S.Afr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Noritren *Lundbeck, Denm.; Lundbeck, Fin.; Lundbeck, Ital.; Lundbeck, Norw.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Norivite *Noristan, S.Afr.†.*
Vitamin B substances (p.1922·1).

Norivite-12 *Noristan, S.Afr.†.*
Cyanocobalamin (p.1980·2).
Anaemias; tonic.

Norizec *Therapharma, Philipp.*
Glimepiride (p.441·1).
Diabetes mellitus.

Norizine *Aspen, S.Afr.†.*
Cyclizine hydrochloride (p.574·2).
Nausea and vomiting; vestibular disorders.

Norkotral Tema *Desitin, Ger.*
Temazepam (p.1030·1).
Sleep disorders.

Norlamine *Biotech, Venez.*
Ofloxacin (p.310·2).
Bacterial infections.

Norlevo *Besins, Belg.; BPL-Meizler, Braz.†; HRA, Denm.; Leiras, Fin.; HRA, Fr.; Gerolymatos, Gr.; Win-Medicare, India; Ferring, Irl.; Angelini, Ital.; HRA, Neth.; HRA, Norw.; Fargin, Port.; Hexal, S.Afr.; Chiesi, Spain; Nycomed, Swed.; Ecosol, Switz.; Abdi, Turk.; Polinac, Venez.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Norlidine *Biotech, Venez.*
Povidone-iodine (p.1659·2).
Vaginal infections.

Norline *Pharmaland, Thai.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Norlip *Unipharm, Israel.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Norlopin *Saba, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Norlut *Cipla, India.*
Norethisterone acetate (p.2119·3).

Norlutate *Pfizer, Canad.†.*
Norethisterone acetate (p.2119·3).
Abnormal uterine bleeding; amenorrhoea; endometriosis.

Normabrain *UCB, Ger.*
Piracetam (p.368·2).
Alcohol withdrawal syndrome; mental function disorders.

Normacol
Note. This name is used for preparations of different composition.
Norgine, Belg.†; Rivex, Canad.; Norgine, Fr.; Norgine, Hong Kong; Norgine, Irl.; Norgine, Ital.; Norgine, Malaysia†; Norgine, NZ; Zuellig, NZ; Norgine, Neth.; Norgine, S.Afr.; Norgine, Singapore; Norgine, Switz.; Norgine, Thai.†; Norgine, UK.
Sterculia (p.1772·1).
Constipation; diverticular disease; ingestion of foreign bodies; ostomy management.

Schering, Mex.†.
Bassorin; frangula bark (p.1732·2).
Constipation.

Normacol a la Bourdaine *Norgine, Fr.†.*
Sterculia (p.1772·1); frangula bark (p.1732·2).
Constipation.

Normacol Antispasmodique *Norgine, Belg.†.*
Sterculia (p.1772·1); alverine citrate (p.1708·1).
Constipation.

Normacol avec bourdaine nouvelle formule *Norgine, Switz.†.*
Sterculia (p.1772·1); frangula (p.1732·2).
Constipation.

Normacol Forte *Norgine, Spain.*
Sterculia (p.1772·1); frangula bark (p.1732·2).
Constipation.

Normacol Lavement *Norgine, Fr.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Normacol Plus *Norgine, Austral.; Norgine, Belg.†; Norgine, Hong Kong; Norgine, Irl.; Norgine, NZ; Zuellig, NZ; Angelini, Port.; Norgine, S.Afr.; Norgine, Singapore; Norgine, UK.*
Sterculia (p.1772·1); frangula bark (p.1732·2).
Bowel evacuation; constipation; diverticular disease; ostomy management.

Normadil *GX, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's disease.

Normafenac *Norma (Νορμα), Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Normafibe *Norgine, Austral.*
Sterculia (p.1772·1).
Constipation; fibre supplement.

Normaflore *Sanofi-Aventis, Hung.*
Bacillus clausii.
Maintenance of gastrointestinal flora.

Normaflu *Wassermann, Ital.†.*
Paracetamol (p.108·1).
Cold and influenza symptoms; fever; pain.

Normagit *Sanofi Synthelabo, Port.†.*
Tiapride hydrochloride (p.1032·1).

Normakut *Gebro, Austria.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Normalac
Note. This name is used for preparations of different composition.
Gynopharm, Chile; Vivax Gynopharm, Venez.
Lynestrenol (p.2112·3).
Progestogen-only oral contraceptive.

Molteni, Pol.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Normalene *Montefarmaco, Ital.*
Bisacodyl (p.1710·1).
Constipation.

Normalin *Noristan, S.Afr.†.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

NormaLine
Note. A similar name is used for preparations of different composition (see below).
Antonetto, Ital.
Glucomannan (p.2312·3).
Dietary supplement in diabetes mellitus and hyperlipidaemias; obesity.

Normaline
Note. A similar name is used for preparations of different composition (see above).
Julphar, UAE; Apothecary, USA.
Sodium chloride (p.1686·1).
Nasal congestion; sodium depletion.

Normalip *Quesada, Arg.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Normalip pro *Abbott, Ger.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Normalite *Codifra, Fr.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Normaloe *Tillomed, UK.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Normalol *Dexxon, Israel.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; migraine; myocardial infarction.

Normamor *Uniao Quimica, Braz.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Normapril *Cazi, Braz.*
Captopril (p.1239·2).
Hypertension.

Normase *Molteni, Ital.; Molteni, Pol.; Molteni, Rus.*
Lactulose (p.1738·2).
Constipation; hepatic cirrhosis; hepatic encephalopathy; hyperammonaemia.

Normasol *Seton, Israel; Medlock Medical, UK.*
Sodium chloride (p.1686·1).
Irrigation solution.

Normastig *Uniao Quimica, Braz.*
Neostigmine metilsulfate (p.631·3).

Normastigmin *Sigmapharm, Austria.*
Neostigmine metilsulfate (p.631·3).
Gastrointestinal atony; myasthenia gravis; reversal of competitive neuromuscular blockade; urinary retention.

Normastigmin mit Pilocarpin *Sigmapharm, Austria.*
Neostigmine bromide (p.631·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma; pre- and post-operative lowering of intraocular pressure; reversal of mydriasis and cycloplegia.

Normastin
Note. This name is used for preparations of different composition.
Hexpharm, Indon.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Metro, Philipp.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Normaten
Note. This name is used for preparations of different composition.
Bago, Chile.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Normaten Plus *Bago, Chile.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Normatens
Note. This name is used for preparations of different composition.
Solvay, Neth.
Moxonidine (p.1345·1).
Hypertension.

ICN, Pol.
⊗ Clopamide (p.1250·1); dihydroergocristine (p.364·2); reserpine (p.1387·3).
Hypertension.

Normatensil *Phoenix, Arg.†.*
⊗ Methyldopa (p.1334·1); guanethidine sulfate (p.1300·2); hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Normatol *Pfizer, Chile.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Normavom *Cryopharma, Mex.*
Difenidol hydrochloride (p.1723·2).
Nausea and vomiting; vertigo.

Normax
Note. This name is used for preparations of different composition.
Ipca, India; Ipca, Rus.
Norfloxacin (p.309·2).
Bacterial infections.

koGen, UK.
Dantron (p.1722·2); docusate sodium (p.1725·1).
These ingredients can be described by the British Approved Name Co-danthrusate.
Constipation.

Normax TZ *Ipca, India.*
Norfloxacin (p.309·2); tinidazole (p.848·3).
Diarrhoea; dysentery.

Normaxin *Systopic, India.*
Clidinium bromide (p.1722·1); chlordiazepoxide (p.968·1); dicycloverine hydrochloride (p.1722·3).
Gastritis; irritable bowel syndrome; peptic ulcer.

Normell *Sanofi-Aventis, Gr.*
Glibenclamide (p.440·1); metformin (p.453·3).
Diabetes mellitus.

Normenta *Ipca, India.*
Piracetam (p.368·2).
Myoclonus.

Normex Plus *Quimica y Farmacia, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Normhydral *Gebro, Austria.*
Anhydrous glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Normicina *Tedec Meiji, Spain†.*
Midecamycin acetate (p.300·2).
Bacterial infections.

Normigel *Molnlycke, Canad.*
Sodium chloride hydrogel (p.1686·1).
Wounds.

Normil *Torrent, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Normison *Sigma, Austral.; Wyeth Lederle, Belg.†; Meda, Fin.; Genopharm, Fr.; Wyeth, Gr.; Wyeth, Irl.†; Wyeth Lederle, Ital.; Zuellig, NZ; EuroCept, Neth.; Teofarma, Port.; Akromed, S.Afr.; Valeant, Switz.*
Temazepam (p.1030·1).
Anxiety; insomnia; premedication.

Normital *Phoenix, Arg.*
⊗ Spironolactone (p.1400·1).
Cirrhosis; heart failure; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Normiten *Abic, Israel.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Normix *Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; Wassermann, Ital.*
Rifaximin (p.330·1).
Gastrointestinal bacterial infections; hepatic encephalopathy; hyperammonaemia; infection prophylaxis in colorectal surgery.

Normlgel *Molnlycke, Fr.*
Sodium chloride (p.1686·1).
Ulcers; wounds.

Normo Gastryl *Sabex, Canad.*
Sodium bicarbonate (p.1673·2); sodium sulfate (p.1771·3); sodium phosphate (p.1682·3).
Gastric hyperacidity.

Normo Nar *Zambon, Spain†.*
Muramidase hydrochloride (p.2348·1); thonzylamine hydrochloride (p.592·1); methylethylaminophenol hydriodide.
Nasal congestion; sinus congestion.

Normobren *Medosan, Ital.*
Acetylcarnitine hydrochloride (p.1932·2).
Cerebrovascular disorders.

Normobron *Chiesi, Gr.*
⊗ Salbutamol (p.1131·2).
Bronchodilator.

Normoc *Merckle, Ger.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Normocard *Polfa Warszawa, Pol.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Normocedon *Biospray, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Normocir *Inkeysa, Spain†.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders; vertigo.

Normodin *Genepharm, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Normodipine *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Polfa Grodzisk, Pol.; Gedeon Richter, Rus.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Normodyne *Schering, USA†.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Normoenzym Forte *Farmstandart, Rus.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Normofat *Soho, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Normofenicol *Normon, Spain†.*
Chloramphenicol sodium succinate (p.240·1).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Bacterial infections.

Normoflex *Degorts, Mex.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Normofundin *Braun, Fin.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normofundin G-5 *Braun, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normofundin OP *Braun, Ger.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Normofundina *Braun, Spain.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normofusin *Fresenius Kabi, Fin.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normogam *Q-Med, Ital.†.*
Gamolenic acid (p.2308·2).
Gamolenic acid deficiency; nutritional supplement.

Normogastryl *UPSA Conseil, Fr.†.*
Sodium bicarbonate (p.1673·2); anhydrous sodium sulfate (p.1771·3); dibasic sodium phosphate (p.1682·3).
Gastrointestinal disorders.

Normogin *Baldacci, Ital.*
Bacilli vaginalis culture.
Vaginal bacterial infections.

Normoglaucon *Tramedico, Belg.; Mann, Ger.; Mann, Malaysia†; Tramedico, Neth.; Mann, Pol.; Lepori, Port.; Mann, Singapore†; Bausch & Lomb, Thai.†; Mann, Thai.†.*
⊗ Metipranolol hydrochloride (p.1883·2); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Normoglucon *Rosch & Handel, Austria.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Normolaxil *Trenker, Belg.*
Lactitol (p.1738·2).
Constipation.

Normolip *Sun, India.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Normo-Loges *Loges, Ger.*
Homoeopathic preparation.

Normolose *Adelco, Gr.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Normolose-H *Adelco, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Normolyt *Gebro, Austria; Gebro, Cz.†; Gebro, Hung.*
Anhydrous glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Normolytoral *Gebro, Switz.*
Anhydrous glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Normomensil *Sedabel, Braz.†.*
Progesterone (p.2125·1); estradiol (p.2097·2).
Menopausal disorders; menstrual disorders.

Normonal *Eisai, Thai.*
⊗ Tripamide (p.1419·2).
Hypertension.

Normoparin *Caber, Ital.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Normopres
Note. This name is used for preparations of different composition.
Delta, Braz.
Nifedipine (p.1350·1).
Hypertension.

Ali, Turk.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Normopresan *Rafa, Israel.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Normopresil *Sanofi-Aventis, Spain.*
⊗ Chlortalidone (p.1243·3); atenolol (p.1217·3).
Hypertension.

Normopress
Note. This name is used for preparations of different composition.
Caber, Ital.
⊗ Atenolol (p.1217·3); indapamide (p.1314·1).
Hypertension.

Alliance, S.Afr.
Methyldopa (p.1334·1).
Hypertension.

Normopril *Otsira, India.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Normoprost *Silesia, Chile†.*
Mepartricin (p.541·1).
Benign prostatic hypertrophy.

Normoprost Compuesto *Temis, Arg.*
Pygeum africanum (p.2192·3); glutamic acid (p.1947·1); alanine (p.1928·1); glycine (p.1947·3).
Prostate disorders.

Normoprost Plus *Temis, Arg.*
Pygeum africanum (p.2192·3); saw palmetto (p.2192·3).
Prostate disorders.

Normorix *Nycomed, Norw.; Nycomed, Swed.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; liver cirrhosis with ascites; oedema.

Normorytmin *Abbott, Arg.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Normosang *Orphan Europe, Cz.; Orphan, Denm.; Orphan, Fin.; Orphan, Fr.; Orphan, Ger.; Orphan, Ital.; Orphan, Neth.; Orphan Europe, Port.; Orphan, Spain; Swedish Orphan, Swed.; Stauffacher, Switz.; Orphan, UK.*
Haem arginate (p.1448·2).
Porphyria.

Normosilen *Megat, Venez.†.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Normoskin *Hautel, Arg.†.*
Aluminium chlorohydrate (p.1588·3).

Normosol *Abbott, Hong Kong†; Hospira, Ital.; Hospira, USA.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normospor *Adcock Ingram, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal fungal infections.

Normosteril *Baxter, Fin.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Normoten *Torrent, Philipp.*
Losartan potassium (p.1326·1).
Hypertension.

Normotensor *Geyer, Braz.†.*
⊗ Furosemide (p.1292·1).

Normothen *Bioindustria, Ital.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Normotherin *Unipharma, Gr.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Normotil
Note. This name is used for preparations of different composition.
Novell, Indon.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

APS, Port.†.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Normotin-R *OTW, Ger.†.*
⊗ Etamivan (p.2156·1); norfenefrine hydrochloride (p.1361·1); heptaminol hydrochloride (p.2319·1).
Hypotension.

Normovite Antianemico *Normon, Spain.*
Folic acid (p.1940·1); ferrous gluceptate (p.1938·3).
Iron and folic acid deficiency.

Normoxidil *Medosan, Ital.†.*
Minoxidil (p.1342·1).
Alopecia.

Normoxin *Viatris, Austria.*
Moxonidine (p.1345·1).
Hypertension.

Normpress *Greater Pharma, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; hypertension; myocardial infarction.

Normudal *Combiphar, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Normulen *Euro Registratie, Neth.; Grunenthal, Spain.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Normurol *Curamed, Ger.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Norocin *Vianex (Βιανεξ), Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Norodol *Ali, Turk.*
Haloperidol (p.1000·2).
Agitation; anxiety; behaviour disorders; hiccups; nausea and vomiting; psychoses.

Norofren *Sanofi Synthelabo, Turk.*
Pimozide (p.1018·1).
Psychoses.

Norogil *Sanofi-Aventis, Braz.*
Dihydroergocristine mesilate (p.364·2); lomifylline (p.2334·3).
Impaired mental function; migraine and other vascular headaches; orthostatic hypotension; thrombosis prophylaxis.

Noronal *Ducto, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Noroseptan *Bros, Gr.*
Isotretinoin (p.1599·2).
Acne.

Norotrop *Ilsan, Turk.*
Piracetam (p.368·2).
Cortical myoclonus.

Noroxin *MSD, Arg.; MSD, Austral.; Merck Frosst, Canad.†; MSD, Chile†; MSD, Fin.†; MSD, Ital.; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Port.; MSD, S.Afr.; MSD, Spain; MSD, Switz.; MSD, Turk.; Merck, USA; Roberts, USA; MSD, Venez.*
Norfloxacin (p.309·2).
Bacterial infections.

Noroxine *MSD-Chibret, Fr.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract; gonococcal cervicitis; gonococcal urethritis.

Nor-Pa *Pliva, Ital.*
⊗ Atenolol (p.1217·3); indapamide (p.1314·1).
Hypertension.

Norpace *Heumann, Ger.†; RPG, India; Pharmacia, S.Afr.; Pfizer, Switz.†; Ali, Turk.; Searle, USA.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Norphen *Atlantic, Singapore; Atlantic, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Dysmenorrhoea; musculoskeletal pain; tension headache.

Norphin *Unichem, India.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Norpid *Greater Pharma, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Norpilen *Andromaco, Chile.*
Venlafaxine (p.430·1).
Depression.

Norplant *Wyeth-Ayerst, Canad.†; Leiras, Cz.†; Djaya Bima Agung, Indon.; Leiras, Indon.; Schering, Malaysia†; Schering, Singapore†; Schering, Swed.†; Schering, Thai.*
Levonorgestrel (p.2121·2).
Progestogen-releasing implantable contraceptive.

Norplus *Imperial, Philipp.*
⊗ Imidapril hydrochloride (p.1313·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Norpramin
Note. This name is used for preparations of different composition.
Aventis, Canad.; Aventis, Mex.†; Hoechst Marion Roussel, USA.
Desipramine hydrochloride (p.387·3).
Depression.

Labesfal, Port.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

CEPA, Spain.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Norpress *Pacific, NZ.*
Nortriptyline hydrochloride (p.413·2).
Aid to smoking withdrawal; depression.

Norpril *Ivax, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Norprolac *Ferring, Austria; Ferring, Canad.; Ferring, Cz.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Novartis, Hong Kong†; Novartis, Hung.; Novartis, Israel; Ferring, Mex.; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Novartis, Rus.; Novartis, S.Afr.; Ferring, Spain; Novartis, Swed.; Ferring, Switz.; Ferring, UK.*
Quinagolide hydrochloride (p.2377·1).
Acromegaly; hyperprolactinaemia; lactation inhibition.

Nor-QD *Watson, USA.*
Norethisterone (p.2119·3).
Progestogen-only oral contraceptive.

Norquinol *Euromex, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Norsa *Shiwa, Thai.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Norsec *Guardian, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Norsed *Sanofi-Aventis, Cz.; Sanofi-Aventis, Port.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Norserin *Norton, Pol.*
Mianserin hydrochloride (p.408·1).
Depression.

Norset *Organon, Fr.*
Mirtazapine (p.409·2).
Depression.

Norsic *Andromaco, Chile.*
Quetiapine (p.1023·2).
Schizophrenia.

Norsol
Note. This name is used for preparations of different composition.
Finadiet, Arg.; Ecosol, Switz.
Norfloxacin (p.309·2).
Bacterial infections.

Bilim, Turk.
⊗ Prednisolone sodium phosphate (p.1541·2).
Inflammatory eye disorders.

Norspan *Mundipharma, Austral.; Mundipharma, Cz.; Norpharma, Denm.; Mundipharma, Port.; Mundipharma, Swed.*
⊗ Buprenorphine (p.29·1).
Pain.

Norspor *Pond's, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Norstene *Rotexmedica, Philipp.; Atral, Port.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Norsulin *Polfa Pabianice, Pol.*
Gliclazide (p.440·3).
Diabetes mellitus.

Nortan *Sanofi Synthelabo, Turk.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Nortase *Asche, Cz.†; Repha, Ger.*
Rizolipase; amylase and protease from *Aspergillus oryzae*.
Pancreatic insufficiency.

Nortec *Ativus, Braz.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Nortelol *Atlantic, Hong Kong; Atlantic, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Nortem *Ivax, Irl.*
Temazepam (p.1030·1).
Insomnia.

Norten *Imperial, Philipp.*
Imidapril hydrochloride (p.1313·3).
Hypertension.

Nortensin *Abbott, Arg.†.*
Trandolapril (p.1416·2).
Hypertension; left-ventricular dysfunction following myocardial infarction.

Nor-Tenz *Grin, Mex.*
Brimonidine (p.1878·3).
Glaucoma.

Norterol *Tecnifar, Port.*
Nortriptyline hydrochloride (p.413·2).
Formerly known as Nortrix.
Anxiety; depression.

North Sea *Biofarma, Venez.†.*
Cod-liver oil (p.1935·2).
Dietary supplement.

Northicalm *Northia, Arg.*
Diphenhydramine (p.577·1); calamine (p.1591·2).

Northiron *Norma (Νορμα), Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Northyx *Centrix, USA.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Nortifen *Otto, Indon.*
Ketotifen fumarate (p.582·2).
Asthma.

Nortimil *Chiesi, Ital.*
Desipramine hydrochloride (p.387·3).
Depression; psychoses.

Nortol *Cafar, Venez.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Nortolan *Anfarm, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Norton *Farmasa, Braz.†.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Nortram *Shin Poong, Philipp.*
Norfloxacin (p.309·2).
Gonorrhoea; urinary-tract infections.

Nortrel *Wyeth, Braz.*
Levonorgestrel (p.2121·2).
Progestogen-only oral contraceptive.

Nortrilen *Lundbeck, Austria; Lundbeck, Belg.; Lundbeck, Cz.; Lundbeck, Ger.; Gerolimatos (Γερολυματος), Gr.; Lundbeck, Hong Kong; Lundbeck, Neth.; Lundbeck, Switz.; Lundbeck, Thai.*
Nortriptyline hydrochloride (p.413·2).
Depression; pain.

Nortrip *Teuto, Braz.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Nortuss *Rosemont, Thai.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Nortussine
Note. This name is used for preparations of different composition.
Norgine, Belg.
Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Norgine, Fr.
Paediatric syrup: Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2); guaifenesin (p.1561·3).
Coughs.

Norgine, Fr.
Syrup: Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2).
Coughs.

Nortussine Mono *Norgine, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Nortylin *Rekah, Israel.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Nortyline *Condrugs, Thai.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Norubin *Cadila, India.*
Daunorubicin (p.709·3).
Malignant neoplasms.

Norum *Chew, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Noruxol *Smith & Nephew, Ital.*
Collagenase (p.2286·2).
Necrotic wounds and ulcers.

Norvadin *Abdi, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Norvas *Pfizer, Mex.; Pfizer, Spain.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Norvasc *Pfizer, Austral.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, USA; Pfizer, Venez.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension; ischaemic heart disease.

Norvask *Pfizer, Indon.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Norvectan
Fardi, Port.
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Fardi, Spain.
Ibuprofen lysine (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Norvedan *Helsinn, Port.†.*
Fentiazac (p.60·1).
Fever; inflammation; pain.

Norventyl *ICN, Canad.†.*
Nortriptyline hydrochloride (p.413·2).
Depression.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Norvetal *Gynopharm, Chile.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Norviken *Vent-3, Arg.*
Diclofenac potassium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Norvir *Abbott, Austral.; Abbott, Belg.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Jpn; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.†; Abbott, S.Afr.; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Ritonavir (p.905·1).
HIV infection.

Norwich Extra Strength *Procter & Gamble, USA.*
Aspirin (p.20·3).
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Norwich Regular Strength *Lee, USA.*
Aspirin (p.20·3).
Fever; pain.

Norxacin *Globo, Braz.†; Siam Bheasach, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norxia *Asian Pharm, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Norxin *Cazi, Braz.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Norzac *Ivax, Irl.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression.

Norzetam *IPFI, Ital.†.*
Piracetam (p.368·2).
Mental function impairment.

Norzol *Rosemont, UK.*
Metronidazole benzoate (p.837·1).
Bacterial infections.

Norzyme *Nordmark, Singapore.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Nos *Dermofarm, Spain†.*
Famotidine (p.1730·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nosatel *Guidotti, Gr.*
Dexketoprofen trometamol (p.73·1).
Pain.

Nosbal *Merck, Mex.*
⊗ Atenolol (p.1217·3).
Hypertension.

Noscaflex
Note. This name is used for preparations of different composition.
Wolfs, Belg.†.
Paediatric syrup: Noscapine camsilate (p.1566·2).
Coughs.

Wolfs, Belg.
Syrup: Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3).
Coughs.

Wolfs, Belg.
Tablets: Noscapine (p.1566·2).
Coughs.

Nosca-Mereprine *Novum, Belg.*
Noscapine hydrochloride (p.1566·3).
Coughs.

Noscapax *Nicholas, Indon.*
⊗ Noscapine (p.1566·2); ephedrine hydrochloride (p.1558·2); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Cough.

Noscorex *Interdelta, Switz.*
Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3).
Coughs; upper respiratory-tract inflammation.

Nose Fresh *Rappai, Switz.†.*
Sea salt (p.1686·1).
Nasal dryness.

Nose Fresh au D-panthenol *Rappai, Switz.*
Sea salt (p.1686·1); dexpanthenol (p.2362·1).
Nasal dryness.

Nosedin *Combiphar, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Noseeze *Goldshield, UK.*
Sesame oil (p.2386·1).
Inflammation and dryness of the nasal mucosa.

Nosik-Lax *Omega, Belg.*
Bisacodyl (p.1710·1).
Constipation.

Nosipren *Collins, Mex.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Nositrol *Cryopharma, Mex.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Nosoap *Valeant, Arg.*
Soap substitute.

No-Sor Nose Balm *Pickles, UK.*
Dibrompropamidine isetionate (p.1642·1); wheat-germ oil (p.2415·1); menthol (p.2340·1); eucalyptus (p.2301·2).

No-Sor Vapour Rub *Pickles, UK.*
Camphor (p.2273·2); turpentine; menthol (p.2340·1); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar wood oil (p.2278·3); thymol (p.1664·3).
Upper respiratory-tract congestion.

Nosox *Hasco-Lek, Pol.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

No-Spa *Chinoin, Cz.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Philipp.; Chinoin, Pol.; Sanofi-Aventis, Pol.; Chinoin, Rus.; Sanofi Synthelabo, Thai.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

No-Spalgin *Sanofi-Aventis, Hung.; Chinoin, Rus.*
Codeine phosphate (p.37·2); drotaverine hydrochloride (p.2298·1); paracetamol (p.108·1).
Pain; tension headache.

Nospan *YSP, Malaysia; Yung Shin, Singapore.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Nospasmin *Sanitas, Chile.*
Pipethanate (p.1762·3).
Smooth muscle spasm.

Nospasmin Compuesto *Sanitas, Chile.*
Metamizole magnesium (p.49·3); pipethanate hydrochloride (p.1762·3).
Nausea and vomiting; smooth muscle spasm.

Nossacin *Benedetti, Ital.*
Cinoxacin (p.243·2).
Bacterial infections of the urinary tract.

Nostaden *Mintlab, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Nostel *Pyridam, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Nostero *Tolmann, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); brompheniramine maleate (p.569·2).
Nasal congestion.

Nosterol *Lamsa, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Nostidyn *Farmaceutica H, Mex.*
Norethisterone enantate (p.2120·1); estradiol valerate (p.2097·3).
Injectable contraceptive.

Nostil
Note. This name is used for preparations of different composition.
Latinofarma, Braz.
Ofloxacin (p.310·2).
Bacterial eye infections.

Deva, Turk.
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Nasal congestion.

Nostimex *Rafarm, Gr.†.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Nostress *Schwartz, Fr.*
Juglans regia; lupulus (p.2335·2); ginseng (p.2312·1).
Stress.

Nostril
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Fr.
Chlorhexidine gluconate (p.1635·3); cetrimonium bromide (p.1635·1).
Nose and throat infections.

Ciba, USA.
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Nostrilet *Osoth, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Nostrilla *Ciba Consumer, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nostroline *Co-Pharma, UK.*
Menthol (p.2340·1); cineole (p.2282·3); geranium oil (p.2311·1).
Nasal congestion.

Notabac *Schwartz, Fr.*
Glucose (p.1945·3); juglans regia; lupulus (p.2335·2); ginseng (p.2312·1).
Aid to smoking withdrawal.

Notacilin *Ortoquimica, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Notagol *Grunenthal, Chile†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Notakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Notem *Ivax, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Noten *Alphapharm, Austral.; Alphapharm, Malaysia; Alphapharm, Singapore.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Notensyl *CTI, Israel.*
Dicycloverine hydrochloride (p.1722·3).
Irritable bowel syndrome; neurogenic intestinal disorders.

Notezine *Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.*
Diethylcarbamazine citrate (p.143·1).
Filariasis.

Notgaz *Automedic, Fr.*
Activated charcoal (p.1435·2); simeticone (p.1770·2).
Dyspepsia; meteorism.

Nothav *Chiron Vaccines, Ital.†.*
A hepatitis A vaccine (p.2214·2).
Active immunisation.

Notidin *Nobel, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Notis *Schwarz, Pol.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Notolac *Farma, Venez.*
Ketorolac trometamol (p.74·2).
Pain.

No-Ton *Standard Chem & Pharm, Thai.†.*
Nabumetone (p.91·2).
Musculoskeletal and joint disorders.

Notorium *Adelco, Gr.*
Bromazepam (p.964·3).
Anxiety disorders.

No-Tos Adultos
Note. This name is used for preparations of different composition.
Medical, Arg.
Lozenges: Hexylresorcinol (p.1647·1); senega (p.1572·3); liquorice (p.1740·3); tolu balsam (p.1574·2); cineole (p.2282·3).
Coughs.

Medical, Arg.
Syrup: ⊗ Sodium benzoate (p.1630·2); ammonium chloride (p.1551·3); ephedrine hydrochloride (p.1558·2); senega (p.1572·3); aconite (p.2246·1); niaouli oil (p.2351·3); tolu (p.1574·2); liquorice (p.1740·3).
Coughs.

No-Tos Biotic *Medical, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

No-Tos Infantil
Note. This name is used for preparations of different composition.
Medical, Arg.
Lozenges: Sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); senega (p.1572·3); liquorice (p.1740·3); ipecacuanha (p.1562·3); tolu balsam (p.1574·2).
Coughs.

Medical, Arg.
Syrup: Sodium benzoate (p.1630·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); liquorice (p.1740·3); tolu balsam (p.1574·2); Desessartz syrup.
Coughs.

No-Tos Mucolitico *Medical, Arg.*
Bromhexine hydrochloride (p.1552·2).
Coughs.

No-Tos Pocket *Medical, Arg.*
Noscapine (p.1566·2); guaifenesin (p.1561·3); benzocaine (p.1854·1); hexylresorcinol (p.1647·1).
Cough.

Notosil *Grunenthal, Chile†.*
Drosera (p.2297·3); quillaia (p.1920·1); pectoral; tolu balsam (p.1574·2).
Coughs.

Notoxin *Szama, Arg.*
Cholesterol; chlorophyll (p.1471·1); turpentine oil (p.2406·3); zinc oxide (p.1621·2).
Burns; skin cleansing; skin infections; ulcers; wounds.

Notozen *Bouzen, Arg.*
Bromhexine (p.1552·2); clofedanol (p.1554·2).
Coughs.

Notpel *Leovan, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Notrab *Microsules, Arg.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Notras *Liba, Turk.*
Aspirin (p.20·3).
Fever; pain.

Notritis *Sanbe, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Notrixum *Novell, Indon.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Notta *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Nottem *Angelini, Ital.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Notul *Mendelejeff, Ital.†.*
Cimetidine hydrochloride (p.1716·3).
Gastritis; gastroduodenitis; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Notusin *Medea, Spain.*
Codeine phosphate (p.37·2).
Coughs.

Notuss *Ache, Braz.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2); dropropizine (p.1557·3).
Cough.

Notuss PD *Stewart Jackson, USA.*
Hydrocodone tartrate (p.63·1); dexchlorpheniramine maleate (p.572·1); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Notuss-Forte *SJ Pharm, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Notuxal *Eurogenerics, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Nourilax *Chefaro, Neth.*
Bisacodyl (p.1710·1).
Constipation.

Nourishake *GNLD, Austral.*
Nutritional supplement (p.1922·1).

Nouriva Repair *Ferndale, USA.*
Emollient.

Noury Hoofdlotion *Alfaco, Neth.*
Malathion (p.2046·1).
Pediculosis.

Nourymag *Nourypharma, Ger.†.*
Magnesium aspartate (p.1679·1).
Magnesium deficiency.

Nourytam *Organon, Ger.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Nova Derm
Note. This name is used for preparations of different composition.
Darier, Mex.
Cream; lotion: Glycolic acid (p.1598·1).
Acne; dry skin disorders.

Darier, Mex.
Topical gel: Glycolic acid (p.1598·1); hydroquinone (p.1598·2); kojic acid (p.1603·3).
Hyperpigmentation disorders.

Nova Paratopina *Lazar, Arg.*
Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Nova Paratropina Compositum *Lazar, Arg.*
Pargeverine hydrochloride (p.1761·1); clonixin lysine (p.37·1).
Colic; dyskinesia; menstrual disorders.

Nova Vizol *Bell, India.*
Hypromellose (p.2144·2).
Dry eyes.

Novaban *Novartis, Belg.; Novartis, Neth.*
Tropisetron hydrochloride (p.1777·2).
Nausea and vomiting induced by cytotoxic therapy; postoperative nausea and vomiting.

Novabritine *GSK, Belg.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Novabupi *Cristalia, Braz.*
⊗ Levobupivacaine hydrochloride (p.1862·1).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

NovaCare *Fielding, USA.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).

Novacef
Note. This name is used for preparations of different composition.
Gador, Arg.; Promeco, Mex.†.
Cefixime (p.224·3).
Bacterial infections.

IFI, Ital.†.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Novacefrex *Sanofi Synthelabo, Port.†.*
Cefradine (p.233·1).
Bacterial infections.

Novacet *Medicis, USA.*
Sulfacetamide sodium (p.335·3); sulfur (p.1614·1).
Acne; seborrhoeic dermatitis.

Novacetol
Note. This name is used for preparations of different composition.
Prater, Chile.
Clotrimazole (p.530·1).
Fungal skin infections; trichomoniasis.

Pharmastra, Fr.
Aspirin (p.20·3); paracetamol (p.108·1); codeine hydrochloride (p.37·2).
Fever; pain.

Novacil *Dovalle, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Novacilina *Tecnofarma, Chile.*
Levofloxacin (p.292·2).
Bacterial infections.

Novacimet *Globo, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Novaclav *Cipla, India.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Novacler *Monserrat, Arg.*
Dipyrone (p.49·2).
Colic; fever; pain.

Novaclox *Cipla, India.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Novaclox LB *Cipla, India.*
Amoxicillin (p.202·2); cloxacillin (p.256·1); lactobacillus (p.2372·3).
Bacterial infections.

Novacloxab *Relyo, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Novacne *Novofarm (Νοβοφαρμ), Gr.*
Isotretinoin (p.1599·2).
Acne.

Novacodin *Vargas, Venez.*
⊗ Ethylmorphine (p.52·2); lobelia (p.2157·2); grindelia (p.2317·2); althaea (p.2253·3); Desessartz; senega (p.1572·3); ammonium acetate (p.1551·2).
Cough.

Novacor *Novatec, Thai.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Novacort
Note. This name is used for preparations of different composition.
Ache, Braz.
⊗ Ketoconazole (p.539·1); neomycin sulfate (p.305·1); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Primus, USA.
⊗ Hydrocortisone acetate (p.1535·2); pramocaine (p.1868·2).
Skin disorders.

Novacrium *Allen, Austria.*
Mivacurium chloride (p.1906·3).
Competitive neuromuscular blocker.

Nova-Dec *Rugby, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Novaderm *Zambon, Braz.*
⊗ Clostebol acetate (p.2087·1); neomycin sulfate (p.305·1).
Infected wounds.

Novador *Novartis, Mex.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Novadral *Pfizer, Austria; Godecke, Ger.†; Pfizer, Switz.; Eczacibasi, Turk.*
⊗ Norfenefrine hydrochloride (p.1361·1).
Hypotension; shock.

Novadrel *Prater, Chile.*
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1).
Fungal skin infections with inflammation.

Novafac *Silesia, Chile.*
10 Tablets, conjugated oestrogens (p.2087·2); 11 tablets conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Novafac 30 *Silesia, Chile.*
17 Tablets, conjugated oestrogens (p.2087·2); 13 tablets conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Novafac CC *Silesia, Chile.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Novafed A *Hoechst Marion Roussel, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Novafem *Silesia, Chile.*
Medroxyprogesterone acetate (p.2113·1); estradiol cipionate (p.2097·2).
Combined injectable contraceptive.

Novafibra *Novartis Consumer, Ital.*
Guar gum (p.442·3).
Gastrointestinal disorders.

Novafix
Note. This name is used for preparations of different composition.
EciFarma, Chile†.
Cleanser for removable dental appliances.

Mucos, Venez.
Dental adhesive: Carmellose (p.2142·1); vinyl copolymer.
Denture fixative.

Mucos, Venez.
Effervescent tablets: Sodium bicarbonate (p.1673·2); potassium peroxomonosulfate; sodium perborate (p.1662·1); sodium lauril ether sulfate (p.2138·3).
Denture cleanser.

Novafix Extra Fuerte *Biotoscana, Chile.*
Vinyl copolymer; carmellose (p.2142·1).
Dental fixative.

Novafix Ultra Fuerte *Romsa, Mex.*
Carmellose sodium (p.2142·1).
Dental fixative.

Novag Grip *Novag, Spain.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly contained chlorphenamine maleate, phenylpropanolamine hydrochloride, and paracetamol.
Cold and influenza symptoms; fever; pain.

Novag Grip Fenilefrina *Novag, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

Novageon *Liferpal, Mex.*
Benzalkonium chloride (p.1629·1); nystatin (p.543·2); diiodohydroxyquinoline (p.832·1).
Vaginal infections.

Novagest Expectorant with Codeine *Major, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Novagon *Novag, Mex.*
Ispaghula (p.1737·1).
Constipation.

Novagreen *Greenpharma, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Novahistex DH *Aventis, Canad.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).
Coughs.

Novahistine DH
Note. This name is used for preparations of different composition.
Aventis, Canad.
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).
Coughs.

Deston, USA.
Dihydrocodeine tartrate (p.48·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms; respiratory allergies.

Novahistine DMX *SmithKline Beecham Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Novain *Agepha, Austria.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Novakom-S *Nobel, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Noval
Note. This name is used for preparations of different composition.
Demo, Gr.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Corsalud, Venez.†.
Dipyrone (p.49·2).
Fever; pain.

Novalac AC *Bayer, Austral.; Menarini, Fr.; Novalac, Malaysia; Neo-Farmaceutica, Port.†; Novalac, Singapore.*
Infant feed (p.1922·1).
Colic; digestive disorders; infant colic.

Novalac AD *Bayer, Austral.; Novalac, Malaysia; Neo-Farmaceutica, Port.†; Novalac, Singapore.*
Infant feed (p.1922·1).
Diarrhoea.

Novalac AO *Neo-Farmaceutica, Port.†.*
Infant feed (p.1922·1).
Constipation.

Novalac AR *Bayer, Austral.; Menarini, Fr.; Novalac, Malaysia; Neo-Farmaceutica, Port.†; Novalac, Singapore.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux in infants; regurgitation.

Novalac Diarinova *Menarini, Fr.*
Infant feed (p.1922·1).
Diarrhoea.

Novalac HA *Bayer, Austral.; Menarini, Fr.; Neo-Farmaceutica, Port.†.*
Infant feed (p.1922·1).
Hypoallergenic feed; infants with a family history of allergy; milk intolerance.

Novalac IT *Bayer, Austral.; Novalac, Malaysia; Novalac, Singapore.*
Infant feed (p.1922·1).
Constipation.

Novalan *Orion, Fin.*
Emollient.
Skin disorders; vehicle for topical drugs.

Novalcina *Sanofi-Aventis, Venez.*
Dipyrone (p.49·2).
Fever; pain.

Novales *Novell, Indon.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Novalexin *Hexa, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Novalgex *Hertz, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Novalgin *Aventis, Austria; Sanofi-Aventis, Cz.; Aventis, Ger.; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Aventis, Israel; Aventis, Neth.; Aventis, Thai.; Aventis, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Novalgina *Aventis, Arg.; Sanofi-Aventis, Braz.; Aventis, Chile†; Sanofi-Aventis, Ital.; Hoeport, Port.†.*
Dipyrone (p.49·2).
Colic; fever; pain.

Novalgine *Sanofi-Aventis, Belg.; Aventis, Fr.†; Aventis, Switz.*
Dipyrone (p.49·2).
Fever; pain.

Novalif *Pharmavita, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Novalona *Andromaco, Chile.*
Hyoscine (p.1733·3); oxazepam (p.1014·2).
Smooth muscle spasm.

Novalox *Santa, Gr.*
Aluminium glycinate (p.1706·2); magnesium oxide (p.1744·1).
Antacid.

Novalucol *AstraZeneca, Swed.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Heartburn.

Novaluzid *AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Malaysia†; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Swed.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium carbonate (p.1743·1).
Dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Novamet *GSK, Denm.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Novamil AR *Bayer, Mex.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Novamilor *Novopharm, Canad.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Novamin *BMS, Braz.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Novamine *Clintec, USA.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Novaminsulfon *Ratiopharm, Ger.; Winthrop, Ger.*
Dipyrone (p.49·2).
Fever; pain.

Novamir *Aledicine, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Novamox
Note. This name is used for preparations of different composition.
Ache, Braz.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Cipla, India.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Multicare, Philipp.
Amoxicillin (p.202·2).
Bacterial infections.

Hexal, Pol.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Novamox AX *Cipla, India.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Novamox LB *Cipla, India.*
Amoxicillin (p.202·2); lactobacillus (p.2372·3).
Bacterial infections.

Novamoxin *Novopharm, Canad.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Novanaest *Gebro, Austria.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Novanox *Pfleger, Ger.*
Nitrazepam (p.1011·2).
Sleep disorders.

Novantron *Wyeth Lederle, Austria; Wyeth, Ger.; Wyeth, Switz.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Novantrone *Sigma, Austral.; Wyeth, Belg.; Wyeth-Ayerst, Canad.†; Wyeth, Cz.†; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Hung.; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia†; Zuellig, NZ; Wyeth, Neth.†; Wyeth, Norw.; Meda, Port.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain; Wyeth, Swed.; Wyeth-Ayerst, Thai.†; Er-Kim, Turk.; Wyeth, UK†; Serono, USA.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms; multiple sclerosis.

Novapam
Note. This name is used for preparations of different composition.
Douglas, NZ.
Chlordiazepoxide hydrochloride (p.968·2).
Anxiety; premedication; skeletal muscle spasm.

Asian Pharm, Thai.
Dipyrone (p.49·2); paracetamol (p.108·1).
Fever; pain.

Novapen *Pinewood, Irl.*
Ampicillin (p.204·1).
Bacterial infections.

Novaphylline *Cooper (Κοπερ), Gr.†.*
Theophylline (p.1140·1).
Asthma; chronic obstructive pulmonary disease; neonatal apnoea and bradycardia.

Novapirina *Novartis Consumer, Ital.*
Diclofenac sodium (p.44·3).
Fever; pain.

Novapres *Novag, Mex.*
Captopril (p.1239·2).
Hypertension.

Novaprin
Note. This name is used for preparations of different composition.
Novag, Mex.
⊗ Danazol (p.2090·2).
Breast cancer; endometriosis; gynaecomastia; hereditary angioedema; mastalgia; menorrhagia; precocious puberty.

Pharmexco, UK.
Ibuprofen (p.64·2).

Novapsyl *Novag, Mex.*
Benzonatate (p.1552·1).
Coughs.

Novaquasol-A *Minerva (Μινερβα), Gr.*
Vitamin A (p.1971·2); panthenol (p.2362·1).

Novarel *Ferring, USA.*
⊗ Chorionic gonadotrophin (p.2085·1).
Male and female infertility.

Novarnela *Andromaco, Chile.*
⊗ Clotrimazole (p.530·1); betamethasone (p.1518·2).
Fungal skin infections with inflammation.

Novarok *Schering, Jpn†.*
Imidapril hydrochloride (p.1313·3).
Hypertension.

Novarona *Dollder, Venez.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Novarrutina *Zurita, Braz.*
Rutoside (p.2305·1); aesculus (p.2248·2); polygonum punctatum; smilax japicanga.
Venous insufficiency.

Novartril *Andromaco, Mex.†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Novas *Innoderm, Philipp.*
Glycerol (p.2314·2).
Skin cleansing; soap substitute.

Novasal *US Pharmaceutical, USA.*
Magnesium salicylate (p.79·2).
Formerly contained magnesium salicylate and phenyltoloxamine citrate.
Inflammation; pain.

Novascabin *PannonPharma, Hung.*
Benzyl benzoate (p.2036·1); dimethyl phthalate (p.2041·3).
Scabies.

Novasen *Novopharm, Canad.*
Aspirin (p.20·3).
Inflammation; pain.

Novasone *Schering-Plough, Arg.; Schering-Plough, Austral.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Novasorin *Vendiz, Philipp.*
Gramicidin (p.286·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye infections.

Novasource *Novartis Consumer, Austral.†; Novartis, Braz.; Novartis Nutrition, Fr.; Novartis Consumer, Ital.; Novartis Consumer, Port.†; Novartis Nutrition, Singapore; Novartis, Turk.*
A range of preparations for enteral nutrition (p.1922·1).

Novasource GI Control *Novartis, Fin.*
Preparation for enteral nutrition (p.1922·1).

Novasource Renal *Novartis, Arg.†; Novartis Nutrition, Hong Kong; Novartis Nutrition, Singapore; Novartis Nutrition, USA.*
Preparation for enteral nutrition in renal failure (p.1922·1).
Renal failure.

Novastan *Mitsubishi, Jpn; Biovitrum, Swed.*
Argatroban (p.1217·1).
Heparin-induced thrombocytopenia; thromboembolic disorders.

Novasten *Novag, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

NovaStep *Schering, Ger.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Novasulfon *Columbia, Mex.†.*
Dapsone (p.261·2).
Kaposi's sarcoma; leprosy; pneumocystis pneumonia; rheumatoid arthritis; skin disorders.

Novasutin *Blausiegel, Braz.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).
Vaginal infections.

Nova-T *Schering, Arg.; Berlex, Canad.; Schering, Chile†; Schering, Fr.; Schering, Ger.; Schering, Hong Kong; Schering, Indon.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Schering, NZ; Schering, Neth.†; Schering, S.Afr.; Schering, Singapore; Schering, Switz.; Schering, Thai.†; Schering, Turk.; Schering, UK; Schering, Venez.*
Copper-wound plastic (p.1935·2) with a silver core (p.2387·1).
Intra-uterine contraceptive device.

Novatax *Cipla, India; Cipla, Venez.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Novate *Blau, Pol.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Novatec *MSD, Belg.; MSD, Neth.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Novativ *Ativus, Braz.*
Sertraline hydrochloride (p.421·3).
Depression.

Novatrex
Note. This name is used for preparations of different composition.
Ache, Braz.
Azithromycin (p.207·1).
Bacterial infections.

Wyeth, Fr.
Methotrexate (p.745·2).
Psoriasis; rheumatoid arthritis.

Novatrim *Promeco, Mex.†.*
Brodimoprim (p.215·3).
Bacterial infections.

Novatropina *Uniao Quimica, Braz.*
Homatropine methylbromide (p.1881·3).
Smooth muscle spasm.

Novavir *Novag, Mex.*
Zidovudine (p.913·3).
HIV infection.

Novaxen *Novag, Mex.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Novazam *Pharmy, Fr.†.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety.

Novazepam *Sigma, Braz.†.*
Bromazepam (p.964·3).
Anxiety.

Novazidine *Medicus, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Novazyd *MSD, Belg.†; MSD, Neth.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Novegam *Chinoin, Mex.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Novek *Santa, Gr.; Ethypharm, Port.; Spyfarma, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Novel *Maver, Chile†.*
Melatonin (p.2338·3).
Sleep disorders.

Novel Ginkgo *Skills, Ital.†.*
Ginkgo biloba (p.2311·1).

Novel Jelly *Novel, Ital.†.*
Royal jelly (p.2382·1).
Nutritional supplement.

Novelas *Solas, Indon.*
Moisturiser.

Noveldexis *Pisa, Mex.*
Cisplatin (p.698·2).
Bladder cancer; ovarian cancer; testicular cancer.

Novelmin *Bunker, Braz.*
Mebendazole (p.148·3).
Worm infections.

Novelon *Organon, India.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Novemina *Lazar, Arg.*
Dipyrone (p.49·2).
Fever; pain.

Noverban *Prolab, Pol.*
Verbascum (p.2413·3).
Upper respiratory-tract disorders.

Noveril *Novartis, Austria; Novartis, Cz.; Novartis, Ger.†; Novartis, Hung.; Novartis, Israel; Novartis, Pol.; Novartis, Switz.*
Dibenzepin hydrochloride (p.388·2).
Depression; nocturnal enuresis.

Noverty *Novell, Indon.*
Betahistine mesilate (p.2265·1).
Ménière's disease.

Novesin *Novartis Ophthalmics, Cz.; Novartis Ophthalmics, Hong Kong†; Novartis Ophthalmics, Malaysia†; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore†; OmniVision, Switz.; Novartis, Thai.; Novartis, Turk.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Novesina *Novartis, Ital.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Novesine *MSD-Chibret, Fr.†; OmniVision, Ger.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Novetron *Noventis, Cz.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Novhepar *Coup, Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Nov'Hepar B-12 *Vincenti, Venez.*
Vitamin B substances; gentian; CNA syrup (p.1922·1).

Novial *Sigma, Braz.; Organon, Ger.; Organon, Mex.; Organon, Venez.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Acne; triphasic oral contraceptive.

Novicarbon *CTI, Israel.*
Activated charcoal (p.1435·2); senna (p.1769·2); rhubarb (p.1768·3); fennel oil (p.2303·1).
Constipation; dyspepsia; flatulence.

Novidat *Temis, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Novidin *Gebro, Austria.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturia; nocturnal enuresis.

Novidrine *Northia, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Novidroxin *Fatol, Ger.†.*
Hydroxocobalamin acetate (p.1980·3).
Arteritis; arthritic and rheumatic pain; neuralgia; neuritis.

Noviform
Note. This name is used for preparations of different composition.
Novartis, Ger.; Meda, Swed.; Novartis, Switz.†.
Bibrocathol (p.2266·1).
Eye disorders.

Teva, Hung.
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Novifort *Novartis Ophthalmics, Ger.†.*
⊗ Bibrocathol (p.2266·1); hydrocortisone acetate (p.1535·2).
Allergic and inflammatory disorders of the eye.

Novigan *Reddy, Rus.*
Ibuprofen (p.64·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).

Noviken *Kendrick, Mex.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Novilax *Eurospital, Ital.*
Sodium lauril sulfoacetate (p.2138·3); sodium citrate (p.1673·3); glycerol (p.2314·2); sorbitol (p.1965·1).
Constipation.

Novimax *Anfarm, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Novina *Novag, Mex.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Novipec *Montavit, Austria.*
⊗ Salverine (p.2383·1); ephedrine (p.1558·1); spike lavender oil (p.2392·1).
Respiratory-tract disorders.

Novirell B Duo *Sanorell, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Dermatoses; neuralgia; neuritis; rheumatic disorders; spinal disorders.

Novirell B Mono *Sanorell, Ger.*
Cyanocobalamin (p.1980·2).
Megaloblastic anaemia; vitamin B deficiency.

Novital *Zambon, Switz.*
Eucalyptus oil (p.2301·2); japanese mint oil (p.2345·2); pine cone oil; citronella oil (p.2284·2); rosemary oil (p.2381·3); cajuput oil (p.2271·2); pine oil (p.2368·2); cypress oil (p.2291·2).
Coughs and colds.

Novitropan *CTI, Israel; CTS, Rus.†.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; nocturnal enuresis.

Novizet *Microsules, Arg.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Novo AC and C *Novopharm, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Novo Aerofil Sedante *Reig Jofre, Spain†.*
Dimeticone (p.1770·2); metoclopramide hydrochloride (p.1747·3); oxazepam (p.1014·2).
Aerophagia; gastrointestinal dystonias; meteorism.

Novo Alerpriv *Montpellier, Arg.*
Desloratadine (p.576·1).
Allergic rhinitis; pruritus; urticaria.

Novo Asat *Gezzi, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Novo B *Novopharm, Canad.*
Vitamin B substances and vitamin C (p.1922·1).

Novo Bacticort *Montpellier, Arg.†.*
⊗ Diflorasone diacetate (p.1529·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Novo Bacticort Complex *Montpellier, Arg.†.*
⊗ Diflorasone diacetate (p.1529·1); gentamicin sulfate (p.282·1); econazole nitrate (p.531·1).
Infected skin disorders.

Novo Benitol *Benitol, Arg.*
Calcium carbonate (p.1714·1); glycocola.
Antacid.

Novo Dermoquinona *Juventus, Spain.*
Mequinol (p.1604·2).
Hyperpigmentation.

Novo E *Novopharm, Canad.*
d-Alpha tocoferil acetate (p.1992·3) or *dl*-alpha tocoferil acetate (p.1992·3).

Novo Fosfostilben *Sandoz, Arg.*
Diethylstilbestrol (p.2094·1).

Novo Geniol *GSK, Arg.*
Ibuprofen (p.64·2).
Fever; pain.

Novo V-K *Novo Nordisk, S.Afr.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Novo Miconol *Fabra, Arg.*
Zinc undecenoate (p.549·3); zinc oxide (p.1621·2); sodium propionate (p.545·3); salicylic acid (p.1612·2).
Skin disorders.

Novo Paramicon *Northia, Arg.*
Econazole (p.531·1).
Fungal infections.

Novo Petrin Novum *OTW, Ger.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Novo Petrin formerly contained paracetamol, propyphenazone, and caffeine.
Fever; pain.

Novo Rino *Bunker, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); sodium chloride (p.1686·1).
Nasal congestion.

Novo Rino-S *Bunker, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Novo Vagran *Finadiet, Arg.†.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Novo Vagran D *Finadiet, Arg.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).

Novo Vegestabil *Labinca, Arg.†.*
Alprazolam (p.960·1); sulpiride (p.1028·3).
Anxiety; depression.

Novo Wilpan *Microsules Bernabo, Arg.†.*
Ibuprofen (p.64·2); phenylephrine (p.1568·1).
Cold symptoms; sinusitis.

Novo-Alprazol *Novopharm, Canad.*
Alprazolam (p.960·1).
Anxiety; sedative.

Novo-Atenol *Novopharm, Canad.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Novo-AZT *Novopharm, Canad.†.*
Zidovudine (p.913·3).
HIV infection.

Novobiocyl *Francia, Ital.†.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Novobroncol *Lafage, Arg.†.*
Camphor (p.2273·2); menthol (p.2340·1); pine oil (p.2368·2); thymol (p.1664·3).
Respiratory-tract disorders.

Novocain *Abbott, Canad.†; Aventis, Ger.†; Hospira, USA.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Novo-Captoril *Novopharm, Canad.; Novopharm, Hong Kong.*
Captopril (p.1239·2).
Heart failure; hypertension.

Novocar *Andromaco, Chile†.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Novo-Carbamaz *Novopharm, Canad.*
Carbamazepine (p.471·3).
Epilepsy.

Novocebrin *Meda, Port.*
Flupirtine maleate (p.61·1).
Fever; pain.

Novocef *Pliva Krakow, Pol.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Novocephal *Fresenius Kabi, Austria.*
Piracetam (p.368·2).
Alcohol or opioid withdrawal syndrome; mental function disorders.

Novo-Cerusol *Bausch & Lomb, Switz.*
Xylene (p.2027·3).
Ear wax removal.

Novo-Cholamine *Novopharm, Canad.*
Colestyramine (p.1252·3).
Bile-acid induced diarrhoea; hypercholesterolaemia; pruritus associated with partial biliary obstruction.

Novocholin *Adler, Austria.*
Herba teucrii; agrimony herb (p.2249·2); rhubarb (p.1768·3); peppermint oil (p.1761·2).
Biliary disorders.

Novocilin
Note. A similar name is used for preparations of different composition (see below).
Ache, Braz.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Novocillin
Note. A similar name is used for preparations of different composition (see above).
Novo Nordisk, S.Afr.†.
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Novo-Cimetine *Novopharm, Canad.*
Cimetidine (p.1716·2).
Histamine H receptor antagonist.

Novo-Clavamoxin *Novopharm, Canad.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Novo-Clopamine *Novopharm, Canad.†.*
Clomipramine hydrochloride (p.386·3).
Depression; obsessive-compulsive disorder.

Novo-Clopate *Novopharm, Canad.*
Dipotassium clorazepate (p.980·1).
Anxiety; sedative.

Novo-Cloxin *Novopharm, Canad.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Novocral *Help, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Novo-Cycloprine *Novopharm, Canad.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Novo-Difenac
Novopharm, Canad.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; osteoarthritis; pain; rheumatoid arthritis.

Novopharm, Hong Kong†.
Diclofenac sodium (p.44·3).
Osteoarthritis; rheumatoid arthritis.

Novodig *Casasco, Arg.†.*
Pancreatin (p.2360·1); dehydrocholic acid (p.2292·2); simeticone (p.1770·2).

Novodigal *Viatris, Austria; Mibe, Ger.*
Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Novodil *OFF, Ital.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Novo-Diltazem *Novopharm, Canad.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Novo-Dimenate *Novopharm, Canad.*
Dimenhydrinate (p.576·2).
Nausea and vomiting; vertigo.

Novo-Dipam *Novopharm, Canad.*
Diazepam (p.986·3).

Novo-Dipiradol *Novopharm, Canad.†.*
Dipyridamole (p.1268·1).
Cardiac disorders.

Novo-Doxylin *Novopharm, Canad.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Novofarma Champu *Novofarma, Arg.*
Undecenoic acid (p.549·2); menthol (p.2340·1).
Dandruff; seborrhoea.

Novofem *Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Hong Kong; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, UK.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Novofemme *Novo Nordisk, Fr.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Novofen *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Thai.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer.

Novofer *Ache, Braz.*
Ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Novo-Ferrogluc *Novopharm, Canad.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Novo-Fibre *Novopharm, Canad.*
Grain and citrus fibre (p.1712·3).
Constipation; fibre supplement.

Novofilin *Ferrer, Spain†.*
Diprophylline (p.1120·2); proxyphylline (p.1130·3); theophylline (p.1140·1).
Obstructive airways disease.

Novo-Flurprofen *Novopharm, Canad.*
Flurbiprofen (p.61·2).
Inflammation; pain.

Novofric *Spefar, Venez.†.*
Methyl salicylate (p.85·3).

Novo-Furantoin *Novopharm, Canad.*
Nitrofurantoin (p.308·1).
Bacterial infections of the urinary tract.

Novogel Ford Medical, UK.
Hydrogel dressing.
Wounds.

Novogent Temmler, Ger.†.
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Novo-Gesic Novopharm, Canad.; Novopharm, Pol.
Paracetamol (p.108·1).
Fever; pain.

Novo-Gesic C Novopharm, Canad.
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

Novogyn Schering, Ital.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Novo-Helisen
Note. This name is used for preparations of different composition.
Allergopharma, Ger.; Allergopharma, Pol.; Allergopharma, Switz.
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.

ACM, Neth.
House-dust mite extract (p.2251·1) (p.2250·2).

Novo-Herklin 2000 Armstrong, Mex.
Permethrin (p.2048·2).
Pediculosis; scabies.

Novo-Hydrazide Novopharm, Canad.
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Novo-Hydrocort Novopharm, Canad.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Novo-Hylazin Novopharm, Canad.
Hydralazine hydrochloride (p.1305·3).
Hypertension.

Novo-Ipramide Novopharm, Canad.
Ipratropium bromide (p.1124·1).
Bronchodilator.

Novo-Keto Novopharm, Canad.
Ketoprofen (p.73·1).
Fever; pain.

Novolax Trima, Israel.
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

NovoLet N Novo Nordisk, Jpn†.
⊗ Isophane insulin injection (human, recombinant) (p.443·2).
Diabetes mellitus.

NovoLet R Novo Nordisk, Jpn†.
⊗ Insulin injection (human, recombinant) (p.443·2).
Diabetes mellitus.

NovoLet 10R,20R, 30R, 40R, 50R Novo Nordisk, Jpn†.
⊗ Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Diabetes mellitus.

Novo-Levocarbidopa Novopharm, Canad.
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Novo-Lexin Novopharm, Canad.
Cefalexin (p.218·2).
Bacterial infections.

Novolin 10/90, 20/80, 30/70, 40/60, 50/50 Novo Nordisk, Canad.
⊗ Mixtures of insulin injection (human, pyr) and isophane insulin injection (human) in the proportions indicated (p.443·2).
Diabetes mellitus.

Novolin 30/70 Novo Nordisk, Mex.
⊗ Mixture of insulin injection (human) and isophane insulin injection (human) respectively in the proportions indicated (p.443·2).
Diabetes mellitus.

Novolin 70/30 Novo Nordisk, Braz.; Novo Nordisk, USA; Roemmers-Klinos, Venez.†.
⊗ A mixture of isophane insulin injection (human) and insulin injection (human) (p.443·2), respectively, in the proportions indicated.
Diabetes mellitus.

Novolin L Novo Nordisk, Braz.†; Pisa, Mex.†; Roemmers-Klinos, Venez.†.
⊗ Insulin zinc suspension (human, monocomponent) (p.443·2).
Diabetes mellitus.

Novolin Lente Novo Nordisk, Canad.†.
⊗ Insulin zinc suspension (crystalline 70%) (human, pyr) (p.443·2).
Diabetes mellitus.

Novolin N Novo Nordisk, Braz.; Novo Nordisk, Jpn; Novo Nordisk, Mex.; Novo Nordisk, USA; Roemmers-Klinos, Venez.†.
⊗ Isophane insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Novolin NPH Novo Nordisk, Canad.
⊗ Isophane insulin injection (human, pyr) (p.443·2).
Diabetes mellitus.

Novolin R Novo Nordisk, Braz.; Novo Nordisk, Jpn; Novo Nordisk, Mex.; Novo Nordisk, USA; Roemmers-Klinos, Venez.†.
⊗ Insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Novolin 10R, 20R, 30R, 40R, and 50R Novo Nordisk, Jpn.
⊗ Mixtures of insulin injection (human, recombinant) 10%, 20%, 30% 40% and 50% and isophane insulin (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Diabetes mellitus.

Novolin Toronto Novo Nordisk, Canad.
⊗ Neutral insulin injection (human, pyr) (p.443·2).
Diabetes mellitus.

Novolin U Novo Nordisk, Braz.†; Novo Nordisk, Jpn†.
⊗ Insulin zinc suspension (human, monocomponent) (p.443·2).
Diabetes mellitus.

Novolin Ultralente Novo Nordisk, Canad.†.
⊗ Insulin zinc suspension (crystalline) (human, pyr) (p.443·2).
Diabetes mellitus.

Novolizer Viatris, Austria.
⊗ Budesonide (p.1520·1).
Asthma.

NovoLog Novo Nordisk, USA.
⊗ Insulin aspart (p.449·3).
Diabetes mellitus.

NovoLog Mix 70/30 Novo Nordisk, USA.
⊗ A mixture of protamine insulin aspart 70% and insulin aspart 30% (p.449·3).
Diabetes mellitus.

Novo-Lorazem Novopharm, Canad.
Lorazepam (p.1004·1).
Anxiety; sedative.

Novom Aldril, Philipp.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal intubation and radiography; gastrointestinal motility disorders; nausea and vomiting.

Novo-Medrone Novopharm, Canad.
Medroxyprogesterone acetate (p.2113·1).

Novo-Meprazine Novopharm, Canad.†.
Levomepromazine maleate (p.1003·1).
Insomnia; nausea; pain; psychoses; vomiting.

Novomet Novo Nordisk, Austral.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Novo-Methacin Novopharm, Canad.
Indometacin (p.66·3).
Inflammation; pain.

Novo-Metoprol Novopharm, Canad.; Novopharm, Hong Kong.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension.

Novomin Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†.
Dimenhydrinate (p.576·2).
Ménière's disease; motion sickness; nausea and vomiting.

Novomit Klonal, Arg.
Metoclopramide (p.1747·3).
Dyspepsia; nausea and vomiting.

No-Vomit IMA, Braz.
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

NovoMix Novo Nordisk, Malaysia.
⊗ A mixture of insulin aspart 30% and protamine insulin aspart 70% (p.449·3).
Diabetes mellitus.

NovoMix 30 Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Belg.; Novo Nordisk, Chile; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Mex.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK.
⊗ A mixture of insulin aspart 30% and protamine insulin aspart 70% (p.449·3).
Diabetes mellitus.

NovoMix 30, 50, and 70 Novo Nordisk, Cz.; Novo Nordisk, Neth.; Novo Nordisk, Port.
⊗ Mixtures of insulin aspart 30%, 50%, or 70% and protamine insulin aspart 70%, 50%, or 30%, respectively (p.449·3).
Diabetes mellitus.

Novo-Mucilax Novopharm, Canad.
Ispaghula (p.1737·1).
Constipation.

Novomyxine Thea, Fr.†.
Framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Novo-Naprox Novopharm, Canad.
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Inflammation; pain.

Novo-Nastizol Bago, Arg.†.
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Formerly contained astemizole and pseudoephedrine sulfate.
Cold and influenza symptoms; nasal congestion.

Novonausin Camps, Spain†.
Sodium citrate (p.1673·3); cerium oxalate (p.1715·3).
Nausea and vomiting.

Novoneural Mugi, Indon.
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Novo-Nidazol Novopharm, Canad.†.
Metronidazole (p.837·1).
Trichomoniasis.

Novo-Nifedin Novopharm, Canad.†.
Nifedipine (p.1350·1).
Angina pectoris.

NovoNorm Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia; Pisa, Mex.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.
Repaglinide (p.457·2).
Diabetes mellitus.

Novopacum Lacefa, Arg.
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Novopan ICN, Hung.†.
Hexobarbital (p.1002·1).
Sleep disorders.

Novopasmil Compuesto Lafedar, Arg.
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Novo-Passit Ivax, Cz.; Ivax, Rus.
Crataegus (p.2289·1); lupulus (p.2335·2); St John's wort (p.422·3); melissa (p.2339·3); passion flower (p.2363·2); sambucus (p.2383·1); valerian (p.2410·1); guaifenesin (p.1561·3).
Anxiety disorders; gastrointestinal disorders; insomnia; irritability; migraine; nervous-system disorders; pruritus.

Novopen Novo Nordisk, S.Afr.†.
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Novo-Pen-VK Novopharm, Canad.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Novo-Peridol Novopharm, Canad.
Haloperidol (p.1000·2).
Nausea and vomiting; psychoses.

Novophane ACM, Fr.
Ciclopirox olamine (p.529·2); salicylic acid (p.1612·2); cade oil (p.1616·1); sodium lactate (p.1673·3); enoxolone (p.50·1).
Dandruff.

Novophane S ACM, Fr.
Ciclopirox olamine (p.529·2); salicylic acid (p.1612·2); cade oil (p.1616·1); ichthammol (p.1599·1); sodium lactate (p.1673·3); enoxolone (p.50·1).
Dandruff.

Novo-Pheniram Novopharm, Canad.
Chlorphenamine maleate (p.571·3).

Novopin MIG neu Schoning-Berlin, Ger.
Mint oil.
Novopin MIG formerly contained menthol.
Gastrointestinal disorders; muscle pain; neuralgia; respiratory-tract congestion.

Novo-Pindol Novopharm, Canad.
⊗ Pindolol (p.1372·1).
Angina pectoris; hypertension.

Novo-Pirocam Novopharm, Canad.
Piroxicam (p.117·3).
Inflammation; pain.

Novo-Plan Polifarma, Turk.
Dipyrone (p.49·2).
Fever; pain.

Novoplas Octapharma, Port.
Plasma (p.1075·2).
Haemorrhagic disorders; idiopathic thrombocytopenic purpura.

Novoplat Pfizer, Mex.†.
Carboplatin (p.693·1).

Novoplatinum Hospira, Port.
Carboplatin (p.693·1).
Malignant neoplasms.

Novopone Santa, Gr.†.
Niflumic acid (p.95·2).
Inflammatory disorders.

Novo-Pramine Novopharm, Canad.
Imipramine hydrochloride (p.400·3).
Depression.

Novo-Pranol Novopharm, Canad.
⊗ Propranolol hydrochloride (p.1380·3).
Cardiac disorders; hypertension; migraine headache; phaeochromocytoma.

Novo-Prazin Novopharm, Canad.
Prazosin hydrochloride (p.1375·2).
Hypertension.

Novoprazol Globo, Braz.†.
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Novo-Profen Novopharm, Canad.
Ibuprofen (p.64·2).
Inflammation; pain.

Novo-Propamide Novopharm, Canad.
Chlorpropamide (p.438·3).
Diabetes mellitus.

Novoprotect Merck dura, Ger.
Amitriptyline hydrochloride (p.376·1).
Depression.

Novoptine Thea, Fr.†.
Cetylpyridinium chloride (p.1635·1).
Eye infections.

Novopulm Viatris, Spain.
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Novopulmon Asta Medica, Braz.†; Viatris, Fr.; Viatris, Ger.
⊗ Budesonide (p.1520·1).
Asthma; obstructive airways disease.

Novo-Purol Novopharm, Canad.
Allopurinol (p.552·2).

Novopyrin Sanofi-Aventis, Hung.
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1).
Pain.

Novopyrine Biosel, Turk.
Dipyrone (p.49·2).
Fever; pain.

Novoquin Rayere, Mex.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Novo-Ranidine Novopharm, Canad.; Novopharm, Hong Kong; Novopharm, Pol.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

NovoRapid Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Canad.; Novo Nordisk, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK.
⊗ Insulin aspart (p.449·3).
Diabetes mellitus.

NovoRapid 30 Mix chu Novo Nordisk, Jpn.
⊗ A mixture of soluble insulin aspart 30% and protamine insulin aspart 70% (p.449·3).
Diabetes mellitus.

Novorin Polfa, Hung.
⊗ Xylometazoline hydrochloride (p.1575·1).
Allergic rhinitis; sinusitis.

Novoris Novofarm (Νοβοφαρμ), Gr.
Risperidone (p.1024·2).
Psychoses.

Novo-Rythro Novopharm, Canad.
Erythromycin estolate (p.269·3) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Novosal Nutrition & Sante, Ital.
Low sodium dietary salt substitute (p.1922·1).

Novo-Salmol Novopharm, Canad.†.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Novoscabin Polon, Pol.
Benzyl benzoate (p.2036·1).
Scabies.

Novosef Eczacibasi, Cz.†; Eczacibasi, Rus.; Eczacibasi, Turk.
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Novo-Semide Novopharm, Canad.
⊗ Furosemide (p.1292·1).
Oedema.

NovoSeven Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Braz.; Novo Nordisk, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Jpn; Novo Nordisk, Malaysia; Novo Nordisk, Mex.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Novo Nordisk, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Novo Nordisk, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, USA.
Eptacog alfa (activated) (p.1066·2).
Haemorrhagic disorders.

Novo-Sorbide Novopharm, Canad.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Novo-Spiroton Novopharm, Canad.
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism.

Novo-Spirozine Novopharm, Canad.
⊗ Hydrochlorothiazide (p.1307·3); spironolactone (p.1400·1).
Hypertension; oedema.

Novostatin Progen, Ital.
Red rice; policosanol (p.1373·3); taurine (p.2395·2); zinc (p.1999·1); nicotinic acid (p.1957·3).
Nutritional supplement.

Novostrep Novo Nordisk, S.Afr.†.
Streptomycin sulfate (p.333·3).
Bacterial infections.

Novosual Del Bel, Arg.†.
Marine algae; chromium tripicolinate (p.1934·3).
Slimming aid.

Novo-Sucralate *Novopharm, Canad.*
Sucralfate (p.1772·2).
Peptic ulcer.

Novo-Sundac *Novopharm, Canad.*
Sulindac (p.126·3).
Inflammation; pain.

Novo-Tears *Saval, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2); hypromellose (p.2144·2); dextran.
Eye congestion; eye irritation.

Novoter *Teofarma, Spain.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Novoter Gentamicina *Teofarma, Spain.*
⊗ Fluocinonide (p.1532·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Novo-Tetra *Novopharm, Canad.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Novo-Theophyl *Novopharm, Canad.; Novopharm, Hong Kong†.*
Theophylline (p.1140·1).
Bronchospasm.

Novothyral *Merck, Austria; Merck, Belg.; Merck, Chile; Merck, Cz.†; Merck, Ger.; Merck, Pol.; Merck, Rus.; Merck, Switz.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Adjunct to antithyroid therapy; goitre; hypothyroidism; thyroiditis.

Novothyrox *Genpharm, USA.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Novotil *Sandoz, Indon.*
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Novo-Timol *Novopharm, Canad.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; hypertension.

Novotiral *Merck, Mex.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Adjunct to antithyroid therapy; euthyroid goitre; hypothyroidism.

Novotossil *Zambon, Belg.†.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Novo-Triamzide *Novopharm, Canad.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Novo-Trimel *Novopharm, Canad.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Novo-Tripramine *Novopharm, Canad.†.*
Trimipramine maleate (p.426·3).
Depression.

Novo-Triptyn *Novopharm, Canad.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Novotussan *Gemballa, Braz.†.*
⊗ Oxeladin (p.1567·1); diphenhydramine (p.577·1); ephedrine (p.1558·1); butamirate citrate (p.1553·1).
Cough.

Novo-Veramil *Novopharm, Canad.; Novopharm, Pol.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Novo-Vites *Novopharm, Canad.*
Multivitamin preparation with or without iron (p.1922·1).

Novoxil *Luper, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Novozithron *Novofarm (Νοβοφαρμ), Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Novozitron *Hexa, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Novumtrax *Pisa, Mex.*
Cytarabine (p.705·1).
Leukaemias; non-Hodgkin's lymphoma.

Novuxol *Smith & Nephew, Neth.; Abbott, Turk.*
Collagenase (p.2286·2).
Wound debridement.

Novynette *Gedeon Richter, Cz.; Sandoz, Denm.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Richter, Pol.; Grunenthal, Port.; Gedeon Richter, Rus.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Nowax *Bell, UK.*
Cineole (p.2282·3); nutmeg oil (p.2355·3); terpineol (p.2396·1); arachis oil (p.2259·1).
Ear wax removal.

Noxacorn *Dexxon, Israel.*
Salicylic acid (p.1612·2); benzocaine (p.1854·1).
Corns; warts.

Noxafil *Schering-Plough, Austral.; Schering-Plough, Cz.; Schering-Plough, Fr.; Schering-Plough, Gr.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Pol.; Schering-Plough, Swed.; Schering-Plough, UK; Schering, USA.*
Posaconazole (p.544·3).
Fungal infections.

Noxalide *Lampugnani, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Noxarel *Genepharm, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Capillary disorders.

Noxebron *Am-Europharma, Philipp.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Noxetine *Novell, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Noxibel *Bago, Arg.*
Mirtazapine (p.409·2).
Depression.

Noxidem *Sandoz, S.Afr.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Noxidil *TO-Chemicals, Thai.*
Minoxidil (p.1342·1).
Heart failure; hypertension.

Noxifen *Interhealthcare, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Nasal congestion.

Noxiflex *Bago, Chile†.*
Diclofenac epolamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Noxigram *FIRMA, Ital.†.*
Cinoxacin (p.243·2).
Bacterial infections of the urinary tract.

Noxine *Sriprasit, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Noxinor *Masa, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Noxivid *Biofarma, Mex.*
Camelia sinensis (p.2416·1); bearberry (p.2263·3); ascorbic acid (p.1983·3).
Antoxidant.

Noxobran *Biomedica-Chemica, Gr.†.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Noxom S *Heel, Ger.*
Homoeopathic preparation.

Noxon *Formenti, Ital.*
Lornoxicam (p.77·3).
Inflammation; pain.

Noxoram *Alkem, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Nox-Pain *T Man, Thai.*
Methyl salicylate (p.85·3); eugenol (p.2301·2); menthol (p.2340·1).
Musculoskeletal and joint pain.

Noxraxin *Osoth, Thai.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Noxtor *Rafarm, Gr.*
Ketotifen fumarate (p.582·2).
Allergic eye disorders.

Noxufen *Medika, Switz.*
Norfloxacin (p.309·2).
Bacterial infections.

Noxworm *Pond's, Thai.†.*
Mebendazole (p.148·3).
Worm infections.

Noxyflex *Innotech, Fr.*
Noxytiolin (p.1654·2).
Intraperitoneal infections.

Noxyflex S *Geistlich, Irl.; Geistlich, UK.*
Noxytiolin (p.1654·2).
Fungal and bacterial infections in body cavities.

Noxzema Triple Clean *Procter & Gamble, Canad.*
Triclosan (p.1665·2).

Nozema *Omega, Belg.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Nozid *Vitalpharma, Belg.†.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2) or magnesium oxide (p.1744·1).
Digestive disorders associated with hyperacidity.

Nozinan
Aventis, Arg.
Levomepromazine (p.1002·3) or levomepromazine hydrochloride (p.1002·3).
Anxiety; depression; pain; premedication; psychoses; sedative.

Gerot, Austria; Sanofi-Aventis, Belg.; Aventis, Canad.; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Aventis, NZ; Aventis, Neth.; Pfizer, Norw.; Aventis, Switz.; Link, UK.
Levomepromazine hydrochloride (p.1002·3) or levomepromazine maleate (p.1003·1).
Tablets were formerly known as Veractil in the *UK*.
Adjunct in general anaesthesia; alcohol withdrawal syndrome; anxiety disorders; depression; disturbed behaviour; insomnia; mania; nausea and vomiting; pain; premedication; psychomotor disorders; psychoses; schizophrenia; sedative; terminal pain and agitation.

Aventis, Denm.
Levomepromazine embonate (p.1003·1), levomepromazine hydrochloride (p.1002·3), or levomepromazine maleate (p.1003·1).
Anxiety; pain; psychoses; withdrawal syndromes.

Sanofi-Aventis, Fin.
Levomepromazine embonate (p.1003·1) or levomepromazine maleate (p.1003·1).
Anxiety; depression; insomnia; pain; psychoses.

Sanofi-Aventis, Irl.
Levomepromazine hydrochloride (p.1002·3).
Psychoses; terminal pain.

Aventis, Israel; Patriot, Philipp.; Vitoria, Port.
Levomepromazine (p.1002·3).
Adjunct to anaesthesia; depression; nausea and vomiting; pain; psychoses; schizophrenia.

Sanofi-Aventis, Ital.; Aventis, Swed.
Levomepromazine maleate (p.1003·1).
Anxiety; depression; hiccups; pain; psychoses; vomiting.

NP-27
Note. This name is used for preparations of different composition.
Farmo Quimica, Chile.
Topical powder: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Farmo Quimica, Chile.
Topical solution: Undecenoic acid (p.549·2); isopropyl alcohol (p.1650·3).
Fungal skin infections.

NP100 Prematures AP-HP *Fresenius Kabi, Fr.*
Glucose, amino-acid, and electrolyte infusion (p.1922·1).
Parenteral nutrition in premature neonates.

NPH Iletin II *Lilly, USA†.*
⊗ Isophane insulin suspension (porcine) (p.443·2).
Diabetes mellitus.

NS *Filorga, Fr.*
A range of nutritional supplements (p.1922·1).

N-Septonex *Infusia, Cz.†.*
Carbaethopendecinium bromide (p.1633·3); chlorhexidine hydrochloride (p.1635·3).
Infected skin disorders; wounds.

N-Statin *Cipla, Austral.†.*
Nystatin (p.543·2).
Oral candidiasis.

NT-Natal *Kee, India.*
Hydroxyprogesterone caproate (p.2110·3).
Threatened and recurrent miscarriage.

NTR *Teofarma, Ital.*
Phenylephrine hydrochloride (p.1568·1); thenyldiamine hydrochloride (p.591·3).
Cold symptoms.

NTZ *Columbia, Mex.†.*
Nitazoxanide (p.842·3).
Cryptosporidiosis.

NTZ Long Acting Nasal *Sterling Health, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Nu Cal *Odan, Canad.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Nu Cal D *Odan, Canad.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).

Nu-Alpraz *Nu-Pharm, Canad.*
Alprazolam (p.960·1).
Anxiety; sedative.

Nu-Amilzide *Nu-Pharm, Canad.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension; oedema.

Nu-Amoxi *Nu-Pharm, Canad.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Nu-Ampi *Nu-Pharm, Canad.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Nuardin *Tramedico, Belg.*
Cimetidine (p.1716·2).
Gastrointestinal disorders associated with hyperacidity.

Nu-Atenol *Nu-Pharm, Canad.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Nu-Baclo *Nu-Pharm, Canad.*
Baclofen (p.1888·1).
Muscle relaxation; skeletal muscle spasticity.

Nubain *Torrex, Austria; Cristalia, Braz.; BMS, Canad.†; BMS, Cz.; Du Pont, Cz.; SERB, Fr.†; BMS, Ger.†; Vianex (Βιανεξ), Gr.; Boots, Hong Kong†; Du Pont, Hong Kong†; Torrex, Hung.; BMS, Israel†; BMS, Malaysia†; Aventis, Mex.†; Boots Healthcare, NZ†; Boots, Philipp.; Sanofi Omnimed, S.Afr.†; BMS, Singapore†; BMS, Switz.; BMS, Thai.; BMS, UK†; Endo, USA; Zuoz, Venez.†.*
Nalbuphine hydrochloride (p.91·3).
Adjunct to general anaesthesia; pain; premedication; respiratory depression caused by opioid drugs.

Nubaina *AstraZeneca, Arg.*
Nalbuphine hydrochloride (p.91·3).
Pain.

Nubak *Kampel Martian, Arg.†.*
Nalbuphine (p.92·2).
Pain.

Nubevital BB *Stiefel, Arg.*
SPF 24: Oxybenzone (p.1608·3); sulisobenzone (p.1614·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Nubevital P *Stiefel, Arg.*
Oxybenzone (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Nubevital Sunblock Ultra *Stiefel, Arg.*
SPF 55: Oxybenzone (p.1608·3); sulisobenzone (p.1614·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Nubral *AB-Consult, Austria; Galderma, Ger.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Nubral 4 *Galderma, Ger.†.*
⊗ Urea (p.1620·2); sodium chloride (p.1686·1).
Dry skin.

Nubral Forte *Galderma, Ger.†.*
⊗ Urea (p.1620·2); sodium chloride (p.1686·1).
Skin disorders.

Nubrex *Hexal, Philipp.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Nu-Capto *Nu-Pharm, Canad.*
Captopril (p.1239·2).
ACE inhibitor.

Nucaza *Nucleus, Neth.*
Azithromycin ethanolate (p.207·3).
Bacterial infections.

Nu-Cephalex *Nu-Pharm, Canad.*
Cefalexin (p.218·2).
Bacterial infections.

Nu-Cidex *Johnson & Johnson, Fr.†.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Nu-Cimet *Nu-Pharm, Canad.*
Cimetidine (p.1716·2).
Histamine H -receptor inhibitor.

Nuclav *Abbott, India.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Nucleo CMP
Note. This name is used for preparations of different composition.
Gobbi, Arg.†.
Disodium cytidine phosphate (p.2291·3); trisodium uridine triphosphate (p.2408·1); hydroxocobalamin acetate (p.1980·3).
Neuralgia; neuritis.

Gross, Braz.
Disodium cytidine phosphate (p.2291·3); trisodium uridine triphosphate (p.2408·1); hydroxocobalamin (p.1980·3).
Neuritis.

Ferrer-Novag, Mex.
Disodium cytidine phosphate (p.2291·3); trisodium uridine triphosphate (p.2408·1).
Neuralgia; peripheral neuropathies.

Ferrer, Spain.
Sodium cytidine monophosphate (p.2291·3); disodium uridine diphosphate (p.2296·1); disodium uridilic acid; sodium uridine triphosphate (p.2408·1).
Neuralgias; neuritis.

Nucleofitol *Silva, Venez.†.*
Glutamic acid; calcium magnesium fytate; thiamine hydrochloride (p.1922·1).
Tonic.

Nucleserina *Medea, Spain.*
Pyridoxine hydrochloride (p.1978·2); ribonucleic acid (p.2379·1); phosphoserine (p.2367·1); glutamine (p.1947·2).
Mental function disorders; tonic.

Nuclosina *ICN, Port.†; Valeant, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nu-Cloxi *Nu-Pharm, Canad.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Nucoa *Rimafar, Spain.*
Isopropyl myristate (p.2029·3).
Skin irritation; ulcers; wounds.

Nucobrox *Bangkok Lab & Cosmetic, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Nucofed *Roberts, USA.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Nucofed Expectorant *Roberts, USA†.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Nucolox *Sigma, Austral.; Sigma, NZ†.*
Ispaghula (p.1737·1); starch (p.1968·1).
Constipation; hypercholesterolaemia.

Nucosef *Pfizer Consumer, Austral.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; upper respiratory-tract congestion.

Nucosef DM *Pfizer Consumer, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Nu-Cotrimox *Nu-Pharm, Canad.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Nucotuss Expectorant *Barre-National, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Nucoxia *Cadila, India.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Nuctalon *Takeda, Fr.*
Estazolam (p.995·1).
Insomnia.

Nuctane
Note. This name is used for preparations of different composition.
Bago, Chile†.
Zopiclone (p.1039·1).
Insomnia.

Armstrong, Mex.†.
Phenytoin sodium (p.495·2).
Epilepsy.

Nudep *Guardian, Indon.*
Sertraline (p.422·1).
Depression.

Nu-Derm
Note. A similar name is used for preparations of different composition (see below).
Obagi, Indon.
A range of skin cleansers and moisturisers.

Nu-derm
Note. A similar name is used for preparations of different composition (see above).
Johnson & Johnson, Ital.
Hydrocolloid dressing.
Ulcers; wounds.

Nu-Derm Alginato *Johnson & Johnson Medical, Arg.*
Calcium alginate (p.1058·1).
Wounds.

Nu-Derm Healthy Skin Protection *Obagi, Indon.*
SPF 35: Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Nu-Derm Hidrocoloide *Johnson & Johnson Medical, Arg.*
Carmellose sodium (p.2142·1).
Wounds.

Nu-Derm Sunblock
Note. This name is used for preparations of different composition.
Obagi, Indon.
SPF 15: Padimate O (p.1609·1); hydroquinone (p.1598·2).
Skin pigmentation disorders; sunscreen.

Obagi, Indon.
SPF 24: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2); betacarotene (p.1930·3).
Sunscreen.

Nu-Diclo *Nu-Pharm, Canad.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Nu-Diltiaz *Nu-Pharm, Canad.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Nudramag *Nufarindo, Indon.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Nuelin
3M, Austral.; 3M, Denm.; 3M, Fin.; 3M, Hong Kong; 3M, Irl.; 3M, Malaysia; 3M, NZ; 3M, Norw.; 3M, Philipp.; 3M, S.Afr.; 3M, Singapore; 3M, Thai.; Zuoz, Venez.
Theophylline (p.1140·1).
Obstructive airways disease.

3M, UK.
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Nuevapina *Fabop, Arg.*
Aspirin (p.20·3).
Fever; pain.

Nueve Lunas *Hexa, Arg.*
Pregnancy test (p.2372·1).

Nuface *Guardian, Indon.*
Tretinoin (p.1618·1).
Acne.

Nufacetam *Nufarindo, Indon.*
Piracetam (p.368·2).
Cerebral infarction.

Nufaclapide *Nufarindo, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Nufaclav *Nufarindo, Indon.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Nufaclind *Nufarindo, Indon.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Nufacobal *Nufarindo, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Nufacort *Nufarindo, Indon.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Nufadex *Nufarindo, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Nufadipect *Nufarindo, Indon.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cough.

Nufadol *Nufarindo, Indon.*
Paracetamol (p.108·1).
Pain.

Nufadoxin *Nufarindo, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1976·3) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Nufadryl Expectorant *Nufarindo, Indon.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Nufafloqo *Nufarindo, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Nufalemzil *Nufarindo, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Nufalev *Nufarindo, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Nufamicron *Nufarindo, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Nufamox *Nufarindo, Indon.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Nufanibrox *Nufarindo, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Nufapolar *Nufarindo, Indon.*
⊗ Desonide (p.1525·1).
Skin disorders.

Nufapotram *Nufarindo, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Nufaprazol *Nufarindo, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Nufapreg *Nufarindo, Indon.*
Promethazine teoclate (p.588·3).
Motion sickness; nausea and vomiting; vertigo.

Nufaprim *Nufarindo, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Nufarol *Rafarm, Gr.*
Sulpiride (p.1028·3).
Psychoses.

Nufasic *Nufarindo, Indon.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal and joint pain; respiratory-tract congestion.

Nufathiam *Nufarindo, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Nufatrac *Nufarindo, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Nufex *RPG, India.*
Cefalexin (p.218·2).
Bacterial infections.

Nufirom *Guardian, Indon.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Nufloxib *Alphapharm, Austral.*
Norfloxacin (p.309·2).
Bacterial infections.

NuFluo *Faromed, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Nufolic *Nufarindo, Indon.*
Folic acid (p.1940·1).
Folic acid supplement.

Nufro *Munir, Turk.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Nugatex *Rafarm, Gr.*
Calcium dobesilate (p.2272·1).
Capillary disorders.

Nu-Gel
Note. This name is used for preparations of different composition.
Johnson & Johnson, Ger.†.
Sodium alginate (p.2141·1); carmellose (p.2142·1); hyetellose (p.2143·3).
Burns; skin ulcers; wounds.

Johnson & Johnson, Irl.
Hydrogel dressing.
Wounds.

Johnson & Johnson, Israel.
Sodium alginate (p.2141·1).
Wounds.

Johnson & Johnson Medical, Fr.†.
Bandage: Povidone (p.2146·1).
Burns; wounds.

Johnson & Johnson, Ital.
Dressing: Povidone (p.2146·1).
Burns; wounds.

Johnson & Johnson, Fr.; Johnson & Johnson, Ital.
Topical gel: Sodium alginate (p.2141·1).
Wounds.

Nu-Gel Hidrogel con Alginato *Johnson & Johnson Medical, Arg.*
Sodium alginate (p.2141·1).
Ulcers.

Nu-Gel Hidrogel en Placa *Johnson & Johnson Medical, Arg.*
Povidone-iodine (p.1659·2).
Wounds.

Nuhair *Polipharm, Thai.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Nuhist *Dayton, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

Nu-Hydral *Nu-Pharm, Canad.*
Hydralazine hydrochloride (p.1305·3).
Hypertension.

Nuicalm *GSK Consumer, Belg.†.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Nu-Indo *Nu-Pharm, Canad.*
Indometacin (p.66·3).
Inflammation; pain.

Nu-Iron *Merz, USA†.*
Polysaccharide-iron complex (p.1960·2).
Iron-deficiency anaemia.

Nu-Iron V *Merz, USA.*
Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); vitamins and calcium (p.1922·1).
Iron-deficiency anaemias.

Nujol *Mantecorp, Braz.; Schering-Plough, Canad.; Schering-Plough, Gr.*
Liquid paraffin (p.2030·3).
Constipation.

Nuklofer Tonik *Radyum, Turk.*
Ferric ammonium citrate (p.1938·1).
Iron deficiency; iron-deficiency anaemia.

Nulacin *Goldshield, UK†.*
Magnesium trisilicate (p.1744·1); heavy magnesium oxide (p.1744·1); calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1); peppermint oil (p.1761·2).
Gastrointestinal hyperacidity.

Nulacin Fermentos *Seid, Spain.*
Amylolytic enzymes; proteolytic enzymes; lipolytic enzymes (p.2360·1); dehydrocholic acid (p.2292·2); procaine (p.1869·2).
Digestive enzyme deficiency.

Nulacta Li *Guardian, Indon.*
Fish oil (p.1362·2); peppermint oil (p.1761·2).
Nutritional supplement for pregnancy and lactation.

Nulagrip C *Medical, Arg.†.*
Ascorbic acid (p.1983·3); salicylic acid (p.1612·2); caffeine (p.1116·3).
Influenza symptoms.

Nularef *Lafedar, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Nularef Cort *Lafedar, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Allergic rhinitis; allergic skin disorders.

Nularef-D *Lafedar, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Cold and influenza symptoms; otitis; rhinitis; sinusitis.

Nulastres *Duncan, Arg.*
Bromazepam (p.964·3).
Anxiety.

Nulcefam *Armoxindo, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Nulcer *Armoxindo, Indon.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nulceran *Euro-Labor, Port.†; Grunenthal, Port.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; gastrointestinal bleeding; peptic ulcer; Zollinger-Ellison syndrome.

Nulcerin *Libropharm, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Nuleron *Teofarma, Ital.*
Magnesium polygalacturonate; calcium pantothenate (p.1959·3); promethazine hydrochloride (p.588·2); dimeticone (p.1770·2).
Gastrointestinal disorders associated with excess gas.

NuLev *Schwarz, USA.*
Hyoscyamine sulfate (p.1736·1).

Nu-Levocarb *Nu-Pharm, Canad.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Nulip *Gufic, India.*
Nucleic acid (p.2355·2).
Viral infections.

Nullatuss *Hofmann & Sommer, Ger.†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Nulobes *Columbia, Arg.*
Tiratricol (p.2177·3).
Obesity.

Nu-Loraz *Nu-Pharm, Canad.*
Lorazepam (p.1004·1).
Anxiety; sedative.

Nu-Lotan *Banyu, Jpn.*
Losartan potassium (p.1326·1).
Hypertension.

Nulox *Nufarindo, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

NuLytely *Zodiac, Braz.; Asofarma, Mex.; Braintree, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Numalin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Numanis *Schering, Spain.*
⊗ Testosterone undecylate (p.2130·2).
Hypogonadism.

Numark *Boehringer Ingelheim Promeco, Mex.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Numark Flu Relief *Numark, UK.*
Paracetamol (p.108·1); phenylephrine (p.1568·1).
Cold and influenza symptoms.

Numark Max Strength Cold & Flu *Numark, UK.*
Paracetamol (p.108·1); phenylephrine (p.1568·1).
Cold and influenza symptoms.

Numark Muscle Rub *Numark, UK.*
Methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Numark Muscle Spray *Numark, UK.*
Glycerol mono salicylate; methyl salicylate (p.85·3); ethyl salicylate (p.52·1).
Musculoskeletal and joint disorders.

Numatol *Spyfarma, Spain.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; tonic.

Numbon *Teva, Israel.*
Nitrazepam (p.1011·2).
Insomnia.

Nu-Medopa *Nu-Pharm, Canad.*
Methyldopa (p.1334·1).
Hypertension.

Numen *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Otitis externa.

Numencial
Note. This name is used for preparations of different composition.
Ivax, Arg.
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Armstrong, Mex.
Sulpiride (p.1028·3); diazepam (p.986·3).
Mixed anxiety depressive states.

Nu-Metop *Nu-Pharm, Canad.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension.

Numoisyn *Align, USA.*
Sorbitol (p.1965·1); macrogol (p.2336·1); malic acid (p.2337·1); electrolytes (p.1667·1).
Saliva substitute.

Numonyl *Sanofi Synthelabo, Mex.†.*
Cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Numonyl C *Sanofi Synthelabo, Mex.*
Chlorphenamine (p.572·2); paracetamol (p.108·1); caffeine (p.1116·3).

Numonyl D *Sanofi Synthelabo, Mex.†.*
Dextromethorphan (p.1555·2).
Coughs.

Numonyl Jarabe *Sanofi Synthelabo, Mex.*
Phenylpropanolamine (p.1569·2); chlorphenamine (p.572·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Numonyl T *Sanofi Synthelabo, Mex.†.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); pseudoephedrine (p.1571·2).
Cold symptoms.

Numonyl Tex *Sanofi Synthelabo, Mex.†.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); pseudoephedrine (p.1571·2); dextromethorphan (p.1555·2).
Cold symptoms.

Numorphan *BMS, Canad.†; Endo, USA.*
⊗ Oxymorphone hydrochloride (p.107·2).
Adjunct to general anaesthesia; anxiety in dyspnoea associated with left ventricular failure and pulmonary oedema; pain; premedication.

Numosol *Medipharm, Chile.*
Oxolamine citrate (p.1567·1).
Respiratory-tract disorders.

Numzident *Goodys, USA†.*
Benzocaine (p.1854·1).
Oral lesions.

Num-Zit
Note. A similar name is used for preparations of different composition (see below).
Silesia, Chile.
Zinc sulfate (p.1999·2).
Dietary supplement.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Numzit
Note. This name is used for preparations of different composition.
Goodys, USA†.
Lotion: Benzocaine (p.1854·1); glycerol (p.2314·2).
Oral lesions.

Goodys, USA†.
Topical gel: Benzocaine (p.1854·1); clove oil (p.2285·1).
Oral lesions.

Nu-Naprox *Nu-Pharm, Canad.*
Naproxen (p.92·3).
Inflammation; pain.

Nu-Natal Advanced *Rising Pharmaceuticals, USA.*
Vitamins; minerals; docusate sodium (p.1725·1) (p.1922·1).

Nu-Nifed *Nu-Pharm, Canad.*
Nifedipine (p.1350·1).
Angina pectoris.

Nuosic *Millimed, Thai.*
Paracetamol (p.108·1); orphenadrine citrate (p.812·1).
Dysmenorrhoea; skeletal muscle pain; tension headache.

Nuovodox *Bergamo, Braz.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Nu-Oxybutyn *Nu-Pharm, Canad.*
Oxybutynin hydrochloride (p.2190·3).

Nupentin *Alphapharm, Austral.; Pacific, NZ.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Nu-Pen-VK *Nu-Pharm, Canad.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Nupercainal
Note. This name is used for preparations of different composition.
Novartis, Braz.; Novartis, India; Materfarma, Port.; LPC, UK.
Cinchocaine hydrochloride (p.1857·3).
Anorectal disorders; haemorrhoids; pain; skin irritation.

Novartis Consumer, Canad.
Cream: Cinchocaine (p.1857·2); domiphen bromide (p.1643·1).
Pain; pruritus.

Novartis Consumer, Canad.; Ciba, USA.
Ointment: Cinchocaine (p.1857·2).
Haemorrhoids; pain; pruritus.

Ciba, USA†.
Suppositories: Zinc oxide (p.1621·2).
Anorectal disorders.

Nu-Pindol *Nu-Pharm, Canad.*
⊗ Pindolol (p.1372·1).
Angina pectoris; hypertension.

Nu-Pirox *Nu-Pharm, Canad.*
Piroxicam (p.117·3).
Inflammation; pain.

Nupra *Grunenthal, Chile†.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Nuprafen *Beximco, Singapore†.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Nu-Prazo *Nu-Pharm, Canad.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Nuprilan *Medinfar, Port.†.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Nuprin *Bristol-Myers Products, USA†.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Nuprin Backache *BMS, USA†.*
Magnesium salicylate (p.79·2).
Pain.

Nu-Prochlor *Nu-Pharm, Canad.*
Prochlorperazine maleate (p.1020·1).
Psychoses; vomiting.

Nur 1 Tropfen Chlorhexidin *One Drop Only, Ger.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Nur 1 Tropfen medizinisches Mundwasser
One Drop Only, Ger.†.
Peppermint oil (p.1761·2); clove oil (p.2285·1); menthol (p.2340·1); sumatra benzoin (p.2394·2).
Mouth and throat disorders.

Nurabax *Ranbaxy, Cz.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Nu-Ranit *Nu-Pharm, Canad.*
Ranitidine hydrochloride (p.1766·1).
Histamine H -receptor antagonist.

Nurasic *TO-Chemicals, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain.

Nureflex *Reckitt Benckiser, Fr.; Boots Healthcare, Ital.*
Ibuprofen (p.64·2).
Fever; juvenile idiopathic arthritis; pain.

Nurezan *Rafarm, Gr.†.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic.

Nuriban *Roux-Ocefa, Arg.*
⊗ Furosemide diethylaminoethanol (p.1294·1).
Diuretic.

Nuriban A *Roux-Ocefa, Arg.*
⊗ Furosemide (p.1292·1) amiloride hydrochloride (p.1209·2).
Oedema.

Nuri-Kapseln *Sanochemia, Austria.*
Halibut-liver oil (p.1948·1); cod-liver oil (p.1935·2).
Vitamin A and D deficiency.

Nuril
Note. This name is used for preparations of different composition.
USV, India.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Almirall, Spain.
Pipemidic acid (p.315·1).
Urinary-tract infections.

Nur-Isterate *Schering, S.Afr.*
Norethisterone enantate (p.2120·1).
Injectable contraceptive.

Nuritrex B12 *Organon, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Nuro-B
Note. This name is used for preparations of different composition.
Rimsa, Mex.
Meloxicam (p.80·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgias; neuritis; neuropathies.

TO-Chemicals, Thai.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuromuscular pain.

Nurocain *Dentsply, Austral.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Nurofast *Boots Healthcare, Ital.*
Ibuprofen (p.64·2).
Fever; pain.

Nurofebryl *Boots Healthcare, Belg.*
Ibuprofen (p.64·2).
Fever; pain.

Nurofen
Boots Healthcare, Austral.; Boots Healthcare, Belg.; Reckitt Benckiser, Cz.; Boots Healthcare, Fr.; Boots, Ger.; Vianex (Βιανεξ), Gr.; Boots, Hong Kong; Boots Healthcare, Irl.; Boots, Israel; Boots Healthcare, Ital.; Reckitt Benckiser, Malaysia; Boots Healthcare, NZ; Boots Healthcare, Neth.; Reckitt Benckiser, Pol.; Reckitt Benckiser, Port.; Boots, Rus.; Boots Healthcare, S.Afr.; Reckitt Benckiser, Singapore; Boots Healthcare, Spain; Boots, Switz.; Boots, Thai.; Abdi, Turk.; Crookes Healthcare, UK.
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Boots Healthcare, Austria.
Ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Pain.

Reckitt Benckiser, Hung.
Ibuprofen (p.64·2) or ibuprofen sodium (p.65·2).
Fever; inflammation; pain.

Nurofen Advance *Reckitt Benckiser, Cz.*
Ibuprofen lysine (p.64·2).
Fever; inflammation; pain.

Nurofen Antigrip *Reckitt Benckiser, Pol.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nurofen CF *Vianex (Βιανεξ), Gr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Viral infections.

Nurofen Cold & Flu *Reckitt Benckiser, Austral.; Reckitt Benckiser, Hung.; Boots Healthcare, Irl.; Boots, Israel; Boots Healthcare, NZ; Boots Healthcare, S.Afr.; Abdi, Turk.; Crookes Healthcare, UK.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nurofen Complex *Boots Healthcare, Spain.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nurofen Migraine *Crookes Healthcare, UK.*
Ibuprofen lysine (p.64·2).
Headache; migraine.

Nurofen Plus *Reckitt Benckiser, Austral.; Boots Healthcare, Irl.; Boots Healthcare, NZ; Reckitt Benckiser, Pol.; Boots, Rus.; Crookes Healthcare, UK.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Fever; pain.

Nurofen Rhume *Boots Healthcare, Fr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Nurofen Sinus *Crookes Healthcare, UK.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nurofen Stopgrip *Reckitt Benckiser, Cz.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Nurofentabs *Boots Healthcare, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Nuroflash *Boots Healthcare, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Nurolasts *Boots Healthcare, Austral.†.*
Naproxen sodium (p.92·3).

Nuromax *Abbott, Canad.†; Glaxo Wellcome, USA†.*
Doxacurium chloride (p.1906·1).
Competitive neuromuscular blocker.

Nuron-E *Icon, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Chronic hepatitis; neuralgia; neuritis; neuropathy; vitamin B deficiency.

Nurosolv *Boots Healthcare, Ital.*
Ibuprofen (p.64·2).
Fever; pain.

Nu-Rox *Laboratorios Chile, Chile.*
Enoxaparin sodium (p.1277·2).
Extracorporeal circulation; myocardial infarction; thromboembolism prophylaxis; unstable angina; venous thrombosis.

Nurse Harvey's Gripe Mixture
Note. This name is used for preparations of different composition.
Harvey Scruton, Israel.
Dill oil (p.2293·3); sodium bicarbonate (p.1673·2).
Infant colic.

Harvey-Scruton, UK.
Dill oil (p.2293·3); caraway oil (p.2277·1); sodium bicarbonate (p.1673·2).
Infant colic.

Nurse Sykes Powders *Anglian, UK.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Nursoy *Wyeth, Arg.†; Wyeth, Braz.; Nestle, Canad.†; Wyeth, Chile; Wyeth, Hong Kong; Wyeth Nutrition, Indon.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Philipp.; Wyeth, Singapore; Wyeth, Venez.*
Soy protein infant feed (p.1922·1).
Cows' milk intolerance; galactokinase deficiency; lactose intolerance.

Nurture Nourishing *Heinz-Wattie, NZ†.*
Preparation for enteral nutrition in pregnancy and lactation (p.1922·1).

Nu-Salt *Cumberland, USA.*
Low sodium dietary salt substitute (p.1922·1).

Nu-Seals *Alliance, Irl.; Alliance, UK.*
Aspirin (p.20·3).
Fever; inflammation; pain; thromboembolic disorders.

Nuso-San *Sandipro, Belg.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Nussidex *Teva, Israel.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Nustasium *Labima, Belg.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Nuta *Osotspa, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Nutacold *Osotspa, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Nutacough *Osotspa, Thai.†.*
Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); chlorphenamine maleate (p.571·3).
Coughs.

Nutamol *Osotspa, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Nutaphake *Sensomed, Philipp.*
Adenosine triphosphate (p.2247·3).
Cataract.

Nu-Tears *Optopics, USA.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Nu-Tears II *Optopics, USA.*
Polyvinyl alcohol (p.2145·3); macrogol 400 (p.2336·3).
Dry eyes.

Nutegen A *Grisi, Mex.†.*
Triclocarban (p.1665·2).
Acne.

Nutegen G *Grisi, Mex.†.*
Coconut oil (p.2029·2); castor oil (p.2278·1); glycerol (p.2314·2).
Seborrhoea.

Nutegen H *Grisi, Mex.†.*
St John's wort (p.422·3).
Skin hypersensitivity.

Nu-Tetra *Nu-Pharm, Canad.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Nutilis *Nutricia, Austral.†; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Port.; Nutricia Clinical, UK.*
Food thickener (p.1922·1).
Dysphagia.

Nutizym Compositum *Merck, Venez.*
Bromelains (p.2269·1); pancreatin (p.2360·1); ox bile (p.2266·3); dimeticone (p.1770·2).
Digestive disorders.

Nutra Fibra *Investigacion, Mex.*
Multivitamin and mineral preparation with fibre (p.1922·1).

Nutrabase *Filorga, Fr.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; magnesium (p.1922·1).
Restoration of normal gastrointestinal flora.

Nutrabiotique *Filorga, Fr.†.*
Nutritional supplement (p.1922·1).

Nutracel
Note. This name is used for preparations of different composition.
Isdin, Spain.
Guanosine (p.2318·1); inosine (p.2325·2); miconazole nitrate (p.541·3); vitamin F (p.2308·2).
Skin disorders.

Baxter, UK.
Glucose and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Nutracort
Galderma, Braz.; Galderma, Chile; Lavipharm, Gr.†; Galderma, Mex.; Healthpoint, USA; Galderma, Venez.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Orion, Fin.†.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Nutra'Creme *Beaubour, Fr.*
Preparation for enteral nutrition (p.1922·1).

Nutra-D *Galderma, Austral.†.*
Emollient.

Nutraderm
Note. This name is used for preparations of different composition.
Galderma, Arg.; Galderma, Braz.; Galderma, Canad.; Galderma, Chile; Orion, Fin.; Galderma, Mex.; Galderma, Philipp.; Healthpoint, USA.
Emollient.
Dry skin; skin disorders; vehicle for topical drugs.

Galderma, Singapore†.
Liquid paraffin (p.2030·3).
Dry skin.

Nutraderme *Filorga, Fr.†.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; minerals; yeast; citrus; lappa; borage (p.1922·1).
Skin care.

Nutradex *Fresenius Kabi, Swed.*
Carbohydrate and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Nutrafem *Bionutra, Singapore.*
Eucommia ulmoides; vigna radiata.
Menopausal disorders.

Nutrafilm *Giscard, Arg.*
Lactic acid (p.2329·3); silanols.
Dry skin.

Nutrafit *Northfield, Philipp.*
Green tea (p.2416·1); levocarnitine (p.1932·2); guarana (p.2416·1); chromium tripicolinate (p.1934·3).
Nutritional supplement.

Nutraforme *Filorga, Fr.†.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; minerals; yeast; guarana (p.1922·1).
Tonic.

Nutraisdin
Note. This name is used for preparations of different composition.
Ingens, Arg.†.
Cream: Dexpanthenol (p.2362·1); zinc oxide (p.1621·2).
Nappy rash.

Isdin, Port.
Cream: Dexpanthenol (p.2362·1); zinc oxide (p.1621·2); borage oil (p.2267·3); vitamin E (p.1992·2).
Napkin rash.

Ingens, Arg.†.
Lotion: Dexpanthenol (p.2362·1).
Moisturiser.

Isdin, Port.
Lotion: Dexpanthenol (p.2362·1); glycerol (p.2314·2); borage oil (p.2267·3); avocado oil.
Nappy rash.

Nutral *Bionutre, Arg.*
Amino acids; minerals; vitamins (p.1922·1).
Nutritional supplement.

Nutralcon *Galderma, Arg.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Nutralipid MCT *ICN, Cz.†; Infusia, Cz.†.*
Lipid (from fractionated soya oil (p.1965·3) and coconut oil (p.2029·2)) infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Nutralipid P *ICN, Cz.†; Infusia, Cz.†.*
Lipid (from fractionated soya oil (p.1965·3)) infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Nutralona *Galderma, Chile†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Nutraloric *Nutraloric, USA.*
Preparation for enteral nutrition (p.1922·1).

Nutrament *Mead Johnson Nutritionals, USA; BMS, Venez.†.*
Preparation for enteral nutrition (p.1922·1).

Nutramigen *Mead Johnson, Austral.; Mead Johnson Nutritionals, Fin.; Mead Johnson, Fr.; Mead Johnson, Hong Kong†; Mead Johnson, Irl.; Mead Johnson, Israel; Mead Johnson, Ital.; BMS, Pol.; Mead*

Johnson, Pol.; Mead Johnson, Port.†; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, UK; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.
Protein hydrolysate preparation for special diets (p.1922·1).
Abdominal colic; atopic dermatitis; carbohydrate intolerance; diarrhoea; disaccharide intolerance; enteral nutrition; food allergies; galactokinase deficiency; galactosaemia; gastro-enteritis; homocystinuria; lactose intolerance; lactose or sucrose intolerance; malabsorption disorders; milk protein sensitivity; protein intolerance; protein malabsorption.

Nutramin *Fresenius Kabi, Cz.; Behrens, Venez.*
A range of amino-acid infusions (p.1922·1).
Parenteral nutrition.

Nutramince *Filorga, Fr.†.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; magnesium; pineapple; citrus; bladderwrack; guarana; black currant; red vine (p.1922·1).
Obesity.

Nutra'Mix *Beaubour, Fr.*
Preparation for enteral nutrition (p.1922·1).

NutraMX *Vita Health, Singapore.*
Multivitamin and mineral preparation with ginkgo biloba, ginseng, glutamine, inositol, and lysine (p.1922·1).

Nutraplus *Galderma, Austral.; Galderma, Braz.; Galderma, Chile†; Galderma, Fr.; Galderma, Hong Kong†; Galderma, Irl.; Galderma, Malaysia; Galderma, Mex.; Galderma, NZ; Pacific, NZ; Galderma, Philipp.; Galderma, Singapore; Galderma, Spain†; Galderma, Switz.; Galderma, Thai.; Liba, Turk.; Galderma, UK; Healthpoint, USA.*
⊗ Urea (p.1620·2).
Dry or hyperkeratotic skin conditions.

Nutrapurete *Filorga, Fr.†.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; magnesium; sorbitol; black currant; black radish; cynara; heather; birch leaf; parsley (p.1922·1).
Tonic.

Nutrarepos *Filorga, Fr.†.*
Fructo-oligosaccharides; lactic-acid producing organisms; vitamins; magnesium; calcium; passion flower; valerian; melissa (p.1922·1).
Sleep disorders; stress.

Nutrasoothe *Brimms, Israel†.*
Avena (p.2262·1).
Skin disorders.

Nutra-Soothe *Pertussin, USA.*
Emollient.

Nutrasorb *Galderma, Mex.*
Acrylate copolymer; glycerol (p.2314·2).
Acne; seborrhoea.

Nutrasweet
Note. This name is used for preparations of different composition.
Merisant, Arg.†.
Aspartame (p.1930·1).
Sugar substitute.
Rider, Chile†.
Aspartame (p.1930·1); maltodextrin (p.1955·3).
Sugar substitute.

Nutra-Tat *Atabay, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Nutravit Light *Investigacion, Mex.*
Protein, multivitamin and mineral supplement (p.1922·1).
Obesity.

Nutrem *Medihealth, Mex.*
Vitamin C (p.1983·3); vitamin E acetate (p.1992·3); vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1); gamolenic acid (p.2308·2); linoleic acid (p.2308·2).
Sun-induced skin damage; wrinkles.

Nutren *Nestle, Braz.; Nestle, Canad.; Nestle, Hong Kong; Nestle, Indon.; Nestle, Israel; Nestle, Malaysia; Nestle, Philipp.; Nestle, Singapore†; Nestle, Thai.; Clintec, USA.*
A range of preparations for enteral nutrition (p.1922·1).

Nutrena *Abbott, Turk.*
Preparation for enteral nutrition (p.1922·1).
Renal failure.

Nutr-E-Sol *Advanced Nutritional Technology, USA.*
Tocofersolan (p.1993·3).
Vitamin E supplement.

Nutre-T *Nucitec, Mex.*
Preparation for enteral nutrition (p.1922·1).

Nutrexon *Nufarindo, Indon.*
Naltrexone hydrochloride (p.1455·2).
Alcohol dependence; opioid dependence.

Nutri 10 *Medisys, Philipp.*
Vitamins; lysine; taurine (p.1922·1).
Nutritional supplement.

Nutri 10 Excel *Medisys, Philipp.*
Vitamin preparation with iron (p.1922·1).
Nutritional supplement.

Nutri Twin *Baxter, Ger.†.*
Amino-acid, electrolyte, and carbohydrate solution (p.1922·1).
Parenteral nutrition.

Nu-Triazide *Nu-Pharm, Canad.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Nutribraun *Braun, Port.*
Amino-acid, electrolyte, and lipid (from soya oil (p.1965·3) and medium-chain triglycerides (p.1956·3)) (p.1922·1).
Parenteral nutrition.

Nutrical *Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).

Nutricalcio *Nutrilab, Braz.†.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Nutricap
Nutrisante, Fr.
Amino-acid, fatty-acid, vitamin, and mineral preparation (p.1922·1).
Hair and nail disorders.
More, Philipp.
Vitamins; minerals; ginseng; lecithin; rutoside; ginkgo biloba; lycopene; lutein; selenium yeast; zeaxanthin (p.1922·1).
Nutritional supplement.
Polinac, Venez.
Nut oil; litothamne; milk protein; yeast; acerola; lecithin; beeswax (p.1922·1).
Dietary supplement.

Nutricee *Pharma Nutria, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Nutricia HA *Nutricia, Fr.*
Infant feed (p.1922·1).
Milk protein allergy.

Nutricomp *Braun, Indon.*
A range of preparations for enteral nutrition (p.1922·1).

Nutricon *Pasadena, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Nutrideen *Bioceuticals, UK.*
Marine protein extract with vitamin C and zinc (p.1922·1).

Nutridrink *Nutricia, Austral.†; Support, Braz.†; Nutricia, Cz.†; Nutricia, Fin.; Nutricia, Indon.; Nutricia, Ital.; Baxter, NZ†; Nutricia, NZ†; Nutricia, Port.*
Preparation for enteral nutrition (p.1922·1).

Nutriesencial *AMG, Arg.†.*
Vitamin and mineral preparation (p.1922·1).

Nutrifac *Rising Pharmaceuticals, USA.*
Vitamin and mineral preparation (p.1922·1).

Nutriflam *Tropica Mas, Indon.*
Serrapeptase (p.2385·3); pancreatin (p.2360·1); lecithin (p.2332·2).
Inflammation.

Nutriflex *Braun, Arg.†; Braun, Chile; Braun, Cz.; Braun, Fin.; Braun, Fr.†; Braun, Ger.; Bioser (Βιοσερ), Gr.; Braun, Hong Kong; Braun, Hung.; Braun, Neth.; Braun, Norw.; Braun, Pol.; Braun, Port.; Braun, Swed.; Braun, Switz.; Braun, Turk.; Braun, UK.*
A range of amino-acid, glucose, and electrolyte infusions (p.1922·1).
Parenteral nutrition.

Nutriflex Lipid
Note. This name is used for preparations of different composition.
Braun, Arg.; Braun, Denm.; Braun, Port.
A range of amino-acid, glucose, lipid, and electrolyte infusions (p.1922·1).
Parenteral nutrition.
Braun, Austria; Bioser (Βιοσερ), Gr.
Amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusions with or without electrolytes (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.
Braun, Cz.; Braun, Fin.; Braun, Ger.; Braun, Hong Kong; Braun, Neth.; Braun, Norw.; Braun, Spain; Braun, Swed.; Braun, Switz.
A range of amino-acid, glucose, lipid (from soya oil (p.1965·3) and medium-chain triglycerides (p.1956·3)), and electrolyte infusions (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Nutriflex Lipide *Braun, Fr.*
Amino-acid, carbohydrate, electrolyte, and lipid (from soya oil (p.1965·3)) infusion (p.1922·1).
Parenteral nutrition.

NutriFocus *Abbott, USA.*
Preparation for enteral nutrition (p.1922·1).

Nutrifol *Pentamedical, Ital.*
Multivitamin and amino-acid preparation (p.1922·1).
Prevention of hair loss.

Nutrigel *Farbo, Ital.†.*
Fructose; soya lecithin (p.2332·2); honey (p.1948·2); royal jelly (p.2382·1).

Nutrigrow
Medisys, Philipp.
Capsules: Chlorella growth factor; taurine; lysine hydrochloride; vitamins; minerals; selenium yeast (p.1922·1).
Nutritional supplement.
Medisys, Philipp.
Syrup: Chlorella growth factor; taurine; lysine hydrochloride; vitamins (p.1922·1).
Nutritional supplement.

NutriHeal *Nestle, USA.*
Preparation for enteral nutrition (p.1922·1).

Nutrihelper *Nutricional, Arg.*
Preparation for enteral nutrition (p.1922·1).

Nutri-Junior *Nutricia, Fin.†; Nutricia, Ital.*
Infant feed (p.1922·1).
Cow's milk, soya protein and other food allergies; hypersensitivity disorders.

Nutrilamine *Braun, Fr.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Nutrilan *Galagen, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Nutrilarm *Thea, Fr.*
Omega-3 fatty-acids; omega-6 fatty acids; vitamins; zinc oxide (p.1922·1).
Dietary supplement for dry eyes.

Nutrilife Pro *Nutrimed, Fr.*
Nutritional supplement (p.1922·1).

Nutrilin
Medifarma, Indon.; Pediatrica, Indon.; Great Eastern, Thai.†; Pediatrica, Thai.†.
Vitamin preparation with or without iron (p.1922·1).
Nutritional supplement.
Pediatrica, Philipp.
Oral drops: Vitamin preparation (p.1922·1) with taurine.
Nutritional supplement.
Pediatrica, Philipp.
Syrup: Vitamin and mineral preparation (p.1922·1) with taurine.
Nutritional supplement.

Nutrilon AR *Nutricia-Bago, Arg.; Nutricia, Fr.; Nutricia, Ital.†; Nutricia, Port.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux in infants; regurgitation.

Nutrilon Lactomin *Nutricia, Port.*
Infant feed (p.1922·1).
Lactose intolerance.

Nutrilon L-K *Nutricia-Bago, Arg.†.*
Infant feed (p.1922·1).
Diarrhoea; lactose intolerance.

Nutrilon Low Lactose *Nutricia, Indon.*
Infant feed (p.1922·1).
Diarrhoea.

Nutrilon Low-Lactose *Nutricia, Cz.†.*
Infant feed (p.1922·1).
Lactose intolerance.

Nutrilon Omneo *Nutricia, Mex.*
Infant feed (p.1922·1).
Digestive disorders.

Nutrilon Pepti *Nutricia-Bago, Arg.; Nutricia, Cz.†; Cow & Gate, Irl.; Nutricia, Ital.; Nutricia, Port.*
Infant feed (p.1922·1).
Cows' milk intolerance; food hypersensitivity.

Nutrilon Pepti-Junior *Nutricia, Mex.*
Infant feed (p.1922·1).
Gastrointestinal disorders.

Nutrilon Soya *Nutricia-Bago, Arg.; Nutricia, Cz.†; Nutricia, Indon.; Nutricia, Indon.; Cow & Gate, Israel; Nutricia, Ital.†; Nutricia, Mex.; Nutricia, Venez.*
Infant feed (p.1922·1).
Cows' milk intolerance; galactosaemia; lactose intolerance.

Nutrilyte *American Regent, USA.*
A range of electrolyte preparations (p.1667·1).
Fluid and electrolyte disorders.

Nutrimaiz SM *Uniao Quimica, Braz.*
Vitamin B substances; glutamic acid; ferric ammonium citrate or ferrous sulfate; magnesium chloride or magnesium sulfate; calcium phosphate (p.1922·1); buclizine hydrochloride (p.570·1); carnitine hydrochloride.
Reduced appetite; tonic.

Nutrimed *Nutrimed, Fr.*
Preparation for enteral nutrition (p.1922·1).

Nutrineal *Baxter, Neth.; Baxter, Port.*
Amino acids; sodium chloride; calcium chloride; magnesium chloride; sodium lactate (p.1670·3).
Peritoneal dialysis.

Nutrineal PD4 *Baxter, Austria; Baxter, Cz.; Baxter, Denm.; Baxter, Ger.; Baxter, Israel; Baxter, Ital.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, UK.*
Sodium chloride; calcium chloride; magnesium chloride; sodium lactate; amino acids (p.1670·3).
Peritoneal dialysis; peritoneal dialysis solution.

Nutrini *Nutricia, Austral.†; Support, Braz.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Pol.; Nutricia, Port.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition in children (p.1922·1).

Nutri-Ped *Stiefel, Braz.†.*
Vitamin B substances; minerals; glutamic acid; buclizine hydrochloride (p.570·1); levocarnitine (p.1922·1).
Nutritional supplement.

Nutriperi Lipid *Braun, Ital.*
An amino-acid, glucose, lipid (from soya oil (p.1965·3) and medium-chain triglycerides (p.1956·3)), and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Nutriplasmal *Braun, Port.; Braun, Spain†.*
An amino-acid, glucose, lipid (from soya oil (p.1965·3)), and electolyte infusion (p.1922·1).
Parenteral nutrition.

NutriPlus *Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).

Nutriplus Lipid *Braun, Ital.*
An amino-acid, glucose, and lipid (from soya oil (p.1965·3) and medium-chain triglycerides (p.1956·3)) infusion with or without electrolytes (p.1922·1).

Nutrir Nutricion Parenteral Total *Fresenius Kabi, Arg.*
Preparation for parenteral nutrition (p.1922·1).

Nutrisan *Novartis, India.*
Multivitamin and mineral preparation (p.1922·1).

NutriScience *Wassen, UK.*
Selenium; antoxidant vitamins; ubidecarenone; plant extracts (p.1922·1).

Nutrisil *Darier, Mex.*
Arachis oil (p.2259·1).
Skin disorders; soap substitute.

Nutri-Soija *Nutricia, Fin.*
Infant feed (p.1922·1).
Cow's milk allergy; lactose intolerance.

Nutrisol *Green Cross, Philipp.; Green Cross Guangzhou, Singapore.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Nutrisol-S *Green Cross, Hong Kong; Tempo Scan Pacific, Indon.; Green Cross, Malaysia†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Nutrison *Nutricia-Bago, Arg.; Nutricia, Austral.†; Nutricia, Cz.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Indon.; Nutricia, Irl.; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Pol.; Nutricia, Port.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition (p.1922·1).
Formerly known as Fortison.

Nutrison MCT *Nutricia Clinical, UK.*
Gluten- and fructose-free, low-lactose preparation for enteral nutrition (p.1922·1).
Fat malabsorption.

Nutrisource Mains *Lancome, Canad.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Nutrispecial Lipid *Braun, Ital.*
An amino-acid, glucose, and lipid (from soya oil (p.1965·3) and medium-chain triglycerides (p.1956·3)) infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Nutritrace *Braun, Fin.; Braun, Neth.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

NutriTwin G *Fresenius Kabi, Austria.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Nutrivance *Avon, Canad.*
A range of multivitamin and mineral preparations (p.1922·1).

Nutrivisc *Novartis, Fr.*
Povidone (p.2146·1).
Dry eyes.

Nutrivit
Note. This name is used for preparations of different composition.
Makros, Braz.†.
Multivitamin and mineral preparation with lysine (p.1922·1).
Dynacren, Ital.†.
Brewer's yeast (p.1998·3).
Medifarma, Mex.†.
Vitamin or vitamin and mineral preparation (p.1922·1).
Anaemias; vitamin deficiency.

Nutrivita *Lloyd, Philipp.*
Vitamin preparation with lysine hydrochloride (p.1922·1).
Nutritional supplement.

Nutri-Vital *Synergia, Fr.*
Vitamin and mineral preparation (p.1922·1).

Nutrizim *Merck, Braz.†.*
Pancreatin (p.2360·1); bromelains (p.2269·1); dimeticone (p.1770·2); ox bile (p.2266·3).
Digestive disorders.

Nutrizima *Mepro, Chile.*
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive disorders.

Nutrizym *Merck, Irl.; Merck, UK.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Nutrizym N *Cascan, Ger.†; GSK, Ger.†.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Nutrocal *Wockhardt, India.*
Preparation for enteral nutrition (p.1922·1).

Nutrocal DM *Wockhardt, India.*
Preparation for enteral nutrition (p.1922·1).

Nutrodrip *Novartis Nutrition, Cz.†; Novartis, Irl.; Novartis Consumer, UK.*
A range of preparations for enteral nutrition (p.1922·1).

Nutrof
Thea, Fr.
Vitamin and mineral preparation (p.1922·1).
Thea, Philipp.
Vitamins; zinc; selenium; glutathione; lutein (p.1922·1).
Nutritional supplement.

Nutrof Omega *Thea, Fr.*
Vitamin and mineral preparation with omega-3 fatty acids (p.1922·1).

Nutrol V *Rolmex, Canad.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

Nutrol A *Rolmex, Canad.*
Halibut-liver oil (p.1948·1).

Nutrol A D *Rolmex, Canad.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).

Nutrol B Complex *Rolmex, Canad.*
A vitamin B preparation (p.1922·1).

Nutrol C *Rolmex, Canad.*
Ascorbic acid (p.1983·3).

Nutrol E *Rolmex, Canad.*
d-Alpha tocoferil acetate (p.1992·3).

Nutrol E plus Zinc & Selenium *Rolmex, Canad.*
Vitamin E, zinc, and selenium (p.1922·1).

Nutrol No 1 *Rolmex, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Nutrolin-B *Cipla, India.*
Lactobacillus (p.2372·3); vitamin B substances (p.1922·1).
Adjunct to antibiotic therapy; aphthous ulcers.

Nutropin *Roche, Canad.; Ipsen, Gr.; Beaufour-Ipsen, Hung.; Ipsen, Ital.; Ipsen, Neth.; Ipsen, Spain; Ipsen, UK; Genentech, USA.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; idiopathic short stature; Turner's syndrome.

NutropinAq *Ipsen, Austral.; Richter, Austria; Ipsen, Belg.; Ipsen, Cz.; Ipsen, Denm.; Ipsen, Fin.; Beaufour, Fr.; Ipsen, Ger.; Ipsen, Norw.; Ipsen, Port.; Ipsen, Swed.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Prader-Willi syndrome; Turner's syndrome.

Nutroplex
Note. This name is used for preparations of different composition.
United American, Hong Kong; United American, Malaysia†; United American, Singapore.
Ferric ammonium citrate (p.1938·1); vitamins; minerals (p.1922·1).
Dietary supplement; iron deficiency; iron-deficiency anaemia.

Great Eastern, Thai.; Pediatrica, Thai.
Multivitamin and mineral preparation with iron (p.1922·1).
Iron-deficiency anaemia; nutritional supplement.

Nutroplex with Iron & Lysine *United American, Hong Kong; United American, Malaysia; United Laboratories, Philipp.; United American, Singapore.*
Multivitamin and mineral preparation with iron and lysine (p.1922·1).
Nutritional supplement; tonic.

Nutroplex Lysine *Great Eastern, Thai.; Pediatrica, Thai.*
Multivitamin and mineral preparation with iron and lysine (p.1922·1).
Iron-deficiency anaemia; nutritional supplement.

Nutrosa *Nutricia-Bago, Arg.*
Glucose (p.1945·3).
Dietary supplement.

Nutrotal *Metro, Philipp.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1); ubidecarenone (p.2407·2); lycopene (p.2335·2); lutein (p.1954·3); minerals; vitamins; garlic (p.2309·2); taurine; radix poligonium multiflori (p.1922·1).
Nutritional supplement.

Nutrox *Tyson, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Nutrozyme
Note. This name is used for preparations of different composition.
Cipla, India.
Capsules: Amylase (p.2256·3); pepsin (p.2365·1).

Cipla, India.
Syrup; tablets: Amylase (p.2256·3); papain (p.2362·3); simeticone (p.1770·2); nicotinamide (p.1957·3); charcoal (p.1435·2).

Nuvacthen *IFET (ΙΦΕΤ), Gr.*
⊗ Tetracosactide (p.1543·3).
Adrenocorticotrophic hormone.

Nuvacthen Depot *Novartis, Spain.*
⊗ Tetracosactide hexa-acetate (p.1544·1).
Adrenocorticotrophic hormone.

Nuvapen *Reig Jofre, Spain.*
Ampicillin sodium (p.204·1).
Bacterial infections.

NuvaRing *Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Canad.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hung.; Organon, Irl.; Organon, Ital.; Organon, Mex.; Organon, Neth.; Organon, Norw.; Organon, Port.; Organon, Rus.; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, USA.*
Etonogestrel (p.2103·1); ethinylestradiol (p.2101·3).
Contraceptive vaginal ring.

Nuvelle *Schering, Denm.; Shepa, Gr.†; Schering, Irl.†; Schering, Ital.; Bayer, NZ; Bayer, Port.; Schering, Spain; Bayer, UK.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Nuvelle Continuous *Bayer, UK.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Nuvelle TS *Farmades, Ital.†.*
Phase I patches, estradiol (p.2097·2); phase II patches, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Nu-Verap *Nu-Pharm, Canad.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Nuvigil *Cephalon, USA.*
⊗ Armodafinil (p.2150·3).
Narcoleptic syndrome; obstructive sleep apnoea; shift-work sleep disorder.

Nuvir *Organon, India.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; osteoporosis.

Nuvision *Guardian, Indon.*
Myrtillus (p.2349·3); vitamin A; betacarotene; vitamin E; lutein (p.1954·3); zeaxanthin (p.1999·1); selenium; zinc (p.1922·1).
Supplement for healthy eyes.

Nuvit *Pharmaland, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anorexia; neurasthenia; neurological disorders; neuropathy; toxaemia of pregnancy.

Nuvoclav *Mugi, Indon.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Nuvorell *Sanorell, Ger.*
Homoeopathic preparation.

Nux Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Nux Vomica N Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Nux Vomica-Homaccord *Peithner, Austria.*
Homoeopathic preparation.

Nux Vomica-Injeel *Peithner, Austria†.*
Homoeopathic preparation.

Nuxal *Pfluger, Ger.*
Homoeopathic preparation.

Nuxil *Dolisos, Canad.†.*
Homoeopathic preparation.

Nuzac *Cipla, India.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Nuzak *Cipla-Medpro, S.Afr.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Nyaderm *Taro, Canad.*
Nystatin (p.543·2).
Fungal and bacterial infections.

Nyal Bronchitis *Valeant, Austral.*
Ammonium chloride (p.1551·3).

Nyal Chesty Cough *ICN, Austral.†.*
Guaifenesin (p.1561·3); glucose (p.1945·3); treacle (p.1969·3).
Coughs; upper respiratory-tract congestion.

Nyal Cold Sore *Valeant, Austral.*
Cream: Menthol (p.2340·1); camphor (p.2273·2).
Cracked lips; herpes labialis.

Nyal Decongestant *Valeant, Austral.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Nyal Dry Cough *ICN, Austral.†.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Nyal Medithroat Anaesthetic Lozenges *ICN, Austral.†.*
Hexylresorcinol (p.1647·1).
Sore mouth and throat.

Nyal Medithroat Gargle *ICN, Austral.†.*
Povidone-iodine (p.1659·2).
Sore throat.

Nyal Plus+ Allergy Relief *ICN, Austral.†.*
Promethazine hydrochloride (p.588·2).

Nyal Plus+ Chesty Cough *ICN, Austral.†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Nyal Plus+ Cold & Flu *ICN, Austral.†.*
Codeine phosphate (p.37·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Nyal Plus+ Day & Night Cold & Flu *ICN, Austral.†.*
Day tablets, paracetamol (p.108·1); codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Nyal Plus+ Day Night Sinus Relief *ICN, Austral.†.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Upper respiratory-tract congestion.

Nyal Plus+ Decongestant *ICN, Austral.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Nyal Plus+ Decongestant Antihistamine *ICN, Austral.†.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).

Nyal Plus+ Dry Cough *ICN, Austral.†.*
Pholcodine (p.1570·2).
Coughs.

Nyal Plus+ Sinus Relief with Antihistamine *ICN, Austral.†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).

Nyal Sinus Relief *ICN, Austral.†.*
Phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract congestion.

Nyal Toothache Drops *Valeant, Austral.*
Benzocaine (p.1854·1); phenol (p.1656·1).
Toothache.

Nycodol *Nycomed, Austria.*
Tramadol hydrochloride (p.130·3).
Pain.

Nycoplus B-Tonin *Nycomed, Norw.*
Vitamin B substances (p.1922·1); caffeine (p.1116·3).
Tonic; vitamin B deficiency.

Nycoplus B-total *Nycomed, Norw.*
Vitamin B substances (p.1922·1).
Vitamin B supplement.

Nycoplus Calcigran *Nycomed, Norw.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Nycoplus C-vitamin *Nycomed, Norw.*
Ascorbic acid (p.1983·3) or calcium ascorbate (p.1984·1).
Vitamin C deficiency.

Nycoplus E *Nycomed, Norw.*
d-Alpha tocopherol (p.1992·2) or *d*-alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Nycoplus Ferro-Retard *Nycomed, Norw.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Nycoplus Neo-Fer *Nycomed, Norw.*
Ferrous fumarate (p.1938·3).
Iron deficiency; iron-deficiency anaemia.

Nycopren *Nycomed, Austria; Sanofi Synthelabo, Neth.†; Nycomed, Switz.; Ardern, UK†.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Nycopren-E *Nycomed, Gr.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Nycovir *Nycomed, Austria.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpes simplex infections; varicella-zoster infections.

Nydrazid *Apothecon, USA.*
Isoniazid (p.288·1).
Tuberculosis.

Nyefax *Douglas, Austral.; Douglas, NZ; Douglas, Thai.; TTN, Thai.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Nylax with Senna *Crookes Healthcare, UK.*
Senna (p.1769·2).
Constipation.

Nylex *Proel, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Nylipark *Pharmanik (Φαρμανικ), Gr.†.*
Sulpiride (p.1028·3).
Psychoses.

Nymiko *Sanbe, Indon.*
Nystatin (p.543·2).
Candidiasis.

Nyogel *Novartis, Austral.; Novartis, Belg.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Irl.; Novartis, Ital.; Novartis, NZ†; Novartis, Neth.; Novartis, Port.; Adcock Ingram, S.Afr.; Novartis, UK.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Nyolol *Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel; Novartis, Malaysia†; Novartis, Mex.; Europhta, Mon.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis Ophthalmics, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Venez.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Nyoxep *Medimar, Gr.*
Ketoconazole (p.539·1).
Fungal scalp disorders.

Nypine *Arrow, Austral.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

NyQuil *Procter & Gamble, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Coughs and cold symptoms.

NyQuil Hot Therapy *Richardson-Vicks, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2).
Coughs and cold symptoms.

NyQuil Nighttime Cold/Flu *Richardson-Vicks, USA.*
Pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Nyquil Sinus *Procter & Gamble, Canad.*
Phenylephrine hydrochloride (p.1568·1); doxylamine succinate (p.578·2); paracetamol (p.108·1).

Nyrin
BPL-Meizler, Braz.†.
Calcium levofolinate (p.1943·3).
Adjuvant to chemotherapy; anaemia; antidote to folic acid antagonists.

Korean United, Malaysia.
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; megaloblastic anaemia; rescue after high-dose methotrexate.

Nysconitrine *Therabel, Belg.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Nysmosons-V *Sons, Mex.*
⊗ Metronidazole (p.837·1); nystatin (p.543·2); fluocinolone acetonide (p.1531·3).
Vaginal infections.

Nystacid *Pharmacare, S.Afr.*
Nystatin (p.543·2).
Candidiasis.

Nystacortone *Spirig, Switz.†.*
⊗ Prednisolone acetate (p.1541·1); nystatin (p.543·2); chlorhexidine hydrochloride (p.1635·3).
Infected skin disorders.

Nystaderm *Dermapharm, Austria; Dermapharm, Ger.*
Nystatin (p.543·2).
Fungal infections.

Nystaderm comp *Dermapharm, Ger.*
⊗ Nystatin (p.543·2); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Nystaform *Bayer, Irl.†; Typharm, UK.*
Nystatin (p.543·2); chlorhexidine hydrochloride (p.1635·3).
Fungal and bacterial skin infections.

Nystaform-HC
Bayer, Irl.†.
⊗ Nystatin (p.543·2); chlorhexidine hydrochloride (p.1635·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Typharm, UK.
⊗ Nystatin (p.543·2); chlorhexidine acetate (p.1635·2) or chlorhexidine hydrochloride (p.1635·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Nystalocal *Organon, Ger.; Medinova, Switz.*
⊗ Dexamethasone (p.1526·1); chlorhexidine hydrochloride (p.1635·3); nystatin (p.543·2).
Infected skin disorders.

Nystamont *IFET (ΙΦΕΤ), Gr.†; Rosemont, UK†.*
Nystatin (p.543·2).
Candidiasis.

Nystamysyn *Farmasyn, Gr.*
Nystatin (p.543·2).
Fungal infections.

Nystan *BMS, UK.*
Nystatin (p.543·2).
Fungal infections.

Nystin *Polipharm, Thai.*
Nystatin (p.543·2); diiodohydroxyquinoline (p.832·1); benzalkonium chloride (p.1629·1).
Vaginal infections.

Nystop *Paddock, USA.*
Nystatin (p.543·2).
Candidiasis.

Nytamel *Clonmel, Irl.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Nytcold Medicine *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Nytol *GSK Consumer, Canad.; GSK, Israel; Stafford-Miller, Ital.†; GSK, Mex.; GSK Consumer, Port.†; GSK Consumer, Spain; GSK Consumer, UK; Block, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Nytol Herbal *GSK Consumer, UK.*
Lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Formerly contained lupulus, Jamaica dogwood, passion flower, pulsatilla, and wild lettuce.
Insomnia.

Nytol Natural Source *GSK Consumer, Canad.*
Valerian (p.2410·1).
Insomnia.

Nyzoc *Nycomed, Austria.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

N-Zen *TC Pharma-Chem, Thai.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

O A R *Colgate Oral Care, Austral.†.*
Sodium nitrite (p.1464·3).
Rust prevention in disinfecting solutions. Not for use on human skin.

O-4 Cycline *Garec, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

OA
Note. This name is used for preparations of different composition.
Mead Johnson, Fr.
Food for special diets (p.1922·1).
Methylmalonic acidaemia; propionic acidaemia.

Interbat, Indon.
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; selenium; zinc (p.1922·1).
Osteoarthritis.

OA Forte *Interbat, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; selenium; zinc; vitamin E (p.1922·1).
Osteoarthritis.

OA Plus *Interbat, Indon.*
Glucosamine (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; selenium; zinc; vitamin E (p.1922·1); dimethyl sulfone (p.2294·1); boron; collagen (p.2286·1).
Osteoarthritis.

OAC Hp7 *AstraZeneca, Philipp.*
Clarithromycin (p.248·2); amoxicillin (p.202·2); omeprazole (p.1753·1).
Helicobacter pylori eradication in peptic ulcer disease.

Oasil *Gap, Gr.*
Chlordiazepoxide hydrochloride (p.968·2).
Anxiety disorders.

Oaxen *Rafarm, Gr.*
Butamirate citrate (p.1553·1).
Cough.

OB Complete *Vertical, USA.*
A range of vitamin and mineral preparations with or without docosahexaenoic acid (p.1922·1).

OB Max *InterMed, Philipp.; Tynor, Philipp.*
Vitamin and mineral preparation with taurine (p.1922·1).
Pre- and post-natal nutritional supplement.

OB Smart SG *InterMed, Philipp.; Tynor, Philipp.*
Vitamins; minerals; taurine; docosahexaenoic acid (p.1362·1); eicosapentaenoic acid (p.1362·1) (p.1922·1).
Pre-natal nutritional supplement.

Obaron *Mepha, Switz.†.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia.

Obat Kutu Rambut Cap Dua Jempol *Konimex, Indon.*
Lindane (p.2045·3).
Pediculosis.

Obbekjaers *Bennett, UK.*
Peppermint oil (p.1761·2).
Irritable bowel syndrome.

Obcin *Scanpharm, Philipp.*
Oxytocin (p.2015·2).
Labour induction; postpartum haemorrhage.

Obdhamin *Solas, Indon.*
Vitamins; minerals; rofufa (docosahexaenoic acid); omega-3; lecithin (p.1922·1).
Nutritional supplement for pregnancy and lactation.

Obecirol *Farmedia, Gr.*
⊗ Budesonide (p.1520·1).
Allergic disorders.

Obeclox *Medix, Mex.*
⊗ Clobenzorex hydrochloride (p.2152·3).
Obesity.

Obeflorine *Lehning, Fr.*
Bladderwrack (p.2384·2); cichorium intybus; couchgrass (p.2288·2); equisetum (p.2299·3); ash leaves (p.2262·1).
Formerly contained bladderwrack, senna leaflets, liquorice root, and ash leaves.
Obesity.

Obegyn Prenatal *Fleming, USA.*
Multivitamin preparation (p.1922·1).

Obendol *Vitae, Mex.*
⊗ Mazindol (p.2157·3).
Obesity.

Oberdol *Diafarm, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Obesan-X *Technikon, S.Afr.*
⊗ Phendimetrazine tartrate (p.2162·1).
Obesity.

Obesidex *Bunker, Braz.†.*
Phenolphthalein (p.1762·1); bladderwrack (p.2384·2); thyroid (p.2177·1).
Obesity.

Obesifran *Faria, Braz.†.*
Phenolphthalein (p.1762·1); bladderwrack (p.2384·2); thyroid (p.2177·1).
Obesity.

Obestat *Cipla, India.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Obetine *Alpro, Spain.*
Almagate (p.1705·1).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Obex-LA *Adcock Ingram, S.Afr.*
⊗ Phendimetrazine tartrate (p.2162·1).
Obesity.

OBH *Berlico Mulia, Indon.*
⊗ Liquorice (p.1740·3); ammonium chloride (p.1551·3); anise oil (p.2258·2); peppermint oil (p.1761·2); lemon oil (p.2332·3); alcohol (p.1625·2).
Cough.

OBHdryl *Ikapharmindo, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); liquorice (p.1740·3); SASA.
Cough.

Obical *Medifarma, Indon.*
Calcium carbonate (p.1714·1); magnesium; phosphorus; colecalciferol; fructo oligosaccharide (p.1922·1).
Calcium deficiency; calcium supplement; osteoporosis.

Obifax *Bioiberica, Spain†.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Obifen *Ayrton, UK.*
Ibuprofen (p.64·2).

Obimin *Westmont, Hong Kong; Westmont, Malaysia; Westmont, Singapore.*
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement during pregnancy and lactation.

Obimin-AF *Medifarma, Indon.; Great Eastern, Thai.; Westmont, Thai.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement during pregnancy and lactation.

Obimin-AZ *Great Eastern, Thai.; Westmont, Thai.*
Ferrous fumarate (p.1938·3); vitamins; minerals (p.1922·1).
Nutritional supplement during pregnancy and lactation.

Obimol *Ayrton, UK.*
Paracetamol (p.108·1).

Obinese *Pfizer, Mex.*
Chlorpropamide (p.438·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

O-Biol *Biol, Arg.*
Nystatin (p.543·2); neomycin sulfate (p.305·1); nitrofurazone (p.309·1); vitamin A (p.1971·2).
Vaginal infections.

O-Biol P *Biol, Arg.*
Nystatin (p.543·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Vaginal infections.

O-Biotic *Zwitter, Gr.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Inflammatory eye disorders.

Obipluz *Darya-Varia, Indon.*
Vitamins; minerals; fish oil; omega-3 fish oil (p.1362·2)(p.1922·1).
Nutritional supplement for pregnancy and lactation.

Obiron Extra *Pfizer Consumer, Austral.†.*
Multivitamin and iron preparation (p.1922·1).

Oblant *Degorts, Mex.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Oblax A-1-1 *Knop, Chile.*
Phenolphthalein (p.1762·1); magnesium oxide (p.1744·1); marine algae.
Bowel evacuation; constipation.

Obleas Chinas *Maver, Chile.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold symptoms.

Obliterol *Faes, Spain†.*
Pantethine (p.1365·3).
Hyperlipidaemias.

Obocil *Samarth, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Obogen *Oboi, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Oboliz *Rafarm, Gr.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Obosan *Rafarm, Gr.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Obracin *EuroCept, Belg.; EuroCept, Neth.; Lilly, Switz.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Obrasone *Cadila, India.*
⊗ Tobramycin sulfate (p.354·2); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Obron-6 *Pfizer, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement for pregnancy and lactation.

Obry *Grin, Mex.*
Tobramycin (p.354·1).
Bacterial eye infections.

Obrydex *Grin, Mex.*
⊗ Tobramycin (p.354·1); dexamethasone phosphate (p.1526·2).
Bacterial eye infections with inflammation.

Obrypre *Grin, Mex.*
⊗ Tobramycin (p.354·1); prednisolone acetate (p.1541·1).
Bacterial eye infections with inflammation.

Obsidan
Note. This name is used for preparations of different composition.
Verman, Fin.
Ferrous glycine sulfate (p.1939·1).
Iron deficiency; iron-deficiency anaemia.

Alpharma-Isis, Ger.; Schwarz, Rus.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; hypertrophic cardiomyopathy; migraine; myocardial infarction; tremor.

Obsidan comp *Verman, Fin.*
Ferrous glycine sulfate (p.1939·1); folic acid (p.1940·1).
Iron and folic acid deficiency.

Obsilazin N *Alpharma-Isis, Ger.†.*
⊗ Propranolol hydrochloride (p.1380·3); dihydralazine sulfate (p.1264·3).
Hypertension.

Obstetrix *Seyer, USA.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Obstinol M *UCB, Ger.*
Liquid paraffin (p.2030·3).
Bowel regulation.

Obstipar *Tecnifar, Port.*
Lactulose (p.1738·2).
Constipation.

Obteran *Prafa, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Obtrex *Pronova, USA.*
Multivitamin and mineral preparation (p.1922·1).

Obusforme
Note. This name is used for preparations of different composition.
Wampole, Canad.†.
Aspirin (p.20·3); methocarbamol (p.1897·3).

Wampole, Canad.†.
Paracetamol (p.108·1); methocarbamol (p.1897·3).

Obusonid *Velka, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Obutin *Hanlim, Singapore.*
Oxybutynin hydrochloride (p.2190·3).
Urinary-tract disorders.

Obynal-M *Medi-Rx, Philipp.*
Vitamin and mineral preparation (p.1922·1).
Pre- and post-natal nutritional supplement.

Ocacin *Novartis, Spain.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye infections.

Ocadrik *Aventis, Fr.†.*
Verapamil (p.1423·2); trandolapril (p.1416·2).
Hypertension.

Ocal
Note. A similar name is used for preparations of different composition (see below).
Omega, Belg.
Mercuric oxycyanide (p.2342·2); boric acid (p.2268·1); sodium chloride (p.1686·1).
Conjunctival inflammation and irritation.

O-Cal
Note. A similar name is used for preparations of different composition (see above).
Pharmics, USA.
A range of vitamin and mineral preparations with iron and folic acid (p.1922·1).

O-Cal Prenatal *Pharmics, USA.*
Vitamin and mineral preparation (p.1922·1).

Occhivit *Giuliani, Ital.†.*
Multivitamin and mineral preparation with myrtillus (p.1922·1).
Nutritional supplement.

Occidal *Ranbaxy, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Occlusal *Medicis, Canad.†; Alliance, Irl.; Alliance, UK; GenDerm, USA.*
Salicylic acid (p.1612·2).
Warts.

Occodem *Pharno-Wedropharm, Ger.*
Homoeopathic preparation.

Occu System *Jagson, India†.*
Hypromellose (p.2144·2).
Dry eyes.

Ocean *Fleming, USA.*
Sodium chloride (p.1686·1).
Nasal irritation.

Ocean Spray *Kivema, Israel.*
Sodium chloride (p.1686·1).
Nasal dryness.

Oceantone *Cantassium Co., UK.*
Green-lipped mussel (p.2317·2).

Ocefax *Roux-Ocefa, Arg.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Oceral *Viatris, Austria; Roche, Braz.; Medika, Switz.; Roche, Turk.*
Oxiconazole nitrate (p.544·2).
Mixed fungal and Gram-positive bacterial infections.

Oceral GB *Yamanouchi, Ger.†.*
Oxiconazole nitrate (p.544·2).
Fungal infections.

Ochozim *Italmex, Mex.*
Pepsin (p.2365·1); trypsin (p.2405·3); chymotrypsin (p.2281·3); amylase (p.2256·3); lipase (p.2360·3); cellulase (p.2279·1); rennet; ox bile extract (p.2266·3); dimeticone (p.1770·2).
Gastrointestinal disorders.

Ocid *Cadila, India; Cadila, Rus.; Zydus Cadila, Singapore.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ociderm-N *Pyridam, Indon.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Ocimix *Panacea, India.*
Ornidazole (p.843·1); ciprofloxacin (p.243·3).
Gastrointestinal infections.

OCL *Abbott, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Oclovir *Roux-Ocefa, Arg.†.*
Rimantadine hydrochloride (p.904·2).
Influenza.

OCM *Gobbi, Arg.*
Chlordiazepoxide hydrochloride (p.968·2).

Ocoxin *SM, Venez.*
Arginine; cysteine; ascorbic acid; zinc sulfate; green tea; manganese sulfate; cinnamon; pyridoxal (p.1922·1).

Ocplex *Octapharma, Cz.; Octapharma, Swed.*
Factor VIII inhibitor bypassing fraction (p.1068·2).
Haemorrhagic disorders.

Ocrix *Biomep, Mex.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Ocsaar *MSD, Israel.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension.

Ocsaar Plus *MSD, Israel.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Octacosanol *Cantassium Co., UK.*
Vitamin E (p.1992·2); octacosanol (p.1373·3).

Octadon P *UCB, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Octafix *Octapharma, Fr.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Octagam *Octapharma, Austral.; Octapharma, Austria; Octapharma, Belg.; Itaca, Braz.†; Bago, Chile†; Octapharma, Cz.; Octapharma, Denm.; Octapharma, Fin.; Octapharma, Fr.; Octapharma, Ger.; IFET (ΙΦΕΤ), Gr.; Octapharma, Gr.; Octapharma, Hong Kong; Octapharma, Hung.; Octapharma, Mex.; Octapharma, NZ; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Rus.; Octapharma, Swed.; Octapharma, Switz.; Octapharma, Thai.; Berk, Turk.; Octapharma, UK; Octapharma, USA.*
Normal immunoglobulin (p.2225·3).
Bone-marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation; primary immunodeficiency; thrombocytopenic purpura.

Octagamocta *Octapharma, Spain.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; immunodeficiency disorders.

Octaglob D *Octapharma, Mex.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Octalbin *Octapharma, Denm.; Octapharma, Fin.; Dankos, Indon.; Octapharma, Mex.; Octapharma, Spain.*
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; hypoproteinaemia; plasma volume expansion.

Octalbine *Octapharma, Fr.; Octapharma, Neth.*
⊗ Albumin (p.1052·1).
Hypovolaemia.

Octamide *Adria, USA.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Octanate *Varifarma, Arg.; Octapharma, Austria; Bago, Chile†; Octapharma, Cz.; Octapharma, Ger.; Octapharma, Gr.; Octapharma, Hung.; Octapharma, Mex.; Octapharma, NZ; Octapharma, Port.; Octapharma, Rus.; Octapharma, Spain; Octapharma, Switz.; Octapharma, Thai.; Berk, Turk.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Octanine *Varifarma, Arg.; Octapharma, Austria; Octapharma, Belg.; Octapharma, Cz.; Octapharma, Ger.; Octapharma, Rus.; Octapharma, Thai.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Octanine F *Octapharma, Hung.; Octapharma, Mex.; Octapharma, Switz.; Berk, Turk.*
Factor IX (p.1068·3).
Haemophilia B.

Octaninef *Octapharma, Port.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Octanyl *Bago, Arg.*
Bromazepam (p.964·3).
Anxiety.

Octanyne *Itaca, Braz.†; Bago, Chile†; Berk, Turk.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Octaplas *Octapharma, Austria; Octapharma, Cz.; Octapharma, Fin.; Octapharma, Ger.; Kedrion, Ital.; Octapharma, Mex.; Octapharma, NZ; Octapharma, Neth.; Octapharma, Norw.; Octapharma, Port.; Octapharma, Swed.; Octapharma, Switz.; Octapharma, UK.*
Plasma (p.1075·2).
Haemorrhagic disorders; reversal of oral anticoagulant effects; thrombocytopenic purpura.

Octaplex *Octapharma, Austria; Octapharma, Ger.; Octapharma, Port.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Octatit *Octapharma, Mex.*
An antithrombin III preparation (p.1054·1).
Antithrombin III deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Octatron *VAAS, Ital.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Octavi *Itaca, Braz.†.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Octegra *Bago, Arg.†; Bayer, Austria; Bago, Chile†; Elpen (Ελπεν), Gr.; Bayer, Hung.; Innova, Ital.; Bayer, Neth.; Vita, Spain.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Octelmin *Schering-Plough, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Octeniderm *Schulke & Mayr, Austria; Farmex, Gr.; Schulke & Mayr, Switz.*
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); octenidine hydrochloride (p.1654·3).
Skin disinfection.

Octenisept *Schulke & Mayr, Austria; Schulke & Mayr, Ger.; Farmex, Gr.; Schulke & Mayr, Switz.*
Octenidine hydrochloride (p.1654·3); phenoxyethanol (p.1657·1).
Skin and mucous membrane disinfection; wounds.

Octex *Degorts, Mex.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Octiban *Degorts, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Octicair *Bausch & Lomb, USA†.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Octil *Genpharm, Israel†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Octilia *Craveri, Arg.†; Bouty, Ital.; SIFI, Rus.; SIFI, Singapore†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation and congestion.

Octim *Ferring, Fr.; Ferring, UK.*
Desmopressin acetate (p.2185·3).
Haemorrhage.

Octin *Cipla-Medpro, S.Afr.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Octinum *Abbott, Turk.*
⊗ Isometheptene hydrochloride (p.2327·1).

Octinum-D *Pharmalex (Φαρμαλεξ), Gr.†.*
Octamylamine (p.2356·1).
Smooth muscle spasm.

Octiveran *Rafarm, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Octocaine *Clarben, Port.; Clarben, Spain; Novocol, USA.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Octodiol *Servier, Cz.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Octofene *Fournier, Fr.†; Fournier, Ital.†; Fournier, Port.†.*
Clofoctol (p.255·3).
Bacterial infections of the respiratory tract.

Octonativ-M *Octapharma, Swed.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Octonox *Pharmacobel, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Octopil *Talcris, Arg.†.*
Piroctone (p.1610·1).
Dandruff.

Octorax *Demo, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Octostim *Ferring, Arg.; Ferring, Austral.; Ferring, Austria; Ferring, Braz.†; Ferring, Canad.; Ferring, Chile; Ferring, Denm.; Ferring, Fin.; Ferring, Ger.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Israel; Ferring, Mex.; Ferring, NZ; Pharmaco, NZ; Ferring, Neth.; Ferring, Norw.; Ferring, Singapore†; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Er-Kim, Turk.*
Desmopressin acetate (p.2185·3).
Diabetes insipidus; haemorrhagic disorders; platelet dysfunction; stimulation of factor VIII activity; uraemia; von Willebrand's disease.

Octrene *Pharmafabre (Φαρμαφαμπρ), Gr.*
Chlorhexidine (p.1635·2); chlorocresol (p.1640·1); hexamidine (p.1646·3).
Disinfection.

Octreoscan *BSM, Austria; Mallinckrodt, Cz.; Tyco, Ital.; Mallinckrodt, Port.; Mallinckrodt, USA.*
Indium-111 pentetreotide (p.2054·1).
Detection and location of neuroendocrine and carcinoid tumours.

OctreoScan *Mallinckrodt, Neth.*
Indium-111 (p.2054·1) pentetreotide.
Diagnosis of gastrointestinal endocrine tumours.

Ocubrax *Alcon, Belg.; Alcon, Hung.†; Alcon Cusi, Spain; Alcon, Turk.*
Diclofenac sodium (p.44·3); tobramycin (p.354·1).
Ocular inflammation and infection following eye surgery.

Ocu-Caine *Ocumed, USA.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

OcuCaps *Akorn, USA.*
Antoxidant, vitamin, and mineral supplement (p.1922·1).

Ocu-Carpine *Ocumed, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Ocuclear *Schering-Plough, Mex.†; Schering-Plough, USA†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis; minor eye irritation.

Ocucoat
Note. This name is used for preparations of different composition.
Storz, Israel.
Hypromellose (p.2144·2).
Adjunct in ocular surgery.
Bausch & Lomb, USA.
Eye drops: ⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.
Bausch & Lomb, USA.
Ocular syringe: Hypromellose (p.2144·2).
Adjunct in ocular surgery.

Ocudiafan *Eczane, Arg.†.*
⊗ Tetryzoline (p.1574·1).
Eye congestion.

Ocudol *Oftalmi, Venez.*
Ketorolac trometamol (p.74·2).
Inflammatory eye disorders.

Ocufen *Allergan, Austral.; Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Fr.; Allergan, Hong Kong†; Allergan, Irl.†; Allergan, Ital.; Allergan, Mex.; Allergan, NZ†; Allergan, S.Afr.; Allergan, Singapore†; Allergan, UK; Allergan, USA; Allergan, Venez.†.*
Flurbiprofen sodium (p.61·2).
Intra-operative miosis inhibition; maintenance of mydriasis during cataract extraction; postoperative eye inflammation; prevention of cystoid macular oedema.

Ocuflox *Allergan, Austral.; Allergan, Canad.; Allergan, Mex.; Allergan, USA.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Ocuflur *Allergan, Austria†; Allergan, Belg.; Allergan, Cz.†; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hung.†; FDC, India; Allergan, Port.†; Allergan, Spain; Allergan, Switz.*
Flurbiprofen sodium (p.61·2).
Intra-operative miosis inhibition; postoperative eye inflammation; prevention of cystoid macular oedema following cataract surgery.

Ocufort *Farmila, Ital.†.*
Multivitamin and mineral preparation (p.1922·1).
Eye disorders; nutritional supplement.

Ocufree *Centaur, India.*
Multivitamin preparation with selenium and zinc (p.1922·1).
Eye disorders.

Ocufri *Allergan, Norw.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Ocugel *Viatris, Belg.*
Carbomer 974P (p.2141·3).
Dry eyes.

Ocuhist *Pfizer Consumer, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye irritation and pruritus.

Oculac *Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis Ophthalmics, Swed.; Novartis, Switz.*
Povidone (p.2146·1) (p.1622·2).
Contact lens wetting solution; dry eyes.

Oculastin *Viatris, Austria; Thea, Neth.; Meda, Port.; Thea, Switz.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Oculerge *Pharmacare, S.Afr.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic conjunctivitis.

Oculex
Interbat, Indon.
Capsules: Myrtillus (p.2349·3); lutein (p.1954·3); betacarotene; vitamin A; vitamin B ; vitamin C; vitamin E; zinc; selenium (p.1922·1).
Eye disorders.
Interbat, Indon.
Syrup: Myrtillus (p.2349·3); lutein (p.1954·3); betacarotene; vitamin A; vitamin B ; vitamin E (p.1922·1).
Eye disorders.

Oculoforte *Restan, S.Afr.†.*
⊗ Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1); tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Oculoheel *Peithner, Austria.*
Homoeopathic preparation.

Oculosan
Note. This name is used for preparations of different composition.
Novartis, Chile; Novartis, Gr.; Novartis, Hong Kong; Novartis, Philipp.; Novartis, Pol.; Adcock Ingram, S.Afr.; Novartis, Thai.
⊗ Zinc sulfate (p.1999·2); naphazoline nitrate (p.1565·2).
Conjunctivitis; eye irritation; irrigation of tear ducts.
Novartis, Indon.
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2); hamamelis (p.2318·2); orange flower water; lavender water; euphrasia.
Eye irritation.
Novartis, Malaysia†.
⊗ Zinc sulfate (p.1999·2); naphazoline hydrochloride (p.1565·2).
Conjunctivitis; eye irritation.
Novartis, Switz.
⊗ Zinc sulfate (p.1999·2); naphazoline nitrate (p.1565·2); hamamelis (p.2318·2); euphrasia (p.2301·3); neroli oil (p.2351·1); lavender oil (p.2331·2).
Eye irritation.

Oculosan N *Novartis, Ger.*
⊗ Zinc sulfate (p.1999·2); naphazoline nitrate (p.1565·2).
Conjunctivitis.

Oculotec *Novartis, Chile.*
Povidone (p.2146·1).
Dry eyes.

Oculotect
Note. This name is used for preparations of different composition.
Novartis, Austria; Novartis, Belg.; Novartis, Gr.; Novartis, Malaysia; Novartis, Neth.; Novartis, Philipp.; Novartis, Port.; Novartis, Spain; Novartis, Turk.; Novartis, UK.
Povidone (p.2146·1).
Dry eyes.
Novartis, Indon.
Vitamin A palmitate (p.1973·1); carbomer 980 (p.2141·3).
Dry eyes.
Novartis Ophthalmics, Singapore.
Povidone (p.2146·1) (p.1622·2).
Dry eyes; wetting solution for contact lenses.
Novartis, Switz.
Vitamin A palmitate (p.1973·1).
Corneal damage; dry eyes.
Novartis, Ger.
Eye drops: Vitamin A palmitate (p.1973·1); hypromellose (p.2144·2).
Dry eyes.
Novartis Ophthalmics, Hung.; Novartis, Pol.
Eye drops: Povidone (p.2146·1).
Dry eyes.
Novartis, Pol.
Eye gel: Vitamin A palmitate (p.1973·1); carbomer 980 (p.2141·3).
Dry eyes.
Novartis, Ger.; Novartis Ophthalmics, Hung.
Ocular gel: Vitamin A palmitate (p.1973·1).
Eye disorders.

Oculotect Fluid *Novartis, Ger.*
Povidone (p.2146·1).
Dry eyes.

Oculotect sine *Novartis, Ger.*
Vitamin A palmitate (p.1973·1).
Eye disorders.

Ocu-Lube *Ocumed, USA.*
White soft paraffin (p.2031·2).
Dry eyes.

Ocumed *Promed, Rus.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ocu-Mycin *Ocumed, USA.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Ocu-Pentolate *Ocumed, USA.*
Cyclopentolate hydrochloride (p.1879·3).

Ocu-Phrin *Ocumed, USA.*
Phenylephrine hydrochloride (p.1568·1).

Ocupol *Centaur, India.*
Polymyxin B sulfate (p.317·3); chloramphenicol (p.239·3).
Bacterial ear or eye infections.

Ocupol-D *Centaur, India.*
⊗ Polymyxin B sulfate (p.317·3); chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Infected inflammatory ear or eye disorders.

Ocupred *Oftalmi, Venez.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Ocupres
Note. A similar name is used for preparations of different composition (see below).
Cadila Pharma, India.
⊗ Timolol (p.1413·1).
Glaucoma; ocular hypertension.

Ocupres-E *Cadila, Rus.*
⊗ Timolol maleate (p.1412·3).

Ocupress
Note. A similar name is used for preparations of different composition (see above).
Genom, Braz.
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma.
Novartis Ophthalmics, USA†.
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Ocuprost *Biocumed, Arg.†.*
Latanoprost (p.1882·1).
Ocular hypertension.

Ocuprostim *Bausch & Lomb, Arg.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma.

Ocurax *Ipca, India.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ocurest *Centaur, India.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); menthol (p.2340·1); camphor (p.2273·2).
Eye irritation.

Ocurest-AH *Centaur, India.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); menthol (p.2340·1); camphor (p.2273·2); chlorphenamine maleate (p.571·3).
Conjunctivitis.

Ocurest-Z *Centaur, India.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2); menthol (p.2340·1); camphor (p.2273·2).
Eye irritation.

Ocusert *Allergan, NZ; Alza, USA†.*
Pilocarpine (p.1884·3).
Glaucoma; ocular hypertension.

Ocusoft Pads *Poen, Arg.†.*
Eyelid cleanser.

Ocusoft VMS *Poen, Arg.†; Ocusoft, USA.*
Multivitamin and mineral preparation (p.1922·1).

Ocusol *ANB, Malaysia; ANB, Thai.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium acetate; sodium citrate (p.1667·1).
Irrigation during eye surgery.

Ocuson *Sanbe, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Ocu-Spor-B *Ocumed, USA.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Eye infections.

Ocu-Spor-G *Ocumed, USA.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Eye infections.

Ocustil *SIFI, Ital.†.*
Sodium hyaluronate (p.2320·1).
Eye protection.

Ocustress
Note. This name is used for preparations of different composition.
Cipla, India.
⊗ Naphazoline hydrochloride (p.1565·2).
Eye disorders.
Farmila, Ital.
Multivitamin preparation with ubidecarenone and ginseng (p.1922·1).
Nutritional supplement.

Ocu-Sulf *Cipla, India.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Ocusulf *Optopics, USA.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Ocu-Tears *Ocumed, USA.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Ocutim *Cipla, India.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ocutob *Centaur, India.*
Tobramycin sulfate (p.354·2).
Bacterial eye infections.

Ocutob-D *Centaur, India.*
⊗ Tobramycin (p.354·1); dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Ocuton *Ritter, Hong Kong.*
⊗ Oxedrine hydrochloride (p.1364·3).
Eye irritation.

Ocutricin
Note. This name is used for preparations of different composition.
Bausch & Lomb, USA.
Eye drops: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Eye infections.
Bausch & Lomb, USA.
Eye ointment: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Eye infections.

Ocutrien *Cantassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Ocu-Trol *Ocumed, USA.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Infected eye disorders.

Ocu-Tropic *Ocumed, USA.*
Tropicamide (p.1886·2).

Ocu-Tropine *Ocumed, USA.*
Atropine sulfate (p.1219·3).

Ocuvit *Cadila, India.*
Vitamin C; vitamin e acetate (p.1922·1).
Antoxidant.

Ocuvite
Note. This name is used for preparations of different composition.
Bausch & Lomb, Arg.; Bausch & Lomb, Canad.; Lederle, Cz.†; Chauvin, Fr.; Bausch & Lomb, Ital.; Bausch & Lomb, Mex.; Bausch & Lomb, Philipp.; Lepori, Port.†; Intrapharm, UK; Bausch & Lomb, USA.
A range of vitamin and mineral preparations (p.1922·1).

Bausch & Lomb, Hong Kong; Mann, Irl.
Vitamin C; vitamin E; selenium; zinc; lutein; zeaxanthin (p.1922·1).
Nutritional supplement for healthy eyes.

Wyeth, Israel; Bausch & Lomb, Singapore.
Multivitamin and mineral preparation with lutein (p.1922·1).
Nutritional supplement for healthy eyes.

Ocuvite Extra *Bausch & Lomb, Mex.*
Vitamin and mineral preparation with glutathione (p.1922·1).

Ocuvite con Luteina *Bausch & Lomb, Mex.*
Vitamins minerals; lutein (p.1922·1).

Ocuvite PreserVision
Bausch & Lomb, Austral.
Betacarotene; vitamin C; vitamin E; zinc (p.1922·1).
Age-related macular degeneration.

Bausch & Lomb, Hong Kong; Bausch & Lomb, Singapore.
Vitamin A; vitamin C; vitamin E; zinc; copper (p.1922·1).
Nutritional supplement for healthy eyes.

Ocylin *Multilab, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Odaban *Petrus, Austral.†; Bracey, UK.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Odace *Darya-Varia, Indon.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Odamesol *Farmanic, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Odamida *Pelayo, Spain.*
Benzalkonium chloride (p.1629·1); zinc chloride (p.1999·1).
Mouth disorders.

Odanet *Pharmanik (Φαρμανικ), Gr.†.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Odanex *Saval, Chile.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Odasol *Genepharm, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oddibil *Gerot, Austria; Sanofi-Aventis, Braz.; Cooperation Pharmaceutique, Fr.; Nattermann, Ger.†.*
Fumitory (p.2307·2).
Biliary-tract disorders; digestive and renal disorders.

Oddispasmol *Ratiopharm, Austria.*
Fumitory (p.2307·2); ethaverine hydrochloride (p.2299·3).
Biliary disorders.

Odemase *Azupharma, Ger.†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Odemin *Santen, Fin.*
⊗ Acetazolamide (p.1875·1).
Epilepsy; glaucoma; oedema.

Odenil *Isdin, Spain.*
Amorolfine hydrochloride (p.523·1).
Fungal skin and nail infections.

Odeston *Pabianice, Rus.*
Hymecromone (p.2323·2).
Biliary-tract disorders.

Odetol *Medichem, Philipp.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Odexan *Sons, Mex.*
⊗ Ampoule I, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin acetate (p.1980·3); ampoule II, dexamethasone sodium phosphate (p.1526·2); lidocaine hydrochloride (p.1862·3).
Neuralgias; neuritis.

Odifam *Dynamic, Philipp.*
Rifampicin (p.325·3).
Meningococcal carriers; tuberculosis.

Odifex *Biochem, India.*
Fexofenadine hydrochloride (p.579·3).
Hypersensitivity reactions.

Odinah *Medichem, Philipp.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Odipin *Sustime, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Odirab *Biochem, India.*
Rabeprazole (p.1765·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Odiron *Medichem, Philipp.*
Vitamin B substances (p.1922·1); iron (p.1949·1).
Iron-deficiency anaemia.

Odiron-C
Medichem, Indon.; Medichem, Malaysia†; Medichem, Singapore.
Ferrous fumarate (p.1938·3); vitamin B substances; vitamin E (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Medichem, Philipp.
Vitamin B substances (p.1922·1); iron (p.1949·1); vitamin E.
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Odisor *Soria Natural, Spain†.*
Chamomile (p.2279·3); fumitory (p.2307·2); centaury (p.2279·1); boldo (p.2267·2).
Digestive disorders.

Odivir Kit *Cipla, India.*
Efavirenz (p.872·3); lamivudine (p.895·1); didanosine (p.870·2).
HIV infection.

Odnatron *Kleva, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Odo-fre *Self-Care Products, UK.*
Parsley seed oil (p.2363·2).

Odol Control Sarro *Colgate, Arg.†.*
Sodium fluoride (p.1962·2); sodium pyrophosphate (p.2390·3); sodium bicarbonate.
Dental caries prophylaxis.

Odol Med Antiplaca *Colgate, Arg.†.*
Sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3); triclosan (p.1665·2); allantoin; guaiazulene.
Dental caries prophylaxis.

Odol Tratamiento de Encias *Colgate, Arg.†.*
Sodium fluoride (p.1962·2); triclosan (p.1665·2); sodium bicarbonate.
Dental caries prophylaxis.

Odongel *Mintlab, Chile.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Odongi *Candioli, Ital.*
Benzalkonium chloride (p.1629·1); eugenol (p.2301·2); tetracaine (p.1871·2).
Dental caries.

Odonid *Daudt, Braz.*
Metronidazole (p.837·1).

Odontal *Streuli, Switz.*
Mint oil (p.2345·2); star anise oil (p.2392·2); clove (p.2284·3); cinnamon (p.2283·1); anise oil (p.2258·2).
Mouth and throat disorders.

Odontalg *Giovanardi, Ital.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Odontalgiche (Dentali) *AFOM, Ital.†; Farmatre, Ital.†; Nova Argentia, Ital.†; Ogna, Ital.†; Sella, Ital.†.*
Eugenol (p.2301·2); chlorobutanol (p.1639·2).
Dental pain.

Odontalgico Dr. Knapp con Vit. B1 *Montefarmaco, Ital.*
Paracetamol (p.108·1); propyphenazone (p.119·3); thiamine hydrochloride (p.1976·1); caffeine (p.1116·3).
Pain.

Odonticina *Pentafarma, Port.*
Roxithromycin (p.331·1).
Bacterial infections.

Odonto-Baby *Eurogenerics, Belg.*
Amylocaine (p.1853·3); chlorphenamine maleate (p.571·3); saffron.
Teeth and gum disorders.

Odontobiotic *Higate, Arg.†.*
Chlorhexidine (p.1635·2); aloe vera (p.1588·2); calendula (p.2273·1).
Mouth disorders.

Odontocromil c Sulfamida *Kin, Spain†.*
Ascorbic acid (p.1983·3); chlorophyllin copper complex sodium (p.1471·1); phenol (p.1656·1); sulfanilamide sodium (p.343·1); zinc chloride (p.1999·1); methyl salicylate (p.85·3); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth inflammation; mouth wounds.

Odonton-Echtroplex *Weber & Weber, Ger.*
Homoeopathic preparation.

Odontovac *Nikkho, Braz.†.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1); bacterial antigens.
Bacterial infections.

Odourless Garlic
Note. This name is used for preparations of different composition.
Blackmores, Austral.
Garlic (p.2309·2); parsley (p.2363·2).
Cold and influenza symptoms.

Vitaplex, Austral.†.
Garlic (p.2309·2); echinacea purpurea (p.2298·1); zinc gluconate (p.1999·2); betacarotene (p.1930·3).
Upper respiratory-tract congestion.

Odoxil *Lupin, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Odranal
Note. This name is used for preparations of different composition.
Raffo, Arg.
Bupropion (p.384·3).
Depression.

Raffo, Chile.
Oxybutynin (p.2190·3).
Neurogenic bladder.

Odric *Shinyaku, Jpn.*
Trandolapril (p.1416·2).
Hypertension.

Odrik *Aventis, Austral.; Asta Medica, Braz.†; Aventis, Denm.; Abbott, Fr.; Abbott, Gr.; Abbott, Irl.; Abbott, NZ; Abbott, Neth.; Vitoria, Port.; Alter, Spain; Sanofi-Aventis, UK†.*
Trandolapril (p.1416·2).
Heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

O-Due *Teofarma, Ital.*
Taurine (p.2395·2).
Vascular disorders.

Odupril *Pharmanik (Φαρμανικ), Gr.†.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Odven SBK *Bioquimed, Mex.*
Venlafaxine hydrochloride (p.427·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; social phobia.

Odycin *Velka, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Oecotrim *Fresenius Kabi, Austria.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Oedemex *Mepha, Switz.*
⊗ Furosemide (p.1292·1).
Forced diuresis; hypertension; oedema.

OeKolp *Kade, Ger.*
Estriol (p.2101·1).
Menopausal disorders; vaginal disorders.

Oekolp *Kade, Pol.*
Estriol (p.2101·1).
Vulvovaginal disorders associated with oestrogen deficiency.

Oemine *Phytobiolab, Fr.*
A range of nutritional supplements (p.1922·1).

Oenobiol *Oenobiol, Fr.*
A range of nutritional supplements (p.1922·1).

Oeparol *Agropharm, Pol.*
Evening primrose oil (p.2302·1).
Dietary supplement.

Oesclim *Paladin, Canad.; Andromaco, Chile†; Fournier, Cz.†; Fournier, Fr.; Fournier, Gr.†; Fournier, Hung.†; Fournier, Pol.; Selena, Swed.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Oesto-Mins *Tyson, USA.*
Multivitamin and mineral preparation (p.1922·1).

Oestraclin *Seid, Spain.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Oestring *Pfizer, Swed.*
Estradiol (p.2097·2).
Vaginal disorders due to oestrogen deficiency.

Oestro Gel *Rontag, Arg.*
Estradiol (p.2097·2).
Oestrogen deficiency.

Oestrodose *Besins, Fr.; Besins International, Israel; Seid, Spain†.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Oestro-Feminal
Note. This name is used for preparations of different composition.
Pfizer, Austria†.
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Pfizer, Switz.†.
Esterified oestrogens (p.2097·1).
Menopausal disorders; osteoporosis.

Oestrofeminal *Mack, Cz.†; Mack, Illert., Ger.†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Oestrogel *Besins, Belg.; Farmoquimica, Braz.; Besins, Cz.; Besins, Fr.; Faran, Gr.; Besins, Hong Kong; Besins, Hung.; Aventis, Irl.†; Besins International, Israel; Besins-Iscovesco, Malaysia; CORNE, Mex.; Besins, Rus.; Besins, Singapore†; Vifor, Switz.; Besins, Thai.; Besins, UK.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis; vaginal atrophy after menopause.

Oestro-Gynaedron M *Artesan, Ger.; Cassella-med, Ger.*
Estriol (p.2101·1).
Oestrogen deficiency; vaginal disorders.

Oestro-Gynaedron Nouveau *Lubapharm, Switz.*
Estriol (p.2101·1).
Adjunct in vaginal surgery; oestrogen deficiency.

OestroTabs Plus Cyclic *Golaz, Switz.†.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Oestrugol N *Atzinger, Ger.†.*
⊗ Estriol (p.2101·1); urea (p.1620·2); thymol (p.1664·3).
Vaginitis.

Ofal *Novartis Ophthalmics, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ofal P *Novartis Ophthalmics, Arg.†.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Ofamix *Rowe-Fleming, Venez.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Ofcin *YSP, Malaysia; Yung Shin, Singapore.*
Ofloxacin (p.310·2).
Bacterial infections.

Oferin *Unipharma, Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Ofertil *Bernofarm, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Ofetaxim *Alkem, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Off *Johnson, Canad.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Off Skintastic *Johnson, Canad.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Off Skintastic with Sunscreen *Johnson, Canad.†.*
Diethyltoluamide (p.2041·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Insect repellent; sunscreen.

Offeno *Offenbach, Mex.†.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders.

Offentina *Offenbach, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Off-Ezy *Del, Canad.; Del, USA.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Off-Ten *Medipharm, Chile.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Ofisolona *Ofimex, Mex.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Ofkozin *Kocak, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

O-Flam *MDM, Ital.*
Fentiazac (p.60·1).
Inflammation; oedema.

Oflazet *Farmedia, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Ofler *Otsira, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofler-TZ *Otsira, India.*
Ofloxacin (p.310·2); tinidazole (p.848·3).

Oflin *Cadila, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflo *TAD, Ger.; Unique, Rus.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflocee *Farmaline, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflocet
Sanofi-Aventis, Fr.
Ofloxacin (p.310·2).
Bacterial infections.

Sanofi-Aventis, Port.
Ofloxacin (p.310·2) or ofloxacin hydrochloride (p.310·2).
Bacterial infections.

Oflocide *Tripharma, Rus.; Abdi, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflocin
Note. This name is used for preparations of different composition.
Farmedia, Gr.
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

GSK, Ital.
Ofloxacin (p.310·2).
Respiratory-tract infections; urinary-tract infections.

Oflodex *Dexcel, Israel.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflodinex *Polpharma, Pol.†.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflodura *Merck dura, Ger.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflogen *Generics, Hung.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflohexal *Hexal, Ger.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofloks *Eczacibasi, Turk.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflomet *Pond's, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflono *SMB, Chile.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Oflono-D *SMB, Chile.*
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Inflammatory eye disorders with infection.

Oflovir *Vir, Spain.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflox *Allergan, Arg.; Stada, Austria; Allergan, Braz.; Allergan, Chile; Basics, Ger.; CT, Ger.; Sandoz, Ger.; Cipla, India; Allergan, Israel; Allergan, Venez.*
Ofloxacin (p.310·2).
Bacterial infections.

O-Flox *Silom, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Oflox D *Cipla, India.*
⊗ Ofloxacin (p.310·2); dexamethasone (p.1526·1).
Infected eye disorders.

Oflox TZ *Cipla, India.*
Ofloxacin (p.310·2); tinidazole (p.848·3).
Bacterial infections.

Ofloxa *LBS, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofloxan *Janssen-Cilag, Braz.†.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofloxbeta *Betapharm, Ger.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofloxcin *Siam Bheasach, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Ofloxin
BPL-Meizler, Braz.†; Zentiva, Rus.
Ofloxacin (p.310·2).
Bacterial infections.

Zentiva, Cz.
Ofloxacin (p.310·2) or ofloxacin hydrochloride (p.310·2).
Bacterial infections.

O-fluor *Onkoworks, Ger.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Ofnifenil *SJA, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ofnimarex *Biospray, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ofodex
Note. This name is used for preparations of different composition.
Atlantis, Mex.
Ear drops: ⊗ Hydrocortisone (p.1535·2); chloramphenicol (p.239·3); benzocaine (p.1854·1).
Otitis externa; otitis media.

Atlantis, Mex.
Eye drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Inflammatory eye disorders with infection.

O-folin *Onkoworks, Ger.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists; folic acid deficiency.

Ofoxin *Zambon, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Oframax
Note. This name is used for preparations of different composition.
Ranbaxy, Cz.†; Ranbaxy, India; Ranbaxy, Rus.; Ranbaxy, S.Afr.; Ranbaxy, Singapore; Ranbaxy, Thai.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ranbaxy, Pol.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Oftabiotico
Note. This name is used for preparations of different composition.
Saval, Chile.
Eye drops: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Saval, Chile.
Eye ointment: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial eye infections.

Oftaboril *Alcon, Mex.*
Boric acid (p.2268·1); borax (p.2268·1); phenylephrine (p.1568·1).
Eye disorders.

Oftabrain *Thea, Ital.*
Quercetin; vitamin E; vitis vinifera (p.1922·1).
Nutritional supplement.

Oftacilox *Alcon, Ital.; Alcon, Port.; Alcon Cusi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Oftaciprox *Laboratorios Chile, Chile.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Oftacon *Saval, Chile; Columbia, Mex.†.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Oftadil *Diba, Mex.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Oftagel *Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Hung.; Santen, Norw.; Santen, Pol.; Ursapharm, Rus.; Santen, Swed.*
Carbomer 974P (p.2141·3).
Dry eyes.

Oftagen *Saval, Chile.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Oftagen Compuesto *Saval, Chile.*
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Bacterial eye infections with inflammation.

Oftaine *Oftalmi, Venez.†.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Oftal *Drawer, Arg.*
Neomycin sulfate (p.305·1); chloramphenicol (p.239·3); phenylephrine hydrochloride (p.1568·1).
Eye infections.

Oftalar *Alcon, Ital.; Alcon, Port.; Alcon Cusi, Spain; Alcon, Turk.*
Pranoprofen (p.119·1).
Inflammatory eye disorders.

Oftalblu *Alfa Intes, Ital.*
Trypan blue (p.2405·2).
Aid in cataract surgery.

Oftalbrax *Eczane, Arg.†.*
Tobramycin (p.354·1).
Bacterial eye infections.

Oftaler *Saval, Chile.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis.

Oftalirio
Saval, Chile.
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1).
Eye congestion.

Columbia, Mex.†.
⊗ Naphazoline (p.1565·1); antazoline (p.567·1).

Oftalmil *Bruschettini, Ital.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc phenolsulfonate (p.1621·3).
Eye irritation.

Oftalmocaina *Allergan, Arg.†.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Oftalmoflogol *Poen, Arg.†.*
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3).
Infected eye disorders.

Oftalmol Ocular *Nupel, Spain.*
⊗ Boric acid (p.2268·1); mercuric cyanide (p.2342·2); naphazoline nitrate (p.1565·2); trinitrophenol (p.2404·3); procaine hydrochloride (p.1869·1).
Eye congestion; infected eye disorders.

Oftalmolets *Alcon, Arg.*
Erythromycin estolate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial eye infections.

Oftalmolosa Cusi *Alcon Cusi, Malaysia.*
Erythromycin (p.269·2).
Bacterial eye infections.

Oftalmotonil *Bausch & Lomb, Arg.*
Brimonidine (p.1878·3).
Glaucoma.

Oftalmotrim *Alcon, Hung.†; Alcon Cusi, Malaysia; Alcon, Port.; Alcon Cusi, Spain; Alcon, Turk.*
Polymyxin B sulfate (p.317·3); trimethoprim (p.355·2).
Bacterial eye infections.

Oftalmotrim Dexa *Alcon Cusi, Spain†.*
⊗ Dexamethasone sodium (p.1526·3); polymyxin B sulfate (p.317·3); trimethoprim (p.355·2).
Bacterial eye infections.

Oftalmowell *UCB, Spain.*
Gramicidin (p.286·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye infections.

Oftalook *Denver, Arg.*
Sodium chloride (p.1686·1).
Dry eyes.

Oftalook Plus *Denver, Arg.*
Hypromellose (p.2144·2).
Dry eyes.

Oftamolol *Alcon, Denm.; Ophtha, Norw.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Oftan
Note. This name is used for preparations of different composition.
Santen, Cz.; Santen, Hong Kong; Santen, Norw.; Santen, Philipp.; Santen, Pol.; Novartis, Switz.†; Santen, Thai.†.
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Santen, Fin.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Oftan Akvakol *Santen, Fin.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Oftan A-Pant *Santen, Fin.*
Vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1).
Eye disorders.

Oftan Atropin *Santen, Fin.†.*
Atropine sulfate (p.1219·3).
Eye disorders.

Oftan Catachrom *Santen, Rus.*
Cytochrome C (p.2291·3); adenosine (p.1202·1); nicotinamide (p.1957·3).
Cataract.

Oftan C-C *Santen, Fin.*
Hydrocortisone capronate; chloramphenicol (p.239·3).
Eye disorders.

Oftan Chlora *Santen, Fin.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Oftan Dexa *Santen, Fin.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Oftan Dexa-Chlora *Santen, Fin.*
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Eye disorders.

Oftan Dexamethason *Santen, Rus.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Oftan Flurekain *Santen, Fin.*
Oxybuprocaine hydrochloride (p.1867·3); fluorescein sodium (p.2306·1).
Adjunct in eye examination.

Oftan IDU *Santen, Hung.†; Santen, Rus.*
Idoxuridine (p.881·2).
Viral eye infections.

Oftan Metaoksedrin *Santen, Fin.†.*
Phenylephrine hydrochloride (p.1568·1).
Production of mydriasis; uveitis.

Oftan Obucain *Santen, Fin.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Oftan Pilocarpin *Santen, Rus.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; reversal of mydriasis.

Oftan Starine *Santen, Fin.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Oftan Syklo *Santen, Fin.†.*
Cyclopentolate hydrochloride (p.1879·3).
Aid in eye examination.

Oftan Timolol *Santen, Hung.; Santen, Rus.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Oftanex *Santen, Cz.†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Oftapinex *Santen, Denm.†; Santen, Fin.†; Santen, Norw.†; Santen, Swed.†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Oftaquin *Columbia, Mex.†.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

Oftaquix *Santen, Cz.; Santen, Denm.; Santen, Fin.; Santen, Ger.; Santen, Hung.; Tubilux, Ital.; Santen, Neth.; Santen, Philipp.; Santen, Pol.; Santen, Port.; Santen, Swed.; Kestrel, UK.*
Levofloxacin (p.292·2).
Bacterial eye infections.

Oftasona N *Saval, Chile.*
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
Eye infections with inflammation.

Oftasona P *Saval, Chile.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Inflammatory eye disorders.

Oftasteril *Alfa Intes, Ital.*
Povidone-iodine (p.1659·2).
Eye irrigation; skin disinfection.

Oftavir *Saval, Chile.*
Aciclovir (p.862·3).
Herpesvirus eye infections.

Oftensin *Polpharma, Cz.†; Polpharma, Pol.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ofterra *Oftalmi, Venez.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Oftic *Saval, Chile.*
Diclofenac sodium (p.44·3).
Eye inflammation following cataract surgery.

Ofticlin *Grin, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial eye infections.

Oftimolo *Farmila, Ital.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Oftinal *Schering-Plough, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Oftipan *Jelfa, Pol.*
Carbomer (p.2141·3).
Dry eyes.

Oftophenazol *Polfa Warszawa, Pol.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic conjunctivitis; eye irritation.

Oftpred *Latinofarma, Braz.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Ofus *Sam Chun Dang, Hong Kong.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Ofzim *Investigaciones Filosoficas y Cientificas, Mex.*
Cocarboxylase (p.1975·2); ribonuclease (p.2378·3).
Bacterial and viral infections.

Ogamma *Otsuka, Jpn†.*
Interferon gamma-n1 (p.893·3).

Ogast *Takeda, Fr.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ogasto *Abbott, Arg.†; Abbott, Chile†; Seber, Port.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ogastoro *Takeda, Fr.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ogastro *Abbott, Braz.; Abbott, Mex.; Abbott, Turk.; Abbott, Venez.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ogen *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Indon.; Pfizer, Mex.†; Pharmacia Upjohn, USA.*
Estropipate (p.2101·2).
Female castration; female hypogonadism; menopausal disorders; oestrogen deficiency; osteoporosis; primary ovarian failure; vulval and vaginal atrophy.

Oglos *Grunenthal, Spain†.*
⊗ Morphine hydrochloride (p.86·3).
Pain; premedication.

OH B12
Pharmacia, Ital.
Hydroxocobalamin (p.1980·3).
Anaemias; liver disorders; neuralgia; neuritis.

Jaba Recordati, Port.
Hydroxocobalamin acetate (p.1980·3).
Neuralgias; neuritis.

Ohexine *Greater Pharma, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

OIF *Otsuka, Jpn.*
Interferon alfa (p.885·1).
Chronic myeloid leukaemia; hepatitis; renal cancer.

Oikamid *Pliva, Cz.*
Piracetam (p.368·2).
Cerebrovascular disorders; dementia; mental function impairment; vertigo.

Oil of Olay
Note. This name is used for preparations of different composition.
Procter & Gamble, Canad.
Octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Procter & Gamble, USA.
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); ensulizole (p.1597·1).
Sunscreen.

Oil of Olay Total Effects *Procter & Gamble, Canad.*
Avobenzone (p.1589·3); ensulizole (p.1597·1); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Oilalfo *Valeant, Arg.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); benzalkonium chloride (p.1629·1).
Seborrhoea.

Oilatum
Note. This name is used for preparations of different composition.
Stiefel, Arg.; Stiefel, Pol.
Liquid paraffin (p.2030·3).
Dry skin disorders; soap substitute.

Stiefel, Canad.
Light liquid paraffin (p.2031·1) or liquid paraffin (p.2030·3).
Dry skin; skin irritation.

Stiefel, Chile; Stiefel, Mex.
Arachis oil (p.2259·1).
Dry skin disorders.

Stiefel, Israel; Stiefel, Ital.
Soap substitute.

Stiefel, NZ.
Light liquid paraffin (p.2031·1).
Dry skin.

Stiefel, Malaysia.
Bar; emollient; shower gel: Light liquid paraffin (p.2031·1).
Dry skin disorders.

Stiefel, Philipp.
Bar; shower gel: Light liquid paraffin (p.2031·1).
Soap substitute.

Stiefel, Malaysia; Stiefel, Philipp.
Cream: Light liquid paraffin (p.2031·1); white soft paraffin (p.2031·2).
Dry skin disorders.

Oilatum AD
Note. This name is used for preparations of different composition.
Stiefel, Fr.†.
Sodium cocoyl isetionate (p.2138·3); triclosan (p.1665·2).
Dry skin; soap substitute.
Stiefel, Ital.†.
Triclosan (p.1665·2).
Atopic dermatitis.

Oilatum Bar Stiefel, Austral.; Stiefel, Hong Kong; Stiefel, Indon.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.
Liquid paraffin (p.2030·3).
Soap substitute.

Oilatum Bath Formula Stiefel, UK.
Light liquid paraffin (p.2031·1).
Dry skin disorders.

Oilatum Body Oil Stiefel, Fr.†.
Liquid paraffin (p.2030·3); jojoba oil.
Dry skin.

Oilatum Cream
Note. This name is used for preparations of different composition.
Stiefel, Fr.†.
Liquid paraffin (p.2030·3); soft paraffin (p.2031·2).
Dry skin.
Stiefel, Hong Kong; Stiefel, Thai.; Stiefel, UK.
Light liquid paraffin (p.2031·1); white soft paraffin (p.2031·2).
Formerly contained arachis oil in the *UK*.
Dry skin disorders; skin irritation.
Stiefel, Indon.; Stiefel, Irl.; Stiefel, S.Afr.; Stiefel, Singapore.
Arachis oil (p.2259·1).
Dry skin disorders; skin irritation.

Oilatum Emollient
Note. This name is used for preparations of different composition.
Stiefel, Austral.; Stiefel, Cz.; Stiefel, Hong Kong; Stiefel, Thai.
Light liquid paraffin (p.2031·1).
Formerly contained light liquid paraffin and acetylated wool alcohols in *Austral*.
Bath additive; dry skin disorders; pruritus.
Stiefel, Fr.; Stiefel, S.Afr.; Stiefel, Singapore.
Liquid paraffin (p.2030·3).
Dry skin disorders.
Stiefel, Irl.
Light liquid paraffin (p.2031·1); acetylated wool alcohols (p.2033·2).
Dry skin; skin irritation.
Stiefel, UK.
Liquid paraffin (p.2030·3); acetylated wool alcohols (p.2033·2).
Dry skin conditions.

Oilatum Fragrance Free Stiefel, UK.
Light liquid paraffin (p.2031·1).
Dry skin disorders.

Oilatum Gel Stiefel, Cz.; Stiefel, Hong Kong; Stiefel, Indon.; Stiefel, Irl.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK.
Light liquid paraffin (p.2031·1).
Dry skin disorders; eczema; skin irritation.

Oilatum Junior
Note. This name is used for preparations of different composition.
Stiefel, Irl.; Stiefel, UK.
Bath additive: Light liquid paraffin (p.2031·1).
Dry skin disorders.
Stiefel, Irl.; Stiefel, UK.
Cream: Light liquid paraffin (p.2031·1); white soft paraffin (p.2031·2).
Dry skin disorders; pruritus.

Oilatum Junior Flare-Up Stiefel, Irl.; Stiefel, UK†.
Light liquid paraffin (p.2031·1); triclosan (p.1665·2); benzalkonium chloride (p.1629·1).
Dry skin disorders; infected eczema.

Oilatum Plus
Note. This name is used for preparations of different composition.
Stiefel, Austral.; Stiefel, Cz.; Stiefel, Hong Kong; Stiefel, Indon.; Stiefel, Irl.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK.
Light liquid paraffin (p.2031·1); triclosan (p.1665·2); benzalkonium chloride (p.1629·1).
Bath additive; eczema; infected eczema.
Stiefel, Pol.
Liquid paraffin (p.2030·3); triclosan (p.1665·2); benzalkonium chloride (p.1629·1).
Infected eczema.

Oilatum Plus Antibacterial Stiefel, Malaysia.
Light liquid paraffin (p.2031·1); triclosan (p.1665·2); benzalkonium chloride (p.1629·1).
Eczema.

Oilatum Scalp Intensive Stiefel, UK.
Ciclopirox olamine (p.529·2); salicylic acid (p.1612·2); panthenol (p.2362·1); menthol (p.2340·1).
Scalp disorders.

Oilatum Scalp Treatment Stiefel, Irl.; Stiefel, UK.
Ciclopirox olamine (p.529·2).
Formerly known as Oilatum Shampoo in the *UK*.
Dry scalp disorders; scalp disorders.

Oilatum Shower Gel Stiefel, Austral.
Light liquid paraffin (p.2031·1).
Dry skin.

Oilatum Soap
Note. This name is used for preparations of different composition.
Stiefel, Fr.†; Stiefel, UK.
Liquid paraffin (p.2030·3).
Dry skin; dry skin disorders.
Stiefel, Irl.
Light liquid paraffin (p.2031·1).
Dry skin disorders.
Stiefel, USA.
Skin cleanser.

Oilezz Organon, Thai.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Acne; biphasic oral contraceptive.

Oil-Free Active Sunscreen Norwood, Canad.†.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Oil-Free Sunblock Tanning Research, Canad.†.
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Oil-Free Sunscreen
Note. This name is used for preparations of different composition.
Avon, Canad.†.
SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.
Norwood, Canad.†.
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Oil-Free Sunspray Estee Lauder, Canad.†.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Oilum Body Scrub and Whitening Galenium, Indon.
Soap substitute.

Oilum Soap Galenium, Indon.
Moisturising soap.

Ojensalve Neutral Ophtha, Denm.; SAD, Denm.
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Blepharitis; protection of eyelid and cornea.

Ojosbel Dermofarm, Spain.
⊗ Hamamelis water (p.2318·2); naphazoline hydrochloride (p.1565·2).
Eye irritation.

Okacid D Cipla, India.
Domperidone (p.1726·2); omeprazole (p.1753·1).

Okacin Novartis Ophthalmics, Arg.; Novartis, Austria; Novartis, Belg.; Novartis Ophthalmics, Braz.†; Novartis, Chile†; Novartis Ophthalmics, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis Ophthalmics, Hung.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia†; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Ciba Vision, Rus.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Venez.
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye infections.

Okacyn Adcock Ingram, S.Afr.
Lomefloxacin hydrochloride (p.295·2).
Bacterial eye infections.

Okaflox M Cipla, India.
Ofloxacin (p.310·2); metronidazole (p.837·1).
Bacterial infections.

Okal
Note. This name is used for preparations of different composition.
Puerto Galiano, Spain.
Chewable tablets: Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.
Puerto Galiano, Spain.
Tablets: Aspirin (p.20·3).
Fever; musculoskeletal, joint and peri-articular disorders; pain.

Okalan D Cipla, India.
Lansoprazole (p.1739·2); domperidone (p.1726·2).

Okalcin Tentan, Switz.†.
Homoeopathic preparation.

Okamycin Cipla, India.
Erythromycin (p.269·2).
Skin infections.

Okanorm Plus Cipla, India.
Metoclopramide hydrochloride (p.1747·3); paracetamol (p.108·1).

Okaril Cipla, India.
⊗ Salbutamol (p.1131·2); bromhexine (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Respiratory-tract disorders.

Okaril Plus Cipla, India.
⊗ Terbutaline sulfate (p.1138·3); bromhexine (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Respiratory-tract disorders.

Okavax Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; Aventis Pasteur, Philipp.; Research Foundation, Philipp.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.
A live attenuated varicella-zoster vaccine (Oka strain) (p.2242·2).
Active immunisation.

Oki Dompe, Ital.; Dompe, Rus.
Ketoprofen lysine (p.73·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Okimus Biocodex, Fr.
Quinine benzoate (p.614·3); crataegus (p.2289·1).
Formerly known as Quinisedine.
Cramps.

Oklaricid Abbott, Gr.†.
Clarithromycin (p.248·2).
Adjunct in Helicobacter pylori eradication; bacterial infections.

Okoubarell Sanorell, Ger.
Homoeopathic preparation.

Okoubasan Sanum-Kehlbeck, Ger.
Homoeopathic preparation.

Okovidit Dioptra, Rus.
Laminaria (p.2330·2).
Eye disorders.

Oksabron Deva, Turk.
Oxolamine phosphate (p.1567·1).
Coughs.

Oksamen Nevzat, Turk.
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Oksiaskaril Aroma, Turk.
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Oksibutin Sandoz, Fin.†.
Oxybutynin hydrochloride (p.2190·3).
Bladder function disorders.

Oksikam Sanofi Synthelabo, Turk.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Oksinazal Eczacibasi, Turk.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Oksitin Med-Care, Turk.
Barrier cream.

Okugest VSM, Neth.
Homoeopathic preparation.

Okuzell Pharmaselect, Austria.
Hypromellose (p.2144·2).
Eye irritation.

O-Lac BMS, Arg.†; Mead Johnson, Austral.†; Mead Johnson, Braz.; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Indon.; Mead Johnson, Ital.; Mead Johnson, Malaysia†; Mead Johnson, Port.†; Mead Johnson, Singapore†; Mead Johnson Nutritionals, Thai.; BMS, Venez.†.
Infant feed (p.1922·1).
Diarrhoea; galactosaemia; lactose intolerance; sucrose intolerance.

Oladin Collins, Mex.
⊗ Salbutamol (p.1131·2).

Olam Valdecasas, Mex.
Kaolin (p.1738·1); pectin (p.2145·2).

Olamin Micro, India.
Ciclopirox olamine (p.529·2).
Fungal skin infections.

Olamin P Delta BKB, Ital.
Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Olamine
Note. A similar name is used for preparations of different composition (see below).
Pharmatrix, Arg.
Aloe vera (p.1588·2); vitamin A; vitamin E; provitamin C.
Skin disorders.

Ol-Amine
Note. A similar name is used for preparations of different composition (see above).
Meuse, Belg.
Multivitamin and mineral preparation (p.1922·1).

Olamyc Sanofi-Aventis, Gr.
⊗ Salicylic acid (p.1612·2); triamcinolone acetonide (p.1544·3); benzalkonium chloride (p.1629·1).
Skin disorders.

Olan Andromaco, Mex.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Olane Phoenix, Arg.
Paroxetine (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Olan-Gin Olan-Kemed, Thai.
Dipyrone (p.49·2).
Lidocaine (p.1862·3) is included in some injections to alleviate the pain of injection.
Fever; pain.

Olapin Merck, Port.
Olanzapine (p.1012·1).
Schizophrenia.

Olartan Menarini, Gr.
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olartan Plus Menarini, Gr.
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Olbad Cordes Ichthyol, Austria; Ichthyol, Ger.
Soya oil (p.1965·3).
Bath additive; skin disorders.

Olbad Cordes comp Ichthyol, Austria.
Soya oil (p.1965·3); shale oil.
Bath additive; skin disorders.

Olbad Cordes F Ichthyol, Ger.
Arachis oil (p.2259·1).
Bath additive; skin disorders.

Olbas
Note. This name is used for preparations of different composition.
Novyphar, Belg.
Peppermint oil (p.1761·2); eugenol (p.2301·2); cajuput oil (p.2271·2); sweet birch oil (p.86·2); juniper oil (p.2328·3); cineole (p.2282·3); menthol (p.2340·1).
Upper respiratory-tract disorders.
Olbas, Ger.
Drops: Peppermint oil (p.1761·2); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); juniper oil (p.2328·3); sweet birch oil (p.86·2).
Cold symptoms; gastrointestinal disorders; headache; neuralgia; pain; rheumatism.
Lane, Pol.; Hanseler, Switz.; Lane, UK.
Inhaler: Cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); menthol (p.2340·1).
Nasal congestion; sinusitis.
Lane, Pol.
Oil: Cajuput oil (p.2271·2); clove oil (p.2285·1); eucalyptus oil (p.2301·2); juniper oil (p.2328·3); peppermint oil (p.1761·2); menthol (p.2340·1); birch oil (p.86·2).
Musculoskeletal and joint pain; nasal congestion.
Hanseler, Switz.
Oil: Peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); cajuput oil (p.2271·2); sweet birch oil (p.86·2); juniper oil (p.2328·3); clove oil (p.2285·1).
Cold symptoms.
Lane, UK.
Oil: Cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); sweet birch oil (p.86·2); clove oil (p.2285·1); juniper oil (p.2328·3); menthol (p.2340·1); dementholised mint oil (p.2345·2).
Nasal congestion.
Hanseler, Switz.
Ointment: Peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); cajuput oil (p.2271·2); sweet birch oil (p.86·2); juniper oil (p.2328·3); poppy-seed oil (p.2371·1).
Cold symptoms; nasal congestion.
Lane, Pol.; Lane, UK.
Pastilles: Eucalyptus oil (p.2301·2); juniper oil (p.2328·3); peppermint oil (p.1761·2); menthol (p.2340·1); birch oil (p.86·2); clove oil (p.2285·1).
Cold symptoms; coughs; sore throat.
Olbas, Ger.
Topical spray: Propane (p.1691·3); isopropyl alcohol (p.1650·3).
Formerly contained ethyl chloride and menthol.
Soft-tissue disorders.

Olbas for Children Lane, UK.
Cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); clove oil (p.2285·1); juniper oil (p.2328·3); menthol (p.2340·1); dementholised mint oil (p.2345·2); methyl salicylate (p.85·3).
Respiratory-tract congestion.

Olbas Powerflu plus Vitamin C Lane, UK.
Tablets, paracetamol (p.108·1); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); tablets, sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Olbemox Pharmacia, Ger.†.
Acipimox (p.1201·2).
Lipid disorders.

Olbendital Italmex, Mex.
Albendazole (p.139·2).
Worm infections.

Olbenorm Norma (Νορμα), Gr.
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Olbetam Pfizer, Austria; Pfizer, Belg.; Searle, Braz.†; Pfizer, Chile; Pfizer, Denm.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Irl.†; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.†; Pfizer, NZ; Pfizer, Neth.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.
Acipimox (p.1201·2).
Hyperlipidaemias.

Ol-Bi KG, Ital.†.
Vitamin B substances (p.1922·1).

Olcadil Novartis, Braz.; Novartis, Port.
Cloxazolam (p.981·1).
Anxiety; premedication; sleep disorders.

Oldamin Fuji, Jpn.
Monoethanolamine oleate (p.2346·2).
Oesophageal varices.

Oldan
Note. This name is used for preparations of different composition.
Inibsa, Spain.
Acemetacin (p.15·1).
Musculoskeletal, joint, and peri-articular disorders.
Andromaco, Venez.†.
Loperamide (p.1741·3).
Diarrhoea.

Oldinot Elea, Arg.
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Oledro
Note. This name is used for preparations of different composition.
Drogsan, Turk.
Oral powder; tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); oxolamine citrate (p.1567·1).
Fever; pain.
Drogsan, Turk.
Paediatric syrup: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Fever; pain.

Oleo Calcarea NewFaDem, Ital.†; Nova Argentia, Ital.†; Ogna, Ital.†.
Aluminium acetate (p.2255·1); glacial acetic acid (p.2244·2); zinc oxide (p.1621·2); calcium oxide (p.2272·3); menthol (p.2340·1).

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Oleo Dermosina Simples *Davi, Port.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Oleo Eletrico *CIF, Braz.†.*
Camphor (p.2273·2); turpentine oil (p.2406·3); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Oleo de Primula *Catarinense, Braz.; Fontovit, Braz.*
Gamolenic acid (p.2308·2); linoleic acid (p.2308·2).

Oleo Tull *Aventis, Ger.*
Soft paraffin (p.2031·2); wool fat (p.2033·2).
Wounds.

Oleobal *Pierre Fabre Dermo Kosmetik, Ger.*
Soya oil (p.1965·3); light liquid paraffin (p.2031·1).
Bath additive; skin disorders.

Oleoban *Medinfar, Port.†.*
Sunflower oil (p.1970·3).
Skin cleansing; skin disorders.

Oleoban Composto *Medinfar, Port.†.*
Sunflower oil (p.1970·3); ichthammol (p.1599·1).
Skin disorders.

Oleoban Gel *Medinfar, Port.†.*
Sunflower oil (p.1970·3); liquid paraffin (p.2030·3).
Dry skin disorders.

Oleoderm
Note. This name is used for preparations of different composition.
Remexa, Mex.
Calcium hydroxide (p.2272·2).
Skin disorders.

Vita, Venez.
Wool fat (p.2033·2); liquid paraffin (p.2030·3).
Emollient.

Oleoderm Plus *Remexa, Mex.*
Calcium hydroxide (p.2272·2); avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

Oleo-Lax *Fada, Arg.*
Propofol (p.1791·1).
General anaesthesia.

Oleomed *Protein, Mex.†.*
Olive oil (p.2356·2).

Oleomed A *Protein, Mex.†.*
Olive oil; zinc; selenium; alpha tocopherol (p.1922·1).

Oleomed C *Protein, Mex.†.*
Olive oil; eicosapentaenoic acid; docosahexaenoic acid; alpha tocopherol (p.1922·1).

Oleomycetin *Agepha, Austria; Winzer, Ger.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Oleomycetin-Prednison *Agepha, Austria; Winzer, Ger.†.*
⊗ Chloramphenicol (p.239·3); prednisone (p.1542·3).
Infected eye disorders.

Oleosint *Apomedica, Austria.*
Diolamine oleate; soya oil (p.1965·3).
Skin disorders.

Oleosorbate *Eumedica, Belg.*
Polysorbate 80 (p.1919·2).
Ear wax removal; rhinitis.

Oleovit *Fresenius Kabi, Austria.*
Vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1).
Eye disorders.

Oleovit A
Note. This name is used for preparations of different composition.
Fresenius Kabi, Austria.
Capsules: Vitamin A palmitate (p.1973·1).
Ear disorders; gastrointestinal disorders; hyperthyroidism; respiratory-tract disorders; skin disorders; urogenital disorders.

Fresenius Kabi, Austria.
Oral drops: Vitamin A (p.1971·2); betacarotene (p.1930·3).
Vitamin A deficiency.

Oleovit A + D
Note. This name is used for preparations of different composition.
Fresenius Kabi, Austria.
Capsules: Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2).
Rickets; vitamin A and D supplementation.

Fresenius Kabi, Austria.
Oral drops: Vitamin A (p.1971·2); betacarotene (p.1930·3); colecalciferol (p.1986·2).
Rickets; vitamin A and D supplementation.

Oleovit A + D$_3$ *Vitamed, Israel†.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Vitamin supplement.

Oleovit D$_3$ *Fresenius Kabi, Austria.*
Colecalciferol (p.1986·2).
Hypoparathyroidism; rickets.

Oleptal *Torrent, Braz.*
Oxcarbazepine (p.490·3).
Epilepsy.

Oleum Rhinale *Weleda, UK.*
Homoeopathic preparation.

Oleum Rhinale Nasal Oil *Weleda, S.Afr.*
Camphor (p.2273·2); mercurius sulfuratus ruber; calendula (p.2273·1); chamomile (p.2279·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); thyme oil (p.2401·2).
Nasal congestion; rhinitis; sinusitis.

Oleum Salviae Comp *Weleda, S.Afr.*
Eucalyptus oil (p.2301·2); fennel oil (p.2303·1); juniper oil (p.2328·3); peppermint oil (p.1761·2); pine silvestris oil (p.2368·2); rosemary oil (p.2381·3); sage oil (p.2382·3); labdanum oil.
Respiratory-tract disorders.

Olexar *Cipla, India.*
Olanzapine (p.1012·1).
Bipolar disorder; schizophrenia.

Olexin *Rayere, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Olf *GNLD, Austral.*
Reishi mushrooms; celery; avena; red sage; damiana; St John's wort; astragalus; angelica; cinnamon; liquorice (p.1922·1).
Tonic.

Olfen
Mepha, Braz.; Mepha, Cz.; Mepha, Hong Kong; Mepha, Hung.†; Mepha, Israel; Mepha, Malaysia; Mepha, Port.; Mepha, Singapore; Mepha, Thai.†.
Diclofenac sodium (p.44·3).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal and biliary colic.

Mepha, Pol.
Diclofenac (p.44·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Mepha, Switz.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Olfex *Bial, Spain.*
⊗ Budesonide (p.1520·1).
Asthma; rhinitis.

Olfi *Ipca, India.*
Ofloxacin (p.310·2).
Bacterial infections.

Olfi TZ *Ipca, India.*
Ofloxacin (p.310·2); tinidazole (p.848·3).
Diarrhoea; dysentery.

Olfosonide *Olvos, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Olibanum RA *Zilly, Ger.*
Homoeopathic preparation.

Olicard *Solvay, Cz.; Solvay, Ger.; Solvay, Hung.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Olicard Retard *Solvay, Rus.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Olicardin *Solvay, Austria.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; myocardial infarction; pulmonary hypertension.

Olicide *Cosmofarma, Port.†.*
Malathion (p.2046·1).
Pediculosis.

OliClinomel
Baxter Immuno, Arg.; Clintec, Austria; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Baxter, Hung.; Baxter, Ital.; Clintec, Neth.; Baxter, Port.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter, UK.
Amino-acid, glucose, and lipid (from olive oil (p.2356·2) and soya oil (p.1965·3)) infusion with or without electrolytes (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Olidermil *Edol, Port.*
Zinc oxide (p.1621·2); almond oil (p.2252·2).
Dry skin.

Olie *SAD, Denm.*
Arachis oil (p.2259·1).
Bowel evacuation; constipation.

Oliflox *ACRAF, Port.*
Prulifloxacin (p.320·1).
Bacterial infections.

Oligobs *CCD, Fr.*
A range of multivitamin and mineral preparations (p.1922·1).

Oligocean *Ido, Fr.†.*
Trace element and mineral preparation derived from shellfish (p.1922·1).
Tonic.

Oligocean Minceur *Ido, Fr.†.*
Marine algae preparation (p.1922·1).
Obesity.

Oligocean Xtra *Ido, Fr.†.*
Mineral preparation derived from shellfish (p.1922·1).

Oligocomplesso *Chimicor, Fr.*
Trace element preparation (p.1922·1).

Oligocure *Labcatal, Fr.*
Manganese gluconate; copper gluconate; colloidal gold (p.1922·1).
Asthenia.

Oligoderm *Labcatal, Fr.*
Manganese gluconate (p.1956·2); copper gluconate (p.1935·3).
Cracked nipples.

Oligoelementos *Braun, Port.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Oligo-elements Aguettant *Aguettant, Fr.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Oligo-Essentials *Merck Medication Familiale, Fr.*
A range of mineral and trace element preparations (p.1922·1).

Oligoforme *Ido, Fr.†.*
A range of nutritional supplements (p.1922·1).

Oligogranul *Boiron, Fr.*
A range of trace element and mineral preparations (p.1922·1).

Oligophytum *Holistica, Fr.*
A range of mineral-rich plant extracts.

Oligoplex *Natural Touch, UK.*
A range of homoeopathic remedies.

Oligorhine *Monin, Fr.*
Copper (p.1935·2); silver (p.2387·1).
Nasal hygiene.

Oligorhine Manganese *Monin, Fr.*
Manganese (p.1956·1); copper (p.1935·2).
Nasal hygiene.

Oligosol *Labcatal, Fr.; Pharmafactory, Switz.*
A range of trace element and mineral preparations (p.1922·1).

Oligossac *Support, Braz.†.*
Maltodextrin (p.1955·3).
Preparation for enteral nutrition.

Oligostandard *Braun, Spain.*
Trace-element preparation (p.1922·1).
Parenteral nutrition.

Oligostim *Dolisos, Fr.*
A range of trace element and mineral preparations (p.1922·1).

Oligovit *Ativus, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Oligo-Yang *Ido, Fr.†.*
Fish cartilage (p.2277·3).
Joint pain.

Olimag *Wassen, Ital.†.*
Magnesium (p.1678·3).
Nutritional supplement.

Olimer *Rontag, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Olimetin *Nizhpharm, Rus.†.*
Peppermint oil (p.1761·2); turpentine oil (p.2406·3); calamus oil; olive oil (p.2356·2); sulfur (p.1614·1).

Olipcis *Sanfer, Mex.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Oliphenicol *Am-Europharma, Philipp.*
Chloramphenicol (p.239·3).
Bacterial infections.

Olit *Cadila, India; Cadila, Singapore; Cadila, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oliten *Rafarm, Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Olivevital *Blackmores, Austral.*
Olive leaf (p.2356·2).
Tonic.

Oliviase *UPSA Conseil, Fr.†.*
Olive leaves (p.2356·2).
Diuresis.

Olivin *Royal, Chile.*
Olanzapine (p.1012·1).
Psychoses.

Olivysat *Ysatfabrik, Ger.*
Olive leaves (p.2356·2).
Prevention of atherosclerosis.

Olmec *Phoenix, Arg.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olmes *Sankyo, Neth.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olmetec *Schering-Plough, Austral.; Sankyo, Austria; Sankyo, Belg.; Pfizer, Braz.; Menarini, Cz.; Sankyo, Denm.; Leiras, Fin.; Sankyo, Fr.; Sankyo, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Israel; Sankyo, Ital.; Kowa, Jpn; Pfizer, Malaysia; Sankyo, Neth.; Sankyo, Norw.; Pfizer, Philipp.; Sankyo, Port.; Pfizer, Singapore; Sankyo, Spain; Sankyo, Switz.; Pfizer, Thai.; Sankyo, UK; Schering-Plough, Venez.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olmetec HCT *Pfizer, Braz.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Olmetec Plus *Schering-Plough, Austral.; Sankyo, Belg.; Sankyo, Ger.; Pfizer, Gr.; Pfizer, Malaysia; Pfizer, Singapore; Sankyo, Switz.; Sankyo, UK.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Olmetec Plus H *Menarini, Cz.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Olmifon *Cephalon, Fr.*
⊗ Adrafinil (p.2149·3).
Mental function impairment in the elderly.

Olmoran *Novartis, Spain.*
Zafirlukast (p.1150·2).
Asthma.

Olocynan *Makros, Braz.†.*
Cynara (p.2291·2); choline (p.1934·2).
Liver disorders.

Ologyn *Labatec, Switz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Olohepat *Makros, Braz.†.*
Liver extract (p.2337·3); iron (p.1949·1); choline (p.1934·2).
Liver disorders.

Olpress *Malesci, Ital.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olren N *Heumann, Ger.†.*
Scopolia carniolica.
Urinary-tract disorders.

Olsar *Menarini, Port.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Olsar Plus *Menarini, Port.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Oltar *Berlin-Chemie, Cz.; Berlin-Chemie, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Olter *Pharmacia, Arg.†.*
Flutamide (p.725·1).
Prostatic cancer.

Oltyl *Europharma, Spain†.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Olux *Mipharm, Neth.†; Stiefel, USA.*
⊗ Clobetasol propionate (p.1522·2).
Psoriasis; scalp disorders.

Olvexya *KRKA, Cz.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Olwexya *KRKA, Hung.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social phobia.

Olworm *Biochem, India.*
Albendazole (p.139·2).
Worm infections.

Olympic Balm *ANB, Thai.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2); cineole (p.2282·3); cajuput oil (p.2271·2); peppermint oil (p.1761·2).
Musculoskeletal, joint, and peri-articular disorders.

Olynth *Pfizer, Austria; McNeil, Cz.; Pfizer Consumer, Ger.; Pfizer, Rus.; Pfizer Consumer, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Olynth Erkaltungsbalsam *Pfizer Consumer, Ger.†.*
Pine silvestris oil (p.2368·2); eucalyptus oil (p.2301·2).
Cold symptoms.

Olynth salin *Pfizer Consumer, Ger.*
Sodium chloride (p.1686·1).
Nasal congestion.

Olyspal *Cosmopharm, Gr.*
⊗ Budesonide (p.1520·1).
Asthma.

Olyster *Cadila, India.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Olzapin *Lek-Am, Pol.*
Olanzapine (p.1012·1).
Bipolar disorder; schizophrenia.

OM3 *Isodisnatura, Fr.*
Fish oil (p.1362·2).
Dietary supplement.

Omaclopil *Lafedar, Arg.*
Pilocarpine (p.1884·3).
Glaucoma; production of miosis.

Omacor *Solvay, Austria; Solvay, Belg.; Pronova, Cz.; Pierre Fabre, Fr.; Solvay, Ger.; Solvay, Gr.; Pronova, Hung.; Solvay, Irl.; Pronova, Neth.; Pfizer, Norw.; Pronova, Philipp.; CPH, Port.; Solvay, Rus.; Ferrer, Spain; AstraZeneca, Thai.; Solvay, UK.*
Omega-3-acid ethyl esters (p.1362·1).
Hyperlipidaemias; secondary prophylaxis of myocardial infarction.

Omaflaxina *Eczane, Arg.†.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

Omapren *Lesvi, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcers; Zollinger-Ellison syndrome.

Omar *Hexal, Pol.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omaron *Nizpharm, Rus.*
Piracetam (p.368·2); cinnarizine (p.573·1).
Cerebrovascular disorders; mental function disorders; migraine; vestibular disorders.

Omaspir *DMG, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Omastin *Beximco, Singapore.*
Fluconazole (p.532·1).
Fungal infections.

Ombravist *Schering, Austria†.*
Galactose (p.1481·1).
Contrast medium for Doppler sonography and echocardiography.

Ombrelle Baume *Ombrelle, Canad.†.*
SPF 30: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Ombrelle Creme *Cosmair, Canad.*
SPF 60: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Ombrelle for Kids *L'Oreal, Canad.†.*
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); ensulizole (p.1597·1); enzacamene (p.1597·1).
Sunscreen.

Ombrelle Kids *Ombrelle, Canad.*
SPF 45: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Ombrelle Lotion
Ombrelle, Canad.
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); ensulizole (p.1597·1).
Formerly contained avobenzone, octocrilene, ecamsule, enzacamene, and octisalate.
Sunscreen.

Ombrelle, Canad.
SPF 30: Avobenzone (p.1589·3); octocrilene (p.1608·3); ensulizole (p.1597·1); ecamsule (p.1596·1).
Sunscreen.

Ombrelle Lotion Extreme *Ombrelle, Canad.*
SPF 30: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Ombrelle Spray *L'Oreal, Canad.†.*
SPF 15: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Ombrelle Spray Sport *Ombrelle, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Ombrelle Sunless Face Cream *L'Oreal, Canad.†.*
SPF 15: Avobenzone (p.1589·3); ecamsule (p.1596·1); enzacamene (p.1597·1); octocrilene (p.1608·3).
Sunscreen.

Ombrelle Sunless Spray Lotion *L'Oreal, Canad.†.*
SPF 15: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Ombrelle Vapo Sport *Ombrelle, Canad.*
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Omca *BMS, Ger.*
Fluphenazine hydrochloride (p.998·1).
Psychoses.

Omcilon A M *BMS, Braz.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1); nystatin (p.543·2).
Infected skin disorders.

Omcilon A Orabase *BMS, Braz.*
⊗ Triamcinolone acetonide (p.1544·3).
Mouth ulceration.

Om-Dicynone *Labomed, Chile†.*
Etamsylate (p.1064·3).
Haemorrhage.

Ome TAD *TAD, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omebeta *Betapharm, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omebloc *Behrens, Venez.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omec *Hexal, Austria.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omecaps *Mayo, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Omed *Ecosol, Switz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omedoc *Docpharm, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omega *Schmidgall, Austria.*
Proxyphylline (p.1130·3); crataegus (p.2289·1); convallaria (p.2287·3).
Cardiac disorders.

Omega-3 *Lysi, Pol.; Gisand, Switz.*
Fish oil (p.1362·2).
Arrhythmias; atherosclerosis; dietary supplement; hyperlipidaemias; hypertension; rheumatic disorders.

Omega 3 *Chauvin, Fr.*
Fish oil (p.1362·2).
Dietary supplement.

Omega III *Nutrifarma, Turk.*
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias; ischaemic heart disease.

Omega 3+ *Proceane, Fr.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Omega 7 *Pharma Nord, UK.*
Sea buckthorn oil (p.2384·2).
Dietary supplement.

Omega 100 *Omega, Arg.*
Carbinoxamine maleate (p.570·2).
Hypersensitivity reactions.

Omega 100 Bronquial *Omega, Arg.*
Guaifenesin (p.1561·3).
Coughs.

Omega 100 Expectorante *Omega, Arg.†.*
Carbinoxamine maleate (p.570·2); ammonium chloride (p.1551·3).
Hypersensitivity reactions.

Omega 100 L *Omega, Arg.*
Loratadine (p.583·3).
Allergic rhinitis; conjunctivitis; urticaria.

Omega 1-step *Omega, Irl.*
Pregnancy test (p.2372·1).

Omegacoeur *Holistica, Fr.*
Omega-3 triglycerides (p.1362·1); herbs (p.1922·1).
Circulatory disorders.

Omega-H3 *Vitabiotics, Cz.†; Vitabiotics, Irl.†; Vitabiotics, UK.*
Multivitamin, mineral, and nutritional preparation (p.1922·1).

Omegaline *Holistica, Fr.*
Borage oil (p.2267·3).
Nutritional supplement.

Omegaline Solaire *Holistica, Fr.*
Borage oil (p.2267·3); carotene; wheat-germ oil; grape-seed oil; vitamin E (p.1922·1).
Photoageing of the skin.

Omegamma *Worwag, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegast *Ulkar, Turk.*
Omeprazole (p.1753·1).

Omegastrol *Ducto, Braz.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegastron *Pharma & Co, Austria.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omegaven
Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Denm.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Hung.; Fresenius, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.; Fresenius Kabi, UK.
Fish oil (p.1362·1).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Cz.; Fresenius Kabi, Port.
Omega-3 marine triglycerides (p.1362·2).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Omegen *Generics, Hung.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omelar Cardio *Obolenskoe, Rus.*
Amlodipine besilate (p.1214·1).

OmeLich *Winthrop, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omelina *Gelpharma, Mex.*
Linseed oil (p.2334·1).
Dietary supplement.

Omelind *Lindopharm, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omelon *YSP, Malaysia.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omenax *Geolab, Braz.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ome-nerton *Dolorgiet, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omenole *Korea United, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omep *UCI, Braz.†; Hexal, Ger.; Sandoz, Hung.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Omepirex *Winthrop, Cz.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Omepra *BA Farma, Port.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

omepra-basan *Schonenberger, Switz.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepradex *Dexcel, Israel.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepral
AstraZeneca, Austral.
Omeprazole magnesium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

AstraZeneca, Jpn.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepralan *Lannacher, Austria.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepramed *Cimed, Braz.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepramix *Ache, Braz.*
Capsules, omeprazole (p.1753·1); tablets, clarithromycin (p.248·2); capsules, amoxicillin trihydrate (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Omeprasec *AstraZeneca, Arg.*
Omeprazole magnesium (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepratop *Topgen, Belg.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer.

Omeprawin *Chinoin, Hung.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprax *Sanitas, Chile.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprazen *Malesci, Ital.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprazid *Nobel, Turk.*
Omeprazole (p.1753·1).

Omeprazin *EMS, Braz.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).

Omeprazostad *Stada, Neth.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprol *Hexal, Cz.; Medichrom, Gr.; Ilsan, Turk.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omepron *Westmont, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeprotec *Hexal, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Omepstad *Stada, Neth.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ome-Puren *Alpharma-Isis, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ome-Q *Juta, Ger.; Q-Pharm, Ger.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omeratio *Ratiopharm, Port.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omerol *Angenerico, Port.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omesal *Rubio, Spain.*
Macrogol (p.2336·1); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Omesar *Menarini, Irl.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Omesec *CCM, Malaysia; CCM, Singapore.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ometec *Technobio, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Ometon *Labesfal, Port.*
Omeprazole sodium (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ometrix *Biotech Naturis, Venez.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement; hyperlipidaemias.

Omevax *Vivax, Venez.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omevell *Novell, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omez
Reddy, Malaysia.
Omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Reddy, Rus.; Reddy, S.Afr.; Reddy, Thai.; Biofarma, Venez.†.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omezol *Alembic, India; Pacific, NZ; Stada, Neth.†; Mepha, Switz.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omezolan *Grunenthal, Port.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omezole *Hovid, Malaysia; Hovid, Singapore.*
Omeprazole (p.1753·1).
Gastric hypersecretory disorders; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omezul *Roemmers-Klinos, Venez.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omic *Astellas, Belg.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omicap *Micro, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omicral *Medico Uno, Hung.*
Itraconazole (p.536·3).
Fungal infections.

Omida comprimes homeopathiques pour la gorge *Omida, Switz.†.*
Homoeopathic preparation.

Omida Gargaline *Omida, Switz.†.*
Homoeopathic preparation.

Omida Rubiderm *Omida, Switz.†.*
Homoeopathic preparation.

Omida Rubisan *Omida, Switz.†.*
Homoeopathic preparation.

Omida Spray Nasal *Omida, Switz.†.*
Homoeopathic preparation.

Omidaline teinture vulneraire homeopathique *Omida, Switz.†.*
Homoeopathic preparation.

Omifin *Aventis, Mex.; Effik, Spain.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; male infertility.

Omilcal
Note. This name is used for preparations of different composition.
Franco-Indian, India.
Syrup: Calcium phosphate (p.1676·2); colecalciferol (p.1986·2); calcium lactate (p.1676·1); vitamin B (p.1980·2).
Calcium deficiency; osteoporosis.

Franco-Indian, India.
Tablets: Calcium phosphate (p.1676·2); colecalciferol (p.1986·2); vitamin B (p.1980·2).
Calcium deficiency; osteoporosis.

Omilipis *Richmond, Arg.*
Carboplatin (p.693·1).
Malignant neoplasms.

Omiloc *Hexal, S.Afr.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ominol *Loren, Mex.†.*
Progesterone (p.2125·1); estradiol (p.2097·2).

Omipix *Biopharm, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omitox *Shreya, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omix *Astellas, Fr.; Astellas, Switz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omizac *Torrent, Philipp.; Torrent, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

OM3junior *Isodisnatura, Fr.*
Fish oil (p.1362·2); vitamin A; vitamin D (p.1922·1).
Dietary supplement.

Ommunal *Altana, Arg.; Leti, Venez.*
Haemophilus influenzae Streptococcus pneumoniae; Klebsiella pneumoniae; Klebsiella ozaenae; Staphylococcus aureus; Streptococcus pyogenes; Streptococcus viridans; Moraxella catarrhalis.
Respiratory-tract infections.

Omnadren
Jelfa, Pol.
⊗ Testosterone phenylpropionate (p.2130·1); testosterone propionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Breast cancer; endometrial cancer; male hypogonadism.
Jelfa, Rus.
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone caproate (p.2131·3); testosterone isocaproate (p.2130·1).
Breast cancer; dysfunctional uterine bleeding; endometriosis; male infertility; menopausal disorders; osteoporosis; ovarian cancer; premenstrual syndrome; testosterone deficiency; uterine fibroids.

Omnalio *Estedi, Spain.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety; insomnia; skeletal muscle spasm.

Omnaris *Sepracor, USA.*
⊗ Ciclesonide (p.1521·3).
Allergic rhinitis.

Omnatax *Nicholas Piramal, India.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Omneo *Nutricia, Port.*
A range of infant feeds (p.1922·1).
Gastrointestinal disorders.

Omnexel *Astellas, Irl.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omnia *Hochstetter, Chile†.*
Camphor (p.2273·2); artemisia abrotanum.

Omnia T *Hochstetter, Chile†.*
Vitamin and mineral preparation (p.1922·1).

Omniabionta Integral *Merck, Norw.†.*
Multivitamin and mineral preparation (p.1922·1).

Omniapharm *Merckle, Ger.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Omnibionta
Merck, Austria.
Multivitamin infusion (p.1922·1).
Merck, Spain†.
Multivitamin and trace element preparation (p.1922·1).
Merck, Swed.†.
Vitamin and mineral preparation (p.1922·1).

Omnibionta Integral *Merck, Belg.†.*
Multivitamin and mineral preparation (p.1922·1).

Omnibus *Polychronus, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Omnic *Eurolab, Arg.; Eurofarma, Braz.; Labomed, Chile; Astellas, Cz.; Yamanouchi, Denm.; Astellas, Fin.; Astellas, Ger.; Astellas, Gr.; Astellas, Hung.; Yamanouchi, Irl.†; Yamanouchi, Israel; Astellas, Ital.; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; Astellas, Port.; Yamanouchi, Rus.; Astellas, Spain.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omnicare Daily Cleaner *Allergan, Austral.; Allergan, NZ.*
Cleaning solution for soft contact lenses (p.1622·2).

Omnicare 1 Step
Note. This name is used for preparations of different composition.
Allergan, Austral.
Solution, hydrogen peroxide (p.1647·3); tablets, neutraliser (p.1622·2).
Disinfecting and neutralising system for soft contact lenses.
Advanced Medical Optics, NZ.
Solution, hydrogen peroxide (p.1647·3); tablets, catalase (p.2278·2) (p.1622·2).
Disinfecting and neutralising system for soft contact lenses.

Omnicef
Note. This name is used for preparations of different composition.
Aristo, India.
Cefotaxime sodium (p.228·1).
Bacterial infections.
Janssen-Cilag, Mex.; Pfizer, Thai.; Abbott, USA.
Cefdinir (p.223·1).
Bacterial infections.

Omniderm *Face, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Inflammatory skin disorders.

Omniflora *Novartis Consumer, Austria.*
Lactobacillus gasseri; Bifidobacterium bifidum (p.2372·3).
Gastrointestinal disorders.

Omniflora Akut *Novartis Consumer, Ger.*
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea.

Omniflora N *Novartis Consumer, Ger.*
Lactobacillus gasseri; Bifidobacterium longum (p.2372·3).
Gastrointestinal disorders.

Omnigel *Cipla, India.*
Diclofenac (p.44·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Omnigeriat *Fabra, Arg.*
Cyproterone acetate (p.2088·2).

Omnigraf *Schering, Spain.*
Iohexol (p.1483·1).
Radiographic contrast medium.

OmniHIB *SmithKline Beecham, USA.*
A haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (p.2213·2).
Active immunisation.

Omnihist LA *WE, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

Omnipaque *Nycomed, Arg.†; Amersham, Austral.; Schering, Austria; Amersham, Belg.; Sanofi Synthelabo, Braz.†; Amersham, Canad.; General Electric, Chile; GE, Cz.; Amersham, Denm.; Amersham, Fin.; Amersham, Fr.; Schering, Ger.; Amersham, Gr.; Amersham Health, Hung.; Nycomed, Israel; Amersham, Ital.; GE Healthcare, NZ; Amersham, Neth.; Amersham, Norw.; Satis, Port.; Nycomed, Rus.; Amersham, Spain; Amersham, Swed.; Schering, Switz.; Nycomed Amersham, UK; GE Healthcare, USA; Sanofi Synthelabo, Venez.†.*
Iohexol (p.1483·1).
Radiographic contrast medium.

Omnipen *Sandoz, Mex.*
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

Omniplex *Vitaplex, Austral.†.*
Multivitamin and mineral supplement with herbs (p.1922·1).
Dietary supplement.

Omniscan *Nycomed, Arg.†; Amersham, Austral.; Amersham, Austria; Amersham, Belg.; Sanofi Synthelabo, Braz.†; Amersham, Canad.; General Electric, Chile; GE, Cz.; Amersham, Denm.; Amersham, Fin.; Amersham, Fr.; Amersham, Ger.; Amersham, Gr.; Amersham Health, Hung.; Nycomed, Israel; Amersham, Ital.; Daiichi, Jpn; GE Healthcare, NZ; Amersham, Neth.; Amersham, Norw.; Satis, Port.; Nycomed, Rus.†; Amersham, Spain; Amersham, Swed.; Amersham, Switz.; Nycomed Amersham, UK; Sanofi Winthrop, USA; Sanofi Synthelabo, Venez.†.*
Gadodiamide (p.1479·1).
Contrast medium for magnetic resonance imaging.

Omnisept *Monchpharma, Ger.†.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea.

Omnitest *Braun, Austral.†.*
Test for glucose in blood (p.2314·1).

Omnitrast *Schering, Spain.*
Iohexol (p.1483·1).
Radiographic contrast medium.

Omnitrope *Sandoz, Austral.; Sandoz, Cz.; Sandoz, Port.; Sandoz, USA.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Prader-Willi syndrome; Turner's syndrome.

Omni-Tuss *Aventis, Canad.†.*
⊗ Codeine resin (p.37·2); phenyltoloxamine resin (p.588·1); chlorphenamine resin (p.572·2); ephedrine resin (p.1558·1); guaiacol carbonate (p.1561·2).
Coughs.

Omnivit with Minerals *Allied, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Omnopon *Bodene, S.Afr.*
Papaveretum (p.105·2) (containing morphine hydrochloride, codeine hydrochloride, and papaverine hydrochloride).
Pain.

Omolin *Chemo, Cz.; Chemo, Neth.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ompranyt *Bial, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Omr-IgG *Omrix, Israel.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; passive immunisation.

Omri-Hep-B *Omrix, Israel.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Omrixate *Omrix, Israel.*
A factor VIII preparation (p.1067·1).
Haemophilia A.

Omsal *Richter, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omsil *Pinewood, Irl.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Omycet *Collins, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

OMZ *Ferron, Indon.; Schwarz, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Onadron *Ulagay, Turk.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Onaka *Max Farma, Ital.*
Pidotimod (p.2367·3).
Immunostimulant.

Onapan *Alpharma, Mex.*
Diazepam (p.986·3).

Oncaspar *Filaxis, Arg.; Medac, Ger.; IFET (ΙΦΕΤ), Gr.; Medac, Pol.; Medac, Rus.; Enzon, USA.*
Pegaspargase (p.682·2).
Acute lymphoblastic leukaemia.

Once a Day *Quest, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Oncet *Wakefield, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Cough and cold symptoms.

Onciplus *Prodotti, Braz.*
⊗ Gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Onclast *Banyu, Jpn†.*
Alendronate sodium (p.1088·1).

Onco Tiotepa *Prasfarma, Spain†.*
Thiotepa (p.778·3).
Malignant neoplasms.

Oncobleocin *Biotoscana, Chile.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Oncocarb *Asta Oncologia, Braz.†; Biotoscana, Chile.*
Carboplatin (p.693·1).
Malignant neoplasms.

Onco-Carbide *Teofarma, Ital.*
Hydroxycarbamide (p.729·1).
Chronic myeloid leukaemia; myelofibrosis; polycythaemia vera; thrombocythaemia.

Oncocarbil *LKM, Arg.*
Dacarbazine (p.706·3).
Malignant neoplasms.

Oncodaunotec *Biotoscana, Chile.*
Daunorubicin hydrochloride (p.709·1).
Leukaemias.

Oncodox *Cipla, India.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Oncoemet *Biotoscana, Chile.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

OncoFem *Helvetia, Cz.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Oncofolic *Medac, Ger.*
Sodium folinate (p.1944·1).
Adjunct to fluorouracil in colorectal cancer; prevention of methotrexate toxicity.

Oncofu *Pfizer, Arg.†.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Oncogem *Cipla, India.*
Gemcitabine hydrochloride (p.727·3).
Malignant neoplasms.

Oncolet *Biochem, India.*
⊗ Letrozole (p.740·2).
Malignant neoplasms.

Oncophos *Cadila, India.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Oncoplat *Medicus, Gr.*
Cisplatin (p.698·2).
Malignant neoplasms.

Oncoplatin *Bergamo, Braz.*
Carboplatin (p.693·1).
Malignant neoplasms.

Oncoplaxel *Biotoscana, Chile.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Oncosal *Inibsa, Spain.*
Flutamide (p.725·1).
Prostatic cancer.

OncoScint *Cytogen, Cz.†.*
Indium-111 satumomab pendetide (p.2054·1).
Diagnosis of colorectal cancer and ovarian cancer.

OncoScint CR 103 *CIS, Spain†.*
Indium-111 satumomab pendetide (p.2054·1).
Diagnosis of colorectal cancer.

OncoScint CR/OV *Cytogen, USA†.*
Indium-111 satumomab pendetide (p.2054·1).
Detection of colorectal and ovarian metastases.

OncoSeeds *Amersham, Austral.*
Iodine-125 (p.2054·2) titanium capsules.
Prostatic cancer.

Oncotam *Mayoly-Spindler, Fr.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Oncotamox *Biotoscana, Chile.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

OncoTax *Helvetia, Cz.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Oncotaxel *Sun, Thai.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Oncotaxina *Pfizer, Arg.†.*
Mitomycin (p.752·1).
Malignant neoplasms.

OncoTICE *Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Canad.; Organon, Denm.; Organon, Fin.; Apogepha, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong†; Organon, Israel; Organon, Ital.; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Pol.; Organon, Port.; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Turk.; Organon, UK; Organon, Venez.*
A BCG vaccine (p.2205·3).
Bladder and urethral cancer.

Oncotron *Sun, India.*
Mitoxantrone (p.754·3).
Malignant neoplasms.

Oncovin *Aspen, Austral.; Stada, Austria; Eurogenerics, Belg.; Lilly, Braz.†; Lilly, Chile†; Pharmacodane, Denm.; Lilly, Fin.†; EG, Fr.; Lilly, Gr.; Sandoz, Mex.; Lilly, Norw.†; Lilly, Port.†; Lilly, S.Afr.†; Stada, Swed.; Lilly, Switz.; Genus, UK; Lilly, USA; Lilly, Venez.†.*
Vincristine sulfate (p.787·1).
Idiopathic thrombocytopenic purpura; malignant neoplasms.

Oncovite *Mission Pharmacal, USA.*
Multivitamin preparation with zinc (p.1922·1).

Onctose a l'Hydrocortisone *Denolin, Belg.*
⊗ Hydrocortisone acetate (p.1535·2); diphenhydramine metilsulfate (p.577·3); lidocaine hydrochloride (p.1862·3).
Cutaneous hypersensitivity Reactions; insect stings; pruritus.

Onda *Vianex (Βιανέξ), Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Ondagen *Billev, Hung.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Ondameton *Farmedia, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Ondanoglax *GSK, Austria.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Ondaren *Pharmanel, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Ondaseprol *Proel, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Ondavell *Novell, Indon.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Ondax *Saval, Chile.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux.

Ondaz *Hexal, Austral.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Ondemet
Zentiva, Cz.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.
Beacon, UK.
Ondansetron (p.1756·3).

Ondensan *Lannacher, Austria.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Ondolen *Menarini, Port.*
⊗ Hydrochlorothiazide (p.1307·3); spironolactone (p.1400·1).
Ascites; hypertension; nephrotic syndrome; oedema.

Ondrejova Mast *Herbacos, Cz.*
Salicylic acid (p.1612·2); lavender oil (p.2331·2).
Skin disorders; ulcers.

Ondroly-A *Boffi, Ital.†.*
Peppermint oil (p.1761·2); clove oil (p.2285·1); menthol (p.2340·1); benzoin tincture (p.2386·2); phenol (p.1656·1).
Dentistry.

Ondrox *LSI, USA.*
Multivitamin, mineral, and amino acid preparation (p.1922·1).

One *Natural Life, Arg.*
Multivitamin and mineral preparation (p.1922·1).

One A Day *Bayer, Arg.†; Bayer, Braz.; Bayer Healthcare, Singapore†; Bayer, Turk.; Bayer, USA.*
A range of vitamin and vitamin and mineral preparations (p.1922·1).

One A Day Advance *Bayer Consumer, Canad.*
Multivitamin and mineral preparations (p.1922·1).

One A Day Cholesterol Health *Bayer Consumer, Canad.†.*
d-Alpha tocoferil acetate (p.1992·3).

One A Day Cold Season *Bayer Consumer, Canad.†.*
Vitamin C (p.1983·3); zinc gluconate (p.1999·2).

One A Day Energy Formula *Bayer Consumer, Canad.*
Multivitamin and mineral preparation (p.1922·1).

One For Baby Bums *PDN, Hong Kong.*
Barrier preparation.
Nappy rash.

One Drop Only *Polinac, Venez.†.*
Mint oil (p.1761·2); clove oil (p.2285·1); menthol (p.2340·1).
Oral hygiene.

One Drop Spray *Polinac, Venez.†.*
Myrrh (p.2349·2); sage (p.2382·3); chamomile (p.2279·3); mint oil (p.1761·2).
Oral hygiene.

One Step *Maurino, Arg.†.*
Hydrogen peroxide 3% (p.1647·3); catalase (p.2278·2) (p.1622·2).
Disinfection and cleaning of contact lenses.

One Step Hand Sanitizer *Belvedere, Canad.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

One Touch *Johnson & Johnson Medical, Arg.; Lifescan, Canad.; Lifescan, Fr.; Lifescan, Irl.; Lifescan, Ital.; Lifescan, Port.; Lifescan, USA.*
Test for glucose in blood (p.2314·1).

One-A-Day Kids Scooby-Doo *Bayer, USA.*
Vitamins; minerals; trace elements (p.1922·1).

One-A-Day Special Wellness Formula for Men *Bayer, Philipp.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

One-A-Day Special Wellness Formula for Women *Bayer, Philipp.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

One-A-Day WeightSmart *Bayer, USA.*
Vitamins; minerals; trace elements (p.1922·1).

Onealfa *Teijin, Jpn.*
Alfacalcidol (p.1986·1).
Disorders of vitamin D metabolism; osteoporosis.

One-Alpha *Leo, Canad.; Leo (Λεω), Gr.; Leo, Hong Kong; Darya-Varia, Indon.; Leo, Indon.; Leo, Irl.; Leo, Israel; Leo, Malaysia; CSL, NZ; Adcock Ingram Critical Care, S.Afr.; Leo, Singapore; Leo, Thai.; Abdi, Turk.; Leo, UK.*
Alfacalcidol (p.1986·1).
Hyperparathyroidism; hypocalcaemia; hypoparathyroidism; hypophosphataemia; osteomalacia; osteoporosis; renal osteodystrophy; rickets; vitamin D deficiency.

Onefin *LKM, Arg.*
Donepezil (p.365·2).

Oneflex *One Pharma, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Onelacne *DNR, Arg.†.*
Amino acids; vitamin B substances (p.1922·1); sulfurated peptides (p.1614·1).
Acne.

Onelaxant-R *Apotex, Philipp.; Pharma 3, Philipp.*
Baclofen (p.1888·1).
Muscle spasticity.

Onemer *Pisa, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Onemin *Apotex, Philipp.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

One-Six-Twelve *Cathay, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

One-Tablet-Daily *Goldline, USA.*
A range of vitamin preparations with or without minerals (p.1922·1).

Onetic 4 *Fahrenheit, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Onetil *Andromaco, Venez.†.*
Furazolidone (p.834·3).
Diarrhoea.

Onetrim *One Pharma, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Onevit *One Pharma, Philipp.*
Vitamin preparation with lysine and taurine (p.1922·1).
Nutritional supplement.

Onexacin *Apotex, Philipp.; Pharma 3, Philipp.*
Ofloxacin (p.310·2).
Chlamydial infection; mycobacterial infection.

Onexid *Korea United, Philipp.*
Clarithromycin (p.248·2).
Bacterial infections.

Onexmol *Best, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Onfor *Fada, Arg.*
Nalbuphine (p.92·2).
Pain.

Ongicil *Mavi, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Onglinex *Medinfar, Port.*
Cystine; pyridoxine hydrochloride (p.1922·1).
Hair and nail disorders.

Onguent aux herbes Keller *UB, Switz.*
Arnica (p.2260·2); calendula (p.2273·1); cineole (p.2282·3); benzoic acid (p.1630·2).
Wounds.

Onguent Hemorrhoidal *Prodemdis, Canad.*
Pramocaine hydrochloride (p.1868·1); zinc sulfate (p.1999·2).
Haemorrhoids.

Onguent nasal Ruedi *Spirig, Switz.*
Mint oil (p.2345·2); camphor oil (p.2273·3).
Nasal dryness.

Onguent Vaporisant *Prodemdis, Canad.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1).

Onic *Nicholas, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Onicit *Schering-Plough, Braz.; Schering-Plough, Chile; Schering-Plough, Mex.; Schering-Plough, Venez.*
Palonosetron hydrochloride (p.1759·3).
Nausea and vomiting induced by cytotoxics.

Onico Fitex *Belmac, Spain†.*
Borogallic acid; salicylic acid (p.1612·2).
Fungal nail infections.

Onirema *Biotech, Venez.*
Nitrazepam (p.1011·2).
Insomnia; premedication.

Onixol *Schering, Arg.†.*
⊗ Trolamine (p.2405·1); sodium sulfate; potassium acetate; urea (p.1620·2); lavender oil.
Nail disorders.

Oniz *Stadmed, India.*
Ornidazole (p.843·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Onko BCG *Biomed Lublin, Pol.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Onkocristin *Onkoworks, Ger.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Onkodox *Onkoworks, Ger.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Onkofluor *Onkoworks, Ger.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Onkomorphin *Onkoworks, Ger.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

Onkoposid *Onkoworks, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Onkostatil *Microsules, Arg.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Onkotrone *Baxter, Austral.; Baxter Oncology, Cz.; Baxter Oncology, Ger.; Baxter, Hung.; Baxter, Ital.; Baxter, Philipp.; Baxter Oncology, UK.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Onkovertin *Braun, Thai.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Plasma volume expansion; shock; thromboembolism prophylaxis.

Onkoxantron *Onkoworks, Ger.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Onlipeg *Promefarm, Ital.*
Macrogol 4000 (p.2336·3).
Constipation.

Only One *Sisu, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Onoact *Ono, Jpn.*
⊗ Landiolol hydrochloride (p.1323·1).
Intra-operative tachyarrhythmias.

Onofin-K *Rayere, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Onon *Ono, Jpn.*
Pranlukast (p.1130·2).
Allergic rhinitis; asthma.

Onopordon Comp B *Weleda, UK.*
Onopordon; cowslip (p.2372·2); hyoscyamus (p.2323·3).
Cardiac disorders.

Onoprose *Alter, Port.†.*
Promelase (p.2373·3).
Inflammation.

Onoton *Sanofi Synthelabo, Chile†; Sanofi Synthelabo, Mex.*
Pancreatin (p.2360·1); hemicellulase (p.2279·1); ox bile extract (p.2266·3); simeticone (p.1770·2).
Adjunct in abdominal radiography; digestive disorders; flatulence; pancreatic disorders.

Onprelen *Genericon, Cz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Onquevit *Sandoz, Mex.*
Citicoline sodium (p.2283·3).
Cerebral disorders.

Onrectal *Herbes Universelles, Canad.*
⊗ Benzocaine (p.1854·1); bismuth subcarbonate (p.1711·1); bismuth subgallate (p.1711·1); hamamelis (p.2318·2); naphazoline hydrochloride (p.1565·2); zinc oxide (p.1621·2).
Haemorrhoids.

Onsenal *Pfizer, Cz.; Pfizer, Fr.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.*
Celecoxib (p.34·2).
Familial adenomatous polyposis.

Onsetron *Arrow, Austral.; Pacific, NZ.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Onsia *Siam Bheasach, Thai.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Onsudil *Jaba, Port.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Onsukil *Otsuka, Spain†.*
⊗ Procaterol (p.1130·3).
Obstructive airways disease.

Ontak *Eisai, USA.*
Denileukin diftitox (p.710·2).
T-cell lymphoma.

Ontop *Systopic, India.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Ontosein *Tedec Meiji, Spain†.*
Orgotein (p.127·3).
Secondary effects of radiotherapy in bladder cancer.

Ontrax *Blausiegel, Braz.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Onufrid *Rafarm, Gr.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).

Onxel *Darrow, Braz.*
Paclitaxel (p.759·1).
Ovarian cancer.

Onxol *Ivax, Cz.; Zenith Goldline, USA.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; malignant neoplasms; non-small cell lung cancer; ovarian cancer.

Onychomal *Hermal, Ger.*
⊗ Urea (p.1620·2).
Nail disorders.

Onychon *Zentiva, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal infections.

Ony-Clear *Pedinol, USA†.*
Benzalkonium chloride (p.1629·1).
Formerly contained triacetin, cetylpyridinium chloride, and chloroxylenol.
Fungal nail infections.

Onylac *Cipla, India.*
Ciclopirox (p.529·2).
Fungal nail infections.

Onymax
Galderma, Ger.
Terbinafine (p.546·3).
Fungal nail and skin infections.

Galderma, Pol.; Galderma, Switz.
Terbinafine hydrochloride (p.546·3).
Fungal nail, scalp, and skin infections.

Opacist ER *Bracco, Ital.; Bracco, Switz.†.*
Meglumine iodamide (p.1481·3).
Contrast medium for urinary-tract radiography.

Opacite *Justesa Imagen, Arg.*
Meglumine gadopentetate (p.1479·2).
Contrast medium for magnetic resonance imaging.

Opacorden *Polpharma, Pol.*
Amiodarone (p.1210·2).
Arrhythmias.

Opacout *Ingens, Arg.*
Disodium inosinate (p.2296·1).
Cataracts.

Opacrile *Bacon, Arg.*
Iopamidol (p.1483·3).
Radiographic contrast agent.

Opagis *Nevzat, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opak *Merkez, Turk.*
Isopropyl alcohol (p.1650·3).
Skin disinfection.

Opalgyne *Innotech, Fr.*
Benzydamine hydrochloride (p.27·3).
Vaginitis.

Opalino *Weltrap, Arg.*
Sodium picosulfate (p.1771·1).
Constipation.

Opalmon *Ono, Jpn.*
Limaprost alfadex (p.1325·1).
Intermittent claudication; thromboangiitis obliterans.

Opam *Wockhardt, India.*
Pioglitazone (p.456·3).
Diabetes mellitus.

Opamox *Orion, Fin.*
Oxazepam (p.1014·2).
Anxiety disorders; depression; insomnia; psychoses.

Opana *Endo, USA.*
⊗ Oxymorphone hydrochloride (p.107·2).
Pain.

Oparsan Con Lisina y L-Glutamina *Sanitas, Chile.*
Vitamins; minerals; amino acids (p.1922·1).
Dietary supplement.

Opas *Co-Pharma, UK.*
Sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Opatanol *Alcon, Belg.; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hung.; Alcon, Irl.; Alcon, Ital.; Alcon, Neth.; Alcon, Norw.; Alcon, Port.; Alcon, Rus.; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, UK.*
Olopatadine hydrochloride (p.586·3).
Allergic conjunctivitis.

Opazimes *Co-Pharma, UK.*
⊗ Aluminium hydroxide (p.1706·2); light kaolin (p.1738·1); belladonna (p.2263·3); morphine hydrochloride (p.86·3).
Diarrhoea; dyspepsia; gastro-enteritis.

Opcon-A *Bausch & Lomb, Canad.; Bausch & Lomb, Hong Kong; Bausch & Lomb, Mex.; Bausch & Lomb, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic or inflammatory disorders of the eye; eye irritation.

Opehex *Hexal, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Openvas
Note. This name is used for preparations of different composition.
LKM, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Pfizer, Spain.
Olmesartan medoxomil (p.1361·1).
Hypertension.

Operand *Redi-Products, USA.*
Povidone-iodine (p.1659·2).
Skin disinfection; vaginal disorders.

Operium *PP Lab, Thai.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Opglucon *Lotus, Malaysia.*
Gliclazide (p.440·3).
Diabetes mellitus.

Ophan *Chew, Thai.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Coughs; nasal congestion.

Ophcillin N *Medicopharm, Austria.*
Benzylpenicillin sodium (p.213·1); sulfadiazine (p.336·2).
Bacterial eye infections.

Ophdilvas N *Mann, Ger.†.*
Vincamine (p.2414·1).
Cerebral and peripheral vascular disorders; circulatory disorders of the eye.

Ophidus *Motima, Fr.*
Lactobacillus acidophilus (p.2372·3); bifidobacterium.
Maintenance of intestinal flora.

Ophtacalm *Chauvin, Fr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Ophtaclair *Chauvin, Fr.*
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irrigation.

Ophtadil *Chauvin, Fr.†.*
⊗ Buphenine hydrochloride (p.2270·2); ethoxazorutoside (p.2304·2); sodium ascorbate (p.1984·1); *d*-alpha tocoferil acetate (p.1992·3).
Ocular vascular disorders.

Ophtagram *Chauvin Ankerpharm, Cz.†; Chauvin ankerpharm, Ger.†; Bausch & Lomb, Port.; Bausch & Lomb, Switz.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Ophtaguttal *Agepha, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2); boric acid (p.2268·1).
Conjunctival irritation.

Ophtal *Ivax, Cz.*
Boric acid (p.2268·1); benzododecinium bromide (p.1631·2).
Eye disorders.

Ophtalin *Ciba Vision, Ital.*
Sodium hyaluronate (p.2320·1).
Eye surgery.

Ophtalin Plus *Novartis, Turk.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Ophtalmin N *Winzer, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Ophtalmine *Cooperation Pharmaceutique, Fr.*
Boric acid (p.2268·1); borax (p.2268·1); red vine (p.2316·3); rose water (p.1472·3); peppermint water (p.1761·2); hamamelis (p.2318·2).
Eye irritation.

Ophtalmotrim *Viatris, Belg.†.*
Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Ophtamedine *Thea, Belg.*
Hexamidine isetionate (p.1646·3).
Eye disorders; otitis; rhinitis.

Ophtasiloxane *Alcon, Fr.*
Dimeticone (p.2032·1).
Corneal burns; prevention of corneal adhesions.

Ophtasone *Bausch & Lomb, Philipp.; Bausch & Lomb, Switz.*
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin sulfate (p.282·1).
Infected eye disorders.

Ophtavit C *Omega, Belg.*
Ascorbic acid (p.1983·3).
Eye disorders.

Ophtaxia *Chauvin, Fr.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride (p.1667·1).
Eye irrigation.

Ophthalin *Ciba Vision, Austral.; Novartis Ophthalmics, Hung.†; Novartis, Irl.†; Ciba Vision, Israel; Zeiss, NZ; Ciba Vision, Thai.; Iocom, UK.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Ophthalmo-Azaphenicol *Galena, Cz.†.*
Azidamfenicol (p.206·3).
Bacterial eye infections.

Ophthalmo-Azulen *Zentiva, Cz.*
Guaiazulene (p.2317·3).
Eye trauma.

Ophthalmo-Evercil *Ivax, Cz.*
Phenylephrine hydrochloride (p.1568·1); esculoside (p.2248·2).
Eye irritation.

Ophthalmo-Framykoin *Zentiva, Cz.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Bacterial eye infections.

Ophthalmo-Framykoin Compositum *Zentiva, Cz.*
⊗ Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); hydrocortisone acetate (p.1535·2).
Eye disorders.

Ophthalmo-Septonex
Note. This name is used for preparations of different composition.
Ivax, Cz.
Eye drops: Carbaethopendecinium bromide (p.1633·3); boric acid (p.2268·1); borax (p.2268·1); guaiazulene (p.2317·3); fennel oil (p.2303·1).
Eye disorders.

Zentiva, Cz.
Eye ointment: Carbaethopendecinium bromide (p.1633·3).
Eye disorders.

Ophthalmo-Timogal *Ivax, Cz.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Ophthetic *Allergan, Austral.†; Allergan, Canad.†; Allergan, NZ; Allergan, USA.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Ophthifluor *Deklerht, USA.*
Fluorescein sodium (p.2306·1).
Ophthalmic diagnostic agent.

Ophtho-Bunolol *Altimed, Canad.†.*
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma.

Ophtho-Tate *Altimed, Canad.†.*
⊗ Prednisolone acetate (p.1541·1).
Eye disorders.

Ophtilan *Lannacher, Austria†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ophtim *Thea, Fr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ophtocain N *Winzer, Ger.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia for ophthalmic procedures.

Ophtopur-Z *Winzer, Ger.*
Zinc sulfate (p.1999·2).
Eye disorders.

Opibion *Otto, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid; vitamin B (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemia; nutritional supplement.

Opibright *Otto, Indon.*
Myrtillus (p.2349·3); betacarotene; vitamin A; vitamin E (p.1922·1).
Eye disorders.

Opicef *Otto, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Opicel *Otto, Indon.*
Barrier preparation.
Dry skin.

Opicillin *Otto, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Opiclam *Otto, Indon.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Gram-positive bacterial infections.

Opidina *BA Farma, Port.†.*
Ticlopidine (p.1412·1).

Opidol *Norpharma, Denm.†; Mundipharma, Swed.†.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Opigesic *Bayer, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Opilax *Otto, Indon.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Opilet *Rafarm, Gr.*
Azelaic acid (p.1589·3).
Acne.

Opilina *Arex, Venez.*
Oxolamine (p.1567·1).
Cough.

Opilina Compuesta *Arex, Venez.*
Oxolamine phosphate (p.1567·1); bromhexine hydrochloride (p.1552·2).
Cough.

Opilon *Hansam, Irl.; Concord, UK.*
Moxisylyte hydrochloride (p.1344·3).
Meniérè's disease; peripheral vascular disorders; Raynaud's syndrome.

Opimox *Otto, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Opineuron *Otto, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Opino
Note. This name is used for preparations of different composition.
Biomo, Ger.
Aescin (p.2248·2).
Venous insufficiency.

Soho, Indon.; Tropon, Indon.
⊗ Buphenine hydrochloride (p.2270·2); aescin (p.2248·2); rosemary oil (p.2381·3); turpentine oil (p.2406·3); melissa oil (p.2339·3).
Phlebitis; soft-tissue injury; thrombophlebitis; varicose veins; venous insufficiency.

Rosch & Handel, Austria.
Tablets: ⊗ Buphenine hydrochloride (p.2270·2); aescin (p.2248·2).
Vascular disorders.

Rosch & Handel, Austria.
Topical gel: ⊗ Buphenine hydrochloride (p.2270·2); aescin (p.2248·2); rosemary oil (p.2381·3); pumilio pine oil (p.2376·3); melissa oil (p.2339·3).
Vascular disorders.

opino N *Biomo, Ger.*
Aescin (p.2248·2).
Soft-tissue disorders.

opino N spezial *Gepepharm, Ger.†.*
⊗ Buphenine hydrochloride (p.2270·2); aescin (p.2248·2).
Soft-tissue disorders; venous insufficiency.

Opino-jel *Menarini, Gr.*
⊗ Buphenine hydrochloride (p.2270·2); aescin (p.2248·2); melissa oil (p.2339·3); pumilio pine oil (p.2376·3); rosemary oil (p.2381·3).
Muscle injuries; thrombophlebitis; varicose veins.

Opiphen *Otto, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Opiren *Almirall, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opistan *Otto, Indon.*
Mefenamic acid (p.80·1).
Fever; menorrhagia; pain.

Opithrocin *Otto, Indon.*
Erythromycin ethyl succinate (p.269·3); erythromycin stearate (p.270·1).
Bacterial infections.

Opixime *Otto, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Opizone *Britannia Pharmaceuticals, UK.*
Naltrexone hydrochloride (p.1455·2).

O-Plat
Note. A similar name is used for preparations of different composition (see below).
Raffo, Arg.; Zodiac, Braz.; Tecnofarma, Chile.
Oxaliplatin (p.757·3).
Mmalignant neoplasms.

Oplat
Note. A similar name is used for preparations of different composition (see above).
Nolver, Venez.
Carboplatin (p.693·1).
Malignant neoplasms.

Opliphon *Fada, Arg.*
Phenytoin (p.495·2).
Epilepsy.

Opm *Meprofarm, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opnol *CCS, Swed.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Opobyl
Note. This name is used for preparations of different composition.
Spedrog, Arg.
Bile salts (p.2266·2); boldo (p.2267·2); belladonna (p.2263·3).
Dyspepsia; hepatobiliary disorders.

Bailly, Fr.; Uriach, Spain.
Aloes (p.1705·2); boldo (p.2267·2).
Constipation.

Opobyl-phyto *Medipharma, Ger.†.*
Greater celandine (p.2317·1); turmeric (p.1473·2).
Biliary-tract disorders.

Opocarbon *Monserrat, Arg.*
Phthalylsulfathiazole (p.315·1); neomycin sulfate (p.305·1); activated charcoal (p.1435·2); kaolin (p.1738·1).
Bowel sterilisation; diarrhoea; gastrointestinal infections.

Opocler *Monserrat, Arg.†.*
Phthalylsulfathiazole (p.315·1); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Opodeldok *Biogal-Teva, Hung.†.*
Sapo stearini; ammonia solution (p.2256·1); camphor (p.2273·2); lavender oil (p.2331·2).
Rheumatic pain.

Opoenterol *Lafage, Arg.†.*
Lactic acid (p.2329·3); homatropine (p.1881·2); papain (p.2362·3); pepsin (p.2365·1).
Muscle spasm.

Opon *Gripin, Turk.*
Aspirin (p.20·3).
Fever; pain.

Oponaf *Juste, Spain.*
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

Opoplex *Valeant, Braz.*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Opo-Veinogene *Zydus, Fr.*
Red vine (p.2316·3); aesculus (p.2248·2); esculoside (p.2248·2).
Haemorrhoids; peripheral vascular disorders.

Opovital B12 *Roux-Ocefa, Arg.*
Vitamin B substances; minerals (p.1922·1).

Opox *Guardian, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Opplin *TNP, Thai.†.*
Boric acid (p.2268·1); borax (p.2268·1); allantoin (p.1588·1); chlorobutanol (p.1639·2); salicylic acid (p.1612·2); zinc sulfate (p.1999·2); hamamelis (p.2318·2).
Eye irritation.

Opra *Actavis, Rus.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Opraclean *Lohmann, Ger.*
Iodoform (p.1650·2).
Dental infections.

Oprad *Cryopharma, Mex.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Opraks *Toprak, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Opram *Armoxindo, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Opramid *IQFA, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Oprane *Vifor, Switz.*
Agnus castus (p.2249·1).
Premenstrual syndrome.

Oprazol *Spirig, Switz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oprazole *Hikma, Cz.†; Atlantic, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Oprazon *Ariston, Braz.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Peptic ulcer.

Opredsone *Greater Pharma, Thai.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Oprezol *Kimia, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Opridan *Farmedia, Gr.*
Isotretinoin (p.1599·2).
Acne.

Opridon *Deva, Turk.*
Opipramol hydrochloride (p.414·1).
Depression.

Oprimol *Taro, Israel; Fako, Turk.*
Opipramol hydrochloride (p.414·1).
Depression.

O'Prin *Dolisos, Canad.†.*
Homoeopathic preparation.

Oprizole *Essenpharma, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Opsacin *PD, Thai.†.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Opsa-His *PD, Thai.†.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic eye disorders; conjunctivitis.

Opsar *PD, Thai.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Opsaram *PD, Thai.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Opsardex *PD, Thai.†.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1).
Bacterial eye and ear infections.

Opsil *Silom, Thai.†.*
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation.

Opsil Tears *Silom, Thai.*
Hypromellose (p.2144·2) (p.1622·2).
Dry eye; wetting solution for hard contact lenses.

Opsil-A *Silom, Thai.*
⊗ Tetryzoline hydrochloride (p.1574·1); antazoline hydrochloride (p.567·1).
Allergic eye disorders.

Opsite *Smith & Nephew, Austral.; Smith & Nephew, Fr.; Smith & Nephew, Ger.†; Smith & Nephew, S.Afr.; Smith & Nephew Healthcare, UK.*
Polyurethane dressing (p.1611·1).
Burns; wounds.

Opsite Flexigrid *Smith & Nephew, Ital.*
Polyurethane dressing (p.1611·1).
Ulcers; wounds.

Opsonat *Pekana, Ger.†.*
Homoeopathic preparation.

Opstres *Multicare, Philipp.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Optacid *Meditop, Hung.*
Sodium hydrogen sulfate; monobasic sodium phosphate (p.1682·3).
Gastrointestinal disorders.

Optacilin *Nycomed, Braz.*
Ampicillin benzathine (p.205·1); ampicillin sodium (p.204·1).
Bacterial infections.

Optaflan *Gallia, Braz.†.*
Nimesulide (p.95·3).

Optaflu *Novartis Vaccines, Cz.; Novartis Vaccines, UK.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Optajun *F5 Profas, Spain.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Optal
Note. This name is used for preparations of different composition.
Olan-Kemed, Thai.
Eye drops: Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Olan-Kemed, Thai.
Eye lotion: Boric acid (p.2268·1); borax (p.2268·1); chlorobutanol (p.1639·2); salicylic acid (p.1612·2).
Eye irritation.

Optalgin *Teva, Israel.*
Dipyrone (p.49·2).
Fever; pain.

Optalia *Boiron, Canad.*
Homoeopathic preparation.

Optalidon
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.†; Novartis Consumer, Port.; Novartis Consumer, Spain.
Propyphenazone (p.119·3); caffeine (p.1116·3).
Pain.

Novartis Consumer, Ger.
Ibuprofen (p.64·2).
Fever; pain.

Novartis Consumer, Ital.
Propyphenazone (p.119·3); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Optalidon N *Novartis Consumer, Ger.*
Propyphenazone (p.119·3); caffeine (p.1116·3).
Pain.

Optalidon Nieuwe Formule *Novartis Consumer, Belg.*
Ibuprofen (p.64·2).
Fever; pain.

Optalidon special NOC *Novartis, Ger.†.*
Dihydroergotamine mesilate (p.618·2); propyphenazone (p.119·3).
Vascular headache.

Optamax *Globo, Braz.†.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Optamid *Proge, Ital.†; Ulagay, Turk.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Optamide *McGloin, Austral.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Optamox
Note. This name is used for preparations of different composition.
Roemmers, Arg.
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Pharma Investi, Chile.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Optaphen *Pascual, Philipp.*
⊗ Pheniramine maleate (p.587·3); naphazoline hydrochloride (p.1565·2).
Allergic eye disorders; eye irritation.

Optasid *Gador, Arg.†.*
Etoposide (p.718·1).
Lung cancer; testicular cancer.

Optavite *Akorn, Canad.; Dioptic, Canad.*
Vitamin and mineral preparation (p.1922·1).

Optazine *Wyeth Consumer, Austral.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Optazine Fresh *Wyeth Consumer, Austral.†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Optazol *Hormona, Mex.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Opteron *GiEnne, Ital.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Opthaflox *Grin, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Opthagen *Pascual, Philipp.*
Gentamicin sulfate (p.282·1).
Conjunctivitis.

Optha-LL *Landson, Indon.*
Lutein (p.1954·3); lycopene; vitamin E; zinc; betacarotene; vitamin A; myrtillus (p.2349·3) (p.1922·1).
Supplement for healthy eyes.

Opthavir *Grin, Mex.*
Aciclovir (p.862·3).
Herpes simplex keratitis.

Opthiparma-S *Alpharma, Mex.†.*
Multivitamin preparation (p.1922·1).

Optibet *Sanbe, Indon.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Optibetol *Polfa Warszawa, Pol.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Optibiol
Nutrisante, Fr.
Nutritional supplement with fatty acids (p.1922·1).
Visual disorders.

Yves Ponroy, Singapore.
Omega-3 triglycerides; phospholipids; lutein; zeaxanthin; cryptoxanthin; vitamin E; vitamin C; zinc; chromium (p.1922·1).
Nutritional supplement for maintenance of eye health.

Polinac, Venez.
Betacarotene; chromium yeast; zinc; yeast; cranberry; egg phospholipids; vegetable oil; fish oil (p.1922·1).
Dietary supplement.

Optic *TP, Thai.*
Boric acid (p.2268·1); chlorobutanol (p.1639·2); borax (p.2268·1).
Eye irritation.

Opticaine *Biocel, Turk.*
Proxymetacaine (p.1870·2).
Local anaesthesia.

Optical *Strallhofer, Austria.*
Multivitamin preparation with calcium carbonate (p.1922·1).

Optical mit Eisen *Strallhofer, Austria.*
Multivitamin preparation with calcium carbonate and ferrous gluconate (p.1922·1).

Opticare PMS *Standard Drug, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Opticide *Pharmaland, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Opti-Clean *Alcon, Braz.; Alcon, USA.*
Cleaning solution for contact lenses (p.1622·2).

Opti-Clean II *Alcon, Canad.*
Cleaning solution for hard and soft contact lenses (p.1622·2).

Opticort *Sandoz, Canad.*
⊗ Framycetin sulfate (p.279·1); gramicidin (p.286·1); dexamethasone sodium metasulfobenzoate (p.1526·2).
Infected eye and ear disorders.

Opticrom *Aventis, Austral.; Melisana, Belg.; Allergan, Canad.; Aventis, Ger.; Aventis, Hong Kong†; Teva, Hung.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Aventis, Switz.; Aventis, Thai.†; Eczacibasi, Turk.; Aventis, UK; Allergan, USA.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; keratitis; keratoconjunctivitis; vernal keratoconjunctivitis.

Opticron *Cooperation Pharmaceutique, Fr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Opticyl *Optopics, USA.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Optiday GQ *Biofarma, Mex.*
A range of vitamin and mineral preparations (p.1922·1).

Optiderm *Hermal, Austria; Hermal, Ger.; Boots Healthcare, Ital.; Herrmann, Pol.; Boots Healthcare, Switz.*
⊗ Urea (p.1620·2); lauromacrogol 400 (p.1916·1).
Dry and pruritic skin disorders.

Optidorm *Dolorgiet, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Optifast VLCD *Novartis Consumer, Austral.*
Preparation for enteral nutrition (p.1922·1).
Obesity.

Optifen *Spirig, Switz.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Optifluor *Diba, Mex.*
Fluorescein sodium (p.2306·1).
Aid to eye examination.

Opti-Free
Note. This name is used for preparations of different composition.
Alcon, Braz.; Alcon, Canad.; Alcon, Fr.; Alcon, NZ; Alcon, S.Afr.; Alcon, USA; Alcon, Venez.†.
A range of preparations for contact lens care (p.1622·2).

Alcon, Mex.
Pancreatin (p.2360·1)(p.1622·2).
Cleansing solution for contact lenses.

Opti-Free Comfort *Alcon, Austral.†.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3) (p.1622·2).
Lubricating and rewetting solution for contact lenses.

Opti-Free Daily *Alcon, Austral.*
Cleansing solution for soft contact lenses (p.1622·2).

Opti-Free Enzimatica *Alcon, Braz.†.*
Pancreatin (p.2360·1) (p.1622·2).
Cleansing and disinfecting of contact lenses.

Opti-Free Enzymatic *Alcon, Austral.†.*
Pancreatin (p.2360·1) (p.1622·2).
Cleansing and disinfecting of soft contact lenses.

Opti-Free Express *Alcon, Austral.; Alcon, Braz.; Alcon, Mex.; Alcon, UK.*
Cleaning, disinfecting, rinsing, and storage solution for soft and disposable contact lenses (p.1622·2).

Opti-Free Multi-Acao *Alcon, Braz.*
Solutions for contact lens care (p.1622·2).

Opti-Free Multiaccion *Alcon, Mex.*
Cleansing, disinfecting, and lubricating solution for contact lenses (p.1622·2).

Opti-Free Multi-Action *Alcon, Austral.†.*
Cleaning, rinsing, disinfecting, storing, and lubricating solution for soft and disposable contact lenses (p.1622·2).

Opti-Free Replenish *Alcon, Braz.*
Disinfecting solution for contact lenses (p.1622·2).

Opti-Free Supra Clens *Alcon, Mex.*
Pancreatin (p.2360·1)(p.1622·2).
Cleansing solution for contact lenses.

Opti-Free Supraclens *Alcon, Braz.*
Pancreatin (p.2360·1) (p.1622·2).
Cleansing of contact lenses.

Optifresh
Note. This name is used for preparations of different composition.
Konimex, Indon.
Polyvinyl alcohol (p.2145·3).
Dry eyes; eye irritation.

Vivax Optipharm, Venez.
⊗ Dextran; hypromellose (p.2144·2).
Dry eyes.

Optigen *Xepa-Soul Pattinson, Hong Kong†.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Optigene *Pfeiffer, USA.*
Electrolytes (p.1667·1).
Eye irrigation.

Optigene 3 *Pfeiffer, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Minor eye irritation.

Opti-Genta *Vitamed, Israel.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Optiject *Codali, Belg.; Guerbet, Fr.*
Ioversol (p.1486·2).
Radiographic contrast medium.

Optil *Opus, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Optilac *Valeant, Arg.*
Chondroitin sulfate sodium (p.2280·3); aprotinin (p.1055·1).
Dry eyes.

Optilast *Asta Medica, Israel; Viatris, UK.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

Optilets
Abbott, Hong Kong†.
Multivitamin and mineral preparation (p.1922·1).

Abbott, USA.
Multivitamin preparation (p.1922·1).

Optilets-M *Abbott, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Optilube *Dioptic, Canad.*
Wool fat (p.2033·2); liquid paraffin (p.2030·3); soft paraffin (p.2031·2).

Optilube PVA *Dioptic, Canad.*
Polyvinyl alcohol (p.2145·3).

Optima *Stanley, Canad.†; Stanley, Israel.*
Multivitamin and mineral preparations (p.1922·1).

Optima IFX *Usana, Mex.*
Vitamin C, zinc, and caroteinoids (p.1922·1).

Opti-Mag *Pierre Fabre, Ital.*
Vitamin B substances; magnesium; zinc (p.1922·1).

Optimal *Inibsa, Port.†.*
Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Optimark *Mallinckrodt, Arg.; Mallinckrodt, Austral.; Tyco, Canad.; Tyco, Cz.; Tyco, Port.; Mallinckrodt, USA.*
Gadoversetamide (p.1480·3).
Contrast medium for magnetic resonance imaging.

Optimax
Note. This name is used for preparations of different composition.
Ferron, Indon.
Lutein (p.1954·3); lycopene (p.2335·2); vitamin E; ascorbic acid; zinc; betacarotene; myrtillus (p.2349·3) (p.1922·1).
Supplement for healthy eyes.

Merck, UK.
Tryptophan (p.427·1).
Depression.

Optimental *Abbott, Canad.*
Preparation for enteral nutrition (p.1922·1).

Optimin
Note. This name is used for preparations of different composition.
Abbott, Mex.
Multivitamin and mineral preparation (p.1922·1).

Essex, Spain†.
Loratadine (p.583·3).
Hypersensitivity reactions.

Optimina Fem *Temis, Arg.*
Pollen; ginseng; vitamins (p.1922·1).
Tonic.

Optimina + Ginseng con Vit *Temis, Arg.†.*
Pollen; ginseng; vitamins (p.1922·1).
Tonic.

Optimina Plus *Temis, Arg.*
Yohimbine hydrochloride (p.2200·2); pollen (p.2370·2); ginseng (p.2312·1); vitamin E.
Erectile dysfunction.

Optimine *Schering, Canad.*
Azatadine maleate (p.568·1).
Hypersensitivity reactions.

Optimoist *Colgate-Palmolive, USA.*
Hyetellose (p.2143·3); electrolytes (p.1667·1); sodium monofluorophosphate (p.1964·3); xylitol (p.1998·2).
Dry mouth.

Optimol *Alphapharm, Austral.†; Santen, Denm.; Duopharma, Hong Kong; Sun, Rus.; Santen, Swed.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Optimus *Gerolymatos, Gr.*
Terbinafine (p.546·3).
Fungal infections.

Optimyxin
Note. This name is used for preparations of different composition.
Sandoz, Canad.
Eye ointment: Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Eye infections.

Sandoz, Canad.
Eye/ear drops: Polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Eye or ear infections.

Optimyxin Plus *Sandoz, Canad.*
Polymyxin B sulfate (p.317·3); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Eye or ear infections.

Optinate *Sanofi-Aventis, Fin.; Lepetit, Ital.; Aventis, Norw.; Aventis, Swed.*
Risedronate sodium (p.1103·3).
Osteoporosis; Paget's disease of bone.

Optinate Combi *Aventis, Swed.*
4 Tablets, risedronate sodium (p.1103·3); 24 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Optinate Omega-3 *First Horizon, USA.*
Tablets, vitamin and mineral preparation with iron and folate (p.1922·1); capsules, docosahexaenoic acid (p.1362·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Dietary supplement.

Optinate Septimum *Aventis, Swed.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Optinem *AstraZeneca, Austria.*
Meropenem (p.297·2).
Bacterial infections.

Optineuron
Note. This name is used for preparations of different composition.
Lupin, India.
Injection: Vitamin B substances (p.1922·1); dexpanthenol (p.2362·1).
Neuropathies.

Lupin, India.
Tablets: Vitamin B substances (p.1922·1).
Neuropathies.

Optipar *Sandoz, Fin.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Optipect Kodein *UCB, Ger.*
Codeine (p.37·2).
Coughs.

Optipect N *UCB, Ger.*
Camphor (p.2273·2); menthol (p.2340·1); peppermint oil (p.1761·2).
Respiratory-tract disorders.

Opti-Plus
Note. This name is used for preparations of different composition.
Alcon, Austral.†.
Pancreatin (p.2360·1) (p.1622·2).
Cleaning solution for soft contact lenses.

Alcon, NZ†.
Cleaning solution for soft contact lenses (p.1622·2).

OptiPranolol *Bausch & Lomb, USA.*
⊗ Metipranolol hydrochloride (p.1883·2).
Glaucoma; ocular hypertension.

Optipred *Prohealth, Philipp.*
⊗ Prednisolone (p.1540·3) or prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Optipres *Cipla, India.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; ocular hypertension.

Optipyrin *Pfleger, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Optiray *Mallinckrodt, Arg.; Mallinckrodt, Austral.; Mallinckrodt, Austria; Codali, Belg.; Tyco, Canad.; Tyco, Cz.; Tyco, Denm.; Tyco, Fin.; Guerbet, Fr.; Tyco, Ger.†; Alfa Medis, Gr.; Tyco, Hung.; Guerbet, Israel; Tyco, Ital.; Mallinckrodt, Neth.; Tyco, Norw.; Tyco, Port.; Tyco, Spain; Tyco, Swed.; Guerbet, Switz.; Tyco, UK; Mallinckrodt, USA.*
Ioversol (p.1486·2).
Radiographic contrast medium.

Opti-safe *Fischer, Israel.*
Flavonoid compounds (p.2304·1); lutein (p.1954·3); myrtillus (p.2349·3); rutoside (p.2305·1); vitamins; minerals (p.1922·1).

Opti-safe AREDS *Fischer, Israel.*
Lutein (p.1954·3); vitamins; minerals (p.1922·1).
Age-related macular degeneration; eye disorders.

Optisedine *Sterop, Belg.*
Lorazepam (p.1004·1).
Anxiety.

Optiskin *Urgo, Fr.*
Polyurethane dressing (p.1611·1).
Wounds.

Opti-Soak
Note. This name is used for preparations of different composition.
Alcon, Austral.†; Alcon, Braz.†; Alcon, Canad.; Alcon, Fr.; Alcon, NZ; Alcon, S.Afr.; Alcon, Venez.†.
Wetting, soaking, and disinfecting solution for rigid gas permeable and hard contact lenses (p.1622·2).

Alcon, Mex.
Polidronium chloride (p.1622·2).
Wetting, disinfecting and storage of gas-permeable and hard contact lenses.

Opti-Soft *Alcon, USA.*
Rinsing and storage solution for soft contact lenses (p.1622·2).

Optisol *Fischer, Israel.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Optison *Mallinckrodt, Arg.†; Amersham, Austria; GE, Cz.; Amersham, Denm.; Amersham, Ger.; Amersham, Gr.; Amersham Health, Hung.; Amersham, Ital.; GE Healthcare, Neth.; GE, Port.; Amersham, Spain; Amersham, Swed.; Amersham, Switz.; Amersham, UK; GE Healthcare, USA.*
Perflutren (p.1488·2) labelled albumin.
Contrast medium for echocardiography.

Optisulin *Sanofi-Aventis, Cz.; Aventis, Neth.; Sanofi-Aventis, Port.*
⊗ Insulin glargine (p.449·3).
Diabetes mellitus.

Opti-Tears
Note. This name is used for preparations of different composition.
Alcon, Braz.
Dextran; hypromellose (p.2144·2) (p.1622·2).
Comfort drops for contact lenses.

Alcon, Canad.; Alcon, S.Afr.; Alcon, UK; Alcon, USA.
Comfort drops for contact lenses (p.1622·2).

Optium
Note. This name is used for preparations of different composition.
Abbott, Arg.; PSI, Ital.; Abbott Diabetes Care, UK.
Test for glucose and ketones in blood.

Medisense, Austral.†.
Test for glucose in blood (p.2314·1).

Columbia, Mex.
Clonixin lysine (p.37·1); caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Vascular headache.

Optium Plus *Abbott, UK.*
Test for glucose in blood (p.2314·1).

Optium Xceed *Abbott, Irl.*
Test for glucose and ketones in blood.

Opti-Up *Varifarma, Arg.†.*
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Optivar *Medpointe, USA.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis.

Optivate *BPL, Singapore; BPL, UK.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Optive *Allergan, USA.*
Carmellose sodium (p.2142·1).
Dry eyes.

Optivit *Leiras, Fin.†.*
Multivitamin and mineral preparation (p.1922·1).

Optivita Plus *Konsuma, Venez.*
Vitamin and mineral preparation (p.1922·1).

Optivite PMT *Optimox, USA.*
Multivitamin and mineral preparation (p.1922·1).
Premenstrual syndrome.

Optiwhite *Pharmatrix, Arg.†.*
⊗ Urea (p.1620·2).
Dental whitener.

OptiZen *InnoZen, USA.*
Polysorbate 80 (p.1919·2).
Dry eyes.

Optizoline *Xepa-Soul Pattinson, Hong Kong.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Opti-Zyme *Alcon, Canad.†; Alcon, USA.*
Pancreatin (p.2360·1) (p.1622·2).
Range of cleansing solutions for contact lenses.

Optobet *Vilco, Gr.*
Diclofenac sodium (p.44·3).
Prevention of miosis in ophthalmic surgery.

Optocain *Molteni, Ital.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Optocef *Bayer, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Optocillin *Bayer, Ger.†.*
Mezlocillin sodium (p.299·3); oxacillin sodium (p.311·3).
Bacterial infections.

Optomicin
Note. A similar name is used for preparations of different composition (see below).
Grin, Mex.
Erythromycin stearate (p.270·1).
Bacterial eye infections.

Optomycin
Note. A similar name is used for preparations of different composition (see above).
Vendiz, Philipp.
Chloramphenicol (p.239·3).
Bacterial eye and ear infections.

Optosol *Otsuka, Thai.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium acetate; sodium citrate (p.1667·1).
Eye irritation.

Optovit *Hermes, Ger.; Vifor, Switz.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Optovit E *Qualiphar, Belg.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency; vitamin E supplement.

Optovite B12 *Normon, Spain.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Optrex
Note. This name is used for preparations of different composition.
Reckitt & Colman, Austral.
⊗ Hamamelis (p.2318·2); naphazoline hydrochloride (p.1565·2).
Formerly known as Optrex Medicated.
Eye irritation.

Schering-Plough, Canad.; Boots Healthcare, Ital.; Optrex, Malaysia; Boots Healthcare, NZ; Reckitt Benckiser, Port.; Optrex, Singapore; Boots Healthcare, Spain; Boots Healthcare, Switz.; Boots, Thai.; Crookes Healthcare, UK.
Hamamelis (p.2318·2).
Dry eyes; eye congestion and irritation.

Pierre Fabre Sante, Fr.
⊗ Chlorobutanol (p.1639·2); salicylic acid (p.1612·2); alcohol (p.1625·2); boric acid (p.2268·1); hamamelis (p.2318·2).
Eye irritation; eye wash.

Optrex Allergy *Crookes Healthcare, UK.*
Sodium cromoglicate (p.1136·3).
Formerly known as Optrex Hayfever Allergy.
Allergic conjunctivitis.

Optrex compresses *Boots Healthcare, Switz.*
Hamamelis (p.2318·2); allantoin (p.1588·1).
Eye irritation.

Optrex Contact Lens Friendly Eye Drops
Reckitt Benckiser, UK.
Sodium hyaluronate (p.2320·1) (p.1622·2).
Dry eyes.

Optrex Hayfever Allergy *Boots Healthcare, NZ.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Optrex Infected Eyes *Reckitt Benckiser, UK.*
Chloramphenicol (p.239·3).
Bacterial conjunctivitis.

Optrex Original *Boots Healthcare, Austral.*
Hamamelis (p.2318·2).
Eye irritation.

Optrex Red Eyes *Crookes Healthcare, UK.*
⊗ Hamamelis (p.2318·2); naphazoline hydrochloride (p.1565·2).
Formerly known as Optrex Clear Eyes.
Eye irritation.

Optrex Red-Eye Relief *Boots Healthcare, NZ.*
⊗ Hamamelis (p.2318·2); naphazoline hydrochloride (p.1565·2).
Eye irritation.

Optrine *Konimex, Indon.*
⊗ Naphazoline (p.1565·1).

Optruma *Lilly, Cz.; Leiras, Fin.†; Pierre Fabre, Fr.; Merckle, Ger.; Menarini, Ital.; Lilly, Neth.; Lilly, Port.; Pensa, Spain.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Optryl *Teva, Israel.*
⊗ Naphazoline (p.1565·1); diphenhydramine hydrochloride (p.577·2).
Eye disorders.

Opturem *Kade, Ger.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

OPV-Merieux *Aventis, S.Afr.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Opyrin *Taisho, Jpn.*
Flufenamate aluminium (p.61·1).
Fever; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Ora *Masa, Thai.*
Lorazepam (p.1004·1).
Anxiety; neuroses.

ORA5 *McHenry, USA.*
Copper sulfate (p.1935·3); potassium iodide (p.2169·2); iodine (p.2169·2).
Minor mouth or throat irritation.

Orabase *BMS, Austral.; Convatec, Canad.†; BMS, Irl.; BMS, Israel†; BMS, NZ; BMS, S.Afr.; Convatec, UK.*
⊗ Carmellose sodium (p.2142·1); pectin (p.2145·2); gelatin (p.1072·1).
Oral and perioral lesions; skin lesions; stoma care.

Orabase Baby *Colgate-Hoyt, USA.*
Benzocaine (p.1854·1).
Mouth disorders.

Orabase Gel *Colgate Oral, USA.*
Benzocaine (p.1854·1).

Orabase HCA *Colgate-Hoyt, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Oral inflammatory and ulcerative lesions.

Orabase Lip *Colgate-Hoyt, USA.*
Benzocaine (p.1854·1); allantoin (p.1588·1); menthol (p.2340·1); camphor (p.2273·2); phenol (p.1656·1).
Minor irritation.

Orabase-B *Colgate-Palmolive, USA.*
Benzocaine (p.1854·1).
Oral lesions.

Orabet
Note. This name is used for preparations of different composition.
Hexal, Austria†; Gea, Denm.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Berlin-Chemie, Ger.
Tolbutamide (p.463·1).
Diabetes mellitus.

Orabetic *Biolab, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Orabiot UD *Elvetium, Arg.†.*
Clarithromycin (p.248·2).
Bacterial infections.

Oracare *Pascual, Philipp.*
Chlorine dioxide (p.1639·1).
Halitosis.

Oracea *CollaGenex, USA.*
Doxycycline (p.267·1).
Rosacea.

Oracef *KRKA, Cz.†; Lilly, Ger.†.*
Cefalexin (p.218·2).
Bacterial infections.

Oracefal *BMS, Fr.*
Cefadroxil (p.218·1).
Bacterial infections.

Oraceftin *Fako, Turk.*
Cefuroxime (p.238·2) or cefuroxime axetil (p.238·2).
Bacterial infections.

Oracilin *Legrand, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Oracilline *Schwarz, Fr.*
Phenoxymethylpenicillin (p.314·1) or benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Oracit *Carolina, USA.*
Sodium citrate (p.1673·3); citric acid (p.2284·1).
Chronic metabolic acidosis; urine alkalinising agent.

Oracort
Note.This name is used for preparations of different composition.
Taro, Canad.; Taro, Israel; AFT, NZ.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Brel, Philipp.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Oracort E *Taro, Israel.*
⊗ Triamcinolone acetonide (p.1544·3); lidocaine hydrochloride (p.1862·3).
Oral lesions.

Oraday *Biolab, Hong Kong; Biolab, Malaysia†; Biolab, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Oradekan *Streger, Mex.*
Multivitamin preparation (p.1922·1).

Oradex *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Chlorhexidine gluconate (p.1635·3).
Gingivitis; mouth ulcers; oral hygiene.

Oradexon
Organon, Belg.
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Organon, Chile; Organon, Indon.; Organon, Neth.; Organon, Philipp.
⊗ Dexamethasone (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hung.; Organon, Port.; Donmed, S.Afr.†; Organon, Thai.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Oradroxil *Lampugnani, Ital.*
Cefadroxil (p.218·1).
Bacterial infections.

Orafen *Technilab, Canad.†.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders; pain.

Orafer Comp *Rhein, Mex.*
Ferrous sulfate (p.1939·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Iron deficiency; iron-deficiency anaemia.

Orafilm *Rowe-Fleming, Venez.†.*
Anthraquinone glycosides (p.1768·3); salicylic acid (p.1612·2).
Mouth disorders.

Oragalin Espasmolitico *Lacer, Spain.*
Azintamide (p.2262·2); hyoscine methobromide (p.1734·1).
Hepatobiliary disorders.

Ora-Gallin *Nycomed, Austria.*
Azintamide (p.2262·2); pancreatin (p.2360·1); cellulase (p.2279·1).
Liver and biliary disorders.

Ora-Gallin compositum *Nycomed, Austria.*
Azintamide (p.2262·2); papaverine hydrochloride (p.2191·3).
Gastrointestinal disorders; liver and biliary disorders.

Ora-Gallin purum *Nycomed, Austria.*
Azintamide (p.2262·2).
Liver and biliary disorders.

Oragard *Colgate-Palmolive, Ital.*
Hydrogen peroxide (p.1647·3).
Mouth disorders.

Oragesic
Note.This name is used for preparations of different composition.
Jean-Marie, Hong Kong.
⊗ Triamcinolone acetonide (p.1544·3); lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Parnell, USA.
Benzyl alcohol (p.1631·3); menthol (p.2340·1).
Formerly known as TiSol.
Minor mouth or throat irritation.

Orahesive *Convatec, Austral.†; Convatec, Canad.†; Convatec, UK.*
⊗ Carmellose sodium (p.2142·1); pectin (p.2145·2); gelatin (p.1072·1).
Dental adhesive; oral and perioral lesions; stoma and fistula care.

Orahex *Pharmahex, Philipp.*
Chlorhexidine gluconate (p.1635·3).
Gingivitis; halitosis; oral hygiene.

Oraica *Esfar, Port.†.*
Orotic acid (p.2358·3); orazamide (p.2357·3).
Gout; hyperuricaemia.

Orajel *Del, Canad.; Sanitas, Chile†; Hand-Prod, Pol.; AHA, UK; Del, USA.*
Benzocaine (p.1854·1).
Minor mouth or throat irritation; toothache.

Orajel Compuesto *Sanitas, Chile†.*
Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); zinc chloride (p.1999·1).
Mouth disorders.

Orajel Mouth Aid
Note.This name is used for preparations of different composition.
Del, USA.
Topical gel: Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); zinc chloride (p.1999·1).
Mouth and lip sores.

Del, USA.
Topical liquid: Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Orajel Mouth Sore Medicine *Del, Canad.*
Benzocaine (p.1854·1); zinc chloride (p.1999·1).
Formerly known as Orajel Mouth Aid.
Oral pain.

Orajel Perioseptic
Note.This name is used for preparations of different composition.
Del, Canad.
Hydrogen peroxide (p.1647·3).
Mouth disorders.

Del, USA.
Urea hydrogen peroxide (p.1666·2).
Oral hygiene; oral inflammation.

Orajel PM *Del, USA.*
Benzocaine (p.1854·1); menthol (p.2340·1); methyl salicylate (p.85·3).
Toothache.

Orajel Ultra Mouth Sore *Del, Canad.*
Benzocaine (p.1854·1); menthol (p.2340·1).
Mouth pain.

Orakef *Leiras, Fin.†.*
Cefalexin (p.218·2).
Bacterial infections.

Orakit *Fada, Arg.*
Potassium chloride (p.1684·3).
Potassium supplement.

Oral Impact *Novartis Consumer, Austral.†; Novartis, Fin.; Novartis Nutrition, Fr.; Novartis Nutrition, Hong Kong.*
Preparation for enteral nutrition in patients at risk of infection (p.1922·1).

Oral Plan *Abbott, Canad.†.*
Triclosan (p.1665·2); cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).
Oral hygiene.

Oral Rehidr Sal Farmasur *Farmasur, Spain†.*
Glucose; potassium iodide; sodium bicarbonate; sodium chloride (p.1672·2).
Oral rehydration therapy.

Oral Rehydration Salts *DHA, Hong Kong; DHA, Malaysia; Pharmaniaga, Malaysia.*
Sodium chloride; sodium citrate; potassium chloride; dextrose monohydrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Oral Spray *Cabassi, Ital.*
Propolis (p.2373·3).

Oral Wound Rinse *Carrington, USA.*
Acemannan hydrogel (p.2244·2).
Mouth disorders.

Oral-Aid *CCM, Malaysia; Beacons, Singapore.*
⊗ Chlorhexidine hydrochloride (p.1635·3); lidocaine (p.1862·3); triamcinolone acetonide (p.1544·3).
Mouth ulcers; sore gums; toothache.

Oralav *Braun, Ger.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Oral-B Anti-Bacterial with Fluoride *Oral-B, Canad.*
Cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).

Oral-B Anti-Cavity Dental Rinse *Oral-B, Canad.*
Sodium fluoride (p.1962·2).

Oral-B Collutorio per la Protezione di Denti e Gengive *Gillette, Ital.*
Cetylpyridinium chloride (p.1635·1); sodium fluoride (p.1962·2).
Prevention of dental disorders.

Oral-B Collutorio Protezione Anti-Carie Fluorinse *Gillette, Ital.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Oral-B Dientes Sensibles con Fluor *Oral-B, Arg.†.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; sensitive teeth.

Oral-B Enjuague Bucal *Oral-B, Arg.†.*
Sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).
Dental caries prophylaxis; oral hygiene.

Oral-B Enjuague Bucal Amosan *Oral-B, Arg.†.*
Sodium perborate (p.1662·1); sodium bitartrate (p.1772·1).
Mouth disorders.

Oral-B Pasta Dentifricia Denti e Gengive *Gillette, Ital.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Oral-B Sensitive *Oral-B, Austral.†; Oral-B, Canad.†; Oral-B, Ital.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; sensitive teeth.

Oralbiotico
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Port.
Oral liquid: Tyrothricin (p.358·2); zinc chloride (p.1999·1).
Mouth and throat infections.
Sanofi Synthelabo, Port.†.
Tablets: Tyrothricin (p.358·2); bacitracin zinc (p.210·3).
Mouth and throat infections.

Oralcam *Landsteiner, Mex.*
Amlodipine camsilate (p.1214·2).
Angina pectoris; hypertension.

Oralcef *Geymonat, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Oraldene *Pfizer Consumer, Irl.; Pfizer Consumer, UK.*
Hexetidine (p.1647·1).
Mouth and throat infections; oral hygiene.

Oraldex *Elmor, Venez.†.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1672·2).
Oral rehydration.

Oraldine *Pfizer Consumer, S.Afr.; Pfizer, Venez.†.*
Hexetidine (p.1647·1).
Mouth and throat infections; mouth disorders.

Oralesper *Pharmacia, Spain†.*
Magnesium chloride hexahydrate; potassium chloride; monobasic potassium phosphate; sodium chloride; sodium phosphate dodecahydrate; sodium lactate; glucose (p.1672·2).
Oral rehydration therapy.

Oralfresh *Maver, Chile.*
Dental gel: Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Oralfresh Citrus *Maver, Chile.*
⊗ Alcohol (p.1625·2); cineole (p.2282·3); zinc chloride (p.1999·1); methyl salicylate (p.85·3); thymol (p.1664·3).
Oral hygiene.

Oralfresh Clasico *Maver, Chile.*
Mouthwash: ⊗ Alcohol (p.1625·2); methyl salicylate (p.85·3); cineole (p.2282·3); thymol (p.1664·3); menthol (p.2340·1).
Oral hygiene.

Oralfresh Menta *Maver, Chile.*
Mouthwash: ⊗ Cetylpyridinium chloride (p.1635·1); alcohol (p.1625·2); domiphen bromide (p.1643·1).
Oral hygiene.

Oralgen *Artu, Neth.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Oralgene
Note. This name is used for preparations of different composition.
Maver, Chile.
Dental gel: Chlorhexidine gluconate (p.1635·3); sodium fluoride (p.1962·2).
Oral hygiene.
Maver, Chile.
Mouthwash: Chlorhexidine gluconate (p.1635·3).
Oral hygiene.
Maver, Chile.
Tablets: Chlorhexidine gluconate (p.1635·3); xylitol (p.1998·2).
Oral hygiene.

Oralife Peppermint
Note. This name is used for preparations of different composition.
Orion, Austral.
Peppermint oil (p.1761·2); chlorhexidine gluconate (p.1635·3).
Dry lips and mouth.
Orion, NZ.
Peppermint oil (p.1761·2); chlorhexidine gluconate (p.1635·3); wool fat (p.2033·2).
Dry, cracked lips.

Oralipin *Roche, Chile.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Oralite *Zuoz, Venez.*
Oral rehydration preparation (p.1672·2).

Oralmedic *Ceuta, UK.*
HybenX (hydroxybenzenesulfonic acid; hydromethoxybenzenesulfonic acid; sulfuric acid).
Mouth ulcers.

Oralmox *Boniscontro & Gazzone, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Oralmuv *LKM, Arg.*
Lamivudine (p.895·1).
HIV infection.

Oralog *Pharmasant, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Oralone Dental *Thames, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Oralovite *Meda, Swed.*
Vitamin B substances with vitamin C (p.1922·1).
Alcoholism; polyneuropathy; vitamin deficiency.

Oralpadon *Stada, Ger.; Stada, Hung.*
Potassium chloride; glucose monohydrate; sodium chloride; sodium acid citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Oralpaedon *Helvepharm, Switz.*
Glucose monohydrate; sodium chloride; potassium chloride; sodium acid citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Oralsone *Gramon, Arg.; Vinas, Spain.*
⊗ Hydrocortisone hydrogen succinate (p.1535·3).
Mouth ulcers.

Oralsone C *Gramon, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Oralsone Topic *Gramon, Arg.*
Rhubarb (p.1768·3); salicylic acid (p.1612·2).
Mouth disorders.

Oral-T *Silom, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Oralten Troche *Agis, Israel.*
Clotrimazole (p.530·1).
Oropharyngeal candidiasis.

Oralube *Orion, NZ.*
Electrolytes (p.1667·1).
Saliva substitute.

Oralvac *Bencard, Ger.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

OraMagic Plus *MPM, USA.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

OraMagicRx *MPM, USA.*
Aloemannon Plus (p.1588·2).
Mouth and throat disorders.

Oramedy *Dong Kook, Singapore.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Oramet *Sandoz, Fin.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Oramide *UAP, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Oramikron *Kocak, Turk.*
Gliclazide (p.440·3).
Diabetes mellitus.

Oramil *Ganassini, Ital.*
Rose honey (p.1948·2).
Oral disinfection.

Oraminax *BA Farma, Port.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Oraminic II *Vortech, USA.*
Brompheniramine maleate (p.569·2).
Hypersensitivity reactions.

Oramorph *Norgine, Belg.; Boehringer Ingelheim, Canad.†; Boehringer Ingelheim, Cz.†; Norgine, Fr.; Norgine, Ger.; Boehringer Ingelheim, Irl.; Molteni, Ital.; Boehringer Ingelheim, Neth.; Molteni, Port.; Norgine, Spain; Boehringer Ingelheim, UK; aai, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Oramox *Antigen, Irl.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Oranerv *More, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Oranex *Farmacom, Pol.*
Azithromycin (p.207·1).
Bacterial infections.

Orange C *Hovid, Malaysia†; Swiss Bio, Malaysia†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Orano *Unison, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Peri-articular disorders; skeletal muscle pain; tension headache.

Oranol *Bayer, Switz.*
Multivitamin preparation (p.1922·1).

Oranor *AF, Mex.*
Norfloxacin (p.309·2).
Bacterial infections.

Oranvit *Pharmacia, Venez.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Orap *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Pharmascience, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.†; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen, Hong Kong; Ethnor, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Fujisawa, Jpn; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Spain; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Gate, USA; Lemmon, USA; Janssen-Cilag, Venez.*
Pimozide (p.1018·1).
Anxiety disorders; behaviour disorders in children; choreas; dyskinesias; paranoia; personality disorders; psychoses; schizophrenia; tics; Tourette syndrome.

Oraphen-PD *Great Southern, USA.*
Paracetamol (p.108·1).
Fever; pain.

Orapred *Alliant, USA; BioMarin, USA.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Oraqix *Dentsply, Denm.; Dentsply, Fin.; Dentsply, Fr.; Dentsply, Neth.; Dentsply, Norw.; Dentsply, Port.; Dentsply, Swed.; Dentsply, UK.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Orascreen *Stafford-Miller, NZ.*
Tolonium chloride (p.2403·1).
Diagnosis of oral cancer.

Ora-Sed *Pfizer, Hong Kong; Rosken, Hong Kong; Pfizer, NZ; Hamilton, Singapore.*
Choline salicylate (p.36·3).
Denture irritation; mouth ulcers; sore gums; teething pain; toothache.

Ora-Sed Jel *Warner-Lambert, Austral.*
Choline salicylate (p.36·3).
Infant teething; mouth lesions.

Orasept
Note. This name is used for preparations of different composition.
Silom, Thai.
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.
Pharmakon, USA.
Oral liquid: Tannic acid (p.2394·3); methylbenzethonium chloride (p.1653·1).
Sore throat.
Pharmakon, USA.
Throat spray: Benzocaine (p.1854·1); methylbenzethonium chloride (p.1653·1); menthol (p.2340·1).
Sore throat.

Oraseptic *Pfizer Consumer, Ital.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Orasic *Otto, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Orasol *Goldline, USA.*
⊗ Benzocaine (p.1854·1); phenol (p.1656·1); alcohol (p.1625·2); povidone-iodine (p.1659·2).

Orasone *Phoenix, Philipp.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Orasorbil *Exterius, Ger.†; Delta, Port.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Orasthin *Aventis, Ger.†.*
Oxytocin (p.2015·2).
Induction and maintenance of labour; postpartum haemorrhage.

Orastina *Sanofi-Aventis, Braz.*
Oxytocin (p.2015·2).
Diagnosis of placental insufficiency or fetal distress; labour induction; lactation deficiency; postpartum haemorrhage.

Oratane *Douglas, Austral.; Douglas, Hong Kong†; Douglas, Malaysia; Darier, Mex.; Douglas, NZ; Pharmaplan, S.Afr.; Douglas, Singapore.*
Isotretinoin (p.1599·2).
Acne.

OraTest *Intertrade, Gr.; Zila, Neth.; Zila, Port.*
Tolonium chloride (p.2403·1).
Diagnosis of malignant neoplasms; diagnosis of mouth cancer.

Oratol *Codilab, Port.*
Salicylic acid (p.1612·2); zinc chloride (p.1999·1).
Mouth and throat disorders.

Oratol F *Codilab, Port.†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Oratrol *Alcon, Belg.†; Alcon, Cz.†; Alkon (Αλκον), Gr.†.*
⊗ Diclofenamide (p.1880·2).
Glaucoma.

Oratuss *Vindex, USA.*
Pentoxyverine citrate (p.1567·3); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).

Oratyn *Durascan, Denm.*
Loratadine (p.583·3).
Allergic rhinitis; hay fever; urticaria.

Oravil *Streuli, Switz.*
Vitamin A acetate (p.1973·1); *d*-alpha tocoferil acetate (p.1992·3).
Dietary supplement.

Oravir *Novartis, Fr.*
Famciclovir (p.876·1).
Varicella-zoster infections.

Oraxim *Malesci, Ital.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Oraxyl *e5, USA.*
Doxycycline hyclate (p.267·1).
Periodontitis.

Orazinc *Mericon, USA.*
Zinc sulfate (p.1999·2).
Dietary supplement.

Orbenil *SLE, Israel.*
Cloxacillin sodium (p.256·1).
Gram-positive bacterial infections.

Orbenin *IFET (ΙΦΕΤ), Gr.; GSK, Neth.†; SmithKline Beecham, Philipp.; GSK, S.Afr.; GSK, Spain; GSK, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Orbenine *Astellas, Fr.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Orbifen *Orbis Consumer, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Orbifen Cold & Flu *Orbis Consumer, UK.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Orbipront *Galenica, Gr.†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Orcal *Lek, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Orcel *Ortec, USA.*
Bioengineered human skin equivalent (p.1613·3).
Wounds.

Orchibion *Bittermedizin, Ger.†.*
⊗ Bovine testicular extract (p.2129·3).
Erectile dysfunction; male menopausal disorders.

Orcilone *Chew, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Orcinol *Julphar, UAE.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1); ammonium chloride (p.1551·3).
Bronchitis; coughs.

Orcl *Shinyaku, Jpn.*
Actarit (p.15·2).
Musculoskeletal and joint disorders.

Ordinal Forte *Asche, Ger.†.*
⊗ Octodrine camsilate (p.1361·1); norfenefrine hydrochloride (p.1361·1).
Circulatory disorders; hypotension.

Ordine *Mundipharma, Austral.*
⊗ Morphine hydrochloride (p.86·3).
Insomnia associated with pain; pain.

Ordov Chesty Cough *Or-Dov, Austral.†.*
Guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2).
Coughs.

Ordov Congested Cough *Or-Dov, Austral.†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Ordov Dry Tickly Cough *Or-Dov, Austral.†.*
Pholcodine (p.1570·2).
Coughs.

Ordov Extra Day & Night Cold and Flu *Or-Dov, Austral.†.*
16 Daytime tablets, codeine phosphate (p.37·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); 8 night-time tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Ordov Febrideine *Or-Dov, Austral.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Ordov Febrigesic *Or-Dov, Austral.†.*
Paracetamol (p.108·1).
Pain.

Ordov Migradol *Or-Dov, Austral.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Pain.

Ordov Sinudec *Or-Dov, Austral.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Ordov Sinus & Hayfever *Or-Dov, Austral.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Orecil NF *Senosiain, Mex.*
⊗ Lidocaine hydrochloride (p.1862·3); ofloxacin (p.310·2); hydrocortisone hydrogen succinate (p.1535·3).
Bacterial ear infections.

Oreda *Hua, Thai.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Oregan *GMP, Indon.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Inflammatory eye disorders.

Oreges *Metro, Philipp.*
Sodium chloride; sodium bicarbonate; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration; vomiting.

Orelox *Sanofi-Aventis, Braz.; Aventis, Cz.†; Sanofi-Aventis, Fr.; Sankyo, Ger.; Altana, Ital.; Aventis, Mex.; Aventis, Neth.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Aventis, Swed.; Aventis, Switz.; Aventis, UK.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Orencia *BMS, Arg.; BMS, Cz.; BMS, Fr.; BMS, Port.; BMS, UK; BMS, USA.*
Abatacept (p.14·1).
Juvenile idiopathic arthritis; rheumatoid arthritis.

Orengedokuto *Tsumura, Jpn.*
Scutellaria root; coptis rhizome; gardenia fruit; phellodendron bark.
Traditional Kampo medicine.

Orenzym *Noventis, Cz.*
Takadiastase (p.2256·3).
Digestive-system disorders.

Oretic *Abbott, USA†.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Orexin *Roberts, USA.*
Vitamin B preparation (p.1922·1).

Orfadin *Orphan, Belg.; Swedish Orphan, Cz.; Orphan, Denm.; Orphan, Fin.; Orphan, Fr.; Orphan, Ger.; Orphan, Neth.; Swedish Orphan, Port.; Orphan, Spain; Swedish Orphan, Swed.; Orphan, USA.*
Nitisinone (p.2354·3).
Hereditary tyrosinaemia type 1.

Orfarin *Orion, Malaysia; Orion, Singapore; Orion, Thai.; Drogsan, Turk.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Orfenal *Remedica, Thai.†.*
Orphenadrine hydrochloride (p.812·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Orfidal *Wyeth, Spain.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; nausea and vomiting associated with chemotherapy.

Orfiril *Desitin, Cz.; Desitin, Denm.; Desitin, Fin.; Desitin, Ger.; Desitin, Hung.; Desitin, Israel; Ranbaxy, Malaysia; Pharmachemie, Neth.; Desitin, Norw.; Desitin, Pol.; Ranbaxy, Singapore†; Desitin, Swed.; Desitin, Switz.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy; mania.

Orflaz Kit *Otsira, India.*
Ornidazole (p.843·1); fluconazole (p.532·1); azithromycin (p.207·1).

Orflex *Chew, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Pain; skeletal muscle spasm.

Orgalutran
Organon, Arg.; Organon, Belg.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Norw.; Organon, Port.; Organon, Rus.; Organon, Singapore; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, Venez.
Ganirelix (p.2105·1).
Controlled ovarian stimulation.

Organon, Austral.; Organon, Braz.; Organon, Canad.; Organon, Hong Kong; Organon, Hung.; Organon, Irl.; Organon, Philipp.
Ganirelix acetate (p.2105·1).
Controlled ovarian stimulation.

Orgametril *Organon, Austria; Organon, Belg.; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.†; Organon, Hung.; Organon, Neth.; Organon, Pol.; Organon, Port.†; Organon, Spain; Organon, Swed.; Organon, Turk.*
Lynestrenol (p.2112·3).
Benign breast disorders; dysfunctional uterine bleeding; endometrial cancer; endometriosis; functional uterine bleeding; hormone replacement therapy; malignant neoplasms; menopausal disorders; menstrual disorders; progestogen-only oral contraceptive; secondary amenorrhoea; uterine hyperplasia.

Organex *Sante Naturelle, Canad.†.*
d-Alpha tocoferil acetate (p.1992·3).

Organidin NR *Wallace, USA.*
Guaifenesin (p.1561·3).
Formerly contained iodinated glycerol.
Coughs.

Organoneuro Cerebral *Gross, Braz.*
Gamma-aminobutyric acid; glutamic acid; calcium phosphate; vitamin B substances (p.1922·1).
Nutritional supplement.

Organoneuro Optico *Gross, Braz.*
Tryptophan; vitamin A; thiamine; riboflavin; ascorbic acid; tocopherol (p.1922·1).
Nutritional supplement.

Orgaplasma *Ardeypharm, Ger.*
Ginseng (p.2312·1).
Tonic.

Orgaran *Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Canad.; Organon, Fr.; Organon, Ger.; IFET (ΙΦΕΤ), Gr.; Pharmaco, NZ; Organon, Neth.; Organon, Port.; Organon, Swed.; Organon, Switz.; Organon, UK; Organon, USA†.*
Danaparoid sodium (p.1255·2).
Deep-vein thrombosis; thromboembolic disorders in patients with heparin-induced thrombocytopenia; thromboembolism prophylaxis.

Orgasulin Mix 30/70 *Organon, Turk.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Orgestriol *Organon, Arg.*
Estriol (p.2101·1).
Urogenital disorders in women associated with oestrogen deficiency.

Orgran *Crombie, NZ.*
Gluten-free pasta (p.1922·1).
Dermatitis herpetiformis; gluten-sensitive enteropathies.

Orhydrate *Pediapharma, Philipp.*
Sodium; chloride; potassium; citrate; magnesium; gluconate; glucose; sucrose (p.1672·2).
Diarrhoea; oral rehydration.

Oributol *Orion, Fin.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Oricitral *TTK, India.*
Sodium acid citrate (p.1673·2).
Urinary alkaliniser.

Oricyclin *Orion, Fin.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Oriens *Galenica, Gr.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Orifer F *Aventis, Canad.*
Multivitamin and mineral preparation (p.1922·1).
Prenatal supplement.

Orifungal *Janssen-Cilag, Arg.*
Ketoconazole (p.539·1).
Fungal infections.

Original Alka-Seltzer Effervescent Tablets *Bayer, USA.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); aspirin (p.20·3).
Hyperacidity.

Original Cabdrivers Expectorant *Merck Consumer, UK.*
Dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1); terpin hydrate (p.1573·3); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2).
Coughs.

Original Grosser Bittner Balsam *Bittner, Rus.*
Cnicus benedictus (p.2285·2); carlina; gentian (p.2310·3); liquorice (p.1740·3); nutmeg (p.2355·2); teriak (peppermint, sage, angelica, ginger); menyanthes (p.2340·3); aniseed (p.2258·2); sweet orange peel (p.2357·2); clove (p.2284·3); bitter orange peel (p.2357·1); centaury (p.2279·1); cubeb (p.2290·1); verbascum (p.2413·3); ginger (p.1732·3); white ash; curcuma; angelica root (p.2258·1); myrrh (p.2349·2); elecampane (p.1558·1); tormentil (p.2403·2); achillea (p.2245·2); iris germanica; calamus (p.2271·3); Curacao rind; absinthium (p.2244·1); camphor (p.2273·2).
Gastrointestinal disorders; lipid disorders; mouth and throat disorders; musculoskeletal, joint, and soft-tissue disorders; nervous disorders; sleep disorders.

Original Herb Cough Drops *Ricola, Canad.*
Achillea (p.2245·2); althaea (p.2253·3); cowslip (p.2372·2); horehound (p.1564·1); mallow (p.2337·2); peppermint leaf (p.1761·2); greater burnet saxifrage (p.2270·3); ribwort plantain (p.2379·1); sage (p.2382·3); sambucus (p.2383·1); thyme (p.2401·1); veronica officinalis.

Original Schneckensirup *Alsitan, Ger.†.*
Snail extract (p.1562·1); thyme (p.2401·1).
Respiratory-tract disorders.

Original Schwedenbitter *Riviera, Cz.*
Gentian (p.2310·3); absinthium (p.2244·1); angelica (p.2258·1); calamus (p.2271·3); tormentil (p.2403·2); myrrh (p.2349·2); taraxacum (p.2395·1); marrubium (p.1564·1); zedoary; nutmeg (p.2355·2); mace (p.2336·1); juglans regia; theriaca electuarium sine opio.
Appetite loss; digestive disorders.

Original Sensodyne *Block, USA.*
⊗ Potassium nitrate (p.1658·3).
Hypersensitive teeth.

Original Silicea Balsam *Hubner, Cz.†.*
Colloidal anhydrous silica (p.2146·2).
Burns; skin disorders; wounds.

Originalsweet *Rider, Chile.*
Aspartame (p.1930·1).
Sugar substitute.

Original-Tinktur N Truw *Truw, Ger.*
Homoeopathic preparation.

Origlucon *Orion, Fin.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Orimed *Oriental, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Orimeten *Novartis, Arg.†; Novartis, Austria†; Novartis, Belg.†; Novartis, Braz.†; Novartis, Chile†; Novartis, Cz.†; Novartis, Ger.†; Novartis, Ital.†; Novartis, Neth.†; Novartis, Rus.†; Novartis, S.Afr.†; Novartis, Spain†; Novartis, UK†.*
⊗ Aminoglutethimide (p.679·1).
Breast cancer; Cushing's syndrome; ectopic ACTH production; hyperaldosteronism; prostatic cancer.

Orimetene *Novartis, Fr.†; Novartis, Hong Kong; Novartis, Malaysia†; Novartis, Switz.†.*
⊗ Aminoglutethimide (p.679·1).
Breast cancer; Cushing's syndrome; hyperaldosteronism; prostatic cancer; suprarenal adenoma.

Orinase *Upjohn, USA.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Orinase Diagnostic *Upjohn, USA.*
Tolbutamide sodium (p.463·2).
Diagnosis of pancreatic adenoma.

Orinse *Centaur, India.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Oriprim *Cadila, Cz.†; Cadila, India; Cadila, Rus.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Oris *SM, Thai.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Oritaxim *Cadila, India; Cadila, Rus.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Oritaxime *Cadila, Thai.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Orivan *Orion, Fin.†.*
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis; staphylococcal infections.

Orivid *Pharmasant, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Orivir *Orion, Denm.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Orizolin *Cadila, Cz.†; Cadila, Rus.*
Cefazolin sodium (p.222·1).
Bacterial infections.

OrLAAM *Newport, Irl.†; Sipaco, Spain†; Roxane, USA†.*
Levacetylmethadol hydrochloride (p.77·1).
Opioid withdrawal syndrome.

Orla-Wax *Alcon, Arg.†.*
Trolamine (p.2405·1).
Ear wax removal.

Orlawax *Alcon, Mex.*
Trolamine (p.2405·1).
Ear wax removal.

Orlaxyl *Alcon, Braz.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Orlept *CP Pharmaceuticals, UK.*
Sodium valproate (p.508·2).
Epilepsy.

Orlobin *Medicus, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Orloc *Orion, Fin.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension; migraine.

Orloc Comp *Orion, Fin.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Orlon *Gynopharm, Chile.*
21 Tablets, norgestimate (p.2121·1); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
Combined oral contraceptive.

Ormigrein *Organon, Braz.*
Paracetamol (p.108·1); ergotamine tartrate (p.620·1); caffeine (p.1116·3); hyoscyamine sulfate (p.1736·1); atropine sulfate (p.1219·3).
Migraine.

Ormil *Atabay, Turk.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Ormir *Neuropharma, Arg.†.*
Midazolam (p.1007·3).

Ormobyl CM *Novartis Consumer, Ital.†.*
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1); polycarbophil calcium (p.1763·3).
Constipation.

Ormodon *Pharmaceutical Enterprises, S.Afr.*
Nitrazepam (p.1011·2).
Insomnia.

Ormox *Orion, Fin.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Ornacol *GSK, S.Afr.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3).
Coughs; nasal congestion.

Ornade-2 *Vianex (Βιανέξ), Gr.*
Chlorphenamine (p.572·2); phenylpropanolamine (p.1569·2).
Decongestant.

Ornate *Pharmaland, Thai.†.*
Mianserin hydrochloride (p.408·1).
Mixed anxiety depressive states.

Ornatrol *Emila, Braz.†.*
Diphenylpyraline hydrochloride (p.578·2); phenylpropanolamine hydrochloride (p.1569·3); isopropamide iodide (p.1736·3).
Nasal congestion.

Ornex
Note. This name is used for preparations of different composition.
SmithKline Beecham, Philipp.
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; nasal congestion; sinusitis.

Ascher, USA.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Ornicetil *Ebewe, Austria; Chiesi, Fr.; Geymonat, Ital.†.*
Ornithine oxoglurate (p.1959·2).
Hepatic encephalopathy; liver disorders; parenteral nutrition; pituitary function testing.

Ornida *Aristo, India.*
Ornidazole (p.843·1).
Protozoal infections.

Ornidone *Tripharma, Turk.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Ornidyl *Marion Merrell Dow, USA.*
Eflornithine hydrochloride (p.833·1).
African trypanosomiasis.

Ornihepat *Faria, Braz.†.*
Arginine (p.1928·2); citrulline (p.1935·1); ornithine (p.1959·2).
Liver disorders.

Ornil *Volchem, Ital.*
-Ornithine (p.1959·2).
Adjunct in dietary management of hypercholesterolaemia.

Ornil KGF *Volchem, Ital.*
-Ornithine oxoglurate (p.1959·2).
Stress.

Ornisid *Tripharma, Rus.; Abdi, Turk.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Ornitaine
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Amino-acid and vitamin B preparation (p.1922·1).
Liver disorders.

Schwarz, Fr.
Ornithine hydrochloride (p.1959·2); betaine (p.2265·2); sorbitol (p.1965·1); citric acid monohydrate (p.2284·1); magnesium oxide (p.1744·1).
Dyspepsia.

Ornitargin *Baldacci, Braz.*
Arginine (p.1928·2); ornithine (p.1959·2); citrulline (p.1935·1).
Parenteral nutrition.

Ornitop *Toprak, Turk.*
Ornidazole (p.843·1).
Anaerobic bacterial infections; protozoal infections.

Ornof *Aristo, India.*
Ornidazole (p.843·1); ofloxacin (p.310·2).

Oroacid *Rosch & Handel, Austria.*
Betaine hydrochloride (p.2265·2); pepsin (p.2365·1).
Hypochlorhydria; loss of appetite.

Orobicin *Fulton, Ital.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Gastrointestinal infections; pre-operative bowel preparation.

Orobiotic *Fortbenton, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Orocal D_3 *Nycomed, Pol.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Orochlor *Triomed, S.Afr.*
Benzocaine (p.1854·1); chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Orochol *Scott-Cassara, Arg.; CSL, Austral.†; Berna, Hong Kong†; Berna, Philipp.; Berna, Switz.*
An oral cholera vaccine (p.2208·1).
Active immunisation.

Orocholin *Rosch & Handel, Austria.*
Choline dihydrogen citrate (p.1934·2); calcium citrate (p.1675·3).
Adjuvant in surgery and radiotherapy; liver protection.

Orocil *Novartis, Gr.*
Benzoxonium chloride (p.1631·2).
Mouth infections.

Orocil Lido *Novartis, Gr.*
Benzoxonium chloride (p.1631·2); lidocaine (p.1862·3).
Mouth and throat disorders.

Orodina *Laboratorios Chile, Chile.*
Cyproheptadine hydrochloride (p.575·1); vitamins; lysine hydrochloride (p.1922·1).
Reduced appetite.

Orofar
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.
Benzoxonium chloride (p.1631·2).
Mouth and throat disorders.

Novartis Consumer, Cz.; Novartis Consumer, Pol.; Novartis Consumer, Port.†; Novartis Consumer, Switz.
Benzoxonium chloride (p.1631·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Orofar Lidocaine *Novartis Consumer, Belg.*
Benzoxonium chloride (p.1631·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Orofar-L *Novartis, Philipp.*
Benzoxonium chloride (p.1631·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Orofen *Sandoz, Denm.*
Ketoprofen (p.73·1).
Dysmenorrhoea; gout; inflammation; musculoskeletal and joint disorders.

Orofeno *Megat, Venez.*
Ketoprofen (p.73·1).
Inflammation; pain.

Orofer *Emcure, Thai.*
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron deficiency; iron-deficiency anaemia.

Oroferon *Kocak, Turk.*
Ferrous sulfate (p.1939·3); mucoproteose.
Iron deficiency; iron-deficiency anaemia.

Oroheks *Tripharma, Turk.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Oroken *Sanofi-Aventis, Fr.*
Cefixime (p.224·3).
Otitis media; pyelonephritis; respiratory-tract infections; urinary-tract infections.

Oromedine *Sanofi-Aventis, Fr.*
Hexamidine isetionate (p.1646·3); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Oromic *Janssen-Cilag, Spain.*
Itraconazole (p.536·3).
Fungal infections.

Oromone *Solvay, Fr.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Oro-NaF *Germiphene, Canad.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Oropigma Gel *Dermoprog, Ital.*
Ubidecarenone (p.2407·2).

Oro-Pivalone *Uhlmann-Eyraud, Switz.*
⊗ Tixocortol pivalate (p.1544·2); bacitracin zinc (p.210·3).
Mouth and throat disorders.

Oropivalone Bacitracine *Pfizer, Fr.†.*
⊗ Tixocortol pivalate (p.1544·2); bacitracin zinc (p.210·3).
Mouth and throat disorders.

Oropram *Pharmaco, Hung.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Oropur *NHS, Fr.*
Parsley oil (p.2363·2); sunflower oil (p.1970·3).
Halitosis.

Ororhinathiol *Sanofi-Aventis, Belg.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Orosanyl *Berna, Ital.†.*
Sodium monofluorophosphate (p.1964·3); cetylpyridinium chloride (p.1635·1).
Gum disorders.

Orosept *Triomed, S.Afr.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Orotre *Theramex, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Orotrex *Medinfar, Port.*
Isotretinoin (p.1599·2).
Acne.

Orovas *Pharma Nutria, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Orovite *Thornton & Ross, Irl.; Thornton & Ross, UK.*
Vitamin B substances with ascorbic acid (p.1922·1).

Orovite '7' *Thornton & Ross, UK.*
Multivitamin preparation (p.1922·1).

Oroxadin *Sanofi-Aventis, Braz.; Sanofi Synthelabo, Mex.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Oroxine *Sigma, Austral.; GSK, Malaysia; GSK, Singapore.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; suppression of thyrotrophin; thyroiditis.

Orozamudol *Viatris, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Orozanol *KRKA, Cz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Orozim *Arex, Venez.*
Pancreatin (p.2360·1).
Digestive disorders.

Orpar *Pharmasant, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Muscle pain.

Orphen *Solas, Indon.*
Chlorphenamine maleate (p.571·3).
Allergic disorders.

Orphenadol *YSP, Malaysia; Yung Shin, Singapore.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain; musculoskeletal pain and spasm.

Orphengesic
Note. This name is used for preparations of different composition.
Bangkok Lab & Cosmetic, Thai.
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Skeletal muscle pain; tension headache.

Par, USA.
Orphenadrine citrate (p.812·1); aspirin (p.20·3); caffeine (p.1116·3).
Musculoskeletal pain.

Orphipal *GSK, India.*
Orphenadrine hydrochloride (p.812·1).
Drug-induced extrapyramidal disorders; parkinsonism.

Orphol *Opfermann, Ger.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Orpic *Pharmacare, S.Afr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Orpidix *Proel, Gr.*
Ketotifen fumarate (p.582·2).
Allergic eye disorders; allergic rhinitis; asthma.

Orravina *Diviser Aquilea, Spain†.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain; thromboembolism prophylaxis.

Orregel *Hoe, Malaysia.*
Cetylpyridinium chloride (p.1635·1); choline salicylate (p.36·3).
Mouth ulcers; oral pain; teething pain.

Orrepaste *Hoe, Malaysia; Hoe, Singapore.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

ORS Bicarbonate *Pharmaniaga, Malaysia.*
Sodium bicarbonate; sodium chloride; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Orsanil *Orion, Fin.†.*
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Psychoses.

Orset *Servipharm, Israel.*
Oral rehydration solution (p.1672·2).
Oral rehydration therapy.

Orsinon *Rekah, Israel.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Orstanorm *Novartis, Fin.; Novartis, Swed.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine; orthostatic hypotension.

Ortanol
Lek, Cz.; Sandoz, Cz.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Lek, Pol.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Orthal Forte *Cipla, India.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3).
Digestive disorders.

Orthangin novo *Altana, Ger.*
Crataegus (p.2289·1).
Heart failure.

Ortho 0.5/35 *Janssen-Ortho, Canad.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho 1/35 *Janssen-Ortho, Canad.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho 7/7/7 *Janssen-Ortho, Canad.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Ortho 777 *Mochida, Jpn.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Ortho Cyclen *Janssen-Cilag, Israel; Ortho McNeil, USA.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho Evra *Ortho McNeil, USA.*
Norelgestromin (p.2119·2); ethinylestradiol (p.2101·3).
Combined transdermal contraceptive.

Ortho Gynest Depot *Janssen-Cilag, Ital.*
Estriol (p.2101·1).
Menopausal disorders.

Ortho Micronor *Ortho McNeil, USA.*
Norethisterone (p.2119·3).
Formerly known as Micronor.
Progestogen-only oral contraceptive.

Ortho Tri-Cyclen *Ortho McNeil, USA.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Orthocel *Biochem, India.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Ortho-Cept *Janssen-Ortho, Canad.; Ortho McNeil, USA.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Orthoclone *Janssen-Cilag, Gr.; Janssen-Cilag, S.Afr.*
Muromonab-CD3 (p.1835·2).
Acute renal, cardiac, or hepatic allograft rejection; immunosuppressant.

Orthoclone OKT3 *Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Cilag, Cz.†; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Cilag, Hong Kong†; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia†; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.†; Gurel, Turk.; Ortho Biotech, USA.*
Muromonab-CD3 (p.1835·2).
Acute cardiac, hepatic, or renal allograft rejection.

Ortho-Creme *Janssen-Cilag, Irl.; Janssen-Cilag, UK†.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Ortho-Dienestrol *Ortho McNeil, USA.*
Dienestrol (p.2093·3).
Atrophic vaginitis; kraurosis vulvae.

Ortho-Est *Janssen-Cilag, S.Afr.; Women First, USA†.*
Estropipate (p.2101·2).
Female castration; female hypogonadism; menopausal disorders; osteoporosis; primary ovarian failure; vulval and vaginal atrophy.

Orthoforms *Janssen-Cilag, UK†.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Ortho-Gynest *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Ger.; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
Estriol (p.2101·1).
Atrophic vaginitis; kraurosis vulvae; menopausal disorders; oestrogen deficiency; pruritus vulvae; vulvovaginal disorders due to oestrogen deficiency.

Ortho-Gynol
Note. This name is used for preparations of different composition.
Janssen-Cilag, Austral.; Janssen-Cilag, NZ.
An octoxinol (p.1917·3).
Contraceptive.

Johnson & Johnson, Canad.
Nonoxinol 9 (p.1917·2).
Contraceptive.

Advanced Care, USA†.
Octoxinol 9 (p.1917·3).
Contraceptive.

Orthokin *Pasteur, Chile.*
Chlorhexidine gluconate (p.1635·3); zinc acetate (p.1999·1); sodium fluoride (p.1962·2).
Oral hygiene.

Ortho-Maren retard *Lubapharm, Switz.*
⊗ Pholedrine sulfate (p.1371·1); norfenefrine hydrochloride (p.1361·1).
Hypotension.

Orthon *Remedina, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Orthonett Novum *Janssen-Cilag, Swed.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ortho-Novum *Cilag, Mex.†.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
Combined oral contraceptive.

Ortho-Novum 1/35 *Codepharma, Fr.; Janssen-Cilag, Mex.; Ortho McNeil, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Ortho-Novum 1/50 *Janssen-Ortho, Canad.†; Ortho McNeil, USA.*
Norethisterone (p.2119·3); mestranol (p.2116·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; endometriosis; menstrual disorders.

Ortho-Novum 7/7/7 *Ortho McNeil, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Ortho-Novum 10/11 *Ortho McNeil, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Biphasic oral contraceptive.

Orthoplex SAD *Bioconcepts, Austral.†.*
Vitamin B substances with trace elements and amino acids (p.1922·1).

Orthosiphonblatter Indischer Nierentee *Heel, Ger.*
Java tea (p.2328·2).
Urinary-tract disorders.

Orthovisc
Note. This name is used for preparations of different composition.
Rivex, Canad.; Vitaresearch, Ger.; Anika, Israel; Surgicraft, UK; Ortho Biotech, USA.
Sodium hyaluronate (p.2320·1).
Osteoarthritis.

Biomeks, Turk.
Hyaluronidase (p.2321·1).
Enhance permeation of subcutaneous or intramuscular injections; promote tissue fluid and blood resorption.

OrthoWash *Omnii, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Orthoxicol Cold & Flu *Johnson & Johnson, Austral.†; Johnson & Johnson, NZ.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; cold symptoms.

Orthoxicol Day & Night *Johnson & Johnson, NZ.*
Day caplets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); night caplets, paracetamol; chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide.
Cold symptoms.

Orthoxicol Day & Night Cold & Flu *Johnson & Johnson, Austral.†.*
Daytime caplets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); night-time caplets, paracetamol; dextromethorphan hydrobromide; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Orthoxicol Night Cold & Flu *Johnson & Johnson, Austral.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Ortisan
Note. This name is used for preparations of different composition.
Ortis, Ital.
Senna (p.1769·2); tamarind (p.1775·3).
Constipation.

Cedar Health, UK.
Fruit and fibre preparation.
Constipation.

Ortitruw *Truw, Ger.*
Homoeopathic preparation.

Orto Dermo P *Normon, Spain.*
Povidone-iodine (p.1659·2).
Burns; skin disinfection; wounds.

Ortociclina *Makros, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Ortocilin *Makros, Braz.†.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1); streptomycin (p.333·3); diphenhydramine (p.577·1).
Bacterial infections.

Ortocol *Mavi, Mex.*
Diclofenac (p.44·2); vitamin B substances (p.1922·1).
Inflammation; neuritis; pain.

Ortodent *Andromaco, Chile†.*
Triclosan (p.1665·2); zinc chloride (p.1999·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis; oral hygiene.

Ortodermina *Sofar, Ital.*
Lidocaine hydrochloride (p.1862·3).
Surface anaesthesia of skin and mucous membranes.

Ortoflan *Medley, Braz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Ortopsique *Psicofarma, Mex.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; epilepsy; insomnia; skeletal muscle spasm.

Ortosep *Rowe-Fleming, Venez.†.*
Cefoperazone (p.227·2).
Bacterial infections.

Ortoserpina *Makros, Braz.†.*
Reserpine (p.1387·3).
Hypertension; Raynaud's syndrome.

Ortosol P *Galderma, Braz.*
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2).
Scalp disorders.

Ortoton *Bastian, Ger.*
Methocarbamol (p.1897·3).
Skeletal muscle spasm and tension.

Ortoton Plus *Bastian, Ger.*
Methocarbamol (p.1897·3); aspirin (p.20·3).
Musculoskeletal, joint, and soft-tissue disorders.

Ortovermim *Makros, Braz.†.*
Piperazine (p.152·3).
Ascariasis; enterobiasis.

Ortoxine *Volta, Chile.*
Chlorhexidine hydrochloride (p.1635·3).
Oral hygiene.

Ortran *Farmaco, Mex.†.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Ortrel *Janssen-Cilag, Venez.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ortrip *Pharmasant, Thai.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Ortrizol *Farcoral, Mex.*
Metronidazole (p.837·1).
Ascariasis; giardiasis; trichomoniasis.

Or-Tyl *Ortega, USA.*
Dicycloverine hydrochloride (p.1722·3).
Functional bowel/irritable bowel syndrome.

Orucote *Aventis, S.Afr.†.*
Ketoprofen (p.73·1).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Orudis
Aventis, Arg.†; Sanofi-Aventis, Austral.; Aventis, Canad.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Ger.†; Aventis, Hong Kong; Aventis, Irl.†; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Spain; Aventis, Swed.; Hawgreen, UK; Wyeth-Ayerst, USA†.
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; renal colic.

Aventis, Mex.
Ketoprofen (p.73·1) or ketoprofen sodium (p.73·3).
Inflammation; pain.

Orugesic *Sanofi-Aventis, Irl.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Oruject *Aventis, S.Afr.†.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Orungal *Janssen-Cilag, Hung.; Janssen-Cilag, Pol.; Janssen-Cilag, Rus.*
Itraconazole (p.536·3).
Fungal infections.

Orungamin *Ozon, Rus.*
Itraconazole (p.536·3).
Fungal infections.

Orunit *Obolenskoe, Rus.*
Itraconazole (p.536·3).
Fungal infections.

Oruvail *Sanofi-Aventis, Austral.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Aventis, Israel; Aventis, Malaysia†; Sanofi-Aventis, NZ; Sanofi-Aventis, Neth.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Thai.; Aventis, UK; Wyeth-Ayerst, USA†.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Oryant *CKD, Philipp.; Unimex, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Orzel *BMS, NZ†.*
Capsules, tegafur (p.776·1); uracil (p.2407·3) (UFT); tablets, calcium folinate (p.1943·3).
Colorectal cancer.

Os *Nutricia-Bago, Arg.*
Food for special diets (p.1922·1).
Metabolic disorders.

OSA *Schmidgall, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Osa gel dentaire aux plantes *Iromedica, Switz.*
Mint oil (p.2345·2); chamomile oil (p.2279·3); sage oil (p.2382·3); clove oil (p.2285·1); propolis (p.2373·3).
Teething pain.

Osa Gel de dentition *Iromedica, Switz.*
Salicylamide (p.121·2); lidocaine hydrochloride (p.1862·3); dexpanthenol (p.2362·1).
Teething pain.

Osa Suppositoires contre douleurs et fievre *Iromedica, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Osadrox *Sandoz, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Osagel *Farmanic, Gr.*
Lidocaine (p.1862·3).
Local anaesthesia.

Osalen *Anpharm, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osaline *Hua, Thai.†.*
Glucose; sodium chloride; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Osamin *Erlimpex, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; zinc (p.1922·1).
Osteoarthritis.

Osangin *Antonetto, Ital.*
Dequalinium chloride (p.1641·3).
Mouth and throat disinfection.

Osanit
Note. This name is used for preparations of different composition.
Zeppenfeldt, Ger.; Iromedica, Switz.
Homoeopathic preparation.

Farmanic, Gr.
Calcitonin (p.1093·1).
Osteoporosis.

Osarbon *Nizhpharm, Rus.*
Acetarsol (p.828·1); boric acid (p.2268·1).

Osaston *Faran, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osaten *Offenbach, Mex.*
Ketotifen (p.582·2).
Hypersensitivity.

Osatrol *Darya-Varia, Indon.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Os-Cal
Note. A similar name is used for preparations of different composition (see below).
Sanofi-Aventis, Braz.; Wyeth, Canad.; Aventis, Hong Kong; SmithKline Beecham Consumer, USA.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Sanofi-Aventis, Singapore.
Calcium (p.1675·2).
Calcium deficiency; calcium supplement.

Oscal
Note. This name is used for preparations of different composition.
Dankos, Indon.
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Aventis, Venez.†.
Calcium carbonate (p.1714·1).
Calcium supplement.

Os-Cal D *Wyeth, Canad.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Oscal D *Sanofi-Aventis, Venez.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D deficiency.

Os-Cal + D
Sanofi-Aventis, Braz.; Aventis, Mex.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteoporosis.

Aventis, Hong Kong; Sanofi-Aventis, Malaysia†; GSK Consumer, USA.
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Sanofi-Aventis, Singapore.
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Os-Cal Forte *SmithKline Beecham Consumer, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Os-Cal Fortified *GSK Consumer, USA.*
Multivitamin and mineral preparation with calcium and iron (p.1922·1).

Os-Cal Plus *SmithKline Beecham, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Os-Cal Ultra *GSK Consumer, USA.*
Vitamin and mineral preparation (p.1922·1).

Oscale *Gache, Venez.*
Calcium from oyster shells (p.1675·2).
Calcium supplement; osteoporosis.

Oscart *Mayoly-Spindler, Fr.*
Glucosamine (p.2313·2).
Joint disorders.

Oscevitin-A *Grasler, Ger.†.*
Calcium phosphate (p.1676·2); vitamin A acetate; colecalciferol; ascorbic acid (p.1922·1).
Calcium deficiency; vitamin deficiency.

Oscillococcinum *Boiron, Austral.; Boiron, Canad.; Silesia, Chile†; Boiron, Fr.; Boiron, Neth.; Boiron, Port.; Boiron, Switz.*
Homoeopathic preparation.

Oscorel *Aventis, Neth.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Osdren *Mintlab, Chile.*
Alendronic acid (p.1088·1).

Osemin *Degorts, Mex.*
⊗ Furosemide (p.1292·1).

Oseofem *Biotenk, Arg.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Oseofort
Silesia, Chile.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Hypocalcaemia; osteoporosis.

Menarini, Spain.
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Oseotal *Chemopharma, Chile.*
Alendronic acid (p.1088·1).
Osteoporosis.

Oseotenk *Biotenk, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Oseototal *Novartis, Spain.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis; Paget's disease of bone.

Osetron *Reddy, Malaysia.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Oseum *Grossman, Mex.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteolysis of malignancy; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Osfit *Kalbe, Indon.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide; boron citrate; zinc sulfate; copper sulfate; chromium picolinate; folic acid; vitamin B ; vitamin B ; silica (p.1922·1).
Osteoporosis.

Osflex *Novell, Indon.*
Sodium hyaluronate (p.2320·1).
Degenerative joint disorders; orthopaedic surgery.

Osfo *Gap, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Osfolate *Baxter Oncology, Fr.*
Calcium folinate (p.1943·3).
Drug-induced megaloblastic anaemias; prevention of methotrexate toxicity.

Osfolato *Lusofarmaco, Ital.*
Calcium folinate (p.1943·3).
Folate deficiency; reversal of methotrexate toxicity.

O-Sid *Siam Bheasach, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Osigraft
Note. This name is used for preparations of different composition.
Howmedica, Cz.; Howmedica, Denm.; Stryker, Gr.; Howmedica, Neth.; Howmedica, Port.; Howmedica, Spain.
Eptotermin alfa (p.1092·3).
Fracture of tibia; promotion of bone formation in fractures.

Stryker, Ital.
Osteogenic protein 1 (p.1092·3).
Tibial fracture.

Osimax
Tempo Scan Pacific, Indon.
Syrup: Calcium hydrogen phosphate (p.1676·1); calcium lactate (p.1676·1); vitamins; lysine hydrochloride; curcuma (p.1922·1).
Nutritional supplement.

Tempo Scan Pacific, Indon.
Tablets: Calcium hydrogen phosphate (p.1676·1); calcium lactate (p.1676·1); vitamins (p.1922·1).
Calcium deficiency; calcium supplement.

Osipine *Fournier, Ital.*
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Osiren
Note. This name is used for preparations of different composition.
Lafedar, Arg.†.
⊗ Spironolactone (p.1400·1).
Hypertension.

Probiomed, Mex.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ositron *Leovan, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Osivan *Leovan, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Oskadon *Supra Ferbindo, Indon.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Oskadryl *Supra Ferbindo, Indon.*
⊗ Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3).
Allergic disorders; cough; nasal congestion.

Oskamag *Supra Ferbindo, Indon.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; peptic ulcer.

Oskana *Velka, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Osmach *Ratiopharm, UK.*
⊗ Fentanyl (p.55·3).
Pain.

Osmil
Note. This name is used for preparations of different composition.
Serono, Arg.†.
Calcitonin (salmon) (p.1093·1).
Bone metastases; hypercalcaemia; osteolysis; osteoporosis; Paget's disease of bone; pancreatitis; sympathetic dystrophy.

Opfermann, Ger.
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Osmitrol *Baxter, Austral.; Baxter, Canad.; Baxter, USA.*
⊗ Mannitol (p.1330·2).
Acute renal failure; cerebral oedema; forced diuresis; osmotic diuretic; raised intra-ocular pressure.

Osmo *TNP, Thai.†.*
Multivitamin preparation with lysine (p.1922·1).

Osmo Soft *Cooperation Pharmaceutique, Fr.*
Carbomers; octylene glycol; glycerol; polyethylene glycol; sodium hydroxide.
Burns.

Osmo-Adalat *Pharma Clal, Israel; Bayer, Rus.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Osmofundin 10% *Braun, Austria.*
⊗ Mannitol (p.1330·2); sodium acetate (p.1673·2); sodium chloride (p.1686·1).
Cataract surgery; cerebral oedema; forced diuresis; oliguria; renal failure.

Osmofundin 15% N *Braun, Cz.†; Braun, Ger.*
⊗ Mannitol (p.1330·2).
Forced diuresis; glaucoma; ocular hypertension; oedema; raised intracranial pressure; renal failure.

Osmofundina *Braun, Port.*
⊗ Mannitol (p.1330·2).
Forced diuresis; ocular hypertension; oedema; raised intracranial pressure; renal failure.

Osmofundina Concentrada *Braun, Spain.*
⊗ Mannitol (p.1330·2).
Ascites; cranial hypertension; glaucoma; oedema; oliguria.

Osmogel
Note. This name is used for preparations of different composition.
Merck Medication Familiale, Fr.
Magnesium sulfate (p.1679·3); lidocaine hydrochloride (p.1862·3).
Soft-tissue disorders.

Alphrema, Ital.
Suleparoid (p.1406·3); hyaluronic acid (p.2320·1); centella (p.1592·3); aescin (p.2248·2).
Venous insufficiency.

Osmoglyn *Alcon, USA.*
Glycerol (p.2314·2).
Glaucoma; raised intra-ocular pressure before ophthalmic surgery.

Osmohes *Fresenius Kabi, Austria; Fresenius Kabi, Hung.†.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Hypovolaemic shock.

Osmolac *Sanofi Synthelabo OTC, Ital.†.*
Lactulose (p.1738·2).
Constipation; hepatic cirrhosis; hepatic encephalopathy.

Osmolak *Biofarma, Turk.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Osmolite *Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Cz.†; Abbott, Fin.; Abbott, Fr.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, NZ; Abbott, Singapore; Abbott, Turk.; Abbott Nutrition, UK; Ross, USA.*
Preparations for enteral nutrition (p.1922·1).

Osmolite HN *Abbott, Arg.; Abbott, Canad.; Abbott, Mex.; Abbott, Philipp.; Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).

Osmonagre *Motima, Fr.*
Evening primrose oil (p.2302·1).
Dry skin; premenstrual syndrome.

Osmopak-Plus *Rougier, Canad.*
Hydrated magnesium sulfate (p.1679·3); benzocaine (p.1854·1).
Superficial inflammatory conditions.

OsmoPrep *Salix, USA.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Osmoran *Rafarm, Gr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Osmorich *Abbott, Ital.*
Preparation for enteral nutrition (p.1922·1).

Osmorol *Pisa, Mex.*
⊗ Mannitol (p.1330·2).

Osmosal *Leiras, Fin.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration solution.

Osmosteril *Fresenius Kabi, Neth.*
⊗ Mannitol (p.1330·2).
Forced diuresis; intra-ocular hypertension; intracranial hypertension; renal failure.

Osmosteril 10% *Fresenius Kabi, Ger.*
⊗ Mannitol (p.1330·2); sodium lactate (p.1673·3).
Forced diuresis; renal failure.

Osmosteril 20% *Fresenius Kabi, Ger.*
⊗ Mannitol (p.1330·2).
Forced diuresis; renal failure.

Osmotan G *Aguettant, Fr.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Osmotil *Hertz, Braz.†.*
Phenazone (p.116·1); lidocaine(p.1862·3).

Osmotol *Chauvin, Fr.*
⊗ Resorcinol (p.1612·1); ephedrine hydrochloride (p.1558·2).
Otitis externa.

Osmovist *Berlex, Canad.†.*
Iotrolan (p.1486·1).
Radiographic contrast medium.

Osmycin *Pharos, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Osnervan *GSK, Ger.*
Procyclidine hydrochloride (p.814·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Osonide *Ranbaxy, India.*
⊗ Ciclesonide (p.1521·3).
Asthma.

Ospamox
Sandoz, Austria; Sandoz, Cz.; Biochemie, Hong Kong; Sandoz, Indon.; Sandoz, Malaysia; Novartis, NZ; Sandoz, Port.; Sandoz, Rus.; Sandoz, Singapore.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sandoz, Gr.; Sandoz, Hung.; Sandoz, Pol.; Sandoz, Venez.
Amoxicillin (p.202·2).
Bacterial infections.

Ospen
Sandoz, Austria.
Benzathine phenoxymethylpenicillin (p.212·3), phenoxymethylpenicillin (p.314·1), or phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

KRKA, Cz.; Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.; KRKA, Rus.; Sandoz, Switz.; Sandoz, Venez.
Benzathine phenoxymethylpenicillin (p.212·3) or phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Novartis, Fr.†; Biochemie, Hong Kong†.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Sandoz, Gr.
Phenoxymethylpenicillin (p.314·1) or benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Singapore.
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Ospexin *Sandoz, Austria; Sandoz, Cz.; Biochemie, Hong Kong; Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Singapore.*
Cefalexin (p.218·2).
Bacterial infections.

Ospocard *Unipack, Austria.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Ospolot *Teva Tuteur, Arg.; Pharmalab, Austral.; AOP Orphan, Austria; Desitin, Cz.; Desitin, Ger.; IFET (ΙΦΕΤ), Gr.; Desitin, Hung.; Desitin, Israel; Desitin, Switz.*
Sultiame (p.504·3).
Behavioural disorders; epilepsy.

Ospor *Merck, Spain.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis; Paget's disease of bone.

Osporin *Hebron, Braz.†.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Ospronim *Intramed, S.Afr.*
⊗ Pentazocine lactate (p.112·3).
Pain.

Ospur Ca *Sanofi Synthelabo, Ger.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Ospur D_3 *Sanofi Synthelabo, Ger.*
Colecalciferol (p.1986·2).
Osteomalacia; osteoporosis; rickets; vitamin D deficiency.

Osra *Hua, Thai.*
Glucose; sodium chloride; sodium citrate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Osseans D3 *Sciencex, Fr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osseocalcina *Normal, Port.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Osseopor *Greenpharma, Braz.*
Calcium carbonate (p.1714·1).

Osseor *Servier, Cz.; Stroder, Ital.; Servier, Neth.; Servier, Port.; Rovi, Spain.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Ossidal *Truw, Ger.*
Homoeopathic preparation.

Ossidrol *Chrispa (Χρισπα), Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Ossin
Note. This name is used for preparations of different composition.
Grunenthal, Cz.†; Grunenthal, Ger.; Grunenthal, Rus.†; Grunenthal, Switz.
Sodium fluoride (p.1962·2).
Osteoporosis.

Basi, Port.
Chondroitin sulfate (p.2280·3).
Osteoarthrosis.

Ossiplex *Gebro, Austria; Gebro, Cz.†; Sanofi Synthelabo, Ger.; Gebro, Hung.†; Segix, Ital.†; Pharmacare, S.Afr.*
Sodium fluoride (p.1962·2); ascorbic acid (p.1983·3).
Osteoporosis.

Ossiten *Roche, Ital.*
Clodronate disodium (p.1095·3).
Multiple myeloma; osteolytic tumours; postmenopausal osteoporosis; primary hyperparathyroidism.

Ossivite *Wyeth, India.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2); calcium carbonate (p.1714·1); calcium hydrogen phosphate (p.1676·1).
Fractures; nutritional supplement; osteomalacia; osteoporosis; rickets.

Ossmax *Ranbaxy, Austral.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ossocal-D *Delta, Braz.*
Calcium carbonate (p.1714·1); ergocalciferol (p.1987·1).
Calcium and vitamin D supplement.

Ossofluor *Streuli, Switz.*
Sodium fluoride (p.1962·2).
Multiple myeloma; osteolytic bone metastases; osteoporosis.

Ossofortin *Strathmann, Ger.†.*
Calcium phosphate (p.1676·2); calcium gluconate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ossofortin D *Strathmann, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ossofortin forte *Strathmann, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ossofortin Plus *Strathmann, Ger.*
Effervescent tablets, calcium carbonate (p.1714·1); colecalciferol (p.1986·2); slow-release tablets, sodium fluoride (p.1962·2).
Osteoporosis.

Ossomax *Gallia, Braz.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ossopan *Germania, Austria; Ache, Braz.; Pierre Fabre, Fr.; Pierre Fabre, Ger.†; TTK, India; Darya-Varia, Indon.; Pierre Fabre, Indon.; Sanofi, Irl.; Pierre Fabre, Mex.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Singapore†; Berna, Spain; Robapharm, Switz.; Pierre Fabre, Thai.; Sanofi Synthelabo, UK†.*
Hydroxyapatite (p.2323·1).
Bbone fractures; calcium and phosphorus deficiency; calcium and phosphorus supplement; dental caries prophylaxis; growth disorders in children; osteomalacia; osteoporosis; rickets.

Ossoral *Dexa, Indon.*
Hydroxyapatite (p.2323·1).
Calcium supplement; osteoporosis.

Ossovit *Interbat, Indon.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2); magnesium; zinc; with or without vitamin K (p.1922·1).
Calcium supplement; osteoporosis.

Osspulvit D_3 *Madaus, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osspulvit S *Madaus, Ger.†.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium deficiency.

Osspulvit S forte *Madaus, Ger.†.*
Calcium phosphate (p.1676·2); vitamins (p.1922·1).

Oss-regen *Pekana, Ger.†.*
Homoeopathic preparation.

OST Vit *Greater Pharma, Thai.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).

Ostac *Roche, Belg.†; Roche, Braz.; Roche, Canad.; Roche, Ger.; Pharmalex (Φαρμαλεξ), Gr.; Roche, Hong Kong; Boehringer Mannheim, Israel; Roche, Neth.; Roche, Port.; Roche, S.Afr.†; Roche, Swed.; Roche, Switz.*
Clodronate disodium (p.1095·3).
Hypercalcaemia; osteolysis of malignancy.

Ostalert *Verisfield, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ostaren *Utopian, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Ostarin *Otto, Indon.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Ostatac *Spedrog, Arg.*
Glucosamine sulfate (p.2313·2).
Osteoarthritis.

Oste *Soho, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; zinc; magnesium (p.1922·1).
Osteoarthritis.

Ostebon *Otsira, India.*
Alfacalcidol (p.1986·1); calcium (p.1675·2).
Formerly known as Alfa Ostebon.

Ostedron *Kleva, Gr.; ICN, Pol.*
Etidronate disodium (p.1097·1).
Hypercalcaemia of malignancy; osteoporosis; Paget's disease of bone.

Ostela *Coronet, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; zinc (p.1922·1).
Osteoarthritis.

Ostelin
Note. This name is used for preparations of different composition.
Medac, Arg.; IFET (ΙΦΕΤ), Gr.; Teofarma, Ital.
Ergocalciferol (p.1987·1).
Vitamin D deficiency; vitamin D supplement; vitamin D deficiency.

Reckitt Benckiser, Austral.
Colecalciferol (p.1986·2).
Formerly contained ergocalciferol.
Vitamin D deficiency.

Ostelox *Sanbe, Indon.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Ostemax *Polpharma, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osten *Takeda, Jpn.*
Ipriflavone (p.1100·1).
Osteoporosis.

Ostenan *Marjan, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ostenil
Note. This name is used for preparations of different composition.
Chemedica, Fr.; Chemedica, Ger.; Chemedica, Switz.; Bio-Gen, Turk.; Chemedica, UK.
Sodium hyaluronate (p.2320·1).
Joint disorders; osteoarthritis.

Polfa Kutno, Pol.
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteo
Note. This name is used for preparations of different composition.
Quest, Canad.†.
Calcium, magnesium, vitamin C, vitamin D, and silicon (p.1922·1).

Healtheries, NZ.
Calcium carbonate (p.1714·1).
Calcium supplement.

Osteo-4 *Manix, Philipp.*
Calcium gluconate (p.1675·3); vitamin B (p.1980·2); colecalciferol (p.1986·2); ascorbic acid (p.1983·3).
Osteoporosis.

Osteo Bi-Flex *Bago, Chile.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3).
Joint disorders.

Osteo Complex *Peter, Ital.*
Calcium; vitamin D; boron; fluoride; zinc; copper; equisetum; lupulus (p.1922·1).
Nutritional supplement for healthy bones.

Osteo D *Teva, Hung.*
Calcitriol (p.1986·2).
Osteopathy; osteoporosis; renal osteodystrophy.

Osteo Support *Pharmagenics, UK.*
Hydroxyapatite (p.2323·1).
Bone disorders.

Osteobion *Centrum, Spain.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis; Paget's disease of bone.

Osteobon
Note. This name is used for preparations of different composition.
Bago, Arg.
Alendronate (p.1088·1).
Osteoporosis.

Otsira, India.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Cipla-Medpro, S.Afr.
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteobon-M *Otsira, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); magnesium oxide; copper sulfate; manganese sulfate; sodium boron; selenium dioxide; chromium picolinate (p.1922·1).
Vitamin D and mineral supplement.

Osteocal *Genopharm, Fr.; Nicholas, Indon.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Osteocal D3 *Genopharm, Fr.; Doetsch, Grether, Switz.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteocal Plus *Nicholas, Indon.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1); magnesium; manganese; zinc; sodium fluoride (p.1922·1).
Calcium deficiency; calcium supplement.

Osteocalcic *Biosintetica, Braz.†.*
Calcium citrate (p.1675·3).
Calcium supplement.

Osteocalcin *Eurodrug, Hong Kong†; Tosi, Ital.†; Eurodrug, Malaysia†; Eurodrug, Thai.†; Arcola, USA.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; neurodystrophies; osteolytic bone pain; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Osteocalcio *Biofarma, Mex.*
Calcium (p.1675·2); ergocalciferol (p.1987·1).
Osteoporosis.

Osteocalmine *Oriental, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Osteocap *Mega Lifesciences, Malaysia.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Osteocaps *Merck, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteocare
Note. This name is used for preparations of different composition.
Vitabiotics, Cz.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); zinc sulfate (p.1999·2); magnesium hydroxide (p.1743·2).
Nutritional supplement; osteomalacia; osteoporosis.

Vitabiotics, Hong Kong; Nobel, Turk.
Calcium (p.1675·2); magnesium (p.1678·3); zinc (p.1999·1); vitamin D (p.1986·1).
Calcium deficiency; calcium supplement.

Vitabiotics, Hung.
Calcium carbonate (p.1714·1); magnesium (p.1678·3); zinc (p.1999·1); colecalciferol (p.1986·2).
Calcium supplement.

Vitabiotics, Indon.; Vitabiotics, Philipp.
Calcium (p.1675·2); magnesium (p.1678·3); zinc (p.1999·1); colecalciferol (p.1986·2).
Calcium and magnesium supplement; nutritional supplement; osteoporosis.

Vitabiotics, UK.
Calcium carbonate (p.1714·1); calcium lactate (p.1676·1); calcium citrate (p.1675·3); magnesium hydroxide (p.1743·2); zinc sulfate (p.1999·2); colecalciferol (p.1986·2).

Osteochondrin S *Dyckerhoff, Ger.*
Ribonucleic acids from cattle and yeast (p.2379·1).
Bone disorders.

Osteocip *Cipla, India.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3).

Osteocis *CIS, Cz.†; CIS, Neth.; CIS, Port.; Schering, UK.*
Technetium-99m disodium oxidronate (p.2055·3).
Bone scintigraphy.

Osteocit *Seaford, Canad.*
Calcium citrate (p.1675·3).
Calcium supplement.

Osteoclar *Amnol, Ital.*
Dimethyl sulfone (p.2294·1); green-lipped mussel (p.2317·2); glucosamine (p.2313·2); collagen (p.2286·1); trace elements.
Nutritional supplement.

Osteocynesine *Boiron, Fr.; Boiron, Neth.; Boiron, Port.*
Homoeopathic preparation.

OsteoD *Teva, Cz.; Teva, Thai.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Osteo-D
Note. This name is used for preparations of different composition.
Solvang, Philipp.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2); simeticone (p.1770·2).
Calcium supplement; hyperacidity.

Med, Turk.
Calcitriol (p.1986·2).
Osteoporosis; renal osteodystrophy.

Osteodidronel *Procter & Gamble, Belg.*
Etidronate disodium (p.1097·1).
Postmenopausal osteoporosis.

Osteodon *Zentiva, Cz.; BioSaude, Port.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Osteodrug *Med-One, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Osteodur *Vivax, Venez.*
Alendronate sodium (p.1088·1).
Hypercalcaemia; osteoporosis.

OsteoEze Bone & Joint Care *Herron, Austral.*
Glucosamine hydrochloride (p.2313·2); calcium carbonate (p.1714·1); vitamin D; vitamin K (p.1922·1).
Joint disorders.

Osteofar *Elofar, Braz.; Fahrenheit, Indon.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Osteofem
Note. This name is used for preparations of different composition.
Grunenthal, Chile†.
Alendronate sodium (p.1088·1).
Osteoporosis.

Kalbe, Indon.
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Osteofene *Rontag, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteofix *Promedica, Ital.*
Ipriflavone (p.1100·1).
Postmenopausal osteoporosis.

Osteoflam *Soho, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); vitamin C; magnesium; zinc; manganese (p.1922·1).
Osteoarthritis.

Osteoflam-MR *Indoco, India.*
Diclofenac sodium (p.44·3); chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Painful muscle spasm.

Osteoflex *Otsira, India.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese sulfate; vitamine E (p.1922·1).
Osteoarthritis.

Osteofluor *Sanofi-Aventis, Neth.*
Sodium fluoride (p.1962·2).
Osteoporosis.

Osteoform *Sigma, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteofos *Cipla, Hong Kong; Cipla, India.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteofos D3 *Menarini, Irl.; Menarini, Ital.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteogel *Pampa, Pol.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium sulfate (p.1679·3).
Calcium and magnesium deficiency; fractures; hypoparathyroidism; long-term immobility; osteomalacia; osteoporosis; tetany.

Osteogenon *Germania, Austria; Pierre Fabre, Cz.; Pierre Fabre, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Rus.*
Hydroxyapatite (p.2323·1).
Calcium and phosphate deficiency; fractures; osteopenia; osteoporosis.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Osteokom *Lapi, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); vitamin C; selenium; zinc; manganese; magnesium glycerophosphate (p.1922·1).
Osteoarthritis.

Osteokom Forte *Lapi, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); selenium; zinc; manganese; magnesium glycerophosphate (p.1922·1).
Osteoarthritis.

Osteo-Life *Viatris, UK.*
Calcium (p.1675·2); colecalciferol (p.1986·2).
Calcium supplement.

Osteolip *Amnol, Ital.*
Thioctic acid (p.2400·2); linoleic acid (p.2308·2); asparagine; vitamins; minerals.
Nutritional supplement.

Osteo-Logic *Quest, Canad.*
Vitamin C; vitamin D; calcium; magnesium; silicon; zinc (p.1922·1).

Osteomar *Dupomar, Arg.†.*
Sodium monofluorophosphate (p.1964·3).
Osteoporosis.

Osteomax *Abdi, Turk.; Oftalmi, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteomeg *Mega Lifesciences, Philipp.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Osteomel *Clonmel, Irl.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteomerck *Merck, Spain.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteomin *Altana, Mex.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Osteomin D *Altana, Mex.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetany.

Osteonate
Note. This name is used for preparations of different composition.
Raffo, Arg.
Alendronate sodium (p.1088·1).
Osteoporosis.

Kalbe, Indon.
Risedronate sodium (p.1103·3).
Osteoporosis.

Osteonic *Nicholas, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; zinc; magnesium (p.1922·1).
Osteoarthritis.

Osteonorm
Note. This name is used for preparations of different composition.
Chrispa (Χρισπα), Gr.
Calcitonin (p.1093·1).
Osteoporosis.

Piam, Ital.
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

OsteoNutri *Medley, Braz.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets.

Osteoplex *Vitaplex, Austral.†.*
Mineral, vitamin, enzyme, and herb preparation (p.1922·1).
Calcium deficiency; osteoporosis.

Osteoplus
Note. A similar name is used for preparations of different composition (see below).
Farmalab, Braz.
Ipriflavone (p.1100·1).
Osteoporosis.

Merckle, Ger.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osteo-Plus
Note. A similar name is used for preparations of different composition (see above).
Rolmex, Canad.
Vitamin D and mineral preparation (p.1922·1).

Osteopor
Note. This name is used for preparations of different composition.
Combiphar, Indon.
Cimicifuga (p.2282·1); red clover (p.2285·1); calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Menopausal disorders; osteoporosis.

Pierre Fabre, Spain.
Hydroxyapatite (p.2323·1).
Osteoporosis.

Osteopro
Note. This name is used for preparations of different composition.
Viatris, Austria.
Sodium monofluorophosphate (p.1964·3).
Osteoporosis.

Health Perception, UK.
Ipriflavone (p.1100·1); calcium (p.1675·2); vitamins; minerals (p.1922·1).
Osteoporosis.

Osteor *Pyridam, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; zinc; selenium (p.1922·1).
Joint disorders.

Osteor Plus *Pyridam, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); ascorbic acid; manganese; magnesium; selenium; zinc; dimethyl sulfone (p.2294·1) (p.1922·1).
Osteoarthritis; supplement for healthy joints.

Osteoral *Ache, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteor-C *Pyridam, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); capsicum (p.2276·2); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Osteorel *Unipharma, Gr.*
Calcium phosphate (p.1676·2).
Calcium deficiency.

Osteos *TAD, Ger.*
Calcitonin (salmon) acetate (p.1094·1).
Hypercalcaemia; malignant osteolysis; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Osteosan *Silesia, Chile.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteosil *Ghimas, Ital.†.*
Equisetum (p.2299·3).
Nutritional supplement.

Osteosil Calcium *Ghimas, Ital.*
Calcium (p.1675·2); equisetum (p.2299·3).
Nutritional supplement.

Osteosol *Amersham, Neth.†.*
Technetium-99m (p.2055·3) medronate.
Bone imaging.

Osteostab *Rottapharm, Ital.*
Clodronate disodium (p.1095·3).
Hyperparathyroidism; multiple myeloma; osteolysis of malignancy; osteoporosis.

Osteoton *Gerolymatos, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Osteotonina *Menarini, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Osteotop *Silesia, Chile†.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Osteotrat *Biosintetica, Braz.†.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Osteotriol *Gry, Ger.; Teva, Rus.†.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy.

Osteovile *Pharmanel, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Osteovis *NCSN, Ital.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Osteovit *Pharmadass, UK.*
Multivitamin, mineral, and trace element preparation (p.1922·1).

Osteovital *Investi, Arg.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Ostepam *Nordic, Fr.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; myeloma; osteolytic bone lesions; Paget's disease of bone.

Osteral *Silanes, Mex.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Ostetan *Alacan, Spain.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis; Paget's disease of bone.

Osteum *Viñas, Spain.*
Etidronate disodium (p.1097·1).
Ectopic ossification; osteoporosis; Paget's disease of bone.

Osteus *Medichrom, Gr.*
Calcium phosphate (p.1676·2).
Calcium deficiency.

Ostical *GSK, Pol.*
Calcium carbonate (p.1714·1); calcium lactate gluconate (p.1676·2).
Calcium deficiency; osteoporosis.

Osticalcin *Biomedica-Chemica, Gr.†.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Ostiderm
Note. This name is used for preparations of different composition.
Pedinol, USA.
Lotion: Aluminium sulfate (p.2255·1); zinc oxide (p.1621·2).
Formerly contained aluminium sulfate and phenol.
Foot odour; hyperhidrosis.

Pedinol, USA.
Roll-on: Aluminium chlorohydrate (p.1588·3); camphor (p.2273·2).
Foot odour; hyperhidrosis.

Ostidil-D3 *KBR, Ital.*
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Ostifix *Farmedia, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

OstiGen *US Food & Pharmaceuticals, USA.*
Vitamin D; vitamin K; minerals (p.1922·1).

Ostinate *Grunenthal, Port.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Ostine *Farma Lepori, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ostion *Lusoterapia, Port.*
Perindopril erbumine (p.1368·3).
Coronary artery disease; heart failure; hypertension.

Ostirein *Farmedia, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Ostitriol *Farmedia, Gr.*
Calcitriol (p.1986·2).
Vitamin D deficiency.

Ostobon *Coloplast, UK.*
A deodorant powder for use with ostomies.

Ostocalcium *GSK, India.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; rickets.

Ostocalcium B-12 *GSK, India.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2); vitamin B (p.1980·2).
Calcium and vitamin D deficiency; rickets.

Ostocavid *Sudmedica, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ostochont
Note. This name is used for preparations of different composition.
Godecke, Ger.†.
Liniment: Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); nonivamide (p.96·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Godecke, Ger.†.
Ointment: Heparin sodium (p.1301·2); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Ostofen *Shiwa, Thai.†.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Ostoforte *Merck Frosst, Canad.*
Ergocalciferol (p.1987·1).
Hypoparathyroidism; phosphataemia; rickets.

Ostogene *Genepharm, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Ostolek *Lek-Am, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ostomax *Unipharma, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ostone-B12 *TP, Thai.*
Calcium (p.1675·2); ergocalciferol (p.1987·1); vitamin B (p.1980·2).
Megaloblastic anaemia; osteomalacia; rickets.

Ostoplus *Meditrina, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Ostopor *Unipharma, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Ostosalm *Pfizer, Gr.; Pharmacia Upjohn, Port.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Ostostabil *Jenapharm, Cz.†; Jenapharm, Ger.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; hyperparathyroidism; osteolysis of malignancy; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Ostovell *Novell, Indon.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Ostowap D_3 *Lek-Am, Pol.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; osteomalacia; osteoporosis; tetany.

Ostram *Merck, Arg.; Merck, Austria; Merck, Chile; Merck-Lipha, Fr.; Merck, Mex.†; Merck Lipha Sante, Pol.; Faes, Spain; Bracco, UK.*
Calcium phosphate (p.1676·2).
Calcium deficiency; calcium supplement; osteoporosis.

Ostram D3 *Merck, Arg.; Merck, Chile; Merck, Port.†.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ostram D_3 *Bracco, Ital.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ostram Vitamine D_3 *Merck-Lipha, Fr.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiencies; osteoporosis.

Ostramont *Chrispa (Χρισπα), Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Ostram-Vit D_3 *Merck, Fin.†.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ostranorm *Nycomed, Denm.†.*
11 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

Ostrid *Otto, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Ostrin Q10 *Qualiphar, Belg.*
Oyster extract; taurine; zinc orotate; ginseng; nicotinamide; ubidecarenone; extramel (p.1922·1).
Tonic.

Ostriol *Cellofarm, Braz.†; Fahrenheit, Indon.*
Calcitriol (p.1986·2).
Hypocalcaemia; hypoparathyroidism; hypophosphataemia; osteoporosis; renal osteodystrophy; rickets.

Ostron *Lifeplan, UK.*
Vitamin D; vitamin B ; folic acid; calcium; magnesium; zinc; boron; copper; manganese (p.1922·1).
Dietary supplement for healthy bones.

Ostronara *Besins, Ger.; Kade, Ger.*
16 Tablets, estradiol valerate (p.2097·3); 12 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; osteoporosis.

Ostro-Primolut *Schering, Ger.†.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Menstrual disorders.

OsvaRen *Fresenius Medical, Cz.*
Calcium acetate (p.1675·2); heavy magnesium carbonate (p.1743·1).
Hyperphosphataemia.

Osvaren *Fresenius Medical, Port.*
Calcium acetate (p.1675·2); magnesium carbonate (p.1743·1).
Hyperphosphataemia in dialysis patients.

Osvical *Alodial, Port.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osvical D *Alter, Spain.*
Calcium pidolate (p.1676·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Osvion Plus *Solas, Indon.*
Ascorbic acid; vitamin E; vitamin D; manganese sulfate; zinc sulfate; selenium; glucosamine (p.2313·2); dimethyl sulfone (p.2294·1); chondroitin sulfate (p.2280·3)(p.1922·1).
Maintenance of healthy joints; osteoarthritis.

Osyra *Astellas, Ital.*
Emollient.

Osyrol *Aventis, Ger.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; liver cirrhosis and ascites; oedema.

Osyrol Lasix *Aventis, Ger.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; hyperaldosteronism; liver cirrhosis; oedema.

Otaci Diyet Life Psyllium Plus *Kurtsan, Turk.*
Ispaghula (p.1737·1); vitamin B substances (p.1922·1).

Otaci Meyanbali *Kurtsan, Turk.*
Menthol (p.2340·1); thymol (p.1664·3); camphor (p.2273·2).
Mouth and throat disorders.

Otaci Musillium *Kurtsan, Turk.*
Ispaghula (p.1737·1).

Otaci Oka Mentol *Kurtsan, Turk.*
Cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3); camphor (p.2273·2).
Mouth and throat disorders.

Otaci Salvia *Kurtsan, Turk.*
Thymol (p.1664·3); menthol (p.2340·1); cineole (p.2282·3); camphor (p.2273·2).
Mouth and throat disorders.

Otalex *Roemmers, Venez.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Otalex G *Ivax, Arg.*
Phenazone (p.116·1); gentamicin sulfate (p.282·1); procaine hydrochloride (p.1869·1).
Otitis externa.

Otalgan
Note.This name is used for preparations of different composition.
Willvonseder, Austria.
Lidocaine hydrochloride (p.1862·3); phenazone (p.116·1).
Earache; otitis media.

Sudmedica, Ger.; SIT, Ital.; Berna, Spain†; Medichemie, Switz.
Procaine hydrochloride (p.1869·1); phenazone (p.116·1).
Earache; otitis media.

Pharmacos, Mex.
⊗ Chloramphenicol (p.239·3); prednisolone (p.1540·3); lidocaine (p.1862·3).
Earache.

Vemedia, Neth.
Lidocaine hydrochloride (p.1862·3).
Earache.

Otamina *Gache, Venez.*
Phenazone (p.116·1).
Earache.

Otan *Vincenti, Venez.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); phenazone (p.116·1).
Ear infections.

Otandrol
Note.This name is used for preparations of different composition.
Andromaco, Chile.
⊗ Chloramphenicol (p.239·3); benzocaine (p.1854·1); betamethasone dipropionate (p.1518·3).
Infected ear disorders.

Andromaco, Venez.†.
Chloramphenicol (p.239·3); lidocaine (p.1862·3).
Ear infections.

Otanol *Etifar, Venez.†.*
Phenazone (p.116·1); sulfanilamide (p.343·1); sulfathiazole (p.343·2).
Ear infections.

Otarex *Teva, Israel.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; premedication; pruritus.

Otari *Rafarm, Gr.*
Calcitriol (p.1986·2).
Vitamin D deficiency.

Otauril *Brasmedica, Braz.†.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); fluocinolone acetonide (p.1531·3); lidocaine (p.1862·3).
Ear disorders.

Otaxem *Best, Mex.*
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Otazol *Bago, Chile†.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); betamethasone sodium phosphate (p.1518·3); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

OTC HP Kit *Biochem, India.*
2 Capsules, omeprazole (p.1753·1); 2 tablets, tinidazole (p.848·3); 2 tablets, clarithromycin (p.248·2).
Peptic ulcer.

Otede *Sanbe, Indon.*
Diphenhydramine hydrochloride (p.577·2).
Allergic rhinitis; nausea and vomiting; urticaria.

Otedram *Psicofarma, Mex.*
Bromazepam (p.964·3).
Nervous disorders.

Otek-AC *FDC, India†.*
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3); acetic acid (p.2244·2).
Ear disorders.

Otek-AC+ *FDC, India.*
⊗ Beclometasone dipropionate (p.1516·2); clotrimazole (p.530·1); chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otex *Dendron, UK.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Otex HC *Cassara, Arg.; D & M, Chile.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Otiborin *Santen, Fin.*
⊗ Boric acid (p.2268·1); alcohol (p.1625·2).
Ear infections.

Otic Domeboro *Bayer, USA.*
Acetic acid (p.2244·2); aluminium acetate (p.2255·1).
Superficial infections of the external auditory canal.

Otic-Care *Parmed, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial ear infections.

Oticerim *Daudt, Braz.*
⊗ Sodium perborate (p.1662·1); urea (p.1620·2).
Ear wax removal.

Oticum *Saval, Chile.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); betamethasone sodium phosphate (p.1518·3); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Otidin *Teva, Israel.*
Phenazone (p.116·1); tetracaine hydrochloride (p.1871·3).
Otitis externa; otitis media.

Otidrops *Hexa, Arg.*
⊗ Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1); prednisolone (p.1540·3).
Earache.

Otifar *Farmaceutica H, Mex.*
⊗ Benzocaine (p.1854·1); chloramphenicol (p.239·3); hydrocortisone (p.1535·2).
External ear disorders.

Otilin *Collins, Mex.*
Lidocaine (p.1862·3); neomycin (p.305·1).

Otimed
Note. A similar name is used for preparations of different composition (see below).
Steierl, Ger.
Homoeopathic preparation.

Oti-Med
Note. A similar name is used for preparations of different composition (see above).
Hyrex, USA†.
⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone (p.1535·2).
Ear disorders.

Otimisin *Bilim, Turk.*
⊗ Prednisolone metasulfobenzoate (p.1542·1); tetracaine hydrochloride (p.1871·3).
Otitis externa.

Otinum *ICN, Pol.; Valeant, Rus.*
Choline salicylate (p.36·3).
Earache; removal of ear wax.

Otipax *Biocodex, Cz.; Biocodex, Fr.; Teva, Hung.; Biocodex, Rus.; Zambon, Switz.*
Lidocaine hydrochloride (p.1862·3); phenazone (p.116·1).
Earache; otitis.

Otirilin *Grunenthal, Venez.*
Phenazone (p.116·1); lidocaine hydrochloride (p.1862·3).
Earache.

Otised *Propan, S.Afr.*
Phenazone (p.116·1); benzocaine (p.1854·1).
Ear infections.

Otitex *Sudmedica, Ger.*
Docusate sodium (p.1725·1).
Removal of ear wax.

OtiTricin *Bausch & Lomb, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Otix *M4, Spain.*
⊗ Dexamethasone phosphate (p.1526·2); polymyxin B sulfate (p.317·3); trimethoprim (p.355·2).
Otitis externa.

Oto Betnovate *Farmoquimica, Braz.*
⊗ Betamethasone valerate (p.1519·1); chlorphenesin (p.529·2); tetracaine hydrochloride (p.1871·3).
Ear disorders.

Oto Biotaer *Investi, Arg.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Formerly contained polymyxin B sulfate, neomycin sulfate, hydrocortisone acetate, and lidocaine hydrochloride.
Otitis externa.

Oto Difusor *Medical, Spain†.*
⊗ Benzocaine (p.1854·1); hyaluronidase (p.2321·1); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); sulfanilamide sodium mesilate (p.343·1).
Ear disorders.

Oto Eni *Grossman, Mex.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2); lidocaine hydrochloride (p.1862·3).
Infected external ear disorders.

Oto Vitna *Quimifar, Spain†.*
⊗ Dexamethasone (p.1526·1); benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
External ear disorders.

Oto Xilodase *Apsen, Braz.*
Lidocaine hydrochloride (p.1862·3); neomycin sulfate (p.305·1); hyaluronidase (p.2321·1).
Ear disorders.

Otobacid N *Torrex Chiesi, Cz.; Asche, Ger.*
⊗ Dexamethasone (p.1526·1); cinchocaine hydrochloride (p.1857·3).
Ear disorders.

Otobel *Sedabel, Braz.†.*
Sulfathiazole (p.343·2); procaine hydrochloride (p.1869·1).
Ear infections.

Otobiotic
Note. This name is used for preparations of different composition.
Denver, Arg.
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Ear disorders.

Schering, USA.
⊗ Polymyxin B sulfate (p.317·3); hydrocortisone (p.1535·2).
Bacterial ear infections.

Oto-Biotic
Note. A similar name is used for preparations of different composition (see above).
Allergan, Braz.†.
⊗ Sulfacetamide sodium (p.335·3); chloramphenicol (p.239·3); tetracaine hydrochloride (p.1871·3); boric acid (p.2268·1); urea (p.1620·2).
Ear infections.

Otobrain *Farmila, Ital.*
Multivitamin preparation with glycerophospholipids and ginkgo biloba (p.1922·1).
Nutritional supplement; tinnitus; vertigo.

Otobrol *Farmoz, Port.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Otocain *Abana, USA.*
Benzocaine (p.1854·1).
Earache.

Otocalm *Parmed, USA†.*
Benzocaine (p.1854·1); phenazone (p.116·1).
Earache.

Otocalma *Salusif, Port.†.*
Procaine hydrochloride (p.1869·1); phenazone (p.116·1); sulfanilamide (p.343·1).
Otitis.

Otocalmia *Medical, Arg.*
Benzocaine (p.1854·1); chlorobutanol (p.1639·2); turpentine oil (p.2406·3).
Ear wax removal; earache.

Otocalmia Biotic *Medical, Arg.*
Neomycin (p.305·1); phenazone (p.116·1); sodium carbonate (p.2389·1); cetrimide (p.1634·1).
Otitis externa.

Otocalmine *Pharmacobel, Belg.*
Phenazone (p.116·1); lidocaine (p.1862·3).
Formerly contained phenazone and procaine hydrochloride.
Ear disorders.

Otoceril *Menarini, Port.*
Paradichlorobenzene (p.2363·1); benzocaine (p.1854·1); chlorobutanol (p.1639·2).
Removal of ear wax.

Otocerol *Lafedar, Arg.*
Phenazone (p.116·1); sodium carbonate (p.2389·1).

Otocerum *Reig Jofre, Spain.*
Phenol (p.1656·1); chlorobutanol (p.1639·2); benzocaine (p.1854·1); turpentine oil (p.2406·3); castor oil (p.2278·1).
Removal of ear wax.

Otociprin *Fardi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Otitis externa.

Otocipro *Fortbenton, Arg.*
⊗ Hydrocortisone (p.1535·2); ciprofloxacin (p.243·3).
Ear infections.

Otociriax *Farmoquimica, Braz.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Otoclean Gotas Oticas *Cassara, Arg.*
Sodium carbonate (p.2389·1); polysorbate 80 (p.1919·2).
Formerly contained sodium bicarbonate, polysorbate 80, cetrimide, phenazone, and neomycin.
Ear wax removal; earache.

Otoclean Solucion de Limpieza *Cassara, Arg.†.*
Docusate sodium (p.1725·1).
Ear wax removal.

Otocomb Otic *BMS, Austral.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); nystatin (p.543·2); gramicidin (p.286·1).
Otitis externa.

Otocort
Note.This name is used for preparations of different composition.
Gemballa, Braz.†.
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B (p.318·2); neomycin (p.305·1); lidocaine (p.1862·3).
Ear disorders.

Biospray, Gr.
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1); acetic acid (p.2244·2).
Otitis externa.

Lemmon, USA.
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Oftalmi, Venez.
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Otitis externa.

Otocuril *Fabra, Arg.*
Phenazone (p.116·1); sulfathiazole sodium (p.343·3); ethacridine lactate (p.1625·1).
Ear disorders.

Oto-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Otodex *Aventis, Austral.*
⊗ Framycetin sulfate (p.279·1); gramicidin (p.286·1); dexamethasone (p.1526·1).
Ear disorders.

Otodol *Farmion, Braz.†.*
Nitrofurazone (p.309·1); neomycin sulfate (p.305·1); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3); dimethyl sulfoxide; menthol (p.2340·1).
Ear disorders.

Otodolor Soft *Ursapharm, Ger.*
Glycerol (p.2314·2).
Removal of ear wax.

Otodon *Organifar, Venez.†.*
Lidocaine (p.1862·3); phenazone (p.116·1).
Earache.

Otofa *Bouchara-Recordati, Fr.; Bouchara, Rus.; Bouchara, Switz.*
Rifamycin sodium (p.329·2).
Otitis.

Otofenicol-D *Allergan, Braz.†.*
⊗ Lidocaine hydrochloride (p.1862·3); dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Ear disorders.

Otoflour *Bell, India.*
Sodium fluoride (p.1962·2).
Conductive deafness; otosclerosis.

Otoflox *Cassara, Arg.*
Ofloxacin (p.310·2).
Otitis externa; otitis media.

Otofluor *SIT, Ital.*
Sodium fluoride (p.1962·2); calcium gluconate (p.1675·3).
Otosclerosis.

Otofren *Pfluger, Ger.*
Homoeopathic preparation.

Otofrin *Quim-Far, Venez.†.*
Phenazone (p.116·1); phenylephrine hydrochloride (p.1568·1); benzocaine (p.1854·1).
Earache.

Otogen Calmante *Rimafar, Spain.*
Benzalkonium chloride (p.1629·1); clove oil (p.2285·1); phenol (p.1656·1); tetracaine hydrochloride (p.1871·3); menthol (p.2340·1).
Ear disorders.

Otogesic *Ethnor, India.*
Acediasulfone (p.200·2); oxymethurea (p.1655·1); cinchocaine (p.1857·2); glycerol (p.2314·2).
Ear disorders.

Otolin *Kalbe, Indon.*
Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3); benzocaine (p.1854·1); nipagin.
Otitis.

Otolisan *Pharma Investi, Chile.*
⊗ Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); betamethasone sodium phosphate (p.1518·3); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Otolitan N farblos *3M, Ger.†.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Earache; otitis.

Otolitan N mit Rivanol *3M, Ger.†.*
Ethacridine lactate (p.1625·1); lidocaine hydrochloride (p.1862·3).
Earache; otitis.

Otoloide *Cimed, Braz.*
Phenol (p.1656·1); procaine hydrochloride (p.1869·1).
Ear disorders.

Otolone *Loren, Mex.†.*
⊗ Hydrocortisone (p.1535·2); chloramphenicol (p.239·3); benzocaine (p.1854·1).
Ear infections.

Otomar-HC *Marnel, USA.*
⊗ Chloroxylenol (p.1640·2); hydrocortisone (p.1535·2); pramocaine hydrochloride (p.1868·1).
Ear disorders.

Otomicina *Medley, Braz.*
Chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otomide *Aclae, Fr.*
Hexamidine isetionate (p.1646·3); lidocaine hydrochloride (p.1862·3).
Otitis.

Otomidone *SIT, Ital.*
Phenazone (p.116·1); procaine hydrochloride (p.1869·1).
Earache.

Otomidrin *Fardi, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); framycetin sulfate (p.279·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otomixyn *EMS, Braz.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otomize *Kite (Κιτε), Gr.; GSK Consumer, Irl.; Stafford-Miller, Israel†; Stafford-Miller, Port.†; GSK Consumer, UK.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Ear disorders; otitis externa.

Otomycin *Taro, Israel.*
Neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1); sodium propionate (p.545·3); benzocaine (p.1854·1); benzyl alcohol (p.1631·3).
Ear infections.

Otomycin-HPN *Misemer, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B (p.318·2).
Bacterial ear infections.

Otonal *Biochimico, Braz.†.*
Paracetamol (p.108·1); zinc bromide; valeric acid.
Vertigo.

Otonina *Berna, Spain†.*
⊗ Benzocaine (p.1854·1); neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Ear disorders.

Otonorthia *Northia, Arg.*
Phenazone (p.116·1); procaine (p.1869·2); gentamicin (p.284·2).
Ear disorders.

Otopain *Interbat, Indon.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Otitis.

Otopax *Vaillant, Ital.*
Procaine hydrochloride (p.1869·1); phenazone (p.116·1).
Earache.

Otopen *Dinafarma, Braz.†.*
Chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Oto-Phen *Adcock Ingram, S.Afr.*
Phenazone (p.116·1).
Earache; otitis.

Oto-Phen Forte *Adcock Ingram, S.Afr.*
⊗ Benzocaine (p.1854·1); ephedrine hydrochloride (p.1558·2); phenazone (p.116·1); potassium hydroxyquinoline sulfate (p.2323·2).
Earache; otitis.

Otopraf *Prafa, Indon.*
Fludrocortisone acetate (p.1530·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otopreven *Fortbenton, Arg.*
Acetic acid (p.2244·2).
Ear infections.

Otoralgyl a la phenylephrine *McNeil, Fr.†.*
Lidocaine hydrochloride (p.1862·3); phenylephrine hydrochloride (p.1568·1); sodium propionate (p.545·3).
Otitis.

Otorinazol *Montpellier, Arg.†.*
Sulfathiazole (p.343·2); atropine sulfate (p.1219·3); niaouli oil (p.2351·3); cineole (p.2282·3).
Cold and influenza symptoms; rhinitis.

Otoryl *Otto, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Otosal *Coup, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Otosamthong *SM, Thai.*
Furaltadone hydrochloride (p.279·2); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Otitis externa; otitis media.

Otosan *Streuli, Switz.*
Procaine hydrochloride (p.1869·1); phenazone (p.116·1).
Ear disorders; earache.

Otosan Natural Ear Drops *Otosan, Ital.†.*
Almond oil (p.2252·2); cajuput oil (p.2271·2); geranium oil (p.2311·1); juniper oil (p.2328·3); chamomile (p.2279·3); propolis (p.2373·3).
Ear wax removal.

Otosat *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Otitis externa.

Otosedol *Pensa, Spain.*
Phenazone (p.116·1); procaine hydrochloride (p.1869·1).
Earache.

Otosedol Biotico *Pensa, Spain.*
Chloramphenicol (p.239·3); benzocaine (p.1854·1); tyrothricin (p.358·2).
Ear disorders.

Otoseptil
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.
⊗ Neomycin sulfate (p.305·1); hydrocortisone (p.1535·2); benzocaine (p.1854·1).
Ear disorders.

Sanitas, Chile.
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Otosol *Norgine, Philipp.*
Docusate sodium (p.1725·1).
Ear wax removal.

Otosporin
Note. This name is used for preparations of different composition.
Investi, Arg.; GSK, Austria; Pfizer Consumer, Belg.†; Farmoquimica, Braz.; GSK, Cz.; GSK, Hong Kong; Teva, Hung.; GSK, Irl.; GSK, Neth.; Wellcome, Port.; GSK, S.Afr.; GSK, Spain; GSK, Switz.; GSK, Thai.†; GSK, UK; Calmic, USA.
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Formerly known as Otosporin GS in *Arg.*
Bacterial ear infections.

Pfizer Consumer, Ital.†.
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial infections of the external ear.

Otosporin C *Investi, Arg.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Formerly known as Otosporin c Ciprofloxacina.
Otitis externa.

Otosporin L *Investi, Arg.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); lidocaine hydrochloride (p.1862·3).
Bacterial ear infections.

Otospray *Stafford-Miller, Switz.†.*
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Ear disorders.

Otosynalar *Roche, Braz.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Oto-Synalar N *Lusomedicamenta, Port.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Formerly contained fluocinolone acetonide.

Otothricinol *Plan, Switz.*
Tyrothricin (p.358·2); phenazone (p.116·1); cetylpyridinium chloride (p.1635·1).
Ear disorders.

Otovix *Ibefar, Braz.†.*
Sulfanilamide (p.343·1); tyrothricin (p.358·2); benzocaine (p.1854·1); phenazone (p.116·1).
Ear disorders.

Otovowen *Weber & Weber, Ger.*
Homoeopathic preparation.

Otowaxol *Norgine, Ger.*
Docusate sodium (p.1725·1).
Removal of ear wax.

Otozambon
Note. This name is used for preparations of different composition.
Zambon, Hong Kong.
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Otitis externa; otitis media; suppurative complications following ear and mastoid surgery.

Zambon, Indon.
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); furaltadone hydrochloride (p.279·2); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Otradrops *Manx, UK.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Otrasel *Cephalon, Fr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Otraspray *Manx, UK.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Otrebuski *Sanofi-Aventis, Pol.*
Ispaghula (p.1737·1); wheat bran (p.1712·3).
Constipation; dietary fibre supplement; hypercholesterolaemia; obesity.

Otreon *Sankyo, Austria; Sankyo, Ital.; Sankyo, Neth.; Sankyo, Spain.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Otrex *Stragen, Pol.*
Diosmin (p.2304·2).
Venous insufficiency.

O-trexat *Onkoworks, Ger.*
Methotrexate (p.745·2).
Malignant neoplasms.

Otriflu *Novartis Consumer, Neth.; Novartis, Norw.; Novartis Consumer, Port.*
Diclofenac potassium (p.44·3).
Fever; pain.

Otrinol *Novartis, Israel†; Novartis Consumer, Switz.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Otrisal *Novartis Consumer, Ger.†.*
Sodium chloride (p.1686·1).
Nasal disorders.

Otrisalin *Novartis, Gr.†; Novartis, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Otriven *Novartis, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Conjunctival disorders.

Otriven Baby *Novartis Consumer, Ger.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Otriven gegen Schnupfen *Novartis Consumer, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Otriven H *Novartis Consumer, Ger.†.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Otriven mit Dexpanthenol *Novartis Consumer, Ger.*
Dexpanthenol (p.2362·1).
Nasal disorders.

Otrivin
Novartis Consumer, Austral.; Novartis Consumer, Austria; Novartis Consumer, Canad.; Novartis Consumer, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Gr.; Novartis Consumer, Hong Kong; Novartis Consumer, Hung.; Novartis, India; Novartis, Indon.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Malaysia; Novartis Consumer, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Rus.; Novartis Consumer, S.Afr.; Novartis OTC, Singapore; Novartis Consumer, Spain; Novartis, Swed.; Novartis Consumer, Switz.; Novartis, Thai.; Ciba Consumer, USA.
⊗ Xylometazoline hydrochloride (p.1575·1).
Aid in rhinoscopy; cold symptoms; nasal congestion; otitis; rhinitis; sinus congestion; sinusitis; upper respiratory-tract congestion.

Otrivin Allergia *Novartis Consumer, Hung.*
Dimetindene maleate (p.576·3); phenylephrine (p.1568·1).
Allergic rhinitis; nasal congestion.

Otrivin Allergy *Novartis Consumer, Pol.*
Dimetindene maleate (p.576·3); phenylephrine hydrochloride (p.1568·1).
Nasal congestion; otitis media; rhinitis; sinusitis.

Otrivin Baby *Novartis Consumer, Ital.*
Sodium chloride (p.1686·1).
Nasal cleansing; nasal dryness.

Otrivin hooikoorts *Novartis Consumer, Neth.†.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Otrivin Menthol *Novartis, Denm.; Novartis, Fin.; Novartis Consumer, Neth.; Novartis, Swed.*
⊗ Xylometazoline hydrochloride (p.1575·1); menthol (p.2340·1); cineole (p.2282·3).
Nasal congestion; rhinitis; sinusitis; upper respiratory-tract congestion.

Otrivin neusallergie azelastine *Novartis Consumer, Neth.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Otrivin neusallergie loratadine *Novartis Consumer, Neth.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Otrivin rhume des foins *Novartis Consumer, Switz.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Otrivin Saline Baby *Novartis Consumer, Austral.*
Sodium chloride (p.1686·1).
Nasal congestion.

Otrivina *Novartis, Arg.; Novartis, Braz.; Novartis Consumer, Port.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Aid in rhinoscopy; nasal congestion; otitis media.

Otrivine *Novartis Consumer, Irl.; Novartis, NZ; Novartis, Turk.; Novartis Consumer, UK.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis; sinusitis.

Otrivine Anti-Allergie *Novartis Consumer, Belg.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Otrivine Anti-Rhinitis *Novartis Consumer, Belg.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; otitis; sinusitis.

Otrivine Menthol *Novartis, NZ.*
⊗ Xylometazoline hydrochloride (p.1575·1); menthol (p.2340·1); eucalyptus (p.2301·2).
Nasal congestion.

Otrivine Mu-Cron *Novartis Consumer, UK.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Otrivine-Antistin *Novartis, Irl.; Novartis, NZ; Novartis Consumer, UK.*
⊗ Xylometazoline hydrochloride (p.1575·1); antazoline sulfate (p.567·1).
Allergic conjunctivitis; eye irritation.

Otrivini *Novartis Consumer, Israel.*
Sodium chloride (p.1686·1).
Nasal congestion.

Otrivin-Menthol *Novartis, Gr.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Otrozol *Pisa, Mex.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections.

Otsu-D5 *Otsuka, Indon.*
Glucose (p.1945·3).
Carbohydrate source; fluid depletion.

Otsuka Cez *Otsuka, Jpn.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Otsuka MV *Otsuka, Jpn; Otsuka, Thai.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Otsu-NS *Otsuka, Indon.*
Sodium chloride infusion (p.1686·1).
Sodium and chloride replacement.

Otsutran *Otsuka, Indon.*
⊗ Dextran 40 (p.1059·1) in electrolytes.
Extracorporeal circulation; plasma volume expansion.

Ottocid *Polifarma, Ital.*
Phenothrin (p.2048·3).
Acaricide.

Ottoclor *Ottolenghi, Ital.†.*
Tosylchloramide sodium (p.1665·1).
Disinfection of skin, wounds, and burns.

Ottogenta *Otto, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Ottopan *Otto, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Ottoprim *Otto, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Ottovis *Fitolife, Ital.*
Royal jelly (p.2382·1); ginseng (p.2312·1); wheatgerm oil (p.2415·1); soya lecithin (p.2332·2); pollen (p.2370·2).
Tonic.

Oturga *Legrand, Braz.*
Tyrothricin (p.358·2); salicylic acid (p.1612·2); boric acid (p.2268·1); procaine hydrochloride (p.1869·1).
Ear disorders.

Ouate Hemostatique *Qualiphar, Belg.*
Ferric chloride (p.2303·3); phenazone (p.116·1).
Haemorrhage.

Oulogram *Ni-The, Gr.*
Tyrothricin (p.358·2); borax (p.2268·1); tannic acid (p.2394·3); thymol (p.1664·3).
Gum disorders.

Out of Africa *Sutton, Canad.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Outgro
Note. This name is used for preparations of different composition.
Medtech, Canad.
Benzocaine (p.1854·1).

Whitehall, USA.
Tannic acid (p.2394·3); chlorobutanol (p.1639·2).
Ingrown toenails.

Outlook *Lifeplan, UK.*
St John's wort; rosemary; avena; vitamin B substances (p.1922·1).

Out-of-Sorts *Potter's, UK.*
Senna (p.1769·2); aloes (p.1705·2); cascara (p.1715·2); taraxacum (p.2395·1); fennel (p.2302·3).
Constipation.

Ouvidonal *Neo Quimica, Braz.*
Chloramphenicol (p.239·3); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Ova *Fada, Arg.†.*
Papaverine (p.2191·3).

Ovace *Coria, USA.*
Sulfacetamide sodium (p.335·3).

Ovadril *Toprak, Turk.*
Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2); lidocaine hydrochloride (p.1862·3).
Pruritus.

Ova-Mit *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Philipp.; Remedica, Singapore; Remedica, Thai.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Ovapac *Pharmathen, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Ovarell *Sanorell, Ger.*
Homoeopathic preparation.

Ovariusedan *Labortecne, Braz.†.*
Plumeria; gossypium; cinnamon oil (p.2283·2); anise oil (p.2258·2).

Ovastat *Medac, Ger.*
Treosulfan (p.783·2).
Ovarian cancer.

Ovazol-V *Gelcaps, Mex.*
Metronidazole (p.837·1).
Vaginal trichomoniasis.

Ovcon 35 *BMS, USA.*
21 Tablets, norethisterone (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Ovcon 50 *BMS, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Overal *Lusofarmaco, Ital.*
Roxithromycin (p.331·1).
Bacterial infections.

Overoid *Valdecasas, Mex.*
Niclosamide (p.151·1).
Worm infections.

Overpon *Valdecasas, Mex.*
Piperazine citrate (p.152·3).
Worm infections.

Ovestal *Hexal, Neth.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Ovesterin *Organon, Norw.; Organon, Swed.*
Estriol (p.2101·1).
Vulvovaginal disorders due to oestrogen deficiency.

Ovestin *Organon, Austral.; Organon, Austria; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong†; Organon, Hung.; Organon, Indon.; Organon, Israel; Organon, Ital.; Organon, Mex.; Pharmaco, NZ; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Organon, Switz.; Organon, Thai.†; Organon, Turk.; Organon, UK; Organon, Venez.*
Estriol (p.2101·1).
Adjunct in cervical smear tests; adjunct in vaginal infections; adjunct in vaginal surgery; atrophic vaginitis; female infertility; genito-urinary disorders due to oestrogen deficiency; menopausal disorders; oestrogen deficiency; osteoporosis; prostatic dysplasia; ulcers associated with uterine or vaginal prolapse.

Ovestinon *Organon, Spain.*
Estriol (p.2101·1).
Oestrogen deficiency.

Ovestrion *Organon, Braz.*
Estriol (p.2101·1).
Menopausal disorders; osteoporosis.

Ovex *Johnson & Johnson MSD Consumer, UK.*
Mebendazole (p.148·3).
Enterobiasis.

Ovide *Medicis, USA.*
Malathion (p.2046·1).
Pediculosis.

Ovidol *Organon, Belg.; Organon, Neth.*
7 Tablets, ethinylestradiol (p.2101·3); 15 tablets, ethinylestradiol; desogestrel (p.2093·2).
Sequential-type oral contraceptive.

Ovidon *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Ovidrel *Serono, Arg.; Serono, Austral.; Serono, Braz.; Novartis, Chile†; Serono, Hong Kong; DKSH, Indon.; Serono, Indon.; Serono, Malaysia; Serono, Mex.; Douglas, NZ; Serono, Philipp.; Serono, Singapore; Serono, Thai.; Serono, USA; Serono, Venez.*
⊗ Choriogonadotropin alfa (p.2085·1).
Male and female infertility.

Ovilow *Svizera, India†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ovinol *Norma (Νορμα), Gr.*
Norfloxacin (p.309·2).
Urinary tract infections.

Ovinum *Biolab, Malaysia; Biolab, Singapore; Biolab, Thai.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; male infertility.

Oviol *Organon, Ger.*
7 Tablets, ethinylestradiol (p.2101·3); 15 tablets, ethinylestradiol; desogestrel (p.2093·2).
28-Day packs also contain 6 inert tablets.
Sequential-type oral contraceptive.

Ovipauz-L *Svizera, India†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ovipreg *Win-Medicare, India.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Ovis Neu *Pfizer Consumer, Ger.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Ovisen *Biomep, Mex.*
Fluoxetine (p.397·3).
Depression.

Oviskin *Dankos, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Ovitrelle
Serono, Belg.; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hung.; Serono, Irl.; Serono, Israel; Serono, Ital.; Serono, Neth.; Serono, Norw.; Serono, Pol.; Serono, Port.; Serono, Rus.; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Turk.; Serono, UK.
⊗ Choriogonadotropin alfa (p.2085·1).
Formerly known as Ovidrelle in some countries.
Female infertility.

Ovoctil *Rafarm, Gr.†.*
Acetylcysteine (p.1548·2).
Mucolytic.

Ovofar *Organon, India.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Ovogin *Valeant, Arg.*
Ketoconazole (p.539·1); clindamycin phosphate (p.251·2).
Vaginal bacterial and fungal infections.

Ovol *Church & Dwight, Canad.; Carter Horner, Hong Kong; Carter Horner, Thai.*
Simeticone (p.1770·2).
Bloating; flatulence; infant colic.

Ovoplex *Wyeth, Spain.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive; menstrual disorders.

Ovoresta *Organon, Braz.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ovoresta M *Organon, Ger.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Ovosiston *Jenapharm, Ger.†.*
Mestranol (p.2116·2); chlormadinone acetate (p.2084·3).
Combined oral contraceptive; menstrual disorders.

Ovostat *Organon, Neth.†.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Ovral
Note. This name is used for preparations of different composition.
Wyeth, Arg.†; Wyeth, Canad.; Wyeth, Gr.†; Wyeth, Mex.; Wyeth, NZ†; Akromed, S.Afr.; Wyeth-Ayerst, USA; Wyeth, Venez.
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Wyeth, India.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; dysfunctional uterine bleeding; endometriosis; menstrual disorders.

Ovran *Wyeth, Irl.†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ovran 30 *Wyeth, UK.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ovranet *Wyeth Lederle, Ital.†.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive.

Ovranette *Wyeth Lederle, Austria; Wyeth, Irl.; Wyeth, UK.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Combined oral contraceptive; endometriosis; menstrual disorders.

Ovrette *Wyeth-Ayerst, USA†.*
Norgestrel (p.2121·2).
Progestogen-only oral contraceptive.

OvuGen *BioGenex, USA†.*
Fertility test (p.2372·1).

Ovukalen *Knop, Chile.*
Homoeopathic preparation.

Ovukit *Monoclonal Antibodies, USA†.*
Fertility test (p.2372·1).

Ovulol *Microsules, Arg.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Ovumix *Elea, Arg.*
Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); centella (p.1592·3); polymyxin B sulfate (p.317·3).
Vulvovaginal infections.

Ovuplan *Key, Austral.*
Fertility test (p.2372·1).

Ovuquick *MediMar, UK; Monoclonal Antibodies, USA†.*
Fertility test (p.2372·1).

Ovurila *Nufarindo, Indon.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal and joint disorders.

Ovutest *Scidia, Arg.†.*
Fertility test (p.2372·1).

Ovysmen *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Ger.†; Janssen-Cilag, Switz.; Janssen-Cilag, UK.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Owencet *Galderma, Arg.†.*
Soap substitute.

Oxa
Note. This name is used for preparations of different composition.
Beta, Arg.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

CT, Ger.
Oxazepam (p.1014·2).
Anxiety disorders; sleep disorders.

Oxa B12 *Beta, Arg.*
⊗ Diclofenac potassium (p.44·3); betamethasone (p.1518·2) or betamethasone sodium phosphate (p.1518·3); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Oxa Forte *Beta, Arg.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Pain.

Oxa Sport *Beta, Arg.*
Diclofenac diethylamine (p.44·3); pridinol mesilate (p.1898·1); benzyl nicotinate (p.28·1); menthol (p.2340·1); lidocaine hydrochloride (p.1862·3); methyl salicylate (p.85·3).
Musculoskeletal, joint, and peri-articular disorders with muscle spasm.

Oxabenz *Actavis, Denm.*
Oxazepam (p.1014·2).
Anxiety.

Oxacant N *Klein, Ger.†.*
Crataegus (p.2289·1); St John's wort (p.422·3); convallaria (p.2287·3); adonis vernalis (p.2248·1); cereus (p.2279·2); scoparium (p.2384·2); melissa (p.2339·3); valerian (p.2410·1); motherwort (p.2347·3).
Cardiac disorders.

Oxacant-forte N *Klein, Ger.†.*
Crataegus (p.2289·1); convallaria (p.2287·3); adonis vernalis (p.2248·1); cereus (p.2279·2).
Cardiac disorders.

Oxacant-Khella N *Klein, Ger.†.*
Crataegus (p.2289·1); convallaria (p.2287·3); adonis vernalis (p.2248·1); cereus (p.2279·2); ammi visnaga (p.2256·1).
Cardiac disorders.

Oxacant-mono *Klein, Ger.*
Crataegus (p.2289·1).
Heart failure.

Oxacant-sedativ *Klein, Ger.*
Crataegus (p.2289·1); motherwort (p.2347·3); melissa (p.2339·3); valerian (p.2410·1).
Nervous cardiac disorders.

Oxacatin *Taro, Israel.*
Oxomemazine (p.587·1); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Coughs.

Oxacil
Note. This name is used for preparations of different composition.
Biochimica, Braz.†.
Oxacillin sodium (p.311·3).
Bacterial infections.

Pharmaniaga, Malaysia†; Raza, Malaysia†.
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Oxaclen *MedGen, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Oxacycle-P *Specifar (Σπεσιφαρ), Gr.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Skin infections.

Oxadisten *Beta, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Inflammation; muscle spasm; pain.

Oxadol *Kedrion, Ital.†; Kedrion, Rus.*
Nefopam hydrochloride (p.94·2).
Pain.

Oxafem *Beta, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Dysmenorrhoea; migraine.

Oxaflam *Fahrenheit, Indon.*
Tenoxicam (p.128·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Oxagesic *Beta, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Fever; pain.

Oxahexal *Hexal, Austria.*
Oxazepam (p.1014·2).
Anxiety disorders; sleep disorders.

Oxaine-M *Wyeth, Gr.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); oxetacaine (p.1867·2).
Antacid.

Oxal *Columbia, Mex.*
Albendazole (p.139·2); quinfamide (p.846·2).
Parasitic infections.

Oxalcor *Corsalud, Venez.*
Oxolamine phosphate (p.1567·1).
Cough.

Oxalgin *Cadila, India.*
Diclofenac sodium (p.44·3).
Allergic conjunctivitis; corneal trauma; eye inflammation; prevention of intra-operative miosis.

Oxalgin-D *Cadila, India.*
Diclofenac sodium (p.44·3).
Pain; renal colic.

Oxalgin-DP *Cadila, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Oxalgin-SR *Cadila, India.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Oxalin *Polfa Warszawa, Pol.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Oxalip *American Taiwan, Thai.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Oxaltie *Bioprofarma, Arg.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Oxalyt *Madaus, Austria.*
Potassium sodium hydrogen citrate (p.1674·2).
Renal calculi.

Oxam *Genexo, Pol.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Oxamet *Ivax, Cz.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Oxamin *Ratiopharm, Fin.*
Oxazepam (p.1014·2).
Anxiety disorders; depression; insomnia.

Oxamp *Sintez, Rus.†.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2); oxacillin sodium (p.311·3).
Bacterial infections.

Oxandrin *CSL, Austral.; Savient, USA.*
⊗ Oxandrolone (p.2123·2).
Bone pain associated with osteoporosis; delayed puberty in boys; growth retardation in boys; protein catabolism; Turner's syndrome in girls; weight loss.

Oxanest *Leiras, Fin.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxanon *Ariston, Braz.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Oxantil *BB, Cz.*
Etofylline (p.1121·1); theophylline (p.1140·1).
Cerebrovascular disorders; ischaemic heart disease; obstructive airways disease.

Oxapax *Sandoz, Denm.*
Oxazepam (p.1014·2).
Anxiety.

Oxapen *Biolab Sanus, Braz.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Oxapron *AG Therapy, Gr.*
Oxaprozin (p.105·3).
Inflammatory disorders.

Oxaprost *Beta, Arg.*
Diclofenac sodium (p.44·3).
Misoprostol (p.2013·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal, joint, and peri-articular disorders.

Oxaquin *Rubio, Spain.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Oxarol *Chugai, Jpn; Maruho, Jpn.*
Maxacalcitol (p.1987·2).
Hyperparathyroidism; psoriasis.

Oxascand *Teva, Swed.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety; sleep disorders.

Oxathos *Medix, Mex.*
Oxolamine citrate (p.1567·1).
Coughs.

Oxatokey *Inkeysa, Spain.*
Oxatomide (p.587·1).
Hypersensitivity reactions.

Oxbarukain *Chauvin ankerpharm, Ger.†.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

OxBipp *Masters, UK.*
Bismuth subnitrate (p.1711·2); iodoform (p.1650·2).

Oxca *Bouzen, Arg.*
Oxcarbazepine (p.490·3).
Epilepsy; neuralgia.

Oxcal *Solas, Indon.*
Calcium hydrogen phosphate (p.1676·1); alpha tocoferil acetate; selenium; betacarotene; vitamin D; zinc sulfate (p.1922·1).
Calcium supplement; osteoporosis.

Oxcarb *Uniao Quimica, Braz.; Cipla, India.*
Oxcarbazepine (p.490·3).
Epilepsy.

Oxcazen *Bouzen, Arg.†.*
Oxcarbazepine (p.490·3).
Epilepsy; neuralgia.

Oxcord *Biosintetica, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Oxelio *Jaldes, Fr.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement for protection against sun-induced skin damage.

Oxelio Topique *Jaldes, Fr.*
Topical vitamin preparation (p.1922·1).
Protection against sun-induced skin damage.

Oxema Improved *Jean-Marie, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1); oxetacaine (p.1867·2).
Gastrointestinal disorders.

Oxemet *GSK, Arg.*
Metformin (p.453·3).
Diabetes mellitus.

Oxeno *Bernabo, Arg.*
Loxoprofen sodium (p.78·1).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Oxeol *AstraZeneca, Fr.*
⊗ Bambuterol hydrochloride (p.1115·3).
Obstructive airways disease.

Oxepa *Abbott, Arg.†; Abbott, Hong Kong; Abbott, Israel; Abbott, Ital.; Abbott, Singapore; Abbott, Turk.; Abbott Nutrition, UK.*
Preparation for enteral nutrition (p.1922·1).
Nutritional support in ventilated patients.

Oxepam *Wyeth, Fin.†.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety disorders.

Oxepar *Azevedos, Port.†.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress syndrome; social phobia.

Oxeron *Itaca, Braz.†.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Oxet *AWD, Ger.†.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorders; post-traumatic stress disorder; social phobias.

Oxetine
Note. This name is used for preparations of different composition.
Hexal, Austral.; Gea, Denm.†.
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Minerva (Μινερβα), Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Pharmaland, Thai.
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Oxetol *Sun, Mex.*
Oxcarbazepine (p.490·3).
Epilepsy; neuropathic pain.

Oxez *AstraZeneca, Gr.*
⊗ Formoterol fumarate (p.1122·1).
Asthma; chronic respiratory failure.

Oxeze *AstraZeneca, Canad.*
⊗ Formoterol fumarate (p.1122·1).
Asthma.

Oxian *Barrenne, Braz.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; vertigo.

Oxibran *Prospa, Port.*
Piracetam (p.368·2).
Mental function impairment.

Oxibron *Montpellier, Arg.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Oxibron NF *Montpellier, Arg.*
⊗ Clenbuterol hydrochloride (p.1120·1); ambroxol hydrochloride (p.1550·3).
Obstructive airways disease.

Oxiburin *Andromaco, Chile†.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Oxibut *Bernabo, Arg.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Oxicalmans *Chobet, Arg.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxicam *Bioprogress, Ital.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Oxicanol *Ivax, Mex.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Oxi-Cell Plus *Lapreven, Venez.†.*
Vitamin A; vitamin E; vitamin C; selenium; zinc; manganese; copper (p.1922·1).
Antoxidant preparation.

Oxiclin *Leti, Venez.†.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Oxicodal *Drugtech, Chile.*
Oxcarbazepine (p.490·3).
Epilepsy.

Oxiderma *Galderma, Spain.*
Benzoyl peroxide (p.1590·2).
Acne.

Oxidermiol Enzima *Farmasur, Spain†.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); trypsin (p.2405·3).
Skin infections; wounds.

Oxidermiol Lassar *Farmasur, Spain†.*
Starch; salicylic acid (p.1612·2); soft paraffin; zinc oxide (p.1621·2).
Skin disorders.

Oxidermos *Neo Dermos, Arg.*
⊗ Lactic acid (p.2329·3); urea (p.1620·2); alpha tocopherol (p.1992·2); sunscreen.

Oxidine *Labocean, Fr.†.*
Antoxidant nutritional supplement (p.1922·1).

Oxifesa *Organifar, Venez.†.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Oxi-Freeda *Freeda, USA.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Oxifungol *Armstrong, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Oxigen *Biosintetica, Braz.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Oxigon *Linker, Gr.*
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Oxiken *Kendrick, Mex.*
Dobutamine hydrochloride (p.1271·2).
Heart failure; shock.

Oxiklorin *Orion, Fin.*
Hydroxychloroquine sulfate (p.604·2).
Light-sensitive skin disorders; lupus erythematosus; rheumatoid arthritis.

Oxilan *Guerbet, USA.*
Ioxilan (p.1487·1).
Radiographic contrast medium.

Oxilin *Pasteur, Chile; Allergan, Ital.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctivitis; eye congestion; nasal congestion; rhinitis.

Oxilium *Buchrucker, Austria; Oxo, Switz.†.*
Tetrachlorodecaoxide (p.2396·3).
Burns; skin disinfection; ulcers; wounds.

Oximar *Dupomar, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Oximar Respiratorio *Dupomar, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Oximen *Orravan, Spain.*
Hydrogen peroxide (p.1647·3); phosphoric acid (p.2367·1).
Haemostasis; skin and mucous membrane disinfection.

Oxin *Sons, Mex.*
Dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2).
Coughs.

Oxine *Corsalud, Venez.†.*
Piperazine hydrate (p.153·1).
Worm infections.

Oxinest *Latinofarma, Braz.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Oxinorm *Medifarm, Venez.*
Vitamin and mineral preparation (p.1922·1).

Oxinovag *Gobbi, Arg.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxinovag Complex *Gobbi, Arg.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Oxipelle *Valeant, Braz.*
Oxiconazole nitrate (p.544·2).
Fungal skin infections.

Oxipen *Behrens, Venez.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Oxiplat *Medac, Cz.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Oxipor *Medtech, Canad.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); benzocaine (p.1854·1).
Skin disorders.

Oxipor VHC
Note. This name is used for preparations of different composition.
SA Druggists Self Med, S.Afr.
⊗ Salicylic acid (p.1612·2); benzocaine (p.1854·1); alcohol (p.1625·2); coal tar (p.1616·2).
Psoriasis.

Whitehall, USA.
Coal tar (p.1616·2).
Formerly contained coal tar, salicylic acid, and benzocaine.
Psoriasis.

Oxipres *Sandoz, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Oxi-Q *Q-Pharma, Arg.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; neurogenic bladder; nocturnal enuresis.

Oxi-Reul *Ultra, Mex.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Oxis *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; Stern, Ger.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; Teva, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; Atenea, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.†; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Venez.†.*
⊗ Formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Oxisept *Demo, Gr.*
Povidone-iodine (p.1659·2).
Mouth infections.

Oxisol *Mediphar, Venez.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Oxisoma *Ecofarm, Ital.*
Soap substitute.

Oxistat *Investi, Arg.; GSK, Mex.; Glaxo Wellcome, USA.*
Oxiconazole nitrate (p.544·2).
Fungal skin infections.

Oxi-T *Collins, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Oxi-Tabs C+E *Ferrosan, Fin.†.*
d-Alpha tocoferil acetate; ascorbic acid; selenium (p.1922·1).
Vitamins C and E and selenium deficiency.

Oxital C *Serral, Mex.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Oxitan *Alternavida, Mex.; Dabur, Thai.*
Oxaliplatin (p.757·3).
Colorectal cancer; neuroblastoma; ovarian cancer.

Oxiterol *INQ, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Oxitina *LKM, Arg.*
Oxybutynin (p.2190·3).

Oxiton *Uniao Quimica, Braz.*
Oxytocin (p.2015·2).

Oxitone *Harson, Philipp.*
Oxytocin (p.2015·2).
Labour induction; missed or incomplete abortion; postpartum haemorrhage.

Oxitopisa *Pisa, Mex.*
Oxytocin (p.2015·2).
Hydatidiform mole; incomplete abortion; labour induction.

Oxitou *Attavet, Fr.*
N-bis-3 aminopropyl dodecylamine; didecyldimethylammonium chloride (p.1642·2); polyhexamide biguanidine hydrochloride.
Disinfection of surfaces, instruments, and rooms.

Oxitover *Llorente, Spain†.*
Mebendazole (p.148·3).
Worm infections.

Oxitraklin *Atlantis, Mex.*
Oxytetracycline (p.312·2).
Bacterial infections.

Oxitrat *ICN, Braz.†.*
Oxiconazole nitrate (p.544·2).
Fungal infections.

Oxivel *Zeller, Switz.†.*
Ginkgo biloba (p.2311·1).
Mental function disorders.

Oxivent *Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Irl.†; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, UK†.*
Oxitropium bromide (p.1129·2).
Obstructive airways disease.

Oxizinco *Elofar, Braz.*
Zinc oxide (p.1621·2); benzalkonium chloride (p.1629·1); cod-liver oil (p.1935·2).
Skin disorders.

Oxizole *Stiefel, Canad.†.*
Oxiconazole nitrate (p.544·2).
Tinea pedis.

Oxken *Kendrick, Mex.*
Ofloxacin (p.310·2).
Bacterial infections.

Oxobron *Diba, Mex.*
Oxolamine citrate (p.1567·1).
Coughs.

Oxocina *Baxter, Mex.†.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Oxodil *Polpharma, Pol.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Oxofenil *Biospray, Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Oxoferin
Note. This name is used for preparations of different composition.
Yamanouchi, Ger.†.
Reaction product of sodium chlorite, sodium hypochlorite, sulfuric acid, potassium chlorate, sodium carbonate-hydrogen peroxide, and sodium peroxide.
Wounds.

Oxochemie, Indon.; Pharos, Indon.; Oxo, Port.; Oxo, Thai.; Vargas, Venez.
Tetrachlorodecaoxide (p.2396·3).
Burns; cicatrisation; infected skin disorders; ulcers; wounds.

Oxogina *Flupal, Venez.*
Naloxone hydrochloride (p.1453·2).
Diagnosis of opioid overdosage; reversal of opioid effects.

Oxoinex *Inexfa, Spain†.*
Oxolinic acid (p.312·2).
Urinary-tract infections.

Oxolam *Quim-Far, Venez.†.*
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Cough.

Oxolavin Compuesto *Vincenti, Venez.*
Oxolamine citrate (p.1567·1); bromhexine hydrochloride (p.1552·2).
Cough.

Oxolvan *Bruluart, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Oxomar *Offenbach, Mex.*
Oxolamine (p.1567·1).
Coughs.

Oxomifer *Reuffer, Mex.*
Oxolamine (p.1567·1).
Coughs.

Oxopurin *Dexxon, Israel.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Oxotil *Vargas, Venez.*
Oxolamine phosphate (p.1567·1).
Cough.

Oxotus *Jofrain, Mex.*
Oxolamine (p.1567·1).
Coughs.

Oxotusin *Allen, Mex.*
Oxolamine (p.1567·1).
Coughs.

Oxo-Val *Saval, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Ox-Pam *Douglas, NZ.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Oxrate *Merind, India.*
Oxcarbazepine (p.490·3).
Epilepsy.

Oxsac *Masa, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Oxsoralen *Valeant, Austral.; Gerot, Austria; Valeant, Braz.; Valeant, Canad.; Raffo, Chile; Gerot, Cz.; Valeant, Hong Kong; Gerot, Hung.; Surya Dermato, Indon.; Italfarmaco, Ital.†; Taisho, Jpn; ICN, Malaysia; Valeant, Mex.; ICN, NZ; ICN, Neth.†; Gerot, Pol.; Gerot, Rus.; Pharmaco, S.Afr.; Valeant, Singapore; Galderma, Spain; ICN, USA.*
Methoxsalen (p.1605·1).
Eczema; lichen planus; mycosis fungoides; photosensitivity; pityriasis lichenoides; psoriasis; skin pigmentation disorders; urticaria; vitiligo.

Oxsoralen Ultra *Valeant, Arg.*
Methoxsalen (p.1605·1).
Psoriasis.

Oxtercid *Interbat, Indon.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Oxtimon *Rotexmedica, Philipp.*
Oxytocin (p.2015·2).
Labour induction; missed abortion.

Oxtin
Note. This name is used for preparations of different composition.
Guardian, Indon.
Oxatomide (p.587·1).
Allergic disorders.

Merck, Venez.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Oxxa *Toprak, Turk.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory disorders with increased mucus.

Oxy
Mentholatum, Austral.; Mentholatum, Canad.; Mentholatum, Cz.; GSK, Hong Kong; SmithKline Beecham, Israel; GSK, Mex.†; GSK Consumer, Neth.; GSK Consumer, UK; SmithKline Beecham Consumer, USA.
Benzoyl peroxide (p.1590·2).
Acne.

Oxy Biciron *S & K, Ger.*
⊗ Oxytetracycline hydrochloride (p.312·3); tramazoline hydrochloride (p.1574·3).
Bacterial eye infections.

Oxy Clean Facial Scrub *GSK Consumer, UK.*
Borax (p.2268·1); triclosan (p.1665·2).
Acne.

Oxy Clean Medicated *SmithKline Beecham, Israel.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Oxy Cleanser
Note. This name is used for preparations of different composition.
GSK Consumer, UK.
Regular: ⊗ Triclosan (p.1665·2); salicylic acid (p.1612·2); alcohol (p.1625·2).
Formerly called Oxy Clean Medicated Cleanser.
Acne.

GSK Consumer, UK.
Sensitive: ⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Oxy Daily Cleaning Pads *Mentholatum, Canad.*
Salicylic acid (p.1612·2).
Acne.

Oxy Daily Facial Cleanser Deep Pore *Mentholatum, Canad.*
Salicylic acid (p.1612·2).
Acne.

Oxy Daily Facial Cleanser Regular *GSK Consumer, Canad.†.*
Triclosan (p.1665·2).
Acne.

Oxy Daily Skin Wash *GSK Consumer, NZ†.*
Triclosan (p.1665·2).
Acne.

Oxy Daily Wash *GSK, Hong Kong.*
Triclosan (p.1665·2).
Skin disorders.

Oxy Dots *GSK Consumer, UK.*
Salicylic acid (p.1612·2); triclosan (p.1665·2).
Spots.

Oxy Duo Pads
Note. This name is used for preparations of different composition.
GSK Consumer, UK.
Regular: ⊗ Triclosan (p.1665·2); salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

GSK Consumer, UK.
Sensitive: ⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Oxy Facial Wash *GSK Consumer, UK.*
Triclosan (p.1665·2).
Skin disorders.

Oxy Finishing Toner *GSK Consumer, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Oxy IR *Purdue, Canad.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxy Medicated Pads *GSK Consumer, Canad.†.*
Salicylic acid (p.1612·2).
Formerly known as Oxy Power Pads.
Acne.

Oxy Medicated Soap *GSK Consumer, Canad.†; SmithKline Beecham, USA.*
Triclosan (p.1665·2).
Acne.

Oxy Night Watch *SmithKline Beecham Consumer, USA.*
Salicylic acid (p.1612·2).

Oxy Sensitive *SmithKline Beecham, Israel.*
Benzoyl peroxide (p.1590·2).
Acne.

Oxy Skin Wash *Mentholatum, Austral.*
Triclosan (p.1665·2).
Acne; skin cleanser.

Oxyace *Unique, Rus.*
Vitamin and mineral preparation (p.1922·1).

Oxyal *Santen, Ger.; Tubilux, Ital.; Europhta, Mon.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Oxyb *ABZ, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Oxybase *Hexal, Ger.†; Novexal, Gr.; Gea, Swed.†.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; incontinence; neurogenic bladder; urinary incontinence.

Oxyben *Santen, Philipp.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Oxybion *Biogal-Teva, Hung.†.*
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Oxyboldine *Cooperation Pharmaceutique, Fr.*
Boldine (p.2267·3); anhydrous sodium sulfate (p.1771·3); monobasic sodium phosphate (p.1682·3).
Dyspepsia.

Oxybugamma *Worwag, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Oxybutin *Holsten, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Oxybuton *Abbott, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Oxybutyn *ICN, Canad.†.*
Oxybutynin hydrochloride (p.2190·3).

Oxycardil *Schwarz, Pol.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Oxycel *Associated Hospital Supply, UK; Becton Dickinson, USA.*
Oxidised cellulose (p.1075·1).
Bleeding in surgical procedures.

Oxyclav *Zak, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Oxycline *General Drugs, Thai.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Oxycod *Rafa, Israel.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxycontin *Raffo, Arg.; Mundipharma, Austral.; Mundipharma, Austria; Mundipharma, Belg.; Zodiac, Braz.; Purdue, Canad.; Tecnofarma, Chile; Mundipharma, Cz.; Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Fr.; Extractum, Hung.; Mundipharma, Hung.; Napp, Irl.; Rafa, Israel; Mundipharma, Ital.; Shionogi, Jpn; Mundipharma, Malaysia; Asofarma, Mex.†; Pharmaco, NZ; Mundipharma, Neth.; Mundipharma, Norw.; Mundipharma, Philipp.; Mundipharma, Port.; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK; Purdue Frederick, USA; Nolver, Venez.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxycort
Tarchomin, Hung.
⊗ Hydrocortisone (p.1535·2); oxytetracycline hydrochloride (p.312·3).
Infected skin disorders.

Jelfa, Pol.
⊗ Hydrocortisone acetate (p.1535·2); oxytetracycline hydrochloride (p.312·3).
Infected ear, eye, and skin disorders.

Jelfa, Rus.; Tarchomin, Rus.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2); oxytetracycline hydrochloride (p.312·3).
Infected skin disorders.

Oxyderm
Note. A similar name is used for preparations of different composition (see below).
Valeant, Canad.
Benzoyl peroxide (p.1590·2).
Acne.

Oxyderme
Note. A similar name is used for preparations of different composition (see above).
Cifarma, Braz.
Nystatin (p.543·2); zinc oxide (p.1621·2).
Prickly heat.

Oxydermine *Wild, Switz.*
Zinc oxide (p.1621·2); lauromacrogol 400 (p.1916·1).
Burns; skin disorders; wounds.

Oxyfast *Purdue Frederick, USA.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxyflux *Rayere, Mex.*
⊗ Clenbuterol hydrochloride (p.1120·1).

OxyGal *CT, Cz.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Oxygeron *Drossapharm, Switz.*
Vincamine (p.2414·1).
Cerebrovascular disease; circulatory eye disorders.

Oxygesic *Mundipharma, Ger.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

OxyIR *Purdue Frederick, USA.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxylim
Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Thai.
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Atlantic, Singapore.
Oxytetracycline (p.312·2).
Bacterial infections.

Oxylin *Allergan, Hong Kong†; Allergan, Mex.; Allergan, Neth.; Allergan, Port.; Allergan, S.Afr.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Allergic conjunctivitis; eye irritation.

Oxymedin *Kade, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Oxymet *Greater Pharma, Thai.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; nasopharyngitis; rhinitis; sinusitis.

Oxymycin
SA Druggists, S.Afr.
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

DDSA Pharmaceuticals, UK.
Oxytetracycline (p.312·2).
Bacterial infections.

Oxynase *Hoe, Malaysia†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Oxy-Nase *Hoe, Singapore.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Oxynium *Unipharma, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Oxyno *Milano, Thai.*
Oxyphencyclimine hydrochloride (p.1759·2).
Gastrointestinal disorders; genito-urinary disorders.

Oxynorm *Mundipharma, Austral.; Mundipharma, Austria; Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Fr.; Napp, Irl.; Pharmaco, NZ; Mundipharma, Neth.; Mundipharma, Norw.; Mundipharma, Singapore; Mundipharma, Spain; Mundipharma, Swed.; Mundipharma, Switz.; Napp, UK.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Oxypan *Adcock Ingram, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Oxypangam *Lichtenstein, Ger.†.*
Di-isopropylammonium dichloroacetate (p.1265·1).
Hypoxia due to circulatory disorders.

Oxyperol *Lemoine, Fr.*
Peru balsam (p.2365·3); zinc oxide (p.1621·2).
Skin irritation.

Oxyphar *Mediphar, Venez.*
Zinc oxide (p.1621·2).
Barrier preparation.

Oxyphyllin *Noventis, Cz.*
Etofylline (p.1121·1).
Cerebrovascular disorders; ischaemic heart disease; obstructive airways disease.

Oxyplastine *CS, Fr.; Wild, Switz.*
Zinc oxide (p.1621·2).
Skin disorders; skin irritation.

Oxyrea *Cadila, India.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Oxysept
Allergan, Austral.†.
Part I, hydrogen peroxide (p.1647·3); part II, rinsing and storage solution (p.1622·2).
Disinfecting, rinsing, and storage solution for soft contact lenses.

Allergan, Braz.; Allergan, USA.
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting solution for contact lenses.

Oxysept Comfort *Visiontech, Arg.*
Tablets, catalase (p.2278·2); hypromellose (p.2144·2); solution, hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting and lubricating solution for contact lenses.

Oxyspas *Cipla, India; Cipla-Medpro, S.Afr.†.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; nocturnal enuresis; urinary incontinence.

Oxytel *Coup, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Oxyterracyna *Chema-Elektromet, Pol.†.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial skin infections.

Oxytetral *Alpharma, Denm.; Alpharma, Norw.; Alpharma, Swed.*
Oxytetracycline hydrochloride (p.312·3).
Acne; bacterial infections.

Oxytetramix *Ashbourne, UK†.*
Oxytetracycline (p.312·2).
Bacterial infections.

Oxythyol *Richard, Fr.*
Zinc oxide (p.1621·2); ichthammol (p.1599·1).
Skin irritation.

Oxytrol *Mayne, Austral.; Paladin, Canad.; Watson, USA.*
Oxybutynin (p.2190·3).
Bladder instability.

Oxyurin *Klonal, Arg.*
Oxybutynin (p.2190·3).
Neurogenic bladder.

Oxyzal *Gordon, USA.*
Hydroxyquinoline sulfate (p.2323·1); benzalkonium chloride (p.1629·1).
Minor skin infections.

Oyo *Polypharm, Ger.†.*
Sodium pangamate (p.2362·1).
Cerebral and peripheral vascular disorders; ischaemic heart disease; migraine.

Oysco *Rugby, USA.*
Calcium carbonate (p.1714·1).
Calcium deficiency; dietary supplement.

Oysco D *Rugby, USA.*
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Oyst-Cal *Goldline, USA.*
Calcium carbonate (p.1714·1).
Calcium deficiency; dietary supplement.

Oyst-Cal-D *Goldline, USA.*
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Oyster Calcium
Note. This name is used for preparations of different composition.
Cypress, USA.
Calcium (oyster shells) (p.1675·2).
Calcium supplement.

Nature's Bounty, USA.
Calcium with vitamins A and D (p.1922·1).
Calcium deficiency; dietary supplement.

Oyster Calcium with Vitamin D
Note. This name is used for preparations of different composition.
Cypress, USA.
Calcium (oyster shells) (p.1675·2); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Nion, USA.
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Oyster Shell Calcium with Vitamin D *Major, USA.*
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Oystercal-D *Nature's Bounty, USA.*
Calcium with vitamin D (p.1922·1).
Calcium deficiency; dietary supplement.

Oz *Aleph, Ital.*
Zinc oxide (p.1621·2).
Skin disorders.

Oz Crema *Apotex, Mex.*
Miconazole (p.541·2).
Fungal skin infections.

Ozapim *Labesfal, Port.*
Clozapine (p.981·1).
Psychoses associated with parkinsonism; schizophrenia.

Ozapin *Ipca, India.*
Olanzapine (p.1012·1).
Bipolar disorder; schizophrenia.

Ozcef *Ranbaxy, Austral.*
Cefaclor (p.217·2).
Bacterial infections.

Ozeltan *Help, Gr.†.*
Nizatidine (p.1751·2).
Peptic ulcer.

Ozen *Pharos, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Ozepam *Ipca, India.*
Clonazepam (p.478·2).
Epilepsy.

Ozeta *Corsalud, Venez.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Musculoskeletal and joint disorders.

Ozex *Toyama, Jpn.*
Tosufloxacin tosilate (p.355·2).
Bacterial infections.

Oziclide *Ranbaxy, Austral.*
Gliclazide (p.440·3).
Diabetes mellitus.

Ozid *Darya-Varia, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ozidia *Pfizer, Fr.*
Glipizide (p.441·3).
Diabetes mellitus.

Ozoken *Kener, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ozole *Ranbaxy, Austral.*
Fluconazole (p.532·1).
Fungal infections.

Ozonol
Note. This name is used for preparations of different composition.
Bayer Consumer, Canad.
Phenol (p.1656·1); zinc oxide (p.1621·2).
Bites and stings; burns; cuts; skin irritation.

GSK Consumer, Port.
Ibuprofen (p.64·2).
Fever; pain.

Ozonol Antibiotic Plus *Bayer Consumer, Canad.*
Polymyxin B sulfate (p.317·3); bacitracin (p.210·3); lidocaine hydrochloride (p.1862·3).
Minor cuts and burns; skin irritation.

Ozonosol
Note. This name is used for preparations of different composition.
Lagos, Arg.†.
SPF 40: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Lagos, Arg.
SPF 55+: Titanium dioxide (p.1617·3); neo heliopan 303; amiloxate (p.1589·1); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Formerly contained titanium dioxide.
Sunscreen.

Ozonyl *Gross, Braz.*
Menthol (p.2340·1); guaiacol (p.1561·2); terpin hydrate (p.1573·3); cineole (p.2282·3); niaouli oil (p.2351·3); camphor (p.2273·2); benzyl cinnamate (p.2264·2).
Respiratory-tract congestion.

Ozonyl Aquoso *Gross, Braz.*
Cineole (p.2282·3); niaouli oil (p.2351·3); guaifenesin (p.1561·3); sodium camsilate (p.2388·3); lidocaine hydrochloride (p.1862·3).
Respiratory-tract congestion.

Ozonyl Expectorante *Gross, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium camsilate (p.2388·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); menthol (p.2340·1).
Respiratory-tract congestion.

Ozopulmin
Note. This name is used for preparations of different composition.
Geymonat, Ital.
Injection; nasal spray: Verbenone (p.2413·3).
Respiratory-system disorders.

Geymonat, Ital.
Suppositories: Verbenone (p.2413·3); pine oil (p.2368·2).
Respiratory-system disorders.

Ozopulmin G
Note. This name is used for preparations of different composition.
Geymonat, Ital.
Suppositories: Verbenone (p.2413·3); pine oil (p.2368·2).
Catarrh; coughs.

Geymonat, Ital.
Syrup: Verbenone (p.2413·3); dextromethorphan hydrobromide (p.1555·2).
Catarrh; coughs.

Geymonat, Ital.
Topical gel: Verbenone (p.2413·3).
Catarrh; coughs.

Ozothin *GSK, Ger.†.*
Oxidation product of turpentine oil Landes (p.2406·3); terpin hydrate (p.1573·3).
Respiratory-tract disorders.

Ozothine
Note. This name is used for preparations of different composition.
Zambon, Fr.
Suppositories: Oxidation products of turpentine oil (p.2406·3).
Respiratory-tract disorders.

Zambon, Fr.
Syrup: Oxidation products of turpentine oil (p.2406·3); sodium benzoate (p.1630·2).
Respiratory-tract disorders.

Ozothine a la Diprophylline *Zambon, Fr.*
Oxidation products of turpentine oil (p.2406·3); diprophylline (p.1120·2).
Respiratory-tract disorders.

Ozovit *Pascoe, Ger.†.*
Magnesium peroxide (p.1651·3).
Constipation; dyspepsia; meteorism.

Ozvir *Ranbaxy, Austral.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ozym *Trommsdorff, Ger.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

3P *Beacons, Singapore†.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Coughs; upper respiratory-tract congestion.

P & S
Note. This name is used for preparations of different composition.
Baker Cummins, USA.
Liquid: Phenol (p.1656·1).
Scalp disorders.

Pendopharm, Canad.
Scalp application: Liquid phenol (p.1656·1).
Psoriasis; seborrhoeic dermatitis.

Pendopharm, Canad.
Shampoo: Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Psoriasis; seborrhoea.

Baker Cummins, USA.
Shampoo: Salicylic acid (p.1612·2).
Seborrhoea.

P & S Plus *Pendopharm, Canad.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Psoriasis; seborrhoeic dermatitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pabafilm *Galderma, Mex.*
Aminobenzoic acid (p.1589·1); oxybenzone (p.1608·3).
Formerly contained padimate O and oxybenzone.
Sunscreen.

Pabal *Ferring, Fr.; Ferring, Hung.; Ferring, Port.; Ferring, UK.*
Carbetocin (p.2005·3).
Uterine atony and haemorrhage following caesarean section.

Pabalat *Sanitas, Chile†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Pabanox *Surya Dermato, Indon.*
Oxybenzone (p.1608·3); padimate O (p.1609·1); titanium dioxide (p.1617·3).
Sunscreen.

Pabasol *Galderma, Mex.*
Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Pabasun *Zydus, Fr.*
Aminobenzoic acid (p.1589·1).
Sunscreen.

Pabialgin P *Polfa Pabianice, Pol.*
Propyphenazone (p.119·3); allobarbital (p.959·3).
Pain.

Pabiprofen *Polfa, Cz.*
Ibuprofen (p.64·2).
Inflammation; pain.

Pabrinex *Link, Irl.; Link, UK.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin deficiency; vitamin supplement.

Pabron Cold & Flu *Taisho, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Allergic rhinitis; cold and influenza symptoms; sinus congestion.

Pabron Cough *Taisho, Malaysia.*
Carbocisteine (p.1553·2).
Cough; respiratory-tract congestion.

Pabron Cough & Aches *Taisho, Malaysia.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cough; fever; nasal congestion; pain.

Pabron Cough & Sinus *Taisho, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders with cough.

Pabron Cough-D *Taisho, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough; nasal congestion.

P-A-C *Upjohn, USA.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Pac Merieux *Aventis Pasteur, Ger.†.*
An acellular pertussis vaccine (p.2230·1).
Active immunisation.

Pacaps *Lunsco, USA.*
Butalbital (p.967·2); caffeine (p.1116·3); paracetamol (p.108·1).

Paceco *Malaysia Chemist, Singapore†.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Cold symptoms; fever; pain.

Paceflex *Gemballa, Braz.†.*
Carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Skeletal muscle spasm.

Pacemol *Gemballa, Braz.†; Malaysia Chemist, Singapore†.*
Paracetamol (p.108·1).
Fever; pain.

Pacerone *Upsher-Smith, USA.*
Amiodarone hydrochloride (p.1210·2).
Ventricular arrhythmias.

Pacetal *Rekah, Israel.*
Phenobarbital (p.492·2); paracetamol (p.108·1).
Fever; pain.

Paceum *Orion, Switz.*
Diazepam (p.986·3).
Convulsions; non-psychotic mental disorders; premedication; skeletal muscle spasm; sleep disorders.

Pacifen *Pacific, NZ.*
Baclofen (p.1888·1).
Skeletal muscle spasm and spasticity.

Pacifene *Sussex, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Pacifenity *Vitaplex, Austral.†.*
Passion flower (p.2363·2); mistletoe (p.2345·3); avena (p.2262·1); valerian (p.2410·1); gentian (p.2310·3); lupulus (p.2335·2); skullcap (p.2388·2); motherwort (p.2347·3).
Herbal relaxant.

Pacimol *Ipca, India; Multichem, NZ; Nat Druggists, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Pacimol-M *Ipca, India.*
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Migraine.

Pacinax *Silesia, Chile.*
Diazepam (p.986·3).
Epilepsy.

Pacinol *Schering-Plough, Denm.†; Schering-Plough, Fin.†; Schering-Plough, Swed.†.*
Fluphenazine hydrochloride (p.998·1).
Confusion and anxiety in the elderly; hiccup; nausea and vomiting; psychoses.

Pacinone *Schering-Plough, Port.*
Halazepam (p.1000·1).
Anxiety.

Pacis *Filaxis, Arg.†; Shire Biologics, Canad.†; Urocor, USA†.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Pacisyn *Syntetic, Denm.*
Nitrazepam (p.1011·2).
Epilepsy; insomnia.

Pacitane *Wyeth, India.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Pacium *Biomed, Spain.*
Diazepam (p.986·3).
Contains pyridoxine hydrochloride.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Pacizox *Ipca, India.*
Paracetamol (p.108·1); diclofenac (p.44·2); chlorzoxazone (p.1894·3).
Skeletal muscle pain, inflammation, and spasm.

Paclikebir *Aspen, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Paclimedac *Medac, Cz.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Pacline *Stragen, Cz.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paclisan *Sanfer, Mex.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Paclit *Alvia (Αλβια), Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Paclitax *Eurofarma, Braz.; Cipla, India; Cipla, Venez.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Paclitaxin *Teva, Belg.; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Neth.*
Paclitaxel (p.759·1).
AIDS-related Kaposi's sarcoma; breast cancer; non small-cell lung cancer; ovarian cancer.

Pacliteva *Teva Tuteur, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Paclitol *Pharmanel, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Paclixel *Novagen, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Pacofen
Note. This name is used for preparations of different composition.
DHA, Singapore.
Codeine phosphate (p.37·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Ulagay, Turk.
S Tablets: Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Ulagay, Turk.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Pacopan *Pharmasant, Thai.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm with pain.

Pactens
Note. This name is used for preparations of different composition.
Galenica, Gr.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; myocardial infarction; phaeochromocytoma.

Merck, Mex.
Naproxen sodium (p.92·3).
Inflammation; pain.

Pacyl *Jagson, India.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Padamin *Fresenius Kabi, Austria; Fresenius Kabi, Hung.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Padax *Adcock Ingram, S.Afr.*
Piperazine citrate (p.152·3).
Worm infections.

Paderyl *Gerda, Fr.*
Codeine phosphate (p.37·2).
Coughs.

Padet *Pharmatrix, Arg.*
Metronidazole (p.837·1).
Rosacea.

Padiacrom *Padia, Ger.*
Sodium cromoglicate (p.1136·3).
Asthma.

Padiafusin *Fresenius Kabi, Austria; Baxter, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Padiafusin OP *Baxter, Ger.*
Potassium-free electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Padiamol *Padia, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Padiamuc *Padia, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Padiatifen *Padia, Ger.†.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma; bronchitis.

Padiken *Kener, Mex.†.*
Amantadine hydrochloride (p.792·3).
Viral infections.

Padma 28 *Tymofarm, Pol.; Padma, Switz.; Cedar Health, UK.*
Aconite; aegle sepiar; amomi fruit; aquilegia; calendula; camphor; cardamom; clove; costus root; hedychii rhizome; lettuce; Iceland moss; liquorice; meliae tausend; myrobalani; ribwort plantain; knotgrass; golden potentilla; sandalwood bark; sidae cordifoliae; valerian; calcium sulfate.
Circulatory disorders; peripheral vascular disorders.

Padma-Lax *Padma, Switz.*
Aloes (p.1705·2); kaolin (p.1738·1); calumba radix (p.2273·2); condurango (p.2287·1); enulae radix; gentian (p.2310·3); myrobalan; sodium bicarbonate (p.1673·2); anhydrous sodium sulfate (p.1771·3); piper longum; frangula bark (p.1732·2); cascara (p.1715·2); rhubarb (p.1768·3); nux vomica (p.2355·3); ginger (p.1732·3).
Constipation.

Padmed Circosan *Padma, Switz.*
Aegle sepiar fructus; amomi fructus; aquilegiae vulgaris herba; calcii sulfas; calendulae flos cum calycibus; cardamomi fructus; caryophylli flos; costi amari radix; dextrocamphora; hedychii rhizoma; lactucae sativae folium; lichen islandicus; liquirtiae radix; meliae tousend fructus; myrobalani fructus; plantaginis herba; polygoni avicularis herba; potentillae aureae herba; santali rubri lignum; sidae cordifoliae herba; aconiti tuber; valerianae radix.
Circulatory disorders.

Padmed Laxan *Padma, Switz.*
Aloes (p.1705·2); calumba radix (p.2273·2); condurango (p.2287·1); frangula bark (p.1732·2); gentian (p.2310·3); elecampane (p.1558·1); kaolin (p.1738·1); myrobalan; sodium bicarbonate (p.1673·2); sodium sulfate (p.1771·3); piper longum; cascara (p.1715·2); rhubarb (p.1768·3); nux vomica (p.2355·3); ginger (p.1732·3).
Constipation.

Padovan Ton *Rayere, Mex.*
Nitazoxanide (p.842·3).
Parasitic infections.

Padrin *Fujisawa, Jpn†.*
Prifinium bromide (p.1764·2).
Adjunct in gastrointestinal examination; pancreatitis; smooth muscle spasm.

Padutin *Wabosan, Austria.*
Kallidinogenase (p.2328·3).
Male infertility.

Paedamin *Paedpharm, Austral.*
Diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Paedialgon *Rosen, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Paediasure *Abbott, Cz.†; Abbott, Irl.; Abbott Nutrition, UK.*
Preparation for enteral nutrition (p.1922·1).

Paediathrocin *Abbott, Ger.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Paediatric Seravit *Scientific Hospital Supplies, Austral.; Nutricia, NZ; Scientific Hospital Supplies, NZ; Scientific Hospital Supplies, UK.*
Multivitamin, mineral, and trace element preparation (p.1922·1).
Dietary supplement; metabolic disorders.

Paedisup *Rosen, Ger.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2).
Fever; pain.

Paf *Lofarma, Ital.*
Bucarbetene.
Scabies.

Paferxin *Liferpal, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Paiazym *Homeosyn, Ital.*
Carica papaya.
Dietary supplement.

Paididont *Metochem, Austria.*
Chamomile (p.2279·3); cetylpyridinium chloride (p.1635·1); lauromacrogol 400 (p.1916·1).
Teething pain.

Paidocin *Promedica, Ital.*
Rokitamycin (p.330·2).
Bacterial infections.

Paidofebril *Aldo, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Paidoflor *Ardeypharm, Ger.*
Lactobacillus acidophilus (p.2372·3).
Gastrointestinal disorders.

Paidolax *Casen Fleet, Spain.*
Glycerol (p.2314·2).
Constipation.

Paidomal *Malesci, Ital.*
Lysine theophyllinate (p.1146·3).
Obstructive airways disease.

Paidorinovit *SIT, Ital.*
⊗ Ephedrine (p.1558·1); cineole (p.2282·3); niaouli oil (p.2351·3).
Nasal congestion.

Paidoterin Descongestivo *Aldo, Spain.*
Chlorphenamine maleate (p.571·3); diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1).
Upper-respiratory-tract congestion.

Paidovit *Andromaco, Chile.*
Vitamin A palmitate; ergocalciferol; ascorbic acid (p.1922·1).
Vitamin A, D, and C deficiency.

Paidozim *Juventus, Spain.*
Amylase (p.2256·3); cellulase (p.2279·1); lipase; metoclopramide (p.1747·3); protease.
Digestive enzyme insufficiency; dyspepsia.

Pain Aid *Zee, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3).

Pain Aid Free *Zee, Canad.*
Paracetamol (p.108·1).

Pain Buster *Prodemdis, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Pain Bust-R II *Continental, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Pain Doctor *Fougera, USA.*
Capsaicin (p.32·3); methyl salicylate (p.85·3); menthol (p.2340·1).
Pain.

Pain Expeller *Galena, Cz.†.*
Nonivamide (p.96·2); camphor (p.2273·2); ammonia 25% (p.2256·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pain & Fever Relief *Brauer, Austral.*
Homoeopathic preparation.

Pain Relieving Ointment *Jamieson, Canad.†.*
Camphor (p.2273·2); menthol (p.2340·1); mentha arvensis; cajuput oil; cinnamon oil; clove oil.

Painagon
Note. This name is used for preparations of different composition.
Be-Tabs, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Be-Tabs, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); meprobamate (p.1006·2); caffeine (p.1116·3).
Pain; pain associated with tension.

Painaid *Zee, USA.*
Aspirin (p.20·3); salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Painaid BRF Back Relief Formula *Zee, USA.*
Magnesium salicylate (p.79·2); paracetamol (p.108·1).
Pain.

Painaid ESF Extra-Strength Formula *Zee, USA.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Painaid PMF *Zee, Canad.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).

Painaid PMF Premenstrual Formula *Zee, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).
Pain.

Painamol *Be-Tabs, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Painamol Plus *Be-Tabs, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Formerly known as Betacod.
Fever; pain.

Painbreak *Riemser, Ger.*
⊗ Morphine sulfate (p.86·3).
Pain.

Paincod *Crown, S.Afr.†.*
Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Paindol *Polipharm, Thai.†.*
Tramadol hydrochloride (p.130·3).
Pain.

PainEaze *Blue Ocean, UK.*
Frankincense (p.2307·1); peppermint (p.1761·2); menthol (p.2340·1); dimethyl sulfone (p.2294·1); eucalyptus (p.2301·2).
Musculoskeletal, joint, and soft-tissue disorders.

Painex
Note.This name is used for preparations of different composition.
Confar, Port.
Diclofenac sodium (p.44·3) or diclofenac diethylamine (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Toprak, Turk.
Etofenamate (p.53·1).
Musculoskeletal and joint pain.

Lagap, UK.
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Painfort *Nolver, Venez.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Pain.

Pain-gesic *Mason, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Pain.

Painil *Be-Tabs, S.Afr.†.*
Ibuprofen (p.64·2).
Fever; pain.

Painkila *Mugi, Indon.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal and joint pain; neuralgia.

Painnox *Charoen, Thai.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Painrelipt-D *Biostam (Βιοσταμ), Gr.*
Piroxicam (p.117·3).
Inflammatory disorders.

Painrite *Columbia, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Painrite SA *Columbia, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Painsik *Best, Mex.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Painstop *Paedpharm, Austral.*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Pain.

Painstop Day-Time Pain Reliever *Paedpharm, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Painstop Night-Time Pain Reliever *Paedpharm, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Pain.

Painza *Siam Bheasach, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal pain.

Painza Cool *Siam Bheasach, Thai.*
Menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Pakinase *Finadiet, Arg.*
Metoclopramide (p.1747·3); amylase (p.2256·3); cellulase (p.2279·1); pancreatin (p.2360·1); dehydrocholic acid (p.2292·2).
Digestive disorders.

Paklitaxfil *Filaxis, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Pakurat *Oriental, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Palacos E *Schering-Plough, Chile†.*
Bone cement (p.2343·3).
Orthopaedic surgery.

Palacos E with Garamycin *Schering-Plough, Austral.*
Methylmethacrylate/methyl acrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos E con Gentamicina *Schering-Plough, Chile.*
Methylmethacrylate-methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos with Garamycin *Schering-Plough, NZ.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos LV avec Gentamicine *Schering-Plough, Belg.†; Schering-Plough, Fr.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos LV with Gentamicin *Schering-Plough, UK.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R *Schering-Plough, Chile; Biomet, Ger.; Merck, Singapore†; Merck, Thai.; Schering-Plough, UK.*
Methylmethacrylate-methylacrylate copolymer (p.2343·3).
Bone cement for orthopaedic surgery.

Palacos R avec Gentamicine *Schering-Plough, Belg.†; Schering-Plough, Fr.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R with Garamycin *Schering-Plough, Austral.; Schering-Plough, S.Afr.*
Methylmethacrylate/methyl acrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R cum Gentamicin *Schering-Plough, Fin.†.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R with Gentamicin *Schering-Plough, UK.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R con Gentamicina *Schering-Plough, Chile.*
Methylmethacrylate-methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palacos R with Gentamycin *Schering-Plough, Gr.†.*
Gentamicin sulfate (p.282·1); methylmethacrylate/methacrylate copolymer (p.2343·3).
Bacterial infections.

Palacril *Pfizer Consumer, Ger.†.*
Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2).
Skin disorders.

Paladac *Warner-Lambert, Mex.†; Pfizer, Turk.*
Vitamin preparation (p.1922·1).

Paladin *Pal Midwest, USA.*
Soft paraffin (p.2031·2); starch (p.1968·1); wool fat (p.2033·2); zinc oxide (p.1621·2); liquid paraffin (p.2030·3); boric acid (p.2268·1); beeswax (p.2028·1); vitamin A (p.1971·2); vitamin D (p.1986·1).
Nappy rash.

Palafer *GSK Consumer, Canad.*
Ferrous fumarate (p.1938·3).
Iron deficiency; iron supplement; iron-deficiency anaemias.

Palafer CF *GSK Consumer, Canad.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Prenatal supplement.

Palamed *Biomet, Ger.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3).
Bone cement for orthopaedic surgery.

Palamed G *Biomet, Ger.*
Methylmethacrylate/methylacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Palan *Lacefa, Arg.†.*
Vitamin A (p.1971·2); neomycin (p.305·1); chlorophyll (p.1471·1).
Wounds.

Palane *Cryopharma, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Palatol *Pascoe, Ger.†.*
Balsam; distillate: Peppermint oil (p.1761·2); niaouli oil (p.2351·3); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2).
Catarrh.

Palatrin *Degorts, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Palatrobil
Note.This name is used for preparations of different composition.
Monserrat, Arg.
Oral drops: Cynara (p.2291·2); wild carrot (p.2415·2); menthol (p.2340·1).
Digestive disorders.

Monserrat, Arg.
Tablets: Dehydrocholic acid (p.2292·2); cynara (p.2291·2).
Digestive disorders.

Palcaps *Breckenridge, USA.*
Pancreatic enzymes (porcine) (p.2360·1).
Pancreatic deficiency.

Palcid *Pharmadica, Thai.†.*
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastroparesis.

Palcol *Jofrain, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Paldar *Valeant, Arg.*
Mupirocin (p.302·3).
Bacterial skin infections.

Paldesic *Rosemont, UK.*
Paracetamol (p.108·1).
Fever; pain.

Paleodina *Liferpal, Mex.*
Dipyrone (p.49·2).
Pain.

Palface *Ace, Neth.*
⊗ Dextromoramide tartrate (p.39·3).
Pain.

Palfium *Antigen, Irl.; Ace, Neth.*
⊗ Dextromoramide tartrate (p.39·3).
Pain.

Palgic *Pamlab, USA.*
Carbinoxamine maleate (p.570·2).
Allergic rhinitis.

Palgic DS *Pan American, USA.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Palgic-D *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2).
Upper respiratory-tract disorders.

Paliatil *Medifarma, Mex.*
⊗ Aminophylline (p.1114·2); atropine (p.1219·2); ephedrine (p.1558·1); phenobarbital (p.492·2).

Palin *Lek, Pol.; Lek, Rus.*
Pipemidic acid (p.315·1).
Bacterial infections; bacterial infections of the urinary tract.

Palistop *Gap, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Paliuryl *Merck Medication Familiale, Fr.*
Rhamnus paliurus.
Stimulation of renal water excretion.

Palladon *Norpharma, Denm.; Mundipharma, Fin.; Mundipharma, Ger.; Mundipharma, Neth.; Mundipharma, Norw.; Mundipharma, Swed.; Mundipharma, Switz.*
⊗ Hydromorphone hydrochloride (p.63·2).
Formerly known as Opidol in *Switz.*
Pain.

Palladone *Mundipharma, Belg.; Mundipharma, Cz.; Extractum, Hung.; Mundipharma, Hung.; Napp, Irl.; Rafa, Israel; Napp, Port.; Napp, UK; Purdue Frederick, USA†.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Pallagicin
Biogal-Teva, Hung.†.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Baxter, Indon.
Doxorubicin (p.712·2).
Malignant neoplasms.

Pallidone *Douglas, NZ.*
⊗ Methadone hydrochloride (p.82·3).
Cough; opioid dependence; pain.

Pallohyman *Remedina, Gr.†.*
Nitrendipine (p.1358·2).
Hypertension.

Palmer's Cocoa Butter Formula *Propharm, Malaysia.*
A range of cocoa butter (p.2033·1) preparations.
Dry skin; skin care.

Palmer's Cocoa Butter Formula Scar Serum
Propharm, Malaysia.
Theobroma oil (p.2033·1); vitamin E; shark-liver oil (p.2386·1); silicone (p.2032·1); onion (p.2356·3).
Scars; stretch marks.

Palmer's Skin Success Acne Medication *Palmer, Malaysia.*
Salicylic acid (p.1612·2).
Acne; skin cleanser.

Palmetto Plus *Usana, Hong Kong†; Usana, Singapore.*
Saw palmetto (p.2192·3); lycopene (p.2335·2); soya isoflavones (p.2391·2).
Nutritional supplement.

Palmicaps *Gelcaps, Mex.†.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Palmiclor *Mayo, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Palmicol
Note.This name is used for preparations of different composition.
Cheplapharm, Ger.
Heavy magnesium carbonate (p.1743·1).
Gastrointestinal disorders; magnesium deficiency.

Otto, Indon.
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Palmifer *Reuffer, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Palmisan *Cheplapharm, Ger.*
Homoeopathic preparation.

Palmisol *Parggon, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Palmitan *Almirall, Chile†.*
Palmidrol (p.2360·1).
Respiratory-tract disorders.

Palmitate-A *Akorn, USA.*
Vitamin A (p.1971·2).

Palmoxan *Gelcaps, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Palohex *Sanofi Synthelabo, Neth.*
Inositol nicotinate (p.1316·1).
Peripheral vascular disorders.

Palomar E *Pal Midwest, USA.*
Vitamin E; boric acid; beeswax; wool fat; liquid paraffin; soft paraffin; starch; zinc oxide.
Skin disorders.

Palon *Unison, Hong Kong†; Unison, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; tremor.

Paloxi *Kalbe, Indon.*
Palonosetron (p.1760·1).
Nausea and vomiting induced by cancer chemotherapy.

Palpipax *Pfizer, Fr.†.*
Meprobamate (p.1006·2); valerian (p.2410·1).
Nervous disorders.

Palpitin-PP *PannonPharma, Hung.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Pals *Glenwood, USA.*
Chlorophyllin copper complex (p.1471·1).
Odour control in ostomy and incontinent patients.

Paltomiel
Note.This name is used for preparations of different composition.
Knop, Chile.
Adult syrup: Eucalyptus (p.2301·2); avocado (p.2262·2); aniseed (p.2258·2); honey (p.1948·2).
Respiratory-tract congestion.

Knop, Chile.
Infant syrup: Eucalyptus (p.2301·2); avocado (p.2262·2); honey (p.1948·2).
Respiratory-tract congestion.

Paltomiel Plus *Knop, Chile.*
⊗ Eucalyptus (p.2301·2); avocado (p.2262·2); honey (p.1948·2); lobelia (p.2157·2); echinacea (p.2298·1).
Respiratory-tract disorders.

Paludrine *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Denm.; AstraZeneca, Fin.†; AstraZeneca, Fr.; AstraZeneca, Ger.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia†; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Port.; AstraZeneca, S.Afr.†; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, UK.*
Proguanil hydrochloride (p.609·2).
Malaria.

Paluken *Kener, Mex.†.*
Chloroquine (p.599·2).
Malaria.

Palukin *Kinder, Braz.*
Quinine hydrochloride (p.612·3) or quinine sulfate (p.612·3).
Malaria.

Paluquina *Quimioterapica, Braz.†.*
Quinine sulfate (p.612·3).
Leg cramps; malaria.

Paluther *Sanofi-Aventis, Braz.*
Artemether (p.598·1).
Malaria.

Palux *Taisho, Jpn.*
Alprostadil (p.2183·2).
Mesenteric arterial portography; patent ductus arteriosus; peripheral vascular disorders; skin ulcers.

Paluxetil *Biochemie, Austria†.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorders; social anxiety disorder.

P-AM
Note. A similar name is used for preparations of different composition (see below).
SHS, Cz.†.
Food for special diets (p.1922·1).
Phenylketonuria.

Pam
Note. A similar name is used for preparations of different composition (see above).
Abbott, NZ†.
Pralidoxime iodide (p.1460·2).
Anticholinesterase antagonist; organophosphorus insecticide poisoning.

Pamacid *Alphapharm, Austral.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pamax *Sanitas, Chile.*
Paroxetine (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Pamba *Nycomed, Cz.; Altana, Ger.*
Aminomethylbenzoic acid (p.1054·1).
Haemorrhage.

Pamdosa *Dosa, Arg.*
Pamidronate disodium (p.1101·1).

Pamecil
Medochemie, Hong Kong.
Ampicillin sodium (p.204·1).
Bacterial infections.

Medochemie, Malaysia.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Medochemie, Singapore†.
Ampicillin (p.204·1).
Bacterial infections.

Pamedox *Medochemie, Hong Kong.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Pamelor *Novartis, Braz.; Novartis, USA.*
Nortriptyline hydrochloride (p.413·2).
Depression; narcoleptic syndrome; pain; panic disorder.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pamergan *Cristalia, Braz.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; insomnia; nausea and vomiting; pain; premedication; sedative.

Pamergan P100 *Martindale Pharmaceuticals, UK.*
⊗ Pethidine hydrochloride (p.113·2); promethazine hydrochloride (p.588·2).
. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Pain; premedication.

Pamerit *Pharmanel, Gr.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; Paget's disease of bone.

Pamid *CTI, Israel.*
⊗ Indapamide (p.1314·1).
Hypertension; oedema.

Pamidran *Mayne, Port.*
Pamidronate disodium (p.1101·1).
Bone metastases; hypercalcaemia of malignancy.

Pamidria *Cipla, India.*
Pamidronate disodium (p.1101·1).
Bone metastases.

Pamidrin *Teva, Belg.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; Paget's disease of bone.

Pamidro-cell *Cell Pharm, Ger.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Pamidrom *Cristalia, Braz.*
Pamidronate disodium (p.1101·1).

Pamidron *Hexal, Ger.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Pamifos *Medac, Denm.; Medac, Fin.; Medac, Ger.; Medac, Hung.; Dabur, India; Vipharm, Pol.; Medac, Spain; Medac, Swed.*
Pamidronate disodium (p.1101·1).
Fibrous dysplasia; hypercalcaemia of malignancy; metastatic bone disease; osteogenesis imperfecta; osteolysis of malignancy; Paget's disease of bone.

Pamine *Kenwood, USA.*
Hyoscine methobromide (p.1734·1).
Peptic ulcer (adjunct).

Pamine FQ Kit *Kenwood, USA.*
Tablets, hyoscine methobromide (p.1734·1); capsules, *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus paracasei*; *Bifidobacterium*; *Streptococcus thermophilus* (p.2372·3) (Flora-Q).

Pamipro *Medac, Neth.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; multiple myeloma; osteolysis of malignancy.

Pamiray *Landsteiner, Mex.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Pamired *Reddy, Malaysia.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolytic metastases in multiple myeloma; Paget's disease of bone.

Pamisol *Mayne, Austral.; Mayne, Hong Kong; Mayne, Malaysia; Mayne, Mex.; Mayne, NZ; Mayne, Singapore; Mayne, Thai.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolysis of malignancy; Paget's disease of bone.

Pamitor *Torrex, Austria; Torrex Chiesi, Cz.; Torrex, Hung.; Torrex, Pol.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; myeloma; osteolysis of malignancy; Paget's disease of bone.

Pamocil *Uno, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Pamol *Nycomed, Denm.; Leiras, Fin.; Interbat, Indon.; Johnson & Johnson, NZ; Nycomed, Norw.*
Paracetamol (p.108·1).
Fever; pain.

Pamorelin *Richter, Austria; Ipsen, Denm.; Ipsen, Ger.; Ipsen, Neth.*
⊗ Triptorelin embonate (p.2135·3).
Prostatic cancer.

Pamoval *Valmor, Venez.†.*
Pyrantel (p.155·2).
Worm infections.

Pamoxan *Coll, Spain.*
Pyrvinium embonate (p.155·3).
Worm infections.

Pamoxet *LKM, Arg.*
Paroxetine (p.414·2).
Depression.

Pampara *Siu Guan, Malaysia.*
Pralidoxime chloride (p.1460·2).
Anticholinesterase overdose; organophosphorus pesticide poisoning.

Pampe *Azevedos, Port.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pamprin *Chattem, Canad.; Chattem, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Pain; premenstrual syndrome.

Pamycon *Biotika, Cz.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial infections.

PAN-2400 *Bio-Tech, USA.*
Lipase; protease; amylase (p.2360·1).
Pancreatic insufficiency.

Pan Amin G *Otsuka, Indon.*
Amino-acid and sorbitol infusion (p.1922·1).
Parenteral nutrition.

Pan C *Freeda, USA.*
Hesperidin (p.2304·3); citrus bioflavonoids complex (p.2304·1); vitamin C (p.1983·3).
Capillary bleeding.

Pan Limpiador AL *Pierre Fabre Dermo-Cosmetique, Arg.*
Soap substitute.

Pan Rhinol *Mann, Ger.*
Dexpanthenol (p.2362·1).
Nasal disorders.

Panabiotin *Panalab, Arg.*
Biotin (p.1931·3).
Alopecia.

Panac *BMS, Mex.*
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Panac K *BMS, Mex.*
Ampicillin potassium (p.205·1); dicloxacillin sodium (p.265·2).
Bacterial infections.

Panacef *Valeas, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Panaco *Beacons, Singapore.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Panacod *Sanofi-Aventis, Fin.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Panacta *Panpharma, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Panadeine *GSK Consumer, Austral.; Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Hong Kong; GSK Consumer, Irl.; Sanofi-Aventis, Malaysia; GSK, NZ; Sanofi-Aventis, Singapore.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Panadeine Plus *GSK Consumer, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Fever; pain.

Panado *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Panado Medsip *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Panado-Co *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Panadol *GSK Consumer, Austral.; GSK Consumer, Belg.; GSK Consumer, Canad.; GSK, Chile; GSK, Cz.; GSK, Fin.; GSK Sante, Fr.; GSK, Gr.; GSK, Hong Kong; GSK Consumer, Hung.; Sterling, Indon.; GSK Consumer, Irl.; GSK, Israel; GSK Consumer, Ital.; GSK Consumer, Malaysia; GSK, NZ; GSK Consumer, Neth.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Rus.; GSK, Singapore; GSK Consumer, Spain; GSK Consumer, Switz.; GSK, Thai.; GSK, Turk.; GSK Consumer, UK; GSK Consumer, USA.*
Paracetamol (p.108·1).
Fever; musculoskeletal disorders; pain.

Panadol Allergy Sinus *GSK Consumer, Austral.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic symptoms; pain; sinus congestion.

Panadol C *GSK Consumer, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Panadol Codeine *GSK Consumer, Belg.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Panadol Cold *GSK Consumer, Malaysia.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Panadol C.
Cold symptoms; rhinitis; sinus congestion.

Panadol Cold & Cough *GSK, Hong Kong.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; cough.

Panadol Cold and Flu
Note. This name is used for preparations of different composition.
GSK Consumer, Austral.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

GSK, Hong Kong.
Paracetamol (p.108·1); vitamin C (p.1983·3); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); terpin hydrate (p.1573·3).
Formerly contained paracetamol, vitamin C, phenylephrine hydrochloride, noscapine, caffeine, and terpin hydrate.
Cold and influenza symptoms.

Panadol Cold & Flu *GSK Consumer, Irl.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Panadol Cold Flu *GSK Consumer, Malaysia.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly known as Panadol CF.
Allergic rhinitis; cold and influenza symptoms; sinus congestion.

Panadol for Cold & Flu *GSK, Singapore.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Panadol Cold & Flu Day *GSK, Hong Kong.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); terpin hydrate (p.1573·3).
Cold symptoms; coughs.

Panadol Cold & Flu Extra *GSK, Hong Kong.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); noscapine (p.1566·2); caffeine (p.1116·3); ascorbic acid (p.1983·3); terpin hydrate (p.1573·3).
Cold symptoms; cough.

Panadol Cold & Flu Hot Remedy *GSK, Hong Kong; GSK, Singapore.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Panadol Cold & Flu Night *GSK, Hong Kong.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Panadol Cold & Flu Plus *GSK, Hong Kong.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Panadol Cold & Flu Relief PE *GSK Consumer, Austral.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; cough.

Panadol for Cold Relief *GSK, Singapore.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Panadol For Cold Relief Extra *GSK, Singapore.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Panadol Comp *GSK, Fin.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Panadol Compuesto *GSK, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Panadol Flu Strength Day & Night PE *GSK Consumer, Austral.*
Day caplets, paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); night caplets, paracetamol; phenylephrine hydrochloride; dextromethorphan hydrobromide; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; cough.

Panadol For Cough and Cold *GSK, Singapore.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine (p.1571·2).
Cold and influenza symptoms; cough.

Panadol Extra *GSK, Cz.; GSK, Gr.; GSK, Hong Kong; GSK Consumer, Hung.; GSK Consumer, Irl.; GSK Consumer, Pol.; GSK Consumer, Port.; GSK Consumer, Rus.; GSK, Singapore; GSK Consumer, Switz.; GSK, Turk.; GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; headache; pain.

Panadol Hot *GSK, Fin.*
Paracetamol (p.108·1); menthol (p.2340·1).
Cold and influenza symptoms; fever; pain.

Panadol Menstrual
Note. This name is used for preparations of different composition.
GSK, Hong Kong.
Paracetamol (p.108·1); caffeine (p.1116·3).
Dysmenorrhoea.

GSK Consumer, Malaysia; GSK, Singapore.
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).
Menstrual disorders.

Panadol Night *GSK Consumer, Irl.; GSK, NZ; GSK Consumer, UK.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold symptoms; fever; insomnia; pain.

Panadol Plus *GSK Consumer, Belg.; GSK, Chile; GSK Consumer, Neth.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Panadol Plus Grip *GSK Consumer, Cz.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Panadol Sinus *GSK Consumer, Austral.; GSK, Hong Kong.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Sinus congestion and pain.

Panadol Sinus Day & Night *GSK Consumer, Austral.*
Day caplets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night caplets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold symptoms; fever

Panadol Sinus Relief PE *GSK Consumer, Austral.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Headache; nasal congestion; sinus pain..

Panadol Ultra
Note. This name is used for preparations of different composition.
GSK Consumer, Cz.; GSK Consumer, Hung.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

GSK, Hong Kong; GSK Consumer, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Panadol+C *GSK, Gr.*
Paracetamol (p.108·1); vitamin C (p.1983·3).
Fever; pain.

Panafcort *Aspen, Austral.; Adcock Ingram, S.Afr.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Panafcortelone *Aspen, Austral.; Aspen, Hong Kong.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Panafen *GSK Consumer, Cz.; GSK, NZ.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Panafen Plus *GSK, Austral.*
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Fever; inflammation; pain.

Panafil *Healthpoint, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2); chlorophyllin copper complex (p.1471·1) or chlorophyllin copper complex sodium (p.1471·1).
Burns; ulcers; wounds.

Panafil-White *Rystan, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).
Burns; ulcers; wounds.

Panaflu Plus *Malaysia Chemist, Singapore†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Panafox *Panpharma, Philipp.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Panagesic *Chemopharma, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Panagesic Con Cafeina *Chemopharma, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Panalba *Help, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Panaldine *Sanofi-Aventis, Jpn.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Panalene *Panalab, Arg.*
Adapalene (p.1587·1).
Acne.

Panaleve *Pinewood, UK.*
Paracetamol (p.108·1).
Fever; pain.

Panalgan *Staufen, Ger.*
Homoeopathic preparation.

Panalgesic *Sanofi Synthelabo, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2).
Pain with tension.

Panalgesic Gold
Note. This name is used for preparations of different composition.
ECR, USA.
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

ECR, USA.
Liniment: Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Panalgine *Atabay, Turk.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Panalgorin *PannonPharma, Hung.*
Dipyrone (p.49·2).
Fever; pain.

Panaline
Note. This name is used for preparations of different composition.
Darier, Mex.†.
Cream: Vitamin E (p.1992·2); zinc oxide (p.1621·2).
Nappy rash.

Darier, Mex.†.
Topical powder: Maize starch (p.1968·1).
Nappy rash.

Panam *Durascan, Denm.; Sandoz, Denm.*
Paracetamol (p.108·1).
Fever; pain.

Panamax *Sanofi Synthelabo, Austral.*
Paracetamol (p.108·1).
Fever; pain.

Panamax Co *Sanofi Synthelabo, Austral.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Panamic TO-Chemicals, Thai.
Mefenamic acid (p.80·1).
Pain.

Pan-Amin Thai Otsuka, Thai.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Panamol Beacons, Singapore.
Paracetamol (p.108·1).
Fever; pain.

Panamor Pharmacare, S.Afr.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Panangin Gedeon Richter, Hung.; Gedeon Richter, Rus.
Magnesium aspartate (p.1679·1); potassium aspartate (p.1684·2).
Angina pectoris; arrhythmias; heart failure; myocardial infarction; neurocirculatory dystonia.

Panaprost Panalab, Arg.
Terazosin (p.1410·3).
Benign prostatic hyperplasia.

Panasol-S Seatrace, USA.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Panasorbe Sanofi-Aventis, Port.
Paracetamol (p.108·1).
Fever; pain.

Panastat Panalab, Arg.
Itraconazole (p.536·3).
Fungal infections.

Pan-Astenico R Vitoria, Port.
Arginine aspartate (p.1928·2).

Panataxel Bioprofarma, Arg.
Paclitaxel (p.759·1).
Malignant neoplasms.

Panatrix Boniscontro & Gazzone, Ital.
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Panatuss DX Seyer, USA.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); dexchlorpheniramine maleate (p.572·1).
Upper respiratory-tract disorders.

Panax Complex Blackmores, Austral.†.
Avena (p.2262·1); fenugreek (p.2303·3); alfalfa (p.2249·2); ginseng (p.2312·1); multivitamins (p.1922·1).
Tonic.

Panaxan Phytofarm Kleka, Pol.
Ginseng (p.2312·1).
Tonic.

Panaxid Norgine, Belg.†.
Nizatidine (p.1751·2).
Gastrointestinal disorders associated with hyperacidity.

Panaxim Panpharma, Philipp.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Panbesy Eurodrug, Hong Kong; Eurodrug, Singapore; Eurodrug, Thai.
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Pancebrin Aspen, S.Afr.†; Lilly, Thai.†.
Multivitamin preparation (p.1922·1).

Panchol Lannacher, Austria.
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pancillin Sandoz, Denm.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Panclasa
Note. This name is used for preparations of different composition.
Atlantis, Mex.
Injection: Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3).
Smooth muscle spasm.

Atlantis, Mex.
Oral solution: Phloroglucinol (p.2366·3).
Infantile colic and dyspepsia.

Pancloflex Denver, Arg.
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).

Panclogesic Denver, Arg.
Paracetamol (p.108·1); diclofenac potassium (p.44·3).
Inflammation; pain.

Panclor Elpen (Ελπεν), Gr.; Polfa Grodzisk, Pol.
Cefaclor (p.217·2).
Bacterial infections.

Pancof Pan American, USA.
Dihydrocodeine tartrate (p.48·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Pancof PD Pan American, USA.
Dihydrocodeine tartrate (p.48·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Pancof XP Pan American, USA.
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Pancof-EXP Pan American, USA.
Dihydrocodeine tartrate (p.48·1); guaifenesin (p.1561·3); pseudoephedrine (p.1571·2).
Coughs.

Pancof-HC Pan American, USA.
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Pancof-XL Pan American, USA.
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Panconium Khandelwal, India.
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Pancoran Novartis, Gr.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Pancrearell Sanorell, Ger.
Homoeopathic preparation.

Pancrease
Note. This name is used for preparations of different composition.
Janssen-Cilag, Austral.; Janssen-Cilag, Belg.†; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Ortho, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, UK†; Ortho McNeil, USA; Janssen-Cilag, Venez.†.
Pancrelipase (p.2360·1).
Cystic fibrosis; malabsorption syndromes; pancreatic insufficiency.

IFET (ΙΦΕΤ), Gr.; Janssen-Cilag, Irl.†.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Pancrease HL Janssen-Cilag, Neth.; Janssen-Cilag, UK.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Pancrecarb Digestive Care, USA.
Lipase; protease; amylase (p.2360·1).
Pancreatic insufficiency.

Pancrecura Abbott, Arg.†.
Pancreatin (p.2360·1).
Pancreatin insufficiency.

Pancrelase DB, Fr.
Fungal cellulase (p.2279·1).
Formerly contained pancreatin (porcine) and fungal cellulase.
Dyspepsia.

Pancreoflat Solvay, Ital.†.
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive-system disorders.

Pancreolan Zentiva, Cz.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Pancreolauryl Inibsa, Spain.
Fluorescein dilaurate (p.2306·1); fluorescein sodium (p.2306·1).
Evaluation of pancreatic function.

Pancreolauryl-Test Sanova, Austria.
Combination pack: 1 Blue capsule, fluorescein dilaurate (p.2306·1); 1 red capsule, fluorescein sodium (p.2306·1).
Evaluation of pancreatic function.

Pancreolauryl-Test N Temmler, Ger.†.
Blue capsules, fluorescein dilaurate (p.2306·1); red capsules, fluorescein sodium (p.2306·1).
Evaluation of pancreatic function.

Pancresil Edmond Pharma, Ital.†.
Dimeticone (p.1770·2); pancreatin (p.2360·1).
Digestive-system disorders.

Pancrex Paines & Byrne, Irl.†; Mipharm, Ital.; Paines & Byrne, NZ; Paines & Byrne, UK.
Pancreatin (p.2360·1).
Cystic fibrosis; malabsorption syndromes; pancreatic insufficiency.

Pancrin Solvay, Austria.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Pancrit Andromaco, Chile.
Cetylpyridinium chloride (p.1635·1); allantoin (p.1588·1).
Mouth and throat disorders.

Pancuron Scott-Cassara, Arg.; Cristalia, Braz.
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Pancurox Hospira, Port.
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Pancutan Purissimus, Arg.
Halibut oil (p.1948·1); gentamicin embonate (p.284·2).
Burns; skin infections; ulcers; wounds.

Pancutan Base Purissimus, Arg.
Halibut oil (p.1948·1).
Skin disorders.

Pandel Silesia, Chile; Galderma, Ger.; Taisho, Jpn; Medinfar, Port.; CollaGenex, USA.
⊗ Hydrocortisone buteprate (p.1535·2).
Skin disorders.

Panderm
Note. This name is used for preparations of different composition.
SJA, Gr.
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Julphar, UAE.
⊗ Nystatin (p.543·2); neomycin sulfate (p.305·1); gramicidin (p.286·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Pandermil Edol, Port.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Pandigal Biospray, Gr.
Butamirate citrate (p.1553·1).
Cough.

Pandrat LKM, Arg.
Pamidronate disodium (p.1101·1).
Osteoporosis.

Panectyl Erfa, Canad.
Alimemazine tartrate (p.566·2).
Coughs; dyspnoea; pruritus.

Pan-Emecort Merck, Braz.†.
⊗ Fluprednidene acetate (p.1533·1); gentamicin sulfate (p.282·1); hydroxyquinoline (p.2323·2).
Skin disorders.

Pan-Enteral Otsuka, Indon.; Thai Otsuka, Thai.
Preparation for enteral nutrition (p.1922·1).

Panfil G Pan American, USA.
Diprophylline (p.1120·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Panfugan Nycomed, Braz.
Mebendazole (p.148·3).
Worm infections.

Pan-Fungex Sanofi-Aventis, Port.
Clotrimazole (p.530·1).
Fungal skin infections.

Panfungol Esteve, Spain.
Ketoconazole (p.539·1).
Fungal infections.

Panfurex Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong.
Nifuroxazide (p.307·2).
Diarrhoea; infectious diarrhoea.

Pangamil Biotech, Venez.
Tinidazole (p.848·3).
Protozoal infections.

Pangastren Laboratorios Chile, Chile.
Metoclopramide (p.1747·3); simeticone (p.1770·2).
Dyspepsia; flatulence; gastro-oesophageal reflux.

Pangavit B Church, Mex.
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgias; neuritis; neuropathies; vitamin B deficiency.

Pangavit Hypak Church, Mex.
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgias; neuritis; neuropathy; vitamin B deficiency.

Pangavit Pediatrico Church, Mex.
Cyproheptadine hydrochloride (p.575·1); cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); riboflavin sodium phosphate (p.1977·3).
Appetite loss; megaloblastic anaemia; vitamin deficiency.

Pangel Pannoc, Belg.
Benzoyl peroxide (p.1590·2).
Acne.

Pangen Urgo, Fr.; Urgo, Ger.†.
Collagen (p.2286·1).
Haemorrhage.

Pangest
Note. This name is used for preparations of different composition.
Beta, Arg.
Pantoprazole sodium (p.1760·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Farmasa, Braz.
Bromopride (p.1713·3).
Gastro-oesophageal reflux; gastroparesis.

Pangestyme Ethex, USA.
Lipase; protease; amylase (p.2360·1).
Pancreatic insufficiency.

Panglobulin American Red Cross, USA†.
A normal immunoglobulin (p.2225·3).

Pangon LBS, Thai.
⊗ Pentazocine lactate (p.112·3).
Pain.

PanGraf Panacea, India.
Tacrolimus (p.1843·1).
Transplant rejection.

Pangramin ALK, Cz.; ALK, Hung.
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Pangrol Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Hung.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Panhematin Abbott, Austral.†; Ovation, USA.
Haematin (p.1448·2).
Acute intermittent porphyria associated with the menstrual cycle.

Panimun Bioral Panacea, India.
Ciclosporin (p.1822·2).
Graft-versus-host disease; transplant rejection.

Panimycin Meiji, Jpn.
Dibekacin sulfate (p.265·2).
Bacterial infections.

Paniodal Adivar, Ital.†.
Povidone-iodine (p.1659·2).
Skin and wound disinfection.

Paniodine Angelini, Ital.†.
Povidone-iodine (p.1659·2).
Skin and wound disinfection.

Panitol
Note. This name is used for preparations of different composition.
Cryopharma, Mex.
Propanidid (p.1791·1).
General anaesthesia.

Pharmaland, Thai.
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Panitone Wesley, USA.
Paracetamol (p.108·1).
Fever; pain.

Paniverin Chinoin, Hung.
Nicotinic acid (p.1957·3); drotaverine hydrochloride (p.2298·1).
Atherosclerosis; cerebrovascular disorders; migraine.

Panklav Hemofarm, Rus.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Pankreaplex mono Schaper & Brummer, Ger.
Javanese turmeric (p.2406·3).
Dyspepsia.

Pankreaplex Neu Schaper & Brummer, Ger.†.
Milk thistle (p.1452·1); syzygium jambolana; condurango (p.2287·1); sarsaparilla (p.2383·3).
Gastrointestinal disorders.

Pankreas M Comp Hanosan, Ger.†.
Homoeopathic preparation.

Pankreas S Comp Hanosan, Ger.†.
Homoeopathic preparation.

Pankrease Janssen-Cilag, S.Afr.
Pancrelipase (p.2360·1).
Pancreatic disorders.

Pankreatan Novartis Consumer, Ger.
Pancreatin (p.2360·1).
Digestive system disorders.

Pankreaticum Hevert, Ger.
Homoeopathic preparation.

Pankreoflat Raffo, Arg.; Solvay, Austria; Solvay, Braz.; Solvay, Ger.; Solvay, Hong Kong†; Solvay, Hung.; Solvay, India; Solvay, Indon.; Solvay, Israel; Altana, Mex.; Solvay, Philipp.; Vitoria, Port.; Solvay, Rus.; Schering, S.Afr.; Faes, Spain; Frik, Turk.
Pancreatin (p.2360·1); simeticone (p.1770·2).
Aerophagia; digestive system disorders; excess gastrointestinal gas; flatulence; meteorism; pancreatic insufficiency; preparation for gastrointestinal examination.

Pankreoflat Sedante Raffo, Arg.†.
Oxazepam (p.1014·2); pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders.

Pankreon Solvay, Denm.†; Solvay, Fin.†; Solvay, Ger.; Solvay, Norw.†; Solvay, Swed.†; Zuoz, Venez.
Pancreatin (p.2360·1).
Cystic fibrosis; digestive system disorders; malabsorption; pancreatic insufficiency.

Pankreon for Children Solvay, Indon.
Pancreatin (p.2360·1); vitamin A; vitamin B ; folic acid (p.1922·1).
Gastrointestinal disorders.

Pankreon Comp Solvay, Indon.
Pancreatin (p.2360·1); ox bile extract (p.2266·3).
Digestive disorders; pancreatic disorders.

Pankreon Compositum Infinity, Venez.
Pancreatic enzymes (p.2360·1); bile extract (p.2266·2).
Digestive disorders.

Pankreon Compuesto Raffo, Arg.†.
Pancreatin (p.2360·1); dehydrocholic acid (p.2292·2); deoxycholic acid (p.2266·3) vitamin B substances (p.1922·1).
Digestive disorders; liver disorders.

Pankreon forte Solvay, Austria.
Pancreatin (p.2360·1).
Digestive system disorders; pancreatic insufficiency.

Pankreon Total Raffo, Arg.
Pancreatin (p.2360·1); papain (p.2362·3); cellulase (p.2279·1); dehydrocholic acid (p.2292·2); simeticone (p.1770·2); metoclopramide hydrochloride (p.1747·3).
Digestive disorders.

Pankreosil Zuoz, Venez.
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Digestive disorders; flatulence.

Pankreozym Raffo, Arg.
Pancreatin (p.2360·1).
Digestive disorders.

Pankrevowen Weber & Weber, Ger.†.
Homoeopathic preparation.

Pankrodigest Desra, Turk.
Pancreatin (p.2360·1); cholic acid (p.2266·3).

Panlem Lemery, Mex.
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Panlid Funke, Cz.
Lidocaine hydrochloride (p.1862·3); allantoin (p.1588·1); dexpanthenol (p.2362·1); cetylpyridinium chloride (p.1635·1).
Burns; wounds.

Panlipol *Mead Johnson, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Panlor *Pan American, USA.*
Paracetamol (p.108·1); caffeine (p.1116·3); dihydrocodeine tartrate (p.48·1).
Pain.

Panmicol *Purissimus, Arg.*
Clotrimazole (p.530·1).
Fungal skin, scalp, and mucous membrane infections.

Panmist LA *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Panmist JR *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

PanMist-DM *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Panmist-S *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Panmyk *Bros, Gr.*
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Skin disorders with fungal infection.

Pannaz *Pan American, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Formerly contained phenylpropanolamine, chlorphenamine, and hyoscine.
Upper respiratory-tract disorders.

Pannocort *Pannoc, Belg.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Pannogel *CS, Fr.*
Benzoyl peroxide (p.1590·2).
Acne.

Pannox *Panpharma, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Panocaps *Breckenridge, USA.*
Pancreatic enzymes (porcine) (p.2360·1).
Pancreatic deficiency.

Panocod *Sanofi Synthelabo, Swed.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Panodil *GSK Consumer, Denm.; GSK, Norw.; GSK Consumer, Swed.*
Paracetamol (p.108·1).
Fever; pain.

Panofen *Liferpal, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Panogastin *Jelfa, Cz.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Panolase *Unichem, India†.*
Pancreatin (p.2360·1); hemicellulase (p.2279·1); ox bile (p.2266·3).
Digestive disorders.

Pan-Ophtal *Winzer, Ger.*
Dexpanthenol (p.2362·1).
Eye disorders.

Panoptic *Bausch & Lomb, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2).
Eye disorders.

Panoptic Lagrimas *Bausch & Lomb, Arg.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Panoral *Lilly, Ger.*
Cefaclor (p.217·2).
Bacterial infections.

Panos *Sankyo, Fr.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Panotil *Zambon, Braz.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Panotile *Zambon, Belg.; Zambon, Fr.; Zambon, Neth.; Zambon, Spain; Zambon, Switz.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Formerly contained polymyxin B sulfate, neomycin sulfate, fludrocortisone acetate, furaltadone hydrochloride, and lidocaine hydrochloride in *Spain*.
Infected ear disorders; otitis externa.

Panotile cipro *Zambon, Ger.*
Ciprofloxacin hydrochloride (p.243·3).
Otitis externa; otitis media.

Panotile N *Zambon, Ger.†.*
Polymyxin B sulfate (p.317·3); fludrocortisone acetate (p.1530·1); lidocaine hydrochloride (p.1862·3).
Ear disorders.

Panotos *Ivax, Arg.*
Dextromethorphan hydrobromide (p.1555·2); bromhexine hydrochloride (p.1552·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Respiratory-tract disorders.

Panoto-S *Rhein, Mex.*
Ivy (p.2328·1).
Cold symptoms.

Panotos NF *Ivax, Arg.*
Bromhexine hydrochloride (p.1552·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract disorders.

Panoxi *Bausch & Lomb, Arg.*
⊗ Oxymetazoline hydrochloride (p.1567·2); vitamin A palmitate (p.1973·1); sodium hyaluronate (p.2320·1).
Eye disorders.

PanOxyl *Stiefel, Austral.; Sanova, Austria; Stiefel, Braz.; Stiefel, Canad.; Stiefel, Fr.; Stiefel, Ger.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Israel; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, NZ; Stiefel, Norw.; Stiefel, Philipp.; Stiefel, Port.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Spain; Qualicare, Switz.†; Stiefel, Thai.; Stiefel, UK; Stiefel, USA; Stiefel, Venez.†.*
Benzoyl peroxide (p.1590·2).
Acne; skin disinfection.

PanOxyl Clear Acne *Stiefel, Canad.*
Salicylic acid (p.1612·2); triclosan (p.1665·2).
Acne.

Panpeptal N *Philopharm, Ger.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Panpiryna *Cyntfarm, Pol.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Panpur *Axcan, Ger.*
Porcine pancreatin (p.2360·1).
Pancreatic insufficiency.

Panpurol *Shinyaku, Jpn†.*
Pipethanate ethobromide (p.1762·2).
Benzyl alcohol (p.1631·3) is included in the injection to alleviate the pain of injection.
Smooth muscle spasm.

Panquil *Pfizer Consumer, Austral.*
Promethazine hydrochloride (p.588·2); paracetamol (p.108·1).
Fever; pain.

Panretin *Bioprofarma, Arg.; Eisai, Cz.; Zeneus, Fr.; Zeneus, Ger.; Galenica, Gr.; Ligand, Neth.; Ferrer, Port.; Eisai, USA.*
Alitretinoin (p.678·1).
Skin lesions in Kaposi's sarcoma.

Panscol *Baker Cummins, USA.*
Salicylic acid (p.1612·2).
Hyperkeratosis.

Pansebase *Sofex, Port.*
Lecithin (p.2332·2); lactic acid (p.2329·3).
Seborrhoeic dermatitis.

Pansebase Composto *Sofex, Port.*
Lecithin (p.2332·2); lactic acid (p.2329·3); ichthammol (p.1599·1).
Pruritus; psoriasis; seborrhoeic dermatitis.

Pansebase Solido *Sofex, Port.†.*
Lecithin (p.2332·2).
Seborrhoea; soap substitute.

Pansements Coricides *SSL, Fr.†.*
Salicylic acid (p.1612·2).
Corns.

Panseptil *Gedis, Ital.*
⊗ Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1); alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Surface disinfection.

Pansoral *Pierre Fabre Oral Care, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.; Pierre Fabre, Switz.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Mouth disorders.

Pansoral Premieres Dents *Pierre Fabre, Fr.*
Althaea (p.2253·3); chamomile (p.2279·3).
Teething pain.

Pansoral Teething *Pierre Fabre, Rus.; Pierre Fabre, Singapore.*
Chamomile (p.2279·3); althaea (p.2253·3); saffron.
Teething pain.

Pansporin *Takeda, Jpn.*
Cefotiam hydrochloride (p.230·1) or cefotiam hexetil hydrochloride (p.230·1).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Panstal N *Cipla, India.*
Pancreatin (p.2360·1).
Digestive disorders.

Panstop *Armoxindo, Indon.*
Dipyrone (p.49·2).
Pain.

Pan-Streptomycin *IFET (ΙΦΕΤ), Gr.†.*
Streptomycin (p.333·3).
Bacterial endocarditis; brucellosis; tuberculosis.

Pansulfox *Stiefel, Chile.*
Benzoyl peroxide (p.1590·2).
Acne.

Pan-Sun *Chauvin, Fr.*
Dexpanthenol (p.2362·1).
Sunburn.

Pantacid
Note. This name is used for preparations of different composition.
Keri, Hung.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux.

Pantafarm, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Pantadolor *Labialfarma, Port.*
Paracetamol (p.108·1).
Fever; pain.

Pantaflux *Pantafarm, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Pantames *Pantafarm, Ital.*
Nimesulide (p.95·3).
Pain.

Pantasol *Pantafarm, Ital.†.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Pantaxin *Panpharma, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Pantec *Cifarma, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Pantecta *Abbott, Ital.; Altana, Spain.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantederm N *Hexal, Ger.*
Zinc oxide (p.1621·2).
Pantederm formerly contained zinc oxide and dexpanthenol.
Skin disorders; wounds.

Pantelmin *Janssen-Cilag, Austria; Janssen-Cilag, Braz.; Janssen, Port.; Janssen-Cilag, Venez.†.*
Mebendazole (p.148·3).
Worm infections.

Pantenil *Quimica Medica, Spain.*
Calcium pantothenate (p.1959·3); mercuric chloride (p.2341·2); aminobenzoic acid (p.1589·1).
Hair, scalp, and skin disorders.

Pantenol *Saba, Turk.*
Dexpanthenol (p.2362·1).
Skin disorders.

Pantenol Plus *Saba, Turk.*
Dexpanthenol (p.2362·1); chlorhexidine hydrochloride (p.1635·3).
Skin disorders.

Panteston *Organon, Fin.; Organon, NZ.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; male infertility; osteoporosis in men; testosterone deficiency in men.

Pantestone
Note. This name is used for preparations of different composition.
Filaxis, Arg.
⊗ Anastrozole (p.681·2).
Malignant neoplasms.

Organon, Fr.
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism.

Pantetina *Pharmafar, Ital.*
Pantethine (p.1365·3).
Hypertriglyceridaemia.

Pantevit *EMS, Braz.*
Pantothenic acid (p.1959·3); vitamin B (p.1979·1); resorcinol (p.1612·1).
Psoriasis.

Panthec *Sanovel, Turk.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panthenol *Chauvin Ankerpharm, Cz.; Jenapharm, Cz.; CT, Ger.; Chauvin ankerpharm, Ger.; Jenapharm, Ger.; Ratiopharm, Ger.; Riemser, Ger.; Sandoz, Ger.; Winthrop, Ger.; Chauvin, Hung.; Jenapharm, Hung.; Chauvin, Rus.; Merckle, Rus.*
Dexpanthenol (p.2362·1).
Burns; eye disorders; herpes labialis; inflammatory disorders of the gastrointestinal tract; mouth and throat disorders; pantothenic acid deficiency; paraesthesias; polyneuropathy; postoperative gastrointestinal atony; respiratory-tract disorders; sensation of burning in feet; skin disorders; skin irritation; ulcers; wounds.

Panthisone *Rekah, Israel.*
⊗ Panthenol (p.2362·1); hydrocortisone acetate (p.1535·2).
Anorectal disorders; skin disorders; wounds.

Panthoderm *Akrikhin, Rus.; Jones, USA.*
Dexpanthenol (p.2362·1).
Burns; skin disorders; ulcers; wounds.

Panthoderm-A *Sanofi Pasteur, Chile.*
Vitamin A palmitate (p.1973·1); panthenol (p.2362·1).
Skin disorders.

Panthogenat *Azupharma, Ger.†.*
Dexpanthenol (p.2362·1).
Wounds.

Pantiban
Note. This name is used for preparations of different composition.
Royal, Chile.
Capsules: Vitamins; minerals; rutoside; ginseng; procaine hydrochloride (p.1869·1) (p.1922·1).
Dietary supplement.

Royal, Chile.
Syrup: Amino acids; vitamins; minerals (p.1922·1).
Dietary supplement.

Pantinol *Gerot, Austria†.*
Aprotinin (p.1055·1).
Hyperfibrinolytic haemorrhage.

Panto
Altana, Canad.
Pantoprazole sodium (p.1760·1).
Gastric hyperacidity.

Ilsan, Turk.
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panto Liquid *Pharmaselect, Austria.*
Panthenol (p.2362·1); phenylmercuric borate (p.1657·3).
Liver disorders; neuropathies; skin disorders; sweating; upper respiratory-tract inflammation.

Pantobamin *Medix, Spain.*
Cyproheptadine (p.575·2); amino acids and vitamins (p.1922·1).
Anorexia; tonic.

Pantobron *Abbott, Mex.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Pantoc *Altana, Port.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantocal *Eurofarma, Braz.*
Pantoprazole sodium (p.1760·1).
Peptic ulcer.

Pantocalcin *Shchelkovskii, Rus.*
Calcium hopantenate (p.2272·2).
Epilepsy; extrapyramidal disorders; mental function disorders; micturition disorders.

Pantocarm *Altana, Spain.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantocas *Casasco, Arg.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantocid *Pharmaplan, S.Afr.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantocort *Ponce, Venez.†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Pantocycline *Chew, Thai.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Pantodac *Zydus, India.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantodrin *Abbott, Spain†.*
Erythromycin (p.269·2).
Acne.

Pantogam *Pik, Rus.*
Calcium hopantenate (p.2272·2).
Cerebrovascular disorders; epilepsy; extrapyramidal disorders; mental function impairment; micturition disorders; paediatric cerebral palsy; psychoses.

Pantogar
Medra, Austria.
Calcium pantothenate; cystine (p.1922·1).
Hair and nail disorders.

Merz, Hong Kong; Merz, Singapore†; Merz, Switz.
Thiamine nitrate, calcium pantothenate; medicinal yeast; cysteine; keratin aminobenzoic acid (p.1922·1).
Hair and nail disorders.

Pantohamum *TSNKB, Rus.†.*
Calcium hopantenate(p.2272·2).
Cerebrovascular disorders; dementia; epilepsy; extrapyramidal disorders; mental function impairment; micturition disorders; paediatric cerebral palsy; stutter.

Pantok *Lacer, Spain.*
Simvastatin (p.1390·2).
Hypercholesterolaemia; ischaemic heart disease.

Pantolax *DeltaSelect, Ger.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Pantoloc *Altana, Austria; Altana, Canad.; Solvay, Canad.; Altana, Denm.; Altana, Hong Kong; Altana, Philipp.; Altana Madaus, S.Afr.; Nycomed, Swed.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantometil *Lersan, Arg.*
Polymyxin B sulfate (p.317·3); gramicidin (p.286·1); neomycin sulfate (p.305·1).
Eye infections.

Pantomicina
Abbott, Arg.
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Abbott, Braz.
Erythromycin (p.269·2) or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Chile; Abbott, Spain.
Erythromycin ethyl succinate (p.269·3) or erythromycin lactobionate (p.270·1).
Bacterial infections.

Abbott, Mex.
Erythromycin ethyl succinate (p.269·3), erythromycin lactobionate (p.270·1), or erythromycin stearate (p.270·1).
Bacterial infections.

Abbott, Venez.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Pantomin *Daiichi, Hong Kong†.*
Pantethine (p.1365·3).
Constipation; hyperlipidaemias; pantothenic acid deficiency.

Pantomucol *Abbott, Arg.†.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1); bromhexine (p.1552·2).
Respiratory-tract infections.

Pantonate *Eagle, Austral.*
Calcium pantothenate (p.1959·3).
Vitamin B supplement.

Pantonic *Mediphar, Venez.*
⊗ Urea (p.1620·2); panthenol (p.2362·1).

Pantop
Altana, Arg.; Zuoz, Venez.
Pantoprazole sodium (p.1760·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Aristo, India.
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

PantoPAC *Altana, Neth.*
Tablets, pantoprazole sodium (p.1760·1); tablets, clarithromycin (p.248·2); tablets, amoxicillin trihydrate (p.202·2).
Peptic ulcer.

Pantopan *Pharmacia, Ital.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantopaz *Hexal, Braz.†.*
Pantoprazole (p.1760·1).
Peptic ulcer.

Pantopept *Biosintetica, Braz.†.*
Pepsin (p.2365·1); amylase (p.2256·3).
Digestive disorders.

Pantorc *Altana, Ital.; Eureco, Neth.; Euro Registratie, Neth.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantosec
Verisfield, Gr.
Pantoprazole (p.1760·1).
Peptic ulcer.

Cipla, India.
Pantoprazole (p.1760·1) or pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantosec D *Cipla, India.*
Pantoprazole (p.1760·1); domperidone (p.1726·2).
Gastro-oesophageal reflux.

Pantosin *Daiichi, Jpn.*
Pantethine (p.1365·3).
Blood disorders; constipation; eczema; hyperlipidaemias; pantothenic acid deficiency; pantothenic acid supplement; streptomycin and kanamycin toxicity.

Pantostin *Simons, Ger.*
⊗ Alfatradiol (p.2082·1).
Formerly contained estradiol.
Alopecia androgenetica.

Pantothen
Note. This name is used for preparations of different composition.
Pharmaselect, Austria.
Panthenol (p.2362·1).
Alcoholism; gastrointestinal tract disorders; liver disorders; muscle cramps; neuropathies; respiratory-tract disorders; skin disorders; sweating.

Streuli, Switz.
Calcium pantothenate (p.1959·3).
Respiratory-tract disorders; skin and mucous membrane disorders.

Pantovigar N *Simons, Ger.*
Thiamine nitrate (p.1976·2); calcium pantothenate (p.1959·3); medicinal yeast (p.1998·3); cystine (p.1937·1); keratin.
Disorders of the hair and nails.

Pantovit *Sanova, Austria.*
Multivitamin preparation (p.1922·1).

Pantovit Vital *Sanova, Austria.*
Multivitamin, iron, and mineral preparation (p.1922·1).

Pantoxon *Aesculapius, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Pantozol
Altana, Belg.; Nycomed, Braz.; Altana, Ger.; Altana, Neth.; Altana, Switz.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Altana, Indon.; Pharos, Indon.; Altana, Mex.
Pantoprazole (p.1760·1) or pantoprazole sodium (p.1760·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Pantozol-Rifun *Byk Gulden, Ger.†; Schwarz, Ger.†.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantpas *Bayer, Turk.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pantrat *Cifarma, Braz.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantricine *Pharmacobel, Belg.†.*
Tyrothricin (p.358·2); lidocaine (p.1862·3).
Sore throat.

Pantrixon *Panpharma, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Pantus *Baliarda, Arg.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Pantyson *Orion, Fin.*
⊗ Hydrocortisone (p.1535·2); dexpanthenol (p.2362·1).
Skin disorders.

Panuron *Troika, Venez.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Panverm *Teuto, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Panvermin *Andromaco, Mex.*
Mebendazole (p.148·3).
Worm infections.

Panvit *Teuto, Braz.; Collins, Mex.†.*
A range of multivitamin preparations with or without minerals (p.1922·1).

Panvitan *Takeda, Jpn.*
Vitamin preparation (p.1922·1).

Panvitan-M *Takeda, Hong Kong†; Takeda, Singapore†; Takeda, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Panvitina BC *Neo Quimica, Braz.†.*
Multivitamin preparation (p.1922·1).

Panvitrop *Nycomed, Braz.*
Methionine (p.1450·1); choline tartrate (p.1934·2); sodium phenylethylacetate; liver extract (p.2337·3); vitamin B substances; tocopherol (p.1922·1); rutoside (p.2305·1).
Liver disorders.

Panwarfin *Abbott, Gr.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Panxeol *Monin, Fr.*
Eschscholtzia californica; passion flower (p.2363·2).
Insomnia; nervous disorders.

Panzer *Wermar, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Panzid *Valda, Ital.*
Ceftazidime (p.234·1).
Bacterial infections.

Panzimine *Malayan, Singapore†.*
Buclizine hydrochloride (p.570·1).
Hypersensitivity reactions; motion sickness; vertigo.

Panzynorm *Strallhofer, Austria; KRKA, Cz.; KRKA, Rus.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Panzynorm forte-N *Axcan, Ger.*
Porcine pancreatin (p.2360·1).
Pancreatic insufficiency.

Panzynorm-N *German Remedies, India.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Panzytrat
Note. This name is used for preparations of different composition.
Technipro, Austral.; Pharmaco, NZ.
Pancrelipase (p.2360·1).
Formerly contained pancreatin in *Austral*.
Pancreatic insufficiency.

Abbott, Braz.; Axcan, Cz.; Axcan, Ger.; Vianex (Βιανεξ), Gr.; Axcan, Hung.; Axcan, Neth.; Axcan, Pol.; Knoll, Rus.†; Vifor, Switz.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Papaine *DB, Fr.*
Carica papaya.
Dyspepsia.

Papasine *Bernabo, Arg.*
Naproxen (p.92·3); tetracycline hydrochloride (p.347·2).
Bacterial infections.

Papatropin *Alpes Chemie, Chile†.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Papaven *Medikon, Indon.*
Graptophyllum pictum; troxerutin (p.2305·1); papain (p.2362·3).
Haemorrhoids; phlebitis; venous insufficiency.

Papaveryl *Vincenti, Venez.*
Papaverine hydrochloride (p.2191·3).
Formerly contained papaverine, belladonna, hyoscyamus, star anise and condurango.
Smooth muscle spasm.

Papaya Enzyme *Nature's Bounty, USA.*
Papain (p.2362·3); amylase (p.2256·3).
Gastrointestinal disorders.

Papenzima *Pfizer, Chile.*
Papain (p.2362·3).
Soft-tissue injury.

Papilock *Santen, Jpn.*
Ciclosporin (p.1822·2).

Papine *Duphar Nezel, Spain.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Paps *Richard, Fr.*
Sulfur (p.1614·1); zinc undecenoate (p.549·3); bismuth subgallate (p.1711·1); menthol (p.2340·1); camphor (p.2273·2); salicylic acid (p.1612·2); zinc oxide (p.1621·2); boric acid (p.2268·1); lavender oil (p.2331·2).
Pruritus.

Papuless *Theraskin, Braz.*
Nicotinamide (p.1957·3).

Pap-Urea *Cypress, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2).

Papytazyme
Note. This name is used for preparations of different composition.
Anglo-French Drugs, Thai.†.
Papain (p.2362·3); pepsin (p.2365·1); amylase (p.2256·3); pancreatin (p.2360·1); ox bile extract (p.2266·3); ginger oleoresin (p.1732·3); activated charcoal (p.1435·2).
Digestive disorders.

Anglo-French Drugs, India.
Syrup: Amylase (p.2256·3); papain (p.2362·3).
Digestive disorders.

Anglo-French Drugs, India.
Tablets: Amylase (p.2256·3); papain (p.2362·3); pancreatin (p.2360·1); ox bile extract (p.2266·3); pepsin (p.2365·1); ginger oleoresin (p.1732·3); activated charcoal (p.1435·2).
Digestive disorders.

Par
Note. This name is used for preparations of different composition.
Daudt, Braz.
Paracetamol (p.108·1); dipyrone (p.49·2).
Fever; pain.

Faran, Gr.
Paracetamol (p.108·1).
Fever; pain.

Par Glycerol *Par, USA.*
Iodinated glycerol (p.1562·2).
Coughs.

Para
Note. This name is used for preparations of different composition.
Medgenix, Belg.; Medican, Canad.†.
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Royal, Chile.
Dimeticone (p.2032·1).
Barrier preparation.

Para GDEK *Millimed, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Para Lentes *Omega, Fr.*
Acetic acid (p.2244·2).
Pediculosis.

Para Piojicida *Raymos, Arg.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Para Plus *Raymos, Arg.; Medgenix, Belg.; Omega, Fr.; Rafa, Israel; Pacific, NZ; Pharmygiene, Rus.*
Malathion (p.2046·1); permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Para Repulsif *Omega, Fr.*
Piperonal (p.2049·1).
Head lice repellent.

Para Special Poux *Omega, Fr.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Para Z Mol *Cabuchi, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Parabact *Cadila, India.*
Norfloxacin (p.309·2); tinidazole (p.848·3).
Bacterial infections; protozoal infections.

Parabowl *Masa, Thai.†.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Parabutol *Prafa, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Paracap *Masa, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Paracare *PSM, NZ.*
Paracetamol (p.108·1).
Fever; pain.

Paracefan *Boehringer Ingelheim, Ger.*
Clonidine (p.1247·1) or clonidine hydrochloride (p.1247·1).
Alcohol withdrawal syndrome; opioid withdrawal syndrome; Tourette syndrome.

Paracemil *Sinterapico, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Paracen *Greenpharma, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Paraceon *Verman, Fin.*
Paracetamol (p.108·1).
Fever; pain.

Paracet *Weifa, Norw.; Osotspa, Thai.; Gripin, Turk.*
Paracetamol (p.108·1).
Fever; pain.

paracet comp *CT, Ger.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Paracetacod
Note. This name is used for preparations of different composition.
Ratiopharm, Ger.†.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Adcock Ingram, S.Afr.
Paracetamol (p.108·1); codeine phosphate (p.37·2); ascorbic acid (p.1983·3).
Pain.

Paracetamol C & F *Pharmaniaga, Malaysia.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms; cough.

Paracetamol comp *Aliud, Ger.; Stada, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Paracetamol Grip NF *Raffo, Arg.*
Paracetamol (p.108·1); bromhexine hydrochloride (p.1552·2); pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Cold and influenza symptoms.

Paracetamol plus
Note. A similar name is used for preparations of different composition (see below).
CT, Ger.†; Ratiopharm, Ger.†.
Paracetamol (p.108·1); caffeine (p.1116·3).
Cold symptoms; pain.

Paracetamol Plus
Note. A similar name is used for preparations of different composition (see above).
Pharmaniaga, Malaysia†.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Paracetamol-C *Hemofarm, Rus.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Paracetol *Prafa, Indon.; Farmacoope, Port.*
Paracetamol (p.108·1).
Fever; pain.

Paracets *Sussex, UK.*
Paracetamol (p.108·1).
Fever; pain.

Paracets Cold Relief *Sussex, UK.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Paracets Plus *Sussex, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Parachoc *Paedpharm, Austral.*
Methylcellulose (p.2145·1); liquid paraffin (p.2030·3).
Constipation.

Paracin *Stadmed, India.*
Paracetamol (p.108·1).
Fever; pain.

Paracip *Cipla, India.*
Paracetamol (p.108·1).
Fever; pain.

Paracip CPM *Cipla, India.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).

Paracip Plus *Cipla, India.*
Paracetamol (p.108·1); diclofenac sodium (p.44·3).
Inflammation; pain.

Paraclear *Roche Consumer, UK.*
Paracetamol (p.108·1).

Paraclim *Elea, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Paracne *Panalab, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Paracod *Cipla, India; Sam-On, Israel.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Paracodamol *Balkanpharma, Rus.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Paracodin
Note. This name is used for preparations of different composition.
Abbott, Austral.; Abbott, Ger.; Abbott, S.Afr.
Dihydrocodeine tartrate (p.48·1).
Coughs.

Abbott, Irl.
Dihydrocodeine tartrate (p.48·1) or dihydrocodeine thiocyanate (p.48·3).
Coughs.

Abbott, Switz.
Dihydrocodeine thiocyanate (p.48·3).
Coughs; diarrhoea.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Abbott, Austria.
Oral drops: Dihydrocodeine thiocyanate (p.48·3); thyme (p.2401·1).
Coughs.

Abbott, Austria.
Syrup: Dihydrocodeine tartrate (p.48·1); althaea (p.2253·3); grindelia (p.2317·2).
Coughs.

Abbott, Austria.
Tablets: Dihydrocodeine tartrate (p.48·1).
Coughs.

Paracodin N *Abbott, Ger.*
Dihydrocodeine tartrate (p.48·1) or dihydrocodeine thiocyanate (p.48·3).
Coughs.

Paracodin retard
Abbott, Ger.†.
Dihydrocodeine polistirex (p.48·3); dihydrocodeine tartrate (p.48·1).
Coughs.

Knoll, Switz.†.
Dihydrocodeine tartrate (p.48·1); dihydrocodeine resin (p.48·3).
Coughs; diarrhoea.

Paracodina
Note.This name is used for preparations of different composition.
Abbott, Spain.
Dihydrocodeine tartrate (p.48·1).
Cough.

Abbott, Ital.
Oral drops: Dihydrocodeine thiocyanate (p.48·3).
Coughs.

Abbott, Ital.
Syrup: Dihydrocodeine tartrate (p.48·1); benzoic acid (p.1630·2).
Coughs.

Paracodine *Pharma Logistics, Belg.*
Dihydrocodeine tartrate (p.48·1).
Paracodine Syrup formerly contained dihydrocodeine tartrate, grindelia, and althaea.
Coughs.

Paracodol *Roche Consumer, Irl.†; Roche Consumer, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Paracof *Imgroma, Neth.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Paracor *Corsalud, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Paractol
Note.This name is used for preparations of different composition.
Temmler, Ger.
Chewable tablets: Simeticone (p.1770·2); aluminium hydroxide gel (p.1706·2).
Gastrointestinal disorders.

German Remedies, India.
Oral liquid: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders with excess gas.

Temmler, Ger.
Oral suspension: Simeticone (p.1770·2); aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

German Remedies, India.
Tablets: Simeticone (p.1770·2); aluminium hydroxide (p.1706·2).
Gastrointestinal disorders with excess gas.

Paradco *Adco, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Paradentol *Leciva, Cz.†.*
Carbaethopendecinium bromide (p.1633·3); dipenditum.
Gingivitis; periodontitis.

Paradenton *Austroplant, Austria.*
Myrrh (p.2349·2); sage leaf (p.2382·3); chamomile flowers (p.2279·3); tannic acid (p.2394·3).
Aphthous ulcers; bleeding gums; bruised gums; gingivitis; periodontitis.

Paraderm *Wyeth Consumer, Austral.†.*
Bufexamac (p.28·3).
Skin disorders.

Paraderm Plus *Wyeth Consumer, Austral.; Wyeth Consumer, NZ.*
Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3); bufexamac (p.28·3).
Burns; insect bites; stings; sunburn.

Paradex
Aspen, Austral.
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

PSM, NZ.
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Fever; pain.

Paradis *Biomedica-Chemica, Gr.*
Clindamycin (p.251·1).
Bacterial infections.

Para-don *Etos, Neth.*
Caffeine (p.1116·3); paracetamol (p.108·1); propyphenazone (p.119·3).
Fever; pain.

Paradote *Sinclair, UK.*
Paracetamol (p.108·1); -methionine (p.1450·2).
These ingredients can be described by the British Approved Name Co-methiamol.
Fever; pain.

Paradrine *DHA, Singapore.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Paradroxil *Gerolimatos (Γερολυματος), Gr.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Paradryl
Note.This name is used for preparations of different composition.
Prafa, Indon.
Injection: Diphenhydramine hydrochloride (p.577·2).
Cough.

Prafa, Indon.
Syrup: ⊗ Ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1); alcohol (p.1625·2); diphenhydramine (p.577·1).
Cough.

Paradryl med efedrin *Ferrosan, Denm.†.*
⊗ Mefenidramium bromide; ephedrine hydrochloride (p.1558·2); ammonium chloride (p.1551·3).
Coughs.

Parafizz *Cipla, India†; Cipla, Malaysia.*
Paracetamol (p.108·1).
Fever; pain.

Paraflex *AstraZeneca, Denm.; Janssen-Cilag, S.Afr.; AstraZeneca, Swed.; Santa, Turk.; McNeil Pharmaceutical, USA.*
Chlorzoxazone (p.1894·3).
Headache; musculoskeletal pain; premedication; skeletal muscle spasm.

Paraflex AN *Janssen-Cilag, Arg.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle pain and spasm.

Paraflex comp *AstraZeneca, Fin.†; AstraZeneca, Swed.†.*
Chlorzoxazone (p.1894·3); aspirin (p.20·3); dextropropoxyphene napsilate (p.40·1).
Headache; musculoskeletal, joint, and peri-articular disorders; skeletal muscle spasm.

Paraflex Crema *Janssen-Cilag, Arg.†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Paraflex Plus *Janssen-Cilag, Arg.*
⊗ Chlorzoxazone (p.1894·3); paracetamol (p.108·1); dexamethasone (p.1526·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Parafludeten *Alter, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Parafon *Janssen-Cilag, Austria; Ethnor, India; Janssen, Philipp.; Johnson & Johnson, S.Afr.; Janssen-Cilag, Thai.; Santa, Turk.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle pain and spasm.

Parafon DSC *Ethnor, India.*
Chlorzoxazone (p.1894·3).
Skeletal muscle spasm.

Parafon Forte *Johnson & Johnson, Canad.; Janssen-Cilag, Mex.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; skeletal muscle spasm.

Parafon Forte DSC *Ortho McNeil, USA.*
Chlorzoxazone (p.1894·3).
Musculoskeletal pain.

Parafortan *Khandelwal, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal and biliary colic.

Para-G *Millimed, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Paragar *Spirig, Switz.*
Liquid paraffin (p.2030·3); agar (p.2140·3); phenolphthalein (p.1762·1).
Constipation.

Paragard T380A *Ortho McNeil, USA.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Paragel *Omega, Gr.*
Liquid paraffin (p.2030·3).
Constipation.

Parageniol *GSK, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Parageniol Caff *GSK, Arg.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Parageniol Grip *GSK, Arg.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Parageniol Grip Caliente *GSK, Arg.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Paraghurt *Actavis, Denm.*
Enterococcus faecium (p.2372·3).
Diarrhoea.

Paragin *Pharmasant, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Paragip *Boiron, Canad.†.*
Homoeopathic preparation.

Paragol N *Streuli, Switz.*
Liquid paraffin (p.2030·3).
Constipation.

Paragoriese-Elikser *Lennon, S.Afr.*
Opium (p.105·1); anise oil (p.2258·2); camphor (p.2273·2).
Abdominal pain; coughs; diarrhoea.

Paragrippe *Boiron, Cz.; Boiron, Fr.; Boiron, Neth.; Boiron, Port.†.*
Homoeopathic preparation.

Parahexal *Hexal, Austral.*
Paracetamol (p.108·1).
Fever; pain.

Para-Hist HD *Pharmics, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Paraiop *Ingens, Arg.*
Latanoprost (p.1882·1).
Ocular hypertension.

Parakapton *Rosch & Handel, Austria; Strallhofer, Austria.*
Paracetamol (p.108·1).
Pain, fever.

Para-4-Kids *Blue Sky, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Parakol *Duopharma, Malaysia.*
Dexchlorpheniramine maleate (p.572·1); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic disorders; cold and influenza symptoms.

Paraks *Adeka, Turk.*
Levamisole (p.147·2).
Ascariasis; trichostrongyliasis.

Paral *Forest Pharmaceuticals, USA.*
Paraldehyde (p.1015·2).
Sedative.

Paralen *Zentiva, Cz.*
Paracetamol (p.108·1).
Fever; pain.

Paralen Extra *Zentiva, Cz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Paralen Hot Drink *Zentiva, Cz.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Paralen Plus *Zentiva, Cz.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Fever; respiratory-tract disorders.

Paralgen *Legrand, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Paralgesic Gold *ECR, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and joint pain.

Paralgin
Note.This name is used for preparations of different composition.
Fawns & McAllan, Austral.
Paracetamol (p.108·1).
Fever; pain.

Weifa, Norw.
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Paralice *Fleet, Austral.†.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Paralief *Clonmel, Irl.*
Paracetamol (p.108·1).
Fever; pain.

Paralink *Rice Steele, Irl.*
Paracetamol (p.108·1).
Fever; pain.

Paralon *Janssen-Cilag, Braz.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Pain; smooth muscle spasm.

Paralymphine *Andromaco, Chile.*
Iodine; manganese glycerophosphate; tannin; calcium phosphate; ferrous phosphate (p.1922·1).
Tonic.

Paralyoc *Cephalon, Fr.*
Paracetamol (p.108·1).
Fever; pain.

Paramax *Sanofi-Aventis, Irl.; GSK, NZ; Sanofi Synthelabo, UK.*
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Gastric stasis; migraine; nausea and vomiting.

Paramax Rap *Vitabalans, Fin.*
Paracetamol (p.108·1).
Fever; pain.

Paramax Rapid *Vitabalans, Cz.; Vitabalans, Hung.*
Paracetamol (p.108·1).
Fever; pain.

Paramax-Cod *Vitabalans, Fin.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Paramed *Group, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Paramet *Wallace, India.*
Paracetamol (p.108·1); metoclopramide (p.1747·3).
Migraine.

Paramettes *Whitehall-Robins, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Paramex *Konimex, Indon.*
Propyphenazone (p.119·3); paracetamol (p.108·1); dexchlorpheniramine maleate (p.572·1); caffeine (p.1116·3).
Fever; pain.

Paramidon *Ilsan, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Paraminan *Zydus, Fr.*
Aminobenzoic acid (p.1589·1).
Photodamage of the skin.

Paramino-Corazida *Basi, Port.*
Aminosalicylic acid (p.201·2).
Tuberculosis.

Paraminol *Franco-Indian, India.*
Aminobenzoic acid (p.1589·1).
Adjunct in vitiligo therapy.

Paramix *Liomont, Mex.*
Nitazoxanide (p.842·3).
Protozoal infections; worm infections.

Paramol
Note.This name is used for preparations of different composition.
Galen, Irl.; SSL, UK.
Paracetamol (p.108·1); dihydrocodeine tartrate (p.48·1).
Coughs; fever; pain.

Dexxon, Israel; General Drugs, Thai.
Paracetamol (p.108·1).
Fever; pain.

Paramol AF Day *Dexxon, Israel.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Paramol AF Night *Dexxon, Israel.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Paramol AF and Shiul Day *Dexxon, Israel.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Paramol AF and Shiul Night *Dexxon, Israel.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Paramol Forte *APT, Hong Kong.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Paramol Plus *Dexxon, Israel.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Paramol TP *TP, Thai.*
Paracetamol (p.108·1).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Fever; pain.

Paramolan *Trima, Israel; Medinfar, Port.*
Paracetamol (p.108·1).
Fever; pain.

Paramolan C *Medinfar, Port.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Paranal *Siam Bheasach, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Paranal-L *Siam Bheasach, Thai.*
Paracetamol (p.108·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Fever; pain.

Paranausine *Eurogenerics, Belg.*
Dimenhydrinate (p.576·2).

Paranomin *Combiphar, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine (p.1569·2).
Cold and influenza symptoms; upper respiratory-tract disorders.

Paranorm *Wallace Mfg Chem., UK.*
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Coughs.

Para-Nox
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Turk.
Forte suppositories; paediatric syrup; S suppositories; tablets: Paracetamol (p.108·1).
Fever; pain.

Sanofi Synthelabo, Turk.
Suppositories: Paracetamol (p.108·1); phenobarbital (p.492·2).
Fever; pain.

Paranox
Note. A similar name is used for preparations of different composition (see above).
Roi Surya, Indon.
SPF 33: Enzacamene (p.1597·1); avobenzone (p.1589·3); oxybenzone (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Paranox F *Roi Surya, Indon.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Paranzol *Collins, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

Parapaed *Ritsert, Ger.; Pinewood, Irl.; AFT, NZ; Pinewood, UK.*
Paracetamol (p.108·1).
Fever; pain.

Parapic *Biomed, Switz.*
Lidocaine hydrochloride (p.1862·3); diphenhydramine hydrochloride (p.577·2); benzalkonium chloride (p.1629·1); menthol (p.2340·1); dexpanthenol (p.2362·1).
Insect stings; skin irritation.

Para-Pio *Gestafarma, Port.†.*
Pyrethrin (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Paraplatin *BMS, Arg.†; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.†; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.†; BMS, Norw.; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA†.*
Carboplatin (p.693·1).
Malignant neoplasms.

Paraplatine *BMS, Fr.*
Carboplatin (p.693·1).
Malignant neoplasms.

Para-plus *Olvos, Gr.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1); malathion (p.2046·1).
Head lice.

Parapres *Almirall, Spain.*
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension.

Parapres Plus *Almirall, Spain.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Parapsyl *Barrenne, Braz.*
Liquid paraffin (p.2030·3); ispaghula (p.1737·1).
Constipation.

Parapsyllium *IPRAD, Fr.*
Ispaghula (p.1737·1); liquid paraffin (p.2030·3); sorbitol (p.1965·1).
Constipation.

Paraqueimol *Ache, Braz.*
Sulfacetamide sodium (p.335·3); trolamine (p.2405·1).
Skin infections.

Parareg *Dompe, Cz.; Dompe, Ital.; Dompe Biotec, Neth.; Dompe, Port.*
Cinacalcet hydrochloride (p.1095·1).
Hypercalcaemia in parathyroid cancer; hyperparathyroidism in dialysis patients with end-stage renal failure.

Parartrin *Cazi, Braz.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Paras *YSP, Malaysia.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Parasedol *Kocak, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Parasidose *Gilbert, Cz.; Gilbert, Fr.; Multichem, NZ.*
Phenothrin (p.2048·3).
Pediculosis.

Parasimed *Cimed, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Parasin *Ache, Braz.*
Albendazole (p.139·2).
Worm infections.

Parasinus *Kocak, Turk.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Fever; pain.

Paraskorbin *Infusia, Cz.†.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Fever; pain.

Parasol *Surya Dermato, Indon.*
Octinoxate (p.1608·2); titanium dioxide (p.1617·3); oxybenzone (p.1608·3).
Sunscreen.

Parasone *Vida, Hong Kong.*
⊗ Dexamethasone (p.1526·1); paracetamol (p.108·1); vitamin B substances (p.1922·1).
Musculoskeletal, joint, and peri-articular disorders.

Para-Speciaal *Chefaro, Neth.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Paraspeed *Nycomed, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Para-Suppo *Orion, Fin.*
Paracetamol (p.108·1).
Fever; pain.

Parat *Asian Pharm, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Paratabs *Actavis, Denm.; Pinewood, Irl.*
Paracetamol (p.108·1).
Fever; pain.

Para-Tabs *Orion, Fin.*
Paracetamol (p.108·1).
Fever; pain.

Paratermol *INQ, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Paratol *Chew, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Paratonico *Multilab, Braz.*
Ferrous sulfate (p.1939·3); phosphoric acid (p.2367·1); aloes (p.1705·2); myrrh (p.2349·2); cinnamon (p.2283·1); nutmeg (p.2355·2).
Reduced appetite.

Paratonina *Farma Lepori, Spain.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Paratral *LA, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Paratropina *Lazar, Arg.*
Homatropine methylbromide (p.1881·3).
Habitual vomiting in infants; hyperchlorhydria; smooth muscle spasm.

Paratropina Antigas *Lazar, Arg.*
Simeticone (p.1770·2); homatropine methylbromide (p.1881·3).
Gastrointestinal spasm.

Paratropina Compuesta *Lazar, Arg.*
Homatropine methylbromide (p.1881·3); metamizole magnesium (p.49·3).
Colic; dysmenorrhoea.

Paratulle *SSL, UK†.*
Yellow soft paraffin (p.2031·3).
Wounds.

Paratusin
Note. This name is used for preparations of different composition.
Prafa, Indon.
Syrup: Noscapine (p.1566·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); paracetamol (p.108·1); succus liquid; pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Prafa, Indon.
Tablets: Noscapine (p.1566·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

Paraverm *Hertz, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Paravertebral LWS *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Parax *Hexal, S.Afr.*
Paroxetine (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Paraxin
Roche, Ger.
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Nicholas Piramal, India.
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Paraxin Ear *Nicholas Piramal, India†.*
Chloramphenicol (p.239·3); benzocaine (p.1854·1).
Otitis.

Parazol *Cazi, Braz.*
Albendazole (p.139·2).
Worm infections.

Parazone *Quality, Hong Kong.*
Paracetamol (p.108·1); chlormezanone (p.968·3).
Dysmenorrhoea; pain; premenstrual syndrome; skeletal muscle spasm.

Parcaine *Ocusoft, USA.*
Proxymetacaine hydrochloride (p.1870·1).

Parcel *Novartis, Braz.*
Paracetamol (p.108·1); dihydroergotamine mesilate (p.618·2); caffeine (p.1116·3).
Migraine.

Parcemol *Synco, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Parcetin *Denver, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Parche Calorub *Hofmann, Chile.*
Methyl salicylate (p.85·3).
Musculoskeletal and joint pain.

Parche Leon Fortificante *Beiersdorf, Chile.*
Capsicum (p.2276·2).
Musculoskeletal and joint disorders.

Parche Negro Belladona *Quimica y Farmacia, Mex.*
Capsicum (p.2276·2); methyl salicylate (p.85·3); colophony (p.2286·2); zinc oxide (p.1621·2); calcium carbonate (p.1714·1); belladonna (p.2263·3); negro de humo.
Musculoskeletal disorders.

Parclen *Lamsa, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Parcono *Milano, Thai.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Parcopa *Schwarz, USA.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Parcoten *Aegis, Hong Kong.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Pardelprin *Alpharma, UK.*
Indometacin (p.66·3).
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders.

Pardex *Parggon, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Pardix *Arlex, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Pardoz *Kalbe, Indon.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Pa-Real *Lampugnani, Ital.*
Royal jelly (p.2382·1).
Nutritional supplement.

Parecid *Proge, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Paredrine *Pharmics, USA†.*
⊗ Hydroxyamfetamine hydrobromide (p.2322·3).
Production of mydriasis.

Paregorique *Lafran, Fr.*
Prepared opium (p.105·1); benzoic acid (p.1630·2); anise oil (p.2258·2); camphor (p.2273·2).
Diarrhoea.

Paremyd *Akorn, USA.*
⊗ Hydroxyamfetamine hydrobromide (p.2322·3); tropicamide (p.1886·2).
Induction of mydriasis with partial cycloplegia.

Parencias *Geminis, Arg.†.*
Ascorbic acid (p.1983·3); benzocaine (p.1854·1); borax (p.2268·1); nicotinic acid (p.1957·3).
Mouth disorders.

Parentamin *Serag-Wiessner, Ger.; Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Parentamin E *Serag-Wiessner, Ger.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Parentamin X-E *Serag-Wiessner, Ger.*
Amino-acid, electrolyte, and xylitol infusion (p.1922·1).
Parenteral nutrition.

Parentamin G E *Serag-Wiessner, Ger.*
Amino-acid, electrolyte, and glucose infusion (p.1922·1).
Parenteral nutrition.

Parentamin GX E *Serag-Wiessner, Ger.†.*
Amino-acid, electrolyte, glucose, and xylitol infusion (p.1922·1).
Parenteral nutrition.

Parentamin Hepa *Serag-Wiessner, Ger.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in liver disease.

Parenteral *Serag-Wiessner, Ger.†.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Parenteral BG *Serag-Wiessner, Ger.†.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Parenteral EK G *Serag-Wiessner, Ger.†.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Parenteral G *Serag-Wiessner, Ger.†.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Parenteral HG *Serag-Wiessner, Ger.†.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Parenteral OP *Serag-Wiessner, Ger.†.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Parenterin *Legrand, Braz.*
Neomycin sulfate (p.305·1); phthalylsulfathiazole (p.315·1); aluminium hydroxide (p.1706·2); pectin (p.2145·2).
Diarrhoea.

Parenzyme *Medley, Braz.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3).
Inflammation.

Parenzyme Ampicilina *Medley, Braz.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3); ampicillin (p.204·1).
Bacterial infections; inflammation.

Parenzyme Analgesico *Medley, Braz.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3); paracetamol (p.108·1).
Inflammation; pain.

Parenzyme Tetraciclina *Medley, Braz.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3); tetracycline hydrochloride (p.347·2).
Bacterial infections; inflammation.

Parepectolin *Vargas, Venez.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Paretin *Sandoz, Hung.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Parexat *Spirig, Switz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Parexel *Zodiac, Braz.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Par-F *Pharmics, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Parfenac *Wyeth-Whitehall, Arg.†; Dermapharm, Austria; Wyeth, Fr.; Riemser, Ger.; Chefaro, Neth.; Home, Port.; Dermapharm, Switz.*
Bufexamac (p.28·3).
Burns; insect stings; musculoskeletal, joint, and periarticular pain; skin disorders.

Parfenac Basisbad *Lederle, Ger.†.*
Arachis oil (p.2259·1); light liquid paraffin (p.2031·1).
Bath additive; dry, pruritic skin disorders.

Parfeno *LKM, Arg.*
Pramipexole (p.814·2).
Parkinsonism.

Pargine *Meda, Fr.*
Arginine aspartate (p.1928·2).
Retarded growth.

Pargitan *Abigo, Swed.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism; spasms in children.

Pargo *Bio-Diat, Ger.†.*
Devil's claw root (p.39·1).
Biliary disorders; degenerative joint disorders; gastrointestinal disorders.

Pari *Ipca, India.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder; social phobia.

Pariet *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Eisai, Ger.; Janssen-Cilag, Gr.; Eisai, Hong Kong; Janssen-Cilag, Hung.; Eisai, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Eisai, Jpn; Eisai, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Eisai, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Eisai, Rus.; Janssen-Cilag, S.Afr.; Eisai, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Eisai, Thai.; Janssen-Cilag, Turk.; Eisai, UK; Janssen-Cilag, Venez.*
Rabeprazole sodium (p.1765·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Parilac *Teva, Israel.*
Bromocriptine mesilate (p.798·1).
Acromegaly; amenorrhoea; galactorrhoea; male and female infertility; parkinsonism; prolactinoma.

Parina *Pharmasant, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Peri-articular disorders; skeletal muscle pain; tension headache.

Parinex *Inquifave, Venez.†.*
⊗ Propranolol (p.1381·1).
Angina pectoris; arrhythmias; hypertension.

Parinix *Richmond, Arg.†.*
Heparin (p.1301·2).

Parinorth *Itaca, Braz.†.*
Heparin (p.1301·2).
Thromboembolic disorders.

Paritrel *Trima, Israel.*
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; influenza A; parkinsonism.

Parixam *Apotex, Philipp.; Pharma 3, Philipp.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Parizac *Lacer, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcers; Zollinger-Ellison syndrome.

Parkadina *Basi, Port.*
Amantadine hydrochloride (p.792·3).
Creutzfeldt-Jakob disease; influenza A; parkinsonism.

Parkemed *Pfizer, Austria; Parke, Davis, Ger.†.*
Mefenamic acid (p.80·1).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Parkexin *Teuto, Braz.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Parkidopa *Cristalia, Braz.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Parkilyne *Generix, S.Afr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Parkinane *Eisai, Fr.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Parkinel *Bago, Arg.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Parkinil *Sanofi-Aventis, Pol.†.*
⊗ Selegiline (p.818·1).
Parkinsonism.

Parkinsan *Lundbeck, Ger.*
Budipine hydrochloride (p.801·3).
Parkinsonism.

Parkinsol *Teuto, Braz.*
Biperiden hydrochloride (p.797·2).
Parkinsonism.

Parkipan *Bioes, Fr.†.*
Trypan blue (p.2405·2); amylocaine hydrochloride (p.1853·3); titanium dioxide (p.1617·3).
Herpes labialis.

Parklen *Neo Quimica, Braz.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Parkopan *Hexal, Ger.; Hexal, Pol.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Parkotil *Lilly, Ger.; Lilly, Hung.†.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Parks *Hommel, Ger.†.*
Pridinol hydrochloride (p.1898·2).
Extrapyramidal disorders; parkinsonism.

Parlac *Pharmacia, Venez.†.*
Glucose; electrolytes (p.1672·2).
Oral rehydration.

Parlatos *Perez Gimenez, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Parlazin *Egis, Cz.; EGIS, Hung.; Egis, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Parlib *Enila, Braz.†.*
⊗ Gonadorelin (p.2106·2).
Female infertility.

Parlide *Pharmacia, Arg.†.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Parlodel *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Meda, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Meda, Gr.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Sandoz, Mex.; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Meda, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Meda, UK; Novartis, USA; Novartis, Venez.*
Bromocriptine mesilate (p.798·1).
Acromegaly; adenomas; amenorrhoea; benign breast disorders; female infertility; galactorrhoea; hyperprolactinaemia; lactation inhibition; male infertility; menstrual disorders; neuroleptic malignant syndrome; parkinsonism; polycystic ovary syndrome; prolactin-dependent male hypogonadism; prolactinoma.

Parmecal *Geymonat, Ital.†; Geymonat, Switz.†.*
Food for special diets (p.1922·1).
Colic; diarrhoea.

Parmodalin *SIT, Ital.*
Tranylcypromine sulfate (p.424·1); trifluoperazine hydrochloride (p.1034·2).
Depression.

Parmol *Hovid, Hong Kong.*
Paracetamol (p.108·1).
Fever; pain.

Par-Natal Plus 1 Improved *Parmed, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Parnate *Schering-Plough, Arg.†; Link, Austral.; GSK, Braz.; GSK, Canad.; GSK, Cz.†; Goldshield, Irl.; Boucher & Muir, NZ; Pharmafrica, S.Afr.; Goldshield, Spain; SmithKline Beecham, USA.*
Tranylcypromine sulfate (p.424·1).
Anxiety disorders; depression.

Parnon *Svizera, India.*
Trihexyphenidyl hydrochloride (p.820·2).
Extrapyramidal disorders.

Parnoxil *Biospray, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Paro aux fluorures d'amines Gelee *Esro, Switz.*
Sodium fluoride (p.1962·2); olaflur (p.1959·2); dectaflur (p.1937·1).
Dental caries prophylaxis.

Parocare *Esro, Switz.†.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Parocetan *Stada, Austria.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Parocin *CEPA, Spain.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Parocline *CSP, Fr.*
Minocycline hydrochloride (p.300·3).
Periodontal infections.

Parodium *Pierre Fabre Oral Care, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.*
Chlorhexidine gluconate (p.1635·3); rhubarb (p.1768·3); formaldehyde (p.1644·2).
Gum disorders; sensitive gums.

Parodontal *Serum-Werk Bernburg, Ger.*
Chamomile (p.2279·3); sage (p.2382·3); lidocaine (p.1862·3).
Mouth inflammation.

Parodontal F5 *Wernigerode, Cz.†.*
Salol (p.122·1); clove oil (p.2285·1); eugenol (p.2301·2); thymol (p.1664·3); sage oil (p.2382·3); spearmint oil (p.2391·3).
Mouth inflammation.

Parodontax
Note. This name is used for preparations of different composition.
Stafford-Miller, Braz.
Echinacea purpurea (p.2298·1); sodium bicarbonate (p.1673·2); chamomile (p.2279·3); myrrh (p.2349·2); rhatany root (p.2378·3).
Oral hygiene.

Madaus, Israel†.
Echinacea (p.2298·1); sodium bicarbonate (p.1673·2); chamomile (p.2279·3); myrrh (p.2349·2); rhatany (p.2378·3); sage oil (p.2382·3); peppermint oil (p.1761·2).
Dental disorders.

GSK Consumer, Ital.
Chlorhexidine (p.1635·2).
Oral hygiene.

GSK, Austria; GSK Consumer, Switz.†.
Mouthwash: Echinacea purpurea (p.2298·1); chamomile (p.2279·3); myrrh (p.2349·2); menthol (p.2340·1); clove oil (p.2285·1); caraway oil (p.2277·1); sage oil (p.2382·3); peppermint oil (p.1761·2); mint oil (p.2345·2).
Inflammation of the mouth and gums; oral hygiene.

GSK, Austria.
Toothpaste: Echinacea purpurea (p.2298·1); sodium bicarbonate (p.1673·2); chamomile (p.2279·3); myrrh (p.2349·2); rhatany root (p.2378·3); sage oil (p.2382·3); peppermint oil (p.1761·2).
Dental caries prophylaxis; oral hygiene.

GSK Consumer, Switz.†.
Toothpaste: Echinacea (p.2298·1); chamomile (p.2279·3); rhatany root (p.2378·3); myrrh (p.2349·2); sodium bicarbonate (p.1673·2); mint oil (p.2345·2); sage oil (p.2382·3).
Dental caries prophylaxis; oral hygiene.

Parodontax F *GSK Consumer, Switz.†.*
Sodium fluoride (p.1962·2); echinacea (p.2298·1); chamomile (p.2279·3); rhatany root (p.2378·3); myrrh (p.2349·2); sodium bicarbonate (p.1673·2); mint oil (p.2345·2); sage oil (p.2382·3).
Dental caries prophylaxis; periodontitis.

Parodontax Fluor *GSK, Arg.*
Echinacea purpura (p.2298·1); chamomile (p.2279·3); sage (p.2382·3); myrrh (p.2349·2); rhatany (p.2378·3); sodium bicarbonate (p.1673·2); sodium fluoride (p.1962·2).
Toothpaste.

Paroex *Pharmadent, Fr.*
Chlorhexidine gluconate (p.1635·3).
Bacterial mouth infections.

Parogen *Generics, Hung.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Parogencyl *Procter & Gamble, Ital.*
Metesculetol sodium (p.2343·2); dexpanthenol (p.2362·1).
Gum disorders.

Parogencyl Bi-Actif *Rider, Chile.*
Metesculetol sodium (p.2343·2); provitamin B.
Gum disorders.

Parogencyl gencives fragilisees *Sanofi Synthelabo OTC, Fr.†.*
⊗ Metesculetol sodium (p.2343·2); dexpanthenol (p.2362·1); alcohol (p.1625·2).
Gum disorders.

Parogencyl Gengive Delicate *Procter & Gamble, Ital.*
Metesculetol sodium (p.2343·2); chlorhexidine (p.1635·2).
Gum disorders.

Parogencyl prevention gencives *Procter & Gamble, Fr.*
Sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1); metesculetol sodium (p.2343·2).
Formerly contained sodium monofluorophosphate, vitamin E, chlorhexidine gluconate, sodium fluoride, and ginkgo biloba.
Gum disorders.

Parogencyl sensibilite gencives *Procter & Gamble, Fr.*
Chlorhexidine gluconate (p.1635·3); metesculetol sodium (p.2343·2).
Gum disorders.

Paroglax *GSK, Austria.*
Paroxetine (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorders; post-traumatic stress disorder; social anxiety disorder.

Parol *Atabay, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Parol Cold *Atabay, Turk.*
Paracetamol (p.108·1); phenylpropanolamine (p.1569·2).
Fever; pain.

Parolex *Hexal, Cz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

ParoLich *Winthrop, Ger.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobias.

Paroma *Sanovel, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Paromerck *Generics, Pol.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Paronal *Christiaens, Belg.; Nycomed, Neth.*
Asparaginase (p.682·1).
Acute lymphocytic leukaemia.

Paronex *Sandoz, Switz.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Paroplak *Procter & Gamble, Fr.*
Chlorhexidine gluconate (p.1635·3); polysorbate 20 (p.1919·1); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Paroser *Pinewood, Irl.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Paroticin *Adelco, Gr.*
Fludrocortisone (p.1530·1); lidocaine (p.1862·3); polymyxin B (p.318·2).
Ear infections.

Parotin *Cipla, India.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Parotur *Cantabria, Spain†.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; social phobia.

Paroven *Novartis Consumer, Austral.; Novartis Consumer, NZ; Novartis Consumer, S.Afr.; Novartis Consumer, UK.*
Oxerutins (p.2304·3).
Chronic venous insufficiency; haemorrhoids; prevention of skin and mucosal reactions to radiotherapy.

Parox
Note. A similar name is used for preparations of different composition (see below).
Teuto, Braz.; Rowex, Irl.
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Parox Meltab
Note. A similar name is used for preparations of different composition (see above).
Saval, Chile.
Paracetamol (p.108·1).
Fever; pain.

Paroxat *Hexal, Austria; Hexal, Ger.; GSK, Hung.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorders; post-traumatic stress disorder; social phobia.

Paroxedura *Merck dura, Ger.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Paroxetop *Streuli, Switz.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Paroxiflex *Stada, Swed.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social anxiety disorder.

Parpicillin *Prafa, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Parsal *Riemser, Ger.*
Ibuprofen (p.64·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Parsel
Note. This name is used for preparations of different composition.
Novartis, Arg.†; Novartis, Chile†; Novartis, Mex.; Novartis, Venez.
Dihydroergotamine mesilate (p.618·2); paracetamol (p.108·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Novartis Consumer, Port.
Paracetamol (p.108·1).
Fever; pain.

Parsilid *Crinos, Ital.†.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Parsimonil *Fabra, Arg.†.*
Flunitrazepam (p.996·2).

Parsistene *Boehringer Ingelheim, Chile†.*
⊗ Fenoterol hydrobromide (p.1121·1).
Premature labour.

Parsitan *Erfa, Canad.*
Profenamine hydrochloride (p.815·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Parsolen *Giempi, Venez.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Parstelin *Novartis, Venez.†.*
Paracetamol (p.108·1).
Fever; pain.

Partamol *Atlantic, Malaysia; Atlantic, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Partane *Taro, Israel.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Partial *Vocate, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Particol *Prafa, Indon.*
⊗ Hydrocortisone acetate (p.1535·2); chloramphenicol (p.239·3).
Infected skin disorders.

Partoben *Purissimus, Arg.*
An anti-D immunoglobulin (p.2204·2).
Immune thrombocytopenic purpura; prevention of rhesus sensitisation.

Partobulin *Baxter, Austria; Immuno, Austria; Baxter, Cz.; Baxter BioScience, Ger.; Baxter, Hong Kong; Baxter, Ital.; Baxter, Pol.; Eczacibasi-Baxter, Turk.; Baxter, UK.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Partogama *Immuno, Braz.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Partogamma *Baxter Immuno, Arg.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Parto-Gamma *Kedrion, Ital.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Partusisten *Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Rus.*
⊗ Fenoterol hydrobromide (p.1121·1).
Fetal distress; premature labour.

Parvemaxol *Chefaro, Neth.*
Clotrimazole (p.530·1).
Tinea pedis.

Parven *Gelpharma, Mex.†.*
Benzonatate (p.1552·1).
Coughs.

Parvid *Genesis, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Parvisedil *SIT, Ital.*
Aminohydroxybutyric acid (p.471·2); valerian (p.2410·1); passion flower (p.2363·2); chamomile (p.2279·3); crataegus (p.2289·1).
Restlessness and insomnia in infants.

Parvlex *Freeda, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B substances with vitamin C (p.1922·1).
Iron-deficiency anaemias.

Parvodex *Jagson, India.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Parvolex *Mayne, Austral.; Bioniche, Canad.; IFET (ΙΦΕΤ), Gr.; Mayne, Hong Kong; UCB, Irl.; Mayne, Malaysia; Mayne, NZ; GSK, S.Afr.; UCB, UK.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory-tract congestion.

Parvon *Jagson, India.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Parvon Forte *Jagson, India.*
Dextropropoxyphene hydrochloride (p.40·1); diclofenac sodium (p.44·3); paracetamol (p.108·1).
Formerly contained dextropropoxyphene hydrochloride and ibuprofen.
Inflammation; rheumatism.

Parvon-N *Jagson, India.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Parvon-Spas *Jagson, India.*
Dextropropoxyphene hydrochloride (p.40·1); dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1).
Smooth muscle spasm.

Parxium *Monte Verde, Arg.*
Pramipexole (p.814·2).
Parkinsonism.

PAS *Kocak, Turk.*
Sodium aminosalicylate (p.201·2).
Tuberculosis.

PAS Sodium *Atlantic, Thai.*
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Pasaden *Schering, Ital.*
Etizolam (p.996·1).
Anxiety; insomnia.

Pasalen *Pharmaland, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Pasalix *Marjan, Braz.*
Passion flower (p.2363·2); salix (p.121·3); crataegus (p.2289·1).
Sedative.

Pascalium *Pharmaten (Φαρματεν), Gr.*
Bromazepam (p.964·3).
Anxiety disorders.

Pascallerg *Pascoe, Ger.*
Homoeopathic preparation.

Pascobilin novo *Pascoe, Ger.†.*
Peppermint leaf (p.1761·2); taraxacum (p.2395·1); cynara (p.2291·2).
Biliary-tract disorders.

Pascofemin *Pascoe, Ger.*
Homoeopathic preparation.

Pascoletten N *Pascoe, Ger.†.*
Aloes (p.1705·2); chamomile (p.2279·3).
Constipation.

Pascoleucyn N *Pascoe, Ger.*
Homoeopathic preparation.

Pascolibrin *Pascoe, Ger.*
Homoeopathic preparation.

Pascomag *Pascoe, Ger.†.*
Bismuth subnitrate (p.1711·2); chamomile (p.2279·3); linseed (p.2333·3).
Gastrointestinal disorders.

Pascomucil *Pascoe, Ger.*
Ispaghula (p.1737·1).
Constipation.

Pasconal forte Nerventropfen *Pascoe, Ger.†.*
Homoeopathic preparation.

Pasconal Nerventropfen *Pascoe, Ger.*
Homoeopathic preparation.

Pasconeural-Injektopas *Pascoe, Ger.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Pascopankreat *Pascoe, Ger.*
Combination pack: Yellow tablets, absinthium (p.2244·1); condurango (p.2287·1); red tablets, pancreatin (porcine) (p.2360·1).
Digestive system disorders.

Pascopankreat novo *Pascoe, Ger.†.*
Caraway oil (p.2277·1); chamomile oil (p.2279·3); condurango (p.2287·1); milk thistle (p.1452·1); fennel (p.2302·3).
Gastrointestinal disorders.

Pascorenal N *Pascoe, Ger.*
Homoeopathic preparation.

Pascosabal *Pascoe, Ger.*
Homoeopathic preparation.

Pascosedon *Pascoe, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3).
Anxiety; sleep disorders.

Pascotox forte-Injektopas *Pascoe, Ger.†.*
Echinacea (p.2298·1).
Tonic.

Pascotox mono *Pascoe, Ger.†.*
Echinacea (p.2298·1).
Tonic.

Pascotox Purpurea *Pascoe, Ger.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Pascovegeton *Pascoe, Ger.†.*
Angelica (p.2258·1).
Gastrointestinal disorders.

Pascoventral *Pascoe, Ger.*
Peppermint leaf (p.1761·2); chamomile (p.2279·3); caraway (p.2276·3).
Gastrointestinal disorders.

Pasedon *Lensa, Spain.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Pasem *Monserrat, Arg.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Callosities; verrucas; warts.

Paser *Jacobus, USA.*
Aminosalicylic acid (p.201·2).
Tuberculosis.

Pasetocin *Kyowa, Jpn.*
Amoxicillin (p.202·2).
Bacterial infections.

Pas-Fatol N *Fatol, Ger.*
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Pasic *Cristalia, Braz.*
Passion flower (p.2363·2); salix (p.121·3); crataegus (p.2289·1).
Anxiety.

Pasidor *Cafar, Venez.*
Passion flower (p.2363·2); valerian (p.2410·1); crataegus (p.2289·1).
Anxiety; sleep disorders.

Pasifen *Andromaco, Chile†.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Pasifluidina *Gache, Venez.*
Passion flower (p.2363·2); valerian (p.2410·1); crataegus (p.2289·1).
Insomnia; nervous disorders.

Pasil *Toyama, Jpn.*
Pazufloxacin mesilate (p.313·2).
Bacterial infections.

Pasinordin *Nordin, Mex.*
Chamomile (p.2279·3); passion flower (p.2363·2); valerian (p.2410·1).
Nervous disorders.

Pasisana *Riemser, Ger.†.*
Herbal and homoeopathic preparation.

Pasivital h *Riemser, Ger.†.*
Homoeopathic preparation.

Pask-Akri *Akrikhin, Rus.*
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Pasmalgin *Ibefar, Braz.†.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3).
Pain; smooth muscle spasm.

Pasminox *Beta, Arg.*
Otilonium bromide (p.2359·1).
Smooth muscle spasm.

Pasminox Somatico *Beta, Arg.*
Otilonium bromide (p.2359·1); diazepam (p.986·3).
Muscle spasm.

Pasmocalm *Bago, Chile†.*
Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Pasmodil *Collins, Mex.*
Dipyrone (p.49·2); butylhyoscine (p.1735·1).
Fever; pain.

Pasmodina *Drawer, Arg.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Pasmodina Compuesta *Drawer, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm.

Pasmolit *Jofrain, Mex.*
Homatropine (p.1881·2).

Pasmosedan *Montpellier, Arg.†.*
Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Pasmosedan Compuesto *Montpellier, Arg.†.*
Pargeverine hydrochloride (p.1761·1); metamizole magnesium (p.49·3).
Smooth muscle spasm.

Pasmovit *Finadiet, Arg.*
Phloroglucinol (p.2366·3) with or without trimethylphloroglucinol (p.2366·3).
Formerly contained hyoscine.
Smooth muscle spasm and pain.

Pasodron *Rider, Chile.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Paspat
Note. This name is used for preparations of different composition.
Sankyo, Braz.†; Sankyo, Ger.†; Altana, Mex.
Staphylococcus aureus; *Staphylococcus epidermidis*; *Streptococcus viridans*; *Streptococcus haemolyticus*; *Streptococcus pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*; *Candida albicans*.
Respiratory-tract infections.

Sankyo, Ital.
Lysate of *Staphylococcus aureus*; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Paspat Oral *Sankyo, Port.*
Staphylococcus aureus; *Streptococcus mitis*; *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Paspertase *Solvay, Austria; Solvay, Ger.†.*
Metoclopramide hydrochloride (p.1747·3); pancreatin (p.2360·1).
Gastrointestinal disorders.

Paspertin *Solvay, Austria; Solvay, Ger.; Solvay, Hung.†; Solvay, Switz.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting; preparation for gastrointestinal radiography.

Pasquam *Sanbe, Indon.*
Dexpanthenol (p.2362·1).
Wounds.

Pasrin *Pharmacare, S.Afr.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders; mixed anxiety depressive states.

Passacanthine *Lafage, Arg.†.*
Belladonna (p.2263·3); convallaria (p.2287·3); crataegus (p.2289·1); passion flower (p.2363·2).
Muscle spasm; nervous disorders.

Passagen *Sandoz, Denm.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Passagix *Obolenskoe, Rus.*
Domperidone (p.1726·2).
Nausea and vomiting.

Passaja *Farmabraz, Braz.†.*
Thymol (p.1664·3); menthol (p.2340·1); camphor (p.2273·2); eugenol (p.2301·2); procaine hydrochloride (p.1869·1).
Oral hygiene.

Passaneuro
Note. This name is used for preparations of different composition.
Bunker, Braz.
Oral suspension: Passion flower (p.2363·2); erythrina mulungu (p.2348·1); melissa (p.2339·3).
Sedative.

Bunker, Braz.
Tablets: Passion flower (p.2363·2); erythrina mulungu (p.2348·1); chamomile (p.2279·3).
Sedative.

Passedan
Note. This name is used for preparations of different composition.
Austroplant, Austria.
Passion flower (p.2363·2); melissa leaf (p.2339·3).
Dystonias; menopausal disorders; sleep disorders.

Austroplant, Cz.
Passion flower (p.2363·2); melissa (p.2339·3); sweet orange peel (p.2357·2); cinnamon (p.2283·1).
Nervous-system disorders.

Passedyl *Urgo, Fr.*
Sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Passelyt
Note. This name is used for preparations of different composition.
Gebro, Austria.
Passion flower (p.2363·2); melissa leaf (p.2339·3).
Anxiety disorders; sleep disorders.

Gebro, Switz.
Passion flower (p.2363·2).
Nervous disorders; sleep disorders.

Passi Catha *Sedabel, Braz.†.*
Passion flower (p.2363·2); crataegus (p.2289·1); salix (p.121·3).
Sedative.

Passibil *Hasco-Lek, Pol.*
Crataegus (p.2289·1); ginkgo biloba (p.2311·1); passion flower (p.2363·2).
Cerebrovascular disorders; mental function impairment; nervous disorders; vertigo.

Passicalm *Gemballa, Braz.†.*
Passion flower (p.2363·2); valerian (p.2410·1); erythrina mulungu (p.2348·1).

Passidon *Ardeypharm, Ger.*
Passion flower (p.2363·2).
Nervous disorders.

Passidorm *DHU, Rus.*
Homoeopathic preparation.

Passifit *Farmstandart, Rus.*
Valerian (p.2410·1); lupulus (p.2335·2); thyme (p.2401·1); crataegus (p.2289·1); mint (p.1761·2).
Insomnia; nervous disorders.

Passiflor *Phytofarm Kleka, Pol.*
Passion flower (p.2363·2).
Insomnia; nervous disorders.

Passiflora *Tamar, Israel.*
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1); orange flower (p.2357·1).
Insomnia; nervousness; tension.

Passiflora Complex
Note. This name is used for preparations of different composition.
Blackmores, Austral.†.
Passion flower (p.2363·2); lupulus (p.2335·2); skullcap (p.2388·2); valerian (p.2410·1); multivitamins (p.1922·1).
Anxiety; insomnia; stress symptoms.

Dolisos, Canad.
Homoeopathic preparation.

Passiflora Compose *Boiron, Fr.†.*
Homoeopathic preparation.

Passiflora Composta *Infabra, Braz.†.*
Crataegus (p.2289·1); erythrina mulungu (p.2348·1); passion flower (p.2363·2).
Sedative.

Passiflora Compound *Vitamed, Israel.*
Passion flower (p.2363·2); valerian (p.2410·1).
Anxiety; insomnia; tension.

Passiflora Curarina *Harras-Curarina, Ger.*
Passion flower (p.2363·2).
Agitation.

Passiflora GHL *Lehning, Fr.*
Homoeopathic preparation.

Passiflorin *Austroplant, Austria.*
Passion flower (p.2363·2).
Nervous disorders; sleep disorders.

Passiflorine
Note. This name is used for preparations of different composition.
Millet Roux, Braz.; Teofarma, Ital.
Passion flower (p.2363·2); crataegus (p.2289·1); salix alba (p.121·3).
Insomnia; sedative.

Jolly-Jatel, Fr.; Chiesi, Spain.
Passion flower (p.2363·2); crataegus (p.2289·1).
Anxiety; insomnia; menopausal disorders; nervous disorders.

Passiflorum *Zuoz, Venez.*
Passion flower (p.2363·2); crataegus (p.2289·1); willow (p.121·3).
Sleep disorders.

Passifuril *Millet Roux, Braz.*
Nifuroxazide (p.307·2).
Diarrhoea.

Passilex *Luper, Braz.†.*
Passion flower (p.2363·2); erythrina mulungu (p.2348·1); melissa (p.2339·3).
Anxiety.

Passilin *Galenogal, Braz.†.*
Benzocaine (p.1854·1); tyrothricin (p.358·2).

Passin *Simons, Ger.*
Crataegus (p.2289·1); passion flower (p.2363·2).
Nervous cardiovascular disorders.

Passinevryl *Clement Thionville, Fr.*
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1).
Insomnia; nervous disorders.

Passionflower Plus *Eagle, Austral.*
Passion flower (p.2363·2); valerian (p.2410·1); skullcap (p.2388·2); lupulus (p.2335·2).
Anxiety; insomnia.

Passispasmin *Herbapol Lublin, Pol.*
Crataegus (p.2289·1); lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Passispasmol *Herbapol Lublin, Pol.*
Crataegus (p.2289·1); lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Pasta Arsenicale *Ogna, Ital.*
⊗ Arsenic trioxide (p.2260·2); lidocaine (p.1862·3); ephedrine hydrochloride (p.1558·2).
Dental disorders.

Pasta boli *Spirig, Switz.*
Salicylic acid (p.1612·2); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pasta Cool *Apomedica, Austria.*
Heparin sodium (p.1301·2); salicylic acid (p.1612·2).
Musculoskeletal and joint disorders; peri-articular disorders; soft-tissue injury.

Pasta d'Agua *Sedabel, Braz.†.*
Zinc oxide (p.1621·2); purified talc (p.1615·2); glycerol (p.2314·2); agua de cal.
Skin disorders.

Pasta Dermic *ICN, Arg.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Pasta Devitalizzante *Ogna, Ital.*
Paraformaldehyde (p.1655·2); lidocaine (p.1862·3).
Dental disorders.

Pasta Dicofarm *Dicofarm, Ital.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3); vitamin E (p.1992·2); vitamin F (p.2308·2).
Skin irritation.

Pasta Iodoformica Radiopaca *Ogna, Ital.*
Iodoform (p.1650·2); parachlorophenol (p.1655·2); camphor (p.2273·2); menthol (p.2340·1).
Dental root canal infections.

Pasta Kappa *Italzama, Ital.*
Barrier preparation.

Pasta Lassar *Valma, Chile; Volta, Chile.*
Zinc oxide (p.1621·2); wool fat (p.2033·2); white soft paraffin (p.2031·2).
Skin disorders.

Pasta de Lassar *Andromaco, Mex.; IQFA, Mex.; Quimica y Farmacia, Mex.*
Zinc oxide (p.1621·2).
Barrier preparation; burns; skin disorders; wounds.

Pasta Lassar Imba *Perez Gimenez, Spain.*
Almond oil (p.2252·2); lanolin; zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Pasta rubra salicylata *Apomedica, Austria.*
Diethylamine salicylate (p.47·2); salicylic acid (p.1612·2); methyl salicylate (p.85·3).
Gout; rheumatism; sciatica; soft-tissue injury; tendinitis.

Pastiglie Valda *Valda, Ital.†.*
Cicliomenol (p.1640·3); enoxolone (p.50·1); menthol (p.2340·1); cineole (p.2282·3).
Catarrh; mouth and throat irritation.

Pastilhas Valda *Canonne, Braz.*
Menthol (p.2340·1); cineole (p.2282·3).
Mouth disorders.

Pastillas De Ambay *Weltrap, Arg.*
Ambay; sulfogaiacol (p.1573·2).
Cough.

Pastillas Antisep Garg L *Procter & Gamble, Spain.*
Ascorbic acid (p.1983·3); cetylpyridinium chloride (p.1635·1); citric acid (p.2284·1); menthol (p.2340·1).
Throat irritation.

Pastillas Antisep Garg M *Procter & Gamble, Spain.*
Camphor (p.2273·2); benzyl alcohol (p.1631·3); tolu balsam (p.1574·2); thymol (p.1664·3); menthol (p.2340·1); eucalyptus (p.2301·2); cetylpyridinium chloride (p.1635·1).
Throat irritation.

Pastillas Dr Andreu *Bayer, Spain.*
Dextromethorphan hydrobromide (p.1555·2); sodium benzoate.
Coughs.

Pastillas Juanola *Farma Lepori, Spain†.*
Cineole (p.2282·3); liquorice (p.1740·3); terpineol (p.2396·1); menthol (p.2340·1).
Coughs; throat irritation.

Pastillas Koki Ment Tiro *Perez Gimenez, Spain.*
Benzocaine (p.1854·1); tyrothricin (p.358·2); menthol (p.2340·1).
Mouth and throat disorders.

Pastillas Lorbi *Bioquimico, Arg.*
Allantoin (p.1588·1); benzocaine (p.1854·1); sulfadiazine (p.336·2).
Mouth and throat disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pastillas Medex *Sidus, Arg.*
Tolu balsam (p.1574·2); benzocaine (p.1854·1); hexylresorcinol (p.1647·1); allantoin (p.1588·1); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Coughs; sore throat.

Pastillas Pectoral Kely *Boots Healthcare, Spain.*
Cineole (p.2282·3); niaouli oil (p.2351·3); senega (p.1572·3); liquorice (p.1740·3); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); terpin monohydrate (p.1573·3).
Respiratory-tract disorders.

Pastilles bronchiques S nouvelle formule *Hanseler, Switz.*
Drosera (p.2297·3); liquorice (p.1740·3); ribwort plantain (p.2379·1); menthol (p.2340·1); anise oil (p.2258·2).
Respiratory-tract congestion.

Pastilles Emser *Siemens, Switz.†.*
Sel d'ems.
Respiratory-tract disorders.

Pastilles Medicinales Vicks *Procter & Gamble, Fr.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); thymol (p.1664·3); tolu balsam (p.1574·2); benzyl alcohol (p.1631·3).
Sore throats.

Pastilles Monleon *Toulade, Fr.*
Methylthioninium chloride (p.1450·3); tolu balsam (p.1574·2); drosera (p.2297·3); hamamelis (p.2318·2).
Mouth and throat disorders.

Pastilles pectorales Demo N *Vifor, Switz.*
Drosera (p.2297·3); ivy (p.2328·1); ipecacuanha (p.1562·3); plantain (p.2369·3); tolu balsam (p.1574·2); anise oil (p.2258·2); orange peel (p.2357·1); eucalyptus oil (p.2301·2); mint oil (p.2345·2); menthol (p.2340·1).
Coughs.

Pastilles pour la gorge formule 535 *Iromedica, Switz.†.*
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Pastrizol *DNA, Mex.*
Omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pastylki Wykrztusne *GSK, Pol.*
Liquorice (p.1740·3); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Pasuma-Dragees *Herchemie, Austria.*
⊗ Methyltestosterone (p.2117·1); alpha tocoferil acetate (p.1992·3); yohimbine hydrochloride (p.2200·2); strychnine glycerophosphate; caffeine (p.1116·3); oxedrine tartrate (p.1364·3).

Pataday *Alcon, USA.*
Olopatadine hydrochloride (p.586·3).
Allergic conjunctivitis.

Patanol *Alcon, Arg.; Alcon, Austral.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Hong Kong; Alcon, Indon.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Pacific, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Olopatadine hydrochloride (p.586·3).
Allergic conjunctivitis.

Pataxel *Vianex (Βιανέξ), Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Pat-Chobet *Chobet, Arg.*
Animal tissue extracts (p.2337·3).
Liver disorders.

Pate a l'Eau Roche-Posay *Roche-Posay, Fr.†.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3); borax (p.2268·1).
Eczema.

Patector *AF, Mex.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Endometrial hyperplasia; endometriosis; female infertility; injectable contraceptive; menstrual disorders.

Patentex *Medra, Austria; Merz, Fin.; PCR, Ger.†; Merz, Hong Kong; Merz, Hung.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Patentex Oval *Merz Consumer, Ger.; Merz, Pol.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Patentex Oval N *Merz, Cz.; Merz, Rus.; Merz, Switz.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Pates Pectorales *UPSA Conseil, Fr.*
Terpin hydrate (p.1573·3); tolu balsam (p.1574·2); cherry-laurel.
Respiratory-tract congestion.

Patox *Wermar, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Patriflex *Largen, Philipp.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Patropin *Rekah, Israel.*
Papaverine hydrochloride (p.2191·3); atropine sulfate (p.1219·3).
Smooth muscle spasm.

Patryl *Biolink, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Patuxan *Collins, Mex.*
Vitamin preparation (p.1922·1).

Pauly *Milupa, Ital.*
Gluten-free foods for special diets (p.1922·1).

Pausafren T *Finadiet, Arg.*
Oxazepam (p.1014·2).
Anxiety.

Pausanol *Leiras, Fin.*
Estriol (p.2101·1).
Menopausal vaginal disorders; oestrogen deficiency.

Pausedal *Alter, Spain.*
Levosulpiride (p.1028·3).
Dyspepsia.

Pausene *Theramex, Ital.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; cyproterone acetate (p.2088·2).
Formerly known as Pausal.
Menopausal disorders.

Pausicaps *Gelcaps, Mex.†.*
Soya isoflavones (p.2391·2).
Menopausal disorders.

Pausigin *Lepori, Port.*
Estriol (p.2101·1).
Vulvovaginal disorders.

Pausogest *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Pavabid *Hoechst Marion Roussel, USA†.*
Papaverine hydrochloride (p.2191·3).
Cerebral and peripheral ischaemia; smooth muscle spasm.

Pavacol-D *Ransom, UK.*
Pholcodine (p.1570·2).
Coughs.

Pavedal *Pharma Investi, Chile.*
⊗ Metolazone (p.1337·2).
Ascites; heart failure; hypertension; nephrotic syndrome; oedema.

Paver *Wermar, Mex.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Paveriwern *Wernigerode, Ger.*
Papaver somniferum.
Gastrointestinal spasm.

Pavertrin *Duncan, Arg.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Paverysat forte N *Ysatfabrik, Ger.*
Greater celandine (p.2317·1).
Biliary-tract and gastrointestinal spasm.

Pavivac *Sevapharma, Cz.*
A mumps vaccine (Jeryl Lynn strain) (p.2225·1).
Active immunisation.

Pavlinox *Medicus, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Pavulon *Organon, Arg.; Organon, Austral.; Organon, Braz.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.†; Organon, Indon.; Organon Teknika, Irl.†; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Port.†; Sanofi Synthelabo, S.Afr.; Organon, Singapore; Organon, Spain†; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, USA†; Organon, Venez.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Pawa-Rutan *Hanosan, Ger.†.*
Homoeopathic preparation.

Pax *Pharmacare, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; premedication.

Paxabel *Marvecs, Ital.*
Macrogol 4000 (p.2336·3).
Constipation.

Paxadorm *Alliance, S.Afr.*
Nitrazepam (p.1011·2).
Insomnia.

Paxam *Alphapharm, Austral.; Pacific, NZ.*
Clonazepam (p.478·2).
Epilepsy.

Paxapride *Sandoz, Arg.*
Cinitapride acid tartrate (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Paxel *Cristalia, Braz.†.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Paxeladine *Beaufour, Fr.*
Oxeladin citrate (p.1567·1).
Coughs.

Paxene *Mayne, Belg.; Norton, Cz.; Faulding, Fr.; Gerolymatos, Gr.; Norton, Hung.; Mayne, Irl.; Mayne, Ital.; Norton, Neth.; Mayne, Port.; Ivax, Rus.; Combino, Spain; Mayne, Swed.; Mayne, UK.*
Paclitaxel (p.759·1).
Breast cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer.

Paxeratio *Ratiopharm, Pol.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Paxetil *Medibial, Port.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Paxical *Intramed, S.Afr.*
Droperidol (p.994·3).
Nausea and vomiting; neuroleptanalgesia; premedication.

Paxidal
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain and associated tension.

Wallace Mfg Chem., UK.
Caffeine (p.1116·3); meprobamate (p.1006·2); paracetamol (p.108·1).

Paxidorm *Pharmaserve, Singapore; Norma, UK.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Paxil *GSK, Arg.; GSK, Canad.; GSK, Jpn; GSK, Mex.; GSK, Rus.; GSK, S.Afr.; GSK, Turk.; GSK, USA; GSK, Venez.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Paxilfar *Tecnifar, Port.*
Tramadol hydrochloride (p.130·3).
Pain.

Paximol *ICM, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Paxirasol *Egis, Cz.; EGIS, Hung.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Paxium *Jaba, Port.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety; muscle spasm.

Paxon
Note. This name is used for preparations of different composition.
Gador, Arg.
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Saval, Chile.
Buspirone hydrochloride (p.965·3).
Anxiety.

Paxon-D *Gador, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Paxoral *Farmasa, Braz.*
Lysate of: *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Diplococcus pneumoniae*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Paxt *Gerard, Irl.*
Paroxetine hydrochloride (p.414·2).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Paxtibi *Biomed, Spain.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Paxtin *Hexal, Pol.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; social phobia.

Paxtine *Alphapharm, Austral.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Paxtrat *Uniao Quimica, Braz.*
Paroxetine hydrochloride (p.414·2).
Depression.

Paxum *East India Pharma, India.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; insomnia; muscle spasm; premedication; status epilepticus; tetanus.

Paxus *Kalbe, Indon.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Paxxet *Unipharm, Israel.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorders.

Paxyl *Faulding, Austral.*
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3); benzalkonium chloride (p.1629·1); allantoin (p.1588·1).
Burns; chapped skin; insect bites; skin abrasions; sunburn; windburn.

Payasanit gastro *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Pazbronquial *Cinfa, Spain.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); sodium citrate (p.1673·3); sulfogaiacol (p.1573·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); menthol (p.2340·1); drosera (p.2297·3); lobelia inflata (p.2157·2); oregano (p.2357·3); grindelia (p.2317·2).
Coughs.

Pazergicel *Proel, Gr.†.*
Etofenamate (p.53·1).
Inflammatory disorders; pain.

Pazeril *Proel, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Pazital *Gebro, Spain.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Pazo *Bristol-Myers Products, USA.*
⊗ Benzocaine (p.1854·1); ephedrine sulfate (p.1558·2); zinc oxide (p.1621·2); camphor (p.2273·2).
Haemorrhoids.

Pazolam *Atral, Port.*
Alprazolam (p.960·1).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Pazolini *Faria, Braz.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Pazucross *Mitsubishi, Jpn.*
Pazufloxacin mesilate (p.313·2).
Bacterial infections.

PB Gel *Lagos, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

PBM Allergy *Boca, USA.*
Brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

PC *Grin, Mex.*
Glycerol (p.2314·2).
Dry eyes.

PC-20 *Millimed, Thai.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

PC 30 V *Terra-Bio, Ger.*
Aesculus (p.2248·2); dexpanthenol (p.2362·1); chamomile (p.2279·3).
Skin disorders; ulcers; wounds.

PC 30 N *Terra-Bio, Ger.*
Chamomile (p.2279·3).
Burns; skin disorders.

PC Regulax *Procare, Austral.†.*
Peppermint leaf (p.1761·2); ispaghula (p.1737·1); slippery elm (p.2388·2); ginger (p.1732·3); pectin (p.2145·2).
Gastrointestinal disorders; haemorrhoids; hyperlipidaemias; varicose veins.

PC Rei-shi *Procare, Austral.†.*
Rei-shi; shi-taki.
Nutritional supplement.

PC-Cap *Alra, USA.*
Dextropropoxyphene hydrochloride (p.40·1); aspirin (p.20·3); caffeine (p.1116·3).

PCE *Abbott, Canad.; Abbott, Hong Kong†; Abbott, USA.*
Erythromycin (p.269·2).
Bacterial infections.

PCF N *Ritsert, Ger.*
Homoeopathic preparation.

PCL *Hoe, Singapore†.*
Codeine phosphate (p.37·2); promethazine (p.588·2).
Coughs.

PCM
Note. This name is used for preparations of different composition.
Hemopharm, Ger.
Paracetamol (p.108·1).
Fever; pain.

Cypress, USA.
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Rhinitis.

PC-Tar *Geritrex, USA.*
Coal tar (p.1616·2).
Scalp disorders.

PDF *Pharmascience, Canad.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

PDP Liquid Protein *Wesley, USA.*
Tryptophan (p.427·1); hydrolysed animal collagen (p.2286·1).
Dietary supplement.

PE *Alcon, USA†.*
⊗ Pilocarpine hydrochloride (p.1884·3); adrenaline acid tartrate (p.1203·2).
Glaucoma; raised intra-ocular pressure.

Peace *YSP, Malaysia.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Peacef *Yung Shin, Singapore.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Pearsol *Pearson, Ital.*
Pyrethrum (p.2049·3).
Insecticide.

Pebegal *Probiomed, Mex.*
Benzonatate (p.1552·1).
Coughs.

Pebenal *Rowe-Fleming, Venez.†.*
Oxacillin (p.312·1).
Bacterial infections.

Pebencil *Valmor, Venez.†.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Pebiot *Mavi, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

PEC *Universal, Hong Kong.*
⊗ Promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2).
Coughs.

Pecasolin *Rafarm, Gr.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Pe-Ce *Gebro, Austria.*
Turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); camphor (p.2273·2); thymol (p.1664·3).
Coughs and cold symptoms.

Peceve *Ipex, Swed.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pecivax *Farmaceutica H, Mex.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Pec-Kao *Corsalud, Venez.†.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Pecof *Glenmark, Philipp.*
⊗ Salbutamol sulfate (p.1131·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with bronchospasm.

Pecol *Casen Fleet, Port.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Pectal *Sedabel, Braz.†.*
Sodium dibunate (p.1573·1); aconite (p.2246·1); cineole (p.2282·3); grindelia (p.2317·2); mikania glomerata; senega (p.1572·3).
Coughs.

Pectapas *Pascoe, Ger.*
Homoeopathic preparation.

Pectin-K *PD Pharm, S.Afr.*
Kaolin (p.1738·1); apple pectin (p.2145·2).
Diarrhoea.

Pecto-Baby *Vifor, Switz.*
Guaifenesin (p.1561·3); pholcodine (p.1570·2); chlorphenamine maleate (p.571·3).
Coughs.

Pectobal Dextro *Clariana, Spain†.*
Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2).
Respiratory-tract disorders.

Pectobonisol *Bonimed, Pol.*
Echinacea purpurea (p.2298·1); liquorice (p.1740·3); peppermint leaf (p.1761·2); ribwort plantain (p.2379·1); thyme (p.2401·1); tilia (p.2402·2).
Respiratory-tract disorders.

Pectobron *Sidus, Arg.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); calcium, sodium and potassium hypophosphite; senega (p.1572·3); tolu balsam (p.1574·2).
Formerly contained sulfogaiacol, sodium benzoate, chlorphenamine maleate, senega, and tolu balsam.
Bronchitis.

Pectobronc *Pediapharm, Chile.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Pectobronc Plus *Pediapharm, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough and cold symptoms.

Pectocalmine *Vifor, Switz.*
⊗ Codeine phosphate (p.37·2); guaifenesin (p.1561·3); ephedrine hydrochloride (p.1558·2); opium (p.105·1); senega (p.1572·3).
Coughs and associated respiratory-tract disorders.

Pectocalmine Junior N *Vifor, Switz.*
Codeine phosphate (p.37·2); tolu balsam (p.1574·2); red-poppy; anethole (p.2258·1).
Coughs and associated respiratory-tract disorders.

Pectocold *Novum, Neth.*
Carbocisteine (p.1553·2).
Cough.

Pectocor N *Riemser, Ger.*
Camphor (p.2273·2).
Cardiac disorders.

Pectoderme *Dolisos, Fr.†.*
α-Pinene (p.2368·3); β-pinene (p.2368·3); myrtol (p.2349·3); lavender oil (p.2331·2); terpineol (p.2396·1); eugenol (p.2301·2); camphor (p.2273·2); cineole (p.2282·3).
Respiratory-tract congestion.

Pectodrill *Pierre Fabre, Cz.; Pierre Fabre, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion; respiratory-tract disorders associated with viscous secretions.

PectoDrill *Pierre Fabre, Pol.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Pectofree *Novum, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Pectomucil *Qualiphar, Belg.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning; respiratory-tract disorders associated with viscous secretions.

Pectoral *Mepha, Hong Kong†.*
Ipecacuanha (p.1562·3); ribwort plantain (p.2379·1); cowslip (p.2372·2); quillaia (p.1920·1); thyme (p.2401·1); senega (p.1572·3).
Coughs.

Pectoral Hebert *Fecofar, Arg.*
Clofedanol hydrochloride (p.1554·2); bromhexine hydrochloride (p.1552·2).
Coughs.

Pectoral Lafedar *Lafedar, Arg.*
Sulfogaiacol (p.1573·2); oxeladin (p.1567·1).
Cough.

Pectoral Lafedar Ninos *Lafedar, Arg.*
Sulfogaiacol (p.1573·2).
Cough.

Pectoral N *Mepha, Switz.*
Plantain (p.2369·3); cowslip (p.2372·2); senega (p.1572·3); thyme (p.2401·1).
Cold symptoms; coughs.

Pectoral Pagliano *Lacefa, Arg.†.*
Bromhexine (p.1552·2).
Formerly contained sodium benzoate and sulfogaiacol.
Coughs.

Pectoral Pasteur *Pasteur, Chile.*
Sodium benzoate (p.1630·2); ammonium chloride (p.1551·3); drosera (p.2297·3); liquorice (p.1740·3).
Respiratory-tract disorders.

Pectorhinyl *Eurogenerics, Belg.*
Phenylephrine hydrochloride (p.1568·1); pholcodine (p.1570·2).
Cough.

Pectorina *Fada, Arg.†.*
Cefalexin (p.218·2).
Bacterial infections.

Pectosan Expectorant *Cooperation Pharmaceutique, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Pectosan N *Streuli, Switz.†.*
Horseradish (p.2320·1); herbes aux cuillers; tolu balsam (p.1574·2); wild thyme (p.2415·3); red-poppy petal (p.1472·3).
Cold symptoms; coughs.

Pectosan Toux Seche *Cooperation Pharmaceutique, Fr.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Pectoserum *Silesia, Chile†.*
Codeine phosphate (p.37·2); noscapine hydrochloride (p.1566·3); ammonium chloride (p.1551·3); sodium benzoate (p.1630·2).
Bronchitis; catarrh; coughs.

Pectosol *Herbapol Pruszkow, Pol.*
Hyssop (p.2323·3); elecampane (p.1558·1); Iceland moss (p.2324·1); soapwort (p.2388·2); thyme (p.2401·1).
Cough; respiratory-tract congestion.

Pectosorin *Richter, Austria.*
Sulfogaiacol (p.1573·2).
Bronchitis; catarrh; coughs.

Pectover *Maver, Chile†.*
Diterbutyl napadisilate sodium; ammonium chloride (p.1551·3).
Coughs.

Pectox
Italfarmaco, Spain.
Carbocisteine (p.1553·2) or carbocisteine lysine (p.1553·3).
Respiratory-tract congestion.

Iromedica, Switz.
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Pectramin *Streuli, Switz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Pectrolyte *Adcock Ingram, S.Afr.*
⊗ Kaolin (p.1738·1); pectin (p.2145·2); chloroform and morphine tincture (p.86·3); sodium lactate; potassium chloride; sodium chloride (p.1672·2).
Diarrhoea.

Pectum *Solas, Indon.*
Cimicifuga (p.2282·1); grindelia (p.2317·2); ginger (p.1732·3); betel; liquorice (p.1740·3); thyme (p.2401·1); honey (p.1948·2).
Cough.

Pectyl *Nycomed, Denm.*
Opium (p.105·1); benzoic acid (p.1630·2); camphor (p.2273·2); glycerol (p.2314·2).
Coughs.

Pectylin-C *Ipca, India†.*
Diphenhydramine (p.577·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Respiratory-tract disorders.

Pectylin-PD *Ipca, India†.*
Diphenhydramine (p.577·1); sodium citrate (p.1673·3); menthol (p.2340·1).
Respiratory-tract disorders.

Pedab *Otto, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Pedameth *Forest Pharmaceuticals, USA†.*
Methionine (p.1450·1).
Control of odour, dermatitis, and ulceration in incontinent adults; nappy rash.

Pedcee *InterMed, Philipp.; Medica Pedia, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Pedea *Orphan Europe, Cz.; Orphan, Denm.; Orphan, Fr.; Orphan, Ger.; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan, UK.*
Ibuprofen (p.64·2).
Closure of patent ductus arteriosus.

Ped-Element *Darrow, Braz.*
Electrolyte (p.1667·1) and trace element (p.1922·1) preparation.
Parenteral nutrition.

Pedia Care Childrens Decongestant *Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

PediaCare Allergy Formula *McNeil Consumer, USA.*
Chlorphenamine maleate (p.571·3).

PediaCare Childrens Cold & Allergy *Pfizer Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms.

PediaCare Childrens Long-Acting Cough *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

PediaCare Childrens Long-Acting Cough Plus Cold *Pfizer Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

PediaCare Childrens Multi-Symptom Cold *Pfizer Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

PediaCare Cough-Cold *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

PediaCare Infant's Decongestant *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

PediaCare Infants Long-Acting Cough *Pfizer Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

PediaCare NightRest Cough-Cold Formula *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Pediacel *Sanofi Pasteur, Austral.; Sanofi Pasteur, Malaysia; Sanofi Pasteur, Mex.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Sanofi Pasteur, Thai.; Aventis Pasteur, UK.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Pediachlor *Pediatrica, Philipp.*
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Pediacof *Sanofi Winthrop, USA.*
Codeine phosphate (p.37·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); potassium iodide (p.2169·2).
Coughs.

Pedia-Col
Note. This name is used for preparations of different composition.
Greater Pharma, Thai.
Syrup: Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Greater Pharma, Thai.
Tablets: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Pediaderm *Andromaco, Chile†.*
Cod-liver oil (p.1935·2); vitamin A (p.1971·2); vitamin D (p.1986·1); zinc oxide (p.1621·2).
Burns; skin irritation; wounds.

Pediaflor *Ross, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis in children.

Pediafortan *Medi-Rx, Philipp.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Pediafortan Forte *Medi-Rx, Philipp.*
Lysine hydrochloride; taurine; vitamins (p.1922·1).
Nutritional supplement.

Pediafortan Forte-GE *Medi-Rx, Philipp.*
Lysine hydrochloride; taurine; chlorella; vitamins (p.1922·1).
Nutritional supplement.

Pediafortan-AS *Medi-Rx, Philipp.*
Buclizine hydrochloride (p.570·1); vitamins (p.1922·1).
Appetite stimulant; tonic.

Pediafortan-C *Medi-Rx, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Pediahist DM
Note. This name is used for preparations of different composition.
Boca, USA.
Oral drops: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Boca, USA.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Pedia-Lax *Fleet, USA.*
Magnesium hydroxide (p.1743·2).
Constipation.

Pedialyte
Abbott, Arg.†.
Glucose; fructose; electrolytes (p.1672·2).
Diarrhoea; oral rehydration therapy.

Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Hong Kong; Abbott, Ital.†; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.†; Abbott, Turk.; Ross, USA; Abbott, Venez.
Glucose and electrolytes (p.1672·2).
Diarrhoea; oral rehydration therapy.

Pedialyte FOS *Abbott, Mex.*
Glucose; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; fructo-oligosaccharides (p.1672·2).
Diarrhoea; oral rehydration therapy.

Pedialyte Mild *Abbott, Philipp.*
Electrolytes (p.1672·2).
Oral rehydration therapy.

Pedialyte SR *Abbott, Mex.*
Glucose; sodium chloride; sodium citrate; potassium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Pediamin *Liferpal, Mex.*
Multivitamin preparation (p.1922·1).

Pediamino PLM *Braun, Chile.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Pediamox *Pediatrica, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Pediapirin *Docta, Spain†.*
Paracetamol (p.108·1).
Fever; pain.

Pediapred *Aventis, Canad.; UCB, USA.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Pediaprofen *Laboratorios Chile, Chile.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Pediarix *SmithKline Beecham, USA.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and recombinant hepatitis B vaccine (p.2212·2).
Active immunisation.

Pediasea *Pediapharm, Chile.*
Sodium chloride (p.1686·1).
Nasal cleansing.

PediaSure *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Fin.†; Abbott, Hong Kong; Abbott, Indon.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Pol.; Abbott, Singapore; Abbott, Thai.; Abbott, Turk.; Abbott Nutrition, USA; Abbott, Venez.*
Preparation for enteral nutrition in children (p.1922·1).

Pediatan *Proethic, USA.*
Chlorphenamine tannate (p.572·2).

Pediatan D *Proethic, USA.*
Chlorphenamine tannate (p.572·2); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Pediatex *Zyber, USA.*
Carbinoxamine maleate (p.570·2) or carbinoxamine tannate.
Allergic rhinitis.

Pediatex-D *Zyber, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2).
Upper respiratory-tract disorders.

Pediatex-DM *Zyber, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; upper respiratory-tract disorders.

Pedia-Tric
Note. A similar name is used for preparations of different composition (see below).
Neckerman, Braz.†.
Oral rehydration solution (p.1672·2).

Pediatric
Note. A similar name is used for preparations of different composition (see above).
Support, Braz.†.
A range of preparations for enteral nutrition (p.1922·1).

Pediatric Decongestant & Cough *Silarx, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Pediatric Electrolyte *Pharmascience, Canad.*
Glucose; fructose; potassium citrate; sodium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration solution.

Pediatrix *Rougier, Canad.*
Paracetamol (p.108·1).
Fever; pain.

Pediazole
Note. This name is used for preparations of different composition.
Abbott, Arg.†; Abbott, Canad.; CSP, Fr.; IFET (ΙΦΕΤ), Gr.; Abbott, Hong Kong†; Abbott, Israel; Abbott, Mex.; Ross, USA; Abbott, Venez.†.
Erythromycin ethyl succinate (p.269·3); acetyl sulfafurazole (p.338·3).
Ear infections; otitis media.

Abbott, Chile†.
Erythromycin ethyl succinate (p.269·3); sulfafurazole (p.338·3); acetyl sulfafurazole (p.338·3).
Otitis media.

Pedi-Boro Soak Paks *Pedinol, USA.*
Aluminium sulfate (p.2255·1); calcium acetate (p.1675·2).
Skin irritation.

Pedibu *Zuoz, Venez.*
Ibuprofen (p.64·2).
Inflammation; pain.

Pedic *Stadmed, India.*
Multivitamin preparation with lysine and zinc (p.1922·1).

Pedicrem *Prieto, Arg.*
Aloe vera (p.1588·2); permethrin (p.2048·2); wheat germ.
Pediculosis.

Pediderm *Cifarma, Braz.*
Deltamethrin (p.2040·1).
Pediculosis; scabies.

Pedi-Dri *Pedinol, USA.*
Nystatin (p.543·2).
Candidiasis.

Pedifan *Vilco, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Pedifen *Atabay, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Pedikurol *Ratiopharm, Austria.*
Clotrimazole (p.530·1).
Fungal skin and nail infections.

Pediletan *Cimed, Braz.*
Lindane (p.2045·3).
Pediculosis.

Pedilin
Note. This name is used for preparations of different composition.
KRKA, Rus.
Malathion (p.2046·1).

Mecom, Turk.
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Respiratory-tract congestion.

Pedilin Ko *KRKA, Rus.*
Tetramethrin (p.2051·1); piperonyl butoxide (p.2049·1).

Pedi-Lotion
Note. This name is used for preparations of different composition.
Medipharm, Venez.
Lotion: Benzalkonium chloride (p.1629·1); menthol (p.2340·1).
Hyperhidrosis.

Medipharm, Venez.
Topical powder: Benzalkonium chloride (p.1629·1); menthol (p.2340·1); camphor (p.2273·2); zinc oxide (p.1621·2).
Hyperhidrosis.

Pedimat *Ilsan, Turk.*
Paracetamol (p.108·1); phenobarbital (p.492·2).
Fever; pain.

Pedimed *Adcock Ingram, S.Afr.*
Aluminium oxide (p.1585·3); magnesium oxide (p.1744·1); methylpolysiloxane (p.1770·2).
Flatulence associated with hyperacidity.

Pedimin *Metiska, Indon.*
Vitamins (p.1922·1).
Nutritional supplement.

Pediotic *Monarch, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial ear infections.

Pediox *Atley, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Pediox-S *Atley, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Pedi-Pro *Pedinol, USA.*
Benzalkonium chloride (p.1629·1); menthol (p.2340·1).
Formerly contained aluminium chlorohydrate, chloroxylenol, menthol, and zinc undecenoate.
Skin infections.

Pedipur *Prolab, Pol.*
Methenamine (p.298·3); zinc oxide (p.1621·2); talc (p.1615·2).
Hyperhidrosis.

Pedi-Relax Anti-callosites *Pierre Fabre Sante, Fr.†.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Callosities.

Pedi-Relax Anti-Transpirant *Pierre Fabre Sante, Fr.*
Methenamine (p.298·3); farnesol.

Pediron *ST, Thai.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia in infants and children.

Pedisol
Note. This name is used for preparations of different composition.
Fischer, Israel.
Cream: Triclosan (p.1665·2); panthenol (p.2362·1); chamomile (p.2279·3); wool fat (p.2033·2).
Dry skin; hard skin.

Fischer, Israel†.
Deodorant spray: Undecenoic acid (p.549·2); menthol (p.2340·1); propylene glycol (p.2374·1); triclosan (p.1665·2).
Foot odour.

Fischer, Israel.
Topical spray: Undecenoic acid (p.549·2); aluminium chlorohydrate (p.1588·3); menthol (p.2340·1); purified talc (p.1615·2).
Foot odour and perspiration.

Peditrace *Fresenius Kabi, Austria; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Baxter, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Pharmacia Upjohn, Israel; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Baxter, NZ; Fresenius Kabi, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore†; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Peditral *RPG, India.*
Sodium chloride; potassium chloride; sodium citrate; anhydrous glucose (p.1672·2).
Oral rehydration therapy.

Peditus *Ilsan, Turk.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract congestion.

Pedituss Cough *Major, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2); potassium iodide (p.2169·2).
Coughs.

Pedivit *Unique, Rus.*
Vitamin and mineral preparation (p.1922·1).

Pedi-Vit-A *Pedinol, USA.*
Vitamin A (p.1971·2).
Irritated or dry skin.

Pedopur *Jacoby, Austria.*
Vitis vinifera (p.2316·3).
Peripheral vascular disorders.

Pedoz *Hamilton, Austral.*
Tetrabromocresol (p.1663·3); undecenoic acid (p.549·2); zinc undecenoate (p.549·3); zinc oxide (p.1621·2).
Hyperhidrosis; skin irritation; tinea pedis.

Pedpain *Columbia, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Pedrin *Aroma, Turk.*
⊗ Guaifenesin (p.1561·3); ephedrine hydrochloride (p.1558·2).
Respiratory-tract congestion.

Pedrolon *Galena, Cz.†.*
⊗ Hydroxyamfetamine hydrobromide (p.2322·3).
Hypotension.

PedTE-PAK *SoloPak, USA.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Pedtrace *American Pharmaceutical, USA.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

PedvaxHIB *MSD, Arg.†; CSL, Austral.; MSD, Braz.; Merck Frosst, Canad.; Chiron Behring, Ger.†; MSD, Hong Kong; MSD, Indon.; MSD, Israel†; MSD, Malaysia†; MSD, Mex.; MSD, Pol.; MSD, Singapore†; MSD, Thai.; MSD, Turk.; Merck, USA.*
A haemophilus influenzae conjugate vaccine (meningococcal protein conjugate) (p.2213·2).
Active immunisation.

Pedvitin *Greater Pharma, Thai.†.*
Multivitamin preparation (p.1922·1).

PeeHoo *Orion, Fin.†.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastric hyperacidity.

Peerless Composition Essence *Potter's, UK.*
Oak bark (p.2355·3); pinus canadensis; poplar bark (p.2371·1); prickly ash bark (p.2417·1); bayberry bark (p.2263·2).
Colds.

Pefamic *PP Lab, Thai.†.*
Mefenamic acid (p.80·1).
Pain.

Pefbid *Alembic, India.*
Pefloxacin (p.313·3).
Bacterial infections.

Peflacin *Sanofi-Aventis, Braz.; Aventis, Gr.†; Sanofi-Aventis, Ital.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Peflacina *Aventis, Mex.; Aventis, Venez.†.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Peflacine *Sanofi-Aventis, Fr.; EGIS, Hung.; Sanofi-Aventis, Indon.; Aventis, Malaysia†; Egis, Pol.; Sanofi-Aventis, Port.; Aventis, Spain†; Aventis, Thai.†; Eczacibasi, Turk.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Pefloden *Vita, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Peflox *Formenti, Ital.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Pefloxidina *Teuto, Braz.†.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Pefrakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Pega *Bailleul, Fr.*
Potassium and arginine phosphocitroglutamate.
Asthenia.

Peganix *Baliarda, Arg.*
⊗ Piroxicam (p.117·3); prednisone (p.1542·3).
Musculoskeletal and joint disorders.

Peganone *Ovation, USA.*
Ethotoin (p.480·3).
Epilepsy.

Pegasys *Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Peginterferon alfa-2a (p.888·3).
Chronic hepatitis B; chronic hepatitis C.

Pegasys RBV *Roche, Austral.; Roche, Canad.; Roche, NZ; Roche, Philipp.*
Injection, peginterferon alfa-2a (Pegasys) (p.888·3); tablets, ribavirin (Copegus) (p.902·3).
Chronic hepatitis C.

Pegatron *Schering-Plough, Arg.†; Schering-Plough, Austral.; Schering-Plough, NZ.*
Capsules, ribavirin (Rebetol) (p.902·3); injection, peginterferon alfa-2b (Intron-A) (p.888·3).
Chronic hepatitis C.

Pegetron *Schering, Canad.*
Capsules, ribavirin (p.902·3); injection, peginterferon alfa-2b (p.888·3).
Chronic hepatitis C.

Pegina *Potter's, UK.*
Calumba (p.2273·2); calamus (p.2271·3); compound cardamom tincture (p.2277·1); magnesium sulfate (p.1679·3); magnesium trisilicate (p.1744·1); rhubarb (p.1768·3).
Dyspepsia; flatulence.

PegIntron *Schering-Plough, Austral.; Schering-Plough, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering, Canad.†; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; Schering-Plough, Fin.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.†; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering, USA; Schering-Plough, Venez.*
Peginterferon alfa-2b (p.888·3).
Chronic hepatitis C.

Peglasta *Roche, Malaysia.*
Pegfilgrastim (p.1070·1).
Neutropenia.

Peglax *Femi Agran, Israel.*
Macrogol 4000 (p.2336·3).
Constipation; stool softener.

Peglyte
Note. This name is used for preparations of different composition.
Pharmascience, Canad.
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Pharmascience, Hong Kong.
Electrolytes (p.1667·1).
Gastrointestinal lavage.

Pegtron *Schering-Plough, Mex.*
Peginterferon alfa-2b (p.888·3).
Chronic hepatitis C.

Pegtron Cotronak Kit *Schering-Plough, Mex.*
Injection, peginterferon alfa-2b (p.888·3); capsules, ribavirin (p.902·3).
Chronic hepatitis C.

Pehacain *Phapros, Indon.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Pehachlor *Phapros, Indon.*
Chlorphenamine maleate (p.571·3).
Allergic disorders.

Peindol *Giempi, Venez.*
Ketoprofen (p.73·1).
Inflammation; pain.

Peinfort *Ebewe, Austria.*
Paracetamol (p.108·1).
Fever; pain.

Peitel *Novag, Spain.*
⊗ Prednicarbate (p.1540·2).
Skin disorders.

Peitoral Angico Pelotense *CIF, Braz.†.*
Iceland moss (p.2324·1); althaea (p.2253·3); cuscuta umbellata; mallow (p.2337·2); liquorice (p.1740·3); piptadenia colubrina; ammonium chloride (p.1551·3); tolu balsam (p.1574·2); sodium benzoate (p.1630·2).
Respiratory-tract congestion.

Peitoral Martel *Galenogal, Braz.†.*
Guaifenesin (p.1561·3); pinho (p.2368·2); honey (p.1948·2); agriao; guaco.

Pekaso *Kenyaku, Hong Kong.*
Mefenamic acid (p.80·1).
Pain.

Peking Ginseng Royal Jelly N *Peking-Boell, Ger.*
Ginseng (p.2312·1); honey; royal jelly.
Tonic.

Peking Royal Jelly N *Peking-Boell, Ger.†.*
Royal jelly (p.2382·1); codonopsis pilosulae; honey.
Tonic.

Pekiron *Kyorin, Jpn.*
Amorolfine hydrochloride (p.523·1).
Fungal skin infections.

Pektodin *Pasifik, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.

Pektrol *KRKA, Rus.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Pel Cupron *Asmopul, Arg.†.*
Porcine skin (p.1613·3).
Burns.

Pelargon *Nestle, Fr.; Nestle, Ital.*
Infant feed (p.1922·1).
Digestive disorders; gastrointestinal disorders.

Pelastin *Sanbe, Indon.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Peledox *Novartis Consumer, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Pelentan *Leciva, Cz.†.*
Ethyl biscoumacetate (p.1284·1).
Thromboembolic disorders.

Pelentanettae *Leciva, Cz.†.*
Ethyl biscoumacetate (p.1284·1).
Thromboembolic disorders.

Pelethrocin *Help, Gr.; Help, Pol.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders; venous insufficiency.

Pelicrep *Raffo, Arg.†.*
⊗ Finasteride (p.2188·3).
Alopecia.

Pelina *MIP, Ger.*
Dexpanthenol (p.2362·1).
Skin and mucous membrane lesions.

Pellexeme *Coup, Gr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Pellit *Engelhard, Hong Kong†; Asta Medica, Thai.†.*
Diphenhydramine hydrochloride (p.577·2); diethyltoluamide (p.2041·1); dimethyl phthalate (p.2041·3).
Allergic skin reactions; insect bites; insect repellent.

Pelmec *Casasco, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Pelmec Duo *Casasco, Arg.*
Amlodipine besilate (p.1214·1); benazepril hydrochloride (p.1223·2).
Hypertension.

Pelo Libre *GSK, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Pelo Libre Protectora *GSK, Arg.*
Acetic acid (p.2244·2).
Pediculosis.

Pelogel *Sulphur Zdroj, Pol.*
Myrtillus (p.2349·3); peppermint oil (p.1761·2).
Gingivitis; periodontitis.

Pelox *Wockhardt, India; Wockhardt, Rus.*
Pefloxacin (p.313·3).
Bacterial infections.

Pelsana Med
Note. This name is used for preparations of different composition.
Schmidgall, Austria.
Bath oil: Sunflower oil (p.1970·3); undecenoic acid (p.549·2).
Skin disorders.

Schmidgall, Austria.
Topical powder: Zinc undecenoate (p.549·3).
Skin disorders.

Pelsano
Note. This name is used for preparations of different composition.
Iromedica, Switz.
Bath additive: Sunflower oil (p.1970·3); undecenoic acid (p.549·2).
Skin disorders.

Iromedica, Switz.
Cream: Zinc oxide (p.1621·2).
Skin disorders.

Iromedica, Switz.
Ointment: Sunflower oil (p.1970·3); dexpanthenol (p.2362·1).
Skin disorders.

Pelset Plus *Muskus, Venez.*
⊗ Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2); urea (p.1620·2).
Scalp disorders.

Peltazon *Grelan, Jpn†.*
⊗ Pentazocine hydrochloride (p.112·2).
Fever; inflammation; pain.

Pelvichthol N *Ichthyol, Ger.*
Ictasol (p.1599·1); benzyl nicotinate (p.28·1).
General pelvic symptoms.

Pelvicillin NF *Temis, Arg.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

PemADD *Mallinckrodt, USA†.*
⊗ Pemoline (p.2161·2).
Attention-deficit hyperactivity disorder.

Pemar *Medipharm, Chile.*
Piroxicam (p.117·3).
Inflammation; pain.

Pemidal *Polfa Pabianice, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Pemine *Lilly, Ital.*
Penicillamine hydrochloride (p.1458·3).
Cystinuria; lead poisoning; rheumatoid arthritis; Wilson's disease.

Pemirox *Santen, Hong Kong; Santen, Thai.*
Pemirolast potassium (p.1129·3).
Allergic eye disorders.

PE-Mix
Note. A similar name is used for preparations of different composition (see below).
Fresenius Kabi, Austria.
Amino-acid, carbohydrate, electrolyte, and lipid (as soya oil (p.1965·3)) infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Pemix
Note. A similar name is used for preparations of different composition (see above).
Almirall, Mex.
Cinitapride acid tartrate (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Pemol *Chinta, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Pen *ABZ, Ger.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pen di Ben *Bago, Arg.*
Benzathine benzylpenicillin (p.212·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pen Mega *1A, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pen Oral *Aventis, Arg.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Penachlor *Dynamic, Philipp.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Penadur *Vesale, Belg.; Wyeth, Gr.; Wyeth, Philipp.; Wyeth Lederle, Port.†; Wyeth-Ayerst, Thai.†; Wyeth, Turk.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections; prevention of acute flares of rheumatoid arthritis.

Penadur 6.3.3 *Wyeth Lederle, Port.†; Wyeth, Turk.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Penagon *Metiska, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Pain.

Penagrand *Ahimsa, Arg.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Penalta *BMS, Fin.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Penamox *Sanfer, Mex.; Tecnimede, Port.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Penamox M *Sanfer, Mex.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Penanyst *PCR, Ger.*
Zinc oxide (p.1621·2); nystatin (p.543·2).
Skin disorders with fungal infections.

Penaten
Note.This name is used for preparations of different composition.
Johnson & Johnson, Canad.
Hamamelis (p.2318·2); zinc oxide (p.1621·2).

Johnson & Johnson, Ger.
Thyme oil (p.2401·2).
Respiratory-tract disorders.

Penatoel *PCR, Ger.†.*
Soya oil (p.1965·3).
Dry skin; skin irritation.

Penbaccin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Penbak *Eczacibasi, Turk.*
Bacampicillin (p.210·2).
Bacterial infections.

Penbene *Ratiopharm, Austria; Ratiopharm, Cz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penbeta *Betapharm, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penbiosyn *Medi-Rx, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Penbiotic *Bernofarm, Indon.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Penbisin *Ulagay, Turk.*
Ampicillin (p.204·1).
Bacterial infections.

Penbritin
GSK, Hong Kong†; GSK, Thai.
Ampicillin (p.204·1).
Bacterial infections.

GSK, Indon.; GSK, Irl.; Hormona, Mex.; GSK, S.Afr.; Chemidex, UK.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

SmithKline Beecham, Philipp.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Penbritin Ex *Hormona, Mex.*
Amoxicillin (p.202·2); bromhexine (p.1552·2).
Respiratory-tract infections.

Penbrosol *Solvang, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); brompheniramine maleate (p.569·2).
Nasal congestion; rhinitis.

Pencarv *General Drugs House, Philipp.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Pencid *Zentiva, Cz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pencil 400 *Prodotti, Braz.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pencil B *Prodotti, Braz.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Pencil P *Prodotti, Braz.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pencilin-V *Teuto, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pencip *Cipla, India.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pencla *Penmix, Thai.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Penclen *Zentiva, Cz.*
Penamecillin.
Bacterial infections.

Penclox *Pisa, Mex.*
Dicloxacillin (p.265·2).
Bacterial infections.

Pencom *Alembic, India.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Pencor *Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Pencotrex *Hua, Thai.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Pencrist *Fako, Turk.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pencroftonum *Pentkroft, Rus.*
Mifepristone (p.2011·2).
Termination of pregnancy.

Pendepon Compositum *Biotika, Cz.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Pendex *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Pendiben Compuesto *Pisa, Mex.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2); benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Pendiben L-A *Pisa, Mex.*
Benzylpenicillin (p.213·1).
Bacterial infections.

Pendine *Alphapharm, Austral.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Pendium *Galenus, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Pendrox *Ipca, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Pendysin *Jenapharm, Ger.*
Benzathine benzylpenicillin (p.212·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Chronic streptococcal infections; syphilis.

Penecare *Reed & Carnrick, USA.*
Emollient.

Penecort *Allergan, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Penederm
Note.This name is used for preparations of different composition.
Penederm, Canad.†.
Cream: Lactic acid (p.2329·3); light liquid paraffin (p.2031·1).
Dry skin.

Penederm, Canad.†.
Lotion: Lactic acid (p.2329·3).
Dry skin.

Penedil *Teva, Israel.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Penegra *Zydus, India.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Pener *Unison, Thai.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Penester *Zentiva, Cz.; Zentiva, Pol.; Zentiva, Rus.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Penetrex *Rhone-Poulenc Rorer, USA†.*
Enoxacin (p.268·3).
Gonorrhoea; urinary-tract infections.

Penetro
Note.This name is used for preparations of different composition.
Daudt, Braz.
Inhalation: Terpineol (p.2396·1); cineole (p.2282·3); menthol (p.2340·1); benzoic acid (p.1630·2).
Respiratory-tract congestion.

Daudt, Braz.†.
Oral solution: Ambroxol hydrochloride (p.1550·3); menthol (p.2340·1); cineole (p.2282·3).
Respiratory-tract congestion.

Penexil *Haller, Braz.†.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Penfantil *Klonal, Arg.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Penfill N *Novo Nordisk, Jpn.*
⊗ Isophane insulin (human, recombinant) (p.443·2).
Diabetes mellitus.

Penfill R *Novo Nordisk, Jpn.*
⊗ Insulin injection (human, recombinant) (p.443·2).
Diabetes mellitus.

Penfill 10R, 20R, 30R, 40R, 50R *Novo Nordisk, Jpn.*
⊗ Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40%, and 50% and isophane insulin injection (human, recombinant) 90%, 80%, 70%, 60%, and 50% respectively (p.443·2).
Diabetes mellitus.

Pengesic *Hovid, Malaysia; Hovid, Philipp.; Hovid, Singapore.*
Tramadol hydrochloride (p.130·3).
Pain.

Pengesod *Grunenthal, Mex.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penglobe *AstraZeneca, Austria; AstraZeneca, Canad.†; AstraZeneca, Cz.†; AstraZeneca, Fr.†; AstraZeneca, Hong Kong†; Biogal-Teva, Hung.†; AstraZeneca, India; AstraZeneca, Ital.; AstraZeneca, Malaysia†; Astra, Mex.†; AstraZeneca, Philipp.; AstraZeneca, Spain†; AstraZeneca, Swed.†; AstraZeneca, Thai.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Pengon *Elpen (Ελπεν), Gr.†.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Penhexal *Hexal, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penhexal VK *Hexal, Austral.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penibiot *Normon, Spain.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penibrin *SLE, Israel; Sandoz, Israel.*
Ampicillin (p.204·1).
Bacterial infections.

Penicigran *Legrand, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penicil *Rimsa, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penicil Dermol *Gador, Arg.†.*
Procaine benzylpenicillin (p.319·2).
Bacterial skin infections.

Penicillat *Azupharma, Ger.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penicillin G Procaine Fortified *Panpharma, Hong Kong.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penicina *Epicaris, Arg.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penicomb *Chrispa (Χρισπα), Gr.*
Econazole (p.531·1).
Fungal skin infections.

Penidural *Astellas, Neth.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Penidural D/F *Yamanouchi, Neth.†.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Penidure *Wyeth, India.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Penigra *Hasco-Lek, Pol.*
Guarana (p.2416·1); muira-puama; schisandra (p.2384·2); saw palmetto (p.2192·3); zinc monomethionine.
Male impotence.

Penikin *Radyum, Turk.*
⊗ Caffeine (p.1116·3); metamizole; ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Penilan *Vitoria, Port.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Penilente LA *Novo Nordisk, S.Afr.†.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Penilente Forte *Novo Nordisk, S.Afr.†.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penilevel
Note.This name is used for preparations of different composition.
Ern, Spain.
Capsules; oral sachets: Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Ern, Spain.
Injection: Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penilevel Retard *Ern, Spain.*
Benzylpenicillin sodium (p.213·1); benzathine benzylpenicillin (p.212·1); phenoxymethylpenicillin calcium (p.314·2).
Bacterial infections; rheumatic fever.

Penilfedrin P *Lersan, Arg.*
Benzylpenicillin potassium (p.213·1).
Bacterial eye infections.

Penimox *IBSA, Switz.†.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Peni-Oral *Vesale, Belg.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penipastil *Casel, Turk.*
Cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Penipot *Antibioticos, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Peniroger *UCB, Spain†.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Penisintex Bronquial *Jorba, Spain†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); bromhexine (p.1552·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Penisodina *Pisa, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Penisol
Note.This name is used for preparations of different composition.
Ivax, Mex.
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Ecosol, Switz.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penkain-K *Bilim, Turk.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Penkaron *Ariston, Braz.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Pen-Kera Ascher, USA.
Emollient and moisturiser.

Penlac Dermik, Canad.; Dermik, USA.
Ciclopirox (p.529·2).
Fungal nail infections.

Penles Nitto Denko, Jpn.
Lidocaine (p.1862·3).
Pain of inserting intravenous needles.

Penlol Pose, Thai.
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

PenMix 10, 20, 30, 40, or 50 Novo Nordisk, Gr.†; Novo Nordisk, NZ.
⊗ Mixtures of insulin injection (human, recombinant) 10%, 20%, 30%, 40%, or 50% and isophane insulin (human, recombinant) 90%, 80%, 70%, 60%, or 50% respectively (p.443·2).
Diabetes mellitus.

Penmox Coronet, Indon.; Aspen, S.Afr.†.
Amoxicillin (p.202·2).
Bacterial infections.

Pennsaid Dimethaid, Canad.; Vianex (Βιανεξ), Gr.; Italchimici, Ital.; Dimethaid, Port.; Dimethaid, UK.
Diclofenac sodium (p.44·3).
Inflammatory disorders; osteoarthritis.

Penodex Rotexmedica, Philipp.
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Penodil Remedica, Hong Kong.
Ampicillin (p.204·1).
Bacterial infections.

Penomor Blooming Fields, Philipp.
Mefenamic acid (p.80·1).
Fever; pain.

Penopril Elpen (Ελπεν), Gr.
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Penoral Medicopharm, Austria.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pen-Os Eczacibasi, Turk.
Benzathine phenoxymethylpenicillin (p.212·3).
Bacterial infections.

Penotran Merck, Hong Kong†.
Hydrargaphen (p.1647·2); potassium dinaphthylmethanedisulfonate.
Vaginal infections.

Penoxil V Pharmaniaga, Malaysia†; Raza, Malaysia†.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penoza Elpen (Ελπεν), Gr.
Glimepiride (p.441·1).
Diabetes mellitus.

Penprocilina Lakeside, Mex.
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Penpurin Elpen (Ελπεν), Gr.
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Penrazol Elpen (Ελπεν), Gr.
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Penrazole Elpen, Singapore.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hypersecretion; peptic ulcer.

Penrite Columbia, S.Afr.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Pensilina Tum, Turk.
Benzylpenicillin (p.213·1).
Bacterial infections.

Pensiral Serral, Mex.
Pentoxifylline (p.1367·2).
Cerebrovascular disorders.

Pensodil Loeffler, Mex.
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Pensordil Elpen (Ελπεν), Gr.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Penstabil Galena, Cz.†; Ivax, Cz.†; Ivax, Hung.†.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Penstad Stada, Austria.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penstapho BMS, Belg.; BMS, Ital.
Oxacillin sodium (p.311·3).
Gram-positive bacterial infections; staphylococcal infections.

Penstaphon BMS, Belg.
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Pensulan Andromaco, Chile.
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); zinc oxide (p.1621·2); aluminium hydroxide (p.1706·2).
Skin infections.

Pensulvit SIFI, Ital.
Tetracycline (p.347·1); sulfamethylthiazole (p.342·1).
Bacterial eye infections.

Penta Fonte, Switz.
Salol (p.122·1); thymol (p.1664·3); menthol (p.2340·1); peppermint oil (p.1761·2); anise oil (p.2258·2).
Mouth and throat disorders; oral hygiene.

Penta 500 Pediatrica, Malaysia†; Pediatrica, Singapore.
Lysine hydrochloride; vitamin B substances (p.1922·1).
Tonic.

Penta-3B Sandoz, Canad.
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Alcoholism; neuritis; vitamin B supplement.

Penta-3B + C Sandoz, Canad.
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2); ascorbic acid (p.1983·3).
Alcoholism; neuritis; vitamin supplement.

Penta-3B Plus Sandoz, Canad.
Multivitamin preparation (p.1922·1).

Pentabil OFF, Ital.†.
Fenipentol (p.2302·3).
Hepatic and biliary-tract disorders.

Pentacard Altana, Indon.; Darya-Varia, Indon.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Pentacarinat Gerot, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.†; Aventis, Denm.; Aventis, Fin.†; Sanofi-Aventis, Fr.; Aventis, Ger.; GSK, Ger.; Sanofi-Aventis, Irl.; Aventis, Israel†; Sanofi-Aventis, Ital.; Sanofi-Aventis, NZ; Aventis, Neth.; Aventis, Port.†; Sanofi-Aventis, Spain; Aventis, Swed.; Sanofi-Aventis, Switz.; Aventis, Thai.; JHC Healthcare, UK; Armour, USA.
Pentamidine isetionate (p.844·2).
African trypanosomiasis; leishmaniasis; Pneumocystis pneumonia.

Pentacarinate IFET (ΙΦΕΤ), Gr.
Pentamidine isetionate (p.844·2).
African trypanosomiasis; leishmaniasis; Pneumocystis pneumonia.

Pentacel Sanofi Pasteur, Canad.
Vial, a haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate)(Act-HIB); ampoule, a diphtheria, tetanus, pertussis, and poliomyelitis vaccine (Quadracel) (p.2212·1).
Active immunisation.

Pentacin Darya-Varia, Indon.
Azapentacene sulfonate sodium (p.2262·2).
Cataract.

Pentacis CIS, Port.; Schering, UK.
Technetium-99m pentetate (p.2055·3).
Assessment of renal function; radionuclide imaging of the brain and lungs; studies of gastro-oesophageal reflux and gastric emptying.

Pentacol Sofar, Ital.
Mesalazine (p.1745·1).
Crohn's disease; ulcerative colitis.

Pentacoq Sanofi Pasteur, Fr.†.
Vial, a haemophilus influenzae conjugate vaccine (tetanus toxoid conjugate) (Act-HIB); syringe, a diphtheria, tetanus, pertussis, and poliomyelitis vaccine (Tetracoq) (p.2212·1).
Active immunisation.

Pentacort Life, Ger.†.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Pentacrin Elpen (Ελπεν), Gr.
Diacerein (p.41·3).
Osteoarthritis.

Pentacrom Penta, Ger.†.
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Pentact-HIB Aventis Pasteur, Braz.†; Sanofi Pasteur, Chile; Sanofi Pasteur, Hong Kong; Pasteur Merieux, Israel; Aventis Pasteur, Philipp.; Aventis, S.Afr.†; Aventis Pasteur, Thai.†; Aventis Pasteur, Turk.
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Pentadecan Viatris, Ger.†.
Pentadecanoic acid glyceride.
Alopecia.

Pentadent Defuen, Arg.†.
Hexetidine (p.1647·1); benzydamine hydrochloride (p.27·3).
Mouth disorders.

Pentaderm Dermatech, Austral.†; Crawford, UK.
5-Methoxypsoralen (p.1607·2).
Eczema; mycosis fungoides; polymorphic light eruption; psoriasis; solar urticaria; vitiligo.

Pentaerythritol Compositum Galena, Pol.
Pentaerithrityl tetranitrate (p.1366·3); glyceryl trinitrate (p.1296·2).
Heart failure.

Pentaferr Pentafarma, Chile.
Sodium ferric gluconate complex (p.1962·2).
Iron-deficiency anaemia.

Pentafresh Careiatrics, Arg.†.
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Pentagin Sankyo, Jpn†.
⊗ Pentazocine hydrochloride (p.112·2).
Fever; inflammation; pain.

Pentaglobin Biogam, Arg.; Biotest, Austria; Pentafarma, Chile; Biotest, Cz.; Biotest, Ger.; Biotest, Gr.; Biotest, Hong Kong; Biotest, Hung.; Biotest, Ital.; Biotest, Malaysia†; Pisa, Mex.; Biotest, Pol.; Mednostica, S.Afr.; Biotest, Singapore; Biotest, Switz.; Biotest, Thai.; Kansuk, Turk.
A normal immunoglobulin (p.2225·3).
Bacterial infection; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Pental Ulagay, Turk.
Thiopental sodium (p.1795·2).
General anaesthesia; raised intracranial pressure in ventilated patients.

Pental Forte Cederroth, Spain†.
Benzalkonium chloride (p.1629·1); mafenide (p.296·2); sulfanilamide (p.343·1); zinc oxide (p.1621·2).
Skin infections.

Pentalac UCI, Braz.†.
Lactulose (p.1738·2).

Pentalgin-N Farmstandart, Rus.
Dipyrone (p.49·2); naproxen (p.92·3); phenobarbital (p.492·2); codeine (p.37·2); caffeine (p.1116·3).
Pain.

Pentaloc Cadila, India.
Pantoprazole (p.1760·1).
Peptic ulcer.

Pentalong Actavis, Cz.; Alpharma-Isis, Ger.
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris.

Pentam IFET (ΙΦΕΤ), Gr.; American Pharmaceutical, USA.
Pentamidine isetionate (p.844·2).
Pneumocystis pneumonia.

Pentamina Hospira, Port.
Pentamidine isetionate (p.844·2).
Leishmaniasis; Pneumocystis pneumonia; trypanosomiasis.

Pentamol Penta, Ger.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Pentamycetin Sandoz, Canad.
Chloramphenicol (p.239·3).
Eye infections.

Pentamycetin-HC Sandoz, Canad.
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Eye and ear infections.

Pentarim Rimsa, Mex.
Thiopental (p.1796·1).
General anaesthesia.

Pentasa Ferring, Arg.; Ferring, Austral.; Ferring, Austria; Ferring, Belg.; Ferring, Braz.†; Ferring, Canad.; Ferring, Chile; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Gerolymatos, Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Irl.; Ferring, Israel; Ferring, Ital.; Kyorin, Jpn; Ferring, Malaysia; Ferring, Mex.; Ferring, NZ; Pharmaco, NZ; Ferring, Neth.; Ferring, Norw.; Ferring, Philipp.; Ferring, Pol.; Ferring, Port.; Ferring, Rus.; Ferring, S.Afr.; Ferring, Singapore; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, UK; Shire, USA.
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Pentasone Sandoz, Canad.
⊗ Gentamicin sulfate (p.282·1); betamethasone sodium phosphate (p.1518·3).
Formerly known as SAB-Pentasone.

Pentaspan Aventis, Braz.†; BMS, Canad.; Aventis, Mex.†; Boots Healthcare, NZ†; Du Pont, USA.
⊗ An etherified starch (p.1065·1).
Leucapheresis; plasma volume expansion.

Pentatec Elpen (Ελπεν), Gr.
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Penta-Thion Sabex, Canad.
Ascorbic acid (p.1983·3); thiamine hydrochloride (p.1976·1).
Vitamin supplement.

Pentatop Pentatop, Ger.
Sodium cromoglicate (p.1136·3).
Hypersensitivity reactions.

Pentavac Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Pentavir
Note. This name is used for preparations of different composition.
Fortbenton, Arg.
Cream: Penciclovir (p.901·2).

Fortbenton, Arg.
Tablets: Famciclovir (p.876·1).

Pentavite Nicholas Piramal, India†.
Ferrous gluconate (p.1939·1); vitamin B substances; calcium gluconate (p.1922·1).
Anaemia.

Penta-Vite Chewable Multi Vitamins with Minerals Bayer Consumer, Austral.
Multivitamin and mineral preparation (p.1922·1).

Penta-Vite Childrens Vitamins with Iron Bayer Consumer, Austral.
Multivitamin preparation with iron (p.1922·1).

Penta-Vite Infant Vitamins Bayer Consumer, Austral.†.
Multivitamin preparation (p.1922·1).

Pentawin Biochem, India.
⊗ Pentazocine lactate (p.112·3).
Pain; premedication.

Pentaxim Sanofi Pasteur, Arg.; Sanofi Pasteur, Hung.; Sanofi Pasteur, Malaysia; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Sanofi Pasteur, Thai.
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and Haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Pentazine VC with Codeine Century, USA.
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Pentazole Profarb, Braz.†.
Mebendazole (p.148·3).
Worm infections.

Pentcillin Toyama, Jpn.
Piperacillin sodium (p.315·2).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Penthotal Abbott, Chile†.
Thiopental sodium (p.1795·2).
Convulsions; general anaesthesia; sedative.

Penthrane Abbott, Austral.†.
Methoxyflurane (p.1789·2).
General anaesthesia.

Penthrox Medical Developments, Austral.; NZ Medical & Scientific, NZ.
Methoxyflurane (p.1789·2).
Pain.

Pentibrom Maver, Mex.
Ampicillin trihydrate (p.204·2); bromhexine hydrochloride (p.1552·2).
Bacterial infections.

Pentibroxil Maver, Mex.
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Penticlox Maver, Mex.
Amoxicillin (p.202·2).
Bacterial infections.

Penticort Wyeth Lederle, Fr.†.
⊗ Amcinonide (p.1516·2).
Skin disorders.

Pentidix Maver, Mex.
Ampicillin (p.204·1); dicloxacillin (p.265·2).
Bacterial infections.

Pentids Sarabhai Piramal, India.
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pentila Biomedica-Chemica, Gr.†.
⊗ Levobunolol hydrochloride (p.1882·3).

Pentilin KRKA, Cz.; KRKA, Pol.; KRKA, Rus.
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Pentin Specifar, Gr.
Gabapentin (p.482·3).
Epilepsy.

Pentiver Maver, Mex.
Ampicillin (p.204·1).
Bacterial infections.

Pento ABZ, Ger.
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Pentobrim Rotexmedica, Philipp.
Thiopental sodium (p.1795·2).
Convulsions; general anaesthesia.

Pentoclave Defuen, Arg.
Erythromycin (p.269·2).
Acne.

Pentoclave Combi Defuen, Arg.
Erythromycin (p.269·2); benzoyl peroxide (p.1590·2).
Acne.

Pentoflux Bouchara-Recordati, Fr.
Pentoxifylline (p.1367·2).
Intermittent claudication; mental function impairment in the elderly.

Pentohexal Hexal, Austria; Salutas, Cz.†; Hexal, Ger.; Hexal, Pol.
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Pentol Sidus, Arg.
Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); centella (p.1592·3).
Vulvovaginal infections.

Pentolab Lamsa, Arg.
Pentoxifylline (p.1367·2).

Pentolair Bausch & Lomb, USA.
Cyclopentolate hydrochloride (p.1879·3).

Pentomer Ratiopharm, Austria; Ratiopharm, Cz.
Pentoxifylline (p.1367·2).
Cerebral, ocular and peripheral vascular disorders; ear disorders.

Pentong HPP, Hong Kong.
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Pento-Puren Alpharma-Isis, Ger.
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Pentorel Khandelwal, India.
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Pentostam *GSK, Israel; GSK, UK.*
Sodium stibogluconate (p.828·2).
Leishmaniasis.

Pentotex *Rotexmedica, Malaysia.*
Thiopental sodium (p.1795·2).
Convulsions; general anaesthesia.

Pentothal *Abbott, Arg.†; Abbott, Austral.; Abbott, Belg.; Hospira, Canad.; Abbott, Denm.; Electra-Box, Fin.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Indon.; Abbott, Israel; Hospira, Ital.; Abbott, Mex.; Hospira, Neth.; Abbott, Norw.; Abbott, Philipp.; Abbott, Singapore†; Hospira, Spain; Electra-Box, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, USA; Abbott, Venez.†.*
Thiopental sodium (p.1795·2).
Convulsions; epilepsy; general anaesthesia; raised intracranial pressure in ventilated patients; regional anaesthesia; sedative.

Pentovena *Iquinosa, Spain†.*
⊗ Hidrosmin (p.2305·2).
Peripheral vascular disorders.

Pentox *Farmasa, Braz.; CT, Ger.; Littman, Philipp.; Abdi, Turk.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Pentoxi *Genericon, Austria; Mepha, Switz.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Pentoxifillene *Dexa, Indon.*
Pentoxifylline (p.1367·2).
Intermittent claudication.

Pentoximed *S Med, Austria.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Pentoxin *Ratiopharm, Fin.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Pentoxy *Heumann, Ger.†.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Pentoxyl-EP *Extractum, Hung.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Pentral *Bunker, Braz.*
Pentoxifylline (p.1367·2).

Pentrax *Medicis, Canad.; Alliance, Irl.; Alliance, UK; GenDerm, USA.*
Coal tar (p.1616·2).
Scalp disorders.

Pentren *Pisa, Mex.*
Omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pentrexyl
BMS, Belg.
Ampicillin (p.204·1) or ampicillin sodium (p.204·1).
Bacterial infections.

BMS, Denm.; BMS, Ital.; BMS, Neth.†; BMS, Norw.
Ampicillin sodium (p.204·1).
Bacterial infections.

BMS, Gr.
Ampicillin (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

BMS, Hong Kong; BMS, Thai.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

BMS, Mex.; BMS, Philipp.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Pentrexyl Expec *BMS, Mex.*
Ampicillin trihydrate (p.204·2); bromhexine hydrochloride (p.1552·2).
Bacterial infections of the respiratory tract.

Pentrexyl-S12-H *BMS, Mex.*
Sultamicillin (p.344·1).
Bacterial infections.

Pen-V
Genericon, Austria; Lannacher, Austria.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

General Drugs, Thai.
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

pen-V-basan *Schonenberger, Switz.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pen-V-Cil *Cifarma, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Pen-Vee *Lioh, Canad.†.*
Benzathine phenoxymethylpenicillin (p.212·3) or phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Pen-Vee K *Wyeth-Ayerst, USA.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penveno *Milano, Thai.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Pen-Ve-Oral *Eurofarma, Braz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penvicilin *Gemballa, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Pen-Vi-K *Sandoz, Mex.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Penvir *Sigma, Braz.*
Famciclovir (p.876·1).
Herpesvirus infections.

Penvir Labia *Sigma, Braz.*
Penciclovir (p.901·2).
Herpes labialis.

Penzital *Shreya, Rus.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

PEP *Galpharm, UK.*
Glucose (p.1945·3); caffeine (p.1116·3).
Fatigue.

Pepar *Glenmark, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Pep-Bloc *Sanbe, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepcid *MSD, Austral.†; MSD, Austria; Johnson & Johnson, Canad.; Merck Frosst, Canad.; Pfizer, Fin.; Woelm, Ger.†; MSD, Irl.; MSD, NZ†; Pfizer Consumer, Neth.; Pfizer, Norw.; McNeil, Spain; Pfizer, Swed.; MSD, Switz.†; Johnson & Johnson MSD Consumer, UK; J&J-Merck, USA; Merck, USA.*
Famotidine (p.1730·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Pepcid Complete *Johnson & Johnson, Canad.; Johnson & Johnson, USA.*
Famotidine (p.1730·1); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Dyspepsia; gastrointestinal hyperacidity; heartburn.

Pepcid Duo *Pfizer, Fin.; Pfizer, Swed.*
Famotidine (p.1730·1); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Dyspepsia; gastrointestinal disorders associated with hyperacidity; heartburn.

Pepcidac *McNeil, Fr.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux.

Pepcidual *McNeil, Ger.; McNeil, Ital.*
Famotidine (p.1730·1); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Pepcidduo *McNeil, Fr.; Pfizer, Norw.*
Famotidine (p.1730·1); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn.

Pepcidin *MSD, Denm.†; MSD, Fin.; MSD, Neth.; MSD, Norw.; MSD, Swed.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepcidina *MSD, Port.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepcidine *MSD, Austral.; MSD, Belg.†; MSD, Hong Kong; MSD, Malaysia; MSD, Mex.; MSD, NZ†; MSD, Philipp.; MSD, Singapore; MSD, Switz.†; M & H, Thai.; MSD, Venez.†.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepcidtwo *Johnson & Johnson MSD Consumer, UK.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); famotidine (p.1730·1).
Dyspepsia; heartburn.

Pepcine *Masa, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepdenal *Macrophar, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepdif *Sanofi Synthelabo, Turk.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepdine *MSD-Chibret, Fr.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepdite *Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Infant feed (p.1922·1).
Bowel disorders; malabsorption syndromes; protein or lactose intolerance.

Pepdual *McNeil, Spain.*
Famotidine (p.1730·1); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastro-oesophageal reflux.

Pepdul *MSD Chibropharm, Ger.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepermentdruppels *Pharmacare, S.Afr.*
Peppermint oil (p.1761·2).
Colic; flatulence.

Pepevit *Diba, Mex.*
Nicotinic acid (p.1957·3).
Hypercholesterolaemia; pellagra.

Pepfamin *Siam Bheasach, Thai.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepfiz *Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Thai.*
Amylase (p.2256·3); papain (p.2362·3); simeticone (p.1770·2).
Dyspepsia; flatulence.

Pepleo *Kayaku, Jpn.*
Peplomycin sulfate (p.763·2).
Malignant neoplasms.

Peponen *Biogal, Pol.; Biogal, Rus.*
Cucurbita oil (p.2290·2).
Benign prostatic hyperplasia.

Peposterol *Herbapol Poznan, Pol.*
Cucurbita oil (p.2290·2).
Benign prostatic hyperplasia.

Pep-Rani *Medinfar, Port.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peprazol *Libbs, Braz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepsaletten N *Cheplapharm, Ger.*
Glutamic acid hydrochloride (p.1947·1).
Gastrointestinal disorders.

Pepsamar *Gador, Arg.; Sanofi-Aventis, Braz.; GSK, Gr.; Lepori, Port.; Sanofi-Aventis, Spain.*
Aluminium hydroxide (p.1706·2).
Antacid; dyspepsia; gastric hyperacidity; hyperphosphataemia; peptic ulcer.

Pepsamar Duo *Gador, Arg.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Pepsamar Plus *Angelini, Port.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Pepsane *Rosa-Phytopharma, Fr.; Mayoly-Spindler, Mex.*
Guaiazulene (p.2317·3); dimeticone (p.1770·2).
Gastro-oesophageal pain; gastrointestinal disorders.

Pepsaplus *Sanofi-Aventis, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Gastric hyperacidity.

Pepsicaps *Hertz, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Pepsi-Chlor *Streuli, Switz.†.*
Betaine (p.2265·2); pepsin (p.2365·1); citric acid (p.2284·1).
Anorexia; diarrhoea; flatulence.

Pepsidol *Laboratorios Chile, Chile†.*
Simeticone (p.1770·2).
Abdominal distension; flatulence.

Pepsitase *Hua, Thai.*
Pepsin (p.2365·1); amylase (p.2256·3); papain (p.2362·3); gentian (p.2310·3); pancreatin (p.2360·1); activated charcoal (p.1435·2); vitamin B .
Digestive disorders.

Pepsivit *Gemballa, Braz.†.*
Carnitine (p.1932·2); buclizine (p.570·1); vitamin B substances (p.1922·1).
Reduced appetite; tonic.

Pepsogel *Legrand, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Pepsytoin *Pond's, Thai.*
Phenytoin sodium (p.495·2).
Epilepsy.

Peptab *Sanofi-Aventis, Port.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Peptac *Ivax, UK.*
Sodium alginate (p.2141·1); sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux; heartburn; hiatus hernia.

Peptamen *Nestle, Braz.; Nestle, Canad.; Nestle, Fr.; Nestle, Hong Kong; Nestle, Indon.; Nestle Clinical, Irl.; Nestle, Israel; Nestle, Ital.; Nestle, Malaysia; Nestle, Philipp.; Nestle, Rus.; Nestle, Thai.; Nestle, UK; Carnation, USA.*
Preparation for enteral nutrition (p.1922·1).
Gastrointestinal disorders.

Peptan *Vianex (Βιανέξ), Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Peptavlon *SERB, Fr.*
Pentagastrin (p.2364·3).
Test of gastric secretory function.

Peptazol *Montpellier, Arg.; Recordati, Ital.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptgel *Teuto, Braz.*
Aluminium hydroxide (p.1706·2).
Antacid.

Pepti-2000 *Nutricia, Cz.†; Nutricia, Indon.*
Preparation for enteral nutrition (p.1922·1).

Peptic Guard *Genpharm, Canad.*
Famotidine (p.1730·1).

Peptic Relief *Rugby, USA.*
Bismuth salicylate (p.1711·1).
Gastrointestinal disorders.

Peptica *Unison, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepticaine *Pfizer, India.*
Oxetacaine (p.1867·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastritis; gastro-oesophageal reflux; hiatus hernia; peptic ulcer.

Peptical *3-OL, Israel.*
Fructose (p.1945·1); glucose (p.1945·3); phosphoric acid (p.2367·1).
Nausea and vomiting.

Pepticum *Grunenthal, Chile†; Andromaco, Cz.†; Librapharm, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepticus *Montpellier, Arg.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptidiutteli *Valio, Fin.†.*
Infant feed (p.1922·1).
Cow's milk and soya protein intolerance.

Peptifar *Tecnimede, Port.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptigal *Biogal-Teva, Hung.†.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Pepti-Junior *Nutricia, Austral.; Nutricia, Fin.; Diele, Fr.; Nutricia, Indon.; Cow & Gate, Irl.; Cow & Gate, Israel; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Port.; Cow & Gate, UK; Nutricia, Venez.†; Roemmers-Klinos, Venez.†.*
Preparation for enteral nutrition (p.1922·1).
Adjunct in gastrointestinal surgery; cow's milk and soya protein intolerance; diarrhoea; digestive disorders; food allergy; food intolerance; malabsorption syndromes; malnutrition; milk protein intolerance.

Peptimax *Ashbourne, UK†.*
Cimetidine (p.1716·2).
Gastrointestinal disorders.

Peptinal
Note.This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastritis; gastro-oesophageal reflux; hyperphosphataemia; peptic ulcer.

Laboratorios Chile, Chile.
Tablets: Aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastritis; gastro-oesophageal reflux; hyperphosphataemia; peptic ulcer.

Peptinal Forte *Laboratorios Chile, Chile.*
Simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium carbonate (p.1743·1).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux.

Peptinex *Novartis Nutrition, Hong Kong; Novartis Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).

Peptisol *Kalbe, Indon.; Sanghiang, Indon.*
High-protein preparation for enteral nutrition (p.1922·1).

Peptisolv *Unison, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptison *Support, Braz.†; Nutricia, Cz.†; Nutricia, Turk.*
Preparation for enteral nutrition (p.1922·1).

Peptisorb *Nutricia, Austral.†; Nutricia, Fin.; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Pol.; Nutricia, Port.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition (p.1922·1).
Disorders of digestion; malabsorption syndromes.

Pepto Diarrhea Control *Procter & Gamble, USA.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Pepto-Bismol
Note.This name is used for preparations of different composition.
Procter & Gamble, Braz.; Procter & Gamble, Mex.; Procter & Gamble (H&B Care), UK; Procter & Gamble, USA; Procter & Gamble, Venez.†; Zuoz, Venez.†.
Bismuth salicylate (p.1711·1).
Adjunct in peptic ulcer; antacid; diarrhoea; dyspepsia; gastric hyperacidity; heartburn; nausea; peptic ulcer.

Procter & Gamble, Canad.
Caplets; oral liquid: Bismuth salicylate (p.1711·1).
Diarrhoea; dyspepsia; nausea; upset stomach.

Procter & Gamble, Canad.
Tablets: Calcium carbonate (p.1714·1); bismuth salicylate (p.1711·1).
Diarrhoea; dyspepsia; nausea; upset stomach.

Peptochol *Grossman, Mex.†.*
Magnesium sulfate (p.1679·3); boldo (p.2267·2); peptone.
Biliary-tract disorders.

Peptoci *Pharmasant, Thai.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Peptomet Remedica, Thai.†.
Domperidone (p.1726·2).
Delayed gastric emptying; gastro-oesophageal reflux.

Peptonorm Unipharma, Gr.
Sucralfate (p.1772·2).
Peptic ulcer.

Peptonum Linfar, Arg.
Bovine amino acids and polypeptides (p.1922·1).
Dietary supplement.

Peptopancreasi Arrow, Braz.
Pepsin (p.2365·1); pancreatin (p.2360·1).
Digestive system disorders.

Pepto-Pancreasi SIT, Ital.†.
Pepsin (p.2365·1); pancreatin (p.2360·1).
Digestive system disorders.

Peptosan Lafit, Braz.†.
Bismuth salicylate (p.1711·1).

Peptovit Vitapan, Braz.†.
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Peptrad Shin Poong, Philipp.
Tramadol hydrochloride (p.130·3).
Pain.

Peptulan Farmasa, Braz.
Bismuth citrate (p.1710·3).
Gastritis; gastrointestinal hyperacidity; peptic ulcer.

Pepzan Douglas, Austral.; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore; Douglas, Thai.†; TTN, Thai.†.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pepzitrat Berlin-Chemie, Ger.
Pepsin (p.2365·1); citric acid (p.2284·1).
Gastrointestinal disorders.

Pepzol APS, Port.†.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Peracil Boniscontro & Gazzone, Ital.
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Peracin Pharmadica, Thai.
Piperacillin sodium (p.315·2).
Bacterial infections.

Peracon
Note. This name is used for preparations of different composition.
Recalcine, Chile.
Cyproheptadine hydrochloride (p.575·1); carnitine hydrochloride; lysine hydrochloride (p.1922·1).
Reduced appetite.

Solvay, Gr.†; Solvay, Indon.
Isoaminile (p.1563·3).
Cough.

Aventis, S.Afr.†.
Isoaminile cyclamate (p.1563·3).
Coughs.

Peracon Expectorant Noristan, S.Afr.†.
Isoaminile cyclamate (p.1563·3); ammonium chloride (p.1551·3).
Coughs.

Peragit Medic, Denm.
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Peralgin Infabra, Braz.†.
Phenylbutazone calcium (p.117·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Peraljin
Note. This name is used for preparations of different composition.
Aroma, Turk.
Caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Aroma, Turk.
Caffeine (p.1116·3); dipyrone (p.49·2).
Fever; pain.

Perasafe Antec, Singapore; Du Pont, Singapore.
Peroxygen-generating system (p.1655·2).
Instrument sterilisation.

Perasian Asian Pharm, Thai.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Perasint Mayne, Ital.
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Perative
Note. This name is used for preparations of different composition.
Giscard, Arg.
Ketoconazole (p.539·1).
Fungal infections.

Abbott, Austral.; Abbott, Braz.; Abbott, Chile; Abbott, Cz.†; Abbott, Fr.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Mex.; Abbott, Philipp.; Abbott, Turk.; Abbott Nutrition, UK; Abbott, Venez.
Preparation for enteral nutrition (p.1922·1).

Peratsin Orion, Fin.
Perphenazine (p.1017·1), perphenazine decanoate (p.1017·1), or perphenazine enantate (p.1017·2).
Nausea and vomiting; psychoses.

Perazin Hasco-Lek, Pol.
Perazine dimaleate (p.1016·3).
Schizophrenia.

Perazyna Galena, Pol.
Perazine dimaleate (p.1016·3).
Psychoses.

Perbel Medipharma, Arg.
Benzyl benzoate (p.2036·1); permethrin (p.2048·2).
Pediculosis.

Perbilen Sanofi-Aventis, Spain.
⊗ Piretanide (p.1372·3).
Hypertension; oedema.

Perbrons Casel, Turk.
Oxolamine (p.1567·1).
Coughs.

Percapyl GSK, Arg.†.
Permethrin (p.2048·2).
Pediculosis.

Percas Ivax, Arg.
Etoposide (p.718·1).
Malignant neoplasms.

Perchloracap Mallinckrodt, USA†.
Potassium perchlorate (p.2174·3).
To reduce accumulation of pertechnetate by the choroid plexus, salivary glands, and thyroid.

Percital Piam, Ital.
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Perclar Parke, Davis, Ital.†.
Mesoglycan sodium (p.2342·3).
Thrombosis prophylaxis.

Perclin Fortbenton, Arg.
Clindamycin phosphate (p.251·2); benzoyl peroxide (p.1590·2).
Acne.

Percocet BMS, Canad.; Taro, Israel; Endo, USA.
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Fever; pain.

Percocyn Landson, Indon.
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Percodan
BMS, Canad.
⊗ Oxycodone hydrochloride (p.106·2); aspirin (p.20·3).
Fever; inflammation; pain.

Taro, Israel; Endo, USA.
⊗ Oxycodone hydrochloride (p.106·2); oxycodone terephthalate (p.106·2); aspirin (p.20·3).
Pain.

Percof Eurofarma, Braz.
Levodropropizine (p.1557·3).
Coughs.

Percoffedrinol N Passauer, Ger.†.
Caffeine (p.1116·3).
Fatigue.

Percogesic Medtech, USA.
Paracetamol (p.108·1); phenyltoloxamine citrate (p.588·1).
Fever; pain.

Percogesic Extra Strength Medtech, USA.
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Pain.

Percolone Endo, USA†.
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Percucor Pharmaselect, Austria†.
Glyceryl trinitrate (p.1296·2); amyl nitrite (p.1437·3); ethyl nicotinate (p.52·1); camphor (p.2273·2).

Percutafeine Pierre Fabre Dermo-Cosmetique, Arg.; Asta Medica, Braz.†; Pierre Fabre Sante, Fr.
Caffeine (p.1116·3).
Cellulite; obesity.

Percutalfa Pierre Fabre Sante, Singapore.
Glycolic acid (p.1598·1); fatty acids.
Prevention of stretch marks.

Percutalgine
Note. This name is used for preparations of different composition.
Besins, Belg.; Piette, Thai.†.
⊗ Dexamethasone acetate (p.1526·1); salicylamide (p.121·2); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Besins, Fr.
⊗ Dexamethasone (p.1526·1) or dexamethasone acetate (p.1526·1); salicylamide (p.121·2); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Peri-articular and soft-tissue disorders.

Besins, Rus.†.
⊗ Dexamethasone acetate (p.1526·1); salicylamide (p.121·2).
Skin disorders.

Percutane Douglas, Austral.
Capsicum oleoresin (p.2276·2); lappa (p.2330·3); arnica (p.2260·2); aloe vera (p.1588·2).
Musculoskeletal and joint disorders.

Percutol Pliva, UK.
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Perderm Schering-Plough, Hong Kong; Schering-Plough, Hung.†; Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Singapore†.
⊗ Alclometasone dipropionate (p.1516·1).
Skin disorders.

Perdiem Novartis Consumer, USA.
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation.

Perdin Merck, Port.
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; schizophrenia.

Perdiphen Spitzner, Ger.†.
⊗ Ephedrine hydrochloride (p.1558·2); paracetamol (p.108·1); diphenylpyraline hydrochloride (p.578·2).
Influenza symptoms.

Perdipina Astellas, Ital.
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Perdipine Astellas, Indon.; Astellas, Jpn.
Nicardipine hydrochloride (p.1348·1).
Heart failure; hypertension.

Perdix Schwarz, Irl.†; Schwarz, Israel; Omnimed, S.Afr.; UCB, UK.
Moexipril hydrochloride (p.1343·2).
Hypertension.

Perdofemina Janssen-Cilag, Belg.
Ibuprofen (p.64·2).
Fever; pain.

Perdogrip Janssen-Cilag, Belg.†.
Paracetamol (p.108·1); vitamin C (p.1983·3).
Cold symptoms.

Perdolan Janssen-Cilag, Belg.
Paracetamol (p.108·1).
Formerly known as Perdolan Mono.
Fever; pain.

Perdolan Codeine Janssen-Cilag, Belg.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Formerly known as Perdolan Duo.
Pain.

Perdolan Compositum
Note. This name is used for preparations of different composition.
Janssen-Cilag, Belg.
Suppositories (adult); Tablets: Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Formerly contained aspirin, paracetamol, caffeine, and codeine phosphate.
Fever; pain.

Janssen-Cilag, Belg.
Suppositories (infant and child): Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Perdolan Mono Janssen-Cilag, Port.†.
Paracetamol (p.108·1).
Fever; pain.

Perdolan Mono C Janssen-Cilag, Belg.†.
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Perdophen Janssen-Cilag, Belg.
Ibuprofen (p.64·2).
Fever; pain.

Perdox PharmaConsult, Hung.
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; schizophrenia.

Perduretas Codeina Nupel, Spain.
Codeine phosphate (p.37·2).
Cough.

Perebron
Laboratorios Chile, Chile; Angelini, Ital.; Elmor, Venez.
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Cough; respiratory-tract disorders.

Santa, Turk.
Oxolamine phosphate (p.1567·1).
Coughs.

Perebron con Miel Elmor, Venez.†.
Oxolamine (p.1567·1); honey (p.1948·2).
Cough.

Peremesin BMS, Ger.†; Meda, Norw.
Meclozine hydrochloride (p.584·3).
Nausea; vertigo; vomiting.

Peremesin N BMS, Ger.†.
Meclozine hydrochloride (p.584·3).
Nausea; vertigo; vomiting.

Peremid Etifar, Venez.†.
Metoclopramide (p.1747·3).
Vomiting.

Perenal Medicus, Gr.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Perenan Sanofi Synthelabo, Hong Kong†; Sanofi Synthelabo, Thai.†.
Codergocrine mesilate (p.363·3).
Behavioural and psychological disorders in the elderly.

Perennia Wyeth Lederle, Austria.
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Perental BPL-Meizler, Braz.†.
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Perenterol UCB, Ger.; Biocodex, Switz.
Saccharomyces boulardii (p.2372·3).
Acne; diarrhoea.

Perenteryl Merck, Chile.
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Peresal Henkel, Ger.†; Ecolab, Ital.
Hydrogen peroxide (p.1647·3); peracetic acid (p.1655·2).
Disinfection of dialysis equipment; instrument disinfection.

Perfadex Vitrolife, Swed.
⊗ Dextran 40 (p.1059·1) in electrolytes.
Organ perfusion before transplantation.

Perfalgan BMS, Austral.; BMS, Austria; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; IFET (ΙΦΕΤ), Gr.; BMS, Hung.; BMS, Irl.; Upsa, Ital.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Spain; BMS, Swed.; UPSA, Switz.; BMS, UK.
Paracetamol (p.108·1).
Fever; pain.

Perfan Belpharma, Belg.; Carinopharm, Ger.; Myogen, Irl.; Biomedica, Ital.; Myogen, Neth.; Aventis, UK.
Enoximone (p.1278·2).
Heart failure.

Perfane OTL, Fr.†.
Enoximone (p.1278·2).
Heart failure.

Perfectil
Vitabiotics, Hong Kong.
Vitamin and mineral preparation with cystine, echinacea, and lappa (p.1922·1).

Vitabiotics, UK.
Multivitamin, amino-acid, mineral, and herbal preparation (p.1922·1).

Perfer Luper, Braz.†.
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Perfluoron Alcon, USA.
Perfluorooctane (p.2365·3).
Ophthalmic tamponade.

Perflux Fresenius Kabi, Austria.
Electrolyte infusion (p.1667·1).
Forced diuresis.

Perfocrat Phytofarm Kleka, Pol.
Crataegus (p.2289·1); St John's wort (p.422·3); melissa (p.2339·3).
Anxiety.

Perfocyn Bell, India.
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3); benzocaine (p.1854·1); acetic acid (p.2244·2).
Ear infections.

Performer Piam, Ital.
Cefaclor (p.217·2).
Bacterial infections.

Perforomist Dey, USA.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Perfracort Fortbenton, Arg.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Perfudal Odin, Spain.
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Perfudan Piam, Ital.†.
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders.

Perfungol
Note. This name is used for preparations of different composition.
Montpellier, Arg.†.
Chlorocresol (p.1640·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Fungal skin infections.

Bago, Chile.
Ointment: Chlorocresol (p.1640·1); nicotinamide (p.1957·3); cholesterol (p.2029·1).
Fungal skin infections.

Bago, Chile.
Topical powder: Chlorocresol (p.1640·1); zinc oxide (p.1621·2); boric acid (p.2268·1).
Fungal skin infections.

Perfus Multivitaminico Rius, Spain.
Carbazochrome (p.1058·2); vitamins (p.1922·1); electrolytes.
Haemorrhage; skeletal muscle disorders.

Perfusalgan BMS, Belg.
Paracetamol (p.108·1).
Fever; pain.

Perfusion mixte Streuli, Switz.
Sodium chloride (p.1686·1) infusion with glucose.
Dehydration.

Perfusion de PAS Bichsel, Switz.†.
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Pergalen Millet-Franklin, Arg.
Sodium apolate (p.1397·1); benzyl nicotinate (p.28·1).
Haematomas; skin ulcers; superficial thrombosis; thrombophlebitis.

Pergamid Pfizer, Arg.
⊗ Aniracetam (p.363·2).
Mental function impairment.

Perganit AstraZeneca, Ital.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; hypertension; pulmonary oedema.

Pergidal Valeas, Ital.
Macrogol 4000 (p.2336·3).
Constipation.

Pergogreen *Faran, Gr.†*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Pergonal *Serono, Arg.†; Serono, Braz.; Serono, Canad.†; Novartis, Chile†; Faran, Gr.†; Serono, Hong Kong; Serum Institute, India; Teva, Israel†; Serono, Mex.†; Serono, Neth.†; Serono, Rus.; Serono, S.Afr.†; Serono, Spain†; Serono, Switz.†; Serono, Turk.; Serono, USA†; Serono, Venez.†.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Pergotime *Serono, Belg.; Serono, Denm.; Serono, Fr.; Serono, Norw.; Serono, Swed.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Pergoveris *Serono, Cz.; Serono, Port.; Merck Serono, UK.*
⊗ Follitropin alfa (p.2104·1); lutropin alfa (p.2112·2).
Female infertility.

Perhip *Hasco-Lek, Pol.*
St John's wort (p.422·3).
Depression.

Peri Solution *Otsuka, Indon.*
Electrolyte infusion with glucose (p.1667·1).
Renal insufficiency.

Periactin *MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Denm.†; MSD, Irl.; Avantgarde, Ital.; MSD, NZ; MSD, Neth.; MSD, S.Afr.; Sigma-Tau, Spain; MSD, Swed.; MSD, Switz.†; M & H, Thai.; MSD, UK; MSD, Venez.†.*
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; hypersensitivity reactions; migraine and other vascular headache; pruritus; reduced appetite; urticaria.

Periactine *MSD-Chibret, Fr.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions.

Periamin *Fresenius Kabi, Spain†.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periamin G *Fresenius Kabi, Austria; Baxter, Ger.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periamin X *Baxter, Ger.*
Amino-acid, xylitol, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periatin *MSD, Braz.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; migraine and other vascular headaches; reduced appetite.

Pericaina *Senese, Ital.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Perical *Besins, Fr.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Pericam *Clonmel, Irl.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Pericate *Unipharm, Israel.*
Haloperidol decanoate (p.1000·2).
Psychoses.

Pericel *Pharmafar, Ital.*
Flavodate sodium (p.2304·2).
Vascular disorders.

Pericephal *Arcana, Austria.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Perichol *Pharmacodane, Denm.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Peri-Colace
Note. This name is used for preparations of different composition.
Wellspring, Canad.†.
Casanthranol (p.1715·1); docusate sodium (p.1725·1).
Constipation.

Purdue, USA.
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Formerly contained casanthranol and docusate sodium.
Constipation.

Perida *Codal Synto, Thai.*
Haloperidol (p.1000·2).
Behaviour disorders in children; psychoses; stuttering; tics.

Peridal *Medley, Braz.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders; nausea and vomiting.

Peridane *Columbia, Mex.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; thrombosis prophylaxis.

Perident *Master, Chile†.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Peridex *Zila, Canad.†; Procter & Gamble, USA.*
Chlorhexidine gluconate (p.1635·3).
Gingivitis.

Peridil *Cryopharma, Mex.*
Azapetine phosphate (p.1222·1).
Peripheral vascular disorders.

Peridin-C *Beutlich, USA.*
⊗ Hesperidin methyl chalcone (p.2305·2); hesperidin complex (p.2304·3); ascorbic acid (p.1983·3).
Capillary bleeding.

Peridisol *Human, Hung.†.*
A range of glucose, sodium chloride, magnesium chloride, calcium chloride, and sodium lactate solutions with or without potassium chloride (p.1670·3).
Peritoneal dialysis.

Peridol *Technilab, Canad.†.*
Haloperidol (p.1000·2).
Behaviour disorders; psychoses; Tourette syndrome.

Peridom-M *Masa, Thai.*
Domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea; vomiting.

Peridon *Lafedar, Arg.; Italchimici, Ital.*
Domperidone (p.1726·2).
Gastrointestinal disorders; gastrointestinal motility disorders.

Peridont *Oftalmi, Venez.*
Chlorhexidine gluconate (p.1635·3).
Gingivitis.

Peridor *Unipharm, Israel.*
Haloperidol (p.1000·2).
Hiccup; psychiatric disorders; Tourette syndrome; vomiting.

Peri-Dos Softgels *Goldline, USA†.*
Docusate sodium (p.1725·1); casanthranol (p.1715·1).
Constipation.

Peridys *Pierre Fabre Sante, Fr.*
Domperidone (p.1726·2).
Dyspepsia; gastro-oesophageal reflux; nausea and vomiting.

Perifas *Otto, Indon.*
Cinnarizine (p.573·1).
Motion sickness; peripheral vascular disorders; vestibular disorders.

Perifem *Organon, Spain.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Perifer H1 *BA Farma, Port.†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Periflex *Braun, Ital.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Perifusin *Fresenius Kabi, Gr.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Perigard *Glenmark, India.*
Perindopril (p.1368·2).
Heart failure; hypertension.

Perigard D *Glenmark, India.*
⊗ Perindopril (p.1368·2); indapamide (p.1314·1).
Hypertension.

Perigard DF *Glenmark, India.*
⊗ Perindopril (p.1368·2); indapamide (p.1314·1).
Hypertension.

Perika *VSM, Belg.; Schwabe, Spain.*
St John's wort (p.422·3).
Depression; tonic.

Perikabiven *Fresenius Kabi, Fr.*
Amino-acid, carbohydrate, lipid (from soya oil (p.1965·3)), and electrolyte infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Perikan *Austroplant, Austria.*
St John's wort (p.422·3).
Depression.

Perikliman *Kwizda, Austria.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Perikursal *Wyeth Lederle, Austria; Wyeth, Ger.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Biphasic oral contraceptive.

Perilax *Nordic Drugs, Denm.; Pharmacare, S.Afr.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Perilox *Drossapharm, Switz.*
Metronidazole (p.837·1).
Rosacea.

Perinace *CCM, Malaysia.*
Perindopril (p.1368·2).
Heart failure; hypertension.

Perinal
Note. This name is used for preparations of different composition.
Tempo Scan Pacific, Indon.
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.
⊗ Hydrocortisone (p.1535·2); lidocaine hydrochloride (p.1862·3).
Anal and perianal pain and pruritus.

Perindan *Medico Uno, Hung.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Perindo *Alphapharm, Austral.*
Perindopril erbumine (p.1368·3).
Atherosclerosis; heart failure; hypertension.

Perinorm *Ipca, India; Ipca, Rus.; Nat Druggists, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; gastritis; gastro-oesophageal reflux; nausea and vomiting; postoperative gastric hypotonia.

Perio-Aid *Dentaid, Chile.*
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

Perio-Aid c Cloruro de Cetilpiridinio *Dentaid, Chile.*
Chlorhexidine gluconate (p.1635·3); cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Periobacter *Naf, Arg.*
Chlorhexidine (p.1635·2); xylitol (p.1998·2).
Mouth infections.

Periobacter Prof Avio *Naf, Arg.*
Chlorhexidine acetate (p.1635·2); thymol (p.1664·3).

Periochip *Dexcel, Denm.; Arriani, Gr.; Dexcel, Israel; Dexcel, Neth.; Dexcel, Norw.; Dexcel, Port.; Vitaflo, Swed.; Dex Biotec, Switz.; Astra, USA.*
Chlorhexidine gluconate (p.1635·3).
Periodontal disease.

Periocline *Sunstar, Jpn.*
Minocycline hydrochloride (p.300·3).
Periodontitis.

Period Pain Relief *Herbal Concepts, UK.*
Alchemilla; motherwort (p.2347·3); valerian (p.2410·1); pulsatilla (p.2376·3); vervain (p.2413·3); helonias (p.2318·3).
Dysmenorrhoea; premenstrual syndrome.

Periodent *Grimberg, Arg.*
Chlorhexidine gluconate (p.1635·3); xylitol (p.1998·2).
Mouth disorders.

Periodentyl
Note. This name is used for preparations of different composition.
GSK, Mex.
Mouthwash: Triclosan (p.1665·2); zinc chloride (p.1999·1); vitamin E acetate (p.1992·3); xylitol (p.1998·2).
Oral hygiene.

GSK, Mex.
Toothpaste: Triclosan (p.1665·2); zinc citrate (p.1999·2); enoxolone (p.50·1); sodium monofluorophosphate (p.1964·3).
Oral hygiene.

Periodil
Note. This name is used for preparations of different composition.
Pharmatrix, Arg.
Dental gel: Chlorhexidine gluconate (p.1635·3).
Oral hygiene; periodontal disorders.

Pharmatrix, Arg.
Mouth spray; mouthwash: Chlorhexidine gluconate (p.1635·3); cetylpyridinium chloride (p.1635·1).
Oral hygiene; periodontal disorders.

Periodontil *Sanofi-Aventis, Braz.*
Spiramycin (p.333·1); metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Periofem Ciclico *Beta, Arg.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Periofem Continuo *Beta, Arg.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Periogard *Colgate Oral, USA.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Periogard Chlorohex *Colgate Oral Care, Austral.†; Colgate-Palmolive, Ger.†; Colgate-Palmolive, Ital.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders; oral hygiene.

Periogard Plus
Note. This name is used for preparations of different composition.
Colgate-Palmolive, Ital.
Oral drops: Cetylpyridinium chloride (p.1635·1).
Gum disorders.

Colgate-Palmolive, Ital.
Toothpaste: Zinc citrate (p.1999·2); sodium monofluorophosphate (p.1964·3).
Gingivitis.

Periokin *Pasteur, Chile.*
Chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis; oral hygiene.

PerioMed *Omnii, USA.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Periosan *Vitae, Mex.*
Doxycycline (p.267·1).
Bacterial infections.

Periostat *Alliance, Irl.; Taro, Israel; CollaGenex, Neth.; Isdin, Port.; Karr, Switz.; Alliance, UK; CollaGenex, USA.*
Doxycycline hyclate (p.267·1).
Pperiodontitis.

Periotret *Verisfield, Gr.*
Metronidazole benzoate (p.837·1).
Bacterial mouth infections.

Perioxidin
Note. This name is used for preparations of different composition.
Andromaco, Chile†.
Chlorhexidine gluconate (p.1635·3).
Oral hygiene.

GSK, Mex.
Dental gel: Chlorhexidine gluconate (p.1635·3).
Mouth infections.

GSK, Mex.
Mouthwash: Chlorhexidine gluconate (p.1635·3); xylitol (p.1998·2).
Gingivitis; periodontitis.

Peripan *Mepha, Braz.*
Pentoxifylline (p.1367·2).

Periphramine *Braun, Spain.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periplasmal *Braun, Ger.; Braun, Hung.†; Braun, Pol.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periplasmal G *Braun, Spain.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periplasmal XE *Braun, Ger.*
Amino-acid, xylitol, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Periplum
Note. This name is used for preparations of different composition.
Fortbenton, Arg.
Fluconazole (p.532·1).
Fungal infections.

Italfarmaco, Ital.
Nimodipine (p.1357·2).
Neurological deficit following cerebral vasospasm.

Peripress *Pfizer, Denm.†; Pfizer, Fin.†.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Peripride *Ipca, India.*
Mosapride citrate (p.1750·3).
Dyspepsia; gastro-oesophageal reflux; gastroparesis.

Periset *Ipca, India.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Perison *Strathmann, Ger.*
Escherichia coli; *Morganella morganii*; *Proteus mirabilis*; *Klebsiella pneumoniae*; *Enterococcus faecalis* (p.2372·3).
Urinary-tract infections.

Peristaltine *Novartis Sante, Fr.*
Cascara (p.1715·2).
Constipation.

Peritofundinas *Braun, Port.*
Glucose; sodium chloride; calcium chloride; magnesium chloride; potassium chloride; sodium lactate (p.1670·3).
Peritoneal dialysis.

Peritol *Egis, Cz.; Medphano, Ger.; EGIS, Hung.; Themis Chemicals, India; Egis, Pol.; Egis, Rus.*
Cyproheptadine hydrochloride (p.575·1).
Allergic skin disorders; angioedema; carcinoid syndrome; hypersensitivity reactions; insect bites; migraine and other vascular headaches; pruritus; reduced appetite; rhinitis.

Peritone *Blackmores, Austral.*
Aloes (p.1705·2); senna (p.1769·2); cascara (p.1715·2); ginger (p.1732·3); cardamom fruit (p.2277·1); peppermint oil (p.1761·2).
Constipation.

Peritoneal *Fresenius Kabi, Gr.*
Calcium; magnesium; sodium chloride; sodium acetate; glucose (p.1670·3).
Peritoneal dialysis.

Peritoneal Lactate *ANB, Thai.*
Anhydrous glucose; sodium chloride; sodium lactate; calcium chloride; magnesium chloride; sodium metabisulfite (p.1670·3).
Peritoneal dialysis.

Peritrast
Kohler, Ger.
Lysine amidotrizoate (p.1477·1).
Radiographic contrast medium.

Kohler, Hung.
Lysine amidotrizoate (p.1477·1) with or without sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Peritrast comp *Kohler, Ger.*
Sodium amidotrizoate (p.1475·3); lysine amidotrizoate (p.1477·1).
Radiographic contrast medium.

Peritrast-Infusio 160/32% *Kohler, Ger.†.*
Lysine amidotrizoate (p.1477·1).
Radiographic contrast medium.

Peritrast-Infusio 180/31% *Kohler, Ger.*
Sodium amidotrizoate (p.1475·3); lysine amidotrizoate (p.1477·1).
Radiographic contrast medium.

Peritrast-Oral CT *Kohler, Ger.*
Lysine amidotrizoate (p.1477·1); sodium amidotrizoate (p.1475·3).
Contrast medium for computer tomography of the abdominal cavity.

Peritrast-Oral-GI *Kohler, Ger.*
Lysine amidotrizoate (p.1477·1).
Contrast medium for gastrointestinal radiography.

Peritrast-RE *Kohler, Ger.*
Lysine amidotrizoate (p.1477·1).
Contrast medium for rectal radiography.

Peritrate *Pfizer, India; Teofarma, Ital.; Pfizer, Thai.*
Pentaerithrityl tetranitrate (p.1366·3).
Angina pectoris.

Peritrol *Orapharma, Neth.*
Minocycline hydrochloride (p.300·3).
Periodontitis.

Perivar *Ipsen, Ger.†*
⊗ Troxerutin (p.2305·1); heptaminol hydrochloride (p.2319·1); ginkgo biloba (p.2311·1).
Haemorrhoids; venous insufficiency.

Perivar Rosskaven *Intersan, Ger.†*
Aesculus (p.2248·2).
Venous insufficiency.

Perivar Venensalbe *Ipsen, Ger.†*
Heparin sodium (p.1301·2).
Soft-tissue injury; vascular disorders.

Perivasc *Alphapharm, Austral.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Periven *Fresenius Kabi, Ital.*
Amino-acid, glucose, lipid (from soya oil (p.1965·3)), and electrolyte infusion (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Perkapil *Kurtsan, Turk.*
Dipyrithione (p.1595·1).
Seborrhoeic dermatitis of the scalp.

Perlane *Medicis, USA.*
Hyaluronic acid (p.2320·1).
Facial wrinkles.

Perlas De PMMA con Gentamicina *Merck, Chile.*
Methylmethacrylate methacrylate copolymer (p.2343·3); gentamicin sulfate (p.282·1).
Bone and soft-tissue infections.

Perlatos *Quesada, Arg.*
Levodropropizine (p.1557·3).
Coughs.

Perlea *Elea, Arg.*
Multivitamin and mineral preparation (p.1922·1).

Perlic *Guidotti, Spain.*
Frovatriptan succinate (p.622·3).
Migraine.

Perlice *Galderma, India.*
Permethrin (p.2048·2).
Pediculosis.

Perlinganit *Gebro, Austria; Schwarz, Cz.; Schwarz, Fin.; Schwarz, Ger.; Schwarz, Hung.†; Schwarz, Philipp.; Schwarz, Pol.; Schwarz, Rus.; Orion, Swed.†; Schwarz, Switz.; Adeka, Turk.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertension; hypertensive crisis; ischaemic heart disease; myocardial infarction.

Perlol *Asian Pharm, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Perloxx *Athlon, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Perludil *Collins, Mex.*
Algestone (p.2082·2); estradiol (p.2097·2).
Menstrual disorders.

Perlutal *Boehringer Ingelheim, Arg.; Boehringer Ingelheim Promeco, Mex.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Endometriosis; female infertility; injectable contraceptive; menstrual disorders.

Perlutan *Boehringer Ingelheim, Braz.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Injectable contraceptive.

Perlutex *Leo, Denm.; Leo, Norw.*
Medroxyprogesterone acetate (p.2113·1).
Endometriosis; menopausal disorders; progestogen; test of ovarian function; uterine cancer.

Permadoze *Alpharma, Port.*
Cyanocobalamin (p.1980·2).
Iron-deficiency anaemia; vitamin B deficiency.

Permafoam *Hartmann, Fr.*
Polyurethane foam dressing (p.1611·1).
Wounds.

Permapen *Roerig, USA.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Permasol *Munir, Turk.*
Potassium permanganate (p.1659·1).
Suppurating eczematous reactions; wounds.

Permaton *Sanval, Braz.†*
Potassium permanganate (p.1659·1).

Permax *Aspen, Austral.; Lilly, Austria; Lilly, Belg.; Shire, Canad.; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Mex.; Aspen, NZ; Lilly, Neth.; Lilly, Port.; Lilly, S.Afr.; Lilly, Switz.; Lilly, Turk.; Athena Neurosciences, USA†.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Permecil *Prieto, Arg.*
Benzyl benzoate (p.2036·1); permethrin (p.2048·2).
Pediculosis.

Permetel *Teuto, Braz.†*
Permethrin (p.2048·2).
Pediculosis.

Permetrix *Galenogal, Braz.†*
Permethrin (p.2048·2).

Permicaps *Bago, Arg.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Permidal *Liferpal, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Permitabs *Centrapharm, UK.*
Potassium permanganate (p.1659·1).
Wound cleansing.

Permite *Galderma, India.*
Permethrin (p.2048·2).
Pediculosis.

Permitil *Panalab, Arg.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Permixon *Pierre Fabre, Arg.; Germania, Austria; Asta Medica, Braz.†; Pierre Fabre, Fr.; Pierre Fabre, Israel; Pierre Fabre, Ital.; Pierre Fabre, Mex.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Singapore; Pierre Fabre, Spain; Robapharm, Switz.; Pierre Fabre, Thai.; Leti, Venez.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia; prostatic adenoma; prostatitis.

Permod *Francia, Ital.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Permotil *Sofar, Ital.*
Domperidone maleate (p.1726·3).
Gastrointestinal disorders.

Permucal *Sankyo, Venez.*
⊗ A heparinoid (p.1305·2); prednisolone (p.1540·3); oxypolyethoxidodecane; hexachlorophene (p.1646·1).
Haemorrhoids.

Permut *Eurofarma, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Permvastat *Permatec, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Permyo *Ferron, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Pernamed *Medifive, Thai.*
Perphenazine (p.1017·1).
Nausea and vomiting; psychoses.

Pernazene *Sanofi Synthelabo, Thai.*
⊗ Tymazoline hydrochloride (p.1575·1).
Nasal congestion.

Pernazine *Atlantic, Thai.*
Perphenazine (p.1017·1).
Nausea and vomiting; psychoses.

Pernazinum *Labor, Pol.*
Perazine dimaleate (p.1016·3).
Anxiety disorders; obsessive-compulsive disorder; psychoses.

Pernexin *Schering, Ital.*
Iron succinyl-protein complex (p.1953·2).
Anaemias; iron deficiency.

Pernionin N *Krewel, Ger.†*
Methyl salicylate (p.85·3); sage oil (p.2382·3).
Circulatory disorders.

Pernionin Thermo Teilbad *Krewel, Ger.*
Benzyl nicotinate (p.28·1).
Formerly known as Pernionin Teil-Bad.
Bath additive; musculoskeletal and joint disorders; peripheral vascular disorders.

Pernionin Thermo Vollbad *Krewel, Ger.*
Benzyl nicotinate (p.28·1).
Pernionin Voll-Bad N formerly contained Norway spruce oil, benzyl nicotinate, and methyl nicotinate.
Bath additive; musculoskeletal and joint disorders.

Pernox *Westwood-Squibb, Canad.; Westwood, USA.*
Polyethylene granules (abrasive) (p.1585·3); sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne.

Perocur
EciFarma, Chile†.
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Hexal, Ger.
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea.

Perofen *Remedica, Hong Kong; Remedica, Malaysia; Remedica, Thai.†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; toothache.

Peroma *Vianex (Βιανέξ), Gr.*
Nilvadipine (p.1357·1).
Hypertension.

Perosall *Biomed Krakow, Pol.*
Pollen allergen extracts (p.2370·2) (p.2250·2).
Hyposensitisation.

Perospir *Slovakofarma, Cz.†*
Thyme (p.2401·1); sambucus (p.2383·1); achillea (p.2245·2); coltsfoot (p.1555·1); urtica (p.2409·3).
Respiratory-tract disorders.

Peroxacne *Isdin, Spain.*
Benzoyl peroxide (p.1590·2).
Acne.

Peroxiben *Isdin, Port.; Isdin, Spain.*
Benzoyl peroxide (p.1590·2).
Acne.

Peroxiben Plus *Isdin, Chile.*
Benzoyl peroxide (p.1590·2).
Acne; seborrhoea.

Peroximicina *LKM, Arg.*
Benzoyl peroxide (p.1590·2); erythromycin (p.269·2).
Acne.

Peroxx *Vianex (Βιανέξ), Gr.†*
Rofecoxib (p.121·1).
Inflammatory disorders.

Peroxy-Dental *Gemi, Pol.*
Hydrogen peroxide 30% (p.1648·1).
Periodontitis.

Peroxygel *Gemi, Pol.*
Hydrogen peroxide 30% (p.1648·1).
Wound disinfection.

Peroxyl *Colgate-Palmolive, Austral.; Colgate, Gr.; Colgate-Palmolive, Neth.; Colgate-Palmolive, UK; Colgate-Palmolive, USA.*
Hydrogen peroxide (p.1647·3).
Mouth disorders.

Perpector *Grossmann, Switz.†*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); potassium iodide (p.2169·2); primula root (p.2372·2); valerian (p.2410·1).
Coughs.

Perphenan *Taro, Israel.*
Perphenazine (p.1017·1).
Anxiety; nervous states; vomiting.

Persantin
Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Gr.; IFET (ΙΦΕΤ), Gr.; Boehringer Ingelheim, Hong Kong; German Remedies, India; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia†; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Unilfarma, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, UK; Boehringer Ingelheim, Venez.
Dipyridamole (p.1268·1).
Angina pectoris; ischaemic heart disease; myocardial infarction; platelet function disorders; stress testing in myocardial perfusion imaging; thromboembolic disorders.

Boehringer Ingelheim, Spain.
Dipyridamole hydrochloride (p.1268·3).
Thrombosis prophylaxis.

Persantine *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, USA.*
Dipyridamole (p.1268·1).
Ischaemic heart disease; thromboembolic disorders; vasodilator in myocardial perfusion imaging.

Persen *Lek, Cz.; Lek, Pol.; Lek, Rus.*
Valerian (p.2410·1); melissa (p.2339·3); peppermint leaf (p.1761·2).
Nervous disorders; sleep disorders.

Persidal *Mersifarma, Indon.*
Risperidone (p.1024·2).
Psychoses.

Persivate *Pharmacare, S.Afr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Perskindol Classic
Note.This name is used for preparations of different composition.
Vifor, Switz.
Bath additive: Pine-needle oil (p.2368·2); orange oil (p.2357·2); lavender oil (p.2331·2); rosemary oil (p.2381·3); lemon oil (p.2332·3); eucalyptus oil (p.2301·2); sweet birch oil (p.86·2); jojoba oil.
Bath additive; cold symptoms; muscle and joint pain; superficial circulatory disorders.

Vifor, Switz.
topical fluid; Topical gel; topical spray; wipes: Menthol (p.2340·1); sweet birch oil (p.86·2); pine-needle oil (p.2368·2); lemon oil (p.2332·3); orange oil (p.2357·2); bergamot oil (p.2265·1); rosemary oil (p.2381·3); lavender oil (p.2331·2); terpineol (p.2396·1); isobornyl acetate.
Muscle and joint pain.

Perskindol Cool *Vifor, Switz.*
Menthol (p.2340·1).
Soft-tissue injury.

Perskindol Cool Arnica *Vifor, Switz.*
Arnica (p.2260·2); menthol (p.2340·1).
Soft-tissue disorders.

Perskindol Ibuprofen acute *Vifor, Switz.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Persol *Wallace, India.*
Benzoyl peroxide (p.1590·2).
Acne.

Persol Forte *Wallace, India.*
Benzoyl peroxide (p.1590·2); sulfur (p.1614·1).
Acne.

Persolv Richter *Lepetit, Ital.†.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Personnel *Therapex, Canad.*
Bismuth salicylate (p.1711·1).
Gastrointestinal disorders.

Personnelle Contre le Rhume *Therapex, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Pert Plus *Procter & Gamble, Canad.*
Pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Pertacel *Aventis Pasteur, Braz.†.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Pertacilon *Elpen (Ελπεν), Gr.; Elpen, Singapore†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Pertaxol *Kleva, Gr.†.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma; hypertension; raised intra-ocular pressure.

Pertensal *Vinas, Spain.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; Raynaud's syndrome.

Pertenso *Ivax, Arg.*
⊗ Clonidine (p.1247·1); bendroflumethiazide (p.1224·1).
Hypertension.

Pertenso N *Sanol, Ger.; Schwarz, Ger.*
⊗ Propranolol hydrochloride (p.1380·3); hydralazine hydrochloride (p.1305·3); bendroflumethiazide (p.1224·1).
Hypertension.

Perti *Reddy, Malaysia†; Reddy, Rus.; Biofarma, Venez.†.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Pertil *AstraZeneca, Spain.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Pertinar *Ivax, Arg.*
Glucosamine sulfate (p.2313·2).
Joint disorders.

Pertiroid *Piam, Ital.*
Potassium perchlorate (p.2174·3).
Hyperthyroidism.

Pertix-Solo-N, Pertix-T, Pertix-Z, and Pertix-L *Hommel, Ger.†.*
Pentoxyverine (p.1567·3) or pentoxyverine citrate (p.1567·3).
Coughs and associated respiratory-tract disorders.

Pertofran *Novartis, Austria; Novartis, Belg.†; Novartis, Fr.†; Novartis, Ger.†; Novartis, NZ†.*
Desipramine hydrochloride (p.387·3).
Depression; pain.

Pertranquil *Aventis, Belg.†.*
Meprobamate (p.1006·2).
Anxiety; insomnia; premedication.

Pertriptyl *Orion, Fin.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Anxiety disorders; depression; schizophrenia.

Pertrombon *Gerot, Austria.*
Sodium nicotinate (p.1958·3); heparin sodium (p.1301·2).
Decubitus ulcer; promote resorption of excess fluid; soft-tissue injury; thrombophlebitis; ulcus cruris; varices.

Pertudoron *Weleda, Austria; Weleda, Fr.; Weleda, Ger; Weleda, S.Afr.*
Homoeopathic preparation.

Pertusan *Argenfarma, Arg.†.*
Centella (p.1592·3).
Haemorrhoids; venous disorders.

Pertussex Compositum *Uhlmann-Eyraud, Switz.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); drosera; galeopsis; thyme; Iceland moss; cowslip.
Coughs and associated respiratory-tract disorders.

Pertussin
Note.This name is used for preparations of different composition.
Knop, Chile.
Homoeopathic preparation.

Medphano, Ger.
Thyme (p.2401·1).
Coughs.

Lewison, Philipp.
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Pertussol *Rekah, Israel.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Coughs.

Peru Stick *Tentan, Switz.*
Lidocaine hydrochloride (p.1862·3); peru balsam (p.2365·3); camphor (p.2273·2); castor oil (p.2278·1).
Chapped and cracked skin; frostbite.

Perubare *Mayoly-Spindler, Switz.†.*
Peru balsam (p.2365·3); thymol (p.1664·3); thyme oil (p.2401·2); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Upper respiratory-tract disorders.

Perubore
Note.This name is used for preparations of different composition.
ACP, Belg.
Peru balsam (p.2365·3); thyme oil (p.2401·2); rosemary oil (p.2381·3); thymol (p.1664·3).
Rhinitis; sinusitis.

Mayoly-Spindler, Fr.
Thyme oil (p.2401·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); thymol (p.1664·3); peru balsam (p.2365·3).
Upper respiratory-tract congestion.

Peru-Lenicet *Athenstaedt, Ger.†.*
Aluminium diacetate hydroxide; aluminium hydroxide gel (p.1706·2); peru balsam (p.2365·3).
Skin disorders; wounds.

Perusliuos-K *Fresenius Kabi, Fin.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Perviam *Janssen-Cilag, Belg.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Pervil *Vianex (Βιανέξ), Gr.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Pervinox *Phoenix, Arg.*
Povidone-iodine (p.1659·2).
Skin, wound, and ulcer disinfection.

Pervinox Clorhexidina *Phoenix, Arg.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Pervinox D *Phoenix, Arg.*
Povidone-iodine (p.1659·2); nonoxinol.
Genital-tract infections.

Pervinox Incoloro *Phoenix, Arg.*
Chlorhexidine gluconate (p.1635·3).
Wound disinfection.

Pervioral *Royal, Chile.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Pervivo
Bittner, Austria.
Manna, camphor; zedoary; angelica; myrrh; gentian; rowan; nutmeg; liquorice; helenin; centaury; clove; galanga; ginger; cnicus benedictus; ivae moschatae; theriac; iridus; verbascum; bitter orange peel; calamus; absinthium; aloes; cubeb; star anise; sweet orange peel; menyanthes.
Gastrointestinal disorders; tonic.

Bittner, Pol.†.
Manna, camphor; curcuma; angelica; myrrh; gentian; nutmeg; dziewiecsilu root; liquorice; omanu root; centaury; clove; galanga; imbiru rhizome; cnicus benedictus; achillea; bitter orange; kosacca rhizome; verbascum; calamus; absinthium; pepper curracao fruit; aniseed; menyanthes leaf.
Dyspepsia; gallbladder disorders; infections; musculoskeletal and joint disorders.

Pervone *Sanofi Synthelabo, Gr.†.*
Dihydroergotamine mesilate (p.618·2).
Migraine; vascular headache.

Perzine *PP Lab, Thai.†.*
Perphenazine (p.1017·1).
Nausea and vomiting; psychoses.

Pesendorfer *Iso, Ger.*
Homoeopathic preparation.

Pesium *Flupal, Venez.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Pespire *Berman, Mex.*
Vitamin B substances (p.1922·1).

Pessarios Profilaticos Rendell *CIF, Braz.†.*
Nonoxinol 10 (p.1917·2).
Vulvovaginal infections.

Pestarin *Provit, Mex.*
Rifampicin (p.325·3).
Bacterial infections.

Petadolex *Weber & Weber, Ger.*
Butterbur (p.2271·1).
Smooth muscle spasms.

Petadolor *Bioforce, Switz.†.*
Butterbur radix (p.2271·1).
Migraine; smooth muscle spasm.

Petaforce V *Bioforce, Ger.*
Butterbur (p.2271·1).
Migraine; urinary-tract spasm.

Pe-Tam *Qualiphar, Belg.*
Paracetamol (p.108·1).
Fever; pain.

Petaxel *Biochem, India.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Peteha
Note. This name is used for preparations of different composition.
Fatol, Hong Kong.
Protionamide (p.320·1).
Tuberculosis.

Fatol, Ger.†.
Injection: Protionamide (p.320·1); nicotinamide (p.1957·3).
Tuberculosis.

Fatol, Ger.
Tablets: Protionamide (p.320·1).
Tuberculosis.

Petercillin *Pharmacare, S.Afr.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Peterkaien *Intramed, S.Afr.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Peterphyllin *Intramed, S.Afr.*
Injection: Aminophylline (p.1114·2).
Obstructive airways disease.

Petibelle *Jenapharm, Ger.; Lusal, Port.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Petina Compound *Jean-Marie, Hong Kong.*
Cyproheptadine hydrochloride (p.575·1); vitamins (p.1922·1).
Appetite loss; tonic.

Petinimid *Gerot, Austria; Gerot, Cz.; Gerot, Pol.; Gerot, Switz.*
Ethosuximide (p.479·3).
Absence seizures.

Petinutin *Pfizer, Austria; Parke, Davis, Ger.; Pfizer, Switz.*
Mesuximide (p.490·1).
Absence seizures; epilepsy.

Petites Pilules Carters *Sofibel, Fr.*
Boldine (p.2267·3); aloes (p.1705·2).
Constipation.

Petnidan *Desitin, Ger.; Desitin, Hung.*
Ethosuximide (p.479·3).
Absence seizures.

Petogen *Medidata, Malaysia†; Pharmacare, Malaysia†; Bodene, S.Afr.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Petrasch-Anthozym N *Asconex, Ger.†.*
Rote beete; ascorbic acid; lactic acid (p.1922·1).
Tonic.

Petroleum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Petsix *Ipca, India†.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Petylyl *Temmler, Ger.; AWD, Pol.*
Desipramine hydrochloride (p.387·3).
Depression.

Pevaryl
Note. This name is used for preparations of different composition.
Valeant, Austral.; Janssen-Cilag, Denm.; Janssen-Cilag, Gr.; Cilag, Hong Kong†; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia†; Pacific, NZ; McNeil, Neth.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Singapore†; Pensa, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, UK; Janssen-Cilag, Venez.
Econazole nitrate (p.531·1).
Fungal skin, nail, and vaginal infections; Gram-positive bacterial infections.

Janssen-Cilag, Belg.; Janssen-Cilag, Cz.; Janssen-Cilag, Fin.; McNeil, Fr.; Janssen-Cilag, Ital.; Janssen-Cilag, Norw.; Janssen-Cilag, S.Afr.
Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal skin and nail infections; Gram-positive bacterial infections.

Janssen-Cilag, Mex.
Econazole (p.531·1).
Fungal skin infections.

Janssen-Cilag, Austria.
Cream; lotion; shampoo; topical solution; topical spray: Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal skin and nail infections; Gram-positive infections.

Janssen-Cilag, Switz.
Cream; lipogel; lotion; shampoo; topical powder; topical solution; topical spray: Econazole (p.531·1) or econazole nitrate (p.531·1).
Fungal skin and scalp infections.

Janssen-Cilag, Switz.
Paste: Econazole nitrate (p.531·1); zinc oxide (p.1621·2).
Fungal skin disorders.

Janssen-Cilag, Austria.
Topical powder: Econazole nitrate (p.531·1); zinc oxide (p.1621·2).
Fungal skin and nail infections; Gram-positive infections.

Pevaryl HP *Janssen, Philipp.*
Econazole nitrate (p.531·1); zinc oxide (p.1621·2).
Fungal skin infections.

Pevazol *Chema-Elektromet, Pol.*
Econazole nitrate (p.531·1).
Fungal skin, nail, and ear infections; mixed fungal and Gram-positive bacterial skin infections.

Pevison *Janssen-Cilag, Gr.*
⊗ Triamcinolone acetonide (p.1544·3); econazole nitrate (p.531·1).
Fungal skin infections with inflammation.

Pevisone *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Cilag, Hong Kong; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia†; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore†; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.†.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin and nail infections with inflammation.

Pexeva *Synthon, USA.*
Paroxetine mesilate (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder.

Pexola *Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Turk.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism.

Pexsig *Sigma, Austral.; Pharmaco, NZ.*
Perhexiline maleate (p.1368·2).
Formerly known as Pexid.
Angina pectoris.

Pezeta-Ciba *Sandoz, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pezide *Greater Pharma, Thai.*
Glipizide (p.441·3).
Diabetes mellitus.

PFD *Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Ital.*
Food for special diets (p.1922·1).
Amino-acid metabolic disorders; amino-acid metabolic disorders in infants and children.

Pfeiffer's Cold Sore *Pfeiffer, USA.*
Sumatra benzoin (p.2394·2); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3).
Oral lesions.

Pfeil *Stada, Ger.†.*
Ibuprofen (p.64·2).
Pain.

P-Fen *Millimed, Thai.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal and joint disorders; pain.

Pfizer Obstetric Lotion *Pfizer Consumer, Singapore†.*
Chlorhexidine gluconate (p.1635·3).
Disinfection and lubrication during gynaecological or obstetric procedures.

Pfizerpen *Pfizer, USA.*
Benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pflugerplex Arnica *Pfluger, Ger.†.*
Homoeopathic preparation.

Pflugerplex Gelsemium *Pfluger, Ger.*
Homoeopathic preparation.

Pflugerplex Lemna *Pfluger, Ger.*
Homoeopathic preparation.

PFT *Nicholas Piramal, India†.*
Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Dyspepsia; flatulence; gastritis; gastrointestinal hyperacidity; hiatus hernia; peptic ulcer.

PG/53 *Raymos, Arg.*
Fertility test (p.2372·1).

P-Glitz *Cipla, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

P-Glitz M *Cipla, India.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

pH4 *Biological E, India.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastritis; gastrointestinal hyperacidity; peptic ulcer.

pH 550
Note. This name is used for preparations of different composition.
Restan, S.Afr.†.
Suspension: Dicycloverine hydrochloride (p.1722·3); aluminium hydroxide gel (p.1706·2); magnesium oxide (p.1744·1); calcium carbonate (p.1714·1); dimethicone (p.1770·2).
Flatulence; gastric hyperacidity; hiatus hernia; peptic ulcer.

Restan, S.Afr.†.
Tablets: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders associated with hyperacidity.

pH Care *Biomedis, Malaysia.*
Glycerol; panthenol; cocamidopropyl betaine; bisabolol; chamomile; citric acid.
Vaginal hygiene.

PH 4 Plus *Sintesina, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Phacobiotic *Bros, Gr.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Phacocef *Bros, Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Phacotrex *Bros, Gr.*
Cefaclor (p.217·2).
Bacterial infections.

Phacovit *Bros, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Phaeva *Schering, Fr.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Phakan
Chauvin, Port.†.
White capsules, glycine (p.1947·3); glutamic acid (p.1947·1); pyridoxine (p.1979·1); blue capsules, cysteine (p.1936·3); vitamin C (p.1983·3).
Cataracts.

Chauvin, Fr.†.
Combination pack: Oral solution, glycine (p.1947·3); glutamic acid (p.1947·1); pyridoxine hydrochloride (p.1978·2); capsules, cysteine hydrochloride (p.1936·3); ascorbic acid (p.1983·3).
Cataracts.

Phakolen *Bausch & Lomb, Switz.†.*
Combination pack: White capsules, glycine (p.1947·3); -glutamic acid (p.1947·1); pyridoxine hydrochloride (p.1978·2); blue capsules, cysteine hydrochloride (p.1936·3); ascorbic acid (p.1983·3).
Prevention of cataract formation.

Phaltrexia *Pharos, Indon.*
Naltrexone hydrochloride (p.1455·2).
Opioid dependence.

Phamopril *Phamos, Ger.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Phamoprofen *Phamos, Ger.†.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Phamoranit *Phamos, Ger.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Phamoxi *Phamos, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Phamuc *Phamos, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with increased or viscous mucus.

Phanalgin *Rekah, Israel.*
Dipyrone (p.49·2).
Fever; pain.

Phanate *Pharmaland, Thai.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression.

Phanatuss Cough *Pharmakon, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Phanerol *Apotex, Philipp.; Pharma 3, Philipp.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hypertrophic subaortic stenosis; migraine; phaeochromocytoma.

Phapax *Lehning, Fr.*
Homoeopathic preparation.

Pharben *Gelpharma, Mex.*
Benzonatate (p.1552·1).
Coughs.

Pharbrix *Sons, Mex.*
1 Ampoule, tetracycline hydrochloride (p.347·2); 1 ampoule, lidocaine hydrochloride (p.1862·3); chlorphenamine maleate (p.571·3); sodium ascorbate (p.1984·1); guaifenesin (p.1561·3).
Bacterial infections.

Pharcilex *Pharmacos, Mex.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Pharcina *Pharmacos, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Phardol mono *Kreussler, Ger.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, soft-tissue, and nerve disorders.

Phardol Rheuma *Kreussler, Ger.†.*
Glycol salicylate (p.62·3); pine silvestris oil (p.2368·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, soft-tissue, and nerve disorders.

Phardol Schmerz *Kreussler, Ger.*
Ketoprofen (p.73·1).
Peri-articular and soft-tissue disorders.

Phardol Warme-Balsam *Kreussler, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Pharemin *Pacific, Philipp.*
Vitamin preparation with iron (p.1922·1).

Pharepa *Pharmatex, Ital.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Pharfed *Pharmaland, Thai.*
Brompheniramine maleate (p.569·2); pseudoephedrine (p.1571·2).
Respiratory-tract congestion.

Pharflox *Pharos, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Pharken *Elanco, Spain.*
Pergolide mesilate (p.812·3).
Parkinsonism.

Pharlecon *Leovan, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Pharlemyron *Leovan, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Pharmacaine *Quimpharma, Mex.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Pharmacard Family Douleurs & Fievre *Pharmacard, Switz.†.*
Paracetamol (p.108·1).
Fever; pain.

Pharmacard Family Maux de gorge *Pharmacard, Switz.†.*
Cetylpyridinium chloride (p.1635·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Mouth and throat disorders.

Pharmacard Family Toux seche *Pharmacard, Switz.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Pharmacen *Alpharma, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Pharmacetin *Olan-Kemed, Thai.*
Chloramphenicol (p.239·3).
Bacterial ear infections.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pharmaceutix *Medipharma, Arg.†.*
Rifampicin (p.325·3).
Bacterial infections.

Pharmacists Creme *Reese, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); capsicum oleoresin.

Pharmacists Lotion *Reese, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); capsicum oleoresin.

Pharma-Col Junior *Pfizer Consumer, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Pharmacort *Human, Philipp.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Pharmacycare Cough Expectorant *Douglas, NZ†.*
Choline theophyllinate (p.1119·3); guaifenesin (p.1561·3).
Coughs.

Pharma-Dentix *Germiphene, Israel.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders; oral hygiene.

Pharmadol *Pharmaland, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Pharmadose alcool *Gilbert, Fr.*
⊗ Alcohol (p.1625·2).
Skin and wound disinfection.

Pharmadose mercuresceine *Gilbert, Fr.†.*
Merbromin (p.1652·1).
Wound and burn disinfection.

Pharmadose teinture d'arnica *Gilbert, Fr.*
Arnica (p.2260·2).
Ecchymoses.

Pharmafet *Ares, Mex.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Pharmafil *Alpharma, Mex.*
Theophylline (p.1140·1).
Obstructive airways disease.

Pharmaflam
Quimpharma, Mex.
Diclofenac resinate (p.46·1).
Fever; inflammation; pain.

Pharmador, S.Afr.†.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Pharmaflex *Braun, Belg.†.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Pharmaflur *Pharmics, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Pharmafort *Boehringer Ingelheim, Arg.*
Ginseng; rutoside; vitamins; minerals (p.1922·1).
Tonic.

Pharmagin *Pharmasant, Thai.*
Metamizole.
Fever; pain.

Pharmagrip *Cinfa, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms; fever; pain.

Pharmakod expectorant *Sanofi-Aventis, Fr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Pharmakod toux seche *Sanofi-Aventis, Fr.*
Pholcodine (p.1570·2).
Coughs.

Pharmalgen *ALK, Belg.; ALK, Denm.; ALK, Neth.; Alk-Abello, Pol.; Trimedal, Switz.; ALK, UK; ALK, USA.*
Venom of *Apis mellifera* (p.2251·1) or *Vespula* spp. (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Pharmalgen Albumin *ALK, Denm.*
⊗ Human albumin (p.1052·1); mannitol (p.1330·2).
Diluent for allergen extracts.

Pharmapress *Pharmacare, S.Afr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Pharmapress Co *Pharmacare, S.Afr.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Pharmatex
Note.This name is used for preparations of different composition.
Raymos, Arg.; Innothera, Cz.; Innotech, Hong Kong; Innotech, Hung.; Agis, Israel†; Sidefarma, Port.; Innotech, Rus.
Benzalkonium chloride (p.1629·1).
Contraceptive.

Innotech, Fr.
Pessaries; tampons; vaginal capsules; vaginal cream; vaginal tablets: Benzalkonium chloride (p.1629·1).
Contraceptive; skin hygiene.

Innotech, Fr.
Topical gel: Hymetellose (p.2143·3); benzalkonium chloride (p.1629·1); glycerol (p.2314·2).
Vaginal lubricant.

Pharmato Matruelle *Boehringer Ingelheim Promeco, Mex.*
Vitamins; minerals; omega-3 triglycerides (p.1922·1).

Pharmaton
Boehringer Ingelheim, Austral.†; Boehringer Ingelheim, Hong Kong; Pharmaton, Israel; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ†; Pharmaton, NZ†; Boehringer Ingelheim, Port.†; Abdi, Turk.; Boehringer Ingelheim Self Medication, UK.
Ginseng; vitamins; minerals (p.1922·1).
Age-related disorders; dietary supplement; nutritional supplement; tonic.

Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Irl.
Vitamins; minerals; ginseng; lecithin (p.1922·1).
Tonic.

Boehringer Ingelheim, Fr.†.
Deanol bitartrate; ginseng; vitamins and minerals (p.1922·1).
Tonic.

Boehringer Ingelheim, Ger.
Multivitamin and mineral preparation with ginseng and essential fatty acids (p.1922·1).

Pharmaton, Malaysia.
Vitamins; minerals; ginseng; lecithin; choline; inositol; linoleic acid; linolenic acid (p.1922·1).
Tonic.

Boehringer Ingelheim, Philipp.
Vitamins; minerals; ginseng; deanol tartrate; rutoside; choline; inositol; linoleic acid; linolenic acid (p.1922·1).

Boehringer Ingelheim, S.Afr.; Pharmaton, Singapore.
Multivitamins; minerals; ginseng; lecithin; rutoside (p.1922·1).
Tonic.

Pharmaton, Thai.
Ginseng; deanol bitartrate; rutoside; lecithin; vitamins; minerals (p.1922·1).
Tonic.

Pharmaton Activit *Boehringer Ingelheim, Cz.*
Ginseng; vitamins; minerals (p.1922·1).
Tonic.

Pharmaton Complex
Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Spain.
Ginseng; deanol tartrate; rutoside; vitamins; minerals (p.1922·1).
Tonic.

Boehringer Ingelheim Promeco, Mex.
Vitamins; minerals; ginseng; rutoside; lecithin; deanol tartrate (p.1922·1).

Pharmaton Kiddi *Boehringer Ingelheim, Braz.*
Amino acids; vitamins; minerals (p.1922·1).

Pharmaton with Selenium *Pharmaton, Malaysia; Pharmaton, Singapore.*
Ginseng; vitamins; minerals; selenium (p.1922·1).
Dietary supplement.

Pharmaton Vital *Boehringer Ingelheim, Hung.*
Vitamins; minerals; ginseng; rutoside; lecithin; deanol tartrate (p.1922·1).
Tonic.

Pharmatovit
Boehringer Ingelheim, Austria.
Multivitamin and mineral preparation (p.1922·1).

Pharmaton, Israel†.
Multivitamin and mineral preparation with lecithin and rutoside (p.1922·1).

Pharmatovit Ginseng *Pharmaton, Switz.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Pharmavoyage Moustiquaires *Katadyn, Fr.*
Mosquito net impregnated with permethrin (Peripel) (p.2048·2) or deltamethrin (p.2040·1).
Insect repellent.

Pharmecort *Pharmex (Φαρμεξ), Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Pharmilin-DM *Therapex, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2).

Pharminil DM *Therapex, Canad.*
Dextromethorphan hydrobromide (p.1555·2).

Pharmix *Apotex, Philipp.; Pharma 3, Philipp.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Pharmorat *Leti, Venez.*
Ginseng (p.2312·1); vitamins; minerals (p.1922·1).
Tonic.

Pharmorubicin *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK.*
Epirubicin hydrochloride (p.716·1).
Formerly known as Farmorubicin in *Thai.*
Malignant neoplasms.

Pharmotidine *Community Pharmacy, Thai.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pharmox *Greenpharma, Braz.*
Amoxicillin (p.202·2).
Bacterial infections.

Pharnax *Pharmaland, Thai.*
Alprazolam (p.960·1).
Mixed anxiety depressive states.

Pharnazine *Pharmaland, Thai.*
Fluphenazine decanoate (p.998·1).
Schizophrenia.

Pharodime *Pharos, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Pharophyllin *Byk, Cz.†.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Pharothrocin *Pharos, Indon.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Pharquinon *Medipharm, Venez.†.*
Hydroquinone (p.1598·2).
Hyperpigmented skin disorders.

Pharyngor *Rappai, Switz.*
Potassium chloride; sodium chloride; magnesium chloride; calcium chloride (p.1667·1).
Dry mouth and throat.

Pharynx *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat infections.

Pharysyx N *Syxyl, Ger.†.*
Homoeopathic preparation.

Pharzil *Pharmaland, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Phase O *Grunenthal, Chile†.*
A range of sunscreen preparations.

Phazyme *GSK Consumer, Canad.; GSK Consumer, USA.*
Simeticone (p.1770·2).
Flatulence.

pHCare *Biomedis, Philipp.*
Dexpanthenol (p.2362·1); glycerol (p.2314·2); chamomile (p.2279·3).
Feminine hygiene.

pH-Derm *Mediphar, Venez.*
A range of barrier preparations, emollients, and skin cleansers.

Phenadex *Dexa, Indon.*
⊗ Promethazine hydrochloride (p.588·2); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); ammonium chloride (p.1551·3); ephedrine hydrochloride (p.1558·2); ascorbic acid (p.1983·3).
Cough.

Phenadine *Quality, Hong Kong.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain and irritation.

Phenadoz *Paddock, USA.*
Promethazine hydrochloride (p.588·2).

Phenaemal *Desitin, Cz.*
Phenobarbital (p.492·2).
Epilepsy.

Phenaemaletten *Desitin, Cz.*
Phenobarbital (p.492·2).
Epilepsy.

Phenahist *Universal, Hong Kong.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); diphenylpyraline hydrochloride (p.578·2).
Cold and influenza symptoms.

Phenameth DM *Major, USA.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Phenamin *Nycomed, Norw.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions; pruritus.

Phenapap *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Phenapap Sinus Headache & Congestion *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Phenaseptic *Rugby, USA.*
Phenol (p.1656·1).
Minor mouth or throat irritation.

Phenate *Alphapharm, Malaysia; Pacific, NZ; Alphapharm, Singapore†; Merck, Singapore†.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

PhenaVent *Ethex, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Phenazin *Mayne, Port.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Phenazine *Pharmaland, Thai.†.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Phenazo *Valeant, Canad.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Phenazopyridine Plus *Breckenridge, USA.*
Phenazopyridine hydrochloride (p.116·2); hyoscyamine hydrobromide (p.1736·1); secbutabarbital (p.1027·2).

Phencodin *Neopharm, Thai.*
Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Coughs.

Phencol *Christo, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); sodium citrate (p.1673·3); ammonium chloride (p.1551·3).
Respiratory-tract disorders.

Phendiridine *TP, Thai.*
Phenazopyridine hydrochloride (p.116·2).
Dysuria; urinary-tract pain.

Phenedrine *Medichem, Philipp.*
Theophylline (p.1140·1).
Asthma.

Phenerbel-S *Rugby, USA.*
Phenobarbital (p.492·2); ergotamine tartrate (p.620·1); belladonna (p.2263·3).

Phenergan
Sanofi-Aventis, Austral.; Sanofi-Aventis, Belg.; Columbia, Canad.†; Aventis, Denm.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Nicholas Piramal, India; Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Aventis, Norw.; Aventis, S.Afr.; Aventis, Thai.; Aventis, UK; Wyeth-Ayerst, USA.
Promethazine hydrochloride (p.588·2).
Allergic rhinitis; anaphylaxis; hypersensitivity reactions; insomnia; motion sickness; nausea and vomiting; parkinsonism; postoperative pain (adjunct); premedication; pruritus; sedative; urticaria.

UCB, Fr.
Promethazine (p.588·2) or promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; insomnia; pruritus.

Phenerine *Pharmacare, S.Afr.*
Orphenadrine hydrochloride (p.812·1).
Parkinsonism.

Phenetone *Cipla, India.*
Phenobarbital (p.492·2).

Phenex *Abbott, Austral.†; Ross, USA.*
Phenylalanine-free preparation for enteral nutrition (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Phenexpect *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Phenexpect CD *DHA, Singapore.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Phenhist DH with Codeine *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Phenhist Expectorant *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Phenhydan
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; neuropathic pain; seizures associated with neurosurgery or head injury; trigeminal neuralgia.

Desitin, Cz.†.
Phenytoin (p.495·2).
Epilepsy; neuralgia.

Phenicol *Vitamed, Israel.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Phenilep *Prafa, Indon.*
Phenytoin sodium (p.495·2).
Epilepsy.

Phenimixin *Vitamed, Israel.*
Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Phenobarb *PP Lab, Thai.†.*
Phenobarbital (p.492·2).
Epilepsy; insomnia; sedative.

Phenobiotic *Bernofarm, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Phenocillin *Streuli, Switz.*
Benzathine phenoxymethylpenicillin (p.212·3) or phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Phenodex *Vesco, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Phenokinon-F *Vesco, Thai.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Pheno-M *Vesco, Thai.*
Medroxyprogesterone acetate (p.2113·1).
Dysfunctional uterine bleeding; endometriosis; progestogen-only injectable contraceptive.

Phenoptic *Optopics, USA†.*
Phenylephrine hydrochloride (p.1568·1).
Funduscopy; open-angle glaucoma; ophthalmic examination; pupil dilatation during surgery; refraction without cycloplegia; uveitis.

Phenoris *Germiphene, Canad.*
Clioquinol (p.254·1); allantoin (p.1588·1); phenol (p.1656·1).
Topical antiseptic.

Phenotal *Asian Pharm, Thai.*
Phenobarbital sodium (p.492·2).
Epilepsy; insomnia; sedative.

Phenotropil *Shchelkovskii, Rus.*
⊗ 4-Phenylpiracetam (p.368·1).
Chronic alcoholism; convulsions; depression; mental function disorders; metabolic and vascular cerebral disorders; obesity.

Phenpro *Ratiopharm, Ger.*
Phenprocoumon (p.1370·2).
Thromboembolic disorders.

Phenprogamma *Worwag, Ger.*
Phenprocoumon (p.1370·2).
Thromboembolic disorders.

Phensedyl
Note. This name is used for preparations of different composition.
Aspen, Austral.†.
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Nicholas Piramal, India.
Chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs.

Aventis, Malaysia†; Aventis, Singapore†; Aventis, Thai.†.
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Cold symptoms; coughs.

Aventis, S.Afr.
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Phensedyl Dry Cough *Sanofi-Aventis, Malaysia.*
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Phensedyl Dry Family Cough *Aventis, NZ†.*
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Phensedyn *Quality, Hong Kong.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs; nasal congestion.

Phensic *Merck Consumer, UK.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Phenybut-Anvi *Antiviral, Rus.†.*
4-Amino-3-phenylbutyric acid hydrochloride.
Alcohol withdrawal syndrome; anxiety disorders; insomnia; motion sickness; obsessive-compulsive disorder; premedication; stammer; ticks; vestibular disorders.

Phenydan *Medsan, Turk.*
Phenytoin sodium (p.495·2).
Epilepsy; trigeminal neuralgia.

Phenyl-Free *Mead Johnson, Chile; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Israel; Mead Johnson, Ital.; Mead Johnson, NZ; BMS, Pol.; Mead Johnson, Pol.; Mead Johnson Nutritionals, USA.*
Food for special diets (p.1922·1).
Formerly known as Lofenalac in the *USA*.
Disorders of phenylalanine metabolism; phenylketonuria.

Phenylgesic *Goldline, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Phenyl-T *Boca, USA.*
Phenylephrine tannate (p.1568·3).
Nasal congestion.

Phenyphrine-Azol *Vitamed, Israel†.*
⊗ Mepyramine maleate (p.585·2); naphazoline hydrochloride (p.1565·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Phenytek *Bertek, USA.*
Phenytoin (p.495·2).
Epilepsy.

Pherazine with Codeine *Halsey, USA.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Pherazine DM *Halsey, USA.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Pherazine VC *Halsey, USA.*
Promethazine hydrochloride (p.588·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract symptoms.

Pherazine VC with Codeine *Halsey, USA.*
Promethazine hydrochloride (p.588·2); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2).
Coughs and cold symptoms.

pH5-Eucerin *Beiersdorf, Chile; BDF, Mex.†; Beiersdorf, Thai.; Beiersdorf, Venez.*
A range of skin cleansing and emollient preparations.

pH5-Eucerin Solar
Note. This name is used for preparations of different composition.
Beiersdorf, Chile†.
Cream SPF 15; Cream SPF 25; Gel SPF 8: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Beiersdorf, Chile†.
Gel SPF 16: Octinoxate (p.1608·2); amiloxate (p.1589·1); avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Beiersdorf, Chile†.
Lotion SPF 20; Lotion SPF 25: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Phexin *GSK, India.*
Cefalexin (p.218·2).
Bacterial infections.

Phezam *Balkanpharma, Rus.*
Cinnarizine (p.573·1); piracetam (p.368·2).
Cerebrovascular disorders; mental function impairment; migraine; motion sickness; vestibular disorders.

Phicon *Williams, USA.*
Pramocaine hydrochloride (p.1868·1); vitamin A (p.1971·2); vitamin E (p.1992·2).
Local anaesthesia.

Phicon-F *Williams, USA.*
Pramocaine hydrochloride (p.1868·1); undecenoic acid (p.549·2).
Fungal skin infections.

Philenterol *Ipsen, Port.*
Macrogol 4000 (p.2336·3).

Philinal *Rekah, Israel.*
Diprophylline (p.1120·2); phenobarbital (p.492·2).
Obstructive airways disease.

Philinet *Rekah, Israel.*
Diprophylline (p.1120·2); phenobarbital (p.492·2).
Obstructive airways disease.

Philipon-S *SJA, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Phillips *GSK, Arg.†.*
Docusate sodium (p.1725·1).
Constipation.

Phillips' Chewable *Bayer, USA.*
Magnesium hydroxide (p.1743·2).
Hyperacidity.

Phillips' Magnesia Tablets *Bayer Consumer, Canad.*
Magnesium hydroxide (p.1743·2).
Constipation; hyperchlorhydria; peptic ulcer.

Phillips' Milk of Magnesia *Bayer Consumer, Canad.; Bayer, USA.*
Magnesium hydroxide (p.1743·2).
Constipation; dyspepsia; gastric hyperacidity.

pHisoDerm *Chattem, USA.*
Skin cleanser.

pHisoHex
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Canad.; Sanofi Winthrop, USA.
Entsufon sodium (p.2299·1); hexachlorophene (p.1646·1).
Skin cleansing; skin disinfection.

Sanofi-Aventis, Malaysia†.
Triclosan (p.1665·2).
Skin infections.

pHisoHex Face Wash *Aspen, Austral.*
Triclosan (p.1665·2).
Acne.

pHisoHex Reformulated *Sanofi Synthelabo, Hong Kong†.*
Triclosan (p.1665·2).
Acne; skin infections.

Phisohex Reformulated *Sanofi-Aventis, Indon.*
Triclosan (p.1665·2).
Skin cleansing.

pHisoHex Reformulated *Sanofi Synthelabo, Singapore†.*
Triclosan (p.1665·2); pyrithione zinc (p.1611·2).
Skin cleanser.

Phisomain *Anios, Fr.*
Octenidine hydrochloride (p.1654·3).
Hand disinfection.

P-Hist *Midlothian, USA.*
Dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2); dexchlorpheniramine maleate (p.572·1); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

P-Hist DM *Midlothian, USA.*
Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Cough.

Phlebodia *Innothera, Pol.; Innothera, Rus.*
Diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

Phlebodril
Note. This name is used for preparations of different composition.
Germania, Austria.
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Venous insufficiency.

Pierre Fabre, Ger.
Butcher's broom (p.2270·3); trimethylhesperidin chalcone (p.2305·2).
Vascular disorders.

Robapharm, Switz.
Butcher's broom (p.2270·3); melilot (p.2339·2).
Venous insufficiency.

Phlebodril mono *Pierre Fabre, Ger.*
Butcher's broom (p.2270·3).
Haemorrhoids; venous insufficiency.

Phlebodril N
Note. This name is used for preparations of different composition.
Pierre Fabre, Ger.
Butcher's broom rhizome (p.2270·3); melilot (p.2339·2); dextran sulfate (p.2293·1).
Vascular disorders.

Robapharm, Switz.
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2).
Haemorrhoids; venous insufficiency.

Phlebogel *Merck-Lipha, Fr.*
⊗ Aescin (p.2248·2); buphenine hydrochloride (p.2270·2).
Chronic venous insufficiency.

Phlebosedol *Lehning, Fr.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2); viburnum (p.2267·1); alchemilla; red vine (p.2316·3).
Haemorrhoids; venous insufficiency.

Phlebostasin *Altana, Switz.*
Aesculus (p.2248·2).
Venous insufficiency.

Phlebostasin compositum *Klinge, Switz.†.*
Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Oedema; phlebitis; soft-tissue disorders; venous insufficiency.

Phlegmol *MedGen, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Phlemasol *Littman, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Phlemex-PE *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Cough; nasal congestion.

Phlexy *Scientific Hospital Supplies, Austral.; SHS, Fr.; Scientific Hospital Supplies, Irl.; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, NZ; SHS, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

Phlexy Vits *Scientific Hospital Supplies, Irl.*
Vitamin, mineral, and trace element preparation (p.1922·1).
Inborn errors of metabolism.

Phlexy-Vits *SHS, Fr.*
A vitamin, mineral, and trace element preparation (p.1922·1).

Phlexyvits *SHS, UK.*
Multivitamin and mineral preparation (p.1922·1).

Phloderm *Herbapol Poznan, Pol.*
Hamamelis (p.2318·2).
Skin disorders.

Phlogantin *Streuli, Switz.*
Camphor (p.2273·2); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); mint oil; kaolin (p.1738·1).
Burns; musculoskeletal and soft-tissue disorders; wounds.

Phlogenzym *Enzimas, Arg.†; Mucos, Austria; Mucos, Cz.; Mucos, Ger.; Mucos, Hung.; Romsa, Mex.; Mucos, Rus.; Mucos, Venez.*
Bromelains (p.2269·1); trypsin (p.2405·3); rutoside (p.2305·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; thrombophlebitis; wounds.

Phlogont *Azupharma, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, and soft-tissue disorders.

Phlogont Rheuma *Azupharma, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, and soft-tissue disorders.

Phlogont-Thermal *Sandoz, Ger.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Phlogosam
Note. This name is used for preparations of different composition.
PannonPharma, Hung.
Ointment: Sodium sulfosalicylate samarate.
Burns; skin disorders; thrombophlebitis.

PannonPharma, Hung.
Topical foam: Dexpanthenol (p.2362·1) lidocaine (p.1862·3); sodium sulfosalicylate samarate.
Skin disorders; thrombophlebitis; wounds.

Phlogosol *PannonPharma, Hung.*
Sodium sulfosalicylate samarate; hexachlorophene (p.1646·1).
Mouth and throat disorders.

Phocium *Pharmasant, Thai.†.*
Calcium phosphate (p.1676·2); calcium carbonate (p.1714·1).
Calcium supplement.

Phocytan *Aguettant, Fr.*
Glucose-1-phosphate disodium, tetrahydrate.
Hypophosphataemia; parenteral nutrition.

Phoenix Lagrimas *Phoenix, Arg.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Eye irritation.

Pholcodex *Pinewood, Irl.*
Pholcodine (p.1570·2).
Coughs.

Pholcolin *Antigen, Irl.*
Pholcodine (p.1570·2).
Coughs.

Pholcolinct *Adcock Ingram, S.Afr.*
Pholcodine (p.1570·2).
Cough.

Pholco-Mereprine *OJG, Belg.*
Doxylamine succinate (p.578·2); pholcodine (p.1570·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Respiratory-tract disorders.

Pholcones Bismuth *Cooperation Pharmaceutique, Fr.*
Guaifenesin (p.1561·3); bismuth succinate (p.1712·1); cineole (p.2282·3).
Respiratory-tract congestion.

Pholdyston *Krewel, Ger.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Pholtex *3M, S.Afr.*
Pholcodine (p.1570·2).
Coughs.

Pholtex Linctus *3M, S.Afr.*
Pholcodine resin complex (p.1570·3); phenyltoloxamine resin complex (p.588·1).
Coughs.

Pholtrate *McGloin, Austral.†.*
Pholcodine (p.1570·2).
Coughs.

Phol-Tussil *Interdelta, Switz.*
Pholcodine (p.1570·2); sodium benzoate (p.1630·2); tolu balsam (p.1574·2).
Coughs.

Phol-Tux *Interdelta, Switz.*
Pholcodine (p.1570·2); ethylmorphine hydrochloride (p.52·2); sulfogaiacol (p.1573·2); belladonna (p.2263·3); senega root (p.1572·3); sodium benzoate (p.1630·2).
Coughs.

Phonal
Note. This name is used for preparations of different composition.
Reig Jofre, Spain.
Lozenges: Bacitracin (p.210·3); benzocaine (p.1854·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Mouth and throat disorders.

Reig Jofre, Spain.
Throat spray: ⊗ Benzalkonium chloride (p.1629·1); dexamethasone sodium phosphate (p.1526·2).
Mouth and throat disorders.

phono Arnica comp *Phonix, Ger.†.*
Homoeopathic preparation.

phono Chol *Phonix, Ger.†.*
Homoeopathic preparation.

phono Gripp *Phonix, Ger.†.*
Homoeopathic preparation.

phono Uren *Phonix, Ger.†.*
Homoeopathic preparation.

phono Ven *Phonix, Ger.†.*
Homoeopathic preparation.

Phor Pain *Goldshield, UK.*
Ibuprofen (p.64·2).
Muscle pain.

Phorpain *Goldshield, Irl.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Phos Kola *Phos-Kola, Braz.†.*
Calcium; medicinal plants (p.1922·1).
Nutritional supplement.

Phoscal *Armoxindo, Indon.*
Calcium carbonate; colecalciferol; vitamin K ; magnesium; phosphorus (p.1922·1).
Nutritional supplement.

PhosChol *American Lecithin, USA.*
Phosphatidyl choline (p.2367·1).
Nutritional supplement.

Phoscortil *Kolassa, Austria.*
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1); aluminium phosphate (p.1707·3).

Phosetamin *Kohler-Pharma, Ger.*
Calcium, magnesium, and potassium salts of phosphorylcolamine.
Electrolyte disorders.

Phos-Ex *Brady, Austria; Nordiatech, Denm.; Vitaline, Fin.; Gry, Ger.; Cablon, Neth.; Vitaline, Norw.; Vitaline, Swed.; Say, Turk.; Vitaline, UK.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Phos-Flur *Colgate Oral, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Phosfoenema *Cristalia, Braz.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Phosfomin *Sarabhai Piramal, India.*
Vitamin B substances; yeast extract; lysine hydrochloride (p.1922·1).
Vitamin B deficiency.

Phosfomin Iron *Sarabhai Piramal, India.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Phosforid *Sun, India.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Phoslo *Pasteur, Chile.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

PhosLo *Fresenius Medical, USA.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Phos-NaK *Cypress, USA.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3); monobasic potassium phosphate (p.1682·2); dibasic potassium phosphate (p.1682·2).
Nutritional supplement.

Phosoforme *Monin, Fr.†.*
Phosphoric acid (p.2367·1).
Urinary-tract disorders.

Phosphalugel *Kolassa, Austria; Yamanouchi, Belg.†; Astellas, Fr.; Astellas, Ger.; Astellas, Port.; Yamanouchi, Rus.; Boehringer Ingelheim, Switz.†.*
Aluminium phosphate (p.1707·3).
Antacid; gastric hyperacidity.

Phosphate-Novartis *Novartis, Canad.*
Monobasic sodium phosphate (p.1682·3); potassium bicarbonate (p.1673·1).
Electrolyte supplement; hypercalciuria.

Phosphates *Pharmascience, Canad.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Phosphate-Sandoz
Note. This name is used for preparations of different composition.
Novartis, Austral.
Monobasic sodium phosphate (p.1682·3).
Hypercalcaemia; rickets.

Novartis, NZ; Novartis, S.Afr.; HK Pharma, UK.
Monobasic sodium phosphate (p.1682·3); sodium bicarbonate (p.1673·2); potassium bicarbonate (p.1673·1).
Hypercalcaemia; hypophosphataemia; rickets.

Phospho-Aio *ICN, Cz.†.*
Electrolyte infusion (p.1667·1).
Parenteral nutrition.

Phosphocalcina Iodada *ClF, Braz.†.*
Sodium carbonate; calcium hypophosphite; sodium hypophosphite; iodine; tannin (p.1672·2).
Oral rehydration therapy.

Phosphoclean *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).
Constipation.

Phosphocol *Mallinckrodt, USA.*
Phosphorus-32 (p.2055·2) in the form of chromic phosphate.
Malignant neoplasms.

Phosphogliv *Farmstandart, Rus.*
Phospholipids; sodium glycyrrhizate.
Liver disorders; skin disorders.

Phospho-Lax *Sofar, Ital.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Constipation.

Phospho-Laxat *Pharma Line, Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).
Constipation.

Phospho-Laxative *RiC, Pol.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Phospholine Iodide *Wyeth, Austral.†; Wyeth-Ayerst, USA†.*
Ecothiopate iodide (p.1881·1).
Convergent strabismus; glaucoma.

Phospholinjodid *Wyeth Lederle, Austria†.*
Ecothiopate iodide (p.1881·1).
Glaucoma.

Phosphoneuros *Bouchara-Recordati, Fr.*
Phosphoric acid (p.2367·1); calcium dihydrogen phosphate (p.2272·1); dibasic sodium phosphate (p.1682·3); magnesium glycerophosphate (p.1679·2).
Hypercalciuria; hypophosphataemic rickets.

Phosphonorm *Medice, Ger.; Salmon, Switz.*
Aluminium chlorohydrate (p.1588·3).
Hyperphosphataemia.

Phosphoprep *Pharmatel, Austral.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Phosphor *Herbapol Lodz, Pol.*
⊗ Ammonium phosphate (p.2256·3); monobasic potassium phosphate (p.1682·2); dibasic sodium phosphate (p.1682·3).
Fractures; hypercalcaemia; hypercalciuria; hypophosphataemia; osteoporosis; renal calculi.

Phosphoral *De Witt, Denm.; Ferring, Fin.; De Witt, Neth.; De Witt, Norw.; Ferring, Swed.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Phosphore Medifa *Medipha, Fr.*
⊗ Monoammonium phosphate (p.2256·3); monobasic potassium phosphate (p.1682·2); manganese glycerophosphate (p.2315·2).
Hypercalciuria; rickets.

Phosphor-Homaccord *Peithner, Austria.*
Homoeopathic preparation.

Phosphorus Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Phospho-Soda *Fleet, Philipp.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Phosphosorb *Fresenius Medical, Cz.; Fresenius Medical, Port.*
Calcium acetate (p.1675·2).
Hyperphosphataemia.

Phosphovitam *Gap, Gr.*
A calcium and multivitamin supplement (p.1922·1).

Phostal *Stallergenes, Cz.; Stallergenes, Ger.; Stallergenes, Ital.; Stallergenes, Pol.; Trimedal, Switz.*
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.

Phostarac *Pharmacia, Arg.†.*
Alendronate sodium (p.1088·1).
Osteolysis; osteoporosis.

Photakne *Bioderma, Fr.†.*
SPF 20: Bisoctrizole (p.1591·2); octil triazone (p.1608·1); avobenzone (p.1589·3); glycolic acid (p.1598·1); salicylic acid (p.1612·2).
Sunscreen for acne-type skin.

Photobarr
Axcan, Cz.; Axcan, Neth.; Axcan, Port.
Porfimer sodium (p.764·3).
Barrett's oesophagus.

Axcan, Fr.
Porfimer (p.764·3).
Barrett's oesophagus.

Photoderm
Note. This name is used for preparations of different composition.
Szama, Arg.
A range of sunscreens.

Bioderma, Venez.
SPF 20: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); octil triazone (p.1608·1); octocrilene (p.1608·3).
Sunscreen.

Photoderm AKN *Bioderma, Venez.*
SPF 20: Glycolic acid (p.1598·1); salicylic acid (p.1612·2); benzoic acid (p.1630·2); dehydroacetic acid (p.1641·2); phenoxyethanol (p.1657·1).
Sunscreen for patients with acne.

Photoderm AR *Dispolab, Chile.*
SPF 50: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1).
Sunscreen.

Photoderm Flush
Note. This name is used for preparations of different composition.
Dispolab, Chile†.
SPF 50: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1).
Sunscreen.

Bioderma, Fr.†.
SPF 50: Bisoctrizole (p.1591·2); octil triazone (p.1608·1); avobenzone (p.1589·3); enzacamene (p.1597·1); ginkgo biloba (p.2311·1); enoxolone (p.50·1).
Sunscreen.

Photoderm Kid *Dispolab, Chile.*
SPF 40: Octinoxate (p.1608·2); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

Photoderm Laser *Bioderma, Fr.†.*
SPF 100: Bisoctrizole (p.1591·2); octil triazone (p.1608·1); avobenzone (p.1589·3); enzacamene (p.1597·1); glabridine; enoxolone (p.50·1).
Sunscreen.

Photoderm Max
Note. This name is used for preparations of different composition.
Bioderma, Ital.
Cream: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Bioderma, Venez.
SPF 60+: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); octocrilene (p.1608·3).
Sunscreen.

Dispolab, Chile; Bioderma, Fr.†; Bioderma, Venez.
SPF 100: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1).
Sunscreen.

Bioderma, Ital.
Topical milk: Octil octanoate; octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3); octocrilene (p.1608·3); zinc oxide (p.1621·2).
Sunscreen.

Photoderm Mineral *Bioderma, Ital.†.*
Octil octanoate; titanium dioxide (p.1617·3).
Sunscreen.

Photoderm SPE *Bioderma, Fr.†.*
SPF 40: UV-Pearls; bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

Photoderm Spot *Dispolab, Chile.*
SPF 100: Bisoctrizole (p.1591·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1).
Sunscreen.

Photoderm THP *Bioderma, Fr.†.*
SPF 30: Bisoctrizole (p.1591·2); octil triazone (p.1608·1); avobenzone (p.1589·3).
Sunscreen.

Photofrin *Axcan, Canad.; Meduna, Ger.; Galenica, Gr.; Axcan, Hung.; Axcan, Israel; Axcan, Neth.; Ferrer, Port.; Sanofi Winthrop, USA.*
Porfimer sodium (p.764·3).
Dysplasia associated with Barrett's oesophagus; endobronchial obstruction; non-small cell lung cancer; oesophageal cancer; papillary bladder cancer.

Photoplex *Allergan, Canad.*
SPF 15: Avobenzone (p.1589·3); octisalate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Photoscreen
Note. This name is used for preparations of different composition.
Pierre Fabre, Arg.†.
SPF 60: Octinoxate (p.1608·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Ducray, Fr.
SPF 60 cream: Octinoxate (p.1608·2); octocrilene (p.1608·3); bemotrizinol (p.1590·2); bisoctrizole (p.1591·2).
Sunscreen.

Ducray, Fr.
SPF 30 gel-cream: Cinnamate; bisoctrizole (p.1591·2); octocrilene (p.1608·3).
Sunscreen.

Ducray, Fr.
SPF 60 milk: Cinnamate; bisoctrizole (p.1591·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Ducray, Fr.
SPF 30 spray: Cinnamate; bisoctrizole (p.1591·2); bemotrizinol (p.1590·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Phototrop *Tubilux, Ital.*
Acetylcarnitine; omega-3 marine triglycerides; ubidecarenone (p.1922·1).
Nutritional supplement.

Phrachedi *Millimed, Thai.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting in pregnancy; radiation sickness.

Phrachedi Balm *Millimed, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Insect bites; musculoskeletal pain; pruritus; sprains.

Phrenilin *Valeant, USA.*
Butalbital (p.967·2); paracetamol (p.108·1).
Tension headache.

Phrenilin w Caffeine and Codeine *Valeant, USA.*
Codeine phosphate (p.37·2); paracetamol (p.108·1); caffeine (p.1116·3); butalbital (p.967·2).
Pain.

Phthizoetham *Akrikhin, Rus.*
Isoniazid (p.288·1); ethambutol (p.275·2).
Tuberculosis.

Phthizopiram *Akrikhin, Rus.*
Isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Phycocyane *Labocean, Fr.†.*
Spirulina (p.2392·1).
Tonic.

Phygelin *Ivax, Mex.*
⊗ Polygeline (p.1077·2).
Plasma volume expansion.

Phylarm *Poen, Arg.; LCA, Fr.†.*
Sodium chloride (p.1686·1); borax (p.2268·1); boric acid (p.2268·1).
Dry eyes; eye irritation; eye wash.

Phyllocontin
Purdue, Canad.; Mahakam Beta, Indon.; Mundipharma, Indon.; Napp, Irl.
Aminophylline (p.1114·2).
Bronchospasm; heart failure; obstructive airways disease.

Pharmafrica, S.Afr.; Napp, UK.
Aminophylline hydrate (p.1114·3).
Asthma; chronic bronchitis; emphysema; heart failure; obstructive airways disease.

Phyllotemp
Mundipharma, Ger.†.
Aminophylline hydrate (p.1114·3).
Obstructive airways disease.

Mundipharma, Switz.†.
Aminophylline (p.1114·2).
Obstructive airways disease.

Phylobid *Wockhardt, India.*
Theophylline (p.1140·1).
Obstructive airways disease.

Phyloday *Wockhardt, India.*
Theophylline (p.1140·1).
Obstructive airways disease.

Phylorinol
Note. This name is used for preparations of different composition.
Schaffer, USA.
Mouthwash: Phenol (p.1656·1); methyl salicylate (p.85·3).
Minor mouth or throat irritation.

Schaffer, USA.
Topical solution: Phenol (p.1656·1); boric acid (p.2268·1); strong iodine solution (p.2169·2).
Oral wounds and infections.

Phymet DTF *GSK, Irl.*
⊗ Methadone hydrochloride (p.82·3).
Opioid addiction; pain.

Phymorax *Medica Korea, Singapore†.*
Hydroxyzine hydrochloride (p.581·2).
Alcohol withdrawal syndrome; anxiety; nausea and vomiting; premedication; skin disorders.

Phy-O *Zekides, Gr.*
Sodium chloride (p.1686·1).

Physeptone *GSK, Austral.; GSK, Hong Kong†; Wellcome, Irl.†; Aspen, S.Afr.; GSK, Singapore†; Martindale Pharmaceuticals, UK.*
⊗ Methadone hydrochloride (p.82·3).
. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Cough; opioid withdrawal syndrome; pain.

Physiodose *Ramini, Ital.; Tripharma, Turk.*
Sodium chloride (p.1686·1).
Eye and nose cleansing; nasal congestion.

Physiogel
Note. This name is used for preparations of different composition.
Stiefel, Fr.; Stiefel, Indon.; Stiefel, Ital.; Stiefel, Malaysia; Stiefel, Philipp.; Stiefel, Singapore; Stiefel, Thai.
Sodium cocoyl isetionate (p.2138·3).
Soap substitute; soap-free cleanser.

Braun, Switz.
⊗ Modified gelatin (p.1072·1) with electrolytes.
Hypovolaemia.

Stiefel, Hong Kong.
Cream; Lotion: Phytosterols (p.1373·1); ceramide; squalane (p.2032·3); phospholipids; triglycerides.
Emollient.

Stiefel, Hong Kong.
Skin cleanser: Sodium cocoyl isetionate (p.2138·3).
Soap substitute.

Physiogesic *Hebert, Canad.*
Diethylamine salicylate (p.47·2).

Physiogine *Organon, Fr.*
Estriol (p.2101·1).
Vulvovaginal disorders due to oestrogen deficiency.

Physioglau *Bausch & Lomb, Port.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Physiologic *Vifor, Switz.*
Sodium chloride (p.1686·1).
Nasal irrigation.

Physiologica
Note. This name is used for preparations of different composition.
Qualiphar, Belg.
Sodium chloride (p.1686·1); sodium hyaluronate (p.2320·1).
Nasal congestion; nasal hygiene.

Qualiphar, Belg.; Gifrer Barbezat, Fr.
Sodium chloride (p.1686·1).
Eye wash; nasal irrigation.

Physiologica Gifrer *Abdi, Turk.*
Sodium chloride (p.1686·1).
Eye irrigation; nasal congestion.

Physiolyte *McGaw, USA.*
Electrolytes (p.1667·1).
Irrigation solution.

Physiomenthol *Hebert, Canad.*
Menthol (p.2340·1).

Physiomer *Sanofi-Aventis, Fr.; Sanofi-Aventis OTC, Ital.; Goemar, Philipp.*
Sea water (p.1686·1).
Nasal congestion; nasal hygiene; nasal irrigation.

Physiomycine *Zambon, Fr.*
Methacycline hydrochloride (p.298·2).
Bacterial infections.

Physioneal *Baxter, Austria; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Baxter, Ital.; Baxter, Neth.; Baxter, Port.; Baxter, Swed.; Baxter, Switz.; Baxter, UK.*
Glucose; calcium chloride; magnesium chloride; sodium chloride; sodium bicarbonate; sodium lactate (p.1670·3).
Peritoneal dialysis.

Physioneal Glucosa *Baxter, Spain.*
Glucose monohydrate; calcium chloride; magnesium chloride; sodium chloride; sodium bicarbonate; sodium lactate (p.1670·3).
Peritoneal dialysis.

Physiorhine *Melisana, Belg.*
Sodium chloride (p.1686·1).
Cleansing of eyelids; nasal irrigation.

Physio-Rub *Hebert, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3).

Physiosoin *Chauvin, Fr.; Bausch & Lomb, Switz.*
Sodium chloride (p.1686·1)(p.1622·2).
Eye wash; nasal irrigation; rinsing solution for contact lens; wound irrigation.

PhysioSol *Abbott, USA.*
Electrolytes (p.1667·1).
Irrigation solution.

Physiotens *Solvay, Austral.; Solvay, Cz.; Solvay, Denm.; Solvay, Fin.; Solvay, Fr.; Solvay, Ger.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Indon.; Solvay, Malaysia; Solvay, Norw.; Solvay, Philipp.; Solvay, Pol.; Solvay, Rus.; Schering, S.Afr.; Solvay, Singapore†; Solvay, Swed.; Solvay, Switz.; Solvay, UK.*
Moxonidine (p.1345·1).
Hypertension.

Physiotherm *Ferrier, Fr.†.*
Natural spring water of Berthemont-les-Bains (p.1667·1).
Nasal irrigation.

Physiotulle
Coloplast, Fr.; Coloplast, Ger.
Carmellose (p.2142·1).
Burns; ulcers; wounds.

Coloplast, UK.
Carmellose sodium (p.2142·1).
Wounds.

Physiotulle-Ag *Coloplast, UK.*
Carmellose (p.2142·1); sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Phytacis *CIS, Neth.; CIS, Port.*
Technetium-99m (p.2055·3) fytate.
Liver scintigraphy.

Phytemag *Lesourd, Fr.*
Magnesium glycerophosphate; apium root; buchu leaf; equisetum; ginger (p.1922·1).
Tonic.

Phytex *Pharmax, Irl.; Forest Laboratories, UK.*
Tannic acid (p.2394·3); boric acid (p.2268·1); salicylic acid (p.1612·2); methyl salicylate (p.85·3); acetic acid (p.2244·2).
Fungal skin and nail infections.

Phytheol *Phytosolba, Fr.*
Zanthoxylum (p.2417·1); fenugreek (p.2303·3); shitake; salix (p.121·3); piroctone olamine (p.1610·1); salicylic acid (p.1612·2); ichthammol (p.1599·1).
Dandruff.

Phytic Acid *Mac, Ital.*
Fytic acid (p.1464·2); glycolic acid (p.1598·1).
Hyperpigmentation disorders.

Phyto Corrective Gel *Dispolab, Chile.*
Arbutin (p.1589·2); pepino; thyme (p.2401·1); bioflavonoids (p.2304·1).
Skin pigmentation disorders.

Phyto Soya
Arkomedika, Fr.; Arkochim, Spain.
Soya (p.1965·3).
Hyperlipidaemia; menopausal disorders.

Arkopharma, Hong Kong.
Soya isoflavones (p.2391·2).
Menopausal disorders.

Phyto Spot *Dispolab, Chile.*
Arbutin (p.1589·2); kojic acid (p.1603·3); thyme (p.2401·1); cucurbitacin.
Skin pigmentation disorders.

Phytobronchin *Steigerwald, Ger.*
Cowslip rhizome (p.2372·2); thyme (p.2401·1).
Cold symptoms.

Phyto-C *Steierl, Ger.*
Homoeopathic preparation.
Formerly known as Phyto-Hypophyson C.

Phytocalm
Note. This name is used for preparations of different composition.
UPSA Conseil, Fr.†.
Valerian (p.2410·1); ballota; crataegus (p.2289·1); passion flower (p.2363·2).
Insomnia; nervous disorders.

Arkopharma, UK.
Passion flower (p.2363·2).
Insomnia; stress and strain.

Phyto-Care *Gattefosse, Hong Kong; Marlyn, Hong Kong.*
Soya isoflavones (p.2391·2).
Menopausal disorders; osteoporosis.

Phytocean *Ido, Fr.†.*
Nutritional supplement (p.1922·1).

Phytocold *Arkopharma, UK.*
Echinacea (p.2298·1).
Colds.

Phytocor *Pharma Dynamics, S.Afr.*
Policosanol (p.1373·3).
Hypercholesterolaemia.

Phytocortal *Steierl, Ger.*
Homoeopathic preparation.

Phytoderm Compositum *Teva, Israel.*
Tolnaftate (p.548·3); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Fungal skin infections.

Phytodiet *Phytodiet, Fr.*
High protein food for special diets (p.1922·1).

Phytodolor *Flordis, Austral.; Madaus, Austria; Steigerwald, Cz.; Steigerwald, Ger.*
Populus (p.2371·1); ash (p.2262·1); solidago (p.2391·1).
Musculoskeletal and joint disorders; neuralgia.

Phytodorma *Hevert, Ger.†.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Phyto-Ease *Marlyn, Hong Kong.*
Soya isoflavones (p.2391·2); saw palmetto (p.2192·3); lycopersicon lycopersicum.
Benign prostatic hyperplasia; nutritional supplement.

Phyto-Embryonnaire *Recherche Botanique, Fr.†.*
Crataegus; birch; black currant; rosa canina; ginkgo biloba; juglans regia (p.1922·1).
Gastrointestinal disorders.

Phytoestrin *Usana, Hong Kong†; Usana, Singapore.*
Soya isoflavones (p.2391·2); dong quai (p.2297·3); cimicifuga (p.2282·1); agnus castus (p.2249·1); liquorice (p.1740·3).
Dietary supplement for women; menopausal disorders; menstrual disorders.

Phytoestrol N *Muller Goppingen, Ger.*
Rhapontic rhubarb (p.1768·3).
Menopausal disorders.

Phytogran *Grandel-Synpharma, Ger.†.*
Lupulus (p.2335·2); St John's wort (p.422·3).
Nervous disorders.

Phytohepar *Steigerwald, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Phytohustil *Steigerwald, Ger.*
Althaea (p.2253·3).
Coughs.

Phyto-L *Steierl, Ger.*
Homoeopathic preparation.
Formerly known as Phyto-Hypophyson L.

Phyto-Laxia *Phytopharma, Switz.*
Frangula bark (p.1732·2); senna (p.1769·2).
Constipation.

Phytolaxin *Hanseler, Switz.*
Aloes (p.1705·2); frangula bark (p.1732·2); senna (p.1769·2).
Constipation.

PhytoLife *Blackmores, Austral.*
Soya bean (p.1965·3); calcium hydrogen phosphate (p.1676·1).
Calcium deficiency; menopausal disorders.

Phytolife Plus *Blackmores, UK.*
Calcium (p.1675·2); soya (p.1965·3).
Menopausal disorders.

Phytolithe *Phytosolba, Fr.†.*
Ichthammol (p.1599·1); cajuput oil (p.2271·2); cade oil (p.1616·1); storax (p.2392·3).
Seborrhoeic dermatitis.

Phytolongbronze *Phytosolba, Fr.*
Betacarotene (p.1930·3); lycopene (p.2335·2); cucurbita (p.2290·2); vitamin E (p.1992·2); raspberry seed oil; wheat germ (p.2415·1).
Tanning aid.

Phytomed Cardio *Phytomed, Switz.*
Crataegus (p.2289·1); passion flower (p.2363·2); rosemary (p.2381·2).
Cardiac disorders.

Phytomed Gastro *Phytomed, Switz.†.*
Angelica (p.2258·1); centaury (p.2279·1); chamomile (p.2279·3); peppermint leaf (p.1761·2); caraway (p.2276·3); potato.
Digestive disorders.

Phytomed Hepato *Phytomed, Switz.†.*
Absinthium (p.2244·1); cynara (p.2291·2); peppermint leaf (p.1761·2); raphanus sativus var. nigra; milk thistle (p.1452·1); taraxacum (p.2395·1).
Digestive disorders.

Phytomed Nephro *Phytomed, Switz.†.*
Silver birch (p.2266·3); solidago virgaurea (p.2391·1); java tea (p.2328·2); juniper (p.2328·2); ononis (p.2357·1); taraxacum (p.2395·1).
Urinary-tract disorders.

Phytomed Nervo *Phytomed, Switz.†.*
Melissa (p.2339·3); passion flower (p.2363·2); bitter orange (p.2357·1); lupulus (p.2335·2).
Agitation; sleep disorders.

Phytomed Prosta *Phytomed, Switz.†.*
Echinacea purpurea (p.2298·1); poplar buds (p.2371·1); saw palmetto (p.2192·3); solidago virgaurea (p.2391·1).
Prostatic pain; urinary disorders.

Phytomed Somni *Phytomed, Switz.†.*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2); lavandula angustifolia.
Sleep disorders.

Phytomelis *Lehning, Fr.*
Hamamelis (p.2318·2); aesculus (p.2248·2).
Haemorrhoids; peripheral vascular disorders.

Phytonoctu *Steigerwald, Ger.*
Melissa (p.2339·3); passion flower (p.2363·2); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Phytopause *Pharma Dynamics, S.Afr.*
Soya isoflavones (p.2391·2).
Dietary supplement; menopausal disorders.

Phytopause BSF *Pharma Dynamics, S.Afr.*
Soya isoflavones (p.2391·2); calcium (p.1675·2); magnesium (p.1678·3); colecalciferol (p.1986·2).
Calcium supplement; osteoporosis.

Phytophanere *Phytosolba, Fr.*
Wheat-germ oil (p.2415·1); carrot oil; borage oil (p.2267·3); rice-bran oil; salmon oil (p.1362·1); yeast (p.1998·3); antilles cherries; fish roe.
Fragile hair and nails.

Phytopharma Calcium *Phytopharma, Switz.*
Calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Phytopure *Lalco, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Phytorelax *Arkopharma, UK.*
Valerian (p.2410·1).
Stress; tension.

Phytoslim *Arkopharma, UK.*
Kelp (p.2384·2).
Obesity.

Phytosolaire *Phytosolba, Fr.*
Betacarotene (p.1930·3); lycopene (p.2335·2); vitamin E (p.1992·2); selenium (p.1961·1); borage oil (p.2267·3); evening primrose oil (p.2302·1).
Tanning aid.

Phytosquame *Phytosolba, Fr.*
Hydnocarpus oil; melaleuca oil (p.2338·2); piroctone olamine (p.1610·1).
Dandruff.

Phytosyl Plus *Vita Health, Singapore†.*
Fibre; *Lactobacillus* species; aloe vera (p.1922·1).
Dietary fibre supplement.

Phytotherapie Titree *Boiron, Fr.*
A range of herbal preparations.

Phytotux *Lehning, Fr.*
Tolu balsam (p.1574·2); Desessartz syrup.
Coughs.

Phytotux H *Homeocan, Canad.*
Homoeopathic preparation.

Phytovein *Catarinense, Braz.*
Aesculus (p.2248·2).
Vascular disorders.

Phytovim *Sante Naturelle, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Phyzidine *Europharm, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

PI Antiseptic Ointment *Hexal, Austral.†.*
Povidone-iodine (p.1659·2).

Piam *Denver, Arg.*
⊗ Tetryzoline (p.1574·1).
Eye disorders.

Piamfucin *Yamanouchi, Rus.†.*
Natamycin (p.543·1).
Fungal infections.

Piascledine
Bernabo, Arg.
Avocado (p.2262·2); soya (p.1965·3).
Arthroses.

Solvay, Braz.; Medicom, Cz.; Expanscience, Fr.; ABC, Ital.; Expanscience, Pol.; Expanscience, Rus.
Avocado oil; soya oil (p.1965·3).
Degenerative joint disorders; dental disorders; gum disorders; mouth disorders; osteoarthritis; phlebitis; skin disorders; skin ulceration.

Rhein, Mex.
Avocado oil; soya (p.1965·3).
Osteoarthritis; rheumatism.

Piat *Salus, Mex.†.*
Miconazole (p.541·2).
Fungal infections.

Pibaksin *Sanbe, Indon.*
Mupirocin (p.302·3).
Skin infections.

Picalm *Grunenthal, Port.*
Piketoprofen (p.117·2) or piketoprofen hydrochloride (p.117·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Picamic *Tropica Mas, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Picamilon *Akrikhin, Rus.*
Sodium N-nicotinyl-gamma-aminobutyrate.

Picapan *DHA, Hong Kong; DHA, Singapore.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Picaplin *Medic+Aid, Philipp.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Piccadilly Foot Ointment *Adco, S.Afr.*
Salicylic acid (p.1612·2).
Calluses; corns.

Picibanil *Chugai, Jpn.*
Picibanil (p.2367·3).
Malignant neoplasms.

Picillin *Laboratorio Farm., Israel†; CT, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) may be included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pickles Antiseptic Cream *Pickles, UK.*
Dibrompropamidine isetionate (p.1642·1).
Burns; scalds; sunburn.

Pickles Chilblain Cream *Pickles, UK.*
Methyl nicotinate (p.85·3).
Chilblains.

Pickles Corn Caps *Pickles, UK.*
Salicylic acid (p.1612·2); colophony (p.2286·2).
Corns.

Pickles Foot Ointment *Ransom, UK.*
Salicylic acid (p.1612·2).
Calluses; corns.

Pickles Smelling Salts *Pickles, UK.*
Strong ammonia solution (p.2256·1); eucalyptus oil (p.2301·2); pine oil (p.2368·2).
Headache; nasal congestion.

Piclodin *Pharos, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Piclodorm *Binnofarm, Rus.*
Zopiclone (p.1039·1).
Insomnia.

Picolax
Note. This name is used for preparations of different composition.
Dendy, Austral.†.
Sodium picosulfate (p.1771·1); magnesium carbonate (p.1743·1); citric acid (p.2284·1).
Bowel evacuation; constipation.

Ferring, Braz.†; Neo-Farmaceutica, Port.
Sodium picosulfate (p.1771·1).
Constipation.

Ferring, Irl.; Ferring, UK.
Sodium picosulfate (p.1771·1); magnesium citrate (p.1743·2).
Bowel evacuation.

Picolaxine *Pharmacobel, Belg.*
Sodium picosulfate (p.1771·1).
Constipation.

Picolite *Picot, Fr.*
Maltodextrin; sucrose; sodium chloride; potassium citrate; citric acid (p.1672·2).
Diarrhoea; oral rehydration therapy.

Picolon *Medic, Denm.*
Sodium picosulfate (p.1771·1).
Constipation.

Picoprep *Pharmatel, Austral.; Pharmatel, Malaysia; Bamford, NZ.*
Sodium picosulfate (p.1771·1); magnesium oxide (p.1744·1); citric acid (p.2284·1).
Bowel evacuation; constipation.

Pico-Salax *Ferring, Canad.*
Sodium picosulfate (p.1771·1); magnesium oxide (p.1744·1); citric acid (p.2284·1).
Bowel evacuation.

Picot *Picot, Fr.†.*
Dextrin (p.1937·1); maltose (p.1956·1).
Sugar substitute.

Picot AR *Picot, Fr.*
Infant feed (p.1922·1).
Regurgitation.

Picot sans Gluten *Picot, Fr.†.*
Food for special diets (p.1922·1).
Coeliac disease.

Picot Sans Lactose *Picot, Fr.†.*
Infant feed (p.1922·1).
Lactose intolerance.

Picutex *Sertex, Arg.*
Quassia (p.2377·1).
Pediculosis.

Picyn *Bernofarm, Indon.*
Sultamicillin (p.344·1).
Bacterial infections.

Pidezol *EGIS, Hung.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Pidilat *Solvay, Ger.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Pidocal *Sanofi Synthelabo, Switz.†.*
Calcium pidolate (p.1676·3); calcium carbonate (p.1714·1).
Calcium deficiency; osteoporosis.

Pidomag *Baldacci, Braz.*
Magnesium pidolate (p.1679·3).
Magnesium deficiency.

Pidoxina *Parggon, Mex.*
Meclozine (p.585·1); pyridoxine (p.1979·1).
Nausea and vomiting; vertigo.

Pidrol *Gache, Venez.*
⊗ Ammonium acetate (p.1551·2); ephedrine hydrochloride (p.1558·2).
Formerly contained ammonium chloride, grindelia, ephedrine hydrochloride, and mepyramine maleate.
Respiratory-tract congestion.

Piecidex
Note. This name is used for preparations of different composition.
Andromaco, Arg.†.
Cream; topical powder: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); sodium propionate (p.545·3); salicylic acid (p.1612·2).
Fungal skin, scalp, and nail infections.

Andromaco, Arg.†.
Topical liquid; topical spray: Undecenoic acid (p.549·2); sodium undecenoate (p.549·3); sodium propionate (p.545·3); propionic acid (p.545·2).
Fungal skin, scalp, and nail infections.

Piecidex NF
Note. This name is used for preparations of different composition.
Andromaco, Arg.
Cream: Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Andromaco, Arg.
Lotion: Bifonazole (p.527·3); diphenhydramine hydrochloride (p.577·2).
Fungal skin infections.

Piel Vital *AM, Arg.*
Betacarotene; vitamins; minerals; methionine (p.1922·1).
Dietary supplement.

Pielograf *Schering, Chile†; Juste, Spain.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Pierami *Fournier, Ital.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Piesital *Demo, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Pi-Fedrin *Flupal, Venez.*
⊗ Sodium benzoate (p.1630·2); ammonium acetate (p.1551·2); drosera (p.2297·3); ephedrine hydrochloride (p.1558·2); mepyramine maleate (p.585·2).
Respiratory-tract congestion.

Pifrol *Arlex, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Pigenil *Pharmafar, Ital.*
Pygeum africanum (p.2192·3).
Prostatic hyperplasia.

Pigitil *Dorom, Ital.*
Pidotimod (p.2367·3).
Immunostimulant.

Pigloss *Bajamed, Mex.*
Glipizide (p.441·3).
Diabetes mellitus.

Pigmal *Gramon, Arg.*
Pirolenoso acid.
Pediculosis.

Pigmanorm
Note. This name is used for preparations of different composition.
Widmer, Ger.
⊗ Hydroquinone (p.1598·2); tretinoin (p.1618·1); hydrocortisone (p.1535·2).
Skin hyperpigmentation.
Widmer, Switz.
⊗ Hydroquinone (p.1598·2); tretinoin (p.1618·1); dexamethasone (p.1526·1); dexpanthenol (p.2362·1); octinoxate (p.1608·2); avobenzone (p.1589·3).
Skin hyperpigmentation.

Pigmentasa *Vinas, Spain.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Pigmentum Castellani *Chema-Elektromet, Pol.*
Boric acid (p.2268·1); resorcinol (p.1612·1); magenta (p.1651·3); phenol (p.1656·1).
Eczema; fungal skin infections; impetigo.

Pigmet *Sandoz, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Pik Gel *Amnol, Ital.*
Centella (p.1592·3); ginkgo biloba (p.2311·1); peppermint (p.1761·2); devil's claw root (p.39·1); menthol (p.2340·1); aesculus (p.2248·2); pineapple; equisetum (p.2299·3); achillea (p.2245·2); ginger (p.1732·3); meadowsweet (p.2338·1); sesamum indicum; myrtillus (p.2349·3).
Circulatory disorders.

Pikovit *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.; Ilsan, Turk.*
Vitamin preparation with or without minerals (p.1922·1).
Nutritional supplement.

Pil *Sophia, Mex.*
Pilocarpine (p.1884·3).
Ocular hypertension; production of miosis.

Pil Keluarga Berencana *Schering, Indon.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Pilder *Quimifar, Spain.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Pildoras Zeninas *Puerto Galiano, Spain.*
Aloes (p.1705·2); cascara (p.1715·2).
Constipation.

Pileabs *Lane, UK.*
Slippery elm bark (p.2388·2); cascara sagrada (p.1715·2).
Haemorrhoids.

Pilelife *Yung Shin, Hong Kong.*
⊗ Lidocaine (p.1862·3); prednisolone acetate (p.1541·1); chlorhexidine hydrochloride (p.1635·3); tocopherol acetate (p.1992·3); alcloxa (p.1587·2).
Anorectal disorders.

Pilem *Uniao Quimica, Braz.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Pilensar *IMA, Braz.*
Lindane (p.2045·3).
Pediculosis; scabies.

Piletabs *Potter's, UK.*
Pilewort (p.2368·1); agrimony (p.2249·2); cascara (p.1715·2); stone root (p.2392·2).
Haemorrhoids.

Pilfood
Serra Pamies, Hong Kong.
Vitamins; methionine; cystine; protein hydrolysate; millet (p.1922·1).
Cedar Health, UK.
Vitamin E; riboflavin; vitamin B ; biotin; pantothenic acid; methionine; cysteine (p.1922·1).
Dietary supplement for healthy hair.

Pil-Food
Serra Pamies, Spain.
Vitamins; amino acids; panicum miliaceum (p.1922·1).
Hair, scalp, and nail disorders.
Vifor, Switz.
Multivitamins and amino acids (p.1922·1); protein hydrolysate; millet.
Hair and nail disorders.

Pil-G Uso *Finadiet, Arg.†.*
Glacial acetic acid (p.2244·2).
Pediculosis.

Pilison *Schering, Austria.*
⊗ Fluocortolone pivalate (p.1532·3); salicylic acid (p.1612·2).
Skin disorders.

Pilka *Novartis Consumer, Austria; Novartis Consumer, Israel; Ferrer, Spain; Novartis Consumer, Switz.†.*
Drosera (p.2297·3); thyme (p.2401·1).
Bronchitis; coughs; throat disorders.

Pilka F *Novartis Consumer, Port.†.*
Drosera (p.2297·3); wild thyme (p.2415·3); pinguicula.
Coughs.

Pilka Forte *Novartis Consumer, Austria.*
⊗ Drosera (p.2297·3); thyme (p.2401·1); ephedrine hydrochloride (p.1558·2).
Coughs.

Pill 72 *Cipla, India.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Pilo *Meda, Belg.; Chauvin, Fr.; Upha, Malaysia†; Grin, Mex.; Novartis, Norw.†.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; hernia of the iris; induction of miosis; reversal of mydriasis and cycloplegia.

Pilobloc *Farmila, Ital.*
⊗ Pilocarpine hydrochloride (p.1884·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Pilobloq *Thea, Fr.*
⊗ Pilocarpine hydrochloride (p.1884·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Pilocan *Latinofarma, Braz.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.

Pilocar
FDC, India.
Pilocarpine nitrate (p.1884·3).
Glaucoma; production of miosis.
Novartis Ophthalmics, USA; Oftalmi, Venez.
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis; raised intra-ocular pressure; reversal of mydriasis.

Pilocarcil *Edol, Port.*
Pilocarpine hydrochloride (p.1884·3).
Ocular hypertension; production of miosis.

Pilocarpol
Lersan, Arg.
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.
Winzer, Ger.†.
Pilocarpine (p.1884·3).
Glaucoma; production of miosis.

Pilocollyre *Cooper (Κοπερ), Gr.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of mydriasis.

Pilodren *Farmila, Ital.†.*
⊗ Pilocarpine hydrochloride (p.1884·3); adrenaline acid tartrate (p.1203·2).
Open-angle glaucoma.

Pilofar *Farmedia, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Pilogel *Alcon, Chile; Alcon, Cz.; Alcon, Hong Kong†; Alcon, Hung.†; Alcon, Irl.; Alcon, Ital.†; Alcon, Neth.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Turk.; Alcon, UK.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Pilokarsol *Sanovel, Turk.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Pilomann *Mann, Ger.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilomann-Ol *Mann, Ger.*
Pilocarpine (p.1884·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilomed *Bausch & Lomb, Arg.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.

Pilopil *Guardian, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Pilopine HS *Alcon, Canad.; Alcon, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis; raised intra-ocular pressure; reversal of mydriasis.

Piloplex *Davi, Port.†.*
Pilocarpine (p.1884·3).
Glaucoma; production of miosis.

Pilopos *Ursapharm, Cz.; Ursapharm, Ger.*
Pilocarpine nitrate (p.1884·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilopt *Allergan, Austral.; Healthcare Logistics, NZ.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Piloptic *Optopics, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; reversal of mydriasis.

Pilopto-Carpine *Lebeh, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Pilorcarpin Puroptal *Agepha, Austria.*
Pilocarpine hydrochloride (p.1884·3).
Intra-ocular hypertension.

Pilosed *Bilim, Turk.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Pilostat *Bausch & Lomb, USA.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; raised intra-ocular pressure; reversal of mydriasis.

Pilostigmin Puroptal *Metochem, Austria.*
Neostigmine bromide (p.631·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma; production of miosis.

Pilo-Stulln *Stulln, Ger.†.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; reversal of drug-induced mydriasis.

Pilosuryl *Pierre Fabre, Fr.*
Pilosella; phyllanthus.
Water retention.

Pilotim *Alcon, Arg.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Pilotina *Genepharm, Gr.†.*
Pilocarpine nitrate (p.1884·3).
Glaucoma; production of mydriasis.

Pilotonina *Farmila, Cz.†; Farmila, Ital.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension; production of miosis.

Pilovate *Cipla, India.*
⊗ Beclometasone dipropionate (p.1516·2); phenylephrine hydrochloride (p.1568·1); lidocaine hydrochloride (p.1862·3).
Skin disorders.

Piloxidil *Chemical Research, Pol.*
Minoxidil (p.1342·1).
Alopecia.

Piloxil *Golaz, Switz.†.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Pilulas Ross *GSK, Braz.*
Aloin (p.1705·3); capsicum (p.2276·2); ipecacuanha (p.1562·3); belladonna (p.2263·3).
Constipation.

Pilulas De Witt's *CIF, Braz.†.*
⊗ Bearberry (p.2263·3); methylthioninium chloride (p.1450·3); fabiana imbricata; juniper (p.2328·2); potassium nitrate (p.1658·3); parapetalifera betulina; cascara (p.1715·2); sodium salicylate (p.124·2).
Urinary-tract infections.

Pilules de Vichy *Omega, Belg.*
Sodium picosulfate (p.1771·1); electrolytes (p.1667·1).
Constipation.

Pilzcin *Kolassa, Austria; Merz, Ger.; Shionogi, Jpn.*
Croconazole hydrochloride (p.530·3).
Fungal skin infections.

Pima *Fleming, USA.*
Potassium iodide (p.2169·2).
Respiratory-tract congestion.

Pima Biciron N *S & K, Ger.*
Natamycin (p.543·1).
Fungal eye infections.

Pimafucin *Astellas, Cz.; Astellas, Fin.; Galderma, Ger.; Yamanouchi, Hung.; Astellas, Neth.; Astellas, Pol.; Yamanouchi, Rus.; Santa, Turk.*
Natamycin (p.543·1).
Fungal mucous membrane, nail, skin, and vaginal infections; trichomoniasis.

Pimafucort *Astellas, Cz.; Astellas, Fin.; Yamanouchi, Hung.; CSL, NZ; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Yamanouchi, Rus.*
⊗ Hydrocortisone (p.1535·2); natamycin (p.543·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Pimidel *KRKA, Rus.*
Pipemidic acid (p.315·1).
Bacterial infections.

Pimiken *Kendrick, Mex.*
Magnesium valproate (p.511·3).
Epilepsy.

Pimoftal *Gerolimatos (Γερολυματος), Gr.†.*
⊗ Budesonide (p.1520·1).
Topical corticosteroid.

Pimple *Ingens, Arg.*
Minocycline (p.300·3).
Acne.

Pimplex *Konimex, Indon.*
Benzoyl peroxide (p.1590·2).
Acne.

Pinaclav *Pinewood, Irl.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Pinaclor *Pinewood, Irl.*
Cefaclor (p.217·2).
Bacterial infections.

Pinadone DTF *Pinewood, Irl.*
⊗ Methadone hydrochloride (p.82·3).
Opioid addiction.

Pinadrina *Pisa, Mex.*
⊗ Adrenaline (p.1203·2).

Pinal S *Atzinger, Ger.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Pin-Alcol *Schoning-Berlin, Ger.*
Menthol (p.2340·1); Norway spruce oil.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; neuritis; pruritus.

Pinam *Alian, Venez.*
Amlodipine besilate (p.1214·1).
Hypertension.

Pinamet *Pinewood, Irl.*
Cimetidine (p.1716·2).
Gastric hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Pinamox *Pinewood, Irl.*
Amoxicillin (p.202·2).
Bacterial infections.

Pinazo *Gache, Venez.*
⊗ Naphazoline nitrate (p.1565·2); mepyramine maleate (p.585·2).
Nasal congestion.

Pinden *Unipharm, Israel.*
⊗ Pindolol (p.1372·1).
Heart failure; hypertension.

Pindione *Lipha Sante, Fr.†.*
Phenindione (p.1369·2).
Thromboembolic disorders.

Pindocor *Merck, Fin.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Pindol *Pacific, NZ.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Pineal *Laborest, Ital.*
Magnesium; nicotinic acid; tryptophan (p.1922·1).
Depression.

Pinedrin *Lisapharma, Ital.†.*
Pumilio pine oil (p.2376·3); thyme (p.2401·1).
Respiratory system disorders.

Pinetarsol
Note. This name is used for preparations of different composition.
Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore; Crawford, UK.
Tar (p.1616·2).
Eczema; psoriasis; skin disorders.
Ego, Austral.
Bar; Gel: Pine tar (p.1616·2).
Skin disorders.
Ego, Austral.
Bath oil: Pine tar (p.1616·2); light liquid paraffin (p.2031·1).
Skin disorders.
Ego, Austral.
Solution: Pine tar (p.1616·2); trolamine laurilsulfate (p.2138·3).
Skin disorders.

Pinex *Alpharma, Denm.; Alpharma, Norw.*
Paracetamol (p.108·1).
Fever; pain.

Pinex Comp *Alpharma, Denm.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Pinex Forte *Alpharma, Norw.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Pinex Major *Alpharma, Norw.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Pinfetil *Novell, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Pinifed *Pinewood, Irl.†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease.

PiniHelix *Apipol, Pol.*
Ivy (p.2328·1); liquorice (p.1740·3); thyme (p.2401·1); pine.
Respiratory-tract disorders.

Pinikehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Piniment
Note. This name is used for preparations of different composition.
Austroplant, Austria.
Balsam: Camphor (p.2273·2); eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); guaiazulene (p.2317·3).
Coughs; gastrointestinal spasm; musculoskeletal and joint disorders; respiratory-tract disorders.
Austroplant, Austria.
Nasal ointment: ⊗ Ephedrine hydrochloride (p.1558·2); camphor (p.2273·2); eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); sage oil (p.2382·3); sunflower oil (p.1970·3).
Nasal congestion.
Austroplant, Austria.
Ointment; topical solution: Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3).
Catarrh; cold and influenza symptoms; cough.

Pinimenthol *Piniol, Switz.†.*
Camphor (p.2273·2); menthol (p.2340·1); orange oil (p.2357·2); pine cone oil; eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3); turpentine oil (p.2406·3); pine-needle oil (p.2368·2).
Influenza; muscle and joint pain; neuralgia.

Pinimenthol Baby *Piniol, Switz.†.*
Eucalyptus oil (p.2301·2); pine-needle oil (p.2368·2); sage oil (p.2382·3); thyme oil (p.2401·2); juniper oil (p.2328·3); peru balsam (p.2365·3).
Respiratory-tract disorders.

Pinimenthol Erkaltungsbad *Spitzner, Ger.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Bath additive; cold symptoms.

Pinimenthol Erkaltungsbad fur Kinder *Spitzner, Ger.*
Eucalyptus oil (p.2301·2).
Bath additive; cold symptoms.

Pinimenthol Erkaltungsbalsam mild *Spitzner, Ger.*
Eucalyptus oil (p.2301·2); Norway spruce oil.
Respiratory-tract congestion.

Pinimenthol Erkaltungsinhalat *Spitzner, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Cold symptoms.

Pinimenthol Erkaltungskapseln *Spitzner, Ger.†.*
Eucalyptus oil (p.2301·2).
Cold symptoms.

Pinimenthol Erkaltungssalbe *Spitzner, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2); menthol (p.2340·1).
Cold symptoms.

Pinimenthol Liquidum *Spitzner, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2); menthol (p.2340·1).
Neuralgia; respiratory-tract disorders; rheumatic disorders; skin ulcer prophylaxis.

Pinimenthol Nasensalbe *Spitzner, Ger.†.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Nasal disorders.

Pinimenthol S *Spitzner, Ger.†.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Bronchitis; cold symptoms.

Pinimenthol-N *Piniol, Switz.†.*
Eucalyptus oil (p.2301·2); pine-needle oil (p.2368·2); menthol (p.2340·1).
Cold symptoms; muscle and joint pain.

Pinimentol *Apotheca Pacis, Pol.*
Eucalyptus oil (p.2301·2); juniper oil (p.2328·3); peppermint oil (p.1761·2); pine oil (p.2368·2).
Neuralgia; respiratory-tract congestion; skeletal muscle pain.

Piniol Erkaltungsbalsam *Spitzner, Ger.†.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2).
Neuritis; respiratory-tract disorders; rheumatic disorders.

Piniol Nasenspray *Spitzner, Ger.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion; rhinitis.

Piniol Pommade Speciale *Piniol, Switz.†.*
Pumilio pine oil (p.2376·3); salicylic acid (p.1612·2).
Musculoskeletal, joint, and soft-tissue disorders.

Pink Bismuth *Perrigo, Israel.*
Bismuth salicylate (p.1711·1).
Abdominal cramps; diarrhoea; dyspepsia; flatulence; nausea.

Pinklot *Stiefel, Arg.*
Sulfur (p.1614·1); resorcinol (p.1612·1); salicylic acid (p.1612·2); calamine (p.1591·2).
Acne.

Pinloc *Orion, Fin.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Pino-Cort *Bell, India.*
⊗ Atropine sulfate (p.1219·3); hydrocortisone acetate (p.1535·2).
Allergic conjunctivitis; corneal burns; pre- and post-medication in ocular surgery.

Pinorec *Novell, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Pinorubin *Mercian, Cz.†.*
Pirarubicin (p.764·1).
Malignant neoplasms.

Pinosol
Note. This name is used for preparations of different composition.
Zentiva, Pol.
Cream: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); thymol (p.1664·3); tocopherol acetate.
Upper respiratory-tract congestion.

Zentiva, Pol.
Inhalation/nose drops: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); thymol (p.1664·3); tocopherol acetate; peppermint oil (p.1761·2); guaiazulene (p.2317·3).
Upper respiratory-tract congestion.

Zentiva, Cz.
Nasal cream: Pine silvestris oil (p.2368·2); eucalyptus oil (p.2301·2); thymol (p.1664·3); alpha tocoferil acetate.
Cold symptoms; nasal congestion; postoperative nasal packing.

Zentiva, Rus.
Nasal cream: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); thymol (p.1664·3); tocoferil acetate.
Adjunct in surgery of nasal cavities; nasal congestion.

Zentiva, Cz.; Zentiva, Rus.
Nasal drops: Pine oil (p.2368·2); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); thymol (p.1664·3); guaiazulene (p.2317·3); alpha tocoferil acetate.
Adjunct in surgery of nasal cavities; nasal congestion; nasopharyngeal inflammation; postoperative nasal packing; respiratory-tract inflammation; rhinitis.

Zentiva, Cz.
Nasal ointment: Menthol (p.2340·1); pine silvestris oil (p.2368·2); eucalyptus oil (p.2301·2); thymol (p.1664·3); alpha tocoferil acetate.
Cold symptoms; nasal congestion; postoperative nasal packing.

Zentiva, Rus.
Nasal ointment: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); menthol (p.2340·1); thymol (p.1664·3); tocoferil acetate.
Adjunct in surgery of nasal cavities; nasal congestion.

Zentiva, Pol.
Ointment: Eucalyptus oil (p.2301·2); pine oil (p.2368·2); thymol (p.1664·3); tocopherol acetate; menthol (p.2340·1).
Upper respiratory-tract congestion.

Pin-Rid *Apothecary, USA.*
Pyrantel embonate (p.155·1).

Pinselina Knapp *Montefarmaco, Ital.*
Benzocaine (p.1854·1); phenol (p.1656·1); thymol (p.1664·3); menthol (p.2340·1).
Mouth disorders.

Pintal *Alet, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Pinvex *Cofasa, Venez.*
Anthraquinone oxymethyl glycosides (p.1768·3); salicylic acid (p.1612·2).
Mouth and throat disorders.

Pin-X *Penn, USA.*
Pyrantel embonate (p.155·1).
Worm infections.

Pin-Xol *Hoe, Malaysia.*
Tar (p.1616·2).
Cleanser for scaly skin; pruritus; skin irritation.

Piodermina *Farmachimici, Ital.*
Sodium fusidate (p.279·3); thyme (p.2401·1); mallow (p.2337·2).
Bacterial skin infections.

Piodrex *Bunker, Braz.*
Permethrin (p.2048·2).
Formerly contained lindane.
Pediculosis; scabies.

Pioglit *Phoenix, Arg.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Piokil Plus *Novapharm, Venez.*
Permethrin (p.2048·2).
Pediculosis.

Pioktanina *Hasco-Lek, Pol.*
Methylrosanilinium chloride (p.1653·1).
Skin infections.

Pioletal *Delta, Braz.*
Permethrin (p.2048·2).
Formerly contained lindane.
Pediculosis.

Piolhol *Simoes, Braz.†.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis; scabies.

Piolhol Plus *Simoes, Braz.†.*
Permethrin (p.2048·2).
Pediculosis.

Piomed *Ipca, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Piomed M *Ipca, India.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Pioral Pasta *Teofarma, Ital.*
Chlorothymol (p.1640·1).
Oral disinfection.

Piorlis *Uriach, Spain.*
Cineole (p.2282·3); eugenol (p.2301·2); peppermint oil (p.1761·2); methyl salicylate (p.85·3); thymol (p.1664·3); tyrothricin (p.358·2).
Gingivitis; gum disinfection; mouth ulcers; pyorrhoea.

Piosafe *Otsira, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Piosafe MF *Otsira, India.*
Pioglitazone hydrochloride (p.456·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Piostop *Hexal, Braz.†.*
Permethrin (p.2048·2).

Piotamax *Omedir, Arg.*
Pioglitazone (p.456·3).
Diabetes mellitus.

Piozil *Farmacoope, Port.*
Benzyl benzoate (p.2036·1).

Piozulin *Cadila, India.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Pipacid *Farmanic, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pipcil *Wyeth Lederle, Belg.†.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Pipeacid *Del Saz & Filippini, Ital.†.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipedac *Teofarma, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipedic *Pharmasant, Thai.†.*
Pipemidic acid (p.315·1).
Bacterial infections of the urinary tract.

Pipefort *Lampugnani, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipemid *Visufarma, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipera *Astrapin, Ger.†; Hameln, Ger.†.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Piperac *Klonal, Arg.†.*
Piperacillin (p.315·2).
Bacterial infections.

Piperacyl *Tempo Scan Pacific, Indon.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Piperato *Ronava, Venez.*
Piperazine adipate (p.152·3); piperazine hydrate (p.153·1).
Worm infections.

Piperawitt DS *Columbia, Mex.†.*
Piperazine (p.152·3).
Worm infections.

Piperazil
Allen, Mex.
Piperazine (p.152·3).
Ascariasis; enterobiasis.

SM, Venez.
Piperazine hydrate (p.153·1).
Ascariasis; enterobiasis.

Piperdin *Etifar, Venez.*
Piperazine hydrate (p.153·1).
Worm infections.

Pipergress *Parggon, Mex.*
Piperazine (p.152·3).
Worm infections.

Piperital *IBI, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pipermed *Medimport, Mex.†.*
Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Pipermel *Basi, Port.*
Piperazine (p.152·3).
Ascariasis; enterobiasis.

Piperonil *Lusofarmaco, Ital.†.*
Pipamperone hydrochloride (p.1019·1).
Insomnia; psychiatric disorders.

Pipersal *Uno, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pipertex *Pharmatex, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Pipertox *Codilab, Port.*
Piperazine (p.152·3).
Worm infections.

Piperzan *Quim-Far, Venez.*
Piperazine hydrate (p.153·1).
Worm infections.

Pipetecan *Richmond, Arg.*
Irinotecan (p.738·1).
Malignant neoplasms.

Pipetexina *Richmond, Arg.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Piplex *Mediderm, Chile.*
Isotretinoin (p.1599·2).
Acne.

Pipolphen *EGIS, Hung.; Egis, Rus.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting; pain; sedative; vertigo.

Piportil
Sanofi-Aventis, Braz.; Sanofi-Aventis, Fr.
Pipotiazine (p.1019·2) or pipotiazine palmitate (p.1019·2).
Psychoses.

Sanofi-Aventis, Hung.; Sanofi-Aventis, Rus.
Pipotiazine (p.1019·2).
Psychoses.

Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Aventis, Neth.†; Aventis, Singapore†; JHC Healthcare, UK.
Pipotiazine palmitate (p.1019·2).
Psychoses.

Piportil L4 *Aventis, Canad.; Aventis, Mex.*
Pipotiazine palmitate (p.1019·2).
Psychoses; schizophrenia.

Piportyl *Sanofi-Aventis, Chile.*
Pipotiazine palmitate (p.1019·2).
Psychoses.

Piportyl L4 *Aventis, Arg.*
Pipotiazine palmitate (p.1019·2).
Psychoses.

Pippen *Pharmaland, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Pipracil *Wyeth-Ayerst, Canad.†; Wyeth, Hong Kong†; Wyeth, India; Wyeth, Malaysia†; Wyeth-Ayerst, Thai.†; Lederle, USA†.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Pipracin *Vitamed, Israel.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Pipraks *Eczacibasi, Cz.†; Eczacibasi, Turk.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Pipralen *Lennon, S.Afr.*
Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Pipram *Sanofi-Aventis, Braz.; Aventis, Fr.; Teofarma, Ital.; Aventis, Neth.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipril *Wyeth, Austral.†; Wyeth Lederle, Austria; Wyeth, Cz.†; Lederle, Ger.†; Wyeth, Gr.; Wyeth, Hung.†; Wyeth, Irl.†; Lederle, Israel†; Lederle, NZ†; Lederle, Switz.†.*
Piperacillin sodium (p.315·2).
Bacterial infections.

Piprine *Be-Tabs, S.Afr.*
Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Piprol *Elfar, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Piptal *Nicholas, Indon.*
Pipenzolate bromide (p.1762·2); phenobarbital sodium (p.492·2).
Colic; smooth muscle spasm.

Piptalin *Deva, Turk.*
Pipenzolate bromide (p.1762·2).

Pipurin *NCSN, Ital.*
Pipemidic acid (p.315·1).
Genitourinary-tract infections.

Pipurol *Zambon, Braz.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Pipzen *Degorts, Mex.*
Pipenzolate bromide (p.1762·2).

Pira *Omega, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Pirabene *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.*
Piracetam (p.368·2).
Alcohol withdrawal syndrome; cerebrovascular disorders; mental function impairment; myoclonus; organic brain disorders; vertigo.

Piracalamina *Szama, Arg.*
Phenol (p.1656·1); mepyramine maleate (p.585·2); calamine (p.1591·2); zinc oxide (p.1621·2).
Contact dermatitis; lichen; pruritus; sunburn.

Piracebral *Hexal, Ger.*
Piracetam (p.368·2).
Mental function disorders.

Piracem *Alet, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Piracemed *Ethimed, Belg.*
Piracetam (p.368·2).
Mental function disorders.

Piracetam Complex *Almirall, Spain†.*
Codergocrine mesilate (p.363·3); piracetam (p.368·2).
Cerebrovascular disorders.

Piracetop *Topgen, Belg.*
Piracetam (p.368·2).
Mental function disorders.

Piracetrop *Holsten, Ger.*
Piracetam (p.368·2).
Mental function disorders.

Piracezine *Minskinterkaps, Rus.*
Piracetam (p.368·2); cinnarizine (p.573·1).
Cerebrovascular disorders; cranial trauma; mental function disorders; migraine; motion sickness; vestibular disorders.

Piradro *Organifar, Venez.†.*
Dipyrone (p.49·2).
Fever; pain.

Piradrops Simple *Organifar, Venez.†.*
Dipyrone (p.49·2).
Fever; pain.

Pirafrin *Diba, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Conjunctival congestion; fever; nasal congestion; pain; rhinitis.

Piraldina *Bracco, Ital.*
Pyrazinamide (p.320·2).
Tuberculosis.

Piraldyne *Medifarm, Turk.*
Rhubarb (p.1768·3); salicylic acid (p.1612·2).
Mouth disorders.

Piralen *Otto, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Piralgina
Note. This name is used for preparations of different composition.
Diba, Mex.
Oral solution: Paracetamol (p.108·1).
Fever; pain.

Diba, Mex.
Tablets: ⊗ Paracetamol (p.108·1); caffeine (p.1116·3); ephedrine hydrochloride (p.1558·2).
Fever; pain; respiratory-tract congestion.

Piralgina 650 *Diba, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Piralgina C *Diba, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Piralyn *Kener, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Piram *General Drugs, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Piramagno *Pharmacos, Mex.†.*
Dipyrone (p.49·2).
Fever; pain.

Piram-D *Pacific, NZ.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders; pain.

Pirament *Ipca, India.*
Piracetam (p.368·2).
Myoclonus.

Piramil *Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.; Sandoz, Thai.; Sandoz, Venez.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Piramin *Elofar, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Pirandall *Randall, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Pirantrim *Keton, Mex.*
Pyrantel embonate (p.155·1).
Worm infections.

Piraside *Upsifarma, Port.†.*
Pyrazinamide (p.320·2).
Tuberculosis.

Piraska *Supra Ferbindo, Indon.*
Pyrantel embonate (p.155·1).
Worm infections.

Pirasmin *Carlo Erba, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Pirasod *Parggon, Mex.*
Dipyrone (p.49·2).

Piratam *GSK, India†; Beacons, Singapore.*
Piracetam (p.368·2).
Alcoholism; behaviour disorders in children; cerebral trauma; cerebrovascular disorders; mental function impairment; senile dementia; sickle-cell disease; vertigo.

Piratin *Quality, Hong Kong.*
Piracetam (p.368·2).
Dementia.

Piratrof *Novell, Indon.*
Piracetam (p.368·2).
Cerebral infarction.

Piratropil *Jelfa, Rus.*
Piracetam (p.368·2).

Pirax
Note. This name is used for preparations of different composition.
Ecosol, Switz.
Piracetam (p.368·2).
Dyslexia; mental function impairment; myoclonus.
Pharmaland, Thai.
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Pirazinid *Kocak, Turk.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pirazinon *Sanval, Braz.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pirdolin *Dermadolin, Turk.*
Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2).
Seborrhoeic dermatitis of the scalp.

Piremol *Loeffler, Mex.*
Paracetamol (p.108·1).
Fever; pain.

piren-basan *Schonenberger, Switz.†.*
Pirenzepine hydrochloride (p.1762·3).
Gastrointestinal disorders associated with hyperacidity.

Piretanyl
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Syrup: Chlorphenamine maleate (p.571·3); dipyrone (p.49·2).
Cold and influenza symptoms.
Pasteur, Chile.
Tablets: Chlorphenamine maleate (p.571·3); dipyrone (p.49·2); caffeine (p.1116·3).
Cold and influenza symptoms.

Pirexin *Cantabria, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Pirexyl *Pasteur, Chile.*
Diclofenac sodium (p.44·3).
Fever; musculoskeletal and joint disorders; pain.

Pirfalin *Farmigea, Ital.*
Pirenoxine sodium (p.2368·3).
Cataracts.

Piridos *Omedir, Arg.*
Pyridostigmine bromide (p.633·3).
Myasthenia gravis.

Pirifur *Rudefsa, Mex.*
Phenazopyridine hydrochloride (p.116·2); nalidixic acid (p.303·3).
Urinary-tract infections.

Pirilene *Sanofi-Aventis, Fr.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pirimat *Duopharma, Hong Kong.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Pirimed *Medihealth, Mex.; Roemmers Medihe, Venez.*
Pyrithione zinc (p.1611·2).
Dandruff; psoriasis; seborrhoea; seborrhoeic dermatitis.

Pirimetan *Richmond, Arg.*
⊗ Propranolol (p.1381·1).

Pirimir *Sanofi Synthelabo, Mex.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Pirinace *Sidus, Arg.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Influenza symptoms.

Pirinovag *Novag, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Piriteze *GSK Consumer, UK.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis.

Piriton *GSK, Hong Kong†; GSK Consumer, Irl.; GSK, Singapore; GSK, Thai.†; GSK Consumer, UK.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Piriton Expectorant *GSK, India; GSK, Thai.†.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; coughs.

Piritos *Biosintex, Arg.*
Bromhexine (p.1552·2); butetamate (p.1553·2).
Respiratory-tract disorders.

Pirium *Janssen-Cilag, Gr.*
Pimozide (p.1018·1).
Psychoses.

Piro *ABZ, Ger.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and soft-tissue disorders.

Piro KD *Kade, Ger.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and soft-tissue disorders.

Piroalgin *Lafedar, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Pirobac *Koni-Cofarm, Chile.*
Benzoyl peroxide (p.1590·2).
Acne.

Pirobeta *Betapharm, Ger.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Pirobutil *Degorts, Mex.*
Dipyrone (p.49·2); butylhyoscine (p.1735·1).
Muscle spasm; pain.

Pirocal *Aliud, Austria.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal joint, and peri-articular disorders; pain.

Pirocam *Ratiopharm, Austria; Dexa, Indon.; Spirig, Switz.; Leti, Venez.†.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Pirodax *Lemery, Mex.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Pirodene *Medikon, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Pirofebran *Globo, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Pirofel *Sanbe, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Pirofen *Deva, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Pirofix *Hexal, Arg.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Piroflam
Note. This name is used for preparations of different composition.
Medipharm, Chile.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.
Lichtenstein, Cz.†; Winthrop, Ger.
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Piroflex *Betapharm, Ger.†.*
Piroxicam (p.117·3).
Musculoskeletal, peri-articular, and soft-tissue disorders.

Piroftal *Bruschettini, Ital.*
Piroxicam (p.117·3).
Eye inflammation; ocular oedema.

Pirogina *Teuto, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Pirogreen *Greenpharma, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Pirohexal-D *Hexal, Austral.; Hexal, NZ.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Pirok *Husnu, Turk.*
Pyrvinium embonate (p.155·3).
Oxyuriasis.

Pirolam *Medana, Pol.*
Ciclopirox olamine (p.529·2).
Fungal and bacterial skin infections; fungal nail infections.

Pirom
Note. This name is used for preparations of different composition.
Sandoz, Denm.
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.
Solmer, Switz.
Balm: Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); cinnamon oil (p.2283·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.
Solmer, Switz.
Embrocation: Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); sweet birch oil (p.86·2); lemon oil (p.2332·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Piromax *Megat, Venez.†.*
Piroxicam betadex (p.117·3).
Inflammation; musculoskeletal and joint disorders.

Piromebrina *Degorts, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Piromed *3DDD, Belg.*
Piroxicam (p.117·3).

Pironal *Bago, Chile.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Pirophen *Pfizer, NZ.*
Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Piro-Phlogont *Azupharma, Ger.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Pirorheum *Hexal, Austria; Hexal, Ger.†; Sandoz, Hung.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

PirorheumA *Hexal, Ger.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Piros *Menarini, Ital.*
Paracetamol (p.108·1).
Fever; pain.

Pirosal *Saba, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Pirosol *Ecosol, Switz.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Pirostad *Stada, Philipp.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Piroval *Valmor, Venez.†.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders.

Pirox *Amat, Austria; Merckle, Cz.†; CT, Ger.; Cipla, India; Hexal, Mex.; Alpharma, Norw.; Medicine Products, Thai.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Piroxal *Alpharma, Fin.*
Piroxicam (p.117·3).
Dysmenorrhoea; musculoskeletal and joint disorders.

Piroxam *Globo, Braz.†; PP Lab, Thai.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Piroxan *Diba, Mex.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint and peri-articular disorders; pain.

pirox-basan *Schonenberger, Switz.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Piroxcin *Polipharm, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Piroxen *Codal Synto, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Piroxene *Solvay, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxgel *Barcino, Spain.*
Coal tar (p.1616·2).
Seborrhoeic dermatitis.

Piroxica *Stada, Hong Kong.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and soft-tissue disorders.

Piroxifar *Elofar, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Piroxifen *Arrow, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxiflam *Sankyo, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxigea *Gea, Denm.†.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal and joint disorders; pain.

Piroxil *Sanval, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxin *Cifarma, Braz.; Ratiopharm, Fin.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; peri-articular and soft-tissue disorders.

Piroxinid *Ducto, Braz.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Piroxiplus *Hebron, Braz.†.*
Piroxicam (p.117·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Piroxistad *Stada, Austria.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Piroxitop *Topgen, Belg.*
Piroxicam (p.117·3).

Piroxsil *Silom, Thai.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Piroxy *Duopharma, Hong Kong†.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Piroxymed *Ethimed, Belg.*
Piroxicam (p.117·3).

Pirrolfungin *Esfar, Port.†.*
Pyrrolnitrin (p.545·3); salicylic acid (p.1612·2); diethyl sebacate (p.1613·1).
Skin infections.

Pirxane *Lisapharma, Ital.†.*
Buflomedil pyridoxal phosphate compound (p.1237·1).
Vascular disorders.

Pirzinol *Solfran, Mex.*
Piperazine (p.152·3).
Worm infections.

Pisacaina *Pisa, Mex.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; ventricular arrhythmias.

Pisatrina *Pisa, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Piscis 3 *Vargas, Venez.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Pistofil *Rafarm, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Pitiren *Savoma, Ital.*
Climbazole (p.529·3); strontium chloride (p.2393·1); lauromacrogol 400 (p.1916·1); levomenol (p.2333·3); menthyl lactate; benzyl alcohol (p.1631·3); vitamin E.
Seborrhoeic dermatitis.

Pitiriax *Cassara, Arg.*
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1).
Dandruff.

Pitocin *Pfizer, India; JHP, USA; Pfizer, Venez.†.*
Oxytocin (p.2015·2).
Incomplete or inevitable abortion; induction of labour; postpartum haemorrhage; uterine inertia.

Pitogin *Ethica, Indon.*
Oxytocin (p.2015·2).
Incomplete abortion; labour induction and enhancement; postpartum haemorrhage.

Piton-S *Organon, Indon.; Organon, Neth.†.*
Oxytocin (p.2015·2).
Incomplete abortion; labour induction; lactation stimulation; postpartum haemorrhage; promotion of lactation; uterine haemorrhage.

Pitressin *Link, Austral.; Parke, Davis, Ger.†; IFET (ΙΦΕΤ), Gr.†; Goldshield, Irl.; Link, NZ; Goldshield, UK; Parke, Davis, USA.*
Argipressin (p.2411·3).
Aid in abdominal radiography; bleeding oesophageal varices; diabetes insipidus; postoperative abdominal distension; postoperative intestinal atony.

Pitrex *Taro, Canad.; Teva, Israel.*
Tolnaftate (p.548·3).
Fungal skin infections.

Pitrion *Rafa, Israel.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Pitrisan
Note. This name is used for preparations of different composition.
Rekah, Israel.
Ointment: Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); allantoin (p.1588·1).
Fungal skin infections.

Rekah, Israel.
Topical solution: Undecenoic acid (p.549·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2); chlorobutanol (p.1639·2); resorcinol (p.1612·1).
Fungal skin infections.

Pityker *Roche-Posay, Fr.†.*
Piroctone olamine (p.1610·1); salicylic acid (p.1612·2).
Dandruff.

Pityol *Zentiva, Cz.*
Ichthammol (p.1599·1); boric acid (p.2268·1); zinc oxide (p.1621·2); guaiazulene (p.2317·3).
Skin disorders.

Pityval
Note. This name is used for preparations of different composition.
Roche-Posay, Arg.†; Roche-Posay, Braz.
Piroctone olamine (p.1610·1); iodopropynyl butyl carbamate (Glicacil) (p.2045·2).
Seborrhoeic dermatitis.

Roche-Posay, Fr.
Piroctone olamine (p.1610·1); iodopropynyl butyl carbamate (Glycacil); thermal water.
Skin irritation.

Roche-Posay, Irl.†.
Emollient.

Pival *Cafar, Venez.†.*
Mebendazole (p.148·3).
Worm infections.

Pivalephrine *Santen, Jpn.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Pivalone *Pfizer, Fr.; Parke, Davis, Neth.†; Pfizer, Singapore; Uhlmann-Eyraud, Switz.*
⊗ Tixocortol pivalate (p.1544·2).
Nasal polyps; rhinitis.

Pivalone compositum *Uhlmann-Eyraud, Switz.*
⊗ Tixocortol pivalate (p.1544·2); neomycin sulfate (p.305·1).
Infected nasal disorders.

Pivalone Neomycin *Parke, Davis, Singapore†.*
⊗ Tixocortol pivalate (p.1544·2); neomycin sulfate (p.305·1).
Infected nasal polyps; rhinitis; sinusitis.

Pivanozolo *Medestea, Ital.*
Miconazole pivoxil chloride (p.542·2).
Fungal infections; Gram-positive bacterial superinfections.

Pixicam *Hexal, S.Afr.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Pixidin *Sanico, Belg.*
Chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders.

Pixor Stick Anti-acne N *Doetsch, Grether, Switz.*
Salicylic acid (p.1612·2); triclosan (p.1665·2).
Acne.

Pixorid *Roemmers-Klinos, Venez.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders; pain.

Pyeloseptyl *Biofarma, Turk.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Pizide *Pharmasant, Thai.*
Pimozide (p.1018·1).
Psychoses.

Pizomed *Medifive, Thai.*
Pizotifen malate (p.624·2).
Anorexia; migraine; reduced appetite.

PK Aid *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Amino-acid preparation without phenylalanine (p.1922·1).
Phenylketonuria.

PK Max *Scientific Hospital Supplies, Irl.*
Food for special diets (p.1922·1).
Phenylketonuria.

PK-Levo *Merz, Ger.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

PK-Merz *Kolassa, Austria; Grunenthal, Chile†; Merz, Cz.; Merz, Ger.; Pharmacare, Gr.†; Merz, Hong Kong; Merz, Hung.; Megapharm, Israel; Merz, Malaysia; Merz, Mex.; Merz, Philipp.; Merz, Switz.*
Amantadine sulfate (p.793·1).
Coma; drug-induced extrapyramidal disorders; influenza A; parkinsonism; postherpetic neuralgia.

PKU *Nutricia-Bago, Arg.; Support, Braz.†; Vitaflo, Irl.; Vitaflo, UK.*
A range of foods for special diets (p.1922·1).
Phenylketonuria.

PKU 2 and 3 *Milupa, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

PKU 1 Mix *Milupa, Ital.*
Food for special diets (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Plac Out *Bernabo, Arg.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat infections; oral hygiene.

Placatus *Noos, Ital.*
Nepinalone hydrochloride (p.1566·1).
Coughs.

Placentex *Mastelli, Ital.*
Polydeoxyribonucleotide (p.2292·3).
Inflammatory and degenerative disorders.

Placentrex
Note. This name is used for preparations of different composition.
David, India.
Injection; topical gel: Placenta extract (human) (p.2337·3).
Postphlebitic ulcer; scars; vitiligo.

David, India.
Topical lotion: Deoxyribonucleic acid (p.2292·3); ribonucleic acid (p.2379·1); tyrosine (p.1971·1).
Vitiligo.

Placidiax *Richmond, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorders.

Placidox *Lupin, India.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm.

Placil *Alphapharm, Austral.*
Clomipramine hydrochloride (p.386·3).
Depression; narcoleptic syndrome; obsessive-compulsive disorder; phobic states.

Placinoral *Robert, Spain.*
Lorazepam pivalate (p.1004·3).
Alcohol withdrawal syndrome; anxiety; insomnia; nausea and vomiting; premedication.

Placis *Chiesi, Spain; Farma-Tek, Turk.*
Cisplatin (p.698·2).
Malignant neoplasms.

Placol *Bennett, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Placor *Rottapharm, Hung.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Plactidil *Novartis, Ital.*
Picotamide (p.1371·2).
Thromboembolic disorders.

Plafonyl *Montpellier, Arg.†.*
Chlordiazepoxide dibudinate (p.968·2); desipramine dibudinate (p.387·3).
Anxiety; depression.

Plagex *Teuto, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Plagon *De Mayo, Braz.*
Metoclopramide (p.1747·3); vitamin B (p.1979·1).
Nausea and vomiting.

Plak Out *Altana, Austria; Altana, Ital.; Inibsa, Port.†; KerrHawe, Switz.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders; oral hygiene.

Plaketar *Biolab Sanus, Braz.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Plamet *Libbs, Braz.*
Bromopride (p.1713·3).
Aid in endoscopy; gastrointestinal disorders; nausea and vomiting.

Plamida *Prodotti, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Plamidasil *Delta, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Plamivon *Bunker, Braz.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Plamox *Vitarum, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Plan *Craveri, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Plan B *Paladin, Canad.; Duramed, USA.*
Levonorgestrel (p.2121·2).
Progestogen-only postcoital contraceptive.

Planak *Fahrenheit, Indon.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Plander *Fresenius Kabi, Ital.*
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Plasma volume expansion.

Plander R *Fresenius Kabi, Ital.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Extracorporeal perfusion; plasma volume expansion; thrombosis prophylaxis.

Planibu *Fahrenheit, Indon.*
Medroxyprogesterone acetate (p.2113·1).
Injectable contraceptive.

Planitrix *Bros, Gr.†.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Planizol *Solfran, Mex.*
Metronidazole (p.837·1).
Amoebiasis.

Planocid *Pulitzer, Ital.†.*
Cefradine (p.233·1).
Bacterial infections.

Planor *Effik, Fr.†.*
Norgestrienone (p.2122·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive; endometriosis; mastalgia; menstrual disorders; polycystic ovary syndrome.

Plant Spray *Dolisos, Canad.*
Homoeopathic preparation.

Planta Lax *Hoeveler, Austria.*
Senna leaf and pod (p.1769·2); frangula bark (p.1732·2); blackberry leaf; chamomile flowers (p.2279·3); coriander (p.2288·1); fennel (p.2302·3).
Constipation.

Plantaben *Altana, Arg.; Nycomed, Braz.; Biotoscana, Chile; Altana, Mex.; Madaus, Spain.*
Ispaghula (p.1737·1).
Constipation; diarrhoea; dietary fibre supplement; diverticular disease; hypercholesterolaemia; irritable colon.

Plantacard N *Madaus, Ger.*
Homoeopathic preparation.

Plantacid *Kalbe, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; epigastric pain; gastric pain; gastritis; peptic ulcer.

Plantactiv *Hochstetter, Chile†.*
Marine algae.
Obesity.

Plantagen *Gemi, Pol.*
Ribwort plantain (p.2379·1).
Respiratory-tract disorders.

Plantaguar *Madaus, Spain.*
Guar gum (p.442·3).
Diabetes mellitus.

Plantax *Farmion, Braz.†.*
Senna (p.1769·2); ispaghula (p.1737·1).
Constipation.

Planten *Whitehall, Israel†; Wyeth Consumer, Ital.*
Ispaghula (p.1737·1).
Constipation; irritable bowel syndrome.

Plantex *Lek, Rus.*
Fennel (p.2302·3); fennel oil (p.2303·1).
Colic; meteorism.

Plantifort *Hasco-Lek, Pol.*
Echinacea purpurea (p.2298·1); ribwort plantain (p.2379·1).
Upper respiratory-tract infections.

Plantiodine Plus *Blackmores, Austral.†.*
Bladderwrack (p.2384·2); alfalfa (p.2249·2); protibel yeast (p.1998·3); rose fruit (p.2381·2); lecithin (p.2332·2).
Tonic.

Plantival *Farmasa, Mex.*
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia; nervous disorders.

Plantival Mono *Schwabe, Switz.†.*
Valerian (p.2410·1); passion flower (p.2363·2).
Nervous disorders; sleep disorders.

Plantival novo *Schwabe, Ger.*
Valerian (p.2410·1); melissa (p.2339·3).
Agitation; sleep disorders.

Plantivenol *Schwabe, Spain.*
Aesculus (p.2248·2).
Venous insufficiency.

Planturol *Farmasan, Ger.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Planum
Note. This name is used for preparations of different composition.
Pharmacia, Ger.
Temazepam (p.1030·1).
Sleep disorders.

Menarini, Ital.
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Plaqacide *Oral-B, Austral.†.*
Chlorhexidine gluconate (p.1635·3).
Oral disorders; prevention of dental plaque.

Plaquenil *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Austral.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi Synthelabo, Canad.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Fin.†; Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Irl.; Sanofi Winthrop, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi-Aventis, NZ; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Rus.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, UK; Sanofi Winthrop, USA†.*
Hydroxychloroquine sulfate (p.604·2).
Juvenile idiopathic arthritis; lupus erythematosus; malaria; photodermatoses; rheumatoid arthritis; Sjögren's syndrome.

Plaquetal *Menarini, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Plaquetil *Rider, Chile.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Plaquinol *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; BioSaude, Port.; Sanofi-Aventis, Venez.*
Hydroxychloroquine sulfate (p.604·2).
Amoebiasis; lupus erythematosus; malaria; photodermatoses; rheumatoid arthritis.

Plardox *Lafedar, Arg.*
Oxeladin citrate (p.1567·1).
Cough.

Plas-Amino *Otsuka, Jpn.*
Amino-acid and glucose infusion (p.1922·1).
Parenteral nutrition.

Plasbumin *Cristalia, Braz.; Bayer, Canad.; Talecris, Canad.; Bayer, Chile; Bayer Biological, Hong Kong; Dipa, Indon.; Bayer, Israel†; Bayer, Ital.; Bayer, Malaysia†; Bayer, Philipp.; GenAsia, Philipp.; Talecris, Rus.; Bayer, Singapore†; Bayer, Spain; Biem, Turk.; Talecris, USA.*
⊗ Albumin (p.1052·1).
Acute liver failure; adult respiratory distress syndrome; burns; cerebral oedema; haemodialysis; haemolytic disease of the newborn; hepatic failure; hypoalbuminaemia; hypoproteinaemia; hypovolaemia; hypovolaemic shock; neonatal hyperbilirubinaemia; plasma volume expansion; shock.

Plasil
Sanofi-Aventis, Braz.; Kimia, Indon.; Lepetit, Ital.; Aventis, Mex.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Duncan, Philipp.; Aventis, Thai.
Metoclopramide (p.1747·3).
Gastrointestinal investigations; gastrointestinal motility disorders; nausea and vomiting.

Plasil Enzimatico *Sanofi-Aventis, Braz.; Aventis, Mex.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2); pancreatin (p.2360·1); sodium dehydrocholate (p.2292·2); bromelains (p.2269·1).
Digestive disorders; gastrointestinal, biliary-tract, and pancreatic disorders.

Plasimine *Isdin, Spain.*
Mupirocin (p.302·3).
Bacterial skin infections.

Plaskine Neomicina *Ipsen, Spain.*
Lysine acexamate (p.2245·2); neomycin undecenoate (p.305·2).
Burns; ulcers; wounds.

Plasma du Dr Quinton *Chimicor, Fr.*
Sea water.

Plasmafusin *Fresenius Kabi, Fin.†; Baxter, Ger.†.*
⊗ Hetastarch (p.1065·1) in sodium chloride.
Hypotension; hypovolaemia; plasma volume expansion; shock.

Plasma-Lyte *Baxter, Austral.; Baxter, Cz.; Baxter, Port.; Baxter, Spain; Baxter, UK; Baxter, USA.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Plasma-Lyte IV *Baxter, NZ†.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Plasma-Lyte A *Baxter, Switz.*
An electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Plasma-Lyte Oral *Baxter, NZ.*
Glucose and electrolyte solution (p.1672·2).
Diarrhoea; oral rehydration solution.

Plasmanate *Dipa, Indon.; Bayer, Israel; Bayer, Malaysia†; Bayer, Philipp.; GenAsia, Philipp.; Talecris, USA.*
⊗ Plasma protein fraction (p.1076·2).
Haemorrhage; hypoproteinaemia; plasma volume expansion; shock.

Plasma-Plex *Armour, USA.*
⊗ Plasma protein fraction (p.1076·2).
Hypoproteinaemia; hypovolaemia.

Plasmarine *Pharmadeveloppement, Fr.*
Mineral preparation (p.1922·1).
Tonic.

Plasmasafe *Kedrion, Ital.*
Plasma (p.1075·2).
Haemorrhagic disorders; reversal of oral anticoagulant effects; thrombocytopenic purpura.

Plasmasteril *Fresenius Kabi, Austria; Fresenius Kabi, Ger.†; Fresenius Kabi, Switz.†; Fresenius Kabi, Turk.*
⊗ Hetastarch (p.1065·1) in sodium chloride.
Hypovolaemia; plasma volume expansion; shock.

Plasmax *Ranbaxy, Thai.*
⊗ Polygeline (p.1077·2) with electrolytes.
Extracorporeal circulation; maintenance of fluid volume during surgery; shock.

Plasminex *Sanbe, Indon.*
Tranexamic acid (p.1080·3).
Dental extraction in haemophiliacs; fibrinolytic haemorrhage; hereditary angioedema.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Plasmion *Fresenius Kabi, Fr.*
⊗ Gelatin (p.1072·1) with electrolytes.
Hypotension; shock.

Plasmodex *Meda, Norw.; Meda, Swed.*
⊗ Dextran 60 (p.1059·3) with electrolytes.
Plasma volume expansion.

Plasmoquine *Medchem, S.Afr.*
Chloroquine sulfate (p.599·3).
Lupus; malaria; rheumatoid arthritis.

Plasmotrim *Mepha, Braz.; Mepha, Thai.†.*
Sodium artesunate (p.598·2).
Malaria.

Plast Apyr Fisiologico *Fresenius Kabi, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Plast Apyr Glucosado *Fresenius Kabi, Spain.*
Glucose (p.1945·3).
Carbohydrate source; fluid and electrolyte disorders.

Plast Apyr Glucosalino *Fresenius Kabi, Spain.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Plastenan *Sanofi Synthelabo, Arg.; Eumedica, Belg.; Kerapharm, Fr.†.*
Sodium acexamate (p.2245·2).
Burns; ulcers; wounds.

Plastenan con Neomicina *Sanofi Synthelabo, Arg.*
Sodium acexamate (p.2245·2); neomycin sulfate (p.305·1).
Ulcers.

Plastenan Neomicina *CPH, Port.†; Chooy, Port.†.*
Sodium acexamate (p.2245·2); neomycin sulfate (p.305·1).
Burns; ulcers; wounds.

Plastesol *CPH, Port.†.*
Acexamic acid (p.2245·2).
Burns; wounds.

Plastranit *UCB, Port.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Plastubol *PannonPharma, Hung.†.*
Methylmethacrylate-butylacrylate-butylmethacrylate co-polymer (p.2343·3); di-isooctyl phthalate.
Burns; skin disorders; wounds.

Plastufer *Valeant, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Plastulen *Stada, Ger.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Plastulen N *Stada, Ger.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Plastules *Wyeth, India.*
Dried ferrous sulfate (p.1939·3); dried yeast (p.1998·3); folic acid (p.1940·1); vitamin B (p.1980·2); liver extract (p.2337·3).
Anaemias; iron deficiency.

Plasvit *Collins, Mex.*
Vitamin and mineral preparation (p.1922·1).

Platamine
Note. This name is used for preparations of different composition.
Pfizer, Arg.; Pfizer, Gr.; Pharmacia, Ital.; Pfizer, Philipp.
Cisplatin (p.698·2).
Malignant neoplasms.

Pfizer, Braz.
Carboplatin (p.693·1).
Malignant neoplasms.

Platenk *Biotenk, Arg.†.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Platiblastin-S *Pfizer, Switz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platicarb *Eurofarma, Braz.†.*
Carboplatin (p.693·1).
Malignant neoplasms.

Platidiam *Pliva, Cz.; Pliva, Hung.; Pliva Lachema, Pol.; Lachema, Rus.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platigren *Sanofi Synthelabo, Cz.†.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis; thromboembolism prophylaxis.

Platin
Note. This name is used for preparations of different composition.
Cadila, India.
Cisplatin (p.698·2).
Malignant neoplasms.

Wockhardt, India.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Platinex *BMS, Ger.; BMS, Ital.; BMS, UK†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platino II *Filaxis, Arg.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platinol *BMS, Arg.†; BMS, Austria; BMS, Belg.; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, Mex.; BMS, NZ; BMS, Norw.; BMS, Philipp.; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS Oncology, USA†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platinostyl *Ivax, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Platinox *Sandoz, Indon.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platinoxan *Baxter, Philipp.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platinum *Colgate-Palmolive, Ital.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Platinum Years *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Platinwas *Chiesi, Spain; Farma-Tek, Turk.*
Carboplatin (p.693·1).
Malignant neoplasms.

Platiran *BMS, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platistil *Pfizer, Mex.†; Kenfarma, Spain†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platistin *Pfizer, Norw.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platistine *Pfizer, Belg.†; Pfizer, Braz.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platium *Rider, Chile.*
Vitamin and mineral preparations (p.1922·1).
Dietary supplement.

Plato *Pharmacare, S.Afr.*
Dipyridamole (p.1268·1).
Platelet function inhibition.

Platof *Sanbe, Indon.*
Pentoxifylline (p.1367·2).
Peripheral vascular disease.

Platosin *Nycomed, Austria; Teva, Belg.; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Indon.; Kyowa, Jpn; Pharmachemie, Malaysia; Pharmachemie, Neth.; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platosin-S *Med, Turk.*
Cisplatin (p.698·2).
Malignant neoplasms.

Platox *Mayne, Cz.*
Oxaliplatin (p.757·3).
Colorectal cancer.

Platsul A
Note. This name is used for preparations of different composition.
Chobet, Arg.
Sulfadiazine silver (p.337·2); vitamin A (p.1971·2); lidocaine (p.1862·3).
Burns; infected skin disorders; ulcers; wounds.

Grunenthal, Chile.
Sulfadiazine silver (p.337·2); lidocaine (p.1862·3); vitamin A (p.1971·2); vitamin D (p.1986·1).
Infected burns and wounds.

Plaudit *SoSe, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Plaunac *Guidotti, Ital.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Plausitin *Carlo Erba OTC, Ital.*
Morclofone (p.1565·1).
Coughs.

Plavix *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Austral.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; BMS, Canad.; Sanofi Synthelabo, Canad.; Sanofi-Aventis, Chile; Sanofi Synthelabo, Cz.; Sanofi, Denm.; BMS, Fin.; Sanofi-Aventis, Fin.; BMS, Fr.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; BMS, Hong Kong; Sanofi Synthelabo, Hong Kong; BMS, Hung.; Sanofi-Aventis, Hung.; Sanofi-Aventis, India; Sanofi-Aventis, Indon.; BMS, Irl.; Sanofi-Aventis, Irl.; Sanofi Synthelabo, Israel; Sanofi-Aventis, Ital.; BMS, Malaysia; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi-Aventis, NZ; BMS, Neth.; Sanofi Synthelabo, Neth.; Sanofi BMS, Norw.; Sanofi Synthelabo, Philipp.; BMS, Pol.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Sanofi Synthelabo, S.Afr.; BMS, Singapore; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; BMS, Swed.; Sanofi Synthelabo, Swed.; BMS, Switz.; Sanofi, Switz.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.; BMS, UK; Sanofi Synthelabo, UK; BMS, USA; Sanofi-Aventis, Venez.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis; myocardial infarction; stroke; thromboembolism prophylaxis; unstable angina.

Plax
Note. This name is used for preparations of different composition.
Pfizer Consumer, Canad.
Sodium benzoate (p.1630·2); sodium laurilsulfate (p.2138·3); sodium salicylate (p.124·2).

Colgate-Palmolive, Ital.†.
Triclosan (p.1665·2); sodium fluoride (p.1962·2).
Dental plaque prevention.

Pfizer Consumer, USA.
Sodium pyrophosphate (p.2390·3); sorbitol (p.1965·1).
Formerly known as Advanced Formula Plax.

Plazeron *Remedica, Hong Kong†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Plecor *Teuto, Braz.†.*
Cefaclor (p.217·2).
Bacterial infections.

Plegicil *Pharmaxim, Denm.; Sanofi Synthelabo, Turk.*
Acepromazine maleate (p.959·2).
Agitation; anxiety disorders; hiccup; nausea and vomiting.

Pleginer *Farma Lepori, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Plegisol *Abbott, Israel; Abbott, NZ; Hospira, Neth.; Abbott, Turk.; Hospira, USA.*
Electrolytes (p.1667·1).
Cardioplegia in open heart surgery.

Plegomazin *Egis, Cz.*
Chlorpromazine hydrochloride (p.969·2).
Agitation; anxiety; mania; nausea and vomiting; pain; premedication; schizophrenia.

Pleiamide *Sanofi-Aventis, Ital.*
Chlorpropamide (p.438·3); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Plemerid *Essenpharma, Philipp.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine (p.1569·2); sodium citrate (p.1673·3).
Respiratory-tract disorders.

Plenacor
Note. This name is used for preparations of different composition.
Bago, Arg.; Bago, Braz.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Armstrong, Mex.
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Plenacor D *Bago, Arg.*
⊗ Atenolol (p.1217·3); hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Plenactol *3M, Chile.*
Orphenadrine citrate (p.812·1).
Musculoskeletal pain.

Plenaer *Valeas, Ital.*
⊗ Salbutamol sulfate (p.1131·3); flunisolide (p.1531·1).
Obstructive airways disease.

Plenax *Merck, Braz.†.*
Cefixime (p.224·3).
Bacterial infections.

Plenaxis *Praecis, USA.*
Abarelix (p.2081·3).
Prostatic cancer.

Plendil *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; Beta, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Astra, USA; AstraZeneca, Venez.*
Felodipine (p.1285·3).
Angina pectoris; hypertension; ischaemic heart disease.

Plendur *Sandoz, Denm.*
Felodipine (p.1285·3).
Hypertension.

Plenidon *Drugtech, Chile.*
Zaleplon (p.1035·3).
Insomnia.

Plenifem *Schering, Arg.†.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; levonorgestrel (p.2121·2).
Menopausal disorders.

Plenigraf
Justesa Imagen, Arg.
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Juste, Spain.
Calcium amidotrizoate (p.1477·1); meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Plenish-K *Pharmacare, S.Afr.*
Potassium chloride (p.1684·3).
Potassium deficiencies.

Plenitude Excell A-3 *L'Oreal, Canad.†.*
SPF 8: Octinoxate (p.1608·2).
Sunscreen.

Plenocedan *Makros, Braz.†.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3).
Smooth muscle spasm.

Plenolyt *Madaus, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Plenosol *Madaus, Ger.*
Homoeopathic preparation.

Plenovid *Tecnofarma, Chile.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Plenovit *Dexter, Arg.*
A range of vitamin and mineral preparations with or without ginseng (p.1922·1).

Plenovit Melatonina *Phoenix, Arg.*
Melatonin (p.2338·3); vitamin B (p.1979·1).
Insomnia.

Plentiva *Wyeth, Malaysia†.*
28 Tablets, conjugated oestrogens (p.2087·2); 28 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Plentiva Cycle 5 *Wyeth, Malaysia†.*
28 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Plenty *Medley, Braz.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Plenum *Duncan, Arg.*
Guaifenesin (p.1561·3).
Coughs.

Plenur *Faes, Spain.*
Lithium carbonate (p.401·3).
Bipolar disorder; depression; neutropenia.

Plenvisol *Diba, Mex.†.*
Vitamin preparation (p.1922·1).

Pleo Vitamin *Inibsa, Spain.*
Multivitamins and minerals (p.1922·1); orotic acid, diethylaminoethanol salt; adenosine phosphate.
Tonic.

Pleocortex B6 *Retrain, Spain†.*
⊗ Suprarenal cortex (p.1543·3); pyridoxine hydrochloride (p.1978·2).
Vomiting.

Pleomix-Alpha *Illa, Ger.†.*
⊗ Thioctic acid (p.2400·2) or trometamol thioctate (p.2400·2).
Diabetic polyneuropathy.

Pleomix-B *Trommsdorff, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Nervous-system disorders.

Pleon *Lacer, Spain.*
Adenine; vitamin B substances; carnitine orotate; fructose diphosphate magnesium; potassium orotate; xanthine (p.1922·1).
Tonic.

Pleon RA *Sanofi Synthelabo, Ger.*
Sulfasalazine (p.1773·2).
Polyarthritis.

Pleosan *Spefar, Venez.†.*
Pyrantel (p.155·2).
Worm infections.

Plepat *Solfran, Mex.*
Vitamin B substances (p.1922·1).
Anaemias.

Plesmet *Link, Irl.; Link, UK†.*
Ferrous glycine sulfate (p.1939·1).
Iron-deficiency anaemia.

Plesonax *Neo Quimica, Braz.*
Bisacodyl (p.1710·1).
Constipation.

Pletaal *Janssen-Cilag, Arg.; Otsuka, Hong Kong; Otsuka, Indon.; Otsuka, Jpn; Otsuka, Malaysia; Otsuka, Philipp.; Otsuka, Thai.*
Cilostazol (p.1245·2).
Intermittent claudication; ischaemic symptoms in arterial occlusion; stroke prophylaxis.

Pletal *Otsuka, UK; Otsuka, USA.*
Cilostazol (p.1245·2).
Intermittent claudication.

Pletil *Pfizer, Braz.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Pletoz *Cipla, India.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Pleumolysin *Ivax, Cz.*
Codeine phosphate (p.37·2); thyme (p.2401·1); gypsophila saponin; aconite (p.2246·1); bitter-orange peel (p.2357·1).
Coughs; respiratory-tract inflammation.

Plex B *Delta, Braz.*
Vitamin B substances (p.1975·1).

Plex Ton *Auad, Braz.†.*
Multivitamin and mineral preparation with lysine (p.1922·1).

Plexade *Etifar, Venez.†.*
Vitamin preparation (p.1922·1).

Plexion *Medicis, USA.*
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne.

Plexium *Lehning, Fr.*
Selenium (p.1961·1).
Muscular disorders; skin disorders.

Plexol *Sandoz, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Plexoton B12 *SoSe, Ital.*
Vitamin B substances (p.1922·1).
Anaemias; liver disorders; tonic.

Plexus
Note. This name is used for preparations of different composition.
Recalcine, Chile.
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Senosiain, Mex.
Ambroxol (p.1550·3); dextromethorphan (p.1555·2).
Cough.

Plexxo *Desitin, Cz.; Desitin, Hung.; Desitin, Neth.†; Desitin, Pol.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Pleyar *Casasco, Arg.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis.

Pliagel *Alcon, Austral.†; Alcon, S.Afr.*
Poloxamer 407 (p.1918·2) (p.1622·2).
Cleaning solution for contact lenses.

Pliaglis *Zars, USA.*
Lidocaine (p.1862·3); tetracaine (p.1871·2).
Local anaesthesia.

Plidan
Note.This name is used for preparations of different composition.
Roemmers, Arg.
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm; spasticity.

Rhein, Mex.; Roemmers, Venez.
Pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Plidan Compuesto *Rhein, Mex.; Roemmers, Venez.*
Pargeverine hydrochloride (p.1761·1); clonixin lysine (p.37·1).
Smooth muscle pain and spasm.

Plidex *Roemmers, Arg.†.*
Diazepam (p.986·3); isopropamide (p.1736·3).
Anxiety; muscle spasm.

Plidex T *Roemmers, Arg.*
Diazepam (p.986·3); trimebutine (p.2404·3).
Gastrointestinal motility disorders.

Plimage *Pliva, Ital.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Plimycol *Pliva, Cz.†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Plinzene *Douglas, NZ.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Plissamur *Ardeypharm, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Plitican *Sanofi-Aventis, Fr.; Synthelabo, Port.†.*
Alizapride hydrochloride (p.1704·3).
Nausea; vomiting.

Plivamol *Pliva, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Plivit C *Pliva, Rus.†.*
Ascorbic acid (p.1983·3).

Plixym *Pliva Krakow, Pol.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Plod Jalovce *Leros, Cz.†.*
Juniper (p.2328·2).
Digestive disorders; urinary-tract disorders.

Plofed *Polfa Warszawa, Pol.*
Propofol (p.1791·1).
General anaesthesia.

Plokim *Solara, Mex.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Plokon *Shinyaku, Hong Kong†; Shinyaku, Thai.*
Piprinhydrinate (p.588·2).
Asthma; cold symptoms; hypersensitivity reactions; Ménière's disease; motion sickness; urticaria.

Plomurol *Valma, Chile.*
Lindane (p.2045·3).
Pediculosis.

Plorinoc *Klonal, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Plostim *Alcon, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Plovacal *Medipharma, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Plumarol *Lacer, Spain.*
Miglitol (p.454·3).
Diabetes mellitus.

Plumger *Fada, Arg.*
Pancuronium bromide (p.1907·3).
Competitive neuromuscular blocker.

Plurair *Libbs, Braz.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Pluravit *Bayer, NZ.*
A range of multivitamin and mineral preparations (p.1922·1).

Plurexid *UCB, Fr.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin and mucous membranes.

Pluribios *Madariaga, Spain.*
Multivitamin preparation with cocarboxylase (p.1922·1).
Eye disorders.

Pluricefo *Northia, Arg.†.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Pluridoxina *Sidefarma, Port.*
Doxycycline fosfatex (p.267·1).
Bacterial infections.

Plurilac *Alphrema, Ital.*
Acacia; inulin; lactulose; mannitol; dimethicone; fennel; mallow; peppermint (p.1712·3).
Dietary fibre supplement; gastrointestinal disorders.

Plurimen *Viatris, Spain.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Pluromineral *Support, Braz.†.*
Mineral preparation (p.1922·1).

Plurisalina *Grifols, Spain.*
Electrolyte injection (p.1667·1) with sodium lactate (p.1673·3).
Fluid and electrolyte disorders.

Plurisemina *Northia, Arg.*
Gentamicin (p.284·2).
Bacterial infections.

Pluritin *Globo, Braz.†.*
Permethrin (p.2048·2).
Pediculosis.

Pluriverm *Medley, Braz.*
Mebendazole (p.148·3).
Worm infections.

Plurivermil *Ibefar, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Pluriviron mono *Stegropharm, Ger.†.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Plurivitamin *Support, Braz.†.*
Vitamin preparation (p.1922·1).

30 Plus
Note.This name is used for preparations of different composition.
Ajantha, Malaysia.
Ginseng (p.2312·1); ashwagandha.
Tonic.

Tanning Research, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

45 Plus *Tanning Research, Canad.*
SPF 45: Octinoxate (p.1608·2); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

50 Plus *Quest, Canad.†.*
Multivitamin preparation (p.1922·1).

Plus Kalium retard *Amino, Switz.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Plus & Plus *Wierhom, Arg.*
Copper oleate (p.2039·1); coconut diethanolamides; sodium laurilsulfate (p.2138·3).
Pediculosis.

30 Plus Sunblock *Tanning Research, Canad.†.*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Plus & White *Wierhom, Arg.†.*
Hydrogen peroxide (p.1647·3); phosphoric acid (p.2367·1); methyl salicylate (p.85·3).
Dental whitener.

Plusabcir *Dosa, Arg.*
Abacavir (p.861·3).
HIV infection.

Plusage *Biosintetica, Braz.*
Soap substitute.
Seborrhoea.

Pluscal *Sanitas, Arg.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Pluscef *Baldacci, Port.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Pluscloran *Sintesina, Arg.*
Chloramphenicol (p.239·3).
Bacterial infections.

Pluscor *Bayer, Ital.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Plusderm *BMS, Arg.†.*
Zinc undecenoate (p.549·3); sodium propionate (p.545·3); diiodohydroxyquinoline (p.832·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Eczema; ulcers; wounds.

Plusderm ATB *BMS, Arg.†.*
Rifamycin sodium (p.329·2).
Infected wounds; skin infections.

Pluseptic *Duncan, Arg.*
Ceftazidime (p.234·1).
Bacterial infections.

Plusflex *Braun, Ital.*
Amino-acid, electrolyte, and glucose infusion (p.1922·1).
Parenteral nutrition.

Plusgel
Note.This name is used for preparations of different composition.
Lagos, Arg.
Piroctone olamine (p.1610·1).
Scalp disorders.

Collins, Mex.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Aerophagia; dyspepsia; gastritis; meteorism; peptic ulcer.

Plusgin
Note.This name is used for preparations of different composition.
Asofarma, Arg.†.
Ciprofloxacin (p.243·3).
Bacterial infections.

Raffo, Chile.
Fluconazole (p.532·1).
Fungal infections.

Plusindol *Randall, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Plusofen *Reckitt Benckiser, Port.*
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Pluspiryna *Polpharma, Pol.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Plusplatin *Dosa, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Plustaxano *Dosa, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Pluston *Ferakon, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Plusvent *Almirall, Spain.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma.

Plusvit *Ecofarm, Ital.*
Octacosanol; yeasts rich in calcium, magnesium, zinc, and iron (p.1922·1).
Tonic.

Pluvio *Lampugnani, Ital.*
Soya oil (p.1965·3); urtica (p.2409·3); avocado oil; saw palmetto (p.2192·3); vitamins.
Nutritional supplement.

Pluviton *Sam-On, Israel.*
Multivitamin and mineral preparation (p.1922·1).

Pluviton B *Sam-On, Israel.*
Vitamin B substances with lysine (p.1922·1).

PM
Note. A similar name is used for preparations of different composition (see below).
New Vision, Canad.†.
Multivitamin preparation (p.1922·1).

pM
Note. A similar name is used for preparations of different composition (see above).
Chiesi, Fr.
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

9PM *Cipla, India.*
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

P-Mega-Tablinen *Winthrop, Ger.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

PMH *Aqualab, Fr.*
Sea water.
Nutritional supplement.

PML Crono
Note.This name is used for preparations of different composition.
Sifi, Canad.†.
Nicotinamide (p.1957·3); vitamin E (p.1992·2).

SIFI, Ital.; SIFI, Singapore†.
Nicotinamide; vitamin E; lutein (p.1922·1).
Nutritional supplement.

PMQ-INGA *Inga, India.*
Primaquine phosphate (p.608·1).
Malaria.

PMS *Homeocan, Canad.*
Homoeopathic preparation.

PMS L21 *Homeocan, Canad.†.*
Homoeopathic preparation.

PMS Support *Vitaplex, Austral.†.*
Vitamins; minerals (p.1922·1); viburnum; buchu (p.2269·3); ginger (p.1732·3); evening primrose oil (p.2302·1).
Muscular cramps; oedema.

PMS-Artificial Tears *Pharmascience, Hong Kong.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

PMS-Baximycin *Pharmascience, Hong Kong†.*
Bacitracin (p.210·3); polymyxin B sulfate (p.317·3).
Burns; wounds.

PMS-Dopazide *Pharmascience, Canad.*
⊗ Methyldopa (p.1334·1); hydrochlorothiazide (p.1307·3).
Hypertension.

PMS-Enemol *Pharmascience, Hong Kong†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

PMS-Levazine *Pharmascience, Canad.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Depression; psychoses.

PMS-Polytrimethoprim *Pharmascience, Canad.*
Trimethoprim sulfate (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

PMT Complex *Cenovis, Austral.†; Vitelle, Austral.†.*
Vitamins; minerals (p.1922·1); ginger (p.1732·3); viburnum; agnus castus (p.2249·1); cimicifuga (p.2282·1); bladderwrack (p.2384·2).
Premenstrual syndrome.

PMT Formula *Vitalia, UK.*
Evening primrose oil (p.2302·1); vitamins (p.1922·1); minerals; valerian (p.2410·1); passion flower (p.2363·2).
Premenstrual syndrome.

PMT Oral Spray *Brauer, Austral.†.*
Homoeopathic preparation.

Pneucid *Scipharm, S.Afr.*
Sodium citrate (p.1673·3); citric acid monohydrate (p.2284·1).
Buffering agent for increasing gastric pH before anaesthesia.

Pneumo 23 *Sanofi Pasteur, Arg.; Aventis Pasteur, Austria; Sanofi Pasteur, Belg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Pasteur Merieux, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; Aventis, NZ; Sanofi Pasteur, Neth.; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Sanofi Pasteur, Port.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pneumo Novum *Sanofi Pasteur, Denm.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pneumodoron 1 *Weleda, Ger.; Weleda, S.Afr.*
Homoeopathic preparation.

Pneumodoron 2 *Weleda, Ger.; Weleda, S.Afr.*
Homoeopathic preparation.

Pneumodoron Nr 1 *Weleda, Austria.*
Homoeopathic preparation.

Pneumodoron Nr 2 *Weleda, Austria.*
Homoeopathic preparation.

Pneumol *Gerolymatos, Gr.*
Carbocisteine (p.1553·2).
Mucolytic.

Pneumol Plus *Gerolymatos, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Pneumopan
Note.This name is used for preparations of different composition.
Gebro, Austria.
Thyme (p.2401·1); equisetum (p.2299·3); ribwort plantain (p.2379·1); sulfogaiacol (p.1573·2).
Coughs.

GSK Sante, Fr.†.
Codeine (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Pneumopect *Gebro, Austria.*
Noscapine (p.1566·2); thyme (p.2401·1); viola.
Coughs.

Pneumopur *Chiron Behring, Ger.†; Chiron, Ital.†.*
A pneumococcal vaccine (capsular polysaccharide, 23-valent) (p.2231·2).
Active immunisation.

Pneumorel *Eutherapie, Fr.; Servier, Hong Kong; Stroder, Ital.; Servier, Port.*
Fenspiride hydrochloride (p.1122·1).
Coughs; respiratory-tract disorders.

Pneumotussin *ECR, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Pneumovax *Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Norw.; Aventis Pasteur, Swed.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pneumovax II *Sanofi Pasteur, Irl.; Aventis Pasteur, UK.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pneumovax 23 *MSD, Arg.; CSL, Austral.; Aventis Pasteur, Belg.†; MSD, Braz.†; Merck Frosst, Canad.; Sanofi Pasteur, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Israel; MSD, Malaysia†; MSD, NZ; Sanofi Pasteur, Neth.; MSD, Pol.; Sanofi Pasteur, Port.; MSD, S.Afr.; MSD, Singapore; Sanofi Pasteur, Switz.; MSD, Thai.†; Merck, USA.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pneumune *Wyeth Lederle, Belg.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

PNTWIN No 3 *Ajinomoto, Thai.†.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Pnu-Imune *Wyeth Lederle, Austria†; Wyeth, Irl.†; Wyeth Lederle, Norw.†; Wyeth Lederle, Port.†; Wyeth Lederle, Swed.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pnu-Imune 23 *Wyeth, Gr.†; Wyeth Lederle, Ital.†; Wyeth, Mex.†; Lederle, Switz.†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pnu-Inmune *Wyeth, Spain†.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

PO 12 *Boehringer Ingelheim, Fr.*
Enoxolone (p.50·1).
Skin irritation.

Po Antisseptico *Bunker, Braz.*
Boric acid (p.2268·1); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Skin disorders.

Po Sum On Medicated Oil *Zen, Israel.*
Peppermint oil (p.1761·2).
Cold symptoms; musculoskeletal, joint, and soft-tissue disorders.

Pobrax *Pharmasant, Thai.†.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Biliary dyskinesia; dysmenorrhoea; dyspepsia; irritable colon; peptic ulcer; ureteric spasm.

Pocin *Polipharm, Thai.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Pocin G *CCM, Malaysia.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Pocin H *CCM, Malaysia.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Otitis.

PocketScan *Lifescan, Irl.*
Test for glucose in blood (p.2314·1).

Poconeol *Dolisos, Fr.†; Plantes et Medecines, Fr.*
A range of homoeopathic preparations.

Pocophage *Pharmasant, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Pocyl *Lacer, Spain†.*
Ibuprofen (p.64·2).
Fever; pain.

Podactin
Note. This name is used for preparations of different composition.
Reese, USA.
Cream: Miconazole nitrate (p.541·3).
Reese, USA.
Topical powder: Tolnaftate (p.548·3).

Podakrin *Pharmasant, Thai.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Podase *Pose, Thai.†.*
Serrapeptase (p.2385·3).
Inflammation; oedema.

Pod-Ben-25 *C & M, USA.*
Podophyllum resin (p.1610·2).
Warts.

Podertonic *Inkeysa, Spain.*
Ferrocholinate (p.1938·2).
Iron-deficiency anaemia.

Podine *Pharmacare, S.Afr.*
Povidone-iodine (p.1659·2).
Burns; mouth and throat disinfection; mouth and throat infections; skin infections; wounds.

Podival *Valmor, Venez.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Podoben *Silva, Venez.†.*
Podophyllum resin (p.1610·2); benzoin tincture (p.2394·2).
Keratolytic.

Podocon *Paddock, USA.*
Podophyllum resin (p.1610·2).
Genital warts.

Podofilia *Bustillos, Mex.*
Podophyllum resin (p.1610·2).
Keratosis; verrucas; warts.

Podofilm *Paladin, Canad.; Enterprises Importfab, Hong Kong.*
Podophyllum resin (p.1610·2).
Warts.

Podofilox *Pharmalex (Φαρμαλέξ), Gr.†.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Podofin *Syosset, USA.*
Podophyllum resin (p.1610·2).
Epitheliomatosis; genital warts; keratoses.

Podomexef *Sankyo, Ger.; Sankyo, Switz.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Podoxin *Cassara, Arg.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Poen Efrina *Poen, Arg.*
Phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

Poenbioptal *Poen, Arg.*
Chloramphenicol (p.239·3); neomycin (p.305·1); phenylephrine (p.1568·1).
Bacterial eye infections.

Poenbioptal NF *Poen, Arg.*
Polymyxin B (p.318·2); neomycin (p.305·1); phenylephrine (p.1568·1).
Eye disorders.

Poenbiotico *Poen, Arg.†.*
Ampicillin sodium (p.204·1).
Bacterial eye infections.

Poencaina *Poen, Arg.; Roemmers Poen, Venez.*
Proxymetacaine (p.1870·2).
Local anaesthesia.

Poenfenicol *Poen, Arg.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Poenflox *Poen, Chile; Roemmers Poen, Venez.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Poenglaucol *Poen, Arg.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Poenglausil *Poen, Arg.†.*
⊗ Dorzolamide (p.1880·3).
Glaucoma.

Poenkerat *Poen, Arg.; Poen, Chile; Roemmers Poen, Venez.*
Ketorolac trometamol (p.74·2).
Cystoid macular oedema; eye inflammation; prevention of intra-operative miosis; uveitis.

Poentimol *Poen, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Poentobral *Roemmers Poen, Venez.*
Tobramycin (p.354·1).
Bacterial eye infections.

Poentobral Plus *Poen, Chile; Roemmers Poen, Venez.*
⊗ Dexamethasone (p.1526·1); tobramycin (p.354·1).
Bacterial eye infections with inflammation.

Pofol *Dong Kook, Singapore†; Dong Kook, Thai.; Ilsan, Turk.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Pogetol *Pharmasant, Thai.*
Chlorpromazine (p.969·1).
Nausea and vomiting; psychoses.

PO-HO bleu *Hanseler, Switz.*
Camphor oil (p.2273·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); turpentine oil (p.2406·3).
Headache; respiratory-tract disorders.

Poikicholan *Lomapharm, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Poikilocard Mono *Lomapharm, Ger.†.*
Crataegus (p.2289·1).
Cardiac disorders.

Poikiven T *Lomapharm, Ger.*
Homoeopathic preparation.

Point *Trima, Israel.*
Naproxen sodium (p.92·3).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Point-Two *Colgate Oral, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Poison Antidote Kit *Bowman, USA.*
Combination pack: Syrup, ipecacuanha (p.1562·3); suspension, charcoal (p.1435·2).
Emergency treatment of poisoning.

Poison Ivy/Oak *Hylands, Canad.*
Homoeopathic preparation.

Polacel *Medikon, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Polagen *Decomed, Port.†.*
Grass pollen extract (p.2250·2).
Allergen immunotherapy.

Polamec *Mecosin, Indon.*
Dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Polamin *Teuto, Braz.†.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Polamine
Note. This name is used for preparations of different composition.
Strand, Malaysia†.
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.
Pharmasant, Thai.
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; rhinorrhoea.

Polantac *Polinac, Venez.*
Magnesium trisilicate (p.1744·1); magnesium oxide (p.1744·1); monobasic sodium phosphate (p.1682·3); carmellose sodium (p.2142·1); bismuth subcarbonate (p.1711·1).
Gastritis; oesophagitis; peptic ulcer.

Polar Ice *Scott, Canad.*
Menthol (p.2340·1).
Musculoskeletal and joint pain.

Polaramex *Schering-Plough, Venez.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2).
Allergic respiratory-tract disorders.

Polaramin *Aesca, Austria; Schering-Plough, Denm.; Schering-Plough, Ital.; Schering-Plough, Norw.; Schering-Plough, Swed.*
Dexchlorpheniramine maleate (p.572·1).
Allergic rhinitis; hypersensitivity reactions; insect bites; pruritus; sunburn; urticaria.

Polaramin Espettorante *Schering-Plough, Ital.*
Dexchlorpheniramine maleate (p.572·1); guaifenesin (p.1561·3); pseudoephedrine sulfate (p.1571·2).
Colds; coughs.

Polaramine *Schering-Plough, Austral.; Schering-Plough, Belg.†; Mantecorp, Braz.; Schering-Plough, Fr.; Schering-Plough, Gr.†; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia; Schering-Plough, Mex.†; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, S.Afr.†; Schering-Plough, Singapore; Schering-Plough, Spain; Essex, Switz.*
Dexchlorpheniramine maleate (p.572·1).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; eczema; insect bites; pruritus; urticaria.

Polaramine Expec *Schering-Plough, Mex.†.*
Dexchlorpheniramine maleate (p.572·1); guaifenesin (p.1561·3); pseudoephedrine sulfate (p.1571·2).
Coughs; rhinitis.

Polaramine Expectorant *Schering-Plough, Belg.†; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Malaysia†; Schering-Plough, Singapore; Schering, USA.*
Dexchlorpheniramine maleate (p.572·1); guaifenesin (p.1561·3); pseudoephedrine sulfate (p.1571·2).
Asthma; cold symptoms; cough; hay fever; respiratory hypersensitivity reactions; rhinitis.

Polaramine Expectorante *Mantecorp, Braz.; Schering-Plough, Spain.*
Dexchlorpheniramine maleate (p.572·1); guaifenesin (p.1561·3); pseudoephedrine sulfate (p.1571·2).
Upper-respiratory-tract disorders.

Polaramine Reformulado *Schering-Plough, Venez.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Polaramine Topico *Schering-Plough, Spain.*
Allantoin (p.1588·1); dexchlorpheniramine maleate (p.572·1).
Cutaneous hypersensitivity reactions.

Polaratyne *Schering-Plough, S.Afr.†.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Polaratyne D *Schering-Plough, S.Afr.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Polaren *Cifarma, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Polarist *Bernofarm, Indon.*
Dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Polaronil *Essex, Ger.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Polaryn *Teuto, Braz.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Polase *Wyeth Lederle, Ital.; Home, Port.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Potassium and magnesium deficiency.

Polase Sport *Wyeth Consumer, Ital.*
Potassium; magnesium; vitamins (p.1922·1).
Nutritional supplement.

Polcortolon
Jelfa, Pol.; Polfa Pabianice, Pol.
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Corticosteroid.
Jelfa, Rus.
Ointment: ⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.
Pabianice, Rus.
Tablets: ⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Polcortolon TC *Medphano, Ger.; Tarchomin, Hung.; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
⊗ Triamcinolone acetonide (p.1544·3); tetracycline hydrochloride (p.347·2).
Infected skin disorders.

Polcortolone *Pabianice, Hung.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Polcotec *Best, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Acid aspiration; aid in gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Polcrom *Polfa Warszawa, Pol.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Poldan *Sanbe, Indon.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Poldanen *Herbapol Poznan, Pol.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Poledin *Pfizer, Spain†.*
Sodium cromoglicate (p.1136·3).
Eye disorders.

Polenat *Natufarma, Arg.*
Pollen (p.2370·2).
Dietary supplement.

Polendiamina *Fada, Arg.†.*
⊗ Diphenhydramine (p.577·1); ephedrine (p.1558·1); guaifenesin (p.1561·3).
Coughs.

Polery
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Fr.
Paediatric syrup: Pholcodine (p.1570·2); erysimin.
Coughs.
Pierre Fabre Sante, Fr.
Syrup: Codeine (p.37·2); erysimin.
Coughs.

Polet *Wermar, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; pain.

Polfenon *Polpharma, Pol.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Polfilin *Polpharma, Pol.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; Ménière's disease; vascular ear and eye disorders.

Polfungicid *ICN, Pol.*
Chlormidazole hydrochloride (p.529·1); salicylic acid (p.1612·2).
Skin and nail infections.

Polhumin Mix-3 *Polfa Tarchomin, Pol.*
⊗ A mixture of insulin injection (human) 30% and isophane insulin (human) 70% (p.443·2).
Diabetes mellitus.

Polhumin N *Polfa Tarchomin, Pol.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

Polhumin R *Polfa Tarchomin, Pol.*
⊗ Neutral insulin injection (human) (p.443·2).
Diabetes mellitus.

Poli ABE *Lesvi, Spain.*
Pyridoxine hydrochloride; vitamin A palmitate; tocoferil acetate (p.1922·1).
Formerly contained pyridoxine hydrochloride, placenta extract, vitamin A palmitate, and tocoferil acetate.
Vitamin A and E deficiency.

Poli B Fuerte *Lamsa, Arg.*
Vitamin B substances (p.1922·1).

Poliacel *Sanofi Pasteur, Arg.†; Aventis Pasteur, Austral.; Aventis Pasteur, Braz.†; Aventis Pasteur, Turk.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Poliacel-Act-Hib *Pasteur Merieux, Israel.*
A diphtheria, tetanus, acellular pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Polial *Ultrapharm, UK.*
Gluten- and lactose-free food for special diets (p.1922·1).
Gluten sensitivity.

Poliamin *Behrens, Venez.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Polibac *Hebron, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Polibar *Infarmed, Belg.; E-Z-EM, Cz.; E-Z-EM, Neth.; E-Z-EM, Port.; E-Z-EM, UK.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Polibar ACB *E-Z-EM, Hung.; E-Z-EM, Israel; Bracco, Switz.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Polibar Rapid *E-Z-EM, Hung.; E-Z-EM, UK.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Polibatrin *Ivax, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Poliben *Auad, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Polibeta B12 *Ceccarelli, Ital.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Polibimbi *Carlo Erba OTC, Ital.†.*
Electrolytes (p.1667·1).
Nasal irrigation.

Polibiotic *Ecobi, Ital.†.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Polibroxol *Polipharm, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Polibutin *Juste, Spain.*
Trimebutine (p.2404·3) or trimebutine maleate (p.2404·3).
Gastrointestinal spasm; nausea and vomiting.

Policano *Rafarm, Gr.*
Isotretinoin (p.1599·2).
Acne.

Poli-Cifloxin *Polipharm, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Policitra *Flupal, Venez.*
Sodium citrate (p.1673·3); potassium citrate (p.1673·2); citric acid (p.2284·2).
Urinary alkalinisation.

Policlavumoxil *EMS, Braz.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Policol *Polipharm, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; cold symptoms; hay fever.

Policold *Polipharm, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms; hay fever; hypersensitivity reactions; nasal congestion.

Policolinosil *Nupel, Spain.*
Amino acids (p.1922·1); liver extract (p.2337·3); pangamic acid (p.2362·1); ribonucleic acid (p.2379·1); thioctic acid (p.2400·2); inositol (p.2325·2); vitamin B substances (p.1922·1).
Liver disorders; tonic.

Policor
Note. This name is used for preparations of different composition.
Gador, Arg.
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Herron, Austral.
Policosanol (p.1373·3).
Hypercholesterolaemia.

Poli-Cycline *Polipharm, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Polidan *Polydan, Rus.*
Sodium nucleospermate.
Leucopenia; thrombocytopenia.

Polidazol *Balldarassi, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Polideltaxin NF *Pharmacos, Mex.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Infected eye disorders.

Polidemisin *Sanbe, Indon.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Poliderms *Uniao Quimica, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Polienzim *Sanitas, Arg.*
Lipase (p.2360·3); protease; cellulase (p.2279·1); amylase (p.2256·3); simeticone (p.1770·2).
Digestive disorders; flatulence.

Poli-Fibrozil *Polipharm, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Polifix *Polinac, Venez.†.*
Sterculia (p.1772·1); borax (p.2268·1).
Denture adhesive.

Polifluidil *Balverda, Ital.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Poli-Flunarin *Polipharm, Thai.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; irritability; memory impairment; migraine; sleep disorders.

Poli-Formin *Polipharm, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Polifrisin *Sanbe, Indon.*
Polymyxin B (p.318·2); neomycin (p.305·1); phenylephrine hydrochloride (p.1568·1).
Bacterial eye infections.

Polifur *Organifar, Venez.†.*
Nitrofurazone (p.309·1).
Bacterial infections.

Poliginax *Solvay, Braz.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); nystatin (p.543·2); tinidazole (p.848·3).
Vulvovaginal infections.

Poligot *Polipharm, Thai.†.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and other vascular headache.

Poligot-CF *Polipharm, Thai.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Poligram *Puebla, Arg.*
Polysaccharides from *Pseudomonas aeruginosa*.
Immunostimulant.

Polijodurato *Farmigea, Ital.*
Sodium iodide (p.2169·2); potassium iodide (p.2169·2); rubidium iodide (p.2382·2); calcium chloride (p.1675·2).
Cataracts.

Polik
Note. This name is used for preparations of different composition.
Meiji, Indon.
Haloprogin; enoxolone (p.50·1).
Fungal skin infections.

Leti, Venez.
Clotrimazole (p.530·1).
Fungal infections.

Polikos *Landson, Indon.*
Policosanol (p.1373·3).
Hypercholesterolaemia; intermittent claudication; platelet aggregation.

Polilevo *Monsanto, Ital.†.*
Arginine hydrochloride (p.1928·2); ornithine hydrochloride (p.1959·2); citrulline (p.1935·1).
Liver disorders.

Polilevo N *Taurus, Ger.†.*
Arginine hydrochloride (p.1928·2); ornithine hydrochloride (p.1959·2); citrulline (p.1935·1).
Liver disorders.

Polimerosa *Nutricia-Bago, Arg.*
Carbohydrate supplement (p.1922·1).
Nutritional supplement.

Polimisin *Kocak, Turk.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye and skin infections.

Polimod *Pharmanel, Gr.; Pharmacia, Ital.*
Pidotimod (p.2367·3).
Immunostimulant.

Polimoxil *Legrand, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Polimucil
Note. This name is used for preparations of different composition.
Byk, Arg.†; Pharmanel, Gr.
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Respiratory-tract disorders with excess mucus.

Chefaro, Ital.
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Polinazolo *Rottapharm, Ital.*
Econazole nitrate (p.531·1).
Fungal balanitis; vulvovaginal candidiasis.

Polinorm *AstraZeneca, Austria.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Polio Sabin *GSK, Israel; GSK, Ital.†; GSK, Mex.; GSK, Philipp.; GSK, Pol.; GSK, Thai.; GSK, Turk.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Poliodine *Gifrer Barbezat, Fr.*
Povidone-iodine (p.1659·2).
Wound and skin disinfection.

polio-elan *Feldhoff, Ger.*
Pumilio pine oil (p.2376·3); rosemary oil (p.2381·3).
Bronchitis; musculoskeletal and joint disorders.

Polioftal *Valeant, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

PolioHib *SBL, Swed.†.*
A poliomyelitis and haemophilus influenzae vaccine (p.2214·1).
Active immunisation.

poliomyelan *Feldhoff, Ger.†.*
⊗ Bovine testicular extract (p.2129·3); bovine placental extract (p.2337·3).
Musculoskeletal and joint disorders.

Polioral *Sclavo, Israel; Chiron Vaccines, Ital.†; Chiron Behring, Malaysia†; Ivax, Mex.; Chiron Vaccines, Philipp.; Biovac, S.Afr.; Chiron, Thai.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Poliorix *IFET (ΙΦΕΤ), Gr.; GSK, Philipp.; GSK, Switz.; GSK, Turk.*
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

Poli-Otico *Roemmers Osmoph, Venez.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2).
Infected ear disorders.

Poliovax-IN *Chiron Vaccines, Ital.*
An inactivated poliomyelitis vaccine (p.2232·1).
Active immunisation.

Polipectol *Fapromed, Arg.†.*
Mepyramine maleate (p.585·2); sulfogaiacol (p.1573·2); caffeine (p.1116·3); ammonium acetate (p.1551·2); tolu balsam (p.1574·2).
Respiratory-tract disorders.

Polipirox *Mayne, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Poliplex *Mead Johnson, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Polipred *Allergan, Braz.*
⊗ Prednisolone acetate (p.1541·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Poli-Relaxane *Polipharm, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain; tension headache.

Polireumin *TRB, Braz.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis.

Poliroxin *Polipharm, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Polirreumin *TRB, Arg.*
Hydroxychloroquine sulfate (p.604·2).
Lupus erythematosus; malaria; rheumatoid arthritis.

Polisan *Milana, Ital.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Polised *Chefaro, Ital.*
Sulfogaiacol (p.1573·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Poliseng *Teuto, Braz.*
Amino acids; mineral; vitamins; ginseng (p.2312·1) (p.1922·1).
Tonic.

Polisep *Drag, Chile†.*
Menthol (p.2340·1); thymol (p.1664·3); salol (p.122·1).
Mouth and throat disorders.

Polisilon *Upsa, Ital.†.*
Aluminium hydroxide (p.1706·2); dimeticone (p.1770·2).
Aerophagia; gastrointestinal disorders associated with hyperacidity.

Polisulfade *Sanobia, Port.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Skin infections.

Politifen *Polipharm, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; bronchitis; hypersensitivity reactions.

Politosse *Pharmacia, Ital.*
Levocloperastine fendizoate (p.1554·3).
Coughs.

Poli-Uretic *Polipharm, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis; hypertension; oedema.

Polivit *Abdi Ibrahim, Indon.; Abdi, Turk.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Polivit C *Abdi, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Polivitam *Lafit, Braz.†.*
Cyproheptadine hydrochloride (p.575·1); vitamin B substances; ascorbic acid (p.1922·1).

Polivitaminas *Valmor, Venez.†.*
Vitamin preparation (p.1922·1).

Polivitaminico *CPH, Port.†.*
Multivitamin preparation (p.1922·1).

Polivitaplex con Minerales *Gache, Venez.*
Vitamin and mineral preparation (p.1922·1).

Polivitaplex Simple *Gache, Venez.*
Vitamin preparation (p.1922·1).

Poliwit *Fisiopharma, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Polixan *Polipharm, Thai.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Muscle pain and spasm.

Polixil B *Haller, Braz.†.*
Polymyxin B sulfate (p.317·3).
Bacterial infections.

Polixin
Note. This name is used for preparations of different composition.
Sophia, Mex.
Eye drops: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Sophia, Mex.
Eye ointment: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); bacitracin (p.210·3).
Bacterial eye infections.

Polizep *Polipharm, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Polizine *Polipharm, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions.

Pollen Royal *Ido, Fr.†.*
Pollen (p.2370·2); propolis (p.2373·3); royal jelly (p.2382·1).
Nutritional supplement.

Pollenase Allergy *Peach, UK.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Pollenase Antihistamine *Peach, UK.*
Chlorphenamine (p.572·2).
Hypersensitivity reactions.

Pollenase Nasal *Peach, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Formerly known as Pollenase Hayfever.
Hypersensitivity reactions.

Pollenna *Nelson, UK.*
Homoeopathic preparation.

Pollenshield *Actavis, UK.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Pollentyme *Pharma Dynamics, S.Afr.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Pollergon *Motima, Fr.*
Pollen (p.2370·2).
Nutritional supplement.

Pollinex *Stallergenes, Belg.†; Allergy Therapeutics, Cz.; Artu, Neth.; Allergy Therapeutics, Pol.; Allergy Therapeutics, UK.*
Grass pollen extracts (p.2370·2)(p.2250·2).
Allergen immunotherapy; diagnosis of allergy.

Pollinex Quattro *Bencard, Ger.*
Pollen extracts (p.2370·2)(p.2250·2).
Allergen immunotherapy.

Pollinex-R *AllerPharma, Canad.*
Aqueous extract of short ragweed pollen (p.2370·2)(p.2250·2).
Allergen immunotherapy of ragweed pollen.

Pollingel *Bracco, Ital.*
Pollen (p.2370·2); royal jelly (p.2382·1).
Nutritional supplement.

Pollingel con Ginkgo Biloba *Bracco, Ital.†.*
Pollen (p.2370·2); ginkgo biloba (p.2311·1).
Nutritional supplement.

Pollingel Ginseng *Bracco, Ital.†.*
Pollen (p.2370·2); ginseng (p.2312·1); honey (p.1948·2).
Nutritional supplement.

Pollinil *Dolisos, Canad.*
Homoeopathic preparation.

Pollinosan *Bioforce, Ger.; Bioforce, Switz.*
Homoeopathic preparation.

Pollinose S *Alsitan, Ger.†.*
Pollen (p.2370·2) (p.2250·2).
Allergen immunotherapy.

Pollivita *Permamed, Switz.*
Butterbur (p.2271·1).
Allergic rhinitis.

Pollstimol *Strathmann, Ger.; Strathmann, Hung.*
Grass pollen extracts (p.2370·2).
Benign prostatic hyperplasia; prostatic disorders; urethritis.

Pollyferm *Nordic, Swed.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Polmesilat *Polon, Pol.*
Pridinol mesilate (p.1898·1).
Skeletal muscle spasm; spasticity.

Polmofen *Yeni, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Polmonin *Farmanic, Gr.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Polocaine *AstraZeneca, Canad.†; AstraZeneca, USA.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Corbadrine (p.2287·3) or corbadrine hydrochloride (p.2287·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Polocard *Polpharma, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Polodina-R *Polon, Pol.*
Povidone-iodine (p.1659·2).
Disinfection of skin and wounds; skin and mucous membrane infections.

Polofar *Ifars, Indon.*
Dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Polol *Geolab, Braz.*
⊗ Propranolol (p.1381·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; pain; phaeochromocytoma; subaortic hypertrophic stenosis; tremor.

Polol-H *Geolab, Braz.*
⊗ Propranolol hydrochloride (p.1380·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Polomigran *Polon, Pol.*
Pizotifen malate (p.624·2).
Migraine.

Polonit *Drovepat, Venez.†.*
Loperamide (p.1741·3).
Diarrhoea.

Polopiryna *Polpharma, Pol.*
Aspirin (p.20·3).
Fever; pain.

Polopiryna C *Polpharma, Pol.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Polopiryna S *Polpharma, Pol.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain; thromboembolism prophylaxis.

Poloren *Loren, Mex.†.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Poloxane *Armoxindo, Indon.*
Aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Flatulence; gastralgia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; meteorism; pyrosis.

Polper B12 *Casasco, Arg.*
Amino acids; vitamin B (p.1922·1).
Dietary supplement.

Polper Calcio-Magnesio *Casasco, Arg.*
Vitamin B substances; vitamin C; calcium carbonate (p.1922·1).
Tonic.

Polper Ginseng *Casasco, Arg.*
Amino acids; cyanocobalamin; ginseng (p.1922·1).
Tonic.

Polper Vascular *Casasco, Arg.*
Dihydroergotamine mesilate (p.618·2); amino acids; vitamin B (p.1922·1).
Cerebrovascular disorders.

Polprazol *Polpharma, Pol.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Polpressin *Polpharma, Pol.†*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Polsen *Polfa Pabianice, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Polseptol *GSK, Pol.*
Povidone-iodine (p.1659·2).
Skin and vaginal infections; ulcers; wounds.

Polstigminum *Pliva Krakow, Pol.*
Neostigmine metilsulfate (p.631·3).
Myasthenia gravis; postoperative ileus; postoperative urinary retention; reversal of competitive neuromuscular blockade.

Poltax *Geolab, Braz.*
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), or diclofenac potassium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Poltaxel *Polfa Tarchomin, Pol.*
Paclitaxel (p.759·1).
Breast cancer; non small-cell lung cancer; ovarian cancer.

Poltram *Polpharma, Pol.*
Tramadol hydrochloride (p.130·3).
Pain.

Poludan *Veropharm, Rus.*
Potassium polyriboadenylate-potassium polyribouridylate (p.2370·2).
Viral eye diseases.

Polvac *Teomed, Switz.*
Pollen allergen extracts (p.2370·2) (p.2250·2).
Allergen immunotherapy.

Polvertic *Medana, Cz.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Polviderm NF *Bajer, Arg.*
Zinc oxide (p.1621·2); benzalkonium chloride (p.1629·1); phenoxyethanol (p.1657·1).
Skin disorders.

Polvilho Antisseptico *Granado, Braz.†*
Salicylic acid (p.1612·2); sulfur (p.1614·1); boric acid (p.2268·1); zinc oxide (p.1621·2).

Polvir *ICN, Pol.*
Denotivir (p.870·2).
Genital herpes; herpes labialis.

Polvo Roge *Casasco, Arg.*
Magnesium oxide (p.1744·1); magnesium carbonate (p.1743·1).
Constipation.

Polvos Alcalinos *Volta, Chile.*
Calcium carbonate (p.1714·1); magnesium oxide (p.1744·1); sodium bicarbonate (p.1673·2); spearmint oil (p.2391·3).
Antacid.

Polvos Antibioticos *Silesia, Chile†.*
Bacitracin (p.210·3); neomycin (p.305·1); sulfathiazole (p.343·2).
Burns; infected skin disorders; wounds.

Polvos Wilfe *Perez Gimenez, Spain†.*
Sulfanilamide (p.343·1); sulfathiazole (p.343·2).
Skin infections.

Poly C
Note.This name is used for preparations of different composition.
Usana, Hong Kong†; Usana, Singapore.
Vitamin C (p.1983·3); flavonoids (p.2304·1).
Antoxidant; vitamin C supplement.

Usana, Mex.
Vitamin C (p.1983·3).
Dietary supplement.

Poly Gel *Alcon, Austral.*
Carbomer (p.2141·3).
Dry eyes; eye irritation.

Poly Pred *Allergan, Spain.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Poly Visc *Alcon, Austral.*
Paraffin (p.2031·2); wool fat (p.2033·2).
Dry eyes.

Poly-Alkohol *Merz Consumer, Ger.*
Isopropyl alcohol (p.1650·3); 1,3-butanediol.
Skin disinfection.

Polyanion *Sigmapharm, Austria.*
Pentosan polysulfate sodium (p.1367·1).
Hyperlipidaemias; thromboembolic disorders.

Poly-B con Vitamina C *Grossman, Mex.*
Vitamin B substances; vitamin C (p.1922·1).

Polybamycin *Shin Poong, Singapore.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Polybe *Gedeon Richter, Hung.*
Vitamin B substances (p.1922·1).

Polybee *Chew, Thai.*
Vitamin B substances with yeast (p.1922·1).

Polybion *Merck, Fin.†; Merck, India; Oro, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B and C deficiency; vitamin B deficiency.

Polybion Forte *Merck, Ger.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Polybion N *Merck, Ger.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Polybon *Pharmasant, Thai.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Anxiety; depression.

Polycal *Nutricia, Austral.†; Nutricia, Hong Kong; Nutricia, Irl.; Baxter, NZ; Nutricia, NZ; Nutricia Clinical, UK.*
Carbohydrate supplement (p.1922·1).

Polycidin
Note.This name is used for preparations of different composition.
Novartis Ophthalmics, Canad.†.
Eye ointment: Bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).
Eye infections.

Novartis Ophthalmics, Canad.†.
Eye/ear drops: Gramicidin (p.286·1); polymyxin B sulfate (p.317·3).
Eye and ear infections.

Polycilline *Mecom, Turk.*
Trimethoprim sulfate (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Polycin *Nakornpatana, Thai.*
Nitrofurazone (p.309·1).
Burns; skin ulcers; wound infections.

Polycin-B *Ocusoft, USA.*
Bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Polycitra *Alza, USA.*
Potassium citrate (p.1673·2); sodium citrate (p.1673·3); citric acid monohydrate (p.2284·1).
Chronic metabolic acidosis; urine alkalinising agent.

Polycitra-K
Note.This name is used for preparations of different composition.
Janssen-Ortho, Canad.
Potassium citrate (p.1673·2).
Hypokalaemia.

Alza, USA.
Potassium citrate (p.1673·2); citric acid monohydrate (p.2284·1).
Chronic metabolic acidosis; urine alkalinising agent.

Polycitra-LC *Alza, USA.*
Potassium citrate (p.1673·2); sodium citrate (p.1673·3); citric acid monohydrate (p.2284·1).
Chronic metabolic acidosis; urine alkalinising agent.

Polyclean *Alcon, Fr.*
Cleansing solution for contact lenses (p.1622·2).

Polyclens *Alcon, Austral.; Alcon, Braz.†; Alcon, Mex.; Alcon, NZ; Alcon, S.Afr.*
Cleaning liquid for contact lenses (p.1622·2).

Poly-Cof *Millimed, Thai.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Polycolvit *Pharmasant, Thai.*
Ferrous fumarate (p.1938·3); vitamin B substances; vitamin C; calcium phosphate (p.1922·1).
Anaemias; vitamin B and C deficiency.

Polycose *Abbott, Austral.; Abbott, Braz.†; Abbott, Canad.; Abbott, Hong Kong; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore†; Abbott Nutrition, UK; Ross, USA.*
Glucose polymers (p.1922·1).
Nutritional carbohydrate supplement.

Polycrol
Note.This name is used for preparations of different composition.
Boots Piramal, India.
Simeticone (p.1770·2); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2).
Gastric hyperacidity; peptic ulcer.

Nicholas, Indon.
Oral gel: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Nicholas, Indon.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Polycrol 400 *Nicholas, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; peptic ulcer.

Polycutan *Agis, Israel.*
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Polydene *Socobom, Belg.*
Piroxicam (p.117·3).

Polyderm
Note.This name is used for preparations of different composition.
Taro, Canad.
Bacitracin zinc (p.210·3); polymyxin B sulfate (p.317·3).
Burns; minor wounds.

Chowgule, India†.
⊗ Prednisolone (p.1540·3); clioquinol (p.254·1); mesulphen (p.1604·3); salicylic acid (p.1612·2).
Infected skin disorders.

Polydex
Note. A similar name is used for preparations of different composition (see below).
Pharmasant, Thai.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Poly-Dex
Note. A similar name is used for preparations of different composition (see above).
Ocusoft, USA.
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Polydexa
Therabel, Belg.; Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong; Neo-Farmaceutica, Port.; Bouchara, Rus.; Bouchara, Singapore; Bouchara, Switz.
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); dexamethasone sodium metasulfobenzoate (p.1526·2).
Infected ear disorders.

Polydexa with Phenylephrine *Bouchara, Rus.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); dexamethasone sodium metasulfobenzoate (p.1526·2); phenylephrine hydrochloride (p.1568·1).
Rhinopharyngitis; sinusitis.

Polydex-N *Aristopharma, Hong Kong.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Inflammatory eye disorders.

Polydiet *DHN, Fr.†.*
Preparation for enteral nutrition (p.1922·1).

Polydine
Note.This name is used for preparations of different composition.
Fischer, Israel; Century, USA.
Povidone-iodine (p.1659·2).
Skin and vaginal infections; skin disinfection.

Pharmasant, Thai.
Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3).
Coughs.

Polydol *Pharmasant, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Dysmenorrhoea; muscle pain; tension headache.

Polydona *Riemser, Ger.*
Povidone-iodine (p.1659·2).
Burns; skin ulcers; wounds.

Polydrop *Pharmasant, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion; rhinorrhoea.

Polydryl *Pharmasant, Thai.*
Diphenhydramine (p.577·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; cough; nasal congestion.

Polyenzyme-I *Chew, Thai.*
Amylase (p.2256·3); papain (p.2362·3); pancreatin (p.2360·1); vitamin B substances (p.1922·1); diphenhydramine hydrochloride (p.577·2); homatropine methylbromide (p.1881·3); simeticone (p.1770·2); activated charcoal (p.1435·2).
Digestive disorders.

Polyenzyme-N *Chew, Thai.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders.

Polyerga *HorFerVit, Ger.*
Polypeptides derived from spleen.
Adjuvant tumour therapy.

Polyfax *GSK, Hong Kong†; Intra Pharma, Irl.; Pliva, UK.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Bacterial infections of the skin and eye.

Polyfed *Biolab, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Polyflam *Socobom, Belg.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Polyfra
Note.This name is used for preparations of different composition.
Alcon, Fr.
Eye drops: ⊗ Framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3); oxedrine tartrate (p.1364·3).
Bacterial eye infections.

Alcon, Fr.
Eye ointment: Framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Polygam *NBI, S.Afr.; American Red Cross, USA.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease.

Polyglobin *Bayer, Ger.; Bayer, Swed.†.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki syndrome; passive immunisation.

Polygot *Pharmasant, Thai.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headaches.

Polygynax
Raymos, Arg.; UCB, Belg.†; Innothera, Cz.; Innotech, Fr.; Innotech, Hong Kong; Innotech, Rus.; Innotech, Singapore.
Neomycin sulfate (p.305·1); nystatin (p.543·2); polymyxin B sulfate (p.317·3).
Vulvovaginal and cervical infections.

UCB, Ger.†.
Neomycin (p.305·1); nystatin (p.543·2); polymyxin B sulfate (p.317·3).
Vulvovaginal infections.

Polygynax Virgo *Innotech, Fr.*
Neomycin sulfate (p.305·1); nystatin (p.543·2); polymyxin B sulfate (p.317·3).
Vulvovaginitis.

Polyhadon *Pharmasant, Thai.*
Haloperidol (p.1000·2).
Alcoholism; schizophrenia.

Poly-Histine *Sanofi Synthelabo, USA†.*
Phenyltoloxamine citrate (p.588·1); mepyramine maleate (p.585·2); pheniramine maleate (p.587·3).
Allergic rhinitis.

Polyionique *AGEPS, Fr.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Poly-Iron *Cypress, USA.*
Polysaccharide-iron complex (p.1960·2).
Iron deficiency.

Poly-Iron Forte *Cypress, USA.*
Polysaccharide-iron complex (p.1960·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Iron-deficiency anaemia; megaloblastic anaemia.

Poly-Joule *Nutricia, Austral.*
Dextrin (p.1937·1).
Nutritional supplement.

Poly-Karaya *Sanofi-Aventis, Fr.*
Sterculia (p.1772·1); povidone (p.2146·1).
Constipation; diarrhoea; meteorism.

Polymagma *Wyeth, Philipp.*
Attapulgite (p.1709·1).
Diarrhoea.

Poly-Micron *Alcon, Mex.*
Neomycin (p.305·1); gramicidin (p.286·1); polymyxin B (p.318·2).
Bacterial eye infections.

Polyminerol *Lavena, Rus.*
Electrolytes (from Pomeranian lakes) (p.1667·1).
Gingivitis; periodontitis.

Polymox *Hormona, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Polymycin
Note.This name is used for preparations of different composition.
Medical Ophthalmics, USA.
Eye drops: Neomycin (p.305·1); polymyxin B (p.318·2); gramicidin (p.286·1).
Eye infections.

Medical Ophthalmics, USA.
Eye ointment: Neomycin (p.305·1); polymyxin B (p.318·2); bacitracin (p.210·3).
Eye infections.

Polynadim *Synthesis, Rus.*
⊗ Diphenhydramine (p.577·1); naphazoline (p.1565·1).
Allergic eye disorders.

Polynase *YSP, Malaysia†.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic conjunctivitis; allergic skin disorders; rhinitis.

Polynerv *More, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Hyperemesis gravidarum; neuritis; neuropathy; vitamin B deficiency.

Polynerv-E with lecithin *More, Philipp.*
Vitamin and mineral preparation with ginseng, lecithin, betacarotene, lutein, lycopene, omega-3, and ubidecarenone (p.1922·1).
Nutritional supplement; tonic.

Polynovate *Pharmasant, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Polyod *Drogsan, Turk.*
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection.

Polyoph *Seng, Hong Kong; Seng, Thai.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Bacterial eye infections.

Polyoxidin *Biosynthesis, Rus.*
Macrogol 20 000 (p.2336·1).
Plasma substitute; plasma volume expansion.

Polyoxidonium *Immapharma, Rus.*
Polyoxydonium.
Burns; hypersensitivity reactions; infections; inflammation; reduction of antineoplastic toxicity; rheumatoid arthritis; secondary immunodeficiency; ulcers.

Polypen
Combiphar, Indon.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

YSS, Philipp.
Ampicillin sodium (p.204·1).
Bacterial infections.

Polyphed *Pharmasant, Thai.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Polypirine *Lehning, Fr.*
Aspirin (p.20·3); caffeine citrate (p.1116·3); meadowsweet (p.2338·1).
Fever; pain.

Polyplex *Phoenix, Arg.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin b sulfate (p.317·3).
Bacterial eye infections.

Polypred
Note. A similar name is used for preparations of different composition (see below).
Pharmasant, Thai.
⊗ Prednisolone (p.1540·3).
Skin disorders.

Poly-Pred
Note. A similar name is used for preparations of different composition (see above).
Allergan, USA.
⊗ Prednisolone acetate (p.1541·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Eye inflammation with bacterial infection.

Polypress
Note.This name is used for preparations of different composition.
Pfizer, Ger.†.
⊗ Prazosin hydrochloride (p.1375·2); polythiazide (p.1373·3).
Hypertension.

Pharmasant, Thai.
Prazosin hydrochloride (p.1375·2).
Hypertension.

Polyquin *Tai Guk, Singapore.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Polyrhinium *Ferrier, Fr.*
Homoeopathic preparation.

Polyrinse *Alcon, Fr.; Alcon, S.Afr.*
Sodium chloride (p.1686·1) (p.1622·2).
Rinsing and soaking solution for contact lenses.

Polysept *Dermapharm, Ger.; Rekah, Israel.*
Povidone-iodine (p.1659·2).
Burns; skin and mucous membrane disinfection; skin ulcers; wounds.

Polyseptol *Qualiphar, Belg.*
Filtrate from culture of: *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa*, and *Escherichia coli*; sulfanilamide (p.343·1); cod-liver oil (p.1935·2).
Infected skin and mucous membrane disorders.

Polysianes
Note.This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
SPF 10; SPF 15; SPF 20: Bisoctrizole (p.1591·2); octocrilene (p.1608·3); cinamate.
Sunscreen.

Pierre Fabre Dermo-Cosmetique, Arg.
SPF 40: Bisoctrizole (p.1591·2); bemotrizinol (p.1590·2); octocrilene (p.1608·3); cinamate; titanium dioxide (p.1617·3).
Sunscreen.

Polysianes Autobronceante *Pierre Fabre Dermo-Cosmetique, Arg.*
Titanium dioxide (p.1617·3); octocrilene (p.1608·3); cinamate; dihydroxyacetone (p.1594·1).
Sunscreen; tanning aid.

Polysilane
Note.This name is used for preparations of different composition.
Sanofi Synthelabo, Hong Kong†; Sanofi Synthelabo, Malaysia†; Sanofi Synthelabo, Singapore†; Sanofi Synthelabo, Thai.
Aluminium hydroxide (p.1706·2); dimethicone (p.1770·2).
Dyspepsia; flatulence; gastritis; heartburn; pyrosis.

UPSA, Switz.
Dimeticone (p.1770·2).
Flatulence; meteorism.

Pharos, Indon.
Oral granules: Dimeticone (p.1770·2); ceratonia (p.2143·2).
Flatulence; gastritis; heartburn; pyrosis.

Pharos, Indon.
Oral suspension; tablets: Magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); dimeticone (p.1770·2).
Flatulence; gastritis; heartburn; pyrosis.

Polysilane Delalande *Sanofi-Aventis, Fr.*
Aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Polysilic III *Beacons, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; meteorism; peptic ulcer.

Polysorb
Note.This name is used for preparations of different composition.
Polisorb, Rus.
Silicon dioxide (p.2146·2).
Food and drug allergy; intestinal infections; poisoning.

Fougera, USA.
Emollient and moisturiser.

Polyspectran
Note.This name is used for preparations of different composition.
Alcon, Ger.
Eye and ear drops: Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial infections of the eye and ear.

Alcon, Ger.
Ointment: Polymyxin B sulfate (p.317·3); bacitracin (p.210·3); neomycin sulfate (p.305·1).
Bacterial infections of the eye, ear, and nose.

Polyspectran G *Alcon, Neth.†.*
Neomycin sulfate (p.305·1); gramicidin (p.286·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Polyspectran Gramicidine *Alcon, Belg.*
Gramicidin (p.286·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Polyspectran HC *Alcon, Ger.*
⊗ Polymyxin B sulfate (p.317·3); bacitracin (p.210·3); hydrocortisone acetate (p.1535·2).
Bacterial and inflammatory eye, ear and nose disorders; skin disorders.

Polyspor *Teva, Hung.*
Polymyxin b sulfate (p.317·3); gramicidin (p.286·1).

Polysporin
Note.This name is used for preparations of different composition.
Pfizer, Braz.
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Skin infections.

GSK, Fin.
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Eye infections.

Pfizer Consumer, S.Afr.
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Burns; skin infections; ulcers; wounds.

Monarch, USA†; Warner-Lambert, USA†.
Polymyxin B sulfate (p.317·3); bacitracin (p.210·3) or bacitracin zinc (p.210·3).
Eye infections; skin infections.

Pfizer Consumer, Canad.
Cream; eye/ear drops: Polymyxin B sulfate (p.317·3); gramicidin (p.286·1).
Bacterial contamination prophylaxis; eye and ear infections; infected skin disorders.

Pfizer Consumer, Canad.
Eye ointment; ointment: Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3).
Eye and ear infections; infected lesions.

Polysporin Complete Antibiotic *Pfizer Consumer, Canad.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); gramicidin (p.286·1); lidocaine (p.1862·3).
Burns; itching; wounds.

Polysporin Itch Relief *Pfizer Consumer, Canad.*
Pramocaine hydrochloride (p.1868·1); zinc acetate (p.1999·1).
Formerly known as Polysporin Pain & Itch.
Insect bites; minor cuts and abrasions; skin irritation.

Polysporin For Kids *Pfizer Consumer, Canad.*
Polymyxin B sulfate (p.317·3); gramicidin (p.286·1); lidocaine hydrochloride (p.1862·3).
Burns; wounds.

Polysporin Plus Pain Relief *Pfizer Consumer, Canad.*
Polymyxin B sulfate (p.317·3); gramicidin (p.286·1); lidocaine hydrochloride (p.1862·3).
Infected burns and wounds; skin pain.

Polysporin Triple Antibiotic *Pfizer Consumer, Canad.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); gramicidin (p.286·1).
Burns; minor wounds.

Polystafana *Sevapharma, Cz.*
A staphylococcal vaccine (p.2239·3).
Active immunisation.

Polysteron 250 *Organon, Venez.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).

Polytab *Pharmasant, Thai.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; pruritus; reduced appetite.

Polytabs-F *Major, USA.*
Multivitamin preparation with fluoride (p.1922·1)(p.1962·2).
Dental caries prophylaxis; dietary supplement.

Polytamin *Brench, Ger.†.*
Vitamins; rutoside; adenosine; aminobenzoic acid; linoleic acid; yeast; minerals; procaine hydrochloride (p.1869·1) (p.1922·1).
Atherosclerosis; tonic.

Polytanol *Pharmasant, Thai.*
Amitriptyline hydrochloride (p.376·1).
Depression; mixed anxiety depressive states.

Polytar
Note.This name is used for preparations of different composition.
Stiefel, Austral.; Stiefel, Braz.; Stiefel, Cz.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Indon.; Stiefel, Irl.; Stiefel, Israel; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Philipp.; Stiefel, Port.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.
Tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2).
Scalp disorders; skin disorders.

Stiefel, Canad.
Wood tar (p.1616·2); mineral tar (p.1616·2).
Seborrhoeic dermatitis.

Stiefel, Pol.; Stiefel, USA.
Coal tar (p.1616·2).
Skin and scalp disorders.

Stiefel, Spain.
Tar (p.1616·2); juniper oil (p.2328·3); coal tar (p.1616·2).
Skin and scalp disorders.

Polytar AF
Note.This name is used for preparations of different composition.
Stiefel, Canad.
Coal tar (p.1616·2); dipyrithione (p.1595·1); salicylic acid (p.1612·2); menthol (p.2340·1).
Scalp disorders.

Stiefel, Cz.; Stiefel, Hung.; Stiefel, UK.
Tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2); pyrithione zinc (p.1611·2).
Scalp disorders.

Stiefel, Pol.
Coal tar (p.1616·2); pyrithione zinc (p.1611·2).
Scalp disorders.

Polytar Emollient *Stiefel, Hong Kong; Stiefel, Irl.†; Stiefel, NZ; Stiefel, UK.*
Tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2); liquid paraffin (p.2030·3).
Aid to ointment and paste removal in psoriasis; skin disorders.

Polytar Liquid *Stiefel, UK.*
Tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2).
Aid to ointment and paste removal in psoriasis; scalp disorders.

Polytar Plus
Note.This name is used for preparations of different composition.
Stiefel, Austral.
Coal tar (p.1616·2).
Scalp disorders.

Stiefel, NZ; Stiefel, UK.
Tar (p.1616·2); cade oil (p.1616·1); coal tar (p.1616·2).
Aid to ointment removal in psoriasis; scalp disorders.

Poly-Tears *Alcon, Austral.; Alcon, NZ.*
⊗ Hypromellose (p.2144·2); dextran 70 (p.1059·3).
Dry eyes.

Polytonyl *UPSA Conseil, Fr.†.*
Vitamin, mineral, and amino-acid preparation (p.1922·1).
Tonic.

Polytopic
Note.This name is used for preparations of different composition.
Sandoz, Canad.
Cream: Polymyxin B sulfate (p.317·3); gramicidin (p.286·1).

Sandoz, Canad.
Ointment: Polymyxin B sulfate (p.317·3); bacitracin (p.210·3).
Infected lesions.

Polytracin *Medical Ophthalmics, USA.*
Bacitracin (p.210·3); polymyxin B (p.318·2).
Eye infections.

Polytrim
GSK, Austria; GSK, Belg.; GSK, Neth.; GSK, S.Afr.†; Pliva, UK†; Allergan, USA.
Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial infections of the eyes and skin.

Allergan, Canad.; GSK, Turk.
Trimethoprim sulfate (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Poly-Tussin *Pharmakon, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Polyvaccinum *Biomed Krakow, Pol.*
Staphylococcus aureus; *Staphylococcus epidermidis*; *Streptococcus pyogenes*; *Streptococcus salivarius*; *Streptococcus pneumoniae*; *Escherichia coli*; *Klebsiella pneumoniae*; *Haemophilus influenzae*; *Corynebacterium pseudodiphtheriticum*; *Moraxella catarrhalis*.
Catarrh; neuralgia; respiratory-tract inflammation; urogenital inflammation.

Polyvalent Snake Antivenom *CSL, Austral.*
A snake antiserum of king brown snake, tiger snake, brown snake, death adder and taipan (p.2238·2).
Passive immunisation.

Poly-Vi-Flor *Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, USA.*
Fluoride (p.1962·2) and vitamin preparation with or without iron (p.1922·1).
Dental caries prophylaxis; dietary supplement.

Poly-Vi-Fluor *Mead Johnson, Braz.*
Multivitamin preparation (p.1922·1) with fluoride (p.1962·2).
Dietary supplement.

Poly-Visc *Alcon, NZ.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Eye lubrication and protection.

Poly-Vi-Sol *BMS, Arg.; Mead Johnson Nutritionals, Canad.; Mead Johnson, Hong Kong; BMS, Mex.; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.†; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Vitamin preparation (p.1922·1).
Formerly known as Enfalac Poly-Vi-Sol in *Canad.*
Dietary supplement.

Polyvit
Note.This name is used for preparations of different composition.
Pharmasant, Thai.
Ferrous fumarate (p.1938·3); riboflavin; vitamin C; folic acid; citric acid (p.1922·1).
Anaemias; vitamin supplement.

Taro, Israel.
Oral drops: Multivitamin preparation (p.1922·1).

Taro, Israel†.
Tablets: Multivitamin and mineral preparation with ginseng (p.1922·1).

Polyvit 30 Plus *Taro, Israel.*
Multivitamin and mineral preparation with ginseng and rutoside (p.1922·1).

Polyvitaplex *Sanofi-Aventis, Hung.*
Vitamin preparation (p.1922·1).
Vitamin deficiency.

Polyxan-Blau N *Ritsert, Ger.*
Homoeopathic preparation.

Polyxan-Blau N comp *Ritsert, Ger.*
Homoeopathic preparation.

Polyxan-Gelb N *Ritsert, Ger.*
Homoeopathic preparation.

Polyxan-Gelb N comp *Ritsert, Ger.*
Homoeopathic preparation.

Polyxan-Grun N *Ritsert, Ger.*
Homoeopathic preparation.

Polyxan-Grun N comp *Ritsert, Ger.*
Homoeopathic preparation.

Polyxen *Pharmasant, Thai.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Polyxicam *Pharmasant, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Polyxit *Pharmasant, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Polyzalip *Pharmasant, Thai.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Polyzym
Note.This name is used for preparations of different composition.
Alcon, Austral.†; Alcon, Braz.; Alcon, Fr.†; Alcon, S.Afr.
Pancreatin (p.2360·1) (p.1622·2).
Contact lens cleaner.

Alcon, NZ.
Cleaning of soft and gas-permeable contact lenses (p.1622·2).

Pomacetin *Neckerman, Braz.†.*
Neomycin (p.305·1); bacitracin (p.210·3).

Pomada Antibiotica *Desma, Spain.*
Bacitracin (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Burns; skin infections; ulcers; wounds.

Pomada Antihemorroidal *Drag, Chile†.*
Zinc (p.1999·1); lidocaine (p.1862·3).
Haemorrhoids.

Pomada Heridas *Asens, Spain†.*
Benzalkonium chloride (p.1629·1); phenazone (p.116·1); sulfanilamide (p.343·1); zinc oxide (p.1621·2).
Skin infections.

Pomada Infantil Vera *Labitec, Spain†.*
Bismuth subnitrate (p.1711·2); boric acid (p.2268·1); talc (p.1615·2); zinc oxide (p.1621·2).
Skin irritation.

Pomada Minancora *Minancora, Braz.*
Benzalkonium chloride (p.1629·1); zinc oxide (p.1621·2); camphor (p.2273·2).
Skin disorders.

Pomada Vitaminica *Pasteur, Chile.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); dexpanthenol (p.2362·1); zinc oxide (p.1621·2).
Skin disorders; wounds.

Pomada Wilfe *Perez Gimenez, Spain.*
Sulfanilamide (p.343·1); sulfathiazole (p.343·2).
Skin infections.

Pomaderme *Legrand, Braz.*
Theobroma oil; boric acid (p.2268·1); zinc oxide (p.1621·2); talc (p.1615·2).
Skin disorders.

Pomadom *Pharmasant, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; epilepsy.

Pomag *KG, Ital.*
Magnesium citrate (p.1743·2); potassium aspartate (p.1684·2); potassium phosphate (p.1682·2).
Magnesium and potassium supplement.

Pomat Ichthyole *Aroma, Turk.*
Ichthammol (p.1599·1).
Eczema.

Pommade au Baume *Zeller, Switz.*
Baume Zeller (sumatra benzoin (p.2394·2), tolu balsam (p.1574·2), myrrh (p.2349·2), red-poppy petal (p.1472·3), absinthium (p.2244·1), achillea (p.2245·2), guaiacum resin (p.2317·3), tormentil (p.2403·2), incense); peru balsam (p.2365·3); camphor (p.2273·2); zinc oxide (p.1621·2); turpentine oil (p.2406·3).
Minor burns and abrasions; skin irritation.

Pommade Congo *Thaler, Switz.†.*
Zinc oxide (p.1621·2).
Minor burns and wounds.

Pommade Ichthyole *Gunsa, Turk.*
Ichthammol (p.1599·1).
Eczema.

Pommade Lelong *Zambon, Fr.†.*
Peru balsam (p.2365·3); vitamin A (p.1971·2).
Skin disorders.

Pommade Maurice *Cooperation Pharmaceutique, Fr.*
Yellow mercuric oxide (p.2341·2).
Eye infections.

Pommade Mo Cochon *Tradiphar, Fr.*
Salicylic acid (p.1612·2).
Callus; corns; verrucae.

Pommade nasale de Nager *Streuli, Switz.*
Camphor oil (p.2273·3); mint oil (p.2345·2).
Nasal congestion.

Pommade Nasale Radix *Streuli, Switz.†.*
Lavender oil (p.2331·2); mint oil (p.2345·2); camphor (p.2273·2); hamamelis (p.2318·2); sea salt (p.1686·1).
Nasal dryness.

Pommade nasale de Ruedi *Streuli, Switz.*
Camphor oil (p.2273·3); mint oil (p.2345·2).
Nasal congestion; nasal dryness.

Pompaton *Nufarindo, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Ponac *Continental Ethicals, S.Afr.*
Mefenamic acid (p.80·1).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Ponalar *Godecke, Ger.†; Coronet, Indon.*
Mefenamic acid (p.80·1).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ponalgic *Antigen, Irl.*
Mefenamic acid (p.80·1).
Menorrhagia; musculoskeletal and joint disorders; pain.

Ponaris *Panalab, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Poncodryl *Armoxindo, Indon.*
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1); sodium citrate (p.1673·3).
Cough.

Poncodryl DMP *Armoxindo, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cold symptoms; cough.

Poncofen *Armoxindo, Indon.*
Mefenamic acid (p.80·1).
Pain.

Poncoflox *Armoxindo, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Poncohist *Armoxindo, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic skin disorders; rhinitis.

Poncolin *Armoxindo, Indon.*
⊗ Chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); sodium citrate (p.1673·3); guaifenesin (p.1561·3).
Cough.

Poncolin D *Armoxindo, Indon.*
⊗ Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); sodium citrate (p.1673·3).
Cough; respiratory-tract congestion.

Ponconeuron *Armoxindo, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis; vitamin B deficiency.

Poncoquin *Armoxindo, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Poncosolvon *Armoxindo, Indon.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Pondactil *Pond's, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Pondactone *Pond's, Thai.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; ascites; hypertension; oedema.

Pondarmett *Pond's, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pondera *Eurofarma, Braz.*
Paroxetine hydrochloride (p.414·2).
Depression.

Pondex *Dexa, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Pondicilina *Nycomed, Braz.*
Cetalkonium chloride (p.1634·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Pondnacef *Pond's, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Pondnadysmen *Pond's, Thai.*
Mefenamic acid (p.80·1).
Pain.

Pondnoxcill *Pond's, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Pondocillin *Leo, Canad.; Leo, Denm.; Leo, Norw.; Leo, Swed.*
Pivampicillin (p.316·3).
Bacterial infections.

Pondperdone *Pond's, Thai.*
Domperidone (p.1726·2).
Dyspepsia; gastrointestinal disorders; nausea and vomiting.

Ponds Prevent *Unilever, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Pondtroxin *Pond's, Thai.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Pondusvitam *IQB, Braz.*
Buclizine (p.570·1); vitamin B substances (p.1922·1).
Reduced appetite; tonic.

Ponflu *Armoxindo, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Cough; influenza symptoms.

Pongesic *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Mefenamic acid (p.80·1).
Pain.

Ponmel *PannonPharma, Hung.; Clonmel, Irl.*
Mefenamic acid (p.80·1).
Pain.

Ponnesia *Asian Pharm, Thai.*
Mefenamic acid (p.80·1).
Pain.

Ponostop *Ni-The, Gr.*
Diethylamine salicylate (p.47·2); camphor (p.2273·2); capsaicin (p.32·3).
Topical relief of rheumatic and other pain.

Ponotex *Adelco, Gr.*
Aspirin (p.20·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Pain.

Ponoxylan *Aventis, NZ†.*
Polynoxylin (p.1658·3).
Skin infections.

Ponsamic *Guardian, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Ponser *Medhaus, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Ponsolit *Biomedica-Chemica, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Ponstan *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.†; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Chemidex, Irl.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer Consumer, NZ; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore†; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Chemidex, UK; Pfizer, Venez.*
Mefenamic acid (p.80·1).
Dysfunctional uterine bleeding; dysmenorrhoea; fever; inflammation; menorrhagia musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; premenstrual syndrome.

Ponstel *Adcock Ingram, S.Afr.; Parke, Davis, USA.*
Mefenamic acid (p.80·1).
Fever; menorrhagia; pain.

Ponstelax *Combiphar, Indon.*
Mefenamic acid (p.80·1).
Pain.

Ponstil *Elea, Arg.*
Mefenamic acid (p.80·1).
Fever; inflammation; menorrhagia; pain.

Ponstil Mujer *Elea, Arg.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Ponstin *Elea, Arg.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Ponstinetas *Elea, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ponstyl *Pfizer, Fr.*
Mefenamic acid (p.80·1).
Pain.

Pontacid *Duopharma, Hong Kong.*
Mefenamic acid (p.80·1).
Pain.

Pontalon *YSP, Malaysia; Yung Shin, Singapore.*
Mefenamic acid (p.80·1).
Pain.

Pontalsic *Bayer, Spain.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Pontaser *Roddensers, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Pontef *Tolmann, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Pontefix *Fimo, Ital.*
Zinc phosphate (p.2000·1).
Cement in dentistry.

Ponti *Sophia, Mex.*
Tetracaine (p.1871·2).
Local anaesthesia.

Pontin *Hexal, Braz.†.*
Mefenamic acid (p.80·1).
Fever; inflammation; pain.

Pontiride *Psicofarma, Mex.*
Sulpiride (p.1028·3).
Anxiety disorders; depression; lactation disorders; movement disorders; obsessive-compulsive disorder; peptic ulcer; schizophrenia; vertigo.

Pontizoc *Nufarindo, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Pontocaine
Hospira, Canad.; Sanofi Winthrop, Israel†.
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Hospira, USA.
Tetracaine (p.1871·2) or tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Pontuc *Novartis, Austria.*
Codergocrine mesilate (p.363·3); nifedipine (p.1350·1).
Hypertension.

Pontyl *Malaysia Chemist, Singapore†.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Pool 8 *Fiori, Ital.*
Amino-acid preparation (p.1922·1).
Nutritional supplement.

Popis *Med-Care, Turk.*
Barrier cream.

Po-Pon-S *Shionogi, USA.*
Multivitamin and mineral preparation (p.1922·1).

POR 8 *Ferring, Austral.; Ferring, Austria; Pharmaco, NZ; Ferring, S.Afr.*
Ornipressin (p.2358·2).
Reduction of bleeding during surgery; variceal haemorrhage.

Poral *Sons, Mex.*
⊗ Chloramphenicol (p.239·3); hydrocortisone (p.1535·2).
Infected eye disorders.

Porazine *Pharmasant, Thai.*
Perphenazine (p.1017·1).
Anxiety; nausea and vomiting.

Porcelana Daytime Formula *Schwarzkopf, Canad.†.*
Hydroquinone (p.1598·2); octinoxate (p.1608·2).

Porcelana Nighttime Formula *Schwarzkopf, Canad.†.*
Hydroquinone (p.1598·2).

Porcoll *MBP, Ger.†.*
Collagen (p.2286·1).
Haemorrhage.

Poremax-C *Orion, Fin.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Porfirin 12 *Teofarma, Ital.*
Haematoporphyrin dihydrochloride (p.2318·1); cyanocobalamin (p.1980·2); inositol (p.2325·2).
Tonic.

Pork Actrapid *Novo Nordisk, UK†.*
⊗ Insulin injection (porcine, highly purified) (p.443·2).
Diabetes mellitus.

Pork Insulatard *Novo Nordisk, UK†.*
⊗ Isophane insulin injection (porcine, highly purified) (p.443·2).
Diabetes mellitus.

Pork Mixtard 30 *Novo Nordisk, UK†.*
⊗ Mixture of neutral insulin injection (porcine, highly purified) 30% and isophane insulin injection (porcine, highly purified) 70% (p.443·2).
Diabetes mellitus.

Pormus *Unison, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Peri-articular disorders; skeletal muscle pain; tension headache.

Poro *YSP, Malaysia; Yung Shin, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Porosal *Alian, Venez.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Porphin *Crawford, UK.*
5-Aminolevulinic acid (p.679·2).
Available only on a named patient basis.
Precancerous skin disorders; skin cancer.

Porphyrocin *Medochemie, Hong Kong†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Porpovan *Cristalia, Braz.*
Propofol (p.1791·1).
General anaesthesia.

Portagen *Mead Johnson, Austral.; Mead Johnson Nutritionals, Canad.; Mead Johnson Nutritionals, Fin.†; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Irl.†; Mead Johnson, Ital.; Mead Johnson, Malaysia†; BMS, Pol.; Mead Johnson, Pol.; Mead Johnson, Port.†; BMS, S.Afr.; Mead Johnson, Singapore†; Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).
Disorders of fat absorption and digestion; lactose intolerance.

Portal *Lek, Cz.; Lek, Hung.; Lek, Rus.*
Fluoxetine hydrochloride (p.391·2).
Anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder.

Portalac *Belupo, Rus.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Portamin *Darrow, Braz.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Portia *Barr, USA.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Portiron *Gedeon Richter, Hung.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension; stroke prophylaxis.

Portiv *Buxton, Arg.*
Pramipexole (p.814·2).
Parkinsonism.

Portolac *Novartis Consumer, Austria†; Novartis Consumer, Belg.; Novartis Consumer, Ital.; Shinyaku, Jpn.*
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy; hyperammonaemia.

Poruxin *Vianex (Βιανεξ), Gr.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Posalfilin *Norgine, Austral.; Norgine, Hong Kong†; Norgine, Irl.; Norgine, Malaysia†; Norgine, NZ; Norgine, S.Afr.; Norgine, Singapore†; Norgine, UK.*
Podophyllum resin (p.1610·2); salicylic acid (p.1612·2).
Warts.

Posanin *Pose, Thai.*
Dipyridamole (p.1268·1).
Ischaemic heart disease; thrombosis prophylaxis.

Posdrink *Catarinense, Braz.*
Aspirin (p.20·3); mepyramine maleate (p.585·2); caffeine (p.1116·3).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Pose-Bac *Pose, Thai.*
Benzalkonium chloride (p.1629·1).
Disinfection.

Pose-Crequat *Pose, Thai.*
Phenolic compound; quaternary ammonium compound.
Disinfection.

Pose-Cresol *Pose, Thai.*
Phenolic compound (p.1656·1).
Hand disinfectant.

Posedene *Pose, Thai.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Pose-Iodophore *Pose, Thai.*
Iodine (p.2169·2).
Disinfection.

Posene *Pose, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Posequat *Pose, Thai.*
Quaternary ammonium compound.
Disinfection.

Posequat with GA *Pose, Thai.*
Glutaral (p.1645·2); quaternary ammonium compound.
Disinfection.

Posicycline *Alcon, Fr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial eye infections.

Posid *Cadila, India; Pharmachemie, Philipp.*
Etoposide (p.718·1).
Malignant neoplasms.

Posidol *Pharmaland, Thai.*
Mebhydrolin napadisilate (p.584·3).
Hypersensitivity reactions.

Posidon *Darrow, Braz.*
Etoposide (p.718·1).
Malignant neoplasms.

Posifenicol *Ursapharm, Ger.*
Azidamfenicol (p.206·3).
Bacterial eye infections.

Posifenicol C *Ursapharm, Ger.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Posiformin *Ursapharm, Ger.*
Bibrocathol (p.2266·1).
Inflammatory eye disorders.

Posiject *Boehringer Ingelheim, Irl.†; Alliance, S.Afr.†; Boehringer Ingelheim, UK†.*
Dobutamine hydrochloride (p.1271·2).
Cardiac stress testing; heart failure.

Posine *Alcon, Fr.†.*
⊗ Oxedrine tartrate (p.1364·3); chlorhexidine gluconate (p.1635·3).
Conjunctival irritation.

Posinova *Orion, Fin.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Posipen *Sanfer, Mex.*
Dicloxacillin sodium (p.265·2).
Gram-positive bacterial infections.

Positivum *Sanova, Austria.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Positon *Iquinosa, Spain.*
⊗ Neomycin sulfate (p.305·1); nystatin (p.543·2); triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Posivil *Orion, Fin.†.*
Aspirin (p.20·3); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms; coughs.

Posivyl *Laboratorios Chile, Chile.*
Paroxetine hydrochloride (p.414·2).
Depression.

Poslov *Cifarma, Braz.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Posnac *Pose, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders.

Posorutin *Ursapharm, Ger.; Ursapharm, Pol.*
Troxerutin (p.2305·1).
Haemorrhoids; vascular eye disorders; venous insufficiency.

Pospargin *Kalbe, Indon.*
Methylergometrine maleate (p.2011·1).
Lochiometra; postpartum haemorrhage; third-stage labour management; uterine atony.

Postacne *Dermik, Canad.†.*
Colloidal sulfur (p.1614·1).
Acne.

Postadoxin N *Rodleben, Ger.*
Meclozine hydrochloride (p.584·3).
Motion sickness; nausea; vomiting.

Postadoxine
Note. This name is used for preparations of different composition.
UCB, Philipp.
Meclozine hydrochloride (p.584·3).
Nausea and vomiting.

UCB, Turk.
Meclozine hydrochloride (p.584·3); vitamin B (p.1978·2).
Motion sickness; nausea and vomiting.

Postafen
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Buclizine hydrochloride (p.570·1).
Reduced appetite.

UCB, Cz.†; UCB, Denm.; UCB, Fin.; UCB, Norw.; UCB, Swed.
Meclozine hydrochloride (p.584·3).
Allergic rhinitis; motion sickness; nausea; urticaria; vertigo; vomiting.

UCB, Ger.†.
Meclozine (p.585·1) or meclozine hydrochloride (p.584·3).
Hypersensitivity reactions; nausea; vomiting.

Postafene *UCB, Belg.; UCB, Gr.†; UCB, Hong Kong.*
Meclozine hydrochloride (p.584·3).
Motion sickness; nausea and vomiting; vertigo.

Postafeno *UCB, Port.†.*
Buclizine (p.570·1).

Postap *Pose, Thai.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Coughs; hypersensitivity reactions; nasal congestion.

Postap Expectorant *Pose, Thai.*
Guaifenesin (p.1561·3); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Coughs; hypersensitivity reactions; nasal congestion.

Postarax *Pose, Thai.†.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; nausea and vomiting; pruritus.

Post-Day *Investigacion, Mex.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Postec *Apsen, Braz.*
⊗ Hyaluronidase (p.2321·1); betamethasone valerate (p.1519·1).

Posterine *Kade, Ger.*
Hamamelis (p.2318·2).
Anorectal disorders.

Posterine Corte *Kade, Ger.†.*
⊗ Hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Posterisan *Mayrhofer, Austria†; Kade, Ger.; Kade, Hong Kong; Kade, Philipp.; Kade, Pol.; Kade, Rus.; Kade, Thai.†.*
Escherichia coli.
Anorectal disorders.

Posterisan cort *Kade, Ger.*
⊗ Hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Posterisan Forte *Kade, Ger.†; Kade, Hong Kong; Kade, Hung.; Kade, Rus.*
⊗ Cell components and metabolic products of *Escherichia coli*; hydrocortisone (p.1535·2).
Anorectal disorders.

Posterisan H *Kade, Pol.*
⊗ *Escherichia coli*; hydrocortisone (p.1535·2).
Anorectal disorders.

Posti N *Kade, Ger.†.*
Rutoside (p.2305·1); esculoside (p.2248·2).
Haemorrhoids; venous insufficiency.

Postinor *Medimpex, Austria; Mithra, Belg.; Gedeon Richter, Cz.; Medimpex, Denm.; Schering, Fin.†; Schering, Gr.; Gedeon Richter, Malaysia; Medimpex, Neth.; Medimpex, Norw.; Schering, Port.; Gedeon Richter, Rus.; Gedeon Richter, Singapore; Schering, Spain; Schering, Swed.; Gedeon Richter, Thai.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Postinor-2 *Gobbi, Arg.; Schering, Austral.; Ache, Braz.; Grunenthal, Chile†; Gedeon Richter, Hong Kong; Tunggal Idaman, Indon.; Gedeon Richter, Israel; DNA, Mex.; Schering, NZ; Medimpex, UK; Aciprosalud, Venez.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Postinor Uno *Ache, Braz.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Postinor-Duo *Richter, Pol.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

PostMI *Focus, UK†.*
Aspirin (p.20·3).
Angina; ischaemic heart disease; myocardial infarction.

Postop *Sensomed, Philipp.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Postopyl *LED, Fr.†.*
Fluoridated polymer; aloe vera (p.1588·2).
Minor skin damage.

Postotic *Sensomed, Philipp.*
⊗ Dexamethasone (p.1526·1); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected ear disorders.

Postoval
Note. This name is used for preparations of different composition.
Wyeth, Braz.†; Wyeth, Chile†.
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; levonorgestrel (p.2121·2).
Menopausal disorders; menstrual disorders.

Akromed, S.Afr.
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2); 7 tablets, inert.
Menopausal disorders; menstrual disorders.

Postuitrin *Ulagay, Turk.*
Oxytocin (p.2015·2).
Caesarean section; incomplete abortion; labour induction; postpartum haemorrhage.

Posture *Whitehall, USA.*
Calcium phosphate (p.1676·2).
Calcium supplement.

Posture D *Wyeth, Mex.*
Tribasic calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteomalacia; osteoporosis; rickets; tetanus.

Posture-D *Whitehall, USA.*
Calcium phosphate (p.1676·2); vitamin D (p.1986·1).
Calcium supplement.

Posyd *Pharmachemie, Indon.*
Etoposide (p.718·1).
Malignant neoplasms.

Potaba *Glenwood, Austria; Glenwood, Canad.; Glenwood, Ger.; IFET (ΙΦΕΤ), Gr.; Glenwood, UK; Glenwood, USA.*
Potassium aminobenzoate (p.2371·1).
Dermatomyositis; morphoea; pemphigus; Peyronie's disease; polymyositis; scleroderma.

Potable Aqua *IBIS, UK; Wisconsin Pharmacal, USA.*
Tetraglycine hydroperiodide (p.1663·3).
Disinfection of drinking water.

Potacol-R *Otsuka, Indon.; Otsuka, Jpn.*
Electrolyte infusion with maltose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders; metabolic acidosis.

Potasalan *Lannett, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Potasi *Eagle, Austral.*
Dibasic potassium phosphate (p.1682·2); potassium citrate (p.1673·2); potassium aspartate (p.1684·2); potassium orotate (p.2358·3).
Potassium supplement.

Potasico *Bieffe, Spain.*
Potassium chloride (p.1684·3); sodium chloride (p.1686·1).
Diabetic ketoacidosis; hypokalaemia.

Potasio C *Dominguez, Arg.*
Potassium chloride (p.1684·3); sodium ascorbate (p.1984·1).
Electrolyte supplement.

Potasion *Sanofi-Aventis, Spain.*
Potassium chloride (p.1684·3).
Potassium depletion.

Potasion Solucion *Sanofi-Aventis, Spain.*
Potassium gluceptate (p.1685·1).
Hypokalaemia.

Potasoral *Armstrong, Mex.*
Potassium gluconate (p.1684·3).
Hypokalaemia.

Potassion *Miba, Ital.*
Potassium succinate (p.1685·1); potassium malate (p.1685·1); potassium citrate (p.1673·2); potassium acid tartrate (p.1764·1); potassium bicarbonate (p.1673·1).
Acidosis; potassium deficiency.

Potassium Iodide and Stramonium Compound *McGloin, Austral.†.*
⊗ Potassium iodide (p.2169·2); stramonium (p.2392·3); lobelia (p.2157·2); liquorice (p.1740·3).
Coughs; respiratory-tract congestion.

Potassium MG *Miba, Ital.†.*
Potassium gluconate (p.1684·3); magnesium hydroxide (p.1743·2).
Magnesium and potassium supplement.

Potassium-Rougier *Rougier, Canad.†.*
Potassium gluconate (p.1684·3).
Potassium supplement.

Potassride *General Drugs, Thai.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Pota-Vi-Kin *Collins, Mex.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Potazen *Medikon, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Potcit *CCM, Malaysia; Beacons, Singapore.*
Potassium citrate (p.1673·2); citric acid (p.2284·1).
Alkalinisation of urine; potassium supplement; urinary-tract infections.

Pot-Citra *Hoe, Malaysia.*
Potassium salts (p.1684·2).
Acidosis; alkalinisation of urine; gout; potassium supplement.

Potekam *Dosa, Arg.*
Topotecan (p.780·2).
Malignant neoplasms.

Poten-Cee *Pascual, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Potenciator *Iquinosa, Spain.*
Arginine aspartate (p.1928·2).
Tonic.

Potencil *Sanitas, Arg.*
Cyproheptadine hydrochloride (p.575·1); arginine hydrochloride; cobamamide (p.1922·1).
Anabolic; reduced appetite.

Potencort *Julphar, UAE.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Potensium gelule *Arkopharma, Fr.*
Potassium bicarbonate (p.1673·1).
Potassium supplement.

Potensium sel de table *Arkopharma, Fr.*
Potassium bicarbonate (p.1673·1); sodium chloride (p.1686·1).
Table salt substitute.

Potensone *Pharmasant, Thai.†.*
Fluphenazine hydrochloride (p.998·1).
Anxiety.

Potentol *Orion, Fin.†.*
⊗ Methyltestosterone (p.2117·1); meprobamate (p.1006·2); yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Potenzia *Lifeplan, UK.*
Vitamins; minerals; saw palmetto; pygeum africanum; urticaria; bearberry; curcumin; tomato (p.1922·1).
Dietary supplement for men.

Potesept *ICN, Hung.†.*
Sulfadimidine (p.338·1); trimethoprim (p.355·2).
Bacterial infections.

Potional *Kleva, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Potklor *Bushnell, India.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Po-Trim *Polipharm, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Potsilo N *Stark, Ger.*
Bisacodyl (p.1710·1); calcium pantothenate (p.1959·3).
Constipation.

Potter's Catarrh Pastilles *Ernest Jackson, UK.*
Pine silvestris oil (p.2368·2); pumilio pine oil (p.2376·3); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); althaea (p.2253·3).
Cough and cold symptoms.

Potters Children's Cough Pastilles *Ernest Jackson, UK.*
Ipecacuanha (p.1562·3); squill (p.1573·1); citric acid (p.2284·1); honey (p.1948·2).
Formerly known as Jacksons Childrens Cough Pastilles.
Coughs.

Potters Decongestant Pastilles *Ernest Jackson, UK.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Coughs; nasal congestion.

Potters Gees Linctus *Ernest Jackson, UK.*
Camphorated opium tincture; squill (p.1573·1); cinnamic acid (p.1640·3); benzoic acid (p.1630·2); glacial acetic acid (p.2244·2); honey (p.1948·2).
Coughs.

Potters Strong Bronchial Catarrh Pastilles *Ernest Jackson, UK.*
Menthol (p.2340·1); benzoin tincture (p.2394·2); anise oil (p.2258·2); peppermint oil (p.1761·2); capsicum oleoresin (p.2276·2).
Catarrh; coughs and cold symptoms.

Potters Sugar Free Cough Pastilles *Ernest Jackson, UK.*
Liquorice (p.1740·3); menthol (p.2340·1); benzoin tincture (p.2394·2); anise oil (p.2258·2); clove oil (p.2285·1); peppermint oil (p.1761·2); capsicum oleoresin (p.2276·2).
Catarrh; cold symptoms; coughs.

Potussan *Pharmasant, Thai.*
Dextromethorphan (p.1555·2).
Coughs.

Poudre du Marcheur *Laphi, Fr.*
Irgasan (p.1665·2); lavender oil (p.2331·2); lemon oil (p.2332·3); pine oil (p.2368·2); zinc oxide (p.1621·2); talc (p.1615·2); starch (p.1968·1).
Foot hygiene; hyperhidrosis.

Poudre Velours *Eurogenerics, Belg.*
Ichthammol (p.1599·1).
Skin disorders.

Povadine *Hua, Thai.*
Povidone-iodine (p.1659·2).
Burns; wound disinfection.

Povanil *Pharmasant, Thai.*
Clonazepam (p.478·2).
Epilepsy.

Povanyl *Omega, Fr.*
Pyrvinium embonate (p.155·3).
Enterobiasis.

Povi Complex *Hexa, Arg.*
Povidone-iodine (p.1659·2).
Skin, mucous membrane, and instrument disinfection.

Povibac *Sertex, Arg.*
Povidone-iodine (p.1659·2).
Skin infections; skin, mucous membrane, wound, and burn disinfection.

Povicler *Monserrat, Arg.*
Povidone-iodine (p.1659·2).
Disinfection.

Poviderm *Farmec, Ital.; Hoe, Malaysia.*
Povidone-iodine (p.1659·2).
Burns; skin and wound disinfection; skin infections; wounds.

Povidine *Stadmed, India; Phoenix, Philipp.; Pharmacia, Venez.†.*
Povidone-iodine (p.1659·2).
Burns; mouth infections; mucous membrane, skin, and wound disinfection; skin infections; vaginal infections; wounds.

Povin *Andromaco, Chile.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); pantothenilic alcohol; zinc oxide (p.1621·2).
Skin disorders.

Poviral *Roemmers, Arg.*
Aciclovir (p.862·3).
Herpesvirus infections.

Poviseptin *Cagdas, Turk.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Povitiol *Biosintex, Arg.*
Povidone-iodine (p.1659·2).
Disinfection.

Powdered C *GNLD, Austral.*
Ascorbic acid and other vitamin C substances (p.1922·1).
Vitamin C deficiency.

Power Orot *Worwag, Ger.*
Magnesium orotate (p.2358·3).
Magnesium deficiency.

Power plus power *Ipca, India†.*
Multivitamin and mineral preparation (p.1922·1).

Powercef *Wockhardt, India.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Powercort *Glenmark, Singapore.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Powergel *Menarini, UK.*
Ketoprofen (p.73·1).
Soft-tissue injury.

Powergyl *Cipla, India.*
Norfloxacin (p.309·2); metronidazole (p.837·1).
Bacterial infections.

PowerMate *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; green tea extract; ginkgo biloba extract; glutathione; acetylcysteine; echinacea; golden seal root; pine bark extract (p.1922·1).
Tonic.

PowerSleep *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; passion flower; valerian; oxitriptan; melatonin (p.1922·1).
Tonic.

PowerVites *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; aminobenzoic acid; inositol; bioflavonoids; bee pollen; folic acid (p.1922·1).
Tonic.

Pozapam *Pharmasant, Thai.*
Prazepam (p.1019·3).
Anxiety.

Pozato *Libbs, Braz.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Pozhexol *Pharmasant, Thai.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

Pozitron-Scan-FDG *Pozitron, Hung.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide for detection of malignant neoplasms by positron-emission tomography.

PPB *Medisys, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Nasal congestion.

PPG *Bago, Chile.*
Policosanol (p.1373·3).
Hypercholesterolaemia.

PPS *Baxter, Ital.*
⊗ Plasma protein fraction (p.1076·2).
Burns; hypovolaemia; shock.

PPSB Conc SD *CAF-DCF, Belg.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

PPSB Konzentrat S-TIM *Baxter BioScience, Ger.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

PR21 *Sigma, Arg.*
Saw palmetto (p.2192·3); pollen (p.2370·2); tomato.
Benign prostatic hyperplasia.

PR Freeze Spray *Crookes Healthcare, UK.*
Dimethyl ether (p.1689·2); dimethoxymethane (p.2294·1).
Muscular pain and stiffness.

PR Heat Spray *Crookes Healthcare, UK.*
Methyl salicylate (p.85·3); ethyl nicotinate (p.52·1); camphor (p.2273·2).
Bruises; muscular and rheumatic pain; sprains.

Pra-Brexidol *Pharmacia, Ger.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Pracap *Darrow, Braz.*
⊗ Finasteride (p.2188·3).
Alopecia.

Pracem *Novag, Mex.*
Dipyridamole (p.1268·1).

Pracne *Grunenthal, Chile.*
Minocycline (p.300·3).
Bacterial infections.

Practazin *Pfizer, Fr.*
⊗ Spironolactone (p.1400·1); altizide (p.1209·1).
Hypertension; oedema.

Practil *Organon, Ital.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Practin *Merind, India.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity disorders; migraine.

Practiser *Serral, Mex.*
Diclofenac (p.44·2).
Inflammation; pain.

Practizol *Collins, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Practo-Clyss *Braun, Belg.; Fresenius Kabi, Ger.; Braun, Switz.†.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Practomil *Braun, Switz.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Practon *Pfizer, Fr.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; myasthenia; oedema.

Pradamin *Valmor, Venez.†.*
Metoclopramide (p.1747·3).

Pradaxa *Boehringer Ingelheim, Cz.; Boehringer Ingelheim, UK.*
Dabigatran etexilate mesilate (p.1254·3).
Thromboembolism prophylaxis following orthopaedic surgery.

Pradente *Dinafarma, Braz.†.*
Procaine hydrochloride (p.1869·1); phenol (p.1656·1).
Mouth and throat disorders.

Pradex *Merck, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Pradif *Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Switz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Pradinolol *Ducto, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Arrhythmias; hypertension.

Praeciglucon *Pfleger, Ger.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Praecineural *Pfleger, Ger.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Glycine (p.1947·3) is included in the tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain; rheumatism.

Praecordin S *Altana, Ger.†.*
Strong camphor oil (p.2273·3); menthol (p.2340·1); benzyl nicotinate (p.28·1).
Cardiac disorders.

Praedex *Fresenius Kabi, Austria.*
⊗ Dextran 1 (p.1058·3).
Prevention of anaphylactic reactions to infusions of dextrans.

Praedyn *Leciva, Cz.†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; male and female infertility.

Praefeminon plus *Cesra, Ger.†.*
Ferric ammonium citrate (p.1938·1); pulsatilla pratensis; valeriana officinalis.
Gynaecological disorders.

Prafamoc *Prafa, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Pragesol *Novell, Indon.*
Dipyrone (p.49·2).
Fever; pain.

Pragmatar
Note. This name is used for preparations of different composition.
GSK, India.
Benzoic acid (p.1630·2); salicylic acid (p.1612·2); menthol (p.2340·1); camphor (p.2273·2).
Dandruff; fungal skin infections; seborrhoeic dermatitis.

Alliance, Irl.; Alliance, UK†.
Coal tar (p.1616·2); sulfur (p.1614·1); salicylic acid (p.1612·2).
Dandruff; scalp disorders; skin disorders.

Pragmaten *Sanofi-Aventis, Chile.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states.

Prairie Gold *Larkhall Laboratories, UK.*
Vitamin E (p.1992·2).

Praize *Ipca, India.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Praize-D *Ipca, India.*
Pantoprazole (p.1760·1); domperidone (p.1726·2).
Gastro-oesophageal reflux.

Prakten *Ilsan, Turk.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; migraine.

Pralax *Pratapa Nirmala, Indon.*
Lactulose (p.1738·2).
Constipation.

Pralenal *Opus, UK†.*
Enalapril maleate (p.1276·1).
Angina pectoris; heart failure; hypertension.

Pralexin *Prafa, Indon.*
Cefalexin (p.218·2).
Bacterial infections.

Pralifan *Inibsa, Spain.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms; multiple sclerosis.

Pralol *Pharmasant, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; hypertension; migraine; myocardial infarction; tremor.

Pralotam *Mediapharm, Gr.*
Citalopram (p.385·3).
Depression.

Pram *Lannacher, Austria; Lannacher, Cz.; Lannacher, Rus.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

Pramace *AstraZeneca, Swed.*
Ramipril (p.1385·3).
Atherosclerosis; diabetic nephropathy; heart failure; hypertension.

Pramalon *Merck, S.Afr.*
Metoclopramide hydrochloride (p.1747·3).
Gastric hypomotility; gastrointestinal examination; nausea and vomiting.

Pramcil *Medipharm, Chile.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

PrameGel *Medicis, Canad.; Bioglan, USA.*
Pramocaine hydrochloride (p.1868·1); menthol (p.2340·1).
Pruritus.

Pramet *Abbott, Port.†.*
Multivitamin and mineral preparation (p.1922·1).

Pramet FA *Abbott, Hong Kong†.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Pramexyl *Epifarma, Ital.*
Citalopram hydrobromide (p.385·3).
Anxiety disorders; depression.

Pramidal *Probiomed, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Pramidalin *Ducto, Braz.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Pramide
Note. This name is used for preparations of different composition.
Winthrop, Port.
Pyrazinamide (p.320·2).
Tuberculosis.

Galeno, Venez.
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Pramidin *CSC, Austria; Medicom, Cz.†; Sirton, Ital.; Crinos, Pol.*
Metoclopramide hydrochloride (p.1747·3).
Diabetic gastroparesis; gastrointestinal disorders; nausea and vomiting.

Pramigel *Carnot, Mex.*
Metoclopramide hydrochloride (p.1747·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal disorders; migraine.

Pramil *Greenpharma, Braz.*
Metoclopramide (p.1747·3).
Gastrointestinal disorders; nausea and vomiting.

Pramilem *Lemery, Mex.*
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Pramilet *Abbott, Malaysia.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Dietary supplement during pregnancy and lactation.

Pramilet FA *Abbott, Singapore; Abbott, Thai.†.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Pramin *Alphapharm, Austral.; Rafa, Israel.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal examination; dyspepsia; gastroparesis; hiccups; nausea and vomiting; peptic ulcer.

Praminal *Merck, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Praminan *Cazi, Braz.*
Imipramine hydrochloride (p.400·3).
Depression.

Pramino *Janssen-Cilag, Cz.; Janssen-Cilag, Ger.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Acne; triphasic oral contraceptive.

Pramolan *Polpharma, Pol.*
Opipramol hydrochloride (p.414·1).
Depression; menopausal disorders; neurosis; sleep disorders.

Pramosone *Ferndale, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Skin disorders.

PramOtic *Hawthorn, USA.*
Chloroxylenol (p.1640·2); pramocaine hydrochloride (p.1868·1).
Bacterial infections of the external ear.

Pramotil *Pisa, Mex.†.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Pramox *Isdin, Spain; Hawthorn, USA.*
Pramocaine hydrochloride (p.1868·1).
Pruritus; skin irritation.

Pramox HC *Dermtek, Canad.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Skin disorders.

Pramur *Prafa, Indon.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones; hypercholesterolaemia; liver disorders.

Pranadox *Pisa, Mex.*
Zidovudine (p.913·3).
HIV infection.

Pranalip *Hexal, S.Afr.*
Pravastatin sodium (p.1374·3).
Coronary heart disease; hypercholesterolaemia.

Prandase *Bayer, Canad.; Agis, Israel.*
Acarbose (p.436·2).
Diabetes mellitus.

Prandin *Medley, Braz.; Novo Nordisk, Cz.; Novo Nordisk, Neth.; Novo Nordisk, Port.; Menarini, Spain; Daiichi Sankyo, UK; Novo Nordisk, USA.*
Repaglinide (p.457·2).
Formerly known as NovoNorm in the *UK*.
Diabetes mellitus.

Prandin E_2 *Pharmacia, S.Afr.*
Dinoprostone (p.2007·1).
Labour induction.

Pranex *Bayer, Venez.*
Acemetacin (p.15·1).
Inflammation; pain.

Pranix *Liferpal, Mex.*
Lansoprazole (p.1739·2).
Peptic ulcer.

Pranofen *Alcon, Gr.*
Pranoprofen (p.119·1).
Inflammatory eye disorders.

Pranoflog *SIFI, Ital.*
Pranoprofen (p.119·1).
Anterior eye inflammation.

Pranolal *Cazi, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Arrhythmias; hypertension.

Pranolol *Alpharma, Norw.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction; phaeochromocytoma; tremor.

Pranoral *Keyerson, Mex.†.*
⊗ Propranolol (p.1381·1).
Hypertension.

Pranosine *Sanfer, Mex.*
Inosine pranobex (p.884·2).
Viral infections.

Pranox *Meda, Belg.*
Pranoprofen (p.119·1).
Eye inflammation.

Prantal *Schering-Plough, Austral.; Schering-Plough, Ital.†; Schering-Plough, NZ.*
Diphemanil metilsulfate (p.2295·2).
Hyperhidrosis.

Pranzo *Vinas, Spain.*
Cyproheptadine hydrochloride (p.575·1); carnitine hydrochloride (p.1933·1); lysine hydrochloride (p.1955·1).
Anorexia; tonic.

Praoz *Actavis, Port.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Praquantel *Atlantic, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Prareduct *Sankyo, Belg.†; Sankyo, Spain.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia.

Prascolend *Ivax, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia.

Prasepine *Pfizer, Thai.*
Prazepam (p.1019·3).
Anxiety; skeletal muscle spasm.

Prasig *Sigma, Austral.†.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Prasikon *Polipharm, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Prasiver *Maver, Mex.*
Pravastatin (p.1375·1).

Prasterol *Lusofarmaco, Ital.*
Pravastatin sodium (p.1374·3).
Cardiovascular disorders; hypercholesterolaemia.

Prastin *Teva, Hung.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Pratazine *Sedabel, Braz.†.*
Sulfadiazine silver (p.337·2).
Skin infections.

Praten *Prafa, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Praticef *Caber, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Praticilin *Prati-Donaduzzi, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Pratiflip *Tiefenbacher, Neth.†.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pratropil *Fahrenheit, Indon.*
Piracetam (p.368·2).
Cerebral trauma; intellectual improvement in children; mental function impairment.

Pratsiol *Douglas, Austral.; Orion, Fin.; Douglas, NZ; Pharmacare, S.Afr.; Orion, Thai.†.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Praux *Fabop, Arg.*
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Prava
Note. This name is used for preparations of different composition.
BMS, S.Afr.
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

BMS, Switz.
Lomustine (p.741·1).
Malignant neoplasms.

Prava Basics *Basics, Ger.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravabeta *Betapharm, Ger.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravachol *BMS, Austral.; BMS, Austria; BMS, Canad.; BMS, Denm.; BMS, Fin.; BMS, Gr.; BMS, Hong Kong; BMS, Indon.; BMS, Malaysia; BMS, NZ; BMS, Norw.; BMS, Singapore; BMS, Swed.; BMS, Turk.; BMS, USA.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia; transplant rejection; unstable angina pectoris.

Pravacol *BMS, Arg.; BMS, Braz.; BMS, Chile; BMS, Mex.; BMS, Port.; BMS, Venez.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Pravadual *BMS, Fr.*
Aspirin (p.20·3); pravastatin (p.1375·1).
Cardiovascular risk reduction.

Pravafact *AG Therapy, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Pravagamma *Worwag, Ger.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravahelp *Help, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

PravaLich *Winthrop, Ger.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravalip
Mibe, Ger.; Lavipharm, Gr.
Pravastatin sodium (p.1375·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Trima, Israel.
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravalipem *Qualitec, Spain†.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hyperlipidaemias.

Pravalong *Faran, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Pravalotin *Mepha, Switz.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia; myocardial infarction; unstable angina pectoris.

Pravamel *Clonmel, Irl.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia; post-transplant hyperlipidaemia in patients on immunosuppressive therapy.

Pravandrea *Ratiopharm, Neth.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravanox *Verisfield, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Pravaselect *Menarini, Ital.*
Pravastatin sodium (p.1374·3).
Cardiovascular disorders; hypercholesterolaemia.

Pravasin *BMS, Ger.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravasine *BMS, Belg.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Pravasta eco *Ecosol, Switz.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia; myocardial infarction; unstable angina pectoris.

Pravastar *Apotex, Hung.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravat *Pinewood, Irl.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Pravatine *Spirig, Switz.*
Pravastatin sodium (p.1374·3).
Coronary heart disease; hypercholesterolaemia.

Pravator *Stancare, India.*
Pravastatin (p.1375·1).
Cardiovascular risk reduction; hyperlipidaemias.

Pravedol *Biomedica-Chemica, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Pravidel *Novartis, Ger.; Novartis, Swed.*
Bromocriptine mesilate (p.798·1).
Acromegaly; amenorrhoea; female infertility; galactorrhoea; hyperprolactinaemia; lactation inhibition; parkinsonism.

Pravidine *Arlex, Mex.*
Stavudine (p.907·1).
HIV infection.

Pravigard PAC *BMS, USA†.*
Tablets, aspirin (p.20·3); tablets, pravastatin sodium (p.1374·3).

Pravil *Duncan, Arg.*
Omeprazole (p.1753·1).
Peptic ulcer.

Pravin *Farmanic, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Pravitin *Rowex, Irl.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia; post-transplant hyperlipidaemia in patients on immunosuppressive therapy.

Pravlon *Prafa, Indon.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin disinfection.

Pravostin *Minerva (Μινέρβα), Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Prax *Ferndale, USA.*
Pramocaine hydrochloride (p.1868·1).
Local anaesthesia.

Praxedol *Probiomed, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Praxel *Laboratorios Chile, Chile; Lemery, Mex.; Lemery, Thai.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Praxilene *Merck, Belg.; Merck-Lipha, Fr.; Remek, Gr.; Merck, Hong Kong; Merck, Indon.; Merck, Irl.; Formenti, Ital.; Merck, Philipp.; Merck, Port.; Merck, Singapore; Faes, Spain; Merck, Switz.; Merck, Thai.; Merck, UK.*
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders; chronic venous ulcer; senile dementia.

Praxinor *Merck-Lipha, Fr.*
⊗ Theodrenaline hydrochloride (p.2400·1); cafedrine hydrochloride (p.1238·2).
Hypotension.

Praxion *Pharos, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Praxis *Ivax, Arg.*
Simeticone (p.1770·2); domperidone (p.1726·2); pancreatin (p.2360·1).
Gastrointestinal disorders.

Praxiten *Wyeth Lederle, Austria; Teofarma, Ger.*
Oxazepam (p.1014·2).
Anxiety disorders; sleep disorders.

Praxona *Roemmers Rowe, Venez.*
Carisoprodol (p.1894·1); dipyrone (p.49·2); salicylamide (p.121·2).
Muscle spasm; pain.

Prayanol *Sanitas, Chile.*
Amantadine hydrochloride (p.792·3).
Influenza; parkinsonism.

Prazac *Orion, Denm.*
Prazosin hydrochloride (p.1375·2).
Heart failure; hypertension; Raynaud's syndrome.

Prazam *Royal, Chile; Grunenthal, Port.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety-depressive states; panic disorder; premenstrual syndrome; sleep disorders.

Prazen *Delta, Braz.*
St John's wort (p.422·3).
Depression.

Prazene *Pfizer, Ital.*
Prazepam (p.1019·3).
Anxiety disorders; psychoneurotic disorders.

Prazentol *Tecnimede, Port.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazex *Sofex, Port.*
Omeprazole (p.1753·1).

Prazidec *Tecnofarma, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazina *Armoxindo, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Prazine
Note. This name is used for preparations of different composition.
Wyeth Lederle, Belg.†; Wyeth, Switz.
Promazine hydrochloride (p.1021·2).
Behaviour disorders in children; nausea; psychoses; sedative; vomiting.

IFET (ΙΦΕΤ), Gr.†.
Levomepromazine hydrochloride (p.1002·3).
Severe anxiety and agitation.

Prazinil *Pierre Fabre, Fr.*
Carpipramine hydrochloride (p.968·1).
Anxiety; psychoses.

Prazite *Asian Pharm, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Prazitral *LA, Arg.*
Praziquantel (p.153·3).
Worm infections.

Prazocip *Cipla, India.*
Prazosin hydrochloride (p.1375·2).

Prazohexal *Hexal, Austral.†.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Prazol
Note. This name is used for preparations of different composition.
Medley, Braz.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Polfa Pabianice, Pol.; Rowe-Fleming, Venez.†.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolan *Liomont, Mex.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolene *Tecnimede, Port.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolex *Greenpharma, Braz.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolin *Pharmanel, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Prazolit *Ivax, Mex.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prazolo *Mintlab, Chile†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Prazonil *Sanval, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Prazotec *Fahrenheit, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Prazotom *Tomnus, Braz.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pre Calent *Wierhom, Arg.*
Pine oil (p.2368·2); eucalyptus (p.2301·2); methyl salicylate (p.85·3); camphor (p.2273·2).
Musculoskeletal disorders.

Pre Clean Mom *Candioli, Ital.*
Permethrin (p.2048·2).
Pediculosis.

Pre Clor *Grin, Mex.*
⊗ Chloramphenicol (p.239·3); prednisone (p.1542·3).
Infected eye disorders.

Pre Dopa *Kyowa, Jpn.*
Dopamine hydrochloride (p.1273·2).
Shock.

Pre Natal *Cenovis, Austral.†.*
Omega-3 marine triglycerides (p.1362·2); folic acid (p.1940·1).
Fatty-acid supplement; prevention of neural tube defects.

Pre Nutrison *Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).

Preabor *Sanbe, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Preastig *Alfa Intes, Ital.*
Multivitamin and mineral preparation with glutathione (p.1922·1).
Nutritional supplement.

Pre-Attain *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Pre-Baby *Avanderm, Mex.*
Pregnancy test (p.2372·1).

Prebutix
Note. This name is used for preparations of different composition.
Pierre Fabre Sante, Fr.
Cream; gel: Ethyl butylacetylaminopropionate (p.2043·1); allantoin (p.1588·1); sunscreen.
Insect repellent.

Pierre Fabre Sante, Fr.
Lotion: Ethyl butylacetylaminopropionate (p.2043·1).
Insect repellent.

Pierre Fabre Sante, Fr.
Topical milk: Ethyl butylacetylaminopropionate (p.2043·1); dextran sulfate (p.2293·1).
Insect bites and stings; insect repellent.

Precaptil *Tecnofarma, Mex.*
Captopril (p.1239·2).
Hypertension.

Precar *Galeno, Venez.†.*
Dipyridamole (p.1268·1).
Heart failure.

Precardin *Farmedia, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

PreCare *Ther-Rx, USA.*
Multivitamin and mineral preparation (p.1922·1).

Precedex *Bago, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Cz.; Abbott, Hong Kong; Abbott, Israel; Abbott, Malaysia; Abbott, Mex.; InterMed, NZ; Abbott, Pol.; Abbott, Singapore†; Abbott, Thai.; Abbott, Turk.; Hospira, USA; Abbott, Venez.†.*
Dexmedetomidine hydrochloride (p.986·2).
Insomnia; postoperative sedation; sedation during surgery; sedation in intubated and mechanically ventilated patients.

Precef
Note. This name is used for preparations of different composition.
BMS, Belg.†.
Ceforanide (p.227·3); -lysine.
Bacterial infections.

Apothecon, Spain.
Cefprozil (p.232·2).
Bacterial infections.

Precicol *Liferpal, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm and pain.

Precidona *Precimex, Mex.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Precifen *Precimex, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Precifenac *Precimex, Mex.*
Diclofenac (p.44·2).
Inflammation; pain.

Precileucin *Precimex, Mex.*
Calcium folinate (p.1943·3).
Megaloblastic anaemia; reduction of folic acid antagonist toxicity.

Precirux *Nafar, Mex.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Precision *Sandoz Nutrition, USA.*
A range of lactose-free preparations for enteral nutrition (p.1922·1).

Precision Plus *Abbott, Arg.; Medisense, Austral.†; Medica, NZ†.*
Test for glucose in blood (p.2314·1).

Pre-Clar *Laboratorios Chile, Chile.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Preconceive *Lane, UK.*
Folic acid (p.1940·1).
Prevention of neural tube defects in pregnancy.

Precortalon aquosum *Organon, Swed.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Precortil *Cazi, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Precortisyl *Aventis, UK.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Precortivit *Menarini, Gr.†.*
⊗ Prednisolone (p.1540·3); neomycin (p.305·1); vitamin A (p.1922·1).
Topical corticosteroid with antimicrobial.

Precosa *Biocodex, Denm.; Biocodex, Fin.; AstraZeneca, Swed.*
Saccharomyces boulardii (p.2372·3).
AIDS-related diarrhoea; antibiotic-associated colitis; antibiotic-associated diarrhoea.

Precose *Duopharma, Malaysia; Bayer, USA.*
Acarbose (p.436·2).
Diabetes mellitus.

Precosol *Wolfs, Belg.†.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Prectal *Infectopharm, Ger.†.*
⊗ Prednisolone acetate (p.1541·1).
Bronchitis; hypersensitivity reactions; laryngotracheal stenosis.

Precyclan *Lisapharm, Fr.*
⊗ Meprobamate (p.1006·2); bendroflumethiazide (p.1224·1); medroxyprogesterone acetate (p.2113·1).
Premenstrual syndrome.

Pred
Note. This name is used for preparations of different composition.
Grin, Mex.
⊗ Prednisolone acetate (p.1541·1) or prednisolone sodium phosphate (p.1541·2).
Inflammatory eye disorders.

Prosel, Philipp.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Allergan, Singapore; Alcon, USA.
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Pred Fort *Allergan, Braz.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Pred Forte *Allergan, Belg.; Allergan, Canad.; Allergan, Chile; Allergan, Fin.; Allergan, Hong Kong; Allergan, Irl.†; Allergan, Israel; Allergan, Malaysia; Allergan, NZ; Allergan, Neth.; Allergan, Philipp.; Allergan, Spain; Allergan, Switz.; Allergan, Thai.; Abdi, Turk.; Allergan, UK; Allergan, USA.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Pred G *Allergan, Chile†; Allergan, USA.*
⊗ Prednisolone acetate (p.1541·1); gentamicin sulfate (p.282·1).
Infected eye disorders.

Pred Mild *Allergan, Braz.; Allergan, Canad.; Allergan, Chile†; Allergan, Hong Kong; Allergan, Irl.; Allergan, Malaysia; Allergan, NZ; Allergan, S.Afr.; Allergan, Switz.; Allergan, Thai.; Allergan, USA.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Pred Oph *Seng, Thai.*
⊗ Prednisolone sodium phosphate (p.1541·2); gentamicin sulfate (p.282·1).
Infected eye and ear disorders.

Preda *Kalbe, Indon.; Sanghiang, Indon.*
Infant feed (p.1922·1).
Malabsorption.

Predalon *Organon, Ger.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; female infertility; hypogonadism.

Predalone *Forest Laboratories, USA†.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Pred-Clysma *Schering, Denm.; Schering, Norw.; Schering, Swed.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Crohn's disease; proctosigmoiditis; ulcerative colitis.

Predcor *Hauck, USA.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Predeltin *Quatromed, S.Afr.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predenema *Forest Laboratories, Hong Kong; Forest, Irl.; Forest Laboratories, UK.*
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1).
Ulcerative colitis.

Predesic *Pred, Fr.†.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to limit its absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Predex *Takeda, Thai.†.*
⊗ Neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Skin disorders.

Predfoam *Forest Laboratories, Hong Kong; Forest, Irl.; Forest Laboratories, UK.*
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1).
Proctitis; ulcerative colitis.

Pre-Dial *Silanes, Mex.*
Metformin (p.453·3).
Diabetes mellitus.

Predicor *Pisa, Mex.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predicorten *Stiefel, Braz.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predictor *Organon, Braz.; Omega, Fr.; Chefaro, Israel; Angelini, Ital.; Chefaro, UK.*
Pregnancy test (p.2372·1).

Predisole *PP Lab, Thai.†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Predison *Cristalia, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predisyr *Phoenix, Philipp.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Predmetil *Eurofarma, Braz.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Predmicin
Note. A similar name is used for preparations of different composition (see below).
EMS, Braz.
⊗ Polymyxin B sulfate (p.317·3); prednisolone (p.1540·3); benzocaine (p.1854·1); clioquinol (p.254·1).
Skin disorders.

Predmix *Aspen, Austral.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Predmycin
Note. A similar name is used for preparations of different composition (see above).
Allergan, Thai.†.
⊗ Prednisolone acetate (p.1541·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Bacterial eye infections.

Predmycin P *Allergan, Belg.*
⊗ Prednisolone acetate (p.1541·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Predmycin-P *Allergan, Philipp.; Allergan, Singapore†.*
⊗ Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Prednabene *Merckle, Ger.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Musculoskeletal, joint, and peri-articular disorders.

Prednax *Geolab, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Prednecort *Yung Shin, Philipp.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Prednefrin
Note.This name is used for preparations of different composition.
Allergan, Arg.; Allergan, Austral.
⊗ Prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Inflammatory eye disorders.

Allergan, Venez.†.
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Prednefrin SF *Allergan, Mex.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Prednersone *General Drugs, Thai.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Prednesol *Phoenix, Irl.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Pred-NF *Grin, Mex.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Predni *Winthrop, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Parenteral corticosteroid.

Predni Azuleno *Lacer, Spain.*
⊗ Chloramphenicol (p.239·3); guaiazulene (p.2317·3); prednisolone (p.1540·3).
Infected skin disorders.

Predni H *Winthrop, Ger.*
⊗ Prednisolone (p.1540·3) or prednisolone acetate (p.1541·1).
Corticosteroid.

Predni M *Winthrop, Ger.*
⊗ Methylprednisolone (p.1538·1).
Oral corticosteroid.

Predni Tablinen *Winthrop, Ger.*
⊗ Prednisone (p.1542·3).
Oral corticosteroid.

Prednicort
Note.This name is used for preparations of different composition.
Continental Pharma, Belg.†.
⊗ Prednisone (p.1542·3).
Corticosteroid.

Otto, Indon.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Behrens, Venez.
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Prednicortelone *Continental Pharma, Belg.†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Predniderma *Caldeira & Marques, Port.†.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1).
Skin disorders.

Prednidib *Diba, Mex.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Prednifarma *Valeant, Arg.*
⊗ Prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Inflammatory eye disorders.

Predniftalmina *Davi, Port.*
⊗ Chloramphenicol (p.239·3); prednisolone (p.1540·3).
Infected eye disorders.

Prednigalen *Galen, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Prednihexal
Hexal, Austria.
⊗ Prednisolone (p.1540·3) or prednisolone acetate (p.1541·1).
Corticosteroid.

Hexal, Ger.
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Prednilem *Lemery, Mex.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Predniocil *Edol, Port.*
⊗ Prednisolone acetate (p.1541·1).
Eye disorders.

Predni-Ophtal *Winzer, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Prednipirine *Lafage, Arg.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predni-POS *Ursapharm, Cz.; Ursapharm, Ger.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Prednisil
Note.This name is used for preparations of different composition.
Silom, Thai.
Cream: ⊗ Prednisolone (p.1540·3).
Skin disorders.

Silom, Thai.†.
Eye drops: ⊗ Prednisolone sodium phosphate (p.1541·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Prednisil-N *Silom, Thai.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Prednisol *Pasadena, USA.*
⊗ Prednisolone tebutate (p.1541·2).
Corticosteroid.

Prednisolon J *Gedeon Richter, Cz.†; Gedeon Richter, Hung.*
⊗ Prednisolone (p.1540·3); clioquinol (p.254·1).
Infected skin disorders.

Prednisolut *Jenapharm, Ger.*
⊗ Prednisolone hydrogen succinate (p.1541·1).
Parenteral corticosteroid.

Prednisona Neomicina *Alcon Cusi, Spain.*
⊗ Neomycin sulfate (p.305·1); prednisone (p.1542·3).
Infected eye disorders.

Prednisonal *Klonal, Arg.*
⊗ Meprednisone (p.1538·1).
Corticosteroid.

Prednitop *Aventis, Austria; Dermapharm, Ger.; Abbott, Switz.*
⊗ Prednicarbate (p.1540·2).
Eczema; skin disorders.

Prednitracin *Novartis Ophthalmics, Hong Kong†; Novartis, Switz.†.*
⊗ Prednisolone acetate (p.1541·1); neomycin sulfate (p.305·1); bacitracin (p.210·3).
Infected eye disorders.

Prednocris *LKM, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Prednol
Note.This name is used for preparations of different composition.
Nevzat, Turk.
Cream; ointment: ⊗ Prednisolone (p.1540·3).
Skin disorders.

Nevzat, Turk.
Injection; tablets: ⊗ Methylprednisolone (p.1538·1) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Prednol-A *Nevzat, Turk.*
⊗ Prednisolone (p.1540·3); clioquinol (p.254·1).
Skin disorders.

Prednox *Pyridam, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Predon *LBS, Malaysia.*
⊗ Prednisolone acetate (p.1541·1).
Corticosteroid.

Predone *Cipla, India.*
⊗ Prednisolone (p.1540·3) or prednisolone acetate (p.1541·1).
Corticosteroid.

Predonium *Servier, Austria; Servier, Hong Kong; Servier, NZ; Servier, Neth.; Servier, Port.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Pred-Phosphate *Medical Ophthalmics, USA.*
⊗ Prednisolone phosphate (p.1542·1).
Eye disorders.

Predsim *Mantecorp, Braz.*
⊗ Prednisolone (p.1540·3) or prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Predsol *Sigma, Austral.; UCB, Irl.; GSK, S.Afr.†; UCB, UK.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Crohn's disease; inflammatory disorders of the ear or eye; proctitis; ulcerative colitis.

Predsolets *SMB, Chile.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Predsol-N *UCB, UK.*
⊗ Prednisolone sodium phosphate (p.1541·2); neomycin sulfate (p.305·1).
Inflammatory disorders of the ear or eye with bacterial infection.

Predsolone *Aspen, Austral.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Predsone *Lennon, Austral.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predual *BMS, Arg.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, clofedanol hydrochloride, pseudoephedrine sulfate, and astemizole.
Respiratory-tract disorders.

Predual DI *Andromaco, Chile†.*
Paracetamol (p.108·1); ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Predual *Andromaco, Chile.*
⊗ Pamabrom (p.1365·3); paracetamol (p.108·1); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Predual Descongestivo
Note.This name is used for preparations of different composition.
BMS, Arg.†.
Syrup: Pseudoephedrine sulfate (p.1571·2); chlorphenamine maleate (p.571·3).
Rhinitis; sinusitis.

BMS, Arg.†.
Tablets: Pseudoephedrine sulfate (p.1571·2); astemizole (p.567·2).
Rhinitis; sinusitis.

Predualito *BMS, Arg.†.*
Paracetamol (p.108·1).
Fever; pain.

Preductal *Servier, Cz.; Servier, Hung.; Anpharm, Pol.; Servier, Pol.; Servier, Rus.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; ischaemic eye and ear disorders; vestibular disorders.

Predval *Sanval, Braz.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Predxal *Armstrong, Mex.*
Telmisartan (p.1409·2).
Hypertension.

Predxal Plus *Armstrong, Mex.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Preface *Centaur, India.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction.

Prefagyl *Oberlin, Fr.†.*
Magnesium chloride (p.1679·1); sodium bicarbonate (p.1673·2); anhydrous sodium sulfate (p.1771·3); dibasic sodium phosphate (p.1682·3).
Gastrointestinal disorders.

Prefamone *Dexo, Switz.†.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Prefem *Labomed, Chile.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Premenstrual syndrome.

Prefemine *Zeller, Switz.*
Agnus castus (p.2249·1).
Premenstrual syndrome.

Preferid *Astellas, Ital.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Preferred Remedies Aches & Pains *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Allergy *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Antacid *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Cold & Flu *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Detoxin *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Fatigue *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Sinus *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Sleep *Reese, USA.*
Homoeopathic preparation.

Preferred Remedies Stress *Reese, USA.*
Homoeopathic preparation.

Prefest *Janssen-Cilag, Arg.; Janssen-Cilag, Braz.; Janssen-Cilag, Mex.; Monarch, USA.*
15 Tablets, estradiol (p.2097·2); 15 tablets, estradiol; norgestimate (p.2121·1).
Formerly known as Ortho-Prefest in the *USA*.
Menopausal disorders; osteoporosis.

Prefesta *Janssen-Cilag, S.Afr.*
Pink tablets, estradiol (p.2097·2); white tablets, estradiol; norgestimate (p.2121·1).
Menopausal disorders.

Prefin *Key, Spain†.*
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Preflam *Cipla-Medpro, S.Afr.*
⊗ Prednisolone (p.1540·3).
Inflammation.

Preflex Daily Cleaner *Alcon, USA.*
Cleansing solution for soft contact lenses (p.1622·2).

Prefolic *Zambon, Ital.*
Calcium mefolinate pentahydrate (p.1932·2).
Antidote to folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Prefrin *Allergan, Arg.; Allergan, Austral.; Allergan, Canad.; Allergan, Hong Kong; Allergan, Israel†; Allergan, Malaysia†; Allergan, NZ; Allergan, S.Afr.; Allergan, Singapore†; Allergan, USA†.*
Phenylephrine hydrochloride (p.1568·1).
Eye congestion; eye irritation.

Prefrin A *Allergan, Canad.; Allergan, Malaysia†; Allergan, Singapore†.*
Mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Allergic eye disorders; eye inflammation; eye irritation.

Prefucet *Rafarm, Gr.*
Citalopram (p.385·3).
Depression.

Pregab *Torrent, India.*
Pregabalin (p.502·2).
Epilepsy; neuropathic pain.

Pregaday *UCB, UK.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Prophylaxis of iron and folic acid deficiency in pregnancy.

Pregamal *GSK, S.Afr.*
Folic acid (p.1940·1); ferrous fumarate (p.1938·3).
Anaemias in pregnancy.

Pregestimil *BMS, Arg.†; Mead Johnson, Austral.; Mead Johnson, Braz.; Mead Johnson, Chile†; Mead Johnson Nutritionals, Fin.; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Irl.; Mead Johnson, Israel; Mead Johnson, Ital.; Mead Johnson, Malaysia†; Mead Johnson, Port.†; Mead Johnson, Singapore†; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, UK†; Mead Johnson Nutritionals, USA; BMS, Venez.†.*
Infant feed (p.1922·1).
Cow's milk intolerance; cystic fibrosis; diarrhoea; disaccharidase deficiency; disaccharide intolerance; food intolerance and allergy; galactokinase deficiency; galactosaemia; inflammatory bowel disease; lactose intolerance; malabsorption syndromes; milk protein intolerance; pancreatic insufficiency; protein intolerance; soya protein intolerance; steatorrhoea; sucrose intolerance.

Preglandin *Ono, Jpn.*
Gemeprost (p.2010·2).
Termination of pregnancy.

Preg-Less *Sigma, Braz.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Combined injectable contraceptive.

Pregmag *ICN, Hung.*
Magnesium citrate (p.1743·2); folic acid (p.1940·1); pyridoxine hydrochloride (p.1978·2).
Magnesium and folic acid supplement.

Pregnacare
Note.This name is used for preparations of different composition.
Vitabiotics, Cz.; Vitabiotics, Hung.; Vitabiotics, Indon.; Nobel, Turk.; Vitabiotics, UK.
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Vitabiotics, Hong Kong.
Capsules: Vitamin and mineral preparation (p.1922·1).
Dietary supplement in pregnancy and lactation.

Vitabiotics, Hong Kong.
Cream: Calendula (p.2273·1); evening primrose oil (p.2302·1); aloe vera (p.1588·2); vitamin C (p.1983·3); vitamin E (p.1992·2); carotenoids; dexpanthenol (p.2362·1).
Skin care during and after pregnancy.

Pregnacare Plus *Vitabiotics, UK.*
Vitamins; minerals; omega-3 DHA (p.1362·1) (p.1922·1).
Dietary supplement in pregnancy and lactation.

Pregnamin *Blooming Fields, Philipp.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement for pregnant and breast-feeding women.

Pregnancy Formula *Eagle, Austral.†.*
Multivitamin, mineral, and amino-acid preparation with bioflavonoids, ginger and lecithin (p.1922·1).
Nutritional supplement.

Pregnasea *Kalbe, Indon.*
Ginger (p.1732·3); vitamin B (p.1979·1).
Nausea and vomiting.

Pregnatal *Scanpharm, Hong Kong.*
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement in pregnancy and lactation.

Pregnavit *Ratiopharm, Austria; Ratiopharm, Cz.; Ratiopharm, Hung.; Merckle, Rus.*
Multivitamin and mineral preparation (p.1922·1).

Pregnavit F *Merckle, Ger.†; Merckle, Rus.*
Multivitamin preparation (p.1922·1).

Pregnazon *Pharmadass, UK.*
Multivitamin, mineral, and trace element preparation (p.1922·1).

Pregnesin *Serono, Ger.†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Delayed puberty in males; infertility in females and males.

Pregnidoxin *UCB, India.*
Meclozine hydrochloride (p.584·3); caffeine (p.1116·3).
Ménière's syndrome; nausea and vomiting.

Pregnorm *Win-Medicare, India.*
⊗ Menotrophin (p.2109·3).
Male and female infertility.

Pregnosis *Key, Austral.; Roche, USA.*
Pregnancy test (p.2372·1).

Pregnospia Duoclon *Bio Merieux, UK†.*
Pregnancy test (p.2372·1).

Pregnosticon *Organon, Israel.*
Pregnancy test (p.2372·1).

Pregnyl *Organon, Arg.; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Canad.†; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Donmed, S.Afr.; Organon, Singapore; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, USA; Organon, Venez.*
⊗ Chorionic gonadotrophin (p.2085·1).
Controlled ovarian hyperstimulation; cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism; male and female infertility; metrorrhagia.

Pregobin *Drugtech, Chile.*
Pregabalin (p.502·2).
Epilepsy; neuralgia; neuropathic pain.

Pregomin *Support, Braz.†; Milupa, Switz.*
Infant feed (p.1922·1).
Carbohydrate malabsorption syndromes; cow's-milk-protein intolerance; digestive system disorders; soya-milk-protein intolerance.

Pregomine *Diele, Fr.*
Nutritional supplement (p.1922·1).
Gastrointestinal disorders.

Pregtenol *Fahrenheit, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

PregVit *Duchesnay, Canad.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement during pregnancy and lactation.

Pregvomit *Fahrenheit, Indon.*
Parathiazine teoclate; pyridoxine hydrochloride (p.1978·2).
Motion sickness; vomiting.

Prehist *Marnel, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Prehist D *Marnel, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract symptoms.

Prejomin *Milupa, Irl.†; Milupa, UK.*
Gluten-free preparation for special diets (p.1922·1).
Galactokinase deficiency; galactosaemia; lactose, sucrose and fructose intolerance; protein intolerance; protein sensitivity.

Prelafal *Akromed, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Prelat *Yung Shin, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Prelectal *Stroder, Ital.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Prelertan *Asofarma, Arg.†.*
Losartan (p.1327·2).
Hypertension.

Prelis *Mibe, Ger.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Prelis comp *Mibe, Ger.*
⊗ Metoprolol tartrate (p.1338·1); chlortalidone (p.1243·3).
Hypertension.

Prelisin *Cosmopharm, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Prelloran *Novartis, Hong Kong†; Novartis Consumer, Switz.†.*
A heparinoid (p.1305·2); glycol salicylate (p.62·3).
Musculoskeletal pain and inflammation; phlebitis; soft-tissue disorders; venous insufficiency.

Preloc *Unison, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Prelon *Faran, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Prelone
Ache, Braz.
⊗ Prednisolone (p.1540·3) or prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Asta Medica, Hong Kong†; Muro, Israel†; Adcock Ingram, S.Afr.; Aero, USA.
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Prelu-2 *Boehringer Ingelheim, USA; Roxane, USA.*
⊗ Phendimetrazine tartrate (p.2162·1).
Obesity.

Prelude *Rendell, UK.*
Nonoxinol 9 (p.1917·2).
Spermicidal contraceptive.

Prelus *Sanofi Synthelabo, Port.†.*
⊗ Isoprenaline hydrochloride (p.1316·3); phenobarbital (p.492·2); ephedrine sulfate (p.1558·2); theophylline (p.1140·1); potassium iodide (p.2169·2).
Asthma; bronchitis; coughs.

Prem *Sigma, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Premagnol *Allen, Mex.†.*
⊗ Prednisone (p.1542·3).
Inflammation; musculoskeletal and joint disorders.

Premandol *Spirig, Switz.*
⊗ Prednisolone acetate (p.1541·1); almond oil (p.2252·2); zinc oxide (p.1621·2).
Skin disorders.

Premaril *Dexxon, Israel†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Premaril MP *Dexxon, Israel†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Premaril Plus MP *Dexxon, Israel†.*
28 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premarin *Wyeth, Arg.; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth Lederle, Belg.†; Wyeth, Braz.; Wyeth, Canad.; Wyeth, Cz.†; Wyeth Lederle, Denm.†; Wyeth, Fin.†; Wyeth Lederle, Fr.†; IFET (ΙΦΕΤ), Gr.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Hung.†; Wyeth, India; Wyeth, Irl.; Wyeth Lederle, Ital.†; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.†; Wyeth, Philipp.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain†; Wyeth, Switz.; Wyeth-Ayerst, Thai.; Wyeth, Turk.; Wyeth, UK; Wyeth-Ayerst, USA; Wyeth, Venez.*
Conjugated oestrogens (p.2087·2).
Amenorrhoea; breast cancer; capillary haemorrhage; dysfunctional uterine bleeding; female hypogonadism; female infertility; menopausal disorders; oestrogen deficiency; osteoporosis; primary ovarian failure; prostatic cancer; uterine haemorrhage; vaginal and vulvar atrophy.

Premarin compositum *Wyeth Lederle, Austria†.*
16 Tablets, conjugated oestrogens (p.2087·2); 12 tablets, conjugated oestrogens; medrogestone (p.2113·1).
Oestrogen deficiency; osteoporosis.

Premarin MPA *Wyeth, Braz.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Atrophic urethritis; atrophic vaginitis; menopausal disorders; oestrogen deficiency; osteoporosis.

Premarin Plus *Wyeth Lederle, Austria; Wyeth, Neth.†; Wyeth Lederle, Port.†; Wyeth, Switz.†.*
28 Tablets, conjugated oestrogens (p.2087·2); 12 tablets, medrogestone (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis; ovarian insufficiency.

Premarina *Wyeth Lederle, Swed.†.*
Conjugated oestrogens (p.2087·2).
Hypogenitalism; menopausal disorders; osteoporosis.

PremarinLite *Wyeth, Neth.†.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders.

Premastan *CORNE, Mex.*
Progesterone (p.2125·1).
Benign breast disorders.

Premaston *Kalbe, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Premdoc *Alltracel, Irl.†.*
Calcium oxidised cellulose (p.1075·1); sodium oxidised cellulose (p.1075·1).
Capillary bleeding.

Preme *TNP, Thai.†.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, seborrhoea, alopecia, and hirsutism in females; oral contraceptive in women with androgenic symptoms.

Premella *Wyeth, Cz.†; Wyeth, Hung.†; Wyeth, Switz.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Premelle *Wyeth Lederle, Belg.†; Wyeth, Braz.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Neth.†; Wyeth, Philipp.; Wyeth Lederle, Port.†; Wyeth, S.Afr.; Wyeth, Singapore†; Wyeth, Spain; Wyeth Lederle, Swed.†; Wyeth-Ayerst, Thai.†; Wyeth, Turk.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Atrophic urethritis; hormone replacement therapy; menopausal disorders; oestrogen deficiency; osteoporosis; vaginal and vulval atrophy.

Premelle Ciclico *Wyeth, Arg.†; Wyeth, Spain; Wyeth, Venez.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premelle Ciclo *Wyeth, Braz.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis; vaginal and vulval atrophy.

Premelle Combinato *Wyeth Lederle, Ital.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premelle Continuo *Wyeth, Arg.†; Wyeth, Venez.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premelle Cycle *Wyeth Lederle, Belg.†; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Neth.†; Wyeth, Philipp.; Wyeth Lederle, Port.†; Wyeth, S.Afr.; Wyeth, Singapore†; Wyeth-Ayerst, Thai.†; Wyeth, Turk.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Atrophic urethritis; atrophic vaginitis; menopausal disorders; oestrogen deficiency; osteoporosis.

Premelle Plus Continuo *Wyeth, Venez.†.*
28 Tablets, conjugated oestrogens (p.2087·2); 28 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premelle S *Wyeth Lederle, Ital.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premelle Sekvens *Wyeth Lederle, Swed.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Oestrogen deficiency; osteoporosis.

Premelle Sequenziale *Wyeth Lederle, Ital.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

PremelleLite *Wyeth, Neth.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Premence *Vitabiotics, Cz.†; Vitabiotics, Hong Kong; Vitabiotics, UK.*
Multivitamin and mineral preparation (p.1922·1).
Premenstrual syndrome.

Pre-Mens
Note. A similar name is used for preparations of different composition (see below).
Sigma, Braz.
Thiamine hydrochloride; pyridoxine hydrochloride; riboflavin; magnesium aspartate; potassium aspartate (p.1922·1).

PreMens
Note. A similar name is used for preparations of different composition (see above).
Phytotec, Hung.; Zeller, Switz.
Agnus castus (p.2249·1).
Premenstrual syndrome.

Prementaid *Potter's, UK.*
Vervain (p.2413·3); motherwort (p.2347·3); pulsatilla (p.2376·3); bearberry (p.2263·3); valerian (p.2410·1).
Premenstrual syndrome.

PremesisRx *Ther-Rx, USA.*
Vitamin B (p.1979·1); vitamin B (p.1980·2); folic acid (p.1940·1); calcium (p.1675·2).
Nausea.

Premherb *MedicHerb, UK.*
Agnus castus (p.2249·1).
Premenstrual syndrome.

Premia *Wyeth, Austral.; Wyeth, NZ†; Wyeth, Switz.†.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premia Continuous *Wyeth, Austral.; Wyeth, NZ.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premia Low *Wyeth, Austral.†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Premicia *Therabel, Fr.*
Hyetellose (p.2143·3); diethylene glycol monoethyl ether.
Vaginal lubricant.

Premid
Note.This name is used for preparations of different composition.
Shire, Denm.
Balsalazide sodium (p.1709·2).
Ulcerative colitis.

Grin, Mex.
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Premig *Sanofi-Aventis, Gr.*
Lysine aspirin (p.79·1); metoclopramide (p.1747·3).
Migraine.

Premio *Bosch, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Premique *Wyeth, Irl.; Wyeth, UK.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premique Cycle *Wyeth, Irl.; Wyeth, UK.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premium *Quest, Canad.*
A range of vitamin and mineral preparations (p.1922·1).

Premium Memori Plus *Green Leaf, Philipp.*
Centella asiatica; bacopa monniera; lecithin; docosahexaenoic acid (p.1922·1).
Nutritional supplement.

Premjact *Pound International, UK.*
Lidocaine (p.1862·3).
Premature ejaculation.

Premosan *Julphar, UAE.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders; gastrointestinal procedures; hiccup; nausea and vomiting.

Prempak
Note.This name is used for preparations of different composition.
Wyeth, Chile†.
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Wyeth, Hong Kong†; Wyeth Lederle, Ital.†; Wyeth, Malaysia†.
21 Tablets, conjugated oestrogens (p.2087·2); 10 tablets, medrogestone (p.2113·1).
Atrophic urethritis; menopausal disorders; oestrogen deficiency; osteoporosis; vaginitis.

Prempak N *Wyeth, S.Afr.*
21 Tablets, conjugated oestrogens (p.2087·2); 10 tablets, medrogestone (p.2113·1).
28-Day packs also contain 7 inert tablets.
Menopausal disorders; osteoporosis.

Prempak-C *Wyeth, Irl.; Wyeth, NZ†; Wyeth, Neth.†; Wyeth, Singapore; Wyeth, UK.*
28 Tablets, conjugated oestrogens (p.2087·2); 12 tablets, norgestrel (p.2121·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Premphase *Wyeth-Ayerst, USA.*
Maroon tablets, conjugated oestrogens (p.2087·2); blue tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Premplus
Note.This name is used for preparations of different composition.
Wyeth Lederle, Belg.†.
28 Tablets, conjugated oestrogens (p.2087·2); 12 tablets, medrogestone (p.2113·1).
Oestrogen deficiency.

Wyeth, Canad.
14 Tablets, conjugated oestrogens (Premarin) (p.2087·2); 14 tablets, medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Prempro *Wyeth-Ayerst, USA.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Prempro Bifasico *Sigma, Braz.*
14 Blue tablets, conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1); 14 red tablets, conjugated oestrogens.
Menopausal disorders.

Prempro Monofasico *Sigma, Braz.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Premsyn PMS *Chattem, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Premular *Flordis, Austral.*
Agnus castus (p.2249·1).
Premenstrual syndrome.

Premunil *Lero, Fr.*
Vitamin E; vitamin B ; minerals (p.1922·1).
Nutritional supplement.

Prenacid *Craveri, Arg.†; SIFI, Ital.; SIFI, Rus.; Teka, Turk.*
⊗ Desonide sodium phosphate (p.1525·2).
Inflammatory eye disorders.

Prenadona *Ariston, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Prenafirst *Cypress, USA.*
Vitamin and mineral preparation (p.1922·1).

Prenafort *Cypress, USA.*
Multivitamin preparation with iron (p.1922·1).

Prenagen *Kalbe, Indon.; Sanghiang, Indon.*
A range of preparations for enteral nutrition (p.1922·1).

Prenal *Tempo Scan Pacific, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Prenalon *Degorts, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Prenamia *Sanbe, Indon.*
Ferrous fumarate (p.1938·3); folic acid; vitamin B ; colecalciferol; calcium carbonate (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Vitamin and mineral supplement in anaemia.

Prenatabs *Cypress, USA.*
A range of multivitamin and mineral preparations (p.1922·1).

Prenatal *Bio-Sante, Canad.; Nutricorp, Canad.; Pharmetics, Canad.; Stanley, Canad.; WN, Canad.; Wyeth, India; Erlimpex, Indon.; Stanley, Israel; Wyeth Consumer, Mex.; Teofarma, Port.; Be-Tabs, S.Afr.; Cypress, USA; Ethex, USA.*
Multivitamin and mineral preparations (p.1922·1).
Docusate sodium (p.1725·1) may be included in this preparation to reduce the constipating effects of iron.
Formerly known as Be-Natal in *S. Afr.*
Nutritional supplement.

Prenatal with Folic Acid *Geneva, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenatal Nutrients *Solgar, UK.*
Multivitamin and mineral preparation (p.1922·1).

Prenatal PC *Integrity, USA.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenatal Plus *Zenith Goldline, USA.*
Multivitamin and mineral preparation with calcium and iron (p.1922·1).

Prenatal Plus Iron *Major, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Prenatal Plus-Improved *Rugby, USA†.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenatal-S *Goldline, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenate *First Horizon, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenatex *Medix, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Prenatin Plus *Soho, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement; tonic.

Prenatin-DF *Soho, Indon.*
Vitamin and mineral preparation (p.1922·1) with ferrous fumarate (p.1938·3) and docosahexaenoic acid (p.1362·1).
Anaemia; nutritional supplement in pregnancy and lactation.

Prenatol *Wyeth, Hong Kong.*
Amino acids; proteins (p.1922·1).
Prevention of stretch marks during pregnancy.

Prenavit
Gynopharm, Chile.
Vitamins; calcium phosphate; ferrous gluconate (p.1922·1).
Dietary supplement.

Vivax, Venez.
Multivitamin and mineral preparation (p.1922·1).

Prenavite *Rugby, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Prenessa *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.*
Perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; heart failure; hypertension.

Prenewel *KRKA, Cz.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Prenisonal *Klonal, Arg.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Prenolin *Dexa, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Prenolol *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Prenolone *Bago, Arg.*
⊗ Meprednisone hemisuccinate (p.1538·1).
Corticosteroid.

Prenomod *AstraZeneca, Arg.†.*
⊗ Atenolol (p.1217·3); hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Prenoretic *AstraZeneca, Arg.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Prenormine *AstraZeneca, Arg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Prent *Gepepharm, Ger.; Bayer, Ital.; Bayer, Port.; Bayer, Turk.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; ischaemic heart disease.

Pre-Nutrison *Nutricia, Port.†.*
Preparation for enteral nutrition (p.1922·1).

Pre-Op *Nutricia, Austral.†; Baxter, NZ; Nutricia, NZ.*
Preparation for enteral nutrition (p.1922·1).
Pre-operative dietary management of surgical patients.

Preotact *Nycomed, Cz.; Nycomed, Gr.; Nycomed, UK.*
Parathyroid hormone (rDNA) (p.1103·1).
Osteoporosis.

Prep *Lennon, S.Afr.*
Borax (p.2268·1); menthol (p.2340·1); thymol (p.1664·3); camphor (p.2273·2); clove oil (p.2285·1); phenol (p.1656·1).
Burns; insect bites; skin disorders; ulcers.

Prep Kit-C *Pharmatel, Austral.*
One sachet, macrogol 3350 (p.2336·3); electrolytes (p.1667·1) (Glycoprep-C); Two sachets, sodium picosulfate (p.1771·1) (PicoPrep).
Bowel evacuation.

Prepacol *Guerbet, Austria; Codali, Belg.; Guerbet, Cz.; Guerbet, Fr.; Guerbet, Ger.*
Combination pack: Tablets, bisacodyl (p.1710·1); oral solution, dibasic sodium phosphate dodecahydrate (p.1682·3); monobasic sodium phosphate dihydrate (p.1682·3).
Bowel evacuation.

Prepacort H *Wyeth Consumer, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1).
Haemorrhoids.

Prepadine *Berk, UK.*
Dosulepin hydrochloride (p.388·2).
Depression.

Prepagel *Frik, Turk.*
Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Musculoskeletal and joint pain.

Pre-Par *Eumedica, Belg.; Belupo, Cz.†; IFET (ΙΦΕΤ), Gr.†; Solvay, Port.†; Reig Jofre, Spain; Eczacibasi, Turk.*
⊗ Ritodrine hydrochloride (p.2017·2).
Fetal distress; premature labour; prevention of uterine contractions during surgery in pregnancy; prevention of uterine hypermotility in labour; production of uterine relaxation.

Preparacion H *Wyeth, Spain.*
Yeast extract (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Preparation H
Note. This name is used for preparations of different composition.
Wyeth Consumer, Austral.†; Wyeth Consumer, Canad.; Wyeth, Cz.; Wyeth, Gr.; Wyeth Consumer, Irl.; Whitehall, Israel; Whitehall, Pol.†; Wyeth, Rus.; SA Druggists Self Med, S.Afr.; Wyeth Consumer, UK.
Live yeast cell extract (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Wyeth Consumer, Hong Kong; Wyeth Consumer, Mex.; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.
Shark-liver oil (p.2386·1); phenylephrine hydrochloride (p.1568·1).
Formerly contained live yeast-cell derivative and shark-liver oil in *Singapore*.
Haemorrhoids.

Wyeth Consumer, USA.
Cream: Phenylephrine hydrochloride (p.1568·1); pramocaine hydrochloride (p.1868·1); glycerol (p.2314·2).
Formerly contained shark-liver oil and phenylephrine hydrochloride.
Anorectal disorders.

Wyeth Sante, Fr.
Rectal cream: Yeast (p.1998·3); halibut-liver oil (p.1948·1).
Haemorrhoids.

Wyeth Sante, Fr.
Suppositories: Butyl aminobenzoate (p.1857·1); yeast (p.1998·3); esculoside (p.2248·2); halibut-liver oil (p.1948·1).
Haemorrhoids.

Whitehall, USA.
Suppositories: Live yeast cell derivative (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Preparation H Clear Gel *Wyeth Consumer, UK.*
Hamamelis (p.2318·2).
Haemorrhoids.

Preparation H Cooling Gel *Wyeth Consumer, Canad.; Whitehall-Robins, USA.*
Hamamelis (p.2318·2); phenylephrine hydrochloride (p.1568·1).
Anorectal disorders; haemorrhoids.

Preparation H Veinotonic *Wyeth Sante, Fr.*
Diosmin (p.2304·2).
Haemorrhoids.

Preparazione Antiemorroidaria *Giuliani, Ital.†.*
⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1).
Haemorrhoids.

Preparazione H *Wyeth Consumer, Ital.*
Yeast cell extract (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Prepcat *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Pre-Pen *Bayer, USA†.*
Penicilloyl-polylysine (p.2364·2).
Diagnosis of penicillin hypersensitivity.

Prepenem *Choongwae, Hong Kong.*
Imipenem (p.286·3); cilastatin (p.243·2).
Bacterial infections.

Prephen *Orion, NZ.*
Substituted phenols.
Disinfection.

Prepidil *Pfizer, Austria; Pfizer, Belg.; Paladin, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Hung.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Spain; Pfizer, Switz.†; Pharmacia Upjohn, USA.*
Dinoprostone (p.2007·1).
Labour induction.

Preptin *Teuto, Braz.†.*
Cyproheptadine hydrochloride (p.575·1).
Reduced appetite.

Prepulsid
Janssen-Cilag, Arg.†; Janssen-Cilag, Austral.†; Janssen-Cilag, Austria†; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile†; Janssen-Cilag, Cz.†; Janssen-Cilag, Denm.†; Janssen-Cilag, Fin.†; Janssen-Cilag, Fr.; Janssen, Hong Kong†; Janssen-Cilag, Irl.†; Janssen-Cilag, Israel; Janssen, Mex.†; Janssen-Cilag, NZ†; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.†; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Spain†; Janssen-Cilag, Swed.†; Janssen-Cilag, Switz.†.
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastroparesis; impaired gastric motility; regurgitation and vomiting in infants; upper-gastrointestinal discomfort.

Janssen-Cilag, Thai.†.
Cisapride (p.1720·3) or cisapride tartrate (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastroparesis; regurgitation and vomiting in babies.

Prepurex *Wellcome, Israel†.*
Pregnancy test (p.2372·1).

Preran *Sanofi-Aventis, Jpn.*
Trandolapril (p.1416·2).
Hypertension.

Preridon *Biomedica-Chemica, Gr.*
Risperidone (p.1024·2).
Psychoses.

Pres *Boehringer Ingelheim, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Pres plus *Boehringer Ingelheim, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Presabet *Royal, Chile†.*
Nitrendipine (p.1358·2).
Hypertension.

Presar *Tedec Meiji, Spain.*
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Presartan *Ipca, Rus.; Giempi, Venez.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Prescaina *Llorens, Spain.*
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Prescal *Novartis, UK.*
Isradipine (p.1319·2).
Hypertension.

Presco *Polipharm, Thai.*
Dextromethorphan hydrobromide (p.1555·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Prescol *Atlantis, Mex.*
Trimebutine (p.2404·3).
Gastrointestinal motility disorders.

Prescription Strength Desenex *Novartis Consumer, USA.*
Topical spray: Miconazole nitrate (p.541·3).
Fungal infections.

Presdeten *Alter, Spain.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Presept *Johnson & Johnson Medical, UK.*
Troclosene sodium (p.1665·3).
Instrument and surface disinfection.

Preserv Nonoxinol-9 *Blausiegel, Braz.*
Nonoxinol 9 (p.1917·2).
Formerly known as Preserv Gel Espermicida.
Contraceptive.

Preservation *Texinfine, Fr.*
Fig (p.1731·3); maize oil (p.1955·2).
Tonic.

Preservex *Movianto, UK.*
Aceclofenac (p.14·3).
Musculoskeletal and joint disorders.

Preservision *Chauvin, Fr.*
Vitamin and mineral preparation (p.1922·1).

PreserVision *Bausch & Lomb, Singapore.*
Vitamin C; vitamin E; zinc oxide; cupric oxide; lutein (p.1922·1).
Dietary supplement.

Preservision Lutein *Bausch & Lomb, USA.*
Vitamins; minerals; lutein (p.1922·1).

Preservision Luteina *Bausch & Lomb, Ital.*
Vitamin and mineral preparation with lutein (p.1922·1).

Presi Regul *Fabra, Arg.*
Enalapril maleate (p.1276·1).
Hypertension.

Presi Regul D *Fabra, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Presid *Ivax, Cz.; Ivax, Hung.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

President's Choice Hand Sanitizer *Belvedere, Canad.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

President's Choice Sport Sunblock
Note. This name is used for preparations of different composition.
Fruit of the Earth, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

President's Choice Sunblock
Note. This name is used for preparations of different composition.
Fruit of the Earth, Canad.
Lotion SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Fruit of the Earth, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Fruit of the Earth, Canad.
Spray SPF 30: Diolamine methoxycinnamate (p.1594·2); octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

President's Choice Sunblock for Babies *Fruit of the Earth, Canad.*
SPF 45: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

President's Choice Sunblock for Children *Fruit of the Earth, Canad.*
SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

President's Choice Sunless Tanning Cream
Fruit of the Earth, Canad.
SPF 15: Octocrilene (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

President's Choice Sunscreen *Fruit of the Earth, Canad.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Presilam *Pasteur, Chile.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Presinex
Pfizer, Arg.; Trima, Israel; Pliva, UK.
Desmopressin acetate (p.2185·3).
Diabetes insipidus; nocturnal enuresis; test of renal concentrating capacity.

Cantabria, Spain.
Desmopressin (p.2185·2).
Diabetes insipidus; nocturnal enuresis.

Presinol *Teofarma, Ger.*
Methyldopa (p.1334·1).
Hypertension.

Presinor *Lafedar, Arg.*
Losartan potassium (p.1326·1).
Hypertension.

Presinor D *Lafedar, Arg.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Presistin *Maver, Mex.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Preslicka *Leros, Cz.*
Equisetum (p.2299·3).
Urinary-tract disorders; wounds.

Preslickova *Megafyt-R, Cz.*
Equisetum (p.2299·3).
Urinary-tract disorders; wounds.

Preslow *AstraZeneca, Port.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Presmin *Latinofarma, Braz.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma.

Preso *Soho, Indon.*
St John's wort (p.422·3).
Depression.

Presocor *Rider, Chile.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Presoken *Kener, Mex.†.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Presokin *Chemopharma, Chile.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Presolar *Cipla, India.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Presolol *Alphapharm, Austral.*
⊗ Labetalol hydrochloride (p.1321·1).
Hypertension.

Presomen *Wyeth, Cz.†; Solvay, Ger.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Presomen Compositum *Wyeth, Cz.†; Solvay, Ger.*
10 Tablets, conjugated oestrogens (p.2087·2); 11 tablets, conjugated oestrogens; medrogestone (p.2113·1). 28-Tablet packs contain 14 tablets, conjugated oestrogens and 14 tablets, conjugated oestrogens plus medrogestone.
Menopausal disorders; osteoporosis.

Presoquim *Kener, Mex.†.*
Diltiazem (p.1267·1).
Hypertension.

Presoquin *Dollder, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Presovasc *Pharmavita, Chile.*
Amlodipine besilate (p.1214·1).
Hypertension.

Prespir *Remexa, Mex.*
Aluminium chloride (p.1588·2); triclosan (p.1665·2); hamamelis (p.2318·2).
Hyperhidrosis.

Press-12 *Genepharm, Gr.; PannonPharma, Hung.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Pressamina *Teofarma, Ital.†.*
⊗ Dimetofrine hydrochloride (p.1268·1).
Hypotension.

Pressat *Biolab Sanus, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Pressel *Legrand, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Presselin All *Combustin, Ger.*
Homoeopathic preparation.

Presselin Arterien K 5 P *Presselin, Ger.†.*
Crataegus (p.2289·1); St John's wort (p.422·3); garlic (p.2309·2); barlauchkraut; java tea (p.2328·2); mistletoe (p.2345·3).
Circulatory disorders.

Presselin Blahungs K 4 N *Presselin, Ger.†.*
Peppermint leaf (p.1761·2); caraway (p.2276·3); fennel (p.2302·3); chamomile (p.2279·3); calamus (p.2271·3); absinthium (p.2244·1); sage (p.2382·3); melissa (p.2339·3).
Digestive-system disorders.

Presselin Dyspeptikum *Presselin, Ger.†.*
Chamomile (p.2279·3); peppermint (p.2331·1); sage (p.2382·3); caraway (p.2276·3); cardamom (p.2277·1); coriander (p.2288·1); fennel (p.2302·3); absinthium (p.2244·1); ginger (p.1732·3).
Biliary disorders; dyspepsia; liver disorders.

Presselin Gold N *Presselin, Ger.†.*
Homoeopathic preparation.

Presselin Heilozon P *Presselin, Ger.†.*
Magnesium citrate (p.1743·2).
Magnesium deficiency.

Presselin Hepaticum P *Presselin, Ger.†.*
Taraxacum (p.2395·1); greater celandine (p.2317·1); milk thistle (p.1452·1).
Liver and biliary-tract disorders.

Presselin HK Herz-Kreislauf *Presselin, Ger.†.*
Homoeopathic preparation.

Presselin MIG F *Presselin, Ger.†.*
Homoeopathic preparation.

Presselin MIG M *Presselin, Ger.†.*
Homoeopathic preparation.

Presselin Nerven K 1 N *Presselin, Ger.†.*
St John's wort (p.422·3); valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Depression; nervous disorders; sleep disorders.

Presselin Nervennahrung N *Combustin, Ger.*
Homoeopathic preparation.

Presselin Nieren-Blasen K 3 *Presselin, Ger.†.*
Birch leaf (p.2266·3); java tea (p.2328·2); equisetum (p.2299·3); urtica root (p.2409·3); solidago virgaurea (p.2391·1); lovage root (p.2335·1); ononis (p.2357·1); bearberry (p.2263·3).
Urinary-tract disorders.

Presselin Osteo *Presselin, Ger.†.*
Homoeopathic preparation.

Presselin Stoffwechsel-Tee Hapeka 225 N *Presselin, Ger.†.*
Chamomile (p.2279·3); stoechados; senna (p.1769·2); fennel (p.2302·3); juniper (p.2328·2); phaseolus (seed-free); equisetum (p.2299·3); couch-grass (p.2288·2).
Constipation.

Pressil *Medinfar, Port.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Pressin *Alphapharm, Austral.; Utopian, Thai.*
Prazosin hydrochloride (p.1375·2).
Benign prostatic hyperplasia; heart failure; hypertension; Raynaud's syndrome.

Pressitan *Iquinosa, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Pressitan Plus *Iquinosa, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Pressodipin *Genepharm, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Pressodopa *Balldarassi, Braz.†.*
Methyldopa (p.1334·1).
Hypertension.

Pressolat *Agis, Israel.*
Nifedipine (p.1350·1).
Hypertension.

Pressomax *Kinder, Braz.*
Captopril (p.1239·2).
Hypertension.

Pressotec *Teuto, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Pressural *Polifarma, Ital.*
⊗ Indapamide (p.1314·1).
Hypertension.

Pressuril *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Pressyn *Ferring, Canad.*
Vasopressin (p.2411·3).
Adjunct in abdominal radiography; diabetes insipidus; postoperative abdominal distension.

Prestarium
Servier, Cz.; Servier, Rus.
Perindopril erbumine (p.1368·3).
Heart failure; hypertension; stroke prophylaxis.

Servier, Pol.
Perindopril arginine (p.1368·2) or perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; heart failure; hypertension.

Prestarium Combi *Servier, Cz.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Prestarium Neo *Servier, Cz.*
Perindopril arginine (p.1368·2).
Cardiovascular risk reduction; heart failure; hypertension.

Prestarium Neo Combi *Servier, Cz.*
⊗ Perindopril arginine (p.1368·2); indapamide (p.1314·1).
Hypertension.

Prestarium Plus *Servier, Pol.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Presterin *Roux-Ocefa, Arg.*
Pyridoxine hydrochloride (p.1978·2); folic acid (p.1940·1); cyanocobalamin (p.1980·2); calcium carbonate (p.1714·1).
Nausea and vomiting in pregnancy; vitamin and mineral supplement.

Prestige *Alvear, Arg.†.*
Test for glucose in blood (p.2314·1).

Prestim *ICN, UK.*
⊗ Timolol maleate (p.1412·3); bendroflumethiazide (p.1224·1).
Hypertension.

Prestodol *Rayere, Mex.*
Clonixin lysine (p.37·1).
Pain.

Prestodol Compuesto *Rayere, Mex.*
Clonixin lysine (p.37·1); hyoscine butylbromide (p.1734·1).
Smooth muscle pain.

Prestole *Almirall, Fr.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Prestrenol *Interbat, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Presun
Note. This name is used for preparations of different composition.
Westwood, USA.
Cream SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Westwood, USA†.
Lotion SPF 15: Aminobenzoic acid (p.1589·1); padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Westwood-Squibb, Canad.†.
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Westwood-Squibb, Canad.†.
SPF 29: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Westwood-Squibb, Canad.†.
SPF 39: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Westwood, USA.
SPF 39; SPF 8: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Presun Active *Bristol-Myers Products, USA.*
SPF 15; SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Presun Facial *Westwood, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Presun for Kids *Bristol-Myers Products, USA; Westwood, USA.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Presun Lip Stick *Westwood, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Presun Moisturizing *Bristol-Myers Products, USA.*
SPF 46: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Presun Moisturizing with Keri
Note. This name is used for preparations of different composition.
Bristol-Myers Products, USA.
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Bristol-Myers Products, USA.
SPF 25: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Presun Sensitive *Westwood-Squibb, Canad.†.*
SPF 28: Titanium dioxide (p.1617·3).
Sunscreen.

Presun Sensitive Skin *Bristol-Myers Products, USA; Westwood, USA.*
SPF 15; SPF 29: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Presun Spray Mist *Bristol-Myers Products, USA.*
SPF 23: Octinoxate (p.1608·2); padimate O (p.1609·1); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Presun Ultra
Westwood-Squibb, Canad.†.
SPF 15; SPF 27; SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Westwood-Squibb, USA.
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Presyc *Pasteur, Chile.*
Capsaicin (p.32·3).
Diabetic neuropathy; musculoskeletal and joint pain; phantom-limb pain; postherpetic neuralgia; pruritus.

Pretanix *Servier, Hung.*
⊗ Indapamide (p.1314·1).
Hypertension.

Pretenol C *Duopharma, Malaysia.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Preterax
Servier, Arg.; Servier, Austria; Servier, Belg.; Servier, Canad.; Therval, Fr.; Servier, Ger.; Servier, Gr.; Servier, Ital.; Servier, Mex.; Servier, Neth.; Servier, Philipp.; Servier, Port.; Servier, S.Afr.; Servier, Singapore; Servier, Spain; Servier, Switz.; Servier, Turk.; Servier, Venez.
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Servier, Irl.
⊗ Perindopril arginine (p.1368·2) or perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Pretifen *Unipharm, Mex.*
Ketotifen (p.582·2).
Asthma.

Pretilon *Sandoz, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Pretts Diet Aid *Milance, USA.*
Alginic acid (p.2140·3); carmellose sodium (p.2142·1); sodium bicarbonate (p.1673·2).

Pretuval *Bayer, Switz.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms; coughs.

Pretuval C *Bayer, Switz.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms; coughs.

Pretz
Note. This name is used for preparations of different composition.
Alcon, Hong Kong†.
Eriodictyon (p.1560·2).
Nasal dryness.

Parnell, Irl.
Moisturising nasal spray.
Nasal dryness.

Parnell, USA.
Sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Pretz-D *Parnell, USA†.*
Phenylephrine hydrochloride (p.1568·1).
Formerly contained ephedrine sulfate.
Nasal congestion.

Prevacid
TAP, Canad.
Lansoprazole (p.1739·2) or lansoprazole sodium.
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Takeda, Jpn; Takeda, Malaysia; Takeda, Philipp.; Takeda, Singapore; Takeda, Thai.; TAP, USA.
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prevacid NapraPAC *TAP, USA.*
Naproxen (p.92·3).
Lansoprazole (p.1739·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Musculoskeletal and joint disorders.

Prevage *Allergan, USA.*
Idebenone (p.367·1).
Skin wrinkles.

Prevagin-Premaril *Dexxon, Israel†.*
Conjugated oestrogens (p.2087·2).
Menopausal vulvovaginal disorders.

Prevalin *Chefaro, Neth.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Prevalina *Andromaco, Chile.*
Mianserin hydrochloride (p.408·1).
Depression.

Prevalite *Upsher-Smith, USA.*
Colestyramine (p.1252·3).

Prevalon *Abello, Spain†.*
Multivitamin and amino-acid preparation (p.1922·1).
Tonic.

Prevan *Vargas, Venez.†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Prevas *Soho, Indon.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma.

Prevax *Biosintetica, Braz.*
Calcium folinate (p.1943·3).

Prevecilina *Grunenthal, Port.*
Clemizole penicillin (p.251·1); benzylpenicillin sodium (p.213·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Prevegyne *Farmalight, Port.†.*
Ascorbic acid (p.1983·3).
Vulvovaginal disorders.

Preven *Biomeks, Turk.; Gynetics, USA†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Postcoital oral contraceptive.

Prevenar *Wyeth, Arg.; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth Lederle, Hung.; Wyeth, Indon.; Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth Lederle, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain; Wyeth, Swed.; Wyeth, Switz.; Wyeth, UK; Wyeth, Venez.*
A pneumococcal conjugate vaccine (7-valent) (p.2231·2).
Active immunisation.

Prevencor
Note. This name is used for preparations of different composition.
Medley, Braz.
Aspirin (p.20·3); simvastatin (p.1390·2).
Atherosclerosis.

Euro Registratie, Neth.; Stephar, Neth.; Almirall, Spain.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Prevent *Agropharm, UK.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Insect repellent.

Preventan *Grunenthal, Chile†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Preventus *Yalacta, Fr.*
Organ extracts.
Tonic.

Prevepen *Grunenthal, Chile.*
Clemizole penicillin (p.251·1).
Bacterial infections.

Prevepen Forte *Grunenthal, Chile.*
Benzylpenicillin sodium (p.213·1); clemizole penicillin (p.251·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Preveral con Codeina *Vargas, Venez.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Cough and cold symptoms.

Preveral con Dextrometorfano *Vargas, Venez.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cough and cold symptoms.

Prevex
Note.This name is used for preparations of different composition.
Simesa, Ital.
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Stiefel, Thai.
Barrier gel.

Trans Canaderm, Canad.
Cream: Yellow soft paraffin (p.2031·3).
Barrier cream.

Trans Canaderm, Canad.
Lotion: Moisturiser.

Prevex B *Trans Canaderm, Canad.; Stiefel, Thai.†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Prevex HC *Trans Canaderm, Canad.; Stiefel, Thai.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Previane *Legrand, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Prevident *Colgate Oral, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Previfem *Andrx, USA.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Previgrip *Socopharm, Fr.*
Inactivated influenza vaccine (p.2218·2).
Active immunisation.

Previnfec *Lacefa, Arg.†.*
Chloroxylenol (p.1640·2).
Disinfection.

Previscan
Note.This name is used for preparations of different composition.
Investi, Arg.
Pentoxifylline (p.1367·2).
Intermittent claudication.

Procter & Gamble, Fr.
Fluindione (p.1290·2).
Thromboembolic disorders.

Previta *Sofex, Port.*
Ticlopidine hydrochloride (p.1411·2).

Prevnar *Wyeth, Canad.; Lederle, Israel; Wyeth-Ayerst, Thai.; Wyeth-Ayerst, USA.*
A pneumococcal conjugate vaccine (7-valent) (p.2231·2).
Active immunisation.

Prevolac *Cosmopharm, Gr.†.*
Azelaic acid (p.1589·3).
Acne.

Prevpac *TAP, USA.*
Capsules, lansoprazole (Prevacid) (p.1739·2); capsules, amoxicillin trihydrate (Trimox) (p.202·2); tablets, clarithromycin (Biaxin) (p.248·2).
Duodenal ulcer associated with Helicobacter pylori infection.

Prevulcer *Cellofarm, Braz.†.*
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prevyol-2 *Legrand, Braz.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Prexan *Lafare, Ital.*
Naproxen (p.92·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgias.

Prexanil *Servier, Cz.*
Perindopril erbumine (p.1368·3).
Cardiovascular risk reduction; heart failure; hypertension.

Prexaton *Alphapharm, Austral.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Prexidine *Expanscience, Fr.*
Chlorhexidine gluconate (p.1635·3).
Mouth infections.

Prexige *Novartis, Arg.; Novartis, Austral.†; Novartis, Braz.; Novartis, Chile; Novartis, Hung.; Novartis, Indon.; Novartis, NZ; Novartis, UK†.*
Lumiracoxib (p.78·1).
Osteoarthritis; pain.

Prexum
Servier, Indon.
Perindopril (p.1368·2).
Heart failure; hypertension; stroke prophylaxis.

Sermedica, Port.; Biogaran, S.Afr.
Perindopril erbumine (p.1368·3).
Heart failure; hypertension; myocardial infarction.

Prexum Plus *Biogaran, S.Afr.*
⊗ Perindopril erbumine (p.1368·3); indapamide (p.1314·1).
Hypertension.

Prezal *Aventis, Neth.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prezatim *Merck, Braz.†.*
Prezatide copper acetate (p.1611·2).
Cicatrisation.

Prezista
Janssen-Cilag, Austral.; Janssen-Cilag, Cz.; Janssen-Cilag, UK.
Darunavir (p.869·1).
HIV infection.

Janssen-Cilag, Port.; Tibotec, USA.
Darunavir ethanolate (p.869·1).
HIV infection.

Prezita *Janssen-Cilag, Gr.*
Darunavir (p.869·1).
HIV infection.

Prezolon *Nycomed, Gr.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Priacin *Pharmacypria, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Priadel
Sanofi-Aventis, Belg.; Sanofi Synthelabo, Malaysia†; Bamford, NZ; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Singapore†; Sanofi Synthelabo, Switz.
Lithium carbonate (p.401·3).
Aggressive or self-mutilating behaviour; bipolar disorder; depression; mania.

Sanofi-Aventis, Irl.; Sanofi-Aventis, UK.
Lithium carbonate (p.401·3) or lithium citrate (p.401·3).
Aggressive or self-harming behaviour; bipolar disorder; depression; mania.

Prialt *Eisai, Cz.; Eisai, Fr.; Elan, Neth.; Eisai, Port.; Eisai, UK; Elan, USA.*
Ziconotide acetate (p.133·3).
Pain.

Prialta *OEP, Philipp.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Pribac *Liferpal, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Pricam *Mintlab, Chile.*
Piroxicam (p.117·3).
Inflammation; pain.

Priciasol *Labima, Belg.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Pricillin *Malayan, Singapore†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Pricital *Lavipharm, Gr.*
Citalopram (p.385·3).
Depression.

Prickly Heat Powder *Church & Dwight, Austral.*
Zinc oxide (p.1621·2).
Chafed skin; eczema; heat rash; prickly heat.

Pricoron *Zentiva, Cz.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Pridam *Pisa, Mex.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Hypotension.

Pridana *Novartis, Port.*
Pirisudanol maleate (p.2369·2).
Mental function disorders.

Pridecil *Farmalab, Braz.*
Bromopride (p.1713·3).
Nausea and vomiting.

Pridesia *Sanbe, Indon.*
Cisapride (p.1720·3).
Gastrointestinal disorders.

Pri-De-Sid *Polipharm, Thai.†.*
Cisapride (p.1720·3).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders; gastroparesis.

Pridio *Quimifar, Spain.*
Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); salicylamide (p.121·2).
Fever; nasal congestion; pain.

Prifen *Soho, Indon.*
Ibuprofen (p.64·2).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Priftin *Hoechst Marion Roussel, USA.*
Rifapentine (p.329·3).
Tuberculosis.

Prigost *Rider, Chile.*
Bromocriptine mesilate (p.798·1).
Hyperprolactinaemia; parkinsonism.

Prikap *Elea, Arg.*
Levodopa (p.804·3); carbidopa (p.803·1).
Carbon monoxide poisoning; manganese poisoning; parkinsonism.

Prilace
Note.This name is used for preparations of different composition.
Arrow, Austral.
Ramipril (p.1385·3).
Heart failure; hypertension.

Sanofi-Aventis, Ital.
⊗ Ramipril (p.1385·3); piretanide (p.1372·3).
Hypertension.

Farma, Venez.
Enalapril maleate (p.1276·1).
Asymptomatic left-ventricular dysfunction; heart failure; hypertension.

Prilagin *Sofar, Ital.*
Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Candidiasis; Gram-positive bacterial infections.

Prilan *Sofex, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Prilcor *Sigma, Braz.*
Lisinopril (p.1325·2).
Hypertension.

Prilitab-HCT *Tiefenbacher, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Prilitaril-HCT *Tiefenbacher, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Prilosec *AstraZeneca, USA.*
Omeprazole (p.1753·1) or omeprazole magnesium (p.1753·1).
Gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Prilosin *Cipla-Medpro, S.Afr.†.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Prilovase *Pentafarma, Port.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Prilpressin *Legrand, Braz.*
Captopril (p.1239·2).
Hypertension.

Priltenk *Biotenk, Arg.*
Enalapril maleate (p.1276·1).
Atherosclerosis; heart failure; hypertension; myocardial infarction.

Prim E *Mega Lifesciences, Malaysia.*
Evening primrose oil (p.2302·1); vitamin E (p.1992·2).
Premenstrual syndrome; skin disorders.

Prima Derm *Metanoia, Fr.*
Barrier preparation.

Primabion *Sandoz, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Migraine; neuritis; neuropathy; peripheral circulatory disorders; vomiting of pregnancy.

Primacaine *IMS, Ital.†.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Prima-Cal *Nupharma, Thai.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Prima-Cal Plus Vit D *Nupharma, Thai.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Primace *Novopharm, Philipp.; Pascual, Philipp.*
Captopril (p.1239·2).
Hypertension.

Primacef *Bergamo, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Primacillin *Medikon, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Primacin *Boucher & Muir, Austral.*
Primaquine phosphate (p.608·1).
Malaria.

Primacine *Pinewood, Irl.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Primacip *Cipla, India.*
Primaquine phosphate (p.608·1).
Malaria.

Primacor *Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Braz.; Sanofi Synthelabo, Canad.†; Sanofi Synthelabo, Hong Kong; Sanofi Winthrop, Israel; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi-Aventis, NZ; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, UK; Sanofi Winthrop, USA.*
Milrinone lactate (p.1341·2).
Heart failure.

Primactam *Meditrina, Gr.*
Tolfenamic acid (p.130·1).
Inflammatory disorders.

Primacton *Streuli, Switz.*
⊗ Spironolactone (p.1400·1).
Cirrhosis with ascites; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Primacy C+AHA *Dispolab, Chile†.*
Ascorbic acid (p.1983·3); glycolic acid (p.1598·1); lactic acid (p.2329·3); zinc sulfate (p.1999·2).
Acne; skin pigmentation disorders.

Primacy Phyto + *Dispolab, Chile†.*
Kojic acid (p.1603·3); bearberry (p.2263·3); thyme (p.2401·1); pepino; citrus bioflavonoids (p.2304·1).
Skin pigmentation disorders.

Primaderm
Note.This name is used for preparations of different composition.
Aventis, Arg.†.
⊗ Prednicarbate (p.1540·2).
Skin disorders.

Roi Surya, Indon.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Primadex *Dexa, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Primadol *Soho, Indon.*
Paracetamol (p.108·1); metoclopramide hydrochloride (p.1747·3).
Fever; migraine; pain.

Primadrill *Pierre Fabre Sante, Fr.*
Althaea (p.2253·3).
Mouth and throat disorders.

Primadryl Plus *Sandoz, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Cough.

Prima-E *Sandoz, Indon.*
d-Alpha tocopherol (p.1992·2).
Antoxidant.

Primafluor *Prima, Braz.†.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Primakinder *Kinder, Braz.*
Primaquine phosphate (p.608·1).
Malaria.

Primalan *Pierre Fabre, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Ital.†; Pierre Fabre, Mex.; Natrapharm, Philipp.; Pierre Fabre, Port.; Pierre Fabre, Rus.*
Mequitazine (p.585·3).
Allergic conjunctivitis; allergic rhinitis; atopic eczema; hypersensitivity reactions; pruritus; urticaria.

Primamet *Lek, Cz.*
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; acute pancreatitis; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Primanol *Jamieson, Canad.†.*
Evening primrose oil (p.2302·1).

Primanol Borage Oil *Jamieson, Canad.*
Evening primrose oil (p.2302·1); borage oil (p.2267·3).

Primaquin *Gynopharm, Chile.*
Estradiol (p.2097·2).
Menopausal disorders.

Primaquin MP *Gynopharm, Chile.*
18 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Primaquin MP Continuo *Gynopharm, Chile.*
Estradiol (p.2097·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Primasef *Nevzat, Turk.*
Sulbactam (p.335·1); cefoperazone (p.227·2).
Bacterial infections.

Primasept Med *Schulke & Mayr, Ger.†.*
Propyl alcohol (p.1660·2); isopropyl alcohol (p.1650·3); orthophenylphenol (p.1655·1).
Hand disinfection.

Primaspan *Orion, Fin.*
Aspirin (p.20·3).
Rheumatoid arthritis; thromboembolism prophylaxis.

Primastick *Omega, Fr.*
Pregnancy test (p.2372·1).

Primatam *Sandoz, Indon.*
Piracetam (p.368·2).
Cerebral trauma; chronic alcoholism; mental function impairment.

Primatene *Whitehall-Robins, USA.*
⊗ Ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Formerly contained ephedrine hydrochloride and theophylline.
Bronchial asthma.

Primatene Mist *Wyeth Consumer, USA.*
⊗ Adrenaline (p.1203·2).
Bronchial asthma.

Primatene Mist Suspension *Wyeth Consumer, USA.*
⊗ Adrenaline acid tartrate (p.1203·2).
Bronchial asthma.

Primatenol *Streuli, Switz.†.*
⊗ Atenolol (p.1217·3).
Angina; arrhythmias; hypertension; myocardial infarction.

Primatenol Plus *Streuli, Switz.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Primatime *Omega, Fr.*
Fertility test (p.2372·1).

Primatour *Viatris, Neth.*
Chlorcyclizine hydrochloride (p.571·2); cinnarizine (p.573·1).
Motion sickness.

Primatuss Cough Mixture 4 *Rugby, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Primatuss Cough Mixture 4D *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Primavax *Vianex (Βιανεξ), Gr.†.*
A diphtheria, tetanus, and hepatitis B vaccine (p.2210·2).
Active immunisation.

Primavent *Boehringer Ingelheim, Philipp.*
⊗ Budesonide (p.1520·1).
Asthma.

Primavera-N *Fabra, Arg.*
Metoclopramide hydrochloride (p.1747·3).
Dyspepsia; nausea and vomiting.

Primaxin *MSD, Austral.; Merck Frosst, Canad.; Vianex (Βιανεξ), Gr.; MSD, NZ; MSD, UK; Merck, USA.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Bacterial infections.

Primazole *Kalbe, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Primbactam *Menarini, Ital.*
Aztreonam (p.209·2).
Gram-negative bacterial infections.

Primcillin *AstraZeneca, Denm.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Primene *Baxter Immuno, Arg.; Baxter, Austral.†; Baxter, Austria; Baxter, Canad.; Baxter, Cz.; Baxter, Fr.; Baxter, Ger.; Baxter, Gr.; Kalbe, Indon.; Baxter, Irl.; Baxter, Mex.†; Clintec, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Spain; Baxter, UK.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in infants.

Primera *Eurofarma, Braz.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Primeral *Sanofi-Aventis, Braz.*
Bromopride (p.1713·3); dimeticone (p.1770·2); pepsin (p.2365·1); α-amylase (p.2256·3); lipase (p.2360·3).
Digestive disorders; nausea and vomiting.

Primeran *Sanofi Synthelabo, Gr.†.*
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Acid aspiration; aid in diagnostic procedures; delayed gastric emptying; gastro-oesophageal reflux disease; nausea and vomiting.

Primesin *Schwarz, Ital.; Schwarz, Switz.*
Fluvastatin sodium (p.1290·2).
Hypercholesterolaemia; ischaemic heart disease.

Primil *Francia, Ital.*
Magnesium; potassium; vitamins (p.1922·1).
Nutritional supplement.

Primiprost *AstraZeneca, India.*
Dinoprostone (p.2007·1).
Labour induction.

Primobolan
Schering, Austral.
⊗ Metenolone enantate (p.2116·3).
Breast cancer in women; osteoporosis.

Schering, Ger.†; Schering, Mex.
⊗ Metenolone acetate (p.2116·3) or metenolone enantate (p.2116·3).
Anabolic; aplastic anaemia; liver disorders; osteoporosis.

Schering, S.Afr.
⊗ Metenolone acetate (p.2116·3).
Aplastic anaemia.

Primobolan Depot *Shepa, Gr.†; Schering, Spain.*
⊗ Metenolone enantate (p.2116·3).
Anabolic.

Primocef *Julphar, UAE.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Primocid *Genepharm, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Primodian Depot *Schering, S.Afr.; Schering, Thai.*
⊗ Estradiol valerate (p.2097·3); testosterone enantate (p.2130·1).
Menopausal disorders; osteoporosis.

Primodium
Ikapharmindo, Indon.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Janssen-Cilag, Swed.
Loperamide oxide (p.1741·2).
Diarrhoea.

Primofenac *Streuli, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Primofol Depot *Schering, Chile†.*
Estradiol valerate (p.2097·3).
Amenorrhoea; oestrogen deficiency.

Primogonyl *Schering, Ger.†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism, hypogonadism, and delayed puberty in males; infertility in females.

Primogyn *Schering, Mex.*
Estradiol valerate (p.2097·3).
Amenorrhoea; menopausal disorders; menorrhagia; oestrogen deficiency; uterine hypoplasia.

Primogyn Depot *Schering, Austral.; Schering, S.Afr.*
Estradiol valerate (p.2097·3).
Amenorrhoea; dysfunctional uterine bleeding; menorrhagia; oestrogen deficiency; uterine hypoplasia.

Primogyna *Schering, Braz.; Schering, Chile†.*
Estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

Primolin *Hovid, Malaysia†; Swiss Bio, Malaysia†; Vita Health, Malaysia†; Tribest, S.Afr.*
Evening primrose oil (p.2302·1).
Dietary supplement; premenstrual syndrome; skin disorders.

Primolin GLA MAX *Swiss Bio, Malaysia†.*
Borage oil (p.2267·3).
Hair, nail, and skin disorders; premenstrual syndrome.

Primolin Total Woman *Swiss Bio, Malaysia†.*
Dong quai; bearberry; ginkgo biloba; capsicum; garlic; centella; evening primrose oil; cimicifuga; taraxacum; ginseng; ginger; liquorice; echinacea; viburnum opulus (p.1922·1).
Menopausal disorders; premenstrual syndrome.

Primolut Depot *Schering, Chile†; Schering, Mex.*
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; female infertility; threatened miscarriage; recurrent miscarriage; uterine hypoplasia.

Primolut N *Schering, Austral.; Schering, Fin.; Schering, Hong Kong; German Remedies, India; Schering, Indon.; Schering, Irl.; Bayer Schering, Malaysia; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, S.Afr.; Bayer, Singapore; Schering, Switz.; Schering, Thai.; Schering, Turk.; Schering, UK.*
Norethisterone (p.2119·3).
Adjunct to oestrogen replacement therapy; amenorrhoea; benign breast disorders; dysfunctional uterine bleeding; endometriosis; malignant neoplasms; menopausal disorders; menorrhagia; postponement of menstruation; premenstrual syndrome; progestogen-only oral contraceptive.

Primolut-Nor *Schering, Arg.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Schering, Cz.†; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Schering, Israel; Schering, Ital.; Schering, Mex.; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, Spain; Schering, Swed.*
Norethisterone acetate (p.2119·3).
Amenorrhoea; benign breast disorders; breast or endometrial cancer; dysfunctional uterine bleeding; endometriosis; female infertility; fibromas; functional uterine haemorrhage; hormone replacement therapy; menopausal disorders; menorrhagia; osteoporosis; postponement of menstruation; progestogen-only oral contraceptive; secondary amenorrhoea; uterine hypoplasia.

Primoniat Depot *Schering, Chile.*
⊗ Testosterone propionate (p.2130·1); testosterone enantate (p.2130·1).
Some injections contain only testosterone enantate.
Aplastic anaemia; breast cancer; male hypogonadism.

Primonil *Teva, Israel.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis.

Primoptic *Allergan, Thai.†.*
Trimethoprim (p.355·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Primoris *Herbarium, Braz.*
Linoleic acid (p.2308·2); oleic acid (p.2030·1); gamolenic acid (p.2308·2).

Primosiston
Note.This name is used for preparations of different composition.
Schering, Arg.; Schering, Mex.†.
Hydroxyprogesterone caproate (p.2110·3); estradiol benzoate (p.2097·2).
Menorrhagia; metrorrhagia.

Schering, Austria; Schering, Braz.; Schering, Chile.
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Dysfunctional uterine bleeding; menorrhagia; polymenorrhoea.

Schering, Switz.†; Schering, Venez.†.
Injection: Hydroxyprogesterone caproate (p.2110·3); estradiol benzoate (p.2097·2).
Metrorrhagia.

Schering, Ger.†; Schering, Switz.; Schering, Venez.†.
Tablets: Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Menstrual disorders.

Primoson-F *Sons, Mex.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Primostat *Schering, Mex.*
Gestonorone caproate (p.2105·3).
Benign prostatic hyperplasia; endometrial cancer.

Primoteston Depot
Schering, Austral.; Schering, Mex.; Schering, NZ.
⊗ Testosterone enantate (p.2130·1).
Aplastic anaemia; breast cancer; male androgen deficiency; male hypogonadism.

Schering, Norw.
⊗ Testosterone enantate (p.2130·1); testosterone propionate (p.2130·1).
Some injections contain only testosterone enantate.
Androgenic; hypogonadism in males.

Primotox *Vitae, Mex.*
Ceftriaxone (p.238·1).
Bacterial infections.

Primotren *Lek, Cz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Primover *Alcon Cusi, Spain.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Primovist *Schering, Austria; Schering, Cz.; Schering, Fin.; Schering, Gr.; Bayer Schering, Hung.; Schering, Neth.; Schering, Norw.; Schering, Swed.; Schering, Switz.; Bayer, UK.*
Sodium gadoxetate (p.1481·1).
Contrast medium for magnetic resonance imaging of the liver.

Primoxil *Sandoz, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Primperan
Sanofi-Aventis, Belg.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Astellas, Jpn; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.
Metoclopramide (p.1747·3) or metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; gastro-oesophageal reflux; gastrointestinal motility disorders; nausea and vomiting.

Sanofi-Aventis, Gr.; Biofarma, Turk.
Metoclopramide (p.1747·3).
Gastrointestinal motility disorders.

Sanofi Synthelabo, Hong Kong; Delagrange, Indon.; Soho, Indon.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi-Aventis, Port.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Berk, UK; Sanofi-Aventis, Venez.
Metoclopramide hydrochloride (p.1747·3).
Aid in gastrointestinal examination; dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders; gastroparesis; nausea; vomiting.

Primperan Compositum *Delagrange, Indon.; Soho, Indon.*
Metoclopramide hydrochloride (p.1747·3); pancreatin (p.2360·1).
Gastrointestinal disorders.

Primperil *Lafedar, Arg.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Primpesasy *Sanofi Synthelabo, Mex.*
Metoclopramide hydrochloride (p.1747·3); dimeticone (p.1770·2).
Aid to gastrointestinal examination; gastritis; hiatus hernia; nausea and vomiting; oesophagitis; peptic ulcer.

Primsoja *Gayoso, Spain.*
Soya (p.1965·3).
Menopausal disorders.

Primsol *Ascent, USA.*
Trimethoprim hydrochloride (p.356·3).
Otitis media; urinary-tract infections.

Primsulfon *Novell, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Primulex *Biogal-Teva, Hung.†.*
⊗ Selegiline hydrochloride (p.817·1).
Dementia; parkinsonism.

Primum *Sandoz, Arg.*
Flunitrazepam (p.996·2).
Hypnotic.

Primunox *Solas, Indon.*
Echinacea purpurea (p.2298·1); phyllanty.
Immunomodulator.

Primyxine *Tradiphar, Fr.†.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Skin and wound infections.

Prinac Ac *Collins, Mex.*
Folic acid (p.1940·1).
Anaemias.

Prinachol *Zurita, Braz.*
Boldo (p.2267·2).
Formerly contained cynara and boldo.
Liver disorders.

Prinarten *Liferpal, Mex.*
Captopril (p.1239·2).
Hypertension.

Prinasma *Medikon, Indon.*
⊗ Ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1).
Asthma.

Princess Prolib *Novartis, Spain†.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; cardiovascular risk reduction; hyperlipidaemias.

Princi B1 + B6 *Sanofi Synthelabo, Neth.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency associated with alcoholism.

Princi-B
Eumedica, Belg.
Vitamin B substances (p.1922·1).
Alcoholism; cardiovascular disorders; drug intoxication; neurogenic pain; rheumatic pain.

Sanofi Synthelabo, Thai.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Beri-beri; neuritis.

Princi-B Fort *Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Diabetic neuropathy; neuralgias; neuritis; tonic; vitamin B deficiency.

Principen *Apothecon, USA.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Principrox *Streuli, Switz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Princol *Provit, Mex.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Prindex *Armstrong, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2).
Upper respiratory-tract congestion.

Prinex *Unipharma, Gr.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Prinil *Mepha, Switz.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Priniser *Serral, Mex.*
Lisinopril (p.1325·2).
Hypertension.

Prinivil *MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Cz.; BMS, Fr.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; BMS, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, NZ; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Singapore; BMS, Spain; Merck, USA; MSD, Venez.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Prinivil Plus *BMS, Spain.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Prinol Plus *Rivero, Arg.†.*
Preparation for enteral nutrition (p.1922·1).

Prinopril *Cifarma, Braz.*
Lisinopril (p.1325·2).
Hypertension.

Prinorm *Valeant, Hung.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Prinox *Andromaco, Arg.*
Alprazolam (p.960·1).
Anxiety; panic attacks; phobias.

Printan *Raffo, Chile.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene.

Prinzide *MSD, Braz.; Merck Frosst, Canad.; BMS, Fr.; Vianex (Βιανεξ), Gr.; BMS, Ital.; MSD, Mex.; MSD, Port.; Mepha, Switz.; Merck, USA.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Prioderm *Meda, Belg.; Norpharma, Denm.; Mundipharma, Fin.; Viatris, Fr.; SSL, Irl.; Rafa, Israel; SSL, NZ; Viatris, Neth.; Mundipharma, Norw.; Mundipharma, Swed.; Mundipharma, Switz.; SSL, UK.*
Malathion (p.2046·1).
Pediculosis; scabies.

Priorin *Bayer, Austria; Roche Consumer, Ger.†; Roche, Turk.*
Millet; calcium pantothenate; cystine (p.1922·1).
Hair and nail disorders.

Priorin N *Bayer, Switz.*
Millet; calcium pantothenate; cystine; wheat-germ oil (p.1922·1).
Hair and nail disorders.

Priorix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Cz.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Smith Kline & French, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
A measles, mumps, and rubella vaccine (attenuated Schwarz, RIT 4385, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

Priorix-Tetra *GSK, Cz.; GSK, NZ; GSK, Port.*
A measles, mumps, rubella, and varicella-zoster vaccine (Schwarz, Jeryl Lynn RIT 4385, Wistar RA 27/3, and OKA strains respectively) (p.2224·1).
Active immunisation.

Priovit 12 *SIT, Ital.*
Multivitamin preparation (p.1922·1).

Priper *Ivax, Arg.*
Pipemidic acid (p.315·1).
Bacterial infections.

Priper Plus *Ivax, Arg.*
Pipemidic acid (p.315·1); phenazopyridine (p.116·3).
Genito-urinary tract infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Pripsen
Note. This name is used for preparations of different composition.
Thornton & Ross, Irl.†.
Piperazine phosphate (p.153·1); sennosides (p.1769·3).
Ascariasis; enterobiasis.

Thornton & Ross, UK†.
Elixir: Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Thornton & Ross, UK.
Oral powder: Piperazine phosphate (p.153·1); senna (p.1769·2).
Ascariasis; enterobiasis.

Thornton & Ross, UK.
Tablets: Mebendazole (p.148·3).
Enterobiasis.

Priretic *Novapharma, Venez.†.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Priscol *IFET (ΙΦΕΤ), Gr.†.*
Tolazoline hydrochloride (p.1415·2).
Eye disorders.

Priscoline *IFET (ΙΦΕΤ), Gr.†.*
Tolazoline hydrochloride (p.1415·2).
Persistent pulmonary hypertension of the newborn.

Prisdal *Almirall, Spain.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder.

Prisma
Note. This name is used for preparations of different composition.
Pasteur, Chile.
Citalopram hydrobromide (p.385·3).
Depression.

Celltech, Ger.†.
Mianserin hydrochloride (p.408·1).
Depression.

Mediolanum, Ital.; Medinfar, Port.
Mesoglycan sodium (p.2342·3).
Chronic venous ulcer; peripheral vascular disorders.

Prismasol *Gambro, Denm.; Gambro, Neth.; Gambro, Port.; Hospal, Spain; Gambro, Swed.*
Glucose; calcium chloride; potassium chloride; magnesium chloride; sodium chloride; sodium bicarbonate; lactic acid (p.1670·3).
Haemodialysis; haemofiltration.

Prisoventril *Simoes, Braz.†.*
Phenolphthalein (p.1762·1); cascara (p.1715·2).
Constipation.

Pristesin F *Unipharm, Mex.*
Prilocaine hydrochloride (p.1868·2).
Felypressin (p.2302·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Pristine *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Ketoconazole (p.539·1).
Dandruff; fungal scalp disorders; pityriasis versicolor; seborrhoeic dermatitis.

Pristinex *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Ketoconazole (p.539·1).
Fungal skin and scalp disorders.

Pristiq *Wyeth, USA.*
Desvenlafaxine succinate (p.388·1).
Depression.

Pristonal *Cifarma, Braz.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pritacort *Molex Ayus, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Pritadol *Alter, Spain.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hyperlipidaemias.

Pritagesic *Molex Ayus, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Pritalinc *Molex Ayus, Indon.*
Lincomycin (p.293·1).
Bacterial infections.

Pritamox *Molex Ayus, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Pritanol
Note. This name is used for preparations of different composition.
Molex Ayus, Indon.
Allopurinol (p.552·2).
Hyperuricaemia.

Alodial, Port.
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Pritaren *Prime, Singapore.*
Diclofenac sodium (p.44·3).
Juvenile idiopathic arthritis.

Pritasma *Molex Ayus, Indon.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Pritavit *Molex Ayus, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Tonic; vitamin B and C deficiency.

Pritor *GSK, Arg.†; GSK, Austral.†; GSK, Braz.; Bayer, Cz.; GSK, Fr.; GSK, Gr.; Bayer, Hung.; GSK, Ital.; GSK, Neth.; GSK, Philipp.; Bayer, Pol.; Bayer, Port.; GSK, Rus.; GSK, Spain; GSK, Turk.; GSK, Venez.*
Telmisartan (p.1409·2).
Hypertension.

Pritor HCT *GSK, Braz.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Pritor Plus *GSK, Gr.; Bayer, Pol.; GSK, Spain; GSK, Turk.; GSK, Venez.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Pritoral *GSK, Chile†.*
Telmisartan (p.1409·2).
Hypertension.

PritorPlus *Bayer, Cz.; GSK, Fr.; Bayer, Hung.; GSK, Ital.; GSK, Neth.; GSK, Philipp.; Bayer, Port.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Privacom *Typharm, UK†.*
Clotrimazole (p.530·1).
Vaginal candidiasis.

Privast *Aurora, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Privigen *CSL Behring, USA.*
A normal immunoglobulin (p.2225·3).
Immune thrombocytopenic purpura; primary immunodeficiency.

Privin *Novartis, Austria; Novartis Consumer, Ger.*
⊗ Naphazoline nitrate (p.1565·2).
Aid to cystoscopy and rhinoscopy; nasal congestion.

Privina *Novartis, Arg.; Novartis, Braz.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Privine *Insight, USA.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Privituss *Mitim, Ital.; Alpharma, Mex.*
Levocloperastine fendizoate (p.1554·3).
Cough; coughs.

Prixar *Lepetit, Ital.; Medcor, Neth.*
Levofloxacin (p.292·2).
Bacterial infections.

Prixin *Richmond, Arg.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Prixina *Faran, Gr.*
Prulifloxacin (p.320·1).
Bacterial infections.

Prixlae *Shou Chan, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders.

Prizelip *Ferakon, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Prizem *Solfran, Mex.†.*
Diazepam (p.986·3).
Anxiety; sedative.

Prizma *Unipharm, Israel.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Prizogen *Vonnace, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Pro Lertus *Tecnofarma, Chile.*
Diclofenac colestyramine (p.46·1).
Inflammation; musculoskeletal and joint disorders; pain.

Pro Ulco *Solvay, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Proacid *Ziololek, Pol.*
Aluminium glycinate (p.1706·2); magnesium carbonate (p.1743·1).
Gastritis; hyperacidity; peptic ulcer.

Proacne *Harbin, Thai.*
Isotretinoin (p.1599·2).
Acne.

Pro-Actidil *Wellcome, Israel†; Wellcome, Spain†.*
Triprolidine hydrochloride (p.592·3).
Hypersensitivity reactions; skin disorders.

Proactin *Schering-Plough, Venez.†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

ProActive *Pharmaton, Switz.*
Multivitamin and mineral preparation with ginseng (p.1922·1).
Dietary supplement; tonic.

Proaf *Abic, Israel.*
⊗ Isoflupredone acetate (p.1537·2); ephedrine hydrochloride (p.1558·2); naphazoline nitrate (p.1565·2).
Rhinitis; sinusitis.

Proagil *HWS OTC, Austria.*
Homoeopathic preparation.

Proair
Note. A similar name is used for preparations of different composition (see below).
Montpellier, Arg.
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

ProAir
Note. A similar name is used for preparations of different composition (see above).
Ivax, USA.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

ProAktiv *Boehringer Ingelheim, Austria.*
A multivitamin and mineral preparation (p.1922·1) with ginseng (p.2312·1).
Tonic.

Proalid *Darier, Mex.*
Tacrolimus (p.1843·1).
Atopic eczema.

Proaller *Pekana, Ger.†.*
Homoeopathic preparation.

ProAmatine *Shire Richwood, USA.*
⊗ Midodrine hydrochloride (p.1341·1).
Orthostatic hypotension.

Proampi *GSK Sante, Fr.*
Pivampicillin (p.316·3).
Bacterial infections.

Proartinal *Provit, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain.

Proasma-T *Medicine Products, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour.

Proaxen *Pentafarma, Port.*
Oxcarbazepine (p.490·3).
Epilepsy; trigeminal neuralgia.

Pro-Banthine *Sigma, Austral.; RPG, India; Soho, Indon.; Sigma, NZ; Aspen, S.Afr.; Concord, UK; Schiapparelli Searle, USA.*
Propantheline bromide (p.1764·3).
Adjunct in gastrointestinal diagnostic procedures; gastritis; gastrointestinal spasm; hyperhidrosis; irritable bowel syndrome; neurogenic bladder; nocturnal enuresis; peptic ulcer; renal colic; urinary incontinence.

Probase 3 *Schering-Plough, UK.*
Emollient.
Dry skin.

Probat *Tanabe, Indon.*
Guaifenesin (p.1561·3).
Cough.

Probax *Fischer, USA.*
Propolis (p.2373·3).
Skin disorders.

Probec *Farmoquimica, Braz.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Probecid *AstraZeneca, Fin.†; AstraZeneca, Norw.; AstraZeneca, Swed.*
⊗ Probenecid (p.558·2).
Adjunct to beta-lactam antibacterials; gout; gouty arthritis.

Probec-T *J&J-Merck, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Probeks *Hebron, Braz.†.*
Aloe vera (p.1588·2).
Skin disorders.

Proben *Aspen, S.Afr.*
⊗ Probenecid (p.558·2).
Gout.

Probendazol *Prodotti, Braz.*
Mebendazole (p.148·3).
Worm infections.

Probenil *Elofar, Braz.*
Amoxicillin (p.202·2).
Bacterial infections.

Probenxil *Cimed, Braz.*
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Inflammation.

Probeta *Allergan, Canad.†.*
⊗ Levobunolol hydrochloride (p.1882·3); dipivefrine hydrochloride (p.2295·3).
Glaucoma; ocular hypertension.

Pro-Bextra *Pfizer, Chile.*
Parecoxib sodium (p.111·3).
Postoperative pain.

Probialbumin *Octafarma, Mex.†.*
⊗ Albumin (p.1052·1).
Plasma volume expansion.

Probigol *Omeofarma, Ital.*
Propolis (p.2373·3); echinacea (p.2298·1).
Oral hygiene.

Probionat *Safetynat, Fr.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Bifidobacterium breve* (p.2372·3).
Maintenance of gastrointestinal flora.

Pro-Bionate *Natren, USA.*
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

Probiotin *Tropica Mas, Indon.*
Clindamycin (p.251·1).
Gram-positive bacterial infections.

Probi-Rho D *Octafarma, Mex.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Probi-Tet *Probifasa, Mex.†.*
Tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Probitor *Sandoz, Austral.; Biochemie, Austria†; Sandoz, Gr.; Sandoz, Malaysia†; Sandoz, Thai.; Sandoz, Venez.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Probivac-B *Probiomed, Mex.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Probizal *Loeffler, Mex.*
Nitrofurazone (p.309·1).
Bacterial vulvovaginal infections.

Problok
Note. This name is used for preparations of different composition.
Esteve, Cz.†.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; variceal haemorrhage; Zollinger-Ellison syndrome.

Terra, Turk.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine.

Probofex *Tridoss, India.*
Ferrous aminoate (p.1950·3); folic acid (p.1940·1); vitamin B ; vitamin B .
Formerly contained ferrous fumarate, folic acid, vitamin B , vitamin B , and nicotinamide.
Iron-deficiency anaemia.

Probrain
Note. A similar name is used for preparations of different composition (see below).
Royal, Chile.
Rivastigmine (p.369·2).
Alzheimer's disease.

ProBrain
Note. A similar name is used for preparations of different composition (see above).
Seven Seas, UK.
Omega-3 triglycerides (p.1362·2); ginkgo biloba (p.2311·1).
Dietary supplement.

Probue *Vesco, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Probufen *Nakornpatana, Thai.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Probuxil *Quimica y Farmacia, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Pro-C *Procare, Austral.†.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Pro-30C *Capo Sole, Ital.†.*
Propolis (p.2373·3).

Procadax *Fulford, India.*
Ceftibuten (p.235·3).
Bacterial infections.

Procadil *Recordati, Ital.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Procal
Note. A similar name is used for preparations of different composition (see below).
Christiaens, Belg.†.
Sodium fluoride (p.1962·2).
Osteoporosis.

Pro-Cal
Note. A similar name is used for preparations of different composition (see above).
Vitaflo, Irl.; Vitaflo, UK.
Preparation for enteral nutrition (p.1922·1).

ProcalAmine *Pisa, Mex.; Eczacibasi-Baxter, Turk.; McGaw, USA; Victus, Venez.*
Amino-acid, glycerol, and electrolyte preparation (p.1922·1).
Parenteral nutrition.

Procalcio *Finadiet, Arg.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis.

Procalm *Naturex, Mex.†.*
St John's wort (p.422·3).
Anxiety; depression.

Procalmil *Arkopharma, Fr.*
St John's wort (p.422·3).
Depression.

Procamide *Zambon, Braz.*
Procainamide hydrochloride (p.1377·2).
Arrhythmias.

Procan *Erfa, Canad.*
Procainamide hydrochloride (p.1377·2).
Arrhythmias.

Procanbid *Monarch, USA.*
Procainamide hydrochloride (p.1377·2).
Formerly called Procan SR.
Ventricular arrhythmias.

Procanest *Gray, Arg.*
Procaine hydrochloride (p.1869·1).
Local anaesthesia.

Procaneural *RAN, Ger.†.*
Procaine hydrochloride (p.1869·1); caffeine (p.1116·3).
Nervous system disorders.

Procaptan *Stroder, Ital.*
Perindopril erbumine (p.1368·3).
Heart failure; hypertension.

Procardia *Pfizer, USA.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Procardin
Note. This name is used for preparations of different composition.
Medochemie, Hong Kong; Medochemie, Singapore.
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Medikon, Indon.
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Procardio *Meprofarm, Indon.*
Crataegus (p.2289·1); salviae miltiorrhizae; notoginseng; levocarnitine (p.1932·2) and levocarnitine tartrate; vitamin B .
Cardiac disorders.

Procardol *Adelco, Gr.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Pro-Cas *Milk Industries, Israel.*
Protein supplement (p.1922·1).

Procasol *Solfran, Mex.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Procavit *EMS, Braz.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Proceane Hypertonique *Proceane, Fr.*
Mineral preparation (p.1922·1).
Nutritional supplement; tonic.

Proceane Isotonique
Note. This name is used for preparations of different composition.
Proceane, Fr.
Nasal spray: Sea water (p.1686·1).
Nasal cleansing; nasal dryness.

Proceane, Fr.
Oral solution: Mineral preparation (p.1922·1).
Nutritional supplement.

Procef *BMS, Austria†; BMS, Chile†; BMS, Gr.; BMS, Hong Kong; Dompe, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, Philipp.; BMS, Port.; BMS, Singapore†; BMS, Switz.; BMS, Thai.; BMS, Venez.*
Cefprozil (p.232·2).
Bacterial infections.

Procefa *Promed, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Procelac *Ivax, Arg.*
Omeprazole (p.1753·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Procephal *Provit, Mex.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Procepim *Meprofarm, Indon.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Proceptin *Beximco, Singapore.*
Omeprazole (p.1753·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Procere *Pyridam, Indon.*
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Procetam *Meprofarm, Indon.*
Piracetam (p.368·2).
Cerebral trauma; chronic alcoholism; mental function impairment.

Procetoken *Bernabo, Arg.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Prochic *Millimed, Thai.*
Colchicine (p.556·1).
Gout.

Prochieve *Columbia, USA.*
Progesterone (p.2125·1).
Amenorrhoea; female infertility.

Prochlor *CCM, Malaysia; Beacons, Singapore.*
Prochlorperazine maleate (p.1020·1).
Anxiety; nausea and vomiting; psychoses; vomiting.

Prochol *Procare, Austral.†.*
Nicotinic acid (p.1957·3); oat bran (p.1712·3).
Hyperlipidaemias.

Prochor *Protein, Mex.†.*
⊗ Propranolol (p.1381·1).
Angina pectoris; hypertension.

Procicar *Medihealth, Mex.*
Zinc oxide (p.1621·2); calamine (p.1591·2).
Wounds.

Prociclide *Crinos, Ital.*
Defibrotide (p.1256·2).
Thrombosis prophylaxis.

Prociclina *Prodotti, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Pro-Cid *Ophthalmic Laboratories, Austral.*
⊗ Probenecid (p.558·2).
Adjunct to beta-lactam antibacterials; gout; reduction of cidofovir-associated nephrotoxicity.

Procilin *IQFA, Mex.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Procilina *Mayo, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Procillin
Note. This name is used for preparations of different composition.
Caps, S.Afr.
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Fako, Turk.
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Procimax *Libbs, Braz.*
Citalopram (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Procimeti *Provit, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Procin *Schering-Plough, Braz.†.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Procinet *Quesada, Arg.*
Tegaserod (p.1776·2).

Procion *Medipharm, Chile.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Procip *Ipca, India†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Procirex *KG, Ital.*
Bromopride hydrochloride (p.1713·3).
Digestive disorders.

Proclimine *Medicine Products, Thai.*
Oxyphencyclimine hydrochloride (p.1759·2).
Gastrointestinal disorders; genito-urinary disorders.

Proclor *Pentafarma, Port.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Procloril *Provit, Mex.*
Chloramphenicol (p.239·3).
Bacterial infections.

Proclose *Probiomed, Mex.*
Octreotide (p.1804·1).
Acromegaly; AIDS-associated diarrhoea; gastrointestinal endocrine tumours; postoperative pancreatic complications; variceal haemorrhage.

Proclozam *Meprofarm, Indon.*
Clobazam (p.477·2).
Anxiety; psychosomatic disorders.

Proclozine *Pharmasant, Thai.*
Prochlorperazine maleate (p.1020·1).
Alcoholism; anxiety; mania; schizophrenia.

Procodin *DHA, Singapore.*
Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Coughs.

Procodine *Medipharma, Hong Kong†.*
⊗ Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Cold and influenza symptoms.

Procof *Pharmacare, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); pholcodine (p.1570·2); guaifenesin (p.1561·3).
Coughs.

Procold
Note. This name is used for preparations of different composition.
Procare, Austral.†.
Ascorbic acid (p.1983·3); horseradish (p.2320·1); verbascum thapsus (p.2413·3); euphorbia hirta (p.2301·3); garlic (p.2309·2).
Respiratory-tract disorders.

Kalbe, Indon.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; influenza and cold symptoms.

Procolic *Meprofarm, Indon.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Procomvax *Aventis Pasteur, Austria; Sanofi Pasteur, Cz.; Chiron Behring, Ger.†; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.*
A haemophilus influenzae and hepatitis B vaccine (p.2213·3).
Active immunisation.

Proconfial *Schwabe, Arg.†.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Procor
Note. This name is used for preparations of different composition.
Unipharm, Israel.
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias; heart failure; myocardial infarction.

Prosel, Philipp.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Procoralan *Servier, Cz.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Irl.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, UK.*
Ivabradine hydrochloride (p.1320·2).
Angina pectoris.

Procordal *Muller Goppingen, Ger.*
Homoeopathic preparation.

Procordal Gold *Staufen, Ger.*
Homoeopathic preparation.

Procordal vertigo *Muller Goppingen, Ger.*
Homoeopathic preparation.

Procort *Roberts, USA.*
⊗ Hydrocortisone (p.1535·2).
Corticosteroid.

Procortin *Homeofarm, Pol.*
⊗ Hydrocortisone butyrate (p.1535·3).
Skin disorders.

Procorum *Abbott, Austria; Abbott, Ger.; Teva, Hung.; Abbott, Ital.; Knoll, Mex.; Abbott, Philipp.; Abbott, Thai.*
Gallopamil hydrochloride (p.1295·3).
Angina pectoris; arrhythmias; hypertension; ischaemic heart disease; myocardial infarction.

Procosa *Usana, Malaysia.*
Glucosamine (p.2313·2).
Osteoarthritis.

Procosa II *Usana, Mex.; Usana, Singapore.*
Glucosamine sulfate; turmeric; vitamins; minerals (p.1922·1).
Dietary supplement.

Procosamine *Usana, Hong Kong†.*
Glucosamine sulfate (p.2313·2); calcium ascorbate (p.1984·1); manganese; silicon.
Osteoarthritis.

Procoutol *Spirig, Switz.*
Triclosan (p.1665·2).
Skin disorders.

Procren *Abbott, Denm.; Abbott, Fin.; Abbott, Norw.; Abbott, Swed.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; prostatic cancer; uterine fibroma.

Procrin *Abbott, Spain.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; female infertility; precocious puberty; prostatic cancer; uterine fibroma.

Procrit *Ortho Biotech, USA.*
⊗ Epoetin alfa (p.1061·1).
Anaemia in cancer patients on chemotherapy; anaemia in zidovudine-treated HIV-infected patients; anaemia of chronic renal failure; pre-operative anaemias.

Proctase-P *Meiji, Thai.*
Proctase; pancreatin (p.2360·1).
Haematoma; inflammation; oedema; respiratory-tract congestion.

Proctena *Infosint, Ital.†.*
Hamamelis; aesculus; paeonia officinalis; cardiospermum halicacabum.

Proctidol *Novartis Consumer, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1).
Haemorrhoids.

Proctium *Esteve, Spain.*
⊗ Calcium dobesilate (p.2272·1); lidocaine hydrochloride (p.1862·3); prednisolone (p.1540·3).
Anorectal disorders.

Procto Synalar *Minerva (Μινερβα), Gr.†.*
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Procto Venart *Casasco, Arg.*
⊗ Ruscogenin (p.2382·2); prednisolone (p.1540·3); cinchocaine hydrochloride (p.1857·3); menthol (p.2340·1); zinc oxide (p.1621·2).
Haemorrhoids.

Proctoacid *Altana, Mex.*
Policresulen (p.1077·2); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Proctocort
Boehringer Ingelheim, Fr.†.
⊗ Hydrocortisone acetate (p.1535·2).
Crohn's disease; haemorrhagic colitis.

Salix, USA.
⊗ Hydrocortisone (p.1535·2) or hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Proctocream HC 2.5% *Schwarz, USA.*
⊗ Hydrocortisone acetate (p.1535·2).
Proctocream HC formerly contained hydrocortisone acetate and pramocaine hydrochloride.
Skin disorders.

Proctocrem *Ronnet, Arg.*
⊗ Lidocaine (p.1862·3); hydrocortisone (p.1535·2); menthol (p.2340·1).
Anorectal disorders.

Proctodan-HC *Odan, Canad.*
⊗ Pramocaine hydrochloride (p.1868·1); hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2).
Anorectal disorders.

Proctofoam
Note. This name is used for preparations of different composition.
Omnimed, S.Afr.†.
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Schwarz, USA.
Pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Proctofoam-HC *Duchesnay, Canad.; Meda, Irl.; Schwarz, Israel; Alloga, Ital.; Meda, UK; Schwarz, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Proctogel *Maver, Chile.*
Tribenoside (p.2403·3); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Procto-Glyvenol
Note. This name is used for preparations of different composition.
Novartis Consumer, Arg.; Novartis, Philipp.; Novartis Consumer, Port.; Novartis Consumer, Rus.
Tribenoside (p.2403·3); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Novartis, Braz.; Novartis Consumer, Cz.; Novartis, Mex.; Novartis Consumer, Pol.; Novartis Consumer, Switz.; Novartis, Turk.; Novartis, Venez.
Tribenoside (p.2403·3); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Anorectal disorders; haemorrhoids.

Novartis, Chile; Novartis, Gr.†.
Tribenoside (p.2403·3); lidocaine (p.1862·3).
Haemorrhoids.

Novartis Consumer, Israel.
Cream; suppositories: Tribenoside (p.2403·3); lidocaine (p.1862·3).
Anorectal disorders.

Novartis Consumer, Israel.
Topical spray: ⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Procto-Ikatral *Baliarda, Arg.*
⊗ OPC; lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2).
Haemorrhoids.

Procto-Jellin *Grunenthal, Ger.†.*
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Procto-Kaban *Asche, Ger.†.*
⊗ Clocortolone pivalate (p.1523·1); clocortolone caproate (p.1523·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Proctol *Odan, Canad.*
⊗ Hydrocortisone (p.1535·2); cinchocaine hydrochloride (p.1857·3); framycetin sulfate (p.279·1); esculoside (p.2248·2).
Anorectal disorders.

Proctolog *Pfizer, Fr.; Menarini, Port.; Pfizer, Singapore; Juste, Spain; Abdi, Turk.*
Ruscogenin (p.2382·2); trimebutine (p.2404·3).
Anorectal disorders; haemorrhoids.

Proctolyn *Recordati, Ital.*
⊗ Fluocinolone acetonide (p.1531·3); ketocaine hydrochloride (p.1862·1).
Anorectal disorders.

Procto-Metadyne *Hexa, Arg.*
⊗ Lidocaine hydrochloride (p.1862·3); phenylephrine hydrochloride (p.1568·1); betamethasone valerate (p.1519·1).
Haemorrhoids.

Proctomyxin HC *Sandoz, Canad.*
⊗ Hydrocortisone (p.1535·2); framycetin sulfate (p.279·1); cinchocaine hydrochloride (p.1857·3); esculoside (p.2248·2).
Anorectal disorders.

Proctonet *Uniderm, Ital.†.*
Mallow (p.2337·2); aesculus (p.2248·2); almond oil (p.2252·2); hamamelis (p.2318·2).
Anorectal disorders; personal hygiene.

Proctonostrum *Zimaia, Port.†.*
⊗ Aluminium acetate (p.2255·1); hydrocortisone acetate (p.1535·2); lidocaine (p.1862·3); zinc oxide (p.1621·2).
Anorectal disorders.

Proctoplex *Knop, Chile.*
Hamamelis (p.2318·2); aesculus (p.2248·2); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Proctopure *Dermofarma, Ital.*
Aescin (p.2248·2); aesculus (p.2248·2); hamamelis (p.2318·2); calendula (p.2273·1); liquorice (p.1740·3); melaleuca (p.2338·2).
Anorectal disorders.

Proctor's Pinelyptus *Ernest Jackson, UK.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); pine silvestris oil (p.2368·2); siberian fir oil.
Coughs; throat irritation.

Proctosan
Note. This name is used for preparations of different composition.
Hertz, Braz.
Azulene (p.2262·3); hamamelis (p.2318·2); lidocaine (p.1862·3); menthol (p.2340·1); aesculus (p.2248·2).
Haemorrhoids.

Stada, Rus.
Bufexamac (p.28·3); bismuth subgallate (p.1711·1); titanium dioxide (p.1617·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Proctosedyl
Note. This name is used for preparations of different composition.
Aventis, Austral.; Aventis, Cz.†; Sanofi-Aventis, NZ; Aventis, UK.
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone (p.1535·2).
Anorectal disorders; haemorrhoids; pruritus ani.

Axcan, Canad.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Hong Kong†; Sanofi-Aventis, Irl.; Sanofi-Aventis, Malaysia; Aventis, Norw.;

Aventis, Philipp.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Swed.†; Aventis, Thai.
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone (p.1535·2); framycetin sulfate (p.279·1); esculoside (p.2248·2).
Anorectal disorders; haemorrhoids.

Hub, India.
⊗ Hydrocortisone acetate (p.1535·2); heparin (p.1301·2); framycetin sulfate (p.279·1); esculoside (p.2248·2); benzocaine (p.1854·1); butyl aminobenzoate (p.1857·1).
Haemorrhoids.

Aventis, Neth.
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone (p.1535·2); framycetin sulfate (p.279·1).
Haemorrhoids.

Bayer, Ital.
Cream: ⊗ Amylocaine (p.1853·3); benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); esculoside (p.2248·2).
Anal pruritus; haemorrhoids.

Bayer, Ital.
Suppositories: ⊗ Benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); esculoside (p.2248·2).
Anal pruritus; haemorrhoids.

Proctosoll *Wassermann, Ital.*
⊗ Benzocaine (p.1854·1); hydrocortisone acetate (p.1535·2); heparin sodium (p.1301·2).
Haemorrhoids.

Proctosone *Technilab, Hong Kong†; Technilab, Malaysia†; Technilab, Pol.*
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1); esculoside (p.2248·2).
Anorectal disorders; haemorrhoids.

Proctosor *Soria Natural, Spain†.*
Shepherd's purse (p.2386·2); hydrastis (p.2321·3); cypress (p.2291·2).
Haemorrhoids; menstrual disorders; uterine fibroids; varices.

Proctospre *Hennig, Cz.†; Hennig, Ger.†.*
Cinchocaine (p.1857·2); chlorquinaldol (p.242·3); diphenylpyraline (p.578·2).
Anogenital disorders; anorectal disorders.

Proctosteroid *Aldo, Spain.*
⊗ Triamcinolone diacetate (p.1544·3).
Proctitis; proctosigmoiditis; ulcerative colitis.

Procto-Synalar
Note. This name is used for preparations of different composition.
Grunenthal, Austria.
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Astellas, Belg.
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3); bismuth subgallate (p.1711·1); menthol (p.2340·1).
Anorectal disorders.

Procto-Synalar N *Minerva (Μινερβα), Gr.; Grunenthal, Switz.*
⊗ Fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Proctozorin-N *Teva, Israel.*
⊗ Hydrocortisone (p.1535·2); allantoin (p.1588·1); benzocaine (p.1854·1); aluminium acetotartrate (p.2255·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Anorectal disorders.

Proctyl *Altana, Arg.; Nycomed, Braz.*
Policresulen (p.1077·2); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders; haemorrhoids.

Proculin *Chauvin Ankerpharm, Cz.†; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Conjunctivitis; eye congestion.

Procur *Douglas, Austral.; Douglas, NZ.*
Cyproterone acetate (p.2088·2).
Androgenisation in females; prostatic cancer; sexual deviation in males.

Procur Plus *Guardian, Indon.*
Essential phospholipids; vitamin B substances (p.1922·1); ginseng (p.2312·1); turmeric (p.1473·2).
Nutritional supplement.

Pro-Cure *MSD, Israel.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Procuta *Expanscience, Fr.*
Isotretinoin (p.1599·2).
Acne.

Procutan
Note. This name is used for preparations of different composition.
Sankyo, Braz.†.
Chloramphenicol (p.239·3); fibrinolysin (p.1287·3); dornase alfa (p.1557·1).
Skin infections.

Schering-Plough, S.Afr.
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Procutane *Lero, Fr.†.*
Fish oil; vitamin B substances; vitamin E; betacarotene; zinc; selenium yeast (p.1922·1).
Nutritional supplement.

Pro-Cute *Ferndale, USA.*
Emollient and moisturiser.

Procyclid *Valeant, Canad.†.*
Procyclidine hydrochloride (p.814·3).
Parkinsonism.

Procyclo *Organon, Ger.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Procythol *Sanofi-Aventis, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Procytox *Baxter, Canad.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Pro-Dafalgan *BMS, Belg.†; BMS, Denm.†; BMS, Fin.†; IFET (ΙΦΕΤ), Gr.; BMS, Israel†; BMS, Norw.; BMS, Port.†; BMS, Swed.†; Upsamedica, Switz.†.*
Propacetamol hydrochloride (p.119·2).
Fever; pain.

Prodafem *Pfizer, Austria; Pfizer, Switz.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; endometriosis; menopausal disorders; menorrhagia.

Prodamox *Rubio, Spain.*
Proglumetacin maleate (p.119·1).
Musculoskeletal, joint, and peri-articular disorders.

Prodasone *Pfizer, Chile.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; dysfunctional uterine bleeding; endometrial hyperplasia.

Prodazol *Protein, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

Prodeine *Dakota, Austral.; Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Cz.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Prodel *Pasteur, Chile.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Prodel B *Pasteur, Chile.*
⊗ Betamethasone (p.1518·2); chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Prodelion *Sandoz, Spain.*
Quinagolide hydrochloride (p.2377·1).
Hyperprolactinaemia.

Prodep *Sun, Rus.; Sun, Thai.*
Fluoxetine hydrochloride (p.391·2).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Pro-depon *BMS, Gr.†.*
Propacetamol (p.119·2).
Postoperative pain.

Proderm
Note. This name is used for preparations of different composition.
Galderma, Braz.; Intra Pharma, Irl.
Emollient.

Dow, USA.
Castor oil (p.2278·1); peru balsam (p.2365·3).
Decubitus ulcers.

Proderma *Cantabria, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Prodermal *Meprofarm, Indon.*
Tioconazole (p.548·2).
Fungal skin infections.

Prodexon *Meprofarm, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Pro-Diaban *Schering, Austria†.*
Glisoxepide (p.442·2).
Diabetes mellitus.

Prodiabet *Bernofarm, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Prodiabin-N *Probiomed, Mex.*
⊗ Isophane insulin injection (human) (p.443·2).
Diabetes mellitus.

Prodiamel *Corsa, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Prodiem Plain *Novartis Consumer, Canad.†.*
Psyllium hydrophilic mucilloid (p.1737·1).
Constipation.

Prodiem Plus *Novartis Consumer, Canad.†.*
Psyllium hydrophilic mucilloid (p.1737·1); senna pod (p.1769·2).
Constipation.

Prodif *Pfizer, Jpn.*
Fosfluconazole (p.535·2).
Fungal infections.

Prodifer *Provit, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Prodigrip *Aventis Pasteur, Spain†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Prodil *Farmasa, Braz.†.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia.

Prodilantin *Pfizer, Fr.*
Fosphenytoin sodium (p.481·3).
Epilepsy.

Prodis *Procare, Austral.†.*
Multivitamins, amino acids, ginseng, and minerals (p.1922·1).
Dietary supplement.

Prodisan *Embil, Turk.*
Azapropazone (p.26·3).
Ankylosing spondylitis; gout; rheumatoid arthritis.

Prodium
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Breckenridge, USA.
Phenazopyridine hydrochloride (p.116·2).
Irritation of the lower urinary tract.

Prodiuret *Sabona, Ger.†.*
Equisetum (p.2299·3).
Oedema; urinary-tract disorders.

Prodofenaco *Prodotti, Braz.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Fever; inflammation; pain.

Prodol *Technikon, S.Afr.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and gum pain.

Prodolina *Boehringer Ingelheim Promeco, Mex.*
Dipyrone (p.49·2).
Fever; pain.

prodolor *Stada, Ger.†.*
Naproxen (p.92·3).
Fever; pain.

Prodomix *Loeffler, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Prodon *AstraZeneca, Swed.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Prodop *Protein, Mex.†.*
Methyldopa (p.1334·1).
Hypertension.

Prodopa *Pacific, NZ.*
Methyldopa (p.1334·1).
Hypertension.

Prodopina *Prodotti, Braz.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Prodopirona *Prodotti, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Prodopressin *Prodotti, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Prodorol *Be-Tabs, S.Afr.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; phaeochromocytoma.

Prodotamol *Prodotti, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Prodoxacilina *Prodotti, Braz.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Prodoxican *Prodotti, Braz.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint and peri-articular disorders.

Prodoxidil *Prodotti, Braz.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Prodoxifilina *Prodotti, Braz.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Prodoxil *Prodotti, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Prodoxin *Prodotti, Braz.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Prodren *Alkon (Αλκον), Gr.†.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Product Code 889 *Scientific Hospital Supplies, Austral.†.*
Preparation for enteral nutrition (p.1922·1).
Methylmalonic acidaemia; propionic acidaemia.

Produvir *Prodotti, Braz.*
Zidovudine (p.913·3).
HIV infection.

Pro-Efferalgan *Upsa, Ital.†; BMS, Spain†.*
Propacetamol hydrochloride (p.119·2).
Pain.

Proendotel *Bausch & Lomb, Ital.*
Cloricromen hydrochloride (p.1251·3).
Thrombotic disorders.

Proepa *MSD, Braz.*
Polyunsaturated fatty acids (p.1922·1).
Thrombosis prophylaxis.

Pro-Epanutin *Pfizer, Austral.†; Pfizer, Austria; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Neth.†; Pfizer, Norw.; Pfizer, Swed.; Pfizer, UK.*
Fosphenytoin sodium (p.481·3).
Epilepsy; seizures associated with neurosurgery or head trauma.

Proesten *Procare, Austral.†.*
Vitamins; minerals (p.1922·1); garlic (p.2309·2); cimicifuga (p.2282·1); viburnum opulus; passion flower (p.2363·2); sarsaparilla (p.2383·3).
Dietary supplement; menopausal disorders.

Proetzonide *Dallas, Arg.*
⊗ Budesonide (p.1520·1).
Asthma.

Proetztotal
Note. This name is used for preparations of different composition.
Dallas, Arg.
Nasal spray: Phenylephrine hydrochloride (p.1568·1); neomycin sulfate (p.305·1); chlorphenamine maleate (p.571·3); gramicidin (p.286·1).

Dallas, Arg.
Nebuliser solution: ⊗ Phenylephrine hydrochloride (p.1568·1); neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).

Prof *Ivax, Arg.*
Chondroitin sulfate A (p.2280·3).
Degenerative joint disorders.

Profact *Aventis, Ger.*
⊗ Buserelin acetate (p.2083·2).
Prostatic cancer.

Profalexina *Prodotti, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Profalin CPS *Mayo, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Profamid *Orion, Denm.; Orion, Fin.*
Flutamide (p.725·1).
Prostatic cancer.

Profar *Organon, India.*
Allylestrenol (p.2082·2).
Benign prostatic hyperplasia.

Profargil *Profarb, Braz.†.*
Metronidazole (p.837·1); vitamin B ; vitamin B ; vitamin B (p.1922·1).
Alcoholism; protozoal infections.

Profasi *Serono, Arg.†; Serono, Austral.; Serono, Austria; Novartis, Chile†; Serono, Cz.†; Serono, Denm.†; Serono, Fin.†; Serono, Gr.†; Serono, Hong Kong; Serono, Hung.†; Serum Institute, India; Serono, Irl.; Serono, Malaysia†; Serono, Mex.†; Serono, NZ; Serono, Neth.†; Serono, Norw.†; Serono, S.Afr.; Serono, Singapore†; Serono, Swed.†; Serono, Switz.†; Serono, Thai.†; Serono, Turk.; Serono, USA; Serono, Venez.†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; dysfunctional uterine bleeding; hypogonadotrophic hypogonadism; male and female infertility; ovulation induction; pituitary dwarfism; recurrent or threatened miscarriage.

Profasi HP *Serono, Braz.; Serono, Canad.; Serono, Ital.†; Serono, Port.†; Serono, Spain†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; erectile dysfunction; hypogonadotrophic hypogonadism; male and female infertility; male androgen insufficiencies; menstrual disorders; metrorrhagia; threatened or recurrent miscarriage.

Profecom *Combiphar, Indon.*
Ketoprofen (p.73·1).
Gout; osteoarthritis; pain; rheumatoid arthritis.

Profed *Medicine Products, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; hay fever; nasal congestion.

Profelan *Pharmachem, UK.*
Arnica (p.2260·2); zinc oxide (p.1621·2); vitamin A; vitamin C; vitamin E (p.1922·1); spearmint oil (p.2391·3).
Musculoskeletal, joint, and soft-tissue injury.

Profelixir *Farcoral, Mex.†.*
Vitamin preparation (p.1922·1).
Tonic.

Profemina *Laboratorios Chile, Chile.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Profemina CC *Laboratorios Chile, Chile†.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone (p.2113·3).
Menopausal disorders; osteoporosis.

Profemina MP *Laboratorios Chile, Chile.*
18 Tablets, conjugated oestrogens (p.2087·2); 12 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Profen *Christo, Hong Kong; Guardian, Indon.; Dinctas, Turk.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Profen II *Ivax, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly contained phenylpropanolamine hydrochloride and guaifenesin.
Coughs.

Profen II DM *Ivax, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Formerly contained phenylpropanolamine hydrochloride, guaifenesin, and dextromethorphan hydrobromide.
Coughs.

Profen Forte DM *Ivax, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Formerly contained phenylpropanolamine hydrochloride, dextromethorphan hydrobromide, and guaifenesin.
Coughs.

Profena *Pond's, Thai.†.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders.

Profenac
Lafit, Braz.†.
Diclofenac resinate (p.46·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Cipla, India.
Diclofenac sodium (p.44·3).

Profenal *Alcon, USA†.*
Suprofen (p.128·1).
Inhibition of intra-operative miosis.

Profenicol *Prodotti, Braz.*
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Profenid *Aventis, Arg.†; Aventis, Austria; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Aventis, Israel; Aventis, Mex.; Pliva Krakow, Pol.; Sanofi-Aventis, Pol.; Vitoria, Port.; Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, Venez.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Profenil
Note.This name is used for preparations of different composition.
Faran, Gr.†.
Ketoprofen (p.73·1); sucralfate (p.1772·2).
Inflammatory disorders.

Pascual, Hong Kong.
Alverine citrate (p.1708·1).
Gastrointestinal spasm.

Profenlax *Grisi, Mex.*
Naproxen (p.92·3); carisoprodol (p.1894·1).

Profeno *Milano, Thai.*
Ibuprofen (p.64·2).
Pain.

Profenol *Behrens, Venez.†.*
Ketoprofen (p.73·1).
Inflammation; pain.

Profenox *Tecnimede, Port.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Profenzol *Farcoral, Mex.*
Mebendazole (p.148·3).
Worm infections.

Profer
Note.This name is used for preparations of different composition.
Aesculapius, Ital.
Iron acetylaspartilate-protein complex (p.1950·3).
Iron deficiency; iron-deficiency anaemias.

Tedec Meiji, Spain.
Ferritin (p.1938·1).
Iron-deficiency anaemia.

Profercol *Best, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders; migraine.

Profergan *Teuto, Braz.*
Promethazine hydrochloride (p.588·2).
Nausea and vomiting; sedative; vertigo.

Profertil *Kalbe, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Profex *Dragenopharm, Israel.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Profiben *Hexal, Mex.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Profiber *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Profibra *Support, Braz.†.*
Dietary fibre supplement (soya polysaccharides) (p.1922·1).

Proficar *Polfarmex, Pol.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Profika *Ikapharmindo, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Profil *Atral, Port.†.*
Amantadine (p.792·3).

Profilas *Kalbe, Indon.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma.

Profilasmim-Ped *Stiefel, Braz.†.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma; urticaria.

Profilate *Grifols, Ger.†; Alpha, Israel.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Profilnine *Grifols, Hong Kong; Alpha, Israel; Grifols, Malaysia; Grifols, Philipp.; Grifols, Singapore; Grifols, Thai.; Grifols, USA.*
A factor IX complex (p.1068·3).
Haemophilia B; haemorrhagic disorders.

Profinal *Julphar, UAE.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, peri-articular and soft-tissue disorders; pain.

Profinal Cold & Sinus *Julphar, UAE.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; sinusitis.

Profinal FM *Julphar, UAE.*
Ibuprofen (p.64·2); caffeine (p.1116·3); mepyramine maleate (p.585·2).
Dysmenorrhoea.

Profinal XP *Julphar, UAE.*
Ibuprofen (p.64·2); caffeine (p.1116·3).
Pain.

Profine *Otsira, India†.*
Progesterone (p.2125·1).

Profinject *Faran, Gr.†.*
Ketoprofen (p.73·1).
Inflammatory disorders.

Profisin *Sanitas, Chile.*
Dicycloverine hydrochloride (p.1722·3); chlordiazepoxide hydrochloride (p.968·2).
Smooth muscle spasm.

Profiten *Pharma Clal, Israel.*
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Profium *De Mayo, Braz.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Proflam *Eurofarma, Braz.*
Aceclofenac (p.14·3).
Inflammation; pain.

Proflavanol
Note.This name is used for preparations of different composition.
Usana, Hong Kong†; Usana, Malaysia; Usana, Singapore.
Vitamin C (p.1983·3) grape seed (p.2316·3); ascorbyl palmitate (p.1629·1).
Antoxidant; dietary supplement; vitamin C supplement.

Usana, Mex.
Grape seed (p.2316·3); vitamin C (p.1983·3).
Dietary supplement.

USANA, USA.
Vitamin C (p.1983·3); flavonoids from grape seed (p.2304·1).
Nutritional supplement.

Proflavanol C *Usana, Canad.*
Calcium ascorbate (p.1984·1); potassium ascorbate (p.1685·1); magnesium ascorbate (p.1679·1); zinc ascorbate (p.1984·3).
Vitamin C supplement.

Proflax *Sidus, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Proflex
Note. A similar name is used for preparations of different composition (see below).
Novartis Consumer, Irl.; Novartis Consumer, UK.
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

ProFLEX
Note. A similar name is used for preparations of different composition (see above).
MZL, S.Afr.
Glucosamine hydrochloride (p.2313·2); calcium carbonate; vitamin C; manganese sulfate (p.1922·1).
Dietary supplement.

ProFLEX 750 *MZL, S.Afr.*
Glucosamine hydrochloride (p.2313·2); dimethyl sulfone (p.2294·1); vitamin C (p.1922·1).
Dietary supplement.

Proflo *Procare, Austral.†.*
Vitamins; minerals (p.1922·1); bioflavonoids (p.2304·1); butcher's broom (p.2270·3); aesculus (p.2248·2); hamamelis (p.2318·2); pulsatilla (p.2376·3).
Dietary supplement; peripheral vascular disorders.

Proflor *Leti, Venez.*
Lactobacillus acidophilus (p.2372·3).
Diarrhoea.

Proflox
Note.This name is used for preparations of different composition.
Therabel, Belg.; Bayer, Gr.; Bialfar, Port.; Esteve, Spain.
Moxifloxacin hydrochloride (p.302·1).
Bacterial infections.

Sigma, Braz.
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Cipla, India.
Pefloxacin mesilate (p.313·3).
Bacterial eye infections.

Pharmasant, Thai.
Ciprofloxacin (p.243·3).
Bacterial infections.

Profloxin *Hexal, Austral.; Clonmel, Irl.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Profluid *Procare, Austral.†.*
Taraxacum (p.2395·1); parsley piert (p.2363·2); bearberry (p.2263·3); juniper (p.2328·2).
Bladder disorders; cystitis; fluid retention.

Proflusak *Akrikhin, Rus.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Profluxol *Ultra, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Profol
Note.This name is used for preparations of different composition.
Medley, Braz.
Buclizine hydrochloride (p.570·1); lysine; tryptophan; vitamin B ; vitamin B (p.1922·1).
Tonic.

Biogalenic, Venez.
Propofol (p.1791·1).
General anaesthesia.

Profolen *Blausiegel, Braz.*
Propofol (p.1791·1).
General anaesthesia.

Profort *Abbott, Braz.*
Preparation for enteral nutrition (p.1922·1).

ProFree *Allergan, USA.*
Papain (p.2362·3) (p.1622·2).
Cleansing solution for contact lenses.

Profrin-A *Allergan, Port.†.*
Mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1); phenazone (p.116·1).
Eye irritation.

Profungal *Kalbe, Indon.; Dankos, Singapore†.*
Ketoconazole (p.539·1).
Fungal infections.

Profurex *Biolab, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Profut *Mecosin, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; allergic skin disorders.

Profylac *Semper, Fin.*
Infant feed (p.1922·1).
Lactose intolerance; milk allergy; soya protein intolerance.

Progandol *Grapharma, Neth.; Almirall, Spain.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Progastric *Combiphar, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Bloating; gastric hyperacidity; peptic ulcer.

Progastrit
Note.This name is used for preparations of different composition.
Hexal, Ger.
Chewable tablets: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1).
Gastrointestinal disorders.

Hexal, Ger.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Progediol *Diba, Mex.†.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Progeffik *Effik, Ital.; Effik, Spain.*
Progesterone (p.2125·1).
Female infertility; menopausal disorders; menstrual disorders; threatened or habitual miscarriage.

Progemox *Proge, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Progemzal *Sandoz, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Progen *Mayo, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Progenar *Menarini, Port.†.*
Progesterone (p.2125·1).
Benign breast disorders.

Progendo *Gynopharm, Chile; Vivax Gynopharm, Venez.*
Progesterone (p.2125·1).
Dysfunctional uterine bleeding; female infertility; menopausal disorders; premenstrual syndrome; recurrent miscarriage.

Proger-F *Streger, Mex.*
Progesterone (p.2125·1); estradiol benzoate (p.2097·2).
Menstrual disorders.

Progering *Silesia, Chile.*
Progesterone (p.2125·1).
Vaginal ring contraceptive.

Progesan *Sanval, Braz.†.*
Medroxyprogesterone acetate (p.2113·1).

Progesic *Xepa-Soul Pattinson, Hong Kong; Metiska, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Progest *Elea, Arg.; Samarth, India†.*
Progesterone (p.2125·1).
Benign breast disorders; dysfunctional uterine bleeding; female infertility; maintenance of early pregnancy; menopausal disorders; menstrual disorders; recurrent and threatened miscarriage.

Progestan *Organon, Neth.; Kocak, Turk.*
Progesterone (p.2125·1).
Hormone replacement therapy; menstrual disorders.

Progestasert *Alza, USA†.*
Progesterone (p.2125·1).
Progestogen-only intra-uterine contraceptive device.

Progesteron-Depot *Jenapharm, Ger.*
Hydroxyprogesterone caproate (p.2110·3).
Female infertility; menstrual disorders; threatened or recurrent miscarriage.

Progesterone-retard Pharlon *Schering, Fr.*
Hydroxyprogesterone caproate (p.2110·3).
Female infertility; menstrual disorders; premature labour; progestogen; threatened or recurrent miscarriage.

Progestogel *Besins, Belg.; Besins, Fr.; Besins, Ger.; Kade, Ger.; Besins, Hong Kong; Lusofarmaco, Ital.†; Azevedos, Port.; Besins, Rus.; Seid, Spain†; Vifor, Switz.; Besins, Thai.; Biopas, Venez.*
Progesterone (p.2125·1).
Benign breast disorders.

Progestol *Sanofi Synthelabo, Ital.†.*
Progesterone (p.2125·1).
Acne; seborrhoea; seborrhoeic alopecia.

Progeston *Meprofarm, Indon.*
Allylestrenol (p.2082·2).
Premature labour; threatened and recurrent miscarriage.

Progestosol *Seid, Spain.*
Progesterone (p.2125·1).
Acne; seborrhoeic dermatitis and associated alopecia.

Progevera *IFET (ΙΦΕΤ), Gr.; Pfizer, Spain.*
Medroxyprogesterone acetate (p.2113·1).
Cancer of breast, kidney, and endometrium; contraception; endometriosis; female infertility; menometrorrhagia; menopausal disorders; menstrual disorders.

Progevera 250 *Pfizer, Spain.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

Proginkgo *Procare, Austral.†.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; tonic.

Proglan *Procare, Austral.†.*
Black currant seed oil (p.2267·1).
Dietary supplement; source of polyunsaturated fatty acids.

Proglicem *Schering-Plough, Arg.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Ital.; Schering-Plough, Neth.; Essex, Switz.*
Diazoxide (p.1257·3).
Hypertension; hypoglycaemia.

Proglycem *Schering, Canad.; IFET (ΙΦΕΤ), Gr.; Baker Norton, USA.*
Diazoxide (p.1257·3).
Hypertensive episodes in nephropathy; hypoglycaemia.

Pro-Gola *Sixtem, Ital.*
Propolis (p.2373·3).

Progor *SMB, Belg.; SMB, Thai.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Progout *Alphapharm, Austral.; Pacific, Hong Kong; Pacific, NZ; Alphapharm, Singapore.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Prograf *Gador, Arg.; Janssen-Cilag, Austral.; Fujisawa, Austria; Janssen-Cilag, Braz.; Astellas, Canad.; Fujisawa, Chile; Astellas, Cz.; Fujisawa, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Vianex (Βιανέξ), Gr.; Fujisawa, Hong Kong; Astellas, Hung.; Astellas, Irl.; Fujisawa, Israel; Astellas, Ital.; Astellas, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Fisher, Neth.; Medac, Neth.; Astellas, Norw.; Janssen, Philipp.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Adcock Ingram Critical Care, S.Afr.; Janssen-Cilag, Singapore; Astellas, Spain; Astellas, Swed.; Fujisawa, Switz.; Janssen-Cilag, Thai.; Eczacibasi, Turk.; Astellas, UK; Astellas, USA; Janssen-Cilag, Venez.*
Tacrolimus (p.1843·1).
Atopic eczema; graft-versus-host disease; lupus nephritis; myasthenia gravis; rheumatoid arthritis; transplant rejection.

Prograft *Fujisawa, Belg.; Astellas, Neth.*
Tacrolimus (p.1843·1).
Transplant rejection.

Progras *Temis, Arg.†.*
Sorbitol (p.1965·1).

Progray *Gray, Arg.*
Propanidid (p.1791·1).
General anaesthesia.

Progress
Note. A similar name is used for preparations of different composition (see below).
Procare, Austral.†.
Ginseng; garlic; multivitamins; minerals; bladderwrack; cramp bark (p.1922·1).
Dietary supplement.

Progresse
Note. A similar name is used for preparations of different composition (see above).
Biosintetica, Braz.
Gabapentin (p.482·3).
Epilepsy.

Progut *ProMed, Cz.*
Sodium picosulfate (p.1771·1).
Constipation.

Proguval *Eberth, Ger.†.*
Ribwort plantain (p.2379·1).
Catarrh; mouth and throat inflammation.

Progyluton *Schering, Chile; Schering, Israel; Bayer Schering, Malaysia; Schering, Mex.; Bayer, Port.; Bayer, Singapore; Schering, Spain; Schering, Venez.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; norgestrel (p.2121·2).
Menopausal disorders; menstrual disorders; oestrogen deficiency; osteoporosis.

Progynon *Schering, Arg.; Schering, Austria; Schering, Denm.; Schering, Swed.; Schering, Thai.*
Estradiol valerate (p.2097·3).
Amenorrhoea; dysfunctional uterine bleeding; menopausal disorders; menorrhagia; menstrual disorders; oestrogen deficiency; osteoporosis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Progynon C *Schering, Austria†; Schering, Ger.†; Schering, Israel†.*
Ethinylestradiol (p.2101·3).
Dysfunctional uterine bleeding; endometrial hyperplasia; menstrual disorders; oestrogen deficiency.

Progynon Depot 10 *Schering, Ger.†.*
Estradiol valerate (p.2097·3).
Amenorrhoea; endometrial hyperplasia; oestrogen deficiency.

Progynova
Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Chile; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Hong Kong; Schering, Indon.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Schering, Rus.; Schering, S.Afr.; Bayer, Singapore; Schering, Switz.; Schering, Thai.; Schering, Venez.
Estradiol valerate (p.2097·3).
Female hypogonadism; menopausal disorders; oestrogen deficiency; osteoporosis.

Schering, Spain; Bayer, UK.
Estradiol (p.2097·2) or estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis.

Prohair *Uniao Quimica, Braz.†; MSD, Chile.*
⊗ Finasteride (p.2188·3).
Alopecia.

Prohance *Regional Health, Austral.; Gerot, Austria; Altana, Belg.; Bracco, Cz.; Bracco, Denm.; Astra Tech, Fin.; Altana, Fr.; Altana, Ger.; Merck, Irl.†; Bracco, Ital.; Eisai, Jpn; Altana, Neth.; Bracco, Norw.; Rovi, Spain; Astra Tech, Swed.; Bracco, Switz.; Bracco, UK; Bracco, USA.*
Gadoteridol (p.1480·2).
Contrast medium for magnetic resonance imaging.

Pro-HDL *Wockhardt, India.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Prohelmin *Hebron, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Prohep *Aventis, S.Afr.*
Liver hydrolysate (p.2337·3); vitamin B (p.1980·2); choline bitartrate (p.1934·2); cysteine (p.1936·3); inositol (p.2325·2).
Liver disorders.

Prohessen *Pharos, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic disorders.

Prohexal *Hexal, S.Afr.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Prohibit
Note. A similar name is used for preparations of different composition (see below).
Sandoz, Indon.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

ProHIBiT
Note. A similar name is used for preparations of different composition (see above).
Pasteur Merieux, USA†.
A haemophilus influenzae conjugate vaccine (diphtheria toxoid conjugate) (p.2213·2).
Active immunisation.

Prohist *Be-Tabs, S.Afr.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; premedication; sedative.

Prohistin *Meprofarm, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Proimbus *Meprofarm, Indon.*
Echinacea (p.2298·1); ganoderma lucidum; calcium pantothenate (p.1959·3).
Immunostimulant.

Projimava *Megafyt-R, Cz.*
Senna (p.1769·2); achillea (p.2245·2); fennel (p.2302·3); peppermint leaf (p.1761·2); liquorice (p.1740·3).
Constipation.

Prokanazol *ProMed, Cz.*
Itraconazole (p.536·3).
Fungal infections.

Proken M *Kendrick, Mex.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; hypertension; myocardial infarction.

Proking *Cetus, Arg.*
Clobutinol (p.1554·2).
Cough.

Proklot *Torrent, Philipp.*
Tranexamic acid (p.1080·3).
Angioedema; fibrinolytic haemorrhage.

Prol *Procare, Austral.†.*
Milk thistle (p.1452·1).
Liver disorders.

Prolacam *Schering, Austria†.*
Lisuride maleate (p.811·1).
Acromegaly; amenorrhoea; female infertility; galactorrhoea; lactation inhibition; mastitis.

Pro-Lacta *Pascual, Philipp.*
Moringa oleifera.
Nutritional supplement.

Prolacta with DHA *Novell, Indon.*
Fish oil (p.1362·2).
Nutritional supplement for infants.

Prolacta with DHA for Mother *Novell, Indon.*
Fish oil (p.1362·2).
Nutritional supplement in pregnancy.

Prolactase *Pharmascience, Canad.*
Tilactase from *Aspergillus oryzae* or *Kluyveromyces lactis* (p.2402·1).
Lactase insufficiency.

Proladone *Pharmalab, Austral.*
⊗ Oxycodone pectinate (p.106·3).
Pain.

Prolair *3M, Fr.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Prolaken *Ivax, Mex.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension.

Prolan *Procare, Austral.†.*
Multivitamin and mineral preparation (p.1922·1).
Anxiety; dietary supplement.

Prolanz *Sunthi Sepuri, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Prolastin *Bayer, Austria; Bayer, Canad.; Talecris, Canad.; Bayer, Ger.; Bayer, Port.; Bayer, USA.*
Alpha -proteinase inhibitor (p.2253·2).
Alpha antitrypsin deficiency.

Prolastina *Bayer, Ital.; Bayer, Spain.*
Alpha -proteinase inhibitor (p.2253·2).
Alpha antitrypsin deficiency.

Prolax *Procare, Austral.†.*
Senna (p.1769·2); prune (p.1765·1).
Constipation.

Prolaxatan *Polfa Lodz, Pol.*
Macrogol 4000 (p.2336·3).
Constipation.

Proldin *Sons, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Prolecin *Promed, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Prolekofen *Lek, Cz.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Prolene *Fonterra, Indon.*
Preparation for enteral nutrition (p.1922·1).

Prolepsi *Mersifarma, Indon.*
Oxcarbazepine (p.490·3).
Epilepsy.

Proleukin *Raffo, Arg.; CSL, Austral.†; Fresenius Kabi, Austria; Chiron, Belg.; Zodiac, Braz.; Chiron, Canad.; Novartis, Cz.; Chiron, Denm.; Chiron, Fr.; Chiron, Ger.; Genesis, Gr.; Chiron, Hong Kong; Novartis, Hung.; Chiron, Irl.; Novartis, Irl.; Chiron, Israel; Chiron, Ital.; Asofarma, Mex.; CSL, NZ; Chiron, Neth.; Chiron, Pol.; Novartis, Port.; CSC, Rus.; Chiron, Singapore†; Chiron, Spain; Proreo, Switz.; Roche, Turk.; Novartis, UK; Chiron, USA.*
Aldesleukin (p.735·1).
Acute megaloblastic leukaemia; bone-marrow transplantation; malignant melanoma; metastatic renal-cell carcinoma; myelodysplastic syndromes; neuroblastoma.

Prolevox *Meprofarm, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Prolic *Sanbe, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Prolief *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Prolifed *Quality, Hong Kong.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Prolifen *Effik, Ital.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility.

Prolift *Pharmacia, Arg.†; Pfizer, Braz.; Pfizer, Chile; Pharmacia, Venez.†.*
Reboxetine mesilate (p.420·3).
Depression.

Proligon *Kee, India†.*
⊗ Chorionic gonadotrophin (p.2085·1).
Hypogonadotrophic hypogonadism; induction of ovulation; male infertility.

Prolipase *Janssen-Cilag, Arg.; Janssen-Cilag, Switz.†.*
Pancrelipase (p.2360·1).
Dyspepsia; pancreatic insufficiency.

Prolipid
Note.This name is used for preparations of different composition.
Unipharma, Gr.
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Indofarma, Pol.
Guazuma ulmifolia; murraya; sonchus arvensis.
Hypercholesterolaemia.

Prolisina E2 *Pfizer, Arg.*
Dinoprostone (p.2007·1).
Labour induction.

Prolisina VR *Pfizer, Arg.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Prolivit *Erlimpex, Indon.*
Phospholipids; vitamin B substances (p.1922·1).
Nutritional supplement.

Prolix *Pharma Nutria, Philipp.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Prolixan *Jacoby, Austria†; Unipharma, Gr.†; ICN, Hung.†; Neves, Port.†.*
Azapropazone (p.26·3).
Ankylosing spondylitis; gout; inflammation; pain; rheumatoid arthritis.

Prolixin *BMS, Turk.; Apothecon, USA†; Princeton, USA†.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Prolohex *Hexal, Philipp.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Proloid S *Pfizer, Mex.†.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Adjunct in hyperthyroidism; hypothyroidism.

Prolol *Merck, Hong Kong†; Dexxon, Israel; Atlantic, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma; tremor.

Prolong *Maver, Chile.*
Lidocaine (p.1862·3).
Erectile dysfunction.

Prolopa *Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Proloprim *GSK, Canad.†; Glaxo Wellcome, USA.*
Trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

Prolubrin *Mayo, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Prolung *Galenium, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Proluton
Note.This name is used for preparations of different composition.
Schering, Arg.; Schering, Austral.
Progesterone (p.2125·1).
Amenorrhoea; progesterone test in secondary amenorrhoea.

Schering, Ital.
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; female infertility; metrorrhagia; progestogen deficiency; threatened or recurrent miscarriage; uterine hypoplasia.

Proluton Depo *Schering, Turk.*
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; female infertility; threatened or recurrent miscarriage.

Proluton Depot *Schering, Arg.; Schering, Austria; Schering, Ger.; IFET (ΙΦΕΤ), Gr.; German Remedies, India; Schering, Israel; Bayer Schering, Malaysia; Schering, Neth.†; Schering, Philipp.; Bayer, Singapore; Schering, Thai.*
Hydroxyprogesterone caproate (p.2110·3).
Amenorrhoea; cancer of breast, uterus, or kidney; dysfunctional uterine bleeding; endometriosis; female infertility; hormone replacement therapy; recurrent and threatened miscarriage; uterine hypoplasia.

Promac *Provit, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Promacet *MCR, USA.*
Paracetamol (p.108·1); butalbital (p.967·2).
Pain.

Promactil *Combiphar, Indon.*
Chlorpromazine (p.969·1).
Nausea and vomiting; psychoses.

Promag *Kalbe, Indon.*
Hydrotalcite (p.1733·3); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Bloating; epigastric pain; gastric hyperacidity; peptic ulcer.

Promag Double Action *Kalbe, Indon.*
Famotidine (p.1730·1); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Promal *Allen, Austria.*
Atovaquone (p.829·2); proguanil hydrochloride (p.609·2).
Malaria.

Promanum *Braun, Port.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Promanum N *Braun, Cz.; Braun, Ger.; Braun, Switz.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Hand disinfection.

Promatussin DM *Lioh, Canad.†.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine (p.1571·2).
Coughs.

Promax *Gerolymatos, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Prome *Interbat, Indon.*
Promethazine hydrochloride (p.588·2); ipecacuanha (p.1562·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Promeal *Volchem, Ital.*
Preparation for enteral nutrition (p.1922·1).

Promecilina *Hexal, Mex.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Promedex
Note.This name is used for preparations of different composition.
Interbat, Indon.
Syrup: Promethazine hydrochloride (p.588·2); dextromethorphan (p.1555·2); ipecacuanha (p.1562·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Respiratory-tract disorders with cough.

Interbat, Indon.
Tablets: Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders with cough.

Promedin *Vargas, Venez.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Promedina *Vargas, Venez.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cough.

Promedyl
Note.This name is used for preparations of different composition.
Upha, Malaysia†.
Codeine phosphate (p.37·2); promethazine (p.588·2).
Coughs.

Beacons, Singapore†; Malaysia Chemist, Singapore†.
⊗ Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Promedyl DM *CCM, Malaysia.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cough; nasal congestion.

Promedyl Plus *CCM, Malaysia.*
Chlorphenamine maleate (p.571·3); pholcodine (p.1570·2).
Coughs.

Promega *Parke, Davis, USA.*
Omega-3 marine triglycerides with vitamin E (p.1362·2).
Dietary supplement.

Promel *Quim-Far, Venez.*
Dipyrone (p.49·2).
Fever; pain.

Promelatonin *Laborest, Ital.†.*
Tryptophan; niacin; magnesium (p.1922·1).
Nutritional supplement; sleep disorders.

Promeno *Interbat, Indon.*
Red clover (p.2285·1).
Menopausal disorders.

Promenorea *Help, Gr.*
Progesterone (p.2125·1).
Menstrual disorders.

Promensil
Note.This name is used for preparations of different composition.
Novogen, Austral.
Red clover (p.2285·1).
Menopausal disorders.

Ikapharmindo, Indon.
Isoflavone (p.2391·2).
Menopausal disorders.

Promesec *Mars, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Promet *Millimed, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; mastocytosis; peptic ulcer; Zollinger-Ellison syndrome.

Prometax *Biosintetica, Braz.; Novartis, Cz.; Novartis, Gr.; Sigma-Tau, Ital.; Novartis, Neth.; Novartis, Port.; Esteve, Spain.*
Rivastigmine hydrogen tartrate (p.369·2).
Alzheimer's disease; dementia in parkinsonism.

Prometazol *Sanval, Braz.*
Promethazine (p.588·2).
Hypersensitivity reactions; nausea and vomiting; sedative.

Prometh with Dextromethorphan *Barre-National, USA.*
Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Prometh VC Plain *Barre-National, USA; Goldline, USA; Warner Chilcott, USA.*
Promethazine hydrochloride (p.588·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; nasal congestion.

Promethawern *Wernigerode, Ger.†.*
Promethazine teoclate (p.588·3).
Anxiety; hypersensitivity reactions; nausea and vomiting; premedication; sleep disorders.

Promethazine Compound Linctus *Medipharma, Hong Kong†.*
⊗ Promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2).
Cold and influenza symptoms.

Promethazine Expectorants *Vitamed, Israel.*
Promethazine hydrochloride (p.588·2); ipecacuanha (p.1562·3); sulfogaiacol (p.1573·2).
Coughs.

Promethazine Ikapharmindo *Ikapharmindo, Indon.*
Promethazine hydrochloride (p.588·2); sulfogaiacol (p.1573·2); citric acid (p.2284·1); sodium citrate (p.1673·3); ipecacuanha (p.1562·3).
Cough.

Promethazine VC with Codeine *Warner Chilcott, USA.*
Promethazine hydrochloride (p.588·2); phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2).

Promethegan *G & W, USA.*
Promethazine hydrochloride (p.588·2).

Prometidine *Cazi, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Prometrium *Schering, Canad.; Rottapharm, Ital.; Solvay, USA.*
Progesterone (p.2125·1).
Adjunct to oestrogen replacement therapy; amenorrhoea; female infertility; menopausal disorders; menstrual disorders; threatened or habitual miscarriage.

Promezol *Promed, Indon.; Vargas, Venez.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Promibasol *Rayere, Mex.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Promibasol-Plus *Rayere, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); metronidazole (p.837·1); nystatin (p.543·2).
Vulvovaginal infections.

Promiced *IQFA, Mex.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Promicin *Mayo, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Promid *Biofarma, Turk.*
Protionamide (p.320·1).
Tuberculosis.

Promidan *Mintlab, Chile.*
Chlormezanone (p.968·3); diazepam (p.986·3).
Skeletal muscle spasm.

Promifen *Wyeth, Venez.†.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders.

Promil Lactose-free *Wyeth, Philipp.*
Infant feed (p.1922·1).
Lactose intolerance.

Prominal *Sanofi Synthelabo, Austral.†.*
Methylphenobarbital (p.490·2).
Epilepsy.

Promincil
Note. This name is used for preparations of different composition.
Chefaro Ardeval, Fr.†.
Capsules: Bladderwrack (p.2384·2); paullinia (p.2416·1); java tea (p.2328·2).
Herbal slimming preparation.

Chefaro Ardeval, Fr.†.
Topical gel: Ivy (p.2328·1); guarana (p.2416·1).
Herbal slimming preparation.

Prominol *MCR, USA.*
Butalbital (p.967·2); paracetamol (p.108·1).
Pain.

Prominox *Alet, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Promise *Wyeth, Mex.†; Wyeth, Singapore.*
Nutritional supplement for children (p.1922·1).

Promisec *Aristo, India.*
Omeprazole (p.1753·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Pro-Misil *Veltipharm, Gr.*
Terbinafine (p.546·3).
Fungal infections.

Pro-Miss *Kato, Pol.*
Paracetamol (p.108·1); caffeine (p.1116·3); mepyramine (p.585·1).
Premenstrual syndrome.

Promit *Medical Specialties, Austral.; Torrex, Austria; Pharmalink, Ger.†; Meda, Hung.; Pharmacia, S.Afr.; Braun, Switz.†; Pharmacia, USA.*
⊗ Dextran 1 (p.1058·3).
Prevention of anaphylactic reactions to infusions of dextran.

Promiten *Meda, Denm.; Pharmalink, Neth.; Meda, Norw.; Meda, Swed.*
⊗ Dextran 1 (p.1058·3).
Prevention of anaphylactic reactions to infusions of dextrans.

Promix *Capo Sole, Ital.†.*
Propolis (p.2373·3); agrumi; echinacea (p.2298·1); clove (p.2284·3).

Promix 3 *Capo Sole, Ital.†.*
Propolis (p.2373·3); myrtillus (p.2349·3); echinacea (p.2298·1); agrumi oil.

Promixin
Note. This name is used for preparations of different composition.
Pyridam, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Profile, UK.
Colistimethate sodium (p.256·3).
Gram-negative bacterial infections.

Promizol *Senosiain, Mex.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Promocard *AstraZeneca, Belg.†; AstraZeneca, Neth.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Promocid *Mugi, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

ProMod *Abbott, Austral.; Abbott, Braz.†; Abbott, Canad.†; Abbott, Chile; Abbott, Ital.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott Nutrition, UK†; Ross, USA.*
Dietary protein supplement (p.1922·1).
Hypoproteinaemia.

Promogran
Note. This name is used for preparations of different composition.
Johnson & Johnson, Fr.; Johnson & Johnson, Ital.
Oxidised cellulose (p.1075·1); collagen (p.2286·1).
Skin ulcers; ulcers; wounds.

Johnson & Johnson, Ger.†.
Collagen (p.2286·1).
Wounds.

Promolan *Sarabhai Piramal, India.*
High-protein dietary supplement (p.1922·1).

Promote *Abbott, Ital.†.*
Preparation for enteral nutrition (p.1922·1).

Promotion *Rayere, Mex.*
Meloxicam (p.80·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and soft-tissue disorders.

Promox *Medreich, Hong Kong; Prosel, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Promoxil *Medpro, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Prompt *Temis, Arg.†.*
Ispaghula (p.1737·1); sennosides (p.1769·3).
Constipation.

Promptcillin Forte *Teva, Hung.*
Benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Promuba *Meprofarm, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Promune *Procare, Austral.†.*
Multivitamin, amino-acid, and mineral preparation with thyme extract (p.1922·1).
Dietary supplement.

Promyrtil *Organon, Chile.*
Mirtazapine (p.409·2).
Depression.

Pronal Dix *Mayo, Mex.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Pronalges *Dexa, Indon.*
Ketoprofen (p.73·1).
Osteoarthritis; pain; rheumatoid arthritis.

Pronapen *Pfizer, Venez.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Pronasteron *Sanval, Braz.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Pronat *Solfran, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Pronaxen *Orion, Fin.; Orion, Swed.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal and joint disorders; pain.

Pronaxil *Streger, Mex.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Pronax-P *Kener, Mex.†.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Pronazol *Diffucap, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Pronemia Hematinic *Lederle, USA.*
Ferrous fumarate (p.1938·3); intrinsic factor concentrate (p.2326·3); vitamin B substances (p.1980·2); folic acid (p.1940·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Pronenen *Cifarma, Braz.*
Vitamin A palmitate (p.1973·1); colecalciferol (p.1986·2); zinc oxide (p.1621·2).
Skin disorders.

Pronergylium *NPC, Fr.†.*
Food for special diet (p.1922·1).
Obesity.

Pronerv *Gerot, Austria.*
Thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathies.

Pronervon *Ivax, Arg.*
Memantine hydrochloride (p.367·1).
Alzheimer's disease.

Pronervon Phyto *Scheffler, Ger.*
Valerian (p.2410·1); passion flower (p.2363·2); melissa (p.2339·3).
Agitation; sleep disorders.

Pronervon T *Scheffler, Ger.*
Temazepam (p.1030·1).
Sleep disorders.

Pronest *BPL-Meizler, Braz.†.*
Propofol (p.1791·1).
General anaesthesia.

Pronestin *Rekah, Israel.*
Benzocaine (p.1854·1); methylthioninium chloride (p.1450·3); thymol (p.1664·3).
Formerly known as Pronaestin.
Gingivitis; mouth hygiene; stomatitis.

Pronestyl *BMS, Austral.; Squibb, Canad.†; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong†; Sarabhai Piramal, India; BMS, Irl.; BMS, Israel†; BMS, NZ; BMS, Neth.; BMS, S.Afr.; BMS, UK†.*
Procainamide hydrochloride (p.1377·2).
Arrhythmias.

Proneurax *Janssen-Cilag, Venez.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Proneurin *Hexal, Ger.*
Promethazine hydrochloride (p.588·2).
Anxiety; hypersensitivity reactions; sleep disorders; vomiting.

Proneurit *Demo, Gr.†.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Proneuron *Meprofarm, Indon.*
Dipyrone (p.49·2); diazepam (p.986·3).
Pain.

Pronicol *Bioresearch, Mex.*
Chloramphenicol (p.239·3).
Gastrointestinal infections.

Pronicy *Kalbe, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic rhinitis; allergic skin disorders.

Pronitol *Fournier SA, Spain.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Pronivel *Elea, Arg.*
⊗ Epoetin (p.1061·1).
Anaemias.

Pronix *Vannier, Arg.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders.

Pronoctan *Schering, Denm.*
Lormetazepam (p.1005·2).
Insomnia; premedication.

Pronoran *Servier, Pol.; Servier, Rus.*
Piribedil (p.813·3).
Intermittent claudication; ischaemic eye disorders; mental function impairment; parkinsonism.

Pronose *UCB, Cz.†; Lusofarmaco, Ital.†.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; rhinitis.

Pronoxen *Farcoral, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Prontalgin *GiEnne, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Prontalgine *Boehringer Ingelheim, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain.

Prontinal *Dompe, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease; rhinitis.

Pronto
Note. This name is used for preparations of different composition.
Del, Canad.
Pyrethrum flower (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Del, USA.
Shampoo: Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Del, USA.
Surface spray: Phenothrin (p.2048·3).
Lice infestation.

Pronto Platamine *Pharmacia, Ital.*
Cisplatin (p.698·2).
Malignant neoplasms.

Prontobario *Gerot, Austria; Bracco, Cz.†; Bracco, Ital.*
Barium sulfate (p.1477·2).
Simeticone (p.1770·2) is included in some preparations to eliminate gas from the gastrointestinal tract before radiography.
Contrast medium for gastrointestinal radiography.

Prontocid N *Braun, Ger.†.*
Formaldehyde (p.1644·2); glutaral (p.1645·2).
Instrument disinfection.

Prontodex *Procter & Gamble, Austria.*
Dextromethorphan (p.1555·2).
Coughs.

Prontoferro *Amsa, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Prontoflex *Medicom, Cz.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue disorders.

Prontofort *Medix, Mex.*
Tramadol hydrochloride (p.130·3).
Pain.

Prontogest *Amsa, Ital.*
Progesterone (p.2125·1).
Adjunct in gynaecological surgery; menstrual disorders; postnatal depression; threatened or recurrent miscarriage.

Prontoket *CSC, Austria; Medicom, Cz.; CSC, Hung.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Prontol *Novag, Mex.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Prontolax
Note. This name is used for preparations of different composition.
Generis, Port.
Ispaghula (p.1737·1).
Colostomy management; constipation; dietary fibre supplement; hypercholesterolaemia; irritable bowel syndrome.

Streuli, Switz.
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Prontomucil *Francia, Ital.*
Guacetisal (p.1561·2).
Respiratory-tract congestion.

Prontonema *Biosintex, Arg.*
Sodium phosphate (p.1682·3).
Bowel evacuation.

Prontopyrin plus *Pfizer Consumer, Ger.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Prontovent *Salus, Ital.†.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Pron-X *Farcoral, Mex.*
Paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Influenza symptoms.

Prootocipro *Fortbenton, Arg.*
⊗ Ciprofloxacin (p.243·3); hydrocortisone (p.1535·2).
Infected eye disorders.

Propa *Jean-Marie, Hong Kong†.*
⊗ Propranolol (p.1381·1).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; migraine; myocardial infarction.

Propa PH *Del, Canad.†.*
Salicylic acid (p.1612·2).
Acne.

Propabloc *Azupharma, Ger.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; migraine.

Propac *Sherwood, USA.*
Dietary protein supplement (p.1922·1).

Propace *Apotex, Mex.*
Metoclopramide (p.1747·3).

Propacet *Lemmon, USA.*
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Pain.

Propacor *Bunker, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).

Propaderm *Shire, Canad.; Kyowa, Jpn; GSK, UK†.*
⊗ Beclometasone dipropionate (p.1516·2).
Skin disorders.

Propain
Note. This name is used for preparations of different composition.
Sankyo, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Restan, S.Afr.†.
Syrup: Promethazine hydrochloride (p.588·2); paracetamol (p.108·1).
Pain and associated tension.

Adcock Ingram, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3).
Pain and associated tension.

Propain Forte *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3); phenobarbital (p.492·2).
Pain and associated tension.

Propain Plus *Sankyo, UK.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Propal *Sandoz, Denm.; Svizera, India.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic subaortic stenosis; migraine; myocardial infarction; tremor; variceal haemorrhage.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Propalem *Lemery, Mex.*
⊗ Propranolol hydrochloride (p.1380·3).
Hypertension.

Propalgin
Note. This name is used for preparations of different composition.
Montpellier, Arg.
Pargeverine (p.1761·1); clonixin lysine (p.37·1).
Muscle spasm; pain.

Kener, Mex.†.
⊗ Propranolol (p.1381·1).
Arrhythmias.

Propalgina Plus *Bayer, Spain.*
Ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Propalol *Globo, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Propalong *TRB, Arg.†.*
⊗ Propranolol hydrochloride (p.1380·3).

Propam *Pacific, NZ.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; premedication; skeletal muscle spasm; sleep disorders; spasticity.

Propamerck *Merck dura, Ger.†.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Propamide *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Propan
UCI, Braz.†;
Buclizine hydrochloride (p.570·1); vitamin B substances; lysine hydrochloride (p.1922·1).
Reduced appetite; tonic.

Pascual, Philipp.
Buclizine hydrochloride (p.570·1); vitamins (p.1922·1).
Nutritional supplement.

Propan Gel-S *Adcock Ingram, S.Afr.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); dicycloverine hydrochloride (p.1722·3); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Propan with Iron *Pascual, Philipp.*
Buclizine hydrochloride (p.570·1); ferrous sulfate (p.1939·3); vitamin B substances (p.1922·1).
Anorexia; tonic.

Propaneitor *Driburg, Arg.*
⊗ Propranolol (p.1381·1).
Migraine.

Propanol *Upha, Malaysia†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction; phaeochromocytoma.

Propanorm *ProMed, Cz.; Pro.Med, Rus.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Propanox *Royton, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Propantel *Gastroenterologicos, Mex.†.*
Propantheline bromide (p.1764·3).

Propanthel *Valeant, Canad.†.*
Propantheline bromide (p.1764·3).
Anticholinergic.

PropapH *Del, USA.*
Salicylic acid (p.1612·2).
Acne.

Propaphenin *Rodleben, Ger.*
Chlorpromazine hydrochloride (p.969·2).
Psychoses; vomiting.

Proparakain-POS *Ursapharm, Ger.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Propargile *Holistica, Fr.*
Propolis (p.2373·3); pollen (p.2370·2); clay.
Digestive disorders.

Propanil *Biofarma, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Proparin *Probiomed, Mex.*
Heparin sodium (p.1301·2).
Anticoagulation in blood transfusion, extracorporeal circulation, and dialysis; thromboembolic disorders.

Propass *Hormel, Hong Kong; Hormel, Singapore.*
Dietary protein supplement (p.1922·1).
Preparation for enteral nutrition.

Propast *CaDiGroup, Ital.*
Zinc oxide (p.1621·2); propolis (p.2373·3); undecenoic acid (p.549·2).
Skin disorders.

Propa-Tabletten *Rentschler, Cz.†.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Propavan *Sanofi Synthelabo, Swed.*
Propiomazine maleate (p.590·1).
Sleep disorders.

Propavent
Note. A similar name is used for preparations of different composition (see below).
GSK, Arg.
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma.

Propavente
Note. A similar name is used for preparations of different composition (see above).
Glaxo Wellcome, Port.
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Coughs.

Propayerst *Wyeth, Arg.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hypertrophic subaortic stenosis; migraine; myocardial infarction; phaeochromocytoma; tremor.

Propayerst Plus *Wyeth, Arg.†.*
⊗ Propranolol hydrochloride (p.1380·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Propecia *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Braz.; Merck Frosst, Canad.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, NZ; MSD, Neth.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Properil *Royal, Chile.*
Captopril (p.1239·2).
Heart failure; hypertension.

Propeshia *MSD, Mex.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Propess *Craveri, Arg.; Ferring, Austria; CSC, Cz.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; CSC, Hung.†; Ferring, Israel; Ferring, Ital.; Ferring, Mex.; Ferring, Neth.; Controlled Therapeutics, Pol.; Ferring, Port.; Ferring, S.Afr.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, UK.*
Dinoprostone (p.2007·1).
Induction and maintenance of labour; termination of pregnancy.

Prophage *Medicine Products, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Prophedin *Siam Bheasach, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; hay fever; rhinitis; upper respiratory-tract congestion.

Pro-Phree *Abbott, Austral.†; Ross, USA.*
Protein-free infant feed supplement (p.1922·1).

Prophthal *Procare, Austral.†.*
Myrtillus (p.2349·3); ginkgo biloba (p.2311·1).
Herbal supplement.

Prophylactin C *GSK, Rus.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Vitamin C deficiency.

Prophyllin *Rystan, USA.*
Sodium propionate (p.545·3); chlorophyllin copper complex (p.1471·1).
Contact dermatoses; dermatophytosis; eczemas; minor burns.

Prophylux *Hennig, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; migraine; myocardial infarction.

Propiden *Sandoz, Denm.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Propil *Pfizer, Braz.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propilracil *Biolab Sanus, Braz.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propimex *Ross, USA.*
A range of methionine- and valine-free preparations for enteral nutrition including an infant feed (p.1922·1).
Methylmalonic acidaemia; propionic acidaemia.

Propine *Allergan, Arg.†; Allergan, Austral.; Allergan, Belg.; Allergan, Braz.; Allergan, Canad.†; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Allergan, Hong Kong; Allergan, Irl.; Allergan, Ital.; Allergan, Malaysia†; Allergan, NZ; Allergan, Norw.; Allergan, Port.†; Allergan, S.Afr.†; Allergan, Singapore†; Allergan, Swed.; Allergan, Thai.†; Allergan, UK; Allergan, USA.*
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma; ocular hypertension.

Propiochrone *IFET (ΙΦΕΤ), Gr.; Schering-Plough, Gr.*
⊗ Betamethasone sodium phosphate (p.1518·3); betamethasone dipropionate (p.1518·3).
Corticosteroid.

Propioform *Schering-Plough, Gr.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Propioformo *Schering-Plough, Venez.†.*
⊗ Betamethasone dipropionate (p.1518·3); clioquinol (p.254·1).
Infected skin disorders.

Propiogenta
Schering-Plough, Gr.
⊗ Betamethasone dipropionate (p.1518·3); gentamicin (p.284·2).
Infected skin disorders.

Schering-Plough, Venez.†.
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Propional *Silanes, Mex.†.*
Naproxen (p.92·3).
Rheumatism.

Propionat *Farmigea, Ital.*
Sodium propionate (p.545·3).
Eye disorders.

Propiosalic *Schering-Plough, Gr.; Schering-Plough, Venez.†.*
⊗ Salicylic acid (p.1612·2); betamethasone dipropionate (p.1518·3).
Skin disorders.

Propiosol *Neo Quimica, Braz.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Propirin *Christo, Hong Kong.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Proplax *Hebron, Braz.†.*
Propolis (p.2373·3); sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).

Proplex *Baxter, Israel; Baxter, Venez.†.*
A factor IX preparation (p.1068·3).
Haemophilia; haemorrhagic disorders.

Proplex T *Baxter-Hyland, Hong Kong†; Baxter, Malaysia†; Baxter, USA.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Proplexo *Prodotti, Braz.*
Vitamin B substances (p.1922·1).

Proplexo C *Prodotti, Braz.*
Vitamin B substances; vitamin C (p.1922·1).

Pro-Plus *Roche Consumer, Irl.; Roche Consumer, UK.*
Caffeine (p.1116·3).
Fatigue.

Propoabbott *Abbott, Braz.*
Propofol (p.1791·1).
General anaesthesia.

Propocam *Abbott, Mex.†.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Propociclina *Laborest, Ital.*
Propolis bioflavonoid (p.2373·3).
Mouth infections.

Propofan *Sanofi-Aventis, Fr.*
Dextropropoxyphene (p.40·1); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Propol *Leti, Venez.†.*
Triglycerides (p.1956·3).
Dietary supplement.

Propolan *Herbapol Wroclaw, Pol.*
Propolis (p.2373·3).
Burns; chilblains; gingivitis; skin infections; sore throat; wounds.

Propolcream *Bucaneve, Ital.*
Propolis (p.2373·3).

Propoleos *Natufarma, Arg.*
Propolis (p.2373·3).
Dietary supplement.

Propolipid *Fresenius Kabi, Swed.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Propolisan *Apipol, Pol.*
Propolis (p.2373·3).
Burns; foot hyperhidrosis; fungal skin infections; wounds.

Propolisept Urtinktur *Johanser, Ger.*
Homoeopathic preparation.

Propolisept-Salbe *Johanser, Ger.*
Propolis (p.2373·3).
Skin disorders.

Propolisol *Apipol, Pol.*
Propolis (p.2373·3).
Mouth and throat disorders; skin disorders.

Propolkit *Ximena Polanco, Chile.*
Propolis (p.2373·3).
Immunostimulant.

Propomill *CaDiGroup, Ital.†.*
Propolis (p.2373·3); chamomile (p.2279·3).
Skin irritation.

Proponol *Help, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Propoten *Biochimico, Braz.†.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Propovan *Cristalia, Braz.*
Propofol (p.1791·1).
General anaesthesia.

Propoven *Fresenius Kabi, UK.*
Propofol (p.1791·1).
General anaesthesia; sedative.

propra *CT, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; tremor.

Propra comp *Ratiopharm, Ger.*
⊗ Propranolol hydrochloride (p.1380·3); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Proprahexal *Hexal, Austria.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety disorders; arrhythmias; hypertension; hyperthyroidism; migraine; phaeochromocytoma; tremor.

Propral *Orion, Fin.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; digitalis toxicity; essential tremor; hypertension; hyperthyroidism; migraine and cluster headache; myocardial infarction; phaeochromocytoma.

Propramed *Cimed, Braz.*
⊗ Propranolol (p.1381·1).

Propranol *HB, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Propranolil *Cifarma, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; gastrointestinal haemorrhage; hypertension; hyperthyroidism; migraine; myocardial infarction; phaeochromocytoma; subaortic hypertrophic stenosis; tremors.

Propranolum *Osorio de Moraes, Braz.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Propranur *Stegropharm, Ger.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism.

Propra-ratiopharm *Ratiopharm, Ger.*
⊗ Propranolol (p.1381·1) or propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; tremor.

Pro-PS
Note. This name is used for preparations of different composition.
Procare, Austral.†.
Cream: Disodium fumarate (p.1597·3); cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Psoriasis.

Procare, Austral.†.
Tablets: Disodium fumarate (p.1597·3); fumaric acid (p.1597·3); vitamins; minerals (p.1922·1).
Psoriasis.

Propulm *SIT, Ital.*
⊗ Procaterol hydrochloride (p.1130·2).
Obstructive airways disease.

Propycil *Admeda, Cz.; Admeda, Ger.; Admeda, Hung.; Admeda, Port.; Pro Concepta, Switz.; Frik, Turk.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propyderm *ACO Hud, Swed.*
Emollient.
Dry skin.

Propyl *Sriprasit, Thai.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propy-Lacticare *Stiefel, Fr.*
Lactic acid (p.2329·3); propylene glycol (p.2374·1).
Dry skin disorders.

Propyless *Schering-Plough, Swed.*
Emollient.
Dry skin.

Propylthiocil *Teva, Israel.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propyl-Thyracil *Paladin, Canad.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Propymal *Katwijk, Neth.*
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

Propyretic *Combiphar, Indon.*
Paracetamol (p.108·1).
Fever.

Pro-Q *CollaGenex, USA.*
Dimeticone (p.2032·1).
Barrier preparation.

ProQuad *Sanofi Pasteur, Cz.; Sanofi Pasteur, Port.; Merck, USA.*
A measles, mumps, rubella, and varicella-zoster vaccine (p.2224·1).
Active immunisation.

Proquiferon *Probiomed, Mex.*
Interferon alfa-2a (p.885·1).
Chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Proquin *Douglas, Austral.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

P-Roquine *PP Lab, Thai.†.*
Chloroquine phosphate (p.599·3).
Malaria.

Pro-Red *Pro-Pharma, USA.*
Hydrocodone tartrate (p.63·1); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Prorelax *Behrens, Venez.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Prorenal *Novell, Indon.*
-3-Methyl-2-oxo-valeric acid; 4-methyl-2-oxo-valeric acid; 2-oxo-3-phenyl-propionic acid; 3-methyl-2-oxo-butyric acid; -2-hydroxy-4-methylthio-butyric acid; amino acids (p.1922·1).
Renal insufficiency.

Prorhinel
Note.This name is used for preparations of different composition.
Novartis Sante, Fr.
Benzododecinium bromide (p.1631·2); polysorbate 80 (p.1919·2).
Rhinopharyngeal infections.

Interdelta, Switz.
Benzododecinium bromide (p.1631·2); sodium chloride (p.1686·1); polysorbate 80 (p.1919·2).
Nasal disorders.

Prorhinite *Novartis Sante, Fr.*
Azelastine (p.568·2).
Allergic rhinitis.

Proris *Pharos, Indon.*
Ibuprofen (p.64·2).
Fever; pain.

Pro-Roxikam *ProMed, Cz.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Pro-Sabona Uno *Sabona, Ger.†.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Prosatietil *Equilibre Attitude, Fr.†.*
Lactoserum glycomacropeptides; red cherry; magnesium oxide; griffonia simplicifolia (p.2317·2) (p.1922·1).
Obesity.

Proscar *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD Chibropharm, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Proscope *Tanabe, Jpn.*
Iopromide (p.1485·1).
Radiographic contrast medium.

Prosdina *Biotech, Venez.†.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Proseda F *Szama, Arg.*
Fluconazole (p.532·1).
Fungal infections.

Prosedal *Loeffler, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Prosedar *Schering-Plough, Port.†.*
Quazepam (p.1022·1).

Prosed/DS *Esprit, USA.*
Methenamine (p.298·3); salol (p.122·1); methylthioninium chloride (p.1450·3); benzoic acid (p.1630·2); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1).
Pain and discomfort of the urinary tract.

Prosed-X *Procare, Austral.†.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Anxiety; insomnia.

Prosek *Eczacibasi, Turk.*
Omeprazole (p.1753·1).

Proselamin *Biosel, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Proseptine *Qualiphar, Belg.*
Ether (p.2023·2).
Skin cleansing.

Proseptine-Plus *Qualiphar, Belg.*
Butylated hydroxytoluene (p.1633·2).
Adhesive plaster remover.

Proserem *Arkofarm, Ital.*
St John's wort (p.422·3).
Depression.

Proserine *Hawon, Thai.*
Cycloserine (p.260·2).
Tuberculosis.

Prosertin *Probiomed, Mex.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Proseval *Solas, Indon.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1); glutamic acid (p.1947·1); vitamin B substances; calcium phosphate (p.1922·1).
Cerebral and peripheral vascular disorders.

Prosgutt *Farmasa, Mex.*
Saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia; urinary-tract disorders.

Pro-Shape *Procare, Austral.†.*
Garcinia quaesita (p.2309·2); chromium trichloride (p.1934·3); pectin (p.2145·2); methylcellulose (p.2145·1); magnesium amino acid chelate (p.1680·1).
Dietary fibre supplement; obesity.

Prosicca *Agepha, Austria.*
Hypromellose (p.2144·2).
Eye irritation.

ProSight Lutein *Major, USA.*
Vitamin and mineral preparation (p.1922·1).

Prosigne *Cristalia, Braz.*
Botulinum A toxin (p.1890·1).

Prosimed *3DDD, Belg.*
Fluoxetine (p.397·3).
Depression.

Prosiston *Schering, Ger.†.*
Norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3).
Menstrual disorders.

Proskin
Note.This name is used for preparations of different composition.
Teofarma, Spain.
Dimeticone (p.2032·1); thiomersal (p.1663·3); zinc oxide (p.1621·2).
Skin disorders.

Julphar, UAE.
Zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Proslender *Procare, Austral.†.*
Gymnema silvestre; dietary fibre (p.1712·3).
Obesity.

Prosmin *Biotenk, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prosneo *Farmoz, Port.*
Flutamide (p.725·1).
Prostatic cancer.

Prosobee *BMS, Arg.†; Mead Johnson, Braz.; Mead Johnson Nutritionals, Fin.; Mead Johnson, Fr.; Mead Johnson, Hong Kong; Mead Johnson, Indon.; Mead Johnson, Irl.; Mead Johnson, Ital.; Mead Johnson, Malaysia; BMS, Pol.; Mead Johnson, Pol.; Mead Johnson, Port.†; Mead Johnson, Singapore; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, UK; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Infant feed (p.1922·1).
Cow's milk allergy; cows' milk intolerance; diarrhoea; for infants with a family history of hypersensitivity; galactokinase deficiency; galactosaemia; lactose, sucrose, and gluten intolerance.

Prosodina *Liferpal, Mex.*
Benzylpenicillin (p.213·1).
Bacterial infections.

Prosogan *Takeda, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Prosolmin *Roemmers Osmoph, Venez.*
Vitamin and mineral preparation (p.1922·1).

Prosolvit *Roemmers Osmoph, Venez.*
Vitamin preparation (p.1922·1).

Prosom *Abbott, USA†.*
Estazolam (p.995·1).
Insomnia.

Proson *Bernofarm, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Proson N *Bernofarm, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Prosoyal *FDC, India.*
Infant feed (p.1922·1).
Intolerance to animal milk; lactose intolerance.

Prospan *Sanova, Austria; Engelhard, Cz.; Merck Medication Familiale, Fr.; Engelhard, Ger.; Farmasyn, Gr.; Engelhard, Malaysia; Engelhard, Pol.; Engelhard, Singapore; Engelhard, Switz.; Roemmers, Venez.*
Ivy (p.2328·1).
Cough and associated respiratory-tract disorders.

Prospaxid *Prospa, Port.*
Nizatidine (p.1751·2).

Prospec *Apotex, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Prosphere *AF, Mex.*
Progesterone (p.2125·1).
Endometrial hyperplasia; endometriosis; female infertility; hirsutism; menopausal disorders; menstrual disorders; premenstrual syndrome; threatened or recurrent miscarriage.

Prospiril *Schering-Plough, Port.*
⊗ Mometasone furoate (p.1539·3).
Asthma.

Prost-I *Procare, Austral.†.*
Vitamins; amino acids; minerals (p.1922·1); devil's claw root (p.39·1); yucca (p.2416·3); salix (p.121·3); green-lipped mussel (p.2317·2); bromelains (p.2269·1); papain (p.2362·3).
Dietary supplement; musculoskeletal and joint disorders.

Prosta *Procare, Austral.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prosta Fink forte *GSK Consumer, Ger.*
Cucurbita (p.2290·2).
Prostatic disorders.

Prosta Urgenin Uno *Madaus, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostabiol *Nutrisante, Fr.*
Cucurbita; acerola; zinc gluconate; pollen (p.1922·1).
Urinary-tract disorders in men.

Prosta-Caps Chassot N *Doetsch, Grether, Switz.*
Cucurbita (p.2290·2); cucurbita oil (p.2290·2); saw palmetto (p.2192·3); echinacea angustifolia (p.2298·1); java tea (p.2328·2); ononis (p.2357·1).
Benign prostatic hyperplasia.

Prostacide *Vida, Port.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostacom *Combiphar, Indon.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostacor *Microgen, Rus.†.*
Prostate extract (bovine) (p.2337·3).
Prostate disorders.

Prostacur
Note.This name is used for preparations of different composition.
Finadiet, Arg.
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Prasfarma, Spain.
Flutamide (p.725·1).
Prostatic cancer.

Prostadilat *Pfizer, Austria.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Prostadirex *Winthrop, Fr.*
Flutamide (p.725·1).
Prostatic cancer.

Prostafilina *BMS, Venez.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Prostafin *Cipan, Port.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostaflor *Sanova, Austria; Bayer, Switz.*
Pollen extract (Cernitin T, Cernitin GBX) (p.2370·2).
Benign prostatic hyperplasia; prostatic disorders.

Prostafort *Knop, Chile.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostaforton *Hexal, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostagalen *Hevert, Ger.*
Urtica root (p.2409·3).
Prostatic disorders.

Prostagutt *Austroplant, Austria.*
Saw palmetto (p.2192·3); populi trem. (p.2371·1); urtica dioica (p.2409·3).
Bladder disorders; prostatic disorders.

Prostagutt forte *Schwabe, Ger.*
Saw palmetto (p.2192·3); urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostagutt Forte *Schwabe, Rus.*
Saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Prostagutt mono *Schwabe, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostagutt uno *Schwabe, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostagutt-F *Schwabe, Switz.*
Saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Prostaherb N *Cesra, Ger.; Cesra, Pol.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostakan
Note.This name is used for preparations of different composition.
ASI, Hung.†.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Schwabe, Malaysia†.
Saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Prostakan Forte *Schwabe, Cz.*
Saw palmetto (p.2192·3); urtica (p.2409·3).
Prostatic disorders.

Prostakan Mono *Schwabe, Cz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostakur *Medikon, Indon.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostal
Note.This name is used for preparations of different composition.
Motima, Fr.
Pollen (p.2370·2).
Tonic.

Teikoku, Jpn.
Chlormadinone acetate (p.2084·3).
Prostatic cancer; prostatic hyperplasia.

Prostalium *Teuto, Braz.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostalizyna *Herbapol Pruszkow, Pol.*
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Prostall *Drugtech, Chile.*
Tamsulosin hydrochloride (p.2197·1).
Prostatic disorders.

Prostamed
Note. A similar name is used for preparations of different composition (see below).
Klein, Ger.; Distrifarma, Port.†.
Cucurbita (p.2290·2); solidago virgaurea (p.2391·1); poplar buds (p.2371·1).
Prostatic disorders; urinary-tract disorders.

ProstaMed
Note. A similar name is used for preparations of different composition (see above).
Bioforce, Switz.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostamed Urtica *Klein, Ger.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Prostamer *Gal, Pol.†.*
Cucurbita oil (p.2290·2); shark-liver oil (p.2386·1).
Benign prostatic hyperplasia.

Prostamid *BDH, India.*
Flutamide (p.725·1).
Prostatic cancer.

Prostamide *Gerolymatos, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Prostamnic *Schwarz, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Prostamol Uno *Berlin-Chemie, Cz.; Berlin-Chemie, Hung.; Menarini, Hung.; Berlin-Chemie, Pol.; Berlin-Chemie, Rus.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostamustin *Azupharma, Ger.†.*
Estramustine meglumine phosphate (p.717·3) or estramustine sodium phosphate (p.717·3).
Prostatic cancer.

Prostan *Medicine Products, Thai.*
Mefenamic acid (p.80·1).
Pain.

Prostanac *Pyridam, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Prostandin *Ono, Jpn.*
Alprostadil alfadex (p.2183·3).
Chronic arterial occlusion; controlled hypotension in surgery; maintenance of patent ductus arteriosus; peripheral vascular disorders.

Prostandril *Pliva, Cz.; Pliva Krakow, Pol.*
Flutamide (p.725·1).
Prostatic cancer.

Prostaneurin *Sanofi Synthelabo, Ger.†.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostanil *Lamsa, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostanon *Pharmachemie, Philipp.*
Flutamide (p.725·1).
Prostatic cancer.

Prostanorm *Vilar, Rus.*
St John's wort (p.422·3); solidago (p.2391·1); liquorice (p.1740·3); echinacea purpurea (p.2298·1).
Prostatitis.

Prostanovag *Gobbi, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostap *Wyeth, Irl.; Wyeth, UK.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; prostatic cancer; uterine fibroids.

Prostaphilin-A *BMS, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Prostaphlin *BMS, Cz.; BMS, Philipp.*
Oxacillin sodium (p.311·3).
Staphylococcal infections.

Prostaphlin-A *BMS, Hong Kong.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Prostaplant
Note.This name is used for preparations of different composition.
Bioplanta, Ger.†; Schwabe, Pol.; Schwabe, Rus.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Marvecs, Ital.
Saw palmetto (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia; micturition disorders.

Prostapol *Herbapol Krakow, Pol.*
Arnica (p.2260·2); shepherd's purse (p.2386·2); St John's wort (p.422·3); solidago (p.2391·1); valerian (p.2410·1); rapeseed.
Benign prostatic hyperplasia.

Prostarell *Sanorell, Ger.*
Homoeopathic preparation.

Prostasal *TAD, Ger.†.*
Sitosterol (p.1373·2).
Prostatic disorders.

Prostasan *Biofarma, Mex.; Bioforce, Switz.; Bioforce, UK.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostascint Kit *Cytogen, Israel.*
Indium-111 capromab pendetide (p.2054·1).
Diagnosis of prostatic cancer.

Prostaserene *Therabel, Belg.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostat
Note. A similar name is used for preparations of different composition

(see below).
Marjan, Braz.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Pro-Stat
Note. A similar name is used for preparations of different composition (see above).
Medical Nutrition, USA.
Preparation for enteral nutrition (p.1922·1).

Prostata *Stada, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostata-Gastreu N R25 *Reckeweg, Ger.*
Homoeopathic preparation.

Prostata-Komplex N Ho-Fu-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Prostatal *Herbarium, Braz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostate Ease *Swiss Herbal, Canad.*
Cucurbita seed oil (p.2290·2); pygeum africanum (p.2192·3); linseed oil (p.2334·1); saw palmetto (p.2192·3).

Prostate Support *Reese, USA.*
Sitosterol (p.1373·2); zinc citrate (p.1999·2).

Prostatic *Schwarz, Pol.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Prostatil
Note.This name is used for preparations of different composition.
Boniscontro & Gazzone, Ital.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Sanofi-Aventis, Neth.
Flutamide (p.725·1).
Prostatic cancer.

Prostatilen *Lekkhim-Kharkov, Rus.*
Prostate extract (bovine) (p.2337·3); glycine; dimethyl sulfoxide.
Prostatitis.

Prostatin F *Abbott, Ger.†.*
Bearberry (p.2263·3); urtica root (p.2409·3).
Prostatitis.

Prostatonin *Madaus, Austria; Pharmaton, Cz.†; Pharmaton, Switz.*
Pygeum africanum (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Prosta-Truw *Truw, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prosta-Urgenin *Madaus, Austria; Madaus, Belg.; Madaus, Cz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prosta-Urgenine *Madaus, Switz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostavasin *Sidus, Arg.; Gebro, Austria; Biosintetica, Braz.; Schwarz, Cz.; Schwarz, Ger.; Schwarz, Hong Kong; Schwarz, Hung.; Schwarz, Ital.; Schwarz, Pol.*
Alprostadil alfadex (p.2183·3).
Arterial occlusion; intermittent claudication; peripheral vascular disorders; thromboangiitis obliterans.

Prostawern *Wernigerode, Ger.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Prostazosina *LKM, Arg.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia.

Prostease *Jamieson, Canad.; Jamieson, Hong Kong.*
Cranberry (p.2289·1); cucurbita seed oil (p.2290·2); pygeum bark (p.2192·3); saw palmetto berry (p.2192·3).
Nutritional supplement.

Prostec *CSC, Austria.*
Mepartricin (p.541·1).
Benign prostatic hyperplasia.

Prostem *Baldacci, Braz.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Prostem Plus *Baldacci, Braz.*
Pygeum africanum (p.2192·3); urtica (p.2409·3).
Benign prostatic hyperplasia.

Prostene *Ivax, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prosteo *Procare, Austral.†.*
Calcium gluconate (p.1675·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); dolomite (p.2297·3).
Calcium supplement.

Prostep *Aveva, Canad.; Lederle, USA.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Prosteren *Cornelli, Ital.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prosterid *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prosterit *Kocak, Turk.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prosterol *Herbapol Poznan, Pol.*
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Prostess *TAD, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Prostex *Medix, Mex.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

ProstGard *Holista, Canad.†.*
Cucurbita seed oil (p.2290·2); saw palmetto berry (p.2192·3); vitamin B (p.1979·1); zinc gluconate (p.1999·2).

Prostica *TAD, Ger.*
Flutamide (p.725·1).
Prostatic cancer.

Prostide *Libbs, Braz.; Sigma-Tau, Ital.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Prostigmin
Valeant, Arg.; ICN, Hong Kong†; ICN, Thai.
Neostigmine (p.631·2).
Atonic constipation; heartburn and flatulence in pregnancy; intestinal atony; Ménière's disease; meteorism; migraine; myasthenia gravis; paroxysmal tachycardia; postoperative urinary retention; reversal of competitive neuromuscular blockade; tinnitus.

Valeant, Austral.; ICN, Austria; Combiphar, Indon.; Valeant, Indon.; ICN, Malaysia†; ICN, Neth.; Valeant, Philipp.; Valeant, Switz.
Neostigmine metilsulfate (p.631·3).
Constipation; flatulence; heartburn; ileus; meteorism; myasthenia gravis; neuralgia; paroxysmal tachycardia; postoperative intestinal atony; postoperative urinary retention; reversal of competitive neuromuscular blockade.

Valeant, Canad.
Neostigmine bromide (p.631·3).
Myasthenia gravis.

ICN, USA.
Neostigmine bromide (p.631·3) or neostigmine metilsulfate (p.631·3).
Myasthenia gravis; postoperative distension and urinary retention; reversal of competitive neuromuscular blockade.

Prostigmina *ICN, Ital.*
Neostigmine metilsulfate (p.631·3).
Gastrointestinal atony; myasthenia gravis; reversal of competitive neuromuscular blockade.

Prostigmine
Pharma Logistics, Belg.; Valeant, Braz.; Raffo, Chile†; CSP, Fr.; ICN, Israel†; Valeant, Mex.; Codifar, Port.; Valeant, Spain.
Neostigmine metilsulfate (p.631·3).
Constipation; ileus; meteorism; myasthenia gravis; paralytic ileus; paroxysmal tachycardia; postoperative urinary retention; reversal of competitive neuromuscular blockade.

IFET (ΙΦΕΤ), Gr.
Neostigmine bromide (p.631·3).
Myasthenia gravis.

Prostin E2 *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Paladin, Canad.; Pfizer, Cz.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Port.; Pfizer, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Pharmacia Upjohn, USA.*
Dinoprostone (p.2007·1).
Gestational trophoblastic tumours; hydatidiform mole; intra-uterine death; labour induction; missed abortion; termination of pregnancy.

Prostin F2 *Pharmacia, Irl.†.*
Dinoprost trometamol (p.2006·3).
Labour induction.

Prostin F2 Alfa *Pfizer, Rus.†.*
Dinoprost trometamol (p.2006·3).

Prostin F2 Alpha *Pfizer, Austral.; Pfizer, Hong Kong; Pharmacia, Israel; Pharmacia, NZ; Pharmacia, S.Afr.*
Dinoprost trometamol (p.2006·3).
Fetal death in-utero; hydatidiform moles; labour induction; termination of pregnancy.

Prostin 15M *Pfizer, Cz.; Pharmacia, NZ.*
Carboprost trometamol (p.2006·1).
Postpartum haemorrhage; termination of pregnancy.

Prostin Pediatrico *Pfizer, Chile.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Prostin VR *Pfizer, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pharmacia, Cz.†; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, India; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Upjohn, USA.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Prostine E_2 *Pfizer, Fr.*
Dinoprostone (p.2007·1).
Hydatidiform mole; labour induction; termination of pregnancy.

Prostine VR *Pfizer, Fr.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Prostinfenem *Pfizer, Denm.; Pfizer, Swed.*
Carboprost trometamol (p.2006·1).
Postpartum haemorrhage; termination of pregnancy.

Prostin/15M *Pfizer, Belg.; Pfizer, Neth.*
Carboprost trometamol (p.2006·1).
Intra-uterine death; postpartum haemorrhage; termination of pregnancy.

Prostiva *Aneid, Port.†.*
Saw palmetto (p.2192·3).
Prostate disorders.

Prostivas *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
Alprostadil (p.2183·2).
Maintenance of patent ductus arteriosus.

Prostodin *AstraZeneca, India.*
Carboprost trometamol (p.2006·1).
Postpartum haemorrhage; termination of pregnancy.

Prostogal *Gal, Pol.†.*
Cucurbita oil (p.2290·2).
Benign prostatic hyperplasia.

Prostogenat *Azupharma, Ger.†.*
Flutamide (p.725·1).
Prostatic cancer.

Prosturol *Farmasierra, Spain.*
Benzydamine hydrochloride (p.27·3); pygeum africanum (p.2192·3).
Prostatic adenoma.

Prost-X L8 *Homeocan, Canad.†.*
Homoeopathic preparation.

Prosulf *CP Pharmaceuticals, Hong Kong; CP, Israel; CP Pharmaceuticals, UK.*
Protamine sulfate (p.1461·2).
Heparin overdosage; neutralisation of heparin activity.

Prosulpin *ProMed, Cz.; Promed, Rus.*
Sulpiride (p.1028·3).
Psychoses; psychosomatic disorders.

Prosure *Abbott, Fr.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Singapore; Abbott, UK.*
Preparation for enteral nutrition (p.1922·1).

Prosymbioflor *Peithner, Austria†.*
Autolysate of: *Escherichia coli*; *Enterococcus faecalis* (p.2372·3).
Immunotherapy.

Pro-Symbioflor *Symbiopharm, Ger.*
Autolysates of: *Escherichia coli*; *Enterococcus faecalis* (p.2372·3).
Gastrointestinal disorders.

Prota *Samarth, India.*
Protamine sulfate (p.1461·2).
Antidote to heparin.

Protab *Eczacibasi, Turk.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); methylpolysiloxane (p.1770·2).

Protact *Coloplast, Fr.*
Barrier cream.

Protactyl *Hexal, Ger.†.*
Promazine hydrochloride (p.1021·2).
Anxiety; neurogenic pain; premedication; pruritus; psychoses; sleep disorders; vomiting.

Protagens *Alcon, Neth.*
Povidone (p.2146·1).
Dry eyes.

Protagent
Alcon, Austria; Alcon, Ger.; Farmex, Gr.; Alcon, Hong Kong; Alcon, Ital.†; Alcon, Switz.; Liba, Turk.
Povidone (p.2146·1) (p.1622·2).
Dry eyes; eye irritation; wetting drops for contact lenses.

Protal *Aurora, Gr.†.*
Enalapril (p.1276·1).
Hypertension.

Protal complex *Medilat, Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Protalgia *Dimportex, Spain.*
Fosfosal (p.62·1).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Protalgine *Probiomed, Mex.*
Lamotrigine (p.485·1).
Epilepsy.

protAlgon *Lavipharm, Gr.*
Paracetamol (p.108·1).
Pain.

Protamox *Armoxindo, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Protan *Apotex, Mex.*
Dextromethorphan (p.1555·2).
Coughs.

Protanol *Teuto, Braz.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Protaphane *Novo Nordisk, Austral.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Ital.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Port.*
⊗ Neutral isophane insulin injection (human, pyr, monocomponent) (p.443·2).
Formerly known as Protaphan in *Ger.*
Diabetes mellitus.

Protaphane HM *Novo Nordisk, Hong Kong; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.*
⊗ Neutral isophane insulin injection (human, monocomponent) (p.443·2).
Diabetes mellitus.

Protaphane MC *Novo Nordisk, Braz.†.*
⊗ Isophane insulin injection (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Protat *Potter's, UK.*
Corn silk (p.2288·1).
Formerly contained corn silk and kava.
Bladder discomfort.

Protaxil *Delta, Port.*
Proglumetacin maleate (p.119·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Protaxol *Provit, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Protaxon *Opfermann, Ger.*
Proglumetacin maleate (p.119·1).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Protaxos *Servier, Malaysia.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Protease *Richmond, Arg.*
Nevirapine (p.899·1).
HIV infection.

Proteazone *IMS, Ital.†.*
Adazone.
Instrument disinfection.

Protec *Protec, UK.*
Dioctyl adipate (p.2042·1).
Insect repellent.

Pro-Tec Sport *Allergan, Canad.*
SPF 20: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Protecadin *Taiho, Jpn.*
Lafutidine (p.1739·2).

Proteccion Ultra *Rider, Chile.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); meradimate (p.1604·2); homosalate (p.1598·1).
Sunscreen.

ProTech *Triton, USA.*
Povidone-iodine (p.1659·2); lidocaine hydrochloride (p.1862·3).
Burns; cuts.

Protecor *Duopharm, Ger.*
Crataegus (p.2289·1); magnesium complex with acid hydrolysate of corn starch; alpha tocoferil acetate (p.1992·3).
Cardiovascular disorders.

Protecor novo *Duopharm, Ger.*
Crataegus (p.2289·1).
Heart failure.

Protectaid *Pirri, Canad.; Pirri, Hong Kong; Sinclair, UK.*
Nonoxinol 9 (p.1917·2); sodium cholate (p.2266·3); benzalkonium chloride (p.1629·1).
Contraceptive.

Protectina *Gross, Braz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Protecto *National Care, Canad.†.*
Benzethonium chloride (p.1630·1); zinc oxide (p.1621·2).
Barrier cream.

Protectol *Daniels, USA.*
Calcium undecenoate (p.549·3).
Bromhidrosis; fungal skin infections; hyperhidrosis; minor skin irritation; nappy rash.

Protector *Quimifar, Spain.*
Loperamide (p.1741·3).
Formerly contained diphenoxylate hydrochloride.
Diarrhoea.

Protectura *Faran, Gr.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Protegra Antioxid *Wyeth-Whitehall, Arg.*
Vitamin and mineral preparation (p.1922·1).

Proteigeno *Lafedar, Arg.*
β-Aminoethanol phosphoric acid; amino acids; pyridoxine (p.1922·1).
Tonic.

Proteika PRO'gram *Proteika, Fr.*
Dietary supplement (p.1922·1).
Obesity.

Protein Free Diet (Product 80056) *Mead Johnson, Austral.†.*
Preparation for infant enteral nutrition (p.1922·1).
Disorders of amino acid metabolism.

Proteinex *Victus, Venez.*
Protein supplement (p.1922·1).

Protein-Free *Mead Johnson, Hong Kong†; Mead Johnson, Ital.†.*
Food for special diets (p.1922·1).

Proteita *Janssen-Cilag, Arg.†.*
Collagen (p.2286·1).
Ulcers; wounds.

Protelos *Servier, Belg.; Servier, Cz.; Servier, Denm.; Servier, Fr.; Servier, Ger.; Servier, Gr.; Servier, Hung.; Servier, Irl.; Servier, Ital.; Servier, Neth.; Servier, Pol.; Servier, Port.; Servier, Spain; Servier, Swed.; Servier, UK.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Protemp *Procare, Austral.†.*
Vitamins; minerals (p.1922·1); bearberry (p.2263·3); parsley piert (p.2363·2); juniper (p.2328·2); viburnum opulus.
Dietary supplement; dysmenorrhoea; premenstrual syndrome.

Proten *Otsuka, Indon.*
Preparation for enteral nutrition (p.1922·1).

Protenac *Enila, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Protenate *Hyland, USA.*
⊗ Plasma protein fraction (p.1076·2).
Hypoproteinaemia; hypovolaemia.

Prote-Neu *Biotenk, Arg.*
A pneumococcal vaccine (14 valent) (p.2231·2).
Active immunisation.

Protensin-M *BMS, S.Afr.*
⊗ Hydroflumethiazide (p.1311·3); reserpine (p.1387·3).
Hypertension.

Proteoferrina *Bayer, Ital.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Proteovir *Richmond, Arg.*
Saquinavir (p.906·1).
HIV infection.

Proteozym *Wiedemann, Ger.*
Bromelains (p.2269·1).
Inflammation.

Proterenal *Phoenix, Arg.†.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Heart block; shock.

Protevis *Allergan, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Protexel *Lab Francais du Fractionnement, Fr.*
Protein C (p.1077·3).
Thromboembolic disorders.

Protexin
Note. This name is used for preparations of different composition.
Probiotics, Singapore.
Lactic-acid producing organisms (p.2372·3); fructo-oligosaccharides.
Diarrhoea.

Combiphar, Indon.
Capsules: *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Bifidobacterium breve* (p.2372·3); *Bifidobacterium longum* (p.2372·3); *Streptococcus thermophilus* (p.2372·3); fructo-oligosaccharides.
Candida infection; constipation; diarrhoea; flatulence; lactose intolerance.

Combiphar, Indon.
Chewable tablets (child); oral sachet (infant): *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus casei* (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus bulgaricus* (p.2372·3); *Bifidobacterium breve* (p.2372·3); *Bifidobacterium infantis* (p.2372·3); *Streptococcus thermophilus* (p.2372·3); fructo-oligosaccharides.
Candidiasis; constipation; diarrhoea; flatulence; lactose intolerance.

Protexin Balance *Probiotics International, Hong Kong.*
Fructo-oligosaccharides; lactic-acid-producing organisms (p.2372·3).
Digestive system disorders.

Protexin Balance+ *Probiotics International, Hong Kong.*
Fructo-oligosaccharides; lactic-acid-producing organisms (p.2372·3); vitamin A; vitamin C; vitamin E (p.1922·1).
Digestive system disorders.

Protexin Restore *Probiotics International, Hong Kong.*
Fructo-oligosaccharides; lactic-acid-producing organisms (p.2372·3).
Digestive system disorders.

Protexin Vitality *Probiotics International, Hong Kong.*
Fructo-oligosaccharides; lactic-acid-producing organisms (p.2372·3); vitamin C (p.1922·1).
Digestive system disorders.

Pro-T-Flor *Columbia, Mex.*
Bifidobacterium longum (p.2372·3); *Enterococcus faecium* (p.2372·3).
Diarrhoea.

Prothanon *Riemser, Ger.*
Dioxopromethazine hydrochloride (p.589·1).
Itching; pruritus.

Prothazin *Rodleben, Cz.; UCB, Cz.; Rodleben, Ger.; Wernigerode, Ger.*
Promethazine hydrochloride (p.588·2).
Anxiety; hypersensitivity reactions; insomnia; motion sickness; premedication; sedative; vomiting.

Prothazine *Strand, Malaysia†.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; motion sickness; nausea and vomiting.

Prothenol *Zwitter, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Prothiaden *Abbott, Austral.; Pharma Logistics, Belg.; Zentiva, Cz.; Abbott, Denm.; Teofarma, Fr.; Abbott, Hong Kong; Abbott, India; Abbott, Irl.; Abbott, Malaysia; Abbott, NZ; Abbott, Neth.; Abbott, Philipp.; Abbott, S.Afr.; Abbott, Singapore; Alter, Spain; Abbott, Thai.†; Abbott, UK.*
Dosulepin hydrochloride (p.388·2).
Depression; mixed anxiety depressive states.

Prothiazine *CTI, Israel.*
Promethazine hydrochloride (p.588·2).
Anxiety; coughs; hypersensitivity reactions; insomnia; nausea; pain; parkinsonism; premedication.

Prothiazine Expectorant *CTI, Israel; CTS, Rus.*
Promethazine hydrochloride (p.588·2); guaifenesin (p.1561·3); ipecacuanha (p.1562·3).
Cough.

Prothicid *Themis Chemicals, India.*
Protionamide (p.320·1).
Tuberculosis.

Prothil *Solvay, Ger.*
Medrogestone (p.2113·1).
Menopausal disorders; progestogenic.

Prothin *Quality, Hong Kong.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Prothiucil *Sanova, Austria.*
Propylthiouracil (p.2175·2).
Hyperthyroidism; ulcerative colitis.

Prothrombinex *CSL, NZ.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothrombinkomplex BaWu *Intersero, Ger.†.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothromplex *Baxter, Cz.; Baxter, Hung.; Baxter, Pol.; Baxter, Spain.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothromplex S-TIM 4 *Immuno, Austria.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothromplex Total S-TIM 4 *Baxter, Switz.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothromplex-T *Immuno, Braz.†.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothromplex-T TIM 4 *Adcock Ingram Critical Care, S.Afr.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Prothuril *Unipharma, Gr.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Prothyra *Sunthi Sepuri, Indon.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; dysfunctional uterine bleeding; endometriosis.

Prothyrid *Sanofi Synthelabo, Austria; Henning, Ger.; Sanofi Synthelabo, Ger.*
Levothyroxine sodium (p.2171·2); liothyronine hydrochloride (p.2174·2).
Hypothyroidism; thyroiditis.

Prothyrysat *Ysatfabrik, Ger.†.*
Lycopus europaeus.
Hyperthyroidism.

Proti 5 *Omega, Fr.*
Nutritional supplement (p.1922·1).

Protiaden *Teofarma, Ital.; Knoll, Switz.†.*
Dosulepin hydrochloride (p.388·2).
Depression; mixed anxiety depressive states.

Protiadene *Teofarma, Port.*
Dosulepin hydrochloride (p.388·2).
Depression.

Protica *Ethica, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Protical *Omega, Fr.*
High protein foods for special diets (p.1922·1).

Protid *Lunsco, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).

Protideal *Protiforme, Fr.†.*
High protein foods for special diets (p.1922·1).

Protiderm *Panalab, Arg.*
Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Fungal nappy rash.

Protidiet *Protidiet, Fr.†.*
Nutritional protein supplement (p.1922·1).

Protifar *Nutricia, Austral.†; Nutricia, Cz.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Hong Kong; Nutricia, Indon.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, NZ; Nutricia, Pol.; Nutricia, Port.; Nutricia, Thai.†; Nutricia Clinical, UK; Nutricia, Venez.*
Dietary protein supplement (p.1922·1).

Protifed *Graha, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; influenza symptoms.

Protiferron *Eumedica, Neth.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Protifortifiant *Omega, Fr.*
Protein enriched nutritional supplement (p.1922·1).

Protina G *Fresenius Kabi, Ital.*
Preparation for enteral nutrition (p.1922·1).

Protina Torre MP *Fresenius Kabi, Ital.†.*
Preparation for enteral nutrition (p.1922·1).

Protinex *Pfizer, India.*
High-protein dietary supplement (p.1922·1).

Protinin *Probifasa, Mex.†.*
Aprotinin (p.1055·1).
Cardiopulmonary bypass; extracorporeal circulation; haemorrhage.

Protinules *Alembic, India.*
High-protein dietary supplement (p.1922·1).

Protiocomb *Akrikhin, Rus.*
Lomefloxacin hydrochloride (p.295·2); protionamide (p.320·1); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Protitus *Mayo, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Protium *Abbott, Irl.; Altana, Irl.; Nycomed, UK.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protobex *Centaur, India.*
Nutritional supplement (p.1922·1).

Proto-Boric *Bell, India.*
⊗ Boric acid (p.2268·1); borax (p.2268·1); naphazoline hydrochloride (p.1565·2); camphor (p.2273·2); menthol (p.2340·1).
Corneal ulcer; inflammatory eye infections.

Protocide *Unipharm, Israel.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Protofen *Kimia, Indon.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Protogyl *Xepa-Soul Pattinson, Malaysia†.*
Metronidazole (p.837·1).
Amoebiasis; genito-urinary-tract infections; vaginal trichomoniasis.

Protol *Procare, Austral.†.*
Vitamins; minerals (p.1922·1); garlic (p.2309·2).
Dietary supplement; viral infections.

Proton *Medinfar, Port.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protone
Aristo, India.
Oral drops: Casein; lysine hydrochloride; carbohydrate; vitamin B substances (p.1922·1).
Tonic.

Aristo, India.
Oral liquid: Ferrous sulfate; casein; carbohydrate; vitamin B substances; zinc sulfate (p.1922·1).
Tonic.

Protoner *Inkeysa, Spain.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protonexa *Medico Uno, Hung.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protonis *Royal, Chile.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Protonix *Wyeth-Ayerst, USA.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Protop *Interbat, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Protopam *Wyeth, Canad.; Wyeth-Ayerst, USA.*
Pralidoxime chloride (p.1460·2).
Organophosphorus insecticide poisoning.

Protopic *Gador, Arg.; Fujisawa, Austria; Fujisawa, Belg.; Roche, Braz.; Astellas, Canad.; Roche, Chile; Astellas, Cz.; Fujisawa, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Ger.; Vianex (Βιανεξ), Gr.; Fujisawa, Hong Kong; Fujisawa, Hung.; Astellas, Indon.; Janssen-Cilag, Indon.; Astellas, Irl.; Fujisawa, Israel; Astellas, Ital.; Astellas, Jpn; Janssen-Cilag, Malaysia; Astellas, Neth.; Astellas, Norw.; Fujisawa, Philipp.; Janssen, Philipp.; Astellas, Pol.; Astellas, Port.; Janssen-Cilag, Singapore; Astellas, Spain; Astellas, Swed.; Fujisawa, Switz.; Janssen-Cilag, Thai.; Astellas, UK; Astellas, USA.*
Tacrolimus (p.1843·1).
Atopic eczema.

Protopy *Astellas, Cz.; Astellas, Neth.; Astellas, Port.*
Tacrolimus (p.1843·1).
Atopic eczema.

Protos *Servier, Arg.; Servier, Austral.; Servier, Braz.; Servier, Hong Kong; Servier, Indon.; Servier, NZ; Servier, Philipp.; Servier, S.Afr.; Servier, Singapore.*
Strontium ranelate (p.1104·2).
Osteoporosis.

Protosin *Streger, Mex.*
Quinfamide (p.846·2).
Intestinal amoebiasis.

Protosol *Kamada, Israel.*
Aprotinin (p.1055·1).
Hyperfibrinolytic haemorrhage; reduction of blood loss in cardiopulmonary bypass.

Protostat *Ortho Pharmaceutical, USA.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; trichomoniasis.

Protosulfil *Roemmers Osmoph, Venez.*
Sulfadiazine silver (p.337·2).
Burns; skin infections.

Protovit
Bayer, Belg.; Roche, Belg.; Bayer, Ital.; Bayer, Spain.
Multivitamin preparation (p.1922·1).

Bayer, Fr.
Vitamin and mineral preparation (p.1922·1).

Protovit N *Bayer, Port.*
Multivitamin preparation (p.1922·1).

Protovit Plus *Bayer, Braz.; Roche, Braz.*
Vitamin preparation (p.1922·1).

ProTract *VRI BioMedical, Austral.*
Lactobacillus fermentum (p.2372·3).
Atopic eczema in infants; irritable bowel syndrome.

Protradon *ProMed, Cz.*
Tramadol hydrochloride (p.130·3).
Pain.

Protrim *Mayo, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Protromplex *Baxter Immuno, Arg.*
A factor IX preparation (p.1068·3).
Haemorrhagic disorders.

Protromplex TIM 3 *Baxter, Ital.*
Factor IX (p.1068·3).
Deficiency of factors II, IX, and X.

Protropin *Roche, Canad.†; Genentech, USA†.*
⊗ Somatrem (p.1799·3).
Growth hormone deficiency.

Protusif *Pyridam, Indon.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Cough; nasal congestion.

Protuss *Horizon, USA†.*
Hydrocodone tartrate (p.63·1); sulfogaiacol (p.1573·2).
Coughs.

Protussa *Abbott, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs.

Protuss-D *Horizon, USA†.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); sulfogaiacol (p.1573·2).
Coughs.

Protuss-DM *Horizon, USA†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Proursan *ProMed, Pol.*
Ursodeoxycholic acid (p.2408·1).
Biliary cirrhosis; biliary reflux; cholesterol gallstones.

Prova *Cadila, India.*
Protein hydrolysate; carbohydrates; minerals (p.1922·1).
Tonic.

Provacsin Nasal *Inmunolab, Arg.*
⊗ Neomycin (p.305·1); naphazoline (p.1565·1).
Nasal congestion.

Provacsin Oral *Wierhom, Arg.*
Lyophilised bacterial antigens; vitamin C (p.1983·3).

Provail *CCM, Malaysia†; CCM, Singapore†.*
Ketoprofen (p.73·1).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Provamed *Promed, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Provames *Sanofi-Aventis, Fr.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Provamicina *Aventis, Mex.; Sanofi-Aventis, Venez.*
Spiramycin (p.333·1).
Bacterial infections; toxoplasmosis.

Provarivax *Sanofi Pasteur, Belg.; Sanofi Pasteur, Neth.*
A varicella-zoster vaccine (OKA strain) (p.2242·2).
Active immunisation.

Provas *Sanol, Ger.; Schwarz, Ger.; Schwarz, Switz.*
Valsartan (p.1420·2).
Heart failure; hypertension; left ventricular dysfunction following myocardial infarction.

Provas comp *Sanol, Ger.; Schwarz, Ger.; Schwarz, Switz.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Provas maxx *Schwarz, Switz.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Provasan *Polfa Grodzisk, Pol.*
Nicametate citrate.
Cerebral and peripheral vascular disorders.

Provasyn *Richter, Philipp.*
Bromocriptine mesilate (p.798·1).
Acromegaly; benign breast disorders; female infertility; lactation inhibition; menstrual disorders; parkinsonism; prolactinomas; puerperal mastitis.

Provatine *Duopharma, Hong Kong†.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Provax
Note. This name is used for preparations of different composition.
Almirall, Port.
Lysates of *Staphylococcus aureus*; *Streptococcus pyogenes*; *Streptococcus viridans*; *Klebsiella pneumoniae*; *Klebsiella ozaenae*; *Streptococcus pneumoniae*; *Haemophilus influenzae*; *Moraxella catarrhalis*.
Respiratory-tract infections.

Vivax, Venez.
Vitamin preparation (p.1922·1) with fish oil and soya lecithin.

Provay *Hormona, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Provegol *SVR, Fr.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Provelle *Pharmacia, Austral.†.*
Maroon tablets, conjugated oestrogens (Premarin) (p.2087·2); blue tablets, medroxyprogesterone acetate (Provera) (p.2113·1).
Menopausal disorders; osteoporosis.

Proven *Douglas, Austral.*
Ibuprofen (p.64·2).
Fever; pain.

Provenal *Boniscontro & Gazzone, Ital.*
Sulodexide (p.1406·3).
Chronic venous ulcer.

Provenen *HWS OTC, Austria; Schwabe, Spain†.*
Aesculus (p.2248·2).
Venous insufficiency.

Proveno N *Madaus, Ger.†.*
Aescin (p.2248·2).
Vascular disorders.

Provenol *Kela, Belg.*
Ibuprofen (p.64·2).
Fever; pain.

Proventil *Schering, USA.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Bronchospasm.

Proventol Expectorant *Sandoz, Indon.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Provera *Pfizer, Austral.; Pharmacia, Austria†; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; IFET (ΙΦΕΤ), Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Grunenthal, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Thai.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.*
Medroxyprogesterone acetate (p.2113·1).
Amenorrhoea; anorexia and cachexia associated with cancer or AIDS; breast cancer; contraception; dysfunctional uterine bleeding; endometrial cancer; endometrial hyperplasia; endometriosis; female infertility; functional uterine bleeding; menopausal disorders; menorrhagia; metrorrhagia; renal cancer; secondary amenorrhoea; test for pregnancy; threatened or recurrent miscarriage.

Provertin-UM TIM 3 *Baxter, Ital.*
Factor VII (p.1066·2).
Factor VII deficiency.

Provetal *Protein, Mex.†.*
Valproic acid (p.508·2).
Epilepsy.

Provexel NS *Multicare, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Provicar *Ivax, Mex.; Elmor, Venez.*
Levocarnitine (p.1932·2).
Carnitine deficiency; levocarnitine deficiency.

Provictol *SVR, Fr.†.*
⊗ Ichthammol (p.1599·1); salicylic acid (p.1612·2); urea (p.1620·2); tridecyl salicylate; allantoin (p.1588·1).
Dandruff.

Provide *Fresenius Kabi, Irl.; Fresenius Kabi, Malaysia†.*
Preparation for enteral nutrition (p.1922·1).

ProvideXtra *Fresenius Kabi, Fin.; Fresenius Kabi, Philipp.; Fresenius Kabi, UK.*
Preparation for enteral nutrition (p.1922·1).
Gastrointestinal disorders; milk protein intolerance.

Provigil
Note. This name is used for preparations of different composition.
Organon, Belg.; Cephalon, Irl.; Lafon, Israel; Dompe Biotec, Ital.; Pharmaplan, S.Afr.; Cephalon, UK; Cephalon, USA.
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome; shift-work sleep disorder; sleep apnoea.

Svizera, India.
⊗ Chorionic gonadotrophin (p.2085·1).
Male and female infertility.

Provigor *Meprofarm, Indon.*
Cistanchis herba; epimedii folium; fenugreek (p.2303·3); sarsaparilla (p.2383·3); cuscutae semen; calcium pantothenate.
Tonic.

Provimin *Ross, USA.*
A protein, vitamin, and mineral preparation for enteral nutrition (p.1922·1).

Provin *Plusandex, Venez.*
Vitamin and mineral preparation (p.1922·1).

Proviodine *Rougier, Canad.; Rougier, Hong Kong.*
Povidone-iodine (p.1659·2).
Burns; mouth infections; skin and mucous membrane disinfection; skin disorders; vaginal infections; wounds.

Provir *Bio-Kem, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Proviron *Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Schering, Chile; Schering, Cz.; Schering, Fin.†; Schering, Ger.†; Schering, Gr.; Schering, Hong Kong†; Schering, Hung.; Schering, Indon.; Schering, Israel; Schering, Ital.; Schering, Mex.; Schering, Neth.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, S.Afr.; Schering, Spain; Schering, Turk.; Schering, UK; Schering, Venez.*
⊗ Mesterolone (p.2116·1).
Androgen deficiency; aplastic anaemia; erectile dysfunction; impaired mental function; male hypogonadism; male infertility.

Proviron Depot *Schering, Venez.*
⊗ Testosterone enantate (p.2130·1).
Androgen deficiency; hypogonadism; male infertility.

Provironum *German Remedies, India; Schering, Malaysia†; Bayer, Singapore; Schering, Thai.*
⊗ Mesterolone (p.2116·1).
Androgen deficiency; erectile dysfunction; hypogonadism; male infertility.

Provirsan *ProMed, Cz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Provisacor *AstraZeneca, Ital.; AstraZeneca, Neth.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Provisc *Alcon, Arg.; Alcon, Austral.; Alcon, Fr.; Alcon, Ger.; Alcon, Hong Kong†; Alcon, Hung.†; Alcon, Irl.†; Alcon, Ital.; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, Venez.†.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Provisual *Poen, Arg.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Provisual Compuesto *Poen, Arg.*
⊗ Gentamicin sulfate (p.282·1); dexamethasone (p.1526·1); tetryzoline hydrochloride (p.1574·1).
Infected eye disorders.

Provita *Scherer, Thai.*
Vitamins; minerals; amino acids (p.1922·1).

Provital
Note. This name is used for preparations of different composition.
Landson, Indon.
Ginseng (p.2312·1); vitamins; liver extract; lysine; glutamic acid; minerals (p.1922·1).
Mental function impairment.

Prohealth, Philipp.
Vitamin and mineral preparation with lysine and taurine (p.1922·1).
Nutritional supplement.

Provital Plus *Landson, Indon.*
Ginseng (p.2312·1); vitamins; lysine; glutamic acid; minerals; lecithin (p.1922·1).
Immunostimulant.

Provitamin A + D + E *Klein, Ger.†.*
Multivitamin preparation (p.1922·1).

Provitamin A-E *Cielle, Ital.*
Vitamin A (p.1971·2); vitamin E (p.1992·2); royal jelly (p.2382·1).
Nutritional supplement.

Provit-Cee *Vitalink, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Proviton *CCM, Malaysia; Provit, Mex.*
Multivitamin and mineral preparation with ginseng, lecithin, and lysine (p.1922·1).

Provive *Zeus, Braz.†; Antibioticos, Mex.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Provixen-N *Biospray, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Provocholine *Methapharm, Canad.; Methapharm, USA.*
Methacholine chloride (p.2343·2).
Diagnosis of bronchial hyperreactivity.

Provokit *Lindopharm, Ger.*
Methacholine chloride (p.2343·2).
Diagnosis of bronchial hyperreactivity.

Provoltar *Sandoz, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Provosal *Gerot, Hung.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Provula *Dexa, Indon.*
⊗ Clomifene citrate (p.2086·1).
Male and female infertility.

Prowess *Harley Street Supplies, UK.*
⊗ Yohimbine hydrochloride (p.2200·2); pemoline (p.2161·2); methyltestosterone (p.2117·1).
Erectile dysfunction.

Prowess Plain *Harley Street Supplies, UK.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Pro-Whey *Milk Industries, Israel.*
Protein supplement (p.1922·1).

Proworm *Hexpharm, Indon.*
Pyrantel embonate (p.155·1).
Worm infections.

Proxacin
Neo Quimica, Braz.; Medreich, Hong Kong.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Polfa Warszawa, Pol.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Fako, Turk.
Ciprofloxacin (p.243·3).
Bacterial infections.

Proxagol *Union Health, Ital.*
Naproxen cetrimonium (p.93·3).
Mouth and throat inflammation.

Proxalin *Degorts, Mex.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Proxalin Plus *Degorts, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; pain.

Proxalyoc *Cephalon, Fr.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Proxatan *Sandoz, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Pro-XB *Biomep, Mex.*
Ibuprofen (p.64·2).
Pain.

Proxcip *Mugi, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Proxem *Hexal, Mex.†.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Proxen *Macarthur, Austral.; Grunenthal, Austria; Roche, Ger.; Medochemie, Hong Kong†; Grunenthal, Switz.; Pharmaland, Thai.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Proxiclav *Prohealth, Philipp.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2) or clavulanic acid (p.250·2).
Bacterial infections.

Proxidan *Meprofarm, Indon.*
d-Alpha tocopherol (p.1992·2).
Antoxidant.

Proxidin *Procare, Austral.†.*
Vitamins; minerals; garlic; eleutherococcus senticosis (p.1922·1).
Dietary supplement.

Proxil *Rottapharm, Ital.*
Proglumetacin maleate (p.119·1).
Inflammation; pain.

Proximax *Integrated Pharmaceutical, Philipp.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Proxime *Leti, Venez.*
Levofloxacin (p.292·2).
Bacterial infections.

Proxin *Strand, Malaysia†.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Proxinor *Medicine Products, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Proxitec *Tecnofarma, Mex.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Proxitor *Combiphar, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Proxivex *Blue Sky, Philipp.; Integrated Pharmaceutical, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Proxol *Sam-On, Israel.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Prox-S *Prosel, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Proxytab *Wockhardt, India.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Proxyvon *Wockhardt, India.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Proyeast *Procare, Austral.†.*
Garlic (p.2309·2); echinacea (p.2298·1); ascorbic acid (p.1983·3); chaparral (p.2280·1); zinc gluconate (p.1999·2); vitamin A (p.1971·2); pau d'arco.
Candidiasis.

Proza *Landson, Indon.; Landson, Singapore.*
Echinacea angustifolia extract (Polinacea) (p.2298·1); ascorbic acid (p.1983·3); zinc picolinate (p.2001·1).
Respiratory-tract infections; tonic.

Prozac *Lilly, Arg.; Lilly, Austral.; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Fr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Philipp.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Dista, Spain; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Fluoxetine hydrochloride (p.391·2).
Anxiety; bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder.

Prozamel *Clonmel, Irl.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Prozatan *UCB, Irl.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Prozef *BMS, S.Afr.*
Cefprozil (p.232·2).
Bacterial infections.

Prozen *Teuto, Braz.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Proziere *Ashbourne, UK†.*
Prochlorperazine maleate (p.1020·1).

Prozin *Lusofarmaco, Ital.*
Chlorpromazine hydrochloride (p.969·2).
Hiccups; pain; premedication; psychiatric disorders; vomiting.

Prozinc *Prohealth, Philipp.*
Zinc sulfate (p.1999·2).
Nutritional supplement.

Prozine
Note. This name is used for preparations of different composition.
Utopian, Thai.
Chlorpromazine hydrochloride (p.969·2).
Psychoses.

Hauck, USA.
Promazine hydrochloride (p.1021·2).
Psychoses.

Prozit *Pinewood, Irl.; Pinewood, UK.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Prozitel *Farcoral, Mex.†.*
Praziquantel (p.153·3).
Neurocysticercosis.

Prozolin *Liferpal, Mex.*
Metronidazole benzoate (p.837·1).

ProZone Body *Darier, Mex.*
SPF 25: Melanin (p.1604·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

ProZone Face
Note. This name is used for preparations of different composition.
Royal, Chile.
Melanin (p.1604·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); homosalate (p.1598·1); titanium dioxide (p.1617·3).
Sunscreen.

Darier, Mex.
SPF 25: Melanin (p.1604·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

ProZone Gel
Royal, Chile.
Melanin (p.1604·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); avobenzone (p.1589·3); homosalate (p.1598·1).
Sunscreen.

Darier, Mex.
SPF 30: Melanin (p.1604·2); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3); homosalate (p.1598·1).
Sunscreen.

ProZone Ultra *Darier, Mex.*
SPF 80: Melanin (p.1604·2); octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); enzacamene (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

ProZone Ultra Fluido *Darier, Mex.*
SPF 60: Octinoxate (p.1608·2); bisoctrizole (p.1591·2); enzacamene (p.1597·1); melanin (p.1604·2); bemotrizinol (p.1590·2); titanium dioxide (p.1617·3).
Sunscreen.

Prozylex *Norma (Νορμα), Gr.†.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Prozyme *Procare, Austral.†.*
Outer layer, pepsin (p.2365·1); bromelains (p.2269·1); glutamic acid hydrochloride (p.1947·1); inner layer, pancreatin (p.2360·1); papain (p.2362·3); bromelains.
Dyspepsia.

Prubagen *Liferpal, Mex.*
⊗ Betamethasone (p.1518·2); clotrimazole (p.530·1); gentamicin (p.284·2).
Infected skin disorders.

Prudencial *Northia, Arg.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Pruderm *Euroderm, Arg.*
Camphor (p.2273·2); menthol (p.2340·1).
Pruritus.

Prudoxin *Healthpoint, USA.*
Doxepin hydrochloride (p.389·1).
Pruritus.

Prudušková *Megafyt-R, Cz.*
Plantain (p.2379·1); wild thyme (p.2415·3); althaea (p.2253·3); liquorice (p.1740·3); tilia (p.2402·2); rose fruit without seeds (p.2381·2).
Coughs; respiratory-tract inflammation.

Prueboi *Temis, Arg.†.*
Egg yolk; soya lecithin (p.2332·2); sunflower oil (p.1970·3).

Pruina *Faes, Spain.*
Senna (p.1769·2); cassia fistula (p.1715·3); coriander (p.2288·1); tamarind (p.1775·3).
Constipation.

Prulit *Vinas, Spain.*
Menthol (p.2340·1).
Formerly known as Nopika.
Insect stings; muscle sprains and strains; pruritus.

Prunacolon *Nycomed, Neth.*
Senna (p.1769·2); dexpanthenol (p.2362·1).
Bowel evacuation; constipation.

Prunasine
Note.This name is used for preparations of different composition.
Christiaens, Belg.
Senna fruit (p.1769·2).
Constipation.

Nycomed, Neth.
Senna (p.1769·2); dexpanthenol (p.2362·1).
Bowel evacuation; constipation.

Prunodiet *DHN, Fr.*
Dietary fibre supplement (p.1922·1).
Constipation.

Prurex *Pentamedical, Ital.*
Piroctone olamine (p.1610·1); enoxolone (p.50·1); butyl aminobenzoate (p.1857·1); benzyl alcohol (p.1631·3); benzyl benzoate (p.2036·1).
Skin irritation.

Pruriced
Note.This name is used for preparations of different composition.
D & M, Chile.
Calamine (p.1591·2); borage oil (p.2267·3); Uriage thermal water.
Pruritus; skin irritation.

Uriage, Fr.
Cream: Calamine (p.1591·2); borage oil (p.2267·3); Uriage thermal water.
Skin irritation.

Uriage, Fr.
Topical gel: Calamine (p.1591·2); glycine (p.1947·3); Uriage thermal water.
Skin irritation.

Pruridermase *Sofex, Port.†.*
Calamine (p.1591·2); diphenhydramine (p.577·1); menthol (p.2340·1).
Pruritus; skin irritation.

Pruridol *Cazi, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Prurigel *Fortbenton, Arg.*
Triclosan (p.1665·2); mallow (p.2337·2); chamomile (p.2279·3).
Scalp disorders.

Prurilite *Eulite, Neth.*
Homoeopathic preparation.

Pruri-med *Permamed, Switz.*
Disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3); lauromacrogol 400 (p.1916·1).
Skin disorders.

Prurimix *Metochem, Austria; Metochem, Cz.†.*
Talc (p.1615·2); zinc oxide (p.1621·2); lauromacrogol 400 (p.1916·1); menthol (p.2340·1); diphenylpyraline hydrochloride (p.578·2).
Skin disorders; skin irritation.

Pruripelen *ICN, Arg.†.*
Calamine (p.1591·2); benzocaine (p.1854·1); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); menthol (p.2340·1).
Pruritus; skin irritation.

Prurisedan
Note.This name is used for preparations of different composition.
Andromaco, Arg.
Cream: Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2).
Allergic skin disorders; insect bites; pruritus; sunburn.

Andromaco, Arg.
Topical powder: Phenol (p.1656·1); camphor (p.2273·2); boric acid (p.2268·1); zinc stearate (p.2139·3); zinc oxide (p.1621·2).
Allergic skin disorders; insect bites; pruritus; sunburn; urticaria.

Prurisedan Antimicotico *Andromaco, Arg.†.*
Bifonazole (p.527·3); diphenhydramine hydrochloride (p.577·2).
Fungal skin and nail infections.

Prurisedan Biotic *Andromaco, Arg.†.*
⊗ Gentamicin sulfate (p.282·1); ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Prurisedan Incolora *Andromaco, Arg.*
Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2).
Pruritus; skin irritation.

Prurisedan Rosa *Andromaco, Arg.*
Phenol (p.1656·1); camphor (p.2273·2); zinc oxide (p.1621·2); diphenhydramine hydrochloride (p.577·2); neocalamine (p.1591·2).
Allergic skin disorders; insect bites; pruritus; sunburn; urticaria.

Prurisedine *Eurogenerics, Belg.*
Albichtyol; chlorobutanol (p.1639·2).
Skin disorders.

Prurix *Stiefel, Arg.; Stiefel, Chile; Stiefel, Mex.*
Camphor (p.2273·2); menthol (p.2340·1).
Pruritus; skin irritation.

Prurizin *Darrow, Braz.*
Hydroxyzine hydrochloride (p.581·2).
Hypersensitivity reactions.

Pryleugan *Temmler, Ger.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis; pain.

Pryltec *Geolab, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Pryltec-H *Geolab, Braz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Pryndette *Aventis, NZ†.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2).
Fever; pain; sedative.

Prysma *Q-Pharma, Arg.; Q Pharma, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Prysoline *Rekah, Israel.*
Primidone (p.503·2).
Epilepsy.

Psaeva *Sevapharma, Cz.†.*
A pseudomonas vaccine (p.2233·2).
Active immunisation.

PSE CPM *Boca, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

PSE MSC *Cypress, USA.*
Pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2).
Cold symptoms; rhinitis; sinusitis.

Pseudo *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Pseudo-Car DM *Geneva, USA.*
Pseudoephedrine hydrochloride (p.1571·2); carbinoxamine maleate (p.570·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Pseudo-Chlor *Geneva, USA; Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Pseudoephedrine T *Pharmaniaga, Malaysia.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Formerly known as Rinafed.
Nasal congestion.

Pseudofrin *Trianon, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).
Congestion.

Pseudo-Gest *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Pseudo-Gest Plus *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Pseudophage *Servier, Fr.*
Sodium alginate (p.2141·1); agar (p.2140·3).
Obesity.

Pseudovac *Biomed Krakow, Pol.*
A pseudomonal vaccine (7-valent) (p.2233·2).
Active immunisation.

Psibeter *BA Farma, Port.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Psico Blocan *Estedi, Spain.*
Chlordiazepoxide hydrochloride (p.968·2); hyoscine methobromide (p.1734·1).
Gastrointestinal spasm.

Psicoasten *Beta, Arg.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Psicocen *Centrum, Spain.*
Sulpiride (p.1028·3).
Anxiety disorders; psychoses; vertigo.

Psicolit *Farmo Quimica, Chile.*
Lithium carbonate (p.401·3).
Mania.

Psiconor *Ivax, Arg.*
Citalopram hydrobromide (p.385·3).
Depression.

Psicosedin *Farmasa, Braz.*
Chlordiazepoxide (p.968·1).
Adjuvant in general anaesthesia; alcohol withdrawal syndrome; anxiety; panic attacks; tension headache; tremor.

Psicosedol *Spedrog, Arg.*
Alprazolam (p.960·1).

Psicosoma Solucion *Ferrer, Spain.*
Magnesium glutamate hydrobromide (p.2337·1); promethazine hydrochloride (p.588·2).
Insomnia; night terrors; sedative.

Psilo-Balsam *Stada, Cz.; Stada, Hung.; Stada, Rus.*
Diphenhydramine hydrochloride (p.577·2).
Allergic skin disorders; pruritus; skin irritation; urticaria.

Psilumax *Columbia, Mex.*
Psyllium seed (p.1737·1); wheat fibre (p.1712·3).
Bowel evacuation; constipation.

Psipax *Merck, Port.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Psiquial *Merck, Braz.; Merck, Venez.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Psiu *Teuto, Braz.*
Cetylpyridinium chloride (p.1635·1); ammonium chloride (p.1551·3).
Respiratory-tract congestion.

PSO
Note.This name is used for preparations of different composition.
CS, Fr.
Cream: ⊗ Kokum butter; urea (p.1620·2).
Seborrhoea.

CS, Fr.
Mousse: Kokum butter; glycerol (p.2314·2).
Soap substitute.

CS, Fr.
Shampoo: ⊗ Kokum butter; urea (p.1620·2); piroctone olamine (p.1610·1).
Dandruff.

Psocortene *Genopharm, Fr.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2); coal tar (p.1616·2).
Skin disorders.

Psoderm *Ilsan, Turk.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Psodermil *Edol, Port.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin and scalp disorders.

Pso-Rad *Pentamedical, Ital.*
Mallow oil; lappa; aloe; bladderwrack; calendula; lavender; tormentil; helichrysum.
Skin disorders.

Psoraderm 5 *Expanscience, Fr.†.*
5-Methoxypsoralen (p.1607·2).
Psoriasis.

Psoradexan *Hermal, Ger.*
⊗ Dithranol (p.1595·2); urea (p.1620·2).
Psoriasis.

Psoraffect *Verisfield, Gr.*
Calcipotriol (p.1591·3).
Psoriasis.

Psoraks *Kurtsan, Turk.*
Dithranol (p.1595·2); salicylic acid (p.1612·2).
Psoriasis.

Psoralon MT *Hermal, Ger.*
Dithranol (p.1595·2); salicylic acid (p.1612·2).
Psoriasis.

Psor-a-set *Hogil, USA.*
Salicylic acid (p.1612·2).

Psor-Asist
Note.This name is used for preparations of different composition.
Sunspot, Austral.
Cream: Sulfur (p.1614·1); salicylic acid (p.1612·2); coal tar (p.1616·2).
Psoriasis.

Sunspot, Austral.
Lotion: ⊗ Sulfur (p.1614·1); salicylic acid (p.1612·2); aloe vera (p.1588·2); urea (p.1620·2).
Psoriasis of the scalp.

Psorasolv *Potter's, UK.*
Starch (p.1968·1); sublimed sulfur (p.1614·1); zinc oxide (p.1621·2); pokeroot (p.2370·1); clivers (p.2284·3).
Psoriasis.

Psorcon *Dermik, USA.*
⊗ Diflorasone diacetate (p.1529·1).
Skin disorders.

Psorcutan *Schering, Austria; Schering, Cz.†; Intendis, Ger.; Intendis, Ital.; Schering, Turk.*
Calcipotriol (p.1591·3).
Psoriasis.

Psorcutan Beta *Schering, Austria; Intendis, Ger.*
⊗ Calcipotriol (p.1591·3); betamethasone dipropionate (p.1518·3).
Psoriasis.

Psorex *GSK, Braz.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Psoriacalm *Phytobiolab, Fr.*
Marine phospholipids (p.1362·2).
Ichthyosis; psoriasis.

Psoriacen *Sanitas, Port.†.*
Calaguala.
Dermatitis; psoriasis.

Psoriasdin *Isdin, Spain.*
Coal tar (p.1616·2).
Keratinisation disorders; psoriasis.

Psoriasis-Bad *Balneopharm, Ger.†.*
Fumaric acid (p.1597·3); disodium fumarate (p.1597·3).
Bath additive; psoriasis.

Psoriasis-Salbe S *Balneopharm, Ger.†.*
Fumaric acid (p.1597·3); allantoin (p.1588·1); methyl salicylate (p.85·3); salicylic acid (p.1612·2).
Psoriasis.

Psoriasis-Solution *Balneopharm, Ger.†.*
Sodium fumarate (p.1597·3).
Psoriasis.

Psoriasis-Sulfur L12 *Homeocan, Canad.†.*
Homoeopathic preparation.

Psoriasis-Tabletten *Balneopharm, Ger.†.*
Sodium fumarate (p.1597·3).
Psoriasis.

Psoriatec *Sirius, USA.*
Dithranol (p.1595·2).
Formerly known as Micanol.
Psoriasis.

Psoriaten *DHU, Rus.*
Homoeopathic preparation.

Psoricreme *Schering-Plough, Neth.*
Dithranol (p.1595·2).
Psoriasis.

Psoriderm
Note.This name is used for preparations of different composition.
Erlimpex, Indon.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Dermal Laboratories, Irl.; Dermal Laboratories, UK.
Coal tar (p.1616·2).
Psoriasis.

Mipharm, Ital.
Dithranol (p.1595·2).
Psoriasis.

Psorigel *Galderma, Austral.†; Galderma, Chile†; Galderma, NZ†; Healthpoint, USA†.*
Coal tar (p.1616·2).
Eczema; psoriasis.

Psorigerb N *Cesra, Ger.†.*
⊗ Salicylic acid (p.1612·2); coal tar (p.1616·2); urea (p.1620·2).
Eczema; psoriasis.

Psorimed *Wolff, Denm.; Wolff, Ger.; Leo (Λεω), Gr.†; Leo, Irl.†; Wolff, Neth.; Wolff, Port.*
Salicylic acid (p.1612·2).
Scalp psoriasis.

Psorin
Note.This name is used for preparations of different composition.
Kinder, Braz.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

LPC, UK.
Ointment: Dithranol (p.1595·2); salicylic acid (p.1612·2); coal tar (p.1616·2).
Psoriasis.

LPC, UK.
Scalp gel: Dithranol (p.1595·2); salicylic acid (p.1612·2); methyl salicylate (p.85·3).
Psoriasis.

Psorinase *IDI, Ital.†.*
⊗ Salicylic acid (p.1612·2); tretinoin (p.1618·1); betamethasone valero-acetate (p.1519·1).
Psoriasis.

Psorinol *Ipca, India.*
Dithranol (p.1595·2).
Psoriasis.

Psorisan *RiC, Pol.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); zinc oxide (p.1621·2).
Skin disorders.

Psoristick *Schering-Plough, Neth.*
Dithranol (p.1595·2).
Psoriasis.

Psovate *Kurtsan, Turk.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Psycholanz *Ipca, India.*
Olanzapine (p.1012·1).
Bipolar disorder; schizophrenia.

Psychoneuroticum (Rowo-578) *Pharmakon, Ger.*
Homoeopathic preparation.

Psychopax *Sigmapharm, Austria; Sigmapharm, Switz.*
Diazepam (p.986·3).
Anxiety disorders; epilepsy; febrile convulsions; premedication; skeletal muscle spasm; sleep disorders.

Psychotonin *Madaus, Austria; Steigerwald, Ger.*
St John's wort (p.422·3).
Anxiety; depression.

Psychotonin Forte *Steigerwald, Cz.†.*
St John's wort (p.422·3).
Anxiety; depression; sleep disorders.

Psychotonin M *Steigerwald, Ger.†.*
St John's wort (p.422·3).
Anxiety; depression.

Psychotonin-sed *Steigerwald, Ger.*
St John's wort (p.422·3); valerian (p.2410·1).
Anxiety; depression; sleep disorders.

Psychotonisol *Phytofarm Kleka, Pol.*
St John's wort (p.422·3); melissa (p.2339·3); passion flower (p.2363·2).
Nervous disorders.

Psycoton *Benedetti, Ital.*
Piracetam (p.368·2).
Mental function impairment.

Psyllogel *Nathura, Ital.*
Psyllium (p.1737·1).
Dietary fibre supplement.

Psyllogel Fermenti *Nathura, Ital.*
Psyllium (p.1737·1); lactic-acid-producing organisms (p.2372·3).
Dietary fibre supplement.

Psynor *Swiss Pharma, Philipp.*
Chlorpromazine hydrochloride (p.969·2).
Anxiety; intractable hiccup; nausea and vomiting; porphyria; psychoses; tetanus.

Psyquil
Sanofi Synthelabo, Austria.
Triflupromazine hydrochloride (p.1035·1).
Agitation; nausea and vomiting; neuroleptanalgesia; schizophrenia; sedative.

Sanofi Synthelabo, Ger.†.
Triflupromazine (p.1035·1) or triflupromazine hydrochloride (p.1035·1).
Agitation; nausea and vomiting; neuroleptanalgesia; premedication.

Psyrazine *Condrugs, Thai.*
Trifluoperazine (p.1034·3).
Anxiety; nausea and vomiting; psychoses.

PSY-stabil *Pekana, Ger.†.*
Homoeopathic preparation.

Psytixol *Pacific, NZ†.*
Flupentixol decanoate (p.997·1).
Schizophrenia.

PTA *Neuropharma, Arg.*
Alprazolam (p.960·1).
Anxiety; depression.

P-Tanna *Prasco, USA.*
Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2).
Upper respiratory-tract disorders.

PTE *American Pharmaceutical, USA.*
A range of trace element preparations (p.1922·1).
Parenteral nutrition.

Pterin *Korea United, Philipp.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

P-Tex *Poly, USA.*
Brompheniramine tannate (p.569·3).
Hypersensitivity reactions.

Ptinolin *Help, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

P-Trovite *Rotexmedica, Malaysia.*
Ampoule 1, thiamine hydrochloride; pyridoxine hydrochloride; riboflavin; ampoule 2, sodium pantothenate; glucose; nicotinamide; ascorbic acid (p.1922·1).
Vitamin deficiency.

Pubergen *Uni-Sankyo, India.*
⊗ Chorionic gonadotrophin (p.2085·1).
Cryptorchidism; delayed puberty; hypogonadotrophic hypogonadism; male and female infertility; oligospermia; pituitary dwarfism; recurrent miscarriage.

Pubex *Tafarm, Gr.*
Phenothrin (p.2048·3).
Pediculosis.

Pudan-Lebertran-Zinksalbe *Bano, Austria.*
Zinc oxide (p.1621·2); peru balsam (p.2365·3); cod-liver oil (p.1935·2).
Burns; decubitus ulcer; nappy rash; wounds.

Puder Plynny
Note. This name is used for preparations of different composition.
Aflofarm, Pol.
Benzocaine (p.1854·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Skin irritation.

Farmina, Pol.
Menthol (p.2340·1); zinc oxide (p.1621·2).
Skin irritation.

Puder Plynny Wysuszajacy *Hasco-Lek, Pol.*
Menthol (p.2340·1); zinc oxide (p.1621·2).
Pruritus.

Puder Plynny z Anestezyna *Hasco-Lek, Pol.*
Benzocaine (p.1854·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Pruritus.

Pudroderm *Pampa, Pol.*
Benzocaine (p.1854·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Skin irritation.

Pudrospan *Gemi, Pol.*
Benzocaine (p.1854·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Pruritus.

Puernol *Formenti, Ital.†.*
Paracetamol (p.108·1).
Fever; pain.

Puiritol *HPP, Hong Kong.*
Ofloxacin (p.310·2).
Bacterial infections.

Pulairmax *Ivax, Denm.*
⊗ Budesonide (p.1520·1).
Asthma.

Pulbil *Fujisawa, Ger.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Pulbronc *Pharmabiotics, Chile.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1); ammonium chloride (p.1551·3).
Coughs.

Pulbronc Simple *Pediapharm, Chile.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Pulcet *Nobel, Turk.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Pulibex *Medinova (Μεντινοβα), Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Pulin *YSP, Malaysia; Yung Shin, Singapore.*
Metoclopramide hydrochloride (p.1747·3).
Adjunct in radiography of the gastrointestinal tract; nausea and vomiting.

Pulkrin *Kinder, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Pulmagol *Pasteur, Chile.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); drosera (p.2297·3); lobelia (p.2157·2).
Respiratory-tract disorders.

Pulmarin *NCSN, Ital.*
Sulfogaiacol (p.1573·2); cineole (p.2282·3); pine oil (p.2368·2); menthol (p.2340·1).
Catarrh.

Pulmax *Ivax, Cz.; Ivax, Hung.; Teva, Port.*
⊗ Budesonide (p.1520·1).
Asthma; obstructive airways disease.

Pulmaxan *AstraZeneca, Ital.*
⊗ Budesonide (p.1520·1).
Asthma.

Pulmeno *Novartis, Spain.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Pulmex
Note. This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis, Chile†; Novartis Consumer, Cz.†; Novartis Consumer, Rus.
Eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); camphor (p.2273·2); peru balsam (p.2365·3).
Coughs; respiratory-tract congestion; respiratory-tract disorders; respiratory-tract inflammation.

Novartis Consumer, Belg.
Benzyl benzoate (p.2036·1); benzyl cinnamate (p.2264·2); camphor (p.2273·2); rosemary oil (p.2381·3); cineole (p.2282·3); vanillin (p.2410·3).
Formerly contained benzyl benzoate, benzyl cinnamate, peru balsam, camphor, rosemary oil, and eucalyptus oil.
Upper respiratory-tract disorders.

Novartis Consumer, Israel.
Peru balsam (p.2365·3); camphor (p.2273·2).
Bronchitis; catarrh; cold symptoms; coughs.

Novartis Consumer, Switz.
Bath additive: Thyme oil (p.2401·2); pine needle oil (p.2368·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); niaouli oil (p.2351·3).
Cold symptoms; coughs.

Novartis Consumer, Switz.
Capsules for inhalation; ointment: Peru balsam (p.2365·3); camphor (p.2273·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3).
Cold symptoms; coughs.

Pulmex Baby
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.
Benzyl benzoate (p.2036·1); benzyl cinnamate (p.2264·2); rosemary oil (p.2381·3); cineole (p.2282·3); vanilline (p.2410·3).
Formerly contained benzyl benzoate, benzyl cinnamate, peru balsam, rosemary oil, and eucalyptus oil.
Upper respiratory-tract disorders.

Novartis Consumer, Cz.†; Novartis Consumer, Pol.; Novartis Consumer, Rus.; Novartis Consumer, Switz.
Rosemary oil (p.2381·3); eucalyptus oil (p.2301·2); peru balsam (p.2365·3).
Cold symptoms; coughs; respiratory-tract congestion.

Pulmiben *Italfarmaco, Port.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Pulmicort *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, Port.; Stuart, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; asthma; bronchitis; croup; nasal polyps; obstructive airways disease.

Pulmicret *AstraZeneca, Ger.†; Stern, Ger.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Pulmictan *Reig Jofre, Spain.*
⊗ Budesonide (p.1520·1).
Asthma.

Pulmidur *AstraZeneca, Ger.†; Stern, Ger.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Pulmilide *Boehringer Ingelheim, Austria.*
⊗ Flunisolide (p.1531·1).
Asthma.

Pulminflamatoria *Ern, Spain†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Pulmison *Boehringer Ingelheim, S.Afr.*
⊗ Prednisone (p.1542·3).
Obstructive airways disease.

Pulmist *Madaus, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Pulmiver *Iapharm, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; allergic skin disorders.

Pulmo Bailly *Bailly, Fr.; DDD, UK.*
Codeine (p.37·2); guaiacol (p.1561·2).
Coughs.

Pulmo Borbalan *Spyfarma, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Pulmo Bronchialcomplex *Hevert, Ger.*
Homoeopathic preparation.

Pulmo Diet *Support, Braz.†.*
Preparation for enteral nutrition (p.1922·1).

Pulmo Lisoflam *Pfizer, Arg.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; asthma; nasal polyps.

Pulmo Menal *Alacan, Spain†.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Pulmo-Bosan *Bock, Ger.†.*
Homoeopathic preparation.

Pulmobrol *Transfarma, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Pulmobron *Mugi, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Pulmocare *Abbott, Arg.; Abbott, Austral.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Thai.†; Abbott, Turk.; Abbott Nutrition, UK; Abbott Nutrition, USA; Abbott, Venez.*
Preparation for enteral nutrition (p.1922·1).
Respiratory system disorders.

Pulmocis *CIS, Cz.; CIS, Neth.; Schering, UK.*
⊗ Technetium-99m (p.2055·3) labelled human albumin macroaggregates.
Lung perfusion scintigraphy; venoscintigraphy.

Pulmoclase *Olvos, Gr.; UCB, Irl.; UCB, Port.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excessive or viscous mucus.

Pulmocler *Monserrat, Arg.*
Bromhexine hydrochloride (p.1552·2); butetamate citrate (p.1553·1).
Respiratory-tract disorders.

Pulmo-Cod *Stadmed, India.*
Multivitamin and calcium preparation (p.1922·1).

Pulmo-Cod (C & G) *Stadmed, India.*
Vitamins and calcium (p.1922·1); creosote (p.1555·1); sulfogaiacol (p.1573·2).
Bronchitis.

Pulmocordio mite SL *Hevert, Ger.†.*
Anise oil (p.2258·2); fennel oil (p.2303·1); liquorice (p.1740·3); thyme (p.2401·1).
Respiratory-tract disorders.

Pulmo-cyl Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Pulmodex *Multicare, Philipp.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Pulmodexane *Bailly, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Pulmofasa *Generfarma, Spain.*
Ammonium camphocarbonate diaminopyridine carboxylate (p.2150·3); calcium pantothenate (p.1959·3); cineole (p.2282·3); senega (p.1572·3); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); tolu balsam (p.1574·2); pine silvestris oil (p.2368·2); anethole (p.2258·1).
Respiratory-tract disorders.

Pulmofluide Simple *AIM, Fr.*
Terpin (p.1573·3); cineole (p.2282·3); sodium benzoate (p.1630·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Pulmoflux *Neo Quimica, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Pulmofor *Vifor, Switz.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Pulmoforte *Osorio de Moraes, Braz.†.*
⊗ Sodium benzoate (p.1630·2); guaifenesin (p.1561·3); lobelia (p.2157·2); potassium iodide (p.2169·2).
Coughs.

Pulmolet *Leti, Venez.*
⊗ Budesonide (p.1520·1).
Asthma.

Pulmolin *Pharos, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pulmoll *GSK Sante, Fr.*
Terpin (p.1573·3); menthol (p.2340·1); amylocaine hydrochloride (p.1853·3).
Throat disorders.

Pulmoll au menthol et a l'eucalyptus *GSK Sante, Fr.*
Menthol (p.2340·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2).
Respiratory-tract disorders.

Pulmomix Forte *Messer Griesheim, Cz.†.*
Nitrous oxide (p.1789·3).
Pulmonary disorders.

Pulmonar *OM, Port.*
Lysates of *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Staphylococcus aureus*; *Streptococcus pyogenes*; *Moraxella catarrhalis.*
Respiratory-tract infections.

Pulmonarom *Rudefsa, Mex.*
Lysate of *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Streptococcus haemolyticus*; *Staphylococcus aureus*; *Moraxella catarrhalis*; *Haemophilus influenzae.*
Respiratory-tract infections.

Pulmo-Neural Serocytol *Serolab, Switz.*
An immunoglobulin (equine).
Cold and influenza symptoms.

Pulmonil *Pampa, Pol.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); juniper oil (p.2328·3); menthol (p.2340·1); pine oil (p.2368·2); thymol (p.1664·3); turpentine oil (p.2406·3).
Cold symptoms.

Pulmonix
Note. This name is used for preparations of different composition.
Biotenk, Arg.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Luper, Braz.†.
Potassium iodide (p.2169·2); sulfogaiacol (p.1573·2); tolu balsam (p.1574·2).
Respiratory-tract congestion.

Pulmonix Grip *Biotenk, Arg.*
Bromhexine hydrochloride (p.1552·2); paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Influenza symptoms.

Pulmonix Plus *Biotenk, Arg.*
Ambroxol hydrochloride (p.1550·3); loratadine (p.583·3).
Respiratory-tract disorders.

Pulmonyl *Euro-Med, Philipp.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Pulmophyllin *Adcock Ingram, S.Afr.*
Theophylline (p.1140·1).
Obstructive airways disease.

Pulmoquin *Labomed, Chile†.*
Codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Pulmor *Drogsan, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Pulmoran *Leros, Cz.*
Sage (p.2382·3); althaea (p.2253·3); knotgrass (p.2329·2); thyme (p.2401·1) urtica (p.2409·3); sambucus (p.2383·1); plantain (p.2379·1); liquorice (p.1740·3); fennel (p.2302·3).
Upper respiratory-tract disorders.

Pulmorell *Sanorell, Ger.*
Homoeopathic preparation.

Pulmo-Rest *Stadmed, India.*
⊗ Bromhexine hydrochloride (p.1552·2); salbutamol (p.1131·2); guaifenesin (p.1561·3).
Coughs associated with obstructive airways disease.

Pulmo-Rest Expectorant *Stadmed, India.*
⊗ Bromhexine hydrochloride (p.1552·2); salbutamol (p.1131·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs associated with obstructive airways disease.

Pulmorex DM *Prodemdis, Canad.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3).

Pulmorien *Sinterapico, Braz.†.*
Sodium camsilate (p.2388·3); dipyrone (p.49·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Pulmorphan *Riva, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Pulmorphan Pediatrique *Riva, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Pulmosal *Azevedos, Port.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with excessive mucus.

Pulmosan
Note. A similar name is used for preparations of different composition (see below).
Gezzi, Arg.
Bromhexine hydrochloride (p.1552·2).
Coughs.

Pulmo-San
Note. A similar name is used for preparations of different composition

(see above).
Zimaia, Port.†.
Brovanexine hydrochloride (p.1553·1).
Coughs.

Pulmosan Aller *Gezzi, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Pulmosan Caramelos *Gezzi, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Pulmoserum *Bailly, Fr.*
Codeine (p.37·2); guaiacol (p.1561·2).
Coughs.

Pulmosina *Labomed, Chile.*
Eucalyptus (p.2301·2); avocado (p.2262·2); pectoral flowers; tolu balsam (p.1574·2); honey (p.1948·2).
Coughs.

Pulmosolvan *Jasper, Braz.†.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Pulmosterin Duo *Normon, Spain.*
Bromhexine (p.1552·2); guaifenesin (p.1561·3); co-trimoxazole (p.258·1).
Respiratory-tract infections.

Pulmosterin Retard *Normon, Spain.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Pulmotabs *Rudefsa, Mex.*
Lysates of *Streptococcus pneumoniae*; *Klebsiella pneumoniae*; *Streptococcus haemolyticus*; *Staphylococcus aureus*; *Moraxella catarrhalis*; *Haemophilus influenzae*.
Respiratory-tract infections.

Pulmotec *Vitamedica, Neth.; Cyclomedica, Port.*
Technetium-99m (p.2055·3) graphites.
Diagnosis of pulmonary embolism.

Pulmotide *Taro, Israel†.*
⊗ Budesonide (p.1520·1).
Asthma.

Pulmo-Timelets *Temmler, Denm.; Temmler, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

Pulmotin
Note. This name is used for preparations of different composition.
Serum-Werk Bernburg, Ger.
Ointment: Anise oil (p.2258·2); camphor (p.2273·2); eucalyptus oil (p.2301·2); thyme oil (p.2401·2); conifer oil; thymol (p.1664·3).
Respiratory-tract disorders.

Serum-Werk Bernburg, Ger.†.
Oral liquid: Thyme (p.2401·1); guaifenesin (p.1561·3).
Bronchitis; catarrh; coughs.

Pulmotin Hustenloser *Serum-Werk Bernburg, Ger.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Pulmotin Inhalat *Serum-Werk Bernburg, Ger.*
Eucalyptus oil (p.2301·2).
Cold symptoms.

Pulmotosse *Delta, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Pulmotropic *Robert, Spain.*
Doxycycline guaiacolsulfonate (p.267·3); muramidase hydrochloride (p.2348·1).
Respiratory-tract infections.

Pulmovance *Meditrina, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Pulmovax *MSD, Mex.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Pulmovent
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Austria†.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders.

Prohealth, Philipp.
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Pulmoverina *Prima, Braz.†.*
Sodium dibunate (p.1573·1); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Coughs.

Pulmovital *Ifusa, Mex.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Coughs.

Pulmoxcel *GX, Philipp.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Pulmoxyl *Micro, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Pulmozyme *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Pol.; Roche, Port.; Genentech, Rus.; Roche, S.Afr.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Turk.; Roche, UK; Genentech, USA.*
Dornase alfa (p.1557·1).
Cystic fibrosis; respiratory-tract congestion.

Pulmus *Merck, Port.*
Sobrerol (p.1572·3).
Respiratory-tract disorders with excessive mucus.

Pulna *Landson, Indon.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pulpomixine *Septodont, Cz.*
⊗ Dexamethasone acetate (p.1526·1); framycetin sulfate (p.279·1); polymyxin B sulfate (p.317·3).
Dental disorders.

Pulsalux *Novartis, Ital.*
Soya oil (p.1965·3); ginkgo biloba (p.2311·1); melilot (p.2339·2); rutoside (p.2305·1).
Circulatory disorders.

Pulsar
Note. This name is used for preparations of different composition.
Phoenix, Arg.
Cisapride (p.1720·3).
Gastro-oesophageal reflux.

Medosan, Ital.
Colextran hydrochloride (p.1254·1).
Glucose metabolic disorders; hyperlipidaemia; obesity.

Pulsar Enzimatico *Phoenix, Arg.†.*
Cisapride (p.1720·3); pancreatin (p.2360·1); simeticone (p.1770·2).
Digestive disorders; gastro-oesophageal reflux; meteorism.

Pulsar Plus *Phoenix, Arg.†.*
Cisapride (p.1720·3); simeticone (p.1770·2).
Gastro-oesophageal reflux; meteorism.

Pulsar-AT Dual *Liomont, Mex.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Pulsatilla Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Pulsit *Precimex, Mex.*
Haloperidol (p.1000·2).
Behaviour disorders in children; psychoses.

Pulsol *Probiomed, Mex.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Pulsor *Tecnimede, Port.*
Calcium pangamate (p.2362·1).

Pulvhydrops Mono *Lomapharm, Ger.†.*
Equisetum (p.2299·3).
Oedema; urinary-tract disorders.

Pulvicin *Biolab, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Pulvinal Beclometasone Dipropionate *Trinity, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Pulvinal Salbutamol *Trinity, UK.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Pulvo *Urgo, Ger.*
Catalase (p.2278·2); hexamidine isetionate (p.1646·3).
Ulcers; wounds.

Pulvo 47
Note. This name is used for preparations of different composition.
Urgo, Fr.†; Fournier, Thai.; Genesis, Turk.
Catalase (p.2278·2); hexamidine isetionate (p.1646·3).
Burns; skin irritation; ulcers; wounds.

Solvay, Gr.
Catalase (p.2278·2); neomycin (p.305·1).
Wound healing.

Pulvo Neomycin *Urgo, Ger.*
Catalase (p.2278·2); neomycin sulfate (p.305·1).
Burns; infected skin disorders; ulcers; wounds.

Pulvo 47 Neomycine *Fournier, Fr.†.*
Catalase (p.2278·2); neomycin sulfate (p.305·1).
Ulcers; wounds.

Puma Balm *SA Druggists Self Med, S.Afr.*
Clove oil (p.2285·1); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); amber oil; turpentine oil (p.2406·3); camphor (p.2273·2); menthol (p.2340·1).
Cold symptoms; musculoskeletal and joint pain; nasal congestion.

Puma Cough Balsam *SA Druggists Self Med, S.Afr.*
Camphor (p.2273·2); anise oil (p.2258·2); menthol (p.2340·1); ammonium chloride (p.1551·3); liquorice (p.1740·3); tolu balsam (p.1574·2).
Coughs; respiratory-tract congestion.

Pumilene Vapo *Montefarmaco, Ital.*
Pumilio pine oil (p.2376·3); cineole (p.2282·3); peppermint oil (p.1761·2).

Pumilsan *Montefarmaco, Ital.*
Dequalinium chloride (p.1641·3).
Mouth and throat disinfection.

Pumonal eco natura *Ecosol, Switz.*
Ivy (p.2328·1).
Coughs.

Pumpan *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Pump-Hep *IFET (ΙΦΕΤ), Gr.†.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Pumpitor *Sanbe, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Puncto E *Grunwalder, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Punol *Biolab, Thai.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Puntol *Velka, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Puntual *Lainco, Spain.*
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Constipation.

Puntualax *Pharbenia, Ital.†.*
Aloes (p.1705·2); rhubarb (p.1768·3).
Constipation.

Puntualex *Lainco, Spain.*
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Bowel evacuation.

Pupilek *Gemi, Pol.*
Allantoin (p.1588·1); zinc oxide (p.1621·2).
Skin irritation.

Pupiletto *Bell, India†.*
Phenylephrine hydrochloride (p.1568·1).
Glaucoma; production of mydriasis.

Pupilla *Wassermann, Ital.*
⊗ Naphazoline nitrate (p.1565·2).
Inflammatory and allergic eye disorders.

Pupilla Antistaminico *Wassermann, Ital.*
⊗ Naphazoline nitrate (p.1565·2); thonzylamine hydrochloride (p.592·1).
Inflammatory and allergic eye disorders.

Pupilla Light *Wassermann, Ital.*
Benzalkonium chloride (p.1629·1); hypromellose; chamomile water; hyssop water; rose water; plantaginis water; mallow water; myrtillus water.
Eye disinfection; eye irritation.

Puraloe *Neo Dermos, Arg.*
Aloe vera (p.1588·2); tretinoin (p.1618·1).
Keratinisation disorders.

Puraloe Nutritivo *Eurolab, Arg.*
Aloe vera (p.1588·2); vitamin A (p.1971·2); collagen (p.2286·1); elastin (p.2286·1).
Skin disorders.

Puraloe Post Solar *Eurolab, Arg.*
Aloe vera (p.1588·2).
Moisturiser.

Puralube
Note. This name is used for preparations of different composition.
Metapharma, Canad.†.
Liquid paraffin (p.2030·3); soft paraffin (p.2031·2).

Fougera, USA.
Eye drops: Polyvinyl alcohol (p.2145·3).

Fougera, USA.
Eye ointment: White soft paraffin (p.2031·2); light liquid paraffin (p.2031·1).
Dry eyes.

Puran T4 *Sanofi-Aventis, Braz.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Purasoft *Neo Dermos, Arg.*
Glycolic acid (p.1598·1); avena (p.2262·1).
Skin disorders.

Purasol *APT, Hong Kong.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Purata *Pharmacare, S.Afr.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Purazine *Pharmacare, S.Afr.*
Cinnarizine (p.573·1).
Nausea; vertigo; vomiting.

Purbac *Pharmacare, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Pur-Bloka *Pharmacare, S.Afr.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; phaeochromocytoma.

Purcelina *Aulo Gelio, Arg.*
Range of moisturisers and emollients.

Purderal *Pharmacare, S.Afr.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Pure Gardens *Awareness, Canad.*
Apple oil; vitamin C; vitamin E; aloe vera; almond oil; olive oil; sesame oil; chamomile; calendula; beeswax; jojoba oil; linseed oil.
Skin disorders.

Pure Health *Lexon, UK.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Pure Omega *BritHealth, UK.*
Fish oil concentrate (p.1362·1).

Pure Plan *Cedar Health, UK.*
Birch; meadowsweet; cynara; taraxacum; lappa; wild pansy; fennel; bladderwrack; tamarind; prune; green tea (p.1922·1).

Pureduct *Rosen, Ger.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Puregon *Organon, Arg.; Organon, Austral.; Organon, Austria; Organon, Belg.; Organon, Braz.; Organon, Canad.; Organon, Chile; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon, Fr.; Organon, Ger.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.; Donmed, S.Afr.†; Organon, Singapore; Organon, Spain; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, UK; Organon, Venez.*
⊗ Follitropin beta (p.2104·1).
Male and female infertility.

PureLan *Medela, Canad.*
Wool fat (p.2033·2).
Nipple care.

Purell *Gojo, Canad.; Pfizer Consumer, Canad.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Puresis *Pharmacare, S.Afr.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Puretam *Biotrends, Gr.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Purethal
Hal, Ger.
Modified allergen extracts of grass, tree, cereals, and plant pollen (p.2370·2) and house dust mite (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Hal, Hung.; Haarlems Allergenen, Pol.
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Hal, Neth.
Aluminium hydroxide adsorbed grass or tree pollen (p.2370·2) (p.2250·2).
Allergen immunotherapy.

Purex *Hasco-Lek, Pol.*
Echinacea purpurea (p.2298·1).
Ulcers; wounds.

Purfalox *Kleva, Gr.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Purfilx *Filaxis, Arg.*
Cyproterone acetate (p.2088·2).

Purgazen *Agepha, Austria.*
Bisacodyl (p.1710·1); dimeticone (p.1770·2).
Bowel evacuation; constipation.

Purge *Fleming, USA†.*
Castor oil (p.2278·1).
Constipation.

Purgolac *Pharmanel, Gr.†.*
Lactulose (p.1738·2).
Constipation.

Purgo-Pil *Qualiphar, Belg.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Purgoxin *Pharmacare, S.Afr.*
Digoxin (p.1259·3).
Cardiac disorders.

Purgyl *Istanbul, Turk.*
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Bowel evacuation; constipation.

Puricap *Richmond, Arg.*
⊗ Anastrozole (p.681·2).

Puricemia *Sanbe, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Puricin *Shiwa, Thai.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Puricos *Pharmacare, S.Afr.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Purid *Sanofi-Aventis, Chile.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Puride *Polipharm, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Purif-Ac Emulsion *Johnson & Johnson Consumer, Fr.*
Salicylic acid (p.1612·2); zinc gluconate (p.1999·2); copper gluconate (p.1935·3); allantoin (p.1588·1).
Acne.

Purif-Ac Gel *Johnson & Johnson Consumer, Fr.*
Hamamelis (p.2318·2); salicylic acid (p.1612·2); zinc gluconate (p.1999·2); copper gluconate (p.1935·3); allantoin (p.1588·1).
Acne.

Purifam *Sunthi Sepuri, Indon.*
Famotidine (p.1730·1).
Endocrine adenoma; peptic ulcer; Zollinger-Ellison syndrome.

Purifol *Metro, Philipp.*
Folic acid (p.1940·1).
Folate deficiency.

Purigel Crisp *Qualiphar, Belg.*
Hamamelis (p.2318·2); benzyl alcohol (p.1631·3); levomenol (p.2333·3); arnica (p.2260·2); menthol (p.2340·1); menthyl acetate.
Soft-tissue injury.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Purigel NF *Qualiphar, Belg.*
Chamomile (p.2279·3); arnica (p.2260·2); dexpanthenol (p.2362·1); menthol (p.2340·1); menthyl lactate; benzyl alcohol (p.1631·3).
Bruising; inflammation; pruritus; skin irritation.

Purigoa *Wyeth Lederle, Austria†.*
Bisacodyl (p.1710·1); docusate sodium (p.1725·1).
Constipation.

Purilon
Coloplast, Arg.; Coloplast, Ger.
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Ulcers; wounds.

Coloplast, Fr.
Carmellose sodium (p.2142·1); calcium alginate (p.1058·1).
Ulcers; wounds.

Purinase *Imperial, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Puri-Nethol *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Fr.; GSK, Ger.; IFET (ΙΦΕΤ), Gr.; GSK, Hong Kong; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK.*
Mercaptopurine (p.744·1).
Auto-immune disorders; inflammatory bowel disease; leukaemias; non-Hodgkin's lymphoma; psoriatic arthritis.

Purinethol *Novopharm, Canad.; Gate, USA.*
Mercaptopurine (p.744·1).
Leukaemias.

Purinol
Note.This name is used for preparations of different composition.
Ratiopharm, Austria; Ratiopharm, Cz.; Pinewood, Irl.; Merckle, Rus.
Allopurinol (p.552·2).
Gout; hyperuricaemia; prophylaxis of uric acid and calcium oxalate stones.

Yeni, Turk.
Methenamine (p.298·3); methenamine anhydromethylenecitrate (p.299·1).
Urinary-tract infections.

Purisole *Fresenius Kabi, Port.*
⊗ Sorbitol (p.1965·1); mannitol (p.1330·2).
Bladder irrigation.

Purisole SM *Fresenius Kabi, Pol.*
⊗ Sorbitol (p.1965·1); mannitol (p.1330·2).
Bladder irrigation.

Purispec *Pharmaspec, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Puristen *Dynamic, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Puritabs *Balmar, NZ.*
Troclosene sodium (p.1665·3).
Water disinfection.

Puritenk *Biotenk, Arg.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Purium *Lennon, S.Afr.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Purivist *Allergan, Cz.; Allergan, Fr.*
Epinastine hydrochloride (p.579·3).
Allergic conjunctivitis.

Purmolax *Hua, Thai.†.*
Phenolphthalein (p.1762·1).
Constipation.

Purmycin *Pharmacare, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Purofilina *Rhein, Mex.†.*
Proxyphylline (p.1130·3).

Puromylon *Pharmacare, S.Afr.*
Nalidixic acid (p.303·3).
Gram-negative bacterial urinary-tract infections.

Puroxan *Eurodrug, Thai.*
Doxofylline (p.1120·3).
Obstructive airways disease.

Puroxel *Lloyd, Philipp.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Purporent *Rowa, Malaysia†.*
Nicotinaldehyde; cineole (p.2282·3); camphor (p.2273·2); ammonii anisatus; pumilio pine oil (p.2376·3); rosemary oil (p.2381·3); aroma oils.
Respiratory-tract congestion.

Purpose *Johnson & Johnson, USA; Merck, USA.*
A range of emollient, cleansing, and moisturising preparations.

Purpuralin *Alcon, Braz.†; Alcon, Hong Kong†.*
Anthocyanosides; betacarotene (p.1930·3).
Eye disorders; hemeralopia.

Pur-Rutin *Andreabal, Switz.*
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

Pursana *Zeller, Switz.*
Sorbitol (p.1965·1); fig (p.1731·3).
Constipation.

Pursenid *Novartis Consumer, Spain.*
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Constipation.

Pursennid
Note.This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Ital.; Novartis, Norw.
Calcium sennoside A (p.1770·1); calcium sennoside B (p.1770·1).
Bowel evacuation; constipation.

Novartis, Denm.
Calcium sennosides (p.1770·1).
Constipation.

Novartis, Fin.; Novartis, Gr.†; Novartis, Swed.; Novartis, Turk.
Senna (p.1769·2).
Bowel evacuation; constipation.

Pursennide *Novartis Sante, Fr.; Novartis Consumer, Port.; Novartis Consumer, Switz.*
Calcium sennosides (p.1770·1).
Constipation.

Pursennid-In *Novartis, India†.*
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Purubex *Eisai, Indon.*
Teprenone (p.1776·3).
Gastric ulcer; gastropathy.

Puru-C *Vitabalans, Fin.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Pusiran *Atlantic, Hong Kong; Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Putaren *PD, Thai.†.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Puvadin *Medochemie, Hong Kong†; Medochemie, Malaysia†.*
Trioxysalen (p.1620·1).
Vitiligo.

Puvasoralen *Crawford, UK.*
Methoxsalen (p.1605·1).
Available on a named-patient basis only.
Mycosis fungoides; psoriasis; vitiligo.

PV Carpine *Allergan, Austral.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma.

PV Jod *Hasco-Lek, Pol.*
Povidone-iodine (p.1659·2).
Disinfection of burns, skin, mucous membranes, ulcers, and wounds; skin and mucous membrane infections.

PV7 Polivitamin *Sanli, Turk.*
Multivitamin preparation (p.1922·1).

PVA *Allergan, Austral.†.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

P-Vate *Osoth, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

PVFK *Lioh, Canad.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

P-Vidine *PP Lab, Thai.†.*
Povidone-iodine (p.1659·2).
Skin, mucous membrane, and wound disinfection.

PVPI *Geyer, Braz.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

P-V-Tussin
Note.This name is used for preparations of different composition.
Numark, USA.
Syrup: Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Numark, USA.
Tablets: Hydrocodone tartrate (p.63·1); phenindamine tartrate (p.587·2); guaifenesin (p.1561·3).
Coughs.

Pyassan *Sanofi-Aventis, Hung.*
Cefalexin (p.218·2).
Bacterial infections.

Pycameth *Tropica Mas, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Pycnogenol Plus *Reese, USA.*
Bioflavonoids (p.2304·1); grape seed (p.2316·3); pycnogenol (p.2368·1).

Pyderma *Pyridam, Indon.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Pygmal *URPAC, Fr.†.*
2,4,5-Trichlorophenol complex with tri-isobutyl phosphate; zinc oxide (p.1621·2); zinc carbonate (p.1621·2).
Acne.

Pykaryl T *Rodleben, Ger.*
Benzyl nicotinate (p.28·1).
Peripheral vascular disorders; rheumatic disorders; soft-tissue injuries.

Pykno *Procare, Austral.†.*
Vitis vinifera (p.2316·3); myrtillus (p.2349·3).
Peripheral vascular disorders; tonic.

Pylaquin *Roi Surya, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Pylera *Axcan, USA.*
Bismuth subcitrate potassium (p.1711·1); metronidazole (p.837·1); tetracycline hydrochloride (p.347·2).
Formerly known as Helizide.
Duodenal ulcer.

Pylison *Brown & Burk, Philipp.*
Lansoprazole (p.1739·2).
Barrett's oesophagus; gastro-oesophageal reflux; peptic ulcer.

Pylobact *Ranbaxy, Rus.*
Capsules, omeprazole (p.1753·1); tablets, clarithromycin (p.248·2); tablets, tinidazole (p.848·3).
Peptic ulcer.

Pylobact Combi *Ranbaxy, Malaysia.*
Tablets, clarithromycin (p.248·2); capsules, omeprazole (p.1753·1); tablets, tinidazole (p.848·3).
Peptic ulcer.

Pylobactel *Galenica, Gr.*
Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pylobactell *Torbet, Cz.; Italchimici, Ital.†; Torbet Laboratories, UK.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pylobactell-13C *Torbet, Neth.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pylokit *Cipla, India.*
Lansoprazole (p.1739·2); tinidazole (p.848·3); clarithromycin (p.248·2).
Peptic ulcer.

Pylopac *Medix, Mex.*
Combination pack: Capsules, lansoprazole (p.1739·2); tablets, clarithromycin (p.248·2); capsules, amoxicillin (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Pylor *Pyridam, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Pylori 13 *Medical Instruments, Switz.†.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for Helicobacter pylori infection.

Pylori Chek *Sorin, Spain†.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for Helicobacter pylori infection.

Pylorid *GSK, Arg.†; GSK, Belg.†; GSK, Braz.; GSK, Denm.†; GSK, Fin.; GSK, Gr.; GSK, Hong Kong†; GSK, Hung.†; GSK, Irl.†; GSK, Ital.; GSK, Neth.†; GSK, Norw.; Glaxo Wellcome, Port.†; GSK, Spain; GSK, Switz.†; GSK, Thai.†; GSK, Turk.; GSK, UK†; GSK, Venez.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Pylorid-KA *GSK, Austral.*
Combination pack: Tablets, ranitidine bismuth citrate (Pylorid) (p.1768·1); tablets, clarithromycin (p.248·2); capsules, amoxicillin trihydrate (p.202·2).
Helicobacter pylori-associated peptic ulcer.

Pylorikit *Neo Quimica, Braz.*
Capsules, lansoprazole (p.1739·2); capsules, amoxicillin trihydrate (p.202·2); tablets, clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Pyloripac *Medley, Braz.*
Capsules, amoxicillin (p.202·2); tablets, clarithromycin (p.248·2); capsules, lansoprazole (p.1739·2).
Helicobacter pylori-associated peptic ulcer.

Pyloriset *Orion, USA.*
Test for gastrointestinal disorders.

Pylorisin *GSK, Austria.*
Ranitidine bismuth citrate (p.1768·1).
Peptic ulcer.

Pyloritrat *Teuto, Braz.*
Capsules, lansoprazole (p.1739·2); capsules, amoxicillin trihydrate (p.202·2); tablets, clarithromycin (p.248·2).
Helicobacter pylori-associated peptic ulcer.

Pynamic *Condrugs, Thai.*
Mefenamic acid (p.80·1).
Pain.

Pynclear *Libra, S.Afr.†.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain and tension.

Pyndale *Ohara, Philipp.*
⊗ Pindolol (p.1372·1).
Angina pectoris; hypertension.

Pynmed
Note.This name is used for preparations of different composition.
Medpro, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Pain with tension.

Medpro, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Pynocare *Mega Lifesciences, Malaysia.*
Vitamin E; vitamin C (p.1922·1).
Dietary supplement.

Pynocare 40 Actisome *Mega Lifesciences, Philipp.*
Procyanidin (p.2368·1); ascorbic acid (p.1983·3); betacarotene (p.1930·3); *d*-alpha tocoferil acetate (p.1992·3).
Melasma.

Pynstop *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); doxylamine succinate (p.578·2).
Fever; pain and associated tension.

Pyocefal *Takeda, Fr.*
Cefsulodin sodium (p.233·3).
Bacterial infections.

Pyodontyl *Sanofi-Aventis, Hong Kong.*
Metesculetol sodium (p.2343·2); allantoin (p.1588·1).
Dental hygiene; gum disorders.

Pyolysin *Serum-Werk Bernburg, Ger.*
Extract of staphylococci, streptococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Micrococcus ovis*-Bouillon; zinc oxide (p.1621·2); salicylic acid (p.1612·2).
Burns; infected skin disorders; skin ulcers; wounds.

Pyorex *Bailly, Fr.*
Ethacridine lactate (p.1625·1); sodium ricinoleate (p.2139·3).
Oral hygiene.

Pyostacine *Sanofi-Aventis, Fr.; Aventis, Israel.*
Pristinamycin (p.319·1).
Bacterial infections; staphylococcal infections.

Pyracon *Hua, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Pyradexon *Pyridam, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Pyradol *Xixia, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Pyrafat *Croma, Austria; Fatol, Ger.; Fatol, Hong Kong.*
Pyrazinamide (p.320·2).
Mycobacterial infections.

Pyrahexal *Hexal, Pol.*
Dipyrone (p.49·2).
Fever; pain.

Pyralfin *Lupin, India.*
Pyrimethamine (p.610·2); sulfadoxine (p.338·1).
Malaria.

Pyralgin *Polpharma, Pol.*
Dipyrone (p.49·2).
Fever; pain.

Pyralginum *GSK, Pol.; Polpharma, Pol.*
Dipyrone (p.49·2).
Fever; pain.

Pyralin *Pfizer, Austral.*
Sulfasalazine (p.1773·2).
Crohn's disease; rheumatoid arthritis; ulcerative colitis.

Pyralvex *Lazar, Arg.; Norgine, Austral.†; Norgine, Austria; Norgine, Belg.; Norgine, Cz.; Norgine, Fr.; Norgine, Ger.; Faran, Gr.; Norgine, Hong Kong; Alpharma, Indon.; Norgine, Irl.; Norgine, Ital.; Norgine, Neth.; Norgine, Philipp.; Norgine, Port.; Norgine, S.Afr.; Norgine, Singapore; Gervasi, Spain; Norgine, Spain; Norgine, Switz.; Norgine, Thai.; Pharmalink, Thai.; PMP, Turk.; Norgine, UK; Konsuma, Venez.†.*
Anthraquinone glycosides (p.1768·3); salicylic acid (p.1612·2).
Denture irritation; mouth and throat disorders.

Pyramen *Pharmachim, Hung.†.*
Piracetam (p.368·2).
Alcoholism; mental function disorders; organic brain disorders.

Pyramet *Cipla, India.*
Pyrimethamine (p.610·2); sulfamethoxazole (p.340·1).
Malaria.

Pyramide *Pharmasant, Thai.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pyramin *Terramedic, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pyranol *Solfran, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Pyrantin *Vickmans, Hong Kong.*
Pyrantel embonate (p.155·1).
Worm infections.

Pyrantrin *Biopharm, Hong Kong†.*
Pyrantel embonate (p.155·1).
Worm infections.

Pyrapam *General Drugs, Thai.*
Pyrantel embonate (p.155·1).
Worm infections.

Pyrasol *Dynamic, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pyratab *Shiwa, Thai.†.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pyravit *Galenium, Indon.*
Isoniazid (p.288·1).
Pyridoxine (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pyrazide *Aventis, S.Afr.†.*
Pyrazinamide (p.320·2).
Tuberculosis.

Pyrazidol *Dalkhimfarm, Rus.*
Pirlindole hydrochloride (p.420·2).
Alcohol withdrawal syndrome; Alzheimer's disease; depression.

Pyrcon *Krewel, Ger.*
Pyrvinium embonate (p.155·3).
Enterobiasis.

Pyrecol *Polipharm, Thai.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; hay fever.

Pyreflor
Note. This name is used for preparations of different composition.
Ferlux, Fr.
Lotion: Permethrin (p.2048·2); piperonyl butoxide (p.2049·1); enoxolone (p.50·1).
Pediculosis.

Ferlux, Fr.
Shampoo: Permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Pyretal *Shiwa, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Pyrethrum Spray *Nelson, UK.*
Homoeopathic preparation.

Pyrex *Novell, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Pyrexin *Meprofarm, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Pyrexon *Wockhardt, India.*
Paracetamol (p.108·1).
Fever; pain.

Pyrflox *Pyridam, Indon.*
Norfloxacin (p.309·2).
Bacterial infections.

Pyricef *Pyridam, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Pyricontin *Modi-Mundipharma, India.*
Vitamin B (p.1979·1).
Vitamin B deficiency.

Pyridiate *Rugby, USA†.*
Phenazopyridine hydrochloride (p.116·2).
Irritation of the lower urinary tract.

Pyridium *Pfizer, Braz.; Pfizer, Canad.†; Pfizer, Chile†; Pfizer, Hong Kong; Pfizer, India; Pfizer, Indon.; Pfizer Consumer, S.Afr.; Warner Chilcott, USA; Pfizer, Venez.†.*
Phenazopyridine hydrochloride (p.116·2).
Pain and irritation of the urinary tract.

Pyridium Plus *Warner Chilcott, USA.*
Phenazopyridine hydrochloride (p.116·2); hyoscyamine hydrobromide (p.1736·1); butalbital (p.967·2).
Urinary-tract pain and spasm, with apprehension.

Pyridol *Pyridam, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Pyridryl *Pyridam, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Allergic symptoms; cough.

Pyridryl Plus *Pyridam, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Allergic symptoms; cough.

Pyrifoam *Dermatech, Austral.; Balmar, NZ; Dermatech, Philipp.*
Permethrin (p.2048·2).
Pediculosis.

Pyrifort *UAP, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Pyrigesic *East India Pharma, India.*
Paracetamol (p.108·1).
Fever; pain.

Pyrilax *Berlin-Chemie, Cz.†; Berlin-Chemie, Ger.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Pyrimel *Catarinense, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Pyrimon *FDC, India.*
⊗ Dexamethasone (p.1526·1); chloramphenicol (p.239·3).
Allergic eye disorders; eye infections; eye trauma.

Pyrinyl II *Barre-National, USA.*
Pyrethrins (p.2049·3); piperonyl butoxide technical (p.2049·1).
Pediculosis.

Pyrinyl Plus *Rugby, USA.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Pyriped *Mintlab, Chile.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Pyrisept
Note. This name is used for preparations of different composition.
Cifarma, Braz.
Phenazopyridine hydrochloride (p.116·2).
Pain and irritation of the urinary tract.

Weifa, Norw.
Cetylpyridinium chloride (p.1635·1).
Disinfection of hands and skin; minor skin infections.

Pyrisone *Beacons, Singapore.*
Pyrimethamine (p.610·2); dapsone (p.261·2).
Malaria.

Pyritil *Biolab, Malaysia; Biolab, Thai.*
Pyritinol hydrochloride (p.369·1).
Organic brain disorders.

Pyrlex *Athlon, USA.*
Mepyramine tannate (p.585·2).
Coryza; nasal congestion.

Pyrlex CB *Athlon, USA.*
Pentoxyverine tannate (p.1567·3); mepyramine tannate (p.585·2).
Cough.

Pyrocaps *Be-Tabs, S.Afr.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Pyrogallic *Gordon, USA.*
Pyrogallol (p.1611·3).
Calluses; verrucas.

Pyrogastrone *Sanofi, Irl.; Sanofi Synthelabo, UK†.*
Carbenoxolone sodium (p.1714·3); alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); sodium bicarbonate (p.1673·2).
Flatulence; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

Pyrogenium *Hanosan, Ger.*
Homoeopathic preparation.

Pyromed *Sanofi Synthelabo, Ger.†.*
Paracetamol (p.108·1).
Fever; pain.

Pyron *Reuffer, Mex.*
Dipyrone (p.49·2).
Pain.

Pyronal *Tanabe, Indon.*
Dipyrone (p.49·2).
Fever.

Pyrosal *Herbapol Wroclaw, Pol.*
Salix (p.121·3); sambucus (p.2383·1); tilia (p.2402·2); coltsfoot leaf (p.1555·1).
Upper respiratory-tract disorders.

Pyroxin *Sanofi-Aventis, Austral.*
Pyridoxine hydrochloride (p.1978·2).
Alcoholism; anaemias; homocystinuria; nausea and vomiting in pregnancy; premenstrual syndrome; radiation sickness.

Pyroxy *Shiwa, Thai.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Pyr-Pam *UCI, Braz.†.*
Pyrvinium embonate (p.155·3).
Enterobiasis.

Pyrsal *Fermon, Spain.*
Dexketoprofen trometamol (p.73·1).
Pain.

Pyrvin *Orion, Fin.*
Pyrvinium embonate (p.155·3).
Worm infections.

Pysolan *Pyridam, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Pytazen *Douglas, NZ.*
Dipyridamole (p.1268·1).
Myocardial infarction; thromboembolic disorders.

Pytest *Tri-Med, USA.*
⊗ Carbon-14 (p.2053·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Pytramic *Pyridam, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Pyverm *Cifarma, Braz.*
Pyrvinium embonate (p.155·3).
Worm infections.

Pyzina *Lupin, India.*
Pyrazinamide (p.320·2).
Tuberculosis.

PZA *Riemser, Ger.; Wernigerode, Ger.; Sandoz, Malaysia; Sandoz, Singapore; Sandoz, Thai.*
Pyrazinamide (p.320·2).
Tuberculosis.

PZA-Ciba *Novartis, India; Sandoz, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

P-Zide *Cadila Pharma, India.*
Pyrazinamide (p.320·2).
Tuberculosis.

Q10 *Pharma Nord, Fr.*
Ubidecarenone (p.2407·2).
Tonic.

Q200 *Pacific, NZ.*
Quinine sulfate (p.612·3).
Malaria; myotonia; nocturnal cramps.

Q300 *Pacific, NZ.*
Quinine sulfate (p.612·3).
Malaria; myotonia; nocturnal cramps.

Q 10 *Sidefarma, Port.*
Ubidecarenone (p.2407·2).
Cardiomyopathy; encephalopathy.

Q Cef *Guardian, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Q & P *Kowa, Jpn.*
Vitamins (p.1922·1); gamma oryzanol (p.2358·3); oxoamidine.
Tonic.

Qari *Mediolanum, Ital.*
Rufloxacin hydrochloride (p.331·3).
Bacterial infections.

Q-Bac *Pose, Thai.*
Chlorhexidine gluconate (p.1635·3).
Disinfection.

QBE Elixir *Eczane, Arg.†.*
Potassium gluconate (p.1684·3).
Potassium supplement.

QDALL *Atley, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

QDALL AR *Atley, USA.*
Chlorphenamine maleate (p.571·3).
Allergic rhinitis.

QED *Omega, Irl.*
Test for alcohol in saliva.

QED A-150 *Prieto, Arg.*
Test for alcohol in blood.

Qidrox *Soho, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Qiflon *Nabiqasim, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Qiftrin *Hexal, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Qinolon *United American, Philipp.; Great Eastern, Thai.; Therapharma, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Qinosyn *Pasteur, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Qinox *Solas, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Qipro *Meprofarm, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Qital *Ethica, Indon.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Q-Roxin *Choongwae, Kor.*
Balofloxacin (p.211·2).
Urinary-tract infections.

QT *Schering-Plough, USA.*
SPF 2: Octinoxate (p.1608·2); dihydroxyacetone (p.1594·1).
Sunscreen.

Q-Tapp DM *Qualitest, USA.*
Dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

QTest *Quidel, USA.*
Pregnancy test (p.2372·1).

QTest Ovulation *Quidel, USA†.*
Fertility test (p.2372·1).

Q-Tussin CF *Qualitest, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Quadblock
Note. This name is used for preparations of different composition.
Hamilton, Austral.
Cream SPF 30+; lotion SPF 30+: Octil triazone (p.1608·1); titanium dioxide (p.1617·3); enzacamene (p.1597·1).
Sunscreen.

Hamilton, Austral.
Stick SPF 30+: Enzacamene (p.1597·1); octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Quadezyme *Pascual, Hong Kong.*
Muramidase hydrochloride (p.2348·1); dequalinium chloride (p.1641·3).
Allergic rhinitis; mouth and throat disorders; sinusitis.

Quadion *Fortbenton, Arg.*
Ketoconazole (p.539·1).
Dandruff; fungal skin infections.

Quadracel *Aventis Pasteur, Austral.; Sanofi Pasteur, Canad.; MSD, NZ.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Quadramet *ARI, Austral.†; CIS, Cz.; CIS, Fr.†; Schering, Ital.; CIS, Neth.; CIS, Port.; Schering, Spain; Schering, UK; Du Pont, USA.*
Samarium-153 lexidronam (p.2055·2).
Metastatic bone pain.

Quadrasa *Norgine, Cz.†; Norgine, Fr.; Norgine, Ital.†.*
Sodium aminosalicylate (p.201·2).
Ulcerative colitis.

Quadrax *Boehringer Ingelheim Promeco, Mex.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Quadriderm
Note. This name is used for preparations of different composition.
Key, Arg.†; Mantecorp, Braz.; Schering-Plough, Hong Kong; Essex, Philipp.; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Essex, Switz.
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Schering-Plough, Arg.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Schering-Plough, Venez.
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); clioquinol (p.254·1).
Infected skin disorders.

Quadriderm NF *Schering-Plough, Mex.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Quadriderme *Schering-Plough, Port.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Quadrikin *Kinder, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Quadrilon *Neo Quimica, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Quadrinal *Knoll, USA.*
⊗ Ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2); theophylline calcium salicylate (p.1146·3); potassium iodide (p.2169·2).
Chronic respiratory disease.

Quadriplus *Delta, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Quadronal ASS comp *AWD, Ger.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Quadronal comp *AWD, Ger.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Quadropril *Viatris, Austria; AWD, Ger.; AWD, Hung.; Meda, Neth.; AWD, Rus.*
Spirapril hydrochloride (p.1399·3).
Hypertension.

Quadrotopic *Vendiz, Philipp.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Quadtab *Medichem, Philipp.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Quagu-Test *Fada, Arg.*
Aprotinin (p.1055·1).

Qual
Note. This name is used for preparations of different composition.
Silanes, Mex.
Paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1); diazepam (p.986·3).
Pain; painful muscle spasm.

Naturissima, Venez.†.
St John's wort (p.422·3).
Depression.

Qualaquin *AR Scientific, USA†.*
Quinine sulfate (p.612·3).

Qualecon *Duncan, Arg.†.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Quali-A *Quality, Hong Kong.*
Tretinoin (p.1618·1).
Acne; photodamaged skin.

Qualiceclor *Quality, Hong Kong.*
Cefaclor (p.217·2).
Bacterial infections.

Qualiclinda *Quality, Hong Kong.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Qualiclovir *Quality, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Qualicor *Quality, Hong Kong.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Qualicren *Quality, Hong Kong.*
Azelaic acid (p.1589·3).
Acne; skin pigmentation disorders.

Qualiderm *Greenpharma, Braz.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Qualidom *Quality, Hong Kong.*
Domperidone (p.1726·2).
Delayed gastric emptying; gastro-oesophageal reflux; nausea and vomiting.

Qualidrox *Quality, Hong Kong.*
Cefadroxil (p.218·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Qualidrozine *Quality, Hong Kong.*
Hydroxyzine hydrochloride (p.581·2).
Pruritus; urticaria.

Quali-Flon *Quality, Hong Kong.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Qualifutin *Quality, Hong Kong.*
Fusidic acid (p.279·3).
Gram-positive bacterial skin infections.

Qualigoline *Quality, Hong Kong.*
Nicergoline (p.2352·1).
Cerebral and peripheral circulatory disorders.

Qualigyl *Quality, Hong Kong.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Quali-itrazole *Quality, Hong Kong.*
Itraconazole (p.536·3).
Fungal infections.

Qualikin *Quality, Hong Kong.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders; oral hygiene.

Qualilaic *Quality, Hong Kong.*
Azelaic acid (p.1589·3).
Acne; skin pigmentation disorders.

Quali-Mentin *Quality, Hong Kong.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Qualipantyl *Quality, Hong Kong.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Qualiphor *Quality, Hong Kong.*
Cefaclor (p.217·2).
Bacterial infections.

Qualipid *Quality, Hong Kong.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease.

Qualiprinol *Quality, Hong Kong.*
Inosine pranobex (p.884·2).
Viral infections.

Qualiquan *Quality, Hong Kong.*
Doxepin hydrochloride (p.389·1).
Depression.

Qualisac *Quality, Hong Kong.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Qualisef *Quality, Hong Kong.*
Cefradine (p.233·1).
Bacterial infections.

Qualisolvon *Quality, Hong Kong.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Qualiton *TO-Chemicals, Thai.*
Guaifenesin (p.1561·3); theophylline (p.1140·1).
Coughs; obstructive airways disease.

Qualitriptine *Quality, Hong Kong.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Qualixamin *Quality, Hong Kong.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage; hereditary angioedema.

Qualizep *Quality, Hong Kong.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1); salicylamide (p.121·2).
Cold and influenza symptoms; rhinitis; sinusitis.

Qualizide *Quality, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Qualizindol *Quality, Hong Kong.*
⊗ Mazindol (p.2157·3).
Obesity.

Quamatel *Gedeon Richter, Cz.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Famotidine (p.1730·1).
Acid aspiration; acute pancreatitis; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Quamiprox *Nufarindo, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Quanil *Teofarma, Ital.*
Meprobamate (p.1006·2).
Anxiety disorders.

Quanilene *Vitae, Mex.*
Fluoxetine (p.397·3).
Depression.

Quantaffirm *Organon Teknika, USA.*
Test for infectious mononucleosis.

Quantalan *BMS, Austria; BMS, Ger.; BMS, Port.; BMS, Switz.*
Colestyramine (p.1252·3).
Biliary-tract disorders; diarrhoea; hypercholesterolaemia; poisoning with phenprocoumon; pruritus associated with biliary obstruction.

Quantor *Almirall, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Quantrel *Pfizer, Indon.; Pfizer, Philipp.; Pfizer, Venez.*
Oxantel embonate (p.152·2); pyrantel embonate (p.155·1).
Worm infections.

Quantum *Perrigo, Israel.*
A range of vitamin and mineral supplements with or without lycopene and lutein (p.1922·1).

Quardin *Mepha, Port.†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Quarelin *Chinoin, Cz.†; Sanofi-Aventis, Hung.*
Dipyrone (p.49·2); caffeine (p.1116·3); drotaverine hydrochloride (p.2298·1).
Migraine; pain.

Quark *Polifarma, Ital.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; renal insufficiency.

Quasar *Abbott, Ital.†.*
Verapamil hydrochloride (p.1421·1).
Hypertension.

Quasense *Watson, USA.*
84 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Quatohex *Braun, Ger.*
Didecyldimethylammonium chloride (p.1642·2); benzalkonium chloride (p.1629·1); biguanidinium acetate; polymeric biguanides.
Surface disinfection.

Quatro-Soda *Aspen, S.Afr.†.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); citric acid (p.2284·1).
Gastric hyperacidity; urinary alkalinisation.

Quatro-Virelon *Chiron Behring, Ger.†.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Quavir *Soho, Indon.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Quazium *Schering-Plough, Ital.†.*
Quazepam (p.1022·1).
Insomnia.

Qucin *Aristo, India.*
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Quecor *Labofarm, Pol.*
Oak bark (p.2355·3).
Diarrhoea.

Quedox *Rayere, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Quefeno *Helfarma, Port.†.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; asthma; urticaria.

Queimalive *Cifarma, Braz.*
Sulfacetamide sodium (p.335·3).
Bacterial skin infections.

Queimax *Farlab, Port.*
Camphor (p.2273·2); potassium hydroxyquinoline sulfate (p.2323·2).
Skin disorders.

Quel *Ipca, India.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Quelacid *Enila, Braz.†.*
Aluminium and calcium chelate.
Gastric hyperacidity.

Quelicin *Abbott, Braz.; Hospira, Canad.; Abbott, Indon.; Hospira, USA.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Quelidrine *Abbott, USA.*
⊗ Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); ephedrine hydrochloride (p.1558·2); phenylephrine hydrochloride (p.1568·1); ammonium chloride (p.1551·3); ipecac fluidextract (p.1562·3).
Coughs.

Quellada
Note. This name is used for preparations of different composition.
Aspen, Austral.; Stafford-Miller, Hong Kong.
Permethrin (p.2048·2).
Pediculosis; scabies.

Stafford-Miller, Irl.†; Searle, S.Afr.†.
Lindane (p.2045·3).
Pediculosis; scabies.

Quellada M *Stafford-Miller, Irl.; GSK Consumer, UK.*
Malathion (p.2046·1).
Pediculosis; scabies.

Quelodin *Ariston, Braz.†.*
Menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); cineole (p.2282·3); camphene (p.2273·2); greater celandine (p.2317·1); phenylpropanol (p.2366·2); olive oil (p.2356·2).
Gallstones.

Quelodin F *Ariston, Arg.*
Greater celandine (p.2317·1); taraxacum (p.2395·1); milk thistle (p.1452·1); linoleic acid (p.2308·2) or magnesium linoleate.
Biliary-tract disorders.

Quem Plus *Prodava, Arg.†.*
Allantoin (p.1588·1); wool fat (p.2033·2).
Barrier cream.

Quemicetina
Rontag, Arg.; Pharmacia, Venez.†.
Chloramphenicol (p.239·3).
Bacterial infections.

Pfizer, Braz.
Chloramphenicol palmitate (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Pfizer, Chile†.
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Pfizer, Mex.
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Quemicetina con Hidrocortisona *Rontag, Arg.*
⊗ Chloramphenicol (p.239·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Quemicetina Nasal Compuesta *Rontag, Arg.*
⊗ Chloramphenicol (p.239·3); ephedrine hydrochloride (p.1558·2); tripelennamine hydrochloride (p.592·2).
Nasal infections.

Quemox *YSP, Malaysia.*
Mebendazole (p.148·3).
Worm infections.

Quenobilan *Estedi, Spain.*
Chenodeoxycholic acid (p.2280·1).
Gallstones.

Quenocol *Zambon, Spain†.*
Chenodeoxycholic acid (p.2280·1).
Gallstones.

Quensyl *Sanofi Synthelabo, Ger.*
Hydroxychloroquine sulfate (p.604·2).
Chronic polyarthritis; lupus erythematosus; malaria.

Quentakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Quepita *Ingers, Cz.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Queratal *Liferpal, Mex.*
Tretinoin (p.1618·1).

Queratopil *D & M, Chile.*
Ammonium lactate (p.1589·2); panthenol (p.2362·1); allantoin (p.1588·1); levomenol (p.2333·3).
Hyperkeratinisation.

Quercus Salbe *Wala, Ger.*
Homoeopathic preparation.

Quer-Out *Atlas, Arg.*
Diclofenac sodium (p.44·3).
Actinic keratosis.

Querto *Altana, Ger.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Quest Gamma EPA Plus *Banner, Malaysia.*
Fish oil concentrate (p.1362·2).
Dietary supplement.

Questax *SVUS, Cz.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Questran *BMS, Arg.; BMS, Austral.; BMS, Belg.; BMS, Braz.; Bristol, Canad.†; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Indon.; BMS, Irl.; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, S.Afr.; BMS, Singapore; Bristol-Myers, Spain†; BMS, Swed.; BMS, Thai.; BMS, UK; Par, USA.*
Colestyramine (p.1252·3).
Adjunct in organophosphorus pesticide poisoning; cholerhoeic enteropathy; diabetic neuropathy; diarrhoea and pruritus associated with biliary-tract disorders; diarrhoea associated with Crohn's disease; hypercholesterolaemia; hyperoxaluria; short bowel syndrome; vagotomy.

Quetanex *Medopharm, Philipp.*
Ketamine hydrochloride (p.1787·1).
General anaesthesia.

Quetapel *Pacific, NZ.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; psychoses.

Quetiazic *Raffo, Arg.*
Quetiapine (p.1023·2).
Psychoses.

Quetidin *Drugtech, Chile.*
Quetiapine (p.1023·2).
Schizophrenia.

Quetin *Zentiva, Cz.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Quetral *Labesfal, Port.*
Ketoprofen (p.73·1).
Gout; musculoskeletal, joint, and peri-articular disorders.

Quetzal *Smaller, Spain.*
St John's wort (p.422·3).
Tonic.

Qugyl *RPG, India.*
Diloxanide furoate (p.832·2); metronidazole (p.837·1).
Amoebiasis; giardiasis.

Quiacort *Euroderm, Arg.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Quiacort G *Euroderm, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Quiacort G Plus *Euroderm, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1); clotrimazole (p.530·1).
Infected skin disorders.

Quibron *Apothecon, USA†.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Bronchospasm.

Quibron-T *Bristol, Canad.†; BMS, Indon.; Roberts, USA†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Quick N Easy *KK, UK.*
Pregnancy test (p.2372·1).

QuickCal *Vitaflo, Irl.; Vitaflo, UK.*
Preparation for enteral nutrition (p.1922·1).

QuickCare *Ciba Vision, Canad.†.*
Range of cleaning, disinfecting, rinsing, and storage solutions for soft contact lenses (p.1622·2).

QuicKlean *Hovid, Malaysia.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

QuickVue *Quidel, USA.*
Pregnancy test (p.2372·1).

Quidex
Note. This name is used for preparations of different composition.
Poen, Arg.
⊗ Ciprofloxacin (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Ferron, Indon.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Quidofril *Serral, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Quiedorm *Fermon, Spain.*
Quazepam (p.1022·1).
Insomnia.

Quiens *Antonetto, Ital.*
St John's wort (p.422·3).
Depression.

Quies auriculaire *Quies, Fr.*
Sea water.
Irrigation solution for ear canal hygiene.

Quiet Days *Cantassium Co., UK.*
Skullcap (p.2388·2); lupulus (p.2335·2); valerian (p.2410·1).

Quiet Life *Lane, UK.*
Motherwort (p.2347·3); wild lettuce (p.2415·2); lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1); thiamine hydrochloride (p.1976·1); riboflavin (p.1977·2); nicotinamide (p.1957·3).
Insomnia; stresses and strains.

Quiet Nite *Cantassium Co., UK.*
Valerian (p.2410·1); lupulus (p.2335·2); lettuce (p.2415·2); passion flower (p.2363·2).
Insomnia.

Quiet Tyme *Cantassium Co., UK.*
Skullcap (p.2388·2); lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1); gentian (p.2310·3); vitamin B substances (p.1922·1).

Quietiline *Sciencex, Fr.*
Bromazepam (p.964·3).
Alcohol withdrawal syndrome; anxiety.

Quietude *Boiron, Fr.*
Homoeopathic preparation.

Quiflox *Teuto, Braz.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quifloxona *Farmaco, Mex.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Quiflural *Rayere, Mex.*
Ofloxacin (p.310·2).
Bacterial infections.

Quik *Valeas, Ital.*
Cloperastine fendizoate (p.1554·3).
Coughs.

Quilagen *Randall, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Quilarex *Ariston, Arg.*
Venlafaxine hydrochloride (p.427·3).

Qui-Lea *Elea, Arg.*
Quinestrol (p.2128·1).
Menopausal disorders.

Quilla simplex *Pharmacia, Swed.*
Ammonium chloride (p.1551·3); quillaia (p.1920·1).
Respiratory-tract disorders.

Quilonium-R *GSK, Philipp.*
Lithium carbonate (p.401·3).
Mania.

Quilonorm *GSK, Austria; Doetsch, Grether, Switz.*
Lithium acetate (p.406·1) or lithium carbonate (p.401·3).
Bipolar disorder; depression; mania.

Quilonum
GSK, Austral.; GSK, S.Afr.
Lithium carbonate (p.401·3).
Bipolar disorder.

Cephalon, Ger.; GSK, Ger.
Lithium acetate (p.406·1) or lithium carbonate (p.401·3).
Bipolar disorder; cluster headache; depression; mania.

Quilox *Cipla, Philipp.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Quimalan *Quimica y Farmacia, Mex.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Quimea *Kleva, Gr.*
⊗ Quinapril (p.1382·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Quimefuran *IQFA, Mex.*
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Quimio-Ped *Stiefel, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Quimobrom *Maver, Mex.*
Erythromycin (p.269·2); bromhexine (p.1552·2).
Bacterial infections.

Quimocyclar *Grossman, Mex.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Quimodril *Italfarmaco, Spain.*
⊗ Trypsin (p.2405·3); chymotrypsin (p.2281·3); teclothiazide potassium (p.1409·1).
Oedema.

Quimofan *Quimica y Farmacia, Mex.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Quimofeina *Quimica y Farmacia, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Quimolactona *Quimica y Farmacia, Mex.†.*
⊗ Spironolactone (p.1400·1).
Hypertension.

Quimolauril *Maver, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Quimosporina *Quimica y Farmacia, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Quimotrip *Collins, Mex.*
Tetracycline (p.347·1); trypsin (p.2405·3); chymotrypsin (p.2281·3).
Bacterial infections.

Quimpe Antibiotico *Quimpe, Spain.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Quimpedor *Quimpe, Spain.*
Caffeine (p.1116·3); phenazone (p.116·1); pyridoxine hydrochloride (p.1978·2); propyphenazone (p.119·3); thiamine hydrochloride (p.1976·1).
Fever; pain.

Quimtadine *Quimpharma, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Quimtadine DSQ *Quimpharma, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; pruritus; rhinitis; urticaria.

Quimtafriol *Quimpharma, Mex.*
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; pruritus; rhinitis; urticaria.

Quinaband *SSL, Austral.†; SSL, UK†.*
Calamine (p.1591·2); clioquinol (p.254·1); zinc oxide (p.1621·2).
Leg ulcers; medicated bandage.

Quinacris *Cristalia, Braz.*
Chloroquine hydrochloride (p.599·2).
Malaria.

Quinaglute *Schering, S.Afr.*
Quinidine gluconate (p.1383·2).
Arrhythmias.

Quinalar *Leti Gentek, Venez.*
Quinapril hydrochloride (p.1382·2).

QuinaLich *Winthrop, Ger.*
Quinapril hydrochloride (p.1382·2).
Hypertension.

QuinaLich comp *Winthrop, Ger.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Quinaplus *Aliud, Ger.; Stada, Ger.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Quinapril comp *Betapharm, Ger.; Hexal, Ger.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Quinapro *Biex, Irl.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Quinaretic *Amide, USA; Leti Gentek, Venez.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Quinarsol *Cipla, India.*
Quinine dihydrochloride (p.612·3) or quinine sulfate (p.612·3).
Malaria.

Quinaspen *Pharmacare, S.Afr.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Quinate *Aspen, Austral.*
Quinine sulfate (p.612·3).
Malaria.

Quinax *Alcon, Hong Kong; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, Singapore; Alcon, Thai.*
Azapentacene polysulfonate sodium (p.2262·2).
Cataract.

Quinazide *Malesci, Ital.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Quinazil *Malesci, Ital.*
Quinapril hydrochloride (p.1382·2) or quinaprilat (p.1382·3).
Heart failure; hypertension.

Quinbisul *Aspen, Austral.*
Quinine bisulfate (p.612·2).
Malaria; nocturnal leg cramps.

Quindoleina *Gastroenterologicos, Mex.†.*
Clioquinol (p.254·1).
Amoebiasis.

Quini *Astra, Mex.†.*
Quinidine bisulfate (p.1383·1).
Arrhythmias.

Quinicardine *Barrenne, Braz.; Adilna, Turk.*
Quinidine sulfate (p.1383·2).
Arrhythmias.

Quinidex *Robins, USA†.*
Quinidine sulfate (p.1383·2).
Arrhythmias.

Quiniduran *Teva, Israel.*
Quinidine bisulfate (p.1383·1).
Arrhythmias.

Quinil *Tillomed, UK.*
Quinapril (p.1382·3).
Heart failure; hypertension.

Quinimax *Sanofi-Aventis, Fr.*
Quinine gluconate (p.614·3) or quinine hydrochloride (p.612·3); quinidine gluconate (p.1383·2) or quinidine hydrochloride (p.1385·1); cinchonine hydrochloride (p.2282·3); cinchonidine hydrochloride (p.2282·3).
Malaria.

Quininga *Inga, India.*
Quinine dihydrochloride (p.612·3) or quinine sulfate (p.612·3).
Malaria.

Quinivax-in *Valda, Ital.†.*
A diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Quinobact *Alcon, India; Nicholas Piramal, India.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Quinobiot *Andromaco, Chile.*
Levofloxacin (p.292·2).
Bacterial infections.

Quinobiotic *Pharos, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quinocin *Vida, Hong Kong.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Quinocort
Note.This name is used for preparations of different composition.
Quinoderm, Irl.†.
⊗ Potassium hydroxyquinoline sulfate (p.2323·2); hydrocortisone (p.1535·2).
Infected skin disorders.

Oftalmi, Venez.
⊗ Ciprofloxacin hydrochloride (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Quinoctal *Fawns & McAllan, Austral.†.*
Quinine sulfate (p.612·3).
Malaria; nocturnal cramps.

Quinoderm *Quinoderm, Irl.; Aventis, S.Afr.; Ferndale, UK.*
Benzoyl peroxide (p.1590·2); potassium hydroxyquinoline sulfate (p.2323·2).
Acne; folliculitis; skin disorders.

Quinoderm Antibacterial Face Wash *Ferndale, UK.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1); detergents.
Skin cleanser; soap substitute.

Quinodermil *Oftalder, Port.†.*
Clioquinol (p.254·1).

Quinodermil-AS *Edol, Port.*
Salicylic acid (p.1612·2); clioquinol (p.254·1).
Infected skin disorders.

Quinodis *Grunenthal, Ger.†.*
Fleroxacin (p.276·2).
Bacterial infections.

Quinoflex *Mepha, Port.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Quinoflox
Biolab Sanus, Braz.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Diba, Mex.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quinoflox Otico *Diba, Mex.*
Ciprofloxacin hydrochloride (p.243·3); lidocaine hydrochloride (p.1862·3).
Bacterial ear infections.

Quinoform
Note. A similar name is used for preparations of different composition (see below).
EMS, Braz.
Norfloxacin (p.309·2).
Bacterial infections.

Quinoforme
Note. A similar name is used for preparations of different composition (see above).
Sanofi Synthelabo, Fr.†.
Basic quinine formate (p.614·3).
Malaria.

Quinoftal *Oftalmi, Venez.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

Quinomed *Bausch & Lomb, Arg.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Quinoret *Darier, Mex.*
Hydroquinone (p.1598·2); vitamin A (p.1971·2).
Skin pigmentation disorders; sun-induced skin damage.

Quinoret Forte *Darier, Mex.*
Hydroquinone (p.1598·2).
Skin pigmentation disorders.

Quinortar *Iquinosa, Spain†.*
Coal tar (p.1616·2); chlorquinaldol (p.242·3); titanium dioxide (p.1617·3).
Skin disorders.

Quinoryl *ACME, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quinosul *Parggon, Mex.*
Diiodohydroxyquinoline (p.832·1).
Diarrhoea.

Quinotic *Oftalmi, Venez.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial ear infections.

Quinotic HC *Oftalmi, Venez.*
⊗ Ciprofloxacin hydrochloride (p.243·3); hydrocortisone (p.1535·2).
Otitis externa.

Quinovid *Mugi, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Quinox *Labesfal, Port.*
Ciprofloxacin (p.243·3) or ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quinoxan *Teuto, Braz.†.*
Ofloxacin (p.310·2).
Bacterial infections.

Quinradon-N *Hua, Thai.*
Diiodohydroxyquinoline (p.832·1); nystatin (p.543·2); boric acid (p.2268·1); phosphoric acid (p.2367·1).
Vaginal infections.

Quinsana Plus *Mennen, USA.*
Tolnaftate (p.548·3).
Fungal skin infections.

Quinsul *Lennon, Austral.*
Quinine sulfate (p.612·3).
Malaria; nocturnal leg cramps.

Quintabs *Freeda, USA.*
A range of vitamin preparations (p.1922·1).

Quintanrix *GSK, Cz.; GSK, Neth.; GSK, Port.*
A diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Quintelmin *EMS, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Quintex *Therabel, Belg.†.*
Butamirate citrate (p.1553·1).
Coughs.

Quintonine *GSK Sante, Fr.*
Cinnamon (p.2283·1); kola (p.2416·1); dried bitter-orange peel (p.2357·1); cinchona bark (p.2282·3); quassia (p.2377·1); gentian (p.2310·3).
Asthenia.

Quintopan *GSK Sante, Fr.†.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); sodium benzoate (p.1630·2).
Coughs.

Quintor
Torrent, Cz.†.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Torrent, Rus.
Ciprofloxacin (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Quiprime *Zynova, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quipro *Andromaco, Cz.†; Stada, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Quiralam *Retrain, Spain.*
Dexketoprofen trometamol (p.73·1).
Pain.

Quirgel *Juste, Spain.*
Dexketoprofen trometamol (p.73·1).
Inflammation; pain.

Quirocaine *Abbott, Mex.*
Levobupivacaine hydrochloride (p.1862·1).
Local anaesthesia.

Quisegen *Lafedar, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Quiss *Jagson, India.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Quit *Aspen Consumer, S.Afr.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Quitacallos *Farmo Quimica, Chile.*
Salicylic acid (p.1612·2) in amyl acetate.
Callouses; keratoses; warts.

Quitadol *Biomep, Mex.*
Paracetamol (p.108·1).
Pain.

Quitadrill *Pierre Fabre Sante, Fr.*
Mequitazine (p.585·3).
Hypersensitivity.

Quitaxon *Nepalm, Fr.*
Doxepin hydrochloride (p.389·1).
Depression.

Quitoso
Note.This name is used for preparations of different composition.
Elisium, Arg.†.
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Lepori, Port.
Permethrin (p.2048·2).
Formerly contained pyrethrins and piperonyl butoxide.
Pediculosis.

Quitoso NF *Elisium, Arg.*
Permethrin (p.2048·2).
Pediculosis.

QuitX *Alphapharm, Austral.*
Nicotine (p.2352·2).
Aid to smoking withdrawal.

Quixidar *GSK, Neth.; GSK, Port.†.*
Fondaparinux sodium (p.1291·1).
Prophylaxis of deep-vein thrombosis; thromboembolic disorders.

Quixil
Note.This name is used for preparations of different composition.
Ethicon, Fr.
Solution I, human clottable proteins; tranexamic acid (p.1080·3); solution II, thrombin (p.1080·1); calcium chloride (p.1675·2).
Haemorrhage.

Omrix, Ger.; Johnson & Johnson, Ital.; Omrix, Neth.
1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); tranexamic acid (p.1080·3); 1 vial, thrombin (p.1080·1); calcium chloride (p.1675·2).
Haemorrhage.

Omrix, Israel.
Human clottable proteins; human alpha thrombin (p.1080·1); calcium chloride (p.1675·2).
Haemorrhage.

Omrix, Port.
Thrombin (p.1080·1); calcium chloride (p.1675·2); plasma (p.1075·2); tranexamic acid (p.1080·3).
Haemorrhage.

Quixin *Santen, USA.*
Levofloxacin (p.292·2).
Bacterial conjunctivitis.

Quntasol *Biosynthesis, Rus.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium acetate (p.1667·1).
Fluid and electrolyte disorders.

Quocel *Rayere, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Quocin *Isdin, Spain.*
Acetic acid (p.2244·2); salicylic acid (p.1612·2).
Callosities.

Quomem *Allen, Austria; Glaxo Allen, Ital.†; GSK, Neth.; GSK, Spain; GSK, Thai.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Quool *Allmi-Care, UK.*
Menthol (p.2340·1).
Musculoskeletal pain.

Quota *Abbott, Ital.*
Mesalazine (p.1745·1).
Ulcerative colitis.

Quotal NF *BMS, Arg.†.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Quotane *Zambon, Fr.*
Quinisocaine hydrochloride (p.1870·3).
Pruritus.

Quotavil *Quality, Hong Kong.*
Ofloxacin (p.310·2).
Bacterial infections.

Quotivit O.E. *Mayoly-Spindler, Fr.*
Multivitamin and mineral preparation (p.1922·1).

Qura *Bernabo, Arg.*
Bromhexine hydrochloride (p.1552·2); pseudoephedrine sulfate (p.1571·2); paracetamol (p.108·1). Formerly contained astemizole, bromhexine hydrochloride, pseudoephedrine sulfate, and paracetamol.
Influenza symptoms.

Qura Nasal *Bernabo, Arg.*
Phenylephrine (p.1568·1).
Nasal congestion.

Qura Plus *Bernabo, Arg.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); bromhexine hydrochloride (p.1552·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Qutifar *Ifars, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

QV
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
Soap substitute; bath additive; emollient.
Skin disorders.

Ego, Malaysia.
Face Moisturising Cream SPF 25: Avobenzone (p.1589·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Emollient; sunscreen.

QV Flare Up *Ego, Malaysia; Ego, Singapore.*
Benzalkonium chloride (p.1629·1); light liquid paraffin (p.2031·1); triclosan (p.1665·2).
Eczema; eczema with staphylococcal infection.

QV Lip Balm
Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.
Avobenzone (p.1589·3); octinoxate (p.1608·2).
Dry, cracked, or chapped lips; sunscreen.

Ego, Austral.
SPF 20: Avobenzone (p.1589·3); octinoxate (p.1608·2).
Dry, cracked, or chapped lips.

Qvar *3M, Arg.†; 3M, Austral.; UCB, Belg.; 3M, Canad.; Ivax, Fr.; Lavipharm, Gr.; 3M, Hong Kong; Ivax, Irl.; 3M, Malaysia; 3M, NZ; Ivax, Neth.; 3M, Philipp.; 3M, S.Afr.; 3M, Singapore†; UCB, Spain†; Ivax, UK; Ivax, USA.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

Q-Vax *CSL, Austral.*
An inactivated Q fever vaccine (p.2233·3).
Active immunisation.

QX 10 *Sigma, Arg.*
Folic acid (p.1940·1); pyridoxine (p.1979·1); cobalamin (p.1980·2); ubidecarenone (p.2407·2).
Folic acid deficiency anaemias; hyperhomocysteinaemia; tonic.

QX 100 *Sigma, Arg.*
Ubidecarenone (p.2407·2).
Chronic fatigue syndrome; mental function impairment.

R & C
GSK Consumer, Canad.
Shampoo: Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

GSK Consumer, Canad.
Spray: Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Surface and textile insecticide.

R Calm *Labima, Belg.*
Diphenhydramine hydrochloride (p.577·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

RA Lotion *Medco, USA.*
Resorcinol (p.1612·1); calamine (p.1591·2); borax (p.2268·1).
Acne.

RA Morph *Pfizer, NZ.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

RabAvert *Merck Frosst, Canad.; Chiron, USA.*
A rabies vaccine (Flury LEP strain) (p.2234·1).
Active immunisation.

Rabbit Balm *Millimed, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Insect bites; musculoskeletal pain and inflammation.

Rabec *Phoenix, Arg.*
Rabeprazole sodium (p.1765·1).
Gastro-oesophageal reflux; peptic ulcer.

Rabeloc *Cadila Pharma, India.*
Rabeprazole sodium (p.1765·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rabicip *Cipla, India.*
Rabeprazole sodium (p.1765·1).
Gastro-oesophageal reflux; peptic ulcer.

Rabies-Imovax *Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Norw.; Sanofi Pasteur, Swed.*
A rabies vaccine (human diploid cell culture) (p.2234·1).
Active immunisation.

Rabigam *NBI, S.Afr.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Rabinefil *Itaca, Braz.†.*
Vinblastine (p.786·3).
Malignant neoplasms.

Rabiodina *Biofarma, Braz.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rabipor *Biovac, S.Afr.*
A rabies vaccine (p.2234·1).
Active immunisation.

Rabipur *CSL, Austral.; Grunenthal, Austria; Novartis Vaccines, Cz.; Socopharm, Fr.; Chiron Vaccines, Ger.; Aventis, India; Chiron Behring, Israel; Chiron, Ital.; Chiron, Neth.; Chiron Vaccines, Philipp.; Novartis Vaccines, Port.; Chiron Vaccines, Thai.; Chiron Vaccines, UK.*
An inactivated rabies vaccine (Flury LEP strain) (p.2234·1).
Active immunisation.

Rabivac *Chiron Behring, Ger.†; Berk, Turk.*
A rabies vaccine (Pitman-Moore strain grown on human diploid cell cultures) (p.2234·1).
Active immunisation.

Rabivax *Serum Institute, India.*
A rabies vaccine (p.2234·1).
Active immunisation.

Rablas *Medichrom, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Rabolan *Rafarm, Gr.*
Losartan (p.1327·2).
Hypertension.

Rabro N *Teofarma, Ger.*
Calcium carbonate (p.1714·1); liquorice (p.1740·3); magnesium oxide (p.1744·1).
Gastrointestinal hyperacidity; heartburn.

Rabugen *Unison, Hong Kong; Unison, Malaysia.*
Domperidone (p.1726·2).
Gastrointestinal disorders; nausea and vomiting.

Rabugen-M *Unison, Thai.*
Domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea and vomiting.

Rabuman *Berna, Hong Kong†; Berna, Switz.; Berna, Thai.†.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Racep *Samjin, Philipp.; Unimex, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Racestyptine *Septodont, Switz.*
Aluminium chloride (p.1588·2).
Dental and gum disorders.

Racetam *Samjin, Singapore.*
Piracetam (p.368·2).
Cerebral trauma; cerebrovascular disorders.

Raclonid *Actavis, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Racol *Otsuka, Jpn.*
Preparation for enteral nutrition (p.1922·1).

Racovel *Cryopharma, Mex.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Radacef *Vianex (Βιανέξ), Gr.*
Ceforanide (p.227·3).
Bacterial infections.

Radacefe *BMS, Port.*
Cefprozil (p.232·2).
Bacterial infections.

Radalgin *Streuli, Switz.*
Nonivamide (p.96·2); methyl nicotinate (p.85·3); glycol salicylate (p.62·3); histamine hydrochloride (p.2319·2).
Musculoskeletal pain; sports injuries.

Radan *Marjan, Braz.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Radanil *Roche, Arg.*
Benznidazole (p.830·3).
American trypanosomiasis.

Radedorm *AWD, Ger.; AWD, Rus.*
Nitrazepam (p.1011·2).
Sleep disorders.

Radepur *AWD, Ger.*
Chlordiazepoxide (p.968·1).
Anxiety disorders; insomnia.

Radermin *Viofar, Gr.*
Etofenamate (p.53·1).
Inflammatory disorders.

RadiaGel *Carrington, USA.*
Acemannan (p.2244·2).
Radiation wounds.

Radialar 280 *Juste, Spain.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Radian-B
Note. This name is used for preparations of different composition.
Radiol, Israel.
Cream: Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, and soft-tissue disorders.

Roche Consumer, Austral.†.
Liniment: Menthol (p.2340·1); camphor (p.2273·2); ammonium salicylate (p.19·2); methyl salicylate (p.85·3); ethyl salicylate (p.52·1).
Musculoskeletal and joint disorders; soft-tissue disorders.

Radiol, Israel.
Liniment; topical spray: Aspirin (p.20·3); menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Ransom, UK.
Liniment; topical spray: Menthol (p.2340·1); camphor (p.2273·2); ammonium salicylate (p.19·2); salicylic acid (p.1612·2); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Roche Consumer, Irl.†.
Lotion; topical spray: Menthol (p.2340·1); camphor (p.2273·2); ammonium salicylate (p.19·2); salicylic acid (p.1612·2).
Musculoskeletal pain.

Roche Consumer, Austral.†.
Rub: Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2).
Musculoskeletal and joint disorders; soft-tissue disorders.

Roche Consumer, Irl.†.
Topical rub: Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); camphor oil (p.2273·3); capsaicin (p.32·3).
Musculoskeletal and soft-tissue disorders.

Ransom, UK.
Topical rub: Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2); camphor oil (p.2273·3).
Musculoskeletal and joint disorders.

Radian-B Ibuprofen *Ransom, UK.*
Ibuprofen (p.64·2).
Musculoskeletal pain; sports injuries.

Radian-B Red Oils *Roche Consumer, UK.*
Methyl nicotinate (p.85·3); expressed mustard oil (p.2349·2).
Musculoskeletal and joint pain.

RadiaPlex Rx *MPM, USA.*
Aloe vera (p.1588·2); sodium hyaluronate (p.2320·1).
Burns; hydrogel dressing; wounds.

Radiavit *Viofar, Gr.*
Diosmin (p.2304·2).
Capillary disorders.

Radicacine *Panalab, Arg.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Radicura *Walker, Arg.*
Boldo (p.2267·2); carqueja; canchalagua.
Digestive disorders.

Radicut
Note. This name is used for preparations of different composition.
Genepharm, Cz.
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Mitsubishi, Jpn.
Edaravone (p.1275·3).
Cerebral infarction.

Radiesse *BioForm, USA.*
Calcium hydroxyapatite (p.2323·1).
Facial lipoatrophy; facial wrinkles and folds.

Radifree *Nikkho, Braz.*
Grape seed (p.2316·3).
Cardiovascular disorders.

Radigen *Medipharm, Chile.*
Risperidone (p.1024·2).
Psychoses.

Radikal *Sandipro, Belg.*
Malathion (p.2046·1).
Pediculosis.

Radilem *Lemery, Mex.*
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Radin *Dexa, Hong Kong; Dexa, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer; Zollinger-Ellison syndrome.

Radina *Amhof, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Radina Dex *Amhof, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Radine *Pond's, Thai.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Radio Salil
Note. This name is used for preparations of different composition.
Vinas, Spain.
Cream: Camphor (p.2273·2); methyl nicotinate (p.85·3); methyl salicylate (p.85·3); salicylic acid (p.1612·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Vinas, Spain.
Spray: Camphor (p.2273·2); diethylamine salicylate (p.47·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Radiogardase *Heyl, USA.*
Prussian blue (p.1461·3).
Exposure to caesium-137 or thallium.

Radiogardase-Cs *Heyl, Cz.; Heyl, Ger.*
Prussian blue (p.1461·3).
Reduction in body-half-life of radiocaesium.

Radiomiron *Schering, Chile.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Radiopaque *Dabur, India.*
Iohexol (p.1483·1).
Radiographic contrast medium.

Radioselectan *Schering, Fr.*
Sodium amidotrizoate (p.1475·3); meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Radipon *Teva, Hung.*
Emetine hydrochloride (p.833·3); phenobarbital (p.492·2); codeine (p.37·2); ammonium chloride (p.1551·3).
Bronchitis.

Radirex *Herbapol Wroclaw, Pol.*
Rhubarb (p.1768·3).
Constipation; obesity.

Radite *Walker, Arg.*
Camellia sinensis (p.2416·1).

Radivit *Molex Ayus, Indon.*
Betacarotene; vitamin E; vitamin C; selenium; zinc (p.1922·1).
Nutritional supplement.

Radix
Note. This name is used for preparations of different composition.
Streuli, Switz.†.
Ointment: Camphor (p.2273·2); methyl salicylate (p.85·3); cod-liver oil (p.1935·2); eucalyptus oil (p.2301·2); mint oil (p.2345·2); sage oil (p.2382·3).
Cold symptoms; musculoskeletal pain; neuralgia.

Streuli, Switz.
Poultice: Aspirin (p.20·3); ichthammol (p.1599·1); chamomile (p.2279·3); methyl salicylate (p.85·3); mint oil (p.2345·2); iodine (p.2169·2).
Burns; cold symptoms; musculoskeletal, joint, and soft-tissue disorders; skin disorders.

Radol
Note. This name is used for preparations of different composition.
Pyridam, Indon.
Tramadol hydrochloride (p.130·3).
Pain.

Julphar, UAE.
Dichloroxylenol (p.1642·2); clorophene (p.1641·1).
Disinfectant.

Rado-Salil *Will-Pharma, Belg.*
Ethyl salicylate (p.52·1); methyl salicylate (p.85·3); glycol salicylate (p.62·3); salicylic acid (p.1612·2); camphor (p.2273·2); menthol (p.2340·1); capsicum oleoresin (p.2276·2).
Lumbago; musculoskeletal, joint, and soft-tissue disorders.

Rado-Spray *Will-Pharma, Belg.†.*
Lidocaine hydrochloride (p.1862·3); glycol salicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal pain; sports injuries.

Raductil *Abbott, Arg.†; Abbott, Mex.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Radycodin *Radyum, Turk.*
⊗ Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); ephedrine (p.1558·1).
Respiratory-tract congestion.

Radyn *Arlex, Mex.*
Ranitidine (p.1766·1).
Gastric hyperacidity; peptic ulcer.

Rafacalcin *Rafarm, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Rafapen V-K *Rafa, Israel.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Rafapen Mega *Rafa, Israel.*
Phenoxymethylpenicillin (p.314·1).
Bacterial endocarditis prophylaxis.

Rafassal *Rafa, Israel.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Rafathricin with Benzocaine *Rafa, Israel.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Rafazocine *Rafa, Israel†.*
⊗ Pentazocine (p.112·2).
Pain.

Rafen *Alphapharm, Austral.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Raffo-Ca *Raffo, Arg.*
Calcium citrate (p.1675·3).
Osteoporosis.

Raffolutil *Raffo, Arg.*
Bicalutamide (p.686·2).

Raffonin *Raffo, Chile.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis.

Raffreddoremed *Iodosan, Ital.*
⊗ Paracetamol (p.108·1); isopropamide iodide (p.1736·3); dimetofrine hydrochloride (p.1268·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Rafocilina *Raffo, Arg.*
Ofloxacin (p.310·2).
Bacterial ear infections.

Rafofer *Raffo, Chile.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Rafree *Reddy, Malaysia.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Raftace
Note.This name is used for preparations of different composition.
Wockhardt, India.
Oral liquid: Sodium alginate (p.2141·1); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2).
Dyspepsia; gastro-oesophageal reflux; hiatus hernia.

Wockhardt, India.
Tablets: Alginic acid (p.2140·3); magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); sodium bicarbonate (p.1673·2).
Dyspepsia; gastro-oesophageal reflux; hiatus hernia.

Raft-Eze *Pinewood, UK.*
Sodium bicarbonate (p.1673·2); sodium alginate (p.2141·1); calcium carbonate (p.1714·1).
Gastro-oesophageal reflux.

Rafton *Ferring, Fr.*
⊗ Budesonide (p.1520·1).
Chronic diarrhoea associated with collagenous colitis.

Ragaden *Ganassini, Ital.*
Cetylpyridinium chloride (p.1635·1).
Nipple disinfection.

Ragex *AGIPS, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Ragonil *Roche, Ecuad.*
Benznidazole (p.830·3).
Protozoal infections.

Rahistin *Kimia, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Raigin *Gelcaps, Mex.†.*
Ginseng (p.2312·1).
Tonic.

Raikocef *Mediolanum, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Raivas *Dexa, Indon.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Cardiac arrest; hypotension.

Ralcidin *Shreya, India.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3).
Cold symptoms.

Ralenost *Ranbaxy, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ralenova *Wyeth, Ger.*
Mitoxantrone hydrochloride (p.754·1).
Multiple sclerosis.

Ralgec *IAE, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Ralgen *Zentiva, Hung.*
Tramadol hydrochloride (p.130·3).
Pain.

Ralgex
Note.This name is used for preparations of different composition.
SSL, UK.
Cream: Glycol salicylate (p.62·3); methyl nicotinate (p.85·3); capsicum oleoresin (p.2276·2).
Musculoskeletal and joint disorders.

SSL, UK.
Topical stick: Glycol salicylate (p.62·3); ethyl salicylate (p.52·1); methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2); menthol (p.2340·1).
Musculoskeletal and joint disorders.

Ralgex Freeze Spray *SSL, UK.*
Isopentane; dimethyl ether (p.1689·2); glycol monosalicylate (p.62·3).
Musculoskeletal and joint disorders.

Ralgex Heat Spray (low-odour) *SSL, UK.*
Glycol monosalicylate (p.62·3); methyl nicotinate (p.85·3).
Musculoskeletal and joint disorders.

Ralicid *Sanochemia, Austria.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; oedema; pain.

Ralinet *Coup, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Ralista *Cipla, India.*
⊗ Raloxifene hydrochloride (p.2128·1).
Osteoporosis.

Ralix *Cypress, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Ralizon *Leovan, Gr.*
Cetirizine hydrochloride (p.570·3).

Ralodantin *Pharmacia, Austral.†.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Ralofekt *Temmler, Ger.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders; vascular disorders of the eye or ear.

Ralopar *Sanofi-Aventis, Port.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Ralovera *Pfizer, Austral.*
Medroxyprogesterone acetate (p.2113·1).
Abnormal uterine bleeding; adjunct to oestrogen therapy; amenorrhoea; endometriosis; malignant neoplasms.

Ralser *Serral, Mex.*
Enalapril (p.1276·1).
Hypertension.

Ralsifen-X *Serral, Mex.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Ralur *Drossapharm, Switz.†.*
Heparin sodium (p.1301·2); indometacin (p.66·3); lauromacrogol 400 (p.1916·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ramace *Sanofi-Aventis, Austral.; AstraZeneca, Belg.; AstraZeneca, Denm.; AstraZeneca, Fin.†; Teva, Hung.; Astra, Mex.†; AstraZeneca, S.Afr.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Ramace Plusz *PharmaConsult, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramadine *Apotex, Philipp.; Pharma 3, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ramcor *Ipca, India.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Ramcor H *Ipca, India.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramend *Queisser, Ger.*
Senna (p.1769·2).
Constipation.

Ramend Krauter *Queisser, Ger.†.*
Senna (p.1769·2); maté (p.2416·1); coriander (p.2288·1); fennel (p.2302·3); aniseed (p.2258·2).
Constipation.

Ramet Dalibour *Tradiphar, Fr.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Skin cleaning and disinfection.

Ramet Pain *Tradiphar, Fr.*
Copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Skin cleansing and disinfection.

Ramfin *Biolab, Malaysia†; Biolab, Thai.†.*
Rifampicin (p.325·3).
Gonorrhoea; leprosy; tuberculosis.

Rami Slijmoplossende *Chefaro, Neth.*
Carbocisteine (p.1553·2).
Coughs.

Ramic *Pinewood, Irl.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; nephropathy.

Ramicard *Stada, Cz.; AWD, Ger.; Stada, Hung.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; hypertension.

Ramicard Plus *AWD, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramicin *Westmont, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Ramicin-ISO *Westmont, Indon.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Leprosy; tuberculosis.

Ramicomp *Genericon, Austria.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramicor *Ranbaxy, Pol.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction.

Ramicor Comb *Ranbaxy, Pol.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramicor D *Sanofi-Aventis, Port.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramicort *GMP, Indon.*
⊗ Hydrocortisone (p.1535·2); chloramphenicol (p.239·3).
Ear disorders.

Rami-Dextromethorfan *Chefaro, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Ramidox *Errekappa, Ital.†.*
Loperamide oxide (p.1741·2).
Diarrhoea.

Ramigamma *Worwag, Ger.*
Ramipril (p.1385·3).
Hypertension.

Ramigamma HCT *Worwag, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramik *Neves, Port.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; nephropathy.

Ramil *Zentiva, Cz.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; nephropathy.

Ramil H *Zentiva, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

RamiLich *Winthrop, Ger.*
Ramipril (p.1385·3).
Hypertension.

RamiLich comp *Winthrop, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramilo *Rowex, Irl.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Ramipharm *1A, Austria; Pharma & Co, Austria.*
Ramipril (p.1385·3).
Heart following myocardial infarction; hypertension.

Ramipharm comb *Pharma & Co, Austria.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramiplus *Aliud, Ger.; Stada, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramipres *Pasteur, Chile; Cipla, India.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Ramipres H *Cipla, India.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramipril comp *ABZ, Ger.; Betapharm, Ger.; CT, Ger.; Hexal, Ger.; Ratiopharm, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramipril HCT *Sandoz, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramipril HCTad *TAD, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramipril Plus *Basics, Ger.; Merck dura, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Rami-Q comp *Juta, Ger.; Q-Pharm, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramiril *Micro, Thai.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction.

Ramistada *Stada, Cz.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; hypertension.

Ramistos *Pasteur, Chile.*
⊗ Codeine (p.37·2); bromoform (p.2269·3); belladonna (p.2263·3); lobelia (p.2157·2); drosera (p.2297·3); grindelia (p.2317·2).
Respiratory-tract disorders.

Ramitab-HCT *Tiefenbacher, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramitens *Rafa, Israel.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension.

Ramitop *Pascual, Philipp.*
Tobramycin (p.354·1).
Eye infections.

Ramitren *Ozone, Cz.*
Ramipril (p.1385·3).
Heart failure; hypertension; nephropathy.

Ramivan *Medipharm, Chile.*
Roxithromycin (p.331·1).
Bacterial infections.

Ramiwin *Zentiva, Hung.; Aventis, S.Afr.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Ramiwin HCT *Zentiva, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramixa Plus H *Ingers, Cz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ramixal *Sandoz, Indon.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Ramlet *Alice Loren, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Ramno Fix *Piam, Ital.*
Lactobacillus rhamnosus; *Lactobacillus casei casei*; *Lactobacillus acidophilus* (p.2372·3); zinc; vitamin B substances (p.1922·1).
Digestive disorders.

Ramno-Flor *Piam, Ital.†.*
Lactic-acid-producing organisms (p.2372·3).
Nutritional supplement.

Ramnoflor Plus *Medifood, Ital.*
Lactic-acid-producing organisms (p.2372·3); zinc; fructo-oligosaccharides; vitamin B substances (p.1922·1).
Restoration of gastrointestinal flora.

Ramoclav *Ranbaxy, Pol.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ramol *Nakornpatana, Thai.*
Paracetamol (p.108·1).
Pain.

Rampicin *Shiwa, Thai.†.*
Rifampicin (p.325·3).
Gonorrhoea; leprosy; tuberculosis.

Rampil *Pharmacare, S.Afr.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension.

Ramses *Durex, Canad.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Ramsons Extract *Andrae, Austria†.*
Allii ursini.
Digestive disorders.

Ramtace *Unison, Thai.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction; nephropathy.

Ramy CE *Grin, Mex.*
Ascorbic acid (p.1983·3).

Ran *Angenerico, Port.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ran H2 *Seid, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ran Lich *Winthrop, Ger.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranamp *Ranbaxy, S.Afr.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Rancef *Ranbaxy, Austral.*
Cefalexin (p.218·2).
Bacterial infections.

Ranceph *Ranbaxy, S.Afr.*
Cefalexin (p.218·2).
Bacterial infections.

Rancil *Ranbaxy, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ranclav
Ranbaxy, S.Afr.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ranbaxy, Thai.
Amoxicillin (p.202·2) or amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Ranclor *Ranbaxy, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Ranclosil *Ranbaxy, S.Afr.†.*
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Rancolid *Biotech, Venez.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Rancor *Ranbaxy, Cz.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Rancotrim *Ranbaxy, Rus.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Rancus *Mersifarma, Indon.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Randa *Kayaku, Jpn.*
Cisplatin (p.698·2).
Malignant neoplasms.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Randex Randall, Mex.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Randikan Randall, Mex.†.
Kanamycin (p.291·3).
Bacterial infections.

Randoclin Ranbaxy, S.Afr.†.
Doxycycline (p.267·1).
Bacterial infections; malaria.

Randum Teofarma, Ital.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Ranepal Liferpal, Mex.
Ranitidine (p.1766·1).
Peptic ulcer.

Ranexa CV Therapeutics, USA.
Ranolazine (p.1386·2).
Angina pectoris.

Ranfen Ranbaxy, S.Afr.
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Ranflocs Ranbaxy, S.Afr.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Ranfradin Ranbaxy, S.Afr.†.
Cefradine (p.233·1).
Bacterial infections.

Rangin Novartis, Hung.
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Rani ABZ, Ger.; Alpharma-Isis, Ger.; Denk, Singapore†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Rani 2 Alphapharm, Austral.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Raniben FIRMA, Ital.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Raniberl Berlin-Chemie, Cz.†; Berlin-Chemie, Ger.; Berlin-Chemie, Pol.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; acute pancreatitis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranibeta Betapharm, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranibloc Wolff, Ger.; Glaxo Allen, Ital.; Behrens, Venez.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Ranic Hexal, Austria; Hexal, Pol.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranicel Laboratorios Chile, Chile.
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastric hyperacidity.

Ranicid M & H, Thai.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Raniclon Sandoz, Gr.
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Raniclor
Note.This name is used for preparations of different composition.
Ciforma, Braz.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranbaxy, USA.
Cefaclor (p.217·2).
Bacterial infections.

Ranicodan Pharmacodane, Denm.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranicur Merck, Fin.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranicux TAD, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranidex OFF, Ital.
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranidil Menarini, Ital.
Ranitidine hydrochloride (p.1766·1).
Gastrointestinal hyperacidity; peptic ulcer gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Ranidin Uniao Quimica, Braz.; Faes, Spain.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranidina Bunker, Braz.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranidine
Greenpharma, Braz.; Biolab, Singapore.
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; reduction of gastrointestinal secretion; Zollinger-Ellison syndrome.

Biolab, Thai.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranidura T Merck dura, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranifarm Continentales, Mex.
Ranitidine (p.1766·1).
Gastric hyperacidity; peptic ulcer.

Ranifesa Organifar, Venez.†.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Raniflex Royton, Braz.†.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranifur Ivax, Mex.
Ranitidine (p.1766·1) or ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranigast Polpharma, Pol.; Polpharma, Rus.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Raniger Streger, Mex.
Ranitidine (p.1766·1).

Ranigyl Pharmaniaga, Malaysia†; Raza, Malaysia†.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Ranihexal Hexal, Austral.; Hexal, S.Afr.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranikur Opco, Denm.†.
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranil Sandoz, Fin.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranilex Molex Ayus, Indon.
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Ranimax Torrent, Pol.
Ranitidine (p.1766·1).
Dyspepsia; heartburn; hyperacidity.

Ranimed Lamsa, Arg.; Ecosol, Switz.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranimerck Merck dura, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranimex Orion, Fin.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranin Pharos, Indon.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Rani-nerton Dolorgiet, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Raninorm Genericon, Austria.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal bleeding; peptic ulcer; Zollinger-Ellison syndrome.

Raniplex Fournier, Fr.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Raniprotect Riemser, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Rani-Q Merck, Swed.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; heartburn.

Ranisan ProMed, Cz.; ProMed, Pol.; Promed, Rus.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; acute pancreatitis; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Ranisen Senosiain, Mex.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranisifar Siphar, Switz.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranitab Basics, Ger.; Ranbaxy, Philipp.; Deva, Turk.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Ranitak Luper, Braz.†.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranital Lek, Cz.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; acute pancreatitis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranitax Saval, Chile.
Ranitidine (p.1766·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitic Investi, Arg.; Hexal, Austral.; Hexal, Ger.; Sandoz, Hung.; Rowex, Irl.; Tillomed, UK.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; heartburn; peptic ulcer; Zollinger-Ellison syndrome.

Ranitidi GNO Arion, Arg.†.
Ranitidine (p.1766·1).
Peptic ulcer.

Ranitidoc Docpharm, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranitil EMS, Braz.; Tillomed, UK.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranitin Prodotti, Braz.; Torrent, Cz.†; Torrent, Pol.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; acute pancreatitis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranitine Azevedos, Port.; Biofarma, Turk.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitinol Ducto, Braz.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranition Sanval, Braz.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranitral LA, Arg.
Ranitidine hydrochloride (p.1766·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitrat Cazi, Braz.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranitul Oriental, Arg.
Ranitidine (p.1766·1).
Peptic ulcer.

Ranityrol Biochemie, Austria†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal haemorrhage; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranitzen Pharlab, Braz.†.
Ranitidine (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranix GSK, Spain; Flupal, Venez.†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranixal Ratiopharm, Fin.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranizac Pharmanel, Gr.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranizan Cafar, Venez.†.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ranizol Eversil, Braz.†.
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ran-Levo Ranbaxy, Mex.
Levofloxacin (p.292·2).
Bacterial infections.

Ranlol Ranbaxy, Malaysia.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ranmino Ranbaxy, Mex.
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Ranmoxy Ranbaxy, S.Afr.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ranobel Nobel, Turk.
Ranitidine hydrochloride (p.1766·1).

Ranocalcin HM Pfluger, Ger.
Homoeopathic preparation.

Ranolta Jean-Marie, Hong Kong.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranopine Pinewood, Irl.
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranopril Ranbaxy, Malaysia.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Ranoprin Ratiopharm, Fin.
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; essential tremor; glaucoma; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; migraine; myocardial infarction.

Ranoxyl
Note.This name is used for preparations of different composition.
Douglas, Austral.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranbaxy, Hong Kong; Ranbaxy, Thai.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ranozol ST, Thai.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Ransim Ranbaxy, Austral.†.
Simvastatin (p.1390·2).

Ranstar Ranbaxy, Mex.
Stavudine (p.907·1).
HIV infection.

Rantac Unique, India†; Unique, Rus.; Medicine Products, Thai.
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Rantag Julphar, UAE.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Rantaksym Ranbaxy, Pol.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Rantec Berk, UK.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranteen Aspen, S.Afr.†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rantex Biotech, Venez.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Ranthrocin Ranbaxy, Singapore.
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Ranticid Kimia, Indon.
Ranitidine hydrochloride (p.1766·1).
Pathological hypersecretory disorders; peptic ulcer.

Rantin Kalbe, Indon.
Ranitidine hydrochloride (p.1766·1).
Pathological hypersecretory disorders; peptic ulcer.

Rantudil Bayer, Cz.; Tropon, Ger.; Goodwill, Hung.; Kowa, Jpn; Bayer, Mex.; Bayer, Philipp.; Bayer, Pol.; Bialfar, Port.; Bayer, Turk.
Acemetacin (p.15·1).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain; thrombophlebitis; vasculitis.

Rantutal Menarini, Gr.
Acemetacin (p.15·1).
Gout; inflammation; musculoskeletal disorders; pain; spondyloarthritis.

Ranuber Valeant, Spain.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ranulin Pisa, Mex.†.
Ranitidine (p.1766·1).

Ranvil Gentili, Ital.†.
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Ranvir *Ranbaxy, Cz.; Ranbaxy, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ranxas *Sandoz, Arg.†.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Ranytisan *Globo, Braz.†.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ranzac *LPC, UK.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastric hyperacidity; heartburn.

Ranzil *Tocogino, Mex.†.*
Ranitidine (p.1766·1).
Peptic ulcer.

Ranzol *Ranbaxy, S.Afr.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Rapacholin AC *Herbapol Wroclaw, Pol.*
Activated charcoal (p.1435·2); cynara (p.2291·2); raphanus sativum; artemisia abrotanum.
Constipation; gallbladder and liver disorders.

Rapacholin C *Herbapol Wroclaw, Pol.*
Activated charcoal (p.1435·2); cynara (p.2291·2); dehydrocholic acid (p.2292·2); mint oil (p.2345·2); raphanus sativum.
Digestive disorders; gallbladder and liver disorders.

Rapacholin Forte *Herbapol Wroclaw, Pol.*
Dehydrocholic acid (p.2292·2); raphanus sativum; mint oil (p.2345·2).
Bile deficiency; constipation; dyspepsia.

Rapaid
Note. This name is used for preparations of different composition.
Rye, Singapore†.
Cream; topical spray: Melaleuca oil (p.2338·2).
Skin irritation.

Rye, Singapore†.
Topical powder: Melaleuca oil (p.2338·2); corn starch; zinc oxide (p.1621·2).
Skin irritation.

Rapaid Antiseptic *Rye, Austral.†.*
Melaleuca oil (p.2338·2).
Minor wounds; skin infections.

Rapaid Itch Relief *Rye, Austral.*
Melaleuca oil (p.2338·2).
Bites; minor wounds; skin infections; skin irritation; stings.

Rapaid Rash-Relief *Rye, Austral.*
Melaleuca oil (p.2338·2); aloe vera (p.1588·2).
Skin disorders.

Rapako comp *Truw, Ger.*
Homoeopathic preparation.

Rapako xylo *Truw, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis.

Rapamic *Cipan, Port.*
Ketoconazole (p.539·1).
Fungal infections.

Rapamune *Wyeth, Arg.; Wyeth, Austral.; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Canad.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Hung.; Wyeth, India; Wyeth, Irl.; Wyeth, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Spain; Wyeth, Swed.; Wyeth, Switz.; Wyeth-Ayerst, Thai.; Wyeth, Turk.; Wyeth, UK; Wyeth-Ayerst, USA; Wyeth, Venez.*
Sirolimus (p.1841·1).
Renal transplant rejection.

Rap-eze *Roche Consumer, UK.*
Calcium carbonate (p.1714·1).
Dyspepsia; heartburn.

Rapiclav
Ipca, India†.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Ipca, Rus.
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Rapicort *Pharmis, Port.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Rapid Strand *Amersham, Austral.*
Iodine-125 (p.2054·2) titanium capsules welded into a silver rod.
Prostatic cancer.

Rapidal *Bial, Spain†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Rapidica *Sarabhai Piramal, India.*
⊗ Neutral insulin injection (porcine, highly purified) (p.443·2).
Diabetes mellitus.

Rapidin *Danlex, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Rapidocaine *Sintetica, Switz.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Arrhythmias; local anaesthesia.

Rapidol
Note. This name is used for preparations of different composition.
Pharmonta, Austria.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Pfizer, Chile; Ranbaxy, Malaysia; Ranbaxy, Singapore.
Paracetamol (p.108·1).
Fever; pain.

RapidVue *Quidel, USA.*
Pregnancy test (p.2372·1).

Rapifast *Verisfield, Gr.*
Losartan (p.1327·2).
Hypertension.

Rapifen *AstraZeneca, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; IFET (ΙΦΕΤ), Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Malaysia†; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Janssen-Cilag, Venez.*
⊗ Alfentanil hydrochloride (p.16·2).
General anaesthesia; induction of anaesthesia; pain during and after surgical procedures; pain in ventilated patients.

Rapignost Basic Screen Plus *Advance Diagnostic, Irl.*
Test for ascorbic acid, glucose, protein, blood, pH, and nitrites in urine.

Rapignost Diabetes Profile *Advance Diagnostic, Irl.*
Test for ketones, ascorbic acid, and glucose in urine.

Rapignost Total Screen LSG *Advance Diagnostic, Irl.*
Test for bilirubin, urobilinogen, pH, glucose, protein, ketones, blood, nitrite, ascorbic acid, leucocytes, and specific gravity in urine.

Rapilax *Merck, Arg.; Hertz, Braz.*
Sodium picosulfate (p.1771·1).
Constipation.

Rapilax Fibras *Merck, Arg.*
Ispaghula (p.1737·1); senna (p.1769·2).
Constipation.

Rapilin *Sun, India.*
Repaglinide (p.457·2).
Diabetes mellitus.

Rapilysin *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Irl.; Roche, Ital.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Port.; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, UK.*
Reteplase (p.1388·1).
Myocardial infarction; thrombosis.

Rapimix *Sarabhai Piramal, India.*
⊗ A mixture of insulin injection (porcine, highly purified) 30% and isophane insulin (porcine, highly purified) 70% (p.443·2).
Diabetes mellitus.

Rapiqure *Brown & Burk, Philipp.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Rapither-AB *Ipca, India.*
Alpha-beta arteether (p.598·3).
Malaria.

Rapitil *Aventis, UK.*
Nedocromil sodium (p.1127·3).
Allergic conjunctivitis; keratoconjunctivitis.

Rapitux *Sigma-Tau, Ital.†.*
Levodropropizine (p.1557·3).
Coughs.

Rapivir *GSK, Mex.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Rapix *Senosiain, Mex.*
Ketorolac (p.75·2).
Pain.

Rapolyte *Ergha, Irl.; koGen, UK.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Rappell *Chefaro, UK.*
Piperonal (p.2049·1).
Head lice repellent.

Rapten Rapid *Hemofarm, Rus.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Raptiva *Serono, Arg.; Serono, Austral.; Serono, Braz.; Serono, Canad.; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Irl.; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Healthcare Logistics, NZ; Serono, Neth.; Serono, Norw.; Serono, Port.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, UK; Genentech, USA.*
Efalizumab (p.1596·1).
Psoriasis.

Raptor *Meditrina, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Rapura *Globopharm, Switz.*
Peru balsam (p.2365·3); camphor (p.2273·2); thymol (p.1664·3); zinc oxide (p.1621·2).
Minor skin lesions.

Rapydan *EUSA, Port.; EUSA, UK.*
Lidocaine (p.1862·3); tetracaine (p.1871·2).
Local anaesthesia.

Raquiferol *Roemmers, Arg.*
Vitamin D (p.1986·1).
Hypoparathyroidism; osteomalacia; renal osteodystrophy; vitamin D deficiency.

Rarical *Janssen-Cilag, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Raricap *Ethnor, India.*
Calcium ferrous citrate (p.1932·1); folic acid (p.1940·1); vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Raricap L *Ethnor, India.*
Calcium ferrous citrate (p.1932·1); vitamin A palmitate; colecalciferol; vitamin B ; vitamin B ; nicotinamide; lysine hydrochloride (p.1922·1).
Iron-deficiency anaemia.

Rarivit *Globo, Braz.†.*
A multivitamin preparation (p.1922·1).

Rasal *Ipsen, Spain†.*
Olsalazine sodium (p.1752·2).
Ulcerative colitis.

Rascordin *Rowe-Fleming, Venez.†.*
Dopamine (p.1274·1).

Raset *Unison, Thai.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Rashfree *Pharmacia, India.*
Benzalkonium chloride (p.1629·1); zinc oxide (p.1621·2).
Nappy rash; skin disinfection.

Rasilez
Note. This name is used for preparations of different composition.
Novartis, Cz.; Novartis, Fr.; Novartis, Port.
Aliskiren (p.1207·1).
Hypertension.

Novartis, UK.
Aliskiren fumarate (p.1206·3).
Hypertension.

Rasilvax *Chiron Vaccines, Ital.†.*
A rabies vaccine (human diploid cell) (p.2234·1).
Active immunisation.

Rasitol *YSP, Malaysia.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Rastinon *Aspen, Austral.; Aventis, Mex.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Rastocin *Pliva, Cz.†; Pliva Krakow, Pol.; Pliva, Rus.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Ratacand *AstraZeneca, Ital.; Euro Registratie, Neth.*
Candesartan cilexetil (p.1238·3).
Heart failure; hypertension; left-ventricular dysfunction.

Ratacand Plus *AstraZeneca, Ital.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ratanhia comp *Weleda, Ger.*
Myrrh (p.2349·2); rhatany root (p.2378·3); aesculus; argentum nitricum; fluorit; kieserit; ol fl. caryophylli; ol eucalypti; ol lavandulae; ol menthae pip; ol salviae off.
Mouth disorders.

Rataril-HCT *Tiefenbacher, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Ratax *Pyridam, Indon.*
Ginseng (p.2312·1); cordyceps sinensis; epimedii; vitamin E acetate; vitamin B substances; zinc sulfate (p.1922·1).
Tonic.

Rati Salil Crema *Gramon, Arg.*
Amyl salicylate (p.19·3); camphor (p.2273·2); turpentine oil (p.2406·3); salicylic acid (p.1612·2); capsaicin (p.32·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil D *Gramon, Arg.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil E *Gramon, Arg.†.*
Magnesium salicylate (p.79·2).
Musculoskeletal, joint, and soft-tissue disorders.

Rati Salil Flex *Gramon, Arg.*
Salicylic acid (p.1612·2); diethylamine salicylate (p.47·2); capsaicin (p.32·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Rati Salil Gel *Gramon, Arg.*
Methyl salicylate (p.85·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Rati Salil Ice *Gramon, Arg.*
Menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rati Salil Pro *Gramon, Arg.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ratic *Atlantic, Singapore; Atlantic, Thai.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ratica *LBS, Thai.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer.

Raticina *Bernabo, Arg.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ratinal *Gracia, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

ratio-Aclavulanate *Ratiopharm, Canad.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

ratioAllerg
Note. This name is used for preparations of different composition.
Ratiopharm, Austria.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Ratiopharm, Ger.†.
Cream: ⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Ratiopharm, Ger.
Nasal spray: ⊗ Beclometasone dipropionate (p.1516·2).
Hay fever.

Ratiopharm, Ger.†.
Topical gel: Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

ratio-Calmydone *Ratiopharm, Canad.*
⊗ Hydrocodone tartrate (p.63·1); etafedrine hydrochloride (p.1560·2); doxylamine succinate (p.578·2).
Coughs.

ratio-Coristex-DH *Ratiopharm, Canad.*
Phenylephrine hydrochloride (p.1568·1); hydrocodone tartrate (p.63·1).
Coughs.

ratio-Cotridin *Ratiopharm, Canad.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

ratio-Cotridin Expectorant *Ratiopharm, Canad.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Ratiodol *Ratiopharm, Spain.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

ratioDolor *Ratiopharm, Austria; Ratiopharm, Ger.†.*
Ibuprofen lysine (p.64·2).
Fever; pain.

ratio-Ectosone *Ratiopharm, Canad.*
⊗ Betamethasone valerate (p.1519·1).
Skin and scalp disorders.

ratio-Emtec-30 *Ratiopharm, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Cold symptoms; pain; upper respiratory-tract disorders.

ratioGast
Note. This name is used for preparations of different composition.
Ratiopharm, Ger.†.
Capsules: Tormentil (p.2403·2).
Diarrhoea.

Ratiopharm, Ger.†.
Oral drops: Anise oil (p.2258·2); fennel oil (p.2303·1); caraway oil (p.2277·1).
Dyspepsia.

Ratiogel *Ratiopharm, Pol.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ratiogrip *Ratiopharm, Spain.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

ratioGrippal + C *Ratiopharm, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

ratio-Hemcort-HC *Ratiopharm, Canad.*
⊗ Hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2).
Anorectal disorders.

ratioHepar *Ratiopharm, Ger.†.*
Cynara (p.2291·2).
Biliary disorders.

ratio-Heracline *Ratiopharm, Canad.*
⊗ Adrenal cortex extract (p.1543·3); testis extract (p.2129·3); liver extract (p.2337·3).
Tonic.

ratio-Ipra Sal UDV *Ratiopharm, Canad.*
⊗ Ipratropium bromide (p.1124·1); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

ratio-Lenoltec No 4 *Ratiopharm, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

ratio-Lenoltec No 1, No 2, No 3 *Ratiopharm, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

ratioMobil *Ratiopharm, Ger.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Ratiomox *Ratiopharm, Neth.*
Moxonidine (p.1345·1).
Hypertension.

ratio-MPA *Ratiopharm, Canad.*
Medroxyprogesterone acetate (p.2113·1).
Progestogenic.

Rationale *Manetti Roberts, Ital.*
Colextran hydrochloride (p.1254·1).
Hyperlipidaemias.

ratio-Oxycocet *Ratiopharm, Canad.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

ratio-Oxycodan *Ratiopharm, Canad.*
⊗ Oxycodone hydrochloride (p.106·2); aspirin (p.20·3).
Pain.

Ratiopharmeva *Ratiopharm, Belg.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgenisation in females.

ratio-Proctosone *Ratiopharm, Canad.*
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone acetate (p.1535·2); framycetin sulfate (p.279·1); esculoside (p.2248·2).
Anorectal disorders.

Ratiopyrin *Ratiopharm, Austria; Ratiopharm, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

ratioSept *Ratiopharm, Ger.*
Rhatany root (p.2378·3).
Mouth and throat inflammation.

RatioSoft *Ratiopharm, Austria.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

ratio-Tecnal *Ratiopharm, Canad.*
Butalbital (p.967·2); caffeine (p.1116·3); aspirin (p.20·3).
Pain; tension.

ratio-Tecnal C *Ratiopharm, Canad.*
Butalbital (p.967·2); caffeine (p.1116·3); aspirin (p.20·3); codeine phosphate (p.37·2).
Pain; tension.

ratio-Theo-Bronc *Ratiopharm, Canad.*
Guaifenesin (p.1561·3); potassium iodide (p.2169·2); theophylline (p.1140·1); mepyramine maleate (p.585·2).
Obstructive airways disease.

ratio-Topilene *Ratiopharm, Canad.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

ratio-Topisalic *Ratiopharm, Canad.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Keratinisation disorders; skin disorders.

ratio-Topisone *Ratiopharm, Canad.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

ratio-Triacomb *Ratiopharm, Canad.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Infected skin disorders.

Raudil *Novag, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

RauwolfiaViscomp *Schuck, Ger.*
Homoeopathic preparation.

Rauwolsan H *Pfluger, Ger.†.*
Homoeopathic preparation.

Rauwolsan HM *Pfluger, Ger.*
Homoeopathic preparation.

Rauzide *Apothecon, USA†.*
⊗ Rauwolfia serpentina (p.1387·1); bendroflumethiazide (p.1224·1).
Hypertension.

Ravalgen *GSK Consumer, Ger.†.*
Garlic oil (p.2309·2).
Age-related vascular changes.

Ravalton *Rafarm, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ravamil *Merck, S.Afr.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Ravenol *Caber, Ital.*
Sulodexide (p.1406·3).
Chronic venous ulcer.

Raveron *Robapharm, Hung.†.*
Prostate extract (p.2337·3).
Prostate disorders.

RaVita *Combiphar, Indon.*
Vitamin C; vitamin B ; vitamin B ; vitamin B ; -lysine (p.1922·1).
Appetite supplement for children.

Ravostan *Santa, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Ravotaf *Mayo, Mex.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract disorders.

Ravotril *Roche, Chile.*
Clonazepam (p.478·2).
Anxiety; epilepsy; panic attacks; social phobia.

Raw Prostate *Natural Life, Arg.†.*
Prostate extract (p.2337·3).
Dietary supplement.

Rawel *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.*
⊗ Indapamide (p.1314·1).
Hypertension.

Raxamida *Arlex, Mex.†.*
Loperamide (p.1741·3).
Diarrhoea.

Raxar *Nitecs, Austral.*
Grepafloxacin hydrochloride.
Bacterial infections.

Raxenol *Euromex, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Raxeto *Dosa, Arg.*
⊗ Raloxifene (p.2128·3).
Osteoporosis.

Raxicam *Unison, Philipp.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Raxide *GX, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ray Block *Del-Ray, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Raycept *Zambon, Port.*
Calcium levofolinate (p.1943·3).
Anaemias; methotrexate toxicity.

Rayepen *Rayere, Mex.†.*
Ampicillin (p.204·1).
Bacterial infections.

Rayonfur *Materfarma, Port.*
Nitrofurazone (p.309·1).
Infected burns, ulcers, and wounds; skin disinfection.

Raypid *Rayere, Mex.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Rayzon *Pharmacia, S.Afr.*
Parecoxib sodium (p.111·3).
Postoperative pain.

Razadyne *Janssen, USA.*
Galantamine hydrobromide (p.366·1).
Formerly known as Reminyl.
Alzheimer's disease.

Razagleda Plus *Dallas, Arg.†.*
Benzocaine (p.1854·1); carmellose (p.2142·1).
Obesity.

Razel *Glenmark, India†.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Razene *Pacific, NZ.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; insect bites; urticaria.

Razepam *TNP, Thai.†.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Razin *CTI, Israel.*
⊗ Phentermine resinate (p.2162·3).
Formerly known as Novirasin.
Obesity.

Razolager *Gerard, Irl.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

RBC
Note. This name is used for preparations of different composition.
Rybar, Irl.
Antazoline hydrochloride (p.567·1); calamine (p.1591·2); cetrimide (p.1634·1).
Pruritus; skin irritation.
Co-Pharma, UK.
Calamine (p.1591·2); dibrompropamidine isetionate (p.1642·1).
Formerly contained antazoline hydrochloride, calamine, and cetrimide.
Insect bites and stings.

R-Cetate *GHP, Thai.†.*
Electrolyte infusion with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

RCF *Ross, USA.*
Carbohydrate-free soy protein feed (p.1922·1).
Carbohydrate intolerance; ketogenic diet.

R-Cin *Lupin, India.*
Rifampicin (p.325·3).
Tuberculosis.

R-Cinex *Lupin, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

R-Cinex Z *Lupin, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

R-Den *TNP, Thai.†.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Reabilan *Nestle, Fr.†; Galagen, USA.*
Preparation for enteral nutrition (p.1922·1).

Reacel-A *Offenbach, Mex.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders.

Reactine
Note. This name is used for preparations of different composition.
Pfizer, Austria; Pfizer Consumer, Belg.; Pfizer Consumer, Canad.; McNeil, Cz.; Pfizer Sante, Fr.; Pfizer Consumer, Ger.; Pfizer Consumer, Mex.; Pfizer Consumer, Neth.; Pfizer, Norw.; Pfizer Consumer, Spain†; Pfizer, Swed.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; pruritus; urticaria.
Cipla, India.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Inflammation; pain.
Pfizer Consumer, Ital.
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Eye congestion and irritation; nasal congestion and irritation.

Reactine Allergy & Sinus *Pfizer Consumer, Canad.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Reactine duo *Pfizer Consumer, Ger.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Reactine Forte *Cipla, India.*
Ibuprofen (p.64·2); paracetamol (p.108·1); diclofenac (p.44·2).
Inflammation; pain.

Reactine Plus
Note. This name is used for preparations of different composition.
Cipla, India.
Diclofenac (p.44·2); paracetamol (p.108·1).
Inflammation; pain.
Pfizer Consumer, Spain.
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Reactine Pseudoephedrine *Pfizer Consumer, Belg.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Reactivan *Merck, S.Afr.*
⊗ Fencamfamin hydrochloride (p.2156·1); vitamins (p.1922·1).
Tonic.

Reacur *LA, Arg.†.*
⊗ Hydrocortisone (p.1535·2); lidocaine (p.1862·3).

Reafix *Gemballa, Braz.†.*
Oral rehydration solution (p.1672·2).
Oral rehydration therapy.

Reagin *Baliarda, Arg.*
Citicoline (p.2283·3).
Cerebrovascular disorders.

Reagin Vascular *Baliarda, Arg.*
Citicoline (p.2283·3); codergocrine mesilate (p.363·3).
Cerebrovascular disorders; mental function impairment; vascular eye disorders.

Real One *Nicholas Piramal, India.*
Aripiprazole (p.962·3).
Schizophrenia.

Realderm *Reall, Switz.*
Zinc oxide (p.1621·2); glycerol (p.2314·2); aluminium acetotartrate (p.2255·1).
Nappy rash; skin irritation.

Realdiet *DHN, Fr.*
A range of preparations for enteral nutrition (p.1922·1).

Realdiron *Teva, Rus.*
Interferon alfa-2b (p.885·1).
Encephalitis; hepatitis B; hepatitis C; malignant neoplasms.

Realdrax *Liferpal, Mex.*
Ibuprofen (p.64·2).
Fever; pain.

Real-Vit *Solfran, Mex.*
Multivitamin preparation (p.1922·1).

Reamberin *Polisan, Rus.*
Meglumine sodium succinate; sodium chloride; potassium chloride; magnesium chloride (p.1667·1).
Detoxification.

Reandron *Bayer, Austral.; Schering, Austria; Schering, Spain.*
⊗ Testosterone undecylate (p.2130·2).
Hypogonadism.

Reanima *Benitol, Arg.*
Caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Reapam *Pfizer, Neth.*
Prazepam (p.1019·3).
Anxiety.

Reasec *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Re-Azo *Reese, USA.*
Phenazopyridine hydrochloride (p.116·2).

Re-B *Unison, Malaysia.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neurological disorders.

Re-B Forte *Unison, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; vitamin B deficiency.

Rebacil *Lisapharma, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

ReBalance *Zeller, Switz.*
St John's wort (p.422·3).
Anxiety disorders; insomnia.

Rebaten *Sigma, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Arrhythmias; hypertension.

Rebetol *Schering-Plough, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.†; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, UK; Schering-Plough, USA; Schering-Plough, Venez.*
Ribavirin (p.902·3).
For use in combination with interferon alfa-2b or peginterferon alfa-2b.
Chronic hepatitis C.

Rebetron *Essex, Arg.†; Schering-Plough, Austral.; Schering, Canad.†; Schering-Plough, NZ; Schering-Plough, S.Afr.†; Schering, USA†.*
Injection, interferon alfa-2b (p.885·1); capsules, ribavirin (p.902·3).
Chronic hepatitis C.

Rebif *Serono, Arg.; Serono, Austral.; Serono, Austria; Serono, Belg.; Serono, Braz.; Serono, Canad.; Novartis, Chile†; Serono, Cz.; Serono, Denm.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Hung.; Serum Institute, India; DKSH, Indon.; Serono, Indon.; Serono, Irl.; Serono, Israel; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Healthcare Logistics, NZ; Serono, Neth.; Serono, Norw.; Serono, Philipp.; Serono, Pol.; Serono, Port.; Serono, Rus.; Serono, S.Afr.; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
Interferon beta-1a (p.891·2).
Anogenital warts; hepatitis; herpesvirus infections; malignant neoplasms; multiple sclerosis.

Rebladerm *Dermoteca, Port.†.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Rebone
Note. A similar name is used for preparations of different composition (see below).
Ache, Braz.
Ipriflavone (p.1100·1).
Osteoporosis.

Re-Bone
Note. A similar name is used for preparations of different composition (see above).
Mallinckrodt, Cz.
Rhenium-186 (p.2055·2) etidronate.
Painful bone metastases; prostatic cancer.

Rebrickovy Caj, Rebrickova Nat *Megafyt-R, Cz.*
Achillea (p.2245·2).
Appetite loss; dyspepsia; pelvic pain; skin disorders; wounds.

Reca *Cantabria, Spain.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Recaflex *Recalcine, Chile.*
Tenoxicam (p.128·2).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders.

Recaflux *Copernico, Ital.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Recal *New Farma, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Recalcin *Hasco-Lek, Pol.*
Chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.

Recalfe *Hebron, Braz.†.*
Alendronic acid (p.1088·1).
Osteoporosis.

Recalm
Note. This name is used for preparations of different composition.
Herbarium, Braz.
Valerian (p.2410·1).
Anxiety; insomnia.
Sanofi-Aventis, Chile.
Valerian (p.2410·1); passion flower (p.2363·2); melissa (p.2339·3); tilia (p.2402·2).
Anxiety; insomnia; irritability.

Recalplex *Cazi, Braz.*
Vitamin B substances (p.1922·1).
Nutritional supplement.

Recamicina *Pharmabiotics, Chile.*
Levofloxacin (p.292·2).
Bacterial infections.

Recarcin *Sanum-Kehlbeck, Ger.†.*
Bacillus firmus.
Immunotherapy.

Recatol Algin *Riemser, Ger.*
Alginic acid (p.2140·3); carmellose sodium (p.2142·1).
Obesity.

Recatol mono *Riemser, Ger.*
Phenylpropanolamine hydrochloride (p.1569·3).
Obesity.

Rec-DZ *Hetero, India.*
Diazepam (p.986·3).
Anxiety; epilepsy; febrile convulsions; premedication; sedative; tetanus.

Receant *Remedina, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Recef *Uno, Ital.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Receptozine *Be-Tabs, S.Afr.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity.

Recessan *Kreussler, Ger.*
Lauromacrogol 400 (p.1916·1).
Mouth inflammation.

Rechol *Pharos, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Recipect *Orion, Fin.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Recit *Gador, Arg.*
Atomoxetine hydrochloride (p.2151·1).
Attention-deficit hyperactivity disorder.

Recita *Ipca, India.*
Escitalopram oxalate (p.391·1).
Depression.

Recital *Unipharm, Israel.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorders.

Reclast *Novartis, USA.*
Zoledronic acid (p.1106·1).
Paget's disease of bone.

Reclide *Reddy, Malaysia; Reddy, Rus.; Biofarma, Venez.†.*
Gliclazide (p.440·3).
Diabetes mellitus.

Reclipsen *Watson, USA.*
21 Tablets, ethinylestradiol (p.2101·3); desogestrel (p.2093·2); 7 tablets, inert.
Combined oral contraceptive.

Reclofen *Combiphar, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Reclomide *Major, USA.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Reclor *Sarabhai Piramal, India.*
Chloramphenicol (p.239·3).
Bacterial infections.

Reco
Note. A similar name is used for preparations of different composition (see below).
TRB, Arg.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

RECO
Note. A similar name is used for preparations of different composition (see above).
GMP, Indon.
Chloramphenicol (p.239·3).
Bacterial eye infections.

Recocef *Julphar, UAE.*
Cefaclor (p.217·2).
Bacterial infections.

Recodryl *GMP, Indon.*
Diphenhydramine hydrochloride (p.577·2).
Allergic rhinitis; motion sickness; urticaria.

Recofen *Reese, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).

Recofen-D *Reese, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).

Recofol *Gobbi, Arg.†; Alphapharm, Austral.; Bayer Schering, Cz.; Schering, Fin.; Curamed, Ger.†; Rafarm, Gr.; Schering, Hung.†; Dexa, Indon.; Leiras, Indon.; Schering, Israel; Pisa, Mex.; Pacific, NZ†; Schering, Neth.; Schering, Norw.†; Organon, Port.†; Schering, Rus.; Merck, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Swed.; Tillotts, Switz.; Schering, Thai.; Er-Kim, Turk.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Recolfar *Fahrenheit, Indon.*
Colchicine (p.556·1).
Gout.

Recoma *Marching, Hong Kong.*
Noscapine (p.1566·2).
Cough.

Recombinant H-B Vax II *MSD, Israel.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Recombinate
Note.This name is used for preparations of different composition.
Baxter, Arg.; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter Bio-Science, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Baxter, Israel; Baxter, Ital.; Baxter, Jpn; Baxter, NZ; Baxter, Neth.; Baxter, Norw.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter BioScience, UK; Baxter, USA.
A factor VIII preparation (recombinant) (p.1067·1).
Haemorrhagic disorders.

Baxter, Port.
Octocog alfa (p.1067·2).
Haemophilia A.

Recombivax *Vianex (Βιανέξ), Gr.†.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Recombivax HB *MSD, Braz.†; Merck Frosst, Canad.; Pasteur Merieux, Ital.†; Aventis, Port.†; Aventis Pasteur, Spain†; Merck, USA.*
A hepatitis B vaccine (recombinant DNA) (p.2215·2).
Active immunisation.

Recomint *GMP, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

Recomvax B *Sanofi Pasteur, Chile; Aventis Pasteur, Philipp.; LG, Philipp.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Reconvan *Fresenius Kabi, Chile; Fresenius Kabi, Ger.†; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.†; Fresenius Kabi, Switz.†; Fresenius Kabi, UK.*
Preparation for enteral nutrition (p.1922·1).

Recormon *Roche, Arg.; Roche, Austria; Asta Medica, Braz.; Roche, Braz.; Roche, Chile; Roche Diagnostics, Cz.†; Roche, Hong Kong; Roche, Indon.; Roche Diagnostics, Israel; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Philipp.; Boehringer Mannheim, Port.†; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Venez.*
⊗ Epoetin beta (p.1061·1).
Anaemias; autologous blood transfusion.

Recort Plus *Reese, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Recosine *Rafarm, Gr.*
Glucosamine (p.2313·2).
Osteoarthritis.

Recotens *Valeant, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Recothrom *Zymo, USA.*
Thrombin (recombinant) (p.1080·1).
Haemorrhage.

Recover *Pharmatrix, Arg.*
A barrier preparation.

Recoveron *Armstrong, Mex.*
Calcium acexamate (p.2245·2) or sodium acexamate (p.2245·2).
Burns; hypocalcaemia; osteoporosis; ulcers; wounds.

Recoveron N *Armstrong, Mex.*
Sodium acexamate (p.2245·2); neomycin sulfate (p.305·1).
Infected burns, ulcers, and wounds; skin infections.

Recoveron NC *Armstrong, Mex.*
Sodium acexamate (p.2245·2) neomycin sulfate (p.305·1).
Infected burns, ulcers, and wounds; skin infections.

Recoxa *Zentiva, Cz.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Recozil *Recon, Singapore.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Recrea *Antula, Fin.; Antula, Swed.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Rectacaine
Note.This name is used for preparations of different composition.
Reese, USA.
Ointment: Phenylephrine hydrochloride (p.1568·1); shark-liver oil (p.2386·1).

Reese, USA.
Suppositories: Phenylephrine hydrochloride (p.1568·1).

Rectagene Medicated Balm *Pfeiffer, USA.*
Yeast (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Rectagene Medicated Rectal Balm *Pfeiffer, USA.*
Benzocaine (p.1854·1); phenylephrine hydrochloride (p.1568·1); bismuth subgallate (p.1711·1); zinc oxide (p.1621·2); mepyramine maleate (p.585·2).
Anorectal disorders.

Rectalad *Church & Dwight, Austral.*
Docusate sodium (p.1725·1).
Bowel evacuation; constipation.

Rectamigdol *Uriach, Spain.*
Bismuth camphocarbonate (p.1712·1).
Sore throat.

Rectanal *Galenus, Pol.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Rectinol *Pfizer Consumer, Austral.*
⊗ Adrenaline (p.1203·2); benzocaine (p.1854·1); zinc oxide (p.1621·2).
Anorectal disorders.

Rectinol HC *Pfizer Consumer, Austral.*
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone (p.1535·2).
Anorectal disorders.

Rectiole *Caldeira & Metelo, Port.*
Glycerol (p.2314·2).
Bowel evacuation; constipation.

Recto Menaderm NF *Menarini, Spain.*
⊗ Beclometasone dipropionate (p.1516·2).
Anorectal disorders.

Rectodelt *Trommsdorff, Cz.; Trommsdorff, Ger.; Trommsdorff, Hung.*
⊗ Prednisone (p.1542·3).
Rectal corticosteroid.

Rectogel *Riva, Canad.*
Benzocaine (p.1854·1); zinc sulfate (p.1999·2).
Anorectal disorders.

Rectogel HC *Riva, Canad.*
⊗ Benzocaine (p.1854·1); zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Rectogesic
Note.This name is used for preparations of different composition.
Ferring, Cz.; ProStrakan, Fr.; ProStrakan, Gr.; ProStrakan, Port.; Cellegy, Singapore; Strakan, UK.
Glyceryl trinitrate (p.1296·2).
Anal fissure; anorectal disorders.

Cellegy, Austral.
Ointment: Glyceryl trinitrate (p.1296·2).
Anal fissure.

Cellegy, Austral.
Topical powder: Zinc oxide (p.1621·2).
Anorectal disorders.

Rectomenaderm *Menarini, Arg.*
⊗ Beclometasone dipropionate (p.1516·2).
Anorectal disorders.

Rectopanbiline *Viatris, Fr.*
⊗ Bile extract (p.2266·3); gelatin (p.1072·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Rectopred *Jacoby, Austria.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Croup.

Rectopulmo Adultos *Salusif, Port.†.*
Camphor (p.2273·2); cineole (p.2282·3); niaouli oil (p.2351·3); quinine sulfate (p.612·3).
Respiratory-tract disorders.

Rectopulmo Infantil *Salusif, Port.†.*
Camphor (p.2273·2); cineole (p.2282·3); niaouli oil (p.2351·3).
Respiratory-tract disorders.

Rectoquotane *Zambon, Fr.*
Quinisocaine hydrochloride (p.1870·3); cetrimide (p.1634·1).
Anorectal disorders.

Recto-Reparil *Madaus, Ital.*
Aescin (p.2248·2); tetracaine hydrochloride (p.1871·3).
Anorectal disorders.

Rectosec *SecFarm, Pol.*
Benzocaine (p.1854·1); Peru balsam (p.2365·3); zinc oxide (p.1621·2); cod-liver oil (p.1935·2).
Anorectal disorders.

Rectoseptal-Neo bismuthe *Actipharm, Switz.*
Bismuth succinate (p.1712·1); cineole (p.2282·3); terpin hydrate (p.1573·3); potassium hydroxyquinoline sulfate hydrate (p.2323·2).
Pharyngeal disorders.

Rectoseptal-Neo simple *Actipharm, Switz.*
Cineole (p.2282·3); terpin hydrate (p.1573·3); potassium hydroxyquinoline sulfate (p.2323·2).
Respiratory-tract disorders.

Rectovalone *Parke, Davis, Neth.†.*
⊗ Tixocortol pivalate (p.1544·2).
Ulcerative colitis.

Rectovasol *Qualiphar, Belg.*
Bismuth subgallate (p.1711·1); bismuth oxyiodogallate (p.1712·1); zinc oxide (p.1621·2); aesculus (p.2248·2); hamamelis (p.2318·2); amylocaine (p.1853·3); peru balsam (p.2365·3).
Haemorrhoids.

Rectozorin
Note.This name is used for preparations of different composition.
Teva, Israel.
Ointment: Bismuth oxychloride (p.1712·1); thymol iodide (p.1664·3); zinc oxide (p.1621·2); benzocaine (p.1854·1); menthol (p.2340·1).
Haemorrhoids.

Teva, Israel.
Suppositories: Bismuth subgallate (p.1711·1); thymol iodide (p.1664·3); zinc oxide (p.1621·2); benzocaine (p.1854·1); menthol (p.2340·1); tannic acid (p.2394·3).
Haemorrhoids.

Recugel *Bausch & Lomb, Arg.*
Dexpanthenol (p.2362·1).
Corneal lesions.

Recuperin-B *Tai Yu, Philipp.*
Vitamin B substances (p.1922·1).
Neuritis; vitamin B deficiency.

Recupex *Wockhardt, India.*
Nutritional supplement (p.1922·1).

Recur *Menarini, Cz.*
Frovatriptan succinate (p.622·3).
Migraine.

Recvalysat *Ysatfabrik, Ger.†.*
Valerian (p.2410·1).
Agitation; sleep disorders.

Recycline *Rekah, Israel.*
Tetracycline hydrochloride (p.347·2).
Bacterial eye and skin infections.

Red Away *Rivex Ophthalmics, Canad.†.*
⊗ Naphazoline hydrochloride (p.1565·2).

Red Cross Toothache *Mentholatum, USA.*
Eugenol (p.2301·2).
Toothache.

Red Kooga *Peter Black, UK.*
Ginseng (p.2312·1).
Tonic.

Red Kooga Co-Q-10 and Ginseng *Peter Black, UK.*
Ginseng (p.2312·1); ubidecarenone (p.2407·2).
Tonic.

Red Off *Laboratorios Chile, Chile.*
⊗ Naphazoline (p.1565·1).
Eye irritation.

Red Off Aqua *Laboratorios Chile, Chile.*
⊗ Naphazoline hydrochloride (p.1565·2); polyvinyl alcohol (p.2145·3).
Eye irritation.

Red Off Plus *Laboratorios Chile, Chile.*
⊗ Antazoline (p.567·1); naphazoline (p.1565·1).
Eye irritation.

Red Oil *Nella, UK.*
Methyl nicotinate (p.85·3); volatile mustard oil (p.2349·2); clove oil (p.2285·1); arachis oil (p.2259·1).
Muscle pain.

Red Seal *Quatromed, S.Afr.*
Merbromin (p.1652·1).
Bacterial infections of mucous membranes; skin cleansing; wounds.

Red Skin *Dossier, Neth.*
Homoeopathic preparation.

Red Throat Spray *Clay Park, USA.*
Phenol (p.1656·1).
Sore throat.

Redac *Gerolymatos, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Redacid *Maver, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Redactiv *Glaxo Wellcome, Mex.†.*
Rifaximin (p.330·1).
Gastrointestinal infections.

Redaflam *Maver, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Redalip *Maver, Mex.*
Bezafibrate (p.1232·1).
Hypercholesterolaemia.

Redap *Galderma, Denm.*
Adapalene (p.1587·1).
Acne.

Redaxa fit *Cheplapharm, Ger.*
Equisetum (p.2299·3).
Water retention.

Redaxin *Konimex, Indon.*
Red yeast rice.
Hyperlipidaemias.

Redentil *Ibefar, Braz.†.*
Aspirin (p.20·3); caffeine (p.1116·3); paracetamol (p.108·1).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; pain.

Redeptin *Janssen-Cilag, Irl.†.*
Fluspirilene (p.999·2).
Schizophrenia.

Redergam *PannonPharma, Hung.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; migraine; peripheral vascular disorders.

Redergin *Lek, Thai.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders; hypertension; migraine and other vascular headache; peripheral vascular disorders.

Redergot *OM, Port.†.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders.

Rediarin *Maver, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Redicalcin *Biosynthesis, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Redicres *Columbia, Mex.*
⊗ Clobenzorex hydrochloride (p.2152·3).
Obesity.

Redicres Rapido *Deutsche, Chile†.*
Glucomannan (p.2312·3).
Hypercholesterolaemia; obesity.

Redimune *ZLB, Switz.*
A normal immunoglobulin (p.2225·3).
Bone marrow transplantation; guillain-Barŕe syndrome; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease.

Redinac *Polfarmex, Pol.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Redipred *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Redisol *MSD, Thai.†.*
Cyanocobalamin (p.1980·2).
Schilling test; vitamin B deficiency.

Rediun-E *Baliarda, Arg.*
⊗ Spironolactone (p.1400·1).
Cirrhosis with ascites; heart failure; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Redol *Elvetium, Arg.†.*
Capsicum oleoresin (p.2276·2).
Neuralgia; osteoarthritis; rheumatoid arthritis.

Redol Comp *Orion, Fin.*
⊗ Dextromethorphan hydrobromide (p.1555·2); salbutamol sulfate (p.1131·3).
Respiratory-tract disorders.

Redolet *Solfran, Mex.†.*
Oxyphenbutazone (p.107·3).
Inflammation.

Redomex *Lundbeck, Belg.*
Amitriptyline hydrochloride (p.376·1).
Depression; pain.

Redopril *Sandoz, Venez.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; myocardial infarction.

ReDormin
Note. This name is used for preparations of different composition.
Flordis, Austral.; Beres, Hung.
Valerian (p.2410·1); lupulus (p.2335·2).
Sleep disorders.

Zeller, Switz.
Syrup: Valerian (p.2410·1).
Sleep disorders.

Zeller, Switz.
Tablets: Valerian (p.2410·1); lupulus (p.2335·2).
Sleep disorders.

Redotex *Medix, Mex.*
⊗ Cathine hydrochloride (p.2152·2); liothyronine (p.2174·2); atropine sulfate (p.1219·3); aloin (p.1705·3); diazepam (p.986·3).
Obesity.

Redotex NF *Medix, Mex.*
⊗ Cathine hydrochloride (p.2152·2); atropine sulfate (p.1219·3); aloin (p.1705·3).
Obesity.

Redotrin *Coup, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Redoxon
Bayer Consumer, Arg.; Bayer Consumer, Austral.†; Bayer, Austria; Roche, Braz.; Bayer Consumer, Canad.; Bayer, Chile†; Bayer, Hong Kong; Bayer, Irl.; Roche, Israel; Bayer, Ital.; Bayer Consumer, Mex.; Roche, NZ; Roche, Neth.†; Bayer, Port.; Bayer, Singapore; Bayer, Spain; Roche, Turk.; Roche Consumer, UK; Roche, Venez.†.
Ascorbic acid (p.1983·3).
Adjunct in iron supplementation; idiopathic methaemoglobinaemia; vitamin C deficiency; vitamin C supplement.

Bayer, Switz.
Ascorbic acid (p.1983·3) and/or sodium ascorbate (p.1984·1).
Malabsorption syndromes; methaemoglobinaemia; vitamin C deficiency; vitamin C supplement.

Roche, Belg.
Effervescent tablets: Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Roche, Belg.
Injection: Sodium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

Roche, Belg.
Tablets: Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Redoxon A *Bayer Consumer, Arg.*
Ascorbic acid (p.1983·3); vitamin A palmitate (p.1973·1).
Vitamin supplement.

Redoxon All Day Defence *Bayer, Singapore.*
Vitamin C (p.1983·3); zinc (p.1999·1).
Vitamin C and zinc supplement.

Redoxon Calciovit *Bayer, Spain.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); pyridoxine hydrochloride.
Bone and dental disorders; calcium deficiency; osteomalacia; rickets.

Redoxon Complex *Bayer, Spain.*
Multivitamin and mineral preparation (p.1922·1).

Redoxon Doble Accion *Bayer Consumer, Arg.*
Ascorbic acid (p.1983·3); zinc citrate (p.1999·2).
Vitamin C and zinc deficiency.

Redoxon Double Action
Bayer, Cz.; Bayer, Irl.
Ascorbic acid (p.1983·3); zinc citrate (p.1999·2).
Vitamin C and zinc deficiency.

Bayer, Hong Kong; Bayer, Indon.; Roche, NZ; Bayer, Singapore; Roche Consumer, UK.
Vitamin C (p.1983·3); zinc (p.1999·1).
Dietary supplement; vitamin C and zinc deficiency; vitamin C and zinc supplement.

Redoxon Double Strength *Bayer Consumer, Austral.*
Ascorbic acid (p.1983·3); zinc (p.1999·1).
Dietary supplement.

Redoxon + Zinc *Bayer, Switz.*
Ascorbic acid (p.1983·3) or sodium ascorbate (p.1984·1); zinc citrate (p.1999·2).
Vitamin C and zinc supplement.

Redoxon Zinco *Roche, Braz.*
Ascorbic acid (p.1983·3); zinc (p.1999·1).

Redoxon + Zink *Bayer, Belg.*
Ascorbic acid (p.1983·3); zinc (p.1999·1).
Vitamin C and zinc supplement.

Redoxon-B *Bayer Consumer, Canad.*
Ascorbic acid; vitamin B substances; magnesium salts (p.1922·1).
Nutritional supplement.

Redoxon-Cal *Bayer Consumer, Canad.*
Ascorbic acid; ergocalciferol; pyridoxine hydrochloride; calcium carbonate (p.1922·1).
Bone and dental disorders; delayed wound and fracture healing; nutritional supplement; osteomalacia; osteoporosis.

Redrate *Sanofi Synthelabo, Port.*
Glucose; sodium chloride; sodium bicarbonate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Redrocin *Unison, Thai.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Redsai Stress *Bunker, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Redseng Polivit *Korhispana, Spain.*
Multivitamin preparation with ginseng (p.2312·1) (p.1922·1).
Tonic.

Redualgas *Sigma, Arg.*
Poliglusam (p.2370·1); bladderwrack (p.2384·2).
Slimming aid.

Reduben *Cofasa, Venez.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Reducar *Gap, Gr.*
Isotretinoin (p.1599·2).
Acne.

Reducealin *Propan, S.Afr.†.*
⊗ Propylhexedrine (p.2163·1); vitamin B substances (p.1922·1).
Obesity.

Reducel *GX, Philipp.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Reducform-F *Ximena Polanco, Chile.*
Lessonia nigrescens; carmellose (p.2142·1); fabiana imbricata; spirulina (p.2392·1); inulin (p.2326·3).
Formerly contained lessonia nigrescens, carmellose, cichorium intybus, fabiana imbricata, and spirulina.
Digestive disorders; obesity.

Reducin *Finadiet, Arg.*
Soya lecithin (p.2332·2).
Dietary supplement.

Reducin-A *Unique, India†.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Reduclim *Farmoquimica, Braz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Reducol
Note. This name is used for preparations of different composition.
MSD, Braz.
Lovastatin (p.1328·2).
Hyperlipidaemias.

Saninter, Port.†.
Oxidised glycerol triester.
Cicatrisation; wounds.

Reductase *Natufarma, Arg.*
Garcinia cambogia (p.2309·2); levocarnitine (p.1932·2).
Obesity.

Reduc-Te *Ximena Polanco, Chile.*
Boldo (p.2267·2); inulin (p.2326·3); fennel (p.2302·3); rosa mosqueta (p.2381·2); equisetum (p.2299·3); tilia (p.2402·2).
Obesity.

Reductel *Degorts, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Reducterol *Elfar, Spain†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Reductil *Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Chile; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Teva, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Philipp.; Abbott, Port.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, UK; Abbott, Venez.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Reducto *Sanova, Austria.*
Monobasic potassium phosphate (p.1682·2); dibasic sodium phosphate (p.1682·3).
Calcium oxalate stones; hypercalcaemia.

Reducto-spezial *Temmler, Ger.*
Monobasic potassium phosphate (p.1682·2); dibasic sodium phosphate dihydrate (p.1682·3).
Calcium oxalate stones; hypercalcaemia; phosphate supplement.

Redudiet *AM, Arg.*
Garcinia cambogia (p.2309·2); centella (p.1592·3); alginic acid (p.2140·3); vitamin E (p.1992·2).
Obesity.

Redufat *Catarinense, Braz.*
Bladderwrack (p.2384·2).
Hypothyroidism; obesity.

Redugluc *Microsules, Arg.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Reduktan *Leros, Cz.*
Bladderwrack (p.2384·2); frangula bark (p.1732·2); sambucus (p.2383·1); senna (p.1769·2); fennel (p.2302·3); petroselinum root; birch leaf (p.2266·3); liquorice (p.1740·3).
Slimming aid.

Redulip *Hexal, Braz.†.*
Tiratricol (p.2177·3).
Obesity.

Redumed *Rimsa, Mex.*
⊗ Sibutramine (p.2164·1); carnitine (p.1932·2).
Obesity.

Redupon *Noristan, S.Afr.†.*
⊗ Ephedrine hydrochloride (p.1558·2); caffeine (p.1116·3); phenolphthalein (p.1762·1).
Obesity.

Reduprec *Ultra, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Redupress *Ache, Braz.†.*
Losartan potassium (p.1326·1).
Hypertension.

Reduprost *Raffo, Arg.*
Tamsulosin (p.2197·2).
Benign prostatic hyperplasia.

Redurate *Alliance, S.Afr.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Redur-PCM *Rivers Edge, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Redusa *Jean-Marie, Hong Kong.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Redusan Plus *Farmalight, Port.†.*
Poliglusam (p.2370·1); vitamin C; nicotinic acid; chromium (p.1922·1).
Slimming aid.

Reduscar *UCI, Braz.†.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Redusec *Solas, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Redustat *Liomont, Mex.*
Orlistat (p.2358·1).
Obesity.

Redusterol *Raffo, Arg.; Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Redusterol Duo *Raffo, Arg.*
Simvastatin (p.1390·2); ezetimibe (p.1284·3).
Hyperlipidaemias.

Redutemp *International Ethical, USA.*
Paracetamol (p.108·1).

Reduten *Sanitas, Chile.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Redutensil *Beta, Arg.†.*
Valsartan (p.1420·2).
Hypertension.

Redutona *Faes, Spain.*
Phenytoin (p.495·2); phenobarbital (p.492·2); aminohydroxybutyric acid (p.471·2); pyridoxine hydrochloride (p.1978·2).
Epilepsy.

Reduvit *Technikon, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Re-Dux *Bernabo, Arg.*
Bismuth citrate (p.1710·3).
Peptic ulcer.

Reduxade *Abbott, Ital.†.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Reduxpain *Kenyaku, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Musculoskeletal, joint, and soft-tissue disorders.

Redvit *Bunker, Braz.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Reedvit *Lafedar, Arg.†.*
Cyanocobalamin (p.1980·2).
Anaemia; neuralgia; neuritis.

Reef Deep Sun Tan Oil *Boots Healthcare, Austral.*
SPF 6: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Reef Sun Tan Oil *Boots Healthcare, Austral.*
SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

Reef Sun'n Surf *Boots Healthcare, Austral.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Reese's Pinworm *Reese, USA.*
Pyrantel embonate (p.155·1).
Worm infections.

ReFacto *Wyeth, Arg.†; Wyeth, Austral.; Genetics Institute, Austria; Wyeth, Belg.; Wyeth, Canad.; Wyeth, Cz.; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Fr.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hung.; Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, NZ; Wyeth, Neth.; Biovitrum, Norw.; Wyeth, Norw.; Wyeth Lederle, Port.; Wyeth, Spain; Biovitrum, Swed.; Wyeth, Swed.; Wyeth, Switz.; Wyeth, UK; Genetics Institute, USA.*
Moroctocog alfa (p.1067·2).
Haemophilia A.

Refador *Pliva, Cz.; Pliva, Hung.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Refagan *Bayer, Indon.*
Salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Refam *Terramedic, Philipp.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and leprosy.

Refam Duo *Terramedic, Philipp.*
Oral suspension, rifampicin (Refam) (p.325·3); syrup, isoniazid (p.288·1) (Terozid Forte).
Vitamin B (p.1978·2) is included in the Terozid Forte preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Refam Pedia Kit *Terramedic, Philipp.*
Oral suspension, rifampicin (Refam) (p.325·3); syrup, isoniazid (p.288·1) (Terozid Forte); oral suspension, pyrazinamide (p.320·2) (Pyramin).
Pyridoxine hydrochloride (p.1978·2) is included in the Terozid Forte preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Refenax Caramelos Expectorantes *Monserrat, Arg.*
Tolu balsam (p.1574·2); niaouli oil (p.2351·3); lidocaine (p.1862·3); hexylresorcinol (p.1647·1); cineole (p.2282·3); menthol (p.2340·1).
Coughs; sore throat.

Refenax Colirio *Monserrat, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye disorders.

Refenax Gotas Nasales *Monserrat, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2).
Nasal congestion.

Refenax Jarabe *Monserrat, Arg.*
Butetamate citrate (p.1553·1); ammonium chloride (p.1551·3); guaifenesin (p.1561·3); pseudoephedrine (p.1571·2); sodium benzoate (p.1630·2); sodium citrate (p.1673·3).
Coughs.

Refenax Lagrimas *Monserrat, Arg.*
Glycerol (p.2314·2).
Eye irritation.

Refenesen *Reese, USA.*
Guaifenesin (p.1561·3).

Refenesen Plus *Reese, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).

Referan *Farmanic, Gr.*
⊗ Aniracetam (p.363·2).
Mental function disorders.

Refesan T *Hanosan, Ger.†.*
Homoeopathic preparation.

Refex *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Cefalexin (p.218·2).
Bacterial infections.

Reflax *Merck, Braz.†.*
Cefaclor (p.217·2).
Bacterial infections.

Reflex *Boots Healthcare, Spain.*
Camphor (p.2273·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3); menthol (p.2340·1).
Rheumatic and muscle pain.

Reflexan *Pharma Investi, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

ReflexGel *Boots Healthcare, Belg.*
Methyl salicylate (p.85·3); camphor (p.2273·2).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Reflexor *Combiphar, Indon.*
Glucosamine (p.2313·2) or glucosamine sulfate potassium chloride (p.2313·2).
Osteoarthritis.

Reflexpatch *Boots Healthcare, Belg.*
Camphor (p.2273·2); methyl salicylate (p.85·3).
Inflammation; pain.

Reflexspray *Boots Healthcare, Belg.*
Methyl salicylate (p.85·3); turpentine oil (p.2406·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal, joint, peri-articular, and soft-tissue pain and inflammation.

Reflin *Ranbaxy, India; Ranbaxy, Rus.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Reflor
Note.This name is used for preparations of different composition.
Sanova, Austria.
Enterococcus faecium (p.2372·3).
Gastrointestinal disorders.

Sanofi Synthelabo, Turk.
Saccharomyces boulardii (p.2372·3).

Reflotron Roche Diagnostics, Irl.
Test for a range of cardiac risk factors in blood, serum, or plasma.

Refludan Pharmion, Austral.; Schering, Austria; Pharma Logistics, Belg.; Berlex, Canad.; Celgene, Cz.; Schering, Denm.†; Aventis, Fin.†; Pharmion, Fr.; Pharmion, Ger.; Schering, Ger.; Hoechst Marion Roussel, Gr.†; Pharmion, Hung.; Pharmion, Irl.; Pharmion, Ital.; Hoechst Marion Roussel, NZ; Pharmion, Neth.; Pharmion, Norw.; Celgene, Port.; Schering, Swed.†; Pharmion, Switz.; Pharmion, UK; Hoechst Marion Roussel, USA.
Lepirudin (p.1323·2).
Acute coronary syndromes; thromboembolic disorders; thromboembolic disorders in patients with heparin-associated thrombocytopenia.

Refludin Key Oncologics, S.Afr.; Pharmion, Spain.
Lepirudin (p.1323·2).
Thromboembolic disorders.

Reflux
Note.This name is used for preparations of different composition.
Monte Verde, Arg.
Ranitidine (p.1766·1).
Gastric hyperacidity; peptic ulcer.

IPS, Neth.
Methenamine mandelate (p.298·3).
Urinary-tract infections.

Refluxine Spirig, Switz.†.
Alginic acid (p.2140·3); sodium bicarbonate (p.1673·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastro-oesophageal reflux.

Refluxon PharmaConsult, Hung.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Refobacin Merck, Austria; Hermal, Ger.; Merck, Ger.; Merck, Venez.†.
Gentamicin sulfate (p.282·1).
Bacterial infections.

Refobacin Bone Cement R Biomet, Singapore.
Gentamicin sulfate (p.282·1); methylmethacrylate/methacrylate copolymer (p.2343·3).
Bone cement for orthopaedic surgery.

Refobacin-Palacos R Biomet, Ger.; Merck, Singapore†; Merck, Thai.
Gentamicin sulfate (p.282·1); methylmethacrylate/methacrylate copolymer (p.2343·3).
Bone cement for orthopaedic surgery; bone infections.

Refolinon Pharmacia, UK.
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Reforce Farmoz, Port.
Fluconazole (p.532·1).
Fungal infections.

Reforgan Nikkho, Braz.
Arginine aspartate (p.1928·2).
Nutritional supplement.

Refortan Berlin-Chemie, Rus.
⊗ Pentastarch (p.1065·1) in sodium chloride.
Haemodilution; hypovolaemia; shock.

Refortrix GSK, Braz.†.
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Refotax Uno, Ital.
Cefotaxime sodium (p.228·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Refractyl Sophia, Mex.
Cyclopentolate (p.1880·1).
Production of mydriasis and cycloplegia.

Refrane Bronce Neo Dermos, Arg.
Oxybenzone (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen; tanning agent.

Refrane Gel Neo Dermos, Arg.
SPF 16: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Refrane P Neo Dermos, Arg.
SPF 18: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); aloe vera (p.1588·2).
Sunscreen.

Refrane Plus Neo Dermos, Arg.
SPF 33: Octinoxate (p.1608·2); oxybenzone (p.1608·3); sulisobenzone (p.1614·3); titanium dioxide (p.1617·3); aloe vera (p.1588·2).
Sunscreen.

Refrane Total Neo Dermos, Arg.
SPF 50: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); ensulizole (p.1597·1).
Sunscreen.

Refrat Cellofarm, Braz.†.
Mycophenolate mofetil (p.1836·2).
Transplant rejection.

Refresh
Note.This name is used for preparations of different composition.
Allergan, Austral.; Allergan, Braz.; Allergan, Canad.; Allergan, Fr.; Alvia (Αλβια), Gr.; Allergan, Israel; Allergan, Malaysia†; Allergan, NZ; Allergan, S.Afr.; Allergan, Singapore†; Allergan, Thai.; Abdi, Turk.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes; eye irritation.

Allergan, Hong Kong.
Carmellose sodium (p.2142·1).
Dry eyes.

Allergan, Mex.
Carbomer (p.2141·3).
Dry eyes.

Allergan, UK.
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Refresh Celluvisc Allergan, Canad.
Carmellose sodium (p.2142·1).
Formerly known as Celluvisc.
Dry eyes.

Refresh Classic Allergan, USA.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Formerly known as Refresh.
Dry eyes.

Refresh Dry Eye Therapy Allergan, USA.
Glycerol (p.2314·2); polysorbate 80 (p.1919·2).
Dry eyes.

Refresh Free Allergan, Arg.†.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Refresh Gel Allergan, Arg.; Allergan, Braz.
Carbomer (p.2141·3).
Dry eyes.

Refresh Lacri-Lube Allergan, Canad.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Formerly known as Lacri-Lube.
Dry eyes.

Refresh Liquigel Allergan, Arg.; Allergan, Austral.; Allergan, Canad.; Allergan, Chile; Allergan, Mex.; Allergan, S.Afr.; Allergan, Venez.
Carmellose sodium (p.2142·1).
Dry eyes; eye irritation; wetting and lubricating of contact lenses.

Refresh Plus Allergan, Canad.; Allergan, Malaysia†; Allergan, Singapore†; Allergan, USA.
Carmellose sodium (p.2142·1).
Dry eyes; eye irritation.

Refresh PM Allergan, USA.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool alcohols (p.2033·2).
Dry eyes.

Refresh Tears Allergan, Arg.; Allergan, Canad.; Allergan, Chile; Allergan, Israel; Allergan, Malaysia†; Allergan, Mex.; Allergan, S.Afr.; Allergan, Singapore†; Allergan, USA; Allergan, Venez.
Carmellose sodium (p.2142·1).
Dry eyes; eye irritation.

Refresh Tears Plus Allergan, Austral.†; Allergan, NZ.
Carmellose sodium (p.2142·1).
Dry eyes.

Refrianex Montpellier, Arg.
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Refrianex Antigripal Montpellier, Arg.
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Refrianex Compuesto Montpellier, Arg.
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); bromhexine hydrochloride (p.1552·2); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Reftax Ranbaxy, S.Afr.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Refulgin Spyfarma, Spain.
Adenosine triphosphate (p.2247·3); hydroxocobalamin acetate (p.1980·3); pyritinol hydrochloride (p.369·1); prosultiamine (p.1975·3).
Mental function disorders.

Refusal Artu, Neth.
Disulfiram (p.2296·2).
Chronic alcoholism.

Refzil-O Ranbaxy, India.
Cefprozil (p.232·2).
Bacterial infections.

Regadrin B Berlin-Chemie, Cz.; Berlin-Chemie, Ger.†.
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Regain
Note. A similar name is used for preparations of different composition (see below).
R&D, USA.
Nutritional supplement in renal failure (p.1922·1).

Regaine
Note. A similar name is used for preparations of different composition (see above).
Pfizer Consumer, Austral.; Pfizer, Austria; Pfizer Consumer, Belg.; Pfizer, Braz.; Pfizer, Chile; McNeil, Cz.; Pfizer, Denm.; Pharmacia, Fin.†; Pfizer Sante, Fr.; Pfizer Consumer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer Consumer, Mex.; Pfizer Consumer, Neth.; Pfizer, Norw.†; Pfizer, Pol.; Janssen-Cilag, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Johnson & Johnson, Singapore; Pfizer Consumer, Spain; Pharmacia, Swed.†; Pfizer Consumer, Switz.; Pfizer, Thai.; Pfizer Consumer, UK; Pharmacia, Venez.†.
Minoxidil (p.1342·1).
Alopecia androgenetica.

Regal Andromaco, Chile†.
Docusate sodium (p.1725·1).
Constipation.

Regalisa Microsules, Arg.†.
Cisapride (p.1720·3).

Regamint Soria Natural, Spain†.
Peppermint leaf (p.1761·2); burnet saxifrage (p.2270·3); liquorice (p.1740·3).
Gastrointestinal disorders.

Regard Smith & Nephew, S.Afr.
Glycerol (p.2314·2).
Lubrication.

Regasec Combiphar, Indon.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Regasinum antallergicum Rowa, Ger.
Homoeopathic preparation.

Regasinum antiinfectiosum N Rowa, Ger.
Homoeopathic preparation.

Regasinum cardiale N Rowa, Ger.
Homoeopathic preparation.

Regasinum hepaticum N Rowa, Ger.
Homoeopathic preparation.

Regastin Combiphar, Indon.
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Regata Konimex, Indon.
Diphenhydramine hydrochloride (p.577·2); calamine (p.1591·2); camphor (p.2273·2).
Skin irritation.

Regavasal Rowa, Ger.
Homoeopathic preparation.

Regaxidil Cantabria, Spain.
Minoxidil (p.1342·1).
Alopecia androgenetica.

Regazym Plus Homeosyn, Ital.†.
Nutritional supplement (p.1922·1).

Regederm Synergia, Fr.
Evening primrose oil (p.2302·1); fish oil; vitamins; minerals (p.1922·1).
Skin disorders.

Regena-Haut G Regenaplex, Ger.
Homoeopathic preparation.

Regena-Haut W Regenaplex, Ger.
Homoeopathic preparation.

Regenaplex Regenaplex, Ger.
Homoeopathic preparation.

Regencel Latinofarma, Braz.
Vitamin A acetate (p.1973·1); aminoacids; chloramphenicol (p.239·3).

Regender Pharmasac, Port.; Alacan, Spain.
Polypodium leucotomos.
Psoriasis; skin disorders.

Regeneresen Dyckerhoff, Ger.
Ribonucleic acid (p.2379·1).
Tonic.

Regenerin Sanova, Austria†.
Procaine hydrochloride (p.1869·1); vitamin A (p.1971·2); vitamin E (p.1992·2).
Reduced mental and physical capacity in the elderly.

Regenesis Elea, Arg.
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Regenesis Max Elea, Arg.
4 Tablets, alendronate sodium (p.1088·1); 28 tablets, calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Regenom Genom, Braz.
Vitamin A acetate (p.1973·1); chloramphenicol (p.239·3); methionine (p.1450·1).
Infected eye disorders.

Regenon Temmler, Denm.; Temmler, Ger.; Doetsch, Grether, Switz.; TTN, Thai.†; Temmler, Thai.†.
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Regental Tecnofarma, Chile.
Nimodipine (p.1357·2).
Alzheimer's disease; cerebrovascular insufficiency; mental function impairment; neurological deficit following subarachnoid haemorrhage.

Regepar Sanofi Synthelabo, Austria.
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Regepithel
Alcon, Ger.
Vitamin A palmitate (p.1973·1); thiamine hydrochloride (p.1976·1); calcium pantothenate (p.1959·3).
Corneal defects.

Alcon, Hong Kong†.
Vitamin A (p.1971·2); thiamine (p.1976·3); calcium pantothenate (p.1959·3).
Eye disorders.

Regeron Vita More, Philipp.
Vitamin preparation with lysine hydrochloride (p.1922·1).
Nutritional supplement.

Regeron Vita with Chlorella
More, Philipp.
Oral drops: Vitamins; zinc sulfate; taurine; chlorella (p.1922·1).
Nutritional supplement.

More, Philipp.
Syrup: Vitamins; zinc sulfate; taurine; lysine; chlorella (p.1922·1).
Nutritional supplement.

Regeron-C More, Philipp.
Vitamin preparation (p.1922·1).
Nutritional supplement.

Regeron-E Plus More, Philipp.
Vitamins (p.1922·1); ferrous sulfate (p.1939·3); buclizine hydrochloride (p.570·1).
Appetite stimulant; nutritional supplement.

Regibloc Intramed, S.Afr.
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Regina Royal Concorde Regina, UK.
Royal jelly (p.2382·1); ginseng (p.2312·1); damiana aphrodisiaca (p.2292·1); saw palmetto (p.2192·3).

Regina Royal Five Regina, UK.
Royal jelly (p.2382·1); bee pollen (p.2370·2); pure honey (p.1948·2).

Regina Royal One Hundred Regina, UK.
Royal jelly (p.2382·1).

Regiocaina Richmond, Arg.
Lidocaine (p.1862·3).
Local anaesthesia.

Regit Landson, Indon.
Domperidone maleate (p.1726·3).
Dyspepsia; nausea and vomiting.

Regitin Novartis, Denm.
Phentolamine mesilate (p.1370·2).
Adrenaline or noradrenaline overdose; phaeochromocytoma.

Regitina Novartis, Arg.; Novartis, Braz.†; Novartis, Venez.†.
Phentolamine mesilate (p.1370·2).
Erectile dysfunction.

Regitine Aspen, Austral.; Novartis, Belg.; IFET (ΙΦΕΤ), Gr.; Novartis, Hung.; Novartis, Israel; Novartis, NZ; Novartis, Neth.; Novartis, S.Afr.†; Novartis, Switz.; Novartis, USA†.
Phentolamine mesilate (p.1370·2).
Dermal necrosis and sloughing following extravasation of noradrenaline; phaeochromocytoma.

Regla pH
Note.This name is used for preparations of different composition.
UCB, Belg.†.
Algeldrate (p.1706·2); light magnesium oxide (p.1744·1).
Gastrointestinal disorders associated with hyperacidity.

UCB, Neth.
Chewable tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

UCB, Gr.†.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1).
Antacid.

UCB, Neth.
Oral suspension: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

UCB, Gr.†.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Antacid.

Regla pH Forte UCB, Belg.†.
Algeldrate (p.1706·2); light magnesium oxide (p.1744·1); aluminium hydroxide-magnesium carbonate co-dried gel(p.1707·2).
Gastric hyperacidity; peptic ulcer.

Reglan CFL, India; Sanofi Synthelabo, Port.†; Schwarz, USA.
Metoclopramide hydrochloride (p.1747·3).
Adjunct in gastrointestinal procedures; diabetic gastroparesis; dyspepsia; gastritis; gastro-oesophageal reflux; nausea and vomiting; postoperative gastric hypotonia.

Reglosedyl Medifarma, Mex.†.
Paregoric (camphorated opium tincture) (p.105·1); viburnum (p.2267·1).
Gastrointestinal spasm.

Reglumax Max Farma, Ital.†.
Reduced glutathione sodium (p.1448·1).
Drug and alcohol poisoning.

Reglus Landson, Indon.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Reglusan Novag, Mex.
Glibenclamide (p.440·1).
Diabetes mellitus.

Regolact Plus Naturmed, Ital.
Lactic-acid-producing organisms (p.2372·3).
Maintenance of normal gastrointestinal flora.

Regoxal Vargas, Venez.
Bisoxatin acetate (p.1712·3).
Bowel evacuation; constipation.

Regranex Janssen-Cilag, Austria; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.; Ethicon, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Port.; Pensa, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Johnson & Johnson, USA.
Becaplermin (p.1590·1).
Diabetic neuropathic ulcers; skin lesions; wounds.

Regripax Biofarma, Mex.
Echinacea (p.2298·1).
Immunostimulant.

Regro *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Minoxidil (p.1342·1).
Alopecia androgenetica; alopecia areata.

Regroe *Dermpharma, Philipp.*
Minoxidil (p.1342·1).
Alopecia.

Regroton *Novartis, Turk.; Rhone-Poulenc Rorer, USA.*
⊗ Chlortalidone (p.1243·3); reserpine (p.1387·3).
Hypertension.

Regrou *Surya Dermato, Indon.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Regrowth *Medicine Products, Thai.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Regucal *Baliarda, Arg.*
Calcium pidolate (p.1676·3).
Calcium supplement.

Regucal D *Baliarda, Arg.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Regucol *Procter & Gamble, Neth.*
Ispaghula (p.1737·1).
Constipation.

Regudig *Beta, Arg.†.*
Guar gum (p.442·3).
Diabetes mellitus; obesity.

Regulacid *Lazar, Arg.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Regulacor-POS *Ursapharm, Ger.*
Crataegus (p.2289·1).
Cardiac disorders.

Regulact *Valeant, Mex.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Regulador Xavier N-1 *Hepacholan, Braz.†.*
Viburnum; gossypium; belladonna (p.2263·3); calcium chloride (p.1675·2).
Menstrual disorders.

Regulador Xavier N-2 *Hepacholan, Braz.†.*
Rhubarb (p.1768·3); savin; belladonna (p.2263·3); ferric ammonium citrate (p.1938·1); citric acid (p.2284·1).
Menstrual disorders.

Regulan *Procter & Gamble, Irl.; Procter & Gamble, UK.*
Ispaghula (p.1737·1).
Constipation; diverticular disease; irritable bowel syndrome.

Regulane *Finadiet, Arg.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ileostomy management.

Regulane AF *Finadiet, Arg.*
Loperamide hydrochloride (p.1741·1); simeticone (p.1770·2).
Diarrhoea; flatulence.

Regular Iletin II *Lilly, USA.*
⊗ Insulin injection (porcine) (p.443·2).
Diabetes mellitus.

Regular Strength Bayer *Sterling Health, USA.*
Aspirin (p.20·3).
Formerly known as Therapy Bayer.
Fever; inflammation; myocardial infarction; pain; transient ischaemic attacks.

Regular Strength Cold Nighttime Relief *WestCan, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).

Regular Strength Sinus Medication *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); doxylamine succinate (p.578·2).

Regulaten *Juste, Spain.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Regulaten Plus *Juste, Spain.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Regulatum *Teuto, Braz.†.*
Agnus castus (p.2249·1).
Menopausal disorders.

Regulax
Note. This name is used for preparations of different composition.
Hexal, Braz.†.
Cotton root bark; plumeria lancifolia; berberis laurina.
Dysmenorrhoea.

Krewel Meuselbach, Cz.†; Krewel Meuselbach, Pol.
Senna (p.1769·2).
Bowel evacuation; constipation.

Regulax N *Krewel, Ger.†.*
Senna (p.1769·2).
Constipation.

Regulax Picosulfat *Krewel, Ger.*
Sodium picosulfate (p.1771·1).
Constipation.

Regulax Pikosulfat *Krewel Meuselbach, Cz.*
Sodium picosulfate (p.1771·1).
Constipation.

Regulax SS *Republic, USA.*
Docusate sodium (p.1725·1).
Constipation.

Reguletts *Husler, Switz.*
Phenolphthalein (p.1762·1).
Constipation.

Regulex *Whitehall-Robins, Canad.†.*
Docusate sodium (p.1725·1).
Constipation.

Regulim *Atlantic, Singapore†; Atlantic, Thai.*
Phenolphthalein (p.1762·1).
Bowel evacuation; constipation.

Regulin *Gea, Denm.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Regulip *Raffo, Arg.*
Salmon oil (p.1362·1).
Hyperlipidaemias.

Reguloid *Rugby, USA.*
Psyllium hydrophilic mucilloid (p.1737·1).
Constipation.

Regulon *Gedeon Richter, Cz.; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Richter, Pol.; Grunenthal, Port.; Gedeon Richter, Rus.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Reguloop *Tunggal Idaman, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Regulose *Novartis Consumer, UK.*
Lactulose (p.1738·2).
Constipation.

Regulton *Abbott, Belg.; Teofarma, Ger.*
⊗ Amezinium metilsulfate (p.1209·2).
Hypotension.

Regultron *Bajamed, Mex.*
Fluoxetine (p.397·3).
Depression.

Regumen *Sanbe, Indon.*
Norethisterone (p.2119·3).
Dysfunctional uterine bleeding; dysmenorrhoea; endometriosis; menorrhagia; postponement of menstruation; premenstrual syndrome.

Regurin *Galen, Irl.; Galen, UK.*
Trospium chloride (p.2198·3).
Bladder instability.

Rehalyt *SAD, Denm.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Rehidralyte *Abbott, Venez.†.*
Glucose; sodium chloride; sodium citrate; potassium citrate (p.1672·2).
Oral rehydration.

Rehidrat *Eurofarma, Braz.; Pharmacia, Irl.; Pharmacia, S.Afr.; Pharmacia, UK†.*
Potassium chloride; sodium citrate dihydrate; sodium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Rehidrosol *Behrens, Venez.†.*
Sodium citrate; potassium chloride; glucose; citric acid (p.1672·2).
Oral rehydration.

Rehsal *Laboratorios Chile, Chile.*
Electrolytes; glucose (p.1672·2).
Oral rehydration therapy.

Rehydralyte *Abbott, Canad.; Abbott, Thai.†; Ross, USA.*
Glucose; potassium citrate; sodium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Rehydrex med glucos *Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Electrolyte infusion with glucose (p.1667·1).
Fluid and electrolyte disorders.

Rehydrex med Glucose *Fresenius Kabi, Denm.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Rehydron *Orion, Rus.*
Sodium chloride; sodium citrate; potassium chloride; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Rehydrosol *Teva, Hung.*
Electrolyte infusion with sorbitol (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Reichamox *Medreich, Hong Kong.*
Amoxicillin (p.202·2).
Bacterial infections.

Reidramax *Cazi, Braz.*
Glucose; sodium citrate; potassium chloride; sodium chloride (p.1672·2).
Oral rehydration therapy.

Reidratante *Catarinense, Braz.*
Glucose; sodium citrate; potassium chloride; sodium chloride (p.1672·2).
Oral rehydration therapy.

Reisedragee Eu Rho *Eu Rho, Ger.†.*
Diphenhydramine hydrochloride (p.577·2); 8-chlorotheophylline.
Nausea; vomiting.

Reisegold
Note. This name is used for preparations of different composition.
Whitehall-Much, Ger.†.
Sugar-coated tablets: Diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3); 8-chlorotheophylline; pyridoxine hydrochloride (p.1978·2).
Motion sickness.

Whitehall-Much, Ger.†.
Tablets: Dimenhydrinate (p.576·2).
Motion sickness.

Reisetabletten *Ratiopharm, Ger.; Stada, Ger.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Rejuva *Stiefel, Canad.*
SPF 30: Avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2).
Sunscreen.

Rejuva-A *Stiefel, Canad.*
Tretinoin (p.1618·1).
Photodamaged skin.

Rejuvan *UAP, Indon.*
Vitamin A; vitamin B ; vitamin E; ferrous fumarate (p.1938·3)(p.1922·1).
Tonic.

Rejuvesol *Cytosol, Israel.*
Sodium pyruvate; inosine; adenine; dibasic sodium phosphate; monobasic sodium phosphate.
Extracorporeal rejuvenation.

Rejuvon *Eurowest, Philipp.*
Vitamin preparation with taurine and lysine (p.1922·1).
Nutritional supplement.

Rekamide *Rekah, Israel.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Rekasitin *Rekah, Israel.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); allantoin (p.1588·1).
Barrier preparation; burns; nappy rash; skin disorders.

Rekawan *Riemser, Ger.*
Potassium chloride (p.1684·3).
Potassium deficiency.

Rekiv *Rekah, Israel.*
Magnesium carbonate (p.1743·1); bismuth subnitrate (p.1711·2); sodium bicarbonate (p.1673·2); frangula bark (p.1732·2); calamus (p.2271·3).
Gastritis; gastrointestinal hyperacidity; peptic ulcer.

Rekod *Rekah, Israel.*
Codeine phosphate (p.37·2).
Coughs; pain.

Rekont *Madaus, Austria.*
Trospium chloride (p.2198·3).
Bladder function disorders.

Rekord B12 *Sigma-Tau, Ital.*
Amino-acid and vitamin B substances (p.1922·1).
Tonic.

Rekord Ferro *Sigma-Tau, Ital.*
Iron succinyl-protein complex (p.1953·2).
Iron deficiency; iron-deficiency anaemia.

Rekostin *Biofarm, Pol.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Rektiolax *Marmir, Pol.*
Sodium laurilsulfate (p.2138·3); sodium citrate (p.1673·3); sorbitol (p.1965·1); glycerol (p.2314·2).
Bowel evacuation; constipation.

Relacon Lax *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Relacon-DM *Cypress, USA†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Relacon-HC *Cypress, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Coughs; upper respiratory-tract congestion.

Relact *Kora, Irl.*
Lactic acid (p.2329·3).
Vaginal discharge.

Relacton-C *Unipharma, Gr.†.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Muscle relaxant; pain.

Reladorm *Tarchomin, Rus.*
Diazepam (p.986·3); cyclobarbital calcium (p.986·1).

Relafen *GSK, Canad.; SmithKline Beecham, USA†.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Relaflex *Hertz, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Pain; smooth muscle spasm.

Relagesic *International Ethical, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Relampago *Ibefar, Braz.†.*
Thymol (p.1664·3); menthol (p.2340·1); neotutocaina; eugenol (p.2301·2).

Relana *Pharbio, Pol.; Cederroth, Spain.*
Melissa (p.2339·3); valerian (p.2410·1).
Anxiety; nervous disorders.

Relana Forte *Pharbio, Pol.*
Valerian (p.2410·1).
Anxiety; insomnia.

Relanium *GSK, Pol.; Medana, Pol.; Polfa Warszawa, Pol.; Warsaw-Polfa, Rus.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; convulsions; eclampsia; epilepsy; premedication; skeletal muscle spasm; tetanus.

Relapamil *Orion, Fin.*
Quinine hydrochloride (p.612·3); diazepam (p.986·3).
Muscle spasm.

Relapax *Cazi, Braz.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm.

Relapaz *Alter, Spain.*
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder.

Relar *Pharmaland, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Muscle pain; tension headache.

Relasin-HCX *Cypress, USA.*
Guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Cough.

Relatene *Mintlab, Chile.*
Ketoprofen (p.73·1).
Inflammation; pain.

Relatrac *Pisa, Mex.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Relavit Fosforo *Seber, Port.*
Glutamine (p.1947·2); thiamine hydrochloride; calcium magnesium fytate.
Mental function disorders.

Relax *Marien, Austria.*
Homoeopathic preparation.

Relax B$^+$ *Vitalia, UK.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2); vitamin B substances (p.1922·1).

Relax and Sleep *Jamieson, Canad.*
Cataria; lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Sleep disorders.

Relaxane *Zeller, Switz.*
Butterbur (p.2271·1); valerian (p.2410·1); passion flower (p.2363·2); melissa (p.2339·3).
Formerly known as Relax.
Nervous disorders; sleep disorders.

Relaxaplex *Vitaplex, Austral.†.*
Valerian (p.2410·1); skullcap (p.2388·2); passion flower (p.2363·2); lupulus (p.2335·2); gentian (p.2310·3).
Herbal sedative.

Relaxar *Bouty, Ital.*
Mephenesin (p.1897·2); methyl nicotinate (p.85·3).
Neuromuscular pain; soft-tissue disorders.

Relaxa-Tabs *Woods, Austral.*
Mepyramine maleate (p.585·2).
Insomnia; nervous tension.

Relaxcol *Cristalfarma, Ital.*
Green clay; fennel (p.2302·3); star anise (p.2392·1); caraway (p.2276·3); fennel oil (p.2303·1); caraway oil (p.2277·1); cinnamon oil (p.2283·2); fruit oligosaccharides.
Gastrointestinal disorders with excess gas.

Relaxibys *Rimafar, Spain†.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Musculoskeletal spasticity.

Relaxil *Arrow, Braz.*
Bromazepam (p.964·3).
Anxiety.

Relaxil-G *PannonPharma, Hung.*
Guaifenesin (p.1561·3).
Skeletal muscle spasm and paralysis.

Relaxine *Trenker, Belg.; Trima, Israel.*
Valerian (p.2410·1).
Insomnia; nervous disorders; nervousness; sleep disorders.

Relaxin-P *Jean-Marie, Hong Kong†.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Painful skeletal muscle spasm.

Relaxit
Note. This name is used for preparations of different composition.
Abigo, Swed.
Sodium bicarbonate (p.1673·2); potassium acid tartrate (p.1764·1); calcium silicate (p.1676·3).
Constipation; faecal incontinence.

Crawford, UK.
Sodium citrate (p.1673·3); sodium laurilsulfate (p.2138·3); sorbic acid (p.1662·2); glycerol (p.2314·2); sorbitol (p.1965·1).
Constipation.

Relaxo *UB, Switz.*
Passion flower (p.2363·2); lupulus (p.2335·2); valerian (p.2410·1); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Relaxon *Veropharm, Rus.†.*
Zopiclone (p.1039·1).
Sleep disturbances.

Relaxophen *Tanta, Canad.*
Paracetamol (p.108·1); methocarbamol (p.1897·3).

Relaxten *Biotenk, Arg.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Relaxyl
Note. This name is used for preparations of different composition.
Nycomed, Austria.
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Thornton & Ross, UK†.
Alverine citrate (p.1708·1).
Irritable bowel syndrome.

Franco-Indian, India.
Ointment: Mephenesin (p.1897·2); methyl nicotinate (p.85·3); capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, and soft-tissue disorders.

Franco-Indian, India.
Slow-release tablets; tablets: Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Franco-Indian, India.
Topical gel: Diclofenac diethylamine (p.44·3).
Soft-tissue disorders.

Relaxyl Plus *Franco-Indian, India.*
Diclofenac sodium (p.44·3); paracetamol (p.108·1).
Gout; musculoskeletal and joint disorders.

Relazepam *Pisa, Mex.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm.

Relcer *Glenmark, Rus.*
Algeldrate (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2); liquorice (p.1740·3).
Dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Relcof PSE *Burel, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Relcofen *Alpharma, UK.*
Ibuprofen (p.64·2).
Fever; pain.

Re-Leaf *Pascual, Philipp.*
Blumea balsamifera.
Oedema; renal calculi.

Releaf for PMS *Lake, USA.*
Pyridoxine hydrochloride (p.1978·2) in a base of natural herbs.
Premenstrual syndrome.

Release *New Vision, Canad.†.*
Vitamin C; manganese (p.1922·1).

Release Ag *Ethicon, Fr.*
Guluronic acid (p.2140·3); carmellose (p.2142·1); silver (p.2387·1).
Ulcers; wounds.

Relefact *Hoechst Marion Roussel, Gr.†.*
Protirelin (p.2175·3).
Thyroid function test.

Relefact LH-RH *Aventis, Austria; Aventis, Cz.†; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Israel; Aventis, Neth.*
⊗ Gonadorelin (p.2106·2).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction; infertility.

Relefact TRH *Aventis, Austria; Odan, Canad.; Aventis, Ger.†; Aventis, Israel; Aventis, Neth.; Aventis, Switz.†.*
Protirelin (p.2175·3).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Relefrina *Klonal, Arg.*
⊗ Prednisolone (p.1540·3); phenylephrine (p.1568·1).
Eye disorders.

Relente *Klonal, Arg.*
Sodium chloride (p.1686·1).

Relenza *GSK, Arg.†; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile†; GSK, Cz.; GSK, Denm.†; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; Glaxo Wellcome, Irl.†; GSK, Israel†; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; Glaxo Wellcome, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.*
Zanamivir (p.913·2).
Influenza.

Relert *Pfizer, Belg.; Pfizer, Fin.; Mack, Israel; Pfizer, Port.; Pfizer, Spain.*
Eletriptan hydrobromide (p.619·3).
Migraine.

Reless *Alk-Scherax, Ger.*
Bee venom extract (p.2251·1) or wasp venom extract (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Relestal *Pediatrica, Philipp.*
Dicycloverine hydrochloride (p.1722·3).
Colic; gastrointestinal disorders.

Relestat *Allergan, Belg.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hung.; Allergan, Irl.; Allergan, Ital.; Allergan, Neth.; Allergan, Pol.; Allergan, Port.; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, UK.*
Epinastine hydrochloride (p.579·3).
Allergic conjunctivitis.

Relexil *Laboratorios Chile, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Reliberan *Geymonat, Ital.†.*
Chlordiazepoxide hydrochloride (p.968·2).
Anxiety disorders.

Relide *Fahrenheit, Indon.*
Glimepiride (p.441·1).
Diabetes mellitus.

Relief
Note. This name is used for preparations of different composition.
Sagmel, Rus.
Shark-liver oil (p.2386·1); phenylephrine hydrochloride (p.1568·1).
Anorectal disorders.

Allergan, USA.
Phenylephrine hydrochloride (p.1568·1).
Minor eye irritation.

Relief Advance *Sagmel, Rus.*
Shark-liver oil (p.2386·1); benzocaine (p.1854·1).
Anorectal disorders.

Relief Ultra *Sagmel, Rus.*
⊗ Hydrocortisone acetate (p.1535·2); zinc sulfate (p.1999·2); shark-liver oil (p.2386·1).
Anorectal disorders.

Relief-Coff *MDI, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Reliev *Schering, Chile.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Reliev 76% *Schering, Chile.*
Sodium amidotrizoate (p.1475·3); meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Relievol Allergy Sinus *Tanta, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Relievol PMS *Tanta, Canad.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Relievol Sinus *Tanta, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Relif *Meda, Spain.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Relifen *Sanwa, Jpn; GSK, S.Afr.*
Nabumetone (p.91·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Relifex *GSK, Braz.†; Meda, Cz.; Meda, Denm.; Meda, Fin.; Meda, Gr.; GSK, Hong Kong†; Meda, Hung.; Meda, Irl.; GSK, Israel; GSK, Mex.; Meda, Norw.; SmithKline Beecham, Philipp.; GSK, Pol.; Meda, Swed.; GSK, Thai.; GSK, Turk.; Meda, UK.*
Nabumetone (p.91·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Religer *Gerard, Irl.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Relimal *Pharmachemie, Philipp.*
⊗ Morphine sulfate (p.86·3).
Pain.

Relipain *Gerolymatos, Gr.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Relisan *Xixia, S.Afr.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Reliser *Serono, Arg.†; Serono, Braz.; Serono, Mex.†; Serono, Venez.†.*
⊗ Leuprorelin acetate (p.2111·1).
Endometriosis; female infertility; prostatic cancer; uterine fibroids.

Relisorm I *Serono, Hung.†.*
⊗ Gonadorelin acetate (p.2106·2).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction.

Relisorm L *Serono, Hong Kong†; Serono, Switz.†.*
⊗ Gonadorelin acetate (p.2106·2).
Diagnosis of infertility; stimulation of ovulation; test of hypothalamic-pituitary-gonadal function.

Relistor *Wyeth, UK; Wyeth, USA.*
Methylnaltrexone bromide (p.1747·2).
Opioid-induced constipation.

Relitone *Garec, S.Afr.*
Nabumetone (p.91·2).
Osteoarthritis; rheumatoid arthritis.

Relium *Tarchomin, Rus.*
Diazepam (p.986·3).

Reliv
Note. This name is used for preparations of different composition.
Meprofarm, Indon.
Thioctic acid (p.2400·2); curcuminoid (p.1473·2); vitamin B substances; phyllanthus niruri.
Liver disorders.

Recip, Swed.
Paracetamol (p.108·1).
Fever; pain.

Relivan *Novell, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour.

Reliveran *Novartis, Arg.*
Metoclopramide (p.1747·3).
Gastro-intestinal motility disorders; gastro-oesophageal reflux; gastrointestinal investigations; nausea and vomiting.

Relivora Komplex *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Relmus *Sanofi-Aventis, Port.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; skeletal muscle spasticity.

Relmus Compositum *Sanofi Synthelabo, Port.†.*
Thiocolchicoside (p.1898·2); aescin (p.2248·2).
Inflammation; musculoskeletal, joint, and soft-tissue injury; oedema; phlebitis; thrombophlebitis.

Relokap *Yeni, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Relova *Meda, Switz.*
Diclofenac sodium (p.44·3).
Gout; inflammation; pain.

Reloxyl
Note. This name is used for preparations of different composition.
RDC, Ital.
Benzoyl peroxide (p.1590·2).
Acne; skin disinfection.

Cheminova, Spain†.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Reloxyl Mucolitico *Cheminova, Spain†.*
Amoxicillin trihydrate (p.202·2); guaifenesin (p.1561·3).
Respiratory-tract infections.

Relpax *Pfizer, Austria; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Ital.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA.*
Eletriptan hydrobromide (p.619·3).
Migraine.

Relsed *Polfa Warszawa, Pol.*
Diazepam (p.986·3).
Convulsions; epilepsy; premedication; skeletal muscle spasm.

Reluri *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Relvene *Expanscience, Fr.*
Oxerutins (p.2304·3).
Chronic venous insufficiency.

Relyomycin *Relyo, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Relyovix *Relyo, Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Rem *Chobet, Arg.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedative.

Remafen *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Remakrim *Medikon, Indon.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2); methyl nicotinate (p.85·3).
Musculoskeletal and joint pain; neuralgia.

Remapro *Mersifarma, Indon.*
Ketoprofen (p.73·1).
Gout; musculoskeletal and joint disorders.

Remasal *Medikon, Indon.*
Aluminium aspirin (p.19·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Rheumatic disorders.

Rematof *Bernofarm, Indon.*
Ketoprofen (p.73·1).
Gout; musculoskeletal and joint disorders.

Remdue *Biomedica, Ital.*
Flurazepam dihydrochloride (p.999·1).
Insomnia.

Remecon *Remexa, Mex.*
Ketoconazole (p.539·1).
Fungal skin infections.

Remedacen *Aventis, Ger.†.*
Dihydrocodeine polistirex (p.48·3).
Coughs.

Remedeine *Napp, UK.*
Paracetamol (p.108·1); dihydrocodeine tartrate (p.48·1).
Pain.

Remederm
Note. This name is used for preparations of different composition.
Widmer, Ger.
⊗ Urea (p.1620·2); vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3); dexpanthenol (p.2362·1).
Skin disorders.

Widmer, Philipp.
⊗ Vitamin A (p.1971·2); vitamin E (p.1992·2); panthenol (p.2362·1); urea (p.1620·2); biostimulines.
Dry skin.

Remederm HC *Widmer, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Remedol *Remedica, Singapore.*
Paracetamol (p.108·1).
Fever; pain.

Remeflin *Recordati, Ital.*
Dimefline hydrochloride (p.2155·1).
Respiratory and circulatory disorders.

Remegel
Note. This name is used for preparations of different composition.
Seton, Neth.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Dyspepsia; heartburn.

SSL, UK.
Calcium carbonate (p.1714·1).
Gastric hyperacidity.

Remegel Wind Relief *SSL, UK.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Dyspepsia; flatulence; heartburn.

Remena *Remedina, Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Remens
Note. This name is used for preparations of different composition.
Svizera, India.
Progesterone (p.2125·1).
Progesterone deficiency.

Bittner, Austr.; Bittner, Rus.
Homoeopathic preparation.

Remergil *Organon, Ger.*
Mirtazapine (p.409·2).
Depression.

Remergon *Organon, Belg.*
Mirtazapine (p.409·2).
Depression.

Remeron *Organon, Arg.; Organon, Austral.; Organon, Austria; Organon, Braz.; Organon, Canad.; Organon, Cz.; Organon, Denm.; Organon, Fin.; Organon (Οργανον), Gr.; Organon, Hong Kong; Organon, Hung.; Organon, Indon.; Organon, Israel; Organon, Ital.; Organon, Malaysia; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Philipp.; Organon, Pol.; Organon, Port.; Organon, Rus.†; Donmed, S.Afr.; Organon, Singapore; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.; Organon, USA; Organon, Venez.*
Mirtazapine (p.409·2).
Depression.

Remestan *Wyeth Lederle, Austria†; Valeant, Ger.*
Temazepam (p.1030·1).
Sleep disorders.

Remestyp *Ferring, Cz.; Ferring, Pol.; Ferring, Rus.†.*
Terlipressin (p.2395·3).
Haemorrhage.

Remethan
Remedica, Hong Kong; Remedica, Malaysia.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Remedica, Singapore†; Remedica, Thai.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Remexal *Permamed, Switz.*
Lauromacrogol 600 (p.1916·1); dimethyl sulfoxide (p.2022·1); glycol salicylate (p.62·3); dexpanthenol (p.2362·1); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Remezine *Remek, Gr.*
Cetirizine (p.571·1).
Allergic disorders.

Remicade *Schering-Plough, Arg.†; Schering-Plough, Austral.; Schering-Plough, Belg.; Mantecorp, Braz.; Schering, Canad.; Schering-Plough, Chile; Centocor, Cz.; Centocor, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Janssen, Hong Kong; Centocor, Hung.; Tanabe, Indon.; Schering-Plough, Irl.; Centocor, Israel; Schering-Plough, Ital.; Tanabe, Jpn; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, NZ; Centocor, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Centocor, Pol.; Schering-Plough, Port.; Centocor, Rus.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Centocor, USA; Schering-Plough, Venez.*
Infliximab (p.69·3).
Ankylosing spondylitis; Crohn's disease; psoriasis; psoriatic arthritis; rheumatoid arthritis; ulcerative colitis.

Remicaine *Adcock Ingram, S.Afr.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Remicalcin + D_3 *Schaper & Brummer, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Remicard *Adcock Ingram, S.Afr.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Remicit *Richmond, Arg.*
⊗ Remifentanil hydrochloride (p.120·1).
Analgesia in anaesthesia.

Remicut *Kowa, Jpn.*
Emedastine fumarate (p.579·2).
Hypersensitivity reactions.

Remid *TAD, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Remiderm *Elvetium, Arg.†.*
Centella (p.1592·3).

Remidex *AstraZeneca, Port.*
⊗ Anastrozole (p.681·2).

Remidol *Farmasierra, Spain†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Remidon *Deva, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Remifemin *Schaper & Brummer, Ger.; Phytotec, Hung.; Merck, Indon.; Merck, Malaysia; Merck, Philipp.; Schaper & Brummer, Pol.; Schaper & Brummer, Singapore; Farmasierra, Spain; Schaper & Brummer, Thai.*
Cimicifuga (p.2282·1).
Menopausal disorders; menstrual disorders.

Remifemin plus *Europharm, Austria; Schaper & Brummer, Ger.*
St John's wort (p.422·3); cimicifuga (p.2282·1).
Menopausal disorders; menstrual disorders.

Remifemin Plus *Phytotec, Hung.*
St John's wort (p.422·3); cimicifuga (p.2282·1).
Menopausal disorders.

Remik *Olinka, Neth.†.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Remikin *Remedina, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Remilev *Ache, Braz.*
Valerian (p.2410·1); lupulus (p.2335·2).

Reminal *Leti, Venez.*
Enalapril maleate (p.1276·1).
Hypertension.

Reminalet *Leti, Venez.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Reminyl *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Shire, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.†; Janssen-Cilag, Port.; Janssen, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Shire, UK.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Remiprostan uno *Schaper & Brummer, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Remisan *Vir, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Remisan Mucolitico *Vir, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Remisil *BioSaude, Port.*
Piroxicam (p.117·3).
Arthroses; peri-articular disorders.

Remisol *Degorts, Mex.*
Methocarbamol (p.1897·3).
Skeletal muscle spasm.

Remisol-Plus *Degorts, Mex.*
Methocarbamol (p.1897·3); aspirin (p.20·3).
Musculoskeletal pain.

Remitex *Bago, Chile.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Remitex D *Bago, Chile.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Remizeral *Raffo, Arg.*
Rivastigmine (p.369·2).
Alzheimer's disease.

RE-186-MM-1 *CIS, Cz.*
Rhenium-186 (p.2055·2) colloidal sulfide.
Joint disorders.

Remnos *DDSA Pharmaceuticals, UK.*
Nitrazepam (p.1011·2).
Insomnia.

Remodil *Remedica, Singapore†.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea.

Remodulin *Orphan, Austral.; Andromaco, Chile; United Therapeutics, Cz.; Bioprojet, Fr.; Galenica, Gr.; United Therapeutics, Israel; Ferrer, Port.; Opopharma, Switz.; United Therapeutics, USA.*
Treprostinil sodium (p.1417·1).
Pulmonary hypertension.

Remontal *Lesvi, Spain.*
Nimodipine (p.1357·2).
Cognitive impairment in the elderly; neurological deficit following subarachnoid haemorrhage.

Remood *Gedeon Richter, Cz.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Remopain *Dexa, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Remora *Nobel, Turk.*
Roxithromycin (p.331·1).
Bacterial infections.

Remotil *Azevedos, Port.*
Domperidone (p.1726·2).
Aid in gastrointestinal examination; dyspepsia; nausea; vomiting.

Remotiv *Bayer, Arg.†; Flordis, Austral.; Torrex, Austria; Ache, Braz.; Bayer, Chile†; Ewopharma, Cz.; Madaus, Ger.; Phytotec, Hung.; Zeller, Israel; Abbott, Mex.; Ewopharma, Pol.; Knoll, S.Afr.†; Zeller, Switz.*
St John's wort (p.422·3).
Anxiety; depression; insomnia; mood disorders; stress.

Remotive *Biofutura, Ital.*
St John's wort (p.422·3).
Depression.

Remotrox *Pharmaceutical Enterprises, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); dried aluminium hydroxide gel (p.1706·2); light magnesium oxide (p.1744·1).
Gastrointestinal disorders.

Remov *Piam, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Remove *Smith & Nephew, Austral.*
Dipropylene glycol methyl ether.
Adhesive remover.

Removil *Liferpal, Mex.*
⊗ Ambroxol (p.1550·3); salbutamol (p.1131·2).
Respiratory-tract disorders.

Remoxil *Ulagay, Turk.*
Amoxicillin sodium (p.202·2).
Bacterial infections.

Remular-S *International Ethical, USA.*
Chlorzoxazone (p.1894·3).
Musculoskeletal pain.

Remy *Sella, Ital.*
Camphor (p.2273·2); ethyl salicylate (p.52·1); menthol (p.2340·1); capsicum oleoresin (p.2276·2).
Rheumatism.

Remycin
Remedica, Hong Kong†.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Remedica, Singapore†.
Doxycycline (p.267·1).
Bacterial infections.

Ren *Yung Shin, Hong Kong.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint and peri-articular disorders; pain.

Rena *Pharmaland, Thai.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Muscle pain; skeletal muscle spasm.

Renabetic *Fahrenheit, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Renabrazin *Fahrenheit, Indon.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Renacalcio *Biocontrol, Arg.*
Calcium carbonate (p.1714·1).
Calcium supplement; hypocalcaemia; osteoporosis.

Renacardon *Fahrenheit, Indon.*
Enalapril maleate (p.1276·1).
Hypertension.

Renacenz *Pharmavita, Chile.*
Peptide extract (Cerebrolysin) (p.2337·3).
Dementia.

Renacidin
Note. This name is used for preparations of different composition.
HLB, Arg.
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Guardian, USA.
Anhydrous citric acid (p.2284·1); gluconolactone (p.2313·1); magnesium carbonate (p.1743·1).
Renal calculi.

Renacor *Dieckmann, Ger.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renadinac *Fahrenheit, Indon.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Renafit *Ikapharmindo, Indon.*
Preparation for enteral nutrition (p.1922·1).
Renal insufficiency.

Renagas *Fahrenheit, Indon.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Nocturnal enuresis; smooth muscle spasm.

Renagel *Genzyme, Austria; Genzyme, Belg.; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hong Kong; Kirin, Hong Kong; Genzyme, Hung.; Genzyme, Irl.; Genzyme, Israel; Genzyme, Ital.; Chugai, Jpn; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Genzyme, Spain; Genzyme, Swed.; Genzyme, Switz.; Genzyme, Turk.; Genzyme, UK; Genzyme, USA.*
Sevelamer hydrochloride (p.1462·1).
Hyperphosphataemia in haemodialysis patients.

Renal Caps *Cypress, USA.*
Multivitamin preparation (p.1922·1).

Renal Care *Abbott, Ital.*
Preparation for enteral nutrition in renal failure (p.1922·1).

Renalapril *Neo Quimica, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Renamel *Clonmel, Irl.†.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; nocturnal enuresis; unstable bladder.

Renamid *Fahrenheit, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Renamil *Kora, UK.*
Preparation for enteral nutrition in renal failure (p.1922·1).

RenAmin *Clintec, USA.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in renal impairment.

Renamoca *Fahrenheit, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Renapepsa *Fahrenheit, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Renapril *Meditop, Hung.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Renapril Plus *Meditop, Hung.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renapro *Kora, UK.*
Protein supplement in dialysis and hypoproteinaemia (p.1922·1).

Renapur *Schering-Plough, Swed.*
Anhydrous potassium citrate (p.1673·2); anhydrous sodium citrate (p.1673·3); anhydrous citric acid (p.2284·1).
Renal calculi.

Renaquil *Fahrenheit, Indon.*
Lorazepam (p.1004·1).
Anxiety; premedication.

Renase *Pharmaland, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hepatic cirrhosis with ascites and oedema; hypertension; oedema.

Renasistin *Fahrenheit, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Renatabs *Hawthorn, USA.*
Vitamin preparation (p.1922·1).
Dietary supplement.

Renatabs with Iron *Hawthorn, USA.*
Yellow tablets, vitamins (p.1922·1); red tablets, iron carbonyl (p.1950·3).
Dietary supplement.

Renatac *Fahrenheit, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Renaton *Korea United, Singapore†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Renator *Fahrenheit, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Renatrim *Solvang, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Rena-Vite *Cypress, USA.*
Vitamin B substances; vitamin C (p.1922·1).

Renax
Note. This name is used for preparations of different composition.
Remedica, Hong Kong.
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Interbat, Indon.
Sericocalyx folium; java tea (p.2328·2); sonchus arvensis folium; plantain (p.2369·3).
Renal calculi.

Everett, USA.
Multivitamin and mineral preparation in renal failure (p.1922·1).

Renaxid *Amuchina, Ital.*
Peracetic acid (p.1655·2).
Haemodialysis equipment disinfection.

Renbiocid *Ist. Chim. Inter., Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Rencef *EciFarma, Chile†.*
Lactulose (p.1738·2).
Bowel evacuation; constipation; hepatic encephalopathy.

Rendapid *Bernofarm, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Rendells *Prisfar, Port.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Rendells Plus *Rendell, NZ†.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Rendetil *Biotecnoquimica, Venez.*
Passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Rendimax *Farmo Quimica, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Renedil *Sanofi-Aventis, Belg.; Aventis, Canad.; Aventis, Neth.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Re/Neph *Pisa, Mex.†.*
Nutritional supplement in renal failure (p.1922·1).

Renese *Pfizer, Belg.†; Pfizer, USA†.*
⊗ Polythiazide (p.1373·3).
Hypertension; oedema.

Renese R *Pfizer, USA†.*
⊗ Polythiazide (p.1373·3); reserpine (p.1387·3).
Hypertension.

Reneuron *Juste, Spain.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Reneuu Invisible Glove *Hoe, Malaysia†.*
Barrier cream.

Renezide *Pharmacare, S.Afr.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Renfort *Pasteur, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Renicin *Teva, Hung.; Lek, Pol.*
Roxithromycin (p.331·1).
Bacterial infections.

Renidac *Tecnofarma, Mex.*
Sulindac (p.126·3).
Inflammation.

Renidur *MSD, Port.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renilon *Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.; Nutricia Clinical, UK.*
Preparation for enteral nutrition (p.1922·1).
Renal impairment.

Renipress *Cazi, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Renipril *APS, Port.†; Farmstandart, Rus.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Renipril HT *Farmstandart, Rus.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renipril Plus *APS, Port.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renistad *Stada, Austria.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Renitec
MSD, Arg.; MSD, Austral.; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Philipp.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Thai.; MSD, Turk.; MSD, Venez.
Enalapril maleate (p.1276·1).
Angina pectoris; heart failure; hypertension; ischaemic heart disease; myocardial infarction; unstable angina.

MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Norw.; MSD, Swed.
Enalapril maleate (p.1276·1) or enalaprilat (p.1276·2).
Heart failure; hypertension; left ventricular dysfunction.

MSD, Spain.
Enalapril (p.1276·1) or enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Renitec Comp *MSD, Fin.; MSD, Norw.; MSD, Swed.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renitec Plus *MSD, Austral.; MSD, Austria; MSD, Fin.; MSD, Hung.; MSD, Neth.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Renitecmax *MSD, Spain.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Reniten *MSD, Switz.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Reniten Plus *MSD, Switz.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Rennie
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.; Bayer, Austria; Bayer, Belg.; Roche, Belg.; Roche, Braz.†; Bayer, Cz.; Bayer, Fin.; Bayer, Fr.; Bayer, Ger.; Roche Nicholas, Israel; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Bayer Consumer, Rus.; Bayer, S.Afr.; Bayer, Singapore; Bayer, Spain; Roche, Swed.; Bayer, Switz.; Roche, Turk.; Roche Consumer, UK.
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Formerly known as Digestif Rennie in *S.Afr.*
Antacid; calcium supplement; dyspepsia; flatulence; gastric hyperacidity; gastric pain; heartburn; pyrosis.

Bayer Consumer, Arg.
Oral liquid: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); sodium alginate (p.2141·1).
Dyspepsia; gastro-oesophageal reflux.

Bayer Consumer, Arg.
Tablets: Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dyspepsia.

Rennie Antacidum *Bayer, Hung.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; heartburn.

Rennie Chewable Tablets *Bayer, Irl.*
Calcium carbonate (p.1714·1).
Formerly known as Rennie Rap-Eze.
Gastric hyperacidity; heartburn.

Rennie Defarin *Roche Consumer, Ger.†.*
Calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1); simeticone (p.1770·2).
Gastrointestinal disorders with meteorism.

Rennie Deflatine *Bayer, Fr.; Bayer, Irl.; Bayer, Neth.; Bayer, Switz.; Roche Consumer, UK.*
Calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn; meteorism.

Rennie Digestif
Note. This name is used for preparations of different composition.
Kolassa, Austria.
Papain (p.2362·3); pancreatin (p.2360·1); calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dyspepsia; flatulence; gastric pain; heartburn; nausea and vomiting.

Bayer, Port.
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Dyspepsia; gastric hyperacidity.

Rennie Duo
Bayer, Austria; Bayer, Neth.; Bayer, Port.
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); alginic acid (p.2140·3) or sodium alginate (p.2141·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux.

Roche Consumer, Irl.†; Roche, Turk.; Roche Consumer, UK.
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1); sodium alginate (p.2141·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Rennie Peppermint *Bayer, Irl.*
Calcium carbonate (p.1714·1); magnesium carbonate (p.1743·1).
Gastric hyperacidity; heartburn.

Rennie Refluxine *Bayer, Neth.*
Calcium carbonate (p.1714·1); light magnesium carbonate (p.1743·1); sodium alginate (p.2141·1).
Gastric hyperacidity; gastro-oesophageal reflux.

Rennie Soft Chews *Roche Consumer, UK.*
Calcium carbonate (p.1714·1).
Dyspepsia; flatulence; heartburn.

Renob Blasen- und Nierentee *Pfleger, Ger.*
Birch leaf (p.2266·3); couch-grass rhizome (p.2288·2); solidago virgaurea (p.2391·1); ononis (p.2357·1); liquorice root (p.1740·3).
Urinary-tract disorders.

Renocil *Farma Lepori, Spain.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Renocis *CIS, Port.; Schering, UK.*
Technetium-99m succimer (p.2055·3).
Radionuclide imaging of the kidney.

Renodiol *Sanbe, Indon.*
⊗ Normethandrone (p.2123·1); methyloestradiol (p.2098·3).
Amenorrhoea.

Renofundina *Braun, Port.*
Calcium chloride; magnesium chloride; potassium chloride; sodium acetate; sodium chloride with or without glucose (p.1670·3).
Haemodialysis.

Renogen *Biomedis, Philipp.*
⊗ Epoetin alfa (p.1061·1).
Anaemia of renal failure; reduction of allogenic blood transfusion.

Renografin *Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Renolip *Remedina, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Reno-M *Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Renopen *Ativus, Braz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Renopress *Eversil, Braz.†.*
Enalapril (p.1276·1).
Hypertension.

Renorell *Sanorell, Ger.*
Homoeopathic preparation.

Renormax *Schering-Plough, Ital.; Italfarmaco, Spain.*
Spirapril hydrochloride (p.1399·3).
Hypertension.

Renotens *Ranbaxy, S.Afr.†.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Renotol *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Renova *Johnson & Johnson, Canad.; Janssen-Cilag, Malaysia†; Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.; Ortho Dermatological, USA.*
Tretinoin (p.1618·1).
Photoageing of the skin; pigmentation disorders.

Renovate *Forder, Arg.†.*
Salicylic acid (p.1612·2).

Renoxacin *SoSe, Ital.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Renpress *Novartis, Cz.; Valeant, Spain.*
Spirapril hydrochloride (p.1399·3).
Heart failure; hypertension.

Rentamine Pediatric *Major, USA.*
⊗ Phenylephrine tannate (p.1568·3); ephedrine tannate (p.1559·1); chlorphenamine tannate (p.572·2); pentoxyverine tannate (p.1567·3).
Coughs and cold symptoms.

Rentibloc *Rentschler, Cz.†; Shire, Ger.*
⊗ Sotalol hydrochloride (p.1398·2).
Angina pectoris; arrhythmias; essential tremor; hypertension; hyperthyroidism; myocardial infarction.

Rentilox *Pharma Line, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Rentop *Montpellier, Arg.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Rentrex *Umeda, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Rentylin *Rentschler, Cz.†; Shire, Ger.*
Pentoxifylline (p.1367·2).
Cerebral, peripheral, and ocular vascular disorders.

Renu *Bausch & Lomb, Austral.; Bausch & Lomb, Braz.†; Bausch & Lomb, Canad.; Chauvin, Fr.; Bausch & Lomb, NZ; Bausch & Lomb, USA.*
A range of solutions for soft contact lens care (p.1622·2).

Renu Enzymatic Cleaner *Bausch & Lomb, USA.*
Subtilisin A (p.2393·3) (p.1622·2).
Cleansing solution for soft contact lenses.

Renu Moistureloc *Chauvin, Fr.*
Cleansing and disinfection solution for soft contact lenses (p.1622·2).

Renu Multiplus *Bausch & Lomb, UK.*
Solution for cleansing, disinfecting, and removal of protein from contact lenses (p.1622·2).

Renu Plus
Note. This name is used for preparations of different composition.
Bausch & Lomb, Braz.†.
Cleaning solution for contact lenses (p.1622·2).

Bausch & Lomb, Mex.
Povidone (p.2146·1)(p.1622·2).
Lubricating solution for contact lenses.

Ren-Ur *Lafedar, Arg.*
⊗ Hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Renusor *Soria Natural, Spain†.*
Corn silk (p.2288·1); couch-grass (p.2288·2); betula alba (p.2266·3); solidago (p.2391·1).
Fluid retention.

Renutryl *Germania, Austria.*
Preparation for enteral nutrition (p.1922·1).

Renutryl 500 *Nestle, Fr.*
Nutritional supplement (p.1922·1).

Renvela *Genzyme, USA.*
Sevelamer carbonate (p.1462·1).
Hyperphosphataemia in chronic renal failure.

Renvol *Otto, Indon.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Renxamin *Kalbe, Indon.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Reocol *Also, Ital.†.*
Tartaric acid; sodium bicarbonate (p.1673·2); anhydrous citric acid; magnesium sulfate (p.1679·3).
Constipation; dyspepsia.

Reodyn *Orion, Fin.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Reoferol *Zimaia, Port.*
Tocoferil nicotinate (p.1415·1).

Reoflen *Novis, Gr.*
Triflusal (p.1418·3).
Thrombosis prophylaxis.

Reoflus *Boniscontro & Gazzone, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Reolase *Difass, Ital.*
Telmesteine (p.1573·3).
Respiratory-tract disorders.

Reolin *Hochland, Israel.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous mucus.

Reomax *Pfizer, Ital.*
⊗ Etacrynic acid (p.1283·1) or sodium etacrynate (p.1283·2).
Oedema.

Reomucil *DOC, Ital.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

ReoPro *Lilly, Arg.†; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Centocor, Cz.; Centocor, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, India; Lilly, Irl.; Centocor, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Centocor, Neth.; Centocor, Norw.; Centocor, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, UK; Centocor, USA; Lilly, USA.*
Abciximab (p.1192·2).
Myocardial infarction; prevention of ischaemic cardiac complications during percutaneous coronary interventions; unstable angina.

Reosan *Serral, Mex.*
Meloxicam (p.80·3).
Inflammation.

Reosil *Cafar, Venez.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Reotal *Kalbe, Indon.*
Pentoxifylline (p.1367·2).
Intermittent claudication.

Reotan *Medicus, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Repalyte *Aventis, Austral.; DHA, Malaysia; DHA, Singapore.*
Sodium chloride; potassium chloride; sodium acid citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Repan *Everett, USA.*
Butalbital (p.967·2); caffeine (p.1116·3); paracetamol (p.108·1).
Pain.

Repan CF *Everett, USA†.*
Paracetamol (p.108·1); butalbital (p.967·2).
Pain.

Repanidal *Leciva, Cz.†.*
Tropesin.
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Reparcillin *New Research, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Reparex *Gynopharm, Chile.*
Vitamin E; selenium (p.1922·1).
Antoxidant preparation.

Reparil
Note. This name is used for preparations of different composition.
Madaus, Cz.; Madaus, Pol.
Aescin (p.2248·2).
Compression spinal cord nerves; haematoma; inflammation; oedema; vascular disorders; venous insufficiency.

Madaus, Austria; Nycomed, Braz.; Madaus, Thai.†.
Injection: Sodium aescinate (p.2248·2).
Back pain; inflammation; oedema; vascular disorders.

Madaus, Austria; Madaus, Belg.; Nycomed, Braz.; Madaus, Ger.; Madaus, Hong Kong; Madaus, Ital.; Madaus, Switz.†; Madaus, Thai.
Tablets: Aescin (p.2248·2).
Capillary fragility; haemorrhoids; inflammation; oedema; pain; postconcussional headache; tenosynovitis; thrombophlebitis; varicose veins; vascular disorders; venous insufficiency.

Madaus, Austria; Nycomed, Braz.; Altana Madaus, S.Afr.; Madaus, Thai.
Topical gel: Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Haematomas; inflammation; muscle and joint pain; soft-tissue injury; sprains; tenosynovitis; thrombophlebitis; varicose veins; vascular disorders; venous insufficiency.

Madaus, Belg.; Madaus, Fr.; Madaus, Hong Kong; Madaus, Switz.
Topical gel: Aescin (p.2248·2); sodium aescin polysulfate (p.2248·2); diethylamine salicylate (p.47·2).
Cicatrisation; inflammation; oedema; soft-tissue injury; thrombophlebitis; vascular disorders; venous insufficiency.

Madaus, Ital.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); diethylamine salicylate (p.47·2).
Soft-tissue disorders.

Nycomed, Braz.
Topical spray: Aescin (p.2248·2); sodium aescin polysulfate (p.2248·2); diethylamine salicylate (p.47·2).
Haemorrhoids; inflammation; soft-tissue injury; venous insufficiency.

Reparil N *Madaus, Hung.; Madaus, Pol.; Abdi, Turk.*
Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Haematoma; musculoskeletal and joint pain; neuralgia; oedema; soft-tissue injury; venous insufficiency.

Reparil-Gel N *Madaus, Cz.; Madaus, Ger.*
Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Inflammation; soft-tissue disorders.

Repariven *Bayer, Chile.*
Aescin (p.2248·2); a heparinoid (p.1305·2); diethylamine salicylate (p.47·2).
Phlebitis; soft-tissue injury; varices.

Reparon *EGIS, Hung.*
Escherichia coli; phenol (p.1656·1).
Anorectal disorders.

Repasma *Lennon, S.Afr.*
⊗ Amobarbital (p.961·3); aminophylline (p.1114·2); ephedrine hydrochloride (p.1558·2).
Asthma.

RepaVen *Madaus, Ital.†.*
Aesculus (p.2248·2); melilot (p.2339·2); rutoside (p.2305·1).
Oedema; venous insufficiency.

Rep-Cartil *Farmoterapia, Arg.*
Collagen (p.2286·1); cartilage (p.2277·3).
Dietary supplement.

Repelente Rep
Note. This name is used for preparations of different composition.
Aulo Gelio, Arg.
Cream; lotion: Citronella oil (p.2284·2).
Insect repellent.

Aulo Gelio, Arg.
Topical spray: Citronella oil (p.2284·2); jojoba oil.
Insect repellent.

Repelex *Sanitas, Chile.*
Compound 5734.
Insect repellent.

Repeltin *Pierre Fabre, Ger.†.*
Alimemazine (p.566·3).
Bronchial asthma or asthma-like complaints; pruritus.

Repentil
Note. This name is used for preparations of different composition.
Raffo, Arg.†.
Melatonin (p.2338·3).
Regulation of circadian rhythm.

Nolver, Venez.
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Repervit *IDI, Ital.†.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Repevax *Aventis Pasteur, Austria; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Port.; Aventis Pasteur, UK.*
A diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Repha Orphon *Repha, Ger.*
Java tea (p.2328·2).
Gout; rheumatism; urinary-tract disorders.

Rephalgin *Repha, Ger.*
Homoeopathic preparation.

Rephalysin C *Repha, Ger.*
Escherichia coli.
Gastrointestinal disorders.

Repha-Os *Repha, Ger.*
Tormentil root (p.2403·2); rhatany root (p.2378·3); myrrh (p.2349·2); anise oil (p.2258·2); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); clove oil (p.2285·1); menthol (p.2340·1).
Mouth and throat disorders.

Rephastasan *Repha, Ger.†.*
Homoeopathic preparation.

Repik Lekarsky *Slovakofarma, Cz.†.*
Agrimony (p.2249·2).
Gastrointestinal disorders; hepato-biliary disorders; inflammatory mouth disorders; inflammatory skin disorders.

Repikovy Caj, Repikova Nat *Megafyt-R, Cz.†.*
Agrimony (p.2249·2).
Diarrhoea; gastrointestinal inflammation; inflammatory disorders of the skin and mucous membranes; wounds.

Repilysin *Roche, Gr.†.*
Reteplase (p.1388·1).
Myocardial infarction.

Repin B_6 *Biopharm, Rus.*
Isoniazid (p.288·1); rifampicin (p.325·3); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Repisan *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Repithel *Mundipharma, Ger.*
Carbomer; phosphatidyl choline (p.2367·1); povidone-iodine (p.1659·2).
Wounds.

Repivate *Xeragen, S.Afr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Replagal *Orphan, Austral.; TKT, Austria; TKT, Belg.; Paladin, Canad.; Shire, Cz.; TKT, Denm.; TKT, Fr.; TKT, Ger.; TKT, Gr.; Shire, Hung.; TKT, Israel; TKT, Ital.; St Ives, NZ; TKT, Neth.; Shire, Port.; TKT, Spain; Drac, Switz.; Shire, UK.*
Agalsidase alfa (p.2252·3).
Fabry disease.

Replasyn *TRB, Arg.†.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Replavit *WN, Canad.*
Vitamin preparation (p.1922·1).

Replena *Abbott, Braz.*
Preparation for enteral nutrition (p.1922·1).

Replenate *BPL, UK.*
A factor VIII preparation (p.1067·1).
Formerly known as 8SM.
Haemophilia A.

Replenine *Paylos, Arg.†; BPL-Meizler, Braz.†; Galenica, Gr.; BPL, Israel; Bio Products, Malaysia; Landsteiner, Mex.; BPL, Singapore; Sodhan, Turk.; BPL, UK.*
A factor IX preparation (p.1068·3).
Haemophilia B.

Replens
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Austral.; Wolfs, Belg.†; Wellspring, Canad.; Mipharm, Ital.; Ipsen, Spain†; Campus, Swed.; Warner-Lambert, USA.
Polycarbophil (p.1763·3).
Vaginal dryness.

Tradiphar, Fr.; Teva, Israel; Adcock Ingram, S.Afr.; Vifor, Switz.; Anglian, UK.
Vaginal lubricant.
Vaginal dryness; vaginal irritation.

Replete *Clintec, USA.*
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Replicare *Smith & Nephew Healthcare, UK.*
Hydrocolloid dressing.
Burns; ulcers; wounds.

Repligen *Panalab, Arg.*
Metronidazole (p.837·1).
Rosacea.

Repliva *Ther-Rx, USA.*
21 Tablets, ferrous glycinate (p.1939·1); ferrous fumarate (p.1938·3); vitamin B ; vitamin C (p.1922·1); 7 tablets, inert.
Succinic acid is included in the active tablets to increase the absorption and availability of iron.
Iron deficiency.

Repocal *Sigma, Braz.*
Calcium amino acid chelate.
Calcium supplement.

Repoflor *Legrand, Braz.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea; restoration of intestinal flora.

Repogen *Libbs, Braz.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Repogen Ciclo *Libbs, Braz.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Repogen Conti *Libbs, Braz.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Repopil *Legrand, Braz.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).

Reposans *Wesley, USA†.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety.

Reposcal D *EMS, Braz.*
Calcium carbonate (p.1714·1); vitamin D (p.1986·1).
Calcium and vitamin D supplement.

Repositol *Astellas, Ital.*
Barrier preparation.

Reposo-Mono *Medgenix, Belg.†.*
Meprobamate (p.1006·2).
Insomnia.

Reposton *Provit, Mex.*
Liver extract (p.2337·3).
Anaemias.

Repotin *Bioclones, S.Afr.*
⊗ Epoetin (p.1061·1).
Anaemias; autologous blood transfusions.

Repovit *Sigma, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Repowine mono *Truw, Ger.†.*
Scoparium (p.2384·2).
Cardiac disorders.

Repozal *Gunsa, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Repreve *GSK, Austral.*
Ropinirole (p.816·2).
Restless legs syndrome.

Reprexain *Watson, USA.*
Hydrocodone tartrate (p.63·1); ibuprofen (p.64·2).
Pain.

Repronex *Ferring, Canad.; Ferring, USA.*
⊗ Menotrophin (p.2109·3).
Female infertility.

Reprost *Andromaco, Chile†.*
Naproxen (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Reprostom *Fahrenheit, Indon.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Reproven N *Hanosan, Ger.*
Homoeopathic preparation.

Reptilase *Disperga, Austria; Pharmadeveloppement, Fr.†; Troikaa, India; Neves, Port.†.*
Haemocoagulase (p.1056·1).
Haemorrhage.

Repursan *Biokanol, Ger.*
Muira puama; kola; vitamins (p.1922·1).
Tonic.

Requiesan *Klein, Ger.*
Eschscholtzia californica; avena (p.2262·1).
Sleep disorders.

Requip *GSK, Arg.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; Beecham, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; SmithKline Beecham, USA.*
Ropinirole hydrochloride (p.816·1).
Parkinsonism; restless legs syndrome.

Res Vin *Geymonat, Ital.*
Vitamins; mineral; rutoside; proanthyocyanidins; resveratrol (p.1922·1).
Circulatory disorders; nutritional supplement.

Resaca *Biotenk, Arg.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Digestive disorders; pain.

Resakal *Puerto Galiano, Spain†.*
Paracetamol (p.108·1).
Fever; pain.

Resalt *Aspen, S.Afr.†.*
Sodium chloride; potassium chloride; glucose; sodium bicarbonate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Resapin *Soho, Indon.*
Reserpine (p.1387·3).
Hypertension.

Resata *Rafarm, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; topical corticosteroid.

Rescold *Klinger, Braz.†.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Rescon *Capellon, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Rescon-DM *Capellon, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Rescon-GG *Capellon, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Rescon-Jr *Capellon, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Rescon-MX *Capellon, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Formerly contained pseudoephedrine hydrochloride, chlorphenamine maleate, and hyoscine methonitrate.
Upper respiratory-tract disorders.

Rescriptor *Pfizer, Austral.; Pfizer, Canad.; Pfizer, Mex.†; Pharmacia Upjohn, USA.*
Delavirdine mesilate (p.869·3).
HIV infection.

RescueFlow *Biophausia, Denm.; Medifront, Fin.; Biophausia, Ger.†; Bioquest, Ger.†; Biophausia, Neth.; Biophausia, Norw.; Biophausia, Port.; Alliance, S.Afr.; Biophausia, Swed.; Vitaline, UK.*
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Hypovolaemic shock; plasma volume expansion.

Rescuesol *Pisa, Mex.†.*
⊗ Dextran 60 (p.1059·3) in sodium chloride.

Rescula *Novartis Ophthalmics, Arg.; Novartis, Austria; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis Ophthalmics, Hung.; Santen, Jpn; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis Ophthalmics, Singapore†; Novartis, Switz.†; Novartis, Thai.; Novartis Ophthalmics, USA†; Novartis, Venez.*
Unoprostone isopropyl (p.1886·3).
Glaucoma; ocular hypertension.

Rescuvolin *Nycomed, Austria; Teva, Belg.; Asta Oncologia, Braz.†; Nettopharma, Denm.†; Nycomed, Fin.†; Medac, Ger.; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Asta Medica, NZ†; Pharmachemie, Neth.; Nycomed, Norw.; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Singapore†; Nycomed, Swed.†; Pharmachemie, Thai.; Teva, Thai.; Er-Kim, Turk.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists; folic acid deficiency; megaloblastic anaemia; reduction of methotrexate toxicity.

Resdil *Pharma 3, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Resectal *Fresenius Kabi, Austria.*
⊗ Sorbitol (p.1965·1); mannitol (p.1330·2).
Bladder and prostate surgery.

Resectisol *Baxter, Turk.; Kendall McGaw, USA†.*
⊗ Mannitol (p.1330·2).
Bladder irrigation.

Reseptyl-Urea *Wagner, Hung.*
⊗ Chloroseptyl; urea (p.1620·2).
Burns; skin infections; wounds.

Reser *TO-Chemicals, Thai.*
⊗ Reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Resfenol *Hertz, Braz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Resfin *Jofrain, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Resflok *Sanbe, Indon.*
Sparfloxacin (p.332·1).
Bacterial infections of the respiratory tract.

Resfolin *Piam, Ital.†.*
Calcium folinate (p.1943·3).
Anaemias; antidote to folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Resfrineo *Neo Quimica, Braz.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold symptoms.

Resfry
Neo Quimica, Braz.
Syrup: Paracetamol (p.108·1); dexchlorpheniramine maleate (p.572·1); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Neo Quimica, Braz.
Tablets: Green tablets, paracetamol (p.108·1); dexchlorpheniramine maleate (p.572·1); caffeine (p.1116·3); yellow tablets, ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Resfryneo *Neo Quimica, Braz.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Influenza symptoms.

Resibant *Bago, Arg.*
Rimonabant (p.2380·3).

Resibelacta *Atral, Port.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Resibron *Ikapharmindo, Indon.*
Piracetam (p.368·2).
Cerebral trauma; chronic alcoholism; mental function impairment.

Resical *Fresenius Medical, Cz.; Fresenius Medical, Port.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Residex P55 *Agropharm, UK.*
Permethrin (p.2048·2).
Mosquito repellent for nets and clothing.

Resilar *Orion, Fin.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Resimatil *Sanofi Synthelabo, Ger.*
Primidone (p.503·2).
Epilepsy.

Resimida *Rowe-Fleming, Venez.†.*
⊗ Furosemide (p.1292·1).
Diuretic.

Resincalcio *Omedir, Arg.; Rubio, Spain; Rubio, Thai.; TTN, Thai.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Resincolestiramina *Rubio, Singapore†; Rubio, Spain; Rubio, Thai.; TTN, Thai.*
Colestyramine (p.1252·3).
Diarrhoea; hypercholesterolaemia; pruritus associated with biliary obstruction.

Resinsodio *Rubio, Singapore; Rubio, Spain; Rubio, Thai.; TTN, Thai.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Resistan *Truw, Ger.†.*
Homoeopathic preparation.

Resistan mono *Truw, Ger.*
Echinacea purpura (p.2298·1).
Immunostimulant.

Resistim *Motima, Fr.*
Lavender oil (p.2331·2); cinnamon oil (p.2283·2); eucalyptus oil (p.2301·2); savory oil (p.2394·3).
Cold symptoms.

Reskuin *Dankos, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Resma *UCB, Belg.*
Zafirlukast (p.1150·2).
Asthma.

Resmavil *Liferpal, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Resochin *Bayer, Austria; Bayer, Ger.; Bayer, India; Bayer, Indon.; Kern, Spain.*
Chloroquine phosphate (p.599·3).
Amoebiasis; connective tissue and collagen disorders; lupus erythematosus; malaria; protozoal infections; rheumatoid arthritis.

Resochina *BayHealth, Port.*
Chloroquine phosphate (p.599·3).
Amoebiasis; lupus erythematosus; malaria; rheumatoid arthritis.

Resodermil *Edol, Port.*
Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Resoferon *Novartis, Gr.; Novartis, Switz.†.*
Ferrous sulfate (p.1939·3).
Succinic acid may be included to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Resograf *Schering, Spain.*
Ferucarbotran (p.1478·1).
Contrast medium for magnetic resonance imaging of the liver.

Resol *Wyeth-Ayerst, USA.*
Glucose; sodium chloride; potassium citrate; citric acid; sodium phosphate; magnesium chloride; calcium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Resolutivo Regium *Uriach, Spain.*
Boldo (p.2267·2); chumbera; equisetum (p.2299·3); sideritide; rosemary (p.2381·2); cynodon; arenaria; melissa (p.2339·3).
Diuresis.

Resolve
Note. This name is used for preparations of different composition.
Ego, Malaysia; Ego, Singapore.
Miconazole nitrate (p.541·3).
Fungal and Gram-positive skin infections; fungal nail infections; fungal vaginal infections.

SSL, UK.
Paracetamol (p.108·1); anhydrous citric acid (p.2284·1); sodium bicarbonate (p.1673·2); potassium bicarbonate (p.1673·1); sodium carbonate anhydrous (p.2389·1); ascorbic acid (p.1983·3).
Dyspepsia; headache.

Ego, Austral.
Balm: Miconazole nitrate (p.541·3); bufexamac (p.28·3).
Fungal skin infections.

Ego, Austral.
Cream; powder; topical solution: Miconazole (p.541·2) or miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Resolve Extra *SSL, UK.*
Paracetamol (p.108·1); sodium bicarbonate (p.1673·2); caffeine (p.1116·3).
Dyspepsia; headache.

Resolve Plus *Ego, Austral.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Formerly known as Fungocort.
Fungal skin infections with inflammation.

Resolve Thrush *Ego, Austral.*
Miconazole nitrate (p.541·3).
Formerly known as Fungo.
Vulvovaginal candidiasis.

Resolve Tinea
Note. This name is used for preparations of different composition.
Ego, Austral.
Cream: Miconazole nitrate (p.541·3); phenethyl alcohol (p.1655·3).
Fungal skin infections.

Ego, Austral.
Topical powder: Miconazole nitrate (p.541·3); zinc oxide (p.1621·2).
Fungal skin infections.

Resolvebohm *Bohm, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Resolve/GP *Allergan, USA.*
Cleansing solution for hard and gas permeable contact lenses (p.1622·2).

Resonium *Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Winthrop, Port.; Sanofi Synthelabo, Swed.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Resonium A *Sanofi Synthelabo, Austral.; Sanofi Synthelabo, Austria; Sanofi Synthelabo, Ger.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi, Irl.†; Sanofi Synthelabo, Malaysia†; Aventis, NZ; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Pol.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, UK.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Resonium Calcium *Sanofi Synthelabo, Canad.; Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Swed.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Resorbane *Spirig, Switz.*
Cineole (p.2282·3); camphor (p.2273·2); niaouli oil (p.2351·3).
Respiratory-tract disorders.

Resorborina
Note. This name is used for preparations of different composition.
Rimafar, Spain.
Mouthwash: ⊗ Benzalkonium chloride (p.1629·1); dexamethasone (p.1526·1); resorcinol (p.1612·1); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Rimafar, Spain†.
Throat spray: ⊗ Benzalkonium chloride (p.1629·1); betamethasone valerate (p.1519·1); tetracaine hydrochloride (p.1871·3).
Mouth and throat disorders.

Resostyl *Lavipharm, Gr.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Resotyl *Drugtech, Chile.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome.

Resource *Novartis, Arg.†; Novartis Consumer, Austral.†; Novartis, Braz.; Novartis Nutrition, Canad.†; Novartis, Fin.; Novartis Nutrition, Fr.; Novartis Nutrition, Hong Kong; Novartis Consumer, Ital.; Novartis Consumer, Port.†; Novartis Nutrition, Singapore; Novartis Consumer, UK; Novartis Nutrition, USA.*
A range of preparations for enteral nutrition (p.1922·1).

Resource Benefiber
Note. This name is used for preparations of different composition.
Novartis Consumer, Ital.
Dietary fibre supplement (p.1712·3).
Novartis Consumer, UK.
Guar gum (p.442·3).
Nutritional supplement.

Resource Energy *Novartis Nutrition, Fr.*
Preparation for enteral nutrition (p.1922·1).
Formerly known as Resource Nutrigil.

Resource Gelificata *Novartis Consumer, Ital.*
Carrageenan (p.2142·3); xanthan gum (p.2147·2); guar gum (p.442·3).
Dysphagia.

Resource Prunogil *Novartis Nutrition, Fr.*
Dietary fibre supplement (p.1922·1).
Constipation.

Resource Rhubagil *Novartis Nutrition, Fr.*
Rhubarb (p.1768·3); black currant (p.2267·1).
Constipation.

Resource ThickenUp *Novartis, Irl.; Novartis Consumer, Ital.; Novartis, NZ; Novartis Consumer, UK.*
Nutritional supplement for thickening foods (p.1922·1).
Dysphagia.

Resovist *Schering, Austral.†; Schering, Austria; Schering, Belg.; Schering, Cz.; Schering, Denm.; Schering, Fin.†; Schering, Ger.; Schering, Gr.; Schering, Israel†; Schering, Ital.; Schering, Neth.; Schering, Norw.; Lusal, Port.; Schering, Spain; Schering, Swed.; Schering, Switz.*
Ferucarbotran (p.1478·1).
Contrast medium for magnetic resonance imaging of the liver.

Resoxym *ICN, Pol.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; otitis media; sinusitis.

Respacal *UCB, Belg.†.*
⊗ Tulobuterol hydrochloride (p.1150·1).
Bronchospasm.

Respa-DM *Respa, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Respa-GF *Respa, USA†.*
Guaifenesin (p.1561·3).

Respahist *Respa, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).

Respaire *Laser, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and cold symptoms; nasal congestion.

Respalis *Nestle, Fr.*
Preparation for enteral nutrition (p.1922·1).
Respiratory insufficiency.

Respalor *Mead Johnson Nutritionals, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).
Respiratory system disorders.

Respa-1st *Respa, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Respatona Chesty Cough & Nasal Congestion *Brauer, Austral.*
Homoeopathic preparation.

Respatona Dry Cough & Nasal Congestion *Brauer, Austral.*
Homoeopathic preparation.

Respatona Head Cold *Brauer, Austral.*
Homoeopathic preparation.

Respatona Nasal Spray Decongestant *Brauer, Austral.*
Homoeopathic preparation.

Respatona Sinus Relief *Brauer, Austral.*
Homoeopathic preparation.

Respatona Sore Throat *Brauer, Austral.*
Homoeopathic preparation.

Respax *Pfizer, Austral.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Respbid *Boehringer Ingelheim, USA†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Resperal *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2); dexchlorpheniramine maleate (p.572·1).
Cough; upper respiratory-tract disorders.

Resperal-DM *Cypress, USA.*
Brompheniramine maleate (p.569·2); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; upper respiratory-tract disorders.

Respexil *MSD, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Respibien *Cinfa, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Respibron *Andromaco, Chile.*
Oxolamine citrate (p.1567·1) or oxolamine phosphate (p.1567·1).
Coughs.

Respicil *Senosiain, Mex.*
Procaine benzylpenicillin (p.319·2); dipyrone (p.49·2).
Bacterial infections.

Respicilin *Haller, Braz.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Respicort *Mundipharma, Ger.†.*
⊗ Budesonide (p.1520·1).
Obstructive airways disease.

Respicur *Altana, Austria; Altana, Ital.*
Theophylline (p.1140·1).
Asthma; bronchospasm; obstructive airways disease.

Respidon *Torrent, Braz.; Torrent, India.*
Risperidone (p.1024·2).
Bipolar disorder; psychoses.

Respidual *Biogalenic, Venez.*
⊗ Ipratropium bromide (p.1124·1); fenoterol hydrobromide (p.1121·1).
Asthma.

Respifor *Nutricia Clinical, Fin.; Nutricia, Irl.; Nutricia, Ital.*
Preparation for enteral nutrition (p.1922·1).
Respiratory disorders.

RespiGam *Medimmune, USA.*
Respiratory syncytial virus immunoglobulins (p.2235·3).
Passive immunisation.

Respigen *Pacific, NZ.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma.

Respilene
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Fr.
Pholcodine (p.1570·2).
Coughs.
Columbia, Mex.†.
Zipeprol (p.1575·3).
Bronchitis; coughs.

Respimex *Pfizer, Arg.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic rhinitis; asthma.

Respimox *Wockhardt, India.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections.

Respinal *Metz, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Respinol *Pharmaceutical Enterprises, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Cold symptoms; rhinitis; sinusitis.

Respinol Compound *Pharmaceutical Enterprises, S.Afr.*
Pholcodine (p.1570·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Cold symptoms; coughs; rhinitis; sinusitis.

Respinorm *Unipharma, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Respiratory-tract disorders.

Respir *Schering-Plough, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Respirea *Dietaroma, Fr.*
Eucalyptus oil; siberian fir oil; peppermint oil; silvestris pine oil; turpentine oil; balsam fir oil; lavender oil.

Respiret *Klonal, Arg.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Respirex *Schering-Plough, Chile.*
Sodium chloride (p.1686·1).
Nasal cleansing.

Respiro *Altana, Ital.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Respirogutt *Bock, Ger.†.*
Homoeopathic preparation.

Respirol *Remedina, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Respiroma *Fournier SA, Spain.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Respisniffers *SA Druggists Self Med, S.Afr.*
Cineole (p.2282·3); pine oil (p.2368·2); chloroxylenol (p.1640·2); turpentine oil (p.2406·3); menthol (p.2340·1).
Bronchitis; cold symptoms; nasal congestion.

Respi-Tann G *Teamm, USA.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cough.

Resplant *Spitzner, Ger.†.*
Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Respocort *Laviphann, Gr.; 3M, NZ.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

Respolin
3M, Chile; 3M, Hong Kong; 3M, Malaysia†; 3M, NZ; 3M, Singapore†; 3M, Thai.†.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease.
Zuoz, Venez.†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Responsar *Bayer, Ital.†.*
Cyfluthrin (p.2039·2).
Insecticide.

Respontin *GSK, Norw.†; Allen & Hanburys, UK.*
Ipratropium bromide (p.1124·1).
Obstructive airways disease.

Resprax *Prodotti, Braz.*
Green tablets, salicylamide (p.121·2); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); yellow tablets, vitamin C (p.1983·3).
Aluminium hydroxide (p.1706·2) is included in the green tablets in an attempt to limit adverse effects on the gastrointestinal mucosa.
Cold and influenza symptoms.

Respreve *Pharmacia, Hong Kong†.*
⊗ Salbutamol (p.1131·2).
Bronchospasm.

Resprim *Alphapharm, Austral.; Teva, Israel; Alphapharm, Malaysia.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Resprin
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.
Paracetamol (p.108·1); carbinoxamine maleate (p.570·2); pentoxyverine citrate (p.1567·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.
Rice Steele, Irl.
Aspirin (p.20·3).
Fever; inflammation; pain.
Janssen-Cilag, Venez.
Paracetamol (p.108·1); pentoxyverine (p.1567·3); phenylephrine (p.1568·1); carbinoxamine (p.570·2).
Cold and influenza symptoms.

Ressital *Biofarma, Turk.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Rest-Aid *Overseas, India.*
Doxylamine succinate (p.578·2).
Nausea and vomiting of pregnancy.

Restal *SFD, Port.†.*
Oxidised glycerol triester.
Cicatrisation; cracked lips; dry skin.

Restameth-SR *Adcock Ingram, S.Afr.†.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Restandol *Organon, Denm.; Organon (Οργανον), Gr.; Organon, Irl.; Organon, UK.*
⊗ Testosterone undecylate (p.2130·2).
Androgen deficiency; aplastic anaemia; breast cancer; male hypogonadism; osteoporosis.

Restasis *Allergan, Arg.; Allergan, Braz.; Allergan, Chile; IFET (ΙΦΕΤ), Gr.; Allergan, Mex.; Allergan, Philipp.; Allergan, Thai.; Allergan, USA; Allergan, Venez.*
Ciclosporin (p.1822·2).
Dry eyes.

Restaslim *Restan, S.Afr.†.*
Phenylpropanolamine hydrochloride (p.1569·3).
Obesity.

Restaurene *Ivax, Arg.*
Sodium acexamate (p.2245·2).
Formerly contained chlorhexidine gluconate and sodium acexamate.
Skin lesions.

Restavit *Woods, Austral.*
Doxylamine succinate (p.578·2).
Insomnia.

Resteclin *Sarabhai Piramal, India.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Restelea *Elea, Arg.*
Risperidone (p.1024·2).
Schizophrenia.

Restex *Roche, Austria; Roche, Ger.*
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Restless legs syndrome.

Restful *Bros, Gr.*
Sulpiride (p.1028·3).
Psychoses.

Restin *Adcock Ingram, S.Afr.*
Valerian (p.2410·1); vitamin B substances (p.1922·1); ascorbic acid.
Restlessness; tension.

Restol *Laboratorios Chile, Chile.*
Domperidone (p.1726·2).
Aid in gastrointestinal investigation; nausea and vomiting; regurgitation in infants.

Restolax *EuroHealth, Philipp.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Restopon *Bros, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Restor *Sandoz, Indon.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Restorativ Glucosamine Muscle and Joint *Holista, Canad.*
Borage oil; boswellia; frankincense; camphor oil; devil's claw; evening primrose oil; glucosamine sulfate; grape seed oil; peppermint oil; rosemary oil (p.1922·1).
Musculoskeletal and joint pain.

Restore CalciCare *Hollister, Canad.*
Calcium sodium alginate (p.1058·1)(p.2141·1).
Wounds.

Restore ORS *Douglas, Austral.*
Glucose; sodium acid citrate; sodium chloride; potassium chloride (p.1672·2).
Diarrhoea; oral replacement therapy.

Restoril
Note. This name is used for preparations of different composition.
Oryx, Canad.; Novartis, USA.
Temazepam (p.1030·1).
Insomnia.
Silesia, Chile†.
Chlormezanone (p.968·3).
Skeletal muscle spasm.

Restovar *Organon, Cz.†; Organon, Swed.*
Lynestrenol (p.2112·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Restrical *Merck Medication Familiale, Fr.*
Liquid paraffin (p.2030·3).
Constipation.

Restructa forte ST *Fides, Ger.†.*
Homoeopathic preparation.

Restructa H *Heel, Neth.*
Homoeopathic preparation.

Restructa SN *Heel, Ger.*
Homoeopathic preparation.

Restwel *Adcock Ingram, S.Afr.*
Doxylamine succinate (p.578·2).
Insomnia.

Restyl *Cipla, India.*
Alprazolam (p.960·1).
Anxiety; panic disorders.

Restyl Forte *Cipla, India.*
Alprazolam (p.960·1); sertraline hydrochloride (p.421·3).
Mixed anxiety depressive states.

Restyl Plus *Cipla, India.*
Alprazolam (p.960·1); sertraline hydrochloride (p.421·3).
Mixed anxiety depressive states.

Restylane *Q-Med, Singapore†; Medicis, USA.*
Hyaluronic acid (p.2320·1).
Facial wrinkles and folds; lip enhancement; skin contour defects.

Resulax *AstraZeneca, Swed.*
Sorbitol (p.1965·1).
Bowel evacuation; constipation.

Resulin *Ist. Chim. Inter., Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Resurmide *IBI, Ital.*
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage.

Resvelife *Q-Med, Ital.†.*
Resveratrol (p.2378·2).
Skin irritation.

Resvica *Dexa, Indon.*
Grape (p.2316·3); garlic (p.2309·2).
Cardiac disorders; hyperlipidaemias.

Resyl *Novartis Consumer, Austria; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis, Swed.; Novartis Consumer, Switz.*
Guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Resyl DM *Novartis Consumer, Ital.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Resyl mit Codein *Novartis Consumer, Austria.*
Guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Resyl Plus *Novartis Consumer, Switz.*
Guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Retabolil *Gedeon Richter, Hung.; Gedeon Richter, Rus.*
⊗ Nandrolone decanoate (p.2118·2).
Anabolic; breast cancer; diabetic retinopathy; muscular dystrophy; osteoporosis.

Retabolin forte *Cimex, Switz.*
Vitamin B substances (p.1922·1).
Neuralgia; neuritis.

Retacillin compositum *Jenapharm, Ger.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2); benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Retacnyl *Galderma, Arg.; Galderma, Braz.†; Galderma, Chile; Galderma, Fr.; Galderma, Hong Kong†; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Thai.; Galderma, Venez.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders; photoageing of the skin.

Retacrit *Hospira, Cz.; Hospira, Port.; Hospira, UK.*
⊗ Epoetin zeta (p.1061·1).
Anaemias; autologous blood transfusion.

Retafer *Orion, Fin.; Orion, Malaysia.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Retafyllin *Orion, Fin.; Orion, Hung.; Orion, Malaysia; Orion, Singapore†; Orion, Thai.*
Theophylline (p.1140·1).
Obstructive airways disease.

Retalzem *Menarini, Hong Kong†.*
Diltiazem hydrochloride (p.1265·1).
Heart failure; hypertension; ischaemic heart disease.

Retamin *Roemmers Osmoph, Venez.*
Ranitidine hydrochloride (p.1766·1).
Gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Retan
Note. A similar name is used for preparations of different composition (see below).
Microsules, Arg.†.
Alprazolam (p.960·1).
Anxiety; panic disorder.

Re-Tann
Note. A similar name is used for preparations of different composition (see above).
Midlothian, USA.
Pentoxyverine tannate (p.1567·3); pseudoephedrine tannate (p.1572·1).
Cough.

Retaphyl *Kimia, Indon.*
Theophylline (p.1140·1).
Asthma.

Ret-A-Pres
Note. A similar name is used for preparations of different composition (see below).
Precimex, Mex.
Tretinoin (p.1618·1).
Acne; actinic keratosis; basal cell carcinoma; photodamaged skin; psoriasis; stretch marks.

Retapres
Note. A similar name is used for preparations of different composition (see above).
Biopharm, Rus.
⊗ Indapamide (p.1314·1).
Hypertension.

Retardex *Qualiphar, Belg.; Periproducts, UK.*
CloSYS II (p.1639·1).
Halitosis; oral hygiene.

Retardillin *Teva, Hung.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Retarpen
Note.This name is used for preparations of different composition.
Sandoz, Arg.; Sandoz, Austria; Sandoz, Cz.; Biochemie, Hung.†; Sandoz, Malaysia; Sandoz, Singapore.
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Septa, Spain.
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Retarpen Balsamico *Reig Jofre, Spain†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); cineole (p.2282·3); guaifenesin (p.1561·3).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Retarpen compositum *Sandoz, Austria.*
Benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2); benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Retarpen Mucolitico *Reig Jofre, Spain†.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1); bromhexine hydrochloride (p.1552·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Respiratory-tract infections.

Retavase *Biovail, Canad.; Boehringer Mannheim, USA.*
Reteplase (p.1388·1).
Myocardial infarction.

Retavit *CTI, Israel.*
Tretinoin (p.1618·1).
Acne.

Retebem *Pfizer, Arg.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Retef *AB-Consult, Austria.*
⊗ Hydrocortisone aceponate (p.1536·2).
Skin disorders.

Retemic *Apsen, Braz.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; urinary incontinence.

Retemicon *Panalab, Arg.*
Oxybutynin (p.2190·3).

Reten *TO-Chemicals, Thai.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Retencal *Megat, Venez.†.*
Nitrendipine (p.1358·2).
Hypertension.

Retens *Chiesi, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Retensin *Unison, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Retep *Hexa, Arg.*
⊗ Furosemide (p.1292·1).

Reteven *Nolver, Venez.*
Oxybutynin (p.2190·3).
Bladder hyperactivity.

Reticne *Cinetic, Arg.*
Tretinoin (p.1618·1).
Skin disorders.

Reticopen *Landson, Indon.*
Lutein (p.1954·3); lycopene; betacarotene; vitamin E; zinc; selenium; vitamin C; vitamin B (p.1922·1).
Age-related macular degeneration; cataract.

Reticulogen Fortificado *Lilly, Spain†.*
Cyanocobalamin (p.1980·2).
Vitamin B   deficiency.

Reticus *Euroderm, Ital.*
⊗ Desonide (p.1525·1).
Skin disorders.

Retigel-A *Gelpharma, Mex.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Retimax *Alcon Cusi, Spain.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Retin-A *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Braz.; Johnson & Johnson, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Cilag, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Cilag, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Ortho Dermatological, USA.*
Tretinoin (p.1618·1).
Acne; hyperpigmentation; keratinisation disorders; photoageing of the skin; wrinkles.

Retinalamin *Geropharm, Rus.*
Retina extract (bovine/porcine) (p.2337·3).
Retinal disorders.

Retinar *Bunker, Braz.*
Vitamin A acetate (p.1973·1).

Reti-Nat *Chauvin, Fr.*
d-Apha tocoferil acetate (p.1992·3); omega-3 triglycerides (p.1362·1).
Nutritional supplement.

Retinei *Janssen-Cilag, Venez.†.*
Tretinoin (p.1618·1).
Acne.

Retinide *Ingens, Arg.*
Isotretinoin (p.1599·2).
Acne.

Retino *Abdi, Turk.*
Tretinoin (p.1618·1).
Acne.

Retinol *INTES, Ital.†.*
Myrtillus (p.2349·3).
Eye disorders.

Retinol-A *Young Again Nutrients, USA.*
Vitamin A palmitate (p.1973·1).
Minor skin disorders.

Retinova *Johnson & Johnson Consumer, Belg.†; Janssen-Cilag, Braz.; Janssen-Cilag, Denm.; RoC, Fr.†; Janssen-Cilag, NZ; Janssen-Cilag, Singapore; Johnson & Johnson, Spain†; Janssen-Cilag, Swed.; Janssen-Cilag, UK†.*
Tretinoin (p.1618·1).
Photoageing of the skin; skin hyperpigmentation.

Retinovit
Note.This name is used for preparations of different composition.
INTES, Ital.
Myrtillus (p.2349·3); vitamin A (p.1971·2); vitamin E (p.1992·2).
Circulatory disorders of the eye.

Pharmacos, Mex.
Vitamin A; alfa tocopherol (p.1922·1).
Vitamin deficiency.

Retirides *OTC, Spain.*
Tretinoin (p.1618·1).
Acne; sunlight-induced skin damage.

Retisdin *Isdin, Port.*
Vitamin A betadex; sunscreens.
UV-induced skin damage.

Retisert *Bausch & Lomb, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Uveitis.

Retisol-A *Stiefel, Canad.*
Tretinoin (p.1618·1).
Acne.

Retitop *Roche-Posay, Fr.†.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders.

Retiva *Vivax Gynopharm, Venez.*
Vitamin A (p.1971·2).
Vitamin A deficiency.

Retivit *Sanbe, Indon.*
Betacarotene (p.1930·3); vitamin C; vitamin E; zinc; copper; selenium; lutein (p.1954·3)(p.1922·1).
Age-related macular degeneration; cataract.

Retodol Compositum *Rimsa, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Retofar *Pfizer, Mex.†.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Retoflam *Ultra, Mex.*
Meloxicam (p.80·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Retoflam F *Ultra, Mex.*
Meloxicam (p.80·3); methocarbamol (p.1897·3).
Musculoskeletal, joint, and periarticular disorders; skeletal muscle spasm.

Retoxil *Alcon, Arg.; Alcon, Mex.*
Vitamin, mineral, and trace element preparation (p.1922·1).
Prevention of macular degeneration.

ReTrieve *Dermatech, Austral.; Dermatech, Hong Kong; Dermatech, Singapore.*
Tretinoin (p.1618·1).
Acne; dry skin disorders; photodamaged skin.

Retroinhi *Dosa, Arg.*
Nelfinavir (p.899·1).
HIV infection.

Retrokor *Korea United, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Retrovir *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Zidovudine (p.913·3).
HIV infection.

Retrovir/3TC Post-HIV Exposure *GSK, S.Afr.†.*
Capsules, zidovudine (Retrovir) (p.913·3); tablets, lamivudine (3TC) (p.895·1).
Prophylaxis of HIV infection.

Rettavate *GSK, Gr.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Retterspitz Ausserlich *Retterspitz, Ger.*
Rosemary oil (p.2381·3); citric acid (p.2284·1); tartaric acid (p.2395·2); alum (p.2254·1); thymol (p.1664·3); arnica (p.2260·2).
Inflammatory disorders.

Retterspitz Darmreinigungspulver ST *Retterspitz, Ger.*
Magnesium sulfate (p.1679·3).
Constipation.

Retterspitz Erkaltungsol *Retterspitz, Ger.*
Eucalyptus oil (p.2301·2).
Cold symptoms; rheumatism.

Retterspitz Heilsalbe ST *Retterspitz, Ger.*
Zinc oxide (p.1621·2).
Skin disorders.

Retterspitz Innerlich *Retterspitz, Ger.*
Citric acid (p.2284·1); tartaric acid (p.2395·2); alum (p.2254·1); thyme oil (p.2401·2).
Gastrointestinal disorders.

Retterspitz Muskel- und Nervenol *Retterspitz, Ger.*
Mint oil (p.2345·2).
Gastrointestinal disorders; musculoskeletal and nerve pain; respiratory-tract congestion.

Retterspitz Quick *Retterspitz, Ger.*
Rosemary oil (p.2381·3); camphor (p.2273·2); menthol (p.2340·1); thymol (p.1664·3); arnica (p.2260·2).
Musculoskeletal and joint disorders; respiratory-tract disorders.

Return *Rafarm, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Retussan *Hanosan, Ger.*
Homoeopathic preparation.

Reubaxona *Farmaceutica H, Mex.*
⊗ Betamethasone sodium phosphate (p.1518·3).
Corticosteroid.

Reucam *CT, Ital.†; Maver, Mex.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Reucid *Otto, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Reucortil *Mayo, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Inflammation; pain.

Reudene *ABC, Ital.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Reudol *Nordin, Mex.*
Arnica (p.2260·2); belladonna (p.2263·3); bryonia (p.2269·3).
Musculoskeletal and joint disorders.

Reufin *Sanitas, Chile.*
Glucosamine sulfate (p.2313·2).
Joint disorders.

Reuflor *Italchimici, Ital.*
Lactobacillus reuteri (p.2372·3).
Restoration of gastrointestinal flora.

Reugast *Basi, Port.†.*
Fenbufen (p.54·3).

Reugel *Grunenthal, Venez.*
Etofenamate (p.53·1); pine oil (p.2368·2); eucalyptus oil (p.2301·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Reuginal *Reuffer, Mex.*
Furazolidone (p.834·3); nifuroxime.
Vaginal infections.

Reumacid *Remek, Gr.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Reumacide *Vitoria, Port.*
Indometacin (p.66·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Reumacor *Herbapol Wroclaw, Pol.*
Salix purpurea (p.121·3); solidago (p.2391·1).
Fever; pain.

Reumacort *Teofarma, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); methyl gentisate (p.85·3).
Muscle and joint pain.

Reumadolor *Bros, Gr.*
Indometacin (p.66·3).
Inflammatory disorders.

Reumador *Slovakofarma, Cz.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Reumafort *Amnol, Ital.*
Dimethyl sulfone (p.2294·1); salix (p.121·3); turmeric (p.1473·2); boswellia (p.2307·1); devil's claw root (p.39·1); minerals.
Joint disorders.

Reumagil *KBR, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Reumaherb *Herbapol Poznan, Pol.*
Echinacea purpurea (p.2298·1); meadowsweet (p.2338·1); devil's claw root (p.39·1).
Degenerative joint disorders.

Reumanisal *Bros, Gr.*
Diacerein (p.41·3).
Osteoarthritis.

Reumaphyt *Phytofarm Kleka, Pol.*
Devil's claw root (p.39·1).
Degenerative joint disorders; tendinitis.

Reumat *Sinterapico, Braz.†.*
Bromelains (p.2269·1); phenylbutazone (p.117·1).

Reumatik *Theiss Naturwaren, Pol.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); pine oil (p.2368·2); turpentine oil (p.2406·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Reumazine *Luper, Braz.†.*
⊗ Prednisolone (p.1540·3); oxyphenbutazone (p.107·3).
Arthritis; inflammation.

Reumil *Pharma Italia, Ital.*
Glucosamine; chondroitin sulfate; thioctic acid; vitamins (p.1922·1).
Cartilage disorders.

Reumilase *MDM, Ital.*
Glucosamine; galactose; glucuronic acid; Devil's claw root; collagen; vitamins (p.1922·1).
Joint disorders.

Reumilase Plus *MDM, Ital.*
Glucosamine hydrochloride; chondroitin sodium sulfate; glucuronate sodium; collagen; devil's claw root; vitamins (p.1922·1).
Joint disorders.

Reumilase SD *MDM, Ital.*
Chondroitin sulfate sodium (p.2280·3); glucosamine (p.2313·2); collagen (p.2286·1); vitamins (p.1922·1).
Joint disorders.

Reumina *Demo, Gr.*
Etofenamate (p.53·1).
Analgesic; inflammatory disorders.

Reumine *Poen, Arg.†.*
Amino-acid, vitamin A, and mineral preparation (p.1922·1).
Lidocaine (p.1862·3) is included in the injection to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Reumix *Makros, Braz.†.*
⊗ Betamethasone (p.1518·2); phenylbutazone (p.117·1).
Aluminium glycinate (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation.

Reumo *UCB, Spain†.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Reumobonisol *Bonimed, Pol.*
Arnica (p.2260·2); camphor (p.2273·2); lavender (p.2331·1); menthol (p.2340·1); white mustard (p.2349·1).
Musculoskeletal and joint disorders; neuralgia.

Reumol *Cabuchi, Arg.*
Camphor (p.2273·2); menthol (p.2340·1); salicylic acid (p.1612·2).

Reumolide *Generis, Port.*
Nimesulide (p.95·3).
Pain.

Reumon *Bial, Port.*
Etofenamate (p.53·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia; pain.

Reumophan *Grisi, Mex.*
Ketoprofen (p.73·1); chlorzoxazone (p.1894·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Reumosol *Herbapol Pruszkow, Pol.*
Achillea (p.2245·2); calendula (p.2273·1); camphor (p.2273·2); chamomile (p.2279·3); equisetum (p.2299·3); menthol (p.2340·1); pine oil (p.2368·2); knotgrass (p.2329·2); salicylamide (p.121·2); salix (p.121·3); soapwort (p.2388·2); myrtillus (p.2349·3); hay.
Rheumatic disorders.

Reumotec *Viofar, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Reumotherm *Farmanic, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Reumoxican *Medinfar, Port.*
Piroxicam (p.117·3).
Inflammation; pain.

Reumpapai *Cowik, Pol.*
Piper retrofractus; cinnamon bark (p.2283·1); liquorice (p.1740·3).
Musculoskeletal and joint disorders; neuralgia.

Reupat *Parggon, Mex.*
Indometacin (p.66·3); methocarbamol (p.1897·3).
Rheumatism.

Reupax *CPH, Port.†*
Flurbiprofen (p.61·2).
Musculoskeletal, joint, and peri-articular disorders.

Reuplex *Farmasa, Braz.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; inflammation; pain.

Reuprofen *Terapeutico, Ital.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Reuquinol *Apsen, Braz.*
Hydroxychloroquine sulfate (p.604·2).
Light-sensitive skin disorders; lupus erythematosus; malaria; rheumatoid arthritis.

Reusan *Reuffer, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Reusin *Sankyo, Spain.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Reutefene *Age D'or, Singapore.*
Lactobacillus reuteri protectis (p.2372·3).
Maintenance of gastrointestinal flora.

Reutenox *Solvay, Spain.*
Tenoxicam (p.128·2).
Calcium stones; gout; musculoskeletal, joint, and peri-articular disorders.

Reuteri *Biogaia, Hong Kong.*
Lactobacillus reuteri (p.2372·3).
Restoration of normal gastrointestinal flora.

Reutrexato *Apsen, Braz.*
Methotrexate (p.745·2).
Rheumatoid arthritis.

Reutricam *Liferpal, Mex.*
Piroxicam (p.117·3).
Fever; musculoskeletal and joint disorders; pain.

Reuxen *Tecnifar, Port.*
Naproxen (p.92·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Revalan *BioFemme, Philipp.*
Mefenamic acid (p.80·1).
Fever; pain.

Revalgin *Shreya, Rus.*
Dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Pain.

Revalid
Ewopharma, Cz.; Vifor, Switz.
Amino acids; vitamins; aminobenzoic acid; millet; wheat germ; dried yeast; minerals (p.1922·1).
Hair and nail disorders.

Ewopharma, Pol.
Methionine; cystine; vitamins; minerals (p.1922·1).
Hair and nail disorders.

Revalintabs *Chefaro, Neth.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Revange *Biosintetica, Braz.†*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Revapol *AF, Mex.*
Mebendazole (p.148·3).
Worm infections.

Revasc *Aventis, Austral.; Canyon, Cz.; Aventis, Fr.†; Novartis, Ger.; Aventis, Gr.†; Aventis, Hung.†; Aventis, NZ; Canyon, Neth.; Aventis, Norw.†; Canyon, Port.; Sanofi-Aventis, Spain; Aventis, Switz.†*
Desirudin (p.1257·1).
Thrombosis prophylaxis following orthopaedic surgery.

Revastin *Neo Quimica, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Revatio *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Hung.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Port.; Pfizer, Swed.; Pfizer, UK; Pfizer, USA.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction; pulmonary hypertension.

Revaxis *Aventis Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Sanofi Pasteur, Switz.; Sanofi Pasteur, UK.*
A diphtheria, tetanus, and poliomyelitis vaccine (p.2212·2).
Active immunisation; active immunisation in infants and children.

Reve *IMO, Ital.*
Valerian (p.2410·1); passion flower (p.2363·2).
Insomnia.

Reveal *BR Pharmaceuticals, UK.*
Pregnancy test (p.2372·1).

Revectina *Solvay, Braz.*
Ivermectin (p.145·2).
Filariasis; onchocerciasis; strongyloidiasis.

Revelatest *Pierre Fabre Sante, Fr.*
Pregnancy test (p.2372·1).

Revellex *Essex, Arg.†; Schering-Plough, S.Afr.*
Infliximab (p.69·3).
Crohn's disease; rheumatoid arthritis.

Revelol *Ipca, India.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; heart failure; hypertension.

Revelplac *Naf, Arg.*
Erythrosine (p.1471·3).
Plaque disclosing agent.

Revelplac 2001 *Naf, Arg.*
Erythrosine (p.1471·3); fluoride.
Plaque disclosing agent.

Revenil *Sanofi-Aventis, Braz.*
⊗ Bufylline (p.1116·3); doxylamine succinate (p.578·2); etafedrine hydrochloride (p.1560·2).
Bronchospastic disorders.

Revenil Dospan *Sanofi-Aventis, Braz.*
⊗ Bufylline (p.1116·3); doxylamine succinate (p.578·2); etafedrine hydrochloride (p.1560·2); phenylephrine hydrochloride (p.1568·1).
Bronchospastic disorders.

Revenil Expectorante *Sanofi-Aventis, Braz.*
⊗ Bufylline (p.1116·3); doxylamine succinate (p.578·2); etafedrine hydrochloride (p.1560·2); guaifenesin (p.1561·3).
Bronchospastic disorders.

Revenox *Collins, Mex.†*
Melatonin (p.2338·3).
Sleep disorders.

Reversa *Dermtek, Canad.*
Glycolic acid (p.1598·1).
Skin disorders requiring exfoliation.

Reversa UV *Dermtek, Canad.*
SPF 15: Glycolic acid (p.1598·1); strontium chloride (p.2393·1) avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Skin disorders.

Reversol *Organon, USA.*
Edrophonium chloride (p.630·3).
Diagnosis of myasthenia gravis; evaluation of emergency treatment of myasthenic crises; reversal of competitive neuromuscular blockade.

Revex *Baxter, USA.*
Nalmefene hydrochloride (p.1452·3).
Opioid poisoning.

Revexan *Nycomed, Swed.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Rev-Eyes *Bausch & Lomb, USA.*
Dapiprazole hydrochloride (p.2292·2).
Reversal of mydriasis.

Revez *Chobet, Arg.*
Naltrexone hydrochloride (p.1455·2).
Alcohol withdrawal syndrome; opioid withdrawal syndrome.

Revia *BMS, Austral.; Torrex, Austria; Cristalia, Braz.; Apotex, Canad.; Torrex Chiesi, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Hong Kong; Torrex, Hung.; BMS, Irl.; BMS, Israel†; BMS, Mex.; BMS, Neth.; BMS, NZ; BMS, Norw.; Sanofi Synthelabo, S.Afr.†; BMS, Spain; Gervasi, Spain; BMS, Swed.; BMS, Thai.; Barr, USA.*
Naltrexone hydrochloride (p.1455·2).
Formerly known as Trexan in *Hong Kong*.
Alcohol withdrawal syndrome; opioid dependence; opioid withdrawal syndrome.

Revi-B *YSP, Malaysia.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Revicain *Wiedemann, Ger.†*
Procaine hydrochloride (p.1869·1); vitamins (p.1922·1).
Tonic.

Revicain comp *Wiedemann, Ger.†*
Procaine hydrochloride (p.1869·1); aescin (p.2248·2); minerals (p.1922·1).
Tonic.

Revicain comp plus *Wiedemann, Ger.†*
Procaine hydrochloride (p.1869·1); aescin (p.2248·2); haematoporphyrin (p.2318·1); vitamins; minerals (p.1922·1).
Tonic.

Revici *Kee, India.*
Citric acid (p.2284·1).
Haemorrhage.

Revici-E *Kee, India.*
Etamsylate (p.1064·3).
Haemorrhagic disorders.

Revicon *United American, Hong Kong; United American, Malaysia; United American, Singapore; Great Eastern, Thai.; United American, Thai.*
Multivitamin and mineral preparation with yeast and methionine (p.1922·1).
Dietary supplement.

Revicon Forte (Improved) *United Laboratories, Philipp.*
Vitamins; minerals; methionine; lysine; inositol; yeast (p.1922·1).
Nutritional supplement.

Revicon Max *United Laboratories, Philipp.*
Vitamins; minerals; ginseng; royal jelly (p.1922·1).
Nutritional supplement; tonic.

Revil *Tecnofarma, Chile.*
Cyproheptadine hydrochloride (p.575·1); vitamins.
Reduced appetite.

Revimine *Uniao Quimica, Braz.*
Dopamine hydrochloride (p.1273·2).
Heart failure; hypotension.

Revion *Norma (Νορμα), Gr.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Revionorm *Norma (Νορμα), Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Revios *Amnol, Ital.*
Minerals; vitamins (p.1922·1); boswellia (p.2307·1).
Joint disorders.

Revirax *Blausiegel, Braz.*
Zidovudine (p.913·3).
HIV infection.

Revital
Note. This name is used for preparations of different composition.
Sivaderm, Arg.
Vitamin A (p.1971·2); glycolic acid (p.1598·1).

Ranbaxy, Malaysia.
Multivitamin and mineral preparation with ginseng, choline, inositol, and methionine (p.1922·1).

Basi, Port.†
Multivitamin preparation (p.1922·1).

Revital Calcium D3 *Ranbaxy, Malaysia.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Dietary supplement.

Revital Ginseng Plus *Ranbaxy, Rus.*
Ginseng; vitamins; minerals; amino acids (p.1922·1).
Tonic.

Revitalift *L'Oreal, Canad.*
SPF 18: Ensulizole (p.1597·1); octinoxate (p.1608·2).
Sunscreen.

Revitaliv *Ultra, Mex.*
Vitamin B substances (p.1922·1).

Revitaliv-C *Ultra, Mex.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgias; neuritis; neuropathy; vitamin B deficiency.

Revitalizing *Crinos, Ital.†*
Glycolic acid (p.1598·1).
Skin disorders.

Revitalose *UCB, Fr.*
Ampoule A, magnesium aspartate (p.1679·1); -leucine (p.1954·3); -lysine hydrochloride (p.1955·1); -phenylalanine (p.1960·1); -valine (p.1971·1); ampoule B, sodium ascorbate (p.1984·1) or ascorbic acid (p.1983·3).
Asthenia.

Revitalose C
Note. This name is used for preparations of different composition.
UCB, Belg.; UCB, Switz.
Amino acids and vitamin C (p.1922·1).
Tonic.

Rivex, Canad.†
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Revitam *Biolab Sanus, Braz.*
A range of multivitamin preparations with or without minerals (p.1922·1).

Revitan *Ranbaxy, Thai.*
Ginseng (p.2312·1); multivitamins and minerals (p.1922·1).
Tonic.

Revitare E *Gelpharma, Mex.*
Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Revitex *Gerbex, Canad.†*
Multivitamin preparation preparation with calcium and iron (p.1922·1).

Revitonil
Note. This name is used for preparations of different composition.
Cederroth, Spain.
Echinacea (p.2298·1).
Immunostimulant.

Lichtwer, UK.
Echinacea (p.2298·1); peppermint (p.1761·2); clove (p.2284·3); aniseed (p.2258·2); liquorice (p.1740·3); fennel (p.2302·3); eucalyptus (p.2301·2).
Cold symptoms

Revitonus C *Sandoz, Canad.*
Ascorbic acid (p.1983·3).
Formerly contained 1 ampoule, ascorbic acid, 1 ampoule, suprarenal cortex extract, testicular extract, and brain extract.
Vitamin C supplement.

Revitron *Gelpharma, Mex.*
Vitamin and mineral preparation (p.1922·1).

Revivan *Zambon, Braz.; AstraZeneca, Ital.*
Dopamine hydrochloride (p.1273·2).
Heart failure; hypotension; shock.

Revivona *Nycomed, Austria.*
Multivitamin preparation (p.1922·1).

Revixil *Gador, Arg.†*
Stavudine (p.907·1).
HIV infection.

Revlimid *Celgene, Cz.; Celgene, Fr.; Celgene, Port.; Celgene, UK; Celgene, USA.*
Lenalidomide (p.739·3).
Multiple myeloma; myelodysplastic syndromes.

Revocon *Sun, India; Capsifar, Port.*
Tetrabenazine (p.2396·2).
Balism; ballism; chorea; dyskinesias; dystonias; tardive dyskinesia.

Revolan *Sanbe, Indon.*
Piracetam (p.368·2).
Cerebral trauma; chronic alcoholism; mental function impairment.

Revolyt *Gunnar Kjems, Denm.*
Glucose; potassium chloride; magnesium sulfate; sodium citrate; sodium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Revulsan *Faria, Braz.†*
⊗ Papaverine diethylbarbiturate (p.2192·1); belladonna (p.2263·3); pentetrazol (p.2162·1).
Smooth muscle spasm.

Revup *Aristo, India.*
Multivitamin and mineral preparation (p.1922·1).

Rewma-Gel *DHU, Rus.*
Homoeopathic preparation.

Rewodina
AWD, Cz.; AWD, Ger.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Dresden, Pol.
Diclofenac (p.44·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Rex *MDM, Ital.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Bone disorders; hypocalcaemia.

Rexacin *Unison, Hong Kong†; Unison, Malaysia; Unison, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Rexalgan *Dompe, Ital.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Rexall Daily Sunblock *Tanning Research, Canad.†*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Rexall Kids Daily Sunblock *Tanning Research, Canad.†*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Rexall Oil-Free Daily Sunblock *Tanning Research, Canad.†*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Rexall Sport Sunblock *Tanning Research, Canad.†*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Rexall Sunblock *Tanning Research, Canad.†*
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Rexamat *Pfizer, Arg.†*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Rexan *Ist. Chim. Inter., Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Rexcof *Cipla, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3).
Coughs.

Rexcof Plus *Cipla, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); menthol (p.2340·1).
Coughs.

Rexer *Organon, Spain.*
Mirtazapine (p.409·2).
Depression.

Rexetin *Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Rexgenta *Areu, Spain.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Rexicam *Otto, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Rexichlor *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Skin disinfection.

Rexidol *Medichem, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Rexil *Metiska, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Rexilan *Am-Europharma, Philipp.*
Rifampicin (p.325·3).
Tuberculosis.

Rexilen *Serra Pamies, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Rexiluven S *Novartis Consumer, Ger.†.*
Aesculus (p.2248·2).
Venous insufficiency.

Reximax *Nufarindo, Indon.*
Arginine hydrochloride; yohimbe; Siberian ginseng (p.2386·3); muira-puama; saw palmetto (p.2192·3); tribulus terrestris (p.2404·1).
Tonic.

Reximide *Duopharma, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Rexitol *Rekah, Israel.*
Chloroxylenol (p.1640·2); terpineol (p.2396·1).
Disinfection.

Rexivin *Collins, Mex.*
Methocarbamol (p.1897·3).
Musculoskeletal pain; rheumatism; skeletal muscle spasm.

Rexner *Casasco, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Rexolate *Hyrex, USA†.*
Sodium thiosalicylate (p.124·3).
Gout; pain; rheumatic fever.

Rexophtal N *Bausch & Lomb, Switz.*
Phenylephrine hydrochloride (p.1568·1).
Conjunctivitis.

Rexort *Takeda, Fr.†.*
Citicoline (p.2283·3).
Cerebrovascular disorders.

Rexorubia *Homeocan, Canad.; Lehning, Fr.*
Homoeopathic preparation.

Rextat *Recordati, Ital.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Reyataz *BMS, Arg.; BMS, Austral.; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Ital.; BMS, Jpn; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, UK; BMS, USA.*
Atazanavir sulfate (p.866·3).
HIV infection.

Rezamid
Note. This name is used for preparations of different composition.
ICN, Arg.†.
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Summers, USA.
Resorcinol (p.1612·1); sulfur (p.1614·1).
Acne.

Rezamid D, Rezamid F, Rezamid M *ICN, Arg.†.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Rezerc *Bevo, Gr.*
Cetirizine (p.571·1).
Hypersensitivity disorders.

Rezosel *Biosel, Turk.*
⊗ Mannitol (p.1330·2).
Bladder irrigation.

Rezplen *Senosiain, Mex.*
Clarithromycin (p.248·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Rezulin *Pfizer, Mex.†.*
Troglitazone (p.463·2).
Diabetes mellitus.

Rezult *Sun, India†.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

RFG-Kit *Poen, Arg.†.*
Fluorescein sodium (p.2306·1).
Aid to eye examination.

R-Gel *Healthline, USA.*
Capsaicin (p.32·3).

R-Gen *Goldline, USA.*
Iodinated glycerol (p.1562·2).
Coughs.

R-Gene *Kabivitrum, USA.*
Arginine hydrochloride (p.1928·2).
Test to assess pituitary reserve for growth hormone.

RG-Q *Combiphar, Indon.*
Ubidecarenone (p.2407·2); *d*-alpha tocopherol (p.1992·2).
Antoxidant.

Rhanitak *Balldarassi, Braz.†.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rhea Superscent Oil *Philusa, Philipp.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); cineole (p.2282·3).
Musculoskeletal, joint, and soft-tissue disorders; pruritus.

Rheaban Maximum Strength *Pfizer, USA†.*
Activated attapulgite (p.1709·1).
Diarrhoea.

RheDQuin *Sanquin, Neth.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhefluin *Zentiva, Cz.; Medika, Switz.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Ascites; hypertension; oedema.

Rhelafen *Lapi, Indon.*
Ibuprofen (p.64·2).
Fever; pain.

Rhelax *Herbapol Wroclaw, Pol.*
Caraway (p.2276·3); fennel (p.2302·3); frangula bark (p.1732·2); rhubarb (p.1768·3).
Constipation; digestive disorders; obesity.

Rhem *Andromaco, Chile†.*
Zaleplon (p.1035·3).
Insomnia.

Rhemid *Zwitter, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Rhemofenax *Duopharma, Hong Kong.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Rhenus med *APS, Ger.†.*
Butcher's broom (p.2270·3).
Venous insufficiency.

Rheobral *Niverpharm, Fr.*
Troxerutin (p.2305·1); vincamine (p.2414·1).
Mental function impairment in the elderly.

Rheodextran *Infusia, Cz.†.*
⊗ Dextran 40 (p.1059·1) in sodium chloride or glucose.
Plasma volume expansion; thrombosis prophylaxis.

Rheoflux *Niverpharm, Fr.*
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

Rheofusin *Fresenius Kabi, Austria†.*
⊗ Dextran 40 (p.1059·1) with electrolytes.
Microcirculatory disorders; thrombosis prophylaxis.

Rheogen *Robugen, Ger.†.*
Aloes (p.1705·2).
Constipation.

Rheogluman *Biokhimik, Rus.*
⊗ Dextran 40 (p.1059·1); mannitol (p.1330·2); sodium chloride.
Plasma volume expansion; shock; thrombosis prophylaxis; vascular disorders.

Rheohes *Braun, Ger.*
⊗ Pentastarch (p.1065·1).
Plasma volume expansion.

Rheomacrodex *Torrex, Austria; Meda, Denm.; Pharmalink, Ger.†; IFET (ΙΦΕΤ), Gr.†; Meda, Hung.; Pharmacia Upjohn, Israel; Pisa, Mex.; Meda, Norw.; Eczacibasi, Rus.; Alliance, S.Afr.; Fresenius Kabi, Spain; Meda, Swed.; Braun, Switz.†; Eczacibasi-Baxter, Turk.; Pharmacia, USA.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Cerebral and peripheral vascular disorders; extracorporeal circulation; hypovolaemia; organ perfusion; plasma volume expansion; prophylaxis of surgical adhesions; shock; thromboembolism prophylaxis.

Rheopolydex *Biosynthesis, Rus.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Extracorporeal circulation; plasma volume expansion; shock; thrombosis prophylaxis; vascular eye disorders.

Rheopolyglukin with Glucose *Biokhimik, Rus.*
⊗ Dextran 40 (p.1059·1) in glucose.
Extracorporeal circulation; plasma volume expansion; shock; thrombosis prophylaxis; vascular eye disorders.

Rheosolon *PannonPharma, Hung.*
⊗ Phenylbutazone (p.117·1); prednisolone (p.1540·3).
Gout; inflammation; musculoskeletal and joint disorders.

Rheotromb *DeltaSelect, Cz.; DeltaSelect, Ger.; DeltaSelect, Hung.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Rhesogam *ZLB, Austria; ZLB, Ger.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhesogamma *Aventis Behring, Arg.; Aventis Behring, Norw.†; ZLB, Spain; Aventis Behring, Swed.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhesogamma P *Sanofi Pasteur, Chile; Statens Serum Institut, Denm.; ZLB, Gr.; ZLB Behring, Mex.; Farma-Tek, Turk.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhesonativ *Octapharma, Cz.; Octapharma, Hung.; Pharmacia, Irl.†; Pharmacia, Malaysia†; Octapharma, Port.; Octapharma, Swed.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhesugam *NBI, S.Afr.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhesuman *Berna, Port.†; Berna, Spain†; Berna, Thai.†; Berna, Turk.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhetoflam *Menarini, Indon.; Sanbe, Indon.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and soft-tissue disorders.

Rheu *Vitasan, Austria.*
Homoeopathic preparation.

Rheubalmin Bad *Hoernecke, Ger.*
Methyl salicylate (p.85·3); isobornyl acetate; camphor (p.2273·2).
Bath additive; musculoskeletal, joint, and soft-tissue disorders.

Rheubalmin Indo *Hoernecke, Ger.*
Indometacin (p.66·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rheubalmin N *Hoernecke, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal and joint disorders; neuralgia.

Rheubalmin Thermo *Hoernecke, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; peripheral vascular disorders.

Rheucastin *Pfluger, Ger.†.*
Homoeopathic preparation.

Rheucostan M *Hanosan, Ger.*
Homoeopathic preparation.

Rheuferm Phyto *Wiedemann, Ger.*
Devil's claw root (p.39·1).
Degenerative joint disorders.

Rheuflam *Standard, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Rheugesal *Mucos, Austria.*
Diethylamine salicylate (p.47·2); flufenamic acid (p.60·3); myrtecaine (p.1867·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rheugesic *Medpro, S.Afr.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Rheuma
Note. This name is used for preparations of different composition.
Peithner, Austria.
Homoeopathic preparation.

Weleda, Austria.
Aconitum napellus (p.2246·1); arnica (p.2260·2); betula folium (p.2266·3); mandragora radix; formica; rosemary oil (p.2381·3).
Musculoskeletal and joint disorders.

Rheuma Bad *Tetesept, Ger.*
Glycol salicylate (p.62·3); methyl nicotinate (p.85·3); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); camphor (p.2273·2).
Musculoskeletal disorders.

Rheuma Denk *Denk, Cz.†.*
Etofenamate (p.53·1).
Musculoskeletal, joint and soft-tissue disorders.

Rheuma Echtroplex *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Rheumabene
Note. This name is used for preparations of different composition.
Ratiopharm, Austria†.
Diclofenac sodium (p.44·3).
Inflammation; pain.

Merckle, Ger.†.
Dimethyl sulfoxide (p.2022·1).
Musculoskeletal, joint, and peri-articular disorders.

Rheumacin *Pacific, NZ.*
Indometacin (p.66·3).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Rheumadoron *Weleda, Austria; Weleda, Fr.; Weleda, S.Afr.; Weleda, UK.*
Homoeopathic preparation.

Rheumadyn PMD *Plantamed, Ger.†.*
Homoeopathic preparation.

Rheuma-Gastreu R46 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Rheuma-Gel *Ratiopharm, Ger.*
Etofenamate (p.53·1).
Musculoskeletal, joint, and soft-tissue disorders.

Rheuma-Hek *Strathmann, Ger.*
Urtica (p.2409·3).
Musculoskeletal and joint disorders.

Rheuma-Hevert *Hevert, Ger.*
Homoeopathic preparation.

Rheumakaps *Steigerwald, Ger.*
Salix (p.121·3).
Fever; headache; musculoskeletal and joint disorders.

Rheuma-Kapseln *Stada, Ger.*
Urtica (p.2409·3).
Rheumatic disorders.

Rheumakur *Darya-Varia, Indon.*
Curcuma oil (p.1473·2).
Fat malabsorption; osteoarthritis; rheumatoid arthritis.

Rheumalan *Hilarys, Canad.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); belladonna (p.2263·3); capsicum oleoresin (p.2276·2); croton oil (p.39·1); eucalyptus oil (p.2301·2); expressed mustard oil (p.2349·2); salicylic acid (p.1612·2).

rheuma-loges *Loges, Ger.*
Homoeopathic preparation.

Rheumamed *Feldhoff, Ger.*
Cayenne pepper (p.2276·2).
Musculoskeletal and joint disorders.

Rheumanox *Charoen, Thai.*
Ibuprofen (p.64·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Rheuma-Pasc *Pascoe, Ger.*
Homoeopathic preparation.

Rheumapill *Supra Ferbindo, Indon.*
Aspirin (p.20·3).
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2) and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Osteoarthritis; rheumatoid arthritis.

Rheumaplus *Medichrom, Gr.†.*
Piroxicam (p.117·3).
Inflammatory disorders.

Rheuma-Salbe
Note. This name is used for preparations of different composition.
Lichtenstein, Cz.†.
Camphor (p.2273·2); benzyl nicotinate (p.28·1); glycol salicylate (p.62·3).
Neuralgia; rheumatic pain; soft-tissue disorders.

Stada, Ger.†.
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; peripheral vascular disorders.

Rheumasalbe
Note. A similar name is used for preparations of different composition (see above).
CT, Ger.†.
Nonivamide (p.96·2); benzyl nicotinate (p.28·1); eucalyptus oil (p.2301·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Rheuma-Salbe N *Winthrop, Ger.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; peripheral vascular disorders.

Rheumasan Moor-Bad S *Sanofi Synthelabo, Ger.†.*
Sodium humate (p.2389·3).
Bath additive; musculoskeletal and joint disorders.

Rheumasan N *Sanofi Synthelabo, Ger.†.*
Salicylic acid (p.1612·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Rheumaselect *Dreluso, Ger.*
Homoeopathic preparation.

Rheuma-Sern *Truw, Ger.*
Devil's claw root (p.39·1).
Dyspepsia; musculoskeletal and joint disorders.

Rheumasit *Medice, Ger.†.*
⊗ Dexamethasone (p.1526·1); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Rheuma-Stada *Stada, Ger.†.*
Urtica leaf (p.2409·3).
Rheumatism.

Rheumatab Salicis *Schuck, Ger.†.*
Salix (p.121·3).
Headache; rheumatic disorders.

Rheumatabletten N *Heel, Ger.*
Homoeopathic preparation.

Rheumatac *Sovereign, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Rheumatex *Wampole, USA.*
Test for rheumatoid factor in serum.

Rheumatic Pain *Cantassium Co., UK.*
Guaiacum resin (p.2317·3); taraxacum (p.2395·1); celery (p.2278·3); menyanthes (p.2340·3).
Muscle and joint pain.

Rheumatic Pain Relief *Herbal Concepts, UK.*
Menyanthes (p.2340·3); guaiacum resin (p.2317·3); capsicum (p.2276·2); capsicum oleoresin (p.2276·2); celery oil (p.2278·3).
Musculoskeletal and joint pain.

Rheumatic Pain Remedy *Potter's, UK.*
Menyanthes (p.2340·3); lappa root (p.2330·3); achillea (p.2245·2); guaiacum resin (p.2317·3).
Musculoskeletal and joint disorders.

Rheumatica *Nelson, UK.*
Homoeopathic preparation.

Rheumatin *Sandoz, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; magnesium; zinc; manganese; selenium; calcium (p.1922·1).
Osteoarthritis.

Rheumatin Forte *Sandoz, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); magnesium; zinc; manganese; selenium; calcium (p.1922·1).
Osteoarthritis.

Rheumatism Rhus Tox L80 *Homeocan, Canad.†.*
Homoeopathic preparation.

Rheumaton *Wampole, USA.*
Test for rheumatoid factor in serum or synovial fluid.

Rheumatrex *Stada, USA.*
Methotrexate (p.745·2) or methotrexate sodium (p.745·2).
Psoriasis; rheumatoid arthritis.

Rheumatropfen N *Heel, Ger.*
Homoeopathic preparation.

Rheumavek *Faran, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Rheumed *Phytomed, Switz.†.*
Homoeopathic preparation.

Rheumeda *Madaus, Ger.*
Homoeopathic preparation.

Rheumesser *Gerot, Austria.*
⊗ Kebuzone (p.72·3); salamidacetic acid (p.121·2); dexamethasone (p.1526·1); cyanocobalamin (p.1980·2) or hydroxocobalamin acetate (p.1980·3). Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Rheumex *Gebro, Austria.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1); allantoin (p.1588·1).
Musculoskeletal and joint disorders; sports injuries.

Rheumitin *Krewel, Ger.†.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and soft-tissue disorders.

Rheumodoron 1 *Weleda, Ger.*
Homoeopathic preparation.

Rheumodoron 2 *Weleda, Ger.*
Homoeopathic preparation.

Rheumodoron 102 A *Weleda, Ger.*
Homoeopathic preparation.

Rheumon *Kolassa, Austria; Bayer, Cz.; Tropon, Ger.; Goodwill, Hung.; Bayer, Pol.; Drossapharm, Switz.; Bayer, Turk.*
Etofenamate (p.53·1).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Rheumosin *Leciva, Cz.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); mustard oil (p.2349·2).
Musculoskeletal, peri-articular and soft-tissue disorders.

Rheumox *Goldshield, Irl.†; Continental Ethicals, S.Afr.; Goldshield, UK†.*
Azapropazone (p.26·3).
Ankylosing spondylitis; gout; osteoarthritis; rheumatoid arthritis.

Rheunervol N *Riemser, Ger.*
Camphor (p.2273·2).
Musculoskeletal and joint disorders.

Rheu-Tarx 1 *Natiris, Venez.*
Rhubarb (p.1768·3); taraxacum (p.2395·1); equisetum (p.2299·3); senna (p.1769·2).
Constipation.

Rheutrop *Kolassa, Austria.*
Acemetacin (p.15·1).
Gout; inflammation; musculoskeletal and joint disorders; thrombophlebitis; vasculitis.

Rhewlin
Upha, Malaysia†.
Diclofenac sodium (p.44·3).
Dysmenorrhoea; musculoskeletal and joint disorders.

Beacons, Singapore.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Rhinaaxia
Agepha, Austria; Thea, Fr.; Ewopharma, Hung.†; Inpharzam, Switz.†.
Magnesium isospaglumate (p.2327·2).
Allergic rhinitis.

Proel, Gr.†.
Magnesium spaglumate (p.2327·2).
Allergic rhinitis.

Farmila, Ital.
Sodium spaglumate (p.2327·2).
Allergic rhinitis.

Rhinadine *Farmaline, Thai.*
Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Hypersensitivity reactions; nasal congestion.

Rhinadvil *Wyeth, Fr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis with headache and fever.

Rhinal
Note. This name is used for preparations of different composition.
Ahimsa, Arg.
⊗ Naphazoline (p.1565·1).
Nasal congestion.

Zentiva, Cz.
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Rhinalar *Roche, Canad.†.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis.

Rhinall *Scherer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Rhinallergy *Boiron, Cz.; Boiron, Fr.*
Homoeopathic preparation.

Rhinamide *Bailly, Fr.*
⊗ Ephedrine hydrochloride (p.1558·2); benzoic acid (p.1630·2).
Congestion of the nose and throat.

Rhinar *TP, Thai.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; respiratory-tract congestion; rhinitis.

Rhinaris *Pharmascience, Canad.*
Macrogol (p.2336·1); propylene glycol (p.2374·1).
Rhinitis.

Rhinaris Nozoil *Pharmascience, Canad.*
Sesame oil (p.2386·1).
Nasal dryness.

Rhinaris Saline *Pharmascience, Canad.*
Sodium chloride (p.1686·1).
Nasal disorders.

Rhinase *Essex, Philipp.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; nasal congestion.

Rhinatate *Major, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract symptoms.

Rhinatate-NF *Major, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

Rhinathiol
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.
Carbocisteine (p.1553·2).
Otitis; respiratory-tract congestion; sinusitis.

Sanofi-Aventis, Port.
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Sanofi-Aventis, Hung.
Cough syrup: Dextromethorphan hydrobromide (p.1555·2).
Cough.

Sanofi-Aventis, Hung.
Expectorant syrup: Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Sanofi-Aventis, Hung.
Nasal spray: ⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Rhinathiol Antirhinitis *Sanofi-Aventis, Belg.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Rhinitis; sinusitis.

Rhinathiol Cold *Sanofi-Aventis, Hung.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Rhinathiol maux de gorge *Sanofi Synthelabo OTC, Fr.†.*
Biclotymol (p.1632·1).
Mouth and throat bacterial infections.

Rhinathiol Promethazine *Sanofi-Aventis, Fr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Switz.*
Carbocisteine (p.1553·2); promethazine hydrochloride (p.588·2).
Cough; respiratory-tract disorders.

Rhinathiol Rhume *Sanofi Synthelabo OTC, Fr.†.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Rhinathiol Toux Seche Pholcodine *Sanofi-Aventis, Fr.*
Pholcodine (p.1570·2).
Coughs.

Rhinathiol Tusso *Sanofi-Aventis, Hung.*
Prenoxdiazine hydrochloride (p.1571·1).
Cough.

Rhinazin *Polfa Warszawa, Pol.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Rhin-Bac *Hasco-Lek, Pol.*
Camphor (p.2273·2); mint oil (p.2345·2); menthol (p.2340·1); methyl salicylate (p.85·3); pine oil (p.2368·2).
Upper respiratory-tract disorders.

Rhinedrine *Cooperation Pharmaceutique, Fr.*
Benzododecinium bromide (p.1631·2).
Nose and throat infections.

Rhinedrine Moisturizing *Jamieson, Canad.†.*
Glycerol (p.2314·2); propylene glycol (p.2374·1).

Rhineton *Be-Tabs, S.Afr.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Rhinex *Stada, Thai.*
Carbocisteine (p.1553·2).
Coughs associated with increased or viscous mucus.

Rhinex mit Naphazolin *Wernigerode, Ger.*
⊗ Naphazoline hydrochloride (p.1565·2).
Rhinitis; sinusitis.

Rhinex mit Tetryzolin *Wernigerode, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion; rhinitis; sinusitis.

Rhinex mit Xylometazolin *Wernigerode, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Rhinidine *Pfizer Consumer, Belg.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion and irritation.

Rhinigine *Xixia, S.Afr.*
Loratadine (p.583·3).
Allergic rhinitis.

Rhinil *Aristopharma, Hong Kong.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Rhiniramine *DHA, Hong Kong; DHA, Singapore.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Rhini-San
Note. A similar name is used for preparations of different composition (see below).
Sandipro, Belg.
Phenylephrine hydrochloride (p.1568·1); diphenylpyraline hydrochloride (p.578·2).
Allergic rhinitis.

Rhinisan
Note. A similar name is used for preparations of different composition (see above).
Alcon, Ger.
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Rhinital *DHU, Rus.*
Homoeopathic preparation.

Rhinitisan *Bioforce, Switz.†.*
Homoeopathic preparation.

Rhinivict *Dermapharm, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Rhino Humex *Urgo, Belg.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Rhinobeta *Betapharm, Ger.†.*
Electrolyte solution (p.1667·1).
Nasal disorders.

Rhinobros *Bros, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Rhinocap
Note. This name is used for preparations of different composition.
Grossmann, Hong Kong; Grossmann, Switz.
Phenylephrine hydrochloride (p.1568·1); dimenhydrinate (p.576·2); caffeine (p.1116·3).
Allergic rhinitis; cold symptoms; nasal congestion; sinus congestion.

Inibsa, Spain.
Phenylephrine hydrochloride (p.1568·1); diphenhydramine hydrochloride (p.577·2).
Formerly contained phenylephrine hydrochloride and carbinoxamine maleate.
Nasal congestion.

Rhinocillin B *Medicopharm, Austria†.*
Bacitracin (p.210·3).

Rhinoclir
Note. This name is used for preparations of different composition.
Febena, Ger.†.
Dexpanthenol (p.2362·1).
Nasal disorders.

Agis, Israel.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Rhinocort
Note. This name is used for preparations of different composition.
AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Pol.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Astra, USA; AstraZeneca, Venez.
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps.

Agis, Israel; Teijin, Jpn.
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Rhinocure *Actipharm, Switz.*
Polysorbate 80 (p.1919·2); sodium chloride (p.1686·1); chamomile (p.2279·3); benzethonium chloride (p.1630·1).
Rhinopharyngeal disorders.

Rhinocure simplex *Actipharm, Switz.*
Polysorbate 80 (p.1919·2); sodium chloride (p.1686·1); benzethonium chloride (p.1630·1).
Rhinopharyngeal disorders.

Rhinodec *Blue Cross, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); brompheniramine maleate (p.569·2).
Nasal congestion; rhinitis.

Rhinodoron *Weleda, Fr.; Weleda, Ger.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3); aloe vera (p.1588·2).
Nasal cleansing; nasal congestion; nasal dryness.

Rhinodose *Pharmanel, Gr.†.*
Sodium chloride (p.1686·1).
Dry nasal mucosa.

Rhinodrin *Montavit, Austria.*
⊗ Diphenhydramine hydrochloride (p.577·2); naphazoline hydrochloride (p.1565·2).
Rhinitis.

Rhinofebral *McNeil, Fr.; Martin, Switz.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); ascorbic acid (p.1983·3).
Cold symptoms; rhinopharyngeal disorders.

Rhinofebryl *Sanofi-Aventis, Belg.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Rhinitis with fever and/or headache.

Rhinofed *Dexa, Indon.*
Pseudoephedrine (p.1571·2); terfenadine (p.590·3).
Rhinitis.

Rhinofluimucil *Zambon, Fr.*
⊗ Acetylcysteine (p.1548·2); tuaminoheptane sulfate (p.1575·1); benzalkonium chloride (p.1629·1).
Rhinopharyngeal congestion.

Rhino-Gastreu N R49 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Rhinogen *IBSA, Switz.*
Sodium hyaluronate (p.2320·1).
Nasal dryness.

Rhinoguttae Argenti diacetylotannici proteinici *Leyh, Ger.*
Silver protein acetyl tannate (p.2387·3).
Nasal congestion.

Rhinoguttae Dexamethasoni cum Naphazolino *Leyh, Ger.†.*
⊗ Dexamethasone (p.1526·1); naphazoline hydrochloride (p.1565·2).
Cold symptoms; rhinitis.

Rhinoguttae pro Infantibus N *Leyh, Ger.*
Silver protein acetyl tannate (p.2387·3).
Nasal congestion.

Rhinohist *Seng, Thai.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; respiratory-tract congestion; rhinorrhoea.

Rhinol *Su-Heung, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Rhinolast *Orion, Irl.; Asta Medica, Israel; Mer-National, S.Afr.; Viatris, UK.*
Azelastine hydrochloride (p.568·2).
Allergic rhinitis.

Rhinolex *Remek, Gr.*
⊗ Ephedrine hydrochloride (p.1558·2).
Nasal congestion.

Rhinomer *Novartis Consumer, Ger.; Novartis Consumer, Port.†; Novartis Consumer, Switz.; Novartis, Turk.*
Sea water (p.1686·1).
Nasal congestion; nasal disorders; nasal irrigation; rhinitis.

Rhinon
Note. This name is used for preparations of different composition.
Petrasch, Austria.
Nasal ointment: ⊗ Naphazoline hydrochloride (p.1565·2); sulfadiazine (p.336·2).
Rhinitis; sinusitis.

Petrasch, Austria.
Nose drops: ⊗ Naphazoline hydrochloride (p.1565·2).
Rhinitis.

Rhinonorm *Merckle, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).

Rhinoperd *Agepha, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2).
Aid in rhinoscopy; rhinitis; sinusitis.

Rhinoperd comp *Agepha, Austria.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2).
Cold symptoms; rhinitis.

Rhinophenazol *Polfa Warszawa, Pol.*
⊗ Antazoline sulfate (p.567·1); naphazoline nitrate (p.1565·2).
Allergic rhinitis; nasal congestion.

Rhinophen-C *Maxi, Thai.†.*
Brompheniramine maleate (p.569·2); vitamin C (p.1983·3).
Hypersensitivity reactions.

Rhinopront
Note. This name is used for preparations of different composition.
Mack, Belg.†; Olvos, Gr.†; Mack, Malaysia†.
Carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1).
Catarrh; cold symptoms; rhinitis; sinusitis.

Zuoz, Venez.†.
Carbinoxamine (p.570·2); phenylpropanolamine (p.1569·2).

Pfizer, Austria; Grunenthal, Chile†; Mack, Cz.†; Mack, Illert., Ger.†; Mack, Hong Kong; Mack, Hung.†; Mack, Singapore†; Mack, Thai.†; Abdi, Turk.
Capsules: Phenylephrine hydrochloride (p.1568·1); carbinoxamine maleate (p.570·2).
Catarrh; cold and influenza symptoms; respiratory-tract congestion; rhinitis; sinusitis.

Mack, Illert., Ger.†.
Nasal spray: ⊗ Tetryzoline hydrochloride (p.1574·1).
Catarrh; colds; hay fever.

Mack, Illert., Ger.†.
Oral liquid: Carbinoxamine polistirex (p.570·2); phenylpropanolamine polistirex (p.1570·2).
Colds; nasal catarrh; rhinitis.

Grunenthal, Chile†.
Oral suspension: Carbinoxamine maleate (p.570·2); phenylpropanolamine (p.1569·2).
Cold and influenza symptoms; rhinitis; sinusitis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Abdi, Turk.
Oral suspension: Phenylpropanolamine polistirex (p.1570·2); carbinoxamine polistirex (p.570·2).
Respiratory-tract congestion.

Mack, Cz.†; Mack, Hong Kong; Mack, Hung.†; Pfizer Consumer, Switz.†.
Syrup: Carbinoxamine polistirex (p.570·2); phenylpropanolamine polistirex (p.1570·2).
Catarrh; cold symptoms; rhinitis; sinusitis.

Rhinopront Kombi *Pfizer Consumer, Ger.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Rhinopront N *Pfizer Consumer, Switz.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Rhinopront formerly contained carbinoxamine maleate and phenylephrine hydrochloride.
Cold symptoms; rhinitis; sinusitis.

Rhinopront Top *Pfizer Consumer, Switz.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Rhinopharyngeal disorders.

Rhinopront-S *Olvos, Gr.†.*
Phenylpropanolamine (p.1569·2); carbinoxamine (p.570·2).
Allergic rhinitis; catarrh.

Rhinos
Dexa, Hong Kong.
Loratadine (p.583·3); pseudoephedrine (p.1571·2).
Allergic rhinitis; cold symptoms.

Dexa, Indon.
Loratadine (p.583·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Rhinosept *Delta, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2); neomycin sulfate (p.305·1).
Nasal congestion.

Rhinoside *Biomedica-Chemica, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Rhinosol *AstraZeneca, Denm.*
⊗ Budesonide (p.1520·1).
Hay fever.

Rhinosovil *Eu Rho, Ger.†.*
⊗ Naphazoline nitrate (p.1565·2); pheniramine maleate (p.587·3).
Nasal congestion; rhinitis.

Rhinospray *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Ger.; Unilfarma, Port.; Boehringer Ingelheim, Spain.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion; otitis media; rhinitis; sinusitis.

Rhinospray Antialergico *Boehringer Ingelheim, Spain.*
⊗ Tramazoline hydrochloride (p.1574·3); chlorphenamine maleate (p.571·3).
Nasal congestion.

Rhinospray Atlantik *Boehringer Ingelheim, Ger.*
Sea water (p.1686·1).
Nasal disorders.

Rhinospray met menthol *Boehringer Ingelheim, Neth.*
⊗ Tramazoline hydrochloride (p.1574·3); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Rhinospray Plus *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Hung.*
⊗ Tramazoline hydrochloride (p.1574·3); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Rhinospray sensitiv *Boehringer Ingelheim, Ger.*
⊗ Tramazoline hydrochloride (p.1574·3); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Rhino-Stas *Stada, Cz.; Stada, Hung.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

Rhinostop *Masterlek, Rus.; IBSA, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; otitis media; rhinitis; sinusitis.

Rhino-Sulfuryl *Legras, Fr.*
⊗ Sodium thiosulfate (p.1466·1); ephedrine hydrochloride (p.1558·2).
Rhinopharyngeal congestion.

Rhinosyn *Great Southern, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Rhinosyn-DM *Great Southern, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Rhinosyn-DMX *Great Southern, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Rhinosyn-X *Great Southern, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Rhinotapp *Dynamic, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Cough; nasal congestion.

Rhinothricinol *Plan, Switz.*
Tyrothricin (p.358·2); eucalyptus oil (p.2301·2).
Rhinopharyngeal infections.

Rhinoton plus *Krewel, Ger.†.*
Sea salt (p.1686·1).
Nasal dryness.

Rhinotrophyl *Jolly-Jatel, Fr.*
Thenoate monoethanolamine (p.351·1).
Formerly contained thenoate monoethanolamine and framycetin sulfate.
Infections of the nose and throat.

Rhinotussal
Note. This name is used for preparations of different composition.
Mack, Cz.†; Mack, Illert., Ger.†; Pfizer Consumer, Switz.; Abdi, Turk.
Capsules: Carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Coughs and associated respiratory-tract disorders; respiratory-tract congestion.

Mack, Illert., Ger.†.
Oral liquid: Dextromethorphan polistirex (p.1556·1); phenylpropanolamine polistirex (p.1570·2); carbinoxamine polistirex (p.570·2).
Coughs and associated respiratory-tract disorders.

Abdi, Turk.
Oral liquid: Phenylpropanolamine (p.1569·2); carbinoxamine maleate (p.570·2); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract congestion.

Mack, Cz.†; Pfizer Consumer, Switz.
Syrup: Phenylpropanolamine polistirex (p.1570·2); carbinoxamine polistirex (p.570·2); dextromethorphan polistirex (p.1556·1).
Coughs and associated respiratory-tract disorders.

Rhinovac *Darrow, Braz.†.*
Antigen extracts (p.2250·2).
Allergen immunotherapy.

Rhinoval C *Pharmavit, Cz.†; BMS, Hung.†.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Rhinovalon *Almirall, Belg.†.*
⊗ Tixocortol pivalate (p.1544·2).
Rhinitis.

Rhinovalon Neomycine *Almirall, Belg.†.*
⊗ Tixocortol pivalate (p.1544·2); neomycin sulfate (p.305·1).
Infective rhinitis.

Rhinovent *Boehringer Ingelheim, Switz.*
Ipratropium bromide (p.1124·1).
Rhinitis.

Rhinovis *CTI, Israel†.*
Carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1).
Rhinitis; sinusitis.

Rhinox *Nycomed, Norw.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Rhinureflex *Boots Healthcare, Fr.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Fever; headache; nasal congestion; rhinitis.

Rhizin *BPRL, Singapore†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Rhodacine *Sandoz, Canad.*
Indometacin (p.66·3).
Gout; musculoskeletal and joint disorders.

Rhodis *Rhodiapharm, Canad.*
Ketoprofen (p.73·1).
Ankylosing spondylitis; osteoarthritis; pain; rheumatoid arthritis.

Rhodogil *Sanofi-Aventis, Spain.*
Spiramycin (p.333·1); metronidazole (p.837·1).
Bacterial infections.

RhoGAM *Ortho Diagnostic, Belg.; Ortho, Hong Kong; Ortho, Hung.; CSL, NZ; Hemat, Turk.; Ortho Diagnostic, USA; Ortho, Venez.†.*
An anti-D immunoglobulin (p.2204·2).
Prevention of rhesus sensitisation.

Rhoival *Byk Gulden, Ger.†; Byk Tosse, Ger.†.*
Agrimony (p.2249·2); solidago virgaurea (p.2391·1); St John's wort (p.422·3); shepherd's purse (p.2386·2); arnica (p.2260·2); valerian (p.2410·1).
Urinary-tract disorders.

Rhonal *Sanofi-Aventis, Spain.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint and peri-articular disorders; pain.

Rho-Nitro *Rhodiapharm, Canad.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Rhophylac *CSL, Cz.; ZLB, Denm.; ZLB, Fin.; Lab Francais du Fractionnement, Fr.; Chiron Vaccines, Ger.; ZLB, Ger.; ZLB, Gr.; Omrix, Israel; ZLB, Ital.; Ivax, Mex.; ZLB, Neth.; ZLB, Norw.; CSL, Port.; ZLB, Swed.; ZLB, Switz.; ZLB, UK; CSL Behring, USA.*
An anti-D immunoglobulin (p.2204·2).
Formerly known as Natead in *Fr.*
Prevention of rhesus sensitisation.

Rhotard *Sovereign, UK.*
⊗ Morphine sulfate (p.86·3).
Pain.

Rhotral *Rhodiapharm, Canad.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; hypertension.

Rhotrimine *Rhodiapharm, Canad.*
Trimipramine maleate (p.426·3).
Depression.

Rhovail *Rhodiapharm, Canad.†.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Rhovane *Rhodiapharm, Canad.*
Zopiclone (p.1039·1).
Insomnia.

Rhuaka *OTC Concepts, UK.*
Cascara (p.1715·2); rhubarb (p.1768·3); senna (p.1769·2).
Constipation.

Rhum Creosotado *Arrow, Braz.*
Creosote (p.1555·1); sodium hypophosphite; calcium hypophosphite (p.1677·1); benzoic acid (p.1630·2).
Respiratory-tract congestion.

Rhumagel *Hoe, Malaysia.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Rhumagrip *Cooperation Pharmaceutique, Fr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Rhumalgan *Sandoz, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Rhumanol *TO-Chemicals, Thai.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Rhumatisme *Gerbex, Canad.*
Methyl salicylate (p.85·3); camphor (p.2273·2); capsicum oleoresin (p.2276·2); trimethylcyclohexanol.

Rhume *Pharmacard, Switz.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Rhumeel *Heel, Neth.*
Homoeopathic preparation.

Rhus Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Rhus Opodeldoc *Knop, Chile.*
Camphor (p.2273·2); rosemary (p.2381·2); thyme (p.2401·1); rhus toxicodendron (p.2378·3); ammonia (p.2256·1).
Musculoskeletal, joint, and soft-tissue disorders.

Rhus toxicodendron Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Rhus-Rheuma-Gel N *DHU, Ger.*
Rhus toxicodendron (p.2378·3); ledum; comfrey (p.2286·3).
Muscle and joint disorders.

Rhynacol *Sunward, Malaysia.*
Pholcodine (p.1570·2); triprolidine hydrochloride (p.592·3).
Cough.

Rhythmiodarone *Farmstandart, Rus.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Rhythmocor *Lannacher, Austria.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rhythmy *Shionogi, Jpn.*
Rilmazafone hydrochloride (p.1024·2).
Insomnia; premedication.

RHZ *Overseas, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

RHZ-Plus *Overseas, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Riabal *Chiesi, Fr.†; IBI, Ital.; Chiesi, Rus.; Fujisawa, Thai.†.*
Prifinium bromide (p.1764·2).
Cholecystopathy; enteritis; gallstones; gastritis; pancreatitis; peptic ulcer; renal calculi; smooth muscle spasm.

Riacen *Promedica, Ital.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Rialam *Labesfal, Port.*
Lorazepam (p.1004·1).
Premedication; status epilepticus.

Riamet *Novartis, Austral.; Novartis, Austria; Novartis, Cz.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Neth.; Novartis, Norw.†; Novartis, Port.; Novartis, Swed.; Novartis, Switz.; Novartis, UK.*
Artemether (p.598·1); lumefantrine (p.605·1).
Malaria.

Riatul *Baliarda, Arg.*
Risperidone (p.1024·2).
Psychoses.

Ribamylase *Ferlux, Fr.*
Alfa amylase (p.2256·3).
Oropharyngeal congestion.

Riban *Arlex, Mex.*
Soya bean (p.1965·3); povidone-iodine (p.1659·2).
Skin disorders.

RibaPak *Par, USA.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Ribapeg *Makiz-Pharma, Rus.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Ribaspheres *Three Rivers, USA.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Ribastamin *Beta, Arg.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Ribastamin Duo *Beta, Arg.*
4 Tablets, risedronate sodium (p.1103·3); 24 tablets calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Ribatab *PRX, USA.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Ribatra *Panalab, Arg.*
⊗ Clobetasol propionate (p.1522·2).
Eczema.

Ribatran *Ferlux, Fr.*
Trypsin (p.2405·3); ribonuclease (p.2378·3); chymotrypsinogen.
Oedema following trauma or surgery.

Ribav *Biosintetica, Braz.*
Ribavirin (p.902·3).
Viral infections.

Ribavin *Lupin, India.*
Ribavirin (p.902·3).
Hepatitis C.

Ribaviron C *Pizarro, Braz.†.*
Ribavirin (p.902·3).
Viral infections.

Ribazole *Getz, Philipp.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Riber *Solvang, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Ribex *Quesada, Arg.*
Vincamine (p.2414·1); cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders.

Ribex Flu *Pfizer Consumer, Ital.†.*
Diclofenac sodium (p.44·3).
Fever; influenza symptoms; pain.

Ribex Nasale *Pfizer Consumer, Ital.†.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Ribex Tosse *Pfizer Consumer, Ital.*
Dropropizine (p.1557·3).
Coughs.

Ribexen con Espettorante *Pfizer Consumer, Ital.*
Dropropizine (p.1557·3); guaifenesin (p.1561·3).
Coughs.

Ribocarbo *Ribosepharm, Ger.*
Carboplatin (p.693·1).
Malignant neoplasms.

Ribocine *Dexa, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Ribodoxo-L *Ribosepharm, Ger.*
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Ribodronat *Ribosepharm, Ger.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Riboepi *Ribosepharm, Ger.*
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Ribofluor *Ribosepharm, Ger.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Ribofolin *Ribosepharm, Ger.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; folic acid deficiency; methotrexate toxicity.

Ribolac *Gebro, Switz.*
Lactobacillus acidophilus (p.2372·3); vitamins (p.1922·1).
Diarrhoea.

Ribolin *Vianex (Βιανεξ), Gr.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ribomicin *Farmigea, Ital.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Ribomunyl
Note. This name is used for preparations of different composition.
Germania, Austria; Silesia, Chile; Pierre Fabre, Fr.†; Pierre Fabre, Ger.; Pharmafabre (Φαρμαφαμπρ), Gr.†; Pierre Fabre, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Robapharm, Switz.
Bacterial ribosomes from, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*; proteoglycan extract from *Klebsiella pneumoniae*.
Respiratory-tract infections.

Pierre Fabre, Cz.
Ribosomes of *Klebsiella pneumoniae*; *Streptococcus pyogenes*; *Haemophilus influenzae*; membrane fraction of *Klebsiella pneumoniae*.
Respiratory-tract infections.

Ribomustin *Ribosepharm, Ger.*
Bendamustine hydrochloride (p.684·1).
Malignant neoplasms.

Ribon *Therabel, Belg.*
Riboflavin (p.1977·2).
Muscle cramps; vitamin B deficiency.

Riboposid *Ribosepharm, Ger.*
Etoposide (p.718·1).
Malignant neoplasms.

Riboquin *Dexa, Indon.*
Chloroquine phosphate (p.599·3).
Malaria.

Ribotal *Adipharm, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Ribotax *Ribosepharm, Ger.*
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.

Ribotrex *Pierre Fabre, Ital.*
Azithromycin (p.207·1).
Bacterial infections.

Ribotripsin *Grin, Mex.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3).

Ribovac
Note.This name is used for preparations of different composition.
Pierre Fabre, Arg.
Ribosomal fractions of *Klebsiella pneumoniae*; membrane fraction of *Klebsiella pneumoniae*.
Formerly contained ribosomal fractions of *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and membrane fraction of *Klebsiella pneumoniae*.
Respiratory-tract infections.

Pierre Fabre, Mex.
Ribosomal fractions of *Klebsiella pneumoniae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Haemophilus influenzae*; membrane fraction of *Klebsiella pneumoniae*.
Respiratory-tract infections.

Ribovir *Plants, Ital.*
Royal jelly (p.2382·1); echinacea (p.2298·1); black currant (p.2267·1).
Nutritional supplement.

Ribo-Wied *Wiedemann, Ger.†.*
Spleen; liver; heart; placenta (p.2337·3).
Tonic.

Ribozym *Sofex, Port.†.*
Ribonucleic acids; glycerophosphates; kola; nicotinamide; thiamine; calcium; sodium (p.1922·1).
Tonic.

Ribrain *Galenica, Gr.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Ribufen *Jofrain, Mex.*
Ibuprofen (p.64·2).
Inflammation; pain; rheumatism.

Ribujet *Chiesi, Spain.*
⊗ Budesonide (p.1520·1).
Asthma.

Ribunal *Combiphar, Indon.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Ribuspir *Torrex Chiesi, Cz.; Chiesi, Gr.*
⊗ Budesonide (p.1520·1).
Asthma; obstructive airways disease.

RIC Calcio *Dominguez, Arg.†.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Rical *Vita Health, Switz.*
Castor oil (p.2278·1).
Constipation.

Ricap *Savio, Ital.*
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Riccovitan *Kropf, Switz.†.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1); ichthammol (p.1599·1); hamamelis (p.2318·2); chamomile (p.2279·3); zinc oxide (p.1621·2).
Burns; nappy rash; superficial wounds; ulcers.

Ricelyt *MM, India.*
Sodium chloride; potassium chloride; sodium citrate; rice (p.1672·2).
Oral rehydration therapy.

Ricerca System *Johnson & Johnson, Ital.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).
Skin, hair, and nail disorders.

Richmond Antiseptic Cream *LPC, UK.*
Cetrimide (p.1634·1).
Burns; skin irritation; wounds.

Ricilaks *Yeni, Turk.*
Castor oil (p.2278·1).
Bowel evacuation.

Ricilina *Pharmabiotics, Chile.*
Azithromycin hydrochloride (p.207·3).
Bacterial infections.

Ricin *Atlantic, Hong Kong; Atlantic, Thai.*
Rifampicin (p.325·3).
Bacterial infections.

Ricipan *Toprak, Turk.*
Castor oil (p.2278·1).
Bowel evacuation.

Ricitel *Tecnofarma, Mex.*
Castor oil (p.2278·1).
Constipation.

Riclasip *Grunenthal, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Riclemed *Pharmacypria, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Ricola *Cedar Health, UK.*
Menthol (p.2340·1); peppermint oil (p.1761·2).
Coughs; nasal congestion; sore throat.

Riconazol *Bunker, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Ricridene *Merck-Lipha, Fr.†.*
Nifurzide (p.307·3).
Diarrhoea.

Rictor *Solfran, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Ricura *Pekana, Ger.†.*
Homoeopathic preparation.

Ricyn *Pascual, Philipp.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis.

RID *Pfizer, USA.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Ridal *Douglas, NZ; Giempi, Venez.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses; schizophrenia.

Ridamin *Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Rid-a-Pain *Pfeiffer, USA.*
Benzocaine (p.1854·1); menthol (p.2340·1); cineole (p.2282·3).
Oral lesions.

Rid-a-Pain HP *Pfeiffer, USA.*
Capsaicin (p.32·3).
Pain.

Ridaq *Pharmacare, S.Afr.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Ridasa *Manuell, Mex.*
Ribonuclease (p.2378·3); dornase alfa (p.1557·1).
Viral infections.

Ridaura *Link, Austral.; GSK, Austria; Astellas, Belg.; GSK, Braz.†; Paladin, Canad.†; Goldshield, Denm.†; Goldshield, Fin.; Astellas, Ger.; Vianex (Βιανέξ), Gr.; Goldshield, Hong Kong; Goldshield, Irl.; Goldshield, Israel; Astellas, Ital.; Boucher & Muir, NZ; Astellas, Neth.; Goldshield, Norw.; Astellas, Port.; Pharmafrica, S.Afr.; Recordati, Spain; Goldshield, Swed.†; Doetsch, Grether, Switz.; Astellas, UK; SmithKline Beecham, USA.*
Auranofin (p.25·3).
Juvenile idiopathic arthritis; psoriatic arthritis; rheumatoid arthritis.

Ridauran *Pierre Fabre, Fr.*
Auranofin (p.25·3).
Rheumatoid arthritis.

Ridazin *Taro, Israel.*
Thioridazine hydrochloride (p.1031·2).
Schizophrenia.

Ridazine *Atlantic, Thai.*
Thioridazine hydrochloride (p.1031·2).
Anxiety; depression; mania; schizophrenia.

Ridcof *Cipla, India.*
Dextromethorphan (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).
Coughs.

Ridenol *RID, USA.*
Paracetamol (p.108·1).

Rideril *DDSA Pharmaceuticals, UK†.*
Thioridazine (p.1031·2).
Schizophrenia.

Ridersweet *Rider, Chile†.*
Aspartame (p.1930·1).
Sugar substitute.

Ridin *Sons, Mex.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Allergic conjunctivitis; coughs; rhinitis.

Ridinox *Bell, India.*
Idoxuridine (p.881·2).
Herpetic keratitis.

Ridiodent *Ogna, Ital.*
Sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).
Dental caries prophylaxis.

Ridol *Gedeon Richter, Hung.†.*
Dacemazine; homatropine methylbromide (p.1881·3); codeine hydrochloride (p.37·2); dipyrone (p.49·2).
Pain; smooth muscle spasm.

Ridon *Anpharm (Ανφαρμ), Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Ridoner *Labochem, Cz.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses.

Ri-Donna *DermoDuemila, Ital.*
Vitamins; selenium; betaine; soya; rhodiola; bacopa moniera; dioscorea; borage (p.1922·1).
Nutritional supplement for women.

Ridron *Baliarda, Arg.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Ridron Pack *Baliarda, Arg.*
Risedronate sodium (p.1103·3); calcium carbonate (p.1714·1).
Osteoporosis.

Riduton Ergo *Francia, Ital.*
Carnitine; betacarotene; glutathione; vitamin C; vitamin E (p.1922·1).
Nutritional supplement.

Ridutox *SoSe, Ital.*
Glutathione (p.1448·1).
Drug-induced neuropathy.

Riduvir *Francia, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

RidWind *ICM, Singapore.*
Simeticone (p.1770·2).
Flatulence; infant colic.

Rielex *Sanval, Braz.*
Dipyrone (p.49·2); orphenadrine citrate (p.812·1); caffeine (p.1116·3).
Skeletal muscle spasm.

RIF
Note. A similar name is used for preparations of different composition (see below).
Armoxindo, Indon.
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Rif
Note. A similar name is used for preparations of different composition (see above).
Kocak, Turk.
Rifamycin sodium (p.329·2).
Bacterial infections.

Rifa
Note.This name is used for preparations of different composition.
Grunenthal, Ger.
Rifampicin (p.325·3) or rifampicin sodium (p.328·2).
Tuberculosis.

Concept, India.
Rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Rifa E *Concept, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol (p.275·2); vitamin B (p.1979·1).
Tuberculosis.

Rifabiotic *Bernofarm, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Rifacilin *Pharmaceutical Co, India.*
Rifampicin (p.325·3).
Tuberculosis.

Rifacin *Prafa, Indon.*
Rifampicin (p.325·3).
Biliary-tract infections; leprosy; meningitis; respiratory infections; tuberculosis.

Rifacol *Vianex (Βιανέξ), Gr.; Formenti, Ital.*
Rifaximin (p.330·1).
Adjuvant in hyperammonaemia; gastrointestinal infections.

Rifacom E-Z *Indoco, India.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1); 2 tablets, pyrazinamide (p.320·2); 1 tablet, ethambutol (p.275·2).
Tuberculosis.

Rifacomb *Ipca, India†; Ipca, Rus.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Pyridoxine (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Rifacomb Plus *Ipca, India†; Ipca, Rus.*
Isoniazid (p.288·1); rifampicin (p.325·3); pyrazinamide (p.320·2).
Tuberculosis.

Rifadecina *Klonal, Arg.†.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis.

Rifadin *Aventis, Arg.; Aventis, Austral.; Aventis, Canad.; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Lepetit, Ital.; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Duncan, Philipp.; Sanofi-Aventis, Port.; Premier, S.Afr.†; Aventis, Swed.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis; bacterial meningitis prophylaxis; treatment of asymptomatic meningococcal carriers.

Rifadine *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.*
Rifampicin (p.325·3) or rifampicin sodium (p.328·2).
Bacterial infections including tuberculosis and leprosy; prophylaxis of meningococcal meningitis.

Rifafour *Aventis, S.Afr.; Aventis, Thai.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol (p.275·2).
Tuberculosis.

Rifagen
Note.This name is used for preparations of different composition.
Genepharm, Gr.
Fluconazole (p.532·1).
Fungal infections.

Llorente, Spain†; General Drugs, Thai.
Rifampicin (p.325·3).
Meningitis; mycobacterial infections.

Rifaldin
Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; IFET (ΙΦΕΤ), Gr.
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis; meningitis.

Sanofi-Aventis, Spain.
Rifampicin sodium (p.328·2).
Bacterial infections including tuberculosis and meningitis.

Rifam *Siam Bheasach, Thai.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and gonorrhoea.

Rifamate *Hoechst Marion Roussel, USA.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Rifamax *Duncan, Philipp.*
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis.

Rifamazid *Polfa Tarchomin, Pol.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Rifamcin *Pond's, Thai.*
Rifampicin (p.325·3).
Tuberculosis.

Rifamed *PannonPharma, Hung.*
Rifampicin (p.325·3).
Brucellosis; leprosy; meningococcal meningitis prophylaxis; tuberculosis.

Rifamor *ICN, Cz.†.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and leprosy.

Rifamp *Neo Quimica, Braz.*
Rifampicin (p.325·3).
Meningitis; tuberculosis.

Rifam-P *PP Lab, Thai.†.*
Rifampicin (p.325·3).
Gonorrhoea; leprosy; tuberculosis.

Rifampyzid *Pond's, Thai.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Rifamtibi *Sanbe, Indon.*
Rifampicin (p.325·3).
Leprosy; tuberculosis.

Rifamycin *Biochem, India.*
Rifampicin (p.325·3).
Tuberculosis.

Rifan *Neo Quimica, Braz.*
Rifamycin sodium (p.329·2).

Rifapiam *Piam, Ital.†.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis.

Rifaprim *Aventis, Arg.; Aventis, Mex.*
Rifampicin (p.325·3); trimethoprim (p.355·2).
Bacterial infections.

Rifasynt *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Thai.†.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and leprosy.

Rifater *Aventis, Austria; Aventis, Canad.; Sanofi-Aventis, Fr.; Grunenthal, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Lepetit, Ital.; Aventis, Mex.; Duncan, Philipp.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Aventis, Switz.; Aventis, Thai.; Aventis, UK; Hoechst Marion Roussel, USA.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Rifaxi *LKM, Arg.*
Ritonavir (p.905·1).
HIV infection.

Rifazid *PannonPharma, Hung.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Rifazida *Pharmacia, Spain†.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Rifcap *Kocak, Turk.*
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis.

Rifedot *Alacan, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Riferina *Bajamed, Mex.*
⊗ Beclometasone (p.1517·2).
Corticosteroid.

Rifex *Winthrop, Port.; Atabay, Turk.*
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis; Gram-positive bacterial infections; tuberculosis.

Rifinah *Aventis, Arg.; Sanofi-Aventis, Fr.; Grunenthal, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Lepetit, Ital.; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Duncan, Philipp.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Aventis, Switz.; Aventis, Thai.; Aventis, UK.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Riflux *Polfarmex, Pol.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rifocin
Aventis, Austria; Lepetit, Ital.
Rifamycin sodium (p.329·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Aventis, Turk.
Rifamycin (p.329·3) or rifamycin sodium (p.329·2). Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rifocina
Aventis, Arg.; Sanofi-Aventis, Port.; Sanofi-Aventis, Venez.
Rifamycin (p.329·3).
Bacterial infections.

Sanofi-Aventis, Braz.
Rifamycin sodium (p.329·2).
Staphylococcal infections.

Rifocine *Sanofi-Aventis, Belg.*
Rifamycin sodium (p.329·2).
Bacterial infections.

Rifocort *Medley, Braz.*
⊗ Rifamycin sodium (p.329·2); prednisolone acetate (p.1541·1).
Skin disorders.

Rifocus *Gerolymatos, Gr.*
Risperidone (p.1024·2).
Psychoses.

Rifocyna *Aventis, Mex.*
Rifamycin sodium (p.329·2).
Impetigo; infected burns and wounds.

Rifoldin *Aventis, Austria.*
Rifampicin (p.325·3).
Asymptomatic Haemophilus influenzae carriers; asymptomatic meningococcal carriers; brucellosis; leprosy; staphylococcal infections; tuberculosis.

Rifoldin INH *Aventis, Austria.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Rifun *Sanol, Ger.; Schwarz, Ger.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rifzin *Pascual, Philipp.*
Capsule, rifampicin (p.325·3); tablet, isoniazid (p.288·1).
Tuberculosis.

Rigenin *Labochem, Cz.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses.

Rigentex *Bracco, Ital.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Riges *Pulitzer, Ital.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Rigesoft *Gedeon Richter, Hung.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Riget *Biolab, Thai.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Rigevidon *Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia; Medimpex, Neth.; Richter, Philipp.; Richter, Pol.; Gedeon Richter, Rus.; Gedeon Richter, Thai.; Aciprosalud, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders.

Rigix *UCB, Austria.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Rigmoz *Elvetium, Arg.†.*
Granisetron hydrochloride (p.1733·1).
Nausea and vomiting.

Rigoletten *Chefaro, Neth.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Rigoran *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Rigotax *Prater, Chile.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Rigotax-D *Prater, Chile.*
Cetirizine (p.571·1); pseudoephedrine (p.1571·2).

Rihest *Otto, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Rikital *Unipharma, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Rikkunshi-to *Tsumura, Jpn.*
Atractylodes lancea rhizome; ginseng; pinellia tuber; poria sclerotium; jujube; citrus unshiu peel; liquorice; ginger.
Traditional Kampo medicine.

Riklinak *Rivero, Arg.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Rikodeine *3M, Austral.*
Dihydrocodeine tartrate (p.48·1).
Coughs.

Rikoderm *3M, Austral.†.*
Light liquid paraffin (p.2031·1); dewaxed wool fat (p.2033·2).
Dry skin disorders.

Rikospray *3M, Ital.*
Aldioxa (p.1587·2); cetylpyridinium chloride (p.1635·1); terpineol (p.2396·1); dimethicone (p.2032·1).
Barrier preparation; skin disinfection.

Rilace *Sanovel, Turk.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Rilace Plus *Sanovel, Turk.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Rilamig *Guidotti, Ital.*
Frovatriptan succinate (p.622·3).
Migraine.

Rilamir *Hexal, Denm.*
Triazolam (p.1033·2).
Insomnia.

Rilan
Note. This name is used for preparations of different composition.
UCI, Braz.†.
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Schering-Plough, Venez.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Allergic respiratory-tract disorders; cold symptoms.

Rilaprost *Guidotti, Ital.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Rilaquin *Microsules, Arg.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Rilasat *Buxton, Arg.*
Riluzole (p.2379·3).
Amyotrophic lateral sclerosis.

Rilast *Esteve, Spain.*
⊗ Formoterol fumarate (p.1122·1); budesonide (p.1520·1).
Obstructive airways disease.

Rilastil *Dermoteca, Port.†.*
SPF 10: Octinoxate (p.1608·2); avobenzone (p.1589·3); zinc oxide (p.1621·2).
Sunscreen.

Rilastil Anti-Oxidante *Dermoteca, Port.†.*
Fish oil; borage; zinc-enriched yeast; lecithin; glyceryl stearate; selenium-enriched yeast; betacarotene; tocoferil acetate (p.1922·1).
Antioxidant; nutritional supplement.

Rilastil Dermo Solar *Dermoteca, Port.*
Tyrosine (p.1971·1); borage oil (p.2267·3); wheat; betacarotene (p.1930·3); bearberry (p.2263·3); alpha tocopherol (p.1992·2); selenium (p.1961·1).

Rilaten *Guidotti, Ital.*
Rociverine (p.2381·1).
Smooth muscle spasm.

Rilatine *Novartis, Belg.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention deficit hyperactivity disorder; narcoleptic syndrome.

Rilcapton *Medochemie, Hong Kong†; Medochemie, Rus.; Medochemie, Singapore.*
Captopril (p.1239·2).
Heart failure; hypertension.

Riledron *Sanofarm, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Rileptid *Egis, Cz.; Egis, Rus.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses.

Rilex *Gry, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle spasticity; skeletal muscle tension.

Rilfit *Apomedica, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); salicylamide (p.121·2); caffeine (p.1116·3).
Fever; pain.

Rilies *Novum, Neth.*
Ketoprofen (p.73·1).
Fever; pain.

Rillus *Kalbe, Indon.*
Lactobacillus reuteri (p.2372·3).
Gastrointestinal disorders; immunostimulant.

Rilow *Indeco, Arg.*
Alprazolam (p.960·1).
Anxiety.

Rilox *Pyridam, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Rilutek *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Aventis, Israel; Aventis, Ital.; Sanofi-Aventis, Jpn; Aventis, Mex.; Sanofi-Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Pol.; Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Rhone-Poulenc Rorer, USA; Sanofi-Aventis, Venez.*
Riluzole (p.2379·3).
Amyotrophic lateral sclerosis.

Rimacid *Ranbaxy, UK.*
Indometacin (p.66·3).

Rimacillin *Ranbaxy, UK.*
Ampicillin (p.204·1).
Bacterial infections.

Rimactan
Sandoz, Austria; Medika, Switz.
Rifampicin (p.325·3) or rifampicin sodium (p.328·2).
Bacterial infections including tuberculosis and leprosy; prophylaxis of meningococcal meningitis.

Sandoz, Denm.; Sandoz, Fr.; Sandoz, Israel; Sandoz, Mex.; Novartis, Neth.†; Sandoz, Norw.; Normal, Port.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Venez.
Rifampicin (p.325·3).
Bacterial infections including tuberculosis and leprosy; prophylaxis of meningococcal meningitis.

Rimactane
Novartis, Hong Kong; Novartis, India; Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Philipp.; Sandoz, S.Afr.; Biochemie, Singapore†; Sandoz, Thai.; Sandoz, UK; Geneva, USA.
Rifampicin (p.325·3).
Bacterial infections including leprosy and tuberculosis; meningococcal meningitis prophylaxis.

Novartis, Irl.
Rifampicin (p.325·3) or rifampicin sodium (p.328·2).
Meningococcal meningitis; mycobacterial infections.

Rimactazid *Sandoz, Denm.; Sandoz, Fin.; Sandoz, Gr.; Sandoz, Indon.; Swedish Orphan, Irl.; Sandoz, Malaysia; Sandoz, Philipp.; Novartis, Rus.; Sandoz, S.Afr.; Sandoz, Singapore; Sandoz, Spain; Sandoz, Swed.; Sandoz, Thai.; Orphan, UK†; Sandoz, Venez.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Mycobacterial infections.

Rimactazid + Z *Novartis, India.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1); 2 tablets, pyrazinamide (p.320·2).
Tuberculosis.

Rimafen *Ranbaxy, UK.*
Ibuprofen (p.64·2).

Rimafungol *Belmac, Spain†.*
Ciclopirox olamine (p.529·2).
Fungal infections.

Rimagrip *Rimafar, Spain.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3); kola (p.2416·1).
Cold and influenza symptoms.

Rimanal *Materfarma, Port.*
A heparinoid (p.1305·2); troxerutin (p.2305·1).
Soft-tissue disorders; thrombophlebitis; venous insufficiency.

Rimapam *Ranbaxy, UK.*
Diazepam (p.986·3).

Rimaped *Pediatrica, Philipp.*
Rifampicin (p.325·3).
Meningococcal meningitis prophylaxis; tuberculosis.

Rimapen *Orion, Fin.*
Rifampicin (p.325·3).
Tuberculosis.

Rimapurinol *Ranbaxy, UK.*
Allopurinol (p.552·2).

Rimarex *Sun, India.*
Moclobemide (p.411·1).
Depression; phobias.

Rimastine *Armstrong, Mex.*
Sulpiride (p.1028·3).
Depression; nausea and vomiting; obsessive-compulsive disorder; schizophrenia; vertigo.

Rimatil *Santen, Jpn.*
Bucillamine (p.2270·1).
Rheumatoid arthritis.

Rimcure *Sandoz, Indon.; Sandoz, Malaysia; Sandoz, Philipp.; Sandoz, S.Afr.; Sandoz, Spain; Sandoz, Swed.; Sandoz, Venez.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Mycobacterial infections.

Rimcure 3-FDC *Sandoz, Thai.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Rimecin *Pharmasant, Thai.*
Rifampicin (p.325·3).
Bacterial infections including tuberculosis, leprosy, and gonorrhoea.

Rimecor *Makiz-Pharma, Rus.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; vascular eye disorders; vestibular disorders.

Rimecure 3-FDC *Novartis, Rus.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Rimevax *GSK, Austral.; SmithKline Beecham, Israel†; GSK, Malaysia†; GSK, Mex.; GSK, NZ; GSK, S.Afr.; GSK, Spain; SmithKline Beecham, Switz.†.*
A measles vaccine (Schwarz strain) (p.2221·3).
Active immunisation.

Rimexel *UCB, Ger.*
⊗ Rimexolone (p.1543·2).
Musculoskeletal and joint disorders.

Rimezone *IAE, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Rimidol *UCB, Swed.†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Rimifon *Pharmion, Fr.; Labatec, Switz.*
Isoniazid (p.288·1).
Tuberculosis and other mycobacterial infections.

Rimivat *Andromaco, Chile.*
Oseltamivir phosphate (p.900·2).
Influenza.

Rimodar *Anglo-French Drugs, India.*
Sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Rimoxallin *Ranbaxy, UK.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Rimoxol *Rimsa, Mex.†.*
Ambroxol (p.1550·3).
Coughs.

Rimpazid *Cadila, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Rimsalin *Rimsa, Mex.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Rimso *Shire, Canad.; Britannia Pharmaceuticals, UK; Research Industries Corp., USA.*
Dimethyl sulfoxide (p.2022·1).
Interstitial cystitis.

Rimstar
Sandoz, Denm.; Sandoz, Fin.; Sandoz, Philipp.; Sandoz, Spain; Sandoz, Swed.
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Mycobacterial infections.

Sandoz, Indon.; Sandoz, S.Afr.; Sandoz, Thai.
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol (p.275·2).
Mycobacterial infections.

Rimstar 4-FDC *Novartis, Rus.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Rimycin *Alphapharm, Austral.*
Rifampicin (p.325·3).
Leprosy; prophylaxis of Haemophilus influenzae type B infection; prophylaxis of meningococcal infection; tuberculosis.

Rin Up *Farma Lepori, Spain†.*
Phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract congestion.

Rinade BID *Econo Med, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Rinadex Compuesto *Diba, Mex.*
⊗ Dexamethasone sodium phosphate (p.1526·2); xylometazoline hydrochloride (p.1575·1); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Infected skin disorders; otitis externa.

Rinadine *Pharmaland, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Rinafort *Schering-Plough, Malaysia; Schering-Plough, Singapore.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Upper respiratory-tract congestion.

Rinaid *Medipharm, Chile.*
Desloratadine (p.576·1).
Allergic rhinitis.

Rinalix *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
⊗ Indapamide (p.1314·1).
Hypertension.

Rinantipiol *Ottolenghi, Ital.†.*
⊗ Silver protein (p.2387·3); resorcinol (p.1612·1); niaouli oil (p.2351·3); adrenaline hydrochloride (p.1203·3); procaine hydrochloride (p.1869·1).
Nasal congestion.

Rinaqua *Farma, Venez.†.*
⊗ Budesonide (p.1520·1).
Nasal polyps; rhinitis.

Rinase *Schering-Plough, Venez.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; cold symptoms.

Rinatec *Boehringer Ingelheim, Irl.; Boehringer Ingelheim, UK.*
Ipratropium bromide (p.1124·1).
Rhinitis; rhinorrhoea.

Rinazina *GSK Consumer, Ital.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Rince Bouche Antiseptique *Atlas, Canad.*
Cetylpyridinium chloride (p.1635·1).

Rindex *Teva, Hung.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Rindobion *Yarindo, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Rinelon *Malesci, Ital.; Schering-Plough, Mex.; Essex, Philipp.; Schering-Plough, S.Afr.†; Menarini, Spain; Schering-Plough, Thai.†.*
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; nasal polyps; sinusitis.

Rinerge *Atral, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Rinex *Triomed, S.Afr.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; cold and influenza symptoms.

Rinexin *Recip, Fin.; Recip, Norw.; Recip, Swed.*
Phenylpropanolamine hydrochloride (p.1569·3).
Rhinitis; urinary incontinence.

Ring N *Mack, Cz.†; Pfizer Consumer, Ger.*
Aspirin (p.20·3); caffeine (p.1116·3); ascorbic acid (p.1983·3).
Cold symptoms; fever; inflammation; pain.

Ringer Lactato Vitulia *Ern, Spain.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte depletion.

Ringerfundin *Braun, Cz.; Braun, Fin.; Braun, Hung.*
Electrolyte infusion with malic acid (p.1667·1).
Fluid and electrolyte disorders.

Ringersteril *Baxter, Fin.*
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Ringeruv *Braun, Cz.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Ringworm Ointment *Douglas, Austral.*
Tolnaftate (p.548·3).
Ringworm.

Rinialer *Bialfar, Port.; Bial, Spain.*
Rupatadine fumarate (p.590·2).
Allergic rhinitis; urticaria.

Rinicold *Shreya, Rus.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Rinicold-Broncho *Shreya, Rus.*
Ambroxol hydrochloride (p.1550·3); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Rinidyl DN *Diba, Mex.*
⊗ Dexamethasone (p.1526·1); phenylephrine (p.1568·1); neomycin (p.305·1).
Formerly contained dexamethasone, polymyxin B, and neomycin.

Rinikind *VSM, Neth.*
Homoeopathic preparation.

Rinil *Recip, Swed.†.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Rinileen *VSM, Neth.*
Homoeopathic preparation.

Rinilyn *Chefaro, Spain†.*
Sodium cromoglicate (p.1136·3).
Hay fever; rhinitis.

Rinisona *Phoenix, Arg.*
⊗ Fluticasone propionate (p.1533·2).
Allergic rhinitis; asthma.

Rinisone *Medley, Braz.*
⊗ Prednisolone sodium phosphate (p.1541·2); ephedrine hydrochloride (p.1558·2); naphazoline nitrate (p.1565·2).
Nasal disorders.

Rinitalmit *Gunsa, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2).
Nasal congestion.

Rinitrin *Svizera, India.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Rinityn *Hovid, Hong Kong; Hovid, Philipp.; Hovid, Singapore.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions; urticaria.

Rinizol *Ilsan, Turk.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Rinlaxer *Taisho, Jpn.*
Chlorphenesin carbamate (p.1894·3).
Skeletal muscle spasm.

Rinnova *Pharmacia, Ital.*
Calcium glycerophosphate; colecalciferol; soya isoflavones (p.2391·2) (p.1922·1).
Menopausal disorders.

Rinnovi *Quinnova, USA.*
⊗ Urea (p.1620·2).
Nail disorders.

Rino Calyptol *SIT, Ital.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Rino Clenil *Chiesi, Ital.; Chiesi, Singapore†; Chiesi, Thai.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Rino Dexa *Sanofi-Aventis, Spain.*
⊗ Chlorphenamine maleate (p.571·3); dexamethasone sodium phosphate (p.1526·2); muramidase hydrochloride (p.2348·1); neomycin sulfate (p.305·1).
Rhinitis; rhinopharyngeal infection; sinusitis.

Rino Ebastel *Almirall, Spain.*
Pseudoephedrine hydrochloride (p.1571·2); ebastine (p.579·1).
Allergic rhinitis.

Rino Naftazolina *Bruschettini, Ital.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Rino Resfenol *Galenogal, Braz.†.*
⊗ Naphazoline (p.1565·1).
Nasal congestion.

Rino-Azetin *UCI, Braz.†.*
Azelastine hydrochloride (p.568·2).
Hypersensitivity reactions.

Rino-B *Cassara, Arg.*
⊗ Budesonide (p.1520·1).
Laryngitis; pharyngitis; rhinitis.

Rinobactil *CEPA, Spain.*
Ebastine (p.579·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Rinobalsamiche *Farmatre, Ital.†; Ramini, Ital.†; Sella, Ital.†.*
Menthol (p.2340·1); niaouli oil (p.2351·3).
Nasal congestion.

Rinobanedif
Note. This name is used for preparations of different composition.
Bago, Chile.
⊗ Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); xylometazoline hydrochloride (p.1575·1); antazoline phosphate (p.567·1).
Rhinitis; sinusitis.

Bayer, Spain.
⊗ Bacitracin zinc (p.210·3); phenylephrine hydrochloride (p.1568·1); neomycin sulfate (p.305·1); prednisolone (p.1540·3); cineole (p.2282·3); niaouli oil (p.2351·3).
Upper respiratory-tract disorders.

Rinoben *Cazi, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Rinoblanco *Alcon Cusi, Spain.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Rinocidina *Valeas, Ital.*
⊗ Tyrothricin (p.358·2); naphazoline nitrate (p.1565·2).
Rhinitis; sinusitis.

Rinoclenil *Elmor, Venez.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Rinocusi Vitaminico *Sanofi-Aventis, Spain.*
Vitamin A (p.1971·2).
Nasal congestion; nasal irritation.

Rinodan *Medipharm, Chile.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene; rhinitis.

Rinodrina *Farma, Venez.†.*
Terfenadine (p.590·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; sinusitis.

Rinofilax *Pediapharm, Chile; Recalcine, Chile.*
Desloratadine (p.576·1).
Allergic rhinitis; urticaria.

Rinofilax AG M *Raffo, Arg.*
⊗ Naphazoline (p.1565·1); neomycin (p.305·1).
Nasal congestion.

Rinofluimucil *Zambon, Braz.; Zambon, Hong Kong; Zambon, Hung.; Zambon, Ital.; Zambon, Port.; Zambon, Rus.; Zambon, Switz.; Zambon, Thai.*
⊗ Acetylcysteine (p.1548·2); tuaminoheptane sulfate (p.1575·1).
Formerly contained acetylcysteine, tuaminoheptane sulfate, and fludrocortisone acetate in *Braz.*
Nasal congestion; rhinitis; sinusitis.

Rinofluimucil-S *Zambon, Ger.†.*
⊗ Acetylcysteine (p.1548·2); tuaminoheptane sulfate (p.1575·1).
Rhinitis; sinusitis.

Rinoflumil *Zambon, Spain.*
⊗ Acetylcysteine (p.1548·2); tuaminoheptane sulfate (p.1575·1).
Rhinitis.

Rinoflux *IMA, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Rinofomentil *SIT, Ital.†.*
⊗ Silver protein (p.2387·3); naphazoline nitrate (p.1565·2); niaouli oil (p.2351·3).
Nasal disorders.

Rinofren *Carnot, Mex.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Allergic rhinitis; hay fever; rhinopharyngitis; sinusitis.

Rinofren Pediatrico *Carnot, Mex.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Rinofrenal
Note. This name is used for preparations of different composition.
Chefaro, Ital.
Sodium cromoglicate (p.1136·3); chlorphenamine maleate (p.571·3).
Rhinitis.

Sigma-Tau, Spain.
Sodium cromoglicate (p.1136·3).
Hay fever; rhinitis.

Rinofrenal Plus *Sigma-Tau, Spain.*
Chlorphenamine maleate (p.571·3); sodium cromoglicate (p.1136·3).
Hay fever; rhinitis.

Rinofrim *Laboratorios Chile, Chile†.*
Phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1); carbinoxamine maleate (p.570·2).
Cold and influenza symptoms; otitis media; rhinitis; sinusitis.

Rinogan *Confar, Port.†.*
Chlorphenamine (p.572·2); phenylpropanolamine (p.1569·2); ascorbic acid (p.1983·3).

Rinogel *Cassara, Arg.*
⊗ Sodium cromoglicate (p.1136·3); naphazoline hydrochloride (p.1565·2).
Allergic rhinitis; epistaxis; nasal surgery.

Rinogerol *Brasmedica, Braz.†.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).

Rinogest *Sanovel, Turk.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Rinoglin *Seber, Port.†.*
Chlorphenamine maleate (p.571·3); sodium cromoglicate (p.1136·3).
Conjunctivitis; eye irritation; rhinitis.

Rinogutt Antiallergico Spray *Boehringer Ingelheim, Ital.*
⊗ Tramazoline hydrochloride (p.1574·3); chlorphenamine maleate (p.571·3).
Allergic rhinitis.

Rinogutt Atlantic *Fher, Ital.*
Glycerol (p.2314·2); copper (p.1935·2).
Nasal cleansing; nasal dryness.

Rinogutt Eucalipto-Fher *Boehringer Ingelheim, Ital.*
⊗ Tramazoline hydrochloride (p.1574·3); cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Rinogutt Spray-Fher *Boehringer Ingelheim, Ital.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Rinojet *Valeas, Ital.†.*
⊗ Betamethasone (p.1518·2); phenylephrine hydrochloride (p.1568·1).
Rhinitis; rhinopharyngitis; sinusitis.

Rinojet SF *Valeas, Ital.†.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infections of the upper respiratory tract.

Rinokid *D & M, Chile.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene.

Rinolan *Berman, Mex.*
Phenylephrine (p.1568·1).

Rinolar *Saba, Turk.*
Menthol (p.2340·1); cineole (p.2282·3); niaouli oil (p.2351·3); benzoin tincture (p.2394·2).
Respiratory-tract disorders.

Rinolast *Farma, Venez.*
Fexofenadine hydrochloride (p.579·3).
Upper respiratory-tract allergies.

Rinolast D *Farma, Venez.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract allergies.

Rino-Lastin *Ache, Braz.*
Azelastine hydrochloride (p.568·2).
Nasal congestion.

Rinolergan *Grunenthal, Chile.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Cold symptoms; rhinitis; sinusitis.

Rinolet *Leti, Venez.*
⊗ Budesonide (p.1520·1).

Rinoliber *Tecnimede, Port.*
Cetirizine hydrochloride (p.570·3).

Rinolic *GMP, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Rinomar
Note. This name is used for preparations of different composition.
Janssen-Cilag, Belg.
Pseudoephedrine hydrochloride (p.1571·2).
Formerly contained cinnarizine, phenylpropanolamine hydrochloride, and isopropamide iodide.
Rhinitis.

Recip, Fin.; Recip, Swed.
Cinnarizine (p.573·1); phenylpropanolamine hydrochloride (p.1569·3).
Allergic rhinitis; nasal congestion; vasomotor rhinitis.

Rinomax
Note. This name is used for preparations of different composition.
Ern, Spain.
Carbinoxamine maleate (p.570·2); pseudoephedrine (p.1571·2).
Nasal congestion.

Oftalmi, Venez.
Kanamycin sulfate (p.291·2); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis with infection.

Rinomex *Pediapharm, Chile.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Cold symptoms; otitis media; rhinitis; sinusitis.

Rinomicine
Note. This name is used for preparations of different composition.
Fardi, Spain.
Oral sachets: Ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); salicylamide (p.121·2).
Influenza and cold symptoms; nasal congestion.

Fardi, Spain.
Tablets: Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); salicylamide (p.121·2).
Influenza and cold symptoms; nasal congestion.

Rinomicine Activada *Fardi, Spain.*
Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); salicylamide (p.121·2).
Influenza and cold symptoms; nasal congestion.

Rinopaidolo *Deca, Ital.*
Niaouli oil (p.2351·3); eucalyptus oil (p.2301·2).
Nasal congestion.

Rinopanteina *DMG, Ital.*
Dexpanthenol (p.2362·1); vitamin A (p.1971·2).
Nasal hygiene.

Rinoparin *Pasteur, Chile†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Rino-Ped *Stiefel, Braz.†.*
Sodium chloride (p.1686·1).
Nasal congestion.

Rinoretard *Pfizer Consumer, Spain†.*
Carbinoxamine (p.570·2); phenylpropanolamine (p.1569·2).
Nasal congestion.

Rinorix *Boehringer Ingelheim, Austria.*
⊗ Tramazoline hydrochloride (p.1574·3).
Rhinitis.

Rinos-A *Farmasa, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Rinosbon *Eversil, Braz.†.*
⊗ Dexamethasone (p.1526·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Nasal disorders.

Rinosedin *Streuli, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Adjunct in rhinoscopy; cold symptoms; otitis media; sinus disorders.

Rinosite *Sanval, Braz.†.*
⊗ Naphazoline hydrochloride (p.1565·2); diphenhydramine hydrochloride (p.577·2); neomycin sulfate (p.305·1).
Nasal congestion.

Rinosol *Cassara, Arg.; Biospray, Gr.*
⊗ Beclometasone dipropionate (p.1516·2).
Allergic rhinitis; asthma.

Rinosone *Faes, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Nasal polyps; rhinitis.

Rinosoro *Farmasa, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Rinostat *RPG, India.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Rinoster *Zwitter, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Rinosteryl *Mintlab, Chile.*
Sodium chloride (p.1686·1).
Nasal congestion.

Rinostil *Deca, Ital.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); thymol (p.1664·3); menthol (p.2340·1).
Rhinopharyngeal congestion.

Rinot *Arex, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold symptoms.

Rinotil *Brasmedica, Braz.†.*
Sodium chloride (p.1686·1); benzalkonium chloride (p.1629·1).
Nasal congestion.

Rinotirfen *Megat, Venez.†.*
Terfenadine (p.590·3); pseudoephedrine hydrochloride (p.1571·2).

Rinotricina *SIT, Ital.*
Tyrothricin (p.358·2).
Rhinitis; sinusitis.

Rinovagos *Valeas, Ital.*
Ipratropium bromide (p.1124·1).
Rhinitis.

Rinoval *Saval, Chile†.*
⊗ Mometasone furoate (p.1539·3).
Rhinitis.

Rinovel *Ern, Spain.*
⊗ Naphazoline nitrate (p.1565·2); neomycin sulfate (p.305·1); prednisolone (p.1540·3).
Congestion and infection of the nose and ear.

Rinoven *Medipharm, Chile.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; upper respiratory-tract congestion.

Rinoven Compuesto *Medipharm, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Bronchitis; cold and influenza symptoms; otitis; rhinitis; sinusitis.

Rinovit *SIT, Ital.*
⊗ Ephedrine (p.1558·1); cineole (p.2282·3); niaouli oil (p.2351·3).
Nasal congestion.

Rinovitex *Alcon Cusi, Spain.*
Vitamin A acetate (p.1973·1).
Nasal irritation.

Rinowash *Markos-Mefar, Ital.*
Sodium chloride (p.1686·1).
Nasal cleansing.

Rinox VX *Vannier, Arg.*
⊗ Oxymetazoline (p.1567·2).
Nasal congestion.

Rins-Aqua *Teva, Hung.*
Water for injections (p.2414·3).

Rins-Ringer *Teva, Hung.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Rins-Sal *Teva, Hung.*
Sodium chloride infusion (p.1686·1).

Rinstead
Note. This name is used for preparations of different composition.
Schering-Plough, UK.
Sugar-free pastilles: Menthol (p.2340·1); cetylpyridinium chloride (p.1635·1).
Denture irritation; mouth ulcers.
Schering-Plough, UK.
Topical gel: Benzocaine (p.1854·1); chloroxylenol (p.1640·2).
Mouth pain; mouth ulcers.

Rinstead Teething Gel *Schering-Plough, UK†.*
Lidocaine (p.1862·3); cetylpyridinium chloride (p.1635·1).
Mouth ulcers; teething pain.

Rintac *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rinvox *Yarindo, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Rinxofay *Umeda, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Rinza *Unique, Rus.*
Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Allergic disorders of the upper respiratory tract; rhinitis; sinusitis.

Rinza Lorsept *Unique, Rus.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).

Rinzasip *Unique, Rus.*
Paracetamol (p.108·1); caffeine (p.1116·3); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

Riodine *Orion, NZ.*
Povidone-iodine (p.1659·2).
Skin and wound disinfection; skin infections.

Riomet *Ranbaxy, Malaysia; Ranbaxy, USA.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Rionit *Buxton, Arg.*
Zoledronic acid (p.1106·1).
Bone metastases; osteoporosis; Paget's disease of bone.

Riopan
Note. This name is used for preparations of different composition.
Altana, Arg.; Altana, Austria; Altana, Belg.; Nycomed, Braz.; Madaus, Fr.; Altana, Ger.; Nycomed, Gr.; Altana, Ital.; Altana, Port.; Altana, Switz.; Whitehall, USA.
Magaldrate (p.1742·3).
Antacid; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; gastrointestinal motility disorders; oesophagitis; peptic ulcer.
Altana, Mex.
Magaldrate (p.1742·3); dimeticone (p.1770·2).
Gastrointestinal disorders associated with hyperacidity.

Riopan Plus *Nycomed, Braz.; Whitehall, USA.*
Magaldrate (p.1742·3); dimeticone (p.1770·2).
Dyspepsia; gastrointestinal disorders.

Riopone *Akromed, S.Afr.*
Magaldrate (p.1742·3).
Gastric hyperacidity.

Riostatin *Adcock Ingram, S.Afr.*
Tetracycline hydrochloride (p.347·2); nystatin (p.543·2); vitamin B substances (p.1922·1); ascorbic acid.
Bacterial infections.

Riotane *Orion, NZ.*
Chlorhexidine gluconate (p.1635·3).
Skin, wound, and instrument disinfection.

Rioven *Novartis, Gr.†.*
Diosmin (p.2304·2).
Capillary disorders.

Rioworm *Adcock Ingram, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Ripedon *EGIS, Hung.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; dementia; schizophrenia.

Ripepral *Verisfield, Gr.*
Risperidone (p.1024·2).
Psychoses.

Ripetomar *Labochem, Cz.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses.

Riphenidate *Technilab, Canad.†.*
⊗ Methylphenidate hydrochloride (p.2159·2).

Ripix *Novartis, Gr.†; Novartis, Ital.; Novartis, Switz.*
⊗ Metipranolol (p.1883·2); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Ripol *Laboratorios Chile, Chile.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Riposon *Vianex (Βιανεξ), Gr.*
Tibezonium iodide (p.2402·1).
Mouth infections.

Ripox *Biomep, Mex.*
Piroxicam (p.117·3).

Ripped Max *Empresa de Nutricion, Arg.*
Chromium tripicolinate (p.1934·3).
Dietary supplement.

Riprazo *Novartis, Cz.; Novartis, Port.*
Aliskiren (p.1207·1).
Hypertension.

Riprocin *IAE, Philipp.*
Rifampicin (p.325·3).
Leprosy; meningococcal meningitis prophylaxis; tuberculosis.

Riptam *Asofarma, Mex.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Risatarun *Ravensberg, Ger.*
⊗ Deanol aceglumate (p.2152·3).
Nervous system disorders.

Rischiaril *Piam, Ital.†.*
⊗ Deanol hemisuccinate (p.2152·3).
Mental function impairment.

Risdonal *Alkaloid, Rus.*
Risperidone (p.1024·2).
Behavioural disturbances; bipolar disorder; psychoses.

Risedon *Buxton, Arg.*
Risedronate sodium (p.1103·3).
Osteoporosis; Paget's disease of bone.

Risedross *Sigma, Braz.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Risek *Getz, Philipp.; Julphar, UAE.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Riselle *Organon, Braz.; Organon, Cz.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Risenar *Minerva (Μινερβα), Gr.*
Risperidone (p.1024·2).
Psychoses.

Risendros *Zentiva, Cz.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Risepro *Valeant, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; schizophrenia.

Risfarmal *Farmalider, Spain.*
Risperidone (p.1024·2).
Autism; dementia; psychoses.

Risgal *Galenus, Gr.*
Risperidone (p.1024·2).
Psychoses.

Risicordin *Heumann, Ger.†.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Ascites; hyperaldosteronism; hypertension; liver cirrhosis; oedema.

Risidon *Merck, Port.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Risidral *Pharmanel, Gr.*
Risperidone (p.1024·2).
Psychoses.

Risina *Tempo Scan Pacific, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Risnia *Cipla, India.*
Risperidone (p.1024·2).
Schizophrenia.

Risocalm *Medifive, Thai.*
Tolperisone hydrochloride (p.1899·3).
Skeletal muscle spasm.

Risofos *Cipla, India.*
Risedronate sodium (p.1103·3).
Osteoporosis.

Risolid *Alpharma, Denm.; Alpharma, Fin.*
Chlordiazepoxide (p.968·1).
Alcohol withdrawal syndrome; anxiety; insomnia; muscle spasm.

Risoniac *Klonal, Arg.†.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Tuberculosis.

Risopent *Boehringer Ingelheim, Venez.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Risordan
Note. This name is used for preparations of different composition.
Elvetium, Arg.†.
Vitamin E acetate (p.1992·3).
Vitamin E deficiency.
Sanofi-Aventis, Fr.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; pulmonary oedema.

Rispadim *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Rispalm *Polychronus, Gr.*
Risperidone (p.1024·2).
Psychoses.

Rispedep *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Rispedolet *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Rispedospes *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Rispefar *Specifar, Gr.*
Risperidone (p.1024·2).
Psychoses.

Rispemar *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Rispen *Zentiva, Cz.; Zentiva, Pol.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses; schizophrenia.

Risper *Bouzen, Arg.*
Risperidone (p.1024·2).
Psychoses.

Rispera *Ingers, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Risperascol *Alet, Gr.*
Risperidone (p.1024·2).
Psychoses.

Risperatio *Ratiopharm, Pol.*
Risperidone (p.1024·2).
Schizophrenia.

Risperdal *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Organon, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Ethnor, India; Alkermes, Indon.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen, Jpn; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Janssen, USA; Janssen-Cilag, Venez.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; mania; psychoses; schizophrenia.

Risperid *Roemmers, Venez.*
Risperidone (p.1024·2).
Psychoses.

Risperin *Gador, Arg.*
Risperidone (p.1024·2).
Psychoses.

Risperinin *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Risperit *Labochem, Cz.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses.

Risperiwin *Winthrop, Pol.*
Risperidone (p.1024·2).
Schizophrenia.

Risperom *Alvia (Αλβια), Gr.*
Risperidone (p.1024·2).
Psychoses.

Risperon *Lek-Am, Pol.*
Risperidone (p.1024·2).
Bipolar disorder; schizophrenia.

Risperoprol *Proel, Gr.*
Risperidone (p.1024·2).
Psychoses.

Rispex *Vannier, Arg.*
Risperidone (p.1024·2).
Psychoses.

Rispid *Panacea, India†.*
Risperidone (p.1024·2).
Psychoses.

Rispimed *Regiomedica, Cz.; Regiomedica, Neth.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; schizophrenia.

Rispimedica *Regiomedica, Neth.*
Risperidone (p.1024·2).
Schizophrenia.

Rispogen *Genepharm, Gr.*
Risperidone (p.1024·2).
Psychoses.

Rispolept *Janssen-Cilag, Pol.; Janssen, Rus.*
Risperidone (p.1024·2).
Autism; behaviour disorders; bipolar disorder; psychoses; schizophrenia.

Rispolin *Janssen-Cilag, Austria.*
Risperidone (p.1024·2).
Psychoses.

Rispolux *Sandoz, Cz.; Sandoz, Hung.; Sandoz, Pol.*
Risperidone (p.1024·2).
Aggressive behaviour in dementia; schizophrenia.

Rispons *Actavis, Hung.*
Risperidone (p.1024·2).
Schizophrenia.

Risset *Pliva, Cz.; Farmacom, Pol.; Pliva, Rus.*
Risperidone (p.1024·2).
Behaviour disorders; bipolar disorder; psychoses; schizophrenia.

Risthal *Pasteur, Chile†.*
Aluminium hydroxide (p.1706·2).
Antacid.

Risto *Medicine Products, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Ristolzit *Leovan, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Ristotadin *Leovan, Gr.*
Loratadine (p.583·3).

Ritalin *Novartis, Austral.; Novartis, Austria; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Hung.; Phoenix, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Swed.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritalina *Novartis, Arg.; Novartis, Braz.; Novartis, Port.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritaline *Novartis, Fr.; IFET (ΙΦΕΤ), Gr.; Novartis, Switz.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritalmex *Valeant, Hung.*
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Ritamine *Demo, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Ritaphen *Triomed, S.Afr.†.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Riteban *Centrum, Spain†.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Ritechol *Niche, Irl.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Rite-Diet *SHS, Fr.†; Scientific Hospital Supplies, Irl.; Nutricia Dietary, UK.*
Low-protein, gluten-free food for special diets (p.1922·1).
Gluten sensitivity; liver disorders; phenylketonuria; renal failure.

Rithmik *Arrow, Austral.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Rithroprol *Proel, Gr.*
Clarithromycin (p.248·2).
Bacterial infections.

Ritin *Eczacibasi, Turk.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Rition *Piam, Ital.*
Glutathione sodium (p.1448·1).
Cisplatin-type drug-induced neuropathy.

Ritmenal *Sanitas, Chile.*
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Ritmetol *ICN, Hung.†.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ritmilan *Biogalenic, Venez.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Ritmocardyl *Sanofi Synthelabo, Arg.; Bago, Chile.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Ritmocit *Asofarma, Arg.†.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Ritmocor
Note. This name is used for preparations of different composition.
Drugtech, Chile.
Propafenone hydrochloride (p.1379·2).
Arrhythmias.
Malesci, Ital.
Quinidine polygalacturonate (p.1383·2).
Arrhythmias.

Ritmodan IFET (ΙΦΕΤ), Gr.†; Aventis, Port.†.
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Sanofi-Aventis, Ital.
Disopyramide (p.1269·1) or disopyramide phosphate (p.1269·2).
Arrhythmias.

Ritmoforine Aventis, Neth.
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Ritmogel Terapeutico, Ital.
Royal jelly (p.2382·1).
Nutritional supplement.

Ritmolol Cryopharma, Mex.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Ritmonorm Abbott, Braz.
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Ritmopuls Belupo, Cz.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Ritomax-L Alkem, India.
Lopinavir (p.896·3); ritonavir (p.905·1).
HIV infection.

Ritomune Cipla, India.
Ritonavir (p.905·1).
HIV infection.

Ritopar Elea, Arg.; Agis, Israel.
⊗ Ritodrine hydrochloride (p.2017·2).
Fetal distress during labour; premature labour; uterine relaxation.

Ritosin Biofarma, Turk.
Roxithromycin (p.331·1).
Bacterial infections.

Ritovir Cristalia, Braz.†.
Ritonavir (p.905·1).
HIV infection.

Ritran Biosynthesis, Gr.
Clarithromycin (p.248·2).
Bacterial infections.

Ritraz Rivero, Arg.
Trace element preparation (p.1922·1).

Ritro Benedetti, Ital.
Flurithromycin ethyl succinate (p.278·1).
Bacterial infections.

Ritrocel Silesia, Chile.
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Ritromine Hexa, Arg.
Norfloxacin (p.309·2).
Bacterial infections.

Ritroprim Klonal, Arg.†.
Rifampicin (p.325·3); trimethoprim (p.355·2).
Bacterial infections.

Rituxan Roche, Canad.; Chugai, Jpn; Genentech, USA; IDEC, USA.
Rituximab (p.767·1).
Non-Hodgkin's lymphoma; rheumatoid arthritis.

Ritvir Rontag, Arg.
Nevirapine (p.899·1).
HIV infection.

Rityne Osoth, Thai.
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Riuclonaz Medipharma, Arg.
Clonazepam (p.478·2).

Riva Intermed, Gr.
Betahistine hydrochloride (p.2265·1).
Vertigo.

Riva D Riva, Canad.
Colecalciferol (p.1986·2).

Rivacefin Rivero, Arg.
Ceftriaxone (p.238·1).
Bacterial infections.

Rivacor Lannacher, Austria.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Rivacor Plus Lannacher, Austria.
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Rivanase Riva, Canad.
⊗ Beclometasone dipropionate (p.1516·2).
Corticosteroid.

Rivanol Chinosolfabrik, Ger.; Prolab, Pol.; Sifa, Turk.
Ethacridine lactate (p.1625·1).
Antiseptic; bacterial infections of skin and mucous membranes; burns; skin disinfection; ulcers; wounds.

Rivanolum ICN, Pol.
Ethacridine lactate (p.1625·1).
Bacterial infections of skin and mucous membranes; burns; wounds.

Rivasa Riva, Canad.
Aspirin (p.20·3).

Rivasol Riva, Canad.
Zinc sulfate (p.1999·2).
Anorectal disorders.

Rivasol HC Riva, Canad.
⊗ Zinc sulfate (p.1999·2); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Rivatril Roche, Fin.
Clonazepam (p.478·2).
Epilepsy.

Rivazol Loeffler, Mex.
Albendazole (p.139·2).
Worm infections.

Rivecrum Rivero, Arg.
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Rivel Emo-Farm, Pol.
Ethacridine lactate (p.1625·1).
Disinfection of skin and mucous membranes; wounds.

Riveparin
Rivero, Arg.
Heparin (p.1301·2).
Anticoagulant.

Lapreven, Venez.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Rivepime Rivero, Arg.
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Rivervan Rivero, Arg.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Rivescal Tar Sifarma, Ital.
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Seborrhoeic dermatitis.

Rivescal ZPT Sifarma, Ital.
Pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Rivial Rivero, Arg.
Multivitamin preparation for infusion (p.1922·1).

Rivilina Rivero, Arg.
Aprotinin (p.1055·1).

Rivistel Delagrange, Port.†.
Alpiropride (p.618·2).
Migraine.

Rivitin BC Lannacher, Austria.
Vitamin B substances and vitamin C (p.1922·1).

Rivocor ProMed, Cz.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Rivodaron ProMed, Cz.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Rivodarone Rivopharm, Switz.†.
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Rivodol Rivopharm, Switz.†.
Paracetamol (p.108·1).
Fever; pain.

Rivoltan Krewel, Ger.
Devil's claw root (p.39·1).
Degenerative joint disorders.

Rivotril Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Cz.; Roche, Denm.; Roche, Fr.; Roche, Ger.; IFET (ΙΦΕΤ), Gr.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, Venez.
Clonazepam (p.478·2).
Anxiety; epilepsy; obsessive-compulsive disorder; panic disorder; status epilepticus; trigeminal neuralgia.

Rivozol Rivopharm, Switz.†.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Rivuclin SIFFRA, Ital.
Vitamins (p.1922·1); lactoferrin (p.2330·1); *Lactobacillus paracasei* (p.2372·3); myrtillus (p.2349·3).
Urinary-tract infections.

Riwa Franzbranntwein Gerlach, Ger.
⊗ Camphor (p.2273·2); alcohol (p.1625·2).
Musculoskeletal, joint, and soft-tissue disorders; poor circulation.

α-Rix GSK, Belg.
An influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Rixapen Menarini, Belg.
Clometocillin potassium (p.255·3).
Bacterial infections.

Rixil Bracco, Ital.
Valsartan (p.1420·2).
Hypertension.

Rixtal Biomep, Mex.
Itraconazole (p.536·3).
Fungal infections.

Rizaben Kissei, Jpn.
Tranilast (p.1149·2).
Allergic conjunctivitis; allergic rhinitis; asthma; atopic eczema; keloids.

Rizact Cipla, India.
Rizatriptan benzoate (p.625·1).
Migraine.

Rizalief MSD, Austria.
Rizatriptan benzoate (p.625·1).
Migraine.

Rizaliv Neopharmed, Ital.
Rizatriptan benzoate (p.625·1).
Migraine.

Rizalt MSD, Israel.
Rizatriptan (p.625·1).
Migraine.

Rizan Novartis, Spain.
Pimecrolimus (p.1609·1).
Atopic eczema.

Rizatan MSD, Neth.
Rizatriptan benzoate (p.625·1).
Migraine.

Rize Silesia, Chile; Mitsubishi, Jpn.
Clotiazepam (p.980·3).
Alcohol withdrawal symptoms; anxiety; autonomic disorders; premedication; sleep disorders.

Rizen Formenti, Ital.
Clotiazepam (p.980·3).
Anxiety disorders; sleep disorders.

Rizodal Guardian, Indon.
Risperidone (p.1024·2).
Psychoses.

Rizonax Novell, Indon.
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

R-Loc Cadila, India.
Ranitidine (p.1766·1) or ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

RMS
Note. This name is used for preparations of different composition.
Asconex, Ger.†.
Lactic acid (p.2329·3).
Skin disorders.

Upsher-Smith, USA.
⊗ Morphine sulfate (p.86·3).
Pain.

RN13 Regeneresen Dyckerhoff, Ger.
Ribonucleic acid (p.2379·1).
Tonic.

Roaccutan Roche, Arg.; Roche, Austria; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Hung.; Roche, Ital.; Roche, Mex.; Roche, Port.†; Roche, Venez.
Isotretinoin (p.1599·2).
Acne.

Roaccutane Roche, Austral.; Roche, Belg.; Roche, Cz.; Roche, Fr.; Roche, Gr.; Roche, Hong Kong; Roche, Irl.; Roche, Israel; Roche, Malaysia; Roche, NZ†; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, S.Afr.; Roche, Singapore; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK.
Isotretinoin (p.1599·2).
Acne.

Roacnetan Roche, Chile.
Isotretinoin (p.1599·2).
Acne.

Roacutan Roche, Braz.; Roche, Spain.
Isotretinoin (p.1599·2).
Acne.

Robafen AC Cough Major, USA.
Guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Robafen DAC Major, USA.
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Robafen DM Major, USA.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Robamox Combiphar, Indon.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Robanul Richmond, Arg.
Epirubicin (p.716·2).
Malignant neoplasms.

RoBathol Pharmaceutical Specialties, USA.
Emollient.

Robax Platinum Wyeth Consumer, Canad.
Methocarbamol (p.1897·3); ibuprofen (p.64·2).
Painful skeletal muscle spasm.

Robaxacet Wyeth Consumer, Canad.
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Musculoskeletal, peri-articular, and soft-tissue pain.

Robaxacet-8 Wyeth Consumer, Canad.
Methocarbamol (p.1897·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Musculoskeletal, peri-articular and soft-tissue pain.

Robaxifen Wyeth Consumer, Mex.; Wyeth, Venez.
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Musculoskeletal pain.

Robaxin Wyeth Consumer, Canad.; Robins, Hong Kong†; Pharmacare, S.Afr.; Faes, Spain; Whitehall, Thai.†; Shire, UK; Schwarz, USA; Wyeth-Ayerst, USA.
Methocarbamol (p.1897·3).
Musculoskeletal pain; skeletal muscle spasm.

Robaxisal Wyeth Consumer, Canad.; Wyeth Consumer, Mex.; Pharmacare, S.Afr.; Ipsen, Spain†; Wyeth, Venez.
Methocarbamol (p.1897·3); aspirin (p.20·3).
Musculoskeletal, peri-articular and soft-tissue pain; painful skeletal muscle spasm.

Robaxisal Compuesto Ipsen, Spain.
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Musculoskeletal pain.

Robaxisal-C Wyeth Consumer, Canad.
Methocarbamol (p.1897·3); aspirin (p.20·3); codeine phosphate (p.37·2).
Musculoskeletal, peri-articular and soft-tissue pain.

Robaz Lavipharm, Gr.; Galderma, Philipp.; Galderma, Thai.
Metronidazole (p.837·1).
Rosacea.

Robencaxil IQFA, Mex.
Procaine benzylpenicillin (p.319·2); benzylpenicillin (p.213·1).
Bacterial infections.

Roberfarin Robert, Spain.
⊗ Dequalinium chloride (p.1641·3); enoxolone (p.50·1); hydrocortisone acetate (p.1535·2); oxetacaine (p.1867·2); tyrothricin (p.358·2).
Mouth and throat inflammation.

Robervital Robert, Spain.
Oxaceprol (p.2359·1); tocoferil sodium succinate.
Dermatomyositis; musculoskeletal and joint disorders.

Robiflam Khandelwal, India.
Methocarbamol (p.1897·3); ibuprofen (p.64·2).
Skeletal muscle spasm.

Robi-Flu Wyeth Consumer, Chile†.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Robigesic Whitehall-Robins, Canad.†.
Paracetamol (p.108·1).
Fever; pain.

Robimen Quim-Far, Venez.
Vitamin B substances (p.1922·1).
Dietary supplement.

Robimycin Robitabs Robins, USA.
Erythromycin (p.269·2).
Bacterial infections.

Robinax Khandelwal, India.
Methocarbamol (p.1897·3).
Skeletal muscle spasm.

Robinaxol Khandelwal, India.
Methocarbamol (p.1897·3); paracetamol (p.108·1).
Skeletal muscle spasm.

Robinia Med Complex Dynamit, Austria.
Homoeopathic preparation.

Robinul
Sigma, Austral.; Torrex, Austria; Eumedica, Belg.; Meda, Denm.; Meda, Fin.; Riemser, Ger.; Robins, Hong Kong†; Healthcare Logistics, NZ; Meda, Norw.; Aspen, S.Afr.; Meda, Swed.; Horizon, USA.
Glycopyrronium bromide (p.2315·3).
Management of cardiac vagal reflexes; peptic ulcer; premedication; protection against muscarinic effects of anticholinesterases used to reverse neuromuscular blockade.

Anpharm, UK.
Injection: Glycopyrronium bromide (p.2315·3).
Intra-operative management of cardiac vagal reflexes; premedication; protection against muscarinic effects of anticholinesterases used to reverse neuromuscular blockade.

Anpharm, UK.
Powder for topical solution: Glycopyrronium bromide (p.2315·3).
Hyperhidrosis.

Robinul-Neostigmin Meda, Denm.; Meda, Fin.; Meda, Norw.; Meda, Swed.
Neostigmine metilsulfate (p.631·3).
Glycopyrronium bromide (p.2315·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Robinul-Neostigmine Eumedica, Belg.; Sintetica, Switz.; Anpharm, UK.
Neostigmine metilsulfate (p.631·3).
Glycopyrronium bromide (p.2315·3) is included in this preparation to protect against the muscarinic actions.
Reversal of competitive neuromuscular blockade.

Robitessin Wyeth, Venez.
Guaifenesin (p.1561·3).
Cough.

Robitessin AC Wyeth, Venez.†.
Guaifenesin (p.1561·3); pheniramine maleate (p.587·3); codeine phosphate (p.37·2).
Cough.

Robitessin Kit Tos Wyeth, Venez.†.
Guaifenesin (p.1561·3).
Cough.

Robitessindem Wyeth, Venez.
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin Wyeth-Whitehall, Arg.†; Wyeth Consumer, Canad.; Robins, Israel; Wyeth Consumer, Mex.; Wyeth Consumer, Singapore; Wyeth, Spain; Wyeth Consumer, Thai.; Robins, USA.
Guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Robitussin AC
Note. This name is used for preparations of different composition.
Wyeth Consumer, Canad.
Guaifenesin (p.1561·3); pheniramine maleate (p.587·3); codeine phosphate (p.37·2).
Coughs.

Robins, USA.
Guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Robitussin Antitussicum Wyeth, Cz.; Wyeth, Hung.; Whitehall, Pol.
Dextromethorphan hydrobromide (p.1555·2).
Cough.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Robitussin Caramelos
Note. This name is used for preparations of different composition.
Wyeth-Whitehall, Arg.†.
Menthol (p.2340·1).
Coughs.

Wyeth, Venez.†.
Menthol (p.2340·1); cineole (p.2282·3).

Robitussin Chesty Cough *Wyeth Consumer, Austral.; Wyeth Consumer, Irl.*
Guaifenesin (p.1561·3).
Formerly known as Robitussin Expectorant in *Irl*.
Cough.

Robitussin for Chesty Coughs *Wyeth Consumer, UK.*
Guaifenesin (p.1561·3).
Cough.

Robitussin for Chesty Coughs with Congestion *Wyeth Consumer, UK.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Robitussin Childrens Cough & Cold *Wyeth Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Robitussin Childrens Cough DM *Wyeth Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin Children's Night Relief *Whitehall, NZ†.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Robitussin with Codeine *Whitehall-Robins, Canad.†.*
Guaifenesin (p.1561·3); pheniramine maleate (p.587·3); codeine phosphate (p.37·2).
Coughs.

Robitussin Cold *Wyeth Consumer, Singapore.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Robitussin Cold & Cough *Wyeth Consumer, Singapore; Robins, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Robitussin Cold, Cough & Flu *Wyeth Consumer, Singapore.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and flu symptoms; coughs; nasal congestion.

Robitussin Cough & Cold *Wyeth Consumer, Canad.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Robitussin Cough, Cold & Flu *Wyeth Consumer, Canad.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and flu symptoms; coughs.

Robitussin Cough Drops *Robins, USA.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).

Robitussin D *Wyeth-Whitehall, Arg.†.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Robitussin DAC *Robins, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Robitussin DM *Wyeth Consumer, Austral.; Wyeth Consumer, Canad.; Wyeth Consumer, Hong Kong; Robins, Israel; Wyeth Consumer, Malaysia†; Wyeth Consumer, Mex.; Wyeth Consumer, NZ; Wyeth, Philipp.; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.; Robins, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin DM Antitusivo *Wyeth, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin DM CoughGels *Wyeth Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin DM-P *Wyeth Consumer, Austral.; Wyeth Consumer, NZ.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal and sinus congestion.

Robitussin Dry Cough *Wyeth Consumer, Irl.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly known as Robitussin Cough Soother.
Coughs.

Robitussin for Dry Coughs *Wyeth Consumer, UK.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin DX *Wyeth Consumer, Austral.; Wyeth Consumer, NZ.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin EX *Wyeth Consumer, Austral.; Wyeth Consumer, NZ.*
Guaifenesin (p.1561·3).
Cough.

Robitussin Expectorans *Wyeth, Cz.; Wyeth, Hung.; Whitehall, Pol.*
Guaifenesin (p.1561·3).
Cough.

Robitussin Expectorant
Note. This name is used for preparations of different composition.
Wyeth Consumer, Hong Kong; Wyeth Consumer, Malaysia†; Wyeth, Philipp.
Guaifenesin (p.1561·3).
Cough.

Whitehall-Robins, Switz.
Acetylcysteine (p.1548·2).
Coughs with viscous mucus.

Robitussin Honey Cold *Whitehall Consumer, NZ.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal and sinus congestion.

Robitussin Honey Cough *Wyeth Consumer, NZ.*
Menthol (p.2340·1); honey (p.1948·2).
Formerly contained dextromethorphan hydrobromide and honey.
Coughs.

Robitussin Honey Cough Syrup *Wyeth Consumer, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin Junior *Wyeth, Cz.; Wyeth, Hung.; Wyeth Consumer, Irl.; Whitehall, Pol.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Robitussin Maximum Strength Cough *Wyeth Consumer, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin Maximum Strength Cough & Cold *Robins, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Robitussin ME *Wyeth Consumer, Austral.; Interphil, Hong Kong; Wyeth Consumer, Hong Kong; Wyeth Consumer, NZ.*
Guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2).
Cough; respiratory-tract congestion.

Robitussin Night Relief *Robins, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); mepyramine maleate (p.585·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Robitussin Paediatric Cough *Wyeth Consumer, Hong Kong.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin PE *Wyeth Consumer, Hong Kong; Wyeth Consumer, Malaysia†; Wyeth, Spain; Robins, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion.

Robitussin Pediatric *Robins, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Robitussin Pediatric Cough & Cold Formula *Robins, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Robitussin Plus *Wyeth Consumer, Irl.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Robitussin Expectorant Plus.
Coughs; nasal congestion.

Robitussin PM Cough & Cold *Wyeth Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Robitussin PS *Wyeth Consumer, Austral.; Wyeth Consumer, NZ; Wyeth Consumer, Singapore; Wyeth Consumer, Thai.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Robitussin PE in *Thai*.
Cough; nasal congestion.

Robitussin Severe Congestion *Wyeth Consumer, Malaysia†; Robins, USA.*
Guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Robovites *Vita Health, Singapore.*
Multivitamin preparation with or without iron or zinc (p.1922·1).

Robovites Multivitamin *Vita Health, Singapore.*
Multivitamins; cod-liver oil; evening primrose oil; echinacea; ginkgo biloba (p.1922·1).

Roburvit *Echo, Ital.*
Royal jelly (p.2382·1).

Robuvalen *Robugen, Ger.†.*
Zinc oxide (p.1621·2).
Eczema; skin lesions.

ROC Chronoblock *Johnson & Johnson, Canad.†.*
Avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

ROC Minesol Actif *Key, Chile.*
SPF 30: Octinoxate (p.1608·2); enzacamene (p.1597·1); bemotrizinol (p.1590·2); bisoctrizole (p.1591·2); titanium dioxide (p.1617·3).
Sunscreen.

ROC Minesol Bronze *Key, Chile.*
SPF 8: Dihydroxyacetone (p.1594·1); octinoxate (p.1608·2); octisalate (p.1608·2); avobenzone (p.1589·3).
Artificial tanning agent; sunscreen.

ROC Minesol Protect
Note. This name is used for preparations of different composition.
Key, Chile.
SPF 30: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); bemotrizinol (p.1590·2).
Sunscreen.

Key, Chile.
SPF 50+; SPF 60: Octinoxate (p.1608·2); enzacamene (p.1597·1); bisoctrizole (p.1591·2); bemotrizinol (p.1590·2); titanium dioxide (p.1617·3).
Sunscreen.

ROC Retinol Actif Pour Day *Johnson & Johnson, Canad.†.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

RoC Sante Soleil *RoC, UK.*
SPF 25: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Formerly known as RoC Total Sunblock.
Sunscreen.

RoC Sunscreen Stick *RoC, UK.*
Dibenzoylmethane (p.1594·1); a cinnamic ester.
Sunscreen.

Rocainol *CICSA, Mex.*
Methyl salicylate (p.85·3); menthol (p.2340·1).

Rocal *ANB, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Rocaltrol *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.†; Roche, Fr.; Roche, Ger.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Calcitriol (p.1986·2).
Hyperparathyroidism; hypocalcaemia; hypoparathyroidism; hypophosphataemia; osteomalacia; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets; vitamin D deficiency.

Rocavit
Note. This name is used for preparations of different composition.
Vitae, Mex.
Capsules: Vitamin and mineral preparation (p.1922·1).

Vitae, Mex.
Injection: Vitamin preparation (p.1922·1).

Vitae, Mex.
Oral drops: Vitamin preparation with lysine (p.1922·1).
Tonic.

Vitae, Mex.
Oral solution: Vitamin preparation with cyproheptadine (p.575·2) (p.1922·1).
Reduced appetite.

Roccaxin *TNP, Thai.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rocefalin *Roche, Spain.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocefin *Roche, Braz.; Roche, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocephalin *Roche, Denm.; Roche, Fin.; Roche, Norw.; Roche, Swed.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in some injections to alleviate the pain of injection.
Bacterial infections.

Rocephin *Roche, Austral.; Roche, Austria; Roche, Canad.; Roche, Cz.†; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocephine *Roche, Belg.; Roche, Fr.; Roche, Switz.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rocer *Otto, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Roceron *Roche, Norw.*
Interferon alfa-2a (p.885·1).
Chronic active hepatitis B; chronic hepatitis C; malignant neoplasms.

Roceron-A *Roche, Denm.†.*
Interferon alfa-2a (p.885·1).
Chronic hepatitis B or C; malignant neoplasms.

Rocgel *Tonipharm, Fr.*
Boehmite.
Gastrointestinal disorders.

Rochagan *Roche, Braz.*
Benznidazole (p.830·3).
American trypanosomiasis.

Rochevit *Bayer, Spain.*
Multivitamin and mineral preparation (p.1922·1).

Rociclyn *Zambon, Neth.†.*
Tolfenamic acid (p.130·1).
Osteoarthritis; rheumatoid arthritis.

Rocid *Max Farma, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Rociject *Sandoz, S.Afr.*
Ceftriaxone (p.238·1).
Bacterial infections.

Rocilin *Rosco, Denm.; Rosco, Norw.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Rocmalat *Strathmann, Hung.†.*
Arginine (p.1928·2); malic acid (p.2337·1).
Liver disorders.

Rocmaline *Fresenius Kabi, Austria; Aerocid, Fr.*
Arginine (p.1928·2); malic acid (p.2337·1).
Liver disorders.

Roco *Bayer, Neth.*
Ibuprofen (p.64·2).
Pain.

Rocornal *UCB, Austria†; Rentschler, Cz.†; UCB, Cz.†; UCB, Ger.; Mochida, Jpn.*
Trapidil (p.1416·3).
Angina pectoris; cerebral haemorrhage; ischaemic heart disease; prevention of restenosis following percutaneous transluminal coronary angioplasty; stroke.

Roctylan *Farmedia, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Roculax *Kalbe, Indon.*
Rocuronium bromide (p.1908·3).
Competitive neuromuscular blocker.

Rocuron *Cristalia, Braz.*
Rocuronium bromide (p.1908·3).
Competitive neuromuscular blocker.

Ro-C-Var *Infinity, Venez.*
Vitamin C (p.1983·3); rose fruit (p.2381·2).
Vitamin C supplement.

Rocygen *Rotexmedica, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Rodakin *Kener, Mex.*
Loratadine (p.583·3).

Rodan *Superlife, Mex.*
Evening primrose oil (p.2302·1); turmeric (p.1473·2); devil's claw root (p.39·1); ulmaria (p.2338·1).
Musculoskeletal and joint disorders.

Rodanol *Lek, Rus.*
Nabumetone (p.91·2).

Rodanol S *Lek, Cz.†; Lek, Hung.†; Lek, Pol.*
Nabumetone (p.91·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rodase *Pond's, Thai.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion; wounds.

Rodavan S *Grunwalder, Ger.*
Dimenhydrinate (p.576·2).
Dizziness; motion sickness; nausea and vomiting.

Rodazid *Pharma Nutria, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Roddexil *Roddensers, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Rodenal *Rekah, Israel.*
Trihexyphenidyl hydrochloride (p.820·2).
Extrapyramidal disorders; parkinsonism.

Rodepan *Pharma Investi, Chile.*
Cyproheptadine hydrochloride (p.575·1); thiamine hydrochloride; pyridoxine hydrochloride; riboflavin sodium phosphate; nicotinamide; ascorbic acid (p.1922·1).
Reduced appetite; tonic.

Rodermil *Edol, Port.*
Metronidazole (p.837·1).
Rosacea.

Rodinac *Geminis, Arg.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; pain.

Rodinac B12 *Geminis, Arg.*
⊗ Betamethasone (p.1518·2); cyanocobalamin (p.1980·2); diclofenac potassium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Rodinac Biotic *Geminis, Arg.*
Amoxicillin trihydrate (p.202·2); diclofenac potassium (p.44·3).
Bacterial infections.

Rodinac Flex *Geminis, Arg.*
Pridinol (p.1898·2); diclofenac (p.44·2).
Inflammation; muscle spasm; pain.

Rodinac Gesic *Geminis, Arg.*
Paracetamol (p.108·1); diclofenac potassium (p.44·3).
Inflammation; pain.

Rodipal *Quesada, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; hypertension.

Rodix *Galeno, Venez.*
Tenoxicam (p.128·2).
Inflammation; musculoskeletal and joint disorders.

Rodogyl *Aventis, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Malaysia; Aventis, Mex.*
Spiramycin (p.333·1); metronidazole (p.837·1).
Mouth infections.

Rodopsin Plus *Baldacci, Ital.*
Vitamin E; copper; zinc; red vine (p.1922·1).

Rodovit *Allen, Mex.*
Vitamin preparation with or without minerals (p.1922·1).

Rofacin *Corsa, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Rofact *Valeant, Canad.*
Rifampicin (p.325·3).
Tuberculosis.

Rofatuss *Rosen, Ger.†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Rofecip Plus *Cipla, India†.*
Rofecoxib (p.121·1); paracetamol (p.108·1).
Musculoskeletal and joint disorders.

Rofen *Akdeniz, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Rofenid *Sanofi-Aventis, Belg.; Nicholas Piramal, India†.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; oedema; pain.

Rofepain *LBS, Thai.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Roferon-A *Roche, Arg.†; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.†; Roche, Chile†; Roche, Cz.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Piramal, India; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.†; Roche, Turk.; Roche, UK; Roche, USA†; Roche, Venez.*
Interferon alfa-2a (p.885·1).
Anogenital warts; chronic hepatitis B; chronic hepatitis C; essential thrombocythaemia; malignant neoplasms; viral infections.

Roferon-A RBV *Roche, NZ.*
Injection, interferon alfa-2a (Roferon-A) (p.885·1); tablets, ribavirin (Copegus) (p.902·3).
Chronic hepatitis C.

Rofetab *Centaur, India†.*
Rofecoxib (p.121·1).
Musculoskeletal and joint disorders; pain.

Rofex *Nicholas Piramal, India†.*
Cefalexin (p.218·2).
Bacterial infections.

Rofib *Aristo, India.*
Rofecoxib (p.121·1).
Osteoarthritis; pain.

Rofixx *Cipla, India†.*
Rofecoxib (p.121·1).
Musculoskeletal and joint disorders.

Rofiz *Wockhardt, India.*
Rofecoxib (p.121·1).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Roflazin *Munir, Turk.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Rofoxin *Royton, Braz.†.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Rofucal *Probiomed, Mex.*
⊗ Hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Rofunil *Rotexmedica, Philipp.*
⊗ Furosemide (p.1292·1).
Oedema.

Rofy *Codal Synto, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Rogaan *Teva, Israel.*
Dextropropoxyphene hydrochloride (p.40·1); aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Cold symptoms; pain.

Rogadermis *Lacefa, Arg.†.*
Vitamin A (p.1971·2).
Burns.

Rogaine *Pfizer, Austria; McNeil Consumer, Canad.; Pfizer, Fin.; Pfizer Consumer, Irl.; Johnson & Johnson, NZ; Pfizer, Norw.; Pfizer, Swed.; Pfizer Consumer, USA.*
Minoxidil (p.1342·1).
Formerly known as Regaine in *Irl.*
Alopecia androgenetica.

Rogasti *Pacific, Israel.*
Famotidine (p.1730·1).
Duodenal ulcer; gastro-oesophageal reflux; Zollinger-Ellison syndrome.

Rogastril *Roemmers, Arg.*
Cinitapride acid tartrate (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Rogelina *Geminis, Arg.†.*
Sodium picosulfate (p.1771·1).
Constipation.

Rogin-E *Bayer, Philipp.*
Ginseng; deanol; royal jelly; lecithin; vitamins; minerals; free fatty acids (p.1922·1).
Nutritional supplement; tonic.

Rogitine *Paladin, Canad.; IFET (ΙΦΕΤ), Gr.†; Alliance, UK.*
Phentolamine mesilate (p.1370·2).
Dermal necrosis and sloughing following intravenous administration of noradrenaline; phaeochromocytoma.

Roglin *Aristo, India.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Roglin-M *Aristo, India.*
Rosiglitazone maleate (p.458·2); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Roglit *Gedeon Richter, Rus.*
Rosiglitazone potassium (p.459·3).
Diabetes mellitus.

Roha-Lax *Abdi, Turk.*
Sennosides (p.1769·3).
Constipation.

rohasal *Roha, Ger.†.*
Absinthium (p.2244·1); aniseed (p.2258·2); kaolin (p.1738·1); calcium phosphate (p.1676·2); dried magnesium sulfate (p.1680·1); calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastrointestinal disorders.

rohasal N *Roha, Ger.†.*
Sodium bicarbonate (p.1673·2); calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1).
Gastrointestinal disorders.

Rohipnol *Roche, Spain.*
Flunitrazepam (p.996·2).
Anxiety; general anaesthesia; insomnia.

Rohto Zi *Mentholatum, UK.*
Camphor (p.2273·2).
Eye irritation.

Rohto Zi Contact *Mentholatum, Austral.†.*
Hyetellose (p.2143·3).
Dry eyes.

Rohto Zi Fresh *Mentholatum, Austral.†.*
Povidone (p.2146·1).
Dry eyes.

Rohydorm *Sigma, Braz.*
Flunitrazepam (p.996·2).
Insomnia.

Rohypnol *Roche, Arg.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Chile†; Leciva, Cz.†; Roche, Denm.†; Roche, Fr.; Roche, Ger.; Roche, Hong Kong; Roche, Irl.; Roche, Mex.; Roche, Neth.; Roche, Norw.†; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Swed.†; Roche, Switz.; Roche, Thai.; Roche, UK†.*
Flunitrazepam (p.996·2).
Induction of anaesthesia; insomnia; premedication.

Roical *Shin Poong, Malaysia; Shin Poong, Singapore.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.

Roidhemo *Pan Quimica, Spain†.*
⊗ Aesculus (p.2248·2); benzyl phenol; benzyl salicylate; ephedrine hydrochloride (p.1558·2); hamamelis (p.2318·2); lactic acid (p.2329·3).
Anorectal disorders.

Roiplon *Menarini, Gr.*
Etofenamate (p.53·1).
Inflammation; musculoskeletal and joint disorders; pain.

Roipnol *Roche, Ital.*
Flunitrazepam (p.996·2).
Insomnia.

Rojema *Self-Care Products, UK.*
Royal jelly (p.2382·1).

Rojobacter *Ferro, Arg.†.*
Merbromin (p.1652·1).
Bacterial infections.

Rokacet *Taro, Israel.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Coughs fever; pain.

Rokacet Plus *Taro, Israel.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Coughs; fever; pain.

Rokadin *Kener, Mex.†.*
Loratadine (p.583·3).
Hypersensitivity.

Rokal *Taro, Israel.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2).
Coughs; fever; pain; rheumatism.

Rokal Plus *Taro, Israel.*
Aspirin (p.20·3); caffeine (p.1116·3); codeine phosphate (p.37·2).
Coughs; fever; pain; rheumatism.

Rokamol *Taro, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Rokamol Plus Codeine *Taro, Israel.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Rokan *Andromaco, Chile; Spitzner, Ger.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function disorders.

Rokanite *Taro, Israel†.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Coughs; fever; pain; rheumatism.

Rokital *Formenti, Ital.*
Rokitamycin (p.330·2).
Bacterial infections.

Roko *Cipla, India.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Roksicap *Caprifarmindo, Indon.; Sanbe, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Roksimin *Il-ko, Turk.*
Roxithromycin (p.331·1).
Bacterial infections.

Roksolit *Eczacibasi, Turk.*
Roxithromycin (p.331·1).
Bacterial infections.

Rokumi-gan *Tsumura, Jpn.*
Rehmannia root; cornus fruit; dioscorea rhizome; alisma rhizome; poria sclerotium; moutan bark.
Traditional Kampo medicine.

Rolab-Amoclav *Sandoz, S.Afr.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Rolab-Anthex *Sandoz, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Rolab-Pen-V-K *Sandoz, S.Afr.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Rolac *Actavis, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Rolac Plus *Wyeth, India.*
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; peptic ulcer.

Rolaids *Pfizer Consumer, USA.*
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Antacid.

Rolaids Antacid *McNeil Consumer, Canad.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2).
Dyspepsia.

Rolaids Extra Strength Softchews *Pfizer Consumer, USA.*
Calcium carbonate (p.1714·1).
Antacid.

Rolaids Multi-Symptom *McNeil Consumer, Canad.; Pfizer Consumer, USA.*
Calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Rolaids Plus Gas Relief *Pfizer Consumer, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).

Rolaids Ultra *McNeil Consumer, Canad.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).

Rolak *Anpharm (Ανφαρμ), Gr.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Rolaket *Elpen (Ελπεν), Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Rolan *Nobel, Turk.*
Mefenamic acid (p.80·1).
Menorrhagia; musculoskeletal and joint disorders; pain.

Rolap *Teva Tuteur, Arg.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Rolar *Pharmaland, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Cold symptoms; coughs; nasal congestion.

Rolatuss Expectorant *Huckaby, USA.*
Phenylephrine hydrochloride (p.1568·1); codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Coughs.

Rolatuss Plain *Major, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Roleca Wacholder *Riemser, Ger.*
Juniper oil (p.2328·3).
Diuretic.

Rolesen *Antibioticos, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Roletra *Ozone, Cz.; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, Singapore; Ranbaxy, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Rolexit *Nufarindo, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Rolicyn *Polfa Tarchomin, Pol.*
Roxithromycin (p.331·1).
Bacterial infections.

Rolicytin *Unipharm, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Rolidan *Gelcaps, Mex.†.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Rolip *LED, Fr.†.*
alpha-Acetyl mandelic acid (p.296·3).
Dry lips.

Rolisporin *Vianex (Βιανέξ), Gr.*
Ceftriaxone (p.238·1).
Bacterial infections.

Roll-On *Shaklee, Canad.†.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Rolodiquim *Quimica y Farmacia, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Rolsical *Sun, India.*
Calcitriol (p.1986·2).
Hypocalcaemia; hypoparathyroidism; osteoporosis; rickets.

Romaken *Kendrick, Mex.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Romaksen *Ulagay, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Romalina *Biotech, Venez.†.*
Nystatin (p.543·2).
Candidiasis.

Romarene *Beaufour, Fr.*
Rosemary (p.2381·2); taraxacum (p.2395·1); kinkeliba (p.2329·2); potassium sodium tartrate (p.1764·1); sodium citrate (p.1673·3).
Dyspepsia.

Romarinex *Dissolvurol, Mon.*
Rosemary (p.2381·2); kinkeliba (p.2329·2).
Biliary-tract disorders.

Romasulan *Biofarm, Rus.*
Chamomile (p.2279·3).
Gastritis, duodenitis, colitis, meteorism; mouth and throat disorders; skin disorders; vaginitis.

Romatim *Kurtsan, Turk.*
Naproxen (p.92·3).
Musculoskeletal and joint pain.

Romaxin *Prohealth, Philipp.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Romazicon *Roche, USA.*
Flumazenil (p.1445·2).
Formerly known as Mazicon.
Benzodiazepine overdosage; reversal of benzodiazepine-induced sedation.

Romazulan *Drovepat, Venez.†.*
Indometacin (p.66·3).
Musculoskeletal and joint disorders.

Rombay *Apotheke Heiligen Dreifaltigkeit, Austria.*
Talc (p.1615·2); zinc oxide (p.1621·2); peru balsam (p.2365·3).
Skin irritation.

Rombellin *Simons, Ger.†; Merz, Switz.*
Biotin (p.1931·3).
Biotin deficiency.

Rombox *GSK, Mex.*
Cefalexin (p.218·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Romesec *Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore.*
Omeprazole (p.1753·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Romet *Mitsubishi, Jpn†.*
Repirinast (p.1131·1).
Asthma.

Rometran-K *Arlex, Mex.*
Ketorolac (p.75·2).
Pain.

Romicef
Note. This name is used for preparations of different composition.
Meprofarm, Indon.
Cefpirome (p.231·3).
Bacterial infections.

Yung Shin, Philipp.
Cefuroxime sodium (p.238·2).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Romicin *Pacific, NZ.*
Roxithromycin (p.331·1).
Bacterial infections.

Romidon *Relyo, Gr.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Romilar
Note. This name is used for preparations of different composition.
Bayer Consumer, Arg.; Bayer Consumer, Mex.; Bayer, Neth.; Bayer, Spain.
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Bayer, Indon.
Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); dexpanthenol (p.2362·1) or panthenol (p.2362·1).
Cough.

Bayer, Thai.
Syrup: Dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); dexpanthenol (p.2362·1).
Coughs.

Bayer, Thai.
Tablets: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Romilar AC *Scot-Tussin, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Romilar Antitussivum *Bayer, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Romilar Mucolyticum *Bayer, Belg.; Roche, Belg.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with accumulation of mucus.

Rominafort *Garden House, Arg.*
Betacarotene; collagen; alpha tocopherol (p.1922·1).
Dietary supplement.

Romir *Diba, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Romisan *Chemo, Neth.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Romiver *Rafarm, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Rommix *Ashbourne, UK†.*
Erythromycin (p.269·2).

Romox-ARL *Ximena Polanco, Chile.*
Rosemary (p.2381·2); rosa mosqueta (p.2381·2).

Romulin *Chew, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Romyk *Lindopharm, Ger.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Ronabin *Unimed, Israel†.*
⊗ Dronabinol (p.1728·1).
Anorexia associated with AIDS; nausea and vomiting induced by cytotoxic therapy.

Ronal
Note. This name is used for preparations of different composition.
Sandoz, Denm.
Flunitrazepam (p.996·2).
Insomnia.

Olvos, Gr.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Ronalgin *Dexa, Indon.*
Dipyrone (p.49·2).
Pain.

Roname *Lacer, Spain.*
Glimepiride (p.441·1).
Diabetes mellitus.

Roncoleukin *Biotech, Rus.*
Interleukin-2 (p.735·1).
Renal cancer; sepsis.

Rondamine-DM *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); brompheniramine maleate (p.569·2).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and carbinoxamine maleate.
Coughs and cold symptoms.

Rondec
Note. This name is used for preparations of different composition.
Abbott, Arg.†; Abbott, Gr.; Abbott, Venez.†.
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Biovail, USA.
Oral drops: Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2).
Allergic and vasomotor rhinitis; nasal congestion.

Biovail, USA.
Syrup: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract disorders.

Rondec Compositum *Abbott, Arg.†.*
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); bromhexine hydrochloride (p.1552·2); paracetamol (p.108·1).
Respiratory-tract disorders.

Rondec-DM
Note. This name is used for preparations of different composition.
Abbott, Thai.†.
Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract disorders.

Alliant, USA.
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Formerly contained carbinoxamine maleate, pseudoephedrine hydrochloride, and dextromethorphan hydrobromide.
Coughs and cold symptoms; respiratory symptoms of allergy.

Rondo *ISA, Arg.*
Saccharin (p.1960·2); cyclamate (p.1936·2).
Sugar substitute.

Rondo Sweet *ISA, Arg.*
Aspartame (p.1930·1); acesulfame potassium (p.1928·1).
Sugar substitute.

Rondover *Iapharm, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Ronem *Fahrenheit, Indon.*
Meropenem (p.297·2).
Bacterial infections.

Ronemox *Nicholas Piramal, India†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ronex *Pharos, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; haemorrhage; hereditary angioedema.

Ronexine *Rekah, Israel.*
Levomepromazine maleate (p.1003·1).
Anxiety; behaviour disorders; tension.

Ronfase *Pfizer, Arg.*
Estradiol valerate (p.2097·3).
Menopausal disorders; osteoporosis; prostatic cancer.

Ronfnyl
Note. This name is used for preparations of different composition.
Anben, Fr.†.
Natural polysaccharides.
Snoring.

Veron, Ger.; Anben, Malaysia†.
Xanthan gum (p.2147·2).
Snoring.

Ronfolic *Rontag, Arg.*
Folic acid (p.1940·1).
Folic acid deficiency.

Ronic *Edol, Port.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Ronistina *Rontag, Arg.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Ronkal *Zentiva, Hung.*
Risperidone (p.1024·2).
Behaviour disorders; schizophrenia.

Rontafor *Pfizer, Arg.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; colorectal cancer; megaloblastic anaemia; reduction of methotrexate toxicity.

Rontagel *Pfizer, Arg.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Rontilona *Alodial, Port.; Alter, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Nasal polyps; rhinitis.

Ronvan *Asta Oncologia, Braz.†.*
Fosfestrol sodium (p.2105·1).
Breast cancer; prostatic cancer.

Ronvir *Pharmacia, Arg.†.*
Didanosine (p.870·2).
HIV infection.

Rooilavental *Lennon, S.Afr.*
Nutmeg (p.2355·2); cinnamon (p.2283·1); red sanders wood; rosemary oil (p.2381·3); lavender oil (p.2331·2).
Dyspepsia; flatulence.

Ropect *Scherer, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Rophelin *Rolmex, Canad.†.*
Ammonium chloride (p.1551·3); tolu balsam (p.1574·2); white pine compound; wild cherry bark (p.2415·2).

Ropi *Cristalia, Braz.*
Ropivacaine hydrochloride (p.1870·3).
Local anaesthesia.

Ropion *Kaken, Jpn.*
Flurbiprofen axetil (p.61·3).
Pain.

Ropramin *Farmanic, Gr.*
Citalopram (p.385·3).
Depression.

Ropril *Aegis, Hong Kong.*
Captopril (p.1239·2).
Heart failure; hypertension.

Ropsil *Medipharm, Chile.*
Clonazepam (p.478·2).
Anxiety; epilepsy; panic disorder.

R.O.R. *Sanofi Pasteur, Fr.*
A measles, mumps, and rubella vaccine (Edmonston 749D, Jeryl Lynn, and Wistar RA 27/3 strains respectively) (p.2223·1).
Active immunisation.

Rorendo *KRKA, Cz.*
Risperidone (p.1024·2).
Schizophrenia.

Rosac *Stiefel, USA.*
Sulfacetamide sodium (p.335·3); sulfur (p.1614·1).
Acne.

Rosaced *Pierre Fabre, Belg.*
Metronidazole (p.837·1).
Rosacea.

Rosadol *Rowe-Fleming, Venez.†.*
Metamizole magnesium (p.49·3).
Dental pain.

Rosagenus *Leovan, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Rosal *Galenium, Indon.*
Salicylic acid (p.1612·2); resorcinol (p.1612·1).
Acne.

Rosalgin *Medicom, Cz.; Lepori, Port.; Farma Lepori, Spain.*
Benzydamine hydrochloride (p.27·3).
Cervicitis; genital hygiene; vulvovaginitis.

Rosaliac *Roche-Posay, Irl.*
Moisturiser.

Rosalox *Medimport, Cz.; Drossapharm, Switz.*
Metronidazole (p.837·1).
Rosacea.

Rosamet *Jadran, Rus.*
Metronidazole (p.837·1).

Rosanil
Note. This name is used for preparations of different composition.
Loeffler, Mex.
Nitazoxanide (p.842·3).
Protozoal infections; worm infections.

Galderma, USA.
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne.

Rosapinol *Steierl, Ger.*
Rosemary oil (p.2381·3).
Circulatory disorders; rheumatic disorders.

Rosarthron *Steierl, Ger.†.*
Rosemary oil (p.2381·3); pumilio pine oil (p.2376·3).
Circulatory disorders; gout; musculoskeletal and joint disorders; neuritis; respiratory-tract disorders.

Rosased *Pierre Fabre, Ital.†.*
Metronidazole (p.837·1).
Rosacea.

Rosasol *Stiefel, Canad.*
Metronidazole (p.837·1); avobenzone (p.1589·3); octinoxate (p.1608·2).
Rosacea.

Rosatil BB *Novag, Mex.†.*
Zinc oxide (p.1621·2).
Nappy rash; skin irritation.

Rosatum Heilsalbe *Wala, Ger.*
Geranium oil (p.2311·1); rose oil (p.2381·2); colloidal silica (p.2146·3).
Skin disorders.

Rosavit C *Biofarma, Mex.*
Ascorbic acid (p.1983·3); rosa mosqueta.
Respiratory-tract disorders.

Rosazol *Alpharma, Fin.*
Metronidazole (p.837·1).
Rosacea.

Roscillin *Ranbaxy, India.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Roscilox *Ranbaxy, Hong Kong.*
Ampicillin trihydrate (p.204·2); cloxacillin sodium (p.256·1).
Bacterial infections.

Rosel *Wermar, Mex.*
Amantadine (p.792·3); chlorphenamine (p.572·2); paracetamol (p.108·1).
Influenza symptoms.

Roseless *Melora, Port.*
Metronidazole (p.837·1).
Rosacea.

Rosemig *Montrose, Cz.*
Sumatriptan (p.625·2).
Migraine.

Roseti *Rafarm, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Rosets *Akorn, USA.*
Rose bengal sodium (p.2381·1).
Ophthalmic diagnostic agent.

Rosic *Pyridam, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Rosiced *Pierre Fabre, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Gr.; Pierre Fabre, Neth.; Pierre Fabre Dermo-Cosmetique, Port.*
Metronidazole (p.837·1).
Rosacea.

Rosicon *Glenmark, India.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Rosicon MF *Glenmark, India.*
Rosiglitazone maleate (p.458·2); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Rosiden *Shin Poong, Singapore.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Rosig *Sigma, Austral.†.*
Piroxicam (p.117·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Rosiglit *Lazar, Arg.*
Rosiglitazone maleate (p.458·2).
Diabetes mellitus.

Rosiglit-Met *Lazar, Arg.*
Rosiglitazone maleate (p.458·2); metformin (p.453·3).
Diabetes mellitus.

Rosil *Siam Bheasach, Thai.*
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Rosilan *Vitoria, Port.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Rosils *Boots Healthcare, Belg.†.*
Noscapine (p.1566·2); phenylephrine hydrochloride (p.1568·1).
Coughs; upper respiratory-tract congestion.

Rosipin *Medico Uno, Hung.*
Risperidone (p.1024·2).
Behaviour disorders; schizophrenia.

Rosital *Faran, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Rosken Skin Repair
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.
Dimeticone (p.2032·1).
Dermatitis; dry skin.

Pfizer, NZ.
Dimeticone (p.2032·1); glycerol (p.2314·2).
Barrier cream; bedsores; dry skin.

Rossepar *KBR, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Iron deficiency; iron-deficiency anaemia.

Rossini *Unipharm, Israel.*
Rosiglitazone hydrochloride.
Diabetes mellitus.

Rossitrol *Polifarma, Ital.*
Roxithromycin (p.331·1).
Bacterial infections.

Rossofolin *Errekappa, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Ro-Strumal NEU (Rowo-221) *Pharmakon, Ger.†.*
Spongia tosta; ovi putamen tosta; magnesium hydrogen phosphate; anhydrous sodium phosphate; terra silicea purificata.
Iodine deficiency.

Rosula *Doak, USA.*
⊗ Sulfacetamide sodium (p.335·3); sulfur (p.1614·1); urea (p.1620·2).
Acne.

Rosula NS *Doak, USA.*
⊗ Sulfacetamide sodium (p.335·3); urea (p.1620·2).
Acne.

Rosumed *Labomed, Chile.*
Rosuvastatin (p.1389·2).
Hypercholesterolaemia.

Rosuvas *Ranbaxy, India.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Rosuvast *Bago, Arg.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Rotadin *Anpharm, Pol.; Egis, Pol.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Rotamat *Unipharma, Gr.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Rotane *Aventis, India.*
Roxatidine acetate hydrochloride (p.1769·1).
Gastro-oesophageal reflux; peptic ulcer.

Rotarix *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Chile; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hung.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Thai.; GSK, UK; GSK, USA; GSK, Venez.*
A live attenuated rotavirus vaccine (RIX4414 strain) (p.2236·1).
Active immunisation.

RotaTeq *MSD, Arg.; CSL, Austral.; Sanofi Pasteur, Cz.; Sanofi Pasteur, Fr.; Sanofi-Aventis, Gr.; MSD, Hung.; Sanofi Pasteur, Hung.; MSD,*

Malaysia; MSD, NZ; Sanofi Pasteur, Pol.; Sanofi Pasteur, Port.; Merck, USA.
A live attenuated oral rotavirus vaccine (pentavalent) (p.2236·1).
Active immunisation.

Roter APC *Imgroma, Neth.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Roter Noscapect *Imgroma, Neth.*
Noscapine hydrochloride (p.1566·3).
Coughs.

Roteroblong Maagtabletten *Imgroma, Neth.*
Bismuth subnitrate (p.1711·2); magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); frangula bark (p.1732·2).
Duodenitis; gastric hyperacidity; gastritis; peptic ulcer.

Rothacin *Julphar, UAE.*
Indometacin (p.66·3).
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders.

Rothonal *Farmamust, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Rothricin *Siam Bheasach, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Rothrin *Iapharm, Gr.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Roth's RKT Tropfen *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Roth's Ropulmin *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Roth's Rotacard *Infirmarius-Rovit, Ger.*
Homoeopathic preparation.

Rotiaz *Richmond, Arg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Rotifar *Duopharma, Hong Kong.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Rotilen *Terapeutico, Ital.*
Methacycline hydrochloride (p.298·2).
Bacterial infections.

Rotocin *Rotexmedica, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Rotomide *Rotexmedica, Philipp.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Rotop Mag-3 *Rossendorf, Cz.†.*
Technetium-99m (p.2055·3) betiatide.
Radionuclide imaging of the kidneys and urinary tract.

Rotova *Katsagonis, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Rotrace *Ace, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Rotram *Ranbaxy, Braz.*
Roxithromycin (p.331·1).
Bacterial infections.

Rotramin *UCB, Spain.*
Roxithromycin (p.331·1).
Bacterial infections.

Rotuss *Scherer, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Roug-Mycin *Pharmanik (Φαρμανικ), Gr.†.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Rouvax *Aventis Pasteur, Braz.†; Sanofi Pasteur, Fr.; Vianex (Βιανεξ), Gr.†; Pasteur Merieux, Israel; Aventis Pasteur, Ital.†; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Aventis, S.Afr.; Aventis Pasteur, Thai.†; Aventis Pasteur, Turk.*
A measles vaccine (Schwarz strain) (p.2221·3).
Active immunisation.

Rovacor *Stancare, India; Ranbaxy, Rus.; Ranbaxy, Singapore.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Rovadin *Otto, Indon.*
Spiramycin (p.333·1).
Bacterial infections; toxoplasmosis.

Rovalcyte *Roche, Fr.; Roche, Port.*
Valganciclovir hydrochloride (p.911·3).
Cytomegalovirus infections.

Rovamicina *Sanofi-Aventis, Braz.; Sanofi-Aventis, Ital.*
Spiramycin (p.333·1).
Bacterial infections.

Rovamycin *Gerot, Austria; Nicholas Piramal, India; Aventis, Norw.; Aventis, Thai.*
Spiramycin (p.333·1).
Bacterial infections; toxoplasmosis.

Rovamycine
Aventis, Arg.; Sanofi-Aventis, Belg.; Aventis, Canad.†; Teofarma, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Aventis, Israel; Aventis, Malaysia; Aventis, Neth.; Aventis, Pol.; Sanofi-Aventis, Port.; Rhone-Poulenc Rorer, Rus.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Switz.; Eczacibasi, Turk.
Spiramycin (p.333·1).
Bacterial infections; cryptosporidiosis; meningococcal meningitis prophylaxis; rheumatic fever prophylaxis; toxoplasmosis.

Sanofi-Aventis, Cz.; Grunenthal, Fr.
Spiramycin (p.333·1) or spiramycin adipate (p.333·2).
Amoebic dysentery; bacterial infections; toxoplasmosis.

Rovartal *Roemmers, Arg.*
Rosuvastatin calcium (p.1389·1).
Cardiovascular risk reduction; hypercholesterolaemia.

Rovelan *EMS, Braz.*
⊗ Furosemide (p.1292·1).

Rovenal *Leciva, Cz.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Rovericlin *SJA, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Roveril *Roux-Ocefa, Arg.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Fever; nasal congestion; pain.

Rovigon
Note.This name is used for preparations of different composition.
Bayer, Austria; Bayer, Belg.; Bayer, Chile; Bayer, Port.; Roche, Switz.
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Dietary supplement; hearing disorders; male infertility; vitamin A and E deficiency.

Bayer, Fr.†; Bayer, Ital.
Vitamin A (p.1971·2); alpha tocoferil acetate (p.1992·3).
Tissue degeneration; vitamin A and vitamin E deficiency.

Nicholas Piramal, India†.
Betacarotene (p.1930·3); vitamin E (p.1992·2).
Disorders of vision.

Bayer, Philipp.
Vitamin A (p.1971·2); vitamin E (p.1992·2).
Vitamin A and E deficiency.

Rovigon G *Roche Consumer, Ger.†.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Rovit *Rolab, S.Afr.†.*
Multivitamin preparation (p.1922·1).

Rovit C *Rolab, S.Afr.†.*
Vitamin C (p.1983·3).
Vitamin C supplement.

Rovoxid *Aurora, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Rowachol
Note.This name is used for preparations of different composition.
Rosch & Handel, Austria; Rowa, Cz.; Rowa, Ger.; Rowa, Hung.; Rowa, Irl.; Rowa-Wagner, Pol.; Bernauer, Switz.
Menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); β-pinene (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3).
Dyspepsia; hepatobiliary disorders.

Raffo, Chile.
Natural terpenes.
Biliary-tract disorders; liver disorders.

Rowa, Hong Kong; Rowa, Israel; Rowa, Malaysia; Rowa, Philipp.; Rowa, Thai.; Meadow, UK; Zuoz, Venez.
Menthol (p.2340·1); menthone (p.2340·2); pinene (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3).
Diabetes mellitus; gallstones; hepatobiliary disorders.

Nexis, Spain.
Menthol (p.2340·1); pinenes (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3); emodin; oxidised terpenes.
Hepatobiliary disorders.

Rowachol comp *Rowa, Ger.†.*
⊗ Menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); β-pinene (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3); deanol benzilate hydrochloride (p.2152·3).
Biliary-tract disorders.

Rowachol-Digestiv *Rowa, Ger.*
Menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); β-pinene (p.2368·3); borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3).
Digestive system disorders; hepatobiliary disorders.

Rowadermat *Rosch & Handel, Austria.*
Carbenoxolone sodium (p.1714·3).
Aphthous ulcers; herpes labialis.

Rowagel *Rowa, Philipp.*
Carbenoxolone sodium (p.1714·3).
Mouth and face lesions.

Rowalind *Rosch & Handel, Austria.*
Nicotinaldehyde; strong ammonia solution (p.2256·1); ammonium chloride (p.1551·3); camphor (p.2273·2); menthol (p.2340·1); rosemary oil (p.2381·3); lavender oil (p.2331·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.

Rowanefrin *Nexis, Spain.*
Anethole (p.2258·1); borneol (p.2268·3); camphene (p.2273·2); rubia tinctorum; oxidised terpenes; pinenes (p.2368·3); fenchone (p.2302·3); cineole (p.2282·3).
Renal calculi; urinary-tract disorders.

Rowapraxin
Rowa, Ger.†.
Pipoxolan (p.2368·3).
Smooth muscle spasms.

Rowa, Hong Kong†; Rowa, Malaysia†.
Pipoxolan hydrochloride (p.2368·3).
Smooth muscle spasm.

Rowarolan
Note.This name is used for preparations of different composition.
Rowa, Irl.
Calcium carbonate (p.1714·1).
Adsorbent in ulcers and sores.

Rowa, Malaysia.
Calcium carbonate (p.1714·1); silica (p.2146·3); talc (p.1615·2).
Minor wounds; ulcers.

Rowasa *Solvay, Fr.; Solvay, USA.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Rowatanal
Note.This name is used for preparations of different composition.
Rowa, Hong Kong; Rowa, Malaysia; Rowa, Singapore.
Bismuth subgallate (p.1711·1); menthol (p.2340·1); zinc oxide (p.1621·2); calcium carbonate (p.1714·1).
Anal irritation; anorectal disorders; haemorrhoids.

Rowa, Irl.
Bismuth subgallate (p.1711·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Anal irritation; haemorrhoids.

Rowatinex
Rosch & Handel, Austria; Rowa, Cz.; Rowa, Ger.; Rowa, Hung.; Rowa, Irl.; Rowa-Wagner, Pol.
α-Pinene (p.2368·3); β-pinene (p.2368·3); camphene (p.2273·2); borneol (p.2268·3); anethole (p.2258·1); fenchone (p.2302·3); cineole (p.2282·3).
Renal calculi; urinary-tract disorders.

Raffo, Chile; Rowa, Hong Kong; Rowa, Israel; Rowa, Malaysia; Rowa, Philipp.; Rowa, Thai.; Zuoz, Venez.
Pinene (p.2368·3); camphene (p.2273·2); borneol (p.2268·3); anethole (p.2258·1); fenchone (p.2302·3); cineole (p.2282·3).
Renal calculi; urinary-tract disorders.

Rowestin *Rowe-Fleming, Venez.†.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Rowo-298 *Pharmakon, Ger.†.*
Homoeopathic preparation.
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.

Rowo-629 *Pharmakon, Ger.†.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Rowo-778 Symphytum Ro-Plex T (Rowo-778) *Pharmakon, Ger.*
Homoeopathic preparation.

Rowo-Sedaphin 138 (Rowo-138) *Pharmakon, Ger.*
Homoeopathic preparation.

Roxacilin *Royton, Braz.†.*
Oxacillin (p.312·1).
Bacterial infections.

Roxalia *Boiron, Canad.*
Homoeopathic preparation.

Roxane *Lavipharm, Gr.†.*
Roxatidine (p.1769·1).
Peptic ulcer.

Roxanol *aai, USA.*
⊗ Morphine sulfate (p.86·3).
Pain.

Roxar *Arrow, Austral.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxazin *Basi, Port.*
Piroxicam (p.117·3).

Roxbi *Sandoz, Indon.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Roxcin *Biolab, Malaysia; Biolab, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxee *Cipla, India.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxem *Aristo, India.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxen *Hua, Thai.†.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Roxene *Benedetti, Ital.*
Piroxicam (p.117·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Roxenil *Caber, Ital.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Roxeptin *Ipca, India; Ipca, Rus.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxeptin-ME *Ipca, India.*
Roxithromycin (p.331·1); ambroxol (p.1550·3).
Respiratory-tract infections associated with viscous mucus.

Roxetin *Cristalia, Braz.*
Paroxetine hydrochloride (p.414·2).
Depression.

Roxflan *Merck, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Roxi *1A, Ger.; Basics, Ger.; CT, Ger.; Fatol, Ger.; TAD, Ger.; Wolff, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxibeta *Betapharm, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxibid *Cadila, India.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxibion *Leiras, Fin.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxibron *Viofar, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxicam *Sanofi Synthelabo, Arg.†.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders; pain.

Roxicet *Roxane, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Roxicillin *Medichrom, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxicin *Atlantic, Hong Kong; Atlantic, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxicodone *aai, USA.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Roxicure *Ajanta, Venez.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxid *Teuto, Braz.†; Alembic, India; Alembic, Singapore.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxiden *Boniscontro & Gazzone, Ital.*
Piroxicam (p.117·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Musculoskeletal, joint, and peri-articular disorders.

Roxidene *Combiphar, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Roxidura *Merck dura, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxifen *TO-Chemicals, Thai.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Roxigamma *Worwag, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxigrun *Grunenthal, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

RoxiHefa *Riemser, Ger.; Wernigerode, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

RoxiHexal *Hexal, Ger.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxihexal *Hexal, Rus.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxiklinge *Fujisawa, Ger.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxilan *Olan-Kemed, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxilox *Roxane, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Roximin *Novis, Gr.; Pharmaland, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Roximstad *Pharmacodane, Denm.*
Roxithromycin (p.331·1).
Bacterial infections.

Roximycin *Alphapharm, Austral.*
Roxithromycin (p.331·1).
Bacterial infections.

Roxin
Note.This name is used for preparations of different composition.
Arrow, Austral.
Norfloxacin (p.309·2).
Bacterial infections.

Ulagay, Turk.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Roxina *Cazi, Braz.*
Roxithromycin (p.331·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Roxine
Note.This name is used for preparations of different composition.
Duopharma, Hong Kong.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Pharmasant, Thai.
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Motion sickness; nausea and vomiting in pregnancy; radiation sickness.

Roxinox Charoen Bhaesaj, Malaysia.
Roxithromycin (p.331·1).
Bacterial infections.

Roxi-paed 1A, Ger.†.
Roxithromycin (p.331·1).
Bacterial infections.

Roxiprin Roxane, USA†.
⊗ Oxycodone hydrochloride (p.106·2); oxycodone terephthalate (p.106·2); aspirin (p.20·3).
Pain.

Roxi-Puren Alpharma-Isis, Ger.
Roxithromycin (p.331·1).
Bacterial infections.

Roxi-Q Juta, Ger.; Q-Pharm, Ger.
Roxithromycin (p.331·1).
Bacterial infections.

Roxiratio Ratiopharm, Pol.
Roxithromycin (p.331·1).
Bacterial infections.

Roxi-saar MIP, Ger.
Roxithromycin (p.331·1).
Bacterial infections.

Roxit Aventis, Ger.†; Sanofi-Aventis, Ital.; Knoll, Neth.†; Noristan, S.Afr.†.
Roxatidine acetate hydrochloride (p.1769·1).
Gastro-oesophageal reflux; gastrointestinal disorders associated with hyperacidity; peptic ulcer.

Roxitan Remedica, Malaysia†.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Roxitazon Alice Loren, Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Roxithro Millimed, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxithro-Lich Winthrop, Ger.
Roxithromycin (p.331·1).
Bacterial infections.

Roxithrostad Stada, Austria.
Roxithromycin (p.331·1).
Bacterial infections.

Roxithroxyl Bangkok Lab & Cosmetic, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitin TP, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitop Farmaline, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitran Neo Quimica, Braz.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitricina Hexal, Braz.†.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitrol Grunenthal, Venez.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitrom Biolab Sanus, Braz.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitromin Sanval, Braz.†.
Roxithromycin (p.331·1).
Bacterial infections.

Roxitron ICN, Pol.; Pentafarma, Port.
Roxithromycin (p.331·1).
Bacterial infections.

Roxium M & H, Thai.
Piroxicam (p.117·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Roxivinol Ferakon, Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Roxivista Cadila, India.
Roxithromycin (p.331·1).
Bacterial infections.

Roxiwas Chiesi, Spain†.
Roxatidine acetate (p.1769·1).
Gastro-oesophageal reflux; peptic ulcer.

Roxlecon Pond's, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxo Unipharm, Israel.
Roxithromycin (p.331·1).
Bacterial infections.

Roxomycin Silom, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxon Karnataka, Philipp.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Roxorin Richmond, Arg.
Doxorubicin (p.712·2).
Malignant neoplasms.

Roxthomed Medicine Products, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxthrin TO-Chemicals, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxto M & H, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxtrocin Greater Pharma, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxulide Hexal, S.Afr.
Roxithromycin (p.331·1).
Bacterial infections.

Roxxibid Cipla-Medpro, S.Afr.
Roxithromycin (p.331·1).
Bacterial infections.

Roxy
Note.This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Sriprasit, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxycam Greater Pharma, Thai.
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Roxydin Biomedis, Thai.; Great Eastern, Thai.
Roxithromycin (p.331·1).
Bacterial infections.

Roxydral Proel, Gr.
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Roxy-Due Phoinix Pharm (Φοινιξ Φαρμ), Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Roxylor Shreya, Rus.
Roxithromycin (p.331·1).
Bacterial infections.

Roxyn Pharmaniaga, Malaysia†; Raza, Malaysia†.
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Roxyrol Concept, India.
Roxithromycin (p.331·1).
Bacterial infections.

Roxyspes Specifar (Σπεσιφαρ), Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Royal E Cielle, Ital.
Royal jelly (p.2382·1); vitamin E (p.1992·2).
Nutritional supplement.

Royal Life Bioceuticals, UK.
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Royalin TO-Chemicals, Thai.
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Roycefax Royton, Braz.†.
Ceftazidime (p.234·1).
Bacterial infections.

Roychlor Waymar, Canad.†.
Potassium chloride (p.1684·3).
Potassium deficiency.

Royen Omedir, Arg.; Rubio, Spain.
Calcium acetate (p.1675·2).
Calcium supplement; hyperphosphataemia.

Royken Kendrick, Mex.
Phytomenadione (p.1995·3).
Haemorrhagic disorders.

Royl 6 Adcock Ingram, S.Afr.
Vitamin B substances with vitamin C (p.1922·1).

Roytrin Royton, Braz.†.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Royvac Kit Waymar, Canad.
Oral solution, magnesium citrate (p.1743·2); 3 tablets, bisacodyl (p.1710·1); 1 suppository, bisacodyl.
Bowel evacuation.

Roza Orva, Turk.
Metronidazole (p.837·1).
Rosacea.

Rozacreme Biorga, Fr.
Metronidazole (p.837·1).
Rosacea.

Rozagel Biorga, Fr.
Metronidazole (p.837·1).
Rosacea.

Rozek Galderma, Venez.
Metronidazole (p.837·1).
Rosacea.

Rozerem Takeda, Fr.; Takeda, Jpn; Takeda, USA.
Ramelteon (p.1024·1).
Insomnia.

Rozex Galderma, Arg.; Galderma, Austral.; AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Cz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Israel; Galderma, Ital.; Galderma, Malaysia; Healthcare Logistics, NZ; Galderma, Neth.; Galderma, Norw.; Galderma, Pol.; Galderma, S.Afr.; Galderma, Singapore; Galderma, Spain; Galderma, Swed.; Galderma, Switz.; Galderma, UK.
Metronidazole (p.837·1).
Rosacea.

Rozicel BMS, Ital.
Cefprozil (p.232·2).
Bacterial infections.

Rozidal Solus, India.
Risperidone (p.1024·2).
Bipolar disorder; psychoses.

Rozolam Farmedia, Gr.
Ciclopirox (p.529·2).
Fungal vaginal infections.

Rozon Ulkar, Turk.
Ranitidine hydrochloride (p.1766·1).

Rozovin Pharmanik (Φαρμανικ), Gr.†.
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Roztwor Elkintona Nr 2 Pliva Krakow, Pol.
Sodium chloride; potassium chloride (p.1667·1).
Fluid and electrolyte disorders.

R-Pril Biochem, India.
Ramipril (p.1385·3).
Heart failure; hypertension.

R-Rax Medicine Products, Thai.
Hydroxyzine hydrochloride (p.581·2).
Pruritus.

R-Tanna
Note.This name is used for preparations of different composition.
Duramed, USA.
Suspension: Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2).
Upper respiratory-tract disorders.

Prasco, USA.
Tablets: Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

R-Tanna S Pediatric Prasco, USA.
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

R-Tannamine Qualitest, USA.
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract symptoms.

R-Tannate Copley, USA; Schein, USA; Warner Chilcott, USA.
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Allergic rhinitis; nasal congestion.

R-Tannic-S Cypress, USA†.
Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2).
Allergic rhinitis; cold symptoms; sinusitis.

R-Tyflam Rayere, Mex.
Piroxicam (p.117·3).
Inflammation; pain.

Rubacina Rubio, Spain.
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rub-Arom Hasco-Lek, Pol.
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); turpentine oil (p.2406·3).
Cold symptoms; musculoskeletal and joint disorders; neuralgia.

Rubeaten Kwizda, Austria; Berna, Port.†; Berna, Switz.
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Rubefric Spefar, Venez.†.
Methyl salicylate (p.85·3); camphor (p.2273·2); chloroform (p.1781·1); Fioraventi balsam.
Rubefacient.

Rubellovac Chiron Behring, Ger.†.
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Rubesal Hamilton, Austral.; Hamilton, Hong Kong.
Diethylamine salicylate (p.47·2); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal and soft-tissue pain.

Rubex
Note.This name is used for preparations of different composition.
BMS, Braz.; BMS Oncology, USA†.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Rice Steele, Irl.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Rubicalm Julphar, UAE.
Diethylamine salicylate (p.47·2); menthol (p.2340·1).
Musculoskeletal pain.

Rubicolan F Syxyl, Ger.
Homoeopathic preparation.

Rubi-Dex Cazi, Braz.
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

Rubidox
Note.This name is used for preparations of different composition.
Pfizer, Arg.†.
Cyproterone acetate (p.2088·2).
Androgenisation in females; prostatic cancer; sexual deviation in males.

Bergamo, Braz.; Sandoz, Indon.; Baxter, Philipp.
Doxorubicin hydrochloride (p.712·2).
Malignant neoplasms.

Medicus, Gr.
Doxorubicin (p.712·2).

RubieFol Rubiepharm, Ger.†.
Folic acid (p.1940·1).
Folic acid deficiency.

RubieMag + E Rubiepharm, Ger.†.
d-Alpha Tocoferil acetate (p.1992·3); magnesium oxide (p.1744·1).
Vitamin E and magnesium deficiency.

RubieMen Rubiepharm, Ger.†.
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vertigo.

RubieMol Rubiepharm, Ger.†.
Paracetamol (p.108·1).
Fever; pain.

RubieNex spezial Rubiepharm, Ger.†.
Ergotamine tartrate (p.620·1); propyphenazone (p.119·3).
Menstrual disorders; migraine.

RubieSed Rubiepharm, Ger.†.
Valerian (p.2410·1); melissa (p.2339·3); passion flower (p.2363·2).
Agitation; sleep disorders.

Rubifarm Pharmacia, Arg.†.
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Rubifen Neuropharma, Arg.; Rubio, Malaysia; AFT, NZ; Rubio, Neth.†; Rubio, Port.; Rubio, Singapore; Rubio, Spain; Rubio, Thai.†; TTN, Thai.†.
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention deficit hyperactivity disorder; mood disorders; narcoleptic syndrome.

Rubifort Kinder, Braz.
Vitamin A palmitate; colecalciferol (p.1922·1).
Vitamin A and D supplement.

Rubilax Pharmachoice, S.Afr.†.
Charcoal (p.1435·2); rhubarb (p.1768·3); senna (p.1769·2).
Constipation.

Rubilem Lemery, Mex.
Daunorubicin hydrochloride (p.709·1).
Malignant neoplasms.

Rubimar Arrow, Cz.
Lamotrigine (p.485·1).
Epilepsy.

Rubimycin Pharmacare, S.Afr.
Erythromycin stearate (p.270·1).
Bacterial infections.

Rubina Eurofarma, Braz.
Epirubicin hydrochloride (p.716·1).
Malignant neoplasms.

Rubiron Pierre Fabre, Arg.
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Rubisan Peithner, Austria; DHU, Cz.; DHU, Ger.; VSM, Neth.; Omida, Switz.†.
Homoeopathic preparation.

Rubital Gemi, Pol.
Althaea (p.2253·3).
Cough; respiratory-tract inflammation.

Rubital Compositum Gemi, Pol.
⊗ Althaea (p.2253·3); ephedrine hydrochloride (p.1558·2).
Cough; respiratory-tract inflammation.

Rubiten Rafarm, Gr.
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Rubiulcer Rubio, Spain.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rubizon-Rheumagel Makara, Austria.
Glycol salicylate (p.62·3); camphor (p.2273·2); benzyl nicotinate (p.28·1); capsaicin (p.32·3).
Chilblains; musculoskeletal and joint disorders; neuralgia.

Rubjovit SIFI, Ital.
⊗ Rubidium iodide (p.2382·2); sodium iodide (p.2169·2); calcium formate (p.2306·3); sodium ascorbate (p.1984·1); thiamine hydrochloride (p.1976·1).
Cataracts.

Rublex D Don, Israel.
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); salicylic acid (p.1612·2).
Musculoskeletal and joint disorders.

Rublex Massage Cream Don, Israel.
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); capsicum oleoresin (p.2276·2).
Musculoskeletal and joint disorders.

Rubocort Rafarm, Gr.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Ruboderm Plus Labcatal, Fr.
Zinc gluconate (p.1999·2); copper gluconate (p.1935·3); gluconolactone (p.2313·1).
Skin disorders.

Rub-on Plus ICM, Singapore†.
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal and soft-tissue pain.

Rubophen *Sanofi-Aventis, Hung.; Zentiva, Hung.*
Paracetamol (p.108·1).
Fever; pain.

Ruboril
Note.This name is used for preparations of different composition.
D & M, Chile.
Enoxolone (p.50·1); levomenol (p.2333·3).
Facial flushing; rosacea.

Darier, Mex.
Barrier cream.

Rubozinc *Labcatal, Fr.*
Zinc gluconate (p.1999·2).
Acne; acrodermatitis enteropathica.

Rubralong *Dovalle, Braz.†.*
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Rubramin *BMS, Philipp.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Rubranova *Mead Johnson, Braz.*
Hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; vitamin B deficiency.

Rubraplex *Sarabhai Piramal, India.*
Ferric ammonium citrate (p.1938·1); folic acid (p.1940·1).
Anaemia.

Rubrargil *IQB, Braz.*
Ferrous sulfate (p.1939·3); vitamin B ; vitamin B ; copper sulfate (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemias.

Rubriment
Note.This name is used for preparations of different composition.
Nycomed, Austria.
Benzyl nicotinate (p.28·1); nonivamide (p.96·2); glycol salicylate (p.62·3); salicylamide (p.121·2); camphor (p.2273·2); turpentine oil (p.2406·3).
Frostbite; joint, muscle, and nerve disorders; peripheral vascular disorders; sport massage.

Riemser, Ger.
Bath additive: Benzyl nicotinate (p.28·1).
Bath additive; peripheral vascular disorders; rheumatism.

Riemser, Ger.
Ointment: Benzyl nicotinate (p.28·1); nonivamide (p.96·2).
Frostbite; inflammation; musculoskeletal and joint disorders; peripheral vascular disorders.

Rubriment-BN *Riemser, Ger.*
Benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; peripheral vascular disorders.

Rubriment-N *Nordmark, Cz.†; Riemser, Ger.†.*
Benzyl nicotinate (p.28·1); glycol salicylate (p.62·3); camphor (p.2273·2).
Frostbite; musculoskeletal, joint, peri-articular, and soft-tissue disorders; peripheral vascular disorders.

Rubrina *Solfran, Mex.†.*
Hydroxocobalamin (p.1980·3).

Rubrinal *Vargas, Venez.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Peripheral neuropathy; vitamin B deficiency.

Rubrinex *Vargas, Venez.*
Cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); thiamine hydrochloride (p.1976·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Peripheral neuropathy.

Rubrobion *Sintofarma, Braz.†.*
Ferric ammonium citrate (p.1938·1); vitamin B substances; inositol; liver extract (p.1922·1).
Iron deficiency; iron-deficiency anaemia.

Rubrociclina *DMG, Ital.†.*
Demeclocycline hydrochloride (p.264·3); erythromycin estolate (p.269·3).
Bacterial infections.

Rubrocortin *Farma Lepori, Spain†.*
⊗ Cyanocobalamin (p.1980·2); suprarenal cortex extract (p.1543·3); liver extract (p.2337·3); inosine (p.2325·2).
Anaemias; tonic.

Rubroferrina *NCSN, Ital.†.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias.

Rubrojunior *Piam, Ital.*
Lactoferrin; zinc; vitamin B substances (p.1922·1).
Nutritional supplement.

Rubromicin *Prati-Donaduzzi, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Rubrovital *Piam, Ital.*
Lactoferrin; vitamin B substances; zinc (p.1922·1).
Tonic.

Rubrum *Nolver, Venez.*
Granisetron (p.1733·1).
Nausea and vomiting.

Rubus Complex *Blackmores, Austral.†.*
Raspberry leaf (p.2378·2); spirulina (p.2392·1); ascorbic acid; mitchella repens; hesperidin (p.2304·3); rutoside (p.2305·1); *d*-alpha tocoferil acid succinate; vitamin B substances (p.1922·1); choline bitartrate; inositol.
Obstetric and gynaecological disorders.

Rucaten Forte *Ivax, Arg.*
Acemetacin (p.15·1); chlorzoxazone (p.1894·3).
Musculoskeletal, joint, and peri-articular disorders.

Rucaten Prednisolona *Ivax, Arg.*
⊗ Acemetacin (p.15·1); prednisolone (p.1540·3); thiamine hydrochloride; cyanocobalamin (p.1922·1).
Gout; musculoskeletal and joint disorders; neuralgia.

Rucin *General Drugs, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Rudd-U *Frankin, Hong Kong†.*
Oxyphencyclimine hydrochloride (p.1759·2); methiosulfonium chloride (p.2343·3).
Stomach discomfort.

Rudesol *Pharmacos, Mex.†.*
Phenylbutazone (p.117·1).
Musculoskeletal and joint disorders.

Rudin *HPP, Hong Kong.*
Roxithromycin (p.331·1).
Bacterial infections.

Rudi-Rouvax *Aventis Pasteur, Braz.†; Aventis Pasteur, Thai.†.*
A measles and rubella vaccine (Schwarz and Wistar RA 27/3 strains respectively) (p.2223·1).
Active immunisation.

Rudistrol *Boiron, Canad.; Boiron, Neth.*
Homoeopathic preparation.

Rudivax *Sanofi Pasteur, Arg.; Aventis Pasteur, Braz.†; Pasteur Merieux, Cz.†; Sanofi Pasteur, Fr.; Aventis Pasteur, Hong Kong†; Pasteur Merieux, Israel; Aventis Pasteur, Ital.†; Sanofi Pasteur, Port.; Aventis, S.Afr.; Aventis Pasteur, Thai.†.*
A live attenuated rubella vaccine (Wistar RA 27/3-M strain) (p.2236·3).
Active immunisation.

Rudocaine *Streuli, Switz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Rudocycline *Streuli, Switz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Rudolac *Streuli, Switz.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Rudopram *Streuli, Switz.*
Citalopram hydrobromide (p.385·3).
Depression; panic attacks.

Rudotel *AWD, Ger.; AWD, Hung.; AWD, Pol.; AWD, Rus.*
Medazepam (p.1006·1).
Anxiety.

Rudoxil *Phoenix, Arg.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Rufebran allergo *Staufen, Ger.*
Homoeopathic preparation.

Rufebran broncho *Staufen, Ger.*
Homoeopathic preparation.

Rufebran gastro *Staufen, Ger.*
Homoeopathic preparation.

Rufebran lympho *Staufen, Ger.*
Homoeopathic preparation.

Rufebran neuro *Staufen, Ger.*
Homoeopathic preparation.

Rufebran regeno *Staufen, Ger.*
Homoeopathic preparation.

Rufebran thyreo *Staufen, Ger.*
Homoeopathic preparation.

Ruflex *Sunpab, Philipp.*
Glucosamine hydrochloride (p.2313·2); manganese (p.1956·1); gotu kola (p.1592·3); ginger (p.1732·3); celery (p.2278·3).
Joint pain and stiffness.

Rufol *Urgo, Fr.*
Sulfamethizole (p.339·3).
Cystitis.

Rug-Derm *Remexa, Mex.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Warts.

Ru-lets *Rugby, USA.*
A range of vitamin preparations (p.1922·1).

Rulicalcin *Aventis, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Rulid *Aventis, Arg.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Leciva, Cz.†; Sanofi-Aventis, Fr.; Aventis, Ger.; Winthrop, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Aventis, Israel; Lepetit, Ital.; Aventis, Malaysia; Aventis, Mex.; Aventis, Philipp.; Aventis, Pol.; Sanofi-Aventis, Rus.; Aventis, Singapore†; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, Venez.*
Roxithromycin (p.331·1).
Bacterial infections.

Rulide *Sanofi-Aventis, Austral.; Aventis, Austria; Aventis, Neth.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Spain.*
Roxithromycin (p.331·1).
Bacterial infections.

Rulofer G *Lomapharm, Ger.*
Ferrous gluconate (p.1939·1).
Iron deficiency.

Rulofer N *Lomapharm, Ger.*
Ferrous fumarate (p.1938·3).
Iron deficiency.

RuLox *Rugby, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Hyperacidity.

RuLox Plus *Rugby, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Rulun *Lacer, Spain.*
⊗ Hydrochlorothiazide (p.1307·3); rauwolfia (p.1387·1); trichlormethiazide (p.1418·3); xantinol nicotinate (p.1433·1).
Hypertension.

Rumadene *Chew, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Rumalaya *Himalaya Herbal, Malaysia.*
Boswellia serrata (p.2307·1); Indian bdellium; galanga; liquorice (p.1740·3); gokhru (p.2404·1); tinospora cordifolia.
Joint pain.

Rumalef *Cadila, India.*
Leflunomide (p.75·3).
Rheumatoid arthritis.

Rumalon *Asta Medica, Braz.†; Recalcine, Chile; Robapharm, Hung.†.*
Cartilage (p.2277·3); bone marrow.
Degenerative joint disorders; inflammation; osteoarthritis.

Rumancek Pravy *Slovakofarma, Cz.†.*
Chamomile (p.2279·3).
Gastrointestinal disorders; inflammatory disorders of the skin and mucous membranes.

Rumasian *Asian Pharm, Thai.*
Ibuprofen (p.64·2).
Osteoarthritis, rheumatoid arthritis.

Rumasin *Gunsa, Turk.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Rumatab *Pharmaland, Thai.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders.

Rumatifen *Chew, Thai.*
Ibuprofen (p.64·2).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Rumatifen-Plus *Chew, Thai.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Rumaxicam *March, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Rumazolidin *Biosel, Turk.*
Naproxen (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Rumicine *Schering-Plough, Fr.†.*
Aspirin (p.20·3); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Rumisedan *Lanpharm, Arg.*
Piroxicam (p.117·3); ascorbic acid (p.1983·3).
Inflammation; pain.

Rumisedan Fuerte *Lafage, Arg.†.*
Piroxicam (p.117·3); carisoprodol (p.1894·1); ascorbic acid; vitamin B substances (p.1922·1).
Inflammation; pain.

Rum-K *Fleming, USA†.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Rumycoz *Shchelkovskii, Rus.*
Itraconazole (p.536·3).
Fungal infections.

Runde *Rafarm, Gr.*
Tetramethrin (p.2051·1); piperonyl butoxide (p.2049·1).
Head, body, and crab lice.

Rupafin *Biosintetica, Braz.; Olvos, Gr.; Uriach, Spain.*
Rupatadine fumarate (p.590·2).
Allergic rhinitis.

Rupan *Medochemie, Hong Kong†; Medochemie, Malaysia†; Medochemie, Thai.†.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Rupecef *Duncan, Arg.†.*
Cefalotin (p.220·2).
Bacterial infections.

Rupedex *Duncan, Arg.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Rupediz *Duncan, Arg.†.*
Diazepam (p.986·3).
Anxiety.

Rupegen *Duncan, Arg.†.*
Gentamicin (p.284·2).
Bacterial infections.

Rupek *Duncan, Arg.*
Phytomenadione (p.1995·3).
Haemorrhage.

Rupemet *Duncan, Arg.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Rupe-N *Duncan, Arg.†.*
Hyoscine (p.1733·3).
Muscle spasm.

Rupe-N Compuesto *Duncan, Arg.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Muscle spasm.

Rupesona B *Duncan, Arg.*
⊗ Meprednisone (p.1538·1).
Formerly contained prednisone.
Corticosteroid.

Rupox *Medipharma, Arg.*
Oxcarbazepine (p.490·3).
Epilepsy.

Rupton
Note.This name is used for preparations of different composition.
SMB, Belg.
Loratadine (p.583·3).
Hypersensitivity reactions.

Dexo, Switz.†.
Brompheniramine maleate (p.569·2); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract disorders.

Ruscimel *Soria Natural, Spain†.*
Hamamelis (p.2318·2); aesculus (p.2248·2); cypress (p.2291·2); butcher's broom (p.2270·3).
Haemorrhoids; venous disorders.

Ruscorectal *Juste, Spain†.*
Ruscogenin (p.2382·2).
Anorectal disorders.

Ruscoroid *Sanofi-Aventis OTC, Ital.*
Ruscogenin (p.2382·2); tetracaine hydrochloride (p.1871·3).
Anorectal disorders.

Ruscus *Llorens, Spain.*
⊗ Cinchocaine hydrochloride (p.1857·3); prednisolone (p.1540·3); ruscogenin (p.2382·2); zinc oxide (p.1621·2); menthol (p.2340·1).
Anorectal disorders.

Rusedal *Byk, Cz.†; Altana, Ger.; Altana, Hung.*
Medazepam (p.1006·1).
Anxiety disorders; insomnia; premedication.

Ruskorex *GSK, Pol.*
Ruscogenin (p.2382·2); tetracaine hydrochloride (p.1871·3).
Anorectal disorders.

Russedyl *Strand, Malaysia†.*
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Allergic rhinitis; coughs; sinusitis.

Russedyl Plus *Pharmaniaga, Malaysia.*
Pholcodine (p.1570·2); promethazine hydrochloride (p.588·2); pseudoephedrine hydrochloride (p.1571·2).
Cough.

Rusyde *CP Pharmaceuticals, UK.*
⊗ Furosemide (p.1292·1).
Oedema.

Rutacid *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Hydrotalcite (p.1733·3).
Duodenitis; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Ruta-Gastreu N R55 *Reckeweg, Ger.*
Homoeopathic preparation.

Rutascorbin *Valeant, Hung.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3).
Haemorrhage; vascular disorders.

Ruthison *Unison, Philipp.*
Roxithromycin (p.331·1).
Bacterial infections.

Ruticalzon *Brady, Austria.*
Colecalciferol (p.1986·2); rutoside (p.2305·1); vitamin C (p.1983·3); calcium citrate (p.1675·3).
Capillary haemorrhage; infections.

Ruticalzon VC *Stegropharm, Ger.†.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3).
Haemorrhagic disorders.

Rutilina *Bernabo, Arg.*
Troxerutin (p.2305·1).
Venous insufficiency.

Rutinacea *Aflofarm, Pol.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Vitamin C supplement.

Rutinice Fortissimo *Menarini, Port.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3).
Haemorrhage.

Rutinion *Biomo, Ger.*
Rutoside (p.2305·1).
Venous insufficiency.

Rutinoscorbin *GSK, Pol.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Vitamin C supplement.

Rutinoscorbin Plus *GSK, Pol.*
Ascorbic acid; rutoside (p.2305·1); selenium; zinc (p.1922·1).
Dietary supplement.

Rutinoven *RiC, Pol.*
Troxerutin (p.2305·1).
Venous insufficiency.

Rutisan CE *Carlo Erba OTC, Ital.†.*
Rutoside (p.2305·1); vitamin C (p.1983·3); vitamin E (p.1992·2).
Vascular disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Rutiscorbin *Fresenius Kabi, Austria†.*
Rutoside (p.2305·1); ascorbic acid (p.1983·3).
Haemorrhage; infections.

Rutisept extra *Ecolab, Ger.*
Isopropyl alcohol (p.1650·3); triclosan (p.1665·2).
Hand disinfection.

Rutiviscal *Sanidom, Austria.*
Garlic (p.2309·2); crataegus (p.2289·1); mistletoe (p.2345·3); rutoside (p.2305·1).
Atherosclerosis.

Rutokal C *Natur Produkt, Pol.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); rutoside (p.2305·1).
Capillary fragility; cold symptoms; dietary supplement.

Rutoven *Herbapol Poznan, Pol.*
Troxerutin (p.2305·1).
Venous insufficiency.

Rutovit C *Polfa Kutno, Pol.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1).
Capillary fragility; cold symptoms.

Rutozym *Mucos, Austria.*
Rutoside (p.2305·1); bromelain (p.2269·1); trypsin (p.2405·3).
Inflammation; musculoskeletal and joint disorders; pain; thrombophlebitis.

Rutying *Super Mayoreo Naturista, Mex.*
Ginseng (p.2312·1).
Tonic.

Ruvamed *Coup, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Ruvetine *Rafarm, Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Ruvominox *Rafarm, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain; prevention of miosis in ophthalmic surgery.

Ruxcine *Mugi, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Ruxicolan *Rafarm, Gr.*
Ticlopidine (p.1412·1).
Thromboembolic disorders.

Ruxim *Samarth, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

RV Paque
Note.This name is used for preparations of different composition.
ICN, Canad.†; ICN, NZ.
Zinc oxide (p.1621·2); octinoxate (p.1608·2).
Sunscreen.

ICN, Malaysia†; ICN, Singapore†; ICN, USA.
Zinc oxide (p.1621·2); cinoxate (p.1593·1).
Sunscreen.

R-Vac *Serum Institute, India.*
A rubella vaccine (Wistar RA 27/3 strain) (p.2236·3).
Active immunisation.

Rycef *Interbat, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Rydene *Astellas, Belg.*
Nicardipine hydrochloride (p.1348·1).
Hypertension.

Rydian *Guardian, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Rye *Rafarm, Gr.*
Bifonazole (p.527·3).
Fungal skin infections.

Rymed *Edwards, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Ryna *Wallace, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Ryna-12 *Wallace, USA.*
Mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Nasal congestion; rhinitis.

Ryna-C *Wallace, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Rynacrom *Aventis, Austral.; Sanofi-Aventis, Irl.; Aventis, Mex.; Aventis, NZ; Aventis, Port.†; Aventis, Singapore†; Aventis, Thai.; Eczacibasi, Turk.; Sanofi-Aventis, UK.*
Sodium cromoglicate (p.1136·3).
Allergic rhinitis.

Rynacrom Compound *Aventis, Malaysia†; Aventis, Thai.†; Eczacibasi, Turk.; Pantheon, UK†.*
⊗ Sodium cromoglicate (p.1136·3); xylometazoline hydrochloride (p.1575·1).
Allergic rhinitis; nasal congestion.

Ryna-CX *Wallace, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); codeine phosphate (p.37·2).
Coughs.

Rynatan
Note.This name is used for preparations of different composition.
Medpointe, USA†.
Azatadine maleate (p.568·1); pseudoephedrine sulfate (p.1571·2).
Cold symptoms.

Medpointe, USA.
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

Rynatanic *Novartis, Arg.†.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).

Rynatus *Novartis, Arg.†.*
⊗ Pentoxyverine tannate (p.1567·3); phenylephrine tannate (p.1568·3) ephedrine tannate (p.1559·1); chlorphenamine tannate (p.572·2).

Rynatuss *Medpointe, USA.*
⊗ Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); ephedrine tannate (p.1559·1); phenylephrine tannate (p.1568·3).
Coughs.

Ryneze *Stewart Jackson, USA.*
Chlorphenamine maleate (p.571·3); hyoscine methonitrate (p.1734·2).
Upper respiratory-tract disorders.

Ryol *Schwarz, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Ryspolit *Polpharma, Pol.*
Risperidone (p.1024·2).
Schizophrenia.

Rythmex *Teva, Israel.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rythmical *Unipharm, Israel.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Rythmodan
Aventis, Austral.; Chugai, Jpn; Aventis, NZ; Aventis, Neth.†; Aventis, S.Afr.
Disopyramide (p.1269·1).
Arrhythmias.

Aventis, Austria; Sanofi-Aventis, Belg.; Aventis, Canad.; Sanofi-Aventis, Fr.; Borg, UK.
Disopyramide (p.1269·1) or disopyramide phosphate (p.1269·2).
Arrhythmias.

Aventis, Cz.†; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Irl.
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Rythmodul *Aventis, Ger.†; IFET (ΙΦΕΤ), Gr.†.*
Disopyramide phosphate (p.1269·2).
Arrhythmias.

Rythmogastryl *Rafarm, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Rythmol *Abbott, Canad.; Abbott, Fr.; Abbott, S.Afr.; Reliant, USA.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rythmonorm *Vianex (Βιανέξ), Gr.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rythocin *Millimed, Thai.*
Erythromycin (p.269·2).
Bacterial infections.

Rytmobeta *Abbott, Ital.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Rytmocard *Abbott, Philipp.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rytmogenat *Azupharma, Ger.†.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rytmonorm *Abbott, Belg.; Abbott, Chile†; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Ger.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Ital.; Abbott, Malaysia†; Abbott, NZ; Abbott, Neth.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rytmonorma *Abbott, Austria.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Rytmopasc *Pascoe, Ger.*
Homoeopathic preparation.

Rytmo-Puren *Alpharma-Isis, Ger.*
Propafenone hydrochloride (p.1379·2).
Arrhythmias.

Ry-Tuss *Cypress, USA†.*
⊗ Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); ephedrine tannate (p.1559·1); phenylephrine tannate (p.1568·3).
Coughs.

Ryvel *Novell, Hong Kong; Novell, Indon.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Ryvina *Rafarm, Gr.†.*
⊗ Pilocarpine hydrochloride (p.1884·3); dipivefrine (p.2295·3).
Glaucoma.

Rywanol *Hasco-Lek, Pol.*
Ethacridine lactate (p.1625·1).
Burns; skin and mucous membrane infections; ulcers; wounds.

Ryzen *UCB, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Ryzo *Soho, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Rzewex *Herbapol Lodz, Pol.*
Rhubarb (p.1768·3).
Constipation.

S-2 *Nephron, USA.*
⊗ Racepinefrine hydrochloride (p.1204·2).
Bronchospasm.

S.8 *Chefaro, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

S Amet *Boehringer Ingelheim, Spain†.*
Ademetionine (p.2247·1).
Depression; liver disorders.

S-26 AR *Wyeth Consumer, Austral.; Wyeth, Chile; Wyeth, Hong Kong†; Wyeth, NZ; Wyeth Lederle, Port.†; Wyeth, Singapore†.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux; gastro-oesophageal regurgitation.

S-26 HA *Wyeth, Hong Kong.*
Infant feed (p.1922·1).
Cows' milk protein allergy.

S-26 Lactose-free *Wyeth, Philipp.*
Infant feed (p.1922·1).
Lactose intolerance.

S-26 LF *Wyeth Consumer, Austral.; Wyeth, Hong Kong†; Wyeth, NZ; Wyeth, Singapore†.*
Infant feed (p.1922·1).
Lactose intolerance.

S-26 Mom *Wyeth, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

S-26 sem Lactose *Wyeth Lederle, Port.†.*
Infant feed (p.1922·1).
Lactose intolerance.

S-26 sin Lactosa *Wyeth, Venez.*
Infant feed (p.1922·1).
Lactose intolerance.

S-26 Soy *Wyeth Consumer, Austral.*
Infant feed (p.1922·1).
Lactose intolerance.

Saak *Yungjin, Singapore†.*
Methyl salicylate (p.85·3); glycol salicylate (p.62·3) menthol (p.2340·1); benzyl alcohol (p.1631·3).
Musculoskeletal and joint pain.

Saaz *Ipca, India.*
Sulfasalazine (p.1773·2).
Rheumatoid arthritis; ulcerative colitis.

SAB Simplex *Pfizer, Austria; Pfizer, Cz.; Parke, Davis, Ger.; Pfizer, Hung.; Pfizer, Rus.*
Simeticone (p.1770·2).
Detergent poisoning; flatulence; gastrointestinal disorders with excess gas; meteorism; reduction of intestinal gas before or after gastrointestinal procedures.

Saba *Lampugnani, Ital.*
Saw palmetto (p.2192·3).
Prostatic hyperplasia.

Sabacur uno *Hexal, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabadilla Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Sabal
Note.This name is used for preparations of different composition.
Sandoz, Ger.; Stada, Ger.
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Medifarm Ducray, Venez.
Saw palmetto (p.2192·3); zinc salicylate (p.1612·3).
Seborrhoea.

Pierre Fabre Dermo-Cosmetique, Arg.; Ducray, Fr.
Shampoo: Saw palmetto (p.2192·3); zinc salicylate (p.1612·3).
Seborrhoea; seborrhoeic dermatitis.

Pierre Fabre, Arg.†.
Topical emulsion: Saw palmetto (p.2192·3); zinc pidolate (p.1614·1).
Seborrhoea.

Sabal uno *Apogepha, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabalax *Saba, Turk.*
Sorbitol (p.1965·1); latanol; sodium citrate (p.1673·3); glycerol (p.2314·2).
Constipation.

Sabalia *Boiron, Canad.*
Homoeopathic preparation.

Sabalin *Lichtwer, UK.*
Saw palmetto (p.2192·3).
Male urinary discomfort.

Saballo *Scherer, Hung.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabalvit *Ruhrpharm, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabanotropico *Perez Gimenez, Spain.*
⊗ Bismuth subgallate (p.1711·1); dexamethasone sodium phosphate (p.1526·2); phenol (p.1656·1); sulfathiazole (p.343·2); tannic acid (p.2394·3); menthol (p.2340·1).
Chilblains; cold-induced skin damage.

Sabatif *Apomedica, Austria.*
Simeticone (p.1770·2); activated charcoal (p.1435·2); sulfur (p.1614·1); rhubarb (p.1768·3); senna leaf (p.1769·2); caraway oil (p.2277·1); fennel oil (p.2303·1).
Dyspepsia; flatulence; laxative.

Sabax Combineb *Adcock Ingram Critical Care, S.Afr.*
⊗ Ipratropium bromide (p.1124·1); salbutamol (p.1131·2).
Obstructive airways disease.

Sabax Dianeal *Adcock Ingram Critical Care, S.Afr.*
Glucose; sodium chloride; sodium lactate; calcium chloride; magnesium chloride (p.1670·3).
Peritoneal dialysis.

Sabax Fosenema *Adcock Ingram Critical Care, S.Afr.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Sabax Gentamix *Adcock Ingram Critical Care, S.Afr.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Sabax Nebrafen *Adcock Ingram Critical Care, S.Afr.*
⊗ Fenoterol hydrobromide (p.1121·1); ipratropium bromide (p.1124·1).
Obstructive airways disease.

SabCaps *Vifor, Switz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabenyl
Note.This name is used for preparations of different composition.
Qualiphar, Belg.
⊗ Chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Hand disinfection.

Sanofi Synthelabo, Gr.†.
Mercurobutol (p.1652·2); sodium laurilsulfate (p.2138·3).
Antiseptic.

Sabima *Atlantis, Mex.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Sabin *Sanofi Pasteur, Arg.; GSK, Belg.†.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Sabofen *Geyer, Braz.†.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Sabonal Uno *Sabona, Ger.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sabonete Sulfuroso *Simoes, Braz.†.*
Sublimed sulfur (p.1614·1).
Seborrhoea.

SAB-Prednase *Sabex, Canad.†.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Eye disorders.

Sabril *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Ovation, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sandoz, Mex.; Aventis, NZ; Sanofi-Aventis, Neth.; Marion Merrell, Pol.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Switz.; Aventis, Turk.; Aventis, UK.*
Vigabatrin (p.513·2).
Epilepsy.

Sabrilan *Agis, Israel.*
Vigabatrin (p.513·2).
Epilepsy.

Sabrilex *Aventis, Denm.; Sanofi-Aventis, Fin.; Euro Registratie, Neth.; Aventis, Norw.; Sanofi-Aventis, Spain; Aventis, Swed.*
Vigabatrin (p.513·2).
Epilepsy.

Sabro *Senosiain, Mex.*
Aloglutamol (p.1705·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal hyperacidity; hiatus hernia; peptic ulcer.

Saburgen-N *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Sabutol *Malaysia Chemist, Singapore†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Saccharofar *Faran, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Sachol zel Stomatologiczny *Jelfa, Pol.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1).
Mouth disorders.

Sacietyl *Finadiet, Arg.*
⊗ Sibutramine (p.2164·1).
Obesity.

Sacin *Labomed, Chile.*
⊗ Diethylpropion (p.2154·3).
Obesity.

Sacnel *Teofarma, Ital.*
Colloidal sulfur (p.1614·1); zinc oxide (p.1621·2); titanium dioxide (p.1617·3); dithiosalicylic acid (p.1595·1); hamamelis leaves (p.2318·2).
Acne; seborrhoeic dermatitis.

Sacolene *EG, Fr.*
Methylenated milk proteins.
Diarrhoea.

Sacsol *Eagle, Austral.†.*
Hexane (p.2024·1); camphor (p.2273·2).
Surgical cement solvent for stoma patients.

Sacsol NF *Eagle, Austral.†.*
Trichloroethane (p.2027·2); camphor (p.2273·2).
Non-flammable surgical cement solvent for stoma patients.

Sactabs *PSM, NZ.*
Saccharin (p.1960·2).
Artificial sweetener.

Sadamin *Pliva Krakow, Pol.*
Xantinol nicotinate (p.1433·1).
Peripheral vascular disorders; thromboembolic disorders.

Sadeltan F *Hautel, Arg.†.*
⊗ Aloe vera (p.1588·2); urea (p.1620·2).
Emollient.

Sadocin *Farcoral, Mex.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Sadol *Catarinense, Braz.*
Iron (p.1949·1); pyridoxine; nicotinamide; caffeine; citric acid (p.1922·1).
Iron deficiency; iron-deficiency anaemias.

Sadolin *Elpen (Ελπεν), Gr.*
Somatostatin (p.1809·1).

SAE *Pasteur, Chile.*
Propyphenazone (p.119·3); adiphenine hydrochloride (p.2248·1); trasentine.
Smooth muscle spasm.

Saetil *Robapharm, Spain.*
Ibuprofen arginine (p.65·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Safarol *Medichrom, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Saf-Clens *Calgon Vestal, USA.*
Wound cleanser.

Safe Tussin 30 *Kramer, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Safemar *Sandoz, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Saferon
Note. This name is used for preparations of different composition.
Glenmark, Malaysia.
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Glenmark, Singapore†.
Iron polymaltose (p.1953·1); folic acid (p.1940·1).
Iron and folic acid deficiency; iron-deficiency anaemia.

Safetin *Dexa, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Safety T *Volta, Chile.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Safeway Nasal *Prodemdis, Canad.*
Sodium chloride (p.1686·1).

Saffid *Safire, Hong Kong.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias; primary prevention of ischaemic heart disease.

Safkit *Biochem, India.*
2 Tablets, secnidazole (p.846·3); 1 tablet azithromycin (p.207·1); 1 tablet, fluconazole (p.532·1).
Bacterial and fungal infections.

Safol *Novell, Indon.*
Propofol (p.1791·1).
General anaesthesia; sedative.

Saforelle
Note. This name is used for preparations of different composition.
IPRAD, Fr.
Sodium laurilsulfate (p.2138·3).
Gynaecological hygiene.

Avanderm, Mex.†; BioSaude, Port.; Medifarm, Venez.
Lappa (p.2330·3).
Skin irritation; soap substitute.

Safrux *CPH, Port.*
Tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2); potassium tartrate (p.1684·3).
Antacid.

Saften *Monserrat, Arg.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; gastrointestinal procedures; nausea and vomiting.

Safyr Bleu *Pharmacare, S.Afr.*
⊗ Naphazoline nitrate (p.1565·2).
Eye irritation.

Safyr Bleu Antihistamine *Aspen, S.Afr.†.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic conjunctivitis; hay fever.

Sagadreps *Diepharmex, Fr.†.*
Biclotymol (p.1632·1).
Formerly known as Hexadreps.
Mouth and throat infections.

Sagalon *Surya Dermato, Indon.*
Doxepin hydrochloride (p.389·1).
Pruritus.

Sagamicin *Kyowa, Jpn; Kyowa, Singapore†.*
Micronomicin sulfate (p.300·2).
Bacterial infections.

Sagaspray *Diepharmex, Fr.*
Biclotymol (p.1632·1).
Mouth disorders; sore throat.

Sagenit *Nizpharm, Rus.*
Dipotassium *meso*-3,4-Bis(*p*-sulfophenyl)hexane (p.2387·1).
Menopausal disorders.

Sagestam *Sanbe, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Sagittaproct *Sagitta, Cz.†.*
Bismuth subgallate (p.1711·1); hamamelis (p.2318·2).
Haemorrhoids.

Saglion *Verisfield, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Sagrosept
Note. This name is used for preparations of different composition.
Schulke & Mayr, Ger.†.
Lotion: Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); lactic acid (p.2329·3).
Hand disinfection.

Schulke & Mayr, Ger.†.
Medicated wipes: Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); benzoic acid (p.1630·2); lactic acid (p.2329·3).
Skin disinfection; surface disinfection; wounds.

Sahne Krim *Eisai, Indon.*
Moisturiser.

Saibokuto *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; poria sclerotium; scutellaria root; magnolia bark; jujube; ginseng; liquorice; perilla herb; ginger.
Traditional Kampo medicine.

Saikokaryukotsuboreito *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; cinnamon bark; poria sclerotium; scutellaria root; jujube; ginseng; oyster shell; longgu; ginger.
Traditional Kampo medicine.

Saikokeishito *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; scutellaria root; liquorice; cinnamon bark; peony root; jujube; ginseng; ginger.
Traditional Kampo medicine.

Saikoseikanto *Tsumura, Jpn.*
Bupleurum root; scutellaria root; phellodendron bark; coptis rhizome; trichosanthes root; liquorice; platycodon root; burdock fruit; gardenia fruit; rehmannia root; peony root; cnidium rhizome; Japanese angelica root; mentha herb; forsythia fruit.
Traditional Kampo medicine.

Saintbois
Note. This name is used for preparations of different composition.
Melisana, Belg.
Ethylmorphine hydrochloride (p.52·2); sulfogaiacol (p.1573·2); belladonna (p.2263·3); tolu balsam (p.1574·2); aconite (p.2246·1); senega (p.1572·3); maidenhair; drosera (p.2297·3).
Cough.

Vifor, Switz.
Ethylmorphine hydrochloride (p.52·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); belladonna (p.2263·3); hyssopus officinalis (p.2323·3); tolu balsam (p.1574·2).
Coughs; respiratory-tract disorders.

Sairei-to *Tsumura, Jpn.*
Bupleurum root; alisma rhizome; pinellia tuber; scutellaria root; atractylodes lancea rhizome; jujube; polyporus sclerotium; ginseng; poria sclerotium; liquorice; cinnamon bark; ginger.
Traditional Kampo medicine.

Saistrat *Biofarma, Braz.†.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

Saizen *Serono, Arg.; Serono, Austral.; Serono, Austria; Serono, Braz.; Serono, Canad.; Novartis, Chile†; Serono, Cz.; Serono, Fin.; Serono, Fr.; Serono, Ger.; Serono, Gr.; Serono, Hong Kong; Serono, Hung.†; Serum Institute, India; DKSH, Indon.; Serono, Indon.; Serono, Irl.; Serono, Ital.; Serono, Malaysia; Serono, Mex.; Healthcare Logistics, NZ; Serono, Norw.; Serono, Philipp.; Merck, Port.; Serono, Rus.; Serono, S.Afr.†; Serono, Singapore; Serono, Spain; Serono, Swed.; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, UK; Serono, USA; Serono, Venez.*
⊗ Somatropin (p.1799·3).
Cachexia and wasting in AIDS; growth disorders in renal failure; growth hormone deficiency; Prader-Willi syndrome; short children born small for gestational age; Turner's syndrome.

Sal Amargo Purificado *Catarinense, Braz.*
Magnesium sulfate (p.1679·3).
Constipation.

Sal de Andrews *GSK, Braz.*
Magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Gastric hyperacidity.

Sal Carolinum Factitium *Ziololek, Pol.*
Sodium sulfate; potassium sulfate; sodium chloride; sodium bicarbonate (p.1667·1).
Biliary-tract disorders; constipation; obesity.

Sal Dietetica *Reccius, Chile.*
Potassium chloride (p.1684·3).
Dietary salt substitute.

Sal Ems Artificiale *Galenus, Pol.*
Sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1); potassium sulfate (p.1684·3); sodium sulfate (p.1771·3); dibasic sodium phosphate (p.1682·3).
Respiratory-tract disorders.

Sal Ems Factitium *Ziololek, Pol.*
Sodium bicarbonate (p.1673·2); sodium bromide (p.2269·2); dibasic sodium phosphate (p.1682·3); sodium chloride (p.1686·1); sodium sulfate (p.1771·3); potassium sulfate (p.1684·3).
Respiratory-tract disorders.

Sal de Fruta Eno
Note. This name is used for preparations of different composition.
GSK, Arg.; GSK, Braz.; GSK Consumer, Spain.
Sodium bicarbonate (p.1673·2); sodium carbonate (p.2389·1); citric acid (p.2284·1).
Gastric hyperacidity.

GSK, Chile.
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Gastrointestinal disorders.

Sal Lite *Rider, Chile.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Dietary salt substitute.

Sal Liviana En Sodio *Reccius, Chile.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Dietary salt substitute.

Sal Vichy Factitium *Ziololek, Pol.*
Sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1); dibasic sodium phosphate (p.1682·3); sodium sulfate (p.1771·3); potassium bicarbonate (p.1673·1).
Gallbladder inflammation; gallstones; gastric hyperacidity.

Sal De Yasta *Bayer, Chile†.*
Sodium bicarbonate (p.1673·2).
Antacid.

Salac
Note. This name is used for preparations of different composition.
Andromaco, Arg.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

GenDerm, USA.
Salicylic acid (p.1612·2).
Acne.

Sal-Acid *Pedinol, USA.*
Salicylic acid (p.1612·2).
Warts.

Salactic Film *Pedinol, USA.*
Salicylic acid (p.1612·2).
Warts.

Salactol *Dermal Laboratories, Irl.; Dermal Laboratories, UK.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; verrucas; warts.

Salagen *Novartis, Austria; Novartis, Belg.; Pfizer, Canad.; Chiron, Cz.†; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; MGI, Hong Kong; Novartis Ophthalmics, Hung.; Novartis, Irl.; MGI, Israel; Novartis, Ital.; Novartis, Neth.; Novartis, Port.; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; American Taiwan, Thai.; Novartis, UK; MGI, USA.*
Pilocarpine hydrochloride (p.1884·3).
Dry mouth; radiation-induced xerostomia; Sjögren's syndrome.

Salamflux *Atlantis, Mex.*
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Salamol
Galena, Cz.†; Ivax, Hong Kong; Ivax, Irl.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ivax, Mex.; Norton, Rus.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Norton, NZ; Ivax, Singapore†; Norton Healthcare, Singapore†; Ivax, UK.
⊗ Salbutamol sulfate (p.1131·3).
Asthma; bronchospasm; obstructive airways disease.

Salapin *AFT, NZ; Pinewood, UK.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; bronchospasm.

Salatac *Dermal Laboratories, Irl.; Dermal, Israel; Dermal Laboratories, UK.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; verrucas; warts.

Salazar *Cadila, India.*
Sulfasalazine (p.1773·2).
Rheumatoid arthritis.

Salazopirina *Jaba Recordati, Port.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Salazoprin *Cazi, Braz.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease.

Salazopryn *Eczacibasi, Turk.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Salazopyrin *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Norw.; Pfizer, Pol.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; proctitis; pyoderma gangrenosum; rheumatoid arthritis.

Salazopyrina *Pfizer, Spain.*
Sulfasalazine (p.1773·2).
Ulcerative colitis.

Salazopyrine *Pfizer, Belg.; Pfizer, Fr.; Pfizer, Neth.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Salbei Curarina *Harras-Curarina, Ger.*
Sage (p.2382·3).
Mouth and throat inflammation.

Salben *Pulmomed, Rus.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbetol *FDC, India.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbomex *Andromaco, Venez.†.*
⊗ Salbutamol sulfate (p.1131·3); bromhexine (p.1552·2).
Asthma.

Salbron *Kalbe, Indon.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbron Expectorant *Kalbe, Indon.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Salbu *Astellas, Ger.; Fatol, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbuair *Aldo-Union, Singapore.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbubreathe *Sandoz, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbudan *Norton, Denm.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbufax *Master Pharma, Ital.†.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; bronchospastic disorders.

Salbuhexal *Hexal, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbulair *Ivax, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbulin
Fada, Arg.†; 3M, Mex.†; Medsan, Turk.; Meda, UK.
⊗ Salbutamol sulfate (p.1131·3).
Asthma; obstructive airways disease.

3M, S.Afr.†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbulind *Lindopharm, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbulis *Proula, Venez.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease; premature labour.

Salbumed
MedGen, Philipp.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Medifarm, Venez.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbumol *GSK, Fr.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; premature labour.

Salbunova *Lavipharm, Gr.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma; chronic respiratory failure.

Salbupp *Dermapharm, Ger.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salburin *Luper, Braz.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salburol *Valmor, Venez.*
⊗ Salbutamol sulfate (p.1131·3).
Asthma.

Salbusian *Asian Pharm, Thai.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutac *Polipharm, Thai.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutalan *Quimica y Farmacia, Mex.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutalin *Hebron, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbutam *Bunker, Braz.; Nobel, Turk.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutamax *Uniao Quimica, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutamol Expectorant *Pharmaniaga, Malaysia.*
⊗ Guaifenesin (p.1561·3); salbutamol sulfate (p.1131·3).

Formerly known as Asmovent Expectorant.
Respiratory-tract disorders.

Salbutan GSK, Venez.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutard Lusofarmaco, Ital.†.
⊗ Salbutamol sulfate (p.1131·3).
Asthma; bronchospastic disorders.

Salbuterol IG, Malaysia†; Medidata, Malaysia†.
⊗ Salbutamol (p.1131·2).
Asthma.

Salbutib Ibfarma, Braz.†.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbutide GSK, Venez.†.
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Salbutol
Altana, Arg.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ilsan, Turk.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbutol Beclo Altana, Arg.
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Salbutral
Cassara, Arg.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

D & M, Chile.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbutral AC Cassara, Arg.; D & M, Chile.
⊗ Salbutamol sulfate (p.1131·3); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Salbutral + Aeromed Cassara, Arg.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salbutrop Altana, Arg.†.
⊗ Salbutamol sulfate (p.1131·3); ipratropium bromide (p.1124·1).
Obstructive airways disease.

Salbuven Pharos, Indon.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salbuven Expectorant Pharos, Indon.
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Salbuvent Nycomed, Denm.; Leiras, Fin.†.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salca Biotech, Venez.
⊗ Furosemide (p.1292·1).
Barbiturate poisoning; heart failure; hepatic cirrhosis with ascites; hypertension; oedema.

Salcal
Note. A similar name is used for preparations of different composition (see below).
Saval, Chile.
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Sal-Cal
Note. A similar name is used for preparations of different composition (see above).
Remedina, Gr.
Calcitonin (p.1093·1).
Osteoporosis.

Salcat Pfizer, Port.
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Salcedol Fardi, Spain.
Potassium sulfate (p.1684·3); sodium bicarbonate (p.1673·2); sodium sulfate (p.1771·3); tartaric acid (p.2395·2).
Constipation; digestive disorders.

Salcemetic Fardi, Spain†.
⊗ Cyclobutyrol (p.2290·3); metoclopramide hydrochloride (p.1747·3); mannitol (p.1330·2).
Gastrointestinal disorders.

Salco Lisapharm, Israel.
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Salcoat Teijin, Jpn.
⊗ Beclometasone dipropionate (p.1516·2).
Stomatitis.

Salcomed Bajamed, Mex.
⊗ Salbutamol (p.1131·2).
Respiratory-tract disorders.

Salda Millimed, Thai.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salder S Medley, Braz.
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne; pityriasis versicolor; seborrhoea.

Saldeva
Note.This name is used for preparations of different composition.
Montpellier, Arg.†.
Carzenide (p.2277·3); atropine methobromide (p.1219·2); metamizole magnesium (p.49·3).
Dysmenorrhoea; premenstrual syndrome.

Bayer, Spain.
Caffeine (p.1116·3); dimenhydrinate (p.576·2); paracetamol (p.108·1).
Dysmenorrhoea.

Saldiam Jelfa, Pol.
Diethylamine salicylate (p.47·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Salena Novartis, Arg.†.
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders.

Sales Fruta Mag Viviar Viviar, Spain.
Magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Constipation; gastrointestinal hyperacidity.

Sales de Frutas P G Perez Gimenez, Spain.
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Constipation; gastrointestinal hyperacidity.

Saletanol D Human, Hung.†.
⊗ Alcohol (p.1625·2) in glucose and sodium chloride infusion.
Ethylene glycol and methyl alcohol poisoning.

Saleto Roberts, USA.
Paracetamol (p.108·1); aspirin (p.20·3); salicylamide (p.121·2); caffeine (p.1116·3).
The name Saleto is also used for a preparation containing ibuprofen.
Pain.

Saleto-200 Roberts, USA.
Ibuprofen (p.64·2).
The name Saleto is also used for a preparation containing paracetamol, aspirin, salicylamide, and caffeine.
Fever; osteoarthritis; pain; rheumatoid arthritis.

Salex Coria, USA.
Salicylic acid (p.1612·2).
Skin and scalp disorders.

Salfer Cofasa, Venez.
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Salfis Argenfarma, Arg.†.
Sodium chloride (p.1686·1).

Salflex Carnrick, USA.
Salsalate (p.122·1).
Musculoskeletal and joint disorders.

Salf-Pas Salf, Ital.
Sodium aminosalicylate (p.201·2).
Tuberculosis.

Salgen Erlimpex, Indon.
Gentamicin (p.284·2).
Skin infections.

Salgen Plus Erlimpex, Indon.
⊗ Gentamicin (p.284·2); betamethasone valerate (p.1519·1).
Infected skin disorders.

Salgim Pulmomed, Rus.
⊗ Salbutamol hemisuccinate (p.1133·2).

Salguer Fada, Arg.†.
Povidone-iodine (p.1659·2).
Disinfection.

Salgydal a la noramidopyrine Bouchara-Recordati, Fr.†.
Dipyrone (p.49·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Salhumin
Note.This name is used for preparations of different composition.
Sanova, Austria.
Bath additive: Sodium humate (p.2389·3); salicylic acid (p.1612·2).
Rheumatic disorders.

Sanova, Austria.
Liniment: Sodium humate (p.2389·3); capsicum (p.2276·2); salicylic acid (p.1612·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); turpentine oil (p.2406·3); camphor (p.2273·2).
Circulatory disorders; muscle, joint, and nerve pain.

Salhumin Gel Bastian, Ger.
Glycol salicylate (p.62·3).
Soft-tissue injury.

Salhumin Rheuma-Bad Bastian, Ger.
Salicylic acid (p.1612·2); sodium humate (p.2389·3).
Bath additive; musculoskeletal and joint disorders.

Salhumin Sitzbad N Bastian, Ger.†.
Salicylic acid (p.1612·2); sodium humate (p.2389·3).
Bath additive; gynaecological disorders.

Salhumin Teilbad N Bastian, Ger.†.
Salicylic acid (p.1612·2); sodium humate (p.2389·3); esculoside (p.2248·2).
Bath additive; circulatory disorders.

Sali D'Achille Terme di Salsomaggiore, Ital.†.
Mineral salt preparation.
Sore feet.

Sali di Salsomaggiore Terme di Salsomaggiore, Ital.
Mineral salt preparation.
Gynaecological disorders; nose and throat disorders.

Sali-Adalat Bayer, Ger.
⊗ Nifedipine (p.1350·1); mefruside (p.1332·1).
Hypertension.

Sali-Aldopur Kwizda, Austria; Hormosan, Ger.†.
⊗ Spironolactone (p.1400·1); bendroflumethiazide (p.1224·1).
Hyperaldosteronism; hypertension; hypokalaemia; liver cirrhosis and ascites; oedema.

Salic Darrow, Braz.
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Keratinisation disorders.

Salicairine Legras, Fr.
Loosestrife (p.2334·3).
Diarrhoea.

Salicalcium CT, Ital.†.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

SaliCept Carrington, USA.
Acemannan (p.2244·2).
Wounds, injuries, and ulcers of the oral mucosa.

Salicil
Note.This name is used for preparations of different composition.
Ducto, Braz.
Aspirin (p.20·3).
Fever; pain.

Bersan, Ital.
Salicylic acid (p.1612·2).
Scalp disorders.

Salicilato de Bismuto Composto Simoes, Braz.†.
Bismuth salicylate (p.1711·1); sodium bicarbonate (p.1673·2); magnesium oxide (p.1744·1); calcium carbonate (p.1714·1); belladonna (p.2263·3).
Diarrhoea; gastric hyperacidity.

Salicin Greenpharma, Braz.
Aspirin (p.20·3).
Fever; pain.

Salicina Ratiopharm, Ital.
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms; pain.

Salicin-C Amnol, Ital.†.
Salix; echinacea; minerals; vitamin C (p.1922·1).
Nutritional supplement.

Salicort Cassara, Arg.
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Formerly contained triamcinolone acetonide and salicylic acid.
Skin disorders.

Salicortex Labofarm, Pol.
Salix purpurea (p.121·3).
Cold symptoms; rheumatic disorders.

Salicort-R Kattwiga, Ger.†.
Homoeopathic preparation.

Salicrem Gezzi, Arg.
Diethylamine salicylate (p.47·2); benzocaine (p.1854·1).
Musculoskeletal and joint disorders.

Salicrem Forte Gezzi, Arg.
Diclofenac diethylamine (p.44·3).
Inflammation; pain.

Salicrem K Gezzi, Arg.
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Salicrem Miconazol Gezzi, Arg.†.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Salicyd Polychronus, Gr.
Salicylic acid (p.1612·2).
Skin disorders.

Salicyl Galderma, Denm.
Salicylic acid (p.1612·2).
Keratinisation disorders.

Salicylcafeina Menarini, Port.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Salicylol Profarm, Pol.
Castor oil (p.2278·1); salicylic acid (p.1612·2).
Keratinisation disorders.

Sali-Decoderm Hermal, Ger.
⊗ Fluprednidene acetate (p.1533·1); salicylic acid (p.1612·2).
Scalp disorders (tincture); skin disorders.

Saliderm Profarm, Pol.
Salicylic acid (p.1612·2).
Keratinisation disorders.

Salidex Braun, Norw.
Anhydrous glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Salidur Omega, Spain.
⊗ Furosemide (p.1292·1); triamterene (p.1417·2).
Hypertension; oedema.

Saliject Omega, Canad.
Sodium salicylate (p.124·2).
Sclerotherapy.

Salikaren Rekah, Israel.
Salicylic acid (p.1612·2).
Keratinisation disorders.

Saliker
Note.This name is used for preparations of different composition.
Roche-Posay, Arg.†; Roche-Posay, Braz.; Roche-Posay, Irl.†.
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1); iodopropynyl butyl carbamate (Glicacil) (p.2045·2).
Dandruff; scalp disorders; seborrhoeic dermatitis.

Roche-Posay, Fr.†.
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1); iodopropynyl butylcarbamate; capryloyl glycine; capryloyl salicylic acid.
Dandruff.

Salilax Orion, Denm.; Orion, Swed.
Magnesium oxide (p.1744·1).
Bowel evacuation.

Salilex Medihealth, Mex.
Salicylic acid (p.1612·2); dexpanthenol (p.2362·1); menthol (p.2340·1); camphor (p.2273·2).
Acne.

Saliment Vida, Hong Kong.
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); menthol (p.2340·1).
Musculoskeletal and joint pain.

Salimetin Luper, Braz.†.
Methyl salicylate (p.85·3); turpentine oil (p.2406·3); menthol (p.2340·1); camphor (p.2273·2); chlorophyllin copper complex sodium (p.1471·1); lavender oil (p.2331·2).
Musculoskeletal and joint disorders.

Salimidin LKM, Arg.
Itraconazole (p.536·3).
Fungal infections.

Salimont Pharmonta, Austria.
Aspirin (p.20·3).
Fever; pain.

Salin Sagmel, Rus.
Sodium chloride (p.1686·1).
Nasal hygiene.

Salinal Julphar, UAE.
Simeticone (p.1770·2).
Adjunct in gastroscopy and bowel radiography; excess gastrointestinal gas.

Salinase
Note.This name is used for preparations of different composition.
TS, Ital.
Vitamin C; vitamin E; potassium aspartate; sodium bicarbonate; magnesium aspartate (p.1922·1).

Pediapharma, Philipp.
Sodium chloride (p.1686·1).
Nasal dryness and congestion.

Salinex Sandoz, Canad.; Muro, USA.
Sodium chloride (p.1686·1).
Nasal hygiene; nasal irritation.

Salinol Sabex, Canad.†.
Macrogol (p.2336·1); propylene glycol (p.2374·1).
Nasal lubricant.

Salinum Crawford, UK.
Polysaccharide-rich linseed extract (p.2333·3).
Dry mouth.

Salipads Galderma, Braz.†.
Salicylic acid (p.1612·2).
Keratinisation disorders; seborrhoea.

Salipax Mepha, Malaysia; Mepha, Pol.; Mepha, Port.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Salipran UCB, Fr.†.
Benorilate (p.27·2).
Pain.

Sali-Prent Bayer, Ger.
⊗ Acebutolol hydrochloride (p.1200·1); mefruside (p.1332·1).
Hypertension.

Salipsor Verisfield, Gr.
Salicylic acid (p.1612·2).
Skin disorders.

Sali-Puren Alpharma-Isis, Ger.†.
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Salisoap
Note.This name is used for preparations of different composition.
Galderma, Braz.
Shampoo: Salicylic acid (p.1612·2); sulfur (p.1614·1).
Seborrhoeic dermatitis.

Galderma, Braz.
Soap: Salicylic acid (p.1612·2); sulfur (p.1614·1); triclosan (p.1665·2).
Seborrhoeic dermatitis.

Salisol Rekah, Israel.
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Keratinisation disorders; skin disinfection.

Salisteril Fresenius Kabi, Switz.†.
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Salistoperm Ursapharm, Ger.†.
Salicylamide (p.121·2); benzocaine (p.1854·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Salitanol Estreptomicina Quimpe, Spain.
Albumin tannate (p.1704·2); dihydrostreptomycin sulfate (p.266·1); sulfathiazole (p.343·2).
Gastrointestinal infections.

Salitil Cifarma, Braz.
Aspirin (p.20·3).
Fever; pain.

Saliva medac Medac, Ger.
Mucin (porcine) (p.2143·3).
Saliva substitute.

Saliva Natura Medac, UK.
Xylitol (p.1998·2); sorbitol (p.1965·1); eriodictyon (p.1560·2).
Dry mouth.

Saliva Orthana
Note. This name is used for preparations of different composition.
Pharmachemie, Neth.
Mucin (p.2143·3).
Dry mouth.
A.S., UK.
Lozenges: Mucin (p.2143·3); xylitol (p.1998·2).
Saliva substitute.
A.S., UK.
Oral spray: Mucin (p.2143·3); xylitol (p.1998·2); sodium fluoride (p.1962·2).
Saliva substitute.

Salivan *Apsen, Braz.*
Carmellose sodium (p.2142·1).
Dry mouth.

Salivart *Gebauer, Canad.; Master, Chile†; Gebauer, Hong Kong; Gebauer, USA.*
Carmellose sodium (p.2142·1); sorbitol (p.1965·1); electrolytes (p.1667·1).
Dry mouth; saliva substitute.

Salivax-HIV *Savi, Mex.†.*
Test for HIV antibodies in saliva.

Saliveze *Wyvern, UK.*
Electrolytes (p.1667·1).
Dry mouth.

Salivia *LKM, Arg.*
Ibuprofen (p.64·2).

Salivix *koGen, UK.*
Malic acid (p.2337·1); calcium lactate (p.1676·1); sodium phosphate (p.1682·3).
Dry mouth.

Salivoral *Novagen, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Salix *Scandinavian Natural Health & Beauty, USA.*
Artificial saliva.

Salkera *Onset, USA.*
Salicylic acid (p.1612·2).
Hyperkeratotic skin disorders.

Salmagne *Fardi, Spain.*
⊗ Magnesium citrate (p.1743·2); magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); mannitol (p.1330·2).
Constipation; digestive disorders.

Salmaplon *Khandelwal, India.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salmax *CCM, Malaysia.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salmetedur *Menarini, Ital.*
⊗ Salmeterol xinafoate (p.1135·1).
Bronchospastic disorders.

Salmeter
Reddy's, India.
⊗ Salmeterol (p.1135·3).
Asthma.
Biofarma, Venez.†.
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Salmiak *Soldan, Ger.†.*
Ammonium chloride (p.1551·3); liquorice (p.1740·3); anise oil (p.2258·2).
Respiratory-tract disorders.

Salmocalcin *Sanofi Synthelabo, Arg.†; Viofar, Gr.; Farmed, Turk.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Salmocide *Atlantis, Mex.*
Furazolidone (p.834·3).
Gastrointestinal infections.

Salmofar *Adipharm (Αδηφαρμ), Gr.†; Lafare, Ital.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Salmol *Atlantic, Hong Kong; Biolab, Malaysia†; Atlantic, Singapore; Atlantic, Thai.; Biolab, Thai.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease; premature labour.

Salmol Expectorant *Biolab, Thai.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Salmon Oil *Gap, Gr.*
Eicosapentaenoic acid (p.1362·1); docosahexaenoic acid (p.1362·1).
Hyperlipidaemias.

Salmoten *Adipharm (Αδηφαρμ), Gr.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Salmundin *Mundipharma, Ger.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Salocef *New Research, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Salodiur *Gerot, Austria.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Salofalk *Cevallos, Arg.; Orphan, Austral.; Merck, Austria; Axcan, Canad.; Biotoscana, Chile; Falk, Cz.; Meda, Fin.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Darya-Varia, Indon.; Falk, Indon.; Falk, Irl.; Abbott, Ital.†; Falk, Malaysia; Farmasa, Mex.; Tramedico, Neth.; Falk, Philipp.; Pharmalink, Philipp.; Falk, Pol.; Falk, Port.; Falk, Singapore; Falk, Spain; Meda, Swed.; Vifor, Switz.; Falk, Thai.; Ali, Turk.; Falk, UK.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Sal-Oil-T *Syosset, USA.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Seborrhoea.

Salomethyl *Mitsubishi-Tokyo, Hong Kong.*
Methyl salicylate (p.85·3); glycol salicylate (p.62·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); thymol (p.1664·3); capsaicin (p.32·3); benzyl nicotinate (p.28·1).
Headache; insect bites; musculoskeletal and soft-tissue disorders; neuralgia; pruritus.

Salonair *Salonpas, UK.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); benzyl nicotinate (p.28·1); glycol salicylate (p.62·3).
Muscle and joint pain.

Salonfer *Biofarma, Braz.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Salongo *Biosarto, Spain.*
Oxiconazole nitrate (p.544·2).
Fungal skin and nail infections.

Salonpas
Note. This name is used for preparations of different composition.
Andromaco, Chile; Vianex (Βιανέξ), Gr.; Hisamitsu, NZ; Pharmaco, NZ; Hisamitsu, USA.
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.
Hisamitsu, Malaysia.
Methyl salicylate (p.85·3); glycol salicylate (p.62·3); menthol (p.2340·1); thymol (p.1664·3); camphor (p.2273·2); tocoferil acetate (p.1992·3).
Musculoskeletal, joint, and soft-tissue disorders; pain.
Salonpas, UK.
Methyl salicylate (p.85·3); glycol salicylate (p.62·3).
Musculoskeletal and joint pain.
Avantgarde, Ital.
Medicated bandage: Menthol (p.2340·1); methyl salicylate (p.85·3); camphor (p.2273·2).
Formerly contained menthol, methyl salicylate, camphor, glycol salicylate, and thymol.
Musculoskeletal, joint, and soft-tissue pain.
Avantgarde, Ital.
Topical spray: Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); benzyl nicotinate (p.28·1); glycol salicylate (p.62·3).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Aqua Patch *Hisamitsu, USA.*
Menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Gel *Hisamitsu, USA.*
Menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Gel Patch *Hisamitsu, USA.*
Capsicum (p.2276·2); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue pain.

Salonpas Hot *Hisamitsu, USA.*
Capsicum (p.2276·2).
Musculoskeletal, joint, and soft-tissue pain.

Salopyrine *Adelco, Gr.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease.

Saloril *Cooper (Κοπερ), Gr.†.*
Acetylcysteine (p.1548·2).
Mucolytic.

Salospir *Unipharma, Gr.*
Aspirin (p.20·3).
Fever; inflammation; pain; thrombosis prophylaxis.

Salospir C-500 *Unipharma, Gr.*
Aspirin (p.20·3); vitamin C (p.1983·3).
Fever; pain.

Salospir Extra *Unipharma, Gr.*
Aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Salotannal *Sanofi-Aventis, Pol.*
Salol (p.122·1); albumin tannate (p.1704·2).
Diarrhoea.

Saloxyl *Herbacos, Cz.*
Ichthammol (p.1599·1); salicylic acid (p.1612·2).
Infected skin disorders.

Salpad *Pharmatrix, Arg.*
Salicylic acid (p.1612·2).
Acne; keratinisation disorders.

Sal-Plant *Pedinol, USA.*
Salicylic acid (p.1612·2).
Warts.

Salrolin *Biofarma, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salsep *Libbs, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Salsil *Embil, Turk.*
Salicylic acid (p.1612·2).
Skin disorders.

Salsitab *Upsher-Smith, USA.*
Salsalate (p.122·1).
Fever; inflammation; pain.

Salsol *Kee, India.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm.

Salsol A *Teva, Hung.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Salspray *Biogalenic, Venez.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Salsyvase *Ipex, Swed.*
Salicylic acid (p.1612·2).
Skin disorders.

Saltadol *Lindopharm, Ger.*
Potassium chloride; sodium chloride; sodium bicarbonate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Salterpyn
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.
Adcock Ingram, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain with tension.

Salticin *Interbat, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Saltlite *Naturissima, Venez.†.*
Sodium chloride; potassium chloride; magnesium carbonate; potassium citrate; glutamic acid (p.1667·1).
Salt substitute.

Saltos
Note. This name is used for preparations of different composition.
Roux-Ocefa, Arg.†.
⊗ Noscapine ascorbate (p.1566·3); papaverine hydrochloride (p.2191·3); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); hydroxyfylline.
Coughs.
Pulmomed, Rus.
⊗ Salbutamol hemisuccinate (p.1133·2).

Saltos Infantil *Roux-Ocefa, Arg.†.*
⊗ Noscapine ascorbate (p.1566·3); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); hydroxyfylline.
Coughs.

Saltrates
Note. This name is used for preparations of different composition.
Uhlmann-Eyraud, Switz.†.
Cream: Triclosan (p.1665·2); methylchloroisothiazolinone (p.1651·2); menthol (p.2340·1); chamomile oil (p.2279·3); St John's wort oil (p.423·2); citronella oil (p.2284·2); lavender oil (p.2331·2).
Dry or painful feet.
Uhlmann-Eyraud, Switz.†.
Topical gel: ⊗ Sodium hydroxide (p.2389·3); trometamol (p.2405·1).
Calluses; corns.

Saltrates Rodell *Uhlmann-Eyraud, Switz.†.*
Chamomile (p.2279·3); St John's wort (p.422·3); sodium bicarbonate (p.1673·2); sodium carbonate anhydrous (p.2389·1); sodium sesquicarbonate; sodium perborate (p.1662·1).
Foot disorders.

Sal-Tropine *Hope, USA.*
Atropine sulfate (p.1219·3).

Salubion *Mepro, Chile.*
Vitamins; minerals; rutin (p.1922·1).
Tonic.

Salubion Ginseng *Mepro, Chile.*
Vitamins; minerals; trace elements; ginseng (p.1922·1).
Tonic.

Saludopin *SIT, Ital.*
⊗ Methyldopa (p.1334·1); butizide (p.1238·1).
Hypertension.

Saluket-H1 *Salus, Mex.*
Ketotifen (p.582·2).
Asthma.

Salumin *Hasco-Lek, Pol.*
Menthol (p.2340·1); sage (p.2382·3); tannic acid (p.2394·3).
Mouth and throat disorders.

Salupran *Protein, Mex.†.*
Naproxen (p.92·3).
Rheumatism.

Salures *Pfizer, Swed.*
⊗ Bendroflumethiazide (p.1224·1).
Hypertension; oedema; renal calculi.

Salures-K *Pfizer, Swed.*
⊗ Bendroflumethiazide (p.1224·1); potassium chloride (p.1684·3).
Hypertension; oedema; renal calculi.

Salurin *Julphar, UAE.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Saluron *Apothecon, USA.*
⊗ Hydroflumethiazide (p.1311·3).
Hypertension; oedema.

Salus Augenschutz-Kapseln NA *Salushaus, Ger.†.*
Myrtillus (p.2349·3); vitamin A palmitate (p.1973·1).
Hypersensitivity to light; night blindness.

Salus Herz-Schutz-Kapseln *Salushaus, Ger.†.*
Crataegus (p.2289·1); alpha tocoferil acetate (p.1992·3); magnesium complex with acid hydrolysate of maize starch.
Cardiovascular disorders.

Salus Mistel-Tropfen *Salushaus, Ger.*
Mistletoe (p.2345·3).
Atherosclerosis.

Salus Multi-Vitamin-Energetikum *Salushaus, Ger.†.*
Multivitamin preparation with plant extracts (p.1922·1).
Tonic; vitamin deficiency.

Salus Venen Krauter Dragees N *Salushaus, Ger.†.*
Aesculus (p.2248·2); melilot (p.2339·2).
Venous insufficiency.

Salusa *Novartis Consumer, S.Afr.†.*
Procaine hydrochloride (p.1869·1); vitamins; haematoporphyrin (p.1922·1).

Saluscor Herz-Schutz *Salushaus, Ger.*
Alpha tocoferil acetate (p.1992·3); magnesium complex with acid hydrolysate of maize starch; crataegus (p.2289·1).
Cardiovascular disorders.

Salutaris *Incaico, Arg.*
Ispaghula (p.1737·1); coriander (p.2288·1); soluble fibre (p.1712·3).
Hypercholesterolaemia; obesity.

Salutensin *Shire Richwood, USA†.*
⊗ Hydroflumethiazide (p.1311·3); reserpine (p.1387·3).
Hypertension.

Salva Sole *Giuliani, Ital.†.*
Vitamins; minerals; ubidecarenone (p.1922·1).
UV-induced skin damage.

Salvacam *Salvat, Spain.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Salvacolina *Salvat, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Salvacolon *Salvat, Spain.*
Bacillus subtilis; vitamins and amino acids (p.1922·1).
Gastrointestinal disorders; restoration of the gastrointestinal flora.

Salvalerg *GSK, Arg.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Salvapen *Salvat, Spain.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Salvapen Mucolitico *Salvat, Spain.*
Amoxicillin trihydrate (p.202·2); bromhexine hydrochloride (p.1552·2).
Respiratory-tract infections associated with viscous mucus.

Salvara *Bittner, Austria.*
Homoeopathic preparation.

Salvarina *Salvat, Spain.*
Caffeine (p.1116·3); dimenhydrinate (p.576·2); ibuprofen (p.64·2).
Dysmenorrhoea.

Salvaxil *Fada, Arg.†.*
Loperamide (p.1741·3).
Diarrhoea.

Salvej Lekarske List *Leros, Cz.*
Sage (p.2382·3).
Diarrhoea; dyspepsia; mouth disorders.

Salvejova Nat *Megafyt-R, Cz.*
Sage (p.2382·3).
Gastrointestinal disorders; mouth inflammation; upper respiratory-tract disorders.

Salvent *Wolff, Ger.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salvex *Vamsler, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Salvex XP *Vamsler, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol (p.1131·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

salvi CAL E-G *Clintec, Cz.†.*
Glucose and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Salvi CAL E-G *Baxter, Pol.*
Glucose and electrolyte infusion (p.1922·1).
Parenteral nutrition.

salviamin E *Clintec, Cz.†.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition.

salviamin G-E *Clintec, Cz.†; Baxter, Ger.*
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

salviamin hepar *Baxter, Ger.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition in liver disease.

Salviamin Hepar *Baxter, Pol.*
Amino-acid and electrolyte infusion (p.1922·1).
Parenteral nutrition in liver disorders.

salviamin nephro *Clintec, Cz.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in kidney disease.

Salviasept *Herbapol Lublin, Pol.*
Achillea (p.2245·2); chamomile (p.2279·3); cineole (p.2282·3); fennel (p.2302·3); marjoram oil (p.2337·3); mint oil (p.2345·2); peppermint (p.1761·2); menthol (p.2340·1); sage (p.2382·3); sage oil (p.2382·3); thyme oil (p.2401·2); thyme (p.2401·1); clove oil (p.2285·1).
Mouth and throat disorders; respiratory-tract congestion.

Salviathymol N *Madaus, Ger.*
Sage oil (p.2382·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); cinnamon oil (p.2283·2); clove oil (p.2285·1); fennel oil (p.2303·1); anise oil (p.2258·2); menthol (p.2340·1); thymol (p.1664·3).
Mouth and throat disorders.

Salvicutan *Lazar, Arg.†.*
Protoporphyrin; vitamin A palmitate (p.1973·1); dequalinium; cetrimonium bromide (p.1635·1).
Burns; skin infections; skin irritation; ulcers; wounds.

Salviette H *Wyeth Consumer, Ital.*
Hamamelis water (p.2318·2); glycerol (p.2314·2).
Anal cleansing; haemorrhoids.

salvilipid *Baxter, Ger.*
Soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Salvital *Reckitt Benckiser, Austral.*
Magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2).
Dyspepsia; nausea.

Salvitos *Ronnet, Arg.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Salvituss *FIRMA, Ital.*
Levodropropizine (p.1557·3).
Coughs.

Salvuron *Sanofi Synthelabo, Hung.†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Salvyl *Petrasch, Austria.*
Undecenoic acid (p.549·2) sulfur (p.1614·1) complex; betanaphthol (p.142·1); salicylic acid (p.1612·2).
Acne; erythrasma; fungal skin infections.

Salvysat *Mayrhofer, Austria; Ysatfabrik, Ger.*
Sage leaf (p.2382·3).
Hyperhidrosis; mouth and throat inflammation.

Salycilina *Upsifarma, Port.†.*
Aspirin (p.20·3).
Fever; pain.

Salyzine *Bell, India†.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Salzone *Wallace Mfg Chem., UK.*
Paracetamol (p.108·1).
Fever; pain.

Samarial *Samjin, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Samarin *Berlin Pharm, Thai.*
Silymarin (p.1452·2).
Liver disorders.

Samaruc *Fabop, Arg.*
Isoxsuprine (p.2327·3).

Sambuco (Specie Composta) *Dynacren, Ital.†.*
Tilia (p.2402·2); sambucus (p.2383·1); meadowsweet (p.2338·1); rose fruit (p.2381·2).
Cold symptoms.

Sambucus Comp *Weleda, S.Afr.*
Homoeopathic preparation.

Sambucus Complex *Blackmores, Austral.†.*
Sambucus (p.2383·1); euphrasia (p.2301·3); echinacea angustifolia (p.2298·1); hydrastis (p.2321·3); euphorbia hirta (p.2301·3); *d*-alpha tocoferil acid succinate (p.1993·1); vitamin A acetate (p.1973·1).
Conjunctivitis; otorrhoea; upper respiratory-tract disorders.

Same Plast *Savoma, Ital.*
Emollient.

Samederm *Savoma, Ital.*
Soap substitute.

Samertan *Bago, Chile.*
Telmisartan (p.1409·2).
Hypertension.

Same-Seb *Savoma, Ital.*
Colloidal sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne; seborrhoea.

Same-Seb Beta *Savoma, Ital.*
Salicylic acid (p.1612·2); glycolic acid (p.1598·1).
Acne.

Sametil *Gestafarma, Port.*
Salicylic acid (p.1612·2); methyl salicylate (p.85·3).
Psoriasis; seborrhoeic dermatitis.

Samezil *KRKA, Cz.; KRKA, Rus.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Samilstin *LPB, Ital.*
Octreotide (p.1804·1).
Acromegaly; diarrhoea associated with immunodeficiency; endocrinal tumours of the gastrointestinal tract; pancreatic fistula; postoperative complications of pancreatic surgery; variceal haemorrhage.

Samixon *Hikma, Cz.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Samjizon *Samjin, Philipp.; Unimex, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

S-Amlip *Cipla, India.*
S-Amlodipine (p.1214·2).
Hypertension.

Samonil *IQFA, Mex.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Samonter *Sanitas, Arg.*
⊗ Mazindol (p.2157·3).
Obesity.

Samox *Seven Stars, Thai.*
Amoxicillin (p.202·2).
Bacterial infections.

Samoxin *Sriprasit, Thai.*
Amoxicillin (p.202·2).
Bacterial infections.

Samson *Sanli, Turk.*
Ferric ammonium citrate (p.1938·1).
Iron deficiency; iron-deficiency anaemia.

Samyr *Abbott, Ital.; Abbott, Mex.*
Ademetionine sulfate tosilate (p.2247·1).
Depression; liver disorders.

Sanabronchiol *Falqui, Ital.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Sanaco *PD, Thai.†.*
Chlorophyll (p.1471·1); benzalkonium chloride (p.1629·1).
Personal hygiene; vaginal douche.

Sanacorte *Labortecne, Braz.†.*
Schinus terebenthifolius; piptadenia columbriana; cereus hildfmanianus; salis angulata.
Cicatrisation.

Sanaderm *Febena, Ger.†.*
Hamamelis (p.2318·2); zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Sanadermil *Vifor, Switz.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Sanadiar *Ibefar, Braz.†.*
Phthalylsulfathiazole (p.315·1); sulfaguanidine (p.339·2); pectin (p.2145·2); aluminium hydroxide (p.1706·2).
Diarrhoea.

Sanadryl *Sanbe, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sulfogaiacol (p.1573·2); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough; respiratory-tract congestion.

Sanadryl DMP *Sanbe, Indon.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough; respiratory-tract congestion.

Sanaflu *Sanbe, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.

Sanaflu Plus *Sanbe, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; cough.

Sanaform *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Sanagas *Ducto, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Sanalepsi N *Roche, Switz.*
Doxylamine succinate (p.578·2).
Hypersensitivity reactions; nervous disorders.

Sanaler *Sanitas, Chile.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Sanaler-D *Sanitas, Chile.*
Cetirizine (p.571·1); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

Sanalgin *Interlogim, Neth.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Sanalgin N *Gebro, Switz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Sanamidol *Inkeysa, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sanaprav *Sankyo, Austria†; Sankyo, Ital.; Daiichi Sankyo, Port.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Sanasar *Hertz, Braz.*
Benzyl benzoate (p.2036·1).
Scabies.

Sana-Scrub *Forder, Arg.†.*
Carica papaya; polyethylene granules.
Skin cleansing.

Sanasepton *Ritsert, Ger.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Sana-Sol *Collett, Fin.; Nycomed, Rus.*
Multivitamin preparation (p.1922·1).

Sanasol *Eczacibasi, Turk.*
Multivitamin preparation (p.1922·1).

Sanason *Lek, Cz.; Lek, Rus.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety; sleep disorders.

Sanasthmax *Asche Chiesi, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; bronchitis.

Sanasthmyl *GSK, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; bronchitis; tracheitis.

Sanatison Mono *Taurus, Ger.*
⊗ Hydrocortisone (p.1535·2).
Burns; skin disorders.

Sanatogen *Key, Austral.†; German Remedies, India; Roche Consumer, Irl.; Roche Consumer, UK.*
Food for special diets (p.1922·1).
Protein supplementation; tonic.

Sanaven *Sankyo, Ger.†.*
A heparinoid (p.1305·2); phenylephrine hydrochloride (p.1568·1).
Venous disorders.

Sanaven MPS *Sankyo, Ger.*
A heparinoid (p.1305·2).
Superficial vascular disorders.

Sanavir *Mayne, Ital.*
Aciclovir (p.862·3).
Herpesvirus infections.

Sanavitan S *Bottger, Ger.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Sanaxin *Sandoz, Austria.*
Cefalexin (p.218·2).
Bacterial infections.

Sanazet *Sanbe, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Sanblex *Medipharm, Chile.*
Sulpiride (p.1028·3).
Behaviour disorders; depression; irritability.

San-B-Plex *Sanbe, Indon.*
Vitamins A, B, C, and D (p.1922·1).
Nutritional supplement for children and infants.

Sancago *Chinta, Thai.*
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2).
Insect bites; musculoskeletal, joint and soft-tissue disorders.

Sancap *Novartis, Gr.†.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Sancazid *Sandoz, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Sancipro *Actavis, Denm.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Sancor Biosalud *Sancor, Arg.*
A range of preparations for enteral nutrition (p.1922·1).

Sancortmycin *Sanbe, Indon.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Skin infections.

Sancotec *Daehan, Singapore.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Sanctura *Allergan, USA; Indevus, USA; Odyssey, USA.*
Trospium chloride (p.2198·3).
Bladder instability.

Sanda *Okasa, Thai.; TTN, Thai.*
Ciclosporin (p.1822·2).
Graft-versus-host disease; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Sandepril *Mersifarma, Indon.*
Maprotiline hydrochloride (p.407·2).
Depression.

Sanderson's Throat Specific
Note.This name is used for preparations of different composition.
Sandersons, UK.
Mixture: Acetic acid (p.2244·2); quassia (p.2377·1); squill (p.1573·1); capsicum (p.2276·2).
Catarrh; sore throat.

Sandersons, UK.
Pastilles: Honey (p.1948·2); squill vinegar (p.1573·1); capsicum (p.2276·2); tolu (p.1574·2); menthol (p.2340·1); cinnamic acid (p.1640·3); benzoic acid (p.1630·2); eucalyptus oil (p.2301·2).
Catarrh; sore throat.

Sandimmun *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Ciclosporin (p.1822·2).
Atopic eczema; graft-versus-host disease; medullary aplasia; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection; uveitis.

Sandimmune *Novartis, Canad.; Novartis, Neth.; Novartis, USA.*
Ciclosporin (p.1822·2).
Graft-versus-host disease; transplant rejection.

Sandival
Note.This name is used for preparations of different composition.
Bouzen, Arg.
Elixir: Bromhexine (p.1552·2).
Respiratory-tract congestion.

Bouzen, Arg.
Tablets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Sandival Desleible *Bouzen, Arg.*
Benzydamine (p.27·3).
Inflammation; pain.

Sandival NF *Bouzen, Arg.†.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2).
Influenza symptoms.

Sandocal
Note.This name is used for preparations of different composition.
Novartis Consumer, Austral.; Novartis Consumer, Irl.; Novartis Consumer, Port.; Novartis Consumer, UK.
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium supplement; hypocalcaemia; osteomalacia; osteoporosis; rickets.

Novartis, India†; Novartis, Venez.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Sandocal with Vit D_3 *Novartis, India.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency; calcium supplement.

Sandocal-D *Sandoz, Ger.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Sandocef *Sandoz, Indon.*
Cefepime hydrochloride (p.223·3).
Bacterial infections.

Sandoglobulin *CSL, Austral.; Novartis, Austria†; ZLB, Denm.; ZLB, Ger.; Luxembourg, Israel; CSL, NZ; Imed, Pol.; ZLB, UK.*
A normal immunoglobulin (p.2225·3).
Auto-immune disorders; bone marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency disorders; Kawasaki disease; passive immunisation; toxic shock syndrome.

Sandoglobulina *Novartis, Arg.†; Novartis, Braz.†; Novartis, Chile†; ZLB, Ital.; Ivax, Mex.; CSL, Port.; Novartis, Venez.†.*
A normal immunoglobulin (p.2225·3).
Auto-immune disorders; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Sandoglobuline *ZLB, Belg.; Demo, Gr.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; neuropathies; passive immunisation.

Sando-K *HK Pharma, UK.*
Potassium bicarbonate (p.1673·1); potassium chloride (p.1684·3).
Hypokalaemia.

Sandolin *Sanli, Turk.*
Salol (p.122·1); mint oil (p.2345·2); star anise oil (p.2392·2).
Oral hygiene.

Sandomigran *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Paladin, Canad.; Novartis, Cz.; Novartis, Hong Kong; ICN, Hung.†; Novartis, Ital.; Novartis, Malaysia; Novartis, NZ; Novartis, Neth.; Novartis, S.Afr.; Novartis, Spain; Novartis, Turk.*
Pizotifen malate (p.624·2).
Anorexia; cluster headache; migraine and vascular headaches.

Sandomigrin *Novartis, Denm.; Novartis, Swed.*
Pizotifen malate (p.624·2).
Cluster headache; migraine.

Sandomiran *Novartis, Venez.†.*
Pizotifen malate (p.624·2).
Migraine.

Sandonorm *Zentiva, Cz.; Novartis, Gr.†; EGIS, Hung.; Novartis, Switz.*
⊗ Bopindolol malonate (p.1235·1).
Angina pectoris; hypertension.

Sandoparin *Sandoz, Austria; Biochemie, Hung.†.*
Certoparin sodium (p.1242·3).
Thromboembolic disorders.

Sandoparine *Novartis, Switz.*
Certoparin sodium (p.1242·3).
Thrombosis prophylaxis.

Sandoretic *Novartis, Switz.*
⊗ Bopindolol malonate (p.1235·1); chlortalidone (p.1243·3).
Hypertension.

Sandosource *Novartis Consumer, Austral.†; Novartis, Braz.; Novartis, Irl.; Novartis, UK.*
Preparation for enteral nutrition (p.1922·1).

Sandosource Peptide *Novartis, Arg.†.*
Preparation for enteral nutrition (p.1922·1).

Sandostatin
Novartis, Arg.; Novartis, Austria; Novartis, Cz.; Novartis, Denm.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Norw.; Novartis, Spain; Novartis, Venez.
Octreotide (p.1804·1) or octreotide acetate (p.1803·2).
Acromegaly; AIDS-associated refractory diarrhoea; carcinoid tumours; complications following pancreatic surgery; gastro-oesophageal haemorrhage; gastrointestinal fistula; gastropancreatic endocrine tumours; variceal haemorrhage.

Novartis, Austral.; Novartis, Braz.; Novartis, Chile; Novartis, Gr.; Novartis, India; Novartis, Indon.; Novartis, Israel; Novartis, Pol.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Swed.; Novartis, Thai.; Novartis, Turk.
Octreotide (p.1804·1).
Acromegaly; AIDS-associated refractory diarrhoea; carcinoid tumours; complications following pancreatic surgery; gastrointestinal fistulas; gastropancreatic endocrine tumours; variceal haemorrhage.

Novartis, Canad.; Novartis, Fin.; Novartis, Ger.; Novartis, Irl.; Novartis, Malaysia; Novartis, NZ; Novartis, Philipp.; Novartis, Singapore; Novartis, UK; Novartis, USA.
Octreotide acetate (p.1803·2).
Acromegaly; AIDS-associated refractory diarrhoea; carcinoid tumours; complications following pancreatic surgery; gastropancreatic endocrine tumours; variceal haemorrhage.

Sandostatina
Novartis, Ital.
Octreotide (p.1804·1).
Acromegaly; diarrhoea associated with immunodeficiency; endocrinal tumours of the gastrointestinal tract; pancreatic fistulae; postoperative complications of pancreatic surgery; variceal haemorrhage.

Novartis, Mex.
Octreotide (p.1804·1) or octreotide acetate (p.1803·2).
Acromegaly; gastrointestinal endocrine tumours; oesophageal haemorrhage; pancreatic fistulae; prevention of complications following pancreatic surgery; refractory diarrhoea associated with HIV infection.

Novartis, Port.
Octreotide acetate (p.1803·2).
Acromegaly; AIDS-associated refractory diarrhoea; gastrointestinal endocrine tumours; pancreatic and gastrointestinal fistulas; prevention of complications following pancreatic surgery; variceal haemorrhage.

Sandostatine
Novartis, Belg.
Octreotide (p.1804·1).
Acromegaly; AIDS-associated refractory diarrhoea; complications following pancreatic surgery; external fistulae of the pancreas and small intestine; gastrointestinal endocrine tumours; variceal haemorrhage.

Novartis, Fr.; Novartis, Neth.; Novartis, Switz.
Octreotide acetate (p.1803·2).
Acromegaly; adenomas; gastrointestinal endocrine tumours; prevention of complications following pancreatic surgery; variceal haemorrhage.

Sandovac *Novartis, Austria.*
An inactivated influenza vaccine (p.2218·2).
Active immunisation.

Sandoz Ca-D *Novartis Consumer, Belg.; Novartis Consumer, Neth.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; calcium and vitamin D supplement; osteoporosis.

Sandoz Calcium
Note. This name is used for preparations of different composition.
Novartis Consumer, Belg.
Effervescent tablets; oral powder: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Formerly known as Calcium-Sandoz.
Bone demineralisation; calcium supplement; osteoporosis; tetany.

Novartis Consumer, Belg.
Injection: Calcium glubionate (p.1675·3).
Formerly known as Calcium-Sandoz.
Hypocalcaemia; potassium poisoning; rickets; tetany.

Sandoz Calcium + D
Note. This name is used for preparations of different composition.
Novartis, Mex.
Effervescent tablets: Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; hypocalcaemia; hypoparathyroidism; osteomalacia; osteoporosis.

Novartis, Mex.
Soluble tablets: Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; hypocalcaemia; hypoparathyroidism; osteomalacia; osteoporosis.

Sandoz Calcium + Vitamine C *Novartis Consumer, Belg.†.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); calcium lactate gluconate (p.1676·2).
Formerly known as Ca-C.
Calcium and vitamin C deficiency.

Sandoz Calcium-C *Novartis Consumer, S.Afr.†.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1); vitamin C (p.1983·3).
Vitamin C and calcium supplement.

Sandoz K *Sandoz, S.Afr.*
Potassium chloride (p.1684·3).
Potassium supplement.

Sandrena *Organon, Austral.; Organon, Braz.; Organon, Chile; Organon, Denm.; Organon, Ger.; Organon, Ital.; Organon, Mex.; Organon, NZ†; Orion, Neth.; Organon, Switz.; Organon, UK.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Sanein *Almirall, Spain.*
Aceclofenac (p.14·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sanelor
Note. This name is used for preparations of different composition.
Omega, Belg.; Schering-Plough, Neth.
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Sanitas, Chile.
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Sanepa Forte *Maver, Chile†.*
Omega-3 marine triglycerides (p.1362·2).

Sanepil *Zentiva, Cz.*
Phenytoin (p.495·2); phenobarbital (p.492·2).
Epilepsy.

Sanerva *Royal, Chile.*
Alprazolam (p.960·1).
Anxiety; panic attacks.

Sanetron *Veltipharm, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Sanexon *Sanbe, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Sanficinate *Dakota, Cz.†.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil therapy; megaloblastic anaemia; methotrexate overdosage.

Sangcya *Lilly, Israel.*
Ciclosporin (p.1822·2).
Psoriasis; transplant rejection; uveitis.

Sangen *Marco Viti, Ital.†.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds and burns.

Sangen Casa
Note. This name is used for preparations of different composition.
Marco Viti, Ital.
Liquid: Benzethonium chloride (p.1630·1); benzalkonium chloride (p.1629·1).
Surface disinfection.

Marco Viti, Ital.
Spray: Orthophenylphenol (p.1655·1); benzalkonium chloride (p.1629·1).
Surface disinfection.

Sangen Sapone Disinfettante *Marco Viti, Ital.*
Triclocarban (p.1665·2).
Skin disinfection.

Sangenor *Mundipharma, Austria.*
Arginine aspartate (p.1928·2).
Tonic.

Sangermina *Sandoz, Ital.*
Bacillus subtilis.
Restoration of intestinal flora.

Sangerol *Novartis Consumer, Switz.*
Lidocaine hydrochloride (p.1862·3); muramidase hydrochloride (p.2348·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Sangobion
Note. This name is used for preparations of different composition.
Merck, Malaysia.
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); vitamin B (p.1980·2); minerals (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Merck Consumer, Singapore.
Ferrous gluconate (p.1939·1); folic acid (p.1940·1); manganese sulfate; copper sulfate; vitamin B (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Merck, Indon.; Merck, Philipp.
Capsules: Ferrous gluconate (p.1939·1); folic acid (p.1940·1); vitamin B (p.1980·2); manganese sulfate; copper sulfate (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias; iron deficiency.

Merck, Indon.; Merck, Philipp.
Syrup: Ferrous gluconate (p.1939·1); vitamin B substances (p.1922·1).
Iron and vitamin B deficiency; iron-deficiency anaemia.

Sangobion ActiFe *Merck, Indon.*
Taurine; ferrazone; vitamin B ; nicotinamide; potassium aspartate; magnesium aspartate (p.1922·1).
Tonic.

Sangofer *Sandoz, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid; vitamin B with intrinsic factor (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Sangotone *Gemballa, Braz.†.*
Ferrous citrate (p.1950·3); choline citrate; copper gluconate; vitamin B substances (p.1922·1).
Iron deficiency; iron-deficiency anaemias.

Sangovitin *Pyridam, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid; vitamin B (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia; nutritional supplement.

Sanguisan N *Coradol, Ger.†.*
Homoeopathic preparation.

Sanguisorbis N *Sabona, Ger.†.*
Homoeopathic preparation.

Sangur-Test *Roche Diagnostics, Austral.†.*
Test for blood in urine.

Sanhelios Capsules a la vitamine A *Ars Vitae, Switz.†.*
Vitamin A palmitate (p.1973·1); wheat-germ oil (p.2415·1).
Vitamin A deficiency.

Sanibiotic *LA, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Sanicel *BMS, Spain.*
Amphotericin B (p.523·2); tetracycline hydrochloride (p.347·2).
Vulvovaginal infections.

Sanicopyrine *Sanico, Belg.*
Paracetamol (p.108·1).
Fever; pain.

Sanicut *Nordin, Mex.*
Calendula (p.2273·1); ledum palustre.
Cicatrisation; pruritus.

Sanidecal *Sanitas, Chile.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Sanidecal-D *Sanitas, Chile.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Saniderm *Quimica y Farmacia, Mex.*
Zinc oxide (p.1621·2).
Burns; nappy rash; skin disorders.

SaniDrox *Sanitas, Ital.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Sanieb *Puerto Galiano, Spain†.*
Glycine (p.1947·3); arginine (p.1928·2); brassica oleracea.
Gastritis; gastrointestinal hyperacidity; peptic ulcer.

Sanifer *Esseti, Ital.*
Sodium ferric gluconate complex (p.1962·2).
Anaemias; oligohaemia in infants.

Saniflam *Sanus, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Saniflor Collutorio *Benedetti, Ital.*
Benzydamine hydrochloride (p.27·3).
Gingivitis.

Sanifolin *Fargim, Ital.*
Calcium folinate (p.1943·3).
Anaemias; antidote to folic acid antagonists; folate deficiency; reduction of aminopterin and methotrexate toxicity.

Sanigermin *Sanitas, Chile.*
Triclosan (p.1665·2).
Hand disinfection; skin infections.

Sanilax *Greenpharma, Braz.*
Paracetamol (p.108·1); carisoprodol (p.1894·1); caffeine (p.1116·3).

Sanilin *Hertz, Braz.*
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1); menthol (p.2340·1).

Sanipirina *Bayer, Ital.*
Paracetamol (p.108·1).
Fever; pain.

Sanipresin *Sanitas, Chile.*
Losartan potassium (p.1326·1).
Hypertension.

Sanipresin-D *Sanitas, Chile.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Saniprostol *Sanitas, Chile.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Saniquiet *Sanitalia, Ital.*
Passion flower; tilia; birch; magnesium; lithium; manganese (p.1922·1).

Sanisop *Pentamedical, Ital.*
Soap substitute.

SaniSteril Deterferri *Sanitas, Ital.*
Benzalkonium chloride (p.1629·1).
Instrument disinfection.

SaniSteril Sterilferri *Sanitas, Ital.*
Glutaral (p.1645·2).
Instrument disinfection.

SaniSteril Strumenti Alcolico *Sanitas, Ital.†.*
Benzalkonium chloride (p.1629·1); isopropyl alcohol (p.1650·3).
Instrument disinfection.

Sani-Supp *G & W, USA.*
Glycerol (p.2314·2).
Constipation.

Saniter Compuesto *Sanitas, Chile.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Sanitos *DB, Fr.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Sanivit *Scherer, Thai.†.*
Multivitamin and mineral preparation with procaine hydrochloride, royal jelly, and lecithin (p.1922·1).

Sanjin Royal Jelly *Super Mayoreo Naturista, Mex.*
Ginseng (p.2312·1).
Tonic.

Sanjukei Panax Ginseng *ITBS, Hong Kong.*
Ginseng (p.2312·1); carotene (p.1930·3); sunflower oil (p.1970·3); vitamin E (p.1992·2).
Dietary supplement.

Sankombi *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Sanlin *Sanbe, Indon.*
Tetracycline phosphate (p.347·2).
Bacterial infections.

Sanmag
Note. This name is used for preparations of different composition.
Sanbe, Indon.
Oral suspension: Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Sanbe, Indon.
Tablets: Magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); papaverine hydrochloride (p.2191·3); chlordiazepoxide hydrochloride (p.968·2); vitamin B substances (p.1922·1).
Gastrointestinal disorders.

Sanmetidin *Sanbe, Indon.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sanmigran *Novartis, Fr.*
Pizotifen malate (p.624·2).
Migraine.

Sanmol *Sanbe, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Sanmyd-P *Santen, Philipp.*
Tropicamide (p.1886·2); phenylephrine hydrochloride (p.1568·1).
Production of mydriasis and cycloplegia.

Sano Tuss *Welti, Switz.*
⊗ Emetine hydrochloride (p.833·3); ethylmorphine hydrochloride (p.52·2); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3); cherry-laurel; tolu balsam (p.1574·2).
Catarrh; coughs.

Sanoderm *Reccius, Chile.*
Allantoin (p.1588·1); zinc oxide (p.1621·2); vitamin A (p.1971·2); vitamin D (p.1986·1).
Skin disorders.

Sanodin *Altana, Spain.*
Carbenoxolone sodium (p.1714·3).
Gingivitis; mouth ulcers.

Sanodril *Sandoz, Venez.*
Cefadroxil (p.218·1).
Bacterial infections.

Sanofil *Herbapol Pruszkow, Pol.*
Achillea (p.2245·2); benzocaine (p.1854·1); calendula (p.2273·1); chamomile (p.2279·3); equisetum (p.2299·3); menthol (p.2340·1); oak bark (p.2355·3); sage (p.2382·3).
Allergic skin disorders; insect bites.

Sanogencive *Plan, Switz.*
Rhatany root (p.2378·3); myrrh (p.2349·2); horseradish (p.2320·1); camphor (p.2273·2).
Gum disorders; oral hygiene.

Sanogyl
Note. This name is used for preparations of different composition.
Tonipharm, Fr.†.
Pink toothpaste: Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Oral hygiene.

Tonipharm, Fr.†.
White toothpaste: Sodium fluoride (p.1962·2).
Oral hygiene.

Sanogyl Fluo *Tonipharm, Fr.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Sanogyl Junior *Tonipharm, Fr.†.*
Sodium monofluorophosphate (p.1964·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Sanomed *Vitalink, Philipp.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Sanomigran *Novartis, Irl.; Novartis, UK.*
Pizotifen malate (p.624·2).
Migraine and other vascular headaches.

Sanopinwern
Note. This name is used for preparations of different composition.
Wernigerode, Ger.
Inhalation: Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2).
Cold symptoms.

Wernigerode, Ger.
Oral drops: Thyme (p.2401·1).
Respiratory-tract congestion.

Sanopinwern T *Wernigerode, Ger.†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Sanopor *Sanus, Gr.*
Calcitonin (p.1093·1).
Osteoporosis.

Sanor *Biolab, Malaysia†; Biolab, Thai.†.*
Dipotassium clorazepate (p.980·1).
Anxiety; epilepsy.

Sanorex *SteriMax, Canad.†; Novartis, Mex.†.*
⊗ Mazindol (p.2157·3).
Obesity.

Sanorin
Note.This name is used for preparations of different composition.
Ivax, Cz.
⊗ Naphazoline nitrate (p.1565·2).
Catarrh; eye congestion; nasal congestion; otitis media.

Galena, Rus.
Nasal emulsion drops: ⊗ Naphazoline nitrate (p.1565·2); eucalyptus oil (p.2301·2).
Nasal congestion.

Galena, Rus.
Nose drops; nose spray: ⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Sanorin-Analergin *Ivax, Cz.; Galena, Rus.*
⊗ Naphazoline nitrate (p.1565·2); antazoline mesilate (p.567·1).
Allergic rhinitis; conjunctivitis.

Sanorinchik *Ivax, Rus.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Rhinitis; sinusitis.

Sanorvil *Dekaz, Gr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Sanostol *Schmidgall, Austria.*
Multivitamin preparation (p.1922·1).

Sanosvit Calcium *Altana, Pol.*
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2).
Calcium supplement; osteoporosis.

Sanovein *Sanus, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency.

Sanovit *Altana, Mex.*
Cobamamide (p.1980·2).
Anaemias; tonic.

Sanoxit *Galderma, Ger.*
Benzoyl peroxide (p.1590·2).
Acne.

Sanoyodo *Cinfa, Spain.*
Povidone-iodine (p.1659·2).
Skin and wound disinfection.

Sanpa *Bilim, Turk.*
Aspartame (p.1930·1).
Sugar substitute.

Sanpicillin *Sanbe, Indon.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Sanprima *Sanbe, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sanpronol *Sanval, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; hypertension.

Sans Soleil Skin Ceuticals *Dispolab, Chile†.*
Dihydroxyacetone (p.1594·1).
Suntanning agent.

Sans-Acne *Galderma, Canad.†.*
⊗ Erythromycin (p.269·2); alcohol (p.1625·2).
Acne.

Sansacne *Galderma, Mex.; Galderma, Philipp.*
Erythromycin (p.269·2).
Acne.

Sansert *Novartis, Canad.*
Methysergide maleate (p.623·1).
Migraine and other vascular headaches.

Sanset *Sanovel, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Sansilla *Vifor International, Switz.*
Aluminium chloride (p.1588·2); calcium hydroxide (p.2272·2); menthol (p.2340·1); orange oil (p.2357·2); lemon oil (p.2332·3); citronella oil (p.2284·2); clove oil (p.2285·1); cinnamon oil (p.2283·2); peppermint oil (p.1761·2).
Mouth and throat disorders.

Sansudor *Boehringer Ingelheim, Switz.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis; intertrigo.

Santa Flora S *Madaus, Ger.*
Homoeopathic preparation.

Santa-E *Sanbe, Indon.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Santaherba *Homeocan, Canad.†; Lehning, Fr.*
Homoeopathic preparation.

Santalyt *Medice, Ger.*
Sodium chloride; glucose; potassium chloride; sodium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Santamex *Santa, Gr.†.*
Carbocisteine (p.1553·2).
Mucolytic.

Santamex-Expectorant *Santa, Gr.†.*
Carbocisteine (p.1553·2).
Respiratory disorders associated with viscous mucus.

Santamin *Santa, Gr.†.*
Codergocrine (p.364·1).
Peripheral vascular disorders.

Santanol *Atabay, Turk.*
Ranitidine hydrochloride (p.1766·1).

Santasal N *Merckle, Ger.*
Aspirin (p.20·3).
Fever; pain.

Santasapina *Bioforce, Switz.*
Pine buds.
Upper respiratory-tract disorders.

Santasapina V *Bioforce, Ger.*
Pine needle.
Catarrh.

Santax S
Asche, Cz.†.
Saccharomyces boulardii (p.2372·3).
Diarrhoea.

Asche Chiesi, Ger.
Saccharomyces cerevisiae (p.1998·3).
Diarrhoea.

Sante Vite *Roemmers-Klinos, Venez.†.*
Piroctone olamine (p.1610·1).
Dandruff.

Sant-E-Gal *ICN, Cz.†.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Santeson *Santen, Philipp.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Santevini *Novartis, India.*
Vitamin B substances; peptone; calcium gluconate (p.1922·1).
Tonic.

Santibi *Sanbe, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Santibi Plus *Sanbe, Indon.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Santin *ISA, Arg.†.*
Magnesium; vitamin C; vitamin B ; passion flower; tilia (p.1922·1).
Dietary supplement.

Santus *Bittner, Austria.*
Homoeopathic preparation.

Santussal *Novartis, Braz.*
Pimethixene (p.588·1); proxyphylline (p.1130·3); ammonium chloride (p.1551·3).
Coughs.

Santyl *Smith & Nephew, Canad.†; Knoll, USA.*
Collagenase (p.2286·2).
Debridement of dermal ulcers and severe burns; wound debridement.

Sanukehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Sanuvis *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Sanval *Lek, Hung.; Lek, Pol.; Lek, Rus.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Sanvapress *Sanval, Braz.*
Enalapril maleate (p.1276·1).
Hypertension.

Sanvisc *Cadila, India.*
Hypromellose (p.2144·2).

Sanvita Immun *Sanamed, Austria.*
Echinacea (p.2298·1).
Respiratory-tract infections.

Sanvita-B *Sanbe, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Sanyrene
Note.This name is used for preparations of different composition.
Urgo, Fr.
Barrier preparation.

Urgo, Ger.
Hyperoxygenated fatty acids of linoleic acid (p.2308·2).
Leg ulcers.

Sanytol *Ideal, Fr.†.*
Permethrin (p.2048·2); phenothrin (p.2048·3); benzyl benzoate (p.2036·1); didecyldimethylammonium chloride (p.1642·2); triclosan (p.1665·2).
House dust mite acaricide.

Sanzur *Garec, S.Afr.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Sanzyme-DS *Uni-Sankyo, India.*
Amylase (p.2256·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); sodium bicarbonate (p.1673·2); simeticone (p.1770·2).
Dyspepsia; flatulence.

Sanzyme-S *Sankyo, Thai.†.*
Cellulase (p.2279·1); lipase (p.2360·3); pancreatin (p.2360·1); sanzyme-N.
Digestive disorders.

Saocin-D *Alcon, Gr.; Pharmex (Φαρμεξ), Gr.*
⊗ Dexamethasone (p.1526·1); neomycin (p.305·1).
Topical corticosteroid with antimicrobial.

Sapec *Riemser, Ger.*
Garlic (p.2309·2).
Hyperlipidaemias.

Saphire *Aset, Turk.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Sapilent *Extractum, Hung.*
Trimipramine (p.426·2).
Depression.

Sapoderm *Reckitt Benckiser, Austral.*
Triclosan (p.1665·2).
Skin cleansing.

Sapol *Kelemata, Ital.*
Sulfur (p.1614·1).
Skin cleanser for oily skin.

Sapona *Konimex, Indon.*
Benzoic acid (p.1630·2); peru balsam (p.2365·3); salicylic acid (p.1612·2).
Fungal skin infections.

Saponarex *Herbapol Pruszkow, Pol.*
Ribwort plantain (p.2379·1); soapwort (p.2388·2); thyme (p.2401·1).
Cough; respiratory-tract congestion.

Sapoven *Hasco-Lek, Pol.*
Aesculus (p.2248·2).
Haematoma; superficial phlebitis; venous insufficiency.

Sapoven AT *Hasco-Lek, Pol.*
Aesculus (p.2248·2); benzocaine (p.1854·1); troxerutin (p.2305·1).
Anorectal disorders.

Sapoven T *Hasco-Lek, Pol.*
Aesculus (p.2248·2); troxerutin (p.2305·1).
Oedema; soft-tissue injury; venous insufficiency.

Sapresta *Taiho, Jpn.*
Aranidipine (p.1216·3).
Hypertension.

Sapriken *Kener, Mex.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Saprimix *Cooper (Κοπερ), Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Sapucai
Note.This name is used for preparations of different composition.
Geminis, Arg.†.
Cream: Permethrin (p.2048·2).
Pediculosis.

Geminis, Arg.†.
Shampoo: Benzyl benzoate (p.2036·1); benzocaine (p.1854·1); permethrin (p.2048·2).
Pediculosis; scabies.

Saquat *Ramini, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds and burns.

Sara *TNP, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Sarafem *Warner Chilcott, USA.*
Fluoxetine hydrochloride (p.391·2).
Premenstrual dysphoric disorder.

Sarai *Steiner, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Sarapin *High Chemical, USA.*
Sarracenia purpurea distillate (p.122·2).
Neuromuscular or neuralgic pain.

Saratoga *Blair, USA.*
Zinc oxide (p.1621·2); boric acid (p.2268·1); cineole (p.2282·3); peru balsam (p.2365·3).
Minor skin irritation.

Sarcoderma *Confar, Port.†.*
Lindane (p.2045·3).
Pediculosis; scabies.

Sarcop *Unipharma, Spain.*
Permethrin (p.2048·2).
Scabies.

Sarcoton *Medley, Braz.*
Disulfiram (p.2296·2).
Alcoholism.

Sarf *Julphar, UAE.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Sarfiram *Bergamo, Braz.*
Sulfiram (p.2050·3).
Scabies.

Sargemag *Viatris, Fr.*
Magnesium carbonate (p.1743·1); magnesium oxide (p.1744·1).
Formerly known as Magnosol.
Magnesium supplement.

Sargenor
Viatris, Fr.; Meda, Port.; Viatris, Spain.
Arginine aspartate (p.1928·2).
Asthenia; tonic.

Viatris, Ital.
Arginine hydrochloride (p.1928·2).
Asthenia; tonic.

Sargenor a la Vitamine C *Viatris, Fr.*
Arginine aspartate (p.1928·2); ascorbic acid (p.1983·3).
Tonic.

Sargenor Plus *Viatris, Ital.*
Arginine hydrochloride (p.1928·2); ascorbic acid (p.1983·3).
Tonic.

Sargenor Sport *Viatris, Ital.*
Leucine; valine; isoleucine; arginine aspartate; vitamin B (p.1922·1).
Nutritional supplement.

Sargisthene *Viatris, Spain.*
Arginine aspartate (p.1928·2).
Asthenia.

Saribal *Gerolymatos, Gr.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Saridine *Atlantic, Thai.*
Sulfasalazine (p.1773·2).
Ulcerative colitis.

Saridon
Note.This name is used for preparations of different composition.
Bayer Consumer, Arg.; Bayer, Austria; Roche, Belg.†; Roche, Braz.; Bayer, Cz.; Bayer, Ger.; Roche, Hong Kong; Bayer, Hung.; Bayer, Indon.; Bayer, Ital.; Bayer, Neth.; Bayer, Pol.; Roche, Rus.; Bayer, Spain; Roche, Switz.†.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Cold and influenza symptoms; fever; pain.

Roche, Chile†; Roche, Venez.†.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Bayer, Philipp.
Paracetamol (p.108·1).
Fever; pain.

Saridon N
Note.This name is used for preparations of different composition.
Bayer, Port.
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Pain.

Roche, Switz.
Ibuprofen sodium (p.65·2).
Fever; pain.

Sarifan Compuesto *Ronava, Venez.†.*
Hyoscine (p.1733·3); dipyrone (p.49·2).

Sarixell *Bayer, Neth.*
Ibuprofen sodium (p.65·2).
Fever; pain.

Sarmel *Anpharm (Ανφαρμ), Gr.*
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections.

Sarna *Stiefel, Austral.; Stiefel, Malaysia; Stiefel, Philipp.; Stiefel, Singapore; Stiefel, Thai.*
Camphor (p.2273·2); menthol (p.2340·1); phenol (p.1656·1).
Burns; dry skin; pruritus; skin irritation; wounds.

Sarna Anti-Itch *Stiefel, USA.*
Camphor (p.2273·2); menthol (p.2340·1).
Poison ivy; poison oak; pruritus; sunburn.

Sarna HC *Stiefel, Canad.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Sarna Sensitive Anti-Itch *Stiefel, USA.*
Pramocaine hydrochloride (p.1868·1).
Pruritus.

Sarna Ultra *Stiefel, USA.*
Pramocaine hydrochloride (p.1868·1); menthol (p.2340·1).

Sarna-P *Stiefel, Canad.*
Pramocaine hydrochloride (p.1868·1); camphor (p.2273·2); menthol (p.2340·1).
Skin irritation.

Sarnapen *Dovalle, Braz.†.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Sarnaton *Royton, Braz.†.*
Benzyl benzoate (p.2036·1).
Scabies.

Sarnezan *Neckerman, Braz.†.*
Benzyl benzoate (p.2036·1).
Scabies.

Sarnilab *Multilab, Braz.*
Benzyl benzoate (p.2036·1).
Scabies.

Sarnodex *Bunker, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Sarnol *Stiefel, Fr.*
Camphor (p.2273·2); menthol (p.2340·1).
Skin disorders.

Saromet *Pfizer, Arg.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm.

Saronil *Artis, Spain.*
Tropisetron hydrochloride (p.1777·2).
Nausea and vomiting.

Saroten *Lundbeck, Austria; Lundbeck, Denm.; Lundbeck, Fin.†; Bayer, Ger.; Gerolymatos, Gr.; Lundbeck, Rus.; Lundbeck, S.Afr.; Lundbeck, Swed.; Lundbeck, Switz.*
Amitriptyline hydrochloride (p.376·1).
Depression; insomnia; nocturnal enuresis; pain.

Sarotena *Lundbeck, India.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Sarotex *Lundbeck, Neth.; Lundbeck, Norw.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis; pain.

Sarox *Biomep, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Sarsaparol Uro *Sabona, Ger.†.*
Homoeopathic preparation.

Sarsapsor *Ysatfabrik, Ger.*
Homoeopathic preparation.

Sartaxal *Sandoz, Indon.*
Losartan potassium (p.1326·1).
Hypertension.

Sarten *Menarini, Cz.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Sarten Plus H *Menarini, Cz.*
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Sarticain *Senese, Ital.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia in dentistry.

Sartol *Stiefel, Spain.*
Menthol (p.2340·1); camphor (p.2273·2).
Insect bites; pruritus; urticaria.

Sarton *Leciva, Cz.†.*
Valsartan (p.1420·2).
Hypertension.

Sartuzin *Help, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Sarval *Baliarda, Arg.*
Valsartan (p.1420·2).
Heart failure; hypertension.

SAS *ICN, Canad.†.*
Sulfasalazine (p.1773·2).
Ulcerative colitis.

Saseem *Pohl, Ger.*
Xylitol (p.1998·2); dexpanthenol (p.2362·1); carrageenan (p.2142·3); sorbic acid (p.1662·2); electrolytes (p.1667·1).
Dry mouth.

Saspryl *Inibsa, Spain†.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint and peri-articular disorders; pain; thromboembolism prophylaxis.

Sastid *Stiefel, Arg.; Stiefel, Braz.; Stiefel, Hong Kong; Stiefel, Indon.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Spain†; Stiefel, Thai.; Stiefel, USA; Stiefel, Venez.†.*
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne; pityriasis versicolor; seborrhoea; tinea versicolor.

Sastid Anti-Fungal *Stiefel, Singapore.*
Clotrimazole (p.530·1).
Fungal skin and vaginal infections.

Sastid Jabon *Stiefel, Chile.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne; pityriasis versicolor; seborrhoea.

Sasulen *Faes, Spain.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Satedon *Protein, Mex.†.*
Azathioprine (p.1818·2).

Satigene *Microsules, Arg.*
Irinotecan hydrochloride (p.737·1).
Malignant neoplasms.

Satil *Biotech, Venez.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Satinique Anti-Dandruff *Amway, Canad.†.*
Pyrithione zinc (p.1611·2).

Sativex *Bayer, Canad.; GW, Canad.*
⊗ Dronabinol (p.1728·1); cannabidiol (p.2274·1).
Neuropathic pain in multiple sclerosis.

Satogesic *Eisai, Thai.; Sato, Thai.*
Indometacin (p.66·3).
Musculoskeletal, peri-articular, and soft-tissue pain.

Saton *Saval, Chile.*
⊗ Sibutramine (p.2164·1).
Obesity.

Satural *Altana, Pol.; Polfarmex, Pol.*
Calcium lactate gluconate (p.1676·2).
Calcium deficiency.

Saturnil *Adelco, Gr.*
Alprazolam (p.960·1).
Anxiety disorders; mixed anxiety-depressive states.

Saubasin *Kleva, Gr.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Saugella
Note. This name is used for preparations of different composition.
Rottapharm, Fr.
Topical gel: Loosestrife (p.2334·3); helichrysum; hyaluronic acid (p.2320·1); glycerol (p.2314·2).
Vaginal dryness.

Rottapharm, Fr.
Topical liquid: Thyme (p.2401·1); sage (p.2382·3); milk serum; lactic acid (p.2329·3).
Skin cleansing.

Saugella Attiva *Rottapharm, Ital.*
Thyme (p.2401·1); sage (p.2382·3).
Personal hygiene.

Saugella Dermolatte *Rottapharm, Ital.*
Chamomile (p.2279·3); sage (p.2382·3).
Soap substitute.

Saugella Dermoliquido *Rottapharm, Ital.*
Sage (p.2382·3).
Personal hygiene.

Saugella Fitothym *Rottapharm, Ital.*
Thyme (p.2401·1); wheat extract; sage (p.2382·3).
Soap substitute.

Saugella Gel *Rottapharm, Ital.*
Vaginal lubricant.

Saugella Idrocrema *Rottapharm, Ital.*
Vaginal lubricant.

Saugella Intilac *Rottapharm, Ital.*
Lactic acid (p.2329·3).
Maintenance of vaginal pH.

Saugella Poligyn 7 *Rottapharm, Ital.*
Thyme (p.2401·1); levomenol (p.2333·3).
Correction of vaginal pH; personal hygiene.

Saugella Salviettine *Rottapharm, Ital.*
Sage (p.2382·3); lactic acid (p.2329·3).
Personal hygiene.

Saugella Solido ph 3.5 *Rottapharm, Ital.*
Sage (p.2382·3).
Soap substitute for oily skin.

Saugella Solido Zolfo *Rottapharm, Ital.*
Sulfur (p.1614·1).
Acne; soap substitute.

Saugella Uomo *Rottapharm, Ital.*
Helichrysum italicum; clove (p.2284·3).
Male personal hygiene.

Saurat *Ivax, Arg.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Savacol Mouth and Throat Rinse *Colgate Oral Care, Austral.*
Chlorhexidine gluconate (p.1635·3).
Minor oral infections; mouth ulcers.

Savarine *AstraZeneca, Fr.*
Proguanil hydrochloride (p.609·2); chloroquine phosphate (p.599·3).
Malaria.

Savarix *Gemi, Pol.*
Aesculus (p.2248·2); benzocaine (p.1854·1); heparin sodium (p.1301·2).
Soft-tissue injury; venous insufficiency.

Savecal *Ibirn, Ital.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Savene *TopoTarget, Cz.; TopoTarget, Gr.; TopoTarget, UK.*
Dexrazoxane (p.1443·1).
Anthracycline extravasation.

Saventrine *IFET (ΙΦΕΤ), Gr.†; Pharmax, Irl.†; Pharmax, Singapore†.*
⊗ Isoprenaline hydrochloride (p.1316·3).
Bradycardia; cardiogenic or endotoxic shock; evaluation of congenital heart defects; heart block; heart failure; overdose of beta blockers or calcium channel blockers; pulmonary hypertension; Stokes-Adams attacks.

Saver *Elmor, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Savex *Sabex, Canad.†.*
Camphor (p.2273·2); menthol (p.2340·1).

Savex 15 *Sabex, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); camphor (p.2273·2).
Sunscreen.

Savex with PABA *Sabex, Canad.†.*
Padimate O (p.1609·1); camphor (p.2273·2); menthol (p.2340·1); salicylic acid (p.1612·2).
Sunscreen.

Savex Sunblock *Sabex, Canad.†.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Savex with Sunscreen *Sabex, Canad.†.*
Camphor (p.2273·2); menthol (p.2340·1); salicylic acid (p.1612·2).

Savilen *Sanofi-Aventis, Gr.*
Ciprofibrate (p.1246·1).
Hyperlipidaemias.

Savior *Abic, Israel; Teva, Israel.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Burn, skin, and wound disinfection.

Savles *Atlas, Arg.*
Emollient.

Savlex *Drogsan, Turk.*
Chlorhexidine (p.1635·2); cetrimide (p.1634·1).
Skin disinfection.

Savlodil *Regent, Canad.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Wound disinfection.

Savlon *Novartis Consumer, Irl.; Boots Healthcare, NZ; Johnson & Johnson, Singapore†.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Insect bites; napkin rash; skin, burn, and wound disinfection; wounds.

Savlon Antiseptic
Note. This name is used for preparations of different composition.
Reckitt & Colman, Austral.
Cream: Cetrimide (p.1634·1); chlorhexidine hydrochloride (p.1635·3).
Skin abrasions; wounds.

Reckitt & Colman, Austral.
Topical powder: Povidone-iodine (p.1659·2).
Burns; fungal skin infections; skin abrasions; wounds.

Savlon Antiseptic Cream *Novartis Consumer, UK.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Savlon Antiseptic Liquid *Novartis Consumer, UK.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Formerly known as Savlon Concentrated Antiseptic.
Skin disinfection.

Savlon Antiseptic Wound Wash *Novartis Consumer, UK.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Savlon Dry *Novartis Consumer, Irl.; Novartis Consumer, UK.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Savonol *Merkez, Turk.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin disinfection.

Savosan *Vianex (Βιανέξ), Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Savrolin *Oro, Turk.*
Chlorhexidine (p.1635·2); cetrimide (p.1634·1).
Skin disinfection.

Saw Palmetto Formula *Quest, Canad.*
Buchu leaf; cayenne; corn silk; kelp; parsley leaf; cucurbita seed; saw palmetto berry (p.1922·1).

Sawmetto Vivo-Livo *Panpharma, Hong Kong†.*
Saw palmetto (p.2192·3); cucurbita oil (p.2290·2); soya oil (p.1965·3).
Benign prostatic hyperplasia.

Sax *Biotech Naturis, Venez.*
Boric acid (p.2268·1).
Vaginal infections.

Saxacid *Biotech Naturis, Venez.*
Acetic acid (p.2244·2); sorbic acid (p.1662·2).
Vaginal infections.

Saxetil *Santa, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Saxion *Duncan, Arg.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Sayana *Pfizer, Cz.*
Medroxyprogesterone acetate (p.2113·1).
Progestogen-only injectable contraceptive.

Sazo *Wallace, India.*
Sulfasalazine (p.1773·2).
Crohn's disease; rheumatoid arthritis; ulcerative colitis.

SB Aurico Ear Drops *Universal, S.Afr.*
Phenol (p.1656·1).
Earache.

SB Blood Purifying Mixture *Universal, S.Afr.*
Magnesium sulfate; potassium citrate; potassium iodide; iron and ammonium citrate (p.1922·1).
Tonic.

SB Cirogin Cough Mixture *Universal, S.Afr.*
Ipecacuanha (p.1562·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Respiratory-tract congestion.

SB Diarrhoea Mixture *Universal, S.Afr.*
Light kaolin (p.1738·1); calcium carbonate (p.1714·1); catechu (p.2278·2).
Diarrhoea.

SB Gripe Water *Universal, S.Afr.*
Sodium bicarbonate (p.1673·2).
Infant colic.

SB Laxative Mixture *Universal, S.Afr.*
Magnesium sulfate (p.1679·3).
Constipation.

SB Rheumatic Ointment *Universal, S.Afr.*
Camphor (p.2273·2); menthol (p.2340·1); turpentine; eucalyptus oil (p.2301·2).
Musculoskeletal and joint disorders.

SB Shisalene *Universal, S.Afr.*
Camphor (p.2273·2); capsicum oleoresin (p.2276·2); turpentine; eucalyptus oil (p.2301·2).
Muscular aches and pains.

SB Strong-Lax *Universal, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

SB Toothache Drops *Universal, S.Afr.*
Clove oil (p.2285·1); chloroform (p.1781·1).
Toothache.

SB Tox Worm *Universal, S.Afr.*
Piperazine citrate (p.152·3).
Ascariasis.

SB 3 Triple Action Pills *Universal, S.Afr.*
Phenolphthalein (p.1762·1); jalap resin (p.1737·3); aloin (p.1705·3); capsicum oleoresin (p.2276·2).
Constipation.

SB Universal Ointment *Universal, S.Afr.*
Starch (p.1968·1); zinc oxide (p.1621·2); coal tar (p.1616·2); phenol (p.1656·1); cod-liver oil (p.1935·2).
Eczema.

SB Unola Corn Remover *Universal, S.Afr.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

SBOB *TNP, Thai.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

SB-Plex *Wescrib, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

SC-300 *Hamilton, Austral.†.*
Coconut oil derivatives.
Barrier cream; skin cleansing.

Scabecid *Stiefel, Fr.†.*
Lindane (p.2045·3).
Pediculosis; scabies.

Scabene *Medican, Canad.†.*
Esdepallethrine (p.2042·3); piperonyl butoxide (p.2049·1).
Scabies.

Scabenzil *Delta, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Scabexyl *Stiefel, Chile†.*
Lindane (p.2045·3).
Pediculosis; scabies.

Scabicid *Kimia, Indon.*
Lindane (p.2045·3); usnic acid (p.2409·3).
Gram-positive bacterial skin infections; scabies.

Scabicin *Fischer, Israel; Cosmofarma, Port.*
Crotamiton (p.1593·2).
Pruritus; scabies.

Scabiex *Rekah, Israel.*
Benzyl benzoate (p.2036·1).
Scabies.

Scabimite *Galenium, Indon.*
Permethrin (p.2048·2).
Scabies.

Scabine *Stadmed, India.*
Lindane (p.2045·3); cetrimide (p.1634·1).
Pediculosis; scabies.

Scabioderm *Bajer, Arg.*
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1); benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Scabioid *Legrand, Braz.*
Benzyl benzoate (p.2036·1).
Scabies.

Scabirax *Innoderm, Philipp.*
Crotamiton (p.1593·2).
Pruritus; scabies.

Scabisan *Chinoin, Mex.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Scabisan Plus *Chinoin, Mex.*
Permethrin (p.2048·2).
Scabies.

Scaboma
Note. This name is used for preparations of different composition.
Glenmark, India.
Cream: Lindane (p.2045·3); benzocaine (p.1854·1).
Pediculosis; scabies.

Glenmark, India.
Lotion: Lindane (p.2045·3).
Pediculosis; scabies.

Scadan
Note. This name is used for preparations of different composition.
Medipharm, Chile.
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Miles, USA.
Tetradonium bromide (p.1634·3); stearyl dimethyl benzyl ammonium chloride.
Seborrhoea.

Scaflam *Mantecorp, Braz.; Lavipharm, Gr.†.*
Nimesulide (p.95·3).
Fever; inflammation; musculoskeletal disorders; pain.

Scaflan *Schering-Plough, Venez.*
Nimesulide (p.95·3).
Fever; osteoarthritis; pain; rheumatic disorders.

Scalid *Uniao Quimica, Braz.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Scalpe *Glenmark, India.*
Ketoconazole (p.539·1); pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Scalpex *Glenmark, Philipp.*
Ketoconazole (p.539·1); pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Scalpicin
Note. This name is used for preparations of different composition.
Combe, Ital.
⊗ Hydrocortisone (p.1535·2); menthol (p.2340·1).
Skin irritation.

Combe, USA.
Salicylic acid (p.1612·2); menthol (p.2340·1).
Formerly contained hydrocortisone, and menthol.

Scalpicin Anti-Dandruff Anti-Itch *Combe, Canad.*
Menthol (p.2340·1); salicylic acid (p.1612·2).

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Scalpicin Capilar *Combe, Spain.*
⊗ Hydrocortisone (p.1535·2).
Scalp disorders.

Scalpin *Specifar (Σπεσιφαρ), Gr.*
Ketoconazole (p.539·1).
Fungal scalp infections.

Scan C *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Scanaflam *Tempo Scan Pacific, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Scanalgin *Tempo Scan Pacific, Indon.*
Dipyrone (p.49·2).
Pain.

Scanarin *Tempo Scan Pacific, Indon.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Scanax *Tempo Scan Pacific, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Scancortin *Scanpharm, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Scandene *Tempo Scan Pacific, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Scanderma *Tempo Scan Pacific, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Scanderma Plus *Tempo Scan Pacific, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).
Infected skin disorders.

Scandexon *Tempo Scan Pacific, Indon.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Scandicain *AstraZeneca, Austria; AstraZeneca, Ger.; Dentsply, Ger.; AstraZeneca, Switz.*
Mepivacaine hydrochloride (p.1866·3).
Local anaesthesia.

Scandicaine *AstraZeneca, Belg.; AstraZeneca, Neth.*
Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scandine *Zambon, Belg.; Zambon, Ital.*
⊗ Ibopamine hydrochloride (p.1312·1).
Heart failure.

Scandinibsa *Inibsa, Port.; Inibsa, Spain.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scandishake *Nutricia, Austral.†; Axcan, Canad.; Nutricia, Fin.; Scientific Hospital Supplies, Irl.; Scandipharm, Israel; Nutricia, Ital.; Nutricia, NZ; Nutricia, Port.; Scientific Hospital Supplies, UK.*
Preparation for enteral nutrition (p.1922·1).

Scanditen *Tempo Scan Pacific, Indon.*
Ketotifen fumarate (p.582·2).
Asthma.

Scandonest *Septodont, Austral.†; Schein, Austria; Septodont, Cz.; Septodont, Denm.; Ogna, Ital.; Pharmodontal, Neth.; Septodont, Norw.; Septodont, Port.; Dental Warehouse, S.Afr.†; Septodont, Switz.*
⊗ Mepivacaine hydrochloride (p.1866·3).
Adrenaline (p.1203·2), noradrenaline (p.1360·1), or noradrenaline acid tartrate (p.1360·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Scanidin *Tempo Scan Pacific, Indon.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine (p.577·1).
Cough.

Scanlin *Quality, Hong Kong.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Scanlux *Sanochemia, Austria; Sanochemia, Cz.; Sanochemia, Gr.; Sanochemia, Hung.; Sanochemica, Neth.; Setfarma, Port.; Sanochemia, Switz.; Sanochemia, UK.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Scanmecob *Tempo Scan Pacific, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Scanneuron *Tempo Scan Pacific, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1980·2); vitamin B (p.1979·1).
Migraine; nausea and vomiting of pregnancy; nervous system disorders; vitamin B deficiency.

Scannotrast *Gerot, Austria.*
Barium sulfate (p.1477·2).
Radiographic contrast medium for CT scanning.

Scannoxyl *Tempo Scan Pacific, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Scanovir *Tempo Scan Pacific, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Scansepta *Tempo Scan Pacific, Indon.*
Povidone-iodine (p.1659·2).
Mouth and throat disorders; skin infections; wounds.

Scantaren *Tempo Scan Pacific, Indon.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Scantensin *Tempo Scan Pacific, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Scantipid *Tempo Scan Pacific, Indon.*
Gemfibrozil (p.1295·3).
Coronary heart disease; hyperlipidaemias.

Scantoma *Tempo Scan Pacific, Indon.*
Bismuth salicylate (p.1711·1).
Diarrhoea.

Scantropil *Tempo Scan Pacific, Indon.*
Piracetam (p.368·2).
Cerebral trauma; chronic alcoholism; mental function impairment.

Scar Cream *Clay Park, USA.*
Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Scarab *Aristo, India.*
Lindane (p.2045·3); cetrimide (p.1634·1).
Pediculosis; scabies.

Scarda *Pharmaland, Thai.*
Piracetam (p.368·2).
Cerebrovascular disorders; mental function disorders.

Scarfade *GAR, Singapore†.*
Dimeticone (p.2032·1); cyclomethicone; polysiloxane.
Scars.

Scat *Cadila, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Scavenger *Aesculapius, Ital.†.*
Glutathione (p.1448·1).
Cisplatin-induced neuropathy.

Scelto *Pharos, Indon.*
Ketorolac trometamol (p.74·2).
Postoperative pain.

Scheinpharm Artificial Tears *Schein, Canad.†.*
Polyvinyl alcohol (p.2145·3).

Scheinpharm Artificial Tears Plus *Schein, Canad.†.*
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).

Scheribar *Schering, Arg.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Schericur *Schering, Arg.; Intendis, Spain.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Scheriderm *Schering, Arg.; Intendis, Mex.*
⊗ Diflucortolone valerate (p.1529·2); isoconazole nitrate (p.536·2); neomycin sulfate (p.305·1).
Infected skin disorders.

Scherilan Crema *Intendis, Ital.*
Zinc oxide (p.1621·2).
Barrier preparation.

Schering Base *Schering, Canad.†.*
Emollient.
Dry skin; topical diluent.

Scheriproct
Note. This name is used for preparations of different composition.
Schering, Arg.; CSL, Austral.; Schering, Austria; Schering, Belg.; Schering, Chile; Schering, Fin.; Asche, Ger.†; Schering, Ger.†; Schering, Irl.; Intendis, Mex.; Intendis, Norw.; Intendis, Port.; Schering, S.Afr.; Schering, Switz.; Valeant, UK; Schering, Venez.
⊗ Prednisolone caproate (p.1541·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders; haemorrhoids; pruritus ani.

Intendis, Spain.
⊗ Prednisolone (p.1540·3); cinchocaine hydrochloride (p.1857·3); menthol (p.2340·1).
Anorectal disorders.

Schering, Thai.†.
⊗ Prednisolone caproate (p.1541·1); cinchocaine hydrochloride (p.1857·3); clemizole undecylate (p.574·1).
Anorectal disorders.

Scheriproct N
Note. This name is used for preparations of different composition.
Schering, Swed.
⊗ Prednisolone caproate (p.1541·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Schering, Thai.
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Scheriproct Neo *Schering, Gr.*
⊗ Cinchocaine hydrochloride (p.1857·3); prednisolone caproate (p.1541·1).
Haemorrhoids.

Scheritonin *Schering, Arg.†.*
Isotretinoin (p.1599·2).
Acne.

Scherogel *Schering, Austria; Asche, Ger.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Schias-Amaro Medicinale *AFOM, Ital.†.*
Rhubarb (p.1768·3); boldo (p.2267·2); cascara (p.1715·2).
Constipation; digestive disorders.

Schiwalys Hemofiltration *Baxter, Swed.*
Electrolyte solution for haemofiltration (p.1670·3).
Some solutions also contain glucose.

Schizopol *Polipharm, Thai.†.*
Haloperidol (p.1000·2).

Schlaf- und Nerventee *Bad Heilbrunner, Ger.*
Valerian (p.2410·1); melissa (p.2339·3); lupulus (p.2335·2).
Nervous disorders.

Schlaf-Nerventee N *Abtswinder, Cz.†.*
Valerian (p.2410·1); melissa (p.2339·3); lupulus (p.2335·2); lavender (p.2331·1); chamomile (p.2279·3); liquorice (p.1740·3); orange flower (p.2357·1).
Anxiety; insomnia.

SchlafTabs *Ratiopharm, Ger.*
Doxylamine succinate (p.578·2).
Sleep disorders.

Schlaftropfen Nr 30 *Doskar, Austria.*
Homoeopathic preparation.

Schlehen Elixir *Weleda, S.Afr.*
Blackthorn (p.2267·2).
Tonic.

Schlehepar N *Hanosan, Ger.†.*
Homoeopathic preparation.

Schleimhaut-Komplex Ho-Fu-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Schmerz-Dolgit *Dolorgiet, Ger.*
Ibuprofen (p.64·2).
Fever; pain; rheumatism.

schnupfen endrine *Asche Chiesi, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Schnupfen Kapseln *Tetesept, Ger.*
Eucalyptus oil (p.2301·2).
Respiratory-tract congestion.

Scholl Athlete's Foot
Note. This name is used for preparations of different composition.
SSL, UK.
Tolnaftate (p.548·3).
Tinea pedis.

Schering-Plough, Canad.†.
Cream: Butenafine hydrochloride (p.528·1).
Tinea pedis.

Schering, Canad.
Gel; powder; spray powder: Tolnaftate (p.548·3).
Tinea pedis.

Scholl Callous *Titan, Turk.*
Salicylic acid (p.1612·2).
Calluses.

Scholl Callus Removal *SSL, UK.*
Salicylic acid (p.1612·2).
Calluses.

Scholl Callus Remover *Schering, Canad.*
Salicylic acid (p.1612·2).
Calluses; corns.

Scholl Clear Away *Schering, Canad.†.*
Salicylic acid (p.1612·2).
Warts.

Scholl Corn & Callus Removal Liquid *SSL, UK.*
Salicylic acid (p.1612·2); camphor (p.2273·2).
Calluses; corns.

Scholl Corn Removal *SSL, UK.*
Salicylic acid (p.1612·2).
Corns.

Scholl Corn Remover *Schering, Canad.*
Salicylic acid (p.1612·2).
Calluses; corns.

Scholl Corn/Callous Removers *Scholl, Israel.*
Salicylic acid (p.1612·2).
Corns and callouses.

Scholl 2-Drop Corn Remedy *Schering, Canad.*
Salicylic acid (p.1612·2).
Calluses; corns.

Scholl Dry Antiperspirant Foot Spray *Schering-Plough, Canad.†.*
Aluminium chlorohydrate (p.1588·3).
Foot odour; foot perspiration.

Scholl One Step *Schering, Canad.†.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Scholl Seal & Heal *SSL, UK.*
Salicylic acid (p.1612·2); camphor (p.2273·2).
Calluses; corns; verrucas; warts.

Scholl Verucca Removal *SSL, UK.*
Salicylic acid (p.1612·2).
Verrucas; warts.

Scholl Warzenfilm *SSL, Switz.*
Salicylic acid (p.1612·2).
Warts.

Scholl Zino *Schering-Plough, Canad.†.*
Salicylic acid (p.1612·2).
Corns.

Schoum *Omega, Fr.*
Fumitory (p.2307·2); ononis (p.2357·1); Jamaica dogwood (p.2328·1); sorbitol (p.1965·1); alverine citrate (p.1708·1).
Gastrointestinal and kidney disorders.

Schrundensalbe Dermi-cyl *Liebermann, Ger.*
Salicylic acid (p.1612·2).
Skin disorders.

Schufen *Kenyaku, Hong Kong; Kenyaku, Thai.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Schupps Melissen Olbad *Schupp, Ger.†.*
Citronella oil (p.2284·2).
Bath additive; nervous disorders.

Schweden-Mixtur H nouvelle formulation *Hanseler, Switz.*
Aloes (p.1705·2); senna (p.1769·2); rhubarb (p.1768·3).
Constipation.

Schwedentrunk Elixier *Infirmarius-Rovit, Ger.*
Angelica (p.2258·1); gentian (p.2310·3); cardamom fruit (p.2277·1); cinnamon (p.2283·1); valerian (p.2410·1).
Digestive-system disorders.

Schwefelbad Dr Klopfer *Austroplant, Austria; Protina, Ger.; Protina, Hung.*
Sulfur (p.1614·1); sodium thiosulfate (p.1466·1).
Bath additive; musculoskeletal and joint disorders; skin disorders.

Schwohepan S *Schwörer, Ger.†.*
Milk thistle (p.1452·1); greater celandine (p.2317·1).
Biliary and gastrointestinal spasm; liver disorders.

Schwoneural N *Schwörer, Ger.*
Homoeopathic preparation.

Schworalgan *Schwörer, Ger.*
Paracetamol (p.108·1); propyphenazone (p.119·3).
Fever; pain.

Schworocard *Schwörer, Ger.*
Homoeopathic preparation.

Schworocor A *Schwörer, Ger.*
Homoeopathic preparation.

Schworosin *Schwörer, Ger.*
Homoeopathic preparation.

Schworotox *Schwörer, Ger.*
Homoeopathic preparation.

Schworotox A *Schwörer, Ger.*
Homoeopathic preparation.

Sciargo *Potter's, UK.*
Shepherd's purse (p.2386·2); wild carrot (p.2415·2); clivers (p.2284·3); bearberry (p.2263·3); juniper berry oil (p.2328·3).
Lumbago; sciatica.

Sci-B-Vac *Scigen, Hong Kong.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

SciLin M30 *SciGen, Philipp.*
⊗ A mixture of soluble insulin (human) 30% and isophane insulin (human) 70% (p.443·2).
Diabetes mellitus.

SciLin N *SciGen, Philipp.*
⊗ Isophane insulin (human) (p.443·2).
Diabetes mellitus.

SciLin R *SciGen, Philipp.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Scillacor *Steigerwald, Ger.†.*
Homoeopathic preparation.

Scillase N *Ziethen, Ger.†.*
Squill (p.1573·1).
Heart failure; kidney disorders.

Scintadren *Nycomed Amersham, UK.*
Selenium-75 (p.2055·3) in the form of 6β-(methyl(Se)seleno)methyl-19-norcholest-5(10)-en-3β-ol.
Adrenal gland imaging.

Scintimun *CIS, Cz.*
Kit for labelling monoclonal antibody (BW 250/183) with technetium-99m (p.2055·3).

Sciomir *CT, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Sciroppo Berta *Berta, Ital.*
Liquorice (p.1740·3); sulfogaiacol (p.1573·2).
Catarrh; coughs.

Sciroppo Fenoglio *AFOM, Ital.†.*
Ferric ammonium citrate (p.1938·1).
Anaemias.

S-Citadep *Cipla, India.*
Escitalopram oxalate (p.391·1).
Depression.

Scitin *Wermar, Mex.*
Trimebutine (p.2404·3).

Scitropin *Scigen, Austral.; Scigen, Hong Kong; Scigen, Singapore†.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

SciTropin *SciGen, Philipp.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency; Turner's syndrome.

Sclerace *Novartis, India.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Scleremo *Bailleul, Fr.*
Chrome alum (p.2280·3); glycerol (p.2314·2).
Varicose veins.

Scleril *AGIPS, Ital.*
Fenofibrate (p.1286·2).
Exudative diabetic retinopathy; hyperlipidaemias; xanthoma.

Sclerobion *Merck, India.*
Vitamin A (p.1971·2); vitamin B (p.1979·1); vitamin E (p.1992·2).
Vitamin A and E deficiency.

Sclerocalcine *Lehning, Fr.*
Homoeopathic preparation.

Sclerodex *Omega, Canad.*
Glucose (p.1945·3); sodium chloride (p.1686·1); phenethyl alcohol (p.1655·3).
Sclerotherapy.

Sclerodine *Omega, Canad.*
Iodine (p.2169·2); sodium iodide (p.2169·2).
Sclerotherapy.

Sclerofin *Ivax, Arg.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Scleromate *Palisades, USA.*
Sodium morrhuate (p.2390·1).
Varicose veins.

Scleron *Weleda, Ger.; Weleda, S.Afr.*
Homoeopathic preparation.

Sclerosol *Bryan, USA.*
Sterile talc (p.1615·2).
Malignant pleural effusion.

Sclerovein *Resinag, Switz.*
⊗ Lauromacrogol 600 (p.1916·1); alcohol (p.1625·2).
Variceal sclerosis.

Sclerovis H *Amnol, Ital.*
Borage (p.2267·3); Iceland moss (p.2324·1); echinacea (p.2298·1); melaleuca; peppermint (p.1761·2); evening primrose (p.2302·1); prunus dulcis; triticum aestivum (p.2415·1).
Emollient.

SCMC *CCM, Malaysia; Beacons, Singapore.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

SCMC Promethazine *CCM, Malaysia†.*
Carbocisteine (p.1553·2); promethazine hydrochloride (p.588·2).
Coughs.

Scoburen *Renaudin, Fr.*
Hyoscine butylbromide (p.1734·1).
Biliary-tract pain; gastrointestinal disorders; gynaecological pain.

Scobutrin *Landson, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Scoline *Mayne, Austral.; Aspen, S.Afr.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Scolmin *Biolink, Philipp.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Scopace *Hope, USA.*
Hyoscine hydrobromide (p.1734·1).
Parkinsonism.

Scopaject *Merck, S.Afr.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Scopamin *Otto, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Scopamin Plus *Otto, Indon.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm.

Scopanil *Pediapharm, Chile.*
Pargeverine (p.1761·1); metamizole magnesium (p.49·3).
Smooth muscle spasm and pain.

Scopas *Asian Pharm, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastro-duodenitis; nausea and vomiting; peptic ulcer; smooth muscle spasm.

Scope *Procter & Gamble, USA.*
Cetylpyridinium chloride (p.1635·1).
Minor mouth or throat irritation.

Scopex *Adcock Ingram, S.Afr.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm.

Scopex Co *Adcock Ingram, S.Afr.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Gastrointestinal spasm; urinary-tract spasm.

Scopinal *Julphar, UAE.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Scopoderm *Novartis, Austria; Novartis, Denm.; Novartis, Fin.; Novartis, Norw.; Novartis, Swed.*
Hyoscine (p.1733·3).
Motion sickness.

Scopoderm TTS *Novartis Sante, Fr.; Novartis Consumer, Ger.; Novartis, Hong Kong†; Enzpharma, NZ; Novartis Consumer, Neth.; Novartis Consumer, UK.*
Hyoscine (p.1733·3).
Intractable cough in terminal illness; motion sickness.

Scopolan *Herbapol Wroclaw, Pol.*
Hyoscine butylbromide (p.1734·1).
Adjunct in radiology; biliary-tract spasm; gastrointestinal spasm; peptic ulcer; spastic constipation; vomiting.

Scopolan Compositum *Herbapol Wroclaw, Pol.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Adjunct in radiology and endoscopy; pancreatitis; peptic ulcer; smooth muscle spasm; vomiting.

Scorbex *Pharmacare, S.Afr.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Scorbolamid *Polpharma, Pol.*
Ascorbic acid (p.1983·3); rutoside (p.2305·1); salicylamide (p.121·2).
Cold symptoms; headache; neuralgia.

Scordal
Note. This name is used for preparations of different composition.
Kattwiga, Ger.†.
Capsules: Herba teucrii.
Cardiovascular disorders; gastrointestinal disorders.

Kattwiga, Ger.†.
Oral drops: Herba teucrii; magnesium chloride (p.1679·1).
Cardiovascular disorders; gastrointestinal disorders.

Scorotox *Kattwiga, Ger.†.*
Homoeopathic preparation.

Scott *GSK Consumer, Venez.*
Vitamins A and D (p.1922·1).
Dietary supplement.

Scott Dandruff Shampoo *Scott, Canad.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Scott Tradicional *GSK Consumer, Venez.*
Cod-liver oil (p.1935·2).
Vitamin A and D deficiency.

Scottopect
Note. This name is used for preparations of different composition.
Nycomed, Austria.
Gel: Turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); thyme oil (p.2401·2); menthol (p.2340·1); camphor (p.2273·2).
Bronchitis; catarrh.

Nycomed, Austria.
Oral drops: Thyme (p.2401·1).
Bronchitis; catarrh.

Nycomed, Austria.
Oral liquid: Thyme (p.2401·1); wild thyme (p.2415·3); ribwort plantain (p.2379·1).
Bronchitis; catarrh.

Scott's Cod Liver *GSK, Thai.*
Vitamins A and D (p.1922·1).

Scott's E Vita *GSK, Indon.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); calcium hypophosphite (p.1677·1).
Vitamin A and D supplement.

Scott's Emulsion
Note. This name is used for preparations of different composition.
GSK, Hong Kong.
Cod-liver oil (p.1935·2).
Dietary supplement.

GSK, Indon.
Cod-liver oil (p.1935·2); calcium hypophosphite (p.1677·1); sodium hypophosphite.
Vitamin A and D deficiency.

SmithKline Beecham, USA.
Vitamins A and D (p.1922·1).

Scott's Emulsion Orange *GSK, Hong Kong.*
Cod-liver oil (p.1935·2); calcium hypophosphite (p.1677·1).
Dietary supplement.

Scott's Emulsion Original *SmithKline Beecham, Hong Kong†.*
Cod-liver oil; capelin oil; calcium hypophosphite; sodium hypophosphite (p.1922·1).
Dietary supplement.

Scott's Hi-Calcium *GSK, Hong Kong.*
Calcium carbonate (p.1714·1).
Calcium supplement.

Scot-Tussin Allergy *Scot-Tussin, USA.*
Diphenhydramine hydrochloride (p.577·2).

Scot-Tussin DM *Scot-Tussin, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Scot-Tussin DM Cough Chasers *Scot-Tussin, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Scot-Tussin Expectorant *Scot-Tussin, USA.*
Guaifenesin (p.1561·3).
Coughs.

Scot-Tussin Original 5-Action *Scot-Tussin, USA.*
Phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3); sodium citrate (p.1673·3); sodium salicylate (p.124·2); caffeine citrate (p.1116·3).
Upper respiratory-tract symptoms.

Scot-Tussin Senior Clear *Scot-Tussin, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

SCR *Pickles, UK.*
Salicylic acid (p.1612·2).
Cradle cap.

Scribcin *Wescrib, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Scripto-Lyte *Adcock Ingram, S.Afr.*
Potassium chloride; sodium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Scripto-Metic *Adcock Ingram, S.Afr.*
Prochlorperazine maleate (p.1020·1).
Anxiety disorders; migraine; nausea and vomiting; vestibular disorders.

Scullcap & Gentian Tablets *Dorwest, UK.*
Skullcap (p.2388·2); valerian (p.2410·1); vervain (p.2413·3); gentian (p.2310·3).
Anxiety; insomnia; irritability.

Sculptra *Sanofi-Aventis, Fr.; Dermik, USA.*
Poly L-lactic acid.
Facial fat loss in HIV infection; scars; skin irregularities.

Scutamil C *Egis, Cz.†; EGIS, Hung.†.*
Carisoprodol (p.1894·1); paracetamol (p.108·1).
Inflammation; musculoskeletal pain and spasm.

SCV 300 *Sigma, Arg.*
dl-alpha tocopherol (p.1992·2); ginkgo biloba (p.2311·1).

SD-Hermal *Hermal, Ger.*
Clotrimazole (p.530·1).
Pityriasis versicolor; seborrhoeic dermatitis.

SDN 200 *Sigma, Arg.*
Valerian (p.2410·1); passion flower (p.2363·2); valepotriates (p.2410·1).
Gastrointestinal disorders; insomnia; nervous disorders.

SEA ORS *SEA Pharm, Thai.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Seabell *Pond's, Thai.†.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; memory disorders; vestibular disorders.

Sea-Cal *Bioceuticals, UK.*
Calcium carbonate (p.1714·1).

Seacalcit *Bergamo, Braz.*
Calcitonin (salmon) (p.1093·1).

Seacor *SPA, Ital.*
Omega-3 triglycerides (p.1362·1).
Hypertriglyceridaemia.

Seaford Liquid Multivite *Seaford, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Seaking *Cipla, India†.*
Cod-liver oil (p.1935·2).

Seaking Plus *Cipla, India†.*
Cod-liver oil (p.1935·2); vitamin E (p.1992·2).

Seal On *Alltracel, Hong Kong†.*
Calcium oxidised cellulose (p.1075·1); sodium oxidised cellulose (p.1075·1).
Haemorrhage.

Seal & Heal *Seton, Cz.†; SSL, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns; verrucas; warts.

Sealdin *Lacer, Spain†.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Sea-Legs *Boots Healthcare, NZ; SSL, UK.*
Meclozine hydrochloride (p.584·3).
Motion sickness.

Seale's Lotion *C & M, USA.*
Sulfur (p.1614·1); borax (p.2268·1); zinc oxide (p.1621·2).
Acne.

Seal-On *Alltracel, Irl.; Beta Healthcare, UK.*
Calcium oxidised cellulose (p.1075·1); sodium oxidised cellulose (p.1075·1).
Capillary haemorrhage.

SeaMist *Schein, USA.*
Sodium chloride (p.1686·1).
Inflammation and dryness of nasal membranes.

Sea-Omega *Rugby, USA.*
Omega-3 marine triglycerides with vitamin E (p.1362·2).
Dietary supplement.

Seasonale *Duramed, USA.*
84 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Combined oral contraceptive.

Seasonique *Duramed, USA.*
84 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, ethinylestradiol.
Combined oral contraceptive.

Seasorb
Coloplast, Arg.
Calcium alginate (p.1058·1); sodium alginate (p.2141·1); carmellose sodium (p.2142·1).
Exudating wounds.

Coloplast, Fr.
Calcium alginate (p.1058·1); carmellose sodium (p.2142·1).
Formerly known as Comfeel Seasorb.
Ulcers; wounds.

SeaSorb Soft *Coloplast, Ger.; Coloplast, UK.*
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Burns; ulcers; wounds.

Seatone *Peter Black, UK.*
Green-lipped mussel (p.2317·2).

Seaze *Arrow, Austral.*
Lamotrigine (p.485·1).
Epilepsy.

Sebacnol
Note. This name is used for preparations of different composition.
Boots Healthcare, Ital.†.
Lotion: Mimosa tenuiflora; glycolic acid (p.1598·1).
Acne.

Boots Healthcare, Ital.†.
Topical gel: Mimosa tenuiflora; urtica (p.2409·3); thyme (p.2401·1); tilia (p.2402·2).
Acne.

Sebamed *Sebapharma, Hong Kong; Sebapharma, Thai.*
A range of skin cleansers and emollients.

Sebamed Suncream 20 *Sebapharma, Thai.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Sebamed Suncream 28 *Sebapharma, Thai.*
Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Sebamed Sunlotion 20 *Sebapharma, Thai.*
SPF 20: Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Seba-Nil *Healthpoint, USA.*
Skin cleanser.
Acne.

Sebapain *Berman, Mex.*
Ketorolac (p.75·2).
Pain.

Sebaquin *Summers, USA.*
Diiodohydroxyquinoline (p.832·1).
Scalp disorders.

Sebasorb *Summers, USA.*
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne.

Sebaxyl *Medipha r, Venez.*
Salicylic acid (p.1612·2); boric acid (p.2268·1); camphor (p.2273·2).
Acne; seborrhoea.

Sebco *Centrapharm, UK.*
Coal tar (p.1616·2); precipitated sulfur (p.1614·1); salicylic acid (p.1612·2).
Scalp disorders.

Sebcur *Dermtek, Canad.*
Salicylic acid (p.1612·2).
Seborrhoea of the scalp.

Sebcur/T *Dermtek, Canad.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Psoriasis of the scalp.

Sebercim *GSK, Ital.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Sebex *Rugby, USA.*
Salicylic acid (p.1612·2); sulfur (p.1614·1).
Seborrhoea.

Sebexol *Devesa, Ger.*
Emollient.
Skin disorders.

Sebexol cum urea *Devesa, Ger.*
⊗ Urea (p.1620·2).
Skin disorders.

Sebex-T *Rugby, USA.*
Coal tar (p.1616·2); sulfur (p.1614·1); salicylic acid (p.1612·2).
Seborrhoea.

Sebidin
GSK, Pol.
Ascorbic acid (p.1983·3); chlorhexidine hydrochloride (p.1635·3).
Mouth and throat disorders; mouth disinfection.

GSK, Rus.
Chlorhexidine (p.1635·2); ascorbic acid (p.1983·3).

Sebiprox *Stiefel, Fr.; Stiefel, Ger.; Stiefel, Ital.; Stiefel, Neth.; Stiefel, Port.; Stiefel, Spain.*
Ciclopirox olamine (p.529·2).
Seborrhoeic dermatitis.

Sebirinse
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, NZ.
Diacetyldimonium chloride; dexpanthenol (p.2362·1); phenethyl alcohol (p.1655·3).
Dandruff; dry scalp and hair disorders.

Ego, Hong Kong.
Diacetyldimonium chloride; panthenol (p.2362·1).
Scalp disorders.

Sebitar
Ego, Austral.; Ego, Hong Kong; Ego, NZ; Ego, Singapore.
Pine tar (p.1616·2); coal tar (p.1616·2); salicylic acid (p.1612·2); undecylenamide (p.549·3).
Skin and scalp disorders.

Ego, Malaysia.
Pine tar (p.1616·2); coal tar (p.1616·2); salicylic acid (p.1612·2); undecenoic acid diethanolamide (p.549·3).
Skin and scalp disorders.

Sebium AKN
Note. This name is used for preparations of different composition.
Dispolab, Chile; Bioderma, Venez.
Zinc gluconate (p.1999·2); salicylic acid (p.1612·2); enoxolone (p.50·1); ginkgo biloba (p.2311·1); AHA esters.
Acne.

Bioderma, Fr.
Lactic acid (p.2329·3); citric acid (p.2284·1); salicylic acid (p.1612·2); zinc gluconate (p.1999·2); enoxolone (p.50·1); ginkgo biloba (p.2311·1).
Seborrhoea.

Sebium Gel *Bioderma, Venez.*
Soap substitute.
Acne.

Sebium H2O
Note. This name is used for preparations of different composition.
Dispolab, Chile.
Zinc gluconate (p.1999·2); copper sulfate (p.1935·3).
Acne.

Bioderma, Venez.
Soap substitute.
Acne.

Sebivo *Novartis, Cz.; Novartis, Indon.; Novartis, Malaysia; Novartis, Port.; Novartis, UK.*
Telbivudine (p.908·1).
Chronic hepatitis B.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Sebizole *Douglas, Austral.; Douglas, Hong Kong†; Douglas, Malaysia†; Douglas, NZ; Douglas, Singapore.*
Ketoconazole (p.539·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Sebo *Chew, Thai.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders.

Sebo Creme *Widmer, Switz.*
⊗ Vitamins (p.1922·1); urea (p.1620·2); triclosan (p.1665·2).
Acne; seborrhoea.

Sebo Fluid *Widmer, Philipp.*
Glyceryl stearate; triclosan (p.1665·2); panthenol (p.2362·1); cetyl alcohol (p.2028·3).
Acne; seborrhoea.

Sebo Shampooing *Widmer, Switz.*
Pyrithione zinc (p.1611·2); disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3); triclosan (p.1665·2).
Scalp disorders.

Seboclear *Szama, Arg.*
Minocycline (p.300·3) or minocycline hydrochloride (p.300·3).
Bacterial skin infections.

Sebolic *D & M, Chile.*
A range of skin and scalp preparations containing melaleuca oil (p.2338·2).
Skin and scalp disorders.

Sebolic Fluido *D & M, Chile.*
SPF 30: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Sebolith *Widmer, Switz.*
Econazole (p.531·1).
Pityriasis versicolor.

Sebomin *Actavis, UK.*
Minocycline hydrochloride (p.300·3).
Acne.

Sebon *Akdeniz, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Sebo-Psor *Widmer, Switz.*
⊗ Dexamethasone (p.1526·1); tretinoin (p.1618·1); urea (p.1620·2).
Scalp disorders.

Seboreks *Can-Sel, Turk.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Seboren *Herbapol Pruszkow, Pol.*
Calamus (p.2271·3); arctium (p.2330·3); pastinaca sativa; urtica (p.2409·3).
Alopecia; dandruff; seborrhoea.

Seborheane
Note. This name is used for preparations of different composition.
Merck Medication Familiale, Fr.
Cream: Glycolic acid (p.1598·1); piroctone olamine (p.1610·1); alpha hydroxy acids; zinc gluconate (p.1999·2); levomenol (p.2333·3); allantoin (p.1588·1); vitamin A palmitate (p.1973·1); vitamin E acetate (p.1992·3).
Seborrhoea; skin irritation.

Merck Medication Familiale, Fr.
Shampoo: Piroctone olamine (p.1610·1); alpha hydroxy acids; zinc lactate.
Dandruff.

Seborrol *Ego, Austral.†; Ego, NZ†.*
Salicylic acid (p.1612·2); resorcinol (p.1612·1); undecylenamide (p.549·3).
Seborrhoea capitis; tinea capitis.

Sebosel *Taro, Israel; Taro, Thai.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Sebo-Soufrol *Gebro, Switz.*
Pyrithione zinc (p.1611·2); sulfur (p.1614·1).
Scalp disorders.

Sebosquam *Expanscience, Fr.*
Ictasol (p.1599·1); cade oil (p.1616·1); climbazole (p.529·3).
Seborrhoeic dermatitis.

Sebren *Ivax, UK.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Sebryl *Bioclon, Mex.*
Allantoin (p.1588·1); clioquinol (p.254·1); coal tar (p.1616·2).
Dandruff; seborrhoeic dermatitis.

Sebryl Plus *Bioclon, Mex.*
Allantoin (p.1588·1); clioquinol (p.254·1); coal tar (p.1616·2); triclosan (p.1665·2).
Dandruff; seborrhoeic dermatitis.

Sebstopp *Pharmacos, Mex.*
Allantoin (p.1588·1); coal tar (p.1616·2); clioquinol (p.254·1).
Seborrhoea.

Sebucare *Westwood-Squibb, USA†.*
Salicylic acid (p.1612·2).
Seborrhoea.

Sebulex
Note. This name is used for preparations of different composition.
Panalab, Arg.
⊗ Panthenol (p.2362·1); salicylic acid (p.1612·2); triclosan (p.1665·2); potassium nitrate (p.1658·3); boric acid (p.2268·1); capsicum (p.2276·2).
Seborrhoea.

Westwood-Squibb, Canad.; Westwood-Squibb, USA.
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Itchy scalp; seborrhoeic dermatitis.

Sebumselen *Juventus, Spain.*
Benzalkonium chloride (p.1629·1); selenium sulfide (p.1613·1).
Skin and scalp disorders.

Sebutone *Westwood-Squibb, Canad.†.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Scalp disorders.

Secabiol *Normon, Spain.*
Carnitine (p.1932·2).
Cardiac disorders; carnitine deficiency.

Secadine *Xixia, S.Afr.*
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Secadrex *Aventis, Neth.†; Italfarmaco, Spain†; Sanofi-Aventis, UK†.*
⊗ Acebutolol hydrochloride (p.1200·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Secalbum *Nutricia-Bago, Arg.*
Calcium caseinate (p.1934·1).
Dietary protein supplement.

Secale Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Secalip *Fournier, Fr.; Fournier SA, Spain.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Secalosan N *Hanosan, Ger.†.*
Homoeopathic preparation.

Secalysat *Ysatfabrik, Ger.*
Homoeopathic preparation.

Secamin *Lab, Port.†.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; mental function disorders.

Secand *Royal, Chile.*
Sorbitol (p.1965·1); malic acid (p.2337·1); electrolytes (p.1667·1).
Saliva substitute.

Secaris *Pharmascience, Canad.*
Macrogol (p.2336·1); propylene glycol (p.2374·1).
Rhinitis.

Secatoxin Forte *Ivax, Cz.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; dementia; hypertension; migraine; thrombosis prophylaxis; vestibular disorders.

Seclodin *Home, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Secnaxidol *EMS, Braz.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnics *Delta, Braz.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnidal *Sanofi-Aventis, Braz.; Aventis, Mex.; Sanofi-Aventis, Venez.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnidalin *Ducto, Braz.*
Secnidazole (p.846·3).
Amoebiasis; trichomoniasis.

Secnihexal *Hexal, Braz.†.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnil *Nicholas Piramal, India.*
Secnidazole (p.846·3).
Amoebiasis; bacterial vaginosis; giardiasis; trichomonal vaginitis.

Secni-Plus *Farmoquimica, Braz.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnitec *Greenpharma, Braz.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnitrol *Biofarma, Braz.†.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Secnivax *Vivax, Venez.*
Secnidazole (p.846·3).
Trichomoniasis.

Secnix *Cifarma, Braz.*
Secnidazole (p.846·3).

Secnizol *UCI, Braz.†.*
Secnidazole (p.846·3).
Bacterial infections; protozoal infections.

Secnol *IPRAD, Fr.*
Secnidazole (p.846·3).
Amoebiasis; giardiasis; trichomoniasis.

Seco *Sriprasit, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Secokapton *Strallhofer, Austria.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine.

Seconal *Flynn, UK; Lilly, USA.*
Secobarbital sodium (p.1027·3).
Insomnia; sedative.

Secotex *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Venez.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Secpel *Medinfar, Port.*
Lactic acid (p.2329·3); lecithin (p.2332·2).
Seborrhoeic dermatitis of the scalp.

Secpel Composto *Medinfar, Port.*
Ichthammol (p.1599·1); lactic acid (p.2329·3); lecithin (p.2332·2).
Psoriasis; scalp disorders.

Secran *Scherer, USA.*
Multivitamin preparation (p.1922·1).

SecreFlo *RepliGen, USA.*
Secretin (synthetic) (p.2384·3).
Assessment of pancreatic function.

Secrelux *Sanochemia, Ger.*
Secretin hydrochloride (p.2384·3).
Diagnosis of Zollinger-Ellison syndrome; test of pancreatic function.

Secrepat *Gayoso, Spain.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); aluminium glycinate (p.1706·2).
Gastric hyperacidity.

Secresol *Permamed, Switz.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Secret 28 *Elea, Arg.; Elea, Mex.*
24 Tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); 4 tablets, inert.
Combined oral contraceptive.

Secretil *Caber, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Secril *Baif, Ital.*
Omega-3 fatty acids (p.1362·1); omega-6 fatty acids (p.2308·2); collagen (p.2286·1).
Dietary supplement.

Sectral *Sanofi-Aventis, Belg.; Aventis, Canad.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Aventis, Hong Kong; Aventis, Irl.†; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Malaysia†; Aventis, Neth.; Polfa Grodzisk, Pol.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Italfarmaco, Spain†; Aventis, Switz.†; Sanofi-Aventis, UK; Reddy, USA.*
⊗ Acebutolol hydrochloride (p.1200·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction; obstructive cardiomyopathy.

Sectrazide *Sanofi-Aventis, Belg.; Aventis, Indon.*
⊗ Acebutolol hydrochloride (p.1200·1); hydrochlorothiazide (p.1307·3).
Angina pectoris; arrhythmias; hypertension.

Secubar *Sandoz, Spain†.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Secubar Diu *Sandoz, Spain.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Secuentex-21 *Pfizer, Mex.*
15 Tablets, mestranol (p.2116·2); 6 tablets, chlormadinone acetate (p.2084·3); mestranol.
Sequential oral contraceptive.

Secural *SecFarm, Pol.*
Nonoxinol 9 (p.1917·2).
Spermicidal contraceptive.

Se-Cure *Everett, USA†.*
Shark cartilage; vitamin E; vitamin C; zinc oxide; selenium (p.1922·1).
Nutritional supplement.

Securgin *Menarini, Ital.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Securil *Yalacta, Fr.*
Propionibacterium freudenreichii.
Maintenance of gastrointestinal flora.

Securo *Valeant, Arg.*
Ivermectin (p.145·2).
Onchocerciasis; scabies.

Securon *Abbott, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Securpres *Pharmacia, Ital.†.*
⊗ Indenolol hydrochloride (p.1315·1).
Angina pectoris; arrhythmias; hypertension.

Seczol
Note. This name is used for preparations of different composition.
Medley, Braz.
Tioconazole (p.548·2); tinidazole (p.848·3).
Fungal vaginal infections.

Valmor, Venez.
Secnidazole (p.846·3).
Protozoal infections.

Sedabel *Sedabel, Braz.†.*
Hyoscine (p.1733·3); dipyrone (p.49·2); atropine sulfate (p.1219·3).
Pain; smooth muscle spasm.

Sedaben *Labima, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Sedabron *Spefar, Venez.†.*
Calcium bromolactobionate (p.967·3).
Anxiety.

Sedacalman *Schwarzwalder, Ger.*
Homoeopathic preparation.

Sedacid *SMB, Belg.; Anabiosis, Gr.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer.

Sedacollyre *Cooperation Pharmaceutique, Fr.*
⊗ Oxedrine tartrate (p.1364·3); berberine hydrochloride (p.2264·3); benzododecinium bromide (p.1631·2).
Eye congestion.

Sedacoron *Ebewe, Austria; Ebewe, Cz.; Ebewe, Hong Kong; Ebewe, Hung.; Ebewe, Rus.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Sedacris *Elea, Arg.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Sedacur *Schaper & Brummer, Ger.; Phytotec, Hung.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Seda-Do *Grasler, Ger.*
Homoeopathic preparation.

Sedadom *Sanidom, Austria.*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety disorders; sleep disorders.

Sedafex *Pharmabiotics, Chile.*
Cefadroxil (p.218·1).
Bacterial infections.

Sedagel
Note. A similar name is used for preparations of different composition (see below).
Roche-Posay, Fr.
⊗ Urea (p.1620·2).
Skin irritation.

Seda-Gel
Note. This name is used for preparations of different composition.
Key, Austral.†.
Lotion: Cetylpyridinium chloride (p.1635·1); chlorhexidine acetate (p.1635·2); lidocaine (p.1862·3).
Mouth ulcers; teething and denture pain.

Key, Austral.
Oral gel: Choline salicylate (p.36·3); menthol (p.2340·1).
Painful mouth disorders.

Sedagul *Wild, Switz.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Sedakatt *Kattwiga, Ger.*
Homoeopathic preparation.

Sedakter *Corsa, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Sedalen Cort *Montefarmaco, Ital.†.*
⊗ Hydrocortisone acetate (p.1535·2); benzocaine (p.1854·1); hamamelis (p.2318·2); aesculus (p.2248·2).
Anorectal disorders.

Sedalene *Cristalia, Braz.; Gunther, Braz.*
Dipyrone (p.49·2); homatropine methylbromide (p.1881·3); papaverine hydrochloride (p.2191·3); adiphenine (p.2247·3) or adiphenine hydrochloride (p.2248·1).
Smooth muscle spasm.

Sedalex *Teuto, Braz.*
Orphenadrine citrate (p.812·1); dipyrone (p.49·2); caffeine (p.1116·3).
Pain; smooth muscle spasm.

Sedalgina *Teuto, Braz.*
⊗ Isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).
Pain.

Sedalgin-Neo *Balkanpharma, Rus.*
Paracetamol (p.108·1); dipyrone (p.49·2); caffeine (p.1116·3); phenobarbital (p.492·2); codeine phosphate (p.37·2).
Fever; pain.

Sedalia *Boiron, Cz.*
Homoeopathic preparation.

Sedalin
Note. This name is used for preparations of different composition.
Dinafarma, Braz.†.
Passion flower (p.2363·2); erythrina mulungu (p.2348·1); crataegus (p.2289·1).

Prodotti, Braz.
Dipyrone (p.49·2); papaverine (p.2191·3); adiphenine (p.2247·3); homatropine methylbromide (p.1881·3).

Elin, Philipp.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Chi Sheng, Thai.†.
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Sedalipid *Steigerwald, Ger.*
Magnesium-pyridoxal-5′-phosphate-glutamate.
Hyperlipidaemias.

Sedalito *Merck, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Sedal-M *Milve, Rus.*
Paracetamol (p.108·1); dipyrone (p.49·2); caffeine (p.1116·3); phenobarbital (p.492·2); codeine phosphate (p.37·2).
Fever; pain.

Sedalmerck
Note.This name is used for preparations of different composition.
Merck, Braz.†.
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Merck, Chile; Merck, Mex.
Paracetamol (p.108·1); caffeine (p.1116·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; fever; pain; rhinitis; sinusitis.

Merck, Spain†.
⊗ Caffeine (p.1116·3); ephedrine hydrochloride (p.1558·2); ethylmorphine hydrochloride (p.52·2); propyphenazone (p.119·3).
Pain.

Sedalmerck TH *Merck, Mex.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Allergic rhinitis; coughs; fever; nasal congestion; pain; sinusitis.

Sedalon *Gunsa, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Sedalpan *Teofarma, Ital.*
Methyl nicotinate (p.85·3); diethylamine salicylate (p.47·2).
Musculoskeletal, joint, and soft-tissue disorders.

Sedam *Hexal, Pol.*
Bromazepam (p.964·3).
Anxiety disorders.

Sedanat *PGN, Arg.*
Valerian (p.2410·1); tilia (p.2402·2); passion flower (p.2363·2).
Insomnia.

Sedangor *Sintesina, Arg.*
Dipyridamole (p.1268·1).

Sedanium-R *Coup, Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Sedans *Ganassini, Ital.*
Amitriptyline hydrochloride (p.376·1); chlordiazepoxide hydrochloride (p.968·2).
Nervous disorders.

Sedante Arceli *Gezzi, Arg.†.*
Passion flower (p.2363·2); melissa (p.2339·3); valerian (p.2410·1); sage (p.2382·3); tilia (p.2402·2).
Sedative.

Sedante Dia *Serranita, Arg.*
Passion flower (p.2363·2); valerian (p.2410·1); tilia (p.2402·2).
Sedative.

Sedante Nativa *Argenfarma, Arg.†.*
Valerian (p.2410·1).
Sedative.

Sedante Noche *Serranita, Arg.*
Passion flower (p.2363·2).
Insomnia.

Sedantol *Recalcine, Chile.*
Diazepam (p.986·3); chlormezanone (p.968·3).
Anxiety; insomnia; skeletal muscle spasm.

Sedanxio *Tilman, Belg.*
Passion flower (p.2363·2).
Anxiety.

Sedapain *Garec, S.Afr.*
Paracetamol (p.108·1); doxylamine succinate (p.578·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain with tension.

Sedapap *Merz, USA.*
Paracetamol (p.108·1); butalbital (p.967·2).
Tension headache.

Sedaperidol *Biosel, Turk.*
Haloperidol (p.1000·2).
Agitation; anxiety; behaviour disorders; hiccups; nausea and vomiting; psychoses.

Seda-Plantina *Plantina, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3); passion flower (p.2363·2); rosemary (p.2381·2).
Agitation; sleep disorders.

Sedaplus *Rosen, Ger.*
Doxylamine succinate (p.578·2).
Hypersensitivity reactions; nocturnal enuresis; premedication; sleep disorders.

Sedapressin *Biospray, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Seda-Rash *Key, Austral.†.*
Zinc oxide (p.1621·2); castor oil (p.2278·1).
Eczema; heat rash; intertrigo; nappy rash.

Sedarene *Jolly-Jatel, Fr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Sedarin *Merck, S.Afr.*
Paroxetine (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Sedariston Konzentrat *Steiner, Ger.*
St John's wort (p.422·3); valerian root (p.2410·1).
Anxiety disorders; sleep disorders.

Sedariston plus *Steiner, Ger.*
Valerian root (p.2410·1); St John's wort (p.422·3); melissa leaf (p.2339·3).
Nervous disorders.

Sedartryl
Note.This name is used for preparations of different composition.
Prater, Chile.
Zaleplon (p.1035·3).
Insomnia.

UPSA Conseil, Fr.†.
Methyl nicotinate (p.85·3); amyl salicylate (p.19·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Sedaselect *Dreluso, Ger.*
Homoeopathic preparation.

Sedaselect D *Dreluso, Ger.*
Lupulus (p.2335·2); valerian (p.2410·1).
Nervous disorders; sleep disorders.

Sedasept *Sanico, Switz.†.*
Cineole (p.2282·3); peppermint oil (p.1761·2); thyme oil (p.2401·2); menthol (p.2340·1); thymol (p.1664·3); methyl salicylate (p.85·3).
Dental inflammation; oral hygiene.

Sedasol eco natura *Ecosol, Switz.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Sedasor *Soria Natural, Spain†.*
Valerian (p.2410·1); crataegus (p.2289·1); passion flower (p.2363·2); spike lavender (p.2391·3).
Anxiety; insomnia; nervous disorders.

Sedaspir *Bride, Fr.*
Codeine phosphate (p.37·2); caffeine (p.1116·3); aspirin (p.20·3).
Pain.

Sedastip *Milte, Ital.*
Fibre (p.1712·3); vitamins (p.1922·1).
Constipation.

Sedasyx *Syxyl, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3).
Nervous disorders; sleep disorders.

Sedatif *Boiron, Austral.*
Homoeopathic preparation.

Sedatif PC *Boiron, Cz.; Boiron, Fr.; Boiron, Port.; Boiron, Switz.*
Homoeopathic preparation.

Sedatif Tiber *Poirier, Fr.*
Crataegus (p.2289·1); passion flower (p.2363·2); potassium bromide (p.2269·2); sodium bromide (p.2269·2).
Anxiety; insomnia.

Sedatil *Boiron, Canad.*
Homoeopathic preparation.
Formerly known as Sedatif PC.

Sedatival
Note.This name is used for preparations of different composition.
Raffo, Arg.†.
Lorazepam (p.1004·1).
Anxiety.

Recalcine, Chile.
Ketazolam (p.1002·2).
Anxiety; skeletal muscle spasm.

Sedativum-Hevert *Hevert, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Anxiety; hypersensitivity reactions; motion sickness; nausea; sleep disorders; vomiting.

Sedatol
Note.This name is used for preparations of different composition.
EG, Ital.
Capsules: Passion flower (p.2363·2); valerian (p.2410·1); crataegus (p.2289·1); chamomile (p.2279·3); piscidia (p.2328·1).
Insomnia.

EG, Ital.
Syrup: Passion flower (p.2363·2); chamomile (p.2279·3); crataegus (p.2289·1); piscidia (p.2328·1); melissa (p.2339·3).
Insomnia.

Sedaton *Actavis, Hung.*
⊗ Fentanyl (p.55·3).
Pain.

Sedatus *Elvetium, Arg.†.*
Bromazepam (p.964·3).
Anxiety.

Sedatuss DM *Trianon, Canad.*
Dextromethorphan hydrobromide (p.1555·2).

Sedatux *EMS, Braz.†.*
⊗ Potassium iodide (p.2169·2); lobelia (p.2157·2); hyoscyamus (p.2323·3).
Respiratory-tract congestion.

Sedazin *Lagap, Switz.*
Lorazepam (p.1004·1).
Anxiety; premedication; sleep disorders.

Sedemol *Melisana, Belg.*
Althaea (p.2253·3); poppy capsule (p.1571·1); borax (p.2268·1); sodium fluoride (p.1962·2); phenol (p.1656·1); cloral hydrate (p.979·1).
Mouth and throat disorders.

Sedepron *Chinoin, Mex.*
Clonixin lysine (p.37·1).
Pain.

Sedergine *BMS, Belg.; Uriach, Spain.*
Aspirin (p.20·3).
Fever; musculoskeletal, joint and peri-articular disorders; pain.

Sedergine C *BMS, Belg.†; Uriach, Spain.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Fever; pain.

Sedergine Vit-C *Abdi, Turk.*
Aspirin (p.20·3); vitamin C (p.1983·3).
Fever; pain.

Sedermyl *Cooperation Pharmaceutique, Fr.*
Isothipendyl hydrochloride (p.582·1).
Insect stings; pruritus.

Sedermyl Actifroid *Cooperation Pharmaceutique, Fr.*
Chamomile oil (p.2279·3); tansy oil; geranium oil (p.2311·1).
Insect stings.

Sedesterol *Poen, Arg.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Sedevil
Note.This name is used for preparations of different composition.
Collins, Mex.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Hypersensitivity reactions; respiratory-tract disorders.

Collins, Mex.
Tablets: Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Sedex *Janssen-Cilag, Port.†.*
Flunitrazepam (p.996·2).

Sediat *Pfleger, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Sedicepan *Serra Pamies, Spain.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; nausea; premedication; vomiting.

Sediclon *Degorts, Mex.*
Dicycloverine (p.1723·1).

Sediel *Sumitomo, Jpn.*
Tandospirone citrate (p.1030·1).
Anxiety; depression; phobias; sleep disorders.

Sedilax *Teuto, Braz.*
Carisoprodol (p.1894·1); diclofenac sodium (p.44·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain; smooth muscle spasm.

Sedilene Procto *Montefarmaco, Ital.†.*
Benzocaine (p.1854·1); aesculus (p.2248·2); hamamelis (p.2318·2).
Anorectal disorders.

Sedilit *Sanitas, Chile.*
Diazepam (p.986·3); chlormezanone (p.968·3).
Anxiety; insomnia; skeletal muscle spasm.

Sedilix
Note.This name is used for preparations of different composition.
Xepa-Soul Pattinson, Malaysia†.
Promethazine hydrochloride (p.588·2); codeine phosphate (p.37·2).
Coughs.

Xepa-Soul Pattinson, Singapore.
⊗ Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Sedilix DM *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); promethazine hydrochloride (p.588·2).
Coughs; nasal congestion; respiratory-tract congestion.

Sedilor *Dolisos, Canad.*
Homoeopathic preparation.

Sedinal *Melisana, Belg.*
Crataegus (p.2289·1); ballota; passion flower (p.2363·2).
Nervous disorders.

Sedinef *Yung Shin, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Sedinfant *Sabona, Ger.†.*
Melissa (p.2339·3).
Gastrointestinal disorders; sleep disorders.

Sedinfant N *Biocur, Ger.†.*
Valerian (p.2410·1); melissa (p.2339·3); passion flower (p.2363·2).
Agitation; excitability; sleep disorders.

Sedinol *SA Druggists Self Med, S.Afr.*
Doxylamine succinate (p.578·2); paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain and associated tension.

Sedioton *Wyeth Lederle, Port.†.*
Ambutonium bromide (p.2255·2); oxazepam (p.1014·2).

Sedival *Meyer Nature, Venez.*
Valerian (p.2410·1); melissa (p.2339·3); passion flower (p.2363·2).
Insomnia.

Sedocalcio *Deca, Ital.*
Calcium lactate (p.1676·1); sodium benzoate (p.1630·2).
Mouth and throat disorders.

Sedocardin *Pfluger, Ger.†.*
Homoeopathic preparation.

Sedo-Efeu *UCB, Austria.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Sedofan *Julphar, UAE.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; rhinitis; upper respiratory-tract congestion.

Sedofan II *Julphar, UAE.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; otitis media; sinusitis.

Sedofan DM *Julphar, UAE.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Sedofan P *Julphar, UAE.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Sedofan T *Julphar, UAE.*
Triprolidine hydrochloride (p.592·3).
Hypersensitivity reactions.

Sedofantil *Recalcine, Chile.*
Calcium bromolactobionate (p.967·3).
Hyperactivity in children.

Sedofarin *Pensa, Spain.*
⊗ Dequalinium chloride (p.1641·3); dexamethasone (p.1526·1); benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Sedofit *Body Spring, Ital.*
Magnesium (p.1678·3); crataegus (p.2289·1); eschscholtzia; passion flower (p.2363·2); tilia (p.2402·2); pyridoxine (p.1979·1).
Anxiety; insomnia.

Sedogastrol *Recalcine, Chile†.*
Chlordiazepoxide hydrochloride (p.968·2); clidinium bromide (p.1722·1).
Gastrointestinal motility disorders; smooth muscle spasm.

Sedogelat *Metochem, Austria.*
Valerian root (p.2410·1); melissa (p.2339·3); passion flower (p.2363·2).
Anxiety disorders; sleep disorders.

Sedol
Note.This name is used for preparations of different composition.
Cazi, Braz.
⊗ Isometheptene hydrochloride (p.2327·1) or isometheptene mucate (p.2327·2); dipyrone (p.49·2); caffeine (p.1116·3).

OFF, Ital.
Propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; influenza symptoms; neuralgia.

Sedolin *Selen, Turk.*
Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2); undecylenamidopropyl betaine.
Scalp disorders.

Sedolox *Kwizda, Austria.*
Zopiclone (p.1039·1).
Insomnia.

Sedomix *Leki Natury, Pol.*
Crataegus (p.2289·1); lupulus (p.2335·2); St John's wort (p.422·3); melissa (p.2339·3); rose fruit (p.2381·2); valerian (p.2410·1); avena (p.2262·1).
Insomnia; nervous disorders.

Sedonat *Soria Natural, Spain.*
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1); bitter orange oil (p.2357·1).
Insomnia; sedative; stress.

Sedonium *Lichtwer, Ger.; Lichtwer, Neth.; Vifor, Switz.; Lichtwer, UK.*
Valerian (p.2410·1).
Agitation; insomnia; sleep disorders.

Sedopal *Lehning, Fr.*
Crataegus (p.2289·1); eschscholtzia californica; melilot (p.2339·2).
Insomnia; nervous disorders.

Sedopan *Norma (Νορμα), Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Sedopect *Andromaco, Chile.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Cold and influenza symptoms; coughs.

Sedopretten *Schoning-Berlin, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sedopuer F *SIT, Ital.*
Passion flower (p.2363·2); valerian (p.2410·1); crataegus (p.2289·1); calcium glycerophosphate (p.1676·1).
Insomnia; nervous disorders.

Sedoran *Raffo, Chile.*
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder.

Sedorrhoide *Cooperation Pharmaceutique, Fr.*
Dodeclonium bromide (p.1642·3); benzocaine (p.1854·1); esculoside (p.2248·2); enoxolone (p.50·1).
Anorectal disorders.

Sedosan-N *Grossmann, Switz.†.*
Crataegus (p.2289·1).
Nervous disorders.

Sedosolvin *Ipca, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); bromhexine (p.1552·2).
Coughs.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Sedotensil *Sanofi Synthelabo, Arg.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Sedotime *Iquinosa, Spain.*
Ketazolam (p.1002·2).
Anxiety; insomnia; skeletal muscle spasm.

Sedotus *Andromaco, Chile†.*
Tolu (p.1574·2); pectoral; drosera (p.2297·3); quillaia (p.1920·1).
Coughs.

Sedotusse *Helsinn, Port.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Sedotussin
Note. This name is used for preparations of different composition.
UCB, Austria.
Pentoxyverine (p.1567·3), pentoxyverine citrate (p.1567·3), or pentoxyverine hydrochloride (p.1567·3).
Coughs.
UCB, Cz.†; UCB, Ger.
Pentoxyverine (p.1567·3) or pentoxyverine citrate (p.1567·3).
Coughs.
UCB, Hung.
Pentoxyverine citrate (p.1567·3).
Coughs.
UCB, Switz.†.
Oral drops: Pentoxyverine citrate (p.1567·3); terpin hydrate (p.1573·3); cineole (p.2282·3); menthol (p.2340·1); thymol (p.1664·3); guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.
UCB, Switz.†.
Suppositories: Pentoxyverine (p.1567·3); terpin hydrate (p.1573·3); terpineol (p.2396·1); cineole (p.2282·3); guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.

Sedotussin Efeu *UCB, Ger.*
Ivy (p.2328·1).
Bronchitis; catarrh.

Sedotussin muco *UCB, Ger.†.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excess or viscous mucus.

Sedotussin plus *UCB, Ger.†.*
Pentoxyverine citrate (p.1567·3); chlorphenamine maleate (p.571·3).
Coughs.

Sedovalin *Streuli, Switz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Sedovanon *Craveri, Arg.*
Clonazepam (p.478·2).
Anxiety disorders; epilepsy.

Sedovegan *Wolff, Ger.†.*
St John's wort (p.422·3).
Depression.

Sedovent *Schworer, Ger.*
Cinnamon (p.2283·1); dried bitter-orange peel (p.2357·1); achillea (p.2245·2); gentian (p.2310·3).
Gastrointestinal disorders.

Sedoxil *Medibial, Port.*
Mexazolam (p.1007·2).
Anxiety disorders.

Sedrofen *Interbat, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Sedron *Gedeon Richter, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Sedural *Rekah, Israel.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain and irritation.

Sedusen *Sanitas, Chile.*
Sulpiride (p.1028·3).
Anxiety; depression; neuroses; psychosomatic disorders.

Seduxen *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; eclampsia; epilepsy; febrile convulsions; panic disorder; premedication; skeletal muscle spasm; spasticity; status epilepticus; tetanus.

Seduxen RG *Gedeon Richter, Cz.†.*
Diazepam (p.986·3); lidocaine hydrochloride (p.1862·3).
Febrile convulsions; premedication; skeletal muscle spasm; status epilepticus; tetanus.

Sef *Nevzat, Turk.*
Cefalexin (p.218·2).
Bacterial infections.

Sefagen *Bilim, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Sefaktil *Drogsan, Turk.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Sefal
Note. This name is used for preparations of different composition.
Marvecs, Ital.
Alfacalcidol (p.1986·1).
Hypoparathyroidism; osteomalacia; osteoporosis; renal osteodystrophy; rickets.
Nobel, Turk.
Cinnarizine (p.573·1).
Motion sickness; nausea and vomiting; peripheral vascular disorders; vestibular disorders.

Sefamax *Nobel, Turk.*
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sefaretic *Unison, Hong Kong; Unison, Thai.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hepatic cirrhosis with ascites; hypertension; hypokalaemia; oedema.

Sefasin *Macrophar, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Sefazol *Nevzat, Turk.*
Cefazolin (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Sefdene *Unison, Hong Kong; Unison, Singapore.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Sefdin *Unichem, India.*
Cefdinir (p.223·1).
Bacterial infections.

Seferin *General Drugs, Thai.*
Aspirin (p.20·3).
Inflammation; musculoskeletal and joint disorders; pain.

Sefloc
Unison, Hong Kong.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension.
Unison, Thai.
⊗ Metoprolol (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Sefmal *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Sefmex *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
⊗ Selegiline hydrochloride (p.817·1).
Alzheimer's disease; parkinsonism.

Sefmic *Unison, Hong Kong; Unison, Thai.*
Mefenamic acid (p.80·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Sefnac *Unison, Thai.*
Diclofenac sodium (p.44·3).
Dysmenorrhoea; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Sefnor *Unison, Singapore†; Unison, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Sefoksim *Fako, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Sefotak *Valeant, Cz.; Eczacibasi, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Sefoxiram *Serral, Mex.*
Cefotaxime (p.229·1).
Bacterial infections.

Seftem *Shionogi, Jpn.*
Ceftibuten (p.235·3).
Bacterial infections.

Seftil *Unison, Hong Kong†; Unison, Malaysia; Unison, Thai.*
Tenoxicam (p.128·2).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders.

Sefulken *Kendrick, Mex.*
Diazoxide (p.1257·3).
Hypertension.

Sefuroks *Eczacibasi, Turk.*
Cefuroxime (p.238·2) or cefuroxime axetil (p.238·2).
Bacterial infections.

Segalin *Galena, Cz.†.*
⊗ Selegiline hydrochloride (p.817·1).
Anorexia nervosa; bulimia nervosa; dementia; depression; obsessive-compulsive disorder; panic disorder; parkinsonism; phobias; post-traumatic stress disorder.

Segamol *Boehringer Ingelheim, Venez.*
⊗ Fenoterol hydrobromide (p.1121·1).
Premature labour; threatened abortion.

Segan *Polpharma, Pol.; Polpharma, Rus.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Segel *Diba, Mex.†.*
Aluminium hydroxide (p.1706·2); glycine (p.1947·3); calcium carbonate (p.1714·1); dimeticone (p.1770·2).
Gastrointestinal hyperacidity.

Seglor *Schwarz, Fr.; Pharmafar, Ital.; Azevedos, Port.*
Dihydroergotamine mesilate (p.618·2).
Migraine and other vascular headaches; orthostatic hypotension; peripheral vascular disorders; vertigo.

Segol *Sanovel, Turk.*
Codergocrine mesilate (p.363·3).
Dementia.

Segurex *Gador, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Seguril *Sanofi-Aventis, Spain.*
⊗ Furosemide (p.1292·1).
Forced diuresis; heart failure; hypertension; nephrotic syndrome; oedema; oliguria; renal failure.

Segurite *Raffo, Arg.*
Levonorgestrel (p.2121·2).
Post-coital oral contraceptive.

SeHCAT *GE Healthcare, Neth.*
Selenium-75 (p.2055·3) tauroselcholic acid.
Gastrointestinal investigation.

Sehydrin *Pharmsintez, Rus.*
Hydrazine sulfate (p.2321·3).
Malignant neoplasms.

Seide *Rafarm, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Seif *Schering, Philipp.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

Seikivita *Ortoquimica, Braz.†.*
Cyanocobalamin; pyridoxine hydrochloride; linolenic acid (p.1922·1).

Seis-B *Apsen, Braz.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Sejungin B21 *Bock, Ger.†.*
Homoeopathic preparation.

Sekalax *Kener, Mex.†.*
Sennosides A and B (p.1769·3).
Constipation.

Sekamisin *Sanli, Turk.*
Oxytetracycline hydrochloride (p.312·3) polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Seki
Zambon, Braz.
Cloperastine fendizoate (p.1554·3).
Coughs.
Zambon, Ital.
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Sekin *Almirall, Belg.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Sekisan *Almirall, Spain.*
Cloperastine fendizoate (p.1554·3) or cloperastine hydrochloride (p.1554·3).
Coughs.

Sekitol *Sinterapico, Braz.†.*
Diphenhydramine (p.577·1); ammonium chloride (p.1551·3).
Coughs.

Sekodin *Akdeniz, Turk.*
Oxolamine citrate (p.1567·1).
Coughs.

Sekolaks *Sanli, Turk.*
Bisacodyl (p.1710·1).

Sekretovit *Boehringer Ingelheim, Austria; Anchor, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Sekretovit Amoxi *Boehringer Ingelheim Promeco, Mex.*
Ambroxol hydrochloride (p.1550·3); amoxicillin trihydrate (p.202·2).
Respiratory-tract infections.

Sekretovit Ex *Anchor, Mex.; Boehringer Ingelheim Promeco, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract infections.

Sekrol *Bilim, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Sekucid
Note. This name is used for preparations of different composition.
Paragerm, Fr.†.
Glutaral (p.1645·2).
Instrument disinfection.
Ecolab, Ital.
Glutaral (p.1645·2); isopropyl alcohol (p.1650·3).
Instrument disinfection.

Sekucid konz *Henkel, Ger.†.*
Glutaral (p.1645·2); isopropyl alcohol (p.1650·3); ethylhexanal (p.1644·1).
Instrument disinfection.

Sekudrill *Henkel, Ger.†; Ecolab, Ital.*
Potassium hydroxide (p.2371·3); propylene glycol (p.2374·1).
Instrument disinfection.

Sekumatic *Ecolab, Ital.*
⊗ Glutaral (p.1645·2); alcohol (p.1625·2); chloroform; acetone.
Instrument disinfection.

Sekumatic FD *Henkel, Ger.†.*
Glutaral (p.1645·2).
Instrument disinfection.

Sekumatic FDR *Henkel, Ger.†.*
Glucoprotamine (p.1645·2); didecylmethylpoly(oxyethyl) ammonium propionate; tributyltetradecylphosphonium chloride.
Surface and instrument disinfection.

Sekusept *Ecolab, Ger.; Ecolab, Ital.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Sekusept Extra N *Ecolab, Ger.; Ecolab, Ital.†.*
Benzalkonium chloride (p.1629·1); glutaral (p.1645·2).
Instrument disinfection.

Sekusept forte *Henkel, Ger.†.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); benzalkonium chloride (p.1629·1).
Instrument disinfection.

Sekusept forte S *Ecolab, Ger.*
Formaldehyde (p.1644·2); glutaral (p.1645·2).
Instrument disinfection.

Sekusept Plus *Ecolab, Ger.*
Glucoprotamine (p.1645·2).
Instrument disinfection.

Sel D *Pharmadeveloppement, Fr.*
Sodium chloride; sodium phosphate; sodium sulfate; sodium iodide; sodium bromide (p.1922·1).
Dietary salt substitute.

Sel d'Ems *Siemens, Switz.†.*
Natural sels d'Ems.
Upper respiratory-tract disorders.

Seladin *YSP, Malaysia; Yung Shin, Singapore.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Selamer *Tymofarm, Pol.*
Shark-liver oil (p.2386·1).
Infections.

Selan *Iquinosa, Spain.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Selanir *Selvi, Ital.†.*
Cefaclor (p.217·2).
Bacterial infections.

Selax *Odan, Canad.*
Docusate sodium (p.1725·1).
Constipation.

Selaxa *Proel, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Selbet *Naturissima, Venez.†.*
Potassium chloride; ammonium chloride; magnesium chloride; calcium formate (p.1667·1).
Salt substitute.

Selbex *Eisai, Jpn; Eisai, Philipp.; Eisai, Thai.*
Teprenone (p.1776·3).
Gastritis; peptic ulcer.

Seldepar *Ilsan, Turk.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selder *Eurolab, Arg.*
Vitamin E; lycopene; soya isoflavones; vitamin C; zinc; selenium (p.1922·1).
Dietary supplement.

Seldiyet *Kocak, Turk.*
Potassium chloride; ammonium chloride; magnesium oxide; glutamic acid (p.1667·1).
Dietary salt substitute.

Seldron *ICM, Singapore.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor.

Selebound *Framingham, Arg.*
Selenium (p.1961·1).
Dietary supplement.

Selecal *Taisho, Jpn.*
⊗ Tilisolol hydrochloride (p.1412·2).
Angina pectoris; hypertension.

Selecid *Leo, Port.†.*
Pivmecillinam hydrochloride (p.317·2).
Salmonella enteritis; urinary-tract infections.

Selecim *Cimex, Switz.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selecom *Fulton, Ital.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Select 1/35 *Dispensapharm, Canad.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Selecta *Libbs, Braz.*
Conjugated oestrogens (p.2087·2); medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Selectadoce *Diba, Mex.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3).
Anaemias; neuritis.

Selectadril *Diba, Mex.†.*
⊗ Metoprolol tartrate (p.1338·1).
Hypertension; myocardial infarction.

Selectafer N *Dreluso, Ger.†.*
Iron sucrose (p.1953·2); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Primary and secondary anaemias; tonic.

Selectan *Schering, Arg.*
Norethisterone acetate (p.2119·3).
Adjunct in hormone replacement therapy.

Selectin *BMS, Ital.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia.

Selecto *Diba, Mex.†.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Selectocalcio *Asta Medica, Braz.†.*
Calcium lactate; ergocalciferol; calcium phosphate; cyanocobalamin; sodium fluoride (p.1922·1).
Nutritional supplement.

Selecto-D *Diba, Mex.†.*
Pancreatin (p.2360·1); dimeticone (p.1770·2).
Pancreatic insufficiency.

Selectofen *Diba, Mex.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Selectofort *Diba, Mex.†.*
Hydroxocobalamin (p.1980·3).
Anaemias; neuritis.

Selectofur *Diba, Mex.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Selectol *Gerot, Austria; Pfizer, Belg.; Sanofi-Aventis, Chile; Leiras, Fin.; Pharmacia, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Shinyaku, Jpn; Aventis, Switz.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; ischaemic heart disease; myocardial infarction; phaeochromocytoma.

Selectomycin *Grunenthal, Ger.*
Spiramycin (p.333·1).
Staphylococcal infections; toxoplasmosis.

Selectovit *Diba, Mex.*
Vitamin B substances (p.1922·1).

Selectra *Sanovel, Turk.*
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Selectrin *Cifarma, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Selectrin Balsamico *Cifarma, Braz.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3); ammonium chloride (p.1551·3).

Selecturon *Gerot, Austria.*
⊗ Celiprolol hydrochloride (p.1242·2); chlortalidone (p.1243·3).
Hypertension.

Selectus
Note. This name is used for preparations of different composition.
Purissimus, Arg.
Dextromethorphan hydrobromide (p.1555·2); bromhexine hydrochloride (p.1552·2).
Coughs.

BA Farma, Port.
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive disorders; obsessive-compulsive disorder.

Selectus FN *Purissimus, Arg.*
Clofedanol hydrochloride (p.1554·2); bromhexine hydrochloride (p.1552·2).
Coughs.

Seledat *Master Pharma, Ital.*
⊗ Selegiline hydrochloride (p.817·1).
Psychiatric disorders.

Seledie *Italfarmaco, Ital.*
Nadroparin calcium (p.1346·1).
Venous thrombosis.

Selefusin *Pisa, Mex.†.*
Selenium (p.1961·1).

Selegam *Hexal, Ger.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selegel
Note. This name is used for preparations of different composition.
Pierre Fabre Dermo-Cosmetique, Arg.
Selenium sulfide (p.1613·1); ictasol (p.1599·1).
Formerly contained selenium sulfide.
Dandruff.

Ducray, Fr.
Selenium sulfide (p.1613·1); ichthammol (p.1599·1).
Formerly contained selenium sulfide.
Seborrhoeic dermatitis.

Medifarm Ducray, Venez.
Selenium sulfide (p.1613·1).
Scalp disorders.

Selegil *Diba, Mex.†.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Selegos *Medochemie, Hong Kong; Medochemie, Malaysia†; Medochemie, Rus.; Medochemie, Singapore.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Seleject *Biosyn, Ger.*
Sodium selenite (p.1961·1).
Selenium deficiency.

Selektine *BMS, Neth.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia; reduction of cardiovascular risk.

Selektine Plus *BMS, Neth.*
Pravastatin sodium (p.1374·3); aspirin (p.20·3).
Cardiovascular risk reduction.

Selemerck *Merck dura, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selemite-B *Blackmores, Austral.*
Selenomethionine.
Selenium deficiency.

Selemun *Biosyn, Ger.†.*
Sodium selenite (p.1961·1).
Selenium deficiency.

Selemycin *Medochemie, Hong Kong†; Medochemie, Malaysia†; Medochemie, Rus.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Selen *Fresenius Kabi, Austria.*
Sodium selenite (p.1961·1).
Dietary supplement.

Selenarell *Sanorell, Ger.*
Homoeopathic preparation.

Selenase *Richter, Austria; Biosyn, Cz.; Biosyn, Ger.; Biosyn, Neth.; Overfarma, Port.; Biosyn, Switz.; Er-Kim, Turk.; Oxford Nutrition, UK.*
Sodium selenite (p.1961·1).
Dietary supplement; selenium deficiency.

Selene
Note. This name is used for preparations of different composition.
Eurofarma, Braz.
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Androgenic symptoms in women; polycystic ovary syndrome.

Vivax, Venez.
dl-Alfa tocoferil acetate; selenium yeast (p.1922·1).
Selenium deficiency; vitamin E deficiency.

Selene-Activ *Wassen, UK.*
Selenium (p.1961·1); broccoli extract; vitamin C; vitamin E; thioctic acid; zinc (p.1922·1).
Dietary supplement.

Selenil *Vita, Venez.*
Selenium sulfide (p.1613·1); sulfur (p.1614·1).
Dandruff.

Selenio Composto *Catarinense, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Selenion *Labcatal, Fr.*
Selenium (p.1961·1).
Muscular disorders; skin disorders.

Selenium Bonus *Lifeplan, UK.*
Selenium; chromium; zinc; vitamins (p.1922·1).
Antoxidant preparation.

Selenium Complexe no 99 *Lehning, Fr.*
Homoeopathic preparation.

Selenium Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Selenium Plus *Sisu, Canad.*
Selenium (p.1961·1); methionine (p.1450·1).

Selenium Vitaplus *Swiss Bio, Malaysia†.*
Multivitamin and mineral preparation with selenium yeast (p.1922·1).
Dietary supplement.

Selenium + Zinc *Pharma Nord, Fr.*
Selenium; zinc; vitamins (p.1922·1).

Selenium-ACE *Merck Medication Familiale, Fr.; Wassen, Ital.; Angelini, Port.†.*
Selenium yeast (p.1961·1); vitamins A,C, and E (p.1922·1).
Nutritional supplement.

Selenium-ACE Extra *Angelini, Port.†.*
Selenium; vitamins; manganese; thioctic acid (p.1922·1).
Nutritional supplement.

Selenix *Novartis Consumer, Port.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor.

Selen-loges *Loges, Ger.*
Sodium selenite (p.1961·1).
Selenium deficiency.

Selenokehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Selenol *Propharma, Denm.*
Selenium sulfide (p.1613·1).
Pityriasis versicolor; seborrhoeic dermatitis.

Selen-Wied *Wiedemann, Ger.*
Homoeopathic preparation.

Sele-Pak *Smith & Nephew SoloPak, USA.*
Selenious acid (p.1961·1).
Parenteral nutrition.

Seleparina *Italfarmaco, Ital.*
Nadroparin calcium (p.1346·1).
Thrombosis prophylaxis.

Selepark *Betapharm, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selepen *APP, Hong Kong; American Pharmaceutical, USA.*
Selenious acid (p.1961·1).
Parenteral nutrition.

Seler *Pasteur, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Selerin *Cipla, India; Anpharm, Pol.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Seles Beta *Schwarz, Ital.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Selexid
Leo, Austria; Leo, Belg.†; Leo, Canad.†; Leo, Fin.; Leo, Fr.; CSL, NZ; Leo, NZ.
Pivmecillinam hydrochloride (p.317·2).
Bacterial infections.

Leo, Denm.; Leo, Norw.; Leo, Swed.
Mecillinam (p.297·1) or pivmecillinam hydrochloride (p.317·2).
Bacterial infections.

Leo (Λεω), Gr.
Mecillinam (p.297·1).
Bacterial infections.

Leo, UK.
Pivmecillinam (p.317·1) or pivmecillinam hydrochloride (p.317·2).
Bacterial infections of the urinary tract.

Selezen *Teofarma, Ital.*
Imidazole salicylate (p.66·3).
Fever; inflammation; pain.

Selfide *TO-Chemicals, Thai.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis.

Selg *Promefarm, Ital.*
Macrogol 4000 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation; constipation.

Selgene *Alphapharm, Austral.; Pacific, NZ†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selg-Esse *Promefarm, Ital.*
Macrogol 4000 (p.2336·3); simeticone (p.1770·2); electrolytes (p.1667·1).
Bowel evacuation.

Selgimed *Hennig, Ger.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selgin *Intas, India; Polfa Pabianice, Pol.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selgina *Andromaco, Chile.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selgine *Teofarma, Fr.*
Sodium chloride (p.1686·1); sea salt.
Mouth disorders.

Selgres *ICN, Pol.*
⊗ Selegiline (p.818·1).
Parkinsonism.

Selimax *Libbs, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Selimax Pulso *Libbs, Braz.*
Azithromycin (p.207·1).
Acne.

Seline *Berlin Pharm, Thai.†.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Selinol *Orion, Swed.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Selipran *BMS, Austria; BMS, Switz.*
Pravastatin sodium (p.1374·3).
Coronary atherosclerosis; hypercholesterolaemia.

Sellon *Unison, Malaysia.*
Selenium sulfide (p.1613·1).
Dandruff; seborrhoeic dermatitis.

Selm *Kener, Mex.*
Methyldopa (p.1334·1).
Hypertension.

Selmac *Prosel, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Selmevit *Farmstandart, Rus.*
Vitamins; minerals; rutoside; thioctic acid; methionine (p.1922·1).

Selobloc *Lagap, Switz.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Selocomp ZOC *Pfizer, Fin.*
⊗ Metoprolol succinate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selofen *Adamed, Pol.*
Zaleplon (p.1035·3).
Insomnia.

Selokeen *AstraZeneca, Neth.*
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Seloken
AstraZeneca, Austria; AstraZeneca, Mex.
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Indon.; AstraZeneca, Ital.; AstraZeneca, Jpn; AstraZeneca, Norw.; AstraZeneca, Swed.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; cardiomyopathy; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction; tremor.

Seloken retard Plus *Sanova, Austria.*
⊗ Metoprolol succinate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Seloken ZOC *AstraZeneca, Fin.; AstraZeneca, Swed.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; migraine; myocardial infarction.

Seloken ZOC/ASA *AstraZeneca, Fin.†; Hassle, Swed.†.*
⊗ Tablets, metoprolol succinate (p.1338·1); tablets, aspirin (p.20·3).
Angina pectoris; myocardial infarction.

Selokomb *Pfizer, Neth.*
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selon
Note. This name is used for preparations of different composition.
Truw, Ger.
Valerian (p.2410·1); lupulus (p.2335·2).
Agitation; sleep disorders.

Genepharm, Gr.
Citalopram (p.385·3).
Depression.

Selopral *Orion, Fin.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Selopres
AstraZeneca, India.
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

AstraZeneca, Mex.
⊗ Metoprolol succinate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selopresin *Pharmacia, Spain†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selopress *AstraZeneca, Braz.*
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selozide *Pfizer, Belg.; Pharmacia, Ital.†.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Selo-Zok *AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Denm.; AstraZeneca, Norw.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction; tremor.

Selozok *AstraZeneca, Fr.*
⊗ Metoprolol succinate (p.1338·1).
Heart failure.

Selpiran *Diba, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Selpiran Compuesto *Diba, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Selpiran-S *Diba, Mex.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Sels Calcaires Nutritifs *Weleda, Fr.*
Combination pack: Homoeopathic preparation.

Selso *Luchon, Fr.*
Sodium chloride (p.1686·1); sulfur (p.1614·1).
Nasal irrigation.

Selsun *Abbott, Arg.†; Church & Dwight, Austral.; Abbott, Austria; Tramedico, Belg.; Farmasa, Braz.; Chattem, Canad.; Volta, Chile; Abbott, Denm.†; Berren, Fin.; Pharmadeveloppement, Fr.; Chattem, Ger.; Abbott, Gr.; Mentholatum, Hong Kong; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Malaysia†; Carter, NZ; Wilson, NZ; Chattem, Neth.; Abbott, Norw.; Chattem, Pol.; Abbott, S.Afr.†; Vitaflo, Swed.; Vifor, Switz.; Chattem, Thai.; Chattem, UK; Chattem, USA.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis; tinea capitis; tinea versicolor.

Selsun Blu *Corman, Ital.*
Selenium sulfide (p.1613·1).
Dandruff.

Selsun Blue *Abbott, Philipp.*
Selenium sulfide (p.1613·1).
Dandruff; seborrhoeic dermatitis; tinea versicolor.

Selsun Plus *Abbott, Ital.†.*
Selenium sulfide (p.1613·1); menthol (p.2340·1).
Dandruff.

Selsun with Provitamin B_5 *Abbott, Canad.†.*
Selenium sulfide (p.1613·1); panthenol (p.2362·1).

Seltoc *Apomedica, Austria.*
Ethenzamide (p.51·3); diphenhydramine hydrochloride (p.577·2); quinine hydrochloride (p.612·3); ascorbic acid (p.1983·3).
Cold symptoms.

Seltomylon *Diba, Mex.†.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Seltouch *Teikoku Seiyaku, Jpn.*
Felbinac (p.54·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Seltrans *Stada, Ger.*
Sodium selenite (p.1961·1).
Selenium deficiency.

Seltrex *Abbott, Venez.†.*
Selenium sulfide (p.1613·1).
Dandruff.

Selukos *Meda, Fin.; Ipex, Ger.†; Ipex, Norw.; Ipex, Swed.*
Selenium sulfide (p.1613·1).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis of the scalp.

Selva N *Unipharma, Gr.†.*
Sodium chloride (p.1686·1).
Nasal congestion.

Selviclor *Selvi, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Selvigon *Asta Medica, Braz.; Sanfer, Mex.*
Pipazetate hydrochloride (p.1570·3).
Cough.

Selvjgon *Sanofi-Aventis, Ital.*
Pipazetate hydrochloride (p.1570·3).
Coughs.

Selvon-C *Prosel, Philipp.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Selxan *Prosel, Philipp.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Selzef *Prosel, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Selzentry *Pfizer, USA.*
Maraviroc (p.897·3).
HIV infection.

Semap *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.†; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.†; Janssen-Cilag, Israel; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Switz.*
Penfluridol (p.1015·3).
Psychoses; schizophrenia.

Semax *Andromaco, Chile†.*
Citalopram (p.385·3).
Depression.

Semble *Merisant, Arg.*
Saccharin sodium (p.1960·3); aspartame (p.1930·1).
Formerly contained saccharin sodium, cyclamate, and sucrose.
Sugar substitute.

Semeth *Greater Pharma, Thai.*
Simeticone (p.1770·2).
Flatulence; meteorism; preparation of gastrointestinal tract for radiological examination or gastroscopy.

Semicid *Whitehall, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Semicillin *Zentiva, Hung.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Semid *Erfar, Gr.*
⊗ Furosemide (p.1292·1).

Semi-Daonil *Aventis, Austral.; Aventis, Hong Kong†; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Port.; Aventis, Switz.; Sanofi-Aventis, UK†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Semi-Euglucon *Roche, Austria; Roche, Fin.; Roche, Hong Kong; Nicholas Piramal, India; Roche, Philipp.; Roche, Port.†; Roche, Switz.†; Roche, Thai.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Semi-Euglucon N *Aventis, Ger.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Semiglen *Biochemie, Austria†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Semi-Glycigon *Aristo, India.*
Gliclazide (p.440·3).
Diabetes mellitus.

Semilente *Novo Nordisk, Ger.†.*
⊗ Insulin zinc suspension (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Semilente MC *Novo Nordisk, Switz.*
⊗ Insulin zinc suspension (amorphous) (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Semipenil *Magis, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Semper *Novartis, Fin.*
Range of nutritional preparations (p.1922·1).

Sempera *Janssen-Cilag, Ger.*
Itraconazole (p.536·3).
Fungal infections.

Semprex *GSK, Austria; GSK, Cz.†; GSK, Fin.†; Pfizer, Fin.†; GSK, Hong Kong; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Philipp.; Glaxo Wellcome, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.†; GSK, Turk.*
Acrivastine (p.566·1).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; angioedema; eczema; urticaria.

Semprex-D *Celltech, USA.*
Acrivastine (p.566·1); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Semuele *Doctum, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Senade *Cipla, India.*
Calcium sennosides (p.1769·3).
Constipation.

Senadex *Biolink, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Senagar *Sigma, Austral.†.*
Senega (p.1572·3); ammonium bicarbonate (p.1551·3); camphor (p.2273·2).
Coughs.

Senalax
Note. This name is used for preparations of different composition.
Naturprodukt, Cz.
Senna (p.1769·2); liquorice (p.1740·3); peppermint (p.1761·2); melissa (p.2339·3); betula (p.2266·3); equisetum (p.2299·3).
Constipation.

Cipla, India; Hasco-Lek, Pol.
Calcium sennosides (p.1769·3).
Constipation.

Senalax K *Hasco-Lek, Pol.*
Frangula bark (p.1732·2); senna (p.1769·2).
Constipation.

Senalina *Omega, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Senalsor *Soria Natural, Spain†.*
Senna (p.1769·2); althaea (p.2253·3); fennel (p.2302·3).
Constipation.

Senan *Ativus, Braz.*
Senna (p.1769·2).
Constipation.

Sencia *Konsuma, Venez.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Sendafur *Andromaco, Venez.†.*
Furazolidone (p.834·3); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Sendicol *Coronet, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Sendoxan *Baxter, Denm.; Baxter, Fin.; Baxter Oncology, Norw.; Baxter, Swed.*
Cyclophosphamide (p.702·1).
Immune system disorders; malignant neoplasms.

Sene *Herbarium, Braz.*
Senna (p.1769·2).
Constipation.

Sene Composta *Infabra, Braz.†.*
Senna (p.1769·2); cassia (p.1715·3); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Senefol *Labofarm, Pol.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Senega and Ammonia *McGloin, Austral.*
Ammonium bicarbonate (p.1551·3); camphor (p.2273·2); liquorice (p.1740·3); senega root (p.1572·3); ammonia solution (p.2256·1).
Cold symptoms.

Seneuval *Qualiphar, Belg.*
Valerian (p.2410·1); passion flower (p.2363·2); crataegus (p.2289·1).
Insomnia; nervousness.

Senexon
Note. This name is used for preparations of different composition.
Gador, Arg.†.
Betacarotene; vitamin E; vitamin C (p.1922·1).
Dietary supplement in vascular disease.

Drugtech, Chile.
Venlafaxine (p.430·1).
Depression.

Rugby, USA.
Sennosides (p.1769·3).
Constipation.

Senexon E *Gador, Arg.†.*
d-Alpha tocoferil acetate (p.1992·3).
Cardiovascular and neurological disorders; vitamin E deficiency.

Senexon Plus *Gador, Arg.*
Betacarotene; vitamin E; vitamin C; selenium; zinc; manganese; copper (p.1922·1).
Antoxidant preparation.

Senflam *Essenpharma, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Sengobil *Plusandex, Venez.*
Ginkgo biloba (p.2311·1); ginseng (p.2312·1).
Circulatory insufficiency; erectile dysfunction; fatigue; mental function impairment.

Senicor *Duopharm, Ger.†.*
Crataegus (p.2289·1).
Heart failure.

Senidrin
Note. This name is used for preparations of different composition.
Unipharm, Mex.
Capsules; tablets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Respiratory-tract disorders.

Unipharm, Mex.
Syrup: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Senikolp *Leiras, Fin.†.*
Sodium estrone sulfate (p.2101·2); estradiol (p.2097·2); broxyquinoline (p.215·3).
Menopausal disorders; oestrogen deficiency.

Senilezol *Edwards, USA.*
Vitamin B substances with iron (p.1922·1).

Senior Multi-One *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Senioral *Belmac, Spain.*
Clocinizine hydrochloride (p.574·1); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract congestion.

Seniospray *Rimafar, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2); chlorphenamine maleate (p.571·3).
Nasal congestion.

Seniovita aktiv *Cesra, Ger.*
Homoeopathic preparation.

Senirex *Algol, Fin.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Senlax *Elmor, Venez.*
Sennosides (p.1769·3).
Constipation.

Senna Plus *Contract Pharmacal, USA.*
Docusate sodium (p.1725·1); sennosides (p.1769·3).
Constipation.

Senna Prompt *Konsyl, USA.*
Sennosides (p.1769·3); ispaghula (p.1737·1).
Constipation.

Senna Smooth *Novartis Consumer, USA.*
Sennosides (p.1769·3).
Constipation.

Senna-Gen *Goldline, USA.*
Senna (p.1769·2).
Constipation.

Sennalax *Lennon, S.Afr.*
Senna (p.1769·2).
Constipation.

SennaPlus *Fleet, Austral.†.*
Senna (p.1769·2).
Constipation.

Sennaprep *Pharmascience, Canad.*
Senna (p.1769·2).
Constipation.

Sennapur *Pharmia, Fin.*
Senna (p.1769·2).
Constipation.

Senna-S
Tanta, Canad.
Senna (p.1769·2); docusate sodium (p.1725·1).
Constipation.

Akyma, USA.
Docusate sodium (p.1725·1); sennosides (p.1769·3).
Constipation.

Senna-Specie Composta *Dynacren, Ital.†.*
Senna (p.1769·2); peppermint leaf (p.1761·2); chamomile (p.2279·3); fennel (p.2302·3).
Constipation.

Sennatab *Pharmascience, Canad.*
Senna (p.1769·2).
Constipation.

Sennesoft *Herron, Austral.*
Docusate sodium (p.1725·1); sennosides (p.1769·3).
Constipation.

Sennetabs *Herron, Austral.*
Sennosides (p.1769·3).
Constipation.

Sennocol *Viatris, Neth.*
Senna (p.1769·2).
Constipation.

Sennove Lusky *Leros, Cz.*
Senna (p.1769·2).
Constipation.

Sennovy List *Megafyt-R, Cz.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Senociclin *Senosiain, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Senodin-AN *BMS, Ital.*
Pheniramine maleate (p.587·3); codeine phosphate (p.37·2).
Coughs.

Senokot
Reckitt Benckiser, Austral.; Reckitt Benckiser, Irl.; Novartis, Mex.; Reckitt Benckiser, NZ; Reckitt Benckiser, S.Afr.; Reckitt Benckiser, Thai.; Konsuma, Venez.
Sennosides (p.1769·3).
Bowel evacuation; constipation.

Reckitt Benckiser, Belg.; Purdue, Canad.; Viatris, Fr.; Reckitt Benckiser, Hong Kong; Reckitt Benckiser, Malaysia; Mundipharma, Norw.; Mundipharma, Philipp.; Pascual, Philipp.; Reckitt Benckiser, Singapore; Ali, Turk.; Reckitt Benckiser, UK; Purdue Frederick, USA.
Senna (p.1769·2).
Bowel evacuation; constipation.

Senokot Direct Relief *Reckitt Benckiser, UK.*
Glycerol (p.2314·2).
Constipation.

Senokot con Docusato *Konsuma, Venez.*
Sennosides (p.1769·3); docusate sodium (p.1725·1).
Constipation.

Senokot Dual Relief *Reckitt Benckiser, UK.*
Senna (p.1769·2); aloes (p.1705·2); cascara (p.1715·2); taraxacum (p.2395·1); fennel (p.2302·3).
Bloating; constipation.

Senokot con Fibra *Konsuma, Venez.†.*
Sennosides (p.1769·3); psyllium (p.1737·1); oat bran (p.1712·3).
Constipation.

Senokot-S *Purdue, Canad.; Purdue Frederick, USA.*
Senna (p.1769·2); docusate sodium (p.1725·1).
Constipation.

Senokotxtra *Purdue Frederick, USA.*
Senna (p.1769·2).
Constipation.

Senol
Note. This name is used for preparations of different composition.
Gemballa, Braz.†.
Allantoin (p.1588·1); aminoacridine (p.1625·2); cinchocaine hydrochloride (p.1857·3); benzocaine (p.1854·1); hydroxyquinoline sulfate (p.2323·1).
Skin disorders.

Bier, Ital.
Cetrimonium bromide (p.1635·1).
Nipple disinfection.

Senolax *Codilab, Port.*
Sennosides A and B (p.1769·3).
Constipation.

Senophile
Note. This name is used for preparations of different composition.
Braun, Belg.; Braun, Fr.†.
Cholesteryl benzoate (p.2029·1); zinc oxide (p.1621·2).
Skin irritation.

Prima, Braz.†.
Ointment: Bismuth subnitrate (p.1711·2).

Prima, Braz.†.
Topical powder: Bismuth subnitrate (p.1711·2); bismuth subgallate (p.1711·1); boric acid (p.2268·1); zinc oxide (p.1621·2).
Skin disorders.

Senorm *Sun, Rus.*
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).

Senosan *Cos Farma, Ital.*
Emollient.

Senpivac *Harson, Philipp.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Senro *Biosarto, Spain.*
Norfloxacin (p.309·2).
Genito-urinary tract infections.

Sensaid *Dentaid, Chile.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental hypersensitivity.

Sensamol *Perrigo, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Sensaton *Temis, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Sensaval *Lundbeck, Swed.*
Nortriptyline hydrochloride (p.413·2).
Depression.

Sensibaby *Ducto, Braz.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2); zinc (p.1999·1).
Skin disorders.

Sensibio
Note. This name is used for preparations of different composition.
Dispolab, Chile; Bioderma, Fr.; Bioderma, Venez.
A range of emollients and soap substitutes.
Skin disorders.

Farmanic, Gr.
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Sensibio DS *Bioderma, Venez.*
Piroctone olamine (p.1610·1); climbazole (p.529·3); sorbitan undecenoate; enoxolone (p.50·1).
Seborrhoeic skin disorders.

Sensibit *Liomont, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Sensibit D *Liomont, Mex.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; nasal congestion.

Sensibit XP *Liomont, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Cough; respiratory-tract congestion.

SensiBloq *Biomedis, Philipp.*
Levobupivacaine hydrochloride (p.1862·1).
Local anaesthesia; pain.

Sensicutan *Harras-Curarina, Austria; Harras-Curarina, Cz.; Harras-Curarina, Ger.*
Levomenol (p.2333·3); heparin sodium (p.1301·2).
Skin disorders.

Sensident *Leti, Venez.†.*
⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3).
Hypersensitive teeth.

Sensiderme *Neo Quimica, Braz.*
Nitrofurazone (p.309·1).
Bacterial skin infections.

Sensifluid *Ducray, Fr.*
Avena (p.2262·1).
Soap substitute.

Sensigard *Copernico, Ital.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sensigel
Note. This name is used for preparations of different composition.
Pierre Fabre Oral Care, Arg.; Pierre Fabre Sante, Fr.; Pierre Fabre, Rus.; Pierre Fabre Sante, Singapore.
⊗ Nicomethanol hydrofluoride (fluorinol) (p.1963·3); potassium nitrate (p.1658·3).
Hypersensitive teeth; sensitive gums.

Pergam, Ital.
Allantoin (p.1588·1); vitamin A; vitamin E; lactic acid (p.2329·3).
Vaginal lubricant.

Sensikol *Nufarindo, Indon.*
Essential phospholipids; vitamin B substances; vitamin E (p.1922·1).
Hypercholesterolaemia.

Sensilacer *Andromaco, Chile†.*
⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3).
Caries prophylaxis; dental hypersensitivity.

Sensilube *CCD, Fr.*
Polyacrylamide; phenoxyethanol; nipastat; citric acid.
Instrument lubricant; vaginal lubricant.

Sensinerv forte *Cesra, Ger.†.*
Valerian root (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Sensiotin *Steigerwald, Ger.*
Homoeopathic preparation.

Sensipar *Amgen, Austral.; Amgen, Canad.; Amgen, NZ; Amgen, USA.*
Cinacalcet hydrochloride (p.1095·1).
Hypercalcaemia in parathyroid cancer; hyperparathyroidism in dialysis patients with end-stage renal disease.

Sensipharma *Alpharma, Mex.*
Lidocaine (p.1862·3).
Local anaesthesia.

Sensiquell *Pergam, Ital.*
Milk protein; allantoin (p.1588·1); lactic acid (p.2329·3).
Maintenance of vaginal pH.

Sensit *Organon, Austria†; UCB, Ger.; Organon (Οργανον), Gr.*
Fendiline hydrochloride (p.1286·1).
Angina pectoris; ischaemic heart disease.

Sensitex *Kinder, Braz.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Sensitiner *Statens Serum Institut, Denm.*
Antigens from *Mycobacterium* spp. (p.2250·2).
Diagnosis of mycobacterial infections.

2Sensitive *Agys, Singapore†.*
⊗ Sodium fluoride (p.1962·2); strontium chloride (p.2393·1); potassium nitrate (p.1658·3).
Receding gums; sensitive teeth.

Sensitive Eyes *Bausch & Lomb, Canad.; Bausch & Lomb, NZ; Bausch & Lomb, USA.*
Range of solutions for contact lenses (p.1622·2).

Sensitivity Protection Crest *Procter & Gamble, USA.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Sensitive teeth.

Sensitram *Libbs, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Sensival *Wallace, India.*
Nortriptyline hydrochloride (p.413·2).
Bipolar disorder; depression.

Sensivision au plantain *Chauvin, Fr.*
Ribwort plantain (p.2379·1).
Eye irritation.

Sensocet *Sensomed, Philipp.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Sensodent *Doetsch, Grether, Switz.†.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Sensodyne
Note. This name is used for preparations of different composition.
GSK Consumer, Canad.
Strontium chloride (p.2393·1).
Hypersensitive teeth.

GSK Consumer, Venez.
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Antisarro *GSK, Arg.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2); tetrapotassium pyrophosphate.
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Antitartaro *GSK, Braz.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Sensodyne Bicarbonato de Sodio *GSK, Arg.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2); sodium bicarbonate (p.1673·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne C/Bicarbonato de Sodio *GSK, Braz.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Sensodyne Cool *Stafford-Miller, Braz.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Formula Original *GSK, Braz.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Sensodyne Fresh Mint *GSK, Braz.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Sensodyne med *GSK, Austria.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Sensodyne Mint
Note. This name is used for preparations of different composition.
Ali, Turk.
Strontium chloride (p.2393·1).
Hypersensitive teeth.

GSK, UK.
Sodium fluoride (p.1962·2); strontium acetate.
Hypersensitive teeth.

Sensodyne Original *GSK, Arg.; GSK, UK.*
Strontium chloride (p.2393·1).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne Protecao Total *GSK, Braz.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Sensodyne Proteccion Total *GSK, Arg.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne-F
Note. This name is used for preparations of different composition.
GSK, Arg.; Stafford-Miller, Braz.; Block, USA.
⊗ Potassium nitrate (p.1658·3); sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis; hypersensitive teeth.

GSK Consumer, Canad.
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Ali, Turk.
Potassium chloride (p.1684·3); sodium monofluorophosphate (p.1964·3).
Hypersensitive teeth.

Stafford-Miller, UK.
Potassium chloride (p.1684·3); sodium fluoride (p.1962·2); triclosan (p.1665·2).
Dental caries prophylaxis; hypersensitive teeth.

Sensodyne-F Gel *Ali, Turk.*
⊗ Potassium nitrate (p.1658·3); sodium fluoride (p.1962·2).
Hypersensitive teeth.

Sensodyne-SC *Block, USA.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

SensoGARD *Block, USA.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

Sensolid *Remedina, Gr.*
Lidocaine (p.1862·3).
Local anaesthesia.

Sensorcaine *AstraZeneca, Canad.; AstraZeneca, India; AstraZeneca, Philipp.; Astra, USA.*
⊗ Bupivacaine hydrochloride (p.1854·3).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Sens-Out *Defuen, Arg.†.*
⊗ Sodium fluoride (p.1962·2); potassium nitrate (p.1658·3).
Hypersensitive teeth.

Sensu *Bausch & Lomb, Arg.*
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis.

Sensur
Note. This name is used for preparations of different composition.
Glenmark, India.
Liniment: Menthol (p.2340·1); camphor (p.2273·2); menthol oil; eucalyptus oil (p.2301·2); clove oil (p.2285·1); cinnamon oil (p.2283·2).
Low back pain.

Glenmark, India.
Lotion: Menthol (p.2340·1); camphor (p.2273·2); menthol oil; eucalyptus oil (p.2301·2); clove oil (p.2285·1); cinnamon oil (p.2283·2); sweet birch oil (p.86·2).
Osteoarthritis.

Glenmark, India.
Topical oil: Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); sweet birch oil (p.86·2).
Rhinitis; sinusitis.

Sentapen *Biogalenic, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sentidol *Medipharm, Chile.*
Venlafaxine (p.430·1) or venlafaxine hydrochloride (p.427·3).
Anxiety; attention-deficit hyperactivity disorder; depression.

Sentinel Ulcer Mixture *Martyn, S.Afr.*
Bismuth and ammonium citrate (p.1712·1); dilute hydrochloric acid (p.2322·1); pepsin (p.2365·1); vitamin B (p.1980·2).
Peptic ulcer.

Sentionyl *ACME, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Senti-Scint *Medi-Radiopharma, Cz.*
⊗ Technetium-99m (p.2055·3) labelled human albumin.
Diagnosis of breast cancer and melanoma; radionuclide imaging of lymphatic system.

Sentril *Biomedis, Indon.; Medifarma, Indon.; Biomedis, Thai.; Great Eastern, Thai.*
Dequalinium chloride (p.1641·3); cetylpyridinium chloride (p.1635·1); ascorbic acid (p.1983·3).
Mouth and throat disorders.

Sentyl *Sunthi Sepuri, Indon.*
Secnidazole (p.846·3).
Amoebiasis; trichomoniasis.

Sepan *Janssen-Cilag, Denm.*
Cinnarizine (p.573·1).
Allergic rhinitis; hay fever; motion sickness; urticaria.

Sepatrem *Leciva, Cz.†.*
⊗ Selegiline hydrochloride (p.817·1).
Alzheimer's disease; anorexia nervosa; bulimia nervosa; depression; obsessive-compulsive disorder; panic disorder; parkinsonism; phobias; post-traumatic stress disorder.

Sepatren *Sumitomo, Jpn.*
Cefpiramide sodium (p.231·2).
Bacterial infections.

Sepcen *Centrum, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Sepdine *PD, Thai.†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin, instrument, and wound disinfection.

Sepex *Key, Arg.†.*
Ceftibuten (p.235·3).
Bacterial infections.

Sepexin
Note. This name is used for preparations of different composition.
Hetero, India.
Cefalexin (p.218·2).
Bacterial infections.

Schering-Plough, S.Afr.†; Schering-Plough, Venez.†.
Ceftibuten (p.235·3).
Bacterial infections.

Sepfadine *TNP, Thai.†.*
Povidone-iodine (p.1659·2).
Burns; skin and soft-tissue disinfection; wounds.

Sephros *YSP, Malaysia†.*
Cefradine (p.233·1).
Bacterial infections.

Sepia *Wermar, Mex.*
Itraconazole (p.536·3); secnidazole (p.846·3).
Parasitic infections.

Sepia Complexe no 20 *Lehning, Fr.†.*
Homoeopathic preparation.

Sepibest *Best, Mex.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias; polydipsia; polyuria.

Sepmax *GSK, India.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Se-Power *Cantassium Co., UK.*
Selenium yeast (p.1961·1); myrtillus (p.2349·3); euphrasia (p.2301·3); vitamin E (p.1992·2); zinc gluconate (p.1999·2); vitamin A (p.1971·2); riboflavin (p.1977·2).

Seprafilm *Genzyme, UK; Genzyme, USA.*
Sodium hyaluronate (p.2320·1); carmellose (p.2142·1).
Prevention of surgical adhesions.

Sepram
Lundbeck, Austria†.
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Depression; obsessive-compulsive disorder; panic attacks.

Lundbeck, Cz.†.
Citalopram hydrochloride (p.385·3).
Agoraphobia; depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Fin.; Lundbeck, Ger.†.
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Seproc *PH&T, Gr.*
Citalopram (p.385·3).
Depression.

Sepsilem *Lemery, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Sepso J *Hofmann & Sommer, Ger.*
Povidone-iodine (p.1659·2).
Burns; infected skin disorders; skin, hand, and mucous membrane disinfection; wounds.

Sepsol *Upha, Malaysia†.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Septacare *Teva, Israel†.*
Chlorhexidine acetate (p.1635·2); cetrimide (p.1634·1).
Burns; genito-urinary disinfection; skin disinfection; wounds.

Septacef *Septa, Spain.*
Cefradine (p.233·1).
Bacterial infections.

Septacin *Chinoin, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Septacin Amoxi *Chinoin, Mex.*
Ambroxol hydrochloride (p.1550·3); amoxicillin trihydrate (p.202·2).
Respiratory-tract infections.

Septacin Ex *Chinoin, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Septacord *Muller Goppingen, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1); crataegus (p.2289·1).
Cardiac disorders.

Septadine
Note. This name is used for preparations of different composition.
Prafa, Indon.; Be-Tabs, S.Afr.
Povidone-iodine (p.1659·2).
Minor throat infections; mouth infections; skin disinfection; skin infections; vaginal infections; wound and burn disinfection; wounds.

Floris, Israel.
⊗ Alcohol (p.1625·2); chlorhexidine (p.1635·2).
Skin disinfection.

Septadine Scrub *Floris, Israel.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Septal *Teva, Israel.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Septalan *Chema-Elektromet, Pol.*
Allantoin (p.1588·1); acriflavinium chloride (p.1625·1).
Burns; psoriasis; ulcers; wounds.

Septalibour *Ducray, Fr.†.*
Avena (p.2262·1); copper sulfate (p.1935·3); zinc sulfate (p.1999·2).
Cleansing of atopic skin.

Septalone *Teva, Israel.*
Chlorhexidine gluconate (p.1635·3).
Burns; disinfection in obstetrics; skin and instrument disinfection; wounds.

Septanest *Schein, Austria; Septodont, Denm.; Ogna, Ital.; Ivoclar, NZ; Pharmodontal, Neth.; Septodont, Port.; Septodont, Switz.; Depro-co, UK.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septanest S *Septodont, Cz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septax *Vianex (Βιανέξ), Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Septeal *Pierre Fabre, Fr.*
Chlorhexidine gluconate (p.1635·3).
Skin and wound disinfection.

Septi-Aid *Pharmaniaga, Malaysia.*
Povidone-iodine (p.1659·2).
Skin and wound disinfection.

Septiane *Roche-Posay, Fr.*
Sunflower seed acid; coconut acid; glycerol (p.2314·2); triclosan (p.1665·2).
Cleanser for sensitive skin.

Septiapaisyl *Merck Medication Familiale, Fr.*
Chlorhexidine gluconate (p.1635·3).
Burn, skin, and wound disinfection.

Septibiotic *Sidus, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

Septi-Bosan *Bock, Ger.†.*
Homoeopathic preparation.

Septicide *Bago, Arg.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Septicol *Streuli, Switz.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Septidiaryl *McNeil, Fr.*
Nifuroxazide (p.307·2).
Diarrhoea.

Septidine *Osoth, Thai.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, burns, and umbilicus.

Septidron *Aventis, S.Afr.†.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Septigyn *Montpellier, Arg.*
Metronidazole (p.837·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); centella (p.1592·3).
Vulvovaginal infections.

Septil *Azevedos, Port.*
Povidone-iodine (p.1659·2).
Burns; skin disinfection; skin infections; ulcers; wounds.

Septilisin
Note. This name is used for preparations of different composition.
Bago, Arg.
Cefalexin (p.218·2).
Bacterial infections.

Grin, Mex.
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial eye infections.

Septinor *IAE, Philipp.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Septiolan *Climax, Braz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Septisan
Note. This name is used for preparations of different composition.
Zentiva, Cz.
2-Aminotridecane adipate.
Upper respiratory-tract disorders.

Cederroth, Spain.
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin, burns, and wounds.

Septi-Soft *Calgon Vestal, USA†.*
Triclosan (p.1665·2).
Skin cleanser.

Septisol
Note. This name is used for preparations of different composition.
Calgon Vestal, USA†.
Foam: Hexachlorophene (p.1646·1).
Skin disinfection.

Calgon Vestal, USA†.
Solution: Triclosan (p.1665·2).
Skin cleanser; skin disinfection.

Septison *Orion, Fin.*
⊗ Prednisolone (p.1540·3); dequalinium chloride (p.1641·3).
Skin disorders.

Septisooth *Pharmachoice, S.Afr.*
Povidone-iodine (p.1659·2).
Burns; skin infections; ulcers; wounds.

Septivon *Omega, Fr.*
Chlorhexidine gluconate (p.1635·3).
Formerly contained triclocarban and detergents.
Skin and mucous membrane disinfection.

Septivon N *Interdelta, Switz.*
Triclocarban (p.1665·2); cetrimonium chloride (p.1635·1).
Hand disinfection; minor skin lesions.

Septobore *Cooper (Κοπερ), Gr.*
⊗ Naphazoline nitrate (p.1565·2); boric acid (p.2268·1).
Ocular irritation.

Septocaine *Septodont, Denm.; Septodont, Fin.; Septodont, Norw.; Septodont, USA.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Septocipro *Lesvi, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Septocoll *Biomet, Ger.*
Collagen (bovine) (p.2286·1); gentamicin sulfate (p.282·1).
Haemorrhage; wounds.

Septofervex *BMS, Pol.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Septofort *Walmark, Cz.; BMS, Hung.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders; mouth and throat infections.

Septogal *Jadran, Rus.*
Benzalkonium chloride (p.1629·1); menthol (p.2340·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); thymol (p.1664·3).

Septol *Teva, Israel.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Septolete *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Benzalkonium chloride (p.1629·1); menthol (p.2340·1); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); thymol (p.1664·3).
Mouth and throat disorders.

Septolete Plus
KRKA, Pol.
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

KRKA, Rus.
Benzocaine (p.1854·1); cetylpyridinium bromide (p.1635·1).

Septolit *Henkel, Ger.†.*
Benzalkonium chloride (p.1629·1); oligo(di(iminoimidocarbonyl)iminohexamethylene).
Surface disinfection.

Septomandolo *IPA, Ital.†.*
Cefamandole nafate (p.220·3).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Septomixine *Septodont, Cz.; Septodont, Switz.*
⊗ Hydrocortisone acetate (p.1535·2); framycetin sulfate (p.279·1).
Dental infections.

Septone *Shiwa, Thai.†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Burns; skin and instrument disinfection; wounds.

Septonex
Note. This name is used for preparations of different composition.
Herbacos, Cz.
Ointment: Hexachlorophene (p.1646·1); carbaethopendecinium bromide (p.1633·3).
Infected skin disorders; ulcers; wounds.

Ivax, Cz.
Powder; spray; topical solution: Carbaethopendecinium bromide (p.1633·3).
Disinfection of surfaces, hands, skin, and mucous membranes; fungal skin infections; wounds.

Septonex Plus *Ivax, Cz.*
Trimecaine (p.1872·3); carbaethopendecinium bromide (p.1633·3).
Burns; wounds.

Septonsil *Pekana, Ger.†.*
Homoeopathic preparation.

Septopal *Merck, Arg.†; Biomet, Austral.; Merck, Austria; Biomet, Belg.; Merck, Braz.; Merck, Cz.†; Merck, Denm.; Biomet, Fin.; Biomet, Ger.; Galenica, Gr.†; Merck, Hong Kong; Merck, Hung.; Merck, India; Merck, Malaysia†; Ortomed, Neth.; Merck, Norw.; Merck, Philipp.; Merck, Port.; Merck, S.Afr.; Merck, Singapore†; Scandimed, Swed.†; Biomet, Switz.; Merck, Thai.; Biomet Merck, UK.*
Gentamicin sulfate (p.282·1); methylmethacrylate-methacrylate copolymer (p.2343·3).
Bacterial infections of bone and soft tissue.

Septosan
Note. This name is used for preparations of different composition.
Stiefel, Fr.
Triclocarban (p.1665·2); triclosan (p.1665·2).
Skin cleansing.

Stiefel, Mex.
Soap: Triclocarban (p.1665·2); triclosan (p.1665·2).
Skin cleansing.

Stiefel, Mex.†.
Topical lotion: Triclosan (p.1665·2).
Soap substitute.

Septosol *Xeragen, S.Afr.*
Phenol (p.1656·1).
Sore throat.

Septosyl *PannonPharma, Hung.*
Sulfadimidine (p.338·1).
Bacterial eye infections.

Septra *GSK, Canad.; Monarch, USA.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Septran *GSK, India; GSK, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Septrin *Sigma, Austral.; GSK, Chile; GSK, Gr.; Sigma, Hong Kong; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Mex.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Singapore†; UCB, Spain; GSK, Thai.†; Genesis, Turk.; GSK, UK.*
Co-trimoxazole (p.258·1).
Bacterial infections; nocardiosis; pneumocystis pneumonia; toxoplasmosis.

Septus *Merck, Port.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Sepurin *Gross, Braz.*
Methenamine (p.298·3); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

Sequacor *Bracco, Ital.*
⊗ Bisoprolol fumarate (p.1234·1).
Heart failure.

Sequals G *Lagos, Arg.*
Rosemary (p.2381·2); enebro (p.1616·1); crataegus (p.2289·1); birch (p.2266·3).
Scalp disorders.

Sequax *Ivax, Arg.*
Clozapine (p.981·1).
Schizophrenia.

Sequennia *Wyeth Lederle, Austria.*
14 Tablets, conjugated oestrogens (p.2087·2); 14 tablets, conjugated oestrogens; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders; osteoporosis.

Sequidot *Novartis, Cz.*
Phase I patch, estradiol (p.2097·2); phase II patch, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Sequilar *Schering, Austria; Schering, Ger.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Biphasic oral contraceptive.

Sequilar ED *Schering, Austral.*
21 Tablets, levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Biphasic oral contraceptive.

Sequinan *Ivax, Arg.*
Risperidone (p.1024·2).
Psychoses.

Sequostat *Jenapharm, Ger.†.*
6 Tablets, ethinylestradiol (p.2101·3); 15 tablets, ethinylestradiol; norethisterone acetate (p.2119·3).
Sequential oral contraceptive.

Ser Damla *Yenisehir, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Seraccel *Serum Institute, India†.*
⊗ Gelatin (p.1072·1).
Priming of heart-lung machine and artificial kidney; shock.

Seracic *IQFA, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Seracin *Pharmaland, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Seractil *Gebro, Austria; Gebro, Cz.; Galenica, Gr.; Gebro, Hung.; GiEnne, Ital.; Grunenthal, Neth.; Biofarm, Pol.; Jaba, Port.; Gebro, Spain; Gebro, Switz.; Genus, UK.*
Dexibuprofen (p.39·2).
Fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Seractiv *Nordic Drugs, Denm.; Nordic Drugs, Norw.*
Dexibuprofen (p.39·2).
Dysmenorrhoea; inflammation; musculoskeletal and joint disorders; osteoarthritis; pain.

Seradex-LA *Allegis, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Serag-HAES *Serag-Weissner, Cz.; Serag-Wiessner, Ger.*
⊗ Pentastarch (p.1065·1) in sodium chloride.
Haemodilution; hypovolaemia; plasma volume expansion.

Seraim *Anglo-French Drugs, India.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; inflammation; pericoronitis.

Seralbumin *Probifasa, Mex.†.*
⊗ Albumin (p.1052·1).
Hypoalbuminaemia; plasma volume expansion; shock.

Seralin *Eczacibasi, Turk.*
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Seralis *Landsteiner, Mex.*
Risedronate sodium (p.1103·3).
Osteoporosis; Paget's disease of bone.

Seralon *Pharmacypria, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Seramed *Medifive, Thai.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Seramine *Arlex, Mex.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Seranex N *Vifor, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Seranex sans codeine *Democal, Switz.†.*
Phenazone (p.116·1); propyphenazone (p.119·3); ethenzamide (p.51·3); benzyl mandelate (p.2264·3); caffeine (p.1116·3).
Pain.

Ser-Ap-Es *Novartis, Indon.; Novartis, Thai.; Ciba, USA†.*
⊗ Reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Seratil *Christo, Hong Kong.*
Prochlorperazine maleate (p.1020·1).
Anxiety; nausea and vomiting; psychoses.

Serato-M *Kee, India.*
Serrapeptase (p.2385·3).
Inflammation; oedema; respiratory-tract congestion.

Serato-M Forte *Kee, India†.*
Serrapeptase (p.2385·3); minerals (p.1922·1).
Inflammation; oedema.

Seravit *SHS, Fr.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Serax *Alpharma, USA.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety.

Seraxol *Serral, Mex.*
⊗ Ambroxol (p.1550·3); clenbuterol (p.1120·1).
Respiratory-tract congestion.

Seraxol-S *Serral, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Serbendazol *Serral, Mex.*
Albendazole (p.139·2).
Worm infections.

Serbo *SJA, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Serbol *IQFA, Mex.*
⊗ Ambroxol (p.1550·3); clenbuterol (p.1120·1).
Respiratory-tract congestion.

Serc *Solvay, Austral.; Solvay, Canad.; Solvay, Fr.; Solvay, Irl.; Altana, Mex.; Solvay, NZ†; Solvay, Philipp.; Solvay, S.Afr.; Solvay, Spain; Solvay, Thai.; Solvay, UK; Zuoz, Venez.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; vertigo; vestibular disorders.

Sercerin *Farmasa, Braz.†.*
Sertraline hydrochloride (p.421·3).
Depression.

Sercim *IQFA, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Serdep
Cipla, India; Cipla-Medpro, S.Afr.
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Fako, Turk.
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Serdol *Labormed, Rus.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Serdolect *Lundbeck, Austria; Lundbeck, Cz.; Lundbeck, Fr.; Lundbeck, Gr.; Lundbeck, Hung.; Lundbeck, Neth.; Lundbeck, Port.; Lundbeck, Rus.; Lundbeck, Switz.; Lundbeck, UK.*
Sertindole (p.1028·1).
Schizophrenia.

Serecid *Douglas, NZ.*
Hydroxyzine hydrochloride (p.581·2).
Alcohol withdrawal syndrome; anxiety; asthma; nausea and vomiting; urticaria.

Serecor *Sanofi-Aventis, Fr.*
Hydroquinidine hydrochloride (p.1312·1).
Arrhythmias.

Seredol *Atlantic, Philipp.*
Haloperidol (p.1000·2).
Behaviour disorders in children; neuroses; psychoses; Tourette syndrome.

Serefrex *Janssen-Cilag, Arg.†.*
Ketanserin (p.1320·2).
Hypertension.

Sereine *Optikem, USA.*
Range of solutions for hard contact lenses (p.1622·2).

Seremaks *Bilim, Turk.*
Ginkgolides (p.2311·3).

Serenace *Sigma, Austral.; Pfizer, Hong Kong; RPG, India; Pfizer, Indon.; Ivax, Irl.; Pharmacia, Malaysia†; Healthcare Logistics, NZ; Pfizer, Philipp.; Pharmacia, S.Afr.; Pharmacia, Singapore†; Ivax, UK.*
Haloperidol (p.1000·2).
Aggression; agitation; alcoholism; anxiety; behaviour disorders in children; bipolar disorder; hiccups; mania; nausea; neuroleptanalgesia; premedication; psychoses; tics; Tourette syndrome; vomiting.

Serenal *Meda, Port.*
Oxazepam (p.1014·2).
Anxiety.

Serenase
Note. This name is used for preparations of different composition.
Almirall, Belg.
Lorazepam (p.1004·1).
Anxiety; insomnia; premedication.

Janssen-Cilag, Denm.; Janssen-Cilag, Fin.
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Disturbed behaviour; movement disorders; nausea and vomiting; pain; psychoses.

Lusofarmaco, Ital.
Haloperidol (p.1000·2).
Alcohol withdrawal syndrome; hiccups; movement disorders; pain; psychoses; vomiting.

Serenata *Torrent, Braz.; Torrent, Philipp.; Torrent, Rus.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serene *Pharmaland, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Serenelfi *Lusofarmaco, Port.†.*
Haloperidol (p.1000·2).

Serengrav *Baldacci, Ital.*
Folic acid (p.1940·1).
Prevention of neural tube defects during pregnancy.

Serenil *Natufarma, Arg.*
Passion flower (p.2363·2); valerian (p.2410·1); tilia (p.2402·2).
Sedative.

Serenoa Complex *Blackmores, Austral.†.*
Equisetum (p.2299·3); saw palmetto (p.2192·3); buchu (p.2269·3); *d*-alpha tocoferil acid succinate (p.1993·1); zinc amino acid chelate (p.2000·1).
Prostate disorders; urinary-tract disorders.

Serenol *Dolisos, Canad.*
Homoeopathic preparation.

Serentil *Boehringer Ingelheim, USA†.*
Mesoridazine besilate (p.1007·1).
Alcoholism; behavioural and personality disorders; schizophrenia.

Serenus *Biolab Sanus, Braz.*
Passion flower (p.2363·2); crataegus (p.2289·1); adonis vernalis (p.2248·1).
Sedative.

Serepax *Sigma, Austral.; Wyeth, Chile†; Wyeth, Denm.; Wyeth, India; Akromed, S.Afr.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety; muscle spasm.

Serepress *Formenti, Ital.*
Ketanserin tartrate (p.1320·2).
Hypertension.

Sereprid *Labomed, Chile.*
Tiapride hydrochloride (p.1032·1).
Alcohol withdrawal syndrome; behaviour disorders; headache; movement disorders.

Sereprile *Sanofi-Aventis, Ital.*
Tiapride hydrochloride (p.1032·1).
Gastrointestinal dyskinesia; movement and behaviour disorders.

Sereprosta *Reprefar, Port.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sereprostat *Pierre Fabre, Arg.†; Robapharm, Spain.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia; prostatic adenoma.

Seresis *Boehringer Ingelheim, Chile; Pharmaton, Malaysia; Boehringer Ingelheim Promeco, Mex.*
Ascorbic acid; grape; tomato; selenium; vitamin E; betacarotene (p.1922·1).
Antoxidant; dietary supplement; skin disorders.

Seresta *Wyeth, Belg.; Biodim, Fr.; EuroCept, Neth.; Wyeth, Switz.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety; sleep disorders.

Serestill *Chemi, Ital.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Seretaide *Glaxo Wellcome, Port.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Seretide
GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; Allen & Hanburys, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; GSK, Venez.
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma; obstructive airways disease.

GSK, Philipp.
⊗ Salmeterol (p.1135·3) or salmeterol xinafoate (p.1135·1); fluticasone (p.1533·2) or fluticasone propionate (p.1533·2).
Obstructive airways disease.

Seretover *Iliafarm, Gr.*
Citalopram (p.385·3).
Depression.

Seretran *Drugtech, Chile.*
Paroxetine hydrochloride (p.414·2).
Depression.

Sereupin *Abbott, Ital.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Serevent *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; Allen & Hanburys, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; Glaxo Wellcome, Port.; Glaxo Wellcome, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; Allen & Hanburys, UK; Glaxo Wellcome, USA; GSK, Venez.*
⊗ Salmeterol xinafoate (p.1135·1).
Asthma; bronchospasm; obstructive airways disease.

Serezac *Pulitzer, Ital.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Serfinato *Basi, Port.†.*
Reserpine (p.1387·3).
Hypertension.

Serformin *Sandoz, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Sergast *Truw, Ger.†.*
Turmeric (p.1473·2).
Digestive system disorders.

Sergimax *Surge, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Seriane *Plantes et Medecines, Fr.*
Hydrolysed milk proteins (p.1922·1).
Stress.

Serianon *Fada, Arg.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Serimel *Clonmel, Irl.*
Sertraline hydrochloride (p.421·3).
Depression.

Serimol *Raza, Hong Kong; Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Paracetamol (p.108·1).
Fever; pain.

Serital *Temmler, Ger.*
Citalopram hydrobromide (p.385·3).
Depression.

Seritral *Serral, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Serivo *Pasteur, Chile.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder.

Serlain *Pfizer, Belg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorders.

Serlan *Rowex, Irl.*
Sertraline hydrochloride (p.421·3).
Depression.

Serless *Truw, Ger.†.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Serlife *Ranbaxy, S.Afr.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder.

Serlift *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Malaysia.*
Sertraline hydrochloride (p.421·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Serlina *Rontag, Arg.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serline *Giempi, Venez.*
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serlof *Kalbe, Indon.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Serlosane *Teva, Hung.*
Sertraline hydrochloride (p.421·3).
Depression.

Sermetrol *Serral, Mex.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Sermicina *Serral, Mex.*
Amikacin (p.200·2).
Bacterial infections.

Sermion *Pfizer, Arg.; Pfizer, Austria; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Sanofi-Aventis, Fr.; Pharmacia, Ger.†; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, Ital.; Tanabe, Jpn; Pfizer, Mex.; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, Rus.; Kenfarma, Spain; Pfizer, Switz.; Pfizer, Thai.; Carlo Erba, Turk.; Pfizer, Venez.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders; cerebral metabolic disorders; dementia; headache; hypertension; mental function impairment; vascular eye disorders; vestibular disorders.

Sermonil *Pharmaland, Thai.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis.

Sermoxol *Serral, Mex.*
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Sernade *Novell, Indon.*
Sertraline hydrochloride (p.421·3).
Depression.

Sern-SL *Lichtwer, Ger.*
Gentian (p.2310·3).
Disorders of digestion.

Serobid *Cipla, India.*
⊗ Salmeterol xinafoate (p.1135·1).
Asthma.

Serobif *Serono, Braz.; Serono, Ital.*
Interferon beta (p.891·2).
Malignant neoplasms; viral infections.

Serocalcin *Serono, Braz.; Serono, Venez.†.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Serocryptin *Serono, Arg.†; Serono, Cz.†; Serono, Hong Kong†; Serono, Hung.†; Serono, Mex.†; Serono, Venez.†.*
Bromocriptine mesilate (p.798·1).
Acromegaly; atherosclerosis; benign breast disorders; female infertility; galactorrhoea; gynaecomastia; hyperprolactinaemia; lactation inhibition; male hypogonadism; parkinsonism; polycystic ovary syndrome; premenstrual syndrome; prolactinoma.

Serocytol *Serolab, Switz.*
A range of equine antisera raised against body tissues and organs.

Seroderm *Casel, Turk.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Serodur *Durascan, Denm.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic attacks; social phobia.

Serofene *Serono, Arg.; Novartis, Chile†; Serono, Ital.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; functional uterine haemorrhage; polycystic ovary syndrome.

Seroflo *Cipla, India.*
⊗ Salmeterol (p.1135·3); fluticasone propionate (p.1533·2).
Asthma.

Serofusine *Braun, Switz.*
Electrolyte infusion with or without glucose (p.1667·1).
Fluid and electrolyte disorders.

Seroglubin *Gador, Arg.; Octafarma, Mex.†.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Serolin *Kalbe, Indon.*
Nicergoline (p.2352·1).
Cerebral and peripheral vascular disorders.

Serolux
Sandoz, Mex.
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Sandoz, Venez.
Sertraline (p.422·1).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Seromex *Ratiopharm, Fin.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Seromida *Itaca, Braz.†.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Seromycin *IFET (ΙΦΕΤ), Gr.; Lilly, Hong Kong; Dura, USA.*
Cycloserine (p.260·2).
Tuberculosis; urinary-tract infections.

Seronex
Note. This name is used for preparations of different composition.
Pharmavita, Chile.
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Medix, Mex.
Domperidone (p.1726·2).
Gastrointestinal motility disorders; nausea and vomiting.

Seronil *Orion, Fin.; Orion, Pol.; Drogsan, Turk.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Seronip *UCI, Braz.†.*
Sertraline hydrochloride (p.421·3).
Depression.

Serophene *Serono, Austral.; Serono, Austria; Serono, Braz.; Serono, Canad.; Serono, Cz.†; Serono, Hong Kong; Serono, Hung.†; Serono, Malaysia†; Serono, Mex.†; Healthcare Logistics, NZ; Serono, Neth.; Serono, S.Afr.†; Serono, Singapore; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, USA; Serono, Venez.; Serono, Venez.*
⊗ Clomifene citrate (p.2086·1).
Formerly known as Serofene in *Braz.* and *Venez.*
Anovulatory infertility; male infertility; menstrual disorders; polycystic ovary syndrome.

Serophta *Thea, Fr.; Farmila, Ital.†.*
Sea water (p.1686·1).
Eye wash.

Serophy *Interdelta, Switz.*
Sodium chloride (p.1686·1).
Nasal disorders.

Seroplex *Lundbeck, Fr.*
Escitalopram oxalate (p.391·1).
Depression; obsessive-compulsive disorder; panic disorder; social anxiety disorder.

Seropram
Lundbeck, Arg.; Lundbeck, Hung.; Lundbeck, Mex.; Lundbeck, Spain.
Citalopram hydrobromide (p.385·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Austria; Lundbeck, Fr.; Lundbeck, Ital.; Lundbeck, Switz.
Citalopram hydrobromide (p.385·3) or citalopram hydrochloride (p.385·3).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Cz.
Citalopram (p.385·3), citalopram hydrobromide (p.385·3), or citalopram hydrochloride (p.385·3).
Anxiety disorders; depression; obsessive-compulsive disorder; panic disorder.

Lundbeck, Gr.; Bayer, Venez.
Citalopram (p.385·3).
Depression.

Seroquel *Bago, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; Biosintetica, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; Astellas, Jpn; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; mania; schizophrenia.

Seroquin *Cipla, India.*
Quetiapine fumarate (p.1022·2).
Schizophrenia.

Seror *Specifar, Gr.*
Citalopram (p.385·3).
Depression.

Seroscand *Scand Pharm, Swed.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; obsessive-compulsive disorder.

Serostim *Serono, Arg.†; Serono, Canad.; Serono, Hong Kong; Serono, Mex.; Serono, USA.*
⊗ Somatropin (p.1799·3).
AIDS-related cachexia or weight loss.

Serotabir *Itaca, Braz.†.*
Cytarabine (p.705·1).
Malignant neoplasms.

Sero-Tet *Green Cross, Malaysia.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Serotone *Temis, Arg.†; Japan Tobacco, Jpn.*
Azasetron hydrochloride (p.1709·2).
Nausea and vomiting associated with antineoplastic therapy.

Serotor *Torrex Chiesi, Hung.*
Citalopram hydrobromide (p.385·3).
Depression.

Serotramin *Medix, Mex.*
⊗ Sibutramine (p.2164·1).
Obesity.

Serotulle *SSL, UK.*
Chlorhexidine acetate (p.1635·2).
Wounds.

Seroxat *GSK, Austria; GSK, Belg.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; Novartis, Turk.; GSK, UK.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; phobias; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Seroxydar *Automedic, Fr.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); aluminium phosphate (p.1707·3); guar gum (p.442·3).
Gastrointestinal disorders.

Serozil *BMS, Turk.*
Cefprozil (p.232·2).
Bacterial infections.

Serozinc *Roche-Posay, Fr.*
Sodium chloride (p.1686·1); zinc sulfate (p.1999·2).
Skin cleansing.

Serpafar *Faran, Gr.*
⊗ Clomifene citrate (p.2086·1).
Anovulatory infertility; diagnosis of hormonal disorders.

Serpasil *Biochemie, Indon.*
Reserpine (p.1387·3).
Hypertension.

Serpax *Wyeth Lederle, Ital.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety; depression; insomnia.

Serpens *Lisapharma, Ital.*
Saw palmetto (p.2192·3).
Prostatic hyperplasia.

Serphamida *Serral, Mex.*
Quinfamide (p.846·2).
Amoebiasis.

Serpicam *Serral, Mex.*
Piroxicam (p.117·3).
Inflammation.

Serracal *Serral, Mex.*
Calcium lactate gluconate (p.1676·2); calcium carbonate (p.1714·1).
Calcium deficiency; osteomalacia; osteoporosis; rickets; tetany.

Serradase *Siam Bheasach, Thai.*
Serrapeptase (p.2385·3).
Adjunct in antibiotic therapy; adjunct in cancer chemotherapy; inflammation; respiratory-tract congestion; wounds.

Serralpina *Serral, Mex.*
Hyoscine butylbromide (p.1734·1).

Serralpina Compuesta *Serral, Mex.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Serralsina *Serral, Mex.*
Loratadine (p.583·3).
Hypersensitivity.

Serranasal *Serra Pamies, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Serranit *Serral, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Serrano *M & H, Thai.*
Serrapeptase (p.2385·3).
Breast engorgement; cystitis; epididymitis; inflammation; oedema; sinusitis.

Serrao *Masa, Thai.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion; wounds.

Serrapep *Asian Pharm, Thai.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion; wounds.

Serrapress *Pharma Dynamics, S.Afr.*
Paroxetine (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Serrason *Unison, Thai.*
Serrapeptase (p.2385·3).
Breast engorgement; cystitis; epididymitis; inflammation; sinusitis; wisdom tooth pericoronitis; wounds.

Serraspec *Serra Pamies, Spain.*
Guaifenesin (p.1561·3).
Coughs.

Serratol *Serral, Mex.*
Difenidol (p.1723·2).
Nausea and vomiting; vertigo.

Serratos *Serra Pamies, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Serrazyme *Shin Poong, Singapore.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Serrin *Macrophar, Thai.*
Serrapeptase (p.2385·3).
Alveolar abscess; breast engorgement; cystitis; epididymitis; inflammation; respiratory-tract congestion; sinusitis; wisdom tooth pericoronitis; wounds.

Serriten *Serral, Mex.*
Verapamil (p.1423·2).
Hypertension.

Serta *Unichem, India.*
Sertraline hydrochloride (p.421·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Sertac *Andromaco, Chile.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Sertacream *Geymonat, Ital.*
Sertaconazole nitrate (p.546·1).
Fungal skin infections.

Sertadepi *Keri, Hung.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder.

Sertaderm *Shire, Ital.*
Sertaconazole nitrate (p.546·1).
Fungal skin infections.

Sertadie *Geymonat, Ital.*
Sertaconazole nitrate (p.546·1).
Vaginal candidiasis.

Sertagen *Generics, Hung.*
Sertraline hdyrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Sertagyn *Shire, Ital.*
Sertaconazole nitrate (p.546·1).
Vaginal candidiasis.

Sertahexal *Hexal, Pol.*
Sertraline hydrochloride (p.421·3).
Depression.

Sertal *Roemmers, Arg.*
Pargeverine (p.1761·1) or pargeverine hydrochloride (p.1761·1).
Smooth muscle spasm.

Sertal Compuesto *Roemmers, Arg.*
Pargeverine (p.1761·1) or pargeverine hydrochloride (p.1761·1); clonixin lysine (p.37·1).
Smooth muscle spasm.

Sertan *ICN, Hung.*
Primidone (p.503·2).
Epilepsy.

Serterol *Serral, Mex.†.*
Probucol (p.1377·1).
Hypercholesterolaemia.

Sertex *Psicofarma, Mex.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Sertidel *Serral, Mex.*
Diltiazem (p.1267·1).
Hypertension.

Sertidine
Note.This name is used for preparations of different composition.
Serral, Mex.
Famotidine (p.1730·1).
Peptic ulcer.

Chew, Thai.
Cimetidine (p.1716·2).
Mastocytosis; peptic ulcer; Zollinger-Ellison syndrome.

Sertinal *Bouzen, Arg.*
⊗ Sibutramine hydrochloride (p.2163·2).
Formerly contained phenylpropanolamine and caffeine.
Obesity.

Sertopic *CPH, Port.*
Sertaconazole nitrate (p.546·1).
Fungal skin infections; vulvovaginal candidiasis.

Sertra *TAD, Ger.*
Sertraline hydrochloride (p.421·3).
Depression.

Sertraniche *Niche, Irl.*
Sertraline hydrochloride (p.421·3).
Depression.

Sertrex *1A, Austria.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Sertrixen *Serral, Mex.*
Naproxen (p.92·3).
Inflammation; pain.

Sertrom *Serral, Mex.*
Roxithromycin (p.331·1).
Bacterial infections.

Sertwin *Zentiva, Hung.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder.

Sertzol *Ranbaxy, S.Afr.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder.

Serum Fizyolojik *Drogsan, Turk.; Merkez, Turk.*
Sodium chloride (p.1686·1).
Nasal congestion.

Serutan *Menley & James, USA.*
Psyllium seed (p.1737·1).
Constipation.

Servambutol *Sandoz, Thai.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Servamox
Sandoz, Mex.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sandoz, Thai.
Amoxicillin (p.202·2).
Bacterial infections.

Servamox CLV *Sandoz, Mex.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Servamox-F *Sandoz, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Servantax *Vannier, Arg.*
Sertraline (p.422·1).
Depression.

Servatrin *Pharmacare, S.Afr.*
⊗ Timolol maleate (p.1412·3); amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Servazolin *Sandoz, Austria; Sandoz, Neth.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Servetinal *Salusif, Port.†.*
Bismuth salicylate (p.1711·1); belladonna (p.2263·3); calcium carbonate (p.1714·1); magnesium hydroxide (p.1743·2); peppermint oil (p.1761·2); sodium bicarbonate (p.1673·2).
Gastric hyperacidity.

Servicef *Sandoz, Mex.*
Cefalexin (p.218·2).
Bacterial infections.

Serviclazide *Sandoz, Thai.*
Gliclazide (p.440·3).
Diabetes mellitus.

Serviclor *Sandoz, Cz.; Sandoz, Mex.; Sandoz, Pol.*
Cefaclor (p.217·2).
Bacterial infections.

Serviclox *Biochemie, Thai.†; Novartis, Thai.†.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Servidapsone *Biochemie, Thai.†; Novartis, Thai.†.*
Dapsone (p.261·2).
Dermatitis herpetiformis; leprosy.

Servidiclox *Biochemie, Thai.†; Novartis, Thai.†.*
Dicloxacillin sodium (p.265·2).
Bacterial infections.

Servidopa *Biochemie, Thai.†; Novartis, Thai.†.*
Methyldopa (p.1334·1).
Hypertension.

Servidoxyne *Sandoz, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Servidrat *Biochemie, Singapore†.*
Glucose; electrolytes (p.1672·2).
Diarrhoea; oral rehydration therapy.

Servidrat Low Sodium *Servipharm, Malaysia†.*
Glucose; sodium chloride; potassium chloride; citric acid; sodium bicarbonate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Serviflox
Sandoz, Singapore.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Novartis, Thai.†; Sandoz, Venez.
Ciprofloxacin (p.243·3).
Bacterial infections.

Servigenta *Sandoz, Mex.; Sandoz, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Servin *Condrugs, Thai.*
Mianserin hydrochloride (p.408·1).
Depression.

Servipen-V *Biochemie, Thai.†; Novartis, Thai.†.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Servipep *Servipharm, Hong Kong†; Biochemie, Hung.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Serviproxan *Sandoz, Thai.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal and joint disorders; pain.

Serviradine *Sandoz, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Servispor *Biochemie, Hung.†; Sandoz, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Servitrim *Sandoz, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Servitrocin *Sandoz, Thai.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Servizol
Sandoz, Mex.
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Sandoz, Philipp.
Metronidazole (p.837·1).
Amoebiasis; bacterial infections; giardiasis; trichomoniasis.

Serzone *BMS, Austral.†; BMS, Braz.†; BMS, Cz.†; BMS, Hong Kong†; BMS, Mex.†; BMS, NZ†; BMS, S.Afr.†; BMS, Singapore†; BMS, USA†.*
Nefazodone hydrochloride (p.412·1).
Depression.

Serzonil *BMS, Israel†.*
Nefazodone hydrochloride (p.412·1).
Depression.

Sesal *Ophtha, Denm.*
⊗ Antazoline hydrochloride (p.567·1); naphazoline hydrochloride (p.1565·2).
Allergic conjunctivitis.

Sesame Street *McNeil Consumer, USA.*
A range of vitamin preparations (p.1922·1).

Sesamoil *Gezzi, Arg.*
Bismuth salicylate (p.1711·1).
Diarrhoea; nausea.

Sesaren *Roemmers, Arg.; Roemmers, Chile; Roemmers, Venez.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social anxiety disorder.

Sesden *Tanabe, Indon.; Tanabe, Jpn; Tanabe, Singapore†.*
Timepidium bromide (p.1777·1).
Premedication for examination of the gastrointestinal or urinary tract; smooth muscle spasm.

Sessoforte *Denk, Hong Kong.*
Vitamins; methyltestosterone; kola; damiana; yohimbine; strychnos; ephedra; testis extract (p.1922·1).
Tonic.

Sestrine *Beta, Arg.*
Repaglinide (p.457·2).
Diabetes mellitus.

Setacol *Hamilton, Austral.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal spasm.

Setakaf *Kurtsan, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Setaloft *Actavis, Cz.; Actavis, Pol.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Setamol *Reckitt Benckiser, Austral.†; Hovid, Hong Kong; Yeni, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Setanol *Vilco, Gr.*
Norfloxacin (p.309·2).
Bacterial infections.

Setaratio *Ratiopharm, Pol.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; obsessive-compulsive disorder; post-traumatic stress disorder.

Setarin *Strand, Malaysia†.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Setarin H *Strand, Malaysia†.*
⊗ Miconazole (p.541·2); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Setatrep *Lemery, Mex.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Setcillin *Strand, Malaysia†.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Setegis
EGIS, Hung.; Egis, Pol.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Egis, Rus.
Terazosin (p.1410·3).
Benign prostatic hyperplasia; hypertension.

Sethro *Strand, Malaysia†.*
Erythromycin ethyl succinate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Setilin *Olgunsoy, Turk.*
Chlorhexidine (p.1635·2); cetrimide (p.1634·1).
Skin disinfection.

Setin
Note.This name is used for preparations of different composition.
Alliance, S.Afr.
Metoclopramide hydrochloride (p.1747·3).
Aid to gastrointestinal examination; gastrointestinal motility disorders; nausea and vomiting.

Siam Bheasach, Thai.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Setiral *Toprak, Turk.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Setlers *Thornton & Ross, UK.*
Calcium carbonate (p.1714·1).
Dyspepsia; flatulence; heartburn; nausea.

Setlers Heartburn & Indigestion Liquid *Stafford-Miller, UK.*
Calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); sodium alginate (p.2141·1).
Dyspepsia; gastro-oesophageal reflux; heartburn.

Setlers Windfree *GSK Consumer, Neth.*
Simeticone (p.1770·2).
Flatulence.

Setlinctus *Strand, Malaysia†.*
Codeine phosphate (p.37·2).
Coughs.

Setmenate *Strand, Malaysia†.*
Dimenhydrinate (p.576·2).
Ménière's disease; migraine; nausea and vomiting; vertigo.

Setmotil *Strand, Malaysia†.*
Diphenoxylate hydrochloride (p.1724·1).
Atropine sulfate (p.1219·3) is included in this preparation to discourage abuse.
Diarrhoea; ostomy management.

Setmoxil *Strand, Malaysia†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Setprodine *Raza, Hong Kong†.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; coughs; sinusitis; upper respiratory-tract congestion.

Setrilan *Essex, Ital.*
Spirapril hydrochloride (p.1399·3).
Hypertension.

Setriox *Selvi, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Setrodan *Pharmathen, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Setromol *Strand, Malaysia†.*
Paracetamol (p.108·1).
Fever; pain.

Setron
Note.This name is used for preparations of different composition.
Slovakofarma, Cz.†.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxic therapy; postoperative nausea and vomiting.

Agis, Israel; Eczacibasi, Turk.
Granisetron (p.1733·1).
Nausea and vomiting induced by cytotoxic therapy or radiotherapy; postoperative nausea and vomiting.

Setrona *Ranbaxy, Austral.*
Sertraline hydrochloride (p.421·3).
Depression; premenstrual dysphoric disorder.

Setronges *Raza, Hong Kong†; Strand, Malaysia†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Setronil *Chemopharma, Chile.*
Citalopram hydrobromide (p.385·3).
Depression; panic attacks.

Setronon *Pliva, Cz.; Pliva Krakow, Pol.; Pliva, Rus.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Setrosone *Strand, Malaysia†.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Setrovel *Novell, Indon.*
Tropisetron hydrochloride (p.1777·2).
Nausea and vomiting induced by cancer chemotherapy.

Setrozole *Strand, Malaysia†.*
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Setsolone *Strand, Malaysia†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Setux *Sanofi-Aventis, Braz.*
Codeine resinate (p.38·3); phenyltoloxamine resinate (p.588·1).
Coughs.

Setux Expectorante *Sanofi-Aventis, Braz.*
Codeine resinate (p.38·3); guaifenesin (p.1561·3); phenyltoloxamine resinate (p.588·1).
Coughs.

Seudotabs *Parmed, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sevacol *Indeco, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Seven Seas *Merck, Hong Kong; Seven Seas, Hong Kong; Merck, Philipp.; Seven Seas, Singapore; Merck, Thai.; Abdi, Turk.; Seven Seas, UK.*
A range of tonics, dietary supplements, and multivitamin preparations (p.1922·1).

Seven Seas Active Sport *Seven Seas, Irl.*
Omega 3 nutrients; gamma linolenic acid; vitamin E; betacarotene; minerals; glucosamine sulphate; chondroitin sulfate; ginger; ginseng (p.1922·1).
Nutritional supplement.

Seven Seas JointCare *Seven Seas, Singapore.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); fish oil (p.1362·2).
Degenerative joint disorders.

Seven Seas JointCare High Strength *Seven Seas, Singapore.*
Cod-liver oil (p.1935·2); fish oil (p.1362·2).
Joint disorders.

Seven Seas JointCare Max *Seven Seas, Singapore.*
Tablets, glucosamine sulfate (p.2313·2); capsules, fish oil (p.1362·2); fish collagen (p.2286·1).
Degenerative joint disorders.

Seven Seas Pulse *Abdi, Turk.*
Cod-liver oil (p.1935·2).
Hyperlipidaemias; ischaemic heart disease.

Sevenal
Valeant, Hung.
Phenobarbital (p.492·2).
Epilepsy.

Chinoin, Mex.†.
Phenobarbital sodium (p.492·2).
Epilepsy.

Sevenaletta *Valeant, Hung.*
Phenobarbital (p.492·2).
Epilepsy.

Several *Duncan, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Severin *Chinoin, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Severon *Profarma, Thai.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sevinol *Schering-Plough, Belg.†.*
Fluphenazine hydrochloride (p.998·1).
Psychoses.

Sevium *Ni-The, Gr.*
Haloperidol (p.1000·2).
Huntington's chorea; psychoses; tics.

Sevlenyl *SJA, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Sevocris *Cristalia, Braz.*
Sevoflurane (p.1793·2).
General anaesthesia.

Sevoran *Abbott, Rus.*
Sevoflurane (p.1793·2).
General anaesthesia.

Sevorane *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.†; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Irl.; Abbott, Israel; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Thai.; Abbott, Turk.; Abbott, Venez.*
Sevoflurane (p.1793·2).
General anaesthesia.

Sevorex *CCS, Swed.*
Precipitated sulfur (p.1614·1); salicylic acid (p.1612·2).
Scalp disorders.

Sevredol *Mundipharma, Austral.; Mundipharma, Cz.; Mundipharma, Fr.; Mundipharma, Ger.; Extractum, Hung.; Mundipharma, Hung.; Napp, Irl.; Douglas, NZ; Mundipharma, Neth.; Norpharma, Pol.; Mundipharma, Port.; Mundipharma, Spain; Mundipharma, Switz.; Napp, UK.*
⊗ Morphine sulfate (p.86·3).
Pain.

Sevre-Long *Mundipharma, Switz.*
⊗ Morphine sulfate (p.86·3).
Pain.

Sexadien *Leo, Denm.†.*
Dienestrol (p.2093·3).
Vulvovaginal disorders associated with oestrogen deficiency.

SF Gel *Cypress, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

SFC Lotion *Stiefel, USA.*
Stearyl alcohol (p.2033·1).
Skin cleanser.

Sfinac *Velka, Gr.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

SG 33 *Sigma, Arg.*
Magnesium oxide (p.1744·1).
Constipation; gastro-oesophageal reflux; hypomagnesaemia.

SG-Glutergen *Terramedic, Philipp.*
Vitamins; cholic acid; grain oil; hematoporphyrin hydrochloride; lecithin; linseed oil; magnesium glutamate; potassium chloride; ginseng; sunflower seed oil; troxerutin (p.1922·1).
Nutritional supplement.

SGM LLM *Sari Husada, Indon.*
Infant feed (p.1922·1).
Low-lactose feed.

Sguardi *Farmigea, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection.

SGX *Medisys, Philipp.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

SH3 *Polifarma, Ital.*
Pyrethrin (p.2049·3).
Pediculosis.

SH-206 *Pharmascience, Canad.*
Acetic acid (p.2244·2); camphor (p.2273·2); lemon oil (p.2332·3); sodium lauril ether sulfate.
Pediculosis.

Shade
Note.This name is used for preparations of different composition.
Schering-Plough, USA.
Gel SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1).
Sunscreen.

Schering-Plough, USA.
Lotion SPF 30; stick SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1); octisalate (p.1608·2).
Sunscreen.

Schering-Plough, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Essex, Chile.
SPF 30; SPF 45: Homosalate (p.1598·1); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); imidazolidinyl urea.
Sunscreen.

Schering-Plough, USA.
SPF 45: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Shade UVAGuard *Schering-Plough, USA.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Shaklee Dandruff Control *Shaklee, Canad.†.*
Pyrithione zinc (p.1611·2).

Shaklee Lip Protection Stick *Shaklee, Canad.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Shakuyaku-kanzo-to *Tsumura, Jpn.*
Liquorice; peony root.
Traditional Kampo medicine.

Shamday Antiforfora *Euroderm, Ital.†.*
Piroctone olamine (p.1610·1); urtica (p.2409·3).
Seborrhoeic dermatitis.

Shampoo Anticaspa *Beiersdorf, Chile.*
Climbazole (p.529·3); piroctone (p.1610·1).
Dandruff.

Shampoo SDE Tar *Essex, Ital.†.*
Coal tar (p.1616·2).
Scalp disorders.

Shampoo SDE Zinc *Essex, Ital.†.*
Pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Shampoo Tersa-Tar *Dermaclin, Mex.†.*
Coal tar (p.1616·2).
Scalp disorders.

Shampoo del Tio Nacho *Bustillos, Mex.*
Norway tar (p.1616·2); resorcinol (p.1612·1).
Scalp disorders; skin disorders.

Shampooing Anti-Pelliculaire *Atlas, Canad.*
Pyrithione zinc (p.1611·2).

Shampooing extra-doux *Widmer, Switz.*
Triclosan (p.1665·2).
Scalp disorders.

Shampooing Traitant Antipelliculaire *Ducray, Fr.†.*
Pyrithione zinc (p.1611·2).
Dandruff.

Shampoux *Qualiphar, Belg.*
Permethrin (p.2048·2); piperonyl butoxide (p.2049·1).
Pediculosis.

Shampoux Repel *Qualiphar, Belg.*
(N-Butyl-N-acetyl)-3-ethylaminopropionate (p.2043·1).
Pediculosis.

Shanvac-B *Shanta, India; Shantha, Philipp.*
A hepatitis B vaccine (surface antigen) (p.2215·2).
Active immunisation.

Sharko Inside *Sahabat, Indon.*
Shark cartilage (p.2277·3).
Angiogenesis inhibitor; inflammation; rheumatism.

Sharkoferrol *Alembic, India.*
Ferric ammonium citrate; calcium gluconate; malt extract; vitamins (p.1922·1).
Nutritional supplement.

Sharkomalt *Haffkine, India.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); malt extract.
Vitamin A and D deficiency.

Sharkovit *Haffkine, India.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Vitamin A and D deficiency.

Sharox
Fahrenheit, Indon.
Cefuroxime (p.238·2).
Bacterial infections.

Fahrenheit, Philipp.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Sheik *Durex, Canad.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Sheik Elite *Schmid, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Sheko *Medipharma, Hong Kong†.*
Zinc oxide (p.1621·2); methyl salicylate (p.85·3).
Skin disorders.

Shellgel *Cytosol, USA.*
Sodium hyaluronate (p.2320·1).
Aid in ophthalmic surgery.

Shelrod-Plus *Medikon, Indon.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; musculoskeletal and joint disorders.

Shelrofen *Medikon, Indon.*
Ibuprofen (p.64·2).
Pain.

Shemol *Grin, Mex.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Shepard's *Dermik, USA.*
Emollient and moisturiser.

Shield *GSK, India.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); zinc oxide (p.1621·2); allantoin (p.1588·1).
Anorectal disorders.

Shields *Ansell, Canad.†.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Shii-ta-ker *Holistica, Fr.*
Lentinus edodes.
Immunostimulant.

Shilshul X *CTI, Israel.*
Loperamide (p.1741·3).
Diarrhoea.

Shinapen *Yung Shin, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Shin-Biofermin S *Takeda, Hong Kong.*
Bifidobacterium bifidum (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Enterococcus faecalis* (p.2372·3).
Constipation; diarrhoea; meteorism.

Shinbit *Schering, Jpn.*
Nifekalant hydrochloride (p.1357·1).
Arrhythmias.

Shincef *Shin Poong, Philipp.; Unimex, Philipp.; Shin Poong, Singapore.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Shincort *YSP, Malaysia; Yung Shin, Singapore; Yung Shin, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Shine Bio-Cal *Yung Shin, Singapore.*
Lithothamnion calcareum; calcium; colecalciferol; magnesium; iodine; boron; selenium (p.1922·1).
Dietary supplement.

Shinfomycin *YSP, Malaysia.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Shinoxol *YSP, Malaysia; Yung Shin, Singapore.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Shintamet *YSP, Malaysia; Yung Shin, Singapore.*
Cimetidine (p.1716·2).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hypersecretion; peptic ulcer; Zollinger-Ellison syndrome.

Shiomarin *Shionogi, Jpn.*
Latamoxef sodium (p.292·1).
Bacterial infections.

Shiseido Benefiance Daytime
Shiseido, Canad.
Cream SPF 15: Octinoxate (p.1608·2).
Formerly contained octinoxate and oxybenzone.
Sunscreen.

Shiseido, Canad.
Emulsion SPF 15: Octinoxate (p.1608·2).
Sunscreen.

Shiseido Skincare Day Essential *Shiseido, Canad.†.*
SPF 10: Avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

Shiseido Skincare Day Protective *Shiseido, Canad.†.*
SPF 15: Titanium dioxide (p.1617·3).
Sunscreen.

Shiseido Skincare Protective *Shiseido, Canad.†.*
Avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

Shiseido Sun Block Lip Treatment *Shiseido, Canad.†.*
Octinoxate (p.1608·2).
Sunscreen.

Shiseido Sun Block Stick *Shiseido, Canad.†.*
Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Shiseido Sun Protection *Shiseido, Canad.†.*
SPF 8: Octinoxate (p.1608·2).
Sunscreen.

Shiseido Sunblock *Shiseido, Canad.†.*
SPF 19: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Shiseido Sunblock Face Cream *Shiseido, Canad.†.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); ensulizole (p.1597·1); titanium dioxide (p.1617·3).
Sunscreen.

Shiseido Translucent Sun Block *Shiseido, Canad.†.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Shiseido Vital-Perfection
Note.This name is used for preparations of different composition.
Shiseido, Canad.†.
Cream: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Shiseido, Canad.†.
Stick: Octinoxate (p.1608·2).
Sunscreen.

Shiulon *Trima, Israel.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Coughs.

Shiwalax *Shiwa, Thai.†.*
Tolperisone hydrochloride (p.1899·3).
Musculoskeletal pain; parkinsonism.

Shokenchuto *Tsumura, Jpn.*
Cinnamon bark; peony root; jujube; liquorice; ginger.
Traditional Kampo medicine.

Shomakakkonto *Tsumura, Jpn.*
Pueraria root; peony root; cimicifuga rhizome; liquorice; ginger.
Traditional Kampo medicine.

Sho-saiko-to *Tsumura, Jpn.*
Bupleurum root; pinellia tuber; scutellaria root; jujube; ginseng; liquorice; ginger.
Traditional Kampo medicine.

Sho-seiryu-to *Tsumura, Jpn.*
Pinellia tuber; liquorice; cinnamon bark; schisandra fruit; asiasarum root; peony root; ephedra herb; ginger.
Traditional Kampo medicine.

Shrizine *SM, Philipp.*
Fluphenazine decanoate (p.998·1).
Schizophrenia.

Shuchibushi N *Tsumura, Jpn.*
Aconitum carmichaeli root.
Traditional Kampo medicine.

Shur-Seal *Milex, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Si o No *Fresh Ones, Arg.†.*
Pregnancy test (p.2372·1).

Siaara *Heptafarma, Port.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Cardiovascular risk reduction; hypertension.

Siadocin *Siam Bheasach, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Siafil *Rider, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Sialexin *Siam Bheasach, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Sialin *Sigmapharm, Austria.*
Carmellose sodium (p.2142·1); electrolytes (p.1667·1).
Saliva substitute.

Sialis *Ultratech, India†.*
Tadalafil (p.2196·2).
Erectile dysfunction.

Sialor *Pharmascience, Canad.; Zuoz, Venez.†.*
Anethole trithione (p.2258·1).
Dry mouth.

Siamdopa *Siam Bheasach, Thai.*
Methyldopa (p.1334·1).
Hypertension.

Siamformet *Siam Bheasach, Thai.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Siamidine *Siam Bheasach, Thai.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Siamik *Siam Bheasach, Thai.*
Amikacin sulfate (p.200·3).
Bacterial infections.

Sia-Mox *Siam Bheasach, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Siampicil *Siam Bheasach, Thai.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Siampraxol *Siam Bheasach, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Siarizine *Siam Bheasach, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Siaten *Italfarmaco, Spain.*
Zopiclone (p.1039·1).
Insomnia.

Sibectan *Vilar, Rus.*
Birch leaf (p.2266·3); milk thistle (p.1452·1); St John's wort (p.422·3); tanacetum.
Liver and biliary tract disorders.

Sibelium *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Pharmascience, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong†; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen, Philipp.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore†; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, Venez.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vertigo; vestibular disorders.

Sibelium Plus *Janssen-Cilag, Arg.*
Flunarizine hydrochloride (p.580·2); nicergoline (p.2352·1).
Migraine; vertigo.

Siberian *Rafarm, Gr.*
⊗ Enalapril (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Siberid *Pyridam, Indon.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Sibet *Glenmark, India.*
Dexibuprofen (p.39·2).
Dental pain; dysmenorrhoea; osteoarthritis.

Sibet-C *IQFA, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Sibicort *Orion, Fin.*
⊗ Hydrocortisone (p.1535·2); chlorhexidine gluconate (p.1635·3).
Infected skin disorders.

Sibilex *Rimsa, Mex.*
⊗ Ambroxol hydrochloride (p.1550·3); salbutamol sulfate (p.1131·3); loratadine (p.583·3).
Respiratory-tract disorders.

Sibital *Mersifarma, Indon.*
Phenobarbital sodium (p.492·2).
Epilepsy.

Siblima *Libbs, Braz.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Siblix *Beta, Arg.*
Aripiprazole (p.962·3).
Bipolar disorder; schizophrenia.

Sibrovita *Permamed, Switz.*
Eucalyptus oil (p.2301·2); orange oil (p.2357·2); lemon oil (p.2332·3); myrtillus oil.
Bronchitis; sinusitis.

Sibudan *Teva Tuteur, Arg.*
Irinotecan (p.738·1).
Malignant neoplasms.

Sibu-Estirol *Bouzen, Arg.*
⊗ Sibutramine (p.2164·1).
Obesity.

Sibunar *Durascan, Denm.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Sibutral *Abbott, Fr.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Sibu-Tratobes *Columbia, Arg.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Sicadentol Plus
Note. This name is used for preparations of different composition.
Geminis, Arg.†.
Tablets: Naproxen (p.92·3).
Inflammation; pain.

Geminis, Arg.†.
Topical liquid: Procaine (p.1869·2); eugenol (p.2301·2).

Sicadol *Rider, Chile.*
Mefenamic acid (p.80·1).
Pain.

Sical *Rottapharm, Spain†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; metastatic bone pain; osteoporosis; Paget's disease of bone.

Sicalan *Loeffler, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Sicaril *Sanofi-Aventis, Gr.*
Malathion (p.2046·1).
Head and crab lice; scabies.

Sicatem *Richmond, Arg.*
Cisplatin (p.698·2).
Malignant neoplasms.

Sicazine *Smith & Nephew, Fr.; Smith & Nephew, Port.*
Sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Siccafluid *Sidus, Arg.; Thea, Fr.; Thea, Ital.; Thea, Neth.; Thea, Philipp.; Thea, Port.; Thea, Spain; Thea, Switz.; Pfizer, Venez.*
Carbomer 974P (p.2141·3).
Dry eyes; eye irritation.

Siccagent *Alcon, Belg.*
Povidone (p.2146·1).
Dry eyes.

Siccalix *Drossapharm, Switz.*
Sea salt (p.1686·1); dexpanthenol (p.2362·1).
Nasal dryness.

Siccapos *Ursapharm, Ger.; Biem, Turk.*
Carbomer 980 (p.2141·3).
Dry eyes.

Siccaprotect *Croma, Austria; Ursapharm, Cz.; Ursapharm, Ger.; Ursapharm, Switz.; Biem, Turk.*
Dexpanthenol (p.2362·1); polyvinyl alcohol (p.2145·3).
Dry eyes; eye irritation.

Sicca-Stulln *Stulln, Ger.*
Hypromellose (p.2144·2).
Dry eyes.

Sicco *AWD, Ger.†.*
⊗ Indapamide (p.1314·1).
Hypertension.

Siccoral
Note. This name is used for preparations of different composition.
Sanova, Austria.
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with viscous mucus.

Drossapharm, Switz.
Sea salt (p.1686·1).
Mouth and throat disorders.

Sicef *Benedetti, Ital.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Siclaxim *Mersifarma, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Siclidon *Sanbe, Indon.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Siclot *Siam Bheasach, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Diabetic retinopathy; intermittent claudication; maintenance of extracorporeal circulation; thromboembolism prophylaxis; unstable angina.

Sico Relax *Rottapharm, Spain†.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; premedication; skeletal muscle spasticity; sleep disorders.

Sicobal *Siam Bheasach, Thai.†.*
Mecobalamin (p.1981·1).
Peripheral neuropathies.

Sicombyl *Christiaens, Belg.*
Salicylic acid (p.1612·2).
Hygiene of the umbilicus in neonates.

Sicon *Pharmacia, Venez.†.*
Simeticone (p.1770·2).
Flatulence.

Sicopax *Indeco, Arg.*
Paroxetine (p.414·2).
Depression.

Sic-Ophtal *Winzer, Ger.*
Hypromellose (p.2144·2).
Dry eyes.

Sicoplus *Columbia, Arg.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Sicor *Sandoz, Hung.*
Simvastatin (p.1390·2).
Coronary artery disease; hyperlipidaemias.

Sicorten *Novartis Consumer, Austria; Novartis Consumer, Belg.†; Bioglan, Ger.†; Novartis, Hong Kong; Amdipharm, Neth.†; Novartis Consumer, Port.†; Sandoz, Spain; Novartis, Switz.; Novartis, Turk.*
⊗ Halometasone (p.1535·1).
Skin disorders.

Sicorten Plus *Riemser, Ger.; Novartis, Hong Kong†; Novartis, Israel†; Novartis Consumer, Port.†; Sandoz, Spain; Novartis, Switz.; Novartis, Venez.†.*
⊗ Halometasone (p.1535·1); triclosan (p.1665·2).
Infected skin disorders.

Sicotral *Indeco, Arg.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Sicriptin *Serum Institute, India.*
Bromocriptine mesilate (p.798·1).
Acromegaly; amenorrhoea; female infertility; galactorrhoea; lactation inhibition; parkinsonism.

Sicrit *Wyeth, Chile†.*
Medroxyprogesterone acetate (p.2113·1).

Sicura3 *Esoform, Ital.†.*
Barrier preparation.

Sicura 3 *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3).
Dental caries prophylaxis.

Sicura3 Fisionorm *Esoform, Ital.*
Zinc oxide (p.1621·2).
Nappy rash.

Sicura3 Medical *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Skin disinfection.

Sidel *Liferpal, Mex.*
Nimesulide (p.95·3).
Pain; rheumatism.

Sidenar *Ivax, Arg.*
Lorazepam (p.1004·1).
Anxiety; behaviour disorders; neuroses.

Sideralce *Lafedar, Arg.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.

Siderblut
Note. This name is used for preparations of different composition.
Investi, Arg.
Controlled-release tablets; paediatric solution: Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Investi, Arg.
Oral drops: Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Siderblut Folic *Investi, Arg.*
Iron polymaltose (p.1953·1); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Iron and folic acid deficiency anaemia.

Siderfol *Raptakos, India.*
Ferrous fumarate (p.1938·3); folic acid; vitamin B ; vitamin B ; copper sulfate (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Sideril *Senosiain, Mex.*
Trazodone (p.426·1).
Depression.

Sideroglobina *Pharmacia, Ital.†.*
Ferritransferrin.
Iron-deficiency anaemia.

Sideron *Itaca, Braz.†.*
Pentamidine (p.845·2).
Pneumocystis pneumonia.

Sidervim *Lafare, Ital.*
Ferrous gluconate (p.1939·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Sidiadryl *Bernofarm, Indon.*
Diphenhydramine hydrochloride (p.577·2).
Allergic disorders.

Sidiadryl Expectorant *Bernofarm, Indon.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Sidomal *Sanitas, Arg.*
Simeticone (p.1770·2); domperidone (p.1726·2); alprazolam (p.960·1).

Siduol *Eisai, Thai.*
Alpha tocoferil calcium succinate (p.1993·3); phytomenadione (p.1995·3); rutoside (p.2305·1); muramidase hydrochloride (p.2348·1); poloxamer 188 (p.1918·1).
Haemorrhoids.

Siduro *Ipex, Swed.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders.

Sieral *Farmedia, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sies *Senosiain, Mex.*
⊗ Hidrosmin (p.2305·2).
Oedema; retinal or subconjunctival disorders.

Siesta-I *Welti, Switz.*
Anhydrous citric acid (p.2284·1); tartaric acid (p.2395·2); magnesium sulfate (p.1679·3); sodium bicarbonate (p.1673·2).
Constipation.

Sievert *Pliva, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sifaclor *Siam Bheasach, Malaysia; Siam Bheasach, Thai.*
Cefaclor (p.217·2).
Bacterial infections.

Sifbem *Sinterapico, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Sifdel *Sinterapico, Braz.†.*
Deltamethrin (p.2040·1).
Pediculosis.

Sificetina *SIFI, Ital.*
Chloramphenicol (p.239·3).
Eye infections.

Sificrom *Craveri, Arg.†; SIFI, Ital.; SIFI, Singapore†.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders; conjunctivitis; keratoconjunctivitis.

Sifiviral *SIFI, Ital.†.*
Aciclovir (p.862·3).
Herpes simplex keratitis.

Si-Fixim *Svizera, India†.*
Cefixime (p.224·3).
Bacterial infections.

Siflex *Siam Bheasach, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Sifloks
Eczacibasi, Rus.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Eczacibasi, Turk.
Ciprofloxacin (p.243·3).
Bacterial infections.

Sifloxan *Sinterapico, Braz.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Sifnolol *Sinterapico, Braz.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Sifpirona *Sinterapico, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Sifpol *Sinterapico, Braz.†.*
Potassium iodide (p.2169·2).

Sifpryl *Sinterapico, Braz.†.*
Enalapril (p.1276·1).
Hypertension.

Siframin *Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Sifrol *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism; restless legs syndrome.

Sifrol/Mirapex *Boehringer Ingelheim, Venez.*
Pramipexole hydrochloride (p.814·1).
Parkinsonism.

Siftrex *Sinterapico, Braz.†.*
Erythromycin (p.269·2).
Bacterial infections.

Siftromin *Sinterapico, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Sigabloc *Alpharma-Isis, Ger.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Sigabroxol *Alpharma-Isis, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with increased or viscous mucus.

Sigacalm *Alpharma-Isis, Ger.†.*
Oxazepam (p.1014·2).
Anxiety; sleep disorders.

Sigacap Cor *Alpharma-Isis, Ger.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Sigacefal *Alpharma-Isis, Ger.†.*
Cefaclor (p.217·2).
Bacterial infections.

Sigacimet *Alpharma-Isis, Ger.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sigacora *Alpharma-Isis, Ger.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Sigadoc *Alpharma-Isis, Ger.†.*
Indometacin (p.66·3).
Musculoskeletal, joint, and soft-tissue disorders; sports injuries.

Sigadoxin
Maver, Chile; Neves, Port.; Medika, Switz.†.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Alpharma-Isis, Ger.†.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.

Sigafam *Rhein, Mex.†.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sigafenac *Alpharma-Isis, Ger.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Sigamopen *Alpharma-Isis, Ger.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sigamuc *Alpharma-Isis, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Bacterial infections of the respiratory tract.

Sigaperidol *Alpharma-Isis, Ger.†; Medika, Switz.†.*
Haloperidol (p.1000·2).
Anxiety; hyperactivity; pain; psychoses; vomiting.

Sigaprim *Alpharma-Isis, Ger.†; Medika, Switz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Sigaprolol *Alpharma-Isis, Ger.†.*
⊗ Metoprolol tartrate (p.1338·1).
Arrhythmias; hypertension; ischaemic heart disease; migraine; myocardial infarction.

Sigapurol N *Medika, Switz.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Sigas *Polipharm, Thai.†.*
Simeticone (p.1770·2).
Flatulence.

Sigatricin *Trahan, Thai.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); benzethonium chloride (p.1630·1).
Mouth and throat disorders.

Siglaton *Vamsler, Philipp.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Siglaton Plus *Vamsler, Philipp.*
Vitamin and mineral preparation with lysine hydrochloride (p.1922·1).
Nutritional supplement.

Sigma CE *Sigma, Arg.*
Vitamin C (p.1983·3); zinc gluconate (p.1999·2).
Vitamin C deficiency; zinc supplement.

Sigma Clav *Sigma, Braz.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Sigma Liquid Antacid *Sigma, Austral.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; heartburn.

Sigma Relief
Note. This name is used for preparations of different composition.
Sigma, Austral.†.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3).
Cold and influenza symptoms; coughs.

Sigma, Hong Kong†.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Sigma Relief Chest Rub *Sigma, Austral.†.*
Camphor (p.2273·2); menthol (p.2340·1).

Sigma Relief Junior *Sigma, Austral.†; Sigma, Hong Kong†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); sodium citrate.
Cold and influenza symptoms; coughs; respiratory-tract congestion.

Sigmacal *Sigma, Arg.*
Calcium citrate (p.1675·3).
Calcium deficiency; osteoporosis.

Sigmacalcidol *Sigma, Braz.*
Alfacalcidol (p.1986·1).
Osteoporosis.

Sigmacalvit *Svizera, India.*
Calcium glubionate (p.1675·3); cyanocobalamin (p.1980·2); colecalciferol (p.1986·2).
Calcium deficiency; tetanus.

Sigmace Plus *Sigma, Arg.*
Vitamin C (p.1983·3); zinc gluconate (p.1999·2).
Vitamin C and zinc supplement.

Sigmachrome *Svizera, India.*
Carbazochrome salicylate (p.1058·2).
Haemorrhage.

Sigmacort *Sigma, Austral.; Sigma, Hong Kong.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Sigmaderm *Svizera, India.*
⊗ Clotrimazole (p.530·1); beclometasone dipropionate (p.1516·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Sigmafem *Sigma, Arg.*
Soya phytoestrogens (p.1965·3); sage phytoestrogens (p.2382·3); angelica (p.2258·1); Siberian ginseng (p.2386·3); vitamin E (p.1992·2); magnesium (p.1678·3).
Dysmenorrhoea; hypercholesterolaemia; mastodynia; menopausal disorders; osteoporosis.

Sigmafen Free *Sigma, Arg.*
Soya isoflavones (p.2391·2); sage phytoestrogens (p.2382·3).
Menopausal disorders.

Sigmaflex *Sigma, Arg.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); calcium carbonate (p.1714·1); phosphorus (p.2367·2); magnesium (p.1678·3).
Joint disorders.

Sigmalac *Sigma, Braz.*
Lactitol (p.1738·2).
Constipation; hepatic encephalopathy.

Sigmalin B_6 *Sigmapharm, Austria.*
Salicylamide (p.121·2); paracetamol (p.108·1); caffeine (p.1116·3); pyridoxine hydrochloride (p.1978·2).
Fever; pain.

Sigmalin B_6 forte *Sigmapharm, Austria.*
Salicylamide (p.121·2); paracetamol (p.108·1); dextropropoxyphene hydrochloride (p.40·1); caffeine (p.1116·3); pyridoxine hydrochloride (p.1978·2).
Fever; pain.

Sigmalin B_6 ohne Coffein *Sigmapharm, Austria.*
Salicylamide (p.121·2); paracetamol (p.108·1); pyridoxine hydrochloride (p.1978·2).
Fever; pain.

Sigman-Haustropfen *Sigmapharm, Austria.*
Peppermint oil (p.1761·2); caraway oil (p.2277·1); dexpanthenol (p.2362·1); chamomile flower (p.2279·3); condurango bark (p.2287·1); liquorice root (p.1740·3); absinthium (p.2244·1); gentian root (p.2310·3); bitter orange peel (p.2357·1).
Gastrointestinal and biliary-tract disorders.

Sigmar Lipo *Sigma, Arg.*
Chromium tripicolinate (p.1934·3).
Obesity.

Sigmart *Chugai, Jpn.*
Nicorandil (p.1349·1).
Angina pectoris.

Sigmasedan *Sigma, Arg.*
Passion flower (p.2363·2); valerian (p.2410·1).
Anxiety; gastrointestinal disorders; insomnia.

Sigmasol *Sigma, Arg.*
Bixa orellana; betacarotene (p.1930·3).
Tanning aid.

Sigmasporin *Sigma, Braz.; Julphar, UAE.*
Ciclosporin (p.1822·2).
Atopic eczema; nephrotic syndrome; psoriasis; rheumatoid arthritis; transplant rejection.

Sigmasporon *Helvetia, Cz.*
Ciclosporin (p.1822·2).
Atopic eczema; graft-versus host disease; nephrotic syndrome; organ transplant rejection; psoriasis; rheumatoid arthritis; uveitis.

Sigmatriol *Sigma, Braz.*
Calcitriol (p.1986·2).
Vitamin D supplement.

Sigmatrofic *Sigma, Arg.*
A range of tissue extracts (p.2337·3).

Sigmavital *Sigma, Arg.*
Amino acid, vitamin, mineral, and lipid preparation (p.1922·1).
Tonic.

Sigmaxin *Fawns & McAllan, Austral.*
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Sigmetadine *Sigma, Austral.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sigmus *Bausch & Lomb, Arg.*
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Signal *Green Turtle Bay Vitamin Co., USA.*
Omega triglycerides (p.1922·1).
Tonic.

Signopam *Tarchomin, Hung.; Polfa Tarchomin, Pol.; Tarchomin, Rus.*
Temazepam (p.1030·1).
Premedication; sleep disorders.

Signum *Amnol, Ital.*
Maritime pine (p.2368·1); aesculus (p.2248·2); bromelains (p.2269·1); vitamin B substances (p.1922·1).
Respiratory-tract inflammation.

Sigtab-M *Roberts, USA.*
Multivitamin and mineral preparation (p.1922·1).

Siguent Hycor *Sigma, Austral.*
⊗ Hydrocortisone acetate (p.1535·2).
Inflammatory eye disorders.

Siguent Neomycin *Sigma, Austral.†.*
Neomycin sulfate (p.305·1).
Skin infections.

Siguon *Leovan, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Siklocap *Kocak, Turk.*
Cycloserine (p.260·2).
Tuberculosis.

Siklomid *Sanovel, Turk.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Sikloplejin *Abdi, Turk.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Siklos *Addmedica, Cz.; Addmedica, Fr.; Addmedica, Port.*
Hydroxycarbamide (p.729·1).
Sickle-cell anaemia.

SIL-1000, -5000 *DORC, Neth.*
Silicone oil (p.2032·1).
Ophthalmic tamponade.

Silabat *Bernofarm, Indon.*
Guaifenesin (p.1561·3); paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Silace *Tanta, Canad.; Silarx, USA.*
Docusate sodium (p.1725·1).
Constipation.

Silace-C *Silarx, USA†.*
Casanthranol (p.1715·1); docusate sodium (p.1725·1).
Constipation.

Silact *Sofar, Ital.*
Tilactase (p.2402·1).
Lactose intolerance.

Siladex *Konimex, Indon.*
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Siladryl *Silarx, USA.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Silafed *Silarx, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Silagra *Cipla, India.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Silain *Teva, Israel.*
Simeticone (p.1770·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Silamox *Prafa, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sil-A-Mox *Silom, Thai.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Silan *Smith & Nephew, Denm.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Dry skin; skin irritation.

Silapap *Silarx, USA.*
Paracetamol (p.108·1).
Fever; pain.

Silapo *Stada, Cz.; Stada, Port.*
⊗ Epoetin zeta (p.1061·1).
Anaemias; autologous blood transfusion.

Silarine *Vir, Spain.*
Silymarin (p.1452·2).
Toxic hepatitis.

Silartrin *Silesia, Chile†.*
Ibuprofen (p.64·2); dipyrone (p.49·2).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation; musculoskeletal and joint disorders; pain.

Silato *Velka, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Silaxa *Temis, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Silbecor *Biotech, S.Afr.*
Sulfadiazine silver (p.337·2).
Burns.

Silbephylline *Minerva (Μινέρβα), Gr.†.*
Diprophylline (p.1120·2).
Asthma; obstructive airways disease.

Silberne *Brady, Austria.*
Cascara (p.1715·2); rhubarb (p.1768·3); ox bile (p.2266·3).
Constipation.

Silcon *Faulding Consumer, Austral.†.*
Dimeticone (p.2032·1); wool fat (p.2033·2).
Barrier preparation.

Silcopen *Valmor, Venez.†.*
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Silcor *Galderma, Arg.†.*
Calcitriol (p.1986·2).
Psoriasis.

Sildec-DM
Note. This name is used for preparations of different composition.
Silarx, USA.
Oral drops: Carbinoxamine maleate (p.570·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Silarx, USA.
Syrup: Brompheniramine maleate (p.569·2); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Sildefil *Pfizer, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Sildegra *Fako, Turk.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Silder *Viofar, Gr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Silegon *Teva, Hung.*
Milk thistle (p.1452·1).
Liver disorders.

Silence *Yung Shin, Hong Kong.*
Lorazepam (p.1004·1).
Anxiety.

Silencium
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Pastilles: Dextromethorphan (p.1555·2); benzocaine (p.1854·1).
Coughs.

Sanofi-Aventis, Braz.
Syrup: Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); sodium citrate (p.1673·3).
Coughs.

Silenil *Biofarm, Pol.*
St John's wort (p.422·3).
Depression.

Silentan *Krewel, Ger.†.*
Nefopam hydrochloride (p.94·2).
Pain.

Sileton *Silesia, Chile†.*
Vitamin and mineral preparation (p.1922·1).
Tonic.

Silettum *Jaldes, Fr.*
Lithothamnium calcareum; palmaria palmata; hydrolysed sesame protein; vitamin B substances (p.1922·1).
Hair disorders.

Silex *Darya-Varia, Indon.*
Guaifenesin (p.1561·3); thyme (p.2401·1); primula (p.2372·2); althaea (p.2253·3); drosera (p.2297·3); wild thyme (p.2415·3); eucalyptus oil (p.2301·2); anise oil (p.2258·2).
Cough.

Silfedrine *Silarx, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Silflam *Silom, Thai.†.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Silfox *Ivax, Arg.*
Diclofenac sodium (p.44·3).
Formerly contained rofecoxib.
Musculoskeletal and joint disorders; pain.

Silfox Flex *Ivax, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint, and peri-articular disorders.

Silgard *MSD, Cz.; MSD, Hung.; MSD, Pol.; MSD, Port.*
A human papillomavirus vaccine (HPV types 6, 11, 16, and 18) (p.2217·3).
Active immunisation.

Silgel *Nagor, UK.*
Silicone (p.2032·1).
Hypertrophic and keloid scars.

Silglos *Uniao Quimica, Braz.*
Sulfadiazine silver (p.337·2).
Skin infections.

Silhouette Duo *Homeocan, Canad.†.*
Homoeopathic preparation.

Silibene *Merckle, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Silic *Ego, NZ.*
Dimeticone (p.2032·1); glycerol (p.2314·2).
Barrier preparation; bed sores; eczema.

Silic 15 *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.*
Dimeticone 350 (p.2032·1).
Barrier preparation; dry skin.

Silica L11 *Homeocan, Canad.†.*
Homoeopathic preparation.

Silica-OK *Wassen, UK.*
Silica; selenium; vitamins (p.1922·1).

Silicare *Orion, NZ†.*
Dimeticone (p.2032·1).
Barrier agent.

Silicea Complexe no 11 *Lehning, Fr.*
Homoeopathic preparation.

Silicic Complex *Procare, Austral.†.*
Equisetum (p.2299·3); silica (p.2146·2); calcium (p.1675·2); potassium (p.1684·2).
Brittle nails and hair; tissue repair.

Silicin *Greater Pharma, Thai.*
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Silicol *Szama, Arg.*
Barrier cream.
Dermatitis; nappy rash; skin irritation.

Silicon *Andromaco, Venez.†.*
Simeticone (p.1770·2).
Flatulence.

Silicsan *Rayere, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Silicur *Hexal, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Silidermil
Note. This name is used for preparations of different composition.
Rottapharm, Spain.
Ointment: Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Skin disorders.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Rottapharm, Spain†.
Topical powder: Cetylpyridinium chloride (p.1635·1); dimeticone (p.2032·1); zinc oxide (p.1621·2).
Skin disorders.

Silidral *Spedrog, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Silidral Plus *Spedrog, Arg.*
4 Tablets, alendronate sodium (p.1088·1); 28 tablets, calcium carbonate (p.1714·1).
Osteoporosis.

Silidron *GSK, Braz.*
Dimeticone (p.1770·2).
Flatulence.

Siligaz
Note. This name is used for preparations of different composition.
Bio-Sante, Canad.; Arkomedika, Fr.
Simeticone (p.1770·2).
Meteorism.

Prater, Chile.
Domperidone (p.1726·2).
Dyspepsia; gastroparesis; nausea and vomiting.

Silimalon *Nikkho, Braz.*
Methionine (p.1450·1); silymarin (p.1452·2).
Liver disorders.

Silimarin *Benedetti, Ital.*
Milk thistle (p.1452·1).
Liver disorders.

Silimarit *Bionorica, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Silimax *Filofarm, Pol.*
Silymarin (p.1452·2).
Liver disorders.

Silimazu *Farmasur, Spain†.*
Silymarin (p.1452·2).
Toxic hepatitis.

Sili-Met-San *Therabel, Belg.; UCB, Switz.†.*
Dimeticone (p.1770·2); calcium pantothenate (p.1959·3).
Aid to gastrointestinal radiographic examination; trapped gastrointestinal gas.

Silina *Bilim, Turk.*
Ampicillin (p.204·1).
Bacterial infections.

Silinove *Motima, Fr.*
Egg shell.
Dietary supplement; fragile hair and nails.

Siliprele *Herbaxt, Fr.*
Equisetum (p.2299·3).
Gastrointestinal and renal disorders.

Silirex *Lampugnani, Ital.*
Silymarin (p.1452·2).
Liver disorders.

Silisan *Merck, Ital.*
Simeticone (p.1770·2); calcium pantothenate (p.1959·3).
Gastrointestinal disorders associated with excess gas; preparation of the stomach for endoscopy and surgery.

Siliumbran *Biotech Naturis, Venez.*
Psyllium (p.1737·1).
Constipation.

Siliver *Farmasa, Braz.*
Milk thistle (p.1452·1).
Liver disorders.

Silkis *AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Chile; Galderma, Cz.; Galderma, Fin.; Galderma, Fr.; Galderma, Ger.; Lavipharm, Gr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Ital.; Galderma, Mex.; Galderma, Neth.; Galderma, Norw.; Galderma, Philipp.; Galderma, Pol.; Galderma, Port.; Galderma, Singapore; Galderma, Spain; Galderma, Switz.; Galderma, UK; Galderma, Venez.*
Calcitriol (p.1986·2).
Psoriasis.

Silky Smooth *Hovid, Malaysia.*
Glycosaminoglycans; tocotrienol.
Spider veins; varicose vains.

Silliver *Abbott, Ital.†.*
Silymarin (p.1452·2).
Liver disorders.

Sillix *Giuliani, Ital.†.*
Dried yeast (p.1998·3); vitamin B substances (p.1922·1).

Sillix C *Giuliani, Ital.†.*
Dried yeast (p.1998·3); vitamin B substances; vitamin C (p.1922·1).
Nutritional supplement.

Silmar *Hennig, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Silmycetin *Silom, Thai.*
Chloramphenicol (p.239·3).
Bacterial eye or ear infections.

Sil-Norboral *Silanes, Mex.*
Glibenclamide (p.440·1); metformin (p.453·3).
Diabetes mellitus.

Siloam *Medimar, Gr.*
Citalopram (p.385·3).
Depression.

Siloderm *Vardhaman, India.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2); calamine (p.1591·2); cetrimide (p.1634·1).
Dermatitis.

Silogin *Diba, Mex.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Silol *Polon, Pol.*
Dimeticone (p.2032·1).
Barrier preparation.

Silomat
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Arg.†; Boehringer Ingelheim, Austria†; Boehringer Ingelheim, Belg.†; Boehringer Ingelheim, Braz.†; Boehringer Ingelheim, Chile†; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Fin.†; Boehringer Ingelheim, Ger.†; Boehringer Ingelheim, Gr.†; Boehringer Ingelheim, Malaysia†; Boehringer Ingelheim, Port.†; Boehringer Ingelheim, Singapore†; Boehringer Ingelheim, Thai.†; Boehringer Ingelheim, Venez.†.
Clobutinol hydrochloride (p.1554·1).
Cough.

Boehringer Ingelheim, Fr.†.
Oral solution; tablets: Clobutinol hydrochloride (p.1554·1).
Coughs.

Boehringer Ingelheim, Fr.†.
Syrup: Clobutinol hydrochloride (p.1554·1); sodium benzoate (p.1630·2).
Coughs.

Silomat Compositum *Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Venez.†.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1).
Bronchospasm; cough.

Silomat DA *Boehringer Ingelheim, S.Afr.†.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1).
Coughs.

Silomat DMP *Boehringer Ingelheim, Ger.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Silomat Plus *Boehringer Ingelheim, Braz.†.*
Clobutinol hydrochloride (p.1554·1); doxylamine succinate (p.578·2).
Coughs.

Silomat-Fher *Boehringer Ingelheim, Ital.†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Silon *Smith & Nephew, Swed.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Barrier cream.

Silopect *Pyridam, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Silostar *Uriach, Spain.*
⊗ Nebivolol hydrochloride (p.1347·1).
Hypertension.

Silovir *Eczacibasi, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Silox-50 *Jean-Marie, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Flatulence; gastritis; gastrointestinal hyperacidity; heartburn.

Siloxan *Nycomed, Norw.*
Simeticone (p.1770·2).
Flatulence; postoperative intestinal gas retention.

Siloxogene *RPG, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal hyperacidity.

Silphen *Silarx, USA.*
Diphenhydramine hydrochloride (p.577·2).

Silphen DM *Silarx, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Silrelax *Silesia, Chile†.*
Chlormezanone (p.968·3); dipyrone (p.49·2).
Musculoskeletal and joint disorders; pain.

Siltussin
Note. This name is used for preparations of different composition.
Silom, Thai.
Guaifenesin (p.1561·3); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Silarx, USA.
Guaifenesin (p.1561·3).
Coughs.

Siltussin DM *Silarx, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Silubin
Grunenthal, Cz.†; Grunenthal, Switz.†.
Buformin hydrochloride (p.438·3).
Diabetes mellitus.

Andromaco, Spain†.
Buformin (p.438·2).
Diabetes mellitus.

Siludane *Darier, Mex.†.*
Ispaghula (p.1737·1).

Siludrox *Eurofarma, Braz.*
Dimeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Flatulence; gastrointestinal hyperacidity.

Silueta Plus *Incaico, Arg.*
Carnitine (p.1932·2); fucus (p.2384·2); garcinia (p.2309·2); equisetum (p.2299·3).
Obesity.

Silum *Mersifarma, Indon.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Silvadene *Aventis, Mex.; Eczacibasi, Turk.; Hoechst Marion Roussel, USA.*
Sulfadiazine silver (p.337·2).
Infected burns; infected ulcers and wounds.

Silvadiazin *Toprak, Turk.; Julphar, UAE.*
Sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Silvamed *Kocak, Turk.*
Sulfadiazine silver (p.337·2).
Infected burns, ulcers and wounds.

Silvaysan *Sanum-Kehlbeck, Ger.*
Milk thistle (p.1452·1).
Liver disorders.

Silvazine *Smith & Nephew, Austral.; Smith & Nephew, NZ; Smith & Nephew, Singapore.*
Sulfadiazine silver (p.337·2); chlorhexidine gluconate (p.1635·3).
Prevention and treatment of infection in burns, ulcers, and wounds.

Silvederma *Asmopul, Arg.†; Expomedica, Port.; Aldo-Union, Rus.; Aldo, Spain; Medifarm, Venez.*
Sulfadiazine silver (p.337·2).
Bacterial skin infections; burns; ulcers; wounds.

Silvercef *Uno, Ital.†.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Silvercel *Johnson & Johnson, Ital.*
Hydroalginate dressing with silver (p.2140·3) (p.2387·1).
Infected wounds.

Silverdin *Deva, Turk.*
Sulfadiazine silver (p.337·2).
Infected burns, ulcers and wounds.

Silverdres *Deverge, Ital.*
Polyurethane dressing with silver (p.1611·1) (p.2387·1).
Burns; wounds.

Silverex *Crosslands, India.*
Sulfadiazine silver (p.337·2); chlorhexidine gluconate (p.1635·3).
Burns; leg ulcers; pressure sores.

Silverit *Proge, Ital.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Silverol *Abic, Israel; Abic-Teva, Thai.†.*
Sulfadiazine silver (p.337·2).
Infected burns; infected skin ulcers; infected wounds.

Silvertone *Resinag, Switz.*
Sulfadiazine silver (p.337·2).
Infected burns, wounds, and ulcers.

Silvespray *Casimiro & Moreira, Port.*
Sulfadiazine silver (p.337·2).
Burns, ulcers, wounds; skin infections.

Silvia Osteo *Alta Care, Ital.*
Calcium phosphate (p.1676·2); lithothamnium calcareum; vitamin B substances (p.1922·1).
Calcium supplement.

Silvin *ICM, Singapore.*
Sulfadiazine silver (p.337·2); chlorhexidine gluconate (p.1635·3).
Infected burns, leg ulcers and pressure sores.

Silybon *Micro, India.*
Silymarin (p.1452·2).
Liver disorders.

Silybum Complex *Blackmores, Austral.†.*
Milk thistle (p.1452·1); garlic (p.2309·2); taraxacum (p.2395·1); nicotinic acid (p.1957·3); sodium sulfate (p.1771·3).
Hypercholesterolaemia; liver and biliary-tract disorders.

Silygal *Ivax, Cz.*
Silymarin (p.1452·2).
Liver disorders.

Silyhexal *Hexal, Austria.*
Milk thistle (p.1452·1).
Liver disorders.

Silymarin Phytosome *Eagle, Austral.†.*
Milk thistle (p.1452·1).
Digestive disorders.

Sily-Sabona *Sabona, Ger.†.*
Milk thistle (p.1452·1).
Liver disorders.

Silzolin *Savio, Ital.†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Sim *Galmed, Cz.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simaal Gel 2 *Schein, USA†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Hyperacidity.

Simacort *Siam Bheasach, Thai.*
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Musculoskeletal, joint, and peri-articular disorders; skin disorders.

Simacron *Tempo Scan Pacific, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Simagel
Note. This name is used for preparations of different composition.
Philopharm, Ger.
Almasilate (p.1705·1).
Gastrointestinal disorders.

Atlantic, Malaysia.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Simaglen *Unison, Hong Kong; Unison, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; systemic mastocytosis; Zollinger-Ellison syndrome.

Simaphil *Philopharm, Ger.*
Magaldrate (p.1742·3).
Gastrointestinal disorders.

Simarc-2 *Fahrenheit, Indon.*
Warfarin sodium (p.1425·2).
Coronary occlusion; venous thrombosis.

Simaspen *Ranbaxy, S.Afr.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Simator *Pinewood, Irl.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simatral *Ethica, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Simbado *Lapi, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simbela *Belupo, Cz.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simbicort *AstraZeneca, Rus.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma.

Simbion *Merck, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Simcard *Cipla, Hong Kong; Cipla, India; Cipla, Malaysia; Cipla-Medpro, S.Afr.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simcef *Erlimpex, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Simchol *Otsira, India; Ikapharmindo, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simcone *TO-Chemicals, Thai.*
Simeticone (p.1770·2).
Flatulence.

Simcor
Note. This name is used for preparations of different composition.
Medikon, Indon.
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Abbott, USA.
Nicotinic acid (p.1957·3); simvastatin (p.1390·2).
Hypercholesterolaemia.

Simcora *Ecosol, Switz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

SimcorHexal *Hexal, Austria†.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Simdax *Abbott, Arg.; Orion, Austria; Abbott, Cz.; Orion, Fin.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Israel; Abbott, Ital.; Abbott, Mex.; Abbott, NZ; Abbott, Norw.; Abbott, Port.; Orion, Rus.; Abbott, Spain; Orion, Swed.; Abbott, Turk.*
Levosimendan (p.1324·3).
Heart failure.

Simeco
Note. This name is used for preparations of different composition.
Wyeth, Gr.; Wyeth, India.
Aluminium hydroxide (p.1706·2); simeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Antacid; flatulence; gastrointestinal hyperacidity; peptic ulcer.

Wyeth, Hong Kong†; Sunthi Sepuri, Indon.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastro-oesophageal reflux.

Wyeth, Philipp.; Whitehall, Thai.†.
Oral suspension: Aluminium hydroxide (p.1706·2); simeticone (p.1770·2); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Wyeth, Philipp.
Tablets: Simeticone (p.1770·2); hydrotalcite (p.1733·3); magnesium hydroxide (p.1743·2).
Flatulence; gastric hyperacidity.

Wyeth Consumer, Thai.; Wyeth, UK.
Tablets: Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity.

Simeco Plus *Eurofarma, Braz.; Wyeth Consumer, Chile†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity; meteorism.

Simecon *Sanitas, Arg.; Chinta, Thai.*
Simeticone (p.1770·2).
Gastrointestinal disorders with excess gas; infant flatulence.

Simecon Antiacido *Sanitas, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Simecrin *Crinos, Ital.*
Simeticone (p.1770·2).
Flatulence.

Simegel *Medipharma, Hong Kong†.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Dyspepsia; flatulence; gastrointestinal hyperacidity; peptic ulcer.

Simelgat Plus *Munir, Turk.*
Magaldrate (p.1742·3); simeticone (p.1770·2).

Simepar
Mepha, Cz.; Mepha, Hong Kong; Mepha, Malaysia; Mepha, Singapore.
Silymarin (p.1452·2); vitamin B substances (p.1922·1).
Biliary-tract disorders; liver disorders; nutritional supplement.

Mepha, Switz.†.
Milk thistle (p.1452·1); vitamin B substances (p.1922·1).
Liver disorders.

Simestat *Simesa, Ital.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Simet *Jelfa, Pol.*
Simeticone (p.1770·2).
Excess gastrointestinal gas.

Simetac *Vida, Hong Kong.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer.

Simet-AF *Soma, Switz.†.*
Simeticone (p.1770·2).
Aid in gastrointestinal procedures; detergent intoxication; flatulence.

Simet-Al *Kato, Pol.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; heartburn; meteorism.

Simetic *Antonetto, Ital.*
Simeticone (p.1770·2).
Flatulence.

Simetrid *Nizpharm, Rus.*
⊗ Fluocinolone acetonide (p.1531·3); bismuth subgallate (p.1711·1); menthol (p.2340·1); trimecaine (p.1872·3).
Anorectal disorders.

Simetyl *M & H, Thai.*
Simeticone (p.1770·2).
Flatulence.

Simex *Hua, Thai.*
Cimetidine (p.1716·2).
Peptic ulcer; Zollinger-Ellison syndrome.

Simgal *Ivax, Cz.; Ivax, Pol.; Galena, Rus.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simicol *CTI, Israel; CTS, Rus.†.*
Simeticone (p.1770·2).
Flatulence; griping pain; infant colic.

Similac 60/40 *Ross, Israel.*
Low-mineral infant feed (p.1922·1).

Similac Advance HA *Abbott, Port.†.*
Infant feed (p.1922·1).
Milk protein allergy.

Similac Advance Hypoalergenica *Abbott, Venez.*
Infant feed (p.1922·1).

Similac Advance LF *Abbott, Indon.; Abbott, Mex.*
Infant feed (p.1922·1).
Lactose intolerance.

Similac Advance libre de lactosa *Abbott, Venez.*
Infant feed (p.1922·1).
Lactose intolerance.

Similac Advance Sin Lactosa *Abbott, Chile.*
Infant feed (p.1922·1).
Lactose intolerance.

Similac Isomil *Abbott, Israel.*
Infant feed (p.1922·1).
Cows milk protein sensitivity.

Similac Lactose Free *Ross, USA.*
Lactose-free infant feed (p.1922·1).
Lactose intolerance.

Similac LF *Abbott, Canad.; Abbott, Hong Kong; Syrio, Ital.; Abbott, Malaysia; Abbott, Thai.*
Lactose-free infant feed (p.1922·1).
Diarrhoea; lactose intolerance.

Similac Mama's Best *Abbott, Indon.*
Nutritional supplement for pregnancy and lactation (p.1922·1).

Similac PM 60/40 *Ross, USA.*
Low-mineral infant feed (p.1922·1).
Hypocalcaemia; renal impairment.

Similac RA *Syrio, Ital.*
Infant feed (p.1922·1).
Hypersensitivity.

Similasan I *Ocusoft, USA.*
Artificial tears.

Similia *Hochstetter, Chile†.*
Hamamelis (p.2318·2).
Haemorrhoids.

Similibus *Knop, Chile.*
Homoeopathic preparation.

Simirex *Sanofi-Aventis, Cz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simlo *Ipca, India; Ipca, Rus.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simoph Tears *Siam Bheasach, Thai.†.*
Hypromellose (p.2144·2) (p.1622·2).
Dry eye; wetting solution for hard contact lenses.

Simovil *MSD, Israel.*
Simvastatin (p.1390·2).
Coronary atherosclerosis; hypercholesterolaemia.

Simoxil *Infosint, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Simoyiam *Siam Bheasach, Thai.*
Flunarizine hydrochloride (p.580·2).
Cerebrovascular disorders; migraine.

Simp *Esoform, Ital.*
Chlorhexidine gluconate (p.1635·3); benzalkonium chloride (p.1629·1).
Skin and wound disinfection.

Simperten *Laboratorios Chile, Chile.*
Losartan potassium (p.1326·1).
Hypertension.

Simperten-D *Laboratorios Chile, Chile.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Simplamox *ISF, Ital.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Simplaqor *Novartis, Gr.; Sandoz, Mex.; Sandoz, Venez.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simple HCG *Brassora, Arg.*
Pregnancy test (p.2372·1).

Simplene *Smith & Nephew, S.Afr.*
⊗ Adrenaline (p.1203·2).
Open-angle glaucoma.

Simplet *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Simplex *Ophtha, Norw.*
Liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Sore and dry skin in the eyelid area.

Simplex-Fieberblasen *Nycomed, Austria.*
Aciclovir (p.862·3).
Herpes labialis.

Simplicity *Vita Health, Canad.†.*
Pregnancy test (p.2372·1).

Simplotan *Pfizer, Austral.; Pfizer, Ger.†; Pierre Fabre, Ger.†.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Simply Cough *McNeil Pharmaceutical, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Simply Sleep *McNeil Consumer, Canad.; McNeil, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Simply Stuffy *McNeil Pharmaceutical, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Simpottantacinque *Esoform, Ital.*
⊗ Benzalkonium chloride (p.1629·1); chlorhexidine gluconate (p.1635·3); alcohol (p.1625·2).
Disinfection of skin, hands, and wounds.

Simprox *Areu, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Simpsons *Medico-Biological Laboratories, UK.*
Zinc stearate (p.2139·3); zinc oxide (p.1621·2); sublimed sulfur (p.1614·1); salicylic acid (p.1612·2).
Skin disorders.

Simratio *Ratiopharm, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simredin *Polfa Kutno, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simron Plus *SmithKline Beecham, USA.*
Vitamin B substances with vitamin C, iron, and folic acid (p.1922·1).

Simrose *Serum Institute, India.*
Evening primrose oil (p.2302·1).
Premenstrual syndrome.

SimStatin *AFT, NZ.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hyperlipidaemias.

Simstin *Biochemie, Austria†.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Simtan *Clonmel, Irl.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simtec *CCM, Hong Kong; CCM, Malaysia.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Simtin *Eurodrug, Hong Kong; Eurodrug, Malaysia; Eurodrug, Philipp.; Eurodrug, Singapore.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simuc *Cypress, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Cough; otitis media; upper respiratory-tract congestion.

Simucin *Siam Bheasach, Thai.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Simulcium G3 *Dermoteca, Port.*
Emollient and moisturiser.
Skin disorders.

Simulect *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA.*
Basiliximab (p.1821·2).
Renal transplant rejection.

Simultan
Note. This name is used for preparations of different composition.
Lazar, Arg.
Valsartan (p.1420·2).
Hypertension.

Andromaco, Chile.
Thioridazine hydrochloride (p.1031·2).
Childhood behaviour disorders; depression; psychoses.

Simultan D *Lazar, Arg.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Simultec *Novartis, Venez.*
Basiliximab (p.1821·2).
Renal transplant rejection.

Simusol *Siam Bheasach, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Simva *Sandoz, Cz.; Basics, Ger.; Hennig, Ger.; Hexal, Ger.; TAD, Ger.; TAD, Neth.†.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

SimvaAPS *APS, Ger.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvabell *Bellwether, Austral.*
Simvastatin (p.1390·2).

Simvabeta *Betapharm, Ger.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvacard *Zentiva, Cz.; AWD, Ger.; Zentiva, Pol.; Leciva, Rus.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvachol *Medicus, Gr.†; Polfa Grodzisk, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvacol *Teva, Hung.; APS, Port.*
Simvastatin (p.1390·2).
Coronary artery disease; hyperlipidaemias.

Simvacor *Lindopharm, Ger.; Kleva, Gr.; Unipharm, Israel; YSP, Malaysia; Polfarmex, Pol.; Pharma Dynamics, S.Afr.; Kleva, Singapore.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvadoc *Docpharm, Ger.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvador *Discovery, UK.*
Simvastatin (p.1390·2).
Hypercholesterolaemia; secondary prevention of coronary heart disease.

Simvadura *Merck dura, Ger.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvafour *Solvay, Belg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvagamma *Worwag, Ger.; Worwag, Hung.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvahex *Hexal, Philipp.; Salutas, Philipp.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvahexal *Hexal, Austral.; Hexal, Pol.; Hexal, Rus.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvakol *Nobel, Turk.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvalark *Leovan, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Simvalid *Polychronus, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Simvalimit *Grindex, Rus.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvalip *Mibe, Ger.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvaprol *Proel, Gr.*
Simvastatin (p.1390·2).

Simvar *Arrow, Austral.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvarcana *Arcana, Austria.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Simvasim *Fariberica, Port.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvasine *Spirig, Switz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvass *Rider, Chile.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvast
Streuli, Switz.
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Julphar, UAE.
Simvastatin sodium (p.1394·1).
Atherosclerosis; hypercholesterolaemia.

Simvastad *Stada, Austria.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Simvastamed *Ethimed, Belg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvasten *Spyfarma, Spain†.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Simvasterol *Polpharma, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvastin *Mepha, Switz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Simvastol *Gedeon Richter, Rus.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvastur *Cantabria, Spain†.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvatin *Lannacher, Austria; Biospray, Gr.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia; hyperlipidaemias.

Simvax *Hexal, Cz.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Simvaxon *Dexxon, Israel.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; coronary atherosclerosis; hypercholesterolaemia.

Simvep *Extractum, Hung.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Simvor *Ranbaxy, Cz.; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, Rus.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simvotin *Stancare, India; Ranbaxy, S.Afr.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Simzor *Gerard, Irl.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sin Colgen Kowa Kaze *Kowa, Jpn.*
⊗ Paracetamol (p.108·1); tranexamic acid (p.1080·3); ethenzamide (p.51·3); chlorphenamine maleate (p.571·3); tipepidine hibenzate (p.1574·2); methylephedrine hydrochloride (p.1564·3).
Cold symptoms.

Sin Mareo x 4 *Perez Gimenez, Spain.*
Dimenhydrinate (p.576·2); belladonna (p.2263·3).
Nausea; vertigo; vomiting.

Sin Q & P Gold *Kowa, Jpn.*
Vitamins (p.1922·1); deer antler velvet; oryzanol (p.2358·3); oxoamidine; caffeine (p.1116·3).
Tonic.

Sin Una Cool Liquid *Kowa, Jpn.*
Diphenhydramine hydrochloride (p.577·2); lidocaine (p.1862·3); levomenthol; dl-camphor (p.2273·2).
Skin irritation.

Sin-A Crud *Quimica y Farmacia, Mex.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Symptoms of overindulgence with food or alcohol.

Sinac *Andromaco, Arg.*
Adapalene (p.1587·1).
Acne.

Sinacid *Rider, Chile.*
Myrtecaine laurilsulfate (p.1867·2); galactane sulfate; aluminium glycinate (p.1706·2).
Gastrointestinal disorders.

Si-Nade *GSK, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; eustachian tube congestion; sinusitis.

Sinadrin Plus *Reese, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dexbrompheniramine maleate (p.569·2).

Sinaf *Taro, Israel.*
⊗ Oxymetazoline hydrochloride (p.1567·2); phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Sinaflan *Akrikhin, Rus.; Nizpharm, Rus.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Sin-A-Gen *Altana, Mex.*
Polysaccharide polysulfuric acid ester; nonoxinol (p.1917·2).
Vaginal contraceptive.

Sinakort-A *Ulagay, Turk.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Sinaler *Cassara, Arg.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; laryngitis; sinusitis.

Sinaler B *Cassara, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Allergic rhinitis; allergic skin disorders; laryngitis; sinusitis.

Sinalfa *Abbott, Denm.; Abbott, Norw.; Abbott, Swed.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Sinalgia
Silesia, Chile†.
Fepradinol hydrochloride (p.60·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Hormona, Mex.
Fepradinol (p.60·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Sinalgico *Bernabo, Arg.*
Ketorolac (p.75·2) or ketorolac trometamol (p.74·2).
Pain.

Sin-Algin *Sanitas, Chile.*
Paracetamol (p.108·1); chlormezanone (p.968·3).
Musculoskeletal and joint disorders; pain.

Sinamida Cicatrizante *Gezzi, Arg.†.*
Ergocalciferol (p.1987·1); zinc oxide (p.1621·2).
Wounds.

Sinamida Econazol *Gezzi, Arg.*
Econazole nitrate (p.531·1).
Fungal skin and vaginal infections.

Sinamida Pies *Gezzi, Arg.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Sinamida Plus *Gezzi, Arg.*
Bifonazole (p.527·3).
Fungal skin infections.

Sinamida-D *Gezzi, Arg.†.*
Zinc oxide (p.1621·2).
Skin disorders.

Sinanem *Nucitec, Mex.*
Vitamin and mineral preparation (p.1922·1).

Sinapause *Organon, Chile; Organon, Mex.*
Estriol succinate (p.2101·1).
Genito-urinary tract disorders associated with oestrogen deficiency.

Sinapdin *Phyto Kemo, Indon.*
Cyproheptadine hydrochloride (p.575·1).
Allergic conjunctivitis; angioedema; rhinitis; urticaria.

Sinapet *Silesia, Chile†.*
⊗ Fenproporex hydrochloride (p.2157·1).
Obesity.

Sinapis nigra N Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Sinapisme Rigollot *SERP, Mon.*
Defatted black mustard paper (p.2349·1).
Respiratory-tract congestion.

Sinaplin *Rimsa, Mex.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Sinapsan *Rodleben, Ger.; Vedim, Ger.*
Piracetam (p.368·2).
Organic brain disorders.

Sinaqua *Sofex, Port.†.*
Barrier preparation.

Sinarden *Vitae, Mex.*
Aciclovir (p.862·3).
Herpes labialis.

Sinarest
Note. This name is used for preparations of different composition.
Ciba, USA.
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Centaur, India.
Nasal drops: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Centaur, India.
Oral drops: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, pseudoephedrine hydrochloride, and chlorphenamine maleate.
Allergic rhinitis; cold and influenza symptoms; otitis media; sinusitis.

Centaur, India.
Syrup: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Formerly contained paracetamol, pseudoephedrine hydrochloride, chlorphenamine maleate, sodium citrate, and menthol.
Allergic rhinitis; cold and influenza symptoms; otitis media; sinusitis.

Centaur, India.
Tablets: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Formerly contained paracetamol, pseudoephedrine hydrochloride, chlorphenamine maleate, and caffeine.
Allergic rhinitis; cold and influenza symptoms; otitis media; sinusitis.

Sinarest Linctus *Centaur, India.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); menthol (p.2340·1).
Coughs.

Sinarest Vapocaps *Centaur, India.*
Camphor (p.2273·2); chlorothymol (p.1640·1); cineole (p.2282·3); menthol (p.2340·1); terpineol (p.2396·1).
Cold symptoms; pharyngitis; sinusitis; upper respiratory-tract congestion.

Sinarest-PD *Centaur, India.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; sinusitis.

Sinarona *Kener, Mex.*
Amiodarone hydrochloride (p.1210·2).
Angina pectoris; arrhythmias.

Sinartrol *Silesia, Chile†; Pharmanel, Gr.; SPA, Ital.*
Piroxicam cinnamate (p.118·2).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Sinasmal *Laboratorios Chile, Chile.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Sinaspril-Paracetamol *Bayer, Neth.*
Paracetamol (p.108·1).
Fever; pain.

Sinaxial
TRB, Arg.
Sialogangliosides (porcine).
Cerebral trauma; peripheral neuropathy.

TRB, Braz.
Polysiagoside (p.2309·1).
Cerebrovascular disorders.

Sincerum *Dallas, Arg.*
Sodium carbonate (p.2389·1); phenazone (p.116·1); neomycin sulfate (p.305·1); cetrimide (p.1634·1).
Ear disorders.

Sincerum Biotic *Dallas, Arg.*
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1).
Infected ear disorders.

Sincerum Biotic L *Dallas, Arg.*
⊗ Neomycin sulfate (p.305·1); dexamethasone (p.1526·1); polymyxin B sulfate (p.317·3); lidocaine hydrochloride (p.1862·3).
Infected ear disorders.

Sincerum Dry *Dallas, Arg.*
Isopropyl alcohol (p.1650·3); glycerol (p.2314·2).
Removal of trapped ear water.

Sincon *CCS, Swed.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Sincrivit *AGIPS, Ital.*
Multivitamin preparation (p.1922·1).

Sincrosa *Ares, Mex.*
Acarbose (p.436·2).
Diabetes mellitus.

Sincrover *CT, Ital.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Sindaxel *Sindan, Pol.*
Paclitaxel (p.759·1).
Breast cancer; non small-cell lung cancer; ovarian cancer.

Sindel *Liferpal, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Sindo *Nordin, Mex.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Sindol *Ahimsa, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Sindopa *Pacific, NZ.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Sindrat *Brasterapica, Braz.†.*
Oral rehydration solution (p.1672·2).
Diarrhoea; oral rehydration therapy.

Sindrolen
Note. This name is used for preparations of different composition.
Temis, Arg.†.
Injection: ⊗ Piroxicam (p.117·3); dexamethasone sodium phosphate (p.1526·2); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3).
Inflammation; muscle spasm; neuritis.

Temis, Arg.†.
Topical gel: Piroxicam (p.117·3).
Inflammation.

Sindrolen Vitaminado *Temis, Arg.†.*
Piroxicam (p.117·3); paracetamol (p.108·1); vitamin B ; vitamin B .
Inflammation; pain.

Sindronat *Sindan, Pol.*
Clodronate disodium (p.1095·3).
Hypercalcaemia of malignancy; osteolysis of malignancy.

Sine-Aid IB *McNeil Consumer, USA.*
Pseudoephedrine (p.1571·2); ibuprofen (p.64·2).

Sine-Aid Maximum Strength *McNeil Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Sinus headache.

Sineamin *Medifood, Ital.*
Protein-free and gluten-free food for special diets (p.1922·1).

Sinease *Schering-Plough, Austral.†.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis.

SinEccH *Alpine, Singapore.*
Arnica (p.2260·2).
Soft-tissue injuries.

Sinecod *Novartis Consumer, Belg.; Novartis Consumer, Cz.; Novartis, Gr.; Novartis Consumer, Hung.; Novartis Consumer, Neth.; Novartis, Philipp.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.*
Butamirate citrate (p.1553·1).
Cough.

Sinecod Tosse Fluidificante *Novartis Consumer, Ital.*
Carbocisteine (p.1553·2).
Catarrh; coughs.

Sinecod Tosse Sedativo *Novartis Consumer, Ital.*
Butamirate citrate (p.1553·1).
Coughs.

Sinedal *Synpharma, Switz.†.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Sinedol *Italmex, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Sinedol Ibuprofen *Hanseler, Switz.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Sinedopa *Duopharma, Hong Kong.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Sinegastrin *Novag, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Sinegrip *Unifarm, Ital.*
Paracetamol (p.108·1); sodium ascorbate (p.1984·1).
Cold and influenza symptoms; fever; pain.

Sinei *Steiner, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Sinekin *Fabop, Arg.*
Biperiden (p.797·2).
Parkinsonism.

Sinemet *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; BMS, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; BMS, Fr.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; BMS, Irl.; MSD, Israel; BMS, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; Pharmalink, Philipp.; MSD, Pol.; MSD, Port.; MSD, S.Afr.; MSD, Singapore; BMS, Spain; MSD, Swed.; MSD, Switz.; M & H, Thai.; MSD, Turk.; BMS, UK.; BMS, USA; MSD, Venez.*
Carbidopa (p.803·1); levodopa (p.804·3).
These ingredients can be described by the British Approved Name Co-careldopa.
Drug-induced extrapyramidal disorders; parkinsonism.

Sinemet-CR *IFET (ΙΦΕΤ), Gr.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Sine-Off Maximum Strength Allergy/Sinus *SmithKline Beecham, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Sine-Off Maximum Strength No Drowsiness Formula *SmithKline Beecham Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Sine-Off Sinus/Cold *Hogil, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Sinepin *Marlborough Pharmaceuticals, UK.*
Doxepin (p.389·2).

Sinequan *Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Erfa, Canad.; Pfizer, Denm.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Irl.; Pfizer, Mex.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Farmasierra, Spain; Pfizer, Thai.; Pfizer, UK†; Roerig, USA.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; mixed anxiety-depressive states.

Sinerbe *Plough, Port.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2); guaifenesin (p.1561·3).
Allergic respiratory-tract disorders; coughs.

Sinergen *Biosintetica, Braz.*
Amlodipine besilate (p.1214·1); enalapril maleate (p.1276·1).
Hypertension.

Sinergina *Faes, Spain.*
Phenytoin (p.495·2).
Epilepsy.

Sinergix *Rimsa, Mex.*
Ketorolac trometamol (p.74·2); tramadol hydrochloride (p.130·3).
Pain.

Sinertec *MSD, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Sinesmin *Best, Mex.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Sinestic *Biofutura, Ital.; Grapharma, Neth.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Sinestron *Medix, Mex.†.*
Lorazepam (p.1004·1).
Anxiety; mixed anxiety depressive states.

Sinex
Note. This name is used for preparations of different composition.
Procter & Gamble, Mex.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Richardson-Vicks, USA.
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Sinexsensi *Procter & Gamble, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Sinezan *Esoform, Ital.*
Pyrethrum flower (p.2049·3); piperonyl butoxide (p.2049·1); diethyltoluamide (p.2041·1).
Insect repellent.

Sinfemix *Imuna, Cz.†.*
Food for special diets (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Sinfenal *Imuna, Cz.†.*
Food for special diets (p.1922·1).
Hyperphenylalaninaemia; phenylketonuria.

Sinfexina *Solara, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Sinfract *Euromex, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Sinfrontal *Muller Goppingen, Ger.*
Homoeopathic preparation.

Sinfung *Denver, Arg.*
Clotrimazole (p.530·1).
Fungal skin infections.

Singastril *Andromaco, Chile†.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Singlauc *Bausch & Lomb, Arg.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Singlet *SmithKline Beecham Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Singloben *Ares, Mex.*
Glipizide (p.441·3).
Diabetes mellitus.

Singril
Note. This name is used for preparations of different composition.
Offenbach, Mex.
Injection: Moroxydine hydrochloride (p.898·2); chlorphenamine (p.572·2); dipyrone (p.49·2).
Cold and influenza symptoms.

Offenbach, Mex.
Syrup: Moroxydine hydrochloride (p.898·2); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Influenza symptoms.

Singrilen *Offenbach, Mex.*
Moroxydine hydrochloride (p.898·2); paracetamol (p.108·1); phenylephrine (p.1568·1); chlorphenamine (p.572·2).
Cold and influenza symptoms.

Singrips *Confar, Port.*
Paracetamol (p.108·1).
Fever; pain.

Singulair *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Dieckmann, Ger.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Montelukast sodium (p.1126·2).
Allergic rhinitis; asthma.

Singulergy *MSD, Port.*
Montelukast sodium (p.1126·2).
Allergic rhinitis.

Sinhcloran *Vitae, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Sinhidron *Vitae, Mex.*
⊗ Chlortalidone (p.1243·3).

Sinif
Note. This name is used for preparations of different composition.
Valmor, Venez.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Valmor, Venez.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Siniphen Nouvelle formule *Singer, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Sinket *Calox, Venez.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Sinkron *Difass, Ital.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders; mental function disorders.

Sinlergia *Sanitas, Arg.†.*
Pseudoephedrine hydrochloride (p.1571·2); terfenadine (p.590·3).
Respiratory-tract disorders.

Sinlip *Gador, Arg.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Sinmaren *Schering, Spain†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Sinmol *Maxfarma, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Sinobid *Biospray, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Sinobiotik *Galenium, Indon.*
⊗ Gentamicin sulfate (p.282·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Sinogan
Sanofi-Aventis, Chile; IFET (ΙΦΕΤ), Gr.; Sanofi-Aventis, Venez.
Levomepromazine (p.1002·3).
Anxiety; insomnia; nausea and vomiting; neuralgia; pain; premedication; psychoses; sedative.

Aventis, Mex.; Sanofi-Aventis, Spain.
Levomepromazine hydrochloride (p.1002·3) or levomepromazine maleate (p.1003·1).
Anxiety; depression; pain; psychoses; sleep disorders.

Sinografin *Squibb Diagnostics, USA.*
Meglumine amidotrizoate (p.1475·3); meglumine adipiodone (p.1475·2).
Contrast medium for hysterosalpingography.

Sinolip *Apotex, Philipp.*
Lisinopril (p.1325·2).
Hypertension; myocardial infarction.

Sinomarin *Omega, Fr.; Gerolymatos, Hong Kong; Genesis, Turk.*
Sea water (p.1686·1).
Nasal cleansing; nasal congestion.

Sinop *Craveri, Arg.†.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Sinophenin *Rodleben, Ger.†; IFET (ΙΦΕΤ), Gr.*
Promazine hydrochloride (p.1021·2).
Anxiety disorders; pain; pre- and postoperative sedative; pruritus; psychoses; sleep disorders; vomiting; withdrawal symptoms.

Sinopil *GSK, India.*
Lacidipine (p.1322·2).
Hypertension.

Sinopren *Ranbaxy, S.Afr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Sinopril
Note. This name is used for preparations of different composition.
Mead Johnson, Gr.†.
Fosinopril (p.1292·1).
Hypertension.

Eczacibasi, Rus.
Lisinopril (p.1325·2).
Heart failure; hypertension.

Sinopryl *Eczacibasi, Turk.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Sinoral *Biolab, Malaysia†; Biolab, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Sinoretik *Eczacibasi, Turk.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Sinorezid *Eczacibasi, Rus.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Sinoric *Mersifarma, Indon.*
Allopurinol (p.552·2).
Hyperuricaemia.

Sinose *Salcura, UK.*
Himalayan rock salt; aloe (p.1588·2); eucalyptus (p.2301·2); hippophaes rhamnoides; manuka (p.2337·3); santalum spicatum; melaleuca oil (p.2338·2); chamomile (p.2279·3); mentha arvensis (p.2345·2); propolis (p.2373·3); urtica (p.2409·3).
Rhinitis.

Sinotar *Lane, UK.*
Althaea (p.2253·3); echinacea (p.2298·1); sambucus (p.2383·1).
Blocked sinuses; catarrh.

Sinova *Combiphar, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinovial
Genevrier, Fr.; IBSA, Malaysia.
Sodium hyaluronate (p.2320·1).
Joint disorders; osteoarthritis.

IBSA, Switz.
Hyaluronic acid (p.2320·1).
Degenerative joint disorders.

Sinovula *Asche, Ger.†.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Combined oral contraceptive; menstrual disorders.

Sinoxis *Hosbon, Spain†.*
Buflomedil hydrochloride (p.1236·3).
Vascular disorders.

Sinozol *Best, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Sinozzard *Cryopharma, Mex.*
Prazosin hydrochloride (p.1375·2).
Hypertension.

Sinpasmon *Sanitas, Chile.*
Pipenzolate bromide (p.1762·2); phenobarbital (p.492·2).
Gastrointestinal disorders.

Sinpebac *Grossman, Mex.*
Mupirocin (p.302·3).
Bacterial skin infections; infected burns, ulcers, and wounds.

Sinpet *Pharmacos Abug, Mex.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Sinpor *Neves, Port.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Sinpro N *Worwag, Ger.*
Paracetamol (p.108·1).
Fever; pain.

Sinquan *Pfizer, Ger.†.*
Doxepin hydrochloride (p.389·1).
Anxiety; depression; sleep disorders; withdrawal syndromes.

Sinquane *Pfizer, Switz.*
Doxepin hydrochloride (p.389·1).
Anxiety disorders; depression.

Sinral *Bernofarm, Indon.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Sinroncar *Millet-Franklin, Arg.*
Polysorbate 80 (p.1919·2).
Nasal hygiene.

Sinsia *Seoul Pharma, Singapore.*
Serrapeptase (p.2385·3).
Inflammation; respiratory-tract congestion.

Sintalgin *Solvay, Braz.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Sintamin *Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Sintar *Medilusa, Port.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Sintaser *Serral, Mex.*
⊗ Propranolol (p.1381·1).
Hypertension.

Sintebron *Sintesina, Arg.*
⊗ Ephedrine (p.1558·1); guaifenesin (p.1561·3).
Coughs.

Sintecal *Menarini, Hung.*
Glimepiride (p.441·1).
Diabetes mellitus.

Sintegran *Sintesina, Arg.*
Metoclopramide (p.1747·3).
Nausea and vomiting.

Sintemicina *Sintesina, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Sintenyl *Sintetica, Switz.*
⊗ Fentanyl citrate (p.55·3).
Pain.

Sintepul *Sintesina, Arg.*
Gentamicin (p.284·2).
Bacterial infections.

Sinterol *Klonal, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Sinthrome *Alliance, UK.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Sintisone *Pfizer, Port.†; Pfizer, Venez.*
⊗ Prednisolone steaglate (p.1541·2).
Corticosteroid.

Sintocef *Boniscontro & Gazzone, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Sintoclar *Boniscontro & Gazzone, Ital.*
Citicoline (p.2283·3).
Parkinsonism.

Sintodian *Pharmacia, Ital.†.*
Droperidol (p.994·3).
Anaesthesia; psychoses.

Sintofenac *Sintofarma, Braz.†.*
Diclofenac sodium (p.44·3).

Sintoftona *SMB, Chile.*
⊗ Chloramphenicol (p.239·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Sintolatt *Lampugnani, Ital.*
Lactulose (p.1738·2).
Constipation.

Sintomicetina *Medley, Braz.*
Chloramphenicol (p.239·3).
Bacterial infections.

Sintomodulina *Italfarmaco, Ital.*
Thymopentin (p.2401·3).
Immunodeficiency.

Sintonal *Europharma, Spain.*
Brotizolam (p.965·2).
Insomnia.

Sintopen *Magis, Ital.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sintoplus *PHT, Ital.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Sintopozid *Actavis, Hung.; Sindan, Pol.*
Etoposide (p.718·1).
Malignant neoplasms.

Sintotrat *Bracco, Ital.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin irritation.

Sintozima *Solvay, Braz.*
Pancreatin (p.2360·1); metoclopramide hydrochloride (p.1747·3); bromelains (p.2269·1); dehydrocholic acid (p.2292·2); cellulase (p.2279·1); dimeticone (p.1770·2).
Digestive disorders.

Sintradon *Synthesis, Rus.*
Tramadol hydrochloride (p.130·3).
Pain.

Sintrocid *Collins, Mex.†.*
Levothyroxine (p.2173·2).
Hypothyroidism.

Sintrom *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Paladin, Canad.; Novartis, Fr.; Novartis, Gr.; Novartis, Israel; Novartis, Ital.; Novartis, Mex.; Novartis, Pol.; Novartis, Port.; Novartis, Spain; Novartis, Switz.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Sintrom Mitis *Novartis, Neth.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Sinuberase *Rudefsa, Mex.*
Lactic-acid-producing organisms (p.2372·3).
Diarrhoea; restoration of normal intestinal flora.

Sinuc *Hexal, Ger.*
Ivy (p.2328·1).
Bronchitis; catarrh.

Sinuclear
Note. This name is used for preparations of different composition.
Garec, S.Afr.
Capsules: Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract congestion.

Garec, S.Afr.
Paediatric syrup: Paracetamol (p.108·1); triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms; nasal congestion.

Sinucon *Salters, S.Afr.†.*
⊗ Paracetamol (p.108·1); ephedrine hydrochloride (p.1558·2); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms; hay fever; sinus congestion.

Sinufed *Trima, Israel.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; sinus congestion.

Sinufed Kid Day *Trima, Israel†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion.

Sinufed Kid Night *Trima, Israel†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic disorders; nasal and sinus congestion.

Sinufed Timecelles *Roberts, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and cold symptoms; nasal congestion.

Sinufin *Ivax, Mex.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Sinu-Flu *Universal, S.Afr.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Cold and influenza symptoms.

Sinuforce *Bioforce, Switz.†.*
Homoeopathic preparation.

Sinuforte *Invar, Rus.*
Cyclamen europaeum.
Sinusitis.

Sinuforton
Note. This name is used for preparations of different composition.
Winthrop, Ger.
Capsules: Anise oil (p.2258·2); cowslip rhizome (p.2372·2); thyme (p.2401·1).
Upper respiratory-tract congestion.

Sanofi Synthelabo, Ger.†.
Oral drops: Anise oil (p.2258·2); eucalyptus oil (p.2301·2); thyme (p.2401·1).
Upper respiratory-tract congestion.

Winthrop, Ger.
Oral liquid: Cowslip rhizome (p.2372·2); thyme (p.2401·1).
Cold symptoms.

Sinugesic *Triomed, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Fever; pain; upper respiratory-tract congestion.

Sinulen *Medibrands, Israel.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Sinulin *Flordis, Austral.†.*
Gentian (p.2310·3); primrose.
Respiratory-tract infections; sinusitis.

Sinumax *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion with fever and pain.

Sinumax Allergy Sinus *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms.

Sinumax Co *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Fever; pain; upper respiratory-tract congestion.

Sinumax Cold & Flu Plus Cough *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Sinumax IB *Janssen-Cilag, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Cold and influenza symptoms; sinusitis.

Sinumed *Triomed, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Sinumine *Maxi, Thai.†.*
Carbinoxamine maleate (p.570·2).
Hypersensitivity reactions.

Sinupan *Ion, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs and cold symptoms; nasal congestion.

Sinupas N *Pascoe, Ger.*
Homoeopathic preparation.

Sinupret *Austroplant, Austria; Bionorica, Cz.; Bionorica, Ger.; Bionorica, Hong Kong; Bionorica, Hung.; Bionorica, Indon.; Darya-Varia, Indon.; Bionorica, Philipp.; Pharmalink, Philipp.; Bionorica, Pol.; Bionorica, Rus.; Bionorica, Singapore; Bionorica, Switz.; Bionorica, Thai.*
Gentian root (p.2310·3); cowslip flower (p.2372·2); sorrel (p.2391·1); sambucus flower (p.2383·1); vervain (p.2413·3).
Respiratory-tract disorders; sinusitis.

Sinurit *Microsules, Arg.†.*
Roxithromycin (p.331·1).
Bacterial infections.

Sinus
Note. This name is used for preparations of different composition.
Homeocan, Canad.; Hylands, Canad.
Homoeopathic preparation.

Pasteur, Chile.
Sodium chloride (p.1686·1).
Nasal congestion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Sinus Excedrin *BMS, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sinus Inhalaciones *Boots Healthcare, Spain.*
Camphor (p.2273·2); cineole (p.2282·3); peppermint oil (p.1761·2); pine silvestris oil (p.2368·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Nasal congestion.

Sinus Pain & Nasal Congestion Relief *Vita Health, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Sinusaid *Sriprasit, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sinusalia *Boiron, Canad.*
Homoeopathic preparation.

Sinuselect *Dreluso, Ger.*
Homoeopathic preparation.

Sinusitis Hevert SL *Hevert, Ger.*
Homoeopathic preparation.

Sinusitis-Weliplex *Weber & Weber, Ger.*
Homoeopathic preparation.

Sinuspax *Homeocan, Canad.; Lehning, Fr.*
Homoeopathic preparation.

Sinus-Relief *Major, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Sinustat *Xixia, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Sinustop *Adcock Ingram Self Medication, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1).
Cold and flu symptoms.

Sinustop with Codeine *Adcock Ingram Self Medication, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1); codeine phosphate (p.37·2).
Cold and flu symptoms.

Sinustop Pro *Murdock, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sinustrat *Zurita, Braz.*
Luffa operculata; sodium chloride (p.1686·1).
Nasal congestion.

Sinustrat Solucao Natural *Zurita, Braz.*
Sodium chloride (p.1686·1).
Nasal congestion.

Sinustrat Vasoconstritor *Zurita, Braz.*
⊗ Sodium chloride (p.1686·1); naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Sinusyx *Syxyl, Ger.*
Homoeopathic preparation.

Sinutab
Note.This name is used for preparations of different composition.
Elea, Arg.; Pfizer Consumer, Belg.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Formerly contained paracetamol, phenylpropanolamine hydrochloride, and phenyltoloxamine citrate.
Influenza symptoms; rhinitis with headache and/or fever.

Pfizer, Braz.
Chlorphenamine maleate (p.571·3); aspirin (p.20·3); caffeine (p.1116·3).
Influenza symptoms.

Pfizer, Chile; Pfizer, Philipp.; Pfizer Consumer, S.Afr.
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1).
Cold symptoms; nasal congestion; otitis; rhinitis; sinus headache; sinusitis.

Pfizer Consumer, Irl.†.
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Allergic rhinitis; cold and influenza symptoms; sinusitis.

Pfizer, Venez.†.
Paracetamol (p.108·1); pseudoephedrine (p.1571·2); chlorphenamine (p.572·2).
Influenza symptoms.

Sinutab II *Janssen-Cilag, Port.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Sinusitis.

Sinutab Advance *Pfizer Consumer, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Upper respiratory-tract disorders.

Sinutab with Codeine
Note.This name is used for preparations of different composition.
Pfizer Consumer, Canad.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Cold symptoms; nasal congestion.

Pfizer Consumer, S.Afr.
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); phenyltoloxamine citrate (p.588·1); codeine phosphate (p.37·2).
Cold and influenza symptoms; sinus headache.

Sinutab Extra Strength
Note.This name is used for preparations of different composition.
Pfizer Consumer, Canad.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms; nasal congestion.

Pfizer, Philipp.
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; nasal congestion; sinus headache; sinusitis.

Sinutab Extra Strength Daytime/Nightime
Pfizer Consumer, Canad.
Tablets (Daytime), pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); tablets (Nightime), pseudoephedrine hydrochloride; paracetamol; diphenhydramine hydrochloride (p.577·2).
Cold symptoms; rhinitis; sinusitis.

Sinutab Extra Strenth (Daytime) *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; nasal congestion.

Sinutab Maximum Strength Sinus Allergy *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Sinutab ND *Pfizer Consumer, S.Afr.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Sinutab Nightime *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; nasal congestion.

Sinutab Non Drowsy *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Sinutab Sinus Non Drowsy.
Cold symptoms; nasal congestion.

Sinutab Non-Drying *Warner-Lambert, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Sinutab NS *Pfizer, Philipp.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Sinutab Regular *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly known as Sinutab Sinus & Allergy.
Cold symptoms; nasal congestion.

Sinutab Sinus Allergy & Pain Relief *Johnson & Johnson, Austral.; Pfizer, NZ†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms; sinus headache; upper respiratory-tract disorders.

Sinutab Sinus (Daytime) Non Drowsy *Pfizer Consumer, Canad.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; nasal congestion.

Sinutab Sinus Maximum Strength *Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Formerly known as Sinutab Sinus Without Drowsiness Maximum Strength and contained pseudoephedrine hydrochloride and paracetamol.
Upper respiratory-tract symptoms.

Sinutab Sinus & Pain Relief *Johnson & Johnson, Austral.; Pfizer, NZ†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; sinus headache; upper respiratory-tract disorders.

Sinutab Without Drowsiness *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Sinutil
Note.This name is used for preparations of different composition.
Vincenti, Venez.
Oral drops: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; post-vaccination symptoms; teething.

Vincenti, Venez.
Syrup: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

SINUtuss DM *WE, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Sinuvent PE *WE, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Sinuzin *Biolab, Malaysia†.*
Chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; cold and influenza symptoms; hay fever; respiratory-tract congestion.

Sinvacor *MSD, Ital.*
Simvastatin (p.1390·2).
Coronary atherosclerosis; hypercholesterolaemia.

Sinvalip *Sigma, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvascor *Baldacci, Braz.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia.

Sinvastacor *Hexal, Braz.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvastamed *Cimed, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvastil *Neo-Farmaceutica, Port.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Sinvastin *Pharlab, Braz.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvatrox *Legrand, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvax *Geolab, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinvaz *Cellofarm, Braz.†; Biofarma, Venez.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sinver *Valmor, Venez.*
Cinnarizine (p.573·1).
Vestibular disorders.

Siochrome
Note.This name is used for preparations of different composition.
David, India.
Injection: Carbazochrome (p.1058·2).
Haemorrhagic disorders.

David, India.
Tablets: Carbazochrome (p.1058·2); menadione sodium bisulfite (p.1995·3); vitamin C (p.1983·3); calcium hydrogen phosphate (p.1676·1).
Haemorrhagic disorders.

Sioconazol *Prati-Donaduzzi, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Siofor *Berlin-Chemie, Cz.; Berlin-Chemie, Ger.; Berlin-Chemie, Pol.; Berlin-Chemie, Rus.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Siokof-P *David, India.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); bromhexine hydrochloride (p.1552·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs; respiratory-tract disorders associated with viscous mucus.

Sioneuron *David, India.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); nicotinamide (p.1957·3); calcium pantothenate (p.1959·3) or dexpanthenol (p.2362·1).
Peripheral neuropathy.

Siopel *Bioglan, Irl.†; Bartlett, S.Afr.; Centrapharm, UK.*
Cetrimide (p.1634·1); dimeticone (p.2032·1).
Barrier cream; napkin rash.

Sioplex *David, India.*
Vitamin B substances; vitamin C (p.1922·1).
Vitamin B and C deficiency.

Sioplex Lysine *David, India.*
Vitamin B substances with lysine hydrochloride (p.1922·1).
Vitamin B deficiency.

Sioplex-Z *David, India.*
Multivitamin preparation with zinc (p.1922·1).
Vitamin B and C deficiency.

Sioril *David, India†.*
Oxyphenbutazone (p.107·3).
Ankylosing spondylitis.

Siozwo
Note.This name is used for preparations of different composition.
Febena, Ger.
Nasal ointment: ⊗ Naphazoline hydrochloride (p.1565·2); peppermint oil (p.1761·2).
Catarrh; nasal congestion; rhinitis.

Febena, Ger.
Nasal solution: Isotonic electrolyte solution (p.1667·1).
Nasal irrigation.

Siozwo Akut *Febena, Ger.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

Siozwo Allerg *Febena, Ger.†.*
Sodium cromoglicate (p.1136·3).
Rhinitis.

Siozwo Sana *Febena, Ger.*
Dexpanthenol (p.2362·1).
Nasal disorders.

Sipam *Siam Bheasach, Thai.*
Diazepam (p.986·3).
Anxiety; insomnia; neuroses; skeletal muscle spasm.

Sipar *Duncan, Arg.*
Pantoprazole (p.1760·1).
Peptic ulcer.

Siparox *Loeffler, Mex.*
Bismuth salicylate (p.1711·1).
Gastrointestinal disorders.

Sipcar *Bernabo, Arg.*
Bromazepam (p.964·3).
Anxiety.

Sipental *Siam Bheasach, Thai.*
Pentoxifylline (p.1367·2).
Cerebral, ocular, and peripheral vascular disorders.

Siphene *Serum Institute, India.*
⊗ Clomifene citrate (p.2086·1).
Female infertility.

Sipiel *Rafarm, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Sipirac *Chemopharma, Chile.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Sipraktin *Ulagay, Turk.*
Cyproheptadine hydrochloride (p.575·1).
Hypersensitivity reactions; migraine.

Sipralexa *Lundbeck, Belg.*
Escitalopram oxalate (p.391·1).
Depression; panic disorder.

Siprion *Orion, Fin.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Siprobel *Nobel, Turk.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Siprofen *Labima, Belg.†.*
Ibuprofen (p.64·2).
Fever; pain.

Siprogut *Bilim, Turk.*
Ciprofloxacin (p.243·3).
Bacterial eye infections.

Siprosan *Drogsan, Turk.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Siqualine *BMS, Mex.*
Fluphenazine (p.998·1).

Siqualone
BMS, Denm.
Fluphenazine hydrochloride (p.998·1).
Psychoses.

BMS, Fin.; BMS, Norw.
Fluphenazine decanoate (p.998·1).
Anxiety; psychoses; senile agitation.

BMS, Swed.
Fluphenazine decanoate (p.998·1) or fluphenazine hydrochloride (p.998·1).
Psychoses.

Siquial *Merck, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Siquil *Sarabhai Piramal, India.*
Triflupromazine hydrochloride (p.1035·1).
Anxiety; nausea and vomiting; psychiatric disorders.

Sir. Ephedrin *Leiras, Fin.*
⊗ Ephedrine hydrochloride (p.1558·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Siraliden *Medana, Pol.*
Nitrofurantoin (p.308·1).
Bacterial infections of the urinary tract.

Siramid *Mersifarma, Indon.*
Pyrazinamide (p.320·2).
Tuberculosis.

Siran *Temmler, Ger.†; Temmler, Israel.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Siranin *Gedeon Richter, Cz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Sirben *Uniao Quimica, Braz.*
Mebendazole (p.148·3).
Worm infections.

Sirdalud *Novartis, Arg.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Ital.; Novartis, Mex.; Novartis, Neth.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, Spain; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Venez.*
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasm; spasticity.

Sirec *Ethica, Indon.*
Yohimbine (p.2200·3); muira-puama; arginine (p.1928·2); ginseng (p.2312·1); honey (p.1948·2); tribulus terrestris (p.2404·1).
Tonic.

Sirepar *Gedeon Richter, Hung.†; Gedeon Richter, Rus.; Gedeon Richter, Thai.*
Liver extract (p.2337·3).
Liver disorders.

Siridone *Chemopharma, Chile.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; vestibular disorders.

Sirigen *Angelini, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds and burns.

Sirio *Chiesi, Ital.*
Melevodopa hydrochloride (p.808·3); carbidopa (p.803·1).
Parkinsonism.

Sirmiogel *Altana, Ital.†.*
Thermal water; hyaluronic acid (p.2320·1); ursolic acid.
Nasal congestion.

Sirodina *Clariana, Spain†.*
Pyridoxine (p.1979·1); sulpiride (p.1028·3).
Nervous disorders; vertigo.

Siroflex *Raldex, Gr.*
Butamirate (p.1553·1).
Cough.

Sirop Cocillana Codeine *Atlas, Canad.*
Codeine phosphate (p.37·2); cocillana (p.1554·3); euphorbia (p.2301·3); senega (p.1572·3); squill (p.1573·1); wild lettuce (p.2415·2).

Sirop Cocillana Compose *Atlas, Canad.*
Cocillana (p.1554·3); euphorbia (p.2301·3); senega (p.1572·3); squill (p.1573·1); wild lettuce (p.2415·2).

Sirop Expectorant *Technilab, Canad.†.*
Guaifenesin (p.1561·3).

Sirop Passi-Par *Parsenn, Switz.†.*
Passion flower (p.2363·2); crataegus (p.2289·1).
Anxiety; insomnia.

Sirop pectoral contre la toux S *Hanseler, Switz.*
Codeine phosphate (p.37·2); drosera (p.2297·3); hyoscyamus (p.2323·3); liquorice (p.1740·3); cowslip (p.2372·2).
Coughs.

Sirop pour le sommeil *Zeller, Switz.†.*
Valerian (p.2410·1).
Sleep disorders.

Sirop S contre la toux et la bronchite *Hanseler, Switz.*
Codeine phosphate (p.37·2); drosera (p.2297·3); hyoscyamus (p.2323·3); liquorice (p.1740·3) primula root (p.2372·2).
Coughs.

Sirop Teyssedre *Bailleul, Fr.*
Alimemazine tartrate (p.566·2).
Formerly contained calcium bromide, cloral hydrate, and calamint.
Allergic disorders; coughs; insomnia.

Sirop des Vosges Expectorant *GSK Sante, Fr.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Sirop des Vosges Toux Seche *GSK Sante, Fr.*
Pholcodine (p.1570·2).
Coughs.

Siropar *Adeka, Turk.*
Piperazine hydrate (p.153·1).
Ascariasis; oxyuriasis.

Siros *Janssen-Cilag, Ger.*
Itraconazole (p.536·3).
Vulvovaginal candidiasis.

Sirotamicin BG *Maigal, Arg.*
⊗ Betamethasone valerate (p.1519·1); gentamicin (p.284·2).

Sirotamicin HC *Maigal, Arg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Siroxyl *Melisana, Belg.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with retention of bronchial secretions.

Sirtal *Sanofi Synthelabo, Austria; Merck dura, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; glossopharyngeal neuralgia; mania; multiple sclerosis; trigeminal neuralgia.

Sirtap *SoSe, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Siruc *Denver, Arg.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Sirupus Pini Compositus *Herbapol Wroclaw, Pol.*
Calcium lactate (p.1676·1); greater celandine (p.2317·1); codeine phosphate (p.37·2); fennel (p.2302·3); pine silvestris (p.2368·2).
Cough and associated respiratory-tract disorders.

Sirupus Tussipini *Hasco-Lek, Pol.*
Calcium lactate (p.1676·1); greater celandine (p.2317·1); codeine phosphate (p.37·2); fennel (p.2302·3); pine silvestris (p.2368·2).
Cough; respiratory-tract congestion.

Sirupus Tussipini D *Hasco-Lek, Pol.*
Calcium lactate (p.1676·1); greater celandine (p.2317·1); fennel (p.2302·3); pine silvestris (p.2368·2).
Cough; respiratory-tract congestion.

Sisare *Organon, Ger.*
11 Tablets, estradiol valerate (p.2097·3); 10 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1).
Menopausal disorders.

Sisare 28 *Organon, Ger.*
White tablets, estradiol valerate (p.2097·3); blue tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); pink tablets, estradiol valerate.
Menopausal disorders.

Sisare mono *Organon, Ger.*
Estradiol (p.2097·2).
Menopausal disorders.

Sisoptin *Themis Chemicals, India.*
Sisomicin sulfate (p.332·1).
Bacterial infections.

Sispres *Ulkar, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Sistalcin *Merck, Venez.*
Pramiverine hydrochloride (p.2372·1).
Smooth muscle spasm.

Sistalcin Compositum *Merck, Venez.*
Pramiverine (p.2372·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Sistalgina *Mepro, Chile†.*
Pramiverine (p.2372·1); dipyrone (p.49·2).
Smooth muscle spasm and pain.

Sistenol *Dexa, Indon.*
Paracetamol (p.108·1); acetylcysteine (p.1548·2).
Fever; pain; respiratory-tract congestion.

Sistral *Ulagay, Turk.*
Chlorphenoxamine hydrochloride (p.572·3).
Hypersensitivity reactions; pruritus.

Sita *Schwarz, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sitem *Inpa, Gr.*
Phenothrin (p.2048·3).
Head, body, and crab lice.

Siterin *UCB, Fin.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Siterone *Rex, NZ.*
Cyproterone acetate (p.2088·2).
Androgen-dependent alopecia, acne, hirsutism, and seborrhoea in females; hypersexuality in males; prostatic cancer.

Siticon *Pharmasant, Thai.*
Simeticone (p.1770·2).
Excess gastrointestinal gas.

Siticox *Sarabhai Piramal, India.*
Rifampicin (p.325·3).
Tuberculosis.

Siticox-INH *Sarabhai Piramal, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Sitinir *Best, Mex.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Sition *Maver, Chile.*
Meloxicam (p.80·3).

Sito-Lande *Sanofi Synthelabo, Ger.†.*
Sitosterol (p.1373·2).
Hyperlipidaemias.

Sitosterin *Schwarz, Ger.*
Phytosterol (p.1373·2).
Benign prostatic hyperplasia.

Sitrac *BPL-Meizler, Braz.†.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Sitraks *Sanofi Synthelabo, Turk.*
Levamisole (p.147·2).
Ascariasis; trichostrongyliasis.

Sitrex PD *Vindex, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Sitriol *Alphapharm, Austral.*
Calcitriol (p.1986·2).
Hypocalcaemia; osteoporosis.

Sitro *Interbat, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Sitrox *Biotenk, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Sitzmarks
Dominguez, Arg.
Radio-opaque markers.
Investigation of gastrointestinal motility.

Konsyl, USA.
Radio-opaque polyvinyl chloride.
Contrast medium for gastrointestinal radiography.

Sival-B *Remek, Gr.*
⊗ Codeine (p.37·2); ephedrine (p.1558·1).
Cough.

Sivastin *Vitapan, Braz.†; Sigma-Tau, Ital.*
Simvastatin (p.1390·2).
Atherosclerosis; hypercholesterolaemia; ischaemic heart disease.

Sivatin *Rowex, Irl.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Siverol *Biomedis, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Sivinar *Anpharm (Ανφαρμ), Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Sivlor *Sidus, Arg.†.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Sivylar *Ranbaxy, Thai.*
Silymarin (p.1452·2).
Carbon tetrachloride poisoning; liver disorders; mushroom poisoning.

Six Din *Senosiain, Mex.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Sixacina *Rider, Chile.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Sixol *Biomep, Mex.*
Colchicine (p.556·1).
Gout.

Siyafen *Gunsa, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Sizopin *Sun, India.*
Clozapine (p.981·1).
Psychoses associated with parkinsonism; schizophrenia.

Sizoril *Meprofarm, Indon.*
Clozapine (p.981·1).
Schizophrenia.

Sizorisp *Ipca, India†.*
Risperidone (p.1024·2).
Schizophrenia.

SJ Liniment *International Dermatologicals, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1); ammonium hydroxide (p.2256·1); coal tar (p.1616·2).

Skab 2 *Pentamedical, Ital.*
Benzyl benzoate (p.2036·1); St John's wort oil (p.423·2); benzyl alcohol (p.1631·3); enoxolone (p.50·1); terpineol (p.2396·1).
Skin cleanser.

Skabicid *Avenat, Cz.†.*
Lindane (p.2045·3).
Scabies.

Skaelud *Propharma, Denm.*
Pyrithione zinc (p.1611·2).
Pityriasis versicolor; seborrhoeic dermatitis.

Skarflex *Pentamedical, Ital.*
Pelvetia canaliculata (p.2384·2); tocoferil acetate (p.1992·3); onion (p.2356·3).
Prevention of scarring.

Skeeter Stik *Triton, USA.*
Lidocaine (p.1862·3); phenol (p.1656·1).
Skin disorders.

Skelan
Note. This name is used for preparations of different composition.
Biomedis, Philipp.
Ibuprofen (p.64·2).
Inflammation; pain.

Great Eastern, Thai.; Therapharma, Thai.
Ibuprofen (p.64·2); paracetamol (p.108·1).
Pain.

Skelan IB *Biomedis, Thai.; Great Eastern, Thai.*
Ibuprofen (p.64·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Skelaxin *King, USA.*
Metaxalone (p.1897·3).
Painful musculoskeletal conditions.

Skelid *Mayne, Austral.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi Synthelabo, Fin.†; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Hung.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Swed.†; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, UK; Sanofi Winthrop, USA.*
Tiludronate disodium (p.1106·1).
Paget's disease of bone.

Skema
Note. This name is used for preparations of different composition.
Pentamedical, Ital.
Cream: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Pentamedical, Ital.
Lotion: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

Skenan *UPSA, Cz.†; BMS, Fr.; Upsa, Ital.†; UPSA, Neth.; Ethypharm, Port.; BMS, Spain.*
⊗ Morphine sulfate (p.86·3).
Pain.

Skiacol *Alcon, Fr.*
Cyclopentolate hydrochloride (p.1879·3).
Production of cycloplegia and mydriasis.

Skiatropine *Bausch & Lomb, Switz.†.*
Atropine sulfate (p.1219·3).
Eye disorders; production of mydriasis and cycloplegia.

Skid *Artesan, Cz.†; Winthrop, Ger.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Skilax *Almirall, Spain.*
Sodium picosulfate (p.1771·1).
Constipation.

Skilone *Corsa, Indon.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Skin Des *Promedico, Israel.*
Isopropyl alcohol (p.1650·3); 1,3-butanediol.
Skin disinfection.

Skin Bond Cement *Smith & Nephew, Austral.†.*
Appliance adhesive.

Skin C *Dispolab, Chile†.*
Emollient containing vitamin C (p.1983·3).

Skin Cap *Volta, Chile.*
Pyrithione zinc (p.1611·2).
Dandruff; seborrhoeic dermatitis.

Skin Care *Dossier, Neth.*
Homoeopathic preparation.

Skin Care Nutrients *Lifeplan, UK.*
Vitamins; minerals; bioflavonoids; cysteine; lecithin; choline; inositol (p.1922·1).
Dietary supplement.

Skin Cleanser & Deodorizer *National Care, Canad.†.*
Benzethonium chloride (p.1630·1).
Skin hygiene in incontinent patients.

Skin Cleansing *Cantassium Co., UK.*
Lappa (p.2330·3); senna (p.1769·2); fumitory (p.2307·2); clivers (p.2284·3).

Skin Clear
Note. This name is used for preparations of different composition.
Potter's, UK.
Ointment: Starch (p.1968·1); sublimed sulfur (p.1614·1); zinc oxide (p.1621·2); melaleuca oil (p.2338·2).
Skin disorders.

Potter's, UK.
Tablets: Echinacea root (p.2298·1).
Skin disorders.

Skin Cure *Young Again Nutrients, USA.*
Pyrithione zinc (p.1611·2).
Skin disorders.

Skin Dry *Darier, Mex.*
Aluminium tetrachlorohydrate (p.1588·3).
Hyperhidrosis.

Skin Eruptions Mixture *Potter's, UK.*
Iris versicolor (p.2327·1); lappa root (p.2330·3); yellow dock (p.2416·3); sarsaparilla (p.2383·3); buchu (p.2269·3); cascara (p.1715·2).
Skin disorders.

Skin Hair & Nails *Natural Life, Arg.*
Vitamins; calcium; iron (p.1922·1).
Dietary supplement.

Skin Healing Cream *Brauer, Austral.†.*
Calendula (p.2273·1); St John's wort (p.422·3).
Bruised fingers and toes; cuts and abrasions; insect bites; skin irritation.

Skin Nail *Aclae, Fr.*
Quassia (p.2377·1); denatonium benzoate (p.2292·3).
Nail disorders.

Skin Prep *Smith & Nephew, Austral.†.*
Film dressing.

Skin Repair *Pfizer, Hong Kong; Rosken, Hong Kong; Pharmacare, Singapore.*
Dimethicone (p.2032·1).
Cracked and dry skin; dermatitis; eczema.

Skin Sec
Note. This name is used for preparations of different composition.
Darrow, Braz.
Moisturiser.

Darrow, Braz.
Lotion; SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Moisturiser; sunscreen.

Skin Shield *Del, USA.*
Dyclonine hydrochloride (p.1861·1); benzethonium chloride (p.1630·1).
Liquid bandage.

Skin So Soft Antibacterial *Avon, Canad.†.*
Lotion: Triclosan (p.1665·2).

Skin Sol P *Maigal, Arg.†.*
Titanium dioxide (p.1617·3).
Sunscreen.

Skin Sol T *Maigal, Arg.*
SPF 35: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); octisalate (p.1608·2).
Sunscreen.

Skinal *Sandoz, Indon.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Skinat *Teofarma, Ital.*
Collagen (p.2286·1).
Prevention of scarring.

Skincalm *Reckitt Benckiser, NZ.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Skin-Cap *Catalysis, Arg.; Invar, Rus.*
Pyrithione zinc (p.1611·2).
Dandruff; seborrhoea; skin disorders.

Skinderm A *Maigal, Arg.*
Vitamin A (p.1971·2).
Skin disorders.

Skinderm CL *Maigal, Arg.*
Collagen (p.2286·1).

Skinderm R *Maigal, Arg.*
Collagen (p.2286·1); elastin (p.2286·1); rosa mosqueta.

Skinderm SIL *Maigal, Arg.*
Silicones (p.2032·1).

Skindure *March, Thai.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Skinfect *Bangkok Lab & Cosmetic, Thai.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Skinman Asept *Ecolab, Ger.*
Propyl alcohol (p.1660·2).
Hand disinfection.

Skinman Soft *Ecolab, Ger.*
Isopropyl alcohol (p.1650·3); benzalkonium chloride (p.1629·1); undecenoic acid (p.549·2).
Skin disinfection.

Skinocyclin *Intendis, Ger.*
Minocycline hydrochloride (p.300·3).
Acne.

Skinoderm *Pharma Clal, Israel.*
Azelaic acid (p.1589·3).
Acne.

Skinola-Fett *Medika, Switz.*
Bath additive.
Dry skin disorders.

Skinoren *Schering, Austral.; Schering, Austria; Schering, Belg.; Intendis, Cz.; Intendis, Denm.; Schering, Fin.; Intendis, Fr.; Intendis, Ger.; Schering, Gr.; Schering, Hong Kong; Intendis, Hung.; Schering, Indon.; Schering, Irl.; Intendis, Ital.; Bayer Schering, Malaysia; CSL, NZ; Intendis, Norw.; Schering, Philipp.; Intendis, Pol.; Intendis, Port.; Schering, Rus.; Schering, S.Afr.; Intendis, Singapore; Intendis, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Valeant, UK.*
Azelaic acid (p.1589·3).
Acne; melasma; rosacea; seborrhoeic dermatitis; skin pigmentation disorders.

Skinovit *Roi Surya, Indon.*
Tretinoin (p.1618·1).
Acne.

Skinsept *Ecolab, Austria.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Skinsept F *Ecolab, Ger.*
Isopropyl alcohol (p.1650·3); chlorhexidine gluconate (p.1635·3); hydrogen peroxide (p.1647·3).
Skin disinfection.

Skinsept G *Ecolab, Ger.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Skinsept mucosa *Ecolab, Austria; Temmentec, Cz.†; Ecolab, Ger.*
⊗ Alcohol (p.1625·2); hydrogen peroxide 30% (p.1648·1); chlorhexidine gluconate (p.1635·3).
Mucous membrane disinfection.

Skintex
Note. This name is used for preparations of different composition.
Galenium, Indon.
Zinc undecenoate (p.549·3); salicylic acid (p.1612·2); formaldehyde (p.1644·1); boric acid (p.2268·1); thymol (p.1664·3); panthenol (p.2362·1).
Fungal skin infections.

Lloyd, Aimee, UK.
Chloroxylenol (p.1640·2); camphor (p.2273·2).
Skin disorders.

SkinVit *Pharmadass, UK.*
Multivitamin, mineral, and amino-acid preparation (p.1922·1).

Skizon *Hexpharm, Indon.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Skleremo *Elvetium, Arg.†.*
Chrome alum (p.2280·3); glycerol (p.2314·2).
Varices.

Sklerofibrat *Merckle, Ger.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Sklerosol N *Febena, Ger.†.*
Colloidal silicon dioxide (p.2146·3).
Hair and nail disorders.

Sklerovenol N *Febena, Ger.†.*
Aesculus (p.2248·2).
Soft-tissue inflammation; venous insufficiency.

Sklerovitol *Lannacher, Austria.*
Nicotinoylprocaine hydrochloride; vitamin B substances (p.1922·1); rutoside (p.2305·1).
Peripheral vascular disorders; reduced mental and physical capacity in the elderly; tonic.

Skopolin *Tems, Turk.*
Hyoscine butylbromide (p.1734·1); dipyrone (p.49·2).

Skudal *White, Arg.†.*
Meloxicam (p.80·3).
Musculoskeletal and joint disorders.

SL B12 *Dominguez, Arg.*
Cyanocobalamin (p.1980·2).
Vitamin B12 deficiency.

Slap *Temis, Arg.*
Aspartame (p.1930·1).
Sugar substitute.

Sleep Aid
Note. This name is used for preparations of different composition.
Tanta, Canad.; Galpharm, UK.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Perrigo, Israel.
Doxylamine succinate (p.578·2).
Insomnia.

Sleep & Insomnia Relief *Brauer, Austral.*
Homoeopathic preparation.

Sleepeaze *Galpharm, UK.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sleep-Ettes D *Reese, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sleep-Eze D *Medtech, Canad.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sleep-Eze V Natural *Medtech, Canad.*
Valerian (p.2410·1).
Sleep disorders.

Sleepeze-PM *SA Druggists Self Med, S.Afr.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sleepia *Pfizer, Austria†; Pfizer, Ger.†; Pfizer Consumer, Switz.†.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sleepwell 2-nite *Rugby, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Slepan *Staufen, Ger.†.*
Homoeopathic preparation.

Slezovy Kvet *Megafyt-R, Cz.*
Mallow flower (p.2337·2).
Upper respiratory-tract inflammation.

Slim Caps *Amino, Switz.*
Phenylpropanolamine hydrochloride (p.1569·3).
Obesity.

Slim 'n Trim *Adcock Ingram Consumer, S.Afr.*
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Slim-D *Biofarma, Mex.*
Carnitine (p.1932·2); garcinia cambogia (p.2309·2); chromium (p.1934·3).
Obesity.

Slimmer *Baif, Ital.*
Piscidia erythrina; fucus vesiculosus; ananas sativa; equisetum arvense; betula alba; ononis spinosa; centella asiatica; orthosiphon stamineus; ruscus aculeatus; lespedeza capitata (p.1922·1).
Nutritional supplement.

Slimum *Ferrier, Fr.*
Homoeopathic preparation.

Slip-iZZZ *Ikapharmindo, Indon.*
Valerian (p.2410·1); passion flower (p.2363·2); calcium; magnesium.
Sleep disorders.

Slippery Elm Stomach Tablets *Potter's, UK.*
Slippery elm bark (p.2388·2); cinnamon oil (p.2283·2); anise oil (p.2258·2); peppermint oil (p.1761·2).
Dyspepsia; flatulence.

Slit One *Alk-Scherax, Ger.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Sloan *Chefaro, Ital.*
Capsicum oleoresin (p.2276·2); glycol monosalicylate (p.62·3); white camphor oil (p.2273·3); pine oil (p.2368·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue pain.

Sloan's Heat Rub *Pfizer Consumer, S.Afr.*
Capsicum oleoresin (p.2276·2); methyl salicylate (p.85·3); methyl nicotinate (p.85·3).
Musculoskeletal pain.

Sloan's Liniment *CCM, Indon.*
Capsicum oleoresin (p.2276·2); camphor oil (p.2273·3); pine oil (p.2368·2); methyl salicylate (p.85·3); turpentine oil (p.2406·3).
Musculoskeletal, joint, and soft-tissue pain; neuralgia.

Sloan's Liniment Rub *Pfizer Consumer, S.Afr.*
Methyl salicylate (p.85·3); camphor (p.2273·2); capsicum oleoresin (p.2276·2); turpentine oil (p.2406·3).
Musculoskeletal pain.

Slo-Bid *Aventis, Mex.†; Rhone-Poulenc Rorer, USA.*
Theophylline (p.1140·1).
Obstructive airways disease.

Slofedipine *Winthrop, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Slofenac *Sterwin, UK.*
Diclofenac sodium (p.44·3).

Slo-Indo *Generics, UK.*
Indometacin (p.66·3).
Inflammation; pain.

Slo-Morph *Helsinn Birex, Irl.†.*
⊗ Morphine sulfate (p.86·3).
Pain.

Slo-Niacin *Upsher-Smith, USA.*
Nicotinic acid (p.1957·3).
Hyperlipidaemia (adjunct); nicotinic acid deficiency; pellagra.

Slo-Phyllin *Merck, Irl.; Merck, UK; Rhone-Poulenc Rorer, USA.*
Theophylline (p.1140·1).
Asthma; bronchitis; bronchospasm; obstructive airways disease.

Slo-Phyllin GG *Rhone-Poulenc Rorer, USA†.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Asthma; bronchospasm.

Slo-Pro *Generics, UK.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; gastrointestinal bleeding; hypertension; hyperthyroidism; migraine; tremor.

Slo-Salt-K *Mission Pharmacal, USA†.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Dehydration; heat prostration; sodium depletion; volume depletion.

Slo-Theo *Ethypharm, Hong Kong.*
Theophylline (p.1140·1).
Obstructive airways disease.

Slovalgin *Zentiva, Cz.*
⊗ Morphine sulfate (p.86·3).
Pain.

Slow Deralin *Abic, Israel.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; hypertension; hyperthyroidism; migraine; tremor.

Slow Fe with Folic Acid *Novartis Consumer, USA.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency.

Slow Release Mega C *Vitaglow, Austral.†.*
Calcium ascorbate (p.1984·1); ascorbic acid (p.1983·3).
Bruising; cold and influenza symptoms; maintenance of oral health; vitamin supplement; wounds.

Slow Release Mega Multi *Vitaglow, Austral.†.*
Multivitamin and mineral preparation (p.1922·1).

Slow-Fe *Novartis Consumer, Canad.; Novartis Consumer, Israel; Novartis Consumer, UK†; Novartis Consumer, USA.*
Dried ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Slow-Fe Folic *Novartis Consumer, Canad.; Novartis Consumer, Israel; Novartis Consumer, UK†.*
Dried ferrous sulfate (p.1939·3); folic acid (p.1940·1).
Iron and folic acid deficiency in pregnancy and lactation.

Slow-K *Novartis, Austral.; Novartis, Canad.; Novartis, Chile; Novartis, Hong Kong; Novartis, Irl.; Novartis, Israel; Novartis, Malaysia; Novartis, NZ; Novartis, Neth.; Novartis, S.Afr.; Alliance, UK; Summit, USA†.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium deficiency; potassium supplement.

Slow-Lopresor *Novartis, Belg.; Novartis, NZ.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Slow-Mag *Wellspring, Canad.†; Curtis, Pol.; Merck, S.Afr.; Purdue, USA.*
Magnesium chloride (p.1679·1).
Magnesium deficiency; magnesium supplement.

Slow-Mag B_6 *Curtis, Pol.*
Magnesium chloride (p.1679·1); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Slow-Sodium *Novartis, Austral.; HK Pharma, UK.*
Sodium chloride (p.1686·1).
Hyponatraemia.

Slow-Trasicor *Novartis, Canad.†; Novartis, NZ†; Novartis, Switz.; Amdipharm, UK.*
⊗ Oxprenolol hydrochloride (p.1365·1).
Angina pectoris; anxiety; arrhythmias; hypertension.

Slow-Trasitensine *Novartis, Switz.*
⊗ Oxprenolol hydrochloride (p.1365·1); chlortalidone (p.1243·3).
Hypertension.

Slozem *Merck, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

SLT *C & M, USA†.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); lactic acid (p.2329·3).
Seborrhoea.

Slumber *Seven Seas, UK.*
Lupulus (p.2335·2); piscidia (p.2328·1); passion flower (p.2363·2); wild lettuce (p.2415·2).
Insomnia.

SM-33 *Bayer Consumer, Austral.*
Salicylic acid (p.1612·2); lidocaine (p.1862·3); tannic acid (p.2394·3); menthol (p.2340·1); thymol (p.1664·3); glycerol (p.2314·2); alcohol.
Teething pain.

SM-33 Adult Formula *Bayer Consumer, Austral.*
Lidocaine (p.1862·3); salicylic acid (p.1612·2); tannins; alcohol.
Mouth ulcers; oral abrasions.

SMA AR *Wyeth, Mex.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

SMA High Energy *SMA Nutrition, Irl.*
Infant feed (p.1922·1).
Growth failure; malabsorption; malnutrition.

SMA LF *SMA Nutrition, Irl.*
Infant feed (p.1922·1).
Lactose intolerance.

SMA Sin Lactosa *Wyeth, Mex.*
Infant feed (p.1922·1).
Lactose intolerance.

SMA Staydown *SMA Nutrition, Irl.; SMA Nutrition, UK.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux; regurgitation.

Smaril *Coup, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

SmartDose *Pro-Med, Austria; Codan Triplus, Swed.†.*
Sodium chloride (p.1686·1).
Diluent for intravenous injections.

Smartfish *Synco, Hong Kong.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

SmartSet GHV *DePuy, Ger.*
Gentamicin sulfate (p.282·1); methylmethacrylate methylacrylate copolymer (p.2343·3).
Bone cement in orthopaedic surgery.

SmartSet HV *DePuy, Ger.*
Methylmethacrylate methylacrylate copolymer (p.2343·3).
Bone cement in orthopaedic surgery.

Smecta *Beaufour-Ipsen, Cz.; Beaufour, Fr.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Beaufour Ipsen, Pol.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Thai.*
Diosmectin (p.1771·1).
Abdominal discomfort; colitis; diarrhoea; dyspepsia; flatulence; gastro-oesophageal reflux; gastrointestinal pain; irritable bowel syndrome; meteorism; peptic ulcer.

Smilitene *Rafarm, Gr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

SMOFlipid *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Swed.; Fresenius Kabi, UK.*
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3); olive oil (p.2356·2); fish oil (p.1362·1).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Smok Quits *Eagle, Austral.†.*
Homoeopathic preparation.

Smoke-Eze *Brauer, Austral.*
Homoeopathic preparation.

Smokeless *Inibsa, Spain.*
⊗ Lobeline sulfate (p.2157·2).
Aid to smoking withdrawal.

Smoking Withdrawal Support *Homeocan, Canad.†.*
Homoeopathic preparation.

Smudal *Rafarm, Gr.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

SMZ-TMP *Apothecon, USA.*
Co-trimoxazole (p.258·1).

Snake Venom Detection *CSL, Austral.*
A range of snake venoms (tiger snake, brown snake, black snake, death adder, taipan) and controls.
Detection and identification of snake venom at bite site, in urine and in blood.

Snell Cell *Wassen, Ital.*
Kola (p.2416·1); guarana (p.2416·1); maté (p.2416·1); garcinia cambogia (p.2309·2); coleus; aesculus (p.2248·2).
Cellulitis.

Snell Patch *Gobbi, Arg.*
Hava tonka; ginkgo biloba (p.2311·1); ivy (p.2328·1); melilot (p.2339·2).
Cellulite.

Snell Progress *Gobbi, Arg.*
Hava tonka; ginkgo biloba (p.2311·1); melilot (p.2339·2).
Cellulite.

Snella *Wierhom, Arg.*
Soya isoflavones (p.2391·2); vitamin D (p.1986·1); vitamin E (p.1992·2).
Menopausal disorders.

Snella Vag *Wierhom, Arg.*
Aloe vera (p.1588·2); vitamin E (p.1992·2).
Vaginal lubricant.

Snell'it *Wassen, Ital.*
Apple vinegar; inulin (p.2326·3).

Snelvit *Grin, Mex.*
Zeaxanthin (p.1999·1); lutein (p.1954·3).
Ocular antoxidant.

Snif *Eurofarma, Braz.; One Pharma, Philipp.*
Sodium chloride (p.1686·1).
Nasal congestion; nasal dryness.

Sniffle Care *Dossier, Neth.*
Homoeopathic preparation.

Snip *Medochemie, Hong Kong†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Snizee *Metz, Philipp.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Allergic rhinitis; cold symptoms.

Sno Pro *Scientific Hospital Supplies, Irl.*
Low-protein, low-phenylalanine food for special diets (p.1922·1).
Disorders of amino-acid metabolism; milk substitute.

Sno Strips *Akorn, USA†.*
Test for tear production.

Sno Tears *Chauvin, Irl.; Bausch & Lomb, UK.*
Polyvinyl alcohol (p.2145·3).
Dry eyes.

Snoffocin *Seven Stars, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Snooze Fast *BDI, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Sno-Pro *Nutricia, Ital.*
Food for special diets (p.1922·1).
Phenylketonuria; renal failure.

Snor-Away
Note.This name is used for preparations of different composition.
Douglas, Austral.†.
Olive oil (p.2356·2); sunflower oil (p.1970·3); almond oil (p.2252·2); sesame oil (p.2386·1); vitamins.
Snoring.

Munro, UK.
Almond oil (p.2252·2); olive oil (p.2356·2); peppermint oil (p.1761·2); sesame oil (p.2386·1); sunflower oil (p.1970·3); vitamins.
Snoring.

Snore Calm *BSSAA, UK.*
Euphrasia officinalis (p.2301·3).
Snoring.

Snore Eze *Brauer, Austral.*
Homoeopathic preparation.

Snore No More *Homeocan, Canad.*
Homoeopathic preparation.

Snore Stop *Nutravite, Canad.*
Homoeopathic preparation.

Snoreeze *Passion for Life, Singapore†.*
Glycerol; olive oil; peppermint oil; soya lecithin; sunflower oil; sweet almond oil; sesame oil; vitamin E; vitamin B (p.1922·1).
Snoring.

Snore-No-More *Anben, Israel.*
Polysaccharides; phosphate; sodium chloride (p.1686·1).
Nasal dryness; snoring.

Snorenz *Enzpharma, NZ.*
Peppermint oil (p.1761·2); olive oil (p.2356·2); sunflower oil (p.1970·3); sesame oil (p.2386·1); almond oil (p.2252·2); vitamins E and B (p.1922·1).
Snoring.

Snorestop *Key Sun, Austral.*
⊗ Homoeopathic preparation.

Snovitel *Akrikhin, Rus.*
Zolpidem tartrate (p.1037·3).

Snow Brand *Snow Brand, Hong Kong.*
A range of preparations for enteral nutrition (p.1922·1).

Snowfire *Pickles, UK.*
Benzoin (p.2394·2); citronella (p.2284·2); thyme oil (p.2401·2); lemon thyme; clove oil (p.2285·1); cade oil (p.1616·1).
Chapped hands; chilblains.

SNP *Quatromed, S.Afr.*
Sodium nitroprusside (p.1397·1).
Hypertension; production of controlled hypotension during surgery.

Snufflebabe *Orthodontiki (Ορθοδοντικη), Gr.†; Ransom, UK.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); thyme oil (p.2401·2).
Common cold; upper respiratory-tract congestion.

Snufflebabe Cradle Cap *Ransom, UK.*
Salicylic acid (p.1612·2).
Cradle cap.

Snup *Stada, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Catarrh; rhinitis.

Snuzaid *Woods, Austral.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Soaclens *Alcon, Austral.; Alcon, Canad.†; Alcon, NZ; Alcon, USA.*
Wetting and storage solution for hard contact lenses (including gas permeable) (p.1622·2).

Soam *Edol, Port.*
Emollient.

Soapelle *Darrow, Braz.*
Liquid soap: Triclosan (p.1665·2); aloe vera (p.1588·2).
Skin disinfection.

Soapex
Note.This name is used for preparations of different composition.
Galderma, Braz.
Liquid soap: Triclosan (p.1665·2).
Skin disinfection.

Galderma, Braz.
Shampoo: Piroctone olamine (p.1610·1).
Seborrhoeic dermatitis.

Galderma, Braz.
Soap: Triclosan (p.1665·2); triclocarban (p.1665·2).
Skin disinfection.

Sobee Plus *Mead Johnson, Indon.*
Infant feed (p.1922·1).
Milk intolerance.

Sobelin
Note.This name is used for preparations of different composition.
Pharmacia, Ger.
Clindamycin hydrochloride (p.251·1), clindamycin palmitate hydrochloride (p.251·1), or clindamycin phosphate (p.251·2).
Bacterial infections.

TO-Chemicals, Thai.
Flunarizine (p.580·3).
Cerebrovascular disorders; migraine; motion sickness; peripheral vascular disorders; vestibular disorders.

Sobrein *Biomedica-Chemica, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Sobrepin *Farmasa, Braz.; Bayer, Ital.; Tedec Meiji, Spain.*
Sobrerol (p.1572·3).
Respiratory-tract congestion.

Sobrepina *Baldacci, Port.*
Nimodipine (p.1357·2).
Cerebral ischaemia; cerebral vasospasm following subarachnoid haemorrhage.

Sobrial *Merck, S.Afr.†.*
Acamprosate calcium (p.958·3).
Alcoholism.

Sobril *Pfizer, Norw.; Pfizer, Swed.*
Oxazepam (p.1014·2).
Alcohol withdrawal syndrome; anxiety disorders; insomnia; non-psychotic mental disorders; premedication.

Sobrium *Ranbaxy, Malaysia.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Sobrius *Fada, Arg.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Socalm *Ranbaxy, India.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Socef *Soho, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Socian *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Port.*
Amisulpride (p.961·1).
Psychoses.

Socid *Soho, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Soclaf *Soho, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Soclor *Soho, Indon.*
Cefaclor (p.217·2).
Bacterial infections.

Socloxin *Olan-Kemed, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Socosep *Cetus, Arg.*
Ketoconazole (p.539·1).
Fungal infections.

Sodanton *Slovakofarma, Cz.†.*
Phenytoin (p.495·2).
Epilepsy; neuralgia; neuropathy.

Sodemethin *Vilco, Gr.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Soden *DHA, Hong Kong; DHA, Singapore.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Soderm *Dermapharm, Ger.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Soderm Plus *Dermapharm, Ger.*
⊗ Betamethasone dipropionate (p.1518·3); salicylic acid (p.1612·2).
Skin disorders.

Soderma *Soho, Indon.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Sodexx Cimetidine *Kwizda, Austria.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux.

Sodexx Famotidine *Kwizda, Austria.*
Famotidine (p.1730·1).
Heartburn.

Sodibic *Aspen, Austral.*
Sodium bicarbonate (p.1673·2).
Bicarbonate replacement in renal failure.

Sodilen *Motima, Fr.*
Pollen (p.2370·2).
Antoxidant.

Sodilin *Collins, Mex.*
Procaine benzylpenicillin (p.319·2).
Bacterial infections.

Sodime *Soho, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Sodiofolin *Medac, Austria; Medac, Port.; Medac, UK.*
Sodium folinate (p.1944·1).
Adjunct to fluorouracil in colorectal cancer; reduction of folic acid antagonist toxicity; reduction of methotrexate toxicity.

Sodiopen *Reig Jofre, Spain.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Sodioral con Inulina *CaDiGroup, Ital.*
Oral rehydration solution with inulin (p.1672·2).
Diarrhoea.

Sodiparin *Baxter Immuno, Arg.*
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Sodipen *Antibioticos, Mex.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Sodipental *Pisa, Mex.*
Thiopental sodium (p.1795·2).
Convulsions; general anaesthesia; increased intracranial pressure in neurosurgery.

Sodip-phylline *Sanofi, Switz.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Sodipryl retard *Sanofi, Switz.*
Naftidrofuryl oxalate (p.1346·2).
Peripheral and cerebral vascular disease.

Sodium Sulamyd *Schering, Canad.†; Schering, USA.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Sodix *Geolab, Braz.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Sodixen *Rayere, Mex.*
Naproxen sodium (p.92·3).
Fever; musculoskeletal and joint disorders; pain.

Sodol Compound *Major, USA.*
Aspirin (p.20·3); carisoprodol (p.1894·1).
Musculoskeletal pain.

Sodolac *Sofex, Port.*
Etodolac (p.52·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sodorant
Note.This name is used for preparations of different composition.
Stiefel, Arg.
Cream: Guaiazulene (p.2317·3); aluminium chlorohydrate (p.1588·3); triclocarban (p.1665·2).
Hyperhidrosis.

Stiefel, Arg.
Deodorant bar: Triclocarban (p.1665·2).
Hyperhidrosis.

Stiefel, Arg.
Deodorant roll-on; topical spray: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Sodox *Pentamedical, Ital.*
Melon; vitamin C; vitamin E (p.1922·1).
Dietary supplement.

Sofarcid *Sofar, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Sofargen *Sofar, Ital.*
Sulfadiazine silver (p.337·2).
Bacterial skin infections; burns; wounds.

Sofasin *Faran, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Sofden *Soho, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Sofderm *Cipla, India.*
Aloe vera (p.1588·2) vitamin E (p.1992·2).

Sofelin *Galenus, Gr.*
Fluoxetine (p.397·3).
Depression.

Sofenol *C & M, USA†.*
Emollient and moisturiser.

Soffodex *Dexxon, Israel.*
Dibasic sodium phosphate (p.1682·3); monobasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Soficlor *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Cefaclor (p.217·2).
Bacterial infections.

Sofidrox *Xepa-Soul Pattinson, Hong Kong†; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Cefadroxil (p.218·1).
Bacterial infections.

Sofilex *Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Cefalexin (p.218·2).
Bacterial infections.

Sofix *Soho, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Soflax
Note.This name is used for preparations of different composition.
Douglas, Austral.
Senna (p.1769·2); docusate sodium (p.1725·1).
Constipation.

Pharmascience, Canad.
Docusate sodium (p.1725·1).
Constipation.

Cipla-Medpro, S.Afr.
Senna (p.1769·2).
Constipation.

Julphar, UAE.
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Sof-lax *Fleet, USA.*
Docusate sodium (p.1725·1).
Stool softener.

Soflax EX *Pharmascience, Canad.*
Bisacodyl (p.1710·1).
Constipation.

Sofloran *Pisa, Mex.*
Isoflurane (p.1785·3).
General anaesthesia.

Sofracort
Aventis, Canad.
⊗ Framycetin sulfate (p.279·1); gramicidin (p.286·1); dexamethasone (p.1526·1).
Ear disorders; eye disorders.

Aventis, India.
⊗ Framycetin sulfate (p.279·1); dexamethasone sodium metasulfobenzoate (p.1526·2); gramicidin (p.286·1).
Infected eye disorders.

Sofradex
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Austral.; Aventis, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, NZ; Aventis, Norw.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Thai.
⊗ Dexamethasone (p.1526·1); framycetin sulfate (p.279·1); gramicidin (p.286·1).
Infected eye and ear disorders.

Aventis, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Malaysia; Aventis, Neth.; Aventis, Switz.; Florizel, UK.
⊗ Dexamethasone sodium metasulfobenzoate (p.1526·2); framycetin sulfate (p.279·1); gramicidin (p.286·1).
Infected eye and ear disorders.

Hub, India.
⊗ Dexamethasone acetate (p.1526·1); framycetin sulfate (p.279·1).
Skin disorders.

Sofradex-F *Hub, India.*
⊗ Dexamethasone acetate (p.1526·1); framycetin sulfate (p.279·1); clotrimazole (p.530·1).
Skin disorders.

Sofraline *Melisana, Belg.*
⊗ Framycetin sulfate (p.279·1); naphazoline nitrate (p.1565·2).
Respiratory-tract disorders.

Soframycin
Note.This name is used for preparations of different composition.
Aventis, India; Aventis, Switz.
Framycetin sulfate (p.279·1).
Bacterial eye infections; burns; otitis externa; skin infections.

Sanofi-Aventis, Irl.; Sanofi-Aventis, UK†.
Eye drops: Framycetin sulfate (p.279·1).
Bacterial eye infections.

Erfa, Canad.; Aventis, S.Afr.
eye drops; Eye ointment: Framycetin sulfate (p.279·1).
Bacterial eye infections.

Aventis, NZ.
Eye/ear drops; eye/ear ointment: Framycetin sulfate (p.279·1).
Bacterial eye and ear infections.

Sanofi-Aventis, Austral.
Eye/ear preparations: Framycetin sulfate (p.279·1).
Bacterial eye and ear infections.

Erfa, Canad.
Nasal spray: Framycetin sulfate (p.279·1); gramicidin (p.286·1); phenylephrine hydrochloride (p.1568·1).
Bacterial nasal infections; nasal congestion.

Sanofi-Aventis, Austral.; Erfa, Canad.; Aventis, Irl.†; Aventis, NZ.
Ointment: Framycetin sulfate (p.279·1); gramicidin (p.286·1).
Bacterial skin infections.

Soframycine *Melisana, Belg.*
Framycetin sulfate (p.279·1).
Bacterial nose and throat infections.

Sofrasolone *Melisana, Belg.*
⊗ Prednisolone acetate (p.1541·1); framycetin sulfate (p.279·1); naphazoline nitrate (p.1565·2).
Allergy or infections of the upper respiratory tract.

Sofra-Tull *Aventis, Austria; Aventis, Ger.†.*
Framycetin sulfate (p.279·1).
Burns; skin infections; ulcers; wounds.

Sofra-Tull sine *Aventis, Ger.*
White soft paraffin (p.2031·2); wool fat (p.2033·2).
Wounds.

Sofra-Tulle *Sanofi-Aventis, Austral.; Erfa, Canad.; Aventis, Fin.†; Aventis, Hong Kong†; Aventis, India; Sanofi-Aventis, Indon.; Aventis, Israel†; Aventis, Malaysia†; Aventis, Norw.†; Aventis, S.Afr.; Aventis, Singapore†; Aventis, Switz.†; Aventis, Thai.; Aventis, UK.*
Framycetin sulfate (p.279·1).
Burns; medicated dressing; skin infections; ulcers; wounds.

Sofrodol *Cantabria, Spain.*
Tramadol (p.132·1).
Pain.

Sof-Sof *CTS, Israel†.*
Phenothrin (p.2048·3).
Pediculosis.

Sof-T *Gynetics, Singapore†.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Soft Corn *SSL, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns.

Soft Kilnits *Andromaco, Chile†.*
Acetic acid (p.2244·2).
Pediculosis.

Soft Lips *Mentholatum, Canad.†.*
SPF 17: Octinoxate (p.1608·2); oxybenzone (p.1608·3); padimate O (p.1609·1).
Sunscreen.

Soft Lips Crystal Ice *Mentholatum, Canad.*
Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Soft Lips French Vanilla *Mentholatum, Canad.*
SPF 20: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Soft Lips Sparkle *Mentholatum, Canad.†.*
SPF 10: Octinoxate (p.1608·2).
Sunscreen.

Soft Lips Tints *Mentholatum, Canad.*
Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Soft Lips Ultra *Mentholatum, Canad.†.*
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Soft Mate *Barnes Hind, NZ†; Pilkington Barnes-Hind, USA.*
A range of solutions for soft contact lenses (p.1622·2).

Soft Mate Consept *Pilkington Barnes-Hind, USA.*
Hydrogen peroxide (p.1647·3) (p.1622·2).
Disinfecting solution for soft contact lenses.

Soft Mate Enzyme Plus Cleaner *Pilkington Barnes-Hind, USA.*
Subtilisin A (p.2393·3) (p.1622·2).
Cleansing solution for soft contact lenses.

Soft U Derm *Galenium, Indon.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Softa Man *Braun, Ger.; Braun, Ital.*
⊗ Alcohol (p.1625·2); propyl alcohol (p.1660·2).
Hand disinfection.

Softab *Alcon, S.Afr.*
Troclosene sodium (p.1665·3)(p.1622·2).
Disinfectant for soft contact lenses.

Sof-Tact *Abbott Diabetes Care, Canad.*
Test for glucose in blood (p.2314·1).

Softa-Man
Note. This name is used for preparations of different composition.
Braun, Cz.
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Hand disinfection.
Braun, Neth.
⊗ Alcohol (p.1625·2); propyl alcohol (p.1660·2).
Hand disinfection.
Braun, Switz.
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2).
Hand disinfection.

Softasept *Braun, Port.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Softasept N *Braun, Ger.; Braun, Switz.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3).
Skin disinfection.

Softene *Melisana, Belg.*
Docusate sodium (p.1725·1); bisacodyl (p.1710·1).
Constipation.

Softeron *Aristo, India.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron and docusate sodium (p.1725·1) is included to reduce the constipating effects of iron.

Softeron-Z *Aristo, India.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); dried yeast (p.1998·3).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Softixol *Schering-Plough, Mex.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with viscous mucus.

Softwear
Note. This name is used for preparations of different composition.
Ciba Vision, Canad.
Sodium chloride (p.1686·1) (p.1622·2).
Rinsing and storage solution for soft contact lenses.
Ciba Vision, NZ.
Rinsing solution for contact lenses (p.1622·2).

Sogilen *Pfizer, Spain.*
Cabergoline (p.802·1).
Parkinsonism.

Sogoon *Steiner, Ger.*
Devil's claw root (p.39·1).
Joint disorders.

Sohobal *Soho, Indon.*
Mecobalamin (p.1981·1).
Peripheral neuropathy.

Sohobion *Soho, Indon.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis; vitamin B deficiency.

Sohoflam *Soho, Indon.*
Nimesulide (p.95·3).
Inflammation; osteoarthritis; pain; peri-articular disorders.

Soholin *Soho, Indon.*
Citicoline (p.2283·3).
Cerebrovascular disorders; head injury; hemiplegia.

Sohopect *Soho, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Sohotin *Soho, Indon.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Soijatutteli *Valio, Fin.†.*
Infant feed (p.1922·1).
Cow's milk allergy; lactose intolerance.

Soin Autobronzant *Clarins, Canad.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Formerly contained avobenzone, octinoxate, octisalate, and oxybenzone.
Sunscreen.

Sojadiol *Sojar, Arg.*
Leciflavone (p.2391·2).
Menopausal disorders; oestrogen deficiency.

Sojar Folico *Sojar, Arg.*
Folic acid (p.1940·1).
Folic acid supplement.

Sojar Men *Sojar, Arg.*
Soya isoflavones (p.2391·2).
Dietary supplement.

Sojar Plus-Calcio *Sojar, Arg.*
Soya protein (p.1965·3); calcium (p.1675·2); soya isoflavones (p.2391·2).
Dietary supplement.

Sojar Pro *Sojar, Arg.*
Soya protein (p.1965·3).
Dietary supplement.

Sojarlech *Sojar, Arg.†.*
Soya protein; vitamins; minerals (p.1922·1).
Dietary supplement.

Sojasterol *Sojar, Arg.†.*
Phytosterols (p.1373·1); isoflavones (p.2391·2); alpha tocopherol (p.1992·2); lecithin (p.2332·2).
Hypercholesterolaemia.

Sojourn *Meridian, USA.*
Sevoflurane (p.1793·2).
General anaesthesia.

Sojyam *Baldacci, Ital.†.*
Yam; soya bean (p.1965·3).
Nutritional supplement for menopausal women.

Sokol *Biofarma, Turk.*
Liquid paraffin (p.2030·3).
Constipation.

Sol Bronce Vital *AM, Arg.*
Betacarotene (p.1930·3); canthaxanthin (p.1470·2).
Tanning aid.

Solac *Soho, Indon.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Solacap *SAT, Spain†.*
Fluconazole (p.532·1).
Fungal infections.

Solacid *Dey's, India.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity.

Solacil *Microsules, Arg.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); dipyrone (p.49·2).
Migraine.

Solacy *Grimberg, Fr.*
Cystine (p.1937·1); sulfur (p.1614·1); vitamin A acetate (p.1973·1); yeast (p.1998·3).
Upper respiratory-tract disorders.

Solage *Galderma, Canad.†; Galderma, USA.*
Mequinol (p.1604·2); tretinoin (p.1618·1).
Sun-induced skin hyperpigmentation.

Solaguttae *Emonta, Austria.*
St John's wort (p.422·3).
Depression; irritability; nervous disorders.

Solamin *Fresenius Kabi, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Solaneuron *Solas, Indon.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Migraine; nausea and vomiting in pregnancy; nervous system disorders; vitamin B deficiency.

Solan-M *Winzer, Ger.*
Vitamin A palmitate (p.1973·1).
Eye disorders.

Solans *Soho, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Solantal *Fujisawa, Jpn†.*
Tiaramide hydrochloride (p.129·3).
Inflammation; pain.

Solapsor *Ysatfabrik, Ger.†.*
Dulcamara (p.2298·1).
Eczema.

Solaquin
Note. This name is used for preparations of different composition.
Valeant, Braz.; Valeant, Mex.
Hydroquinone (p.1598·2); padimate O (p.1609·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Skin hyperpigmentation.
Valeant, Hong Kong; Valeant, Singapore; Crawford, UK; ICN, USA.
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Solaquin Forte
Note. This name is used for preparations of different composition.
Valeant, Arg.
Hydroquinone (p.1598·2); padimate O (p.1609·1); dioxybenzone (p.1594·2).
Skin hyperpigmentation.
Valeant, Canad.†.
Hydroquinone (p.1598·2); padimate (p.1609·1); dioxybenzone (p.1594·2); oxybenzone (p.1608·3).
Skin hyperpigmentation.
ICN, USA.
Cream: Hydroquinone (p.1598·2); padimate O (p.1609·1); dioxybenzone (p.1594·2); oxybenzone (p.1608·3).
Skin hyperpigmentation.
ICN, Malaysia.
SPF 17: Hydroquinone (p.1598·2) with sunscreens.
Skin hyperpigmentation.
ICN, USA.
Topical gel: Hydroquinone (p.1598·2); padimate O (p.1609·1); dioxybenzone (p.1594·2).
Skin hyperpigmentation.

Solar Block *Mentholatum, Austral.†.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octocrilene (p.1608·3).
Sunscreen.

Solar Block Baby *Mentholatum, Austral.†.*
Octinoxate (p.1608·2); enzacamene (p.1597·1); zinc oxide (p.1621·2).
Sunscreen.

Solar Block Surf/Sport *Mentholatum, Austral.†.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); octocrilene (p.1608·3); octil triazone (p.1608·1).
Sunscreen.

Solaraze *CSL, Austral.; Shire, Denm.; Meda, Fin.; Shire, Fr.; Shire, Ger.; Shire, Irl.; Shire, Ital.; Shire, Norw.; Shire, Port.; Meda, Swed.; Shire, UK; Skye, USA.*
Diclofenac sodium (p.44·3).
Actinic keratoses.

Solarcaine
Note. This name is used for preparations of different composition.
Mantecorp, Braz.
Benzocaine (p.1854·1).
Local anaesthesia.
Schering-Plough, Canad.; Schering-Plough, USA.
Benzocaine (p.1854·1); triclosan (p.1665·2).
Local anaesthesia; skin pain or irritation; sunburn.
Vifor, Switz.
Lidocaine (p.1862·3).
Minor skin lesions and burns.
Balmar, NZ.
Lotion: Benzocaine (p.1854·1); camphor (p.2273·2); menthol (p.2340·1); triclosan (p.1665·2).
Sunburn.
Schering-Plough, UK†.
Topical gel: Aloe vera (p.1588·2); lidocaine (p.1862·3).
Cuts; insect bites; sunburn.
Balmar, NZ.
Topical spray: Benzocaine (p.1854·1).
Local anaesthesia; skin irritation.
Schering-Plough, UK.
Topical spray: Benzocaine (p.1854·1); triclosan (p.1665·2).
Minor skin injuries; sunburn.

Solarcaine Aloe Extra Burn Relief *Schering-Plough, USA.*
Lidocaine (p.1862·3); aloe vera (p.1588·2).
Local anaesthesia.

Solarcaine Aloe Vera *Balmar, NZ.*
Aloe vera (p.1588·2).
Minor burns; skin irritation; sunburn.

Solarcaine Aloe Vera Gel *Essex, Chile.*
Lidocaine hydrochloride (p.1862·3); aloe vera (p.1588·2).
Sunburn.

Solarcaine Lidocaine *Schering-Plough, Canad.*
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Burns; sunburn; wounds.

Solarcaine Spray Aerosol *Essex, Chile.*
Isopropyl alcohol (p.1650·3); triclosan (p.1665·2); benzocaine (p.1854·1).
Skin irritation.

Solarcaine Stop Itch *Schering-Plough, Canad.*
Papain (p.2362·3).
Skin pain and irritation.

Solardril Composto *Bunker, Braz.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2).

Solare *Galenium, Indon.*
SPF 15; SPF 30: Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Solaren *Herbapol Pruszkow, Pol.*
Turmeric (p.1473·2).
Biliary-tract disorders.

Solarex
Note. This name is used for preparations of different composition.
Schering-Plough, Venez.†.
Gel SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.
Schering-Plough, Venez.†.
Lotion SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Solarisol *Solara, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Solarsal *Arex, Venez.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Solart *Pfizer, Ital.†.*
Acemetacin (p.15·1).
Musculoskeletal and joint disorders.

Solatran *GSK, Belg.†; GSK, S.Afr.; Doetsch, Grether, Switz.*
Ketazolam (p.1002·2).
Anxiety; nervous disorders; skeletal muscle spasm.

Solaurit *Thursday, Austral.†.*
Homoeopathic preparation.

Solavert *Arrow, Austral.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Solaxin *Eisai, Hong Kong; Eisai, Indon.*
Chlorzoxazone (p.1894·3).
Skeletal muscle spasm.

Solaze *Solvang, Philipp.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

SolBar
Note. This name is used for preparations of different composition.
Person & Covey, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.
Dispolab, Chile†; Person & Covey, USA.
SPF 30; SPF 50: Oxybenzone (p.1608·3); octocrilene (p.1608·3); octinoxate (p.1608·2).
Sunscreen.
Person & Covey, Canad.†.
SPF 50: Octocrilene (p.1608·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Solblastin *Hospira, Port.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Solcer *Solara, Mex.*
Omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Solcibrol *Solfran, Mex.*
Ambroxol (p.1550·3); amoxicillin (p.202·2).
Respiratory-tract infections.

Solciclina *Solfran, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Solclin *Solfran, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Solcode *Reckitt Benckiser, Austral.*
Aspirin (p.20·3); codeine phosphate (p.37·2).
Fever; pain.

Solcoderm *Solco, Hong Kong; ICN, Malaysia†; ICN, Rus.; Valeant, Switz.*
Nitric acid (p.2355·1); acetic acid (p.2244·2); oxalic acid (p.2359·2); lactic acid (p.2329·3); copper nitrate trihydrate (p.1936·1).
Anogenital warts; benign skin growths; keratoses; naevi; verrucas; warts.

Solco-Derman *Valeant, Ger.*
Glacial acetic acid (p.2244·2); oxalic acid (p.2359·2); nitric acid (p.2355·1); lactic acid (p.2329·3); copper nitrate (p.1936·1).
Anogenital warts; keratoses; verrucas.

Solcogyn *Solco, Cz.†; ICN, Pol.; Valeant, Switz.*
Nitric acid (p.2355·1); acetic acid (p.2244·2); oxalic acid dihydrate (p.2359·2); zinc nitrate.
Benign cervical lesions; cervical and uterine disorders.

SolcoKerasal *ICN, Pol.*
⊗ Salicylic acid (p.1612·2); urea (p.1620·2).
Keratinisation disorders.

Solcoseryl *Valeant, Arg.; ICN, Austria; Valeant, Cz.; Solco, Hong Kong; Pharos, Indon.; Solco, Indon.; Taiho, Jpn; Valeant, Malaysia; ICN, Neth.†; Valeant, Philipp.; ICN, Pol.; ICN, Rus.; Valeant, Singapore; Diafarm, Spain; Valeant, Switz.; ICN, Thai.*
Protein-free calf blood extract (p.2337·3).
Abrasions; burns; cerebral and peripheral vascular disorders; eye injury; frostbite; mouth and throat disorders; peptic ulcer; radiation-induced skin damage; skin grafts; skin ulceration; soft-tissue disorders; ulcers; wounds.

Solcoseryl Dentaire *Valeant, Switz.*
Protein-free calf blood extract (p.2337·3); lauromacrogol 400 (p.1916·1).
Mouth disorders.

Solcoseryl Dental *Kamp, Arg.†; ICN, Austria; Valeant, Ger.; Solco, Hong Kong; Pharos, Indon.; Solco, Indon.; Valeant, Malaysia; Valeant, Philipp.; ICN, Rus.; Valeant, Singapore; ICN, Thai.; Solco, Thai.*
Protein-free calf blood extract (p.2337·3); lauromacrogol 400 (p.1916·1).
Dental adhesive; mouth and gum disorders.

Solcosplen *Strathmann, Ger.†.*
Calf spleen extract (p.2337·3).
Menopausal disorders.

Solcosplen C *Strathmann, Ger.*
Cimicifuga (p.2282·1).
Menopausal disorders.

Solco-Trichovac *Valeant, Cz.†.*
Lactobacillus acidophilus (p.2372·3).
Vaginal infections.

SolcoTrichovac *Solco, Rus.; Valeant, Switz.*
Lactobacillus rhamnosus (p.2372·3); *Lactobacillus vaginalis*; *Lactobacillus fermentum* (p.2372·3); *Lactobacillus salivarius*.
Bacterial vaginosis; trichomoniasis; vaginal infections.

SolcoTrichovac Lyophilisat *Valeant, Switz.*
Lactobacillus acidophilus (p.2372·3).
Vaginal infections.

Solco-Urovac *Solco, Cz.†.*
Escherichia coli; *Proteus mirabilis*; *Proteus morganii*; *Klebsiella pneumoniae*; *Enterococcus faecalis* (p.2372·3).
Urinary-tract infections.

Solcovagin *ICN, Rus.*
Nitric acid (p.2355·1); acetic acid (p.2244·2); oxalic acid (p.2359·2); zinc nitrate.
Vaginal disorders.

Soldactone *Continental Pharma, Belg.; Pfizer, Neth.; Pharmacia, Norw.†; Pfizer, Switz.*
⊗ Potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypokalaemia; liver cirrhosis with ascites and oedema; oedema.

Soldermil *Edol, Port.*
SPF 15: A range of sunscreens.

Soldermil Ecran Total *Edol, Port.†.*
SPF 24: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Soldesam *Farmacologico Milanese, Ital.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Soldesanil *Diapit, Gr.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Soldextam *Solas, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Soldrin
Note.This name is used for preparations of different composition.
Andromaco, Chile.
Tiabendazole (p.156·2).
Worm infections.

Pisa, Mex.
Ear drops: ⊗ Hydrocortisone (p.1535·2); chloramphenicol (p.239·3); benzocaine (p.1854·1).
Otitis externa.

Pisa, Mex.
Eye drops: ⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Solecin *Echo, Ital.*
⊗ Soya lecithin (p.2332·2); wheat germ (p.2415·1); gelatin (p.1072·1); glycerol (p.2314·2); betacarotene (p.1930·3).
Nutritional supplement.

Soledum *Cassella-med, Cz.†; Cassella-med, Ger.*
Cineole (p.2282·3).
Bronchitis; respiratory-tract disorders; sinusitis.

Soledum Balsam *Cassella-med, Ger.*
Cineole (p.2282·3).
Respiratory-tract disorders.

Soledum Hustensaft *Cassella-med, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh; coughs.

Soledum Hustentropfen *Cassella-med, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh; coughs.

Soledum med *Cassella-med, Ger.†.*
Chamomile oil (p.2279·3).
Nasal congestion; rhinitis.

Soleil Ecran *Osler, Fr.†.*
SPF 20; SPF 30: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Soleil Expert Sun Care *Lancome, Canad.*
SPF 15: Avobenzone (p.1589·3); octocrilene (p.1608·3); octisalate (p.1608·2).
Formerly known as UV Expert and contained avobenzone, octinoxate, and octisalate.
Sunscreen.

Solemil *Neckerman, Braz.†.*
Neomycin sulfate (p.305·1); benzethonium chloride (p.1630·1); vitamin A (p.1971·2); vitamin D (p.1986·1).
Skin infections.

Solenil *Fortbenton, Arg.*
SPF 15; SPF 4; SPF 8: Octinoxate (p.1608·2); benzophenones.
Sunscreen.

Solenil Pantalla Fisica *Fortbenton, Arg.*
Octinoxate (p.1608·2); benzophenone; titanium dioxide (p.1617·3).
Sunscreen.

Solenil Post Solar *Fortbenton, Arg.*
Aloe vera (p.1588·2); vitamin E (p.1992·2).

Solesmin *Cipla, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Soleton *Cryopharma, Mex.*
Zaltoprofen (p.133·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Solevita *Permamed, Switz.*
St John's wort (p.422·3).
Agitation; depression; sleep disorders.

Solex A15 *Dermol, USA†.*
Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Solexa *Pfizer, Austria; Pfizer, Ital.†; Pfizer, Neth.; Medinfar, Port.*
Celecoxib (p.34·2).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Solfa *Takeda, Jpn.*
Amlexanox (p.1115·2).
Allergic rhinitis; asthma.

Solfac *Bayer, Ital.*
Cyfluthrin (p.2039·2).
Insecticide.

Solfen *Antigen, Irl.†.*
Ibuprofen (p.64·2).
Fever; pain.

Solfidin *Rontag, Arg.*
Clonazepam (p.478·2).
Epilepsy; panic attacks.

Solfranicol *Solfran, Mex.*
Chloramphenicol (p.239·3); tetracycline (p.347·1).
Bacterial infections.

Solfurol *Solfran, Mex.*
Furazolidone (p.834·3); clioquinol (p.254·1).
Diarrhoea.

Solganal *Schering, Canad.†; Schering-Plough, Israel; Schering, USA.*
Aurothioglucose (p.26·2).
Rheumatoid arthritis.

Solgenta *Oftalmi, Venez.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Solgol *BMS, Ger.; Sanofi-Aventis, Spain.*
⊗ Nadolol (p.1345·2).
Angina pectoris; arrhythmias; hypertension; migraine.

Solhidrol *Solara, Mex.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Solia
Note.This name is used for preparations of different composition.
Unison, Thai.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Prasco, USA.
21 Tablets, ethinylestradiol (p.2101·3); desogestrel (p.2093·2); 7 tablets, inert.
Combined oral contraceptive.

Solian *Sanofi-Aventis, Austral.; Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Irl.; Synthelabo, Israel; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Mex.; Sanofi-Aventis, NZ; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Turk.; Sanofi Synthelabo, UK.*
Amisulpride (p.961·1).
Depression; psychoses.

Solibay *Bayer, Mex.†.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Solibone *Quimica y Farmacia, Mex.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteomalacia; osteoporosis; rickets; tetany.

Solicam *SMB, Belg.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Solidago Hevert Complex *Hevert, Ger.*
Homoeopathic preparation.

Solidagoren mono *Klein, Ger.*
Solidaga virgaurea (p.2391·1).
Urinary-tract disorders.

Solidagoren N *Klein, Ger.*
Solidago virgaurea (p.2391·1); potentilla anserina; equisetum (p.2299·3).
Urinary-tract disorders.

Solidagosan N *Hanosan, Ger.*
Homoeopathic preparation.

Solidon *Adelco, Gr.*
Chlorpromazine hydrochloride (p.969·2).
Agitation; psychoses.

Solimed *Farmedia, Gr.*
Salicylic acid (p.1612·2).
Skin disorders.

Solin *Saval, Chile.*
Lidocaine hydrochloride (p.1862·3).
Pain during injection.

Solinase *Yamanouchi, Jpn†.*
Pamiteplase (p.1365·3).

Solinfec *Ifars, Indon.*
Ketoconazole (p.539·1).
Fungal skin infections.

Solinitrina *Almirall, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; induction of hypotension in surgery; myocardial infarction; pulmonary oedema.

Solipred *Solara, Mex.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Soliris *Alexion, Cz.; Alexion, Fr.; Alexion, Port.; Alexion, UK; Alexion, USA.*
Eculizumab (p.2298·3).
Paroxysmal nocturnal haemoglobinuria.

Solivito N *Fresenius Kabi, Irl.; Fresenius Kabi, UK.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Sol-Jod *Ecobi, Ital.†.*
Iodine (p.2169·2).
Oral antisepsis.

Solkan *Solfran, Mex.*
Kanamycin (p.291·3).
Bacterial infections.

Sollival *Sirval, Ital.*
Emollient.

Solmag *Ecosol, Switz.†.*
Magnesium aspartate (p.1679·1).
Arrhythmias; magnesium deficiency; magnesium supplement.

Solmavin *Mavi, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Solmucaine *IBSA, Switz.*
Acetylcysteine (p.1548·2); tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Upper respiratory-tract disorders with viscous mucus.

Solmucalm *IBSA, Switz.*
Acetylcysteine (p.1548·2); chlorphenamine maleate (p.571·3).
Coughs.

Solmucol *IBSA, Cz.; Genevrier, Fr.; IBSA, Hong Kong; IBSA, Hung.; Fidia, Ital.; IBSA, Neth.; IBSA, Philipp.; Sonix, Philipp.; Pharmacare, S.Afr.; Genevrier, Singapore†; Bioiberica, Spain†; IBSA, Switz.*
Acetylcysteine (p.1548·2).
Eye disorders; paracetamol overdosage; prevention of urinary-tract toxicity induced by cyclophosphamide or ifosfamide; respiratory-tract congestion.

Solmux *Westmont, Hong Kong; Medifarma, Indon.; UAP, Indon.; United Laboratories, Philipp.; Great Eastern, Thai.; Pediatrica, Thai.; Westmont, Thai.*
Carbocisteine (p.1553·2).
Cough; otitis media; respiratory-tract congestion; sinusitis.

Solmux-Broncho (Reformulated) *United Laboratories, Philipp.*
⊗ Salbutamol (p.1131·2); carbocisteine (p.1553·2).
Cough associated with viscous mucus.

Solnasin *Polpharma, Pol.*
Sodium chloride (p.1686·1).
Nasal congestion.

Soloc *Goldshield, UK†.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Solocalm *Bernabo, Arg.*
Piroxicam (p.117·3) or piroxicam betadex (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Solocalm Plus
Note.This name is used for preparations of different composition.
Bernabo, Arg.
Injection: ⊗ Piroxicam (p.117·3); trometamol (p.2405·1); pyridoxine hydrochloride; dexamethasone (p.1526·1).
Musculoskeletal, joint and peri-articular disorders.

Bernabo, Arg.
Tablets: ⊗ Piroxicam (p.117·3); carisoprodol (p.1894·1); dexamethasone (p.1526·1); pyridoxine hydrochloride.
Musculoskeletal, joint, and peri-articular disorders.

Solocalm-B *Bernabo, Arg.*
Piroxicam (p.117·3); thiamine hydrochloride; pyridoxine hydrochloride; cyanocobalamin.
Inflammation; neuritis.

Solocalm-Flex *Bernabo, Arg.*
Piroxicam (p.117·3); carisoprodol (p.1894·1).
Musculoskeletal and joint disorders.

Solo-care *Ciba Vision, Austral.; Ciba Vision, Braz.*
Cleansing, rinsing, disinfecting and storing solution for soft contact lenses (p.1622·2).

Solocare *Ciba Vision, NZ†.*
Cleaning, disinfecting, rinsing, and storage solution for soft contact lenses (p.1622·2).

Solo-care Aqua *Ciba Vision, Canad.*
Cleansing, rinsing, disinfecting, and storage solution for soft contact lenses (p.1622·2).

Solo-care Hard *Ciba Vision, Canad.†.*
Cleansing, rinsing, conditioning, storage, and wetting solution for hard and gas permeable contact lenses (p.1622·2).

Solodyn *Medicis, USA.*
Minocycline hydrochloride (p.300·3).
Acne.

Solof *Farmaceutica H, Mex.*
Diclofenac sodium (p.44·3).
Inflammation and pain following eye surgery; inflammatory eye disorders; inhibition of miosis during cataract surgery; prevention of cystoid macular oedema.

Sol-O-Flex *Inmunolab, Arg.*
Povidone (p.2146·1).
Dry eyes.

Solokinase *Otsira, India.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Solomet *Orion, Fin.*
⊗ Methylprednisolone (p.1538·1), methylprednisolone acetate (p.1538·2), or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Solomet c bupivacain hydrochlorid *Orion, Fin.*
⊗ Methylprednisolone acetate (p.1538·2); bupivacaine hydrochloride (p.1854·3).
Musculoskeletal, joint, and peri-articular disorders.

Solomycin *Ipca, India.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Solon *Taisho, Jpn.*
Sofalcone (p.1772·1).
Gastritis; peptic ulcer.

Solone *Fawns & McAllan, Austral.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Solosa *Sanofi-Aventis, Gr.; Guidotti, Ital.; Aventis, Philipp.*
Glimepiride (p.441·1).
Diabetes mellitus.

Solosin *Aventis, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

SoloSite *Smith & Nephew, Austral.*
Carmellose sodium (p.2142·1); allantoin (p.1588·1).
Wounds.

Solosprin *Zydus, India.*
Isosorbide mononitrate (p.1318·3); aspirin (p.20·3).
Angina pectoris; myocardial infarction.

Solotrate *Zydus Cadila, Thai.*
Isosorbide mononitrate (p.1318·3).
Ischaemic heart disease; pulmonary hypertension.

Solotrim *Hexal, Austria.*
Trimethoprim (p.355·2).
Bacterial infections.

Solotron *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Solotuss *Hawthorn, USA.*
Pentoxyverine tannate (p.1567·3).
Cough.

Solovite *Solgar, UK.*
Multivitamin and mineral preparation (p.1922·1).

Solox *Douglas, NZ.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Solpadeine *GSK Consumer, Cz.; GSK Consumer, Hung.†; GSK Consumer, Irl.; GSK Consumer, Pol.; GSK Consumer, Rus.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Cold and influenza symptoms; fever; pain.

Solpadeine Headache *GSK Consumer, UK.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Solpadeine Max *GSK Consumer, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Fever; pain.

Solpadeine Migraine *GSK, UK.*
Ibuprofen (p.64·2); codeine (p.37·2).
Migraine.

Solpadeine Plus *GSK Consumer, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Solpadol *Sanofi-Aventis, Irl.; Sanofi-Aventis, Neth.; Sanofi-Aventis, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol 30/500.
Pain.

Solpaflex
Note.This name is used for preparations of different composition.
GSK, Cz.; SmithKline Beecham, Denm.†; GSK Consumer, Hung.; GSK Consumer, Rus.
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

GSK Consumer, UK.
Ibuprofen (p.64·2); codeine phosphate (p.37·2).
Fever; pain.

Solpat *Parggon, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Solpenox *Solas, Indon.*
Amoxicillin (p.202·2).
Bacterial infections.

Solphride *Solvang, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Solphyllex *Adcock Ingram, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1); diphenylpyraline hydrochloride (p.578·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Solphyllin *Adcock Ingram, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1).
Obstructive airways disease.

Solpic *Medical, Port.†.*
Mepyramine maleate (p.585·2); calamine (p.1591·2); benzocaine (p.1854·1).
Skin irritation.

Solplem *Essenpharma, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Solplex 40 *Fresenius Kabi, Ital.†.*
⊗ Dextran 40 (p.1059·1) in sodium chloride.
Peripheral arteriopathy; plasma volume expansion.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Solplex 70 *Fresenius Kabi, Ital.†.*
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Plasma volume expansion; thrombosis prophylaxis.

Solprene *Farmigea, Ital.*
⊗ Prednisolone sodium phosphate (p.1541·2); neomycin sulfate (p.305·1).
Infected eye disorders.

Solpres *Biotech, Venez.*
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Solprin
Reckitt Benckiser, Austral.
Aspirin (p.20·3).
Fever; inhibition of platelet aggregation; pain.

Reckitt Benckiser, NZ.
Calcium aspirin (p.23·3).
Inflammation; pain.

Solsavit *Solfran, Mex.*
Vitamin B ; vitamin B (p.1922·1).
Anaemias; neuritis.

Soltacina *Solara, Mex.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; pain.

Soltadol *Solara, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Soltamox *Rosemont, UK; Cytogen, USA.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer.

Soltice *Oakhurst, USA.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Muscle, joint, and soft-tissue pain; neuralgia.

Soltin *Oftalmi, Venez.*
⊗ Chlorphenamine maleate (p.571·3); naphazoline hydrochloride (p.1565·2).
Allergic conjunctivitis.

Soltric *ICN, Mex.†.*
Mebendazole (p.148·3).
Worm infections.

Soltrictor con Lagrifilm *Allergan, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2); polyvinyl alcohol (p.2145·3).
Eye irritation.

Soltrim
Note.This name is used for preparations of different composition.
Bruluart, Mex.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Almirall, Spain.
Sulfamethoxazole lysine (p.341·3); trimethoprim (p.355·2).
Bacterial infections; pneumocystis pneumonia.

Soltrimox *Richmond, Arg.*
Ceftriaxone (p.238·1).
Bacterial infections.

Solubacter *Boots Healthcare, Fr.*
Triclocarban (p.1665·2).
Disinfection of skin and mucous membranes.

Solubeol *Azevedos, Port.†.*
Cypress oil (p.2291·2); eucalyptus oil (p.2301·2); hyssop oil (p.2323·3); lavender oil (p.2331·2); pine silvestris oil (p.2368·2).
Respiratory-tract disorders.

Solubilax *Rafarm, Gr.*
Cefotaxime (p.229·1).
Bacterial infections.

Solu-Biloptin *Schering, UK†.*
Calcium iopodate (p.1484·3).
Contrast medium for biliary-tract radiography.

Solubitrat *Sanova, Austria.*
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1); java tea (p.2328·2).
Urinary-tract disorders.

Solucao Aminon *JP, Braz.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Solucao Aminorin *JP, Braz.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Solucaps *Medix, Mex.*
⊗ Mazindol (p.2157·3).
Obesity.

Solucel
Note.This name is used for preparations of different composition.
Stiefel, Spain.
Benzoyl peroxide (p.1590·2).
Acne.

Sanofi-Aventis, Venez.
Colloidal infusion.
Extracorporeal circulation; plasma volume expansion.

Solu-Celestan *Aesca, Austria.*
⊗ Betamethasone disodium phosphate (p.1518·3).
Corticosteroid.

Solucer *Fortbenton, Arg.*
Trolamine polypeptide oleate-condensate (p.2405·1).
Ear wax removal.

Soluchrom *Cooperation Pharmaceutique, Fr.*
Merbromin sodium (p.1652·1).
Skin, burn and wound disinfection.

Solucion Detergente *Reccius, Chile.*
Sodium lauril ether sulfate (p.2138·3).

Solucion DP *Pisa, Mex.†.*
Glucose; sodium chloride; calcium chloride; magnesium chloride; sodium lactate (p.1670·3).
Peritoneal dialysis.

Solucion Fisio *Cinfa, Spain.*
Sodium chloride (p.1686·1).
Nasal congestion.

Solucion De Lugol *Volta, Chile†.*
Iodine (p.2169·2); sodium iodide (p.2169·2).
Disinfection.

Solucion Oral *Naf, Arg.*
Electrolytes (p.1667·1); xylitol (p.1998·2); hypromellose (p.2144·2).
Dry mouth.

Solucion Schoum *Expanscience, Spain.*
Boldo (p.2267·2); fumitory (p.2307·2); hamamelis (p.2318·2); melissa (p.2339·3); rhubarb (p.1768·3); piscidia (p.2328·1); peppermint oil (p.1761·2); hydrastis (p.2321·3); ethyl alcohol; glycerol.
Hepatobiliary disorders.

Solucis *Pharma-Marketing, Hung.; Aesculapius, Ital.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Soluclear *Vivax Optipharm, Venez.*
⊗ Pheniramine maleate (p.587·3); naphazoline hydrochloride (p.1565·2).
Inflammatory eye disorders.

Solu-Cortef *Pfizer, Austral.; Pfizer, Belg.; Pharmacia, Braz.†; Pfizer, Canad.; Pfizer, Chile; Pharmacia, Cz.†; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pharmacia, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Port.; Pfizer, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, UK; Upjohn, USA; Pfizer, Venez.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Solu-Crom *Sabex, Canad.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Solu-Dacortin *Merck, Austria.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Soludacortin *Bracco, Ital.†.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Solu-Dacortina *Merck, Port.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Solu-Dacortine *Merck, Belg.†; Merck, Switz.†.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Soludactone *Pfizer, Fr.*
⊗ Potassium canrenoate (p.1374·1).
Ascites; hyperaldosteronism; hypokalaemia; oedema.

Soludamin *Kleva, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Solu-Decortin H *Merck, Cz.†; Merck, Ger.*
⊗ Prednisolone sodium succinate (p.1541·2).
Corticosteroid.

Soluderme *Schering-Plough, Port.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Soludor *Lehning, Fr.*
Homoeopathic preparation.

Soludril Antiussivum *Pierre Fabre, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Soludril Expectorans *Pierre Fabre, Belg.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Solufen *Winthrop, Fr.; Azevedos, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Solufilina *BOI, Spain.*
Etamiphylline hydrochloride (p.1120·3).
Angina pectoris; heart failure; myocardial infarction; obstructive airways disease.

Solufos *Busto, Spain.*
Fosfomycin calcium (p.278·2) or fosfomycin sodium (p.278·2).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Solugastril *Pfizer, Austria; Pfizer Consumer, Ger.*
Aluminium hydroxide (p.1706·2); calcium carbonate (p.1714·1).
Duodenitis; dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer.

Solugel
Note.This name is used for preparations of different composition.
Stiefel, Arg.; Stiefel, Braz.; Stiefel, Canad.; Stiefel, Chile; Stiefel, Mex.; Stiefel, Venez.†.
Benzoyl peroxide (p.1590·2).
Acne.

Johnson & Johnson, Austral.
Hydrogel dressing.
Burns; wounds.

Solu-Hex *Intra, Venez.*
Hexachlorophene (p.1646·1).
Disinfection.

Solukapton *Strallhofer, Austria.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Solulexin *Duopharma, Hong Kong.*
Cefalexin (p.218·2).
Bacterial infections.

Solulip *Pharmanik (Φαρμανικ), Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Solum Ol *Wala, Ger.*
Aesculus (p.2248·2); equisetum (p.2299·3); lavender oil (p.2331·2); solum uliginosum.
Musculoskeletal and joint disorders; neuralgia.

Solumag
Note.This name is used for preparations of different composition.
Kolassa, Austria; Boehringer Ingelheim, Fr.†; Intermed, Gr.; Geymonat, Ital.
Magnesium pidolate (p.1679·3).
Anxiety related hyperventilation; dysmenorrhoea; eclampsia and other obstetric disorders; magnesium deficiency; nervous hyperexcitability associated with magnesium deficiency; premature labour.

Hexal, S.Afr.
Magnesium oxide (p.1744·1).
Magnesium deficiency.

Solu-Medrol
Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Hong Kong; Pfizer, Hung.; Pharmacia, India; Pfizer, Indon.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, USA; Pfizer, Venez.
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Pfizer, Fr.
⊗ Methylprednisolone hydrogen succinate (p.1538·2).
Corticosteroid.

Pfizer, Gr.
⊗ Methylprednisolone hydrogen succinate (p.1538·2) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Solu-Medrone *Pharmacia, Irl.; Pfizer, UK.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Solumerin *Ariston, Arg.*
Benzethonium chloride (p.1630·1); tyrothricin (p.358·2); cetylpyridinium chloride (p.1635·1); butimerin.
Burns; mouth disorders; skin infections; ulcers; wounds.

Solumidazol *Diba, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Solu-Moderin *Pfizer, Spain.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Solumol *C & M, USA.*
Vehicle for topical preparations.

Soluna *Elea, Arg.*
Quinestrol (p.2128·1); etynodiol diacetate (p.2103·2).
Combined oral contraceptive; dysmenorrhoea.

Solunac *Systopic, India.*
Diclofenac (p.44·2).
Gout; musculoskeletal and joint disorders.

Solunovar Compuesto *Vincenti, Venez.*
Benzydamine hydrochloride (p.27·3); cetylpyridinium chloride (p.1635·1).
Mouth disorders.

Solupen N *Winzer, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Rhinitis; sinusitis.

Solupred
Note.This name is used for preparations of different composition.
Ingens, Arg.
⊗ Prednisolone (p.1540·3); phenylephrine (p.1568·1).
Eye disorders.

Sanofi-Aventis, Fr.
⊗ Prednisolone metasulfobenzoate sodium (p.1541·1).
Corticosteroid.

Solu-Pred
Note. A similar name is used for preparations of different composition (see above).
Cellofarm, Braz.†.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Solupren *Bergamo, Braz.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Soluprick *ALK, Port.*
Histamine hydrochloride (p.2319·2) (p.2250·2).
Diagnosis of hypersensitivity.

Soluprick SQ *ALK, Cz.; ALK, Denm.; ALK, Fin.; ALK, Neth.; ALK, Swed.*
Allergen extracts (p.2250·2).
Diagnosis of hypersensitivity.

Solural *Antibioticos, Mex.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium lactate; glucose (p.1672·2).
Oral rehydration therapy.

Solurex *Hyrex, USA†.*
⊗ Dexamethasone acetate (p.1526·1) or dexamethasone sodium phosphate (p.1526·2).
Corticosteroid.

Soluric *Unipharma, Gr.*
Allopurinol (p.552·2).
Gout; hyperuricaemia associated with cancer chemotherapy; kidney stones.

Solurin *JP, Braz.†.*
Electrolytes (p.1670·3).
Haemodialysis solution.

Solurrinol *Teofarma, Spain.*
Potassium chlorate (p.2371·3); sodium bicarbonate (p.1673·2); sodium chloride (p.1686·1).
Nasal congestion.

Solus *Lifeplan, UK.*
Multivitamin, mineral, and nutritional preparation (p.1922·1).

Solusprin *Bioresearch, Spain†.*
Lysine aspirin (p.79·1).
Fever; musculoskeletal, joint and peri-articular disorders; pain; thromboembolism prophylaxis.

Soluston *Rafa, Israel†.*
Chenodeoxycholic acid (p.2280·1).
Cholesterol gallstones.

Solustrep
Note.This name is used for preparations of different composition.
Bergamo, Braz.
Streptokinase (p.1402·3).
Thromboembolic disorders.

Caps, S.Afr.
Streptomycin sulfate (p.333·3).
Tuberculosis.

Solustres *Finadiet, Arg.*
Tetracycline hydrochloride (p.347·2); papain (p.2362·3).
Bacterial infections.

Solutan
Note.This name is used for preparations of different composition.
Galena, Cz.†.
⊗ Ephedrine hydrochloride (p.1558·2); tolu balsam (p.1574·2); sodium iodide (p.2169·2); fennel oil (p.2303·1); procaine hydrochloride (p.1869·1); hyoscyamine (p.1736·1); quillaia saponin (p.1920·1); bitter almond.
Obstructive airways disease.

Galena, Rus.
⊗ Belladonna (p.2263·3); dill oil (p.2293·3); saponin (p.1920·1); procaine hydrochloride (p.1869·1); ephedrine hydrochloride (p.1558·2); sodium iodide (p.2169·2); tolu balsam (p.1574·2); bitter almond water.

Soluteb *Mentiterm, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Solutina *Alcon, Mex.*
⊗ Pheniramine maleate (p.587·3); naphazoline hydrochloride (p.1565·2).
Conjunctivitis.

Solutio Cordes *Ichthyol, Ger.*
Ictasol (p.1599·1).
Scalp disorders.

Solutio Cordes Dexa N *Ichthyol, Ger.*
⊗ Dexamethasone (p.1526·1).
Scalp disorders.

Solutio Thomas cum Procaino *Ardeapharma, Cz.*
Magnesium chloride (p.1679·1); potassium chloride (p.1684·3); procaine hydrochloride (p.1869·1).
Cardioplegia.

Solution Antiseptique Stella *Lohmann, Belg.†.*
⊗ Alcohol (p.1625·2); ether (p.2023·2).
Skin and instrument disinfection.

Solution Stago Diluee *Pharmadeveloppement, Fr.*
Boldo (p.2267·2); chamomile (p.2279·3); kinkeliba (p.2329·2); solidago (p.2391·1).
Digestive disorders.

Solutrast *Altana, Ger.*
Iopamidol (p.1483·3).
Radiographic contrast medium.

Solutrat *Sandoz, Arg.*
Ursodeoxycholic acid (p.2408·1).
Gallstones.

Solutricine Expectorant *Sanofi-Aventis, Fr.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Solutricine Maux de Gorge
Note.This name is used for preparations of different composition.
Sanofi-Aventis, Fr.
Lozenges: Tetracaine hydrochloride (p.1871·3).
Formerly contained tyrothricin and tetracaine hydrochloride.
Mouth and throat disorders.

Sanofi-Aventis, Fr.
Pastilles: Biclotymol (p.1632·1).
Formerly known as Solutricine Vitamine C and contained tyrothricin and ascorbic acid.
Mouth and throat infections.

Sanofi-Aventis, Fr.
Throat spray: Tetracaine hydrochloride (p.1871·3); hexamidine isetionate (p.1646·3).
Mouth and throat disorders.

Soluver *Dermtek, Canad.*
Salicylic acid (p.1612·2).
Verrucas.

Soluver Plus *Dermtek, Canad.*
Salicylic acid (p.1612·2).
Warts.

Soluvit *Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Gr.; Fresenius Kabi, Ital.; Fresenius Kabi, Norw.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Spefar, Venez.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Soluvit N *Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Baxter, Ger.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Pharmacia Upjohn,*

Israel; Fresenius Kabi, Malaysia; Fresenius Kabi, NZ; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore†; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Soluvit Neu *Fresenius Kabi, Austria.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Soluvit Novum *Fresenius, Belg.*
Multivitamin preparation (p.1922·1).
Parenteral nutrition.

Soluvite *Pharmics, USA.*
Multivitamin preparation with fluoride (p.1962·2)(p.1922·1).
Dental caries prophylaxis; dietary supplement.

Solu-Volon A *Dermapharm, Austria.*
⊗ Triamcinolone acetonide dipotassium phosphate (p.1545·1).
Corticosteroid.

Soluwax *Hoe, Malaysia; Hoe, Singapore.*
Docusate sodium (p.1725·1).
Ear wax removal.

Soluzione Darrow *Diaco, Ital.*
Electrolyte infusion (p.1667·1).
Infantile diarrhoea.

Soluzione Schoum *Sanofi-Aventis, Ital.*
Fumitory (p.2307·2); ononis (p.2357·1); piscidia (p.2328·1).
Painful spasm of the urinary and biliary tracts.

Soluzyme *Lupin, India.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3).
Inflammation; oedema.

Solv-Ac T *Acemed, Hung.†.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Solvanol *Medipharm, Chile.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1); ammonium chloride (p.1551·3).
Coughs.

Solvazinc *Provalis, Irl.; koGen, UK.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Solve Dandruff *Redken, Canad.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

SolvEasy *Ego, Austral.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Solvente Indoloro *Fada, Arg.; Monserrat, Arg.; Northia, Arg.; Veinfar, Arg.*
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Pain during injection.

Solvertyl *ICN, Pol.*
Ranitidine (p.1766·1).
Acid aspiration; excess gastric acidity; peptic ulcer.

Solvetan *GSK, Gr.*
Ceftazidime (p.234·1).
Bacterial infections.

Solvex
Note.This name is used for preparations of different composition.
Merz, Ger.
Reboxetine mesilate (p.420·3).
Depression.

Teva, Israel.
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Solvex Liquido Fungicida *Schering, Arg.†.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2); chlorothymol (p.1640·1).
Fungal skin infections.

Solvezink *AstraZeneca, Ger.†; Stern, Ger.†; AstraZeneca, Norw.; AstraZeneca, Swed.*
Zinc sulfate (p.1999·2).
Acne; acrodermatitis enteropathica; ulcers; wounds; zinc deficiency.

Solviflu *Boots Healthcare, Ital.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Solvin
Note.This name is used for preparations of different composition.
Mexin, India.
Bromhexine hydrochloride (p.1552·2); phenylpropanolamine hydrochloride (p.1569·3).
Formerly contained bromhexine hydrochloride and pseudoephedrine hydrochloride.
Cold symptoms, cough; sinusitis.

Loren, Mex.†.
Povidone-iodine (p.1659·2).
Oral hygiene; skin disinfection.

Solvinex *Meprofarm, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Solving *MDM, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Solvipect *Nycomed, Norw.*
Guaifenesin (p.1561·3); liquorice (p.1740·3).
Coughs.

Solvipect comp *Nycomed, Norw.*
Guaifenesin (p.1561·3); liquorice (p.1740·3); ethylmorphine hydrochloride (p.52·2).
Coughs.

Solvisol *Solfran, Mex.*
Multivitamin preparation (p.1922·1).

Solvita Baby *Solas, Indon.*
Vitamins; lysine hydrochloride; sodium fluoride; docosahexaenoic acid; omega-3; omega-6 (p.1922·1).
Nutritional supplement.

Solvita Plus *Solas, Indon.*
Vitamins; lysine hydrochloride; calcium pantothenate; calcium gluconate (p.1922·1).
Vitamin and calcium supplement.

Solvium *Chefaro, Port.; Chefaro, Spain.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Solvobil
Note.This name is used for preparations of different composition.
Farmasa, Braz.
Cynara (p.2291·2); boldo (p.2267·2); cascara (p.1715·2); belladonna (p.2263·3); peppermint leaf (p.1761·2); juniper oil (p.2328·3).
Liver disorders.

Silesia, Chile.
Ursodeoxycholic acid (p.2408·1).
Gallstones.

Recordati, Ital.
Sodium cholate (p.2266·3); nicotinamide (p.1957·3); boldo (p.2267·2); cascara (p.1715·2).
Constipation.

Solvolan *KRKA, Cz.; KRKA, Hung.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Solvolin *Drossapharm, Switz.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders with viscous mucus.

Solvopret
Note.This name is used for preparations of different composition.
Bionorica, Austria.
Gentian (p.2310·3); primula flower (p.2372·2); rumex (p.2391·1); sambucus (p.2383·1); verbena.
Catarrh.

Bionorica, Thai.; Pharmalink, Thai.
Thyme (p.2401·1); ivy (p.2328·1).
Bronchitis.

Solvopret TP *Bionorica, Thai.; Pharmalink, Thai.*
Thyme (p.2401·1); primrose root (p.2372·2).
Bronchitis.

Solvoxine *Solvang, Philipp.*
Oxytocin (p.2015·2).
Labour induction; lactation promotion; missed abortion; postpartum bleeding.

Solyptol
Note.This name is used for preparations of different composition.
Faulding, Austral.†.
Cream: Benzalkonium chloride (p.1629·1); allantoin (p.1588·1).
Abrasions; burns; cuts; insect bites.

Faulding, Austral.†.
Soap: Triclosan (Irgasan) (p.1665·2).

Faulding, Austral.†.
Topical liquid: Pine oil (p.2368·2); chloroxylenol (p.1640·2).
Abrasions; cuts; insect bites.

Som *Satori, Fr.†.*
A range of nutritional supplements (p.1922·1).

Soma *Carter Horner, Canad.†; Wallace, USA.*
Carisoprodol (p.1894·1).
Musculoskeletal pain.

Soma Complex *Teofarma, Ital.†.*
Carisoprodol (p.1894·1); dipyrone (p.49·2).
Musculoskeletal and joint pain and spasm.

Soma Compound *Medpointe, USA†.*
Carisoprodol (p.1894·1); aspirin (p.20·3).
Musculoskeletal disorders.

Soma Compound with Codeine *Medpointe, USA†.*
Carisoprodol (p.1894·1); aspirin (p.20·3); codeine phosphate (p.37·2).
Musculoskeletal disorders.

Somabion *Medicus, Gr.*
Somatostatin acetate (p.1809·2).
Upper gastrointestinal tract haemorrhage.

Somac
Note.This name is used for preparations of different composition.
Altana, Austral.; Pfizer, Fin.; Pfizer, NZ; Altana, Norw.
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Belmac, Spain.
Citalopram hydrobromide (p.385·3).
Depression; obsessive-compulsive disorder; panic disorder.

Somacid *Collins, Mex.*
Carisoprodol (p.1894·1).
Skeletal muscle spasm.

Somac-MA *Altana, Austral.*
Tablets, pantoprazole sodium (Somac) (p.1760·1); capsules, amoxicillin trihydrate (Amoxil) (p.202·2); tablets, metronidazole (Flagyl) (p.837·1).
Peptic ulcer.

Somadril *Alpharma, Denm.†; Alpharma, Norw.†; Alpharma, Swed.†.*
Carisoprodol (p.1894·1).
Pain; skeletal muscle spasm.

Somadril Comp *Alpharma, Fin.†; Alpharma, Swed.†.*
Carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Musculoskeletal and joint disorders; pain.

Somadril Compound *Actavis, Indon.*
Carisoprodol (p.1894·1); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Somaflam *Wallace, India.*
Carisoprodol (p.1894·1); ibuprofen (p.64·2).
Inflammation; pain; skeletal muscle spasm.

Somaflex *Cosmopharm, Gr.†.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Somagerol *Riemser, Ger.*
Lorazepam (p.1004·1).
Anxiety disorders; premedication; sleep disorders.

Somalgen *Bago, Arg.*
Talniflumate (p.1573·2).
Inflammation.

Somalgesic *Church, Mex.*
Naproxen (p.92·3); carisoprodol (p.1894·1).
Musculoskeletal, joint, and peri-articular disorders.

Somalgin *Sigma, Braz.*
Aspirin (p.20·3).
Aluminium glycinate (p.1706·2) and magnesium carbonate (p.1743·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Fever; inflammation; pain; thrombosis prophylaxis.

Somalium *Ache, Braz.*
Bromazepam (p.964·3).
Anxiety; insomnia.

Somanol + Ethanol *Braun, Fin.*
⊗ Sorbitol (p.1965·1); mannitol (p.1330·2); alcohol (p.1625·2).
Urological irrigation.

Somapam *Pacific, NZ†.*
Temazepam (p.1030·1).
Insomnia; premedication.

Somaplus *Cazi, Braz.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; sedative; skeletal muscle spasm.

Somarexin *Lalco, Canad.*
Vitamin B substances and iron (p.1922·1).

Somarexin & C *Lalco, Canad.*
Vitamin B substances, vitamin C, calcium, and iron (p.1922·1).

Somargen *Vocate, Gr.*
Somatostatin (p.1809·1).

Somaritin *Anpharm (Ανφαρμ), Gr.*
Somatostatin (p.1809·1).

Somasedan *Quesada, Arg.*
Bromazepam (p.964·3); clebopride (p.1722·1); simeticone (p.1770·2).

Somastin
Faran, Gr.
Somatostatin (p.1809·1).
Upper gastrointestinal tract haemorrhage.

Serum Institute, India.
Somatostatin acetate (p.1809·2).
Diabetic ketoacidosis; gastrointestinal haemorrhage; pancreatic, biliary, and intestinal fistulae; postoperative complications following pancreatic surgery.

Somatin *Torrex, Austria; Torrex, Hung.†.*
Somatostatin acetate (p.1809·2).
Gastro-endocrine tumours; gastrointestinal haemorrhage; intestinal and pancreatic fistulae; prevention of complications following pancreatic surgery.

Somatolan *Lannacher, Austria.*
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Somatoline *Manetti Roberts, Ital.*
Levothyroxine (p.2173·2); aescin (p.2248·2).
Adipose states with cellulite.

Somatosan *Dem, Turk.*
Somatostatin acetate (p.1809·2).
Gastrointestinal haemorrhage.

Somatran *Andromaco, Chile.*
Sumatriptan (p.625·2).
Migraine.

Somatrel *Ferring, Denm.†.*
⊗ Somatorelin acetate (p.1808·3).
Test for growth hormone deficiency.

Somatron *Volchem, Ital.*
-Arginine (p.1928·2); -ornithine (p.1959·2).
Nutritional supplement.

Somatrop *Biosintetica, Braz.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency.

Somatulina *Ipsen, Port.; Ipsen, Spain.*
Lanreotide acetate (p.1803·1).
Acromegaly; carcinoid syndrome; neuroendocrine tumours.

Somatuline *Sidus, Arg.; Ipsen, Austral.; Richter, Austria; Ipsen, Belg.; Biosintetica, Braz.†; Ipsen, Cz.; Ipsen, Fin.; Beaufour, Fr.; Ipsen, Ger.; Ipsen, Gr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Ipsen, Irl.; Pharma Biotech, Israel; Ipsen, Neth.; Beaufour Ipsen, Pol.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Swed.; Ipsen, Switz.; Ipsen, UK; Tercica, USA.*
Lanreotide acetate (p.1803·1).
Acromegaly; carcinoid syndrome; carcinoid tumours; neuroendocrine tumours; thyrotrophic adenoma.

Somatyl *Teofarma, Ital.*
Betaine sodium aspartate (p.2265·2).
Digestive disorders.

Somavert *Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Cz.; Pharmacia, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Irl.; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.; Pfizer, UK; Pharmacia, USA.*
Pegvisomant (p.1807·1).
Acromegaly.

Somazina
Temis, Arg.; Ferrer-Novag, Mex.; CPH, Port.
Citicoline sodium (p.2283·3).
Cerebrovascular disorders.

Solvay, Braz.; Ferrer, Spain; Ferrer, Thai.; Leti, Venez.
Citicoline (p.2283·3).
Asthenia; cerebral ischaemia; head injury; mental function impairment; stroke.

Andromaco, Chile.
Citicoline (p.2283·3) or citicoline sodium (p.2283·3).
Cerebral oedema; cerebral trauma; cerebrovascular disorders; dyskinesia; mental function impairment; parkinsonism.

Somazine *Patriot, Philipp.*
Citicoline (p.2283·3).
Cerebral insufficiency.

Somergan *Elmor, Venez.*
Lindane (p.2045·3).
Pediculosis; scabies.

Somerol *Soho, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Somese *Pfizer, Chile; Pfizer, Malaysia; Pfizer, Venez.*
Triazolam (p.1033·2).
Insomnia.

Somiaton *Serono, Spain†.*
Somatostatin acetate (p.1809·2).
Pancreatic fistulae; variceal haemorrhage.

Somidem *Alphapharm, Austral.; Duopharma, Malaysia.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Somin *YSP, Malaysia; Yung Shin, Singapore.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Sominex
Note.This name is used for preparations of different composition.
EMS, Braz.
Passion flower (p.2363·2); crataegus (p.2289·1); valerian (p.2410·1).
Sedative.

GSK Consumer, Canad.; SmithKline Beecham Consumer, USA.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Prater, Chile.
Valerian (p.2410·1).
Sleep disorders.

Thornton & Ross, UK.
Promethazine hydrochloride (p.588·2).
Insomnia.

Sominex Herbal *Thornton & Ross, UK.*
Lupulus (p.2335·2); valerian (p.2410·1); passion flower (p.2363·2).
Insomnia.

Sominex Pain Relief *SmithKline Beecham Consumer, USA.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Insomnia.

Somit *Gador, Arg.*
Zolpidem (p.1038·2).
Insomnia.

Somnal *Stada, Austria.*
Zopiclone (p.1039·1).
Insomnia.

Somnatrol *Abbott, Arg.†.*
Estazolam (p.995·1).
Insomnia.

Somnidoron *Weleda, Fr.*
Homoeopathic preparation.

Somnil
Note.This name is used for preparations of different composition.
Tecnofarma, Chile.
Zolpidem tartrate (p.1037·3).
Insomnia.

SA Druggists Self Med, S.Afr.
Doxylamine succinate (p.578·2).
Insomnia.

Somnipax *Bago, Chile†.*
Zaleplon (p.1035·3).
Sleep disorders.

Somnipron *Sanitas, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Somnite *Norgine, Irl.†; Norgine, UK.*
Nitrazepam (p.1011·2).
Insomnia.

Somnium *Fresenius Kabi, Austria†; Vifor, Switz.*
Lorazepam (p.1004·1); diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Somno *Saval, Chile.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Somnol *Grindeks, Hung.; Grindex, Rus.*
Zopiclone (p.1039·1).
Insomnia.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Somnor *Orion, Fin.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Somnosan *Hormosan, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Somnote *Breckenridge, USA.*
Cloral hydrate (p.979·1).
Sedative.

Somnovit *Teofarma, Spain.*
Loprazolam (p.1003·3).
Insomnia.

Somnubene *Ratiopharm, Austria.*
Flunitrazepam (p.996·2).
Sleep disorders.

Somnuvis S *Truw, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2); kava (p.2328·3).
Nervous disorders; sleep disorders.

Somnwell *Huntley, UK.*
Cloral betaine (p.979·1).
Insomnia.

Somoblon *Vannier, Arg.†.*
Codergocrine mesilate (p.363·3).
Cerebrovascular disorders.

Somol *Maver, Chile.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Somonal *Juste, Spain.*
Somatostatin acetate (p.1809·2).
Pancreatic fistulae; variceal haemorrhage.

Sompraz *Sun, India.*
Esomeprazole (p.1729·3).
Gastro-oesophageal reflux; peptic ulcer.

Somsanit *Kohler, Ger.*
Sodium oxybate (p.1794·2).
General anaesthesia.

Sonadryl *Allergan, Arg.*
Pilocarpine nitrate (p.1884·3).
Glaucoma; ocular hypertension.

Sonalent *Aledicine, Gr.*
Azelaic acid (p.1589·3).
Acne.

Sonap *Sriprasit, Thai.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sonapax *Jelfa, Rus.*
Thioridazine (p.1031·2).

Sonata *Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Ger.; Wyeth, Gr.; Wyeth, Hung.; Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, Mex.†; Wyeth, Neth.; Meda, Port.; Biohorm, Spain; Wyeth, Swed.; Wyeth, Switz.; Wyeth, UK†; King, USA.*
Zaleplon (p.1035·3).
Insomnia.

Sondalis *Nestle, Fr.; Nestle Clinical, Irl.; Nestle, Ital.†; Nestle, UK†.*
A range of preparations for enteral nutrition (p.1922·1).
Now known as Clinutren Junior in the *UK*.

Sondex-Of *Sons, Mex.*
⊗ Neomycin sulfate (p.305·1); dexamethasone sodium phosphate (p.1526·2).
Infected eye disorders.

Sondinal *Zuoz, Venez.†.*
Phenylephrine (p.1568·1); carbinoxamine (p.570·2).

Sone *Fawns & McAllan, Austral.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Sonebon *Sigma, Braz.*
Nitrazepam (p.1011·2).
Epilepsy; insomnia.

Soneriper *Pharmasant, Thai.*
Tolperisone hydrochloride (p.1899·3).
Obliterative vascular disorders; parkinsonism; skeletal muscle spasm.

Soneryl *Concord, UK.*
Butobarbital (p.967·2).
Insomnia.

Sonexa-C *Aristopharma, Hong Kong.*
⊗ Chloramphenicol (p.239·3); dexamethasone sodium phosphate (p.1526·2).
Bacterial eye infections with inflammation.

Songar *Valeas, Ital.*
Triazolam (p.1033·2).
Insomnia.

Songha *Kwizda, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Port.†.*
Valerian (p.2410·1); melissa (p.2339·3).
Anxiety disorders; insomnia; nervous disorders.

Songha Night *Pharmaton, Cz.†; Pharmaton, Israel; Pharmaton, Switz.*
Valerian (p.2410·1); melissa (p.2339·3).
Insomnia; nervous disorders.

Sonhare *Boehringer Ingelheim, Braz.*
Valerian (p.2410·1); melissa (p.2339·3).
Sedative.

Sonicor *GMP, Indon.*
⊗ Methylprednisolone (p.1538·1).
Oral corticosteroid.

Sonicur *Solvay, Spain.*
Anethole trithione (p.2258·1).
Dry mouth.

Sonidal *Alet, Gr.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Sonidar *Julphar, UAE.*
⊗ Budesonide (p.1520·1).
Asthma.

Sonide *Gufic, India.*
Sodium nitroprusside (p.1397·1).
Hypertension; mitral regurgitation.

Sonifilan *Kaken, Jpn.*
Sizofiran (p.770·2).
Radiotherapy enhancement for uterine cervical cancer.

Sonigen *GMP, Indon.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Sonin
Note. This name is used for preparations of different composition.
Sinterapico, Braz.†.
Pimethixene maleate (p.588·1).
Respiratory-tract disorders in children.

Merck, Ger.
Loprazolam (p.1003·3).
Sleep disorders.

Sonnenbrandspray *Jacoby, Austria.*
Homoeopathic preparation.

Sonodor *Vitafarma, Spain.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions; insomnia.

Sonofit *Arkochim, Spain†.*
Crataegus (p.2289·1); eschscholtzia californica; passion flower (p.2363·2).
Insomnia; nervous disorders.

Sonol *Elanda, Pol.*
Menthol (p.2340·1); salicylic acid (p.1612·2); thymol (p.1664·3).
Herpesvirus infections.

Sonoprel *Makiz-Pharma, Rus.*
⊗ Tablets, indapamide (p.1314·1); tablets, cilazapril (p.1244·3).
Hypertension.

Sonoripan *Marjan, Braz.*
Valerian (p.2410·1).
Sedative.

SonoRx *Bracco, USA.*
Simeticone coated cellulose (p.1770·2).
Adjunct in ultrasound imaging.

SonoVue *Bracco, Austria; Altana, Belg.; Bracco, Cz.; Bracco, Denm.; Astra Tech, Fin.; Altana, Fr.; Gerolymatos, Gr.; Bracco, Ital.; Bracco, Neth.; Bracco, Norw.; Bracco, Port.; Astra Tech, Swed.; Bracco, Switz.; Bracco, UK.*
Sulfur hexafluoride (p.1489·1).
Ultrasound contrast medium.

Sonridor *GSK, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Sonridor Caf *GSK, Braz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Sonrisal *GSK, Braz.*
Aspirin (p.20·3); sodium carbonate anhydrous (p.2389·1); sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Dyspepsia; pain.

Sons *Sons, Mex.*
Difenidol (p.1723·2).
Nausea and vomiting.

Sons Piral *Sons, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Sons Vit *Sons, Mex.*
Multivitamin preparation (p.1922·1).

Soolan *Julphar, UAE.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Soorphenesin *Kade, Ger.†.*
Chlorphenesin (p.529·2).
Fungal and bacterial infections of the vagina.

Sootha *Nelson, UK.*
Homoeopathic preparation.

Soothaderm *Pharmakon, USA.*
Mepyramine maleate (p.585·2); benzocaine (p.1854·1); zinc oxide (p.1621·2).
Pruritus.

Soothake Toothache Gel *Ransom, UK.*
Clove oil (p.2285·1).
Toothache.

Soothake Toothache Tincture *Pickles, UK.*
Clove oil (p.2285·1); lidocaine (p.1862·3).

Soothe *Alimera, USA.*
Polysorbate 80 (p.1919·2); Restoryl (Drakeol-15 and Drakeol-35).
Dry eyes.

Soothe Aid *Zee, Canad.*
Hexylresorcinol (p.1647·1).

Soothe & Cool *Medline, USA.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Nappy rash.

Soothe XP *Bausch & Lomb, USA.*
Liquid paraffin (p.2030·3); light liquid paraffin (p.2031·1); polysorbate 80 (p.1919·2).
Dry eyes.

Soothelip *Bayer, Irl.†; Bayer Consumer, UK.*
Aciclovir (p.862·3).
Herpes labialis.

Soothe'n Heal *Mentholatum, Austral.*
Hydrous wool fat (p.2033·3); glycerol (p.2314·2); benzyl alcohol (p.1631·3).
Dry skin.

Soothers Triple Action *Ernest Jackson, UK.*
Hexylresorcinol (p.1647·1).
Sore throat.

Soothex *Jamieson, Canad.†.*
Allantoin (p.1588·1).

Soothing Eye Wash *Bausch & Lomb, Philipp.*
Boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation; eye wash.

Soothing Ice Rub *Scott, Canad.*
Menthol (p.2340·1).

Soothol *Ayrton, UK.*
Cajuput oil (p.2271·2); rosemary oil (p.2381·3); arachis oil (p.2259·1).
Ear wax removal.

Soov Bite *Ego, Austral.; Ego, Hong Kong; Ego, Malaysia; Ego, NZ; Ego, Singapore.*
Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1); menthol (p.2340·1).
Insect bites; pruritus; stings.

Soov Burn *Ego, Austral.; Ego, NZ.*
Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1).
Minor burns; minor cuts; sunburn.

Soov Cream *Ego, Austral.; Ego, Hong Kong; Ego, NZ; Ego, Singapore.*
Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Abrasions; burns; haemorrhoids; sunburn.

Soov Gel *Ego, NZ.*
Lidocaine hydrochloride (p.1862·3); cetrimide (p.1634·1).
Insect bites; stings.

Soov Prickly Heat
Ego, Austral.; Ego, Singapore†.
Salicylic acid (p.1612·2); zinc oxide (p.1621·2); light liquid paraffin (p.2031·1).
Heat rash.

Ego, Hong Kong; Ego, Malaysia†.
Salicylic acid (p.1612·2); zinc oxide (p.1621·2); liquid paraffin (p.2030·3).
Heat rash.

Sopain-Plus *Medichrom, Gr.*
Muramidase (p.2348·1); papain (p.2362·3); bacitracin (p.210·3).
Oral antiseptic.

Sopa-K *Pharmanik (Φαρμανικ), Gr.*
Potassium gluconate (p.1684·3).
Hypokalaemia; potassium depletion.

Sopalamin 3B *Melisana, Belg.; Farmanic, Gr.*
Vitamin B substances (p.1922·1).
Alcoholism; neurogenic pain; vitamin B deficiency.

Sopalamine 3B *Technilab, Canad.†.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Sopalamine 3B Plus C *Technilab, Canad.†.*
Multivitamin preparation (p.1922·1).

Sopax *Zimaia, Port.*
Nordazepam (p.1012·1).
Anxiety.

Sopental *Continental Ethicals, S.Afr.*
Pentobarbital sodium (p.1016·1).
Insomnia; sedative.

Sophidone *BMS, Fr.*
⊗ Hydromorphone hydrochloride (p.63·2).
Pain.

Sophipren *Sophia, Mex.; Elmor, Venez.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Sophivir *Sophia, Mex.*
Aciclovir (p.862·3).
Herpes simplex keratitis.

Sophixin *Sophia, Mex.; Elmor, Venez.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial eye infections.

Sophtal
Note. This name is used for preparations of different composition.
Alcon, Fr.
Eye drops: Salicylic acid (p.1612·2).
Eye irritation.

Alcon, Fr.
Eye lotion: Salicylic acid (p.1612·2); borax (p.2268·1); rose water.
Eye irritation.

Sophtal-POS N *Ursapharm, Cz.; Ursapharm, Ger.*
Salicylic acid (p.1612·2).
Eye irritation; inflammatory eye disorders.

Sopirom *Soho, Indon.*
Cefpirome (p.231·3).
Bacterial infections.

Sopodorm *ICN, Pol.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedation in artificially ventilated patients.

Sopolcort N *Jelfa, Rus.*
⊗ Hydrocortisone hydrogen succinate (p.1535·3).
Corticosteroid.

Soporin *Herbamed, Switz.*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2); melissa (p.2339·3).
Sleep disorders.

Sopral *Sopharma, Rus.†.*
Omeprazole (p.1753·1).

Sopralan *Mersifarma, Indon.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Sopras *UCB, Neth.; UCB, Spain.*
Levocetirizine hydrochloride (p.583·2).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Soprazon *Kleva, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Soprol *Wyeth Lederle, Fr.†; Helsinn Birex, Irl.*
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Soprost *Soho, Indon.*
Saw palmetto (p.2192·3); cucurbita (p.2290·2); zinc picolinate (p.2001·1).
Benign prostatic hyperplasia.

Soproxen *Berlin Pharm, Singapore; Berlin Pharm, Thai.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and soft-tissue inflammation; pain.

Sopulmin *Scharper, Ital.*
Sobrerol (p.1572·3).
Respiratory-tract disorders.

Soquette *Barnes Hind, Arg.*
Polyvinyl alcohol (p.2145·3); benzalkonium chloride (p.1629·1) (p.1622·2).
Wetting and storage solution for contact lenses.

Soraderm *Stafford-Miller, Norw.†.*
Coal tar (p.1616·2).
Psoriasis; seborrhoeic dermatitis.

Soragel *ICM, Singapore.*
Choline salicylate (p.36·3); cetylpyridinium chloride (p.1635·1).
Denture irritation; mouth disorders; teething.

Soral *Help, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Soramin *Darrow, Braz.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Sorbalgon *Hartmann, Fr.*
Calcium alginate (p.1058·1).
Ulcers; wounds.

Sorbangil *Pfizer, Norw.; Pfizer, Swed.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Sorbenor *Casen Fleet, Spain.*
Arginine aspartate (p.1928·2).
Tonic.

Sorbexyl *Aledicine, Gr.*
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Sorbicet *Bouzen, Arg.*
Cetrimide (p.1634·1).
Disinfection.

Sorbiclis *SIT, Ital.*
Sorbitol (p.1965·1); docusate sodium (p.1725·1).
Constipation.

Sorbidilat *AstraZeneca, Switz.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Sorbidin *Alphapharm, Austral.; Merck, Indon.; Alphapharm, Malaysia†; Merck, Malaysia†; Merck, Thai.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; ischaemic heart disease.

Sorbidon Hydrate *Gordon, USA†.*
Emollient.
Dry skin; hyperkeratosis.

Sorbifer *Egis, Cz.; EGIS, Hung.; Multicare, Philipp.; Egis, Pol.; Egis, Rus.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron supplement; iron-deficiency anaemia.

Sorbilax *Pfizer, Austral.*
Sorbitol (p.1965·1).
Constipation.

Sorbiline *Franco-Indian, India.*
Tricholine citrate (p.1934·2); sorbitol (p.1965·1).
Biliary and liver disorders.

Sorbimon *Ratiopharm, Cz.; Ratiopharm, Hung.†.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure.

Sorbisterit *Fresenius Medical, Austria; Pentafarma, Chile; Fresenius Medical, Cz.†; Fresenius Medical, Ger.; Fresenius Medical, Neth.; Fresenius Medical, Switz.*
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Sorbitrate *Nicholas Piramal, India; Zeneca, USA†.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Sorbon *Unipharm, Israel.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders.

Sorbonit Lek, Pol.
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure.

Sorbsan Seton Scholl, Austral.†; Coffey, Irl.; Braun, Ital.†; Braun, Port.†; Maersk, UK.
Calcium alginate (p.1058·1).
Burns; ulcers; wounds.

Sorcal
Note. This name is used for preparations of different composition.
Wyeth, Braz.
Calcium polystyrene sulfonate (p.1438·2).
Hyperkalaemia.

Polipharm, Thai.†.
Calcium carbonate (p.1714·1).
Calcium supplement.

Sore Mouth Gel Boots, Thai.
Lidocaine (p.1862·3); cetylpyridinium chloride (p.1635·1); menthol (p.2340·1); cineole (p.2282·3).
Oral pain.

Sore Throat Hylands, Canad.
Homoeopathic preparation.

Sore Throat Chewing Gum Or-Dov, Austral.†.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); vitamin C (p.1983·3).
Sore throat.

Sore Throat L39 Homeocan, Canad.
Homoeopathic preparation.

Sore Throat Lozenges Sutton, Canad.
Benzocaine (p.1854·1); menthol (p.2340·1).

Sorebral Condrugs, Thai.
Cinnarizine (p.573·1).
Cerebrovascular disorders; migraine; peripheral vascular disorders; vestibular disorders.

Soredine Cooper (Κοπερ), Gr.†.
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Soren Daewon, Hong Kong†.
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sorest Ranbaxy, India.
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Soriacur Medica, Arg.†.
Coal tar (p.1616·2).
Psoriasis.

Sorial Fortbenton, Arg.
Coal tar (p.1616·2).
Psoriasis.

Soriatane Roche, Canad.; Roche, Fr.; Stiefel, USA.
Acitretin (p.1586·1).
Keratinisation disorders; lichen planus; psoriasis.

Soridermal Mintlab, Chile.
Ketoconazole (p.539·1).
Fungal skin infections.

Sorine Ache, Braz.
Sodium chloride (p.1686·1).
Nasal congestion.

Sorine Adulto Ache, Braz.
⊗ Sodium chloride (p.1686·1); naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Sorine Pediatrico Ache, Braz.
Sodium chloride (p.1686·1).
Formerly known as Sorine Infantil.
Nasal congestion.

Sorini Asia Pharma, Philipp.
Nimesulide (p.95·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Sorlex Genesis, Philipp.
Cefalexin (p.218·2).
Bacterial infections.

Sorliv Ipca, India.
Sorbitol (p.1965·1); tricholine citrate (p.1934·2).
Liver disorders.

Sormodren Abbott, Austria; Abbott, Ger.; Teofarma, Ital.; Abbott, Turk.
Bornaprine hydrochloride (p.797·3).
Drug-induced extrapyramidal disorders; hyperhidrosis; parkinsonism.

Sormon Gerard, Irl.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Sornil Utopian, Thai.
Isosorbide dinitrate (p.1317·3).
Angina pectoris.

Soro de Manutencao H Labesfal, Port.†.
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Soro Nasal Osorio de Moraes, Braz.†.
Sodium chloride (p.1686·1).
Nasal congestion.

Sorol Citrate Dismed, S.Afr.
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Soroliv Teuto, Braz.
Sodium chloride (p.1686·1).
Nasal congestion.

Soroneo Neo Quimica, Braz.
Sodium chloride (p.1686·1).
Nasal congestion; nasal hygiene.

Soropon Axxess, Canad.
Tyrothricin (p.358·2); trolamine polypeptide cocoate condensate (p.2405·1).
Scalp disorders.

Sorot Petrasch, Austria; Ravensberg, Ger.
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Sorov Soho, Indon.
Spiramycin (p.333·1).
Bacterial infections.

Sorsis
Note. This name is used for preparations of different composition.
Fortbenton, Arg.
Cream: ⊗ Coal tar (p.1616·2); triamcinolone (p.1544·2).
Skin disorders.

Fortbenton, Arg.
Shampoo: Salicylic acid (p.1612·2); coal tar (p.1616·2).
Dandruff; seborrhoea.

Sorsis Beta Fortbenton, Arg.
⊗ Salicylic acid (p.1612·2); betamethasone (p.1518·2); coal tar (p.1616·2).
Skin disorders.

Sortal Biotech, Venez.
Losartan potassium (p.1326·1).
Hypertension.

Sortis Pfizer, Austria; Pfizer, Cz.; Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.; Pfizer, Hung.; Parke, Davis, Pol.; Pfizer, Port.; Pfizer, Switz.
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Sosefen SoSe, Ital.
Ketotifen fumarate (p.582·2).
Allergic rhinitis.

Sosefluss SoSe, Ital.
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Sosegon
Yamanouchi, Jpn†; Sanofi-Aventis, Spain.
⊗ Pentazocine hydrochloride (p.112·2).
Pain.

Sanofi Synthelabo, Port.†.
⊗ Pentazocine hydrochloride (p.112·2) or pentazocine lactate (p.112·3).
Pain.

Sanofi Synthelabo, Thai.†.
⊗ Pentazocine lactate (p.112·3).
Pain.

Sosenol Adcock Ingram, S.Afr.
⊗ Pentazocine (p.112·2).
Pain.

Sosmin Santa, Gr.
Pravastatin (p.1375·1).
Hyperlipidaemias.

Sostac Laboratorios Chile, Chile.
Fluoxetine (p.397·3).
Depression.

Sostatin Faran, Gr.
Ketoconazole (p.539·1).
Fungal infections.

Sostel Richmond, Arg.
Paroxetine (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Sostenon Organon, Mex.
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Androgen deficiency; male hypogonadism; osteoporosis.

Sostilar Pfizer, Belg.
Cabergoline (p.802·1).
Hyperprolactinaemia.

Sostril
Note. This name is used for preparations of different composition.
GSK, Ger.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Vargas, Venez.
Albendazole (p.139·2).
Worm infections.

Sota ABZ, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sota Lich Winthrop, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotab Douglas, Austral.†.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotabet Gea, Denm.†; Gea, Swed.†.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotabeta Betapharm, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotacor Investi, Arg.; BMS, Austral.; BMS, Austria; BMS, Braz.; Bristol, Canad.†; BMS, Denm.; BMS, Fin.; BMS, Hong Kong; BMS, Irl.; BMS, Israel†; BMS, Jpn†; BMS, Malaysia; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, S.Afr.; BMS, Singapore; BMS, Swed.; BMS, UK.
⊗ Sotalol hydrochloride (p.1398·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Sotagamma Worwag, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotahexal Hexal, Austral.; Hexal, Austria; Hexal, Cz.; Hexal, Ger.; Sandoz, Hung.; Hexal, NZ; Hexal, Pol.; Hexal, Rus.; Hexal, S.Afr.
⊗ Sotalol hydrochloride (p.1398·2).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Sotalex BMS, Belg.; BMS, Cz.; BMS, Fr.; BMS, Ger.; BMS, Hung.; BMS, Ital.; BMS, Philipp.; BMS, Rus.; BMS, Switz.
⊗ Sotalol hydrochloride (p.1398·2).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; hyperthyroidism; myocardial infarction.

Sotalin Ratiopharm, Fin.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotalodoc Docpharm, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotamed S Med, Austria.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotanorm Medicopharm, Austria.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotaper BMS, Mex.
⊗ Sotalol (p.1399·1).
Arrhythmias; hypertension.

Sotapor BMS, Spain.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sota-Puren Alpharma-Isis, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotarit Ilsan, Turk.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotaryt Azupharma, Ger.†.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sota-saar MIP, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotastad Stada, Austria; Stada, Ger.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotatic Fahrenheit, Indon.
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Sotazide BMS, S.Afr.
⊗ Sotalol hydrochloride (p.1398·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Sotaziden N BMS, Ger.
⊗ Nadolol (p.1345·2); bendroflumethiazide (p.1224·1).
Hypertension.

Sotens Soho, Indon.
Noni; garlic (p.2309·2); nicotinamide (p.1957·3).
Tonic.

Sotilen Medochemie, Hong Kong†; Medochemie, Thai.
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Sotoger Gerard, Irl.
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Sotomycin Bros, Gr.
Clindamycin phosphate (p.251·2).
Acne.

Sotovastin Bros, Gr.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Sotovon Bros, Gr.
Citalopram (p.385·3).
Depression.

Sotradecol Elkins-Sinn, USA.
Sodium tetradecyl sulfate (p.2139·2).
Varicose veins.

Sotret Ranbaxy, Hung.; Ranbaxy, Thai.; Ranbaxy, USA.
Isotretinoin (p.1599·2).
Acne.

Sotrexe Ranbaxy, Mex.
Isotretinoin (p.1599·2).
Acne.

Sotropil Soho, Indon.
Piracetam (p.368·2).
Cerebral trauma; mental function impairment.

Soufrane Sanofi-Aventis OTC, Fr.
Thenoate sodium (p.351·1).
Nasopharyngeal infections.

Soufrol Gebro, Switz.
Mesulphen (p.1604·3).
Bath additive; musculoskeletal and joint disorders; skin disorders.

Soufrol TP Gebro, Switz.†.
Medicinal mud; sulfur (p.1614·1).
Musculoskeletal and joint disorders.

Sove Ipca, India.
Zolpidem tartrate (p.1037·3).
Insomnia.

Sovel Novartis, Ger.†.
Norethisterone acetate (p.2119·3).
Menstrual disorders.

Soventol
Note. This name is used for preparations of different composition.
Abbott, Austria; Rentschler, Ger.; Vianex (Βιανεξ), Gr.†; Oramon, Neth.; Oramon, Pol.
Bamipine lactate (p.568·3).
Allergic disorders; burns; frostbite; insect stings; jellyfish stings; pruritus; skin irritation; sunburn; urticaria.

Nicholas Piramal, India†.
Bamipine lactate (p.568·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Bronchitis; coughs.

Soventol HC Rentschler, Ger.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Soviclor Collins, Mex.
Aciclovir (p.862·3).
Herpesvirus infections.

Sovipan Novis, Gr.
Aceclofenac (p.14·3).
Ankylosing spondylitis; inflammation; osteoarthritis; pain; rheumatoid arthritis.

Soxacol Cusi, Venez.†.
Sulfafurazole (p.338·3).
Bacterial eye infections.

Soxietas Soho, Indon.
Alprazolam (p.960·1).
Anxiety; panic disorder.

Soxsup Richmond, Arg.
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Soy 50 Gross, Braz.
Soya isoflavones (p.2391·2).

Soy Forte with Black Cohosh Cenovis, Austral.†.
Soya (p.1965·3); cimicifuga (p.2282·1); calcium hydrogen phosphate (p.1676·1); colecalciferol (p.1986·2); magnesium oxide (p.1744·1).
Menopausal disorders; osteoporosis.

Soya Diet Support, Braz.†.
A range of soya-based preparations for enteral nutrition (p.1922·1).

Soya Meno Medana, Pol.
Soya (p.1965·3).
Menopausal disorders.

Soyac Support, Braz.†.
Soy protein preparation for enteral nutrition (p.1922·1).

Soyacal Grifols, Arg.; Grifols, Cz.; Grifols, Ger.; Grifols, Ital.†; Green Cross, Philipp.; Labesfal, Port.; Grifols, Spain.
Soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Soyal FDC, India†.
Food for special diets (p.1922·1).
Lactose intolerance; milk intolerance.

Soyalac Nutricia-Loma Lindar, USA.
Lactose-free soy protein infant feed (p.1922·1).

Soyaloid Serral, Mex.
Soya flour (p.1965·3); povidone (p.2146·1).
Bath additive; skin disorders.

Soyaloid Apruri Serral, Mex.
Soya flour (p.1965·3); pramocaine hydrochloride (p.1868·1); zinc acetate (p.1999·1).
Skin disorders.

Soyaven Delicias, Mex.
Food for special diets (p.1922·1).
Food allergies; lactose and cow's milk intolerance.

Soydex Darier, Mex.
Soya flour (p.1965·3); povidone (p.2146·1).
Bath additive; skin disorders.

Soyfem Biofarm, Pol.
Soya (p.1965·3).
Menopausal disorders.

Soyfemme Ache, Braz.
Soya isoflavones (p.2391·2).
Menopausal disorders.

Soymen Irmed, Ital.
Soya (p.1965·3); vitamins (p.1922·1).
Menopausal disorders.

Soymen Gel Irmed, Ital.
Soya isoflavones (p.2391·2).
Vaginal dryness.

SoyPlus Lifeplan, UK.
Soya isoflavones (p.2391·2); folic acid (p.1940·1).
Dietary supplement.

SP95 DHN, Fr.
Protein and vitamin preparation (p.1922·1).
Nutritional supplement.

SP 54 Bene-Chemie, Hong Kong†; Bene, Hung.; Bene, Malaysia.
Pentosan polysulfate sodium (p.1367·1).
Soft-tissue disorders; thromboembolic disorders; thrombosis prophylaxis.

SP Cream Curacel, Austral.†.
⊗ Melaleuca oil (p.2338·2); salicylic acid (p.1612·2); solanum lycopersicum leaf; urea (p.1620·2).
Keratoses; sunspots; warts.

SP Troches Meiji, Indon.; Meiji, Malaysia; Meiji, Singapore.
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Spablock Masa, Thai.
Drotaverine hydrochloride (p.2298·1).
Postoperative pain; smooth muscle spasm.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Spabucol *Phoinix Pharm (Φοινιξ Φαρμ), Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Spacovin *Biopharm, Rus.; MJ Biopharm, Thai.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Spacyl *Proel, Gr.†.*
Acetylcysteine (p.1548·2).
Mucolytic.

Spagall *Sanova, Austria.*
p,α-Dimethylbenzyl alcohol nicotinate (p.2294·2); naphthylacetic acid (p.2350·2); caroverine (p.2277·3).
Hepatobiliary disorders.

Spagulax *Biodiphar, Belg.; Almirall, Fr.*
Ispaghula (p.1737·1).
Constipation.

Spagulax au Citrate de Potassium *Almirall, Fr.*
Ispaghula (p.1737·1); potassium citrate (p.1673·2).
Constipation.

Spagulax K *Biodiphar, Belg.*
Ispaghula (p.1737·1); potassium citrate (p.1673·2); potassium bicarbonate (p.1673·1).
Constipation.

Spagulax Mucilage *Almirall, Fr.*
Ispaghula (p.1737·1).
Constipation.

Spagulax Sorbitol *Biodiphar, Belg.*
Ispaghula (p.1737·1); sorbitol (p.1965·1).
Constipation.

Spagulax au Sorbitol *Almirall, Fr.*
Ispaghula (p.1737·1); sorbitol (p.1965·1).
Constipation.

Spagymun *Spagyros, Switz.*
Echinacea angustifolia flowers and roots; echinacea purpura flowers and roots (p.2298·1); eupatorium perfoliatum.
Immune stimulant.

Spagyrom *Spagyros, Switz.*
Echinacea angustifolia flowers and roots; echinacea purpura flowers and roots (p.2298·1); clove oil (p.2285·1); cinnamon oil (p.2283·2); juniper oil (p.2328·3); lavender oil (p.2331·2); chamomile oil (p.2279·3); peppermint oil (p.1761·2); rosemary oil (p.2381·3); savory oil (p.2394·3); thyme oil (p.2401·2).
Common cold; mouth and throat disorders.

Spai *INTES, Ital.*
Sodium chloride; potassium chloride; calcium chloride; magnesium chloride; sodium acetate; sodium citrate (p.1667·1).
Adjunct in otorhinolaryngeal procedures; cleaning solution for contact lens; ocular irrigation.

Spalda Sabal *Leo, Cz.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Spalox *Umeda, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spalt
Note. This name is used for preparations of different composition.
Sanova, Austria†.
Phenazone salicylate (p.116·1); salicylamide (p.121·2); caffeine (p.1116·3).
Pain.
Whitehall-Much, Ger.
Ibuprofen (p.64·2).
Fever; pain.
Santa, Turk.
Paracetamol (p.108·1); benzyl mandelate (p.2264·3); caffeine (p.1116·3).
Fever; pain.

Spalt N *Wyeth Consumer, Neth.*
Phenazone (p.116·1); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Spalt Schmerz-Gel *Whitehall-Much, Ger.†.*
Diisopropanolamine felbinac (p.54·3).
Musculoskeletal, joint, and soft-tissue disorders.

Spalt Schmerztabletten *Whitehall-Much, Ger.†.*
Aspirin (p.20·3); paracetamol (p.108·1).
Pain.

Spamilan *Anpharm, Pol.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Spamus *T Man, Thai.†.*
Tolperisone hydrochloride (p.1899·3).
Parkinsonism; skeletal muscle spasm.

Span C *Freeda, USA.*
Citrus bioflavonoids complex (p.2304·1); ascorbic acid (p.1983·3).
Capillary bleeding.

Span Plex *Collins, Mex.*
Calcium pantothenate (p.1959·3).
Vitamin supplement.

Spancef *Medikon, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Spanidin *Kayaku, Cz.; Kayaku, Jpn.*
Gusperimus hydrochloride (p.1834·3).
Renal transplant rejection.

Spanish Tummy Mixture *Potter's, UK.*
Blackberry root bark; catechu (p.2278·2).
Diarrhoea.

Span-K *Aspen, Austral.; Aspen, Hong Kong; Aspen, NZ.*
Potassium chloride (p.1684·3).
Potassium deficiency.

Spanor *Bailleul, Fr.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Spara *Dainippon, Jpn.*
Sparfloxacin (p.332·1).
Bacterial infections.

Sparaplaie *Urgo, Fr.*
Benzalkonium chloride (p.1629·1).
Wounds.

Sparax *Utopian, Thai.*
Drotaverine hydrochloride (p.2298·1).
Postoperative pain; smooth muscle spasm.

Sparbact *Ipca, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Sparcip *Cipla, India.*
Sparfloxacin (p.332·1).
Respiratory-tract infections.

Spardac *Cadila, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Spardrops *Cipla, India.*
Sparfloxacin (p.332·1).
Bacterial eye infections.

Sparflo *Reddy, Rus.*
Sparfloxacin (p.332·1).
Bacterial infections.

Sparine *Wyeth Lederle, Denm.†; Meda, Fin.†; Wyeth, Gr.†; Akromed, S.Afr.*
Promazine hydrochloride (p.1021·2).
Agitation; alcohol withdrawal syndrome; anxiety; disturbed behaviour; hiccup; nausea; pain; premedication; psychoses; sedative; vomiting.

Sparkal *Gea, Denm.; Sandoz, Fin.; Hexal, Swed.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Hypertension; liver cirrhosis with ascites; oedema.

Sparkles *Lafayette, USA.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); simeticone (p.1770·2).
Adjunct in endoscopy; flatulence.

Sparkling White Eye Drops *Adcock Ingram, S.Afr.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Allergic eye inflammation.

Sparksol *Viatris, Ital.†.*
Amino-acid preparation with vitamin B (p.1922·1).

Sparos *Pharos, Indon.*
Sparfloxacin (p.332·1).
Bacterial infections of the respiratory tract.

Sparquin *Aristo, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Sparta *Pharmasant, Thai.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Spartiol *Klein, Ger.*
Sarothamnus scoparius (p.2384·2).
Arrhythmias.

Spartocine *UCB, Belg.†; UCB, Fin.*
Ferrous aspartate (p.1938·2).
Iron deficiency; iron-deficiency anaemias.

Spartocine N *UCB, Ger.†.*
Ferrous aspartate (p.1938·2).
Iron-deficiency anaemia.

Sparvista *Cadila, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Sparx *Wockhardt, India.*
Sparfloxacin (p.332·1).
Bacterial infections.

Spascopan *Bangkok Lab & Cosmetic, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spascupreel *Heel, Ger.*
Homoeopathic preparation.

Spascupreel S *Heel, Cz.*
Homoeopathic preparation.

Spasdic *Medicine Products, Thai.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Spasdon *Ad-Drugstel, Philipp.*
Dicycloverine hydrochloride (p.1722·3).
Gastrointestinal spasm.

Spasen *FIRMA, Ital.*
Otilonium bromide (p.2359·1).
Gastrointestinal pain and spasm.

Spasen Somatico *FIRMA, Ital.*
Otilonium bromide (p.2359·1); diazepam (p.986·3).
Gastrointestinal pain and spasm.

Spasfon *Therabel, Belg.; Cephalon, Fr.; Rafarm, Gr.*
Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3).
Smooth muscle spasm.

Spasfon-Lyoc *Cephalon, Fr.*
Phloroglucinol (p.2366·3).
Smooth muscle spasm.

Spasgan *Wockhardt, Rus.*
Fenpiverinium bromide (p.2303·2); dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).

Spasgone *Chew, Thai.*
Paracetamol (p.108·1); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm with pain.

Spasgone-H *Chew, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spashi *GMP, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spashi Plus *GMP, Indon.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle spasm.

Spaslic *Berlico Mulia, Indon.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spasma *Stella, Belg.†.*
⊗ Morphine hydrochloride (p.86·3); hyoscine hydrobromide (p.1734·1).
Biliary and renal colic; pain; premedication.

Spasmag
Note. This name is used for preparations of different composition.
Grimberg, Fr.
Capsules; dispersible tablets; oral solution: Magnesium sulfate (p.1679·3); dried yeast (p.1998·3).
Magnesium deficiency.
Grimberg, Fr.
Injection: Magnesium sulfate (p.1679·3).
Eclampsia; magnesium deficiency; torsades de pointes.

Spasmal *Prafa, Indon.*
Dipyrone (p.49·2); belladonna (p.2263·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Spasmalgan *Apogepha, Ger.*
Denaverine hydrochloride.
Smooth muscle spasm.

Spasmalgin *Sam-On, Israel.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Smooth muscle spasm.

Spasmalgon *Sopharma, Pol.; Balkanpharma, Rus.; Sopharma, Rus.*
Fenpiverinium bromide (p.2303·2); dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).
Fever; migraine; musculoskeletal and joint pain; pain; smooth muscle spasm.

Spasmalin *Torrent, Rus.*
Fenpiverinium bromide (p.2303·2); dipyrone (p.49·2); pitofenone hydrochloride (p.2369·2).
Pain.

Spasman *Merckle, Ger.†.*
Demelverine hydrochloride (p.2292·3); trihexyphenidyl hydrochloride (p.820·2).
Smooth muscle spasm.

Spasman scop *Merckle, Ger.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spasmed *ProMed, Cz.*
Trospium chloride (p.2198·3).
Bladder hyperactivity.

Spasmend *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); mephenesin (p.1897·2).
Pain; skeletal muscle spasm.

Spasmeridan *UCB, Ital.*
Diazepam (p.986·3); hyoscine methobromide (p.1734·1).
Gastrointestinal pain and spasm.

Spasmex
Note. This name is used for preparations of different composition.
Biol, Arg.; Rider, Chile; ProMed, Cz.; Pfleger, Ger.; Pfleger, Israel; Pfleger, Rus.; Er-Kim, Turk.
Trospium chloride (p.2198·3).
Bladder hyperactivity; bladder instability; nocturnal enuresis; smooth muscle spasms; urinary incontinence.
Scharper, Ital.
Injection: Phloroglucinol (p.2366·3).
Painful spasm of the biliary and urinary tracts.
Scharper, Ital.
Suppositories; tablets: Phloroglucinol (p.2366·3); trimethylphloroglucinol (p.2366·3).
Painful spasm of the biliary and urinary tracts.

Spasmhalt *Pendopharm, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); methocarbamol (p.1897·3).

Spasmhalt-ASA *Pendopharm, Canad.*
Aspirin (p.20·3); codeine phosphate (p.37·2); methocarbamol (p.1897·3).

Spasminal *Hexpharm, Indon.*
Dipyrone (p.49·2); belladonna (p.2263·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Spasmine
Note. This name is used for preparations of different composition.
Norgine, Belg.
Alverine citrate (p.1708·1).
Irritable bowel syndrome.
Jolly-Jatel, Fr.
Valerian (p.2410·1); crataegus (p.2289·1).
Insomnia; nervous disorders.

Spasmium
Note. This name is used for preparations of different composition.
Sanova, Austria.
Caroverine (p.2277·3) or caroverine hydrochloride (p.2277·3).
Smooth muscle spasm; tinnitus.
Soho, Indon.
Alverine citrate (p.1708·1); chlordiazepoxide hydrochloride (p.968·2).
Peptic ulcer; smooth muscle pain and spasm.

Spasmium comp *Sanova, Austria.*
Caroverine (p.2277·3); metamizole calcium (p.49·3).
Painful smooth muscle spasm.

Spasmo Claim *Apomedica, Austria.*
Turmeric (p.1473·2); benzyl mandelate (p.2264·3); *p*,α-dimethylbenzyl alcohol (p.2294·2); peppermint oil (p.1761·2); caraway oil (p.2277·1); fennel oil (p.2303·1); lemon oil (p.2332·3); camphor (p.2273·2); thymol (p.1664·3); guaiazulene (p.2317·3).
Gastrointestinal disorders.

spasmo gallo sanol *Sanol, Ger.†.*
Greater celandine (p.2317·1); turmeric (p.1473·2).
Biliary and gastrointestinal spasm.

spasmo gallo sanol N *Sanol, Ger.; Schwarz, Ger.*
Peppermint oil (p.1761·2).
Formerly known as spasmo gallo sanol mint.
Gastrointestinal and biliary-tract spasm.

Spasmo Inalgon Neu *Fresenius Kabi, Austria.*
Dipyrone (p.49·2).
Painful smooth muscle spasm.

Spasmo-Apotel *Unipharma, Gr.*
Paracetamol (p.108·1); hyoscine butylbromide (p.1734·1).
Pain; spasmolytic.

Spasmo-Barbamin *Streuli, Switz.†.*
Propyphenazone (p.119·3); adiphenine hydrochloride (p.2248·1); diphenhydramine hydrochloride (p.577·2).
Painful smooth muscle spasm.

Spasmo-Barbamine compositum *Streuli, Switz.†.*
Propyphenazone (p.119·3); adiphenine hydrochloride (p.2248·1); diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2).
Painful smooth muscle spasm.

Spasmo-Canulase *Novartis, Philipp.; Novartis Consumer, S.Afr.; Novartis Consumer, Switz.*
Metixene hydrochloride (p.811·3); dimeticone (p.1770·2); pancreatin (p.2360·1); cellulase (p.2279·1); pepsin (p.2365·1); glutamic acid hydrochloride (p.1947·1); sodium dehydrocholate (p.2292·2).
Abdominal cramps associated with flatulence; dyspepsia; irritable bowel syndrome; meteorism.

Spasmo-Cibalgin *Novartis Consumer, Switz.†.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3).
Painful smooth muscle spasm.

Spasmo-Cibalgin comp *Novartis Consumer, Switz.†.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3); codeine phosphate (p.37·2).
Painful smooth muscle spasm.

Spasmo-Cibalgin S *Novartis, Ger.†.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3).
Smooth muscle spasm.

Spasmo-Cibalgina *Novartis, Ital.†.*
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3).
Painful smooth muscle spasm.

Spasmocip *Cipla, India.*
Dextropropoxyphene (p.40·1); paracetamol (p.108·1).
Pain.

Spasmocip Plus *Cipla, India.*
Dextropropoxyphene (p.40·1); paracetamol (p.108·1); dicycloverine hydrochloride (p.1722·3).
Muscle spasm; pain.

Spasmocor *Viatris, Austria.*
Glyceryl trinitrate (p.1296·2); pentaerithrityl tetranitrate (p.1366·3); nicotinic acid (p.1957·3); benzyl mandelate (p.2264·3).
Angina pectoris; heart failure; peripheral vascular spasm.

Spasmoctyl *Menarini, Arg.; Guidotti, Spain.*
Otilonium bromide (p.2359·1).
Gastrointestinal spasm; irritable bowel syndrome.

Spasmocyclon *3M, Ger.†.*
Cyclandelate (p.1254·1).
Cerebrovascular disorders; migraine; vestibular disorders.

Spasmodex *Crinex, Fr.†.*
Dihexyverine hydrochloride (p.1723·3).
Gastrointestinal disorders.

Spasmodil *ABC, Ital.*
Pipethanate ethobromide (p.1762·2).
Gastrointestinal spasm and hypermotility; premedication for endoscopy and radiography; urinary and biliary spasm and dyskinesia.

Spasmofen *Meda, Swed.*
⊗ Hyoscine methonitrate (p.1734·2); papaverine hydrochloride (p.2191·3); morphine hydrochloride (p.86·3); noscapine hydrochloride (p.1566·3); codeine hydrochloride (p.37·2).
Pain; smooth muscle spasm.

Spasmofides S *Fides, Ger.†.*
Homoeopathic preparation.

Spasmoflexon *Aristo, India†.*
Paracetamol (p.108·1); dicycloverine hydrochloride (p.1722·3).

Spasmogel *Alliance, S.Afr.*
Dicycloverine hydrochloride (p.1722·3); light magnesium oxide (p.1744·1); aluminium hydroxide (p.1706·2).
Dyspepsia; flatulence; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Spasmoject F *Syxyl, Ger.*
Homoeopathic preparation.

Spasmol *Farmstandart, Rus.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Spasmolina *Synteza, Pol.*
Alverine citrate (p.1708·1).
Smooth muscle spasm.

Spasmolit *Meprofarm, Indon.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spasmoliv *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spasmolyt *Madaus, Austria; Madaus, Ger.*
Trospium chloride (p.2198·3).
Bladder function disorders; smooth muscle spasm.

Spasmo-Lyt *Madaus, Denm.; Meda, Fin.; Madaus, Thai.*
Trospium chloride (p.2198·3).
Bladder function disorders.

Spasmomen *Menarini, Belg.; Menarini, Cz.; Menarini, Hong Kong; Berlin-Chemie, Hung.; Menarini, Hung.; Dexa, Indon.; Menarini, Indon.; Menarini, Ital.; Menarini, Port.*
Otilonium bromide (p.2359·1).
Gastrointestinal spasm; irritable bowel syndrome; irritable colon; premedication for gastrointestinal procedures; smooth muscle spasm.

Spasmomen Somatico *Menarini, Ital.*
Otilonium bromide (p.2359·1); diazepam (p.986·3).
Gastrointestinal spasm.

Spasmo-Mucosolvan *Boehringer Ingelheim, Ger.*
⊗ Clenbuterol hydrochloride (p.1120·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Spasmonal
Note. This name is used for preparations of different composition.
Trenker, Belg.†.
Mebeverine hydrochloride (p.1744·2).
Irritable bowel syndrome.

Norgine, Hong Kong; Norgine, Irl.; Norgine, Malaysia†; Norgine, Singapore; Norgine, Thai.; Norgine, UK.
Alverine citrate (p.1708·1).
Diverticular disease; dysmenorrhoea; irritable bowel syndrome; smooth muscle spasm.

Spasmonal Fibre *Norgine, UK†.*
Sterculia (p.1772·1); alverine citrate (p.1708·1).
Hypertonic colon; irritable bowel syndrome.

Spasmo-Nervogastrol *Sanofi Synthelabo, Ger.†.*
Butinoline phosphate (p.2271·1); calcium carbonate (p.1714·1); bismuth subnitrate (p.1711·2).
Gastrointestinal disorders.

Spasmonil
Note. This name is used for preparations of different composition.
Cipla, India.
Injection: Dicycloverine hydrochloride (p.1722·3).
Smooth muscle spasm.

Cipla, India.
Oral drops: Dicycloverine hydrochloride (p.1722·3); dimeticone (p.1770·2).
Smooth muscle spasm.

Cipla, India.
Tablets: Dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Spasmonil Forte *Cipla, India.*
Mefenamic acid (p.80·1); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Spasmonil Plus *Cipla, India.*
Dicycloverine hydrochloride (p.1722·3); mefenamic acid (p.80·1).
Smooth muscle pain and spasm.

Spasmopan *Zentiva, Cz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); pitofenone hydrochloride (p.2369·2); fenpiverinium bromide (p.2303·2).
Painful smooth muscle spasm.

Spasmo-Panalgine *Atabay, Turk.*
Paracetamol (p.108·1); allobarbital (p.959·3); adiphenine hydrochloride (p.2248·1).
Fever; pain.

Spasmophen *Polfa Pabianice, Pol.*
Oxyphenonium bromide (p.1759·2).
Gastrointestinal spasm; peptic ulcer.

Spasmoplex *Madaus, Port.*
Trospium chloride (p.2198·3).
Urinary incontinence.

Spasmoplus
Note. This name is used for preparations of different composition.
Novartis, Austria; Novartis, Belg.†.
Propyphenazone (p.119·3); drofenine hydrochloride (p.1727·3); codeine phosphate (p.37·2).
Painful smooth muscle spasm.

Novartis, Ital.
Propyphenazone (p.119·3); codeine phosphate (p.37·2).
Pain.

Spasmopriv
Note. This name is used for preparations of different composition.
Winthrop, Fr.
Mebeverine hydrochloride (p.1744·2).
Gastrointestinal and biliary-tract spasm.

Senosiain, Mex.; Eurodrug, Singapore; Eurodrug, Thai.
Fenoverine (p.2303·2).
Irritable bowel syndrome; smooth muscle spasm.

Spasmo-Proxyvon
Note. This name is used for preparations of different composition.
Wockhardt, India.
Capsules: Dicycloverine hydrochloride (p.1722·3); dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Smooth muscle spasm.

Wockhardt, India.
Injection: Dicycloverine (p.1723·1).
Smooth muscle spasm.

Spasmo-Proxyvon Forte *Wockhardt, India.*
Dicycloverine (p.1723·1); diclofenac sodium (p.44·3).
Smooth muscle spasm.

Spasmorelax *Lindopharm, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Spasmo-Rhoival TC *Madaus, Ger.*
Trospium chloride (p.2198·3).
Bladder function disorders.

Spasmosan *Scanpharm, Philipp.*
Hyoscine butylbromide (p.1734·1).
Diagnostic aid in radiology and endoscopy; smooth muscle spasm.

Spasmosedine *DB, Fr.†.*
Crataegus (p.2289·1).
Formerly contained crataegus and phenobarbital.
Cardiac disorders; nervous disorders.

Spasmosol *Streuli, Switz.*
⊗ Morphine hydrochloride (p.86·3); codeine hydrochloride (p.37·2); noscapine hydrochloride (p.1566·3); atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3).
Pain.

Spasmo-Solugastril *Pfizer, Austria; Pharmacia, Ger.†.*
Aluminium hydroxide (p.1706·2); butinoline phosphate (p.2271·1); calcium carbonate (p.1714·1).
Gastrointestinal cramp and acid pain; gastrointestinal disorders.

Spasmosyx F *Syxyl, Ger.*
Homoeopathic preparation.

Spasmotropin *Legrand, Braz.*
Dipyrone (p.49·2); papaverine hydrochloride (p.2191·3); homatropine methylbromide (p.1881·3).
Smooth muscle spasm.

Spasmo-Urgenin *Madaus, Austria; Neo-Farmaceutica, Port.†; Byk Madaus, S.Afr.†; Madaus, Spain; Madaus, Thai.*
Trospium chloride (p.2198·3); echinacea (p.2298·1); saw palmetto (p.2192·3).
Genito-urinary tract spasm and pain; prostatic hyperplasia; prostatitis.

Spasmo-Urgenin TC *Madaus, Ger.*
Trospium chloride (p.2198·3).
Bladder function disorders.

Spasmo-Urgenine Neo *Madaus, Switz.*
Trospium chloride (p.2198·3).
Urinary-tract disorders.

Spasmoveralgin Neo *Slovakofarma, Cz.†.*
⊗ Propyphenazone (p.119·3); phenobarbital (p.492·2); papaverine hydrochloride (p.2191·3); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); atropine methobromide (p.1219·2).
Smooth muscle spasm.

Spasmowern *Wernigerode, Ger.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Spasmoxyl *Berner, Fin.†.*
Oxybutynin hydrochloride (p.2190·3).
Bladder function disorders.

Spasrax *Overseas, India.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Colitis; dyspepsia; gastritis; irritable bowel disorder; peptic ulcer.

Spassirex *Winthrop, Fr.*
Phloroglucinol (p.2366·3).
Smooth muscle pain and spasm.

Spasticol *Farmina, Pol.*
Belladonna (p.2263·3); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Spasticone *Farmaline, Thai.*
Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Colic; gastrointestinal spasm.

Spastrex *Propan, S.Afr.†.*
Oxyphenonium bromide (p.1759·2).
Gastrointestinal and urinary-tract spasm.

Spasuret *Pierre Fabre, Ger.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Spasuri *Pharmasant, Thai.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Spasyt *TAD, Ger.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; urinary incontinence.

Spatab *Sriprasit, Thai.†.*
Hyoscine butylbromide (p.1734·1).
Gastrointestinal and urinary-tract disorders; smooth muscle spasm.

Spatam *Myung In, Singapore.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Spatanil *Farmanic, Gr.*
Cetirizine hydrochloride (p.570·3).

Spatix *Bioprogress, Ital.†.*
Suleparoid (p.1406·3).
Vascular disorders with a risk of thrombosis.

Spaxim *Sandoz, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Spaziron *Farmamust, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Spazmol *Deva, Turk.*
Hyoscine butylbromide (p.1734·1).

Spazmol Plus *Deva, Turk.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).

Spazmo-Valibrin *Mulda, Turk.*
Diazepam (p.986·3); oxyphencyclimine hydrochloride (p.1759·2).

Spazol *Siam Bheasach, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Spazoverin *Shreya, Rus.*
Drotaverine hydrochloride (p.2298·1).

Speciafoldine *Sanofi-Aventis OTC, Fr.*
Folic acid (p.1940·1).
Nutritional deficiency; prevention of neural tube disorders.

Specialflex *Braun, Ital.*
Amino-acid, electrolyte, and glucose infusion (p.1922·1).
Parenteral nutrition.

Specicef-N *Specifar (Σπεσιφαρ), Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Speci-Chol *Pekana, Ger.†.*
Homoeopathic preparation.

Species Carvi comp *Weleda, Austria†.*
Aniseed (p.2258·2); urtica (p.2409·3); fennel (p.2302·3); caraway (p.2276·3).
Flatulence; gastrointestinal cramp.

Species Cholagogae Planta *Leros, Cz.*
Elecampane (p.1558·1); rhubarb (p.1768·3); agrimony (p.2249·2); marrubium (p.1564·1); raspberry leaf (p.2378·2).
Biliary-tract disorders.

Species Diureticae Planta *Leros, Cz.†.*
Birch leaf (p.2266·3); parsley root (p.2363·2); equisetum (p.2299·3); rubus fruticosus; ononis (p.2357·1).
Diuretic.

Species nervinae *Kwizda, Austria.*
St John's wort (p.422·3); valerian (p.2410·1); melissa leaf (p.2339·3); peppermint leaf (p.1761·2).
Anxiety disorders; sleep disorders.

Species Nervinae Planta *Leros, Cz.*
Chamomile (p.2279·3); St John's wort (p.422·3); melissa (p.2339·3); peppermint leaf (p.1761·2); lupulus (p.2335·2); valerian (p.2410·1).
Anxiety; insomnia; neurasthenia.

Species Pectorales Planta *Leros, Cz.*
Verbascum (p.2413·3); fennel (p.2302·3); liquorice (p.1740·3); peppermint leaf (p.1761·2); plantain (p.2379·1); althaea (p.2253·3); coltsfoot leaf (p.1555·1).
Respiratory-tract disorders.

Species Urologicae Planta *Leros, Cz.*
Birch leaf (p.2266·3); bearberry (p.2263·3); ononis (p.2357·1); parsley root (p.2363·2); knotgrass (p.2329·2); sambucus (p.2383·1); urtica (p.2409·3); achillea (p.2245·2).
Urinary-tract inflammation.

Specific Nerve Pain Remedy *Group, S.Afr.*
⊗ Oral liquid, salicylamide (p.121·2); caffeine (p.1116·3); alcohol (p.1625·2); tablets, aspirin (p.20·3).
Fever; pain.

Specifthir *Specifar (Σπεσιφαρ), Gr.†.*
Malathion (p.2046·1).
Head and crab lice; scabies.

Specilid *Alet, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Specinor *Specifar (Σπεσιφαρ), Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; gastrointestinal ulcer.

Spec-Pen-V-K *Specpharm, S.Afr.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Spectazole *Ortho Dermatological, USA.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Spectin *Cipla, India.*
Spectinomycin hydrochloride (p.332·3).
Bacterial infections.

Spectolab *Multilab, Braz.*
Potassium iodide (p.2169·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Spec-Topistin *Specpharm, S.Afr.*
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Spectra *Solus, India.*
Doxepin (p.389·2).
Depression.

Spectraban
Note. This name is used for preparations of different composition.
Stiefel, Braz.†.
Aminobenzoic acid (p.1589·1).
Sunscreen.

Stiefel, Chile†.
Oxybenzone (p.1608·3); octinoxate (p.1608·2); homosalate (p.1598·1).
Sunscreen.

Stiefel, Braz.
Gel SPF 20; spray SPF 20: Oxybenzone (p.1608·3); homosalate (p.1598·1); octinoxate (p.1608·2).
Sunscreen.

Stiefel, Braz.
Lotion; stick: Padimate O (p.1609·1); avobenzone (p.1589·3).
Sunscreen.

Stiefel, Arg.
SPF 18: Dioxybenzone (p.1594·2); octinoxate (p.1608·2).
Sunscreen.

Stiefel, Mex.
SPF 18; SPF 20: Oxybenzone (p.1608·3); homosalate (p.1598·1); octinoxate (p.1608·2).
Sunscreen.

Stiefel, Thai.
SPF 19: Zinc oxide (p.1621·2).
Sunscreen.

Stiefel, Arg.
SPF 20: Oxybenzone (p.1608·3); homosalate (p.1598·1); octinoxate (p.1608·2).
Sunscreen.

Stiefel, UK†.
SPF 25: Padimate O (p.1609·1); aminobenzoic acid (p.1589·1).
Sunscreen.

Stiefel, Malaysia.
SPF 60: Zinc oxide (p.1621·2); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Spectraban 19 *Stiefel, Philipp.*
Zinc oxide (p.1621·2).
Sunscreen.

Spectraban 55 *Stiefel, Chile; Stiefel, Mex.*
SPF 55: Oxybenzone (p.1608·3); octinoxate (p.1608·2); sulisobenzone (p.1614·3); titanium dioxide (p.1617·3).
Sunscreen.

Spectraban 60
Stiefel, Hong Kong.
Avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Stiefel, Singapore.
SPF 60: Avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Spectraban T *Stiefel, Braz.*
Padimate O (p.1609·1); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Spectraban Ultra
Note. This name is used for preparations of different composition.
Stiefel, S.Afr.
Avobenzone (p.1589·3); padimate O (p.1609·1); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Stiefel, UK.
SPF 28: Padimate O (p.1609·1); avobenzone (p.1589·3); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Stiefel, Thai.
SPF 28+: Padimate O (p.1609·1); avobenzone (p.1589·3); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Stiefel, Braz.; Stiefel, Mex.
SPF 30: Avobenzone (p.1589·3); Padimate O (p.1609·1); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Stiefel, Chile.
SPF 30: Padimate O (p.1609·1); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Spectraban Ultra 28 *Stiefel, Philipp.*
Padimate O (p.1609·1); avobenzone (p.1589·3); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Spectracef *GSK, Gr.; Bayer, Mex.; GSK, Port.; GSK, Spain; Purdue, USA.*
Cefditoren pivoxil (p.223·2).
Bacterial infections.

Spectracil *Alliance, S.Afr.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Spectramox *Alliance, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Spectrapain *Alliance, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Spectrapain Forte *Alliance, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Spectrasone *Alliance, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Spectratet *Schwulst, S.Afr.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Spectrem *Armoxindo, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Spectrim *Alliance, S.Afr.; TO-Chemicals, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Spectro Derm *GSK Consumer, Canad.*
Skin cleanser.
Cleansing of abraded and irritated skin.

Spectro Gluvs *Block, Canad.†.*
Barrier cream.

Spectro Gram *GSK Consumer, Canad.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of skin and hands.

Spectro Jel *GSK Consumer, Canad.; Recsei, USA.*
Skin cleanser.

Spectro Tar
Note. This name is used for preparations of different composition.
Spectropharm, Canad.†.
Shampoo: Chlorhexidine gluconate (p.1635·3); coal tar (p.1616·2).
Scalp disorders.

Spectropharm, Canad.†.
Skin wash: Coal tar (p.1616·2).
Eczema; psoriasis.

Spectrocef *Epifarma, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Spectrocin *Iquinosa, Spain†.*
Gramicidin (p.286·1); neomycin sulfate (p.305·1).
Infected burns; infected wounds; skin infections; superficial eye infections.

Spectrocin Plus *Numark, USA†.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin (p.210·3); lidocaine (p.1862·3).
Bacterial skin infections.

Spectrocycline *Westmont, Indon.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Spectroflex *Baxter, Mex.†.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Spectroxyl *Ecosol, Switz.*
Amoxicillin (p.202·2).
Bacterial infections.

Spectrum
Note. This name is used for preparations of different composition.
Sigma-Tau, Ital.
Ceftazidime (p.234·1).
Bacterial infections.

Johnson & Johnson Medical, UK.
⊗ Alcohol (p.1625·2); quaternary ammonium compounds.
Formerly contained alcohol, chlorhexidine gluconate, and quaternary ammonium compounds.
Surface disinfection.

Spedamyl *Help, Gr.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Spedifen
Zambon, Fr.; Zambon, Hung.
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, and peri-articular disorders; pain.

Zambon, Hong Kong; Zambon, Indon.; Zambon, Malaysia; Zambon, Switz.
Ibuprofen arginine (p.65·2).
Fever; inflammation; musculoskeletal and joint disorders; pain; soft-tissue injury.

Spediol *Med-One, Gr.†.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Spedralgin sans codeine *Democal, Switz.†.*
Paracetamol (p.108·1); phenazone (p.116·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Spegic *Dynamic, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Spektracef *Abdi, Turk.*
Cefditoren pivoxil (p.223·2).
Bacterial infections.

Spektramox *AstraZeneca, Denm.; AstraZeneca, Fin.†; AstraZeneca, Swed.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Spel *Silesia, Chile.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Speman *Himalaya, Rus.*
Orchis mascula (p.2357·3); hygrophila auriculata; lactuca serriola; dolichos pruriens; suvarnavang; argyreia speciosa; tribulus terrestris (p.2404·1); leptadenia reticulata; parmelia perlata.
Benign prostatic hyperplasia; male infertility.

Speman Forte *Himalaya, Rus.*
Orchis mascula (p.2357·3); asteracantha longifolia seed; lactuca serriola; itchy velvet bean seed; suvarnavang; argyreia speciosa; tribulus terrestris (p.2404·1); leptadenia reticulata stalk; parmelia perlata; rauwolfia serpentina (p.1387·1).
Sexual function disorders in men.

Spencer's Bronchitis *McGloin, Austral.†.*
Ammonium chloride (p.1551·3); codeine phosphate (p.37·2); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; throat irritation.

Spenglersan *Apotheke Roten Krebs, Austria.*
A range of homoeopathic bacterial antigens.

Spenglersan Kolloid *Meckel, Ger.*
Homoeopathic preparation.

Speridan *Actavis, Pol.; Actavis, Rus.*
Risperidone (p.1024·2).
Schizophrenia and other psychoses.

Speridol *Sandoz, Gr.*
⊗ Bisoprolol (p.1234·2).
Hypertension.

Spermatex *Shreya, Rus.*
Benzalkonium chloride (p.1629·1).
Contraceptive.

Spersacarpin *OmniVision, Ger.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; reversal of mydriasis.

Spersacarpine *Novartis Ophthalmics, Hong Kong†; Novartis Ophthalmics, Malaysia†; OmniVision, Switz.*
Pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Spersacet *Novartis Ophthalmics, Hong Kong†; Novartis, Switz.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections; dacryocystitis.

Spersacet C *Restan, S.Afr.†; Novartis, Switz.†.*
Sulfacetamide sodium (p.335·3); chloramphenicol (p.239·3).
Bacterial eye infections; lachrymo-nasal irrigation.

Spersadex *OmniVision, Ger.; Novartis, Hong Kong†; OmniVision, Norw.; Adcock Ingram, S.Afr.; OmniVision, Switz.; Novartis, Turk.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye and ear disorders.

Spersadex Comp *Novartis, Chile†; Novartis, Denm.; Novartis Ophthalmics, Ger.†; Novartis, Hong Kong; Novartis Ophthalmics, Hung.†; Novartis, Indon.; Novartis, Malaysia†; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore†; Novartis, Switz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Infected eye disorders.

Spersadex Compositum *Novartis Ophthalmics, Cz.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Inflammatory eye infections.

Spersadex Compound *Novartis, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Inflammatory eye disorders.

Spersadex med kloramfenikol *Novartis, Norw.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3).
Inflammatory eye infections.

Spersadexolin *Novartis Ophthalmics, Ger.†.*
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3); tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Spersadexoline
Novartis, Gr.†; Novartis, Thai.
⊗ Chloramphenicol (p.239·3); dexamethasone (p.1526·1); tetryzoline hydrochloride (p.1574·1).
Bacterial eye infections with inflammation.

Novartis Ophthalmics, Hong Kong†; Novartis, Malaysia; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore†; Novartis, Switz.†.
⊗ Dexamethasone sodium phosphate (p.1526·2); chloramphenicol (p.239·3); tetryzoline hydrochloride (p.1574·1).
Bacterial eye infections with inflammation.

Spersallerg *Novartis, Chile; Novartis Ophthalmics, Cz.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis Ophthalmics, Hung.; Novartis, Malaysia; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Rus.; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Switz.; Novartis, Thai.*
⊗ Antazoline hydrochloride (p.567·1); tetryzoline hydrochloride (p.1574·1).
Allergic conjunctivitis; hay fever.

Spersamide *Adcock Ingram, S.Afr.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Spersanicol *Novartis Ophthalmics, Hong Kong†; Novartis, Indon.; Novartis Ophthalmics, Malaysia†; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore†; Novartis, Switz.†.*
Chloramphenicol (p.239·3).
Bacterial eye infections; lachrymo-nasal irrigation.

Spersapolymyxin *OmniVision, Switz.; Novartis, Thai.*
Polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Bacterial eye infections.

Spersatear *Adcock Ingram, S.Afr.*
Hypromellose (p.2144·2).
Dry eyes.

Sperti *Wyeth, Venez.†.*
Shark-liver oil (p.2386·1).
Haemorrhoids.

Sperti Plus Preparacion H *Wyeth Consumer, Arg.*
Shark-liver oil (p.2386·1); phenylephrine hydrochloride (p.1568·1).
Haemorrhoids.

Sperti Praparation H
Note. This name is used for preparations of different composition.
Whitehall-Much, Ger.†.
Yeast (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Wyeth Lederle, Austria†.
Rectal gel: Hamamelis (p.2318·2).
Haemorrhoids.

Wyeth Lederle, Austria.
Rectal ointment; suppositories: Yeast (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Sperti Preparacao H *Home, Port.*
Yeast (p.1998·3); shark-liver oil (p.2386·1).
Anorectal disorders.

Sperti Preparacion H *Wyeth-Whitehall, Arg.†.*
Shark-liver oil (p.2386·1).
Haemorrhoids.

Sperti Preparacion H Clear Gel *Wyeth Consumer, Chile†.*
Hamamelis (p.2318·2).
Haemorrhoids.

Sperti Preparation H *Wyeth Consumer, Chile; Wyeth Consumer, Neth.; Whitehall-Robins, Switz.*
Yeast (p.1998·3); shark-liver oil (p.2386·1).
Anorectal disorders; haemorrhoids.

Spesicor *Leiras, Fin.*
⊗ Metoprolol succinate (p.1338·1) or metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hyperthyroidism; migraine; myocardial infarction.

Speton *Temmler, Port.†.*
Halazone (p.1646·1).

SPF 15 For Body *Shaklee, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Spherex *Pharmacia, Ger.*
Amilomer 25-45 (p.2255·3).
Adjuvant to antineoplastics in liver cancer.

Spherulin *ALK, USA.*
Coccidioidin (p.2285·2).
Skin test for coccidioidomycosis.

Sphingogel *LED, Fr.†.*
Phytosphingosine; mandelic acid (p.296·3); malic acid (p.2337·1); citric acid (p.2284·1); salicylic acid (p.1612·2).
Acne.

S.P.H.P. *Cantassium Co., UK.*
Prostate gland (p.2337·3); spinal cord (p.2337·3); calcium hypophosphite (p.1677·1); nicotinamide (p.1957·3); lecithin (p.2332·2); wheat germ (p.2415·1); kola (p.2416·1); vitamin A (p.1971·2); vitamin D (p.1986·1).

Spidifen *Zambon, Belg.; Zambon, Neth.; Zambon, Port.*
Ibuprofen arginine (p.65·2).
Fever; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Spidox *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Spidufen *Zambon, Braz.*
Ibuprofen arginine (p.65·2).
Inflammation; pain.

Spifen *Zambon, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Spigelon *Peithner, Austria.*
Homoeopathic preparation.

Spigrow for Boys *Phoenix, Philipp.*
Notoginseng; spirulina; atractylodis macrocephalae; lycium; pseudostellariae; carthamus (p.1922·1).
Nutritional supplement.

Spigrow for Girls *Phoenix, Philipp.*
Notoginseng; spirulina; dong quai; rehmannia; paeonia alba; chuanxiong (p.1922·1).
Nutritional supplement.

Spinefe *FHC, Port.*
⊗ Ephedrine hydrochloride (p.1558·2).
Hypotension in anaesthesia.

Spir *Pierre Fabre, Fr.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Spirabiotic *Kimia, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Spiracin *TO-Chemicals, Thai.*
Spiramycin (p.333·1).
Bacterial infections.

Spiractin *Alphapharm, Austral.; Pharmacare, S.Afr.*
⊗ Spironolactone (p.1400·1).
Heart failure; hepatic cirrhosis with ascites or oedema; hirsutism in females; hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Spiradan *Kalbe, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Spiralgine *Spirig, Switz.*
Mefenamic acid (p.80·1).
Fever; inflammation; pain.

Spiranter *Interbat, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Spiraphan *Kattwiga, Ger.*
Homoeopathic preparation.

Spirasin *Sanbe, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Spiraxin *Bama, Spain.*
Rifaximin (p.330·1).
Gastrointestinal infections; hepatic encephalopathy.

Spirbon *Fresenius Kabi, Austria.*
⊗ Chlorphenoxamine hydrochloride (p.572·3); ephedrine hydrochloride (p.1558·2); emetine hydrochloride (p.833·3).
Respiratory-tract disorders.

Spiresis *Orion, Fin.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; liver cirrhosis with ascites; oedema.

Spirial
Note. This name is used for preparations of different composition.
SVR, Ital.
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

SVR, Fr.
Cream: Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

SVR, Fr.
Roll-on deodorant: Aluminium chlorohydrate (p.1588·3); triethyl citrate (p.2404·1); allantoin (p.1588·1).
Hyperhidrosis.

Spiricort *Spirig, Switz.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Spiridazide *SIT, Ital.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Hyperaldosteronism.

Spirillon *Worwag, Ger.†.*
Mineral (p.1667·1) and trace element (p.1922·1) preparation.

Spirit Salicyl *Floris, Israel.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne; keratinisation disorders.

Spirit Whitfield *Floris, Israel.*
Salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Fungal skin infections.

Spiritus Contra Tussim Drops *Weleda, S.Afr.*
Angelica (p.2258·1); clove (p.2284·3); cinnamon (p.2283·1); coriander (p.2288·1); melissa (p.2339·3); nutmeg (p.2355·2); lemon oil (p.2332·3); cherry-laurel.
Coughs.

Spiriva *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Pfizer, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Pfizer, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Pfizer, Norw.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Pfizer, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Pfizer, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Boehringer Ingelheim, USA; Pfizer, USA; Boehringer Ingelheim, Venez.*
Tiotropium bromide (p.1148·3).
Obstructive airways disease.

Spirix *Nycomed, Denm.; Leiras, Fin.; Nycomed, Norw.; Nycomed, Swed.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; hypertension; liver cirrhosis with ascites; oedema.

Spiro *CT, Ger.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Spiro comp *Ratiopharm, Ger.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; hyperaldosteronism; liver cirrhosis; nephrotic syndrome; oedema.

Spiro Compositum *Merckle, Cz.†.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; hyperaldosteronism; liver cirrhosis; nephrotic syndrome; oedema.

Spirobene *Ratiopharm, Austria.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; oedema.

Spirobeta *Betapharm, Ger.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Spirocort *AstraZeneca, Arg.; AstraZeneca, Denm.; Simesa, Ital.*
⊗ Budesonide (p.1520·1).
Asthma; bronchitis; nasal polyps; rhinitis.

Spiroctan *Biolab Sanus, Braz.; Ferlux, Fr.; Roche, Venez.†.*
⊗ Spironolactone (p.1400·1).
Adjuvant in myasthenia; hyperaldosteronism; hypertension; oedema.

Spiroctazine *Ferlux, Fr.*
⊗ Spironolactone (p.1400·1); altizide (p.1209·1).
Hypertension; oedema.

Spiro-D *Winthrop, Ger.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Ascites; hyperaldosteronism; oedema.

Spiroderm *Pharmacia, Ital.†.*
⊗ Spironolactone (p.1400·1).
Acne.

Spirofur *Bruno, Ital.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Hypertension; oedema.

Spirogamma *Worwag, Ger.*
⊗ Spironolactone (p.1400·1).
Ascites; hyperaldosteronism; oedema.

Spirohexal *Hexal, Austria.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; oedema.

Spiroject *Syxyl, Ger.†.*
Homoeopathic preparation.

Spirola *Kalbe, Indon.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; hypertension; hypokalaemia; oedema.

Spirolang *SIT, Ital.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension.

Spirolept *Thea, Fr.; Pro Vaccine, Switz.*
An inactivated leptospirosis vaccine (p.2221·1).
Active immunisation.

Spirolone *Berk, Cz.†; APS, Hung.†.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; hypertension; liver cirrhosis with ascites; nephrotic syndrome; oedema.

Spirometon *Belmac, Spain.*
⊗ Bendroflumethiazide (p.1224·1); spironolactone (p.1400·1).
Hypertension; oedema.

Spiromide *RPG, India.*
⊗ Furosemide (p.1292·1); spironolactone (p.1400·1).
Hypertension; oedema.

Spiromix *Boniscontro & Gazzone, Ital.*
Spiramycin (p.333·1).
Bacterial infections.

Spiron
Note. This name is used for preparations of different composition.
Andromaco, Chile.
Risperidone (p.1024·2).
Schizophrenia.

Orion, Denm.; Ratiopharm, Hung.
⊗ Spironolactone (p.1400·1).
Hepatic cirrhosis with ascites; hyperaldosteronism; oedema.

Spironex *PP Lab, Thai.†.*
⊗ Spironolactone (p.1400·1).
Ascites; hypertension; oedema; primary aldosteronism.

Spirono *Genericon, Austria; Alpharma-Isis, Ger.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; liver cirrhosis with ascites and oedema; oedema.

Spirono comp *Genericon, Austria.*
⊗ Spironolactone (p.1400·1); furosemide (p.1292·1).
Hyperaldosteronism; oedema.

Spironol *Pharbita, Israel; Polfa Grodzisk, Pol.*
⊗ Spironolactone (p.1400·1).
Hepatic cirrhosis; hyperaldosteronism; hypertension; hypokalaemia; oedema.

Spironolacton Plus *Heumann, Ger.†.*
⊗ Spironolactone (p.1400·1) furosemide (p.1292·1).
Ascites; oedema.

Spironone *Dexo, Fr.*
⊗ Spironolactone (p.1400·1).
Adjuvant in myasthenia; hyperaldosteronism; hypertension; oedema.

Spironothiazid *Desma, Ger.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Ascites; hyperaldosteronism; hypertension; oedema.

Spiropent *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Ital.; Teijin, Jpn; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Philipp.; Boehringer Ingelheim, Spain†.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Asthma; bronchitis; bronchospasm; emphysema; obstructive airways disease; stress urinary incontinence.

Spiroscand *Enapharm, Swed.†.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; liver cirrhosis with ascites; oedema.

Spirosine *Faran, Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Spirospare *Ashbourne, UK†.*
⊗ Spironolactone (p.1400·1).
Ascites; heart failure; nephrotic syndrome; oedema; primary hyperaldosteronism.

Spirostada comp *Stada, Ger.†.*
⊗ Spironolactone (p.1400·1); bendroflumethiazide (p.1224·1).
Ascites; hyperaldosteronism; hypertension; oedema.

Spirotone *Pacific, NZ.*
⊗ Spironolactone (p.1400·1).
Aldosteronism; heart failure; hepatic cirrhosis with ascites; hirsutism; hypertension; hypokalaemia; nephrotic syndrome; oedema.

Spirotop *Topgen, Belg.*
⊗ Spironolactone (p.1400·1).
Cirrhosis with ascites; heart failure; hyperaldosteronism; hypertension.

Spirox *Copernico, Ital.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Spirsa *Alter, Spain†.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Spirumate *Anugerah Pharmindo, Indon.*
Spirulina (p.2392·1).
Immunostimulant.

Spitacid *Ecolab, Ger.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3); benzyl alcohol (p.1631·3).
Hand disinfection.

Spitaderm *Paragerm, Fr.†; Paragerm, Indon.; Ecolab, Ital.; Ecolab, Neth.*
Isopropyl alcohol (p.1650·3); chlorhexidine gluconate (p.1635·3); hydrogen peroxide (p.1647·3).
Skin disinfection.

Spitalen *Erfa, Belg.†.*
Virginiamycin (p.361·2); neomycin sulfate (p.305·1).
Bacterial infections.

Spitomin *EGIS, Hung.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders; depression; sedative.

Spizef *Grunenthal, Austria; Grunenthal, Ger.*
Cefotiam hydrochloride (p.230·1).
Bacterial infections.

SPL *Delmont, USA.*
Two strains of lysed *Staphylococcus aureus* in solution (p.2239·3).
Staphylococcal infection.

Splendil *AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Jpn†.*
Felodipine (p.1285·3).
Angina pectoris; hypertension.

Splenocarbine *Lesourd, Fr.*
Activated charcoal (p.1435·2).
Gastrointestinal disorders.

Splentir *Unipharma, Gr.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Spm-OK *Marfarma, Ital.*
Vitamins; magnesium; zinc; borage oil; griffonia simplicifolia; agnus castus (p.1922·1).
Nutritional supplement.

Spofagnost *Galena, Cz.†; Ivax, Cz.†.*
Glucose (p.1945·3).
Test of glucose tolerance.

Spofalyt-Kalium *Galena, Cz.†.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Spofaplast *Chemopharma, Cz.*
Salicylic acid (p.1612·2).
Calluses; corns.

Spofax *Zentiva, Cz.*
Carmellose calcium (p.2142·1); bismuth subgallate (p.1711·1); cinchocaine hydrochloride (p.1857·3).
Haemorrhoids.

Spolera *OTW, Ger.*
Acmella ciliata.
Soft-tissue injuries.

SpondylAT *Altmann, Ger.*
Thorium-X chloride.
Ankylosing spondylitis.

Spondylon
Note. This name is used for preparations of different composition.
Riemser, Ger.
Capsules: Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Riemser, Ger.
Embrocation: Methyl nicotinate (p.85·3); camphor (p.2273·2).
Muscular and neuromuscular disorders.

Spondylonal *ICN, Ger.†.*
Multivitamin preparation (p.1922·1).

Spondyvit *Valeant, Ger.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Spongostan *Johnson & Johnson, Ger.; Johnson & Johnson, Ital.*
⊗ Gelatin (p.1072·1).
Haemorrhage.

Sponif *Slovakofarma, Cz.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Sponsin *Farmasan, Ger.*
Codergocrine mesilate (p.363·3).
Adjuvant for mental function disorders; cervical disc syndrome; hypertension.

Sponwiga *Kattwiga, Ger.†.*
Homoeopathic preparation.

Spophyllin *Zentiva, Cz.*
Theophylline (p.1140·1).
Obstructive airways disease.

Sporacid
Note. This name is used for preparations of different composition.
Ferron, Indon.
Itraconazole (p.536·3).
Fungal infections.

IMS, Ital.†.
Glutaral (p.1645·2).
Instrument disinfection.

Sporahexal *Hexal, Austral.*
Cefalexin (p.218·2).
Bacterial infections.

Sporal *Janssen-Cilag, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Sporal mono *Muller Goppingen, Ger.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Sporanox *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Cipharmed, Fr.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Janssen, USA; Janssen-Cilag, Venez.*
Itraconazole (p.536·3).
Fungal infections.

Sporasec *Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Itraconazole (p.536·3); secnidazole (p.846·3).
Vulvovaginal infections.

Sporaxyl *Bangkok Lab & Cosmetic, Thai.*
Ketoconazole (p.539·1).
Fungal skin infections.

Sporcid *Fresenius Kabi, Ger.*
Glutaral (p.1645·2); formaldehyde (p.1644·2).
Instrument disinfection.

Sporend *Mugi, Indon.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Sporetik *Sanbe, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Sporex
Note. This name is used for preparations of different composition.
Tempo Scan Pacific, Indon.
Ketoconazole (p.539·1).
Fungal skin infections.

IMS, Ital.†.
Glutaral (p.1645·2).
Instrument disinfection.

Toprak, Turk.
Itraconazole (p.536·3).
Fungal infections.

Sporfen *Medinfar, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Sporicef *Ranbaxy, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Sporicidin *IMS, Ital.*
Glutaral-phenate complex (p.1645·3).
Instrument and surface disinfection.

Sporidex *Ozone, Cz.; Ranbaxy, India; Ranbaxy, Malaysia; Ranbaxy, Philipp.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Sporidox Plus *IMS, Ital.*
Peracetic acid (p.1655·2).
Instrument disinfection.

Sporiline *Schering-Plough, Fr.†.*
Tolnaftate (p.548·3).
Fungal skin infections.

Sporinex *Medochemie, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Sporizole *Target, Gr.*
Itraconazole (p.536·3).
Fungal infections.

Sporlab *Biolab, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Sporlac *Uni-Sankyo, India.*
Lactobacillus sporogenes (p.2372·3).
Antibiotic-associated diarrhoea; moniliasis.

Spornar *Charoen, Thai.*
Itraconazole (p.536·3).
Fungal infections.

Sporostatin *Mantecorp, Braz.*
Griseofulvin (p.535·2).
Fungal infections.

Sporoxyl *Bangkok Lab & Cosmetic, Thai.*
Ketoconazole (p.539·1).
Fungal infections.

Sport 30 Sunblock *Tanning Research, Canad.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sportenine *Boiron, Canad.†; Boiron, Fr.*
Homoeopathic preparation.

Sportino *Harras-Curarina, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Sportino Akut *Harras-Curarina, Austria†; Harras-Curarina, Ger.*
Glycol salicylate (p.62·3); arnica (p.2260·2).
Musculoskeletal, joint, and soft-tissue disorders.

Sportium *Lyron, Switz.*
Heparin sodium (p.1301·2); allantoin (p.1588·1); dexpanthenol (p.2362·1).
Soft-tissue injuries; venous insufficiency.

Sports Ice Bruising Relief *Brauer, Austral.*
Arnica (p.2260·2).
Soft-tissue injury.

Sports Ice Joint & Muscle *Brauer, Austral.*
Homoeopathic preparation.

Sports Multi *Cenovis, Austral.†.*
Multivitamin and mineral preparation (p.1922·1).

Sportscreme *Thompson, USA.*
Trolamine salicylate (p.132·3).
Muscle, joint, and soft-tissue pain; neuralgia.

Sportscreme Ice *Thompson, USA.*
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Sportsmega *Cantassium Co., UK.*
Multivitamin and mineral preparation (p.1922·1).

Sportupac M *Terra-Bio, Ger.*
Aesculus (p.2248·2); aescin (p.2248·2).
Bruising.

Sportusal *Permamed, Switz.*
Lauromacrogol 400 (p.1916·1); dimethyl sulfoxide (p.2022·1); heparin sodium (p.1301·2); glycol salicylate (p.62·3); dexpanthenol (p.2362·1).
Soft-tissue trauma; superficial thrombophlebitis; varices.

Sportusal Spray sine heparino *Permamed, Switz.*
Lauromacrogol 400 (p.1916·1); dimethyl sulfoxide (p.2022·1); glycol salicylate (p.62·3); dexpanthenol (p.2362·1); menthol (p.2340·1); camphor (p.2273·2).
Musculoskeletal, joint, and soft-tissue disorders.

Spotof *CCD, Fr.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Spotoway *Health & Diet Food Co., UK.*
Chlorhexidine (p.1635·2).
Skin irritation and spots.

Spozol *Delta, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Spralyn *Salus, Mex.*
Sodium cromoglicate (p.1136·3).
Asthma.

Spray Anti-Septico *Johnson & Johnson, Braz.*
Lidocaine hydrochloride (p.1862·3); benzethonium chloride (p.1630·1).

Spray du Marcheur *Laphi, Fr.*
Irgasan (p.1665·2); triclocarban (p.1665·2).
Foot hygiene.

Spray Mint *Kivema, Israel.*
Menthol (p.2340·1); sorbitol (p.1965·1).
Nasal dryness.

Spray nasal comp pour adultes *Spirig, Switz.*
⊗ Naphazoline nitrate (p.1565·2); phenylephrine (p.1568·1).
Nasal congestion.

Spray nasal pour enfants *Spirig, Switz.*
Phenylephrine (p.1568·1).
Nasal congestion; rhinitis.

Spray de Proteccion Total *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Spray Solaire Bronzage Securite *Clarins, Canad.†.*
SPF 15: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Spraydil *SMB, Belg.*
Phenylephrine hydrochloride (p.1568·1).
Rhinitis.

Spray-on Bande *Eagle, Austral.†.*
Copovidone (p.2146·1).
Plastic skin preparation for colostomies and ileostomies.

Spray-Pax *Omega, Fr.; Pharmygiene, Rus.*
Pyrethrum (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Spray-Tish *Boehringer Ingelheim, Austral.*
⊗ Tramazoline hydrochloride (p.1574·3).
Nasal congestion.

Spray-Tish Menthol *Boehringer Ingelheim, Austral.*
⊗ Tramazoline hydrochloride (p.1574·3); menthol (p.2340·1); cineole (p.2282·3); camphor (p.2273·2).
Nasal congestion.

Sprayzoin *Geritrex, USA.*
Benzoin compound tincture.
Skin disorders.

Sprediol *Stroder, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Spregal
Note. This name is used for preparations of different composition.
Omega, Fr.; Olvos, Gr.; Pharmygiene, Neth.; Pharmygiene, Rus.; Medpro, S.Afr.
Esdepallethrine (p.2042·3); piperonyl butoxide (p.2049·1).
Scabies.

Wolff, Ger.
Bioallethrin (p.2036·2); piperonyl butoxide (p.2049·1).
Scabies.

Spren *Sigma, Austral.†.*
Aspirin (p.20·3).
Fever; inhibition of platelet aggregation; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Spreor *Inava, Fr.†*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Sprilon *Smith & Nephew, Irl.; Ayrton, UK.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2).
Barrier preparation; eczema; pressure sores; skin fissures; skin ulcers.

Sprimeo *Novartis, Cz.*
Aliskiren (p.1207·1).
Hypertension.

Sprinsol *Fortune, Hong Kong†.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Sprintec *Barr, USA.*
21 Tablets, ethinylestradiol (p.2101·3); norgestimate (p.2121·1); 7 tablets, inert.
Combined oral contraceptive.

Sprycel *BMS, Arg.; BMS, Austral.; BMS, Cz.; BMS, Fr.; BMS, Gr.; BMS, Hung.; BMS, Indon.; BMS, Malaysia; BMS, NZ; BMS, UK; BMS, USA.*
Dasatinib (p.708·2).
Acute lymphoblastic leukaemia; chronic myeloid leukaemia.

SPS *Carolina, USA.*
Sodium polystyrene sulfonate (p.1465·1).
Hyperkalaemia.

Sputopur *Teva, Hung.*
Acetylcysteine (p.1548·2).
Respiratory-tract disorders with increased or viscous mucus.

Spyrocon *Interbat, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Squam
Note. This name is used for preparations of different composition.
Gador, Arg.
Dental gel: Etidronate disodium (p.1097·1); sodium fluoride (p.1962·2); sodium monofluorophosphate (p.1964·3).
Dental caries prevention.
Gador, Arg.
Toothpaste: Etidronate disodium (p.1097·1); calcium pyrophosphate; sodium fluoride (p.1962·2).
Dental caries prevention.

Squamasol *Ichthyol, Austria; Ichthyol, Ger.*
Salicylic acid (p.1612·2).
Scalp disorders.

Squa-med
Note. This name is used for preparations of different composition.
Phoenix, Hung.
⊗ Pyrithione zinc (p.1611·2); disodium sulfosuccinated undecenoic acid monoethanolamide (p.549·3); urea (p.1620·2).
Scalp disorders.
Permamed, Switz.
Pyrithione zinc (p.1611·2); sodium undecylamide MEA-sulfosuccinate.
Formerly contained pyrithione zinc, sodium undecylamide MEA-sulfosuccinate, and urea.
Scalp disorders.

Squaphane *Biorga, Fr.*
Malic acid (p.2337·1); climbazole (p.529·3); miconazole (p.541·2); cade oil (p.1616·1).
Dandruff.

Squaphane E *Biorga, Fr.*
Climbazole (p.529·3); miconazole (p.541·2); cade oil (p.1616·1); levomenol (p.2333·3).
Dandruff.

Squaphane Masque-Creme *Biorga, Fr.*
Climbazole (p.529·3); miconazole (p.541·2); salicylic acid (p.1612·2); cade oil (p.1616·1); ichthammol (p.1599·1).
Scalp disorders.

Squaphane P *Biorga, Fr.*
Climbazole (p.529·3); miconazole (p.541·2); salicylic acid (p.1612·2); cade oil (p.1616·1); melaleuca oil (p.2338·2).
Dandruff.

Squaphane S *Biorga, Fr.*
Climbazole (p.529·3); miconazole (p.541·2); salicylic acid (p.1612·2); cade oil (p.1616·1); resorcinol (p.1612·1).
Scalp disorders.

Squibb-B Complex *BMS, Indon.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

SRC Expectorant *Edwards, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Coughs.

SRE Serocytol *Serolab, Switz.*
An immunoglobulin (equine).
Infections.

Srilane *Merck, Belg.; Merck-Lipha, Fr.; Merck-Lipha, Hong Kong†.*
Idrocilamide (p.1897·2).
Pain in peri-articular and soft-tissue disorders; skeletal muscle spasm; superficial phlebitis.

SRM-Rhotard *Alliance, S.Afr.; Amarin, Singapore†.*
⊗ Morphine sulfate (p.86·3).
Pain.

SRO *Rivero, Arg.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Oral rehydration.

Sronyx *Watson, USA.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Combined oral contraceptive.

SSD *Abbott, Canad.†; Par, USA.*
Sulfadiazine silver (p.337·2).
Burns; wounds.

SSKI *Upsher-Smith, USA.*
Potassium iodide (p.2169·2).
Respiratory-tract disorders.

SSP *Eurolab, Arg.*
Range of dietary supplements (p.1922·1).

SST *Intsel, Fr.; Medac, UK.*
Sorbitol (p.1965·1); macrogol (p.2336·1); malic acid (p.2337·1); sodium citrate (p.1673·3).
Dry mouth.

SSZ *Gufic, India.*
Sulfadiazine silver (p.337·2).
Fungal corneal infections.

ST-52 *Baxter Oncology, Fr.†.*
Fosfestrol sodium (p.2105·1).
Prostatic cancer.

ST 37 *Numark, USA.*
Hexylresorcinol (p.1647·1).
Antiseptic.

St Bonifatius-Tee *Kolassa, Austria.*
Equisetum (p.2299·3); citrus aurantium (p.2357·1); tilia flower (p.2402·2); boldo leaf (p.2267·2); juniper wood (p.2328·2).
Formerly contained equisetum, frangula bark, senna leaf, valerian root, citrus aurantium, tilia flower, boldo leaf, juniper wood, and rhubarb.
Biliary-tract disorders; diuretic.

S-T Forte 2 *Scot-Tussin, USA.*
Chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

St. Jakobs-Balsam *Cheplapharm, Ger.*
Zinc oxide (p.1621·2).
Wounds.

St James Balm *Medico-Biological Laboratories, UK.*
⊗ Zinc oxide (p.1621·2); ichthammol (p.1599·1); salicylic acid (p.1612·2); urea (p.1620·2).
Skin disorders.

St Johnswort Compound *Potter's, UK.*
Juniper oil (p.2328·3); St John's wort (p.422·3); salix (p.121·3); cimicifuga (p.2282·1); skullcap (p.2388·2).
Sciatica.

St. Joseph Adult Chewable *Schering-Plough, USA.*
Aspirin (p.20·3).

St Luke's Oil *British Dispensary, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); thyme oil (p.2401·2).
Muscle pain; soft-tissue injury.

St Luke's Sports Oil *British Dispensary, Thai.*
Methyl salicylate (p.85·3); menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Muscle pain; soft-tissue injury.

St Mary's Thistle Plus *Eagle, Austral.*
Milk thistle (p.1452·1); myrtillus (p.2349·3); taraxacum (p.2395·1).
Liver tonic; peripheral vascular disorders; psoriasis.

Staaldruppels *Lennon, S.Afr.*
Ferric chloride (p.2303·3).
Iron-deficiency anaemias; minor haemorrhage.

Stabactam *Fahrenheit, Indon.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Stabicilline *Vifor, Switz.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Stabilanol *Pharmathen, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Stabimed *Braun, Ger.*
Cocopropylene-diamine.
Instrument disinfection.

Stabisol *Berlin-Chemie, Rus.*
⊗ Hetastarch (p.1065·1).
Haemodilution; hypovolaemia; shock.

Stabixin *Fahrenheit, Indon.*
Cefoperazone sodium (p.227·1).
Bacterial infections.

Stablon
Servier, Arg.; Serdia, India; Servier, Indon.; Servier, Malaysia; Servier, Philipp.; Servier, Singapore.
Tianeptine (p.424·1).
Depression; mixed anxiety depressive states.
Servier, Austria; Servier, Braz.; Ardix, Fr.; Servier, Mex.; Servier, Port.; Servier, Thai.; Servier, Turk.; Servier, Venez.
Tianeptine sodium (p.423·3).
Anxiety; depression; mixed anxiety depressive states.

Stacare *Nufarindo, Indon.*
Lycopene (p.2335·2); selenium (p.1961·1); zinc (p.1999·1).
Prostate disorders.

Stacer *Atral, Port.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Stacin *Macrophar, Thai.*
Erythromycin (p.269·2).
Bacterial infections.

Stada Gurgellosung *Stada, Ger.†.*
Dequalinium chloride (p.1641·3).
Mouth disorders.

Stada K *Stada, Hong Kong.*
Ketoconazole (p.539·1).
Dandruff.

Stada Uno *Stada, Singapore; Stada, Thai.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension; ischaemic heart disease.

Stadaglicin *Stada, Cz.†; Stada, Hong Kong; Stada, Hung.†; Stada, Malaysia.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Stadalax *Stada, Cz.; Stada, Ger.†; Stada, Hung.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Stadamet *Stada, Cz.; Stada, Hung.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Stadapress *Stada, Cz.*
⊗ Quinapril hydrochloride (p.1382·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Stadaquel *Stada, Cz.*
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.

Stadelant *Chrispa (Χρισπα), Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Stadenace *Stada, Philipp.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Stadium *Sanfer, Mex.; Menarini, Neth.*
Dexketoprofen trometamol (p.73·1).
Pain.

Stadol *BMS, Canad.†; BMS, Chile†; BMS, Mex.; BMS, Philipp.; BMS, Rus.; Apothecon, USA.*
Butorphanol tartrate (p.32·1).
Pain; premedication.

Stadovir *Stada, Austria.*
Aciclovir (p.862·3).
Herpes labialis.

Stadyl *Medipharma, Hong Kong†.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3).
Cold and influenza symptoms.

Stafal *Sevapharma, Cz.*
Antistaphylococcal phages (p.2239·3).
Staphylococcal infections.

Stafcil *Aurobindo, Philipp.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Staficilin N *BMS, Braz.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Staficort *Verisfield, Gr.*
⊗ Betamethasone valerate (p.1519·1); fusidic acid (p.279·3).
Infected skin disorders.

Stafilon *AGIPS, Ital.*
Methacycline hydrochloride (p.298·2).
Bacterial infections.

Stafine *Kocak, Turk.*
Sodium fusidate (p.279·3).
Staphylococcal infections.

Staflex *Magna, USA.*
Phenyltoloxamine citrate (p.588·1); paracetamol (p.108·1).
Pain.

Staflocil *Orion, Fin.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Stafloxin *Westmont, Philipp.*
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Bacterial infections.

Staforin *Kalbe, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Stafoxil *Yamanouchi, Neth.†.*
Flucloxacillin sodium (p.277·1).
Bacterial infections.

Stagesic *Huckaby, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Stagid *Merck-Lipha, Fr.; Merck, Port.*
Metformin embonate (p.453·3).
Diabetes mellitus.

Stago N *Uhlmann-Eyraud, Switz.†.*
Greater celandine (p.2317·1); turmeric (p.1473·2); cynara (p.2291·2); boldo (p.2267·2).
Biliary-tract disorders.

Stahist *Huckaby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hyoscyamine sulfate (p.1736·1); hyoscine hydrobromide (p.1734·1); atropine sulfate (p.1219·3).
Formerly contained phenylpropanolamine hydrochloride, phenylephrine hydrochloride, chlorphenamine maleate, hyoscyamine sulfate, hyoscine hydrobromide, and atropine sulfate.
Upper respiratory-tract symptoms.

Stalcare *Epifarma, Ital.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Stalene *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.*
Fluconazole (p.532·1).
Fungal infections.

Staleth *Stadmed, India.*
Lithium carbonate (p.401·3).
Bipolar disorder; hypomania; mania.

Stalev *Novartis, Philipp.*
Levodopa (p.804·3); carbidopa (p.803·1); entacapone (p.804·1).
Parkinsonism.

Stalevo *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Orion, Cz.; Orion, Denm.; Orion, Fin.; Novartis, Fr.; Orion, Ger.; Novartis, Gr.; Novartis, Hong Kong; Orion, Hung.; Novartis, Indon.; Orion, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Orion, Neth.; Orion, Norw.; Orion, Pol.; Orion, Port.; Orion, Rus.; Novartis, Singapore; Novartis, Spain; Orion, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Orion, UK; Novartis, USA; Novartis, Venez.*
Levodopa (p.804·3); carbidopa (p.803·1); entacapone (p.804·1).
Parkinsonism.

Staloral
Stallergenes, Cz.; Stallergenes, Ger.; Stallergenes, Ital.; Stallergenes, Pol.
Allergen extracts (p.2250·2).
Allergen immunotherapy; hyposensitisation.
Trimedal, Switz.
Pollen allergen extracts (p.2370·2)(p.2250·2).
Allergen immunotherapy.

Stamar *LKM, Arg.*
Stavudine (p.907·1).
HIV infection.

Stamaril *Sanofi Pasteur, Arg.; Aventis Pasteur, Austral.; Sanofi Pasteur, Belg.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Aventis Pasteur, Malaysia†; Aventis, NZ; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Aventis Pasteur, Pol.; Sanofi Pasteur, Port.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.; Aventis Pasteur, Turk.; Aventis Pasteur, UK; Zuoz, Venez.†.*
A yellow fever vaccine (17D strain) (p.2243·2).
Active immunisation.

Stamifen *Finmedical, Ital.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis.

Stamin *Faran, Gr.*
Piracetam (p.368·2).
Mental function disorders.

Stamina *Chi Sheng, Thai.*
Vitamin B substances with glucose (p.1922·1).

Stamino *Tropica Mas, Indon.*
Glutamine (p.1947·2); echinacea (p.2298·1); ascorbic acid (p.1983·3).
Immunostimulant.

Stamlo *Biofarma, Venez.†.*
Amlodipine besilate (p.1214·1).
Angina pectoris; heart failure; hypertension.

Stamoist E *Huckaby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Stamonevrol *Biostam (Βιοσταμ), Gr.*
Sulpiride (p.1028·3).
Psychoses.

Stamyl *Konsuma, Venez.*
Pancreatin (p.2360·1); hemicellulase (p.2279·1); ox bile (p.2266·3); simeticone (p.1770·2).
Digestive disorders.

Stanalin *Erlimpex, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Stanback Headache *GSK Consumer, USA.*
Aspirin (p.20·3); salicylamide (p.121·2); caffeine (p.1116·3).
Pain.

Stancef *Biomedis, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Standacillin
Sandoz, Austria; Biochemie, Cz.†.
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.
Sandoz, Hung.; Sandoz, Malaysia.
Ampicillin sodium (p.204·1).
Bacterial infections.
Biochemie, Indon.; Sandoz, Singapore.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Standard III *Aguettant, Fr.†.*
Electrolyte preparation (p.1667·1).
Parenteral nutrition.

Standard XXI *Bioquimico, Arg.*
Benzyl alcohol (p.1631·3); diethyltoluamide (p.2041·1); ethyl butylacetylaminopropionate (p.2043·1).
Pediculosis.

Stangyl *Aventis, Ger.*
Trimipramine maleate (p.426·3) or trimipramine mesilate (p.426·3).
Anxiety; depression.

Stanhexidine *Omega, Canad.*
Chlorhexidine gluconate (p.1635·3).

Stanidine *Apotex, Philipp.; Pharma 3, Philipp.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hyperlipidaemias.

Stanilo *Pharmacia, Ger.*
Spectinomycin hydrochloride (p.332·3).
Gonorrhoea.

Stanol *Body Research, Thai.†.*
⊗ Stanozolol (p.2129·1).
Anabolic; hereditary angioedema.

Stanza *Hexpharm, Indon.*
Mefenamic acid (p.80·1).
Fever; pain.

Staphlex
Alphapharm, Malaysia; Pacific, NZ.
Flucloxacillin sodium (p.277·1).
Gram-positive bacterial infections.

Merck, Singapore; Pacific, Singapore.
Flucloxacillin (p.277·1).
Bacterial infections.

Staphycid
Trenker, Belg.
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Staphylococcal and streptococcal infections.

Trenker, Thai.
Flucloxacillin (p.277·1).
Bacterial infections.

Staphyclox *Norma (Νορμα), Gr.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Staphylex
Alphapharm, Austral.
Flucloxacillin sodium (p.277·1).
Gram-positive coccal infections.

GSK, Ger.
Flucloxacillin magnesium (p.277·1) or flucloxacillin sodium (p.277·1).
Bacterial infections.

Staphypan *Berna, Switz.†.*
Staphylococci.
Staphylococcal infections.

Starasid *Kayaku, Jpn.*
Cytarabine ocfosfate (p.706·1).
Malignant neoplasms.

Starazolin *Polpharma, Pol.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Conjunctivitis.

Starcef
Note. This name is used for preparations of different composition.
Dexa, Indon.
Cefixime (p.224·3).
Bacterial infections.

FIRMA, Ital.
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Starclaf *Pharos, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Starezin *Aledicine, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Starform *Novartis, Braz.; Novartis, Venez.*
Tablets, nateglinide (p.455·2); tablets, metformin hydrochloride (p.453·2).
Diabetes mellitus.

Staril *BMS, UK.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Starkid *Protidiet, Fr.†.*
Nutritional supplement for children (p.1922·1).

Starlix *Novartis, Arg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.†; Novartis, Fin.; Merck, Ger.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ†; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Nateglinide (p.455·2).
Diabetes mellitus.

Starmelox *Minerva (Μινερβα), Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

StarMuno
Note. This name is used for preparations of different composition.
Kalbe, Indon.
Caplet: Echinacea angustifolia extract (Polinacea) (p.2298·1); black elderberry (p.2383·1); zinc picolinate (p.2001·1); ascorbic acid (p.1983·3).
Immunostimulant.

Kalbe, Indon.
Syrup: Echinacea angustifolia extract (Polinacea) (p.2298·1) black elderberry (p.1983·3); zinc picolinate (p.2001·1).
Immunostimulant.

Starnoc *Servier, Canad.*
Zaleplon (p.1035·3).
Insomnia.

Starogyn *Leiras, Fin.*
Broxyquinoline (p.215·3).
Vaginal infections.

Star-Otic *Stellar, USA.*
Glacial acetic acid (p.2244·2); aluminium acetate (p.2255·1); boric acid (p.2268·1).
Ear infection.

Starox *Grunenthal, Chile†.*
Gatifloxacin (p.281·1).
Bacterial infections.

Star-Pen *Sandoz, Austria.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Starsis *Astellas, Jpn.*
Nateglinide (p.455·2).
Diabetes mellitus.

Start NP *ICN, Arg.†.*
⊗ Gentamicin sulfate (p.282·1); hydrocortisone acetate (p.1535·2); ketoconazole (p.539·1).
Infected skin disorders.

Startonyl *Torrex, Austria; Seber, Port.*
Citicoline (p.2283·3).
Cerebrovascular disorders; head injury.

Starval *Ranbaxy, India.*
Valsartan (p.1420·2).
Hypertension; myocardial infarction.

Starxon *Interbat, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Stas
Note. This name is used for preparations of different composition.
Stada, Cz.†.
Cetylpyridinium chloride (p.1635·1); dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Faran, Gr.
Itraconazole (p.536·3).
Fungal infections.

stas Erkaltungssalbe *Stada, Ger.†.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Cold symptoms.

stas Erkaltungssalbe mild *Stada, Ger.†.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Cold symptoms.

stas Nasentropfen, Nasenspray *Stada, Ger.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis.

stas-Hustenloser *Stada, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

stas-Hustenstiller N *Stada, Ger.†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Stasiva *Pharmanel, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Stat-Crit *Wampole, USA.*
Test for haematocrit/haemoglobin measurement.

Statex *Pharmascience, Canad.†; Pharmascience, Singapore.*
⊗ Morphine sulfate (p.86·3).
Pain.

Staticin *Westwood-Squibb, Canad.†; Westwood, USA†.*
Erythromycin (p.269·2).
Acne.

Staticum *Uriach, Spain.*
Glisentide (p.442·1).
Diabetes mellitus.

Statifil *Tiefenbacher, Neth.*
Pravastatin sodium (p.1374·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Statiflex G *Braun, Switz.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Statinal *Alet, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Statinclyne *Cazi, Braz.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Statinum *Medichrom, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Stativer *Iapharm, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Statosan *Sanus, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Statrol *Alcon, Belg.; Alcon, Cz.†; Alkon (Αλκον), Gr.†; Alcon, Philipp.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Staurodorm
Sanova, Austria.
Flurazepam hydrochloride (p.999·1).
Sleep disorders.

Madaus, Belg.
Flurazepam (p.999·1).
Insomnia.

Staurodorm Neu *Dolorgiet, Ger.*
Flurazepam (p.999·1).
Sleep disorders.

Stavacin *Biol, Arg.*
Staphylococcus aureus.
Staphylococcal infections.

Staveran *Polpharma, Pol.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension; ischaemic heart disease.

Stavid *Hovid, Malaysia.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Stavir *Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
Stavudine (p.907·1).
HIV infection.

Stavit *Nufarindo, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Stavubergen *Paylos, Arg.*
Stavudine (p.907·1).
HIV infection.

Stay Alert *Apothecary, USA.*
Caffeine (p.1116·3).
Fatigue.

Staybla *Ono, Jpn.*
Imidafenacin (p.2190·2).
Bladder hyperactivity.

Stay-Wet 3 *Sherman, USA.*
Cleansing, wetting, and soaking solution for gas permeable contact lenses (p.1622·2).

Stay-Wet 4 *Sherman, USA.*
Wetting solutions for hard contact lenses (p.1622·2).

Stazepine *Polpharma, Hung.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; epilepsy; trigeminal neuralgia.

Stazol *Bernofarm, Indon.*
Cilostazol (p.1245·2).
Peripheral vascular disorders; stroke prophylaxis.

Stazor *Adipharm, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

STD *Intramed, S.Afr.*
Sodium tetradecyl sulfate (p.2139·2).
Varicose veins.

Stecort-NM *Stancare, India.*
⊗ Beclometasone dipropionate (p.1516·2); neomycin sulfate (p.305·1); miconazole nitrate (p.541·3).
Infected skin lesions.

Stediril
Note. This name is used for preparations of different composition.
Wyeth, Cz.†; Wyeth, Fr.; Wyeth, Ger.†.
Norgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; endometriosis; menstrual disorders.

Wyeth, Neth.; Wyeth, Pol.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Stediril 30 *Wyeth, Belg.; Wyeth, Ger.†; Wyeth, Switz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Stediril D *Wyeth Lederle, Austria; Wyeth Lederle, Belg.†; Wyeth, Ger.†; Wyeth, Switz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive; endometriosis; menstrual disorders.

Stedon *Adelco, Gr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; premedication; skeletal muscle spasm; sleep disorders; status epilepticus; tetanus.

Steerometz *Metz, Philipp.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Stefolant *SJA, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Steicardin N *Steigerwald, Ger.*
Homoeopathic preparation.

Steicorton *Steigerwald, Ger.†.*
Crataegus (p.2289·1).
Heart failure.

Steinaclox *Medichrom, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Steiprostat *Steigerwald, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Steirocall N *Steierl, Ger.*
Homoeopathic preparation.

Steiroderm *Steierl, Ger.*
Homoeopathic preparation.

Steiroplex *Steierl, Ger.*
Homoeopathic preparation.

Steitraz *Landsteiner, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Stelabid *GSK, Canad.†; Armstrong, Mex.*
Isopropamide iodide (p.1736·3); trifluoperazine hydrochloride (p.1034·2).
Gastrointestinal disorders.

Stelapar *Schering-Plough, Arg.; GSK, Braz.†.*
Trifluoperazine hydrochloride (p.1034·2); tranylcypromine sulfate (p.424·1).
Mixed anxiety depressive states; psychoses.

Stelatopia *Interbat, Indon.*
A range of cleansing and moisturising preparations.

Stelax *Arrow, Austral.; Arrow, Hong Kong.*
Baclofen (p.1888·1).
Multiple sclerosis; muscle spasm or spasticity.

Stelazine *Schering-Plough, Arg.; Link, Austral.; GSK, Braz.; Vianex (Βιανέξ), Gr.; GSK, Indon.; Pharos, Indon.; Goldshield, Irl.; Armstrong, Mex.; Boucher & Muir, NZ; Pharmafrica, S.Afr.; Goldshield, UK.*
Trifluoperazine hydrochloride (p.1034·2).
Agitation; alcoholism; anxiety; anxiety and associated depression; behaviour disorders; bipolar disorder; nausea and vomiting; neuroses; psychoses; schizophrenia.

Stelea *Elea, Arg.†.*
Stavudine (p.907·1).
HIV infection.

Stelium *Ni-The, Gr.*
Trifluoperazine hydrochloride (p.1034·2).
Psychoses.

Stella *Alpharma, Fin.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Stellatropine *Lohmann, Belg.*
Atropine sulfate (p.1219·3).
Arrhythmias; cholinesterase inhibitor intoxication; premedication.

Stellorphinad *Lohmann, Belg.*
⊗ Morphine hydrochloride (p.86·3).
Acute pulmonary oedema; pain; premedication.

Stellorphine *Lohmann, Belg.*
⊗ Morphine hydrochloride (p.86·3).
Acute pulmonary oedema; pain; premedication.

Stelminal *Coup, Gr.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Stelpon *Sandoz, Indon.*
Mefenamic acid (p.80·1).
Fever; menorrhagia; pain.

Stemeral *Pharmanik (Φαρμανικ), Gr.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Stemetil
Aventis, Austral.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ.
Prochlorperazine (p.1020·1), prochlorperazine maleate (p.1020·1), or prochlorperazine mesilate (p.1020·1).
Anxiety; Menière's disease; migraine; nausea; psychoses; vertigo; vestibular disorders; vomiting.

Aventis, Canad.; Aventis, S.Afr.
Prochlorperazine mesilate (p.1020·1).
Anxiety; migraine; nausea; psychoses; vestibular disorders; vomiting.

Aventis, Denm.; Sanofi-Aventis, Fin.; Teofarma, Ital.; Aventis, Norw.; Aventis, Swed.
Prochlorperazine (p.1020·1) or prochlorperazine maleate (p.1020·1).
Adjunct to analgesia; alcohol and opioid withdrawal syndromes; anxiety; migraine; nausea; neuroses; paranoid state; psychoses; schizophrenia; vertigo; vestibular disorders; vomiting.

Aventis, Hong Kong; Sanofi-Aventis, Malaysia†; Castlemead, UK.
Prochlorperazine maleate (p.1020·1) or prochlorperazine mesilate (p.1020·1).
Anxiety; mania; migraine; psychoses; schizophrenia; vestibular disorders.

Nicholas Piramal, India; Aventis, Neth.; Sanofi-Aventis, Singapore.
Prochlorperazine (p.1020·1).
Anxiety; migraine; nausea; psychoses; vestibular disorders; vomiting.

Aventis, Thai.
Prochlorperazine maleate (p.1020·1).
Alcohol and opioid withdrawal syndromes; anxiety; Ménière's disease; nausea and vomiting; schizophrenia; vertigo.

Stemgen *Amgen, Austral.; Amgen, Canad.; Amgen, NZ.*
Ancestim (p.1054·1).
Mobilisation of autologous peripheral blood progenitor cells.

Stemiz *Cadila, India†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Stemzine *Aventis, Austral.*
Prochlorperazine maleate (p.1020·1).
Nausea and vomiting; psychoses; vertigo.

Sten *Atlantis, Mex.*
⊗ Prasterone (p.2124·2); testosterone propionate (p.2130·1); testosterone cipionate (p.2129·3).
Androgenic; breast cancer; erectile dysfunction; hypogonadism; loss of libido in females.

Stenirol *Guardian, Indon.*
⊗ Methylprednisolone (p.1538·1).
Oral corticosteroid.

Stenobronchial *Giovanardi, Ital.*
Sulfogaiacol (p.1573·2); wild thyme (p.2415·3); tolu balsam (p.1574·2).
Coughs, catarrh.

Stenocrat *Schwabe, Ger.†.*
Ammi visnaga fruit (p.2256·1); crataegus leaves, flowers, and fruit (p.2289·1).
Angina pectoris.

Stenocrat mono *Schwabe, Ger.*
Crataegus (p.2289·1).
Heart failure.

Stenoptin *Teofarma, Ger.†.*
Verapamil hydrochloride (p.1421·1); isosorbide dinitrate (p.1317·3).
Angina pectoris; myocardial infarction.

Stenosara *Ibefar, Braz.†.*
Vitamin B substances; minerals (p.1922·1).

Stenox *Atlantis, Mex.*
⊗ Fluoxymesterone (p.2103·3).
Androgenic; erectile dysfunction; hypogonadism.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Steocalcin *Christiaens, Belg.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteolysis; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Steocar *Christiaens, Belg.*
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; osteoporosis.

Steocin *SoSe, Gr.; SoSe, Ital.†.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Steopor *Otto, Indon.*
Calcium phosphate (p.1676·2); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); vitamin C; vitamin B ; vitamin K ; magnesium; copper; manganese; zinc (p.1922·1).
Calcium supplement; osteoporosis.

Steovit D3 *Christiaens, Belg.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Step 2 *Candioli, Ital.*
Extract of *Triticum aestivum* (p.2415·1).
Aid to removal of lice eggs.

Stephadilat-S *Bros, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder; panic disorder.

Steradent *Reckitt Benckiser, India.*
Sodium perborate (p.1662·1).
Denture cleanser.

Sterades *Galderma, Ital.*
⊗ Desonide (p.1525·1).
Skin disorders.

Steramin *Formenti, Ital.†.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds, burns, and mucous membranes.

Steramina G *Formenti, Ital.*
Benzalkonium chloride (p.1629·1).
Disinfection of wounds, burns, vagina, hands, instruments, surfaces, and skin.

Steranios *Anios, Fr.*
Glutaral (p.1645·2).
Instrument disinfection.

Sterapred *Merz, USA.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Sterax *Galderma, Belg.†; Galderma, Chile†; Galderma, Switz.†.*
⊗ Desonide (p.1525·1).
Skin disorders.

Ster-Dex *Novartis, Fr.*
⊗ Oxytetracycline (p.312·2); dexamethasone (p.1526·1).
Eye disorders.

Sterets *SSL, UK.*
Isopropyl alcohol (p.1650·3).
Skin disinfection.

Sterets H
Seton, Israel.
Isopropyl alcohol (p.1650·3); chlorhexidine gluconate (p.1635·3).
Skin disinfection.

SSL, UK.
Isopropyl alcohol (p.1650·3); chlorhexidine acetate (p.1635·2).
Skin disinfection.

Sterex *International Dermatologicals, Canad.*
Coal tar (p.1616·2); salicylic acid (p.1612·2); sulfur (p.1614·1).
Scalp disorders.

Sterex Plus *International Dermatologicals, Canad.*
⊗ Coal tar (p.1616·2); hydrocortisone (p.1535·2); salicylic acid (p.1612·2); sulfur (p.1614·1).

Sterginox *Novofarm (Νοβοφαρμ), Gr.*
Itraconazole (p.536·3).
Fungal infections.

Stericef *Ipca, India†; Ipca, Rus.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Stericlens *Pharmachem, UK.*
Sodium chloride (p.1686·1).
Wound irrigation.

Steridine *Xeragen, S.Afr.*
Povidone-iodine (p.1659·2).
Burns; mouth and throat infections; skin infections; wounds.

Steridol *Biocure, Ital.†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Disinfection.

Steridrolo *Molteni, Ital.*
Tosylchloramide sodium (p.1665·1).
Disinfection of wounds, burns, and external genitals.

Steridrolo a rapida idrolisi *Molteni, Ital.†.*
Halazone (p.1646·1).
Water purification.

Sterigel *SSL, UK.*
Hemicellulose (p.2143·1).
Ulcers; wounds.

Sterigin *Merck, Austria.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Sterigynon *Arcana, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Acne and hirsutism in women; oral contraceptive in women with androgen-associated symptoms.

Steril Zeta
Note. This name is used for preparations of different composition.
Zeta, Ital.
Cream: Triclosan (p.1665·2); usnic acid (p.2409·3); hamamelis (p.2318·2); cod-liver oil (p.1935·2).
Disinfection of burns and wounds.

Zeta, Ital.
Topical powder: Triclosan (p.1665·2); usnic acid (p.2409·3); zinc oxide (p.1621·2); zinc stearate (p.2139·3).
Disinfection of burns and wounds.

Sterilene
Note. This name is used for preparations of different composition.
Gifrer Barbezat, Fr.
Cetrimide (p.1634·1).
Skin and wound disinfection.

Amsa, Ital.
Cetrimonium tosilate (p.1635·1).
Vaginal disinfection.

Sterillium *Rivadis, Fr.†; Bode, Ger.; Pharma-Chemie, Gr.; Bode, Neth.; Beiersdorf, Switz.†.*
Mecetronium etilsulfate (p.1652·1); isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2).
Hand disinfection; skin disinfection.

Sterillium Virugard *Bode, Ger.*
⊗ Alcohol (p.1625·2).
Hand disinfection.

Sterilon
Boots Healthcare, Belg.
Chlorhexidine gluconate (p.1635·3) or chlorhexidine hydrochloride (p.1635·3).
Disinfection of skin and wounds; skin disorders.

Boots Healthcare, Neth.
Chlorhexidine gluconate (p.1635·3).
Skin disinfection; wounds.

Sterimar *United Medical, Braz.†; Mepro, Chile; Fumouze, Fr.; Veron, Ger.†; Fumouze, Hong Kong; Intra Pharma, Irl.; Fumouze, Israel; Baldacci, Ital.; Fumouze, Malaysia; Church, Mex.; Viatris, Port.†; Fumouze, Singapore; Doetsch, Grether, Switz.†; GSK, Turk.; Carter-Wallace, UK.*
Sea water (p.1686·1).
Nasal cleansing; nasal congestion; nasal dryness; nasal hygiene; nasal irrigation.

Sterimar Cu *Baldacci, Ital.*
Sea water (p.1686·1); copper (p.1935·2).
Nasal cleansing.

Sterimar Mn *Baldacci, Ital.*
Sea water (p.1686·1); manganese (p.1956·1).
Nasal irrigation.

Sterimycine *Novartis, Fr.†.*
Kanamycin sulfate (p.291·2); polymyxin B sulfate (p.317·3).
Eye infections.

Steri-Neb Cromogen *Galena, Cz.†.*
Sodium cromoglicate (p.1136·3).
Asthma.

Steri-Neb Salamol
Galena, Cz.†; Ivax, Irl.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Norton, Pol.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Sterinor *Heumann, Ger.†.*
Co-tetroxazine (p.257·3).
Bacterial infections.

Steripaste *Medlock Medical, UK.*
Zinc oxide (p.1621·2).
Ulcers.

Steripet *GE, Port.*
Fluorine-18 labelled fludeoxyglucose (p.2053·3).
Radionuclide for detection of malignant neoplasms by positron emission tomography.

Steripod *Medlock Medical, UK.*
Sodium chloride (p.1686·1).
Irrigation solution.

Steripod Chlorhexidine Gluconate *SSL, UK.*
Chlorhexidine gluconate (p.1635·3).
Formerly known as Steripod Pink.
Skin disinfection.

Steripod Chlorhexidine Gluconate with Cetrimide *SSL, UK†.*
Chlorhexidine gluconate (p.1635·3); cetrimide (p.1634·1).
Skin disinfection.

Steri/Sol *Pfizer Consumer, Canad.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Sterisol Fermentmycin *Intramed, S.Afr.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Sterisol Peridiasol *Intramed, S.Afr.*
Glucose; sodium chloride; sodium lactate; calcium chloride; magnesium chloride (p.1670·3).
Peritoneal dialysis.

Steriwipe *Helapet, UK.*
Isopropyl alcohol (p.1650·3).
Surface disinfection.

Sterizol *Vendiz, Philipp.*
Sulfadiazine silver (p.337·2).
Burns; leg ulcers.

Sterko *Biovena, Pol.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Sterlane *Pharmadeveloppement, Fr.*
Lauryloxypropyl-β-aminobutyric acid; dodecylamino-propyl-β-aminobutyric acid; miristalkonium chloride (p.1653·3).
Skin cleansing; skin infections.

Stern Biene Fenchelsirup *Altana, Ger.†.*
Fennel oil (p.2303·1).
Upper respiratory-tract disorders associated with viscous mucus.

Sterocort *Taro, Israel.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Steroderm
Note. This name is used for preparations of different composition.
Medikon, Indon.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Vendiz, Philipp.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Sterodex *Fischer, Israel.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Inflammatory eye disorders.

Sterodome *Faran, Gr.†.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Sterofrin *Alcon, Austral.*
⊗ Prednisolone acetate (p.1541·1).
Inflammatory and allergic eye disorders.

Sterofundin *Braun, Austria; Braun, Ger.; Braun, Hung.; Braun, Pol.*
A range of electrolyte infusions with or without glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Sterofundin BG *Braun, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Sterofundin HEG *Braun, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Sterofundin M *Braun, Neth.*
Electrolyte infusion (p.1667·1) with malic acid (p.2337·1).
Acidosis.

Sterofundin VG *Braun, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Sterogyl
Note. This name is used for preparations of different composition.
Spedrog, Arg.
Colecalciferol (p.1986·2).
Osteoporosis; vitamin D deficiency.

DB, Fr.; IFET (ΙΦΕΤ), Gr.
Ergocalciferol (p.1987·1).
Vitamin D deficiency.

Sterolone *Francia, Ital.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Steromien *Aspen, S.Afr.†.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Steron *West-Coast, Thai.*
Norethisterone (p.2119·3).
Benign breast disorders; endometriosis; menstrual disorders; postponement of menstruation.

Steronase Aq *Aventis, Israel.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Steronide *Galderma, Braz.†.*
⊗ Desonide (p.1525·1).
Skin disorders.

Steropotassium *Sterop, Belg.*
Potassium chloride (p.1684·3).
Hypokalaemia.

Steroprim *Sterop, Belg.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sterosan *Lachifarma, Ital.*
Benzalkonium chloride (p.1629·1); orthophenylphenol (p.1655·1).
Skin, wound, and burn disinfection.

Steros-Anal *BMS, Austria; BMS, Ger.†.*
⊗ Triamcinolone acetonide (p.1544·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Sterosone *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Sterostatine *Sterop, Belg.†.*
Nystatin (p.543·2).
Fungal infections.

Sterovag *SecFarm, Pol.*
⊗ Chloroxylenol (p.1640·2); formosulfathiazole (p.278·1); urea (p.1620·2).
Vulvovaginal disorders.

Sterozinil *Aesculapius, Ital.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Sterylip *Sanofarm, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Ster-Zac
Note. This name is used for preparations of different composition.
Medlock Medical, UK.
Bath additive: Triclosan (p.1665·2).
Skin disinfection.

SSL, UK†.
Skin cleanser: Hexachlorophene (p.1646·1).
Skin disinfection.

Stesiron *Alpharma, Denm.†; Alpharma, Fin.†; Alpharma, Norw.†.*
Buspirone hydrochloride (p.965·3).
Alcoholism; anxiety.

Stesolid *Chemomedica, Austria; Alpharma, Cz.; Alpharma, Denm.; Alpharma, Fin.; Alpharma-Isis, Ger.; Remek, Gr.; Alpharma, Hong Kong; Alpharma, Hung.; Actavis, Indon.; Alpharma, Irl.; CTI, Israel; CSL, NZ; Dumex, NZ; Alpharma, Neth.; Alpharma, Norw.; Actavis, Port.; Actavis, Singapore; Ipsen, Spain; Alpharma, Swed.; Team Medica, Switz.; Dumex-Alpharma, Thai.†; Alpharma, UK.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; convulsions; eclampsia; epilepsy; febrile convulsions; insomnia; neuroses; premedication; sedative; skeletal muscle spasm; spasticity; status epilepticus; tetanus; withdrawal syndromes.

Stevencillin *Rafarm, Gr.*
Amoxicillin (p.202·2).
Bacterial infections.

Steviadulri *Tanki, Arg.*
Stevia rebaudiana (p.1969·1).
Sugar substitute for diabetics.

Sthamizide *Filadams, Philipp.*
Ethambutol hydrochloride (p.274·1); isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Sthenorex *Pharmygiene, Fr.†.*
Fenugreek (p.2303·3); pollen (p.2370·2).
Anorexia.

Stibenyl *Pharmanel, Gr.*
Ramipril (p.1385·3).
Hypertension.

Stibenyl HCT *Pharmanel, Gr.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Stibium Comp *Weleda, S.Afr.*
Hamamelis (p.2318·2); aesculus (p.2248·2); stibium met.
Anorectal disorders.

Stick Ecran Total *Vichy, Canad.*
SPF 25: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Stick Labial de Proteccion Total *Pierre Fabre Dermo-Cosmetique, Arg.†.*
Titanium dioxide (p.1617·3); cinnamate.
Sunscreen.

Stiedex *Stiefel, UK†.*
⊗ Desoximetasone (p.1525·2); salicylic acid (p.1612·2).
Skin and scalp disorders.

Stiedex LP *Stiefel, UK†.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Stiefcortil *Stiefel, Arg.; Stiefel, Braz.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Stiefel Acne Gel *Stiefel, Cz.*
Isotretinoin (p.1599·2).
Acne.

Stiefotrex *Gabriel, Gr.*
Isotretinoin (p.1599·2).
Acne.

Stiemazol *Stiefel, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections.

Stiemycin *Stiefel, Arg.; Stiefel, Braz.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, NZ; Stiefel, Neth.; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore; Stiefel, Thai.; Stiefel, UK.*
Erythromycin (p.269·2).
Acne; bacterial skin infections.

Stiemycine *Sanova, Austria; Stiefel, Ger.; Qualicare, Switz.†.*
Erythromycin (p.269·2).
Acne.

Stieprox *Stiefel, Arg.; Stiefel, Austral.; Sanova, Austria; Stiefel, Canad.; Stiefel, Cz.; Stiefel, Denm.; Stiefel, Fin.; Gabriel, Gr.; Stiefel, Hong Kong; Stiefel, Irl.; Stiefel, Malaysia; Stiefel, NZ; Stiefel, Norw.; Stiefel, Philipp.; Stiefel, Pol.; Stiefel, Singapore; Stiefel, Thai.*
Ciclopirox olamine (p.529·2).
Dandruff; scalp pruritus; seborrhoeic dermatitis.

Stieproxal *Stiefel, Arg.*
Ciclopirox olamine (p.529·2); salicylic acid (p.1612·2).
Scalp disorders.

Stieva-A *Stiefel, Austral.; Stiefel, Canad.; Stiefel, Chile; Stiefel, Hong Kong; Stiefel, Malaysia; Stiefel, Mex.; Stiefel, Philipp.; Stiefel, Singapore; Stiefel, Thai.*
Tretinoin (p.1618·1).
Acne; photoageing of the skin.

Stievamycin *Stiefel, Arg.; Stiefel, Canad.; Stiefel, Chile; Stiefel, Mex.*
Tretinoin (p.1618·1); erythromycin (p.269·2).
Acne.

Stigmicarpin *Bros, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Stigmosan *Pharmamagist, Hung.*
Neostigmine metilsulfate (p.631·3).
Gastrointestinal motility disorders; myasthenia gravis; postoperative urinary retention; reversal of competitive neuromuscular blockade.

Stilamin *Serono, Arg.†; Serono, Braz.; Serono, Canad.; Serono, Cz.†; Vianex (Βιανέξ), Gr.; Serono, Hong Kong; Serono, Hung.†; Serum Institute, India†; DKSH, Indon.; Serono, Indon.; Serono, Ital.; Serono, Malaysia; Serono, Mex.†; Serono, Neth.†; Serono, Port.†; Serono, S.Afr.; Serono, Singapore; Serono, Switz.; Serono, Thai.; Serono, Turk.; Serono, Venez.*
Somatostatin acetate (p.1809·2).
Biliary, pancreatic, and intestinal fistulae; diabetic ketoacidosis; diarrhoea; gastrointestinal and pancreatic cancers; gastrointestinal haemorrhage; growth hormone deficiency; hormone-dependent tumours; pancreatitis; postoperative complications following pancreatic surgery; rheumatoid arthritis; short-bowel syndrome; variceal haemorrhage.

Stilaze *Sandipro, Belg.*
Lormetazepam (p.1005·2).
Insomnia.

Stildem *Arrow, Austral.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Stilene *Omega, Belg.*
Dipropylene glycol salicylate (p.62·3); capsicum oleoresin (p.2276·2).
Musculoskeletal, joint, nerve, and soft-tissue pain.

Stileran *Combiphar, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Pain.

Stilex
Note. This name is used for preparations of different composition.
Farmanic, Gr.
Butamirate citrate (p.1553·1).
Cough.

Abdi, Turk.
Mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3); dexpanthenol (p.2362·1).
Skin disorders.

Vifor, Switz.
Cream: Mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3); calcium levulinate (p.1676·2); menthol (p.2340·1).
Minor burns; skin disorders.

Vifor, Switz.
Fluigel; topical gel; topical spray: Mepyramine maleate (p.585·2); lidocaine hydrochloride (p.1862·3); dexpanthenol (p.2362·1).
Minor burns; skin disorders.

Stilgrip *Hertz, Braz.*
Chlorphenamine (p.572·2); phenylephrine (p.1568·1); paracetamol (p.108·1).
Cold and influenza symptoms.

Stiliden *Lifepharma, Ital.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Stilizan *Frik, Turk.*
Trifluoperazine hydrochloride (p.1034·2).
Agitation; anxiety; behaviour disorders; nausea and vomiting; psychoses.

Still *Allergan, Braz.; Allergan, Mex.*
Diclofenac sodium (p.44·3).
Inflammatory eye disorders; inhibition of miosis during cataract surgery.

Stilla *Teva, Israel.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Stilla Decongestionante *Angelini, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Stilla Delicato *Angelini, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection; eye irritation.

Stillacor *Wolff, Ger.*
β-Acetyldigoxin (p.1201·2).
Arrhythmias; heart failure.

Stillargol *Mayoly-Spindler, Fr.*
Silver protein (p.2387·3).
Eye infections.

Stillergy *Angelini, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1); pheniramine maleate (p.587·3).
Eye irritation and congestion.

Stilnoct *Sanofi-Aventis, Belg.; Sanofi Synthelabo, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Irl.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, UK.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Stilnox *Sanofi-Aventis, Austral.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Ger.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Synthelabo, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Sanofi-Aventis, Venez.*
Zolpidem tartrate (p.1037·3).
Anxiety; insomnia.

Stilomagic *Antipiol, Ital.†.*
Ammonia (p.2256·1); hamamelis (p.2318·2); almond oil (p.2252·2).
Insect repellent.

Stiloz *Glenmark, India†.*
Cilostazol (p.1245·2).
Intermittent claudication.

Stilpane
Note. This name is used for preparations of different composition.
Pharmacare, S.Afr.
Capsules: Paracetamol (p.108·1); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Pain and associated tension.

Pharmacare, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Formerly contained paracetamol, codeine phosphate, promethazine hydrochloride, and camphorated opium tincture.
Fever; pain.

Pharmacare, S.Afr.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Stilpidem *Quality, Hong Kong.*
Zolpidem (p.1038·2).
Insomnia.

Stilux *EMS, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Eye disorders.

Stimate *CSL Behring, USA.*
Desmopressin acetate (p.2185·3).
Haemophilia A; von Willebrand's disease.

Stimilfar *Lusofarmaco, Port.†.*
Piracetam (p.368·2); vincamine (p.2414·1).

Stimol *Biocodex, Fr.; Casana, Indon.; Biocodex, Rus.; Perez Gimenez, Spain.*
Citrulline malate (p.1935·1).
Asthenia; tonic.

Stimolfit *Body Spring, Ital.*
Senna (p.1769·2); rhubarb (p.1768·3); cascara (p.1715·2); peppermint leaf (p.1761·2); threonine (p.1971·1); inositol (p.2325·2).
Gastrointestinal disorders.

Stimox *Solas, Indon.*
Echinacea (p.2298·1); vitamins; bovine colostrum (p.2208·1); phyllanty.
Immunomodulator.

Stimtes *Lilly, Ital.†.*
Collagen (bovine) (p.2286·1).
Skin ulcers; wounds.

Stimu-ACTH *Ferring, Fr.*
⊗ Corticorelin triflutate (p.1523·2).
Diagnosis of adrenocortical dysfunction.

Stimubral *Lusofarmaco, Port.†.*
Piracetam (p.368·2).

Stimu-GH *Ferring, Fr.*
⊗ Somatorelin acetate (p.1808·3).
Diagnosis of hypothalamic-pituitary dysfunction.

Stimulance *Nutricia, Fr.; Nutricia, Ital.; Baxter, NZ; Nutricia, NZ; Nutricia, Port.†.*
Dietary fibre supplement (p.1712·3).

Stimulex *Cipan, Port.*
Vitamin B substances (p.1922·1).
Tonic; vitamin B deficiency.

Stimu-LH *Ferring, Fr.*
⊗ Gonadorelin (p.2106·2).
Diagnosis of hypothalamic-pituitary-gonadal dysfunction.

Stimulit *Fahrenheit, Indon.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Stimulnerv *Columbia, Arg.*
Ginseng; glucurolactone; phosphorylcolamine; potassium aspartate; magnesium aspartate; vitamin B (p.1922·1).
Tonic.

Stimuloton *Egis, Cz.; Egis, Hong Kong; EGIS, Hung.; Egis, Pol.; Egis, Rus.*
Sertraline hydrochloride (p.421·3).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Stimunal
Note. This name is used for preparations of different composition.
Poirier, Fr.
Capsules; syrup: Vitamin and mineral preparation (p.1922·1).

Poirier, Fr.
Spray: Zinc gluconate; copper gluconate; manganese gluconate; ascorbic acid; pyridoxine hydrochloride; calendula officinalis.
Cleansing of nose, mouth, and throat.

Stimuno *Dexa, Indon.*
Phyllanthus niruri.
Immunomodulator.

Stimuplexe *Lehning, Fr.*
Cobalt gluconate; manganese glycerophosphate; zinc gluconate; copper gluconate; lysine hydrochloride; phosphoric acid (p.1922·1).
Asthenia.

Stimu-TSH *Ferring, Fr.*
Protirelin (p.2175·3).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Stimycine *Stiefel, Belg.; Stiefel, Fr.*
Erythromycin (p.269·2).
Acne.

Sting-Eze *Wisconsin Pharmacal, USA.*
Diphenhydramine hydrochloride (p.577·2); camphor (p.2273·2); phenol (p.1656·1); benzocaine (p.1854·1); cineole (p.2282·3).
Pruritus.

Sting-Kill *Randob, USA.*
Benzocaine (p.1854·1); menthol (p.2340·1).
Insect bites and stings; minor skin irritation.

Stingose *Johnson & Johnson, Austral.; Hamilton, Hong Kong; Johnson & Johnson, NZ; Eden, S.Afr.†; Thornton & Ross, UK.*
Aluminium sulfate (p.2255·1).
Bites and stings.

Stioxyl *Sylak, Swed.†.*
Benzoyl peroxide (p.1590·2).
Acne.

Stipo *Repha, Ger.†.*
⊗ Thuja; lycopodium; lemna min.; pulsatilla; mezereum; kal. bichrom.; hydrastis; benzocaine (p.1854·1); ephedrine hydrochloride (p.1558·2); naphazoline hydrochloride (p.1565·2).
Nasal disorders.

Stiprox *Stiefel, Braz.; Stiefel, Chile; Stiefel, Fr.; Stiefel, Ital.; Stiefel, Mex.*
Ciclopirox olamine (p.529·2).
Dandruff; fungal skin infections; seborrhoeic dermatitis.

Stiproxal *Stiefel, Fr.*
Ciclopirox olamine (p.529·2); salicylic acid (p.1612·2).
Dandruff.

Stivate *Stiefel, Thai.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Stixenil *Alter, Ital.*
Bisacodyl (p.1710·1).
Constipation.

Stocof *Chew, Thai.*
Guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); terpin hydrate (p.1573·3).
Coughs; nasal congestion.

Stocrin *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Israel; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Venez.*
Efavirenz (p.872·3).
HIV infection.

Stodal
Note. This name is used for preparations of different composition.
Key Sun, Austral.†; Boiron, Canad.; Boiron, Fr.
Homoeopathic preparation.

Boiron, Cz.; Boiron, Port.
Anemone pulsatilla; rumex crispus; bryonia dioica; ipeca; spongia tosta; sticta pulmonaria; antimonium tartaricum; myocarde; coccus cacti; drosera; tolu balsam (p.1574·2); senega (p.1572·3).
Coughs.

Stoffwechseltee N *Abtswinder, Cz.†.*
Birch leaf (p.2266·3); equisetum (p.2299·3); urtica (p.2409·3); ononis (p.2357·1); solidago (p.2391·1); fennel (p.2302·3); rose fruit (p.2381·2); peppermint leaf (p.1761·2); liquorice (p.1740·3).
Fluid retention.

Stofilan *Christiaens, Belg.; Lek, Hong Kong.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral circulatory disorders; hypertension; mental function impairment; migraine and other vascular headache.

Stogar *UCB, Jpn.*
Lafutidine (p.1739·2).
Peptic ulcer.

STOI-X *Apomedica, Austria.*
Selenium disulfide (p.1613·1).
Dandruff.

Stolax *Sanbe, Indon.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Stolina *Almirall, Spain.*
Cyproheptadine cyclamate (p.575·2); amino acids and cyanocobalamin (p.1922·1).
Anorexia; tonic; weight loss.

Stomaax *Theralab, Canad.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Stomaax Plus *Atlas, Canad.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Stomabococin *Bock, Ger.†.*
Homoeopathic preparation.

Stomac
Note. This name is used for preparations of different composition.
Greater Pharma, Thai.
Oral liquid: Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Greater Pharma, Thai.
Tablets: Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); atropine sulfate (p.1219·3); peppermint oil (p.1761·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Stomacain *Combiphar, Indon.*
Aluminium hydroxide-magnesium carbonate-calcium carbonate coprecipitate (p.1707·2) (p.1714·1).
Dyspepsia; gastric hyperacidity; gastritis; peptic ulcer.

Stomacer *Sandoz, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Stomach Calm *Brauer, Austral.*
Homoeopathic preparation.

Stomach Mixture *Potter's, UK.*
Bismuth and ammonium citrate (p.1712·1); taraxacum (p.2395·1); gentian root (p.2310·3); compound rhubarb tincture (p.1768·3).
Dyspepsia.

Stomachysat N *Ysatfabrik, Ger.†.*
Absinthium (p.2244·1); achillea (p.2245·2); gnaphalium dioicum; peppermint leaf (p.1761·2).
Gastrointestinal disorders.

Stomacine *Plan, Switz.*
Pepsin (p.2365·1); condurango (p.2287·1); cardamom (p.2277·1); quassia (p.2377·1).
Digestive disorders; flatulence; loss of appetite; meteorism.

Stomadon *Soho, Indon.*
Belladonna (p.2263·3); peppermint oil (p.1761·2); aluminium magnesium silicate (p.2141·2).
Gastric hyperacidity; peptic ulcer.

Stoma-Gastreu S R5 *Reckeweg, Ger.*
Homoeopathic preparation.

Stomagel *Darya-Varia, Indon.*
Calcium carbonate (p.1714·1); magnesium trisilicate (p.1744·1); silicone emulsion SE-2; bentonite (p.2141·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Stomahesive
Note. This name is used for preparations of different composition.
Convatec, Fr.
Barrier paste.
Fistulae; stoma care.

Convatec, Austral.
Topical paste: Butyl monoester polymer with ethanol.
Colostomies and ileostomies.

BMS, NZ.
Topical paste; topical powder: ⊗ Carmellose sodium (p.2142·1); gelatin (p.1072·1); pectin (p.2145·2).
Stoma care.

BMS, NZ†; Convatec, UK.
Topical wafer: ⊗ Carmellose sodium (p.2142·1); gelatin (p.1072·1); pectin (p.2145·2); polyisobutylene.
Stoma care.

Convatec, Austral.†.
Wafer: ⊗ Carmellose sodium (p.2142·1); gelatin (p.1072·1); pectin (p.2145·2); polyisobutylene.
Colostomies and ileostomies.

Stomakon *Biolab Sanus, Braz.†.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Stomaran *Leros, Cz.*
Calamus (p.2271·3); angelica (p.2258·1); chamomile (p.2279·3); centaury (p.2279·1); St John's wort (p.422·3); agrimony (p.2249·2); peppermint leaf (p.1761·2); rubus fruticosus; fennel (p.2302·3).
Digestive disorders; reduced appetite.

Stomargil *Motima, Fr.*
Myrtillus (p.2349·3); argile verte (illite); vegetable carbon (p.1473·3); cinnamon oil (p.2283·2); melissa oil (p.2339·3).
Aid to digestion.

Stomasal Med *Mauermann, Ger.†.*
Aluminium hydroxide (p.1706·2); magnesium oxide (p.1744·1); lupulus (p.2335·2); peppermint leaf (p.1761·2); agrimony (p.2249·2); calamus (p.2271·3); chlorophyllin (p.1471·1).
Gastrointestinal disorders.

Stomatidine *Bosnalijek, Rus.*
Hexetidine (p.1647·1).
Mouth and throat disorders.

Stomatosan *Slovakofarma, Cz.†.*
Clove (p.2284·3); comfrey (p.2286·3); thyme (p.2401·1); achillea (p.2245·2); tormentil (p.2403·2); sage (p.2382·3); vervain (p.2413·3); alliaria; prunella.
Oral inflammation.

Stomatosol *Elanda, Pol.*
Arnica (p.2260·2); oak (p.2355·3); tormentil (p.2403·2).
Mouth disorders.

Stomec *Medicine Products, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Stomedine *GSK Sante, Fr.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity.

Stomet *Valda, Ital.*
Cimetidine (p.1716·2).
Gastrointestinal hyperacidity.

Stomffler *Loeffler, Mex.*
Metronidazole benzoate (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Stomffler Plus *Loeffler, Mex.*
Metronidazole benzoate (p.837·1); diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Stomigen *Steiner, Ger.†.*
Magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastrointestinal hyperacidity; peptic ulcer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Stomygen
Note. This name is used for preparations of different composition.
Stomygen, Ital.
Mouth spray: Cetylpyridinium chloride (p.1635·1).
Halitosis.

Stomygen, Ital.
Mouthwash: Sodium monofluorophosphate (p.1964·3); cetylpyridinium chloride (p.1635·1).
Oral hygiene.

Stongel *Cazi, Braz.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Stop *Oral-B, USA.*
Stannous fluoride (p.1967·3).
Dental caries prophylaxis.

Stop X *Apex, Indon.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); eugenol (p.2301·2); benzyl nicotinate (p.28·1).
Musculoskeletal and joint pain; neuralgia.

Stop Cold *Darya-Varia, Indon.; Pharos, Indon.*
Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); triprolidine hydrochloride (p.592·3); guaifenesin (p.1561·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Stop Espinilla Normaderm *Capilares, Spain.*
Benzoyl peroxide (p.1590·2).
Acne.

Stop Hemo *Brothier, Fr.; Avgerinos, Gr.†.*
Calcium alginate (p.1058·1).
Burns; haemostatic; skin disorders; wounds.

Stop Itch
Note. A similar name is used for preparations of different composition (see Stopitch, below).
Dermatech, Austral.; Schering-Plough, Canad.†; Balmar, NZ.
Papain (p.2362·3).
Insect bites; jelly fish stings; minor burns; skin irritation; skin rashes.

Stopain
Note. This name is used for preparations of different composition.
Chew, Thai.
Cream: Methyl salicylate (p.85·3); menthol (p.2340·1); eugenol (p.2301·2); thymol (p.1664·3); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal pain.

Chew, Thai.
Topical gel: Menthol (p.2340·1).
Musculoskeletal pain.

Stopaler *LKM, Arg.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Stop-Allerg *Genop, S.Afr.*
Sodium cromoglicate (p.1136·3).
Formerly known as Vistacrom.
Allergic conjunctivitis.

Stopangin
Note. This name is used for preparations of different composition.
Ivax, Rus.
Hexetidine (p.1647·1); methyl salicylate (p.85·3); anise oil (p.2258·2); eucalyptus oil (p.2301·2); neroli oil (p.2351·1); sassafras oil (p.2383·3); peppermint oil (p.1761·2); menthol (p.2340·1).
Mouth and throat disorders.

Galena, Cz.; Ivax, Cz.
Gargle: Hexetidine (p.1647·1); anise oil (p.2258·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); methyl salicylate (p.85·3); sassafras oil (p.2383·3); peppermint oil (p.1761·2); clove oil (p.2285·1).
Mouth and throat disorders.

Galena, Cz.; Ivax, Cz.
Throat spray: Hexetidine (p.1647·1); anise oil (p.2258·2); eucalyptus oil (p.2301·2); neroli oil (p.2351·1); sassafras oil (p.2383·3); peppermint oil (p.1761·2).
Mouth and throat disorders.

Stoparen *Anfarm, Gr.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Stopayne
Note. This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Capsules; tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Fever; pain.

Adcock Ingram, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

StopBleed *Ransom, UK.*
Micro-dispersed oxidised cellulose (p.1075·1).
Minor cuts and grazes.

Stopcold *UCB, Spain.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Stopen *Berman, Mex.*
Di-iodo-kaolin-pectin-sulfa.
Diarrhoea; gastrointestinal infections.

Stoperan *US Pharmacia, Pol.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Stopex *Medical, Port.†.*
Sulfathiazole (p.343·2).
Vaginal infections.

Stopit *Rafa, Israel.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Stopitch
Note. A similar name is used for preparations of different composition (see Stop Itch, above).
Adcock Ingram, S.Afr.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Stop-Itch Plus *Dermatech, Singapore.*
Papain (p.2362·3); hamamelis (p.2318·2); sodium pidolate (p.1614·1).
Insect bites; jelly fish stings; minor burns; rashes; scratches; sunburn.

Stoplip *Apotex, Hung.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Stop-Mag *Medikon, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Stopmun *Medikon, Indon.*
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Nausea and vomiting.

Stoppot *Parafarm, Pol.*
Methenamine (p.298·3).
Foot hyperhidrosis.

Stoptoss *Delta, Braz.*
Ammonium chloride (p.1551·3); diphenhydramine hydrochloride (p.577·2).
Cough.

Stoptussin *Ivax, Cz.; Galena, Rus.*
Butamirate citrate (p.1553·1); guaifenesin (p.1561·3).
Cough.

Stoptussin-Fito *Galena, Rus.*
Plantago (p.2379·1); thyme (p.2401·1); wild thyme (p.2415·3).
Cough.

Stopvom *Cadila, India.*
Domperidone (p.1726·2).
Nausea and vomiting.

Storvas *Ranbaxy, Malaysia.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Stovalid N *Cesra, Ger.†.*
Peppermint leaf (p.1761·2); absinthium (p.2244·1); fennel (p.2302·3); chamomile (p.2279·3); aniseed (p.2258·2); caraway (p.2276·3); angelica root (p.2258·1); calamus root (p.2271·3); gentian root (p.2310·3).
Appetite loss; dyspepsia.

Stoxil *Dermatech, Austral.*
Idoxuridine (p.881·2).
Herpes simplex infections of the skin and mucous membranes.

STpase *Cadila, India.*
Streptokinase (p.1402·3).
Thromboembolic disorders.

Strafortin *Strathmann, Ger.†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Osteoporosis.

Strains Cream *Nelson, UK.*
Homoeopathic preparation.

Stranoval *Teofarma, Ital.*
⊗ Betamethasone valerate (p.1519·1); dextran sulfate (p.2293·1).
Peripheral vascular disorders; soft-tissue disorders.

Stratasin *Landsteiner, Mex.*
Indometacin (p.66·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Strath Gouttes contre la toux *Bio-Strath, Switz.*
Thyme (p.2401·1); cowslip (p.2372·2); yeast lysate.
Coughs.

Strath Gouttes pour le coeur *Bio-Strath, Switz.*
Crataegus (p.2289·1); passion flower (p.2363·2); yeast lysate.
Cardiac disorders.

Strath Gouttes pour le foie et la bile *Bio-Strath, Switz.*
Thistle seed; cynara (p.2291·2); mint leaf; yeast lysate.
Digestive system disorders.

Strath Gouttes pour l'estomac *Bio-Strath, Switz.*
Chamomile (p.2279·3); liquorice (p.1740·3); gentian (p.2310·3); yeast lysate.
Digestive-system disorders; loss of appetite.

Strath Gouttes pour les muqueuses *Bio-Strath, Switz.*
Sage (p.2382·3); chamomile (p.2279·3); yeast lysate.
Mouth and throat inflammation.

Strath Gouttes pour le nerfs et contre l'insomnie *Bio-Strath, Switz.*
Valerian (p.2410·1); passion flower (p.2363·2); mint leaf; yeast lysate.
Nervous disorders; sleep disorders.

Strath Gouttes pour les reins et la vessie *Bio-Strath, Switz.*
Bearberry (p.2263·3); taraxacum (p.2395·1); yeast lysate.
Urinary-tract disorders.

Strath Gouttes pour les veines *Bio-Strath, Switz.*
Aesculus (p.2248·2); cowslip (p.2372·2); yeast lysate.
Venous insufficiency.

Strath Gouttes Rhumatisme *Bio-Strath, Switz.*
Salix (p.121·3); cowslip (p.2372·2); yeast lysate.
Musculoskeletal and joint disorders.

Strattera *Lilly, Arg.; Lilly, Austral.; Lilly, Belg.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Thai.; Lilly, UK; Lilly, USA.*
Atomoxetine hydrochloride (p.2151·1).
Attention deficit hyperactivity disorder.

Strediazin c Atapulguita
Note. This name is used for preparations of different composition.
Rowe-Fleming, Venez.†.
Oral suspension: Attapulgite (p.1709·1); pectin (p.2145·2); aluminium hydroxide (p.1706·2).
Diarrhoea.

Rowe-Fleming, Venez.†.
Tablets: Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Strefen *Reckitt Benckiser, Fr.; Crookes Healthcare, UK.*
Flurbiprofen (p.61·2).
Sore throat.

Strength *Potter's, UK.*
Damiana (p.2292·1); kola (p.2416·1); saw palmetto (p.2192·3).
Tonic.

Strepfen *Reckitt Benckiser, Austral.; Reckitt Benckiser, Cz.; Reckitt Benckiser, Hung.; Boots Healthcare, NZ; Reckitt Benckiser, Port.; Boots, Rus.*
Flurbiprofen (p.61·2).
Sore throat.

Strepsils
Note. This name is used for preparations of different composition.
Reckitt & Colman, Austral.; Boots Healthcare, Belg.; Reckitt Benckiser, Canad.; Reckitt Benckiser, Cz.; Boots, Denm.; Boots, Fin.; Boots Healthcare, Fr.; Vianex (Βιανέξ), Gr.; Boots, Hong Kong; Reckitt Benckiser, Hung.; Boots Healthcare, Irl.; Boots, Israel; Reckitt Benckiser, Malaysia; Boots Healthcare, NZ; Boots Healthcare, Neth.; Reckitt Benckiser, Pol.; Boots, Rus.; Boots Healthcare, S.Afr.; Reckitt Benckiser, Singapore; Boots Healthcare, Spain; Novartis, Swed.; Abdi, Turk.; Crookes Healthcare, UK.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Boots, Philipp.
Gargle: Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); chloroxylenol (p.1640·2).
Sore throat.

Boots, Philipp.
Lozenges: Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Strepsils Anesthetic Formula *Reckitt Benckiser, Canad.*
Hexylresorcinol (p.1647·1).
Sore throat.

Strepsils Butter Menthol Capsicum *Boots, Thai.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Mouth and throat disorders.

Strepsils C *Abdi, Turk.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); vitamin C (p.1983·3).
Sore throat.

Strepsils Cherry *Reckitt Benckiser, Canad.†.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1).
Nasal congestion; sore throat.

Strepsils Chesty Cough
Note. This name is used for preparations of different composition.
Boots Healthcare, Austral.†.
Guaifenesin (p.1561·3).
Cough.

Reckitt Benckiser, Malaysia; Boots, Thai.
Ambroxol hydrochloride (p.1550·3).
Cough.

Strepsils Cough *Boots Healthcare, NZ.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Strepsils Cough Lozenge *Reckitt Benckiser, Malaysia.*
Liquorice (p.1740·3); ocimum sanctum; adhatoda; piper longum; ginger (p.1732·3).
Cough; sore throat.

Strepsils Cough Relief *Reckitt & Colman, Austral.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Strepsils Cough Syrup *Reckitt Benckiser, Malaysia.*
Adhatoda; ocimum sanctum; liquorice (p.1740·3); hedychium spicatum; ginger (p.1732·3); piper longum.
Cough; respiratory-tract congestion; sore throat.

Strepsils Dry Cough *Boots Healthcare, Austral.†; Boots Healthcare, NZ; Boots, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Strepsils Dual Action
Boots, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); lidocaine hydrochloride (p.1862·3).
Sore throat.

Boots Healthcare, Irl.
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Sore throat.

Strepsils Echinacea Defence *Boots Healthcare, NZ.*
Ascorbic acid (p.1983·3); echinacea (p.2298·1).
Cold symptoms.

Strepsils Eucalyptus Menthol *Boots Healthcare, S.Afr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1).
Sore throat.

Strepsils Extra *Reckitt & Colman, Austral.; Boots Healthcare, Irl.; Crookes Healthcare, UK.*
Hexylresorcinol (p.1647·1).
Sore throat.

Strepsils Intensive *Boots Healthcare, Irl.; Reckitt Benckiser, Pol.*
Flurbiprofen (p.61·2).
Formerly known as Strepsils DoloIntensive in *Pol.*
Sore throat.

Strepsils Lidocaina *Boots Healthcare, Spain.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine (p.1862·3).
Formerly known as Strepsils con Anestesico.
Mouth and throat disorders.

Strepsils Lidocaine *Boots, Fr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine hydrochloride (p.1862·3).
Mouth disorders; sore throat.

Strepsils + Lidocaine *Boots Healthcare, Belg.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Mouth disorders; sore throat.

Strepsils Menthol *Boots Healthcare, Belg.; Boots, Fin.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1).
Mouth disorders; nasal congestion; sore throat.

Strepsils Menthol a Eucalyptus *Reckitt Benckiser, Cz.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Sore throat.

Strepsils Menthol en Eucalyptus *Boots Healthcare, Neth.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Sore throat.

Strepsils Menthol and Eucalyptus *Reckitt Benckiser, Hung.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Sore throat.

Strepsils with Menthol and Eucalyptus *Boots, Israel.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1); eucalyptus oil(p.2301·2).
Sore throat.

Strepsils Mentollu *Abdi, Turk.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); menthol (p.2340·1).
Sore throat.

Strepsils Miel-Citron *Boots Healthcare, Fr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Strepsils Orange-C *Boots Healthcare, S.Afr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); ascorbic acid (p.1983·3); menthol (p.2340·1).
Sore throat.

Strepsils Pain Relief *Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore.*
Hexylresorcinol (p.1647·1).
Sore throat.

Strepsils Plus
Reckitt & Colman, Austral.; Reckitt Benckiser, Hung.; Boots, Israel; Boots, Rus.; Boots Healthcare, S.Afr.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine hydrochloride (p.1862·3).
Sore throat.

Reckitt Benckiser, Cz.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Sore throat.

Strepsils Plus Anaesthetic *Boots Healthcare, NZ; Boots, Thai.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); lidocaine hydrochloride (p.1862·3).
Sore throat.

Strepsils +Plus Anaesthetic *Boots Healthcare, Irl.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); lidocaine hydrochloride (p.1862·3) or lidocaine (p.1862·3).
Sore throat.

Strepsils Plus Vit C *Boots, Thai.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); vitamin C (p.1983·3).
Sore throat.

Strepsils Sinaasappel en Vitamine C *Boots Healthcare, Neth.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); ascorbic acid (p.1983·3).
Sore throat.

Strepsils Soothing Honey & Lemon *Boots Healthcare, S.Afr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Strepsils Sugar Free *Boots, Thai.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1).
Sore throat.

Strepsils Vit C *Boots Healthcare, Belg.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Mouth disorders; sore throat.

Strepsils Vitamin C
Reckitt Benckiser, Cz.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); sodium ascorbate (p.1984·1).
Sore throat.

Reckitt Benckiser, Hung.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Sore throat.

Boots Healthcare, Irl.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); vitamin C (p.1983·3).
Sore throat.

Strepsils with Vitamin C
Boots, Israel; Boots Healthcare, NZ.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); vitamin C (p.1983·3).
Sore throat.

Crookes Healthcare, UK.
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); sodium ascorbate (p.1984·1).
Sore throat.

Strepsils con Vitamina C *Boots Healthcare, Spain.*
Sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3); dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Sore throat.

Strepsils Vitamine C *Boots Healthcare, Fr.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3); ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Sore throat.

Strepsils Zinc Cold Relief *Reckitt & Colman, Austral.*
Zinc gluconate (p.1999·2); sodium ascorbate (p.1984·1); ascorbic acid (p.1983·3).
Cold symptoms.

Strepsils Zinc Defence *Boots Healthcare, NZ; Crookes Healthcare, UK†.*
Ascorbic acid (p.1983·3); zinc gluconate (p.1999·2).
Cold symptoms.

Strepsilspray Lidocaine *Boots Healthcare, Fr.*
Amylmetacresol (p.1628·3); dichlorobenzyl alcohol (p.1642·1); lidocaine (p.1862·3).
Mouth disorders; sore throat.

Strepsinol *Reckitt Benckiser, Cz.*
Hexylresorcinol (p.1647·1).
Mouth and throat disorders.

Streptase *Aventis Behring, Arg.; Aventis, Austral.; Aventis, Austria; ZLB, Belg.; CSL, Braz.; CSL Behring, Canad.; Sanofi-Aventis, Chile†; CSL, Cz.; ZLB, Denm.; ZLB, Fin.; ZLB, Fr.; ZLB, Ger.; IFET (ΙΦΕΤ), Gr.; ZLB Behring, Hong Kong; CSL, Hung.; Aventis, India; Dexa, Indon.; ZLB, Indon.; Aventis, Irl.†; Aventis Behring, Israel; Aventis, Ital.†; Aventis, Malaysia†; ZLB Behring, Mex.; Healthcare Logistics, NZ; ZLB, Neth.; ZLB, Norw.; Aventis Behring, Pol.; CSL, Port.; Aventis, S.Afr.; ZLB, Spain; ZLB, Swed.; ZLB, Switz.; Aventis, Thai.; Aventis Behring, UK; Aventis, USA; Sanofi-Aventis, Venez.*
Streptokinase (p.1402·3).
Myocardial infarction; thromboembolic disorders.

Strepto *General Drugs, Thai.*
Streptomycin sulfate (p.333·3).
Bacterial infections including tuberculosis.

Strepto-Erbazide *Mac, India†.*
Streptomycin sulfate (p.333·3); methaniazide sodium (p.298·3).
Tuberculosis.

Strepto-Fatol *Fatol, Cz.; Fatol, Ger.*
Streptomycin sulfate (p.333·3).
Bacterial infections including tuberculosis.

Strepto-Hefa *Riemser, Ger.; Wernigerode, Ger.*
Streptomycin sulfate (p.333·3).
Bacterial infections including tuberculosis.

Streptokin *Cristalia, Braz.*
Streptokinase (p.1402·3).
Thromboembolic disorders.

Streptomagma
Note. This name is used for preparations of different composition.
Wyeth, Turk.
Attapulgite (p.1709·1); pectin (p.2145·2).

Wyeth Lederle, Ital.
Oral suspension: Dried aluminium hydroxide (p.1706·2); heavy kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Vargas, Venez.
Oral suspension: Attapulgite (p.1709·1).
Diarrhoea.

Wyeth Lederle, Ital.
Tablets: Activated attapulgite (p.1709·1); pectin (p.2145·2); dried aluminium hydroxide (p.1706·2).
Diarrhoea.

Vargas, Venez.
Tablets: Attapulgite (p.1709·1); pectin (p.2145·2).
Diarrhoea.

Streptonase *Blausiegel, Braz.*
Streptokinase (p.1402·3).
Thromboembolic disorders.

Streptopur *Sanofi Pasteur, Ital.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Streptosil L PMC *Fher, Ital.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Streptosil con Neomicina-Fher *Boehringer Ingelheim, Ital.*
Neomycin sulfate (p.305·1); sulfathiazole (p.343·2).
Bacterial skin infections.

Streptozyme *Wampole, USA.*
Test for streptococcal extracellular antigens in blood, plasma, and serum.

Streptuss *Boots, Philipp.; Boots Healthcare, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Streptuss kriebelhoest *Boots Healthcare, Neth.†.*
Noscapine hydrochloride (p.1566·3).
Cough.

Streptuss vastzittende hoest *Boots Healthcare, Neth.†.*
Bromhexine hydrochloride (p.1552·2).
Cough.

Streptuss-AX *Boots, Thai.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Stresam *Biocodex, Fr.*
Etifoxine hydrochloride (p.996·1).
Anxiety.

Stresnil *Aristo, India.*
Melatonin (p.2338·3); alprazolam (p.960·1).
Sleep disorders.

Stress *Homeocan, Canad.*
Homoeopathic preparation.

Stress 600 *Nion, USA.*
Multivitamin and mineral preparation (p.1922·1).

Stress B Complex *GFR, Canad.; Pharmetics, Canad.; Moore, USA.*
A range of vitamin and mineral preparations (p.1922·1).

Stress Formula *Wampole, Canad.; Nature's Bounty, USA.*
A range of vitamin preparations with or without minerals (p.1922·1).
Nutritional supplement.

Stress Formula B Compound plus Vitamin C *Quest, Canad.†.*
Vitamin B substances and vitamin C (p.1922·1).

Stress Formula c/Zinc *Natural Life, Arg.*
Vitamins; copper; zinc (p.1922·1).

Stress L72 *Homeocan, Canad.*
Homoeopathic preparation.

Stress Plex C *Jamieson, Canad.*
Vitamin B substances, vitamin C, and zinc (p.1922·1).

Stress Tab *Shoppers Drug Mart, Canad.†.*
Vitamin B substances and vitamin C (p.1922·1).

Stress Tab with Iron *Shoppers Drug Mart, Canad.†.*
Multivitamin preparation with iron (p.1922·1).

Stress Tab with Zinc *Shoppers Drug Mart, Canad.†.*
Multivitamin preparation with zinc (p.1922·1).

Stressan *Teuto, Braz.*
Vitamin and mineral preparation (p.1922·1).

Stresscaps *Wyeth, India.*
Vitamin B substances with vitamin C (p.1922·1).

Stressease *Jamieson, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Stressen *Medosan, Ital.*
Amino-acid and vitamin preparation (p.1922·1).
Tonic.

Stressigal *Anfarm, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Stressless
Note. This name is used for preparations of different composition.
Faran, Gr.
Fluoxetine hydrochloride (p.391·2).
Depression.

Dendron, UK.
Lupulus (p.2335·2); skullcap (p.2388·2); valerian (p.2410·1); vervain (p.2413·3).
Stress.

Stressliv *Cifarma, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Stresson *Nutricia, Austral.†; Support, Braz.†; Nutricia, Fin.†; Nutricia, Irl.†; Nutricia, Ital.†; Baxter, NZ; Nutricia, NZ; Nutricia, Turk.*
Preparations for enteral nutrition (p.1922·1).

Stresson Multifibra *Nutricia, Port.†.*
Preparation for enteral nutrition (p.1922·1).

Stresstabs *Wyeth-Whitehall, Arg.; Wyeth Consumer, Braz.; Wyeth Consumer, Canad.; Wyeth Consumer, Hong Kong†; Wyeth Consumer, Mex.; Wyeth, Philipp.; Wyeth Consumer, Port.†; Wyeth Consumer, Thai.; Lederle, USA.*
A range of vitamin preparations with or without minerals (p.1922·1).
Nutritional supplement; tonic.

Stresstabs with Zinc *Lederle, Israel.*
Multivitamin preparation with copper and zinc (p.1922·1).

Stresstabs + Zinc *Lederle, Cz.†.*
Multivitamin and mineral preparation (p.1922·1).

Stresstein *Sandoz Nutrition, USA.*
Preparation for enteral nutrition (p.1922·1).
Stress.

Striacol *Solara, Mex.*
Pravastatin sodium (p.1374·3).
Hypercholesterolaemia.

Striadyne *Genopharm, Fr.*
Adenosine triphosphate, disodium salt (p.2247·3).
Arrhythmias.

Striafissan *Cana, Gr.†.*
Benzyl nicotinate (p.28·1); vitamins A, E, F.
Stretch marks prophylaxis.

Strialisin *MDM, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Striant *CytoChemia, Ger.; Ardana, Irl.; Ardana, Neth.; Ardana, Port.; Ardana, UK; Columbia, USA.*
⊗ Testosterone (p.2129·3).
Male hypogonadism; testosterone deficiency.

Striatal *Tecnifar, Port.*
α-Dihydroergocryptine mesilate (p.364·2).
Parkinsonism.

Striaton *Abbott, Ger.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Stricef *Biofarma, Venez.*
Cefalexin (p.218·2).
Bacterial infections.

Stricort *Biofarma, Venez.*
⊗ Hydrocortisone sodium succinate (p.1536·1).
Corticosteroid.

Strictus *Fada, Arg.†.*
Chlorhexidine (p.1635·2).
Disinfection.

Stri-Dex Antibacterial Cleansing *Sterling, USA.*
Triclosan (p.1665·2).

Stri-Dex Clear *Sterling, USA.*
Salicylic acid (p.1612·2).

Stri-Dex Face Wash *Sterling Health, USA.*
Triclosan (p.1665·2).
Skin cleanser.

Stri-Dex Pads *Glenbrook, USA.*
⊗ Salicylic acid (p.1612·2); alcohol (p.1625·2).
Acne.

Strimox *Biofarma, Venez.*
Amoxicillin (p.202·2).
Bacterial infections.

Stringan *Strallhofer, Austria.*
Polyphloretin phosphate; phenylephrine (p.1568·1).
Nasal congestion.

Strix *Ferrosan, Rus.*
Myrtillus (p.2349·3); betacarotene (p.1930·3).
Eye disorders.

Strixone *Lapreven, Venez.*
Ceftriaxone (p.238·1).
Bacterial infections.

Strizole *Solara, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Strocain
Note. This name is used for preparations of different composition.
Eisai, Hong Kong; Eisai, Singapore; Eisai, Thai.
Oxetacaine (p.1867·2); polymigel.
Gastrointestinal disorders.

Eisai, Jpn.
Oxetacaine (p.1867·2).
Gastrointestinal disorders.

Strocain P *Eisai, Indon.*
Polymigel.
Abdominal pain; bloating; gastric hyperacidity; nausea.

Strodival *Meda, Ger.*
Ouabain (p.1364·2).
Arrhythmias; heart failure.

Strogen *Strathmann, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Strogen Uno *Strathmann, Hung.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Stromag *Guardian, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; peptic ulcer.

Stromba *IFET (ΙΦΕΤ), Gr.; Sanofi Synthelabo, Irl.†.*
⊗ Stanozolol (p.2129·1).
Anabolic; angioedema; cutaneous vasculitis; osteoporosis; Raynaud's syndrome; scleroderma; thromboembolic disorders.

Stromectol *MSD, Austral.; MSD-Chibret, Fr.; Maruho, Jpn; MSD, NZ; MSD, Neth.; Merck, USA.*
Ivermectin (p.145·2).
Lymphatic filariasis; onchocerciasis; scabies; strongyloidiasis.

Stromic *Strathmann, Ger.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Stronazon *Alpharma, UK.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

StrongStart *Savage, USA.*
Multivitamin and mineral preparation (p.1922·1).

Strongus *Franconpharm, Ger.†.*
Garlic (p.2309·2).
Hyperlipidaemia.

Strophantab *Fides, Ger.†.*
Homoeopathic preparation.

Strophanthin-Herztabletten compositum *Cosmochema, Ger.†.*
Homoeopathic preparation.

Strophanthus *Phytomed, Switz.*
Homoeopathic preparation.

Strophanthus comp *Heel, Ger.*
Homoeopathic preparation.

Strotan *Strathmann, Ger.*
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

StroVac *Strathmann, Ger.*
Escherichia coli; *Morganella morganii*; *Proteus mirabilis*; *Klebsiella pneumoniae*; *Enterococcus faecalis* (p.2372·3).
Urinary-tract infections.

Strovite *Everett, USA.*
A range of vitamin and mineral preparations (p.1922·1).

Strox *Dabur, India†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Strubelin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

StructoKabiven *Fresenius Kabi, Austria; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, UK.*
Amino-acids, glucose, and lipid infusion with or without electrolytes (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Structolipid
Fresenius Kabi, Austria; Fresenius Kabi, Fin.; Fresenius Kabi, Hung.; Fresenius Kabi, Ital.; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, UK.
Triglycerides from coconut oil (p.1956·3) and soya oil (p.1965·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition.

Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Gr.; Pharmaco, NZ; Fresenius Kabi, Norw.; Fresenius Kabi, Thai.
Triglycerides (p.1956·3).
Contains egg phospholipids.
Lipid infusion for parenteral nutrition;.

Structolipide *Fresenius Kabi, Fr.*
Triglycerides from coconut oil (p.1956·3) and soya oil (p.1965·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Structum *Pierre Fabre, Arg.; Pierre Fabre, Fr.; Pierre Fabre, Mex.; Pierre Fabre, Rus.; Robapharm, Switz.*
Chondroitin sulfate sodium (p.2280·3).
Degenerative joint diseases; osteoarthritis.

Strumazol *Christiaens, Belg.; Organon, Neth.; Organon, Philipp.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Strumeel *Biotecnoquimica, Venez.*
Spongia tosta; calcium jodatum; fucus vesiculosus.
Homeopathic preparation.

Strumex *Robugen, Ger.†.*
Sodium iodide (p.2169·2).
Iodine-deficiency disorders.

Stryphnasal *Truw, Ger.†.*
⊗ Adrenalone hydrochloride (p.2248·2).
Epistaxis.

Stryphnasal N *Truw, Ger.*
Bismuth subgallate (p.1711·1).
Epistaxis.

Stryphnon *Sanova, Denm.†.*
⊗ Adrenalone hydrochloride (p.2248·2).
Haemorrhage.

St-Tissues *Bode, Ger.*
Isopropyl alcohol (p.1650·3); propyl alcohol (p.1660·2); mecetronium etilsulfate (p.1652·1).
Surface disinfection.

Stuart Formula *J&J-Merck, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Stuart Prenatal *Integrity, USA.*
Multivitamin and mineral preparation with folic acid and iron (p.1922·1).
Dietary supplement in pregnancy.

Stuartnatal 1+1 *Wyeth-Ayerst, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Dietary supplement in pregnancy.

Stuartnatal Plus *Integrity, USA.*
Multivitamin and mineral preparation (p.1922·1).

Stud *Pound International, UK.*
Lidocaine (p.1862·3).
Premature ejaculation.

Stud 100 *Key, Austral.; Trupharm, Israel.*
Lidocaine (p.1862·3).
Premature ejaculation.

Stugerina *Hexal, Braz.†.*
Cinnarizine (p.573·1).
Vertigo.

Stugeron *Janssen-Cilag, Arg.; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Chile; Gedeon Richter, Cz.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Gedeon Richter, Hung.; Ethnor, India; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen, Philipp.; Janssen, Port.; Gedeon Richter, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore†; Esteve, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, UK; Johnson & Johnson MSD Consumer, UK; Janssen-Cilag, Venez.*
Cinnarizine (p.573·1).
Cerebral, peripheral and ocular vascular disorders; migraine; motion sickness; nausea and vomiting; vascular headaches; vertigo; vestibular disorders.

Stugin *Bangkok Lab & Cosmetic, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Stuidruppels *Lennon, S.Afr.*
Valerian (p.2410·1); cassia oil (p.2278·1); nutmeg oil (p.2355·3); rosemary oil (p.2381·3); spike lavender oil (p.2392·1); asafetida (p.2261·3).
Colic; flatulence.

Stullmaton *Stulln, Ger.†.*
Centaury (p.2279·1); arnica (p.2260·2); melissa (p.2339·3); chamomile (p.2279·3); absinthium (p.2244·1); spruce tips; trace elements.
Gastrointestinal disorders.

Stunarone *Janssen-Cilag, Israel.*
Cinnarizine (p.573·1).
Vestibular disorders.

Stuno *Milano, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Stutgeron *Janssen-Cilag, Austria.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

STV *Ivax, Arg.*
Stavudine (p.907·1).
HIV infection.

Stye *Del, USA.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Formerly contained yellow mercuric oxide.
Dry eyes.

stypro *Curasan, Ger.*
⊗ Gelatin (p.1072·1).
Haemostatic.

Styptanon
Organon, Austria.
Estriol sodium succinate (p.2101·1).
Capillary haemorrhage.

Organon, Braz.
Estriol succinate (p.2101·1).
Haemorrhage; thrombocytopenia.

Styptin *German Remedies, India.*
Norethisterone acetate (p.2119·3).
Endometriosis; mastalgia; menstrual disorders; postponement of menstruation.

Stypto-Caine *Pedinol, USA.*
Aluminium chloride (p.1588·2); tetracaine (p.1871·2); hydroxyquinoline sulfate (p.2323·1).
Bleeding in minor wounds.

Styptocid
Note. This name is used for preparations of different composition.
Stadmed, India.
Injection: Carbazochrome (p.1058·2).
Haemorrhagic disorders.

Stadmed, India.
Tablets: Carbazochrome (p.1058·2); menadione sodium bisulfite (p.1995·3); rutoside (p.2305·1); vitamin C (p.1983·3); vitamin D (p.1986·1); calcium hydrogen phosphate (p.1676·1).
Haemorrhagic disorders.

Styptocip *Cipla, India†.*
Carbazochrome (p.1058·2); menadione sodium bisulfite (p.1995·3); ascorbic acid (p.1983·3); rutoside (p.2305·1); calcium hydrogen phosphate (p.1676·1).

Styptysat *Ysatfabrik, Ger.*
Shepherd's purse (p.2386·2).
Haemorrhagic disorders.

Suadian *Intendis, Ital.*
Naftifine hydrochloride (p.542·3).
Fungal skin and nail infections.

Sual *Del Bel, Arg.*
Bladderwrack (p.2384·2).
Dietary supplement.

Sualim *D & M, Chile.*
Soap substitute.

Suavederm *Greenpharma, Braz.*
Zinc (p.1999·1); calcitriol (p.1986·2); vitamin A (p.1971·2); triclosan (p.1665·2).

Suavene *Remexa, Mex.*
⊗ Avena (p.2262·1); urea (p.1620·2); calendula (p.2273·1); chamomile (p.2279·3).
Skin disorders.

Suavigel *D & M, Chile.*
Levomenol (p.2333·3); enoxolone (p.50·1).
Emollient.

Suavisan *Medical, Arg.†.*
Hexylresorcinol (p.1647·1); benzocaine (p.1854·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Suavisan N *Medical, Arg.*
Hexylresorcinol (p.1647·1); neomycin (p.305·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Suavisol *Barnes Hind, Arg.*
Cleansing solution for soft contact lenses (p.1622·2).

Suavit Calcio *Dinafarma, Braz.†.*
Vitamin B ; ergocalciferol; calcium chloride (p.1922·1).
Nutritional supplement.

Suaviter *Quidnovi, Ital.*
Aspartame (p.1930·1).
Sugar substitute.

Suavithiol *Lersan, Arg.*
⊗ Naphazoline hydrochloride (p.1565·2); chlorphenamine maleate (p.571·3).
Eye disorders.

Suavuret *Organon, Spain.*
Ethinylestradiol (p.2101·3); desogestrel (p.2093·2).
Combined oral contraceptive.

Sub Tensin *Altana, Spain.*
Nitrendipine (p.1358·2).
Hypertension.

Subamycin *Dey's, India.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Subcutin N *Ritsert, Ger.*
Benzocaine (p.1854·1).
Mouth and throat disorders.

Subcuvia *Baxter, Austria; Baxter, Belg.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter BioScience, Ger.; Baxter, Gr.; Baxter, Neth.; Baxter, Pol.; Baxter, Port.; Baxter, Swed.; Baxter BioScience, Turk.; Baxter BioScience, UK.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; passive immunisation.

Subdue *Novartis Nutrition, Canad.†; Mead Johnson, NZ†.*
Preparation for enteral nutrition (p.1922·1).
Inflammatory bowel disease; malabsorption disorders.

Subelan *Pharmavita, Chile.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression.

Subgam *BPL, UK.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia.

Subitene *Unifarm, Ital.*
Ibuprofen sodium (p.65·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Subitol *Toprak, Turk.*
Oxolamine phosphate (p.1567·1).
Coughs.

Sublimaze *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Irl.; Janssen-Cilag, NZ; Janssen, Philipp.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK; Janssen, USA.*
⊗ Fentanyl citrate (p.55·3).
Adjunct to general anaesthesia; analgesia in anaesthesia; neuroleptanalgesia; pain; premedication.

Sublivac *Hal, Ger.*
Allergen extracts of pollen (p.2370·2), house dust mites (p.2251·1), and skin (p.2251·1) (p.2250·2).
Allergen immunotherapy.

Sublivac B.E.S.T. *Hal, Neth.†.*
Allergen extracts (glycerolinated) (p.2250·2).
Allergen immunotherapy.

Suboffen *Offenbach, Mex.†.*
Pseudoephedrine (p.1571·2).
Nasal congestion.

Suboxone *Schering-Plough, Cz.; Schering-Plough, Fr.; Schering-Plough, Malaysia; Reckitt Benckiser, NZ; Schering-Plough, Port.; Schering-Plough, UK; Reckitt Benckiser, USA.*
⊗ Buprenorphine hydrochloride (p.29·1).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Opioid withdrawal syndrome.

Subreum *Altana, Austria; Altana, Ger.; OM, Port.†.*
Immunoactive fraction of *Escherichia coli*.
Chronic polyarthritis; rheumatoid arthritis.

Subroxine *Substipharm, Fr.*
Roxithromycin (p.331·1).
Bacterial infections.

Substitol *Mundipharma, Austria.*
⊗ Morphine sulfate (p.86·3).
Substitution therapy in opiate dependence.

Subsyde *Raptakos, Thai.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders; pain.

Subutex *Reckitt Benckiser, Austral.; Aesca, Austria; Schering-Plough, Belg.; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Israel; Essex, Ital.; Schering-Plough, Malaysia†; Schering-Plough, Norw.; Schering-Plough, Port.; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, UK; Reckitt Benckiser, USA.*
⊗ Buprenorphine hydrochloride (p.29·1).
Opioid withdrawal syndrome.

Sucadermil *Edol, Port.*
Salicylic acid (p.1612·2); sulfur (p.1614·1); cade oil (p.1616·1).
Skin disorders.

Sucari *Jean-Marie, Hong Kong.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Sucaryl
Note. This name is used for preparations of different composition.
Abbott, Austral.; Abbott, NZ.
Calcium cyclamate (p.1936·3) or sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute; sweetening agent.

Abbott, Braz.; Abbott, Canad.†.
Sodium cyclamate (p.1936·3).
Sugar substitute.

Rider, Chile†; Abbott, Fr.
Sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute.

Merisant, Arg.
Oral liq: Glucose (p.1945·3); sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute.

Merisant, Arg.
Oral powder: Calcium cyclamate (p.1936·3); saccharin sodium (p.1960·3); sucrose (p.1969·2).
Sugar substitute.

Merisant, Arg.
Tablets: Aspartame (p.1930·1); saccharin (p.1960·2).
Sugar substitute.

Successia *Wyeth Lederle, Fr.†.*
16 Tablets, estradiol (p.2097·2); 12 tablets, estradiol; gestodene (p.2105·2).
Menopausal disorders; osteoporosis.

Succi *Scott-Cassara, Arg.†.*
Suxamethonium (p.1912·1).
Depolarising neuromuscular blocker.

Succicaptal *SERB, Fr.*
Succimer (p.1466·2).
Mercury and lead poisoning.

Succinolin *Amino, Switz.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Succinyl *Taro, Israel; Asta Medica, Malaysia†; Pharmalink, Thai.; Sidefarma, Thai.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Succitrat *Ariston, Braz.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Succnil Colin *Uniao Quimica, Braz.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Succus Cineraria Maritima *Walker Pharmacal, USA.*
Homoeopathic preparation.

Sucedal *Pharma Investi, Chile.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Sucee *Biolab, Thai.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-dependent acne, alopecia, and hirsutism in females; oral contraceptive in women with androgenic symptoms.

Suclear *HPP, Hong Kong.*
Gliclazide (p.440·3).
Diabetes mellitus.

Sucontral *Harras-Curarina, Ger.*
Coutarea latiflora (p.2288·3).
Diabetes mellitus.

Sucrabest *Combustin, Ger.*
Sucralfate (p.1772·2).
Peptic ulcer.

Sucrafen *LSP, Thai.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucrafilm *Sigma, Braz.*
Sucralfate (p.1772·2).
Peptic ulcer.

Sucrager *Nutrifar, Ital.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucraid *Orphan Medical, USA.*
Sacrosidase (p.2382·2).
Sucrase deficiency.

Sucral *Bioprogress, Ital.†; Ranbaxy, Thai.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucralan *Lannacher, Austria; Lannacher, Cz.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucralbene *Ratiopharm, Austria.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucralfin *Sanofi-Aventis, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucralmax *Quesada, Arg.*
Sucralfate (p.1772·2).
Peptic ulcer.

Sucralose *Julphar, UAE.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucralstad *Stada, Austria†.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucralum *Inibsa, Port.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucramal *Sanofi-Aventis, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucramed *S Med, Austria.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucranorm *ACME, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Sucraphil *Philopharm, Ger.†.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Sucrase *Zydus, India.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Sucrate *Lamda (Λαμδα), Gr.†; Lisapharma, Ital.; Lisapharma, Thai.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucrato *Armstrong, Mex.*
Tripotassium dicitratobismuthate (p.1711·2).
Dyspepsia; peptic ulcer.

Sucredulcor *Pierre Fabre Sante, Fr.†.*
Saccharin (p.1960·2).
Sugar substitute.

Sucrets
Note. This name is used for preparations of different composition.
Heritage, Canad.
Dyclonine hydrochloride (p.1861·1).
Sore throat.

SmithKline Beecham, Israel†.
Hexylresorcinol (p.1647·1).
Sore throat.

Sucrets Childrens Formula *Insight, USA.*
Dyclonine hydrochloride (p.1861·1).
Formerly known as Sucrets Childrens Sore Throat.
Sore throat.

Sucrets Children's Formula *SmithKline Beecham, Israel†.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Sucrets Complete *Insight, USA.*
Dyclonine hydrochloride (p.1861·1); menthol (p.2340·1).
Sore throat.

Sucrets Cough Control *Heritage, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Sore throat.

Sucrets Defense Kids Formula *Insight, USA.*
Vitamin C (p.1983·3); zinc (p.1999·1); glutathione (p.1448·1).
Sore throat.

Sucrets DM *Insight, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Sucrets Extra Strength *Heritage, Canad.*
Hexylresorcinol (p.1647·1).
Sore throat.

Sucrets Herbal *Insight, USA.*
Menthol (p.2340·1); pectin (p.2145·2).
Sore throat.

Sucrets for Kids *Heritage, Canad.*
Dyclonine hydrochloride (p.1861·1).

Sucrets Maximum Strength *SmithKline Beecham, Israel†.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Sucrets Maximum Strength Sore Throat *Insight, USA.*
Dyclonine hydrochloride (p.1861·1); menthol (p.2340·1).
Sore throat.

Sucrets Original Formula Sore Throat Original Mint *Insight, USA.*
Hexylresorcinol (p.1647·1).
Sore throat.

Sucrets Original Formula Sore Throat Wild Cherry *Insight, USA.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Sucrets Throat Spray *Insight, USA.*
Dyclonine hydrochloride (p.1861·1).
Sore throat.

Sucrin *Rafa, Israel.*
Sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute.

Sucron *Terramedic, Philipp.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Sucroril *Sofar, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sucrox *Biocontrol, Arg.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Sucryl *Rafarm, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Suczulen mono *Abbott, Ger.†.*
Liquorice (p.1740·3).
Peptic ulcer.

Sudafed *Pfizer Consumer, Austral.; GSK, Fr.; GSK, India; GSK, Indon.; Pfizer Consumer, Irl.; GSK, Mex.; GSK, Pol.; Janssen-Cilag, Port.; GSK, Singapore; GSK, Turk.; Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; rhinitis; sinusitis; upper respiratory-tract congestion.

Sudafed for Children *Pfizer, NZ†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sudafed Cold & Cough
Note. This name is used for preparations of different composition.
Pfizer Consumer, Canad.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Warner-Lambert, USA.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Sudafed Cold & Flu *Pfizer Consumer, Canad.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Sudafed Cold & Sinus *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Nasal congestion.

Sudafed Day/Nightime Relief *Johnson & Johnson, NZ.*
Day tablets, pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night tablets, pseudoephedrine hydrochloride; paracetamol; triprolidine hydrochloride (p.592·3).
Cold and influenza symptoms.

Sudafed Decongestant *Pfizer Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sudafed Ekspektoran *GSK, Turk.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin.
Upper respiratory-tract congestion.

Sudafed Expectorant *GSK, Hong Kong†; GSK, Indon.; GSK, S.Afr.†; GSK, Singapore.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; upper respiratory-tract congestion.

Sudafed Head Cold & Sinus *Pfizer Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms; sinus pain.

Sudafed 12 Hour Relief *Johnson & Johnson, NZ.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sudafed Inhalant Oil *Pfizer Consumer, UK.*
Eucalyptus oil (p.2301·2); menthol (p.2340·1); peppermint oil (p.1761·2).
Nasal congestion.

Sudafed Non-Drying Sinus *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Sudafed PE *Johnson & Johnson, Austral.; Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion; sinus congestion.

Sudafed PE Multi-Symptom Cold & Cough *Pfizer, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Sudafed PE Nighttime Cold *Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Sudafed PE Sinus Allergy & Pain Relief *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Allergic rhinitis; nasal congestion; sinusitis.

Sudafed PE Sinus and Allergy and Pain Relief *Pfizer, NZ.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Hay fever; hypersensitivity reactions; nasal congestion; sinus pain.

Sudafed PE Sinus Day & Night *Johnson & Johnson, Austral.*
Day tablets, phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); night tablets, phenylephrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Sinusitis.

Sudafed PE Sinus Day and Night Relief *Pfizer, NZ.*
Day tablets, phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); night tablets, phenylephrine hydrochloride; paracetamol; chlorphenamine maleate (p.571·3).
Sinus pain.

Sudafed PE Sinus Headache *Pfizer Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Sudafed PE Sinus Pain Relief *Johnson & Johnson, Austral.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Nasal congestion; sinusitis.

Sudafed PE Sinus and Pain Relief *Pfizer, NZ.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Nasal congestion; sinus pain.

Sudafed Plus
Note. This name is used for preparations of different composition.
Pfizer Consumer, UK.
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis.

Wellcome, USA.
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Sudafed Severe Cold *Warner-Lambert, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Sudafed Sinus
Note. This name is used for preparations of different composition.
GSK, S.Afr.
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Warner-Lambert, USA.
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Nasal congestion.

Sudafed Sinus Advance *Pfizer Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Cold symptoms; sinusitis.

Sudafed Sinus & Allergy *Pfizer Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly known as Sudafed Cold & Allergy.

Sudafed Sinus & Anti-inflammatory Pain Relief *Johnson & Johnson, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).
Formerly known as Sudafed Congestion & Sinus Pain Relief.

Sudafed Sinus Day & Night Relief *Johnson & Johnson, Austral.*
Day tablets, pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); night tablets, pseudoephedrine hydrochloride; paracetamol; triprolidine hydrochloride (p.592·3).
Formerly known as Sudafed Daytime/Nightime Relief.

Sudafed Sinus & Nasal Decongestant *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion; nasal congestion.

Sudafed Sinus Pain *GSK, S.Afr.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Sudafed Sinus Pain & Allergy Relief *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; nasal congestion; sinus disorders; sinus pain.

Sudafed Sinus Pain Relief *Johnson & Johnson, Austral.; Johnson & Johnson, NZ.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Nasal congestion; sinus pain and congestion.

Sudagesic *GSK, S.Afr.†.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Sudal *Atley, USA†.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Sudarub *Pfizer Consumer, UK.*
Menthol (p.2340·1); eucalyptus (p.2301·2); camphor (p.2273·2).
Respiratory-tract congestion.

Sudevil Vita *Altana, Arg.*
Cyproheptadine hydrochloride (p.575·1); vitamins.
Reduced appetite.

Sudhinol *Rextar, India.*
Dextropropoxyphene (p.40·1); paracetamol (p.108·1).
Pain.

Sudinet *Aurora, Gr.*
Nimesulide (p.95·3).
Inflammatory disorders.

Sudis *Andromaco, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Sudocrem *Tosara, UK.*
Zinc oxide (p.1621·2); benzyl benzoate (p.2036·1); benzyl cinnamate (p.2264·2); benzyl alcohol (p.1631·3).
Nappy rash; skin irritation; wounds.

Sudomyl *PSM, NZ.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Sudosian *Asian Pharm, Thai.†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; obstructive airways disease; rhinitis.

Suero Antiofidico Polivalente *Biol, Arg.*
Viper venom antiserum (*Crotalus durissus, Bothrops alternatus, Bothrops neuwiedii*) (p.2238·2).
Passive immunisation.

Suero Fisiologico *Rider, Chile†; Braun, Spain; Cinfa, Spain†.*
Sodium chloride (p.1686·1).
Diluent for parenteral administration of drugs; fluid and electrolyte disorders; nasal congestion.

Suero Fisiologico Isoton *Braun, Spain.*
Sodium chloride (p.1686·1).
Fluid and electrolyte disorders.

Suero Glucosado Isotonico *Braun, Spain.*
Glucose (p.1945·3).
Carbohydrate source.

Suero Glucosalino *Braun, Spain.*
Glucose (p.1945·3); sodium chloride (p.1686·1).
Carbohydrate source; fluid and electrolyte disorders.

Suero Potassico Bieffe ME *Bieffe, Spain†.*
Potassium chloride (p.1684·3); sodium chloride (p.1686·1).
Diabetic ketoacidosis; hypokalaemia.

Suero Ringer Braun *Braun, Spain.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte depletion.

Sueroral *Casen Fleet, Spain.*
Glucose; potassium chloride; sodium citrate; sodium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy; vomiting.

Sufed *TO-Chemicals, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Sufenta *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Indon.; Janssen-Cilag, Malaysia†; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Turk.; Taylor, USA†.*
⊗ Sufentanil citrate (p.125·1).
Analgesia in anaesthesia; general anaesthesia; pain; sedative.

Suffisance *Plumbland, Arg.*
Sulfur (p.1614·1); salicylic acid (p.1612·2); resorcinol (p.1612·1).
Acne.

Sufil *Elfar, Spain.*
Mebendazole (p.148·3).
Worm infections.

Sufisal *Silanes, Mex.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Sufortan *Sanfer, Mex.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; rheumatoid arthritis; Wilson's disease.

Sufralem *Solvay, Port.†.*
Anethole trithione (p.2258·1).
Dry eyes; dry mouth.

Sufrexal
Janssen-Cilag, Belg.; Janssen-Cilag, Port.†; Janssen-Cilag, Thai.†.
Ketanserin tartrate (p.1320·2).
Hypertension.

Janssen-Cilag, Mex.
Ketanserin (p.1320·2).
Anal fissures; burns; cervical ulcers; skin ulcers; wounds.

Sufrexal P *Janssen-Cilag, Mex.*
Ketanserin (p.1320·2); benzocaine (p.1854·1).
Anal fissures.

Sugafor *Megahealth, Chile.*
Sucralose (p.1969·1).
Sugar substitute.

Suganril *Sarabhai Piramal, India.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Sugar *Uno, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sugar Bloc *Cantassium Co., UK.*
Gymnema silvestre; chromium orotate (p.2358·3).
Diet aid.

Sugarbil *Novag, Spain.*
Cyclobutyrol sodium (p.2290·3); magnesium sulfate (p.1679·3); sorbitol (p.1965·1).
Constipation; hepatobiliary disorders.

Sugarfree *Cadila, Rus.*
Aspartame (p.1930·1).
Sugar substitute.

Sugarless C *Cenovis, Austral.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C supplement.

Sugast *Selvi, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sugiran *Pensa, Spain.*
Alprostadil alfadex (p.2183·3).
Peripheral vascular disease.

Sugril *Siam Bheasach, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Suguan *Aventis, Ital.†.*
Glibenclamide (p.440·1); phenformin hydrochloride (p.455·3).
Diabetes mellitus.

Suguan M *Sanofi-Aventis, Ital.*
Glibenclamide (p.440·1); metformin hydrochloride (p.453·2).
Diabetes mellitus.

Suifac *Sandoz, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Suiflox *Sandoz, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Suimel *Oriental, Arg.*
Saccharin sodium (p.1960·3); glucose (p.1945·3); cyclamate.
Sugar substitute.

Suipen *Sandoz, Mex.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Sukar-Sin
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Liquid: Sodium cyclamate (p.1936·3); saccharin sodium (p.1960·3).
Sugar substitute.

Laboratorios Chile, Chile.
Tablets: Saccharin sodium (p.1960·3).
Sugar substitute.

Sukcee *Indian Drugs, India.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Adjunct in wounds and infections; scurvy.

Sukepar *Biochimico, Braz.†.*
Liver extract (p.2337·3).
Liver disorders.

Sukolin *Orion, Fin.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Sukontrol *Rafarm, Gr.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Sul 10 *Grin, Mex.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Suladrin *Catarinense, Braz.*
Sulfadiazine (p.336·2).
Bacterial infections.

Sulam
Note. This name is used for preparations of different composition.
Siam Bheasach, Thai.
Injection: Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Bacterial infections.

Siam Bheasach, Thai.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Sulamid *Baldacci, Ital.*
Amisulpride (p.961·1).
Depression.

Sulamp *Galeno, Venez.*
Sultamicillin (p.344·1).
Bacterial infections.

Sular *Bayer, Belg.; Bayhealth, Spain; Horizon, USA.*
Nisoldipine (p.1358·1).
Angina pectoris; hypertension.

Sularyn *Arlex, Mex.*
Sulfadiazine (p.336·2).
Bacterial infections.

Sulazine *Chatfield Laboratories, UK.*
Sulfasalazine (p.1773·2).
Inflammatory bowel disease; rheumatoid arthritis.

Sulbacef *Biochem, India.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Sulbacin
Note. This name is used for preparations of different composition.
Unichem, India.
Injection: Sulbactam (p.335·1); ampicillin (p.204·1).
Bacterial infections.

Unichem, Malaysia.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Unichem, India; Unichem, Malaysia.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Sulbacta *Olan-Kemed, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulbacter *Cellofarm, Braz.†.*
Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Sulbaksit *Tum, Turk.*
Sulbactam (p.335·1); ampicillin (p.204·1).
Bacterial infections.

Sulbamox
Note. This name is used for preparations of different composition.
Farmasa, Braz.
Amoxicillin trihydrate (p.202·2); pivsulbactam (p.335·1).
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Bago, Chile.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); pivsulbactam (p.335·1) or sulbactam sodium (p.335·1).
Bacterial infections.

Sulcain *Shinyaku, Hong Kong†; Shinyaku, Jpn; Shinyaku, Singapore†; Shinyaku, Thai.†.*
Ethyl *p*-piperidinoacetylaminobenzoate (p.1861·2); magcerin.
Gastric pain; gastritis; nausea; pyrosis.

Sulcef *Medochemie, Rus.; Siam Bheasach, Thai.*
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Sulcid
Note.This name is used for preparations of different composition.
Ulagay, Turk.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Ulagay, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Sulcoline *Teva Tuteur, Arg.*
Vinorelbine (p.789·2).
Malignant neoplasms.

Sulcolon *Bernofarm, Indon.*
Sulfasalazine (p.1773·2).
Ankylosing spondylitis; rheumatoid arthritis; seronegative spondylarthritis; ulcerative colitis.

Sulcran *Silesia, Chile.*
Sucralfate (p.1772·2).
Peptic ulcer.

Sulcrate *Axcan, Canad.*
Sucralfate (p.1772·2).
Gastrointestinal haemorrhage; peptic ulcer.

Sulderm *Innoderm, Philipp.*
Sulfur (p.1614·1).
Acne; scabies; seborrhoeic dermatitis.

Suldiamin *Fortbenton, Arg.†.*
Sulfur (p.1614·1).
Seborrhoea.

Suldox *Actavis, Indon.*
Pyrimethamine (p.610·2); sulfadoxine (p.338·1).
Malaria.

Sulen *Farmacologico Milanese, Ital.†.*
Sulindac (p.126·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Suleo-M *SSL, UK†.*
Malathion (p.2046·1).
Pediculosis.

Sulexon *Ranbaxy, Spain.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint and peri-articular disorders; pain.

Sulf-10 *Novartis Ophthalmics, USA.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Sulfa 10 *Meda, Belg.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfa Cloran *Grin, Mex.*
Chloramphenicol (p.239·3); sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfa Hidro *Grin, Mex.*
⊗ Hydrocortisone acetate (p.1535·2); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Sulfac *Ocusoft, USA.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfacet *Oftalmi, Venez.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfacetam *Medical, Spain†.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Sulfacet-R *Dermik, Canad.; Dermik, USA.*
Sulfacetamide sodium (p.335·3); colloidal sulfur (p.1614·1).
Acne; bacterial folliculitis; rosacea; seborrhoeic dermatitis.

Sulfachloramphenicol *Novartis, Gr.*
Chloramphenicol (p.239·3); sulfacetamide sodium (p.335·3).
Eye infections.

Sulfacid *Fischer, Israel.*
Sulfacetamide sodium (p.335·3).
Eye infections.

Sulfacollyre *Sterop, Belg.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfacort *Oftalmi, Venez.*
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1).
Infected eye disorders.

Sulfacyl *Synthesis, Rus.†.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfaderm *Kinder, Braz.*
Sulfadiazine silver (p.337·2).

Sulfadiazina de Plata *Denver, Arg.; Richet, Arg.*
Sulfadiazine silver (p.337·2); vitamin A (p.1971·2); lidocaine (p.1862·3).

Sulfadiazinac *Catarinense, Braz.†.*
Sulfadiazine (p.336·2).
Bacterial infections.

Sulfagrand *Ahimsa, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulfamide *Medical Ophthalmics, USA.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Sulfamylon *Bertek, USA.*
Mafenide acetate (p.296·2).
Burns.

Sulfanicole *Cooper (Κοπερ), Gr.*
Chloramphenicol (p.239·3); sulfacetamide sodium (p.335·3).
Eye infections.

Sulfanoral T *Sidus, Arg.*
Tyrothricin (p.358·2); cresol (p.1641·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Sulfaplat *Lafedar, Arg.*
Sulfadiazine silver (p.337·2); vitamin A palmitate (p.1973·1); lidocaine (p.1862·3).

Sulfarhin *Santa, Turk.*
⊗ Ephedrine hydrochloride (p.1558·2); naphazoline hydrochloride (p.1565·2); menthol (p.2340·1); cineole (p.2282·3); antazoline (p.567·1).
Nasal congestion.

Sulfarinol *Galenus, Pol.*
⊗ Naphazoline nitrate (p.1565·2); sulfathiazole (p.343·2).
Nasal congestion.

Sulfarlem *Eurogenerics, Belg.; Solvay, Belg.†; EG, Fr.; Noristan, S.Afr.†; Solvay, Switz.*
Anethole trithione (p.2258·1).
Biliary-tract disorders; dry eye; dry mouth; dyspepsia; liver disorders; saliva deficiency.

Sulfa-Sedemol *Melisana, Belg.*
Sulfanilamide camsilate (p.343·1); phenol (p.1656·1); borax (p.2268·1); althaea (p.2253·3); poppy capsule (p.1571·1); sodium fluoride (p.1962·2); cloral hydrate (p.979·1).
Mouth and throat disorders.

Sulfasil *Purna, Belg.*
Sulfadiazine silver (p.337·2).
Burns.

Sulfatina *Geyer, Braz.†.*
Atropine sulfate (p.1219·3).

Sulfato Ferroso Composto *Legrand, Braz.*
Ferrous sulfate (p.1939·3); thiamine nitrate (p.1976·2); copper sulfate (p.1935·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Sulfatofer
Note.This name is used for preparations of different composition.
Neo Quimica, Braz.†.
Oral drops; oral liquid: Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Neo Quimica, Braz.†.
Tablets: Ferrous sulfate (p.1939·3); copper sulfate (p.1935·3); thiamine hydrochloride (p.1976·1); riboflavin (p.1977·2).
Anaemias.

Sulfatral *LA, Arg.*
Sulfadiazine (p.336·2).
Bacterial skin infections.

Sulfatral-Cerio *LA, Arg.†.*
Sulfadiazine (p.336·2); cerous nitrate (p.1593·1).
Bacterial skin infections.

Sulfatril *Hua, Thai.*
Sulfadiazine (p.336·2); sulfadimidine (p.338·1); sulfamerazine (p.339·3).
Bacterial infections.

Sulfatrim
Note.This name is used for preparations of different composition.
Sanofi Synthelabo, Turk.
Trimethoprim (p.355·2); sulfadiazine (p.336·2).
Rheumatic fever prophylaxis; toxoplasmosis.

Schein, USA.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Sulfawal *Novag, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulfer Plus *Delta, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Sulfergan Composto *Legrand, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Sulferro *Fontovit, Braz.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Sulferrol *Bunker, Braz.*
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Sulfestrep *Pisa, Mex.*
Streptomycin (p.333·3).
Bacterial infections.

Sulfex *Xepa-Soul Pattinson, Hong Kong.*
Sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulfile
Monsanto, Ital.†.
⊗ Arginine timonacicate (p.1928·3).
Liver disorders.

Angelfarma, Port.
⊗ Arginine tidiacicate (p.1928·3).
Liver disorders.

Sulfinav *LKM, Arg.*
Efavirenz (p.872·3).
HIV infection.

Sulfinona *Basi, Port.†.*
Sulfinpyrazone (p.559·2).

Sulfintestin Neomicina *Normon, Spain.*
Dihydrostreptomycin sulfate (p.266·1); formosulfathiazole (p.278·1); neomycin sulfate (p.305·1).
Gastrointestinal infections.

Sulfitrat *Teuto, Braz.†.*
Sulfiram (p.2050·3).

Sulfoam *Doak, USA.*
Sulfur (p.1614·1).
Formerly contained salicylic acid.
Dandruff; seborrhoea.

Sulfobarina *Rowe-Fleming, Venez.†.*
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Sulfoid Trimetho *Valdecasas, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulfoil *C & M, USA†.*
Soap-free skin cleanser.

Sulfolax *Major, USA.*
Docusate calcium (p.1724·3).
Constipation.

Sulfometh *Hua, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulfona *Zimaia, Port.; Orsade, Spain.*
Dapsone (p.261·2).
Leprosy.

Sulfo-Olbad Cordes *Ichthyol, Ger.†.*
Shale oil; soya oil (p.1965·3).
Bath additive; skin disorders.

Sulfopino *Schoning-Berlin, Ger.†.*
Colloidal sulfur (p.1614·1).
Bath additive; joint disorders; neuralgia; skin disorders.

Sulforcin *Healthpoint, USA.*
Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Sulfort *Arlex, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulfo-Salicyl *Life, Israel.*
Salicylic acid (p.1612·2); sulfur (p.1614·1); Dead Sea minerals.
Psoriasis; seborrhoea.

Sulfo-Schwefelbad *Strallhofer, Austria.*
Sulfur (p.1614·1); sodium hydroxide (p.2389·3).
Musculoskeletal and joint disorders; skin disorders.

Sulfotrim *Gea, Denm.†; Hexal, Neth.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Sulfoxyl *Stiefel, USA.*
Benzoyl peroxide (p.1590·2); sulfur (p.1614·1).
Acne.

Sulfredox *Rubiepharm, Ger.†.*
Aluminium sodium silicate (p.1707·3); sulfur (p.1614·1); calcium carbonate (p.1714·1); sodium ascorbate; trace elements.
Digestive system disorders.

Sulfur Complexe no 12 *Lehning, Fr.*
Homoeopathic preparation.

Sulfur Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Sulfurell *Sanorell, Ger.*
Homoeopathic preparation.

Sulfuretten *Stulln, Ger.†.*
Sulfur (p.1614·1); sodium thiosulfate (p.1466·1).
Dermatoses; lead, arsenic, or mercury poisoning; metabolic disorders.

Sulfuryl
Note.This name is used for preparations of different composition.
Legras, Fr.
Bath additive: Sulfurated aluminium sodium silicate (p.1707·3); precipitated sulfur (p.1614·1).
Arthroses; skin disorders.

Legras, Fr.
Chewable tablets; inhalation tablets: Sulfurated aluminium sodium silicate (p.1707·3).
Respiratory-tract congestion.

Legras, Fr.
Soap: Sulfurated aluminium sodium silicate (p.1707·3); precipitated sulfur (p.1614·1).
Skin disorders.

Sulgan 99
Note.This name is used for preparations of different composition.
Klosterfrau, Austria.
Ointment; suppositories: Ethyl linoleate (p.2308·2); ethyl linolenate; benzocaine (p.1854·1); dichlorobenzyl alcohol (p.1642·1); aluminium chlorohydrate (p.1588·3); hamamelis (p.2318·2); camphor (p.2273·2); menthol (p.2340·1); zinc oxide (p.1621·2).
Anorectal disorders.

Klosterfrau, Austria.
Rectal wipes: Benzocaine (p.1854·1); dichlorobenzyl alcohol (p.1642·1); hamamelis (p.2318·2); chamomile water (p.2279·3); camphor (p.2273·2); menthol (p.2340·1).
Anorectal disorders.

Sulgan N
Note.This name is used for preparations of different composition.
Doetsch, Grether, Switz.
Ointment; suppositories: Ethyl linoleate (p.2308·2); ethyl linolenate; lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3); dichlorobenzyl alcohol (p.1642·1); camphor (p.2273·2); menthol (p.2340·1); triclosan (p.1665·2).
Anorectal disorders.

Doetsch, Grether, Switz.
Wipes: Dichlorobenzyl alcohol (p.1642·1); lidocaine hydrochloride (p.1862·3); camphor (p.2273·2); menthol (p.2340·1).
Anorectal disorders.

Sulidamor *Damor, Ital.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Sulide *TAD, Ital.*
Nimesulide (p.95·3).
Pain.

Sulidek *Wermar, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Sulidin *Embil, Turk.*
Nimesulide (p.95·3).
Musculoskeletal and joint pain.

Sulidor *Quiraus, Port.*
Nimesulide (p.95·3).
Peri-articular disorders.

Sulifur *Ivax, Mex.*
Sulindac (p.126·3).
Pain; rheumatism.

Sulimed *Decafarma, Port.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Sulindal *Chibret, Spain.*
Sulindac (p.126·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Sulix *Rider, Chile.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Sulkine *Zambon, Spain†.*
Levosulpiride (p.1028·3).
Dyspepsia.

Sullivan *Medhaus, Philipp.*
Amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Sulmasque *C & M, USA.*
Sulfur (p.1614·1).
Acne.

Sulmetin *Sanofi Synthelabo, Spain†.*
Magnesium sulfate (p.1679·3).
Procaine hydrochloride (p.1869·1) is included in the intramuscular injection to alleviate the pain of injection.
Convulsions; tachycardia; vertigo.

Sulmetin Papaver *Sanofi-Aventis, Spain.*
Atropine methobromide (p.1219·2); magnesium sulfate (p.1679·3); papaverine hydrochloride (p.2191·3); propyphenazone (p.119·3).
Pain; smooth muscle spasm.

Sulmetin Papaverina
Note.This name is used for preparations of different composition.
Sanofi Synthelabo, Spain†.
Injection: Magnesium sulfate (p.1679·3); papaverine hydrochloride (p.2191·3).
Procaine hydrochloride (p.1869·1) is included in the intramuscular injection to alleviate the pain of injection.
Convulsions; hypertension; smooth muscle spasm; tachycardia.

Sanofi Synthelabo, Spain†.
Tablets: Atropine methobromide (p.1219·2); magnesium gluconate (p.1679·2); papaverine hydrochloride (p.2191·3); propyphenazone (p.119·3).
Pain due to smooth muscle spasm.

Sulmycin *Aesca, Austria; Essex, Ger.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Sulmycin mit Celestan-V *Essex, Ger.*
⊗ Gentamicin sulfate (p.282·1); betamethasone valerate (p.1519·1).
Infected skin disorders.

Sulmyn *Sons, Mex.*
Kanamycin (p.291·3).
Bacterial infections.

Sulned *Pizzard, Mex.*
Neomycin (p.305·1); polymyxin B (p.318·2); gramicidin (p.286·1).
Bacterial eye infections.

Sulnil *Allergan, Braz.*
Chloramphenicol (p.239·3); sulfacetamide sodium (p.335·3).
Bacterial eye infections.

Sulobil *Atlantis, Mex.*
Chenodeoxycholic acid (p.2280·1).
Cholesterol gallstones.

Sulocten *Microsules, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Sulodil *Viofar, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Sulorane *Baxter, Israel.*
Desflurane (p.1781·3).
General anaesthesia.

Sulotil *Recalcine, Chile.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Sulp *Hexal, Ger.†.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vestibular disorders.

Sulpan *Sanofi-Aventis, Braz.*
Sulpiride (p.1028·3); bromazepam (p.964·3).
Depression.

Sulperason *Pfizer, Rus.*
Cefoperazone sodium (p.227·1); sulbactam sodium (p.335·1).
Bacterial infections.

Sulperazon
Note.This name is used for preparations of different composition.
Pfizer, Arg.†; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Malaysia; Pfizer, Pol.; Pfizer, Thai.; Pfizer, Venez.
Sulbactam sodium (p.335·1); cefoperazone sodium (p.227·1).
Bacterial infections.

Pfizer, Chile; Pfizer, Turk.
Sulbactam (p.335·1); cefoperazone (p.227·2).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Pfizer, Jpn†.
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Sulperazone *Pfizer, Philipp.*
Cefoperazone sodium (p.227·1); sulbactam sodium (p.335·1).
Bacterial infections.

Sulphargin *Tallinn, Rus.*
Sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Sulpho-Lac *Doak, USA.*
Sulfur (p.1614·1); zinc sulfate (p.1999·2).
Acne.

Sulpilan *Labomed, Chile.*
Sulpiride (p.1028·3).
Depression; psychoses.

Sulpir *Sanofi Synthelabo, Turk.*
Sulpiride (p.1028·3).
Schizophrenia.

Sulpirol *Hexal, Cz.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vertigo.

Sulpitil *Pfizer, UK†.*
Sulpiride (p.1028·3).
Schizophrenia.

Sulpivert *Hennig, Ger.*
Sulpiride (p.1028·3).
Depression; schizophrenia; vestibular disorders.

Sulpor *Rosemont, UK.*
Sulpiride (p.1028·3).
Schizophrenia.

Sulprim *Prafa, Indon.; Berman, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulquipen *Bohm, Spain.*
Cefalexin (p.218·2).
Bacterial infections.

Sultamat *Atabay, Turk.*
Sultamicillin (p.344·1).
Bacterial infections.

Sultamicina *Spefar, Venez.†.*
Sultamicillin (p.344·1).
Bacterial infections.

Sultamilan *Alian, Venez.*
Sultamicillin (p.344·1).
Bacterial infections.

Sultanol *GSK, Austria; GSK, Ger.; Schwarz, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Sultasid
Note.This name is used for preparations of different composition.
Toprak, Turk.
Injection: Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Toprak, Turk.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Sultasin *Synthesis, Rus.*
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Sultax *Ipca, India.*
Cefotaxime sodium (p.228·1); sulbactam sodium (p.335·1).
Bacterial infections.

Sulterline *TP, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Sultibac *Biofarma, Turk.*
Sultamicillin (p.344·1).
Bacterial infections.

Sultiprim *Keyerson, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sulton *Geymonat, Ital.*
Calcium folinate (p.1943·3).
Anaemias; antidote to folic acid antagonists; reduction of aminopterin and methotrexate toxicity.

Sultrimmix *Bernofarm, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sultrin *Janssen-Cilag, Belg.†; Janssen-Cilag, Gr.; Janssen-Cilag, Irl.†; Cilag, Philipp.; Janssen-Cilag, Port.†; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK†; Ortho McNeil, USA.*
Sulfabenzamide (p.335·2); sulfacetamide (p.335·3); sulfathiazole (p.343·2).
Bacterial vaginitis and cervicitis.

Sultrona *Cryopharma, Mex.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Sultroquin *Farcoral, Mex.†.*
Clioquinol (p.254·1); homatropine (p.1881·2); phthalylsulfathiazole (p.315·1).
Gastrointestinal disorders.

Sulvi *Grin, Mex.*
⊗ Naphazoline hydrochloride (p.1565·2); sulfacetamide sodium (p.335·3).
Infected eye disorders.

Suma-B *Chinoin, Mex.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; neuritis; neuropathy; vitamin B deficiency.

Sumacal *Sherwood, USA.*
Glucose polymers (p.1922·1).
Carbohydrate source.

Sumaclina *Alodial, Port.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Sumagesic *Medifarma, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Sumagran *Pacific, NZ.*
Sumatriptan succinate (p.625·2).
Migraine.

Sumal *Purissimus, Arg.*
⊗ Bendroflumethiazide (p.1224·1); homatropine methylbromide (p.1881·3); dipyrone (p.49·2).
Premenstrual syndrome.

Sumamed *Pliva, Cz.; Pliva, Hung.; Pliva Krakow, Pol.; Pliva, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Sumamigren *Polpharma, Cz.; Polpharma, Pol.*
Sumatriptan succinate (p.625·2).
Migraine.

Sumapen
Note.This name is used for preparations of different composition.
Medichem, Philipp.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Great Eastern, Thai.; Westmont, Thai.
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Sumario *Rafarm, Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Sumatab *Alphapharm, Austral.*
Sumatriptan succinate (p.625·2).
Migraine.

Sumatran *Fako, Turk.*
Sumatriptan (p.625·2).
Cluster headache; migraine.

Sumax *Libbs, Braz.*
Sumatriptan succinate (p.625·2).
Migraine.

Sumedium *Milano, Thai.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Sumenan *Spedrog, Arg.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Sumetrolim *Egis, Cz.; EGIS, Hung.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Sumial *Icaro, Spain.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; arrhythmias; gastrointestinal haemorrhage; hypertension; hyperthyroidism; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma; tremor.

Sumidin *Pharmaland, Thai.*
Serrapeptase (p.2385·3).
Inflammation; oedema; respiratory-tract congestion.

Sumiferon *Sumitomo, Jpn.*
Interferon alfa (p.885·1).
Hepatitis B and C; malignant neoplasms; myelopathy; subacute sclerosing panencephalitis.

Sumigra
Sandoz, Cz.
Sumatriptan succinate (p.625·2).
Migraine.

Sandoz, Pol.
Sumatriptan (p.625·2).
Migraine.

Sumigrene *Sigma-Tau, Ital.†.*
Sumatriptan succinate (p.625·2).
Cluster headache; migraine.

Suminat *Sun, India.*
Sumatriptan succinate (p.625·2).
Migraine.

Sumir *Craveri, Arg.†.*
Azithromycin (p.207·1).
Bacterial infections.

Sumitrex *Bajamed, Mex.*
Sumatriptan (p.625·2).
Migraine.

Summavac *Cassara, Arg.*
A range of bacterial and fungal allergen extracts (p.2250·2).
Hypersensitivity reactions.

Summavit *Bioprogress, Ital.†.*
Multivitamin preparation (p.1922·1).

Summavit ME *Armstrong, Arg.†.*
Vitamin and mineral preparation (p.1922·1).

Summers Eve *Fleet, Singapore†; De Witt, UK; Fleet, USA.*
A range of feminine hygiene preparations.

Summers Eve Anti-Itch *Fleet, USA.*
Pramocaine hydrochloride (p.1868·1); glycerol (p.2314·2).
Vaginal itching.

Summers Eve Disposable
Note.This name is used for preparations of different composition.
Fleet, Austral.†.
Fresh Scent: Phenol (p.1656·1).
Vaginal cleanser.

Fleet, USA.
Solution: Vinegar (p.2244·2).
Vaginal disorders.

Fleet, Austral.
Vinegar and Water: Vinegar (p.2244·2).
Vaginal cleanser.

Summers Eve Feminine
Note.This name is used for preparations of different composition.
Fleet, Austral.
Bath additive; topical liquid; topical spray: Soap substitute.
Vaginal hygiene.

Fleet, Austral.
Topical powder: Octoxinol 9 (p.1917·3); benzethonium chloride (p.1630·1).
Intertrigo; vaginal irritation.

Summer's Eve Hierbas *Rider, Chile†.*
Citric acid (p.2284·1); sodium benzoate (p.1630·2); sodium citrate (p.1673·3); octoxinol 9 (p.1917·3).
Vaginal hygiene.

Summers Eve Medicated *Fleet, Malaysia; Fleet, USA.*
Povidone-iodine (p.1659·2).
Vaginal disorders.

Summers Eve Post-Menstrual *Fleet, USA.*
Sodium laurilsulfate (p.2138·3); monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3); sodium chloride (p.1686·1); edetic acid (p.1445·1).
Vaginal disorders.

Summer's Eve Vinagre y Agua *Rider, Chile†.*
Vinegar (p.2244·2); benzoic acid (p.1630·2).
Vaginal hygiene.

Sumo *Interbelle, Arg.*
Phenothrin (p.2048·3).
Pediculosis.

Sumo Full Contact *Elea, Arg.*
Cyclopentaxyloxane (p.2032·1); dimeticone (p.2032·1).
Pediculosis.

Sumopen *Cofasa, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sumoxil *Medichem, Philipp.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Sumycin *Apothecon, USA.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Sun Defense Lip Block *Norman, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Defense Sunblock *Norman, Canad.*
SPF 25: Octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Defense Sunscreen *Norman, Canad.†.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Kids *Avon, Canad.*
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1).
Formerly contained avobenzone, octinoxate, octisalate, and oxybenzone.
Sunscreen.

Sun Lip Balm *Avon, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Management Extensive Protection *Kay, Canad.*
Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Management Lip Protection *Kay, Canad.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Management Sensible Protection *Kay, Canad.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Pacer
Note.This name is used for preparations of different composition.
Amway, Canad.†.
SPF 15; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Amway, Canad.†.
SPF 30: Octocrilene (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sun Sunblock
Note.This name is used for preparations of different composition.
Avon, Canad.†.
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Avon, Canad.†.
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sunazol *Sunward, Malaysia†.*
Ketoconazole (p.539·1).
Fungal infections.

Sun-Benz *Sun, Canad.†.*
Benzydamine hydrochloride (p.27·3).
Oropharyngeal mucositis; sore throat.

Sunblock for Body *Estee Lauder, Canad.†.*
SPF 15; SPF 25: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Sunblock for Face *Estee Lauder, Canad.†.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Sunblock Lotion
Note.This name is used for preparations of different composition.
Tanning Research, Canad.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Tanning Research, Canad.
SPF 30: Homosalate (p.1598·1); octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Suncodin *Aventis, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); phenyltoloxamine citrate (p.588·1); caffeine (p.1116·3).
Fever; pain; sinus congestion.

Sundir *Sons, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Sundown
Note.This name is used for preparations of different composition.
Johnson & Johnson, Austral.†.
SPF 15; SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnson & Johnson, Braz.
SPF 15; SPF 20; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnson & Johnson, USA.
SPF 15; SPF 30; SPF 8: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Johnson & Johnson, Braz.
SPF 30: Bemotrizinol (p.1590·2); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Johnson & Johnson, Braz.
SPF 50: Bemotrizinol (p.1590·2); titanium dioxide (p.1617·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Formerly contained octinoxate, meradimate, oxybenzone, octocrilene, and titanium dioxide.
Sunscreen.

Sundown Active *Johnson & Johnson, Austral.†.*
SPF 15: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Sundown Baby *Johnson & Johnson, Braz.*
SPF 30: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Sundown Cabelos *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Sundown Clear Gel *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Sundown C/Repelente *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Sundown Facial *Johnson & Johnson, Braz.*
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Sundown Gold
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.
SPF 2; SPF 4: Oxybenzone (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Johnson & Johnson, Braz.
SPF 6: Oxybenzone (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Sundown Kids *Johnson & Johnson, Braz.*
SPF 15; SPF 30: Bemotrizinol (p.1590·2); octinoxate (p.1608·2); octocrilene (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Sundown Kids Colour
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.
SPF 15: Bemotrizinol (p.1590·2); octocrilene (p.1608·3); octinoxate (p.1608·2).
Sunscreen.

Johnson & Johnson, Braz.
SPF 30: Bemotrizinol (p.1590·2); octocrilene (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Sundown Labial *Johnson & Johnson, Braz.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sundown Mousse *Johnson & Johnson, Braz.*
SPF 25: Octocrilene (p.1608·3); octinoxate (p.1608·2); bemotrizinol (p.1590·2).
Sunscreen.

Sundown Pos-Sol *Johnson & Johnson, Braz.*
Moisturiser.

Sundown Sport
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Johnson & Johnson, USA.
SPF 15: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Sundown Spray
Note. This name is used for preparations of different composition.
Johnson & Johnson, Braz.
SPF 15: Octinoxate (p.1608·2); octocrilene (p.1608·3); oxybenzone (p.1608·3).
Sunscreen.

Johnson & Johnson, Braz.
SPF 30: Bemotrizinol (p.1590·2); octinoxate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

SuNerven *Lane, UK.*
Motherwort (p.2347·3); vervain (p.2413·3); valerian (p.2410·1); passion flower (p.2363·2).
Stresses and strains.

Sun-Glizide *Sunward, Hong Kong; Sunward, Malaysia.*
Gliclazide (p.440·3).
Diabetes mellitus.

Sunglucon *Sunward, Hong Kong.*
Glipizide (p.441·3).
Diabetes mellitus.

Sunicaine *Unipharm, Mex.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Suniderma *Galderma, Spain.*
⊗ Hydrocortisone aceponate (p.1536·2).
Skin disorders.

Suniton *Sunward, Malaysia.*
Orphenadrine citrate (p.812·1); paracetamol (p.108·1).
Musculoskeletal pain; tension headache.

Sunkist *Ciba, USA.*
Ascorbic acid (p.1983·3).

Sunmax 30 *Stiefel, Braz.*
Oxybenzone (p.1608·3); homosalate (p.1598·1); octinoxate (p.1608·2); enzacamene (p.1597·1).
Sunscreen.

Sunmax 60 *Stiefel, Braz.*
Avobenzone (p.1589·3); titanium dioxide (p.1617·3); octil triazone (p.1608·1); homosalate (p.1598·1).
Sunscreen.

Sunmax Acqua
Note. This name is used for preparations of different composition.
Stiefel, Braz.
Gel SPF 20: Ensulizole (p.1597·1); sulisobenzone (p.1614·3).
Sunscreen.

Stiefel, Braz.
Spray SPF 20: Avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1).
Sunscreen.

Sunmax Autobronzeador *Stiefel, Braz.*
Dihydroxyacetone (p.1594·1); erythrulose (p.1597·1).
Artificial suntan.

Sunmax Junior *Stiefel, Braz.*
SPF 35: Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Sunnie *Green Turtle Bay Vitamin Co., USA.*
Vitamins; minerals; glutamine; St John's wort; betaine; ginkgo biloba (p.1922·1).
Tonic.

Sun-Off *Mediphar, Venez.*
Ensulizole triethanolamine.
Sunscreen.

Sun-Off Baby *Mediphar, Venez.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Sunolut *Sunward, Malaysia.*
Norethisterone (p.2119·3).
Dysfunctional uterine bleeding; endometriosis; menopausal disorders; menstrual disorders.

Sunpla *SK, Kor.*
Eptaplatin (p.716·3).
Gastric cancer.

Sunpraz *Sun, Rus.*
Pantoprazole sodium (p.1760·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sunprox *Sunward, Malaysia.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Sunrythm *Asubio, Jpn.*
Pilsicainide hydrochloride (p.1371·2).
Arrhythmias.

Sunscreen Lotion
Note. This name is used for preparations of different composition.
Norwood, Canad.
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Scott, Canad.†.
SPF 15: Oxybenzone (p.1608·3); octinoxate (p.1608·2); octisalate (p.1608·2).
Sunscreen.

Therapex, Canad.
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Norwood, Canad.†.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Therapex, Canad.
SPF 30: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Norwood, Canad.
SPF 45: Octinoxate (p.1608·2); octocrilene (p.1608·3); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sunscreen Lotion Ecran
Note. This name is used for preparations of different composition.
Prodemdis, Canad.
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Prodemdis, Canad.
SPF 30: Avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2); ensulizole (p.1597·1).
Sunscreen.

Sunseekers
Note. This name is used for preparations of different composition.
Avon, Canad.†.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Avon, Canad.†.
SPF 30; SPF 6: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sunsense
Note. This name is used for preparations of different composition.
Ego, Malaysia†.
Cream SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Ego, Singapore†.
Cream SPF 30+; Face Milk SPF 30+; Ultra SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Ego, Hong Kong†.
Cream SPF 50: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Ego, Malaysia†.
Cream SPF 50; face milk SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Ego, Hong Kong†.
Face Milk SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Ego, Hong Kong.
Gel SPF 30+: Amiloxate (p.1589·1); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Ego, NZ†.
SPF 15+: Titanium dioxide (p.1617·3); oxybenzone (p.1608·3); avobenzone (p.1589·3); ethylhexyl cinnamate.
Sunscreen.

Ego, Austral.
Topical gel SPF 30: Octinoxate (p.1608·2); amiloxate (p.1589·1); oxybenzone (p.1608·3); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Sunsense Aftersun *Ego, Austral.*
Emollient.
Dry skin.

Sunsense Anti-Ageing *Ego, Singapore.*
Octinoxate (p.1608·2); bemotrizinol (p.1590·2); bisoctrizole (p.1591·2); glycolic acid (p.1598·1).
Sunscreen.

Sunsense Clear *Ego, Singapore.*
SPF 35+: Amiloxate (p.1589·1); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Sunsense Clear Mist
Ego, Hong Kong.
Avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Ego, Malaysia.
SPF 35+: Avobenzone (p.1589·3); enzacamene (p.1597·1); octil triazone (p.1608·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Sunsense Daily Face
Note. This name is used for preparations of different composition.
Ego, Austral.
SPF 30+: Titanium dioxide (p.1617·3); avobenzone (p.1589·3); oxybenzone (p.1608·3); octil triazone (p.1608·1).
Formerly contained octinoxate, titanium dioxide, oxybenzone, and enzacamene.
Sunscreen.

Ego, Singapore†.
SPF 30+: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); enzacamene (p.1597·1).
Sunscreen.

Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
SPF 100+: Titanium dioxide (p.1617·3); avobenzone (p.1589·3); octil triazone (p.1608·1); oxybenzone (p.1608·3).
Formerly contained titanium dioxide, enzacamene, and octinoxate.
Sunscreen.

Sunsense Lip Balm
Note. This name is used for preparations of different composition.
Ego, Austral.
SPF 30+: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Ego, Hong Kong†; Ego, Malaysia†; Ego, Singapore†.
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3).
Sunscreen.

Sunsense Low Irritant
Ego, Singapore†.
SPF 20: Titanium dioxide (p.1617·3).
Sunscreen.

Ego, Austral.
SPF 30: Titanium dioxide (p.1617·3).
Sunscreen.

Ego, Hong Kong†; Ego, Malaysia†.
SPF 30+: Titanium dioxide (p.1617·3).
Sunscreen.

Sunsense Milk *Ego, Singapore.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1).
Sunscreen.

Sunsense Milk Mist *Ego, Hong Kong; Ego, Malaysia.*
SPF 30+: Enzacamene (p.1597·1); avobenzone (p.1589·3); octinoxate (p.1608·2).
Sunscreen.

Sunsense Sport
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, Singapore†.
Cream SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); enzacamene (p.1597·1).
Sunscreen.

Ego, Hong Kong†; Ego, Malaysia†.
Cream SPF 100+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); enzacamene (p.1597·1).
Sunscreen.

Ego, Singapore.
Gel SPF30+: Oxybenzone (p.1608·3); octinoxate (p.1608·2); avobenzone (p.1589·3); enzacamene (p.1597·1); amiloxate (p.1589·1).
Sunscreen.

Ego, Malaysia.
Gel SPF 30+: Amiloxate (p.1589·1); avobenzone (p.1589·3); enzacamene (p.1597·1); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Ego, Hong Kong†; Ego, Malaysia†; Ego, Singapore†.
Milk SPF 30+: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); enzacamene (p.1597·1); oxybenzone (p.1608·3); avobenzone (p.1589·3); ensulizole (p.1597·1).
Sunscreen.

Ego, Austral.
Topical milk SPF 30: Titanium dioxide (p.1617·3); octinoxate (p.1608·2); enzacamene (p.1597·1); ensulizole (p.1597·1); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Sunsense Sport Gel *Ego, Malaysia.*
SPF 30+: Amiloxate (p.1589·1); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); oxybenzone (p.1608·3).
Sunscreen.

Sunsense Sun Sensitive *Ego, Hong Kong.*
SPF 60: Titanium dioxide (p.1617·3).
Sunscreen.

Sunsense and Sunsense Ultra *Ego, Austral.*
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Sunsense Sunsenstive *Ego, Malaysia.*
SPF 60: Titanium dioxide (p.1617·3).
Sunscreen.

Sunsense Toddler Milk
Note. This name is used for preparations of different composition.
Ego, Austral.; Ego, Hong Kong.
SPF 30+: Oxybenzone (p.1608·3); titanium dioxide (p.1617·3); avobenzone (p.1589·3); octil triazone (p.1608·1).
Sunscreen.

Ego, Malaysia†.
SPF 30+: Avobenzone (p.1589·3); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Formerly contained amiloxate and octinoxate.
Sunscreen.

Ego, Singapore†.
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); amiloxate (p.1589·1).
Sunscreen.

Ego, Malaysia; Ego, Singapore.
SPF 50: Titanium dioxide (p.1617·3); oxybenzone (p.1608·3); avobenzone (p.1589·3); octil triazone (p.1608·1).
Sunscreen.

Sunsense Ultra
Note. This name is used for preparations of different composition.
Crawford, UK.
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3).
Sunscreen.

Ego, Hong Kong; Ego, Malaysia; Ego, Singapore.
SPF 100+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); enzacamene (p.1597·1); avobenzone (p.1589·3); ensulizole (p.1597·1).
Sunscreen.

Sunspot *Sunspot, Austral.*
Salicylic acid (p.1612·2).
Actinic keratoses; hard skin.

Sunstop
Note. This name is used for preparations of different composition.
UAS, Philipp.
SPF 16: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

UAS, Philipp.
SPF 30+: Zinc oxide (p.1621·2); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Suntrim *Macrophar, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Sunvasc *Sunward, Malaysia.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Sunvite Multiple *Sundown, Venez.†.*
Vitamin and mineral preparation (p.1922·1).

Sunya *Stragen, Cz.; Stragen, UK.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Suopinchon *Siu Guan, Malaysia.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Supa Biocal Vitahealth *Herbal Revival, Malaysia†; Swiss Bio, Malaysia†.*
Calcium citrate (p.1675·3); microcrystalline hydroxyapatite (p.2323·1).
Dietary supplement.

Supa C *Vitaplex, Austral.†.*
Calcium ascorbate (p.1984·1).
Vitamin C deficiency.

Supa Formula 3 Plus *Scherer, Malaysia†; Swiss Bio, Malaysia†.*
Multivitamin and mineral preparation with choline, inositol, linoleic acid, and methionine (p.1922·1).
Dietary supplement.

Supa-Boost *Vitaplex, Austral.†.*
Multivitamin and mineral preparation with rutoside (p.1922·1).

Supacef *GSK, India.*
Cefuroxime (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Supadol *Whitehall, Fr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Supartz *Smith & Nephew, UK†; Smith & Nephew, USA.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis of the knee; synovial fluid replacement.

Super Antioxidant Plus *Lifeplan, UK.*
Vitamins; minerals; fish oil; starflower oil; garlic oil (p.1922·1).
Antoxidant preparation.

Super Anti-Oxydant Formula *Equilibre Attitude, Fr.†.*
Nutritional supplement (p.1922·1).

Super B *Bullivants, Austral.*
Vitamin B substances with ascorbic acid (p.1922·1).
Dietary supplement.

Super B1 *Christo, Hong Kong.*
Thiamine hydrochloride (p.1976·1).
Vitamin B supplement.

Super B Complex *Sisu, Canad.*
Vitamin B substances (p.1922·1).
Nutritional supplement.

Super B Plus *Vitaglow, Austral.†.*
Vitamin B substances; vitamin C; lysine hydrochloride; magnesium oxide; potassium sulfate; zinc amino acid chelate (p.1922·1).
Dietary supplement; tonic.

Super B Stress *Roche Consumer, Austral.†.*
Vitamin B substances; vitamin C; minerals; passion flower (p.1922·1).
Dietary supplement.

Super Banish *Smith & Nephew, Austral.†.*
Silver nitrate (p.2387·2); ethylene thiourea.
Ostomy deodorant.

Super Beta Prostate *Young Again Products, USA.*
Sitosterol (p.1373·2); minerals (p.1922·1).
Dietary supplement.

Super C *Quest, Canad.*
Ascorbic acid (p.1983·3).

Super Cal-C Bio *Eagle, Austral.*
Calcium ascorbate (p.1984·1); bioflavonoids (p.2304·1).
Vitamin C deficiency.

Super City Block *Clinique, Canad.*
SPF 25: Titanium dioxide (p.1617·3).
Sunscreen.

Super Corega *GSK, Braz.*
Denture fixative.

Super Cough *Medipharma, Hong Kong†.*
⊗ Ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Cold and influenza symptoms.

Super Cromer Orto *Normon, Spain.*
Merbromin (p.1652·1).
Wound disinfection.

Super D Perles *Roberts, USA.*
Vitamins A and D (p.1922·1).

Super Daily *Lee-Adams, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Super Energex Plus *Sante Naturelle, Canad.*
Vitamin B substances, minerals, kola, and liver extract (p.1922·1).

Super 28 Formula *Reese, USA.*
Multivitamin, mineral, and herbal preparation (p.1922·1).

Super GLA *Cantassium Co., UK.*
Gamma linolenic acid (from vegetable oils) (p.2308·2).

Super Hi Potency *Nion, USA.*
Multivitamin and mineral preparation (p.1922·1).

Super Ivy Dry *Ivy Corp, USA.*
Zinc acetate (p.1999·1); benzyl alcohol (p.1631·3).
Minor skin irritation.

Super Kids *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Super Mega B+C *Quest, UK.*
Vitamin B substances; vitamin C (p.1922·1).

Super Once A Day *Quest, Canad.; Quest, UK.*
Multivitamin and mineral preparation (p.1922·1).

Super Quints *Freeda, USA.*
Vitamin B substances (p.1922·1).

Super Soluble Duocal *Nutricia, Ital.*
Low-electrolyte, protein-free carbohydrate preparation for special diets (p.1922·1).

Super Soluble Maxipro HBV *Scientific Hospital Supplies, Austral.†.*
Preparation for enteral nutrition (p.1922·1).
Hypoproteinaemia.

Super Stress Mega B plus Vitamin C *Quest, Canad.*
Vitamin B substances and vitamin C (p.1922·1).

Super Sustagen *Mead Johnson, Venez.*
Preparation for enteral nutrition (p.1922·1).

Super Tetra *Darya-Varia, Indon.; Pharos, Indon.*
Tetracycline phosphate (p.347·2).
Bacterial infections.

Super Vikaps *Reese, USA.*
Multivitamin and mineral preparation (p.1922·1).

Super Vita Vim *Jamieson, Canad.; Jamieson, Hong Kong.*
Multivitamin and mineral preparation (p.1922·1).

Superace *BMS, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Superal *Liferpal, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Superal Ex *Liferpal, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2).
Respiratory-tract disorders.

Superal Jarabe *Liferpal, Mex.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Respiratory-tract disorders.

Superamin *Vianex (Βιανέξ), Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Superan *Sanofi-Aventis, Braz.*
Alizapride hydrochloride (p.1704·3).
Nausea and vomiting.

Superanabolon *Spofa, Cz.*
⊗ Nandrolone phenylpropionate (p.2118·3).
Anabolic; metastatic breast cancer; osteoporosis.

Superantioxidante *Natural Life, Arg.*
Betacarotene; vitamin C; vitamin E; selenium (p.1922·1).
Antoxidant preparation.

Supercad *Faran, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Supercod *Vivax, Venez.*
Cod-liver oil (p.1935·2).
Dietary supplement.

Superdophilus *Natren, USA.*
Lactobacillus acidophilus (p.2372·3).
Dietary supplement.

SuperEPA *Advanced Nutritional Technology, USA.*
Omega-3 marine triglycerides (p.1362·2).
Dietary supplement.

Superfade
Note.This name is used for preparations of different composition.
Sunspot, Austral.
Hydroquinone (p.1598·2); salicylic acid (p.1612·2); dexpanthenol (p.2362·1); padimate O (p.1609·1); vitamin E.
Skin hyperpigmentation.

Sunspot, Hong Kong.
Hydroquinone (p.1598·2); salicylic acid (p.1612·2).
Skin hyperpigmentation.

Superhist *Eurofarma, Braz.*
Dexchlorpheniramine maleate (p.572·1); aspirin (p.20·3); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Formerly contained chlorphenamine maleate, ascorbic acid, aspirin, and caffeine.
Cold and influenza symptoms.

Superlipid *Almirall, Spain†.*
Probucol (p.1377·1).
Hyperlipidaemias.

Supero *Lifepharma, Ital.*
Cefuroxime sodium (p.238·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Superol *Chefaro, Neth.*
Hydroxyquinoline sulfate (p.2323·1).
Burns; sore throat; wounds.

Superoxylase *Lero, Fr.*
Bioflavonoids; vitamin C; zinc; vitamin E; betacarotene; carotenoids; manganese; selenium; yeast (p.1922·1).
Antoxidant preparation.

Superpep *Hermes, Ger.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Superplex-T *Major, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Superpyrin *Medicamenta, Cz.*
Aloxiprin (p.18·3).
Fever; pain.

SuperSkin *CliniMed, UK.*
Enbucrilate (p.2290·2).
Barrier preparation.

Super-Tabs *SA Druggists Self Med, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Supertar *ICN, Arg.†.*
Coal tar (p.1616·2).
Scalp disorders.

Supertendin *UCB, Ger.*
⊗ Dexamethasone acetate (p.1526·1); lidocaine hydrochloride (p.1862·3).
Formerly known as Supertendin-Depot.
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Supertendin 2000 N *Thiemann, Ger.†.*
⊗ Dexamethasone (p.1526·1); lidocaine hydrochloride (p.1862·3).
Neuralgia; neuritis; painful inflammatory musculoskeletal and joint disorders.

Supertonic *Diafarm, Spain.*
Amino-acid preparation with cyanocobalamin (p.1922·1).
Tonic.

Supervax *Cassara, Arg.*
A hepatitis B vaccine (p.2215·2).
Active immunisation.

Supervit *New Pharma, Venez.*
Vitamin and mineral preparation (p.1922·1).

Supervitaminico *ISA, Arg.*
Vitamins; magnesium; guarana (p.1922·1).
Formerly known as Herbaccion Supervitaminico.

Supeudol *Sandoz, Canad.*
⊗ Oxycodone hydrochloride (p.106·2).
Pain.

Suphera *Hawthorn, USA.*
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne; rosacea; seborrhoeic dermatitis.

Supirocin *Glenmark, India; Glenmark, Singapore.*
Mupirocin (p.302·3).
Bacterial skin infections; burns; wounds.

Supirocin-B *Glenmark, India.*
⊗ Mupirocin (p.302·3); betamethasone dipropionate (p.1518·3).
Infected skin disorders.

Suplac *Biolab, Singapore†; Biolab, Thai.*
Bromocriptine mesilate (p.798·1).
Amenorrhoea; galactorrhoea; lactation inhibition; male and female infertility.

Suplan *Hebron, Braz.†.*
Glucose; vitamins; minerals (p.1922·1).
Nutritional supplement.

Suplar *Schwarz, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Suplasyn *Bioniche, Canad.; Chiesi, Fr.; Merckle, Ger.; Dipa, Indon.; Premier, Irl.; Devries, Israel; Bioniche Teoranta, Singapore; Robapharm, Switz.; Pliva, UK.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis; synovial fluid replacement.

Supledin *Luper, Braz.†.*
Multivitamin preparation with or without minerals (p.1922·1).

Suplena *Abbott, Arg.†; Abbott, Austral.; Abbott, Cz.†; Abbott, Hong Kong; Abbott, Irl.; Abbott, Israel; Ross, Israel; Abbott, Mex.; Abbott, NZ; Abbott, Philipp.; Abbott, Singapore; Abbott, Turk.; Abbott Nutrition, UK; Abbott Nutrition, USA.*
Preparation for enteral nutrition in renal failure (p.1922·1).

Suplentin *Pasteur, Philipp.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); clavulanic acid (p.250·2) or potassium clavulanate (p.250·2).
Bacterial infections.

Suplevit *EMS, Braz.; Riva, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Supligol *Lazar, Arg.†.*
⊗ Estradiol cipionate (p.2097·2); testosterone enantate (p.2130·1).
Menopausal disorders; osteoporosis.

Supligol NF *Lazar, Arg.*
⊗ Prasterone enantate (p.2124·2); estradiol valerate (p.2097·3).
Menopausal disorders.

Supo Gliz *Perez Gimenez, Spain.*
Glycerol (p.2314·2).
Constipation.

Supofen *Basi, Port.*
Paracetamol (p.108·1).
Fever; pain.

Supositorio Hamamelis Composto *Simoes, Braz.†.*
Hamamelis (p.2318·2); aesculus (p.2248·2); lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Supositorios Senosiain *Senosiain, Mex.*
Glycerol (p.2314·2).
Constipation.

Supotron *Remedina, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Supoviol *Andromaco, Chile.*
Nonoxinol 9 (p.1917·2).
Vaginal contraceptive.

Supplemin-C *Metro, Philipp.*
Vitamin B substances; vitamin C; lysine (p.1922·1).
Nutritional supplement.

Suppletive *Dermoteca, Port.*
Moisturiser.
Dry skin.

Supplex *Cedar Health, UK.*
Green-lipped mussel (p.2317·2).
Joint disorders.

Supplin *Sandoz, Hung.; Sandoz, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Suppomaline *Solvay, Fr.*
Belladonna (p.2263·3); codeine phosphate (p.37·2); caffeine (p.1116·3); paracetamol (p.108·1).
Fever; pain.

Support Formula *Quest, Canad.*
Vitamin B substances; vitamin E; chromium; inositol; ubidecarenone (p.1922·1).

Supportan *Fresenius Kabi, Chile; Fresenius Kabi, Cz.†; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.†; Fresenius Kabi, Switz.†; Fresenius Kabi, Turk.*
Preparation for enteral nutrition (p.1922·1).

Suppositoires contre les hemorroides *Weleda, Switz.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2); antimony.
Haemorrhoids.

Supprelin *Indevus, USA.*
⊗ Histrelin acetate (p.2109·2).
Precocious puberty.

Supra *Valeant, Mex.*
Lidamidine hydrochloride (p.1740·2).
Gastrointestinal disorders.

Supra Flu *Kimia, Indon.*
Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cough; influenza symptoms.

Supraalox *Sanofi-Aventis, Spain.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; peptic ulcer.

Suprabion *Merck, Venez.*
Pyridoxine hydrochloride (p.1978·2).

Supracain *Zentiva, Cz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Supracalm *Tecnofarma, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Supracam *Raffo, Arg.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Supracefa *Helm, Port.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Suprachlor *Meprofarm, Indon.*
Chloramphenicol (p.239·3).
Bacterial infections.

Supracid *Viatris, Austria.*
⊗ Spironolactone (p.1400·1); hydrochlorothiazide (p.1307·3).
Hyperaldosteronism; hypertension; oedema.

Supracof *Loeffler, Mex.*
Benzonatate (p.1552·1).
Coughs.

Supracombin *Grunenthal, Cz.†; Grunenthal, Ger.†; Grunenthal, Switz.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Supracordin *Denk, Cz.†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease; migraine; Raynaud's syndrome.

Supracortin 3 *Boots, Thai.†; Hermal, Thai.†.*
⊗ Fluprednidene acetate (p.1533·1); neomycin sulfate (p.305·1); cloxiquine (p.530·3).
Infected skin disorders.

Supracream *Boots, Thai.†; Hermal, Thai.†.*
Emollient barrier cream.
Dry skin; nappy rash.

Supracyclin *Grunenthal, Austria; Grunenthal, Ger.; Grunenthal, Pol.*
Doxycycline (p.267·1).
Bacterial infections.

Supracycline *Grunenthal, Switz.*
Doxycycline (p.267·1).
Bacterial infections.

Supradol *Liomont, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Supradyn *Bayer Consumer, Arg.; Bayer Consumer, Austral.; Bayer, Austria; Roche, Braz.; Bayer, Chile; Bayer, Cz.†; Bayer, Hong Kong; Bayer, Hung.; Piramal, India; Roche, Israel; Bayer, Ital.; Roche, Mex.†; Roche, NZ†; Bayer, Pol.; Bayer, Port.; Bayer Consumer, Rus.; Bayer, Singapore; Bayer, Switz.; Roche, Thai.; Roche, Turk.; Roche Consumer, UK; Roche, Venez.†.*
A range of vitamin preparations with or without minerals (p.1922·1).
Dietary supplement.

Supradyn Ginseng *Bayer, Chile.*
Vitamins; minerals; ginseng; rutoside (p.1922·1).
Dietary supplement.

Supradyn Vital *Bayer, Fr.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Supradyn Vital 50+ *Bayer, Switz.*
Multivitamin and mineral preparation with ginseng (p.1922·1)(p.2312·1).

Supradyne *Bayer, Fr.*
Multivitamin and mineral preparation (p.1922·1).

Suprafen *Genbay, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Suprafenid *Meprofarm, Indon.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, and peri-articular disorders.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Suprafol *Investi, Arg.*
Folic acid (p.1940·1).
Folic acid deficiency; megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Supragesic
Note. This name is used for preparations of different composition.
Beta, Arg.
Dextropropoxyphene hydrochloride (p.40·1) or dextropropoxyphene napsilate (p.40·1) ibuprofen (p.64·2) or ibuprofen lysine (p.64·2).
Pain.

Pharmaceutical Enterprises, S.Afr.
Capsules: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain.

Pharmaceutical Enterprises, S.Afr.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Suprahyal *Zodiac, Braz.; Tecnofarma, Chile; Asofarma, Mex.; Nolver, Venez.*
Sodium hyaluronate (p.2320·1).
Osteoarthritis; rheumatoid arthritis.

Supralan *Siam Bheasach, Thai.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Supralan-N *Siam Bheasach, Thai.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Supraler *Panalab, Arg.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; allergic skin disorders; pruritus.

Supralip *Solvay, Port.; Fournier, Thai.; Fournier, UK.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Supramol *Sam-On, Israel†.*
Paracetamol (p.108·1).
Fever; pain.

Supramox
Grunenthal, Austria; Meprofarm, Indon.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Grunenthal, Switz.†.
Amoxicillin (p.202·2).
Bacterial infections.

Supramycin *Grunenthal, Ger.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Supran *Teva, Israel.*
Cefixime (p.224·3).
Bacterial infections.

Supranal *Dexa, Indon.*
Dipyrone (p.49·2); caffeine (p.1116·3); thiamine nitrate (p.1976·2).
Pain.

Suprane *Baxter Immuno, Arg.; Baxter, Austral.; Baxter, Austria; Baxter, Canad.; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; Kalbe, Indon.; Baxter, Ital.; Baxter, Malaysia; Baxter, Mex.†; Baxter, NZ; Baxter, Neth.; Baxter, Philipp.; Baxter, Pol.; Baxter, Port.; AstraZeneca, S.Afr.; Baxter, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Baxter Anaesthesia, UK; Ohmeda, USA; Baxter, Venez.†.*
Desflurane (p.1781·3).
General anaesthesia.

Supranettes *Alcon, Venez.†.*
Calendula (p.2273·1); hamamelis (p.2318·2).
Eyelid cleanser.

Supranettes Naturalag *Alcon, Mex.*
Calendula (p.2273·1); hamamelis (p.2318·2).
Skin hygiene.

Supraneuron *Bayer, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Alcohol withdrawal syndrome; movement disorders; nausea and vomiting; neuritis; vitamin B deficiency.

Supranitrin *Gap, Gr.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Suprapen *GSK, S.Afr.*
Amoxicillin trihydrate (p.202·2); flucloxacillin sodium (p.277·1).
Bacterial infections.

Supraproct-S *Julphar, UAE.*
⊗ Betamethasone valerate (p.1519·1); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Suprarenin *Aventis, Austria; Aventis, Ger.*
⊗ Adrenaline hydrochloride (p.1203·3).
Adjunct to local anaesthesia; anaphylactic shock; circulatory collapse; hypersensitivity reactions; shock.

Suprasec *Janssen-Cilag, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Suprasma *Dexa, Indon.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Suprasorb *Lohmann, Fr.*
Polyurethane foam dressing (p.1611·1).
Wounds.

Supprasten *Gross, Braz.†.*
⊗ Suprarenal cortex (p.1543·3); ascorbic acid (p.1983·3); pentetrazol (p.2162·1).
Impaired mental function.

Suprastin *EGIS, Hung.; Egis, Rus.*
Chloropyramine hydrochloride (p.571·3).
Hypersensitivity reactions.

Supratonin *Grunenthal, Ger.*
⊗ Amezinium metilsulfate (p.1209·2).
Hypotension.

Supra-Vir *Trima, Israel.*
Aciclovir (p.862·3).
Herpesvirus infections.

Supraviran *Grunenthal, Cz.†; Grunenthal, Ger.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Supravit *Roche, Turk.*
Multivitamin preparation (p.1922·1).

Supravital *Liferpal, Mex.*
Royal jelly (p.2382·1); garlic (p.2309·2).
Dietary supplement.

Supravit-C *Su-Heung, Philipp.*
Ascorbic acid (p.1983·3).
Nutritional supplement; vitamin C deficiency.

Supravite *Nobel, Canad.*
Vitamin B substances and iron (p.1922·1).

Suprax *Aventis, Canad.; Gedeon Richter, Cz.; Astellas, Ger.; Gedeon Richter, Hung.; Sanofi-Aventis, Irl.; Wyeth Lederle, Ital.; Hikma, Rus.; Eczacibasi, Turk.; Aventis, UK; Lupin, USA.*
Cefixime (p.224·3).
Bacterial infections.

Suprazen *Medi-Rx, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Suprazid *Armoxindo, Indon.*
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Suprecur *Aventis, Austria; Aventis, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Galen, Ger.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Mochida, Jpn; Aventis, Neth.†; Aventis, Norw.; Aventis, Swed.; Aventis, Turk.; Aventis, UK.*
⊗ Buserelin acetate (p.2083·2).
Endometriosis; ovarian stimulation for in-vitro fertilisation; precocious puberty; prostatic cancer; uterine fibroids.

Suprefact
Aventis, Arg.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Aventis, Cz.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK.
⊗ Buserelin acetate (p.2083·2).
Breast cancer; endometriosis; ovulation induction; precocious puberty; prostatic cancer; uterine fibroids.

Aventis, Israel.
⊗ Buserelin (p.2083·2) or buserelin acetate (p.2083·2).
Endometriosis; ovulation induction; prostatic cancer; uterine fibroids.

Suprekof *Kramer, Philipp.*
Guaifenesin (p.1561·3).
Cough.

Suprekof DM *Kramer, Philipp.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Suprelip *BMS, Cz.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Suprema *Biolab Sanus, Braz.*
Norethisterone acetate (p.2119·3); estradiol (p.2097·2).
Menopausal disorders.

Supremase *Pentafarma, Port.*
Fluconazole (p.532·1).
Fungal infections.

Supremin *Pliva Krakow, Pol.*
Butamirate citrate (p.1553·1).
Cough.

Supremunn *Ivax, Mex.*
Ciclosporin (p.1822·2).
Atopic eczema; Crohn's disease; nephrotic syndrome; rheumatoid arthritis; transplant rejection; uveitis.

Suprenil *Ulagay, Turk.*
⊗ Sulfacetamide sodium (p.335·3); prednisolone acetate (p.1541·1); phenylephrine hydrochloride (p.1568·1).
Infected eye disorders.

Supres *Merck Frosst, Canad.†.*
⊗ Methyldopa (p.1334·1); chlorothiazide (p.1243·1).
Hypertension.

Supresol *Mayne, Ital.*
⊗ Methylprednisolone sodium succinate (p.1538·2).
Parenteral corticosteroid.

Supressin *Pfizer, Austria.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Suprex *Terramedic, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Suprim *Hovid, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections; protozoal infections.

Suprima-Broncho *Shreya, Rus.*
Adhatoda; liquorice (p.1740·3); turmeric (p.1473·2); ocimum sanctum; ginger (p.1732·3); solanum xanthocarpum piper longum; cardamom (p.2277·1).
Respiratory-tract disorders.

Suprima-Kof *Shreya, Rus.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Suprimal
Note. This name is used for preparations of different composition.
Temis, Arg.
Mesalazine (p.1745·1).
Inflammatory bowel disease.

IPS, Neth.
Meclozine hydrochloride (p.584·3).
Motion sickness.

Suprima-Lor *Shreya, Rus.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Mouth and throat disorders.

Suprima-Nos *Shreya, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Suprima-Plus *Shreya, Rus.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); thymol (p.1664·3); turpentine oil (p.2406·3).
Catarrh; musculoskeletal and joint disorders.

Suprimox *Rexcel, India.*
Amoxicillin (p.202·2); cloxacillin (p.256·1).
Bacterial infections.

Suprin *Degorts, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Supristol *Noristan, S.Afr.†.*
Co-trifamole (p.257·3).
Bacterial infections.

Suprium *Sanofi-Aventis, Fin.*
Sulpiride (p.1028·3).
Depression; psychoses.

Suprivent *Cadila, India.*
⊗ Salbutamol sulfate (p.1131·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Suprivent-A *Cadila, India.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3); ambroxol (p.1550·3); menthol (p.2340·1).
Coughs.

Supro *Soprolin, Fr.*
Silicon (p.2032·1); magnesium (p.1678·3); boron; zinc (p.1999·1); aluminium (p.2254·1).
Foot deodorant.

Suprotide *Fresenius Kabi, Ital.*
Nutritional supplement (p.1922·1).

Suracton *Actipharm, Switz.†.*
Minerals; pyridoxine hydrochloride (p.1978·2).
Tonic.

Sural *Sanofi-Aventis, Cz.; Extractum, Hung.; Sanofi-Aventis, Hung.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Suralgan *Monsanto, Ital.†.*
Tiaprofenic acid (p.129·2).
Inflammation; pain.

Surazem *Pfizer, Neth.*
Diltiazem hydrochloride (p.1265·1).
Hypertension.

Surbex
Abbott, Canad.; Abbott, Malaysia.
Vitamin B substances with ascorbic acid (p.1922·1).
Nutritional supplement; vitamin supplement.

Abbott, USA.
A range of vitamin preparations (p.1922·1).

Surbex with C *Abbott, Hong Kong; Abbott, Singapore†.*
Vitamin B substances with vitamin C (p.1922·1).
Vitamin B and C deficiencies.

Surbex plus Iron *Abbott, Canad.*
Vitamin B substances with ascorbic acid and ferrous sulfate (p.1922·1).
Nutritional supplement.

Surbex plus Zinc *Abbott, Canad.*
Vitamin B substances with ascorbic acid and zinc sulfate (p.1922·1).
Nutritional supplement.

Surbex T *Abbott, Hong Kong; Abbott, India; Abbott, Singapore; Abbott, Thai.†.*
Vitamin B substances with vitamin C (p.1922·1).
Vitamin B and C deficiencies.

Surbex with Zinc *Abbott, Hong Kong†; Abbott, Malaysia; Abbott, Singapore.*
Multivitamin preparation with zinc (p.1922·1).
Nutritional supplement.

Surbex-T *Abbott, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C supplement.

Surbronc *Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Fr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Surbu-Gen-T *Goldline, USA.*
Vitamin B substances with vitamin C (p.1922·1).

Sure Step *Johnson & Johnson Medical, Arg.*
Test for glucose (p.2314·1).

SureLac *Caraco, USA.*
Tilactase (p.2402·1).
Lactose intolerance.

Sure-Lax *Chefaro, UK.*
Senna (p.1769·2).
Constipation.

Sure-Lax (Herbal) *Chefaro, UK.*
Aloes (p.1705·2); fennel (p.2302·3); valerian (p.2410·1); cnicus benedictus (p.2285·2).
Constipation.

Surelen *Bayer, Fr.*
Pyridoxine hydrochloride; adenosine phosphate; potassium aspartate; nicotinamide; ascorbic acid (p.1922·1).
Tonic.

Sureptil *Sanofi-Aventis, Braz.*
Cinnarizine (p.573·1); heptaminol acefyllinate (p.1123·2).
Vascular disorders.

Sureskin *Euromedex, Fr.*
Carmellose sodium (p.2142·1).
Burns; ulcers; wounds.

Suretin *Allergan, Mex.*
Tazarotene (p.1617·1).
Acne; psoriasis.

Surfactal *Boehringer Ingelheim, Ital.*
Ambroxol hydrochloride (p.1550·3).
Neonatal surfactant deficiency; prevention of bronchopulmonary complications following surgery.

Surfactante B *Richet, Arg.*
Bovine pulmonary surfactant (p.2375·3).

Surfacten *Mitsubishi, Jpn.*
Bovine pulmonary extract (p.2375·3).
Respiratory distress syndrome.

Surfactil *Farmion, Braz.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Surfak
Aventis, Canad.†.
Docusate sodium (p.1725·1).
Constipation.

Upjohn, USA.
Docusate calcium (p.1724·3).
Constipation.

Surfanios *Anios, Fr.*
Hydrochlorides of amino acids; didecyldimethylammonium chloride (p.1642·2).
Surface disinfection.

Surfaz
Note. This name is used for preparations of different composition.
Franco-Indian, India.
Cream; topical solution; vaginal tablets: Clotrimazole (p.530·1).
Balanitis; fungal skin and vaginal infections.

Franco-Indian, India.
Ear drops: Clotrimazole (p.530·1); lidocaine (p.1862·3).
Fungal ear infections.

Surfaz-SN *Franco-Indian, India.*
⊗ Clotrimazole (p.530·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Surfol *Stiefel, USA.*
Emollient.

Surfolase *Pharmacia, Ital.; Lepori, Port.†.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Surfont *Ardeypharm, Ger.*
Mebendazole (p.148·3).
Worm infections.

Surfortan *IPRAD, Fr.*
Lysine; potassium phosphate; pyridoxine hydrochloride (p.1922·1).
Tonic.

Surgam
Sanofi-Aventis, Austral.; Aventis, Canad.; Zentiva, Cz.; Grunenthal, Fr.; Aventis, Ger.; Sanofi-Aventis, Hung.; Aventis, Irl.; Aventis, NZ; Aventis, Neth.; Roussel, Pol.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Aventis, Thai.†; Aventis, Turk.; Sanofi-Aventis, UK.
Tiaprofenic acid (p.129·2).
Gout; inflammation; musculoskeletal, joint, periarticular, and soft-tissue disorders; oedema; pain.

Aventis, Mex.
Tiaprofenic acid (p.129·2) or tiaprofenic acid trometamol salt (p.129·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Surgamyl *Aventis, Denm.; Sanofi-Aventis, Fin.; Scharper, Ital.*
Tiaprofenic acid (p.129·2).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Inflammation; musculoskeletal and joint disorders; pain.

Surge *SA Druggists Self Med, S.Afr.*
Yellow phenolphthalein (p.1762·1).
Constipation.

Surgel *Ulmer, USA.*
Carmellose sodium (p.2142·1); propylene glycol (p.2374·1); glycerol (p.2314·2).
Vaginal lubricant.

Surgestone *Sanofi-Aventis, Fr.; Sanofi-Aventis, Port.*
Promegestone (p.2127·3).
Fibroids; mastalgia; menopausal disorders; menstrual disorders.

Surgicel *Ethicon, Fr.; Johnson & Johnson Medical, USA.*
Oxidised cellulose (p.1075·1).
Haemorrhage.

Surgicoll *GfE, Ger.†.*
Collagen (p.2286·1).
Haemorrhage.

Surgi-Gel *Orion, NZ.*
Lubricating gel.

Surgras Physiologique *Roche-Posay, Arg.†; Roche-Posay, Braz.†.*
Soap substitute.

Suril *Ibirn, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Sur-Lax *Jean-Marie, Hong Kong.*
Sodium picosulfate (p.1771·1).
Constipation; stool softener.

Surlid *Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Swed.*
Roxithromycin (p.331·1).
Bacterial infections.

Surmenalit *Faes, Spain.*
Sulbutiamine (p.1976·1).
Vitamin B1 deficiency.

Surmontil
Aspen, Austral.; Nicholas Piramal, India†; Aventis, Israel; Aventis, S.Afr.; Aventis, Venez.†.
Trimipramine (p.426·2).
Agitation; anxiety; depression; dumping syndrome; insomnia; lypotaemia; mixed anxiety depressive states; neuroses; pain.

Aventis, Canad.†; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Hong Kong; Sanofi-Aventis, Irl.; Healthcare Logistics, NZ; Aventis, Neth.†; Aventis, Norw.; Patriot, Philipp.; Vitoria, Port.; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, UK; Barr, USA; Duramed, USA.
Trimipramine maleate (p.426·3).
Anxiety; depression; insomnia; irritable bowel syndrome.

Sanofi-Aventis, Fr.; Aventis, Switz.
Trimipramine maleate (p.426·3) or trimipramine mesilate (p.426·3).
Depression; pain.

Sanofi-Aventis, Ital.
Trimipramine (p.426·2) or trimipramine maleate (p.426·3).
Depression.

Surnox *Sanofi-Aventis, Spain.*
Ofloxacin hydrochloride (p.310·2).
Bacterial infections.

Suronit *Degorts, Mex.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Surpas
Note. A similar name is used for preparations of different composition (see below).
Sandoz, Indon.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Surpass
Note. A similar name is used for preparations of different composition (see above).
Wrigley, USA.
Calcium carbonate (p.1714·1).
Dyspepsia; heartburn.

Surplex *Seng, Thai.*
Vitamin B substances; ascorbic acid (p.1922·1).
Intravenous vitamin supplement.

Surquina *Innotech, Fr.*
Quinine hydrochloride (p.612·3).
Malaria.

Sursum *Abiogen, Ital.*
Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Survanta *Abbott, Arg.; Abbott, Austral.; Abbott, Austria; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Indon.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Philipp.; Abbott, Pol.; Abbott, S.Afr.; Abbott, Singapore; Abbott, Spain; Abbott, Switz.; Abbott, Thai.; Abbott, UK; Ross, USA; Abbott, Venez.*
Beractant (p.2375·3).
Neonatal respiratory distress syndrome.

Survanta-Vent *Abbott, Norw.; Abbott, Swed.†.*
Beractant (p.2375·3).
Neonatal respiratory distress syndrome.

Survector *Servier, Braz.†; Teravix, Port.†.*
Amineptine hydrochloride (p.375·3).
Depression.

Survimed *Fresenius Kabi, Cz.†; Fresenius Kabi, Irl.; Fresenius Kabi, Ital.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.†; Fresenius Kabi, Switz.†; Fresenius Kabi, UK.*
Preparation for enteral nutrition (p.1922·1).

Survimed Renal *Diamedica, Venez.†.*
Preparation for enteral nutrition (p.1922·1).

Survon-T *Sandoz, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C supplement.

Susano *Halsey, USA.*
Atropine sulfate (p.1219·3); hyoscine hydrobromide (p.1734·1); hyoscyamine hydrobromide (p.1736·1) or hyoscyamine sulfate (p.1736·1); phenobarbital (p.492·2).
Gastrointestinal disorders.

Suscard *Forest, Irl.; AstraZeneca, Swed.; Forest Laboratories, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Suspensio Visnevski cum Pice Liquida Herbacos *Herbacos, Cz.*
Bismuth tribromphenate (p.1712·1); tar (p.1616·2); castor oil (p.2278·1).
Skin disorders.

Suspension Antiacida *Denver, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

Suspension Antiacida con Simeticona *Denver, Arg.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).

Sustac
Note. This name is used for preparations of different composition.
Pfizer, Arg.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

KRKA, Hung.; Forest, Irl.; KRKA, Rus.; Forest Laboratories, UK†.
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Sustacal *Novartis, Braz.; Mead Johnson, Indon.; Mead Johnson, Israel; Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).

Sustagen *BMS, Arg.; Novartis Consumer, Austral.; Mead Johnson, Braz.; Mead Johnson, Chile; Mead Johnson, Hong Kong†; Mead Johnson, Indon.; Mead Johnson, NZ; Mead Johnson, Philipp.; Mead Johnson Nutritionals, Thai.†; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Preparation for enteral nutrition (p.1922·1).

Sustain
Note. This name is used for preparations of different composition.
Support, Braz.†.
Preparation for enteral nutrition (p.1922·1).

Zee, USA.
Sodium chloride; calcium carbonate; potassium chloride (p.1667·1).

Sustained Release C *Blackmores, Austral.*
Vitamin C (p.1983·3); bioflavonoids (p.2304·1); hesperidin (p.2304·3); rose fruit (p.2381·2); rutoside (p.2305·1).
Formerly known as Sustained Release Buffered C.
Vitamin C supplement.

Sustaire *Pfizer, USA†.*
Theophylline (p.1140·1).
Asthma; bronchospastic disorders.

Sustanon *Organon, Cz.; Organon, Hong Kong; Organon, Ital.; Pharmaco, NZ.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Androgen deficiency; male hypogonadism; masculinisation in gender reassignment of females; osteoporosis in males.

Sustanon 100 *Organon, Austral.; Organon, India; Organon, Irl.; Organon, Neth.; Organon, UK.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1).
Androgen deficiency; female breast cancer; male hypogonadism; male osteoporosis; testosterone deficiency.

Sustanon 250 *Organon, Arg.; Organon, Austral.; Organon, Belg.; Organon, Fin.; Organon, India; Organon, Indon.; Organon, Irl.; Organon, Israel; Organon, Malaysia; Organon, Neth.; Donmed, S.Afr.; Organon, Singapore; Organon, Turk.; Organon, UK.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Androgen deficiency; delayed puberty; female breast cancer; male hypogonadism; male infertility; male osteoporosis; supportive therapy for female-to-male transsexuals; testosterone deficiency.

Sustemial *Malesci, Ital.*
Ferrous gluconate (p.1939·1).
Anaemias; iron deficiency.

Sustenan *Organon, Chile.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; osteoporosis.

Sustenan 250 *Organon, Chile.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Male hypogonadism; osteoporosis.

Sustenium *Menarini, Ital.*
Fosfocreatinine disodium (p.2307·1).
Muscle disorders.

Sustenon 250 *Organon, Port.*
⊗ Testosterone propionate (p.2130·1); testosterone phenylpropionate (p.2130·1); testosterone isocaproate (p.2130·1); testosterone decanoate (p.2130·1).
Male hypogonadism; osteoporosis.

Sustiva *BMS, Canad.; BMS, Cz.; BMS, Fr.; BMS, Ger.; BMS, Irl.; BMS, Ital.; BMS, Neth.; BMS, Port.; BMS, Spain; BMS, UK; BMS, USA.*
Efavirenz (p.872·3).
HIV infection.

Sustonit *Polfa Warszawa, Pol.; Polfa, Rus.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Sustrate *BMS, Braz.*
Propatylnitrate (p.1380·2).
Angina pectoris.

Sustress Plus *Sankyo, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Sutac *Sriprasit, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

SuTan *Cypress, USA.*
Pseudoephedrine tannate (p.1572·1); dexchlorpheniramine tannate (p.572·2).
Allergic rhinitis.

SuTan DM *Cypress, USA.*
Pseudoephedrine tannate (p.1572·1); dextromethorphan tannate (p.1556·1); dexchlorpheniramine tannate (p.572·2).
Allergic rhinitis; cold symptoms; cough.

Sutent *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Cz.; Pfizer, Fr.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Port.; Pfizer, UK; Pfizer, USA.*
Sunitinib malate (p.771·3).
Gastrointestinal stromal tumours; renal cell carcinoma.

Sutif *Farma Lepori, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Sutin *Loren, Mex.†.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2); cod-liver oil (p.1935·2); benzalkonium chloride (p.1629·1); zinc oxide (p.1621·2).
Keratinisation disorders.

Sutrico *LKM, Arg.*
⊗ Finasteride (p.2188·3).
Alopecia.

Sutrico Tar *LKM, Arg.*
Coal tar (p.1616·2).
Scalp disorders.

Sutril *Novag, Spain.*
⊗ Torasemide sodium (p.1416·1).
Hypertension; oedema.

Sutriptan *Verisfield, Gr.*
Sumatriptan (p.625·2).
Migraine.

Su-Tuss DM *Cypress, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Su-Tuss HD *Cypress, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Suvalan *GSK, Austral.*
Sumatriptan succinate (p.625·2).
Migraine.

Suveal *Densmore, Fr.*
A range of vitamin and mineral preparations (p.1922·1).

Suvenyl *Chugai, Jpn.*
Sodium hyaluronate (p.2320·1).
Knee pain associated with rheumatoid arthritis or osteoarthritis.

Suvit *Cofasa, Venez.*
Vitamin B substances (p.1922·1).

Suxidina *Seid, Spain.*
Aspergillus oryzae; dimeticone (p.1770·2); metoclopramide hydrochloride (p.1747·3); oxazepam hemisuccinate (p.1014·3).
Aerophagia; digestive disorders; meteorism.

Suxilep *Jenapharm, Cz.†; Wernigerode, Cz.†; Jenapharm, Ger.; Jenapharm, Rus.*
Ethosuximide (p.479·3).
Absence seizures.

Suxinutin *Pfizer, Austria; Pfizer, Chile; Pfizer, Fin.; Parke, Davis, Ger.†; Pfizer, Hung.†; Pfizer, Swed.; Pfizer, Switz.†.*
Ethosuximide (p.479·3).
Epilepsy.

Suyodil *Continentales, Mex.*
Clioquinol (p.254·1); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Svedocain *Inibsa, Spain.*
Bupivacaine hydrochloride (p.1854·3).
Local anaesthesia.

Sveltanet *Ferakon, Gr.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Svir *Cristalia, Braz.†.*
Saquinavir (p.906·1).
HIV infection.

Sviroxit *Rafarm, Gr.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Svitalark *Leovan, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

SVM-Polypac-A *More, Philipp.*
2 Tablets, ethambutol hydrochloride (p.274·1); isoniazid (p.288·1); 1 capsule, rifampicin (p.325·3); 3 tablets, pyrazinamide (p.320·2).
Pyridoxine hydrochloride (p.1978·2) is included in the ethambutol and isoniazid tablets for the prophylaxis of peripheral neuropathy.
Tuberculosis.

SVR 50B *SVR, Fr.*
SPF 50: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

SVR 30 B, 60 B, and 100 B *SVR, Fr.*
SPF 30, 60, and 100: Bisoctrizole (p.1591·2); a cinnamate derivative; a dibenzoylmethane derivative; octil triazone (p.1608·1); enzacamene (p.1597·1); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); thermophe-rol.
Sunscreen.

SVR Creme Antimoustique *SVR, Fr.†.*
Dimethyl phthalate (p.2041·3); metatoluamide.
Insect repellent.

Svudin *Cristalia, Braz.†.*
Stavudine (p.907·1).
HIV infection.

Swarm *Pickles, UK.*
Hamamelis (p.2318·2); dibrompropamidine isetionate (p.1642·1); calamine (p.1591·2).
Insect bites and stings.

Sweatosan N *Novartis Consumer, Ger.*
Sage (p.2382·3).
Hyperhidrosis.

Swecon *YSP, Malaysia.*
Hydrotalcite (p.1733·3).
Gastric hyperacidity; gastritis; peptic ulcer.

Sween Cream *Coloplast, USA.*
Barrier cream.

Sweet 'n Low *Dietary Foods, UK.*
Acesulfame potassium (p.1928·1); aspartame (p.1930·1).
Sugar substitute.

Sweet 'n' Low *Biogalenic, Venez.†.*
Aspartame (p.1930·1); acesulfame (p.1928·1).
Sugar substitute.

Sweeta C *Combiphar, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Sweetcee *Chew, Thai.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Swiff *Berlin Pharm, Thai.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Swim-Ear *Metapharma, Canad.†; Co-Pharma, UK; Fougera, USA.*
Isopropyl alcohol (p.1650·3); glycerol (p.2314·2).
Ear disorders; removal of trapped ear water.

Swiss Herb Cough Drops *Ricola, Canad.*
Althaea (p.2253·3); burnet (p.2270·3); horehound (p.1564·1); mallow (p.2337·2); menthol (p.2340·1); parsley piert (p.2363·2); peppermint oil (p.1761·2); plantago cordata; thyme (p.2401·1); veronica officinalis with or without ascorbic acid (p.1983·3).

Swiss One *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Swiss-Kal SR *Byk Madaus, S.Afr.†.*
Potassium chloride (p.1684·3).

SX-22 *Sigma, Arg.*
Vitamins; echinacea (p.2298·1); caffeic acid; phytosterols (p.1373·1); linolenic acid; oleic acid; palmitic acid; inulin; cichoric acid; betaine; triterpenes (p.1922·1).
Infections.

Syberian *Biofarm, Pol.*
Siberian ginseng (p.2386·3).
Tonic.

Sy-Clinomel *Baxter, Mex.†.*
A range of amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusions (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Sycot *Stadmed, India.*
Trifluoperazine hydrochloride (p.1034·2); trihexyphenidyl hydrochloride (p.820·2).
Schizophrenia.

Sydepres *Rotexmedica, Philipp.*
Fluphenazine decanoate (p.998·1).
Psychoses.

Sydnopharm *Sopharma, Rus.*
Molsidomine (p.1343·3).
Angina pectoris.

Sydolil *Rhein, Mex.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); aspirin (p.20·3).
Headache including migraine.

Sygen *TRB, Braz.*
Monosialoganglioside sodium (p.2309·1); electrolytes.
Cerebrovascular disorders.

Sykofen *Silom, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; bronchitis; hypersensitivity reactions.

Sylador *Sanofi-Aventis, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Sylicaps *Herbapol Lublin, Pol.*
Milk thistle (p.1452·1).
Liver disorders.

Sylicynar *Herbapol Poznan, Pol.*
Cynara (p.2291·2); silymarin (p.1452·2).
Atherosclerosis; liver disorders.

Sylimarol *Herbapol Pruszkow, Pol.*
Milk thistle (p.1452·1).
Liver disorders.

Syliverin *Aflofarm, Pol.*
Silymarin (p.1452·2).
Liver disorders.

Sylivit *Herbapol Poznan, Pol.*
Milk thistle (p.1452·1); vitamins.
Liver disorders.

Sylk *Sylk, UK.*
Vaginal lubricant.

Syllact *Wallace, USA.*
Ispaghula (p.1737·1).
Constipation.

Syltrifil *Filadams, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Symadal M *Chauvin ankerpharm, Ger.*
Dimethicone 200 (p.2032·1).
Barrier preparation.

Symax *Capellon, USA.*
Hyoscyamine sulfate (p.1736·1).
Control of gastrointestinal secretions; cystitis; gastrointestinal spasm; heart block; parkinsonism; renal colic; rhinitis.

Symbial *Galderma, Neth.*
⊗ Urea (p.1620·2); sodium chloride (p.1686·1).
Skin disorders.

Symbicord *AstraZeneca, S.Afr.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma.

Symbicort *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Budesonide (p.1520·1); formoterol fumarate (p.1122·1).
Asthma; obstructive airways disease.

Symbioflor 1 *Symbiopharm, Ger.; SymbioPharm, Hung.*
Cells and autolysate of *Enterococcus faecalis* (p.2372·3).
Gastrointestinal disorders; upper respiratory-tract infections.

Symbioflor 2 *Symbiopharm, Ger.; SymbioPharm, Hung.*
Cells and autolysate of *Escherichia coli*.
Gastrointestinal disorders.

Symbioflor E. coli *Peithner, Austria.*
Live cells and autolysate of *Escherichia coli*.
Formerly known as Symbioflor II.
Gastrointestinal disorders; infections.

Symbioflor Enterococcus *Peithner, Austria.*
Live cells and autolysate of *Enterococcus faecalis* (p.2372·3).
Formerly known as Symbioflor I.
Gastrointestinal disorders; infections.

Symbioflor-Antigen *Symbiopharm, Ger.†.*
Escherichia coli.
Immunotherapy.

Symbion *Merck, Venez.*
Vitamin and mineral preparation (p.1922·1).

Symbiotik *Cadila, India.*
Amoxicillin trihydrate (p.202·2); cloxacillin sodium (p.256·1); *Lactobacillus sporogenes* (p.2372·3).
Bacterial infections.

Symbyax *Lilly, Arg.†; Lilly, Chile; Lilly, Mex.; Lilly, USA.*
Olanzapine (p.1012·1); fluoxetine hydrochloride (p.391·2).
Bipolar disorder.

Symfona *Medichemie, Switz.*
Ginkgo biloba (p.2311·1).
Cerebrovascular disorders.

Symglic *SymPhar, Pol.*
Glimepiride (p.441·1).
Diabetes mellitus.

Symla *SymPhar, Neth.*
Lamotrigine (p.485·1).
Epilepsy.

Symlin *Amylin, USA.*
Pramlintide acetate (p.457·1).
Diabetes mellitus.

Symmetrel *Novartis, Austral.; BMS, Canad.; Novartis, Gr.; Novartis, Hong Kong†; Novartis, Irl.; Novartis, NZ; Novartis, Neth.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Switz.; Alliance, UK; Endo, USA; Novartis, Venez.†.*
Amantadine hydrochloride (p.792·3).
Drug-induced extrapyramidal disorders; herpes zoster; influenza A; parkinsonism.

Symoron *Astellas, Neth.*
⊗ Methadone hydrochloride (p.82·3).
Opioid addiction; pain.

Symoxyl *Sarabhai Piramal, India.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Symoxyl-LB *Sarabhai Piramal, India.*
Amoxicillin trihydrate (p.202·2); lactic acid bacillus (p.2372·3).
Bacterial infections.

Sympal *Berlin-Chemie, Ger.*
Dexketoprofen trometamol (p.73·1).
Pain.

Sympalept *Streuli, Switz.*
⊗ Oxedrine tartrate (p.1364·3).
Circulatory disorders; hypotension.

Sympaneurol *Sanofi-Aventis, Fr.*
Crataegus (p.2289·1); passion flower (p.2363·2); valerian (p.2410·1).
Formerly contained phenobarbital, crataegus, passion flower, and valerian.
Nervous disorders; sleep disorders.

Sympathomim *Extractum, Hung.*
⊗ Oxedrine tartrate (p.1364·3).
Hypotension.

Sympathyl *Innotech, Fr.*
Crataegus (p.2289·1); eschscholtzia californica; magnesium oxide (p.1744·1).
Nervous disorders; sleep disorders.

Sympatol *Kwizda, Austria; Boehringer Ingelheim, Ital.*
⊗ Oxedrine tartrate (p.1364·3).
Hypotension.

Sympavagol *Novartis Sante, Fr.*
Passion flower (p.2363·2); crataegus (p.2289·1).
Nervous disorders; sleep disorders.

Symphocal *Teva, Israel.*
Oxolamine citrate (p.1567·1).
Coughs.

Symphytum Ro-Plex (Rowo-776) *Pharmakon, Ger.†.*
Homoeopathic preparation.

Symphytum-Komplex *Woelm, Ger.†.*
Homoeopathic preparation.

Symptofed *Adcock Ingram, S.Afr.*
Pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Synacol CF *Roberts, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Synacort *Syntex, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Synacthen
Novartis, Austral.; Novartis, Austria; Novartis, Chile; Novartis, Israel; Novartis, Venez.
⊗ Tetracosactide or tetracosactide zinc phosphate complex (p.1543·3).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency; hypsarrhythmia; infantile spasms; multiple sclerosis.

Novartis, Belg.; Novartis, Cz.†; Novartis, Denm.; Novartis, Ger.; Novartis, Irl.; Novartis, Ital.; Novartis, Neth.; Novartis, Port.; Novartis, Rus.; Novartis, Swed.; Novartis, Switz.; Alliance, UK.
⊗ Tetracosactide hexa-acetate (p.1544·1).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency.

Novartis, NZ.
⊗ Tetracosactide hexa-acetate (p.1544·1) or tetracosactide hexa-acetate zinc phosphate complex (p.1544·1).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency.

Synacthen Depot
Novartis, Canad.; Novartis, Rus.; Novartis, Turk.
⊗ Tetracosactide zinc hydroxide complex (p.1543·3).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency.

Novartis, Ger.; Novartis, S.Afr.; Novartis, Switz.; Alliance, UK.
⊗ Tetracosactide hexa-acetate (p.1544·1).
Formerly known as Synacthen Retard in *Switz.*
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency.

Synacthene *Novartis, Fr.; IFET (ΙΦΕΤ), Gr.*
⊗ Tetracosactide (p.1543·3).
Adrenocorticotrophic hormone; diagnosis of adrenocortical insufficiency; infantile spasms; multiple sclerosis.

Synadrenol *Keyerson, Mex.†.*
⊗ Metoprolol (p.1338·1).
Hypertension.

Syn-A-Gen *Vifor, Switz.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Synagis *Abbott, Arg.; Abbott, Austral.; Abbott, Belg.; Abbott, Braz.; Abbott, Canad.; Abbott, Chile; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Med Immune, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, NZ; Abbott, Neth.; Abbott, Norw.; Abbott, Pol.; Abbott, Port.; Abbott, S.Afr.; Abbott, Singapore†; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Turk.; Abbott, UK; Medimmune, USA; Abbott, Venez.*
Palivizumab (p.2235·3).
Respiratory syncytial virus infection.

Synalar *Grunenthal, Austria; Astellas, Belg.; Medicis, Canad.; AstraZeneca, Cz.†; Bioglan, Denm.; Jolly-Jatel, Fr.†; Minerva (Μινερβα), Gr.; CS, Hong Kong; Bioglan, Hung.†; Bioglan, Irl.†; Bioglan, Malaysia†; Syntex, Mex.; AFT, NZ; Bioglan, Norw.; Stiefel, Philipp.; Lusomedicamenta, Port.; Bartlett, S.Afr.; Astellas, Spain; Bioglan, Swed.; Grunenthal, Switz.; Sanofi Synthelabo, Thai.; GP, UK; Medicis, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Synalar Bi-Otic *Astellas, Belg.; Yamanouchi, Neth.†.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Inflammatory ear infections.

Synalar C *Bioglan, Irl.†; Syntex, Mex.; Bartlett, S.Afr.; GP, UK.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Synalar med Chinoform *Bioglan, Denm.; Bioglan, Norw.*
⊗ Fluocinolone acetonide (p.1531·3); clioquinol (p.254·1).
Infected skin disorders.

Synalar N
Note. This name is used for preparations of different composition.
Grunenthal, Austria; CS, Hong Kong; Bioglan, Hung.†; Bioglan, Irl.†; Bioglan, Malaysia†; Lusomedicamenta, Port.; Bartlett, S.Afr.; Grunenthal, Switz.; Sanofi Synthelabo, Thai.; GP, UK.
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Syntex, Mex.
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); phenylephrine hydrochloride (p.1568·1).
Nasal and sinus disorders.

Synalar Nasal *Astellas, Spain.*
⊗ Phenylephrine hydrochloride (p.1568·1); fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Nasal congestion and infection.

Synalar Neo *Syntex, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Synalar Neomicina *Astellas, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Synalar O *Syntex, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); lidocaine hydrochloride (p.1862·3).
Otitis externa.

Synalar Oftalmico *Syntex, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Infected eye disorders.

Synalar Otic *Stiefel, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1).
Otitis externa.

Synalar Otico *Astellas, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Ear disorders.

Synalar Rectal *Lusomedicamenta, Port.; Astellas, Spain.*
⊗ Bismuth subgallate (p.1711·1); fluocinolone acetonide (p.1531·3); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1).
Anorectal disorders.

Synalar Rectal Simple *Astellas, Spain.*
⊗ Fluocinolone acetonide (p.1531·3).
Anorectal disorders.

Synaleve *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Pain and associated tension.

Synalgo *Geymonat, Ital.*
Naproxen aminobutanol (p.93·3).
Gout; musculoskeletal and joint disorders; neuralgia; sciatica.

Synalgos-DC *Leitner, USA.*
Dihydrocodeine tartrate (p.48·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Synalotic *Astellas, Spain.*
⊗ Fluocinolone acetonide (p.1531·3); ciprofloxacin hydrochloride (p.243·3).
Otitis externa.

Synap *Adcock Ingram, S.Afr.*
Paracetamol (p.108·1); dextropropoxyphene napsilate (p.40·1); diphenhydramine hydrochloride (p.577·2); caffeine (p.1116·3).
Pain.

Synapausa *Organon, Port.†.*
Estriol succinate (p.2101·1).
Oestrogen deficiency.

Synapause *Donmed, S.Afr.*
Estriol (p.2101·1).
Oestrogen deficiency.

Synapause E *Organon, Ger.*
Estriol (p.2101·1).
Menopausal disorders.

Synapause-E$_3$ *Organon, Neth.*
Estriol (p.2101·1).
Adjunct in cervical smear tests; menopausal disorders; oestrogen deficiency.

Synaprosyn *Roche, Venez.†.*
Naproxen (p.92·3).
Inflammation; musculoskeletal and joint disorders; pain.

Synarel *Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pharmacia, Hong Kong†; Pharmacia, Hung.†; Pfizer, Irl.; Pharmacia, Israel; Pfizer, Mex.†; Pharmacia, NZ†; Pfizer, Neth.; Pharmacia, Pol.; Pharmacia, S.Afr.; Pfizer, Spain; Ali, Turk.; Pfizer, UK; Searle, USA.*
⊗ Nafarelin acetate (p.2117·3).
Endometriosis; female infertility; ovulation stimulation for in-vitro fertilisation; precocious puberty; uterine fibroids.

Synarela *Pfizer, Denm.; Pfizer, Fin.; Pharmacia, Ger.; Pfizer, Norw.; Pfizer, Swed.*
⊗ Nafarelin acetate (p.2117·3).
Endometriosis; ovarian stimulation for in-vitro fertilisation; uterine fibroids.

Synarome *Faran, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Synastone *Auden McKenzie, UK.*
⊗ Methadone hydrochloride (p.82·3).
Opioid withdrawal syndrome.

Synax *Biofarma, Turk.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Synbetamine *Synco, Hong Kong.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions; inflammatory eye disorders.

Synbio *Kalbe, Indon.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium longum* (p.2372·3); fructo oligosaccharides.
Digestive disorders.

Synbion *Synco, Hong Kong.*
vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

SynBiotics-3 *NutraCea, USA.*
Bifidobacterium longum (p.2372·3); *Lactobacillus rhamnosus* (p.2372·3); *Lactobacillus plantarum*; *Saccharomyces boulardii* (p.2372·3).

Synbrozil *Synco, Hong Kong.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Syncarpin-N *Winzer, Ger.†.*
Pilocarpine hydrochloride (p.1884·3); neostigmine bromide (p.631·3).
Glaucoma; reversal of mydriasis.

Synchlolim *Atlantic, Thai.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Synchloramin *Synco, Hong Kong.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Synchrocell *Dermoteca, Port.*
Acediosmin; aescin (p.2248·2); acetyl glucosamine (p.2313·2); glucuronic acid (p.2314·1).
Cellulite.

Synchro-Levels *Alphrema, Ital.*
Vitamin, amno-acid, mineral, and fatty acid preparation (p.1922·1).

Synchrorose *Dermoteca, Port.*
Silymarin (p.1452·2); acetyl glucosamine (p.2313·2); *dl*-alpha tocoferil acetate (p.1992·3); hyaluronic acid (p.2320·1).
High skin coloration.

Synchrovit *Dermoteca, Port.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3); acetyl glucosamine (p.2313·2); glucuronic acid (p.2314·1); hyaluronic acid (p.2320·1).
High skin coloration.

Synclar *Cipla, Hong Kong; Cipla, India.*
Clarithromycin (p.248·2).
Bacterial infections.

Synclovir *Synco, Hong Kong.*
Aciclovir (p.862·3).
Herpes simplex infections.

Syncloxil *Jumont, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Synco-CFN *Synco, Hong Kong.*
⊗ Clotrimazole (p.530·1); fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Syncofit *Synco, Hong Kong.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract congestion.

Syncoforte *Synco, Hong Kong.*
Vitamin B substances (p.1922·1).
Vitamin B deficiencies.

Syncomet *Synco, Hong Kong.*
Cimetidine (p.1716·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Syncoquin *Synco, Hong Kong.*
Chloroquine phosphate (p.599·3).
Amoebic hepatitis; lupus erythematosus; malaria; rheumatoid arthritis.

Syncortyl *Sanofi-Aventis, Fr.*
Desoxycortone acetate (p.1525·3).
Mineralocorticoid deficiency.

Syncro *Fontovit, Braz.*
Vitamin and mineral preparation (p.1922·1).

Syncumar *Valeant, Hung.; ICN, Pol.*
Acenocoumarol (p.1201·1).
Thromboembolic disorders.

Syndol
Note. This name is used for preparations of different composition.
Roche, Chile.
Ketorolac trometamol (p.74·2).
Pain.

SSL, Irl.; Adcock Ingram, S.Afr.; SSL, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2); caffeine (p.1116·3).
Pain.

Bilim, Turk.
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Syndopa *Sun, India; Sun, Rus.; Sun, Thai.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Syneclav *Coronet, Indon.*
Amoxicillin (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Synedil *Erempharma, Fr.*
Sulpiride (p.1028·3).
Anxiety; behaviour disorders in children; psychoses.

Synemol *Medicis, USA.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Syneolona *Synco, Hong Kong.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Syneophylline *Synco, Hong Kong.*
Diprophylline (p.1120·2).
Obstructive airways disease.

Synera *Ferndale, USA.*
Lidocaine (p.1862·3); tetracaine (p.1871·2).
Local anaesthesia.

Synerbiol *Nutergia, Fr.*
Marine fish oil (p.1362·2).
Nutritional supplement.

Synercid
Aventis, Arg.†; Aspen, Austral.; Aventis, Austria; Aventis, Fin.†; Nordic, Fr.; Aventis, Ger.†; Aventis, Irl.; Aventis, Israel; Healthcare Logistics, NZ; Aventis, Neth.; Aventis, Pol.; Sanofi-Aventis, Spain; Aventis, Swed.†; Nordic, UK.
Quinupristin mesilate (p.322·1); dalfopristin mesilate (p.322·1).
Bacterial infections.
Sanofi-Aventis, Braz.; Monarch, Canad.; Monarch, Cz.; Sanofi-Aventis, Gr.; Monarch, Hung.; Sanofi-Aventis, Ital.; Aventis, Mex.†; Monarch, Port.; Aventis, S.Afr.†; Aventis, Switz.†; Monarch, USA.
Quinupristin (p.322·3); dalfopristin (p.322·3).
Bacterial infections.

Synerga *Laves, Ger.*
Cell-free lysate of *Escherichia coli*.
Allergies.

Synergistic Selenium *Quest, Canad.*
Selenium, vitamin C, and vitamin E (p.1922·1).

Synergomycin *Abbott, Ger.†.*
Erythromycin ethyl succinate (p.269·3); bromhexine hydrochloride (p.1552·2).
Bacterial infections of the respiratory tract.

Synergon *Merck-Lipha, Fr.; Biofarma, Turk.*
Progesterone (p.2125·1); estrone (p.2101·2).
Amenorrhoea; menopausal disorders.

Synergy Defense *Awareness, Canad.*
Amylase; protease; cellulase; lactase; diastase; invertase.
Digestive aid.

Syner-Kinase *Syner-Med, UK.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Synermed *Vitalink, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Synermox *Douglas, NZ.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Synerpril *MSD, Austria; MSD, Denm.; MSD, Swed.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Synespramid *Ultra, Mex.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal motility disorders; nausea and vomiting.

Syneudon *Krewel, Ger.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Synfase *Pfizer, Norw.; Pfizer, Swed.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3). 28-Day packs also contains 7 inert tablets.
Triphasic oral contraceptive.

Synflex *Altimed, Canad.†; Roche, Hong Kong†; Darya-Varia, Indon.; Syntex, Indon.; Roche, Irl.; Recordati, Ital.; Roche, Malaysia; Roche, NZ; Roche, S.Afr.; Roche, Thai.; Roche, UK.*
Naproxen sodium (p.92·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Syngasy *Ultra, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Syngel *Will-Pharma, Belg.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); magnesium hydroxide (p.1743·2); magnesium trisilicate (p.1744·1); lidocaine hydrochloride (p.1862·3).
Gastritis; gastro-oesophageal reflux.

Synglarin *Chibret, Port.*
Montelukast sodium (p.1126·2).
Allergic rhinitis.

Syngynon *Jenapharm, Ger.†.*
Hydroxyprogesterone caproate (p.2110·3); estradiol benzoate (p.2097·2).
Menstrual disorders.

Synitidine *Synco, Hong Kong.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Synizoral *Synco, Hong Kong.*
Ketoconazole (p.539·1).
Fungal infections.

Synkapton *Strallhofer, Austria.*
Ergotamine tartrate (p.620·1); dimenhydrinate (p.576·2); caffeine (p.1116·3).
Migraine and other vascular headaches.

Synmethasone *Synco, Hong Kong.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Synobel *Yamanouchi, Spain†.*
⊗ Clioquinol (p.254·1); fluocinolone acetonide (p.1531·3).
Infected skin disorders.

Synocrom
Italchimici, Ital.
Sodium hyaluronate (p.2320·1).
Knee disorders.
Dee, UK.
Hyaluronic acid (p.2320·1).
Joint disorders.

Synodium *Synco, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Synol *Filadams, Philipp.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; uric acid nephropathy.

Synostep *Ultra, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Syn-O-Vits *Osoth, Thai.*
Multivitamin preparation with lysine (p.1922·1).

Synoxicam *Synco, Hong Kong.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Synparyn *Ultra, Mex.*
Albendazole (p.139·2).
Worm infections.

Synphase *Pharmacia, Hong Kong†; Pharmacia, UK.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Triphasic oral contraceptive.

Synphasec *Grunenthal, Ger.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3).
Triphasic oral contraceptive.

Synphasic *Pharmacia, Austral.; Pfizer, Canad.; Pfizer, NZ.*
Ethinylestradiol (p.2101·3); norethisterone (p.2119·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Synpitan *Deva, Turk.*
Oxytocin (p.2015·2).
Caesarean section; incomplete abortion; labour induction; postpartum haemorrhage.

Synrelin *Pfizer, Arg.*
⊗ Nafarelin acetate (p.2117·3).
Endometriosis; female infertility; precocious puberty; uterine fibroids.

Synrelina *Pfizer, Switz.*
⊗ Nafarelin acetate (p.2117·3).
Endometriosis.

Syntaris *Docpharma, Belg.; Roche, Cz.; Dermapharm, Ger.; Roche, Irl.†; Recordati, Ital.; Ivax, Neth.; Roche, Switz.†; Ivax, UK.*
⊗ Flunisolide (p.1531·1).
Allergic rhinitis.

Syntarpen *Polfa Tarchomin, Pol.*
Cloxacillin sodium (p.256·1).
Staphylococcal infections.

Syntemax *Pascual, Philipp.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected ear disorders.

Syntemucol *Synteza, Pol.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Syntest *Breckenridge, USA.*
⊗ Esterified oestrogens (p.2097·1); methyltestosterone (p.2117·1).
Menopausal disorders.

Syntestan *Teofarma, Ger.*
⊗ Cloprednol (p.1523·1).
Asthma; polyarthritis.

Synthamin *Baxter, Austral.; Baxter, Ger.; Baxter, Irl.; Baxter, NZ; Baxter, Spain; Baxter, Switz.; Baxter, UK.*
Amino-acid infusion with or without electrolytes and glucose (p.1922·1).
Parenteral nutrition.

Synthocilin *Pharmaceutical Co, India.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Synthol
Note.This name is used for preparations of different composition.
Eumedica, Belg.
Cloral hydrate (p.979·1); menthol (p.2340·1); resorcinol (p.1612·1); veratrol.
Skin and mucous membrane disorders.
GSK Sante, Fr.
Menthol (p.2340·1); resorcinol (p.1612·1); salicylic acid (p.1612·2); veratrol.
Formerly contained cloral hydrate, menthol, resorcinol, salicylic acid, and veratrol.
Insect stings; mouth and throat disorders; soft-tissue trauma.

Synthomanet *Remedina, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Synthomycin *Nizpharm, Rus.*
Chloramphenicol (p.239·3).
Bacterial infections.

Synthomycine *Abic, Israel; Rekah, Israel; Teva, Israel.*
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Synthroid *Abbott, Braz.; Abbott, Canad.; Abbott, USA.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; thyroid-stimulating hormone suppression.

Synti *Medochemie, Malaysia†.*
Dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Syntocinon *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Hong Kong; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Novartis, Malaysia; Sandoz, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Port.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Alliance, UK; Novartis, Venez.*
Oxytocin (p.2015·2).
Caesarean section; incomplete abortion; induction and maintenance of labour; lactation induction; lochiometra; mastitis; missed abortion; postpartum haemorrhage; postpartum uterine atony; termination of pregnancy; third-stage labour induction.

Syntoclox *Codal Synto, Thai.*
Cloxacillin sodium (p.256·1).
Bacterial infections.

Syntometrin *Novartis, Ger.†.*
Methylergometrine maleate (p.2011·1); oxytocin (p.2015·2).
Delivery of the placenta; postpartum haemorrhage.

Syntometrine *Novartis, Austral.; Novartis, Hong Kong†; Novartis, Irl.; Novartis, Malaysia; Novartis, NZ; Novartis, S.Afr.; Alliance, UK.*
Ergometrine maleate (p.2009·2); oxytocin (p.2015·2).
Management of third-stage labour; postpartum haemorrhage.

Syntonol *Codal Synto, Thai.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; hypertension; phaeochromocytoma; tremor.

Syntophyllin *BB, Cz.; Zentiva, Cz.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Syntopic *Vendiz, Philipp.*
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Syntostigmin *BB, Cz.; Zentiva, Cz.*
Neostigmine bromide (p.631·3) or neostigmine metilsulfate (p.631·3).
Decreased gastrointestinal motility; glaucoma; myasthenia gravis; reversal of competitive neuromuscular blockade; urinary retention.

Synum C *Biosyn, Ger.†.*
Ascorbic acid (p.1983·3).
Methaemoglobinaemia; vitamin C deficiency.

Synvisc *Gobbi, Arg.; Genzyme, Austral.; Novartis, Braz.; Genzyme, Canad.; Novartis, Chile; Genzyme, Fr.; Wyeth, Ger.; Nicholas Piramal, India; Biomatrix, Israel†; Genzyme, Ital.; Genzyme, Malaysia; Novartis, Mex.; Bayer, NZ; Genzyme, Pol.; Genzyme, Singapore; Medhouse, Swed.; Genzyme, Switz.; Genzyme Biosurgery, Thai.; Wyeth, Turk.; Biomatrix, UK; Wyeth-Ayerst, USA; Novartis, Venez.*
Hylan G-F 20 (p.2320·2).
Degenerative joint disorders; osteoarthritis; synovial fluid replacement.

Synvomin *Synco, Hong Kong.*
Promethazine teoclate (p.588·3).
Nausea and vomiting.

Syprine *Aton, USA.*
Trientine dihydrochloride (p.1467·3).
Wilson's disease.

Syprol *Rosemont, UK.*
⊗ Propranolol hydrochloride (p.1380·3).

Syracol CF *Roberts, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Syraprim *Galen, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Syrea *Medac, Ger.*
Hydroxycarbamide (p.729·1).
Chronic myeloid leukaemia; essential thrombocythaemia; polycythaemia vera.

Syrop Prawoslazowy Zlozony *Gemi, Pol.*
⊗ Althaea (p.2253·3); ephedrine hydrochloride (p.1558·2).
Respiratory-tract infections.

Syrop Sosnowy Zlozony *Aflofarm, Pol.; Herbapol Lublin, Pol.*
Calcium lactate; greater celandine; codeine phosphate (p.37·2); pimpinella anisum; pinus silvestris.
Cough and associated respiratory-tract disorders.

Syrup DM *Therapex, Canad.*
Dextromethorphan hydrobromide (p.1555·2).

Syrup DM-D *Therapex, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Syrup DM-D-E *Therapex, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).

Syrup DM-E *Therapex, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Syruped *Brel, Philipp.*
⊗ Prednisolone sodium phosphate (p.1541·2).
Corticosteroid.

Syrvite *Barre-National, USA; Major, USA; Moore, USA.*
Multivitamin preparation (p.1922·1).

Syscan *Torrent, India; Torrent, Philipp.; Torrent, Rus.*
Fluconazole (p.532·1).
Fungal infections.

Syscor *Bayer, Austria; Bayer, Belg.; AstraZeneca, Braz.; Bayer, Cz.†; Bayer, Fin.; Bayer, Gr.; Bayer, Ital.; Bayer, NZ; Zeneca, S.Afr.†; Bayhealth, Spain; AstraZeneca, Switz.†; Forest Laboratories, UK.*
Nisoldipine (p.1358·1).
Angina pectoris; heart failure; hypertension.

Systabon *Merck, Indon.*
Pramiverine hydrochloride (p.2372·1).
Post-operative pain; smooth muscle spasm.

Systaflam *Systopic, India.*
Chlorzoxazone (p.1894·3); diclofenac sodium (p.44·3); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Systane
Note.This name is used for preparations of different composition.
Alcon, Arg.; Alcon, Canad.; Alcon, Chile; Alcon, Fr.; Alcon, Hong Kong; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, Philipp.; Alcon, Singapore; Alcon, Thai.; Alcon, Venez.
Macrogol 400 (p.2336·3); propylene glycol (p.2374·1).
Dry eyes; eye irritation.
Alcon, Ger.; Alcon, Irl.; Alcon, UK.
Hydroxypropyl guar.
Dry eyes; eye irritation.

Systen *Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Fr.; Janssen-Cilag, Hung.†; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Systen Conti *Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Gr.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Systen Sequi *Janssen-Cilag, Braz.; Janssen-Cilag, Cz.; Janssen-Cilag, Gr.; Janssen-Cilag, Pol.; Janssen-Cilag, Switz.*
4 Patches, estradiol (p.2097·2); 4 patches, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Systepin *Klinge, Irl.†.*
Nifedipine (p.1350·1).
Hypertension; ischaemic heart disease.

Systilan *Biomedica-Chemica, Gr.†.*
Cisapride (p.1720·3).
Gastrointestinal motility disorders.

Systogen *Infusia, Cz.†.*
Carboxycellulose calcium; cellulose (p.2143·1).
Exudative wounds and ulcers.

Systral *Viatris, Ger.; Asta Medica, Hong Kong†; Asta Medica, Indon.; Transfarma, Philipp.; Sidefarma, Port.; Meda, Thai.; Pharmalink, Thai.; Ulagay, Turk.*
Chlorphenoxamine hydrochloride (p.572·3).
Allergic skin disorders; burns; eczema; frostbite; insect bites; pruritus; skin irritation; stings; sunburn; urticaria.

Systral C *Viatris, Ger.†.*
Chlorphenoxamine hydrochloride (p.572·3); caffeine (p.1116·3).
Hypersensitivity reactions.

Systral Hydrocort *Viatris, Ger.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Sytron *Link, UK.*
Sodium feredetate (p.1962·1).
Iron-deficiency anaemia.

Syu *Anglo-French Drugs, India.*
Nutritional supplement (p.1922·1).

Syviman N *Muller Goppingen, Ger.†.*
Comfrey (p.2286·3); mistletoe (p.2345·3).
Joint disorders.

Syxal *Syxyl, Ger.†.*
St John's wort (p.422·3).
Depression.

Szorbit *Human, Hung.†.*
Sorbitol (p.1965·1).
Carbohydrate source.

T-1 *Osoth, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

T-3
Note. A similar name is used for preparations of different composition (see below).
Unipharma, Gr.
Liothyronine sodium (p.2174·1).
Hypothyroidism.

T3
Note. A similar name is used for preparations of different composition (see above).
Hoe, Singapore.
Triclosan (p.1665·2); melaleuca oil (p.2338·2).
Acne.

T4 *Montpellier, Arg.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism; thyroid cancer; thyroiditis.

T-4 *Unipharma, Gr.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

T5 *MC, Ital.†*
Glutaral (p.1645·2).
Instrument disinfection.

T3 Acne *Hoe, Malaysia.*
Triclosan (p.1665·2); melaleuca oil (p.2338·2).
Acne.

T3 Actin *Hoe, Malaysia.*
Tretinoin (p.1618·1).
Acne.

T. Polio *Aventis Pasteur, Fr.†.*
A tetanus and poliomyelitis (inactivated) vaccine (p.2241·1).
Active immunisation.

TA Baume *Bencard, Ger.*
Allergen extracts of tree pollen (p.2370·2)(p.2250·2).
Allergen immunotherapy.

TA Graser *Bencard, Ger.*
Allergen extracts of grass pollen (p.2370·2)(p.2250·2).
Allergen immunotherapy.

TA MIX *Bencard, Ger.*
Allergen extracts of mixed pollens (p.2370·2)(p.2250·2).
Allergen immunotherapy.

TA Osoth *Osoth, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tabalon *Teofarma, Ger.; Aventis, Mex.*
Ibuprofen (p.64·2).
Fever; gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; pain.

Tabarell *Sanorell, Ger.*
Homoeopathic preparation.

Tabas *Meprofarm, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Tab-A-Vite *Major, USA.*
A range of vitamin preparations (p.1922·1).

Tabcin *Bayer, Austria.*
Ibuprofen (p.64·2).
Pain.

Tabcin Alergia *Bayer Consumer, Arg.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Tabcin Antigripal *Bayer Consumer, Arg.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Formerly contained paracetamol, butetamate citrate, caffeine, and phenylephrine hydrochloride.
Cold and influenza symptoms.

Tabcin Caliente Descongestivo NF *Bayer Consumer, Arg.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Tabcin Compuesto *Bayer Consumer, Arg.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Tabcin Expectorante *Bayer, Arg.†.*
Ambroxol hydrochloride (p.1550·3).
Coughs.

Tabcin Impakt *Bayer, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2).
Cold and influenza symptoms.

Tabcin Trend *Bayer, Pol.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Taben 450 *Wassen, Ital.†.*
Magnesium; potassium; sodium; taurine (p.1922·1).
Nutritional supplement.

Taberil *Pharmacypria, Gr.*
Paroxetine (p.414·2).
Depression.

Tabex *Sopharma, Bulg.; Pharmachim, Hung.†; Sopharma, Pol.; Sopharma, Rus.*
Cytisine (p.2291·3).
Aid to smoking withdrawal; nicotine dependence.

Tabine *BPL-Meizler, Braz.†; Korea United, Philipp.*
Cytarabine (p.705·1).
Malignant neoplasms.

Tabletas Antiacidas *Pasteur, Chile.*
Magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Tabletas Phillips *GSK, Chile.*
Calcium carbonate (p.1714·1); aluminium hydroxide-sorbitol complex (p.1706·2) (p.1965·1); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Tabletas Quimpe *Quimpe, Spain.*
⊗ Atropine methonitrate (p.1219·3); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); ephedrine hydrochloride (p.1558·2); phenazone (p.116·1); propyphenazone (p.119·3).
Upper respiratory-tract disorders.

Tabletes Valda *Canonne, Braz.†.*
Menthol (p.2340·1); cineole (p.2282·3); terpineol (p.2396·1); thymol (p.1664·3).
Mouth and throat disorders.

Tabletki Przeciw Grypie *Cyntfarm, Pol.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold and influenza symptoms.

Tabletki Przeciw Niestrawnosci *Labofarm, Pol.*
Caraway (p.2276·3); frangula bark (p.1732·2); peppermint (p.1761·2); milk thistle (p.1452·1); taraxacum (p.2395·1).
Digestive disorders.

Tabletki Tonizujace *Labofarm, Pol.*
Crataegus (p.2289·1); motherwort; melilotus.
Cardiac disorders.

Tabletki Uspokajajace *Labofarm, Pol.*
Lupulus (p.2335·2); motherwort; melissa; valerian (p.2410·1).
Insomnia; nervous disorders.

Tablibut *Andromaco, Venez.†.*
Cetylpyridinium chloride (p.1635·1).
Sore throat.

Tabloid *GSK, USA.*
Tioguanine (p.779·1).
Acute myeloid leukaemia.

Tabonuco *Vargas, Venez.*
⊗ Ipecacuanha (p.1562·3); ephedrine hydrochloride (p.1558·2); sodium benzoate (p.1630·2).
Respiratory-tract congestion.

Tabotamp *Johnson & Johnson, Ger.; Johnson & Johnson, Ital.*
Oxidised cellulose (p.1075·1).
Surgical haemorrhage.

Tabphyn *ProStrakan, UK.*
Tamsulosin hydrochloride (p.2197·1).

Tabrin *Sanofi-Aventis, Gr.*
Ofloxacin (p.310·2) or ofloxacin hydrochloride (p.310·2).
Bacterial infections.

Tabritis *Potter's, UK.*
Sambucus (p.2383·1); achillea (p.2245·2); prickly ash bark (p.2417·1); lappa (p.2330·3); clivers (p.2284·3); poplar bark (p.2371·1); bearberry (p.2263·3); senna (p.1769·2).
Musculoskeletal and joint disorders.

Tabrol *Aristo, India.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Tabulan *Biotech, Venez.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tabulettae Laxantes *ICN, Pol.*
Aloes (p.1705·2); althaea (p.2253·3); caraway (p.2276·3); frangula bark (p.1732·2).
Constipation; dyspepsia.

Tac *Parnell, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

TAC Esofago *Bracco, Ital.*
Barium sulfate (p.1477·2).
Contrast medium for computerised tomography of the oesophagus.

Tacardia *Penn, Arg.*
Losartan (p.1327·2).
Hypertension.

Tacardia D *Penn, Arg.*
⊗ Losartan (p.1327·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tace *Gynopharm, Chile.*
Levonorgestrel (p.2121·2).
Post-coital oral contraceptive.

Tacef *Vianex (Βιανέξ), Gr.†.*
Cefmenoxime hydrochloride (p.225·2).
Bacterial infections.

Tacex *Probiomed, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tachidol *Angelini, Ital.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Tachiflu *Angelini, Ital.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; influenza symptoms; pain.

Tachifludec *Angelini, Ital.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Fever; influenza symptoms; pain.

Tachinotte *Angelini, Ital.*
Paracetamol (p.108·1); promethazine hydrochloride (p.588·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; coughs.

Tachipirin *Elmor, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Tachipirina *Angelini, Ital.*
Paracetamol (p.108·1).
Fever; pain.

Tachmalcor *Dresden, Cz.; AWD, Ger.*
Detajmium bitartrate (p.1257·2).
Arrhythmias.

TachoComb *Nycomed, Austria; Hafslund Nycomed, Cz.†; Nycomed, Ger.†; Nycomed, Hong Kong; Nycomed, Hung.†; Nycomed, Rus.; Nycomed, Thai.†.*
Equine collagen (p.2286·1); human fibrinogen (p.1070·1); bovine thrombin (p.1080·1); bovine aprotinin (p.1055·1).
Exudation; haemorrhage.

Tacholiquin *Sigmapharm, Austria; Bene, Ger.*
Tyloxapol (p.1921·3).
Respiratory-tract disorders associated with increased or viscous mucus.

TachoSil
Nycomed, Austria; Nycomed, Cz.; Nycomed, Denm.; Leiras, Fin.; Nycomed, Fr.; Nycomed, Ger.; Nycomed, Ital.; Nycomed, Neth.; Nycomed, Norw.; Nycomed, Port.; Nycomed, Spain; Nycomed, Swed.; Nycomed, Switz.; Nycomed Amersham, UK.
Fibrinogen (p.1070·1); thrombin (p.1080·1);
On contact with physiological fluids this forms a fibrin glue (p.1069·3).
Haemorrhage.

Tachotop N *Nycomed, Ger.†.*
Collagen (p.2286·1).
Haemorrhage.

Tachydaron *AWD, Ger.†.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Tachynerg Campher Herzsalbe *Eberth, Ger.*
Benzyl nicotinate (p.28·1); camphor (p.2273·2).
Cardiac disorders.

Tachystin *Chauvin Ankerpharm, Cz.; Chauvin ankerpharm, Ger.; Chauvin Ankerpharm, Hung.; Chauvin, Rus.*
Dihydrotachysterol (p.1986·3).
Hypocalcaemia; hypoparathyroidism; osteomalacia; pseudohypoparathyroidism; tetany.

Tacicul *Denver, Arg.*
Losartan potassium (p.1326·1).
Hypertension.

Tacidine *Alphapharm, Austral.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Tacigen *Krugher, Ital.*
Gentamicin sulfate (p.282·1).
Infected skin disorders.

Tacines *Denver, Arg.*
⊗ Ciprofloxacin (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

Tacinol *Polipharm, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tacirel *Servier, Port.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris.

Taclar *Polfa Tarchomin, Pol.*
Clarithromycin (p.248·2).
Bacterial infections; peptic ulcer.

Taclipaxol *Biochimico, Braz.†.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Taclix *Cellofarm, Braz.†.*
Paclitaxel (p.759·1).
Ovarian cancer.

Taclonex *Warner Chilcott, USA.*
⊗ Calcipotriol (p.1591·3); betamethasone dipropionate (p.1518·3).
Psoriasis.

Taclorpil *Spefar, Venez.†.*
Trifluoperazine hydrochloride (p.1034·2).
Anxiety; psychoses; vomiting.

Tacna *LKM, Arg.*
Terbinafine (p.546·3).
Fungal infections.

Tacraf *Panalab, Arg.*
Tacrolimus (p.1843·1).
Atopic eczema.

Tacrinal *Biosintetica, Braz.†.*
Tacrine hydrochloride (p.370·2).
Alzheimer's disease.

Tacroinmun *LKM, Arg.*
Tacrolimus (p.1843·1).

Tacron
Note. This name is used for preparations of different composition.
Korea United, Singapore†.
Ticlopidine hydrochloride (p.1411·2).
Atherosclerosis; peripheral vascular disease.

Farmasierra, Spain.
Naproxen (p.92·3).
Fever; gout; musculoskeletal and joint disorders; pain.

Tacro-Tic *Cinetic, Arg.*
Tacrolimus (p.1843·1).
Atopic eczema.

Tacroz *Glenmark, India†.*
Tacrolimus (p.1843·1).
Atopic eczema.

Tacryl *Abigo, Denm.†.*
Methdilazine (p.585·3).
Hay fever; rhinitis; urticaria.

tactu-mobil *Feldhoff, Ger.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal and joint disorders.

tactu-nerval *Feldhoff, Ger.†.*
⊗ Bovine testicular extract (p.2129·3); bovine placental extract (p.2337·3).
Musculoskeletal disorders; nervous disorders.

TAD
Biomedica, Hong Kong.
Glutathione (p.1448·1).
Alcohol, drug, or organophosphorus poisoning; liver disorders; radiation injury.

Biomedica, Ital.
Glutathione sodium (p.1448·1).
Prophylaxis of neuropathy induced by cisplatin analogues.

Tadacip *Cipla, India.*
Tadalafil (p.2196·2).
Erectile dysfunction.

Tadalin *Munir, Turk.*
Sodium cyclamate (p.1936·3).
Sugar substitute.

Tadegan *Tarbis, Spain.*
⊗ Torasemide (p.1415·3).
Hypertension; oedema.

Tadenan *Roche, Austria; Fournier, Cz.; Fournier, Fr.; Fournier, Gr.; Fournier, Hung.†; Fournier, Ital.; Fournier, Philipp.; Fournier, Pol.; Fournier, Port.†; Fournier, Rus.; Fournier, Switz.; Fournier, Thai.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia; prostatic adenoma.

Tadenom *Aventis, Mex.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Tadex *Orion, Fin.; Atafarm, Turk.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer.

Tadim *Allertec, Gr.*
Colistimethate sodium (p.256·3).
Cystic fibrosis.

Tadinar-C *Arlex, Mex.*
Loratadine (p.583·3); ambroxol (p.1550·3).
Respiratory-tract disorders.

Tadol *Pharmacodane, Denm.*
Tramadol hydrochloride (p.130·3).
Pain.

Tadolak *Saba, Turk.*
Etodolac (p.52·2).
Osteoarthritis; rheumatoid arthritis.

Tafen *Lek, Cz.; Lek, Pol.; Lek, Rus.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps; obstructive airways disease.

Tafenil *Asofarma, Mex.*
Flutamide (p.725·1).
Prostatic cancer.

Tafil *Pfizer, Denm.; Pharmacia, Ger.; Pfizer, Mex.; Pfizer, Venez.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; mixed anxiety depressive states; panic disorder.

Tafirol *Sidus, Arg.; Asofarma, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Tafirol AC *Asofarma, Mex.*
Paracetamol (p.108·1); diclofenac potassium (p.44·3).
Fever; inflammation; pain.

Tafirol Artro *Sidus, Arg.*
Paracetamol (p.108·1); diclofenac potassium (p.44·3).
Musculoskeletal and joint disorders.

Tafirol Flex *Asofarma, Mex.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Muscle spasm; pain.

Tafloc *Pharmacare, S.Afr.*
Ofloxacin (p.310·2).
Bacterial infections.

Taflosin *Menarini, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Taflox *Fariberica, Port.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Tafocex *Pliva, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Tafoxam *Biopharm, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Tafril *Polfa Tarchomin, Pol.*
Cefradine (p.233·1) or cefradine with L-arginine.
Bacterial infections.

Tafrom *Cipla, India.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Tagadine *Duopharma, Hong Kong†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Tagal *Probiomed, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Tagaliv *Teuto, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Tagamet
Key, Arg.†; GSK, Austral.; Vianex (Βιανέξ), Gr.; GSK, Hong Kong; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, Neth.; GSK, Norw.; GSK, Philipp.; Smith Kline & French, Port.; GSK, Singapore; GSK, Spain; SmithKline Beecham, Switz.†; GSK, Thai.†; Chemidex, UK; GSK, UK.
Cimetidine (p.1716·2).
Acid aspiration; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatic insufficiency; peptic ulcer; scleroderma oesophagitis; short-bowel syndrome; Zollinger-Ellison syndrome.

GSK, Belg.; GSK, Canad.†; Axcan, Fr.; GSK, Ger.; GSK, Ital.; GSK, S.Afr.; GSK, Swed.; GSK, USA.
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; adjunct in cystic fibrosis; anaphylactic shock; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

GSK, Braz.
Cimetidine hydrochloride (p.1716·3).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

TAGG *Eagle, Austral.†.*
Benzalkonium chloride (p.1629·1); lauromacrogol 400 (p.1916·1).
Deodorant detergent for ostomies.

Tagonis *GSK, Ger.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Tagren *KRKA, Cz.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Taguinol *Spyfarma, Spain.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Taharmayim *Medentech, Israel.*
Troclosene sodium (p.1665·3).
Water purification.

Taharsept *Medentech, Israel.*
Troclosene sodium (p.1665·3).
Instrument, surface, and equipment disinfection.

Tahartaf *Medentech, Israel.*
Troclosene sodium (p.1665·3).
Equipment disinfection.

Tahor *Pfizer, Fr.*
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Tai Ginseng N *Poehlmann, Ger.*
Ginseng; crataegus; vitamins (p.1922·1).
Tonic.

Taido *Cetem, Fr.*
Glycerol (p.2314·2); honey (p.1948·2); collagen (p.2286·1).
Vaginal lubricant.

Taigalor *Nycomed, Ital.*
Lornoxicam (p.77·3).
Inflammation; pain.

Taingel *Cabassi, Ital.*
Royal jelly; pollen; ginseng; eleutherococcus (p.1922·1).
Nutritional supplement.

Tainol *Elmor, Venez.†.*
Paracetamol (p.108·1); caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2).
Headache.

Tairal *Rottapharm, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Takadol *Expanscience, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Takata *Madariaga, Spain.*
Senna (p.1769·2).
Formerly contained aloin, belladonna, and phenolphthalein.
Constipation.

Takecef *Sofar, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Takelin *Mersifarma, Indon.*
Citicoline (p.2283·3).
Cerebrovascular disorders; head injury.

Takepron *Takeda, Hong Kong; Takeda, Jpn.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Takesulin *Takeda, Jpn.*
Cefsulodin sodium (p.233·3).
Mepivacaine hydrochloride (p.1866·3) is included in the intramuscular injection to alleviate the pain of injection.
Pseudomonal infections.

Taketiam *Takeda, Fr.*
Cefotiam hexetil hydrochloride (p.230·1).
Bacterial infections.

Takigrip *Farma Lepori, Spain†.*
Ibuprofen sodium (p.65·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Takil *Marjan, Braz.*
Tinidazole (p.848·3); tioconazole (p.548·2).
Vaginal infections.

Takiprina *Lepori, Port.*
Paracetamol (p.108·1).
Fever; pain.

Takomen *Inquifave, Venez.†.*
⊗ Bumetanide (p.1237·1).
Diuretic.

Taks *Codal Synto, Malaysia†; Codal Synto, Thai.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders.

Takus *Pharmacia, Ger.*
Ceruletide tris(diethylamine) (p.2279·2).
Diagnostic agent; paralytic ileus; postoperative atony.

Talacen *Sanofi Winthrop, USA.*
⊗ Pentazocine hydrochloride (p.112·2); paracetamol (p.108·1).
Pain.

Talam *Arrow, Austral.*
Citalopram hydrobromide (p.385·3).
Depression.

Talasa NF *Andromaco, Arg.*
Butamirate citrate (p.1553·1).
Coughs.

Talavir *Sigma-Tau, Ital.*
Valaciclovir hydrochloride (p.911·1).
Herpes zoster infections.

Talcef *Ipca, India†; Ipca, Rus.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Talcid *Bayer, Austria; Bayer, Cz.; Bayer, Ger.; Bayer, Gr.; Bayer, Hung.; Bayer, Israel†; Bayer, Mex.; Bayer, Neth.; Bayer, Pol.; Bayer, Rus.; Bayer, Spain; Bayer, Turk.*
Hydrotalcite (p.1733·3).
Antacid; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Talcilina *Ronnet, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Talco Alivio *Simoes, Braz.†.*
Purified talc (p.1615·2); starch (p.1968·1); zinc oxide (p.1621·2); salol (p.122·1); boric acid (p.2268·1); sulfur (p.1614·1); menthol (p.2340·1); camphor (p.2273·2); salicylic acid (p.1612·2).
Pruritus.

Talema *Biotech, Venez.*
Diazepam (p.986·3).
Aggression; anxiety; delirium tremens; epilepsy; mania.

Talerc *Boehringer Ingelheim, Braz.*
Epinastine hydrochloride (p.579·3).
Hypersensitivity reactions.

Taleum *EGIS, Hung.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; asthma.

Talflex *Bago, Chile.*
Ketoprofen (p.73·1).
Gout; inflammation; musculoskeletal, joint peri-articular, and soft-tissue disorders; pain.

Talgan *Anpharm (Ανφαρμ), Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Talgesil *Duopharma, Malaysia.*
⊗ Fentanyl (p.55·3).
Analgesia during anaesthesia; general anaesthesia; premedication.

Talgo *Ern, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Talicix *Alter, Spain.*
Clarithromycin (p.248·2).
Bacterial infections.

Talidat *Merck, Austria; Bolder, Cz.; Cheplapharm, Ger.; Merck, Neth.; Merck, Port.†.*
Hydrotalcite (p.1733·3).
Dyspepsia; gastric hyperacidity; heartburn.

Talion
Note. This name is used for preparations of different composition.
Tanabe, Jpn.
Bepotastine besilate (p.569·1).
Allergic rhinitis; pruritus; urticaria.

Herbapol Krakow, Pol.
Taraxacum (p.2395·1).
Digestive disorders; liver and biliary-tract disorders.

Talirax *Demo, Gr.†.*
⊗ Fluorometholone (p.1532·3).
Inflammatory eye disorders.

Taliviform *Pharmacos, Mex.†.*
Clioquinol (p.254·1); papaverine (p.2191·3).
Diarrhoea.

Talizer *Serral, Mex.*
Thalidomide (p.2397·1).
Adjunct in HIV infection; leprosy.

Talliton *Egis, Cz.; EGIS, Hung.; Egis, Rus.*
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.

Talnur *Sandoz, Arg.*
⊗ Fentanyl (p.55·3).
Pain.

Talofen *Fournier, Ital.*
Promazine hydrochloride (p.1021·2).
Anxiety; intractable hiccup; pain; psychoses; vomiting.

Talofilina *Novartis, Braz.*
Theophylline (p.1140·1).
Obstructive airways disease.

Talohexal *Hexal, Austral.*
Citalopram hydrobromide (p.385·3).
Depression.

Taloken *Kendrick, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Talol *Saval, Chile.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Talomil *Adcock Ingram, S.Afr.†.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Talopram *Alvia (Αλβια), Gr.*
Citalopram (p.385·3).
Depression.

Talopron *Biomedica-Chemica, Gr.*
Citalopram (p.385·3).
Depression.

Talotren *Novartis, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Talowin
Note. This name is used for preparations of different composition.
Costec, Arg.
Cream: Aloe vera (p.1588·2); dexpanthenol (p.2362·1).
Emollient.

Costec, Arg.
Shampoo: Chloroxylenol (p.1640·2).
Dandruff; seborrhoea.

Taloxa *Aesca, Austria; Schering-Plough, Belg.; Schering-Plough, Cz.†; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Hung.; Schering-Plough, Ital.; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Port.; Schering-Plough, Swed.; Essex, Switz.*
Felbamate (p.481·1).
Epilepsy; Lennox-Gastaut syndrome.

Talozin *Adeka, Turk.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Talpramin *Psicofarma, Mex.*
Imipramine hydrochloride (p.400·3).
Anxiety; depression; hyperhidrosis of the hands; myoclonus; nocturnal enuresis; pain; parasomnias; urinary incontinence.

Talquistina *Lesvi, Spain.*
Calamine (p.1591·2).
Insect bites; pruritus.

Talseclin *BMS, Chile†.*
Tetracycline (p.347·1); amphotericin b (p.523·2).
Fungal vulvovaginal infections; trichomoniasis.

Talso *Sanofi Synthelabo, Ger.; Winthrop, Ger.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Talsutin *BMS, Braz.; BMS, Hong Kong; BMS, Indon.; BMS, Malaysia†; BMS, Venez.†.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).
Bacterial and fungal vaginal infections.

Taludon *Sigma, Braz.†.*
Phenytoin (p.495·2); glutamic acid (p.1947·1).
Epilepsy.

Taluron *Geolab, Braz.†.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Talusin *Abbott, Ger.; Abbott, Pol.*
Proscillaridin (p.1382·1).
Heart failure.

Taluvian *Abbott, Gr.†; Abbott, Ital.†; Armstrong, Mex.; Esteve, Spain†.*
Apomorphine hydrochloride (p.795·1).
Erectile dysfunction.

Talval *Lipha, Switz.*
Idrocilamide (p.1897·2).
Musculoskeletal and joint disorders.

Talvosilen *Sigmapharm, Austria; Bene, Cz.; Bene, Ger.; Bene, Hung.; Bene, Pol.; Milupa, Switz.†.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Talwin
Hospira, Canad.; Sanofi Synthelabo, Canad.
⊗ Pentazocine hydrochloride (p.112·2) or pentazocine lactate (p.112·3).
Adjunct to general anaesthesia; pain; premedication.

Abbott, Israel†; Hospira, Ital.; Sanofi Winthrop, USA.
⊗ Pentazocine lactate (p.112·3).
Pain; premedication.

Talwin Compound *Sanofi Winthrop, USA†.*
⊗ Pentazocine hydrochloride (p.112·2); aspirin (p.20·3).
Pain.

Talwin NX *Sanofi Winthrop, Israel†; Sanofi Winthrop, USA.*
⊗ Pentazocine hydrochloride (p.112·2).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Talzic *Elmor, Venez.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Tam *Alacan, Spain.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Tamagon *Medochemie, Hong Kong; Medochemie, Malaysia†.*
Terfenadine (p.590·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Tamalis *Uriach, Cz.*
Rupatadine fumarate (p.590·2).
Allergic rhinitis; urticaria.

Tamaril *Marjan, Braz.*
Senna (p.1769·2); tamarind (p.1775·3); cassia pulp (p.1715·3); liquorice (p.1740·3); coriander (p.2288·1).
Constipation.

Tamarine
Note. This name is used for preparations of different composition.
GSK, Arg.†.
Tamarind (p.1775·3); anthraquinone glycosides.
Constipation.

GSK, Chile.
Senna (p.1769·2); tamarind (p.1775·3); prune (p.1765·1); apple.
Constipation.

GSK Sante, Fr.
Tamarind (p.1775·3); senna (p.1769·2).
Constipation.

Wyeth Consumer, Ital.
Tamarind (p.1775·3); cassia (p.1715·3); senna (p.1769·2); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Barrenne, Braz.
Capsules: Tamarind (p.1775·3); cassia (p.1715·3); senna (p.1769·2); coriander (p.2288·1).
Constipation.

Barrenne, Braz.
Oral gel: Tamarind (p.1775·3); cassia pulp (p.1715·3); senna (p.1769·2); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Tamarix *Hebron, Braz.†.*
Tamarind (p.1775·3); cassia pulp (p.1715·3); senna (p.1769·2); coriander (p.2288·1); liquorice (p.1740·3).
Constipation.

Tamax *Fresenius Kabi, Austria.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Tambac *Cadila, India.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Tambocor *Sidus, Arg.†; 3M, Austral.; 3M, Belg.; 3M, Canad.; 3M, Chile; 3M, Cz.; 3M, Denm.; 3M, Fin.; 3M, Ger.; IFET (ΙΦΕΤ), Gr.; 3M, Hong Kong; 3M, Irl.; 3M, Israel; 3M, Malaysia; 3M, Mex.; 3M, NZ; 3M, Neth.; 3M, Norw.; 3M, Philipp.; 3M, S.Afr.; 3M, Singapore; 3M, Swed.; 3M, Switz.; 3M, Thai.; 3M, UK; Graceway, USA.*
Flecainide acetate (p.1288·1).
Arrhythmias.

Tambutec *Tecnofarma, Mex.*
Ethambutol (p.275·2).
Tuberculosis.

Tamcocin *Pyridam, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Tamec *Ecosol, Switz.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamex *Serral, Mex.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Hypersensitivity reactions.

Tamexin *Ratiopharm, Fin.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamictor *Avansor, Fin.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamifen *Medochemie, Cz.†; Medochemie, Hong Kong†; Medochemie, Rus.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer; mastalgia.

Tamiflu *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA.*
Oseltamivir phosphate (p.900·2).
Influenza.

Tamigen *Solfran, Mex.*
Gentamicin (p.284·2).
Bacterial infections.

Tamik *IPRAD, Fr.; Marcofina, Hong Kong†.*
Dihydroergotamine mesilate (p.618·2).
Migraine; orthostatic hypotension; venous insufficiency.

Tamilan *Gador, Arg.†.*
⊗ Magnesium pemoline (p.2161·3).
Fatigue; mental function impairment.

Tamin *MSD, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Taminol *Medicus, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Tamipro *Jelfa, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamiram *Eurofarma, Braz.*
Levofloxacin (p.292·2).
Bacterial infections.

Tamisa *Eurofarma, Braz.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Tamixan *Andromaco, Venez.†.*
Mebendazole (p.148·3).
Worm infections.

Tamixol *Indeco, Arg.*
Pentoxifylline (p.1367·2).

Tamizam *Zambon, Belg.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Tamoa *Biotech, Venez.*
Pyrantel embonate (p.155·1).
Worm infections.

Tamodex *Biochem, India†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Tamofen *Hexal, Arg.†; Schering, Austria†; Aventis, Canad.; Aventis, Denm.†; Leiras, Fin.; Kalbe, Indon.; Pharmacia, Irl.†; Rhodia, Israel; Douglas, NZ; Schering, Singapore; Douglas, Thai.†; TTN, Thai.†; Er-Kim, Turk.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer.

Tamofene *Aventis, Fr.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamokadin *Kade, Ger.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamol *Ilsan, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Tamolan *Olan-Kemed, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tamolem *Laboratorios Chile, Chile†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Tamooex *BPL-Meizler, Braz.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamopham *Phamos, Ger.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamophar *Julphar, UAE.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer.

Tamoplex *Nycomed, Austria; Teva, Belg.; Asta Oncologia, Braz.†; Teva, Cz.; Detsaves (Ντετσαβες), Gr.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Pharmachemie, Philipp.; Pharmachemie, S.Afr.; Pharmachemie, Thai.; Teva, Thai.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Tamosin *Sigma, Austral.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamox *Cristalia, Braz.†; 1A, Ger.; ABZ, Ger.; Gry, Ger.; Teva, Ger.; Rowex, Irl.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxan *Kener, Mex.†; Tecnimede, Port.*
⊗ Tamoxifen citrate (p.772·3).

Tamoxasta *Baxter Oncology, Ger.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxen *Douglas, Austral.; CTI, Israel.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxene *Lisapharma, Ital.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxi *Generics, Israel.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoximerck *Merck dura, Ger.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxin *Eurofarma, Braz.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxis *Bioprofarma, Arg.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Tamoxistad *Stada, Ger.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tamoxsta *Baxter, Philipp.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer; endometrial cancer.

Tamper *Gap, Gr.*
Cimetidine (p.1716·2).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Tampo *TNP, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Tamposit N *Scheffler, Ger.†.*
Lauromacrogol 400 (p.1916·1) zinc oxide (p.1621·2); bismuth subnitrate (p.1711·2).
Anorectal disorders.

Tampositorien H *Scheffler, Ger.†.*
Hamamelis (p.2318·2).
Anorectal disorders.

Tampositorien mit Belladonna *Provita, Austria.*
Belladonna (p.2263·3); guaiazulene (p.2317·3); hamamelis (p.2318·2).
Anorectal disorders.

Tamsec *Walmark, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsil *Arrow, Austral.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Tamsol *Gedeon Richter, Hung.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsu *Rowex, Irl.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsudil *Actavis, Hung.; Actavis, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsugen *Generics, Hung.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

TamsuLek *Lek, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsulon *Zodiac, Braz.; Nolver, Venez.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsumin *Ratiopharm, Fin.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamsuna *Sandoz, Arg.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamurox *Ranbaxy, Cz.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tamyl *Ci & Di, Ital.†.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Tanac
Note.This name is used for preparations of different composition.
Del, USA.
Lipstick: Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); tannic acid (p.2394·3).
Sore lips.

Del, Canad.†; Del, USA.
Topical gel: Allantoin (p.1588·1); dyclonine hydrochloride (p.1861·1).
Herpes labialis.

Del, Canad.
Topical liquid: Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1); tannic acid (p.2394·3).

Del, USA.
Topical liquid: Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1).
Mouth ulcers; sore gums.

Tanac Dual Core *Del, USA.*
Benzocaine (p.1854·1); tannic acid (p.2394·3); allantoin (p.1588·1); benzalkonium chloride (p.1629·1); padimate O (p.1609·1).
Oral lesions.

Tanacain *Ipsen, Gr.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Tanacet *Herbal Laboratories, Canad.; Herbal Laboratories, UK.*
Feverfew (p.622·2).
Migraine.

Tanaceto *Herbarium, Braz.*
Feverfew (p.622·2).
Migraine.

Tanadopa *Tanabe, Jpn†.*
Docarpamine (p.1272·3).
Heart failure.

Tanafed DMX *First Horizon, USA.*
Dextromethorphan tannate (p.1556·1); dexchlorpheniramine tannate (p.572·2); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Tanafed DP *First Horizon, USA.*
Pseudoephedrine tannate (p.1572·1); dexchlorpheniramine tannate (p.572·2).
Upper respiratory-tract disorders.

Tanagel *Durban, Spain.*
Belladonna (p.2263·3); gelatin tannate (p.2394·3); opium (p.105·1).
Colitis; diarrhoea; gastroenteritis.

Tanagel Papeles *Durban, Spain.*
Gelatin tannate (p.2394·3).
Diarrhoea.

TanaHist PD *Larken, USA.*
Chlorphenamine tannate (p.572·2).

Tanakan *Phoenix, Arg.; Ipsen, Belg.; Abbott, Braz.; Ipsen, Cz.; Beaufour, Fr.; Beaufour-Ipsen, Hong Kong; Beaufour-Ipsen, Hung.; Beaufour-Ipsen, Malaysia; Farmasa, Mex.†; Beaufour Ipsen, Pol.; Beaufour-Ipsen, Rus.; Beaufour-Ipsen, Singapore; Ipsen, Thai.; Mecom, Turk.; Leti, Venez.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; cerebral ischaemia; deafness; dizziness; mental function impairment; tinnitus; vascular ear and eye disorders; venous insufficiency; vertigo; vestibular disorders.

Tanakene *Ipsen, Spain; Intersan, Switz.*
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function disorders.

Tanalone *Labima, Belg.*
Albumin tannate (p.1704·2); pectin (p.2145·2).
Diarrhoea.

Tanamof *Amhof, Arg.*
Latanoprost (p.1882·1).
Ocular hypertension.

Tanap *Ingers, Cz.*
Trandolapril (p.1416·2).
Heart failure; hypertension; left-ventricular dysfunction following myocardial infarction.

Tanapress *Tanabe, Indon.*
Imidapril hydrochloride (p.1313·3).
Hypertension.

Tanasid *Pfizer Consumer, Spain†.*
Aluminium hydroxide (p.1706·2); sodium carbonate (p.2389·1).
Gastrointestinal hyperacidity.

Tanatril *Craveri, Arg.; Gerot, Austria; Solvay, Cz.; Algol, Fin.; Beaufour, Fr.; Kwizda, Ger.; Gerolimatos (Γερολυματος), Gr.; Tanabe, Hong Kong; Elder, India; Tanabe, Jpn; Tanabe, Malaysia; Jelfa, Pol.; Delta, Port.†; Tanabe, Singapore; Tanabe, Thai.; Trinity, UK.*
Imidapril hydrochloride (p.1313·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tanavat *Microsules, Arg.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Tancilina *Raymos, Arg.†.*
Tetracycline (p.347·1).
Bacterial infections.

Tandax *Sandoz, Mex.*
Naproxen sodium (p.92·3).
Inflammation; pain.

Tandem *US Pharmaceutical, USA.*
Ferrous fumarate (p.1938·3); polysaccharide-iron complex (p.1960·2).
Iron deficiency.

Tandem DHA *US Pharmaceutical, USA.*
Vitamins; iron; docosahexaenoic acid; eicosapentaenoic acid (p.1922·1).

Tandem F *US Pharmaceutical, USA.*
Iron (p.1949·1); folic acid (p.1940·1).

Tandem OB *US Pharmaceutical, USA.*
Vitamins; minerals (p.1922·1).

Tandem Plus *US Pharmaceutical, USA.*
Vitamins; minerals (p.1922·1).

Tandemact *Takeda, Cz.; Takeda, Fr.; Takeda, Port.*
Glimepiride (p.441·1); pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Tandene *Bunker, Braz.*
Carisoprodol (p.1894·1); diclofenac sodium (p.44·3); paracetamol (p.108·1); caffeine (p.1116·3).
Smooth muscle spasm.

Tanderalgin *Delta, Braz.*
Carisoprodol (p.1894·1); caffeine (p.1116·3); diclofenac sodium (p.44·3); paracetamol (p.108·1).

Tanderon *Pharmaland, Thai.*
Tolperisone hydrochloride (p.1899·3).
Skeletal muscle spasm.

Tandial *Solfran, Mex.†.*
Diazepam (p.986·3).

Tandiur *Raymos, Arg.*
⊗ Hydrochlorothiazide (p.1307·3).

Tandix *Azevedos, Port.*
⊗ Indapamide (p.1314·1).
Hypertension.

Tandpyndruppels *Lennon, S.Afr.*
Camphor oil (p.2273·3); opium (p.105·1); capsicum (p.2276·2); chloroform spirit; chloroform (p.1781·1); camphor (p.2273·2); catechu (p.2278·2).
Toothache.

Tandrexin *Sintofarma, Braz.†.*
Ampicillin (p.204·1).
Bacterial infections.

Tandriflan *Uniao Quimica, Braz.*
Paracetamol (p.108·1); carisoprodol (p.1894·1); diclofenac sodium (p.44·3); caffeine (p.1116·3).

Tandrilax *Ache, Braz.*
Paracetamol (p.108·1); carisoprodol (p.1894·1); diclofenac sodium (p.44·3); caffeine (p.1116·3).
Skeletal muscle spasm.

TanDur DM *Proethic, USA.*
Dextromethorphan tannate (p.1556·1); dexchlorpheniramine tannate (p.572·2); pseudoephedrine tannate (p.1572·1).
Upper respiratory-tract disorders.

Tanezox *Microsules, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Tanfedin *Roemmers Rowe, Venez.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Tanflex *Combiphar, Indon.; Abdi, Turk.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders.

Tanganil *Pierre Fabre, Fr.*
Acetylleucine (p.2245·1).
Vertigo.

Tangenol *Bucca, Spain†.*
Eugenol (p.2301·2); procaine hydrochloride (p.1869·1); tannic acid (p.2394·3).
Dental disorders.

Tangyn *Choongwae, Philipp.; Unimex, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Tanidina *Robert, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tanilas *Ipsen, Gr.*
Macrogol (p.2336·1).
Constipation.

Taninal *Herbapol Wroclaw, Pol.*
Albumin tannate (p.1704·2).
Diarrhoea; dyspepsia; food poisoning.

Tanizona *Offenbach, Mex.*
Naproxen (p.92·3).
Inflammation.

Tanko-Buskas *Fako, Turk.*
Hyoscine butylbromide (p.1734·1); medazepam (p.1006·1).

Tannacomp *Nordmark, Cz.†; Rentschler, Ger.*
Albumin tannate (p.1704·2); ethacridine lactate (p.1625·1).
Diarrhoea.

Tannalbin *Medicopharm, Austria; Rentschler, Ger.; Oramon, Neth.†.*
Albumin tannate (p.1704·2).
Diarrhoea.

Tannic-12 *Cypress, USA.*
Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2).
Coughs.

Tannidin Plus *GD, Ital.*
Betacarotene (p.1930·3); selenium (p.1961·1); vitamin E (p.1992·2).
Antoxidant.

Tannisol *GD, Ital.*
Betacarotene (p.1930·3).
Sunscreen.

Tanno-Hermal
Note.This name is used for preparations of different composition.
Boots Healthcare, Ital.
Barrier preparation.

Boots Healthcare, Switz.
Talc (p.1615·2); zinc oxide (p.1621·2); tannic acid (p.2394·3).
Skin disorders.

Tannolact *Galderma, Ger.*
Condensation product of urea-sodium cresolsulfonic acid.
Hyperhidrosis; skin disorders.

Tannolil *Li-il, Ger.†.*
Tannic acid (p.2394·3); aluminium sulfate (p.2255·1).
Haemorrhoids; hyperhidrosis; skin irritation.

Tannopon *Orion, Fin.*
Opium (p.105·1); belladonna (p.2263·3); bismuth salicylate (p.1711·1); albumin tannate (p.1704·2).
Diarrhoea.

Tannosynt
Note.This name is used for preparations of different composition.
Hermal, Austria; Boots Healthcare, Switz.
2,6-Bis-N’ (2-hydroxy-3-sulfo (5-methyl-)benzyl)-ureidomethyl-phenol(ev. p-cresol) disodium.
Burns; skin disorders.

Hermal, Ger.
Tannic acid (p.2394·3).
Burns; hyperhidrosis; skin disorders.

Tanol *Akdeniz, Turk.*
Calamine (p.1591·2); zinc oxide (p.1621·2); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Pruritus.

Tanoral *Parmed, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract symptoms.

Tanrix *GSK, Ital.†.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Tanser *VP, Spain.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tansiloprost *Finadiet, Arg.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Tansinel *ACME, Philipp.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tanston *Pfizer, Chile.*
Mefenamic acid (p.80·1).
Inflammation; pain.

Tantafed *Tanta, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).

Tantaphen *Tanta, Canad.*
Paracetamol (p.108·1).
Fever; pain.

Tantum
Note.This name is used for preparations of different composition.
CSC, Austria; 3M, Canad.; Medicom, Cz.; Faran, Gr.; Angelini, Indon.; Soho, Indon.; Angelini, Ital.; Chefaro, Neth.; Angelini, Pol.; Lepori, Port.; Santa, Turk.; Elmor, Venez.
Benzydamine hydrochloride (p.27·3).
Gynaecological disorders; inflammation; mouth and throat disorders; musculoskeletal pain and inflammation; oedema; peri-articular and soft-tissue disorders; peripheral venous insufficiency; phlebitis; thrombophlebitis; vaginitis; venous insufficiency.

Farma Lepori, Spain.
Cream; gel; ointment: Benzydamine hydrochloride (p.27·3).
Peri-articular and soft-tissue disorders.

Farma Lepori, Spain.
Throat spray: Benzydamine hydrochloride (p.27·3); hexamidine di-isetionate (p.1646·3).
Mouth and throat disorders.

Tantum Activ Gola *Angelini, Ital.*
Flurbiprofen (p.61·2).
Mouth and throat disorders.

Tantum Rosa *CSC, Ger.; CSC, Hung.; Lepori, Port.*
Benzydamine hydrochloride (p.27·3).
Vulvovaginal infections.

Tantum Rose *Angelini, Rus.*
Benzydamine hydrochloride (p.27·3).
Vulvovaginal disorders.

Tantum Verde
Note. This name is used for preparations of different composition.
CSC, Ger.; CSC, Hung.; Angelini, Rus.; Farma Lepori, Spain; Elmor, Venez.
Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation.

Lepori, Port.
Mouthwash: Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation.

Lepori, Port.
Pastilles: Benzydamine hydrochloride (p.27·3); benzocaine (p.1854·1).
Mouth and throat pain and inflammation.

Lepori, Port.
Pastilles (sugar-free): Benzydamine hydrochloride (p.27·3).
Mouth and throat pain and inflammation.

Tantumar *CSC, Austria.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders; soft-tissue injury.

Tanvimil *Raymos, Arg.*
A range of vitamin preparations with or without minerals (p.1922·1).

Tanvimil Ginseng *Raymos, Arg.*
Vitamins; minerals; ginseng (p.1922·1).

Tanvimil Isoflavonas
Note. This name is used for preparations of different composition.
Raymos, Arg.
Cream: Soya isoflavones (p.2391·2).
Moisturiser.

Raymos, Arg.
Tablets: Soya isoflavones; alpha tocopherol; lecithin (p.1922·1).
Dietary supplement.

Tanvimil Isoflavonas Caclcio D3 *Raymos, Arg.*
Soya isoflavones; calcium citrate; colecalciferol (p.1922·1).
Dietary supplement.

Tanyl *Taro, Israel; Intramed, S.Afr.*
⊗ Fentanyl citrate (p.55·3).
Adjunct to general anaesthesia; pain; premedication.

Tanyz *KRKA, Cz.; KRKA, Hung.; KRKA, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

TAO *Pfizer, USA†.*
Troleandomycin (p.357·1).
Bacterial infections.

Tapal-2 *GSK, Chile†.*
⊗ Aspirin (p.20·3); caffeine (p.1116·3); cinnamedrine hydrochloride (p.2283·1).
Menstrual disorders.

Tapanol *Republic, USA†.*
Paracetamol (p.108·1).
Fever; pain.

Tapazol *Lilly, Braz.; Lilly, Mex.; Lilly, Venez.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Tapazole *Paladin, Canad.; Teofarma, Ital.; Pharmalink, Philipp.; Dista, Switz.†; Lilly, Thai.; Lilly, USA.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Taponoto *Teofarma, Spain.*
Potassium carbonate.
Removal of ear wax.

Taporin *Probiomed, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taprocil *Plus, Gr.*
Citalopram (p.385·3).
Depression.

Taprodex *Provit, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Tapros *Takeda, Indon.*
⊗ Leuprorelin (p.2111·1).
Endometriosis; prostatic cancer.

Tapsin Analgesico *Maver, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tapsin 2 Analgesico *Maver, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tapsin Compuesto *Maver, Chile.*
Paracetamol (p.108·1); noscapine hydrochloride (p.1566·3); caffeine (p.1116·3); sodium ascorbate (p.1984·1).
Cold and influenza symptoms.

Tapsin Compuesto con Clorfenamina *Maver, Chile.*
Paracetamol (p.108·1); noscapine hydrochloride (p.1566·3); caffeine (p.1116·3); sodium ascorbate (p.1984·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Tapsin Compuesto Dia/Noche Plus *Maver, Chile.*
Day sachet, paracetamol (p.108·1); noscapine hydrochloride (p.1566·3); caffeine (p.1116·3); sodium ascorbate (p.1984·1); night sachet, paracetamol; noscapine hydrochloride; caffeine; sodium ascorbate; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Tapsin Compuesto DN *Maver, Chile.*
Day capsules, paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); ascorbic acid (p.1983·3); night capsules, paracetamol; caffeine; noscapine hydrochloride; ascorbic acid; chlorphenamine maleate (p.571·3).
Cold symptoms.

Tapsin Infantil *Maver, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Tapsin Limonada Dia *Maver, Chile†.*
Paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); ascorbic acid (p.1983·3).
Influenza symptoms.

Tapsin Limonada D.N. *Maver, Chile†.*
Day sachets, paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); ascorbic acid (p.1983·3); night sachets, paracetamol; caffeine; noscapine hydrochloride; ascorbic acid; chlorphenamine maleate (p.571·3).
Influenza symptoms.

Tapsin Limonada Noche *Maver, Chile†.*
Paracetamol (p.108·1); caffeine (p.1116·3); noscapine hydrochloride (p.1566·3); ascorbic acid (p.1983·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Tapsin Nocturno *Maver, Chile.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).

Tapsin Periodo Menstrual *Maver, Chile.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Menstrual disorders.

Tapsin SC *Maver, Chile.*
Paracetamol (p.108·1).
Fever; pain.

Tapzol con Neomicina *Rayere, Mex.†.*
Kaolin (p.1738·1); pectin (p.2145·2); neomycin (p.305·1).
Diarrhoea.

Tar Isdin Champu *Isdin, Spain.*
Coal tar (p.1616·2).
Scalp disorders.

Tar Isdin Plus *Isdin, Spain†.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Scalp disorders.

Tara *Polipharm, Thai.*
Miconazole nitrate (p.541·3).
Fungal skin, hair, and nail infections.

Taradyl *Roche, Belg.*
Ketorolac trometamol (p.74·2).
Pain.

Taraleon *Zilly, Ger.†.*
Taraxacum (p.2395·1).
Biliary-tract disorders; diuretic; dyspepsia; loss of appetite.

Taranis LeucinAde *DHN, Fr.*
Food for special diets (p.1922·1).
Formerly known as LeucinAde.
Leucinosis.

Taranis Phenylade *DHN, Fr.*
Food for special diets (p.1922·1).
Formerly known as Phenylade (.
Phenylketonuria.

Taraphilic *Medco, USA.*
Coal tar (p.1616·2).
Skin disorders.

Tara-Plus *Polipharm, Thai.*
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3).
Fungal skin and nail infections.

Tarassaco (Specie Composta) *Dynacren, Ital.†.*
Taraxacum (p.2395·1); silymarin (p.1452·2); zedoary; peppermint leaf (p.1761·2); caraway (p.2276·3).
Biliary disorders; herbal tea.

Taraten *Polipharm, Thai.*
Clotrimazole (p.530·1).
Fungal skin infections.

Taraxacum Compuesto *Hochstetter, Chile†.*
Homoeopathic preparation.

Taraxacum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Taraxin *TO-Chemicals, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Allergic skin disorders; pruritus; sedative.

Tarband *Seton Scholl, Austral.†.*
Coal tar (p.1616·2); zinc oxide (p.1621·2).
Leg ulcers; medicated bandage; skin disorders.

Tarcefandol *Polfa Tarchomin, Pol.*
Cefamandole (p.220·3).
Bacterial infections.

Tarcefoksym
Polfa Tarchomin, Pol.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Tarchomin, Rus.
Cefotaxime (p.229·1).
Bacterial infections.

Tarceva
Roche, Arg.; Roche, Austral.; Roche, Belg.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, Singapore; Roche, Swed.; Roche, Switz.; Roche, UK; Genentech, USA.
Erlotinib hydrochloride (p.717·1).
Non-small cell lung cancer; pancreatic cancer.

Roche, Fr.; Roche, Israel.
Erlotinib (p.717·2).
Non-small cell lung cancer.

Tarcevis *Polfa Tarchomin, Pol.†.*
Cefetamet pivoxil (p.224·3).
Bacterial infections.

Tardan *Odan, Canad.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Scalp disorders.

Tarden *Mecom, Turk.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Tardigal *Lilly, Ger.†.*
Digitoxin (p.1259·1).
Heart failure.

Tardocillin *Infectopharm, Ger.*
Benzathine benzylpenicillin (p.212·1).
Tolycaine hydrochloride (p.1872·2) is included in this preparation to alleviate the pain of injection.
Long-term treatment of rheumatic fever.

Tardyferon *Germania, Austria; Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Ger.; Pharmafabre (Φαρμαφαμπρ), Gr.; Gedeon Richter, Hung.; Pierre Fabre, Pol.; Pierre Fabre, Port.; Pierre Fabre, Rus.; Pierre Fabre, Spain; Robapharm, Switz.; Pierre Fabre, Turk.*
Ferrous sulfate (p.1939·3); with or without mucoproteose.
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Tardyferon B_9 *Pierre Fabre, Fr.; Pierre Fabre, Singapore†.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); with or without mucoproteose.
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency.

Tardyferon-Fol *Germania, Austria; Pierre Fabre, Cz.; Pierre Fabre, Ger.; Gedeon Richter, Hung.; Pierre Fabre, Mex.; Pierre Fabre, Pol.; Pierre Fabre, Port.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); with or without mucoproteose.
Ascorbic acid (p.1983·3) may be included in this preparation to increase the absorption and availability of iron.
Iron and folic acid deficiency; iron-deficiency anaemia.

Tardyl *Extractum, Hung.†.*
Amobarbital (p.961·3); glutethimide (p.1000·1); promethazine hydrochloride (p.588·2).
Anxiety disorders; sleep disorders.

Tareg *Biosintetica, Braz.†; Novartis, Chile; Novartis, Fr.; Novartis, Ital.; Jaba Recordati, Port.; Novartis, S.Afr.*
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Tareg-D *Novartis, Chile.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Taremis *Krolton, Arg.*
Metronidazole (p.837·1).

Tarfazolin *Polfa Tarchomin, Pol.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Tarflex *Stiefel, Braz.*
Coal tar (p.1616·2).
Skin disorders.

Targel
Note. This name is used for preparations of different composition.
Lagos, Arg.; Odan, Canad.
Coal tar (p.1616·2).
Psoriasis; scalp disorders.

Organifar, Venez.†.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid; peptic ulcer.

Targel SA *Odan, Canad.*
Coal tar solution (p.1616·2); salicylic acid (p.1612·2).
Psoriasis.

Target
Note. This name is used for preparations of different composition.
Wyeth Lederle, Austria†.
Felbinac (p.54·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Lisapharma, Hong Kong; Lisapharma, Ital.; Lisapharma, Malaysia.
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Targifor *Sanofi-Aventis, Braz.*
Arginine aspartate (p.1928·2).
Nutritional supplement.

Targifor C *Sanofi-Aventis, Braz.*
Arginine aspartate (p.1928·2); ascorbic acid (p.1983·3).
Nutritional supplement.

Targobone *Biomet, Ger.*
Collagen (bovine) (p.2286·1); teicoplanin (p.344·3).
Bone defects.

Targocid *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Vianex (Βιανεξ), Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Astellas, Jpn; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Pol.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Venez.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Targosid *Lepetit, Ital.; Sanofi-Aventis, Port.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Targretin *Bioprofarma, Arg.; Andromaco, Chile; Eisai, Cz.; Ligand, Denm.; Zeneus, Fr.; Zeneus, Ger.; Galenica, Gr.; Ligand, Hung.; Zeneus, Irl.; Sigma-Tau, Ital.; Ligand, Neth.; Ferrer, Port.; Ferrer, Spain; Cephalon, UK; Eisai, USA.*
Bexarotene (p.686·1).
Cutaneous T-cell lymphoma.

Targus *Abbott, Braz.*
Flurbiprofen (p.61·2).
Gout; musculoskeletal and joint disorders; pain.

Taricin *Akrikhin, Rus.*
Ofloxacin (p.310·2).
Bacterial infections.

Tariflox *Cipla, India; Lapi, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Tariflox Plus *Cipla, India.*
Ofloxacin (p.310·2); ornidazole (p.843·1).
Bacterial infections.

Tarimyl *Leti, Venez.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Tarivid
Aventis, Austria; Sanofi-Aventis, Belg.; Aventis, Cz.; Aventis, Ger.; Gedeon Richter, Hung.; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Irl.; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Port.; Aventis, S.Afr.; Aventis, UK.
Ofloxacin (p.310·2) or ofloxacin hydrochloride (p.310·2).
Bacterial infections.

Aventis, Denm.; Sanofi-Aventis, Fin.; Daiichi, Hong Kong; Santen, Hong Kong; Aventis, Israel; Daiichi, Jpn; Santen, Jpn; Daiichi, Malaysia; Sanofi-Aventis, Pol.; Sanofi-Aventis, Rus.; Daiichi, Singapore; Aventis, Swed.; Aventis, Switz.; Daiichi, Thai.; Aventis, Turk.
Ofloxacin (p.310·2).
Bacterial infections.

Daiichi, Indon.; Kalbe, Indon.
Ear drops; tablets: Ofloxacin (p.310·2).
Bacterial infections.

Ferron, Indon.; Santen, Indon.
Eye drops: Ofloxacin (p.310·2).
Eye infections.

Tarjen *Samakeephaesaj, Thai.†.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Tarjena *Union Drug, Thai.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Tarka *Abbott, Arg.†; Abbott, Austral.; Abbott, Austria; Abbott, Canad.; Abbott, Cz.; Abbott, Denm.; Abbott, Fin.†; Abbott, Fr.; Abbott, Ger.; Abbott, Gr.; Abbott, Hung.; Abbott, Indon.; Abbott, Ital.; Abbott, Mex.; Abbott, Neth.; Abbott, Philipp.; Abbott, Pol.; Abbott, Port.; Abbott, Rus.; Abbott, S.Afr.; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, Turk.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Verapamil hydrochloride (p.1421·1); trandolapril (p.1416·2).
Hypertension.

Tarlene *Medco, USA.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Seborrhoea.

Tarmed *Stiefel, Chile; Stiefel, Ger.; Gabriel, Gr.; Stiefel, Mex.; Stiefel, Port.; Stiefel, Spain.*
Coal tar (p.1616·2).
Chronic eczema; psoriasis; scalp disorders; seborrhoeic dermatitis.

Tarnasol *Liconsa, Port.*
Losartan potassium (p.1326·1).
Diabetic nephropathy; heart failure; hypertension; stroke prophylaxis.

Taro Gel
Note. This name is used for preparations of different composition.
Taro, Canad.†; AFT, NZ†.
Sterile lubricating jelly.

Taro, Israel.
Propylene glycol (p.2374·1); glycerol (p.2314·2).
Lubricating gel.

Tarocidin *Taro, Israel.*
Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3).
Blepharitis; conjunctivitis.

Tarocidin D *Taro, Israel.*
⊗ Chloramphenicol (p.239·3); polymyxin B sulfate (p.317·3); dexamethasone sodium phosphate (p.1526·2).
Blepharitis; conjunctivitis.

Taroctyl *Taro, Israel.*
Chlorpromazine hydrochloride (p.969·2).
Psychiatric disorders; vomiting.

Tarodent *Taro, Israel.*
Chlorhexidine gluconate (p.1635·3).
Mouth disorders.

Tarodex *Taro, Israel.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Taroflox *Sanofi-Aventis, Cz.*
Ofloxacin (p.310·2).
Bacterial infections.

Taromentin *Polfa Tarchomin, Pol.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Taron *Biotech, Venez.*
Albendazole (p.139·2).
Worm infections.

Tarontal *Sanofi-Aventis, Gr.; Bernofarm, Indon.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Tarophed *Taro, Israel.*
Pseudoephedrine hydrochloride (p.1571·2).
Aural and nasal congestion.

Taro-Sone *Taro, Canad.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Tarsime *Polfa Tarchomin, Pol.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Tarsum *Summers, USA.*
Coal tar (p.1616·2); salicylic acid (p.1612·2).
Seborrhoea.

Tartar Control Listerine *Pfizer Consumer, UK.*
Zinc chloride (p.1999·1).
Tooth tartar.

Tartar Control Listerine Antiseptic *Pfizer Consumer, S.Afr.*
Thymol (p.1664·3); zinc chloride (p.1999·1).
Mouth and throat disorders; oral hygiene.

Tartephedreel *Peithner, Austria.*
Homoeopathic preparation.

Tartriakson *Polfa Tarchomin, Pol.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tarvexol *Sandoz, Arg.; Novartis, Braz.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Tarytar *Stiefel, Chile†.*
Cade oil (p.1616·1); tar (p.1616·2); arachis oil (p.2259·1); coal tar (p.1616·2).
Scalp disorders.

Tarzol *Unipharm, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Tasakal *Offenbach, Mex.†.*
Sodium dibunate (p.1573·1); guaifenesin (p.1561·3); homatropine methylbromide (p.1881·3).
Coughs.

Tasedan *Hormona, Mex.*
Estazolam (p.995·1).
Insomnia; premedication.

Tasep *IPS, Spain.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Tasigna *Novartis, Cz.; Novartis, Port.; Novartis, Switz.; Novartis, UK; Novartis, USA.*
Nilotinib hydrochloride (p.756·1).
Chronic myeloid leukaemia.

Tasker *Doctum, Gr.*
Cetirizine (p.571·1).
Hypersensitivity disorders.

Tasmacyclin Akne *Gebro, Switz.*
Doxycycline (p.267·1).
Acne.

Tasmaderm *Gebro, Switz.*
Motretinide (p.1608·1).
Acne.

Tasmar *Valeant, Arg.; Roche, Austria; Pharma Logistics, Belg.; Valeant, Braz.; Roche, Chile; Valeant, Cz.; Valeant, Denm.; Valeant, Fin.; ICN, Fr.; Valeant, Ger.; Valeant, Gr.; Roche, Hong Kong†; Valeant, Hung.; Valeant, Irl.; ICN, Ital.; Valeant, Mex.; Pacific, NZ; Valeant, Neth.; Valeant, Philipp.; Valeant, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Valeant, Spain; Roche, Swed.; Valeant, Switz.; Valeant, UK; Roche, USA.*
Tolcapone (p.819·2).
Parkinsonism.

Tasonade *Sanofarm, Gr.*
Citalopram (p.385·3).
Depression.

Tasovak *Kendrick, Mex.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Tatig *Bioindustria, Ital.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder.

Tationil *Roche, Ital.*
Glutathione sodium (p.1448·1).
Prevention of cisplatin-induced neuropathy.

Tau Kit *Isomed, Spain.*
⊗ Carbon-13 labelled urea (p.2277·1).
Test for gastrointestinal Helicobacter pylori infection.

Taucaron *Roemmers, Venez.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders; pain.

Taucor *Sigma-Tau, Spain.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Taufone *Synthesis, Rus.†.*
Taurine (p.2395·2).

Tauglicolo
Note. This name is used for preparations of different composition.
SIT, Ital.
Bromhexine hydrochloride (p.1552·2); sulfogaiacol (p.1573·2).
Respiratory-tract congestion.
Siam Bheasach, Thai.
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with increased or viscous mucus.

Tauliz *Sanofi-Aventis, Ital.*
⊗ Piretanide (p.1372·3).
Hypertension; oedema.

Taural *Roemmers, Arg.*
Ranitidine (p.1766·1) or ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Tauramin *Grifols, Spain.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Taurargin *Baldacci, Braz.*
Arginine; taurine; ditetraethylammonium phosphate (p.1922·1).
Nutritional supplement.

Tauredon *Altana, Austria; Nycomed, Cz.; Altana, Ger.; IFET (ΙΦΕΤ), Gr.; Altana, Hung.†; Altana, Neth.; Altana, Port.; Altana, Switz.*
Sodium aurothiomalate (p.122·2).
Juvenile idiopathic arthritis; psoriatic arthritis; rheumatoid arthritis.

Taurex *Medica Pedia, Philipp.*
Taurine (p.2395·2).
Nutritional supplement.

Tauro *Teofarma, Ital.*
Tauroursodeoxycholic acid (p.2408·2).
Gallstones.

Taurobetina *Zambon, Spain†.*
Adenosine phosphate dipotassium (p.2247·3); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2); uridine phosphate (p.2408·1); taurine (p.2395·2).
Neuromuscular metabolic disorders.

Taurolin *Chemomedica, Austria; Boehringer Ingelheim, Ger.; DeVriMed, Neth.; Geistlich, Switz.*
Taurolidine (p.344·2).
Bacterial infections.

Tautax *Veropharm, Rus.*
Docetaxel (p.710·3).
Breast cancer; head and neck cancer; non-small-cell lung cancer; ovarian cancer.

Tautoss *Sigma-Tau, Spain.*
Levodropropizine (p.1557·3).
Coughs.

Tau-Tux *Sigma-Tau, Ital.*
Levodropropizine (p.1557·3).
Coughs.

Tauval *Sigma-Tau, Spain†.*
Valerian (p.2410·1).
Anxiety; insomnia.

Tauxib *Addenda, Ital.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Tauxolo *SIT, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Tavacor *Savio, Ital.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Tavag *Germandre, Fr.*
Sodium phosphate (p.1682·3); lactose (p.1954·1).
Maintenance of vaginal pH.

Tavanic *Aventis, Arg.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Mex.; Aventis, Neth.; Sanofi-Aventis, Port.; Sanofi-Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Turk.; Aventis, UK; Sanofi-Aventis, Venez.*
Levofloxacin (p.292·2).
Bacterial infections.

Tavan-SP 54 *Aventis, S.Afr.*
Pentosan polysulfate sodium (p.1367·1).
Hyperlipidaemias; thromboembolic disorders.

Tavegil *Novartis Consumer, Ger.; Novartis Consumer, Ital.†; Novartis Consumer, Neth.; Novartis Consumer, Spain; Novartis Consumer, UK.*
Clemastine fumarate (p.573·2).
Allergic conjunctivitis; allergic rhinitis; hypersensitivity reactions; insect bites; insect stings; pruritus; sunburn.

Tavegyl *Novartis, Austria; Novartis, Cz.; Novartis, Denm.; Novartis, Indon.; Novartis, Philipp.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, S.Afr.; Novartis, Swed.; Novartis Consumer, Switz.; Novartis, Turk.*
Clemastine fumarate (p.573·2).
Allergic rhinitis; allergic skin disorders; anaphylaxis; eczema; hypersensitivity reactions; insect bites and stings; pruritus; urticaria.

Taver *Medochemie, Malaysia; Medochemie, Thai.*
Carbamazepine (p.471·3).
Epilepsy; glossopharyngeal neuralgia; trigeminal neuralgia.

Tavexyl *Rayere, Mex.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Tavidan
Note. This name is used for preparations of different composition.
Baldacci, Ital.
Suleparoid (p.1406·3).
Thrombosis prophylaxis.
Stada, Thai.†.
Fenoverine (p.2303·2).
Smooth muscle spasm and pain.

Tavinex *Hexa, Arg.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Tavinex Antigripal *Hexa, Arg.*
Paracetamol (p.108·1); butetamate citrate (p.1553·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Tavinex Expectorante *Hexa, Arg.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Tavinex Expectotabs *Hexa, Arg.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with viscous mucus.

Tavipec *Montavit, Austria; Montavit, Thai.*
Spike lavender oil (p.2392·1).
Coughs; respiratory-tract disorders.

Tavist *Novartis Consumer, Canad.; Novartis, Mex.; Wander, Philipp.; Novartis Consumer, Port.*
Clemastine fumarate (p.573·2).
Allergic rhinitis; allergic skin disorders; cold symptoms; hypersensitivity reactions; insect bites and stings; pruritus; urticaria.

Tavist Allergy *Novartis, USA.*
Clemastine fumarate (p.573·2).
Formerly known as Tavist-1.
Allergic rhinitis.

Tavist ND *Novartis, USA.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Tavist-D *Novartis, Mex.†.*
Clemastine fumarate (p.573·2); phenylpropanolamine hydrochloride (p.1569·3).
Allergic rhinitis; nasal congestion.

Tavitan *DCF, Port.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Tavolax nouvelle formule *Vifor, Switz.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Tavonin *Flordis, Austral.†; VSM, Belg.; VSM, Neth.*
Ginkgo biloba (p.2311·1).
Age-related mental function disorders; dementia; peripheral vascular disorders.

Tavor
Note. This name is used for preparations of different composition.
Tecnofarma, Chile.
Fluconazole (p.532·1).
Fungal infections.
Wyeth, Cz.†; Wyeth, Ger.; Wyeth, Gr.; Wyeth Lederle, Ital.
Lorazepam (p.1004·1).
Anxiety; epilepsy; insomnia; premedication; psychoses; psychosomatic disorders; status epilepticus.
Asofarma, Mex.
Oxybutynin chloride (p.2190·3).
Neurogenic bladder.
Gentek, Venez.
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Tavu *Pfizer, Port.*
⊗ Timolol maleate (p.1412·3); latanoprost (p.1882·1).
Glaucoma; ocular hypertension.

Taxagon *Ivax, Arg.*
Trazodone hydrochloride (p.424·3).
Depression.

Taxcef *Ranbaxy, Cz.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taxegram *Sanbe, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taxen *Sandoz, Indon.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Taxenan *Mavi, Mex.*
Naproxen (p.92·3); paracetamol (p.108·1).
Formerly contained naproxen.
Fever; pain.

Taxfeno *Raffo, Arg.*
⊗ Tamoxifen (p.775·1).

Taxibon *Farma, Venez.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taxifur *Ivax, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Taxilan
Note. This name is used for preparations of different composition.
Bergamo, Braz.
Paclitaxel (p.759·1).
Breast cancer; non-small cell lung cancer; ovarian cancer.
Lundbeck, Ger.
Perazine dimalonate (p.1016·2).
Psychoses.

Taxima *Prodotti, Braz.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taximax *Nufarindo, Indon.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taxime *Pharmatex, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Taxobine *Stada, Port.*
Paclitaxel (p.759·1).

Taxocef *Toprak, Turk.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Taxocris *LKM, Arg.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Taxodiol *Tecnofarma, Chile.*
Paclitaxel (p.759·1).
Ovarian cancer.

Taxofen *Blausiegel, Braz.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Taxogen *Genepharm, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Taxol *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Jpn; BMS, Malaysia; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA.*
Paclitaxel (p.759·1).
Breast cancer; gastric cancer; Kaposi's sarcoma; non-small cell lung cancer; ovarian cancer; testicular cancer.

Taxoprol *Proel, Gr.*
Paclitaxel (p.759·1).
Malignant neoplasms.

Taxotere *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Jpn; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Aventis, Pol.; Aventis, Port.; Sanofi-Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Sanofi-Aventis, UK; Sanofi-Aventis, USA; Sanofi-Aventis, Venez.*
Docetaxel (p.710·3).
Breast cancer; gastric cancer; head and neck cancer; non-small cell lung cancer; ovarian cancer; prostatic cancer.

Taxus
Note. This name is used for preparations of different composition.
Beta, Arg.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.
Tecnofarma, Chile; Asofarma, Mex.; Nolver, Venez.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Taxyl *Solfran, Mex.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Taycovit *Ivax, Arg.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

Tayderm *Acos, Ital.*
Zinc oxide (p.1621·2).
Skin disorders.

Tazac *Aspen, Austral.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Tazact *Cipla, India.*
Tazobactam sodium (p.344·2); piperacillin (p.315·2).
Bacterial infections.

Tazalux *Sandoz, Neth.*
Ceftazidime (p.234·1).
Bacterial infections.

Tazamel *Clonmel, Irl.*
Mirtazapine (p.409·2).
Depression.

Tazamol *Polfa Tarchomin, Pol.*
Paracetamol (p.108·1).
Fever; pain.

Tazepam *Tarchomin, Rus.*
Oxazepam (p.1014·2).
Anxiety.

Tazepen *Elpen (Ελπεν), Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Tazepin *Climax, Braz.†.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Tazicef *Shin Poong, Philipp.; Hospira, USA.*
Ceftazidime (p.234·1).
Bacterial infections.

Tazidan *Alkem, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Tazidem Orchid, Philipp.
Ceftazidime (p.234·1).
Bacterial infections.

Tazidif Fidia, Ital.
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Tazidime Lilly, Canad.†; Lilly, USA.
Ceftazidime (p.234·1).
Bacterial infections.

Tazidron Meditrina, Gr.
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Taziject Sandoz, S.Afr.
Ceftazidime (p.234·1).
Bacterial infections.

Taziken Kendrick, Mex.†.
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour.

Tazobac Wyeth, Ger.; Wyeth Lederle, Ital.; Sanofi Pasteur, Port.; Wyeth, Switz.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tazobax Generix, S.Afr.
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Tazobion Medicus, Gr.
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Tazocel Wyeth, Spain.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazocilline Wyeth, Fr.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazocin Wyeth, Austral.; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Canad.; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Gr.; Wyeth, Hong Kong; Wyeth, Hung.; Wyeth, Indon.; Wyeth, Irl.; Lederle, Israel; Wyeth Lederle, Ital.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, NZ; Wyeth, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth, S.Afr.; Wyeth, Singapore; Wyeth, Swed.; Wyeth-Ayerst, Thai.; Wyeth, Turk.; Wyeth, UK.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tazofast Ipca, India.
Tazobactam sodium (p.344·2); piperacillin (p.315·2).
Bacterial infections.

Tazonam Wyeth, Arg.; Wyeth Lederle, Austria; Wyeth, Chile.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazopen Biochem, India.
Tazobactam sodium (p.344·2); piperacillin sodium (p.315·2).
Bacterial infections.

Tazopril Wyeth, Venez.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazorac Allergan, Canad.; Pierre Fabre, Cz.; Allergan, USA.
Tazarotene (p.1617·1).
Acne; photo-ageing of the skin; psoriasis.

Tazorex Demo, Gr.
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Tazoxil Haller, Braz.†.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazpen
Cellofarm, Braz.†.
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Biofarma, Venez.
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Tazret Glenmark, India†.
Tazarotene (p.1617·1).
Acne; psoriasis.

Taztia Andrx, USA.
Diltiazem hydrochloride (p.1265·1).
Hypertension.

Tazumara Bayer Schering, Cz.
Fludarabine phosphate (p.721·1).
Chronic lymphocytic leukaemia.

Tazusin Efarmes, Spain†.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

TB Vit 6 Meprofarm, Indon.
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

TB ZET Meprofarm, Indon.
Pyrazinamide (p.320·2).
Tuberculosis.

TBR/X Ximena Polanco, Chile.
Homoeopathic preparation.

3TC GSK, Arg.; GSK, Austral.; GSK, Canad.; GSK, Hong Kong; GSK, Indon.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, S.Afr.; GSK, Switz.
Lamivudine (p.895·1).
HIV infection.

3TC Complex GSK, Arg.
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

3TC/AZT Elea, Arg.
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

3TC/Epivir GSK, Chile.
Lamivudine (p.895·1).
HIV infection.

3TC-HBV GSK, Indon.
Lamivudine (p.895·1).
Chronic hepatitis B.

TCP
Note. This name is used for preparations of different composition.
Pfizer Consumer, S.Afr.
Halogenated phenols; phenol (p.1656·1); sodium salicylate (p.124·2).
Burns; disinfection; insect bites; mouth and throat infections; wounds.

Chefaro, UK.
Cream: Chloroxylenol (p.1640·2); triclosan (p.1665·2); halogenated phenols; phenol (p.1656·1); sodium salicylate (p.124·2).
Minor skin disorders; skin disinfection.

Chefaro, UK.
Liquid: Halogenated phenols; phenol (p.1656·1).
Formerly contained halogenated phenols, phenol, and sodium salicylate.
Minor skin disorders; mouth ulcers; sore throat.

Chefaro, UK.
Lozenges: Hexylresorcinol (p.1647·1).
Sore throat.

Chefaro, UK.
Ointment: Iodine (p.2169·2); phenol (p.1656·1); sodium salicylate (p.124·2); methyl salicylate (p.85·3); precipitated sulfur (p.1614·1); tannic acid (p.2394·3); camphor (p.2273·2); salicylic acid (p.1612·2).
Haemorrhoids; minor skin disorders; pruritus.

TD Leti, Spain.
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Td Adsorbed Sanofi Pasteur, Canad.
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

TD Spray Iso Mack Pfizer, Ger.
Isosorbide dinitrate (p.1317·3).
Ischaemic heart disease.

Td-Impfstoff Sanofi Pasteur, Ger.
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of older children and adults.

TDL Patriot, Philipp.
Tramadol hydrochloride (p.130·3).
Pain.

Td-Polio Sanofi Pasteur, Canad.
An adsorbed diphtheria, tetanus, and inactivated poliomyelitis vaccine (p.2212·2).
Active immunisation.

Td-pur Grunenthal, Austria; Chiron Vaccines, Ger.
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of older children and adults.

Td-Rix GSK, Ger.
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation of older children and adults.

Td-Virelon Chiron Vaccines, Ger.; Berna, Switz.
A diphtheria, tetanus, and poliomyelitis vaccine (p.2212·2).
Active immunisation.

Te Anatoxal Berna, Hong Kong; Berna, Malaysia†; Berna, NZ; Berna, Philipp.; Berna, Singapore†; Berna, Thai.; Berna, USA.
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Te Laxante Valma, Chile.
Senna (p.1769·2); rosa mosqueta; boldo (p.2267·2); baylahuen; spearmint (p.2391·3).
Constipation.

Tea Test Asofarma, Arg.
Pregnancy test (p.2372·1).

Tea Tree & Witch Hazel Cream Lane, UK.
Hamamelis (p.2318·2); eucalyptus oil (p.2301·2); methyl salicylate (p.85·3); camphor (p.2273·2); melaleuca oil (p.2338·2); zinc oxide (p.1621·2).
Skin disorders.

Tealep Raffo, Arg.
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Tealine Arkomedika, Fr.†.
Java tea (p.2328·2); green tea (p.2416·1).
Slimming aid.

Tear drops
Note. A similar name is used for preparations of different composition (see below).
Faran, Gr.†.
Carbomer (p.2141·3).
Dry eye.

Teardrops
Note. A similar name is used for preparations of different composition (see above).
Novartis Ophthalmics, Canad.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

TearGard Lee, USA.
Hyetellose (p.2143·3).
Artificial tears.

Teargel Novartis Ophthalmics, Arg.†; Adcock Ingram, S.Afr.
Carbomer (p.2141·3).
Dry eyes.

Tear-Gel Novartis Ophthalmics, Canad.
Carbomer 980 (p.2141·3).
Dry eyes.

Teargen Goldline, USA.
Artificial tear solution.
Dry eyes.

Tearisol Novartis Ophthalmics, USA.
Hypromellose (p.2144·2).
Dry eyes.

Tears Sanbe, Indon.
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Tears Again
Note. This name is used for preparations of different composition.
Optima, Ger.
Soya lecithin (p.2332·2); vitamin A palmitate (p.1973·1); alpha tocopherol (p.1992·2).
Dry eyes; eye irritation.

Ocusoft, USA.
Eye drops: Polyvinyl alcohol (p.2145·3).
Dry eyes.

Ocusoft, USA.
Eye drops: Carmellose sodium (p.2142·1).
Dry eyes.

Ocusoft, USA.
Eye ointment: White soft paraffin (p.2031·2); liquid paraffin (p.2030·3).
Dry eyes.

Tears Again MC Ocusoft, USA.
Hypromellose (p.2144·2).
Dry eyes.

Tears Encore Vision, Canad.
Polysorbate 80 (p.1919·2).
Dry eyes.

Tears Humectante Alcon Cusi, Spain.
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Tears Lubricante Alcon Cusi, Spain†.
Wool fat (p.2033·2); white soft paraffin (p.2031·2).
Dry eyes.

Tears Naturale
Note. This name is used for preparations of different composition.
Alcon, Arg.; Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Gr.; Alcon, Hung.; Alcon, Irl.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.†; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA.
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Alcon, Austria.
Carbomer 974P (p.2141·3).
Dry eyes.

Alcon, Hong Kong.
Duasorb water-soluble polymeric system.
Dry eyes.

Tears Naturale II Alcon, Indon.
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Tears Naturale Forte Alcon, Canad.; Alcon, Hong Kong.
⊗ Dextran 70 (p.1059·3); glycerol (p.2314·2); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Tears Naturale PM Alcon, Canad.
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); wool fat (p.2033·2).
Dry eyes.

Tears Plus Allergan, Austral.; Allergan, Canad.; Allergan, NZ†; Allergan, Neth.; Allergan, S.Afr.; Allergan, Switz.†; Allergan, USA.
Polyvinyl alcohol (p.2145·3); povidone (p.2146·1).
Dry eyes.

Tears Renewed
Note. This name is used for preparations of different composition.
Akorn, USA.
Eye drops: ⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2).
Dry eyes.

Akorn, USA.
Eye ointment: White soft paraffin (p.2031·2); light liquid paraffin (p.2031·1).
Dry eyes.

Teatrois DB, Fr.
Tiratricol (p.2177·3).
Thyroid disorders.

Tebamide G & W, USA†.
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Tebantin Gedeon Richter, Rus.
Gabapentin (p.482·3).
Epilepsy; neuropathic pain.

Tebegran Collins, Mex.
Sumatriptan succinate (p.625·2).
Migraine.

tebesium Riemser, Ger.; Wernigerode, Ger.
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

tebesium Duo Riemser, Ger.; Wernigerode, Ger.
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

tebesium Trio Riemser, Ger.; Wernigerode, Ger.
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

tebesium-s Riemser, Ger.; Wernigerode, Ger.
Isoniazid (p.288·1).
Tuberculosis.

Tebetane Compuesto Elfar, Spain.
Alanine (p.1928·1); glycine (p.1947·3); glutamic acid (p.1947·1); pygeum africanum (p.2192·3).
Prostatic disorders.

Tebis Plus H Teva, Cz.
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tebloc Lafare, Ital.†.
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Tebofortan Austroplant, Austria; ASI, Hung.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; mental function impairment; vestibular disorders.

Tebofortin Schwabe, Switz.†.
Ginkgo biloba (p.2311·1).
Mental function impairment; vertigo.

Tebokan
Note. This name is used for preparations of different composition.
Grunenthal, Chile†; Austroplant, Cz.; Schwabe, Cz.; Vianex (Βιανέξ), Gr.; Pharmalink, Philipp.; Schwabe, Philipp.; Schwabe, Switz.; Leti, Venez.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; intermittent claudication; mental function impairment; vascular disorders.

Abdi, Turk.
Ginkgolides (p.2311·3).
Dementia; peripheral vascular disorders.

Tebonin Austroplant, Austria; Nycomed, Braz.; Schwabe, Ger.; ASI, Hung.†; Farmasa, Mex.; Schwabe, Singapore.
Ginkgo biloba (p.2311·1).
Cerebral and peripheral vascular disorders; intermittent claudication; mental function impairment; tinnitus; vertigo; vestibular disorders.

Teboven Farmasa, Mex.
Troxerutin (p.2305·1).
Venous insufficiency.

Te-Br Provit, Mex.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tebraxin Bracco, Ital.
Rufloxacin hydrochloride (p.331·3).
Bacterial infections.

Tebrazid Continental Pharma, Belg.; Valeant, Canad.
Pyrazinamide (p.320·2).
Tuberculosis.

Tebruxim Bruluagsa, Mex.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Tecam Vargas, Venez.†.
Tenoxicam (p.128·2).
Inflammation; musculoskeletal and joint disorders; pain.

Teceeme Nutricia-Bago, Arg.
Medium-chain triglycerides (p.1956·3).
Nutritional supplement.

Tecelac Biotest, Ger.†; Pisa, Mex.; Biotest, Pol.
Antithymocyte globulin (p.1817·3).
Transplant rejection.

Teceos CIS, Neth.
Technetium-99m (p.2055·3) butedronate.
Bone scanning.

Tecfazolina Openfar, Spain.
Cefazolin sodium (p.222·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Tecflu Columbia, Mex.
Fluorouracil (p.722·2).
Malignant neoplasms.

TechneScan DMSA Mallinckrodt, Cz.; Mallinckrodt, Neth.
Technetium-99m succimer (p.2055·3).
Radionuclide imaging of the kidney.

TechneScan DTPA Mallinckrodt, Cz.; Mallinckrodt, Neth.; Mallinckrodt, Port.
Technetium-99m trisodium calcium pentetate (p.2055·3).
Radionuclide imaging of the kidney, lungs, and gastrointestinal tract.

TechneScan HDP BSM, Austria; Mallinckrodt, Cz.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Tyco, Spain; Mallinckrodt, USA.
Technetium-99m disodium oxidronate (p.2055·3).
Bone scintigraphy.

TechneScan HIG Mallinckrodt, Cz.
Technetium-99m labelled immunoglobulin G (p.2055·3).
Localisation of arthritis.

TechneScan HSA Mallinckrodt, Cz.; Mallinckrodt, Neth.
⊗ Technetium-99m labelled albumin (p.2055·3).
Blood circulation studies; radionuclide imaging of the heart.

TechneScan LyoMAA *BSM, Austria; Mallinckrodt, Neth.*
⊗ Technetium 99-m labelled albumin macroaggregates (p.2055·3).
Diagnostic agent; lung scintigraphy; venoscintigraphy.

TechneScan Lyomaa *Mallinckrodt, Cz.; Tyco, Spain.*
⊗ Technetium-99m labelled albumin macroaggregates (p.2055·3).
Diagnostic agent; lung perfusion studies; vein scintigraphy.

TechneScan MAG3 *BSM, Austria; Mallinckrodt, Cz.; Tyco, Ital.; Mallinckrodt, Neth.; Mallinckrodt, Port.; Tyco, Spain.*
Technetium-99m betiatide (p.2055·3).
Radionuclide investigation of renal function.

TechneScan PYP *Mallinckrodt, Cz.; Mallinckrodt, Neth.*
Technetium-99m pyrophosphate (p.2055·3).
Labelling of erythrocytes for use in blood pool scintigraphy and detection of gastrointestinal bleeding.

TechneScan Q12 *Mallinckrodt, Cz.†.*
Technetium-99m trifosmin/furomin (p.2055·3).
Cardiac imaging.

Techniques Anti-Dandruff *Avon, Canad.†.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Techxafort *Pharmatechnica, Philipp.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Tecipul *Mochida, Jpn.*
Setiptiline maleate (p.422·3).
Depression.

Teclizima *Reuffer, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Tecnid *Ativus, Braz.*
Secnidazole (p.846·3).
Bacterial infections; protozoal infections.

Tecnocarb *Zodiac, Braz.*
Carboplatin (p.693·1).
Malignant neoplasms.

Tecnocris *Zodiac, Braz.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Tecnofen *Columbia, Mex.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tecnoflut *Zodiac, Braz.*
Flutamide (p.725·1).
Prostatic cancer.

Tecnofox *Tecnimede, Port.*
Levocloperastine fendizoate (p.1554·3).
Cough.

Tecnolip *Tecnifar, Port.*
Lovastatin (p.1328·2).
Atherosclerosis; hypercholesterolaemia.

Tecnomax
Note. This name is used for preparations of different composition.
Raffo, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Zodiac, Braz.
Epirubicin hydrochloride (p.716·1).

Tecnomet *Zodiac, Braz.*
Methotrexate (p.745·2).
Malignant neoplasms; rheumatoid arthritis.

Tecnomicina *Zodiac, Braz.*
Bleomycin sulfate (p.687·1).
Malignant neoplasms.

Tecnoplatin *Zodiac, Braz.; Columbia, Mex.*
Cisplatin (p.698·2).
Malignant neoplasms.

Tecnosal *Tecnifar, Port.*
Triflusal (p.1418·3).
Thrombosis prophylaxis.

Tecnotax *Zodiac, Braz.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Tecnotecan *Zodiac, Braz.*
Irinotecan hydrochloride (p.737·1).
Malignant neoplasms.

Tecnovorin *Zodiac, Braz.*
Calcium folinate (p.1943·3).
Adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists; megaloblastic anaemias.

Tecol *Biotech, Venez.†.*
Omeprazole (p.1753·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Teconam *Asian Pharm, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal and joint disorders.

Tecprazin *Tecnofarma, Mex.*
Praziquantel (p.153·3).
Parasitic infections.

Tecta *Altana, Mex.*
Pantoprazole magnesium (p.1760·2).
Acid aspiration; dyspepsia; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Teczem *Hoechst Marion Roussel, USA.*
Enalapril maleate (p.1276·1); diltiazem malate (p.1267·1).
Hypertension.

Teczine *Crosslands, India.*
Levocetirizine (p.583·2).
Allergic rhinitis; urticaria.

Teddy-C *Community Pharmacy, Thai.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Tedicumar *Estedi, Spain.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Tedifebrin *Estedi, Spain.*
Ibuprofen (p.64·2).
Fever; gout; musculoskeletal, joint, and peri-articular disorders; pain.

Tediprima *Estedi, Spain.*
Trimethoprim (p.355·2).
Genito-urinary infections.

Tedipulmo *Estedi, Spain.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Tedivax *GSK, Belg.*
An adsorbed diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Tedol *Edol, Port.*
Ketoconazole (p.539·1).
Fungal infections.

Tedrigen *Goldline, USA.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2).
Bronchospasm.

Teedex *Rice Steele, Irl.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Fever; pain.

Teejel *Meda, Belg.; SSL, Irl.; Rafa, Israel.*
Choline salicylate (p.36·3).
Gum and mouth pain; oral lesions; teething.

Teen Derm *Fouchard, Chile†; Roemmers-Klinos, Venez.†.*
Glycolic acid (p.1598·1).

Teenstick *Arkopharma, UK.*
Clove oil (p.2285·1); geranium oil (p.2311·1); palmarosa oil; melaleuca oil (p.2338·2); ylang ylang oil (p.2416·3); Dixeol.
Acne.

Teer-Linola-Fett *Wolff, Ger.*
Coal tar (p.1616·2).
Skin disorders.

Teer-Linola-Fett N *Wolff, Cz.†.*
Coal tar (p.1616·2).
Skin disorders.

Teeth Tough *Vitamed, Israel.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Teetha *Nelson, UK.*
Homoeopathic preparation.
Formerly known as Teething Granules.

Teething *Hylands, Canad.*
Homoeopathic preparation.

Teething Relief *Brauer, Austral.*
Homoeopathic preparation.

Tefaclor *TO-Chemicals, Thai.†.*
Cefaclor (p.217·2).
Bacterial infections.

Tefamin *Recordati, Ital.*
Aminophylline (p.1114·2) or theophylline (p.1140·1).
Asthma; bronchospasm.

Tefavinca *Bohm, Spain.*
Vincamine (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Tefilin *Hermal, Ger.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tefine *Herbacos, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Tefirax *G Pharm, Fr.*
Raffinose; levomenol (p.2333·3).
Pruritus; skin irritation.

Teflan *Uniao Quimica, Braz.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Teflut *Blausiegel, Braz.*
Flutamide (p.725·1).
Prostatic cancer.

Tefor *Organon, Turk.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Tefudex *Korea United, Philipp.*
Tegafur (p.776·1); uracil (p.2407·3).
Malignant neoplasms.

Tega *Pharmacia, Venez.†.*
Thiamine hydrochloride; riboflavin; nicotinamide; pyridoxine hydrochloride; hydroxocobalamin (p.1922·1).
Liver disorders.

Tegagen
3M, Arg.†.
Calcium alginate (p.1058·1).
Ulcers; wounds.

3M, Canad.†.
Calcium-sodium alginate (p.1058·1)(p.2141·1).
Wounds.

Tegarod *Cinetic, Arg.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome.

Tegasir *Andromaco, Chile.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome in females.

Tegasorb
Note. This name is used for preparations of different composition.
Novartis, Arg.†.
Hydrocolloid dressing.
Burns; ulcers; wounds.

3M, Canad.
⊗ Pectin (p.2145·2); gelatin (p.1072·1); and/or carmellose (p.2142·1).
Wounds.

Tegeline *Lab Francais du Fractionnement, Fr.; Er-Kim, Turk.*
A normal immunoglobulin (p.2225·3).
Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; Kawasaki disease; passive immunisation; retinochoroiditis.

Tegens *Sanofi-Aventis OTC, Ital.; Sanofi-Aventis, Port.*
Myrtillus (p.2349·3).
Capillary disorders; venous insufficiency.

Tegibs *Torrent, India.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome in women.

Tegod *Cipla, India.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome in women.

Tegreen *Pharmanex, USA.*
Green tea (p.2416·1).
Dietary supplement.

Tegretal *Novartis, Chile; Novartis, Ger.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetic neuropathy; epilepsy; multiple sclerosis; neuralgia.

Tegretard *Cristalia, Braz.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; epilepsy; neuralgias.

Tegretol *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; depression; diabetes insipidus; diabetic neuropathy; epilepsy; glossopharyngeal neuralgia; mania; neuropathic pain; polydipsia; polyuria; status epilepticus; trigeminal neuralgia.

Tegrex *Neo Quimica, Braz.*
Carbamazepine (p.471·3).
Epilepsy.

Tegrezin *Cazi, Braz.*
Carbamazepine (p.471·3).
Epilepsy.

Tegrin *Reedco, USA.*
Coal tar (p.1616·2).
Skin disorders.

Tegrin-HC *Block, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Tegrital *Novartis, India.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; trigeminal neuralgia.

Teguphen *Lupin, India†.*
Terfenadine (p.590·3); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs.

Teicon *Ariston, Braz.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Teiconin *Biochimico, Braz.†.*
Teicoplanin (p.344·3).
Bacterial infections.

Teicox *Richmond, Arg.*
Teicoplanin (p.344·3).
Bacterial infections.

Teicozid *Bergamo, Braz.*
Teicoplanin (p.344·3).
Bacterial infections.

Teiklonal *Klonal, Arg.*
Teicoplanin (p.344·3).
Bacterial infections.

Tejel *Johnson & Johnson, Spain.*
Coal tar (p.1616·2).
Scalp disorders.

Tejuntivo *Iquinosa, Spain.*
Oxaceprol (p.2359·1).
Musculoskeletal, joint, and peri-articular disorders; osteoporosis; soft-tissue injury.

Tekarin *Med-One, Gr.*
Vidarabine (p.912·2).
Herpesvirus infections.

Tekaval *Asofarma, Arg.†.*
Valproate semisodium (p.508·2).
Epilepsy.

Tekdent *Leti, Venez.†.*
Strontium chloride (p.2393·1).
Hypersensitive teeth.

Tekfema *Rivero, Arg.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Tekmisin *Sanli, Turk.*
Troleandomycin (p.357·1).
Streptococcal and pneumococcal infections.

Tekturna
Novartis, Cz.; Novartis, Port.
Aliskiren (p.1207·1).
Hypertension.

Novartis, USA.
Aliskiren fumarate (p.1206·3).
Hypertension.

Teladar *Dermol, USA†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Telament *Adcock Ingram Consumer, S.Afr.*
Simeticone (p.1770·2).
Gripe; infant colic.

Telarix *Help, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Telaroid *Cetus, Arg.*
Meloxicam (p.80·3).
Inflammation.

Telbibur N *Fatol, Ger.†.*
Cyanocobalamin (p.1980·2); nicotinamide (p.1957·3); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Liver disorders.

Teldane *Aventis, Mex.†.*
Terfenadine (p.590·3).
Allergic rhinitis; allergic skin disorders.

Teldane D *Aventis, Mex.†.*
Terfenadine (p.590·3); pseudoephedrine (p.1571·2).
Allergic rhinitis.

Teldanex *Aventis, Denm.†; Aventis, Norw.†; Aventis, Swed.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; urticaria.

Teldrin *SmithKline Beecham Consumer, USA.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Telebrix
Codali, Belg.; Guerbet, Braz.†; Tyco, Canad.; Guerbet, Hung.; Guerbet, Israel.
Meglumine ioxitalamate (p.1487·1) and/or sodium ioxitalamate (p.1487·2).
Radiographic contrast medium.

Rudefsa, Mex.
Meglumine ioxitalamate (p.1487·1).
Radiographic contrast medium.

Telebrix 12 *Guerbet, Fr.; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.*
Sodium ioxitalamate (p.1487·2).
Radiographic contrast medium.

Telebrix 30 *Temis, Arg.; Rider, Chile; Guerbet, Cz.; Guerbet, Fr.; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.; Quifoven, Venez.*
Meglumine ioxitalamate (p.1487·1).
Radiographic contrast medium.

Telebrix 35 *Rider, Chile; Guerbet, Cz.; Guerbet, Fr.; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.; Quifoven, Venez.*
Sodium ioxitalamate (p.1487·2); meglumine ioxitalamate (p.1487·1).
Radiographic contrast medium.

Telebrix 38 *Temis, Arg.*
Meglumine ioxitalamate (p.1487·1); sodium ioxitalamate (p.1487·2).
Radiographic contrast medium.

Telebrix Coronario *Temis, Arg.*
Meglumine ioxitalamate (p.1487·1); sodium ioxitalamate (p.1487·2).
Radiographic contrast medium.

Telebrix Gastro *Codali, Belg.; Guerbet, Cz.; Guerbet, Fr.; Guerbet, Ger.; R+N, Gr.; Guerbet, Hung.; Guerbet, Israel; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.*
Meglumine ioxitalamate (p.1487·1).
Contrast medium for gastrointestinal radiography.

Telebrix Hystero *Temis, Arg.; Codali, Belg.; Guerbet, Fr.; R+N, Gr.†; Guerbet, Neth.; Martins & Fernandes, Port.; Guerbet, Switz.; Quifoven, Venez.*
Meglumine ioxitalamate (p.1487·1).
Contrast medium for hysterosalpingography.

Telebrix N 180 and 300 *Guerbet, Ger.*
Meglumine ioxitalamate (p.1487·1).
Contrast medium for urinary-tract radiography.

Telectol *Obolenskoe, Rus.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; menopausal disorders; vascular eye disorders; vestibular disorders.

Teledol *Casasco, Arg.*
Ketorolac trometamol (p.74·2).
Pain.

Telen *Yamanouchi, Ger.†.*
Tripotassium dicitratobismuthate (p.1711·2).
Duodenal ulcer.

Telergon II *Medicalfarm, Ital.*
Royal jelly (p.2382·1).
Nutritional supplement.

Tele-Stulln *Stulln, Ger.*
⊗ Naphazoline hydrochloride (p.1565·2) or naphazoline nitrate (p.1565·2).
Blepharitis; conjunctivitis.

Telexin *Biofarma, Braz.†*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Telfast *Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Aventis, Ger.; Procter & Gamble, Ger.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Lepetit, Ital.; Sanofi-Aventis, Malaysia; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Sanofi-Aventis, Spain; Aventis, Swed.; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK.*
Fexofenadine hydrochloride (p.579·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; atopic asthma; urticaria.

Telfast Decongestant *Aventis, Austral.; Aventis, NZ†.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; nasal congestion.

Telfast Plus *Sanofi-Aventis, Indon.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Telfast-D *Aventis, Hong Kong; Sanofi-Aventis, Malaysia; Sanofi-Aventis, Singapore.*
Fexofenadine hydrochloride (p.579·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Telma *Glenmark, India.*
Telmisartan (p.1409·2).
Hypertension.

Telma-H *Glenmark, India†.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Telmitin *Nakornpatana, Thai.*
Niclosamide (p.151·1).
Cestode infections.

Telmox *Sandoz, Arg.*
Amoxicillin (p.202·2).
Bacterial infections.

Telnase *Aventis, Austral.; Aventis, NZ.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Telo *Uriach, Spain.*
Cefditoren pivoxil (p.223·2).
Bacterial infections.

Telo Cypro *Relax, Ital.†.*
Copper wire (p.1935·2).
Headache; insomnia; muscle spasm; musculoskeletal and joint disorders; pain.

Telos *Nycomed, Ger.*
Lornoxicam (p.77·3).
Osteoarthritis; rheumatoid arthritis.

Telpres *Nicholas Piramal, India.*
Telmisartan (p.1409·2).
Hypertension.

Telpres-H *Nicholas Piramal, India.*
⊗ Telmisartan (p.1409·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Telset *Medipharm, Chile.*
Tioconazole (p.548·2).
Fungal and Gram-positive bacterial skin infections.

Telsimox *Ad-Drugstel, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Telsomet *Spefar, Venez.†.*
Diazepam (p.986·3).
Anxiety; epilepsy; skeletal muscle spasm.

Teltonal *Hexal, Ger.*
Devil's claw root (p.39·1).
Joint disorders.

Telugren *Royal, Chile.*
Clotrimazole (p.530·1).
Fungal skin infections.

Telugren Plus *Royal, Chile.*
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Fungal and Gram-positive bacterial skin infections with inflammation.

Teluron *Schering, Jpn.*
Terguride (p.819·2).
Galactorrhoea; hyperprolactinaemia; suppression of lactation.

Telus *Elvetium, Arg.†.*
Ranitidine (p.1766·1).
Peptic ulcer.

Telviran *EGIS, Hung.*
Aciclovir (p.862·3).
Herpesvirus infections.

Telvodin *Ivax, Arg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Telzer *GSK, Mex.*
Fosamprenavir calcium (p.877·1).
HIV infection.

Telzir *GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Fosamprenavir calcium (p.877·1).
HIV infection.

Temaco *Nakornpatana, Thai.*
Theophylline (p.1140·1).
Obstructive airways disease.

Temaze *Alphapharm, Austral.*
Temazepam (p.1030·1).
Insomnia.

Temazep *CT, Ger.*
Temazepam (p.1030·1).
Sleep disorders.

Temerit *Menarini, Fr.*
⊗ Nebivolol (p.1347·1).
Heart failure; hypertension.

Temesta *Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Denm.; Wyeth, Fin.; Biodim, Fr.; Wyeth, Neth.; Wyeth, Swed.; Wyeth, Switz.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; insomnia; mixed anxiety depressive states; nausea and vomiting; premedication; sedative; status epilepticus.

Temetex *Teofarma, Ital.; Roche, Turk.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Temgesic
Kirby, Arg.†; Reckitt Benckiser, Austral.; Aesca, Austria; Schering-Plough, Belg.; Schering-Plough, Cz.; Schering-Plough, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Hong Kong; Reckitt Benckiser, Irl.; Schering-Plough, Ital.; Schering-Plough, Malaysia†; Schering-Plough, Mex.; Reckitt Benckiser, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.†; Schering-Plough, UK.
⊗ Buprenorphine hydrochloride (p.29·1).
Pain.

Mantecorp, Braz.
⊗ Buprenorphine (p.29·1) or buprenorphine hydrochloride (p.29·1).
Pain.

Temic *Uno, Ital.*
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Temigran *Teva, Israel.*
Ergotamine tartrate (p.620·1); chlorcyclizine (p.571·2); caffeine (p.1116·3); codeine phosphate (p.37·2).
Vascular headache.

Temisartan *Temis, Arg.*
Losartan potassium (p.1326·1).

Temistac *Temis, Arg.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Temodal *Schering-Plough, Arg.†; Schering-Plough, Austral.; Schering-Plough, Austria; Schering-Plough, Belg.; Schering-Plough, Braz.; Schering, Canad.; Schering-Plough, Chile; Schering-Plough, Cz.; SP, Denm.; Schering-Plough, Fin.; Schering-Plough, Fr.; Essex, Ger.; Schering-Plough, Gr.; Schering-Plough, Hong Kong; Schering-Plough, Hung.; Schering-Plough, Indon.; Schering-Plough, Irl.; Schering-Plough, Israel; Schering-Plough, Ital.; Schering-Plough, Malaysia; Schering-Plough, Mex.; Schering-Plough, NZ; Schering-Plough, Neth.; Schering-Plough, Norw.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Port.; Schering-Plough, Rus.; Schering-Plough, S.Afr.; Schering-Plough, Singapore; Schering-Plough, Spain; Schering-Plough, Swed.; Essex, Switz.; Schering-Plough, Thai.; Schering-Plough, Turk.; Schering-Plough, UK; Schering-Plough, Venez.*
Temozolomide (p.776·3).
Malignant glioma; malignant melanoma.

Temodar *Schering, USA.*
Temozolomide (p.776·3).
Anaplastic astrocytoma; glioblastoma multiforme.

Temovate *PharmaDerm, USA.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Temoxol *Schering-Plough, S.Afr.†.*
Temozolomide (p.776·3).
Malignant glioma; metastatic malignant melanoma.

Temp Tab *National Vitamin, USA.*
Sodium chloride (p.1686·1); potassium chloride (p.1684·3).
Electrolyte disorders.

Tempain *Blooming Fields, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Tempalgin *Pharmachim, Rus.*
Dipyrone (p.49·2); triacetonamine tosilate (p.1033·2).
Fever; pain.

Tempanginol *Balkanpharma, Rus.*
Dipyrone (p.49·2); triacetonamine tosilate (p.1033·2).
Fever; pain.

Temperal *Allen, Mex.; Diviser Aquilea, Spain†.*
Paracetamol (p.108·1).
Fever; pain.

Temperax *Bago, Chile.*
Citalopram hydrobromide (p.385·3).
Depression.

Tempil *Temmler, Ger.†.*
Ibuprofen (p.64·2).
Fever; pain.

Tempil N *Temmler, Ger.*
⊗ Diphenylpyraline hydrochloride (p.578·2); metamfepramone hydrochloride (p.2343·1); aspirin (p.20·3).
Cold symptoms.

Tempire *Collins, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Templadol *Andromaco, Chile.*
Mefenamic acid (p.80·1).
Pain.

Tempo
Note. This name is used for preparations of different composition.
Akdeniz, Turk.
Paracetamol (p.108·1).
Fever; pain.

Thompson, USA.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2); calcium carbonate (p.1714·1).
Hyperacidity.

Tempofin *Collins, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Tempolax *Hommel, Ger.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Tempo-Rinolo *Aventis, Ital.†.*
Phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Nasal congestion.

Temporol *Orion, Irl.†.*
Carbamazepine (p.471·3).
Epilepsy; trigeminal neuralgia.

Tempra
Note. This name is used for preparations of different composition.
Mead Johnson Nutritionals, Canad.; BMS, Indon.; BMS, Philipp.; Mead Johnson Nutritionals, Thai.; Mead Johnson Nutritionals, USA; BMS, Venez.
Paracetamol (p.108·1).
Fever; pain.

BMS, Mex.
Chewable tablets; oral drops; suppositories; syrup; tablets: Paracetamol (p.108·1).
Fever; pain.

BMS, Mex.†.
Injection: Propacetamol hydrochloride (p.119·2).
Fever; pain.

Tempra CD *BMS, Mex.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Tempra MF *BMS, Mex.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tempragrip
Note. This name is used for preparations of different composition.
BMS, Venez.
Oral granules: Paracetamol (p.108·1); pheniramine maleate (p.587·3).
Formerly contained paracetamol and chlorphenamine.

BMS, Venez.
Tablets: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Tempragrip Dia y Noche *BMS, Venez.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Influenza symptoms.

Tempraplus *BMS, Venez.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tempre *Collins, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Temprin *Continentales, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Temrevac-HB *Vaxines, Philipp.*
A hepatitis B vaccine (recombinant) (p.2215·2).
Active immunisation.

Temserin *Vianex (Βιανεξ), Gr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Temsofen *Tems, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Temtabs *Fawns & McAllan, Austral.*
Temazepam (p.1030·1).
Insomnia.

Temzzard *Pizzard, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Tenace *Combiphar, Indon.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Tenacid *Sigma-Tau, Ital.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tenadin *Opco, Denm.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; hay fever; urticaria.

Tenadren *Sigma, Braz.*
⊗ Propranolol hydrochloride (p.1380·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tenadrin *Hua, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; nasal congestion.

Tenag *Marjan, Braz.*
Agnus castus (p.2249·1).

Tenalgin *Vida, Port.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenapril *Dexa, Indon.*
Ramipril (p.1385·3).
Heart failure; hypertension.

Tenaron *Sandoz, Arg.; Pharma Investi, Chile.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Tenasil *Homeofarm, Pol.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Tenavit *Marjan, Braz.*
Folic acid; pyridoxine hydrochloride; cyanocobalamin (p.1922·1).

Tenax *Siam Bheasach, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenaxum
Servier, Cz.; EGIS, Hung.
Rilmenidine phosphate (p.1388·3).
Hypertension.

Servier, Pol.
Rilmenidine (p.1388·3).
Hypertension.

Tenazide *Combiphar, Indon.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tenblok *Kimia, Indon.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ten-Bloka *Pharmacare, S.Afr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tencas *Casasco, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left-ventricular dysfunction.

Tencas D *Casasco, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tencef *Tedec Meiji, Port.; Tedec Meiji, Spain.*
Cefminox sodium (p.226·1).
Bacterial infections.

Tencet *Hauck, USA.*
Paracetamol (p.108·1); butalbital (p.967·2); caffeine (p.1116·3).
Formerly known as G-1.
Pain.

Tenchlor *Pharmacare, S.Afr.; Berk, UK.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tencilan *Finadiet, Arg.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Tencon *International Ethical, USA.*
Paracetamol (p.108·1); butalbital (p.967·2).

Tendan *Lamda (Λαμδα), Gr.†.*
Buspirone hydrochloride (p.965·3).
Anxiety disorders.

Tenderdol *Vifor, Switz.*
Choline salicylate (p.36·3); cetalkonium chloride (p.1634·1); levomenol (p.2333·3).
Mouth disorders.

TenderWet *IVF, Switz.†.*
Xanthan gum (p.2147·2).
Wounds.

Tendigrip *Pietrasanta, Ital.*
Zinc oxide (p.1621·2).

Tendolon *Elpen (Ελπεν), Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Tendox *Chefaro, Neth.*
Benzoyl peroxide (p.1590·2).
Acne.

Tendrin *Pisa, Mex.*
⊗ Ephedrine (p.1558·1).

Tendro *Tentan, Switz.*
Hamamelis (p.2318·2); euphrasia (p.2301·3); dexpanthenol (p.2362·1).
Dry eyes; eye irritation.

Tenecha *Drovepat, Venez.†.*
Pyrantel embonate (p.155·1).
Worm infections.

Teneretic *AstraZeneca, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenervan *Rafarm, Gr.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Tenescan *Maver, Mex.*
Clotrimazole (p.530·1).
Fungal infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Tenex *Reddy, USA.*
Guanfacine hydrochloride (p.1301·1).
Hypertension.

Tenibex *Lemery, Mex.*
Albendazole (p.139·2).
Worm infections.

Tenidon *Gerard, Denm.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenif *AstraZeneca, Belg.; AstraZeneca, UK.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Teniken *Kener, Mex.*
Praziquantel (p.153·3).
Parasitic infections.

Tenitran *Pfizer, Ital.†.*
Tenitramine (p.1410·2).
Angina pectoris; heart failure.

Tenitrat *Catarinense, Braz.*
Devil's claw root (p.39·1).
Inflammation.

Teniverme *Basi, Port.*
Flubendazole (p.145·1).
Worm infections.

Ten-K *Summit, USA.*
Potassium chloride (p.1684·3).
Hypokalaemia; potassium depletion.

Tenkdol *Biotenk, Arg.*
Ketorolac trometamol (p.74·2).
Pain.

Tenliv *Ativus, Braz.*
Feverfew (p.622·2).
Migraine.

Teno *Ipca, India.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tenobio *Biofarma, Braz.†.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenoblock *Leiras, Fin.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Tenocam *Eurofarma, Braz.†; M & H, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenocard *Klonal, Arg.*
Nimodipine (p.1357·2).

Tenochek
Ipca, India.
⊗ Atenolol (p.1217·3); amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Ipca, Rus.
⊗ Atenolol (p.1217·3); amlodipine (p.1214·2).
Angina pectoris; hypertension.

Tenoclor *Nicholas Piramal, India.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenocor *Merck, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tenofax *Sandoz, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tenofed *Ipca, India.*
⊗ Atenolol (p.1217·3); nifedipine (p.1350·1).
Angina pectoris; hypertension.

Tenoftal
Note.This name is used for preparations of different composition.
Klonal, Arg.†.
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma.

Teuto, Braz.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Tenoksan *Drogsan, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Tenoktil *Eczacibasi, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Tenol *Masa, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Tenolin *Technilab, Canad.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tenoloc *Zentiva, Cz.*
⊗ Celiprolol hydrochloride (p.1242·2).
Angina pectoris; hypertension.

Tenolol *Ipca, India; Ipca, Rus.; IPCA, Singapore; Siam Bheasach, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tenolol-AM *Ipca, India.*
⊗ Atenolol (p.1217·3); amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Tenolol-D *Ipca, India†.*
⊗ Atenolol (p.1217·3); indapamide (p.1314·1).
Hypertension.

Tenolone *Lusofarmaco, Ital.†.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenomax *Boniscontro & Gazzone, Ital.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tenopres *Sidus, Arg.†.*
Losartan potassium (p.1326·1).
Hypertension.

Tenopres D *Sidus, Arg.†.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tenoprin *Ratiopharm, Fin.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; myocardial infarction.

Tenopt *Sigma, Austral.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Tenor-Bloc *Intas, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tenordate *AstraZeneca, Fr.*
⊗ Nifedipine (p.1350·1); atenolol (p.1217·3).
Hypertension.

Tenoret *AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Singapore; AstraZeneca, Thai.†; AstraZeneca, UK.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tenoretic *AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, Cz.; Pfizer, Denm.; AstraZeneca, Fr.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Thai.†; Abdi, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Tenoric *Ipca, India; Ipca, Rus.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenormin *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, Cz.; Pfizer, Denm.; AstraZeneca, Ger.; Cana, Gr.; AstraZeneca, Hong Kong; Nicholas Piramal, India; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, Neth.; Pfizer, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; Pfizer, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Tenormine *AstraZeneca, Fr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tenorox *Oxford Laboratories, Rus.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

Tenostat *Apotex, Philipp.; Pharma 3, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tenotec *Ache, Braz.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenovate *GSK, India.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Tenovate G *GSK, India.*
⊗ Clobetasol propionate (p.1522·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Tenovate M *GSK, India.*
⊗ Clobetasol propionate (p.1522·2); miconazole nitrate (p.541·3).
Infected skin disorders.

Tenox
Note.This name is used for preparations of different composition.
Orion, Fin.; Orion, Irl.
Temazepam (p.1030·1).
Anxiety; insomnia; premedication.

Lamda (Λαμδα), Gr.†; Charoen, Thai.; Biofarma, Turk.
Tenoxicam (p.128·2).
Gout; inflammatory disorders; musculoskeletal, joint, and peri-articular disorders.

KRKA, Hung.; KRKA, Pol.
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Tenoxen *Biosintetica, Braz.†.*
Tenoxicam (p.128·2).
Musculoskeletal, joint, and peri-articular disorders.

Tenoxil *Olan-Kemed, Thai.*
Tenoxicam (p.128·2).
Musculoskeletal, joint, and peri-articular disorders.

Tenoxin *Roemmers-Klinos, Venez.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tenoxol *Boniscontro & Gazzone, Ital.*
Neltenexine (p.1566·1).
Respiratory-tract disorders.

Tenpril *Lisapharma, Ital.*
Captopril (p.1239·2).
Heart failure; hypertension.

Ten-Quat *Esoform, Ital.*
Benzalkonium chloride (p.1629·1).
Surface disinfection.

Tens *Unilfarma, Port.; Boehringer Ingelheim, Venez.†.*
Lacidipine (p.1322·2).
Hypertension.

Tensaar *Kimia, Indon.*
Losartan potassium (p.1326·1).
Hypertension.

Tensadiur *Savio, Ital.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tensaldin *Delta, Braz.*
⊗ Caffeine (p.1116·3); isometheptene hydrochloride (p.2327·1) or isometheptene mucate (p.2327·2); dipyrone (p.49·2).
Migraine.

Tensaliv *Neo Quimica, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Tensamin *Zentiva, Cz.*
Dopamine hydrochloride (p.1273·2).
Heart failure; hypovolaemia; shock.

Tensamon *Sanitas, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal disorders.

Tensan *Arcana, Austria.*
Nilvadipine (p.1357·1).
Hypertension.

Tensanil *Savio, Ital.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Tensazol *Tecnifar, Port.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension; ischaemic heart disease; myocardial infarction; unstable angina pectoris.

Tenserpil *Gentek, Venez.†.*
Losartan potassium (p.1326·1).
Hypertension.

Tensiane *Greenpharma, Braz.*
Cimicifuga (p.2282·1).

Tensiben *Soria Natural, Spain†.*
Olive oil (p.2356·2); crataegus (p.2289·1); betula alba (p.2266·3).
Arrhythmias; hypertension.

Tensibloc *Towa, Philipp.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Tensicap *Sanbe, Indon.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tensidif *Medifarm, Turk.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Tensidol *Kenyaku, Thai.†.*
Haloperidol (p.1000·2).
Anxiety; psychiatric disorders.

Tensig *Sigma, Austral.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tensigal *Ivax, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Tensikey *Inkeysa, Spain.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tensikey Complex *Inkeysa, Spain.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tensil *Best, Mex.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension.

Tensilol *LA, Arg.*
⊗ Atenolol (p.1217·3).
Hypertension.

Tensilon *ICN, USA.*
Edrophonium chloride (p.630·3).
Diagnosis of myasthenia gravis; reversal of competitive neuromuscular blockade.

Tensimin *Unique, India†; Pasteur, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Tensinor *Abdi, Turk.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Tensinorm *Medikon, Indon.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Tensiocap *Giscard, Arg.*
Pilocarpine (p.1884·3).

Tensiocomplet *Medea, Spain.*
⊗ Hydralazine hydrochloride (p.1305·3); hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Tensiomax *Bago, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Tensiomin *Egis, Cz.; UCB, Ger.; Egis, Hong Kong; EGIS, Hung.; Egis, Thai.†.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tensiomin-Cor *UCB, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tensionorme *Lisapharm, Fr.*
⊗ Bendroflumethiazide (p.1224·1); reserpine (p.1387·3).
Hypertension.

Tensioval *Sanval, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Tensipine *Genus, UK.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Tensiplex *Francia, Ital.†.*
Vinburnine phosphate (p.2414·1).
Cerebrovascular disorders; mental function impairment.

Tensispes *Alet, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Tensiton *Infusia, Cz.†.*
⊗ Dextran 70 (p.1059·3) in sodium chloride.
Hypovolaemia.

Tensium
Note.This name is used for preparations of different composition.
Baliarda, Arg.
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; mixed anxiety depressive states; panic attacks.

DDSA Pharmaceuticals, UK.
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; skeletal muscle spasm.

Tensium Gastric *Baliarda, Arg.*
Alprazolam (p.960·1); domperidone (p.1726·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Tensival *Solvay, Port.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tensivask *Dexa, Indon.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Tenso Stop *Esteve, Spain.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Tenso Stop Plus *Esteve, Spain.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tensobon *Schwarz, Ger.; Coronet, Indon.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension.

Tensobon comp *Schwarz, Ger.; Upsamedica, Switz.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension.

Tensocardil *Esteve, Spain.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Tensodin *Ativus, Braz.*
Amlodipine besilate (p.1214·1).
Hypertension.

Tensodox *Recalcine, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Tensofar *Pharma Investi, Chile.*
Nitrendipine (p.1358·2).
Hypertension.

Tensoflux *Hennig, Ger.*
⊗ Bendroflumethiazide (p.1224·1); amiloride hydrochloride (p.1209·2).
Ascites; hypertension; oedema; renal calculi.

Tensogard *BMS, Ital.*
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Tensogradal *Almirall, Spain.*
Nitrendipine (p.1358·2).
Hypertension.

Tensoliv *Laboratorios Chile, Chile.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Irritable colon.

Tensolve *Pharmacare, S.Afr.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain.

Tensomax *Leti, Venez.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Tensonit *Ivax, Arg.*
Olmesartan medoxomil (p.1361·1).
Hypertension.

Tensopin *Leti, Venez.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Tensoprel *Rubio, Singapore†; Rubio, Spain.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tensopril
Note.This name is used for preparations of different composition.
Ivax, Arg.; MSD, Israel.
Lisinopril (p.1325·2).
Heart failure; hypertension.
Ivax, Irl.†; Irex, Port.†; Ivax, UK.
Captopril (p.1239·2).
Heart failure; hypertension.

Tensopril D *Ivax, Arg.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tensopyn *Mirren, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); doxylamine succinate (p.578·2); caffeine (p.1116·3).
Pain and associated tension.

Tensoril *Apotex, Philipp.; Pharma 3, Philipp.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tensostad *Stada, Ger.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tensotec
Lavipharm, Gr.†.
Moexipril (p.1343·3).
Hypertension.
Ranbaxy, Malaysia†; Schwarz, Malaysia†; Neo-Farmaceutica, Port.
Moexipril hydrochloride (p.1343·2).
Hypertension.

Tensotin *Julphar, UAE.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Tensozide *BMS, Ital.*
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tenstaten *Ipsen, Cz.†; Beaufour, Fr.*
⊗ Cicletanine hydrochloride (p.1244·3).
Hypertension.

Tenston
Note.This name is used for preparations of different composition.
Adcock Ingram, S.Afr.
Sustained-release capsules; sustained-release tablets: Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Fever; pain.
Adcock Ingram, S.Afr.
Syrup: Promethazine hydrochloride (p.588·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.
Adcock Ingram, S.Afr.
Tablets: Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2); meprobamate (p.1006·2).
Fever; pain.

Tensulan *Marjan, Braz.*
Vitamin preparation (p.1922·1).

Tensuril *Cristalia, Braz.*
Diazoxide (p.1257·3).
Hypertension; hypoglycaemia.

Tentepanil *Medinova (Μεντινοβα), Gr.*
Tenoxicam (p.128·2).
Inflammatory disorders.

Tentex *Himalaya, Rus.*
Abelmoschus moschatus; withania somnifera; argyreia speciosa; dolichos pruriens; trivanga bhasma; shilajeet (mineral pitch); saffron (p.1472·3); nux vomica (p.2355·3); makardhwaj; orchis mascula (p.2357·3); anacyclus pyrethrum; sida cordifolia; bombax ceiba; black pepper (p.2364·3).
Erectile dysfunction.

Tentil *Rafarm, Gr.*
Potassium iodide (p.2169·2); sodium iodide (p.2169·2).
Glaucoma.

Tentrini *Nutricia, Austral.†; Support, Braz.†; Nutricia, Fin.; Nutricia, Fr.; Nutricia, Irl.; Nutricia, Ital.; Nutricia, Port.; Nutricia Clinical, UK.*
A range of preparations for enteral nutrition (p.1922·1).

Tenturdiyot *Aroma, Turk.; Cagdas, Turk.; Drogsan, Turk.; Merkez, Turk.; Oro, Turk.*
Iodine (p.2169·2); sodium iodide (p.2169·2).
Minor cuts and abrasions.

Tenualax *Bago, Arg.*
Lactulose (p.1738·2).
Constipation; gastrointestinal enteropathy; hepatic encephalopathy.

Tenuate *Aventis, Austral.; Aventis, Canad.; Aventis, USA†.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Tenuate Dospan *Aventis, NZ; Adcock Ingram, S.Afr.*
⊗ Diethylpropion hydrochloride (p.2154·3).
Obesity.

Tenutan *PannonPharma, Hung.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Tenutex *Bioglan, Swed.*
Disulfiram (p.2296·2); benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Tenvasc *Interbial, Port.*
Cilnidipine (p.1245·2).

Tenvatil *Drugtech, Chile.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

Tenvic *Investi, Arg.*
Iron polymaltose (p.1953·1); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Iron and folic acid deficiency.

Tenxil *Unison, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Teobag *Eczacibasi-Baxter, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teobid *Farma, Venez.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teoden *Biosintetica, Braz.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Teodosis *Welt, Arg.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teofedril *Pfizer, Venez.†.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2).
Asthma.

Teofilab *Multilab, Braz.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teofylamin *Medic, Denm.; SAD, Denm.*
Aminophylline (p.1114·2).
Obstructive airways disease.

Teofyllamin *Ipex, Swed.*
Aminophylline (p.1114·2).
Asthma; neonatal apnoea; pulmonary oedema.

Teogrand *Ahimsa, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Teokap *Nobel, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teolixir *Biogalenica, Spain.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Teolixir Compositum *Biogalenica, Spain.*
⊗ Guaifenesin (p.1561·3); prednisolone (p.1540·3); theophylline (p.1140·1).
Obstructive airways disease.

Teolong *Abbott, Braz.; Knoll, Mex.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teomuc *Biolab Sanus, Braz.*
Ambroxol theophyllinate (p.1114·2).
Respiratory-tract disorders.

Teonibsa *Inibsa, Port.†.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; pulmonary oedema.

Teophyl *IQB, Braz.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teoptic *Novartis, Irl.; Novartis, Neth.; Restan, S.Afr.; Novartis, UK.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma; ocular hypertension.

Teoremac *Sanfer, Mex.*
Glucametacin (p.62·2).
Fever; inflammation; pain.

Teoremin *Asta Medica, Braz.*
Glucametacin (p.62·2).
Musculoskeletal, joint, and peri-articular disorders.

Teosal *Dexa, Indon.*
⊗ Salbutamol sulfate (p.1131·3); theophylline (p.1140·1).
Obstructive airways disease.

Teosel *Biosel, Turk.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teosona *Phoenix, Arg.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teosona Sol *Phoenix, Arg.*
Theophylline (p.1140·1); theophylline monoethanolamine (p.1146·3).
Obstructive airways disease.

Teoston *Ariston, Braz.*
Theophylline (p.1140·1).
Asthma; bronchodilator.

Teotard *KRKA, Cz.†; KRKA, Rus.*
Theophylline (p.1140·1).
Obstructive airways disease.

Teovent
Note.This name is used for preparations of different composition.
Schering-Plough, Port.†.
Theophylline (p.1140·1).
Asthma.
Recip, Swed.
Choline theophyllinate (p.1119·3).
Obstructive airways disease.

Tepanil *Norma (Νορμα), Gr.†.*
Nitrendipine (p.1358·2).
Hypertension.

Tepavil *Almirall, Spain.*
Sulpiride (p.1028·3).
Anxiety; psychoses; vertigo.

Tepaxin *Takeda, Indon.*
Cefalexin (p.218·2).
Bacterial infections.

Tepazepam *Gentek, Venez.†.*
Sulpiride (p.1028·3); diazepam (p.986·3).
Anxiety; depression.

Tepazepan *Almirall, Spain.*
Diazepam (p.986·3); pyridoxine (p.1979·1); sulpiride (p.1028·3).
Anxiety; neurosis; psychoses; psychosomatic disorders.

Teperin *Extractum, Hung.*
Amitriptyline hydrochloride (p.376·1).
Bipolar disorder; depression; neuropathies.

Tepilta *ICN, Austria; Valeant, Ger.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); oxetacaine (p.1867·2).
Dyspepsia; gastritis; gastro-oesophageal reflux; heartburn; hiatus hernia; peptic ulcer.

Tepox Cal *Stada, Spain.*
Calcium pidolate (p.1676·3).
Calcium deficiency; osteoporosis.

Tepox Cal D *Stada, Spain.*
Calcium pidolate (p.1676·3); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Teprix *Gramon, Arg.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Tequin *BMS, Arg.†; BMS, Austral.; BMS, Braz.; BMS, Canad.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Philipp.; BMS, S.Afr.; BMS, Singapore†; BMS, Thai.†; BMS, USA†.*
Gatifloxacin (p.281·1).
Bacterial infections.

Tequinol *Otto, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Tera *TAD, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Terablock *Pfleger, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Terace Zinc *Konsuma, Venez.*
Ascorbic acid (p.1983·3); zinc sulfate (p.1999·2).
Vitamin C deficiency.

Teraciton *Ariston, Braz.†.*
Tetracycline (p.347·1).
Bacterial infections.

Teraclox *Ivax, Mex.*
Cefaclor (p.217·2).
Bacterial infections.

Teradal *Organifar, Venez.†.*
⊗ Spironolactone (p.1400·1).
Diuretic.

Teradi *GMP, Indon.*
Attapulgite (p.1709·1).
Diarrhoea.

Teradin *Yeni, Turk.*
Terfenadine (p.590·3).
Allergic rhinitis; urticaria.

Teradyl *Hua, Thai.*
Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Coughs.

Terafin *Fako, Turk.*
Terbinafine (p.546·3).
Fungal infections of the skin and nails.

Teraflem *Konsuma, Venez.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Terafluss *Madaus, Ital.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Tera-Gel *Geritrex, USA.*
Coal tar (p.1616·2).
Scalp disorders.

Teragran
BMS, Chile†.
Multivitamin and iron preparation (p.1922·1).
Dietary supplement in children.
BMS, Mex.
Vitamin and mineral preparation (p.1922·1).

Teragran JR *BMS, Braz.*
Multivitamin preparation (p.1922·1).

Teragran M *BMS, Braz.; BMS, Chile†.*
Multivitamin and mineral preparation (p.1922·1).

Teragrip
Note.This name is used for preparations of different composition.
Konsuma, Venez.
Capsules; oral granules (adult): Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.
Konsuma, Venez.
Oral drops; paediatric oral granules; syrup: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Teragrip D *Konsuma, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Teragrip Plus.
Cold symptoms.

Teragrip Forte Dia *Konsuma, Venez.*
Paracetamol (p.108·1); pseudoephedrine (p.1571·2) or pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Teragrip Forte Dia/Forte Noche *Konsuma, Venez.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; chlorphenamine maleate (p.571·3).
Cold symptoms.

Teragrip Forte Noche *Konsuma, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Teragrip Plus *Konsuma, Venez.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Cold symptoms.

Teragripem *Konsuma, Venez.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms.

Terak *Akorn, USA.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye infections.

Teralithe *Sanofi-Aventis, Fr.*
Lithium carbonate (p.401·3).
Bipolar disorder; psychoses.

Teramic *Andromaco, Chile.*
Itraconazole (p.536·3).
Fungal infections.

Teramoxyl *Terramedic, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Teranar *Apogepha, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Teranex *Innoderm, Philipp.*
Glycolic acid (p.1598·1).
Skin cleansing.

Terap *Sanitas, Chile.*
Midazolam maleate (p.1007·3).
Insomnia; premedication.

Terapova *Ivax, Mex.*
Conjugated oestrogens (p.2087·2).
Menopausal disorders; osteoporosis.

Teraprost *Malesci, Ital.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Teraquin *Fortbenton, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

Terasep *Fada, Arg.*
Cefotaxime (p.229·1).
Bacterial infections.

Teraside *Krugher, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Terasin *YSP, Malaysia.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Terasma *Medikon, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terasma Expectorant *Medikon, Indon.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Teratos *Konsuma, Venez.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Cough.

Teraumon *Smaller, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Terazid *Madaus, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Terazoflo *Gry, Ger.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Terazol *Janssen-Ortho, Canad.; Janssen-Cilag, S.Afr.; Ortho McNeil, USA.*
Terconazole (p.548·1).
Vulvovaginal candidiasis.

Terazosabb *Abbott, Belg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Terbac *Syntex, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Terbafin
Kleva, Gr.
Terbinafine (p.546·3).
Fungal skin infections.
Pacific, NZ.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbasmin *Euro Registratie, Neth.; AstraZeneca, Spain; Ern, Spain.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terbasmin Expectorante *Ern, Spain.*
⊗ Guaifenesin (p.1561·3); terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terbenol *Bernabo, Arg.*
Diosmin (p.2304·2).
Capillary fragility; venous insufficiency.

Terbenol Duo *Bernabo, Arg.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Terbicil *Pharmacare, S.Afr.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbi-Derm *Cinetic, Arg.*
Terbinafine (p.546·3).
Fungal infections.

Terbiderm *Dermapharm, Ger.; Dermapharm, Neth.; Richter, Pol.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbifil *Ecosol, Switz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin, nail, and scalp infections.

Terbifin *Cipla, Hong Kong; Cipla, India.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbigalen *Galen, Ger.*
Terbinafine hydrochloride (p.546·3).
Fungal nail and skin infections.

Terbigen *Generics, Hung.*
Terbinafine hydrochloride (p.546·3).
Fungal infections.

TerbiGen *Generics, Pol.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbigram *Lavipharm, Gr.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Terbihexal *Hexal, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terbin *Gabriel, Gr.; Eczacibasi, Turk.*
Terbinafine (p.546·3).
Fungal infections of the skin and nails.

Terbinavita *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Terbinox *Unique, Rus.*
Terbinafine (p.546·3) or terbinafine hydrochloride (p.546·3).
Fungal infections.

Terbiox *Rivero, Arg.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Terbiprol *Proel, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Terbisil
Gedeon Richter, Cz.; Gedeon Richter, Hung.; Richter, Pol.; Santa, Turk.
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.
Gedeon Richter, Rus.
Terbinafine (p.546·3).
Fungal skin and nail infections.

Terbiskin *Biospray, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Terbisol *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Terbistad *Stada, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Terbosil *Silom, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Coughs; obstructive airways disease.

Terbron *Biolab, Hong Kong; Biolab, Malaysia†; Biolab, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma; obstructive airways disease.

Terbron Expectorant *Biolab, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Terbuken *Kener, Mex.*
⊗ Terbutaline sulfate (p.1138·3).

Terbul *Teofarma, Ger.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terbulin *Vitamed, Israel; IG, Malaysia†; Medidata, Malaysia†; Medichem, Philipp.; Great Eastern, Thai.; Westmont, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma; obstructive airways disease; premature labour.

Terbuno *Milano, Thai.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terbuta *Christo, Hong Kong.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Terbutil *Uniao Quimica, Braz.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma.

Terbuturmant *Dermapharm, Ger.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Tercef *Balkanpharma, Rus.*
Ceftriaxone (p.238·1).
Bacterial infections.

Tercian
Sanofi-Aventis, Fr.
Cyamemazine (p.985·3) or cyamemazine tartrate (p.985·3).
Aggression; anxiety; depression; psychoses.
Vitoria, Port.
Cyamemazine tartrate (p.985·3).
Anxiety; depression; psychoses; withdrawal syndromes.

Terco-C *Hua, Thai.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Terco-D *Hua, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Coughs.

Terekol *Panalab, Arg.*
Terbinafine hydrochloride (p.546·3).
Fungal skin, hair, and nail infections.

Terelit *Farmasan, Ger.†.*
Doxycycline hyclate (p.267·1); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections associated with increased or viscous mucus.

Tereonsit *Hautel, Arg.†.*
Sage (p.2382·3); trolamine (p.2405·1).

Terfacef *Sanbe, Indon.*
Ceftriaxone (p.238·1).
Bacterial infections.

Terfamex *Medix, Mex.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Terfanil *Cafar, Venez.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Terfedura *Merck dura, Ger.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Terfemax *Temis, Arg.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Terfemundin *Mundipharma, Ger.†.*
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Terfenadina DG *Phoenix, Arg.†.*
Terfenadine (p.590·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; otitis media; sinusitis.

Terfex *Mediderm, Chile; Vivax Gynopharm, Venez.*
Terbinafine hydrochloride (p.546·3).
Fungal infections.

Terfimed *ProMed, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Terfin
Note. This name is used for preparations of different composition.
Elea, Arg.; Teva, Hung.
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.
Pharmacodane, Denm.†; Interbat, Indon.
Terfenadine (p.590·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Terfinil *Biomedica-Chemica, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Terfinor *Alet, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Terflurazine *Lennon, S.Afr.*
Trifluoperazine hydrochloride (p.1034·2).
Delirium tremens; mania; schizophrenia.

Terfungin *Tiefenbacher, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Tergal *Norton, Cz.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Tergecef *Astellas, Philipp.; Medichem, Philipp.*
Cefixime (p.224·3).
Bacterial infections.

Tergecin *Fujisawa, Philipp.; Medichem, Philipp.*
Ceftizoxime (p.236·3).
Bacterial infections.

Tergil *MM, India.*
⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Tergil-T *MM, India.*
⊗ Terbutaline sulfate (p.1138·3); theophylline (p.1140·1).
Obstructive airways disease.

Tergynan
Note. This name is used for preparations of different composition.
Bouchara, Fr.
Metronidazole (p.837·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Formerly contained ternidazole, neomycin sulfate, nystatin, and prednisolone metasulfobenzoate sodium.
Vaginitis.
Bouchara, Rus.
⊗ Ternidazole (p.848·2); neomycin sulfate (p.305·1); nystatin (p.543·2); prednisolone (p.1540·3).
Vaginitis.

Terican *Landsteiner, Mex.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Tericin AT *Ativus, Braz.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).
Bacterial and fungal vulvovaginal infections.

Teridin *KRKA, Cz.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Teril *Alphapharm, Austral.; Alphapharm, Hong Kong; Merck, Indon.; Taro, Israel; Pacific, NZ; Taro, UK†; Taro, USA.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgias; polydipsia; polyuria.

Terioxan *Shin Poong, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Teripol *Landsteiner, Mex.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Terivalidin *Gerot, Austria; Aventis, S.Afr.*
Terizidone (p.347·1).
Bacterial infections; tuberculosis.

Terizidex *Collect, Braz.*
Terizidone (p.347·1).
Tuberculosis.

Terizin *Seoul Pharma, Singapore.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Terkur *Orva, Turk.*
Aluminium chlorohydrate (p.1588·3).
Hyperhidrosis.

Terloc
Ivax, Arg.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Laboratorios Chile, Chile.
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Terloc Duo *Ivax, Arg.*
Amlodipine besilate (p.1214·1); benazepril (p.1223·3).
Hypertension.

Terlomexin *Effik, Fr.*
Fenticonazole nitrate (p.531·3).
Candidiasis.

Termacet *Toprak, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Termalgin *Novartis, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Termalgin Codeina *Novartis, Spain.*
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Termalgine *Novartis, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Termalgine Plus *Novartis, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Termasil *Hasco-Lek, Pol.*
Salix purpurea (p.121·3); sambucus nigra (p.2383·1); tilia (p.2402·2); verbascum (p.2413·3).
Fever.

Termicef *Nufarindo, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Termicon *Farmstandart, Rus.*
Terbinafine (p.546·3) or terbinafine hydrochloride (p.546·3).
Fungal skin, mucous membrane, and nail infections.

Termin C *Terramedic, Philipp.*
Vitamin preparation with iron (p.1922·1).
Nutritional supplement.

Termisil *Genepharm, Gr.; Ferron, Indon.*
Terbinafine (p.546·3).
Fungal skin infections.

Termizol *Ivax, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Termocatil *Gelos, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Termofren *Roemmers, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Termogrip *Ronnet, Arg.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); bromhexine hydrochloride (p.1552·2).
Cold and influenza symptoms.

Termogripe C
Luper, Braz.†.
Syrup: Chlorphenamine maleate (p.571·3); caffeine (p.1116·3); salicylamide (p.121·2); ascorbic acid (p.1983·3).
Cold and influenza symptoms.
Luper, Braz.†.
Tablets: Green tablets, chlorphenamine maleate (p.571·3); caffeine (p.1116·3); salicylamide (p.121·2); yellow tablets, ascorbic acid (p.1983·3).
Cold and influenza symptoms.

Termol *Uniao Quimica, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Termonal *Sanval, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Termonil *Liferpal, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Termo-Niofen *Megahealth, Chile.*
Ibuprofen (p.64·2); paracetamol (p.108·1).
Fever; pain.

Termo-Ped *Stiefel, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Termopirona *Neo Quimica, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Termoprin *Cazi, Braz.*
Dipyrone (p.49·2).
Fever; pain.

Termorex *Konimex, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Termorex Plus *Konimex, Indon.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Termosan *Dom, Spain.*
Camphor (p.2273·2); capsicum oleoresin (p.2276·2); methyl salicylate (p.85·3); salicylic acid (p.1612·2); turpentine oil (p.2406·3); menthol (p.2340·1); lavender oil (p.2331·2); thyme oil (p.2401·2); eucalyptus oil (p.2301·2).
Muscle pain; soft-tissue disorders; upper respiratory-tract disorders.

Termotrin *Loren, Mex.†.*
Paracetamol (p.108·1).
Fever; pain.

Termox *Solvang, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Ternadin *Dunar, Spain.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Ternaf *Rowex, Irl.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Ternel *Medinova (Μεντινοβα), Gr.*
Diltiazem (p.1267·1).
Angina pectoris; hypertension.

Ternelax *Wander, Philipp.*
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasm; spasticity.

Ternex *Tripharma, Turk.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat pain and inflammation; musculoskeletal and joint pain.

Ternolol *Hovid, Hong Kong; Hovid, Malaysia†; Hovid, Singapore†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Ternovag *Novag, Mex.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Terocaps *Medix, Mex.*
Garcinia cambogia (p.2309·2).
Obesity.

Terodul *Degorts, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Terol *Cipla, India.*
Tolterodine tartrate (p.2198·1).
Urinary-tract disorders.

Terolinal *Chrispa (Χρισπα), Gr.*
Lisinopril (p.1325·2).
Hypertension.

Terolut *Solvay, Fin.*
Dydrogesterone (p.2096·2).
Endometriosis; menopausal disorders; menstrual disorders.

Teromol *Aldo, Spain.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease.

Teronac *ICN, Hung.†; Novartis, Indon.; Novartis, Singapore; Novartis, Switz.†.*
⊗ Mazindol (p.2157·3).
Obesity.

Terost *Ativus, Braz.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Terostrant *Chrispa (Χρισπα), Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Teroxina *Bruluagsa, Mex.*
Cefadroxil (p.218·1).
Bacterial infections.

Terozid *Terramedic, Philipp.*
Isoniazid (p.288·1).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Terpect
Note.This name is used for preparations of different composition.
Themis Chemicals, India.
Syrup: ⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Obstructive airways disease.
Themis Chemicals, India.
Tablets: ⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Obstructive airways disease.

Terphylate *Overseas, India.*
⊗ Terbutaline sulfate (p.1138·3); bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Terphylin *Themis Chemicals, India.*
⊗ Terbutaline sulfate (p.1138·3); etofylline (p.1121·1).
Obstructive airways disease.

Terpichol *Herbapol Wroclaw, Pol.*
Borneol (p.2268·3); camphene (p.2273·2); cineole (p.2282·3); menthol (p.2340·1); menthone (p.2340·2); α-pinene (p.2368·3); β-pinene (p.2368·3).
Hepatobiliary disorders.

Terplex *Biomep, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Terpone *Rosa-Phytopharma, Fr.*
Terpin (p.1573·3); Siberian fir oil; niaouli oil (p.2351·3); eucalyptus oil (p.2301·2).
Respiratory-tract disorders.

Terponil *Vitafarma, Spain.*
Oxidised terpenes; terpin (p.1573·3).
Respiratory-tract disorders.

Terposen *Vir, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Terra-Cortril
Note.This name is used for preparations of different composition.
Pfizer, Arg.
⊗ Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Infected skin disorders.
Pfizer, Belg.; Pfizer, Braz.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Indon.; Pfizer, Norw.
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Infected skin disorders.
Pfizer, Indon.
⊗ Oxytetracycline (p.312·2); hydrocortisone (p.1535·2).
Infected eye disorders.
Pfizer, USA; Pfizer, Venez.†.
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2).
Infected eye, ear, and skin disorders.
Pfizer, S.Afr.
Eye/ear drops; eye/ear ointment: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Ear infections; eye infections.
Farmasierra, Spain.
Eye/ear ointment: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Eye or ear disorders.
Pfizer, S.Afr.; Farmasierra, Spain.
Ointment: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.
Pfizer, UK†.
Ointment: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Terracortril
Note.This name is used for preparations of different composition.
Pfizer, Swed.
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2).
Infected skin disorders; otitis externa.
Mann, Ger.†.
Cream; ointment; topical spray: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2); polymyxin B sulfate (p.317·3).
Burns; infected skin disorders; wounds.
Mann, Ger.†.
Eye drops; eye ointment: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Eye disorders.
Pfizer, Switz.†.
Eye/ear drops: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Infected ear and eye disorders.
Pfizer, Switz.†.
Ointment; topical spray: ⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2); polymyxin B sulfate (p.317·3).
Infected skin disorders.

Terra-Cortril Gel Steraject met polymyxine-B *Pfizer, Neth.†.*
⊗ Oxytetracycline calcium (p.312·3); hydrocortisone (p.1535·2); polymyxin B sulfate (p.317·3).
Sinusitis.

Terracortril med polymyxin B *Pfizer, Swed.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Infected ear and eye disorders; otitis externa.

Terra-Cortril met polymyxine-B *Pfizer, Neth.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Blepharitis squamosa; inflammatory ear infections.

Terracortril N *Mann, Ger.*
⊗ Betamethasone sodium phosphate (p.1518·3); gentamicin sulfate (p.282·1).
Infected and inflammatory eye disorders.

Terra-Cortril Nistatina *Pfizer, Arg.†.*
⊗ Oxytetracycline calcium (p.312·3) or oxytetracycline hydrochloride (p.312·3); hydrocortisone (p.1535·2); nystatin (p.543·2).
Infected skin disorders.

Terra-Cortril P *Pfizer, Fin.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Infected ear disorders; infected eye disorders.

Terra-Cortril Polymyxin B *Pfizer, Norw.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Ear disorders.

Terra-Cortril + Polymyxine B *Pfizer, Belg.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2); polymyxin B sulfate (p.317·3).
Infected inflammatory ear or eye disorders.

Terrados *Pfizer, Mex.*
Oxytetracycline (p.312·2).
Acne; rosacea.

Terraferron *Terramedic, Philipp.*
Ferrous sulfate (p.1939·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Folic acid and vitamin B deficiency; iron deficiency; iron-deficiency anaemia.

Terrafor *Terrafor, Fr.*
Octalite.
Digestive disorders.

Terrakal *Offenbach, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Terramicina
Note.This name is used for preparations of different composition.
Pfizer, Arg.; Pfizer, Venez.
Oxytetracycline (p.312·2).
Bacterial infections.
Pfizer, Braz.
Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.
Pfizer, Mex.
Capsules; injection; tablets: Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3).
Lidocaine (p.1862·3) is included in the injection to alleviate the pain of injection.
Bacterial infections.
Farmasierra, Spain.
Capsules; eye ointment; tablets: Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3).
Bacterial infections.
Pfizer, Mex.
Ointment: Oxytetracycline (p.312·2); polymyxin B sulfate (p.317·3).
Bacterial skin infections.
Farmasierra, Spain.
Ointment: Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Skin infections.

Terramicina c/Polimixina *Pfizer, Braz.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye infections; bacterial skin infections.

Terramicina con Polimixina B
Pfizer, Arg.†.
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial skin infections.
Pfizer, Venez.
Oxytetracycline (p.312·2); polymyxin B (p.318·2).
Bacterial eye and skin infections.

Terramycin
Note.This name is used for preparations of different composition.
Mann, Ger.†; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Turk.
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye and skin infections.
Pfizer, India; Pfizer, Indon.
Oxytetracycline hydrochloride (p.312·3).
Lidocaine hydrochloride (p.1862·3) may be included in the injection to alleviate the pain of injection.
Bacterial infections.
Pfizer, Israel.
Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial infections of the eye or skin.
Pfizer, Gr.; Pfizer, Singapore†; Pfizer, USA†.
Capsules: Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.
Pfizer, S.Afr.†; Pfizer, Singapore.
Eye ointment: Oxytetracycline (p.312·2); polymyxin B sulfate (p.317·3).
Bacterial eye infections.
Pfizer, Thai.
Eye ointment; ointment: Oxytetracycline (p.312·2) or oxytetracycline hydrochloride (p.312·3); polymyxin B (p.318·2) or polymyxin B sulfate (p.317·3).
Eye infections; infected skin disorders.
Pfizer, USA†.
Injection: Oxytetracycline (p.312·2).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.
Pfizer, S.Afr.
Ointment: Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Skin infections.
Pfizer, Gr.
Ointment; topical powder: Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Formerly known as Terramycin with Polymyxin.
Skin infections.

Terramycin N *Mann, Ger.*
Gentamicin sulfate (p.282·1).
Bacterial eye infections.

Terramycin Plus *Pfizer, Philipp.*
Polymyxin B sulfate (p.317·3); bacitracin zinc (p.210·3); neomycin sulfate (p.305·1).
Skin infections.

Terramycin Poly
Note.This name is used for preparations of different composition.
Pfizer, Indon.
Eye ointment: Oxytetracycline (p.312·2); polymyxin B (p.318·2).
Eye infections.
Pfizer, Indon.
Ointment: Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Skin infections.

Terramycin Polymyxin B *Pfizer, Denm.; Pfizer, Norw.; Pfizer, Swed.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial skin and eye infections.

Terramycin with Polymyxin B *Pfizer, Hong Kong; Pfizer, USA.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial eye and skin infections.

Terramycin SF *Pfizer, India.*
Oxytetracycline hydrochloride (p.312·3); vitamin B substances (p.1975·1).
Bacterial infections.

Terramycine + Polymyxine B *Pfizer, Belg.*
Oxytetracycline hydrochloride (p.312·3); polymyxin B sulfate (p.317·3).
Bacterial infections.

Terranumonyl *Columbia, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Terrasil *Silom, Thai.†.*
Oxytetracycline (p.312·2); polymyxin B sulfate (p.317·3).
Eye infections.

Terrell *Minrad, USA.*
Isoflurane (p.1785·3).
General anaesthesia.

Terricil *Edol, Port.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial eye infections.

Tersaken *Kener, Mex.†.*
Zinc (p.1999·1).

Tersaseptic
Note.This name is used for preparations of different composition.
Trans Canaderm, Canad.
Triclosan (p.1665·2).
Skin cleanser; skin disorders.
Dermaclin, Mex.†; Doak, USA.
Soap substitute.
Acne.

Tersa-Tar *Trans Canaderm, Canad.*
Coal tar (p.1616·2).
Psoriasis; seborrhoea.

Tersif *Baliarda, Arg.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tersigan *Boehringer Ingelheim, Jpn.*
Oxitropium bromide (p.1129·2).

Tersigat *3M, Fr.†; Boehringer Ingelheim, Venez.†.*
Oxitropium bromide (p.1129·2).
Asthma; obstructive airways disease.

Tersoderm Anticaspa *Defuen, Arg.†.*
Biotin (p.1931·3); undecenoic acid diethanolamide (p.549·3); piroctone olamine (p.1610·1); jojoba oil.
Scalp disorders.

Tersoderm Cabellos Grasos *Defuen, Arg.†.*
Biotin; sulfur (p.1614·1); undecenoic acid amide; triclosan (p.1665·2); coconut oil (p.2029·2).
Scalp disorders.

Tersoderm Plus *Defuen, Arg.†.*
Ketoconazole (p.539·1).
Dandruff; seborrhoeic dermatitis.

Tertensif *Servier, Cz.; Servier, Pol.; Danval, Spain.*
⊗ Indapamide (p.1314·1).
Hypertension; oedema.

Tertroxin *Sigma, Austral.; GSK, Cz.†; GSK, NZ; Aspen, S.Afr.; GSK, Thai.†; Goldshield, UK†; GSK, Venez.†.*
Liothyronine sodium (p.2174·1).
Now known as Liothyronine Sodium Tablets in the UK.
Hyperthyroidism; hypothyroidism; myxoedema.

Tervalon
Note.This name is used for preparations of different composition.
Lazar, Arg.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.
Zentiva, Hung.
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Terveson *Doctum, Gr.*
Lovastatin (p.1328·2).
Hypercholesterolaemia.

Terysol *SM, Venez.*
⊗ Furosemide (p.1292·1).
Hypercalcaemia; hypertension; oedema; oliguria.

Terzine *Seven Stars, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders.

Terzolin *McNeil, Ger.; Janssen-Cilag, Switz.*
Ketoconazole (p.539·1).
Pityriasis versicolor; scalp disorders; seborrhoeic dermatitis.

Tesacof *Novartis, Mex.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Tesalin *Zeller, Switz.*
Butterbur (p.2271·1).
Hayfever.

Tesalitos *Novartis, Mex.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold symptoms; coughs.

Tesalon *Novartis, Mex.*
Benzonatate (p.1552·1).
Coughs.

Tesavel *MSD, Cz.; MSD, Port.*
Sitagliptin (p.460·2).
Diabetes mellitus.

Tesical *Sintesina, Arg.*
Mebendazole (p.148·3).
Worm infections.

Tesin *Hexal, Pol.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Teslac *BMS, Chile†; BMS Oncology, USA†.*
⊗ Testolactone (p.778·2).
Breast cancer.

Teslascan *Nycomed, Austria; Amersham, Belg.; GE, Cz.; Amersham, Denm.†; Amersham, Fin.†; Amersham, Fr.; Amersham, Ger.; Amersham, Gr.; Amersham Health, Hung.; Amersham, Ital.; GE Healthcare, NZ; GE Healthcare, Neth.; Amersham, Norw.; GE, Port.; Amersham, Spain; Amersham, Swed.; Amersham, Switz.; Nycomed Amersham, UK; Nycomed, USA.*
Mangafodipir trisodium (p.1487·2).
Contrast medium for magnetic resonance imaging.

Tesofan-J *Ivax, Mex.*
Diphenhydramine (p.577·1); dextromethorphan (p.1555·2).
Cold symptoms; coughs.

Tesol *Vianex (Βιανέξ), Gr.†.*
⊗ Dorzolamide (p.1880·3); timolol (p.1413·1).
Glaucoma.

Tesopalmed Forte cum Yohimbine *Trima, Israel.*
⊗ Yohimbine hydrochloride (p.2200·2); strychnine nitrate (p.2393·2).
Erectile dysfunction.

Tesopen *Collins, Mex.*
Benzonatate (p.1552·1).
Coughs.

Tesoprel *UCB, Ger.*
Bromperidol (p.965·1) or bromperidol lactate (p.965·2).
Schizophrenia.

Tesoren *Galeno, Venez.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Tess
Note.This name is used for preparations of different composition.
Biolab Sanus, Braz.
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Troikaa, India.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions and inflammation.

Tessalon *Forest Pharmaceuticals, USA.*
Benzonatate (p.1552·1).
Coughs.

Tessamag con Codeina *Vargas, Venez.*
Ipecacuanha (p.1562·3); codeine phosphate (p.37·2).
Cough.

Tessifol *Zimaia, Port.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Test Pack Plus *Abbott, Chile†; Abbott, UK.*
Pregnancy test (p.2372·1).

Testanon 25 *Organon, India.*
⊗ Testosterone propionate (p.2130·1).
Androgen deficiency; osteoporosis.

Testanon 50 *Organon, India.*
⊗ Testosterone phenylpropionate (p.2130·1).
Androgen deficiency; osteoporosis.

Tes-Tape *Lilly, Austral.†.*
Test for glucose in urine (p.2314·1).

testasa e *Chefaro, Ger.†.*
Yohimbe extract.
Male sexual exhaustion.

Testerell *Sanorell, Ger.*
Homoeopathic preparation.

Testex *Q Pharma, Spain.*
⊗ Testosterone cipionate (p.2129·3) or testosterone propionate (p.2130·1).
Aplastic anaemia; endometriosis; female breast cancer; lactation inhibition; male hypogonadism and androgen deficiency; menopausal disorders; osteoporosis.

Testim *Ipsen, Belg.; Ipsen, Fin.; Ipsen, Ger.; Ipsen, Gr.; Ipsen, Irl.; Ipsen, Ital.; Ipsen, Neth.; Ipsen, Port.; Ipsen, Spain; Ipsen, Swed.; Ipsen, UK; Auxilium, USA.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Testisan *Mintlab, Chile.*
Phthalylsulfathiazole (p.315·1); nifuroxazide (p.307·2).

Testocaps *Organon, Belg.; Organon, Chile.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; osteoporosis.

Testoderm *Ferring, Austria; Ferring, Switz.†; Alza, USA†.*
⊗ Testosterone (p.2129·3).
Hypogonadism.

Testo-Enant *Geymonat, Ital.*
⊗ Testosterone enantate (p.2130·1).
Androgenic; breast cancer; fibroids.

Testofran *Faria, Braz.†.*
Yohimbine (p.2200·3); vitamin B ; vitamin E; calcium inositohexaphosphate; magnesium inositohexaphosphate; magnesium stearate.
Erectile dysfunction.

Testogel *Schering, Austral.; Besins, Denm.; Schering, Fin.; Jenapharm, Ger.; Schering, Irl.; Schering, Ital.; Besins, Neth.; Besins, Norw.; Besins, Port.; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, UK.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Testonus *Profarb, Braz.†.*
⊗ Methyltestosterone (p.2117·1); vitamin B ; vitamin E.
Breast cancer in females; cryptorchidism; delayed puberty in males; erectile dysfunction; hypogonadism in males.

Testopatch *Pierre Fabre, Cz.; Pierre Fabre, Fr.; Pierre Fabre, Port.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Testopel *Bartor Pharmacal, USA.*
⊗ Testosterone (p.2129·3).
Androgen deficiency; delayed puberty.

Testoprim-D *Tocogino, Mex.*
⊗ Testosterone (p.2129·3).
Androgenic.

Testosterone Implants *Organon, UK.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Testosteronum Prolongatum *Jelfa, Pol.*
⊗ Testosterone enantate (p.2130·1).
Breast cancer; endometrial cancer; male hypogonadism.

Testotard *Chephasaar, Ger.†.*
Flutamide (p.725·1).
Prostatic cancer.

Testoviron
Schering, Gr.
⊗ Testosterone enantate (p.2130·1).
Androgen deficiency; aplastic anaemia; breast cancer; male hypogonadism.

Schering, Ital.
⊗ Testosterone enantate (p.2130·1); testosterone propionate (p.2130·1).
Androgenic; breast cancer.

Testoviron 100 *Schering, Thai.†.*
⊗ Testosterone propionate (p.2130·1); testosterone enantate (p.2130·1).
Erectile dysfunction; male hypogonadism; male menopause.

Testoviron 250 *Schering, Austria.*
⊗ Testosterone enantate (p.2130·1).
Aplastic anaemia in men; erectile dysfunction; female breast cancer; male hypogonadism.

Testoviron Depot
Schering, Hong Kong; Schering, Israel; Schering, Neth.†; Bayer, Port.; Schering, Swed.; Schering, Switz.; Schering, Thai.
⊗ Testosterone enantate (p.2130·1).
Formerly known as Testoviron 250 in *Thai*.
Androgen deficiency in males; aplastic anaemia; breast cancer; endometrial cancer; erectile dysfunction; male hypogonadism; male impotence; male infertility.

German Remedies, India.
⊗ Testosterone propionate (p.2130·1); testosterone enantate (p.2130·1).
Androgen deficiency; aplastic anaemia; breast cancer; male hypogonadism.

Testoviron Depot 50 *Schering, Ger.†.*
⊗ Testosterone enantate (p.2130·1); testosterone propionate (p.2130·1).
Hypogonadism in men.

Testoviron Depot 100 *Schering, Arg.; Schering, Ger.†; Schering, Spain.*
⊗ Testosterone enantate (p.2130·1); testosterone propionate (p.2130·1).
Aplastic anaemia; breast cancer; endometrial cancer; hepatic cirrhosis; lactation inhibition; male hypogonadism; male infertility; osteoporosis.

Testoviron Depot 135 *Schering, Denm.*
⊗ Testosterone enantate (p.2130·1); testosterone propionate (p.2130·1).
Breast cancer; male hypogonadism.

Testoviron Depot 250 *Schering, Arg.; Schering, Denm.; Jenapharm, Ger.; Schering, Ger.; Schering, Spain.*
⊗ Testosterone enantate (p.2130·1).
Aplastic anaemia; breast cancer; endometrial cancer; hepatic cirrhosis; lactation inhibition; male hypogonadism; male infertility; osteoporosis.

Testovis *SIT, Ital.*
⊗ Testosterone propionate (p.2130·1).
Androgenic; breast disorders; fibroids; menstrual disorders.

Testpack hCG-Urine *Abbott, Irl.*
Pregnancy test (p.2372·1).

TestPack Plus hCG-Urine *Abbott, USA.*
Pregnancy test (p.2372·1).

Testred *Valeant, USA.*
⊗ Methyltestosterone (p.2117·1).
Androgen replacement therapy; breast cancer.

Teta Extra *Fresenius Kabi, Ger.*
Didecyldimethylammonium chloride (p.1642·2); polihexanide (p.1658·2).
Surface disinfection.

Tetabulin *Baxter Immuno, Arg.; Baxter, Austria; Immuno, Austria; Baxter, Cz.; Immuno, Hong Kong†; Baxter, Irl.; Baxter, Ital.; Baxter, Pol.; Baxter BioScience, UK†.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetabuline *Baxter, Belg.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetacid *Interpharm, Austria.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn.

Tetagam *ZLB, Austria; CSL, Port.; NBI, S.Afr.; ZLB, Switz.; Sanofi Pasteur, Thai.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagam N *ZLB, Ger.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagam P *Dexa, Indon.; ZLB, Indon.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagamma *Hardis, Ital.†.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagamma P *ZLB, Spain.*
An tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagam-P *ZLB, Gr.; Zydus, India; ZLB Behring, Philipp.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetaglobuline *Aventis Pasteur, Cz.†; Pasteur Merieux, Israel.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetagrip *Sanofi Pasteur, Fr.*
A tetanus and influenza vaccine (p.2241·1).
Active immunisation.

Tetalin *Pharmasant, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tetamun SSW *SmithKline Beecham, Ger.†.*
A tetanus vaccine (p.2240·1).
Active immunisation.

Tetamyn *Bioclon, Mex.*
A tetanus vaccine (p.2240·1).
Active immunisation.

Tetanea *Aventis Pasteur, Philipp.; Aventis Pasteur, Turk.*
A tetanus immunoglobulin (equine) (p.2239·3).
Passive immunisation.

Tetanobulin *Immuno, Braz.†; Baxter BioScience, Ger.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetanogamma *CSL, Braz.; ZLB Behring, Mex.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetanol *Elea, Arg.; Grunenthal, Austria; Chiron Vaccines, Ger.; Novartis Vaccines, Hung.; Aventis, Mex.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Tetanos Quick Stick *Ingen, Fr.†.*
Test for tetanus antibodies.

Tetanus-Gamma *Kedrion, Ital.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

TetaQuin *Sanquin, Neth.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Teta-S *Fresenius Kabi, Ger.*
Didecylmethylalkoxiammonium propionate; cocospropylenediamineguanidinium diacetate; polihexanide (p.1658·2).
Surface disinfection.

Tetatox *Berna, Ital.†.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Tetavax *Sanofi Pasteur, Arg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Chile; Aventis Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Malaysia†; Aventis Pasteur, Neth.†; Sanofi Pasteur, Norw.; Aventis Pasteur, Philipp.; Aventis, S.Afr.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Tetaven *Baxter, Ital.†.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetesept
Note.This name is used for preparations of different composition.
Merz, Pol.
Ascorbic acid (p.1983·3); cetylpyridinium chloride (p.1635·1); dequalinium chloride (p.1641·3).
Mouth and throat disorders.

Kolassa, Austria.
⊗ Dequalinium chloride (p.1641·3); cetylpyridinium chloride (p.1635·1); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Bacterial infections of the mouth and throat.

Tetesept Angidin *Merz, Cz.†.*
Dequalinium chloride (p.1641·3); cetylpyridinium chloride (p.1635·1); ascorbic acid (p.1983·3).
Mouth and throat disorders.

Tetesept Badekonzentrat Erkaltungs Bad N *Tetesept, Ger.†.*
Eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); thyme oil (p.2401·2); pine needle oil (p.2368·2); camphor (p.2273·2).
Bath additive; cold symptoms; neuralgia; peripheral vascular disorders; rheumatism.

Tetesept Badekonzentrat Rheuma Bad *Tetesept, Ger.†.*
Glycol salicylate (p.62·3); methyl nicotinate (p.85·3); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); camphor (p.2273·2).
Bath additive; circulatory disorders; musculoskeletal and joint disorders.

Tetesept Bademedizin Erkaltungs Intensiv Bad N *Tetesept, Ger.†.*
Eucalyptus oil (p.2301·2); Norway spruce oil; thyme oil (p.2401·2).
Bath additive; cold symptoms.

Tetesept Erkaltungs *Tetesept, Ger.*
Thyme (p.2401·1).
Respiratory-tract disorders.

Tetesept Erkaltungs Balsam N mentholfrei *Tetesept, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2); camphor (p.2273·2).
Respiratory-tract disorders.

Tetesept Hals-activ *Tetesept, Ger.*
Usnea barbata (p.2409·3).
Mouth and throat disorders.

Tetesept Husten Saft *Tetesept, Ger.*
Ribwort plantain (p.2379·1).
Respiratory-tract congestion.

Tetesept Husten Tropfen *Tetesept, Ger.*
Ribwort plantain (p.2379·1).
Cold symptoms; mouth and throat inflammation.

Tethexal *Hexal, Ger.†.*
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasticity.

Tetig *Teva, Hung.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Tetinox *Silanes, Mex.*
A tetanus vaccine (p.2240·1).
Active immunisation.

Tetmosol *AstraZeneca, Braz.; Nicholas Piramal, India; AstraZeneca, Mex.†; AstraZeneca, S.Afr.; AstraZeneca, Singapore†.*
Sulfiram (p.2050·3).
Scabies.

Tetra
Sanbe, Indon.; Nevzat, Turk.
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Atlantis, Mex.
Tetracycline (p.347·1).
Bacterial infections.

Tetra Central *Pharmasant, Thai.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetra Hubber *Valeant, Spain†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetrabact *Cipla, India.*
Tetracycline (p.347·1).
Bacterial infections.

Tetraben *Cazi, Braz.*
Tetracycline (p.347·1).
Bacterial skin infections.

Tetrac *Zwitter, Gr.*
Tetracycline hydrochloride (p.347·2).
Acne.

Tetracem *Crown, S.Afr.†.*
Oxytetracycline (p.312·2).
Bacterial infections.

Tetrachel *Berk, Cz.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetracilil *Greenpharma, Braz.*
Tetracycline (p.347·1).
Bacterial infections.

Tetracina *Bunker, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetraclin *Teuto, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetracoq *Aventis Pasteur, Belg.†; Aventis Pasteur, Braz.†; Vianex (Βιανέξ), Gr.; Pasteur Merieux, Israel; Aventis Pasteur, Malaysia†; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.†; Aventis Pasteur, Thai.†; Aventis Pasteur, Turk.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Tetract-HIB *Aventis Pasteur, Braz.†; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Indon.; Pasteur Merieux, Israel; Sanofi Pasteur, Malaysia†; Aventis Pasteur, Philipp.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain†; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.*
A diphtheria, tetanus, pertussis, and haemophilus influenzae conjugate vaccine (p.2211·1).
Active immunisation.

Tetraderm *Teuto, Braz.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); tolnaftate (p.548·3); clioquinol (p.254·1).
Infected skin disorders.

Tetradin *Caldeira & Metelo, Port.*
Disulfiram (p.2296·2).
Chronic alcoholism; nickel dermatitis.

Tetradox
Note.This name is used for preparations of different composition.
Richmond, Arg.
Paracetamol (p.108·1).
Fever; pain.

Ranbaxy, Singapore; Ranbaxy, Thai.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Fako, Turk.
Doxycycline (p.267·1).
Bacterial infections; malaria; oral herpes simplex infections.

Tetragel *Multilab, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetra-Gelomyrtol *Sanova, Austria; Pohl, Ger.*
Oxytetracycline hydrochloride (p.312·3); myrtol (p.2349·3).
Bronchitis; sinusitis.

Tetragynon *Schering, Denm.†; Schering, Fr.†; Schering, Ger.†; Schering, Norw.†; Bayer, Port.; Schering, Switz.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Postcoital oral contraceptive.

Tetrahelmin *Luper, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Tetrakain *Novartis Ophthalmics, Swed.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Tetralet *Fako, Turk.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetralgin *Craveri, Arg.*
Ergotamine (p.621·3); caffeine (p.1116·3); chlorphenamine (p.572·2); dipyrone (p.49·2); metoclopramide (p.1747·3).
Migraine.

Tetralgin APC *Craveri, Arg.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tetralgin Novo *Craveri, Arg.*
Ergotamine (p.621·3); caffeine (p.1116·3); chlorphenamine (p.572·2); dipyrone (p.49·2); domperidone (p.1726·2).
Migraine.

Tetralim *Vana, Thai.†.*
Tetracycline phosphate complex (p.347·2).
Bacterial infections.

Tetralisal *Galderma, Mex.*
Lymecycline (p.296·1).
Acne.

Tetralution *Merckle, Ger.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetralysal
Galderma, Arg.; AB-Consult, Austria; Galderma, Belg.; Galderma, Braz.; Galderma, Denm.; Galderma, Fin.; Galderma, Fr.; Galderma, Hong Kong; Galderma, Hung.; Galderma, Irl.; Galderma, Ital.; Healthcare Logistics, NZ; Galderma, Norw.; Galderma, Philipp.; Galderma, S.Afr.; Galderma, Swed.; Galderma, Switz.; Galderma, UK; Galderma, Venez.
Lymecycline (p.296·1).
Acne; bacterial infections.

Galderma, Pol.
Lymecycline hydrochloride.
Acne; rosacea.

Tetram *Biotech, Venez.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Tetra-Mag *Cypress, USA.*
Magnesium salicylate (p.79·2); phenyltoloxamine citrate (p.588·1).

Tetramax *Luper, Braz.†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetramdura *Merck dura, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle spasm.

Tetramel *Aspen, S.Afr.†.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Tetramicin *EMS, Braz.†.*
Tetracycline hydrochloride (p.347·2) or tetracycline phosphate complex (p.347·2).
Bacterial infections.

Tetramil *Farmigea, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1); pheniramine maleate (p.587·3).
Conjunctivitis; eye irritation and congestion.

Tetramin *Adeka, Turk.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetramizotil *Osorio de Moraes, Braz.†.*
Tetramisole (p.156·2).
Nematode infections.

Tetran *Wagner, Hung.*
Oxytetracycline hydrochloride (p.312·3).
Bacterial infections.

Tetrana *Atlantic, Thai.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetran-Hydrocortison *Wagner, Hung.*
⊗ Oxytetracycline hydrochloride (p.312·3); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Tetrano *Milano, Thai.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetrapar *Parggon, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrapres *Precimex, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrapulmo
Note. This name is used for preparations of different composition.
Medley, Braz.
Capsules; syrup: Sodium camsilate (p.2388·3); chlorphenamine maleate (p.571·3); dipyrone (p.49·2); guaifenesin (p.1561·3); terpin hydrate (p.1573·3).
Cold and influenza symptoms.

Medley, Braz.
Injection: Dipyrone (p.49·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3); cineole (p.2282·3); niaouli oil (p.2351·3); sodium camsilate (p.2388·3). Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Cold and influenza symptoms.

Tetraratio *Ratiopharm, Pol.*
Tetrazepam (p.1031·1).
Painful skeletal muscle spasm.

Tetrarco *Armoxindo, Indon.*
Tetracycline hydrochloride (p.347·2).
Skin infections.

Tetra-saar *MIP, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasticity.

Tetrasine *Optopics, USA†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Minor eye irritation.

Tetrasine Extra *Optopics, USA†.*
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·1).
Minor eye irritation.

Tetraspan *Braun, Cz.; Braun, Hung.; Braun, Port.*
⊗ An etherified starch (p.1065·1) in electrolytes.
Plasma volume expansion; shock.

Tetraspir *Globo, Braz.†.*
Tetracycline (p.347·1).
Bacterial infections.

Tetravac *Aventis Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Fin.; Sanofi Pasteur, Fr.; Aventis Pasteur, Ger.†; Vianex (Βιανέξ), Gr.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; Sanofi Pasteur, Port.; Sanofi Pasteur, Swed.; Sanofi Pasteur, Switz.*
A diphtheria, tetanus, acelllular pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Tetraxil *Delta, Braz.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tetraxim *Sanofi Pasteur, Hung.; Sanofi Pasteur, Malaysia; Aventis Pasteur, Philipp.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Tetraxin *Sanofi Pasteur, Thai.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Tetrazep *CT, Ger.*
Tetrazepam (p.1031·1).
Skeletal muscle tension and spasticity.

Tetra-Zil *Arlex, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrazol *Grin, Mex.*
⊗ Tetryzoline (p.1574·1).
Dry eyes.

Tetrerba *Pfizer, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrex
BMS, Austral.; BMS, S.Afr.
Tetracycline hydrochloride (p.347·2).
Adjunct in intestinal amoebiasis; bacterial infections.

BMS, Braz.; Bristol, USA.
Tetracycline phosphate complex (p.347·2).
Bacterial infections.

Hormona, Mex.
Tetracycline (p.347·1).
Bacterial infections.

Tetrex-F *BMS, S.Afr.*
Tetracycline hydrochloride (p.347·2); nystatin (p.543·2).
Bacterial infections; candidiasis.

Tetrib *Ibfarma, Braz.†.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrilin *MIP, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Tetrim *IQFA, Mex.*
Tetracycline (p.347·1).
Bacterial infections.

Tetrin *Interbat, Indon.*
Tetracycline phosphate (p.347·2).
Bacterial infections.

Tetrisal *MIP, Ger.*
Sodium chloride (p.1686·1).
Dry nose; nasal congestion.

Tetroid *Ache, Braz.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Tetryvil *Hasco-Lek, Pol.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion; rhinitis; sinusitis.

Tet-Tox *CSL, Austral.; CSL, NZ.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Tetuman *Berna, Hong Kong†; Berna, Malaysia†; Berna, Port.†; Berna, Spain†; Berna, Switz.; Berna, Thai.†; Berna, Turk.*
A tetanus immunoglobulin (p.2239·3).
Passive immunisation.

Teufelskralle *CT, Ger.; Merck dura, Ger.; Ratiopharm, Ger.; Stada, Ger.*
Devil's claw root (p.39·1).
Joint disorders.

Teutocilin *Teuto, Braz.†.*
Oxacillin sodium (p.311·3).
Bacterial infections.

Teutoformin *Teuto, Braz.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Teutomicin *Teuto, Braz.*
Neomycin sulfate (p.305·1); bacitracin zinc (p.210·3).

Teutoss *Teuto, Braz.†.*
⊗ Potassium iodide (p.2169·2); ephedrine hydrochloride (p.1558·2); belladonna (p.2263·3); stramonium (p.2392·3).
Respiratory-tract congestion.

Teutovit-E *Teuto, Braz.*
Tocoferil acetate (p.1992·3).

Teutrin *Teuto, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Tevacutan *Teva, Israel.*
⊗ Clotrimazole (p.530·1); dexamethasone (p.1526·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Tevacycline *Teva, Israel.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tevaderm *Teva, Israel.*
⊗ Isoconazole nitrate (p.536·2); diflucortolone valerate (p.1529·2).
Infected skin disorders.

Tevanate *Gry, Ger.; Gerolymatos, Gr.; Teva, Rus.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Tevapirin *Teva, Israel.*
Aspirin (p.20·3).
Thrombosis prophylaxis.

Tevax *GSK, Belg.†.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

Teveten *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Solvay, Canad.; Solvay, Cz.; Solvay, Denm.; Solvay, Fin.; Solvay, Fr.; Procter & Gamble, Ger.; Solvay, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Hung.; Solvay, Irl.; Solvay, Neth.; Solvay, Norw.; Solvay, Philipp.; Solvay, Pol.; Solvay, Port.; Solvay, Rus.; Solvay, S.Afr.; Solvay, Swed.; Solvay, Switz.; Solvay, Thai.; Solvay, UK; KOS, USA.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Teveten Comp *Solvay, Denm.; Solvay, Fin.; Solvay, Norw.; Solvay, Swed.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Teveten HCT *Abbott, USA.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Teveten Plus *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Solvay, Canad.; Procter & Gamble, Ger.; Solvay, Ger.; Solvay, Gr.; Solvay, Hong Kong; Solvay, Irl.; Solvay, Neth.; Solvay, Philipp.; Solvay, Port.; Solvay, Rus.; Solvay, Switz.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Teveten Plus H *Solvay, Cz.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tevetens *Solvay, Spain.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Tevetens Plus *Solvay, Spain.*
⊗ Eprosartan mesilate (p.1281·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tevetenz *Solvay, Ital.*
Eprosartan mesilate (p.1281·1).
Hypertension.

Tevoril *Proel, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Tevox *Actavis, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Tev-Tropin *Gate, USA.*
⊗ Somatropin (p.1799·3).
Growth hormone deficiency.

Texa *Pharma Dynamics, S.Afr.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions; pruritus.

Texacort *JSJ, USA.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Texate *Columbia, Mex.*
Methotrexate (p.745·2).
Malignant neoplasms.

Texicam *Deutsche, Chile†.*
Tenoxicam (p.128·2).
Inflammation; musculoskeletal and joint disorders.

Texis *Atlantis, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Texodil *Grunenthal, Fr.*
Cefotiam hexetil hydrochloride (p.230·1).
Bacterial infections of the respiratory-tract.

Texot *Filaxis, Arg.*
Docetaxel (p.710·3).
Malignant neoplasms.

Texoven *Tecnofarma, Mex.*
Benzonatate (p.1552·1).
Coughs.

Texx *Krewel, Ger.*
St John's wort (p.422·3).
Anxiety; depression.

Teylor *Dom, Spain.*
Simvastatin (p.1390·2).
Hyperlipidaemias; secondary prophylaxis of ischaemic heart disease.

TFT *SofLens, S.Afr.*
Trifluridine (p.910·3).
Herpes simplex keratitis.

TFT Ophtiole *Tramedico, Neth.*
Trifluridine (p.910·3).
Viral eye infections.

TFT-Thilo *Liba, Turk.*
Trifluridine (p.910·3).
Herpes simplex eye infections.

T/Gel
Note. This name is used for preparations of different composition.
Neutrogena, Fr.
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1).
Scalp and hair disorders.

Neutrogena, Israel; Johnson & Johnson, UK.
Coal tar (p.1616·2).
Scalp disorders.

T-Gen *Goldline, USA†.*
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

T-Gesic *Williams, USA.*
Paracetamol (p.108·1); hydrocodone tartrate (p.63·1).
Pain.

THA *Woods, Austral.*
Tacrine hydrochloride (p.370·2).
Postoperative respiratory stimulant; reversal of competitive neuromuscular blockade.

Thacapzol *Recip, Swed.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Thaden *Pharmacare, S.Afr.*
Dosulepin hydrochloride (p.388·2).
Depression; mixed anxiety depressive states.

Thais *Besins, Fr.*
Estradiol (p.2097·2).
Menopausal disorders.

Thalamag *IPRAD, Fr.*
Magnesium oxide (p.1744·1); sea water.
Magnesium supplement.

Thalamag fer B$_9$ *IPRAD, Fr.*
Magnesium oxide; sea water; ferrous sulfate; folic acid (p.1922·1).
Tonic.

Thalgo Tonic *Thalgo, Fr.*
Spirulina (p.2392·1); magnesium (p.1678·3); ginseng (p.2312·1); vitamins (p.1922·1).
Tonic.

Thalitone *Monarch, USA.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Thalix *Dabur, India.*
Thalidomide (p.2397·1).
Erythema nodosum leprosum; multiple myeloma.

Thalizide *Ipca, India.*
⊗ Chlortalidone (p.1243·3).
Hypertension.

Thalomid *Celgene, USA.*
Thalidomide (p.2397·1).
Erythema nodosum leprosum; multiple myeloma.

Tham *Abbott, Austral.; Kohler, Ger.*
⊗ Trometamol (p.2405·1).
Metabolic acidosis.

Thamesol *Diaco, Ital.*
⊗ Trometamol (p.2405·1).
Metabolic acidosis.

Thankgod *Panacea, India.*
Euphorbia (p.2301·3).
Haemorrhoids.

Thateron *Faran, Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

t/h-basan *Sandoz, Switz.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

The a l'avoine sauvage de Vollmer *Dunner, Switz.*
Avena (p.2262·1); urtica (p.2409·3); St John's wort (p.422·3); alchemilla alpinae.
Nervous disorders.

The Chambard-Tee *Brady, Austria.*
Senna leaf (p.1769·2); althaea leaf (p.2253·3); peppermint leaf (p.1761·2); melissa leaf (p.2339·3); hyssopus officinalis (p.2323·3); anthyllidis flower; calendula (p.2273·1); cyanae flower.
Constipation.

The Ginseng King *Medicalfarm, Ital.*
Fish milk; fish brain extract; cod-liver extract; myrtillus; acacia honey; fructose; ginseng (p.1922·1).
Nutritional supplement.

The Guard Seichojo *Kowa, Jpn.*
Bacillus natto; lactic-acid-producing organisms (p.2372·3); dimeticone (p.1770·2); swertia; cinnamon bark (p.2283·1); fennel (p.2302·3); methiosulfonium chloride (p.2343·3); magnesium carbonate (p.1743·1); calcium carbonate (p.1714·1).
Carminative; flatulence.

The Salvat *Leros, Cz.*
Boldo (p.2267·2); marrubium (p.1564·1); agrimony (p.2249·2); taraxacum (p.2395·1); frangula bark (p.1732·2); chamomile (p.2279·3); peppermint leaf (p.1761·2).
Liver and biliary-tract disorders.

Theanorf *Thea, Ital.*
Norfloxacin (p.309·2).
Bacterial eye infections.

Thecort *Guardian, Indon.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Theinol *Bailly, Fr.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Thelban *Biolab, Malaysia†.*
Albendazole (p.139·2).
Worm infections.

Thelin *CSL Biotherapies, Austral.; Encysive, Cz.; Encysive, Fr.; Encysive, Port.; Encysive, UK.*
Sitaxentan sodium (p.1396·3).
Pulmonary hypertension.

Thelmox *Remedica, Malaysia.*
Mebendazole (p.148·3).
Worm infections.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Themibutol *Themis Chemicals, India.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Thenil *Interbat, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Theo *CT, Ger.*
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Theo-2 *SMB, Belg.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theo-24 *Pharmacia, Ital.; UCB, USA.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theo Max *Desarrollo, Spain†.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Theo PA *GSK, India.*
Theophylline (p.1140·1).
Bronchospasm.

Theo-Asthalin *Cipla, India.*
⊗ Salbutamol sulfate (p.1131·3); theophylline (p.1140·1).
Obstructive airways disease.

Theobid *Cipla, India.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theobric *Remidex, India.*
⊗ Terbutaline sulfate (p.1138·3); theophylline (p.1140·1).
Asthma; bronchitis.

Theobron *Interbat, Indon.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theo-Bros *Bros, Gr.*
Theophylline (p.1140·1).
Asthma; neonatal apnoea and bradycardia; obstructive airways disease.

Theochodil *GMP, Indon.*
⊗ Ephedrine hydrochloride (p.1558·2); theophylline (p.1140·1).
Asthma; bronchitis.

Theochron *Forest Pharmaceuticals, USA.*
Theophylline (p.1140·1).
Asthma; reversible bronchospasm in chronic bronchitis and emphysema.

Theoclear *Central Pharmaceuticals, USA†.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

Theoday *Cipla, India.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theodrine *Rugby, USA.*
⊗ Theophylline (p.1140·1); ephedrine hydrochloride (p.1558·2); phenobarbital (p.492·2).
Bronchospasm.

Theo-Dur *AstraZeneca, Arg.†; AstraZeneca, Canad.†; AstraZeneca, Cz.†; AstraZeneca, Denm.; AstraZeneca, Fin.†; Lavipharm, Gr.; AstraZeneca, Hong Kong†; Recordati, Ital.; AstraZeneca, Norw.; AstraZeneca, Philipp.; Pharmacia, Spain; AstraZeneca, Swed.; Schering-Plough, Turk.*
Theophylline (p.1140·1).
Asthma; heart failure; neonatal apnoea and bradycardia; obstructive airways disease; paroxysmal dyspnoea.

Theodur *Mitsubishi, Jpn.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theofol *Leiras, Fin.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theofol Comp *Leiras, Fin.*
Theophylline (p.1140·1); guaifenesin (p.1561·3).
Obstructive airways disease.

Theolair *3M, Belg.; 3M, Canad.; 3M, Ger.†; 3M, Ital.; 3M, Neth.; 3M, Spain; 3M, Switz.; 3M, USA.*
Theophylline (p.1140·1).
Asthma; bronchitis; emphysema; heart failure; obstructive airways disease; paroxysmal dyspnoea.

Theolin *Upha, Malaysia†; Beacons, Singapore.*
Theophylline (p.1140·1).
Asthma; obstructive airways disease.

Theolong *Eisai, Jpn.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theomax DF *Barre-National, USA; Schein, USA.*
⊗ Theophylline (p.1140·1); ephedrine sulfate (p.1558·2); hydroxyzine hydrochloride (p.581·2).
Bronchospasm.

Theoped *Cipla, India.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theophar *Julphar, UAE.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theophen *Pharmacare, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1).
Obstructive airways disease.

Theophen Comp *Pharmacare, S.Afr.*
Theophylline (p.1140·1); etofylline (p.1121·1); diphenylpyraline hydrochloride (p.578·2); ammonium chloride (p.1551·3).
Coughs.

Theophtard *Teva, Hung.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theophyllard *Byk, Cz.†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theophylline Expectorant *Pharmaniaga, Malaysia.*
Guaifenesin (p.1561·3); theophylline (p.1140·1).
Obstructive airways disease.

Theopirina *Dovalle, Braz.†.*
Orphenadrine (p.812·2); dipyrone (p.49·2); caffeine (p.1116·3).
Skeletal muscle spasm.

Theoplus
Germania, Austria; Pharmafabre (Φαρμαφαμπρ), Gr.; Pierre Fabre, Singapore†.
Theophylline hydrate (p.1140·2).
Asthma; neonatal apnoea and bradycardia; obstructive airways disease.

Pierre Fabre, Cz.; Pierre Fabre, Pol.; Altana Madaus, S.Afr.; Pierre Fabre, Spain.
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Theospirex
Gebro, Austria; Novartis, Hung.
Theophylline (p.1140·1) or theophylline sodium glycinate (p.1146·3).
Obstructive airways disease.

Biofarm, Pol.
Theophylline (p.1140·1).
Obstructive airways disease.

Theostat *Pierre Fabre, Fr.*
Theophylline hydrate (p.1140·2).
Asthma; obstructive airways disease.

Theotard *CTI, Israel.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theotex *Terapeutico, Ital.*
Metalkonium chloride (p.1652·3).
Personal hygiene; skin disinfection.

Theotrim *Trima, Hong Kong; Trima, Israel; Trima, Thai.*
Theophylline (p.1140·1).
Obstructive airways disease.

Theovent *GSK, Pol.; Schering, USA†.*
Theophylline (p.1140·1).
Asthma; obstructive airways disease; reversible bronchospasm.

Theovix *Bros, Gr.*
Erdosteine (p.1560·1).
Mucolytic.

Theo-X *Carnrick, USA†.*
Theophylline (p.1140·1).
Obstructive airways disease.

Thephidron *Combiphar, Indon.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders.

Theprubicine *Sanofi-Aventis, Fr.*
Pirarubicin (p.764·1).
Breast cancer.

Ther *Laboratorios Chile, Chile.*
Tegaserod maleate (p.1776·1).
Irritable bowel syndrome.

Thera Hematinic *Major, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Thera Tears *Novartis, Mex.†.*
Carmellose (p.2142·1).
Dry eyes; eye irritation.

Therabex *Combiphar, Indon.*
Vitamin B substances; ascorbic acid (p.1922·1).
Vitamin B and C supplement.

Therabid *Mission Pharmacal, USA†.*
Multivitamin preparation (p.1922·1).

Therabloc *Therapharma, Philipp.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Therac *C & M, USA†.*
Sulfur (p.1614·1); salicylic acid (p.1612·2).
Acne.

Theracap *GE, Cz.; GE Healthcare, Neth.; GE, Port.; Nycomed Amersham, UK.*
Iodine-131 (p.2054·3) as sodium iodide.
Hyperthyroidism; thyroid cancer.

Theraclox *Great Eastern, Thai.; Therapharma, Thai.*
Cloxacillin (p.256·1).
Bacterial infections.

Theracne *Theraskin, Braz.*
Triclosan (p.1665·2).
Acne.

Theracof Plus *Reese, USA.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); diphenhydramine hydrochloride (p.577·2).

Theracort *Theraskin, Braz.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

TheraCys *Sanofi Pasteur, USA.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Theradol *Therabel, Neth.*
Tramadol hydrochloride (p.130·3).
Pain.

Theraflex *Sagmel, Rus.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Osteoarthritis.

TheraFlu
Note. This name is used for preparations of different composition.
Novartis, Mex.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Novartis, Turk.
Powder for oral solution: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Respiratory-tract congestion.

Novartis, Turk.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Respiratory-tract congestion.

TheraFlu 24 *Novartis, Mex.*
Pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Allergic rhinitis.

Theraflu Bro *Novartis Consumer, Rus.*
Rosemary oil (p.2381·3); eucalyptus oil (p.2301·2); Peru balsam (p.2365·3); camphor (p.2273·2).
Respiratory-tract disorders.

Theraflu Caplets Nighttime Severe Cold *Novartis Consumer, USA.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

TheraFlu CM *Novartis, Mex.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

TheraFlu CN *Novartis, Mex.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

TheraFlu Cold & Cough *Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Theraflu Cough *Novartis, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

TheraFlu Daytime Severe Cold *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).
Cold symptoms.

TheraFlu Ex *Novartis, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Theraflu ExtraGRIP *Novartis Consumer, Pol.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); pheniramine maleate (p.587·3).
Cold and influenza symptoms.

Theraflu Extratab *Novartis Consumer, Rus.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Respiratory-tract disorders.

TheraFlu Flu & Chest Congestion Non-Drowsy *Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly known as TheraFlu Maximum Strength Flu & Congestion Non-Drowsy.
Upper respiratory-tract disorders.

TheraFlu Flu and Cold
Note. This name is used for preparations of different composition.
Patheon, Rus.
Paracetamol (p.108·1); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Influenza symptoms.

Novartis, USA.
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold and flu symptoms.

TheraFlu Flu, Cold & Cough *Novartis, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

TheraFlu Forte *Novartis, Turk.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Theraflu KV *Novartis Consumer, Rus.*
Guaifenesin (p.1561·3).
Respiratory-tract disorders with viscous mucus.

Theraflu Lar *Novartis Consumer, Rus.*
Benzoxonium chloride (p.1631·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

TheraFlu N 12 *Novartis, Mex.*
Pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Allergic rhinitis.

TheraFlu Ninos VP *Novartis, Mex.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold symptoms.

TheraFlu Non-Drowsy Severe Cold *Novartis Consumer, USA.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as TheraFlu Non-Drowsy Formula Maximum Strength.
Coughs and cold symptoms.

TheraFlu Severe Cold *Novartis Consumer, USA.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Formerly known as TheraFlu Maximum Strength NightTime Formula Flu, Cold & Cough.
Coughs and cold symptoms.

TheraFlu TD *Novartis, Mex.*
Paracetamol (p.108·1); pseudoephedrine sulfate (p.1571·2); loratadine (p.583·3).
Allergic rhinitis.

TheraFlu Tenalif *Novartis, Mex.*
Oxeladin citrate (p.1567·1); ambroxol hydrochloride (p.1550·3).
Formerly known as Tenalif.
Respiratory-tract disorders with increased or viscous mucus.

Theraflu Thinstrips Daytime Cough & Cold
Novartis Consumer, USA.
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Theraflu Thinstrips Nighttime Cold & Cough *Novartis, USA.*
Diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

TheraFlu Vapor Stick *Novartis, USA.*
Camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal pain; upper respiratory-tract congestion.

Theraflu Zatoki *Novartis Consumer, Pol.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Thera-Flur *Colgate Oral, USA.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Theragen *Reese, USA.*
Capsaicin (p.32·3).

Theragenerix *Goldline, USA.*
A range of vitamin preparations (p.1922·1).

Theragenerix-H *Goldline, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Thera-gesic *Mission Pharmacal, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal and joint pain.

Theragran *Mead Johnson Nutritionals, USA.*
A range of vitamin preparations (p.1922·1).

Theragran AntiOxidant *BMS, USA.*
Vitamins A, C, and E with minerals (p.1922·1).

Theragran-M *Sarabhai Piramal, India; BMS, S.Afr.; BMS, Thai.†.*
Multivitamin and mineral preparation (p.1922·1).

Theralen *Aventis, Swed.*
Alimemazine tartrate (p.566·2).
Alcoholism; anxiety; behaviour disorders; hypersensitivity reactions; premedication; sleep disorders; vomiting.

Theralene *Sanofi-Aventis, Belg.; UCB, Fr.*
Alimemazine tartrate (p.566·2).
Cough; hypersensitivity reactions; insomnia; premedication; pruritus.

Theralene Pectoral Nourrisson *Celltech, Fr.†.*
Alimemazine tartrate (p.566·2); ammonium acetate (p.1551·2); tolu balsam (p.1574·2).
Coughs.

Theralexin *UAP, Indon.*
Cefalexin (p.218·2).
Bacterial infections.

Thera-M *Major, USA.*
Multivitamin preparation with minerals and folic acid (p.1922·1).

Theramycin Z *Medicis, USA†.*
Erythromycin (p.269·2).
Acne.

Theranal *Bayer, Neth.*
Bismuth subnitrate (p.1711·2); zinc oxide (p.1621·2); lidocaine (p.1862·3).
Haemorrhoids.

Theranex *Medifarma, Indon.; UAP, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolytic haemorrhage.

Theranyl *Sofus, Swed.†.*
⊗ Nicotinic acid (p.1957·3); salicylic acid (p.1612·2); trometamol (p.2405·1).
Musculoskeletal and joint disorders.

TheraPatch Cold Sore *Lectec, USA.*
Lidocaine (p.1862·3); camphor (p.2273·2).
Herpes labialis.

Therapeutic Bath Goldline, USA.
Emollient and moisturiser.

Therapeutic Bath Oil Lander, Canad.†.
Liquid paraffin (p.2030·3); wool fat (p.2033·2).
Skin disorders.

Therapeutic Mineral Ice Novartis, USA.
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Therapeutic Skin Lotion Scott, Canad.†.
Lanolin oil (p.2033·2); liquid paraffin (p.2030·3).
Skin disorders.

Therapeutic Soothing Ice Jamieson, Canad.†.
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Therapsor Theraskin, Braz.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Therapy Ice Major, USA.
Menthol (p.2340·1).

Therasa Pharmachemie, Belg.†.
Aspirin (p.20·3).
Thromboembolic disorders.

Therasona Theraskin, Braz.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Therasound AG Therapy, Gr.
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Theratar Theraskin, Braz.
Coal tar (p.1616·2).
Skin disorders.

TheraTears Advanced Vision, USA.
Carmellose sodium (p.2142·1).
Dry eyes.

Theravee Vangard, USA.
A range of vitamin preparations (p.1922·1).

Theravee Hematinic Vangard, USA.
Iron (p.1949·1); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Theravim Nature's Bounty, USA.
A range of vitamin preparations (p.1922·1).

Theravit Sagmel, Rus.
Vitamin and mineral preparations (p.1922·1).

Theravite Barre-National, USA.
Multivitamin preparation (p.1922·1).

Therems Rugby, USA.
A range of vitamin preparations (p.1922·1).

Therevac Plus Jones, USA.
Docusate sodium (p.1725·1); glycerol (p.2314·2); benzocaine (p.1854·1); soft soap (p.2139·2).
Constipation.

Therevac SB Jones, USA.
Docusate sodium (p.1725·1); glycerol (p.2314·2); soft soap (p.2139·2).
Constipation.

Thermal Provita, Austria; Alpharma, Norw.†.
Ethyl nicotinate (p.52·1); diethylamine salicylate (p.47·2).
Musculoskeletal and joint disorders; neuralgia.

Thermal FIX UV Vichy, Canad.
SPF 20: Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3).
Formerly known as Thermal S-UV.
Sunscreen.

Thermazene Sherwood, USA.
Sulfadiazine silver (p.337·2).
Infected burns.

Thermo Burger Ysatfabrik, Ger.
Capsicum (p.2276·2).
Musculoskeletal and joint disorders.

Thermo Rub Rolmex, Canad.
Methyl salicylate (p.85·3); menthol (p.2340·1); cineole (p.2282·3).

Thermocream Sterop, Belg.
Methyl salicylate (p.85·3); menthol (p.2340·1); capsicum oleoresin (p.2276·2).
Musculoskeletal disorders.

Thermocutan Streuli, Switz.†.
Nonivamide (p.96·2); ethyl nicotinate (p.52·1); benzyl nicotinate (p.28·1); aminophenazone salicylate (p.19·1).
Chilblains; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Thermo-Doline Tripharma, Turk.
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal and joint pain.

Thermoflex Santa, Turk.
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal and joint pain.

Thermo-Gel Prodemdis, Canad.
Camphor (p.2273·2); menthol (p.2340·1); benzocaine (p.1854·1); thymol (p.1664·3).

Thermogene Montefarmaco, Ital.
Capsicum oleoresin (p.2276·2).
Musculoskeletal and joint pain.

Thermo-Menthoneurin Byk Gulden, Ger.†; Roland, Ger.†.
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Thermo-Rheumon Kolassa, Austria; Bayer, Cz.†; Tropon, Ger.†; Bayer, Hung.†; Bayer, Pol.; Bayer, Turk.
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Thermo-Rheumon N Tropon, Ger.†.
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, and soft-tissue disorders.

Thermo-Roiplon Menarini, Gr.
Etofenamate (p.53·1); benzyl nicotinate (p.28·1).
Musculoskeletal and joint disorders.

Thermorub
Note. A similar name is used for preparations of different composition (see below).
Pharmaniaga, Malaysia.
Methyl salicylate (p.85·3); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Musculoskeletal pain.

Thermo-Rub
Note. A similar name is used for preparations of different composition (see above).
Adcock Ingram, S.Afr.
Methyl salicylate (p.85·3).
Muscular pain; rheumatism.

Thermosenex Riemser, Ger.
Camphor (p.2273·2); glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal and joint disorders; neuralgia; sprains.

Theryttrex Nordion, Neth.†.
Yttrium-90 (p.2057·1) chloride.
Radiolabelling of carrier molecules.

Thesit Gepepharm, Ger.†.
Lauromacrogol 400 (p.1916·1); mepivacaine hydrochloride (p.1866·3).
Burns; insect stings; skin disorders.

Thevier GSK, Ger.
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thex Forte Lee, USA.
Vitamin B and C preparation (p.1922·1).

Thiaben UCI, Braz.†.
Tiabendazole (p.156·2).
Nematode infections.

Thiabena UCI, Braz.†.
Tiabendazole (p.156·2); neomycin sulfate (p.305·1).
Skin infections.

Thiabene Ratiopharm, Cz.
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Thiabet Wolff, Ger.
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Thiacomin Medichrom, Gr.†.
Thiocolchicoside (p.1898·2).
Muscle spasm.

Thialgin Zentiva, Cz.
Tiaprofenic acid (p.129·2).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Thiambiotic Prafa, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Thiamcin General Drugs, Thai.
Thiamphenicol (p.351·1).
Bacterial infections.

Thiamet Ethica, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Thiamfilex Molex Ayus, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Thiamika Ikapharmindo, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Thiaminose Climax, Braz.†.
Ascorbic acid; thiamine hydrochloride; glucose (p.1922·1).
Nutritional supplement.

Thiamycin Interbat, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Thianax Cazi, Braz.
Tiabendazole (p.156·2).
Worm infections.

Thiavit Julphar, UAE.
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Thiazid-comp Wolff, Ger.
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Thicazol Ethica, Indon.
Ketoconazole (p.539·1).
Fungal infections.

Thick & Easy Hormel, Hong Kong; Fresenius Kabi, Irl.; Hormel, Israel; Hormel, Singapore.
Food thickener (p.1922·1).
Dysphagia.

Thickened Juice Baxter, NZ†; Nutricia, NZ†.
Nutritional supplement (p.1922·1).
Dysphagia.

Thickhead Principle Healthcare, UK.
Vitamins; minerals; activated charcoal (p.1922·1).
Dietary supplement.

Thidim Kalbe, Indon.
Ceftazidime (p.234·1).
Bacterial infections.

Thilo Tears Alcon, Belg.
Carbomer (p.2141·3).
Dry eyes.

Thiloadren Alcon, Austria.
⊗ Dipivefrine hydrochloride (p.2295·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Thiloadren N Alcon, Ger.
⊗ Dipivefrine hydrochloride (p.2295·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Thilocanfol Alcon, Ger.
Azidamfenicol (p.206·3).
Bacterial eye infections.

Thilocanfol C Alcon, Ger.
Chloramphenicol (p.239·3).
Bacterial eye infections.

Thilocof Pharmex (Φαρμεξ), Gr.
Azidamfenicol (p.206·3).
Formerly contained chloramphenicol.
Eye infections.

Thilocombin Alkon (Αλκον), Gr.†.
⊗ Dipivefrine hydrochloride (p.2295·3); pilocarpine (p.1884·3).
Glaucoma.

Thilodexine Pharmex (Φαρμεξ), Gr.
⊗ Dexamethasone sodium metasulfobenzoate (p.1526·1).
Inflammatory eye disorders; skin disorders.

Thilodigon Alcon, Austria†; Alcon, Ger.
⊗ Guanethidine monosulfate (p.1300·2); dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Thilodrin Alcon, Gr.
⊗ Dipivefrine hydrochloride (p.2295·3).
Glaucoma.

Thilogel Alcon, Gr.
Carbomer (p.2141·3).
Dry eyes.

Thilol Farmex, Gr.
Trifluridine (p.910·3).
Herpes simplex infections in the eye.

Thilomaxine Liba, Turk.
Tobramycin (p.354·1).
Bacterial eye infections.

Thilo-micine Farmex, Gr.
Tobramycin (p.354·1).
Eye infections.

Thilomicine Dex Farmex, Gr.
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Thilomide Farmex, Gr.; Liba, Turk.
Lodoxamide trometamol (p.2334·2).
Allergic conjunctivitis.

Thilonium Alkon (Αλκον), Gr.†.
⊗ Befunolol (p.1878·2).
Glaucoma.

Thilorbin Alcon, Cz.†; Alcon, Ger.
Oxybuprocaine hydrochloride (p.1867·3); fluorescein sodium (p.2306·1).
Ophthalmic procedures.

Thilo-Tears Alcon, Ger.; Alcon, Neth.; Liba, Turk.
Carbomer (p.2141·3).
Dry eyes.

Thilotim Alcon, Gr.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Thiloxedine Pharmex (Φαρμεξ), Gr.†.
⊗ Dexamethasone (p.1526·1).
Topical corticosteroid.

Thimelon Ethica, Indon.
⊗ Methylprednisolone (p.1538·1) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Thimerfesa Organifar, Venez.†.
Thiomersal (p.1663·3); merbromin (p.1652·1).
Disinfection.

Thinber Fiber Complex Dapha, Philipp.
Fruit fibre; glucomannan; gelatin; oat fibre; red clover; apple vinegar; yeast chromium; magnesium stearate (p.1922·1).
Dietary fibre supplement.

Thinz SA Druggists Self Med, S.Afr.
⊗ Cathine hydrochloride (p.2152·2).
Obesity.

Thiobitum Riemser, Ger.
Ichthammol (p.1599·1).
Skin disorders.

Thiocase Almirall, Spain.
Thiomucase (p.2400·2).
Cellulitis; haemorrhoids; obesity; premenstrual syndrome; soft-tissue disorders.

Thiocilline Abdi, Turk.
Bacitracin (p.210·3); neomycin sulfate (p.305·1).
Bacterial eye and skin infections.

Thiocodin
Note.This name is used for preparations of different composition.
Bros, Gr.
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Unia, Pol.
Codeine phosphate (p.37·2); sulfogaiacol (p.1573·2).
Cough.

Thioctacid
Viatris, Austria; Meda, Cz.; Viatris, Ger.; Viatris, Rus.
⊗ Thioctic acid (p.2400·2) or trometamol thioctate (p.2400·2).
Amanita poisoning; cerebral metabolic disorders in the elderly; diabetic and alcoholic neuropathy; liver disorders.

Viatris, Hung.; Bayer, Mex.
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Thiodantol Rekah, Israel.
Isothipendyl hydrochloride (p.582·1).
Skin irritation.

Thiodazine Sun, Rus.
Thioridazine hydrochloride (p.1031·2).

Thioderon Shionogi, Jpn.
⊗ Mepitiostane (p.2116·1).
Breast cancer; renal anaemia.

Thiogamma
Worwag, Cz.; Worwag, Hung.; Worwag, Pol.
Thioctic acid (p.2400·2).
Diabetic neuropathy.

Worwag, Ger.; Worwag, Rus.
Meglumine thioctate (p.2400·2) or thioctic acid (p.2400·2).
Diabetic neuropathy.

Thiola Sigma, Austral.†; Santen, Hong Kong†; Coop. Farm., Ital.; Mission Pharmacal, USA.
Tiopronin (p.1467·1).
Cataract; liver disorders; mercury poisoning; prevention of cystine renal calculi.

Thiomed Medifive, Thai.
Thioridazine hydrochloride (p.1031·2).
Anxiety; mania; schizophrenia.

Thiomersalate SA Druggists, S.Afr.
Thiomersal (p.1663·3).
Skin disinfection; skin infections; wounds.

Thiomucase Farmasa, Braz.
Mucopolysaccharidase (p.2400·2); amylase (p.2256·3); chymotrypsin (p.2281·3).
Oedema.

Thionembutal Abbott, Braz.
Thiopental sodium (p.1795·2).
General anaesthesia.

Thiopentax Cristalia, Braz.
Thiopental sodium (p.1795·2).
General anaesthesia.

Thiophenicol
Sanofi-Aventis, Fr.
Thiamphenicol (p.351·1) or thiamphenicol glycinate hydrochloride (p.351·1).
Bacterial infections.

Sanofi Synthelabo, Turk.
Thiamphenicol (p.351·1).
Bacterial infections.

Thioplex Adienne, Ital.; Amgen, USA.
Thiotepa (p.778·3).
Malignant neoplasms.

Thioprine Alphapharm, Austral.; Pacific, NZ.
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Thioril
Torrent, India.
Thioridazine hydrochloride (p.1031·2).
Schizophrenia.

Torrent, Rus.
Thioridazine (p.1031·2) or thioridazine hydrochloride (p.1031·2).
Depression; psychoses.

Thiorubrol Adroka, Switz.†.
Trolamine thioricinol sulfate.
Muscle and joint pain; skin disorders.

Thiosan Azevedos, Port.†.
Sulfiram (p.2050·3).
Pediculosis; scabies.

Thiosept Terrapharm, Austria.
Shale oil.
Hyperhidrosis; inflammation; musculoskeletal and joint disorders; peripheral vascular disorders; skin disorders.

Thiosia Asian Pharm, Thai.
Thioridazine hydrochloride (p.1031·2).
Anxiety; depression.

Thiosol Coop. Farm., Ital.
Tiopronin (p.1467·1).
Respiratory-tract congestion.

Thiospot Dermoteca, Port.
Thiolin; ascorbyl palmitate (p.1629·1); tartaric acid (p.2395·2); salicylic acid (p.1612·2).
Hyperpigmentation disorders.

Thiovalone Pfizer, Fr.
⊗ Tixocortol pivalate (p.1544·2); chlorhexidine gluconate (p.1635·3).
Inflammation of the mouth and throat.

Thioxene Esseti, Ital.†.
Glutathione sodium (p.1448·1).
Alcohol or drug poisoning; ionising radiation damage.

Thiozine Pinewood, Irl.†.
Thioridazine hydrochloride (p.1031·2).
Schizophrenia.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Thiprasolan *Lamsa, Arg.*
Alprazolam (p.960·1).
Anxiety; depression.

Thiramil *Farmedia, Gr.*
Fluoxetine (p.397·3).
Depression.

Thiroyd *Greater Pharma, Thai.*
Thyroid (p.2177·1).
Hypothyroidism.

Thislacol *Metiska, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Thixit *Douglas, NZ.*
Tiotixene hydrochloride (p.1032·3).
Psychoses.

Thomaeamin X E *DeltaSelect, Ger.†.*
Amino-acid, electrolyte, and xylitol infusion (p.1922·1).
Parenteral nutrition.

Thomaeamin hepar *DeltaSelect, Ger.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition in liver failure.

Thomaeamin n *DeltaSelect, Ger.†.*
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Thomaegelin *DeltaSelect, Ger.†.*
⊗ Gelatin polysuccinate (p.1072·1) in Ringer acetate.
Hypovolaemia.

Thomaejonin *DeltaSelect, Ger.†.*
A range of electrolyte infusions with or without carbohydrate (p.1667·1).
Fluid and electrolyte disorders.

Thomaemannit *DeltaSelect, Ger.†.*
⊗ Mannitol (p.1330·2).
Fluid retention; renal failure.

Thomapyrin *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Cz.†; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Turk.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Thomapyrin akut *Boehringer Ingelheim, Ger.†.*
Aspirin (p.20·3).
Fever; pain.

Thomapyrin C *Boehringer Ingelheim, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Pain.

Thomapyrin mit Vitamin C *Boehringer Ingelheim, Austria.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Thomapyrine *Boehringer Ingelheim, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Thomasin *Apogepha, Ger.*
⊗ Etilefrine hydrochloride (p.1284·1).
Hypotension.

Thombran *Boehringer Ingelheim, Ger.*
Trazodone hydrochloride (p.424·3).
Depression.

Thorazine
GSK, Philipp.
Chlorpromazine hydrochloride (p.969·2).
Behavioural disorders in children; intractable hiccup; nausea and vomiting; porphyria; premedication; psychoses.

SmithKline Beecham, USA†.
Chlorpromazine (p.969·1) or chlorpromazine hydrochloride (p.969·2).
Acute intermittent porphyria; adjunct in tetanus; bipolar disorder; hiccups; nausea and vomiting; premedication; psychoses; severe behavioural disorders in children.

Thoreus *GSK, Hung.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Threchop *Collins, Mex.*
Diiodohydroxyquinoline (p.832·1); furazolidone (p.834·3); homatropine (p.1881·2).
Amoebic dysentery.

Threolone *Abic, Israel.*
⊗ Prednisolone (p.1540·3); chloramphenicol (p.239·3).
Infected skin disorders.

Threptin Micromix *Raptakos, India.*
Nutritional supplement (p.1922·1).

Thriazol *Alpharma, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Thriolan *Antor, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Thrionipen *Antor, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Thriostaxil *Medinova (Μεντινοβα), Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Thriusedon *Biospray, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Throat Discs *SmithKline Beecham, USA.*
Capsicum (p.2276·2); peppermint oil (p.1761·2); liquid paraffin (p.2030·3).
Sore throat.

Throat Lozenges
Note. This name is used for preparations of different composition.
Novopharm, Canad.
Cetylpyridinium chloride (p.1635·1).

Novopharm, Canad.
Benzocaine (p.1854·1); cetylpyridinium chloride (p.1635·1).

Throaties Anti-Bacterial Pastilles *Ernest Jackson, UK.*
Amylmetacresol (p.1628·3).
Sore throat.

Throaties Pastilles
Note. This name is used for preparations of different composition.
Ernest Jackson, UK.
Blackcurrant flavour: Honey (p.1948·2); menthol (p.2340·1).
Coughs; sore throat.

Ernest Jackson, UK.
Original flavour: Benzoin tincture (p.2394·2); menthol (p.2340·1).
Coughs; sore throat.

Throatsil *Millimed, Thai.*
Dichlorobenzyl alcohol (p.1642·1); amylmetacresol (p.1628·3).
Mouth and throat disorders.

Throatsil-CBS *Millimed, Thai.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Throatsil-DEX *Millimed, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Thrombace Neo *Drossapharm, Switz.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Thrombareduct *Sandoz, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue disorders; soft-tissue injury.

Thrombate *Bayer, Canad.; Talecris, Canad.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Thrombate III *Talecris, USA.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Thrombhibin *Immuno, Austria.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Thrombinar *Jones, USA.*
Thrombin (p.1080·1).
Minor haemorrhage.

Thrombo AS *Merck, Chile.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Thrombo Aspilets *Medifarma, Indon.*
Aspirin (p.20·3).
Thromboembolic disorders.

Thrombo ASS *Lannacher, Austria; Lannacher, Rus.*
Aspirin (p.20·3).
Thromboembolism prophylaxis.

Thrombocid
Note. This name is used for preparations of different composition.
Sigmapharm, Austria.
Pentosan polysulfate sodium (p.1367·1); guaiazulene (p.2317·3); thymol (p.1664·3).
Soft-tissue injury; vascular disorders.

Bene, Cz.
Pentosan polysulfate sodium (p.1367·1); pumilio pine oil (p.2376·3); rosemary oil (p.2381·3); melissa oil (p.2339·3).
Soft-tissue injury.

Bene-Chemie, Hong Kong.
Pentosan polysulfate sodium (p.1367·1); guaiazulene (p.2317·3).
Haemorrhoids; insect stings; sunburn; superficial phlebitis; venous insufficiency.

Lacer, Spain.
Pentosan polysulfate sodium (p.1367·1).
Formerly contained pentosan polysulfate sodium and thymol.
Haematoma; varicose veins.

Bene, Ger.; Neo-Farmaceutica, Port.; Milupa, Switz.
Ointment: Pentosan polysulfate sodium (p.1367·1); guaiazulene (p.2317·3); thymol (p.1664·3).
Burns; insect bites; soft-tissue disorders; superficial vascular disorders.

Bene, Ger.†; Neo-Farmaceutica, Port.†.
Suppositories: Pentosan polysulfate sodium (p.1367·1); aluminium monostearate; guaiazulene (p.2317·3).
Anorectal disorders.

Bene, Ger.; Neo-Farmaceutica, Port.; Milupa, Switz.
Topical gel: Pentosan polysulfate sodium (p.1367·1); rosemary oil (p.2381·3); pumilio pine oil (p.2376·3); melissa oil (p.2339·3).
Soft-tissue disorders; superficial vascular disorders; venous insufficiency.

Thrombodine *Lannacher, Austria.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Thrombogen *Johnson & Johnson Medical, USA†.*
Thrombin (p.1080·1).
Bleeding from small blood vessels.

Thrombohexal *Hexal, Austria.*
Dipyridamole (p.1268·1); aspirin (p.20·3).
Glomerulonephritis; peripheral arterial disorders.

Thromboparin *Alfa Wassermann, Gr.*
Parnaparin (p.1366·1).
Thrombosis prophylaxis.

Thrombophob
Note. This name is used for preparations of different composition.
Abbott, Ger.
Heparin sodium (p.1301·2).
Soft-tissue injury; vascular disorders.

Abbott, Austria; Nordmark, Indon.; Tunggal Idaman, Indon.
Ointment: Heparin sodium (p.1301·2); benzyl nicotinate (p.28·1).
Phlebitis; soft-tissue injury; superficial vascular disorders; varices; venous insufficiency.

German Remedies, India.
Ointment: Heparin (p.1301·2); benzyl nicotinate (p.28·1).
Soft-tissue disorders.

Abbott, Austria; Nordmark, Indon.; Tunggal Idaman, Indon.
Topical gel: Heparin sodium (p.1301·2).
Phlebitis; soft-tissue injury; superficial vascular disorders; varices; venous insufficiency.

German Remedies, India; Aventis, S.Afr.
Topical gel: Heparin (p.1301·2).
Soft-tissue disorders; superficial vascular disorders.

Thrombophob-S *Abbott, Austria.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Thromboreductin *Orpha-Devel, Austria; Orpha-Devel, Cz.; Mayne, Hong Kong; Orphan, Hung.; AOP Orphan, Indon.; AOP, Malaysia.*
Anagrelide hydrochloride (p.2257·1).
Thrombocythaemia.

Thrombostad *Stada, Austria.*
Aspirin (p.20·3).
Migraine; thrombotic disorders.

Thrombostat *Pfizer, Austral.†; Pfizer, Canad.†; Pfizer, NZ; Parke, Davis, USA.*
Thrombin (p.1080·1).
Haemorrhage.

Thrombotrol-VF *CSL, Austral.; CSL, NZ.*
Antithrombin III (p.1054·1).
Antithrombin III deficiency.

Thromyn *Zynova, Philipp.*
Roxithromycin (p.331·1).
Bacterial infections.

Throsyn *Pharmacare, S.Afr.*
Roxithromycin (p.331·1).
Bacterial infections.

Thuja Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Thuja N Oligoplex *Madaus, Ger.*
Homoeopathic preparation.

Thujaderm *Knop, Chile.*
Thuja (p.2400·3).
Warts.

Thunas Eye Drops *Thuna, Canad.†.*
Boric acid (p.2268·1); borax (p.2268·1).

Thunas Hyperacidity Tablets *Thuna, Canad.†.*
Magnesium hydroxide (p.1743·2); aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); simeticone (p.1770·2).

Thunas Laxative *Thuna, Canad.†.*
Cascara (p.1715·2); senna (p.1769·2); bryony; fennel (p.2302·3); liquorice (p.1740·3); juglans; leptandra.

Thunas Pile *Thuna, Canad.†.*
⊗ Benzocaine (p.1854·1); bismuth subcarbonate (p.1711·1); ephedrine sulfate (p.1558·2); zinc oxide (p.1621·2).
Haemorrhoids.

Thunas Salve for Rheumatic Pains *Thuna, Canad.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).

Thunas Tab for Menstrual Pain *Thuna, Canad.†.*
Motherwort (p.2347·3); senecio (p.2385·1); sodium salicylate (p.124·2); teucrium scorodonia; viburnum (p.2267·1).

Thuya Complexe no 37 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 37.

Thybon *Henning, Ger.; Sanofi Synthelabo, Ger.*
Liothyronine hydrochloride (p.2174·2).
Hypothyroidism.

Thycapzol *Hexal, Denm.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Thymazen *Polfa Warszawa, Pol.*
⊗ Tymazoline hydrochloride (p.1575·1).
Nasal congestion; sinusitis.

Thymcal *Nufarindo, Indon.*
⊗ Paracetamol (p.108·1); ephedrine hydrochloride (p.1558·2); chlorphenamine maleate (p.571·3); calcium gluconate (p.1675·3); ammonium chloride (p.1551·3); thyme (p.2401·1); ammonium bromide (p.2269·2); sassafras oil (p.2383·3).
Coughs.

Thymi Syrup *Vitamed, Israel.*
Thyme (p.2401·1).
Coughs.

Thymian Erkaltungs-Bad *Li-il, Ger.*
Thyme oil (p.2401·2).
Bath additive; respiratory-tract disorders; skin disorders.

Thymipin N
Note. This name is used for preparations of different composition.
Novartis Consumer, Ger.†.
Cream: Thyme (p.2401·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Bronchitis; catarrh; coughs.

Novartis Consumer, Ger.
Oral drops; suppositories; syrup: Thyme (p.2401·1).
Bronchitis; catarrh; coughs.

Thymiverlan *Verla, Ger.*
Thyme (p.2401·1).
Respiratory-tract disorders.

Thymodepressin *Peptos, Rus.*
Thymodepressin.
Neutropenia; psoriasis; rheumatoid arthritis.

Thymodrosin N *Gubler, Switz.†.*
Guaifenesin (p.1561·3); thyme (p.2401·1); drosera (p.2297·3); ribwort plantain (p.2379·1); liquorice (p.1740·3).
Respiratory-tract disorders.

Thymo-Glanduretten *Biosyn, Ger.†.*
Bovine thymus extract (p.2401·3).
Immunotherapy.

Thymoglobulin *Genzyme, Canad.; Genzyme, Ger.; Aventis, India.*
An antithymocyte immunoglobulin (rabbit) (p.1817·3).
Transplant rejection.

Thymoglobuline *Sanova, Austria; Genzyme, Belg.; Aventis Pasteur, Braz.†; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Gerolymatos, Gr.; IFET (ΙΦΕΤ), Gr.; Genzyme, Hong Kong; Imtix Sangstat, Israel; Imtix, Ital.; Genzyme, Malaysia; Genzyme, Neth.; Genzyme, Pol.; Aventis, S.Afr.; Genzyme, Singapore; Pacific Biosciences, Singapore; Sangstat, Singapore; Genzyme, Swed.; Genzyme, Switz.; Aventis Pasteur, Thai.†; Aventis Pasteur, Turk.; Genzyme, UK.*
An antithymocyte immunoglobulin (rabbit) (p.1817·3).
Aplastic anaemia; graft-versus-host disease; immunosuppressive therapy; transplant rejection.

Thymoject *Biosyn, Ger.; Loges, Ger.*
Bovine thymus extract (p.2401·3).
Immunological disorders.

Thymol Mouthwash Red *Orion, NZ†.*
Thymol (p.1664·3); menthol (p.2340·1).
Halitosis; mouth and throat infections.

Thymomel *Ivax, Cz.*
Thyme (p.2401·1); wild thyme (p.2415·3); plantain (p.2379·1).
Respiratory-tract congestion.

Thymophysin *CytoChemia, Ger.*
Thymus extract (p.2401·3).
Immunotherapy.

Thymorell *Sanorell, Ger.*
Homoeopathic preparation.

Thymoseptine *Tilman, Belg.*
Thyme (p.2401·1); wild thyme (p.2415·3); ammonium acetate (p.1551·2).
Formerly contained thyme and wild thyme.
Respiratory-tract disorders; sore throat.

Thymoval *Smetana, Austria.*
Cowslip (p.2372·2); valerian (p.2410·1); thyme (p.2401·1).
Coughs.

Thymowied *Wiedemann, Ger.†.*
Calf thymus extract (p.2401·3).
Immunotherapy.

Thymunes *Eagle, Austral.*
Thymus (p.2401·3).

Thymusin N *Streuli, Switz.*
Thyme (p.2401·1).
Coughs.

Thym-Uvocal *Strathmann, Ger.*
Calf thymus extract (p.2401·3).
Immunotherapy.

Thyprotect *Henning, Ger.; Sanofi Synthelabo, Ger.*
Potassium iodide (p.2169·2).
Blockade of thyroid uptake of radioiodine.

Thyradin-S *Teikoku, Jpn.*
Levothyroxine sodium (p.2171·2).
Goitre; hypothyroidism.

Thyrax *Organon, Belg.; Organon, Cz.†; Organon, Indon.; Organon, Neth.; Organon, Philipp.; Organon, Port.; Organon, Venez.*
Levothyroxine sodium (p.2171·2).
Diagnostic suppression of thyroid activity; euthyroid goitre; hypothyroidism; thyroid cancer.

Thyreocomb *Berlin-Chemie, Rus.*
Levothyroxine sodium (p.2171·2); liothyronine (p.217·2); potassium iodide (p.2169·2).

Thyreocomb N *Berlin-Chemie, Ger.†.*
Levothyroxine (p.2173·2); potassium iodide (p.2169·2).
Iodine-deficiency disorders.

Thyreogutt *Austroplant, Austria.*
Motherwort (p.2347·3); lycopus europaeus.
Hyperthyroidism; mastalgia; tachycardia.

Thyreogutt mono *Schwabe, Ger.*
Lycopus europaeus.
Mastalgia; mild hyperthyroidism.

thyreo-loges comp *Loges, Ger.*
Homoeopathic preparation.

thyreo-loges N *Loges, Ger.*
Lycopus europaeus.
Hyperthyroidism.

Thyreo-Pasc N *Pascoe, Ger.*
Homoeopathic preparation.

Thyreostat II *Herbrand, Ger.†.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Thyreotom
Berlin-Chemie, Cz.; Berlin-Chemie, Ger.†.
Liothyronine (p.2174·2); levothyroxine (p.2173·2).
Hypothyroidism.

Berlin-Chemie, Rus.
Liothyronine (p.2174·2); levothyroxine sodium (p.2171·2).

Thyrex *Sandoz, Austria.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thyro-4 *Faran, Gr.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thyro-Block *Carter Horner, Canad.†; Wallace, USA.*
Potassium iodide (p.2169·2).
Prevention of thyroid uptake of radioiodine.

Thyrogen *Genzyme, Austria; Genzyme, Belg.; Biobras, Braz.†; Genzyme, Canad.; Genzyme, Cz.; Genzyme, Denm.; Genzyme, Fin.; Genzyme, Fr.; Genzyme, Ger.; Genzyme, Gr.; Genzyme, Hung.; Genzyme, Israel; Genzyme, Ital.; Genzyme, Neth.; Genzyme, Norw.; Genzyme, Pol.; Genzyme, Port.; Genzyme, Singapore; Genzyme, Spain; Genzyme, Swed.; Genzyme, UK; Genzyme, USA.*
Thyrotropin alfa (p.2177·2).
Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients; measurement of serum thyroglobulin.

Thyrohex *Hexal, Philipp.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thyrohormone *Ni-The, Gr.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thyrolar *Forest Pharmaceuticals, USA.*
Liothyronine sodium (p.2174·1); levothyroxine sodium (p.2171·2).
Evaluation of thyroid function; hypothyroidism; TSH suppression.

Thyroliberin *Merck, Ger.*
Protirelin (p.2175·3).
Assessment of pituitary and thyroid function.

Thyroliberin TRH *Merck, Austria†.*
Protirelin (p.2175·3).
Test for thyroid-pituitary function.

Thyromazol *Abdi, Turk.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Thyronajod *Henning, Ger.; Sanofi Synthelabo, Ger.*
Levothyroxine sodium (p.2171·2); potassium iodide (p.2169·2).
Hypothyroidism.

Thyrosan *Sun-Farm, Pol.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

ThyroShield *Fleming, USA.*
Potassium iodide (p.2169·2).

Thyrosit *Sriprasit, Thai.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Thyrostat *Ni-The, Gr.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Thyrotardin N *Henning, Ger.; Sanofi Synthelabo, Ger.*
Liothyronine hydrochloride (p.2174·2).
Hypothyroidism.

Thyrozol *Merck, Chile; Merck, Cz.; Merck, Ger.; Merck, Indon.; Merck, Pol.; Merck, Rus.; Merck, Singapore.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Thytropar *USV, Israel†.*
Thyrotrophin (p.2177·2).
Diagnosis of hypothyroidism.

TI Baby Natural *Fischer, USA.*
SPF 16: Titanium dioxide (p.1617·3).
Sunscreen.

TI Lite *Fischer, USA.*
SPF 15: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

TI Screen
Note. This name is used for preparations of different composition.
Pedinol, USA.
SPF 15; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Pedinol, USA.
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); octocrilene (p.1608·3).
Sunscreen.

TI Screen Natural *Pedinol, USA.*
SPF 16: Titanium dioxide (p.1617·3).
Sunscreen.

TI Screen Sports *Pedinol, USA.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

TI Screen Sunless *Pedinol, USA.*
SPF 17; SPF 23: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Tia Puppy *Nordin, Mex.*
Hamamelis (p.2318·2).
Varices.

Tiabenzol *Teuto, Braz.†.*
Tiabendazole (p.156·2).
Worm infections.

Tiabet *Tunggal Idaman, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Tiabexol *Offenbach, Mex.*
Cyanocobalamin (p.1980·2); thiamine (p.1976·3).
Vitamin supplement.

Tiacob *Hexal, Neth.*
Tiapride hydrochloride (p.1032·1).
Neuroleptic-induced tardive dyskinesia.

Tiaden *Gap, Gr.*
⊗ Amiloride hydrochloride (p.1209·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Tiadil *All-Gen, Neth.; Basi, Port.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension; myocardial infarction.

Tiadilon *Crinex, Fr.*
⊗ Arginine tidiacicate (p.1928·3).
Liver disorders.

Tiadipona *Abbott, Spain.*
Bentazepam (p.964·2).
Anxiety disorders; insomnia.

Tiadol *Bunker, Braz.*
Tiabendazole (p.156·2).

Tiadyl *Abbott, Arg.*
Candesartan cilexetil (p.1238·3).
Hypertension.

Tiadyl Plus *Abbott, Arg.*
⊗ Candesartan cilexetil (p.1238·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tiaglib *Tunggal Idaman, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Tiajac *Jacobsen, Neth.*
Tiapride hydrochloride (p.1032·1).
Neuroleptic-induced tardive dyskinesia.

Tiakem *Sanofi Synthelabo, Cz.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension.

Tial *Lindopharm, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tialin *Roemmers, Venez.*
Sertraline hydrochloride (p.421·3).
Depression.

Tialipol *Lafedar, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Tialorid *Polpharma, Pol.*
⊗ Amiloride (p.1210·1); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Tial-Z *Perfarma, Ital.*
Levomenol (p.2333·3); allantoin (p.1588·1).
Skin irritation.

Tiamidexal *Silanes, Mex.*
⊗ 1 Ampoule, cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); 1 ampoule, dexamethasone sodium phosphate (p.1526·2).
Gout; musculoskeletal, joint, and peri-articular disorders; neuritis.

Tiamidon *Medipharma, Arg.*
Thiamine; pyridoxine; vitamin B (p.1922·1).

Tiamin *Ducto, Braz.*
Vitamin B substances (p.1922·1).

Tiaminal B$_{12}$ *Silanes, Mex.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Neuralgia; neuritis; vitamin B deficiencies.

Tiaminal B$_{12}$ Trivalente *Silanes, Mex.*
Cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgia; neuritis; pernicious anaemia; vitamin B deficiencies.

Tiamol *Taro, Canad.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Tiamon Mono *Temmler, Ger.*
Dihydrocodeine tartrate (p.48·1).
Coughs.

Tianak *Wermar, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Tianex *Inter, Venez.†.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.

Tiaplex *Delta, Braz.*
Tiabendazole (p.156·2).
Worm infections.

Tiapra *Zentiva, Cz.*
Tiapride hydrochloride (p.1032·1).
Alcohol withdrawal syndrome; dementia; Huntington's chorea; movement disorders.

Tiapridal
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong†; Sanofi-Aventis, Hung.; Sanofi Synthelabo, Neth.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Synthelabo, Rus.; Sanofi Synthelabo, Switz.
Tiapride hydrochloride (p.1032·1).
Aggression; agitation; alcohol withdrawal syndrome; anxiety; behaviour disorders; choreic movements; drug-induced extrapyramidal disorders; dyskinesias; pain; withdrawal syndromes.

Tiapridex *Sanofi Synthelabo, Ger.*
Tiapride hydrochloride (p.1032·1).
Chorea; drug-induced extrapyramidal disorders.

Tiaprizal *Sanofi-Aventis, Spain.*
Tiapride hydrochloride (p.1032·1).
Anxiety; attention-deficit hyperactivity disorder; movement disorders; nausea and vomiting.

Tiaprofen *Bioprogress, Ital.†.*
Tiaprofenic acid (p.129·2).
Inflammation; pain.

Tiarix *Casasco, Arg.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; social phobia.

Tiaryt *Fahrenheit, Indon.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Tiasar *Pentafarma, Port.*
Losartan potassium (p.1326·1).
Heart failure; hypertension.

Tiastad *Stada, Neth.*
Tiapride hydrochloride (p.1032·1).
Neuroleptic-induced tardive dyskinesia.

Tiatral 100 SR *Novartis, Switz.*
Aspirin (p.20·3).
Thromboembolic disorders.

Tiaven *Loren, Mex.†.*
Vitamin B substances (p.1922·1).

Tiazac
Note. This name is used for preparations of different composition.
Biovail, Canad.; Forest Pharmaceuticals, USA.
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Biopharm, Chile.
Pioglitazone (p.456·3).
Diabetes mellitus.

Tiazam *Vocate, Gr.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Tiazet *Ratiopharm, Neth.*
Tiapride hydrochloride (p.1032·1).
Neuroleptic-induced tardive dyskinesia.

Tiazinol *Cipan, Port.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tiba *Pharmaland, Thai.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Tiberal *Roche, Belg.; SERB, Fr.; Roche, NZ; Roche, Switz.; Roche, Venez.†.*
Ornidazole (p.843·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Tibial *Neo Quimica, Braz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Tibifor *Lisapharma, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Tibigon *Hexpharm, Indon.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Tibinide *Recip, Swed.*
Isoniazid (p.288·1).
Tuberculosis.

Tibirim INH *Stancare, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Tibitol
Pharmaceutical Co, India.
Ethambutol (p.275·2).
Tuberculosis.

Mersifarma, Indon.
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Tiboclim *Panalab, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Tibofem *Organon, Arg.; Cipla, India.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Tibolvivax *Organon, Cz.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Tibomax *Zydus, India.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Ticalma *Kelemata, Ital.*
Valerian root (p.2410·1).
Sedative.

Ticar *GSK, USA.*
Ticarcillin sodium (p.352·2).
Bacterial infections.

Ticard *Sanbe, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis.

Ticarpen *GSK, Fr.; GSK, Neth.; SmithKline Beecham, Spain.*
Ticarcillin sodium (p.352·2).
Bacterial infections.

Ticathion *Pliva, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Ticavent *Caber, Ital.*
⊗ Fluticasone propionate (p.1533·2).
Rhinitis.

Ticdine *Fascino, Thai.†.*
Ticlopidine hydrochloride (p.1411·2).
Intermittent claudication; stroke prophylaxis; thromboembolism prophylaxis; unstable angina pectoris.

Tice *Organon, USA.*
A BCG vaccine (p.2205·3).
Active immunisation; bladder cancer.

Ticinan *Formenti, Ital.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

Ticinil *Boehringer Ingelheim, Venez.*
Phenylbutazone (p.117·1) or phenylbutazone calcium (p.117·1).
Osteoarthritis; rheumatoid arthritis.

Tickly Cough & Sore Throat Relief *Herbal Concepts, UK.*
Hyssop (p.2323·3); senega (p.1572·3); liquorice (p.1740·3).
Coughs and cold symptoms; sore throat.

Ticlapsor *Abiogen, Ital.*
Tacalcitol (p.1615·1).
Psoriasis.

Ticlid *Sanofi Synthelabo, Arg.; Roche, Austral.; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Roche, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Indon.; Sanofi Synthelabo, Malaysia; Syntex, Mex.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi Synthelabo, S.Afr.†; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.; Roche, USA; Sanofi-Aventis, Venez.*
Ticlopidine hydrochloride (p.1411·2).
Cerebrovascular disorders; intermittent claudication; maintenance of extracorporeal circulation; peripheral vascular disease; stroke prophylaxis; thromboembolic disorders.

Ticlidil *CTI, Israel.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis; thrombosis prophylaxis.

Ticlo *Schwarz, Pol.; Schwarz, Rus.; Greater Pharma, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Peripheral vascular disease; thromboembolic disorders.

Ticlobal *Baldacci, Braz.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Ticlobest *Otsira, India.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Ticlocard *Kocak, Turk.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Ticlodix *Vitoria, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Ticlodone *Sanofi Synthelabo, Austria; Gerolymatos, Gr.; Sigma-Tau, Ital.; Almirall, Spain.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Ticlogi *Ibirn, Ital.†.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Ticlomed *Leurquin, Fr.†.*
Ticlopidine hydrochloride (p.1411·2).
Intermittent claudication; maintenance of extracorporeal circulation; thrombosis prophylaxis.

Ticlon *Interbat, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis.

Ticlop *Zydus, India.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Ticlopat *BioSaude, Port.*
Ticlopidine hydrochloride (p.1411·2).
Intermittent claudication; maintenance of extracorporeal circulation; stroke prophylaxis; thromboembolism prophylaxis.

Ticlopid *Cipla, India.*
Ticlopidine hydrochloride (p.1411·2).

Ticlopin *Gentek, Venez.†.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Ticlopine *Sunward, Malaysia; Umeda, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Maintenance of extracorporeal circulation; thromboembolism prophylaxis.

Ticloproge *Proge, Ital.†.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ticocin *Cipla, India.*
Teicoplanin (p.344·3).
Gram-positive bacterial infections.

Ticoflex *Uno, Ital.†.*
Naproxen aminobutanol (p.93·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgias.

Ticolcin *Tecnofarma, Mex.*
Colchicine (p.556·1).
Gout; liver cirrhosis.

Ticon *Hauck, USA.*
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Ticopar *Julphar, UAE.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

TicoVac *Baxter, Denm.; Baxter, Fin.; Baxter, Fr.; Baxter, Ital.; Baxter, Norw.; Masta, UK.*
A tick-borne encephalitis vaccine (p.2241·1).
Separate preparations are available for adults and for children.
Formerly known as FSME-Immun in the *UK*.
Active immunisation.

Ticuring *Lapi, Indon.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Tidact
YSP, Malaysia; Yung Shin, Singapore.
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Yung Shin, Philipp.
Clindamycin hydrochloride (p.251·1) or clindamycin phosphate (p.251·2).
Bacterial infections.

Tiddy *Sriprasit, Thai.†.*
Multivitamin and mineral preparation with lysine (p.1922·1).

Tidigesic *Sun, India†.*
⊗ Buprenorphine (p.29·1).
Pain.

Tidomet *Torrent, Philipp.; Torrent, Rus.; Torrent, Singapore.*
Carbidopa (p.803·1); levodopa (p.804·3).
Parkinsonism.

Tiebinafin *Tiefenbacher, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Tielle
Note.This name is used for preparations of different composition.
Ethicon, Fr.
Polyurethane foam dressing (p.1611·1).
Ulcers; wounds.

Johnson & Johnson, Ger.†; Johnson & Johnson, Ital.; Johnson & Johnson Medical, UK.
Foamed hydrogel.
Skin ulcers; wounds.

Tienam *MSD, Belg.; MSD, Braz.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tienor *Farmaka, Ital.*
Clotiazepam (p.980·3).
Anxiety; insomnia.

Tierlite *Bros, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Tifell *Bucca, Spain†.*
Cineole (p.2282·3); cresol (p.1641·1); eugenol (p.2301·2); formaldehyde (p.1644·2).
Mouth infections.

Tifen *Andromaco, Chile†.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Tiffy
Note.This name is used for preparations of different composition.
Medochemie, Hong Kong.
Paracetamol (p.108·1).
Fever; pain.

TNP, Thai.†.
Syrup: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms; hay fever.

TNP, Thai.†.
Tablets: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms; hay fever.

Tiffy Dey *TNP, Thai.†.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; hay fever; upper respiratory-tract congestion.

Tiffy Fu *TNP, Thai.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Tiffyrub *TNP, Thai.†.*
Menthol (p.2340·1); camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3).
Cold symptoms; coughs; nasal congestion.

Tifinidat *Tiefenbacher, Neth.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder.

Tifistat *Tiefenbacher, Neth.†.*
Pravastatin sodium (p.1374·3).
Hyperlipidaemias; reduction of cardiovascular risk.

Tiflodipine *TAD, Port.*
Amlodipine maleate (p.1214·2).
Angina pectoris; hypertension.

Tifox *Chong Kun Dang, Ital.†.*
Cefoxitin sodium (p.230·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Tigal *Sanovel, Turk.*
Terbinafine (p.546·3).
Fungal infections of the skin and nails.

Tigan
Note.This name is used for preparations of different composition.
Monarch, USA; Roberts, USA.
Capsules; injection: Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Roberts, USA†.
Suppositories: Trimethobenzamide hydrochloride (p.592·2); benzocaine (p.1854·1).
Nausea and vomiting.

Tigason *Chugai, Jpn.*
Etretinate (p.1597·2).
Keratinisation disorders; oral lichen planus; psoriasis.

Tigel IRM *Mepro, Chile.*
Coal tar (p.1616·2).
Scalp disorders.

Tiger Balm
Note.This name is used for preparations of different composition.
Olvos, Gr.
Camphor (p.2273·2); cajuput oil (p.2271·2); cinnamon oil (p.2283·2); menthol (p.2340·1).
Topical analgesic.

SSL, UK.
Cajuput oil (p.2271·2); camphor (p.2273·2); clove oil (p.2285·1); menthol (p.2340·1).
Musculoskeletal pain.

Tiger Balm Red
Note.This name is used for preparations of different composition.
Haw Par, Austral.
Cajuput oil (p.2271·2); camphor (p.2273·2); cassia oil (p.2278·1); clove oil (p.2285·1); menthol (p.2340·1).
Muscular aches and pains.

Haw Par, Canad.
Camphor (p.2273·2); menthol (p.2340·1); cajuput oil (p.2271·2); cinnamon oil (p.2283·2); clove oil (p.2285·1); peppermint oil (p.1761·2).

Rafa, Israel.
Camphor (p.2273·2); menthol (p.2340·1); cajuput oil (p.2271·2); dementholised mint oil (p.2345·2); clove oil (p.2285·1).

Tiger Balm Rot *Tiger, Cz.†.*
Camphor (p.2273·2); menthol (p.2340·1); clove oil (p.2285·1); cajuput oil (p.2271·2); peppermint oil (p.1761·2); cinnamon oil (p.2283·2).
Musculoskeletal and joint pain; respiratory-tract disorders.

Tiger Balm Ultra *Haw Par, Canad.*
Camphor (p.2273·2); cajuput oil (p.2271·2); cinnamon oil (p.2283·2); clove oil (p.2285·1); peppermint oil (p.1761·2).

Tiger Balm White
Note.This name is used for preparations of different composition.
Haw Par, Austral.; Rafa, Israel.
Cajuput oil (p.2271·2); camphor (p.2273·2); clove oil (p.2285·1); menthol (p.2340·1); dementholised mint oil (p.2345·2).
Muscular aches and pains.

Haw Par, Canad.
Camphor (p.2273·2); menthol (p.2340·1); cajuput oil (p.2271·2); clove oil (p.2285·1); peppermint oil (p.1761·2).

Tiger Balsam Rot *Klosterfrau, Austria.*
Camphor (p.2273·2); menthol (p.2340·1); cajuput oil (p.2271·2); peppermint oil (p.1761·2); clove oil (p.2285·1); cinnamon oil (p.2283·2).
Muscle pain.

Tiger Liniment *Haw Par, Canad.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).

Tiger Ol *Tiger, Cz.†.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2); lavender oil (p.2331·2).
Musculoskeletal, joint, and soft-tissue pain.

Tiger Snake *Commonwealth Serum, Hong Kong.*
A tiger snake venom antisera (p.2238·2).
Snake bite.

Tiglio (Specie Composta) *Dynacren, Ital.†.*
Tilia (p.2402·2); sambucus (p.2383·1); meadowsweet (p.2338·1).
Cold symptoms; herbal tea.

Tigreat *Menarini, Fr.*
Frovatriptan (p.622·3).
Migraine.

Tigridol *Phytomedica, Fr.*
Camphor (p.2273·2); menthol (p.2340·1); clove oil (p.2285·1); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2); cinnamon oil (p.2283·2).
Pain.

Tikacillin *AstraZeneca, Swed.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Tikl *Monserrat, Arg.*
Ketoconazole (p.539·1).
Scalp disorders.

Tikleen *Ipca, India†; Ipca, Rus.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis.

Tiklid *Sanofi Synthelabo, Austria; Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Tiklyd *Sanofi Synthelabo, Ger.; Sanofi-Aventis, Port.*
Ticlopidine hydrochloride (p.1411·2).
Thrombosis prophylaxis.

Tikol *Eurodrug, Thai.†.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Tikosyn *Pfizer, USA.*
Dofetilide (p.1272·3).
Arrhythmias.

Tilad *Sanofi-Aventis, Spain.*
Nedocromil sodium (p.1127·3).
Asthma.

Tilade *Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.†; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Ger.; Sanofi-Aventis, Gr.; Aventis, Hong Kong†; Aventis, Hung.†; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, NZ; Aventis, Neth.; Sanofi-Aventis, Rus.; Aventis, Switz.†; Eczacibasi, Turk.; Sanofi-Aventis, UK; Monarch, USA†.*
Nedocromil sodium (p.1127·3).
Allergic conjunctivitis; allergic rhinitis; asthma; bronchitis; obstructive airways disease.

Tilalgin *Grunenthal, Neth.; Grunenthal, Port.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Tilarin *Aventis, Austria; Aventis, Cz.†; Aventis, Fin.†; Sanofi-Aventis, Ital.; Aventis, Switz.*
Nedocromil sodium (p.1127·3).
Allergic rhinitis.

Tilatil *Roche, Braz.*
Tenoxicam (p.128·2).
Musculoskeletal, joint, and peri-articular disorders.

Tilavist *Aventis, Austria; Aventis, Cz.†; Aventis, Denm.; Aventis, Fin.†; Sanofi-Aventis, Fr.; Aventis, Irl.†; Aventis, Israel; Sanofi-Aventis, Ital.; Aventis, Neth.; Aventis, Norw.; Sanofi-Aventis, Port.; Teofarma, Spain; Aventis, Swed.; Aventis, Switz.*
Nedocromil sodium (p.1127·3).
Allergic conjunctivitis.

Tilazem *Elea, Arg.; Pfizer, Chile; Pfizer, Mex.; Pfizer, S.Afr.; Pfizer, Venez.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension; reduction of ciclosporin nephrotoxicity following renal transplant.

Tilcin *Vida, Port.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Tilcitin *Roche, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Tilcotil *Roche, Austria; Roche, Belg.; Roche, Chile; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Hong Kong; Teva, Hung.; Roche, Indon.; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Port.; Roche, S.Afr.; Roche, Spain†; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, Venez.†.*
Tenoxicam (p.128·2).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Tildiem *Sanofi-Aventis, Belg.; Chemopharma, Chile; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Irl.; Sanofi-Aventis, Ital.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Philipp.; Sanofi Synthelabo, Switz.; Ulkar, Turk.; Sanofi Synthelabo, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; arrhythmias; hypertension; myocardial ischaemia.

Tildomet *Greenpharma, Braz.*
Methyldopa (p.1334·1).
Hypertension.

Tilekin *Kinder, Braz.*
Paracetamol (p.108·1).
Pain.

Tilene *Francia, Ital.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Tilexim *Caber, Ital.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Tilferan *Vocate, Gr.†.*
Etidronate disodium (p.1097·1).
Osteoporosis; Paget's disease of bone.

Tilflam *Dexa, Indon.*
Tenoxicam (p.128·2).
Gout; musculoskeletal and joint disorders.

Tili *ABZ, Ger.†.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tili Comp *1A, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilia Fe *Watson, USA.*
21 Tablets, norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
Triphasic oral contraceptive.

Tilicomp *Betapharm, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidalor *Hexal, Ger.†.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidin comp *Aliud, Ger.; Hexal, Ger.; Stada, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidin N *Sandoz, Ger.; Winthrop, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidin plus *Ratiopharm, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidin-saar *MIP, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilidon *Interbat, Indon.*
Domperidone (p.1726·2).
Gastrointestinal disorders.

Tilidura *Merck dura, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tiligetic *Azupharma, Ger.†.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilimerck *Merck dura, Ger.†.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilios *Microsules, Arg.*
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Tili-Puren *Alpharma-Isis, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tiliros *Labofarm, Pol.*
Ascorbic acid (p.1983·3); rose flower (p.2381·2); tilia (p.2402·2).
Cough; sore throat.

Tilium *Janssen-Cilag, Venez.*
Domperidone (p.1726·2).
Gastrointestinal motility disorders.

Tiliv *Ativus, Braz.*
Black currant (p.2267·1).

Tiliv L *Ativus, Braz.*
Borage oil (p.2267·3).

Tilker *Sanofi Synthelabo, Denm.; Sanofi Synthelabo, Norw.†; Sanofi-Aventis, Port.; Sanofi-Aventis, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Tilko *Kocak, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Till *Amnol, Ital.*
Triclosan (p.1665·2); alkylamidobetaine.
Personal hygiene.

Tilmat *Douglas, NZ.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; arrhythmias; hypertension; migraine; myocardial infarction.

Tilnalox *CT, Ger.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tilodene *Alphapharm, Austral.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Tilodrin *Meyer, Venez.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tiloetca Combi *Tillomed, UK.*
Etidronate disodium (p.1097·1); calcium carbonate (p.1714·1).
Osteoporosis.

Tilofyl *Tillomed, UK.*
⊗ Fentanyl (p.55·3).
Pain.

Tiloket *Tillomed, UK.*
Ketoprofen (p.73·1).
Formerly known as Ketil.
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders.

Tilolec *Tillomed, UK†.*
Levodopa (p.804·3); carbidopa (p.803·1).
These ingredients can be described by the British Approved Name Co-careldopa.
Parkinsonism.

Tilomix *Nufarindo, Indon.*
Dextromethorphan hydrobromide (p.1555·2); noscapine (p.1566·2); chlorphenamine maleate (p.571·3).
Cough or pain due to allergy.

Tilonax *Cifarma, Braz.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Tilopin *Unison, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Peripheral vascular disease; thrombosis prophylaxis.

Tiloptic *MSD, Israel.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Tiloryth *Tillomed, UK.*
Erythromycin (p.269·2).
Bacterial infections.

Tiloxican *Hexal, Braz.†.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tilsan *Otto, Indon.*
Maprotiline hydrochloride (p.407·2).
Depression.

Tilstigmin *Tablets, India.*
Neostigmine bromide (p.631·3) or neostigmine metilsulfate (p.631·3).
Myasthenia gravis.

Tiltis *Euroderm, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Tilur *Drossapharm, Switz.*
Acemetacin (p.15·1).
Musculoskeletal, joint, and peri-articular disorders; superficial thrombophlebitis.

Timab *LKM, Arg.*
Diazepam (p.986·3).
Anxiety.

Timabak *Agepha, Austria; Thea, Belg.; Allergan, Braz.; Pfizer, Chile; Thea, Fr.; Pharmex (Φαρμεξ), Gr.; Thea, Hong Kong; Thea, Philipp.; Thea, Port.; Pfizer, Singapore; Thea, Spain.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timacar *MSD, Denm.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; glaucoma; hypertension; migraine; myocardial infarction.

Timacor *Substipharm, Fr.*
⊗ Timolol maleate (p.1412·3).
Angina pectoris; hypertension; myocardial infarction.

Timact *Fahrenheit, Indon.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Tim-Ak *Dioptic, Canad.†.*
⊗ Timolol maleate (p.1412·3).
Raised intra-ocular pressure.

Timarol *Laboratorios Chile, Chile.*
Tramadol hydrochloride (p.130·3).
Pain.

Timasen *Asta Medica, Braz.†.*
Tramadol hydrochloride (p.130·3).
Pain.

Timax *Agepha, Austria.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timazol *Sriprasit, Thai.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Time Action B Complex with C *Hall, Canad.*
Vitamin B substances; vitamin C (p.1922·1).

Time Release Nutrition Mega B + C Complex *Swiss Bio, Malaysia†.*
Vitamin B substances (p.1975·1); vitamin C (p.1983·3).
Dietary supplement.

Time Released Balanced B *Lee-Adams, Canad.*
Vitamin B substances (p.1922·1).

Time-Cee
Note. This name is used for preparations of different composition.
Danlex, Philipp.
Syrup: Ascorbic acid (p.1983·3); vitamin B substances; chlorella growth factor (p.1922·1).
Vitamin C deficiency.

Danlex, Philipp.
Tablets: Ascorbic acid (p.1983·3); calcium phosphate dibasic (p.1676·1).
Vitamin C deficiency.

Timecef *Aventis, Austria; Lepetit, Ital.; Aventis, NZ.*
Cefodizime sodium (p.226·1).
Lidocaine hydrochloride (p.1862·3) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Timed *Bausch & Lomb, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timed 0.5 *Bausch & Lomb, Arg.*
⊗ Timolol maleate (p.1412·3); hyaluronic acid (p.2320·1).
Glaucoma.

Timed Action Balanced B *Hall, Canad.*
Vitamin B substances (p.1922·1).

Timed D *Bausch & Lomb, Arg.*
⊗ Timolol maleate (p.1412·3); dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension.

Timed Release Ester C *General Nutrition, Canad.*
Calcium ascorbate (p.1984·1).

Timed Release Mega Men *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Timed Release Swiss One *Swiss Herbal, Canad.†.*
Range of multivitamin and mineral preparations (p.1922·1).

Timed Release Ultra Mega *General Nutrition, Canad.*
Range of multivitamin and mineral preparations (p.1922·1).

Timed Release Womens Ultra Mega *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Timenten *SmithKline Beecham, Switz.†.*
Ticarcillin sodium (p.352·2); potassium clavulanate (p.250·2).
Bacterial infections.

Timentin *GSK, Austral.; GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Cz.; GSK, Gr.; GSK, Hong Kong; GSK, India; SmithKline Beecham, Irl.†; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; GSK, Rus.; GSK, UK; SmithKline Beecham, USA.*
Ticarcillin sodium (p.352·2); potassium clavulanate (p.250·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Timezol *Penn, Arg.; Richmond, Arg.*
Omeprazole (p.1753·1).
Peptic ulcer.

Timi *Sriprasit, Thai.*
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3).
Fungal skin and nail infections with inflammation.

Timicolid *Pfizer Consumer, Ital.†.*
Dithranol (p.1595·2).
Psoriasis.

Timicon *MSD, Ital.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma; ocular hypertension.

Timisol *Ecosol, Switz.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timivudin *Landsteiner, Mex.*
Zidovudine (p.913·3).
HIV infection.

Timo (Specie Composta) *Dynacren, Ital.†.*
Thyme (p.2401·1); fennel (p.2302·3); ribwort plantain (p.2379·1); liquorice (p.1740·3).
Coughs; herbal tea.

Timo-COMOD *Croma, Austria; Ursapharm, Cz.; Ioltech, Fr.; Ursapharm, Ger.; Ursapharm, Malaysia†; Ursapharm, Neth.; Ursapharm, Pol.; Ursapharm, Switz.; Biem, Turk.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timodine *Reckitt Benckiser, Irl.; Reckitt Benckiser, UK.*
⊗ Nystatin (p.543·2); hydrocortisone (p.1535·2).
Infected skin disorders.

Timodose *Pharmanel, Gr.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Timodrop *Biolab, Thai.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

TimoEDO *Mann, Ger.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoferol *Elerte, Fr.*
Ferrous sulfate (p.1939·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Timoftal *Agepha, Austria; Sanovel, Turk.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoftol *MSD, Spain.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timogal *Galena, Cz.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timogel *Thea, Port.; Thea, Spain.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoglau *Edol, Port.*
⊗ Timolol maleate (p.1412·3).
Ocular hypertension.

Timoglau Plus *Edol, Port.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Glaucoma.

Timoglobulina *Genzyme, Arg.; Sanofi Pasteur, Chile; Genzyme, Port.; Genzyme, Spain.*
An antithymocyte immunoglobulin (p.1817·3).
Aplastic anaemia; graft-versus-host disease; transplant rejection.

Timohexal *Hexal, Austria; Hexal, Cz.; Hexal, Ger.; Hexal, Pol.; Hexal, Rus.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timolabak *Thea, Ital.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timolast *Alcon, Malaysia.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timolen *Davi, Port.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoler *Lersan, Arg.*
⊗ Timolol maleate (p.1412·3).
Ocular hypertension.

Timolide *Merck Frosst, Canad.†; Merck, USA.*
⊗ Timolol maleate (p.1412·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Timolo *Bell, India.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timolpres *Vannier, Arg.*
⊗ Timolol (p.1413·1).
Glaucoma.

Timolux *Tubilux, Ital.; AFT, NZ.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timomann *Mann, Ger.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timonil *Desitin, Cz.; Desitin, Ger.; Desitin, Hung.; Desitin, Israel; Desitin, Pol.; Desitin, Switz.; CP Pharmaceuticals, UK†.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; depression; diabetes insipidus; diabetic neuropathy; epilepsy; glossopharyngeal neuralgia; mania; multiple sclerosis; trigeminal neuralgia.

Timo-Optal *Olan-Kemed, Thai.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timop *Laboratorios Chile, Chile.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Tim-Ophtal *Agepha, Austria; Winzer, Ger.; Sanbe, Indon.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timo-POS *Ursapharm, Belg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Timoptic *MSD, Arg.; MSD, Austria; Merck Frosst, Canad.; MSD, Pol.; MSD, Switz.; MSD, Turk.; Merck, USA.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoptol *MSD, Austral.; MSD, Belg.; MSD, Braz.; Zentiva, Cz.; MSD-Chibret, Fr.; MSD, Hong Kong; MSD, Irl.; MSD, Ital.; Santen, Jpn; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Philipp.; Pharmalink, Philipp.; Chibret, Port.; MSD, S.Afr.; MSD, Singapore; MSD, Thai.; MSD, UK; MSD, Venez.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timoptolgel *MSD, Belg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Timoptol-XE *MSD, Austral.; MSD, Chile.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosan *Santen, Denm.; Santen, Fin.; Santen, Norw.; Santen, Swed.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosil *Silom, Thai.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosine *Chibret, Ger.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosoft *Scharper, Ital.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosol *MSD, Turk.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timosopt *MSD, Port.*
⊗ Timolol maleate (p.1412·3); dorzolamide hydrochloride (p.1880·2).
Glaucoma.

Timo-Stulln *Stulln, Ger.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timox *Desitin, Ger.*
Oxcarbazepine (p.490·3).
Epilepsy.

Timozzard *Pizzard, Mex.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Timpacil *Diba, Mex.*
⊗ Neomycin (p.305·1); dexamethasone (p.1526·1).
Infected ear disorders.

Timpanol *Hexal, Braz.†.*
Procaine hydrochloride (p.1869·1); phenol (p.1656·1).
Ear infections; earache.

Timpilo *MSD, Arg.†; MSD, Austral.; MSD, Austria; Merck Frosst, Canad.†; MSD, Cz.†; MSD, Denm.†; MSD, Fin.†; MSD-Chibret, Fr.†; Chibret, Ger.†; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Israel; MSD, Malaysia†; MSD, NZ; MSD, Norw.†; MSD, Singapore†; MSD, Swed.†; MSD, Switz.†.*
⊗ Timolol maleate (p.1412·3); pilocarpine hydrochloride (p.1884·3).
Aphakia; glaucoma; ocular hypertension.

Timpron *Berk, UK†.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Timsopt *MSD, Austria.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma.

Tinacef *Richmond, Arg.*
Ceftazidime (p.234·1).
Bacterial infections.

Tinactin *Schering-Plough, Canad.; Schering-Plough, Philipp.; Schering-Plough, USA.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tinaderm *Key, Arg.†; Schering-Plough, Austral.; Schering-Plough, Chile; Fulford, India; Schering-Plough, Irl.†; Schering-Plough, Ital.†; Schering-Plough, Malaysia†; Schering-Plough, Mex.; Schering-Plough, NZ†; Schering-Plough, S.Afr.; Schering-Plough, Singapore†; Schering-Plough, Spain; Schering-Plough, UK; Schering-Plough, Venez.*
Tolnaftate (p.548·3).
Fungal skin, hair, and nail infections.

Tinaderm Extra *Schering-Plough, Austral.*
Clotrimazole (p.530·1).
Fungal skin infections.

Tinaderme *Plough, Port.*
Tolnaftate (p.548·3).
Fungal skin and nail infections.

Tinaderm-M *Schering-Plough, Irl.; Schering-Plough, UK.*
Tolnaftate (p.548·3); nystatin (p.543·2).
Fungal skin and nail infections.

Tinalox *Sandoz, Belg.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Tinasin *Giempi, Venez.*
Simvastatin (p.1390·2).
Cerebral ischaemia; hypercholesterolaemia; ischaemic heart disease.

Tinasol *Fischer, Israel.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tinasolve *Rye, Singapore†.*
Melaleuca oil (p.2338·2); triclosan (p.1665·2).
Fungal skin infections.

Tinatox *Riemser, Ger.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tinax *Eurofarma, Braz.*
⊗ Epoetin (p.1061·1).
Anaemias.

Tinazole *General Drugs, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

TinBen *Ferndale, USA.*
Barrier preparation.

TinCoBen *Ferndale, USA.*
Barrier preparation.

Tindamax *Presutti, USA.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Tindol *Ranbaxy, Malaysia.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Tineafax *Douglas, Austral.*
Tolnaftate (p.548·3).
Tinea pedis.

Tineafine *Spirig, Switz.*
Terbinafine hydrochloride (p.546·3).
Fungal, skin, scalp, and nail infections.

Tineal *Reddy, Hung.*
Terbinafine hydrochloride (p.546·3).
Fungal infections.

Tinerol *Roche, Spain†.*
Ornidazole (p.843·1).
Amoebiasis; anaerobic bacterial infections; giardiasis.

Ting *Heritage Consumer, USA.*
Miconazole nitrate (p.541·3).
Formerly contained tolnaftate.
Fungal skin infections.

Tingosan *Bittner, Austria.*
Homoeopathic preparation.

Tini *Codal Synto, Thai.†.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Tiniasil *Loeffler, Mex.*
Ketoconazole (p.539·1).
Vulvovaginal candidiasis.

Tiniazol *Liferpal, Mex.*
Ketoconazole (p.539·1).
Fungal skin, nail, and vaginal infections.

Tiniba *Zydus, India; Cadila, Rus.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Tinidafyl *Jagson, India.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Tinidafyl Plus *Jagson, India.*
Tinidazole (p.848·3); diloxanide furoate (p.832·2); dimeticone (p.2032·1).
Amoebiasis.

Tinidol *Ipca, India†.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Tinifas *Cipla, India.*
Tinidazole (p.848·3).
Fungal infections.

Tinkair *Italchimici, Cz.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; nasal polyps.

T-Inmun *Mediderm, Chile.*
Tacrolimus (p.1843·1).
Atopic eczema.

Tinnic *Nicholas, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Tinnitin *Sanova, Austria.*
Caroverine hydrochloride (p.2277·3).
Smooth muscle spasm; tinnitus.

Tinok AF *Rekah, Israel.*
Sodium chloride (p.1686·1).
Nasal congestion.

Tinoral *Uniao Quimica, Braz.*
Tinidazole (p.848·3).
Fungal infections.

Tinox *Gynopharm, Chile; Vivax Gynopharm, Venez.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Tinoxal *Loeffler, Mex.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tinsenol *Medipharm, Chile†.*
Thioridazine (p.1031·2).
Attention-deficit disorder; behaviour disorders; sleep disorders.

Tinset *Janssen-Cilag, Arg.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.†; Janssen-Cilag, Chile; Janssen-Cilag, Fr.; Janssen-Cilag, Gr.; Cilag, Hong Kong†; Janssen-Cilag, Indon.; Formenti, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Neth.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.*
Oxatomide (p.587·1).
Allergic conjunctivitis; allergic rhinitis; asthma; dermatitis; hypersensitivity reactions; pruritus; urticaria.

Tinsole *Erfar, Gr.*
Povidone-iodine (p.1659·2).

Tintura Benjui *Orion, Fin.†.*
Camphor (p.2273·2); menthol (p.2340·1).
Respiratory-tract congestion.

Tintus *Orion, Fin.*
Guaifenesin (p.1561·3).
Coughs.

Tinver *Pilkington Barnes-Hind, USA.*
Sodium thiosulfate (p.1466·1); salicylic acid (p.1612·2); isopropyl alcohol (p.1650·3).
Pityriasis versicolor.

Tinvista *Cadila, India.*
Tinidazole (p.848·3).
Protozoal infections.

Tinvista-CF *Cadila, India.*
Tinidazole (p.848·3); ciprofloxacin (p.243·3).
Bacterial infections; protozoal infections.

Tinvista-NF *Cadila, India.*
Tinidazole (p.848·3); norfloxacin (p.309·2).
Bacterial infections; protozoal infections.

Tiobarbital *Braun, Spain.*
Thiopental sodium (p.1795·2).
Epilepsy; general anaesthesia.

Tiobec *Laborest, Ital.*
Thioctic acid (p.2400·2); vitamins (p.1922·1).
Neuropathies; nutritional supplement.

Tiobec Crema *Laborest, Ital.*
Thioctic acid (p.2400·2).
Premature skin ageing.

Tiocalmina *Polifarma, Ital.*
Sulfogaiacol (p.1573·2); dropropizine (p.1557·3).
Coughs.

Tiocan *Toprak, Turk.*
Tioconazole (p.548·2).
Fungal skin and nail infections.

Tiocell *Adilna, Turk.*
Tioconazole (p.548·2).
Fungal skin and nail infections.

Tiochax *Plusandex, Venez.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Tioconax *Delta, Braz.*
Tioconazole (p.548·2).
Fungal infections.

Tiocosol *OFF, Ital.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Catarrh; coughs.

Tioctan *Purissimus, Arg.; Rothpharma, Austria; Fujisawa, Jpn†.*
Thioctic acid (p.2400·2).
Diabetic neuropathy; subacute necrotising encephalomyelopathy; thioctic acid supplement; vestibular deafness.

Tioctan-S *Leiras, Fin.†.*
Vitamin B substances; ascorbic acid; dehydrocholic acid (p.1922·1).
Vitamin B deficiency.

Tiof *Saval, Chile; Columbia, Mex.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Tiof Plus *Saval, Chile.*
⊗ Dorzolamide hydrochloride (p.1880·2); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Tiofen *Sanovel, Turk.*
Thiamphenicol (p.351·1).
Bacterial infections.

Tiofeniclin *Sanofi Synthelabo, Mex.*
Thiamphenicol (p.351·1).
Bacterial infections.

Tiofort *Amnol, Ital.*
Thioctic acid (p.2400·2); linoleic acid (p.2308·2); asparagine (p.1929·3); vitamins; minerals.
Nutritional supplement.

Tioguaialina *Montefarmaco, Ital.*
Sulfogaiacol (p.1573·2).
Catarrh; coughs.

Tiomicol *Panalab, Arg.*
Tioconazole (p.548·2).
Fungal skin and nail infections.

Tionamid *Kocak, Turk.*
Protionamide (p.320·1).
Tuberculosis.

Tionamil *Ideco, Ital.†.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); terpin hydrate (p.1573·3).
Coughs.

Tionazen *Cazi, Braz.*
Tioconazole (p.548·2).
Fungal infections.

Tioner *Gebro, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Tiorfan *Bago, Braz.; Bioprojet, Fr.; Trommsdorff, Ger.; Ferrer, Port.; Ferrer, Spain.*
Racecadotril (p.1765·2).
Diarrhoea.

Tiorilene *Difass, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Tiosalis *Teva Tuteur, Arg.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Tioside *Caber, Ital.*
Thiocolchicoside (p.1898·2).
Neuromuscular pain; parkinsonism; spasticity.

Tiotau *Damor, Ital.†.*
Taurosteine.
Respiratory-tract congestion.

Tiotil *Abigo, Swed.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Tiova *Cipla, India.*
Tiotropium bromide (p.1148·3).
Obstructive airways disease.

Tiovalone *Juste, Spain†.*
⊗ Tixocortol pivalate (p.1544·2).
Nasal polyps; rhinitis.

Tioxad *Fahrenheit, Indon.*
Pentoxifylline (p.1367·2).
Intermittent claudication.

Tioxal *Solfran, Mex.†.*
Vitamin B ; vitamin B (p.1922·1).

Tipac *Mintlab, Chile.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Tiparol *AstraZeneca, Swed.*
Tramadol hydrochloride (p.130·3).
Pain.

Tiperal *Clonmel, Irl.†.*
⊗ Propranolol hydrochloride (p.1380·3).
Angina pectoris; anxiety; arrhythmias; essential tremor; hypertension; migraine; myocardial infarction; obstructive cardiomyopathy; phaeochromocytoma.

Tiperin *Sanitas, Chile.*
Amitriptyline (p.376·1); chlordiazepoxide (p.968·1).
Depression associated with anxiety.

Tipidin *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ticlopidine hydrochloride (p.1411·2).
Stroke prophylaxis.

Tipidine *Seven Stars, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Diabetic retinopathy; intermittent claudication; thromboembolism prophylaxis; unstable angina pectoris.

Tipkin *TP, Thai.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Tiplac
Note.This name is used for preparations of different composition.
Euro-Labor, Port.†; Grunenthal, Port.†.
Lysine aspirin (p.79·1).
Thrombosis prophylaxis.

Roemmers, Venez.
Haloperidol (p.1000·2) or haloperidol decanoate (p.1000·2).
Behaviour disorders; psychoses.

Tipo II *Gerolymatos, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Tipodex *Ern, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tipotaf *Vitamed, Israel.*
Sodium chloride (p.1686·1).
Eye wash; nasal congestion.

Tipuric *Clonmel, Irl.*
Allopurinol (p.552·2).
Gout; prophylaxis of uric acid and calcium oxalate stones.

Tiq'Aouta *Omega, Fr.*
Diethyltoluamide (p.2041·1); dimethyl phthalate (p.2041·3); enoxolone (p.50·1).
Insect repellent.

Tirabicin *Kleva, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Tiracaspa *Hexal, Braz.†.*
Cetrimonium bromide (p.1635·1).
Seborrhoeic dermatitis.

Tiracrin *Geymonat, Ital.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Tiradine *British Dispensary, Thai.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders.

Tiralcol *Sidepal, Braz.†.*
Homoeopathic preparation.

Tiratosse *DM, Braz.†.*
Guaifenesin (p.1561·3); oxomemazine (p.587·1); paracetamol (p.108·1); sodium benzoate (p.1630·2).
Coughs.

Tirdicef *Bernofarm, Indon.*
Cefotaxime (p.229·1).
Bacterial infections.

Tirfen *Megat, Venez.†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Tirgon *McNeil, Ger.*
Bisacodyl (p.1710·1).
Constipation.

Tiriz *Lapi, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Tirizin *Lannacher, Austria.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Tirlor *Sandoz, Gr.; Sandoz, Malaysia; Sandoz, Singapore; Sandoz, Thai.; Sandoz, Venez.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; asthma; hypersensitivity reactions.

Tirmaclo *Mersifarma, Indon.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Tirocal *Cryopharma, Mex.*
Calcitriol (p.1986·2).
Hypocalcaemia; hypoparathyroidism; osteoporosis; renal osteodystrophy; rickets.

Tirocular *Angelini, Ital.; Lepori, Port.*
Acetylcysteine (p.1548·2).
Corneal disorders; dry eyes.

Tirodril *Estedi, Spain.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Tiroide Amsa *Amsa, Ital.*
Levothyroxine sodium (p.2171·2); liothyronine sodium (p.2174·1).
Hypothyroidism.

Tiroide Vister *Teofarma, Ital.*
Thyroglobulin (p.2177·1).
Hypothyroidism.

Tiroidin *Neo Quimica, Braz.*
Levothyroxine sodium (p.2171·2).

Tiroidine *Rudefsa, Mex.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Tiroler Steinol *Tiroler, Austria.*
Yellow soft paraffin (p.2031·3); yellow beeswax (p.2028·1); hydrous wool fat (p.2033·3); white soft paraffin (p.2031·2).
Skin disorders.

Tiromel *Abdi, Turk.*
Liothyronine sodium (p.2174·1).
Hypothyroidism.

Tiropa *Rotta, Port.*
Ticlopidine hydrochloride (p.1411·2).

Tirosint *Amsa, Ital.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Tirotax *Sandoz, Austria; Sandoz, Hung.; Sandoz, Mex.; Sandoz, Neth.; Sandoz, Pol.; Sandoz, Venez.*
Cefotaxime sodium (p.228·1).
Lidocaine (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Tirotrin *Globo, Braz.†.*
Neomycin (p.305·1); tyrothricin (p.358·2).
Mouth and throat disorders.

Tirovarina *Biol, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders.

Tirovel *Duncan, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Tirozol 5/10 *Merck, Chile†.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Tirs *Skills, Ital.*
Benzalkonium chloride (p.1629·1); hypromellose (p.2144·2).
Dry eyes; eye disinfection.

Tisacef *Metiska, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Tisacid *ICN, Hung.*
Hydrotalcite (p.1733·3).
Gastritis; gastro-oesophageal reflux; gastrointestinal hyperacidity; heartburn; peptic ulcer.

Tisadyne *ICN, Cz.†.*
Magnesium aluminium subcarbonate hexahydrate.
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer.

Tisamid *Orion, Cz.†; Orion, Fin.*
Pyrazinamide (p.320·2).
Tuberculosis.

Tisana Kelemata
Note.This name is used for preparations of different composition.
Kelemata, Ital.
Granules; tablets: Senna (p.1769·2).
Constipation.

Kelemata, Ital.
Tea; teabags: Senna (p.1769·2); couch-grass (p.2288·2); guaiacum; hyssop (p.2323·3); parietaria; peppermint leaf (p.1761·2); sarsaparilla (p.2383·3); aniseed (p.2258·2); melissa (p.2339·3).
Constipation.

Tisane antirhumatismale *Sidroga, Switz.*
Spearmint (p.2391·3); passion flower (p.2363·2); salix (p.121·3).
Rheumatism.

Tisane calmante pour les enfants *Sidroga, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3); orange flowers (p.2357·1); passion flower (p.2363·2).
Nervous excitement; sleep disorders.

Tisane contre les refroidissements *Sidroga, Switz.*
Rose fruit (p.2381·2); sambucus (p.2383·1); chamomile (p.2279·3); tilia (p.2402·2); wild thyme (p.2415·3).
Cold symptoms.

Tisane Diuretique *Sidroga, Switz.*
Birch leaf (p.2266·3); bean pods; urtica (p.2409·3); equisetum (p.2299·3).
Urinary-tract disorders.

Tisane favorisant l'allaitement *Sidroga, Switz.*
Aniseed (p.2258·2); fennel (p.2302·3); caraway (p.2276·3); melissa (p.2339·3).
Lactation stimulant.

Tisane hepatique et biliaire *Sidroga, Switz.*
Cynara (p.2291·2); boldo (p.2267·2); taraxacum (p.2395·1); milk thistle (p.1452·1); peppermint leaf (p.1761·2); achillea (p.2245·2).
Digestive system disorders.

Tisane Hepatique de Hoerdt *Iderne, Fr.*
Absinthium (p.2244·1); achillea (p.2245·2); agrimony (p.2249·2); boldo (p.2267·2); centaury (p.2279·1); couch-grass (p.2288·2); menyanthes (p.2340·3); sage (p.2382·3).
Liver and biliary-tract disorders.

Tisane laxative *Sidroga, Switz.*
Fennel (p.2302·3); senna (p.1769·2); star anise (p.2392·1); liquorice (p.1740·3).
Constipation.

Tisane laxative H nouvelle formulation *Hanseler, Switz.*
Senna (p.1769·2).
Constipation.

Tisane pectorale et antitussive *Sidroga, Switz.*
Sage (p.2382·3); althaea (p.2253·3); fennel (p.2302·3); iceland moss (p.2324·1); red-poppy petal (p.1472·3); plantain (p.2369·3); star anise (p.2392·1); liquorice (p.1740·3); thyme (p.2401·1).
Coughs; respiratory-tract congestion.

Tisane pectorale pour les enfants *Sidroga, Switz.*
Althaea (p.2253·3); cowslip flower (p.2372·2); plantain (p.2369·3); liquorice (p.1740·3); thyme (p.2401·1).
Cold symptoms.

Tisane pour le coeur et la circulation *Sidroga, Switz.*
Birch leaf (p.2266·3); motherwort (p.2347·3); spearmint (p.2391·3); melissa (p.2339·3); crataegus (p.2289·1).
Cardiac and circulatory disorders.

Tisane pour l'estomac *Sidroga, Switz.*
Calamus (p.2271·3); chamomile (p.2279·3); spearmint (p.2391·3); melissa (p.2339·3); achillea (p.2245·2); centaury (p.2279·1).
Digestive-system disorders.

Tisane pour nourissons et enfants *Sidroga, Switz.*
Fennel (p.2302·3); chamomile (p.2279·3); tilia (p.2402·2); melissa (p.2339·3); peppermint leaf (p.1761·2); vervain (p.2413·3).
Flatulence.

Tisane pour les problemes de prostate *Sidroga, Switz.*
Urtica (p.2409·3); peppermint leaf (p.1761·2); ginger (p.1732·3); clove (p.2284·3); cinnamon (p.2283·1).
Prostate disorders.

Tisane pour les reins et la vessie *Sidroga, Switz.*
Bearberry (p.2263·3); birch leaf (p.2266·3); Java tea (p.2328·2); lovage root (p.2335·1); peppermint leaf (p.1761·2); juniper (p.2328·2).
Urinary-tract disorders.

Tisane pour le sommeil et les nerfs *Sidroga, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2); spearmint (p.2391·3); melissa (p.2339·3); orange flower (p.2357·1).
Nervous excitation; sleep disorders.

Tisane Provencale No 1 *Tisane Provencale, Switz.*
Senna (p.1769·2); althaea (p.2253·3).
Constipation.

Tisane relaxante N *Sidroga, Switz.†.*
Valerian (p.2410·1); lavender flower (p.2331·1); melissa (p.2339·3); passion flower (p.2363·2).
Nervous tension.

Tisasen
ICN, Cz.†.
Senna (p.1769·2).
Constipation.

Valeant, Hung.
Sennosides A and B (p.1769·3).
Bowel evacuation; constipation.

Tisept *Seton, Israel; Medlock Medical, UK.*
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Disinfection of burns and wounds; skin disinfection.

Tisercin
Egis, Cz.
Levomepromazine hydrochloride (p.1002·3) or levomepromazine maleate (p.1003·1).
Anxiety; depression; hiccups; insomnia; pain; premedication; psychoses; vomiting.

EGIS, Hung.
Levomepromazine maleate (p.1003·1).
Psychoses.

Egis, Pol.; Egis, Rus.
Levomepromazine (p.1002·3).
Anxiety disorders; epilepsy; general anaesthesia; insomnia; mixed anxiety depressive states; obsessive-compulsive disorder; pain; psychoses.

Tisit *Pfeiffer, USA.*
Pyrethrins (p.2049·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Tismafam *Metiska, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Tismalin *Metiska, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Tismamisin *Metiska, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Tismazol *Metiska, Indon.*
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Tisobrif *Chiesi, Spain.*
Isoniazid (p.288·1); rifampicin (p.325·3).
Pyridoxine hydrochloride (p.1978·2) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Tisogen *Bioprofarma, Arg.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer; small-cell lung cancer.

Tison
Note.This name is used for preparations of different composition.
Landson, Indon.
⊗ Methylprednisolone (p.1538·1).
Oral corticosteroid.

Veropharm, Rus.
Thioridazine (p.1031·2).
Agitation; alcohol withdrawal syndrome; behaviour disorders; bipolar disorder; depression; pruritus; psychoses; tics.

Tisorek *Microsules Bernabo, Arg.†.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Tispol Ibu-DD *McNeil, Ger.*
Ibuprofen lysine (p.64·2).
Fever; pain.

Tisseel
Baxter, Canad.; Baxter, Hong Kong; Immuno, Israel; Baxter, UK.
1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); 1 vial, aprotinin (p.1055·1); 2 vials, thrombin (p.1080·1); 1 vial, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Dural sealing; haemorrhage; wounds.

Adcock Ingram Critical Care, S.Afr.
Clottable protein (fibrinogen) (p.1080·1).
Haemostatic; wounds.

Tisseel Duo *Baxter, Austral.*
1 syringe, aprotinin (p.1055·1); fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); 1 syringe, calcium chloride (p.1675·2); thrombin (p.1080·1);
On mixing this forms a fibrin glue (p.1069·3).
Adjunct in colostomy closure; haemostasis during surgery.

Tisseel Duo Quick
Baxter, Denm.
1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); aprotinin (p.1055·1); factor XIII (p.1069·2); plasminogen (p.1373·2); 1 vial, thrombin (p.1080·1); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Baxter, Fin.
⊗ 1 Vial, plasma protein (p.1076·2); fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); aprotinin (p.1055·1); 1 vial, thrombin (p.1080·1); calcium chloride (p.1675·2)
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Swed.
⊗ 1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); aprotinin (p.1055·1); albumin (p.1052·1); 1 vial, thrombin (p.1080·1); plasma protein (p.1076·2); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Tisseel VH *Eczacibasi-Baxter, Turk.*
Fibrinogen (p.1070·1); aprotinin (p.1055·1); thrombin (p.1080·1); calcium chloride (p.1675·2).
Haemorrhage.

Tissucol
Baxter Immuno, Arg.
Fibrinogen (p.1070·1); factor XIII (p.1069·2); aprotinin (p.1055·1); thrombin (p.1080·1); calcium chloride (p.1675·2)
On mixing this forms a fibrin glue (p.1069·3).

Baxter, Austria; Baxter, Cz.; Baxter, Fr.; Baxter, Mex.†.
1 Ampoule, fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); 1 ampoule, aprotinin (p.1055·1); 2 ampoules, thrombin (p.1080·1); 1 ampoule, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Immuno, Braz.†.
1 Ampoule, fibrinogen (p.1070·1); 1 ampoule, aprotinin (p.1055·1); 2 ampoules, thrombin (p.1080·1); 1 ampoule, calcium chloride (p.1675·2)
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Ital.
⊗ Plasma protein fraction (p.1076·2); aprotinin (p.1055·1); thrombin (p.1080·1); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Neth.
1 Vial, aprotinin (p.1055·1); 2 vials, calcium chloride (p.1675·2); thrombin (p.1080·1); 1 vial, fibrinogen (p.1070·1); factor XIII (p.1069·2); fibronectin (p.2304·1); 1 vial, calcium chloride;
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Switz.
1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); 1 vial, aprotinin (p.1055·1); 2 vials, thrombin (p.1080·1); 1 vial, calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Tissucol Duo
Baxter, Belg.
1 Syringe, aprotinin (p.1055·1); factor XIII (p.1069·2); fibrinogen (p.1070·1); fibronectin (p.2304·1); plasminogen (p.1373·2); 1 syringe, calcium chloride (p.1675·2); thrombin (p.1080·1);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Neth.
1 Vial, aprotinin (p.1055·1); fibrinogen (p.1070·1); factor XIII (p.1069·2); fibronectin (p.2304·1); 1 vial, calcium chloride (p.1675·2); thrombin (p.1080·1);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Port.
1 Vial, aprotinin (p.1055·1); factor XIII (p.1069·2); fibrinogen (p.1070·1); 1 vial, calcium chloride (p.1675·2); thrombin (p.1080·1);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Baxter, Spain.
1 Vial, fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); aprotinin (p.1055·1); 1 vial, thrombin (p.1080·1); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage.

Tissucol Duo Quick *Baxter Immuno, Arg.†; Baxter, Austria.*
1 Syringe, coagulable protein; fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); aprotinin (p.1055·1); 1 syringe, thrombin (p.1080·1); calcium chloride (p.1675·2)
On mixing this forms a fibrin glue (p.1069·3).
Wounds.

Tissucol Duo S *Baxter BioScience, Ger.; Baxter, Switz.*
⊗ 1 ampoule: plasma protein fraction (p.1076·2); fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); aprotinin (p.1055·1); 1 ampoule: thrombin (p.1080·1); calcium chloride (p.1675·2);
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

Tissucol-Kit *Baxter BioScience, Ger.; Baxter, Hung.*
⊗ 1 Ampoule: plasma protein fraction (p.1076·2); fibrinogen (p.1070·1); fibronectin (p.2304·1); factor XIII (p.1069·2); plasminogen (p.1373·2); 1 ampoule: aprotinin (p.1055·1); 2 ampoules: thrombin (p.1080·1); 1 ampoule: calcium chloride (p.1675·2)
On mixing this forms a fibrin glue (p.1069·3).
Haemorrhage; wounds.

TissuCone *Baxter BioScience, Ger.*
Collagen (p.2286·1).
Haemorrhage.

TissuFleece *Baxter BioScience, Ger.*
Collagen (p.2286·1).
Haemorrhage.

TissuFoil *Baxter BioScience, Ger.*
Collagen (p.2286·1).
Haemorrhage.

Tissulest *Liferpal, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction; hypercholesterolaemia.

Tisuderma *Cinfa, Spain.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Skin infections with inflammation.

Tis-U-Sol *Baxter, USA.*
Electrolytes (p.1667·1).
Irrigation solution.

Titan *Barnes Hind, Arg.; Pilkington Barnes-Hind, USA.*
Cleansing solution for hard contact lenses (p.1622·2).

Titanoral *McNeil, Fr.*
Diosmin (p.2304·2).
Capillary fragility; haemorrhoids; venous insufficiency.

Titanorein *McNeil, Spain.*
Carrageenan (p.2142·3); titanium dioxide (p.1617·3); lidocaine (p.1862·3).
Haemorrhoids.

Titanoreine
Note.This name is used for preparations of different composition.
McNeil, Fr.
Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Anorectal disorders.

Martin, Cz.†.
Cream: Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); lidocaine (p.1862·3).
Anorectal disorders.

Martin, Switz.†.
Ointment: Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); lidocaine (p.1862·3).
Anorectal disorders.

Martin, Cz.†; Martin, Switz.†.
Suppositories: Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Anorectal disorders.

Titanoreine Lidocaine *McNeil, Fr.*
Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2); lidocaine (p.1862·3).
Anorectal disorders.

Titanox *Demo, Gr.; Demo, Thai.†.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; sedative.

Titenil *Geolab, Braz.†.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Titralac *Benitol, Arg.†; 3M, Austral.; Cana, Gr.; 3M, Hong Kong; 3M, NZ; Nycomed, Norw.; 3M, S.Afr.; 3M, UK†; Zuoz, Venez.*
Calcium carbonate (p.1714·1); with or without glycine.
Antacid; calcium supplement; dyspepsia; gastric hyperacidity; gastritis; heartburn; hyperphosphataemia; peptic ulcer.

Titralac Extra Strength *3M, USA.*
Calcium carbonate (p.1714·1).
Hyperacidity.

Titralac Plus *3M, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).
Hyperacidity.

Titralac-Sil *3M, Austral.†; 3M, Malaysia†; 3M, NZ†; 3M, Singapore†.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2); glycine.
Dyspepsia; flatulence; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

Titralgan *Berlin-Chemie, Ger.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Formerly contained phenazone, paracetamol, and caffeine.
Pain.

Ti-Tre *Teofarma, Ital.*
Liothyronine sodium (p.2174·1).
Hypothyroidism.

Titretta S *Berlin-Chemie, Ger.*
Propyphenazone (p.119·3); codeine phosphate (p.37·2).
Pain.

Titretta Schmerz *Berlin-Chemie, Ger.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Titus *Help, Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Tivarun *Rafarm, Gr.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Tivilac *Fahrenheit, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement for pregnant and lactating women.

Tivirlon *Coup, Gr.*
Lisinopril (p.1325·2).
Hypertension.

Tivision *Bell, India.*
Lidocaine hydrochloride (p.1862·3).
Eye-strain.

Tivitis *Llorens, Spain.*
⊗ Gramicidin (p.286·1); methylthioninium chloride (p.1450·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); tetryzoline hydrochloride (p.1574·1).
Bacterial eye infections.

Tivomit *Berlico Mulia, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

Tixair *Madaus, Fr.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Tixobar *Justesa Imagen, Arg.; AstraZeneca, Austral.†.*
Barium sulfate (p.1477·2).
Radiography of gastrointestinal tract.

Tixycolds *Novartis Consumer, UK.*
Diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Tixycolds Cold and Allergy *Novartis Consumer, UK.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis; sinusitis.

Tixylix
Note.This name is used for preparations of different composition.
Nicholas Piramal, India.
Promethazine hydrochloride (p.588·2); pholcodine citrate (p.1570·3); phenylpropanolamine hydrochloride (p.1569·3).
Cough.

Aventis, Malaysia†; Aventis, NZ.
Promethazine hydrochloride (p.588·2); pholcodine citrate (p.1570·3).
Coughs.

Pharmacare, S.Afr.
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2).
Coughs and cold symptoms.

Tixylix Baby Syrup *Novartis Consumer, UK.*
Glycerol (p.2314·2).
Coughs.

Tixylix Chest Rub *Aspen, Austral.†; Aventis, NZ.*
Cineole (p.2282·3); terpineol (p.2396·1); pine oil (p.2368·2); rosemary oil (p.2381·3); thyme oil (p.2401·2).
Nasal congestion.

Tixylix Chesty Cough *Novartis Consumer, Irl.; Novartis Consumer, UK.*
Guaifenesin (p.1561·3).
Coughs.

Tixylix Cough & Cold *Novartis Consumer, UK.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); pholcodine (p.1570·2).
Coughs and cold symptoms.

Tixylix Daytime *Novartis Consumer, UK.*
Pholcodine (p.1570·2).
Coughs.

Tixylix Daytime Childrens Decongestant *Aspen, Austral.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Upper respiratory-tract congestion.

Tixylix Flu *Aspen Consumer, S.Afr.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Tixylix Nightime *Aspen, Austral.*
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2).
Cough.

Tixylix Night-Time *Novartis Consumer, UK.*
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2).
Coughs.

Tixyplus *Novartis Consumer, UK.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Cold and influenza symptoms.

Tizan *Sun, Thai.*
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasm; spasticity.

Tizine *Hua, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Tizonil M *Biofarma, Braz.†.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vaginal infections.

Tizorol *Rudefsa, Mex.*
Thiamazole (p.2176·3).
Hyperthyroidism.

Tizos *Dexa, Indon.*
Ceftizoxime (p.236·3).
Bacterial infections.

Tizoxim *Richmond, Arg.†.*
Cefotaxime (p.229·1).
Bacterial infections.

TJ-15 Tsumura Oren-Gedoku-To *Tsumura, Cz.†.*
Scutellaria; hoelen; gardenia; phellodendron.
Cardiovascular disorders; respiratory-tract and gastrointestinal haemorrhage.

TJ-96 Tsumura Saiboku-To *Tsumura, Cz.†.*
Bupleuri; pinellia; hoelen; scutellaria; magnolia; suanzaorentang; ginseng; liquorice; perilla; ginger.
Anxiety; asthma; bronchitis; hypersensitivity reactions.

TJ-23 Tsumura Toki-Shakuyaku-San *Tsumura, Cz.†.*
Paeonia; atractylodis lanceae; alismatis; hoelen; cnidium; angelica.
Female infertility; menopausal disorders; menstrual disorders; oedema and haemorrhoids in pregnancy.

TKC *Royal, Chile.*
Ketoconazole (p.539·1).
Scalp disorders.

T-long *AWD, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

TMG Folic *Douglas, NZ†.*
Betaine; folic acid; vitamin B (p.1922·1).
Nutritional supplement.

Tmide *Cadila, India.*
Tropicamide (p.1886·2).

T-Minic *Novartis, India.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; upper respiratory-tract congestion.

T-Minic Plus *Novartis, India.*
Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold symptoms; upper respiratory-tract congestion.

TMP *Ratiopharm, Ger.†; Pacific, NZ.*
Trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

TMS *TAD, Ger.*
Co-trimoxazole (p.258·1).
Bacterial infections.

T3Mycin *Hoe, Malaysia; Hoe, Singapore.*
Clindamycin phosphate (p.251·2).
Acne.

TNKase *Roche, Canad.; Genentech, USA.*
Tenecteplase (p.1410·1).
Myocardial infarction.

TO Gel *TO-Chemicals, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Toa *Wyeth Consumer, Mex.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Tobacin *Aristo, India.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobacoff *Colfarm, Pol.*
Anise oil (p.2258·2); peppermint oil (p.1761·2); guarana (p.2416·1); tormentil (p.2403·2).
Aid to smoking withdrawal.

Tobazon *Bell, India.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobazon DM *Bell, India.*
⊗ Tobramycin sulfate (p.354·2); dexamethasone sodium phosphate (p.1526·2).
Inflammation and infection following cataract surgery.

Tobe *Laboratorios Chile, Chile.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Tobedoce *Jofrain, Mex.*
Vitamin B substances (p.1922·1).

Tobel *Nobel, Turk.*
Tobramycin (p.354·1).
Bacterial infections.

Tobi
Teva Tuteur, Arg.; MSD, Austral.; Croma, Austria; Solvay, Belg.; Novartis, Cz.; Chiron, Denm.; Orphan, Fin.; Chiron, Fr.; Chiron, Ger.; Novartis, Gr.; Novartis, Hung.; Novartis, Irl.; Chiron, Israel; Dompe, Ital.; Baxter, NZ†; Novartis, Neth.; Chiron, Norw.; Novartis, Port.; Chiron, Spain; Swedish Orphan, Swed.; Vifor, Switz.; Novartis, UK; Pathogenesis, USA.
Tobramycin (p.354·1).
Pseudomonal infections in cystic fibrosis.

Chiron, Canad.; Chiron, Pol.
Tobramycin sulfate (p.354·2).
Pseudomonal infections in cystic fibrosis.

Tobicor *Medika, Switz.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Tobicor Plus *Medika, Switz.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tobin *Medika, Switz.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Tobitil *Ranbaxy, India; Ranbaxy, S.Afr.†.*
Tenoxicam (p.128·2).
Dysmenorrhoea; gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Tobolacer *Lacer, Spain.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Tobra *Lilly, Mex.†.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobra Gobens *Normon, Spain.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobrabact *Novartis, Ital.; Medicom, Neth.; Novartis, Spain.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrabiotic *Denver, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrabiotic D *Denver, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections with inflammation.

Tobra-cell *Cell Pharm, Ger.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobracin *Latinofarma, Braz.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobracin D *Latinofarma, Braz.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Tobracort *Tetrafarm, Arg.; Genom, Braz.; Antibioticos, Mex.; Vivax Optipharm, Venez.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Tobradex *Alcon, Arg.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Alcon, NZ; Alcon, Neth.; Alcon, Philipp.; Alcon, Pol.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Gervasi, Spain; Alcon, Switz.; Alcon, Thai.; Alcon, UK; Alcon, USA; Alcon, Venez.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Ear disorders; infected eye disorders.

Tobradiclo *Pharmadorf, Arg.*
Tobramycin (p.354·1); diclofenac sodium (p.44·3).
Eye inflammation and infection following cataract surgery.

Tobradistin *Dista, Spain†.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobradosa *Dosa, Arg.*
Tobramycin (p.354·1).
Bacterial infections.

Tobrafen *Zwitter, Gr.; Alcon, Switz.*
Diclofenac sodium (p.44·3); tobramycin (p.354·1).
Inflammatory eye disorders with infection; postoperative eye inflammation.

Tobragan *Allergan, Arg.; Allergan, Braz.; Allergan, Chile.*
Tobramycin (p.354·1).
Bacterial infections.

Tobragan D *Allergan, Arg.; Allergan, Chile; Allergan, Venez.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Tobra-Gobens *Normon, Port.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobral *Alcon, Ital.*
Tobramycin (p.354·1).
Bacterial infections of the eye and external ear.

Tobralex *Alcon, Irl.†.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobra-M *Bausch & Lomb, Braz.†.*
Tobramycin (p.354·1).
Bacterial infections.

Tobramaxin *Alcon, Ger.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobramina *Lilly, Braz.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobranax *Vivax Optipharm, Venez.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobraneg *Elder, India.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobranet *Tetrafarm, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobranom *Genom, Braz.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrased *Bilim, Turk.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrasix *Lilly, Austria.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobrasol *Ocusoft, USA; Oftalmi, Venez.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrasone *Cadila, Rus.*
⊗ Tobramycin sulfate (p.354·2); dexamethasone sodium phosphate (p.1526·2).
Infected inflammatory eye disorders.

Tobrastill *Bruschettini, Ital.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobratlas *Atlas, Arg.*
Diclofenac sodium (p.44·3); tobramycin (p.354·1).
Eye inflammation and infection following cataract surgery.

Tobrex *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Israel; Alcon, Malaysia; Alcon, Mex.; Pacific, NZ; Alcon, Neth.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrexan *Alcon, Port.; Alcon Cusi, Spain.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobridavi *Davi, Port.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobrin
Note. This name is used for preparations of different composition.
Laboratorios Chile, Chile.
Tobramycin (p.354·1).
Bacterial eye infections.

Solfran, Mex.
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Tobrin-D *Laboratorios Chile, Chile.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections with inflammation.

Tobrosopt *Polfa Warszawa, Pol.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobryne *Fahrenheit, Indon.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tobsin *Ulagay, Turk.*
Tobramycin (p.354·1).
Bacterial eye infections.

Tobutol *General Drugs, Thai.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Tocalfa *Marvecs, Ital.*
dl-Alpha tocoferil acetate (p.1992·3); vitamin A (p.1971·2).
Vitamin A and E deficiency.

Tocalm *Prater, Chile.*
Ambroxol (p.1550·3).
Respiratory-tract congestion.

Tocasol *Mediderm, Chile.*
Imiquimod (p.881·3).
Anogenital warts.

Tocef *Bernofarm, Indon.*
Cefixime (p.224·3).
Bacterial infections.

Toclapekt *UCB, Fin.†.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Toclase
UCB, Denm.†; UCB, Fin.; UCB, Norw.; UCB, Swed.; UCB, Thai.
Pentoxyverine citrate (p.1567·3) or pentoxyverine hydrochloride (p.1567·3).
Coughs.

UCB, Hong Kong; UCB, Turk.
Pentoxyverine hydrochloride (p.1567·3).
Coughs.

UCB, Philipp.
Pentoxyverine citrate (p.1567·3).
Cough.

Toclase Expectorant
Note. This name is used for preparations of different composition.
UCB, Fin.
Pentoxyverine citrate (p.1567·3); terpin hydrate (p.1573·3).
Coughs.

UCB, Fr.†.
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Toclase Toux Seche *UCB, Fr.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Tocline *Rontag, Arg.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Toco *Pharma 2000, Fr.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Tocobion *Medikon, Indon.*
Thiamine disulfide (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); vitamin E (p.1992·2).
Digestive disorders; nausea and vomiting of pregnancy; nervous system disorders; neurasthenia; reduced appetite.

Tocoderm *Tocogino, Mex.*
Tretinoin (p.1618·1).
Hyperkeratosis.

Tocodrine *Medichemie, Switz.†.*
⊗ Buphenine hydrochloride (p.2270·2).
Inhibition of uterine contraction.

Toco-E *CCM, Malaysia.*
d-Tocotrienols (p.1992·2).
Nutritional supplement.

Tocolion *Sciencex, Fr.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Tocomizol *Tocogino, Mex.†.*
Ketoconazole (p.539·1).
Fungal infections.

Toconal *Cryopharma, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Tocopa *Arkopharma, Fr.*
Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Tocopherine *Soho, Indon.*
Vitamin E (p.1992·2).
Fatigue; muscular dystrophy; recurrent miscarriage; vitamin E deficiency.

Tocorectal *Spedrog, Arg.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine hydrochloride (p.1868·1).
Anorectal disorders.

Tocorell *Sanorell, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Tocovenos *Fresenius Kabi, Austria.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Tocovid
Note. This name is used for preparations of different composition.
Hovid, Hong Kong; Hovid, Singapore.
Vitamin E; squalene; phytosterol complex; phyto-carotenoid complex (p.1922·1).
Vitamin E supplement.

Hovid, Malaysia.
Mixed tocotrienols (p.1992·2).
Dietary supplement.

Tocovid Emulsion Plus *Hovid, Malaysia.*
Evening primrose oil; carotenoids; omega-3 marine triglycerides; mixed tocotrienols (p.1922·1).
Dietary supplement.

Tocovid Suprabio *Hovid, Malaysia; Hovid, Philipp.*
Vitamin E; squalene; phytosterol complex; phytocarotenoid complex (p.1922·1).
Dietary supplement.

Tocovital *Steigerwald, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Tocrat *Sanofi Synthelabo, Arg.†.*
Nitrendipine (p.1358·2).
Hypertension.

Today *Allendale, Canad.; Allendale, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Today Ovulation Test *Omega, Irl.*
Fertility test (p.2372·1).

Todenac *Oftalmi, Venez.*
Tobramycin sulfate (p.354·2); diclofenac sodium (p.44·3).
Infected eye disorders.

Todex *Oftalmi, Venez.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Todexin *Tomnus, Braz.†.*
Cefalexin (p.218·2).
Bacterial infections.

Todexona *SMB, Chile.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Bacterial eye infections with inflammation.

Todolac *Norpharma, Denm.*
Etodolac (p.52·2).
Gout; inflammation; musculoskeletal and joint disorders.

Toepedo *Dendron, UK.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2).
Fungal skin infections.

Tofago *TO-Chemicals, Thai.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Migraine and other vascular headache.

Tofen
Note. This name is used for preparations of different composition.
Beximco, Singapore†.
Ketotifen (p.582·2).
Asthma; hypersensitivity reactions.

Utopian, Thai.
Ibuprofen (p.64·2).
Inflammation; musculoskeletal and joint disorders; pain.

Toff MD *Panacea, India.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Cold symptoms; coughs; sinus congestion.

Toflam *Lafedar, Arg.*
⊗ Tobramycin (p.354·1); betamethasone (p.1518·2); tetryzoline (p.1574·1).
Eye disorders.

Toflamixina *Novartis Ophthalmics, Arg.; Novartis Ophthalmics, Braz.†.*
Tobramycin (p.354·1).
Bacterial eye infections.

Toflamixina Plus *Novartis Ophthalmics, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Toflex *TO-Chemicals, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Tofranil
Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Canad.; Novartis, Fr.; Dolorgiet, Ger.; Novartis, Hong Kong†; No-

vartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, NZ; Novartis, Philipp.; Novartis, Port.; Novartis, S.Afr.; Novartis, Swed.†; Novartis, Switz.; Novartis, Turk.; Novartis, Venez.
Imipramine hydrochloride (p.400·3).
Chronic pain syndromes; depression; night terrors; nocturnal enuresis; pain; panic disorder.

Novartis, Braz.; Novartis, Mex.; Novartis, Spain; Novartis, USA.
Imipramine embonate (p.400·3) or imipramine hydrochloride (p.400·3).
Anxiety disorders; chronic pain syndrome; depression; nocturnal enuresis; pain; panic attacks; parasomnias; sleep disorders.

Novartis, UK†.
Imipramine (p.400·2) or imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis.

Tofupill *Se-cure, Singapore†.*
Tofu; linseed (p.2333·3).
Also known as Femarelle.
Menopausal disorders.

Togal
Note.This name is used for preparations of different composition.
Togal, Ger.
Paracetamol (p.108·1).
Fever; pain.

Togal, Neth.
Aspirin (p.20·3).
Fever; pain.

Togal Akut Ibuprofen *Togal, Ger.*
Ibuprofen (p.64·2).
Fever; pain.

Togal ASS *Togal, Ger.; Togal, Switz.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Togal Classic *Togal, Ger.*
Aspirin (p.20·3); lithium citrate (p.401·3); quinine dihydrochloride (p.612·3).
Fever; inflammation; pain.

Togal Kopfschmerzbrause + Vitamin C *Togal, Ger.*
Aspirin (p.20·3); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Pain.

Togal Mobil-Gel *Togal, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal and soft-tissue disorders.

Togal Mobil-Gel mit ketoprofen *Togal, Ger.*
Ketoprofen (p.73·1).
Peri-articular and soft-tissue disorders.

Togal Mono *Sanova, Austria.*
Aspirin (p.20·3).
Fever; pain.

Togamycin *Pharmacia, Arg.†; Pharmacia, Israel†.*
Spectinomycin hydrochloride (p.332·3).
Chancroid; gonorrhoea.

Togasan *Togal, Ger.*
d-Alpha tocopherol (p.1992·2).

Togine *Utopian, Thai.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders.

Togrel *Ivax, Arg.*
Levomepromazine maleate (p.1003·1).
Anxiety; psychoses.

Togrisol *Solfran, Mex.*
Aspirin (p.20·3); caffeine (p.1116·3).
Cold symptoms.

Toilax *Orion, Denm.; Orion, Fin.; Orion, Irl.; Sandoz, Neth.; Orion, Norw.; Orion, Swed.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Tointex *GSK, Pol.*
Allantoin (p.1588·1); heparin sodium (p.1301·2).
Hyperkeratosis; keloids.

Tokakujokito *Tsumura, Jpn.*
Peach kernel; cinnamon bark; rhubarb; liquorice; mirabilitum.
Traditional Kampo medicine.

Token *Intendis, Ital.*
⊗ Calcipotriol (p.1591·3); betamethasone dipropionate (p.1518·3).
Psoriasis.

Toki-shakuyaku-san *Tsumura, Jpn.*
Peony root; atractylodes lancea rhizome; alisma rhizome; poria sclerotium; cnidium rhizome; angelica acutiloba root.
Traditional Kampo medicine.

Tokolirio *Tocogino, Mex.*
Zinc (p.1999·1); boric acid (p.2268·1).
Eye disorders.

Tokovit A + E *Hasco-Lek, Pol.*
Vitamin A palmitate (p.1973·1); *d*-alpha tocopherol (p.1992·2).
Vitamin A and E deficiency.

Tokovit E *Hasco-Lek, Pol.*
Tocopherol (p.1992·2).
Atherosclerosis; ischaemic heart disease; vitamin E deficiency.

Tokovitan *Orion, Fin.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Tol *Leti, Ger.; Novartis, Ger.; Eco, S.Afr.†.*
Allergen extracts (p.2250·2).
Hyposensitisation.

Tol 12 *Saval, Chile.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); vitamin B (p.1980·2).
Neuralgia; neuritis; reduced appetite; tonic.

Tol 12 Plus *Saval, Chile.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Vitamin B deficiency.

Tol Total *Saval, Chile.*
Vitamin preparation with or without minerals (p.1922·1).
Dietary supplement.

Tolan *Solfran, Mex.*
Methyl salicylate (p.85·3).
Soft-tissue injury.

Tolargin *GSK, Pol.*
Atropine methonitrate (p.1219·3); dipyrone (p.49·2); papaverine hydrochloride (p.2191·3).
Smooth muscle spasm.

Tolbetol *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Labetalol hydrochloride (p.1321·1).
Angina pectoris; hypertension.

Tolbin
Note.This name is used for preparations of different composition.
Elea, Arg.
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Unison, Hong Kong†; Unison, Malaysia; Unison, Singapore†.
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease; premature labour.

Unison, Thai.
Expectorant: ⊗ Terbutaline sulfate (p.1138·3); guaifenesin (p.1561·3).
Cough; obstructive airways disease.

Unison, Thai.
Syrup; tablets: ⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Tolchicine *TO-Chemicals, Thai.*
Colchicine (p.556·1).
Gout.

Tolcrem *Solfran, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Toldex *Bial, Port.*
Aspirin (p.20·3).
Fever; pain; thromboembolic disorders.

Tolectin
Janssen-Cilag, Austria†.
Tolmetin (p.130·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Janssen-Ortho, Canad.†; Janssen-Cilag, S.Afr.; Janssen-Cilag, Switz.†; Santa, Turk.; Ortho McNeil, USA.
Tolmetin sodium (p.130·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Janssen-Cilag, Mex.
Tolmetin (p.130·3) or tolmetin sodium (p.130·2).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Toledomin *Asahi, Jpn.*
Milnacipran hydrochloride (p.409·2).
Depression.

Tolep *Novartis, Ital.*
Oxcarbazepine (p.490·3).
Epilepsy.

Tolerade *Aspen, Austral.*
Imipramine hydrochloride (p.400·3).
Depression; nocturnal enuresis.

Tolerancia Extrema *Pierre Fabre Dermo-Cosmetique, Arg.*
Emollient; skin cleanser.
Skin irritation.

Tolerane
Note.This name is used for preparations of different composition.
Alcon, Arg.
Flurbiprofen (p.61·2).
Inflammatory eye disorders.

Bago, Chile.
Disulfiram (p.2296·2).
Alcoholism.

Tolerex *Procter & Gamble, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Toleriane *Roche-Posay, Arg.†; Roche-Posay, Braz.; Roche-Posay, Irl.*
Emollient.
Dry skin; skin irritation.

Tolestan *Roemmers, Arg.*
Cloxazolam (p.981·1).
Anxiety.

Tolexine *Biorga, Fr.*
Doxycycline (p.267·1).
Bacterial infections; rosacea.

Tolfamic *Medinova (Μεντινοβα), Gr.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Tolfrinic *Ascher, USA.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Tolgin *Saval, Chile.*
Vitamins; minerals; ginseng (p.1922·1).
Asthenia; tonic.

Tolid *Dolorgiet, Ger.*
Lorazepam (p.1004·1).
Anxiety; premedication; sleep disorders.

Toliken *Pharmex (Φαρμεξ), Gr.*
Clindamycin (p.251·1).
Acne.

Toliman *Scharper, Ital.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders.

Tolimed *Medifive, Thai.*
Mianserin hydrochloride (p.408·1).
Depression.

Tolinase *Pharmacia Upjohn, USA†.*
Tolazamide (p.462·3).
Diabetes mellitus.

Tolindol *Meuse, Belg.*
Proglumetacin maleate (p.119·1).
Musculoskeletal, joint, and peri-articular disorders.

Tollwutglobulin *Sanofi Pasteur, Ger.*
A rabies immunoglobulin (p.2233·3).
Passive immunisation.

Tollwut-Impfstoff (HDC) *Sanofi Pasteur, Ger.*
A rabies vaccine (human diploid cell) (p.2234·1).
Active immunisation.

Tolma *Pasteur, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Tolmex *Flupal, Venez.*
Bromhexine hydrochloride (p.1552·2); pentoxyverine citrate (p.1567·3).
Cough.

Tolmicen *Pharmacia, Ital.†; Pharmacia, NZ; Pharmacia Upjohn, Port.†.*
Tolciclate (p.548·3).
Fungal skin infections.

Tolmicil *Pharmacia-Upjohn, Gr.†.*
Tolciclate (p.548·3).
Fungal skin infections.

Tolmicol *Pharmacia, Braz.†.*
Tolciclate (p.548·3).
Fungal skin infections.

Tolmide *Beacons, Singapore.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Tolmin *Sandoz, Denm.*
Mianserin hydrochloride (p.408·1).
Depression.

Tolmix *Rowe-Fleming, Venez.†.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Tolnaderm *Sterfil, India; Hoe, Malaysia; Hoe, Philipp.; Marketlink, Philipp.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tolnaftan *Roemmers Osmoph, Venez.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tolodina *Estedi, Spain†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Toloran *Rayere, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Toloxane *Beta, Arg.†.*
Rofecoxib (p.121·1).
Dysmenorrhoea; osteoarthritis.

Toloxim *Merck, Port.*
Mebendazole (p.148·3).
Worm infections.

Toloxin
Note.This name is used for preparations of different composition.
Biolab Sanus, Braz.†.
Metamizole magnesium (p.49·3).
Fever; pain.

TO-Chemicals, Thai.
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Tolperis *ICN, Pol.*
Tolperisone hydrochloride (p.1899·3).
Intermittent claudication; skeletal muscle pain and spasm.

Tolrest *Biosintetica, Braz.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress; premenstrual dysphoric disorder; social phobia.

Toltem *Temis, Arg.*
Tolterodine tartrate (p.2198·1).
Bladder instability.

Toluidinblau *Kohler, Cz.; Kohler, Ger.*
Tolonium chloride (p.2403·1).
Methaemoglobinaemia.

Tolu-Sed DM *Scherer, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Tolvin *Organon, Ger.*
Mianserin hydrochloride (p.408·1).
Depression.

Tolvon *Organon, Austral.; Organon, Austria; Organon, Braz.; Organon, Denm.; Organon, Fin.; Organon, Hong Kong; Organon, Hung.; Organon, Irl.; Organon, Mex.; Pharmaco, NZ; Organon, Neth.; Organon, Norw.; Organon, Port.; Organon, Swed.; Organon, Switz.; Organon, Thai.; Organon, Turk.*
Mianserin hydrochloride (p.408·1).
Depression; mixed anxiety depressive states; sleep disorders.

Tolydol *Ipca, India.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Tolzep *Tolmann, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Tomaag *Yarindo, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Tomabef *Salus, Ital.†.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Tomaflex *Boehringer Ingelheim, Cz.*
Ibuprofen (p.64·2).
Fever; pain.

Tomag *Temis, Arg.†.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity.

Tomanil *Altana, Arg.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuritis; oedema.

Tomanil Flex *Altana, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Tomapyrin *Boehringer Ingelheim, Cz.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; inflammation; pain.

Tomapyrin C *Boehringer Ingelheim, Cz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; inflammation; pain.

Tomat *Apsen, Braz.*
Lycopene (Lyc-O-Mato); vitamin A; vitamin E (p.1922·1).
Lycopene and vitamin supplement.

Tomcin *General Drugs, Thai.*
Erythromycin estolate (p.269·3) or erythromycin stearate (p.270·1).
Bacterial infections.

Tomevit *Spyfarma, Spain.*
Adenosine triphosphate; arginine aspartate; glutathione; hydroxocobalamin acetate; lysine hydrochloride; pyritinol hydrochloride (p.1922·1).
Tonic.

Tomid *Gufic, India†.*
Metoclopramide hydrochloride (p.1747·3).
Motion sickness; vomiting.

Tomiko *Wermar, Mex.*
Ketoconazole (p.539·1).
Fungal infections.

Tomiporan *Toyama, Jpn.*
Cefbuperazone sodium (p.222·3).
Bacterial infections.

Tomiron *Toyama, Jpn.*
Cefteram pivoxil (p.235·2).
Bacterial infections.

Tomit *Interbat, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; nausea and vomiting.

Tomocat *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Tomoray *Varifarma, Arg.*
Meglumine amidotrizoate (p.1475·3) with/without sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Tompril *Tomnus, Braz.†.*
Captopril (p.1239·2).
Heart failure; hypertension.

Tomudex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Fin.†; AstraZeneca, Fr.; AstraZeneca, Hong Kong†; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; Ben Venue, Rus.; AstraZeneca, S.Afr.†; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Switz.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, Venez.†.*
Raltitrexed (p.766·1).
Colorectal cancer.

Tomycin *Orion, Fin.*
Tobramycin sulfate (p.354·2).
Bacterial infections.

Tomycine *Novartis Ophthalmics, Canad.†.*
Tobramycin (p.354·1).
Bacterial eye infections.

Ton Was *Chiesi, Spain.*
Vitamin B substances (p.1922·1); ginseng (p.2312·1).
Tonic.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ton-A *Mergers Drugfil, Philipp.*
Multivitamin and mineral preparation (p.1922·1) with calcium (oyster shell) (p.1675·2).
Calcium deficiency; nutritional supplement.

Tonacal D3 *Lifepharma, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Tonactil *Arkomedika, Fr.†.*
Kola (p.2416·1); ginseng (p.2312·1).
Asthenia.

Tonaflan *Tomnus, Braz.†.*
Diclofenac (p.44·2).
Inflammation; pain.

Tonal *Beta, Arg.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; pain.

Tonalgen *Andromaco, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal pain.

Tonalin *Knop, Chile.*
Essential fatty acids (p.1922·1).
Dietary supplement.

Tonamil *Ecobi, Ital.*
Thonzylamine (p.592·1).
Conjunctivitis; rhinitis; skin irritation.

Tonar *Sandoz, Indon.*
Amino-acid preparation (p.1922·1).
Chronic renal insufficiency.

Tonaril *Laboratorios Chile, Chile.*
Trihexyphenidyl (p.820·3).
Drug-induced extrapyramidal disorders; parkinsonism.

Tonaton *Sankyo, Braz.*
⊗ Yohimbine (p.2200·3); fevillea trilobata; labiadas; ephedrine hydrochloride (p.1558·2); atropine methonitrate (p.1219·3).
Erectile dysfunction.

Tonavir *Richmond, Arg.*
Stavudine (p.907·1).
HIV infection.

Tonavital *Recalcine, Chile.*
Amino acids; vitamins; minerals (p.1922·1).
Tonic.

Tonazox *Tomnus, Braz.†.*
Ketoconazole (p.539·1).
Fungal infections.

Toncard-Do *Grasler, Ger.*
Homoeopathic preparation.

Toncils *Vitabalans, Fin.*
Chlorhexidine hydrochloride (p.1635·3); benzocaine (p.1854·1).
Mouth and throat disorders.

Tondex *Hormona, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Tondinel H *Pfluger, Ger.*
Homoeopathic preparation.

Tonekin *Assistance, Arg.*
Chromium tripicolinate (p.1934·3).

Tonekin Plus *Assistance, Arg.†.*
Chromium tripicolinate (p.1934·3); levocarnitine (p.1932·2).
Dietary supplement.

Toneon *Raffo, Arg.†.*
Minoxidil (p.1342·1).
Alopecia.

Tonergon *Farmedia, Gr.*
Dihydroergocristine (p.364·2).
Peripheral vascular disorders.

Toness *Angelini, Ital.†.*
Proxazole citrate (p.2375·1).
Smooth muscle relaxant; vascular disorders.

Tonginal *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Toniazol *Nicholas Piramal, India†.*
Vitamin B substances (p.1975·1); glucose (p.1945·3); bitter orange peel (p.2357·1); absinthium (p.2244·1).
Tonic.

Tonibral *GNR, Port.†.*
⊗ Deanol hemisuccinate (p.2152·3).
Tonic.

Tonic Yeast *Seven Seas, UK.*
Yeast (p.1998·3); vitamin B substances (p.1922·1).
Formerly known as Phillips P.T.Y. Yeast Tablets.

Tonicalcium *Bouchara-Recordati, Fr.*
-Lysine ascorbate (p.1984·3); calcium ascorbate (p.1984·1).
Asthenia.

Tonice
Note. This name is used for preparations of different composition.
Produfarma, Port.
Oral liquid: ⊗ Deanol pidolate (p.2152·3); magnesium aminobenzoate; ascorbic acid.
Tonic.

Produfarma, Port.
Syrup: ⊗ Deanol pidolate (p.2152·3); calcium gluceptate; lysine hydrochloride.
Tonic.

Tonico Blumen *Luper, Braz.†.*
Ferrous sulfate (p.1939·3); phosphoric acid; aloes; myrrh; mace; cinnamon.
Anaemias.

Tonico Juventus *Juventus, Spain.*
Cyproheptadine hydrochloride (p.575·1); cobamamide (p.1980·2).
Tonic.

Tonico Pasteur *Pasteur, Chile.*
Vitamin and mineral preparation (p.1922·1).
Tonic.

Tonicum *Terrapharm, Austria; SIT, Ital.†.*
Vitamins (p.1922·1); caffeine; lactic acid.
Tonic.

Tonicum B12 *SIT, Ital.*
Amino acids; vitamin B (p.1922·1).

Tonid *Milano, Thai.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Tonikum *Bayer, Indon.*
Vitamin B ; vitamin B ; nicotinamide (p.1975·1); alcohol.
Nutritional supplement.

Tonikum Bode *Bode, Indon.; Tempo Scan Pacific, Indon.*
Vitamin B substances; ascorbic acid; liver extract; sodium glycerophosphate; manganese sulfate; caffeine; potassium aspartate; magnesium aspartate (p.1922·1).
Tonic.

Tonilax *Merck Medication Familiale, Fr.*
Frangula bark (p.1732·2); aloes (p.1705·2).
Constipation.

Toniline *Nuvia, Fr.*
Amino-acid preparation (p.1922·1).
Nutritional supplement.

Tonimax *Soria Natural, Spain.*
Siberian ginseng (p.2386·3); rosemary oil (p.2381·3); savory oil (p.2394·3).
Fatigue.

Tonimed *Boehringer Ingelheim, Austria.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and soft-tissue disorders.

Tonimer
Note. This name is used for preparations of different composition.
Ganassini, Fr.
Panthenol (p.2362·1); hyaluronic acid (p.2320·1); chondrus; gigartinia; ascophyllum; laminaria (p.2384·2); vitamin E (p.1992·2).
Nasal disorders.

Dermoteca, Port.†; Berko, Turk.
Sea water (p.1686·1).
Nasal cleansing; nasal congestion; nasal disorders.

Tonimer Baby *Ganassini, Fr.*
Sea water (p.1686·1).
Nasal disorders; nasal hygiene.

Tonimol *Herbes Universelles, Canad.*
Multivitamin preparation (p.1922·1).

Tonipan *Alpharma, Norw.*
Vitamin B substances with manganese (p.1922·1).
Vitamin B deficiency.

Tonique D *Vifor, Switz.*
Vitamins; minerals; ginseng; rutoside (p.1922·1).
Tonic.

Tonique D nouvelle formule *Vifor, Switz.*
Vitamins; minerals; ginseng; kola; caffeine citrate (p.1922·1).
Tonic.

Tonique Vegetal *Lehning, Fr.*
Homoeopathic preparation.

Tonizin *Betapharm, Ger.*
St John's wort (p.422·3).
Depression.

Tono *Milano, Thai.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tonobexol *Novartis Ophthalmics, Arg.*
⊗ Betaxolol hydrochloride (p.1231·2).
Glaucoma.

Tonocalcin *Alfa Wassermann, Cz.; Alfa Wassermann, Gr.; Alfa Wassermann, Indon.; Tempo Scan Pacific, Indon.; Wassermann, Ital.†; Merck, Mex.†; Alfa Wassermann, Pol.; Alfa Wassermann, Thai.; Santa, Turk.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteolysis of malignancy; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Tonocaltin *Biara, Port.; Bama, Spain; Zambon, Spain.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; osteolysis of malignancy; osteoporosis; Paget's disease of bone.

Tonocard *Astra, USA†.*
Tocainide hydrochloride (p.1415·1).
Ventricular arrhythmias.

Tonocardin *Pliva, Rus.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Tono-Cis *Laboratorios Chile, Chile†.*
Cisapride (p.1720·3).
Gastro-oesophageal reflux; gastrointestinal motility disorders.

Tonofer *ABC, Ital.*
Vitamin and iron preparation (p.1922·1).

Tonoferon
Note. This name is used for preparations of different composition.
East India Pharma, India.
Oral drops: Colloidal iron hydroxide (p.1950·3); lysine hydrochloride (p.1955·1); vitamin B (p.1980·2); folic acid (p.1940·1).
Iron-deficiency anaemias.

East India Pharma, India.
Paediatric syrup; syrup: Colloidal iron hydroxide (p.1950·3); folic acid (p.1940·1); vitamin B (p.1980·2).
Iron-deficiency anaemias.

Tonoferrin *Ulagay, Turk.*
Ferric ammonium citrate (p.1938·1).
Iron deficiency; iron-deficiency anaemia.

Tonofit *Body Spring, Ital.*
Vitamins; magnesium; phenylalanine; ginkgo biloba; eleutherococcus (p.1922·1).
Tonic.

Tonoflex *Sanitas, Chile.*
Paracetamol (p.108·1); chlorzoxazone (p.1894·3).
Skeletal muscle spasm and pain.

Tonofolin *Teofarma, Ital.*
Calcium folinate (p.1943·3).
Megaloblastic anaemias.

Tonoftal *Essex, Ger.*
Tolnaftate (p.548·3).
Fungal skin infections.

Tonogen
Note. This name is used for preparations of different composition.
Gedeon Richter, Hung.
⊗ Adrenaline (p.1203·2).
Anaphylaxis; asthma; circulatory collapse; glaucoma; haemorrhage; nasal disorders.

ABC, Ital.
Haematoporphyrin hydrochloride (p.2318·1); cyanocobalamin (p.1980·2).
Tonic.

Tonogen S *ABC, Ital.*
Vitamin and mineral preparation with ginkgo biloba (p.1922·1).

Tonoglutal *Wild, Switz.*
Glutamic acid; sodium hydroxybenzylphosphinate; ascorbic acid; magnesium glycerophosphate; thiamine nitrate (p.1922·1).
Tonic.

Tonojug *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Tonoklen *Farmabraz, Braz.†.*
Muira-puama; erythroxylon catuaba.
Tonic.

Tonopan
Note. This name is used for preparations of different composition.
Novartis, Austria; Novartis, Braz.; Sandoz, Mex.; Novartis, Spain; Novartis Consumer, Switz.†.
Caffeine (p.1116·3); dihydroergotamine mesilate (p.618·2); propyphenazone (p.119·3).
Facial neuralgia; migraine and other vascular headaches.

Novartis Consumer, Switz.
Diclofenac potassium (p.44·3).
Fever; pain.

Tonopaque *Mallinckrodt, USA.*
Barium sulfate (p.1477·2).
Contrast medium for gastrointestinal radiography.

Tonoplus *IBC, Ital.†.*
⊗ Arginine oxoglurate (p.1928·3); aceglutamide (p.2244·2).
Tonic.

Tonopron ACD *Sanitas, Chile†.*
Vitamin and mineral preparation (p.1922·1).
Tonic.

Tonopron Fuerte Con Vit. B12 *Sanitas, Chile.*
Vitamin B substances with or without liver extract (p.1922·1).
Tonic.

Tonopron Ginseng *Sanitas, Chile.*
Vitamins; minerals; ginseng; rutoside; deanol tartrate (p.1922·1).
Tonic.

Tonopron Jarabe *Sanitas, Chile.*
Vitamins; inositol (p.1922·1).
Tonic.

Tonosol *Unifa, Port.*
Multivitamin preparation (p.1922·1).

Tonoten *Dollder, Venez.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Tonotensil *Laboratorios Chile, Chile.*
Lisinopril (p.1325·2).
Heart failure; hypertension.

Tonotensil D *Laboratorios Chile, Chile.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Tonovit *Remek, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Tonovital Antioxidante *Bago, Arg.*
Tocopherol acetate; vitamin C; betacarotene; zinc; selenium (p.1922·1).
Antoxidant preparation.

Tonovital E *Bago, Arg.*
Tocopherol acetate (p.1992·2).

Tonovital Plus Antioxidante *Bago, Arg.*
Tocopherol acetate; vitamin C; betacarotene; zinc; copper; selenium; manganese (p.1922·1).
Antoxidant preparation.

Tonox *Utopian, Thai.*
Tenoxicam (p.128·2).
Gout; musculoskeletal, joint, and peri-articular disorders.

Tonsan akut *Bittner, Austria.*
Homoeopathic preparation.

Tonsan chronisch *Bittner, Austria.*
Homoeopathic preparation.

Tonsan-Akut *Bittner, Rus.*
Homoeopathic preparation.

Tonsan-K *Bittner, Austria.*
Homoeopathic preparation.

Tonsilgon *Bionorica, Ger.*
Althaea (p.2253·3); chamomile (p.2279·3); equisetum (p.2299·3); juglans regia; achillea (p.2245·2); oak bark (p.2355·3); taraxacum (p.2395·1).
Respiratory-tract infections.

Tonsilgon N *Bionorica, Rus.*
Althaea (p.2253·3); chamomile (p.2279·3); equisetum (p.2299·3); juglans regia; achillea (p.2245·2); oak bark (p.2355·3); taraxacum (p.2395·1).
Upper respiratory-tract disorders.

Tonsiline *Oakhurst, USA.*
Tolu balsam (p.1574·2); iron chloride; magnesium carbonate; glycerol; alcohol.
Mouth and throat disorders.

Tonsillitis PMD *Bionorica, Ger.†.*
Homoeopathic preparation.

Tonsillol *Ratiopharm, Austria.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Tonsillopas *Pascoe, Ger.*
Homoeopathic preparation.

Tonsillosyx *Syxyl, Ger.*
Homoeopathic preparation.

Tonsilotren *DHU, Rus.*
Homoeopathic preparation.

Tonsiotreen *VSM, Neth.*
Homoeopathic preparation.

Tonsiotren *Peithner, Austria.*
Homoeopathic preparation.

Tonsiotren H *DHU, Ger.*
Homoeopathic preparation.

Tonsipret *Bionorica, Ger.; Bionorica, Rus.*
Homoeopathic preparation.

Tonterin *Fortune, Hong Kong†.*
Caffeine (p.1116·3); propyphenazone (p.119·3); thiamine (p.1976·3).
Fever; pain.

Tonum *Almirall, Spain.*
Ketorolac trometamol (p.74·2).
Pain.

Tonun *Biotech, Venez.*
Domperidone (p.1726·2).
Gastro-oesophageal reflux.

Tonus *Lab, Port.†.*
Distigmine bromide (p.630·2).

Tonval *Saval, Chile.*
Vitamins; calcium gluconate; lysine (p.1922·1).
Tonic.

Toothache Drops *ICN, NZ†.*
Phenol (p.1656·1); benzocaine (p.1854·1); camphor (p.2273·2); peppermint oil (p.1761·2); clove oil (p.2285·1).
Toothache.

Toothache Gel *Roberts, USA.*
Benzocaine (p.1854·1); clove oil (p.2285·1).
Toothache.

Top C *Lane, UK.*
Rose fruit (p.2381·2); acerola; ascorbic acid (p.1983·3).
Vitamin C deficiency.

Top Calcium *Esseti, Ital.*
Calcium carbonate (p.1714·1).
Calcium depletion; calcium supplement.

Top dent fluor *Meda, Swed.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Top Life Diet *Sidus, Arg.†.*
Garcinia cambogia (p.2309·2); chromium tripicolinate (p.1934·3); soya lecithin (p.2332·2).
Dietary supplement.

Top Life Energizante *Sidus, Arg.†.*
Ginseng; guarana; *dl*-alpha tocoferil acetate; magnesium oxide; levocarnitine; wheat-germ oil (p.1922·1).
Dietary supplement.

Top Life Memory *Sidus, Arg.†.*
Ginseng (p.2312·1); ginkgo biloba (p.2311·1).
Dietary supplement.

Top Life Relax *Sidus, Arg.†.*
Valerian (p.2410·1); passion flower (p.2363·2); tilia (p.2402·2).
Dietary supplement.

Top Life Superantioxidante *Sidus, Arg.†.*
dl-Alpha tocoferil acetate; calcium ascorbate; betacarotene; selenium (p.1922·1).
Dietary supplement.

Topaal *Pierre Fabre Sante, Fr.*
Alginic acid (p.2140·3); colloidal aluminium hydroxide (p.1706·2); magnesium carbonate (p.1743·1); silicon dioxide (p.2146·2).
Gastro-oesophageal reflux.

Topaben-N *British Dispensary, Thai.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Skin disorders.

Topace *Fawns & McAllan, Austral.*
Captopril (p.1239·2).
Hypertension.

Topaceta *Streuli, Switz.*
Aluminium acetotartrate (p.2255·1); chamomile (p.2279·3); arnica (p.2260·2).
Skin disorders; soft-tissue injury.

Topadol *Teva, Israel.*
Ketorolac trometamol (p.74·2).
Pain.

Topal *Pierre Fabre, UK.*
Aluminium hydroxide (p.1706·2); light magnesium carbonate (p.1743·1); alginic acid (p.2140·3).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux.

Topalgic *Sanofi-Aventis, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Topalgon *Lavipharm, Gr.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Topalkan *Pierre Fabre Sante, Fr.*
Alginic acid (p.2140·3); aluminium hydroxide (p.1706·2); silicon dioxide (p.2146·2); magnesium carbonate (p.1743·1).
Gastro-oesophageal reflux.

Topamac *Janssen-Cilag, Arg.; Janssen-Cilag, Gr.; Janssen-Cilag, India.*
Topiramate (p.506·2).
Epilepsy.

Topamate *Cipla, India.*
Topiramate (p.506·2).
Epilepsy.

Topamax *Janssen-Cilag, Austral.; Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Ger.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Janssen-Cilag, Turk.; Janssen-Cilag, UK; Ortho McNeil, USA; Janssen-Cilag, Venez.*
Topiramate (p.506·2).
Bipolar disorder; epilepsy; migraine; neuropathic pain.

Toparal *Novag, Mex.*
Methyldopa (p.1334·1).
Hypertension.

Topase *Medica Korea, Hong Kong†.*
Pancreatin (p.2360·1); ox bile (p.2266·2); dimethicone (p.1770·2); hemicellulase (p.2279·1).
Adjunct in radiological procedures; dyspepsia.

Topasel *Boehringer Ingelheim, Spain.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Combined injectable contraceptive.

Topazolam *Topgen, Belg.*
Alprazolam (p.960·1).
Anxiety.

Topcal D3 *Grunenthal, Belg.†.*
Calcium citrate (p.1675·3); colecalciferol (p.1986·2).

Top-Cat *Varifarma, Arg.*
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Topcillin *Kalbe, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Topcoid *Uniao Quimica, Braz.*
A heparinoid (p.1305·2).

Topcort
Note. This name is used for preparations of different composition.
Cipla, Hong Kong; Cipla, India.
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Sanbe, Indon.
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Top-Dal *Randall, Mex.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea; ostomy management.

Topdent *Leti, Venez.†.*
Sodium monofluorophosphate (p.1964·3); sodium sulfate (p.1771·3).
Dental caries prophylaxis; oral hygiene.

Toperit *LKM, Arg.*
Erythromycin (p.269·2).
Acne.

Topestin *Labinca, Arg.†.*
Topotecan hydrochloride (p.780·1).
Malignant neoplasms.

Topfans *OP, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Topfena *Zydus, Fr.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Topgesic *Kimia, Indon.*
Mefenamic acid (p.80·1).
Pain.

Topher-E *Scherer, Hong Kong.*
α-Tocopherol (p.1992·2).
Vitamin E supplement.

Topialyse
Note. This name is used for preparations of different composition.
SVR, Ital.
Gamolenic acid (p.2308·2); borage oil (p.2267·3).
Nutritional supplement.

SVR, Fr.
Bath oil; capsules: Borage oil (p.2267·3); vitamin E (p.1992·2).
Skin disorders.

SVR, Fr.
Soap substitute: Glycine; borage oil (p.2267·3); vitamin E (p.1992·2).
Skin cleansing.

Topialyse Fluide *SVR, Fr.*
Shea butter; glycine; tocoferil acetate (p.1992·3); dipotassium glycyrrhizate (p.2316·2); borage oil (p.2267·3); cucurbitine; allantoin (p.1588·1).
Dry skin; skin irritation.

Topialyse Plus *SVR, Fr.*
Shea butter; glycine; tocoferil acetate (p.1992·3); dipotassium glycyrrhizate (p.2316·2); borage oil (p.2267·3); cucurbitine; allantoin (p.1588·1).
Dry skin; skin irritation.

Topic *Syntex, USA.*
Benzyl alcohol (p.1631·3); camphor (p.2273·2); menthol (p.2340·1).
Pruritus.

Topic 10 *Nigy, Fr.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin; skin irritation.

Topicaina *Braun, Spain†.*
Butyl aminobenzoate hydrochloride (p.1857·1); benzocaine (p.1854·1); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Topicaine *Biomed, NZ.*
⊗ Tetracaine hydrochloride (p.1871·3); lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Topical *Tecnimede, Port.*
Bifonazole (p.527·3).
Fungal infections.

Topicasone *Franco-Indian, India.*
⊗ Betamethasone benzoate (p.1518·3).
Skin disorders.

Topicasone with Neomycin *Franco-Indian, India.*
⊗ Betamethasone benzoate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Topicide *Konimex, Indon.*
Lindane (p.2045·3); hexachlorophene (p.1646·1); salicylic acid (p.1612·2).
Scabies.

Topicil *Douglas, Hong Kong†; Douglas, Malaysia; Douglas, NZ; Douglas, Singapore.*
Clindamycin phosphate (p.251·2).
Acne.

Topico Dentición Vera *Labitec, Spain†.*
Sodium bromide (p.2269·2); borax (p.2268·1); ethylene glycol; musk; anemone pulsatilla; menthol.
Toothache.

Topicort *Dermik, Canad.; Taro, USA.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Topicorte *Aventis, Neth.; Aventis, Thai.*
⊗ Desoximetasone (p.1525·2).
Skin disorders.

Topicorten V *Trima, Israel.*
⊗ Flumetasone pivalate (p.1531·1); clioquinol (p.254·1).
Infected skin disorders.

Topicorten-Tar *Trima, Israel.*
⊗ Flumetasone pivalate (p.1531·1); coal tar (p.1616·2); salicylic acid (p.1612·2).
Skin disorders.

Topicrem *Nigy, Singapore.*
⊗ Urea (p.1620·2); glycerol (p.2314·2).
Dry skin disorders.

Topicrem Traitement PV *Nigy, Fr.*
Piroctone olamine (p.1610·1).
Skin disorders.

Topictal *Raffo, Arg.*
Topiramate (p.506·2).
Epilepsy.

Topicycline *Shire, Irl.; Amdipharm, UK.*
Tetracycline hydrochloride (p.347·2).
Acne.

Topiderm *Olvos, Gr.*
Flutrimazole (p.535·2).
Fungal skin infections.

Topidexa *Kinder, Braz.*
⊗ Dexamethasone acetate (p.1526·1).
Skin disorders.

Topifort *Franco-Indian, India.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Topifram *Aventis, Thai.*
⊗ Desoximetasone (p.1525·2); framycetin sulfate (p.279·1); gramicidin (p.286·1).
Infected skin disorders.

Topigel *Clarben, Port.*
Benzocaine (p.1854·1).
Local anaesthesia.

Topigen *Vendiz, Philipp.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Topiglos *Kinder, Braz.*
Cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Barrier preparation.

Topilact 12 *Fouchard, Chile†.*
Ammonium lactate (p.1589·2).
Dry skin.

Topilone *Chew, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Topimax *Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Norw.; Janssen-Cilag, Swed.*
Topiramate (p.506·2).
Epilepsy; migraine.

Topionic *Almirall, Spain.*
Povidone-iodine (p.1659·2).
Skin, burn, and wound disinfection.

Topiragis *Egis, Cz.*
Topiramate (p.506·2).
Epilepsy; migraine.

Topirex *Indeco, Arg.*
Topiramate (p.506·2).
Epilepsy.

Topisalen *Trima, Israel.*
⊗ Flumetasone pivalate (p.1531·1); salicylic acid (p.1612·2).
Skin disorders.

Topisel *Galenium, Indon.*
Selenium sulfide (p.1613·1).
Fungal skin and scalp disorders.

Topisolon
Note. This name is used for preparations of different composition.
Aventis, Austria; Aventis, Irl.†; Abbott, Switz.
⊗ Desoximetasone (p.1525·2).
Burns; skin disorders.

Aventis, Ger.
Fatty ointment; ointment: ⊗ Desoximetasone (p.1525·2).
Burns; skin disorders.

Aventis, Ger.†.
Topical solution: ⊗ Desoximetasone (p.1525·2); salicylic acid (p.1612·2).
Scalp disorders; skin disorders.

Topisolon mit Salicylsaure *Aventis, Austria.*
⊗ Desoximetasone (p.1525·2); salicylic acid (p.1612·2).
Skin disorders.

Topison *Libbs, Braz.*
⊗ Mometasone furoate (p.1539·3).
Skin disorders.

Topisone *Technilab, Canad.†.*
⊗ Betamethasone dipropionate (p.1518·3).
Skin disorders.

Topi-Spray *Bial, Port.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).

Topistin
Elpen (Ελπεν), Gr.
Ciprofloxacin (p.243·3).
Bacterial infections.

AFT, NZ.
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Topivate *Qestmed, S.Afr.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Topix *Solas, Indon.*
Salicylic acid (p.1612·2); undecenoic acid (p.549·2); benzoic acid (p.1630·2).
Fungal akin infections.

Topixidil *Flupal, Venez.*
Minoxidil (p.1342·1).
Alopecia.

Topizol *Douglas, Austral.*
Clotrimazole (p.530·1).
Fungal skin infections.

Topkin *Biomet, Ger.*
Lactid caprolactone copolymer.
Wounds.

Topla *Cipla-Medpro, S.Afr.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Toplexil
Note. This name is used for preparations of different composition.
Melisana, Belg.
Oxomemazine (p.587·1); guaifenesin (p.1561·3); sodium benzoate (p.1630·2); paracetamol (p.108·1).
Coughs.

Sanofi-Aventis, Braz.
Oxomemazine hydrochloride (p.587·1); guaifenesin (p.1561·3); paracetamol (p.108·1); sodium benzoate (p.1630·2).
Coughs.

Sanofi-Aventis, Fr.; Sanofi-Aventis, Neth.
Oxomemazine (p.587·1).
Formerly contained oxomemazine and guaifenesin in *Fr.*
Formerly contained oxomemazine, guaifenesin, and sodium benzoate in *Neth.*
Coughs.

Sanofi-Aventis, Indon.
Oxomemazine (p.587·1); guaifenesin (p.1561·3).
Cough in allergic disorders.

Aventis, Israel; Aventis, Switz.
Oxomemazine (p.587·1); guaifenesin (p.1561·3); sodium benzoate (p.1630·2).
Coughs.

Top-Mag *Aerocid, Fr.*
Magnesium pidolate (p.1679·3).
Magnesium deficiency.

Top-Nitro *Schering-Plough, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Topokebir *Aspen, Arg.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer.

Toposar *Gensia, USA.*
Etoposide (p.718·1).
Small-cell lung cancer; testicular cancer.

Toposin *Pharmachemie, Neth.*
Etoposide (p.718·1).
Malignant neoplasms.

Topotag *Pharmacia, Arg.†.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer; small cell lung cancer.

Topotel *Dabur, India; Dabur, Thai.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer; small-cell lung cancer.

Toppyc *Johnson & Johnson, Braz.†.*
Permethrin (p.2048·2).

Topramine *Condrugs, Thai.*
Imipramine (p.400·2).
Depression; nocturnal enuresis.

Topramoxin *Toprak, Turk.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Toprec *Aventis, Cz.†; Grunenthal, Fr.*
Ketoprofen (p.73·1).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Toprek *Sanofi-Aventis, Ital.*
Ketoprofen (p.73·1).
Pain.

Toprel *Drugtech, Chile.*
Topiramate (p.506·2).
Epilepsy.

Topresid *Biomedis, Philipp.*
Etoposide (p.718·1).
Malignant neoplasms.

Toprilem *Lemery, Mex.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Toprim *TNP, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Toprol *AstraZeneca, Austral.; AstraZeneca, USA.*
⊗ Metoprolol succinate (p.1338·1).
Angina pectoris; heart failure; hypertension.

Topron *Chinoin, Mex.*
Nifuroxazide (p.307·2).
Gastro-enteritis.

Top-Sabona *Sabona, Ger.†.*
Peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); rosemary oil (p.2381·3).
Musculoskeletal and joint disorders; neuralgia.

Topsiton *Triomed, S.Afr.*
Vitamins; anhydrous caffeine; calcium gluconate; calcium citrate (p.1922·1).
Tonic.

Topstar *Leti, Venez.†.*
Ketoconazole (p.539·1).
Dandruff; seborrhoea.

Topster *Sofar, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Inflammatory bowel disease.

Topsy *Galenium, Indon.*
Lidocaine (p.1862·3); prilocaine (p.1868·2).
Local anaesthesia.

Topsym *Grunenthal, Austria; Grunenthal, Ger.; Grunenthal, Switz.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Topsym polyvalent
Note. This name is used for preparations of different composition.
Grunenthal, Austria; Grunenthal, Switz.
⊗ Fluocinonide (p.1532·1); gramicidin (p.286·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Grunenthal, Ger.
⊗ Fluocinonide (p.1532·1); neomycin sulfate (p.305·1); nystatin (p.543·2).
Infected skin disorders.

Topsymin *Grunenthal, Switz.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Topsymin F *Grunenthal, Austria.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Topsyn *Medicis, Canad.; Teofarma, Ital.; Syntex, Mex.*
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Topsyn-Y *Syntex, Mex.*
⊗ Fluocinonide (p.1532·1); clioquinol (p.254·1).
Infected skin disorders.

Toptear *Poen, Chile; Roemmers Poen, Venez.*
Sodium hyaluronate (p.2320·1).
Dry eyes; eye irritation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Toptrix *Merck, Port.*
Topiramate (p.506·2).
Epilepsy; migraine.

Topzole *Altana Madaus, S.Afr.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Toquilone compositum *Medichemie, Switz.†.*
Methaqualone (p.1007·2); diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Toracard *AWD, Ger.*
⊗ Torasemide (p.1415·3).
Heart failure; oedema.

Toracin *Sam Chun Dang, Hong Kong.*
Tobramycin (p.354·1).
Bacterial eye infections.

Toradiur *Roche, Ital.*
⊗ Torasemide sodium (p.1416·1).
Ascites; heart failure; oedema; renal failure.

Toradol *Roche, Austral.; Roche, Braz.; Roche, Canad.; Roche, Denm.; Roche, Fin.; Roche, Hong Kong; Roche, Indon.; Roche, Malaysia; Roche, Norw.; Roche, Philipp.; Roche, Port.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, UK; Roche, USA†.*
Ketorolac trometamol (p.74·2).
Pain.

Tora-Dol *Recordati, Ital.; Roche, S.Afr.; Roche, Switz.*
Ketorolac trometamol (p.74·2).
Musculoskeletal disorders; pain; renal and biliary colic.

Toragamma *Worwag, Ger.*
⊗ Torasemide (p.1415·3).
Heart failure; hypertension; oedema; renal failure.

Toragesic *Sigma, Braz.*
Ketorolac trometamol (p.74·2).
Inflammation; pain.

Toral *Ivax, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Toramide *Spirig, Switz.*
⊗ Torasemide (p.1415·3).
Ascites; hypertension; oedema.

Toramine *Otto, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Toranex *Alternavida, Mex.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer.

Torasem *Mepha, Switz.*
⊗ Torasemide (p.1415·3).
Ascites; hypertension; oedema.

Toraseptol *Vita, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Torasic *Kalbe, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Torasid *Gry, Ger.*
⊗ Torasemide (p.1415·3).
Heart failure; hypertension; oedema.

Torasis *Ecosol, Switz.*
⊗ Torasemide (p.1415·3).
Hypertension; nephrotic syndrome; oedema; renal failure.

Toraxan *Schering-Plough, Arg.*
Loratadine (p.583·3); ambroxol hydrochloride (p.1550·3).
Allergic respiratory-tract disorders with excess mucous.

Torbetol
Note. This name is used for preparations of different composition.
Torbet, Irl.
Cetrimide (p.1634·1); benzalkonium chloride (p.1629·1); hexachlorophene (p.1646·1).
Acne.

Torbet Laboratories, UK.
Cetrimide (p.1634·1); chlorhexidine gluconate (p.1635·3).
Acne.

Torecan
Novartis, Austria.
Thiethylperazine malate (p.591·3) or thiethylperazine maleate (p.592·1).
Nausea; vertigo; vomiting.

Novartis, Chile; Novartis, Ital.; Novartis, Mex.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Roxane, USA.
Thiethylperazine maleate (p.592·1).
Motion sickness; nausea; vertigo; vestibular disorders; vomiting.

KRKA, Cz.; KRKA, Pol.
Thiethylperazine malate (p.591·3).
Cerebrovascular atherosclerosis; nausea; vestibular disorders; vomiting.

EGIS, Hung.; KRKA, Rus.
Thiethylperazine (p.591·3).
Nausea and vomiting; vestibular disorders.

Torella *Pol-Nil, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Torem
Roche, Arg.; Roche, Swed.; Roche, UK.
⊗ Torasemide (p.1415·3).
Hypertension; oedema.

Berlin-Chemie, Ger.; Roche, Switz.
⊗ Torasemide (p.1415·3) or torasemide sodium (p.1416·1).
Heart failure; hypertension; oedema; renal failure.

Toremol *Niadas, Gr.*
Glimepiride (p.441·1).
Diabetes mellitus.

Torendo *KRKA, Hung.*
Risperidone (p.1024·2).

Torental *Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.*
Pentoxifylline (p.1367·2).
Intermittent claudication; mental function impairment in the elderly; vascular disorders.

Torfan H *Abbott, Arg.†.*
Pseudoephedrine hydrochloride (p.1571·2); clofedanol (p.1554·2); guaifenesin (p.1561·3); carbinoxamine maleate (p.570·2); sodium benzoate (p.1630·2).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, guaifenesin, and carbinoxamine maleate.
Coughs.

Torgyn *Raffo, Arg.*
Clindamycin (p.251·1).
Vaginal bacterial infections.

Torgyn Duo *Monte Verde, Arg.*
Clindamycin (p.251·1); ketoconazole (p.539·1).
Vaginal infections.

Torid *Trima, Israel.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Toridran-N *Streger, Mex.*
Bromhexine (p.1552·2).
Respiratory-tract congestion.

Torimibe *Baliarda, Arg.*
Tablets, atorvastatin calcium (p.1218·3); tablets, ezetimibe (p.1284·3).
Hypercholesterolaemia.

Torin *Veropharm, Rus.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Torio *Unison, Thai.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Toriol *Lesvi, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Torisel *Wyeth, Cz.; Wyeth, Fr.; Wyeth Lederle, Port.; Wyeth, USA.*
Temsirolimus (p.777·2).
Renal cell carcinoma.

Torivas *Baliarda, Arg.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Torkol *Sandoz, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Torlasporin *Torlan, Spain.*
Cefalexin (p.218·2).
Bacterial infections.

Torlos *Torrent, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Torlos H *Torrent, Braz.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Tormentan *Leros, Cz.*
Myrtillus (p.2349·3); tormentil (p.2403·2); burnet (p.2270·3); chamomile (p.2279·3); sage (p.2382·3); peppermint leaf (p.1761·2); liquorice (p.1740·3).
Diarrhoea; dyspepsia; meteorism.

Tormentile Forte *Farmina, Pol.*
Borax (p.2268·1); ichthammol (p.1599·1); tormentil (p.2403·2); zinc oxide (p.1621·2).
Burns; skin disorders; wounds.

Tormentiol *GSK, Pol.*
Borax (p.2268·1); ichthammol (p.1599·1); tormentil (p.2403·2); zinc oxide (p.1621·2).
Wounds.

Tornalate *Dura, USA.*
⊗ Bitolterol mesilate (p.1116·2).
Asthma; bronchospasm.

Tornix *Steierl, Ger.*
Crataegus (p.2289·1); valerian (p.2410·1); passion flower (p.2363·2); rutoside (p.2305·1).
Cardiac disorders.

Torocef *Torrent, Rus.*
Ceftriaxone (p.238·1).
Bacterial infections.

Torolac *Lupin, India.*
Ketorolac trometamol (p.74·2).
Pain.

Torpain *Ikapharmindo, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Torpas *Sanofi-Aventis, Venez.*
Tiaprofenic acid (p.129·2).
Inflammation; pain.

Torrat *Roche, Ger.†; Roche, Hong Kong†.*
⊗ Metipranolol (p.1883·2); butizide (p.1238·1).
Hypertension.

Torrem *Roche, Belg.*
⊗ Torasemide (p.1415·3).
Hypertension; oedema.

Torsilax *Neo Quimica, Braz.*
Caffeine (p.1116·3); carisoprodol (p.1894·1); diclofenac sodium (p.44·3); paracetamol (p.108·1).

Torva *Liferpal, Mex.*
Ambroxol (p.1550·3); dextromethorphan (p.1555·2).
Cough.

Torvacard *Zentiva, Cz.; Zentiva, Hung.; Zentiva, Pol.; Zentiva, Rus.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Torval *Torrent, Braz.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Torvast *Pfizer, Ital.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Torvastin *Biomedica-Chemica, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Torvic *Arlex, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Torymycin *Chinta, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Tos Mai *Gayoso, Spain.*
Dextromethorphan hydrobromide (p.1555·2); benzocaine (p.1854·1); guaiacol (p.1561·2); sodium benzoate (p.1630·2).
Cough.

Tosambrex *Sertex, Arg.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Toscacalm *Genepharm, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Toscalmin *Benitol, Arg.*
Bromhexine (p.1552·2).
Coughs.

Toscamycin-R *Genepharm, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Toscof *Cipla, India.*
⊗ Bromhexine (p.1552·2); terbutaline sulfate (p.1138·3); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Tosdiazina *Clariana, Spain†.*
Tolu balsam (p.1574·2); erythromycin stearate (p.270·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Tosdrope *Schering-Plough, Port.*
Dexchlorpheniramine maleate (p.572·1); pseudoephedrine sulfate (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Tosedrin Compuesto *Lafedar, Arg.*
Noscapine (p.1566·2); guaifenesin (p.1561·3).
Coughs.

Toseina *Italfarmaco, Port.; Italfarmaco, Spain.*
Codeine phosphate (p.37·2).
Cough.

Tosicalcin *Pharmanel, Gr.*
Calcitonin (p.1093·1).
Hypercalcaemia; osteoporosis; Paget's disease of bone.

Tosidrin *Fardi, Spain.*
Dihydrocodeine tartrate (p.48·1).
Cough.

Tosifan *Precimex, Mex.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tosifar *Bial, Spain.*
Fominoben hydrochloride (p.1561·1).
Respiratory-tract disorders.

Tosilab *Labomed, Chile†.*
Codeine phosphate (p.37·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs.

Tosrhimatiol *Sanofi Synthelabo, Spain†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tossamine *Novartis Consumer, Switz.*
Codeine phosphate (p.37·2); noscapine (p.1566·2).
Coughs.

Tossamine plus *Novartis Consumer, Switz.*
⊗ White capsules (daytime), codeine phosphate (p.37·2); noscapine (p.1566·2); *dl*-methylephedrine hydrochloride (p.1564·3); blue capsules (nighttime), codeine phosphate; noscapine; diphenhydramine hydrochloride (p.577·2).
Coughs.

Tossanil *Galenogal, Braz.†.*
Sodium benzoate (p.1630·2); tolu balsam (p.1574·2); guaifenesin (p.1561·3); menthol (p.2340·1).
Coughs.

Tosse *Novartis, Gr.*
Ambroxol (p.1550·3).
Mucolytic.

Tossec *Klonal, Arg.*
Butamirate (p.1553·1).
Coughs.

Tossefluid *Ribex, Ital.†.*
Carbocisteine (p.1553·2).
Catarrh; coughs.

Tossemed *Iodosan, Ital.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Tosseque *Medinfar, Port.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Tossex *Sarabhai Piramal, India.*
Codeine phosphate (p.37·2); chlorphenamine maleate (p.571·3); menthol (p.2340·1); sodium citrate (p.1673·3).
Coughs.

Tossex-S *Sarabhai Piramal, India.*
Chlorphenamine maleate (p.571·3); codeine phosphate (p.37·2).
Coughs.

Tossilerg *Bunker, Braz.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Tossin *Grunenthal, Chile†.*
Codeine (p.37·2); phenyltoloxamine (p.588·1).
Coughs.

Tossivitan *Sedabel, Braz.†.*
Guaifenesin (p.1561·3); potassium iodide (p.2169·2); oxeladin (p.1567·1).
Coughs.

Tossoral *Recordati, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tostop *Fabop, Arg.*
Bromhexine (p.1552·2).
Cough.

Tostran *Ferring, Cz.; ProStrakan, Port.; ProStrakan, UK.*
⊗ Testosterone (p.2129·3).
Male hypogonadism.

Tostrex *ProStrakan, Swed.*
⊗ Testosterone (p.2129·3).
Hypogonadism.

Totacef *BMS, Hung.†; BMS, Israel†; BMS, Ital.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Totaforte *Viatris, Neth.†; Sidefarma, Port.†.*
Multivitamin and mineral preparation (p.1922·1).

Total
Note. This name is used for preparations of different composition.
Allergan, Canad.†.
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Cleansing, wetting, and soaking solution for hard and gas permeable contact lenses.

Allergan, USA.
Cleansing, soaking and wetting solution for hard contact lenses (p.1622·2).

Total Care *AMO, Austral.*
A range of preparations for care of hard and gas permeable contact lenses (p.1622·2).

Total Cover Sunblock *Clinique, Canad.*
SPF 30: Octinoxate (p.1608·2); homosalate (p.1598·1); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Total Eclipse *Triangle, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3); lisadimate (p.1604·1).
Sunscreen.

Total Eclipse Moisturizing *Triangle, USA.*
SPF 15: Padimate O (p.1609·1); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Total Formula *Vitaline, USA.*
A range of vitamin preparations (p.1922·1).

Total Magnesiano *Temis, Arg.*
Magnesium (as halogen salts) (p.1922·1).
Tonic.

Total Magnesiano Antioxidante *Temis, Arg.*
Magnesium lactate; alpha-tocoferil acetate (p.1922·1).
Magnesium and vitamin E deficiency.

Total Magnesiano B6 *Temis, Arg.*
Magnesium citrate (p.1743·2); pyridoxine (p.1979·1).
Magnesium and vitamin B deficiency.

Total Magnesiano E *Temis, Arg.*
Oral powder, magnesium chloride; magnesium sulfate; magnesium phosphate; magnesium carbonate; ginseng; caffeine; tablets, vitamin E (p.1922·1).
Tonic.

Total Magnesiano Energizante *Temis, Arg.*
Vitamin B substances; ascorbic acid; calcium carbonate; magnesium carbonate; magnesium sulfate (p.1922·1).
Tonic.

Total Magnesiano Fem *Temis, Arg.*
Vitamin B substances; vitamin C; calcium carbonate; magnesium carbonate; magnesium sulfate (p.1922·1).
Dietary supplement.

Total Magnesiano con Ginseng *Temis, Arg.*
Magnesium chloride; magnesium sulfate; magnesium phosphate; magnesium carbonate (p.1678·3); ginseng (p.2312·1); caffeine (p.1116·3).

Total Magnesiano Limon *Temis, Arg.*
Magnesium chloride; magnesium fluoride; magnesium sulfate; magnesium phosphate (p.1922·1).
Magnesium deficiency; renal calculi.

Total Magnesiano NF *Temis, Arg.*
Magnesium oxide; vitamin E acetate (p.1922·1).
Magnesium and vitamin E supplement.

Total Magnesiano Sport *Temis, Arg.*
Magnesium (as halogen salts); ginseng; arginine aspartate; citrulline; B vitamins; ascorbic acid; trimethylxanthine; zinc sulfate; cobalt chloride (p.1922·1).
Dietary supplement.

Total Magnesiano Stress *Temis, Arg.*
Magnesium pidolate; thiamine hydrochloride; pyridoxine hydrochloride (p.1922·1).
Magnesium deficiency; renal calculi.

Total Magnesiano con Vit C *Temis, Arg.*
Vitamin C; magnesium carbonate or magnesium chloride; magnesium fluoride; magnesium sulfate; magnesium phosphate (p.1922·1).
Tonic.

Total Magnesiano con Vitaminas y Minerales *Temis, Arg.*
Vitamin and mineral preparation (p.1922·1) with ginseng (p.2312·1).
Tonic.

Total Man *Swiss Bio, Malaysia†.*
Ginseng (p.2312·1); saw palmetto (p.2192·3); sarsaparilla (p.2383·3); centella (p.1592·3); ginkgo biloba (p.2311·1); garlic (p.2309·2); parsley (p.2363·2); damiana (p.2292·1); ginger (p.1732·3); liquorice (p.1740·3); echinacea (p.2298·1); capsicum (p.2276·2).
Prostate disorders; tonic.

Total Solucion *Amo, Arg.; Visiontech, Arg.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Cleansing, wetting, and soaking solution for hard and gas permeable contact lenses.

Total Vitamins *Natural Life, Arg.*
Vitamin and mineral preparation (p.1922·1).

Total Woman *Vitaglow, Austral.†.*
A range of multivitamin and mineral preparations (p.1922·1).
Dietary supplement.

Totalbloc Maximum Protection *Creative Brands, Austral.†.*
SPF 15+: Padimate O (p.1609·1); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Totalens *Allergan, Braz.†.*
Polyvinyl alcohol (p.2145·3) (p.1622·2).
Cleaning solution for contact lenses.

Totalflora *Roux-Ocefa, Arg.*
Lactobacillus acidophilus (p.2372·3); *Lactobacillus bifidus*; *Bacillus subtilis*; yeast; bacteriophages.
Restoration of gastrointestinal flora.

Totalip *Guidotti, Ital.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Totalos Plus *Pierre Fabre, Arg.*
Collagen (p.2286·1); proteoglycans; amino acids; hydroxyapatite (p.2323·1).
Mineral supplement; osteogenesis imperfecta; osteomalacia; osteoporosis.

Totalprost *Teva, Hung.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Totam
Hikma, Port.
Cefotaxime sodium (p.228·1).
Bacterial infections.

Cipla-Medpro, S.Afr.†.
Cefotaxime (p.229·1).
Bacterial infections.

Totamine *Baxter, Fr.*
Amino-acid, electrolyte, and vitamin infusion (p.1922·1).
Parenteral nutrition.

Totapen *BMS, Fr.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Totaretic *CP Pharmaceuticals, UK.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
These ingredients can be described by the British Approved Name Co-tenidone.
Hypertension.

Totasedan *Recalcine, Chile.*
Bromazepam (p.964·3).
Anxiety.

Totect *TopoTarget, USA.*
Dexrazoxane (p.1443·1).
Reduction of doxorubicin cardiotoxicity.

Totelle *Wyeth, Braz.; Wyeth, Chile; Wyeth, Denm.†; Wyeth Lederle, Ital.†; Wyeth Lederle, Swed.†.*
Estradiol (p.2097·2); trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelle Ciclico *Wyeth, Arg.; Wyeth, Venez.*
Pink tablets, estradiol (p.2097·2); red tablets, estradiol; trimegestone (p.2135·2).
Menopausal disorders.

Totelle Ciclo *Wyeth, Braz.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelle Continuo *Wyeth, Arg.; Wyeth, Chile; Wyeth, Mex.; Wyeth, Venez.*
Estradiol (p.2097·2); trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelle Cycle *Wyeth Lederle, Belg.†.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelle Secuencial *Wyeth, Mex.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelle Sekvens *Wyeth, Fin.†; Wyeth Lederle, Norw.†; Wyeth Lederle, Swed.†.*
14 Tablets, estradiol (p.2097·2); 14 tablets, estradiol; trimegestone (p.2135·2).
Menopausal disorders; osteoporosis.

Totelmin *Dovalle, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Totephan
Expanscience, Fr.
Cream: Glycerol; cholesterol; oleic acid; urea (p.1922·1).
Hair and nail tonic.

Expanscience, Fr.
Oral powder: Plant proteins; vitamins; minerals (p.1922·1).
Hair and nail tonic.

Tot'Hema *Innotech, Fr.; Confar, Port.; Innotech, Rus.*
Ferrous gluconate (p.1939·1); manganese gluconate (p.1956·2); copper gluconate (p.1922·1).
Iron-deficiency; iron-deficiency anaemia.

Totifen *Elpen (Ελπεν), Gr.*
Ketoprofen (p.73·1).
Inflammatory disorders.

Totilac *Kalbe, Indon.*
Sodium lactate (p.1673·3); potassium chloride (p.1684·3); calcium chloride (p.1675·2).
Resuscitation in post cardiac surgery.

Totocortin *Winzer, Ger.*
⊗ Dexamethasone sodium phosphate (p.1526·2).
Eye disorders.

Totonik *Pharmaceutical Enterprises, S.Afr.*
Vitamins; potassium glycerophosphate; caffeine; ferrous sulfate (p.1922·1).
Tonic.

Tottizim *SoSe, Ital.*
Ceftazidime (p.234·1).
Gram-negative bacterial infections.

Toularynx
Note. This name is used for preparations of different composition.
Qualiphar, Belg.
Codeine phosphate (p.37·2).
Coughs.

Qualiphar, Belg.
Codeine phosphate (p.37·2); euphorbia (p.2301·3).
Cough.

Touristil *Janssen-Cilag, Belg.*
Cinnarizine (p.573·1); domperidone maleate (p.1726·3).
Dyspepsia; motion sickness; nausea; sleep disorders; vertigo; vomiting.

Touro LA *Dartmouth, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Touro A & H *Dartmouth, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Allergic rhinitis; nasal congestion.

Touro Allergy *Dartmouth, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Rhinitis; upper respiratory-tract congestion.

Touro CC *Dartmouth, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Touro DM *Dartmouth, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Touro Ex *Dartmouth, USA†.*
Guaifenesin (p.1561·3).
Coughs.

Touxium Antitussivum *SMB, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Toux-San *Sandipro, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tovalt *Biovail, USA.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Tovene *Stada, Ger.*
Diosmin (p.2304·2).
Venous insufficiency.

Toverine *TO-Chemicals, Thai.*
Drotaverine hydrochloride (p.2298·1).
Smooth muscle spasm.

Toviaz
Pfizer, Cz.
Fesoterodine (p.2188·2).
Bladder hyperactivity.

Pfizer, Port.; Pfizer, UK.
Fesoterodine fumarate (p.2188·2).
Bladder hyperactivity; bladder instability.

T.O.Vir *TO-Chemicals, Thai.*
Zidovudine (p.913·3).
HIV infection.

Toxal *Rayere, Mex.†.*
Oxolamine (p.1567·1).
Coughs.

Toxam *LA, Arg.†.*
Bromhexine (p.1552·2); clofedanol (p.1554·2).
Cough.

Toxambay *LA, Arg.*
Bromhexine (p.1552·2); clofedanol (p.1554·2).
Cough.

Toxepasi *Roche, Ital.†.*
Cogalactoisomerase sodium (p.2285·3).
Hyperbilirubinaemia.

Toxex *Pekana, Ger.†.*
Homoeopathic preparation.

Toxicarb *SERB, Fr.; IFET (ΙΦΕΤ), Gr.*
Activated charcoal (p.1435·2).
Poisoning.

Toxicerna *Fides, Ger.†.*
Homoeopathic preparation.

Toxicol *Eagle, Austral.*
Vitamin B substances with mineral, herbal, and nutritional agents (p.1922·1).

toxi-loges
Note. This name is used for preparations of different composition.
Loges, Ger.
Injection; oral drops; tablets: Homoeopathic preparation.
The injection was formerly known as toxi-L 90 N.

Loges, Ger.
Oral liquid: Echinacea purpurea (p.2298·1).
Respiratory- and urinary-tract infections.

Toximer
Note. This name is used for preparations of different composition.
Ratiopharm, Austria.
Suppositories: Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Ratiopharm, Austria.
Tablets: Propyphenazone (p.119·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Toximer C *Merckle, Ger.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Toxiselect *Dreluso, Ger.*
Homoeopathic preparation.

Toxogonin *Merck, Austria; Merck, Chile; Merck, Cz.; Merck, Ger.; Merck, Neth.; Merck, S.Afr.; Merck, Swed.*
Obidoxime chloride (p.1456·2).
Organophosphorus poisoning.

Toxogonine *Merck, Switz.*
Obidoxime chloride (p.1456·2).
Organophosphorus poisoning.

Toxol *Antibioticos, Mex.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Toxolen *Drovepat, Venez.†.*
Oxolamine (p.1567·1).
Cough.

Tozolden *Denver, Arg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

T+P *Lamda (Λαμδα), Gr.*
⊗ Timolol (p.1413·1); pilocarpine (p.1884·3).
Glaucoma.

TP-1 *Serono, Cz.†.*
Thymostimulin (p.2401·3).
Immunotherapy.

TPE 1800 GX *Baxter, Ger.†.*
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

TPH *Baxter, Ital.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition for neonates and infants.

T-Phyl *Purdue Frederick, USA.*
Theophylline (p.1140·1).
Asthma; bronchospasm.

TP-Ophtal *Winzer, Ger.*
⊗ Pilocarpine hydrochloride (p.1884·3); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

TPT *Elvetium, Arg.†.*
Topotecan (p.780·2).
Malignant neoplasms.

Trabar *Mepha, Cz.†; Mepha, Israel.*
Tramadol hydrochloride (p.130·3).
Pain.

Trabecan *Teva, Hung.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Trabex *Guidotti, Spain.*
Calcium phosphate (p.1676·2); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Trabilin *Mepha, Braz.*
Tramadol hydrochloride (p.130·3).

Trabit
Note. This name is used for preparations of different composition.
Mepha, Thai.†.
Injection: ⊗ Ampoule A, phenylbutazone sodium (p.117·1); salamidacetic acid (p.121·2); dexamethasone (p.1526·1); ampoule B, vitamin B (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in each ampoule to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Mepha, Thai.†.
Rectal capsules: ⊗ Phenylbutazone (p.117·1); dexamethasone (p.1526·1); vitamin B (p.1980·2).
Musculoskeletal and joint disorders.

Trablok *Lemery, Mex.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Trabona *Leiras, Fin.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Trac Tabs 2X *Hyrex, USA†.*
Methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1); benzoic acid (p.1630·2); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

Tracefusin *Pisa, Mex.*
Trace-element preparation (p.1922·1).

Tracel *Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
Trace-element preparation (p.1922·1).
Parenteral nutrition.

Tracelyte *Sanderson, Chile.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Tracetin *Otto, Indon.*
Neomycin sulfate (p.305·1); bacitracin (p.210·3).
Skin infections.

Tracheo Fresh *Rappai, Switz.†.*
Sea salt (p.1686·1).
Tracheal lubricant; tracheostomy care.

Trachiform *Philopharm, Ger.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1); mint oil (p.2345·2); menthol (p.2340·1).
Mouth and throat disorders.

Trachisan
Note. This name is used for preparations of different composition.
Engelhard, Cz.
Lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Engelhard, Ger.†; Farmasyn, Gr.; Engelhard, Hong Kong†; Engelhard, Malaysia†; Engelhard, Switz.†.
Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3); tyrothricin (p.358·2).
Mouth and throat disorders.

Engelhard, Singapore†.
Gargle: Chlorhexidine gluconate (p.1635·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Engelhard, Singapore.
Lozenges: Chlorhexidine gluconate (p.1635·3); lidocaine (p.1862·3); tyrothricin (p.358·2).
Mouth and throat disorders.

Trachisan Halsschmerztabletten *Engelhard, Ger.*
Lidocaine hydrochloride (p.1862·3).
Sore throat.

Trachisan N *Engelhard, Ger.†.*
Chlorhexidine gluconate (p.1635·3).
Mouth and throat disorders.

Trachitol *Kernpharm, Neth.*
Lidocaine hydrochloride (p.1862·3); alum (p.2254·1); propyl hydroxybenzoate (p.1649·2).
Sore throat.

Trachon *Bernofarm, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Tracidol *YSP, Malaysia.*
Tramadol hydrochloride (p.130·3).
Pain.

Tracilarin *Norma (Νορμα), Gr.†.*
Cefradine (p.233·1).
Bacterial infections.

Tracine *Medicine Products, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tracitrans *Fresenius Kabi, Fr.*
Electrolyte (p.1667·1) and trace element preparation (p.1922·1).
Parenteral nutrition.

Tracitrans Plus
Note. This name is used for preparations of different composition.
Fresenius Kabi, Chile; Fresenius Kabi, Ger.; Fresenius Kabi, Mex.
Electrolyte (p.1667·1) and trace-element preparation (p.1922·1).
Parenteral nutrition.

Fresenius Kabi, Neth.
Trace element preparation (p.1922·1).
Parenteral nutrition.

Tracleer *Actelion, Austral.; Pharma Logistics, Belg.; Actelion, Canad.; Actelion, Cz.; Actelion, Denm.; Orphan, Fin.; Actelion, Fr.; Actelion, Ger.; Actelion, Gr.; Actelion, Hung.; Actelion, Irl.; Actelion, Israel; Actelion, Ital.; Actelion, Malaysia; Healthcare Logistics, NZ; Actelion, Neth.; Actelion, Norw.; Actelion, Port.; Actelion, Singapore; Actelion, Spain; Actelion, Swed.; Actelion, Switz.; Actelion, Thai.; Pharmalink, Thai.; Actelion, UK; Actelion, USA.*
Bosentan (p.1235·2).
Pulmonary hypertension; systemic sclerosis.

Tracne *Interbat, Indon.*
Tretinoin (p.1618·1).
Acne.

Tracnox *Pharlab, Braz.†.*
Itraconazole (p.536·3).
Fungal infections.

Traconal *Ache, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Traconax *Luper, Braz.†.*
Itraconazole (p.536·3).
Fungal infections.

Tracozon *Ariston, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Tracrium *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Denm.†; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Philipp.; GSK, Pol.; Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Tractil *Ronava, Venez.†.*
Thiocolchicoside (p.1898·2).
Muscle spasm.

Tractocile
Ferring, Arg.; Ferring, Austria; Ferring, Belg.; Ferring, Braz.†; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Detsaves (Ντετσαβες), Gr.; Ferring, Hong Kong; Ferring, Hung.; Ferring, Irl.; Ferring, Ital.; Ferring, Malaysia; Ferring, Mex.; Pharmaco, NZ; Ferring, Neth.; Ferring, Norw.; Ferring, Pol.; Ferring, Port.; Ferring, S.Afr.; Ferring, Spain; Ferring, Swed.; Ferring, Switz.; Ferring, UK.
Atosiban acetate (p.2005·3).
Premature labour.

Tractoduo *Quesada, Arg.*
Bisacodyl (p.1710·1).
Bowel evacuation.

Tractoven
Amnol, Ital.
Capsules: Centella; melilot; rutoside; vitamin E (p.1922·1).
Nutritional supplement.

Amnol, Ital.†.
Cream: Hedera; birch; aesculus; equisetum; myrtillus; centella; vitamin E (p.1922·1).

Tracur *Cristalia, Braz.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Tracurix *Richmond, Arg.*
Atracurium (p.1905·3).
Competitive neuromuscular blocker.

Tracuron *Scott-Cassara, Arg.*
Atracurium (p.1905·3).
Competitive neuromuscular blocker.

Tracutil *Braun, Arg.; Braun, Chile; Braun, Cz.; Braun, Fr.†; Braun, Ger.; Braun, Hung.; Braun, Pol.; Braun, Port.; Braun, Switz.; Braun, Turk.*
Mineral and trace element preparation (p.1922·1).
Parenteral nutrition.

Tracyclin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Tetracycline hydrochloride (p.347·2).
Acne.

Tracyne *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Tetracycline hydrochloride (p.347·2).
Bacterial infections.

Tradea *Psicofarma, Mex.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder; narcoleptic syndrome.

Tradef *Walmark, Cz.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradelia *Wolff, Ger.*
Estradiol (p.2097·2).
Menopausal disorders.

Tradexol *Columbia, Mex.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Tradil *Nordic, Swed.*
Dexibuprofen (p.39·2).
Inflammation; pain.

Tradiver *Aurora, Gr.†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Tradol *Alpharma-Isis, Ger.†; Rowex, Irl.; Grunenthal, Mex.; Shin Poong, Singapore†.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradolan *Lannacher, Austria; Lannacher, Denm.; Nordic Drugs, Fin.; Lannacher, Norw.; Nordic, Swed.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradolgesic *Bangkok Lab & Cosmetic, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradon *Lilly, Ger.†.*
⊗ Pemoline (p.2161·2).
Hyperactivity in older children.

Tradonal *Meda, Belg.; Asta Medica, Cz.†; Temmler, Cz.†; Asta Medica, Hong Kong†; Viatris, Ital.; Viatris, Neth.; Transfarma, Philipp.; Viatris, Spain; Meda, Thai.; Pharmalink, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradorec *Recordati, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradosik *Sanbe, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Tradox *Andromaco, Chile.*
Lamotrigine (p.485·1).
Epilepsy.

Tradyl *Interbat, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Traflan *Bayer, Venez.*
Etofenamate (p.53·1).
Inflammation; pain.

Traflash *Viatris, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Trafloxal *Tramedico, Belg.; Tramedico, Neth.*
Ofloxacin (p.310·2).
Bacterial eye infections.

Trafuril *Faran, Gr.†.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Tragesik *Kalbe, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Traitement PV *Nigy, Fr.*
Piroctone olamine (p.1610·1).
Dandruff.

Tralen *Pfizer, Braz.; Pfizer, Venez.*
Tioconazole (p.548·2).
Fungal skin infections.

Tralgi *IPI, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders.

Tralgiol *Stada, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Tralgit *Zentiva, Cz.*
Tramadol hydrochloride (p.130·3).
Pain.

Trali *Pfizer, Arg.*
Sodium picosulfate (p.1771·1).
Bowel evacuation; constipation.

Tralic *Andromaco, Mex.*
Tramadol hydrochloride (p.130·3).
Pain.

Tralinser *Interpharma, Chile.*
Sertraline (p.422·1).
Depression.

Tralodie *GiEnne, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Trama *Kade, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramabene *Ratiopharm, Austria; Ratiopharm, Cz.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramabeta *Betapharm, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramacet *Janssen-Cilag, Arg.; Janssen-Ortho, Canad.; Janssen-Cilag, Mex.; Janssen-Cilag, S.Afr.; Janssen-Cilag, UK.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Fever; pain.

Tramacip *Cipla, India.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramacip Plus *Cipla, India.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Tramada *Charoen Bhaesaj, Malaysia.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadex *Dexcel, Israel.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadil *Union Drug, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadin *Ratiopharm, Fin.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadoc *Docpharm, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadolor *Hexal, Austria; Hexal, Ger.; Sandoz, Hung.; Ilsan, Turk.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadon *Cristalia, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Trama-Dorsch *Pharmaselect, Ger.†.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramadura *Merck dura, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramagetic *Leiras, Fin.; Azupharma, Ger.†; Nycomed, Neth.; Nycomed, Norw.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramagit *Krewel Meuselbach, Cz.; Krewel, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramahexal *Sandoz, Austral.; Hexal, Pol.; Hexal, S.Afr.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramake *Galen, Irl.; koGen, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Trama-Klosidol *Bago, Arg.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramal *Altana, Arg.; CSL, Austral.; Grunenthal, Austria; Pfizer, Braz.; Grunenthal, Chile; Grunenthal, Cz.; Leciva, Cz.; Orion, Fin.; Grunenthal, Ger.; Vianex (Βιανεξ), Gr.; Grunenthal, Hong Kong; Grunenthal, Indon.; Pharos, Indon.; Tec-O-Pharm, Israel; Sanofi Synthelabo, Malaysia†; CSL, NZ; Grunenthal, Neth.; Grunenthal, Philipp.; Sanofi Synthelabo, Philipp.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Janssen-Cilag, S.Afr.; Grunenthal, Singapore; Grunenthal, Switz.; Sanofi Synthelabo, Thai.; Grunenthal, Venez.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramalan *Hexal, Arg.†.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramalgic *Nycomed, Hung.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramalin *EG, Ital.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramaliv *Teuto, Braz.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramamed *S Med, Austria; Medifive, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramapine *Pinewood, Irl.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramastad *Stada, Austria.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramax *Pond's, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramazac *Cadila, India; Zydus, S.Afr.*
Tramadol hydrochloride (p.130·3).
Pain.

Trambo *Alpharma, Fin.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramcod *Polfa Warszawa, Pol.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramed *Bajamed, Mex.*
Tramadol (p.132·1).
Pain.

Tramedo *Alphapharm, Austral.; Pacific, NZ.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramelene *Ethypharm, Neth.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramex *Antigen, Irl.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramic *TO-Chemicals, Thai.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders.

Tramil *Wyeth Consumer, Irl.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Traminer *Ativus, Braz.*
Valerian (p.2410·1).
Anxiety.

Tramisal *Beaufour, Fr.*
Ginkgo biloba (p.2311·1).
Mental function impairment in the elderly; peripheral vascular disorders.

Tramium *SMB, Belg.; SMB, Singapore.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramkor *Samjin, Philipp.; Unimex, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramo *Jean-Marie, Hong Kong.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramoda *LBS, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramsilone *Greater Pharma, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tramsone *Hoe, Malaysia.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tramulief *Sovereign, UK.*
Tramadol (p.132·1).
Pain.

Tramundal *Mundipharma, Austria.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramundin *Mundipharma, Austria; Mundipharma, Cz.; Mundipharma, Ger.; Mundipharma, Malaysia; Mundipharma, Philipp.; Norpharma, Pol.; Mundipharma, Switz.*
Tramadol hydrochloride (p.130·3).
Pain.

Tramus *Dexa, Indon.*
Atracurium besilate (p.1902·1).
Competitive neuromuscular blocker.

Tramy *Neves, Port.*
Tramadol hydrochloride (p.130·3).
Pain.

Tran *Gal, Pol.; Vitamex, Pol.*
Cod-liver oil (p.1935·2).
Vitamin A, D, and E deficiency.

Tran z Olejem Wiesiolkowym *Gal, Pol.†.*
Cod-liver oil (p.1935·2); evening primrose oil (p.2302·1).
Atopic eczema; vitamin A and fatty acid supplement.

Tranalpha *Alphapharm, Austral.*
Trandolapril (p.1416·2).
Hypertension.

Tranarest *Zydus, India.*
Tranexamic acid (p.1080·3).
Fibrinolysis; menorrhagia.

Tranavan *Polipharm, Thai.†.*
Lorazepam (p.1004·1).
Anxiety.

Tranax *Cipla, India.*
Alprazolam (p.960·1).
Anxiety.

Tranazol *Farmasa, Braz.†.*
Itraconazole (p.536·3).
Fungal infections.

Trancap *TP, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; dystonias; insomnia; mixed anxiety depressive states.

Tranclor *Siam Bheasach, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; dystonias; mixed anxiety depressive states.

Trancolon *Fujisawa, Jpn†.*
Mepenzolate bromide (p.1745·1).
Irritable bowel syndrome.

Trancolon P *Fujisawa, Jpn†.*
Mepenzolate bromide (p.1745·1); phenobarbital (p.492·2).
Irritable bowel syndrome.

Trancon *Condrugs, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; dystonias; mixed anxiety depressive states.

Trancopal Dolo *Kade, Ger.*
Flupirtine maleate (p.61·1).
Pain.

Trandate *Sigma, Austral.; GSK, Austria; GSK, Belg.; Shire, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fr.; IFET (ΙΦΕΤ), Gr.; Sigma, Hong Kong; UCB, Irl.; GSK, Israel; Teofarma, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; Glaxo Wellcome, Port.†; GSK, S.Afr.; GSK, Singapore; Kern, Spain; GSK, Swed.; GSK, Switz.; UCB, UK; Prometheus, USA; GSK, Venez.†.*
⊗ Labetalol hydrochloride (p.1321·1).
Angina pectoris; controlled hypotension; hypertension.

Trandiur *Teofarma, Ital.*
⊗ Labetalol hydrochloride (p.1321·1); chlortalidone (p.1243·3).
Hypertension.

Trandor *Biolab Sanus, Braz.†.*
Fenoprofen calcium (p.55·2).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Trandrozine *Asian Pharm, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Trane *Omega, Arg.*
Chlorpropamide (p.438·3).
Diabetes mellitus.

Tranex *Malesci, Ital.*
Tranexamic acid (p.1080·3).
Haemorrhage.

Tranexid *Dexa, Indon.*
Tranexamic acid (p.1080·3).
Fibrinolysis; hereditary angioedema.

Tranfib *Cipla, India.*
Tranexamic acid (p.1080·3).

Tranfib MF *Cipla, India.*
Tranexamic acid (p.1080·3); mefenamic acid (p.80·1).

Trangina *Alpharma, UK.*
Isosorbide mononitrate (p.1318·3).
Formerly known as Monosorb.
Angina pectoris.

Trangorex *Sanofi-Aventis, Spain; Sanofi-Aventis, Venez.*
Amiodarone hydrochloride (p.1210·2).
Arrhythmias.

Tranimet *Royton, Braz.†.*
Cimetidine (p.1716·2).
Peptic ulcer.

Tranject *Merck, S.Afr.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; premedication; psychoses; status epilepticus; tetanus.

Trankil *Rotexmedica, Philipp.*
Diazepam (p.986·3).
Anxiety; delirium tremens; epilepsy; skeletal muscle spasm; tetanus.

Trankilium *Ni-The, Gr.*
Lorazepam (p.1004·1).
Anxiety disorders; insomnia; status epilepticus.

Trankimazin *Pfizer, Spain.*
Alprazolam (p.960·1).
Anxiety disorders.

Trankitec *Tecnofarma, Mex.*
Magnesium valproate (p.511·3).
Epilepsy.

Tranko-Buskas *Fako, Turk.*
Medazepam (p.1006·1); hyoscine butylbromide (p.1734·1).
Anxiety.

Tranon *Recip, Swed.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders; hereditary angioedema.

Tranoxy *Biolink, Philipp.*
Oxytocin (p.2015·2).
Labour induction; lactation induction; missed abortion; postpartum haemorrhage.

Tran-Q *Guardian, Indon.*
Buspirone (p.966·2).
Anxiety.

Tranqipam *Pharmacare, S.Afr.*
Lorazepam (p.1004·1).
Alcohol withdrawal syndrome; anxiety; premedication; sedative.

Tranquase *Azupharma, Ger.†.*
Diazepam (p.986·3).
Anxiety; premedication; skeletal muscle spasm.

Tranquil *Pharmadass, UK.*
Magnolia; valerian (p.2410·1); St John's wort (p.422·3).
Formerly contained crataegus, tilia flower, viburnum, and hawthorn oil.

Tranquilyn *Link, UK†.*
⊗ Methylphenidate hydrochloride (p.2159·2).
Attention-deficit hyperactivity disorder.

Tranquinal *Bago, Arg.; Bago, Braz.*
Alprazolam (p.960·1).
Anxiety; insomnia.

Tranquinal Soma *Bago, Arg.*
Alprazolam (p.960·1); sulpiride (p.1028·3).
Psychosomatic disorders.

Tranquirit *Sanofi-Aventis, Ital.*
Diazepam (p.986·3).
Anxiety; epilepsy; insomnia; psychoses.

Tranquital *Novartis Sante, Fr.*
Valerian (p.2410·1); crataegus (p.2289·1).
Insomnia; nervous disorders.

Tranquo *Boehringer Ingelheim, Belg.*
Oxazepam (p.1014·2).
Anxiety disorders.

Transacalm *Norgine, Fr.*
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders.

TransAct *Boots Healthcare, S.Afr.*
Flurbiprofen (p.61·2).
Musculoskeletal, joint, and soft-tissue disorders.

Transact Lat *Abbott, Ital.; Abbott, Port.*
Flurbiprofen (p.61·2).
Musculoskeletal pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

TransActLAT *Knoll, Cz.†.*
Flurbiprofen (p.61·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Transamin *Nikkho, Braz.; Nikolakopoulos (Νικολακοπουλος), Gr.; Daiichi, Hong Kong; Daiichi, Indon.; Otto, Indon.; Daiichi, Jpn; Daiichi, Malaysia; Daiichi, Thai.*
Tranexamic acid (p.1080·3).
Haemorrhage; inflammation.

Transamine *Fako, Turk.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders.

Transannon *Pharmacia, Ger.†; Pfizer, Switz.†.*
21 Tablets, conjugated oestrogens (p.2087·2); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Transantor *Antor, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Transbronchin *Viatris, Ger.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Transbroncho *Kalbe, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with excess or viscous mucus.

Transcalcium *Verisfield, Gr.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Transcop *Recordati, Ital.*
Hyoscine (p.1733·3).
Motion sickness.

TransCyte *Smith & Nephew, UK; Smith & Nephew, USA.*
Bioengineered human skin equivalent (p.1613·3).
Burns.

Transderm Scop *Novartis Consumer, USA.*
Hyoscine (p.1733·3).
Motion sickness.

Transderma B *Szama, Arg.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Transderma H *Szama, Arg.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Transdermal-NTG *Warner Chilcott, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Transderm-Nitro *Novartis, Canad.; Novartis, Philipp.; Novartis, USA.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; phlebitis.

Transderm-V *Novartis, Canad.*
Hyoscine (p.1733·3).
Motion sickness.

Transdiol *Hexal, Arg.†.*
Estradiol (p.2097·2).
Menopausal disorders.

Transene *Sanofi-Aventis, Ital.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia; nervous disorders.

Transfert *Piam, Ital.†.*
Carnitine (p.1932·2).
Carnitine deficiency.

Transformal *Schwabe, Arg.†.*
Ginseng (p.2312·1).
Tonic.

Transiderm-Nitro *Novartis, Austral.; Novartis, Fin.; Novartis, Irl.; Novartis, Neth.; Novartis, Norw.; Novartis, Swed.; Novartis, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; prophylaxis of phlebitis and extravasation.

Transilane
Note. This name is used for preparations of different composition.
Innotech, Fr.
Ispaghula (p.1737·1).
Constipation.

Innotech, Hong Kong.
Psyllium hemicellulose (p.1737·1).
Constipation.

Transimune *Troikaa, India.*
Azathioprine (p.1818·2).
Auto-immune disorders; organ transplantation.

Transipeg
Note. This name is used for preparations of different composition.
Bayer Consumer, Arg.; Roche, Austria; Bayer, Belg.; Bayer, Fr.; Bayer, Neth.; Roche, Rus.; Mundipharma, Switz.
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Constipation.

Bayer, Port.; Roche, Turk.
Macrogol 3350 (p.2336·3).
Constipation.

Transipen *Demo, Gr.*
⊗ Indapamide (p.1314·1).
Hypertension.

Transix *Christiaens, Belg.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Translipo-Triple *Centaur, India.*
⊗ Beclometasone dipropionate (p.1516·2); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Transmer *Tradiphar, Fr.†.*
⊗ Promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2).
Motion sickness.

Transmetil
Boehringer Ingelheim, Arg.†.
Ademetionine (p.2247·1).

Abbott, Cz.; Abbott, Ital.
Ademetionine butanedisulfonate (p.2247·1).
Liver disorders.

Transmin *Vargas, Venez.*
Menthol (p.2340·1); cineole (p.2282·3); camphor (p.2273·2).

Transmuco *Kalbe, Indon.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders with excess or viscous mucus.

Transoddi *Lipha Sante, Fr.†.*
Cinametic acid (p.2282·2).
Dyspepsia.

Transorbin *Roche, Gr.†.*
Macrogol (p.2336·3).
Laxative.

Transoxyl *Ferraz, Lynce, Port.†.*
Almitrine dimesilate (p.2149·3); raubasine (p.1386·3).

Trans-Plantar *Westwood-Squibb, Canad.; Prater, Chile†.*
Salicylic acid (p.1612·2).
Keratinisation disorders; plantar warts.

Transpulmin
Note. This name is used for preparations of different composition.
Viatris, Cz.
Eucalyptus oil (p.2301·2); pumilio pine oil (p.2376·3).
Cold symptoms.

Transfarma, Thai.†.
Pipazetate hydrochloride (p.1570·3).
Coughs.

Asta Medica, Braz.†.
Aerosol: Cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Coughs.

Ache, Braz.
Suppositories: Camphor (p.2273·2); guaiacol (p.1561·2); cineole (p.2282·3); menthol (p.2340·1).
Respiratory-tract congestion.

Ache, Braz.
Syrup: Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Transpulmin Baby *Viatris, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Cold symptoms.

Transpulmin Balsam
Note. This name is used for preparations of different composition.
Viatris, Ger.
Cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2).
Cold symptoms.

Transfarma, Philipp.
Camphor (p.2273·2); chamomile (p.2279·3); cineole (p.2282·3); menthol (p.2340·1); sage oil (p.2382·3).
Cold and influenza symptoms; cough; respiratory congestion.

Transpulmin Balsamo *Ache, Braz.*
Camphor (p.2273·2); guaiacol (p.1561·2); cineole (p.2282·3); menthol (p.2340·1).
Respiratory-tract congestion.

Transpulmin G *Transfarma, Philipp.*
Guaifenesin (p.1561·3).
Cough.

Transpulmin Kinderbalsam S *Viatris, Ger.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Cold symptoms.

Transpulmin N *Meda, Switz.*
Camphor (p.2273·2); cineole (p.2282·3); menthol (p.2340·1).
Respiratory-tract congestion.

Transpulmina
Note. This name is used for preparations of different composition.
Meda, Port.
Adult and paediatric suppositories; adult ointment: Camphor (p.2273·2); cineole (p.2282·3); menthol (p.2340·1).
Respiratory-tract disorders.

Meda, Port.
Paediatric ointment: Camphor (p.2273·2); cineole (p.2282·3).
Respiratory-tract disorders.

Transpulmina Gola *Bayer, Ital.*
Dequalinium chloride (p.1641·3); menthol (p.2340·1); cineole (p.2282·3).
Mouth and throat infections.

Transpulmina Tosse
Note. This name is used for preparations of different composition.
Bayer, Ital.
Pastilles: Guaifenesin (p.1561·3); menthol (p.2340·1); cineole (p.2282·3); camphor (p.2273·2).
Catarrh; coughs.

Bayer, Ital.
Syrup: Guaifenesin (p.1561·3); menthol (p.2340·1); cineole (p.2282·3).
Catarrh; coughs.

Transtec *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Denm.; AWD, Ger.; Grunenthal, Ger.; Grunenthal, Hung.; Napp, Irl.; Formenti, Ital.; Grunenthal, Mex.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Grunenthal, Spain; Grunenthal, Switz.; Napp, UK.*
⊗ Buprenorphine (p.29·1).
Pain.

Transulose *Axcan, Fr.; Pharmasearch, Neth.*
Lactulose (p.1738·2); liquid paraffin (p.2030·3); white soft paraffin (p.2031·2).
Constipation.

Transvane *Omega, Belg.*
Thurfyl salicylate (p.129·1); hexyl nicotinate (p.63·1); ethyl nicotinate (p.52·1); benzocaine (p.1854·1).
Musculoskeletal, joint, and soft-tissue disorders.

Transvasin *Thornton & Ross, Irl.*
Ethyl nicotinate (p.52·1); hexyl nicotinate (p.63·1); thurfyl salicylate (p.129·1).
Rheumatic and muscular pain; sprains; strains.

Transvasin Heat Rub *Thornton & Ross, UK.*
Ethyl nicotinate (p.52·1); hexyl nicotinate (p.63·1); thurfyl salicylate (p.129·1).
Musculoskeletal and joint pain; sprains; strains.

Transvasin Heat Spray *Thornton & Ross, UK.*
Glycol salicylate (p.62·3); diethylamine salicylate (p.47·2); methyl nicotinate (p.85·3).
Musculoskeletal and joint pain.

Transvercid *Pierre Fabre, Fr.; Pierre Fabre Dermo-Cosmetique, Port.*
Salicylic acid (p.1612·2).
Warts.

Trans-Ver-Sal *Westwood-Squibb, Canad.; Prater, Chile†; Difa, Ital.; Darier, Mex.*
Salicylic acid (p.1612·2).
Calluses; keratinisation disorders; verrucas; warts.

Trans-Ver-Sal AdultPatch *Doak, USA.*
Salicylic acid (p.1612·2).
Verrucas.

Trans-Ver-Sal PediaPatch *Doak, USA.*
Salicylic acid (p.1612·2).
Formerly known as PediaPatch.
Warts.

Trans-Ver-Sal PlantarPatch *Doak, USA.*
Salicylic acid (p.1612·2).
Formerly known as Trans-Plantar.
Warts.

Transvital *Gynopharm, Chile.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Transzone *Par, USA.*
Melatonin (p.2338·3).

Trant *Maver, Chile.*
Trazodone hydrochloride (p.424·3).
Depression.

Trantalol *Pinewood, Irl.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Tranvagal *Essex, Chile†.*
Parapenzolate bromide (p.1761·1); chlordiazepoxide (p.968·1).
Gastrointestinal disorders.

Tranvit *Gal, Pol.*
Cod-liver oil (p.1935·2); colecalciferol (p.1986·2); vitamin A (p.1971·2).
Vitamin A and D deficiency.

Tranxal *CTI, Israel.*
Dipotassium clorazepate (p.980·1).
Alcohol withdrawal syndrome; anxiety.

Tranxen *Sanofi-Aventis, Venez.*
Dipotassium clorazepate (p.980·1).
Anxiety.

Tranxene *Sanofi-Aventis, Belg.; Abbott, Canad.†; Sanofi Synthelabo, Cz.†; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Boehringer Ingelheim, Irl.†; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Thai.; Boehringer Ingelheim, UK†; Ovation, USA.*
Dipotassium clorazepate (p.980·1).
Agitation; alcohol and drug withdrawal syndromes; anxiety; disturbed behaviour; epilepsy; insomnia; mixed anxiety depressive states; neuroses; premedication; psychoses; seizures; tension; tetanus; tetany.

Tranxilene *Sanofi-Aventis, Braz.; Sanofi Synthelabo, Turk.*
Dipotassium clorazepate (p.980·1).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Tranxilium *Sanofi Synthelabo, Arg.; Sanofi Synthelabo, Austria; Rider, Chile; Sanofi Synthelabo, Ger.; Euro Registratie, Neth.; Sanofi-Aventis, Spain; Sanofi Synthelabo, Switz.*
Dipotassium clorazepate (p.980·1).
Agitation; alcohol withdrawal syndrome; anxiety; convulsions; delirium tremens; insomnia; premedication.

Tranxilium Digest *Sanofi Synthelabo, Arg.*
Dipotassium clorazepate (p.980·1); sulpiride (p.1028·3).
Anxiety; digestive disorders; peptic ulcer.

Tranxilium N *Sanofi Synthelabo, Ger.*
Nordazepam (p.1012·1).
Anxiety; sleep disorders.

Tranzicalm *Vocate, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Trapanal *Altana, Ger.; Altana, Hung.†.*
Thiopental sodium (p.1795·2).
General anaesthesia.

Trapax *Wyeth, Arg.*
Lorazepam (p.1004·1).
Anxiety; epilepsy; nausea and vomiting; premedication.

Traplicina *Degorts, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Trasedal *Elerte, Fr.†.*
Tramadol hydrochloride (p.130·3).
Pain.

Trasicor *Novartis, Austria; Novartis, Canad.; Novartis, Denm.†; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Sanofi Synthelabo, Hung.†; Sandoz, Neth.; Novartis, Spain; Novartis, Switz.; Novartis, Turk.; Amdipharm, UK.*
⊗ Oxprenolol hydrochloride (p.1365·1).
Angina pectoris; anxiety; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; myocardial infarction; phaeochromocytoma.

Trasidrex *Goldshield, UK.*
⊗ Oxprenolol hydrochloride (p.1365·1); cyclopenthiazide (p.1254·1).
These ingredients can be described by the British Approved Name Co-prenozide.
Hypertension.

Trasik *Fahrenheit, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Trasitensin *Novartis, Austria; Novartis, Ger.†; Novartis, Gr.; Teofarma, Ital.; Novartis, Spain.*
⊗ Oxprenolol hydrochloride (p.1365·1); chlortalidone (p.1243·3).
Hypertension.

Trasitensine *Novartis, Fr.*
⊗ Oxprenolol hydrochloride (p.1365·1); chlortalidone (p.1243·3).
Hypertension.

Traskolan *Jelfa, Pol.†.*
Aprotinin (p.1055·1).
Hyperfibrinolytic haemorrhage.

Trastocir *Ivax, Arg.*
Cilostazol (p.1245·2).
Peripheral vascular disorders.

Trasylol *Bayer, Austral.†; Bayer, Austria†; Bayer, Belg.†; Bayer, Braz.†; Bayer, Canad.†; Bayer, Chile†; Bayer, Cz.†; Bayer, Denm.†; Bayer, Fin.†; Bayer, Fr.†; Bayer, Ger.†; Bayer, Gr.†; Bayer, Hong Kong†; Bayer, Hung.†; Bayer, Indon.; Bayer, Malaysia†; Bayer, Mex.†; Bayer, NZ†; Bayer, Neth.†; Bayer, Pol.†; Bayer, Rus.†; Bayer, S.Afr.†; Bayer, Singapore†; Bayer, Spain†; Bayer, Swed.†; Bayer, Switz.†; Bayer, Thai.†; Bayer, Turk.†; Bayer, UK†; Bayer, USA†; Bayer, Venez.†.*
Aprotinin (p.1055·1).
Antidote to thrombolytic therapy; haemorrhage; reduction of blood loss or transfusion requirements in coronary bypass operations; shock.

Tratacne *Valeant, Arg.*
Tretinoin (p.1618·1); erythromycin (p.269·2).
Acne.

Tratenamin *Duncan, Arg.†.*
Lorazepam (p.1004·1).
Anxiety.

Tratfer *Cazi, Braz.†.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Tratinal *Serral, Mex.*
Pravastatin (p.1375·1).
Hypercholesterolaemia.

Tratobes *Columbia, Arg.*
⊗ Diethylpropion hydrochloride (p.2154·3); fenproporex hydrochloride (p.2157·1); diazepam (p.986·3).
Obesity.

Tratomax
Note. This name is used for preparations of different composition.
Lafedar, Arg.
Pessaries: ⊗ Metronidazole (p.837·1); nystatin (p.543·2); dexamethasone (p.1526·1); lidocaine (p.1862·3); neomycin sulfate (p.305·1).
Vulvovaginal infections.

Lafedar, Arg.
Tablets: Metronidazole (p.837·1); nystatin (p.543·2).
Fungal infections; trichomoniasis.

Tratul *Gerot, Austria.*
Diclofenac (p.44·2) or diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Biliary and renal colic; fever; gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Tratzol *Cazi, Braz.*
Itraconazole (p.536·3).
Fungal infections.

Trauma Relief *Brauer, Austral.†.*
Homoeopathic preparation.

Traumac *Catarinense, Braz.*
Benzocaine (p.1854·1); camphor (p.2273·2); lavender (p.2331·1); turpentine oil (p.2406·3); menthol (p.2340·1); methyl salicylate (p.85·3).
Musculoskeletal and joint disorders.

TraumaCal *Mead Johnson, Austral.†; Novartis Nutrition, Canad.; Mead Johnson, NZ†; Mead Johnson Nutritionals, USA.*
Preparation for enteral nutrition (p.1922·1).
Stress.

Traumacel P *Synapse, Irl.*
Calcium oxidised cellulose (p.1075·1).
Capillary bleeding.

Trauma-cyl *Liebermann, Ger.*
Chamomile oil (p.2279·3); sage oil (p.2382·3); arnica (p.2260·2); aesculus (p.2248·2); hamamelis (p.2318·2).
Soft-tissue injury; vascular disorders.

Trauma-cyl N Complex *Liebermann, Ger.*
Homoeopathic preparation.

Trauma-Dolgit *Dolorgiet, Ger.*
Ibuprofen (p.64·2).
Musculoskeletal and joint disorders; sports injuries.

Traumagel *Sanval, Braz.*
Methyl salicylate (p.85·3); camphor (p.2273·2); turpentine oil (p.2406·3).
Musculoskeletal and joint disorders.

Traumakatt *Kattwiga, Ger.*
Homoeopathic preparation.

Traumal *Novartis Consumer, Ital.†.*
Oxerutins (p.2304·3); a heparinoid (p.1305·2).
Bruises; sprains.

Traumalgyl *Pharmadeveloppement, Fr.*
Mephenesin (p.1897·2); diethylamine salicylate (p.47·2); lidocaine (p.1862·3).
Muscular pain.

Traumalitan *3M, Ger.†.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Traumalix *Drossapharm, Switz.*
Etofenamate (p.53·1).
Peri-articular and soft-tissue disorders.

TraumAmine *Eczacibasi-Baxter, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Traumanase *Cassella-med, Ger.; Aventis, Switz.*
Bromelains (p.2269·1).
Inflammation; oedema.

Traumaplant *Kwizda, Austria; Harras-Curarina, Cz.; Harras-Curarina, Ger.; Cofasa, Venez.*
Comfrey (p.2286·3).
Musculoskeletal, joint, and soft-tissue disorders; wounds.

Trauma-Puren *Alpharma-Isis, Ger.†.*
Heparin sodium (p.1301·2); menthol (p.2340·1); glycol salicylate (p.62·3).
Haematoma; inflammation; phlebitis.

Traumaril *Madaus, Cz.†.*
Sodium aescinate (p.2248·2).
Cerebral trauma; inflammation; oedema.

Trauma-Salbe kuhlend *Mayrhofer, Austria.*
Methyl salicylate (p.85·3); camphor (p.2273·2); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Trauma-Salbe Rodler 301 N *Woelm, Ger.†.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3).
Cold symptoms; musculoskeletal, joint, and peri-articular disorders.

Trauma-Salbe Rodler 302 N *Woelm, Ger.†.*
Camphor (p.2273·2); turpentine oil (p.2406·3); eucalyptus oil (p.2301·2).
Muscle and joint injuries.

Trauma-Salbe warmend *Mayrhofer, Austria.*
Methyl salicylate (p.85·3); capsicum (p.2276·2); turpentine oil (p.2406·3).
Musculoskeletal, joint, and soft-tissue disorders.

Traumasenex *Riemser, Ger.*
Glycol salicylate (p.62·3).
Rheumatism; soft-tissue disorders.

Traumasept *Wolff, Ger.*
Povidone-iodine (p.1659·2).
Burns; skin and mucous membrane disinfection; skin infections; ulcers; vaginal infections; wounds.

Traumasik *Medikon, Indon.*
Tramadol (p.132·1).
Pain.

Traumasive *Hexal, Ger.*
Hydrocolloid dressing.
Burns; wounds.

Traumazol *Chinoin, Mex.*
Ethyl chloride (p.1861·2).
Local anaesthesia; muscle cramps; soft-tissue disorders.

Traumazym *Mucos, Austria.*
Rutoside (p.2305·1); bromelains (p.2269·1); trypsin (p.2405·3).
Inflammation; musculoskeletal and joint disorders; pain; thrombophlebitis.

Traumed *Herbarium, Braz.†.*
Arnica (p.2260·2); ginkgo biloba (p.2311·1); aesculus (p.2248·2); menthol (p.2340·1); camphor (p.2273·2).

Traumeel *Peithner, Austria; Heel, Cz.; Heel, Neth.; Heel, USA; Biotecnoquimica, Venez.*
Homoeopathic preparation.

Traumeel S *Heel, Ger.; Heel, S.Afr.*
Homoeopathic preparation.

Traumicid
Note. This name is used for preparations of different composition.
Sanofi Pasteur, Chile.
Clonixin lysine (p.37·1).
Inflammation; pain.

Montefarmaco, Ital.†.
Methylbenzethonium chloride (p.1653·1); chlorothymol (p.1640·1).
Wound disinfection.

Traumon *Kolassa, Austria; Bayer, Cz.; Tropon, Ger.; Goodwill, Hung.†; Bayer, Pol.*
Etofenamate (p.53·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Traumox *Medpro, S.Afr.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal, joint, and peri-articular disorders.

Traumselamin *Biosel, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Trausan *Vitoria, Port.*
Citicoline sodium (p.2283·3).
Cerebrovascular disorders.

Travacalm *Key, Austral.*
Dimenhydrinate (p.576·2); hyoscine hydrobromide (p.1734·1); caffeine (p.1116·3).
Motion sickness.

Travacalm HO *Key, Austral.*
Hyoscine hydrobromide (p.1734·1).
Motion sickness.

Travacalm Natural *Key, Austral.*
Ginger (p.1732·3).
Motion sickness.

Travad
Note. This name is used for preparations of different composition.
Baxter, Austral.†.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Baxter, Mex.†.
Sodium citrate (p.1673·3); sodium phosphate (p.1682·3).
Bowel evacuation.

Travahex *Baxter, Fin.*
Chlorhexidine acetate (p.1635·2).
Skin, wound, and mucous membrane disinfection.

Travamin *Rekah, Israel.*
Dimenhydrinate (p.576·2).
Motion sickness; radiation sickness.

Travamine *ICN, Canad.†.*
Dimenhydrinate (p.576·2).

Travasept *Baxter, Israel; Baxter, UK.*
Cetrimide (p.1634·1); chlorhexidine acetate (p.1635·2).
Disinfection of burns and wounds; skin disinfection.

Travasol *Baxter Immuno, Arg.; Baxter, Canad.; Teva, Israel; Baxter, Mex.†; Clintec, Neth.; Baxter, USA.*
Amino-acid infusion with or without carbohydrate and electrolytes (p.1922·1).
Parenteral nutrition.

Travasorb *Clintec, USA.*
A range of preparations for enteral nutrition (p.1922·1).

Travatan *Alcon, Arg.; Alcon, Austral.; Alcon, Austria; Alcon, Belg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Cz.; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.; Alcon, Indon.; Alcon, Irl.; Alcon, Israel; Alcon, Ital.; Alcon, Malaysia; Alcon, Mex.; Pacific, NZ; Alcon, Neth.; Alcon, Norw.; Alcon, Philipp.; Alcon, Pol.; Alcon, Port.; Alcon, Rus.; Alcon, S.Afr.; Alcon, Singapore; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Thai.; Alcon, Turk.; Alcon, UK; Alcon, USA; Alcon, Venez.*
Travoprost (p.1886·1).
Glaucoma; ocular hypertension.

Travazol *Bilim, Turk.*
⊗ Isoconazole nitrate (p.536·2); diflucortolone valerate (p.1529·2).
Infected skin disorders.

Traveget *Cafar, Venez.*
Belladonna (p.2263·3); ergotamine tartrate (p.620·1); phenobarbital (p.492·2).

Travel Aid *WestCan, Canad.†.*
Dimenhydrinate (p.576·2).
Nausea; vomiting.

Travel Sickness
Note. This name is used for preparations of different composition.
Homeocan, Canad.
Homoeopathic preparation.

Cantassium Co., UK.
Ginger (p.1732·3).

Travel Sickness Cocculus L73 *Homeocan, Canad.†.*
Homoeopathic preparation.

Travel Well *M4, Spain.*
Dimenhydrinate (p.576·2).
Motion sickness.

Travelaide *Yauyip, Austral.†.*
Ginger (p.1732·3); cardamom (p.2277·1); slippery elm (p.2388·2).
Motion sickness.

Travelan *Anadis, Austral.*
Bovine colostrum (p.2208·1).
Travellers' diarrhoea.

Travelbac *Healthcare Innovations, UK.*
Bacterial extracts; vitamin B substances; yeast (p.1922·1).
Dietary supplement for travellers.

Traveleeze *Ernest Jackson, UK.*
Meclozine hydrochloride (p.584·3); ginger (p.1732·3).
Motion sickness.

Travel-Gum *Viatris, Austria; Meda, Cz.*
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Travelgum *Health-Care, Gr.; Viatris, Ital.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting.

Travelin *VSM, Neth.*
Homoeopathic preparation.

Travella *Nelson, UK.*
Homoeopathic preparation.

Travello *Pharmacia, Denm.†; Pfizer, Norw.; Pfizer, Swed.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Travelmin *Roux-Ocefa, Arg.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease; vertigo.

Travert *Baxter, USA.*
Invert sugar (p.1949·1); electrolytes (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Travex *Meda, Port.*
Tramadol hydrochloride (p.130·3).
Pain.

Travex One *Tropon, Ger.; Viatris, Ger.*
Tramadol hydrochloride (p.130·3).
Pain.

Traviata *Andromaco, Chile.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic attacks; social phobia.

Travilan *Anfarm, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Travisco *Farmalab, Braz.; Master Pharma, Ital.*
Trapidil (p.1416·3).
Ischaemic heart disease; prevention of restenosis following angioplasty; thromboembolism prophylaxis.

Travocort *Schering, Austria; Schering, Belg.; Intendis, Ger.; Schering, Gr.; Schering, Hong Kong; Schering, Indon.; Schering, Irl.; Intendis, Ital.; Bayer Schering, Malaysia; Schering, Philipp.; Intendis, Pol.; Intendis, Port.; Schering, Rus.; Schering, S.Afr.; Intendis, Singapore; Schering, Switz.; Schering, Thai.; Schering, Turk.*
⊗ Isoconazole nitrate (p.536·2); diflucortolone valerate (p.1529·2).
Skin disorders with fungal infection.

Travogen
Schering, Austria.
Isoconazole (p.536·2) or isoconazole nitrate (p.536·2).
Fungal skin and nail infections.

Schering, Belg.; Asche, Ger.†; Schering, Ger.†; Schering, Gr.; Schering, Hong Kong; Intendis, Ital.; Bayer Schering, Malaysia; Schering, Philipp.; Intendis, Pol.; Schering, Rus.; Intendis, Singapore; Schering, Switz.; Schering, Thai.; Schering, Turk.
Isoconazole nitrate (p.536·2).
Bacterial vaginosis; erythrasma; fungal infections of the skin, vulva, and vagina.

Travogyn *Ativus, Braz.*
Tioconazole (p.548·2); tinidazole (p.848·3).
Formerly contained tioconazole and tiabendazole.
Vaginal infections.

Trawell *Viatris, Switz.*
Dimenhydrinate (p.576·2).
Motion sickness.

Trawell compositum *Meda, Switz.*
Dimenhydrinate (p.576·2); caffeine (p.1116·3); pyridoxine hydrochloride (p.1978·2).
Motion sickness.

Trax *Arlex, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Traxam *Goldshield, Irl.; Wyeth Lederle, Ital.; Goldshield, UK.*
Felbinac (p.54·3).
Musculoskeletal, joint, and peri-articular disorders; soft-tissue injuries.

Traxamic *Systopic, India†.*
Tranexamic acid (p.1080·3).
Fibrinolysis; menorrhagia.

Traxaton *Combustin, Ger.*
Oak bark (p.2355·3).
Diarrhoea.

Traxonol *Geolab, Braz.†.*
Itraconazole (p.536·3).
Fungal infections.

Tray-Te *Gray, Arg.*
Tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Trazec *Novartis, Cz.; Novartis, Neth.; Novartis, Port.*
Nateglinide (p.455·2).
Diabetes mellitus.

Trazel *Behrens, Venez.*
Trace element preparation (p.1922·1).
Parenteral nutrition.

Trazep *Fahrenheit, Indon.*
Diazepam (p.986·3).
Convulsions; premedication.

Trazer *Pulitzer, Ital.*
Itraconazole (p.536·3).
Fungal infections.

Trazidex *Sophia, Mex.; Elmor, Venez.*
⊗ Tobramycin sulfate (p.354·2); dexamethasone (p.1526·1).
Infected eye disorders.

Trazil
Sophia, Mex.
Tobramycin sulfate (p.354·2).
Bacterial eye infections.

Elmor, Venez.†.
Tobramycin (p.354·1).
Bacterial eye infections.

Trazinac *Sophia, Mex.; Elmor, Venez.*
Diclofenac sodium (p.44·3); tobramycin sulfate (p.354·2).
Adjunct to eye surgery; bacterial eye infections.

Trazo *Medifive, Thai.*
Trazodone hydrochloride (p.424·3).
Anxiety; depression.

Trazodil *Unipharm, Israel.*
Trazodone hydrochloride (p.424·3).
Depression.

Trazograf *Juste, Spain.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Trazograph *Unique, Rus.*
Meglumine amidotrizoate (p.1475·3) with or without sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Trazolan *Continental Pharma, Belg.; Pfizer, Neth.*
Trazodone hydrochloride (p.424·3).
Depression.

Trazone *Tecnifar, Port.*
Trazodone hydrochloride (p.424·3).
Depression.

Trazorel *ICN, Canad.†.*
Trazodone hydrochloride (p.424·3).
Depression.

Trazoteva *Teva Tuteur, Arg.*
Docetaxel (p.710·3).
Breast cancer; non-small cell lung cancer.

Trazyl *Angelini, Ital.*
⊗ Ibopamine hydrochloride (p.1312·1).
Diagnosis of glaucoma; postoperative ocular hypotension; production of mydriasis.

TRD-Contin *Modi-Mundipharma, India.*
Tramadol hydrochloride (p.130·3).
Pain.

Treanda *Cephalon, USA.*
Bendamustine hydrochloride (p.684·1).
Chronic lymphocytic leukaemia.

Trebanol *Collins, Mex.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension; myocardial infarction.

Trebe *Diba, Mex.†.*
Vitamin B substances (p.1922·1).
Neuritis.

Trebon *Unipharma, Gr.*
Acetylcysteine (p.1548·2).
Respiratory disorders associated with viscous mucus.

Trecator *IFET (ΙΦΕΤ), Gr.; Wyeth-Ayerst, USA.*
Ethionamide (p.275·3).
Tuberculosis.

Trecifan *Vocate, Gr.*
Isotretinoin (p.1599·2).
Acne.

Trecloran *Collins, Mex.*
Chloramphenicol (p.239·3); tetracycline (p.347·1).
Bacterial infections.

Treda *Sanfer, Mex.*
Neomycin sulfate (p.305·1); pectin (p.2145·2); kaolin (p.1738·1).
Gastro-enteritis.

Tredalat *Bayer, Ger.*
⊗ Nifedipine (p.1350·1); acebutolol hydrochloride (p.1200·1).
Angina pectoris; hypertension.

Tredemine *Sanofi-Aventis, Fr.; IFET (ΙΦΕΤ), Gr.*
Niclosamide (p.151·1).
Tapeworm infections.

Tredol *Aegis, Hong Kong.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

tregor *Hormosan, Ger.*
Amantadine sulfate (p.793·1).
Parkinsonism.

Trekpleister Anti-Worm *Marel, Neth.†.*
Mebendazole (p.148·3).
Worm infections.

Trekpleister APC *Marel, Neth.†.*
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Trekpleister Diarreeremmer *Marel, Neth.†.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Trekpleister Hoesttabletten *Marel, Neth.†.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Trekpleister Laxeerdragees *Marel, Neth.†.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Trekzalf *Boots Healthcare, Neth.*
Ichthammol (p.1599·1).
Pustules.

Trelibec *Mintlab, Chile.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trellium Plus *Breckenridge, USA.*
Phenazopyridine hydrochloride (p.116·2); hyoscyamine hydrobromide (p.1736·1); butalbital (p.967·2).

Treloc *AstraZeneca, Ger.; Promed, Ger.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Trelstar
Pfizer, Mex.†.
⊗ Triptorelin (p.2135·2).

Pharmacia, USA.
⊗ Triptorelin embonate (p.2135·3).
Prostatic cancer.

Tremac *Sanovel, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Tremafarm *Raffo, Chile†.*
Fluoxetine (p.397·3).
Mixed anxiety depressive states.

Tremaril *Novartis, Hung.; LPB, Ital.*
Metixene hydrochloride (p.811·3).
Parkinsonism.

Tremarit *AWD, Ger.*
Metixene hydrochloride (p.811·3).
Parkinsonism and other hyperkinetic disorders.

Tremax *Hexal, Mex.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Tremblex *Janssen-Cilag, Belg.; Janssen-Cilag, Neth.*
Dexetimide hydrochloride (p.803·2).
Drug-induced extrapyramidal disorders.

Tremenza *Sanbe, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Influenza symptoms.

Tremesal *Grunenthal, Venez.*
Doxycycline (p.267·1).
Bacterial infections.

Tremexal *Cosmopharm, Gr.*
Flutamide (p.725·1).
Prostatic cancer.

Tremix *Pliva, Spain.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Tremoforat *Klein, Ger.†.*
Belladonna (p.2263·3).
Parkinsonism.

Tremonorm *Teva, Rus.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Tremopar *Acis, Ger.†.*
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Tremoquil *Astra, Swed.†.*
Metixene hydrochloride (p.811·3).
Parkinsonism.

Tren *YSP, Malaysia.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders; hereditary angioedema.

Trenantone *Takeda, Austria; Takeda, Ger.*
⊗ Leuprorelin acetate (p.2111·1).
Breast cancer; endometriosis; prostatic cancer; uterine fibroids.

Trenat *Interbat, Indon.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; vascular eye disorders.

Trenaxin *Yung Shin, Philipp.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders.

Trendar PMS *Whitehall-Robins, Canad.†.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Trendinol *Vita, Spain†.*
Nitrendipine (p.1358·2).
Hypertension.

Trenelone *Schering-Plough, Port.*
Dexchlorpheniramine maleate (p.572·1).
Hypersensitivity reactions.

Trenfyl *Pharos, Indon.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Trenlin *CCM, Hong Kong; CCM, Malaysia; CCM, Singapore.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders.

Trentadil *Christiaens, Belg.; UCB, Fr.*
Bamifylline hydrochloride (p.1116·1).
Asthma; obstructive airways disease.

Trental *Aventis, Arg.; Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Braz.; Aventis, Canad.; Sanofi-Aventis, Chile; Sanofi-Aventis, Cz.; Aventis, Denm.; Sanofi-Aventis, Fin.; Aventis, Ger.; Aventis, Hong Kong; Sanofi-Aventis, Hung.; Aventis, India; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Norw.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Sanofi-Aventis, Port.; Aventis, Rus.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Switz.; Aventis, Thai.; Aventis, Turk.; Aventis, UK; Hoechst Marion Roussel, USA; Sanofi-Aventis, Venez.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; circulatory disorders of the eye or ear; inner ear disorders; intermittent claudication; otosclerosis; stroke.

Trentilin *Santa, Turk.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Trentin *Ikapharmindo, Indon.*
Tretinoin (p.1618·1).
Acne.

Trentox *Ferron, Indon.*
Pentoxifylline (p.1367·2).
Intermittent claudication.

Trenxy *Darya-Varia? Danpac, Indon.*
Pentoxifylline (p.1367·2).
Peripheral vascular disorders.

Treo
Note. This name is used for preparations of different composition.
Pfizer, Denm.; Pfizer, Fin.; Pfizer, Swed.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Biopharm, USA.
SPF 15; SPF 30; SPF 8: Octocrilene (p.1608·3); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); citronella oil (p.2284·2).
Sunscreen.

Treo comp *Pfizer, Swed.*
Aspirin (p.20·3); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain.

Treomycin *Chew, Thai.*
Thiamphenicol (p.351·1).
Bacterial infections.

Trepal *Okasa, Thai.; TTN, Thai.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Trepar *Korea United, Philipp.*
Dactinomycin (p.707·2).
Malignant neoplasms.

Treparin *NCSN, Ital.*
Sulodexide (p.1406·3).
Thrombosis prophylaxis.

Trepetan *Alpharma, Mex.*
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Trepidan *Max Farma, Ital.*
Prazepam (p.1019·3).
Anxiety.

Trepiline *Pharmacare, S.Afr.*
Amitriptyline hydrochloride (p.376·1).
Mixed anxiety depressive states.

Trepina *Alpharma, Mex.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; neuralgia.

Trepol *Lemery, Mex.*
Dipyridamole (p.1268·1).
Cardiovascular disorders.

Trepress *Novartis, Austria; Sandoz, Ger.*
⊗ Oxprenolol hydrochloride (p.1365·1); hydralazine hydrochloride (p.1305·3); chlortalidone (p.1243·3).
Hypertension.

Tres *Sandoz, Philipp.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1) (Rimactazid); 1 tablet, ethambutol (p.275·2).
Tuberculosis.

Tres Orix Forte *Almirall, Hong Kong; Almirall, Spain†.*
Cyproheptadine orotate (p.575·2); amino acids and vitamins (p.1922·1).
Anorexia; constitutional thinness; growth retardation; tonic; weight loss.

Tres-Be
Note. This name is used for preparations of different composition.
Cafar, Venez.
Capsules: Cobamamide (p.1980·2); benfotiamine (p.1975·2); pyridoxal phosphate (p.1978·2).
Neuritis.

Cafar, Venez.
Injection: Cobamamide (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuritis.

Tresite F *Temis, Arg.*
⊗ Liothyronine (p.2174·2); flumetasone pivalate (p.1531·1).
Skin disorders.

Tresivac *Serum Institute, India.*
A live attenuated measles, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

Tresleen *Pfizer, Austria.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic attacks; post-traumatic stress disorder; social phobia.

Tresos B *Eagle, Austral.*
Vitamin, amino-acid, and mineral preparation (p.1922·1).
Dietary supplement.

Tressliv *Cifarma, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Tretax *Teva, Cz.†.*
Altretamine (p.678·2).
Ovarian cancer.

Tretin *Gerolymatos, Gr.*
Isotretinoin (p.1599·2).
Acne.

Tretinac *Spirig, Switz.*
Isotretinoin (p.1599·2).
Acne.

Tretinak *Medicine & Business, Hung.*
Isotretinoin (p.1599·2).
Acne.

Tretinax *Roemmers Rowe, Venez.*
Tretinoin (p.1618·1).
Acne.

Tretinex *Medana, Pol.*
Isotretinoin (p.1599·2).
Acne.

Tretinoderm *Defuen, Arg.*
Tretinoin (p.1618·1).
Acne; photodamaged skin.

Tretinon *YSP, Malaysia.*
Tretinoin (p.1618·1).
Acne.

Tretin-X *Triax, USA.*
Tretinoin (p.1618·1).
Acne.

Treupel Dolo Ibuprofen *Meda, Switz.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Treupel Dolo Paracetamol *Viatris, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Treupel Grippe *Meda, Switz.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Treupel sans codeine *Asta Medica, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1).
Fever; pain.

Treupel simplex *Viatris, Switz.†.*
Aspirin (p.20·3); paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms.

Treuphadol *Treupha, Switz.*
Paracetamol (p.108·1).
Fever; pain.

Treuphadol Plus *Treupha, Switz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Trevilor *Wyeth, Ger.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Trevina *Orion, Denm.*
70 Tablets, estradiol valerate (p.2097·3); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Trev-Iron *Metro, Philipp.*
Ferrous fumarate (p.1938·3); vitamin B substances (p.1922·1).
Anaemias; dietary supplement.

Trevis *Kolassa, Austria; Unilab, Hung.*
Lactobacillus acidophilus (p.2372·3); *Bifidobacterium animalis*; *Lactobacillus bulgaricus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3).
Diarrhoea.

Trex *Saval, Chile.*
Azithromycin (p.207·1).
Bacterial infections.

Trexall *Barr, USA.*
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Trexan
Note. This name is used for preparations of different composition.
Orion, Fin.; Orion, Hung.; Orion, Pol.
Methotrexate (p.745·2).
Graft-versus-host disease; malignant neoplasms; psoriasis; psoriatic arthritis; rheumatoid arthritis; transplant rejection.

BMS, Malaysia†; BMS, Singapore†; Du Pont, USA.
Naltrexone hydrochloride (p.1455·2).
Opioid dependence.

Atafarm, Turk.
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Trexen *Asofarma, Mex.*
Clindamycin phosphate (p.251·2).
Bacterial vaginitis.

Trexen Duo *Asofarma, Mex.*
Clindamycin phosphate (p.251·2); ketoconazole (p.539·1).
Vaginal infections.

Trexeron *Itaca, Braz.†.*
Methotrexate (p.745·2).
Malignant neoplasms; rheumatoid arthritis.

Trexil *Medic+Aid, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Trexina *Vitarum, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Trexirol NF *Armstrong, Arg.†.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Trexofin *Cheil, Singapore.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Trexol *Atlantis, Mex.*
Tramadol hydrochloride (p.130·3).
Pain.

Trexydin *Ranbaxy, Malaysia†.*
Terfenadine (p.590·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Trexyl *Ranbaxy, India†.*
Terfenadine (p.590·3).
Allergic rhinitis; urticaria.

Trezalka v Nalevovych Sacchich *Leros, Cz.*
St John's wort (p.422·3).
Depression; nervous disorders.

Trezalkova Nat *Megafyt-R, Cz.*
St John's wort (p.422·3).
Anxiety; depression.

Trezalkovy Caj *Megafyt-R, Cz.*
St John's wort (p.422·3).
Anxiety; depression.

Trezam *Glenmark, India†.*
Aztreonam (p.209·2).
Bacterial infections.

TRH *Ferring, Arg.; UCB, Belg.; Ferring, Braz.†; Berlin-Chemie, Cz.†; Ferring, Ger.; IFET (ΙΦΕΤ), Gr.; Ferring, Israel; Er-Kim, Turk.*
Protirelin (p.2175·3).
Assessment of hypothalamic-pituitary-thyroid function.

TRH Prem *Novartis Consumer, Spain.*
Protirelin (p.2175·3).
Evaluation of thyroid function.

Trhelea *Elea, Arg.*
Protirelin (p.2175·3).
Diagnosis of hypothalamic-pituitary-thyroid dysfunction.

Tri Act *Bernofarm, Indon.*
Aluminium hydroxide (p.1706·2); magnesium trisilicate (p.1744·1); dimeticone (p.1770·2).
Gastric hyperacidity; gastritis; peptic ulcer.

Tri Hachemina *Medea, Spain.*
Inositol (p.2325·2); calcium pantothenate (p.1959·3); aminobenzoic acid (p.1589·1) or sodium aminobenzoate (p.2388·3).
Infertility; skin disorders.

Tri Vit with Fluoride *Barre-National, USA†.*
Multivitamin preparation with fluoride (p.1962·2)(p.1922·1).
Dental caries prophylaxis; dietary supplement.

Triac *Ache, Braz.†.*
Tiratricol (p.2177·3).
Thyroid disorders.

Triacana *Sidus, Arg.; Andromaco, Chile†; Laphal, Fr.†.*
Tiratricol (p.2177·3).
Lipodystrophy; obesity; thyroid disorders; treatment of cellulite.

Triacef *Unison, Thai.*
Ceftriaxone (p.238·1).
Bacterial infections.

Triacel *Sanofi Pasteur, Arg.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Triacet *Lemmon, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triacid *Lampugnani, Ital.*
Lactobacillus acidophilus (p.2372·3); lactic acid (p.2329·3); soya (p.1965·3).
Restoration of vaginal and urinary-tract flora.

Triacomb *Ratiopharm, Canad.†; Technilab, Hong Kong; Technilab, Pol.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Anal and vulvar pruritus; infected skin disorders.

Triacor *Aventis, Arg.; Sanofi-Aventis, Gr.; Aventis, Mex.*
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Triacort *Pharmatex, Ital.; Akrikhin, Rus.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Triad *Forest Pharmaceuticals, USA.*
Butalbital (p.967·2); paracetamol (p.108·1); caffeine (p.1116·3).
Tension headache.

Triada *Loren, Mex.†.*
Vitamin B substances (p.1922·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.

Tri-Adcortyl *BMS, UK.*
⊗ Nystatin (p.543·2); triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Bacterial and fungal skin infections; otitis externa.

Triadene *Bayer, UK.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Triphasic oral contraceptive.

Triaderm
Note.This name is used for preparations of different composition.
Taro, Canad.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Ivax, Cz.
⊗ Triamcinolone acetonide (p.1544·3); chloroxine (p.242·2).
Infected skin disorders.

Triadex *Interbat, Indon.*
Diphenhydramine hydrochloride (p.577·2); guaifenesin (p.1561·3); sodium citrate (p.1673·3); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms; cough.

Triafemi *Effik, Fr.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triagynon *Schering, Spain.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triaken *Kendrick, Mex.*
Ceftriaxone sodium (p.237·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Triaklim *Gedeon Richter, Cz.†; Gedeon Richter, Hung.; Gedeon Richter, Rus.*
18 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; norethisterone acetate (p.2119·3); pink tablets, estradiol.
Menopausal disorders; osteoporosis.

Trial AG *Zee, USA.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Trial Antacid *Zee, USA.*
Calcium carbonate (p.1714·1).
Antacid.

Trial Combi *Beta, Arg.*
2 Patches, estradiol (p.2097·2); 2 patches, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Trial Gel *Beta, Arg.*
Estradiol (p.2097·2).
Oestrogen deficiency.

Trial Gest *Beta, Arg.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Trial Pack *Beta, Arg.†.*
Patches, estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders.

Trial Sat *Beta, Arg.*
Estradiol (p.2097·2).
Menopausal disorders.

Trialix *Aventis, Austria; Sanofi-Aventis, Irl.; Aventis, Switz.*
⊗ Ramipril (p.1385·3); piretanide (p.1372·3).
Hypertension.

Triallin *Iromedica, Switz.*
Ginseng (p.2312·1); garlic (p.2309·2); ginkgo biloba (p.2311·1); crataegus (p.2289·1).
Mental function impairment; vertigo.

Trialmin *Menarini, Spain.*
Gemfibrozil (p.1295·3).
Hyperlipidaemias.

Trialona *Alter, Spain.*
⊗ Fluticasone propionate (p.1533·2).
Asthma.

Trialone *Janssen-Cilag, S.Afr.*
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Trialyn *Trianon, Canad.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Triam
Winthrop, Ger.
⊗ Triamcinolone (p.1544·2) or triamcinolone acetonide (p.1544·3).
Corticosteroid.

Denk, Hong Kong; Denk, Singapore†.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Hyrex, USA†.
⊗ Triamcinolone diacetate (p.1544·3).
Corticosteroid.

Triam Tiazida R *Normal, Port.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Triama *Samakeephaesaj, Thai.†.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triam-A *Hyrex, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Triamaxco *Ashbourne, UK†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
These ingredients can be described by the British Approved Name Co-triamterzide.
Hypertension; oedema.

Triamcinal *Polychronus, Gr.*
⊗ Triamcinolone (p.1544·2).
Allergic rhinitis.

Triamcinolon Compositum *Galena, Cz.†.*
⊗ Triamcinolone acetonide (p.1544·3); chloroxine (p.242·2).
Skin disorders.

Triamcinolon E *Zentiva, Cz.*
⊗ Triamcinolone acetonide (p.1544·3); chloroxine (p.242·2).
Skin disorders.

Triamcinolon S *Zentiva, Cz.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Skin disorders.

Triamcinolon-Galena *Galena, Cz.†; Ivax, Cz.†.*
Mousse: ⊗ Triamcinolone acetonide (p.1544·3); chloroxine (p.242·2).
Skin disorders.

Triamcinolon-Ivax
Note.This name is used for preparations of different composition.
Ivax, Cz.
Lotion: ⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Ivax, Cz.
Tincture: ⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2); carbaethopendecinium bromide (p.1633·3).
Skin disorders.

Triamciterap
Note.This name is used for preparations of different composition.
Frasca, Arg.
⊗ Triamcinolone (p.1544·2).
Skin disorders.

Medica, Arg.†.
Emollient.

Triam-Co *Ivax, Hong Kong†; Norton, Rus.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Hypertension; oedema.

Triamco *Ivax, UK.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
These ingredients can be described by the British Approved Name Co-triamterzide.
Hypertension; oedema.

Triamcort
Interbat, Indon.
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Helvepharm, Switz.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

TriamCreme *Winthrop, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triamer *Aventis Pasteur, Belg.†.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation of infants and young children.

Triamgalen *Galen, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triamhexal *Hexal, Austria; Hexal, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Triamid *Beta, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Triaminic
Note.This name is used for preparations of different composition.
Novartis Consumer, Ital.
Nasal spray: ⊗ Chlorphenamine maleate (p.571·3); oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Novartis, India†.
Syrup; tablets: Phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Triaminic Syrup formerly contained phenylpropanolamine hydrochloride and chlorphenamine maleate.
Cold symptoms; otitis media; rhinitis.

Novartis Consumer, Ital.
Tablets: Phenylpropanolamine hydrochloride (p.1569·3); pheniramine maleate (p.587·3); mepyramine maleate (p.585·2); caffeine (p.1116·3).
Cold symptoms.

Triaminic Allergy Congestion *Novartis Consumer, Canad.†; Novartis Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal and sinus congestion.

Triaminic Allergy Sinus & Headache *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Triaminic AM Decongestant Formula *Novartis Consumer, USA†.*
Pseudoephedrine hydrochloride (p.1571·2).

Triaminic AM Non-Drowsy Cough & Decongestant *Novartis Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Triaminic Batuk *Novartis, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Colds; coughs.

Triaminic Chest & Nasal Congestion *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Triaminic Cold & Allergy *Novartis Consumer, Canad.; Novartis, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly contained chlorphenamine maleate and phenylpropanolamine hydrochloride.
Cold and allergy symptoms; nasal and sinus congestion.

Triaminic Cold & Cough *Novartis Consumer, Canad.; Novartis Consumer, Israel; Novartis, USA.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; cold symptoms; upper respiratory-tract congestion.

Triaminic Cold, Cough & Fever *Novartis Consumer, Israel.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; coughs.

Triaminic Cold & Cough Thin Strips *Novartis, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; cough.

Triaminic Cold & Fever *Novartis Consumer, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Triaminic Cold & Nightime Cough *Novartis Consumer, Canad.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Triaminic Cold & Sore Throat *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Triaminic Cough
Note.This name is used for preparations of different composition.
Novartis Consumer, Israel; Novartis, USA.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; upper respiratory-tract congestion.

Novartis Consumer, Canad.
Chewable tablets; lozenges: Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Novartis Consumer, Canad.†.
Syrup: Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal and sinus congestion.

Triaminic Cough & Cold *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).

Triaminic Cough & Congestion *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Triaminic Cough & Fever *Novartis Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Formerly known as Triaminic Cold, Cough & Fever.
Cold and influenza symptoms; coughs.

Triaminic Cough with Mucous *Novartis Consumer, Israel.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs; upper respiratory-tract congestion.

Triaminic Cough & Runny Nose *Novartis, USA.*
Diphenhydramine hydrochloride (p.577·2).
Coughs.

Triaminic Cough & Sore Throat
Note.This name is used for preparations of different composition.
Novartis Consumer, USA.
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Coughs and cold symptoms.

Novartis Consumer, Canad.
Oral Liquid; tablets (chewable): Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).

Novartis Consumer, Canad.
Syrup: Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Triaminic CS *Wander, India†.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine (p.1569·2).
Cold symptoms; otitis media; rhinitis.

Triaminic Daytime Cough & Cold *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).

Triaminic DM *Novartis Consumer, Canad.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Triaminic DM Expectorant *Novartis Consumer, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Triaminic DM Nighttime *Novartis Consumer, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; nasal congestion.

Triaminic Expectorant
Note.This name is used for preparations of different composition.
Novartis Consumer, Canad.†.
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Coughs; nasal congestion.

Novartis, Indon.
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Colds; coughs.

Triaminic Flu, Cough & Fever *Novartis Consumer, USA.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Formerly contained paracetamol, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and chlorphenamine maleate.
Coughs and cold symptoms.

Triaminic Infant Decongestant Plus Cough *Novartis Consumer, USA.*
Dextromethorphan (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Triaminic Infant Oral Decongestant *Novartis, USA†.*
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Triaminic Infant Thin Strips Decongestant *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Triaminic Long Acting Cough *Novartis Consumer, Canad.; Novartis Consumer, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Triaminic Night Time Cold & Cough *Novartis Consumer, USA.*
Diphenhydramine hydrochloride (p.577·2); phenylephrine hydrochloride (p.1568·1).
Formerly contained pseudoephedrine hydrochloride, chlorphenamine maleate, and dextromethorphan hydrobromide.
Coughs and cold symptoms.

Triaminic Nighttime Cough & Cold *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); diphenhydramine hydrochloride (p.577·2).

Triaminic Nighttime Flu *Novartis Consumer, Canad.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Triaminic Pediatric Drops *Novartis Consumer, Canad.*
Pseudoephedrine hydrochloride (p.1571·2).

Triaminic Pilek *Novartis, Indon.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Triaminic Softchews *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract disorders.

Triaminic Sore Throat Spray *Novartis Consumer, USA.*
Phenol (p.1656·1).
Sore throat.

Triaminic Thin Strips Cold *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Triaminic Thin Strips Cough & Congestion *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).

Triaminic Thin Strips Nasal Congestion *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1).

Triaminic Thin Strips Nighttime Cough & Runny Nose *Novartis Consumer, Canad.*
Diphenhydramine hydrochloride (p.577·2).

Triaminic Throat Pain & Cough *Novartis Consumer, Canad.; Novartis, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs; cold symptoms; sore throat.

Triaminic Toddler Congestion *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1).

Triaminic Toddler Cough & Cold *Novartis Consumer, Canad.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).

Triaminic Vapor Patch *Novartis Consumer, USA.*
Camphor (p.2273·2); menthol (p.2340·1).

Triaminicflu *Novartis Consumer, Ital.*
Paracetamol (p.108·1); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Triaminicol DM *Novartis Consumer, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs; nasal congestion.

Triamizide *Pacific, NZ.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Hypertension; oedema.

Triamonide *Forest Pharmaceuticals, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Triampoen *Poen, Arg.*
⊗ Triamcinolone (p.1544·2).
Eye disorders.

Triampur Compositum *AWD, Ger.; Pliva, Rus.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

TriamSalbe *Winthrop, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triamsicort *Diba, Mex.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Triamteren comp *GenerICon, Austria; CT, Ger.; Ratiopharm, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triamteren HCT *Aliud, Ger.; Betapharm, Ger.; Sandoz, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triamteren tri-comp *Sandoz, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3); propranolol hydrochloride (p.1380·3).
Hypertension.

Triamteren-H *3M, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triamteril *Deva, Turk.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).

Triamvirgi *Fisiopharma, Ital.*
⊗ Triamcinolone acetonide (p.1544·3).
Parenteral corticosteroid.

Trian *Demo, Gr.*
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Trianal
Note. This name is used for preparations of different composition.
Will-Pharma, Belg.; Will-Pharma, Neth.
⊗ Triamcinolone acetonide (p.1544·3); lidocaine hydrochloride (p.1862·3).
Anal eczema and pruritus; haemorrhoids.

Trianon, Canad.
Aspirin (p.20·3); caffeine (p.1116·3); butalbital (p.967·2).
Pain; sedative.

Trianal C *Trianon, Canad.*
Aspirin (p.20·3); caffeine (p.1116·3); butalbital (p.967·2); codeine phosphate (p.37·2).
Pain; sedative.

Triancil *Apsen, Braz.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Trianol
Note. This name is used for preparations of different composition.
Pharma Nutria, Philipp.
Allopurinol (p.552·2).
Hyperuricaemia.

Lek, Rus.
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Triapin *Aventis, Austria; Sanofi-Aventis, Irl.; Aventis, Neth.; Aventis, Philipp.; Aventis, UK.*
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Triapten *Riemser, Ger.*
Foscarnet sodium (p.877·3).
Herpes simplex infections of the skin and mucous membranes.

Triarese *Hexal, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Triasox *Berna, Spain†.*
Tiabendazole (p.156·2).
Worm infections.

Triaspar *Beta, Arg.*
Cabergoline (p.802·1).
Parkinsonism.

Triasporin *Italfarmaco, Ital.*
Itraconazole (p.536·3).
Fungal infections.

Triastad HCT *Stada, Austria.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triastonal *Schwarz, Ger.*
Sitosterol (p.1373·2).
Benign prostatic hyperplasia.

Triasyn *Sanofi-Aventis, Austral.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hung.*
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Triatec *Sanofi-Aventis, Braz.; Sanofi-Aventis, Chile; Aventis, Denm.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi-Aventis, Indon.; Sanofi-Aventis, Ital.; Aventis, Norw.; Sanofi-Aventis, Port.; Aventis, Swed.; Aventis, Switz.*
Ramipril (p.1385·3).
Atherosclerosis; cardiovascular risk reduction; diabetic nephropathy; glomerular nephropathy; heart failure; hypertension; ischaemic heart disease; myocardial infarction; renal insufficiency.

Triatec-8 *Trianon, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine citrate (p.1116·3).
Coughs; fever; pain.

Triatec-30 *Trianon, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Coughs; fever; pain.

Triatec Comp *Aventis, Denm.; Aventis, Swed.; Aventis, Switz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Triatec Composto *Sanofi-Aventis, Port.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Triatec D *Sanofi-Aventis, Braz.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Triatec HCT *Sanofi-Aventis, Ital.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Triatec Plus *Sanofi-Aventis, Gr.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Triativ *Ativus, Braz.*
St John's wort (p.422·3).
Agitation; depression; sleep disorders.

Triatop *Janssen-Cilag, Arg.†; Janssen-Cilag, Ital.; Janssen-Cilag, Mex.; Janssen-Cilag, Thai.†.*
Ketoconazole (p.539·1).
Scalp disorders.

Triatus *Kocak, Turk.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Triaval *Orion, Switz.*
70 Tablets, estradiol valerate (p.2097·3); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Triavil *Merck Frosst, Canad.†; Lotus, USA†.*
Perphenazine (p.1017·1); amitriptyline hydrochloride (p.376·1).
Mixed anxiety depressive states; schizophrenia.

Tri-A-Vite F *Major, USA.*
Multivitamin preparation with fluoride (p.1922·1).

Triax *Taro, Israel.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triaxis *Sanofi Pasteur, Neth.*
A diphtheria, tetanus, pertussis, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Triaxon *Teuto, Braz.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triaxone *Julphar, UAE.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triaxton *Ariston, Braz.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triaz *Medicis, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Triazi *Itaca, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

triazid *CT, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triazine *Pharmacare, S.Afr.*
Cyclizine hydrochloride (p.574·2).
Motion sickness; vertigo.

Triazol
Note. This name is used for preparations of different composition.
Biolab Sanus, Braz.
Fluconazole (p.532·1).
Fungal infections.

Ducray, Fr.†.
Clotrimazole (p.530·1); crotamiton (p.1593·2); zinc salicylate (p.1612·3).
Dandruff.

Tribakin *Farcoral, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Triban
Note. This name is used for preparations of different composition.
Solfran, Mex.
Vitamin B ; vitamin B (p.1922·1).
Anaemias; neuritis.

Great Southern, USA†.
Trimethobenzamide hydrochloride (p.592·2); benzocaine (p.1854·1).

Tribdoze *Labortecne, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Tribe 12 *Pharmacos, Mex.*
Vitamin B substances (p.1922·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Anaemias; neuritis.

Tribedoce *Bruluart, Mex.*
Hydroxocobalamin (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgia; neuritis.

Tribedoce Compuesto *Bruluart, Mex.*
1 Ampoule, diclofenac sodium (p.44·3); 1 ampoule, thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis.

Tribedoxyl
Note. This name is used for preparations of different composition.
Aventis, Mex.†.
Capsules: Cyanocobalamin (p.1980·2); benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2).
Anaemias; neuralgias; neuritis; neuropathies.

Aventis, Mex.†.
Injection: Hydroxocobalamin acetate (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Anaemias; neuralgias; neuritis; neuropathies.

Tribeksol *Deva, Turk.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Vitamin B deficiency.

Tribemin *Sam-On, Israel.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Megaloblastic anaemia; neuralgias.

Tribena *Vitae, Mex.*
Vitamin preparation (p.1922·1).
Anaemias; neuritis.

Tribesian *Asian Pharm, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; migraine; neuralgia; neuritis.

Tribesona *ITF, Chile.*
⊗ Clotrimazole (p.530·1); dexamethasone acetate (p.1526·1).
Infected skin disorders.

Tribestan *Teguhsindo, Indon.; Sopharma, Rus.*
Tribulus terrestris (p.2404·1).
Atherosclerosis; hypercholesterolaemia; male infertility; menopausal symptoms; stimulant.

Tribiocort *Biosintex, Arg.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2); miconazole (p.541·2).
Infected skin disorders.

Tribion *Universal, Hong Kong.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B supplement.

Tribiot *Grin, Mex.*
Neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); bacitracin (p.210·3).
Bacterial eye infections.

Tribiotic *Kato, Pol.*
Bacitracin zinc (p.210·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Wounds.

Tri-Biozene *Reese, USA.*
Bacitracin (p.210·3); polymyxin B sulfate (p.317·3); neomycin sulfate (p.305·1); pramocaine hydrochloride (p.1868·1).

Triblix *Lamsa, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Tribonat *Fresenius Kabi, Norw.; Fresenius Kabi, Swed.*
⊗ Trometamol (p.2405·1); electrolytes (p.1667·1).
Buffer; metabolic and respiratory acidosis.

Tribost *Ethica, Indon.*
Echinacea (p.2298·1); phyllanthus niruri; black elderberry.
Immunostimulant.

Tribudat *Santa, Turk.*
Trimebutine maleate (p.2404·3).

Tri-Buffered ASA *Zee, Canad.*
Aspirin (p.20·3).
Calcium carbonate (p.1714·1), magnesium carbonate (p.1743·1), and magnesium oxide (p.1744·1) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.

Tributina *Lafedar, Arg.*
Trimebutine maleate (p.2404·3).
Gastrointestinal motility disorders.

Tribux *Biofarm, Pol.*
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders.

TriBvit *Merck, Belg.*
Folic acid; cyanocobalamin; pyridoxine hydrochloride (p.1922·1).
Vitamin deficiency.

Tricaine-MPS *RPG, India.*
Oxetacaine (p.1867·2); simeticone (p.1770·2); aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; peptic ulcer.

Trical-D
Note. This name is used for preparations of different composition.
Knop, Chile.
Calcium carbonate (p.1714·1); calcium phosphate (p.1676·2); calcium gluconate (p.1675·3); colecalciferol (p.1986·2).
Dietary supplement.

Svizera, India.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium deficiency.

Tricalma *Sanofi-Aventis, Chile.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic attacks.

Tricalvit *Gemballa, Braz.†.*
Vitamin and mineral preparation (p.1922·1).

Trican *Pfizer, Israel.*
Fluconazole (p.532·1).
Fungal infections.

Tricandil *Grunenthal, Belg.†; SPA, Ital.; Prospa, Port.*
Mepartricin (p.541·1).
Candidiasis; fungal vaginal infections; trichomoniasis.

Tricangine *Asta Medica, Braz.†.*
Mepartricin (p.541·1); tetracycline (p.347·1).
Bacterial and fungal vulvovaginal infections.

Tricardia *Meditec, Israel.*
Folic acid (p.1940·1); vitamin B (p.1979·1); vitamin B (p.1980·2).
Elevated homocysteine levels.

Tricban *Greenpharma, Braz.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Tricef
Note. This name is used for preparations of different composition.
Merck, Austria; Merck, Chile; Bialport, Port.; Astra, Swed.†.
Cefixime (p.224·3).
Bacterial infections.

Eurofarmaco, Ital.†.
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Tricefi *Roemmers-Klinos, Venez.*
Ceftriaxone (p.238·1).
Bacterial infections.

Tricefin *Dexa, Indon.; Dexa, Singapore.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tricen *Alter, Spain.*
Verapamil hydrochloride (p.1421·1); trandolapril (p.1416·2).
Hypertension.

Tricephin *Atlantic, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tricept *Cuprocept, S.Afr.†.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Tricerol *Pharmacia, Braz.; Armstrong, Mex.†.*
Etofibrate (p.1284·2).
Atherosclerosis; hyperlipidaemias.

Trichazole *Pharmacare, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Trichex *Gerot, Austria.*
Metronidazole (p.837·1).
Gardnerella vaginalis infections; trichomoniasis.

Tri-Chlor *Gordon, USA.*
Trichloroacetic acid (p.1620·1).
Warts.

Trichlorol *Lysoform, Ger.*
Tosylchloramide sodium (p.1665·1).
Surface disinfection.

Trichobiol *Therasophia, Fr.*
Amino-acid, mineral, vitamin, and herbal preparation (p.1922·1).
Skin, hair, and nail disorders.

Trichodazol *Sanbe, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Trichol *Galenium, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Trichonas *Pharmasant, Thai.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Trichopol *Polpharma, Rus.*
Metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Trichostatic *Pharos, Indon.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

Trichotine *Schwarz, USA.*
Sodium laurilsulfate (p.2138·3); sodium perborate (p.1662·1); sodium chloride (p.1686·1).
Vaginal disorders.

Trichovagil *Ni-The, Gr.*
Metronidazole (p.837·1).
Vaginal infections.

Trichozole *Pacific, NZ.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Tri-Ciclomex *Gynopharm, Chile.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triciclor *Wyeth, Spain.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Tri-Cidal *ICM, Singapore†.*
⊗ Alcohol (p.1625·2); isopropyl alcohol (p.1650·3); triclosan (p.1665·2).
Hand and skin disinfection.

Triciderm *Ni-The, Gr.*
Tyrothricin (p.358·2).
Skin infections.

Tricidine *Pfizer Consumer, Belg.†.*
Tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Tricidine Dequalinium *Pfizer Consumer, Belg.†.*
Dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Tricifa *Richet, Arg.†.*
Piroxicam (p.117·3).
Inflammation.

Tricigel *Corsalud, Venez.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Antacid.

TriCilest *Janssen-Cilag, Austria; Codepharma, Fr.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Thai.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Acne; triphasic oral contraceptive.

Tricilon *Organon, Braz.†.*
Medroxyprogesterone (p.2113·3).
Injectable contraceptive.

Tricin *Catarinense, Braz.†.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Tricivir *GSK, Arg.; GSK, Chile.*
Abacavir sulfate (p.861·3); lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Tricker *Meprofarm, Indon.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Triclin *Solfran, Mex.†.*
Tetracycline (p.347·1).
Bacterial infections.

Tricloderm *APT, Hong Kong.*
Clotrimazole (p.530·1).
Fungal skin infections.

Triclofem *Tunggal Idaman, Indon.*
Medroxyprogesterone acetate (p.2113·1).
Injectable contraceptive.

Triclonam *CTI, Israel.*
Triclofos sodium (p.1034·1).
Insomnia; sedative.

Tricloryl
GSK, India.
Triclofos sodium (p.1034·1).
Insomnia; sedative.

Galen, Irl.†.
Triclofos (p.1034·2).
Hypnotic; sedative.

Triclose *Finderm, Ital.*
Azanidazole (p.830·3).
Vaginal trichomoniasis.

Tricocet *Legrand, Braz.*
Nystatin (p.543·2).
Fungal infections.

Tricocilin B *EMS, Braz.*
Tetracycline (p.347·1); amphotericin B (p.523·2).
Vaginal infections.

Tricodazole *Proel, Gr.*
Metronidazole (p.837·1).
Rosacea.

Tricodein *ICN, Austria; Valeant, Switz.†.*
Codeine phosphate (p.37·2).
Coughs.

Tricodene Cough & Cold *Pfeiffer, USA.*
Mepyramine maleate (p.585·2); codeine phosphate (p.37·2).
Coughs and cold symptoms.

Tricodene Sugar Free *Pfeiffer, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Tricoderm F *Farmachimici, Ital.*
Salicylic acid (p.1612·2); piroctone olamine (p.1610·1); ichthammol (p.1599·1).
Scalp disorders.

Tricodex *Ecofarm, Ital.*
Amino-acid, vitamin, and mineral preparation (p.1922·1).
Hair and nail disorders.

Tricofarma *Valeant, Arg.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Tricofin *Raymos, Arg.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Tricogyn *Pharmaland, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis.

Tricolam *Farmasierra, Spain.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Tricolocion *Valeant, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Tricolpex *Bunker, Braz.*
⊗ Metronidazole (p.837·1); nystatin (p.543·2); urea (p.1620·2).
Vulvovaginal infections.

Tricomax
Note. This name is used for preparations of different composition.
Cassara, Arg.
Copper; zinc; selenium (p.1922·1).
Dietary supplement.

Cazi, Braz.
⊗ Metronidazole (p.837·1); nystatin (p.543·2); muramidase hydrochloride (p.2348·1); urea (p.1620·2); benzalkonium chloride (p.1629·1).
Vaginal infections.

Tricomed *Hua, Thai.*
Metronidazole (p.837·1).
Trichomoniasis; vaginitis.

Tricomycin *Terramedic, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Triconal *Valeant, Arg.*
Vitamin A; ascorbic acid; calcium pantothenate; methionine; arginine; pyridoxine hydrochloride; lecithin (p.1922·1).
Dietary supplement.

Triconazole *Quality, Hong Kong.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections with inflammation.

Triconex *Multicare, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Triconidazol *Andromaco, Chile†.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Tricoplus *Defuen, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Tricoplus Conef *Defuen, Arg.†.*
⊗ Lotion, minoxidil (p.1342·1); tablets, finasteride (p.2188·3).
Alopecia androgenetica.

Tricor
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Chile.
Adenosine (p.1202·1).
Arrhythmias; diagnosis of arrhythmias.

Teijin, Jpn; Abbott, USA.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Tricort *Cadila, India.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Tricortin
Note. This name is used for preparations of different composition.
Fidia, Ital.
Phosphatides (p.2332·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Peripheral and central nervous system disorders.

Fidia, Thai.†.
Phospholipids; pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Metabolic and circulatory disorders of the brain.

Tricortone *Fawns & McAllan, Austral.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Tricovivax *Medinfar, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Tricowas B *Chiesi, Spain.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Tricox *Themis Chemicals, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Tricoxane *ICN, Arg.†; ITF, Chile.*
Minoxidil (p.1342·1).
Alopecia.

Tricoxen *IDI, Ital.*
Ubidecarenone acetate (p.2407·2).

Tricoxidil *Pfizer Consumer, Ital.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Tricozole *Pharmasant, Thai.*
⊗ Econazole nitrate (p.531·1); triamcinolone acetonide (p.1544·3).
Fungal skin infections with inflammation.

Tricozone *Hua, Thai.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Tricur *Andromaco, Arg.*
⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Tri-Cyclen *Janssen-Ortho, Canad.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Acne; triphasic oral contraceptive.

Tridanil-H *Ultra, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Tridecon *Medi-Rx, Philipp.*
Chlorphenamine maleate (p.571·3); phenylpropanolamine hydrochloride (p.1569·3).
Nasal congestion.

Tridel *Choongwae, Philipp.; Unimex, Philipp.*
Metronidazole (p.837·1).
Protozoal infections.

Tridelta *Ceccarelli, Ital.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Trident *Adams, Canad.*
Xylitol (p.1998·2).
Dental caries prophylaxis.

Triderm
Note. This name is used for preparations of different composition.
Schering-Plough, Hong Kong; Schering-Plough, Israel; Schering-Plough, Mex.; Schering-Plough, Philipp.; Schering-Plough, Pol.; Schering-Plough, Rus.; Schering-Plough, Singapore; Essex, Switz.; Schering-Plough, Venez.
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Del-Ray, USA.
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triderm 5 *ICIM, Ital.*
Barrier preparation.

Triderm Crema *ICIM, Ital.*
Zinc oxide (p.1621·2).

Triderm Zeta *ICIM, Ital.*
Zinc oxide (p.1621·2).
Skin disorders.

Tridermal *Panalab, Arg.*
⊗ Ketoconazole (p.539·1); hydrocortisone acetate (p.1535·2); gentamicin sulfate (p.282·1).
Infected skin disorders.

Triderm-C *Schering-Plough, Malaysia.*
⊗ Betamethasone dipropionate (p.1518·3); clotrimazole (p.530·1).
Fungal skin infections.

Tridesilon
Note. This name is used for preparations of different composition.
Clay Park, USA†.
Cream; ointment: ⊗ Desonide (p.1525·1).
Skin disorders.

Clay Park, USA†.
Ear drops: ⊗ Desonide (p.1525·1); acetic acid (p.2244·2).
Superficial ear infections with inflammation.

Tridesonit *CS, Fr.*
⊗ Desonide (p.1525·1).
Skin disorders.

Tridestan N *Gador, Arg.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Tridestra *Orion, UK.*
70 Tablets, estradiol valerate (p.2097·3); 14 tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); 7 tablets, inert.
Menopausal disorders; osteoporosis.

Tridetarmon *Roemmers Rowe, Venez.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1); clioquinol (p.254·1).
Infected skin disorders.

Tridette *Gador, Arg.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Tridez *Sandoz, Indon.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Tridigestivo Soubeiran *Chobet, Arg.*
Pancreatin (p.2360·1); takadiastase (p.2256·3); pepsin (p.2365·1).
Digestive disorders.

Tridil *Cristalia, Braz.; Boots, Hong Kong†; Du Pont, Hong Kong†; Sanofi Synthelabo, S.Afr.; Faulding, USA†; Zuoz, Venez.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; control of blood pressure during surgery; heart failure; ischaemic heart disease.

Tridin
Rottapharm, Chile†; Rottapharm, Cz.; Rotta, Hong Kong; Rottapharm, Hung.; Rottapharm, Ital.
Glutamine monofluorophosphate (p.1965·1); calcium gluconate (p.1675·3); calcium citrate (p.1675·3).
Osteoporosis.

Opfermann, Ger.
Sodium monofluorophosphate (p.1964·3); calcium gluconate (p.1675·3); calcium citrate (p.1675·3).
Osteoporosis.

Tridin Forte *Opfermann, Ger.*
Sodium monofluorophosphate (p.1964·3); calcium carbonate (p.1714·1).
Osteoporosis.

Triditol-G *Loyal Advance, Hong Kong.*
⊗ Triamcinolone acetonide (p.1544·3); gentamicin sulfate (p.282·1); diphenhydramine hydrochloride (p.577·2); tolnaftate (p.548·3).
Inflamed bacterial and fungal skin infections.

Tridocemine *Aventis, Port.†.*
Injection: Vitamin B (p.1980·3).
Anaemia; neuralgia; neuritis; tonic.

Tridol *Grunenthal, Austria.*
⊗ Buprenorphine (p.29·1).
Pain.

Tridomose *Aventis, S.Afr.*
⊗ Gestrinone (p.2106·1).
Endometriosis.

Tridyl *Condrugs, Thai.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Triefect *Geminis, Arg.†.*
⊗ Ketoconazole (p.539·1); gentamicin sulfate (p.282·1); hydrocortisone acetate (p.1535·2).
Infected skin disorders.

Triella *Codepharma, Fr.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Tri-Emcortina *Merck, Arg.†.*
⊗ Fluprednidene acetate (p.1533·1); neomycin sulfate (p.305·1); chloroquine (p.599·2).
Infected skin disorders.

Triene *Wassermann, Ital.*
Polyenacid (p.2308·2).
Barrier preparation; burns; skin irritation; wounds.

Trienter *Farmedia, Gr.*
Trimebutine (p.2404·3).
Gastrointestinal disorders.

Trienyl *Lek, Pol.*
Fish oil (p.1362·2).
Atherosclerosis; cardiovascular disorders; cerebrovascular disorders; hyperlipidaemias.

Triesence *Alcon, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Inflammatory eye disorders.

Triette *Stada, Ger.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triexidyl *Cristalia, Braz.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

Trifacilina *Bago, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Trifalac *Medicus, Gr.*
Dibasic sodium phosphate (p.1682·3); phosphoric acid (p.2367·1).
Constipation.

Trifamox
Note. This name is used for preparations of different composition.
Bago, Arg.
Amoxicillin (p.202·2).
Bacterial infections.

Bago, Braz.
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); pivsulbactam (p.335·1) or sulbactam sodium (p.335·1).
Bacterial infections.

Trifamox Bronquial *Bago, Arg.*
Amoxicillin trihydrate (p.202·2); brovanexine hydrochloride (p.1553·1).
Bacterial infections of the respiratory tract.

Trifamox Bronquial Duo *Bago, Arg.*
Amoxicillin trihydrate (p.202·2); ambroxol hydrochloride (p.1550·3).
Respiratory-tract infections.

Trifamox Duo *Bago, Arg.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Trifamox IBL *Bago, Arg.; Armstrong, Mex.; Bago, Rus.*
Amoxicillin sodium (p.202·2) or amoxicillin trihydrate (p.202·2); pivsulbactam (p.335·1) or sulbactam sodium (p.335·1).
Bacterial infections.

Trifas
Note. This name is used for preparations of different composition.
Silesia, Chile†.
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Berlin-Chemie, Cz.†.
⊗ Torasemide (p.1415·3) or torasemide sodium (p.1416·1).
Liver cirrhosis with ascites; oedema.

Berlin-Chemie, Pol.
⊗ Torasemide (p.1415·3).
Oedema.

Trifed *Hikma, Cz.†; Interbat, Indon.; Nakornpatana, Thai.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Allergic rhinitis; cold symptoms; nasal congestion; sinusitis.

Trifed Expectorant *Hikma, Cz.†.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3); guaifenesin (p.1561·3).
Coughs.

Trifed-C Cough *Geneva, USA.*
Pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3).
Coughs and cold symptoms.

Trifedrin
Note. This name is used for preparations of different composition.
Farmoquimica, Braz.
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3); sulfogaiacol (p.1573·2).
Cough.

Otto, Indon.
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Cold symptoms; sinusitis.

Trifeme *Wyeth, Austral.; Wyeth, NZ.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, inert.
Triphasic oral contraceptive.

Tri-Femoden *Schering, Fin.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trifen
Note. This name is used for preparations of different composition.
Hertz, Braz.
Paracetamol (p.108·1).
Fever; pain.

Be-Tabs, S.Afr.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Aroma, Turk.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trifene *Medinfar, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Triffadiane *Polinac, Venez.†.*
Centella (p.1592·3).
Stretch marks.

Trifibra Mix *Sanofi-Aventis, Braz.*
Bran (p.1712·3).
Constipation; dietary supplement.

Triflexor *Combiphar, Indon.*
Glucosamine (p.2313·2); chondroitin (p.2280·3); dimethyl sulfone (p.2294·1).
Osteoarthritis.

Triflucan *Pfizer, Arg.; Pfizer, Fr.; Pfizer, Israel; Pfizer, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Trifluid *Otsuka, Jpn.*
Carbohydrate and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Triflumann *Mann, Ger.*
Trifluridine (p.910·3).
Herpesvirus keratitis.

Triflumed *Medifive, Thai.*
Trifluoperazine (p.1034·3).
Anxiety; nausea and vomiting; psychoses.

Triflux *Scharper, Ital.*
Triflusal (p.1418·3).
Thromboembolic disorders.

Trifolium Complex *Blackmores, Austral.†.*
Yellow dock (p.2416·3); taraxacum (p.2395·1); red clover (p.2285·1); lappa (p.2330·3); zinc amino acid chelate (p.2000·1); vitamin A acetate (p.1973·1).
Skin disorders.

Triforam *Foramen, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Triforte *Rafarm, Gr.†.*
Vitamin B substances (p.1922·1).

Trifosfaneurina *Lepori, Port.*
Cocarboxylase chloride (p.1976·3).
Neuralgia; neuritis; neuromuscular disorders.

Trifosfaneurina B2 B12 *Farma Lepori, Spain†.*
Cyanocobalamin; riboflavin phosphate sodium; thiamine phosphate (p.1922·1).
Vitamin B deficiency.

Trifyba *Sanofi Synthelabo, Irl.†.*
Wheat grain extract (p.1712·3).
Bowel disorders; constipation; haemorrhoids; stoma management.

Trigan *Cadila, Rus.*
Dicycloverine hydrochloride (p.1722·3).

Trigan-D *Cadila, India; Cadila, Rus.*
Dicycloverine hydrochloride (p.1722·3); paracetamol (p.108·1).

Trigastril *Pfizer, Austria; Pfizer Consumer, Ger.*
Aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); calcium carbonate (p.1714·1).
Gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn; peptic ulcer.

Tri-Gel *Vida, Hong Kong.*
⊗ Triamcinolone acetonide (p.1544·3); lidocaine (p.1862·3); cetrimide (p.1634·1).
Oral lesions.

Trigen *Rimsa, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Trigesico *BMS, Chile.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Cold symptoms; pain.

Triginet *KRKA, Cz.; KRKA, Pol.*
Lamotrigine (p.485·1).
Bipolar disorder; epilepsy.

Trigliceril CM *Support, Braz.*
Preparation for enteral nutrition (p.1922·1).

Triglide *Sciele, USA.*
Fenofibrate (p.1286·2).
Hypercholesterolaemia.

Triglistab *Arkomedika, Fr.*
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias.

Triglobe *AstraZeneca, Braz.; AstraZeneca, Malaysia†; AstraZeneca, Philipp.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Bacterial infections.

Triglyx *Ingers, Cz.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Trigoa *Wyeth, Ger.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trigogine *Atlantic, Hong Kong; Atlantic, Singapore; Atlantic, Thai.*
Codergocrine mesilate (p.363·3).
Cerebral and peripheral vascular disorders; mental function impairment.

Trigolax *Coup, Gr.*
Potassium sodium tartrate (p.1764·1).
Laxative.

Trigon Depot *BMS, Spain.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Trigon Rectal *BMS, Spain.*
⊗ Lidocaine (p.1862·3); triamcinolone acetonide (p.1544·3).
Anorectal disorders.

Trigon Topico *BMS, Spain.*
⊗ Amphotericin B (p.523·2); gramicidin (p.286·1); neomycin sulfate (p.305·1); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Trigrip *Stada, Cz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Trigyn *Continental Pharma, Thai.†.*
Tinidazole (p.848·3).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Trigynera *Schering, Gr.*
Ethinylestradiol (p.2101·3); gestodene (p.2105·2).
Combined oral contraceptive.

Tri-Gynera *Bayer, Port.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trigynon *Schering, Austria; Schering, Belg.; Schering, Ital.; Schering, Neth.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trigynovin *Schering, Spain.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

TriHEMIC
Wyeth, Philipp.
Ferrous fumarate (p.1938·3); vitamin B (p.1980·2); intrinsic factor concentrate (p.2326·3); folic acid (p.1940·1); vitamin E.
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of ferrous fumarate. Docusate sodium (p.1725·1) is included to reduce the constipating effects of ferrous fumarate.
Anaemias.

Lederle, USA.
Ferrous fumarate (p.1938·3); vitamin B substances (p.1980·2); intrinsic factor concentrate (p.2326·3); folic acid (p.1940·1); vitamin E.
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of ferrous fumarate; docusate sodium (p.1725·1) is included to reduce the constipating effects of ferrous fumarate.
Anaemias.

Triherpine *Novartis Ophthalmics, Cz.†; Novartis Ophthalmics, Hong Kong†; Novartis Ophthalmics, Hung.†; Novartis, Ital.; Novartis, Switz.†; Novartis, Thai.*
Trifluridine (p.910·3).
Herpes simplex infections of the eye.

Trihexy *Geneva, USA.*
Trihexyphenidyl hydrochloride (p.820·2).
Parkinsonism.

TriHIBit *Sanofi Pasteur, USA.*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Trihistalex *Wolfs, Belg.*
Diphenhydramine hydrochloride (p.577·2); cinchocaine hydrochloride (p.1857·3); nicotinamide (p.1957·3).
Cutaneous hypersensitivity reactions; pain.

Trihistan *Gea, Denm.†; Weifa, Norw.†.*
Chlorcyclizine hydrochloride (p.571·2).
Hypersensitivity reactions; motion sickness; nausea; urticaria; vertigo.

Tri-Hydroserpine *Rugby, USA†.*
⊗ Hydrochlorothiazide (p.1307·3); reserpine (p.1387·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Triiodothyronine Injection *Goldshield, UK.*
Liothyronine sodium (p.2174·1).
Myxoedema coma.

Trijec *Landson, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tri-K *Century, USA.*
Potassium acetate (p.1684·2); potassium bicarbonate (p.1673·1); potassium citrate (p.1673·2).
Hypokalaemia; potassium depletion.

Trikacide *Pharmascience, Canad.*
Metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Trikal *IBN, Ital.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Tri-Kort *Keene, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Trikozol *Orion, Fin.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; antibiotic-associated colitis; Crohn's disease; eradication of Helicobacter pylori in peptic ulcer; protozoal infections.

Trikvilar *Schering, Fin.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trilac
Note. This name is used for preparations of different composition.
Novell, Indon.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Allergon, Pol.
Bifidobacterium bifidum (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus delbrueckii*.
Constipation; restoration of gastrointestinal flora.

Trilafon
Schering-Plough, Belg.†; Schering, Canad.; Schering-Plough, Indon.; Schering-Plough, Mex.†; Schering-Plough, Philipp.; Essex, Switz.; Schering, USA†.
Perphenazine (p.1017·1).
Anxiety; hiccup; nausea; pain; premedication; pruritus; psychoses; vomiting.

Schering-Plough, Denm.; Schering-Plough, Norw.
Perphenazine (p.1017·1) or perphenazine decanoate (p.1017·1).
Alcohol or opioid withdrawal syndromes; anxiety; hiccups; nausea; psychoses; vomiting.

Schering-Plough, Ital.; Schering-Plough, Pol.
Perphenazine (p.1017·1) or perphenazine enantate (p.1017·2).
Anxiety; depression; hiccups; nausea and vomiting; pain; psychoses.

Schering-Plough, Neth.; Schering-Plough, S.Afr.†.
Perphenazine enantate (p.1017·2).
Anxiety; nausea; psychoses; tension; vomiting.

Schering-Plough, Swed.
Perphenazine (p.1017·1), perphenazine decanoate (p.1017·1), or perphenazine enantate (p.1017·2).
Nausea; psychoses; vomiting.

Trilagavit *Lagap, Switz.*
Thiamine hydrochloride (p.1976·1) or thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Peripheral neuropathies.

Trilam *Gerard, Irl.*
Triazolam (p.1033·2).
Insomnia.

Trilax *Hexal, Braz.†.*
Carisoprodol (p.1894·1); diclofenac sodium (p.44·3); paracetamol (p.108·1); caffeine (p.1116·3).

Tri-Legest *Barr, USA.*
21 Tablets, norethisterone acetate (p.2119·3); ethinylestradiol (p.2101·3); 7 tablets, ferrous fumarate (p.1938·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trileptal *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Oxcarbazepine (p.490·3).
Bipolar disorder; epilepsy; neuropathic pain.

Trileptin *Novartis, Israel.*
Oxcarbazepine (p.490·3).
Epilepsy.

Tri-Levlen *Berlex, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trilifan *Schering-Plough, Fr.*
Perphenazine enantate (p.1017·2).
Psychoses.

Trilip *Elea, Arg.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Trilisate *Purdue, Canad.†; Purdue Frederick, USA†.*
Choline magnesium trisalicylate (p.36·2).
Musculoskeletal and joint disorders.

Triliver *Northia, Arg.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2); miconazole (p.541·2).
Infected skin disorders.

Triloc *AstraZeneca, Austria.*
⊗ Metoprolol tartrate (p.1338·1); hydrochlorothiazide (p.1307·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Trilog *Hauck, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Trilombrin *Farmasierra, Spain.*
Pyrantel embonate (p.155·1).
Worm infections.

Trilone *Hauck, USA†.*
⊗ Triamcinolone diacetate (p.1544·3).
Corticosteroid.

Trilor
Note. This name is used for preparations of different composition.
Loren, Mex.†.
Oral suspension: Furazolidone (p.834·3); clioquinol (p.254·1); homatropine (p.1881·2); kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Loren, Mex.†.
Tablets: Furazolidone (p.834·3); clioquinol (p.254·1); homatropine (p.1881·2).
Diarrhoea.

Trilosil *Silom, Thai.†.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Triloxane *Vickmans, Hong Kong.*
Magnesium hydroxide (p.1743·2) or magnesium trisilicate (p.1744·1); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Triludan *Aventis, Port.†; Aventis, S.Afr.†.*
Terfenadine (p.590·3).
Allergic rhinitis; asthma; cutaneous hypersensitivity reactions; hypersensitivity reactions.

Tri-Luma
Galderma, Arg.; Galderma, Braz.; Galderma, Chile; Galderma, Hong Kong; Galderma, Malaysia; Galderma, Mex.; Galderma, Philipp.; Galderma, Singapore; Galderma, Thai.; Galderma, Venez.
⊗ Hydroquinone (p.1598·2); tretinoin (p.1618·1); fluocinolone acetonide (p.1531·3).
Facial melasma; skin hyperpigmentation.

Galderma, USA.
⊗ Hydroquinone (p.1598·2); tretinoin (p.1618·1); fluocinolone (p.1531·3).
Facial melasma.

TriLyte *Schwarz, USA.*
Macrogol 3350 (p.2336·3); electrolytes (p.1667·1).
Bowel evacuation.

Trim
Note. This name is used for preparations of different composition.
Saval, Chile.
Trimebutine maleate (p.2404·3).
Gastrointestinal disorders.

M & H, Malaysia†; M & H, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Trima *Jin Yang, Malaysia.*
Trimebutine maleate (p.2404·3).
Gastritis; irritable bowel syndrome.

Tri-Mactex *Gynopharm, Chile.*
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trimadan *Dankos, Indon.*
Clotrimazole (p.530·1).
Fungal skin infections.

Trimag *Uniao Quimica, Braz.†.*
Tiratricol (p.2177·3).
Thyroid disorders.

Trimate-Ace *Sankyo, Thai.†.*
Vitamin B substances with vitamin E (p.1922·1).

Trimate-E *Kimia, Indon.*
Benfotiamine (p.1975·2); pyridoxine hydrochloride (p.1978·2); hydroxocobalamin (p.1980·3); *dl*-alpha tocoferil acetate (p.1992·3).
Anaemia; musculoskeletal pain; neuralgia; neuritis; tonic.

Trimaxazole *Beacons, Singapore.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trimaze *Garec, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections.

Trimazide *Major, USA†.*
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Trimazol *Vannier, Arg.; Upha, Malaysia†.*
Clotrimazole (p.530·1).
Fungal skin infections.

Trimeba *Bajamed, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Trimecor *Corsalud, Venez.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trimecryton *Leciva, Cz.†.*
⊗ Dihydroergocristine mesilate (p.364·2); chlortalidone (p.1243·3); metipranolol (p.1883·2).
Hypertension.

Trimedal *Novartis, Braz.*
Dimetindene maleate (p.576·3); rutoside (p.2305·1); paracetamol (p.108·1); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Trimedat *Italfarmaco, Ital.†.*
Trimebutine maleate (p.2404·3).
Gastrointestinal spasm; irritable bowel disease; oesophageal motility disorders.

Trimedil *Novartis Consumer, Austria.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1); dimetindene maleate (p.576·3); ascorbic acid (p.1983·3); oxerutins (p.2304·3).
Cold symptoms.

Trimedin *Kleva, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Trimedor *Biomedica-Chemica, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Trim-Elim *Reese, USA†.*
Caffeine (p.1116·3); potassium salicylate; salicylamide (p.121·2).

Trimelot *Rafarm, Gr.*
Oxaprozin (p.105·3).
Inflammatory disorders.

Trimepaz *Master, Chile†.*
Doxylamine succinate (p.578·2).
Insomnia.

Trimephar *Am-Europharma, Philipp.*
Co-trimoxazole (p.258·1).
Urinary-tract infections.

Trimepol *Ingens, Arg.*
Trimethoprim (p.355·2); polymyxin B (p.318·2).
Bacterial eye infections.

Trimepol D *Ingens, Arg.*
⊗ Trimethoprim (p.355·2); polymyxin B (p.318·2); dexamethasone sodium phosphate (p.1526·2).
Bacterial eye infections.

Trimepranol *Medicamenta, Cz.*
⊗ Metipranolol (p.1883·2) or metipranolol fumarate (p.1883·2).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; tremor.

Tri-Merci *Organon, Rus.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trimesan *Sun-Farm, Pol.*
Trimethoprim (p.355·2).
Bacterial infections; pneumocystis pneumonia.

Trime/Sulfa *Quimica y Farmacia, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimetabol
Note.This name is used for preparations of different composition.
Arrow, Braz.; Uriach, Spain.
Cyproheptadine acefyllinate (p.575·2); lysine hydrochloride; carnitine hydrochloride; vitamin B substances (p.1922·1).
Reduced appetite; tonic.
Zimaia, Port.†.
Cyproheptadine acefyllinate (p.575·2).
Appetite stimulant.

Trimetaratio *Ratiopharm, Pol.*
Trimetazidine hydrochloride (p.1419·2).
Ischaemic eye disorders; ischaemic heart disease; ischaemic vestibular disorders.

Trimetazide *Pabianice, Rus.*
Trimetazidine (p.1419·2).
Angina pectoris; vascular eye disorders; vestibular disorders.

Trimetho comp *Strallhofer, Austria.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimethox *Caps, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimetin *Vitabalans, Fin.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Trimetin Duplo *Vitabalans, Fin.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Respiratory-tract and urinary-tract infections.

Trimetoger *Streger, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimeton *Schering-Plough, Ital.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions; motion sickness; vomiting.

Trimetoprim Sulfa *Calox, Venez.†; SM, Venez.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimetoprim-Sulfa *Gea, Norw.†.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trimetox *Rimsa, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimetrox *Richmond, Arg.*
⊗ Tamoxifen (p.775·1).
Breast cancer.

Trimetyl-HIDA *Rez, Cz.*
Technetium-99m mefenin (p.2055·3).
Radionuclide imaging of the biliary tract and liver.

Trimevert *Med-One, Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Trimex *Ratiopharm, Fin.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Trimexazol *Sanofi-Aventis, Braz.; Valeant, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; protozoal infections.

Trimexazole *CCM, Malaysia; Pharmasant, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimexine *Valeant, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Trimexole *Rayere, Mex.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trimexole Compositum *Rayere, Mex.*
Co-trimoxazole (p.258·1); guaifenesin (p.1561·3).
Respiratory-tract infections.

Trimezol *Biofarma, Braz.†; Mugi, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trimezole *Malayan, Singapore†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trim-Fit *Quest, Canad.*
Bitter orange; enzyme blend; camelia sinensis; kelp; lipoic acid; hypericum; tonalin (p.1922·1).

Tri-Micon *Beacons, Singapore.*
⊗ Betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3); gentamicin sulfate (p.282·1).
Infected skin disorders.

Trimicon *Unison, Thai.*
⊗ Miconazole nitrate (p.541·3); triamcinolone acetonide (p.1544·3).
Infected skin disorders.

Trimicro *Microsules, Arg.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Trimidura *Merck dura, Ger.*
Trimipramine maleate (p.426·3).
Depression.

Trimin sulfa *AstraZeneca, Swed.†.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Urinary-tract infections.

Trimine *Ecosol, Switz.*
Trimipramine maleate (p.426·3).
Depression; pain.

Triminetta *Sandoz, Denm.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Triphasic oral contraceptive.

Trimineurin *Hexal, Ger.*
Trimipramine maleate (p.426·3).
Depression.

Triminex *Konimex, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Tri-Minulet *Wyeth, Austral.†; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Cz.; Wyeth, Denm.†; Wyeth, Fin.†; Wyeth, Fr.; Wyeth, Gr.; Wyeth, Hung.†; Wyeth, Irl.; Wyeth Lederle, Ital.; Wyeth, Neth.†; Wyeth, Pol.; Wyeth Lederle, Port.; Akromed, S.Afr.; Wyeth, Spain; Wyeth, Switz.; Wyeth, UK†.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
28-day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trimiron *Pharmaco, NZ†; Organon, Swed.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

TriMix
Note. A similar name is used for preparations of different composition (see below).
Fresenius Kabi, Austria.
Amino-acid, carbohydrate, and lipid (from soya oil (p.1965·3)) infusions (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Tri-Mix
Note. A similar name is used for preparations of different composition (see above).
Wedgewood, USA.
Papaverine (p.2191·3); alprostadil (p.2183·2); phentolamine (p.1370·3).
Erectile dysfunction.

Trimline *Lane, Pol.*
Xanthogenic fibre; vitamins; trace elements (p.1922·1).
Obesity.

Trimocom *Jumont, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimoks *Atabay, Turk.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trimol *Julphar, UAE.*
Co-trimoxazole (p.258·1).
Bacterial infections; nocardiosis; pneumocystis pneumonia; toxoplasmosis.

Trimol-A *Julphar, UAE.*
Trimethoprim (p.355·2).
Bacterial infections; pneumocystis pneumonia.

Trimonase *Mipharm, Ital.*
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Trimonil *Desitin, Denm.; Desitin, Norw.; Desitin, Swed.*
Carbamazepine (p.471·3).
Alcohol withdrawal syndrome; benzodiazepine withdrawal syndrome; bipolar disorder; diabetes insipidus; diabetic neuropathy; epilepsy; mania; neuralgias.

Trimonit *Sanofi-Aventis, Pol.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Trimopan *Orion, Denm.; Orion, Fin.; Berk, UK.*
Trimethoprim (p.355·2).
Urinary-tract and respiratory-tract infections.

Trimo-San *Cooper, USA.*
Hydroxyquinoline sulfate (p.2323·1); boric acid (p.2268·1); borax (p.2268·1); sodium laurilsulfate (p.2138·3); glycerol (p.2314·2).
Vaginal deodoriser.

Trimovate *GSK, UK.*
⊗ Clobetasone butyrate (p.1522·3); oxytetracycline calcium (p.312·3); nystatin (p.543·2).
Skin disorders with bacterial or fungal infection.

Trimovax *Sanofi Pasteur, Arg.; Aventis Pasteur, Braz.†; Pasteur Merieux, Cz.†; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.†; Aventis, S.Afr.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.; Zuoz, Venez.†.*
A measles, mumps, and rubella vaccine (Schwarz, Urabe Am 9, and Wistar RA 27/3M strains, respectively) (p.2223·1).
Active immunisation.

Trimox
Delta, Braz.
Amoxicillin (p.202·2).
Bacterial infections.
Apothecon, USA.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Trimoxal *Elmor, Venez.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Trimoxazole *Sandoz, Austral.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimoxis *Genesis, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimoxsul *Interbat, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimpex *Roche, USA.*
Trimethoprim (p.355·2).
Urinary-tract infections.

Trim-S *Dynamic, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trimstat *Fada, Arg.†.*
Metronidazole (p.837·1).
Bacterial infections; protozoal infections.

Trimulex *Medi-Rx, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Trimycin *BioFemme, Philipp.*
Bacitracin (p.210·3); neomycin (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial skin infections.

Trimycin-H *BioFemme, Philipp.*
⊗ Bacitracin (p.210·3); hydrocortisone (p.1535·2); neomycin (p.305·1); polymyxin B sulfate (p.317·3).
Skin infections.

Trimzol *Randall, Mex.; Schwulst, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trinagesic *Adcock Ingram, S.Afr.*
Meprobamate (p.1006·2); paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain and associated tension.

Trinalin
Note.This name is used for preparations of different composition.
Schering, Canad.; Schering-Plough, Mex.†; Key, USA†.
Azatadine maleate (p.568·1); pseudoephedrine sulfate (p.1571·2).
Allergic rhinitis; nasal congestion; respiratory-tract congestion.
Norma (Νορμα), Gr.
Levocarnitine (p.1932·2).
Carnitine deficiency; myocardial ischaemia.

Trinalion *Neo-Farmaceutica, Port.*
Nimodipine (p.1357·2).
Cerebral ischaemia; cerebral vasospasm following subarachnoid haemorrhage.

Tri-Nasal *Muro, USA.*
⊗ Triamcinolone acetonide (p.1544·3).
Allergic rhinitis.

Trinate *Cypress, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Trinavet *Collins, Mex.†.*
Vitamin B substances (p.1922·1).
Neuritis.

Trinelax *Protein, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trinell Pro *Beres, Hung.*
Paracetamol (p.108·1); propyphenazone (p.119·3); caffeine (p.1116·3).
Fever; pain.

Trinergic *Unichem, India.*
Vitamin preparation with ginseng and zinc (p.1922·1).
Tonic.

Trinergot *Atlantis, Mex.*
Caffeine (p.1116·3); ergotamine tartrate (p.620·1).
Migraine and other vascular headaches.

TriNessa *Watson, USA.*
21 Tablets, norgestimate (p.2121·1); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Trinestril *Sanofi-Aventis, Braz.*
⊗ Estradiol hexahydrobenzoate (p.2097·3); testosterone hexahydrobenzoate (p.2131·3); hydroxyprogesterone enantate (p.2110·3).
Menopausal disorders.

Trineurin *Orion, Fin.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Trineurovita *Maver, Mex.*
Hydroxocobalamin acetate (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neuralgias; neuritis; neuropathy; vitamin B deficiency.

Trineurovita Compuesto *Maver, Mex.*
⊗ 1 Ampoule, hydroxocobalamin acetate (p.1980·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); 1 ampoule, dexamethasone sodium phosphate (p.1526·2); lidocaine hydrochloride (p.1862·3).
Inflammation; neuralgias; neuritis.

Trinevrina B6 *Guidotti, Ital.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Neuralgias; neuritis; radiation sickness; toxicosis.

Trinicalm *Torrent, India.*
Trifluoperazine (p.1034·3).
Anxiety; mixed anxiety depressive states; schizophrenia; senile agitation.

Trinicalm Forte *Torrent, India.*
Chlorpromazine hydrochloride (p.969·2); trifluoperazine hydrochloride (p.1034·2); trihexyphenidyl hydrochloride (p.820·2).
Schizophrenia.

Trinicalm Plus *Torrent, India.*
Trifluoperazine hydrochloride (p.1034·2); trihexyphenidyl hydrochloride (p.820·2).
Schizophrenia.

Trinidex *Diaco, Ital.*
Glucose, vitamin, and sodium chloride infusion (p.1922·1).
Carbohydrate source; fluid and electrolyte disorders.

Trinigyn *Grunenthal, Mex.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Trinipatch *Solvay, Belg.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Lavipharm, Israel†; Sanofi Synthelabo, Neth.; Helsinn, Port.†; Vita, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Triniplas *Novartis, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Trinispray *Sanofi-Aventis, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Triniton *Apogepha, Ger.*
⊗ Dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Trinitrina *Pharmafar, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Trinitrine *Sanofi, Switz.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; pulmonary oedema.

Trinitrine Simple Laleuf *Santa, Gr.†.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Trinitron *Quesada, Arg.*
Glyceryl trinitrate (p.1296·2); caffeine (p.1116·3).
Angina pectoris.

Trinitrosan *Merck, Ger.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; controlled hypotension; heart failure; hypertensive crisis; myocardial infarction.

Trinizol *UCI, Braz.†.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Trinizol M *UCI, Braz.†.*
Tinidazole (p.848·3); miconazole nitrate (p.541·3).
Vulvovaginal infections.

Trinolon *Kimia, Indon.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Trinolone *Nida, Singapore.*
⊗ Triamcinolone acetonide (p.1544·3).
Oral lesions.

Trinordiol
Note.This name is used for preparations of different composition.
Wyeth, Arg.; Wyeth Lederle, Austria; Wyeth, Belg.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Denm.; Wyeth, Fin.†; Wyeth, Fr.; Wyeth, Ger.†; Wyeth, Gr.†; Wyeth, Hong Kong†; Wyeth, Hung.; Sunthi Sepuri, Indon.; Wyeth, Indon.; Wyeth, Irl.; Wyeth-Ayerst, Israel†; Wyeth Lederle, Ital.†; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Neth.; Wyeth, Norw.; Wyeth, Philipp.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, Singapore; Wyeth, Swed.; Wyeth, Switz.; Wyeth, UK†; Wyeth, Venez.
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Combined oral contraceptive; menstrual disorders; triphasic oral contraceptive.

Chiesi, Spain.
Delapril hydrochloride (p.1256·2).
Hypertension.

Tri-Norinyl *Searle, USA.*
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trinorm *Nycomed, Denm.†.*
18 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; norethisterone (p.2119·3).
Menopausal disorders; osteoporosis.

TRI-Normin *Teofarma, Ger.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3); hydralazine hydrochloride (p.1305·3).
Hypertension.

Trinotecan *Filaxis, Arg.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Trinotrex *Faria, Braz.†.*
Tetracycline (p.347·1); muramidase (p.2348·1).
Bacterial infections.

Trinovin *Novogen, Austral.*
Red clover (p.2285·1).
Prostate disorders.

Trinovum
Janssen-Cilag, Austria; Janssen-Cilag, Belg.; Janssen-Cilag, Braz.†; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Ger.; Cilag, Hong Kong†; Janssen-Cilag, Neth.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK.
Norethisterone (p.2119·3); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Janssen-Cilag, Pol.
Ethinylestradiol (p.2101·3); norethisterone acetate (p.2119·3).
Triphasic oral contraceptive.

Trinsicon
Lilly, Thai.†.
Cobalamin (p.1980·2); ferrous fumarate (p.1938·3); folic acid (p.1940·1) liver (p.2337·3) and stomach (p.2337·3) concentrate.
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

UCB, USA.
Ferrous fumarate (p.1938·3); vitamin B substances (p.1980·2); intrinsic factor (liver-stomach preparation) (p.2326·3); folic acid (p.1940·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Anaemias.

Trintek *Goldshield, UK.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris.

Trio D *LED, Fr.†.*
Liquorice (p.1740·3).
Hyperpigmentation disorders.

Trio S *LED, Fr.†.*
SPF 50: Ensulizole (p.1597·1); octocrilene (p.1608·3); octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Trio Val *Saval, Chile.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Trio Val Dia y Noche *Saval, Chile.*
Night tablets, paracetamol (p.108·1); pseudoephedrine (p.1571·2); chlorphenamine (p.572·2); day tablets, paracetamol; pseudoephedrine.
Cold and influenza symptoms.

TrioBe *Recip, Denm.; Recip, Fin.; Recip, Norw.; Recip, Swed.*
Folic acid; cyanocobalamin; pyridoxine hydrochloride (p.1922·1).
Vitamin B and folic acid deficiency.

Triocaps *Vifor, Switz.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Triocetin *OFF, Ital.†.*
Troleandomycin (p.357·1).
Bacterial infections.

Trio-D *Fouchard, Chile†.*
Hydroquinone (p.1598·2); alpha hydroxy acids; ascorbic acid (p.1983·3).
Skin pigmentation disorders.

Triodanin *Norma (Νορμα), Gr.†.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Triodeen *Schering, Neth.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trioden *Schering, Austral.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Triodena *Schering, Austria; Bayer Schering, Hung.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triodene *Schering, Belg.; Schering, Irl.†; Schering, S.Afr.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Triofan *Vifor, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1); carbocisteine (p.1553·2).
Upper respiratory-tract disorders.

Triofed *Pharmasant, Thai.; Barre-National, USA.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Triofix *Medichem, Philipp.*
Rifampicin (p.325·3); isoniazid (p.288·1); pyrazinamide (p.320·2).
Tuberculosis.

Triofusin *Kalbe, Indon.*
Carbohydrate infusion (p.1922·1).
Parenteral nutrition.

Triofusin E *Kalbe, Indon.*
Carbohydrate, electrolyte, and vitamin infusion (p.1922·1).
Parenteral nutrition.

Triolip *Sofar, Ital.*
Omega-3 triglycerides (p.1362·1).
Dietary supplement.

Triomar
Note.This name is used for preparations of different composition.
Aroma Life, Israel.
Omega-3 triglycerides (p.1362·1); omega-9 triglycerides.
Hyperlipidaemias; joint disorders; skin disorders; ulcerative colitis.

Pharmagic, Ital.
Omega-3 marine triglycerides (p.1362·2).
Hyperlipidaemias; joint disorders; skin disorders.

Triomer *Vifor, Switz.*
Sterile sea water (p.1686·1).
Nasal disorders.

Triomin *Xixia, S.Afr.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Triomune *Cipla, India; Cipla-Medpro, S.Afr.; Cipla, Venez.*
Lamivudine (p.895·1); stavudine (p.907·1); nevirapine (p.899·1).
HIV infection.

Trionetta *Schering, Norw.; Schering, Swed.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trioptec *Dergam, Fr.*
Vitamins; minerals; evening primrose oil; fish oil (p.1922·1).
Aid in preventing ocular degeneration.

Trioral/HCT *Aliud, Austria.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Triostat *Jones, USA.*
Liothyronine sodium (p.2174·1).
Evaluation of thyroid function; hypothyroidism.

Triostee *Tropica Mas, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1).
Osteoarthritis.

Triosules *Microsules, Arg.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Triotann *Prasco, USA.*
Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2); chlorphenamine tannate (p.572·2).
Allergic rhinitis; nasal congestion.

Tri-Otic *Pharmics, USA†.*
⊗ Chloroxylenol (p.1640·2); pramocaine hydrochloride (p.1868·1); hydrocortisone (p.1535·2).
Inflammatory ear infections.

Triovit *KRKA, Rus.*
Betacarotene; tocopherol acetate; ascorbic acid; selenium (p.1922·1).

Triox *Solara, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triox NF *Andromaco, Chile.*
Naproxen sodium (p.92·3).
Fever; musculoskeletal, joint, and soft-tissue disorders; pain.

Trioxal *Polpharma, Pol.*
Itraconazole (p.536·3).
Fungal infections.

Trioxazin *Extractum, Hung.*
Trimetozine (p.1035·2).
Alcohol withdrawal syndrome; anxiety disorders; neuropathies; premenstrual syndrome.

Trioxina *Uniao Quimica, Braz.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Triozine *Pharmasant, Thai.*
Trifluoperazine hydrochloride (p.1034·2).
Anxiety; nausea and vomiting; psychoses.

Tripac-Cyano *Adcock Ingram, S.Afr.*
4 Vials, sodium thiosulfate (p.1466·1); 2 vials, sodium nitrite (p.1464·3); 6 vials, amyl nitrite (p.1437·3).
Cyanide poisoning.

Tripacel *Aventis Pasteur, Austral.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Aventis Pasteur, Malaysia†; CSL, NZ; Connaught, NZ; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.*
An adsorbed diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Tripanzym *Sanbe, Indon.*
Pancreatin (p.2360·1); simeticone (p.1770·2).
Flatulence; meteorism.

Triparen *Otsuka, Indon.; Otsuka, Jpn.*
Carbohydrate and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Triparsean *Pantofarma, Spain.*
Piketoprofen hydrochloride (p.117·2).
Formerly contained piketoprofen or piketoprofen hydrochloride.
Peri-articular and soft-tissue disorders.

Tripe P *Universal, Hong Kong.*
Promethazine hydrochloride (p.588·2); pholcodine (p.1570·2); phenylpropanolamine hydrochloride (p.1569·3).
Coughs and cold symptoms.

Tripedia *Sanofi Pasteur, USA.*
A diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation of infants and young children.

Tripel *Corsa, Indon.*
Tripelennamine hydrochloride (p.592·2).
Allergic skin disorders; insect bites; pruritus; sunburn.

Tripenem *Dexa, Indon.*
Meropenem (p.297·2).
Bacterial infections.

Triperidol *Ethnor, India.*
Trifluperidol (p.1035·1) or trifluperidol hydrochloride (p.1035·1).
Psychoses.

Triphasil *Wyeth, Austral.; Wyeth, Canad.; Wyeth, NZ; Akromed, S.Afr.; Wyeth-Ayerst, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Triphidus *Motima, Fr.*
Lactobacillus acidophilus; bifidobacterium; lactobacillus bulgaricus (p.2372·3).
Maintenance of gastrointestinal flora.

Triphimox *Lloyd, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Tripid *Teguhsindo, Indon.*
Turmeric (p.1473·2); ginseng (p.2312·1); essential phospholipids; vitamin E (p.1922·1).
Liver disorders.

Tripirol *Tecnofarma, Mex.*
Piroxicam (p.117·3).
Inflammation.

Triple Antigen *Commonwealth Serum, Hong Kong†; GSK, India; Haffkine, India; Serum Institute, India; CSL, NZ.*
A diphtheria, tetanus and pertussis vaccine (p.2210·3).
Active immunisation.

Triple Blend Echinacea *Swiss Herbal, Canad.*
Echinacea angustifolia; echinacea purpurea; echinacea pallida (p.2298·1).

Triple Care Cleanser *Smith & Nephew, Austral.†; Smith & Nephew, Canad.†.*
Emollient and skin cleanser.
Skin disorders associated with incontinence.

Triple Care Cream *Smith & Nephew, Canad.†.*
Zinc oxide (p.1621·2).

Triple Paste *Summers, USA.*
Zinc oxide (p.1621·2).
Nappy rash.

Triple Protection Moisture Lotion *Beiersdorf, Canad.†.*
SPF 15: Octinoxate (p.1608·2); octisalate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Triple-B *Hua, Thai.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Tri-Plen *Aventis, S.Afr.*
Ramipril (p.1385·3); felodipine (p.1285·3).
Hypertension.

Triplex
Note.This name is used for preparations of different composition.
LKM, Arg.
⊗ Miconazole (p.541·2); betamethasone valerate (p.1519·1); gentamicin (p.284·2).
Infected skin disorders.

Sriprasit, Thai.
Trifluoperazine hydrochloride (p.1034·2).
Anxiety; nausea and vomiting; psychoses.

Triplex AD *Breckenridge, USA.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); mepyramine maleate (p.585·2).
Upper respiratory-tract disorders.

Tripo *Hua, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; hay fever; rhinitis; upper respiratory-tract congestion.

Tripohist D *Breckenridge, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract disorders.

Tripondil *Alphrema, Ital.*
Day tablets, levocarnitine tartrate; fennel; faseolamina; chromium polynicotinate; calcium phosphate; pyridoxine hydrochloride; night tablets, pineapple; selenium-rich yeast; bioflavonoids; equisetum (p.1922·1).
Obesity.

Triposed *Halsey, USA.*
Pseudoephedrine hydrochloride (p.1571·2); triprolidine hydrochloride (p.592·3).
Upper respiratory-tract symptoms.

Tripote *Dexa, Indon.*
Damiana (p.2292·1); Siberian ginseng (p.2386·3); muira-puama.
Infertility; tonic.

Tripoten *Dexa, Pol.*
Siberian ginseng (p.2386·3); ptychopetalum olocoides; damiana (p.2292·1).
Erectile dysfunction.

Tripress *Pacific, NZ.*
Trimipramine maleate (p.426·3).
Depression.

Tri-Previfem *Teva, USA.*
21 Tablets, norgestimate (p.2121·1); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Triprim
Note.This name is used for preparations of different composition.
Sigma, Austral.; Ratiopharm, Austria; Ratiopharm, Cz.; GSK, NZ†; Roche, S.Afr.†.
Trimethoprim (p.355·2).
Bacterial infections.

Pharmaland, Thai.
Co-trimoxazole (p.258·1).
Bacterial infections.

Triprodrine *Asian Pharm, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; hay fever; respiratory-tract congestion; rhinitis.

Tri-Profen *3M, Austral.*
Ibuprofen (p.64·2).
Fever; inflammation; musculoskeletal and joint disorders; pain.

Tri-Profen Cold & Flu *3M, Austral.†.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Tripsol *Cazi, Braz.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Tripsor *Orion, Fin.*
Trioxysalen (p.1620·1).
Lichen obtusus; lichen planus; psoriasis.

Tripsyline *Polipharm, Thai.†.*
Amitriptyline (p.376·1).
Depression.

Tripta *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Triptafen *Goldshield, UK.*
Amitriptyline hydrochloride (p.376·1); perphenazine (p.1017·1).
Mixed anxiety depressive states.

Triptagic *Tempo Scan Pacific, Indon.*
Sumatriptan succinate (p.625·2).
Migraine.

Triptilin *Ulagay, Turk.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Triptizol *SIT, Ital.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Tript-OH *Sigma-Tau, Cz.; Sigma-Tau, Ital.; Sigma-Tau, Switz.*
Oxitriptan (p.414·1).
Depression; migraine; myoclonus; sleep disorders.

Triptone *Del, USA.*
Dimenhydrinate (p.576·2).
Motion sickness.

Triptyl *Orion, Fin.*
Amitriptyline hydrochloride (p.376·1).
Depression; insomnia; migraine; muscle spasm; pain.

Triptyline *Medifive, Thai.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Tripulmin *Hexal, Braz.†.*
Sodium camsilate (p.2388·3); oxeladin citrate (p.1567·1); guaifenesin (p.1561·3); menthol (p.2340·1); cineole (p.2282·3).
Respiratory-tract congestion.

Tripulmin Balsamico *Hexal, Braz.†.*
Camphor (p.2273·2); cineole (p.2282·3); guaiacol (p.1561·2); menthol (p.2340·1).
Cough.

Tripur *Galeno, Venez.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Tripvac *Biological E, India.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Triquilar *Schering, Arg.; Schering, Austral.; Schering, Braz.; Berlex, Canad.; Schering, Chile; Schering, Cz.; Schering, Denm.; Schering, Ger.; Shepa, Gr.†; Schering, Hong Kong†; Bayer Schering, Hung.; German Remedies, India; Schering, Indon.; Schering, Malaysia†; Schering, Mex.; Bayer, NZ; Schering, Pol.; Bayer, Port.; Schering, Rus.; Schering, Singapore†; Schering, Switz.; Schering, Thai.; Schering, Turk.; Schering, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Tri-Regol *Gedeon Richter, Cz.; Gedeon Richter, Hong Kong; Gedeon Richter, Hung.; Gedeon Richter, Malaysia†; Richter, Pol.; Gedeon Richter, Rus.; Aciprosalud, Venez.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets or 7 tablets ferrous fumarate.
Triphasic oral contraceptive.

Triregol *Sandoz, Swed.*
Ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2).
Triphasic oral contraceptive.

Triresid K *Pliva, Rus.*
⊗ Reserpine (p.1387·3); dihydralazine sulfate (p.1264·3); hydrochlorothiazide (p.1307·3); potassium chloride (p.1684·3).

Trirubin *Uniao Quimica, Braz.†.*
Vitamin B (p.1980·2); vitamin B (p.1976·3); vitamin B (p.1979·1).
Megaloblastic anaemia; vitamin B deficiency.

Tris *Fresenius Kabi, Austria; Braun, Ger.*
⊗ Trometamol (p.2405·1).
Citrate intoxication following blood transfusion; metabolic acidosis; respiratory acidosis.

Trisan *Dermtek, Canad.†.*
Triclosan (p.1665·2).
Skin cleanser.

Trisekvens *Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Norw.; Novo Nordisk, Swed.*
18 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Trisel *Klonal, Arg.*
Vitamin B ; pyridoxine; thiamine (p.1922·1).

Trisenox *Cell Therapeutics, Austria; Infarmed, Belg.; Cephalon, Cz.; Cephalon, Fr.; Cell Therapeutics, Gr.; Cell Therapeutics, Ital.; Shinyaku, Jpn; Cell Therapeutics, Neth.; Cell Therapeutics, Spain; Cephalon, UK; Cephalon, USA.*
Arsenic trioxide (p.2260·2).
Acute promyelocytic leukaemia.

Triseptil
Note. This name is used for preparations of different composition.
Gedis, Ital.
Chlorhexidine gluconate (p.1635·3).
Hand disinfection.

Degorts, Mex.
Tinidazole (p.848·3).
Amoebiasis; giardiasis; trichomoniasis.

Trisequens *Novo Nordisk, Arg.; Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Medley, Braz.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Fr.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, Malaysia†; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, Rus.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Isdin, Spain; Novo Nordisk, Switz.; Novo Nordisk, Turk.; Novo Nordisk, UK.*
18 Tablets, estradiol (p.2097·2); 10 tablets, estradiol; norethisterone acetate (p.2119·3).
Hormone replacement therapy; menopausal disorders; oestrogen deficiency; osteoporosis.

Trisiston *Jenapharm, Cz.†; Jenapharm, Ger.; Jenapharm, Pol.; Jenapharm, Rus.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Trisofort *Westmont, Philipp.*
Isoniazid (p.288·1).
Vitamin B substances (p.1975·1) are included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Trisolaren *Pharmex (Φαρμεξ), Gr.*
Trioxysalen (p.1620·1).

Trisoralen *ICN, Arg.†.*
Trioxysalen (p.1620·1).
Vitiligo.

Trisorb *Alcon, Braz.*
⊗ Dextran 70 (p.1059·3); hypromellose (p.2144·2); glycerol (p.2314·2).
Dry eyes; eye irritation.

Trisorcin *Merckle, Ger.†.*
Penicillamine (p.1456·2).
Cystinuria; heavy-metal poisoning; polyarthritis; scleroderma; Wilson's disease.

Trisporal *Janssen-Cilag, Neth.*
Itraconazole (p.536·3).
Fungal infections.

Tri-Sprintec *Barr, USA.*
21 Tablets, norgestimate (p.2121·1); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Tristan *Medikon, Indon.*
Tribulus terrestris (p.2404·1); damiana (p.2292·1); ginseng (p.2312·1).
Tonic.

Tri-Statin II *Rugby, USA.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Skin disorders.

TriStep *Schering, Ger.†.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Triphasic oral contraceptive.

Tristina *Mac, India†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Trisufin *Loren, Mex.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Trisul *Pacific, NZ.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trisulfa *Berlico Mulia, Indon.*
Sulfadiazine (p.336·2); sulfadimidine (p.338·1); sulfamerazine (p.339·3).
Bacterial infections.

Trisulfose *Wyeth, India.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia; toxoplasmosis.

Trisulprim *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Urinary-tract infections.

Tritab
Note. This name is used for preparations of different composition.
Sidus, Arg.
Azithromycin (p.207·1).
Bacterial infections.

Medichem, Philipp.
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Tritace *Aventis, Arg.; Sanofi-Aventis, Austral.; Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Sanofi-Aventis, Hong Kong; Sanofi-Aventis, Hung.; Sanofi-Aventis, Irl.; Aventis, Israel; Sanofi-Aventis, Malaysia; Aventis, Mex.; Aventis, NZ; Aventis, Neth.; Aventis, Philipp.; Sanofi-Aventis, Pol.; Aventis, S.Afr.; Sanofi-Aventis, Singapore; Aventis, Thai.; Aventis, UK.*
Ramipril (p.1385·3).
Cardiovascular risk reduction; diabetic nephropathy; heart failure; hypertension; myocardial infarction; nephropathy; stroke prophylaxis.

Tritace Comp *Aventis, Israel.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tritace-HCT *Aventis, Arg.; Sanofi-Aventis, Hung.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tritan *Eon, USA.*
Chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Allergic rhinitis; nasal congestion.

Tri-Tannate *Rugby, USA.*
Phenylephrine tannate (p.1568·3); chlorphenamine tannate (p.572·2); mepyramine tannate (p.585·2).
Upper respiratory-tract symptoms.

Tri-Tannate Plus Pediatric *Rugby, USA.*
⊗ Phenylephrine tannate (p.1568·3); ephedrine tannate (p.1559·1); chlorphenamine tannate (p.572·2); pentoxyverine tannate (p.1567·3).
Coughs and cold symptoms.

Tritanrix HB *GSK, India; GSK, Indon.; GSK, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, S.Afr.; GSK, Spain; GSK, Thai.; GSK, Turk.; GSK, Venez.†.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Tritanrix HB + HIB *GSK, NZ.*
Tritanrix-HB, a diphtheria, tetanus, pertussis, and hepatitis B vaccine; Hiberix, a haemophilus influenzae conjugate vaccine (p.2211·2).
Active immunisation.

Tritanrix HB + Hiberix *GSK, Mex.*
A diphtheria, tetanus, pertussis, hepatitis B, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Tritanrix HB-HIB *GSK, Arg.*
A diphtheria, tetanus, pertussis, haemophilus influenzae, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Tritanrix HEPB *GSK, Cz.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation of infants and young children.

Tritanrix-HepB *GSK, Neth.*
A diphtheria, tetanus, pertussis, and hepatitis B vaccine (p.2211·2).
Active immunisation.

Tritazide *Aventis, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Cz.; Aventis, Mex.; Aventis, Neth.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Tritenk *Biotenk, Arg.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Tritet *Akromed, S.Afr.*
Tetracycline hydrochloride (p.347·2); chlortetracycline hydrochloride (p.243·1); demeclocycline hydrochloride (p.264·3).
Bacterial infections.

Tri-Thiazid *Stada, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Heart failure; hypertension; oedema.

Tri-Thiazid Reserpin *Stada, Ger.†.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3); reserpine (p.1387·3).
Hypertension.

Triticum *Lepori, Port.*
Trazodone hydrochloride (p.424·3).
Depression.

Tritopan *Klonal, Arg.*
Bromazepam (p.964·3).
Anxiety.

Tri-Torrat *Roche, Ger.†.*
⊗ Metipranolol (p.1883·2); butizide (p.1238·1); dihydralazine sulfate (p.1264·3).
Hypertension.

Trittico
CSC, Austria; Faran, Gr.; Angelini, Hong Kong; CSC, Hung.; Aziende, Israel; Angelini, Ital.; Angelini, Pol.; Angelini, Rus.; Angelini, Singapore; ACRAF, Switz.; Elmor, Venez.
Trazodone hydrochloride (p.424·3).
Anxiety; benzodiazepine withdrawal; depression; erectile dysfunction; insomnia; neuroleptanalgesia; pain; premedication.

Laboratorios Chile, Chile.
Trazodone (p.426·1) or trazodone hydrochloride (p.424·3).
Alcohol withdrawal syndrome; anxiety; depression; schizophrenia.

Trittico AC *Medicom, Cz.*
Trazodone hydrochloride (p.424·3).
Depression.

TriTuss *Everett, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Trituss-A *Everett, USA.*
Carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Triv *Boyle, USA.*
Hydroxyquinoline sulfate (p.2323·1); alkyl aryl sulfonate; edetic acid (p.1445·1); sodium sulfate (p.1771·3).
Vaginal disorders.

Tri-V Plus *Sagmel, Rus.*
Betacarotene; alpha-tocoferil acetate; ascorbic acid; zinc oxide; sodium selenate; copper oxide (p.1922·1).

Trivagel N *Marjan, Braz.*
⊗ Dexamethasone phosphate (p.1526·2); neomycin sulfate (p.305·1); nystatin (p.543·2); tyrothricin (p.358·2).
Vulvovaginal disorders.

Trivanex *Pharmasant, Thai.*
Griseofulvin (p.535·2).
Fungal infections.

Trivastal
Servier, Arg.; Servier, Braz.; Servier, Ger.; Servier, Gr.; Serdia, India; Servier, Malaysia; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, Turk.; Servier, Venez.
Piribedil (p.813·3).
Cerebral and peripheral vascular disorders; intermittent claudication; mental function impairment; parkinsonism; vascular eye disorders; vestibular disorders.

Eutherapie, Fr.
Piribedil (p.813·3) or piribedil mesilate (p.813·3).
Mental function impairment in the elderly; parkinsonism; peripheral vascular disorders; vascular eye disorders.

Trivastan *Stroder, Ital.*
Piribedil (p.813·3).
Vascular disorders.

Trivax-AD *Chiron Vaccines, UK.*
An adsorbed diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation of infants and young children.

Trive-1000 *Baxter, Gr.†.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Trivedon *Cipla, India.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris.

Trivemil *Baxter, Ital.†.*
An amino-acid, lipid (from soya oil (p.1965·3)), and carbohydrate preparation (p.1922·1).
Parenteral nutrition.

Tri-Vi-Flor *Mead Johnson Nutritionals, Canad.†; Mead Johnson Nutritionals, USA.*
Multivitamin preparation (p.1922·1) with fluoride (p.1962·2).
Dental caries prophylaxis; vitamin supplement.

Tri-Vi-Fluor *BMS, Arg.; Mead Johnson, Braz.*
Sodium fluoride (p.1962·2); vitamin A; vitamin D; vitamin C (p.1922·1).
Dental caries prophylaxis; vitamin supplement.

Trivimine *Remek, Gr.*
Vitamin B substances (p.1922·1).

Trivina *Pharmacia, Belg.†; Aspen, S.Afr.; Orion, Swed.*
70 White tablets, estradiol valerate (p.2097·3); 14 blue tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); 7 yellow tablets, inert.
Menopausal disorders; osteoporosis.

Triviraten *Scott-Cassara, Arg.; Berna, Hong Kong†; Berna, Malaysia†; Berna, NZ; Berna, Philipp.; Berna, Spain†; Berna, Switz.; Berna, Thai.†; Berna, Turk.*
A measles, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

Tri-Vi-Sol *BMS, Arg.; Mead Johnson, Braz.; Mead Johnson Nutritionals, Canad.; Mead Johnson, Hong Kong†; BMS, Mex.; Mead Johnson Nutritionals, USA; Mead Johnson, Venez.*
Vitamin preparation (p.1922·1).
Formerly known as Enfalac Tri-Vi-Sol in *Canad*.
Vitamin supplement.

Trivisol *Mead Johnson, Chile.*
Vitamin A; vitamin C; vitamin D (p.1922·1).
Vitamin supplement.

Tri-Vi-Sol with Fluoride *Mead Johnson Nutritionals, Canad.*
Vitamins, A, D, and C (p.1922·1); potassium fluoride. Formerly known as Enfalac Tri-Vi-Sol with Fluoride.
Dental caries prophylaxis; vitamin supplement.

Tri-Vi-Sol with Iron *Mead Johnson Nutritionals, USA.*
Multivitamin preparation with iron (p.1922·1).

Tri-Vitamin *Schein, USA.*
Vitamins A, C, and D (p.1922·1).

Trivitamin Fluoride Drops *Schein, USA.*
Multivitamin preparation with fluoride (p.1962·2)(p.1922·1).

Trivitana DM *Merck, Chile.*
Vitamin A; vitamin B ; vitamin E (p.1922·1).
Dietary supplement.

Trivitana Q10 *Merck, Chile.*
Vitamin A; vitamin B; vitamin E; ubidecarenone (p.1922·1).
Dietary supplement.

Trivit-B *TP, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; vitamin B deficiency.

Trivivac *Sevapharma, Cz.*
A measles, mumps, and rubella vaccine (Schwarz, Jeryl Lynn, and Wistar RA 27/3 strains, respectively) (p.2223·1).
Active immunisation.

Trivon *Great Eastern, Thai.; Therapharma, Thai.*
Vitamin B ; vitamin B ; vitamin B   (p.1922·1).
Tonic.

Trivora *Watson, USA.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3). 28-Day packs also contain 7 inert tablets.
Triphasic oral contraceptive.

Trivorin *Lemery, Mex.*
Ribavirin (p.902·3).
Viral infections.

Trivudin *Richmond, Arg.*
Lamivudine (p.895·1); zidovudine (p.913·3); abacavir (p.861·3).
HIV infection.

Tri-Wycillina *Pharmacia, Ital.†.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin potassium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Trixate *Rontag, Arg.*
Methotrexate (p.745·2).
Gestational trophoblastic disorders; psoriasis; rheumatoid arthritis.

Trixera *Silesia, Chile; Avene, Fr.; Medifarm, Venez.*
Emollient.
Dry skin disorders.

Trixicam *Vitarum, Arg.*
Piroxicam (p.117·3).
Inflammation; pain.

Trixilan *Chrispa (Χρισπα), Gr.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Trixilem *Laboratorios Chile, Chile; Lemery, Mex.; Lemery, Rus.†; Lemery, Thai.*
Methotrexate (p.745·2).
Malignant neoplasms; mycosis fungoides; rheumatoid arthritis.

Trixne *Pharmatrix, Arg.*
Erythromycin (p.269·2).
Acne.

Trixol *Ferro, Arg.†.*
Hyoscyamus (p.2323·3); belladonna (p.2263·3); boldo (p.2267·2); valerian (p.2410·1); atropine sulfate (p.1219·3); phenobarbital sodium (p.492·2); papaverine hydrochloride (p.2191·3).

Trixone *LBS, Malaysia; LBS, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Trixophin *Shenzhen, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Trixotene *Labinca, Arg.†.*
Docetaxel (p.710·3).
Malignant neoplasms.

Trixzol *Westmont, Indon.; Great Eastern, Thai.; Westmont, Thai.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Triyosom *Justesa Imagen, Arg.*
Meglumine amidotrizoate (p.1475·3); and/or sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Triyotex *Medix, Mex.*
Liothyronine sodium (p.2174·1).
Hypothyroidism.

Triz *Indoco, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Trizedon *Servier, Indon.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris.

Trizidine *Pharmasant, Thai.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; tinnitus; vertigo.

Trizina *Francia, Ital.*
Cefatrizine propylene glycol (p.221·3).
Bacterial infections.

Trizine *DHA, Malaysia; Phoenix, Philipp.*
Sulfadiazine (p.336·2); trimethoprim (p.355·2).
Bacterial infections.

Trizinet *Ivax, Mex.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Trizivar *GSK, S.Afr.*
Abacavir sulfate (p.861·3); lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Trizivir *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore†; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Abacavir sulfate (p.861·3); lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Trizol
Note. This name is used for preparations of different composition.
Royal, Chile.
Lamotrigine (p.485·1).
Epilepsy.

Kocak, Turk.
Fluconazole (p.532·1).
Fungal infections.

Trizole *Medifarma, Indon.; Pediatrica, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Trizolin *Remedica, Malaysia; Remedica, Singapore†; Remedica, Thai.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Trobicin *Pharmacia, Austral.; Pfizer, Austria; Pfizer, Belg.; Pharmacia, Braz.†; Pfizer, Hong Kong; Pharmacia, India; Pharmacia, Ital.; Pfizer, Mex.; Pfizer, Port.†; Pfizer, Rus.†; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pharmacia, Venez.†.*
Spectinomycin hydrochloride (p.332·3).
Chancroid; gonorrhoea.

Trobicine *Pfizer, Fr.*
Spectinomycin hydrochloride (p.332·3).
Gonorrhoea.

Troc *Melisana, Belg.*
Aspirin (p.20·3); caffeine hydrate (p.1117·1); paracetamol (p.108·1).
Fever; pain.

Troca Cationi *Laborest, Ital.*
Magnesium; potassium; zinc (p.1667·1).
Mineral deficiencies; stress; viral infections.

Troca Donna *Laborest, Ital.*
Vitamin and mineral preparation (p.1922·1).

Troca Flu *Laborest, Ital.*
Zinc; magnesium; potassium; vitamin C; vitamin A (p.1922·1).
Candidiasis; viral infections.

Troca Flu Rino *Laborest, Ital.*
Zinc gluconate (p.1999·2).
Cold symptoms.

Troca Flu Spray Nasale *Laborest, Ital.*
Sodium chloride (p.1686·1); sulfur (p.1614·1).
Nasal cleansing.

Trocacin *Nakornpatana, Thai.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Trocaine *Roberts, USA.*
Benzocaine (p.1854·1).
Obesity; sore throat.

Trocal *Roberts, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Trochain *Adcock Ingram, S.Afr.*
Cetrimide (p.1634·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Trociletas *Streger, Mex.*
Cetylpyridinium (p.1635·1).
Mouth and throat infections.

Trociletas B *Streger, Mex.*
Cetylpyridinium (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Trocium *Strand, Malaysia†.*
Calcium lactate (p.1676·1).
Calcium deficiency.

Trodeb *Tropica Mas, Indon.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Trodex *Tropica Mas, Indon.*
⊗ Dexamethasone (p.1526·1); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Trodorol *Andromaco, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Trodrine *Malayan, Singapore†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Trofalgon *Madariaga, Spain.*
Cyanocobalamin (p.1980·2); muramidase hydrochloride (p.2348·1).
Anorexia; tonic; weight loss.

Trofen *TP, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Trofentyl *Troikaa, India.*
⊗ Fentanyl citrate (p.55·3).
Adjunct in general anaesthesia; analgesia in anaesthesia; neuroleptanalgesia.

Troferit *Chinoin, Mex.*
Dropropizine (p.1557·3).
Coughs.

Trofesil *Solfran, Mex.*
Multivitamin preparation (p.1922·1).

Trofina *Rowe-Fleming, Venez.†.*
Amino acids; vitamins (p.1922·1).
Dietary supplement.

Trofinan *Biol, Arg.*
⊗ Dexamethasone phosphate (p.1526·2).
Corticosteroid.

Trofinerv *Bausch & Lomb, Ital.*
Omega-3 marine triglycerides (p.1362·2); vitamins (p.1922·1).
Nutritional supplement.

Trofinerv Antiox *Bausch & Lomb, Ital.*
Omega-3 triglycerides (p.1362·1); gamolenic acid (p.2308·2); vitamins; minerals (p.1922·1).
Nutritional supplement.

Trofo 5 *Uniderm, Ital.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); hyaluronic acid (p.2320·1); chamomile oil (p.2279·3).
Skin disorders.

Trofocalcium *Fournier, Ital.†.*
Vitamin D and calcium preparation (p.1922·1).
Calcium depletion; metabolic bone disorders.

Trofocard *Unipharma, Gr.*
Magnesium aspartate (p.1679·1); magnesium chloride (p.1679·1).
Hypomagnesaemia.

Trofocell *SoSe, Ital.*
Multivitamin preparation (p.1922·1).

Trofodermin
Note. This name is used for preparations of different composition.
Pfizer, Braz.; Chefaro, Ital.; Pfizer, Thai.†.
⊗ Clostebol acetate (p.2087·1); neomycin sulfate (p.305·1).
Burns; skin infections; skin trauma; skin ulcers; wounds.

Pfizer, Chile.
⊗ Clostebol (p.2087·1).
Skin disorders.

Trofodermin Neomicina *Pfizer, Chile.*
⊗ Clostebol acetate (p.2087·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Trofodermin-S *Pfizer, Mex.†.*
⊗ Clostebol (p.2087·1).
Skin disorders.

Trofogin *Farmigea, Ital.*
Estriol (p.2101·1).
Cervicitis; menopausal disorders; oestrogen deficiency.

Troforex Pepsico *Reig Jofre, Spain.*
Cyproheptadine hydrochloride (p.575·1); amino acids and hydroxocobalamin (p.1922·1); pepsin (p.2365·1).
Anorexia; tonic; weight-loss.

Trofoseptine *Boehringer Ingelheim, Fr.†.*
Sodium acexamate (p.2245·2); neomycin sulfate (p.305·1).
Infected ulcers.

Trofselamin *Biosel, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Trogiar *Tropica Mas, Indon.*
Metronidazole (p.837·1).
Amoebiasis; bacteroides fragilis infections; giardiasis; trichomoniasis.

Trogyl *Otto, Indon.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Trojan *Church & Dwight, Canad.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

Trok *Eurofarma, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3).
Fungal skin infections.

Troken *Bago, Arg.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolic disorders.

Trok-N *Eurofarma, Braz.*
⊗ Ketoconazole (p.539·1); betamethasone dipropionate (p.1518·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Trolab *Hermal, Neth.*
A range of allergen extract (p.2250·2).
Diagnosis of allergic contact dermatitis.

Trolac *Bernofarm, Indon.*
Ketorolac trometamol (p.74·2).
Postoperative pain.

Trolip *Dexa, Hong Kong†; Dexa, Indon.; Dexa, Philipp.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Trolit *Silesia, Chile.*
Levonorgestrel (p.2121·2); ethinylestradiol (p.2101·3).
Menstrual disorders; triphasic oral contraceptive.

Trolovol *Asta Medica, Cz.†; Dexo, Fr.; Dexo, Port.*
Penicillamine (p.1456·2).
Chronic hepatitis; cystinuria; heavy-metal poisoning; rheumatoid arthritis; scleroderma; Wilson's disease.

Tromadil *Biolab, Thai.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Tromagesic *Themis Chemicals, India.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Tromalyt *Neo-Farmaceutica, Port.; Madaus, Spain.*
Aspirin (p.20·3).
Stroke prophylaxis; thrombosis prophylaxis.

Tromasin *Elea, Arg.†.*
Papain (p.2362·3).
Inflammation.

Tromasin con Aspirina *Parke, Davis, Arg.†.*
Papain (p.2362·3); aspirin (p.20·3).
Inflammation; pain.

Tromax *Aristo, India.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Trombenal *Bago, Arg.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Trombex *Leciva, Cz.†.*
Heparin sodium (p.1301·2).
Soft-tissue disorders; superficial vascular disorders.

Trombless *Nizpharm, Rus.*
Heparin sodium (p.1301·2).
Soft-tissue disorders; superficial vascular disorders.

Trombofob
Note. This name is used for preparations of different composition.
Knoll, Braz.
Ointment: Heparin sodium (p.1301·2); benzyl nicotinate (p.28·1).
Soft-tissue injury; superficial vascular disorders.

Knoll, Braz.
Topical gel: Heparin sodium (p.1301·2).
Superficial vascular disorders.

Tromboject *Omega, Canad.*
Sodium tetradecyl sulfate (p.2139·2).
Varicose veins.

Trombolisin *Proge, Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Tromboliz *Kocak, Turk.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Trombonot *Penn, Arg.*
Cilostazol (p.1245·2).

Tromboparin
Baxter Immuno, Arg.†; Gerolimatos (Γερολυματος), Gr.†; Elmor, Venez.
Parnaparin (p.1366·1).
Thromboembolic disorders.

BioSaude, Port.
Parnaparin sodium (p.1366·1).

Trombopat *Pentafarma, Port.*
Ticlopidine hydrochloride (p.1411·2).
Extracorporeal circulation; stoke prophylaxis; thrombosis prophylaxis.

Trombosol *Orion, Fin.*
Heparin sodium (p.1301·2); benzyl nicotinate (p.28·1).
Soft-tissue injury; superficial vascular disorders.

Trombovar *E-Z-EM, Canad.†; Innothera, Fr.; Bouty, Ital.; Promedica, Malaysia†; Innothera, Neth.; Promedica, Rus.*
Sodium tetradecyl sulfate (p.2139·2).
Cysts; oesophageal varices; varicose veins.

Trombyl *Pfizer, Swed.*
Aspirin (p.20·3).
Angina pectoris; myocardial infarction; prevention of cerebrovascular ischaemia.

Tromcardin *Trommsdorff, Cz.; Trommsdorff, Ger.; Trommsdorff, Hung.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Angina pectoris; arrhythmias; heart failure; myocardial infarction; potassium and magnesium deficiency.

Tromcor *Integrated Pharmaceutical, Philipp.*
Aspirin (p.20·3).
Thromboembolic disorders.

Tromderm *Silesia, Chile.*
Sertaconazole nitrate (p.546·1).
Fungal skin infections; seborrhoeic dermatitis.

Tromedal *Farcoral, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Tromicina *Offenbach, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Tromix *Ariston, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Tromlipon *Trommsdorff, Ger.*
⊗ Thioctic acid (p.2400·2) or trometamol thioctate (p.2400·2).
Diabetic neuropathy.

Trommcardin *Jacoby, Austria.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Arrhythmias; digitalis intoxication; heart failure; myocardial infarction; potassium and magnesium deficiency.

Trommgallol *Jacoby, Austria.*
Cyclobutyrol sodium (p.2290·3); cynarine (p.2291·2); sorbitol (p.1965·1); magnesium sulfate (p.1679·3).
Hepatobiliary disorders.

Trompersantin *Boehringer Ingelheim, Mex.†.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Tromphyllin *Trommsdorff, Ger.*
Theophylline (p.1140·1).
Obstructive airways disease.

Troneo *TNP, Thai.†.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat infections.

Tronex *Tocogino, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Tronolane
Note. This name is used for preparations of different composition.
Lee, USA.
Cream: Pramocaine hydrochloride (p.1868·1); zinc oxide (p.1621·2).
Haemorrhoids.

Monticello, USA.
Suppositories: Phenylephrine hydrochloride (p.1568·1).
Formerly contained zinc oxide.
Haemorrhoids.

Tronotene *Teofarma, Ital.*
Pramocaine hydrochloride (p.1868·1).
Burns; haemorrhoids; pruritus.

Tronothane *Abbott, Fr.; Abbott, USA.*
Pramocaine hydrochloride (p.1868·1).
Anal pain and pruritus; local anaesthesia.

Tronoxal *Prasfarma, Spain.*
Ifosfamide (p.731·3).
Malignant neoplasms.

Tronsalan *Medipharm, Chile.*
Trazodone hydrochloride (p.424·3).
Bulimia; depression; diabetic neuropathy; migraine.

Tropamid *Bilim, Turk.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Tropargal *Sanofi-Aventis, Spain.*
Diazepam (p.986·3); nortriptyline hydrochloride (p.413·2).
Depression with anxiety or agitation.

Troparin *Sandoz, Austria; Biochemie, Cz.†.*
Certoparin sodium (p.1242·3).
Thromboembolism prophylaxis.

Troparin compositum *Sandoz, Austria.*
Certoparin sodium (p.1242·3); dihydroergotamine mesilate (p.618·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Thromboembolism prophylaxis.

Troparinum *Extractum, Hung.*
Papaverine hydrochloride (p.2191·3); phenobarbital (p.492·2); homatropine methylbromide (p.1881·3).
Asthma; gastrointestinal disorders.

Tropaverin *Etifar, Venez.†.*
Papaverine (p.2191·3).

Tropex
Note. This name is used for preparations of different composition.
Rowa, Hong Kong; Rowa, Irl.
Phenazone (p.116·1).
Ear wax removal; inflammatory ear disorders; otitis media.

Rowa, Singapore.
Phenazone (p.116·1); glycerol (p.2314·2).
Ear wax removal; otitis media.

Tropfen bei Regelbeschwerden Nr 36 *Doskar, Austria.*
Homoeopathic preparation.

Tropfen bei Verletzungen *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen gegen Akne *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen gegen Insektenstiche *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen gegen Kreislaufbeschwerden *Jacoby, Austria.*
Homoeopathic preparation.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Tropfen gegen Leber-Galle Beschwerden *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen gegen Prostatabeschwerden *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen gegen Venenbeschwerden *Jacoby, Austria.*
Homoeopathic preparation.

Tropfen zur unspezifischen Abwehrsteigerung Nr 9 *Doskar, Austria.*
Homoeopathic preparation.

TrophaAmine *Eczacibasi-Baxter, Turk.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Trophamine *Braun, Hong Kong†; Pisa, Mex.; Braun, Spain; McGaw, USA; Victus, Venez.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition; parenteral nutrition in children.

Tropharma *Alpharma, Mex.*
Erythromycin stearate (p.270·1).
Bacterial infections.

Trophicard *Kohler, Ger.; Kohler-Pharma, Ger.*
Potassium aspartate (p.1684·2); magnesium aspartate (p.1679·1).
Cardiac disorders; magnesium or potassium deficiency.

Trophicreme *Grunenthal, Fr.*
Estriol (p.2101·1).
Postmenopausal vulvovaginal disorders.

Trophigil *Grunenthal, Fr.*
Lactobacillus casei var *rhamnosus* (p.2372·3); estriol (p.2101·1); progesterone (p.2125·1).
Atrophic vaginitis; pre- and postoperative gynaecological care.

Trophires
Note. This name is used for preparations of different composition.
Sanofi Synthelabo, Spain†.
Nasal drops: Cineole (p.2282·3); cypress oil (p.2291·2); myrtle oil (p.2349·3); thenoate sodium (p.351·1).
Nasal cleansing.

Sanofi-Aventis, Fr.
Suppositories: Eucalyptus oil (p.2301·2); thenoate sodium (p.351·1).
Respiratory-tract disorders.

Sanofi Synthelabo, Spain†.
Suppositories; syrup: Pholcodine (p.1570·2).
Cough.

Sanofi-Aventis, Fr.
Syrup: Pholcodine (p.1570·2); thenoate sodium (p.351·1); eucalyptus oil (p.2301·2).
Coughs.

Trophires Compose *Sanofi-Aventis, Fr.*
Paracetamol (p.108·1); eucalyptus oil (p.2301·2); thenoate sodium (p.351·1).
Fever; respiratory-tract disorders.

Trophoseptine *Theramex, Port.*
Promestriene (p.2127·3); chlorquinaldol (p.242·3).
Vaginal infections.

Trophox *Raptakos, India.*
High-protein dietary supplement (p.1922·1).

Trophysan *Baxter, Fr.†.*
Amino-acid, glycine, mineral, and vitamin infusion (p.1922·1).
Parenteral nutrition.

Tropicacyl *Akorn, USA.*
Tropicamide (p.1886·2).
Induction of mydriasis and cycloplegia.

Tropical Blend Dark Tanning
Note. This name is used for preparations of different composition.
Schering-Plough, USA.
Lotion SPF 4: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
Oil SPF 4: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 2: Homosalate (p.1598·1).
Sunscreen.

Tropical Blend Dry Oil
Note. This name is used for preparations of different composition.
Schering-Plough, USA.
SPF 2: Homosalate (p.1598·1).
Sunscreen.

Schering-Plough, USA.
SPF 4: Homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Tropical Blend Tan Magnifier *Schering-Plough, USA.*
SPF 2; SPF 4: Trolamine salicylate (p.132·3).
Sunscreen.

Tropical Gold Dark Tanning
Note. This name is used for preparations of different composition.
Goldline, USA.
SPF 2: Octinoxate (p.1608·2); padimate O (p.1609·1).
Sunscreen.

Goldline, USA.
SPF 4: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Tropical Gold Sunblock
Note. This name is used for preparations of different composition.
Goldline, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Goldline, USA.
SPF 30: Octinoxate (p.1608·2); octisalate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3).
Sunscreen.

Tropical Gold Sunscreen *Goldline, USA.*
SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Tropicee Plus *Multicare, Philipp.*
Ascorbic acid; taurine; lysine hydrochloride (p.1922·1).
Nutritional supplement; vitamin C deficiency.

Tropicil Top *Edol, Port.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Tropico
Note. This name is used for preparations of different composition.
Bell, India.
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Perez Gimenez, Spain†.
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Nasal congestion.

Tropico Plus *Bell, India.*
Phenylephrine hydrochloride (p.1568·1); tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Tropicol *Thea, Belg.*
Tropicamide (p.1886·2).
Production of mydriasis.

Tropicur *Roche, Arg.*
Mefloquine hydrochloride (p.605·3).
Malaria.

Tropidene *Tropica Mas, Indon.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders; pain.

Tropidrol *Tropica Mas, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Tropidryl Plus *Tropica Mas, Indon.*
Diphenhydramine hydrochloride (p.577·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Cough.

Tropifen *Organifar, Venez.†.*
Papaverine hydrochloride (p.2191·3); hyoscyamus (p.2323·3); phenobarbital sodium (p.492·2).
Muscle spasm.

Tropifer *Tropica Mas, Indon.*
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; folic acid; vitamin B (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron supplement; iron-deficiency anaemia.

Tropilex *Prafa, Indon.*
Piracetam (p.368·2).
Behavioural disorders in children; cerebral trauma; chronic alcoholism; enuresis; mental function impairment.

Tropimil *Farmigea, Ital.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Tropinal *Sigma, Braz.*
Dipyrone (p.49·2); homatropine methylbromide (p.1881·3); hyoscine butylbromide (p.1734·1); hyoscyamine hydrobromide (p.1736·1).
Smooth muscle spasm.

Tropindol *Lans, Rus.†.*
Tropisetron hydrochloride (p.1777·2).
Nausea and vomiting.

Tropineuron *Tropica Mas, Indon.*
Dipyrone (p.49·2); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis.

Tropinom *Genom, Braz.*
Tropicamide (p.1886·2).
Production of mydriasis and cycloplegia.

Tropioftal F *Denver, Arg.*
Tropicamide (p.1886·2); phenylephrine hydrochloride (p.1568·1).
Production of cycloplegia and mydriasis.

Tropisol *Protein, Mex.†.*
Captopril (p.1239·2).
Hypertension.

Tropistan *Tropica Mas, Indon.*
Mefenamic acid (p.80·1).
Pain.

Tropium *DDSA Pharmaceuticals, UK.*
Chlordiazepoxide hydrochloride (p.968·2).
Alcohol withdrawal syndrome; anxiety.

Tropivag *Finadiet, Arg.*
Lactobacillus rhamnosus (p.2372·3).
Restoration of vaginal flora.

Tropivag Plus *Finadiet, Arg.*
Lactobacillus rhamnosus (p.2372·3); progesterone (p.2125·1); estriol (p.2101·1).
Vaginal disorders.

Tropixal *Demo, Gr.*
Tropicamide (p.1886·2).
Production of mydriasis.

Tropix-HC *Alpharma, Mex.*
Captopril (p.1239·2).
Heart failure; hypertension; myocardial infarction.

Tropocer *Megat, Venez.*
Nimodipine (p.1357·2).
Dementia; neurological deficit following subarachnoid haemorrhage; vertigo.

Tropoderm *Kolassa, Austria.*
⊗ Neomycin sulfate (p.305·1); diphenylpyraline hydrochloride (p.578·2); buphenine hydrochloride (p.2270·2); hydrocortisone (p.1535·2).

Tropofin *Coup, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Tropyn *Zafiro, Mex.*
Atropine sulfate (p.1219·3).
Gastrointestinal disorders; organophosphorus pesticide poisoning; premedication.

Trorix *Baxter, Chile.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Trosderm *Chefaro, Spain.*
Tioconazole (p.548·2).
Fungal skin infections.

Trosic *General Drugs, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Trosid *Pfizer, Spain; Sankyo, Spain.*
Tioconazole (p.548·2).
Fungal skin and nail infections; vulvovaginal candidiasis.

Trospi *Medac, Ger.*
Trospium chloride (p.2198·3).
Bladder instability.

Trosycort *Pfizer, Fin.*
⊗ Tioconazole (p.548·2); hydrocortisone acetate (p.1535·2).
Inflammatory fungal skin infections with secondary bacterial infection.

Trosyd
Note. This name is used for preparations of different composition.
Pfizer, Arg.; Pfizer, Austria; Pfizer Consumer, Canad.†; Pfizer, Fin.; Teofarma, Fr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer Consumer, Ital.; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Thai.
Tioconazole (p.548·2).
Fungal and Gram-positive bacterial infections of the skin, nails, and vagina.

Pfizer Consumer, Switz.
Cream; topical spray: Tioconazole (p.548·2).
Fungal and bacterial skin infections.

Pfizer, Switz.†.
Topical solution: Tioconazole (p.548·2); undecenoic acid (p.549·2).
Fungal and bacterial infections of the skin and nails.

Trosyl *Pfizer, Irl.; Pfizer, UK.*
Tioconazole (p.548·2).
Fungal and bacterial infections of the nails.

Trotil *Globo, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Trovan
Note. This name is used for preparations of different composition.
Pfizer, Gr.†; Pfizer, Mex.†.
Trovafloxacin mesilate (p.357·2).
Bacterial infections.

Pfizer, Canad.†; Pfizer, USA†.
Injection: Alatrofloxacin mesilate (p.200·2).
Bacterial infections.

Pfizer, Canad.†; Pfizer, USA†.
Tablets: Trovafloxacin mesilate (p.357·2).
Bacterial infections.

Troviakol *Tropica Mas, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Troxeratio *Ratiopharm, Pol.*
Troxerutin (p.2305·1).
Venous insufficiency.

Troxescorbin *Synteza, Pol.*
Troxerutin (p.2305·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms; vascular disorders.

Troxevazin *Balkanpharma, Rus.*
Troxerutin (p.2305·1).

Troxeven
Note. This name is used for preparations of different composition.
Typen, Arg.†.
Troxerutin (p.2305·1) aescin (p.2248·2).
Oedema; venous disorders.

Kreussler, Ger.
Troxerutin (p.2305·1).
Venous disorders.

Troxxil *Laboratorios Chile, Chile.*
Tinidazole (p.848·3).
Anaerobic bacterial infections; protozoal infections.

Troxyderm *Ecofarm, Ital.*
Multivitamin, amino-acid, and mineral preparation with myrtillus (p.1922·1).
Nutritional supplement; skin disorders.

Trozet *Dabur, India.*
⊗ Letrozole (p.740·2).
Breast cancer.

Trozocina *Sigma-Tau, Ital.*
Azithromycin (p.207·1).
Bacterial infections.

Trozolet *Tecnofarma, Chile; Nolver, Venez.*
⊗ Anastrozole (p.681·2).
Breast cancer.

Trozolite *Raffo, Arg.*
⊗ Anastrozole (p.681·2).
Malignant neoplasms.

Trozyman *IQB, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Tru
Note. This name is used for preparations of different composition.
Elea, Arg.
Pyrvinium embonate (p.155·3).
Oxyuriasis.

Pasteur, Chile.
Sulfathiazole sodium (p.343·3); lidocaine hydrochloride (p.1862·3).
Otitis.

Tru Compuesto *Elea, Arg.*
Mebendazole (p.148·3); tinidazole (p.848·3).
Worm infections.

Tructum *Nolver, Venez.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Trudexa *Abbott, Neth.*
Adalimumab (p.15·2).
Ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis.

True Test *Mekos, Denm.; Gamida-Medequip, Israel; Glaxo Wellcome, Mex.†; CSL, NZ; NZ Medical & Scientific, NZ; Glaxo Wellcome, USA.*
A range of allergen-impregnated patches (p.2250·2).
Diagnosis of allergic contact dermatitis.

Truetest *Mekos, Port.*
A range of allergen-impregnated patches (p.2250·2).
Diagnosis of allergic contact dermatitis.

Trufree
Nutricia Dietary, UK.
Gluten-free, wheat-free flours and foods for special diets (p.1922·1).
Gluten sensitivity.

Cantassium Co., UK.
Tablets: Multivitamin and mineral preparation (p.1922·1).

Trumsal *Centrum, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Trunal *Ferron, Indon.; Heumann, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Truoxin *Helsinn Birex, Irl.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Truphylline *G & W, USA†.*
Aminophylline (p.1114·2).
Asthma; bronchospasm.

Trusil *Unipharma, Gr.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Trusopt *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Chibret, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Irl.; MSD, Israel; MSD, Ital.; MSD, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Norw.; Pharmalink, Philipp.; MSD, Pol.; Chibret, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Swed.; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
⊗ Dorzolamide hydrochloride (p.1880·2).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Trust Pill *Pond's, Philipp.*
21 Tablets, ethinylestradiol (p.2101·3); levonorgestrel (p.2121·2); 7 tablets, ferrous fumarate (p.1938·3).
Combined oral contraceptive; menstrual disorders.

Truvada *Gador, Arg.; Gilead, Austral.; Gilead, Cz.; Orphan, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Irl.; Gilead, Ital.; Stendhal, Mex.; Gilead, NZ; Gilead, Neth.; Gilead, Port.; Gilead, Spain; Swedish Orphan, Swed.; Gilead, UK; Gilead, USA.*
Emtricitabine (p.873·3); tenofovir disoproxil fumarate (p.908·3).
HIV infection.

Truvit *Solas, Indon.*
Vitamins; calcium gluconate; docosahexaenoic acid; lysine hydrochloride; bovine colostrum (p.1922·1).
Nutritional supplement.

Truxa
Note. This name is used for preparations of different composition.
Raffo, Arg.†.
Piroxicam (p.117·3).
Inflammation.

Asofarma, Mex.
Azithromycin (p.207·1).
Bacterial infections.

Truxa R *Raffo, Arg.†.*
Piroxicam (p.117·3).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Inflammation.

Truxal
Lundbeck, Austria; Lundbeck, Denm.; Lundbeck, Neth.; Lundbeck, Norw.; Lundbeck, Rus.; Lundbeck, Swed.; Lundbeck, Switz.
Chlorprothixene hydrochloride (p.977·2).
Agitation; alcohol and drug withdrawal syndromes; anxiety; behaviour disorders; depression; mania; neuroses; pain; psychoses; sleep disorders; vomiting.

Lundbeck, Fin.
Chlorprothixene (p.977·2).
Anxiety; pain; psychoses; sedative.

Lundbeck, Ger.
Chlorprothixene (p.977·2) or chlorprothixene hydrochloride (p.977·2).
Psychoses.

Lundbeck, Hung.
Chlorprothixene acetate (p.977·2) or chlorprothixene hydrochloride (p.977·2).
Alcohol withdrawal syndrome; anxiety disorders; behaviour disorders in the elderly; epilepsy; opioid withdrawal syndrome; psychoses.

Truxaletten *Lundbeck, Austria; Lundbeck, Switz.*
Chlorprothixene hydrochloride (p.977·2).
Alcohol and drug withdrawal syndromes; anxiety disorders; behaviour disorders in children; depression; mania; neuroses; pain; psychoses; sleep disorders; vomiting.

Try *Roche Nicholas, Fr.*
Vaginal lubricant.

Tryasol *Wernigerode, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Trycam *Douglas, Thai.†; TTN, Thai.†.*
Triazolam (p.1033·2).
Insomnia.

Trycet *Auriga, USA; Tryon, USA.*
Dextropropoxyphene napsilate (p.40·1); paracetamol (p.108·1).
Pain.

Trymo *Raptakos, India.*
Tripotassium dicitratobismuthate (p.1711·2).
Peptic ulcer.

Trypsin *PannonPharma, Hung.†.*
Trypsin (p.2405·3); procaine hydrochloride (p.1869·1); calcium acetate (p.1675·2).
Ulcers; wounds.

Trypsone *Grifols, Cz.; Grifols, Spain.*
Alpha -proteinase inhibitor (p.2253·2).
Congenital alpha antitrypsin deficiency.

Tryptal *Unipharm, Israel.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Tryptan *Valeant, Canad.*
Tryptophan (p.427·1).
Adjunct in treatment of depression and bipolar disorder.

Tryptanol *MSD, Arg.; MSD, Austral.; MSD, Braz.; MSD, Hong Kong†; MSD, Malaysia; MSD, Mex.; MSD, S.Afr.; M & H, Thai.; MSD, Venez.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Tryptizol *MSD, Austria; MSD, Belg.; MSD, Denm.†; MSD, Neth.; MSD, Norw.†; MSD, Port.; Neurogard, Spain; MSD, Swed.; MSD, Switz.*
Amitriptyline hydrochloride (p.376·1).
Bulimia; depression; neuropathic pain; nocturnal enuresis; postherpetic neuralgia.

Tryptoferm *Gaschler, Ger.†.*
Pancreatin (p.2360·1).
Inflammatory disorders.

Tryptomer *Merind, India.*
Amitriptyline hydrochloride (p.376·1).
Depression; nocturnal enuresis.

Tryptonat *Safetynat, Fr.*
Griffonia (p.2317·2); chamomile (p.2279·3); magnesium (p.1678·3).
Appetite disorders; mood disorders.

Tryptozen 5-HTP *Erjean, Fr.*
Preparation for enteral nutrition (p.1922·1).

T-Samag *Vargas, Venez.*
Thyme (p.2401·1); castanea vulgaris.
Cough.

T-Stat *Westwood-Squibb, Canad.†; BMS, Mex.; BMS, Singapore†; Westwood-Squibb, USA†.*
Erythromycin (p.269·2).
Acne.

TT 380 *CCD, Fr.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

TT Vaccine *Bio Farma, Malaysia; Bio Farma, Thai.*
An adsorbed tetanus vaccine (p.2240·1).
Active immunisation.

TTC *Investigaciones Filosoficas y Cientificas, Mex.†.*
Thiamine (p.1976·3).
Irritability; nervous disorders.

TTD-B$_3$-B$_4$ *Tradiphar, Fr.*
Disulfiram (p.2296·2); nicotinamide (p.1957·3); adenine (p.2247·2).
Alcoholism.

Tuaplex *Cetus, Arg.*
Pyridoxine; phosphoserine; glutamine (p.1922·1).
Tonic.

Tuaredon *IFET (ΙΦΕΤ), Gr.†.*
Sodium aurothiomalate (p.122·2).

Tuba *Kurtsan, Turk.*
Salicylic acid (p.1612·2); acetic acid (p.2244·2).
Calluses.

Tubarine
Note. This name is used for preparations of different composition.
Spedrog, Arg.
Troxerutin (p.2305·1); aescin (p.2248·2).
Haemorrhoids; venous insufficiency.

Wellcome, Israel†.
Tubocurarine chloride (p.1912·3).
Competitive neuromuscular blocker.

Tuberbut *LKM, Arg.*
Tobramycin (p.354·1).
Bacterial infections.

Tubergen-Test *Chiron Behring, Ger.†.*
Tuberculin (p.2405·3).
Sensitivity test.

Tubersol *Sanofi Pasteur, Canad.; Aventis, NZ; Sanofi Pasteur, USA.*
Tuberculin purified protein derivative (p.2405·3).
Diagnosis of tuberculosis.

Tubersol PPD *Parisis, Spain†.*
Tuberculins (p.2405·3).
Diagnostic agent.

Tubertest *Sanofi Pasteur, Fr.*
Tuberculin (p.2405·3).
Test for tuberculin sensitivity.

Tubial *SVR, Fr.†.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Tubilux *Transdermal, UK.*
Sodium chloride (p.1686·1).
Nasal dryness; nasal hygiene.

Tubilysin *Orion, Fin.*
Isoniazid (p.288·1).
Tuberculosis.

Tubocin *Antibiotic, Cz.†.*
Rifampicin (p.325·3).
Bacterial infections.

Tucks
Note. This name is used for preparations of different composition.
Pfizer Consumer, Canad.
Hamamelis (p.2318·2); glycerol (p.2314·2).
Haemorrhoids; vaginal cleansing.

Warner-Lambert, USA.
Gel; pads: Hamamelis (p.2318·2); glycerol (p.2314·2).
Perianal cleansing.

Pfizer Consumer, USA.
Ointment: Pramocaine hydrochloride (p.1868·1); zinc oxide (p.1621·2).
Formerly known as Anusol-HC and contained hydrocortisone acetate.
Anorectal disorders; skin disorders.

Pfizer Consumer, USA.
Suppositories: Benzyl alcohol (p.1631·3); soybean oil (p.1965·3); tocoferil acetate (p.1992·3).
Formerly known as Anusol.
Anorectal disorders.

Tuclase
UCB, Belg.; UCB, Gr.; UCB, Ital.
Pentoxyverine hydrochloride (p.1567·3).
Cough.

UCB, Neth.
Pentoxyverine citrate (p.1567·3) or pentoxyverine hydrochloride (p.1567·3).
Coughs.

Tudcabil *Pharmacia, Ital.†.*
Tauroursodeoxycholic acid (p.2408·2).
Biliary disorders.

Tuderm-N *Meprofarm, Indon.*
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Tudiab *Meprofarm, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Tueor *Sofar, Ital.*
Barrier cream.

Tugesal *Meprofarm, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Tuinal *Flynn, UK; Lilly, USA.*
Secobarbital sodium (p.1027·3); amobarbital sodium (p.961·3).
Insomnia; sedative.

Tukol *Atlantis, Mex.*
Guaifenesin (p.1561·3).
Coughs.

Tukol-D *Atlantis, Mex.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tukson *Sons, Mex.†.*
Oxolamine (p.1567·1).
Coughs.

Tulgrasum Antibiotico *Desma, Spain.*
Bacitracin zinc (p.210·3) neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Burns; skin disorders; skin ulcers; wounds.

Tulgrasum Cicatrizante *Desma, Spain.*
Glycine; benzyl benzoate (p.2036·1); benzalkonium chloride (p.1629·1); amino acids.
Burns; skin disorders; skin ulcers; wounds.

Tulip
Note. This name is used for preparations of different composition.
Lek, Cz.; Lek, Pol.; Lek, Rus.
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Wermar, Mex.
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Tulipe-R *Coup, Gr.†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Tulita *Gedeon Richter, Hung.*
Estradiol (p.2097·2); norethisterone acetate (p.2119·3).
Menopausal disorders; osteoporosis.

Tulle Gras *Solvay, Fr.*
White soft paraffin (p.2031·2).
Burns; ulcers; wounds.

Tulle Gras Lumiere *Solvay, Fr.†.*
Peru balsam (p.2365·3).
Burns.

Tulle Vaseline *Stella, Belg.†.*
Yellow soft paraffin (p.2031·3); liquid paraffin (p.2030·3).
Burns; wounds.

Tulotract *Ardeypharm, Ger.*
Lactulose (p.1738·2).
Constipation; hepatic encephalopathy.

Tulox *Mintlab, Chile.*
Oxolamine (p.1567·1).
Coughs.

Tulzol *Bentley, Cz.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tuma *Robugen, Ger.*
Ivy (p.2328·1).
Respiratory-tract disorders.

Tumarol *Robugen, Ger.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); menthol (p.2340·1).
Cold symptoms.

Tumarol Kinderbalsam *Robugen, Ger.*
Eucalyptus oil (p.2301·2); pine silvestris oil (p.2368·2).
Cold symptoms.

Tumarol N *Iromedica, Switz.†.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); menthol (p.2340·1).
Cold symptoms.

Tumarol-N *Robugen, Ger.*
Camphor (p.2273·2); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Cold symptoms.

Tumax *Sriprasit, Thai.*
Chlordiazepoxide hydrochloride (p.968·2); clidinium bromide (p.1722·1).
Gastrointestinal disorders; peptic ulcer; smooth muscle spasm.

Tumdi *Sriprasit, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Tumetil *Boehringer Ingelheim, Venez.*
Mexiletine hydrochloride (p.1339·2).
Arrhythmias.

Tummy Ease *Cadila, India.*
Ferula asafetida (p.2261·3); trachyspermum ammi; gardenia gummifera; ginger (p.1732·3); black pepper (p.2364·3).
Stomach disorders.

Tumoglin *Pfluger, Ger.*
Homoeopathic preparation.

Tums
Note. This name is used for preparations of different composition.
GSK Consumer, Canad.; GSK, Gr.; GSK Consumer, Irl.†; GSK, Israel; GSK, Mex.; GSK, Philipp.; GSK Consumer, Port.; Group, S.Afr.; GSK Consumer, UK; GSK, USA; GSK Consumer, Venez.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement; dyspepsia; flatulence; gastric hyperacidity; heartburn; nausea.

GSK Consumer, Cz.
Calcium carbonate (p.1714·1); heavy magnesium carbonate (p.1743·1).
Dyspepsia; gastric hyperacidity; peptic ulcer.

Tums Plus *SmithKline Beecham, USA.*
Calcium carbonate (p.1714·1); simeticone (p.1770·2).

Tundra *Frasca, Arg.*
Naproxen (p.92·3).
Inflammation.

Tuneluz *Baldacci, Port.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Tunelzin *Rafarm, Gr.†.*
Paracetamol (p.108·1).
Fever; pain.

Tunik *Baliarda, Arg.*
Ademetionine (p.2247·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Depression; osteoarthritis.

Tunik B12 *Baliarda, Arg.*
Ademetionine (p.2247·1); vitamin B   (p.1980·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Depression; liver disorders; osteoarthritis.

Tunitol-BX *Streger, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Tuosomin *Schering, Thai.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer.

Tupast *Kleva, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Turbaund *Rafarm, Gr.*
Tolfenamic acid (p.130·1).
Inflammation; musculoskeletal and joint disorders; pain.

Turbinal *Valeas, Ital.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Turbocalcin *GSK, Ital.†.*
Elcatonin (p.1093·2).
Hypercalcaemia; osteoporosis; Paget's disease of bone; reflex sympathetic dystrophy.

Turbogesic *Laboratorios Chile, Chile.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Turbonatal *Medipharm, Chile.*
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Turbovit *Medipharm, Chile.*
Multivitamin preparation with or without minerals (p.1922·1).
Tonic.

Turexan Capilla *Turimed, Switz.*
⊗ Cetrimonium bromide (p.1635·1); urea (p.1620·2); dexpanthenol (p.2362·1).
Scalp disorders.

Turexan Creme *Turimed, Switz.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Barrier cream; skin disorders.

Turexan Douche *Turimed, Switz.*
Undecenoic acid (p.549·2).
Skin disorders; soap substitute.

Turexan Emulsion *Turimed, Switz.†.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); triclosan (p.1665·2).
Skin disorders; soap substitute.

Turexan Lotion *Turimed, Switz.*
⊗ Urea (p.1620·2); dexpanthenol (p.2362·1).
Skin disorders.

Turfa *Worwag, Ger.*
⊗ Triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension; oedema.

Turgent Colageno *Stiefel, Arg.*
⊗ Collagen (p.2286·1); octinoxate (p.1608·2); urea (p.1620·2).
Dry skin disorders.

Turgent Emulsion *Stiefel, Arg.*
⊗ Octinoxate (p.1608·2); urea (p.1620·2).
Dry skin.

Turifam *Reuffer, Mex.*
Rifampicin (p.325·3).
Bacterial infections.

Turimonit *Jenapharm, Ger.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris; heart failure; pulmonary hypertension.

Turimycin *Jenapharm, Ger.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Turinal *Gedeon Richter, Cz.†; Gedeon Richter, Hong Kong; Gedeon Richter, Malaysia†; Richter, Philipp.; Gedeon Richter, Rus.; Gedeon Richter, Singapore.*
Allylestrenol (p.2082·2).
Premature labour; threatened or recurrent miscarriage.

Turineurin *Jenapharm, Cz.†; Jenapharm, Ger.*
St John's wort (p.422·3).
Depression; nervous disorders.

Turiplex *Jenapharm, Cz.†.*
Cucurbita (p.2290·2).
Benign prostatic hyperplasia.

Turisan *Turimed, Switz.*
Cetrimonium bromide (p.1635·1).
Acne; skin disinfection.

Turisteron *Jenapharm, Ger.†.*
Ethinylestradiol propanesulphonate (p.2102·1).
Prostatic cancer.

Turixin *GSK, Ger.*
Mupirocin calcium (p.302·3).
Nasal carriage of staphylococci.

Turm *Biores, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Turmerik *Knop, Chile.*
Turmeric (p.1473·2).
Liver disorders; musculoskeletal and joint disorders.

Turnera comp *Pfluger, Ger.†.*
Homoeopathic preparation.

Turoptin *Bausch & Lomb, Ital.; Novartis, Switz.†; Novartis, Turk.*
⊗ Metipranolol (p.1883·2).
Glaucoma; ocular hypertension.

Turox *Farmacox, Port.*
Etoricoxib (p.53·1).
Gout; osteoarthritis; rheumatoid arthritis.

Turpan *Corsa, Indon.*
Paracetamol (p.108·1).
Fever; pain.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Turresis *Winthrop, Port.*
Ethambutol hydrochloride (p.274·1).
Tuberculosis.

Turulington Tincture *Lennon, S.Afr.*
Benzoin (p.2394·2); storax (p.2392·3); tolu balsam (p.1574·2); aloes (p.1705·2).
Bronchitis; coughs; minor wounds.

Tusabron *Bago, Chile.*
⊗ Clobutinol hydrochloride (p.1554·1); orciprenaline sulfate (p.1129·1); ammonium chloride (p.1551·3).
Coughs.

Tusana-D *Cypress, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Tusant *Lupin, India†.*
Terfenadine (p.590·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tusapres *Sandoz, Indon.*
Theophylline (p.1140·1); guaifenesin (p.1561·3); diphenhydramine hydrochloride (p.577·2).
Bronchospasm; cough; respiratory-tract disorders with excess mucus.

Tusben *Benedetti, Ital.*
Dimemorfan phosphate (p.1557·1).
Coughs.

Tuscalman
Note. This name is used for preparations of different composition.
Kwizda, Austria; Desma, Switz.
Oral drops; suppositories: Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3).
Bronchitis; catarrh; coughs; laryngitis; sore throat.

Desma, Spain.
Suppositories; syrup: Noscapine hydrochloride (p.1566·3).
Coughs.

Kwizda, Austria.
Syrup: Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3); althaea (p.2253·3); sambucus (p.2383·1).
Bronchitis; catarrh; coughs; laryngitis; sore throat.

Desma, Switz.
Syrup: Noscapine hydrochloride (p.1566·3); guaifenesin (p.1561·3); althaea (p.2253·3).
Respiratory-tract disorders.

Tusco *Hua, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tuscolgen *Great Eastern, Thai.; Westmont, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Coughs.

Tusdec-DM *Cypress, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract disorders.

Tusdec-HC *Cypress, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1).
Coughs.

Tuselin Descongestivo *Korhispana, Spain.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

Tuseptil *Munir, Turk.*
Guaifenesin (p.1561·3); diphenhydramine hydrochloride (p.577·2); phenylpropanolamine hydrochloride (p.1569·3).
Respiratory-tract congestion.

Tuseran
Note. This name is used for preparations of different composition.
Medichem, Hong Kong.
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Formerly contained dextromethorphan hydrobromide, guaifenesin, phenylpropanolamine hydrochloride, chlorphenamine maleate, and paracetamol.
Coughs and cold symptoms.

Medifarma, Indon.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cold symptoms; cough.

Tuseran Forte *Medifarma, Indon.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms; cough.

Tuseran Forte (Reformulated) *United Laboratories, Philipp.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); paracetamol (p.108·1).
Cold symptoms; cough.

Tuseran Pedia DMP *Medifarma, Indon.; UAP, Indon.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cough; nasal congestion; rhinitis.

Tuseran (Reformulated) *Medichem, Philipp.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); guaifenesin (p.1561·3).
Cough.

Tusibron
Note. This name is used for preparations of different composition.
Kener, Mex.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Kenwood, USA.
Guaifenesin (p.1561·3).
Coughs.

Tusibron-DM *Kenwood, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tusical *Andromaco, Mex.*
Benzonatate (p.1552·1).
Coughs.

Tusigen
Note. This name is used for preparations of different composition.
Bago, Chile.
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs.

Liomont, Mex.
Zipeprol hydrochloride (p.1575·3).
Coughs.

Tusilan *Landson, Indon.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Tusilen *Allen, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Coughs; respiratory-tract congestion.

Tusilen Pediatrico *Allen, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); paracetamol (p.108·1).
Coughs; fever.

Tusilin *Mecom, Turk.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Tusitato *Ivax, Mex.*
Benzonatate (p.1552·1).
Cough.

Tusitinas *Pensa, Spain†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tusminal *Medipharm, Chile.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tusminal Compuesto *Medipharm, Chile†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough and cold symptoms.

Tusnel-HC *Llorens, USA.*
Hydrocodone tartrate (p.63·1); brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Tusno *Milano, Thai.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2).
Coughs.

Tusolven *Vedim, Port.†.*
Ambroxol acefyllinate (p.1114·2).
Obstructive airways disease.

Tusorama *Quimifar, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tuspel *Indoco, India.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs.

Tuspel Plus *Indoco, India.*
⊗ Bromhexine hydrochloride (p.1552·2); terbutaline (p.1139·1); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs associated with obstructive airways disease.

Tuspress *Indoco, India.*
Dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3); menthol (p.2340·1).
Cold symptoms; coughs; nasal congestion.

Tusquit *Xixia, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

tuss *Rentschler, Ger.†.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders associated with increased mucus.

Tuss Hustenstiller *Rentschler, Ger.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussa *Silom, Thai.*
Guaifenesin (p.1561·3).
Coughs.

Tussafed HC *Everett, USA†.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs.

Tussafed-EX *Everett, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Coughs; respiratory-tract congestion.

Tussafed-HCG *Everett, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Allergic rhinitis; cold symptoms; coughs.

Tussafin Expectorant *Rugby, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Coughs.

Tussafug *Robugen, Ger.*
Benproperine phosphate (p.1552·1).
Coughs.

Tussal Antitussicum *Biofarm, Pol.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tussal Expectorans *Biofarm, Pol.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Tussall *Everett, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); dexbrompheniramine maleate (p.569·2).
Coughs; nasal congestion.

Tussalpront *Pfizer Consumer, Switz.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussamag
Note. This name is used for preparations of different composition.
Teofarma, Ital.
Wild thyme (p.2415·3); castanea leaves.
Respiratory-tract congestion.

CT, Rus.; Ratiopharm, Rus.
Thyme (p.2401·1).
Cough.

Montavit, Austria.
Ointment: Spike lavender oil (p.2392·1); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); camphor (p.2273·2).
Bronchitis; catarrh; coughs.

Montavit, Austria.
Oral liquid: Thyme (p.2401·1); castanea vulgaris.
Bronchitis; catarrh; coughs.

Tussamag Balsam *CT, Rus.*
Pine oil (p.2368·2); eucalyptus oil (p.2301·2).

Tussamag Complex *Teofarma, Ital.*
Wild thyme (p.2415·3); dropropizine (p.1557·3).
Coughs.

Tussamag Erkaltungsbalsam N *CT, Ger.†.*
Eucalyptus oil (p.2301·2); pine needle oil (p.2368·2).
Catarrh.

Tussamag Hustenlosung *CT, Ger.*
Thyme (p.2401·1).
Formerly Tussamag Hustentropfen N.
Bronchitis; catarrh.

Tussamag Hustensaft N *CT, Ger.*
Thyme (p.2401·1).
Bronchitis; catarrh.

Tussamag Nasenspray *CT, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Tussanil Compositum *Vifor, Switz.†.*
Noscapine (p.1566·2); drosera (p.2297·3); liquorice (p.1740·3); eucalyptus oil (p.2301·2); peppermint oil (p.1761·2).
Coughs.

Tussanil DH *Misemer, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Tussanil N *Vifor, Switz.*
Noscapine hydrochloride (p.1566·3).
Coughs.

Tussanil Plain *Misemer, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Tussantiol *Medisa, Switz.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with increased mucus.

Tussanyl *Giovanardi, Ital.*
Sulfogaiacol (p.1573·2); grindelia (p.2317·2).
Catarrh; coughs.

Tussar-2 *Rhone-Poulenc Rorer, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Tussar DM *Rhone-Poulenc Rorer, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Tussar SF *Rhone-Poulenc Rorer, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs.

Tusscodin *Lannacher, Austria.*
Nicocodine hydrochloride (p.1566·2).
Coughs.

Tuss-DM *Hyrex, USA†.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Tussed *Hexal, Ger.†.*
Clobutinol hydrochloride (p.1554·1).
Coughs.

Tussefar *Faran, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Tusselin *Faran, Gr.*
Erdosteine (p.1560·1).
Mucolytic.

Tussend *Monarch, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Coughs.

Tussi-12 *Wallace, USA.*
Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); phenylephrine tannate (p.1568·3).
Coughs.

Tussi-12 D *Wallace, USA.*
Pentoxyverine tannate (p.1567·3); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Coughs.

Tussibron *Sella, Ital.*
Oxolamine citrate (p.1567·1).
Coughs.

Tussicare DG *ST, Thai.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussicom *Sanofi-Aventis, Pol.*
Acetylcysteine (p.1548·2).
Cystic fibrosis; respiratory-tract congestion.

Tussi-12D S *Wallace, USA.*
Pentoxyverine tannate (p.1567·3); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Tussidane *Elerte, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussidermil N *Li-il, Ger.*
Eucalyptus oil (p.2301·2).
Catarrh; musculoskeletal and joint disorders.

Tussidex *Hasco-Lek, Pol.; Xepa-Soul Pattinson, Singapore†.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tussidex Forte *Xepa-Soul Pattinson, Malaysia†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussidoron *Weleda, Fr.*
Thyme (p.2401·1); drosera (p.2297·3).
Coughs.

Tussidrill *Pierre Fabre, Cz.; Pierre Fabre, Spain.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

TussiDrill *Pierre Fabre, Pol.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tussifen *Hexal, Braz.†.*
Belladonna (p.2263·3); jaborandi; eucalyptus (p.2301·2); ginger (p.1732·3); siparuna guyanensis; lantana camara; mikania glomerata.
Respiratory-tract congestion.

Tussiflex D *Abbott, Braz.*
Dropropizine (p.1557·3).
Coughs.

Tussiflorin forte *Pascoe, Ger.†.*
Ivy (p.2328·1); primula root (p.2372·2); thyme (p.2401·1).
Asthma; bronchitis.

Tussiflorin Hustensaft *Pascoe, Ger.†.*
Vogelknoterichkraut; sanikelkraut; hohlzahnkraut; primula root (p.2372·2).
Asthma; bronchitis; coughs.

Tussiflorin Hustenstiller *Pascoe, Ger.†.*
Thyme (p.2401·1); drosera (p.2297·3).
Cold symptoms; coughs.

Tussiflorin Hustentropfen *Pascoe, Ger.†.*
Vogelknoterichkraut; sanikelkraut; hohlzahnkraut; primula root (p.2372·2).
Asthma; bronchitis; coughs.

Tussiflorin Thymian *Pascoe, Ger.*
Thyme (p.2401·1).
Bronchitis; respiratory-tract congestion.

Tussigon
Note. This name is used for preparations of different composition.
Novell, Indon.
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); pseudoephedrine (p.1571·2); sodium citrate (p.1673·3).
Cold symptoms; cough.

King, USA.
Hydrocodone tartrate (p.63·1); homatropine methylbromide (p.1881·3).
Cough.

Tussikind *VSM, Neth.†.*
Homoeopathic preparation.

Tussilen *Ivax, Cz.*
⊗ Drosera (p.2297·3); thyme oil (p.2401·2); gypsophila saponin; ephedrine hydrochloride (p.1558·2).
Respiratory-tract inflammation.

Tussilene
Note. This name is used for preparations of different composition.
Zydus, Fr.†.
Carbocisteine (p.1553·2).
Respiratory-tract disorders.

Azevedos, Port.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussilinct *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Tussiliv *Delta, Braz.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Tussils *Boots, Hong Kong; Reckitt Benckiser, Malaysia; Reckitt Benckiser, Singapore; Boots, Thai.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tussimag Codein *Montavit, Austria.*
Codeine phosphate (p.37·2); castanea vulgaris.
Bronchitis; catarrh; coughs.

Tussimont *Pharmonta, Austria.*
Senega (p.1572·3); thyme (p.2401·1); bitter-orange (p.2357·1).
Coughs.

Tussin
Note. This name is used for preparations of different composition.
Ivax, Cz.
Butamirate citrate (p.1553·1).
Coughs.

Sagmel, Rus.
Guaifenesin (p.1561·3).
Cough.

Tussin Antitussive *Stanley, Canad.†.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Tussin Antitussive, Expectorant, Decongestant *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).

Tussin Children's DM *Stanley, Canad.†.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).

Tussin Expectorant *Stanley, Canad.†.*
Guaifenesin (p.1561·3).

Tussin Plus *Sagmel, Rus.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

TUSSinfant N *Rubiepharm, Ger.†.*
Primula root (p.2372·2); thyme (p.2401·1).
Cold symptoms.

Tussinol *Johnson & Johnson, Austral.*
Pholcodine (p.1570·2).
Cough.

Tussinol for Dry Coughs *Pfizer Consumer, Austral.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussinol Expectorant *Johnson & Johnson, Austral.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cough.

Tussionex *Aventis, Canad.*
Hydrocodone resin complex (p.63·2); phenyltoloxamine resin complex (p.588·1).
Coughs.

Tussionex Pennkinetic *Celltech, USA.*
Hydrocodone polistirex (p.63·2); chlorphenamine polistirex (p.572·2).
Coughs and cold symptoms.

Tussi-Organidin DM NR *Victory, USA.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tussi-Organidin NR *Victory, USA.*
Codeine phosphate (p.37·2); guaifenesin (p.1561·3).
Coughs.

Tussipax
Note. This name is used for preparations of different composition.
Bailleul, Fr.
Oral solution; tablets: Ethylmorphine hydrochloride (p.52·2); codeine (p.37·2).
Coughs.

Bailleul, Fr.
Syrup: Ethylmorphine hydrochloride (p.52·2); codeine (p.37·2); tolu balsam (p.1574·2); pectoral concentrate.
Coughs.

Tussipect
Note. This name is used for preparations of different composition.
Qualiphar, Belg.; Qualiphar, Neth.
Dextromethorphan hydrobromide (p.1555·2).
Cough; coughs.

Herbapol Poznan, Pol.
Syrup: ⊗ Ephedrine hydrochloride (p.1558·2); thyme (p.2401·1); saponin.
Cough and associated respiratory-tract disorders.

Herbapol Poznan, Pol.
Tablets: ⊗ Ephedrine hydrochloride (p.1558·2); liquorice (p.1740·3); saponin.
Cough and associated respiratory-tract disorders.

Tussiplex *Vifor, Switz.†.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); pholcodine (p.1570·2); guaifenesin (p.1561·3).
Coughs; upper respiratory-tract inflammation.

Tussi-Pres *Kramer, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Cough.

Tussirex *Scot-Tussin, USA.*
Codeine phosphate (p.37·2); pheniramine maleate (p.587·3); phenylephrine hydrochloride (p.1568·1); sodium citrate (p.1673·3); sodium salicylate (p.124·2); caffeine citrate (p.1116·3); menthol (p.2340·1).
Coughs.

Tussisana N *Muller Goppingen, Ger.*
Homoeopathic preparation.

Tussisedal *Elerte, Fr.*
Noscapine (p.1566·2); promethazine (p.588·2); polysorbate 85 (Tween 85).
Coughs.

Tussistin *DHU, Ger.; VSM, Neth.*
Homoeopathic preparation.

Tussistin N *DHU, Ger.*
Homoeopathic preparation.

Tussitot *Adcock Ingram, S.Afr.*
Diphenhydramine hydrochloride (p.577·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Tussivit *Ducto, Braz.†.*
Potassium iodide (p.2169·2); guaifenesin (p.1561·3).
Coughs.

Tussizone *Mallinckrodt, USA.*
Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2).
Upper respiratory-tract disorders.

Tuss-LA *Hyrex, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Tusso Rhinathiol *Sanofi-Aventis, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Formerly known as Rhinathiol Antitussivum.
Coughs.

Tussocal *Agis, Israel†.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Coughs; nasal congestion.

Tussodan DM *Odan, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Tusso-DF *Everett, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Tussodina *Dovalle, Braz.†.*
Sodium dibunate (p.1573·1); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2).
Cough.

Tusso-HC *Everett, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Cough.

Tussol
Note. This name is used for preparations of different composition.
Ibefar, Braz.†.
Oxomemazine hydrochloride (p.587·1); sodium benzoate (p.1630·2); guaifenesin (p.1561·3); potassium iodide (p.2169·2); ipecacuanha (p.1562·3).
Cough.

Amnol, Ital.
Myrtillus (p.2349·3); thyme (p.2401·1); tilia (p.2402·2); liquorice (p.1740·3).
Respiratory-tract disorders.

Tussolvina *Pfizer, Ital.*
Nepinalone hydrochloride (p.1566·1).
Coughs.

Tussophedrine New Formula *Trima, Israel.*
⊗ Ephedrine hydrochloride (p.1558·2); dextromethorphan hydrobromide (p.1555·2); sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2).
Tussophedrine formerly contained codeine phosphate, ephedrine hydrochloride, sulfogaiacol, and sodium benzoate.
Coughs.

Tussoret *Maxmedic, Ger.*
Codeine phosphate (p.37·2).
Coughs.

Tussoretardin *Fujisawa, Austria.*
⊗ White day capsules, pentoxyverine citrate (p.1567·3); methylephedrine hydrochloride (p.1564·3); blue night capsules, pentoxyverine citrate; diphenhydramine hydrochloride (p.577·2).
Coughs.

Tussosedan *Teva, Israel.*
⊗ Pheniramine maleate (p.587·3); ephedrine hydrochloride (p.1558·2); codeine phosphate (p.37·2); ammonium chloride (p.1551·3).
Coughs.

Tussplex *Breckenridge, USA.*
Hydrocodone tartrate (p.63·1); mepyramine maleate (p.585·2); phenylephrine hydrochloride (p.1568·1).
Cold symptoms; cough.

Tuss-Tan *Econolab, USA.*
⊗ Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); ephedrine tannate (p.1559·1).
Upper respiratory-tract symptoms.

Tusstat *Century, USA.*
Diphenhydramine hydrochloride (p.577·2).
Coughs.

Tussucalman *Ibefar, Braz.†.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); ammonium chloride (p.1551·3); ipecacuanha (p.1562·3); liquorice (p.1740·3); belladonna (p.2263·3).
Cough.

Tussycalm *Sanofi-Aventis, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tutofusin *Baxter, Ger.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders; peritoneal irrigation.

Tutofusin BG *Baxter, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin BX *Baxter, Ger.*
Electrolyte infusion with xylitol (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin G5 *Baxter, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin H G5 *Baxter, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin K 10 *Baxter, Ger.†.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Tutofusin K 80 *Baxter, Ger.†.*
Electrolyte infusion with xylitol and glucose (p.1667·1).
Potassium deficiency in cardiac disorders.

Tutofusin LC *Kalbe, Indon.*
Amino-acids; electrolytes; sorbitol; vitamins (p.1922·1).
Liver disorders.

Tutofusin NS X *Baxter, Ger.†.*
Electrolyte infusion with xylitol (p.1667·1).
Fluid and electrolyte disorders.

Tutofusin OP *Baxter, Ger.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Tutofusin OP X *Baxter, Ger.†.*
Electrolyte infusion with xylitol (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin OP G *Baxter, Ger.*
Electrolyte infusion with glucose (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin OpS *Kalbe, Indon.*
Electrolyte infusion with sorbitol (p.1667·1).
Carbohydrate source; fluid and electrolyte disorders.

Tutofusin S *Baxter, Ger.†.*
Sodium chloride (p.1686·1); sodium acetate (p.1673·2); sorbitol (p.1965·1).
Fluid retention; renal failure.

Tutoplast Dura *Tutogen, Ger.*
Absorbable collagen from dehydrated human dura mater (p.2286·1).
Repair or closure of body tissue.

Tutoplast Fascia lata *Tutogen, Ger.*
Dehydrated human fascia lata (p.2286·1).
Repair of joints and tendons.

Tutoseral *Streuli, Switz.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Tuttozem N *Strathmann, Ger.*
⊗ Dexamethasone (p.1526·1).
Skin disorders.

Tuulix *Verman, Fin.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Tux *Pfizer Consumer, Belg.†.*
⊗ Ethylmorphine hydrochloride (p.52·2); codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3); sodium benzoate (p.1630·2); sodium camsilate (p.2388·3); senega (p.1572·3); senna (p.1769·2); tolu balsam (p.1574·2).
Colds; coughs; respiratory disorders.

Tuxi *Leiras, Fin.; Weifa, Norw.*
Pholcodine (p.1570·2).
Coughs.

Tuxium *Galephar, Fr.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Tuzalos *Sanbe, Indon.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylpropanolamine hydrochloride (p.1569·3); chlorphenamine maleate (p.571·3).
Cough; fever; nasal congestion; pain.

Tuzanil *Bohm, Spain.*
Pygeum africanum (p.2192·3).
Benign prostatic hyperplasia.

Tuzzil *IQFA, Mex.*
Benzonatate (p.1552·1).
Coughs.

T-Vites *Freeda, USA.*
Multivitamin preparation with minerals (p.1922·1).

TVMox *T Man, Thai.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Twelve Resin-K *Key, USA.*
Vitamin B (p.1980·2).

Twice *Angelini, Ital.*
⊗ Morphine sulfate (p.86·3).
Pain.

Twice-A-Day *Major, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Twilite *Pfeiffer, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Twina *T Man, Thai.*
⊗ Clotrimazole (p.530·1); betamethasone valerate (p.1519·1).
Inflammatory skin disorders.

Twinject *Paladin, Canad.*
⊗ Adrenaline (p.1203·2).
Anaphylaxis.

Twin-K *Boots, USA†.*
Potassium gluconate (p.1684·3); potassium citrate (p.1673·2).
Hypokalaemia; potassium depletion.

Twinkle Calamine *Pharmaniaga, Malaysia.*
Calamine (p.1591·2); zinc oxide (p.1621·2).
Dermatitis.

Twinline *Otsuka, Jpn.*
Preparation for enteral nutrition (p.1922·1).

Twinrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; SmithKline Beecham, USA; GSK, Venez.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p.2217·1).
Separate preparations are available for infants and children and for adults.
Active immunisation.

TwinVisc *Ioltech, Ger.*
Sodium hyaluronate (p.2320·1).
Aid in eye surgery.

Two Cal HN *Abbott, Austral.; Abbott, Irl.; Abbott, Mex.; Abbott, NZ.*
Preparation for enteral nutrition (p.1922·1).

TwoCal *Abbott, Ital.*
Preparation for enteral nutrition (p.1922·1).

TwoCal HN *Abbott, Hong Kong; Abbott Nutrition, UK; Ross, USA.*
Preparation for enteral nutrition (p.1922·1).

Two-Septol *Cyntfarm, Pol.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Tyason *Combiphar, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Tyavax *Sanofi Pasteur, Fr.*
An inactivated hepatitis A and typhoid (Vi capsular polysaccharide) vaccine (p.2217·2).
Active immunisation.

Tybikin *M & H, Thai.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Tycoytycoy *Bouzen, Arg.*
Povidone-iodine (p.1659·2).
Disinfection.

Tycveolum *Europe Biofarm, Rus.*
Cucurbita oil (p.2290·2).
Atherosclerosis; benign prostatic hyperplasia; burns; colitis; gastritis; haemorrhoids; liver and biliary-tract disorders; skin disorders; vaginal disorders.

Tydadex *Lennon, S.Afr.*
Tolbutamide (p.463·1).
Diabetes mellitus.

Tydamine *Pharmacare, S.Afr.*
Trimipramine maleate (p.426·3).
Depression; nocturnal enuresis; obsessive-compulsive disorder.

Tyflen *Brasterapica, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Tygacil *Wyeth, Arg.; Wyeth, Austral.; Wyeth, Braz.; Wyeth, Chile; Wyeth, Cz.; Wyeth, Gr.; Wyeth, Hung.; Wyeth, Indon.; Wyeth, Malaysia; Wyeth, Mex.; Wyeth, Pol.; Wyeth Lederle, Port.; Wyeth, UK; Wyeth, USA; Wyeth, Venez.*
Tigecycline (p.353·2).
Intra-abdominal infections; skin and skin structure infections.

Tykerb
GSK, Austral.; GSK, USA.
Lapatinib tosilate (p.739·1).
Breast cancer.

GSK, Malaysia.
Lapatinib.
Breast cancer.

Tyklid *Sanofi Torrent, India.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolic disorders.

Tylalgin *Geolab, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Tyleflan *Eversil, Braz.†.*
Paracetamol (p.108·1).
Fever; pain.

Tylenol *Johnson & Johnson, Arg.†; Johnson & Johnson, Austral.†; Janssen-Cilag, Braz.; McNeil Consumer, Canad.; Johnson & Johnson, Hong Kong†; Johnson & Johnson, Irl.†; Janssen-Cilag, Mex.; Johnson & Johnson, Neth.; Janssen, Philipp.; Janssen-Cilag, Port.; Janssen-Cilag, S.Afr.; Johnson & Johnson, Singapore; McNeil, Spain; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; McNeil Consumer, USA; Johnson & Johnson, Venez.*
Paracetamol (p.108·1).
Cold symptoms; fever; pain.

Tylenol Aches & Strains *McNeil Consumer, Canad.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Muscular aches and strains.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Tylenol Allergy Complete Multi-Symptom *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Formerly known as Tylenol Allergy Sinus Maximum Strength.
Upper respiratory-tract symptoms.

Tylenol Allergy Complete NightTime *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Formerly known as Tylenol Allergy Sinus NightTime Maximum Strength.

Tylenol Allergy Multi-Symptom *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Tylenol Allergy Sinus *Johnson & Johnson, Austral.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Upper respiratory-tract symptoms.

Tylenol Allergy Sinus Day & Night *McNeil, USA.*
Day capsules, pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); night capsules, pseudoephedrine hydrochloride; diphenhydramine hydrochloride (p.577·2); paracetamol.
Upper respiratory-tract disorders.

Tylenol Allergy Sinus (Multi-Symptom Relief) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergy symptoms; sinus pain and congestion.

Tylenol Allergy Sinus (Nighttime) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Allergy symptoms; sinus pain and congestion.

Tylenol Allergy-D *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).
Allergy symptoms; sinus pain and congestion.

Tylenol Chest Congestion Daytime *McNeil Consumer, USA.*
Paracetamol (p.108·1); guaifenesin (p.1561·3).
Upper respiratory-tract disorders.

Tylenol Children's Cold *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Tylenol Children's Cold Plus Cough *McNeil Consumer, USA.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Tylenol Childrens Plus Cold Nighttime *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold symptoms.

Tylenol with Codeine *Janssen-Ortho, Canad.; McNeil Consumer, Canad.; Janssen-Cilag, Thai.; McNeil, USA.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Tylenol Cold *McNeil, Hong Kong†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Allergic rhinitis; cold symptoms.

Tylenol Cold (Chest Congestion) *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Upper respiratory-tract symptoms.

Tylenol Cold Children's *McNeil Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergy symptoms; cold symptoms.

Tylenol Cold Complete Formula *McNeil Consumer, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Tylenol Cold (Daytime) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Tylenol Cold DM *McNeil Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Tylenol Cold & Flu
Note. This name is used for preparations of different composition.
Johnson & Johnson, Austral.†.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Janssen-Cilag, S.Afr.
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Tylenol Cold & Flu (Nighttime Relief) *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Tylenol Cold & Flu Non-Drowsy *Johnson & Johnson, Austral.†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Tylenol Cold and Flu Powder *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Tylenol Cold Infant's *McNeil Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Allergy symptoms; cold symptoms.

Tylenol Cold Medication *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms.

Tylenol Cold (Nighttime) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cold symptoms.

Tylenol Cold Non-Drowsy *McNeil Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Tylenol Cold Severe Congestion *McNeil Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs and cold symptoms.

Tylenol Cough *McNeil Consumer, Canad.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2).
Coughs; fever; pain; sore throat.

Tylenol Cough with Decongestant *McNeil Consumer, Canad.†.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs; fever; nasal congestion; pain; sore throat.

Tylenol DC *Janssen-Cilag, Braz.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Tylenol Decongestant *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Tylenol Flu (Daytime Relief) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Influenza symptoms.

Tylenol Flu Maximum Strength *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Tylenol Flu Maximum Strength Non-Drowsy *McNeil Consumer, USA.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Tylenol Flu NightTime *McNeil Consumer, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2); pseudoephedrine hydrochloride (p.1571·2).

Tylenol Flu (Nighttime Relief) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); diphenhydramine hydrochloride (p.577·2).
Influenza symptoms.

Tylenol Infants Drops Plus Cold *McNeil Consumer, USA.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Congestion; fever; pain.

Tylenol Menstrual *McNeil Consumer, Canad.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3); mepyramine maleate (p.585·2).
Premenstrual syndrome.

Tylenol Night Pain *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia with pain.

Tylenol No 1 *Janssen-Ortho, Canad.; McNeil Consumer, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Tylenol No 4 with Codeine *Janssen-Ortho, Canad.; McNeil Consumer, Canad.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Tylenol No 2 with Codeine or Tylenol No 3 with Codeine *Janssen-Ortho, Canad.; McNeil Consumer, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Fever; pain.

Tylenol Plus Cold & Cough Infants *McNeil, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Formerly known as Tylenol Infants Cold Decongestant & Fever Reducer Plus Cough.
Cold symptoms; cough.

Tylenol PM *Janssen-Cilag, S.Afr.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia with pain.

Tylenol PM Extra Strength *McNeil Consumer, USA.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Insomnia.

Tylenol Severe Allergy *McNeil Consumer, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Hypersensitivity symptoms.

Tylenol Sinus
Note. This name is used for preparations of different composition.
Johnson & Johnson, Austral.†; McNeil Consumer, Canad.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; sinus and nasal congestion; sinus pain; sinusitis.

Janssen-Cilag, Mex.
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion; rhinitis; rhinopharyngitis.

Tylenol Sinus Children's *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; sinusitis.

Tylenol Sinus Congestion & Pain Nighttime Caplets *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Cold and influenza symptoms.

Tylenol Sinus Congestion & Pain Severe Daytime Caplets *McNeil Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Tylenol Sinus (Daytime Relief) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; sinusitis.

Tylenol Sinus (Nighttime Relief) *McNeil Consumer, Canad.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2).
Cold symptoms; sinusitis.

Tylenol Sinus Non-Drowsy *McNeil Consumer, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Upper respiratory-tract symptoms.

Tylenol Sore Throat Daytime *McNeil Consumer, USA.*
Paracetamol (p.108·1).
Sore throat.

Tylenol Sore Throat Nighttime *McNeil Consumer, USA.*
Diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1).
Sore throat.

Tylenol Ultra Relief *McNeil Consumer, Canad.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tylephen *IQB, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Tylex
Note. This name is used for preparations of different composition.
Janssen-Cilag, Braz.; Schwarz, Irl.; UCB, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol 30/500.
Pain.

Janssen-Cilag, Mex.; Janssen-Cilag, Venez.
Paracetamol (p.108·1).
Fever; pain.

Tylex CD *Janssen-Cilag, Mex.; Janssen-Cilag, Venez.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain.

Tylex Flu *Janssen-Cilag, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms; coughs.

Tylidol *Teuto, Braz.*
Paracetamol (p.108·1).
Fever; pain.

Tylol *Nobel, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Tylol Hot *Nobel, Turk.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); pseudoephedrine (p.1571·2).
Respiratory-tract congestion.

Tylol Plus *Nobel, Turk.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Tylonic *Metiska, Indon.*
Allopurinol (p.552·2).
Hyperuricaemia.

Tylox *Ortho McNeil, USA.*
⊗ Oxycodone hydrochloride (p.106·2); paracetamol (p.108·1).
Pain.

Tymedon *Ace, Philipp.*
Loperamide hydrochloride (p.1741·1).
Colostomy or ileostomy management; diarrhoea.

Tymelyt *Lundbeck, Cz.†; Lundbeck, Denm.†; Lundbeck, Swed.†.*
Lofepramine hydrochloride (p.407·1).
Depression.

Tymol *Pharmaland, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Tympagesic *Savage, USA†.*
Phenylephrine hydrochloride (p.1568·1); phenazone (p.116·1); benzocaine (p.1854·1).
Earache.

Tympalgine *Therabel, Belg.†.*
Phenazone (p.116·1); lidocaine hydrochloride (p.1862·3).
Formerly contained phenazone and procaine hydrochloride.
Otitis.

Tymsal *Herbapol Krakow, Pol.*
Sage (p.2382·3); thyme (p.2401·1).
Upper respiratory-tract disorders.

Tynostan *Tynor, Philipp.*
Mefenamic acid (p.80·1).
Fever; musculoskeletal and joint disorders; pain.

Typherix *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Cz.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, UK.*
A typhoid vaccine (Vi capsular polysaccharide) (p.2241·2).
Active immunisation.

Typhim *Aventis Pasteur, Turk.*
A typhoid vaccine (Vi capsular polysaccharide) (p.2241·2).
Active immunisation.

Typhim Vi *Sanofi Pasteur, Arg.; Aventis Pasteur, Austral.; Aventis Pasteur, Austria; Sanofi Pasteur, Belg.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Aventis Pasteur, Fin.†; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Cadila, India; Sanofi Pasteur, Indon.; Sanofi Pasteur, Irl.; Pasteur Merieux, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; MSD, NZ; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Spain; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, UK; Sanofi Pasteur, USA; Zuoz, Venez.†.*
A typhoid vaccine (Vi capsular polysaccharide) (p.2241·2).
Active immunisation.

Typhoral *Aventis, India.*
An oral typhoid vaccine (attenuated Ty21a Berna strain) (p.2241·2).
Active immunisation.

Typhoral L *Chiron Vaccines, Ger.*
A live oral typhoid vaccine (p.2241·2).
Active immunisation.

Typhovax *Green Cross, Malaysia†.*
A typhoid vaccine (Vi capsular polysaccharide) (p.2241·2).
Active immunisation.

Typh-Vax *CSL, Austral.; CSL, NZ.*
An oral typhoid vaccine (attenuated Ty21a Berna strain) (p.2241·2).
Active immunisation.

Typofen *Kleva, Gr.*
⊗ Atenolol (p.1217·3); chlortalidone (p.1243·3).
Hypertension.

TYR *Medifood, Ital.*
Food for special diets (p.1922·1).
Tyrosinaemia.

TYR 1 and 2 *Nutricia-Bago, Arg.*
Food for special diets (p.1922·1).
Metabolic disorders.

TYR Express *Vitaflo, UK.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Tyrazol *Astellas, Fin.*
Carbimazole (p.2167·3).
Hyperthyroidism.

Tyrenol *Remedina, Gr.†.*
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Tyrex *Ross, USA.*
Phenylalanine- and tyrosine-free preparation for enteral nutrition (p.1922·1).
Tyrosinaemia types I, II, and III.

Tyricine *Christo, Hong Kong.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Bacterial mouth and throat infections.

Tyrocaine *Synco, Hong Kong.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat infections.

Tyrocombine *Hanseler, Switz.*
Tyrothricin (p.358·2); neomycin sulfate (p.305·1); benzethonium chloride (p.1630·1).
Infected skin disorders; infected wounds.

Tyrodone *Major, USA.*
Hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).

Tyro-Drops *Centrapharm, Belg.*
Tyrothricin (p.358·2); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Tyroplus *Enila, Braz.†.*
Liothyronine sodium (p.2174·1); levothyroxine (p.2173·2).
Thyroid disorders.

Tyroqualine *Spirig, Switz.*
Tyrothricin (p.358·2); dequalinium chloride (p.1641·3); lidocaine hydrochloride (p.1862·3).
Mouth and throat disorders.

Tyros *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Alkaptonuria; tyrosinaemia.

Tyroseng *Eagle, Austral.†.*
Tyrosine (p.1971·1); eleutherococcus senticosis (p.2386·3); calcium glycerophosphate (p.1676·1); phosphatidyl choline (p.2367·1); vitamin B substances (p.1922·1).
Dietary supplement.

Tyrosin TU *Bencard, Ger.*
Mixed allergen extracts (p.2250·2).
Allergen immunotherapy.

Tyrosolvetten *Altana, Ger.†.*
Cetylpyridinium chloride (p.1635·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Tyrosolvetten-C *Altana, Ger.†.*
Cetylpyridinium chloride (p.1635·1); ascorbic acid (p.1983·3).
Mouth and throat infections.

Tyrosum *Summers, USA.*
Skin cleanser.

Tyrosur
Note. This name is used for preparations of different composition.
Engelhard, Hong Kong†.
Tyrothricin (p.358·2).
Infected skin disorders; infected wounds.

Engelhard, Hung.
Tyrothricin (p.358·2); cetylpyridinium chloride (p.1635·1).
Infected skin disorders; infected wounds.

Engelhard, Ger.
Topical gel: Tyrothricin (p.358·2); cetylpyridinium chloride (p.1635·1).
Infected wounds.

Engelhard, Ger.
Topical powder: Tyrothricin (p.358·2).
Infected skin disorders; infected wounds and burns.

Tyrothricin *Streuli, Switz.*
Tyrothricin (p.358·2); ethacridine lactate (p.1625·1); lidocaine hydrochloride (p.1862·3); menthol (p.2340·1); mint oil (p.2345·2).
Mouth and throat disorders.

Tyrothricin Co *Jean-Marie, Hong Kong.*
Tyrothricin (p.358·2); codeine phosphate (p.37·2); benzocaine (p.1854·1).
Sore throat.

Tyrothricin comp *Provita, Austria.*
Tyrothricin (p.358·2); neomycin sulfate (p.305·1); benzalkonium chloride (p.1629·1); benzocaine (p.1854·1).
Mouth and throat disorders.

Tyrothricin compositum *Provita, Austria.*
Tyrothricin (p.358·2); neomycin sulfate (p.305·1); benzocaine (p.1854·1); camphor (p.2273·2).
Ear disorders.

Tyrothricine + Gramicidine *Vifor, Switz.*
Tyrothricin (p.358·2); gramicidin (p.286·1); tetracaine hydrochloride (p.1871·3); benzethonium chloride (p.1630·1).
Mouth and throat disorders.

Tyrozets *MSD, Irl.; Johnson & Johnson MSD Consumer, UK.*
Tyrothricin (p.358·2); benzocaine (p.1854·1).
Mouth and throat disorders.

Tysabri *Biogen, Austral.; Elan, Cz.; Genesis, Gr.; Biogen, Port.; Biogen, UK; Biogen, USA†; Elan, USA.*
Natalizumab (p.2350·2).
Crohn's disease; multiple sclerosis.

Tytanoreina
Note. This name is used for preparations of different composition.
Martin, Pol.†.
Cream: Carrageenan (p.2142·3); lidocaine hydrochloride (p.1862·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Anorectal disorders.

Martin, Pol.†.
Suppositories: Carrageenan (p.2142·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Anorectal disorders.

Tytin *Merind, India.*
Tyrothricin (p.358·2); benzocaine (p.1854·1); phenazone (p.116·1); hexylresorcinol (p.1647·1).
Ear infections.

Tyvera *Auden McKenzie, UK.*
Thiamine hydrochloride (p.1976·1).
Thiamine deficiency.

Tyverb *GSK, Fr.; GSK, Switz.; GSK, UK.*
Lapatinib tosilate (p.739·1).
Breast cancer.

Tyzeka *Novartis, USA.*
Telbivudine (p.908·1).
Chronic hepatitis B.

Tyzine *Mack, Cz.†; Pfizer, Denm.; Pfizer, Ger.†; Pfizer, Hung.; Pfizer, Rus.; Kenwood, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Conjunctivitis; eye irritation; hay fever; nasal congestion; pharyngitis; rhinitis; sinusitis.

Tyzine Xylo *Pfizer, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).

T-ZA *Siam Bheasach, Thai.*
Zidovudine (p.913·3).
HIV infection.

Tzarevet X *CTI, Israel.*
Calcium carbonate (p.1714·1).
Antacid; calcium supplement.

Tzoali *Kendrick, Mex.†.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

U Lactin *Cosmofarma, Port.*
⊗ Urea (p.1620·2); alpha hydroxy acids.
Dry skin disorders.

UAA *Econo Med, USA.*
Methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1); benzoic acid (p.1630·2); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

UAD-Otic *UAD, USA.*
⊗ Hydrocortisone (p.1535·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Bacterial ear infections.

Ubenzima *Pentafarma, Port.*
Ubidecarenone (p.2407·2).
Cardiac disorders.

Ubicardio *Tosi, Ital.†.*
Ubidecarenone (p.2407·2).
Cardiac disorders; coenzyme Q10 deficiency.

Ubicondrial *Medicamed, Port.†.*
Ubidecarenone (p.2407·2).
Cardiac disorders.

Ubicor *Magis, Ital.*
Ubidecarenone (p.2407·2).
Coenzyme Q10 deficiency.

Ubidenone *Esseti, Ital.*
Ubidecarenone (p.2407·2).
Cardiac disorders; coenzyme Q10 deficiency.

Ubidex *OFF, Ital.*
Ubidecarenone (p.2407·2).
Cardiac disorders; coenzyme Q10 deficiency.

Ubimaior *Chiesi, Ital.*
Ubidecarenone (p.2407·2).
Coenzyme Q10 deficiency.

Ubi-Q *Eisai, Indon.; Fourtts, Singapore.*
Ubidecarenone (p.2407·2).
Antoxidant; nutritional supplement.

Ubistesin *Espe, Austria; 3M Espe, Belg.†; 3M Espe, Cz.; 3M, Denm.; 3M, Fin.; 3M Espe, Ger.; 3M Espe, Hong Kong; 3M, Hung.; Espe, Ital.; 3M, Neth.; 3M, Port.; Espe, Switz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline (p.1203·2) or adrenaline hydrochloride (p.1203·3) may be included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ubistesin Adrenalinee *3M, Fr.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ubit *Otsuka, Port.*
⊗ Carbon-13 urea (p.2277·1).
Diagnosis of Helicobacter pylori infection.

Ubiten
Note. This name is used for preparations of different composition.
Labomed, Chile.
Levocarnitine; ubidecarenone; magnesium; vitamin C; aspartic acid (p.1922·1).
Dietary supplement.

Lifepharma, Ital.†.
Ubidecarenone (p.2407·2).
Cardiac disorders; coenzyme Q10 deficiency.

Ubivis *AGIPS, Ital.*
Ubidecarenone (p.2407·2).
Cardiac disorders; coenzyme Q10 deficiency.

Ubizol *Alodial, Port.*
⊗ Fluticasone propionate (p.1533·2).
Skin disorders.

Ublosid *Costec, Arg.†.*
Triclosan (p.1665·2); aluminium chlorohydrate (p.1588·3).

Ubretid *Nycomed, Austria; Nycomed, Cz.; Nycomed, Fin.†; Apogepha, Ger.; Nycomed, Ger.; IFET, Gr.; Nycomed, Hong Kong; Amersham Health, Hung.†; Nycomed, Neth.; Nycomed, Pol.; Nycomed, Rus.; Nycomed, Singapore; Nycomed, Switz.; Aventis, UK.*
Distigmine bromide (p.630·2).
Atonic constipation; myasthenia gravis; neurogenic bladder; postoperative gastrointestinal motility disorders; postoperative urinary retention; skeletal muscle paralysis; urinary incontinence.

UBTest *Otsuka, Neth.*
⊗ Carbon-13 (p.2277·1) labelled urea.
Diagnosis of Helicobacter pylori infection.

Ubtest *Otsuka, Spain.*
⊗ Carbon-13-labelled urea (p.2277·1).
Test for Helicobacter pylori infection.

UCD 1and 2 *Nutricia-Bago, Arg.*
Food for special diets (p.1922·1).
Metabolic disorders.

Ucecal *UCB, Austria; UCB, Cz.†; UCB, Spain†; UCB, Turk.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia; metastatic bone pain; osteoporosis; Paget's disease of bone; pancreatitis; reflex sympathetic dystrophy.

Ucee D *Merck, Ger.†.*
Dexpanthenol (p.2362·1).
Skin lesions.

Ucemine PP *UCB, Belg.*
Nicotinamide (p.1957·3).
Nicotinamide deficiency.

Ucephan *Ucyclyd, USA.*
Sodium benzoate (p.1630·2); sodium phenylacetate (p.2390·2).
Hyperammonaemia.

Ucerax *UCB, UK.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Ucetal *Serral, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

UCG-Slide *Wampole, USA.*
Pregnancy test (p.2372·1).

Ucholine *M & H, Thai.*
Bethanechol chloride (p.2265·3).
Neurogenic bladder; urinary retention.

U-Closone *Hoe, Malaysia.*
⊗ Clobetasone butyrate (p.1522·3).
Skin disorders.

Ucort
Note. A similar name is used for preparations of different composition (see below).
YSP, Malaysia.
⊗ Urea (p.1620·2); hydrocortisone acetate (p.1535·2).
Dry skin disorders.

U-Cort
Note. A similar name is used for preparations of different composition (see above).
Taro, USA.
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

UDC *Hexal, Ger.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders; cholesterol gallstones; dyspepsia.

UDCA *Ferring, Arg.*
Ursodeoxycholic acid (p.2408·1).
Liver and biliary-tract disorders.

Udesogel *Faran, Gr.*
⊗ Budesonide (p.1520·1).
Skin disorders.

Udesospray *Faran, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Udicil *Pharmacia, Ger.*
Cytarabine (p.705·1).
Leukaemias; non-Hodgkin's lymphoma.

Udihep *Win-Medicare, Thai.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; dyspepsia; hepatitis.

Udiliv *Solvay, India.*
Ursodeoxycholic acid (p.2408·1).
Cholestatic liver disease; cholesterol gallstones.

Udima *Dermapharm, Austria; Dermapharm, Ger.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Udocaine *Umeda, Thai.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias; local anaesthesia.

Udramil *Aventis, Ger.†.*
Verapamil hydrochloride (p.1421·1); trandolapril (p.1416·2).
Hypertension.

Udrik *Abbott, Ger.*
Trandolapril (p.1416·2).
Heart failure following myocardial infarction; hypertension.

Udzapen *Terramedic, Philipp.*
Ketoprofen (p.73·1).
Osteoarthritis; pain; rheumatoid arthritis.

U-Enema *Unison, Thai.*
Sodium chloride (p.1686·1).
Bowel evacuation; constipation.

Ufarin *Schering, Chile.*
Isoconazole nitrate (p.536·2).
Fungal and Gram-positive bacterial vaginal infections; fungal skin infections.

Ufexil
Demo, Gr.
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Naveh, Israel; Multichem, NZ.
Ciprofloxacin lactate (p.243·3).
Bacterial infections.

Uflahex *Hexal, Philipp.; Salutas, Philipp.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Ufocard *Proel, Gr.*
Nitrendipine (p.1358·2).
Hypertension.

Ufocollyre *Proel, Gr.*
Sodium cromoglicate (p.1136·3).
Eye allergy.

Ufonitren *Proel, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ufor *Valdecasas, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity.

Ufoxillin *Proel, Gr.†.*
Cefaclor (p.217·2).
Bacterial infections.

UFT *BMS, Arg.; BMS, Austria; BMS, Belg.; BMS, Braz.; Merck, Cz.; Merck-Lipha, Fr.; Merck, Ger.; Merck, Gr.; BMS, Hong Kong; Merck, Hung.; BMS, Israel†; BMS, Ital.; Taiho, Jpn; Taiho, Malaysia; BMS, Mex.; Merck, Neth.; BMS, Norw.; Merck, Philipp.; Merck, Port.; Taiho, Rus.; BMS, S.Afr.; Taiho, Singapore; BMS, Spain; BMS, Swed.; BMS, Thai.; BMS, Turk.*
Tegafur (p.776·1); uracil (p.2407·3).
Malignant neoplasms.

Uftoral *BMS, Denm.; BMS, UK.*
Tegafur (p.776·1); uracil (p.2407·3).
Colorectal cancer.

UFUR *American Taiwan, Thai.*
Tegafur (p.776·1); uracil (p.2407·3).
Breast cancer; colorectal cancer; gastric cancer.

Ugal *Diba, Mex.†.*
Cimetoxine.
Peptic ulcer.

Ugotrex *Rafarm, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Ugurol *Rottapharm, Ital.*
Tranexamic acid (p.1080·3).
Haemorrhagic disorders.

Ujostabil *Felgentrager, Ger.†.*
Ammonium polystyrene sulfonate (p.1465·3); potassium polystyrene sulfonate (p.1460·2); magnesium polystyrene sulfonate (p.1465·3); sodium polystyrene sulfonate (p.1465·1).
Renal calculi.

Ukel *Gray, Arg.*
Midazolam maleate (p.1007·3).

Ukidan *Serono, Gr.†; Serum Institute, India†; Serono, Port.†.*
Urokinase (p.1420·1).
Thromboembolic disorders.

UL 250 *Merck, Port.†.*
Saccharomyces boulardii (p.2372·3).
Restoration of normal gastrointestinal flora.

U-Lactin *Allerderm, Singapore.*
⊗ Lactic acid (p.2329·3); urea (p.1620·2).
Dry skin disorders.

U-Lactin Foot Cream *Fischer, Israel.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Skin disorders of the foot.

U-Lactin Forte *Fischer, Israel.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Skin disorders.

Ulax-C *Ultra, Mex.*
⊗ Salbutamol sulfate (p.1131·3); ambroxol hydrochloride (p.1550·3).
Obstructive airways disease.

Ulax-F *Ultra, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Ulcaid
Ranbaxy, Austral.
Ranitidine (p.1766·1).

Ranbaxy, S.Afr.
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; heartburn.

Ulcar *Sanofi-Aventis, Fr.*
Sucralfate (p.1772·2).
Peptic ulcer.

Ulcecaps *INQ, Braz.†.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcecur *Ferring, Port.†.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcedin
Note. This name is used for preparations of different composition.
AGIPS, Ital.
Cimetidine (p.1716·2).
Gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Sons, Mex.†.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcedine *Sanofi-Aventis, Braz.; UAP, Indon.; ICN, Mex.†; Great Eastern, Thai.; Westmont, Thai.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; systemic mastocytosis; Zollinger-Ellison syndrome.

Ulcefam *Unison, Philipp.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcefate *Siam Bheasach, Thai.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcefor *Elofar, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Ulcegel *TO-Chemicals, Thai.*
Dried aluminium hydroxide gel (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity; heartburn; peptic ulcer.

Ulcekon *FDC, India†.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Ulcelac
Note. This name is used for preparations of different composition.
Bago, Arg.
Famotidine (p.1730·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Bago, Chile.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcemed *Medica Korea, Philipp.; Unimex, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcemet *TO-Chemicals, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcemex *Recalcine, Chile.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Ulcenol *Elmor, Venez.*
Famotidine (p.1730·1).
Gastritis; oesophagitis; peptic ulcer; Zollinger-Ellison syndrome.

Ulcenon *Legrand, Braz.; Unison, Philipp.*
Cimetidine (p.1716·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcepraz *Novartis, Philipp.*
Pantoprazole (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Ulcerac *Delta, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Ulceracid *Luper, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulceragon *Torrent, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulceral
Note. This name is used for preparations of different composition.
Aliud, Austria.
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Vamsler, Philipp.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Tedec Meiji, Spain.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulceran
Note. This name is used for preparations of different composition.
Medochemie, Cz.†; Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Rus.; Medochemie, Singapore; Medochemie, Thai.
Famotidine (p.1730·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatic disorders; peptic ulcer; Zollinger-Ellison syndrome.

Teva, Hung.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Sandoz, Indon.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer.

Ulceranin *Otto, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcerase *Smith & Nephew, Port.*
Collagenase (p.2286·2).
Burns; ulcers; wounds.

Ulcerease *Med-Derm, USA.*
Liquefied phenol (p.1656·1).
Mouth and throat pain.

Ulcerfen *Finadiet, Arg.*
Cimetidine (p.1716·2).
Gastritis; peptic ulcer.

Ulcergo *ACME, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer.

Ulcerid *Lapi, Indon.*
Famotidine (p.1730·1).
Endocrine adenoma; peptic ulcer; Zollinger-Ellison syndrome.

Ulceridina *Kinder, Braz.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ulceridine *Normal, Port.†.*
Cimetidine (p.1716·2).

Ulcerit *Hexal, Braz.†.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Ulcerix *Oboi, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcerlmin *Chugai, Jpn.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Ulcermate *Jaba Recordati, Port.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer; variceal haemorrhage.

Ulcermin *Jaba Recordati, Port.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer.

Ulcerocin *Cimed, Braz.*
Ranitidine (p.1766·1).
Peptic ulcer.

Ulcerol *APS, Port.†.*
Ranitidine hydrochloride (p.1766·1).
Gastrointestinal hyperacidity; peptic ulcer.

Ulcertec
Note. This name is used for preparations of different composition.
DHA, Malaysia; DHA, Singapore.
Sucralfate (p.1772·2).
Peptic ulcer.

Tecnimede, Port.
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcesep *Centrum, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcetab *Lennon, S.Afr.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcetal *Colfarm, Pol.*
Hydrotalcite (p.1733·3).
Gastric hyperacidity; gastro-oesophageal reflux; heartburn; peptic ulcer.

Ulcetrax *Salvat, Spain†.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcevarin *Bajer, Arg.†.*
Oxerutin (p.2304·3); vitamin A palmitate (p.1973·1).
Inflammation; phlebitis; skin disorders.

Ulcevit *Bruluart, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcex *Guidotti, Ital.*
Ranitidine hydrochloride (p.1766·1).
Gastritis or duodenitis associated with acid hypersecretion; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcid
Note. This name is used for preparations of different composition.
Sandoz, Indon.
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; heartburn.

Astellas, Irl.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcidine
Note. This name is used for preparations of different composition.
ICN, Canad.†.
Famotidine (p.1730·1).

Pharmaniaga, Malaysia†; Raza, Malaysia†.
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Spirig, Switz.
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcim *Quatromed, S.Afr.*
Cimetidine hydrochloride (p.1716·3).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcimax *Cipla, India.*
Famotidine (p.1730·1).
Peptic ulcer.

Ulcimer *Labesfal, Port.*
Sucralfate (p.1772·2).
Peptic ulcer.

Ulcimet *Farmasa, Braz.; Polipharm, Thai.*
Cimetidine (p.1716·2).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcin *Biolab, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcinax *Neo Quimica, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Ulcinil *Farmoz, Port.*
⊗ Tibolone (p.2134·1).
Menopausal disorders; osteoporosis.

Ulciram *Vargas, Venez.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; peptic ulcer.

Ulcitag *Sedabel, Braz.†.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcitrat *Bunker, Braz.*
Cimetidine (p.1716·2).
Peptic ulcer.

Ulco-cyl L Ho-Len-Complex *Liebermann, Ger.*
Homoeopathic preparation.

Ulcoderma *Abbott, Mex.*
Collagenase (p.2286·2); chloramphenicol (p.239·3).
Burns; skin ulcers; wounds.

Ulcodina *SoSe, Ital.†.*
Cimetidine (p.1716·2).
Gastritis and duodenitis associated with acid hypersecretion; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcofam *Codal Synto, Thai.†.*
Famotidine (p.1730·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Ulcogant *Merck, Austria; Merck, Belg.; Merck, Cz.; Merck, Ger.; Merck, Hung.; Merck, Neth.; Merck, Switz.*
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer.

Ulcogastrin *Biospray, Gr.†.*
Nizatidine (p.1751·2).
Peptic ulcer.

Ulcoid *Valdecasas, Mex.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity; sleep disorders.

Ulcoid-Zol *Valdecasas, Mex.†.*
Astemizole (p.567·2).
Hypersensitivity.

Ulcomedina *De Salute, Ital.†.*
Cimetidine (p.1716·2).
Gastritis and duodenitis associated with acid hypersecretion; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcomet *Medochemie, Hong Kong.*
Cimetidine (p.1716·2).
Acid aspiration; adjunct in pancreatic insufficiency; gastric hypersecretion; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer.

Ulcometin *Ratiopharm, Austria.*
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; hypersensitivity reactions; peptic ulcer; Zollinger-Ellison syndrome.

Ulcometion *Reig Jofre, Spain.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcon *Farma, Venez.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcoprotect *Azupharma, Ger.†.*
Pirenzepine hydrochloride (p.1762·3).
Gastrointestinal disorders.

Ulcoren *Medley, Braz.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcosan *Ivax, Cz.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcosin *Ivax, Hung.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcostad *Stada, Austria.*
Cimetidine (p.1716·2) or cimetidine hydrochloride (p.1716·3).
Acid aspiration; gastro-oesophageal reflux disease; gastrointestinal haemorrhage; hypersensitivity reactions; peptic ulcer; Zollinger-Ellison syndrome.

Ulcotenal *Recordati, Spain.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflex; peptic ulcer; Zollinger-Ellison syndrome.

Ulcotenk *Biotenk, Arg.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcourona *Neuropharma, Arg.†.*
Idebenone (p.367·1).
Cerebrovascular disorders.

Ulc-Out *Raffo, Chile.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulcozol
Bago, Arg.
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Merck Bago, Braz.†.
Omeprazole (p.1753·1).
Peptic ulcer.

Ulcrafate *Polipharm, Thai.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcrast *Boniscontro & Gazzone, Ital.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulcratex *Recalcine, Chile.*
Esomeprazole magnesium (p.1729·2).
Gastro-oesophageal reflux; peptic ulcer.

Ulcrux *Prater, Chile†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Ulcumaag *Pyridam, Indon.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Ulcumet *Soho, Indon.*
Cimetidine (p.1716·2).
Duodenitis; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulcu-Pasc *Pascoe, Ger.†.*
Liquorice (p.1740·3); chamomile (p.2279·3).
Gastrointestinal disorders.

Ulcuran *Abfar, Turk.*
Ranitidine hydrochloride (p.1766·1).

Ulcurilen *Austroplant, Austria.*
Allantoin (p.1588·1); neomycin sulfate (p.305·1); chlorocresol (p.1640·1); alpha tocoferil acetate (p.1992·3).
Ulcers; wounds.

Ulcurilen N
Note. This name is used for preparations of different composition.
Spitzner, Ger.†.
Ointment: Allantoin (p.1588·1); chlorocresol (p.1640·1); neomycin sulfate (p.305·1).
Infected skin disorders; wounds.

Spitzner, Ger.†.
Topical powder: Allantoin (p.1588·1); neomycin sulfate (p.305·1); alpha tocoferil acetate (p.1992·3).
Infected skin disorders; wounds.

Ulcusan
Note. This name is used for preparations of different composition.
Kwizda, Austria.
Famotidine (p.1730·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; stress-related ulcer; Zollinger-Ellison syndrome.

Pyridam, Indon.
Cimetidine (p.1716·2).
Pathological hypersecretory disorders; peptic ulcer.

Ulcyte *Alphapharm, Austral.*
Sucralfate (p.1772·2).
Peptic ulcer.

Uldadin *Collins, Mex.†.*
Nizatidine (p.1751·2).
Peptic ulcer.

Uldapril *Collins, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulfam *Soho, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Ulfamet *TO-Chemicals, Thai.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulfamid *KRKA, Cz.; KRKA, Pol.; KRKA, Rus.*
Famotidine (p.1730·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; hiatus hernia; pancreatic disorders; peptic ulcer; Zollinger-Ellison syndrome.

Ulfaprim *Hexpharm, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Ul-Flam *Ultra, Mex.*
Nimesulide (p.95·3).
Fever; inflammation; pain.

Ulflex *Utopian, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Ulgamax *Jelfa, Pol.*
Calcium carbonate (p.1714·1); dimeticone (p.1770·2); magnesium carbonate (p.1743·1).
Gastric hyperacidity.

Ulgarine *Sandoz, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulgastran *Polfa Grodzisk, Pol.*
Sucralfate (p.1772·2).
Peptic ulcer.

Ulgastrin
Note.This name is used for preparations of different composition.
Biomep, Mex.
Ranitidine (p.1766·1).
Peptic ulcer.

Diedenhofen, Thai.
Liquorice (p.1740·3); bismuth subnitrate (p.1711·2); aluminium sodium silicate (p.1707·3); anhydrous sodium sulfate (p.1771·3).
Gastritis; heartburn; peptic ulcer.

Ulgel
Note.This name is used for preparations of different composition.
Dabur, India†.
Magaldrate (p.1742·3); simeticone (p.1770·2).
Flatulence; gastritis; gastrointestinal hyperacidity; peptic ulcer.

Liferpal, Mex.
Aluminium (p.2254·1); magnesium (p.1678·3); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

Ulgut *Shionogi, Jpn.*
Benexate hydrochloride betadex (p.1710·1).
Gastritis; peptic ulcer.

Ulis *Globalpharma, Ital.*
Cimetidine (p.1716·2).
Gastritis and duodenitis associated with acid hypersecretion; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulkodin *Precimex, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulkowis *Temmler, Ger.†.*
Bismuth subnitrate (p.1711·2).
Dyspepsia; peptic ulcer.

Ullus Kapseln N *Polypharm, Ger.†.*
Liquorice (p.1740·3); chamomile (p.2279·3).
Gastrointestinal disorders.

Ulmarin *Precimex, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Ulmely *Ultra, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; mixed anxiety depressive states; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Ulmicy *Ultra, Mex.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections.

Ulmo *Pyridam, Indon.*
Famotidine (p.1730·1).
Pathological hypersecretory disorders; peptic ulcer.

Ulmodhyl *Sons, Mex.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ulone *3M, Canad.*
Clofedanol hydrochloride (p.1554·2).
Coughs.

Ulpafie *Ultra, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Ulpafie Compuesto *Ultra, Mex.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Allergic rhinitis; hay fever; sinusitis.

Ulpafie-N *Ultra, Mex.*
Paracetamol (p.108·1); naproxen (p.92·3).
Fever; pain.

Ulpax *Hormona, Mex.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulprazole *Polipharm, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulran *KRKA, Cz.†; Pasteur, Philipp.; KRKA, Rus.†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastric hyperacidity; gastro-oesophageal reflux; gastrointestinal haemorrhage; pancreatic disorders; peptic ulcer; Zollinger-Ellison syndrome.

Ulsafate *Combiphar, Indon.*
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Ulsal *Gebro, Austria.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; stress-related ulcer; Zollinger-Ellison syndrome.

Ulsanic *Chugai, Hong Kong; Teva, Israel; Pharmacare, S.Afr.; Chugai, Thai.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Ulsaven *Collins, Mex.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; hyperchlorhydria; peptic ulcer; Zollinger-Ellison syndrome.

Ulsek *Standard, Philipp.*
Omeprazole (p.1753·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulsen *Senosiain, Mex.*
Omeprazole (p.1753·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulserch *Serch, Arg.†.*
Pantoprazole (p.1760·1).

Ulserral *Serral, Mex.*
Cimetidine (p.1716·2).
Peptic ulcer.

Ulsicral *Ikapharmindo, Indon.*
Sucralfate (p.1772·2).
Duodenal ulcer.

Ulsidex *Dexa, Indon.*
Sucralfate (p.1772·2).
Peptic ulcer.

Ulsikur *Hexpharm, Indon.*
Cimetidine (p.1716·2).

Ultac *Cipla, India.*
Ranitidine (p.1766·1).
Peptic ulcer.

Ultacit *Aventis, Neth.*
Hydrotalcite (p.1733·3).
Gastric hyperacidity.

Ultak *Cipla-Medpro, S.Afr.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultane *Abbott, S.Afr.; Abbott, USA.*
Sevoflurane (p.1793·2).
General anaesthesia.

Ultec *Berk, UK†.*
Cimetidine (p.1716·2).
Dyspepsia; heartburn.

Ulticadex *Rafarm, Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Ulticer *Medreich, Hong Kong.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultidin
Note.This name is used for preparations of different composition.
Geolab, Braz.
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Gelcaps, Mex.
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultilac N *Bittermedizin, Ger.*
Almasilate (p.1705·1); calcium carbonate (p.1714·1); skimmed milk powder.
Gastrointestinal disorders.

Ultilap *Ultra, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Ultilox *Coronet, Indon.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux.

Ultimag *Mirren, S.Afr.*
Magnesium chloride (p.1679·1); zinc oxide (p.1621·2).
Magnesium and zinc supplement.

Ultiva *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Abbott, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.†; Elan, Irl.†; GSK, Israel; GSK, Ital.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Abbott, USA; GSK, Venez.*
⊗ Remifentanil hydrochloride (p.120·1).
Adjunct to anaesthesia; analgesia and sedation in mechanically ventilated patients; analgesia in anaesthesia; postoperative pain.

Ultizol *Vitae, Mex.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultop *KRKA, Cz.; KRKA, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ultra Adsorb *Lainco, Spain.*
Activated charcoal (p.1435·2).
Diarrhoea.

Ultra Augenschutz *Provita, Austria.*
Actinoquinol sodium (p.2246·3).
Protection of the eyes from ultraviolet radiation.

Ultra Chloraseptic
Note.This name is used for preparations of different composition.
Prestige, UK.
Gargle: Phenol (p.1656·1).
Sore throat.

Prestige, UK.
Throat spray: Benzocaine (p.1854·1).
Sore throat.

Ultra Clearasil *Boots, Philipp.*
Benzoyl peroxide (p.1590·2).
Acne.

Ultra Corega *GSK, Braz.; Stafford-Miller, Braz.*
Denture fixative.

Ultra Derm *Reese, USA†.*
Emollient and moisturiser.

Ultra Energizer *Equilibre Attitude, Fr.†.*
Guarana; mate; kola; avena; ginseng; ginkgo biloba; minerals; vitamins; octacosanol; sodium molybdate (p.1922·1).
Tonic.

Ultra Heartburn Relief *Galpharm, UK.*
Famotidine (p.1730·1).
Dyspepsia; heartburn.

Ultra Mega Softgels without Iron *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Ultra Mide *Pharmascience, Canad.; Baker Cummins, USA.*
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Ultra Quercitin *Jamieson, Canad.*
Urtica (p.2409·3); perilla fruit; quercetin (p.2305·1).

Ultra Strength Heat Rub *Hyde, Canad.†.*
Methyl salicylate (p.85·3); menthol (p.2340·1).

Ultra Stress *Nutrifarma, Turk.*
Vitamin B substances; vitamin C (p.1922·1).

Ultra Tears *Alcon, USA.*
Hypromellose (p.2144·2).
Dry eyes.

Ultra TechneKow *Mallinckrodt, Neth.*
Technetium-99m (p.2055·3).
Diagnostic radionuclide scintigraphy.

Ultra Technekow FM *Mallinckrodt, Cz.*
Technetium-99m as sodium pertechnetate (p.2055·3).
Radionuclide imaging of the thyroid gland, saliva gland, stomach, and brain.

Ultra TechneKow FM *Mallinckrodt, Port.*
Technetium-99m pertechnetate (p.2055·3).

Ultra Vita Time *Nature's Bounty, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Ultra Vita-Min *Equilibre Attitude, Fr.†.*
Nutritional supplement (p.1922·1).

Ultrabase *Schering, S.Afr.†; Valeant, UK.*
Emollient.
Dry skin; pharmaceutical diluent.

Ultrabeta *Vitoria, Port.*
⊗ Salmeterol xinafoate (p.1135·1).
Obstructive airways disease.

Ultrabiotic *Bago, Chile.*
Mupirocin (p.302·3).
Bacterial skin infections; infected burns and wounds.

Ultrabiotique *Nutrisante, Fr.*
Lactococcus lactis (p.2372·3); *Lactobacillus casei* (p.2372·3); *Bifidobacterium bifidum* (p.2372·3).
Restoration of gastrointestinal flora.

ULTRAbrom *WE, USA.*
Pseudoephedrine hydrochloride (p.1571·2); brompheniramine maleate (p.569·2).
Upper respiratory-tract symptoms.

Ultrac *Tecnofarma, Chile.*
Vitamins; minerals; ginseng; rutoside; deanol tartrate (p.1922·1).
Dietary supplement; tonic.

Ultrac E *Tecnofarma, Chile.*
Vitamins; minerals; ginseng; rutoside; deanol tartrate (p.1922·1).
Dietary supplement; tonic.

Ultrac Q10 *Tecnofarma, Chile.*
Vitamins; minerals; ginseng; rutoside; ubidecarenone (p.1922·1).
Dietary supplement.

Ultracain *Aventis, Cz.†; Aventis, Ger.; Sanofi-Aventis, Rus.; Normon, Spain; Aventis, Turk.*
Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain Dental *Aventis, Austria.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain D-S *Aventis, Cz.†; Aventis, Ger.; Sanofi-Aventis, Hung.; Aventis, Neth.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain D-Suprarenin *Sanofi-Aventis, Fin.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracain hyperbar *Aventis, Ger.†.*
Articaine hydrochloride (p.1854·1).
Local anaesthesia.

Ultracain Suprarenin *Aventis, Ger.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracaine D-S *Aventis, Switz.*
⊗ Articaine hydrochloride (p.1854·1).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ultracal
Note.This name is used for preparations of different composition.
Baliarda, Arg.
Saw palmetto (p.2192·3); pygeum africanum (p.2192·3).
Prostate disorders.

Mead Johnson, Austral.†; Novartis Nutrition, Hong Kong; Mead Johnson, NZ; Mead Johnson, Philipp.; Mead Johnson Nutritionals, USA.
Preparation for enteral nutrition (p.1922·1).

Ultracalcium *Temis, Arg.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Ultracalcium D3 *Temis, Arg.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Ultracarbon *Merck, Ger.; Merck Consumer, Singapore; Merck, Thai.*
Activated charcoal (p.1435·2).
Acute poisoning; diarrhoea; drug overdosage; flatulence.

UltraCare
Note. A similar name is used for preparations of different composition (see below).
AMO, Canad.; Allergan, USA.
Disinfecting solution, hydrogen peroxide solution 3% (p.1647·3); neutralising tablets, catalase (p.2278·2) (p.1622·2).
Contact lens care.

Ultracare
Note. A similar name is used for preparations of different composition (see above).
Optident, UK.
Benzocaine (p.1854·1).
Local anaesthesia.

UltraCare Daily Cleaner *Allergan, Canad.†.*
Cleaning solution for soft contact lenses (p.1622·2).

Ultracef *BMS, Irl.*
Cefadroxil (p.218·1).
Bacterial infections.

Ultracele *Ultratech, India†.*
Celecoxib (p.34·2).

Ultracet *Janssen-Cilag, Braz.; Janssen, Hong Kong; Janssen-Cilag, Malaysia; Janssen-Cilag, Singapore; Janssen-Cilag, Thai.; Ortho McNeil, USA; Janssen-Cilag, Venez.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Ultracillin *Caps, S.Afr.*
Benzathine benzylpenicillin (p.212·1); benzylpenicillin sodium (p.213·1); procaine benzylpenicillin (p.319·2).
Bacterial infections.

Ultracod *Zentiva, Cz.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
Pain.

Ultracortene H *Novartis, Switz.†.*
⊗ Prednisolone sodium tetrahydrophthalate (p.1542·1).
Corticosteroid.

Ultracortenol
Novartis, Arg.; Novartis, Austria; Novartis, Hong Kong.
⊗ Prednisolone acetate (p.1541·1).
Inflammatory eye disorders.

Novartis, Belg.; Novartis, Israel; Novartis, Switz.
⊗ Prednisolone pivalate (p.1541·1).
Inflammatory eye disorders.

Novartis Ophthalmics, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Ger.; Novartis Ophthalmics, Hung.; Novartis, Neth.; Novartis, Norw.; Novartis Ophthalmics, Swed.
⊗ Prednisolone acetate (p.1541·1) or prednisolone pivalate (p.1541·1).
Inflammatory eye disorders.

Ultracortin *Collins, Mex.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Inflammation.

Ultracur S *Schering, Arg.*
⊗ Fluocortolone (p.1532·2); fluocortolone caproate (p.1532·2).
Skin disorders.

Ultra-Demoplas *Godecke, Ger.†.*
⊗ Dexamethasone (p.1526·1); prednisolone (p.1540·3); lidocaine hydrochloride (p.1862·3).
Musculoskeletal and joint disorders.

Ultraderm
Note. A similar name is used for preparations of different composition (see below).
Ecobi, Ital.
⊗ Fluocinolone acetonide (p.1531·3).
Skin disorders.

Ultraderme
Note. A similar name is used for preparations of different composition (see above).
Richelet, Fr.†.
Saccharomyces boulardii (p.2372·3).
Seborrhoea.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ultradermis *ICN, Arg.†.*
Gentamicin sulfate (p.282·1).
Bacterial skin infections.

Ultradina *Brasmedica, Braz.†.*
Silver (p.2387·1).
Diarrhoea.

Ultradol *Procter & Gamble, Canad.†.*
Etodolac (p.52·2).
Osteoarthritis; pain; rheumatoid arthritis.

Ultrafastin *Medana, Pol.*
Ketoprofen lysine (p.73·3).
Musculoskeletal, joint, and peri-articular pain.

Ultrafen
Note. This name is used for preparations of different composition.
Beximco, Singapore.
Diclofenac (p.44·2).
Gout; musculoskeletal and joint disorders; pain.

Dinctas, Turk.
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Ultrafer *Farmoquimica, Braz.*
Iron polymaltose (p.1953·1).
Iron-deficiency anaemia.

Ultrafil *Grunenthal, Venez.†.*
Sweet birch oil (p.86·2).
Musculoskeletal, joint, and soft-tissue disorders.

Ultrafina *Ultratech, India†.*
⊗ Finasteride (p.2188·3).

Ultraflox *Bal, Thai.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ultraflu *Pliva, Ital.*
Acetylcysteine (p.1548·2).
Respiratory-tract congestion.

Ultrafort *Brasmedica, Braz.†.*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Ultra-Freeda *Freeda, USA.*
Multivitamin and mineral preparation (p.1922·1).

Ultragesic *Medic+Aid, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Ultragin *Wyeth, India.*
Paracetamol (p.108·1).
Fever; pain.

Ultragrip
Note. This name is used for preparations of different composition.
Mugi, Indon.
Caplets: Paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3); dexchlorpheniramine maleate (p.572·1); dextromethorphan hydrobromide (p.1555·2).
Allergic symptoms; colds; coughs; fever; influenza.

Mugi, Indon.
Syrup: Paracetamol (p.108·1); phenylpropanolamine maleate (p.1570·2); dextromethorphan hydrobromide (p.1555·2).
Colds and influenza symptoms; cough.

Ultra-K *Melisana, Belg.*
Potassium gluconate (p.1684·3).
Potassium depletion.

Ultralan
Note. This name is used for preparations of different composition.
Schering, Chile†; Schering, Philipp.
⊗ Fluocortolone (p.1532·2) or fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2).
Skin disorders.

Intendis, Fr.; Schering, Hong Kong.
⊗ Fluocortolone (p.1532·2); fluocortolone caproate (p.1532·2).
Skin disorders.

Galagen, USA.
Lactose-free, gluten-free preparation for enteral nutrition (p.1922·1).

Schering, Austria; Intendis, Ital.; Schering, Mex.†.
Cream: ⊗ Fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Ger.†.
Cream; lotion: ⊗ Fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Israel.
Cream; ointment: ⊗ Fluocortolone (p.1532·2); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Turk.
Cream; ointment: ⊗ Fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Austria.
Fatty ointment; ointment: ⊗ Fluocortolone (p.1532·2); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Ger.†; Intendis, Ital.; Intendis, Mex.†.
Ointment: ⊗ Fluocortolone (p.1532·2); fluocortolone caproate (p.1532·2).
Skin disorders.

Schering, Austria; Asche Chiesi, Ger.; Schering, Ger.; Schering, Ital.; Schering, Turk.
Tablets: ⊗ Fluocortolone (p.1532·2).
Corticosteroid.

Ultralan Crilane *Schering, Turk.*
⊗ Fluocortolone pivalate (p.1532·3); salicylic acid (p.1612·2).
Skin disorders.

Ultralan M *Intendis, Spain.*
⊗ Fluocortolone (p.1532·2).
Skin disorders.

Ultralanum Plain *Meadow, UK.*
⊗ Fluocortolone (p.1532·2) or fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2).
Skin disorders.

Ultralente *Novo Nordisk, USA.*
⊗ Insulin zinc suspension (bovine) (p.443·2).
Diabetes mellitus.

Ultra-Levura *BMS, Spain; Gervasi, Spain.*
Saccharomyces boulardii (p.2372·3).
Restoration of the gastrointestinal flora.

Ultra-Levure *Biocodex, Fr.; Petsiavas (Πετσιαβας), Gr.; Biocodex, Switz.*
Saccharomyces boulardii (p.2372·3).
Diarrhoea; restoration of gastrointestinal flora.

Ultram *Ortho McNeil, USA.*
Tramadol hydrochloride (p.130·3).
Pain.

Ultra-Mag *Germania, Austria.*
Magnesium gluconate (p.1679·2).
Magnesium deficiency.

Ultra-Mg *Melisana, Belg.*
Magnesium gluconate (p.1679·2).
Magnesium deficiency; neuromuscular hyperexcitability.

Ultramicina
Note. This name is used for preparations of different composition.
Q-Pharma, Arg.
Ciprofloxacin (p.243·3).
Bacterial infections.

Lisapharma, Ital.†.
Fosfomycin calcium (p.278·2) or fosfomycin sodium (p.278·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Q Pharma, Spain.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ultramicina Plus *Dom, Spain†.*
⊗ Ciprofloxacin (p.243·3); fluocinolone acetonide (p.1531·3).
Otitis externa.

Ultramidol *Winthrop, Port.*
Bromazepam (p.964·3).
Anxiety.

Ultramol *Sterwin, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Fever; pain.

Ultramop *Canderm, Canad.*
Methoxsalen (p.1605·1).
Psoriasis; vitiligo.

Ultramox *Royton, Braz.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Ultran *Randall, Mex.*
Ranitidine (p.1766·1).
Acid aspiration; gastric hypersecretion; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Ultra-Natal *Ethex, USA.*
Multivitamin and mineral preparation with carbonyl iron (p.1949·1) (p.1922·1).
Nutritional supplement in pregnancy and postnatal period.

Ultraneural *Raffo, Arg.*
Gabapentin (p.482·3).
Epilepsy.

Ultrapen *UAP, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Ultrapenil *Vir, Spain.*
Ampicillin sodium (p.204·1); ampicillin benzathine (p.205·1).
Bacterial infections.

Ultraproct
Note. This name is used for preparations of different composition.
Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Chile; Intendis, Fr.; Asche, Ger.†; Schering, Ger.†; Schering, Irl.; Intendis, Ital.; Intendis, Mex.; CSL, NZ; Schering, Philipp.; Schering, Turk.; Meadow, UK.
⊗ Fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders; haemorrhoids.

Intendis, Braz.; Schering, Hong Kong†; Schering, Indon.
⊗ Fluocortolone pivalate (p.1532·3); fluocortolone caproate (p.1532·2); cinchocaine hydrochloride (p.1857·3); clemizole undecylate (p.574·1).
Anorectal disorders.

Intendis, Port.
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Schering, Rus.
⊗ Fluocortolone pivalate (p.1532·3); cinchocaine hydrochloride (p.1857·3).
Anorectal disorders.

Ultraproct N *Schering, Hong Kong; Schering, Indon.*
⊗ Fluocortolone pivalate (p.1532·3); lidocaine hydrochloride (p.1862·3).
Anorectal disorders.

Ultraquin
Note. This name is used for preparations of different composition.
Panalab, Arg.
Levofloxacin (p.292·2).
Bacterial infections.

Canderm, Canad.
Hydroquinone (p.1598·2); padimate O (p.1609·1); oxybenzone (p.1608·3).
Skin hyperpigmentation; sunscreen.

Ultraquin Plain *Canderm, Canad.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Ultrase *Axcan, Canad.; Axcan, USA.*
Pancrelipase (p.2360·1).
Pancreatic enzyme deficiency.

Ultraskin *Albephar, Venez.*
Octinoxate (p.1608·2); oxybenzone (p.1608·3); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Ultrasol-F *Fresenius Kabi, Ger.*
Formaldehyde (p.1644·2); glyoxal (p.1646·1); glutaral (p.1645·2); benzalkonium chloride (p.1629·1).
Surface disinfection.

Ultrassol *Cosmofarma, Port.†.*
Octinoxate (p.1608·2); avobenzone (p.1589·3); octisalate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3); zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

UltraTag *Mallinckrodt, Neth.*
Technetium-99m (p.2055·3) stannous chloride.
Red blood cell labelling.

UltraTag RBC *Mallinckrodt, Cz.*
Technetium-99m labelled stannous chloride (p.2055·3).
Red blood cell labelling.

Ultratard *Novo Nordisk, Austral.†; Novo Nordisk, Belg.†; Novo Nordisk, Fin.†; Novo Nordisk, Fr.†; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Irl.†; Novo Nordisk, Ital.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.†; Novo Nordisk, Port.†; Novo Nordisk, Spain†; Novo Nordisk, Swed.; Novo Nordisk, UK†.*
⊗ Insulin zinc suspension (crystalline) (human, pyr, monocomponent) (p.443·2).
Formerly known as Human Ultratard.
Diabetes mellitus.

Ultratard HM *Novo Nordisk, Austria; Novo Nordisk, Cz.†; Novo Nordisk, Hong Kong; Novo Nordisk, Malaysia†; Novo Nordisk, Pol.; Novo Nordisk, S.Afr.†; Novo Nordisk, Singapore†; Novo Nordisk, Switz.*
⊗ Insulin zinc suspension (crystalline) (human) (p.443·2).
Diabetes mellitus.

Ultravate *Westwood-Squibb, Canad.; Westwood-Squibb, USA.*
⊗ Ulobetasol propionate (p.1546·2).
Skin disorders.

Ultra-Vinca *Tecnimede, Port.*
Vinpocetine (p.2414·2).
Cerebral and peripheral vascular disorders.

Ultraviral *Raffo, Arg.*
Lamivudine (p.895·1).
HIV infection.

Ultraviral Duo *Raffo, Arg.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Ultravisin *Farmigea, Ital.*
Myrtillus (p.2349·3); *dl*-alpha tocoferil acetate (p.1992·3).
Vascular retinopathy; vision disorders.

Ultravist *Schering, Austral.; Schering, Austria; Schering, Belg.; Berlex, Canad.†; Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering, Gr.; Bayer Schering, Hung.; Schering, Israel; Schering, Ital.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Bayer, Port.; Schering, Rus.; Schering, S.Afr.; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, UK; Berlex, USA.*
Iopromide (p.1485·1).
Contrast medium for computerised tomography.

Ultravite *Stanley, Canad.†.*
Vitamin and mineral preparation (p.1922·1).

Ultraxime *Pediatrica, Philipp.*
Cefixime (p.224·3).
Bacterial infections.

Ultrazac *Zydus, India.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Ultrazyme *Visiontech, Arg.; AMO, Austral.; Farmasa, Braz.†; AMO, Canad.; Allergan, NZ; Allergan, USA.*
Subtilisin A (p.2393·3) (p.1622·2).
Cleanser for contact lenses.

Ultren *Sanova, Austria.*
Vitamin A acetate (p.1973·1); ascorbic acid (p.1983·3).
Cold and influenza symptoms; vitamin deficiency.

Ultreon *Pfizer, Ger.*
Azithromycin (p.207·1).
Mycobacterial infections.

Ultrepyl *Ultra, Mex.*
Carbamazepine (p.471·3).
Diabetic neuropathy; epilepsy; neuralgias.

Ultrex *Carrington, USA.*
Acemannan (p.2244·2).
Wounds.

Ultrimin *Mintlab, Chile.*
Ergotamine tartrate (p.620·1); dipyrone (p.49·2); chlorphenamine maleate (p.571·3); caffeine (p.1116·3).
Migraine.

Ultromep *Ultra, Mex.*
Omeprazole (p.1753·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulxit *Sandoz, Austria.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Ulzec *Triomed, S.Afr.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Ulzol *Pliva, Hung.; Dabur, India†; Ethica, Indon.; Pliva Krakow, Pol.; Pliva, Rus.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Um Instante *Farmabraz, Braz.†.*
Tetracaine (p.1871·2); eugenol (p.2301·2); phenol (p.1656·1); menthol (p.2340·1).
Mouth disorders.

Umafen *Umeda, Thai.*
Ibuprofen (p.64·2).
Fever; musculoskeletal and joint disorders; pain.

Umamett *Umeda, Thai.*
Cimetidine (p.1716·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Uman-Big *Kedrion, Ital.†.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Uman-Cig *Kedrion, Ital.†.*
A cytomegalovirus immunoglobulin (p.2208·3).
Passive immunisation.

Uman-Complex DI *Kedrion, Ital.*
A factor IX preparation (p.1068·3).
Deficiency of factors II, IX or X.

Uman-Cry DI *Kedrion, Ital.†.*
Factor VIII (p.1067·1).
Factor VIII deficiency.

Uman-Gamma *Kedrion, Ital.†.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; passive immunisation.

Uman-Serum *Kedrion, Ital.*
⊗ Plasma protein fraction (p.1076·2).
Hypoproteinaemia; shock.

Uman-Vzig *Kedrion, Ital.†.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Umaren *EGIS, Hung.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Umasam *Szama, Arg.*
Undecenoic acid monoethanolamide (p.549·3).
Fungal skin infections; seborrhoea.

Umatrope *Lilly, Fr.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Umbrella
Note. This name is used for preparations of different composition.
Medihealth, Mex.
Zinc oxide (p.1621·2); octinoxate (p.1608·2); oxybenzone (p.1608·3); enzacamene (p.1597·1).
Sunscreen.

Roemmers Medihe, Venez.
A range of sunscreen preparations.

Umbrella Plus *Medihealth, Mex.*
SPF 30+: Octinoxate (p.1608·2); bisoctrizole (p.1591·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Sunscreen.

Umbrium *Kwizda, Austria.*
Diazepam (p.986·3).
Anxiety disorders; skeletal muscle spasm; sleep disorders.

Umckaloabo *Iso, Ger.; Farmasa, Mex.*
Pelargonium reniforme/sidoides (p.2311·1).
Respiratory-tract infections; upper respiratory-tract infections.

Umckalor *Schwabe, Rus.*
Pelargonium sidoides (p.2311·1).
Upper respiratory-tract infections.

Umckan *Farmoquimica, Braz.*
Pelargonium sidoides (p.2311·1).
Respiratory-tract infections.

Umecta *JSJ, USA.*
⊗ Urea (p.1620·2).
Nail and skin disorders.

Umeda Para-J *Umeda, Thai.*
Paracetamol (p.108·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Fever; pain.

Umine *Douglas, NZ†; Douglas, Singapore†.*
⊗ Phentermine hydrochloride (p.2162·2).
Obesity.

Umoder *Rafarm, Gr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Umolit *Rafarm, Gr.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Umprel *Novartis, Austria.*
Bromocriptine mesilate (p.798·1).
Parkinsonism.

Umuline NPH *Lilly, Fr.*
⊗ Isophane insulin injection (human, prb) (p.443·2).
Formerly known as Umuline Protamine Isophane (NPH).
Diabetes mellitus.

Umuline Profil 30 *Lilly, Fr.*
⊗ A mixture of neutral insulin injection (human, prb) 30% and isophane insulin injection (human, prb) 70% respectively (p.443·2).
Diabetes mellitus.

Umuline Rapide *Lilly, Fr.*
⊗ Neutral insulin injection (human, prb) (p.443·2).
Diabetes mellitus.

Umuline Zinc *Lilly, Fr.†.*
⊗ Insulin zinc suspension (human, prb) (crystalline) (p.443·2).
Diabetes mellitus.

Umuline Zinc Compose *Lilly, Fr.†.*
⊗ Insulin zinc suspension (human, prb) (amorphous 30%, crystalline 70%) (p.443·2).
Diabetes mellitus.

Una A Gel *Kowa, Jpn.*
⊗ Dexamethasone acetate (p.1526·1); crotamiton (p.1593·2); cinchocaine hydrochloride (p.1857·3).

Una De Gato *Hochstetter, Chile†.*
Uncaria tomentosa.
Inflammation.

Una Repellent *Kowa, Jpn.*
Diethyltoluamide (p.2041·1); N-(2-ethylhexyl)-bicyclo(2,2,1)-hepta-5-en-2,3-dicarboxyimide.
Insect repellent.

Unacefin *Fako, Turk.*
Ceftriaxone (p.238·1).
Lidocaine (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Unacid *Pfizer, Ger.*
Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Bacterial infections.

Unacid PD *Pfizer, Ger.*
Sultamicillin (p.344·1) or sultamicillin tosilate (p.344·1).
Bacterial infections.

Unacim *Pfizer, Fr.*
Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Unagen *Medifarma, Indon.*
Dipyrone (p.49·2).
Pain.

Unakalm *Tecnifar, Port.*
Ketazolam (p.1002·2).
Anxiety.

Un-Alfa *Leo, Fr.*
Alfacalcidol (p.1986·1).
Hypocalcaemia; hypoparathyroidism; renal osteodystrophy; rickets.

Unalium *Guardian, Indon.*
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Unalmes *Biofarma, Braz.†; Andromaco, Chile.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Combined injectable contraceptive.

Unamine *Unison, Thai.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions; pruritus.

Unamol *Senosiain, Mex.*
Cisapride (p.1720·3).
Constipation; dyspepsia; gastro-oesophageal reflux; gastrointestinal motility disorders; gastroparesis.

Unaril *Unison, Thai.*
Enalapril (p.1276·1).
Heart failure; hypertension.

Unasal *Senosiain, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal infections of the skin, nails, and scalp.

UN-Aspirin *Zee, USA.*
Paracetamol (p.108·1).
Fever; pain.

Unasyn
Note. This name is used for preparations of different composition.
Pfizer, Chile; Pfizer, Israel; Pfizer, Rus.; Pfizer, USA.
Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Bacterial infections.

Pfizer, Indon.
Sultamicillin (p.344·1).
Bacterial infections.

Pfizer, Austria; Pfizer, Braz.; Pfizer, Cz.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Philipp.; Pfizer, Singapore; Farmasierra, Spain; Pfizer, Thai.; Pfizer, Venez.
Injection: Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Lidocaine hydrochloride (p.1862·3) is included in some intramuscular injections to alleviate the pain of injection.
Bacterial infections.

Pfizer, Pol.
Injection: Ampicillin (p.204·1); sulbactam (p.335·1).
Bacterial infections.

Pfizer, Ital.
Oral suspension: Sultamicillin (p.344·1).
Bacterial infections.

Pfizer, Braz.; Pfizer, Philipp.; Farmasierra, Spain†.
Oral suspension; tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Pfizer, Cz.; Pfizer, Hung.
Oral suspension; tablets: Sultamicillin (p.344·1) or sultamicillin tosilate (p.344·1).
Bacterial infections.

Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, Pol.; Pfizer, Singapore; Pfizer, Venez.
Oral suspension; tablets: Sultamicillin (p.344·1).
Bacterial infections.

Pfizer, Austria; Pfizer, Ital.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Pfizer, Thai.
Tablets: Sultamicillin (p.344·1).
Bacterial infections.

Unasyna
Note. This name is used for preparations of different composition.
Pfizer, Chile.
Sultamicillin (p.344·1).
Bacterial infections.

Pfizer, Arg.; Pfizer, Mex.
Injection: Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Bacterial infections.

Pfizer, Mex.
Oral suspension: Sultamicillin (p.344·1).
Bacterial infections.

Pfizer, Arg.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Unasyn-S *Pfizer, Jpn†.*
Ampicillin sodium (p.204·1); sulbactam sodium (p.335·1).
Bacterial infections.

Unat
Roche, Austria; Roche, Ger.
⊗ Torasemide (p.1415·3) or torasemide sodium (p.1416·1).
Heart failure; hypertension; oedema; renal insufficiency.

Roche, Chile†; Roche, Hong Kong; Roche, S.Afr.; Roche, Thai.
⊗ Torasemide (p.1415·3).
Cirrhosis with ascites; heart failure; hypertension; nephrotic syndrome; oedema.

Unathene *Streuli, Switz.*
Dexpanthenol (p.2362·1); mint oil (p.2345·2); camphor oil (p.2273·3).
Nasal disorders.

Unatol *Streuli, Switz.*
Vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1); allantoin (p.1588·1); mint oil (p.2345·2); camphor oil (p.2273·3).
Nasal disorders.

Unava *Sandoz, Arg.*
Gliclazide (p.440·3).
Diabetes mellitus.

Uncadol *Knop, Chile.*
Uncaria tomentosa.
Inflammation; musculoskeletal, joint, and peri-articular disorders.

Uncough *Yung Shin, Hong Kong.*
Cloperastine (p.1554·3).
Coughs.

Undecyl *Kimia, Indon.; Rekah, Israel.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Undelenic *Gordon, USA.*
Undecenoic acid (p.549·2).
Fungal skin infections.

Underacid *Pliva, Spain.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Underan *Saval, Chile.*
Mupirocin (p.302·3).
Bacterial skin infections.

Undestor *Organon, Arg.; Organon, Belg.†; Organon, Cz.; Organon, Pol.; Organon, Swed.*
⊗ Testosterone undecylate (p.2130·2).
Male hypogonadism; male infertility; osteoporosis.

Undex *Melisana, Switz.*
Clotrimazole (p.530·1).
Fungal foot infections.

Undofen *GSK, Pol.*
Cetylpyridinium chloride (p.1635·1); undecenoic acid (p.549·2).
Fungal and bacterial skin infections.

Undo-Pate *Ilsan, Turk.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin and nail infections.

Undo-Talk *Ilsan, Turk.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3); boric acid (p.2268·1); salicylic acid (p.1612·2).
Fungal skin infections.

Unex Amarum *Repha, Ger.†.*
Gentian (p.2310·3); absinthium (p.2244·1); ginger (p.1732·3).
Appetite loss; dyspepsia; meteorism.

Unexym MD S *Repha, Ger.*
Pancreatin (p.2360·1); betaine hydrochloride (p.2265·2).
Digestive disorders.

Unexym mono *Repha, Ger.*
Pancreatin (p.2360·1).
Pancreatic disorders.

Ung Vernleigh *Adcock Ingram, S.Afr.*
Sulfanilamide (p.343·1); merbromin (p.1652·1); peru balsam (p.2365·3); cod-liver oil (p.1935·2).
Burns; ulcers; wounds.

Ungava *Aerokure, Canad.*
Diethyltoluamide (p.2041·1).
Insect repellent.

Ungel *Stiefel, Arg.*
Triclocarban (p.1665·2).
Dandruff.

Ungolen *Slovakofarma, Cz.†.*
Milk thistle (p.1452·1); cnicus benedictus (p.2285·2); peppermint leaf (p.1761·2); agrimony (p.2249·2); achillea (p.2245·2); fennel (p.2302·3); taraxacum (p.2395·1).
Biliary disorders; digestive disorders.

Unguentacid *Mucos, Ger.*
Linoleic acid triglyceride (p.2308·2); vitamin A palmitate (p.1973·1); *dl*-alpha tocoferil acetate (p.1992·3).
Skin disorders.

Unguentine *Mentholatum, USA.*
Phenol (p.1656·1); zinc oxide (p.1621·2); eucalyptus oil (p.2301·2); thyme oil (p.2401·2).
Pain in minor burns.

Unguentine Maximum Strength *Lee, USA.*
Benzocaine (p.1854·1); resorcinol (p.1612·1).

Unguentine Plus *Mentholatum, USA.*
Lidocaine hydrochloride (p.1862·3); chloroxylenol (p.1640·2); phenol (p.1656·1).
Skin disorders.

Unguento del Bebe *Nordin, Mex.*
Zinc (p.1999·1).
Skin disorders.

Unguento Callicida Naion *Puerto Galiano, Spain.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Callosities.

Unguento Cruz *Tocogino, Mex.*
Sulfathiazole (p.343·2); zinc (p.1999·1).

Unguento Dermico Antibiotico
Note. This name is used for preparations of different composition.
Drag, Chile†.
Neomycin (p.305·1); polymyxin B (p.318·2).
Bacterial skin infections.

Laboratorios Chile, Chile.
Neomycin (p.305·1); bacitracin (p.210·3).
Bacterial skin infections.

Unguento Leon *Beiersdorf, Chile.*
Methyl salicylate (p.85·3); camphor (p.2273·2).
Musculoskeletal and joint disorders.

Unguento de la Madre *Nordin, Mex.*
Vitamins; allantoin (p.1588·1); zinc (p.1999·1).
Skin disorders.

Unguento Morry *Teofarma, Spain.*
Salicylic acid (p.1612·2).
Calluses.

Unguento Picrato de Butesin *Abbott, Braz.*
Butyl aminobenzoate picrate (p.1857·1).
Skin disorders.

Unguento Sulfatiazol Rojtier *Nordin, Mex.*
Sulfathiazole (p.343·2); zinc (p.1999·1).
Skin infections.

Unguentolan
Note. This name is used for preparations of different composition.
Heyl, Ger.
Cod-liver oil (p.1935·2).
Wounds.

Gebro, Switz.
Cod-liver oil (p.1935·2); vitamin A acetate (p.1973·1).
Burns; superficial wounds.

Unguentum contra haemorrhoides PCH
Pharmachemie, Neth.
Lidocaine hydrochloride (p.1862·3).
Haemorrhoids.

Unguentum lymphaticum *PGM, Ger.*
Hemlock; colchicum (p.558·1); digitalis (p.1258·3); podophyllum (p.1610·2); hyoscyamus (p.2323·3); calendula (p.2273·1).
Lymphatic disorders.

Unguentum M *Boots Healthcare, Irl.; Crookes Healthcare, UK.*
Emollient.
Barrier cream; dry skin; nappy rash; pharmaceutical vehicle.

Unguentum Molle *Profarma, Cz.†.*
Emollient.
Dry skin disorders.

Unguentum Simplex L *Lachema, Cz.†.*
Emollient.
Dry skin disorders.

Unguentum Undecylenicum *Chema-Elektromet, Pol.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Ungvita
Note. This name is used for preparations of different composition.
Bayer Consumer, Austral.†.
Cream: Zinc oxide (p.1621·2).
Minor cuts and abrasions; skin disorders.

Bayer Consumer, Austral.; Roche, NZ.
Ointment: Vitamin A palmitate (p.1973·1).
Chafed skin; cracked heels; cracked nipples; dry skin; minor burns; skin trauma.

Uni Amox *Uniao Quimica, Braz.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Uni B Complex Poliv *Uniao Quimica, Braz.†.*
Vitamin B substances (p.1922·1).

Uni Bromazepax *Uniao Quimica, Braz.*
Bromazepam (p.964·3).
Anxiety.

Uni Carbamaz *Uniao Quimica, Braz.*
Carbamazepine (p.471·3).
Epilepsy; neuritis.

Uni Cetotifen *Uniao Quimica, Braz.†.*
Ketotifen fumarate (p.582·2).

Uni Clonazepax *Uniao Quimica, Braz.*
Clonazepam (p.478·2).
Anxiety; epilepsy.

Uni Dexa *Uniao Quimica, Braz.*
⊗ Dexamethasone acetate (p.1526·1) or dexamethasone phosphate (p.1526·2).
Formerly known as Uni Dexametason.
Corticosteroid.

Uni Diamicron *Servier, Belg.; Servier, Spain.*
Gliclazide (p.440·3).
Diabetes mellitus.

Uni Diazepax *Uniao Quimica, Braz.*
Diazepam (p.986·3).
Anxiety.

Uni Doxiciclin *Uniao Quimica, Braz.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Uni Fenicol *Genom, Braz.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Uni Gliben *Uniao Quimica, Braz.†.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Uni Haloper *Uniao Quimica, Braz.*
Haloperidol (p.1000·2).
Psychoses.

Uni Hioscin *Uniao Quimica, Braz.*
Hyoscine butylbromide (p.1734·1).
Muscle spasm.

Uni Imiprax *Uniao Quimica, Braz.*
Imipramine (p.400·2).
Depression; nocturnal enuresis; pain.

Uni Masdil *Esteve, Spain.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Uni Propralol *Uniao Quimica, Braz.*
⊗ Propranolol hydrochloride (p.1380·3).
Arrhythmias; hypertension.

Uni Salve *Smith & Nephew, Austral.†.*
Soft paraffin (p.2031·3).
Barrier cream; minor skin irritations.

Uni Timolol *Unimed, Cz.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Uni Vir *Uniao Quimica, Braz.*
Aciclovir (p.862·3).
Herpesvirus infections.

Uni-Ace *URL, USA.*
Paracetamol (p.108·1).

Uniakum
Note. This name is used for preparations of different composition.
Gache, Venez.
Oral drops: Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Gache, Venez.
Tablets: Paracetamol (p.108·1); caffeine (p.1116·3); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Unibac *Lilly, Belg.†.*
Dirithromycin (p.266·2).
Bacterial infections.

Unibaryt-R *IFET (ΙΦΕΤ), Gr.*
Barium sulfate (p.1477·2).
Radiographic contrast medium.

Unibase *Warner Chilcott, USA.*
Vehicle for topical preparations.

Unibasis *Pampa, Pol.*
White soft paraffin (p.2031·2); liquid paraffin (p.2030·3); glycerol (p.2314·2).
Skin disorders.

Unibenestan *Sanofi-Aventis, Spain.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Unibios Simple *Fabra, Arg.*
Dipyrone (p.49·2).
Fever; inflammation; pain.

Unibron *Unipharm, Mex.*
⊗ Salbutamol (p.1131·2).
Asthma.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Unicaine
Note. This name is used for preparations of different composition.
Thea, Belg.
Oxybuprocaine hydrochloride (p.1867·3).
Local anaesthesia.

Unipharm, Mex.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Unical Sooft, Ital.†.
Calcium carbonate (p.1714·1).
Calcium deficiency; calcium supplement.

Unicalm Raffo, Arg.
Ketorolac (p.75·2).
Formerly contained rofecoxib.
Inflammation; pain.

Unicap
Note. This name is used for preparations of different composition.
Pharmacia, Braz.; Pharmacia, Cz.†; Ferrosan, Rus.†; Upjohn, USA; Pharmacia, Venez.†.
Vitamin preparations with or without minerals (p.1922·1).

Unison, Thai.
Paracetamol (p.108·1).
Fever; pain.

Unicap M Pfizer, Philipp.
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Unicap T Eczacibasi, Turk.
Vitamin and mineral preparation (p.1922·1).

Unicarbazan Unichem, India.
Diethylcarbamazine citrate (p.143·1); chlorphenamine maleate (p.571·3).
Filariasis; tropical eosinophilia.

Unicet Bal, Thai.
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders.

Uni-Check Exxe, Ital.
Test for glucose in blood (p.2314·1).

Unichol Merck, Austria.
Hymecromone (p.2323·2).
Biliary-tract disorders.

Unicid Prospa, Ital.†.
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Unicide Unison, Thai.
Niclosamide (p.151·1).
Cestode infections.

Unicil 3/1 Unipharm, Mex.
Procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Unicil 6:3:3 Unipharm, Mex.
Benzathine benzylpenicillin (p.212·1); procaine benzylpenicillin (p.319·2); benzylpenicillin sodium (p.213·1).
Bacterial infections.

Unicil L-A Unipharm, Mex.
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Unicil Mega Unipharm, Mex.
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Unicilina Reig Jofre, Spain.
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Uniclar Schering-Plough, Arg.; Essex, Chile; Essex, Ital.†; Schering-Plough, Mex.; Schering-Plough, Venez.†.
⊗ Mometasone furoate (p.1539·3).
Allergic rhinitis; nasal polyps; sinusitis.

Uniclonax Unison, Philipp.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Uniclophen Unimed, Cz.
Diclofenac sodium (p.44·3).
Inflammatory eye disorders; intraoperative miosis inhibition; ocular pain; prevention of postoperative cystoid macular oedema.

Uniclor Solfran, Mex.
Chloramphenicol (p.239·3).
Bacterial infections.

Uni-Colex Universal, Hong Kong.
Guaifenesin (p.1561·3).
Coughs.

Unicomplex-T & M Rugby, USA.
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).

Unicontin Modi-Mundipharma, India; Meda, Port.
Theophylline (p.1140·1).
Obstructive airways disease.

Unicordium Organon, Fr.
Bepridil hydrochloride (p.1225·1).
Angina pectoris.

Unidasa Roux-Ocefa, Arg.
Hyaluronidase (p.2321·1).

Unidazol Zuoz, Venez.
Secnidazole (p.846·3).
Protozoal infections.

Uniderm
Note. This name is used for preparations of different composition.
Smith & Nephew, Austral.†.
Moisturiser.

Schering-Plough, Denm.; Schering-Plough, Swed.
⊗ Hydrocortisone (p.1535·2).
Anogenital pruritus; eczema; skin disorders.

Unison, Hong Kong; Unison, Malaysia; Unison, Singapore; Unison, Thai.
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Pharmaniaga, Malaysia†; Raza, Malaysia†.
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Unipharm, Mex.
Sodium fusidate (p.279·3).
Bacterial skin infections.

Unidermo Uniderm, Ital.
Lactic acid (p.2329·3); collagen (p.2286·1).
Skin cleansing.

Unidet Pfizer, Canad.
Tolterodine tartrate (p.2198·1).
Bladder instability.

Unidie Fournier SA, Spain.
Cefonicid sodium (p.226·2).
Bacterial infections.

Unidor Sanofi-Aventis, Spain.
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Unidoscor Biotech, Venez.†.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Unidox
Note. A similar name is used for preparations of different composition (see below).
Yamanouchi, Cz.†; Astellas, Neth.; Astellas, Pol.; Yamanouchi, Rus.
Doxycycline (p.267·1).
Bacterial infections.

Uni-Dox
Note. A similar name is used for preparations of different composition (see above).
Unipharm, Mex.
Diclofenac sodium (p.44·3); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy.

Unidrin D Unipharm, Mex.
Pseudoephedrine (p.1571·2); chlorphenamine (p.572·2).
Influenza symptoms.

Unidrol Unichem, India†.
⊗ Methylprednisolone acetate (p.1538·2).
Corticosteroid.

Unidrox ACRAF, Cz.; Angelini, Ital.
Prulifloxacin (p.320·1).
Bacterial infections.

Uni-Dur Schering-Plough, Cz.†; Schering-Plough, Mex.†.
Theophylline (p.1140·1).
Obstructive airways disease.

Unienzyme
Note. This name is used for preparations of different composition.
Unichem, India.
Oral liquid: Amylase (p.2256·3); papain (p.2362·3).
Dyspepsia; flatulence.

Unichem, India.
Tablets: Amylase (p.2256·3); papain (p.2362·3); simeticone (p.1770·2); nicotinamide (p.1957·3); activated charcoal (p.1435·2).
Dyspepsia; flatulence.

Unif Tek, Thai.
⊗ Triamcinolone acetonide (p.1544·3).
Skin and scalp disorders.

Uni-Febrin Universal, Hong Kong.
Paracetamol (p.108·1).
Fever; pain.

Unifed Altaire, USA.
Pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion.

Uni-Fedra Compound Universal, Hong Kong.
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); codeine phosphate (p.37·2).
Coughs; nasal congestion.

Unifedrine Uniao Quimica, Braz.
⊗ Ephedrine sulfate (p.1558·2).

Uni-Fenil Unipharm, Mex.†.
Diclofenac (p.44·2).
Inflammation; pain.

Unifenitoin Uniao Quimica, Braz.
Phenytoin (p.495·2) or phenytoin sodium (p.495·2).
Epilepsy.

Unifenobarb Uniao Quimica, Braz.
Phenobarbital (p.492·2).
Epilepsy.

Unifer
Note. This name is used for preparations of different composition.
Rider, Chile.
Ferrous gluceptate (p.1938·3).
Iron deficiency; iron-deficiency anaemia.

Tosi, Ital.†.
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Grossman, Mex.
Iron carbonyl (p.1950·3).
Iron deficiency; iron-deficiency anaemia.

Uniferfol Grossman, Mex.
Iron carbonyl (p.1950·3); folic acid (p.1940·1).
Folic acid deficiency; iron-deficiency anaemia.

Unifiber Niche, USA.
Powdered cellulose (p.2143·1).
Constipation.

Unifibre Niche, Singapore†.
Dietary fibre supplement (p.1922·1).
Constipation.

Unifilin Uniao Quimica, Braz.
Aminophylline (p.1114·2).
Asthma.

Uniflex Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore†.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Uniflex-N Xepa-Soul Pattinson, Malaysia†.
⊗ Betamethasone valerate (p.1519·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Uniflox
Note. This name is used for preparations of different composition.
Raffo, Arg.
Levofloxacin (p.292·2).
Bacterial infections.

Bayer, Fr.
Ciprofloxacin hydrochloride (p.243·3).
Cystitis; gonococcal urethritis.

Uniflu with Gregovite C Alliance, UK.
Uniflu tablets, phenylephrine hydrochloride (p.1568·1); caffeine (p.1116·3); codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); paracetamol (p.108·1); Gregovite C tablets, ascorbic acid (p.1983·3).
Cold and influenza symptoms; nasal congestion.

Unifluid Thea, Fr.
Povidone (p.2146·1).
Dry eyes.

Unifungicid Unia, Pol.
Chlormidazole hydrochloride (p.529·1).
Fungal and bacterial skin and nail infections.

Unifungin Unipharma, Gr.
Econazole (p.531·1).
Fungal skin infections.

Unifyl Mundipharma, Austria; Mundipharma, Switz.
Theophylline (p.1140·1).
Obstructive airways disease.

Unigamol Norgine, Ger.†.
Evening primrose oil (p.2302·1).
Atopic eczema.

Unigan Unison, Hong Kong; Unison, Thai.
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Unigo Unison, Hong Kong; Unison, Thai.
Metronidazole (p.837·1).
Amoebiasis; anaerobic bacterial infections; trichomoniasis; vaginosis.

Uni-Gold hCG Kora, Irl.
Pregnancy test (p.2372·1).

Unigrip Uniao Quimica, Braz.
Paracetamol (p.108·1).
Fever; pain.

Unigyn
Note. This name is used for preparations of different composition.
Sigma, Braz.
Secnidazole (p.846·3).
Protozoal infections.

Uniderm, Ital.
Lactic acid (p.2329·3).
Personal hygiene; vaginal douche.

Unihep Leo, Irl.†.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Unihist Unison, Hong Kong; Unison, Thai.
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Allergic rhinitis; asthma; cold symptoms.

Unihype Samjin, Philipp.; Unimex, Philipp.
Captopril (p.1239·2).
Hypertension.

Unijab Rotexmedica, Singapore.
Algestone acetophenide (p.2082·1); estradiol benzoate butyrate.
Combined injectable contraceptive.

Uni-Kaotin Universal, Hong Kong.
Kaolin (p.1738·1); pectin (p.2145·2).
Diarrhoea.

Uniket Lacer, Spain.
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Uni-Kinase Unichem, India.
Urokinase (p.1420·1).
Thromboembolic disorders.

Uniklar Nevzat, Turk.
Clarithromycin (p.248·2).
Bacterial infections.

Unikpef Unique, Rus.
Pefloxacin mesilate (p.313·3).
Bacterial infections.

Unil Umeda, Thai.
Glibenclamide (p.440·1).
Diabetes mellitus.

Unilair 3M, Cz.†; 3M, Ger.
Theophylline (p.1140·1).
Obstructive airways disease.

Unilan Laquifa, Port.
Alprazolam (p.960·1).
Anxiety; panic disorder.

Unilarm Novartis Ophthalmics, Hung.†; Europhta, Mon.
Sodium chloride (p.1686·1).
Dry eye.

Uniloc Nycomed, Denm.; Nycomed, Norw.; Nycomed, Swed.†.
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Unilong Altana, Spain†.
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Unilux Sanochemia, Ger.
Iopamidol (p.1483·3).
Radiographic contrast medium.

Unima Unison, Hong Kong; Unison, Malaysia.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Uni-Ma Unison, Thai.
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation; constipation.

Unimax AstraZeneca, Austria; AstraZeneca, Cz.†; AstraZeneca, Fin.; AstraZeneca, Ger.; Promed, Ger.; AstraZeneca, Neth.; AZ, Port.; AstraZeneca, Switz.
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Unimazole Unipharma, Gr.
Thiamazole (p.2176·3).
Hyperthyroidism.

Unimedrol Uniao Quimica, Braz.
⊗ Methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Unimer LDPSA, Fr.
Sea water.
Nasal cleansing.

Unimezol Unichem, India†.
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections; ulcerative gingivitis.

Unimicebrina Sanofi Synthelabo, Spain†.
Ascorbic acid (p.1983·3).
Adjunct in iron therapy; vitamin C deficiency.

Unimol Unison, Thai.
Paracetamol (p.108·1).
Fever; pain.

Unimox Unison, Hong Kong; Unison, Singapore; Unison, Thai.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Uninapro Unifarm, Ital.
Naproxen sodium (p.92·3).
Fever; pain.

Uniparin Aventis, Austral.†.
Heparin sodium (p.1301·2).
Thromboembolic disorders.

Uni-Per Unimex, Philipp.; Yuhan, Philipp.
Simvastatin (p.1390·2).
Hyperlipidaemias.

Uni-Phen Universal, Hong Kong.
Ammonium chloride (p.1551·3); sodium citrate (p.1673·3); diphenhydramine hydrochloride (p.577·2); menthol (p.2340·1).
Coughs; nasal congestion.

Uni-Pholco Universal, Hong Kong.
Pholcodine (p.1570·2).
Coughs.

Uniphyl Purdue, Canad.; Adcock Ingram, S.Afr.; Purdue Frederick, USA.
Theophylline (p.1140·1).
Bronchospasm; obstructive airways disease.

Uniphyllin Mundipharma, Ger.; Unipharma, Gr.
Theophylline (p.1140·1).
Asthma; neonatal apnoea and bradycardia; obstructive airways disease.

Uniphyllin Continus Napp, Irl.; Napp, UK.
Theophylline (p.1140·1).
Asthma; bronchospasm; heart failure; obstructive airways disease.

Uniplex
Note. This name is used for preparations of different composition.
Cimed, Braz.
Amino-acid, vitamin, and mineral preparation (p.1922·1).

Aristopharma, Hong Kong.
Vitamin B substances (p.1922·1).
Vitamin B supplement.

Unipharma, Gr.†.
Aciclovir (p.862·3).
Herpes simplex infections.

Uni-Plex
Note. A similar name is used for preparations of different composition (see above).
Universal, Hong Kong.
Vitamin B substances (p.1922·1).
Vitamin B supplement.

Uniplus Angelini, Ital.
Oxolamine citrate (p.1567·1); propyphenazone (p.119·3).
Influenza symptoms; oral inflammation; otorhinolaryngeal inflammation; tracheobronchitis.

Uniprazol *Uniao Quimica, Braz.*
Omeprazole (p.1753·1).
Peptic ulcer.

Unipred *Osoth, Thai.*
⊗ Prednisolone (p.1540·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Unipres *KRKA, Cz.; KRKA, Hung.*
Nitrendipine (p.1358·2).
Hypertension.

Unipril *AstraZeneca, Ital.*
Ramipril (p.1385·3).
Heart failure; hypertension; renal insufficiency.

Uniprildiur *AstraZeneca, Ital.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Uniprofen *Uniao Quimica, Braz.*
Ibuprofen (p.64·2).
Inflammation; pain.

Unique PH *Alcon, Braz.*
Cleansing and wetting solution for hard contact lenses (p.1622·2).

Unique Plus *Eurofarma, Braz.*
Sodium monofluorophosphate (p.1964·3).
Dental caries prophylaxis.

Uniquin *Biochemie, Austria; Madaus, Ital.; Medinfar, Port.; GSK, S.Afr.*
Lomefloxacin hydrochloride (p.295·2).
Bacterial infections.

Uni-Ramine *Universal, Hong Kong.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Uni-Ramine CE *Universal, Hong Kong.*
⊗ Codeine phosphate (p.37·2); ephedrine hydrochloride (p.1558·2); ammonium chloride (p.1551·3); chlorphenamine maleate (p.571·3).
Coughs.

Uni-Ramine Expectorant *Universal, Hong Kong.*
Chlorphenamine maleate (p.571·3); ammonium chloride (p.1551·3); sodium citrate (p.1673·3).
Coughs.

Uniranz *Unimex, Philipp.; Yungjin, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Unirelaxed *Alpharma, Mex.*
Naproxen (p.92·3).
Fever; inflammation; pain.

Uniren
Unison, Hong Kong.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders.

Unison, Malaysia; Unison, Singapore.
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Unison, Thai.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Uniretic *Schwarz, Philipp.; Schwarz, USA.*
⊗ Moexipril hydrochloride (p.1343·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Uniroid-HC *Chemidex, UK.*
⊗ Cinchocaine hydrochloride (p.1857·3); hydrocortisone (p.1535·2).
Anorectal disorders.

Unisal *MSD, Switz.†*
Diflunisal (p.47·2).
Inflammation; pain.

Uniscrub *Seton, Israel†.*
Chlorhexidine gluconate (p.1635·3).
Skin disinfection.

Unisedil *Laquifa, Port.*
Diazepam (p.986·3).
Anxiety disorders; skeletal muscle spasm.

Unisedyl *Union, Singapore†.*
⊗ Codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2); ephedrine hydrochloride (p.1558·2).
Coughs.

Unisept *Seton, Israel†; Medlock Medical, UK.*
Chlorhexidine gluconate (p.1635·3).
Disinfection of burns, mucous membranes, skin, and wounds.

Unisol *Alcon, USA.*
Rinsing and storage solutions for soft contact lenses (p.1622·2).

Unisolve *Smith & Nephew, Austral.†*
Dipropylene glycol methyl ether; isopropyl alcohol (p.1650·3); isoparaffin.
Medical adhesive remover.

Unisom
Note.This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Pfizer Consumer, Canad.; Pfizer, Hong Kong; Pfizer Consumer, Mex.†; Pfizer Consumer, NZ.
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Pfizer, Israel; Pfizer, Philipp.; Pfizer, Turk.
Doxylamine succinate (p.578·2).
Insomnia.

Unisom-2 *Pfizer Consumer, Canad.*
Doxylamine succinate (p.578·2).
Insomnia.

Unisom Natural Source *Pfizer Consumer, Canad.†.*
Valerian (p.2410·1).
Insomnia.

Unisom with Pain Relief *Pfizer Consumer, USA.*
Paracetamol (p.108·1); diphenhydramine hydrochloride (p.577·2).
Insomnia; pain.

Unisom SleepTabs *Pfizer Consumer, USA.*
Doxylamine succinate (p.578·2).
Insomnia.

Unison Enema
Note.This name is used for preparations of different composition.
Unison, Hong Kong.
Sodium chloride (p.1686·1).
Bowel evacuation; constipation.

Unison, Thai.
Macrogol (p.2336·1); sodium chloride.
Constipation.

Unison Ointment *Unison, Thai.*
Chloramphenicol (p.239·3).
Bacterial skin infections.

Unistep hCG *Orion, USA.*
Pregnancy test (p.2372·1).

Unistin *BPL-Meizler, Braz.†.*
Cisplatin (p.698·2).
Malignant neoplasms.

Unitaxel *Korea United, Philipp.*
Paclitaxel (p.759·1).
Breast cancer; ovarian cancer.

United American Tiki Tiki Plus *General Drug, Philipp.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

United American Tiki Tiki Star *General Drug, Philipp.*
Vitamins; taurine; lysine (p.1922·1).
Nutritional supplement.

United Home Burn Ointment *General Drug, Philipp.*
Benzocaine (p.1854·1); eucalyptus oil (p.2301·2); boric acid (p.2268·1).
Burns; itching.

United Home Calactate *General Drug, Philipp.*
Calcium lactate (p.1676·1).
Calcium supplement; osteoporosis.

United Home Fersulfate Iron *General Drug, Philipp.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

United Home Glydolax *General Drug, Philipp.*
Glycerol (p.2314·2).
Constipation.

United Home Whitfield's Ointment *United Laboratories, Philipp.*
Salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Ringworm; tinea infections.

Unitens *AstraZeneca, Gr.*
Felodipine (p.1285·3); ramipril (p.1385·3).
Hypertension.

Unithroid *Lannett, USA.*
Levothyroxine sodium (p.2171·2).
Hypothyroidism.

Unitidazin *Uniao Quimica, Braz.*
Thioridazine hydrochloride (p.1031·2).

Unitifed
Note.This name is used for preparations of different composition.
Union, Singapore†.
Linctus: Codeine phosphate (p.37·2); triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Formerly known as Unitifed Compound.
Allergic rhinitis; cold symptoms; coughs; nasal and upper respiratory-tract congestion; sinusitis.

Union, Singapore†.
Syrup: Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; coughs; nasal and upper respiratory-tract congestion; sinusitis.

Unitin *Unipharm, Mex.*
Ranitidine (p.1766·1).
Peptic ulcer.

Unitinase *BPL-Meizler, Braz.†.*
Streptokinase (p.1402·3).
Thromboembolic disorders.

Unitone
Note.This name is used for preparations of different composition.
D & M, Chile; Darier, Mex.
Betacarotene (p.1930·3); avobenzone (p.1589·3); octinoxate (p.1608·2).
Skin pigmentation disorders.

Roemmers-Klinos, Venez.†.
SPF 15: Betacarotene (p.1930·3); nanotalasferase; sunscreens.
Skin pigmentation disorders.

Unitone 4 *D & M, Chile.*
Hydroquinone (p.1598·2); kojic acid (p.1603·3).
Skin pigmentation disorders.

Unitrac *Kalbe, Indon.; Dankos, Malaysia.*
Itraconazole (p.536·3).
Fungal infections.

Unitral *Unison, Philipp.*
Tramadol hydrochloride (p.130·3).
Pain.

Uni-Tranxene *Sanofi-Aventis, Belg.*
Dipotassium clorazepate (p.980·1).
Anxiety; mixed anxiety depressive states.

Unitrexate *BPL-Meizler, Braz.†.*
Methotrexate (p.745·2).
Malignant neoplasms.

Unitril *Kener, Mex.†.*
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Unitrim *Unipharma, Gr.*
Metronidazole (p.837·1).
Rosacea.

Unitron PEG *Schering, Canad.*
Peginterferon alfa-2b (p.888·3).
Chronic hepatitis C.

Unitul Complex *Bama, Spain†.*
Sodium acexamate (p.2245·2); sulfadiazine silver (p.337·2).
Burns; ulcers; wounds.

Unitulle *Aventis, Austral.†.*
White soft paraffin (p.2031·2).
Burns; skin ulcers; wounds.

Unituss *Unison, Thai.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); sodium citrate (p.1673·3); menthol (p.2340·1).
Coughs; nasal congestion.

Unituss HC *URL, USA.*
Hydrocodone tartrate (p.63·1); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Uni-tussin DM *URL, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Unival
Note.This name is used for preparations of different composition.
Recalcine, Chile.
Lansoprazole (p.1739·2).
Peptic ulcer.

Senosiain, Mex.
Sucralfate (p.1772·2).
Gastritis; peptic ulcer.

Univasc *Schwarz, Philipp.; Adeka, Turk.; Schwarz, USA.*
Moexipril hydrochloride (p.1343·2).
Hypertension.

Uni-Vasin *Universal, Hong Kong.*
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); phenylpropanolamine hydrochloride (p.1569·3).
Upper respiratory-tract disorders.

Univate *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Univer *Cephalon, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Universal Earache Drops *Universal, S.Afr.*
Phenazone (p.116·1); procaine hydrochloride (p.1869·1); potassium hydroxyquinoline sulfate (p.2323·2).
Ear disorders.

Universal Eye Drops *Universal, S.Afr.*
Phenylephrine hydrochloride (p.1568·1); boric acid (p.2268·1).
Eye inflammation; eye irritation.

Universal Nasal Drops *Universal, S.Afr.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline nitrate (p.1565·2).
Allergic rhinitis; sinusitis.

Universal Throat Lollies *Universal, S.Afr.*
Cetylpyridinium chloride (p.1635·1).
Mouth and throat infections.

Uni-Vico *Universal, Hong Kong.*
Vitamin preparation (p.1922·1).

Univit *Unifarm, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Univol *Carter Horner, Canad.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders associated with hyperacidity.

Uniwarfin *Unichem, India.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Uniwash *Smith & Nephew, Austral.†.*
Skin cleanser.

UniXan *Norpharma, Denm.*
Theophylline (p.1140·1).
Obstructive airways disease.

Unixime *FIRMA, Ital.*
Cefixime (p.224·3).
Bacterial infections.

Unizef *Samjin, Philipp.; Unimex, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; conjunctivitis; urticaria.

Unizen *Unison, Hong Kong; Unison, Malaysia; Unison, Singapore†; Unison, Thai.*
Serrapeptase (p.2385·3).
Adjunct in antibacterial therapy; alveolar abscess; breast engorgement; cystitis; epididymitis; respiratory-tract congestion; sinusitis; wisdom tooth pericoronitis; wounds.

Unizink *Kohler, Ger.; Kohler-Pharma, Ger.*
Zinc aspartate (p.2000·1).
Zinc deficiency.

Unizitro *Tecnimede, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Unizol *Farmoquimica, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Unizox *Korea United, Philipp.*
Ceftizoxime sodium (p.236·2).
Bacterial infections.

Unizuric *Quimica y Farmacia, Mex.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Unizyme *Ciba Vision, Canad.*
Subtilisin (p.2393·3) (p.1622·2).
Protein removal from contact lenses.

Unkei-to *Tsumura, Jpn.*
Ophiopogon tuber; pinellia tuber; angelica acutiloba root; liquorice; cinnamon bark; peony root; cnidium rhizome; ginseng; moutan bark; evodia fruit; ginger; gelatin.
Traditional Kampo medicine.

Uno *Ratiopharm, Cz.*
Diclofenac sodium (p.44·3).
Rheumatoid arthritis.

Uno-Ciclo *Biochimico, Braz.†.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Injectable contraceptive.

Uno-Enantone *Takeda, Ger.†.*
⊗ Leuprorelin acetate (p.2111·1).
Prostatic cancer.

Uno-Lin *3M, Denm.†.*
Theophylline hydrate (p.1140·2).
Obstructive airways disease.

Unoplex *Offenbach, Mex.*
Vitamin preparation (p.1922·1).

Unoprost
Note.This name is used for preparations of different composition.
Apsen, Braz.
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia.

Guidotti, Ital.
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Unorox *Centaur, India†.*
Roxithromycin (p.331·1).
Bacterial infections.

Unotex *Truw, Ger.†.*
Homoeopathic preparation.

Uno-Vit *Wiedemann, Ger.*
dl-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Unoximed *Tai Yu, Philipp.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Unprozy *Condrugs, Thai.*
Fluoxetine hydrochloride (p.391·2).
Mixed anxiety depressive states; obsessive-compulsive disorder.

Unsayna
Note.This name is used for preparations of different composition.
Pfizer, Arg.†.
Injection: Sulbactam sodium (p.335·1); ampicillin sodium (p.204·1).
Bacterial infections.

Pfizer, Arg.†.
Tablets: Sultamicillin tosilate (p.344·1).
Bacterial infections.

Unseiin *Tsumura, Jpn.*
Rehmannia root; peony root; cnidium rhizome; Japanese angelica root; scutellaria root; phellodendron bark; coptis rhizome; gardenia fruit.
Traditional Kampo medicine.

Untano *Rafarm, Gr.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Unthecol *Bernofarm, Indon.*
Dipyrone (p.49·2); hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Unwind Herbal Nytol *GSK Consumer, UK.*
Valerian (p.2410·1); lupulus (p.2335·2); wild lettuce (p.2415·2).
Insomnia; stress.

UO *YSP, Malaysia; Yung Shin, Singapore.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Uonin *Unison, Hong Kong; Unison, Malaysia; Unison, Thai.*
Roxithromycin (p.331·1).
Bacterial infections; meningitis prophylaxis.

U-Oscine *Umeda, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

U-Pasta *Kowa, Jpn.*
Sucrose (p.1969·2); povidone-iodine (p.1659·2).
Skin ulcers.

Upbutol *Unique, Rus.*
Ethambutol hydrochloride (p.274·1).

Upderm *Genepharm, Gr.*
Clindamycin phosphate (p.251·2).
Bacterial skin and vaginal infections.

Upelva *Pekana, Ger.†.*
Homoeopathic preparation.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Upfen *UPSA Conseil, Fr.*
Ibuprofen (p.64·2).
Fever; pain.

Upha C *CCM, Malaysia.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Upha Dextrophan *CCM, Malaysia.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Upha Lozenges *CCM, Malaysia.*
Dequalinium chloride (p.1641·3); tyrothricin (p.358·2).
Mouth and throat infections.

Uphacol *Upha, Malaysia†.*
Dicycloverine hydrochloride (p.1722·3); simeticone (p.1770·2).
Flatulence; gastrointestinal spasm.

Uphadeq *CCM, Malaysia†.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

Uphadyl CD *Upha, Malaysia†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); codeine phosphate (p.37·2).
Coughs.

Uphadyl Forte *CCM, Malaysia.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Uphageron *CCM, Malaysia.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; nausea; vertigo.

Uphalexin *CCM, Malaysia; Upha, Singapore.*
Cefalexin (p.218·2).
Bacterial infections.

Uphalyte *CCM, Malaysia; Upha, Singapore.*
Glucose; sodium chloride; sodium bicarbonate; potassium chloride (p.1672·2).
Diarrhoea; oral rehydration therapy.

Uphamol *CCM, Malaysia.*
Paracetamol (p.108·1).
Fever; pain.

Uphamol Flu *CCM, Malaysia.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Influenza symptoms.

Uphanormin *Upha, Malaysia†.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Uphastatin *Upha, Malaysia†.*
Nystatin (p.543·2).
Candidiasis.

Uphavit *CCM, Malaysia.*
Vitamin preparation (p.1922·1).
Dietary supplement.

Uphavit Plus *CCM, Malaysia.*
Multivitamin and mineral preparation (p.1922·1).

Uphaxicam *CCM, Malaysia.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Uphazhexol *Upha, Malaysia†.*
Trihexyphenidyl hydrochloride (p.820·2).
Drug-induced extrapyramidal disorders; parkinsonism.

Upixon *Bayer, Indon.*
Piperazine (p.152·3).
Ascariasis; oxyuriasis.

Uplores *Sanbe, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Upodine *Umeda, Thai.*
Povidone-iodine (p.1659·2).
Disinfection of skin, wounds, and burns.

Upperzin *Randril, Philipp.*
Erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Upren *Casel, Turk.*
Ibuprofen (p.64·2).
Fever; inflammation; pain.

Uprima *Abbott, Arg.†; Abbott, Austria†; Abbott, Belg.†; Abbott, Braz.; Abbott, Chile†; Abbott, Cz.†; Abbott, Denm.†; Abbott, Fin.†; Abbott, Fr.†; Abbott, Ger.†; Abbott, Gr.†; Abbott, Hong Kong†; Abbott, Hung.†; Abbott, Irl.†; Abbott, Ital.†; Abbott, NZ†; Abbott, Neth.†; Abbott, Norw.†; Abbott, Port.†; Abbott, S.Afr.†; Abbott, Spain†; Abbott, Swed.†; Abbott, Switz.†; Abbott, UK†; Abbott, Venez.†.*
Apomorphine hydrochloride (p.795·1).
Erectile dysfunction.

Uprox *United Pharma, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

U-Proxyn *Unison, Thai.*
Naproxen (p.92·3).
Gout; musculoskeletal and joint disorders.

Upsa C *BMS, Belg.*
Ascorbic acid (p.1983·3).
Methaemoglobinaemia; vitamin C deficiency.

Upsalgin-N *BMS, Gr.*
Aspirin (p.20·3).
Fever; inflammation; pain.

Upsarin *UPSA, Cz.†; BMS, Pol.*
Aspirin (p.20·3).
Fever; pain; thrombosis prophylaxis.

Upsarin C *BMS, Cz.; BMS, Hung.†; BMS, Pol.*
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms; fever; pain; thrombosis prophylaxis.

Upsaton *BMS, Gr.*
Magnesium aspartate; potassium aspartate; calcium fructoheptonate; lysine; vitamin B ; vitamin C (p.1922·1).
Tonic.

Upsavit C *BMS, Belg.*
Ascorbic acid (p.1983·3).
Methaemoglobinaemia; vitamin C deficiency.

Upsavit Tonic *UPSA, Cz.†.*
Calcium fructoheptonate; magnesium aspartate; potassium aspartate; ascorbic acid; pyridoxine hydrochloride; nicotinamide (p.1922·1).
Dietary supplement; tonic.

Upset Stomach *Homeocan, Canad.†.*
Homoeopathic preparation.

Uracet *Umeda, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Uracid *Wesley, USA.*
Methionine (p.1450·1).
Odour, dermatitis, and ulceration in incontinent adults.

Uraciflor *Medicus, Gr.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Uracil *Pharmasant, Thai.*
Propylthiouracil (p.2175·2).
Hyperthyroidism.

Uractone *SPA, Cz.†; SPA, Ital.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; oedema.

Uractonum *Medochemie, Singapore.*
⊗ Spironolactone (p.1400·1).
Heart failure; hyperaldosteronism; hypertension; liver cirrhosis with oedema; nephrotic syndrome.

Uracyst *Stellar, Canad.*
Chondroitin sulfate sodium (p.2280·3).
Replacement of glycosaminoglycan layer in the bladder.

Uracyst Test Kit *Stellar, Canad.*
Chondroitin sulfate sodium (p.2280·3); potassium chloride (p.1684·3).
Test for and treatment of bladder-wall glycosaminoglycan deficiency.

Urader Lactato *Medihealth, Mex.*
⊗ Urea (p.1620·2); lactic acid (p.2329·3).
Dry skin disorders.

Ural *Sigma, Austral.; Abbott, Malaysia; Abbott, NZ.*
Sodium bicarbonate (p.1673·2); sodium citrate (p.1673·3); anhydrous citric acid (p.2284·1); tartaric acid (p.2395·2).
Dyspepsia; dysuria; gout; urinary alkalinisation; urinary-tract infections.

Uralyt Urato *Madaus, Spain.*
Citric acid (p.2284·1); potassium citrate (p.1673·2).
Hypocitraturia; renal calculi; renal tubular acidosis.

Uralyt-U *Madaus, Austria; Madaus, Belg.; Madaus, Cz.; Madaus, Ger.; Madaus, Israel; Madaus, Ital.; Neo-Farmaceutica, Port.; Altana Madaus, S.Afr.; Madaus, Switz.†; Madaus, Thai.*
Potassium sodium hydrogen citrate (p.1674·2).
Cystinuria; porphyria cutanea tarda; renal calculi; urinary alkalinisation.

Uramilon *Biomedica-Chemica, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Uramol *Stiefel, Chile; Stiefel, Mex.*
⊗ Urea (p.1620·2).
Dry skin.

Uramox *Taro, Israel.*
⊗ Acetazolamide (p.1875·1).
Acute mountain sickness; glaucoma; oedema.

Urandil *Zentiva, Cz.†; Zentiva, Pol.*
⊗ Chlortalidone (p.1243·3).
Hypertension; oedema.

Uraplex *Madaus, Cz.; Arriani, Gr.; Wassermann, Ital.; Madaus, Spain.*
Trospium chloride (p.2198·3).
Bladder instability; urinary incontinence.

Urapro *Eagle, Austral.†.*
Saw palmetto (p.2192·3); lycopersicon esculentum; hydrastis (p.2321·3); urtica (p.2409·3); zinc gluconate (p.1999·2); nickel; ferrous phosphate.
Nutritional supplement.

Urarthone *Homeocan, Canad.; Lehning, Fr.*
Homoeopathic preparation.

Urasal *Carter Horner, Canad.†.*
Methenamine (p.298·3).
Urinary-tract infections.

Urasin *TNP, Thai.†.*
⊗ Furosemide (p.1292·1).
Forced diuresis; heart failure; oedema.

Urasix *HB, Braz.*
⊗ Furosemide (p.1292·1).

Urazol *Tecnofarma, Chile.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability.

Urbal *Merck, Spain.*
Sucralfate (p.1772·2).
Gastrointestinal haemorrhage; peptic ulcer.

Urbanil *Sanofi-Aventis, Braz.; Aventis, Port.†.*
Clobazam (p.477·2).
Anxiety; epilepsy.

Urbanol *Sanofi Synthelabo, S.Afr.*
Clobazam (p.477·2).
Alcohol withdrawal syndrome; anxiety; premedication.

Urbanyl *Sanofi-Aventis, Fr.; Aventis, Switz.*
Clobazam (p.477·2).
Alcohol withdrawal syndrome; anxiety; epilepsy.

Urbason
Aventis, Austria; Aventis, Cz.†; Aventis, Ger.; Sanofi-Aventis, Ital.; Sanofi-Aventis, Spain.
⊗ Methylprednisolone (p.1538·1) or methylprednisolone sodium succinate (p.1538·2).
Corticosteroid.

Sanofi-Aventis, Indon.
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Urcyston Planta *Leros, Cz.*
Chamomile (p.2279·3); sambucus (p.2383·1); bearberry (p.2263·3); equisetum (p.2299·3); myrtillus (p.2349·3); solidago (p.2391·1); thyme (p.2401·1).
Urinary-tract disorders.

Urdafalk *Darya-Varia, Indon.; Falk, Indon.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones; liver disorders.

Urdahex *Kalbe, Indon.*
Ursodeoxycholic acid (p.2408·1).
Gallstones; hepatitis.

Urdes *Errekappa, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary disorders.

Urdox *CP Pharmaceuticals, UK.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones.

Urdrim *Urbion, Spain†.*
Astemizole (p.567·2).
Hypersensitivity reactions.

Ureacin *Pedinol, USA.*
⊗ Urea (p.1620·2).
Dry skin; hyperkeratosis.

Ureacort *Orva, Turk.*
⊗ Hydrocortisone acetate (p.1535·2); urea (p.1620·2).
Skin disorders.

Ureaderm Lactato *Medihealth, Mex.; Roemmers Medihe, Venez.*
⊗ Urea (p.1620·2); sodium lactate (p.1673·3).
Dry skin; hyperkeratosis.

Ureadin
Note. This name is used for preparations of different composition.
Isdin, Arg.; Medley, Braz.
⊗ Urea (p.1620·2).
Dry skin; hyperkeratotic skin disorders.

Isdin, Port.
⊗ Urea (p.1620·2); glycolic acid (p.1598·1); salicylic acid (p.1612·2).
Hyperkeratotic skin disorders.

Ureadin 10 and 20 *Isdin, Chile; Isdin, Port.*
⊗ Urea (p.1620·2).
Hyperkeratotic skin disorders.

Ureadin 30 *Isdin, Chile.*
⊗ Urea (p.1620·2); dimeticone (p.2032·1); arginine (p.1928·2); lactic acid (p.2329·3); allantoin (p.1588·1).
Dry skin; hyperkeratotic skin disorders.

Ureadin Facial
Note. This name is used for preparations of different composition.
Isdin, Chile.
⊗ Urea (p.1620·2); borage oil (p.2267·3); ceramide; sunscreens.
Dry skin.

Isdin, Arg.
SPF 10: ⊗ Urea (p.1620·2); borage oil (p.2267·3); ceramide 3; glycerol (p.2314·2); vitamin E acetate; lactic acid (p.2329·3); octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3).
Face cream containing sunscreens.

Isdin, Port.
SPF 10: ⊗ Urea (p.1620·2); glycerol (p.2314·2); borage oil (p.2267·3); sunscreens.
Dry skin.

Ureadin Forte *Isdin, Chile; Isdin, Port.*
⊗ Urea (p.1620·2); glycolic acid (p.1598·1); nicotinamide (p.1957·3); salicylic acid (p.1612·2).
Dry skin disorders; hyperkeratotic skin disorders.

Ureadin Maos *Isdin, Port.*
⊗ Urea (p.1620·2); glycerol (p.2314·2); lactic acid (p.2329·3).
Dry skin.

Ureadin Pediatrics *Isdin, Chile.*
⊗ Urea (p.1620·2); gamolenic acid (p.2308·2).
Skin disorders.

Ureadin 10 Plus *Isdin, Port.*
⊗ Urea (p.1620·2); dexpanthenol (p.2362·1).
Dry skin disorders.

Ureadin Rx DB *Isdin, Chile.*
⊗ Urea (p.1620·2); Ureadyl; glycerol (p.2314·2); lauromacrogol 400 (p.1916·1); rosa mosqueta oil; centella triterpenes (p.1592·3); allantoin (p.1588·1); panthenol (p.2362·1); arginine; bioecolia; dextran sulfate (p.2293·1); vitamin E acetate; carnosita; aloe vera (p.1588·2).
Dry skin; hyperkeratotic foot disorders.

Ureadin Rx PS *Isdin, Chile.*
⊗ Urea (p.1620·2); Ureadyl; salicylic acid (p.1612·2); lauromacrogol 400 (p.1916·1); allantoin (p.1588·1); sorbitol; nicotinamide (p.1957·3).
Psoriasis.

Ureadin Rx RD *Isdin, Chile.*
⊗ Urea (p.1620·2); Ureadyl; panthenol (p.2362·1); hyaluronic acid (p.2320·1); glycerol (p.2314·2); lauromacrogol 400 (p.1916·1); allantoin (p.1588·1); panthenol (p.2362·1); arginine; vitamin E; aloe vera (p.1588·2); nicotinamide (p.1957·3).
Dry skin; skin irritation.

Ureaphil *Abbott, USA.*
⊗ Urea (p.1620·2).
Cerebral oedema; raised intra-ocular pressure.

Ureata S *Fides, Ger.†.*
⊗ Urea (p.1620·2); alpha tocoferil acetate (p.1992·3).
Skin disorders; ulcers.

Ureax *Cellofarm, Braz.†.*
Hydroxycarbamide (p.729·1).
Malignant neoplasms.

Urecare *Orion, Austral.; Orion, Hong Kong; Delta West, Malaysia†; Pfizer Consumer, Singapore†.*
⊗ Urea (p.1620·2).
Dry skin disorders; eczema.

Urecholine *MSD, Israel†; MSD, Thai.†; Barr, USA; Duramed, USA.*
Bethanechol chloride (p.2265·3).
Congenital megacolon; neurogenic bladder; postoperative abdominal distension; urinary retention.

Urecortin *Proel, Gr.*
⊗ Dexamethasone (p.1526·1); urea (p.1620·2).
Skin disorders.

Urecrem *Ethicus, Arg.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Urecrem Hidro *Ethicus, Arg.*
⊗ Urea (p.1620·2); ammonium lactate (p.1589·2).
Dry skin disorders.

Urederm *Hamilton, Austral.; Hamilton, Hong Kong; Roi Surya, Indon.; Orva, Turk.*
⊗ Urea (p.1620·2).
Dry skin; hyperkeratotic skin disorders; skin irritation.

Uree *Boiron, Canad.; Riva, Canad.*
⊗ Urea (p.1620·2).

Uregyt
Egis, Cz.†; Egis, Rus.
⊗ Etacrynic acid (p.1283·1).
Oedema.

PannonPharma, Hung.
⊗ Sodium etacrynate (p.1283·2).
Oedema.

Ureina *Confar, Port.†.*
Parietaria officinalis.

Urekolin *Grunenthal, Chile†.*
Norfloxacin (p.309·2).
Bacterial urinary-tract infections.

Urelief Plus *Cypress, USA.*
Phenazopyridine hydrochloride (p.116·2); hyoscyamine hydrobromide (p.1736·1); secbutabarbital sodium (p.1027·2).
Lower urinary-tract disorders.

Urelium Neu *Europharm, Austria.*
Ammi visnaga fruit (p.2256·1); solidago virgaurea (p.2391·1); taraxacum (p.2395·1); aescin (p.2248·2).
Renal calculi.

Urelle *Pharmelle, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Urem *Mayrhofer, Austria†; Kade, Ger.*
Ibuprofen (p.64·2).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Uremide *Alphapharm, Austral.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema.

Uremol *Stiefel, Arg.; Trans Canaderm, Canad.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Uremol-HC *Trans Canaderm, Canad.*
⊗ Hydrocortisone acetate (p.1535·2); urea (p.1620·2).
Skin disorders.

Uren *Laboratorios Chile, Chile.*
⊗ Hydrochlorothiazide (p.1307·3); triamterene (p.1417·2).
Hypertension; oedema.

Ureotop *Dermapharm, Ger.*
⊗ Urea (p.1620·2).
Skin disorders.

Ureotop + VAS *Dermapharm, Ger.*
⊗ Urea (p.1620·2); tretinoin (p.1618·1).
Keratinisation disorders.

Urequin *Craveri, Arg.*
Oxybutynin (p.2190·3).
Bladder instability.

Uresan *Menarini, Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Uresix *Sanbe, Indon.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema.

Uretic *Merck, S.Afr.*
⊗ Furosemide (p.1292·1).
Hepatic cirrhosis; oedema.

Uretren Comp *Orion, Fin.*
⊗ Triamterene (p.1417·2); trichlormethiazide (p.1418·3).
Hypertension; oedema.

Uretron *Marin, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Urex
Note.This name is used for preparations of different composition.
Fawns & McAllan, Austral.; Fawns & McAllan, Hong Kong; Biosel, Turk.
⊗ Furosemide (p.1292·1).
Hypertension; oedema; oliguria; renal failure.

Vatring, USA.
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Urezol *Euromex, Mex.*
Phenazopyridine (p.116·3).
Urinary-tract disorders.

Urfadyn PL *Zambon, Belg.*
Nifurtoinol (p.307·3).
Urinary-tract infections.

Urfamycin
Zambon, Hong Kong; Sermmitr, Thai.; Zambon, Thai.
Thiamphenicol (p.351·1) or thiamphenicol glycinate hydrochloride (p.351·1).
Bacterial infections.

Zambon, Indon.; Zambon, Spain†; Bilim, Turk.
Thiamphenicol (p.351·1).
Bacterial infections.

Urfamycine
Zambon, Belg.
Thiamphenicol (p.351·1) or thiamphenicol glycinate hydrochloride (p.351·1).
Bacterial infections.

Zambon, Switz.
Thiamphenicol glycinate hydrochloride (p.351·1).
Bacterial infections.

Urfekol *Medikon, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Urgendol *Win-Medicare, India.*
Tramadol hydrochloride (p.130·3).
Pain.

Urgenin
Note.This name is used for preparations of different composition.
Thursday, Austral.†; Madaus, Austria; Madaus, Belg.; Madaus, Hong Kong; Madaus, Israel.
Echinacea purpurea (p.2298·1); saw palmetto (p.2192·3).
Benign prostatic hyperplasia; bladder instability; bladder irritability; prostatic disorders.

Madaus, Spain.
Echinacea angustifolia (p.2298·1); saw palmetto (p.2192·3); esculoside (p.2248·2).
Prostatic and urinary-tract disorders.

Urgenin Cucurbitae oleum *Madaus, Ger.*
Cucurbita seed oil (p.2290·2).
Benign prostatic hyperplasia; urinary-tract disorders.

Urginol *Panalab, Arg.*
Tolterodine tartrate (p.2198·1).
Bladder instability.

Urgis *Cetus, Arg.*
Ranitidine (p.1766·1).
Peptic ulcer.

Urgo *Urgo, Cz.*
Ibuprofen (p.64·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Urgo Activ Huhneraugenpflaster *Urgo, Ger.†.*
Salicylic acid (p.1612·2).
Calluses; corns.

Urgo Cor *Urgo, Pol.*
Salicylic acid (p.1612·2).
Calluses; corns.

Urgocall *Faes, Spain†.*
Salicylic acid (p.1612·2).
Calluses; corns.

Urgocor *Urgo, Cz.; Crefar, Port.*
Salicylic acid (p.1612·2).
Calluses; corns.

Urgofroid *Urgo, Fr.*
Butane isobutane propane; menthol (p.2340·1).
Peri-articular and soft-tissue disorders.

Urgomed *Urgo, Fr.*
Carmellose (p.2142·1).
Burns; wounds.

Urgosorb
Note.This name is used for preparations of different composition.
Urgo, Fr.
Calcium alginate (p.1058·1); carmellose (p.2142·1).
Ulcers; wounds.

Urgo, Ger.
Calcium alginate (p.1058·1).
Wounds.

Urgotul
Urgo, Fr.
Carmellose (p.2142·1).
Burns; ulcers; wounds.

Urgo, Ger.
Carmellose sodium (p.2142·1).
Burns; wounds.

Urgotul S.Ag
Note.This name is used for preparations of different composition.
Urgo, Fr.
Carmellose (p.2142·1); sulfadiazine silver (p.337·2).
Burns.

Urgo, Ger.
Sulfadiazine silver (p.337·2).
Burns.

Uriage *Saninter, Port.*
A range of emollients, moisturisers, and soap substitutes.

Uriage Crema Extrema *D & M, Chile.*
SPF 90: Titanium dioxide (p.1617·3); aluminium hydroxide (p.1706·2); octinoxate (p.1608·2); zinc oxide (p.1621·2).
Sunscreen.

Uriage Desodorante Tri-Actif *D & M, Chile.*
Aluminium chlorohydrate (p.1588·3); ethylhexylglycerin (p.1644·1); triethyl citrate (p.2404·1).
Hyperhidrosis.

Uriage Extreme *Saninter, Port.*
SPF 60: Cinnamate; titanium dioxide (p.1617·3).
Sunscreen.

Uriage IP 90 *Uriage, Fr.†.*
SPF 100: Octinoxate (p.1608·2); titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Uriage IP 60 Mineral *Uriage, Fr.†.*
SPF 100: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).

Uriage Protector Solar *D & M, Chile.*
SPF 60: Bisoctrizole (p.1591·2); octinoxate (p.1608·2); avobenzone (p.1589·3); octil triazone (p.1608·1).
Sunscreen.

Uriage Stick Levres *Uriage, Fr.†.*
SPF 35: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Uriage Stick Solaire Extreme *Uriage, Fr.†.*
SPF 90: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Uri-Alk *Medchem, S.Afr.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); anhydrous citric acid (p.2284·1).
Gastrointestinal hyperacidity; urinary alkalinisation.

Uribac *Precimex, Mex.†.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uriben *Rosemont, UK.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Uribenz *RAN, Ger.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Uribeta *Probiomed, Mex.*
Interferon beta-1b (p.891·2).
Multiple sclerosis.

Urica *Sandoz, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Uricad *Great Eastern, Thai.; Westmont, Thai.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Uricalm *Cipla, Austral.†.*
Sodium bicarbonate (p.1673·2); anhydrous sodium citrate (p.1673·2); anhydrous citric acid (p.2284·1); tartaric acid (p.2395·2).
Urinary alkalinisation.

Uricemil *Cristalia, Braz.†; Molteni, Ital.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

UriCheck 2 *Sekunjalo, S.Afr.*
Test for ketones and glucose in urine.

UriCheck 3 *Sekunjalo, S.Afr.*
Test for protein, blood, and glucose in urine.

UriCheck 5 *Sekunjalo, S.Afr.*
Test for protein, pH, blood, ketones, and glucose in urine.

UriCheck 9 *Sekunjalo, S.Afr.*
Test for leucocytes, nitrite, urobilinogen, protein, pH, blood, ketones, bilirubin, and glucose in urine.

UriCheck 10 *Sekunjalo, S.Afr.*
Test for leucocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose in urine.

UriCheck Glucose *Sekunjalo, S.Afr.*
Test for glucose in urine.

UriCheck 3L *Sekunjalo, S.Afr.*
Test for leucocytes, protein, blood, and glucose in urine.

UriCheck 4L *Sekunjalo, S.Afr.*
Test for leucocytes, nitrite, protein, blood, and glucose in urine.

UriCheck 5N *Sekunjalo, S.Afr.*
Test for nitrite, protein, pH, blood, ketones, and glucose in urine.

UriCheck 2S *Sekunjalo, S.Afr.*
Test for protein and glucose in urine.

Uricine *Millimed, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastro-duodenitis; peptic ulcer; postoperative nausea and vomiting; smooth muscle spasm.

Uricleanse *Douglas, Austral.†.*
Cranberry (p.2289·1).
Urinary-tract disorders.

Uriclin *Astellas, Neth.; Astellas, Port.*
Solifenacin succinate (p.2196·1).
Bladder hyperactivity.

Uricnol *Kimia, Indon.*
Allopurinol (p.552·2).
Gout; uric acid and calcium oxalate renal stones.

Uricodue *Benedetti, Ital.*
Allopurinol (p.552·2); benziodarone (p.555·3).
Hyperuricaemia.

Uricon *Altana Madaus, S.Afr.*
Trospium chloride (p.2198·3).
Bladder instability.

Uriconorme *Streuli, Switz.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Uricont *Rider, Chile.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; urinary incontinence.

Uricosal *Biotech, Austral.†.*
Citric acid monohydrate (p.2284·1); potassium citrate (p.1673·2).
Urinary alkalinisation.

Uricosyx *Syxyl, Ger.†.*
Homoeopathic preparation.

Uricovac *Sanofi Synthelabo, Austria.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia; psoriasis; psoriatic arthritis.

Uricozyme *Sanofi Synthelabo, Ital.†.*
Urate oxidase (p.560·2).
Hyperuricaemia.

Uricrim *Mediphar, Venez.*
⊗ Urea (p.1620·2).
Keratolytic.

Uridactone *Faran, Gr.†.*
⊗ Spironolactone (p.1400·1).
Heart failure; liver cirrhosis; malignant ascites; nephrotic syndrome; oedema; primary hyperaldosteronism.

Urideal *Dolisos, Fr.†.*
Pilosella.
Gastrointestinal disorders; renal disorders.

Uridon *Panalab, Arg.*
Cranberry (p.2289·1); ascorbic acid (p.1983·3).
Dietary supplement.

Uridon Modified *Rugby, USA†.*
Methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1); benzoic acid (p.1630·2); methylthioninium chloride (p.1450·3).
Urinary-tract infections.

Uridoz *Therabel, Fr.*
Fosfomycin trometamol (p.278·2).
Cystitis.

Uriduct *TAD, Ger.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia.

Urief *Daiichi, Jpn; Kissei, Jpn.*
Silodosin (p.2196·1).
Benign prostatic hyperplasia.

Uriflex C *SSL, UK.*
Chlorhexidine gluconate (p.1635·3).
Urinary catheter care.

Uriflex G *Coloplast, UK.*
Citric acid (p.2284·1); sodium bicarbonate (p.1673·2); light magnesium oxide (p.1744·1); disodium edetate (p.1463·3).
Urinary catheter care.

Uriflex R *Coloplast, UK.*
Citric acid (p.2284·1); light magnesium carbonate (p.1743·1); gluconolactone (p.2313·1); disodium edetate (p.1463·3).
Urinary catheter care.

Uriflex S *Coloplast, UK.*
Sodium chloride (p.1686·1).
Urinary catheter care.

Uriflex W *Coloplast, UK.*
Sterile pyrogen free water (p.2414·3).
Urinary catheter care.

Uri-Flor *AGIPS, Ital.*
Nalidixic acid (p.303·3).
Gram-negative bacterial infections of the urinary tract.

Urifron *Probiomed, Mex.*
Interferon alfa-2b (p.885·1).
Hepatitis B; hepatitis C; malignant neoplasms.

Urigon *Demo, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Urihexal *Hexal, S.Afr.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder; nocturnal enuresis.

Urikal *Rafa, Israel.*
Sodium citrate (p.1673·3); sodium bicarbonate (p.1673·2); citric acid (p.2284·1); sodium carbonate (p.2389·1).
Urinary-tract infections.

Uriken *Kener, Mex.†.*
Pipemidic acid (p.315·1).

Urikoliz *Ilsan, Turk.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Urilin *Faria, Braz.†.*
Oxolinic acid (p.312·2).
Urinary-tract infections.

Urimar-T *Marnel, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Urimax
Note.This name is used for preparations of different composition.
Bros, Gr.†.
Ofloxacin (p.310·2).
Bacterial infections.

Cipla, India.
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Xanodyne, USA.
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Lower urinary-tract disorders.

Urimax F *Cipla, India.*
⊗ Tamsulosin hydrochloride (p.2197·1); finasteride (p.2188·3).
Benign prostatic hyperplasia.

Urimet *Roemmers-Klinos, Venez.†.*
SPF 15: ⊗ Urea (p.1620·2); sunscreen.
Emollient; sunscreen.

Urinase *Eagle, Austral.†.*
Saw palmetto (p.2192·3); echinacea (p.2298·1); maize (p.2288·1); buchu (p.2269·3); hydrastis (p.2321·3); sassafras (p.2383·3); bearberry (p.2263·3); minerals.
Prostatitis; urinary bladder disorders.

Urinefrol *Lafage, Arg.†.*
Sarsaparilla (p.2383·3); liquorice (p.1740·3).

Urineg *Armoxindo, Indon.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Urinex *Kern, Switz.*
Birch leaf (p.2266·3); buchu (p.2269·3); barbiflore; bearberry (p.2263·3); haricot bean; equisetum (p.2299·3); solidago virgaurea (p.2391·1); meadowsweet (p.2338·1); calamus (p.2271·3); calendula (p.2273·1).
Urinary-tract disorders.

Urinol *Lennon, S.Afr.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Urinorm *Torii, Jpn; OTL, Spain.*
Benzbromarone (p.555·2).
Gout; hyperuricaemia.

Urinox *Charoen Bhaesaj, Malaysia; Charoen, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Urinter *Interbat, Indon.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Urion *Altana, Austria†; Zambon, Fr.; Altana, Ger.; Sanofi-Aventis, Neth.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Uripax *YSP, Malaysia.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Uripiser *Serral, Mex.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uri-Plus Rubia L3 *Homeocan, Canad.†.*
Homoeopathic preparation.

Uriprim *Bial, Port.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Uripurinol *Azupharma, Ger.†.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Urirex-K *Aspen, S.Afr.*
⊗ Hydrochlorothiazide (p.1307·3); potassium chloride (p.1684·3).
Hypertension; oedema.

Urisalic *Mediphar, Venez.†.*
⊗ Betamethasone (p.1518·2); salicylic acid (p.1612·2); urea (p.1620·2).
Skin disorders.

Urisan *Tedec Meiji, Spain.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uriscreen *Medical Industries, Austral.†.*
Test for bacteriuria, haematuria, and pyuria.

Urisec *Odan, Canad.*
⊗ Urea (p.1620·2).
Dry skin conditions.

Urised *PolyMedica, USA.*
Methenamine (p.298·3); salol (p.122·1); methylthioninium chloride (p.1450·3); benzoic acid (p.1630·2); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1).
Lower urinary-tract infection or spasm.

Urisedon *Unipharma, Gr.†.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Urisept NF *Schering-Plough, Arg.*
Co-trimoxazole (p.258·1).
Formerly contained co-trimoxazole and phenazopyridine hydrochloride.
Bacterial infections; pneumocystis pneumonia.

Uriseptic *SDA, USA.*
Methenamine (p.298·3); salol (p.122·1); methylthioninium chloride (p.1450·3); benzoic acid (p.1630·2); atropine sulfate (p.1219·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Uriseptin *Mulda, Turk.*
Nitrofurantoin (p.308·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Urisoda *Omni-Protech, India.*
Sodium bicarbonate (p.1673·2); tartaric acid (p.2395·2); citric acid (p.2284·1).
Urinary alkalinisation.

Urisol *Stadmed, India.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Urisor *Soria Natural, Spain†.*
Bearberry (p.2263·3); calluna vulgaris; java tea (p.2328·2).
Urinary-tract infections.

Urispadol *Abigo, Denm.*
Flavoxate hydrochloride (p.2190·1).
Neurogenic bladder.

Urispas *Altana, Austria; Altana, Belg.; Paladin, Canad.†; Recordati, Cz.†; Negma, Fr.; Shire, Hong Kong; Bushnell, India; Shire, Irl.; Shire, Malaysia; Altana, Neth.; Jaba Recordati, Port.; Pharmacia, S.Afr.; Shire, Singapore; Robapharm, Switz.; Fako, Turk.; Shire, UK; SmithKline Beecham, USA.*
Flavoxate hydrochloride (p.2190·1).
Bladder disorders; female genital-tract spasm; urinary-tract disorders; urinary-tract spasm.

Uristix *Bayer, Austral.; Bayer Diagnostics, Irl.; Bayer Diagnostics, UK; Bayer, USA.*
Test for glucose and protein in urine.

Uristix 4 *Bayer, USA.*
Test for glucose, protein, nitrite, and leucocytes in urine.

UriSym *Vindex, USA†.*
Methenamine (p.298·3); salol (p.122·1); monobasic sodium phosphate (p.1682·3); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract disorders.

Uritab *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Allopurinol (p.552·2).
Hyperuricaemia.

Uritact *Cypress, USA.*
Hyoscyamine sulfate (p.1736·1); methenamine (p.298·3); salol (p.122·1); atropine sulfate (p.1219·3); methylthioninium chloride (p.1450·3); benzoic acid (p.1630·2).
Lower urinary-tract disorders.

Uritest *Bayer Diagnostics, Fr.*
Test for glucose, protein, nitrite, and leucocytes in urine.

Uritest 2 *Bayer Diagnostics, Fr.; Bayer Diagnostici, Ital.*
Test for leucocytes and nitrites in urine.

Uritos *Kyorin, Jpn.*
Imidafenacin (p.2190·2).
Bladder hyperactivity.

Uritracin *BioFemme, Philipp.; Great Eastern, Thai.; United American, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Uritrat *Libbs, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Urixin *Abbott, Indon.; Abbott, Malaysia†; Abbott, Philipp.*
Pipemidic acid (p.315·1).
Bacterial infections.

Urizine *Unison, Singapore†; Unison, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vertigo; vestibular disorders.

Urizone *Adcock Ingram, S.Afr.*
Fosfomycin trometamol (p.278·2).
Urinary-tract Escherichia coli infections.

Urlix *Precimex, Mex.†.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Uro Angiografin *Schering, Spain.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Uro Blue *McNeil, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Uroalquine *Rider, Chile.*
Sodium citrate (p.1673·3); potassium citrate (p.1673·2); anhydrous citric acid (p.2284·1).
Acidosis; gout; renal calculi.

Urobacid *Tyrol, Austria†; Sandoz, Gr.; Sandoz, Malaysia; Sandoz, Philipp.; Biochemie, Singapore†.*
Norfloxacin (p.309·2).
Bacterial infections.

Urobactam *Bristol-Myers, Spain†.*
Aztreonam (p.209·2).
Bacterial infections.

Uro-Bactrim *Roche, Arg.†.*
Co-trimoxazole (p.258·1); phenazopyridine (p.116·3).
Urinary-tract infections.

Uro-Baxapril *Brasmedica, Braz.†.*
Co-trimoxazole (p.258·1); phenazopyridine (p.116·3).
Urinary-tract infections.

Urobine *Eschol, Singapore†.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Urobiotic *Hexal, Braz.†.*
Phenazopyridine hydrochloride (p.116·2); ampicillin (p.204·1).
Urinary-tract infections.

Urobiotic-250 *Pfizer, USA.*
Oxytetracycline hydrochloride (p.312·3); sulfamethizole (p.339·3); phenazopyridine hydrochloride (p.116·2).
Genito-urinary infections.

Uroc *Lampugnani, Ital.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Urocalun *Shinyaku, Hong Kong; Shinyaku, Jpn; Shinyaku, Singapore.*
Quercus salicina (p.2355·3).
Renal calculi.

Urocarb *Hamilton, Austral.*
Bethanechol chloride (p.2265·3).
Neurogenic bladder; urinary retention.

Urocard *Stada, Austria.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Uro-Cephoral *Merck, Ger.*
Cefixime (p.224·3).
Bacterial infections.

Urochinasi *IFET (ΙΦΕΤ), Gr.*
Urokinase (p.1420·1).
Thromboembolic disorders.

Urocid-K *Aymed, Turk.*
Potassium citrate (p.1673·2).
Hyperchloraemic acidosis.

UroCiproxin *Bayer, Turk.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Urocit-K *Orphan, Austral.; Mission Pharmacal, Hong Kong; Mission Pharmacal, Malaysia; Mission Pharmacal, Singapore†; Mission Pharmacal, USA.*
Potassium citrate (p.1673·2).
Renal calculi; urinary alkalinising agent.

Uroclar *Eurodrug, Philipp.*
Rufloxacin hydrochloride (p.331·3).
Urinary-tract infections.

Uroclasio NF *Italmex, Mex.*
Potassium citrate (p.1673·2); citric acid (p.2284·1).
Renal calculi; urinary alkalinisation.

Uroctal *Almirall, Hong Kong; Almirall, Spain.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Uroctrin *Legrand, Braz.*
Co-trimoxazole (p.258·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Urodene *OFF, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Urodie *Keryos, Ital.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Urodil phyto *Selz, Ger.†.*
Birch leaf (p.2266·3); solidago virgaurea (p.2391·1); java tea (p.2328·2).
Urinary-tract disorders.

Urodin *Streuli, Switz.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Urodixin *Santa, Gr.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Urodonal *Farmabraz, Braz.†.*
Theobromine (p.1140·1); methenamine (p.298·3).
Hyperuricaemia.

Urofen *Teuto, Braz.†.*
Sulfamethoxypyridazine (p.342·1); nitrofurantoin (p.308·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Urofin *Mertens, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Uroflo *Abbott, Austria.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Uroflox
Note. This name is used for preparations of different composition.
Farmion, Braz.†; Bialfar, Port.
Norfloxacin (p.309·2).
Bacterial infections.

Armstrong, Mex.; Eurodrug, Thai.
Rufloxacin hydrochloride (p.331·3).
Bacterial infections.

Urofort *Leki Natury, Pol.*
Bearberry (p.2263·3); solidago (p.2391·1); urtica (p.2409·3).
Urinary-tract disorders.

Urofos *Panalab, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Urofossat *Dreluso, Ger.*
Homoeopathic preparation.

Urogem *Prodotti, Braz.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Urogesic *Atlantic, Singapore; Edwards, USA.*
Phenazopyridine hydrochloride (p.116·2).
Irritation of the lower urinary tract; urinary-tract disorders.

Urogesic Blue *Edwards, USA.*
Methenamine (p.298·3); monobasic sodium phosphate (p.1682·3); salol (p.122·1); methylthioninium chloride (p.1450·3); hyoscyamine sulfate (p.1736·1).
Urinary-tract infections.

Urogetix *Ifars, Indon.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract pain.

Urogliss *Montavit, Neth.*
Chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Catheterisation.

Urogliss-S *Montavit, Neth.*
Chlorhexidine hydrochloride (p.1635·3).
Catheterisation.

Urogotan A *Silesia, Chile.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Urografin
Bayer, Austral.; Schering, Austria†; Schering, Denm.; German Remedies, India; Schering, Israel†; Bayer, NZ; Schering, Neth.; Schering, S.Afr.; Schering, Spain; Schering, Swed.; Schering, Switz.†.
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Schering, Cz.†.
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urografin 150 and 370 *Bayer, UK.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urografin Meglumin *Schering, Denm.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urografina *Schering, Arg.; Schering, Braz.; Bayer, Port.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urografine *Schering, Belg.†.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urographin *Schering, Rus.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urogutt *Farmasa, Mex.; Pharmalink, Thai.; Schwabe, Thai.*
Saw palmetto (p.2192·3).
Benign prostatic hyperplasia.

Uro-Hytrin *Abbott, Belg.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Urokatt *Kattwiga, Ger.*
Homoeopathic preparation.

Urokit *Casasco, Arg.*
Potassium citrate (p.1673·2).
Renal calculi.

Uroknop *Knop, Chile.*
Lithium carbonicum; colchicum; methenamine (p.298·3); tartaric acid (p.2395·2).
Gout; hyperuricaemia.

Uro-KP-Neutral *Star, USA.*
Mineral preparation (p.1922·1).
Phosphorus supplement.

Urol *Apogepha, Ger.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Urol methin *Apogepha, Ger.*
Methionine (p.1450·1).
Urinary acidification in antibiotic therapy.

Urol pros *Apogepha, Ger.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Urolene Blue *Star, USA.*
Methylthioninium chloride (p.1450·3).
Cyanide poisoning; cystitis: urethritis; drug-induced methaemoglobinaemia.

Urolin *Polfa Grodzisk, Pol.*
Pipemidic acid (p.315·1).
Bacterial infections of the urinary tract.

Uro-Linfol *Omega, Arg.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

uro-loges *Loges, Ger.*
Homoeopathic preparation.
Formerly known as uro-L 90 N.

Urologicka Cajova Smes *Megafyt-R, Cz.*
Birch leaf (p.2266·3); bearberry (p.2263·3); peppermint leaf (p.1761·2); ononis (p.2357·1); parsley (p.2363·2); herniaria (p.2319·1).
Urinary-tract disorders.

Urologicum-Echtroplex *Weber & Weber, Ger.†.*
Homoeopathic preparation.

Urologin *Delta, Braz.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract disorders.

Urolosin *Boehringer Ingelheim, Spain.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Urolux *Sanochemia, Ger.*
Meglumine amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urolux Retro *Sanochemia, Ger.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for urinary-tract radiography.

Uro-Mag *Blaine, USA.*
Magnesium oxide (p.1744·1).
Hyperacidity; magnesium deficiency.

Uromed *Cimed, Braz.*
Bearberry (p.2263·3).

Uromes *Sanfer, Mex.*
Mesna (p.1449·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Uromethin *Apogepha, Ger.†.*
Methionine (p.1450·1).
Phosphate calculi; urinary acidification.

Uro-Micinovo *Bago, Chile.*
Co-trimoxazole (p.258·1); phenazopyridine (p.116·3).
Urinary-tract infections.

Uromil *IPRAD, Fr.*
Bearberry (p.2263·3); green tea (p.2416·1).
Urinary-tract disorders.

Uromiro *Gerot, Austria; Bracco, Switz.†.*
Meglumine iodamide (p.1481·3).
Radiographic contrast medium.

Uromiro 24%, 36%, and 300 *Bracco, Ital.†.*
Meglumine iodamide (p.1481·3).
Radiographic contrast medium.

Uromiro 340 and 420 *Bracco, Ital.†.*
Meglumine iodamide (p.1481·3); sodium iodamide (p.1482·1).
Radiographic contrast medium.

Uromiro 300 Sodico *Bracco, Ital.†.*
Sodium iodamide (p.1482·1).
Radiographic contrast medium.

Uromiron *Schering, Venez.*
Meglumine iodamide (p.1481·3).
Radiographic contrast medium.

Uromitexan *Sandoz, Arg.†; Baxter, Austral.; Baxter, Austria; Baxter, Belg.; Baxter, Canad.; Baxter, Chile; Baxter, Cz.; Baxter, Denm.; Baxter, Fin.; Baxter Oncology, Fr.; Baxter Oncology, Ger.; Baxter, Gr.; Baxter, Hong Kong; Baxter, Hung.; German Remedies, India; Baxter, Indon.; Asta Medica, Irl.; Baxter, Ital.; Shionogi, Jpn; Baxter Oncology, Malaysia†; Baxter, Mex.†; Baxter, NZ; Baxter, Neth.; Baxter Oncology, Norw.; Baxter, Philipp.; Baxter Oncology, Pol.; Baxter, Port.; Aventis, S.Afr.; Baxter Oncology, Singapore; Prasfarma, Spain; Baxter, Swed.; Baxter, Switz.; Baxter, Thai.; Eczacibasi-Baxter, Turk.; Baxter Oncology, UK†.*
Mesna (p.1449·2).
Now known as Mesna in the *UK*.
Reduction of oxazaphosphorine urotoxicity.

Uromix *Agropharm, Pol.*
Betula; orthosiphon aristatus; solidago (p.2391·1).
Gout; rheumatism; skin disorders; urinary-tract disorders.

Uromont *Montavit, Austria.*
⊗ Dexamethasone (p.1526·1); chlorhexidine hydrochloride (p.1635·3); lidocaine hydrochloride (p.1862·3).
Stricture prevention following transurethral procedures.

Uro-Munal *Medice, Ger.†.*
Escherichia coli.
Urinary-tract infections.

Uromunal *Leti, Venez.*
Escherichia coli.
Immunostimulant.

Uromykol *Maxmedic, Ger.*
Clotrimazole (p.530·1).
Fungal skin infections.

Uron *Aksu, Turk.*
Methenamine anhydromethylenecitrate (p.299·1).
Urinary-tract infections.

Uronalin *Vitae, Mex.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Uronase *Mochida, Jpn.*
Urokinase (p.1420·1).
Myocardial infarction.

Uro-Nebacetin N *Altana, Ger.*
Neomycin sulfate (p.305·1).
Urinary-tract infections.

Uronefrex *Robert, Spain.*
Acetohydroxamic acid (p.2245·1).
Renal calculi due to bacterial urease.

Uronid *Euro Registratie, Neth.; Recordati, Spain.*
Flavoxate hydrochloride (p.2190·1).
Bladder instability; urinary-tract disorders.

Uronor *Abbott, Ger.†.*
Potassium citrate (p.1673·2); potassium bicarbonate (p.1673·1); anhydrous citric acid (p.2284·1).
Renal calculi.

Uronorm *Wassermann, Ital.†.*
Cinoxacin (p.243·2).
Urinary-tract infections.

Uronovag
Note. This name is used for preparations of different composition.
Gobbi, Arg.
Norfloxacin (p.309·2).
Bacterial infections.

Novag, Mex.
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uropac *EMS, Braz.*
Sulfamethoxypyridazine (p.342·1); nitrofurantoin (p.308·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Uropan *Kocak, Turk.*
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; nocturnal enuresis.

Urophytum *Arkomedika, Fr.†.*
Buchu (p.2269·3); bearberry (p.2263·3).
Urinary-tract disorders.

Uropielon *Legrand, Braz.*
Ampicillin (p.204·1); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Uropimid *CT, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uropimide *Rider, Chile.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uropipedil *Viamedica, Spain.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uropipemid *AF, Mex.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Uroplant *Biomo, Ger.†.*
Solidago virgaurea (p.2391·1).
Urinary-tract disorders.

Uroplex *Sintofarma, Braz.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Uropol *IMA, Braz.*
Co-trimoxazole (p.258·1).
Formerly contained co-trimoxazole and phenazopyridine.
Urinary-tract infections.

Uropol-S *Pohl, Ger.*
Chondroitin sulfate sodium (p.2280·3).
Interstitial cystitis.

Uro-POS *Croma, Austria; Ursapharm, Ger.*
Urtica (p.2409·3).
Micturition disorders in males; prostatic hyperplasia.

Uro-Pract *Ebewe, Austria†.*
Sodium chloride (p.1686·1).
Bladder irrigation; maintenance of bladder catheters.

Uroprost *Hasco-Lek, Pol.*
Arnica (p.2260·2); shepherd's purse (p.2386·2); St John's wort (p.422·3); solidago (p.2391·1); valerian (p.2410·1); rapeseed.
Benign prostatic hyperplasia.

Uroprot *Laboratorios Chile, Chile; Lemery, Mex.*
Mesna (p.1449·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Uropurat *Kwizda, Austria.*
Bearberry (p.2263·3); herniaria (p.2319·1); equisetum (p.2299·3); ononis (p.2357·1).
Urinary-tract disorders.

Uropyrine *Sterop, Belg.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract disorders.

Uroquidan *UCB, Spain.*
Urokinase (p.1420·1).
Intra-ocular haemorrhage; thromboembolic disorders.

Urorenal *Schwabe, Ger.†.*
Birch leaf (p.2266·3).
Urinary-tract disorders.

Urosal *Vis, Pol.*
Methenamine (p.298·3); salol (p.122·1).
Biliary-tract disorders; gastrointestinal disorders; urinary-tract disorders.

Urosan *AGIPS, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Urosedac *Eurolab, Arg.*
Cranberry (p.2289·1); vitamin C (p.1983·3).
Vitamin C supplement.

Uroselect *Dreluso, Ger.*
Homoeopathic preparation.

Urosept *Herbapol Poznan, Pol.*
Birch (p.2266·3); chamomile (p.2279·3); petroselinum sativum; phaseolus vulgaris; cranberry (p.2289·1); potassium citrate (p.1673·2); sodium citrate (p.1673·3).
Urinary-tract disorders.

Uroseptal *Bago, Arg.; Bago, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Uroseptol *Fresenius Kabi, Ger.†.*
Ethacridine lactate (p.1625·1).
Urinary-tract infections.

Urosetic *Finmedical, Ital.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Urosin
Note. This name is used for preparations of different composition.
Roche, Austria.
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

YSP, Malaysia.
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Yeni, Turk.
Ofloxacin (p.310·2).
Bacterial infections.

Urosiphon *Pierre Fabre Sante, Fr.*
Java tea (p.2328·2).
Diuretic; slimming aid.

Urospasmon *Heumann, Ger.†.*
Nitrofurantoin (p.308·1); sulfadiazine (p.336·2); phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Urospasmon sine *Heumann, Ger.†.*
Nitrofurantoin (p.308·1); sulfadiazine (p.336·2).
Urinary-tract infections.

Urospes-N *Specifar (Σπεσιφαρ), Gr.*
Norfloxacin (p.309·2).
Bacterial infections.

Urostad *Stada, Cz.; Stada, Hung.; Stada, Pol.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Uro-Stilloson *Farco, Ger.†.*
⊗ Dexamethasone (p.1526·1); lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Urinary-tract disorders.

Urostix *Bayer, India.*
Test for glucose and protein in urine.

Uro-Tablinen *Winthrop, Ger.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Uro-Tainer
Note. This name is used for preparations of different composition.
Braun, Belg.†.
Chlorhexidine acetate (p.1635·2).
Urinary catheter care; urinary-bladder lavage.

Isramedcom, Israel†.
Sodium chloride (p.1686·1).
Maintenance of indwelling urinary catheters.

Uro-Tainer M *Braun, UK.*
Sodium chloride (p.1686·1).
Vehicle for intravesical administration of drugs.

Uro-Tainer Solution R *Braun, UK.*
Citric acid (p.2284·1); gluconolactone (p.2313·1); light magnesium carbonate (p.1743·1).
Urinary catheter care.

Uro-Tainer Suby G *Braun, UK.*
Citric acid (p.2284·1); light magnesium oxide (p.1744·1); sodium bicarbonate (p.1673·2).
Urinary catheter care.

Uro-Tarivid *Aventis, Ger.; Aventis, Israel.*
Ofloxacin (p.310·2).
Bacterial infections.

Urotem *Temis, Arg.*
Norfloxacin (p.309·2).
Bacterial infections of the urinary tract.

Urotem Dol *Temis, Arg.*
10 Tablets, norfloxacin (p.309·2); 10 tablets, phenazopyridine (p.116·3).
Bacterial infections of the urinary tract.

Uroton *Biovena, Pol.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder.

Urotone *Samarth, India.*
Bethanechol chloride (p.2265·3).
Neurogenic bladder; urinary retention.

Urotonine *VHB, India†.*
Bethanechol chloride (p.2265·3).
Neurogenic bladder; urinary retention.

Urototal *Fortbenton, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Urotractan *Klinge, Ger.*
Methenamine hippurate (p.298·3).
Urinary-tract infections.

Urotractin *Eurodrug, Hong Kong; Sanbe, Indon.; Zambeletti, Indon.; Teofarma, Ital.; Eurodrug, Malaysia†; Eurodrug, Singapore; Eurodrug, Thai.*
Pipemidic acid (p.315·1).
Genito-urinary-tract infections.

Urotricef *Merck, Chile.*
Cefixime (p.224·3).
Bacterial infections.

Urotril *Hexal, Braz.†.*
Phenazopyridine hydrochloride (p.116·2).
Urinary-tract infections.

Urotrim *Medana, Pol.*
Trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

Urotrol *Almirall, Spain.*
Tolterodine tartrate (p.2198·1).
Bladder instability.

Uro-Vaxom *Altana, Austria; Solvay, Belg.; OM, Cz.; Sanofi Synthelabo, Ger.; Gap, Gr.; Grunenthal, Mex.; OM, Philipp.; Pharmalink, Philipp.; OM, Pol.; OM, Port.; OM, Rus.; OM, Switz.*
Escherichia coli.
Bacterial infections of the urinary tract.

Urovec *Collins, Mex.*
Phenazopyridine (p.116·3); sulfafurazole (p.338·3); tetracycline (p.347·1).
Urinary-tract infections.

Urovison *Schering, Ger.†; Schering, Neth.†.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Radiographic contrast medium.

Urovisona *Schering, Arg.*
Meglumine amidotrizoate (p.1475·3); sodium amidotrizoate (p.1475·3).
Contrast medium for urography.

Uroxacin
Note. This name is used for preparations of different composition.
Lazar, Arg.
Norfloxacin (p.309·2).
Bacterial infections of the genito-urinary tract.

Malesci, Ital.†.
Cinoxacin (p.243·2).
Urinary-tract infections.

Uroxal
Note. This name is used for preparations of different composition.
Fournier, Cz.; Fournier, Hung.
Oxybutynin hydrochloride (p.2190·3).
Bladder instability; nocturnal enuresis; urge incontinence; urinary incontinence.

Sandoz, Indon.
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Uroxate *General Drugs, Thai.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

UroXatral *Sanofi Synthelabo, Arg.; Sanofi-Aventis, Chile; Sanofi Synthelabo, Ger.; Fisher, Neth.; Sanofi Synthelabo, USA.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Uroxazol-N *Bunker, Braz.*
Norfloxacin (p.309·2).
Bacterial infections.

Uroxin
Note. This name is used for preparations of different composition.
Unison, Hong Kong; Unison, Singapore.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Unison, Thai.
Ciprofloxacin (p.243·3).
Bacterial infections.

Julphar, UAE.
Norfloxacin (p.309·2).
Bacterial infections.

Uroxina *Farmalab, Braz.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Urpem *Zwitter, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Ursacol *Zambon, Braz.; Zambon, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursa-Fenol *Farmex, Gr.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Ursa-Fin *Farmex, Gr.*
⊗ Tetryzoline (p.1574·1).
Eye inflammation.

Ursidesox *Duncan, Arg.*
Ursodeoxycholic acid (p.2408·1).
Renal calculi.

Ursilon *IBI, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursinus Inlay-Tabs *Novartis, USA.*
Pseudoephedrine hydrochloride (p.1571·2); aspirin (p.20·3).
Upper respiratory-tract symptoms.

Urso *Axcan, Canad.; Heumann, Ger.†; Mitsubishi, Jpn; Axcan, USA.*
Ursodeoxycholic acid (p.2408·1).
Cholestatic liver disorders; cholesterol gallstones; liver disorders; primary biliary cirrhosis.

Urso Mix *Stada, Ger.†.*
Chenodeoxycholic acid (p.2280·1); ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones.

Ursobil *ABC, Ital.*
Ursodeoxycholic acid (p.2408·1) or sodium sulfate ursodeoxycholate.
Biliary-tract disorders.

Ursobilane *Estedi, Spain.*
Ursodeoxycholic acid (p.2408·1).
Gallstones.

Ursocam *Polfarmex, Pol.*
Ursodeoxycholic acid (p.2408·1).
Gallstones; hepatobiliary cirrhosis.

Ursochol *Zambon, Belg.; Zambon, Cz.; Zambon, Ger.; Zambon, Neth.; Zambon, Spain; Zambon, Switz.*
Ursodeoxycholic acid (p.2408·1).
Biliary dyspepsia; cholesterol gallstones; dyspepsia; gallstones; hepatopathy with cholestasis; primary biliary cirrhosis.

Ursodamor *Damor, Ital.*
Sodium succinate ursodeoxycholate (p.2408·2).
Biliary-tract disorders.

Ursodexil *EG, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursodiol *Bioprogress, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursofalk *Orphan, Austral.; Merck, Austria; Codali, Belg.; Biotoscana, Chile; Falk, Cz.; Falk, Ger.; Galenica, Gr.; Falk, Hong Kong; Falk, Hung.; Falk, Irl.; Rafa, Israel; Abbott, Ital.†; Falk, Malaysia; Farmasa, Mex.; St Ives, NZ; Tramedico, Neth.; Falk, Norw.; Falk, Philipp.; Pharmalink, Philipp.; Falk, Pol.; Falk, Port.; Falk, Singapore; Meda, Swed.; Vifor, Switz.; Falk, Thai.; Ali, Turk.; Provalis, UK.*
Ursodeoxycholic acid (p.2408·1).
Biliary obstruction; cholestatic liver disorders; cholesterol gallstones; dyspepsia; gastric reflux; gastritis; hepatitis; primary biliary cirrhosis; sclerosing cholangitis.

Ursoflor *SoSe, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursogal *Galen, UK.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones.

Ursolac *Biomedica, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursolin *Berlin Pharm, Thai.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; dyspepsia; liver disorders.

Ursolisin *Magis, Ital.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursolit *CTI, Israel.*
Ursodeoxycholic acid (p.2408·1).
Gallstones; liver disorders.

Ursolvan *Sanofi-Aventis, Fr.*
Ursodeoxycholic acid (p.2408·1).
Cholestasis; cholesterol gallstones.

Ursomax *Altius, Arg.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; cholesterol gallstones.

Ursopol *ICN, Pol.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones; hepatobiliary cirrhosis.

Ursoproge *Proge, Ital.†.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders.

Ursosan *ProMed, Cz.; Mitsubishi-Tokyo, Hong Kong; Mitsubishi, Jpn†; Pro.Med, Rus.*
Ursodeoxycholic acid (p.2408·1).
Biliary-tract disorders; cholesterol gallstones; liver disorders.

Ursotan *Aventis, S.Afr.†.*
Ursodeoxycholic acid (p.2408·1).
Cholesterol gallstones.

Urticalcin *Bioforce, Ger.†; Bioforce, Switz.*
Homoeopathic preparation.

Urticaprostat uno *Azupharma, Ger.†.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Urtigen *Sons, Mex.*
Astemizole (p.567·2).
Hypersensitivity.

Urtikalma *Fecofar, Arg.*
Calamine (p.1591·2); diphenhydramine hydrochloride (p.577·2).
Pruritus.

Urtipret *Bionorica, Ger.†.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Urtivac *Darrow, Braz.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Urtivit *Ruhrpharm, Ger.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Urtix *Labofarm, Pol.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Urtotre *Lafare, Ital.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Urupan *Merckle, Ger.†.*
Dexpanthenol (p.2362·1).
Wounds.

Urzac *Quesada, Arg.*
Ursodeoxycholic acid (p.2408·1).
Gallstones.

Usaltron *Maver, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Usamema *Icon, Philipp.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; uterine bleeding.

Usana AO Pro *Usana, Mex.*
Multivitamin preparation (p.1922·1).

Usana Min *Usana, Mex.*
Mineral preparation (p.1922·1).

Usanatal *Icon, Philipp.*
Vitamin and mineral preparation with ferrous fumarate and folic acid (p.1922·1).
Nutritional supplement for pregnancy and lactation.

Usanimals
Usana, Hong Kong†.
Multivitamin and mineral preparation with hesperidin (p.1922·1).

Usana, Mex.
Vitamin and mineral preparation (p.1922·1).

Usana, Singapore.
Vitamins; minerals; polynutrients (p.1922·1).

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Usar Fibras *Phoenix, Arg.†.*
Liquid paraffin (p.2030·3); cellulose (p.2143·1); agar (p.2140·3).
Constipation.

Usedent *Neckerman, Braz.†.*
Procaine (p.1869·2); phenol (p.1656·1); menthol (p.2340·1).
Local anaesthesia.

Usix *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
⊗ Furosemide (p.1292·1).
Ascites; hypertension; oedema.

Uskan *Desitin, Ger.*
Oxazepam (p.1014·2).
Anxiety; sleep disorders.

Usneabasan *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Usnicon *Eczane, Arg.†.*
Benzalkonium chloride (p.1629·1).
Disinfection.

U-Spa *Sriprasit, Thai.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Ustilakehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Ustimon *Sigmapharm, Austria.*
Hexobendine hydrochloride (p.1305·2).
Cardiac disorders.

Ustiosan *Kelemata, Ital.*
Procaine hydrochloride (p.1869·1); lidocaine hydrochloride (p.1862·3); hydroxyquinoline sulfate (p.2323·1).
Minor wounds and burns; skin irritation.

Usualix *Phoenix, Arg.*
⊗ Ephedrine hydrochloride (p.1558·2); phenazone (p.116·1).
Allergic conjunctivitis; eye irritation.

UT 380 *CCD, Fr.; Amnol, Ital.*
Copper-wound plastic (p.1935·2).
Intra-uterine contraceptive device.

Utabon *Uriach, Singapore; Uriach, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Utac *Millimed, Thai.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Utahzone *Daewon, Hong Kong.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Utalk *Kurtsan, Turk.*
Undecenoic acid (p.549·2); zinc undecenoate (p.549·3).
Fungal skin infections.

Utefos *Prasfarma, Spain.*
Tegafur (p.776·1).
Malignant neoplasms.

Utel *Farmex, Gr.*
Loratadine (p.583·3).
Allergic disorders.

Uteplex *Biodim, Fr.*
Trisodium uridine triphosphate (p.2408·1).
Musculoskeletal disorders.

Utergin *Svizera, India.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage; puerperal sepsis; uterine bleeding; uterine subinvolution.

Uterine *Omega, Arg.*
Isoxsuprine hydrochloride (p.2327·3).
Premature labour; threatened miscarriage.

Uterjin *Biofarma, Turk.*
Methylergometrine maleate (p.2011·1).
Postpartum haemorrhage.

Uterone *Jagson, India.*
Progesterone (p.2125·1).
Assisted conception; dysfunctional uterine bleeding; premenstrual syndrome; puerperal depression; recurrent miscarriage.

Utiblack *Rafarm, Gr.*
Lidocaine (p.1862·3).
Mouth disorders.

Uticina *SoSe, Ital.*
Norfloxacin (p.309·2).
Bacterial urinary-tract infections.

Uticox *Yer, Spain.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Utidol *Diba, Mex.*
Dipyrone (p.49·2).
Fever; pain.

Utiflox *Blue Sky, Philipp.*
Norfloxacin (p.309·2).
Bacterial infections.

Utilin *Sanum-Kehlbeck, Ger.*
Bacillus subtilis.
Immunotherapy.

Utilin H *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Utilin N *Sanum-Kehlbeck, Ger.†.*
Bacillus subtilis.
Gout; musculoskeletal and joint disorders; skin disorders.

Utilin S *Sanum-Kehlbeck, Ger.*
Mycobacterium phlei.
Immunotherapy.

Utin *Cipla-Medpro, S.Afr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Utinor *Neopharmed, Ital.; Unison, Philipp.; MSD, UK.*
Norfloxacin (p.309·2).
Bacterial infections.

Utira *Hawthorn, USA.*
Hyoscyamine sulfate (p.1736·1); methylthioninium chloride (p.1450·3); monobasic sodium phosphate (p.1682·3); methenamine (p.298·3); salol (p.122·1).
Urinary-tract pain and irritation.

Utisept *ST, Thai.*
Trimethoprim (p.355·2).
Urinary-tract infections.

utk *TAD, Ger.*
Urtica (p.2409·3).
Benign prostatic hyperplasia.

Utoin *Umeda, Thai.*
Phenytoin sodium (p.495·2).
Arrhythmias; epilepsy; seizures following neurosurgery; status epilepticus.

Utolid *Utopian, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Utolincomycin *Utopian, Thai.*
Lincomycin hydrochloride (p.293·2).
Gram-positive bacterial infections.

Utoral *BPL-Meizler, Braz.†; Korea United, Philipp.*
Fluorouracil (p.722·2).
Malignant neoplasms.

Utovlan *Pharmacia, UK.*
Norethisterone (p.2119·3).
Breast cancer; endometriosis; menstrual disorders.

Utrex *Sandoz, Indon.*
Pipemidic acid (p.315·1).
Urinary-tract infections.

Utrogest *Besins, Ger.; Kade, Ger.*
Progesterone (p.2125·1).
Menopausal disorders.

Utrogestan *Pfizer, Arg.; Viatris, Austria; Besins, Belg.; Farmoquimica, Braz.; Besins, Cz.; Besins, Fr.; Faran, Gr.; Besins, Hong Kong; Besins, Hung.; Sanofi-Aventis, Irl.; Besins International, Israel; Besins-Iscovesco, Malaysia†; CORNE, Mex.; Jaba Recordati, Port.; Besins, Rus.; Medi Challenge, S.Afr.; Besins, Singapore†; Seid, Spain; Vifor, Switz.; Besins, Thai.; Ferring, UK; Biopas, Venez.*
Progesterone (p.2125·1).
Benign breast disorders; endometriosis; female infertility; menopausal disorders; menstrual disorders; premature labour; premenstrual syndrome; progesterone deficiency; recurrent and threatened miscarriage; uterine fibroids.

UV IX *Sons, Mex.†.*
⊗ Ciprofloxacin (p.243·3); dexamethasone (p.1526·1).
Infected eye disorders.

UV Derm *Cipla, India†.*
Titanium dioxide (p.1617·3).
Sunscreen.

UV Protectant *Norwood, Canad.*
SPF 15: Avobenzone (p.1589·3); octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

UV Protective *Kiehls, USA.*
Avobenzone (p.1589·3); ecamsule (p.1596·1); octocrilene (p.1608·3).
Sunscreen.

UV Sport Gel *Boots, Austral.†.*
SPF 15+: Octinoxate (p.1608·2); octisalate (p.1608·2); octocrilene (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

UV Triplegard
Note. This name is used for preparations of different composition.
Boots Healthcare, Austral.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

Boots Healthcare, Austral.
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); zinc oxide (p.1621·2).
Sunscreen.

UV Triplegard Hydrating Face Lotion *Boots Healthcare, Austral.*
SPF 20: Octinoxate (p.1608·2); oxybenzone (p.1608·3); avobenzone (p.1589·3).
Sunscreen.

UV Triplegard Kids *Boots Healthcare, Austral.*
SPF 30+: Octinoxate (p.1608·2); enzacamene (p.1597·1); avobenzone (p.1589·3); zinc oxide (p.1621·2).
Sunscreen.

UV Triplegard Sensitive Skin *Boots Healthcare, Austral.†.*
SPF 20: Titanium dioxide (p.1617·3).
Sunscreen.

UV Triplegard Sunstick & Lip Balm *Boots Healthcare, Austral.*
SPF 30+: Octinoxate (p.1608·2); octocrilene (p.1608·3); zinc oxide (p.1621·2).
Sunscreen.

UV Triplegard Watersports *Boots Healthcare, Austral.†.*
SPF 30 +: Octinoxate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

UV Ultrablock *Boots Healthcare, NZ†.*
SPF 15; SPF 20; SPF 30+: Padimate O (p.1609·1); oxybenzone (p.1608·3).
Sunscreen.

Uva Ursi Complexe no 9 *Lehning, Fr.*
Homoeopathic preparation.
Formerly known as Complexe no 9.

Uvacin *Lichtwer, UK.*
Taraxacum (p.2395·1); bearberry (p.2263·3).
Female bladder discomfort.

Uvadex *Johnson & Johnson, Cz.; Therakos, Fr.; Therakos, USA.*
Methoxsalen (p.1605·1).
Cutaneous T-cell lymphoma.

Uvagen *Medifarm, Venez.*
Resveratrol; vitamins A, C, and E; zinc; selenium; ubidecarenone; yeast (p.1922·1).
Antoxidant.

Uvalysat *Ysatfabrik, Ger.*
Bearberry leaf (p.2263·3).
Urinary-tract infections.

Uvamin *Mepha, Israel.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Uvamine retard *Mepha, Switz.*
Nitrofurantoin (p.308·1).
Urinary-tract infections.

Uvanox *Knop, Chile.*
Grape (p.2316·3).
Lymphoedema; sight disorders; venous insufficiency.

Uvasal *GSK, Arg.*
Sodium bicarbonate (p.1673·2); citric acid (p.2284·1); sodium carbonate (p.2389·1).
Formerly contained tartaric acid, sodium bicarbonate, citric acid, caffeine, and magnesium sulfate.
Dyspepsia.

Uvasal Tums *GSK, Arg.*
Calcium carbonate (p.1714·1).
Formerly known as Tums.
Gastric hyperacidity.

Uva-Ursi Complex *Blackmores, Austral.†.*
Taraxacum (p.2395·1); clivers (p.2284·3); bearberry (p.2263·3); buchu (p.2269·3).
Bloating; dysuria; fluid retention; prostatitis; renal calculi; urethritis.

Uva-Ursi Plus *Eagle, Austral.†.*
Bearberry (p.2263·3); parsley (p.2363·2); taraxacum (p.2395·1); zanthoxylum (p.2417·1).
Cystitis; fluid retention.

Uvavid *Naturex, Mex.†.*
Bearberry (p.2263·3).
Antoxidant.

Uvavit *Kolassa, Austria.*
Multivitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy.

Uveblock *Roemmers-Klinos, Venez.†.*
Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Uvedose *Crinex, Fr.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Uvega *Hormona, Mex.*
Lidocaine hydrochloride (p.1862·3).
Otitis externa.

Uveil PS *Medihealth, Mex.; Roemmers Medihe, Venez.*
Titanium dioxide (p.1617·3).
Sunscreen.

Uveline *Martin-Johnson & Johnson, Fr.†.*
Methylhydroxyquinoline metilsulfate (p.2343·3).
UV-induced eye irritation.

Uversan *Medana, Pol.*
Bearberry (p.2263·3).
Disturbances of gastrointestinal flora; urinary-tract infections.

Uvestat *Thea, Belg.*
Methylhydroxyquinoline metilsulfate (p.2343·3).
Light-induced eye irritation.

Uvesterol *Crinex, Fr.*
Multivitamin preparation (p.1922·1).

Uvesterol D *Crinex, Fr.*
Ergocalciferol (p.1987·1).
Vitamin D deficiency.

Uvicel *Degorts, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Uvicin *Steigerwald, Ger.†.*
Homoeopathic preparation.

Uvicol *Alcon, Fr.*
⊗ Actinoquinol (p.2246·3); oxedrine hydrochloride (p.1364·3).
Eye congestion.

Uvimag B_6 *Zambon, Fr.*
Magnesium glycerophosphate (p.1679·2); pyridoxine hydrochloride (p.1978·2).
Vitamin and mineral supplementation.

Uvirgan mono *Abbott, Ger.*
Cucurbita (p.2290·2).
Urinary-tract disorders.

Uvirgan N *Abbott, Ger.†.*
Urtica (p.2409·3); cucurbita (p.2290·2); ononis (p.2357·1).
Urinary-tract disorders.

Uvistat
Note. This name is used for preparations of different composition.
LPC, UK†.
SPF 15: Octinoxate (p.1608·2); avobenzone (p.1589·3).
Sunscreen.

LPC, UK.
SPF 20; SPF 30: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3); octocrilene (p.1608·3); bisoctrizole (p.1591·2).
Sunscreen.

LPC, UK.
SPF 50: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3); octocrilene (p.1608·3); bisoctrizole (p.1591·2); amiloxate (p.1589·1).
Sunscreen.

Uvistat Eye Drops *LPC, UK.*
Hypromellose (p.2144·2); dexpanthenol (p.2362·1).
Dry eyes.

Uvistat Lipscreen
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Irl.
SPF 25; SPF 30: Avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

LPC, UK.
SPF 50: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3); octocrilene (p.1608·3); bemotrizinol (p.1590·2).
Sunscreen.

Uvistat Lotion *Boehringer Ingelheim, Irl.*
SPF 15; SPF 20; SPF 30; SPF 50: Octinoxate (p.1608·2); avobenzone (p.1589·3); titanium dioxide (p.1617·3).
Sunscreen.

Uvless *Theraskin, Braz.*
Panthenol (p.2362·1).
Skin disorders.

UV-Luar *Luar, Arg.*
Hydroxymethylquinoline.
Sunscreen.

Uvox *Solvay, India.*
Fluvoxamine maleate (p.399·3).
Depression; obsessive-compulsive disorder.

Uwobletten novum *Hevert, Ger.*
Homoeopathic preparation.

Uxalun *Sandoz, Arg.; Novartis, Braz.*
Oxaliplatin (p.757·3).
Colorectal cancer; malignant neoplasms.

Uxen *Aventis, Arg.*
Amitriptyline hydrochloride (p.376·1).
Depression.

Uxicolin *Pisa, Mex.*
Suxamethonium chloride (p.1909·3).
Depolarising neuromuscular blocker.

Uzara *Hertz, Braz.†.*
Dipyrone (p.49·2); hyoscine (p.1733·3).
Pain; smooth muscle spasm.

Uze Active *Biosintex, Arg.*
Quassia (p.2377·1); acetic acid (p.2244·2).
Pediculosis.

Uzel *Taiho, Jpn.*
Folinic acid (p.1943·3).

Uzix *Rafarm, Gr.*
Amikacin sulfate (p.200·3).
Bacterial infections.

3V *Julphar, UAE.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Migraine; neuralgia; neuritis; neuropathy; rheumatic pain.

V Day 1612 *PP Lab, Thai.†.*
Prosultiamine; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

V Day Lozenges *PP Lab, Thai.†.*
Dequalinium chloride (p.1641·3).
Mouth and throat infections.

V Day Milk *PP Lab, Thai.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastric hyperacidity.

V Day Zepam *PP Lab, Thai.†.*
Diazepam (p.986·3).
Anxiety; insomnia.

V Infusionslosung *Baxter, Ger.†.*
Electrolyte infusion (p.1667·1).
Fluid and electrolyte disorders.

Vaben *Rafa, Israel.*
Oxazepam (p.1014·2).
Agitation; anxiety.

Vabeta *Edol, Port.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Vabicin *Atlantic, Thai.*
Spectinomycin hydrochloride (p.332·3).
Gonorrhoea.

Vabon *Biolab, Malaysia†; Biolab, Thai.*
⊗ Danazol (p.2090·2).
Benign breast disorders; endometriosis; gynaecomastia; hereditary angioedema; menorrhagia; precocious puberty.

Vac Antigripal *Leti, Spain.*
Inactivated polyvalent influenza vaccines (whole virion or split virion) (p.2218·2).
Active immunisation.

Vac Antiparotiditis *Aventis Pasteur, Spain†.*
A mumps vaccine (p.2225·1).
Active immunisation.

Vac Antipolio Or *Celltech, Spain†.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Vac Antirrubeola *Aventis Pasteur, Spain†; SmithKline Beecham, Spain†.*
A rubella vaccine (RA 27/3) (p.2236·3).
Active immunisation.

Vac Polio Sabin *GSK, Spain.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Vac Poliomielitica *Berna, Spain.*
A poliomyelitis vaccine (p.2232·1).
Active immunisation.

Vacanyl *Vana, Thai.†.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Vacciflu *Solvay, Austria; Solvay, Neth.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Vaccin DTP *Pasteur Vaccins, Fr.†.*
A diphtheria, tetanus, and poliomyelitis (inactivated) vaccine (p.2212·2).
Active immunisation.

Vaccin Meningococcique *Vianex (Βιανεξ), Gr.*
A meningococcal vaccine (groups A and C, or A, C, Y, and W135) (p.2224·1).
Active immunisation.

Vaccin Rubeole *Vianex (Βιανεξ), Gr.*
A rubella vaccine (p.2236·3).
Active immunisation.

Vaccin TP *Pasteur Vaccins, Fr.†.*
A tetanus and poliomyelitis (inactivated) vaccine (p.2241·1).
Active immunisation.

Vaccine Antipoliomyelitique/Merieux *Vianex (Βιανεξ), Gr.†.*
An oral poliomyelitis vaccine (Sabin) (p.2232·1).
Active immunisation.

Vaccino Antipiogeno *Bruschettini, Ital.†.*
A vaccine prepared from *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*.
Active immunisation against pyogenic bacterial infections.

Vaccino Antipneumocatarrale *Bruschettini, Ital.†.*
A vaccine prepared from *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
Bacterial infections of the respiratory tract.

Vacer *Sandoz, Mex.*
Nimodipine (p.1357·2).
Ischaemic neurological deficit following subarachnoid haemorrhage; mental function impairment; vertigo.

Vacidox *Gynopharm, Chile.*
Estriol (p.2101·1).
Menopausal vulvovaginal disorders.

Vacillin *Atlantic, Thai.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Vacina Acel Ads Contra Dif, Tet, Coq e Polio Inat Comb C/Vac Conj Contra Hib *Sanofi Pasteur, Braz.*
An adsorbed diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2211·3).
Active immunisation.

Vacina Acel Ads Contra Dif, Tet e Coq *Sanofi Pasteur, Braz.*
An adsorbed diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Vacina Adsorvida Contra Dif, Tet, Coq Acel, Polio Inat Hepat B (Rec) e Hib Conj *Sanofi Pasteur, Braz.*
A diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Vacina Anti-Rabica Humana *Sanofi Pasteur, Braz.*
A rabies vaccine (p.2234·1).
Active immunisation.

Vacina Catarral *Berna, Port.†.*
Pneumococci; *Staphylococcus aureus*; *Staphylococcus albus*; streptococci; *Klebsiella pneumoniae*; *Moraxella catarrhalis*; *Haemophilus influenzae*.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel *GSK, Braz.*
A diphtheria, tetanus and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel e HIB *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel Hepat.B r-DNA, Polio Inat e HIB *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis, and haemophilus influenzae vaccine (p.2211·2).
Active immunisation.

Vacina Comb. Contra Dif.-Tet,-Pert. Acel, Polio Inat e HIB *GSK, Braz.*
A diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Vacina Comb. Contra Dif.-Tet.-Pert.Acel e Hepat.B *GSK, Braz.*
A diphtheria, tetanus, acellular pertussis, and hepatitis B (recombinant) vaccine (p.2211·2).
Active immunisation.

Vacina Comb. Contra Dift.-Tet.-Coq.Acel *GSK, Braz.*
A diphtheria, tetanus, and acellular pertussis vaccine (p.2210·3).
Active immunisation.

Vacina Comb. Contra Hepatite A e B *GSK, Braz.*
An inactivated hepatitis A and recombinant hepatitis B vaccine (p.2217·1).
Active immunisation.

Vacina Comb. Contra Sarampo, Caxumba e Rubeola *GSK, Braz.*
A measles, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

Vacina Conj Contra Haemophilus Influenzae Tipo B *GSK, Braz.*
A haemophilus influenzae vaccine (tetanus toxoid conjugate) (p.2213·2).
Active immunisation.

Vacina Conj Com Proteina Tetanica Contra Haemophilus influenzae Tipo B *Sanofi Pasteur, Braz.*
A haemophilus influenzae vaccine (tetanus protein conjugate) (p.2213·2).
Active immunisation.

Vacina Contra A Varicela (Virus Atenuado) *MSD, Braz.*
A varicella-zoster (Oka/Merck) vaccine (p.2242·2).
Active immunisation.

Vacina Contra Gripe *GSK, Braz.; Sanofi Pasteur, Braz.; Solvay, Braz.*
An influenza vaccine (p.2218·2).
Active immunisation.

Vacina Contra Hepatite A *GSK, Braz.; MSD, Braz.; Sanofi Pasteur, Braz.*
An inactivated hepatitis A vaccine (p.2214·2).
Active immunisation.

Vacina Contra Hepatite B *GSK, Braz.; MSD, Braz.; Sanofi Pasteur, Braz.*
A recombinant hepatitis B vaccine (p.2215·2).
Active immunisation.

Vacina Contra Sarampo, Caxumba e Rubeola *Sanofi Pasteur, Braz.*
A measle, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

Vacina Contra Varicela *GSK, Braz.; Sanofi Pasteur, Braz.*
A varicella-zoster (Oka strain) vaccine (p.2242·2).
Active immunisation.

Vacina Meningococica A+C *Sanofi Pasteur, Braz.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Vacina Meningococica Conjugada Grupo C *Asta Oncologia, Braz.; Wyeth, Braz.*
A meningococcal C conjugate vaccine (diphtheria CRM protein conjugate) (p.2224·1).
Active immunisation.

Vacina Oral Contra Colera e Diarrreia Causada Por ETEC *Sanofi Pasteur, Braz.*
An inactivated oral cholera vaccine (p.2208·1).
Active immunisation.

Vacina Pneumococica Conjugada 7-valate *Wyeth, Braz.*
A pneumococcal conjugate vaccine (7-valent, diphtheria CRM protein conjugate) (p.2231·2).
Active immunisation.

Vacina Pneumococica Polivalente *MSD, Braz.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Vacina Pneumococica Polivalente Pneumo 23 *Sanofi Pasteur, Braz.*
A pneumococcal vaccine (23-valent) (p.2231·2).
Active immunisation.

Vacina Poliomielitica *Aventis Pasteur, Braz.†.*
An oral poliomyelitis vaccine (p.2232·1).
Active immunisation.

Vacina de Virus Inativado Contra Gripe *GSK, Braz.*
An influenza vaccine (p.2218·2).
Active immunisation.

Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola *MSD, Braz.*
Measles, mumps, and rubella vaccine (p.2223·1).
Active immunisation.

Vacinolone *Atlantic, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Vaclox *Atlantic, Thai.*
Cloxacillin (p.256·1).
Bacterial infections.

Vacolax *Atlantic, Thai.*
Bisacodyl (p.1710·1).
Constipation.

Vacontil *Medochemie, Hong Kong†; Medochemie, Malaysia; Medochemie, Singapore.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Vacopan *Atlantic, Malaysia; Atlantic, Singapore; Atlantic, Thai.*
Hyoscine butylbromide (p.1734·1).
Gastro-duodenitis; nausea and vomiting; peptic ulcer; smooth muscle spasm.

Vacrax *Samchully, Malaysia; Samchully, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vacromil *Gynopharm, Chile.*
⊗ Goserelin acetate (p.2108·2).

Vactyph *Zydus, India.*
A typhoid vaccine (Vi capsular polysaccharide) (p.2241·2).
Active immunisation of adults and children.

Vacudol *Xixia, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Vacudol Forte *Xixia, S.Afr.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Vacu-Mix Plus with CMW gentamicin *Johnson & Johnson, NZ.*
Polymethylmethacrylate (p.2343·3); gentamicin sulfate (p.282·1).
Bone cement for orthopaedic surgery.

Vacuna Adsorbida Pentavalente *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussus, poliomyelitis, and haemophilus influenzae vaccine (p.2212·1).
Active immunisation.

Vacuna Adsorbida Tetravalente *Sanofi Pasteur, Venez.*
A diphtheria, tetanus, pertussus, and poliomyelitis vaccine (p.2211·3).
Active immunisation.

Vacuna Antigripal *Sanofi Pasteur, Spain.*
An influenza vaccine (p.2218·2).
Active immunisation.

Vacuna Antimeningococic A+C *Sanofi Pasteur, Spain.*
A meningococcal vaccine (groups A and C) (p.2224·1).
Active immunisation.

Vacuna Antipiogena *Biol, Arg.*
A vaccine containing micro-organisms responsible for skin infections.
Active immunisation.

Vacuna Antirrabica *Sanofi Pasteur, Spain.*
A rabies vaccine (p.2234·1).
Active immunisation.

Vacuna Doble *Biol, Arg.*
A diphtheria and tetanus vaccine (p.2210·1).
Active immunisation.

Vacuna Haptenica *Puebla, Arg.*
Polysaccharides from *Pseudomonas aeruginosa*; proteins from *Klebsiella pneumoniae*.
Immunotherapy.

Vacuna Liofilizadas Broncopulmonar *Casasco, Arg.*
A vaccine prepared from micro-organisms responsible for respiratory-tract infections.
Active immunisation.

Vacuna Liofilizadas Piodermitis *Casasco, Arg.*
A vaccine prepared from micro-organisms responsible for skin infections.
Active immunisation.

Vacuna Purificada *Sanofi Pasteur, Venez.*
An influenza vaccine (p.2218·2).
Active immunisation.

Vacuna Sabin *Zuoz, Venez.†.*
A poliomyelitis vaccine (p.2232·1).
Active immunisation.

Vacuna Tetract-HIB *Zuoz, Venez.†.*
A diphteria, tetanus, pertussis, and haemophilus influenzae vaccine (p.2211·1).
Active immunisation.

Vacuna Triple *Biol, Arg.; Purissimus, Arg.*
A diphtheria, tetanus, and pertussis vaccine (p.2210·3).
Active immunisation.

Vacuna Triple MSD *Sanofi Pasteur, Spain.*
A measles, mumps, and rubella vaccine (attenuated Enders, Jeryl Lynn, and Wistar RA 27/3 strains respectively) (p.2223·1).
Active immunisation.

Vacuobil *Ivax, Arg.*
Methylenedioxycinnamic acid (p.2343·3).
Liver and biliary-tract disorders.

Vacuobil Plus *Ivax, Arg.*
Methylenedioxycinnamic acid (p.2343·3); metoclopramide hydrochloride (p.1747·3); simeticone (p.1770·2).
Gastrointestinal disorders.

Vadarex *Bell, UK.*
Methyl salicylate (p.85·3); menthol (p.2340·1); sweet birch oil (p.86·2); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2).
Musculoskeletal pain.

Vadel *Ivax, Arg.*
Ezetimibe (p.1284·3).
Hyperlipidaemias.

Vademin-Z *Hauck, USA; Roberts, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vaden *Help, Gr.†.*
Acetylcysteine (p.1548·2).
Mucolytic.

Vadicate *Inkeysa, Spain†.*
Vincamine hydrochloride (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Vadilex *Sanofi-Aventis, Fr.*
Ifenprodil tartrate (p.1313·1).
Arteriopathy.

Vadinar *Serral, Mex.*
Dipyridamole (p.1268·1).
Thromboembolic disorders.

Vadiral *Mediderm, Chile.*
Valaciclovir (p.911·2).
Viral infections.

Vaditon *Euro Registratie, Neth.; Madaus, Spain.*
Fluvastatin sodium (p.1290·2).
Atherosclerosis; hypercholesterolaemia.

Vadolax *Ogna, Ital.†.*
Cascara (p.1715·2); cynara (p.2291·2).
Constipation.

Vadosilan *BMS, Mex.*
Isoxsuprine (p.2327·3).
Peripheral and cerebral vascular disorders; premature labour.

Vaff *Shin Poong, Philipp.*
Clotrimazole (p.530·1).
Vulvovaginal candidiasis.

Vafluson *Kleva, Gr.†.*
Ketoconazole (p.539·1).
Fungal infections.

Vag Oral *IQB, Braz.*
Allergen extracts (p.2250·2).
Allergen immunotherapy.

Vagaka *Vana, Thai.†.*
Mebendazole (p.148·3).
Worm infections.

Vagantin *Riemser, Ger.*
Methanthelinium bromide (p.1747·2).
Gastrointestinal disorders.

Vagantyl *Sidus, Arg.*
Mosapride citrate (p.1750·3).
Dyspepsia; gastritis; gastro-oesophageal reflux.

Vagarne
Note.This name is used for preparations of different composition.
Organon, Arg.†.
Pessaries: Nimorazole (p.842·2); clotrimazole (p.530·1).
Fungal infections; protozoal infections.
Organon, Arg.†.
Tablets: Nimorazole (p.842·2).
Fungal infections; protozoal infections.

Vagarsol *Aspen, S.Afr.*
Diiodohydroxyquinoline (p.832·1); cetylpyridinium chloride (p.1635·1); aminoacridine hydrochloride (p.1625·1); boric acid (p.2268·1).
Vaginal infections.

Vagi Biotic *Cimed, Braz.*
⊗ Nystatin (p.543·2); metronidazole (p.837·1); benzalkonium chloride (p.1629·1); urea (p.1620·2).
Vulvovaginal infections.

Vagi C *Marjan, Braz.*
Ascorbic acid (p.1983·3).
Vaginal disorders.

Vagi-C *Taurus, Ger.*
Ascorbic acid (p.1983·3).
Vaginal disorders.

Vagicillin *Schur, Ger.*
Neomycin sulfate (p.305·1).
Vaginal infections.

Vagicin *Charoen, Thai.*
Diiodohydroxyquinoline (p.832·1); nystatin (p.543·2); chloramphenicol (p.239·3).
Vaginal infections.

Vagiclin *Mediapharm, Gr.*
Clindamycin (p.251·1).
Bacterial vaginal infections.

Vagicural *Raymos, Arg.*
⊗ Hydrocortisone (p.1535·2); neomycin (p.305·1); nitrofurazone (p.309·1); vitamin A (p.1971·2); thymol (p.1664·3); tyrothricin (p.358·2).
Vaginal infections.

Vagicural Plus *Raymos, Arg.*
Centella (p.1592·3); metronidazole (p.837·1); miconazole (p.541·2); neomycin (p.305·1); polymyxin B (p.318·2).
Vaginal infections.

Vagifem *Novo Nordisk, Austral.; Novo Nordisk, Austria; Novo Nordisk, Belg.; Novo Nordisk, Canad.; Silesia, Chile; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.; Novo Nordisk, Ger.; Novo Nordisk, Gr.; Novo Nordisk, Hong Kong; Novo Nordisk, Hung.; Novo Nordisk, Irl.; Novo Nordisk, Israel; Novo Nordisk, Ital.; Novo Nordisk, NZ; Novo Nordisk, Neth.; Novo Nordisk, Norw.; Novo Nordisk, Philipp.; Novo Nordisk, Pol.; Isdin, Port.; Novo Nordisk, S.Afr.; Novo Nordisk, Singapore; Isdin, Spain; Novo Nordisk, Swed.; Novo Nordisk, Switz.; Novo Nordisk, Thai.; Novo Nordisk, Turk.; Novo Nordisk, UK; Novo Nordisk, USA.*
Estradiol (p.2097·2).
Atrophic vaginitis; menopausal disorders; osteoporosis; vulvovaginal disorders.

Vagiflor *Asche Chiesi, Ger.*
Lactobacillus acidophilus (p.2372·3).
Disorders of the vaginal flora; vaginitis.

Vagi-Gard Medicated Cream *Lake, USA.*
Benzocaine (p.1854·1); benzalkonium chloride (p.1629·1).
Vaginal irritation.

Vagi-Gard Personal Lubricating Gel *Lake, USA.*
Vaginal lubricant.

Vagi-Hex *Drossapharm, Ger.; Drossapharm, Switz.*
Hexetidine (p.1647·1).
Vaginitis.

Vagiklin *Kinder, Braz.*
Tetracycline hydrochloride (p.347·2); amphotericin B (p.523·2).

Vagil *PP Lab, Thai.†*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Vagilen *Farmigea, Ital.*
Metronidazole (p.837·1).
Trichomoniasis.

Vagimax *Prodotti, Braz.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vulvovaginal infections.

Vagimid *Apogepha, Ger.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Vagimycin *BMS, Philipp.*
Amphotericin B (p.523·2); tetracycline (p.347·1).
Vaginitis.

Vaginex *QHP, USA.*
Tripelennamine hydrochloride (p.592·2).
External vaginal irritation.

Vaginyl *DDSA Pharmaceuticals, UK.*
Metronidazole (p.837·1).

Vagisan
Note. This name is used for preparations of different composition.
Sidus, Arg.
Dihydrostreptomycin sulfate (p.266·1); tyrothricin (p.358·2); nitrofurazone (p.309·1).
Vaginal infections.
Wolff, Ger.
Lactic acid (p.2329·3); sodium lactate (p.1673·3).
Vaginitis.

Vagisan Compuesto *Sidus, Arg.*
Dihydrostreptomycin sulfate (p.266·1); tyrothricin (p.358·2); nitrofurazone (p.309·1); clotrimazole (p.530·1).
Vaginal infections.

Vagisil
Note. This name is used for preparations of different composition.
Combe, Canad.
Benzocaine (p.1854·1); resorcinol (p.1612·1).
External vaginal irritation.
Combe, Ital.
Lidocaine (p.1862·3); chlorothymol (p.1640·1).
Anal and vulvar pruritus.
Combe, UK.
Lidocaine (p.1862·3).
Vaginal and rectal pruritus.
Combe, USA.
Cream: Benzocaine (p.1854·1); resorcinol (p.1612·1).
Skin disorders.
Combe, USA.
Topical powder: Aloes (p.1705·2); liquid paraffin (p.2030·3); benzethonium chloride (p.1630·1).
Vaginal disorders.

Vagistat-1 *Novartis, USA.*
Tioconazole (p.548·2).
Vulvovaginal candidiasis.

Vagistat-3 *Novartis, USA.*
Miconazole nitrate (p.541·3).
Fungal vaginal infections.

Vagistin *Combiphar, Indon.*
Metronidazole (p.837·1); nystatin (p.543·2).
Vaginal infections.

Vagi-Sulfa *Janssen-Cilag, Braz.*
⊗ Sulfathiazole (p.343·2); sulfacetamide (p.335·3); sulfabenzamide (p.335·2); urea (p.1620·2).
Vaginal infections.

Vagitrene *Eurofarma, Braz.*
Wheat germ (p.2415·1).
Vulvovaginal disorders.

Vagitrin-N *Bunker, Braz.*
⊗ Dexamethasone phosphate (p.1526·2); nystatin (p.543·2); neomycin sulfate (p.305·1); tyrothricin (p.358·2); sodium propionate (p.545·3); boric acid (p.2268·1).
Vulvovaginal infections.

Vagitrol-V *Bayer Consumer, Mex.*
⊗ Fluocinolone acetonide (p.1531·3); metronidazole (p.837·1); nystatin (p.543·2).
Cervicitis; vaginitis; vulvitis.

Vagizol *Kimia, Indon.*
Metronidazole (p.837·1).
Vaginal trichomoniasis.

Vagmycin *BMS, S.Afr.*
Tetracycline (p.347·1); amphotericin B (p.523·2).
Vaginal infections.

Vagoclyss *Grossmann, Switz.*
Lactic acid (p.2329·3).
Vaginal infections and irritation.

Vagomine *Qualiphar, Belg.†*
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Vagopax *Jaba Recordati, Port.*
Pargeverine (p.1761·1).
Smooth muscle spasm.

Vagoplex *Makros, Braz.†*
Reserpine (p.1387·3); homatropine methylbromide (p.1881·3); hyoscine hydrobromide (p.1734·1).
Smooth muscle spasm.

Vagostabil *Cristalfarma, Ital.*
Crataegus (p.2289·1); melissa (p.2339·3); magnesium (p.1678·3).
Anxiety disorders.

Vagostabyl *Leurquin, Fr.*
Crataegus (p.2289·1); calcium lactate (p.1676·1); melissa (p.2339·3); magnesium thiosulfate (p.1466·1).
Insomnia; nervous disorders.

Vagostal *Gynea, Spain.*
Famotidine (p.1730·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Vagostesyl *Gross, Braz.*
Atropine sulfate (p.1219·3); papaverine hydrochloride (p.2191·3); phenobarbital (p.492·2); leptolobium elegans; passion flower (p.2363·2).
Smooth muscle spasm.

Vagothyl *Polfa, Cz.; Pabianice, Hung.; Polfa Pabianice, Pol.; Pabianice, Rus.*
Policresulen (p.1077·2).
Burns; capillary bleeding; haemorrhage; inflammatory skin disorders; mouth and throat disorders; nipple care in lactation; ulcers; urinary-tract infections; urological disorders; vulvovaginal disorders; wounds.

Vagran
Note. This name is used for preparations of different composition.
Finadiet, Arg.
Loratadine (p.583·3).
Formerly contained astemizole.
Allergic rhinitis; urticaria.
Dollder, Venez.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vagran D *Finadiet, Arg.*
Loratadine (p.583·3); pseudoephedrine sulfate (p.1571·2).
Formerly contained astemizole and pseudoephedrine sulfate.
Rhinitis; sinusitis.

Vagyl *Atlantic, Thai.*
Metronidazole (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Valamin 12 *Pisa, Mex.†*
Hydroxocobalamin (p.1980·3).

Valaplex *Laboratorios Chile, Chile.*
Valsartan (p.1420·2).
Hypertension.

Valaplex-D *Laboratorios Chile, Chile.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Valavir *Orion, Fin.; Alodial, Port.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Valaxona *Actavis, Denm.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; spasticity.

Valbet
Note. This name is used for preparations of different composition.
Delta, Braz.; Biolab, Thai.
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.
Lupin, India.
Cream: ⊗ Betamethasone valerate (p.1519·1); miconazole nitrate (p.541·3); neomycin sulfate (p.305·1).
Infected skin disorders.
Lupin, India.
Scalp application: ⊗ Betamethasone valerate (p.1519·1).
Infected scalp disorders.

Valbet-N *Biolab, Thai.*
⊗ Betamethasone (p.1518·2); neomycin (p.305·1).
Infected skin disorders.

Valbil *CHR, Ger.; CPH, Port.*
Febuprol (p.2302·2).
Biliary-tract disorders; dyspepsia.

Valcatil *Panalab, Arg.*
Methionine; cystine; gelatin (p.1922·1).
Hair and nail disorders.

Valcatil Plus *Panalab, Arg.*
Biotin; cystine; methionine; gelatin; pyridoxine hydrochloride; calcium pantothenate; zinc (p.1922·1).

Valcivir *Cipla, India.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Valclair *Durbin, UK.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; epilepsy; premedication; skeletal muscle spasm.

Valclan *Wandel, Mex.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Valcontin *Modi-Mundipharma, India.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Valcote
Abbott, Arg.; Abbott, Chile.
Valproic acid (p.508·2) or valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; migraine.
Abbott, Venez.
Valproate semisodium (p.508·2).
Epilepsy; mania; migraine.

Valcox *Unichem, India.*
Parecoxib sodium (p.111·3).
Postoperative pain.

Valcyte *Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Roche, USA.*
Valganciclovir hydrochloride (p.911·3).
Cytomegalovirus infection.

Valda
Note. This name is used for preparations of different composition.
Canonne, Braz.†
Menthol (p.2340·1); cineole (p.2282·3); thymol (p.1664·3); terpineol (p.2396·1).
Mouth disorders.
Bayer Consumer, Canad.
Menthol (p.2340·1); cineole (p.2282·3); thymol (p.1664·3); terpin hydrate (p.1573·3); guaiacol (p.1561·2).
Coughs.
GSK Sante, Fr.; GSK, Hong Kong†; SmithKline Beecham Consumer, Irl.†; GSK Consumer, Port.†
Menthol (p.2340·1); cineole (p.2282·3); thymol (p.1664·3); terpineol (p.2396·1); guaiacol (p.1561·2).
Throat disorders.
Sterling, Indon.
Chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1); guaifenesin (p.1561·3).
Cold symptoms; cough.

Valda Propoli
Note. This name is used for preparations of different composition.
Valda, Ital.
Pastilles: Propolis (p.2373·3); menthol (p.2340·1); eucalyptus oil (p.2301·2).
Sore throat.
Valda, Ital.
Throat spray: Propolis (p.2373·3); peppermint oil (p.1761·2); eucalyptus oil (p.2301·2); cinnamon oil (p.2283·2); coriander oil (p.2288·1); rosemary oil (p.2381·3).
Throat disorders.

Valda Respiraverde *Valda, Ital.*
Levomenthol; eucalyptus oil (p.2301·2).
Sore throat.

Valda Timo e Limone *Valda, Ital.*
Lemon oil (p.2332·3); eucalyptus oil (p.2301·2); thyme oil (p.2401·2); menthol (p.2340·1).
Sore throat.

Valdefer *Valdecasas, Mex.*
Ferrous sulfate (p.1939·3).
Iron-deficiency anaemia.

Valderma
Note. This name is used for preparations of different composition.
Roche Consumer, Irl.†; Ransom, UK.
Cream: Potassium hydroxyquinoline sulfate (p.2323·2); chlorocresol (p.1640·1).
Acne; skin disorders.
Roche Consumer, UK.
Soap: Triclocarban (p.1665·2).
Acne.

Valdiff *Ipca, India†.*
Valdecoxib (p.132·3).
Dysmenorrhoea; osteoarthritis; rheumatoid arthritis.

Valdig-N Burger *Ysatfabrik, Ger.†*
Convallaria (p.2287·3).
Heart failure.

Valdimex *Mersifarma, Indon.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety; premedication; sedative; skeletal muscle spasm.

Valdispert *Solvay, Belg.†; Solvay, Cz.†; Solvay, Ger.†; Solvay, Neth.; Solvay, Port.; Solvay, Spain; Solvay, Switz.*
Valerian (p.2410·1).
Anxiety; insomnia; nervous disorders.

Valdispert comp *Solvay, Ger.†*
Valerian (p.2410·1); lupulus (p.2335·2).
Anxiety; sleep disorders.

Valdispert Complex *Solvay, Spain.*
Passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Valditas *Solvay, Port.*
Valerian (p.2410·1).

Valdixx
Note. This name is used for preparations of different composition.
Cipla, India.
Injection: Parecoxib sodium (p.111·3).
Pain.
Cipla, India†.
Tablets: Valdecoxib (p.132·3).
Pain.

Valdone *Cadila, India†.*
Valdecoxib (p.132·3).

Valdone-P *Cadila, India.*
Parecoxib (p.112·1).

Valdorm
Note. This name is used for preparations of different composition.
Barrenne, Braz.
Valerian (p.2410·1).
Anxiety; insomnia.
Valeas, Ital.
Flurazepam monohydrochloride (p.999·1).
Insomnia.

Valdren *MH Consulting, Cz.*
Mirtazapine (p.409·2).
Depression.

Valeans *Valeas, Ital.*
Alprazolam (p.960·1).
Anxiety.

Valecid *Depofarma, Ital.*
Cefonicid sodium (p.226·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Valeclor *Francia, Ital.*
Cefaclor (p.217·2).
Bacterial infections.

Valederm *Stiefel, Arg.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Valemia *Sanbe, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Valemine *Vamsler, Philipp.*
Chlorphenamine maleate (p.571·3).
Hypersensitivity reactions.

Valenium *Kenyaku, Thai.†*
Diazepam (p.986·3).
Anxiety.

Valerbet *Polipharm, Thai.†*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Valerecen *Abigo, Swed.*
Valerian (p.2410·1).
Sedative.

Valergen *Hyrex, USA.*
Estradiol valerate (p.2097·3).
Female castration; female hypogonadism; menopausal vasomotor symptoms; prevention of breast engorgement; primary ovarian failure; prostatic cancer; vulval and vaginal atrophy.

Valerial *Zambon, Belg.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Valerian *Vitaplex, Austral.†*
Motherwort (p.2347·3); valerian (p.2410·1); skullcap (p.2388·2); populus (p.2371·1); capsicum (p.2276·2).
Herbal sedative.

Valerian Passiflora and Hops *Lifeplan, UK.*
Vitamins; minerals; kava kava; passion flower; motherwort; wild lettuce; scullcap; lupulus; valerian (p.1922·1).
Herbal supplement.

Valerian Plus Herbal Plus Formula 12 *Vitelle, Austral.†*
Valerian (p.2410·1); passion flower (p.2363·2); dibasic potassium phosphate (p.1682·2); magnesium oxide (p.1744·1).
Insomnia; smooth muscle spasm.

Valeriana comp novum *Hevert, Ger.*
Diphenhydramine hydrochloride (p.577·2); valerian (p.2410·1).
Valeriana comp formerly contained diphenhydramine hydrochloride, bitter-orange peel, chamomile, lupulus, kava, valerian, and peppermint oil.
Anxiety; nervous disorders.

Valeriana Diates *Provefarma, Arg.*
Valerian (p.2410·1); thiamine (p.1976·3).
Herbal supplement.

Valeriana forte N *Hevert, Ger.†*
Diphenhydramine hydrochloride (p.577·2); valerian (p.2410·1).
Sedative.

Valeriana mild *Hevert, Ger.†*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Valeriana Oligoplex *Madaus, Arg.*
Melissa (p.2339·3); valerian (p.2410·1); avena (p.2262·1).
Sedative.

Valeriana Orto *Normon, Spain.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Valeriana Relax Diates *Provefarma, Arg.*
Valerian (p.2410·1); melissa (p.2339·3); calcium pantothenate (p.1959·3).
Herbal supplement.

Valeriana (Specie Composta) *Dynacren, Ital.†*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3); peppermint leaf (p.1761·2); bitter-orange peel (p.2357·1).
Insomnia.

Valerianaheel *Peithner, Austria.*
Homoeopathic preparation.

Valeriane *Nikkho, Braz.*
Valerian (p.2410·1).
Sleep disorders.

Valeric *Atlantic, Singapore†; Atlantic, Thai.†*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Valerimed *Cimed, Braz.*
Valerian (p.2410·1).
Sleep disorders.

Valerin *Fontovit, Braz.; Aflofarm, Pol.*
Valerian (p.2410·1).
Anxiety; insomnia; nervous disorders.

Valerina Day Time *Lichtwer, UK.*
Valerian (p.2410·1); melissa (p.2339·3).
Strain; stress.

Valerina Night-Time *Lichtwer, UK.*
Valerian (p.2410·1); lupulus (p.2335·2); melissa (p.2339·3).
Insomnia.

Valerix *Ativus, Braz.*
Valerian (p.2410·1).
Anxiety; sleep disturbances.

Valerocalma *Piam, Ital.†.*
Centranthus ruber.
Insomnia; sedative.

Valeron *Konimex, Indon.*
⊗ Diflucortolone valerate (p.1529·2).
Skin disorders.

Valesono *Neves, Port.†.*
Valerian (p.2410·1); passion flower (p.2363·2).
Alcohol withdrawal syndrome; anxiety disorders; insomnia; smoking cessation.

Valetol *Herbacos, Cz.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Valeton *Rekah, Israel.*
Valerian (p.2410·1).
Nervous disorders.

Valette *Schering, Austral.; Schering, Austria; Jenapharm, Ger.; Berlifarma, Port.*
Dienogest (p.2094·1); ethinylestradiol (p.2101·3).
Androgen-dependent acne in females; combined oral contraceptive.

Valexime *Depofarma, Ital.*
Ceftriaxone sodium (p.237·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Gram-negative bacterial infections.

Valezen *Teuto, Braz.*
Valerian (p.2410·1).
Anxiety.

Valfam *Valdecasas, Mex.*
Loperamide (p.1741·3).
Diarrhoea.

Valfiran *Sanval, Braz.*
Sulfiram (p.2050·3).
Pediculosis; scabies.

Valflex *Sanval, Braz.*
Cefalexin (p.218·2).
Bacterial infections.

Valherpes *GSK, Spain.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Validol
Note. This name is used for preparations of different composition.
Farmak, Pol.
Menthyl valerate.
Gastrointestinal spasm; migraine; motion sickness; neurosis; neurovegetative disorders.

Hakay, Turk.
Hydroxyzine hydrochloride (p.581·2).
Anxiety; pruritus.

Valiflox *Baliarda, Arg.*
Levofloxacin (p.292·2).
Bacterial infections.

Valifol *Valdecasas, Mex.*
Isoniazid (p.288·1).
Tuberculosis.

Valin Baldrian *Sanova, Austria.*
Valerian (p.2410·1); citronella oil (p.2284·2).
Nervous disorders; sleep disorders.

Valinor *Baxter, Fr.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Valiquid *Roche, Ger.*
Diazepam (p.986·3).
Anxiety disorders; premedication; skeletal muscle spasm; sleep disorders.

Valirem *Genepharm, Gr.*
Sulpiride (p.1028·3).
Psychoses.

Valisanbe *Sanbe, Indon.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; muscular disorders; neuroses; premedication; psychosomatic disorders; sedative; status epilepticus.

Valisone *Schering, Canad.; Schering, USA.*
⊗ Betamethasone valerate (p.1519·1).
Scalp disorders; skin disorders.

Valisone-G *Schering, Canad.*
⊗ Betamethasone valerate (p.1519·1); gentamicin sulfate (p.282·1).
Infected skin disorders.

Valium *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Denm.; Roche, Fr.; Roche, Ger.; Piramal, India; Roche, Indon.; Roche, Irl.; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Port.; Roche, S.Afr.; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, USA; Roche, Venez.†.*
Diazepam (p.986·3).
Agitation; alcohol withdrawal syndrome; childhood nightmares and somnambulism; convulsions; delirium tremens; eclampsia; epilepsy; febrile convulsions; insomnia; panic attacks; premedication; sedative; skeletal muscle spasm; spasticity; status epilepticus; tetanus.

Valix *Sintofarma, Braz.†.*
Diazepam (p.986·3).
Anxiety.

Valixa
Roche, Arg.; Roche, Venez.
Valganciclovir (p.912·1).
Cytomegalovirus retinitis.

Roche, Chile; Roche, Neth.
Valganciclovir hydrochloride (p.911·3).
Cytomegalovirus retinitis.

Vallergan *Aventis, Austral.; Sanofi-Aventis, Irl.; Sanofi-Aventis, NZ; Aventis, Norw.; Aventis, S.Afr.; Castlemead, UK.*
Alimemazine tartrate (p.566·2).
Adjunct in anaesthesia; premedication; pruritus; sedative; sleep disorders; urticaria.

Vallup *Herbapol Lodz, Pol.*
Lupulus (p.2335·2); valerian (p.2410·1).
Insomnia; nervous disorders.

Valmane
Note. This name is used for preparations of different composition.
Pharmaselect, Austria; Solvay, Gr.
Valepotriates (p.2410·1).
Anxiety disorders; nervous disorders.

Solvay, Braz.
Valerian (p.2410·1).
Anxiety disorders.

Valmecon *Valmor, Venez.†.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Antacid; flatulence.

Valmetrol-3 *Valdecasas, Mex.*
Calcitriol (p.1986·2); colecalciferol (p.1986·2).
Hyperparathyroidism; hypocalcaemia; hypoparathyroidism; osteomalacia; osteoporosis; rickets.

Valmicin *Sanval, Braz.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Valmocel *IAE, Philipp.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Valmox *IAE, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Valnar *Ivax, Arg.*
Valproate semisodium (p.508·2).
Bipolar disorder; epilepsy; migraine.

Valocordin-Diazepam *Krewel, Ger.*
Diazepam (p.986·3).
Anxiety disorders; sleep disorders.

Valofyt Neo *Leros, Cz.*
Valerian (p.2410·1); crataegus (p.2289·1); lupulus (p.2335·2); lavender (p.2331·1); melissa (p.2339·3); avena (p.2262·1); salix (p.121·3); angelica (p.2258·1); peppermint leaf (p.1761·2).
Insomnia; nervous disorders.

Valoid
GSK, Hong Kong†.
Cyclizine (p.574·2).
Acid aspiration; nausea; vestibular disorders; vomiting.

Amdipharm, Irl.; GSK, S.Afr.; CeNeS, UK.
Cyclizine hydrochloride (p.574·2) or cyclizine lactate (p.574·2).
Motion sickness; nausea; vestibular disorders; vomiting.

AFT, NZ.
Cyclizine lactate (p.574·2).
Acid aspiration; nausea; vestibular disorders; vomiting.

Valonorm *Zenith, UK.*
Atropine sulfate (p.1219·3); peppermint oil (p.1761·2); magnesium carbonate (p.1743·1); magnesium trisilicate (p.1744·1); calcium carbonate (p.1714·1); sodium bicarbonate (p.1673·2); aluminium hydroxide (p.1706·2).
Dyspepsia; gastrointestinal spasm.

Valontan *Recordati, Ital.*
Dimenhydrinate (p.576·2).
Motion sickness.

Valopin *Julphar, UAE.*
Sodium valproate (p.508·2).
Epilepsy.

Valopon *Biomedica-Chemica, Gr.†.*
Piroxicam (p.117·3).
Inflammatory disorders.

Valopride *Pharmafar, Ital.*
Bromopride (p.1713·3).
Gastrointestinal disorders.

Valoran *Medochemie, Hong Kong; Medochemie, Thai.†.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Valorel *Royal, Chile.*
Etofenamate (p.53·1).
Peri-articular and soft-tissue disorders.

Valoron *Parke, Davis, Belg.†; Galena, Cz.†; Ivax, Cz.†; Pfizer, S.Afr.; Pfizer, Switz.*
Tilidine hydrochloride (p.129·3).
Pain.

Valoron N *Godecke, Ger.; Parke, Davis, Ger.; Pfizer, Ger.*
Tilidine hydrochloride (p.129·3) or tilidine phosphate (p.130·1).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Valosin *Svizera, India.*
Valethamate bromide (p.1778·3).
Colic; labour induction.

Valoxin
Note. This name is used for preparations of different composition.
Sanval, Braz.
Digoxin (p.1259·3).
Arrhythmias; heart failure.

Plus, Gr.
Meloxicam (p.80·3).
Inflammatory disorders.

Valpakine *Sanofi-Aventis, Braz.*
Sodium valproate (p.508·2).
Bipolar disorder; epilepsy.

Valpam *Arrow, Austral.; Arrow, Hong Kong.*
Diazepam (p.986·3).
Alcohol withdrawal syndrome; anxiety disorders; skeletal muscle spasm; spasticity.

Valpar *Valdecasas, Mex.*
Metronidazole benzoate (p.837·1).
Amoebiasis; giardiasis; trichomoniasis.

Valparin *Torrent, India; Torrent, Singapore; Torrent, Thai.*
Sodium valproate (p.508·2).
Epilepsy.

Valparin XR *Torrent, Rus.*
Sodium valproate (p.508·2); valproic acid (p.508·2).
Epilepsy.

Valparina *Valdecasas, Mex.*
Pyridoxine (p.1979·1).
Vitamin deficiency.

Valpax *Drugtech, Chile.*
Clonazepam (p.478·2).
Epilepsy; panic disorder.

Valpeda *Ransom, UK.*
Halquinol (p.286·2).
Skin infections.

Valpex *Ivax, Arg.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Valpiform *General Dietary, UK.*
A range of gluten-free foods (p.1922·1).

Valpin *Recalcine, Chile.*
Octatropine methylbromide (p.1752·1); phenobarbital (p.492·2).
Colic; vomiting in infants.

Valpinax *Crinos, Ital.*
Octatropine methylbromide (p.1752·1); diazepam (p.986·3).
Gastrointestinal spasm.

Val-Plus *Edmond Pharma, Ital.†.*
Valerian (p.2410·1); passion flower (p.2363·2).
Insomnia; sedative.

Valporal *Teva, Israel.*
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

Valprene *Teuto, Braz.*
Sodium valproate (p.508·2).
Epilepsy.

Valpression *Menarini, Ital.*
Valsartan (p.1420·2).
Hypertension.

Valpro *Alphapharm, Austral.; Aliud, Ger.; TAD, Ger.; Alphapharm, Hong Kong.*
Sodium valproate (p.508·2).
Epilepsy; mania.

Valpro Beta *Betapharm, Ger.*
Sodium valproate (p.508·2).
Epilepsy.

Valprodura *Merck dura, Ger.*
Sodium valproate (p.508·2).
Epilepsy.

Valproflux *Hennig, Ger.†.*
Sodium valproate (p.508·2).
Epilepsy.

Valprolept *Hexal, Ger.†.*
Sodium valproate (p.508·2).
Epilepsy.

Valprolim *Winthrop, Port.*
Sodium valproate (p.508·2).
Epilepsy.

Valpron *Farma, Venez.*
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

ValproNa *Teva, Ger.†.*
Sodium valproate (p.508·2).
Epilepsy.

Valprosid *Armstrong, Mex.†.*
Valproic acid (p.508·2) or sodium valproate (p.508·2).
Epilepsy.

Valrate CR *Ipca, India.*
Sodium valproate (p.508·2).
Epilepsy.

Valrian *Leiras, Fin.*
Valerian (p.2410·1).
Nervous disorders; sleep disorders.

Vals *Esteve, Spain.*
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Valsacor *KRKA, Cz.*
Valsartan (p.1420·2).
Heart failure; hypertension; myocardial infarction.

Valsartan/HCTZ *Novartis, Austria†.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Valsedan *Cederroth, Spain.*
Valerian (p.2410·1).
Insomnia; nervous disorders.

Valsera *Polifarma, Ital.*
Flunitrazepam (p.996·2).
Insomnia.

Valstar *Anthra, Israel; Celltech, USA†.*
Valrubicin (p.784·2).
Bladder cancer.

Valsweet *Valma, Chile.*
Aspartame (p.1930·1).
Sugar substitute.

Valtaxin *Indevus, Canad.*
Valrubicin (p.784·2).
Bladder cancer.

Valtec *Cipla, India.*
Sodium valproate (p.508·2).
Epilepsy.

Valto *Nufarindo, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Valtran *Pfizer, Belg.*
Tilidine hydrochloride (p.129·3).
Naloxone hydrochloride (p.1453·2) is included in this preparation to discourage abuse.
Pain.

Valtrax *Valeas, Ital.*
Diazepam (p.986·3); isopropamide iodide (p.1736·3).
Gastrointestinal spasm.

Valtrex *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Braz.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Fin.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, Norw.; GSK, Philipp.; Wellcome, Port.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Valtrian *Medley, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Valtropin *BioPartners, Cz.; BioPartners, Port.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Turner's syndrome.

Valublock V *Valuge, Arg.*
SPF 29: Bisoctrizole (p.1591·2); octinoxate (p.1608·2).
Sunscreen.

Val-Uno *Edmond Pharma, Ital.†.*
Valerian (p.2410·1).
Insomnia; sedative.

Valupass *Knop, Chile.*
Valerian (p.2410·1); lupulus (p.2335·2); passiflora coerulea.
Depression; insomnia; nervous disorders.

Valus *Glenmark, India†.*
Valdecoxib (p.132·3).
Dysmenorrhoea; osteoarthritis; rheumatoid arthritis.

Valus Insta *Glenmark, India†.*
Valdecoxib (p.132·3); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders.

Valused *Hasco-Lek, Pol.*
Lupulus (p.2335·2); passion flower (p.2363·2); valerian (p.2410·1).
Insomnia; nervous disorders; vegetative neurosis.

Valus-P *Glenmark, India†.*
Parecoxib sodium (p.111·3).
Pain.

Valus-XT *Glenmark, India†.*
Valdecoxib (p.132·3); tizanidine hydrochloride (p.1898·2).
Musculoskeletal pain and spasm.

Valved *GMP, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold and influenza symptoms.

Valved DM *GMP, Indon.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2).
Cough.

Valverde Artischocke *Novartis Consumer, Ger.†.*
Cynara (p.2291·2).
Digestive disorders.

Valverde Baldrian Hopfen bei Einschlafstorungen und zur Beruhigung *Novartis Consumer, Ger.†.*
Valerian (p.2410·1); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Valverde Boutons de fievre creme *Sidroga, Switz.*
Melissa (p.2339·3).
Herpes labialis.

Valverde Coeur
Note. This name is used for preparations of different composition.
Novartis Consumer, Switz.†.
Oral drops: Crataegus leaves, flowers, and fruit (p.2289·1); passion flower (p.2363·2).
Cardiac disorders.

Sidroga, Switz.
Tablets: Crataegus leaves and fruit (p.2289·1); passion flower (p.2363·2); lupulus (p.2335·2); valerian (p.2410·1).
Cardiac disorders.

Valverde Constipation dragees *Sidroga, Switz.*
Fig (p.1731·3); senna (p.1769·2); butterbur root (p.2271·1).
Formerly know as Valverde Dragées laxatives.
Constipation.

Valverde Constipation sirop *Sidroga, Switz.*
Fig (p.1731·3); senna (p.1769·2).
Formerly known as Valverde Sirop laxatif.
Constipation.

Valverde Detente dragees *Sidroga, Switz.*
Butterbur root (p.2271·1); passion flower (p.2363·2); valerian (p.2410·1); melissa (p.2339·3).
Nervous disorders.

† This preparation may no longer be actively marketed ⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Valverde Monchspfeffer bei Menstruationsbeschwerden Novartis Consumer, Ger.†.
Agnus castus (p.2249·1).
Mastalgia; menstrual disorders.

Valverde Prostate capsules Sidroga, Switz.
Urtica (p.2409·3).
Prostate disorders.

Valverde regulateur du transit intestinal granules Novartis Consumer, Switz.†.
Ispaghula (p.1737·1).
Constipation.

Valverde Sommeil
Note. This name is used for preparations of different composition.
Novartis Consumer, Switz.†.
Syrup: Valerian (p.2410·1).
Sleep disorders.
Sidroga, Switz.
Tablets: Lupulus (p.2335·2); valerian (p.2410·1).
Sleep disorders.

Valverde Traubensilberkerze Novartis Consumer, Ger.†.
Cimicifuga (p.2282·1).
Menopausal disorders.

Valverde Vitalite dragees Novartis Consumer, Switz.†.
Ginkgo biloba (p.2311·1).
Memory function impairment; tonic.

Valvexin EuroHealth, Philipp.
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Valvir Soho, Indon.
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Valviska Tentan, Switz.
Valerian (p.2410·1); melissa (p.2339·3); mint leaf.
Nervous disorders; sleep disorders.

Vamazole Nakornpatana, Thai.
Clotrimazole (p.530·1).
Fungal skin infections.

Vamcee Vamsler, Philipp.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vamcloxil Vamsler, Philipp.
Cloxacillin (p.256·1).
Bacterial infections.

Va-Mengoc-BC Caif, Arg.; Enila, Braz.†.
A meningococcal vaccine (groups B and C) (p.2224·1).
Active immunisation.

Vamgesic Vamsler, Philipp.
Mefenamic acid (p.80·1).
Fever; pain.

Vamin Pharmatel, Austral.; Fresenius Kabi, Austria; Baxter, Canad.†; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Pharmacia Upjohn, Israel; Fresenius Kabi, Malaysia; Baxter, NZ†; Fresenius Kabi, NZ†; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Swed.; Fresenius Kabi, UK.
Amino-acid infusion with or without electrolytes (p.1922·1).
Parenteral nutrition.

Vamin EF Fresenius Kabi, Ital.†.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vamin con Glucosa Fresenius Kabi, Spain.
Amino-acid infusion with glucose and electrolytes (p.1922·1).
Parenteral nutrition.

Vamin Glucose Pharmatel, Austral.; Fresenius Kabi, Gr.†; Fresenius Kabi, Hong Kong; Fresenius Kabi, Indon.; Fresenius Kabi, Irl.; Pharmacia Upjohn, Israel; Fresenius Kabi, Malaysia; Fresenius Kabi, Neth.; Fresenius Kabi, Port.; Fresenius Kabi, Thai.†; Fresenius Kabi, UK.
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vamin Glukos Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vamin Glukos Combi Fresenius Kabi, Fin.†.
1 infusion, amino-acid, glucose, and electrolyte infusion (Vamin Glukos) (p.1922·1); 1 infusion, soya oil (Intralipid) (p.1965·3).
Parenteral nutrition.

Vamin mit Glukose Fresenius Kabi, Austria.
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vamin N/I Fresenius Kabi, Fin.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vamina Fresenius Kabi, Switz.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vamina Glucose Fresenius Kabi, Switz.
Amino-acid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vamine Fresenius Kabi, Turk.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vamine Glucose Fresenius Kabi, Fr.
Amino-acid, glucose, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vamine Glukoz Fresenius Kabi, Turk.
Amino-acid and glucose infusion (p.1922·1).
Parenteral nutrition.

Vamin-Glu+Intralipid Fresenius Kabi, Gr.
Amino-acid, lipid, carbohydrate, and electrolyte infusion (p.1922·1).
Parenteral nutrition.

Vaminolac Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Norw.; Fresenius Kabi, Swed.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vaminolact Fresenius Kabi, Austria; Fresenius Kabi, Cz.†; Fresenius Kabi, Fr.; Fresenius Kabi, Hong Kong; Pharmacia, Irl.; Pharmacia Upjohn, Israel; Fresenius Kabi, Malaysia; Baxter, NZ†; Fresenius Kabi, NZ†; Fresenius Kabi, Neth.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Singapore†; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, UK.
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vamistol Demo, Gr.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vamlo Ranbaxy, Malaysia.
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Vamogyl Vamsler, Philipp.
Metronidazole (p.837·1).
Amoebiasis; trichomoniasis.

Vamosef Vamsler, Philipp.
Cefradine (p.233·1).
Bacterial infections.

Vamsoxid Vamsler, Philipp.
Isoniazid (p.288·1).
Vitamin B (p.1979·1) is included in this preparation for the prophylaxis of peripheral neuropathy.
Tuberculosis.

Vamysin Teva, Belg.
Vancomycin (p.358·3).
Antibiotic-associated colitis; Gram-positive bacterial infections.

Vanadiol Simoes, Braz.†.
Vitamin B substances with sodium and calcium glycerophosphates (p.1922·1).
Vitamin B deficiency; vitamin B supplement.

Vanadyl Best, Mex.
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Vanafen Atlantic, Thai.
Chloramphenicol (p.239·3).
Bacterial eye or ear infections.

Vanafen-S Atlantic, Singapore†.
Chloramphenicol (p.239·3).
Eye infections.

Vanamide Dermik, USA.
⊗ Urea (p.1620·2).
Dry skin.

Vanaurus Pisa, Mex.
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis due to Clostridium difficile; bacterial infections.

Vancam Abbott, Mex.†.
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis due to Clostridium difficile; bacterial infections.

Vancel Darrow, Braz.
Carboplatin (p.693·1).
Malignant neoplasms.

Vancenase Schering, USA†.
⊗ Beclometasone dipropionate (p.1516·2).
Nasal polyps; rhinitis.

Vancep Fahrenheit, Indon.
Vancomycin hydrochloride (p.358·3).
Staphylococcal infections.

Vanclomin Teuto, Braz.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vanco Cell Pharm, Ger.; Bayer, Ital.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancoabbott Abbott, Braz.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancobehr Behrens, Venez.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancocid Biochimico, Braz.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancocin Lilly, Arg.†; Lilly, Austral.; Lilly, Belg.; Lilly, Canad.; Lilly, Cz.; Lilly, Denm.†; Lilly, Fin.†; Lilly, Hong Kong; Hungaro-Gen, Hung.; AstraZeneca, India; Flynn, Irl.; Lilly, Israel†; Lilly, Malaysia†; Sandoz, Mex.; Lilly, NZ†; Lilly, Neth.; Lilly, Norw.†; GSK, Philipp.; Lilly, Pol.; Lilly, Rus.; Sandoz, S.Afr.; NordMedica, Swed.; Medika, Switz.; Lilly, Thai.†; Lilly, UK; ViroPharma, USA.
Vancomycin hydrochloride (p.358·3).
Antibiotic-associated colitis; bacterial infections.

Vancocina ABL, Braz.; Lilly, Braz.; Lilly, Chile†; Lilly, Ital.; Lilly, Port.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancocine Lilly, Fr.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancogen Alkem, Thai.
Vancomycin hydrochloride (p.358·3).
Gram-positive bacterial infections.

Vancogram Biochem, India.
Vancomycin (p.358·3).
Bacterial infections.

Vancoled Wyeth, Cz.†; Lederle, Israel†; Lederle, USA.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancolon Julphar, UAE.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancomax Klonal, Arg.†.
Vancomycin (p.358·3).

Vanconorth Itaca, Braz.†.
Vancomycin (p.358·3).
Bacterial infections.

Vancoplus Royton, Braz.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancorin Hemat, Turk.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vanco-saar MIP, Ger.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancoscand Scand Pharm, Swed.†.
Vancomycin hydrochloride (p.358·3).
Gram-positive bacterial infections.

Vancoson Ariston, Braz.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancotenk Biotenk, Arg.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vanco-Teva Teva, Israel.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancotex Pharmatex, Ital.; Pharmatex, Malaysia.
Vancomycin hydrochloride (p.358·3).
Bacterial infections; staphylococcal infections.

Vancotrat Uniao Quimica, Braz.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vancox Lemery, Mex.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vandazole Upsher-Smith, USA.
Metronidazole (p.837·1).
Vaginal infections.

Vanderbumin Ivax, Mex.
⊗ Albumin (p.1052·1).
Hypovolaemia; shock.

Vanderm Agis, Israel†.
⊗ Methylprednisolone aceponate (p.1539·1).
Eczema; neurodermatitis.

Vandifen Crisdy-Na, Philipp.
Mefenamic acid (p.80·1).
Pain.

Vandisul Vannier, Arg.†.
Disulfiram (p.2296·2).
Alcoholism.

Vandix Wandel, Mex.
Amoxicillin (p.202·2).
Bacterial infections.

Vandol Schering-Plough, Philipp.; Schering-Plough, S.Afr.†; Schering-Plough, Venez.
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Burns; skin disorders; skin irritation; wounds.

Vandral Wyeth, Spain.
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social phobia.

Vanesin Biostam (Βιοσταμ), Gr.
Carbocisteine (p.1553·2); sobrerol (p.1572·3).
Mucolytic.

Vanesten Atlantic, Singapore†; Atlantic, Thai.
Clotrimazole (p.530·1).
Fungal skin infections.

Vanestrin-V Loeffler, Mex.
Metronidazole (p.837·1).
Vaginal infections.

Vaneular Medichem, Philipp.
Vitamin B substances (p.1975·1).
Neuralgia; neuropathy; vitamin B deficiency.

Vanex Expectorant Abana, USA.
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3); hydrocodone tartrate (p.63·1).
Coughs.

Vanex-HD Abana, USA.
Phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1).
Coughs and cold symptoms.

Vanicream
Note. This name is used for preparations of different composition.
Pharmaceutical Specialties, USA.
Vehicle for topical preparations; moisturiser.
Pharmaceutical Specialties, USA.
Lip protectant SPF 30: Titanium dioxide (p.1617·3).
Sunscreen.
Pharmaceutical Specialties, USA.
SPF 15; SPF 30; SPF 35; SPF 60: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Vanid Unison, Thai.
Flunarizine (p.580·3).
Cerebral and peripheral vascular disorders; migraine; vertigo.

Vaniqa CSL Biotherapies, Austral.; Shire, Cz.; Shire, Fr.; Shire, Ger.; Shire, Irl.; Shire, Ital.; Shire, Neth.; Shire, Port.; Shire, Spain; Shire, UK; SkinMedica, USA.
Eflornithine hydrochloride (p.833·1).
Facial hirsutism in women.

Vanish Silesia, Chile.
Desogestrel (p.2093·2).
Progestogen-only oral contraceptive.

Vanlid Cipla, India.
Vancomycin (p.358·3).
Staphylococcal infections.

Vanmoxol Wandel, Mex.
Amoxicillin (p.202·2); ambroxol (p.1550·3).
Respiratory-tract infections.

Vanmycetin FDC, India.
Chloramphenicol (p.239·3).
Bacterial eye infections; corneal ulcer; trachoma.

Vanocin Stratus, USA.
Sulfacetamide sodium (p.335·3).
Acne; rosacea; seborrhoeic dermatitis.

Vanogel Faran, Gr.
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Vanos Medicis, USA.
⊗ Fluocinonide (p.1532·1).
Skin disorders.

Vanoxide-HC Dermik, USA.
⊗ Benzoyl peroxide (p.1590·2); hydrocortisone (p.1535·2).
Acne; seborrhoea.

Vanquin Pfizer Consumer, Canad.†; Pfizer, Denm.; Pfizer, Norw.; Pfizer, Swed.
Pyrvinium embonate (p.155·3).
Enterobiasis.

Vanquish Glenbrook, USA.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Aluminium hydroxide (p.1706·2) and magnesium hydroxide (p.1743·2) are included in this preparation in an attempt to limit adverse effects on the gastrointestinal mucosa.
Pain.

Vansame Valuge, Arg.
⊗ Vitamin A (p.1971·2); alpha tocopherol (p.1992·2); urea (p.1620·2).
Dry skin disorders.

Vansame G Valuge, Arg.
Glycolic acid (p.1598·1).
Dry skin disorders.

Vansame GS Valuge, Arg.
Glycolic acid (p.1598·1); salicylic acid (p.1612·2).
Acne.

Vansame Plus Valuge, Arg.
Glycolic acid (p.1598·1); vitamin A (p.1971·2); salicylic acid (p.1612·2).
Dry skin disorders.

Vansil IFET (ΙΦΕΤ), Gr.†.
Oxamniquine (p.151·3).
Schistosomiasis.

Vantal Grossman, Mex.
Benzydamine hydrochloride (p.27·3).
Mouth and throat inflammation; peri-articular disorders; soft-tissue disorders; vulvovaginitis.

Vantas Indevus, Malaysia; Valeras, USA.
⊗ Histrelin acetate (p.2109·2).
Prostatic cancer.

Vantelin Kowa, Jpn.
Indometacin (p.66·3); levomenthol.

Vanticon Phoenix, Arg.†.
Zafirlukast (p.1150·2).
Asthma.

Vantin
Note. This name is used for preparations of different composition.
Best, Mex.
Naproxen (p.92·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.
Pharmacia Upjohn, USA.
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Vantoxyl Bruluart, Mex.
Pentoxifylline (p.1367·2).
Cerebral, ocular, and peripheral vascular disorders.

Vantux Grunenthal, Chile†; Royal, Chile.
Zinc sulfate; gelatin; amino acids (p.1922·1).
Dietary supplement; hair and nail disorders.

Vantux Plus Royal, Chile.
Methionine; cystine; zinc chelate; biotin (p.1922·1).
Dietary supplement.

Vaopin N Riemser, Ger.
Camphor (p.2273·2).
Insect stings; pruritus.

Vapesin Boehringer Ingelheim, Venez.
Feprazone (p.60·2).
Inflammation.

Vapoflu Recalcine, Chile.
⊗ Clobutinol (p.1554·2); orciprenaline (p.1129·2); ammonium chloride (p.1551·3).
Coughs.

Vapolatum Inhalador *Maver, Chile.*
Camphor (p.2273·2); methyl salicylate (p.85·3); menthol (p.2340·1).

Vapolatum Labial *Maver, Chile†.*
Camphor (p.2273·2); methyl salicylate (p.85·3).

Vapolatum Unguento *Maver, Chile.*
Methyl salicylate (p.85·3); camphor (p.2273·2).

Vaponefrin *Aventis, Canad.*
⊗ Racepinefrine hydrochloride (p.1204·2).
Bronchospasm.

Vapores Pyt *Fardi, Spain.*
Peru balsam (p.2365·3); cypress (p.2291·2); eucalyptus oil (p.2301·2); niaouli oil (p.2351·3); diplotaxis tenuifolia; abies pectinata; pine silvestris oil (p.2368·2); beech.
Upper respiratory-tract congestion.

Vaporil *Gestafarma, Port.*
Belladonna (p.2263·3); eucalyptus oil (p.2301·2); benzoin (p.2394·2); thyme oil (p.2401·2); lavender oil (p.2331·2); camphor (p.2273·2).
Nasal congestion.

Vaporisateur Medicamente *Multi-Pro, Canad.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3).

Vaporizing Colds Rub *Lander, Canad.*
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1).

Vaporizing Ointment *Prodemdis, Canad.*
Camphor (p.2273·2); cedar; eucalyptus oil (p.2301·2); menthol (p.2340·1); nutmeg oil (p.2355·3); thymol (p.1664·3); turpentine.

Vaposyrup *Phamar (Φαμαρ), Gr.†.*
Dextromethorphan (p.1555·2).
Cough.

Vapour Rub *Numark, UK.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2); menthol (p.2340·1).

Vaprasil *Loeffler, Mex.*
Pravastatin (p.1375·1).
Atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction; hypercholesterolaemia.

Vapresan *Temis, Arg.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Vapresan Diur *Temis, Arg.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Vaprisol *Astellas, USA.*
Conivaptan hydrochloride (p.2287·2).
Hyponatraemia.

VAQTA *MSD, Arg.; CSL, Austral.; Aventis Pasteur, Belg.†; MSD, Braz.†; Merck Frosst, Canad.; MSD, Cz.; Aventis Pasteur, Fin.†; Sanofi Pasteur, Fr.†; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; Aventis Pasteur, Irl.†; MSD, Israel; Sanofi Pasteur, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, NZ; MSD, Neth.; Aventis Pasteur, Norw.†; MSD, Pol.; Sanofi Pasteur, Port.; MSD, Rus.; MSD, Singapore; Sanofi Pasteur, Spain; Aventis Pasteur, Swed.†; Pro Vaccine, Switz.†; MSD, Thai.; MSD, Turk.; Aventis Pasteur, UK; Merck, USA.*
An inactivated hepatitis A vaccine (p.2214·2).
Separate preparations are available for children and adolescents and for adults.
Active immunisation.

Varaxil *Merck, Mex.*
Captopril (p.1239·2).
Hypertension.

Vardolin *Help, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Varedet *Fada, Arg.*
Vancomycin (p.358·3).
Staphylococcal infections.

Varemoid *Novartis, Philipp.*
Oxerutins (p.2304·3).
Haemorrhoids.

Varexan *Novartis, Hung.*
Valsartan (p.1420·2).
Hypertension.

Varexan HCT *Novartis, Hung.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Varfine *Teofarma, Port.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Varginko *Infinity, Venez.*
Ginkgo biloba (p.2311·1).
Tonic.

Variargil *Logogen, Spain.*
Alimemazine tartrate (p.566·2).
Hypersensitivity reactions.

Varicare *Andromaco, Chile†.*
Aesculus (p.2248·2); hamamelis (p.2318·2).
Haemorrhoids; venous insufficiency.

Varicela Biken *Sanofi Pasteur, Arg.; Sanofi Pasteur, Chile.*
A live attenuated varicella-zoster vaccine (OKA strain) (p.2242·2).
Active immunisation.

Varicell *Eversil, Braz.†.*
Partially hydrolysed keratin; senna (p.1769·2); sublimed sulfur (p.1614·1); potassium acid tartrate (p.1764·1).

Varicellon *ZLB, Ger.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Varicex *Lohmann, Ital.*
Zinc oxide (p.1621·2).
Medicated dressing.

Varicid *Lacer, Spain.*
Aesculus (p.2248·2).
Diarrhoea; skin disorders; venous insufficiency.

Varicofit *Body Spring, Ital.*
Ginkgo biloba (p.2311·1); myrtillus (p.2349·3); pungitopo; taraxacum (p.2395·1); centella (p.1592·3); bioflavonoids (p.2304·1); vitamin C (p.1983·3).
Circulatory disorders.

Varicogel *Wassermann, Ital.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2).
Peripheral vascular disorders.

Varicose Ointment *Potter's, UK.*
Cade oil (p.1616·1); hamamelis (p.2318·2); zinc oxide (p.1621·2).
Skin irritation due to varicosity.

Varicoss *Cifarma, Braz.*
Coumarin (p.2288·2); troxerutin (p.2305·1).
Vascular disorders.

Varicylum N *Liebermann, Ger.*
Homoeopathic preparation.

Varicylum-S *Liebermann, Ger.*
Chamomile oil (p.2279·3); sage oil (p.2382·3); arnica (p.2260·2); aesculus (p.2248·2); hamamelis (p.2318·2).
Haemorrhoids; soft-tissue injury; vascular disorders.

Varidasa *Wyeth, Arg.†; Wyeth, Mex.; Wyeth Lederle, Port.†; Cantabria, Spain.*
Streptokinase (p.1402·3); streptodornase (p.2393·1).
Extravasation; inflammation; local removal of blood clots; oedema; tissue damage.

Varidase *Wyeth, Austral.†; Dermapharm, Austria; Meda, Denm.; Meda, Fin.; Riemser, Ger.; Wyeth, Irl.†; Wyeth Lederle, Ital.†; Meda, Norw.; Meda, Swed.; Wyeth, UK†.*
Streptokinase (p.1402·3); streptodornase (p.2393·1).
Bruising; burns; haematoma; inflammation; local removal of blood clots, fibrin, and purulent matter; oedema; skin ulcers; wounds.

Variderm *Profarm, Pol.*
Benzocaine (p.1854·1); menthol (p.2340·1); zinc oxide (p.1621·2).
Burns; pruritus; skin irritation.

Varidoid *General Drugs, Thai.*
A heparinoid (p.1305·2).
Haematoma; oedema; phlebitis; scars; sunburn; thrombosis; varicose veins.

Varidoxo *Varifarma, Arg.*
Doxorubicin (p.712·2).
Malignant neoplasms.

Varigestrol *Varifarma, Arg.*
Megestrol (p.2115·1).

Varigloban *Kreussler, Ger.†.*
Sodium iodide (p.2169·2); iodine (p.2169·2).
Haemorrhoids; varicose veins.

Variglobin *Globopharm, Switz.†.*
Sodium iodide (p.2169·2); iodine (p.2169·2).
Varicose veins.

Varihes *Fresenius Kabi, Austria; Fresenius Kabi, Switz.†; Eczacibasi-Baxter, Turk.*
⊗ Hetastarch (p.1065·1).
Fluid depletion; hypovolaemia; shock.

Varihesive *Convatec, Port.†.*
⊗ Carmellose sodium (p.2142·1); gelatin (p.1072·1); pectin (p.2145·2).
Skin ulcers; wounds.

Varikromo *Geyer, Braz.†.*
Glycerol (p.2314·2); chrome alum (p.2280·3).

Varilise *Ativus, Braz.*
Aesculus (p.2248·2).
Haemorrhoids; varices.

Varilrix *GSK, Arg.; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK; GSK, Venez.*
A live attenuated varicella-zoster vaccine (OKA strain) (p.2242·2).
Active immunisation.

Varimer *Varifarma, Arg.*
Mercaptopurine (p.744·1).
Malignant neoplasms.

Varimesna *Varifarma, Arg.*
Mesna (p.1449·2).

Varimine *Atral, Port.*
Multivitamin and mineral preparation (p.1922·1).

Varipan *Danene, S.Afr.*
Paracetamol (p.108·1).
Fever; pain.

Variplant *Knop, Chile.*
Homoeopathic preparation.

Variplex *Knop, Chile.*
Homoeopathic preparation.

Varipox *Zydus, India.*
A live attenuated varicella-zoster vaccine (OKA strain) (p.2242·2).
Active immunisation.

VariQuin *Sanquin, Neth.*
A varicella zoster immunoglobulin (p.2242·1).
Passive immunisation.

Varisedan *Monserrat, Arg.*
Rutoside (p.2305·1); garlic (p.2309·2).
Peripheral vascular disorders.

Varisedan Gel *Wierhom, Arg.*
Ivy (p.2328·1); bladderwrack (p.2384·2); camphor (p.2273·2); menthol (p.2340·1).
Venous insufficiency.

Varison
Note. This name is used for preparations of different composition.
Euro-Labor, Port.†; Grunenthal, Port.†.
Myrtillus (p.2349·3).
Haemorrhoids; metrorrhagia; venous insufficiency.

Grunenthal, Port.
Aesculus (p.2248·2).
Venous insufficiency.

Varitect *Biogam, Arg.; Biotest, Austria; Biotest, Cz.†; Biotest, Ger.; IFET (ΙΦΕΤ), Gr.; Biotest, Hong Kong; Intra Pharma, Irl.; Biotest, Israel; Biotest, Ital.; Biotest, Pol.; Boehringer Ingelheim, Port.; Biotest, Singapore; Biotest, Switz.; Biotest, Thai.; Rak, Turk.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Variton *Hormona, Mex.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Haemorrhoids; venous insufficiency.

Varivax *CSL, Austral.; MSD, Braz.†; Merck Frosst, Canad.; Sanofi Pasteur, Fr.; Sanofi Pasteur, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; Sanofi Pasteur, Irl.; Sanofi Pasteur, Ital.; MSD, Malaysia†; MSD, Mex.; MSD, NZ; Sanofi Pasteur, Port.; MSD, Singapore†; Sanofi Pasteur, Spain; Sanofi Pasteur, Switz.; Aventis Pasteur, UK; Merck, USA.*
A live, attenuated varicella-zoster vaccine (Oka/Merck strain) (p.2242·2).
Active immunisation.

VariZIG *Cangene, Canad.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Varizol
Note. This name is used for preparations of different composition.
Simoes, Braz.†.
Oral solution: Rutoside (p.2305·1); calcium pantothenate (p.1959·3); hamamelis (p.2318·2).
Haemorrhoids.

Simoes, Braz.†.
Topical gel: Rutoside (p.2305·1); panthenol (p.2362·1); aesculus (p.2248·2); hamamelis (p.2318·2); lidocaine (p.1862·3).
Haemorrhoids.

Varlane *Schering, Belg.†.*
⊗ Fluocortin butyl (p.1532·2).
Burns; skin disorders; stings.

Varlex *Arlex, Mex.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Varmec *Kleva, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Varnoline *Organon, Fr.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Varoc *Pyridam, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Varson *Almirall, Spain.*
Nicergoline (p.2352·1).
Vascular disorders.

Vartalan *Drugtech, Chile.*
Valsartan (p.1420·2).
Hypertension.

Vartalan D *Drugtech, Chile.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Vartalon
Note. This name is used for preparations of different composition.
Labinca, Arg.†.
Low-molecular-weight polypeptides; amino acids (p.1922·1).
Osteoarthritis.

Asofarma, Mex.
Glucosamine sulfate (p.2313·2).
Musculoskeletal and joint disorders.

Nolver, Venez.
Glucosamine (p.2313·2).
Osteoarthritis.

Vartalon Complemento *Sandoz, Arg.*
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Joint disorders; osteoarthritis.

Vartalon Compositum *Asofarma, Mex.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate sodium (p.2280·3).
Musculoskeletal, joint, and peri-articular disorders.

Vartalon Duo *Sandoz, Arg.*
Chondroitin sulfate sodium (p.2280·3); glucosamine sulfate (p.2313·2).
Joint disorders.

Vartalon K *Sandoz, Arg.*
Glucosamine sulfate potassium chloride (p.2313·2).
Musculoskeletal and joint disorders.

Vartelon *Christo, Hong Kong.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Vartelon-B *Christo, Hong Kong.*
Diclofenac sodium (p.44·3); vitamin B ; vitamin B ; vitamin B (p.1922·1).
Inflammation; musculoskeletal and joint disorders; pain.

Vas
Note. A similar name is used for preparations of different composition (see below).
Geymonat, Ital.
Suleparoid (p.1406·3).
Thrombosis prophylaxis.

V-AS
Note. A similar name is used for preparations of different composition (see above).
Medicine Products, Thai.
Aspirin (p.20·3).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Vasactife *Ferring, Port.*
Ginkgo biloba (p.2311·1).
Vascular disorders.

Vasactin *Ebewe, Austria.*
Calcium dobesilate (p.2272·1).
Capillary disorders; venous insufficiency.

Vasa-Gastreu N R63 *Reckeweg, Ger.*
Homoeopathic preparation.

Vasalen *Millimed, Thai.*
Diclofenac sodium (p.44·3).
Biliary colic; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal colic.

Vasalgin *Extractum, Hung.*
Proxibarbal (p.1022·1).
Headache; migraine; Raynaud's syndrome.

Vasaprostan *Schwarz, Rus.*
Alprostadil alfadex (p.2183·3).
Arterial occlusion.

Vasaten *Leti, Venez.*
Valsartan (p.1420·2).
Hypertension.

Vasaten HCT *Leti, Venez.*
⊗ Valsartan (p.1420·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Vascace *Roche, Irl.; Roche, Israel; Roche, Philipp.; Roche, UK.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Vascace Plus *Roche, Israel; Roche, Philipp.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Vascal
Note. This name is used for preparations of different composition.
Viatris, Austria.
Carbasalate calcium (p.33·3).
Thromboembolism prophylaxis.

Schwarz, Ger.
Isradipine (p.1319·2).
Hypertension.

Vascalpha *Alpharma, UK.*
Felodipine (p.1285·3).
Hypertension.

Vascard *Adcock Ingram, S.Afr.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Vascardin *Nicholas, Indon.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

Vascase *Roche, Braz.; Roche, Gr.; Roche, Neth.; Pfizer, Port.*
Cilazapril (p.1244·3).
Heart failure; hypertension.

Vascase Plus *Roche, Braz.; Roche, Gr.; Pfizer, Port.*
⊗ Cilazapril (p.1244·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Vascer *Uniao Quimica, Braz.*
Pentoxifylline (p.1367·2).
Hypertension.

Vascin *Helm, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Vasclin *Libbs, Braz.*
Aspirin (p.20·3); isosorbide mononitrate (p.1318·3).
Angina pectoris; myocardial infarction; unstable angina.

Vascocitrol *Aerocid, Fr.*
Citroflavonoids (p.2304·1); ascorbic acid (p.1983·3); light magnesium carbonate (p.1743·1).
Venous insufficiency.

Vascodin *Help, Gr.*
Amlodipine (p.1214·2).
Angina pectoris; hypertension.

Vascoman *Takeda, Ital.*
Manidipine hydrochloride (p.1330·2).
Hypertension.

Vascon *Fahrenheit, Indon.*
⊗ Noradrenaline acid tartrate (p.1360·1).
Cardiac arrest; hypotension.

Vascopan *Strand, Malaysia†.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Vascor
Note. This name is used for preparations of different composition.
CCM, Malaysia; Upha, Singapore†; Biolab, Thai.
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia; hyperlipidaemias.

Therapharma, Philipp.
Imidapril hydrochloride (p.1313·3).
Hypertension.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Ortho McNeil, USA†.
Bepridil hydrochloride (p.1225·1).
Angina pectoris.

Vascord *Neckerman, Braz.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Vascoride *Therapharma, Philipp.*
⊗ Imidapril hydrochloride (p.1313·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Vascorim *Vida, Port.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Vascoten *Medochemie, Hong Kong; Medochemie, Malaysia; Medochemie, Singapore; Medochemie, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Vasculat *Boehringer Ingelheim, Braz.*
Bamethan sulfate (p.1222·3).
Peripheral vascular disorders.

Vasculene *Finmedical, Ital.*
Flunarizine hydrochloride (p.580·2).
Migraine.

Vasculin *Biolab, Malaysia†; Biolab, Thai.*
Codergocrine mesilate (p.363·3).
Mental function impairment.

Vasculoflex *Baliarda, Arg.†.*
Flunarizine (p.580·3).
Migraine.

Vascunormyl *Alcon, Fr.†.*
Cyclandelate (p.1254·1).
Intermittent claudication; vascular eye disorders.

Vascuprax *Ikapharmindo, Indon.; Lipha, Indon.*
Naftidrofuryl oxalate (p.1346·2).
Cerebral and peripheral vascular disorders.

Vasdalat *Hexpharm, Indon.; Kalbe, Singapore†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Vasdilat *Marvecs, Ital.*
Isosorbide mononitrate (p.1318·3).
Ischaemic heart disease.

Vaselastic *Recalcine, Chile†.*
Buflomedil hydrochloride (p.1236·3).
Cerebral and peripheral vascular disorders; vestibular disorders.

Vaselatum *Stiefel, Spain.*
Liquid paraffin (p.2030·3); benzalkonium chloride (p.1629·1); triclosan (p.1665·2).
Eczema.

Vaselina *Catarinense, Braz.*
White soft paraffin (p.2031·2).

Vaselina Boricada *Orravan, Spain.*
Boric acid (p.2268·1); white soft paraffin (p.2031·2).
Skin disorders; urethral or rectal lubricant.

Vaselina Mentolada *Puerto Galiano, Spain†.*
White soft paraffin (p.2031·2); menthol (p.2340·1).
Skin disorders; urethral or rectal lubricant.

Vaseline *Unilever, Canad.; Lever, UK.*
White soft paraffin (p.2031·2).
Barrier preparation; minor skin disorders.

Vaseline Borique *Ni-The, Gr.*
White soft paraffin (p.2031·2); boric acid (p.2268·1).

Vaseline Gomenolee *Gomenol, Fr.*
Niaouli oil (p.2351·3); white soft paraffin.
Nasal disoreders.

Vaseline Intensive Care
Note. This name is used for preparations of different composition.
Chesebrough-Pond's, USA.
SPF 15; SPF 8; SPF4: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Chesebrough-Pond's, USA.
SPF 25: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Chesebrough-Pond's, USA.
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Vaseline Intensive Care Active Sport *Chesebrough-Pond's, USA.*
SPF 15; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Vaseline Intensive Care Baby
Note. This name is used for preparations of different composition.
Chesebrough-Pond's, USA.
SPF 15: Titanium dioxide (p.1617·3); zinc oxide (p.1621·2).
Sunscreen.

Chesebrough-Pond's, USA.
SPF 30+: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Vaseline Intensive Care Blockout *Chesebrough-Pond's, USA.*
SPF 40: Padimate (p.1609·1); octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2); titanium dioxide (p.1617·3).
Sunscreen.

Vaseline Intensive Care No Burn No Bite *Chesebrough-Pond's, USA.*
SPF 15; SPF 8: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Vaseline Intensive Care-Total Care *Unilever, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Vaseline Lip Therapy *Unilever, Canad.†.*
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3); white soft paraffin.
Sunscreen.

Vaseline Oxyde Zinc *Ni-The, Gr.*
White soft paraffin (p.2031·2); zinc oxide (p.1621·2).

Vaseline Pur *Ni-The, Gr.*
White soft paraffin (p.2031·2).

Vaselitulle *Solvay, Fr.*
White soft paraffin (p.2031·2).
Burns; ulcers; wounds.

Vaselpin *Faran, Gr.*
Roxithromycin (p.331·1).
Bacterial infections.

Vaseretic *Merck Frosst, Canad.; Biovail, USA.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Vasexten
Note. This name is used for preparations of different composition.
Bernabo, Arg.
Olmesartan medoxomil (p.1361·1).
Hypertension.

Solvay, Belg.; Astellas, Cz.; Astellas, Gr.; Italfarmaco, Ital.; Astellas, Neth.; Astellas, Port.
Barnidipine hydrochloride (p.1222·3).
Hypertension.

Vasian *Asian Pharm, Thai.*
Codergocrine mesilate (p.363·3).
Mental function disorders.

Vasican *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract disorders associated with increased or viscous mucus.

Vasilip *KRKA, Cz.; KRKA, Hong Kong; EGIS, Hung.; KRKA, Pol.; KRKA, Rus.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Vasilium *BioSaude, Port.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Vaslip *Biolab Sanus, Braz.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Vasmulax *Integrated Pharmaceutical, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Vaso Rimal *Rimafar, Spain†.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; neurosensorial ischaemia.

Vasobion *Merck, Mex.*
Pyridoxine hydrochloride; cyanocobalamin; folic acid (p.1922·1).
Vitamin deficiency.

Vasobrain *Errekappa, Ital.*
Phospholipids; vitamin E; ginkgo biloba (p.2311·1) (p.1922·1).
Mental function disorders.

Vasobrain Plus *Errekappa, Ital.*
Papaya; thioctic acid; ginkgo biloba (p.2311·1); vitamins (p.1922·1).
Mental function impairment; tonic.

Vasobral *Chiesi, Fr.; Chiesi, Hong Kong; Geymonat, Ital.†; Chiesi, Rus.*
Dihydroergocryptine mesilate (p.364·2); caffeine (p.1116·3).
Cerebral and peripheral vascular disorders; headache; mental function impairment; migraine; Raynaud's syndrome; vestibular disorders.

Vasocard *Abfar, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Vasocardin *Zentiva, Cz.; Zentiva, Rus.*
⊗ Metoprolol tartrate (p.1338·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; migraine; myocardial infarction.

Vasocardol *Aventis, Austral.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Vasocedine *Qualiphar, Belg.*
⊗ Naphazoline nitrate (p.1565·2).
Nasal congestion.

Vasocedine Pseudoephedrine *Qualiphar, Belg.*
Pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Vasocidin *Novartis Ophthalmics, Canad.†; Novartis, USA.*
⊗ Prednisolone sodium phosphate (p.1541·2); sulfacetamide sodium (p.335·3).
Eye inflammation with bacterial infection.

Vasocine *Novartis Ophthalmics, USA.*
⊗ Prednisolone acetate (p.1541·1); sulfacetamide sodium (p.335·3).
Infected eye disorders.

VasoClear *Novartis Ophthalmics, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2); polyvinyl alcohol (p.2145·3).
Minor eye irritation.

VasoClear A *Novartis Ophthalmics, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Vasocon *Novartis Ophthalmics, Canad.†; Ciba Vision, USA†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Vasocon-A *Novartis Ophthalmics, Canad.†; Novartis Ophthalmics, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); antazoline phosphate (p.567·1).
Eye irritation.

Vasoconstrictor Pensa *Pensa, Spain.*
⊗ Naphazoline hydrochloride (p.1565·2).
Nasal congestion.

Vasocor
Note. This name is used for preparations of different composition.
Azevedos, Port.†.
Quinapril hydrochloride (p.1382·2).
Heart failure; hypertension.

Medika, Switz.
Enalapril maleate (p.1276·1).
Heart failure; hypertension; left ventricular dysfunction.

Vasodexa *Llorens, Spain.*
⊗ Dexamethasone phosphate (p.1526·2); tetryzoline hydrochloride (p.1574·1).
Inflammatory eye disorders.

Vasodil *Altana, Mex.*
Ginkgo biloba (p.2311·1).
Cerebral, ocular, and peripheral vascular disorders.

Vasodilan *Apothecon, USA.*
Isoxsuprine hydrochloride (p.2327·3).
Cerebrovascular disorders; peripheral vascular disorders.

Vasodin *Teofarma, Ital.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; heart failure; hypertension.

Vasodip *Dexcel, Israel.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Vasodipin *Merck, Port.*
⊗ Indapamide (p.1314·1).
Hypertension.

Vasodipina *Neo Quimica, Braz.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Vasodual *Janssen-Cilag, Arg.†.*
Calcium dobesilate (p.2272·1); cinnarizine (p.573·1).
Vascular disorders.

Vaso-E-Bion *Rodisma, Ger.*
Troxerutin (p.2305·1); *dl*-alpha tocoferil acetate (p.1992·3).
Vascular disorders.

Vasofed *Antigen, Irl.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Vasofen *Tubilux, Ital.*
Chloramphenicol sodium hemisuccinate (p.240·1); phenylephrine (p.1568·1); mepyramine maleate (p.585·2).
Eye disorders.

Vasoflex *Bago, Chile†.*
Nimodipine (p.1357·2).
Cerebral ischaemia.

Vasoforte N *Krugmann, Ger.†.*
Aesculus (p.2248·2).
Venous insufficiency.

Vasofrinic *Trianon, Canad.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Respiratory congestion.

Vasofrinic DH *Trianon, Canad.*
Chlorphenamine maleate (p.571·3); hydrocodone tartrate (p.63·1); pseudoephedrine hydrochloride (p.1571·2).

Vasofrinic Plus *Trianon, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory congestion.

Vasofyl *Ivax, Mex.*
Pentoxifylline (p.1367·2).
Cerebral, ocular, and peripheral vascular disorders.

Vasogard *Biosintetica, Braz.*
Cilostazol (p.1245·2).
Cerebral and peripheral vascular disorders.

Vasogen *Forest, Irl.; Forest Laboratories, UK.*
Dimeticone (p.2032·1); zinc oxide (p.1621·2); calamine (p.1591·2).
Barrier cream; nappy rash.

Vasojet *Uniao Quimica, Braz.*
Lisinopril (p.1325·2).
Hypertension.

Vasokor *Medikon, Indon.*
Dipyridamole (p.1268·1).
Angina pectoris; myocardial infarction; thromboembolic disorders.

Vasolan *Dexxon, Israel†.*
Isoxsuprine hydrochloride (p.2327·3).
Intermittent claudication; thromboangitis obliterans.

Vasolapril *Deva, Turk.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Vasolat *Prater, Chile†.*
Enalapril maleate (p.1276·1).
Hypertension.

Vasolipid *Braun, Fin.; Braun, Norw.; Braun, Swed.*
Soya oil (p.1965·3); medium-chain triglycerides (p.1956·3).
Contains egg lecithin.
Lipid infusion for parenteral nutrition.

Vasomed *Chemopharma, Chile.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Vasomil *Pharmacare, S.Afr.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias.

Vasomine *Teuto, Braz.†.*
Dopamine hydrochloride (p.1273·2).

Vasomotal *Solvay, Ger.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Vason *Sandoz, Indon.*
⊗ Betamethasone valerate (p.1519·1).
Skin disorders.

Vasonase *Astellas, Spain.*
Nicardipine hydrochloride (p.1348·1).
Angina pectoris; cerebrovascular disorders; hypertension.

Vasonett *INTES, Ital.†.*
Vincamine (p.2414·1).
Cerebrovascular insufficiency.

Vasonit *Lannacher, Austria; Lannacher, Cz.; Lannacher, Rus.*
Pentoxifylline (p.1367·2).
Cerebral and peripheral vascular disorders; hearing loss; vascular eye disorders.

Vasoplan *Nevzat, Turk.*
Pentoxifylline (p.1367·2).
Vascular disorders.

Vasoplant *Leti, Venez.*
Aesculus (p.2248·2).

Vasopos N *Ursapharm, Cz.; Ursapharm, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Vasopren *Sopharma, Rus.†.*
Enalapril (p.1276·1).
Heart failure; hypertension.

Vasopress *Richter, Philipp.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Vasopril
Note. This name is used for preparations of different composition.
Indeco, Arg.; Biolab Sanus, Braz.
Enalapril maleate (p.1276·1).
Hypertension.

BMS, Israel†.
Fosinopril sodium (p.1291·3).
Heart failure; hypertension.

Vasopril Plus
Note. This name is used for preparations of different composition.
Biolab Sanus, Braz.
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

BMS, Israel†.
⊗ Fosinopril sodium (p.1291·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Vasoprost *Esteve, Port.*
Alprostadil alfadex (p.2183·3).
Peripheral vascular disease.

Vasopt *Bausch & Lomb, Ital.*
Ginkgo biloba (p.2311·1); vitamin E acetate (p.1992·3); minerals (p.1922·1).
Vascular disorders of the eye.

Vasorbate *Arcana, Austria.*
Isosorbide dinitrate (p.1317·3).
Angina pectoris; heart failure; myocardial infarction.

Vasorema *Inverni della Beffa, Ital.†.*
Suleparoid (p.1406·3).
Thrombosis prophylaxis.

Vasoretic *MSD, Ital.*
⊗ Enalapril maleate (p.1276·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Vasorinil *Euroderm OTC, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Vasosan *Felgentrager, Cz.†; Felgentrager, Ger.; Felgentrager, Pol.*
Colestyramine (p.1252·3).
Cholestasis-associated pruritus; cholegenic diarrhoea; hypercholesterolaemia.

Vasoserc *Mecom, Turk.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Vasostad *Stada, Philipp.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Vasosterone *Angelini, Ital.*
⊗ Hydrocortisone (p.1535·2); tetryzoline hydrochloride (p.1574·1).
Nasal congestion.

Vasosterone Antibiotico *Angelini, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); tetryzoline hydrochloride (p.1574·1); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Rhinitis.

Vasosterone Collirio *Angelini, Ital.*
⊗ Hydrocortisone acetate (p.1535·2); tetryzoline hydrochloride (p.1574·1); neomycin sulfate (p.305·1).
Eye disorders.

Vasosterone Oto *Angelini, Ital.*
⊗ Flumetasone pivalate (p.1531·1); gentamicin sulfate (p.282·1).
Otitis externa.

Vasosulf *Ciba Vision, USA.*
Sulfacetamide sodium (p.335·3); phenylephrine hydrochloride (p.1568·1).
Eye infections.

Vasosuprina Ilfi *Lusofarmaco, Ital.*
Isoxsuprine hydrochloride (p.2327·3).
Premature labour; threatened miscarriage.

Vasotec
Merck Frosst, Canad.
Enalapril maleate (p.1276·1) or enalaprilat (p.1276·2).
Heart failure; hypertension.
Biovail, USA.
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Vasotenal *Roemmers, Arg.; Pharma Investi, Chile; Roemmers, Venez.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Vasotenal EZ *Roemmers, Arg.*
Simvastatin (p.1390·2); ezetimibe (p.1284·3).
Hypercholesterolaemia.

Vasotin *Metiska, Indon.*
Dipyridamole (p.1268·1).
Angina pectoris; thrombosis prophylaxis.

Vasoton *Ariston, Braz.*
Verapamil hydrochloride (p.1421·1).
Arrhythmias; hypertension.

Vasotonal *Amnol, Ital.*
Aescin; caffeine; ruscus; centella; arnica; hedera; capsicum; ginkgo biloba; menthol.
Skin disorders.

Vasotonin
Note. This name is used for preparations of different composition.
Merz, Ger.†.
Capsules: Aesculus (p.2248·2).
Haemorrhoids; vascular disorders.
Merz, Ger.†.
Topical gel: Arnica (p.2260·2).
Musculoskeletal, joint, and soft-tissue disorders; superficial thrombophlebitis.

Vasotop *Cipla, India.*
Nimodipine (p.1357·2).
Prevention of neurological deficits following subarachnoid haemorrhage.

Vasotrate *Torrent, Singapore.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Vasovist *Bayer Schering, Cz.; Schering, Gr.; Bayer Schering, Hung.; Schering, Neth.; Schering, Port.; Schering, UK.*
Gadofosveset trisodium (p.1479·2).
Contrast medium for magnetic resonance angiography.

Vasovitol *Lannacher, Austria.*
Vitamin A palmitate (p.1973·1); alpha tocoferil acetate (p.1992·3).
Vitamin A and E deficiency.

Vasoxen *Ulagay, Turk.*
⊗ Nebivolol (p.1347·1).
Hypertension.

Vasoxine *Wellcome, Irl.†.*
⊗ Methoxamine hydrochloride (p.1333·3).
Hypotension.

Vaspit *Asche, Ger.†; Intendis, Ital.; Intendis, Spain.*
⊗ Fluocortin butyl (p.1532·2).
Burns; insect stings; skin disorders.

Vassor *Gerolymatos, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Vastamox *Danlex, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Vastan *ICN, Pol.; Meyer, Venez.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Vastarel *Servier, Arg.; Servier, Austria; Servier, Braz.; Grunenthal, Chile; Servier, Denm.; Biopharma, Fr.; Servier, Gr.; Servier, Hong Kong; Servier, Irl.; Stroder, Ital.; Servier, Malaysia; Servier, Philipp.; Servier, Port.; Servier, Singapore; Servier, Thai.; Servier, Turk.; Servier, Venez.*
Trimetazidine hydrochloride (p.1419·2).
Angina pectoris; ischaemic heart disease; Ménière's disease; neurosensorial ischaemia; peripheral vascular disorders; tinnitus; vascular eye disorders; vertigo; vestibular disorders.

Vastat *Pensa, Spain.*
Mirtazapine (p.409·2).
Depression.

Vastatifix *Tiefenbacher, Neth.*
Pravastatin sodium (p.1374·3).
Hyperlipidaemias; reduction of cardiovascular risk.

Vastatil *Cifarma, Braz.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Vastatin *Vocate, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Vastazor *Vocate, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Vastecel *Medix, Mex.*
Aspirin (p.20·3).

Vasten *Sanofi-Aventis, Fr.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; hypercholesterolaemia.

Vastensium *Salvat, Spain.*
Nitrendipine (p.1358·2).
Hypertension.

Vastigo *Dexa, Indon.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Vastil *Pharmanel, Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Vastilan *Aldril, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias; ischaemic heart disease.

Vastin *AstraZeneca, Austral.*
Fluvastatin sodium (p.1290·2).
Hypercholesterolaemia.

Vastina *Penn, Arg.*
Atorvastatin (p.1219·1).
Hypercholesterolaemia.

Vastinol *TO-Chemicals, Thai.*
Trimetazidine hydrochloride (p.1419·2).
Ischaemic heart disease.

Vaston *Medis, Cz.*
Atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Vastribil *Farmasan, Ger.†.*
Troxerutin (p.2305·1).
Vascular disorders.

Vastripine *Medinova (Μεντινοβα), Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Vastus
Note. This name is used for preparations of different composition.
Sandoz, Arg.
Albendazole (p.139·2).
Worm infections.
Tecnofarma, Chile.
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Vasylox *Douglas, Austral.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2); cineole (p.2282·3); menthol (p.2340·1).
Nasal congestion.

Vatacil *Elin, Philipp.*
Ampicillin sodium (p.204·1).
Bacterial infections.

Vatanal *Farmo Quimica, Chile.*
Cod-liver oil (p.1935·2); a macrogol lauril ether (p.1916·1); chlorocarvacrol (p.1639·3).
Anorectal disorders.

Va-t'en *Melisana, Switz.*
Aspirin (p.20·3); lactic acid (p.2329·3).
Calluses.

Vatran *Valeas, Ital.*
Diazepam (p.986·3).
Anxiety; eclampsia; epilepsy; premedication; psychosomatic disorders; skeletal muscle spasm.

Vatrem *Kener, Mex.*
Piroxicam (p.117·3).

Vavifor *Medifarma, Mex.†.*
Vitamin B substances; minerals (p.1922·1).
Dietary supplement.

Vaxem Hib *Chiron Vaccines, Ital.; Fustery, Mex.†; Chiron Vaccines, Philipp.; Chiron, Thai.*
A haemophilus influenzae conjugate vaccine (diphtheria protein conjugate) (p.2213·2).
Active immunisation.

Vaxicum NA *Worwag, Ger.†.*
Camphor oil (p.2273·3); rosemary oil (p.2381·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Vaxigrip *Sanofi Pasteur, Arg.; Aventis Pasteur, Austral.; Aventis Pasteur, Austria; Sanofi Pasteur, Belg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Canad.; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Denm.; Sanofi Pasteur, Fin.; Aventis Pasteur, Fr.†; Vianex (Βιανεξ), Gr.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Hung.; Sanofi Pasteur, Indon.; Aventis Pasteur, Israel; Sanofi Pasteur, Ital.; Sanofi Pasteur, Malaysia; MSD, NZ; Sanofi Pasteur, Neth.; Sanofi Pasteur, Norw.; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Sanofi Pasteur, Port.; Aventis, S.Afr.; Sanofi Pasteur, Singapore; Sanofi Pasteur, Swed.; Sanofi Pasteur, Thai.; Aventis Pasteur, Turk.*
An inactivated influenza vaccine (split virion) (p.2218·2).
Active immunisation.

Vaxim HIB *Aventis, India.*
A haemophilus influenzae conjugate vaccine (p.2213·2).
Active immunisation.

Vaxipar *Chiron Vaccines, Ital.†.*
A mumps vaccine (Urabe strain) (p.2225·1).
Active immunisation.

Vaxitiol *Bouty, Ital.*
Lactobacillus sporogenes (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3); *Bifidobacterium bifidum* (p.2372·3); vitamins; minerals (p.1922·1).
Maintenance of normal gastrointestinal flora.

Vaxman *Tolmann, Philipp.*
Amoxicillin (p.202·2).
Bacterial infections.

Vaxolem *Lemery, Mex.*
Pentoxifylline (p.1367·2).

Vaxosin *Norton, Pol.*
Doxazosin mesilate (p.1275·1).
Hypertension.

Vazaprostan *Schwarz, Rus.*
Alprostadil alfadex (p.2183·3).

Vazigam *NBI, S.Afr.*
A varicella-zoster immunoglobulin (p.2242·1).
Passive immunisation.

Vazim *Sandoz, Indon.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Vazkor *Deva, Turk.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

VaZol-D *WraSer, USA.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2).
Upper respiratory-tract disorders.

Vazosin *Biotenk, Arg.*
Doxazosin (p.1275·2).
Benign prostatic hyperplasia; hypertension.

Vazotab *WraSer, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Vazotan *WraSer, USA.*
Phenylephrine hydrochloride (p.1568·1); brompheniramine maleate (p.569·2); pentoxyverine citrate (p.1567·3).
Upper respiratory-tract disorders.

Vazotuss HC *WraSer, USA.*
Hydrocodone tannate (p.63·2); brompheniramine tannate (p.569·3); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Vazy *Sigma, Braz.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

V-Bloc *Kalbe, Indon.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Vcanalare *Vebas, Ital.†.*
Orthophenylphenol (p.1655·1).
Root canal disinfection.

VCF *Apothecus, Canad.; Silesia, Chile†; Apothecus, USA.*
Nonoxinol 9 (p.1917·2).
Contraceptive.

V-Crima *Vitamed, Israel.*
Povidone (p.2146·1); hyetellose (p.2143·3).
Formerly contained povidone and hypromellose.
Dry eyes.

V-D-Bone *Verisfield, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

V-Dec-M *Seatrace, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Ve *Tecnifar, Port.*
Vitamin E (p.1992·2).
Vitamin E supplement.

Vecasten *Marjan, Braz.*
Melilot (p.2339·2).
Venous insufficiency.

Veclam *Malesci, Ital.*
Clarithromycin (p.248·2).
Bacterial infections.

Vecredil *Jagson, India.*
Ethacridine lactate (p.1625·1).
Termination of pregnancy.

Vectarion *Servier, Belg.†; Servier, Braz.; Servier, Denm.; Eutherapie, Fr.; Servier, Irl.; Servier, Port.; Servier, Spain.*
Almitrine dimesilate (p.2149·3).
Obstructive airways disease; respiratory depression; respiratory failure.

Vectavir *Novartis Consumer, Austral.; Novartis, Austria; Novartis Consumer, Belg.; Novartis, Braz.; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis Consumer, Ger.†; GSK, Gr.; Novartis, Hong Kong†; Novartis, Hung.†; Novartis Consumer, Israel†; Novartis, Ital.; Novartis, NZ†; Novartis Consumer, Neth.; Novartis, Norw.; Novartis Consumer, Spain; Novartis, Swed.; Novartis, Turk.; Novartis Consumer, UK.*
Penciclovir (p.901·2).
Herpes labialis.

Vectibix *Amgen, Cz.; Amgen, Port.; Amgen, UK; Amgen, USA.*
Panitumumab (p.761·1).
Colorectal cancer.

Vectidan *Bago, Chile†.*
Nicotinic acid (p.1957·3).
Peripheral vascular disorders; skin ulcers.

Vectocilina *Panalab, Arg.*
Azithromycin (p.207·1).
Bacterial infections.

Vectra-P *Cipla, India†.*
Valdecoxib (p.132·3); paracetamol (p.108·1).
Pain.

Vectrine *Pharma 2000, Fr.; Dexa, Indon.*
Erdosteine (p.1560·1).
Respiratory-tract congestion.

Vectrum Calcium *Akrikhin, Rus.*
Colecalciferol (p.1986·2); phytomenadione (p.1995·3); ascorbic acid (p.1983·3); pyridoxine hydrochloride (p.1978·2); calcium carbonate (p.1714·1).
Calcium and vitamin deficiency; osteoporosis.

Vecural *Richmond, Arg.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Vecuron *Scott-Cassara, Arg.; Cristalia, Braz.; Pharmakin Korea, Venez.*
Vecuronium bromide (p.1913·1).
Competitive neuromuscular blocker.

Vedium *Medikon, Indon.*
Hesperidin (p.2304·3); diosmin (p.2304·2).
Haemorrhoids; phlebitis; venous insufficiency.

Vedrin *Polifarma, Ital.†.*
Xantinol nicotinate (p.1433·1).
Peripheral vascular disorders.

Veemycin *Osoth, Thai.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Veenac *Medicine Products, Thai.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Veetids *Apothecon, USA.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Vefarol *Vamsler, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Vefed *PP Lab, Thai.†.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms; nasal congestion.

Vefluxan *Sanofi Synthelabo, Arg.†.*
Troxerutin (p.2305·1); bamethan (p.1222·3).
Haemorrhoids; varices.

Vefren
Note. This name is used for preparations of different composition.
Baliarda, Arg.†.
Cream: Piroxicam (p.117·3).
Inflammation; pain.
Baliarda, Arg.
Tablets: Ibuprofen (p.64·2).
Formerly contained piroxicam and paracetamol.
Fever; inflammation; pain.

Vefron *Opus Materia, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting.

Vegacillin *Biogal-Teva, Hung.†.*
Phenoxymethylpenicillin (p.314·1).
Bacterial infections.

Vegal *Jofrain, Mex.*
Dipyrone (p.49·2).
Pain.

Veganin
Note. This name is used for preparations of different composition.
Johnson & Johnson, Austral.
Aspirin (p.20·3); codeine phosphate (p.37·2).
Fever; pain.
Pfizer Consumer, Irl.†; Aspen, S.Afr.†.
Aspirin (p.20·3); paracetamol (p.108·1); codeine phosphate (p.37·2).
Fever; pain; rheumatism.
Chefaro, UK.
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Formerly contained aspirin, paracetamol, and codeine phosphate.
Fever; pain.

Veganin Plus *Pfizer Consumer, Irl.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Cold and influenza symptoms; pain.

Veganine *Pfizer Sante, Fr.†.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Vegantalgin H *GSK, Pol.*
Paracetamol (p.108·1); hyoscine butylbromide (p.1734·1).
Gastrointestinal procedures; smooth muscle spasm.

Vege Swiss One *Swiss Herbal, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Vegebom *Vegebom, Fr.*
Cineole (p.2282·3); cajuput oil (p.2271·2); sassafras oil (p.2383·3); cedar oil (p.2278·3); camphor (p.2273·2); menthol (p.2340·1); nutmeg oil (p.2355·3); bay-laurel oil.
Musculoskeletal, joint, and peri-articular disorders.

Vegelax *Biologiques de l'Ile-de-France, Fr.†.*
Senna (p.1769·2); boldo (p.2267·2); cynara (p.2291·2).
Constipation.

Vegenat *Alchemy, UK.*
Preparation for enteral nutrition (p.1922·1).

Vegestabil *Sandoz, Arg.*
Sulpiride (p.1028·3); dipotassium clorazepate (p.980·1).
Psychosomatic disorders.

Vegestabil Digest *Sandoz, Arg.*
Domperidone (p.1726·2); bromazepam (p.964·3); simeticone (p.1770·2).

Vegetable Cough Remover *Potter's, UK.*
⊗ Capsicum (p.2276·2); cimicifuga (p.2282·1); ipecacuanha (p.1562·3); lobelia (p.2157·2); pleurisy root (p.2370·1); skullcap (p.2388·2); skunk cabbage

(p.2388·2); valerian (p.2410·1); elecampane (p.1558·1); marrubium (p.1564·1); hyssop (p.2323·3); anise oil (p.2258·2); liquorice (p.1740·3).
Coughs.

Vegetal Tonic *Homeocan, Canad.*
Homoeopathic preparation.
Formerly contained artemisia, avena sativa, china, cinnamomum, frangula, gentiana, and podophyllum.

Vegetallumina *Recordati, Ital.*
Camphor (p.2273·2); aluminium subacetate (p.2255·1); methyl salicylate (p.85·3); thyme oil (p.2401·2).
Soft-tissue and peri-articular disorders.

Vegetarian Protein Supplement *GNLD, Austral.*
Nutritional supplement (p.1922·1).

Vegetex *Lane, UK.*
Celery (p.2278·3); menyanthes (p.2340·3); cimicifuga (p.2282·1).
Muscular pain.

Vegetoserum
Note. This name is used for preparations of different composition.
Zydus, Fr.
Adult syrup: Ethylmorphine hydrochloride (p.52·2); grindelia (p.2317·2).
Coughs.

Aerocid, Fr.
Paediatric syrup: Ethylmorphine hydrochloride (p.52·2); orange flowers (p.2357·1).
Coughs.

Vegevit B_{12} *Lane, Pol.*
Cyanocobalamin (p.1980·2); brewer's yeast (p.1998·3).
Vitamin B deficiency.

Vegital *Steierl, Ger.†.*
Homoeopathic preparation.

Veglysin *Rowe-Fleming, Venez.†.*
Tribenoside (p.2403·3).
Haemorrhoids; phlebitis; varices.

Veil *Blake, UK.*
A covering cream.
Concealment of birth marks, scars, and disfiguring skin disease.

Veinamitol *Negma, Belg.; Negma, Fr.; Negma, Hung.†; SEDR, Israel†.*
Troxerutin (p.2305·1).
Capillary impairment; chronic venous insufficiency; haemorrhoids.

Veineva *CCD, Fr.*
Diosmin (p.2304·2).
Capillary disorders; haemorrhoids; venous insufficiency.

Veinobiase *Fournier, Fr.*
Black currant (p.2267·1); butcher's broom (p.2270·3); ascorbic acid (p.1983·3).
Haemorrhoids; venous insufficiency.

Veinofytol *Tilman, Belg.*
Aesculus (p.2248·2).
Capillary disorders; venous insufficiency.

Veino-Gouttes-N *Phytomed, Switz.†.*
Aesculus (p.2248·2); melilot (p.2339·2); butcher's broom (p.2270·3).
Venous insufficiency.

Veinophytum *Arkomedika, Fr.†.*
Aesculus (p.2248·2); red vine (p.2316·3).
Capillary disorders; haemorrhoids; venous insufficiency.

Veinopress A3 and A4 *Innothera, Fr.*
Zinc oxide (p.1621·2).
Care after variceal surgery; lymphoedema; post-sclerotherapy care; ulcers; venous insufficiency.

Veinostase *Merck Medication Familiale, Fr.*
Aesculus (p.2248·2); hamamelis (p.2318·2); cypress (p.2291·2); ascorbic acid (p.1983·3).
Capillary fragility; haemorrhoids; venous insufficiency.

Veinotonyl *Merck-Lipha, Fr.*
Aesculus (p.2248·2); metesculetol sodium (p.2343·2).
Peripheral vascular disorders.

Vejicur *Schering, Spain.*
A BCG vaccine (p.2205·3).
Bladder cancer.

Vekfanol *Faran, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Vekfazolin *Faran, Gr.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Velafax *Pliva Krakow, Pol.; Pliva, Rus.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Velamox
Sigma, Braz.
Amoxicillin (p.202·2).
Bacterial infections.

Mediolanum, Ital.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Velaned *Fada, Arg.†.*
Piroxicam (p.117·3).

Velaril *Roemmers-Klinos, Venez.*
Clonidine hydrochloride (p.1247·1).
Hypertension.

Velasor *Vocate, Gr.*
Tenoxicam (p.128·2).
Inflammatory disorders.

Velaspir *Norton, Pol.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Velaxin *Egis, Cz.; EGIS, Hung.; Egis, Pol.; Egis, Rus.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social phobia.

Velban *Lilly, Braz.†; Lilly, USA.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Velbastine *Korea United, Philipp.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Velbe *Lilly, Arg.†; Aspen, Austral.; Stada, Austria; Eurogenerics, Belg.; Lilly, Chile†; Pharmacodane, Denm.; Lilly, Fin.†; EG, Fr.; Lilly, Ger.†; Lilly, Gr.; Lilly, Hong Kong†; Crinos, Ital.; Lilly, Mex.†; Stada, Neth.; Pharmacodane, Norw.; Lilly, Port.†; Stada, Swed.; Medika, Switz.; Genus, UK; Lilly, Venez.†.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Velcade *Janssen-Cilag, Arg.; Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Ortho, Canad.; Janssen-Cilag, Chile; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Fin.; Janssen-Cilag, Fr.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Janssen-Cilag, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; Janssen-Cilag, Neth.; Janssen-Cilag, Norw.; Janssen, Philipp.; Janssen-Cilag, Pol.; Janssen-Cilag, Port.; Janssen-Cilag, Rus.; Janssen-Cilag, Singapore; Janssen-Cilag, Spain; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, Thai.; Ortho Biotech, UK; Millenium, USA; Janssen-Cilag, Venez.*
Bortezomib (p.689·2).
Mantle cell lymphoma; multiple myeloma.

Velcox *Novell, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Veldom *Viofar, Gr.*
Clindamycin (p.251·1).
Vaginal infections.

Veldrol *Collins, Mex.*
Tramadol hydrochloride (p.130·3).
Pain.

Velexina *Klonal, Arg.*
Cefalexin (p.218·2).
Bacterial infections.

Veliten *Zambon, Fr.*
Vitamins (p.1922·1); rutoside (p.2305·1).
Vascular disorders.

Velivet *Barr, USA.*
21 Tablets, desogestrel (p.2093·2); ethinylestradiol (p.2101·3); 7 tablets, inert.
Triphasic oral contraceptive.

Velkacalcin *Velka, Gr.*
Calcitonin (salmon) (p.1093·1).
Osteoporosis.

Velkacet *Velka, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Velkaderm *Velka, Gr.*
Clindamycin (p.251·1).
Vaginal infections.

Velkalov *Velka, Gr.*
Lovastatin (p.1328·2).

Velkastatin *Velka, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Vellutan *Abiogen, Ital.*
Tacalcitol (p.1615·1).
Psoriasis.

Velmonit *Bayer, Spain†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Velocef *BMS, Spain.*
Cefradine (p.233·1).
Bacterial infections.

Velodan *Lesvi, Spain.*
Loratadine (p.583·3).
Hypersensitivity reactions.

Velodyne *Dexa, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

velopural *Optimed, Ger.†.*
⊗ Hydrocortisone acetate (p.1535·2).
Skin disorders.

Velorin *Remedica, Hong Kong; Remedica, Philipp.; Remedica, Singapore†; Remedica, Thai.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Velorium *Polychronus, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Velosalic *Schering-Plough, Chile.*
⊗ Mometasone furoate (p.1539·3); salicylic acid (p.1612·2).
Hyperkeratotic skin disorders; psoriasis.

Velosef *BMS, Belg.; BMS, Chile†; BMS, Hong Kong; BMS, Indon.; BMS, Irl.; BMS, NZ†; BMS, Neth.; BMS, Port.†; BMS, UK; Apothecon, USA†.*
Cefradine (p.233·1).
Bacterial infections.

Velostin *Solas, Indon.*
Portulaca; chamomile (p.2279·3); aloe vera (p.1588·2); vitamin E (p.1992·2).
Vaginal disorders.

Velosulin *Novo Nordisk, Belg.; Novo Nordisk, Cz.; Novo Nordisk, Denm.; Novo Nordisk, Fin.†; Novo Nordisk, Fr.†; Novo Nordisk, Ger.; Novo Nordisk, Jpn; Novo Nordisk, Neth.; Novo Nordisk, Norw.†; Novo Nordisk, Port.; Novo Nordisk, Swed.†; Novo Nordisk, UK†.*
⊗ Insulin injection (human, emp) (p.443·2).
Formerly known as Human Velosulin.
Diabetes mellitus.

Velosulin HM *Novo Nordisk, NZ; Novo Nordisk, Switz.†.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Velosulin Human BR *Novo Nordisk, USA†.*
⊗ Insulin injection (human, emp) (p.443·2).
Diabetes mellitus.

Velosulin MC *Novo Nordisk, NZ.*
⊗ Neutral insulin injection (porcine, monocomponent) (p.443·2).
Diabetes mellitus.

Veloudiet *DHN, Fr.†.*
Preparation for enteral nutrition (p.1922·1).

Velpro *Alpharma, Mex.*
Benzonatate (p.1552·1).
Cough.

Velsay *Sons, Mex.*
Naproxen (p.92·3).
Musculoskeletal, joint, and peri-articular disorders; pain.

Velsay-S Compuesto *Sons, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Veltex *Adcock Ingram, S.Afr.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Veltifer *Rafarm, Gr.*
Iron polymaltose (p.1953·1).
Iron deficiency.

Veltion *Faran, Gr.*
Mupirocin (p.302·3).
Bacterial skin infections.

Velvachol *Healthpoint, USA.*
Vehicle for topical preparations.

Vemizol *CCM, Malaysia.*
Albendazole (p.139·2).
Worm infections.

Vemol *PP Lab, Thai.†.*
Paracetamol (p.108·1).
Fever; pain.

Ven Hex *Elmor, Venez.†.*
Salicylic acid (p.1612·2).
Dandruff.

Venacol
Note. This name is used for preparations of different composition.
Mugi, Indon.
Thiamphenicol (p.351·1).
Bacterial infections.

Llorens, Spain.
Aescin (p.2248·2); esculoside (p.2248·2); heparin sodium (p.1301·2); ruscogenin (p.2382·2).
Oedema; peripheral vascular disorders.

Venacorn *Filofarm, Pol.*
Dihydroergocristine mesilate (p.364·2); esculoside (p.2248·2); rutoside (p.2305·1).
Cerebral and peripheral vascular disorders; migraine; venous insufficiency.

Venactive
Note. This name is used for preparations of different composition.
Les 3 Chenes, Ital.
Centella (p.1592·3); aesculus (p.2248·2); hamamelis (p.2318·2).
Tired legs.

Farmila, Ital.†.
Bioflavonoids (p.2304·1); omega-3 triglycerides (p.1362·1); centella (p.1592·3).
Vascular disorders.

Venacton *Klein, Ger.†.*
Aesculus (p.2248·2); scoparium (p.2384·2); St John's wort (p.422·3); milk thistle (p.1452·1); hamamelis (p.2318·2).
Venous insufficiency.

Venactone *Benedetti, Ital.†.*
⊗ Potassium canrenoate (p.1374·1).
Hyperaldosteronism; hypertension.

Venafleur *Bloem Beheer, Neth.*
Homoeopathic preparation.

Venaflon *Teuto, Braz.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Venous insufficiency.

Venaforce *Bioforce, UK.*
Aesculus (p.2248·2).
Venous insufficiency.

Venafort *Teuto, Braz.*
Aesculus (p.2248·2).
Oedema; venous insufficiency.

Venalax *Jumont, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Venalitan *3M, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Venalot *Nycomed, Braz.; Schaper & Brummer, Ger.; Altana, Mex.*
Coumarin (p.2288·2); troxerutin (p.2305·1).
Haemorrhoids; soft-tissue injury; superficial vascular disorders; venous and lymphatic insufficiency.

Venalot H *Nycomed, Braz.*
Coumarin (p.2288·2); heparin (p.1301·2).
Soft-tissue injury.

Venalot mono *Schaper & Brummer, Ger.†.*
Coumarin (p.2288·2).
Soft-tissue injury.

Venalot N *Schaper & Brummer, Ger.†.*
⊗ Coumarin (p.2288·2); rutoside sodium sulfate (p.2305·2).
Peripheral vascular disorders.

Venalot novo *Schaper & Brummer, Ger.†.*
Aesculus (p.2248·2).
Venous insufficiency.

Venalta
Note. This name is used for preparations of different composition.
Alta Care, Ital.
Aesculus (p.2248·2); arnica (p.2260·2); grape (p.2316·3); ginkgo biloba (p.2311·1); hamamelis (p.2318·2); cypress oil (p.2291·2); lemon oil (p.2332·3); sage oil (p.2382·3); mint oil (p.2345·2); lavender oil (p.2331·2).

Alta Care, Ital.
Red vine (p.2316·3); vitamin E; vitamin C (p.1922·1).
Circulatory disorders.

Venapulse *Pharmacare, S.Afr.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Venaron *Teguhsindo, Indon.*
Oxerutins (p.2304·3).
Haemorrhoids; varices.

Venart *Casasco, Arg.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Haemorrhoids; venous insufficiency.

Venartel *Andromaco, Chile.*
Citrus bioflavonoids (p.2304·1); diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

Venastat *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Hung.; Boehringer Ingelheim Promeco, Mex.; Boehringer Ingelheim, Pol.*
Aesculus (p.2248·2).
Chronic venous insufficiency.

Venavit N *UB, Switz.*
Aesculus (p.2248·2).
Venous insufficiency.

Venbig *Kedrion, Ital.; Kedrion, Port.*
A hepatitis B immunoglobulin (p.2214·3).
Passive immunisation.

Vencipon N *Artesan, Ger.†.*
⊗ Ephedrine hydrochloride (p.1558·2); phenolphthalein (p.1762·1).
Obesity.

Vendal *Lannacher, Austria; Lannacher, Cz.; Polfa Warszawa, Pol.; Liba, Turk.*
⊗ Morphine hydrochloride (p.86·3).
Pain.

Vendazol *Zuoz, Venez.*
Albendazole (p.139·2).
Worm infections.

Venderol *Beacons, Singapore.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ven-Detrex *Therabel, Belg.*
Diosmin (p.2304·2).
Peripheral vascular disorders.

Vendrex *IQB, Braz.*
Diclofenac sodium (p.44·3).

Venelbin ruscus *Biocur, Ger.†.*
Butcher's broom (p.2270·3).
Chronic venous insufficiency; haemorrhoids.

Venen Krauter NT *Salushaus, Ger.*
Aesculus (p.2248·2); melilot (p.2339·2).
Venous insufficiency.

Venen-Dragees *CT, Ger.†.*
Aesculus (p.2248·2).
Venous insufficiency.

Venen-Fluid *CT, Ger.*
Aesculus (p.2248·2).
Phlebitis; soft-tissue injury; varices.

Venengel *Ratiopharm, Ger.†.*
Heparin sodium (p.1301·2); arnica (p.2260·2); aesculus (p.2248·2).
Soft-tissue injury; vascular disorders.

Venen-Salbe N *CT, Ger.†.*
Aesculus (p.2248·2); esculoside (p.2248·2).
Bruising; oedema; varices.

Venen-Tabletten *Stada, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venentabs *Ratiopharm, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venen-Tropfen N *Bioforce, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venescin *Herbapol Wroclaw, Pol.*
Aesculus (p.2248·2); esculoside (p.2248·2); rutoside (p.2305·1).
Haemorrhoids; venous insufficiency.

Venex *Decomed, Port.*
Diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

Vengesic *Collins, Mex.†.*
⊗ Methocarbamol (p.1897·3); phenylbutazone (p.117·1); dexamethasone (p.1526·1); aluminium hydroxide (p.1706·2).
Inflammation; musculoskeletal and joint disorders.

Venidium *Ivax, Arg.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Haemorrhoids; venous insufficiency.

Venilon *Teijin, Jpn.*
A normal immunoglobulin (p.2225·3).
Infections.

Venimmun *Aventis Behring, Ger.†; Centeon, Ital.†; Centeon, Pol.*
A normal immunoglobulin (p.2225·3).
Auto-immune disorders; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki syndrome; passive immunisation.

Venimmun N *ZLB, Austria; CSL, Cz.*
A normal immunoglobulin (p.2225·3).
Idiopathic thrombocytopenic purpura; passive immunisation.

Venimmuna *CSL, Braz.*
A normal immunoglobulin (p.2225·3).
Passive immunisation.

Venirene *Winthrop, Fr.*
Diosmin (p.2304·2).
Capillary disorders; haemorrhoids; venous insufficiency.

Venisse *Bago, Arg.*
Yellow tablets, gestodene (p.2105·2); ethinylestradiol (p.2101·3); red tablets, inert.
Combined oral contraceptive.

Venitan
Lek, Cz.; Lek, Pol.
Aesculus (p.2248·2).
Haematoma; neuralgia; oedema; venous insufficiency.

Lek, Rus.
Aescin (p.2248·2).

Venitrin *3M, Ital.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; hypertensive crises; left-ventricular failure; myocardial infarction.

Venla *Unipharm, Israel.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Venlax *Saval, Chile.*
Venlafaxine (p.430·1) or venlafaxine hydrochloride (p.427·3).
Anxiety; depression.

Venlaxin *Eurofarma, Braz.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Venlift *Torrent, Braz.*
Venlafaxine hydrochloride (p.427·3).
Depression; obsessive-compulsive disorder.

Venlor *Cipla, India; Cipla-Medpro, S.Afr.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; social phobia.

Veno V *Decafarma, Port.*
Diosmin (p.2304·2).
Oedema; vascular disorders.

Veno Gel *Madaus, Thai.*
Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Thrombophlebitis; varicose veins.

Veno SL *Ursapharm, Ger.*
Troxerutin (p.2305·1).
Vascular disorders.

Venobene *Ratiopharm, Austria.*
Heparin sodium (p.1301·2); dexpanthenol (p.2362·1).
Anorectal disorders; soft-tissue injury; superficial vascular disorders.

Venobiase *Fournier, Ger.†.*
Butcher's broom rhizome (p.2270·3); black currant (p.2267·1).
Venous insufficiency.

Venobiase mono *Fournier, Ger.†.*
Butcher's broom rhizome (p.2270·3).
Haemorrhoids; venous insufficiency.

veno-biomo *Biomo, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venocur Triplex *Abbott, Braz.*
Rutoside (p.2305·1); aesculus (p.2248·2); miroton.
Venous insufficiency.

Venodin *Amnol, Ital.*
Diosmin (p.2304·2); hesperidin (p.2304·3); melilot (p.2339·2); vitamins (p.1922·1).
Circulatory disorders.

Venodura *Merck dura, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venofer
Note. This name is used for preparations of different composition.
Quesada, Arg.; Aspen, Austral.; Fresenius, Belg.; Genpharm, Canad.; Andromaco, Chile; Vifor, Cz.; Vifor, Denm.; Vifor, Fin.; Therabel, Fr.; Fresenius Medical, Ger.; Genesis, Gr.; Vifor, Hong Kong; Vifor, Hung.; Combiphar, Indon.; Vifor, Indon.; Vifor, Israel; Vifor, Malaysia; Healthcare Logistics, NZ; Vifor, Neth.; Renapharma, Norw.; Ferraz, Lynce, Port.; Altana Madaus, S.Afr.; Vifor, Singapore; Uriach, Spain; Renapharma, Swed.; Vifor International, Switz.; Vifor, Thai.; Abdi, Turk.; Syner-Med, UK; American Regent, USA; Zuoz, Venez.
Iron sucrose (p.1953·2).
Dialysis-induced anaemia; iron deficiency; iron-deficiency anaemia.

Lek, Pol.
Polysaccharide-iron complex (p.1960·2).
Iron deficiency.

Venoferrum *Altana, Mex.*
Iron sucrose (p.1953·2).
Iron-deficiency anaemia.

Venofit
Note. This name is used for preparations of different composition.
Hochstetter, Chile†.
Homoeopathic preparation.

Arkochim, Spain.
Butcher's broom (p.2270·3); melilot (p.2339·2); hamamelis (p.2318·2).
Peripheral vascular disorders.

Venofortan *Ariston, Braz.†.*
Aescin (p.2248·2); vitamin B (p.1976·3).
Venous insufficiency.

Venoforton *Leki Natury, Pol.*
Aesculus (p.2248·2); arnica (p.2260·2); crataegus (p.2289·1); ginkgo biloba (p.2311·1); mistletoe (p.2345·3).
Atherosclerosis; cerebral and peripheral vascular disorders.

Venoful *Garden House, Arg.*
Centella (p.1592·3); ginkgo biloba (p.2311·1); hamamelis (p.2318·2); aesculus (p.2248·2).
Haemorrhoids; oedema; varices.

Venofundin *Braun, Arg.; Braun, Denm.; Braun, Fin.; Braun, Ger.; Vioser, Gr.; Braun, Neth.; Braun, Port.; Braun, Swed.; Braun, Switz.; Braun, UK.*
⊗ An etherified starch (p.1065·1).
Hypovolaemia; plasma volume expansion; shock.

Venogamma *Veripalvelu, Fin.†.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Venoglobulin *Alpha, Israel; Mitsubishi, Jpn; Grifols, Singapore†; Alpha Therapeutic, USA†.*
A normal immunoglobulin (p.2225·3).
Agammaglobulinaemia; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation.

Venoglobulina *Zuoz, Venez.†.*
A normal immunoglobulin (p.2225·3).

Venoglobulin-S *Alpha, Hong Kong†; Grifols, Malaysia†; Grifols, Thai.†.*
A normal immunoglobulin (p.2225·3).
Idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease.

Venogyl *Teva, Israel.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Venokatt *Kattwiga, Ger.*
Homoeopathic preparation.

Veno-Kattwiga N *Kattwiga, Ger.†.*
Aescin (p.2248·2); procaine hydrochloride (p.1869·1).
Vascular disorders.

veno-L 90 N *Loges, Ger.†.*
Homoeopathic preparation.

Venolan *Polfa Grodzisk, Pol.*
Troxerutin (p.2305·1).
Phlebitis; venous insufficiency.

Venolen *Pharma Line, Ital.*
Troxerutin (p.2305·1).
Capillary fragility; venous insufficiency.

Venolep *Farma Lepori, Spain.*
⊗ Hidrosmin (p.2305·2).
Venous insufficiency.

Venolife *Akrikhin, Rus.*
Troxerutin (p.2305·1); dexpanthenol (p.2362·1); heparin sodium (p.1301·2).
Soft-tissue injury; venous insufficiency.

veno-loges N *Loges, Ger.*
Homoeopathic preparation.

Venomenhal *Hal, Ger.; Hal, Hung.; Haarlems Allergenen, Pol.*
Allergen extracts of bee venom (p.2251·1) and wasp venom (p.2251·1) (p.2250·2).
Allergen immunotherapy; diagnosis and desensitisation of wasp and bee stings.

Venomhal *Hal, Neth.†.*
Aqueous bee venom (p.2251·1) and wasp venom (p.2251·1)(p.2250·2).
Allergen immunotherapy.

Venomil *Bencard, Ger.; Miles, USA.*
Allergen extract of bee venom (p.2251·1) or wasp venom (p.2251·1)(p.2250·2).
Allergen immunotherapy.

Venoparil
Note. This name is used for preparations of different composition.
Neo-Farmaceutica, Port.†.
Tablets: Aescin (p.2248·2).
Haemorrhoids; joint pain; oedema; venous insufficiency.

Neo-Farmaceutica, Port.
Topical gel: Aescin (p.2248·2); diethylamine salicylate (p.47·2).
Musculoskeletal, joint, and soft-tissue injury; thrombophlebitis; varices.

Venoplant *VSM, Belg.; Schwabe, Ger.; Schwabe, Pol.; Schwabe, Rus.*
Aesculus (p.2248·2).
Venous insufficiency.

Venoplant AHS *Schwabe, Ger.†.*
Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Soft-tissue injury; venous insufficiency.

Venoplant comp *Schwabe, Switz.*
Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Scars; soft-tissue injuries; venous insufficiency.

Venoplant top *Schwabe, Ger.†.*
Hamamelis (p.2318·2).
Skin inflammation; varices.

Venoplant-N *Schwabe, Switz.†.*
Aesculus (p.2248·2); heparin sodium (p.1301·2).
Scars; soft-tissue injuries; venous insufficiency.

Venoplus *Also, Ital.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2); milk thistle (p.1452·1).
Alterations in capillary permeability; varicose veins; venous dilatation.

Venopril *Luper, Braz.†.*
Captopril (p.1239·2).
Hypertension.

Venopyronum *Abbott, Ger.*
Aesculus (p.2248·2).
Venous insufficiency.

Venopyronum N *Abbott, Ger.†.*
Aesculus (p.2248·2).
Venous insufficiency.

Venorell *Sanorell, Ger.*
Homoeopathic preparation.

Venorix *Medinfar, Port.*
Dermatan sulfate sodium (p.1256·3).

Venoruton
Note. This name is used for preparations of different composition.
Novartis, Arg.; Novartis Consumer, Austria; Novartis Consumer, Belg.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis Consumer, Ger.; Novartis, Gr.; Novartis, Hong Kong†; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, Spain; Novartis Consumer, Switz.; Novartis, Turk.
Oxerutins (p.2304·3).
Chronic venous insufficiency; diabetic retinopathy; haemorrhoids; retinopathy; skin reactions following radiotherapy; soft-tissue disorders; soft-tissue injury; varices; vascular disorders; vascular reactions following radiotherapy.

Novartis, Braz.; Novartis, Philipp.; Novartis, Thai.
Troxerutin (p.2305·1).
Chronic venous insufficiency; diabetic retinopathy; haemorrhoids; oedema; varices; varicose dermatitis; venous ulcers.

Novartis Consumer, Rus.
Rutoside (p.2305·1).
Haemorrhoids; venous insufficiency.

Venoruton Emulgel *Novartis Consumer, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders.

Venoruton Heparin *Novartis Consumer, Austria.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial venous disorders.

Venos *Soho, Indon.*
Butcher's broom (p.2270·3); centella (p.1592·3).
Haemorrhoids; varicose veins.

Venos Cough Mixture *GSK Consumer, UK.*
Glucose (p.1945·3); treacle (p.1969·3).
Coughs.

Venos Expectorant *GSK Consumer, Irl.; GSK Consumer, UK.*
Guaifenesin (p.1561·3); liquid glucose (p.1945·3); treacle (p.1969·3).
Coughs.

Venos Honey & Lemon
Note. This name is used for preparations of different composition.
GSK Consumer, Irl.
Ammonium chloride (p.1551·3); ipecacuanha (p.1562·3); liquid glucose (p.1945·3); honey (p.1948·2); lemon juice.
Coughs.

GSK Consumer, UK.
Purified honey (p.1948·2); glucose (p.1945·3).
Coughs; sore throat.

Venos for Kids *GSK Consumer, UK.*
Guaifenesin (p.1561·3).
Coughs.

Ven-o-sal *Bilim, Turk.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Venoselect N *Dreluso, Ger.*
Homoeopathic preparation.

Venoserin *Labomed, Chile.*
Butcher's broom (p.2270·3).
Venous insufficiency.

Venosin *Fujisawa, Austria.*
Aesculus (p.2248·2).
Chronic venous insufficiency; oedema; superficial vascular disorders.

Venosman *Pharmanel, Gr.†.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Vascular disorders.

Venosmil *Sidus, Arg.; Vitoria, Port.; Faes, Spain.*
⊗ Hidrosmin (p.2305·2).
Capillary disorders; haemorrhoids; inflammatory skin disorders; peripheral vascular disorders; venous insufficiency.

Venosmine *Geymonat, Ital.*
Diosmin (p.2304·2).
Peripheral vascular disorders.

Venostasin
Note. This name is used for preparations of different composition.
Altana, Switz.
Aesculus (p.2248·2).
Venous insufficiency.

Fujisawa, Austria.
Capsules; ointment; oral drops; topical gel: Aesculus (p.2248·2).
Chronic venous insufficiency; soft-tissue injury.

Ariston, Arg.; Ariston, Braz.†.
Controlled-release capsules: Aesculus (p.2248·2).
Venous insufficiency.

Klinge, Ger.
Controlled-release capsules; cream: Aesculus (p.2248·2).
Inflammation; venous insufficiency.

Ariston, Arg.
Tablets: Aescin (p.2248·2); vitamin B (p.1976·3).
Venous insufficiency.

Ariston, Arg.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Soft-tissue injury; venous insufficiency.

Ariston, Braz.†.
Topical gel: Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3); thiamine nitrate (p.1976·2).
Venous insufficiency.

Klinge, Ger.
Topical gel: Aescin (p.2248·2).
Formerly contained aescin, heparin sodium, and glycol salicylate.
Soft-tissue injury; vascular disorders.

Venostasin compositum *Fujisawa, Austria.*
Aescin (p.2248·2); heparin sodium (p.1301·2); glycol salicylate (p.62·3).
Chronic venous insufficiency; soft-tissue injury.

Veno-Tebonin N *Schwabe, Ger.†.*
⊗ Ginkgo biloba (p.2311·1); heptaminol hydrochloride (p.2319·1); troxerutin (p.2305·1).
Haemorrhoids; vascular disorders.

Venoton *Dermofarma, Ital.*
Bioflavonoids (p.2304·1); melilot (p.2339·2); docosahexaenoic acid (p.1362·1); aesculus (p.2248·2); vitamins.
Nutritional supplement.

Venotonin *Phytofarm Kleka, Pol.*
Aesculus (p.2248·2).
Haemorrhoids; soft-tissue oedema; venous insufficiency.

Venotop *Novartis, Austria.*
Dihydroergotamine tartrate (p.618·3); troxerutin (p.2305·1).
Chronic venous insufficiency.

Venotrauma *Also, Ital.†.*
Aesculus (p.2248·2); hamamelis (p.2318·2); heparin sodium (p.1301·2).
Soft-tissue disorders.

Venotrex *Pliva Krakow, Pol.*
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

Venotrulan Trox *Truw, Ger.*
Troxerutin (p.2305·1).
Venous insufficiency.

Venovaz *Cifarma, Braz.*
Diosmin (p.2304·2); hesperidin (p.2304·3).
Venous insufficiency.

Venoxil *Mavi, Mex.*
Cinnarizine (p.573·1).

Venozel *Emo-Farm, Pol.*
Diclofenac sodium (p.44·3); aescin (p.2248·2); tribenoside (p.2403·3).
Oedema; rheumatoid arthritis; tendinitis.

Vensa *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Vent Retard *BOI, Spain†.*
Theophylline (p.1140·1).
Heart failure; obstructive airways disease; paroxysmal dyspnoea.

Ventadur *UCB, Spain.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventamol
Pinewood, Irl.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Hovid, Malaysia†.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm.

Ventamol Expectorant *Hovid, Malaysia†.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Bronchospasm.

Ventar *GX, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventar EXP *GX, Philipp.*
⊗ Guaifenesin (p.1561·3); salbutamol (p.1131·2).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Ventarone *Umeda, Thai.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Ventavis *Schering, Arg.†; Schering, Chile; Bayer Schering, Cz.; Schering, Denm.; Schering, Fin.; Schering, Fr.; Schering, Ger.; Schering,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Gr.; Schering, Hong Kong; Bayer Schering, Hung.; Schering, Indon.; Schering, Irl.; Italfarmaco, Ital.; Schering, Neth.; Schering, Norw.; Schering, Pol.; Schering, Port.; Bayer, Singapore; Schering, Spain; Schering, Swed.; Schering, UK; CoTherix, USA.
Iloprost trometamol (p.1313·1).
Pulmonary hypertension.

Venter
Note. This name is used for preparations of different composition.
Vent-3, Arg.
Paracetamol (p.108·1); salicylamide (p.121·2); ascorbic acid (p.1983·3); phenylephrine hydrochloride (p.1568·1).
Influenza symptoms.

KRKA, Cz.; KRKA, Hung.; KRKA, Pol.; KRKA, Rus.
Sucralfate (p.1772·2).
Gastro-oesophageal reflux; hyperphosphataemia; peptic ulcer.

Venterol *Greater Pharma, Thai.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventexxair *Schwarz, Fr.†.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Venteze
Note. This name is used for preparations of different composition.
Biolab, Philipp.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract disorders.

Pharmacare, S.Afr.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Venticoll *GE Healthcare, Neth.*
⊗ Technetium-99m (p.2055·3) albumin nanocolloid.
Radioimaging of the lungs.

Venticort *Oftalmi, Venez.*
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Asthma.

Ventide
GSK, Arg.; GSK, Chile; GSK, Hong Kong; GSK, Indon.; GSK, Mex.; GSK, Singapore†; GSK, Thai.†; GSK, Turk.; GSK, Venez.
⊗ Salbutamol (p.1131·2); beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease.

GSK, Austria.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3); beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Ventilan *Glaxo Wellcome, Port.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

Ventilastin
Viatris, Fr.; Viatris, Ger.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Viatris, Spain.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ventilat *Boehringer Ingelheim, Ger.†.*
Oxitropium bromide (p.1129·2).
Obstructive airways disease.

Ventisol *Ivax, Mex.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity.

Ventmax
Chiesi, Ital.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Trinity, UK.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventnaze *Pharmacare, S.Afr.*
⊗ Beclometasone dipropionate (p.1516·2).
Hay fever; rhinitis.

Vento-Broncho *San Marino, Philipp.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Vento-Broncho G *San Marino, Philipp.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Cough.

Ventodisk
GSK, Canad.; GSK, S.Afr.†; GSK, Switz.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease.

GSK, Pol.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ventodisks *GSK, Cz.†; GSK, Fr.†; GSK, Hong Kong; Allen & Hanburys, Irl.†; GSK, Turk.; Allen & Hanburys, UK†.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease.

Ventoflu *Finmedical, Ital.*
⊗ Flunisolide (p.1531·1).
Asthma; bronchitis; rhinitis.

Ventolair *Ivax, Ger.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Ventolase *Juste, Spain.*
⊗ Clenbuterol hydrochloride (p.1120·1).
Obstructive airways disease.

Ventoliber *Tecnimede, Port.*
⊗ Ambroxol hydrochloride (p.1550·3); clenbuterol hydrochloride (p.1120·1).
Respiratory-tract disorders.

Ventolin
GSK, Arg.; Allen & Hanburys, Austral.; GSK, Belg.; GSK, Canad.; GSK, Hong Kong; GSK, Indon.; GSK, Malaysia; GSK, Mex.; GSK, Rus.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, Venez.†.
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease; premature labour; status asthmaticus.

GSK, Cz.; GSK, Hung.; Allen & Hanburys, Irl.; GSK, Israel; GSK, Ital.; GSK, NZ; GSK, Neth.; GSK, S.Afr.; Allen & Hanburys, UK; Glaxo Wellcome, USA.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Bronchospasm; obstructive airways disease; premature labour; status asthmaticus.

GSK, Philipp.; GSK, Pol.
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ventolin Compuesto *GSK, Arg.†.*
⊗ Salbutamol (p.1131·2); guaifenesin (p.1561·3).
Respiratory-tract congestion.

Ventolin Espettorante *GSK, Ital.†.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Bronchial congestion; bronchospasm.

Ventolin Expectorant
GSK, Hong Kong; GSK, Indon.; GSK, Malaysia; GSK, Thai.
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Bronchospasm; coughs; obstructive airways disease associated with increased or viscous mucus.

GSK, Philipp.
⊗ Salbutamol (p.1131·2); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Ventolin Flogo *GSK, Ital.†.*
⊗ Beclometasone dipropionate (p.1516·2); salbutamol (p.1131·2).
Obstructive airways disease.

Ventoline
GSK, Denm.; GSK, Fr.; GSK, Norw.; GSK, Swed.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease; premature labour.

GSK, Fin.
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventomol *APT, Hong Kong.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Ventoplus *Phoenix, Arg.*
⊗ Levosalbutamol hydrochloride (p.1125·3).
Obstructive airways disease.

Ventor *Rafarm, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Ventorlin *GSK, India.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Obstructive airways disease.

Ventosal *Essenpharma, Philipp.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Ventox *Leiras, Fin.†.*
Oxitropium bromide (p.1129·2).
Obstructive airways disease.

Ventracid N *Repha, Ger.*
Sodium bicarbonate (p.1673·2); pancreatin (p.2360·1); curcuma (p.1473·2).
Gastrointestinal disorders.

Ventre Livre *CIF, Braz.†.*
Cascara (p.1715·2); docusate sodium (p.1725·1).
Constipation.

Ventricon N *Syxyl, Ger.*
Bismuth subnitrate (p.1711·2); calcium carbonate (p.1714·1); magnesium oxide (p.1744·1).
Gastrointestinal disorders.

Ventricor *Faromed, Austria†.*
⊗ Sotalol hydrochloride (p.1398·2).
Arrhythmias.

Ventrigutt N *Hanosan, Ger.*
Homoeopathic preparation.

ventri-loges N *Loges, Ger.*
Absinthium (p.2244·1); calamus (p.2271·3); gentian (p.2310·3).
Appetite loss; dyspepsia.

Ventrux *Cernelle, Switz.†.*
Enterococcus faecium (p.2372·3).
Gastrointestinal disorders; restoration of intestinal flora.

Venucreme *Permamed, Switz.*
Heparin sodium (p.1301·2); glycol salicylate (p.62·3); dimethyl sulfoxide (p.2022·1); lauromacrogol 600 (p.1916·1); dexpanthenol (p.2362·1).
Phlebitis; soft-tissue disorders; venous insufficiency.

Venugel *Permamed, Switz.*
Heparin sodium (p.1301·2); glycol salicylate (p.62·3); dimethyl sulfoxide (p.2022·1); lauromacrogol 600 (p.1916·1); dexpanthenol (p.2362·1).
Phlebitis; soft-tissue disorders; venous insufficiency.

Venusmin *Bushnell, India.*
Diosmin (p.2304·2).
Bleeding during intra-uterine device use; haemorrhoids; menorrhagia; metrorrhagia; varicose veins.

Venustas Antiforfora *BPR, Ital.†.*
Cinchona succirubra (p.2282·3).
Seborrhoeic dermatitis.

Venutabs *Permamed, Switz.*
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

Venxin *Decomed, Port.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; mixed anxiety depressive states; panic disorder; social phobia.

Venyl *Dolisos, Fr.†.*
⊗ Butcher's broom (p.2270·3); hesperidin methyl chalcone (p.2305·2); ascorbic acid (p.1983·3).
Haemorrhoids; peripheral vascular disorders.

Venzadril *More, Philipp.*
⊗ Salbutamol sulfate (p.1131·3); guaifenesin (p.1561·3).
Respiratory-tract disorders associated with bronchospasm and excess mucus.

Vepan *Indoco, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Vepen *Lacefa, Arg.†.*
Vitamin A; vitamin C; vitamin D; minerals (p.1922·1).

Vepesid *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; Bristol, Canad.; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Philipp.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore†; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA.*
Etoposide (p.718·1).
Malignant neoplasms.

Vepeside *Genopharm, Fr.*
Etoposide (p.718·1).
Malignant neoplasms.

Vepicombin *Nycomed, Denm.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Vepiltax *Tecnofarma, Mex.*
Verapamil (p.1423·2).
Hypertension.

Vera *ABZ, Ger.; CT, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Verabeta *Betapharm, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veracaps *Sigma, Austral.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Veracapt *Ebewe, Austria.*
Verapamil hydrochloride (p.1421·1); captopril (p.1239·2).
Hypertension.

Veracef *BMS, Mex.; BMS, Venez.*
Cefradine (p.233·1).
Bacterial infections.

Veracol *Demo, Gr.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Veracolate
Note. This name is used for preparations of different composition.
Elea, Arg.; Pfizer, Thai.
Bile salts (p.2266·2); cascara (p.1715·2); phenolphthalein (p.1762·1); capsicum oleoresin (p.2276·2).
Biliary-tract disorders; constipation; intestinal motility disorders.

Aspen, S.Afr.†.
Cascara sagrada (p.1715·2); phenolphthalein (p.1762·1).
Constipation.

Veracor *Dexxon, Israel; Cofasa, Venez.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veracur *Typharm, UK.*
Formaldehyde (p.1644·2).
Verrucas; warts.

Veracuril *Fada, Arg.*
Oxytocin (p.2015·2).
Labour induction.

Veradin *Novartis, Chile†.*
Paracetamol (p.108·1); aspirin (p.20·3); caffeine (p.1116·3).
Pain.

Veradol *Serch, Arg.†.*
Naproxen (p.92·3).
Inflammation; pain.

Veragamma *Worwag, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veragel
Note. This name is used for preparations of different composition.
United American, Hong Kong; Great Eastern, Thai.; United American, Thai.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); dimethicone (p.1770·2); dicycloverine hydrochloride (p.1722·3).
Dyspepsia; gastric hyperacidity; gastritis; heartburn; peptic ulcer.

UAP, Indon.
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2).
Gastrointestinal disorders.

Veragel DMS *United American, Singapore.*
Aluminium hydroxide-magnesium carbonate co-dried gel (p.1707·2); dimeticone (p.1770·2); dicycloverine hydrochloride (p.1722·3).
Duodenitis; dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; gastrointestinal motility disorders; heartburn; peptic ulcer; pylorospasm.

Verahexal *Hexal, Austral.; Hexal, Cz.; Hexal, Ger.; Hexal, S.Afr.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; obstructive hypertrophic cardiomyopathy.

Verakard *Nycomed, Norw.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veraken *Kener, Mex.*
Verapamil (p.1423·2).

Veral
Note. This name is used for preparations of different composition.
Investi, Arg.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Herbacos, Cz.; SL-Farma, Hung.†.
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Zentiva, Pol.
Diclofenac (p.44·2).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Veraldid *Chobet, Arg.*
Troxerutin (p.2305·1); magnesium ascorbate (p.1679·1).
Varices.

Vera-Lich *Winthrop, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veraligral *Sanofi Synthelabo, Mex.*
Veralipride (p.1035·2).
Menopausal disorders.

Veralipral *Finadiet, Arg.*
Veralipride (p.1035·2).
Menopausal disorders.

Veralipral T *Finadiet, Arg.*
Veralipride (p.1035·2); bromazepam (p.964·3).
Menopausal disorders.

Veralipril *Sanofi Synthelabo, Ital.†.*
Veralipride (p.1035·2).
Menopausal disorders.

Veraljin *Radyum, Turk.*
Dipyrone (p.49·2).
Fever; pain.

Veraloc *Orion, Denm.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veralox *Demo, Gr.*
Omeprazole (p.1753·1).
Acid aspiration; eradication of Helicobacter pylori in combination with antimicrobials; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Veramex *Sanofi Synthelabo, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Veramil
Ducto, Braz.; Orion, Irl.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Themis Chemicals, India.
Verapamil (p.1423·2).
Angina pectoris; arrhythmias; hypertension.

Veramina *Roux-Ocefa, Arg.*
Fosfomycin calcium (p.278·2) or fosfomycin sodium (p.278·2).
Bacterial infections.

Veramon *Sofar, Ital.*
Propyphenazone (p.119·3); paracetamol (p.108·1).
Fever; pain.

Veramyst *GSK, USA.*
⊗ Fluticasone furoate (p.1533·2).
Allergic rhinitis.

Veranorm *Alpharma-Isis, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veranzol *Collins, Mex.*
Albendazole (p.139·2).
Worm infections.

Verap *Rowex, Irl.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Verapabene *Ratiopharm, Austria.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; heart failure; hypertension; hypertrophic obstructive cardiomyopathy.

Verapal *Lafedar, Arg.†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias.

Verapam *Streuli, Switz.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; cardiomyopathy; coronary spasm; hypertension; myocardial infarction.

Verapime *Demo, Gr.*
Cefepime (p.224·1).
Bacterial infections.

Verapin *Berlin Pharm, Thai.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; heart failure; hypertension.

Veraplex *Teva Tuteur, Arg.; Teva, Belg.; Pharmachemie, Indon.; Pharmachemie, Malaysia; Teva, Rus.*
Medroxyprogesterone acetate (p.2113·1).
Breast cancer; endometrial cancer.

Verapress *Dexcel, Israel; Dexcel, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Veraptin *Boniscontro & Gazzone, Ital.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Verasal *TAD, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veraskin *Pharma 2000, Fr.*
Aloe vera (p.1588·2).
Skin disorders; superficial burns and wounds.

Veraspir *Alodial, Port.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Obstructive airways disease.

Verastad *Stada, Austria.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; hypertrophic cardiomyopathy; myocardial infarction.

Veraten *Elea, Arg.*
⊗ Carvedilol (p.1241·3).
Heart failure; hypertension.

Veratide *Basics, Ger.*
⊗ Verapamil hydrochloride (p.1421·1); triamterene (p.1417·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Veratran *Shire, Fr.*
Clotiazepam (p.980·3).
Alcohol withdrawal syndrome; anxiety.

Veratropan Composto *IQB, Braz.*
Hyoscine (p.1733·3); dipyrone (p.49·2).
Muscle spasm; pain.

Veratrum Med Complex *Dynamit, Austria.*
Homoeopathic preparation.

Veraval *Sanval, Braz.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veravorin *Rafarm, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; megaloblastic anaemia.

Verax *Tosi, Hong Kong; Princeps, Ital.*
Benzydamine hydrochloride (p.27·3).
Mouth and throat disorders; vulvovaginal disorders.

Verazinc *Forest Pharmaceuticals, USA.*
Zinc sulfate (p.1999·2).
Dietary supplement.

Verbascum Complex *Blackmores, Austral.†.*
Verbascum thapsus (p.2413·3); marrubium vulgare (p.1564·1); pleurisy root (p.2370·1); liquorice (p.1740·3); ascorbic acid (p.1983·3); vitamin A acetate (p.1973·1).
Respiratory system disorders.

Verbinaf *Pliva, Cz.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Verbital *Faran, Gr.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Verboril
Note. This name is used for preparations of different composition.
TRB, Arg.
Doxycycline hyclate (p.267·1).
Bacterial infections.

Chemedica, Austria; Faran, Gr.
Diacerein (p.41·3).
Osteoarthritis.

Verbram *Antibioticos, Mex.*
Tobramycin (p.354·1).
Bacterial eye infections.

Vercef *Ranbaxy, Cz.; Ranbaxy, Hong Kong; Ranbaxy, Hung.; Ranbaxy, Malaysia; Ranbaxy, Pol.; Ranbaxy, Rus.; Ranbaxy, S.Afr.; Ranbaxy, Singapore; Ranbaxy, Thai.*
Cefaclor (p.217·2).
Bacterial infections.

Vercite *Abbott, Ital.*
Pipobroman (p.763·3).
Chronic myeloid leukaemia; polycythaemia vera.

Vercol *Viofar, Gr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Vercure *Tempo Scan Pacific, Indon.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Vercyte *Abbott, Fr.*
Pipobroman (p.763·3).
Polycythaemia vera.

Verdal
Note. This name is used for preparations of different composition.
Olvos, Gr.
⊗ Fluprednidene (p.1533·1); miconazole (p.541·2).
Fungal skin infections with inflammation.

Falqui, Ital.†.
Aspirin (p.20·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; influenza symptoms; pain.

Verdazol *Pharlab, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Verdeso *Connetics, USA.*
⊗ Desonide (p.1525·1).

Verdilac *Cryopharma, Mex.*
Verapamil (p.1423·2).
Angina pectoris; arrhythmias.

Verecolene CM *GSK Consumer, Ital.*
Bisacodyl (p.1710·1).
Constipation.

Veregen *Bradley, USA.*
Sinecatechins (p.1613·2).
Anogenital warts.

Verel *Astellas, Ital.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3); copper acetate (p.2287·3).
Hard skin; verrucas; warts.

Verelait *Bouty, Ital.*
Lactulose (p.1738·2).
Constipation.

Verelan *OEP, Philipp.; Schwarz, USA.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Verfid *Continentales, Mex.*
Piperazine (p.152·3).
Amoebiasis; worm infections.

Vergentan *Sanofi Synthelabo, Ger.*
Alizapride hydrochloride (p.1704·3).
Nausea and vomiting; radiation sickness.

Vergeturine *Bailleul, Fr.*
Vitamins (p.1922·1).
Skin disorders.

Vergo *Pacific, NZ.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Vergon *Marnel, USA†.*
Meclozine hydrochloride (p.584·3).

Vericaps *Ovelle, Irl.*
Salicylic acid (p.1612·2).
Warts.

Vericin *Giempi, Venez.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; vestibular disorders.

Vericordin *Lazar, Arg.*
⊗ Atenolol (p.1217·3).
Angina pectoris; hypertension.

Vericordin Compuesto *Lazar, Arg.*
⊗ Atenolol (p.1217·3); hydrochlorothiazide (p.1307·3); amiloride hydrochloride (p.1209·2).
Hypertension.

Vericort *Viofar, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; topical corticosteroid.

Verilax *Bernabo, Arg.*
Sodium picosulfate (p.1771·1).
Constipation.

Verile *Medikon, Indon.*
Salicylic acid (p.1612·2); boric acid (p.2268·1); resorcinol (p.1612·1); allantoin (p.1588·1); triclosan (p.1665·2).
Acne.

Verintex *Pekana, Ger.†.*
Homoeopathic preparation.

Verintex N *Pekana, Ger.†.*
Homoeopathic preparation.

Verisan
Note. This name is used for preparations of different composition.
CT, Ital.
Citalopram hydrochloride (p.385·3).
Anxiety disorders; depression.

Knoll, Mex.†.
Aesculus (p.2248·2).
Venous insufficiency.

Veriscal D *Faes, Spain.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency; osteoporosis.

Verisop *Gerard, Irl.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension; supraventricular tachycardia.

Verispasmin *Recordati, Gr.*
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Verladyn *Verla, Ger.*
Dihydroergotamine mesilate (p.618·2).
Hypotension; migraine and related vascular headaches.

Verla-Lipon *Verla, Ger.*
Thioctic acid (p.2400·2) or ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Verlost *Rafarm, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Vermalon *Vargas, Venez.*
Mebendazole (p.148·3).
Worm infections.

Vermazol *Ulagay, Turk.*
Mebendazole (p.148·3).
Worm infections.

Vermectil *Cifarma, Braz.*
Ivermectin (p.145·2).
Filariasis; onchocerciasis; pediculosis; scabies; strongyloidiasis.

Vermex *Hua, Thai.*
Piperazine citrate (p.152·3).
Ascariasis; enterobiasis.

Vermi *Quimpe, Spain.*
Piperazine adipate (p.152·3).
Worm infections.

Vermiben *Cifarma, Braz.*
Mebendazole (p.148·3).
Worm infections.

Vermiclase *Cifarma, Braz.*
Albendazole (p.139·2).
Worm infections.

Vermicol *Degorts, Mex.*
Mebendazole (p.148·3).
Worm infections.

Vermidil *Diba, Mex.*
Mebendazole (p.148·3).
Worm infections.

Vermidon
Note. This name is used for preparations of different composition.
Ilsan, Turk.
Syrup: Paracetamol (p.108·1).
Fever; pain.

Ilsan, Turk.
Tablets: Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Vermidon Cold *Ilsan, Turk.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); pseudoephedrine (p.1571·2).
Respiratory-tract congestion.

Vermidon Hot *Ilsan, Turk.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); phenylephrine (p.1568·1).
Fever; pain.

Vermifran *Faria, Braz.†.*
Piperazine hydrate (p.153·1).
Ascariasis; enterobiasis.

Vermifuge *Sorin-Maxim, Fr.†.*
Piperazine hydrate (p.153·1).
Intestinal nematode infections.

Vermilan *Quimica y Farmacia, Mex.†.*
Albendazole (p.139·2).
Worm infections.

Vermilen *Quimioterapica, Braz.†.*
Piperazine (p.152·3).
Ascariasis; enterobiasis.

Vermilen Composto *Quimioterapica, Braz.†.*
Piperazine (p.152·3); tiabendazole (p.156·2).
Worm infections.

Vermin
Note. This name is used for preparations of different composition.
Ratiopharm, Fin.
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Streger, Mex.
Piperazine (p.152·3).
Worm infections.

Vermin Plus *Streger, Mex.*
Albendazole (p.139·2).
Intestinal nematode infections.

Vermin-Dazol *Streger, Mex.*
Mebendazole (p.148·3).
Worm infections.

Vermine *Pharmasant, Thai.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Verminon *Simoes, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Vermirax *Johnson & Johnson, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Vermis *Utopian, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections.

Vermisen *Novag, Mex.*
Albendazole (p.139·2).
Worm infections.

Vermisol *Khandelwal, India.*
Levamisole (p.147·2).
Worm infections.

Vermital *Elofar, Braz.*
Albendazole (p.139·2).
Worm infections.

Vermixide *Polipharm, Thai.*
Albendazole (p.139·2).
Worm infections.

Vermizym *Bittermedizin, Ger.†.*
Papain (p.2362·3).
Worm infections.

Vermoil *Farmo Quimica, Chile.*
Albendazole (p.139·2).
Worm infections.

Vermol *Faria, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Vermoplex *Cimed, Braz.*
Mebendazole (p.148·3).
Worm infections.

Vermoral *Legrand, Braz.*
Mebendazole (p.148·3).
Worm infections.

Vermox *Janssen-Cilag, Austral.; Janssen-Cilag, Belg.; Janssen-Ortho, Canad.; Janssen-Cilag, Cz.; Janssen-Cilag, Denm.; Janssen-Cilag, Ger.; Janssen-Cilag, Gr.; Janssen, Hong Kong; Gedeon Richter, Hung.; Janssen-Cilag, Indon.; Janssen-Cilag, Irl.; Janssen-Cilag, Israel; Janssen-Cilag, Ital.; Janssen-Cilag, Malaysia; Janssen-Cilag, Mex.; Janssen-Cilag, NZ; McNeil, Neth.; Janssen-Cilag, Norw.; Richter, Pol.; Gedeon Richter, Rus.; Janssen-Cilag, S.Afr.; Janssen-Cilag, Swed.; Janssen-Cilag, Switz.; Janssen-Cilag, UK; Janssen, USA.*
Mebendazole (p.148·3).
Worm infections.

Vermox-Plus *Janssen-Cilag, Mex.*
Mebendazole (p.148·3); quinfamide (p.846·2).
Worm infections.

Vernarin *Nakornpatana, Thai.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; migraine; motion sickness; vestibular disorders.

Vernies *Parke, Davis, Spain.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure; myocardial infarction.

Vernleigh Baby Cream *Adcock Ingram, S.Afr.*
Zinc oxide (p.1621·2); starch.
Skin disorders.

Verocod *Viofar, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Verodex *Opus Materia, Gr.*
Bicalutamide (p.686·2).
Prostatic cancer.

Verogalid *Ivax, Cz.; Ivax, Hung.†; Galena, Rus.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction; obstructive hypertrophic cardiomyopathy.

Verolax *Angelini, Ital.; Lepori, Port.; Farma Lepori, Spain.*
Glycerol (p.2314·2).
Constipation.

Verolin *Demo, Gr.†.*
Serrapeptase (p.2385·3).
Inflammatory disorders.

Verona
Note. This name is used for preparations of different composition.
Solas, Indon.
Javanese turmeric (p.2406·3); milk thistle (p.1452·1); lecithin (p.2332·2).
Liver disorders.

Herbion, Rus.
Tribulus terrestris (p.2404·1); withania; dolichos pruriens; argyreia speciosa.
Sexual functional disorders in men.

Veroptin *Ilsan, Turk.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Veroptinstada *Stada, Ger.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Verorab *Sanofi Pasteur, Arg.; Aventis Pasteur, Braz.†; Sanofi Pasteur, Chile; Sanofi Pasteur, Cz.; Sanofi Pasteur, Hong Kong; Sanofi Pasteur, Indon.; Sanofi Pasteur, Malaysia; Aventis Pasteur, Philipp.; Aventis Pasteur, Pol.; Aventis, S.Afr.; Sanofi Pasteur, Thai.; Sanofi Pasteur, Venez.*
A rabies vaccine (Wistar PM/WI 38-1503-3M strain) (p.2234·1).
Active immunisation.

Verospiron *Gedeon Richter, Cz.; Hormosan, Ger.; Gedeon Richter, Hung.; Richter, Pol.; Gedeon Richter, Rus.*
⊗ Spironolactone (p.1400·1).
Hepatic cirrhosis with ascites; hyperaldosteronism; hypertension; hypokalaemia; nephrotic syndrome; oedema.

Verotina *Libbs, Braz.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder; premenstrual dysphoric disorder.

Verotonil *Bago, Chile†.*
Vitamins; minerals; ginseng; rutoside; lecithin (p.1922·1).
Dietary supplement; tonic.

Veroven *Lepori, Port.*
⊗ Hidrosmin (p.2305·2).
Chronic venous insufficiency.

Veroxil
Note. This name is used for preparations of different composition.
Anfarm, Gr.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Baldacci, Ital.
⊗ Indapamide (p.1314·1).
Hypertension.

Verpamil *Orion, Fin.; Orion, Malaysia; Pacific, NZ; Orion, Singapore.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension; myocardial infarction.

Verpir *Kleva, Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Verpirol *Proula, Venez.*
Piperazine (p.152·3).
Ascariasis; oxyuriasis.

Verra-med *Phoenix, Hung.; Permamed, Switz.*
Tretinoin (p.1618·1); salicylic acid (p.1612·2); dimethyl sulfoxide (p.2022·1).
Warts.

Verruca Hermal *Olvos, Gr.*
Salicylic acid (p.1612·2); fluorouracil (p.722·2).
Verrucas.

Verruca Removal *SSL, Cz.*
Salicylic acid (p.1612·2).
Verrucas.

Verrucare *Medinfar, Port.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3); fluorouracil (p.722·2).
Warts.

Verrucid *Galen, Ger.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Verruclean *LDA, Arg.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Verrufilm
Note. This name is used for preparations of different composition.
Biorga, Fr.; Isopharm, Hong Kong.
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Medinfar, Port.; SSL, Switz.†.
Salicylic acid (p.1612·2).
Corns; verrucas; warts.

Verrugard *Atlas, Arg.*
Salicylic acid (p.1612·2); tretinoin (p.1618·1); dimethyl sulfoxide.
Warts.

Verrugon *Ransom, UK.*
Salicylic acid (p.1612·2).
Verrucas.

Verrulia *Boiron, Fr.*
Homoeopathic preparation.

Verrulyse-Methionine *CS, Fr.*
Magnesium oxide (p.1744·1); methionine (p.1450·1); calcium glycerophosphate (p.1676·1); ferric glycerophosphate (p.2315·2); manganese glycerophosphate (p.2315·2).
Warts.

Verrumal
Note. This name is used for preparations of different composition.
Hermal, Austria; Hermal, Cz.; Hermal, Ger.; Hermal, Hong Kong; Hermal, Hung.; Hermal, Israel; Hermal, Malaysia; Hermal, Singapore; Boots Healthcare, Switz.; Boots, Thai.; Hermal, Thai.
Fluorouracil (p.722·2); salicylic acid (p.1612·2); dimethyl sulfoxide (p.2022·1).
Warts.

Herrmann, Pol.; Almirall, Port.
Fluorouracil (p.722·2); salicylic acid (p.1612·2).
Actinic keratoses; verrucas; warts.

Verrupan *Pharmadeveloppement, Fr.*
Thuja (p.2400·3); salicylic acid (p.1612·2); lactic acid (p.2329·3).
Warts.

Verrupatch *Vinas, Spain.*
Salicylic acid (p.1612·2).
Warts.

Verruplan *Vinas, Spain.*
Salicylic acid (p.1612·2).
Warts.

Verrupor *Sella, Ital.*
Trichloroacetic acid (p.1620·1).
Hard skin; verrucas; warts.

Verrutol *Orva, Turk.*
Salicylic acid (p.1612·2); fluorouracil (p.722·2).
Warts.

Verrutopic *Andromaco, Arg.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Hyperkeratosis; warts.

Verrutopic AS *Andromaco, Arg.*
Salicylic acid (p.1612·2).
Warts.

Verrutrix *Pharmatrix, Arg.*
Salicylic acid (p.1612·2).
Warts.

Verrux *Theraskin, Braz.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Hard skin; keratinisation disorders; warts.

Verruxane *ICN, Arg.†.*
Salicylic acid (p.1612·2).
Warts.

Versa *Humco, USA.*
A range of pharmaceutical bases.

Versacaps *Seatrace, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Versal *Schering-Plough, Denm.†; Schering-Plough, Norw.†; Pro Medica, Swed.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Versalba *Faran, Gr.*
Bendazac (p.27·1).
Inflammatory skin conditions.

Versamiv *Novag, Mex.*
Diiodohydroxyquinoline (p.832·1).
Amoebiasis.

Versant *Imperial, Philipp.*
Felodipine (p.1285·3).
Hypertension.

Versatic *Duncan, Arg.*
Cefadroxil (p.218·1).
Bacterial infections.

Versatil
Note. This name is used for preparations of different composition.
Unipharma, Gr.
⊗ Celiprolol hydrochloride (p.1242·2).
Hypertension.

Stadmed, India†.
Rofecoxib (p.121·1).
Osteoarthritis; pain; rheumatoid arthritis.

Versatis *Grunenthal, Fr.; Grunenthal, Rus.; Grunenthal, UK.*
Lidocaine (p.1862·3).
Local anaesthesia; postherpetic neuropathic pain.

Versed
Roche, Canad.†; Roche, USA†.
Midazolam hydrochloride (p.1007·3).
General anaesthesia; premedication; sedative.

Roche, Fr.
Midazolam (p.1007·3).
Sedative.

Versef *Ranbaxy, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Versel *Valeo, Canad.*
Selenium sulfide (p.1613·1).
Fungal skin infections.

Versiclear *Hope, USA.*
Sodium thiosulfate (p.1466·1); salicylic acid (p.1612·2).
Fungal infections.

Versid *Mulda, Turk.*
Mebendazole (p.148·3).
Worm infections.

Versigen *Chew, Thai.*
Gentamicin (p.284·2).
Bacterial skin infections.

Versilon *Mersifarma, Indon.*
Betahistine mesilate (p.2265·1).
Ménière's disease.

Versiva *Convatec, Ital.; Convatec, Port.†.*
Foamed hydrogel.
Burns; wounds.

Versol *Aguettant, Fr.†; Aguettant, UK.*
Sodium chloride (p.1686·1) or water for irrigation.

Versterkdruppels *Lennon, S.Afr.*
Cinchona bark (p.2282·3); gentian (p.2310·3); dried bitter-orange peel (p.2357·1); quassia (p.2377·1).
Dyspepsia.

Versus *CSC, Austria; Angelini, Ital.*
Bendazac (p.27·1).
Skin disorders.

Vertab *Trinity, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; hypertension.

Verteblan *Demo, Gr.†.*
Dihydroergotamine (p.618·2).
Migraine.

Vertebralon N *Eberth, Ger.†.*
Glycol salicylate (p.62·3); nonivamide (p.96·2); salicylic acid (p.1612·2).
Musculoskeletal, joint, and soft-tissue disorders.

Vertel *Bial, Port.†.*
Pyrantel embonate (p.155·1).

Vertex
Note. This name is used for preparations of different composition.
Meprofarm, Indon.
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Carnot, Mex.†.
Mebendazole (p.148·3).
Worm infections.

Vertigeron *Greenpharma, Braz.*
Cinnarizine (p.573·1).
Vestibular disorders.

Vertigil *Cipla, India.*
Cinnarizine (p.573·1); domperidone (p.1726·2).

Vertiginkgo *Midax, Ital.*
Ginkgo biloba (p.2311·1); vitamin C; vitamin E; manganese (p.1922·1).
Nutritional supplement.

Vertigium *Neo Quimica, Braz.*
Flunarizine hydrochloride (p.580·2).

Vertigo Hevert SL *Hevert, Ger.*
Homoeopathic preparation.

Vertigoheel *Peithner, Austria; Heel, Cz.; Heel, Ger.; Heel, Neth.; Heel, S.Afr.; Heel, USA.*
Homoeopathic preparation.

Vertigo-Hevert *Hevert, Ger.*
Homoeopathic preparation.

Vertigo-Meresa *Dolorgiet, Ger.*
Sulpiride (p.1028·3).
Ménière's disease.

Vertigon *Gerard, Irl.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

vertigo-neogama *Hormosan, Ger.*
Sulpiride (p.1028·3).
Vestibular disorders.

Vertigopas *Pascoe, Ger.*
Homoeopathic preparation.

Vertigo-Vomex *Astellas, Ger.; Galenica, Gr.*
Dimenhydrinate (p.576·2).
Nausea; vertigo; vestibular disorders.

Vertilate *Crisdy-Na, Philipp.*
Betahistine mesilate (p.2265·1).
Ménière's disease; vertigo.

Vertilium *Macrophar, Thai.*
Flunarizine (p.580·3).
Migraine; vestibular disorders.

Vertin *Solvay, India.*
Betahistine hydrochloride (p.2265·1).
Ménière's syndrome; vertigo.

Vertipam *Orion, Fin.*
Diazepam (p.986·3); cyclizine hydrochloride (p.574·2); nicotinic acid (p.1957·3).
Vestibular disorders.

Vertiron *Cipla, India.*
Cinnarizine (p.573·1).

Vertirosan *Sigmapharm, Austria.*
Dimenhydrinate (p.576·2).
Migraine; motion sickness; nausea and vomiting; vestibular disorders.

Vertirosan Vitamin B_6 *Sigmapharm, Austria.*
Dimenhydrinate (p.576·2); pyridoxine hydrochloride (p.1978·2).
Migraine; motion sickness; nausea and vomiting; vestibular disorders.

Vertisal *Silanes, Mex.*
Metronidazole (p.837·1) or metronidazole benzoate (p.837·1).
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Vertiserc *Solvay, Ital.*
Betahistine hydrochloride (p.2265·1).
Vestibular disorders.

Vertisin *Littman, Philipp.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness; vestibular disorders.

Vertivom *GMP, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastrointestinal disorders.

Vertix *Ache, Braz.*
Flunarizine hydrochloride (p.580·2).
Vertigo.

Vertizine *Bernofarm, Indon.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; motion sickness.

Vertizine D *Ache, Braz.*
Dihydroergocristine mesilate (p.364·2); flunarizine hydrochloride (p.580·2).
Vertigo.

Vertizole *Rayere, Mex.*
Mebendazole (p.148·3).
Worm infections.

Vertuss *Madaus, Ital.*
Ivy (p.2328·1).
Coughs.

Verucid
Note. This name is used for preparations of different composition.
Galderma, Denm.; Galderma, Norw.
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Hard skin; warts.

Agis, Israel†.
Salicylic acid (p.1612·2); fluorouracil (p.722·2); dimethyl sulfoxide (p.2022·1).
Warts.

Lepori, Port.†.
Salicylic acid (p.1612·2).

Verufil *Stiefel, Spain.*
Lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Verunec *Savoma, Ital.*
⊗ Salicylic acid (p.1612·2); lactic acid (p.2329·3); urea (p.1620·2).
Hard skin; verrucas; warts.

Verus *Unipharma, Gr.*
Citalopram (p.385·3).
Depression.

Verutex *Roche, Braz.*
Fusidic acid (p.279·3).
Bacterial skin infections.

Verutex B *Roche, Braz.*
⊗ Fusidic acid (p.279·3); betamethasone valerate (p.1519·1).
Infected skin disorders.

Verutil *Novartis, Venez.*
Troxerutin (p.2305·1).
Haemorrhoids; phlebitis; varices.

Very-Test *Serch, Arg.†.*
Pregnancy test (p.2372·1).

Verytracin *Diba, Mex.†.*
Erythromycin (p.269·2).
Bacterial infections.

Very-Vit *Diba, Mex.†.*
Vitamin and mineral preparation (p.1922·1).

Verzat *Randril, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Verzatec *Medinfar, Port.*
Ramipril (p.1385·3).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Verzol *Delta, Braz.*
Mebendazole (p.148·3).
Worm infections.

Verzum *Elofar, Braz.*
Cinnarizine (p.573·1).
Vertigo.

Vesadol *Janssen-Cilag, Fr.†.*
Haloperidol (p.1000·2); buzepide metiodide (p.1714·1).
Gastrointestinal spasms associated with anxiety.

Vesagex *Rybar, Irl.; Co-Pharma, UK.*
Cetrimide (p.1634·1).
Burns; minor wounds; skin disorders; skin injuries, irritation, and inflammation.

Vesagex Heelbalm *Co-Pharma, UK.*
⊗ Allantoin (p.1588·1); peppermint oil (p.1761·2); urea (p.1620·2); moisturisers.
Dry, cracked skin on the heels and soles of the feet.

Vesalion *Nova Argentia, Arg.*
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Vesalion B12 *Nova Argentia, Arg.*
⊗ Diclofenac potassium (p.44·3); betamethasone (p.1518·2); cyanocobalamin (p.1980·2).
Neuralgias.

Vesalion Flex *Nova Argentia, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Inflammation; muscle spasm; pain.

Vesalion Gesic *Nova Argentia, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Vesanoid *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.†; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Tretinoin (p.1618·1).
Acute promyelocytic leukaemia.

Vescopolamine *Vesco, Thai.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Vesdil *AstraZeneca, Ger.; Promed, Ger.; AstraZeneca, Switz.*
Ramipril (p.1385·3).
Heart failure; hypertension; myocardial infarction; nephropathy.

Vesdil plus *AstraZeneca, Ger.; Promed, Ger.*
⊗ Ramipril (p.1385·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Vesema *Pharmex (Φαρμεξ), Gr.*
Citalopram (p.385·3).
Depression.

Vesicare *Eurolab, Arg.; Arrow, Austral.; Astellas, Belg.; Astellas, Cz.; Yamanouchi, Denm.; Astellas, Fin.; Astellas, Fr.; Astellas, Gr.; Astellas, Hung.; Astellas, Indon.; Astellas, Jpn; CSL, NZ; Astellas, Neth.; Astellas, Norw.; Astellas, Pol.; Astellas, Port.; Astellas, Rus.; Astellas, S.Afr.; Astellas, Spain; Astellas, Swed.; Astellas, UK; GSK, USA.*
Solifenacin succinate (p.2196·1).
Bladder hyperactivity; bladder instability.

Vesiherb *Cesra, Ger.; Ruhrpharm, Ger.*
Cucurbita (p.2290·2).
Prostatic disorders.

Vesiker *Astellas, Ital.*
Solifenacin succinate (p.2196·1).
Bladder instability disorders.

Vesikur *Astellas, Ger.*
Solifenacin succinate (p.2196·1).
Urinary incontinence.

Vesilac *Yung Shin, Philipp.*
Bisacodyl (p.1710·1).
Bowel evacuation; constipation.

Vesirig *Aguettant, Fr.†.*
Sodium chloride (p.1686·1).
Lavage and irrigation.

Vesitirim *Astellas, Irl.*
Solifenacin succinate (p.2196·1).
Bladder instability.

Vesix *Leiras, Fin.*
⊗ Furosemide (p.1292·1).
Hypertension; oedema; renal failure.

Vesnidan *Medipharm, Chile.*
Hesperidin (p.2304·3); diosmin (p.2304·2).
Haemorrhoids; venous insufficiency.

Vesoph *Vesco, Thai.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1).
Infected eye and ear disorders.

Vesparax
Note.This name is used for preparations of different composition.
Lazar, Arg.
Quetiapine fumarate (p.1022·2).
Bipolar disorder; schizophrenia.
UCB, Port.†.
Hydroxyzine (p.581·2); brallobarbital (p.964·3); secobarbital (p.1027·3).

Vesprocin *Vesco, Thai.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Vesprolid-HCL *Vesco, Thai.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; rhinitis; upper respiratory-tract congestion.

Vessel
Note.This name is used for preparations of different composition.
Farmion, Braz.†.
Cinnarizine (p.573·1).
Peripheral vascular disorders; vertigo.
Wassermann, Ital.; BioSaude, Port.
Sulodexide (p.1406·3).
Thrombosis prophylaxis; venous ulcer.

Vessel Due *Elmor, Venez.*
Sulodexide (p.1406·3).
Thromboembolic disorders.

Vessel Due F *Alfa Wassermann, Cz.; Alfa Wassermann, Hung.; Wassermann, Malaysia; Wassermann, Philipp.; Alfa Wassermann, Pol.; Alfa Wassermann, Rus.*
Sulodexide (p.1406·3).
Thrombosis; thrombosis prophylaxis.

Vesselvite *Bajamar, USA.*
Folic acid; vitamin B ; vitamin B ; vitamin E (p.1922·1).

Vessiflex *Wassermann, Ital.†.*
Sulodexide (p.1406·3); aminopropylone (p.19·1).
Inflammation; injuries associated with pain and swelling.

Vestaclav *Xepa-Soul Pattinson, Malaysia†.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Vestam *Pharmasant, Thai.*
Ketoprofen (p.73·1).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Vestan *Vesco, Thai.*
Mefenamic acid (p.80·1).
Musculoskeletal and joint disorders; pain.

Vestax *Vargas, Venez.*
Paracetamol (p.108·1).
Fever; pain.

Vesthromycin *Vesco, Thai.*
Roxithromycin (p.331·1).
Bacterial infections.

Vestibo *Actavis, Rus.*
Betahistine hydrochloride (p.2265·1).
Vestibular disorders.

Vesxacin *Vesco, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Vesyca *YSP, Malaysia.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Vetamol *Viofar, Gr.*
Norfloxacin (p.309·2).
Urinary-tract infections.

Vetansil *IQB, Braz.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm.

Vethisel *Rafarm, Gr.†.*
Cefradine (p.233·1).
Bacterial infections.

Vethoine *Wolfs, Belg.*
Phenytoin (p.495·2); phenobarbital (p.492·2); cascara (p.1715·2).
Epilepsy.

Vetilax *Helm, Port.*
Ispaghula (p.1737·1).
Constipation.

Vetio *Ivax, Arg.*
Mitomycin (p.752·1).
Malignant neoplasms.

Vetiprost *Ivax, Arg.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Vetren *Altana, Austria; Opfermann, Ger.*
Heparin sodium (p.1301·2).
Soft-tissue injury; superficial vascular disorders; venous insufficiency.

Vexamet *Vamsler, Philipp.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Vexicam *Chrispa (Χρισπα), Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Vexol *Alcon, Austria; Alcon, Braz.; Alcon, Canad.; Alcon, Cz.†; Alcon, Denm.; Alcon, Fin.; Alcon, Fr.; Alcon, Ger.; Alcon, Gr.; Alcon, Hong Kong; Alcon, Hung.†; Alcon, Irl.; Alcon, Ital.; Alcon, Mex.; Alcon, Neth.; Alcon, Norw.; Alcon, Port.; Alcon Cusi, Spain; Alcon, Swed.; Alcon, Switz.; Alcon, Turk.; Alcon, UK; Alcon, USA.*
⊗ Rimexolone (p.1543·2).
Allergic conjunctivitis; inflammatory eye disorders; uveitis.

Vexolon *Alcon, Belg.*
⊗ Rimexolone (p.1543·2).
Inflammatory eye disorders.

Vexor *Cadila, India.*
Venlafaxine (p.430·1).
Depression.

Vexotil *Biomep, Mex.*
Enalapril (p.1276·1).
Hypertension.

Vexurat *Medinova (Μεντινοβα), Gr.*
Famotidine (p.1730·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Veybirol-Tyrothyricine *Pierre Fabre, Fr.†.*
Solution A: formaldehyde (p.1644·2); solution B: tyrothricin (p.358·2).
Mouth infections.

Vfend *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Roerig, USA.*
Voriconazole (p.550·1).
Fungal infections.

Vi Rid-Ready *Geritrex, USA.*
Octyldecyldimethylammonium chloride (p.1654·3); dioctyldimethylammonium chloride (p.1642·3); didecyldimethylammonium chloride (p.1642·2); benzalkonium chloride (p.1629·1).
Disinfectant.

Via Mal *Altana, Ital.*
Aspirin (p.20·3); caffeine (p.1116·3).
Aluminium hydroxide (p.1706·2) is included in this preparation in an attempt to limit the adverse effects of aspirin on the gastrointestinal mucosa.
Fever; pain.

Via Mal Traumagel *Altana, Ital.*
Diethylamine salicylate (p.47·2); heparin sodium (p.1301·2); menthol (p.2340·1).
Soft-tissue disorders.

Viabom *CPH, Port.*
Dimenhydrinate (p.576·2).
Motion sickness; vertigo.

Viaclav *Kalbe, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Viactiv *McNeil Consumer, Canad.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement.

Viadent *Colgate-Palmolive, Canad.†.*
Sanguinaria (p.2383·2); sodium monofluorophosphate (p.1964·3).
Dental plaque; gingivitis.

Viaderm-KC *Taro, Canad.; AFT, NZ.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); nystatin (p.543·2); gramicidin (p.286·1).
Infected skin disorders.

Viadetres *Alacan, Spain†.*
Hydroxocobalamin (p.1980·3); pyritinol hydrochloride (p.369·1); prosultiamine (p.1975·3).
Vitamin B deficiency.

Viadil *Pharma Investi, Chile.*
Pargeverine hydrochloride (p.1761·1).
Nausea and vomiting; smooth muscle spasm.

Viadil Compuesto *Pharma Investi, Chile.*
Pargeverine hydrochloride (p.1761·1); metamizole magnesium (p.49·3).
Smooth muscle spasm and pain.

Viadoxin *Pyridam, Indon.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Viadur *Alza, USA†.*
⊗ Leuprorelin acetate (p.2111·1).
Prostatic cancer.

Viafen *Novartis Consumer, Ital.*
Bufexamac (p.28·3).
Dermatitis; insect stings; pruritus.

Viafurox *Fada, Arg.†.*
⊗ Furosemide (p.1292·1).
Diuresis.

Viagra *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Ital.; Pfizer, Jpn; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pfizer, USA; Pfizer, Venez.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Viajesan *Calox, Venez.*
Dimenhydrinate (p.576·2).
Nausea; vertigo.

Vialebex *Lab Francais du Fractionnement, Fr.*
⊗ Albumin (p.1052·1).
Hyperbilirubinaemia; plasma volume expansion.

Vial's tonischer Wein *Eberth, Ger.*
Calcium phospholactate; beef extract; cinchonine; wine.
Tonic.

Viani *Allen, Austria; GSK, Ger.; Allen, Gr.†; Euro Registratie, Neth.*
⊗ Salmeterol xinafoate (p.1135·1); fluticasone propionate (p.1533·2).
Asthma; obstructive airways disease.

Viapres *Crinos, Ital.*
Lacidipine (p.1322·2).
Hypertension.

Viarex *Schering-Plough, Israel.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma.

Viarin *Schering-Plough, Neth.*
⊗ Beclometasone dipropionate (p.1516·2).
Rhinitis.

Viarox *Essex, Ger.†; Schering-Plough, S.Afr.†.*
⊗ Beclometasone dipropionate (p.1516·2).
Asthma; obstructive airways disease; rhinitis.

Viartril
Rottapharm, Chile†.
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in the injection to alleviate the pain of injection.
Degenerative joint disorders.
Faran, Gr.; Bioresearch, Mex.†.
Glucosamine (p.2313·2).
Osteoarthritis.

Viartril Flex *Spedrog, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).

Viartril NF *Spedrog, Arg.*
Diclofenac sodium (p.44·3).
Viartril formerly contained rofecoxib.
Gout; inflammation; musculoskeletal and joint disorders; pain.

Viartril S
Rotta, Hong Kong; Rottapharm, Ital.†; Rotta, Malaysia; Pharmalink, Philipp.; Rotta, Philipp.; Delta, Port.; Rotta, Singapore.
Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Degenerative joint disorders; osteoarthritis.
Alian, Venez.
Glucosamine (p.2313·2).
Osteoarthritis.
Rotta, Thai.
Capsules; oral powder: Glucosamine sulfate (p.2313·2).
Musculoskeletal and joint disorders.
Rotta, Thai.
Injection: Glucosamine sulfate (p.2313·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Musculoskeletal and joint disorders.

Viasek *Leti, Venez.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Viasil *SM, Venez.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Viaspan *BMS, Austria; BMS, Fin.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανεξ), Gr.; Boots, Hong Kong; Du Pont, Hong Kong; BMS, Ital.; BMS, Malaysia†; BMS, Port.; BMS, Singapore†; BMS, Spain; BMS, Swed.*
Solution for flushing and cold storage of donor organs.

ViaSpan *BMS, Denm.; BMS, Neth.*
Solution for flushing and cold storage of donor organs.

ViATIM *Sanofi Pasteur, Ger.; Sanofi Pasteur, Irl.; Sanofi Pasteur, Neth.; Sanofi Pasteur, Port.; Aventis Pasteur, UK.*
An inactivated hepatitis A and typhoid (Vi capsular polysaccharide) vaccine (p.2217·2).
Active immunisation.

Viatol *Axcan, Fr.*
Anhydrous glucose; sodium chloride; potassium citrate (p.1672·2).
Diarrhoea; oral rehydration therapy.

Viatopin *GSK, Hung.*
Topotecan hydrochloride (p.780·1).
Ovarian cancer; small-cell lung cancer.

Viatromb *CSC, Austria; Medicom, Cz.*
Heparin sodium (p.1301·2).
Muscle and peri-articular disorders; oedema; phlebitis; soft-tissue injuries; superficial venous disorders; thrombophlebitis; ulcus cruris; varices.

Viavox *Sankyo, Venez.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Viaxal *Menarini, Gr.*
Dexketoprofen (p.73·3).
Inflammatory disorders.

Viaxol *Maver, Mex.*
Ambroxol (p.1550·3).
Respiratory-tract disorders.

Viazem *Biovail, Denm.†; Gea, Swed.†; Genus, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Vi-Balsabron *Lacefa, Arg.†.*
Noscapine (p.1566·2); guaifenesin (p.1561·3); chlorphenamine (p.572·2).
Coughs.

Vibazine *Medibios, India†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Vibeden *Hexal, Denm.*
Hydroxocobalamin (p.1980·3).
Megaloblastic anaemia; vitamin B deficiency.

Vibee *Biolab, Malaysia†; Biolab, Philipp.; Biolab, Singapore.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Vitamin B deficiency.

Viberol Tirotricina *Teofarma, Spain.*
Formaldehyde (p.1644·2); tyrothricin (p.358·2).
Mouth and throat inflammation; oral hygiene.

Vibion *Jean-Marie, Hong Kong.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgias; neuritis; neuropathies; vitamin B deficiency.

Vibolex E *MIP, Ger.*
d-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Vibovit *Polfa Kutno, Pol.*
A range of vitamin preparations with or without minerals (p.1922·1).

Vibracina *Invicta, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Vibradox *Sandoz, Denm.*
Doxycycline (p.267·1).
Bacterial infections.

Vibrafesa *Organifar, Venez.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Vibragel *Novartis Consumer, Arg.*
Dimetindene maleate (p.576·3); phenylephrine (p.1568·1).
Nasal congestion.

Vibral *Solvay, Braz.*
Dropropizine (p.1557·3).
Cough.

Vibralen *Proula, Venez.†.*
Metoclopramide (p.1747·3); pyridoxine (p.1979·1).
Gastrointestinal disorders.

Vibramicina
Pfizer, Arg.; Pfizer, Chile.
Doxycycline (p.267·1).
Bacterial infections; malaria.
Pfizer, Braz.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.
Pfizer, Mex.
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.
Pfizer, Port.
Doxycycline carrageenate (p.267·3).
Amoebiasis; bacterial infections; malaria.

Vibramicina C *Pfizer, Venez.*
Doxycycline (p.267·1).
Bacterial infections.

Vibramox *Pyridam, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Vibramycin
Pfizer, Austral.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK.
Doxycycline hyclate (p.267·1).
Bacterial infections; intestinal amoebiasis; malaria.
Pfizer, Austria; Pfizer, Ger.†; KRKA, Rus.; Pfizer, UK.
Doxycycline (p.267·1).
Bacterial infections.
Pfizer, Denm.†.
Doxycycline carrageenate (p.267·3).
Bacterial infections.
Pfizer, Gr.
Doxycycline (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.
Pfizer, Hung.†.
Doxycycline calcium (p.267·1).
Bacterial infections; intestinal amoebiasis; malaria.
Pfizer, Israel.
Doxycycline calcium chelate (p.267·1) or doxycycline hyclate (p.267·1).
Bacterial infections.
Pfizer, Swed.
Doxycycline carrageenate (p.267·3) or doxycycline hyclate (p.267·1).
Bacterial infections.
Pfizer, USA.
Doxycycline (p.267·1), doxycycline calcium (p.267·1), or doxycycline hyclate (p.267·1).
Bacterial infections.

Vibramycine
Pfizer, Belg.
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.
Pfizer, Switz.
Doxycycline (p.267·1).
Bacterial infections; malaria.

Vibramycine N *CS, Fr.*
Doxycycline (p.267·1).
Bacterial infections.

Vibra-S *Pfizer, Neth.†.*
Doxycycline (p.267·1).
Bacterial infections.

Vibratab *Pfizer, Belg.*
Doxycycline (p.267·1).
Bacterial infections; malaria.

† This preparation may no longer be actively marketed
⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Vibra-Tabs *Pfizer, Austral.; Pfizer, Canad.; Pfizer, USA.*
Doxycycline hyclate (p.267·1).
Bacterial infections; intestinal amoebiasis; malaria.

Vibraveineuse *Pfizer, Switz.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Vibravenos *Pfizer, Austria; Pfizer, Ger.†; IFET (ΙΦΕΤ), Gr.†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Vibravenosa *IFET (ΙΦΕΤ), Gr.†; Pfizer, Spain.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Vibrocil
Note.This name is used for preparations of different composition.
Novartis Consumer, Austria; Novartis Consumer, Cz.; Novartis Consumer, Ger.†; Novartis, Hong Kong†; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Port.; Novartis Consumer, Rus.; Novartis Consumer, Switz.
Dimetindene maleate (p.576·3); phenylephrine (p.1568·1).
Allergic rhinitis; cold and influenza symptoms; nasal congestion; otitis media; rhinorrhoea; sinusitis.

Novartis Consumer, S.Afr.
Dimetindene maleate (p.576·3); phenylephrine (p.1568·1); neomycin sulfate (p.305·1).
Nasal infections; rhinitis; sinusitis.

Novartis Consumer, Belg.†.
Capsules: Dimetindene maleate (p.576·3); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis; sinusitis.

Novartis Consumer, Belg.
Nasal drops; nasal gel; nasal spray: Dimetindene maleate (p.576·3); phenylephrine (p.1568·1).
Rhinitis; sinusitis.

VibrocilFen *Novartis Consumer, Port.*
Phenylephrine (p.1568·1).
Nasal congestion.

Vibrocil-S
Novartis, Gr.
Dimetindene (p.577·1); phenylephrine (p.1568·1).
Antihistamine; nasal decongestant.

Novartis Consumer, S.Afr.
Dimetindene maleate (p.576·3); phenylephrine (p.1568·1).
Nasal and sinus congestion.

Vibrumin *General Drugs, Thai.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Vibtil *Therabel, Belg.*
Tilia (p.2402·2).
Digestive disorders.

Viburcol *Peithner, Austria; Heel, Cz.; Heel, S.Afr.*
Homoeopathic preparation.

Viburcol N *Heel, Ger.*
Homoeopathic preparation.

Vibuzol *Sandoz, Arg.*
Ribavirin (p.902·3).
Chronic hepatitis C.

Vi-C *Sam-On, Israel.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vicalvit *Polfa Kutno, Pol.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Vicalvit D *Polfa Kutno, Pol.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D supplement; osteoporosis.

Vicam *Keene, USA.*
Vitamin B substances (p.1922·1).
Parenteral nutrition.

Vica-Natal *Armoxindo, Indon.*
Vitamins; calcium carbonate; iron; iodine (p.1922·1).
Nutritional supplement; tonic.

Vicapan N *Merckle, Ger.†.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Vi-Caps *Grossmann, Hong Kong; Grossmann, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Vicard *Abbott, Austria.*
Terazosin hydrochloride (p.1410·2).
Hypertension.

Vicardol *Penn, Arg.*
⊗ Carvedilol (p.1241·3).
Hypertension.

Viccillin *Meiji, Indon.; Meiji, Thai.*
Ampicillin sodium (p.204·1) or ampicillin trihydrate (p.204·2).
Bacterial infections.

Viccillin-S *Meiji, Thai.*
Ampicillin (p.204·1); cloxacillin (p.256·1).
Bacterial infections.

Viccillin-SX *Meiji, Indon.*
Sultamicillin (p.344·1).
Bacterial infections.

Vi-Ce *Novartis, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vicebrol *Biofarm, Cz.; Biofarm, Pol.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; dementia.

Vicee *Prafa, Indon.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C deficiency; vitamin C supplement.

Vicefar *Biofarm, Pol.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vicefeno *Fabra, Arg.*
Dextropropoxyphene hydrochloride (p.40·1) or dextropropoxyphene napsilate (p.40·1); dipyrone (p.49·2).
Pain.

Vicemex *Cimex, Hong Kong†; Cimex, Switz.†.*
Vitamin C (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vicenrik *Fada, Arg.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

ViCetamol *Gebro, Austria; Gebro, Hung.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Cold symptoms; fever; pain.

Vichy Dercos Shampooing Antipelliculaire *Vichy, Fr.*
Selenium sulfide (p.1613·1); salicylic acid (p.1612·2).
Dandruff.

Vichy-Autobronzant *Vichy, Canad.†.*
SPF 7: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1).
Sunscreen.

Vichy-Creme Ecran Total *Vichy, Canad.†.*
SPF 25: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Vichy-Lait Ecran Enfants *Vichy, Canad.*
SPF 35: Avobenzone (p.1589·3); octocrilene (p.1608·3); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Vichy-Lait Ecran Extreme *Vichy, Canad.*
SPF 60: Avobenzone (p.1589·3); enzacamene (p.1597·1); ecamsule (p.1596·1); titanium dioxide (p.1617·3).
Sunscreen.

Vici *Monico, Ital.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vick 44 *Procter & Gamble, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Vick 44 Exp *Procter & Gamble, Arg.; Procter & Gamble, Mex.*
Guaifenesin (p.1561·3).
Coughs.

Vick Inalador *Procter & Gamble, Braz.*
Camphor (p.2273·2); menthol (p.2340·1); methyl salicylate (p.85·3); Siberian fir oil.
Nasal congestion.

Vick Pastilhas *Procter & Gamble, Braz.*
Cineole (p.2282·3); menthol (p.2340·1); camphor (p.2273·2); tolu balsam (p.1574·2).

Vick Pyrena *Procter & Gamble, Braz.*
Paracetamol (p.108·1); vitamin C (p.1983·3).
Cold and influenza symptoms.

Vick Sinex *Procter & Gamble, Arg.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Vick Vaporub
Note.This name is used for preparations of different composition.
Procter & Gamble, Arg.†.
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); siberian fir oil.
Nasal congestion.

Procter & Gamble, Braz.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); turpentine oil (p.2406·3); thymol (p.1664·3).
Nasal congestion.

Procter & Gamble, Mex.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Cold symptoms.

Vick Vaporub Inhalador *Procter & Gamble, Mex.*
Menthol (p.2340·1); camphor (p.2273·2).
Cold symptoms; nasal congestion.

Vick Vaporub NF *Procter & Gamble, Arg.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Nasal congestion.

Vick Vitapyrena *Procter & Gamble, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Vick Vitapyrena Forte *Procter & Gamble, Arg.*
Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Vick Xarope *Procter & Gamble, Braz.*
Guaifenesin (p.1561·3).
Coughs.

Vickmiel *Procter & Gamble, Arg.*
Guaifenesin (p.1561·3).
Cough.

Vicks *Famar, Gr.*
Ibuprofen (p.64·2); pseudoephedrine (p.1571·2).

Vicks Acta Plus *Procter & Gamble, S.Afr.*
Pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3); sodium citrate (p.1673·3); chloroform (p.1781·1); cetylpyridinium chloride (p.1635·1).
Coughs.

Vicks Acta Plus Expectorant *Procter & Gamble, S.Afr.*
Guaifenesin (p.1561·3).
Coughs.

Vicks Baby Balsam
Note.This name is used for preparations of different composition.
Procter & Gamble, Ital.†.
Cineole (p.2282·3); lavender oil (p.2331·2); rosemary oil (p.2381·3); aloe vera (p.1588·2).
Nasal congestion.

Procter & Gamble, NZ.
Eucalyptus oil (p.2301·2); rosemary oil (p.2381·3); lavender oil (p.2331·2); aloe vera (p.1588·2).

Vicks Blue Drops *Procter & Gamble, Austral.*
Menthol (p.2340·1); peppermint oil (p.1761·2).
Throat irritation.

Vicks Chest Congestion Relief *Procter & Gamble, Canad.*
Guaifenesin (p.1561·3).

Vicks Children's NyQuil Allergy/Head Cold *Richardson-Vicks, USA.*
Pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Upper respiratory-tract symptoms.

Vicks Children's Nyquil Cold & Cough *Procter & Gamble, Canad.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).

Vicks Children's NyQuil Cold & Cough Relief *Procter & Gamble, USA.*
Chlorphenamine maleate (p.571·3); dextromethorphan hydrobromide (p.1555·2).
Coughs and cold symptoms.

Vicks Cough Drops *Procter & Gamble, USA.*
Menthol (p.2340·1).
Sore throat.

Vicks Cough Lozenges with Honey *Procter & Gamble (H&B Care), UK.*
Dextromethorphan (p.1555·2).
Cough.

Vicks 44 Cough Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Cough Syrup
Note.This name is used for preparations of different composition.
Procter & Gamble, Austral.
Pentoxyverine citrate (p.1567·3); menthol (p.2340·1).
Coughs.

Procter & Gamble, S.Afr.
Sodium citrate (p.1673·3); citric acid (p.2284·1); cetylpyridinium chloride (p.1635·1).
Coughs.

Vicks Cough Syrup for Chesty Coughs *Procter & Gamble, Austral.†; Procter & Gamble (H&B Care), UK.*
Guaifenesin (p.1561·3).
Cough.

Vicks Cough Syrup with Honey for Dry Coughs *Procter & Gamble (H&B Care), UK.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Vicks Cough Syrup with Honey for Dry & Irritating Coughs *Procter & Gamble (H&B Care), UK.*
Levomenthol.
Cough.

Vicks Daymed
Note.This name is used for preparations of different composition.
Procter & Gamble (H&B Care), UK.
Capsules: Paracetamol (p.108·1); caffeine (p.1116·3); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Procter & Gamble (H&B Care), UK.
Hot drink powder: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Vicks DayQuil Cold & Flu Multi-symptom Relief *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); paracetamol (p.108·1).

Vicks DayQuil Multi-Symptom Cold/Flu Relief *Procter & Gamble, USA.*
Phenylephrine hydrochloride (p.1568·1); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Formerly contained pseudoephedrine hydrochloride, dextromethorphan hydrobromide, and paracetamol.
Coughs.

Vicks DayQuil Sinus & Pain Relief *Procter & Gamble, Canad.*
Pseudoephedrine hydrochloride (p.1571·2); ibuprofen (p.64·2).

Vicks DayQuil Sinus Pressure & Pain Relief *Procter & Gamble, USA.*
Pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).

Vicks Decongestant *Procter & Gamble, S.Afr.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinorrhoea; sinusitis.

Vicks 44E *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Vicks Expectorant *Procter & Gamble, Fr.*
Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Vicks Flu-Action *Procter & Gamble, Ital.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Vicks Formula 44
Note.This name is used for preparations of different composition.
Procter & Gamble, Canad.
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Procter & Gamble, NZ.
Dextromethorphan hydrobromide (p.1555·2); menthol (p.2340·1).
Cough.

Procter & Gamble, Spain†.
Anethole (p.2258·1); cetylpyridinium chloride (p.1635·1); dextromethorphan (p.1555·2); benzocaine (p.1854·1); peppermint oil (p.1761·2); menthol (p.2340·1).
Coughs.

Vicks Formula 44D Cough & Head Congestion Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1).
Coughs and cold symptoms.

Vicks Formula 44E *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Vicks Formula 44M *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).
Coughs and cold symptoms.

Vicks Formula 44M Cough, Cold, & Flu Relief *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3); paracetamol (p.108·1).

Vicks Formule 44 Calmine *Procter & Gamble, Switz.*
Dextromethorphan (p.1555·2) or dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Formule 44 Expectine *Procter & Gamble, Switz.*
Guaifenesin (p.1561·3).
Respiratory-tract disorders with viscous mucus.

Vicks Hoestsiroop *Procter & Gamble, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Inalador *Procter & Gamble, Port.*
Menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Vicks Inalante *Procter & Gamble, Ital.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); pine oil (p.2368·2).
Nasal congestion.

Vicks Inhalador *Procter & Gamble, Spain.*
Camphor (p.2273·2); menthol (p.2340·1).
Nasal congestion.

Vicks Inhaler
Note.This name is used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, NZ.
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); pumilio pine oil (p.2376·3).
Nasal congestion.

Procter & Gamble, Canad.; Procter & Gamble, Fr.
Menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Procter & Gamble (H&B Care), UK.
Menthol (p.2340·1); camphor (p.2273·2); siberian fir oil.
Nasal congestion.

Vicks Inhaler N *Procter & Gamble, Switz.*
Menthol (p.2340·1); camphor (p.2273·2); methyl salicylate (p.85·3); pine needle oil.
Nasal congestion.

Vicks Medinait
Note.This name is used for preparations of different composition.
Procter & Gamble, Ital.
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Procter & Gamble, Spain†; Procter & Gamble, Switz.
⊗ Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); ephedrine sulfate (p.1558·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Vicks MediNait
Note. A similar name is used for preparations of different composition (see above).
Eczacibasi, Turk.
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Respiratory-tract congestion.

Vicks Medinite
Note.This name is used for preparations of different composition.
Procter & Gamble, S.Afr.
⊗ Paracetamol (p.108·1); ephedrine sulfate (p.1558·2); doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2).
Cold and influenza symptoms.

Procter & Gamble (H&B Care), UK.
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Cold symptoms.

Vicks Menthol Cough Drops *Procter & Gamble, USA.*
Menthol (p.2340·1); thymol (p.1664·3); eucalyptus oil (p.2301·2); camphor (p.2273·2); tolu balsam (p.1574·2).
Sore throat.

Vicks 44 Non-Drowsy Cold & Cough Liqui-Caps *Procter & Gamble, USA.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).

Vicks Nyquil Cold & Flu *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); doxylamine succinate (p.578·2).

Vicks NyQuil LiquiCaps *Richardson-Vicks, USA.*
Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); doxylamine succinate (p.578·2).
Coughs and cold symptoms.

Vicks NyQuil Multi-Symptom Cold Flu Relief *Procter & Gamble, USA.*
Doxylamine succinate (p.578·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold symptoms.

Vicks NyQuil Sinus *Procter & Gamble, USA.*
Phenylephrine hydrochloride (p.1568·1); doxylamine succinate (p.578·2); paracetamol (p.108·1).
Upper respiratory-tract disorders.

Vicks Paracetamol *Procter & Gamble, Neth.*
Paracetamol (p.108·1).
Fever; pain.

Vicks Pastihas *Procter & Gamble, Port.*
Dextromethorphan (p.1555·2).
Cough.

Vicks Pastil *Eczacibasi, Turk.*
Vitamin C (p.1983·3).
Sore throat.

Vicks Pectoral *Procter & Gamble, Fr.*
Pentoxyverine citrate (p.1567·3).
Coughs.

Vicks Pediatric Formula 44D *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Coughs and cold symptoms.

Vicks Pediatric Formula 44E *Richardson-Vicks, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Vicks Pediatric Formula 44M *Procter & Gamble, Canad.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Cold symptoms.

Vicks Pediatric Formula 44M Cough & Cold Relief *Procter & Gamble, USA.*
Pseudoephedrine hydrochloride (p.1571·2); dextromethorphan hydrobromide (p.1555·2); chlorphenamine maleate (p.571·3).
Coughs and cold symptoms.

Vicks Rhume *Procter & Gamble, Fr.†.*
Ibuprofen (p.64·2); pseudoephedrine hydrochloride (p.1571·2).
Rhinitis.

Vicks Sinex
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, Ital.; Procter & Gamble, NZ; Procter & Gamble, Switz.
⊗ Oxymetazoline hydrochloride (p.1567·2); menthol (p.2340·1); camphor (p.2273·2); cineole (p.2282·3).
Cold symptoms; nasal congestion.

Procter & Gamble, Belg.; Procter & Gamble, Canad.; Procter & Gamble, Fin.; Procter & Gamble, Neth.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion; rhinitis; rhinopharyngitis.

Procter & Gamble (H&B Care), UK.
Capsules: Paracetamol (p.108·1); phenylephrine hydrochloride (p.1568·1).
Cold and influenza symptoms.

Procter & Gamble (H&B Care), UK.
Nasal spray: ⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Vicks Sinex 12-Hour *Procter & Gamble, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Formerly known as Sinex Long Acting.
Nasal congestion.

Vicks Spray *Procter & Gamble, Spain.*
⊗ Oxymetazoline hydrochloride (p.1567·2); menthol (p.2340·1).
Nasal congestion.

Vicks Throat Drops *Procter & Gamble, Austral.†; Procter & Gamble, Canad.; Procter & Gamble, NZ.*
Menthol (p.2340·1).
Coughs; throat irritation.

Vicks Tosse Fluidificante *Procter & Gamble, Ital.*
Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Vicks Tosse Pastiglie *Procter & Gamble, Ital.*
Dextromethorphan (p.1555·2).
Coughs.

Vicks Tosse Sedativo *Procter & Gamble, Ital.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Toux Seche *Procter & Gamble, Fr.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Vapodrops
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.
Menthol (p.2340·1); eucalyptus oil (p.2301·2).
Nasal congestion; sore throat.

Procter & Gamble, NZ.
Menthol (p.2340·1).

Vicks Vapodrops with Butter and Menthol *Procter & Gamble, Austral.*
Menthol (p.2340·1).
Nasal congestion; sore throat.

Vicks VapoDry *Eczacibasi, Turk.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Vicks Vapomist *Procter & Gamble, S.Afr.*
Sodium chloride (p.1686·1).
Nasal congestion.

Vicks Vapor Inhaler *Procter & Gamble, USA.*
⊗ Levmetamfetamine (p.1564·1).
Nasal congestion.

Vicks Vaporub
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.; Procter & Gamble, Belg.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); thymol (p.1664·3).
Cold symptoms; muscle pain; rhinitis; rhinopharyngitis; sinusitis.

Procter & Gamble, Canad.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2).
Cold symptoms.

Procter & Gamble, Fin.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); thymol (p.1664·3).
Cold and influenza symptoms.

Procter & Gamble, Fr.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); thymol (p.1664·3).
Respiratory congestion.

Procter & Gamble, Ital.; Procter & Gamble, Port.; Procter & Gamble (H&B Care), UK.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Nasal congestion; upper respiratory-tract disorders.

Procter & Gamble, Neth.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); thymol (p.1664·3).
Cold and influenza symptoms.

Procter & Gamble, NZ; Procter & Gamble, Swed.†.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); cedar wood oil (p.2278·3); thymol (p.1664·3).
Cold and influenza symptoms; nasal congestion.

Procter & Gamble, S.Afr.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); turpentine oil (p.2406·3); thymol (p.1664·3).
Catarrh; cold symptoms; nasal congestion; sinusitis.

Procter & Gamble, Spain.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine; thymol (p.1664·3).
Upper-respiratory-tract disorders.

Eczacibasi, Turk.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); thymol (p.1664·3); turpentine oil (p.2406·3).
Respiratory-tract disorders.

Procter & Gamble, USA.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); cedar leaf oil (p.2400·3); nutmeg oil (p.2355·3); turpentine oil (p.2406·3).

Vicks Vaporub N *Procter & Gamble, Switz.*
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); cedar leaf oil (p.2400·3); thymol (p.1664·3).
Upper respiratory-tract disorders.

Vicks Vapositoop *Procter & Gamble, Neth.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Vapospray *Procter & Gamble, Port.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

Vicks VapoSyrup *Eczacibasi, Turk.*
Guaifenesin (p.1561·3).
Respiratory-tract congestion.

Vicks Vaposyrup Antitussif *Procter & Gamble, Belg.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Vaposyrup for Chesty Coughs *Procter & Gamble (H&B Care), UK.*
Guaifenesin (p.1561·3).
Coughs.

Vicks Vaposyrup for Dry Coughs *Procter & Gamble (H&B Care), UK.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Vicks Vaposyrup Expectorant *Procter & Gamble, Belg.*
Guaifenesin (p.1561·3).
Coughs.

Vicks Vaposyrup for Tickly Coughs *Procter & Gamble (H&B Care), UK.*
Menthol (p.2340·1).
Coughs.

Vicks Vapotab *Procter & Gamble, Neth.*
Dextromethorphan (p.1555·2).
Coughs.

Vicks Victors Dual Action Cough Drops *Richardson-Vicks, USA.*
Menthol (p.2340·1); eucalyptus oil (p.2301·2).

Vicks Vital
Note. This name is used for preparations of different composition.
Procter & Gamble, Austral.†.
Vitamin C (p.1983·3).
Sore throat.

Procter & Gamble (H&B Care), UK†.
Ascorbic acid (p.1983·3); zinc acetate (p.1999·1).

Vicks Xarope Antitussico *Procter & Gamble, Port.*
Dextromethorphan hydrobromide (p.1555·2).
Cough.

Vick-Zyrt *Vickmans, Hong Kong.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Vi-Claro *Abbott, Chile†.*
⊗ Naphazoline hydrochloride (p.1565·2).
Eye irritation.

Viclor *Richet, Arg.*
Paracetamol (p.108·1).
Fever; pain.

Viclor Grip *Richet, Arg.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3); levophenylephrine (p.1568·3).

Vicloran *Cryopharma, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viclovir *Precimex, Mex.*
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Vicmafen *Offenbach, Mex.*
Diclofenac diethylamine (p.44·3).
Inflammation.

Vicodin *Abbott, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Vicodin Tuss *Abbott, USA.*
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Vicog *Marjan, Braz.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders.

Vicombil *Bial, Port.*
Multivitamin preparation (p.1922·1).

Vicomin A C *Chefaro, Spain.*
Ascorbic acid (p.1983·3); vitamin A palmitate (p.1973·1).
Deficiency of vitamins A and C.

Vicon *UCB, USA.*
A range of vitamin preparations with or without minerals (p.1922·1).

Vicoprofen *Abbott, USA.*
Hydrocodone tartrate (p.63·1); ibuprofen (p.64·2).
Pain.

Vicrom *Aventis, Israel; Aventis, NZ.*
Sodium cromoglicate (p.1136·3).
Asthma; bronchitis.

Victan *Sanofi Synthelabo, Arg.†; Sanofi-Aventis, Belg.; Sanofi-Aventis, Fr.; Sanofi Synthelabo, Mex.; CPH, Port.; Sanofi Synthelabo, Thai.*
Ethyl loflazepate (p.995·3).
Alcohol withdrawal syndrome; anxiety; psychosomatic disorders; sleep disorders.

Victoril *Unipharm, Israel†.*
Dibenzepin (p.388·2).
Depression.

Victrix *Farmasa, Braz.*
Omeprazole (p.1753·1) or omeprazole sodium (p.1753·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer.

Vida Cough *Vida, Hong Kong.*
Chlorphenamine maleate (p.571·3); bromhexine hydrochloride (p.1552·2); pentoxyverine citrate (p.1567·3); guaifenesin (p.1561·3).
Cold and influenza symptoms; cough.

Vida Famodine *Vida, Hong Kong.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Vida Fenadine *Vida, Hong Kong†.*
Terfenadine (p.590·3).
Hypersensitivity reactions.

Vida Flatugel *Vida, Hong Kong.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Gastrointestinal disorders.

Vida Neurotab *Vida, Hong Kong.*
Vitamin B (p.1975·2); vitamin B (p.1978·2); vitamin B (p.1980·2).
Muscle and joint pain; neuralgia; neuritis; vitamin B deficiency.

Vida Salirub *Vida, Hong Kong.*
Methyl salicylate (p.85·3); menthol (p.2340·1); eucalyptus oil (p.2301·2); cajuput oil (p.2271·2).
Insect bites; muscle pain; pruritus; soft-tissue disorders.

Vida-Butaline *Vida, Hong Kong.*
⊗ Terbutaline sulfate (p.1138·3).
Asthma; chronic bronchitis.

Vidaclofen-Plus *Vida, Hong Kong.*
Diclofenac sodium (p.44·3); vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Musculoskeletal, joint, and soft-tissue disorders; neuralgias; neuritis.

Vidaclovir *Vida, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vidadrine *Vida, Hong Kong.*
Pseudoephedrine (p.1571·2).
Allergic rhinitis; nasal congestion.

Vi-Dailin *Abbott, Port.*
Multivitamin preparation (p.1922·1).

Vidalat *Vida, Hong Kong.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Vidalidine *Vida, Hong Kong.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold and influenza symptoms; nasal congestion.

Vidamil *Alpharma, Mex.*
Vitamin A palmitate (p.1973·1); ascorbic acid (p.1983·3); colecalciferol (p.1986·2).
Respiratory-tract infections; skin disorders.

Vidan *Vianex (Βιανέξ), Gr.*
Mefenamic acid (p.80·1).
Inflammation; musculoskeletal and joint disorders; pain.

Vidaperamide *Vida, Hong Kong.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Vidapirocam *Vida, Hong Kong.*
Piroxicam (p.117·3).
Musculoskeletal and joint disorders.

Vidapril *Angelfarma, Port.*
Captopril (p.1239·2).
Heart failure; hypertension.

Vidaspan *Vida, Hong Kong.*
Hyoscine butylbromide (p.1734·1).
Smooth muscle spasm.

Vidastat *Therapharma, Hong Kong; Darya-Varia, Indon.; Therapharma, Philipp.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; coronary heart disease; hypercholesterolaemia.

Vidatapp *Vida, Hong Kong.*
Brompheniramine maleate (p.569·2) phenylephrine hydrochloride (p.1568·1) phenylpropanolamine hydrochloride (p.1569·3).
Cold and influenza symptoms.

Vidatapp Forte *Vida, Hong Kong.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1); bromhexine hydrochloride (p.1552·2); paracetamol (p.108·1).
Cold and influenza symptoms; rhinitis.

Vidatifen *Vida, Hong Kong.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Vidatril *Vida, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Rheumatic disorders.

Vi-Daylin *Abbott, Canad.; Abbott, Hong Kong; Abbott, Malaysia; Abbott, NZ; Abbott, Philipp.; Adcock Ingram Consumer, S.Afr.; Abfar, Turk.; Ross, USA.*
A range of vitamin preparations with or without minerals (p.1922·1).
Nutritional supplement.

Vidaylin *Pharmacia, India; Abbott, Singapore; Abbott, Thai.†.*
A range of vitamin preparations with or without minerals or lysine (p.1922·1).

Vidaylin L *Abbott, Indon.*
Vitamins; lysine hydrochloride; choline; inositol (p.1922·1).
Nutritional supplement; tonic.

Vi-Daylin plus Iron *Abbott, Israel; Adcock Ingram Consumer, S.Afr.*
Multivitamin preparation with iron (p.1922·1).

Vi-Daylin/F *Ross, USA.*
A range of vitamin and fluoride (p.1962·2) preparations (p.1922·1).

Vidaza *Pharmion, USA.*
Azacitidine (p.683·3).
Myelodysplastic syndromes.

Vid-COMOD *Ursapharm, Rus.*
Povidone (p.2146·1).
Dry eyes.

Vi-De$_3$ *Sanova, Austria; Wild, Switz.*
Colecalciferol (p.1986·2).
Osteomalacia; rickets; vitamin D supplement.

Vi-Dea-C *Degorts, Mex.*
Vitamin A; vitamin D; ascorbic acid (p.1922·1).

Videcalcio *Verisfield, Gr.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Videne *Adams, Hong Kong; Adams, Thai.; Adams, UK.*
Povidone-iodine (p.1659·2).
Burns; skin disinfection; wounds.

Video-Light *Euroderm OTC, Ital.*
Benzalkonium chloride (p.1629·1).
Eye disinfection.

Video-Mill *Euroderm OTC, Ital.*
⊗ Naphazoline nitrate (p.1565·2).
Conjunctivitis.

Video-Net *Interdelta, Switz.†.*
⊗ Phenylephrine hydrochloride (p.1568·1); rutoside sodium sulfate (p.2305·2).
Eye irritation.

Videorelax *SIFI, Ital.†.*
Chlorhexidine gluconate (p.1635·3); tilia (p.2402·2); chamomile (p.2279·3).
Eye disinfection; eye irritation.

Viderm *Ganassini, Ital.†.*
Hydroxyquinoline sulfate (p.2323·1); enoxolone (p.50·1).
Wound disinfection.

Vidermina *Ganassini, Ital.*
Copper usnate (p.2409·3).
Vaginal disinfection.

Videx *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Malaysia; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS, USA; BMS, Venez.*
Didanosine (p.870·2).
HIV infection.

Vidilac *Kite (Κιτε), Gr.*
Hypromellose (p.2144·2).
Dry eyes.

Vidintal *Tunggal Idaman, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Vidirakt S *Mann, Ger.*
Povidone (p.2146·1).
Dry eyes.

Vidisep *Kimia, Indon.*
Povidone-iodine (p.1659·2).
Burns; wounds.

Vidisept *Mann, Ger.; Mann, Pol.*
Povidone (p.2146·1).
Dry eyes.

Vidisept N *Mann, Malaysia†; Bausch & Lomb, Philipp.; Bausch & Lomb, Singapore; Mann, Singapore.*
Povidone (p.2146·1).
Dry eyes; eye irritation.

Vidisic *Riel, Austria; Tramedico, Belg.; Bausch & Lomb, Braz.†; Mann, Cz.; Mann, Ger.; Mann, Hung.; Mann, Irl.; Mann, Malaysia†; Tramedico, Neth.; Bausch & Lomb, Philipp.; Mann, Pol.; Lepori, Port.; Mann, Rus.; Bausch & Lomb, Singapore; Mann, Singapore; Bausch & Lomb, Thai.; Mann, Thai.; Pharmalink, Thai.*
Carbomer (p.2141·3).
Dry eyes.

Vidisic PVP *Tramedico, Neth.*
Povidone (p.2146·1).
Dry eyes.

Vidora *Ferlux, Fr.*
Indoramin hydrochloride (p.1315·1).
Migraine.

Vidovir *Vida, Port.*
Aciclovir (p.862·3).

Vidox *Epicaris, Arg.*
Mupirocin (p.302·3).
Bacterial skin infections.

Vidyn *Sigma, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Vie Ca Rad *Multi-Pro, Canad.*
Betacarotene, selenium, vitamin C, and vitamin E (p.1922·1).

VienOks *Toprak, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Viepax *Dexcel, Israel.*
Venlafaxine hydrochloride (p.427·3).
Depression.

Viessia *Lemery, Mex.*
Vinorelbine (p.789·2).

Vieta *Bunker, Braz.*
dl-Alpha tocoferil acetate (p.1992·3).

Viewgam *Bacon, Arg.; Landsteiner, Mex.*
Meglumine gadopentetate (p.1479·2).
Contrast medium for magnetic resonance imaging.

Viewgel *Taiho, Jpn.*
Hydrogel wound dressing.

Vifaderm *Vianex (Βιανέξ), Gr.*
Terbinafine (p.546·3).
Fungal skin infections.

Vifarcap *Farcoral, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Vifazolin *Vianex (Βιανέξ), Gr.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Vifenac *Vifor, Switz.*
Diclofenac epolamine (p.44·3) or diclofenac potassium (p.44·3).
Fever; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Vi-Fer *Deva, Turk.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Vitamin C (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Viferon *Feron, Rus.*
Interferon alpha-2b (recombinant) (p.885·1).
Infections.

Vi-Ferrin *Elofar, Braz.*
Iron chelate (p.1950·3); folic acid (p.1940·1); cyanocobalamin (p.1980·2).
Iron deficiency; iron-deficiency anaemias.

Viflox *Tropica Mas, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Vifloxina *Vitae, Mex.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Vifolyt *Rayere, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Viforcit *Vifor International, Switz.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vifortol *Elea, Arg.*
Vitamin and mineral preparation (p.1922·1) with ginseng (p.2312·1).

Vifortol Prenatal *Elea, Arg.*
Vitamins; ferrous sulfate (p.1939·3); calcium carbonate (p.1922·1).
Iron-deficiency anaemia; nutritional supplement in pregnancy and lactation.

Vig
Note. This name is used for preparations of different composition.
Key, Austral.†.
Chewable tablets: Guarana (p.2416·1); ginseng (p.2312·1); ginkgo biloba (p.2311·1); glucose (p.1945·3).
Tonic.

Key, Austral.
Tablets: Guarana (p.2416·1); ginseng (p.2312·1); ginkgo biloba (p.2311·1).
Tonic.

Vig Recovery *Key, Austral.†.*
Guarana (p.2416·1); vitamin B substances; vitamin C (p.1922·1).
Hangover.

Vigam *BPL-Meizler, Braz.†; BPL, Israel; Bio Products, Malaysia; Landsteiner, Mex.; BPL, Singapore†; BPL, Thai.; Sodhan, Turk.; BPL, UK.*
A normal immunoglobulin (p.2225·3).
Bone-marrow transplantation; Guillain-Barré syndrome; hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; Kawasaki disease; passive immunisation; primary immunodeficiency.

Vigamed *Cimed, Braz.*
Phentolamine mesilate (p.1370·2).
Erectile dysfunction.

Vigamox *Alcon, Arg.; Alcon, Braz.; Alcon, Canad.; Alcon, Chile; Alcon, Hong Kong; Alcon, Israel; Alcon, Malaysia; Alcon, Philipp.; Alcon, Singapore; Alcon, Thai.; Alcon, USA; Alcon, Venez.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial eye infections.

Vigamoxi *Alcon, Mex.*
Moxifloxacin hydrochloride (p.302·1).
Bacterial eye infections.

Vigantol *Merck, Cz.; Merck, Ger.; Merck, Hung.; Merck, Pol.; Merck, Port.; Merck, Rus.*
Colecalciferol (p.1986·2).
Hyperparathyroidism; hypocalcaemia; hypoparathyroidism; osteomalacia; osteopathy; osteoporosis; rickets; spasmophilia; tetany; vitamin D deficiency.

Vigantoletten
Merck, Austria.
Colecalciferol-cholesterin.
Rickets prophylaxis.

Merck, Ger.; Merck, Pol.
Colecalciferol (p.1986·2).
Hyperparathyroidism; osteomalacia; osteoporosis; rickets; tetany; vitamin D deficiency.

Vigarol *Vickmans, Hong Kong.*
Liquid paraffin (p.2030·3).
Constipation.

Vigasil *Loeffler, Mex.*
Miconazole nitrate (p.541·3).
Fungal vulvovaginal infections.

Vi-Gel *Diamond, Philipp.*
Indometacin (p.66·3).
Inflammation; pain.

Vigencial *Estedi, Spain.*
Methylrosanilinium chloride (p.1653·1).
Skin infections.

Vigicer *Beta, Arg.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome.

Vigil *Torrex Chiesi, Cz.; Cephalon, Ger.; Torrex, Pol.*
⊗ Modafinil (p.2160·3).
Narcoleptic syndrome; obstructive sleep apnoea; sleep disorders related to shift work.

Vigilia *Grands Espaces, Fr.*
Tilia (p.2402·2); vervain (p.2413·3).
Nervous disorders.

Vigiten *Wyeth Lederle, Belg.†.*
Lorazepam (p.1004·1).
Anxiety disorders; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

Vigodana *Loges, Hong Kong†.*
α-Tocoferil acetate; orotic acid; procaine hydrochloride; haematoporphyrin; magnesium aspartate; magnesium oxide; magnesium sulfate (p.1922·1).
Tonic.

vigodana N *Loges, Ger.*
Alpha tocoferil acetate; orotic acid; haematoporphyrin; magnesium aspartate; magnesium oxide; dried magnesium sulfate (p.1922·1).
Tonic.

Vigofortal *Pasteur, Chile.*
⊗ Strychnine sulfate (p.2393·2); sodium phosphate; potassium phosphate; phosphoric acid (p.1922·1).
Asthenia; tonic.

Vigomar Forte *Marlop, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Vigor *US Pharmacia, Pol.*
A range of vitamin and mineral preparations (p.1922·1).

Vigor Plus
Note. This name is used for preparations of different composition.
Q-Pharma, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Andromaco, Chile†.
Vitamin and mineral preparation (p.1922·1).
Dietary supplement.

Vigor-ACE *United American, Philipp.*
Vitamin A; vitamin C; vitamin E; selenium; zinc; lecithin (p.1922·1).
Nutritional supplement.

Vigor-Ace *United American, Singapore.*
Vitamin A; vitamin C; vitamin E; selenium; zinc; lecithin (p.1922·1).
Tonic.

Vigoran
Note. This name is used for preparations of different composition.
Vifor, Switz.†.
⊗ Ginseng (p.2312·1); deanol tartrate (p.2152·3); magnesium orotate (p.2358·3).
Tonic.

Konsuma, Venez.
Ginseng (p.2312·1); vitamins; minerals (p.1922·1).
Tonic.

Vigortol *Rugby, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vigortonic *Arkochim, Spain.*
Cinnamon (p.2283·1); ginseng (p.2312·1); kola (p.2416·1).
Fatigue.

Vigorvit *Vamsler, Philipp.*
Vitamins; taurine; lysine; chlorella growth factor (p.1922·1).
Nutritional supplement.

Vigour S *Restan, S.Afr.†.*
Haematoporphyrin; cyanocobalamin; caffeine; yeast extract (p.1922·1).
Tonic.

Vigrande *Eczacibasi, Turk.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Vigranon B *Wallace Mfg Chem., UK.*
Vitamin B substances (p.1922·1).

Vigrasol *Giempi, Venez.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Vikatron *Ariston, Braz.*
Phytomenadione (p.1995·3).

Vikela *Gerot, Austria; HRA, Fr.†; Perryment, Neth.*
Levonorgestrel (p.2121·2).
Postcoital oral contraceptive.

Viken *Kendrick, Mex.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Viking *Rafarm, Gr.*
Lovastatin (p.1328·2).
Hyperlipidaemias.

Vikonon *Neo Laboratories, UK.*
Calcium glycerophosphate; calciferol; thiamine hydrochloride; α-tocoferil acid succinate (p.1922·1).
Vitamin supplement.

Vikrol *Mavi, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Vilacril *Leovan, Gr.†.*
Diclofenac sodium (p.44·3).
Topical anti-inflammatory.

Viladil *Berlin Pharm, Thai.*
Ticlopidine hydrochloride (p.1411·2).
Thromboembolism prophylaxis.

Viladol Plus *Loeffler, Mex.*
Hyoscine butylbromide (p.1734·1); paracetamol (p.108·1).
Smooth muscle pain and spasm.

Vilan *Lannacher, Austria; Lannacher, Denm.; Organon, Neth.†; Symedic, Switz.*
Nicomorphine hydrochloride (p.95·1).
Pain; premedication; smooth muscle spasm.

Vilapon *Metiska, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Gastro-oesophageal reflux; nausea and vomiting.

Vilbine *Richmond, Arg.†.*
Vinorelbine (p.789·2).
Malignant neoplasms.

Vilerm *Siam Bheasach, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viliron *Otto, Indon.*
Vitamin B substances; liver extract; iron; copper (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron. Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.
Tonic.

Vilne *Dosa, Arg.*
Vinorelbine (p.789·2).
Malignant neoplasms.

Vilona *Valeant, Mex.*
Ribavirin (p.902·3).
Viral infections.

Vilonet *Wyeth, Cz.†.*
Desogestrel (p.2093·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Vilonit *Kleva, Gr.*
Diclofenac sodium (p.44·3).
Inflammatory disorders.

Vilox *Behrens, Venez.*
Vitamin and mineral preparation (p.1922·1) with lutein/zeaxanthin.

Vilpin *Pliva Krakow, Pol.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Viltar *Dallas, Arg.*
Loperamide (p.1741·3).
Diarrhoea.

Vilterm *Drag, Chile†.*
⊗ Betamethasone (p.1518·2); gentamicin (p.284·2).
Infected skin disorders.

Vilvom *Medimar, Gr.*
Butamirate (p.1553·1).
Cough.

Vi-Magna *Wyeth, India.*
Multivitamin preparation (p.1922·1).

Vimax
Note. This name is used for preparations of different composition.
Roemmers, Arg.; Roemmers, Chile.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Bio2, Fr.†.
Fish oil; yeast cultured in selenium-rich medium; vitamins; minerals (p.1922·1).
Nutritional supplement.

Vimepan *Collins, Mex.†.*
Vitamin preparation (p.1922·1).

Vimeral *ICN, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Vimetrol *Vamsler, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Viminate *Barre-National, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vimineral *Offenbach, Mex.*
Vitamin and mineral preparation (p.1922·1).

Vi-Mineral *Deva, Turk.*
Vitamin and mineral preparation (p.1922·1).

Viminfort *Solfran, Mex.*
Multivitamin and mineral preparation (p.1922·1).

Vimoli *Vitamed, Israel.*
Paracetamol (p.108·1).
Fever; pain.

Vimotadine *Casasco, Arg.*
Codergocrine (p.364·1).
Cerebrovascular disorders.

Vimultisa *Fabra, Arg.*
Diclofenac potassium (p.44·3).
Inflammation.

Vin Tonique de Vial *Eberth, Switz.†.*
Cinchona alkaloids (p.2282·3); calcium phosphate (p.1676·2); lactic acid (p.2329·3); beef extract; sweet wine.
Tonic.

Vinalac *Novogen, UK.*
Lactobacillus rhamnosus (p.2372·3); vitamins; minerals (p.1922·1).
Dietary supplement in pregnancy and breast feeding.

Vinarine *LKM, Arg.*
Vinorelbine (p.789·2).
Malignant neoplasms.

Vinatal *Triomed, S.Afr.; British Dispensary, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Vinate GT *Breckenridge, USA.*
Vitamin and mineral preparation with iron and folic acid (p.1922·1).
Docusate sodium (p.1725·1) is included in this preparation to reduce the constipating effects of iron.

Vinblasin *Teva, Belg.*
Vinblastine sulfate (p.785·3).
Malignant neoplasms.

Vinblax *Baxter, Mex.†.*
Vincristine sulfate (p.787·1).
Idiopathic thrombocytopenic purpura; malignant neoplasms.

Vinca *Substipharm, Fr.†.*
Vincamine (p.2414·1).
Mental function impairment in the elderly.

Vincacen *Centrum, Spain.*
Vincamine hydrochloride (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Vincadar *Aventis, Ital.†.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Vincagil *Roussel, Port.†.*
Vincamine (p.2414·1).

Vincaminol *Biomed, Spain.*
Vincamine hydrochloride (p.2414·1).
Cerebral trauma; cerebrovascular disorders; circulatory disorders of the eye, ear, nose, and throat; vestibular disorders.

Vincapan *Aventis, Mex.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Vinca-Ri *INTES, Ital.†.*
Vincamine hydrochloride (p.2414·1).
Disorders of cerebral, ocular, and vestibular perfusion.

Vincasar *Pfizer, Mex.†.*
Vincristine sulfate (p.787·1).

Vincasar PFS *Sicor, USA.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vinca-Treis *Ecobi, Ital.*
Vincamine (p.2414·1).
Cerebrovascular disorders.

Vincent's Powders *Roche Consumer, Austral.†.*
Aspirin (p.20·3).
Fever; pain.

Vinces *Ivax, Arg.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vincetron *Biosintetica, Braz.†.*
Piracetam (p.368·2); codergocrine mesilate (p.363·3).
Mental function impairment.

Vincidal *Rayere, Mex.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Vincidol *Salvat, Spain.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Vincigrip *Salvat, Spain.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); paracetamol (p.108·1).
Formerly contained chlorphenamine maleate, phenylpropanolamine hydrochloride, and paracetamol.
Cold and influenza symptoms; fever; pain.

Vinciseptil Otico *Salvat, Spain.*
⊗ Benzydamine hydrochloride (p.27·3); fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3); tetracaine hydrochloride (p.1871·3).
Ear disorders.

Vincitos *Salvat, Spain.*
Dextromethorphan hydrobromide (p.1555·2); pseudoephedrine hydrochloride (p.1571·2).
Cold symptoms; cough.

Vincizina *Pfizer, Braz.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vinco-Abfuhr-Perlen *OTW, Ger.†.*
Bisacodyl (p.1710·1).
Constipation.

Vincosedan *Nupel, Spain.*
Diazepam (p.986·3).
Contains pyridoxine.
Alcohol withdrawal syndrome; anxiety; febrile convulsions; insomnia; skeletal muscle spasm.

Vincrifil *Itaca, Braz.†.*
Vincristine (p.788·1).
Malignant neoplasms.

Vincrisin *Teva, Belg.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vincristex *Cristalia, Braz.†.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vincrisul *Stada, Spain.*
Vincristine sulfate (p.787·1).
Idiopathic thrombocytopenic purpura; malignant neoplasms.

Vindacin *Best, Mex.*
Sulindac (p.126·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Vinecort *Genepharm, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis; skin disorders.

Vinelbine
Dabur, India.
Vinorelbine (p.789·2).
Breast cancer; non-small-cell lung cancer.

Dabur, Thai.
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Vinera *Ativus, Braz.*
Grape (p.2316·3).
Capillary disorders.

Vineuron *Vamsler, Philipp.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Vingel *BMS, Port.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; gastritis; heartburn; peptic ulcer.

Vingional *Fabra, Arg.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Vinho Ferruginoso *Phos-Kola, Braz.†; Teuto, Braz.†.*
Ferric ammonium citrate (p.1938·1).
Iron deficiency; iron-deficiency anaemias.

Vinilex *Alternavida, Mex.*
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Vinitus *Rafarm, Gr.*
⊗ Carteolol hydrochloride (p.1241·1).
Glaucoma.

Vinkebir *Aspen, Arg.*
Vinorelbine (p.789·2).

Vinkhum *Frasca, Arg.*
Vincamine (p.2414·1).

Vino Nordin Vitaminado *Nordin, Mex.*
Vitamin B substances (p.1922·1).

Vinocard Q10 *Marjan, Braz.*
Ubidecarenone (p.2407·2).
Co-enzyme Q10 deficiency.

Vinone *Hikma, Port.†.*
Enoxacin (p.268·3).
Bacterial infections.

Vinorel
Eriochem, Arg.
Vinorelbine (p.789·2).
Malignant neoplasms.

Capsifar, Port.
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Vinorgen *Bioprofarma, Arg.*
Vinorelbine tartrate (p.789·1).
Breast cancer; non-small cell lung cancer.

Vinotel *Dabur, Philipp.*
Vinorelbine tartrate (p.789·1).
Malignant neoplasms.

Vinpocen *Pharmasant, Thai.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; vascular eye disorders.

Vinpo-E *Hexpharm, Indon.*
Vitamin E (p.1992·2).
Antioxidant; vitamin E deficiency.

Vinpoton *Polfa Grodzisk, Pol.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; vascular ear and eye disorders.

Vinpotropile *Kanonfarma, Rus.*
Vinpocetine (p.2414·2); piracetam (p.368·2).
Asthenia; cerebrovascular disorders; mental function disorders; migraine; motion sickness; parkinsonism; vestibular disorders.

Vinracine
BPL-Meizler, Braz.†.
Vincristine (p.788·1).
Malignant neoplasms.

Korean United, Malaysia.
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vinsen *Chew, Thai.*
Naproxen (p.92·3).
Dysmenorrhoea; gout; musculoskeletal and joint disorders.

Vintec *Columbia, Mex.*
Vincristine sulfate (p.787·1).
Malignant neoplasms.

Vintene *Baxter, Fr.*
Amino-acid infusion (p.1922·1).
Parenteral nutrition.

Vintix *Roemmers, Venez.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Vinzam *Almirall, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Vio Celestoderm *Schering-Plough, Venez.†.*
⊗ Betamethasone valerate (p.1519·1); clioquinol (p.254·1).
Infected skin disorders.

Viocort *Aspen, S.Afr.*
⊗ Hydrocortisone acetate (p.1535·2); diiodohydroxyquinoline (p.832·1).
Skin disorders.

Viodine *Orion, Austral.†; Orion, NZ†.*
Povidone-iodine (p.1659·2).
Burns; herpes labialis; skin disinfection; skin infections; sore throat; wounds.

Viodor *Aspen, S.Afr.*
Diiodohydroxyquinoline (p.832·1); benzocaine (p.1854·1).
Skin infections with pruritus.

Vioform-Hydrocortisone *Paladin, Canad.; Novartis Consumer, Irl.; Novartis Consumer, UK.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Anogenital intertrigo; infected insect bites; infected skin disorders.

Vioformio-Hidrocortisona *Novartis, Braz.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Skin disorders.

Vioformo *Novartis, Mex.*
Clioquinol (p.254·1).
Skin infections.

Vioformo-Cort *Novartis, Mex.*
⊗ Clioquinol (p.254·1); hydrocortisone (p.1535·2).
Infected skin disorders.

Viogen-C *Goldline, USA.*
Vitamin B substances with vitamin C and minerals (p.1922·1).

Viohydrocort *Combiphar, Indon.*
⊗ Hydrocortisone acetate (p.1535·2); clioquinol (p.254·1); camphor (p.2273·2).
Skin disorders; skin infections.

Viojen *Gunsa, Turk.*
Methylrosanilinium chloride (p.1653·1).
Wound disinfection.

Viokase
Note. This name is used for preparations of different composition.
Axcan, Canad.; Axcan, USA.
Pancrelipase (p.2360·1).
Pancreatic insufficiency.

Pharmacare, S.Afr.
Pancreatin (p.2360·1).
Pancreatic insufficiency.

Viola *Sanopharm, Switz.*
Viola tricolor (p.2415·2); zinc oxide (p.1621·2); almond oil (p.2252·2).
Skin disorders.

Violin *TO-Chemicals, Thai.*
⊗ Salbutamol (p.1131·2).
Obstructive airways disease.

Vioneurin *Continental Pharma, Belg.†.*
Cyanocobalamin (p.1980·2); thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Alcohol withdrawal syndrome; chronic alcoholism; vitamin B deficiency.

Vioneurin-6 *Galenica, Gr.*
Vitamin B substances (p.1922·1).

Vionin *IPI, Indon.*
Folic acid; biotin; nicotinamide; vitamin E; methionine; choline (p.1922·1).
Nutritional supplement.

Vionin NF *Tempo Scan Pacific, Indon.*
Silymarin (p.1452·2); methionine (p.1450·1); essential phospholipids; zinc; vitamin B (p.1922·1).
Liver disorders.

Vioplex-T *Biospray, Gr.*
Neomycin (p.305·1); bacitracin (p.210·3).
Bacterial infections.

Viopor *Otto, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; magnesium; selenium; zinc (p.1922·1).
Osteoarthritis.

Viopor-M *Otto, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); dimethyl sulfone (p.2294·1); vitamin C; vitamin E; manganese; magnesium; selenium; zinc (p.1922·1).
Osteoarthritis.

Vioquin *Gracia, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Vioridon *Viofar, Gr.*
Baclofen (p.1888·1).
Spasticity.

Viosept *Jelfa, Pol.*
Clioquinol (p.254·1); domiphen bromide (p.1643·1); tripelennamine hydrochloride (p.592·2).
Skin infections.

Viosex *Galeno, Venez.*
Sildenafil (p.2195·1).
Erectile dysfunction.

Vioson *Unison, Philipp.*
Ofloxacin (p.310·2).
Bacterial infections.

Viostin Com *Pharos, Indon.*
Glucosamine sulfate (p.2313·2); chondroitin sulfate (p.2280·3); vitamin C; manganese; selenium (p.1922·1).
Osteoarthritis.

Viostin Com DS *Pharos, Indon.*
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); manganese (p.1922·1).
Osteoarthritis.

Viostin S *Pharos, Indon.*
Chondroitin sulfate (p.2280·3).
Osteoarthritis.

Viotisone *Unison, Hong Kong; Unison, Thai.*
Ofloxacin (p.310·2).
Bacterial infections.

Vioxx *MSD, Arg.†; MSD, Austral.†; MSD, Austria†; MSD, Belg.†; MSD, Braz.†; Merck Frosst, Canad.†; MSD, Cz.†; MSD, Denm.†; MSD, Fin.†; MSD-Chibret, Fr.†; MSD, Ger.†; Vianex (Βιανεξ), Gr.†; MSD, Hong Kong†; MSD, Hung.†; MSD, Irl.†; MSD, Israel†; MSD, Ital.†; MSD, Malaysia†; MSD, Mex.†; MSD, NZ†; MSD, Neth.†; MSD, Norw.†; MSD, Port.†; MSD, S.Afr.†; MSD, Singapore†; MSD, Spain†; MSD, Swed.†; MSD, Switz.†; MSD, Thai.†; MSD, UK†; Merck, USA†; MSD, Venez.†.*
Rofecoxib (p.121·1).
Osteoarthritis; pain; rheumatoid arthritis.

Vioxxakut *MSD, Swed.†.*
Rofecoxib (p.121·1).
Pain.

Vioxxalt *MSD, Denm.†.*
Rofecoxib (p.121·1).
Pain.

Viper *Pascual, Philipp.*
2 Tablets, pyrazinamide (p.320·2); 1 capsule, rifampicin (p.325·3); 1 tablet, isoniazid (p.288·1); 1 tablet, ethambutol (p.275·2); 1 tablet, vitamins and minerals (p.1922·1) (Vitalivin-E).
Tuberculosis.

Viperfav *Sanofi Pasteur, Fr.*
European viper venom antiserum (p.2238·2).
European viper bite.

Viplan *Medipharm, Chile.*
Pargeverine hydrochloride (p.1761·1).
Nausea and vomiting; smooth muscle spasm.

Viplan Compuesto *Medipharm, Chile.*
Pargeverine hydrochloride (p.1761·1); metamizole magnesium (p.49·3).
Pain; smooth muscle spasm.

Viplena *K2 Pharmacare, Chile.*
Orlistat (p.2358·1).
Obesity.

Viplex *Riva, Canad.*
Vitamin B substances and iron (p.1922·1).

Viplura *IQFA, Mex.*
Vitamin preparation (p.1922·1).

Viplus *Parggon, Mex.*
Naproxen sodium (p.92·3); paracetamol (p.108·1).
Fever; pain.

Vipocem *Alodial, Port.*
Vinpocetine (p.2414·2).
Cerebrovascular disorders; vascular disorders of the eye and ear.

Vipodo *Novag, Mex.*
Podophyllum (p.1610·2).
Keratolytic.

Vipral *Ivax, Arg.*
Sulpiride (p.1028·3).
Colitis; dyspepsia; irritable colon; peptic ulcer; psychosomatic disorders.

Vipram *Novell, Indon.*
Spiramycin (p.333·1).
Bacterial infections.

Vipratox nova *Serum-Werk Bernburg, Ger.*
Vipera ammodytes toxin; camphor (p.2273·2).
Vipratox formerly contained Vipera ammodytes toxin, methyl salicylate, and camphor.
Musculoskeletal, joint, and soft-tissue disorders.

Vipres *Uriach, Spain.*
Enalapril maleate (p.1276·1); nitrendipine (p.1358·2).
Hypertension.

Viprosal B
Note. This name is used for preparations of different composition.
Talinn, Cz.†; Tallinn, Rus.
Snake venom (*Vipera berus*); camphor (p.2273·2); salicylic acid (p.1612·2); turpentine oil (p.2406·3).
Cutaneous and subcutaneous pain; musculoskeletal, joint, and peri-articular pain; neuralgia.

Tallin, Pol.
Viper toxin; salicylic acid (p.1612·2); menthol (p.2340·1); siberian fir oil.
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Viproxil *Andromaco, Chile.*
Pargeverine hydrochloride (p.1761·1).
Nausea and vomiting; smooth muscle spasm.

Viproxil Compuesto *Andromaco, Chile.*
Pargeverine hydrochloride (p.1761·1); metamizole magnesium (p.49·3).
Pain; smooth muscle spasm.

Vipsogal *Galenika, Hung.†; Harley Street Supplies, UK.*
⊗ Betamethasone dipropionate (p.1518·3); fluocinonide (p.1532·1); gentamicin sulfate (p.282·1); salicylic acid (p.1612·2); panthenol (p.2362·1).
Keratinisation disorders; psoriasis; skin disorders.

Viquin Forte *ICN, Canad.†.*
Hydroquinone (p.1598·2); glycolic acid (p.1598·1) in a sunscreen basis.
Skin pigmentation disorders.

Viraban *AFT, NZ.*
Aciclovir (p.862·3).
Herpes labialis.

Viracept *Roche, Arg.†; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Pfizer, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Japan Tobacco, Jpn; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, UK; Agouron, USA; Roche, Venez.*
Nelfinavir mesilate (p.898·2).
HIV infection.

Viracillina *Infosint, Ital.†.*
Piperacillin sodium (p.315·2).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Viractin *Medibrands, Canad.*
Tetracaine hydrochloride (p.1871·3).

Virafer *Teofarma, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Viraferon *Schering-Plough, Cz.; Schering-Plough, Fr.; Schering-Plough, Mex.†; Schering-Plough, Neth.; Schering-Plough, Port.; Schering-Plough, UK.*
Interferon alfa-2b (p.885·1).
Chronic hepatitis B; chronic hepatitis C.

ViraferonPeg *Schering-Plough, Cz.; Schering-Plough, Fr.; Schering-Plough, Irl.; Schering-Plough, Neth.; Schering-Plough, Port.; Schering-Plough, UK.*
Peginterferon alfa-2b (p.888·3).
Chronic hepatitis C.

Viragil *Steierl, Ger.*
Homoeopathic preparation.

Virainhi *Dosa, Arg.*
Nevirapine (p.899·1).
HIV infection.

Viralief *Clonmel, Irl.*
Aciclovir (p.862·3).
Herpes simplex skin infections.

Viralis *GMP, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viramid *Valeant, Braz.*
Ribavirin (p.902·3).
Viral infections.

Viramixal *Panalab, Arg.*
Valaciclovir (p.911·2).
Herpesvirus infections.

Viramune *Boehringer Ingelheim, Arg.; Boehringer Ingelheim, Austral.; Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Braz.; Boehringer Ingelheim, Canad.; Boehringer Ingelheim, Chile; Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Denm.; Boehringer Ingelheim, Fin.; Boehringer Ingelheim, Fr.; Boehringer Ingelheim, Ger.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Hong Kong; Boehringer Ingelheim, Hung.; Boehringer Ingelheim, Indon.; Boehringer Ingelheim, Irl.; Boehringer Ingelheim, Israel; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Jpn; Boehringer Ingelheim, Malaysia; Boehringer Ingelheim, Mex.; Boehringer Ingelheim, NZ; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Norw.; Boehringer Ingelheim, Pol.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Rus.; Boehringer Ingelheim, S.Afr.; Boehringer Ingelheim, Singapore; Boehringer Ingelheim, Spain; Boehringer Ingelheim, Swed.; Boehringer Ingelheim, Switz.; Boehringer Ingelheim, Thai.; Boehringer Ingelheim, Turk.; Boehringer Ingelheim, UK; Roxane, USA; Boehringer Ingelheim, Venez.*
Nevirapine (p.899·1).
HIV infection.

Viranet *LKM, Arg.*
Valaciclovir (p.911·2).

Virasolve *Hamilton, Austral.; Rosken, Hong Kong†; Pfizer, NZ.*
Idoxuridine (p.881·2); lidocaine hydrochloride (p.1862·3); benzalkonium chloride (p.1629·1).
Herpes simplex infections of the mouth and skin.

Virasorb *Thornton & Ross, UK.*
Aciclovir (p.862·3).
Herpes labialis.

Viratin *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Viratop *Topgen, Belg.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viravan *Pediamed, USA.*
Phenylephrine tannate (p.1568·3); mepyramine tannate (p.585·2).

Viravan-DM *Pediamed, USA.*
Dextromethorphan tannate (p.1556·1); mepyramine tannate (p.585·2); phenylephrine tannate (p.1568·3).
Upper respiratory-tract disorders.

Virax *Alpharma-Isis, Ger.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viraxy *General Drugs, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virazide *Valeant, Austral.; Armoxindo, Indon.; Grossman, Mex.*
Ribavirin (p.902·3).
Influenza; respiratory syncytial virus infection.

Virazole *Pharma Logistics, Belg.; UCI, Braz.†; Valeant, Canad.; Valeant, Ger.; Valeant, Hong Kong; Galenika, Hung.†; ICN, Ital.; ICN, Neth.; Valeant, Rus.; Valeant, Singapore; Valeant, Spain; Medilink, Swed.; Valeant, Switz.†; ICN, UK; ICN, USA.*
Ribavirin (p.902·3).
Haemorrhagic fever with renal syndrome; influenza; respiratory syncytial virus infection.

Vircella *Galenium, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vir-Complex *Cristalia, Braz.†.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Vircovir *Corsa, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virdam *Pyridam, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virdex *Fulton, Ital.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); aminophenazone (p.19·1).
Migraine.

Virdos *UCB, Neth.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; urticaria.

Virdox *Lacer, Spain†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Viread *Gador, Arg.; Gilead, Austral.; Gilead, Austria; UCB, Belg.; Gilead, Canad.; Gilead, Chile; Gilead, Cz.; Gilead, Denm.; Orphan, Fin.; Gilead, Fr.; Gilead, Ger.; Gilead, Gr.; Gilead, Hung.; Gilead, Irl.; Neopharm, Israel; Gilead, Ital.; Stendhal, Mex.; Gilead, NZ; Gilead, Neth.; Gilead, Norw.; Gilead, Pol.; Gilead, Spain; Swedish Orphan, Swed.; Chemedica, Switz.; Gilead, UK; Gilead, USA.*
Tenofovir disoproxil fumarate (p.908·3).
Chronic hepatitis B; HIV infection.

Viregyt *EGIS, Hung.*
Amantadine hydrochloride (p.792·3).
Influenza; parkinsonism.

Viregyt K *Egis, Pol.*
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Viregyt-K *Egis, Cz.*
Amantadine hydrochloride (p.792·3).
Influenza; parkinsonism.

Virerpin *Kleva, Gr.*
Vidarabine (p.912·2).
Herpesvirus infections.

Virest *Hovid, Hong Kong; Hovid, Malaysia†; Hovid, Philipp.; Hovid, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virestat *Liferpal, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vireth *Ethica, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virexen *Will-Pharma, Belg.†; Will Pharma, Neth.; Ferraz, Lynce, Port.†; Vinas, Spain.*
Idoxuridine (p.881·2) in dimethyl sulfoxide.
Herpesvirus infections of the skin and mucous membranes.

Virfen *Specifar (Σπεσιφαρ), Gr.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Virflutam *Infosint, Ital.†.*
Flutamide (p.725·1).
Prostatic cancer.

Virgan *Sidus, Arg.; Thea, Belg.; Santen, Cz.; Thea, Fr.; Thea, Philipp.; Thea, Pol.; Thea, Port.; Bausch & Lomb, UK†.*
Ganciclovir (p.879·1).
Herpesvirus eye infections.

Virgilocard *Sanova, Austria.*
Crataegus (p.2289·1); absinthium (p.2244·1).
Cardiac disorders in the elderly.

Virginiana Gocce Verdi *Kelemata, Ital.†.*
⊗ Naphazoline nitrate (p.1565·2).
Eye congestion.

Virgogel *Virgo, Philipp.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastric hyperacidity; peptic ulcer.

Virgomine *Virgo, Philipp.*
Chlorphenamine maleate (p.571·3).
Allergic and inflammatory skin disorders.

Virgovit *Virgo, Philipp.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Virherpes *Pensa, Spain.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Viridal *Schwarz, Ger.; Schwarz, Irl.; Schwarz, Ital.; UCB, UK.*
Alprostadil alfadex (p.2183·3).
Erectile dysfunction.

Viridil *Roemmers Rowe, Venez.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Viridin *Davi, Port.*
Trifluridine (p.910·3).
Viral eye infections.

Virigen
Note. This name is used for preparations of different composition.
Actavis, Denm.
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Organon, Turk.
⊗ Testosterone undecylate (p.2130·2).
Androgen deficiency.

Virilan *Gebro, Austria.*
Alprostadil alfadex (p.2183·3).
Erectile dysfunction.

Virilis-Gastreu S R41 *Reckeweg, Ger.*
Homoeopathic preparation.

Virilit *Jenapharm, Ger.*
Cyproterone acetate (p.2088·2).
Androgen-dependent acne, alopecia, hirsutism, and seborrhoea in women; erectile dysfunction; prostatic cancer.

Virilon
Note. This name is used for preparations of different composition.
Temis, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Luper, Braz.†.
Ginseng; catuaba; muira-puama; vitamins (p.1922·1).

Star, USA.
Capsules: ⊗ Methyltestosterone (p.2117·1).
Androgen replacement therapy; breast cancer; male hypogonadism; postpartum breast engorgement; prepubertal cryptorchidism.

Star, USA†.
Injection: ⊗ Testosterone cipionate (p.2129·3).

Virin *Strand, Malaysia†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Viripotens *Microsules, Arg.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Virkon *Antec, Singapore; Du Pont, Singapore.*
Peroxygen compounds (p.1655·2).
Surface disinfection.

Virless *YSP, Malaysia; Yung Shin, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virlix *UCB, Austria; Farchim, Cz.†; UCB, Denm.†; Sanofi-Aventis, Fr.; Mediolanum, Ital.†; GSK, Mex.; UCB, Norw.†; GSK, Philipp.; Pliva Krakow, Pol.; Vedim, Port.; Lacer, Spain; Bilim, Turk.; Grunenthal, Venez.†.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; urticaria.

Virlix Plus *Lacer, Spain.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Virlix-D *GSK, Mex.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; eye irritation; nasal congestion.

Virman Plus *Corypharma, Ital.*
Vitamin E; nicotinic acid; zinc (p.1922·1).
Nutritional supplement.

Virmax *Bago, Chile†.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Virmen *Menarini, Spain.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viro *Rentschler, Cz.†.*
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Virobin
Note. This name is used for preparations of different composition.
Pharmabiotics, Chile.
Oseltamivir phosphate (p.900·2).
Influenza.

Bock, Ger.†.
Homoeopathic preparation.

Virobis
Note. This name is used for preparations of different composition.
Aventis, S.Afr.†.
Cream: Moroxydine hydrochloride (p.898·2); cetrimide (p.1634·1); diphenhydramine hydrochloride (p.577·2).
Viral infections of the skin.

Aventis, S.Afr.†.
Tablets: Moroxydine hydrochloride (p.898·2); atropine methonitrate (p.1219·3); hyoscine methonitrate (p.1734·2).
Viral infections.

Virobron *Temis, Arg.*
Nimesulide (p.95·3).
Inflammation.

Virobron B12 NF *Temis, Arg.*
⊗ Betamethasone (p.1518·2); vitamin B (p.1980·2); diclofenac potassium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders; neuritis.

Virobron Gel *Temis, Arg.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint and soft-tissue disorders.

Virobron NF *Temis, Arg.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders; pain.

Viroclear *Christo, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viroclon *Medicus, Gr.*
Zidovudine (p.913·3).
HIV infection.

Viro-Do *Grasler, Ger.*
Homoeopathic preparation.

Viroflu *Sanofi Pasteur, UK.*
An influenza vaccine (surface antigen) (p.2218·2).
Active immunisation.

Virogerm *Zedchem, S.Afr.*
Glutaral (p.1645·2).
Instrument disinfection.

Virogon *Silom, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virohep-A *Scott-Cassara, Arg.*
A hepatitis A vaccine (p.2214·2).
Active immunisation.

Virokill *Biogal-Teva, Hung.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virolan *Olan-Kemed, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Virolex
KRKA, Cz.; KRKA, Pol.; KRKA, Rus.
Aciclovir (p.862·3).
Herpesvirus infections.

KRKA, Hung.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

ViroMed *S Med, Austria.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viromed *Medicine Products, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viromidin *Alcon Cusi, Spain.*
Trifluridine (p.910·3).
Herpes simplex infections of the eye.

Viron Wart Lotion *Odan, Canad.*
Glacial acetic acid (p.2244·2); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Verrucae.

Vironida *Laboratorios Chile, Chile.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viropect *DHU, Ger.*
Homoeopathic preparation.

Virophta *Allergan, Fr.*
Trifluridine (p.910·3).
Viral infections of the eye.

Viropox *LSP, Thai.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viroptic *Theramed, Canad.; Glaxo Wellcome, USA; Monarch, USA.*
Trifluridine (p.910·3).
Herpes simplex keratitis and keratoconjunctivitis.

Virormone
Paines & Byrne, Thai.†.
⊗ Testosterone propionate (p.2130·1).
Female breast cancer; male hypogonadism.

Nordic, UK.
⊗ Testosterone (p.2129·3) or testosterone propionate (p.2130·1).
Breast cancer; cryptorchidism; delayed puberty; male hypogonadism.

Virorrever *Richmond, Arg.*
Efavirenz (p.872·3).
HIV infection.

Virosil *Saba, Turk.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virosol *Phoenix, Arg.*
Amantadine hydrochloride (p.792·3).
Parkinsonism; viral infections.

Virostatic *Cassara, Arg.*
Aciclovir (p.862·3).
Herpes labialis.

Virostav *Ranbaxy, Malaysia.*
Stavudine (p.907·1).
HIV infection.

Virotec *Vida, Port.*
Zidovudine (p.913·3).
HIV infection.

Virovir *Opus, UK.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viroxil *Quimica y Farmacia, Mex.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Virozid *Teuto, Braz.†.*
Zidovudine (p.913·3).
HIV infection.

Virpes *Bernofarm, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virtamox *Infosint, Ital.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Virtaz-200 *Fahrenheit, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virubact *Biosyn, Ger.†.*
Homoeopathic preparation.

Virucalm *Zambon, Fr.; Zambon, Switz.*
Aciclovir (p.862·3).
Herpes labialis.

Virucid
Note. This name is used for preparations of different composition.
Hofmann, Austria†.
Amantadine hydrochloride (p.792·3).
Influenza A; parkinsonism.

Aegis, Hong Kong.
Aciclovir (p.862·3).
Herpesvirus infections.

Viruderm *Cinfa, Spain.*
Aciclovir (p.862·3).
Herpes simplex infection.

Virudermin *Robugen, Ger.; Iromedica, Switz.*
Zinc sulfate (p.1999·2).
Herpes labialis.

Virules *Kimia, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Virulex
Note. This name is used for preparations of different composition.
Drossapharm, Switz.
Greater celandine (p.2317·1).
Herpes labialis.

Pose, Thai.
Hand gel; hand rub: Triclosan (p.1665·2).
Skin disinfection.

Pose, Thai.
Powder for solution: Monopersulfate compound; sodium chloride; sulphamic acid.
Instrument disinfection.

Virulex Forte *Pascual, Hong Kong.*
Moroxydine hydrochloride (p.898·2); paracetamol (p.108·1); atropine methonitrate (p.1219·3); hyoscine methonitrate (p.1734·2).
Viral infections.

Virulizin *Mayne, Mex.*
Ox bile extract (p.2266·3).
Malignant melanoma.

Viru-Merz *Therabel, Belg.†; Grunenthal, Chile†; Merz, Cz.; Merz, Hong Kong; Merz, Hung.; Combiphar, Indon.; Merz, Indon.; Merz, Israel; Merz, Malaysia; Merz, Neth.†; Merz, Philipp.; Merz, Pol.; Medinfar, Port.; Merz, Singapore†.*
Tromantadine hydrochloride (p.911·1).
Herpes simplex infections of the skin and mucous membranes.

Viru-Merz Serol *Kolassa, Austria; Merz, Ger.; Pharmacare, Gr.; Merz, Rus.; Merz, Switz.*
Tromantadine hydrochloride (p.911·1).
Herpes simplex infections of the skin and mucous membranes.

Virunguent *Hermal, Ger.; Hermal, Malaysia†; Hermal, Port.†; Hermal, Singapore; Boots Healthcare, Switz.*
Idoxuridine (p.881·2) in dimethyl sulfoxide.
Herpes simplex infections of the skin and mucous membranes.

Virunguent P *Hermal, Ger.†.*
⊗ Idoxuridine (p.881·2); prednisolone (p.1540·3).
Herpes simplex infections.

Virupos *Ursapharm, Ger.; Biem, Turk.*
Aciclovir (p.862·3).
Herpes simplex eye infections.

Viru-Salvysat *Ysatfabrik, Ger.†.*
Sage (p.2382·3).
Mouth and throat infections.

Virusan *Rekah, Israel†.*
Idoxuridine (p.881·2).
Herpes simplex eye infections.

Viruseen *Hommel, Ger.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Viruserol *Novartis Consumer, Ital.†.*
Tromantadine hydrochloride (p.911·1).
Herpesvirus infections of the skin.

Viru-Serol *Merz, Mex.; Lacer, Spain.*
Tromantadine hydrochloride (p.911·1).
Herpesvirus infections of the skin and mucous membranes.

Virusteril *Biospray, Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Virustop *Pulitzer, Ital.†.*
Inosine pranobex (p.884·2).
Immunodeficiency; viral infections.

Viruxan *Sigma-Tau, Ital.*
Inosine pranobex (p.884·2).
Immunodeficiency; viral infections.

Virval *GSK, Spain.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Virzin *Dermapharm, Ger.*
Aciclovir (p.862·3).
Herpesvirus infections.

Visacor *AstraZeneca, Port.*
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.

Visadron *Boehringer Ingelheim, Austria; Boehringer Ingelheim, Belg.; Boehringer Ingelheim, Cz.†; Alcon, Ger.; Boehringer Ingelheim, Ital.†; Boehringer Ingelheim, Neth.; Unilfarma, Port.; Boehringer Ingelheim, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Conjunctivitis; eye irritation.

Visaline *Bausch & Lomb, Switz.*
⊗ Buphenine hydrochloride (p.2270·2); betacarotene (p.1930·3); alpha tocopherol (p.1992·2); ascorbic acid (p.1983·3).
Eye disorders.

Visalmin *Bunker, Braz.*
Chloramphenicol (p.239·3).
Bacterial eye infections.

Visamin *Bittner, Austria.*
Homoeopathic preparation.

Visancort *Sanbe, Indon.*
⊗ Hydrocortisone (p.1535·2); clioquinol (p.254·1); camphor (p.2273·2).
Skin disorders; skin infections.

Visano N *Kade, Ger.†.*
Meprobamate (p.1006·2).
Anxiety disorders; gastrointestinal disorders; insomnia.

VisanoCor N *Kade, Ger.†.*
Pentaerithrityl tetranitrate (p.1366·3); diphenhydramine hydrochloride (p.577·2).
Cardiac disorders.

Visano-mini N *Kade, Ger.†.*
Meprobamate (p.1006·2).
Anxiety disorders; sleep disorders.

Visazul *Neo Quimica, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc phenolsulfonate (p.1621·3); berberine sulfate (p.2264·3).

Viscaplus *Sifarma, Ital.*
Marine cartilage; amino acids; minerals; antioxidants (p.1922·1).
Alopecia; nutritional supplement.

Viscard *Norma (Νορμα), Gr.†.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Viscasan *Bioforce, Ger.†.*
Homoeopathic preparation.

Visceralgine
Exel, Belg.†.
Tiemonium iodide (p.1776·3).
Smooth muscle spasm.

Organon, Fr.; Organon, Indon.
Tiemonium metilsulfate (p.1776·3).
Smooth muscle spasm.

Visceralgine Forte *Organon, Fr.†.*
Tiemonium metilsulfate (p.1776·3); dipyrone (p.49·2).
The tablets formerly contained tiemonium metilsulfate, dipyrone, and codeine phosphate.
Pain; smooth muscle spasms.

Visclair *Sinclair, Irl.; Sinclair, UK.*
Mecysteine hydrochloride (p.1564·2).
Respiratory-tract disorders with excessive or viscous mucus.

Visco *Aristo, India.*
Alginic acid (p.2140·3) or sodium alginate (p.2141·1); magnesium hydroxide (p.1743·2); aluminium hydroxide (p.1706·2); simeticone (p.1770·2).
Gastric hyperacidity; heartburn.

Viscoat *Alcon, Arg.; Alcon, Austral.; Alcon, Fr.; Alcon, Ger.; Alcon, Hong Kong†; Alcon, Hung.†; Alcon, Ital.; Alcon, Malaysia; Alcon, NZ; Alcon, Philipp.; Alcon, S.Afr.; Alcon, Singapore; Alcon, Thai.; Alcon, Turk.; Alcon, USA; Alcon, Venez.†.*
Chondroitin sulfate sodium (p.2280·3); sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Viscoblast *DMG, Ital.*
Carboxymethyl betaglucan; n-hydroxymethylglycinate.

Viscoblast Mono *DMG, Ital.*
Carboxymethyl betaglucan.

Viscofresh *Allergan, Spain.*
Carmellose sodium (p.2142·1).
Dry eyes.

Viscol *Liba, Turk.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Viscolex *Pinewood, Irl.*
Carbocisteine (p.1553·2).
Respiratory-tract disorders with excessive or viscous mucus.

Viscolyt *Gea, Denm.†.*
Bromhexine hydrochloride (p.1552·2).
Dry eyes; respiratory-tract congestion.

Viscomucil *ABC, Ital.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Visconisan N *Hanosan, Ger.†.*
Homoeopathic preparation.

Viscopaste *Smith & Nephew, Irl.*
Zinc oxide (p.1621·2).
Dermatitis; leg ulcers; medicated bandage; varicose eczema.

Viscopaste PB7 *Smith & Nephew, Ital.; Smith & Nephew, S.Afr.; Smith & Nephew, UK.*
Zinc oxide (p.1621·2).
Medicated bandage.

Visc-Ophtal *Winzer, Ger.*
Carbomer (p.2141·3).
Dry eyes.

Viscophyll *Krewel, Ger.†.*
Mistletoe (p.2345·3); bladderwrack (p.2384·2).
Circulatory disorders.

Viscorapas duo *Pascoe, Ger.†.*
Convallaria (p.2287·3); crataegus (p.2289·1).
Heart failure.

Viscoseal *Chemedica, Ger.; Chemedica, Malaysia; Chemedica, Switz.; Chemedica, UK.*
Sodium hyaluronate (p.2320·1).
Synovial fluid replacement in arthroscopy or joint lavage.

Viscotears *Novartis Ophthalmics, Arg.; Novartis, Austral.; Novartis, Braz.; Novartis, Chile; Novartis, Denm.; Novartis, Fin.; Novartis, Hong Kong; Novartis, Israel; Novartis, Mex.; Ciba Vision, NZ; Novartis, Norw.; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Novartis, Turk.; Novartis, UK; Novartis, Venez.*
Carbomer (p.2141·3).
Dry eyes; eye irritation.

Viscoteina *Iquinosa, Spain.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Viscoter *Novartis, Gr.*
Carbomer (p.2141·3).
Dry eyes.

Viscotiol *Celltech, Fr.†.*
Letosteine (p.1563·3).
Respiratory-tract congestion.

Viscotirs *Novartis, Ital.*
Carbomer (p.2141·3).
Dry eyes.

Viscotraan *Adcock Ingram, S.Afr.*
Hypromellose (p.2144·2).
Dry eyes.

Viscozyme *Roche, Chile.*
Dornase alfa (p.1557·1).
Cystic fibrosis.

Viscum album H *Pfluger, Ger.*
Homoeopathic preparation.

Viscysat *Ysatfabrik, Ger.*
Mistletoe (p.2345·3).
Circulatory disorders.

Visderm *Wyeth-Ayerst, Thai.†.*
⊗ Amcinonide (p.1516·2).
Skin disorders.

Visderm H *Darier, Mex.*
⊗ Amcinonide (p.1516·2).
Inflammatory skin disorders.

Visebad *Otto, Indon.*
Vitamin preparation (p.1922·1).
Nutritional supplement.

Visial *Cadila, India.*
Sodium hyaluronate (p.2320·1).

Vi-Siblin *Pfizer, Denm.; Pfizer, Fin.; Recip, Norw.; Recip, Swed.*
Ispaghula (p.1737·1).
Constipation; irritable bowel syndrome.

Vi-Siblin S *Recip, Swed.*
Ispaghula (p.1737·1); sorbitol (p.1965·1).
Constipation; irritable bowel syndrome.

Visicol *Salix, USA.*
Monobasic sodium phosphate (p.1682·3); dibasic sodium phosphate (p.1682·3).
Bowel evacuation.

Visidic *Laboratorios Chile, Chile.*
Polyvinyl alcohol (p.2145·3).
Dry eyes; eye irritation.

Visinal *Stada, Cz.†.*
Valerian (p.2410·1); passion flower (p.2363·2); lupulus (p.2335·2).
Nervous disorders; sleep disorders.

Visine *Pfizer Consumer, Belg.; McNeil, Cz.; Pfizer, Fin.; Pfizer, Gr.; Pfizer, Hung.; Pfizer, India; Pfizer, Indon.; Pfizer, Israel; Pfizer Consumer, Ital.; Pfizer, Malaysia; Johnson & Johnson, NZ; Pfizer, Philipp.; Pfizer, Pol.; Janssen-Cilag, Port.; Pfizer, Rus.; Pfizer Consumer, S.Afr.; Johnson & Johnson, Singapore; Pfizer Consumer, Switz.; Pfizer, Thai.; Pfizer, Turk.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye congestion; eye irritation.

Visine AC *Pfizer, Hong Kong; Pfizer, Israel.*
⊗ Tetryzoline hydrochloride (p.1574·1); zinc sulfate (p.1999·2).
Formerly known as Visine Allergy Relief.
Eye irritation.

Visine AD *Pfizer Consumer, Mex.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Visine Advance Allergy *Pfizer Consumer, Canad.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).

Visine Advance Triple Action *Pfizer Consumer, Canad.*
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3); dextran 70 (p.1059·3); povidone (p.2146·1).

Visine Advance True Tears *Pfizer Consumer, Canad.*
Hypromellose (p.2144·2).
Dry eyes.

Visine Advanced Relief
Note. This name is used for preparations of different composition.
Pfizer Consumer, Austral.; Johnson & Johnson, NZ.
⊗ Tetryzoline hydrochloride (p.1574·1); dextran 70 (p.1059·3); macrogol 400 (p.2336·3); povidone (p.2146·1).
Dry eyes; eye irritation.

Pfizer, Philipp.
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Visine Allergy
Note. This name is used for preparations of different composition.
Pfizer, Austral.†; Pfizer Consumer, Canad.
⊗ Tetryzoline hydrochloride (p.1574·1); zinc sulfate (p.1999·2).
Eye irritation or congestion.

Johnson & Johnson, NZ.
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Allergic conjunctivitis; eye irritation.

Visine Allergy with Antihistamine *Pfizer Consumer, Austral.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).

Visine Allergy Relief *Pfizer, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1); zinc sulfate (p.1999·2).
Eye irritation.

Visine Contact Lens *Pfizer Consumer, Canad.*
Hypromellose (p.2144·2)(p.1622·2).
Eye irritation during contact lens wear.

Visine for Contacts *Pfizer, Hong Kong.*
Hypromellose (p.2144·2); glycerol (p.2314·2) (p.1622·2).
Eye irritation during contact lens wear.

Visine Cool
Note. This name is used for preparations of different composition.
Pfizer Consumer, Canad.
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3).
Formerly known as Visine Moisturizing.
Eye irritation.

Pfizer, Philipp.
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Visine D *Pfizer, Arg.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Visine Extra
Note. This name is used for preparations of different composition.
Pfizer, Indon.
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol (p.2336·1).
Dry eyes; eye irritation.

Pfizer Consumer, Mex.
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3); povidone (p.2146·1); dextran 70 (p.1059·3).
Eye irritation.

Visine Intensiv *Pfizer Consumer, Ger.*
Tamarind seed polysaccharide.
Dry eyes.

Visine Lagrimas *Pfizer, Arg.*
Glycerol (p.2314·2); hypromellose (p.2144·2); macrogol 400 (p.2336·3).
Dry eyes.

Visine LR *Pfizer, Indon.; Pfizer Consumer, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Visine Moisturizing *Pfizer, Hong Kong; Pfizer, USA†.*
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3).
Dry eyes; eye irritation.

Visine Mude *Pfizer Consumer, Ger.*
Tamarind seed polysaccharide.
Eye irritation.

Visine Original *Pfizer Consumer, Austral.; Pfizer Consumer, Canad.; Pfizer, Hong Kong; Pfizer Consumer, USA.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Visine Plus *Pfizer, Arg.*
⊗ Dextran 70 (p.1059·3); macrogol 400 (p.2336·3); povidone (p.2146·1); tetryzoline hydrochloride (p.1574·1).
Dry eyes; eye irritation.

Visine Pure Tears *Pfizer Consumer, USA.*
Glycerol (p.2314·2); hypromellose (p.2144·2); macrogol 400 (p.2336·3).
Dry eyes.

Visine Refresh *Pfizer, Philipp.*
Macrogol 400 (p.2336·3); glycerol (p.2314·2); hypromellose (p.2144·2).
Dry eyes; eye irritation.

Visine Revive *Pfizer Consumer, Austral.†.*
⊗ Tetryzoline hydrochloride (p.1574·1); macrogol 400 (p.2336·3).
Dry eyes; eye irritation.

Visine Tears *Pfizer Consumer, USA.*
Glycerol (p.2314·2); hypromellose (p.2144·2); macrogol 400 (p.2336·3).
Dry eyes.

Visine Trockene Augen *Pfizer Consumer, Ger.*
Povidone (p.2146·1); carbomer 974P; medium-chain triglycerides (p.1956·3).
Dry eyes.

Visine True Tears *Pfizer Consumer, Austral.†.*
Glycerol (p.2314·2); hypromellose (p.2144·2); macrogol 400 (p.2336·3).
Dry eyes.

Visine Workplace *Pfizer Consumer, Canad.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Eye irritation.

Visine Yxin *Pfizer Consumer, Ger.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Visine-A *Pfizer Consumer, USA.*
⊗ Naphazoline hydrochloride (p.1565·2); pheniramine maleate (p.587·3).
Eye disorders.

Visiol *Chemedica, Ger.; Chemedica, Malaysia; Chemedica, Switz.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Visio-Max *Wassen, UK.*
Selenium; vitamins; bilberry (p.1922·1).

Vision Care Enzymatic Cleaner *Alcon, USA.*
Pancreatin (p.2360·1) (p.1622·2).
Cleansing solution for soft contact lenses.

Visionace *Vitabiotics, UK.*
Vitamin, mineral, and nutrient preparation (p.1922·1).
Eye disorders.

Visional Gotas *Maver, Chile.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye congestion.

VisionBlue *DORC, Neth.; Dutch Ophthalmic, USA.*
Trypan blue (p.2405·2).
Ophthalmic stain.

Visionex *Usana, Malaysia; Beacons, Singapore.*
Lutein; zinc; vitamin C (p.1922·1).
Dietary supplement for healthy eyes.

Visionom *Genom, Braz.*
Hamamelis (p.2318·2); chamomile (p.2279·3).
Eye disorders.

Visipaque *Amersham, Austral.; Amersham, Austria; Amersham, Belg.; Sanofi Synthelabo, Braz.†; Amersham, Canad.; General Electric, Chile; GE, Cz.; Amersham, Denm.; Amersham, Fin.; Amersham, Fr.; Amersham, Ger.; Amersham, Gr.; Amersham Health, Hung.; Nycomed, Israel; Amersham, Ital.; GE Healthcare, NZ; Amersham, Neth.; Amer-*

sham, Norw.; Satis, Port.; Nycomed, Rus.†; Amersham, Spain; Amersham, Swed.; Amersham, Switz.; Amersham, UK; Amersham, USA.
Iodixanol (p.1482·2).
Radiographic contrast medium.

Visiplex *Bunker, Braz.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2); boric acid (p.2268·1); borax (p.2268·1).
Ocular congestion.

Visivit *Soho, Indon.*
Myrtillus (p.2349·3); vitamin A (p.1971·2).
Supplement for healthy eyes.

Viskaldix *Novartis, Belg.; Novartis, Braz.; Novartis, Chile; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; EGIS, Hung.; Novartis, Irl.; Novartis, Malaysia; Novartis, Neth.; Novartis, Philipp.; Egis, Rus.; Novartis, Switz.; Novartis, Thai.†; Amdipharm, UK; Novartis, Venez.†.*
⊗ Pindolol (p.1372·1); clopamide (p.1250·1).
Hypertension.

Viskazide *Novartis, Canad.*
⊗ Pindolol (p.1372·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Viskeen *Novartis, Neth.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension.

Visken *Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Egis, Cz.†; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; EGIS, Hung.; Novartis, India; Novartis, Irl.; Teofarma, Ital.; Novartis, Mex.; Novartis, Philipp.; Novartis, Pol.; Egis, Rus.; Novartis, Swed.; Novartis, Turk.; Amdipharm, UK; Novartis, USA; Novartis, Venez.†.*
⊗ Pindolol (p.1372·1).
Angina pectoris; arrhythmias; hypertension; hyperthyroidism; hypertrophic obstructive cardiomyopathy; ischaemic heart disease; myocardial infarction; phaeochromocytoma.

Viskene *Novartis, Switz.*
⊗ Pindolol (p.1372·1).
Cardiac disorders; hypertension.

Viskenit *Novartis, Austria.*
⊗ Pindolol (p.1372·1); isosorbide dinitrate (p.1317·3).
Angina pectoris.

Viskoferm *Nordic, Swed.*
Acetylcysteine (p.1548·2).
Bronchitis.

Viskose ojendraber *Ophtha, Denm.*
Sodium chloride (p.1686·1).
Dry eyes.

Vislin *Alcon, Braz.*
⊗ Tetryzoline hydrochloride (p.1574·1); methylthioninium chloride (p.1450·3).
Ocular congestion.

Vislube *Chemedica, Ger.; Chemedica, Malaysia; Chemedica, Switz.*
Sodium hyaluronate (p.2320·1) (p.1622·2).
Dry eyes in contact lens wearers.

Vislus *Northia, Arg.*
⊗ Nitrofurazone (p.309·1); ephedrine (p.1558·1); phenazone (p.116·1); diphenhydramine (p.577·1).
Eye disorders.

Vismed *Hamilton, Austral.†; Thea, Fr.†; Chemedica, Ger.; Chemedica, Hong Kong; Tubilux, Ital.; Chemedica, Malaysia; Chemedica, Switz.*
Sodium hyaluronate (p.2320·1)(p.1622·2).
Formerly known as Vislube in *Hong Kong*.
Dry eyes; eye irritation; lubrication for contact lens.

Visodin *Allergan, Braz.*
⊗ Tetryzoline hydrochloride (p.1574·1); methylthioninium chloride (p.1450·3).
Ocular congestion.

Visofid *Fidia, Ital.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne, alopecia, and hirsutism in females.

Visolin *Darya-Varia, Indon.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Visolon *Igefarma, Braz.*
⊗ Naphazoline (p.1565·1); benzalkonium chloride (p.1629·1); zinc sulfate (p.1999·2); berberine sulfate (p.2264·3).
Ocular congestion.

Visolux *Brasmedica, Braz.†.*
⊗ Tetryzoline (p.1574·1); methylthioninium chloride (p.1450·3).
Eye disorders.

Visolvit *GSK, Pol.*
Vitamin preparation (p.1922·1).

Visonest *Allergan, Braz.*
Proxymetacaine hydrochloride (p.1870·1).
Local anaesthesia.

Visopt *Sigma, Austral.†.*
Phenylephrine (p.1568·1).
Eye irritation and congestion.

Visotone
Note.This name is used for preparations of different composition.
British Dispensary, Thai.
Eye drops: Phenylephrine hydrochloride (p.1568·1); boric acid (p.2268·1); borax (p.2268·1); sodium chloride (p.1686·1).
Eye irritation.

British Dispensary, Thai.
Eye solution: Boric acid (p.2268·1); borax (p.2268·1); salicylic acid (p.1612·2); zinc sulfate (p.1999·2).
Eye irritation.

Visoy *Wyeth Lederle, Port.†.*
Soy protein infant feed (p.1922·1).
Gastro-enteritis; intolerance to cow's milk, lactose, or sucrose.

Vispring *Pfizer Consumer, Spain.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Conjunctival congestion; eye irritation.

Vistabel *Allergan, Cz.; Allergan, Denm.; Allergan, Fin.; Allergan, Fr.; Alvia (Αλβια), Gr.; Allergan, Hung.; Allergan, Norw.; Allergan, Port.; Allergan, Spain; Allergan, Swed.; Allergan, Switz.; Allergan, UK.*
Botulinum A toxin (p.1890·1).
Glabellar lines.

Vistabex *Allergan, Ital.*
Botulinum A toxin (p.1890·1).
Facial wrinkles.

Vista-Cetamide *Martindale, Hong Kong†.*
Sulfacetamide (p.335·3).
. There is no connection between Martindale, The Complete Drug Reference and Martindale, Hong Kong.
Eye infections.

Vistacloran *Allergan, Arg.†.*
⊗ Chloramphenicol succinate (p.241·3); naphazoline hydrochloride (p.1565·2).
Bacterial eye infections.

Vistadrox *Cadila, India.*
Cefadroxil (p.218·1).
Bacterial infections.

Vistafrin *Allergan, Spain.*
Phenylephrine hydrochloride (p.1568·1).
Eye irritation.

Vistagan *Allergan, Austria; Allergan, Cz.; Allergan, Ger.; Alvia (Αλβια), Gr.; Allergan, Hung.; Allergan, Ital.; Allergan, Switz.; Allergan, Venez.*
⊗ Levobunolol hydrochloride (p.1882·3).
Glaucoma; ocular hypertension.

Vista-Methasone *Martindale Pharmaceuticals, UK.*
⊗ Betamethasone sodium phosphate (p.1518·3).
. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Inflammatory disorders of the ear, eye, or nose.

Vista-Methasone N *Martindale Pharmaceuticals, UK.*
⊗ Betamethasone sodium phosphate (p.1518·3); neomycin sulfate (p.305·1).
. There is no connection between Martindale, The Complete Drug Reference and Martindale Pharmaceuticals.
Inflammatory disorders of the ear, eye, or nose with bacterial infection.

Vista-Phenicol *Martindale, Hong Kong†.*
Chloramphenicol (p.239·3).
. There is no connection between Martindale, The Complete Drug Reference and Martindale, Hong Kong.
Blepharitis; conjunctivitis.

Vistaril *Pfizer, USA.*
Hydroxyzine embonate (p.581·2).
Anxiety; premedication; pruritus; sedative.

Vistazine *Keene, USA†.*
Hydroxyzine hydrochloride (p.581·2).
Anxiety; hypersensitivity reactions.

VisThesia *Ioltech, Ger.*
Sodium hyaluronate (p.2320·1).
Adjunct in eye surgery.

Vistide *Pfizer, Austral.; Pharmacia, Austria; Pfizer, Belg.; Pharmacia, Cz.; Pfizer, Fr.; Pharmacia, Ger.; Pharmacia-Upjohn, Gr.†; Pfizer, Ital.; Pfizer, Neth.; Pfizer, Port.; Pharmacia, Spain; Pfizer, Switz.; Pharmacia, UK; Gilead, USA.*
Cidofovir (p.867·3).
Cytomegalovirus retinitis; HIV infection.

Vistil *Santen, Ger.; Tubilux, Ital.*
Polyvinyl alcohol (p.2145·3).
Dry eyes; eye irritation.

Vistimon *Jenapharm, Ger.†; Jenapharm, Malaysia†.*
⊗ Mesterolone (p.2116·1).
Androgen deficiency; androgen replacement.

Visto *GMP, Indon.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Vistoxyn *Allergan, Ger.; Allergan, Switz.†.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Conjunctival disorders; conjunctivitis; eye irritation.

Vistrum *Pharos, Indon.*
Bovine colostrum (p.2208·1); fructo-oligosaccharide; zinc.
Nutritional supplement.

Visu Q10 *Visufarma, Ital.*
Ubidecarenone (p.2407·2); vitamin E; lutein (p.1922·1).
Antioxidant.

Visual *Hexal, Braz.†.*
⊗ Zinc sulfate (p.1999·2); boric acid (p.2268·1); borax (p.2268·1); naphazoline hydrochloride (p.1565·2).
Ocular congestion.

Visual-Eyes *Optopics, USA.*
Electrolyte solution (p.1667·1).
Eye irrigation.

Visublefarite *Visufarma, Ital.*
⊗ Betamethasone (p.1518·2); sulfacetamide sodium (p.335·3); tetryzoline phosphate (p.1574·1).
Blepharitis.

Visubril *Allergan, Arg.*
⊗ Tetryzoline hydrochloride (p.1574·1); methylthioninium chloride (p.1450·3).
Eye inflammation.

Visucloben *Visufarma, Ital.*
⊗ Clobetasone butyrate (p.1522·3).
Eye disorders.

Visucloben Antibiotico *Visufarma, Ital.*
⊗ Clobetasone butyrate (p.1522·3); bekanamycin sulfate (p.211·3).
Infected eye disorders.

Visucloben Decongestionante *Visufarma, Ital.*
⊗ Clobetasone butyrate (p.1522·3); tetryzoline hydrochloride (p.1574·1).
Eye congestion, irritation, and inflammation.

Visudine *Novartis, Gr.*
Verteporfin (p.784·3).
Choroidal neovascularisation; neovascular (wet) age-related macular degeneration.

Visudyne *Novartis Ophthalmics, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis Ophthalmics, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Hong Kong; Parkedale, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Israel; Novartis, Ital.; Novartis, Jpn; Novartis, Malaysia; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis Ophthalmics, Singapore; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis Ophthalmics, UK; Novartis Ophthalmics, USA; Novartis, Venez.*
Verteporfin (p.784·3).
Neovascular (wet) age-related macular degeneration.

Visuglican *Visufarma, Ital.*
Sodium cromoglicate (p.1136·3); chlorphenamine maleate (p.571·3).
Conjunctivitis.

Visu-len *DermoDuemila, Ital.*
Lutein; selenium; zinc; vitis vinifera; thioctic acid (p.1922·1).
Nutritional supplement.

Visumetazone *Visufarma, Ital.*
⊗ Dexamethasone (p.1526·1).
Inflammatory eye disorders.

Visumetazone Antibiotico *Visufarma, Ital.*
⊗ Bekanamycin sulfate (p.211·3); tetryzoline hydrochloride (p.1574·1); betamethasone (p.1518·2).
Eye infections associated with inflammation and congestion.

Visumetazone Antistaminico *Visufarma, Ital.*
⊗ Dexamethasone (p.1526·1); chlorphenamine maleate (p.571·3).
Conjunctivitis.

Visumetazone Decongestionante *Visufarma, Ital.*
⊗ Dexamethasone (p.1526·1); tetryzoline hydrochloride (p.1574·1).
Conjunctivitis; eye congestion and irritation; scleritis.

Visumidriatic *Visufarma, Ital.*
Tropicamide (p.1886·2).
Production of mydriasis.

Visumidriatic Fenilefrina *Visufarma, Ital.*
Tropicamide (p.1886·2); phenylephrine hydrochloride (p.1568·1).
Production of mydriasis.

Visustrin *McNeil, Ital.*
⊗ Tetryzoline hydrochloride (p.1574·1); methylthioninium chloride (p.1450·3).
Conjunctival oedema; eye congestion and irritation.

Visu-ton *DermoDuemila, Ital.*
Lutein; myrtillus; vitis vinifera; vitamin A; vitamin B (p.1922·1).
Nutritional supplement.

Visymplex Plus *Eadriex, Philipp.*
Vitamin preparation with or without lysine hydrochloride (p.1922·1).
Nutritional supplement.

Vi-Syneral *Sanofi Pasteur, Chile; USV, India; Grossman, Mex.*
Vitamin preparation with or without minerals (p.1922·1).
Dietary supplement.

Vi-Syneral GE *Beta, Arg.*
Vitamin preparation with or without minerals (p.1922·1).

Vit C-Mile *Osoth, Thai.*
Ascorbic acid (p.1983·3); sodium ascorbate.
Vitamin C deficiency.

Vit Eparin *Teofarma, Ital.*
Heparin sodium (p.1301·2); tocoferil acetate (p.1992·3).
Ocular haemorrhage and its sequelae.

Vita *Poen, Arg.*
Vitamin A acetate; vitamin E; vitamin P (p.1922·1).
Vitamin supplement.

Vita Anti-Ox *Uniao Quimica, Braz.*
Vitamins A, C, and E; minerals (p.1922·1).

Vita 3B *Riva, Canad.*
Vitamin B substances (p.1922·1).

Vita B Compound 100 *Vita Pharm, Canad.†.*
Vitamin B substances (p.1922·1).

Vita 3B plus C *Riva, Canad.*
Vitamin B substances with vitamin C (p.1922·1).

Vita B-Co *Hovid, Malaysia†; Swiss Bio, Malaysia†.*
Vitamin B substances (p.1922·1).
Dietary supplement.

Vita Bee *Rugby, USA.*
Multivitamin preparation (p.1922·1).

Vita Buer-G-plus
Altana, Switz.
Capsules: Multivitamin and mineral preparation with kola and ginseng (p.1922·1).
Tonic.

Altana, Switz.
Oral liquid: Multivitamin and mineral preparation with ginseng (p.1922·1).
Tonic.

Vita Buerlecithin
Roland, Cz.†; Altana, Ger.†; Altana, Switz.
Soya lecithin (p.2332·2); vitamins (p.1922·1).
Dietary supplement; tonic.

Altana, Pol.
Lecithin; vitamins (p.1922·1).
Tonic.

Vita C
Vitaglow, Austral.†.
Calcium ascorbate (p.1984·1).
Cold and influenza symptoms; wounds.

CCM, Malaysia.
Vitamin C (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vita Calmag Zn *Vita Health, Singapore†.*
Calcium (p.1675·2); magnesium (p.1678·3); zinc (p.1999·1).
Calcium deficiency; osteoporosis.

Vita Care Q_{10} *Jemo-Pharm, Pol.*
Ubidecarenone (p.2407·2).
Cardiovascular disorders; periodontitis; tonic.

Vita C-R15 *Reckeweg, Cz.*
Homoeopathic preparation.

Vita C-R15 forte *Reckeweg, Cz.*
Homoeopathic preparation.

Vita Cris *Cris Flower, Ital.†.*
Multivitamin preparation (p.1922·1).
Nutritional supplement.

Vita D *LA, Arg.*
Vitamin D (p.1986·1).
Vitamin D deficiency.

Vita Dino Buddies *Vita Pharm, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Vita E *Vitaglow, Austral.†.*
d-Alpha tocopherol (p.1992·2).
Antoxidant; dry skin disorders; wounds.

Vita Ferin C *Geistlich, Switz.*
Multivitamin and mineral preparation (p.1922·1).

Vita Grip *Sinterapico, Braz.*
Ascorbic acid (p.1983·3); caffeine (p.1116·3); salicylamide (p.121·2); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Vita K *Uniao Quimica, Braz.*
Phytomenadione (p.1995·3).
Vitamin K deficiency bleeding.

Vita Menal *Alacan, Spain.*
Cyproheptadine hydrochloride (p.575·1); amino acids; cyanocobalamin (p.1922·1); fosforylethanolamine.
Tonic.

Vita Multicap *Sriprasit, Thai.*
Vitamins; minerals; choline bitartrate; inositol; methionine (p.1922·1).

Vita Natal
Note.This name is used for preparations of different composition.
Vita Health, Singapore.
Capsules: Multivitamin and mineral preparation with folic acid (p.1922·1).
Dietary supplement in pregnancy.

Vita Health, Singapore.
Cream: Evening primrose oil (p.2302·1); jojoba oil.
Dry skin; massage therapy during and after pregnancy.

Vita Senior *Uniao Quimica, Braz.*
Vitamins; minerals; ginseng (p.1922·1).

Vita SL *Dynamic, Philipp.*
Vitamins; hematoporphyrin hydrochloride; magnesium carbonate; orotic acid; lysine hydrochloride; lecithin; ginseng; royal jelly (p.1922·1).
Nutritional supplement.

Vita SL with lecithin *Dynamic, Philipp.*
Vitamins; calcium lactate; lysine hydrochloride; lecithin (p.1922·1).
Nutritional supplement.

Vita SL Plus *Dynamic, Philipp.*
Vitamins; zinc; lysine; taurine; chlorella growth factor (p.1922·1).
Nutritional supplement.

Vita Stress *Vita Pharm, Canad.†.*
Multivitamin preparation (p.1922·1).

Vita-Apinol *Slovakofarma, Cz.†.*
Apilac.
Asthenia; asthma; atherosclerosis; bronchitis; menopausal disorders; skin disorders; ulcers.

Vita-B *Shiwa, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Vitamin B deficiency.

Vita-B1 *Vitabalans, Fin.*
Thiamine hydrochloride (p.1976·1).
Vitamin B deficiency.

Vita-B2 *Vitabalans, Fin.*
Riboflavin (p.1977·2).
Vitamin B deficiency.

Vita-B6 *Vitabalans, Fin.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Vitabact *Novartis, Fr.; Novartis Ophthalmics, Hung.†; Novartis, Rus.; Pharmaregie, Rus.; Novartis Ophthalmics, Switz.†.*
Picloxydine hydrochloride (p.1658·2).
Bacterial eye infections.

Vitabase Complexo Vitaminico C/Minerais *Johnson & Johnson, Braz.†.*
A vitamin and mineral preparation (p.1922·1).

Vitabase Vitamina C *Johnson & Johnson, Braz.†.*
Vitamin C (p.1983·3).

Vitabe *Andromaco, Chile.*
Pyridoxine hydrochloride (p.1978·2).
Vitamin B deficiency.

Vita-Bel *Offenbach, Mex.*
Vitamin B substances; lysine; iron (p.1922·1).
Appetite loss.

Vitaber A E *Llorens, Spain.*
Di-isopropylammonium dichloroacetate (p.1265·1); vitamin A acetate (p.1973·1); tocoferil acetate (p.1992·3).
Deficiency of vitamins A and E; eye disorders; infertility; recurrent miscarriage; skin disorders.

Vitabin *Perivita, Neth.*
Terbinafine hydrochloride (p.546·3).
Fungal skin infections.

Vitabiol *Ulagay, Turk.*
Multivitamin preparation (p.1922·1).

Vitabiol C *Ulagay, Turk.*
Vitamin C (p.1983·3).
Vitamin C deficiency.

Vitabiol C-Fort *Ulagay, Turk.*
Vitamin B substances; vitamin C (p.1922·1).
Leave the -Fort to distinguish from earlier entry for Vitabiol C.

Vitabion
Note. This name is used for preparations of different composition.
Cipla, India.
Multivitamin preparation (p.1922·1).

GMP, Indon.
Ferrous gluconate (p.1939·1); manganese sulfate; copper sulfate; vitamin B ; folic acid (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron deficiency; iron-deficiency anaemia.

Unison, Malaysia.
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B deficiency; vitamin B supplement.

Unison, Thai.
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Neuritis; neuropathy.

Vitabite *Vitaflo, Irl.*
Food for special diet (p.1922·1).
Disorders requiring protein restriction.

Vita-Bob *Scot-Tussin, USA.*
Multivitamin preparation (p.1922·1).

Vitaburon *Elmor, Venez.†.*
Shark-liver oil (p.2386·1).
Dietary supplement.

Vita-C *Shaklee, Canad.†; Vitabalans, Fin.; Freeda, USA.*
Ascorbic acid (p.1983·3).
Dietary supplement; scurvy; vitamin C deficiency.

Vitac *Sanofi-Aventis, Chile.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Vita-C Derms's *LDA, Arg.*
Ascorbic acid (p.1983·3); hyaluronic acid (p.2320·1).

Vita-C R15 *Reckeweg, Ger.†.*
Homoeopathic preparation.

Vita-Cal *Columbia, S.Afr.; Pharmasant, Thai.*
Calcium; vitamins (p.1922·1).
Calcium and vitamin supplement; vitamin and mineral deficiencies.

Vitacal
Note. This name is used for preparations of different composition.
Vita Health, Singapore.
Effervescent tablets: Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; osteoporosis.

Vita Health, Singapore.
Tablets: Calcium (p.1675·2).
Calcium deficiency; osteoporosis.

Vitacal + D
Scherer, Malaysia†; Swiss Bio, Malaysia†.
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Dietary supplement.

Vita Health, Singapore.
Calcium (p.1675·2); vitamin D (p.1986·1).
Calcium deficiency; osteoporosis.

Vita-Cal Mag with Zinc and Vitamin D *Vita Pharm, Canad.†.*
Calcium; magnesium; zinc; vitamin D (p.1922·1).

Vita-Cal Plus *Shaklee, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Vita-Calc *Pharmavit, Cz.†.*
Colecalciferol (p.1986·2); pyridoxine hydrochloride; ascorbic acid; calcium carbonate (p.1714·1) (p.1922·1).
Osteoporosis; vitamin supplement.

Vitacalc *BMS, Hung.†.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1); colecalciferol (p.1986·2); pyridoxine hydrochloride (p.1978·2).
Vitamin and calcium deficiency.

Vitacalcin *Zentiva, Cz.*
Calcium carbonate (p.1714·1).
Calcium deficiency; osteomalacia; osteoporosis.

Vitacalcin D *Slovakofarma, Cz.†.*
Calcium carbonate (p.1714·1); colecalciferol (p.1986·2).
Calcium and vitamin D deficiency.

Vitacal-D *Otto, Indon.*
Calcium carbonate (p.1714·1); magnesium oxide; colecalciferol (p.1986·2).
Nutritional supplement.

Vitacap *Medicap, Thai.*
Multivitamin and mineral preparation (p.1922·1).

VitaCarn *Kendall McGaw, USA.*
Carnitine (p.1932·2).
Carnitine deficiency.

Vitace *Prisfar, Port.*
Echinacea purpurea (p.2298·1); vitamin C; zinc (p.1922·1).
Tonic.

Vita-Ce *Chemedica, Switz.†.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vitacelsia Plus *Prisfar, Port.*
Multivitamin and mineral preparation (p.1922·1).

Vitacharm *Veropharm, Rus.*
Vitamin preparation (p.1922·1).

Vitachol *Landson, Indon.*
Lecithin; vitamins; ferrous fumarate (p.1938·3); copper; iodine (p.1922·1).
Nutritional supplement for pregnancy and lactation.

Vitacic *Omega, Belg.; Novartis Ophthalmics, Hung.†; Europhta, Mon.; Novartis Ophthalmics, Rus.†.*
Adenosine (p.1202·1); cytidine (p.2291·3); disodium guanylate (p.2296·1); thymidine (p.2401·2); uridine (p.2407·3).
Corneal damage.

Vitacid *Theraskin, Braz.; Surya Dermato, Indon.; Yabrofarma, Port.†.*
Tretinoin (p.1618·1).
Acne; photoageing.

Vitacid Plus *Theraskin, Braz.*
⊗ Tretinoin (p.1618·1); hydroquinone (p.1598·2); fluocinolone acetonide (p.1531·3).
Skin disorders.

Vitacimin *Takeda, Indon.; Takeda, Thai.*
Ascorbic acid (p.1983·3).
Circulatory disorders; skin pigmentation disorders; vitamin C deficiency; vitamin C supplement.

Vitacimin Sweetlet *Takeda, Hong Kong.*
Ascorbic acid (p.1983·3); sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Vitacip *Cipla, India.*
Multivitamin preparation with ginseng (p.1922·1).

Vitacitrus *Vitemat, Braz.†.*
Ascorbic acid (p.1983·3).

Vitacon *Polfa Warszawa, Pol.*
Phytomenadione (p.1995·3).
Coagulation disorders.

Vitacor *UB, Switz.*
Crataegus (p.2289·1).
Cardiac disorders.

Vitacortil *Hexa, Arg.*
⊗ Betamethasone dipropionate (p.1518·3); gentamicin sulfate (p.282·1); clotrimazole (p.530·1).
Infected skin disorders.

Vitacrecil *Ferraz, Lynce, Port.†.*
Cystine; gelatin; zinc sulfate; ferrous sulfate; calcium pantothenate; pyridoxine hydrochloride (p.1922·1).
Hair, skin, and nail disorders.

Vitacur *Lapi, Indon.*
Curcuminoid; betacarotene; vitamin B substances; vitamin D; calcium pidolate; fructo-oligosaccharide (p.1922·1).
Reduced appetite; vitamin supplement.

Vitadece *Klonal, Arg.*
Ascorbic acid; vitamin A; vitamin D (p.1922·1).
Vitamin supplement.

Vita-Dermacide *CS, Fr.*
Nicotinamide (p.1957·3); glutamic acid (p.1947·1); tryptophan (p.427·1).
Irritative dermatitis.

Vitaderme *Cristalia, Braz.*
Vitamin A; colecalciferol; vitamin E (p.1922·1); allantoin (p.1588·1).
Barrier preparation.

Vitadesan *Sanval, Braz.*
Vitamin A palmitate (p.1973·1); ergocalciferol (p.1987·1).

Vitadol-C *Karicare, NZ.*
Vitamin A, C, and D (p.1922·1).
Vitamin supplement.

Vitadoze *Neckerman, Braz.†.*
Cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Vitadral *Wernigerode, Ger.*
Vitamin A palmitate (p.1973·1).
Vitamin A deficiency.

Vitadye *Dermatech, Austral.; ICN, Malaysia†.*
Dihydroxyacetone (p.1594·1).
Vitiligo.

Vitadyn *Bilim, Turk.*
Vitamin and mineral preparation (p.1922·1).

Vitadyn C *Oftalmi, Venez.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vita-E
Ache, Braz.
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Vitabalans, Fin.†.
d-Alpha tocoferil acetate (p.1992·3) or *d*-alpha tocoferil succinate (p.1993·1).
Vitamin E deficiency.

Worwag, Ger.; Cambridge Healthcare, UK.
d-Alpha tocopherol (p.1992·2) or *d*-alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Vitae *Vivax, Venez.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

VitaEPA
Scherer, Malaysia†; Swiss Bio, Malaysia†.
Omega-3 triglycerides (p.1362·1).
Dietary supplement.

Vita Health, Singapore.
Docosahexaenoic acid (p.1362·1); eicosapentaenoic acid (p.1362·1).
Hyperlipidaemias.

VitaEPA Plus
Scherer, Malaysia†; Swiss Bio, Malaysia†.
Omega-3 triglycerides (p.1362·1); evening primrose oil (p.2302·1).
Dietary supplement.

Vita Health, Singapore.
Eicosapentaenoic acid (p.1362·1); evening primrose oil (p.2302·1).
Circulatory disorders; hyperlipidaemias; inflammation.

Vitafardi C B12 *Fardi, Spain.*
Ascorbic acid (p.1983·3); hydroxocobalamin (p.1980·3).
Deficiency of vitamins B and C.

Vitafem *Vita Pharm, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitaferol *Otto, Indon.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Vitaferro
Hexal, Arg.†.
Ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Hexal, Ger.
Ferrous gluconate (p.1939·1) or ferrous sulfate (p.1939·3).
Iron deficiency; iron-deficiency anaemia.

Vitafissan N *Uhlmann-Eyraud, Switz.*
Caseine hydrolysate (Labiline) (p.1934·1); vitamins A and E (p.1922·1); linoleic acid (p.2308·2); linolenic acid (p.1362·1).
Skin disorders.

Vitafizz C *Hexa, Arg.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vitafluid *Mann, Ger.*
Vitamin A palmitate (p.1973·1).
Eye disorders.

Vitaflur *Maver, Chile.*
Sodium fluoride (p.1962·2).

Vitafol
Note. This name is used for preparations of different composition.
Cipla, India.
Folic acid (p.1940·1).
Folic acid deficiency.

Everett, USA.
Syrup: Ferric pyrophosphate (p.1938·1); folic acid (p.1940·1); vitamin B substances (p.1922·1).
Iron-deficiency anaemias.

Everett, USA.
Tablets: Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Vitafol-OB *Everett, USA.*
Vitamin and mineral preparation (p.1922·1).

Vitafol-PN *Everett, USA.*
Vitamin and mineral preparation (p.1922·1).

Vitaforce *Pharma-Natura, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).

Vitaforce Acerola C *Pharma-Natura, S.Afr.*
Acerola; rosehip; green pepper; blackcurrant; ascorbic acid; sodium ascorbate; rutoside; citrus bioflavonoids; hesperidin; tissue salts (Combin J) (p.1922·1).
Dietary supplement; vitamin C deficiency.

Vitaforce C *Pharma-Natura, S.Afr.*
Ascorbic acid (p.1983·3).
Dietary supplement; vitamin C deficiency.

Vitaforce E *Pharma-Natura, S.Afr.*
Vitamin E (p.1992·2).
Dietary supplement; vitamin E deficiency.

Vitaforce Massif-C *Pharma-Natura, S.Afr.*
Ascorbic acid (p.1983·3).
Dietary supplement; vitamin C deficiency.

Vitaforce Nutri-B *Pharma-Natura, S.Afr.*
Vitamin B substances; potassium phosphate; lecithin; yeast (p.1922·1).
Dietary supplement.

Vitaforte *Rimsa, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitafusal *Serum-Werk Bernburg, Ger.*
⊗ An etherified starch (p.1065·1) with electrolytes.
Plasma volume expansion; shock.

Vitagama Fluor *Almirall, Spain.*
Sodium fluoride (p.1962·2); vitamins (p.1922·1).
Vitamin and fluoride deficiencies.

Vita-Gard *GNLD, Austral.*
Vitamins; zinc oxide; citrus bioflavonoids (p.1922·1).

Vitagel *Mann, Ger.*
Vitamin A palmitate (p.1973·1).
Eye disorders.

Vitagen *Cadila, India.*
Vitamin B substances (p.1922·1).

Vitagenol
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Arg.†.
Ginseng (p.2312·1).
Mental function impairment; tonic.

Sanofi Synthelabo, Chile†.
Betacarotene; vitamin C; vitamin E; selenium (p.1922·1).
Dietary supplement.

Vitagenol Plus *Boehringer Ingelheim, Arg.*
Ginseng; minerals; vitamins (p.1922·1).
Tonic.

Vita-Gerin
Chemomedica, Austria.
Deanol orotate; vitamins; minerals; adenosine; choline bitartrate (p.1922·1).
Tonic.

Geistlich, Switz.
Deanol orotate; vitamins; minerals; rutoside; choline bitartrate (p.1922·1).
Tonic.

Vita-Gerin N *Cassella-med, Ger.*
Deanol orotate; magnesium orotate; vitamins; minerals; choline bitartrate (p.1922·1).
Tonic.

Vitageyer B *Geyer, Braz.†.*
Vitamin B substances (p.1922·1).

Vitageyer C *Geyer, Braz.†.*
Ascorbic acid (p.1983·3).

Vitaglumil *Salusif, Port.†.*
Vitamin B substances; ascorbic acid (p.1922·1).
Tonic.

Vita-Grin *Grin, Mex.*
Vitamin and mineral preparation (p.1922·1).

Vitagripe *Berna, Spain†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Vitagutt Knoblauch *Schwarzhaupt, Ger.†.*
Garlic oil (p.2309·2).
Circulatory disorders.

Vitagutt Vitamin E *Schwarzhaupt, Ger.†.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

VitaHES *Serum-Werk Bernburg, Ger.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Plasma volume expansion; shock.

Vita-Hexin *Streuli, Switz.*
Chlorhexidine gluconate (p.1635·3); vitamin A palmitate (p.1973·1); cod-liver oil (p.1935·2); zinc oxide (p.1621·2).
Skin lesions.

Vita-Iodurol *Novartis, Rus.*
Adenosine (p.1202·1); magnesium chloride; calcium chloride; nicotinic acid.

Vitaject *Syxyl, Ger.†.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Vitamin B deficiency.

Vitak *Dicofarm, Ital.*
Phytomenadione (p.1995·3).
Vitamin K deficiency; vitamin K supplement.

Vitakid *Pharmaland, Thai.*
Multivitamin preparation with lysine (p.1922·1).
Tonic.

Vita-Kid *Solgar, UK; Solgar, USA.*
Multivitamin preparation (p.1922·1).

Vitakids *Vitalink, Philipp.*
Vitamins; taurine; lysine; chlorella growth factor (p.1922·1).
Nutritional supplement.

Vital *Yu Sheng, Singapore.*
Glucosamine sulfate (p.2313·2).
Joint and cartilage disorders.

Vital Ear Oil *Medikon, Indon.*
Thymol (p.1664·3); menthol (p.2340·1); camphor (p.2273·2).
Otitis.

Vital Eyes *Novartis Consumer, UK.*
Lavender (p.2331·1); orange flower (p.2357·1); hamamelis (p.2318·2); euphrasia (p.2301·3).
Eye irritation.

Vital High Nitrogen *Abbott, Hong Kong; Ross, USA.*
Preparation for enteral nutrition (p.1922·1).

Vital HN *Abbott, Austral.; Abbott, Canad.†; Abbott, NZ.*
Preparation for enteral nutrition (p.1922·1).

Vitalac BL *Sari Husada, Indon.*
Infant feed (p.1922·1).
Lactose intolerance.

Vitalaif *Medix, Mex.*
Multivitamin and mineral preparation with ginseng (p.1922·1).

Vita-Lea *Shaklee, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).
Dietary supplement.

Vitalen C *Dovalle, Braz.†.*
Paracetamol (p.108·1); chlorphenamine (p.572·2); phenylephrine (p.1568·1); caffeine (p.1116·3).
Cold and influenza symptoms.

Vitaler
Note.This name is used for preparations of different composition.
EMS, Braz.†.
Oral solution: Buclizine (p.570·1); lysine; tryptophan; cyanocobalamin; vitamin B (p.1922·1).
Reduced appetite; tonic.
EMS, Braz.†.
Tablets: Vitamin B substances; sodium glycerophosphate; calcium glycerophosphate; manganese hypophosphite; lysine hydrochloride; iron choline citrate (p.1922·1).
Reduced appetite; tonic.

Vitalets *Freeda, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Vitalex *Molex Ayus, Indon.*
Ferrous fumarate (p.1938·3); folic acid; vitamin B ; colecalciferol; calcium carbonate (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Vitaleyes *Novartis Ophthalmics, Fr.†.*
Multivitamin and trace-element preparation (p.1922·1).
Nutritional supplement for healthy eyes.

Vitalil K *Linfar, Arg.*
A range of dietary supplements (p.1922·1).

Vitaline *Bioglan, Austral.†.*
Lysine (p.1955·1); zinc oxide (p.1621·2).
Herpes simplex lesions.

Vitalipid *Fresenius, Belg.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Baxter, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hung.; Fresenius Kabi, Ital.; Baxter, NZ†; Fresenius Kabi, NZ†; Fresenius Kabi, Norw.; Fresenius Kabi, Port.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Thai.*
Vitamins A, D , E, and K for infusion (p.1922·1).
Parenteral nutrition.

Vitalipid N *Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Hong Kong; Pharmacia Upjohn, Israel; Fresenius Kabi, Malaysia; Fresenius Kabi, Pol.; Fresenius Kabi, Rus.; Fresenius Kabi, Singapore†; Fresenius Kabi, Switz.; Fresenius Kabi, Turk.*
Vitamins A, D , E, and K for infusion (p.1922·1).
Parenteral nutrition.

Vitalipid Neu *Fresenius Kabi, Austria.*
Vitamins A, D, E, and K for infusion (p.1922·1).
Contains egg lipid.
Parenteral nutrition.

Vitalipide *Fresenius Kabi, Fr.*
Vitamins A, D , E, and K for infusion (p.1922·1).
Parenteral nutrition.

Vitalitan *Ducto, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Vitalium *Farma Lepori, Spain.*
St John's wort (p.422·3).
Sleep disorders; tonic.

Vitalivin-E Reformulated *Pascual, Philipp.*
Vitamins; minerals; lysine hydrochloride (p.1922·1).
Nutritional supplement.

Vitalix *Roemmers, Arg.*
Iron polymaltose (p.1953·1).
Iron deficiency; iron-deficiency anaemia.

Vitalix Complex *Roemmers, Arg.*
Iron polymaltose (p.1953·1); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Anaemias.

Vitalize *Scot-Tussin, USA.*
Ferric pyrophosphate (p.1938·1); vitamin B substances with -lysine (p.1922·1).
Iron-deficiency anaemias.

Vital-Kapseln *Ratiopharm, Ger.†.*
Siberian ginseng (p.2386·3).
Tonic.

Vitalle *Allen, Mex.†.*
Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Vitalmin Nutraenergy *Recalcine, Chile.*
Preparation for enteral nutrition (p.1922·1).

Vitalmix Action *Montefarmaco, Ital.*
Carnitine; chromium; amino acids; maté; rhodiola rosea (p.1922·1).

Vitalmix Complex *Montefarmaco, Ital.*
Myrtillus; guarana; ginseng; royal jelly; bioflavonoids; vitamins (p.1922·1).
Nutritional supplement.

Vitalmix Fos *Montefarmaco, Ital.*
Phosphorylserine; eleutherococcus; arginine aspartate; ginkgo biloba; royal jelly (p.1922·1).
Nutritional supplement.

Vitalmix Junior *Montefarmaco, Ital.*
Vitamin B ; folic acid; iron; royal jelly; amino acids; phosphorylserine (p.1922·1).
Nutritional supplement.

Vita-Logos *Sigma-Tau, Switz.†.*
Cyanocobalamin; amino acids (p.1922·1).
Tonic.

Vitalong C TRC *Bernofarm, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vitalorange *GSK, Mex.*
Vitamin A (p.1971·2); colecalciferol (p.1986·2).
Nutritional supplement.

Vitalpen *Labomed, Chile.*
Flucloxacillin (p.277·1).
Gram-positive bacterial infections.

Vitalux
Novartis Ophthalmics, Canad.; Novartis, Chile; Novartis, Fr.; Novartis, Hong Kong; Novartis, Mex.; Novartis, Philipp.; Novartis, Turk.
A multivitamin and mineral preparation (p.1922·1).
Antioxidant preparation; nutritional supplement.
Medivis, Ital.
Betacarotene; vitamins; minerals; soya lecithin; beeswax; wheat-germ oil (p.1922·1).
Novartis, Thai.
Multivitamin and mineral preparation with lutein (p.1922·1).
Novartis, Venez.
Vitamins; zinc gluconate; manganese gluconate; selenium yeast (p.1922·1).
Nutritional supplement.

Vitalux Plus
Novartis Ophthalmics, Arg.
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.
Medivis, Ital.
Vitamins; lecithin; luteine; gelatin; monoglycerides; iron oxides (p.1922·1).
Nutritional supplement.
Novartis, Mex.; Novartis Ophthalmics, Singapore; Novartis, Venez.
Vitamin and mineral preparation with lutein (p.1922·1).
Nutritional supplement.
Novartis, UK
Lutein; vitamin C; vitamin E; zinc; copper; nicotinamide (p.1922·1).

Vitalyn *Fontovit, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Vitam Doce *Frasca, Arg.*
Cyanocobalamin (p.1980·2).

Vitamag *Pharmacare, S.Afr.*
Vitamin B substances; magnesium; zinc (p.1922·1).
Vitamin and mineral supplement.

Vitamam 1 *Novell, Indon.*
Vitamins; minerals; ginger; fructo oligosaccharide (p.1922·1).
Nutritional supplement in pregnancy.

Vitamam 2 *Novell, Indon.*
Capsules, vitamins; minerals; fructo oligosaccharide (p.1922·1); capsules, ferrous fumarate (p.1938·3).
Nutritional supplement in pregnancy.

Vitamam 3 *Novell, Indon.*
Capsules, vitamins; minerals; fructo oligosaccharide (p.1922·1); capsules, ferrous fumarate (p.1938·3).
Nutritional supplement in pregnancy.

Vita-Max *Herbarium, Braz.†.*
Betacarotene; vitamin C; vitamin E; selenium (p.1922·1).

Vitamax *GSK, Rus.*
Vitamins; minerals; royal jelly; ginseng; wheat-germ oil; soya phosphatides; safflower oil; -arginine; -lysine; orotic acid; deanol tartrate; pollen (p.1922·1).
Tonic.

Vitamedin
Note.This name is used for preparations of different composition.
Sankyo, Hong Kong.
Vitamin B substances (p.1922·1).
Anaemias; neuritis; rheumatic disorders; sciatica.
Sankyo, Thai.†.
Benfotiamine (p.1975·2); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anaemias; neural disorders.

Vita-Mefren *Novartis Consumer, Belg.†.*
Chlorhexidine gluconate (p.1635·3); vitamin A palmitate (p.1973·1).
Burns; infected skin disorders; ulcers; wounds.

Vitamen *Beta, Ital.*
Protein and multivitamin preparation (p.1922·1).

Vita-Merfen
Novartis Consumer, Hung.†.
Chlorhexidine gluconate (p.1635·3); benzoxonium chloride (p.1631·2); vitamin A (p.1971·2).
Burns; minor wounds.
Novartis Consumer, Switz.
Chlorhexidine gluconate (p.1635·3); benzoxonium chloride (p.1631·2); vitamin A palmitate (p.1973·1).
Minor wounds and burns.

Vita-Merfen NF *Novartis Consumer, Israel.*
Chlorhexidine gluconate (p.1635·3); benzoxonium chloride (p.1631·2); vitamin A (p.1971·2).
Burns; wounds.

Vita-Merfen Soins dermatologiques *Novartis Consumer, Switz.†.*
⊗ Urea (p.1620·2).
Dry skin.

Vitamex C *Konimex, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Vitamfenicolo *Tubilux, Ital.*
Chloramphenicol (p.239·3) or chloramphenicol sodium succinate (p.240·1).
Bacterial eye infections.

Vitamice *Greenpharma, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Vitamidyne A and D *Fischer, Israel.*
Vitamin A (p.1971·2); vitamin D (p.1986·1).
Vitamin A and D deficiency.

Vitamin A Acid *Dermik, Hong Kong.*
Tretinoin (p.1618·1).
Acne.

Vitamin B duo *Jenapharm, Ger.*
Thiamine hydrochloride (p.1976·1); pyridoxine hydrochloride (p.1978·2).
Neurological system disorders.

Vitamin C-500 YSP *YSP, Malaysia.*
Ascorbic acid (p.1983·3); calcium pantothenate (p.1959·3); sodium ascorbate (p.1984·1).
Vitamin C deficiency.

Vitamin C-Calcium *Herbrand, Ger.†.*
Calcium carbonate (p.1714·1); ascorbic acid (p.1983·3).
Calcium deficiency; cold symptoms.

Vitamin F *Klosterfrau, Austria.*
Ethyl linoleate (p.2308·2).
Skin disorders; wounds.

Vitamin for the Hair *Natural Life, Arg.*
Vitamin and mineral preparation (p.1922·1).

Vitamina A Composta *Labesfal, Port.*
Vitamin A; vitamin D (p.1922·1).

Vitamina C Plus *ISA, Arg.*
Vitamin B substances; vitamin C; betacarotene (p.1922·1).

Vitamina C-Complex *Natural Life, Arg.*
Rose fruit (p.2381·2); citrus bioflavonoids (p.2304·1); rutoside (p.2305·1); hesperidin (p.2304·3) complex; red cherry (p.1472·2).
Vitamin C supplement.

Vitamina F99 Topica *Vitafarma, Spain.*
Peru balsam (p.2365·3); vitamin F (p.2308·2).
Skin disorders.

Vitaminac Retard *Confar, Port.*
Vitamin C (p.1983·3).

Vitaminal *Proula, Venez.*
Vitamin B substances (p.1922·1).
Neuropathies; vitamin B supplement.

Vitamine 15 *Solco, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitamine F99 *Doetsch, Grether, Switz.†.*
Ethyl linoleate (p.2308·2); ethyl linolenate.
Burns; skin disorders; ulcers; wounds.

Vitamineral *ACO, Swed.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitaminoftalmina *Davi, Port.*
Vitamin A palmitate (p.1973·1).
Eye disorders.

Vitaminol *Bio-Sante, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Vitaminorum *Sigma, Austral.*
Multivitamin preparation (p.1922·1).

Vitamins Only *Solgar, UK.*
Multivitamin preparation (p.1922·1).

Vitaminum B Compositum *Pliva Krakow, Pol.; Polfa Kutno, Pol.; Polfa Warszawa, Pol.; Polfarmex, Pol.*
Vitamin B substances (p.1922·1).

Vitamon *Cipla, India.*
Ferric ammonium citrate (p.1938·1); folic acid (p.1940·1); vitamin B (p.1980·2).

Vitamon K *Omega, Belg.*
Phytomenadione (p.1995·3).
Vitamin K deficiency bleeding.

Vitamoren *IAE, Philipp.*
Multivitamins with calcium (p.1922·1).
Nutritional supplement.

Vitamult *CTI, Israel.*
Multivitamin preparation (p.1922·1).
Tonic.

VitaMulti *Otto, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement in pregnancy and lactation.

Vitamuruine *Medgenix, Belg.*
Vitamin A acetate (p.1973·1).
Burns; skin disorders; wounds.

Vitamycetin *Wyeth, India.*
Chloramphenicol (p.239·3) or chloramphenicol palmitate (p.239·3).
Bacterial infections.

Vitan
Note. A similar name is used for preparations of different composition (see below).
Antigen, Irl.†.
Multivitamin or multivitamin and mineral preparation (p.1922·1).

Vit-A-N
Note. A similar name is used for preparations of different composition (see above).
Farmigea, Ital.
Vitamin A acetate (p.1973·1).
Blepharitis; corneal ulcer; keratitis; keratoconjunctivitis.

Vitana-EZ *Kenyaku, Thai.*
Multivitamin and mineral preparation with iron and dehydrocholic acid (p.1922·1).
Tonic.

Vita-Nat *Laboratorios Chile, Chile.*
Vitamin A; colecalciferol; ascorbic acid (p.1922·1).
Vitamin A, D, and E supplement.

Vitaneed *Sherwood, USA.*
Lactose-free preparation for enteral nutrition (p.1922·1).

Vitaneral *Natufarma, Arg.*
Multivitamin and mineral preparation (p.1922·1).

Vitanerv *Unison, Philipp.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).
Neuralgia; neuritis; neuropathy; vitamin B deficiency.

Vitaneurin *Takeda, Jpn.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).

Vitaneuron
Note.This name is used for preparations of different composition.
Luper, Braz.†.
Vitamin B (p.1980·2); vitamin B (p.1976·3).
Megaloblastic anaemias; vitamin B deficiency.
Tunggal Idaman, Indon.
Vitamin B ; vitamin B ; vitamin B ; vitamin C; vitamin E (p.1922·1).
Nutritional supplement.

Vitanidia *Lusoterapia, Port.*
Sulbutiamine (p.1976·1).

Vitanol *Stiefel, Spain.*
Tretinoin (p.1618·1).
Acne; photodamaged skin.

Vitanol-A *Stiefel, Arg.†; Stiefel, Braz.*
Tretinoin (p.1618·1).
Acne; keratinisation disorders; skin disorders; skin hyperpigmentation.

Vitanox *Mediherb, Austral.*
Vitis vinifera (p.2316·3); green tea (p.2416·1); turmeric (p.1473·2); rosemary (p.2381·2).
Circulatory disorders.

Vitanumonyl C *Sanofi Synthelabo, Mex.*
Ascorbic acid (p.1983·3); chlorphenamine (p.572·2); paracetamol (p.108·1).

Vitap *GMP, Indon.*
Adenosine triphosphate (p.2247·3); vitamin B (p.1979·1).
Fatigue; skeletal muscle atrophy.

Vitapan *Provita, Austria.*
Cod-liver oil (p.1935·2).
Vitamin A and D deficiency.

Vita-Ped *Stiefel, Braz.*
Retinol palmitate; ascorbic acid; colecalciferol (p.1922·1).

Vitapelen *ICN, Arg.†.*
Vitamin A (p.1971·2); vitamin D (p.1986·1); zinc oxide (p.1621·2).
Skin disorders.

Vitaphakol *Alcon Cusi, Spain.*
Adenosine (p.1202·1); cytochrome C (p.2291·3); nicotinamide (p.1957·3); sodium succinate (p.2391·1); sorbitol (p.1965·1).
Cataracts.

Vitaplex
Provita, Austria..
Multivitamin preparation (p.1922·1).
Nutritional supplement.
Bernofarm, Indon.
Vitamins; omega-3; bovine colostrum (p.1922·1).
Nutritional supplement.
Blue Cross, Philipp.
Vitamins; taurine; lysine; zinc; chlorella growth factor (p.1922·1).
Nutritional supplement.

Vitaplex mineral *Pfizer, Swed.*
Multivitamin and mineral preparation (p.1922·1).

VitaPlus
Note. A similar name is used for preparations of different composition (see below).
Sari Husada, Indon.
Preparation for enteral nutrition (p.1922·1).

Vita-Plus
Note. A similar name is used for preparations of different composition (see above).
Scot-Tussin, USA.
A range of vitamin and mineral preparations (p.1922·1).

Vitaplus B *Douglas, NZ†.*
Vitamin B substances; vitamin C; calcium (p.1922·1).
Vitamin and calcium supplement.

Vitaplus B Plus *Adcock Ingram Consumer, S.Afr.*
Vitamin B substances; vitamin C; calcium (p.1922·1).
Vitamin and calcium supplement.

Vitaplus C Plus *Adcock Ingram Consumer, S.Afr.*
Ascorbic acid (p.1983·3); calcium (p.1675·2).
Vitamin C and calcium supplement.

Vita-Plus E *Scot-Tussin, USA.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Vita-PMS *Bajamar, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vitapole *Ponce, Venez.†.*
Vitamin B substances (p.1922·1).

Vita-POS
Note.This name is used for preparations of different composition.
Ursapharm, Ger.
Vitamin A palmitate (p.1973·1); liquid paraffin (p.2030·3); light liquid paraffin (p.2031·1); wool fat (p.2033·2); white soft paraffin (p.2031·2).
Eye disorders.
Ursapharm, Rus.
Vitamin A palmitate (p.1973·1).
Eye disorders.

Vita-Preg *Vitelle, Austral.†.*
Omega-3 marine triglycerides (p.1362·2); folic acid (p.1940·1).
Fatty-acid supplement in pregnancy; prevention of neural tube defects.

Vitaprost *Nizpharm, Rus.*
Bovine prostate extract (Samprost) (p.2337·3).
Prostatitis.

Vitaquick *Vitaflo, Irl.*
Thickening agent (p.1922·1).
Dysphagia.

Vitaquin *Surya Dermato, Indon.*
Hydroquinone (p.1598·2).
Skin hyperpigmentation.

Vitar *Vita, Venez.†.*
Cade oil (p.1616·1); ammonium laurilsulfate (p.2138·3).
Psoriasis; seborrhoea.

Vitaral
Jelfa, Pol.
Vitamin and mineral preparation (p.1922·1).
Vitamin and mineral deficiency.

Kenyaku, Thai.
Vitamins; minerals; rutoside; dehydrocholic acid; liver concentrate (p.1922·1).
Vitamin and mineral deficiency.

Vitareds *Gallivit, Fr.*
Vitamin and mineral preparation with or without lutein (p.1922·1).

Vitarex *Pasadena, USA.*
Multivitamin and mineral preparation with iron (p.1922·1).

Vitarnin *Grossmann, Hong Kong; Grossmann, Switz.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitarubin *Streuli, Switz.*
Cyanocobalamin (p.1980·2) or hydroxocobalamin acetate (p.1980·3).
Anaemias; neurological disorders; vitamin B deficiency.

Vitasana-Lebenstropfen *Riemser, Ger.†.*
Gentian; calamus; menyanthes; melissa; achillea; peppermint leaf; crataegus; rosemary; rue; lupulus; valerian; juniper; aniseed; fennel; caraway; herba marjoranae.
Tonic.

Vitasavoury *Vitaflo, UK.*
High energy sip feed (p.1922·1).

Vitascor *ICN, Hung.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Vitascorbol *Cooperation Pharmaceutique, Fr.*
Ascorbic acid (p.1983·3) with or without sodium ascorbate (p.1984·1).
Asthenia; vitamin C deficiency.

Vitaseptol *Europhta, Mon.*
Thiomersal (p.1663·3).
Ocular antiseptic.

Vitaseve *Rider, Chile.*
Calcium ascorbate (p.1984·1).
Vitamin C supplement.

Vitasilin *Casel, Turk.*
Tetracycline hydrochloride (p.347·2).
Bacterial skin infections.

Vitaslim *Soho, Indon.*
Poliglusam (p.2370·1); garcinia cambogia (p.2309·2); levocarnitine fumarate (p.1933·1); chromium picolinate (p.1934·3); vitamin C (p.1983·3).
Obesity.

Vitasma *Basi, Port.†.*
⊗ Ephedrine hydrochloride (p.1558·2); meprobamate (p.1006·2); prednisolone (p.1540·3); choline theophyllinate (p.1119·3).

VitaSohn *Antonetto, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Vitasol F *LA, Arg.*
Vitamins A, C, and D with fluoride (p.1922·1).

Vitaspectrum *Veropharm, Rus.*
Vitamin and mineral preparation (p.1922·1).

Vitasprint *Balverda, Ital.†.*
-Phosphoserine (p.2367·1); cyanocobalamin (p.1980·2); glutamine (p.1947·2).
Tonic.

Vitasprint B_{12} *Wyeth, Ger.†.*
-Phosphoserine (p.2367·1); cyanocobalamin (p.1980·2); glutamine (p.1947·2).
Vitamin B deficiency.

Vitasprint Complex *Balverda, Ital.†; Whitehall-Robins, Switz.*
Dexfosfoserine (p.2367·1); arginine hydrochloride (p.1928·2); -phosphothreonine; glutamine (p.1947·2); hydroxocobalamin (p.1980·3).
Tonic.

Vita-Squares *GNLD, Austral.*
Vitamin and mineral preparation (p.1922·1).

Vitathion
Note. A similar name is used for preparations of different composition (see below).
Servier, Fr.
Ascorbic acid (p.1983·3); thiamine hydrochloride (p.1976·1); inositocalcium.
Asthenia.

Vita-Thion
Note. A similar name is used for preparations of different composition (see above).
Servier, S.Afr.
Vitamins; glutathione; sodium adenosine triphosphate; calcium fytate (p.1922·1).
Tonic.

Vitathion-ATP *Servier, Canad.*
Ascorbic acid; adenosine triphosphate; calcium inositohexaphosphate; glutathione; magnesium inositohexaphosphate; thiamine (p.1922·1).
Stress conditions.

Vitaton
Allen, Mex.
Vitamin B substances (p.1922·1).

Vita Health, Singapore.
Vitamins; minerals; bee pollen; cysteine; ginseng; kelp; lecithin; lysine; royal jelly; yeast (p.1922·1).

Vitaton Alpha Vitahealth *Hovid, Malaysia†; Swiss Bio, Malaysia†.*
Multivitamin and mineral preparation with inositol and lecithin (p.1922·1).
Nutritional supplement.

Vitaton Gold Vitahealth *Hovid, Malaysia†; Swiss Bio, Malaysia†.*
Multivitamin and mineral preparation with ginseng, lecithin, and rutoside (p.1922·1).
Nutritional supplement.

Vitatona *Brauer, Austral.*
Angelica (p.2258·1); ascorbic acid (p.1983·3); kola nitida (p.2416·1); vitamin B substances (p.1922·1); alfalfa (p.2249·2); ginseng (p.2312·1); urtica (p.2409·3); aurum muriaticum; calcarea phosphorica; ferrum metallicum; ferrum phosphoricum; hypericum perforatum; kali phosphoricum; magnesia phosphorica; phosphoricum acidum.
Tonic.

Vitatonin *Ipex, Swed.*
Multivitamins (p.1922·1); caffeine (p.1116·3); vin. vermuth.; alcohol.
Tonic.

Vitatonus *Bunker, Braz.*
Thiamine nitrate (p.1976·2); pyridoxine hydrochloride (p.1978·2); cyanocobalamin (p.1980·2).

Vitatonus Dexa *Bunker, Braz.*
⊗ Vitamin B substances (p.1922·1); dexamethasone (p.1526·1) or dexamethasone phosphate (p.1526·2).

Vitatrans *Medice, Ger.*
Ethylenediamine thioctate (p.2400·2).
Diabetic polyneuropathy.

Vitatress *Veropharm, Rus.*
Vitamin and mineral preparation (p.1922·1).

Vitatron *VAAS, Ital.*
Amino-acid preparation with vitamins and minerals (p.1922·1).
Nutritional supplement.

Vitaveran Folico *Hormona, Mex.*
Vitamin and mineral preparation (p.1922·1).

Vitavir *Infosint, Ital.†.*
Vitamins; minerals; carnitine tartrate; ginseng; ginkgo biloba (p.1922·1).
Nutritional supplement.

Vita-Vision
Note. A similar name is used for preparations of different composition (see below).
Teguhsindo, Indon.
Myrtillus (p.2349·3); lutein (p.1954·3); vitamin A (p.1971·2).
Dietary supplement for eye disorders.

Vitavision
Note. A similar name is used for preparations of different composition (see above).
Oftalmi, Venez.
Vitamins; minerals; lutein; zeaxanthin (p.1922·1).
Dietary supplement for eye disorders.

Vitavitin *Sriprasit, Thai.*
Vitamin B substances (p.1922·1).
Neuritis; vitamin B deficiency.

Vitavox Pastillas *Escaned, Spain†.*
⊗ Camphor (p.2273·2); cineole (p.2282·3); chlorophyll (p.1471·1); ephedrine hydrochloride (p.1558·2); niaouli oil (p.2351·3); menthol (p.2340·1); sulfanilamide sodium mesilate (p.343·1); peppermint (p.1761·2).
Mouth and throat disorders.

Vita-Worth B Complex *General Nutrition, Canad.†.*
Vitamin B substances (p.1922·1).

Vitawund *Novartis Consumer, Austria.*
Chlorhexidine gluconate (p.1635·3); halibut-liver oil (p.1948·1).
Burns; wounds.

Vitax Derm *Ativus, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Vitaxicam *Ferrer, Singapore; Robert, Spain.*
Piroxicam (p.117·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Vitayde C *Saval, Chile.*
Vitamin A; vitamin C; vitamin D (p.1922·1).
Dietary supplement.

Vitazell E *Kohler-Pharma, Ger.*
d-Alpha tocopherol (p.1992·2).
Vitamin E deficiency.

Vitazinc
Note. A similar name is used for preparations of different composition (see below).
Medlink, Philipp.
Vitamins; lysine; taurine; zinc (p.1922·1).
Nutritional supplement.

Vitazink
Note. A similar name is used for preparations of different composition (see above).
Strathmann, Ger.
Zinc sulfate (p.1999·2).
Zinc deficiency.

Vitazon *Intra, Venez.†.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

Vitazulen *Leciva, Cz.†.*
Alpha tocoferil acetate (p.1992·3); guaiazulene (p.2317·3).
Nasal inflammation.

Vitazym *Kalbe, Indon.*
Amylase (p.2256·3); protease; lipase (p.2360·3); docosahexaenoic acid (p.1362·1); dimeticone (p.1770·2); vitamin B substances (p.1922·1).
Digestive disorders; liver and bile disorders.

Vitazyme
Note.This name is used for preparations of different composition.
East India Pharma, India.
Capsules: Amylase (p.2256·3); lactic acid bacillus (p.2372·3).
Dyspepsia; restoration of a normal gastrointestinal flora.

East India Pharma, India.
Oral drops; oral liquid: Amylase (p.2256·3); cinnamon oil (p.2283·2); caraway oil (p.2277·1); cardamom oil (p.2277·2).
Dyspepsia.

Vitcaroten *Viternat, Braz.†.*
Betacarotene (p.1930·3).
Nutritional supplement.

Vit-C-Lutsch *Sanochemia, Austria.*
Ascorbic acid (p.1983·3); calcium ascorbate (p.1984·1); hesperidin phosphate (p.2305·2).
Vitamin C deficiency.

Vitec *Pharmaceutical Specialties, USA.*
dl-Alpha tocoferil acetate (p.1992·3).
Skin disorders.

Vitecaf
Note.This name is used for preparations of different composition.
SIFI, Ital.
Eye drops: Rolitetracycline (p.330·3); chloramphenicol (p.239·3).
Infected eye disorders.

SIFI, Ital.
Eye ointment: Tetracycline hydrochloride (p.347·2); chloramphenicol (p.239·3); calcium pantothenate (p.1959·3).
Infected eye disorders.

Vitef *Teofarma, Ital.*
Polyenacid (p.2308·2).
Skin disorders.

Vit-E-Far *Farcoral, Mex.*
Alpha tocopherol (p.1992·2).

Vitelle Nesentials *Fielding, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vitelle Nestabs *Fielding, USA.*
Multivitamin and mineral preparation with iron and folic acid (p.1922·1).
Prenatal supplement.

Vitelle Nestrex *Fielding, USA†.*
Pyridoxine hydrochloride (p.1978·2).
Pyridoxine deficiency.

Vitelsix *Unison, Thai.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Loss of appetite; vitamin B deficiency.

Vit-E-Nat *Infinity, Venez.*
d-Alpha tocoferil acetate (p.1992·3).
Antoxidant.

Vitenol *Ponce, Venez.†.*
Vitamin A (p.1971·2); ergocalciferol (p.1987·1); panthenol (p.2362·1).
Skin disorders.

Vitenon *Ativus, Braz.*
Agnus castus (p.2249·1).
Menopausal disorders.

Viteral
Note.This name is used for preparations of different composition.
Be-Tabs, S.Afr.
Multivitamin and mineral preparation (p.1922·1).
Formerly known as Be-Vital.

Vivax, Venez.
Vitamin E (p.1992·2).
Vitamin E deficiency.

Vitercal C *Cifarma, Braz.*
Ascorbic acid (p.1983·3); calcium carbonate (p.1714·1).
Calcium and vitamin C supplement.

Vitergan Master *Marjan, Braz.*
Ginseng; vitamins; minerals (p.1922·1).

Vitergan Pre-natal *Marjan, Braz.*
A multivitamin and mineral preparation (p.1922·1).

Vitergan Zinco *Marjan, Braz.*
A range of multivitamin and mineral preparations (p.1922·1).

Vitergyl C *Cifarma, Braz.*
Ascorbic acid (p.1983·3).
Vitamin C supplement.

Viternum *Labomed, Chile; Senosiain, Mex.; OM, Port.; Juste, Spain.*
Cyproheptadine, pyridoxal phosphate salt (p.575·2).
Allergic rhinitis; reduced appetite; tonic; urticaria.

Viternum Vitaminado *Labomed, Chile.*
Cyproheptadine pyridoxal phosphate (p.575·2); vitamins (p.1922·1).
Reduced appetite; tonic.

Viterra *Pfizer Consumer, Ital.†; Pfizer, Mex.†; Pfizer, Port.†; Pfizer, Thai.*
Multivitamin and mineral preparation (p.1922·1).

Vitestable *Alcor, Spain.*
Royal jelly; ginseng; tocopherol (p.1922·1).
Tonic.

Vit-E-Var *Infinity, Venez.*
dl-Alpha tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Vitex *Herbarium, Braz.*
Agnus castus (p.2249·1).
Menstrual disorders.

Vitexid *Svizera, India.*
Spirulina (p.2392·1); vitamin B substances (p.1975·1); vitamin E (p.1992·2).
Vitamin B and E deficiency.

Vitexir *Yeni, Turk.*
Vitamin B substances (p.1922·1).
Vitamin B deficiency.

Viticalm *Atlas, Arg.*
Grape (p.2316·3).
Dry skin.

ViTicolor *Crawford, UK.*
Dihydroxyacetone (p.1594·1); erythrulose (p.1597·1).
Vitiligo.

Viticromin *Auad, Braz.†.*
Vitamin B substances (p.1922·1); brosimum gaudichandii.
Vitiligo.

Vitinelin *Antor, Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Vitintra *Fresenius Kabi, Neth.*
Vitamins A, D , E, and K for infusion (p.1922·1).
Parenteral nutrition.

Vition *Meditop, Hung.*
Zinc asparate (p.2000·1); magnesium aspartate (p.1679·1); monobasic potassium phosphate (p.1682·2); dibasic potassium phosphate (p.1682·2).
Arrhythmias; mineral supplement.

Vitiral *Scherer, Thai.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitiron *Mepha, Hong Kong; Mepha, Switz.*
Multivitamin and mineral preparation (p.1922·1).

Vitis Encias Colutorio *Dentaid, Chile.*
Metesculetol sodium (p.2343·2); dexpanthenol (p.2362·1); cetylpyridinium chloride (p.1635·1); zinc lactate.
Oral hygiene.

Vitis Encias Pasta *Dentaid, Chile.*
Metesculetol sodium (p.2343·2); dexpanthenol (p.2362·1); cetylpyridinium chloride (p.1635·1); zinc lactate; sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Vitis Pasta *Dentaid, Chile.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Vitisival *Valmor, Venez.*
Vitamin B substances; lysine hydrochloride (p.1922·1).

Vitium *Teuto, Braz.†.*
Grape (p.2316·3).

Vitix
Note. A similar name is used for preparations of different composition (see below).
Valeant, Arg.
Superoxide dismutase (p.127·3); catalase (p.2278·2).
Vitiligo.

ViTiX
Note. A similar name is used for preparations of different composition (see above).
ACM, Fr.
Cucurbita (p.2290·2).
Skin depigmentation disorders.

Vitizin *Ativus, Braz.*
Multivitamin and mineral preparation (p.1922·1).

Vitizin Beta *Ativus, Braz.*
Betacarotene (p.1930·3).

Vitizin E *Ativus, Braz.*
Tocoferil acetate (p.1992·3).

Vitlipid N *Pharmacia, Irl.; Fresenius Kabi, UK.*
Vitamins A, D , E, and K for infusion (p.1922·1).
Parenteral nutrition.

Vitnatal *SM, Venez.*
Vitamins; folic acid; ferrous fumarate (p.1922·1).
Nutritional supplement for pregnancy and breast feeding.

Vitneurin *GSK, India.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2); dexpanthenol (p.2362·1).
Neuropathies.

Vito Bronches *Duchesnay, Canad.†.*
Diphenylpyraline hydrochloride (p.578·2); dextromethorphan hydrobromide (p.1555·2); potassium iodide (p.2169·2); sodium citrate (p.1673·3).

Vitobel *Vianex (Βιανέξ), Gr.†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Vitocalcit *SJA, Gr.*
Alfacalcidol (p.1986·1).
Vitamin D deficiency.

Vitogen *Stanley, Canad.†.*
A range of vitamin preparations with or without minerals (p.1922·1).

Vitol *Orion, Fin.*
Vitamin A or vitamin A palmitate; colecalciferol or ergocalciferol (p.1922·1).
Vitamins A and D deficiency.

Vitole E *Medana, Pol.*
d-Alpha tocopherol (p.1992·2).
Atherosclerosis; ischaemic heart disease.

Vitolide *Pharmout, Port.*
Nimesulide (p.95·3).
Osteoarthritis; pain.

Vitomin *Cipla, India.*
Multivitamin preparation (p.1922·1).

Vitonal *SM, Venez.*
Vitamin B substances (p.1922·1).
Vitamin B supplement.

Vitonal-F *Tempo Scan Pacific, Indon.*
Vitamin B substances; ferrous fumarate (p.1938·3); copper; manganese (p.1922·1).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemia.

Vitonic *Cypress, USA.*
Vitamin B substances; minerals (p.1922·1).
Dietary supplement.

Vitonico *Legrand, Braz.*
Ferrous sulfate; phosphoric acid; aloes; myrrh; nutmeg; clove (p.1922·1).
Iron-deficiency anaemias; tonic.

Vitonil *Gemballa, Braz.†.*
Orotic acid; vitamin B substances (p.1922·1).
Nutritional supplement.

Vitop
Note. This name is used for preparations of different composition.
Fahrenheit, Indon.
Myrtillus (p.2349·3); betacarotene; vitamin C; vitamin B (p.1922·1).
Antioxidant; dietary supplement for healthy eyes.
Olan-Kemed, Thai.
Vitamins; minerals; choline bitartrate; rutoside; methionine; inositol (p.1922·1).

Vitoport *Christo, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Degenerative joint disorders.

Vitorange *Unipharma, Gr.*
Vitamin C (p.1983·3).

Vitosal *Ziethen, Ger.†.*
⊗ Vitamins (p.1922·1); rutoside sodium sulfate (p.2305·2); arnica (p.2260·2); sage (p.2382·3); peppermint oil (p.1761·2).
Gum disorders.

Vitotal *Tecnofarma, Chile.*
Ascorbic acid; vitamin E; betacarotene; magnesium (p.1922·1).
Dietary supplement.

Vit-Porphyrin *Teofarma, Ital.†.*
Haematoporphyrin dihydrochloride (p.2318·1); nicotinamide (p.1957·3).
Tonic.

Vitrace *Columbia, S.Afr.*
Multivitamin and mineral preparation (p.1922·1).
Tonic.

Vitral *Darya-Varia, Indon.; Pharos, Indon.*
Vitamin and mineral preparation (p.1922·1).
Nutritional supplement.

Vitrase *Ista, USA.*
Hyaluronidase (p.2321·1).
Adjunct in subcutaneous urography; adjuvant to increase the absorption and dispersion of injected drugs; hypodermoclysis.

Vitrasert *Bausch & Lomb, Austral.†; Bausch & Lomb, Spain†; Bausch & Lomb, USA.*
Ganciclovir (p.879·1).
Cytomegalovirus retinitis.

Vitravene *Novartis Ophthalmics, Ger.†; Novartis Ophthalmics, Switz.†; Novartis Ophthalmics, USA†.*
Fomivirsen sodium (p.876·3).
Cytomegalovirus retinitis.

Vitrena *Grunenthal, Ger.†; Orion, Ger.†.*
White tablets, estradiol valerate (p.2097·3); blue tablets, estradiol valerate; medroxyprogesterone acetate (p.2113·1); pink tablets,estradiol valerate.
Menopausal disorders.

Vitreoclar *SIFI, Ital.*
Red vine; minerals; vitamin E; amino acids (p.1922·1).
Connective tissue disorders; nutritional supplement.

Vitreoclar Crono *SIFI, Ital.*
Glucosamine; vitamin E; collagen (p.1922·1).
Nutritional supplement.

Vitreolent
Theodoridis, Gr.
Calcium iodide (p.1553·2); sodium iodide (p.2169·2).
Glaucoma.
Novartis, Hong Kong; Novartis Ophthalmics, Malaysia†; Novartis, Philipp.; Pharm Supply, Pol.; Novartis Ophthalmics, Singapore†; Novartis, Switz.
Potassium iodide (p.2169·2); sodium iodide (p.2169·2).
Cataract; clouding and haemorrhage of the vitreous humour.

Vitreolux *Novartis, Ital.*
Vitamins; bioflavonoids; betacarotene; glucosamine; zinc; methionine; myrtillus; yeast (p.1922·1).
Nutritional supplement.

Vitreosan *DMG, Ital.*
Potassium bicarbonate; magnesium oxide; vitamin C (p.1922·1).
Nutritional supplement.

Vitrex *Naturex, Mex.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitrexon *Vargas, Venez.*
Ascorbic acid (p.1983·3).

Vitrimix *Fresenius Kabi, Denm.†; Fresenius Kabi, Indon.; Fresenius Kabi, Norw.†; Fresenius Kabi, Port.; Fresenius Kabi, Swed.†; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.*
Amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusion with or without electrolytes(p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Vitrimix KV *Fresenius Kabi, Fr.; Fresenius Kabi, Hong Kong; Pharmacia, Irl.; Fresenius Kabi, Malaysia†; Fresenius Kabi, Neth.; Fresenius Kabi, UK†.*
Amino-acid, glucose, and lipid (from soya oil (p.1965·3)) infusion with or without electrolytes (p.1922·1).
Contains egg phospholipids.
Parenteral nutrition.

Vitro-Mega *Solas, Indon.*
Vitamins; minerals; docosahexaenoic acid; omega-3 (p.1922·1).
Nutritional supplement.

Vitromicin *Vitapan, Braz.†.*
Gentamicin (p.284·2).
Bacterial infections.

Vitromix *Fresenius Kabi, Austria.*
Amino-acid, glucose, lipid (from soya oil (p.1965·3)), and electrolyte infusion (p.1922·1).
Contains egg lecithin.
Parenteral nutrition.

Vitron *Pharmaland, Thai.*
Vitamin B (p.1976·3); vitamin B (p.1979·1); vitamin B (p.1980·2).
Anorexia; neurasthenia; neurological disorders; neuropathy; toxaemia of pregnancy.

Vitron-C *Heritage Consumer, USA.*
Ferrous fumarate (p.1938·3).
Ascorbic acid (p.1983·3) is included in this preparation to increase the absorption and availability of iron.
Iron-deficiency anaemias.

Vitrosups *Llorens, Spain.*
Glycerol (p.2314·2).
Constipation.

Vitrum *Unipharm, Pol.; Unipharm, Rus.*
A range of vitamin and mineral preparations (p.1922·1).

Vits *Profarb, Braz.†.*
Multivitamin and mineral preparation (p.1922·1).

Vitspo *Orva, Turk.*
Methoxsalen (p.1605·1).
Eczema; psoriasis; vitiligo.

Vitulpas *Drag, Chile†.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Vit-u-pept *Plantina, Ger.†.*
Weisskohl; bismuth subcarbonate (p.1711·1); heavy magnesium carbonate (p.1743·1); sodium bicarbonate (p.1673·2).
Gastrointestinal disorders.

Vitussin
Note. This name is used for preparations of different composition.
Vitamed, Israel.
Guaifenesin (p.1561·3).
Coughs.
Cypress, USA.
Hydrocodone tartrate (p.63·1); guaifenesin (p.1561·3).
Coughs.

Vi-Uril *Bago, Chile.*
Tamsulosin hydrochloride (p.2197·1).
Benign prostatic hyperplasia.

Viusid *Interbat, Indon.; SM, Venez.*
Glycyrrhizinic acid; malic acid; glucosamine; zinc sulfate; arginine; glycine; ascorbic acid; vitamin B substances (p.1922·1).
Nutritional supplement in immunodeficiency; supplement in viral infections.

Vivabec *Lexon, UK.*
⊗ Beclometasone dipropionate (p.1516·2).
Hypersensitivity reactions.

Vivace
Note. This name is used for preparations of different composition.
Chiesi, Gr.
Delapril (p.1256·2); manidipine (p.1330·2).
Actavis, Pol.
Ramipril (p.1385·3).
Cardiovascular risk reduction; heart failure; hypertension; myocardial infarction; non-diabetic nephropathy.

Vivacor
Note. This name is used for preparations of different composition.
AstraZeneca, Braz.
Rosuvastatin calcium (p.1389·1).
Hypercholesterolaemia.
Anpharm, Pol.
⊗ Carvedilol (p.1241·3).
Angina pectoris; heart failure; hypertension.
Lexon, UK.
⊗ Bisoprolol fumarate (p.1234·1).
Angina pectoris; hypertension.

Vivactil *Barr, USA; Duramed, USA.*
Protriptyline hydrochloride (p.420·2).
Depression.

Vivacton *Remedina, Gr.*
Vitamin B substances; lysine (p.1922·1).

Vivadone *Lexon, UK.*
Domperidone maleate (p.1726·3).
Dyspepsia.

Viva-Drops *Vision, USA.*
Polysorbate 80 (p.1919·2).
Formerly known as Vit-A-drops.
Dry eyes.

Vivaglobin *ZLB, Belg.; CSL, Cz.; ZLB, Fr.; ZLB, Ger.; ZLB, Gr.; CSL, Hung.; ZLB, Neth.; CSL, Port.; ZLB, UK; CSL Behring, USA.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura; immunodeficiency; passive immunisation.

Vival *Alpharma, Norw.*
Diazepam (p.986·3).
Anxiety; skeletal muscle spasm; sleep disorders.

Vivalan *AstraZeneca, Belg.†; Menarini, Belg.†; AstraZeneca, Cz.†; AstraZeneca, Fr.†; AstraZeneca, Ger.†; AstraZeneca, Port.†.*
Viloxazine hydrochloride (p.430·3).
Depression.

Vivalcid *Polychronus, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folate deficiency.

Vivalessence *Motima, Fr.*
A range of preparations containing essential oils and plant extracts (p.1922·1).
Tonic.

Vivamag *Madaus, Fr.†.*
Magnesium lactate (p.1679·2).
Magnesium deficiency.

Vivamyne *Wyeth, Fr.*
Multivitamin preparation (p.1922·1).

Vivance *Vivance, Fr.†.*
Nutritional supplement (p.1922·1).

Vivanza *Medley, Braz.; Bayer, Cz.; GSK, Ital.†; Bayer, Neth.; Bayer, Port.*
Vardenafil hydrochloride (p.2199·3).
Erectile dysfunction.

Vivarin *SmithKline Beecham Consumer, USA.*
Caffeine (p.1116·3).
Fatigue.

Vivatak *Lexon, UK†.*
Ranitidine (p.1766·1).
Dyspepsia; gastric hyperacidity; heartburn.

Vivatec *MSD, Denm.†; MSD, Fin.; MSD, Norw.; MSD, Swed.†.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Vivatec Comp *MSD, Fin.; MSD, Norw.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Vivax *Osoth, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Vivaxim *Aventis Pasteur, Austral.; Sanofi Pasteur, Canad.; Sanofi Pasteur, Malaysia; Sanofi-Aventis, NZ.*
A typhoid (Vi capsular polysaccharide) and inactivated hepatitis A vaccine (p.2217·2).
Active immunisation.

Vivaxine *Nakorn, Thai.†.*
Sulfadoxine (p.338·1); pyrimethamine (p.610·2).
Malaria.

Vivazid *MSD, Denm.†.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Vivelle
Note. This name is used for preparations of different composition.
Janssen-Cilag, Austria.
Norgestimate (p.2121·1); ethinylestradiol (p.2101·3).
Acne; triphasic oral contraceptive.
Novartis, Belg.; Novartis, Canad.†; Novartis, USA.
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Vivelle Dot *Novartis, Denm.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Vivelledot *Novartis, Fr.*
Estradiol (p.2097·2).
Menopausal disorders; osteoporosis.

Vivena AR *Dieterba, Ital.*
Infant feed (p.1922·1).
Gastro-oesophageal reflux.

Vivena HA *Dieterba, Ital.*
Infant feed (p.1922·1).
Cow's milk intolerance.

Vivene *Theratech, Fr.†.*
Aesculus (p.2248·2); troxerutin (p.2305·1).
Haemorrhoids; peripheral vascular disorders.

Viverdal *Uniao Quimica, Braz.*
Risperidone (p.1024·2).
Psychoses.

Vivicrom *Nucare, UK.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis.

Vividrin *Riel, Austria; Mann, Cz.†; Mann, Ger.; Kite (Κιτε), Gr.; Mann, Irl.; Mann, Malaysia†; Tramedico, Neth.; Bausch & Lomb, Philipp.; Mann, Pol.; SofLens, S.Afr.†; Bausch & Lomb, Singapore; Mann, Singapore; Gebro, Switz.; Bausch & Lomb, Thai.; Mann, Thai.; Pharmalink, Thai.; Nucare, UK.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis; keratoconjunctivitis.

Vividrin akut Azelastin *Mann, Ger.*
Azelastine hydrochloride (p.568·2).
Allergic conjunctivitis; allergic rhinitis.

Vividrin Loratadin *Mann, Ger.†.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Vivimed *Riel, Austria.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Vivin C
Note. This name is used for preparations of different composition.
Menarini, Ital.
Aspirin (p.20·3); ascorbic acid (p.1983·3).
Cold and influenza symptoms; fever; pain.
Alter, Port.
Ascorbic acid (p.1983·3).
Cold and influenza symptoms; tonic.

Vivinox Day *Mann, Ger.*
Valerian (p.2410·1); lupulus (p.2335·2); passion flower (p.2363·2).
Formerly known as Vivinox N.
Nervous disorders; sleep disorders.

Vivinox Sleep *Mann, Ger.*
Diphenhydramine hydrochloride (p.577·2).
Sleep disorders.

Viviolax *GFC, Mex.†.*
Prune (p.1765·1).
Constipation.

Vivioptal *Mann, Irl.; Novum, Mex.; Pharma-Global, UK.*
Multivitamin and mineral preparation (p.1922·1).

Viviplus *Mann, Ger.†.*
St John's wort (p.422·3).
Depression.

Vivir *Unison, Thai.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vivitar *Armstrong, Mex.*
⊗ Spironolactone (p.1400·1).
Bartter's syndrome; heart failure; hirsutism associated with polycystic ovary syndrome; hyperaldosteronism; hypertension; metabolic syndrome; myocardial infarction; oedema; premenstrual syndrome.

Vivitrol *Alkermes, USA.*
Naltrexone hydrochloride (p.1455·2).
Withdrawal syndromes.

Vivolan *Orion, Fin.†.*
Emollient.
Skin disorders; vehicle for topical drugs.

Vivonex *Novartis, Arg.†; Novartis Consumer, Austral.†; Novartis, Braz.; Novartis Nutrition, Hong Kong; Promeco, Mex.†; Novartis Nutrition, Singapore†; Procter & Gamble, USA.*
Preparation for enteral nutrition (p.1922·1).

Vivorax *Cadila, Rus.*
Aciclovir (p.862·3).

Vivotif *Scott-Cassara, Arg.; CSL, Austral.; Kwizda, Austria; Qualiphar, Belg.; Berna, Canad.; Biosano, Chile; Berna, Denm.; Berna, Fin.; Niddapharm, Ger.†; Berna, Hong Kong; Berna, Indon.; Celltech, Irl.†; Berna, Ital.; Berna, Malaysia; CSL, NZ; Berna, Neth.; Berna, Norw.; Berna, Philipp.; Berna, Port.†; Byk Madaus, S.Afr.†; Berna, Singapore; Berna, Spain; SBL, Swed.; Berna, Switz.; Berna, Thai.; Masta, UK; Berna, USA.*
A live oral typhoid vaccine (p.2241·2).
Active immunisation.

Vivradoxil *Alpharma, Mex.*
Doxycycline (p.267·1).
Bacterial infections.

Vivural *Procter & Gamble, Ger.†.*
Calcium carbonate (p.1714·1).
Calcium deficiency.

Vixalerg *Cassara, Arg.*
⊗ Chlorphenamine maleate (p.571·3); dexamethasone (p.1526·1).
Allergic conjunctivitis; allergic rhinitis; angioedema; pruritus; urticaria.

Vixcef *Bago, Arg.*
Cefixime (p.224·3).
Bacterial infections.

Vixiderm E *Valeant, Arg.*
Benzoyl peroxide (p.1590·2).
Acne.

Vixidone *Valeant, Arg.*
⊗ Dexamethasone (p.1526·1); chlorphenamine maleate (p.571·3).

Vixidone L *Valeant, Arg.*
Loratadine (p.583·3).
Allergic rhinitis; urticaria.

Vixidone LB *Valeant, Arg.*
⊗ Loratadine (p.583·3); betamethasone (p.1518·2).
Allergic rhinitis; angioedema; urticaria.

Vixidone T *ICN, Arg.†.*
⊗ Dexamethasone (p.1526·1); terfenadine (p.590·3).

Vixin *Sons, Mex.†.*
Chloramphenicol (p.239·3).
Bacterial infections.

Vixmicina *Uniao Quimica, Braz.*
Chloramphenicol sodium succinate (p.240·1).
Bacterial infections.

Vixorfit *Gezzi, Arg.*
Glycerol (p.2314·2).
Eye irritation.

Viza *Royal, Chile.*
Aripiprazole (p.962·3).
Schizophrenia.

Vi-Zac *UCB, USA.*
Multivitamin and mineral preparation (p.1922·1).

Vizerul *Montpellier, Arg.; Dollder, Venez.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Vizole *MM, India.*
Levamisole (p.147·2) or levamisole hydrochloride (p.147·2).
Worm infections.

Vizoptal *Medical, Port.†.*
Chlorobutanol (p.1639·2).

Vizylac *Unichem, India.*
Lactobacillus sporogenes (p.2372·3); vitamin B substances (p.1922·1).
Imbalance of intestinal flora.

Vlanodrin *Cosmopharm, Gr.*
Terazosin (p.1410·3).
Benign prostatic hyperplasia.

Vlenolys *Intermed, Gr.*
Acetylcysteine (p.1548·2).
Paracetamol poisoning.

VM-2000 *Solgar, UK.*
Multivitamin and mineral preparation (p.1922·1).

VM 26 *BMS, Ger.*
Teniposide (p.778·1).
Malignant neoplasms.

V-Nolone *Vesco, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Joint disorders; keloids.

VNS 45 *Sigma, Arg.*
Vitamin E (p.1992·2); hamamelis (p.2318·2); aesculus (p.2248·2); centella (p.1592·3); ginkgo biloba (p.2311·1); arginine; flavonoids; tanins; triterpene acids; asiaticoside; rutoside (p.2305·1); aescin (p.2248·2).
Atherosclerosis; erectile dysfunction; haemorrhoids; mental function impairment; venous insufficiency.

Vobaderm *Hermal, Ger.*
⊗ Fluprednidene acetate (p.1533·1); miconazole nitrate (p.541·3).
Infected skin disorders.

Vobamyk *Hermal, Ger.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Vocadys *Cooperation Pharmaceutique, Fr.*
Enoxolone (p.50·1); lidocaine hydrochloride (p.1862·3); erysimum.
Sore throat.

Vocalzone *Kestrel, UK.*
Menthol (p.2340·1); peppermint oil (p.1761·2); myrrh (p.2349·2); liquorice (p.1740·3).
Throat irritation.

Vocara *Bittner, Austria; Bittner, Rus.*
Homoeopathic preparation.

Vocarxil *Quality, Hong Kong.*
Glucosamine sulfate (p.2313·2).
Rheumatic disorders.

Vodelan *Rayere, Mex.*
Ciprofloxacin (p.243·3); phenazopyridine (p.116·3).
Urinary-tract infections.

Vodol *Uniao Quimica, Braz.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Vogalene *Aventis, Denm.; Schwarz, Fr.*
Metopimazine (p.1750·2).
Nausea and vomiting.

Vogalib *Schwarz, Fr.*
Metopimazine (p.1750·2).
Nausea and vomiting.

Vogast *Fako, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Voir *Velka, Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Voker *YSP, Malaysia.*
Famotidine (p.1730·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Volamin *Volchem, Ital.*
Amino-acid preparation (p.1922·1).
Fatigue; liver disorders.

Volcidol-S *Pharmasant, Thai.*
Tramadol hydrochloride (p.130·3).
Pain.

Volcolon *Pfizer, Neth.*
Ispaghula (p.1737·1).
Constipation.

Voldal *Novartis, Fr.*
Diclofenac sodium (p.44·3).
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders; renal colic.

Voldilex *Solas, Indon.*
Cimicifuga (p.2282·1); vitamin E (p.1992·2).
Menopausal symptoms.

Volequin *Dexa, Indon.*
Levofloxacin (p.292·2).
Bacterial infections.

Volfenac
Collins, Mex.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

General Drugs, Thai.
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Volfenn *Jean-Marie, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain; renal and biliary colic.

Volforte *Omicron, Arg.*
Diclofenac (p.44·2).
Inflammation.

Volibris *GSK, UK.*
Ambrisentan (p.1209·1).
Pulmonary hypertension.

Volinol *Pyridam, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Vollmers praparierter gruner N *Salushaus, Ger.*
Avena (p.2262·1); urtica (p.2409·3); alchemilla.
Urinary-tract disorders.

Volmac *GSK, Ger.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Volmatik *Mugi, Indon.*
Diclofenac sodium (p.44·3).
Gout; musculoskeletal and joint disorders.

Volmax *GSK, Cz.†; GSK, Denm.; GSK, Hong Kong; GSK, Indon.; GSK, Israel†; Glaxo Allen, Ital.; GSK, Malaysia; GSK, Mex.; GSK, NZ; Glaxo Wellcome, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.†; GSK, Turk.; Allen & Hanburys, UK; Muro, USA†.*
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Volnac *TO-Chemicals, Thai.*
Diclofenac sodium (p.44·3).
Fever; inflammation; pain.

Volog *BMS, Turk.*
⊗ Halcinonide (p.1535·1).
Skin disorders.

Vologen *Antigen, Irl.†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Volon *Dermapharm, Austria; Dermapharm, Ger.*
⊗ Triamcinolone (p.1544·2).
Corticosteroid.

Volon A
Dermapharm, Austria.
⊗ Triamcinolone acetonide (p.1544·3).
Corticosteroid.

Dermapharm, Ger.
⊗ Triamcinolone acetonide (p.1544·3) or triamcinolone acetonide dipotassium phosphate (p.1545·1).
Corticosteroid.

Volon A antibiotikahaltig *Dermapharm, Austria.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1); gramicidin (p.286·1).
Skin disorders.

Volon A antibiotikahaltig N *BMS, Ger.†.*
⊗ Triamcinolone acetonide (p.1544·3); neomycin sulfate (p.305·1).
Skin disorders.

Volon A Tinktur *Dermapharm, Austria.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Otitis externa; skin disorders.

Volon A Tinktur N *Dermapharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3); salicylic acid (p.1612·2).
Otitis externa; skin disorders.

Volon A-Rhin *BMS, Ger.†.*
⊗ Triamcinolone acetonide (p.1544·3); phenylephrine hydrochloride (p.1568·1).
Rhinitis; sinusitis.

Volon A-Schuttelmix *Dermapharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3); zinc oxide (p.1621·2).
Skin disorders.

Volon A-Zinklotion *Dermapharm, Austria.*
⊗ Triamcinolone acetonide (p.1544·3); zinc oxide (p.1621·2).
Skin disorders.

Volonimat *Dermapharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Volonimat N *Dermapharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Volonimat Plus N *Dermapharm, Ger.*
⊗ Triamcinolone acetonide (p.1544·3); nystatin (p.543·2).
Eczema with secondary yeast infection.

Volonten *Viofar, Gr.*
Nimesulide (p.95·3).
Inflammation; musculoskeletal disorders; pain.

Volpan *Bilim, Turk.*
Paracetamol (p.108·1).
Fever; pain.

Volplex *Maelor, UK.*
⊗ Succinylated gelatin (p.1072·1) in sodium chloride.
Blood volume expansion.

Volraman *LPC, UK.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal disorders; pain.

Volsaid *Trinity, UK.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Volta *T Man, Thai.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Voltadex *Dexa, Indon.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

Voltadol *Novartis Consumer, Ital.*
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular pain and inflammation.

Voltadyn *Novartis, Cz.*
Glucosamine hydrochloride (p.2313·2).
Osteoarthritis of the knee.

Voltaflan *Bunker, Braz.*
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).

Voltaflex *EMS, Braz.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Voltamicin *Novartis, Austria; Ciba Vision, Cz.†; Novartis Ophthalmics, Hung.†; Novartis, Ital.†; Novartis Ophthalmics, Singapore†; Novartis, Switz.*
Diclofenac sodium (p.44·3); gentamicin sulfate (p.282·1).
Bacterial eye infections and inflammation.

Voltanac *Pharmasant, Thai.*
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Voltapatch *Novartis Consumer, Belg.*
Diclofenac sodium (p.44·3).
Inflammation; pain.

Voltaren
Novartis, Arg.; Novartis, Ital.; Novartis, Ital.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Adjunct in cataract surgery; gout; inflammation; inflammatory eye disorders; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal and biliary colic.

Novartis, Austral.; Novartis, Cz.; Novartis, Fin.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Israel; Novartis, Mex.; Novartis, Port.; Novartis, Rus.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Biliary and renal colic; eye inflammation; fever; gout; inflammation; inhibition of intraoperative miosis; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; prevention of cystoid macular oedema.

Novartis, Austria.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Cystoid macular oedema; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; prevention of intraoperative miosis; renal and biliary colic.

Novartis, Belg.; Novartis Consumer, Belg.; Novartis, Chile; Novartis, Indon.; Novartis, Malaysia; Novartis, Singapore; Novartis, Spain; Novartis, Thai.
Diclofenac diethylamine (p.44·3), or diclofenac sodium (p.44·3).
Adjunct in eye surgery; eye inflammation; eye pain following laser surgery; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; prevention of cystoid macular oedema following cataract extraction; renal and biliary colic.

Novartis, Braz.; Novartis, Norw.; Novartis, Swed.; Novartis, Turk.; Novartis, USA; Novartis, Venez.
Diclofenac sodium (p.44·3).
Gout; inflammation; inflammation following cataract surgery; musculoskeletal, joint, and peri-articular disorders; pain; pain and photophobia following corneal surgery.

Novartis, Canad.; Novartis, Denm.; Novartis, Gr.; Novartis, Neth.
Diclofenac potassium (p.44·3) or diclofenac sodium (p.44·3).
Eye inflammation; gout; inflammation; musculoskeletal and joint disorders; pain; prevention of intra-operative cystoid macular oedema and miosis; renal and biliary colic.

Novartis, Ger.; Novartis Consumer, Ger.
Diclofenac (p.44·2), diclofenac colestyramine (p.46·1), diclofenac diethylamine (p.44·3), diclofenac epolamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and soft-tissue disorders; oedema; pain.

Novartis, NZ.
Diclofenac (p.44·2), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Biliary colic; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; renal colic.

Novartis, Philipp.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Gout; inflammation; keratectomy pain; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain; postoperative eye inflammation; prevention of intra-operative miosis; renal and biliary colic.

Novartis, Pol.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; oedema; pain; renal colic.

Novartis, S.Afr.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Voltaren Colirio *Novartis Ophthalmics, Arg.; Novartis Ophthalmics, Braz.*
Diclofenac sodium (p.44·3).
Eye inflammation.

Voltaren Dolo *Novartis, Switz.*
Diclofenac diethylamine (p.44·3) or diclofenac potassium (p.44·3).
Fever; inflammation; pain.

Voltaren Emulgel *Novartis, Switz.*
Diclofenac diethylamine (p.44·3).
Musculoskeletal, joint, peri-articular and soft-tissue disorders.

Voltaren Flex *Novartis, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Voltaren Forte *Novartis, Arg.; Novartis, Mex.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Pain.

Voltaren Migra *Novartis, Arg.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Voltaren Ophta *Novartis Ophthalmics, Hung.; Novartis, Switz.; Novartis, Turk.*
Diclofenac sodium (p.44·3).
Allergic conjunctivitis; cystoid macular oedema; ocular pain and inflammation; prevention of miosis during eye surgery.

Voltaren Ophtha *Novartis Ophthalmics, Austral.; Novartis Ophthalmics, Canad.; Novartis, Ger.; Novartis, Hong Kong; Novartis, Indon.; Novartis, Israel; Novartis, NZ; Novartis, Norw.; Adcock Ingram, S.Afr.; Novartis Ophthalmics, Singapore; Novartis Ophthalmics, Swed.*
Diclofenac sodium (p.44·3).
Cystoid macular oedema; inhibition of miosis during cataract surgery; ocular pain and inflammation; reversal of peri-operative miosis.

Voltaren Plus *Novartis, Ger.*
Diclofenac sodium (p.44·3); codeine phosphate (p.37·2).
Pain.

Voltaren T *Novartis, Swed.*
Diclofenac potassium (p.44·3).
Pain.

Voltarendolo *Novartis Sante, Fr.*
Diclofenac potassium (p.44·3).
Fever; pain.

Voltarene
Novartis, Switz.
Diclofenac (p.44·2), diclofenac potassium (p.44·3), diclofenac resinate (p.46·1), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Novartis, Fr.
Eye drops: Diclofenac sodium (p.44·3).
Eye pain; inflammation following eye surgery; inhibition of intraoperative miosis.

Novartis, Fr.
Injection; suppositories; sustained-release tablets; tablets; topical gel: Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders; oedema; renal colic.

Voltarol
Novartis, Irl.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Gout; musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Novartis, UK.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), diclofenac epolamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Voltarol Ophtha *Novartis, Irl.; Novartis, UK.*
Diclofenac sodium (p.44·3).
Anterior eye inflammation; inflammation and pain following eye surgery; inhibition of peri-operative miosis; prevention of cystoid macular oedema.

Voltatrauma *Novartis Consumer, Ital.*
Oxerutin (p.2304·3); sodium calcium methylgalactopolysulfate.
Minor trauma.

Voltax *Poehlmann, Ger.†.*
Phospholipids; muira-puama; adenosine; vitamins (p.1922·1).
Tonic.

Volten Oftalmi, Venez.
Diclofenac sodium (p.44·3).
Cystoid macular oedema; eye inflammation; intra-operative miosis inhibition; uveitis.

Voltenac Sanofi-Aventis, Pol.
Diclofenac sodium (p.44·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Voltfast Novartis, Ital.; Novartis, NZ.
Diclofenac potassium (p.44·3).
Inflammation; pain.

Voltil Ardeypharm, Ger.†.
Protein-free extract of bovine spleen (p.2337·3).
Gastrointestinal disorders; peripheral and cerebral vascular disorders; skin disorders.

Voltric UCB, Spain†.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Voltrix Bunker, Braz.
Diclofenac diethylamine (p.44·3), diclofenac potassium (p.44·3), or diclofenac resinate (p.46·1).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Volulyte Fresenius Kabi, UK.
⊗ An etherified starch (p.1065·1) with electrolytes.
Plasma volume expansion.

Volumax D 40 Blausiegel, Braz.†.
⊗ Dextran 40 (p.1059·1) in sodium chloride or glucose.
Plasma volume expansion.

Volumax D 70 Blausiegel, Braz.†.
⊗ Dextran 70 (p.1059·3) in sodium chloride or glucose.
Plasma volume expansion.

Volutine Geymonat, Ital.†.
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Volutol Lemery, Mex.†.
Carbamazepine (p.471·3).
Epilepsy.

Voluven Fresenius Kabi, Arg.; Fresenius Kabi, Austria; Fresenius Kabi, Chile; Fresenius Kabi, Cz.; Fresenius Kabi, Denm.; Fresenius Kabi, Fin.; Fresenius Kabi, Fr.; Fresenius Kabi, Ger.; Fresenius Kabi, Gr.; Fresenius Kabi, Hong Kong; Fresenius Kabi, Hung.; Fresenius Kabi, Indon.; Fresenius Kabi, Ital.; Fresenius Kabi, Malaysia; Fresenius Kabi, Mex.; Fresenius Kabi, Neth.; Fresenius Kabi, Norw.; Fresenius Kabi, Philipp.; Fresenius Kabi, Pol.; Fresenius Kabi, Port.; Fresenius Kabi, Rus.; Fresenius Kabi, S.Afr.; Fresenius Kabi, Spain; Fresenius Kabi, Swed.; Fresenius Kabi, Switz.; Fresenius Kabi, Thai.; Fresenius Kabi, Turk.; Fresenius Kabi, UK; Hospira, USA.
⊗ An etherified starch (p.1065·1).
Haemodilution; hypovolaemia; plasma volume expansion.

Volverac TP, Thai.
Diclofenac sodium (p.44·3).
Inflammation following cataract surgery; postoperative cystoid macular oedema; prevention or reduction of intraoperative miosis.

Vomacur Hexal, Ger.
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Vomceran Kalbe, Indon.
Ondansetron (p.1756·3).
Nausea and vomiting.

Vomet Ulagay, Turk.
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Vometa Dexa, Indon.
Domperidone (p.1726·2).
Gastrointestinal disorders.

Vometil Cipla, India.
Prochlorperazine maleate (p.1020·1).

Vomex A Astellas, Ger.; Galenica, Gr.; IFET (ΙΦΕΤ), Gr.
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Vomidex Dexa, Indon.
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Vomidon Be-Tabs, S.Afr.
Domperidone (p.1726·2).
Adjunct in gastrointestinal radiology; gastrointestinal disorders.

Vomidone Pharos, Indon.
Domperidone maleate (p.1726·3).
Dyspepsia; nausea and vomiting.

Vomidrine Azevedos, Port.
Dimenhydrinate (p.576·2).
Motion sickness; nausea; vertigo; vomiting.

Vomifene Adcock Ingram, S.Afr.
Buclizine hydrochloride (p.570·1); pyridoxine (p.1979·1).
Motion sickness; nausea; vertigo; vomiting.

Vomilat Kalbe, Indon.
Pyridoxine hydrochloride (p.1978·2); folic acid (p.1940·1).
Vitamin B and folic acid supplement in pregnancy.

Vominar Charoen, Thai.†.
Dimenhydrinate (p.576·2).
Motion sickness, vertigo, nausea and vomiting.

Vominate Cipla, India.
Doxylamine succinate (p.578·2); pyridoxine (p.1979·1).

Vominil Sedabel, Braz.†.
Metoclopramide (p.1747·3); vitamin B (p.1979·1).
Nausea and vomiting.

Vominorm Cipla, India.
Metoclopramide (p.1747·3).
Nausea and vomiting.

Vomiof Stadmed, India.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics and radiotherapy.

Vomipram Corsa, Indon.
Metoclopramide (p.1747·3).
Gastrointestinal disorders.

Vomisin Rayere, Mex.
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vestibular disorders.

Vomistop Cipla, India; Gracia, Indon.
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Vomitas Kalbe, Indon.
Domperidone (p.1726·2).
Dyspepsia; nausea and vomiting.

Vomitin Akdeniz, Turk.
Trimethobenzamide hydrochloride (p.592·2).
Nausea and vomiting.

Vomitoran Norma (Νορμα), Gr.
Roxithromycin (p.331·1).
Bacterial infections.

Vomitrol Pharos, Indon.
Metoclopramide (p.1747·3).
Delayed gastric emptying; gastrointestinal procedures.

Vomitron Berlin Pharm, Thai.†.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics or radiotherapy.

Vomitusheel Peithner, Austria.
Homoeopathic preparation.

Vonau Biolab Sanus, Braz.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Voncon Lilly, Gr.
Vancomycin (p.358·3).
Bacterial infections.

Vondem Demo, Gr.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Vontrol Enila, Braz.†; GSK, Chile; Sanfer, Mex.
Difenidol hydrochloride (p.1723·2).
Nausea and vomiting; vertigo; vestibular disorders.

Vonum Gerot, Austria.
Indometacin (p.66·3); lauromacrogol 400 (p.1916·1).
Musculoskeletal, joint, and soft-tissue disorders.

Vonum Cutan Winthrop, Cz.
Indometacin (p.66·3).
Inflammation; musculoskeletal, joint, and soft-tissue disorders.

Vopac Athlon, USA.
Codeine phosphate (p.37·2); paracetamol (p.108·1).
Pain.

Vopar Unison, Thai.
Levodopa (p.804·3); benserazide hydrochloride (p.796·3).
Parkinsonism.

Vopax Haller, Braz.†.
Metoclopramide hydrochloride (p.1747·3).
Nausea and vomiting.

V-Optic Vitamed, Israel.
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Voraclor Lafare, Ital.
Aciclovir (p.862·3).
Herpesvirus infections.

Vorange DHA, Hong Kong; DHA, Singapore.
Ascorbic acid (p.1983·3).
Vitamin C deficiency.

Voratadine Vida, Hong Kong.
Loratadine (p.583·3).
Allergic rhinitis; skin disorders.

Vorcum Pfizer, Venez.
Voriconazole (p.550·1).
Fungal infections.

Vo-Remi Offenbach, Mex.
Meclozine (p.585·1); pyridoxine (p.1979·1).
Nausea and vomiting.

Voren
Medikon, Indon.
Diclofenac (p.44·2) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, and peri-articular disorders.

YSP, Malaysia; Yung Shin, Philipp.; Yung Shin, Singapore.
Diclofenac sodium (p.44·3).
Fever; gout; inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Voren Plus YSP, Malaysia.
Diclofenac sodium (p.44·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Vorigeno Inibsa, Spain†.
Hyoscine hydrobromide (p.1734·1).
Motion sickness.

VoriNa Teva, Belg.; Teva, Cz.; Onkoworks, Ger.; Teva, Hung.; Pharmachemie, Neth.; Teva, Port.
Sodium folinate (p.1944·1).
Adjunct to fluorouracil in colorectal cancer; antidote to folic acid antagonists; reduction of folic-acid antagonist toxicity; reduction of methotrexate toxicity.

Voroste Combiphar, Indon.
Alendronate sodium (p.1088·1).
Osteoporosis; Paget's disease of bone.

Vorst Bernabo, Arg.
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Vorth Glenmark, India†.
Valdecoxib (p.132·3).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Vorth Insta Glenmark, India†.
Valdecoxib (p.132·3); methyl salicylate (p.85·3).
Musculoskeletal, joint, and soft-tissue disorders; pain.

Vorth-P Glenmark, India.
Parecoxib sodium (p.111·3).
Pain.

Vorth-XT Glenmark, India†.
Valdecoxib (p.132·3); tizanidine hydrochloride (p.1898·2).
Musculoskeletal pain and spasm.

Vosedon Sanbe, Indon.
Domperidone (p.1726·2).
Gastrointestinal disorders.

VoSoL Wilson, NZ; Wallace, USA†.
Propylene glycol diacetate (p.1919·3); acetic acid (p.2244·2); benzethonium chloride (p.1630·1).
Otitis externa.

VoSoL HC Carter Horner, Canad.†; Wallace, USA†.
⊗ Propylene glycol diacetate (p.1919·3); acetic acid (p.2244·2); benzethonium chloride (p.1630·1); hydrocortisone (p.1535·2).
Otitis externa.

VoSpire Odyssey, USA.
⊗ Salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Vostar Medis, Denm.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders.

Vosteon Meprofarm, Indon.
Glucosamine hydrochloride (p.2313·2); chondroitin sulfate (p.2280·3); ipriflavone (p.1100·1); calcium citrate (p.1675·3).
Osteoarthritis.

Votag Ativus, Braz.
Marine polyunsaturated fatty acids (p.1362·2).
Dietary supplement.

Votalen Marching, Hong Kong.
Diclofenac diethylamine (p.44·3) or diclofenac sodium (p.44·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia; neuritis.

Votamed Medifive, Thai.
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Votaxil Cafar, Venez.
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Votrace Verisfield, Gr.
Calcitriol (p.1986·2).
Psoriasis.

Votum Berlin-Chemie, Ger.; Menarini, Switz.
Olmesartan medoxomil (p.1361·1).
Hypertension.

Votum Plus Berlin-Chemie, Ger.; Menarini, Switz.
⊗ Olmesartan medoxomil (p.1361·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Voveran Novartis, India.
Diclofenac (p.44·2), diclofenac diethylamine (p.44·3), or diclofenac sodium (p.44·3).
Allergic conjunctivitis; eye inflammation and pain; gout; musculoskeletal, joint, and soft-tissue disorders; prevention of miosis in cataract surgery.

Voxam Sandoz, Austral.
Fluvoxamine maleate (p.399·3) =www.mydr.com.au 6.08.
Depression; obsessive-compulsive disorder.

Voxamine Armstrong, Mex.
Difenidol hydrochloride (p.1723·2).
Nausea and vomiting; vertigo.

Voxate Masa, Thai.
Flavoxate hydrochloride (p.2190·1).
Urinary-tract disorders.

Voxfor Escaned, Spain.
⊗ Dextromethorphan hydrobromide (p.1555·2); ephedrine hydrochloride (p.1558·2); guaifenesin (p.1561·3).
Cold symptoms.

Voxin
Note. This name is used for preparations of different composition.
Vianex (Βιανεξ), Gr.†.
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Gracia, Indon.
Levofloxacin (p.292·2).
Bacterial infections.

Voxoll Aldril, Philipp.
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Voxpax Homeocan, Canad.; Lehning, Fr.
Homoeopathic preparation.

Voxsuprine Major, USA.
Isoxsuprine hydrochloride (p.2327·3).
Cerebrovascular and peripheral vascular disorders.

V-Pen Orion, Fin.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

VP-Gen Bioprofarma, Arg.
Etoposide (p.718·1).
Malignant neoplasms.

V-piryna Natur Produkt, Pol.
Aspirin (p.20·3); ascorbic acid (p.1983·3); caffeine (p.1116·3).
Cold and influenza symptoms.

VP-Syrup Phamar (Φαμαρ), Gr.†.
Guaifenesin (p.1561·3).
Cough.

VP-Tec Columbia, Mex.
Etoposide (p.718·1).
Small cell lung cancer; testicular cancer.

VR Curacel, Austral.†.
Dextran sulfate (p.2293·1); allantoin (p.1588·1); zinc oxide (p.1621·2); melaleuca oil (p.2338·2); alpha tocoferil acetate; vitamin A palmitate.
Herpes labialis; postherpetic neuralgia; tinea pruritus.

Vraap Inverni della Beffa, Ital.†.
Vincamine (p.2414·1).
Disorders of cerebral, ocular, and vestibular circulation.

Vratizolin Jelfa, Pol.
Denotivir (p.870·2).
Bacterial skin infections; herpesvirus infections of skin and mucous membranes.

Vrbovkova Nat Megafyt-R, Cz.
Epilobium.
Benign prostatic hyperplasia; gastrointestinal disorders.

Vreya Stragen, Cz.
Ethinylestradiol (p.2101·3); cyproterone acetate (p.2088·2).
Androgen-induced acne, seborrhoea, and hirsutism in women; combined oral contraceptive.

Vridol Rafa, Israel†.
Troxerutin (p.2305·1).
Haemorrhoids; venous insufficiency.

VSL#3 Sigma-Tau, USA.
Bifidobacterium breve (p.2372·3); *Bifidobacterium longum* (p.2372·3); *Bifidobacterium infantis* (p.2372·3); *Lactobacillus acidophilus* (p.2372·3); *Lactobacillus plantarum*; *Lactobacillus paracasei*; *Lactobacillus bulgaricus* (p.2372·3); *Streptococcus thermophilus* (p.2372·3).
Irritable bowel syndrome; pouchitis; ulcerative colitis.

V-Tablopen Viatris, Ger.†.
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

V-Tabur Vitamed, Israel.
⊗ Alcohol (p.1625·2); chlorhexidine gluconate (p.1635·3).
Skin and umbilical cord disinfection.

V-Talgin Vitamed, Israel.
Dipyrone (p.49·2).
Fever; pain.

V-Tears Vitamed, Israel.
Hyetellose (p.2143·3).
Dry eyes.

Vuclodir Richmond, Arg.
Lamivudine (p.895·1).
HIV infection.

Vudirax Blausiegel, Braz.
Lamivudine (p.895·1).
HIV infection.

Vueffe Baldacci, Braz.†; Baldacci, Ital.†.
Peptides derived from bovine factor VIII (p.1067·1).
Haemorrhage.

Vulamox Ethica, Indon.
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Vulbegal Coup, Gr.
Flunitrazepam (p.996·2).
Insomnia.

Vulcase Teofarma, Fr.
Aloes (p.1705·2).
Constipation.

Vulcasid Atlantis, Mex.
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Vulmizolin Biotika, Cz.
Cefazolin sodium (p.222·1).
Bacterial infections.

Vulnizol Gelpharma, Mex.
Nitrofurazone (p.309·1).
Vaginal infections.

Vulnofilin Compuesto Lazar, Arg.†.
⊗ Red blood cells (p.1078·3); protoporphyrin; papain (p.2362·3); tyrothricin (p.358·2); dequalinium.
Wounds.

Vulnopur Deverge, Ital.
Decylglucoside; sodium chloride (p.1686·1); aloe vera (p.1588·2); silver chloride (p.2387·1).
Burns; cleansing of skin and mucous membranes; wounds.

Vulnostimulin Dermapharm, Ger.
Wheat germ (p.2415·1).
Burns; wounds.

Vulnusan Sopharma, Rus.
Pomeranian lakes extract.
Abscess; pyogenic wounds; ulcers.

Vulpuran *Rosch & Handel, Austria.*
Lead plaster-mass (p.2332·2); chamomile oil (p.2279·3); St John's wort oil (p.423·2); cod-liver oil (p.1935·2); elemi; colophony (p.2286·2); emplastrum minii; turpentine oil (p.2406·3); peru balsam (p.2365·3); oxycholesterin.
Furuncles; ulcers; wounds.

Vumix *Sun, Mex.*
Fluvoxamine (p.400·1).
Depression.

Vumon *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Braz.; BMS, Canad.; BMS, Chile; BMS, Cz.†; IFET (ΙΦΕΤ), Gr.; BMS, Hong Kong; BMS, Israel†; BMS, Ital.; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Pol.; BMS, Port.; BMS, S.Afr.; BMS, Singapore†; BMS, Spain; BMS Oncology, USA.*
Teniposide (p.778·1).
Malignant neoplasms.

Vunot *Medipharma, Arg.*
Sertraline (p.422·1).
Depression.

Vunsu *Costec, Arg.†.*
Padimate O (p.1609·1).
Sunscreen.

Vurdon *Help, Gr.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Vuscobras *Vargas, Venez.*
Hyoscine butylbromide (p.1734·1); oxazepam (p.1014·2).
Muscle spasm.

Vykmin *Valeant, Hong Kong.*
Multivitamin and mineral preparation (p.1922·1).

Vyrohexal *Hexal, S.Afr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Vytinal *Legrand, Braz.*
Multivitamin, amino-acid, and mineral preparation (p.1922·1).

Vytone *Sanofi-Aventis, USA.*
⊗ Hydrocortisone (p.1535·2); diiodohydroxyquinoline (p.832·1).

Vytorin *MSD, Arg.; MSD, Austral.; MSD, Austria; MSD, Braz.; MSD, Chile; Vianex (Βιανέξ), Gr.; MSD, Hong Kong; Schering-Plough, Hong Kong; Schering-Plough, Indon.; Schering-Plough, Ital.; MSD, Malaysia; Schering-Plough, Malaysia; MSD, Mex.; MSD, NZ; MSD, Neth.; MSD, Philipp.; Schering-Plough, Philipp.; MSD, Singapore; Schering-Plough, Singapore; Merck, USA; Schering-Plough, USA; MSD, Venez.*
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Hypercholesterolaemia.

Vytral *Alpharma, Mex.*
Vitamin and mineral preparation (p.1922·1).

Vyvanse *New River, USA.*
⊗ Lisdexamfetamine mesilate (p.2157·1).
Attention-deficit hyperactivity disorder.

V-Z Vax *Green Cross, Philipp.*
A live, attenuated varicella-zoster vaccine (p.2242·2).
Active immunisation.

V-Zoline *Vitamed, Israel.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Wadil *Biomep, Mex.*
Metformin (p.453·3); glibenclamide (p.440·1).
Diabetes mellitus.

Wakamoto *Wakamoto, Hong Kong†.*
Aspergillus; *Eremothecium ashbyii*; lactobacteriaceae; dried yeast; diastase; protease; lipase; vitamin B substances; amino acids (p.1922·1).
Tonic.

Wake-Up Tablets *Adrem, Canad.*
Caffeine (p.1116·3).
Stimulant.

Wala Baume nasal *Wala, Switz.*
Berberis vulgaris; blackthorn (p.2267·2); Peru balsam (p.2365·3); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2); silicic acid.
Nasal inflammation.

Wala Baume nasal doux *Wala, Switz.*
Berberis vulgaris; blackthorn (p.2267·2); peru balsam (p.2365·3); silicic acid.
Nasal disorders.

Wala Echinacea *Wala, Switz.*
Echinacea (p.2298·1); calendula (p.2273·1); sage (p.2382·3); eucalyptus globulus; argentum nitricum; tonsillae palatinae bovis; gingiva bovis.
Mouth and throat disorders.

Wala Pulmonium suc contre la toux *Wala, Switz.*
Ribwort plantain (p.2379·1); Norway spruce; butterbur (p.2271·1).
Coughs.

Walacort *Wallace, India.*
⊗ Betamethasone (p.1518·2).
Corticosteroid.

Walagesic *Wallace, India†.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Pain.

Walamycin *Wallace, India.*
Colistin sulfate (p.256·2).
Bacterial diarrhoea.

Walaphage *Wallace, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Walavin *Wallace, India.*
Griseofulvin (p.535·2).
Fungal infections of the skin, hair, and nails.

Waldheim Abfuhrdragees forte *Sanochemia, Austria.*
Aloes (p.1705·2); phenolphthalein (p.1762·1); hard soap (p.2139·3).
Formerly known as Abführdragees.
Bowel evacuation; constipation.

Waldheim Abfuhrdragees mild *Sanochemia, Austria.*
Aloes (p.1705·2); frangula bark (p.1732·2); hard soap (p.2139·3).
Formerly known as Abführdragees mild.
Constipation.

Waldheim Husten *Sanochemia, Austria.*
Guaifenesin (p.1561·3).
Coughs.

Waldheim Influvidon *Sanochemia, Austria.*
Salicylamide (p.121·2); caffeine (p.1116·3); propyphenazone (p.119·3); hesperidin phosphate (p.2305·2); calcium ascorbate (p.1984·1); piprinhydrinate (p.588·2).
Formerly known as Influvidon.
Cold and influenza symptoms.

Waldheim Rheuma-Creme *Sanochemia, Austria.*
Salicylamide (p.121·2).
Musculoskeletal, joint, and soft-tissue disorders.

Waldheim Schmerztabletten *Sanochemia, Austria.*
Propyphenazone (p.119·3); paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Waldheim Sport- und Rheuma-Fluid *Sanochemia, Austria.*
Salicylamide (p.121·2); camphor (p.2273·2).
Musculoskeletal, joint, and soft-tissue disorders; sports injuries.

Walesolone *MBD, Singapore.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Walix *Silesia, Chile; Fidia, Ital.*
Oxaprozin (p.105·3).
Gout; musculoskeletal, joint, and peri-articular disorders.

Walyte *Wallace, India.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Oral rehydration therapy.

Wamag *Hasco-Lek, Pol.*
Calcium glubionate (p.1675·3); calcium lactobionate (p.1676·2); magnesium lactate (p.1679·2).
Calcium and magnesium supplement.

Wampole
Note. This name is used for preparations of different composition.
Ponce, Venez.†.
Oral emulsion: Cod-liver oil (p.1935·2); yeast (p.1998·3).
Dietary supplement.

Ponce, Venez.†.
Oral liquid: Vitamin B substances (p.1922·1).
Dietary supplement.

Wampole Bronchial Cough Syrup *Wampole, Canad.†.*
Ammonium chloride (p.1551·3); aralia racemosa; poplar buds (p.2371·1); sanguinaria (p.2383·2); senega (p.1572·3); white pine; wild cherry (p.2415·2).

Wampole Vitamin Syrup *Wampole, Canad.*
Vitamin B substances with iron (p.1922·1).

Wandonorm *Novartis, Ger.†.*
⊗ Bopindolol malonate (p.1235·1).
Hypertension.

Wanmycin *DHA, Hong Kong; DHA, Malaysia†; DHA, Singapore.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Wanse *Yu Sheng, Singapore.*
Ferrous fumarate (p.1938·3); cyanocobalamin (p.1980·2); folic acid (p.1940·1).
Anaemias.

Waran *Nycomed, Swed.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Warca *Pharmasant, Thai.*
Mebendazole (p.148·3).
Worm infections.

Warf *Cipla, India.*
Warfarin sodium (p.1425·2).
Thromboembolic disorders.

Warfant *Antigen, Irl.*
Warfarin sodium clathrate (p.1425·3).
Thromboembolic disorders.

Warfarex *Grindex, Rus.*
Warfarin sodium clathrate (p.1425·3).
Thromboembolic disorders.

WariActiv *Ritter, Ger.; Ritter, Hong Kong.*
Ethyl chloride (p.1861·2).
Local anaesthesia.

Wari-Diclowal *Ritter, Malaysia†.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal, joint, and peri-articular disorders; pain.

Waridipin *Ritter, Hong Kong†.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension.

Warimazol *Ritter, Hong Kong†.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginitis.

Wari-Procomil *Ritter, Hong Kong; Ritter, Thai.†.*
⊗ Yohimbine hydrochloride (p.2200·2); methyltestosterone (p.2117·1); testis extract (p.2129·3); kola (p.2416·1); lecithin (p.2332·2); muira-puama.
Erectile dysfunction.

Wariviron *Ritter, Hong Kong.*
Aciclovir (p.862·3).
Herpes simplex infections.

Warix *Drossapharm, Switz.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Warme-Gel *Ratiopharm, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular and soft-tissue disorders; neuralgia; peripheral vascular disorders.

Wart Remover *Glades, USA; Rugby, USA; Stiefel, USA.*
Salicylic acid (p.1612·2).

Wartec *Stiefel, Austral.; Stiefel, Belg.; Stiefel, Braz.; Stiefel, Canad.; Stiefel, Chile†; Stiefel, Cz.; Stiefel, Denm.; Stiefel, Fin.; Stiefel, Fr.†; Stiefel, Ger.; Gabriel, Gr.; Stiefel, Hong Kong; Stiefel, Hung.; Stiefel, Ital.; Stiefel, Mex.; Stiefel, NZ; Stiefel, Neth.; Stiefel, Norw.; Stiefel, Pol.; Stiefel, S.Afr.; Stiefel, Singapore; Rottapharm, Spain; Sylak, Swed.*
Podophyllotoxin (p.1610·2).
Anogenital warts.

Wartex *Ransom, UK.*
Salicylic acid (p.1612·2).
Warts.

Warticon *Stiefel, Irl.; Stiefel, UK.*
Podophyllotoxin (p.1610·2).
Genital warts.

Wartner *Shield, Irl.; Naveh, Israel; PSM, NZ; Passion for Life, UK.*
Dimethyl ether (p.1689·2); propane (p.1691·3).
Verrucas; warts.

Wart-Off *Pfizer, Philipp.; Pfizer, USA.*
Salicylic acid (p.1612·2).
Calluses; corns; warts.

Waruzol
Note. This name is used for preparations of different composition.
Pharmanik (Φαρμανικ), Gr.†.
Astemizole (p.567·2).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Intermedica, Switz.
Acetic acid (p.2244·2); lactic acid (p.2329·3); salicylic acid (p.1612·2).
Warts.

Warz-ab Extor *Ohropax, Switz.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns; warts.

Warzen-Alldahin *Roha, Ger.†.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; warts.

Warzenmittel *Sanova, Austria.*
Monochloroacetic acid (p.1608·1).
Warts.

Warzin *Rosch & Handel, Austria.*
Lactic acid (p.2329·3).
Warts.

Wash E45 *Crookes Healthcare, UK.*
Soap substitute.
Dry skin.

Wasp-Eze *SSL, UK.*
Mepyramine maleate (p.585·2); benzocaine (p.1854·1).
Insect bites; stings.

Water Babies
Note. This name is used for preparations of different composition.
Schering-Plough, USA.
SPF 15: Octinoxate (p.1608·2); oxybenzone (p.1608·3).
Sunscreen.

Schering-Plough, USA.
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); homosalate (p.1598·1); octisalate (p.1608·2).
Sunscreen.

Schering-Plough, USA.
SPF 45: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octocrilene (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Water Babies Little Licks *Schering-Plough, USA.*
SPF 30: Octinoxate (p.1608·2); oxybenzone (p.1608·3); octisalate (p.1608·2).
Sunscreen.

Water Naturtabs *Larkhall Laboratories, UK.*
Bladderwrack (p.2384·2); lappa (p.2330·3); ground ivy (p.2317·2); clivers (p.2284·3).

Water Pill c Potasio *Natural Life, Arg.†.*
Buchu (p.2269·3); bearberry (p.2263·3); parsley (p.2363·2); juniper (p.2328·2); potassium gluconate (p.1684·3).
Diuretic.

Watershed
Note. This name is used for preparations of different composition.
Potter's, UK.
Oral mixture: Wild carrot (p.2415·2); pellitory; buchu (p.2269·3); juniper (p.2328·2); clivers (p.2284·3).
Water retention.

Potter's, UK.
Tablets: Buchu (p.2269·3); parsley piert (p.2363·2); bearberry (p.2263·3); juniper oil (p.2328·3).
Water retention.

Waucosin *Proel, Gr.†.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Waxolve *Bell, India.*
Paradichlorobenzene (p.2363·1); benzocaine (p.1854·1); chlorobutanol (p.1639·2); turpentine oil (p.2406·3).
Ear wax removal.

Waxsol *Norgine, Austral.; Norgine, Hong Kong; Alpharma, Indon.; Norgine, Irl.; Norgine, Malaysia†; Norgine, NZ; Zuellig, NZ; Norgine, Singapore; Norgine, Thai.; Pharmalink, Thai.; Norgine, UK.*
Docusate sodium (p.1725·1).
Ear wax removal.

Waxsol NF *Norgine, S.Afr.*
Docusate sodium (p.1725·1).
Ear wax removal.

Waxwane *Thornton & Ross, UK†.*
Turpentine oil (p.2406·3); terpineol (p.2396·1); chloroxylenol (p.1640·2).
Ear wax removal.

4-Way Fast Acting *Novartis, USA.*
⊗ Phenylephrine hydrochloride (p.1568·1); naphazoline hydrochloride (p.1565·2); mepyramine maleate (p.585·2).
Nasal congestion.

4-Way Long Lasting *Bristol-Myers Products, USA.*
⊗ Oxymetazoline hydrochloride (p.1567·2).
Nasal congestion.

4-Way Menthol *Novartis Consumer, USA.*
Phenylephrine hydrochloride (p.1568·1); menthol (p.2340·1).
Nasal congestion.

4-Way Moisturizing Relief *Novartis Consumer, USA.*
Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

WCS Dusting Powder *Weleda, UK.*
Homoeopathic preparation.

Wecesin
Note. This name is used for preparations of different composition.
Weleda, Ger.
Homoeopathic preparation.

Weleda, S.Afr.; Weleda, Switz.†.
Arnica (p.2260·2); calendula (p.2273·1); echinacea (p.2298·1); quarz; stibium met.
Burns; cicatrisation; skin abrasions; skin disorders; ulcers; wounds.

Wechseltee St Severin *Smetana, Austria.*
Passion flower (p.2363·2); valerian (p.2410·1); lupulus (p.2335·2); St John's wort (p.422·3); melissa (p.2339·3); crataegus (p.2289·1); mistletoe (p.2345·3).
Anxiety disorders; menopausal disorders; nervousness; sleep disorders.

Weewa ORS *Millimed, Thai.*
Sodium chloride; potassium chloride; sodium citrate; glucose (p.1672·2).
Diarrhoea; oral rehydration therapy.

Weifa-Calcium *Weifa, Thai.*
Calcium carbonate (p.1714·1).
Calcium supplement; osteoporosis.

Weifapenin *Weifa, Norw.*
Phenoxymethylpenicillin potassium (p.314·2).
Bacterial infections.

Weight Control *Homeocan, Canad.*
Homoeopathic preparation.

Weight Loss Aid *Herbal Concepts, UK.*
Taraxacum (p.2395·1); bladderwrack (p.2384·2); boldo (p.2267·2).
Slimming aid.

Weight Loss Kit *Dolisos, Canad.*
Homoeopathic preparation.

Weimerquin *Biokanol, Ger.*
Chloroquine phosphate (p.599·3).
Malaria.

Weiscal *Valdecasas, Mex.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Weiscalina *Valdecasas, Mex.†.*
Phenylephrine hydrochloride (p.1568·1).
Nasal congestion.

Weisen-U *Shigaken, Singapore†.*
Methiosulfonium chloride (p.2343·3); amylase (p.2256·3); aluminium hydroxide (p.1706·2).
Dyspepsia; flatulence; gastrointestinal hyperacidity; heartburn.

Welchol *Sankyo, USA.*
Colesevelam hydrochloride (p.1252·1).
Hypercholesterolaemia.

Weleda Fieber- und Zahnungszapfchen *Weleda, Ger.*
Homoeopathic preparation.

Weleda Hamorrhoidalzapfchen *Weleda, Ger.*
Hamamelis (p.2318·2); aesculus (p.2248·2); stibium metall.
Anorectal disorders.

Weleda Heilsalbe *Weleda, Ger.*
Homoeopathic preparation.

Weleda-Rheumasalbe M *Weleda, Ger.*
Basil (p.2263·2); camphor (p.2273·2); fluorit; castanospermum oil; venice turpentine; sea water (p.1686·1); murmeltierfett; rosemary oil (p.2381·3).
Frostbite; gout; musculoskeletal, joint, and soft-tissue disorders.

Well-Beeing *Panacea, India†.*
Curcumin (p.1471·2); ginger (p.1732·3); valerian (p.2410·1).
Menstrual disorders.

Wellbutrin *GSK, Arg.; GSK, Braz.; Biovail, Canad.; GSK, Chile; GSK, Cz.; GSK, Hong Kong; GSK, Hung.; GSK, Mex.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, USA; GSK, Venez.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Wellcid *Klinger, Braz.†.*
Permethrin (p.2048·2).

Wellconal *GSK, Hong Kong†; Aspen, S.Afr.*
Dipipanone hydrochloride (p.49·1); cyclizine hydrochloride (p.574·2).
Pain; vomiting.

Wellcoprim
GSK, Austria; GSK, Fr.†.
Trimethoprim (p.355·2).
Bacterial infections of the urinary tract.

GSK, Neth.†.
Trimethoprim (p.355·2) or trimethoprim lactate (p.356·3).
Bacterial infections of the urinary tract.

Welldorm *Alphashow, UK.*
Cloral betaine (p.979·1) or cloral hydrate (p.979·1).
Formerly contained dichloralphenazone.
Insomnia.

Wellferon *GSK, Cz.†; GSK, Ital.†; GSK, Rus.; GSK, Thai.†.*
Interferon alfa-n1 (p.885·1).
Anogenital warts; chronic hepatitis B; chronic hepatitis C; malignant neoplasms.

Wellman
Vitabiotics, UK.
Multivitamin and mineral preparation (p.1922·1).

Vitabiotics, Hong Kong.
Capsules: Vitamins; minerals; ginseng; bioflavonoids; garlic; amino acids (p.1922·1).

Vitabiotics, Hong Kong.
Oral liquid: Vitamins; minerals; ginseng; green tea; cynara (p.1922·1).

Wellvone *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Ital.; GSK, Neth.; Wellcome, Port.; GSK, S.Afr.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, UK.*
Atovaquone (p.829·2).
Pneumocystis pneumonia; toxoplasmosis.

Wellwoman *Potter's, UK.*
Achillea (p.2245·2); motherwort (p.2347·3); tilia (p.2402·2); skullcap (p.2388·2); valerian (p.2410·1).
Menopausal disorders.

Welsan Lipocream *Weluga, Hong Kong.*
Gamolenic acid (p.2308·2); vitamin C (p.1983·3); vitamin E (p.1992·2).
Barrier preparation; corticosteroid cream diluent; dry skin disorders.

Welticilina *Welt, Arg.*
Ampicillin (p.204·1).
Bacterial infections.

Welt-Sulfazol *Welt, Arg.*
Sulfathiazole (p.343·2).
Burns; skin infections; wounds.

Wemid *Bernabo, Arg.*
Erythromycin (p.269·2) or erythromycin ethyl succinate (p.269·3).
Bacterial infections.

Wenflox *Raffo, Arg.*
Norfloxacin (p.309·2).
Bacterial infections.

Wepox *Wockhardt, India.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Westcarbox *Lloyd, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Westcort *BMS, Braz.; Westwood-Squibb, Canad.; BMS, Mex.; Westwood-Squibb, USA.*
⊗ Hydrocortisone valerate (p.1536·1).
Skin disorders.

Westfimox *Lloyd, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Wet *Fidia, Ital.*
Electrolytes (p.1667·1).
Nasal irrigation.

Wet Stuff *Universal, Hong Kong.*
Glycerol (p.2314·2).
Vaginal and rectal lubricant.

Wet-COMOD *Ursapharm, Ger.; Visufarma, Ital.*
Povidone (p.2146·1).
Dry eyes.

Wetol *Beta, Arg.*
Pilocarpine hydrochloride (p.1884·3).
Radiotherapy-induced xerostomia; Sjögren's syndrome.

White Cloverine *Medtech, USA.*
Barrier preparation.

Whitfield *Malaysia Chemist, Singapore†.*
Salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Parasitic skin infections.

Whitfields (Benzoic Acid Compound) Ointment *McGloin, Austral.*
Benzoic acid (p.1630·2); salicylic acid (p.1612·2).
Fungal skin infections.

Wiacid *Landson, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; pathological hypersecretory disorders; peptic ulcer.

Wiaflox *Landson, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Wiamox *Landson, Indon.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Wiatrim *Landson, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Wibi *Healthpoint, USA.*
Moisturiser.

Wibotin H *Pfluger, Ger.*
Homoeopathic preparation.

Wicaran *Widmer, Fin.*
⊗ Tretinoin (p.1618·1); dexpanthenol (p.2362·1); urea (p.1620·2).
Keratinisation disorders.

Wicarba *Widmer, Fin.*
⊗ Vitamin A palmitate (p.1973·1); dexpanthenol (p.2362·1); urea (p.1620·2).
Skin disorders.

Wick Daymed Erkaltungs
Note. This name is used for preparations of different composition.
Wick, Ger.
Capsules: Dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1); phenylpropanolamine hydrochloride (p.1569·3).
Cold symptoms.

Wick, Ger.
Powder for oral liquid: Paracetamol (p.108·1); guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1); ascorbic acid (p.1983·3).
Cold symptoms.

Wick Erkaltungs-Saft fur die Nacht *Procter & Gamble, Austria.*
⊗ Doxylamine succinate (p.578·2); ephedrine sulfate (p.1558·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold symptoms.

Wick Erste Abwehr *Wick, Ger.*
Viscous nasal gel.
Cold prophylaxis.

Wick Formel 44 *Procter & Gamble, Austria.*
Dextromethorphan (p.1555·2).
Coughs.

Wick Formel 44 Husten-Loser *Wick, Ger.*
Guaifenesin (p.1561·3).
Coughs and associated respiratory-tract disorders.

Wick Formel 44 Husten-Stiller *Wick, Ger.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Wick Formel 44 plus Husten-Pastillen *Procter & Gamble, Austria.*
Dextromethorphan (p.1555·2).
Coughs.

Wick Formel 44 plus Husten-Pastillen S *Wick, Ger.*
Dextromethorphan (p.1555·2).
Catarrh; coughs.

Wick Formel 44 Plus Hustenstiller *Procter & Gamble, Austria.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Wick Formula 44 kohogescillapito *Procter & Gamble, Hung.†.*
Dextromethorphan hydrobromide (p.1555·2).
Coughs.

Wick Formula 44 kopteto *Procter & Gamble, Hung.†.*
Guaifenesin (p.1561·3).
Coughs.

Wick Hustensaft *Procter & Gamble, Austria.*
Dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); sodium citrate (p.1673·3).
Coughs.

Wick Inhalierstift N *Wick, Ger.*
Menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Wick Medinait
Note. This name is used for preparations of different composition.
Procter & Gamble, Cz.†.
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); doxylamine succinate (p.578·2); pseudoephedrine hydrochloride (p.1571·2).
Cold and influenza symptoms.

Wick, Ger.
⊗ Doxylamine succinate (p.578·2); ephedrine sulfate (p.1558·2); dextromethorphan hydrobromide (p.1555·2); paracetamol (p.108·1).
Cold and influenza symptoms.

Wick Sinex
Note. This name is used for preparations of different composition.
Procter & Gamble, Austria.
⊗ Oxymetazoline hydrochloride (p.1567·2); menthol (p.2340·1); camphor (p.2273·2); cineole (p.2282·3).
Cold symptoms.

Wick, Ger.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Catarrh; nasal congestion.

Wick Sulagil *Wick, Ger.*
Lidocaine hydrochloride (p.1862·3); dequalinium chloride (p.1641·3); cetylpyridinium chloride (p.1635·1).
Mouth and throat disorders.

Wick Vaporub
Note. This name is used for preparations of different composition.
Procter & Gamble, Austria.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); nutmeg oil (p.2355·3); cedar wood oil (p.2278·3); turpentine oil (p.2406·3); thymol (p.1664·3).
Catarrh; coughs and cold symptoms.

Wick, Ger.
Menthol (p.2340·1); camphor (p.2273·2); eucalyptus oil (p.2301·2); turpentine oil (p.2406·3).
Catarrh; cold symptoms; coughs.

Procter & Gamble, Pol.
Camphor (p.2273·2); eucalyptus oil (p.2301·2); menthol (p.2340·1); thymol (p.1664·3); turpentine oil (p.2406·3); nutmeg oil (p.2355·3); cedar oil.
Respiratory-tract disorders.

Wick-Inhalierstift *Procter & Gamble, Austria.*
Menthol (p.2340·1); camphor (p.2273·2).
Nasal congestion.

Wicne *Widmer, Fin.*
Triclosan (p.1665·2); salicylic acid (p.1612·2); colloidal sulfur (p.1614·1); colloidal silica (p.2146·2).
Acne.

Wicnecarb *Widmer, Fin.*
⊗ Pyridoxine hydrochloride (p.1978·2); triclosan (p.1665·2); colloidal sulfur (p.1614·1); urea (p.1620·2).
Acne.

Wicnelact *Widmer, Fin.*
Triclosan (p.1665·2); zinc sulfate (p.1999·2); lactic acid (p.2329·3); magnesium sulfate (p.1679·3); salicylic acid (p.1612·2).
Acne; seborrhoea.

Wicnevit *Widmer, Fin.*
⊗ Vitamin A palmitate (p.1973·1); triclosan (p.1665·2); pyridoxine hydrochloride (p.1978·2); dexpanthenol (p.2362·1); urea (p.1620·2).
Acne; seborrhoea.

Wida D5 and D10 *Widatra Bhakti, Indon.*
Glucose (p.1945·3).
Carbohydrate source; fluid replacement.

Wida NSI *Widatra Bhakti, Indon.*
Sodium chloride (p.1686·1).
Irrigation solution for surgical procedures.

WIDAHES *Widatra Bhakti, Indon.*
⊗ An etherified starch (p.1065·1) in sodium chloride.
Haemodilution; plasma volume expansion.

Widecillin *Meiji, Indon.*
Amoxicillin (p.202·2) or amoxicillin trihydrate (p.202·2).
Bacterial infections.

Widrox *Landson, Indon.*
Cefadroxil (p.218·1).
Bacterial infections.

Wiedimmun
Note. This name is used for preparations of different composition.
Wiedemann, Ger.
Injection: Homoeopathic preparation.

Wiedemann, Ger.†.
Oral drops: Echinacea purpurea (p.2298·1).
Respiratory-tract infections.

Wiedimmun N *Wiedemann, Ger.*
Homoeopathic preparation.

Wigraine *Organon, USA†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3).
Vascular headache.

Wilate *Octapharma, Ger.; Octapharma, Port.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Wild Cherry-Slippery Elm Formula *Quest, Canad.†.*
Cayenne; chickweed; marrubium; kelp; liquorice; verbascum; pleurisy root; saw palmetto berry; slippery elm; wild cherry bark.

Wildkrauterol special K *Johanser, Ger.*
Peppermint oil (p.1761·2).
Gastrointestinal disorders; respiratory-tract disorders; skeletal muscle and nerve pain.

Wilfactin *Lab Francais du Fractionnement, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανέξ), Gr.*
Von Willebrand factor (p.1082·3).
Haemorrhagic disorders; von Willebrand factor deficiency.

Wilkinson *Mega, Turk.*
Coal tar (p.1616·2); sulfur (p.1614·1); savon noir; calcium carbonate (p.1714·1).
Eczema; psoriasis.

Will-Anal *Will Pharma, Neth.*
⊗ Lidocaine hydrochloride (p.1862·3); triamcinolone acetonide (p.1544·3).
Anorectal disorders.

Willgo *Panacea, India†.*
Nimesulide (p.95·3).
Osteoarthritis; pain; rheumatoid arthritis.

Willlong *Will-Pharma, Belg.*
Glyceryl trinitrate (p.1296·2).
Angina pectoris; heart failure.

Willospon *Will-Pharma, Neth.†.*
⊗ Gelatin foam (p.1072·1).
Haemostatic dressing.

Willospon Forte *Will-Pharma, Neth.†.*
Collagen (p.2286·1).
Haemostatic dressing.

Willydina *Tocogino, Mex.*
Dextromethorphan (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Wilpan Antigripal *Bernabo, Arg.*
Phenylephrine hydrochloride (p.1568·1); vitamin C (p.1983·3); pentoxyverine citrate (p.1567·3); paracetamol (p.108·1).
Influenza symptoms.

Wilpan C *Microsules Bernabo, Arg.†.*
Phenylephrine hydrochloride (p.1568·1); pentoxyverine citrate (p.1567·3); astemizole (p.567·2); vitamin C (p.1983·3).
Influenza symptoms.

Wilprafen
Yamanouchi, Ger.†; Astellas, Rus.
Josamycin (p.291·1) or josamycin propionate (p.291·1).
Bacterial infections.

Mack, Hung.†.
Josamycin (p.291·1).
Bacterial infections.

Wilsim *Hizon, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Wilstart *Lab Francais du Fractionnement, Fr.*
Von Willebrand factor(p.1082·3).
Von Willebrand's disease.

Wilvit *Sons, Mex.*
Vitamin and mineral preparation with ginseng (p.1922·1).

Wilzin *Orphan Europe, Cz.; Orphan, Fr.; Orphan, Ger.; Orphan, Ital.; Orphan, Neth.; Orphan, Pol.; Orphan Europe, Port.; Orphan, Spain; Orphan, UK.*
Zinc acetate (p.1999·1).
Wilson's disease.

Winadol *Konsuma, Venez.†.*
Paracetamol (p.108·1).
Fever; pain.

Winaflox *Dynamic, Philipp.*
Norfloxacin (p.309·2).
Bacterial infections.

Winar *Apogepha, Ger.†.*
Urtica root (p.2409·3).
Benign prostatic hyperplasia.

Winasorb *K2 Pharmacare, Chile; Rudefsa, Mex.*
Paracetamol (p.108·1).
Fever; pain.

Winasorb Flex *K2 Pharmacare, Chile.*
Chlorzoxazone (p.1894·3); paracetamol (p.108·1).
Skeletal muscle spasm and pain.

Winasorb Flu DN *K2 Pharmacare, Chile.*
Day tablets, paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); night tablets, paracetamol; pseudoephedrine hydrochloride; chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Winasorb UP *K2 Pharmacare, Chile.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Pain.

Winatin *Ifars, Indon.*
Loratadine (p.583·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Wincef *Fujisawa, Jpn†.*
Cefoselis sulfate (p.228·1).
Bacterial infections.

Wincoram
Sanofi Synthelabo, Cz.†; Sanofi Synthelabo, Ger.†.
Amrinone (p.1215·1).
Heart failure.

Sanofi Synthelabo, Spain†.
Amrinone lactate (p.1215·1).
Heart failure.

Wind & Dyspepsia Relief *Herbal Concepts, UK.*
Ginger (p.1732·3); hydrastis (p.2321·3); myrrh (p.2349·2); rhubarb (p.1768·3); valerian (p.2410·1); taraxacum (p.2395·1).
Dyspepsia; flatulence.

Wind-Eze *GSK Consumer, UK.*
Simeticone (p.1770·2).
Formerly known as Setlers Wind-Eze.
Flatulence.

Windol *Dermapharm, Ger.*
Bufexamac (p.28·3).
Inflammatory skin disorders.

Windol Basisbad *Dermapharm, Ger.†.*
Liquid paraffin (p.2030·3); soya oil (p.1965·3).
Bath additive; skin disorders.

Windoxa *Sanofi-Aventis, Cz.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Wingel *Sanofi Synthelabo, Mex.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); dimeticone (p.1770·2).
Flatulence; gastric hyperacidity.

40 Winks *Roberts, USA.*
Diphenhydramine hydrochloride (p.577·2).
Insomnia.

Winlomylon *Adcock Ingram, S.Afr.*
Nalidixic acid (p.303·3).
Gram-negative bacterial urinary-tract infections.

Winnipeg *Selvi, Ital.*
Bacampicillin hydrochloride (p.210·2).
Bacterial infections.

Winofit *Wockhardt, India.*
Vitamin E; vitamin C; vitamin A; eicosapentaenoic acid; docosahexaenoic acid; zinc sulfate; folic acid; manganese sulfate; chromium tripicolinate; selenium dioxide (p.1922·1).
Tonic.

Winol *Raffo, Arg.*
Irinotecan hydrochloride (p.737·1).
Colorectal cancer.

Winpac *Sanofi Synthelabo, Chile†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2).
Nasal congestion; pain; sinusitis.

Winpain *Brunel, S.Afr.†.*
Paracetamol (p.108·1).
Fever; pain.

Winpar *Ares, Mex.*
Cinnarizine (p.573·1).
Cerebral and peripheral vascular disorders; nausea and vomiting; vestibular disorders.

Winpred *Valeant, Canad.*
⊗ Prednisone (p.1542·3).
Corticosteroid.

WinRho *CSL, Austral.; Itaca, Braz.†; Cangene, Canad.; Cangene, Gr.; Cangene, Hong Kong; Cangene, Israel; Baxter, NZ; Cangene, Philipp.; Cangene, Port.; Baxter, UK; Baxter, USA.*
An anti-D immunoglobulin (p.2204·2).
Idiopathic thrombocytopenic purpura; prevention of rhesus sensitisation.

Winstrol *Zambon, Spain; Ovation, USA†.*
⊗ Stanozolol (p.2129·1).
Anabolic; anaemia in renal failure; hereditary angioedema.

Wintanyl *Winthrop, Cz.*
⊗ Fentanyl (p.55·3).
Pain.

Winter AP *Merck, Braz.*
Dexbrompheniramine maleate (p.569·2); pseudoephedrine sulfate (p.1571·2).
Respiratory-tract congestion.

Wintogeno *Actavis, Malaysia; Alpharma, Singapore†.*
Methyl salicylate (p.85·3); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Wintogeno Extra *Actavis, Indon.*
Methyl salicylate (p.85·3); levomenthol.
Musculoskeletal pain; soft-tissue injury.

Wintomilon *Sanofi Synthelabo, Port.†.*
Nalidixic acid (p.303·3).
Urinary-tract infections.

Wintomylon *Sanofi Synthelabo, Arg.†; Sanofi-Aventis, Braz.; Sanofi Synthelabo, Chile†; Sanofi Synthelabo, Hong Kong; Sanofi Synthelabo, Mex.*
Nalidixic acid (p.303·3).
Gram-negative bacterial gastro-intestinal and urinary-tract infections.

Winton *Sanofi-Aventis, Spain.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Dyspepsia; gastrointestinal hyperacidity.

Wintus *Ilsan, Turk.*
Paracetamol (p.108·1); dextromethorphan hydrobromide (p.1555·2); phenylephrine hydrochloride (p.1568·1); chlorphenamine maleate (p.571·3).
Respiratory-tract congestion.

Wirbelsaule- und Gelenkstropfen Nr 2 *Doskar, Austria.*
Homoeopathic preparation.

Wisamt *Procter & Gamble, Austria†.*
Resorcinol (p.1612·1); sulfur (p.1614·1).
Acne.

Wisamt N *Procter & Gamble, Ger.†.*
Sulfur (p.1614·1); resorcinol (p.1612·1).
Acne.

Wismut comp *Ratiopharm, Ger.†.*
Bismuth subcarbonate (p.1711·1); anhydrous aluminium hydroxide (p.1706·2); dimethicone (p.1770·2); magnesium trisilicate gel (p.1744·1).
Gastrointestinal disorders.

Wisperdon *Faran, Gr.*
Risperidone (p.1024·2).
Psychoses.

Witch Doctor *Fleet, Austral.†; De Witt, UK.*
Hamamelis (p.2318·2).
Insect bites; skin disorders; skin irritation.

Witch Sunsore *De Witt, UK.*
Hamamelis (p.2318·2).
Sunburn.

Witdulsies *Lennon, S.Afr.*
Ethyl nitrite (p.2300·2).
Asthma; cold symptoms; fever; vertigo.

Witromin *Pisa, Mex.*
Erythromycin (p.269·2).
Bacterial infections.

Witte Kruis *Viatris, Neth.*
Paracetamol (p.108·1); caffeine (p.1116·3).
Fever; pain.

Witty *Gezzi, Arg.*
Permethrin (p.2048·2).
Pediculosis.

Wizol *Landson, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

WND *Mead Johnson, Fr.*
Food for special diets (p.1922·1).
Urea cycle disorders.

Wobe-Mugos
Note. This name is used for preparations of different composition.
Mucos, Austria.
Pancreatic proteolytic enzymes (p.2337·3); calf thymus (p.2401·3); pisum sativum; lens esculenta; papain (p.2362·3).
Adjunct to treatment of malignant neoplasms.

Mucos, Cz.†.
Papain (p.2362·3); trypsin (p.2405·3); chymotrypsin (p.2281·3); thymus extract (p.2401·3).
Adjunct to treatment of malignant neoplasms; adjunct to treatment of viral infections.

Romsa, Mex.
Papain (p.2362·3); trypsin (p.2405·3); chymotrypsin (p.2281·3).
Inflammatory and degenerative disorders; varicella-zoster infections.

Wobe-Mugos E *Mucos, Ger.†; Mucos, Rus.*
Trypsin (p.2405·3); chymotrypsin (p.2281·3); papain (p.2362·3).
Malignant neoplasms; reduction of adverse effects of radiation and chemotherapy; viral infections.

Wobenzimal
Note. This name is used for preparations of different composition.
Vitafarma, Spain†.
Ointment: Papaya enzymes; lens sculenta enzymes; pisum sativum enzymes; pancreatin (p.2360·1); vitamin A (p.1971·2); thyme (p.2401·1); tocopherol (p.1992·2); vitamin F (p.2308·2).
Inflammation; oedema.

Vitafarma, Spain†.
Tablets: Papaya; lens sculenta; pisum sativum; pancreatin (p.2360·1); thyme (p.2401·1).
Inflammation; oedema; peripheral vascular disorders.

Wobenzym *Mucos, Austria; Mucos, Cz.; Romsa, Mex.; Mucos, Rus.*
Pancreatin (p.2360·1); papain (p.2362·3); bromelains (p.2269·1); trypsin (p.2405·3); lipase (p.2360·3); amylase (p.2256·3); chymotrypsin (p.2281·3); rutoside (p.2305·1).
Immunostimulant; inflammation; musculoskeletal, joint, and soft-tissue disorders; oedema.

Wobenzym N
Note. This name is used for preparations of different composition.
Mucos, Venez.
Pancreatin (p.2360·1); trypsin (p.2405·3); chymotrypsin (p.2281·3); bromelains (p.2269·1); papain (p.2362·3); rutoside (p.2305·1).
Inflammation.

Mucos, Ger.†.
Ointment: Bromelains (p.2269·1); trypsin (p.2405·3).
Inflammation; oedema.

Mucos, Ger.
Tablets: Pancreatin (p.2360·1); bromelains (p.2269·1); papain (p.2362·3); rutoside (p.2305·1).
Inflammation; thrombophlebitis.

Wokadine *Wockhardt, India; Wockhardt, Rus.*
Povidone-iodine (p.1659·2).
Burns; disinfection of hands, skin and mucous membranes; mouth and throat disorders; skin infections; vaginal infections; wounds.

Wokex-2 *Wockhardt, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1).
Tuberculosis.

Wokex-3 *Wockhardt, India.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1); 1 tablet, ethambutol (p.275·2).
Tuberculosis.

Wokex-4 *Wockhardt, India.*
1 Tablet, rifampicin (p.325·3); isoniazid (p.288·1); vitamin B (p.1979·1); 2 tablets, pyrazinamide (p.320·2); 1 or 2 tablets, ethambutol (p.275·2).
Tuberculosis.

Wolff Basis *Wolff, Cz.*
Emollient.
Pharmaceutical diluent; skin disorders.

Wolo Bain antirefroidissement *Merz, Switz.*
Eucalyptus oil (p.2301·2); pine-needle oil (p.2368·2); thyme oil (p.2401·2); menthol (p.2340·1); camphor (p.2273·2).
Bath additive; bronchitis; cold symptoms.

Wolo Medicinal bain antirhumatismal *Merz, Switz.*
Pine-needle oil (p.2368·2); rosemary oil (p.2381·3); methyl salicylate (p.85·3).
Bath additive; musculoskeletal and joint disorders.

Woloderma
Note. This name is used for preparations of different composition.
Adroka, Switz.†.
Soap substitute.
Skin disorders.

Adroka, Switz.†.
Bath additive: Almond oil (p.2252·2); liquid paraffin (p.2030·3).
Skin disorders.

Adroka, Switz.†.
Topical lotion: Sodium lactate (p.1673·3); almond oil (p.2252·2).
Skin disorders.

Woman Formula *Avon, Canad.†.*
Vitamin and mineral preparation (p.1922·1).

Womens Change Formula *General Nutrition, Canad.†.*
Multivitamin and mineral preparation (p.1922·1).

Womens Exclusive Formula *Natural Life, Arg.†.*
Vitamin and mineral preparation (p.1922·1).

Women's Formula Herbal Formula 3 *Vitelle, Austral.†.*
Angelica (p.2258·1); cimicifuga (p.2282·1); blue cohosh (p.2267·2); pulsatilla (p.2376·3); agnus castus (p.2249·1).
Menstrual disorders.

Womens Support *General Nutrition, Canad.†.*
Vitamin C; vitamin D; calcium; magnesium; silicon dioxide (p.1922·1).

Women's Timed Release Ultra Mega without Iron *General Nutrition, Canad.*
Multivitamin and mineral preparation (p.1922·1).

Womens Tylenol Multi-Symptom Menstrual Relief *McNeil Consumer, USA.*
⊗ Paracetamol (p.108·1); pamabrom (p.1365·3).

Womosol Solar *Costec, Arg.†.*
SPF 12: Padimate O (p.1609·1).
Sunscreen.

Wonder Ice *Pedinol, USA.*
Menthol (p.2340·1).
Muscle, joint, and soft-tissue pain; neuralgia.

Wondergel *Lake, USA.*
Vaginal lubricant.

Wonderkroonessens *Lennon, S.Afr.*
Rhubarb (p.1768·3); gentian (p.2310·3); valerian (p.2410·1); ginger (p.1732·3); elecampane (p.1558·1); aloes (p.1705·2); camphor (p.2273·2); potassium carbonate.
Constipation; dyspepsia; flatulence.

Wondra *Richardson-Vicks, USA.*
Emollient and moisturiser.

Wontizem *Daewon, Hong Kong.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Woods' Peppermint Antitussive *Kalbe, Indon.*
Dextromethorphan hydrobromide (p.1555·2); diphenhydramine hydrochloride (p.577·2).
Cough with allergy.

Woods' Peppermint Expectorant *Kalbe, Indon.*
Bromhexine hydrochloride (p.1552·2); guaifenesin (p.1561·3).
Cough.

Woodward's Diaper Rash *Pharmacare, Canad.*
Zinc oxide (p.1621·2).
Nappy rash.

Woodwards Gripe Water
Note. This name is used for preparations of different composition.
Pharmacare, Canad.; LRC, Israel; SSL, Thai.; SSL, UK.
Dill oil (p.2293·3); sodium bicarbonate (p.1673·2).
Infant colic; wind in infants.

Seton, Pol.
Fennel oil (p.2303·1); sodium bicarbonate (p.1673·2).
Infant colic.

Woodwards Inhalant *Aspen Consumer, S.Afr.*
Cineole (p.2282·3); chloroxylenol (p.1640·2); pine oil (p.2368·2); turpentine oil (p.2406·3); menthol (p.2340·1).
Respiratory-tract disorders.

Woodwards Teething Gel *SSL, UK.*
Lidocaine hydrochloride (p.1862·3); cetylpyridinium chloride (p.1635·1).
Denture irritation; mouth ulcers; teething pain.

Wormgo *Pharmacare, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Wormicide *Greater Pharma, Thai.*
Praziquantel (p.153·3).
Trematode infections.

Wormin *Cadila Pharma, India; Cadila, Rus.*
Mebendazole (p.148·3).
Worm infections.

Wormstop *Be-Tabs, S.Afr.*
Mebendazole (p.148·3).
Worm infections.

Wosulin 30/70 *Pentafarma, Chile.*
⊗ A mixture of neutral insulin injection (human) 30% and isophane insulin injection (human) 70% (p.443·2).
Diabetes mellitus.

Wosulin Biphasic 30/70 and 50/50 *Wockhardt, India.*
⊗ Mixtures of neutral insulin injection (human, highly purified) 30% and 50% and isophane insulin injection (human, highly purified) 70% and 50% respectively (p.443·2).
Diabetes mellitus.

Wosulin-N *Pentafarma, Chile; Wockhardt, India.*
⊗ Neutral insulin injection (human) (p.443·2).
Diabetes mellitus.

Wosulin-R *Pentafarma, Chile; Wockhardt, India.*
⊗ Insulin injection (human) (p.443·2).
Diabetes mellitus.

Wotinex *Wockhardt, India.*
Tinidazole (p.848·3); diloxanide furoate (p.832·2).
Amoebiasis.

Wound Cleanser *Geritrex, USA.*
Chlorophyllin copper complex (p.1471·1); vitamin E (p.1992·2); zinc (p.1999·1).

Wrinkle Defence *Sunspot, Austral.†.*
SPF 15+: Oxybenzone (p.1608·3); octinoxate (p.1608·2) in a moisturising base.
Emollient; sunscreen.

W-Tal *Costec, Arg.*
Soap substitute.

W-Tropfen *Hofmann & Sommer, Ger.*
Salicylic acid (p.1612·2); lactic acid (p.2329·3).
Calluses; corns.

Wulnasin *OTC, Switz.*
Cetylpyridinium chloride (p.1635·1); allantoin (p.1588·1); dexpanthenol (p.2362·1); lidocaine hydrochloride (p.1862·3).
Skin lesions.

Wund- und Brandgel *Wala, Ger.*
Homoeopathic preparation.

Wund- und Heilsalbe N *Riemser, Ger.†.*
Dexpanthenol (p.2362·1).
Skin disorders.

Wundesin *Gebro, Austria.*
Povidone-iodine (p.1659·2).
Wounds.

Wund-und Heilcreme N *Riemser, Ger.*
Dexpanthenol (p.2362·1).
Skin disorders.

Wyamine *Wyeth-Ayerst, USA†.*
⊗ Mephentermine sulfate (p.1332·3).
Hypotension; shock.

Wyanoids Relief Factor *Wyeth-Ayerst, USA.*
Live yeast cell derivative (p.1998·3); shark-liver oil (p.2386·1).
Haemorrhoids.

Wycillin *Eurofarma, Braz.*
Procaine benzylpenicillin (p.319·2); benzylpenicillin potassium (p.213·1).
Bacterial infections.

Wycillina *Pharmacia, Ital.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Wycort *Wyeth, India.*
⊗ Hydrocortisone acetate (p.1535·2).
Corticosteroid.

Wycort c Neomycin *Wyeth, India.*
⊗ Hydrocortisone acetate (p.1535·2); neomycin sulfate (p.305·1).
Anal or vulval pruritus; burns; infected skin disorders; skin ulcers; wounds.

Wydase *Wyeth, Chile†; Wyeth-Ayerst, USA†.*
Hyaluronidase (p.2321·1).
Adjunct in eye surgery; adjunct in subcutaneous urography; adjuvant to increase the absorption and dispersion of drugs; hypodermoclysis.

Wydora *Riemser, Ger.*
Indoramin hydrochloride (p.1315·1).
Hypertension.

Wydox *YSS, Philipp.*
Oxacillin sodium (p.311·3).
Staphylococcal infections.

Wygesic *Wyeth, India; Wyeth-Ayerst, USA†.*
Dextropropoxyphene hydrochloride (p.40·1); paracetamol (p.108·1).
Fever; pain.

Wylaxine *Omega, Belg.*
Bisoxatin acetate (p.1712·3).
Bowel evacuation; constipation.

Wymesone *Wyeth, India.*
⊗ Dexamethasone (p.1526·1).
Corticosteroid.

Wypresin *Wyeth Lederle, Austria†.*
Indoramin hydrochloride (p.1315·1).
Hypertension.

Wysolone *Wyeth, India.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Wysoy *Wyeth, Irl.; Wyeth, UK.*
Lactose-free food for special diets (p.1922·1).
Cows' milk or lactose intolerance; galactokinase deficiency; galactosaemia.

Wytens *Wyeth, Fr.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Wytensin *Wyeth-Ayerst, USA.*
Guanabenz acetate (p.1299·3).
Hypertension.

X-2 *Investigaciones Filosoficas y Cientificas, Mex.*
Cocarboxylase (p.1975·2).
Thiamine deficiency.

Xacin *Pharmasant, Thai.*
Norfloxacin (p.309·2).
Bacterial infections.

Xadaren *Pliva, Cz.†.*
Flutamide (p.725·1).
Prostatic cancer.

Xadorek *Minerva (Μινέρβα), Gr.*
Citalopram (p.385·3).
Depression.

Xagrid *LCA, Belg.; Shire, Cz.; Shire, Denm.; Orphan, Fin.; Shire, Fr.; Shire, Ger.; Genesis, Gr.; Shire, Irl.; Shire, Ital.; Shire, Neth.; Shire, Norw.; Shire, Spain; Swedish Orphan, Swed.; Opopharma, Switz.; Shire, UK.*
Anagrelide hydrochloride (p.2257·1).
Essential thrombocythaemia.

Xal *Pharmadeveloppement, Fr.*
Potassium chloride; ammonium chloride; calcium formate; glutamic acid (p.1667·1).
Dietary salt substitute.

Xalacom *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Pfizer, Spain; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Pfizer, Venez.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Xalatan *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, Mex.; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pfizer, S.Afr.; Pfizer,*

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Singapore; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, Turk.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.
Latanoprost (p.1882·1).
Glaucoma; ocular hypertension; raised intra-ocular pressure.

Xalazin *Astellas, Hung.; Caber, Ital.†.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Xalazina *HLB, Arg.*
Mesalazine (p.1745·1).
Inflammatory bowel disease.

Xalcom *Pfizer, Denm.; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Swed.*
⊗ Latanoprost (p.1882·1); timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Xaliplat *Richmond, Arg.*
Oxaliplatin (p.757·3).
Malignant neoplasms.

Xalotina *Richmond, Arg.†.*
Amoxicillin (p.202·2).
Bacterial infections.

Xalyn-Or *Atlantis, Mex.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Xamamina *Bracco, Ital.*
Dimenhydrinate (p.576·2).
Motion sickness.

Xamamine *Adilna, Turk.*
Dimenhydrinate (p.576·2).
Motion sickness; nausea and vomiting; vertigo; vestibular disorders.

Xame *Lisapharma, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Xanacine *Medicine Products, Thai.*
Alprazolam (p.960·1).
Anxiety.

Xanaes *Klonal, Arg.*
Azelastine hydrochloride (p.568·2).
Eye disorders.

Xanagis *Agis, Israel.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states; panic disorders.

Xanalin *Silom, Thai.*
Neomycin sulfate (p.305·1); polymyxin B (p.318·2); gramicidin (p.286·1).
Bacterial eye infections.

Xanator *Genepharm, Gr.*
Atorvastatin (p.1219·1).
Hyperlipidaemias.

Xanax *Pfizer, Arg.; Pharmacia, Austral.; Pfizer, Belg.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pharmacia, NZ; Pfizer, Neth.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.†; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Eczacibasi, Turk.; Pfizer, UK; Pfizer, USA.*
Alprazolam (p.960·1).
Alcohol withdrawal syndrome; anxiety; depression; mixed anxiety-depressive states; panic disorder.

Xanazole *Virgo, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Xanbon *Kissei, Jpn.*
Ozagrel sodium (p.2359·2).
Cerebral thrombosis; cerebral vasospasm.

Xanda *Teguhsindo, Indon.*
Curcuma; fructo-oligosaccharide; lysine; taurine; inositol (p.1922·1).
Reduced appetite.

Xanef *MSD, Ger.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Xanidil *Zentiva, Cz.*
Xantinol nicotinate (p.1433·1).
Cerebral and peripheral vascular disorders.

Xanidine
Berlin Pharm, Singapore.
Ranitidine (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Berlin Pharm, Thai.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Xanol
Note. This name is used for preparations of different composition.
Phoenix, Arg.
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Pharmasant, Thai.
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Xanolam *Garec, S.Afr.†.*
Alprazolam (p.960·1).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Xanomel *PannonPharma, Hung.†; Clonmel, Irl.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Xanor *Pfizer, Austria; Pfizer, Fin.; Pfizer, Norw.; Pfizer, Philipp.; Pharmacia, S.Afr.; Pfizer, Swed.*
Alprazolam (p.960·1).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Xantervit *SIFI, Ital.*
Xanthopterin (p.2416·2); multivitamins (p.1922·1).
Ocular trauma and lesions.

Xantervit Antibiotico *SIFI, Ital.*
Xanthopterin (p.2416·2); chloramphenicol (p.239·3); multivitamins (p.1922·1).
Ocular trauma and lesions.

Xantervit Eparina *SIFI, Ital.*
Xanthopterin (p.2416·2); heparin sodium (p.1301·2); multivitamins (p.1922·1).
Ocular burns.

Xanthium
SMB, Belg.; SMB, Singapore†.
Theophylline hydrate (p.1140·2).
Obstructive airways disease.

Galephar, Fr.†; SMB, Thai.; Galepharma, Turk.
Theophylline (p.1140·1).
Asthma; obstructive airways disease.

Xanthomax *Ashbourne, UK†.*
Allopurinol (p.552·2).

Xantina B12 *Prodotti, Braz.†.*
Methionine (p.1450·1); choline (p.1934·2); vitamin B substances (p.1975·1); liver extract (p.2337·3); with or without manganese (p.1956·1) and gastric mucosa extract (p.2337·3).
Liver disorders.

Xantinon B12 *Nycomed, Braz.*
Methionine (p.1450·1); vitamin B substances (p.1975·1); choline chloride (p.1934·2); liver extract (p.2337·3); with or without manganese (p.1956·1) and gastric mucosa extract (p.2337·3).
Liver disorders.

Xantinon Complex *Nycomed, Braz.*
Acetylmethionine (p.1450·2); inositol (p.2325·2); choline citrate (p.1934·2); betaine hydrochloride (p.2265·2); cyanocobalamin (p.1980·2); pyridoxine hydrochloride (p.1978·2).
Liver disorders.

Xantium *Wyeth Lederle, Ital.†.*
Protirelin tartrate (p.2176·2).
Neurological deficit.

Xantromid *Richmond, Arg.*
Methotrexate (p.745·2).
Malignant neoplasms.

Xantrosin *Teva, Belg.*
Mitoxantrone hydrochloride (p.754·1).
Malignant neoplasms.

Xanturenasi *Teofarma, Ital.*
Pyridoxine hydrochloride (p.1978·2).
Age-related metabolic disorders; epilepsy; migraine; skin disorders; tremor; vomiting in pregnancy.

Xanturic *Pyridam, Indon.*
Allopurinol (p.552·2).
Gout; hyperuricosuria.

Xanurace *Ace, Philipp.*
Allopurinol (p.552·2).
Hyperuricaemia.

Xanvit *Soho, Indon.*
Curcuminoid; vitamin B substances (p.1922·1).
Tonic.

Xao Pil *Ingens, Arg.*
Pilocarpine (p.1884·3).
Glaucoma; production of miosis.

Xao T *Ingens, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Xao-Dex *Giscard, Arg.†.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Xapnev *Merck, Port.*
Venlafaxine hydrochloride (p.427·3).
Anxiety; depression; panic disorder; social phobia.

Xapro *Jenapharm, Ger.*
Estriol (p.2101·1).
Vulvovaginal disorders.

Xarator *Parke, Davis, Ital.†.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Xarb *Nicholas Piramal, India.*
Irbesartan (p.1316·1).
Diabetic nephropathy; hypertension.

Xarb-H *Nicholas Piramal, India.*
⊗ Irbesartan (p.1316·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Xarope Antigripal *Basi, Port.†.*
Codeine (p.37·2); ethylmorphine (p.52·2); sulfogaiacol (p.1573·2).
Coughs.

Xarope de Caraguata *Sanval, Braz.†.*
Annona muricata; bromoform (p.2269·3); sodium benzoate (p.1630·2); aconite (p.2246·1); belladonna (p.2263·3); tolu balsam (p.1574·2); grindelia (p.2317·2).
Coughs.

Xarope 44E *Procter & Gamble, Braz.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Xarope Iodo-Suma *Iodo Suma, Braz.†.*
Potassium iodide (p.2169·2); anchietea salutaris; bowdichia virgilioides; echinodorus macrophyllus; gentian (p.2310·3).
Coughs.

Xarope de Macas Reinetas *Gestafarma, Port.*
⊗ Senna (p.1769·2); mannitol (p.1330·2); apple pulp.
Constipation.

Xarope Neo *Neo Quimica, Braz.*
Potassium iodide (p.2169·2).
Coughs.

Xarope Peitoral de Ameixa Composto *Simoes, Braz.†.*
⊗ Sodium benzoate (p.1630·2); bromoform (p.2269·3); lobelia (p.2157·2); grindelia (p.2317·2); aconite (p.2246·1); eucalyptus oil (p.2301·2).
Coughs.

Xarope Sao Joao *Uniao Quimica, Braz.†.*
Bromoform (p.2269·3); sodium benzoate (p.1630·2); sulfogaiacol (p.1573·2); belladonna (p.2263·3); aconite (p.2246·1); mulungu (p.2348·1); tar (p.1616·2); tolu balsam (p.1574·2).
Coughs.

Xartan *Adamed, Pol.*
Losartan potassium (p.1326·1).
Hypertension.

Xasmun *VP, Spain.*
Norfloxacin (p.309·2).
Genito-urinary tract infections.

Xatral *Sanofi Synthelabo, Austria; Sanofi-Aventis, Belg.; Sanofi-Aventis, Braz.; Sanofi Synthelabo, Canad.; Sanofi-Aventis, Cz.; Sanofi Synthelabo, Denm.; Sanofi-Aventis, Fin.; Sanofi-Aventis, Fr.; Sanofi-Aventis, Gr.; Sanofi Synthelabo, Hong Kong; Sanofi-Aventis, Indon.; Sanofi-Aventis, Irl.; Synthelabo, Israel; Sanofi-Aventis, Ital.; Sanofi-Aventis, Malaysia; Sanofi Synthelabo, Mex.; Sanofi Synthelabo, Neth.; Sanofi Synthelabo, Norw.; Sanofi Synthelabo, Philipp.; Sanofi Synthelabo, S.Afr.; Sanofi-Aventis, Singapore; Sanofi Synthelabo, Swed.; Sanofi Synthelabo, Switz.; Sanofi Synthelabo, Thai.; Sanofi Synthelabo, Turk.; Sanofi Synthelabo, UK; Sanofi-Aventis, Venez.*
Alfuzosin hydrochloride (p.2183·1).
Benign prostatic hyperplasia.

Xavin
Note. This name is used for preparations of different composition.
Extractum, Hung.
Xantinol nicotinate (p.1433·1).
Cerebral and peripheral vascular disorders.

Caber, Ital.
⊗ Budesonide (p.1520·1).
Asthma; croup.

Xazal *UCB, Spain.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; urticaria.

X-Cam *Meprofarm, Indon.*
Meloxicam (p.80·3).
Osteoarthritis; rheumatoid arthritis.

Xclair *Ashbourne, UK.*
Levomenol (p.2333·3); enoxolone (p.50·1); hyaluronic acid (p.2320·1); vitis vinifera (p.2316·3); telmesteine (p.1573·3).
Radiation dermatitis.

Xebramol *Medicine Products, Thai.*
Paracetamol (p.108·1).
Fever; pain.

Xebyl *Basi, Port.*
Chenodeoxycholic acid (p.2280·1).
Gallstones.

Xedec *Cypress, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Xedenol *Baliarda, Arg.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Xedenol B12 *Baliarda, Arg.*
⊗ Diclofenac sodium (p.44·3); betamethasone (p.1518·2) or betamethasone phosphate (p.1519·1); cyanocobalamin (p.1980·2) or hydroxocobalamin (p.1980·3).
Peri-articular disorders.

Xedenol Flex *Baliarda, Arg.*
Diclofenac sodium (p.44·3); pridinol mesilate (p.1898·1).
Musculoskeletal and joint disorders.

Xedenol Gesic *Baliarda, Arg.*
Diclofenac potassium (p.44·3); paracetamol (p.108·1).
Inflammation; pain.

Xeed-2 *Panacea, India.*
Rifampicin (p.325·3); isoniazid (p.288·1).
Tuberculosis.

Xeed-4 *Panacea, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol hydrochloride (p.274·1); pyrazinamide (p.320·2).
Tuberculosis.

Xeed-3E *Panacea, India.*
Rifampicin (p.325·3); isoniazid (p.288·1); ethambutol hydrochloride (p.274·1).
Tuberculosis.

Xefo *Nycomed, Austria; Nycomed, Cz.; Nycomed, Denm.; Nycomed, Gr.; Nycomed, Hung.; Nycomed, Israel; Pharmacia, S.Afr.; Nycomed, Swed.; Nycomed, Switz.; Nycomed, Thai.†; Abdi, Turk.*
Lornoxicam (p.77·3).
Inflammation; musculoskeletal, joint, and peri-articular disorders; pain; sciatica.

Xefocam *Nycomed, Rus.*
Lornoxicam (p.77·3).
Osteoarthritis; pain; rheumatoid arthritis.

Xefotil *Sandoz, Austria.*
Cefixime (p.224·3).
Bacterial infections.

Xelent *Westmont, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

Xelevia
MSD, Cz.; Vianex (Βιανέξ), Gr.
Sitagliptin (p.460·2).
Diabetes mellitus.

MSD, Port.
Sitagliptin phosphate (p.460·2).
Diabetes mellitus.

Xeloda *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Chugai, Jpn; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, Rus.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Capecitabine (p.691·3).
Breast cancer; colorectal cancer; gastric cancer.

Xeltic *Unison, Hong Kong; Unison, Thai.*
Glibenclamide (p.440·1).
Diabetes mellitus.

Xemos *Recalcine, Chile.*
⊗ Salmeterol (p.1135·3).
Asthma.

Xenaderm *Healthpoint, USA.*
Trypsin (p.2405·3); Peru balsam (p.2365·3); castor oil (p.2278·1).

Xenalon *Mepha, Cz.†; Mepha, Switz.*
⊗ Spironolactone (p.1400·1).
Hyperaldosteronism; hypertension; nephrotic syndrome; oedema.

Xenam *CPH, Port.*
Captopril (p.1239·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Xenar *Wassermann, Ital.†.*
Naproxen (p.92·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

Xenazine *OPi, Fr.; Megapharm, Israel; AFT, NZ; Cambridge, UK.*
Tetrabenazine (p.2396·2).
Ballism; Huntington's chorea; movement disorders.

Xendin *Salus, Mex.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Xenetic *Temis, Arg.*
Iobitridol (p.1481·2).
Radiographic contrast medium.

Xenetix *Temis, Arg.; Guerbet, Austria; Codali, Belg.; Rider, Chile; Guerbet, Cz.; Guerbet, Denm.; Guerbet, Fin.; Guerbet, Fr.; Guerbet, Ger.; Hospital Line, Gr.; Guerbet, Hung.; Guerbet, Israel; Guerbet, Ital.; Guerbet, Neth.; Guerbet, Norw.; Martins & Fernandes, Port.; Guerbet, Spain; Gothia, Swed.; Guerbet, Switz.; Quifoven, Venez.*
Iobitridol (p.1481·2).
Radiographic contrast medium.

Xenical *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Indon.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Malaysia; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Norw.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Orlistat (p.2358·1).
Obesity.

Xenid *Ranbaxy, Fr.*
Diclofenac epolamine (p.44·3) or diclofenac sodium (p.44·3).
Dysmenorrhoea; musculoskeletal, joint, and peri-articular disorders; renal colic.

Xeniplus *Elea, Arg.*
Orlistat (p.2358·1).
Obesity.

Xenna *US Pharmacia, Pol.†.*
Senna (p.1769·2).
Bowel evacuation; constipation.

Xenobid *Shreya, India.*
Naproxen (p.92·3) or naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and soft-tissue disorders; pain.

Xenoprom *Novell, Indon.*
Cefpirome sulfate (p.231·3).
Bacterial infections.

Xenovate *Aspen, S.Afr.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Xentafid *Fidia, Ital.*
Benzydamine hyaluronate (p.27·3).
Mouth and throat disorders.

Xentic *United Pharma, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Xeomin *Merz, Ger.; Grunenthal, Port.; Merz, UK.*
Botulinum A toxin (p.1890·1).
Blepharospasm; spasmodic torticollis.

Xepabet *Metiska, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Xepacillin *Metiska, Indon.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Xepadergin *Metiska, Indon.*
Codergocrine mesilate (p.363·3).
Mental function impairment in the elderly.

Xepalat *Metiska, Indon.*
Nifedipine (p.1350·1).
Angina pectoris; hypertension.

Xepalium *Metiska, Indon.*
Flunarizine (p.580·3).
Dizziness; migraine; peripheral vascular disorders.

Xepamet *Metiska, Indon.; Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Cimetidine (p.1716·2).
Acid aspiration; adjunct in pancreatic insufficiency; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Xepamol *Metiska, Indon.*
Paracetamol (p.108·1).
Fever; pain.

Xepaneuron *Metiska, Indon.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Morning sickness; nervous system disorders; vitamin B deficiency.

Xepanicol
Xepa-Soul Pattinson, Hong Kong; Xepa-Soul Pattinson, Malaysia†.
Chloramphenicol (p.239·3).
Bacterial eye infections.

Metiska, Indon.
Chloramphenicol palmitate (p.239·3).
Bacterial infections.

Xepaprim *Metiska, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Xepare *Metiska, Indon.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Xepasone *Xepa-Soul Pattinson, Singapore†.*
⊗ Prednisolone (p.1540·3).
Corticosteroid.

Xepathritis *Metiska, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Xepazym *Metiska, Indon.*
Lipase (p.2360·3); amylase (p.2256·3); protease; dimeticone (p.1770·2).
Aerophagia; flatulence.

Xepin *Bioglan, Irl.†; Cambridge Healthcare, UK.*
Doxepin hydrochloride (p.389·1).
Pruritus.

Xepol *Pharmalink, Swed.*
A normal immunoglobulin (p.2225·3).
Hypogammaglobulinaemia; idiopathic thrombocytopenic purpura.

Xerac AC *Dispolab, Chile; Person & Covey, USA.*
Aluminium chloride (p.1588·2).
Hyperhidrosis.

Xeracil *Xeragen, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Xeradin *Metiska, Indon.*
Ranitidine (p.1766·1).
Pathological hypersecretory disorders; peptic ulcer.

Xeragel *Dispolab, Chile.*
Silica (p.2146·2); dimeticone (p.2032·1).
Barrier ointment; wounds.

Xeramax
Note. This name is used for preparations of different composition.
Xeragen, S.Afr.†.
Syrup: Paracetamol (p.108·1); codeine phosphate (p.37·2); promethazine hydrochloride (p.588·2).
Fever; pain.

Xeragen, S.Afr.†.
Tablets: Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain with tension.

Xeramel *Qestmed, S.Afr.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Xerand *Roche-Posay, Arg.†; Roche-Posay, Braz.; Roche-Posay, Fr.; Roche-Posay, Irl.*
Emollient.
Dry skin; skin irritation.

Xeraspor *Qestmed, S.Afr.*
Clotrimazole (p.530·1).
Fungal skin infections; vulvovaginal candidiasis.

Xerazole *Qestmed, S.Afr.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Xeredien *Valeas, Ital.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Xergic *Alphapharm, Austral.; Pacific, NZ.*
Fexofenadine hydrochloride (p.579·3).
Allergic rhinitis; urticaria.

Xerial
Note. This name is used for preparations of different composition.
SVR, Fr.
A range of emollients.
Dry skin and scalp disorders; hyperkeratotic skin disorders.

SVR, Ital.
⊗ Urea (p.1620·2); allantoin (p.1588·1); emollients.
Dry skin.

Xeristar *Boehringer Ingelheim, Cz.; Boehringer Ingelheim, Gr.; Boehringer Ingelheim, Ital.; Boehringer Ingelheim, Neth.; Boehringer Ingelheim, Port.; Boehringer Ingelheim, Spain.*
Duloxetine hydrochloride (p.389·3).
Depression; diabetic neuropathy.

Xerobase *Cassara, Arg.*
⊗ Urea (p.1620·2).
Dry skin disorders.

Xerocap *Vianex (Βιανεξ), Gr.*
Pilocarpine hydrochloride (p.1884·3).
Xerostomia.

Xerodent *Alpharma, Fin.; Alpharma, Norw.; Alpharma, Swed.*
Sodium fluoride (p.1962·2); malic acid (p.2337·1).
Dental caries prophylaxis; dry mouth.

Xeroderm *Roche-Posay, Arg.†; Roche-Posay, Fr.; Dermol, USA†.*
Emollient.
Dry skin disorders.

Xerogesic *Crown, S.Afr.†.*
Paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3); meprobamate (p.1006·2).
Pain and associated tension.

Xeroprim *Crown, S.Afr.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Xerotens *Covan, S.Afr.†.*
Doxylamine succinate (p.578·2); paracetamol (p.108·1); codeine phosphate (p.37·2); caffeine (p.1116·3).
Pain and associated tension.

Xerotic *Neo Dermos, Arg.*
Moisturiser.

Xerotil *Boniscontro & Gazzone, Ital.*
⊗ Midodrine hydrochloride (p.1341·1).
Hypotension.

Xerumenex *Meda, Belg.*
Trolamine polypeptide oleate-condensate (p.2405·1).
Cleansing of external ear before otoscopy; removal of impacted ear wax.

Xet *Zydus, India; Zydus, S.Afr.*
Paroxetine (p.414·2).
Anxiety disorders; depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Xetanor *Actavis, Pol.*
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorders; panic disorder; social phobia.

Xetin *Belmac, Spain.*
Paroxetine hydrochloride (p.414·2).
Anxiety; depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; social phobia.

Xetinol *Sandoz, Austria.*
Cefixime (p.224·3).
Bacterial infections.

Xevolac *Novell, Indon.*
Ketorolac trometamol (p.74·2).
Pain.

Xeztron *Tolmann, Philipp.*
Cefaclor (p.217·2).
Bacterial infections.

X-Flam *Combiphar, Indon.*
Diclofenac potassium (p.44·3).
Inflammation; pain.

Xflu *GSK, S.Afr.†.*
An influenza vaccine (p.2218·2).
Active immunisation.

Xibradex *Vannier, Arg.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Xibrax *Vannier, Arg.*
Tobramycin (p.354·1).
Bacterial eye infections.

Xibrom *Ista, USA.*
Bromfenac sodium (p.28·2).
Postoperative eye pain and inflammation.

Xicam *Pharmasant, Thai.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Xicane *Sanofi Synthelabo, Arg.†.*
Naproxen (p.92·3).
Gout: inflammation; musculoskeletal, joint, and periarticular disorders; pain.

Xicil *Rottapharm, Spain.*
Glucosamine sulfate (p.2313·2).
Rheumatic disorders.

Xiclav *Lannacher, Austria.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Xiclovir *Lazar, Arg.*
Aciclovir (p.862·3).
Herpesvirus infections.

Xidan EDO *Mann, Ger.*
Sodium hyaluronate (p.2320·1).
Dry eyes.

Xidanef *Codal Synto, Malaysia†; Codal Synto, Thai.†.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Xiemed *Medifive, Thai.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Xiety *Lapi, Indon.*
Buspirone hydrochloride (p.965·3).
Anxiety.

Xifaxan *Alfa Wassermann, Pol.; Salix, USA.*
Rifaximin (p.330·1).
Escherichia coli associated travellers' diarrhoea; gastrointestinal infections; hepatic encephalopathy.

Xigris *Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Canad.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, India; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.*
Drotrecogin alfa (activated) (p.1078·1).
Sepsis.

Xilanic
Note. This name is used for preparations of different composition.
Filaxis, Arg.
Paroxetine hydrochloride (p.414·2).
Depression; obsessive-compulsive disorder; panic disorder; social phobia.

Bosch, Philipp.
Amoxicillin sodium (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Xilatril *Darier, Mex.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Xilinum *Farmila, Ital.†.*
Acinetobacter xilinum; vitamins (p.1922·1).
Diarrhoea; disturbances of the intestinal flora.

Xilocler *Monserrat, Arg.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Xilodase *Apsen, Braz.*
Neomycin sulfate (p.305·1); lidocaine (p.1862·3); hyaluronidase (p.2321·1).
Infected skin disorders.

Xilo-Mynol *Curaden, Ital.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xilonibsa
Note. This name is used for preparations of different composition.
Inibsa, Spain.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in the injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Inibsa, Port.
Injection; topical spray: ⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) or noradrenaline (p.1360·1) is included in the injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Inibsa, Port.†.
Topical paste: Lidocaine hydrochloride (p.1862·3); tetracaine hydrochloride (p.1871·3).
Local anaesthesia.

Xilopar
Note. This name is used for preparations of different composition.
Filaxis, Arg.
Ribavirin (p.902·3).

Elan, Austria; Cephalon, Ger.; Zeneus, Ital.; Cephalon, Port.
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Xilox *Guidotti, Hung.*
Nimesulide (p.95·3).
Pain.

Xiltrop *Tropica Mas, Indon.*
Amoxicillin (p.202·2).
Bacterial infections.

Xim *Ipca, India.*
Cefixime (p.224·3).
Bacterial infections.

Ximaken *Kendrick, Mex.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Ximede *Combiphar, Indon.*
Nimesulide (p.95·3).
Inflammation; pain.

Ximex Cylowam *Konimex, Indon.*
Ciprofloxacin hydrochloride (p.243·3).
Eye infections.

Ximex Konigen *Konimex, Indon.*
Gentamicin sulfate (p.282·1).
Eye infections.

Ximex Opticom *Konimex, Indon.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Ximex Optixitrol *Konimex, Indon.*
⊗ Dexamethasone sodium phosphate (p.1526·2); neomycin sulfate (p.305·1); polymyxin B sulfate (p.317·3).
Infected eye disorders.

Ximovan *Aventis, Ger.*
Zopiclone (p.1039·1).
Insomnia.

Ximve *Farma-Projekt, Pol.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Xina *Finadiet, Arg.†.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal and joint disorders; pain.

Xinamin *Mavi, Mex.*
Vitamin B substances (p.1922·1).

Xinamod *Proge, Ital.*
Amoxicillin trihydrate (p.202·2); potassium clavulanate (p.250·2).
Bacterial infections.

Xinder *D & M, Chile.*
⊗ Clobetasol propionate (p.1522·2).
Skin disorders.

Xinebrom *Virgo, Philipp.*
Bromhexine hydrochloride (p.1552·2).
Respiratory-tract congestion.

Xinflex *Terramedic, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Xinplex *Craveri, Arg.*
Orlistat (p.2358·1).
Obesity.

Xinsidona *Padro, Spain.*
Pamidronate disodium (p.1101·1).
Hypercalcaemia of malignancy; osteolytic bone lesions; Paget's disease of bone.

Xintoprost *Richmond, Arg.†.*
Vinblastine (p.786·3).
Malignant neoplasms.

Xipa *TAD, Ger.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Xipagamma *Worwag, Ger.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Xipa-Isis *Alpharma-Isis, Ger.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Xipamid *German Remedies, India.*
⊗ Xipamide (p.1434·1).
Hypertension; oedema.

Xipen *Best, Mex.*
Pentoxifylline (p.1367·2).
Cerebral, ocular, and peripheral vascular disorders.

Xipral *Silanes, Mex.*
Pravastatin sodium (p.1374·3).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Xiprine *Swedpharm, Chile.*
Glipizide (p.441·3).
Diabetes mellitus.

Xipro *Terramedic, Philipp.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Xiprocan *Protein, Mex.†.*
Amoxicillin (p.202·2).
Bacterial infections.

XiraHist DM *Hawthorn, USA.*
Dextromethorphan hydrobromide (p.1555·2); carbinoxamine maleate (p.570·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Xiral *Hawthorn, USA†.*
Chlorphenamine maleate (p.571·3); pseudoephedrine hydrochloride (p.1571·2); hyoscine methonitrate (p.1734·2).
Allergic rhinitis; cold symptoms; sinusitis.

XiraTuss *Hawthorn, USA.*
Pentoxyverine tannate (p.1567·3); chlorphenamine tannate (p.572·2); phenylephrine tannate (p.1568·3).
Coughs; nasal congestion.

Xismox *Genus, UK.*
Isosorbide mononitrate (p.1318·3).

Xiten *Grunenthal, Chile†.*
⊗ Beclometasone dipropionate (p.1516·2).
Obstructive airways disease.

Xitocin *Cryopharma, Mex.*
Oxytocin (p.2015·2).
Labour induction; postpartum haemorrhage; uterine atony.

Xitrocin *Polfa Pabianice, Pol.*
Roxithromycin (p.331·1).
Bacterial infections.

XLEU Analog *SHS, Fr.*
Food for special diets (p.1922·1).
Isovaleric acidaemia.

XLYS Analog *SHS, Fr.*
Food for special diets (p.1922·1).
Hyperlysinaemia.

XLYS Low Try Analog *SHS, Fr.*
Food for special diets (p.1922·1).
Glutaric aciduria.

XLys Low Try Maxamaid *Scientific Hospital Supplies, UK.*
Lysine- and tryptophan-free food (p.1922·1).
Glutaric aciduria.

X-M *Yenisehir, Turk.*
Calcium sennosides (p.1770·1) (p.1770·1).
Bowel evacuation; constipation.

X-Met *Glenmark, India.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Xmet *Glenmark, Malaysia; Glenmark, Philipp.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

XMET Analog *Scientific Hospital Supplies, Austral.; SHS, Fr.; Scientific Hospital Supplies, Irl.*
Infant feed (p.1922·1).
Homocystinuria; hypermethioninaemia.

XMET, Cys Analog *SHS, Fr.*
Food for special diets (p.1922·1).
Sulfite oxidase deficiency.

XMET Homidon *Scientific Hospital Supplies, Irl.*
Food for special diets (p.1922·1).
Homocystinuria; hypermethioninaemia.

XMET Maxamaid *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, Irl.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Formerly known as Maxamaid RVHB in the *UK*.
Homocystinuria; hypermethioninaemia.

XMET Maxamum *Scientific Hospital Supplies, Austral.; Support, Braz.†; Scientific Hospital Supplies, Irl.; Nutricia, NZ; Scientific Hospital Supplies, NZ.*
Food for special diets (p.1922·1).
Homocystinuria; hypermethioninaemia.

XMTVI Analog *Scientific Hospital Supplies, Austral.; Support, Braz.†; SHS, Fr.; SHS, Israel.*
Infant feed (p.1922·1).
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Asadon *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Maxamaid *Scientific Hospital Supplies, Austral.; Support, Braz.†; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Formerly known as Maxamaid XMET, THRE, VAL, ISOLEU in the *UK*.
Methylmalonic acidaemia; propionic acidaemia.

XMTVI Maxamum *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).
Formerly known as XMet, Thre, Val, Isoleu Maxamum.
Methylmalonic acidaemia; propionic acidaemia.

Xodol *Victory, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Xofemina *Farmaceutica H, Mex.*
Medroxyprogesterone acetate (p.2113·1); estradiol cipionate (p.2097·2).
Injectable contraceptive.

Xolaam *Ranbaxy, Fr.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2).
Gastrointestinal disorders.

Xolair *Novartis, Arg.; Novartis, Austral.; Novartis, Belg.; Novartis, Canad.; Novartis, Cz.; Novartis, Fr.; Novartis, Gr.; Novartis, Hung.; Novartis, Israel; Novartis, Malaysia; Novartis, NZ; Novartis, Pol.; Novartis, Port.; Novartis, Singapore; Novartis, Swed.; Novartis, UK; Genentech, USA; Novartis, Venez.*
Omalizumab (p.1128·2).
Asthma.

Xolegel *Barrier Therapeutics, USA.*
Ketoconazole (p.539·1).
Fungal skin infections.

Xolegel Duo *Barrier Therapeutics, USA.*
Topical gel, ketoconazole (p.539·1); shampoo, pyrithione zinc (p.1611·2).
Seborrhoeic dermatitis.

Xolin *Ratiopharm, Norw.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Rhinitis; sinusitis.

Xolof *Saval, Chile.*
Tobramycin (p.354·1).
Bacterial eye infections.

Xolof D *Saval, Chile.*
⊗ Tobramycin (p.354·1); dexamethasone (p.1526·1).
Infected eye disorders.

Xolvax *Vivax, Venez.*
Ambroxol hydrochloride (p.1550·3).

Xomolix *ProStrakan, Cz.; ProStrakan, Port.*
Droperidol (p.994·3).
Nausea and vomiting.

Xonatil *Precimex, Mex.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Xon-Ce *Kalbe, Indon.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Xopenex *Sepracor, USA.*
⊗ Levosalbutamol hydrochloride (p.1125·3) or levosalbutamol tartrate (p.1125·3).
Obstructive airways disease.

Xorim *Sandoz, Hung.; Sandoz, Pol.; Sandoz, Venez.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Xorimax *Sandoz, Cz.; Sandoz, Hung.; Sandoz, Philipp.; Sandoz, Pol.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Xorin *Pyridam, Indon.*
Roxithromycin (p.331·1).
Bacterial infections.

Xorovir *Kwizda, Pol.*
Aciclovir (p.862·3).
Herpesvirus infections.

Xorox
Kwizda, Austria; Kwizda, Cz.†.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections.

Kite (Κιτε), Gr.†; Filiz, Turk.
Aciclovir (p.862·3).
Herpesvirus infections.

Xorpic *Andromaco, Port.†; Grunenthal, Port.†.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Xorufec *Antibioticos, Mex.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Xotilon *Pyridam, Indon.*
Tenoxicam (p.128·2).
Musculoskeletal, joint, and peri-articular disorders.

Xozacil *Columbia, Mex.†.*
Benzylpenicillin sodium (p.213·1).
Bacterial infections.

Xozal *UCB, Gr.*
Levocetirizine hydrochloride (p.583·2).
Hypersensitivity reactions.

XP Analog *Scientific Hospital Supplies, Austral.; Support, Braz.†; SHS, Israel; Nutricia, Ital.; Nutricia, NZ; Scientific Hospital Supplies, NZ.*
Infant feed (p.1922·1).
Phenylketonuria.

XP Analog LCP *SHS, Fr.; Scientific Hospital Supplies, Irl.*
Food for special diets (p.1922·1).
Formerly known as Analog XP in *Fr.*
Phenylketonuria.

XP Maxamaid *Scientific Hospital Supplies, Austral.; Support, Braz.†; SHS, Fr.; Scientific Hospital Supplies, Irl.; SHS, Israel; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

XP Maxamum *Scientific Hospital Supplies, Austral.; Support, Braz.†; SHS, Fr.; Scientific Hospital Supplies, Irl.; SHS, Israel; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Phenylketonuria.

X-Pain *ST, Thai.*
Methyl salicylate (p.85·3); eugenol (p.2301·2); menthol (p.2340·1).
Musculoskeletal, joint, and soft-tissue disorders.

Xpe SPC *Faria, Braz.†.*
Sulfogaiacol (p.1573·2); sodium benzoate (p.1630·2); bromoform (p.2269·3); grindelia (p.2317·2).
Coughs.

Xpect *Hawthorn, USA.*
Guaifenesin (p.1561·3).
Coughs.

Xpect-AT *Hawthorn, USA.*
Guaifenesin (p.1561·3); pentoxyverine citrate (p.1567·3).
Coughs; respiratory-tract congestion.

Xpect-PE *Hawthorn, USA.*
Guaifenesin (p.1561·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract congestion.

Xphen Tyr Analog *SHS, Israel.*
Food for special diets (p.1922·1).
Phenylketonuria; tyrosinaemia.

XPhen, Tyr Analog *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).
Tyrosinaemia.

Xphen, Tyr Analog *SHS, Fr.*
Food for special diets (p.1922·1).
Tyrosinaemia.

XPhen, Tyr Maxamaid *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Tyrosinaemia.

XPhen, Tyr Maxamum *Scientific Hospital Supplies, Austral.*
Food for special diets (p.1922·1).
Tyrosinaemia.

X-Praep *Viatris, Neth.*
Sennosides (p.1769·3).
Bowel evacuation; constipation.

X-Prep
Mundipharma, Austria; Purdue, Canad.; Mundipharma, Cz.†; Mundipharma, Ger.†; Lavipharm, Gr.; Viatris, Ital.; Ferring, Mex.; Mundipharma, Norw.; Meda, Port.; Mundipharma, Switz.; Gray, USA.
Senna (p.1769·2).
Bowel evacuation; constipation.

Viatris, Fr.; Extractum, Hung.; Mundipharma, Hung.; Norpharma, Pol.; Adcock Ingram, S.Afr.; Viatris, Spain.
Sennosides A and B (p.1769·3).
Bowel evacuation.

X-Prep Bowel Evacuant Kit-1 *Gray, USA.*
Combination pack: 2 tablets, standardised senna concentrate (p.1769·2); docusate sodium (p.1725·1) (Senokot-S); oral liquid, senna (X-Prep); 1 suppository, bisacodyl (Rectolax) (p.1710·1).
Bowel evacuation.

XPT Analog *Support, Braz.†.*
Tyrosine and phenylalanine-free food for special diets (p.1922·1).
Tyrosinaemia.

XPT Maxamaid *Support, Braz.†.*
Tyrosine and phenylalanine-free food for special diets (p.1922·1).
Tyrosinaemia.

XPT Tyrosidon *Scientific Hospital Supplies, UK.*
Tyrosine- and phenylalanine-free amino-acid preparation (p.1922·1).
Tyrosinaemia.

XPTM Analog *SHS, Fr.†.*
Food for special diets (p.1922·1).
Tyrosinaemia.

XPTM Tyrosidon *Scientific Hospital Supplies, Austral.; Scientific Hospital Supplies, UK.*
Food for special diets (p.1922·1).
Tyrosinaemia.

X-Seb *Pharmascience, Canad.; Baker Cummins, USA.*
Salicylic acid (p.1612·2).
Seborrhoea; skin and scalp disorders.

X-Seb Plus *Pharmascience, Canad.; Baker Cummins, USA.*
Pyrithione zinc (p.1611·2); salicylic acid (p.1612·2).
Scalp disorders.

X-Seb T *Pharmascience, Canad.; Baker Cummins, USA.*
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Scalp disorders; seborrhoea.

X-Seb T Plus
Note. This name is used for preparations of different composition.
Pharmascience, Canad.
Salicylic acid (p.1612·2); coal tar (p.1616·2); menthol (p.2340·1).
Scalp disorders.

Ivax, USA.
Salicylic acid (p.1612·2); coal tar (p.1616·2).
Formerly contained salicylic acid, coal tar, and menthol.
Scalp disorders.

Xsert *Cadila, India.*
Sertraline hydrochloride (p.421·3).
Depression.

X'tac *Upha, Malaysia.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; reduction of gastric acid secretion; Zollinger-Ellison syndrome.

X-Tar *Dormer, Canad.*
Salicylic acid (p.1612·2); coal tar (p.1616·2); menthol (p.2340·1).
Scalp disorders.

X-Tardine *Pharmasant, Thai.*
Povidone-iodine (p.1659·2).
Skin disinfection.

Xtenda *Orchid, Philipp.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Xtendrol *Atlantis, Mex.*
⊗ Oxandrolone (p.2123·2).
Anabolic; osteoporosis; Turner's syndrome.

X'tor *Ipca, India.*
Atorvastatin calcium (p.1218·3).
Hyperlipidaemias.

Xtrair *Behrens, Venez.*
Eucalyptus oil (p.2301·2); camphor (p.2273·2).

X-Trant *Natco, India.*
Estramustine phosphate (p.717·3).
Prostatic cancer.

Xuclamin *Sons, Mex.*
Clarithromycin (p.248·2).
Bacterial infections.

Xumadol *ITF, Chile; Italfarmaco, Spain.*
Paracetamol (p.108·1).
Fever; pain.

Xuprin *Solvay, Austria.*
Isoxsuprine resinate (p.2327·3).
Peripheral vascular disorders.

Xuric *Craveri, Arg.*
Colchicine (p.556·1).
Gout.

Xuric-A *Craveri, Arg.*
Colchicine (p.556·1); allopurinol (p.552·2).
Gout.

Xusal *UCB, Ger.*
Levocetirizine hydrochloride (p.583·2).
Hypersensitivity reactions.

Xuzal *UCB, Mex.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; urticaria.

Xycalm *Ipca, India.*
Alprazolam (p.960·1).
Anxiety.

Xycam *Pharmacare, S.Afr.*
Piroxicam (p.117·3).
Gout; musculoskeletal and joint disorders.

Xyclomed *Korea United, Philipp.*
Cyclophosphamide (p.702·1).
Malignant neoplasms.

Xydep *Arrow, Austral.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; premenstrual dysphoric disorder; social phobia.

Xylanaest *Gebro, Austria.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylesine *Amino, Switz.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Xylestesin
Note. This name is used for preparations of different composition.
Espe, Austria; Espe, Switz.†.
Lidocaine (p.1862·3); cetrimonium bromide (p.1635·1).
Local anaesthesia.

Cristalia, Braz.
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) or noradrenaline acid tartrate (p.1360·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Espe, Cz.†.
Lidocaine (p.1862·3).
Local anaesthesia.

Xylestesin Pumpspray *3M Espe, Ger.†.*
Lidocaine (p.1862·3); cetrimonium bromide (p.1635·1).
Local anaesthesia.

Xylestesin, Xylestesin-F *3M Espe, Ger.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Noradrenaline hydrochloride (p.1360·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-A *3M, Cz.†; Espe, Cz.†; 3M, Hong Kong; 3M, NZ.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-A, Xylestesin centro *3M Espe, Ger.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-F *Espe, Switz.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Noradrenaline hydrochloride (p.1360·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-S *3M Espe, Ger.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Noradrenaline hydrochloride (p.1360·2) and adrenaline hydrochloride (p.1203·3) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylestesin-S "special" *Espe, Switz.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline hydrochloride (p.1203·3) and noradrenaline hydrochloride (p.1360·2) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylia *Sandoz, Austria.*
Cyproterone acetate (p.2088·2); ethinylestradiol (p.2101·3).
Androgen-associated acne and hirsutism in women.

Xylisol *Cassara, Arg.*
Sodium chloride (p.1686·1).
Nasal hygiene; sinusitis.

Xylit *Braun, Ger.; DeltaSelect, Ger.*
Xylitol (p.1998·2).
Carbohydrate source; fluid disorders.

Xylo *CT, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Xylo Siozwo *Febena, Ger.†.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Xylocain
AstraZeneca, Austria; AstraZeneca, Denm.; AstraZeneca, Fin.; Dentsply, Fin.; AstraZeneca, Ger.; Dentsply, Ger.; AstraZeneca, Norw.; AstraZeneca, Swed.; AstraZeneca, Switz.
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Arrhythmias; endoscopy; local anaesthesia; pain.

AstraZeneca, Turk.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Xylocain CO_2 *AstraZeneca, Switz.*
Lidocaine (p.1862·3); carbon dioxide.
Local anaesthesia.

Xylocain f.d. Kardiologie *AstraZeneca, Ger.*
Lidocaine hydrochloride (p.1862·3).
Arrhythmias.

Xylocaina
AstraZeneca, Arg.; AstraZeneca, Braz.; AstraZeneca, Chile; AstraZeneca, Ital.; Dentsply, Ital.; AstraZeneca, Mex.
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2), adrenaline acid tartrate (p.1203·2), or noradrenaline (p.1360·1) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia; pain.

AstraZeneca, Port.; Inibsa, Spain.
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

AstraZeneca, Venez.†.
Lidocaine (p.1862·3).
Local anaesthesia.

Xylocaine
AstraZeneca, Austral.; Dentsply, Austral.; AstraZeneca, Canad.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, India; AstraZeneca, In-

don.; AstraZeneca, Irl.; AstraZeneca, Malaysia; AstraZeneca, Neth.; AstraZeneca, Singapore; AstraZeneca, Thai.; AstraZeneca, USA.
⊗ Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) or adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Arrhythmias; catheterisation; endoscopy; instrument insertion; local anaesthesia; pain.

AstraZeneca, Cz.; AstraZeneca, Israel; AstraZeneca, S.Afr.
Lidocaine (p.1862·3).
Endoscopy; local anaesthesia.

AstraZeneca, Fr.; AstraZeneca, NZ; Dentsply, NZ; AstraZeneca, Philipp.; AstraZeneca, Pol.
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2), adrenaline acid tartrate (p.1203·2), or naphazoline nitrate (p.1565·2) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

AstraZeneca, Belg.
Injection: ⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

AstraZeneca, UK; Dentsply, UK.
Injection; topical solution: ⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline tartrate (p.1203·2) is included in the injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

AstraZeneca, Belg.
Ointment; topical gel; topical spray: Lidocaine (p.1862·3) or lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

AstraZeneca, UK.
Topical spray: Lidocaine (p.1862·3).
Local anaesthesia; minor skin injuries.

Xylocaine with Chlorhexidine *AstraZeneca, NZ†.*
Lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Local anaesthesia.

Xylocaine Jelly with Chlorhexidine *AstraZeneca, Austral.*
Lidocaine hydrochloride (p.1862·3); chlorhexidine gluconate (p.1635·3).
Catheterisation; endoscopy; local anaesthesia.

Xylocaine Special Adhesive *AstraZeneca, Austral.*
Lidocaine hydrochloride (p.1862·3).
Topical anaesthesia in dentistry.

Xylocaine Visquese *AstraZeneca, Belg.*
Lidocaine hydrochloride (p.1862·3).
Adjunct in radiology and endoscopy; painful oral and oesophageal conditions.

Xylocard *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Canad.; AstraZeneca, Fr.; AstraZeneca, Hong Kong†; AstraZeneca, India; AstraZeneca, Malaysia†; AstraZeneca, NZ; AstraZeneca, Philipp.; AstraZeneca, Port.†; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.†.*
Lidocaine hydrochloride (p.1862·3).
Status epilepticus; ventricular arrhythmias.

Xylocitin *Jenapharm, Ger.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylocitin cor *Jenapharm, Ger.*
Lidocaine hydrochloride (p.1862·3).
Ventricular arrhythmias.

Xylo-COMOD *Croma, Austria; Ursapharm, Cz.; Ursapharm, Ger.†; Ursapharm, Neth.; Biem, Turk.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; rhinitis; sinusitis.

Xyloderm *AstraZeneca, Mex.*
⊗ Lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2); clotrimazole (p.530·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Xylogel
Note. This name is used for preparations of different composition.
Pediapharma, Philipp.
Xylitol (p.1998·2).
Dental caries prophylaxis; gum, mouth and lip sores; teething pain.

Polfa Warszawa, Pol.
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; otitis media; sinusitis.

Xylol *Demo, Gr.*
Lidocaine (p.1862·3).
Local anaesthesia.

Xylolin *Julphar, UAE.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal and sinus congestion.

Xyloma *Jean-Marie, Hong Kong.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; otitis media.

Xylo-Mepha *Mepha, Switz.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Xylonest *AstraZeneca, Ger.; Dentsply, Ger.; AstraZeneca, Switz.*
⊗ Prilocaine hydrochloride (p.1868·2).
Adrenaline acid tartrate (p.1203·2) or felypressin (p.2302·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xyloneural *Gebro, Austria; Strathmann, Ger.; Gebro, Switz.*
Lidocaine hydrochloride (p.1862·3).
Headache; local anaesthesia; migraine; tinnitus; vertigo.

Xylonor
Note. This name is used for preparations of different composition.
Schein, Austria.
Lidocaine (p.1862·3); cetrimide (p.1634·1).
Local anaesthesia.

Prats, Spain.
Lidocaine hydrochloride (p.1862·3); cetrimonium bromide (p.1635·1).
Local anaesthesia.

Ogna, Ital.
Injection: ⊗ Lidocaine hydrochloride (p.1862·3).
Noradrenaline acid tartrate (p.1360·1) or adrenaline acid tartrate (p.1203·2) is included in some injections as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Ogna, Ital.; Septodont, Switz.
Topical spray: Lidocaine (p.1862·3); cetrimonium bromide (p.1635·1).
Local anaesthesia.

Xylonor Especial *Prats, Spain.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline (p.1203·2) and noradrenaline acid tartrate (p.1360·1) are included in this preparation as vasoconstrictors to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylonor 2% Sin Vasoconst *Prats, Spain.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Xyloplyin *Dentsply, Denm.; Globopharm, Switz.†.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this injection as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xyloplyina *Dentsply, Ital.*
⊗ Lidocaine hydrochloride (p.1862·3).
Adrenaline acid tartrate (p.1203·2) is included in this preparation as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylo-POS *Ursapharm, Ger.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Xyloproct
Note. This name is used for preparations of different composition.
AstraZeneca, Austral.; AstraZeneca, Fin.†; AstraZeneca, Irl.; AstraZeneca, NZ; AstraZeneca, Swed.; AstraZeneca, UK.
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium acetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders; pruritus vulvae.

AstraZeneca, Braz.; AstraZeneca, Norw.
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium subacetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

AstraZeneca, Hong Kong; Astra, Israel†.
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

AstraZeneca, Malaysia.
⊗ Lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium subacetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

Xyloproct Plus *AstraZeneca, Mex.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2); aluminium subacetate (p.2255·1); zinc oxide (p.1621·2).
Anorectal disorders.

Xyloprocto *AstraZeneca, Arg.*
⊗ Lidocaine (p.1862·3); hydrocortisone acetate (p.1535·2).
Anorectal disorders.

Xylorane *Ranbaxy, Mex.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Xylorin *GSK, Pol.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; sinusitis.

Xylorinse *Pediapharma, Philipp.*
Xylitol (p.1998·2); sodium fluoride (p.1962·2); cetylpyridinium chloride (p.1635·1).
Dental caries prophylaxis; oral hygiene.

Xylotocan *AstraZeneca, Ger.†.*
Tocainide hydrochloride (p.1415·1).
Ventricular arrhythmias.

Xylotox *Adcock Ingram, S.Afr.; Dentsply, UK†.*
⊗ Lidocaine hydrochloride(p.1862·3).
Adrenaline (p.1203·2), adrenaline acid tartrate (p.1203·2), or noradrenaline (p.1360·1) is included in some preparations as a vasoconstrictor to diminish absorption and localise the effect of the local anaesthetic.
Local anaesthesia.

Xylovit *Vitamed, Israel.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion.

Xylozan *Demo, Gr.*
Lidocaine (p.1862·3).
Local anaesthesia.

Xymel *Clonmel, Irl.*
Tramadol hydrochloride (p.130·3).
Pain.

Xymelin *Nycomed, Rus.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Nasal congestion; otitis media; sinusitis.

Xyntha *Wyeth, USA.*
A factor VIII preparation (recombinant) (p.1067·1).
Haemophilia A.

Xyralid *Auriga, USA.*
⊗ Lidocaine hydrochloride (p.1862·3); hydrocortisone acetate (p.1535·2).
Skin disorders.

Xyrem *UCB, Cz.; UCB, Neth.; UCB, Port.; UCB, UK; Orphan Medical, USA.*
Sodium oxybate (p.1794·2).
Cataplexy in narcoleptic syndrome.

Xyzal *UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Hong Kong; UCB, Hung.; UCB, Indon.; UCB, Irl.; UCB, Ital.; UCB, Malaysia; UCB, Neth.; UCB, Norw.; UCB, Philipp.; Vedim, Pol.; UCB, Port.; UCB, Rus.; UCB, S.Afr.; UCB, Singapore; UCB, Switz.; UCB, Thai.; UCB, UK; UCB, USA.*
Levocetirizine hydrochloride (p.583·2).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Xyzall *UCB, Austria; UCB, Belg.; UCB, Fr.*
Levocetirizine hydrochloride (p.583·2).
Allergic rhinitis; urticaria.

8Y *Galenica, Gr.*
A factor VIII preparation (p.1067·1).
Haemorrhagic disorders.

Yacesal *Smaller, Spain.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Yacriton *Flupal, Venez.*
Vitamin B substances; inositol (p.1922·1).

Yacutin *Boots Healthcare, Spain.*
Benzyl benzoate (p.2036·1); lindane (p.2045·3).
Pediculosis; scabies.

Yadegal Compuesto *Rayere, Mex.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); chlorphenamine maleate (p.571·3).
Coughs; respiratory-tract congestion.

Yadid *Gezzi, Arg.*
Urea hydrogen peroxide (p.1666·2).
Ear wax removal.

Yadine *Schering, Cz.; Bayer Schering, Hung.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Yakona *Tentan, Switz.*
St John's wort (p.422·3).
Nervous disorders.

Yakona N *Tentan, Switz.†.*
St John's wort (p.422·3); kava (p.2328·3).
Anxiety; nervous tension.

Yal *Jacoby, Austria; Trommsdorff, Cz.; Trommsdorff, Ger.; Trommsdorff, Hung.†; Gebro, Switz.*
Docusate sodium (p.1725·1); sorbitol (p.1965·1).
Bowel evacuation; constipation.

Yalone *Yarindo, Indon.*
⊗ Methylprednisolone (p.1538·1).
Corticosteroid.

Yalta Corn Salve *Technikon, S.Afr.*
Salicylic acid (p.1612·2).
Callouses; corns.

Yalu *Lacefa, Arg.†.*
Quassia (p.2377·1); acetic acid (p.2244·2).
Pediculosis.

Yamatetan *Yamanouchi, Jpn†.*
Cefotetan disodium (p.229·3).
Bacterial infections.

Yamcon *Sidus, Arg.†.*
Wild yam.
Menopausal disorders.

Yanal *Benitol, Arg.*
⊗ Atropine (p.1219·2); adrenaline (p.1203·2).
Asthma.

Yanthi Baby & Bath Powder *Minorock Mandiri, Indon.*
Zinc oxide (p.1621·2); magnesium carbonate (p.1743·1); talc (p.1615·2).
Nappy rash; skin irritation.

Yanthi Baby Oil *Minorock Mandiri, Indon.*
Wool fat (p.2033·2); nipagin; coconut oil (p.2029·2); liquid paraffin (p.2030·3).
Emollient.

Yanurax *Fada, Arg.†.*
Norfloxacin (p.309·2).
Bacterial infections.

Yapamicin *Novag, Mex.*
Ampicillin (p.204·1).
Bacterial infections.

Yara *Pharmacypria, Gr.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer.

Yariba *Dendron, UK.*
Kola (p.2416·1).
Fatigue.

Yariflam *Yarindo, Indon.*
Diclofenac potassium (p.44·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Yarina *Schering, Rus.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Yarisma *Yarindo, Indon.*
⊗ Terbutaline sulfate (p.1138·3).
Obstructive airways disease.

Yariven *Yarindo, Indon.*
Ibuprofen (p.64·2).
Fever; pain.

Yasmin *Schering, Arg.; Schering, Austral.; Schering, Austria; Schering, Belg.; Schering, Braz.; Berlex, Canad.; Schering, Chile; Schering, Denm.; Schering, Fin.; Schering, Ger.; Schering, Gr.; Schering, Hong Kong; Schering, Indon.; Schering, Irl.; Schering, Israel; Schering, Ital.; Bayer Schering, Malaysia; Schering, Mex.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Philipp.; Schering, Pol.; Bayer, Port.; Schering, S.Afr.; Schering, Singapore; Schering, Spain; Schering, Swed.; Schering, Switz.; Schering, Thai.; Schering, Turk.; Bayer, UK; Bayer, USA; Schering, Venez.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Yasminelle *Schering, Arg.; Schering, Cz.; Bayer Schering, Hung.; Schering, Neth.; Schering, Pol.; Berlex, Port.*
Drospirenone (p.2095·2); ethinylestradiol betadex clathrate (p.2102·1).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Yasnal *KRKA, Cz.; KRKA, Pol.*
Donepezil hydrochloride (p.364·3).
Alzheimer's disease.

Yasta
Note. This name is used for preparations of different composition.
Bayer Consumer, Arg.
Sodium bicarbonate (p.1673·2); sodium carbonate (p.2389·1); caffeine (p.1116·3); tartaric acid; sodium citrate.
Dyspepsia; gastric hyperacidity.

Bayer, Chile.
Aspirin (p.20·3); sodium bicarbonate (p.1673·2); citric acid (p.2284·1).
Dyspepsia; pain.

Yatrox *Vita, Spain.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Yatushan Plus *Trima, Israel†.*
Diphenhydramine hydrochloride (p.577·2); diethyltoluamide (p.2041·1); dimethyl phthalate (p.2041·3).
Insect bites; insect repellent.

Yavon *Yarindo, Indon.*
Bromhexine hydrochloride (p.1552·2).
Cough.

YAZ *Schering, Braz.; Bayer, USA.*
Drospirenone (p.2095·2); ethinylestradiol betadex clathrate (p.2102·1).
Acne; combined oral contraceptive; premenstrual dysphoric disorder; premenstrual syndrome.

Ybecor *Rafarm, Gr.*
⊗ Fluticasone (p.1533·2).
Allergic rhinitis; skin disorders.

Yderm *Liferpal, Mex.*
⊗ Clioquinol (p.254·1); fluocinolone (p.1531·3).
Infected skin disorders.

Ydroquinidine *Remek, Gr.*
Quinidine (p.1383·1).
Arrhythmias.

Ye & To *Landson, Indon.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); guaifenesin (p.1561·3).
Cold and influenza symptoms.

Yeast Clear *Dolisos, Canad.†.*
Homoeopathic preparation.

Yeast Vite *Thornton & Ross, UK.*
Caffeine (p.1116·3); vitamin B substances (p.1922·1); dried yeast (p.1998·3).
Tonic.

Yeastafort *Kimia, Indon.*
Brewer's yeast; vitamin B ; vitamin B ; nicotinamide (p.1922·1).
Acne vulgaris; vitamin B deficiency.

Yeast-Gard *Lake, USA.*
Homoeopathic preparation.

Yeast-X
Note. This name is used for preparations of different composition.
Fleet, USA†.
Powder: Corn starch (p.1968·1); zinc oxide (p.1621·2).

Fleet, USA†.
Suppositories: Pulsatilla (p.2376·3).

Yectafer *AstraZeneca, Arg.*
Iron sorbitol (p.1953·1).
Iron-deficiency anaemia.

Yectafer Complex *AstraZeneca, Arg.*
Iron sorbitol (p.1953·1); folic acid (p.1940·1); hydroxocobalamin (p.1980·3).
Anaemias.

Yectames *Grossman, Mex.*
Algestone acetophenide (p.2082·1); estradiol enantate (p.2097·3).
Injectable contraceptive.

Yectamicina *Grossman, Mex.; Novapharma, Venez.†.*
Gentamicin sulfate (p.282·1).
Bacterial infections.

Yectamid *Collins, Mex.*
Amikacin sulfate (p.200·3).
Gram-negative bacterial infections.

Yectaspirin *Northia, Arg.*
Lysine aspirin (p.79·1).

Yectolin *Grossman, Mex.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Yelets *Freeda, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Yellon *Zentiva, Cz.*
Aescin beta (p.2248·2).
Inflammation; oedema; venous insufficiency.

Yelnac *CS, Fr.†.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Yemifer-HE *Ultra, Mex.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1).
Folate deficiency; iron-deficiency anaemia.

Yendol *Faes, Spain.*
Caffeine (p.1116·3); chlorphenamine maleate (p.571·3); paracetamol (p.108·1); salicylamide (p.121·2).
Cold and influenza symptoms; coughs.

Yenizin *Yeni, Turk.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Yentreve *Lilly, Belg.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Boehringer Ingelheim, Ger.; Lilly, Ger.; Lilly, Gr.; Lilly, Irl.; Lilly, Ital.; Boehringer Ingelheim Promeco, Mex.; Lilly, Neth.; Lilly, Norw.; Lilly, Port.; Boehringer Ingelheim, Swed.; Lilly, Swed.; Lilly, UK.*
Duloxetine hydrochloride (p.389·3).
Stress urinary incontinence in women.

Yepotin *Ivax, Mex.*
⊗ Epoetin alfa (p.1061·1).
Anaemias; autologous blood transfusion.

Yerba Diet *ISA, Arg.*
Vitamin B ; magnesium; mate (p.2416·1); bladderwrack (p.2384·2); green tea (p.2416·1); passion flower (p.2363·2) (p.1922·1).
Dietary supplement.

Yerba Santa *Roemmers Osmoph, Venez.*
Sodium benzoate (p.1630·2); polygala (p.1572·3); pentoxyverine citrate (p.1567·3); eriodictyon (p.1560·2); tolu balsam (p.1574·2).
Cough.

Yesan *Rafarm, Gr.*
⊗ Timolol maleate (p.1412·3).
Glaucoma.

Yestamin *Peter Black, UK.*
Vitamin B substances; ascorbic acid; iron (p.1922·1).

Yesterday *Argenfarma, Arg.†.*
Sulfathiazole (p.343·2).

YF-Vax *Sanofi Pasteur, Canad.; Sanofi Pasteur, USA.*
A yellow fever vaccine (17D strain) (p.2243·2).
Active immunisation.

Ygielle *Frezyderm, Gr.*
Clindamycin phosphate (p.251·2).
Vaginal infections.

Yira *Schering, Neth.; Schering, Spain†.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Yirala *Schering, Austria.*
Drospirenone (p.2095·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

Yisadin *Spefar, Venez.*
Erythromycin estolate (p.269·3).
Bacterial infections.

Yisafer *Spefar, Venez.*
Ferrous gluconate (p.1939·1).
Iron-deficiency anaemia.

Ylox *Fortbenton, Arg.*
Minoxidil (p.1342·1).
Alopecia.

Ymea
Note.This name is used for preparations of different composition.
Chefaro, Spain.
Cimicifuga (p.2282·1).
Menopausal disorders.

Chefaro, UK.
Soya (p.1965·3); lupulus (p.2335·2); cucurbita (p.2290·2).
Menopausal disorders.

Yocon *Glenwood, Austria; Glenwood, Canad.; Laboratorios Chile, Chile; Glenwood, Ger.; Glenwood, USA.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Yocoral *Infarmed, Belg.; Intsel, Fr.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Yodacua *Manuell, Mex.*
Povidone-iodine (p.1659·2).
Water purification.

Yodalmina *Vita, Venez.†.*
Iodine (p.2169·2); sodium iodide (p.2169·2); salicylic acid (p.1612·2); benzoic acid (p.1630·2).
Skin disinfection; skin infections.

Yodasep *Galeno, Venez.†.*
Povidone-iodine (p.1659·2).
Skin disinfection; skin infections.

Yodine *Manuell, Mex.*
Povidone-iodine (p.1659·2).
Infected burns, ulcers, or wounds; mouth and throat infections; seborrhoeic dermatitis; skin infections; skin, mucous membrane, and instrument disinfection; vaginal infections.

Yodofrixon Salicilado *Purissimus, Arg.†.*
Methyl salicylate (p.85·3); iodine (p.2169·2).

Yodolactina *Manuell, Mex.*
Iodocasein (p.2170·1).
Goitre; immunostimulant; obesity; obstructive airways disease; rheumatoid disorders; sclerosis; tuberculosis.

Yodolin *Hexa, Arg.*
Sodium picosulfate (p.1771·1).
Constipation.

Yodon *Sam-On, Israel.*
Povidone-iodine (p.1659·2).
Burns; skin disorders; wounds.

Yodoxin *Glenwood, USA.*
Diiodohydroxyquinoline (p.832·1).
Intestinal amoebiasis.

Yodozona *Offenbach, Mex.*
Furazolidone (p.834·3); clioquinol (p.254·1); pectin (p.2145·2); kaolin (p.1738·1); homatropine methylbromide (p.1881·3).
Diarrhoea.

Yodsaben *Nufarindo, Indon.*
Salicylic acid (p.1612·2); benzoic acid (p.1630·2); iodine (p.2169·2).
Fungal skin infections.

Yoduk *Recordati, Spain.*
Potassium iodide (p.2169·2).
Iodine deficiency.

Yohimex *Fortbenton, Arg.†.*
Yohimbine (p.2200·3).

Yokel *Bros, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Yokukansan *Tsumura, Jpn.*
Atractylodes lancea rhizome; poria sclerotium; cnidium rhizome; uncaria thorn; Japanese angelica root; bupleurum root; liquorice.
Traditional Kampo medicine.

Yolecol *Altana, Arg.*
Mesalazine (p.1745·1).
Anorectal disorders; proctitis; ulcerative colitis.

Yomax *Apsen, Braz.*
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction; orthostatic hypotension.

Yomesan *Bayer, Belg.; Bayer, Cz.†; Bayer, Denm.†; Bayer, Ger.; IFET (ΙΦΕΤ), Gr.; Bayer, Israel; Bayer, Ital.; Bayer, Neth.; Bayer, S.Afr.; Bayer, Swed.; Bayer, Thai.; Bayer, Turk.; IDIS, UK.*
Niclosamide (p.151·1).
Available on a named-patient basis in the *UK*.
Diphyllobothriasis; hymenolepiasis; taeniasis.

Yomogi
Emonta, Austria.
Saccharomyces boulardii (p.2372·3).
Acne; diarrhoea.

Ardeypharm, Ger.
Saccharomyces cerevisiae (p.1998·3).
Acne; diarrhoea.

Yonal *Arex, Venez.*
Guaifenesin (p.1561·3); dextromethorphan hydrobromide (p.1555·2).
Cough.

Yondelis *Pharma Mar, Cz.; Pharma Mar, Fr.*
Trabectedin (p.781·3).
Soft-tissue sarcoma.

Yonka *Andromaco, Chile.*
Potassium gluconate (p.1684·3).
Hypokalaemia.

Yontal *Duncan, Arg.*
⊗ Salbutamol (p.1131·2).
Asthma.

Yosenob *Nufarindo, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Youngflex Massage 168 *Youngflex, Canad.*
Menthol (p.2340·1); cajuput oil (p.2271·2); eucalyptus oil (p.2301·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Your Choice *Amcon, USA.*
Saline rinsing and storage solutions for soft contact lenses (p.1622·2) (p.1686·1).

Yovis *Sigma-Tau, Ital.*
Streptococcus salivarius subsp. *thermophilus*; *Bifidobacterium breve*; *B. infantis*; *B. longum*; *Lactobacillus acidophilus*; *L. plantarum*; *L. casei*; *L. delbrueckii* subsp. *bulgaricus*; *Enterococcus faecium* (p.2372·3).
Disturbance of gastrointestinal flora.

Yovita *Pharma Italia, Ital.*
Lactic-acid-producing organisms (p.2372·3); vitamins (p.1922·1).
Disturbances of the intestinal flora; nutritional supplement.

Yperod *Faran, Gr.*
⊗ Mometasone (p.1540·1).
Skin disorders.

Ypsiloheel *Heel, Cz.*
Homoeopathic preparation.

Ypsiloheel N *Heel, Ger.*
Homoeopathic preparation.

Yris *Kwizda, Austria.*
Gestodene (p.2105·2); ethinylestradiol (p.2101·3).
Combined oral contraceptive.

YSE *Monin, Fr.*
Zinc gluconate (p.1999·2); kola (p.2416·1).
Asthenia.

YSE Glutamique *Monin, Fr.*
Zinc gluconate (p.1999·2); glutamic acid (p.1947·1).
Asthenia.

Ysol 206 *Rabi & Solabo, Fr.*
Acetic acid (p.2244·2); camphor (p.2273·2); Java citronella oil (p.2284·2); sodium laurilsulfate (p.2138·3).
Pediculosis.

Ystal *Corsalud, Venez.†.*
Diphenhydramine hydrochloride (p.577·2).
Hypersensitivity reactions.

Ystheal *Pierre Fabre Dermo-Cosmetique, Arg.; Silesia, Chile.*
Retinaldehyde (p.1612·2).
Dry skin; photodamaged skin; pigmentation disorders.

Ytracis *CIS, Cz.; CIS, Hung.; CIS, Neth.; CIS, Port.; Schering, Spain; Schering, UK.*
Yttrium-90 (p.2057·1).
For radiolabelling of Zevalin.

Yttriga *QSA, Cz.*
Ytrrium-90 (p.2057·1).
Radiolabelling.

Yucomy *YSP, Malaysia; Yung Shin, Singapore.*
Ketoconazole (p.539·1).
Fungal infections.

Yudinef *Unimex, Philipp.; Yuhan, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Yugoxil *Elin, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Yunir *Eurodrug, Mex.*
Pinazepam (p.1019·1).
Alcohol withdrawal syndrome; anxiety; epilepsy; insomnia; premedication; skeletal muscle spasm.

Yuredol *Grossman, Mex.*
Cyclobenzaprine hydrochloride (p.1895·2); clonixin lysine (p.37·1).
Skeletal muscle spasm and pain.

Yurelax *Valeant, Spain.*
Cyclobenzaprine hydrochloride (p.1895·2).
Skeletal muscle spasm.

Yusin *Maigal, Arg.*
⊗ Oxymetazoline (p.1567·2).
Eye disorders; nasal congestion.

Yusin Tears I *Maigal, Arg.*
Sodium chloride (p.1686·1).
Dry eyes.

Yusin Tears II *Maigal, Arg.*
Sodium chloride (p.1686·1); hyaluronic acid (p.2320·1).
Dry eyes.

Yutopar *Galenica, Gr.; Solvay, Hong Kong†; Solvay, India; Solvay, Indon.; Durbin, UK.*
⊗ Ritodrine hydrochloride (p.2017·2).
Fetal distress; premature labour.

Yuyo *Incaico, Arg.*
Aloe vera (p.1588·2); cascara (p.1715·2).
Constipation.

Yvano *Rafarm, Gr.*
⊗ Timolol (p.1413·1); pilocarpine (p.1884·3).
Glaucoma.

Yxin *Pfizer, Ger.†.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye disorders.

Yxin Tears *Pfizer Consumer, Ger.*
Povidone (p.2146·1).
Dry eyes.

Yzop Lekarsky *Slovakofarma, Cz.†.*
Hyssopus (p.2323·3).
Coughs; sore throat.

3Z *Jaba Recordati, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Z Frin *Grin, Mex.*
Zinc sulfate (p.1999·2); phenylephrine hydrochloride (p.1568·1).
Eye disorders.

Zaarpress *Sigma, Braz.*
Losartan potassium (p.1326·1).
Hypertension.

Zaart *Cipla, India.*
Losartan potassium (p.1326·1).
Hypertension.

Zaart-H *Cipla, India.*
⊗ Losartan potassium (p.1326·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Zaba *Wyeth Lederle, Austria.*
Multivitamin and mineral preparation (p.1922·1).

Zabel *Alphapharm, Austral.*
Terbinafine hydrochloride (p.546·3).
Fungal skin and nail infections.

Zaby *Rafarm, Gr.*
Netilmicin (p.307·1).
Bacterial infections.

Zabysept *Rafarm, Gr.*
⊗ Naphazoline nitrate (p.1565·2); zinc sulfate (p.1999·2).
Ocular irritation.

ZAC *Ikapharmindo, Indon.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Zacare Kit *Hawthorn, USA.*
Cleansing lotion, benzoyl peroxide (p.1590·2) (Zaclir); topical gel, sodium hyaluronate (p.2320·1) (Hylira).
Acne.

Zacetin *Medica Korea, Singapore†.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Zacin *Lavipharm, Gr.; Zeneus, Irl.; Cephalon, UK.*
Capsaicin (p.32·3).
Osteoarthritis; topical relief of rheumatic pain.

Zaclir *Hawthorn, USA.*
Benzoyl peroxide (p.1590·2).
Acne.

Zacnan *Merck-Lipha, Fr.*
Minocycline hydrochloride (p.300·3).
Bacterial infections.

Zacne *Bial, Port.*
Benzoyl peroxide (p.1590·2); miconazole nitrate (p.541·3).
Acne.

ZacPac *Altana, Ger.*
Tablets, pantoprazole sodium (p.1760·1); tablets, amoxicillin trihydrate (p.202·2); tablets, clarithromycin (p.248·2).
Peptic ulcer.

Zactin *Alphapharm, Austral.; Merck, Indon.; Alphapharm, Singapore; Merck, Singapore.*
Fluoxetine hydrochloride (p.391·2).
Depression; obsessive-compulsive disorder.

Zactos *Lilly, Mex.*
Pioglitazone (p.456·3).
Diabetes mellitus.

Zadaxin *Ahimsa, Arg.; SciClone, Hong Kong; SciClone, Indon.; Tempo Scan Pacific, Indon.; Sciclone, Ital.; Sciclone, Malaysia; Columbia, Mex.; SciClone, Philipp.; Sciclone, Singapore; Sciclone, Thai.†.*
Thymalfasin alfa (p.2400·3).
Adjuvant in influenza and hepatitis B vaccination; chronic hepatitis B; chronic hepatitis C; immunomodulator; influenza vaccination in immunodeficient patients.

Zadec *Novartis, Philipp.*
Ketotifen fumarate (p.582·2).
Allergic disorders; asthma.

Zaden *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Zad-G *Gufic, India.*
Zinc sulfate (p.1999·2); sulfadiazine sodium (p.336·2).
Bacterial skin infections.

Zadim *Samarth, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Zadine
Note.This name is used for preparations of different composition.
Schering-Plough, Austral.; Schering-Plough, Hong Kong†; Schering-Plough, Malaysia†; Schering-Plough, NZ†; Schering-Plough, Singapore†.
Azatadine maleate (p.568·1).
Allergic skin disorders; hypersensitivity reactions; rhinitis.

UCI, Braz.†.
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Zadino *Milano, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Zaditen
Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Paladin, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, Indon.; Novartis, Irl.; Novartis, Israel; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Wander, Philipp.; Novartis, Port.; Novartis, Rus.; Adcock Ingram, S.Afr.; Novartis, S.Afr.; Novartis, Singapore; Novartis Ophthalmics, Singapore; Novartis, Spain; Novartis Ophthalmics, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, Venez.
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis; allergic disorders; allergic rhinitis; allergic skin disorders; asthma; atopic dermatitis; bronchitis; hypersensitivity reactions; urticaria.

Novartis, Pol.
Ketotifen (p.582·2) or ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Zaditor *Novartis Ophthalmics, Canad.; Novartis, USA.*
Ketotifen fumarate (p.582·2).
Allergic conjunctivitis.

Zadolina *Salus, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Zadorin *Mepha, Hong Kong†; Mepha, Malaysia†.*
Doxycycline hyclate (p.267·1).
Bacterial infections.

Zadorine *Mepha, Switz.*
Doxycycline hyclate (p.267·1).
Bacterial infections; malaria.

Zaedema Crono *Farmila, Ital.*
Vitamins; minerals; zeaxanthin; calendula; vitis vinifera; lycopene (p.1922·1).
Nutritional supplement.

Zaedoc *Ashbourne, UK†.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Zaf *Ares, Mex.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Zafen
Zambon, Ital.†.
Ibuprofen arginine (p.65·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Zambon, Neth.
Ibuprofen (p.64·2) or ibuprofen arginine (p.65·2).
Musculoskeletal, joint, and peri-articular disorders; pain.

Zambon, Port.
Ibuprofen (p.64·2).

Zafibral *Medochemie, Hong Kong†; Medochemie, Singapore.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Zafidol *Zafiro, Mex.*
Ketorolac trometamol (p.74·2).
Pain.

Zafimida *Zafiro, Mex.*
⊗ Furosemide (p.1292·1).
Forced diuresis; hypertension; oedema.

Zafin *Saval, Chile.*
Paracetamol (p.108·1); tramadol hydrochloride (p.130·3).
Pain.

Zafirasmal *Klonal, Arg.†.*
Zafirlukast (p.1150·2).
Asthma.

Zafiron *Adamed, Pol.*
⊗ Formoterol fumarate (p.1122·1).
Obstructive airways disease.

Zafirst *Chiesi, Ital.*
Zafirlukast (p.1150·2).
Asthma.

Zafitral *Rafarm, Gr.*
Risperidone (p.1024·2).
Psychoses.

Zafluox *Infosint, Ital.†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Zagam *Aventis, Cz.†; Bertek, USA†.*
Sparfloxacin (p.332·1).
Bacterial infections.

Zagorine *Rafarm, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zagyl *Xixia, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Zahnerol N *Dr Janssen, Ger.†.*
Benzocaine (p.1854·1).
Dental disorders.

Zahnkugelchen *Jacoby, Austria.*
Homoeopathic preparation.

Zahnungstropfen Escatitona *Madaus, Ger.*
Homoeopathic preparation.

Zainexpect *Strand, Malaysia†.*
Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Zainexpect C & F *Strand, Malaysia†.*
Paracetamol (p.108·1); pseudoephedrine hydrochloride (p.1571·2); dextromethorphan (p.1555·2).
Coughs and cold symptoms.

Zainexpect CD *Strand, Malaysia†.*
Codeine phosphate (p.37·2); diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3).
Coughs.

Zakoprosin *CSC, Austria.*
Oxaprozin (p.105·3).
Musculoskeletal, joint, and peri-articular disorders.

Zalain *Temis, Arg.†; Mayrhofer, Austria†; Pharmacia, Braz.; Andromaco, Chile; GSK, Cz.†; Trommsdorff, Ger.; Ferrer, Hong Kong; EGIS, Hung.; Geymonat, Ital.†; Ferrer, Malaysia†; Ferrer, Philipp.; Ferrer, Rus.; Ferrer, Singapore; Cantabria, Spain; Ferrer, Thai.; Adeka, Turk.; Leti, Venez.*
Sertaconazole nitrate (p.546·1).
Fungal skin and nail infections; vulvovaginal candidiasis.

Zalasta *KRKA, Cz.; KRKA, Pol.; KRKA, Port.*
Olanzapine (p.1012·1).
Bipolar disorder; mania; schizophrenia.

Zaldiar *Grunenthal, Austria; Grunenthal, Belg.; Grunenthal, Chile; Grunenthal, Cz.; Grunenthal, Fr.; Grunenthal, Ger.; Grunenthal, Mex.; Grunenthal, Neth.; Grunenthal, Pol.; Grunenthal, Port.; Grunenthal, Rus.; Grunenthal, Spain; Grunenthal, Switz.; Grunenthal, Venez.*
Tramadol hydrochloride (p.130·3); paracetamol (p.108·1).
Pain.

Zalep *Cipla, India.*
Zaleplon (p.1035·3).
Insomnia.

Zallyre *Europhta, Mon.*
Sodium cromoglicate (p.1136·3).
Allergic eye disorders.

Zalpen *YSS, Philipp.*
Benzathine benzylpenicillin (p.212·1).
Bacterial infections.

Zaludecni Cajova Smes *Megafyt-R, Cz.*
Absinthium (p.2244·1); achillea (p.2245·2); peppermint leaf (p.1761·2); lovage root (p.2335·1); St John's wort (p.422·3); liquorice (p.1740·3); fennel (p.2302·3).
Digestive disorders.

Zalvor *GSK, Belg.; GSK, Turk.*
Permethrin (p.2048·2).
Pediculosis; scabies.

Zalvos *Demo, Philipp.*
Ciprofloxacin hydrochloride (p.243·3) or ciprofloxacin lactate (p.243·3).
Bacterial infections.

Zamacort *Aventis, Mex.*
⊗ Triamcinolone acetonide (p.1544·3).
Asthma.

Zamadol *Bergamo, Braz.; Meda, Irl.; Viatris, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Zamalin *Rafarm, Gr.*
Cefprozil (p.232·2).
Bacterial infections.

Zamanon *Aventis, S.Afr.*
Dolasetron mesilate (p.1725·3).
Nausea and vomiting associated with cytotoxic therapy; postoperative nausea and vomiting.

Zamboprim *Vamsler, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Zam-Buk
Note. This name is used for preparations of different composition.
Key, Austral.†.
Eucalyptus oil (p.2301·2); camphor (p.2273·2); thyme oil (p.2401·2); colophony (p.2286·2); sassafras oil (p.2383·3).
Minor skin disorders.

Roche, S.Afr.†.
Eucalyptus oil (p.2301·2); camphor (p.2273·2); thyme oil (p.2401·2); sassafras oil (p.2383·3).
Burns; chapped hands; insect bites; muscular pain; pruritus; wounds.

Zamene *Menarini, Spain.*
⊗ Deflazacort (p.1524·3).
Corticosteroid.

Zamenit *Unipharma, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency.

Zametrixal *Ferakon, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Zamicet *Hawthorn, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Zamudol *Viatris, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Zamur *Mepha, Pol.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zanaflex *Shire, Canad.; Zeneus, Irl.; Cephalon, UK; Acorda, USA.*
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasticity.

Zanamet *TO-Chemicals, Thai.*
Ranitidine (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zandid *Kocak, Turk.*
Ranitidine hydrochloride (p.1766·1).

Zandil *Therapharma, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zandine *Duncan, Flockhart, Irl.†.*
Ranitidine hydrochloride (p.1766·1).
Gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zanedip *Recordati, Ital.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Zanfel *Zanfel, USA.*
Polyethylene granules (p.1585·3) in a surfactant base.
Urushiol-induced contact dermatitis.

Zanicor *Delta, Port.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Zanidex *Dexcel, Israel.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer.

Zanidip *Solvay, Austral.; Kwizda, Austria; Zambon, Belg.; Medley, Braz.; Andromaco, Chile; Meda, Denm.; Leiras, Fin.; Bouchara-Recordati, Fr.; Galenica, Gr.; Schwarz, Hong Kong; Kwizda, Hung.; Solvay, Indon.; Helsinn Birex, Irl.; Recordati, Malaysia; Sanfer, Mex.; Muir Hutchinson, NZ; Meda, Norw.; Fournier, Philipp.; Jaba Recordati, Port.; Pharmaplan, S.Afr.; Recordati, Singapore†; Recordati, Spain; Meda, Swed.; Robapharm, Switz.; Fournier, Thai.; Recordati, UK; Elmor, Venez.*
Lercanidipine hydrochloride (p.1324·2).
Hypertension.

Zanipram *Vocate, Gr.*
Citalopram (p.385·3).
Depression.

Zanizal *Bruno, Ital.†.*
Nizatidine (p.1751·2).
Gastro-oesophageal reflux; peptic ulcer.

Zanoc *Delta, Braz.*
Ketoconazole (p.539·1).
Fungal infections; seborrhoeic dermatitis.

Zanocin *Ranbaxy, Cz.; Ranbaxy, Hung.; Stancare, India; Ranbaxy, Malaysia; Ranbaxy, Mex.; Ranbaxy, Rus.; Ranbaxy, S.Afr.*
Ofloxacin (p.310·2).
Bacterial infections.

Zanosar *Pfizer, Canad.; Pfizer, Fr.; IFET (ΙΦΕΤ), Gr.; Pharmacia, Israel; Gensia, USA.*
Streptozocin (p.771·2).
Pancreatic cancer.

Zanovic *Virgo, Philipp.*
Mefenamic acid (p.80·1).
Musculoskeletal and joint disorders; pain.

Zanprol *GSK, UK.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux.

Zantac
GSK, Arg.
Ranitidine (p.1766·1) or ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastric hyperacidity; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; Pfizer Consumer, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Jpn; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, Turk.; GSK, UK; Boehringer Ingelheim, USA; GSK, USA; GSK, Venez.
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; duodenitis; dyspepsia; gastric hyperacidity; gastritis; gastro-oesophageal reflux; gastrointestinal haemorrhage; heartburn; pancreatitis; peptic ulcer; scleroderma oesophagitis; Zollinger-Ellison syndrome.

Zantadin *Soho, Indon.*
Ranitidine hydrochloride (p.1766·1).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Zantarac *GSK, Austria.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; heartburn.

Zantic *GSK, Ger.; GSK, Switz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; dyspepsia; gastro-oesophageal reflux; gastrointestinal haemorrhage; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Zantidon *Siam Bheasach, Thai.*
Ranitidine (p.1766·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zantipres *FIRMA, Ital.*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Zantipride *FIRMA, Ital.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zantril *Abbott, Arg.†.*
⊗ Isoprenaline sulfate (p.1316·3); calcium iodide (p.1553·2).
Asthma.

Zantron *Pyridam, Indon.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Zanzipik *Alckamed, Ital.*
Insect repellent.

Zapain *Goldshield, UK.*
Paracetamol (p.108·1); codeine phosphate (p.37·2).
These ingredients can be described by the British Approved Name Co-codamol.
Pain.

ZapAn *Icon, Philipp.*
Mefenamic acid (p.80·1).
Pain.

Zapedia *Pascual, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

Zapine *Taiwan Biotech, Malaysia.*
Clozapine (p.981·1).
Schizophrenia.

Zaplon *Torrent, India†.*
Zaleplon (p.1035·3).
Insomnia.

Zaponex *Ivax, UK.*
Clozapine (p.981·1).
Psychoses in parkinsonism; schizophrenia.

Zappelin *Iso, Ger.*
Homoeopathic preparation.

Zaprine *Hexal, S.Afr.*
Azathioprine (p.1818·2).
Auto-immune disorders; transplant rejection.

Zapto *Pharmacare, S.Afr.*
Captopril (p.1239·2).
Heart failure; hypertension.

Zapto Co *Pharmacare, S.Afr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

ZapTron *Ratiopharm, Cz.*
Galantamine hydrobromide (p.366·1).
Alzheimer's disease.

Zaramol *APS, Port.†.*
Paracetamol (p.108·1).
Fever; pain.

Zarator *Phoenix, Arg.; Pfizer, Chile; Pfizer, Denm.; Pfizer, Gr.; Euro Registratie, Neth.; Pfizer, Port.; Parke, Davis, Spain.*
Atorvastatin calcium (p.1218·3).
Cardiovascular risk reduction; hypercholesterolaemia.

Zarcop *Mintlab, Chile.*
Doxylamine succinate (p.578·2).

Zardil *Unison, Thai.*
Ranitidine (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zarelix *Liconsa, Port.*
Venlafaxine hydrochloride (p.427·3).
Depression; panic disorder.

Zarent *Aventis, Ital.†.*
⊗ Nedocromil sodium (p.1127·3); salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Zarex *Dexcel, Israel†.*
Famotidine (p.1730·1).
Gastric hyperacidity; heartburn.

Zargus *Biosintetica, Braz.*
Risperidone (p.1024·2).
Psychoses.

Zaricort *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Fungal skin infections with inflammation.

Zarin *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Miconazole nitrate (p.541·3).
Fungal infections of the skin, nails, and mucous membranes.

Zariviz *Sanofi-Aventis, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Zarocs *Pharmazam, Spain.*
Roxatidine acetate hydrochloride (p.1769·1).
Gastro-oesophageal reflux; peptic ulcer.

Zarom *Pyridam, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Zarondan *Pfizer, Denm.*
Ethosuximide (p.479·3).
Absence seizures.

Zarontin *Elea, Arg.; Pfizer, Austral.; Pfizer, Belg.; Erfa, Canad.; Pfizer, Fr.; IFET (ΙΦΕΤ), Gr.; Pfizer, Gr.; Pfizer, Irl.; Parke, Davis, Israel†; Pfizer, Ital.; Pfizer, NZ; Pfizer, Neth.†; Pfizer, S.Afr.; Pfizer, Spain†; Pfizer, UK; Parke, Davis, USA.*
Ethosuximide (p.479·3).
Absence seizures; myoclonic seizures.

Zaroxolyn *Aventis, Canad.; Heumann, Ger.†; IFET (ΙΦΕΤ), Gr.†; Celltech, Hong Kong; Medeva, Israel; Teofarma, Ital.; Novartis, S.Afr.†; UCB, USA.*
⊗ Metolazone (p.1337·2).
Ascites; hypertension; oedema.

Zaroxolyne *Novartis, Switz.†.*
⊗ Metolazone (p.1337·2).
Hypertension; oedema.

Zarv *Ativus, Braz.*
Aesculus (p.2248·2).
Haemorrhoids.

Zaso *Cadila Pharma, India.*
Zaleplon (p.1035·3).
Insomnia.

Zasten *Novartis, Spain.*
Ketotifen (p.582·2).
Allergic rhinitis; asthma.

Zasterid *Richter, Pol.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Zatin *Wermar, Mex.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Zatofug *Wolff, Ger.†.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Zatrol *Andromaco, Chile.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zatur *CCD, Fr.†.*
Oxybutynin hydrochloride (p.2190·3).
Neurogenic bladder disorders.

Zavedos *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Austria; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Irl.; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Philipp.; Pharmacia, Pol.; Pfizer, Port.; Pharmacia, Rus.; Pharmacia, S.Afr.; Pfizer, Singapore; Kenfarma, Spain; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Carlo Erba, Turk.; Deva, Turk.; Pharmacia, UK; Pfizer, Venez.*
Idarubicin hydrochloride (p.731·1).
Acute leukaemias; breast cancer.

Zavesca *Pharma Logistics, Belg.; Actelion, Canad.; Actelion, Cz.; Actelion, Denm.; Actelion, Fin.; Actelion, Fr.; Actelion, Ger.; Actelion, Gr.; Actelion, Hung.; Teva, Israel; Actelion, Ital.; Actelion, Neth.; Actelion, Norw.; Actelion, Port.; Actelion, Spain; Actelion, Swed.; Actelion, Switz.; Actelion, UK; Actelion, USA.*
Miglustat (p.2345·2).
Gaucher disease.

Zaxem *UCB, Austria.*
Butenafine hydrochloride (p.528·1).
Fungal skin infections.

Zaxetina *Dunar, Spain†.*
Fluoxetine hydrochloride (p.391·2).
Bulimia; depression; mixed anxiety depressive states; obsessive-compulsive disorder.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Zaxine *Bama, Spain.*
Rifaximin (p.330·1).
Gastrointestinal infections.

Zayasel *Salvat, Spain.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia; hypertension.

Zazole *PharmaDerm, USA.*
Terconazole (p.548·1).
Fungal vaginal infections.

Z-Bec
Note. This name is used for preparations of different composition.
Gap, Gr.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.
Wyeth Consumer, Thai.
Multivitamin preparation with zinc (p.1922·1).
Robins, USA.
Multivitamin and mineral preparation (p.1922·1).

Z-Bec Plus *Gap, Gr.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Z-Cof *Zyber, USA.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3).
Coughs.

Z-Cof HC *Zyber, USA.*
Hydrocodone tartrate (p.63·1); chlorphenamine maleate (p.571·3); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Z-Crim *Alpharma, Mex.*
Zinc (p.1999·1).
Skin disorders.

Zcure *Natrapharm, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

Z-Dorm *Hexal, S.Afr.*
Zopiclone (p.1039·1).
Insomnia.

Zdroj *Sulphur Zdroj, Pol.*
Sulfur (p.1614·1); sodium chloride; bromide; iodide; borate.
Scalp disorders.

Ze Caps *Everett, USA†.*
Zinc gluconate (p.1999·2); vitamin E (p.1992·2).
Dietary supplement.

Zeadema *Farmila, Ital.*
Multivitamin and mineral preparation with zeaxantina and red vine (p.1922·1).
Antoxidant nutritional supplement.

ZeaSorb
Note. This name is used for preparations of different composition.
Stiefel, Arg.; Stiefel, Austral.; Stiefel, Canad.; Stiefel, Chile†; Stiefel, Irl.; Stiefel, Thai.; Stiefel, UK.
Aldioxa (p.1587·2); chloroxylenol (p.1640·2); cellulose (p.2143·1).
Bromhidrosis; hyperhidrosis; intertrigo; napkin rash; prickly heat; prophylaxis of fungal skin infections; skin irritation; tinea pedis.
Stiefel, Fr.
Aldioxa (p.1587·2); cellulose (p.2143·1); magnesium silicate (p.2144·3).
Hyperhidrosis.
Stiefel, Indon.; Stiefel, Malaysia†; Stiefel, Philipp.; Stiefel, S.Afr.; Stiefel, Singapore.
Aldioxa (p.1587·2); chloroxylenol (p.1640·2).
Bromhidrosis; fungal skin infections; hyperhidrosis; intertrigo; nappy rash; tinea pedis.

ZeaSorb AF
Note. This name is used for preparations of different composition.
Stiefel, Canad.
Tolnaftate (p.548·3).
Fungal skin infections.
Stiefel, Chile; Stiefel, USA.
Miconazole nitrate (p.541·3).
Fungal skin infections.

Zeben *Siam Bheasach, Thai.*
Albendazole (p.139·2).
Worm infections.

Zebeta *Barr, USA.*
⊗ Bisoprolol fumarate (p.1234·1).
Hypertension.

Zebrak *Royal, Chile.*
Citalopram (p.385·3).
Depression.

Zebu *Pond's, Thai.*
⊗ Salbutamol (p.1131·2).
Bronchospasm.

Zeclar *Abbott, Cz.†; Orion, Fin.; Abbott, Fr.; Abbott, Port.*
Clarithromycin (p.248·2).
Bacterial infections.

Zeclaren *Vianex (Βιανέξ), Gr.*
Clarithromycin (p.248·2).
Adjunct in Helicobacter pylori eradication; bacterial infections.

Zecnil *Ferring, Ital.†.*
Somatostatin acetate (p.1809·2).
Diabetic ketoacidosis; gastrointestinal haemorrhage; prevention of complications following pancreatic surgery.

Zecovir *Guidotti, Ital.*
Brivudine (p.867·3).
Herpes zoster infections.

Zeda *Verisfield, Gr.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Zedax *Andromaco, Chile†.*
Zopiclone (p.1039·1).
Insomnia.

Zedchem PVP-I *Zedchem, S.Afr.*
Povidone-iodine (p.1659·2).
Burns; disinfection of skin and mucous membranes; skin infections; ulcers; wounds.

Zedex *Wockhardt, India; Wockhardt, Rus.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs; respiratory-tract disorders associated with viscous mucus.

Zedex-P *Wockhardt, India.*
Bromhexine hydrochloride (p.1552·2); dextromethorphan hydrobromide (p.1555·2); ammonium chloride (p.1551·3); menthol (p.2340·1); pseudoephedrine hydrochloride (p.1571·2).
Coughs; respiratory-tract disorders associated with viscous mucus.

Zeditapp *Medhaus, Philipp.*
Phenylpropanolamine hydrochloride (p.1569·3); brompheniramine maleate (p.569·2).
Cough; nasal congestion.

Zedprex *Adeka, Turk.*
Fluoxetine hydrochloride (p.391·2).
Bulimia nervosa; depression; obsessive-compulsive disorder.

Zeecof *Cipla, India.*
Diphenhydramine (p.577·1); guaifenesin (p.1561·3); bromhexine (p.1552·2); ammonium chloride (p.1551·3); menthol (p.2340·1).
Coughs.

Zeefra *Bouchara-Recordati, Fr.; Bouchara-Recordati, Hong Kong.*
Cefradine (p.233·1).
Bacterial infections.

Zeel
Note. This name is used for preparations of different composition.
Heel, Ger.†.
Homoeopathic preparation.
Heel, S.Afr.
Injection: Cartilago suis; funiculus umbilicalis suis; embryo suis; placenta suis; rhus toxicodendron; arnica; dulcamara; symphytum; sanguinaria; sulfur; nadid; coenzyme A; thioctic acid; natrium oxalaceticum.
Musculoskeletal and joint disorders.
Heel, S.Afr.
Ointment; tablets: Cartilago suis; funiculus umbilicalis suis; embryo suis; placenta suis; rhus toxicodendron; flor arnicae; dulcamara; symphytum; sanguinaria; sulfur; acidum silicicum colloidale; nadid; coenzyme A; thioctic acid; natrium oxalaceticum.
Musculoskeletal and joint disorders.

Zeel comp *Heel, Ger.*
Homoeopathic preparation.

Zeel Compositum *Heel, Cz.*
Homoeopathic preparation.

Zeel P *Heel, Ger.†.*
Homoeopathic preparation.

Zeel Plus *Peithner, Austria.*
Homoeopathic preparation.

Zeel Salbe *Heel, Cz.*
Homoeopathic preparation.

Zeel T *Heel, Ger.†.*
Homoeopathic preparation.

Zee-Seltzer *Zee, USA.*
Aspirin (p.20·3); citric acid (p.2284·1); sodium bicarbonate (p.1673·2).

Zeet Expectorant
Note. This name is used for preparations of different composition.
Alembic, India.
Syrup: Diphenhydramine hydrochloride (p.577·2); ammonium chloride (p.1551·3); guaifenesin (p.1561·3); bromhexine hydrochloride (p.1552·2); menthol (p.2340·1).
Coughs.
Alembic, India.
Tablets: Bromhexine hydrochloride (p.1552·2); phenylpropanolamine hydrochloride (p.1569·3).
Coughs.

Zeet Linctus *Alembic, India.*
Dextromethorphan hydrobromide (p.1555·2); guaifenesin (p.1561·3); phenylpropanolamine hydrochloride (p.1569·3).
Coughs.

Zefa *M & H, Thai.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Zefan *Drogsan, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zefaxone *M & H, Thai.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Zefazone *Upjohn, USA†.*
Cefmetazole sodium (p.225·3).
Bacterial infections.

Zefecort *Vocate, Gr.*
⊗ Budesonide (p.1520·1).

Zeffix *GSK, Arg.†; GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.†; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, Singapore; Glaxo Wellcome, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, Turk.; GSK, UK.*
Lamivudine (p.895·1).
Chronic hepatitis B; HIV infection.

Zefidim *Kalbe, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Zefin *Millimed, Thai.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Zefipime *Vocate, Gr.*
Cefepime (p.224·1).
Bacterial infections.

Zefiran *Ilsan, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zefnart *Torii, Jpn.*
Liranaftate (p.540·3).
Fungal skin infections.

Zefocent *Samjin, Philipp.; Unimex, Philipp.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Zefol *Akdeniz, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zefort *Merkez, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zefral *United American, Philipp.*
Cefixime (p.224·3).
Bacterial infections.

Zefroxe *Ranbaxy, S.Afr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zefsolin *Oro, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zeftam *M & H, Thai.*
Ceftazidime (p.234·1).
Bacterial infections.

Zeftrix *Kalbe, Indon.*
Ceftriaxone sodium (p.237·1).
Bacterial infections.

Zefxon *Biolab, Thai.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zegen *United American, Philipp.*
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Zegerid *Santarus, USA.*
Omeprazole (p.1753·1); sodium bicarbonate (p.1673·2).
Formerly contained omeprazole.
Gastro-oesophageal reflux; peptic ulcer.

Zegren *Lapi, Indon.*
Diclofenac sodium (p.44·3).
Musculoskeletal and joint disorders.

Zehu-Ze *Teva, Israel.*
Permethrin (p.2048·2).
Pediculosis.

Zeid *Senosiain, Mex.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Zela *Unison, Thai.*
Albendazole (p.139·2).
Worm infections.

Zelapar *Valeant, Arg.; Cephalon, UK; Cardinal Health, USA.*
⊗ Selegiline hydrochloride (p.817·1).
Parkinsonism.

Zelavel *Novell, Indon.*
Ofloxacin (p.310·2).
Bacterial infections.

Zeldilon *Zeler, Port.*
Minoxidil (p.1342·1).
Alopecia androgenetica.

Zeldox
Pfizer, Arg.; Pfizer, Austria; Pfizer, Chile; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Ger.; Pharmacia, Ger.; Pfizer, Hong Kong; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Norw.; Pfizer, Philipp.; Pfizer, Port.; Pfizer, Spain; Pfizer, Swed.
Ziprasidone hydrochloride (p.1036·2) or ziprasidone mesilate (p.1036·2).
Bipolar disorder; mania; schizophrenia.
Pfizer, Austral.; Mack, Rus.; Pfizer, Singapore; Pfizer, Thai.
Ziprasidone hydrochloride (p.1036·2).
Bipolar disorder; schizophrenia.
Pfizer, Hung.
Ziprasidone (p.1036·2) or ziprasidone mesilate (p.1036·2).
Bipolar disorder; schizophrenia.
Pfizer, Pol.
Ziprasidone (p.1036·2).
Schizophrenia.

Zeleven *Iator, Gr.*
Butamirate (p.1553·1).
Cough.

Zelface *Ferron, Indon.*
Azelaic acid (p.1589·3).
Acne.

Zelfin *Randall, Mex.*
Albendazole (p.139·2).
Worm infections.

Zelian *Rafarm, Gr.*
Buflomedil hydrochloride (p.1236·3).
Peripheral vascular disorders.

Zelicrema *Biomedica-Chemica, Gr.*
Azelaic acid (p.1589·3).
Acne.

Zeliderm *Vinas, Spain.*
Azelaic acid (p.1589·3).
Acne.

Zeliris *Sanbe, Indon.*
Azelaic acid (p.1589·3).
Acne.

Zelis *Prospa, Ital.*
Piroxicam cinnamate (p.118·2).
Musculoskeletal and joint disorders.

Zelitrex *GSK, Belg.; GSK, Denm.; GSK, Fr.; GSK, Ital.; GSK, Neth.; GSK, S.Afr.*
Valaciclovir hydrochloride (p.911·1).
Herpesvirus infections.

Zelium
Note. This name is used for preparations of different composition.
Abbott, Port.
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.
Masa, Thai.
Flunarizine (p.580·3).
Cerebrovascular disorders; migraine.

Zelix *Ativus, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Zelixa *Biofarm, Pol.*
⊗ Sibutramine hydrochloride (p.2163·2).
Obesity.

Zellaforte *Novum, Mex.; Zellaforte, Switz.*
Vitamin and mineral preparation (p.1922·1).

Zellaforte N Plus *Eurim, Ger.†.*
⊗ Nikethamide calcium thiocyanate (p.2161·2); inositol nicotinate (p.1316·1); pholedrine sulfate (p.1371·1).
Tonic.

Zellaforte plus *ICN, Austria.*
Procaine hydrochloride; haematoporphyrin; ferrous sulfate; vitamins (p.1922·1).
Tonic.

Zeller Sommeil *Zeller, Switz.*
Valerian (p.2410·1); lupulus (p.2335·2).
Sleep disorders.

Zeller-Augenwasser *Herchemie, Austria.*
Saffron; fennel oil; zinc sulfate (p.1999·2).
Eye inflammation and irritation.

Zellox-II *Hoe, Malaysia; Hoe, Singapore.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Dyspepsia; flatulence; gastric hyperacidity; gastritis; gastro-oesophageal reflux; heartburn.

Zelmac *Novartis, Arg.; Novartis, Austral.†; Novartis, Braz.; Novartis, Chile; Novartis, Cz.†; Novartis, Hong Kong; Novartis, Indon.; Novartis, Israel; Novartis, Malaysia†; Novartis, Mex.; Novartis, NZ; Novartis, Rus.†; Novartis, Singapore; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, Venez.*
Tegaserod maleate (p.1776·1).
Constipation; irritable bowel syndrome in women.

Zelmar *Biomedica-Chemica, Gr.*
Loratadine (p.583·3).
Allergic rhinitis; pruritus.

Zelnorm *Novartis, Canad.; Novartis, Philipp.; Novartis, S.Afr.; Novartis, USA†.*
Tegaserod maleate (p.1776·1).
Chronic constipation; irritable bowel syndrome in women.

Zeloram *Epifarma, Ital.*
Lorazepam (p.1004·1).
Anxiety; insomnia.

Zeloxim *Bilim, Turk.*
Meloxicam (p.80·3).
Ankylosing spondylitis; osteoarthritis; rheumatoid arthritis.

Zem *Faran, Gr.†.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zema
Note. This name is used for preparations of different composition.
Union Drug, Thai.
Cream: Clotrimazole (p.530·1).
Fungal skin infections.
Union Drug, Thai.
Lotion: Phenol (p.1656·1); resorcinol (p.1612·1); salicylic acid (p.1612·2).
Infected skin disorders.

Zemaira *Aventis Behring, USA.*
Alpha -proteinase inhibitor (p.2253·2).
Alpha -proteinase inhibitor deficiency.

Zemalex *Italfarmaco, Port.*
Piketoprofen hydrochloride (p.117·2).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; phlebitis.

Zemax *Cipla-Medpro, S.Afr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Zemide *Alpharma-Isis, Ger.†.*
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.

Zemon *Neolab, UK.*
Isosorbide mononitrate (p.1318·3).
Angina pectoris.

Zemox *Varipharm, Ger.†.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Zemplar *Abbott, Austral.; Abbott, Austria; Abbott, Canad.; Abbott, Cz.; Abbott, Fin.; Abbott, Ger.; Abbott, Gr.; Abbott, Hong Kong; Abbott, Hung.; Abbott, Irl.; Abbott, Ital.; Abbott, Malaysia; Abbott, Mex.; Abbott, Neth.; Abbott, Norw.; Abbott, Port.; Abbott, Singapore; Abbott, Spain; Abbott, Swed.; Abbott, Switz.; Abbott, UK; Abbott, USA; Abbott, Venez.*
Paricalcitol (p.1987·2).
Hyperparathyroidism; renal osteodystrophy.

Zemtard *Galen, UK.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zemtrial *IAE, Philipp.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zemuron *Organon, Arg.†; Organon, Canad.; Organon, USA.*
Rocuronium bromide (p.1908·3).
Competitive neuromuscular blocker.

Zemyc *Pharos, Indon.*
Fluconazole (p.532·1).
Fungal infections.

Zenalb *Paylos, Arg.†; BPL-Meizler, Braz.†; Galenica, Gr.; Bio Products, Malaysia; BPL, Singapore; BPL, Thai.; Sodhan, Turk.; BPL, UK.*
⊗ Albumin (p.1052·1).
Burns; extracorporeal circulation; hypoalbuminaemia; hypovolaemic shock; plasma volume expansion.

Zenapax *Roche, Arg.; Roche, Austral.; Roche, Austria; Roche, Belg.†; Roche, Braz.; Roche, Canad.; Roche, Chile; Roche, Cz.; Roche, Denm.; Roche, Fin.; Roche, Fr.; Roche, Ger.; Roche, Gr.; Roche, Hong Kong; Roche, Hung.; Roche, Irl.; Roche, Israel; Roche, Ital.; Roche, Mex.; Roche, NZ; Roche, Neth.; Roche, Philipp.; Roche, Pol.; Roche, Port.; Roche, S.Afr.; Roche, Singapore†; Roche, Spain; Roche, Swed.; Roche, Switz.; Roche, Thai.; Roche, Turk.; Roche, UK; Roche, USA; Roche, Venez.*
Daclizumab (p.1833·1).
Renal transplant rejection.

Zenavan *Bial, Spain.*
Etofenamate (p.53·1).
Pain; peri-articular disorders.

Zenaxin *Maver, Mex.*
Albendazole (p.139·2).
Worm infections.

ZenCare *Hoe, Malaysia.*
Glycerol (p.2314·2).
Soap substitute.

Zencef *Lapreven, Venez.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Zenchent *Watson, USA.*
21 Tablets, ethinylestradiol (p.2101·3); norethisterone (p.2119·3); 7 tablets, inert.
Combined oral contraceptive.

Zenda *TNP, Thai.†.*
Niclosamide (p.151·1); phenolphthalein (p.1762·1).
Worm infections.

Zendhin *DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zendol *Serum Institute, India.*
⊗ Danazol (p.2090·2).
Benign breast disease; endometriosis.

Zenemia *Verisfield, Gr.*
Calcium folinate (p.1943·3).
Antidote to folic acid antagonists; folic acid deficiency.

Zenfektol *Olgunsoy, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zengac *Fisiopharma, Ital.*
Vancomycin hydrochloride (p.358·3).
Bacterial infections.

Zeniac
Note. This name is used for preparations of different composition.
LED, Fr.†.
Lotion: Mandelic acid (p.296·3); salicylic acid (p.1612·2); ammonium lactate (p.1589·2).
Acne.
LED, Fr.†.
Roll-on: Mandelic acid (p.296·3); salicylic acid (p.1612·2); sulfur (p.1614·1).
Acne.
LED, Fr.†.
Topical gel: Lappa-biotin-zinc complex (p.2330·3) (p.1931·3) (p.1999·1).
Skin cleansing.

Zeniac LP *LED, Fr.†.*
Mandelic acid (p.296·3); salicylic acid (p.1612·2); ammonium lactate (p.1589·2); lappa-biotin-zinc complex (p.2330·3) (p.1931·3) (p.1999·1).
Acne.

Zeniac LP Fort *LED, Fr.†.*
Mandelic acid (p.296·3); tartaric acid (p.2395·2); salicylic acid (p.1612·2); ammonium lactate (p.1589·2).
Acne.

Zenkain *Gunsa, Turk.*
⊗ Tetryzoline hydrochloride (p.1574·1).
Eye irritation.

Zenmolin *DHA, Hong Kong.*
⊗ Salbutamol sulfate (p.1131·3).
Bronchospasm.

Zenodian *CT, Ital.†.*
Sucralfate (p.1772·2).
Gastritis; gastro-oesophageal reflux; peptic ulcer.

Zenostig *Ozone, Cz.*
Betahistine hydrochloride (p.2265·1).
Ménière's disease.

Zenoxone *Biorex, UK.*
⊗ Hydrocortisone (p.1535·2).
Skin disorders.

Zenpro *Xepa-Soul Pattinson, Malaysia†; Xepa-Soul Pattinson, Singapore.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zenriz *Pyridam, Indon.*
Cetirizine hydrochloride (p.570·3).
Rhinitis; urticaria.

Zensil *Silom, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zentan *Ilsan, Turk.*
Benzalkonium chloride (p.1629·1).
Skin disinfection.

Zentavion *Vita, Spain.*
Azithromycin (p.207·1).
Bacterial infections.

Zentel *GSK, Austral.; GSK, Braz.; GSK, Chile; GSK, Cz.; GSK, Fr.; IFET (ΙΦΕΤ), Gr.; Vianex (Βιανέξ), Gr.; GSK, India; GSK, Ital.; GSK Consumer, Malaysia; GSK, Mex.; GSK, Philipp.; GSK, Pol.; GSK Consumer, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Switz.; GSK, Thai.; GSK, Venez.*
Albendazole (p.139·2).
Echinococcosis; giardiasis; worm infections.

Zentius *Roemmers, Arg.; Pharma Investi, Chile.*
Citalopram hydrobromide (p.385·3).
Depression.

Zentralin *Pasteur, Chile.*
Flunarizine hydrochloride (p.580·2).
Cerebral and peripheral vascular disorders; sleep disorders; vestibular disorders.

Zentramin Bastian N *Bastian, Ger.*
Electrolyte preparation (p.1667·1).
Hypersensitivity disorders; psychosomatic disorders; tetanus.

Zenusin *Mepha, Port.*
Nifedipine (p.1350·1).
Angina pectoris; heart failure; hypertension; myocardial infarction; Raynaud's syndrome.

Zenzera *Bangkok Lab & Cosmetic, Thai.*
Albendazole (p.139·2).
Worm infections.

Zeoklamin *Ferakon, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Zepac *Ist. Chim. Inter., Ital.*
Heparin calcium (p.1301·2).
Thromboembolic disorders.

Zepan *Jofrain, Mex.*
Diazepam (p.986·3).
Anxiety.

Zepax *Yoo Young, Philipp.*
Cefoxitin sodium (p.230·2).
Bacterial infections.

Zepaz *Royal, Chile.*
Escitalopram (p.391·1).
Depression; panic disorder.

Zepdril *Aldril, Philipp.; Lloyd, Philipp.*
Cefradine (p.233·1).
Bacterial infections.

Zepelin
Note. This name is used for preparations of different composition.
Boehringer Ingelheim, Ital.
Feprazone (p.60·2).
Inflammation; pain.
Kowa, Jpn; Wakamoto, Jpn.
Acitazanolast (p.2246·1).
Allergic conjunctivitis.

Zepelindue *Boehringer Ingelheim, Ital.†.*
Ketoprofen lysine (p.73·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Zepharyl *Medi-Rx, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Zephiran *Sanofi Winthrop, USA.*
Benzalkonium chloride (p.1629·1).
Eye, bladder, urethra, and body cavity irrigation; skin, mucous membrane, and wound disinfection; vaginal douching.

Zepholin
Note. This name is used for preparations of different composition.
Genepharm, Gr.
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.
Astellas, Irl.
Theophylline (p.1140·1).
Bronchospasm.

Zephrex *Sanofi Synthelabo, USA.*
Pseudoephedrine hydrochloride (p.1571·2); guaifenesin (p.1561·3).
Coughs.

Zepiken *Kener, Mex.*
Carbamazepine (p.471·3).

Zepilen *AFT, NZ; Medochemie, Thai.†.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Zeplex *M & H, Thai.*
Cefalexin (p.218·2).
Bacterial infections.

Zepobrax *Farmaline, Thai.†.*
Chlordiazepoxide (p.968·1); clidinium bromide (p.1722·1).
Smooth muscle spasm.

Zeporin *Dynamic, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Zepose *Cipla, India.*
Diazepam (p.986·3).

Zeppeliton *Pol-Nil, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Zepral *Ikapharmindo, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zeprat *Solfran, Mex.†.*
Diazepam (p.986·3).
Anxiety; sedative.

Zeprid *Nobel, Turk.*
Sulpiride (p.1028·3).
Schizophrenia.

Zepril *Richmond, Arg.*
Abacavir (p.861·3).
HIV infection.

Zeprosil *Xixia, S.Afr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Zeptag *Bosch, Philipp.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Zeptol *Sun, Rus.; Sun, Thai.*
Carbamazepine (p.471·3).
Bipolar disorder; epilepsy; glossopharyngeal neuralgia; trigeminal neuralgia.

Zeptrigen *Westmont, Philipp.*
Ceftazidime (p.234·1).
Bacterial infections.

Zera *Tecnimede, Port.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Zeramil *Coup, Gr.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zerelin *Biomedica-Chemica, Gr.*
Meloxicam (p.80·3).
Inflammatory disorders.

Zerella *Schering, Austria†; Theramex, Ital.*
Estradiol (p.2097·2).
Menopausal disorders.

Zerene *Meda, Cz.; Biofutura, Ital.; Wyeth, Neth.; Meda, Port.*
Zaleplon (p.1035·3).
Insomnia.

Zeridame *Actavis, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Zerinetta *Boehringer Ingelheim, Ital.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Zerinoflu *Boehringer Ingelheim, Ital.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3); sodium ascorbate (p.1984·1).
Cold and influenza symptoms.

Zerinol-Fher *Boehringer Ingelheim, Ital.*
Paracetamol (p.108·1); chlorphenamine maleate (p.571·3).
Cold and influenza symptoms.

Zerit *BMS, Arg.; BMS, Austral.; BMS, Austria; BMS, Belg.; BMS, Canad.; BMS, Chile; BMS, Cz.; BMS, Denm.; BMS, Fin.; BMS, Fr.; BMS, Ger.; BMS, Gr.; BMS, Hong Kong; BMS, Hung.; BMS, Indon.; BMS, Irl.; BMS, Israel†; BMS, Ital.; BMS, Jpn; BMS, Malaysia†; BMS, Mex.; BMS, NZ; BMS, Neth.; BMS, Norw.; BMS, Pol.; BMS, Port.; BMS, Rus.; BMS, S.Afr.; BMS, Singapore; BMS, Spain; BMS, Swed.; BMS, Switz.; BMS, Thai.; BMS, Turk.; BMS, UK; BMS Oncology, USA; BMS, Venez.*
Stavudine (p.907·1).
HIV infection.

Zeritavir *BMS, Braz.*
Stavudine (p.907·1).
HIV infection.

Zerlin *Pharos, Indon.*
Sertraline (p.422·1).
Depression.

Zerlubron *Rafarm, Gr.†.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Zermed *Medicine Products, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; hypersensitivity reactions.

Zeroac *Mavi, Ital.*
Azelaic acid (p.1589·3); phosphatidyl choline (p.2367·1).
Acne.

Zerobase *Zeroderma, UK.*
Liquid paraffin (p.2030·3).
Diluent for topical steroids; dry skin; emollient.

Zerocid *Sun, Rus.*
Omeprazole (p.1753·1).
Peptic ulcer.

Zerodol *Ipca, India.*
Aceclofenac (p.14·3).
Inflammation; pain.

Zerodol-MR *Ipca, India.*
Aceclofenac (p.14·3); paracetamol (p.108·1); tizanidine hydrochloride (p.1898·2).
Muscle pain, inflammation, and spasm.

Zerodol-P *Ipca, India.*
Aceclofenac (p.14·3); paracetamol (p.108·1).
Fever; inflammation; pain.

Zeroflog *Valeas, Ital.*
Diclofenac (p.44·2).
Mouth and throat disorders.

Zeroform *Konimex, Indon.*
Loperamide (p.1741·3).
Diarrhoea.

Zeropain *Konimex, Indon.*
Menthol (p.2340·1); methyl salicylate (p.85·3); eugenol (p.2301·2); benzyl nicotinate (p.28·1).
Musculoskeletal, joint, peri-articular, and soft-tissue pain; neuralgia.

Zeropenem *Aventis, Arg.†.*
Meropenem (p.297·2).
Bacterial infections.

Zerosorin SN *Schuck, Ger.*
Homoeopathic preparation.

Zerospasm *Proel, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Zerpex *Menarini, Belg.*
Brivudine (p.867·3).
Herpes zoster infections.

Zerpyco *Atlantis, Mex.*
Pinaverium bromide (p.2368·1).
Gastrointestinal motility disorders; gastrointestinal spasm.

Zerrsox *Pharmatechnica, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Zerru B-Plex *Pharmatechnica, Philipp.*
Vitamin B ; vitamin B ; vitamin B (p.1922·1).
Neuritis; vitamin B deficiency.

Zerrucee *Pharmatechnica, Philipp.*
Ascorbic acid (p.1983·3).
Vitamin C deficiency; vitamin C supplement.

Zertalin *Collins, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Zertine *Bangkok Lab & Cosmetic, Hong Kong; Farmaline, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; urticaria.

Zesger *Gerard, Irl.*
Lisinopril (p.1325·2).
Diabetic nephropathy; heart failure; hypertension; myocardial infarction.

Zesger Plus *Gerard, Irl.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Ze-Spas *Kee, India.*
Dicycloverine hydrochloride (p.1722·3); mefenamic acid (p.80·1).
Smooth muscle spasm.

Zestagesic *Ad-Drugstel, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Zestam *Dankos, Indon.*
⊗ Betamethasone (p.1518·2); dexchlorpheniramine maleate (p.572·1).
Allergic disorders.

Zestan
Note. This name is used for preparations of different composition.
Clonmel, Irl.
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.
Ad-Drugstel, Philipp.
Mefenamic acid (p.80·1).
Pain.

Zestapron *Unipharma, Gr.†.*
Butamirate citrate (p.1553·1).
Cough.

Zestoretic *AstraZeneca, Arg.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, Denm.; AstraZeneca, Fr.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; Abdi, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Zestril *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile†; AstraZeneca, Denm.; AstraZeneca, Fin.†; AstraZeneca, Fr.; Cana, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ†; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Port.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; Abdi, Turk.; AstraZeneca, UK; AstraZeneca, USA.*
Lisinopril (p.1325·2).
Diabetic nephropathy; diabetic retinopathy; heart failure; hypertension; myocardial infarction.

Zeta N *Bergamon, Ital.*
Usnic acid (p.2409·3).
Vaginal disinfection.

Zetacet *Stiefel, USA.*
Sulfur (p.1614·1); sulfacetamide sodium (p.335·3).
Acne.

Zetagal *Elpen (Ελπεν), Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Zetalax *Zeta, Ital.*
Glycerol (p.2314·2).
Constipation.

Zetalerg *UCI, Braz.†.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Zetamax *Pfizer, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Zetamicin *Menarini, Ital.*
Netilmicin sulfate (p.306·3).
Bacterial infections.

Zetapron *Unipharma, Gr.*
Butamirate citrate (p.1553·1).
Cough.

Zetar *Dermik, Hong Kong; Dermik, USA.*
Coal tar (p.1616·2).
Scalp disorders.

Zetarina *Zafiro, Mex.*
Dopamine hydrochloride (p.1273·2).
Extracorporeal circulation; hypotension; shock.

Zetavir *Liferpal, Mex.†.*
Aciclovir (p.862·3).
Herpes simplex infections.

Zetavit *Zeta, Ital.*
Multivitamin and mineral preparation (p.1922·1).

Zetavudin *Richmond, Arg.*
Zidovudine (p.913·3); lamivudine (p.895·1).
HIV infection.

Zetaxim *Wockhardt, India.*
Cefotaxime sodium (p.228·1).
Bacterial infections.

Zethrinal *Biomedica-Chemica, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Zetia *Schering-Plough, Arg.; Mantecorp, Braz.; Merck, USA; Schering-Plough, USA; Schering-Plough, Venez.*
Ezetimibe (p.1284·3).
Hypercholesterolaemia.

Zetifen *Cadila, Rus.*
Ketotifen fumarate (p.582·2).

Zetilox *Minerva (Μινερβα), Gr.*
Itraconazole (p.536·3).
Fungal infections.

Zetion *Nevzat, Turk.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Zetir *Abbott, Braz.; Rodleben, Ger.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Zetitec *UCI, Braz.†.*
Ketotifen fumarate (p.582·2).
Hypersensitivity reactions.

Zetitor *Glenmark, India†.*
Ezetimibe (p.1284·3); atorvastatin calcium (p.1218·3).
Hypercholesterolaemia.

Zetix *Recalcine, Chile.*
Zopiclone (p.1039·1).
Insomnia.

Zeto *Unipharm, Israel.*
Azithromycin (p.207·1).
Bacterial infections.

Zetofen *Adcock Ingram, S.Afr.*
Ketotifen fumarate (p.582·2).
Allergic rhinitis; allergic skin disorders; asthma.

Zetomax *Adcock Ingram, S.Afr.*
Lisinopril (p.1325·2).
Heart failure; hypertension; myocardial infarction.

Zetomax Co *Adcock Ingram, S.Afr.*
⊗ Lisinopril (p.1325·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Zetop *Alliance, S.Afr.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders; pruritus.

Zetoridal *Duncan, Arg.†.*
Haloperidol (p.1000·2).

Zetran *Masa, Thai.*
Dipotassium clorazepate (p.980·1).
Anxiety; insomnia.

Zetrinal *Tripharma, Rus.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity reactions.

Zetron
Note.This name is used for preparations of different composition.
Libbs, Braz.
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal; depression.

Vocate, Gr.
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Biolab, Thai.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxics or radiotherapy; postoperative nausea and vomiting.

Zetrotax *Richmond, Arg.*
Zidovudine (p.913·3).
HIV infection.

Zetsim *Mantecorp, Braz.*
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Hyperlipidaemias.

Zevalin *Berlex, Canad.; Bayer Schering, Cz.; Schering, Denm.†; Schering, Fin.; Schering, Fr.; Schering, Ger.; Bayer Schering, Hung.; Schering, Irl.; Schering, Ital.; Bayer, NZ; Schering, Neth.; Schering, Norw.; Schering, Pol.; Schering, Port.; Schering, Spain; Schering, Swed.; Schering, Switz.; Bayer, UK; Cell Therapeutics, USA.*
Ibritumomab tiuxetan (p.730·2).
For radiolabelling with indium-111 or yttrium-90.
Non-Hodgkin's lymphoma.

Zevin *Biolab, Hong Kong; Biolab, Malaysia; Biolab, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Zevit *GSK, India.*
Vitamin preparation with zinc (p.1922·1).

Zexate
Dabur, Philipp.; Biogalenic, Venez.
Methotrexate (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Dabur, Thai.
Methotrexate sodium (p.745·2).
Malignant neoplasms; psoriasis; rheumatoid arthritis.

Z-Fin *Ultra, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Z-Fluor *Novartis Consumer, Belg.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis.

Z-gen *Goldline, USA.*
Multivitamin and mineral preparation (p.1922·1).

Ziac *Merck, Arg.; Merck, Chile; Merck, Philipp.; Barr, USA; Merck, Venez.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Ziagen
GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Canad.; GSK, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA.
Abacavir sulfate (p.861·3).
HIV infection.

GSK, Venez.
Abacavir (p.861·3) or abacavir sulfate (p.861·3).
HIV infection.

Ziagenavir *GSK, Arg.; GSK, Braz.; GSK, Mex.; GSK, Thai.*
Abacavir sulfate (p.861·3).
HIV infection.

Ziak *Merck, S.Afr.*
⊗ Bisoprolol fumarate (p.1234·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Ziana *Medicis, USA.*
Clindamycin phosphate (p.251·2); tretinoin (p.1618·1).
Acne.

Ziatir *Richmond, Arg.*
Imatinib mesilate (p.733·1).
Chronic myeloid leukaemia.

Ziaxal *Abbott, Port.*
Verapamil hydrochloride (p.1421·1); trandolapril (p.1416·2).
Hypertension.

Ziaxel *Abbott, Gr.; Abbott, NZ; Abbott, Neth.*
Verapamil hydrochloride (p.1421·1); trandolapril (p.1416·2).
Hypertension.

Zibac *Fahrenheit, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Zibelant *Chrispa (Χρισπα), Gr.*
Tenoxicam (p.128·2).
Gout; inflammation; osteoarthritis; pain; rheumatoid arthritis; spondyloarthropathies.

Zibil *Sandoz, Mex.*
⊗ Salbutamol (p.1131·2) or salbutamol sulfate (p.1131·3).
Obstructive airways disease.

Zibor *Menarini, Cz.; Berlin-Chemie, Hung.; Amdipharm, UK.*
Bemiparin sodium (p.1223·1).
Thromboembolic disorders.

Zibramax *Guardian, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Zibren *Sigma-Tau, Ital.*
Acetylcarnitine or acetylcarnitine hydrochloride (p.1932·2).
Cerebrovascular disorders; peripheral neuropathy.

Zicet *Jin Yang, Hong Kong; Jin Yang, Malaysia.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zicho *Nicholas, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Ziclin *Knoll, S.Afr.*
Gliclazide (p.440·3).
Diabetes mellitus.

Ziclob *Farmo Quimica, Chile.*
Cyclobenzaprine hydrochloride (p.1895·2).
Musculoskeletal spasm.

Ziclovir *Vitapan, Braz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zicomplex *Ipca, India†.*
Vitamin B complex with zinc (p.1922·1).

Ziconal *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Ketoconazole (p.539·1).
Fungal infections.

Zidepril *Minerva (Μινερβα), Gr.*
⊗ Captopril (p.1239·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Zideron *Norma (Νορμα), Gr.*
Dextropropoxyphene hydrochloride (p.40·1).
Pain.

Zidic-C *Arlex, Mex.*
Zidovudine (p.913·3).
HIV infection.

Zidicef *Precimex, Mex.*
Ceftazidime (p.234·1).
Bacterial infections.

Zidifec *Caprifarmindo, Indon.; Sanbe, Indon.*
Ceftazidime (p.234·1).
Bacterial infections.

Zidima *Fabop, Arg.*
Ceftazidime (p.234·1).
Bacterial infections.

Zidimox *Farmoz, Port.*
Ceftazidime (p.234·1).
Bacterial infections.

Zidin *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Trimetazidine (p.1419·2).
Angina pectoris.

Zidis *Pond's, Thai.†.*
Zidovudine (p.913·3).
HIV infection.

Zidofen *Genepharm, Gr.*
Ketotifen (p.582·2).
Allergic eye disorders.

Zidolam *Eurofarma, Braz.*
Lamivudine (p.895·1); zidovudine (p.913·3).
HIV infection.

Zidonil *Rafarm, Gr.*
Fluconazole (p.532·1).
Fungal infections.

Zidorex *Ipca, India†.*
Zidovudine (p.913·3).
HIV infection.

Zidoril *Unifa, Port.*
⊗ Finasteride (p.2188·3).
Benign prostatic hyperplasia.

Zidoval *3M, Denm.; 3M, Fin.; 3M, Israel; 3M, Ital.; 3M, Norw.; 3M, Spain; 3M, Swed.; 3M, UK.*
Metronidazole (p.837·1).
Bacterial vaginosis; trichomoniasis.

Zidovimm *Anfarm, Gr.*
Aciclovir (p.862·3).
Labial and genital herpes simplex infections.

Zidovir *Cristalia, Braz.†; Cipla, India; Protein, Mex.†; Cipla, Venez.*
Zidovudine (p.913·3).
HIV infection.

Zidovusan *Sanval, Braz.†.*
Zidovudine (p.913·3).
HIV infection.

Zidrevir *Kleva, Gr.*
Zidovudine (p.913·3).
HIV infection.

Ziegella *Peterer, Switz.*
Juniper oil (p.2328·3); ethyl nicotinate (p.52·1); rosemary oil (p.2381·3); sage oil (p.2382·3); St John's wort oil (p.423·2); lavender oil (p.2331·2); pine-needle oil (p.2368·2); calendula oil (p.2273·1).
Musculoskeletal and joint disorders; neuritis.

Zienam *MSD, Arg.; MSD, Austria; MSD, Ger.; MSD, Venez.*
Imipenem (p.286·3); cilastatin sodium (p.243·1).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Zient *Essex, Chile; MSD, Cz.; Schering-Plough, Mex.; Schering-Plough, Venez.*
Ezetimibe (p.1284·3).
Atherosclerosis; hypercholesterolaemia; sitosterolaemia.

ZI-Factor *Veropharm, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Zifartel *Continentales, Mex.*
Praziquantel (p.153·3).
Cysticercosis.

Zifin *Fahrenheit, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Zigabal *Tecnimede, Port.*
Oxcarbazepine (p.490·3).
Epilepsy.

Ziga-Gel *Bangkok Lab & Cosmetic, Thai.*
Aluminium hydroxide (p.1706·2); magnesium hydroxide (p.1743·2); simeticone (p.1770·2).
Flatulence; gastrointestinal hyperacidity; peptic ulcer.

Zigmadone *Virgo, Philipp.*
Povidone-iodine (p.1659·2).
Skin and mucous membrane disinfection; wounds.

Zihlava *Slovakofarma, Cz.†.*
Urtica (p.2409·3).
Renal calculi.

Zikaral *Sanovel, Turk.*
Tenoxicam (p.128·2).
Musculoskeletal and joint disorders.

Ziken *Kendrick, Mex.*
Mesna (p.1449·2).
Prevention of urotoxicity due to oxazaphosphorine antineoplastics.

Ziks *Nnodum, USA.*
Methyl salicylate (p.85·3); menthol (p.2340·1); capsaicin (p.32·3).
Musculoskeletal, joint, and soft-tissue disorders; neuralgia.

Zil *Sarabhai Piramal, India.*
Ornidazole (p.843·1).
Formerly contained tinidazole.
Amoebiasis; anaerobic bacterial infections; giardiasis; trichomoniasis.

Zilaben *Cristalia, Braz.*
Benzyl benzoate (p.2036·1).
Pediculosis; scabies.

Zilactin
Note.This name is used for preparations of different composition.
Zila, Philipp.
⊗ Tannic acid (p.2394·3); alcohol (p.1625·2).
Canker sores; cold sores; fever blisters.

Blairex, USA.
Benzyl alcohol (p.1631·3).
Formerly contained tannic acid.
Herpes labialis.

Zilactin Baby *Zila, Canad.*
Benzocaine (p.1854·1).
Teething.

Zilactin Cold Sore Gel *Blairex, Canad.*
Benzyl alcohol (p.1631·3).
Lip lesions; mouth ulcers.

Zilactin Tooth & Gum Pain Reliever *Blairex, Canad.*
Benzocaine (p.1854·1).

Zilactin Toothache Swab *Zila, Canad.*
Benzocaine (p.1854·1).
Toothache.

Zilactin-B *Blairex, Canad.*
Benzocaine (p.1854·1).
Mouth disorders.

Zilactin-B Medicated *Zila, USA.*
Benzocaine (p.1854·1).
Canker sores.

Zilactin-E *Hexa, Arg.†.*
Ergotamine tartrate (p.620·1); caffeine (p.1116·3); aspirin (p.20·3).
Migraine.

Zilactin-L *Blairex, Canad.; Blairex, USA.*
Lidocaine (p.1862·3).
Herpes labialis.

Zilactin-Lip *Zila, Canad.*
SPF 24: Octinoxate (p.1608·2); homosalate (p.1598·1); oxybenzone (p.1608·3); dimeticone (p.2032·1); menthol (p.2340·1).
Herpes labialis.

Ziladent *Zila, Philipp.*
⊗ Alcohol (p.1625·2); lidocaine (p.1862·3).
Mouth pain.

Zilast *Ipca, India.*
Cilostazol (p.1245·2).
Intermittent claudication.

Zildem *Adcock Ingram, S.Afr.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zilden *Genepharm, Gr.*
Diltiazem hydrochloride (p.1265·1).
Angina pectoris; hypertension.

Zileze *Pinewood, Irl.; Opus, UK†.*
Zopiclone (p.1039·1).
Insomnia.

Zilfic *Mintlab, Chile.*
Sildenafil citrate (p.2193·1).
Erectile dysfunction.

Zilion *Cadila, India.*
Zidovudine (p.913·3).
HIV infection.

Zilip *Keryos, Ital.*
Penciclovir (p.901·2).
Herpes labialis.

Zilisten *Demo, Gr.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Zilium *Wolfs, Belg.*
Domperidone maleate (p.1726·3).
Delayed gastric emptying; nausea and vomiting.

Zillt *KRKA, Rus.*
Clopidogrel bisulfate (p.1250·2).
Thromboembolism prophylaxis.

Zilongjin *Longshunrong, Philipp.*
Astragalus; angelica (p.2258·1).
Nutritional supplement.

Zilop *Nicholas, Indon.*
Gemfibrozil (p.1295·3).
Coronary heart disease; hyperlipidaemias.

Zilopur *Apsen, Braz.*
Allopurinol (p.552·2).
Gout.

Ziloxican *Zimaia, Port.†.*
Meloxicam (p.80·3).
Osteoarthrosis; rheumatoid arthritis.

Zilutrol *Abbott, Switz.†.*
Meloxicam (p.80·3).
Arthroses.

Zimadoce *Rubio, Spain.*
Cobamamide (p.1980·2).
Tonic.

Zimaina *Zimaia, Port.†.*
Aspirin (p.20·3); caffeine (p.1116·3).
Fever; pain.

Zimaks *Bilim, Turk.*
Cefixime (p.224·3).
Bacterial infections.

Zimalgin *Shreya, India.*
Paracetamol (p.108·1); caffeine (p.1116·3); codeine phosphate (p.37·2).
Pain.

Zimanel *Proge, Ital.*
Cefotaxime sodium (p.228·1).
Lidocaine hydrochloride (p.1862·3) is included in this preparation to alleviate the pain of injection.
Bacterial infections.

Zimaquin *Gynopharm, Chile.*
⊗ Clomifene citrate (p.2086·1).
Female and male infertility; menstrual disorders.

Zimbacol *Link, UK.*
Bezafibrate (p.1232·1).
Hyperlipidaemias.

Zimerol *Cetus, Arg.*
Orotic acid (p.2358·3); dehydrocholic acid (p.2292·2); deoxycholic acid (p.2266·3); homatropine (p.1881·2).
Liver disorders.

Zimeton *Sons, Mex.*
Pancreatin (p.2360·1); bile salts (p.2266·2); simeticone (p.1770·2).
Digestive disorders.

Zimicina *Hexal, Braz.†.*
Azithromycin (p.207·1).
Bacterial infections.

Zimmex *Silom, Thai.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia.

Zimocel *SIT, Ital.*
Dried yeast (p.1998·3).

Zimoclone *Gerard, Irl.*
Zopiclone (p.1039·1).
Insomnia.

Zimor *Rubio, Malaysia; Rubio, Singapore; Rubio, Spain; Rubio, Thai.†; TTN, Thai.†.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zimotris *Italmex, Mex.*
Amylase (p.2256·3); lipase (p.2360·3); pepsin (p.2365·1); chymotrypsin (p.2281·3); trypsin (p.2405·3).
Digestive disorders; pancreatic insufficiency.

Zimovane *Meda, Irl.; Aventis, UK.*
Zopiclone (p.1039·1).
Insomnia.

Zimox
Note. This name is used for preparations of different composition.
Faran, Gr.
Levodopa (p.804·3); carbidopa (p.803·1).
Parkinsonism.

Pfizer, Ital.
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Zimpax *PharmaConsult, Hung.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Zimpels Erkaltungskomplex I *Staufen, Ger.*
Homoeopathic preparation.

Zimpels Nieren- und Hautkomplex *Staufen, Ger.*
Homoeopathic preparation.

Zimstat *Alphapharm, Austral.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Zimulti *Sanofi-Aventis, Cz.; Sanofi-Aventis, Port.*
Rimonabant (p.2380·3).
Obesity.

Zimuvite *Pediapharma, Philipp.*
Ascorbic acid; betacarotene; *dl*-alfa tocoferil acetate; zinc gluconate (p.1922·1).
Immune stimulant; tonic.

Zimycan *Barrier Therapeutics, Belg.; Barrier Therapeutics, Neth.; Barrier Therapeutics, Port.*
Miconazole nitrate (p.541·3).
Fungal skin infections.

Zinabol *Makros, Braz.†.*
Cobamamide (p.1980·2).
Reduced appetite; tonic.

Zinacef
GSK, Belg.; GSK, Braz.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.†; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.
Cefuroxime sodium (p.238·2).
Bacterial infections.

GSK, Philipp.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Bacterial infections.

Zinadiur *Errekappa, Ital.*
⊗ Benazepril hydrochloride (p.1223·2); hydrochlorothiazide (p.1307·3).
Hypertension.

Zinadol *GSK, Gr.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zinadril *Errekappa, Ital.*
Benazepril hydrochloride (p.1223·2).
Heart failure; hypertension.

Zinamide *CSL, Austral.; MSD, Irl.†; MSD, NZ.*
Pyrazinamide (p.320·2).
Tuberculosis.

Zinaplex *Pediatrica, Philipp.*
Pyrazinamide (p.320·2).
Tuberculosis.

Zinasen *Atral, Port.*
Flunarizine hydrochloride (p.580·2).
Migraine; vertigo.

Zinat *GSK, Switz.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zinaxin *Bionax, Thai.†; Eurovita, Thai.†; Vita Healthcare, UK.*
Ginger (p.1732·3).
Musculoskeletal and joint disorders.

Zinaxin Plus *Bionax, Malaysia†; Eurovita, Malaysia†; Eurovita, Thai.*
Ginger (p.1732·3); alpinia galanga.
Musculoskeletal and joint disorders.

Zinbee *Pediapharma, Philipp.*
Zinc gluconate (p.1999·2).
Nutritional supplement; zinc deficiency.

Zinc for Acne *Natural Life, Arg.*
Zinc; vitamin C; Vitamin B ; vitamin A; vitamin E (p.1922·1).

Zinc B, E & C *Puritan Quartz, Thai.†.*
Multivitamin preparation with zinc (p.1922·1).

Zinc + C250 *Vitaplex, Austral.†.*
Zinc amino acid chelate (p.2000·1); ascorbic acid (p.1983·3).
Zinc deficiency.

Zinc C Plus *Vitaglow, Austral.†.*
Zinc amino acid chelate (p.2000·1); ascorbic acid (p.1983·3); vitamin B substances (p.1922·1).
Inflammation; skin disorders; wounds.

Zinc Cream White *McGloin, Austral.*
SPF 30+: Zinc oxide (p.1621·2); octinoxate (p.1608·2); enzacamene (p.1597·1).
Skin abrasions; skin irritation; sunscreen.

Zinc Lotion *Vitamed, Israel.*
Zinc oxide (p.1621·2).
Skin irritation.

Zinc Plus
Note. This name is used for preparations of different composition.
Cenovis, Austral.
Zinc amino acid chelate (p.2000·1); vitamins and minerals (p.1922·1).
Zinc deficiency.

Swiss Herbal, Canad.
Zinc gluconate (p.1999·2); zinc proteinate; vitamin C (p.1983·3).

Zinc Supplement *Vitaplex, Austral.†.*
Zinc gluconate (p.1999·2); vitamins and minerals (p.1922·1).
Zinc deficiency.

Zinc Zenith *Eagle, Austral.*
Zinc amino acid chelate (p.2000·1); ascorbic acid (p.1983·3); pyridoxine hydrochloride (p.1978·2); minerals (p.1922·1).
Zinc supplement.

Zincaband *SSL, Austral.†; Medlock Medical, UK.*
Zinc oxide (p.1621·2).
Eczema; leg ulcers; medicated bandage.

Zinc-ACE *Wassen, UK.*
Zinc; vitamins (p.1922·1).

Zinca-Pak *Smith & Nephew SoloPak, USA.*
Zinc sulfate (p.1999·2).
Additive for intravenous total parenteral nutrition solutions.

Zincaps *Aspen, Austral.; Aspen, Hong Kong; Healthcare Logistics, NZ; ST, Thai.*
Zinc sulfate (p.1999·2).
Zinc supplement.

Zincas *Farmapol, Pol.*
Zinc hydroaspartate (p.2000·1).
Aggression; depression; erectile dysfunction; growth disorders in children; immunological disorders; nervous disorders; schizophrenia; skin disorders; wounds.

Zincate *Paddock, USA.*
Zinc sulfate (p.1999·2).
Dietary supplement.

Zincation *Isdin, Spain.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Zincation Plus *Isdin, Spain.*
Pyrithione zinc (p.1611·2); coal tar (p.1616·2).
Scalp disorders.

Zincfrin *Alcon, Austral.; Alcon, Belg.; Alcon, Canad.; Alcon, Denm.; Alcon, Fin.†; Alcon, Ger.; Alcon, Malaysia†; Alcon, Mex.; Alcon, NZ; Alcon Cusi, Spain†; Alcon, Swed.; Alcon, USA.*
Phenylephrine hydrochloride (p.1568·1); zinc sulfate (p.1999·2).
Conjunctivitis; eye congestion; eye irritation.

Zincfrin Antihistaminicum *Alcon, Belg.†.*
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Conjunctival congestion; eye irritation.

Zincfrin-A *Alcon, Canad.; Alcon, Fin.†; Alcon, Mex.; Alcon, S.Afr.*
⊗ Antazoline phosphate (p.567·1); naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Allergic conjunctivitis.

Zinc-Imizol *Farmigea, Ital.*
⊗ Zinc sulfate (p.1999·2); naphazoline nitrate (p.1565·2).
Conjunctivitis, alone or associated with blepharitis.

Zinco *Berko, Turk.*
Zinc sulfate (p.1999·2).
Zinc deficiency; zinc supplement.

Zinco All' Acqua *Sella, Ital.†*
Zinc oxide (p.1621·2).
Skin disorders.

Zinco C *Berko, Turk.*
Zinc sulfate (p.1999·2); vitamin C (p.1983·3).
Zinc deficiency; zinc supplement.

Zinco Sulpha *Bell, India.*
Sulfacetamide sodium (p.335·3); zinc sulfate (p.1999·2).
Eye infections.

Zincod *Vitamed, Israel.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); kaolin (p.1738·1).
Nappy rash; skin irritation.

Zincoderm *Taro, Canad.; Bersan, Ital.*
Zinc oxide (p.1621·2).
Skin disorders.

Zincoderma *Confar, Port.*
Zinc oxide (p.1621·2).
Cicatrisation.

Zincofax *Pfizer Consumer, Canad.*
Zinc oxide (p.1621·2).
Nappy rash.

Zincol *Sam-On, Israel.*
Zinc sulfate (p.1999·2).
Skin ulcers; wounds; zinc deficiency.

Zincolok *Allergan, Braz.*
⊗ Zinc sulfate (p.1999·2); naphazoline hydrochloride (p.1565·2).
Ocular congestion.

Zincomed *UCB, UK.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zincometil *Farmila, Ital.*
Benzalkonium chloride (p.1629·1); zinc sulfate (p.1999·2).
Eye disinfection.

Zincon *Lederle, USA.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Zincopan *Gunther, Braz.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zincopto *Armoxindo, Indon.*
⊗ Naphazoline hydrochloride (p.1565·2); zinc sulfate (p.1999·2).
Eye irritation.

Zincoral *Mavi, Ital.*
Zinc and copper supplement (p.1922·1).

Zincosol *Bioceuticals, UK.*
Zinc sulfate (p.1999·2).

Zincovit *Labomed, Chile.*
Vitamin A; vitamin C; vitamin E; zinc (p.1922·1).
Dietary supplement.

Zincovit C *Theraskin, Braz.*
Multivitamin preparation with copper and zinc (p.1922·1).

Zincoxid *Framingham, Arg.*
Zinc oxide (p.1621·2).
Dietary supplement.

ZinCream *Medinova, Switz.*
Zinc oxide (p.1621·2).
Nappy rash; wounds.

Zincstic *Ideal Health, UK.*
Zinc oxide (p.1621·2); titanium dioxide (p.1617·3).
Sunscreen.

Zinctab *Pharmasant, Thai.†.*
Zinc (p.1999·1).
Zinc supplement.

Zincteral *Polfa, Cz.; Polfa Kutno, Pol.*
Zinc sulfate (p.1999·2).
Skin disorders; zinc deficiency; zinc supplement.

Zincum Hevert N *Hevert, Ger.*
Homoeopathic preparation.

Zincum valerianicum-Hevert *Hevert, Ger.*
Homoeopathic preparation.

Zincuprin *Sun-Farm, Pol.*
Copper hydroaspartate; zinc hydroaspartate (p.2000·1).
Copper and zinc deficiency.

Zincvit *Kenwood, USA.*
Multivitamin and mineral preparation (p.1922·1).

Zindaclin
Pharma Logistics, Belg.; Strakan, Singapore; Cantabria, Spain.
Clindamycin (p.251·1).
Acne.

Crawford, Cz.; Astellas, Ger.; Strakan, Irl.; Taro, Israel; Wolff, Malaysia; Pliva Krakow, Pol.; Astellas, Port.; Crawford, UK.
Clindamycin phosphate (p.251·2).
Acne.

Zindacline *Astellas, Fr.*
Clindamycin phosphate (p.251·2).
Acne.

Zindal *Prosel, Philipp.*
Clindamycin hydrochloride (p.251·1).
Bacterial infections; protozoal infections.

Zinecard
Pfizer, Canad.
Dexrazoxane (p.1443·1).
Prevention of doxorubicin cardiotoxicity.

Pharmacia Upjohn, USA.
Dexrazoxane hydrochloride (p.1443·1).
Prevention of doxorubicin cardiotoxicity.

Zinek-AIO *ICN, Cz.†.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zineli *Rafarm, Gr.*
Sodium cromoglicate (p.1136·3).
Allergic conjunctivitis; allergic rhinitis.

Zineryt *Eurolab, Arg.; Astellas, Belg.; Astellas, Cz.; Hermal, Ger.; Astellas, Hung.; Astellas, Irl.; Astellas, Ital.; Astellas, Neth.; Astellas, Pol.; Astellas, Port.; Yamanouchi, Rus.; Astellas, S.Afr.; Astellas, Spain; Astellas, UK.*
Erythromycin (p.269·2); zinc acetate (p.1999·1).
Acne.

Zinetac *GSK, India.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Zinetrin *Stiefel, Braz.*
Cetirizine (p.571·1).
Hypersensitivity reactions.

Zinex *Verheilen, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zinfect *Verisfield, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zingo *Anesiva, USA.*
Lidocaine hydrochloride (p.1862·3).
Local anaesthesia.

Zink beta *Betapharm, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zink Verla *Verla, Ger.*
Zinc gluconate (p.1999·2).
Zinc deficiency.

Zinkamin *Merck, Austria†; Falk, Ger.*
Bis(-histidinato) zinc (p.2000·1).
Zinc deficiency.

Zinkan *Wyeth Consumer, Neth.*
Dexphenothrin (p.2048·3); piperonyl butoxide (p.2049·1).
Pediculosis.

Zinkaspart *Twardy, Ger.*
Zinc aspartate (p.2000·1).
Zinc deficiency.

Zinkbrause *Verla, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zink-Calmitol *OBA, Denm.†.*
Camphor (p.2273·2); hyoscyamus oil (p.2323·3); menthol (p.2340·1); zinc oxide (p.1621·2).
Pruritus.

Zink-D Longoral *Artesan, Ger.; Cassella-med, Ger.*
Zinc gluconate (p.1999·2).
Zinc deficiency.

Zinkit *Worwag, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zink'N'Swim *Or-Dov, Austral.†.*
SPF 15+: Zinc oxide (p.1621·2).
Sunscreen.

Zinkokehl *Sanum-Kehlbeck, Ger.*
Homoeopathic preparation.

Zinkolie *Boots Healthcare, Neth.*
Zinc oxide (p.1621·2).
Skin disorders.

Zinkorell *Sanorell, Ger.*
Homoeopathic preparation.

Zinkorot *Worwag, Ger.*
Zinc orotate (p.2358·3).
Zinc deficiency.

Zinkorotat-POS *Ursapharm, Cz.*
Zinc orotate (p.2358·3).
Zinc deficiency.

Zinkotase *Biosyn, Ger.*
Zinc aspartate (p.2000·1).
Zinc deficiency.

Zinkpaste *Riemser, Ger.*
Zinc oxide (p.1621·2).
Skin disorders; skin ulcers; wounds.

Zink-Ratiopharm *Ratiopharm, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Zinksalbe *CT, Ger.*
Zinc oxide (p.1621·2); cod-liver oil (p.1935·2); glycerol (p.2314·2).
Wounds.

Zinksalbe Dialon *Engelhard, Ger.†.*
Zinc oxide (p.1621·2).
Skin disorders; wounds.

Zinksalbe Lichtenstein *Winthrop, Ger.*
Zinc oxide (p.1621·2).
Skin disorders.

Zink-Sandoz *Sandoz, Ger.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zinkzalf *Boots Healthcare, Neth.*
Zinc oxide (p.1621·2).
Skin disorders.

Zinmet *Mercury, Philipp.*
Promethazine hydrochloride (p.588·2).
Hypersensitivity reactions; nausea and vomiting; premedication; vestibular disorders.

Zinnat
GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Etex, Chile; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Hong Kong; GSK, Hung.; GSK, Indon.; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; Duncan, Philipp.; GSK, Pol.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Swed.; GSK, Thai.; GSK, UK; GSK, Venez.
Cefuroxime axetil (p.238·2).
Bacterial infections.

GSK, Fr.; GSK, Mex.
Cefuroxime axetil (p.238·2) or cefuroxime sodium (p.238·2).
Lidocaine hydrochloride (p.1862·3) may be included in some intramuscular injections to alleviate the pain of injection.
Formerly known as Curoxime in *Fr.*
Bacterial infections.

GSK, Turk.
Cefuroxime sodium (p.238·2).
Bacterial infections.

Zinnkraut-Tropfen *Bio-Diat, Ger.†.*
Equisetum (p.2299·3).
Urinary-tract disorders.

Zinnober D6 *Weleda, S.Afr.*
Homoeopathic preparation.

Zino *Soll (Σωλλ), Gr.*
Salicylic acid (p.1612·2).
Calluses.

Zinocep *Glaxo Allen, Ital.*
Cefuroxime sodium (p.238·2).
Bacterial infections.

Zinograf *Cellofarm, Braz.†.*
Ciclosporin (p.1822·2).
Transplant rejection.

Zinopin *Pynogin, UK.*
Pycnogenol (p.2368·1); ginger (p.1732·3).
Deep-vein thrombosis prophylaxis for travellers; motion sickness.

Zinopril *Teuto, Braz.*
Lisinopril (p.1325·2).
Hypertension.

Zinovat *Unipharma, Gr.*
Fluoxetine hydrochloride (p.391·2).
Depression.

Zinoxime *Montrose, Cz.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zinsomine *Christo, Hong Kong.*
Diphenhydramine hydrochloride (p.577·2); cetrimide (p.1634·1); zinc oxide (p.1621·2).
Dermatitis; pruritus.

Zintion *Drogsan, Turk.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Zintona *Grunwalder, Ger.; Chrisana, Switz.*
Ginger (p.1732·3).
Digestive system disorders; dizziness; gastric pain; motion sickness; nausea; vomiting.

Zintrepid *Essex, Chile; Schering-Plough, Mex.; Schering-Plough, Venez.*
Ezetimibe (p.1284·3); simvastatin (p.1390·2).
Hypercholesterolaemia.

Zinulin *Sarabhai Piramal, India.*
⊗ Insulin zinc injection (porcine) (30% amorphous, 70% crystalline) (p.443·2).
Diabetes mellitus.

Zinvit *Blackmores, Austral.*
Zinc sulfate (p.1999·2); magnesium sulfate (p.1679·3); vitamin B substances (p.1922·1).
Herpes labialis; mouth ulcers; skin disorders; wounds; zinc deficiency.

Zinvit C *Blackmores, Austral.*
Zinc sulfate (p.1999·2); magnesium sulfate (p.1679·3); ascorbic acid (p.1983·3).
Herpes labialis; mouth ulcers; skin disorders; wounds.

Zinvit G *Blackmores, Austral.*
Zinc sulfate (p.1999·2); magnesium sulfate (p.1679·3); vitamin B substances (p.1922·1).
Skin disorders; zinc deficiency.

Ziohex *Hexal, Philipp.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Ziox *Stratus, USA.*
⊗ Papain (p.2362·3); urea (p.1620·2); chlorophyllin copper complex (p.1471·1).

Zip-A-Dol *Labialfarma, Port.*
Ibuprofen (p.64·2).
Fever; pain.

Ziperid *Valeant, Hung.; ICN, Pol.*
Risperidone (p.1024·2).
Behaviour disorders; behavioural disorders; bipolar disorder; schizophrenia.

Zipos *Alodial, Port.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zipra *Columbia, Mex.*
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Ziprax *Cipla, India.*
Cefixime (p.224·3).
Bacterial infections.

Ziprol *Baldacci, Braz.*
Pantoprazole sodium (p.1760·1).
Peptic ulcer.

Zipsydon *Sun, India.*
Ziprasidone (p.1036·2).
Schizophrenia.

Ziptek *UCB, Gr.*
Cetirizine hydrochloride (p.570·3).
Hypersensitivity disorders.

Zipzoc *Smith & Nephew, Denm.; Smith & Nephew, Fin.; Smith & Nephew, Irl.; Smith & Nephew, Neth.; Smith & Nephew, Port.; Smith & Nephew Healthcare, UK.*
Zinc oxide (p.1621·2) impregnated stocking.
Leg ulcers; venous insufficiency.

Zipzoc Salvstrumpa *Smith & Nephew, Swed.*
Zinc oxide (p.1621·2).
Formerly known as Salvstrumpa.
Skin ulcers; vascular disorders.

Ziradryl *Parke, Davis, USA.*
Diphenhydramine hydrochloride (p.577·2); zinc oxide (p.1621·2); camphor (p.2273·2).
Pruritus.

Ziravir *Keryos, Ital.*
Famciclovir (p.876·1).
Herpesvirus infections.

Zirconia *Wermar, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Ziremex *Demo, Gr.*
Nimodipine (p.1357·2).
Neurological deficit following subarachnoid haemorrhage.

Zirpine *Pinewood, Irl.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Zirtec *UCB, Ital.*
Cetirizine hydrochloride (p.570·3).
Conjunctivitis; rhinitis; urticaria.

Zirtek *UCB, Austria†; UCB, Gr.†; UCB, Irl.; UCB, UK.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Zirvit *Ativus, Braz.*
A range of vitamin and mineral preparations (p.1922·1).

Zirvit Beta *Ativus, Braz.*
Betacarotene (p.1930·3).
Photosensitivity; vitamin A deficiency.

Zirvit E *Ativus, Braz.*
Tocoferil acetate (p.1992·3).
Vitamin E deficiency.

Zismirt *Gerard, Irl.*
Mirtazapine (p.409·2).
Depression.

Zispin *Organon, Irl.; Organon, UK.*
Mirtazapine (p.409·2).
Depression.

Zistic *Bernofarm, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Zita *LPC, UK.*
Cimetidine (p.1716·2).
Gastrointestinal disorders associated with hyperacidity.

Zitalgin *Josper, Braz.†.*
Dipyrone (p.49·2).
Fever; pain.

Zitanid *Novell, Indon.*
Tizanidine hydrochloride (p.1898·2).
Skeletal muscle spasm.

Zitazonium *Egis, Cz.; Egis, Hong Kong; EGIS, Hung.; Egis, Malaysia; Egis, Philipp.; Egis, Rus.; Egis, Thai.*
⊗ Tamoxifen citrate (p.772·3).
Anovulatory infertility; breast cancer; endometrial cancer; mastalgia.

Zitep *Andromaco, Mex.*
Sulfadiazine silver (p.337·2).
Burns; wounds.

Zithran *Ranbaxy, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Zithrocin *Biochem, India; Unique, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Zithro-Due *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zithroflam *Rimsa, Mex.*
Azithromycin (p.207·1); nimesulide (p.95·3).
Bacterial infections.

Zithrogen *Xixia, S.Afr.*
Azithromycin (p.207·1).
Bacterial infections.

Zithromax *Pfizer, Austral.; Pfizer, Austria; Pfizer, Canad.; Pfizer, Chile; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Israel; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Switz.; Pfizer, Thai.; Pfizer, UK; Pfizer, USA.*
Azithromycin (p.207·1).
Bacterial infections.

Zithropan *Vocate, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zithrotel *Anpharm (Ανφαρμ), Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zithroxyn *Help, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zitoxil *Elmor, Venez.*
Minoxidil (p.1342·1).
Alopecia.

Zitrax *Genepharm, Gr.*
Azithromycin (p.207·1).
Bacterial infections.

Zitrazol *Novell, Indon.*
Itraconazole (p.536·3).
Fungal infections.

Zitril *Cazi, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Zitrocin *Pliva-Lachema, Cz.; Pliva, Hung.*
Azithromycin (p.207·1).
Bacterial infections.

Zitroken *Kendrick, Mex.*
Azithromycin (p.207·1).
Bacterial infections.

Zitrolid *Shchelkovskii, Rus.*
Azithromycin (p.207·1).
Bacterial infections.

Zitromax *Pfizer, Arg.; Pfizer, Belg.; Pfizer, Braz.; Pfizer, Denm.; Pfizer, Ital.; Pfizer, Spain; Pfizer, Turk.; Pfizer, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Zitromil *Ducto, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Zitroneo *Neo Quimica, Braz.*
Azithromycin (p.207·1).
Bacterial infections.

Zitrotek *Pfizer, Turk.*
Azithromycin (p.207·1).
Bacterial infections.

Zitrozina *Neves, Port.*
Azithromycin (p.207·1).
Bacterial infections.

Zittec *Vesco, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; insect bites.

Zitumex *Rafarm, Gr.*
Piroxicam (p.117·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Zival *Valmor, Venez.*
Azithromycin (p.207·1).
Bacterial infections.

Zivas *Pascual, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias; ischaemic heart disease.

Ziverone *Rayere, Mex.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zix *Recalcine, Chile†.*
Meloxicam (p.80·3).
Inflammation; musculoskeletal and joint disorders; pain.

Ziz *Chatfield Laboratories, UK.*
Promethazine hydrochloride (p.588·2).
Insomnia.

Z-Kraft *Hexal, Arg.†.*
Zinc sulfate (p.1999·2).
Zinc deficiency.

Zlatobylova Nat *Megafyt-R, Cz.*
Solidago (p.2391·1).
Urinary-tract disorders.

Zleep *Wockhardt, India.*
Zolpidem (p.1038·2).
Insomnia.

Zlucnikova Cajova Smes *Megafyt-R, Cz.*
Agrimony (p.2249·2); marrubium (p.1564·1); rhubarb (p.1768·3); peppermint leaf (p.1761·2).
Biliary-tract disorders.

Z-Max
Note. A similar name is used for preparations of different composition (see below).
Schering-Plough, Mex.†.
Phentolamine mesilate (p.1370·2).
Erectile dysfunction.

ZMax
Note. A similar name is used for preparations of different composition (see above and below).
Pfizer, Philipp.
Azithromycin (p.207·1).
Respiratory-tract infections.

Zmax
Note. A similar name is used for preparations of different composition (see above).
Pfizer, USA.
Azithromycin (p.207·1).
Acute bacterial sinusitis; community-acquired pneumonia.

ZN Xampu *Stiefel, Braz.*
Zinc (p.1999·1).
Seborrhoea.

Zn-Fusin *Pisa, Mex.†.*
Zinc sulfate (p.1999·2).

ZNP *Stiefel, Arg.†; Stiefel, Canad.; Stiefel, Chile; Stiefel, Fr.; Stiefel, Ital.; Stiefel, Mex.; Stiefel, USA.*
Pyrithione zinc (p.1611·2).
Dandruff; pityriasis versicolor; seborrhoeic dermatitis; skin disorders.

Znupril *Velka, Gr.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus.

Zobacide *Garec, S.Afr.*
Metronidazole (p.837·1).
Anaerobic bacterial infections; protozoal infections.

Zobactam *Vocate, Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Zoben *Pharmaniaga, Malaysia.*
Albendazole (p.139·2).
Worm infections.

Zobid *SM, Philipp.*
Diclofenac sodium (p.44·3).
Gout; inflammation; musculoskeletal and joint disorders; pain.

Zobrixol *Natrapharm, Philipp.*
Ambroxol hydrochloride (p.1550·3).
Respiratory-tract congestion.

Zocardis *Menarini, Rus.*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Zocef *Ranbaxy, Malaysia.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zocolip *Durascan, Denm.*
Simvastatin (p.1390·2).
Hypercholesterolaemia.

Zocor *MSD, Arg.; MSD, Austral.; MSD, Belg.; MSD, Braz.; Merck Frosst, Canad.; MSD, Chile; MSD, Cz.; MSD, Denm.; MSD, Fin.; MSD-Chibret, Fr.; Dieckmann, Ger.; Vianex (Βιανεξ), Gr.; MSD, Hong Kong; MSD, Hung.; MSD, Indon.; MSD, Irl.; Neopharmed, Ital.; MSD, Malaysia; MSD, Mex.; MSD, Neth.; MSD, Norw.; MSD, Philipp.; MSD, Pol.; MSD, Port.; MSD, Rus.; MSD, S.Afr.; MSD, Singapore; MSD, Spain; MSD, Switz.; MSD, Thai.; MSD, Turk.; MSD, UK; Merck, USA; MSD, Venez.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction; hypercholesterolaemia.

Zocord *MSD, Austria; MSD, Swed.*
Simvastatin (p.1390·2).
Coronary heart disease; hypercholesterolaemia; ischaemic heart disease.

Zocord/ASA *MSD, Swed.†.*
Tablets, simvastatin (p.1390·2); tablets, aspirin (p.20·3).
Coronary atherosclerosis.

Zocovin *TO-Chemicals, Thai.*
Aciclovir (p.862·3).
Herpes simplex infections of the skin and mucous membranes.

Zodac *Zentiva, Cz.; Zentiva, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Zodalin *Elpen (Ελπεν), Gr.†.*
Codergocrine (p.364·1).
Peripheral vascular disorders.

Zodatron *Rafarm, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Zodeac *Econo Med, USA.*
Ferrous fumarate (p.1938·3); folic acid (p.1940·1); multivitamins and minerals (p.1922·1).
Iron-deficiency anaemias.

Zoderm
Note.This name is used for preparations of different composition.
GSK, India.
Oxiconazole nitrate (p.544·2); benzoic acid (p.1630·2).
Fungal skin infections.

Doak, USA.
Benzoyl peroxide (p.1590·2); urea (p.1620·2).
Acne.

Zodin *Trommsdorff, Ger.; Galenica, Gr.; Pronova, Neth.; Ferrer, Port.*
Omega-3-acid ethyl esters (p.1362·1).
Hyperlipidaemias; myocardial infarction.

Zodol *Saval, Chile.*
Tramadol hydrochloride (p.130·3).
Pain.

Zodorm *Unipharm, Israel.*
Zolpidem (p.1038·2).
Insomnia.

Zodormdura *Merck dura, Ger.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Zodurat *Pohl, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Zofadep *Biopharm, Philipp.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Zofen *Pharmaland, Thai.*
Pizotifen (p.624·2).
Anorexia; reduced appetite.

Zofenil *Menarini, Fr.; Menarini, Irl.; Menarini, Port.; Menarini, Spain; Menarini, Switz.*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Zofenil Plus *Menarini, Port.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zofenilduo *Menarini, Fr.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zofepril *Menarini, Gr.*
Zofenopril (p.1434·3).
Hypertension.

Zofepril Plus *Menarini, Gr.*
⊗ Zofenopril (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zofer *Adeka, Turk.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by cytotoxic therapy or radiotherapy; postoperative nausea and vomiting.

Zoff
Note. This name is used for preparations of different composition.
Smith & Nephew, Austral.
Dipropylene glycol methyl ether.
Adhesive plaster remover.

Smith & Nephew Healthcare, UK.
Trichloroethane (p.2027·2).
Adhesive plaster removal.

Zofil *Menarini, Neth.*
Zofenopril (p.1434·3).
Hypertension; myocardial infarction.

Zoflut *Cipla, India.*
⊗ Fluticasone propionate (p.1533·2).
Inflammatory skin disorders.

Zoflux *Libbs, Braz.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Zofora *Pharmy, Fr.†.*
Piroxicam (p.117·3).
Musculoskeletal, joint, and peri-articular disorders.

Zofran
GSK, Arg.; GSK, Austral.; GSK, Belg.; GSK, Hong Kong; GSK, Indon.; GSK, Israel; GSK, Malaysia; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; Glaxo Wellcome, Port.; GSK, Rus.; GSK, S.Afr.; GSK, Singapore; GSK, Spain; GSK, Switz.; GSK, Turk.; Glaxo Wellcome, USA; GSK, Venez.
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

GSK, Austria; GSK, Braz.; GSK, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Ger.; GSK, Hung.; GSK, Irl.; GSK, Ital.; GSK, Pol.; GSK, Swed.; GSK, Thai.; GSK, UK.
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

GSK, Philipp.
Ondansetron (p.1756·3).
Nausea and vomiting.

Zofredal *Kalbe, Indon.*
Risperidone (p.1024·2).
Psychoses.

Zofron *GSK, Gr.*
Ondansetron hydrochloride (p.1756·3).
Chemotherapy or radiotherapy-induced nausea and vomiting.

Zoiral *Aegis, Hong Kong.*
Clomipramine hydrochloride (p.386·3).
Depression; obsessive-compulsive disorder; panic disorder.

Zoiron *Multicare, Philipp.*
Ferrous fumarate (p.1938·3); vitamins (p.1922·1).
Iron deficiency; nutritional supplement.

Zok-Zid *Pfizer, Belg.; Pfizer, Denm.*
⊗ Metoprolol succinate (p.1338·1); hydrochlorothiazide (p.1307·3).
Hypertension.

Zol *Braun, Philipp.*
Metronidazole (p.837·1).
Anaerobic bacterial infections.

Zolac *Xepa-Soul Pattinson, Malaysia†.*
Bromocriptine mesilate (p.798·1).
Parkinsonism.

Zolacort *GMP, Indon.*
⊗ Miconazole nitrate (p.541·3); hydrocortisone (p.1535·2).
Infected skin disorders.

Zolacos CP *AstraZeneca, Austral.*
⊗ Tablets, bicalutamide (Cosudex) (p.686·2); implant, goserelin (Zoladex) (p.2108·1).
Prostatic cancer.

Zoladex *AstraZeneca, Arg.; AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.; AstraZeneca, Canad.; AstraZeneca, Chile; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Ger.; Promed, Ger.; Stern, Ger.; AstraZeneca, Gr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Indon.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Malaysia; AstraZeneca, Mex.; AstraZeneca, NZ; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; AstraZeneca, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; Zeneca, USA; AstraZeneca, Venez.*
⊗ Goserelin acetate (p.2108·2).
Breast cancer; controlled ovarian stimulation; endometriosis; female infertility; presurgical endometrial thinning; prostatic cancer; uterine fibroids.

Zolafren *Adamed, Pol.; Adamed, Port.*
Olanzapine (p.1012·1).
Bipolar disorder; mania; schizophrenia.

Zolagel *GMP, Indon.*
Miconazole nitrate (p.541·3).
Fungal skin and nail infections.

Zolam *Stadmed, India.*
Alprazolam (p.960·1).
Anxiety; mixed anxiety depressive states.

Zolamid *Mayne, Port.*
Midazolam hydrochloride (p.1007·3).

Zolamox *Cazi, Braz.*
⊗ Acetazolamide (p.1875·1).
Glaucoma.

Zolanix *Stiefel, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Zolapin *BPL-Meizler, Braz.†.*
Clozapine (p.981·1).
Psychoses.

Zolargene *Pentafarma, Port.*
Loratadine (p.583·3).

Zolaten *Sigma, Austral.†; Sigma, NZ.*
Aciclovir (p.862·3).
Herpes labialis.

Zolax *Sanovel, Turk.*
Fluconazole (p.532·1).
Fungal infections.

Zolben
Note. This name is used for preparations of different composition.
Sanofi-Aventis, Braz.
Albendazole (p.139·2).
Worm infections.

Novartis, Chile; Sanopharm, Switz.
Paracetamol (p.108·1).
Fever; pain.

Zolben C *Sanopharm, Switz.*
Paracetamol (p.108·1); ascorbic acid (p.1983·3).
Fever; pain.

Zoldaben *Neckerman, Braz.†.*
Mebendazole (p.148·3).
Worm infections.

Zoldan *Vitapan, Braz.†.*
Albendazole (p.139·2).
Worm infections.

Zoldan-A *Cryopharma, Mex.†.*
⊗ Danazol (p.2090·2).

Zoldem *Lannacher, Austria; Hexal, Ger.; Anglo-French Drugs, India; Gerard, Irl.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zoldicam *Rayere, Mex.*
Fluconazole (p.532·1).
Fungal infections.

Zoldorm *Ecosol, Switz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zoldria *Cipla, India; Cipla, Venez.*
Zoledronic acid (p.1106·1).
Bone metastases; hypercalcaemia of malignancy; metastatic bone disease.

Zole *Rexcel, India.*
Miconazole nitrate (p.541·3).
Fungal and Gram-positive bacterial skin infections.

Zole-F *Rexcel, India.*
⊗ Miconazole nitrate (p.541·3); fluocinolone acetonide (p.1531·3).
Fungal and Gram-positive bacterial skin infections.

Zoleprim *PP Lab, Thai.†.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Zoleptil *Avalanche, Cz.; Italfarmaco, Port.; Orion, UK.*
Zotepine (p.1040·1).
Schizophrenia.

Zoles *Simoes, Braz.†.*
Mebendazole (p.148·3); tiabendazole (p.156·2).
Worm infections.

Zoleta *Ranbaxy, India.*
Imatinib mesilate (p.733·1).
Chronic myeloid leukaemia; gastrointestinal stromal cancer.

Zolfin *Ipca, India†.*
Cefazolin (p.222·1).
Bacterial infections.

Zolicef *BMS, Austria; Millimed, Thai.; Apothecon, USA†.*
Cefazolin sodium (p.222·1).
Lidocaine hydrochloride (p.1862·3) may be included in the intramuscular injection to alleviate the pain of injection.
Bacterial infections.

Zolico *Farma Lepori, Spain.*
Folic acid (p.1940·1).
Folic acid deficiency; prevention of neural tube defects.

Zolidan *BPL-Meizler, Braz.†.*
Midazolam (p.1007·3).
Insomnia.

Zoliden *Unipharma, Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Zoliderm *Pharmaniaga, Malaysia†; Raza, Malaysia†.*
Econazole nitrate (p.531·1).
Fungal skin infections.

Zolidime *Collins, Mex.†.*
⊗ Phenylbutazone (p.117·1); aspirin (p.20·3); dexamethasone (p.1526·1).
Inflammation; musculoskeletal and joint disorders.

Zolief *Genthon, Hong Kong.*
Zopiclone (p.1039·1).
Insomnia.

Zolim *Schwarz, Ger.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zolimed *Unison, Thai.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Zolin
Note. This name is used for preparations of different composition.
Itaca, Braz.†.
Cefazolin (p.222·1).
Bacterial infections.

Abigo, Swed.†.
⊗ Oxymetazoline hydrochloride (p.1567·2).
Rhinitis; sinusitis.

Zolina
Note. This name is used for preparations of different composition.
Llorens, Spain.
⊗ Boric acid (p.2268·1); naphazoline hydrochloride (p.1565·2).
Eye irritation.

Megat, Venez.
Ciprofloxacin (p.243·3).
Bacterial infections.

Zoline *Pyridam, Indon.*
Mebhydrolin napadisilate (p.584·3).
Allergic disorders.

Zolinza *Merck, USA.*
Vorinostat (p.790·1).
Cutaneous T-cell lymphoma.

Zoliparin *Mann, Ger.*
Aciclovir (p.862·3).
Herpes simplex eye infections.

Zolistam *Angelini, Ital.; Sanofi-Aventis, Port.*
Mizolastine (p.586·1).
Allergic conjunctivitis; allergic rhinitis; allergic rhinoconjunctivitis; urticaria.

Zolistan *Novag, Spain.*
Mizolastine (p.586·1).
Allergic rhinitis; urticaria.

Zolium *Inibsa, Port.†.*
Gamolenic acid (p.2308·2); vitamin E (p.1992·2).
Premenstrual symptoms.

Zolival *Virgo, Philipp.; Reig Jofre, Spain.*
Cefazolin sodium (p.222·1).
Bacterial infections.

Zolken *Kener, Mex.*
Itraconazole (p.536·3).
Fungal infections.

Zolldenol *Novis, Gr.*
Omeprazole (p.1753·1).
Peptic ulcer.

Zollocid *Landson, Indon.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolmed *Medhaus, Philipp.*
Co-trimoxazole (p.258·1).
Bacterial infections; pneumocystis pneumonia.

Zolmia *Fahrenheit, Indon.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolmic *Delta, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Zolmicol *Geolab, Braz.*
Ketoconazole (p.539·1).
Fungal infections.

Zolmid *Laboratorios Chile, Chile.*
Midazolam (p.1007·3).
General anaesthesia; premedication; sedative.

Zolnod *Rowex, Irl.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolnoxs *Pharmacare, S.Afr.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolodorm *Richmond, Arg.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Zoloft
Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Canad.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pfizer, Ger.; Pfizer, Gr.; Pfizer, Hong Kong; Pfizer, Hung.; Pfizer, Indon.; Pfizer, Ital.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Neth.; Pfizer, Philipp.; Pfizer, Pol.; Pfizer, Port.; Pfizer, Rus.; Pfizer, S.Afr.; Pfizer, Singapore; Pfizer, Swed.; Pfizer, Switz.; Pfizer, Thai.; Pfizer, USA; Pfizer, Venez.
Sertraline hydrochloride (p.421·3).
Depression; mixed anxiety depressive states; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder; premenstrual dysphoric disorder; social phobia.

Pfizer, Norw.
Sertraline (p.422·1) or sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorder.

Zoloral *Ikapharmindo, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Zolotrin *Specifar, Gr.*
Sertraline (p.422·1).
Depression.

Zolpibell *Bellwether, Austral.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpic *Polpharma, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpidex *Giempi, Venez.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpidohexal *Hexal, Austria.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpidol *Dolorgiet, Neth.*
Zolpidem tartrate (p.1037·3).
Insomnia.

ZolpiGen *Generics, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpihexal *Hexal, S.Afr.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpi-Lich *Winthrop, Ger.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Zolpi-Med *Medika, Switz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpimerck *Generics, Cz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpinox *SVUS, Cz.; Krewel, Ger.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolpi-Q *Juta, Ger.; Q-Pharm, Ger.*
Zolpidem tartrate (p.1037·3).
Sleep disorders.

Zolpra *Ranbaxy, Mex.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolpramex *Sinterapico, Braz.†.*
Omeprazole (p.1753·1).
Peptic ulcer.

Zolsana *KRKA, Cz.; KRKA, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zolstan *Reddy, Malaysia; Biofarma, Venez.†.*
Fluconazole (p.532·1).
Fungal infections.

Zolstatin *Aurantis, Braz.†; Biochimico, Braz.†.*
Fluconazole (p.532·1).
Fungal infections.

Zolt *Orion, Fin.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zoltec *Pfizer, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Zoltem *Nobel, Turk.*
Ondansetron hydrochloride (p.1756·3).
Nausea and vomiting induced by cytotoxic therapy or radiotherapy; postoperative nausea and vomiting.

Zoltenk *Biotenk, Arg.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolterol *CCM, Hong Kong; CCM, Malaysia; CCM, Singapore.*
Diclofenac sodium (p.44·3).
Inflammation; musculoskeletal, joint, peri-articular, and soft-tissue disorders; pain.

Zoltren *Teuto, Braz.*
Fluconazole (p.532·1).
Fungal infections.

Zoltrim *Sandoz, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Zoltum *AstraZeneca, Fr.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zolvastin *Medlink, Philipp.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Zolvera *Rosemont, UK.*
Verapamil hydrochloride (p.1421·1).
Angina pectoris; arrhythmias; hypertension.

Zomacton *Ferring, Austria; Ferring, Belg.; Ferring, Cz.; Ferring, Denm.; Ferring, Fin.; Ferring, Fr.; Ferring, Ger.; Ferring, Gr.; Ferring, Hung.†; Ferring, Irl.; Ferring, Ital.; Ferring, Neth.; Ferring, Norw.; Ferring, Port.; Ferring, Spain; Ferring, Swed.; Er-Kim, Turk.; Ferring, UK.*
⊗ Somatropin (p.1799·3).
Growth disorders in renal failure; growth hormone deficiency; Prader-Willi syndrome; Turner's syndrome.

Zomel *Clonmel, Irl.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zomepral *Laboratorios Chile, Chile.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zomera *Novartis, Israel.*
Zoledronic acid (p.1106·1).
Bone metastases; hypercalcaemia of malignancy; multiple myeloma.

Zometa *Novartis, Arg.; Novartis, Austral.; Novartis, Austria; Novartis, Belg.; Novartis, Braz.; Novartis, Canad.; Novartis, Chile; Novartis, Cz.; Novartis, Denm.; Novartis, Fin.; Novartis, Fr.; Novartis, Ger.; Novartis, Gr.; Novartis, Hong Kong; Novartis, Hung.; Novartis, India; Novartis, Indon.; Novartis, Irl.; Novartis, Ital.; Novartis, Malaysia; Novartis, Mex.; Novartis, NZ; Novartis, Neth.; Novartis, Norw.; Novartis, Philipp.; Novartis, Pol.; Novartis, Port.; Novartis, Rus.; Novartis, S.Afr.; Novartis, Singapore; Novartis, Spain; Novartis, Swed.; Novartis, Switz.; Novartis, Thai.; Novartis, Turk.; Novartis, UK; Novartis, USA; Novartis, Venez.*
Zoledronic acid (p.1106·1).
Bone metastases; hypercalcaemia of malignancy; metastatic bone disease; multiple myeloma; osteoarthritis; osteoblastic lesions; osteolysis of malignancy; Paget's disease of bone.

Zometic *Chemopharma, Chile.*
Zopiclone (p.1039·1).
Insomnia.

Zomig *AstraZeneca, Austral.; AstraZeneca, Austria; AstraZeneca, Belg.; AstraZeneca, Braz.†; AstraZeneca, Canad.; AstraZeneca, Cz.; AstraZeneca, Denm.; AstraZeneca, Fin.; AstraZeneca, Fr.; AstraZeneca, Hong Kong; AstraZeneca, Hung.; AstraZeneca, Irl.; AstraZeneca, Israel; AstraZeneca, Ital.; AstraZeneca, Mex.; AstraZeneca, Neth.; AstraZeneca, Norw.; AstraZeneca, Philipp.; AstraZeneca, Pol.; AstraZeneca, Port.; IPR, Rus.; AstraZeneca, S.Afr.; AstraZeneca, Singapore; AstraZeneca, Spain; AstraZeneca, Swed.; AstraZeneca, Switz.; AstraZeneca, Thai.; AstraZeneca, Turk.; AstraZeneca, UK; AstraZeneca, USA; AstraZeneca, Venez.*
Zolmitriptan (p.628·1).
Migraine.

Zomigon *AstraZeneca, Arg.; AstraZeneca, Gr.*
Zolmitriptan (p.628·1).
Migraine.

Zomigoro *AstraZeneca, Fr.*
Zolmitriptan (p.628·1).
Migraine.

Zomiren *KRKA, Pol.*
Alprazolam (p.960·1).
Anxiety disorders.

Zomni *Jean-Marie, Hong Kong.*
Zopiclone (p.1039·1).
Insomnia.

Zomorph *Link, UK.*
⊗ Morphine sulfate (p.86·3).
Pain.

Zon *Antula, Fin.; Antula, Norw.; Antula, Swed.*
Ketoprofen (p.73·1).
Musculoskeletal and joint disorders; soft-tissue disorders; sports injuries.

Zonadin *Pliva-Lachema, Cz.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zonaker *Grin, Mex.*
Sodium hyaluronate (p.2320·1).

Zonal *Kalbe, Indon.*
Eperisone hydrochloride (p.1897·1).
Skeletal muscle spasm.

Zonalon *Medicis, Canad.†; Medicis, USA.*
Doxepin hydrochloride (p.389·1).
Pruritus.

Zonap *Unichem, India†.*
Zopiclone (p.1039·1).
Insomnia.

Zonatian *LKM, Arg.*
Isotretinoin (p.1599·2).
Acne.

Zoncef *AGIPS, Ital.†.*
Cefoperazone sodium (p.227·1).
Lidocaine hydrochloride (p.1862·3) is included in the intramuscular injection to alleviate the pain of injection.
Gram-negative bacterial infections.

Zondar *Niverpharm, Fr.*
Diacerein (p.41·3).
Osteoarthritis.

Zondra *Liomont, Mex.*
Alendronate sodium (p.1088·1).
Osteoporosis.

Zone-A *UAD, USA.*
⊗ Hydrocortisone acetate (p.1535·2); pramocaine (p.1868·2).

Zonef *Unison, Thai.*
Cefuroxime (p.238·2).
Bacterial infections.

Zonegran *Eisai, Cz.; Eisai, Fr.; Eisai, Ger.; Eisai, Hung.; Eisai, Irl.; Eisai, Neth.; Eisai, Port.; Eisai, Spain; Eisai, Swed.; Eisai, UK; Eisai, USA.*
Zonisamide (p.515·2).
Epilepsy.

Zonite *Menley & James, USA.*
Benzalkonium chloride (p.1629·1); edetic acid (p.1445·1); sodium acetate (p.1673·2); propylene glycol (p.2374·1); menthol (p.2340·1); thymol (p.1664·3).
Vaginal disorders.

Zonix *Mintlab, Chile.*
Zopiclone (p.1039·1).

Zonoct *Pharmacodane, Denm.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zoo Chews *Hall, Canad.†.*
Vitamin preparation (p.1922·1).

Zoo Chews with Iron *Hall, Canad.†.*
Vitamin preparation with iron (p.1922·1).

Zoodermina Cream *Bajer, Arg.*
Vitamin A palmitate (p.1973·1) spermaceti; beeswax (p.2028·1).
Emollient.

Zoom *Fabop, Arg.*
⊗ Salbutamol (p.1131·2).
Asthma.

Zop *Hexal, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopam *Pharmasant, Thai.*
Diazepam (p.986·3).
Anxiety; insomnia; neuroses; skeletal muscle spasm.

Zopax *Cipla-Medpro, S.Afr.*
Alprazolam (p.960·1).
Anxiety disorders; mixed anxiety depressive states; panic disorder.

Zopax Plus *Cipla, India.*
⊗ Alprazolam (p.960·1); propranolol hydrochloride (p.1380·3).

Zophralen *Demo, Gr.*
Ondansetron (p.1756·3).
Nausea and vomiting induced by chemotherapy.

Zophren *GSK, Fr.*
Ondansetron (p.1756·3) or ondansetron hydrochloride (p.1756·3).
Nausea and vomiting.

Zopicalm *Temmler, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopicalma *VP, Spain.*
Zopiclone (p.1039·1).
Insomnia.

Zopiclodura *Merck dura, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopicon *Intas, India.*
Zopiclone (p.1039·1).
Insomnia.

Zopigen *Generics, Hung.; Xixia, S.Afr.*
Zopiclone (p.1039·1).
Insomnia.

Zopimed *Adcock Ingram, S.Afr.*
Zopiclone (p.1039·1).
Insomnia.

Zopinox *Orion, Fin.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopi-Puren *Alpharma-Isis, Ger.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopiratio *Ratiopharm, Pol.*
Zopiclone (p.1039·1).
Sleep disorders.

Zopirol *Phoenix, Arg.*
⊗ Timolol maleate (p.1412·3).
Glaucoma; ocular hypertension.

Zopitan *Clonmel, Irl.*
Zopiclone (p.1039·1).
Insomnia.

Zopitin *Vitabalans, Cz.*
Zopiclone (p.1039·1).
Insomnia.

Zopivane *Cipla-Medpro, S.Afr.*
Zopiclone (p.1039·1).
Insomnia.

Zopranol *Menarini, Gr.; Guidotti, Ital.; Menarini, Neth.; Menarini, Port.; Guidotti, Spain.*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Zopranol Plus *Menarini, Gr.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zoprazide *Guidotti, Ital.*
⊗ Zofenopril calcium (p.1434·3); hydrochlorothiazide (p.1307·3).
Hypertension.

Zoprol *Toprak, Turk.*
Lansoprazole (p.1739·2).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zoprotec *Ulagay, Turk.*
Zofenopril calcium (p.1434·3).
Hypertension; myocardial infarction.

Zorac *Allergan, Austria; Pierre Fabre, Belg.; Allergan, Braz.†; Bioglan, Fin.†; Pierre Fabre, Fr.; Pierre Fabre Dermo Kosmetik, Ger.; Pierre Fabre, Gr.; Allergan, Irl.; Pierre Fabre, Israel; Pierre Fabre, Ital.; Pierre Fabre, Pol.; Pierre Fabre, Spain; Allergan, Swed.†; Pierre Fabre, Switz.; Allergan, UK.*
Tazarotene (p.1617·1).
Acne; psoriasis.

Zoracilin *Suan, Gr.*
Piperacillin (p.315·2); tazobactam (p.344·3).
Bacterial infections.

Zorail *Vita, Spain.*
Enalapril maleate (p.1276·1); nitrendipine (p.1358·2).
Hypertension.

Zorak *Allergan, S.Afr.*
Tazarotene (p.1617·1).
Psoriasis.

Zoral
Note. This name is used for preparations of different composition.
DHA, Hong Kong; DHA, Malaysia; DHA, Singapore.
Aciclovir (p.862·3).
Herpesvirus infections.

Andromaco, Mex.
Omeprazole (p.1753·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zoralin *Medikon, Indon.*
Ketoconazole (p.539·1).
Fungal infections.

Zoran *Reddy, Rus.; Reddy, Singapore†; Biofarma, Venez.†.*
Ranitidine hydrochloride (p.1766·1).
Dyspepsia; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zoratio *Ratiopharm, Pol.*
Zolpidem tartrate (p.1037·3).
Insomnia.

Zorax *Sunward, Malaysia†; Sunward, Singapore.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zoraxin *Duopharma, Hong Kong.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zorbtive *Serono, USA.*
⊗ Somatropin (p.1799·3).
Short bowel syndrome.

Zorced *Collins, Mex.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; cerebrovascular risk reduction; hypercholesterolaemia.

Zorclone *Ivax, Irl.*
Zopiclone (p.1039·1).
Insomnia.

Zordyl *Julphar, UAE.*
Chlorhexidine (p.1635·2).
Oral hygiene.

Zoref *Glaxo Allen, Ital.; Glaxo Wellcome, Port.*
Cefuroxime axetil (p.238·2).
Bacterial infections.

Zorel *Ferron, Indon.*
Aciclovir (p.862·3).
Herpes simplex skin and mucous membrane infections.

Zorem *Pliva, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Zorex *Shchelkovskii, Rus.*
Dimercaprol (p.1444·1); calcium pantothenate (p.1959·3).
Cardiac glycoside poisoning; chronic alcoholism; heavy metal poisoning.

Zorkenil *Unipharma, Gr.*
Azelaic acid (p.1589·3).

Zorotop *Medika, Switz.*
Loperamide hydrochloride (p.1741·1).
Diarrhoea.

Zoroxin *MSD, Austria; MSD, Belg.; MSD, Denm.†.*
Norfloxacin (p.309·2).
Bacterial infections.

ZORprin *Par, USA.*
Aspirin (p.20·3).
Fever; osteoarthritis; pain; rheumatoid arthritis.

Zorstat *Pliva, Rus.*
Simvastatin (p.1390·2).

Zortrix *Ativus, Braz.*
Salix (p.121·3).
Fever; inflammation; pain.

Zoru *E-Z-EM, Belg.†.*
Tartaric acid (p.2395·2); sodium bicarbonate (p.1673·2); dimeticone (p.1770·2).
Gastrointestinal radiography.

Zostavax *Sanofi Pasteur, Cz.; Sanofi Pasteur, Port.; Merck, USA.*
A live varicella-zoster vaccine (Oka strain) (p.2242·2).
Active immunisation.

Zostevir *Menarini, Cz.; Menarini, Gr.*
Brivudine (p.867·3).
Herpes zoster infections.

Zostex *Berlin-Chemie, Ger.; Menarini, Port.; UFSA, Turk.*
Brivudine (p.867·3).
Herpes zoster infections.

Zostrix *Link, Austral.; Medicis, Canad.; Rafa, Israel; AFT, NZ; Rodlen, USA.*
Capsaicin (p.32·3).
Diabetic neuropathy; osteoarthritis; post-surgical pain; postherpetic neuralgia; rheumatoid arthritis.

Zostrum *Galderma, Ger.; Galderma, Irl.†.*
Idoxuridine (p.881·2) in dimethyl sulfoxide.
Herpes labialis; herpes zoster.

Zostydol *Guidotti, Spain†.*
Brivudine (p.867·3).
Herpes zoster infections.

Zosul *Cipla, India.*
Cefoperazone sodium (p.227·1); sulbactam sodium (p.335·1).
Bacterial infections.

Zosvir *Elea, Arg.†.*
Famciclovir (p.876·1).
Herpesvirus infections.

Zosyn *Wyeth, India; Lederle, USA.*
Piperacillin sodium (p.315·2); tazobactam sodium (p.344·2).
Bacterial infections.

Zoter
Note. This name is used for preparations of different composition.
Gap, Gr.
Pravastatin (p.1375·1).
Hyperlipidaemias.

Interbat, Indon.
Aciclovir (p.862·3).
Herpesvirus infections.

Zotex-PE *Vertical, USA.*
Brompheniramine maleate (p.569·2); phenylephrine hydrochloride (p.1568·1).
Upper respiratory-tract disorders.

Zotinar *Cipan, Port.*
⊗ Desonide (p.1525·1).
Skin disorders.

Zotinar-N *Cipan, Port.*
⊗ Desonide (p.1525·1); neomycin sulfate (p.305·1).
Infected skin disorders.

Zoto-HC *Horizon, USA.*
⊗ Chloroxylenol (p.1640·2); pramocaine hydrochloride (p.1868·1); hydrocortisone (p.1535·2).
Formerly known as Xotic.
Ear disorders.

Zoton *Wyeth, Austral.; Wyeth, Irl.; Neopharm, Israel; Wyeth Lederle, Ital.; Wyeth, NZ†; Wyeth, UK.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; gastrointestinal hyperacidity; peptic ulcer; Zollinger-Ellison syndrome.

Zotral *Polpharma, Pol.*
Sertraline hydrochloride (p.421·3).
Depression; obsessive-compulsive disorder.

Zotran *Pfizer, Chile.*
Alprazolam (p.960·1).
Anxiety; panic attacks.

Zotrim *Sigma, UK.*
Maté (p.2416·1); guarana (p.2416·1); damiana (p.2292·1).
Slimming aid.

Zotrole *Pinewood, Irl.*
Lansoprazole (p.1739·2).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zov800 *Wellcome, Port.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zovast *Darya-Varia, Indon.; Cipla, Philipp.*
Simvastatin (p.1390·2).
Cardiovascular risk reduction; hypercholesterolaemia.

Zovatin *Eczacibasi, Rus.; Eczacibasi, Turk.*
Simvastatin (p.1390·2).
Atherosclerosis; cardiovascular risk reduction; hypercholesterolaemia.

Zovia *Watson, USA.*
Ethinylestradiol (p.2101·3); etynodiol diacetate (p.2103·2).
28-Day packs also contain 7 inert tablets.
Combined oral contraceptive.

Zovir *GSK, Denm.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zovirax
GSK, Arg.; GSK, Canad.; GSK, Cz.; GSK, Fr.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.; GSK, India; GSK, Indon.; GSK, Israel; GSK, Ital.; Santen, Jpn; GSK, Malaysia; GSK, Philipp.; GSK, Pol.; GSK, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Turk.
Aciclovir (p.862·3).
Herpesvirus infections.

GSK, Austral.; GSK, Austria; GSK, Belg.; GSK Consumer, Belg.; GSK, Braz.; GSK, Chile; GSK, Fin.; GSK, Ger.; GSK, Irl.; GSK, Mex.; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Rus.; GSK, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; Biovail, USA; Glaxo Wellcome, USA.
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections; HIV infection.

GSK, Venez.
Aciclovir sodium (p.862·3).
Herpesvirus infections.

Zoxan
Note. This name is used for preparations of different composition.
Pfizer, Fr.; Euro Registratie, Neth.
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

FDC, India.
Ciprofloxacin (p.243·3).
Bacterial infections.

Zoxil *Xixia, S.Afr.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Zoxon *Zentiva, Cz.; Zentiva, Pol.; Leciva, Rus.*
Doxazosin mesilate (p.1275·1).
Benign prostatic hyperplasia; hypertension.

Zoylex *BPL-Meizler, Braz.†.*
Aciclovir (p.862·3).
Herpesvirus infections.

ZP 11 *Revlon, Canad.†.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

ZP Dermil *Edol, Port.*
Pyrithione zinc (p.1611·2).
Scalp disorders.

Z-Pak *Pfizer, Canad.*
Azithromycin (p.207·1).
Bacterial infections.

Z-Plus *Dormer, Canad.*
Pyrithione zinc (p.1611·2); menthol (p.2340·1).
Dandruff; seborrhoeic dermatitis.

ZSC *Sigma, Austral.*
Zinc oxide (p.1621·2); starch (p.1968·1); chlorphenesin (p.529·2); talc (p.1615·2).
Hyperhidrosis; nappy rash; skin irritation.

Zubes *Ernest Jackson, UK.*
Menthol (p.2340·1); anise oil (p.2258·2).

Zubes Blackcurrant *Ernest Jackson, UK.*
Citric acid (p.2284·1); menthol (p.2340·1); anise oil (p.2258·2).

Zubes Honey & Lemon *Ernest Jackson, UK.*
Honey (p.1948·2); citric acid (p.2284·1); menthol (p.2340·1).

Zuckli *Berlin-Chemie, Rus.*
Saccharin sodium (p.1960·3); sodium cyclamate (p.1936·3).
Sugar substitute.

Zucoflaxin *Zuiko, Philipp.*
Cefalexin (p.218·2).
Bacterial infections.

Zudem *Aldril, Philipp.*
Cefpodoxime proxetil (p.232·1).
Bacterial infections.

Zufalm *Ratiopharm, Cz.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Zuflax *Richmond, Arg.*
Isoflurane (p.1785·3).
General anaesthesia.

Zuidex *Q-Med, UK.*
Dextranomer (p.1593·3); hyaluronic acid (p.2320·1).
Female stress urinary incontinence.

zuk Schmerzgel, zuk Schmerzsalbe *Altana, Ger.†.*
Glycol salicylate (p.62·3).
Musculoskeletal, joint, peri-articular, and soft-tissue disorders; neuralgia.

zuk thermo *Altana, Ger.†.*
Glycol salicylate (p.62·3); benzyl nicotinate (p.28·1).
Musculoskeletal and joint disorders.

Zukedib *Loeffler, Mex.*
Glimepiride (p.441·1).
Diabetes mellitus.

Zulboral *Farmedia, Gr.*
Sodium cromoglicate (p.1136·3).
Nasal allergy.

Zuledin *Demo, Gr.*
Chlorpromazine hydrochloride (p.969·2).
Agitation; psychoses.

Zuleptan *Bago, Chile.*
Mirtazapine (p.409·2).
Anxiety; depression; insomnia.

Zulex *Almirall, Spain.*
Acamprosate calcium (p.958·3).
Alcoholism.

Zulmedx *Bajamed, Mex.*
Omeprazole (p.1753·1).
Peptic ulcer.

Zultrop *Tropica Mas, Indon.*
Co-trimoxazole (p.258·1).
Bacterial infections.

Zumablok *Sandoz, Indon.*
⊗ Atenolol (p.1217·3).
Angina pectoris; arrhythmias; hypertension.

Zumaderm-N *Sandoz, Indon.*
⊗ Fluocinolone acetonide (p.1531·3); neomycin sulfate (p.305·1).
Infected skin disorders.

Zumadiac *Sandoz, Indon.*
Gliclazide (p.440·3).
Diabetes mellitus.

Zumafen *Sandoz, Indon.*
Amoxicillin (p.202·2); clavulanic acid (p.250·2).
Bacterial infections.

Zumafib *Sandoz, Indon.*
Fenofibrate (p.1286·2).
Hyperlipidaemias.

Zumaflox *Sandoz, Indon.*
Ciprofloxacin (p.243·3).
Bacterial infections.

Zumalgic *Erempharma, Fr.*
Tramadol hydrochloride (p.130·3).
Pain.

Zumalin *Sandoz, Indon.*
Lincomycin hydrochloride (p.293·2).
Bacterial infections.

Zumamet *Sandoz, Indon.*
Metformin hydrochloride (p.453·2).
Diabetes mellitus.

Zumaran *Sandoz, Indon.*
Ranitidine hydrochloride (p.1766·1).
Peptic ulcer; Zollinger-Ellison syndrome.

Zumasid *Sandoz, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zumatab *Sandoz, Indon.*
Thiamphenicol (p.351·1).
Bacterial infections.

Zumatic *Sandoz, Indon.*
Clindamycin (p.251·1).
Bacterial infections.

Zumatram *Sandoz, Indon.*
Tramadol hydrochloride (p.130·3).
Pain.

Zumatrol *Sandoz, Indon.*
Metoclopramide hydrochloride (p.1747·3).
Anorexia; dyspepsia; nausea and vomiting.

Zumazol *Sandoz, Indon.*
Ketoconazole (p.539·1).
Fungal skin infections.

Zumba
Note. This name is used for preparations of different composition.
Novum, Mex.
Vitamins; minerals; damiana; guarana; arginine (p.1922·1).
Crefar, Port.
Yohimbine hydrochloride (p.2200·2).
Erectile dysfunction.

Zumenon *Solvay, Austral.; Solvay, Austria; Solvay, Belg.; Solvay, Fin.; Solvay, Neth.; Solvay, Port.; Solvay, Switz.; Solvay, UK.*
Estradiol (p.2097·2).
Menopausal disorders; oestrogen deficiency; osteoporosis.

Zumilin *Farmedia, Gr.*
Azelaic acid (p.1589·3).
Acne.

Zumorin *Sons, Mex.*
Ampicillin trihydrate (p.204·2).
Bacterial infections.

Zundic *Raffo, Arg.*
Amlodipine besilate (p.1214·1).
Angina pectoris; hypertension.

Zurcal *Novartis, Arg.†; Nycomed, Austria; Novartis, Braz.; Novartis, Chile; Altana, Mex.; Altana, Port.; Nycomed, Switz.*
Pantoprazole sodium (p.1760·1).
Gastritis; gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zurcale *Altana, Belg.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Zurcazol *Nycomed, Gr.*
Pantoprazole sodium (p.1760·1).
Gastro-oesophageal reflux; peptic ulcer.

Zurfix *Phoinix Pharm (Φοινιξ Φαρμ), Gr.*
Ranitidine hydrochloride (p.1766·1).
Conditions where gastric acid reduction is beneficial; gastric hypersecretion including Zollinger-Ellison syndrome; peptic ulcer.

Zurim *Atral, Port.*
Allopurinol (p.552·2).
Gout; hyperuricaemia.

Zurinel *Prater, Chile.*
Atorvastatin (p.1219·1).

Zurocid *Farmilia, Gr.*
Simvastatin (p.1390·2).
Hyperlipidaemias.

Zuvair *Reddy's, India.*
Zafirlukast (p.1150·2).
Asthma.

Z-Vita *Pediapharma, Philipp.*
Lysine hydrochloride; vitamin B substances; zinc gluconate (p.1922·1).
Nutritional supplement.

Z-Xtra *Magna, USA.*
Mepyramine maleate (p.585·2); benzocaine (p.1854·1); zinc oxide (p.1621·2).
Skin disorders.

Zyatrol *Smith Kline & French, Port.*
Ropinirole hydrochloride (p.816·1).

Zyban *GSK, Austral.; GSK, Austria; GSK, Belg.; GSK, Braz.; Biovail, Canad.; GSK, Cz.; GSK, Denm.; GSK, Fin.; GSK, Fr.; GSK, Ger.; GSK, Gr.; GSK, Hong Kong; GSK, Hung.†; GSK, India; GSK, Irl.; GSK, Israel; GSK, Ital.; GSK, Malaysia; GSK, NZ; GSK, Neth.; GSK, Norw.; GSK, Pol.; Glaxo Wellcome, Port.; GSK, S.Afr.; GSK, Singapore; GSK, Swed.; GSK, Switz.; GSK, Turk.; GSK, UK; Glaxo Wellcome, USA; GSK, Venez.†.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Zycalcit *Cadila, India.*
Calcitonin (salmon) (p.1093·1).
Hypercalcaemia of malignancy; metastatic bone pain; osteoporosis; Paget's disease of bone.

Zycel *Cadila, India.*
Celecoxib (p.34·2).
Osteoarthritis; rheumatoid arthritis.

Zycin *Cadila, India; Interbat, Indon.*
Azithromycin (p.207·1).
Bacterial infections.

Zyclir *Arrow, Austral.*
Aciclovir (p.862·3) or aciclovir sodium (p.862·3).
Herpesvirus infections; HIV infection.

Zyclorax *Mugi, Indon.*
Aciclovir (p.862·3).
Herpesvirus infections.

Zydalis *Zydus, India.*
Tadalafil (p.2196·2).
Erectile dysfunction.

Zydan *SM, Venez.*
Benzydamine (p.27·3).
Mouth and throat inflammation.

Zyderm *Collagen, Austral.; Collagen, Ger.†; McGhan, Ger.†; McGhan, Hong Kong†; Inamed, Singapore†.*
Collagen (bovine) (p.2286·1).
Lidocaine (p.1862·3) is included in this preparation to alleviate the pain of injection.
Skin contour defects.

Zydinol *More, Philipp.*
Paracetamol (p.108·1).
Fever; pain.

Zydol *CSL, Austral.; Grunenthal, Irl.; Grunenthal, Port.; Grunenthal, UK.*
Tramadol hydrochloride (p.130·3).
Pain.

Zydone *Endo, USA.*
Hydrocodone tartrate (p.63·1); paracetamol (p.108·1).
Pain.

Zydowin *Zydus, India.*
Zidovudine (p.913·3).
HIV infection.

Zyfetor *Allen, Austria.*
⊗ Dutasteride (p.2188·1).
Benign prostatic hyperplasia.

Zyflo *Critical Therapeutics, USA.*
Zileuton (p.1151·2).
Asthma.

Zyflox
Note. This name is used for preparations of different composition.
Promed, Indon.
Ofloxacin (p.310·2).
Bacterial infections.
Zydus, Philipp.
Ciprofloxacin hydrochloride (p.243·3).
Bacterial infections.

Zygium *Solara, Mex.*
Calcitriol (p.1986·2).
Hypoparathyroidism; osteoporosis; pseudohypoparathyroidism; renal osteodystrophy; rickets.

Zykinase *Cadila, India.*
Streptokinase (p.1402·3).
Thromboembolic disorders.

Zykolat-EDO *Mann, Ger.*
Cyclopentolate hydrochloride (p.1879·3).
Production of mydriasis and cycloplegia.

Zylapour *Farmanic, Gr.*
Allopurinol (p.552·2).
Gout; hyperuricaemia associated with cancer chemotherapy; kidney stones.

Zylfina *Merck, Port.*
⊗ Finasteride (p.2188·3).
Alopecia androgenetica.

Zylium *Farmasa, Braz.*
Ranitidine hydrochloride (p.1766·1).
Acid aspiration; gastro-oesophageal reflux; gastrointestinal haemorrhage; peptic ulcer; Zollinger-Ellison syndrome.

Zyllergy *Dexcel, Israel.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Zyllt *KRKA, Pol.*
Clopidogrel bisulfate (p.1250·2).
Atherosclerosis.

Zylohist *Zydus, Philipp.*
Loratadine (p.583·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zylol *Teva, Israel.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; uric acid nephropathy.

Zyloprim *Sigma, Austral.; GSK, Canad.; GSK, Mex.; GSK, Philipp.; GSK, S.Afr.; Faro, USA.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; renal calculi.

Zyloram *Ranbaxy, Cz.; Ranbaxy, Hung.*
Citalopram hydrobromide (p.385·3).
Depression; panic disorder.

Zyloric *GSK, Austria; SMB, Belg.; GSK, Braz.; GSK, Chile; GSK, Fin.; GSK, Fr.; Mibe, Ger.; GSK, Gr.; Sigma, Hong Kong; GSK, India; GSK, Indon.; GSK, Irl.; Wellcome, Israel†; GSK, Ital.; GSK, Malaysia; GSK, Neth.; GSK, Norw.; GSK, Pol.; Vitoria, Port.; GSK, Singapore; Faes, Spain; GSK, Swed.; GSK, Switz.; GSK, Thai.; GSK, UK; GSK, Venez.*
Allopurinol (p.552·2).
Gout; hyperuricaemia; hyperuricosuria; renal calculi.

Zylotin *Virgo, Philipp.*
Carbocisteine (p.1553·2).
Cough.

Zymacap *Roberts, USA.*
Multivitamin preparation (p.1922·1).

Zymacter *Remedina, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Zymad *Novartis Sante, Fr.*
Colecalciferol (p.1986·2).
Vitamin D deficiency.

Zyma-D2 *Novartis Sante, Fr.†.*
Ergocalciferol (p.1987·1).
Vitamin D deficiency.

Zymaduo *Novartis Sante, Fr.*
Sodium fluoride (p.1962·2); colecalciferol (p.1986·2).
Dental caries prophylaxis; rickets.

Zymafluor *Novartis Consumer, Austria; Novartis Consumer, Cz.; Novartis Sante, Fr.; Novartis Consumer, Ger.; Novartis Consumer, Hung.; Novartis Consumer, Israel; Novartis Consumer, Ital.; Novartis Consumer, Neth.; Novartis Consumer, Pol.; Novartis Consumer, Port.; Novartis Consumer, S.Afr.; Novartis Consumer, Spain†; Novartis Consumer, Switz.; Novartis, Thai.; Novartis, Turk.*
Sodium fluoride (p.1962·2).
Dental caries prophylaxis; fluoride supplement.

Zymafluor D *Novartis Consumer, Ger.*
Sodium fluoride (p.1962·2); colecalciferol (p.1986·2).
Dental caries prophylaxis; rickets.

Zymamed *Novartis Consumer, Austria.*
Diclofenac potassium (p.44·3).
Fever; pain.

Zymanta *Asofarma, Mex.*
Clonazepam (p.478·2).
Anxiety; epilepsy.

Zymar *Allergan, Braz.; Allergan, Canad.; Allergan, Chile; Allergan, Mex.; Allergan, Philipp.; Allergan, Singapore; Allergan, Thai.; Allergan, USA.*
Gatifloxacin (p.281·1).
Bacterial eye infections.

Zymaran *Allergan, Arg.*
Gatifloxacin (p.281·1).
Bacterial eye infections.

Zyme E *Blooming Fields, Philipp.*
Vitamin E (p.1992·2).
Vitamin E deficiency.

Zymechol *Blooming Fields, Philipp.*
Omega-3 fish oil (p.1362·2).
Hyperlipidaemias.

Zymed *Millimed, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zymelin *Nycomed, Denm.; Leiras, Fin.†; Nycomed, Norw.; Nycomed, Swed.*
⊗ Xylometazoline hydrochloride (p.1575·1).
Otitis; rhinitis; sinusitis.

Zymelytic *Blooming Fields, Philipp.*
Carbocisteine (p.1553·2).
Respiratory-tract congestion.

Zymine *Vindex, USA.*
Triprolidine hydrochloride (p.592·3) or triprolidine tannate (p.593·1).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zymine HC *Vindex, USA.*
Hydrocodone tartrate (p.63·1); triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).

Zymine-D *Vindex, USA.*
Triprolidine hydrochloride (p.592·3); pseudoephedrine hydrochloride (p.1571·2).

Zymizinc *Aguettant, Fr.†.*
Zinc gluconate (p.1999·2).
Zinc deficiency.

Zymoplex
Note. This name is used for preparations of different composition.
Genepharm, Gr.
⊗ Tamoxifen citrate (p.772·3).
Breast cancer.
Sanofi, Switz.†.
Pancreatic protease and amylase (p.2337·3); enzymes of *Aspergillus oryzae*; amylase (p.2256·3); protease; cellulase (p.2279·1); lipase; dimethicone (p.1770·2).
Dyspepsia; flatulence.

Zymoptic *Cooper (Κοπερ), Gr.†.*
⊗ Carteolol (p.1241·2).
Glaucoma.

Zymoxyl *Blooming Fields, Philipp.*
Amoxicillin trihydrate (p.202·2).
Bacterial infections.

Zynace *Xepa-Soul Pattinson, Malaysia†.*
Enalapril maleate (p.1276·1).
Heart failure; hypertension.

Zynal *Korean Drug, Singapore†.*
Naproxen sodium (p.92·3).
Gout; musculoskeletal, joint, and peri-articular disorders; pain.

Zyncet *Unichem, Rus.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Zyneva *Medicus, Gr.*
Mitoxantrone (p.754·3).
Malignant neoplasms.

Zynicor *Zydus, India.*
Nicorandil (p.1349·1).
Angina pectoris.

Zyno *Bangkok Lab & Cosmetic, Thai.*
⊗ Triamcinolone acetonide (p.1544·3).
Skin disorders.

Zynor *Ivax, Irl.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; pruritus; urticaria.

Zynox *Intramed, S.Afr.*
Naloxone hydrochloride (p.1453·2).
Opioid overdosage; reversal of opioid depression.

Zyntabac *GSK, Neth.; GSK, Port.; GSK, Spain.*
Bupropion hydrochloride (p.383·1).
Aid to smoking withdrawal.

Zynzol *Lannacher, Cz.*
⊗ Anastrozole (p.681·2).
Breast cancer.

† This preparation may no longer be actively marketed

⊗ Contains a substance whose use may be restricted in certain sports (see p.vii)

Zyolaif *Medimar, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Zyom *Zydus, Philipp.*
Omeprazole (p.1753·1).
Gastro-oesophageal reflux; peptic ulcer; Zollinger-Ellison syndrome.

Zyomet *Goldshield, UK.*
Metronidazole (p.837·1).
Rosacea.

Zyon *Minerva (Μινέρβα), Gr.*
Pravastatin (p.1375·1).
Hyperlipidaemias.

Zypi *Schwarz, Philipp.*
Pioglitazone hydrochloride (p.456·1).
Diabetes mellitus.

Zyplast *Luxurians, Arg.†; Collagen, Austral.; Collagen, Ger.†; McGhan, Ger.†; McGhan, Hong Kong†; Inamed, Singapore†.*
Collagen (p.2286·1).
Lidocaine (p.1862·3) may be included in this preparation to alleviate the pain of injection.
Skin contour defects.

Zyplo *Pfizer, Braz.; Armstrong, Mex.*
Levodropropizine (p.1557·3).
Coughs.

Zypraz *Kalbe, Indon.*
Alprazolam (p.960·1).
Anxiety; panic disorder.

Zyprexa
Lilly, Arg.; Lilly, Austral.; Lilly, Austria; Lilly, Belg.; Lilly, Braz.; Lilly, Chile; Lilly, Cz.; Lilly, Denm.; Lilly, Fin.; Lilly, Fr.; Lilly, Ger.; Lilly, Gr.; Lilly, Hong Kong; Lilly, Hung.; Lilly, Indon.; Lilly, Irl.; Lilly, Israel; Lilly, Ital.; Lilly, Malaysia; Lilly, Mex.; Lilly, NZ; Lilly, Neth.; Lilly, Norw.; Lilly, Philipp.; Lilly, Pol.; Lilly, Port.; Lilly, Rus.; Lilly, S.Afr.; Lilly, Singapore; Lilly, Spain; Lilly, Swed.; Lilly, Switz.; Lilly, Thai.; Lilly, Turk.; Lilly, UK; Lilly, USA; Lilly, Venez.
Olanzapine (p.1012·1).
Bipolar disorder; dementia; mania; schizophrenia.
Lilly, Canad.
Olanzapine (p.1012·1) or olanzapine tartrate.
Psychoses.

Zyquin *Cadila, India.*
Gatifloxacin (p.281·1).
Bacterial infections.

Zyrac *Osoth, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; hypersensitivity reactions; insect bites.

Zyrantol *Leovan, Gr.*
Ambroxol hydrochloride (p.1550·3).
Respiratory disorders associated with viscous mucus.

Zyrazine *British Dispensary, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; insect bites.

Zyrcon *Condrugs, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; allergic skin disorders.

Zyrex *Masa, Thai.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders.

Zyrlex *UCB, Swed.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; pruritus; urticaria.

Zyrrigin *Unison, Philipp.*
Cetirizine hydrochloride (p.570·3).
Allergic rhinitis; urticaria.

Zyrtec *Rontag, Arg.; UCB, Austral.; UCB, Austria; UCB, Belg.; GSK, Braz.; GSK, Chile; UCB, Cz.; UCB, Denm.; UCB, Fin.; UCB, Fr.; UCB, Ger.; UCB, Hong Kong; UCB, Hung.; UCB, India; UCB, Jpn; UCB, Malaysia; UCB, Mex.; Pharmabroker, NZ; UCB, Neth.; UCB, Norw.; UCB, Philipp.; Vedim, Pol.; UCB, Port.; UCB, Rus.; UCB, S.Afr.; UCB, Singapore; UCB, Spain; UCB, Switz.; UCB, Thai.; UCB, Turk.; Pfizer, USA; Pfizer, Venez.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; asthma; hypersensitivity reactions; insect bites; pruritus; urticaria.

Zyrtec D *UCB, Pol.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Zyrtec Decongestant *Pharmabroker, NZ.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis; cold symptoms.

Zyrtec Duo *UCB, Ger.†.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic rhinitis.

Zyrtec-D *Rontag, Arg.; GSK, Braz.; GSK, Chile†; UCB, Hong Kong; UCB, Hung.; UCB, Malaysia; UCB, Mex.; UCB, Thai.; Pfizer, USA; Pfizer, Venez.*
Cetirizine hydrochloride (p.570·3); pseudoephedrine hydrochloride (p.1571·2).
Allergic conjunctivitis; allergic rhinitis; nasal congestion.

Zytaz *Cadila, India.*
Ceftazidime (p.234·1).
Bacterial infections.

Zytee *Raptakos, India.*
Choline salicylate (p.36·3).
Aphthous ulcers; denture irritation; teething pain.

Zytofen *Medicine Products, Thai.*
Ketotifen fumarate (p.582·2).
Asthma; hypersensitivity reactions.

Zytram *Pharmaco, NZ; Napp, Port.; Zambon, Spain.*
Tramadol hydrochloride (p.130·3).
Pain.

Zytrim *Merckle, Ger.*
Azathioprine (p.1818·2).
Auto-immune disorders; organ transplant rejection.

Zytrin *Stadmed, India.*
Terazosin hydrochloride (p.1410·2).
Benign prostatic hyperplasia.

Zytual *Leovan, Gr.*
⊗ Budesonide (p.1520·1).
Allergic rhinitis.

Zyvir *Novartis, Port.*
Famciclovir (p.876·1).
Herpesvirus infections.

Zyvox *Pfizer, Arg.; Pfizer, Austral.; Pfizer, Braz.; Pfizer, Chile; Pfizer, Hong Kong; Pharmacia, Hung.†; Pfizer, Indon.; Pfizer, Irl.; Pfizer, Malaysia; Pfizer, NZ; Pfizer, Philipp.; Pfizer, Rus.; Pfizer, Singapore; Pfizer, Thai.; Pfizer, UK; Pharmacia Upjohn, USA; Pfizer, Venez.*
Linezolid (p.293·3).
Gram-positive bacterial infections.

Zyvoxam *Pfizer, Canad.; Pfizer, Mex.*
Linezolid (p.293·3).
Gram-positive bacterial infections.

Zyvoxid *Pfizer, Austria; Pfizer, Belg.; Pfizer, Cz.; Pfizer, Denm.; Pfizer, Fin.; Pfizer, Fr.; Pharmacia, Ger.; Pfizer, Gr.; Pharmacia, Hung.†; Pharmacia, Israel; Pharmacia, Ital.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, Pol.; Pfizer, Port.; Pfizer, S.Afr.; Pfizer, Spain; Pfizer, Swed.; Pfizer, Switz.*
Linezolid (p.293·3).
Formerly known as Zyvox in *Israel*.
Gram-positive bacterial infections.

Zyx *Biofarm, Pol.*
Cetirizine hydrochloride (p.570·3).
Allergic conjunctivitis; allergic rhinitis; urticaria.

Zyxem *Farmalab, Braz.; GSK, Mex.*
Levocetirizine hydrochloride (p.583·2).
Allergic conjunctivitis; allergic rhinitis; allergic skin disorders; urticaria.

Directory of Manufacturers

The names and addresses of the manufacturers or distributors of the products and proprietary medicines mentioned in Martindale are listed below in alphabetical order of the abbreviated names used in the Preparations section.

1A, Austria. 1A Pharma GmbH, Sandleitengasse 15, A-1160 Vienna, Austria.
1A, Ger. 1 A Pharma GmbH, Keltenring 1 + 3, 82041 Oberhaching, Germany.
url: www.1apharma.de
1A, Hung. 1A Pharma, Pf 66, 1301 Budapest, Hungary.
url: www.1apharma.hu
1A, Pol. See *Hexal, Pol.*
2K, Denm. 2K Pharma A/S, H P Christensens Vej 1, 3000 Helsingor, Denmark.
url: www.2kpharma.com
3DDD, Belg. 3DDD NV, Diestersteenweg 349, 3510 Kermt, Belgium.
3M, Arg. 3M Argentina S.A.C.I.F.I.A., Los Arboles 842, 1686 Hurlingham, Buenos Aires, Argentina.
url: www.3m.com
3M, Austral. 3M Pharmaceuticals P/L, P.O. Box 101, Pennant Hills, NSW 2120, Australia.
url: www.3m.com
3M, Belg. 3M Pharma SA/NV, Hermeslaan 7, 1831 Diegem, Belgium.
url: www.mmm.com
3M, Canad. 3M Pharmaceuticals, P.O. Box 5757, London, Ontario, N6A 4T1, Canada.
url: www.3m.com
3M, Chile. 3M Chile SA, Santa Isabel 1001, Santiago, Chile.
3M, Cz. See *3M, UK.*
3M, Denm. 3M Pharma, Fabriksparken 15, 2600 Glostrup, Denmark.
url: www.3m.com/dk
3M, Fin. Suomen 3M Oy/3M Pharma, Lars Sonckin kaari 6, PL 90, 02601 Espoo, Finland.
url: www.3m.com
3M, Fr. Laboratoires 3M Santé, Bd de l'Oise, 95029 Cergy-Pontoise cdx, France.
url: www.3m.com
3M, Ger. 3M Medica, Hammfelddamm 11, 41460 Neuss, Germany.
url: www.3mmedica.de
3M, Hong Kong. 3M Hong Kong Ltd, 5/F Victoria Ctr, 15 Watson Rd, North Point, Hong Kong.
url: www.3m.com
3M, Hung. 3M Hungária Kft, Váci út 178, 1138 Budapest, Hungary.
3M, Irl. See *United Drug, Irl.*
3M, Israel. 3M Israel Ltd, 91 Medinat Haehudim St, P.O. Box 2042, Herzliya 46120, Israel.
url: www.3m.com
3M, Ital. 3M Italia S.p.A., Via S Bovio 3, Loc. S Felice, 20090 Segrate (MI), Italy.
url: www.3m.com
3M, Malaysia. 3M Malaysia Sdn Bhd, Bangunan 3M, 6 Persiaran Tropicana, 47410 Petaling Jaya, Selangor, Malaysia.
url: www.3m.com
3M, Mex. 3M Mexico S.A. de C.V., Av. Santa Fe No. 55, 01210 Mexico D.F., Mexico.
url: www.3m.com.mx
3M, Neth. 3M Pharma Nederland BV, Industrieweg 23, 2382 NW Zoeterwoude, Netherlands.
url: www.3m.com
3M, Norw. 3M Pharma, Hvamv.6, Postboks 100, 2013 Skjetten, Norway.
url: www.3m.com/no
3M, NZ. 3M Pharmaceuticals, C.P.O. Box 2201, Auckland, New Zealand.
url: www.3m.com
3M, Philipp. 3M Pharmaceuticals, 18/F PCI Bank Tower II, Makati Ave, Makati City, Philippines.
3M, Pol. 3M Poland Sp. zo.o., al. Katowicka 117, Kajetany, 05-830 Nadarzyn, Poland.
url: www.3m.pl
3M, Port. See *Agostinho, Port.*
3M, S.Afr. 3M SA (Pty) Ltd, Private Bag X926, Rivonia 2128, South Africa.
url: www.3m.com
3M, Singapore. See *Zuellig, Singapore.*
3M, Spain. 3M España, Juan Ignacio Luca de Tena 19-25, 28027 Madrid, Spain.
url: www.3m.com
3M, Swed. 3M Svenska AB, 191 89 Sollentuna, Sweden.
url: www.3m.se
3M, Switz. 3M (Schweiz) AG, Eggstrasse 93, 8803 Rüschlikon, Switzerland.
url: www.3m.com
3M, Thai. See *Diethelm, Thai.*
url: www.3m.com
3M, UK. 3M Health Care Ltd, Ashby Rd, Loughborough, Leicestershire, LE11 1EP, UK.
url: www.3m.com/uk
3M, USA. 3M Pharmaceuticals, 3M Center, St Paul, MN 55133-1000, USA.
url: www.3m.com
3M Espe, Belg. See *3M, Belg.*
3M Espe, Cz. See *3M Espe, Ger.*
3M Espe, Ger. 3M ESPE AG, ESPE Platz, 82229 Seefeld, Germany.
url: www.3mespe.de
3M Espe, Hong Kong. See *3M, Hong Kong.*
3-OL, Israel. 3-OL Ltd, P.O. Box 3906, Petach Tikva, Israel.
7 Oaks, USA. 7 Oaks Pharmaceutical Corp., 161 Harry Stanley Drive, Easley, SC 29640, USA.
url: www.7oakspharma.com
Aacifar, Port. Aacifar Produtos Químicos e Farmacêuticos Lda, Av. José Malhoa 16-B 2, 1070-159 Lisbon, Portugal.
AAH, UK. AAH Pharmaceuticals Ltd, Sapphire Court, Walsgrave Triangle Park, Coventry, Warwickshire, CV2 2TX, UK.
url: www.aah-hospitalservice.co.uk
aai, USA. aai Pharma Inc., 2320 Scientific Park Drive, Wilmington, NC 28405, USA.
url: www.aaipharma.com
aar, Ger. aar pharma GmbH & Co. KG, Alleestr. 11, 42853 Remscheid, Germany.
url: www.aar.de
AB, Ital. AB Analitica S.r.l., Via Svizzera16, 35127 Padua, Italy.
url: www.abanalitica.it
Abana, USA. See *Jones, USA.*
Abatron, UK. Abatron Ltd, Chapel St, Potton, Sandy, Bedfordshire, SG19 2PT, UK.
Abbott, Arg. Abbott Laboratories Argentina S.A., Ing. Butty 240, Piso 13, 1001 Capital, Buenos Aires, Argentina.
url: www.abbott.com
Abbott, Austral. Abbott Australasia P/L, P.O. Box 101, Cronulla, NSW 2230, Australia.
url: www.abbottlabs.com.au
Abbott, Austria. Abbott GmbH, Perfektastrasse 86, A-1230 Vienna, Austria.
url: www.abbott.com
Abbott, Belg. Abbott SA, Parc Scientific, Rue du Bosquet 2, 1348 Louvain-la-Neuve, Belgium.
url: www.abbott.com
Abbott, Braz. Abbott Laboratórios do Brasil Ltda, Rua Michigan 735, 4566905 São Paulo, SP, Brazil.
url: www.abbottbrasil.com.br
Abbott, Canad. Abbott Laboratories Ltd, P.O. Box 6150, Station Centre-Ville, Montreal, Quebec, H3C 3K6, Canada.
url: www.abbott.ca
Abbott, Chile. Abbott Laboratories de Chile Ltda, El Salto 5380, Huechuraba, Santiago, Chile.
Abbott, Cz. Abbott Laboratories sro, Šafaňkova 17, 120 00 Prague 2, Czech Republic.
url: www.abbott.com
Abbott, Denm. Abbott Laboratories A/S, Smakkedalen 6, 2820 Gentofte, Denmark.
url: www.abbott.dk
Abbott, Fin. Abbott Oy, Pihatörmä 1 A, 02240 Espoo, Finland.
url: www.abbott.fi
Abbott, Fr. Abbott-France, 10 rue d'Arcueil, Silic 233, 94528 Rungis cdx, France.
url: www.abbott.fr
Abbott, Ger. Abbott GmbH & Co. KG, Max-Planck-Ring 2, 65205 Wiesbaden, Germany.
url: www.abbott.de
Abbott, Gr. Abbott (Hellas) S.A., 512 Vouliagmenis Ave, 174 56 Alimos, Greece.
url: www.abbott.com
Abbott, Hong Kong. Abbott Laboratories Ltd, 20/F AIA Tower, 183 Electric Rd, North Point, Hong Kong.
url: www.abbott.com
Abbott, Hung. Abbott Laboratories (Magyarország) Kft, Teve u 1/a-c, 1139 Budapest, Hungary.
Abbott, India. Abbott Laboratories (India) Pvt Ltd, 17 R Kamani Marg, Mumbai 400 001, India.
url: www.abbott.co.in
Abbott, Indon. Abbott PT, Menara Jamsostek Lt 23, Jakarta, DKI Jaya, Indonesia.
Abbott, Irl. Abbott Laboratories, Ireland Ltd, 4051 Kingswood Drive, Citywest Business Campus, Dublin 24, Ireland.
url: www.abbott.ie
Abbott, Israel. Abbott Laboratories S.A., Atidim Science Park, Bldg 4, P.O. Box 58099, Tel Aviv 61580, Israel.
url: www.abbott.com
Abbott, Ital. Abbott S.p.A., Via Pontina Km 52, 04010 Campoverde (Latina), Italy.
url: www.abbott.com
Abbott, Jpn. Abbott Japan Co Ltd, 2-53 Shiromi 2-chome, Chuo-ku, Osaka, Japan.
Abbott, Malaysia. Abbott Laboratories (M) Sdn Bdh, 22 Jln Pemaju U1/15, Seksyen U1, Hicom-Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia.
url: www.abbott.com.my
Abbott, Mex. Abbott Laboratories de Mexico S.A. de C.V., Av. Coyoacan 1622, Benito Juarez del Valle, 03100 Mexico D.F., Mexico.
url: www.abbott.com
Abbott, Neth. Abbott BV, Postbus 727, 2132 WT Hoofddorp, Netherlands.
url: www.abbott.com
Abbott, Norw. Abbott Norge AS, Nesoyv.4, Postboks 123, 1361 Billingstad, Norway.
url: www.abbott.no
Abbott, NZ. Abbott Laboratories (NZ) Ltd, P.O. Box 35-128, Naenae, Lower Hutt, New Zealand.
url: www.abbott.com
Abbott, Philipp. Abbott Labs (Phils) Inc., 102 EDSA, Cor Madison Ave, Mandaluyong City, Philippines.
Abbott, Pol. Abbott Laboratories Poland Sp. zo.o., ul. Domaniewska 41, 02-672 Warsaw, Poland.
url: www.abbott.pl
Abbott, Port. Abbott Laboratórios, Lda, Rua Cidade de Córdova, 1, Alfragide, 2720 Amadora, Portugal.
url: www.abbott.com
Abbott, Rus. Abbott Laboratories SA, 9 Dimitrovsky per., 103031 Moscow, Russia.
url: www.abbott.com
Abbott, S.Afr. Abbott South Africa (Pty) Ltd, P.O. Box 7208, Weltevredenpark, Johannesburg 1715, South Africa.
url: www.abbott.com
Abbott, Singapore. Abbott Laboratories (S) Pte Ltd, 1 Maritime Square, 12-01 Harbour Front Centre, S 099253, Singapore.
url: www.abbott.com.sg
Abbott, Spain. Abbott Laboratories, Josefa Valcarcel 48, 28027 Madrid, Spain.
url: www.abbott.com
Abbott, Swed. Abbott Scandinavia AB, Box 509, 169 29 Solna, Sweden.
url: www.abbott.se
Abbott, Switz. Abbott AG, Neuhofstrasse 23, Postfach, 6341 Baar, Switzerland.
url: www.abbott.com
Abbott, Thai. Abbott Laboratories Ltd, 2/4 Nai Lert Tower, 5th and 9th Floor, Wireless Rd, Lumpini, Pathumwan, Bangkok 10330, Thailand.
url: www.abbott.co.th
Abbott, Turk. Abbott Laboratuarları Ltd. Şti., Ekinciler Caddesi, Hedef Plaza K:6, Kavacyk/Beykoz, İstanbul, 81640, Turkey.
url: www.abbott.com
Abbott, UK. Abbott Laboratories Ltd, Abbott House, Norden Rd, Maidenhead, Berkshire, SL6 4XE, UK.
url: www.abbottuk.com
Abbott, USA. Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-3500, USA.
url: www.abbott.com
Abbott, Venez. Abbott Laboratories C.A., Aptdo Postal No. 1412, Caracas 1010, Venezuela.
url: www.abbott.com
Abbott Diabetes Care, Canad. See *Abbott Diabetes Care, USA.*
Abbott Diabetes Care, Fr. Abbott Diabetes Care (Lab), 12 rue de la Couture, B.P. 20235, 94528 Rungis cdx, France.
Abbott Diabetes Care, UK. See *Abbott, UK.*
Abbott Diabetes Care, USA. Abbott Diabetes Care Inc., 1360 South Loop Rd, Alameda, CA 94502, USA.
Abbott Diagnostics, Ital. Abbott S.p.A. Divisione Diagnostici, Via Mar della Cina 262, 00100 Rome, Italy.
url: www.abbott.com
Abbott Nutrition, UK. See *Abbott, UK.*
Abbott Nutrition, USA. Abbott Nutrition, 625 Cleveland Ave, Columbus, OH 4325-1724, USA.
url: www.abbottnutrition.com
ABC, Fr. ABC Pharmacare SAS, Normandial, 2 av du Pays-de-Caen, 14460 Colombelles, France.
ABC, Ital. ABC Farmaceutici S.p.A., C.so Vittorio Emanuele 72, 10121 Turin, Italy.
url: www.abcfarmaceutici.it
ABC, Port. See *Pierre Fabre, Port.*
AB-Consult, Austria. AB-Consult Handels-GmbH, Eichenstrasse 32, A-1120 Vienna, Austria.
Abdi, Rus. Abdi Ibrahim Pharmaceutical, Barklaya St 6, str 26, 121086 Moscow, Russia.
url: www.abdiibrahim.com
Abdi, Turk. Abdi İbrahim İlaç San. ve Tic. A.Ş., Kore Şehitleri Cad. No: 19, Zincirlikuyu, İstanbul, Turkey.
url: www.abdiibrahim.com
Abdi Ibrahim, Indon. See *Combiphar, Indon.*
Abello, Spain. See *MSD, Spain.*
Abfar, Turk. See *Fako, Turk.*
Abic, Israel. See *Teva, Israel.*
Abic-Teva, Thai. See *RX, Thai.*
Abigo, Denm. Abigo A/S, Birkholmvej 28, Osted, 4000 Roskilde, Denmark.
Abigo, Swed. Abigo Medical AB, 436 32 Askim, Sweden.
url: www.abigo.com
Abiogen, Ital. Abiogen Pharma S.p.A., Via Meucci 36, 56014 Ospedaletto (PI), Italy.
ABL, Braz. Antibioticos do Brasil Ltda, Rod. Gal. Milton T de Souza SP 332 Km 1, 13150000 Cosmopolis, São Paulo, Brazil.
Able, USA. Able Laboratories Inc., 6 Hollywood Court, South Plainfield, NJ 07080, USA.
url: www.ablelabs.com
Abnoba, Ger. Abnoba Heilmittel GmbH, Hohenzollernstr. 16, 75177 Pforzheim, Germany.
url: www.abnoba.de
Abraxis, USA. Abraxis Oncology, 11777 San Vicente Blvd, Suite 550, Los Angeles, CA 90049, USA.
url: www.abraxisoncology.com
Abtswinder, Cz. Abtswinder Naturheilmittel GmbH, Czech Republic.
ABZ, Ger. AbZ-Pharma GmbH, Dr. Georg-Spohn-Str. 7, 89143 Blaubeuren, Germany.
url: www.abz-pharma.de
AC Helcor, Hung. Ac Helcor-Hungary Kft, Madarász Viktor u 27 VIII em. 50, 1131 Budapesy, Hungary.
Acambis, USA. Acambis, 38 Sidney St, Cambridge, MA 02139, USA.
url: www.acambis.com
acaSan, Austria. acaSan Pharma GmbH, Rauchfangkehrergasse 7/17, A-1150 Vienna, Austria.
Accentia, USA. Accentia Biopharmaceuticals, 324 South Hyde Park Ave, Suite 350, Tampa, FL 33606, USA.
url: www.accentia.net
Accurex, Canad. Accurex Health Care Manufacturing Inc., 20 Sage Court, Brantford, Ontario, N3R 7T4, Canada.
Ace, Neth. Ace Pharmaceuticals, P.O. Box 1262, 3890 BB Zeewolde, Netherlands.
url: www.ace-pharm.nl
Ace, Philipp. Ace Pharmaceuticals Inc., 101 Don Vicente St, Don Antonio Heights, Commonwealth Ave, Quezon City, Philippines.
Acemed, Hung. See *PannonPharma, Hung.*
Ache, Braz. Ache Laboratórios Farmacêuticos S.A., Rodovia Presidente Dutra Km 222.2, 07034-904 Guarulhos, São Paulo, Brazil.
url: www.ache.com.br
Aciprosalud, Venez. Importadora Aciprosalud C.A., Av. Libertador, c/Calle Alameda, Edif. Folgana, Piso 9 Of.9-A El Rosal, Caracas, Venezuela.
Acis, Ger. acis Arzneimittelvertrieb GmbH, Bajurwarenring 14, 82041 Oberhaching, Germany.
url: www.acis.de
Acis, Hung. Acis-Pharma Kft, Hársfa u 20, 2089 Telki, Hungary.
Aclae, Fr. Aclae Santé, 64 rue Anatole-France, 92300 Levallois-Perret, France.
ACM, Fr. Laboratoires ACM, 9 bis blvd Jean-Jaurès, 92100 Boulogne, France.
ACM, Neth. ACM Ooms Allergie BV, Comeniuslaan 65, 3706 XC Zeist, Netherlands.
ACME, Philipp. See *Lantaka, Philipp.*
Acme, USA. Acme United Corp., 1931 Black Rock Turnpike, Fairfield, CT 06432, USA.
url: www.acmeunited.com
ACO, Swed. ACO AB, Box 501, Nasbypark, 183 25 Täby, Sweden.
url: www.pharmacia.se
ACO Hud, Denm. See *Cosmea, Denm.*
ACO Hud, Fin. ACO Pharma Oy, Pihatörmä 1A, 02240 Espoo, Finland.
ACO Hud, Norw. See *ACO Hud, Swed.*
ACO Hud, Swed. ACO Hud AB, Box 622, 194 26 Upplands Väsby, Sweden.
url: www.aconordic.com
Acorda, USA. Acorda Therapeutics, 15 Skyline Drive, Hawthorn, NY 10532, USA.
Acorus, Irl. See *Acorus, UK.*
Acorus, UK. Acorus Therapeutics Ltd, High Crane Lodge, Hamsterley, County Durham, DL13 3QS, UK.
url: www.acorus-therapeutics.com
Acos, Ital. See *Bersan, Ital.*
ACP, Belg. A.C.P. S.C, Rue Georges Moreau 174, 1070 Brussels, Belgium.
ACRAF, Cz. See *ACRAF, Ital.*

ACRAF, Ital. ACRAF SpA, Viale Amelia 70, 00181 Rome, Italy.
ACRAF, Neth. See *ACRAF, Ital.*
ACRAF, Port. See *ACRAF, Ital.*
ACRAF, Switz. ACRAF AG, Route de Moncor 10, 1752 Villars-sur-Glâne, Switzerland.
ACS, Austral. ACS International PL, 20 Clarice Rd, Box Hill, South Victoria 3128, Australia.
ACS Dobfar, Ital. ACS Dobfar S.p.A., V.le Addetta 6/8/10, 20067 Tribiano, Italy.
ACS Dobfar, Switz. ACS Dobfar Info SA, Casai, 7749 Campascio, Switzerland.
Actavis, Cz. See *Avalanche, Cz.*
Actavis, Denm. Actavis Nordic A/S, Ornegardsvej 16, 2820 Gentofte, Denmark.
url: www.actavis.dk
Actavis, Fin. Actavis Oy, Sinimäentie 8b, 02630 Espoo, Finland.
url: www.actavis.fi
Actavis, Hung. Actavis Hungary Kft, 7 Bartha B St, H-4032 Debrecen, Hungary.
url: www.actavis.hu
Actavis, Indon. Actavis, KP Gandaria Km 28, Jl Raya Jakarta Bogor, 13010 Jakarta, DKI Jaya, Indonesia.
Actavis, Malaysia. See *Apex, Malaysia.*
Actavis, Pol. Actavis Polska Sp. z.o.o., ul. Odrowąża 15, 03-310 Warsaw, Poland.
url: www.actavis.com
Actavis, Port. Actavis AS Sucursal, Rua Virgílio Correira 11, 1600-219 Lisbon, Portugal.
Actavis, Rus. Actavis, Tubal St 17/4, str. 2, 127051 Moscow, Russia.
Actavis, Singapore. See *Delfi, Singapore.*
Actavis, Swed. Actavis AB, Drottninggatan 11, 252 21 Helsingborg, Sweden.
url: www.actavis.se
Actavis, UK. Actavis UK Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK.
url: www.actavis.co.uk
Actavis, USA. Actavis Pharma, 14 Commerce Drive, Cranford, NJ 07016, USA.
url: www.actavis.com
Actelion, Austral. Actelion Pharmaceuticals Australia Pty Ltd, P.O. Box 372, Frenchs Forest, NSW 1640, Australia.
url: www.actelion.com
Actelion, Canad. Actelion Pharmaceuticals Canada Inc., 2525 Daniel-Johnson Blvd, Suite 205, Laval, Quebec, H7T 1S9, Canada.
url: www.actelion.com
Actelion, Cz. Actelion Pharmaceuticals Ltd, Belgicka 115/40, 1200 00 Prague 2, Czech Republic.
url: www.actelion.com
Actelion, Denm. See *Actelion, Swed.*
Actelion, Fin. See *Actelion, Swed.*
Actelion, Fr. Actelion Pharmaceuticals France SAS, 18 rue Royale, 75008 Paris, France.
url: www.actelion.com
Actelion, Ger. Actelion Pharmaceuticals Deutschland GmbH, Munzinger Strasse 1, 79111 Freiburg, Germany.
url: www.actelion.de
Actelion, Gr. Actelion Pharmaceuticals Hellas SA, 7 Paleologou St, Chalandri, 152 32 Athens, Greece.
url: www.actelion.com
Actelion, Hung. See *Actelion, UK.*
Actelion, Irl. See *Allphar, Irl.*
Actelion, Israel. Actelion Pharmaceutical Israel Ltd, 3 Hayetzira St, Ramat-Gan 52521, Israel.
url: www.actelion.com
Actelion, Ital. Actelion Pharmaceuticals Italia Srl, Viale Mascheroni 29, 20145 Milan, Italy.
Actelion, Malaysia. See *Zuellig, Malaysia.*
Actelion, Neth. See *Actelion, UK.*
Actelion, Norw. See *Swedish Orphan, Norw.*
Actelion, Port. Actelion Pharmaceuticals Portugal Lda, Praça Marquês de Pombal 15 - 8, 1250-163 Lisbon, Portugal.
url: www.actelion.com
Actelion, Singapore. See *Zuellig, Singapore.*
Actelion, Spain. Actelion Pharmaceuticals España S.L., Via Augusta 281, 3B, 08017 Barcelona, Spain.
url: www.actelion.com
Actelion, Swed. Actelion Pharmaceuticals Sverige AB, Svärdvägen 3 A, 182 33 Danderyd, Sweden.
url: www.actelion.com
Actelion, Switz. Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, 4123 Allschwil, Switzerland.
url: www.actelion.com
Actelion, Thai. See *Zuellig, Thai.*
Actelion, UK. Actelion Pharmaceuticals UK Ltd, BSI Building, 13th Floor, 389 Chiswick High Rd, Chiswick, London, W4 4AL, UK.
url: www.actelion.com
Actelion, USA. Actelion Pharmaceuticals US Inc., 5000 Shoreline Court, Suite 200, South San Francisco, CA 94080, USA.
url: www.actelion.com
Acti Diffusion, Fr. Acti Diffusion Nature, ZI St-Martin, B.P. 10229, 83406 Hyéres cdx, France.
Actipharm, Switz. Actipharm SA, 42 rue Prevost-Martin, 1211 Geneva 9, Switzerland.
Acupharm, S.Afr. Acupharm (Pty) Ltd, 43 Richards Drive, Halfway House 1685, South Africa.
Adamed, Cz. See *Adamed, Pol.*
Adamed, Hung. See *Adamed, Pol.*
Adamed, Pol. Adamed Sp. zo.o., Pieńków 149, 05-152 Czosnów k/Warsaw, Poland.
url: www.adamed.com.pl
Adamed, Port. See *Adamed, Pol.*
Adams, Canad. See *Pfizer Consumer, Canad.*
Adams, Hong Kong. See *LCH, Hong Kong.*
Adams, Thai. See *Pharmaland, Thai.*
Adams, UK. Adams Healthcare Ltd, Lotherton Way, Garforth, Leeds, South Yorkshire, LS25 2JY, UK.
url: www.adams-healthcare.co.uk
Adams, USA. Adams Laboratories Inc., 14801 Sovereign Rd, Fort Worth, TX 76155-2645, USA.
url: www.adamslabs.com
Adams Confectionery, UK. See *Ernest Jackson, UK.*
Adco, S.Afr. Adco Drug Co (Pty) Ltd, 491 Sydney Rd, Durban 4000, South Africa.
Adcock Ingram, S.Afr. Adcock Ingram Pharmaceuticals Ltd, Adcock Ingram Park, 17 Harrison Ave, Bryanston 2021, South Africa.
url: www.adcock.co.za
Adcock Ingram Consumer, S.Afr. See *Adcock Ingram, S.Afr.*
Adcock Ingram Critical Care, S.Afr. Adcock Ingram Critical Care, P.O. Box 6888, Johannesburg 2000, South Africa.
url: www.adcock.co.za
Adcock Ingram Self Medication, S.Afr. See *Adcock Ingram, S.Afr.*
Addenda, Ital. Addenda Pharma Srl, Viale Shakespeare 47, 00144 Rome, Italy.
Addmedica, Cz. See *Addmedica, Fr.*
Addmedica, Fr. Addmedica, 84 rue d'Amsterdam, 75009 Paris, France.
Addmedica, Port. See *Addmedica, Fr.*
Ad-Drugstel, Philipp. Ad-Drugstel Pharmaceutical Lab., Unit A, 2/F Ad-Drugstel Building, 75 Tandang Sora Ave, Quezon City, Philippines.
Adeka, Turk. Adeka İlaç ve Kimyasal Ürünler San. ve Tic. A.Ş., General Cahit Aybar Sok., Akademiler sitesi E Blok. No. 5, Zincirlikuyu, İstanbul, 80600, Turkey.
url: www.adeka.com.tr
Adelco, Gr. Adelco Chromatourgia Athinon, E. Colocotronis Bros. S.A., 37 Pireos Str., 183 46 Moschato, Greece.
url: www.adelco.gr
Adesil, Arg. Lab. Adesil S.A., Tabare 1033, 1437 Buenos Aires, Argentina.
Adienne, Ital. Adienne Srl, Via Broseta 64/B, 24100 Bergamo (BG), Italy.
url: www.adienne.com
Adilna, Turk. Adilna, Turkey.
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Adipharm (Αδηφαρμ), Gr. See *Adipharm, Gr.*
Adivar, Ital. See *Angelini, Ital.*
Adler, Austria. Adler-Apotheke, Wahringer Strasse 149, A-1180 Vienna, Austria.
Adler, Switz. Adler Apotheke, Dr Urs Reinhard AG, Untertor 39, Postfach 1241, 8401 Winterthur, Switzerland.
Admeda, Cz. See *Admeda, Ger.*
Admeda, Ger. Admeda Arzneimittel GmbH, Heinrich-Hertz-Str. 77, 22085 Hamburg, Germany.
url: www.admeda.de
Admeda, Hung. See *Admeda, Ger.*
Admeda, Port. See *Admeda, Ger.*
Adolphs, USA. Adolphs, 75 Merritt Blvd, Trumbull, CT 06611, USA.
Adrem, Canad. Adrem Ltd, 2000 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.
Adria, USA. See *Pfizer, USA.*
Adroka, Switz. Adroka AG, Postfach, 4123 Allschwil, Switzerland.
url: www.adroka.ch
Advance, Singapore. See *Wellchem, Singapore.*
Advance, USA. Advance, 2201-F 5th Avenue, Ronkonkoma, NY 11779, USA.
Advance Diagnostic, Irl. Advance Diagnostic Products Ltd, Church Rd, Greystones, Co. Wicklow, Ireland.
Advanced, Singapore. Advanced Medi Mart Pte Ltd, 53 Kim Keat Rd, 05-02C Mun Hean Building, S 328823, Singapore.
Advanced Biotechnologies, Israel. See *Rafa, Israel.*
Advanced Care, USA. Advanced Care Products, 199 Grandview Rd, Skillman, NJ 08558-9418, USA.
url: www.jnj.com
Advanced Magnetics, Israel. See *Dexxon, Israel.*
Advanced Medical Optics, Austral. See *AMO, Austral.*
Advanced Medical Optics, NZ. Advanced Medical Optics, 3-5 Westfield Place, Mt Wellington, Auckland, New Zealand.
url: www.amo-inc.com
Advanced Medical Optics, UK. See *Allergan, UK.*
Advanced Nutritional Technology, USA. Advanced Nutritional Technology Inc., P.O. Box 2130, 6988 Sierra Court, Dublin, CA 94568-2641, USA.
url: www.antlab.com
Advanced Sterilization Products, USA. Advanced Sterilization Products, a Johnson & Johnson Company, 33 Technology Drive, Irvine, CA 92618-9824, USA.
url: www.sterrad.com
Advanced Vision, USA. Advanced Vision Research, 12 Alfred St., Suite 200, Woburn, MA 01801, USA.
url: www.theratears.com
Advancis, USA. Advancis Pharmaceutical Corp., 20425 Seneca Meadows Parkway, Germantown, MD 20876, USA.
Aegis, Hong Kong. See *Universal, Hong Kong.*
Aegis, Singapore. See *Zyfas, Singapore.*
Aero, USA. Aero Pharmaceuticals, 3848 FAU Bv-ld, Suite 100, Boca Raton, FL 33431, USA.
url: www.aeropharmaceuticals.com
Aeroceuticals, USA. See *Graham-Field, USA.*
Aerocid, Fr. Laboratoires Aérocid, 248 bis, rue Gabriel-Peri, 94230 Cachan, France.
Aerokure, Canad. Aerokure International Inc., 330 Racine St, St-Elie d'Orford, Quebec, J0B 2S0, Canada.
Aesca, Austria. Aesca GmbH, Badener Strasse 23, A-2514 Traiskirchen, Austria.
Aesculapius, Ital. Aesculapius Farmaceutici S.r.l., Via Cozzaglio 24, 25125 Brescia, Italy.
Aesthetic Plus, Singapore. See *Wellchem, Singapore.*
AF, Mex. A.F. Laboratorios, Aplicaciones Farmaceuticas S.A. de C.V., Heriberto Frias No. 1035, Benito Juarez del Valle, 03100 Mexico D.F., Mexico.
Afamia, Hung. Afamia Trade Kft, Vahot u 1, 1119 Budapest, Hungary.
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AFT, NZ. AFT Pharmaceuticals, P.O. Box 33-203, Takapuna, Auckland, New Zealand.
url: www.aftpharm.com
AG Therapy, Gr. A.G. Therapy, Koritsas 13, 145 61 Kifisia, Greece.
AGA, Denm. See *AGA, Swed.*
AGA, Fr. Lab. AGA Medical SA, Rue de l'Oasis, 31300 Toulouse, France.
AGA, Gr. AGA, Greece.
AGA, Swed. AGA AB, 181 81 Lidingö, Sweden.
url: www.agahealthcare.com
Age D'or, Singapore. Age D'or Healthcare Pte Ltd, 51 Ayer Rajah Crescent, 07-01/02, S 139948, Singapore.
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Agepha, Austria. Agepha GmbH, Gasselberg 53-54, A-8564 Gaisfeld, Austria.
Agepharm, Fr. Agepharm, Airspace, rue Gagarine, F33185 Le Haillan, France.
AGEPS, Fr. AGEPS, Agence Générale des Equipements et Produits de Santé, Établissement Pharmaceutique des Hôpitaux de Paris, 7 rue du Fer-à-Moulin, B.P. 09, 75221 Paris cdx 5, France.
url: www.ap-hop-paris.fr
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Agis, Israel. See *Perrigo, Israel.*
Agostinho, Port. António Pacheco Agostinho, SA, Rua Rodrigues Sampaio 15, 1169-012 Lisbon, Portugal.
Agouron, USA. See *Pfizer, USA.*
Agrichem, Hung. Agrichem Kft, Kárpát u 50 111/9, 1133 Budapest, Hungary.
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Aguettant, UK. Aguettant Ltd., Bishops House, Bishops Road, Claverham, Somerset, BS49 4NF, UK.
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Agys, Singapore. See *Pan-Malayan, Singapore.*
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Ahn-Gook, Philipp. See *Medhaus, Philipp.*
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Airflow, NZ. Airflow Products, P.O. Box 1485, Wellington, New Zealand.
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AJC, Rus. See *LDP, Rus.*
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Ajinomoto, Thai. See *Far East, Thai.*, and *Zuellig, Thai.*
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Akita, UK. See *Manx, UK.*
Akorn, Canad. See *Dioptic, Canad.*
Akorn, Israel. See *Tradis-Gat, Israel.*
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Akromed, S.Afr. See *Wyeth, S.Afr.*
Aksu, Turk. Aksu Farma Tıbbi Ürünler San. ve Tic. A.Ş., Rıfkı Tongsir Cad. No. 58, Idealtepe-Küçükyalı, İstanbul, Turkey.
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Akzo, Braz. Akzo Nobel Ltda, Al. Vicente Pinzon 144 cj23, 04547-130 São Paulo, SP, Brazil.
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Alacan, Spain. See *ASAC, Spain.*
Alamo, USA. Alamo Pharmaceuticals LLC, 8501 Wilshire Blvd, Suite 318, Beverly Hills, CA 90211-3119, USA.
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Alaven, USA. Alaven Pharmaceuticals LLC, 2260 Northwest Parkway, Marietta, GA 30067, USA.
url: www.alavenpharm.com
Alba Thyment, Pol. Alba Thyment Sp. zo.o., ul. J Kossaka 21, 60-760 Poznań, Poland.
url: www.albathyment.com.pl
Albephar, Venez. Lab. Albephar, Av Alameda, Qta Gabor, Lomas San Rafael La Florida, 1050 Caracas, Venezuela.
Albert, S.Afr. See *Hoechst Marion Roussel, S.Afr.*
Alcala, Spain. Alcala Farma, Ctra M-300 Km 29.920, Alcalá de Henares, 28802 Madrid, Spain.
url: www.alcala-farma.es
Alchemy, S.Afr. Alchemy Pharmaceuticals CC, 21 Dadoo Ave., Mackenzieville, Nigel 1490, South Africa.
Alchemy, UK. Alchemy, Alchemy House, 38 East St, Andover, Hampshire, SP10 1ES, UK.
Alckamed, Ital. Alcka-Med S.r.l., Piazzale Principessa Clotilde 8, 20121 Milano, Italy.
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Alcon, Belg. Alcon-Couvreur SA/NV, Rijksweg 14, 2870 Puurs, Belgium.
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Alcon, Braz. Alcon Laboratórios do Brasil Ltda, Avenida Nações Unidas 12.495 3 andar, 4578902 Brooklin Novo, São Paulo, Brazil.
url: www.alconlabs.com
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Alcon, Ger. Alcon Pharma GmbH, Blankreutestr. 1, 79108 Freiburg, Germany.
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Alcon, Irl. See *Allphar, Irl.*

Alcon, Israel. See *Luxembourg, Israel.*

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Alcon, NZ. Alcon Laboratories Ltd, P.O. Box 14-562, Panmure, Auckland, New Zealand.
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Alcon, Philipp. Alcon Lab (Phils) Inc., 3/F LGI Building, Ortigas Ave, Green Hills, San Juan, Metro Manila, Philippines.

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Alcon, Rus. Alcon Moscow, Nikolayamskaya 54, 109004 Moscow, Russia.
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Alcon Cusi, Malaysia. See *Alcon, Malaysia,* and *Summit, Malaysia.*

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Aldo, Spain. Aldo Union, Baronesa de Malda 73, Esplugas de Llobregat, 08950 Barcelona, Spain.
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Aldo-Union, Hong Kong. See *Hong Kong Medical, Hong Kong.*

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Aldo-Union, Rus. See *Invar, Rus.*

Aldo-Union, Singapore. See *Green Cross, Singapore.*

Aldo-Union, Thai. See *Greater Pharma, Thai.*

Aldril, Philipp. Aldril Pharmaceuticals, Suite 402-403, Cedar Exec Blg II, 26 Timog Ave, Cor Scout Tobias St, Quezon City, Philippines.

Aledicine, Gr. Aledicine, Menandrou 58, 104 32 Athens, Greece.

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Alembic, Rus. Alembic Ltd, Donskaya St 18/7, str. 1, Of. 3, 119049 Moscow, Russia.

Alembic, Singapore. See *Zyfas, Singapore.*

Alembic Products, UK. Alembic Products Ltd, River Lane, Saltney, Chester, Cheshire, CH4 8RQ, UK.
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Alenfarma, Port. Alenfarma Especialidades Farmacêuticas Lda, R. Dr. António Loureiro Borges 3, Arquiparque Miraflores, 1495-131 Algés, Portugal.

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Alexion, Cz. See *Alexion, Fr.*

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Alexion, Port. See *Alexion, Spain.*

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url: www.alxn.com

Alexion, UK. Alexion Pharma UK, 3000 Cathedral Hill, Guildford, Surrey, GU2 7YB, UK.
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Alexion, USA. Alexion Pharmaceuticals Inc, 352 Knotter Drive, Cheshire, CT 06410, USA.
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Alfa Biotech, Ital. See *Wassermann, Ital.*

Alfa Intes, Ital. Industria Terapeutica Splendore - Oftalmoterapica ALFA, Via F.lli Bandiera 26, 80026 Casoria (NA), Italy.

Alfa Medis, Gr. Alfa Medisyst, 115 26 Athens, Greece.

Alfa Wassermann, Cz. See *Medicom, Cz.*

Alfa Wassermann, Gr. See *Demo, Gr.*

Alfa Wassermann, Hung. See *CSC, Hung.*

Alfa Wassermann, Indon. See *Tempo Scan Pacific, Indon.*

Alfa Wassermann, Pol. Alfa Wassermann Polska Sp. zo.o., ul. Grójecka 186 m 317, 02-390 Warsaw, Poland.
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Alfa Wassermann, Rus. See *CSC, Rus.*

Alfa Wassermann, Thai. See *Charoen, Thai.*

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Ali, Turk. Ali Raif İlaç Sanayii Ltd. Şti., Haseyad II., Kısım No.228, İkitelli, İstanbul, Turkey.
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Alimera, USA. Alimera Sciences, 6120 Windward Parkway, Suite 290, Alpharetta, GA 30005, USA.

Alinter, UK. Alinter Ltd, New Abbey Court, 51-53 Stert St, Abingdon, Oxfordshire, OX14 3HB, UK.
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Aliud, Ger. Aliud Pharma GmbH & Co. KG, Gottlieb-Daimler-Str 19, 89150 Laichingen, Germany.
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Aliud, Hung. See *Medicine & Business, Hung.*

ALK, Austria. Alk-Abello Allergie-Service GmbH, Backermuhlweg 59, A-4030 Linz, Austria.
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ALK, Belg. See *ALK, Neth.*

ALK, Cz. See *ALK, Denm.*

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ALK, Hung. See *Spiromed, Hung.*

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Alkaloid, Cz. See *ProMed, Cz.*

Alkaloid, Rus. See *Sotex, Rus.*

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Alkapharm, Singapore. See *Wellchem, Singapore.*

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Alkem, Thai. See *Kaspa, Thai.*

Alkermes, Indon. See *Janssen-Cilag, Indon.*

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Alkon (Αλκον), Gr. See *Alcon, Gr.*

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Allcura, Ger. allcura Naturheilmittel GmbH, Reichendaker 7, 97877 Wertheim, Germany.
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Allegis, USA. Allegis Pharmaceuticals, 276 Nissan Parkway, B-2, Canton, MS 39056, USA.
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Allen, Austria. See *GSK, Austria.*

Allen, Gr. See *GSK, Gr.*

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Allen, Spain. See *GSK, Spain.*

Allen & Hanburys, Austral. See *GSK, Austral.*

Allen & Hanburys, Irl. See *GSK, Irl.*

Allen & Hanburys, UK. See *GSK, UK.*

Allendale, Canad. See *Allendale, USA.*

Allendale, USA. Allendale Pharmaceuticals Inc., 73 Franklin Turnpike, Allendale, NJ 07401, USA.
url: www.allendalepharm.com

Allens, UK. Allens & Co. (Anglesey) Ltd, Freshwinds, Pentraeth, Isle of Anglesey, Gwynedd, LL75 8YF, UK.
url: www.allenshealthcare.co.uk

Allerbio, Fr. Laboratoires Allerbio, 55270 Varennes-en-Argonne, France.
url: www.allerbio.fr

Allerderm, Singapore. See *Green Cross, Singapore.*

Allerex, Canad. Allerex Laboratory Ltd, P.O. Box 13307, Kanata, Ontario, K2K 1X5, Canada.

Allergan, Arg. Allergan-Loa S.A.I.C. y F., Av. del Libertador 498, Piso 20 Sect. Sur, 1001 Buenos Aires, Argentina.
url: www.allergan.com

Allergan, Austral. Allergan Australia P/L, 77 Ridge St, Gordon, NSW 2072, Australia.
url: www.allergan.com

Allergan, Austria. Pharm-Allergan GmbH, Wienerbergstrasse 11 Twin Tower, A-1100 Vienna, Austria.
url: www.allergan.com

Allergan, Belg. Allergan SA, Meir 44 A, 2000 Antwerp, Belgium.
url: www.allergan.com

Allergan, Braz. Allergan Produtos Farmacêuticos Ltda, Av. Cardoso de Melo 1955 13 andar, 4548005 São Paulo, Brazil.

Allergan, Canad. Allergan Inc., 110 Cochrane Dr., Markham, Ontario, L3R 9S1, Canada.
url: www.allergan.com

Allergan, Chile. Laboratorios Alllergan Ltda, Vitacura 2736, Piso 15, Las Condes, Santiago, Chile.

Allergan, Cz. See *Eco-Med-Poll, Cz.*

Allergan, Denm. Allergan A/S, Produktionsvej 14, 2600 Glostrup, Denmark.
url: www.allergan.com

Allergan, Fin. Allergan Norden AB, Rajatorpantie 41 C, 01640 Vantaa, Finland.
url: www.allergan.com

Allergan, Fr. Allergan France, Font de l'Orme, av Dr Maurice-Donat, B.P. 442, 06254 Mougins, France.
url: www.allergan.fr

Allergan, Ger. Pharm-Allergan GmbH, Pforzheimer Str.160, 76275 Ettlingen, Germany.
url: www.allergan.de

Allergan, Hong Kong. Allergan Asia Ltd, Unit 3012 30/F Metroplaza Tower 1, 223 Hing Fong Rd, Kwai Fong, N.T., Hong Kong.
url: www.allergan.com

Allergan, Hung. See *Inthera, Hung.*

Allergan, India. Allergan India Pvt Ltd, 1st Floor, North Wing, Silver Jubilee Block, Mission Road, 3rd Cross, Behind Unity Building Complex, Bangalore 560 027, India.
url: www.agnindia.com

Allergan, Irl. Allergan Pharmaceuticals Ireland Ltd, Castlebar Rd, Westport, Co. Mayo, Ireland.
url: www.allergan.com

Allergan, Israel. See *Tradis-Gat, Israel.*

Allergan, Ital. Allergan S.p.A., Via S Quasimodo 134/138, 00100 Rome EUR (Rome), Italy.
url: www.allergan.com

Allergan, Malaysia. See *Diethelm, Malaysia.*

Allergan, Mex. Allergan, S.A. de C.V., Mier y Pesado 126, Col Del Valle, 03100 Mexico D.F., Mexico.
url: www.allergan.com

Allergan, Neth. Allergan BV, Postbus 446, 3430 AK Nieuwegein, Netherlands.
url: www.allergan.com

Allergan, Norw. See *Allergan, Swed.*

Allergan, NZ. Allergan Pharmaceuticals, P.O. Box 1873, Auckland 1, New Zealand.
url: www.allergan.com

Allergan, Philipp. See *Zuellig, Philipp.*

Allergan, Pol. See *Ewopharma, Pol.*

Allergan, Port. Allergan S.A., Av. Do Forte 3 - Edif. Suécia IV, 1 Piso, 2795-504 Carnaxide, Portugal.
url: www.allergan.com

Allergan, Rus. See *Family Health, Rus.*

Allergan, S.Afr. Allergan Pharmaceuticals (Pty) Ltd, P.O. Box 3911, Halfway House 1685, South Africa.
url: www.allergan.com

Allergan, Singapore. See *JDH, Singapore.*

Allergan, Spain. Allergan S.A.U., Edificio La Encina, Plaza de la Encina 10-11, 28760 Madrid, Spain.
url: www.allergan.com

Allergan, Swed. Allergan Norden AB, Business Campus, 194 81 Upplands Väsby, Sweden.
url: www.allergan.se

Allergan, Switz. Allergan AG, Feldmoosstrasse 6, 8853 Lachen, Switzerland.
url: www.allergan.com

Allergan, Thai. See *Maxim, Thai.*

Allergan, UK. Allergan Ltd, 1st Floor Marlow International, The Parkway, Marlow, Buckinghamshire, SL7 1YL, UK.
url: www.allergan.com

Allergan, USA. Allergan Pharmaceuticals Inc., 2525 Dupont Dr., P.O. Box 19534, Irvine, CA 92623-9534, USA.
url: www.allergan.com

Allergan, Venez. Laboratorios Allergan, Hans Neumann, Ed. Corimon, Pso.3, Merck S.A., Cortijos de Lourdes, Caracas, Venezuela.
url: www.allergan.com

Allergan Herbert, USA. See *Allergan, USA.*

Allergomed, Switz. Allergomed AG, Erlenstrasse 29, Postfach 117, 4106 Therwil, Switzerland.

Allergon, Pol. See *Krotex, Pol.*

Allergopharma, Ger. Allergopharma Joachim Ganzer KG, Hermann-Korner-Str. 52, 21465 Reinbek, Germany.
url: www.allergopharma.de

Allergopharma, Pol. Allergopharma Nexter Sp. zo.o., ul. Jordana 7B, 40-056 Katowice, Poland.
url: www.nexter.pl

Allergopharma, Switz. See *Allergomed, Switz.*

Allergy Therapeutics, Cz. Allergy Therapeutics sro, Na Výtoni 12, 128 00 Prague 2, Czech Republic.
url: www.allergytherapeutics.com

Allergy Therapeutics, Pol. See *Pliva Krakow, Pol.*

Allergy Therapeutics, UK. Allergy Therapeutics Ltd, Dominion Way, Worthing, West Sussex, BN14 8SA, UK.
url: www.allergytherapeutics.com

AllerPharma, Canad. AllerPharma Inc., 133 The West Mall, Unit 8, Toronto, Ontario, M9C 1C2, Canada.
url: www.allerpharma.com

Allertec, Gr. Allertec Hellas A.E., 18 Faethonos Str., 55 132 Kalamaria, Greece.
url: www.allertec.gr

All-Gen, Neth. All-Gen Pharmaceuticals & Generics BV, Papelaan 85G, 2252 EG Voorschoten, Netherlands.

Alliance, Irl. See *United Drug, Irl.*

Alliance, S.Afr. Alliance Pharmaceuticals Ltd, P.O. Box 261269, Excom 2023, South Africa.
url: www.alliancepharmaceuticals.co.za

Alliance, UK. Alliance Pharmaceuticals Ltd, Avonbridge House, Bath Rd, Chippenham, Wiltshire, SN15 2BB, UK.
url: www.alliancepharma.co.uk

Alliance, USA. Alliance Pharmaceuticals, 4660 La Jolla Village Drive, Suite 825, San Diego, CA 92122, USA.
url: www.allp.com

Alliant, USA. Alliant Pharmaceuticals Inc, 312 Maxwell Rd, Suite 400, Alpharetta, GA 30004, USA.
url: www.alliantpharma.com

Allied, S.Afr. Allied Pharmaceuticals Ltd, P.O. Box 5237, Rivonia 2128, South Africa.

Allmedica, Ger. Allmedica Arzneimittel GmbH, Schillerstr. 4, 37269 Eschwege, Germany.

Allmi-Care, UK. Allmi-Care Ltd, U20 Lenton Business Centre, Lenton Boulevard, Nottingham, Nottinghamshire, NG7 2BY, UK.
url: www.quool.co.uk

Alloga, Ital. Alloga Italia Srl, Via Moggia 75/A, 16033 Lavagna (GE), Italy.
url: www.alloga-europe.com

Alloga, Switz. Alloga AG, Buchmattstrasse 10, 3401 Burgdorf, Switzerland.

Allphar, Irl. Allphar Services Ltd, Belgard Rd, Tallaght, Dublin 24, Ireland.
url: www.allphar.ie

Alltracel, Hong Kong. See *Mekim, Hong Kong.*

Alltracel, Irl. Alltracel Pharma Ltd, Alltracel House, Church Place, Sallynoggin, Co. Dublin, Ireland.
url: www.alltracel.com

Almi, Spain. Almi, La Granja 82, Pol. Industrial, Alcobendas, 28108 Madrid, Spain.

Almirall, Belg. Almirall Prodesfarma, Medialaan 32 B 4, 1800 Vilvoorde, Belgium.
url: www.almirallprodesfarma.com

Almirall, Chile. See *Grunenthal, Chile.*

Almirall, Denm. See *Nycomed, Denm.*

Almirall, Fr. Almirall SAS (Lab), 1 bd Victor, 75015 Paris, France.
url: www.almirall.es

Almirall, Ger. Almirall GmbH, Oskar-Messter-Str. 29, 85737 Ismaning, Germany.
url: www.almirallprodesfarma.com

Almirall, Hong Kong. See *Sincerity, Hong Kong.*

Almirall, Ital. Almirall SpA, Via Vespucci 2, 20124 Milan, Italy.

Almirall, Mex. Almirall S.A. de C.V., Avenida Alborada 124, piso 13, Colonia Parques del Pedregal, 14010 Mexico D.F., Mexico.
url: www.almirallprodesfarma.com

Almirall, Neth. Almirall, Netherlands.

Almirall, Norw. See *Nycomed, Norw.*

Almirall, Port. Almirall Lda, Rua João Chagas 53A, 2 Escritório 201, 1495-072 Alges, Portugal.
url: www.almirallprodesfarma.com

Almirall, Rus. See *Nycomed, Rus.*

Almirall, Singapore. See *Zyfas, Singapore.*

Almirall, Spain. Almirall Prodesfarma S.A., Rda Gral Mitre 151, 08022 Barcelona, Spain.
url: www.almirall.es

Alodial, Port. Alodial Farmacêutica Lda, Estrada Marco do Grilo, Zemouto, 2830 Coina, Portugal.

Alpa, Cz. Alpa sro, Velke Meziříči, Czech Republic.

Alpes Chemie, Chile. Alpes Chemie SA, Av. Pedro de Valdivia 1307, Providencia, Santiago, Chile.

Alpha, Hong Kong. See *Keller, Hong Kong.*

Alpha, Israel. See *Medogar, Israel.*

Alpha, NZ. Alpha Pharmaceuticals Ltd, P.O. Box 705, Palmerston North, New Zealand.

Alpha Therapeutic, Ital. Alpha Therapeutic Italia SpA, Piazza Media 3, 20121 Milan, Italy.

Alpha Therapeutic, Singapore. Alpha Therapeutic Asia Pte Ltd, 1 Maritime Square, 10-33A World Trade Centre, S 099253, Singapore.
url: www.alphather.com

Alpha Therapeutic, USA. See *Grifols, USA.*

Alphapharm, Austral. Alphapharm P/L, P.O. Box 36, Camperdown, NSW 1450, Australia.
url: www.alphapharm.com.au

Alphapharm, Hong Kong. See *LCH, Hong Kong.*

Alphapharm, Malaysia. See *Summit, Malaysia,* and *Zuellig, Malaysia.*

Alphapharm, Singapore. See *Zuellig, Singapore.*

Alphapharm, Thai. See *JDH Borneo, Thai.*

Alpharma, Cz. See *Alpharma, Norw.*

Alpharma, Denm. Alpharma ApS, Dalslandsgade 11 (postboks 1736), 2300 Copenhagen S, Denmark.
url: www.alpharma.dk

Alpharma, Fin. Alpharma Oy, Sinimäentie 10 B, 02630 Espoo, Finland.
url: www.alpharma.fi

Alpharma, Fr. Alpharma France, 40 rue Lecuyer, 93300 Aubervilliers, France.
url: www.alpharma.fr

Alpharma, Hong Kong. See *Primal, Hong Kong.*

Alpharma, Hung. Alpharma Gyógyszervegyeszeti Kft, Szállás u 3, 1107 Budapest, Hungary.

Alpharma, Indon. Alpharma PT, Jl Majapahit 101, Semarang 50249, Indonesia.

Alpharma, Irl. See *Actavis, UK.*

Alpharma, Malaysia. See *Apex, Malaysia.*

Alpharma, Mex. Laboratorios Alpharma, S.A. de C.V., Renato Leduc 363, Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.alpharma.com

Alpharma, Neth. Alpharma BV, Baarnsche Dijk 1, 3741 LN Baarn, Netherlands.

Alpharma, Norw. Alpharma AS, Harbitzalleen 3, Postboks 158 Skøyen, 0212 Oslo, Norway.
url: www.alpharma.no

Alpharma, Port. Alpharma ApS, Rua Virgílio Correia 11A, 1600-219 Lisbon, Portugal.
url: www.alpharma.pt

Alpharma, Singapore. See *Pharmed, Singapore,* and *Sime Darby, Singapore.*

Alpharma, Swed. Alpharma AB, Nordenflychtsvägen 74, 112 89 Stockholm, Sweden.
url: www.alpharma.se

Alpharma, Switz. See *Dumex, Switz.*

Alpharma, UK. See *Actavis, UK.*

Alpharma, USA. Alpharma USPD Inc, 7205 Windsor Blvd, Baltimore, MD 21244, USA.
url: www.alpharmauspd.com

Alpharma-Isis, Ger. Alpharma-Isis GmbH & Co. KG, Elisabeth-Selbert-Str. 1, 40764 Langenfeld, Germany.
url: www.alpharma.de

Alphashow, UK. Alphashow Ltd, 35A High St, Marlborough, Wiltshire, SN8 1LW, UK.

Alphrema, Ital. Alphrema S.r.l., Via 4 Novembre 92, 20021 Bollate (MI), Italy.

Alpine, Singapore. Alpine, Singapore.

Alpro, Spain. See *Almirall, Spain.*

Alra, USA. Alra Laboratories Inc., 3850 Clearview Court, Gurnee, IL 60031, USA.

Alsi, Canad. Alsi Cie Ltee, 150 rue Seigneuriale, Beauport, Quebec, G1E 3B3, Canada.

Alsitan, Ger. Alsitan GmbH & Co. KG, Am Buhl 16-18, 86926 Greifenberg, Germany.
url: www.alsitan.com

Also, Ital. Also S.p.A., Viale Monte Rosa 96, 20149 Milan, Italy.

Alta Care, Ital. Alta Care Laboratoires, Via Ildebrando Vivanti 188, 00144 Rome (RM), Italy.
url: www.altacare.com

Altaire, USA. Altaire Pharmaceuticals Inc., P.O. Box 849, 311 West Lane, Aquebogue, NY 11931, USA.
url: www.otcdruggist.com

Altana, Arg. Altana Pharma SA, Tronador 4890, 1430 Buenos Aires, Argentina.

Altana, Austral. Altana Pharma Pty Ltd, Level 2, 71 Epping Rd, North Ryde, NSW 2113, Australia.
url: www.altana.com

Altana, Austria. Altana Pharma GmbH, Ketzergasse 2000, A-1235 Vienna, Austria.

Altana, Belg. Altana Pharma SA/NV, Lambroekstraat 5 C, 1831 Diegem, Belgium.
url: www.altanapharma.be

Altana, Canad. AltanaPharma Inc., 1275 North Service Rd W, 7th Floor, Oakville, Ontario, L6M 3G4, Canada.
url: www.altanapharma.ca

Altana, Cz. See *Altana, Ger.*

Altana, Denm. See *Nycomed, Denm.*

Altana, Fr. ALTANA Pharma S.A.S., 389 rue du Pressoir, 77350 le Mee-sur-Seine, France.
url: www.altana.com

Altana, Ger. Altana Pharma Deutschland GmbH, Moltkestr. 4, 78467 Constance, Germany.
url: www.altanapharma.de

Altana, Gr. See *Nycomed, Gr.*

Altana, Hong Kong. Altana Pharma (HK), 608, 6/F, Devon House, Taikoo Place, Quarry Bay, Hong Kong.
url: www.altanapharma.com

Altana, Hung. Altana Pharma AG Képviselet, Hermina út 17, 1146 Budapest, Hungary.

Altana, Indon. See *Darya-Varia, Indon.,* and *Pharos, Indon.*

Altana, Irl. Altana Ltd, Unit 2051 Castle Drive, Citywest Business Campus, Dublin 24, Ireland.

Altana, Ital. Altana Pharma SpA, Via Libero Temolo 4, 20126 Milan, Italy.

Altana, Malaysia. Altana Pharma, 74 Jln Universiti, 46200 Petaling Jaya, Selangor, Malaysia.

Altana, Mex. Altana Pharma S.A. de C.V., Av Primero de Mayo No. 130, Col. San Andres Atoto, 53519 Naucalpan de Juarez., Mexico.
url: www.altana.com

Altana, Neth. Altana, Jupiterstraat 250, 2132 HK Hoofddorp, Netherlands.
url: www.altanapharma.nl

Altana, Norw. See *Pfizer, Norw.*

Altana, Philipp. Altana Pharmaceuticals, 5/F King's Court Bldg 1, 2129 Chino Roces Ave, Makati City, Philippines.
url: www.altana.com

Altana, Pol. Altana Pharma Sp. zo.o., al. Jerozolimskie 146 A, 02-305 Warsaw, Poland.
url: www.altanapharma.com

Altana, Port. Produtos Farmacêuticas Altana Pharma Lda, Quinta da Fonte, Edifício Gil Eanes, Porto Salvo, 2770-192 Paco d'Arcos, Portugal.

Altana, S.Afr. Altana Madaus Pty Ltd, 1st Floor, Uplands 12, The Woodlands, ZA-2080 Woodmead, Sandton, South Africa.
url: www.altana.com

Altana, Singapore. See *Diethelm, Singapore.*

Altana, Spain. Altana Pharma, Francisca Delgado 1, Parque Empresarial, Arryo de la Vega – Alcobendas, 28108 Madrid, Spain.
url: www.altanapharma.es

Altana, Switz. Altana Pharma Ltd, Bachstrasse 10, 8280 Kreuzlingen, Switzerland.

Altana, Thai. See *Zuellig, Thai.*

Altana, USA. Altana Inc., 60 Baylis Rd, P.O. Box 2006, Melville, NY 11747, USA.
url: www.altanainc.com

Altana Consumer, Ger. See *Altana, Ger.*

Altana Madaus, S.Afr. See *Altana, S.Afr.*

AltaSelect, Ital. AltaSelect, Via XXIV Maggio 62/A, 37057 San Giovanni Lupatoto (VR), Italy.

Alter, Ital. Laboratori Alter srl, Via Egadi 7, 20144 Milan (MI), Italy.

Alter, Port. Alter, SA, Estrada Marco do Grilo, Zemouto, 2830 Coina, Portugal.

Alter, Spain. Alter, Mateo Inurria 30, 28036 Madrid, Spain.
url: www.alter.es

Alterna, Canad. See *Alterna, USA.*

Alterna, Ital. Alterna Farmaceutici S.r.l., Via dei Pestagalli 7, 20138 Milan, Italy.

Alterna, USA. Alterna LLC, Suite 1409, 89 Headquarters Plaza, Norristown, New Jersey, 07960, USA.

Alternavida, Mex. See *Savi, Mex.*

Alternova, Denm. Alternova ApS, Industriparken 23-25, 2750 Ballerup, Denmark.
url: www.alternova.dk

Alternova, Fin. Oy Alternova AV, Valkjarventie 1, 02130 Espoo, Finland.
url: www.alternova.fi

Altimed, Canad. See *Ratiopharm, Canad.*

Altius, Arg. Altius Farmaceutica SA, Vuelta de Obligado 2680, Piso 7 B, Buenos Aires, Argentina.

Altmann, Ger. Altmann Therapie GmbH & Co. KG, Gesellensteig 15, 38229 Salzgitter, Germany.
url: www.atsz.de

Alva, USA. Alva-Amco Pharmacal Inc., 7711 North Meremac Ave, Niles, IL 60714-3423, USA.
url: www.alva-amco.com

Alvear, Arg. Laboratorio Alvear, Av. Rivadavia 14644, Piso 1 A, 1704 Ramos Mejia, Buenos Aires, Argentina.

Alvia (Αλβια), Gr. ALVIA AE, 18o chlm. L. Athinon-Marathonos, 153 44 Pallini, Greece.

Alza, Canad. See *Janssen-Ortho, Canad.*

Alza, Irl. See *Cambridge, UK.*

Alza, USA. Alza Corp., 1900 Charleston Ave, Mountain View, CA 94039-7210, USA.
url: www.alza.com

AM, Arg. Laboratorio A.M. Farma Activ, Italia 743, 2000 Rosario, Santa Fe, Argentina.

Amarin, Singapore. See *Kyowa, Singapore.*

Amat, Austria. Amat Pharma Trading GmbH, Walfischgasse 6, A-1010 Vienna, Austria.

AMBI, USA. See *Nutrition 21, USA.*

Ambix, USA. Ambix Laboratories Inc., 210 Orchard St, Rutherford, NJ 07073, USA.

Amcon, USA. Amcon Laboratories, 40 North Rock Hill Rd, St Louis, MO 63119, USA.
url: www.amcon-labs.com

Amcron, Thai. Amcron Enterprise Co. Ltd, 2711 Pattanakarn Rd, Suan Luang, Bangkok 10250, Thailand.

Amdipharm, Cz. See *Amdipharm, Irl.*

Amdipharm, Denm. See *Amdipharm, UK.*

Amdipharm, Fin. See *Amdipharm, UK.*

Amdipharm, Irl. Amdipharm Ltd, Temple Chambers, 3 Burlington Rd, Dublin 4, Ireland.

Amdipharm, Neth. See *Amdipharm, UK.*

Amdipharm, Norw. See *Amdipharm, UK.*

Amdipharm, Port. See *Amdipharm, Irl.*

Amdipharm, UK. Amdipharm Plc, Regency House, Miles Gray Rd, Basildon, Essex, SS14 3AF, UK.
url: www.amdipharm.com

Ameda, Port. See *Ameda, UK.*

Ameda, UK. Ameda Egnell Ltd, Belvedere Trading Estate, Taunton, Somerset, TA1 1BH, UK.
url: www.ameda.demon.co.uk

Amedius, Philipp. See *PharmAsia, Philipp.*

Amenite, Arg. Laboratorio Amenite, Caracas 4721, 1419 Buenos Aires, Argentina.

American Lecithin, USA. American Lecithin Co., 115 Hurley Rd, Unit 2B, Oxford, CT 06478, USA.

American Medical, USA. American Medical Industries, 28045 Ashley Circle 106, Libertyville, IL 60048, USA.
url: www.ezhealthcare.com

American Pharmaceutical, USA. American Pharmaceutical Partners Inc., 10866 Wiltshire Blvd, Suite 1270, Los Angeles, CA 90024, USA.
url: www.appdrugs.com

American Red Cross, USA. American Red Cross, 1616 Ft Myer Drive 17th Floor, Arlington, VA 22209-3100, USA.
url: www.redcross.org

American Regent, USA. See *Luitpold, USA.*

American Taiwan, Thai. American Taiwan Biopharm Co Ltd, Unit 1806, 18 Fl, The Millennia Bldg, 62 Langsuan Rd, Lumpini, Prathumwan, Bangkok 10330, Thailand.

American Urologicals, USA. American Urologicals Inc., 10031 Pines Blvd, Suite 216, Pembroke Pines, FL 33024, USA.

Amerifit, USA. Amerifit Pharma Inc., 11 State St, Woburn, MA 01801, USA.
url: www.amerifit.com

AmerisourceBergen, USA. AmerisourceBergen Corp., 1300 Morris Drive, Suite 100, Chesterbrook, PA 19087, USA.
url: www.amerisourcebergen.com

Amersham, Austral. Amersham Health Pty Ltd, Unit 4, 2 Eden Park Drive, North Ryde, NSW 2113, Australia.
url: www.amershamhealth.com

Amersham, Austria. Amersham Health Handels GmbH, Lembockgasse 49, A-1230 Vienna, Austria.
url: www.amershamhealth.at

Amersham, Belg. See *GE, Belg.*

Amersham, Canad. Amersham Health Inc., 1166 South Service Rd West, Oakville, Ontario, L6L 5T7, Canada.
url: www.amershamhealth-ca.com

Amersham, Denm. Amersham Health A/S, Slotsmarken 15, 2970 Horsholm, Denmark.
url: www.amershamhealth.com

Amersham, Fin. Oy Amersham Health AB, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.amershamhealth.com

Amersham, Fr. Amersham Health SA, 140 av Jean-Lolive, 93500 Pantin, France.
url: www.amershamhealth.com

Amersham, Ger. See *Amersham Buchler, Ger.*

Amersham, Gr. Amersham Health AE, 139 Plapouta & Lamias Str., 141 21 N Heraklion, Greece.
url: www.amershamhealth.com

Amersham, Ital. Amersham Health, Via dei Giardini 7, 20121 Milan, Italy.

Amersham, Neth. Amersham Health BV, Cygne Centre, 5612 AP Eindhoven, Netherlands.

Amersham, Norw. Amersham Health AS, Nycov. 2, Postboks 4220 Nydalen, 0401 Oslo, Norway.
url: www.amershamhealth.no

Amersham, NZ. Amersham Health Ltd, P.O. Box 101-241, North Shore Mail Centre, Auckland, New Zealand.
url: www.amershamhealth.com

Amersham, Spain. Amersham Health, Ronda de Poniente, 12, Tres Cantos, 28760 Madrid, Spain.
url: www.amershamhealth.es

Amersham, Swed. Amersham Health AB, Box 602, 16926 Solna, Sweden.
url: www.amershamhealth.com

Amersham, Switz. Amersham Health AG, Postfach, 8820 Wadenswill, Switzerland.
url: www.ge.com

Amersham, UK. Amersham Health, The Grove Centre, White Lion Rd, Amersham, Buckinghamshire, HP7 9LL, UK.
url: www.amershamhealth.co.uk

Amersham, USA. See *Amersham Biosciences, USA.*

Amersham Biosciences, USA. Amersham Biosciences Corp., 800 Centennial Avenue, P.O. Box 1327, Piscataway, NJ 08855-1327, USA.
url: www.amersham.com

Amersham Buchler, Ger. Amersham Buchler GmbH & Co. KG, Fraunhoferstr. 7, 85737 Ismaning b. Munich, Germany.
url: www.amershamhealth.de

Amersham Health, Hung. Amersham Health (CEE) Handels GmbH Magyarországi Közvetlen Kereskedelmi Képviselete, Konkoly-Thege Miklós út 29-33, 1121 Budapest, Hungary.

Amerx, USA. Amerx Health Care Corp., 1150 Cleveland St, Suite 410, Clearwater, FL 33755, USA.

Am-Europharma, Philipp. Am-Europharma Corp., Km 16, West Service Rd, South Superhighway, Parañaque City, Philippines.
url: www.am-europharma.com

AMG, Arg. AMG Farma SRL, Moron 2681, Buenos Aires, Argentina.

Amgen, Austral. Amgen Australia P/L, P.O. Box 410, North Ryde, NSW 1670, Australia.
url: www.amgen.com

Amgen, Austria. Amgen GmbH, Prinz Eugen-Strasse 8-10, A-1040 Vienna, Austria.
url: www.amgen.at

Amgen, Belg. Amgen SA, Ave Ariane 5, 1200 Brussels, Belgium.
url: www.amgen.be

Amgen, Canad. Amgen Canada Inc., 6755 Mississauga Rd, Suite 400, Mississauga, Ontario, L5N 7Y2, Canada.
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Amgen, Fin. Amgen AB, PL 75, 02201 Espoo, Finland.
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Amgen, Fr. Amgen, 192 av Charles-de-Gaulle, 92200 Neuilly-sur-Seine, France.
url: www.amgen.fr

Amgen, Ger. Amgen GmbH, Hanauer Str. 1, 80992 Munich, Germany.
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Amgen, Hong Kong. See *IDS, Hong Kong.*

Amgen, Hung. See *Amgen, Neth.*

Amgen, Irl. See *United Drug, Irl.*

Amgen, Israel. See *Megapharm, Israel.*

Amgen, Ital. Amgen Spa, Via E Tazzoli 6, 20154 Milan, Italy.

Amgen, Neth. Amgen Europe BV, Minervum 7061, 4817 ZG Breda, Netherlands.
url: www.amgen.nl

Amgen, Norw. Amgen, Kronprinsensg 1, 0251 Oslo, Norway.
url: www.amgen.com

Amgen, NZ. Amgen New Zealand, a branch of Amgen Australia Pty Ltd, P.O. Box 9-104, Newmarket, Auckland, New Zealand.
url: www.amgen.com

Amgen, Pol. Amgen Sp. zo.o., al. Jana Pawła II 25, 00-854 Warsaw, Poland.
url: www.amgen.com

Amgen, Port. Amgen Biofarmaceutica, Lda, Tagus Park, Edifício Eastécnica, 2780-920 Porto Salvo, Portugal.
url: www.amgen.com

Amgen, Spain. Amgen S.A., Moll de Barcelona s/n, World Trade Centre, 08039 Barcelona, Spain.
url: www.amgen.es

Amgen, Swed. Amgen AB, Box 34107, 100 26 Stockholm, Sweden.
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Amgen, Switz. Amgen Switzerland AG, Alpenquai 30, 6002 Lucerne, Switzerland.

Amgen, UK. Amgen Ltd, 240 Cambridge Science Park, Milton Rd, Cambridge, Cambridgeshire, CB4 4WD, UK.
url: www.amgen.com

Amgen, USA. Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA.
url: www.amgen.com

Amhof, Arg. Lab. Amhof Maurino S.A., Nogoya 4811/15, 1407 Buenos Aires, Argentina.

Amide, USA. Amide Pharmaceuticals Inc., 101 East Main Street, Little Falls, NJ 07424, USA.
Amido, Fr. Laboratoires Amido, 37 av Gabriel-Peri, 92500 Rueil-Malmaison, France.
Amino, Switz. Amino AG, Althofstrasse 12, 5432 Neuenhof, Switzerland.
Amirose, UK. Amirose International, 249 Cranbrook Rd, Ilford, Essex, UK.
Amis, Pol. Amis Medica Sp. zo.o., ul. Poleczki 23, 02-822 Warsaw, Poland.
url: www.amismedica.pl
Amnol, Ital. Amnol Chimica Biologica S.r.l., C.so della Vittoria 12/b, 28100 Novara (NO), Italy.
url: www.amnol.net
Amo, Arg. See *Visiontech, Arg.*
AMO, Austral. Advanced Medical Optics, Level 1, 77 Ridge St, Gordon, NSW 2072, Australia.
url: www.amo-inc.com
AMO, Canad. AMO Canada Co., Unit 2, 80 Whitehall Drive, Markham, Ontario, L3R 0P3, Canada.
AMO, Singapore. See *JDH, Singapore.*
AMO, UK. AMO (UK) Ltd, Jupiter House, Mercury Park, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.
Amphastar, Canad. See *Amphastar, USA.*
Amphastar, USA. Amphastar Pharmaceuticals Inc., 11570 6th St, Rancho Cucamonga, CA 91730, USA.
url: www.amphastar.com
Amsa, Ital. Amsa S.r.l., Passeggiata Ripetta 22, 00186 Rome, Italy.
Amsco, Singapore. Amsco Healthcare Marketing Pte Ltd, 10 Pandan Cres., 02-05 UE Tech Park, S 128466, Singapore.
Amsco, USA. See *Steris, USA.*
Amternes, Denm. Amternes Laegemiddelregistreringskontor I/S, Amsträdsforeningen, Dampfaergevej 22 (postboks 2593), 2100 Copenhagen O, Denmark.
Amuchina, Ital. Amuchina S.p.A., Via Pontasso 13, 16015 Casella (GE), Italy.
Amvis, Gr. AMVIS, Menandrou 54, 104 32 Athens, Greece.
url: www.amvis.gr
Amway, Canad. Amway Corp., 375 Exeter Rd, London, Ontario, N5Y 5V6, Canada.
url: www.amway.com
Amylin, USA. Amylin Pharmaceuticals, Inc., 9360 Towne Centre Drive, Ste. 110, San Diego, CA 92121, USA.
Ana, Austria. ana, Vienna, Austria.
Anabiosis, Gr. Anabiosis Hellas, Al. Panagouli 50, 142 31 N. Ionia, Greece.
Anadis, Austral. Anadis Ltd, Australia.
Anasco, Fin. Anasco Oy, PL 480, 00181 Helsinki, Finland.
ANB, Malaysia. See *Sime Darby, Malaysia.*
ANB, Thai. ANB Laboratories Co. Ltd, 39/1 Ram-Intra Rd, Kanayao, Bangkok 10230, Thailand.
url: www.anblab.com
Anben, Fr. Anben Pharma, 14 av P. Mendes-France, 67300 Schiltigheim, France.
url: www.ronfnyl.com
Anben, Israel. See *Kivema, Israel.*
Anben, Malaysia. See *Antah, Malaysia.*
Anchor, Mex. Anchor Farma SA de CV, Calle 28 2625, 44940 Guadalajara Zona Industrial, Jalisco, Mexico.
Andersen, Norw. Jan F. Andersen A/S, Postboks 1132 Flattum, 3501 Honefoss, Norway.
url: www.jfa-as.no
Andrae, Austria. Andrae GmbH, Marinonigasse 2-6, A-1210 Vienna, Austria.
Andre, India. Andre Laboratories Pvt Ltd, 495/7 & 8 GIDC, Makarpura, Vadodara 390 101, India.
Andreabal, Switz. Andreabal AG, Rudolfstrasse 2, 4054 Basle, Switzerland.
url: www.andreabal.ch
Andromaco, Arg. Laboratorios Andrómaco S.A.I.C.I., Ingeniero Huergo 1145, 1107 Buenos Aires, Argentina.
url: www.andromaco.com.ar
Andromaco, Chile. Laboratorios Andromaco SA, Av. Quilin 5273, Penalolen, Santiago, Chile.
Andromaco, Cz. See *Grunenthal, Spain.*
Andromaco, Mex. Industria Farmacéutica Andrómaco, S.A. de C.V., Andrómaco No. 104, Col. Ampliación Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.
url: www.andromaco.com.mx
Andromaco, Port. Laboratórios Andrómaco, Lda, Rua Alfredo da Silva 16, 2720-028 Amadora, Portugal.
Andromaco, Rus. See *Grunenthal, Rus.*
Andromaco, Spain. See *Grunenthal, Spain.*
Andromaco, Venez. Laboratorios Andrómaco C.A., Av.Los Próceres y Fco Fajardo, Edif. Kern, Urb. San Bernadino, Caracas, Venezuela.
Andrx, USA. Andrx Pharmaceuticals Inc., 4001 SW 47th Ave, Fort Lauderdale, FL 33314, USA.
url: www.andrx.com
Aneid, Port. Aneid, Lda, Rua José Florindo, Quinta da Pedra, Bloco B, R/C A, 2750-401 Cascais, Portugal.
url: www.aneid.pt
Anesiva, USA. Anesiva Inc., 650 Gareway Blvd, South San Francisco, CA 94080, USA.
url: www.anesiva.com
Anfarm, Gr. See *Anpharm (Ανφαρμ), Gr.*
Anfarm, Rus. See *Medochemie, Rus.*
Anfarm, Thai. See *JDH Borneo, Thai.*
Angelfarma, Port. Angelfarma Lda, Rua João Chagas 53, Piso 3, 1495-764 Cruz Quebrada - Dafundo, Portugal.
Angelini, Hong Kong. See *IDS, Hong Kong.*
Angelini, Indon. See *Soho, Indon.*
Angelini, Israel. See *Rafa, Israel.*
Angelini, Ital. Aziende Chimiche Riunite Angelini Francesco S.p.A., Viale Amelia 70, 00100 Rome, Italy.
Angelini, Philipp. See *Croma, Philipp.*
Angelini, Pol. See *Medagro, Pol.*
Angelini, Port. Angelini, Rua João Chagas 53, Piso 3, 1495-072 Alges, Portugal.
Angelini, Rus. See *CSC, Rus.*
Angelini, Singapore. See *Indrugco, Singapore.*
Angenerico, Ital. Angenerico SpA, Via Nocera Umbra 75, 00181 Rome (RM), Italy.
Angenerico, Port. Angenérico Lda, Rua João Chagas 53, Piso 3, 1495-072 Alges, Portugal.
Anglian, UK. Anglian Pharma Plc, P.O. Box 161, Hitchin, Hertfordshire, SG4 7WE, UK.
url: www.anglianpharma.com
Anglo-French Drugs, India. Anglo-French Drugs & Industries Ltd, 41, 3rd Cross, S.S.I. Area, V Block, Rajaji Nagar, Bangalore 560 010, India.
url: www.anglofrenchpharma.com
Anglo-French Drugs, Thai. Anglo-French Drugs.
Anika, Israel. See *Rafa, Israel.*
Anios, Fr. Laboratoires Anios, Pavé du Moulin, 59260 Lille-Hellemmes, France.
url: www.anios.com
Ankerpharm, Cz. See *Chauvin Ankerpharm, Cz.*
Anmarate, S.Afr. Anmaraté (Pty) Ltd, P.O. Box 9350, George, Western Cape, South Africa.
url: www.anmarate.co.za
Anpharm (Ανφαρμ), Gr. ANFARM ELLAS AE, Perikleous 27, 152 32 Chalandri, Greece.
Anpharm, Pol. Anpharm Przedsiębiorstwo Farmaceutyczne, ul. Annopol 6 B, 03-236 Warsaw, Poland.
url: www.anpharm.com.pl
Anpharm, Rus. See *Servier, Rus.*
Anpharm, UK. See *Antigen, UK.*
Anroch, Spain. Anroch Pharma, C/Noruega 9, 28971 Griñon, Madrid, Spain.
Ansell, Canad. Ansell Canada Inc., 105 Lauder St, Cowansville, Quebec, J2K 2K8, Canada.
url: www.ansell.com
Ansell, Fr. Ansell SA, 2 bd du Moulin-à-vent, B.P. 78395, 95805 Cergy-Pontoise cdx, France.
url: www.anselleurope.com
Ansell, NZ. See *Ebos, NZ.*
Antah, Malaysia. Antah Pharma Sdb Bhd, 3 Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
Antec, Singapore. See *Pharmacon, Singapore.*
Anthra, Israel. See *Rafa, Israel.*
Antibiotic, Cz. Antibiotic Co, Czech Republic.
Antibioticos, Mex. Antibioticos de Mexico S.A. de C.V., Las Flores No. 56., Col. la Candelaria, Deleg. Coyoacan, 04380 Mexico D.F., Mexico.
Antibioticos, Spain. Antibioticos Farma, Ctra M-134 Km 1.5, Alcalá de Henares, 28903 Madrid, Spain.
Antigen, Hong Kong. See *Universal, Hong Kong.*
Antigen, Irl. Antigen Pharmaceuticals Ltd, Monarch Industrial Estate, Belgrade Rd, Tallaght, Dublin 24, Ireland.
url: www.antigenpharma.com
Antigen, Israel. See *Pharmateam, Israel.*
Antigen, UK. Antigen Pharmaceuticals Ltd, 82 Waterloo Rd, Southport, Merseyside, PR8 4QW, UK.
url: www.antigenpharma.com
Antipiol, Ital. Laboratorio di Chimica Medica dell' Antipiol S.n.c., Via S. Benigno 26, 10154 Turin, Italy.
Antistress, Switz. Antistress AG, Gesellschaft fur Gesundheitsschutz, Fluhstrasse 30, 8640 Rapperswil, Switzerland.
url: www.antistress.ch
Antiviral, Rus. Antiviral ZAO, Prof. Popova ul. 15/17, 197376 Saint Petersburg, Russia.
url: www.an-vi.ru
Anto, Ger. See *Juta, Ger.*
Antonetto, Ital. Marco Antonetto S.p.A., Via Arsenale 29, 10121 Turin, Italy.
Antor, Gr. ANTOR, Omirou 4, 151 26 Marousi, Greece.
Antula, Fin. See *Algol, Fin.*
Antula, Norw. See *Antula, Swed.*
Antula, Swed. Antula Healthcare AB, Odengatan 106, 113 22 Stockholm, Sweden.
url: www.antula.se
Anugerah Pharmindo, Indon. Anugerah Pharmindo Lestari (APL) PT, Jl Pulolentut Kav II E/4, Kawasan Industri Pulogadung, 13920 Jakarta, Indonesia.
url: www.aplcare.com
AOP, Malaysia. See *Summit, Malaysia.*
AOP Orphan, Austria. AOP Orphan Pharmaceuticals AG, Graf Starhemberggasse 34/3, A-1040 Vienna, Austria.
AOP Orphan, Indon. AOP Orphan, Indonesia.
Apex, Austral. See *Apex, NZ.*
Apex, Indon. Apex Pharma Indonesia PT, Menara Batavia 12th Floor, Jl KH Mas Mansyur Kav 126, 10220 Jakarta, Indonesia.
Apex, Malaysia. Apex Pharmacy (Marketing) Sdn Bhd, 24-30 Jalan PJS 11/5, Bandar Sunway, 46150 Petaling Jaya, Selangor, Malaysia.
Apex, NZ. Apex Health & Nutrition, P.O. Box 97588, South Aukland Mail Centre, Aukland, New Zealand.
url: www.apexrepel.com
Apipol, Pol. Apipol-Farma Przedsiębiorstwo Pszczelarsko-Farmaceutyczne, ul. H Cegielskiego 2, 32-400 Myślenice, Poland.
url: www.apipol.com.pl
Apivita, Gr. Apivita SA, 3 Koletti St, 144 52 Metamorfosi Attikis, Greece.
url: www.apivita.com
Aplicare, USA. Aplicare Inc., 50 E Industrial Rd, Branford, CT 06405, USA.
url: www.aplicare.com
Apogepha, Cz. See *Medex, Cz.*
Apogepha, Ger. Apogepha Arzneimittel GmbH, Kyffhauserstr. 27, 01309 Dresden, Germany.
url: www.apogepha.de
Apogepha, Port. See *Apogepha, Ger.*
Apogepha, Thai. See *Zuellig, Thai.*
Apomedica, Austria. Apomedica GmbH, Roseggerkai 3, A-8011 Graz, Austria.
Aponova, Austria. Aponova Pharma Handels GmbH, Niederhart 100, A-6253 Hart, Austria.
Apotex, Canad. Apotex Inc., 150 Signet Dr., Weston, Ontario, M9L 1T9, Canada.
url: www.apotex.ca
Apotex, Cz. Apotex ČR sro, Salvátorská 10, 110 00 Prague 1, Czech Republic.
url: www.apotex.cz
Apotex, Denm. See *Orphan, Denm.*
Apotex, Hong Kong. See *Hind Wing, Hong Kong.*
Apotex, Hung. See *Keri, Hung.*
Apotex, Malaysia. See *Pharmaforte, Malaysia.*
Apotex, Mex. See *Protein, Mex.*
Apotex, Neth. See *Apotex, UK.*
Apotex, NZ. Apotex NZ Ltd, Private Bag 102-995, North Shore Mail Centre, Auckland, New Zealand.
url: www.apotexnz.co.nz
Apotex, Philipp. See *One Pharma, Philipp.*
Apotex, Pol. Apotex Inc., Oddział w Warszawie, ul. Homera 46, 04-624 Warsaw, Poland.
Apotex, Rus. See *Sun Ventures, Rus.*
Apotex, S.Afr. Apotex S.A. (Pty) Ltd, C/o Watt and Fleming Streets, Meadowdale Ext. 1, South Africa.
Apotex, Singapore. See *Pharmaforte, Singapore.*
Apotex, UK. Apotex Europe Ltd, 22 Clarendon Rd, Leeds, Yorkshire, LS2 9NZ, UK.
Apotex, USA. Apotex Corp., 50 Lakeview Parkway, Suite 127, Vernon Hills, IL 60061, USA.
url: www.apotexcorp.com
Apotheca, Singapore. Apotheca Marketing Pte Ltd, 63 Hillview Ave, 09-12 Lam Soon Industrial Building, S 669569, Singapore.
url: www.apotheca.com.sg
Apotheca Pacis, Pol. Apotheca Pacis SC, ul. Broniewskiego 23, 44-217 Rybnik-Nowiny, Poland.
Apothecary, USA. Apothecary Products Inc., 11750 12th Ave S, Burnsville, MN 55337, USA.
Apothecon, Neth. Apothecon BV, Nijverheidsweg 3, 3771 ME Barneveld, Netherlands.
Apothecon, Spain. Apothecon, Ctra Antigua de Ajalvir Km 2.200, Alcalá de Henares, 28864 Madrid, Spain.
Apothecon, USA. See *BMS, USA.*
Apothecus, Canad. See *Apothecus, USA.*
Apothecus, USA. Apothecus Inc., 20 Audrey Ave, Oyster Bay, NY 11771, USA.
Apotheke Gnadenmutter, Austria. Apotheke zur Gnadenmutter, Hauptplatz 4, A-8630 Mariazell, Austria.
Apotheke Heiligen Dreifaltigkeit, Austria. Apotheke zur Heiligen Dreifaltigkeit, Kirchengasse 5, A-2460 Bruck a. d. Leitha, Austria.
Apotheke Heiligen Rupertus, Austria. Apotheke zum Heiligen Rupertus, Maxglaner Hauptstrasse 13, A-5020 Salzburg, Austria.
Apotheke Roten Krebs, Austria. Apotheke zum Roten Krebs, Lichtensteg 4, A-1011 Vienna, Austria.
APP, Hong Kong. See *LCH, Hong Kong.*
APPI, Hong Kong. See *Pharmalink, Hong Kong.*
Approved Prescription Services, UK. See *Teva, UK.*
APR, Switz. APR Applied Pharma Research SA, Via Corti 5, 6828 Balerna, Switzerland.
url: www.apr.ch
APS, Cz. See *APS, Ger.*
APS, Ger. APS Pharma GmbH, Angelsrieder Feld 22, 82234 Wessling, Germany.
APS, Hung. APS/Berk, Istenhegyi út 50-52/a, 1125 Budapest, Hungary.
APS, Port. Farma-APS, Lda, Rua José Galhardo 3, 1750-131 Lisbon, Portugal.
url: www.farma-aps.com
Apsen, Braz. Apsen Farmacêutica SA, Rua La Paz 37/67, 04755-020 São Paolo, SP, Brazil.
url: www.apsen.com.br
APT, Hong Kong. APT Pharma Ltd, 3/F, 4/F & 6B Tai Fung Industrial Bldg, 61 Hung To Rd, Kwun Tong, Kowloon, Hong Kong.
Aptus, NZ. Aptus, P.O. Box 39-070, Wellington, New Zealand.
Aqualab, Fr. Laboratoires Aqualab, ZI Nord, B.P. 36, 470 av de Lossburg, 69480 Anse, France.
Aquamarine, UK. Aquamarine Products Ltd, Unit 2b, Eppingdene, Ivy Chimneys, Epping, Essex, CM16 4EL, UK.
Aquilea, Spain. Laboratorios Diviser-Aquilea S.L., Pont Reixat 5, Saint Just Desvern, 08960 Barcelona, Spain.
url: www.aquilea.com
AR Scientific, USA. Ar Scientific, 1100 Orthodox St, Philadelphia, PA 19124, USA.
Arab, Malaysia. See *Antah, Malaysia.*
Arafarma, Spain. Arafarma Group, C/Fray Gabriel de San Antonio, Marchamalo, 19180 Guadalajara, Spain.
Arcana, Austria. Arcana Arzneimittel GmbH, Zimbagasse 5, A-1147 Vienna, Austria.
Archea, Ger. Archea Pharma Dr Makosi GmbH, Tiergartenstr. 4-6, 64646 Heppenheim, Germany.
url: www.archea-pharma.com
Archifar, Thai. See *TP, Thai.*
Archimedes, UK. Archimedes Pharma UK Ltd, 250 South Oak Way, Green Park, Reading, Berkshire, RG2 6UG, UK.
url: www.archimedespharma.com
Arco, USA. Arco Pharmaceuticals Inc., 105 Orville Dr., Bohemia, NY 11716, USA.
Arcola, USA. Arcola Laboratories, P.O. Box 1200, Collegeville, PA 19426, USA.
Arcolab, Philipp. See *Metz, Philipp.*
Ardana, Irl. Ardana Ltd, MODE Medical, 10 Sandyford Hall Walk, Dublin 18, Ireland.
url: www.ardana.co.uk
Ardana, Neth. See *Ardana, UK.*
Ardana, Port. See *Ardana, UK.*
Ardana, UK. Ardana Bioscience Ltd, 58 Queen St, Edinburgh, EH2 3NS, UK.
url: www.ardana.co.uk
Ardeapharma, Cz. Ardeapharma as, Třeboňská 229, 373 63 Ševětin, Czech Republic.
url: www.ardeapharma.cz
Ardern, UK. Ardern Healthcare Ltd, Pipers Brook Farm, Eastham, Tenbury Wells, Worcestershire, WR15 8NP, UK.
url: www.ardernhealthcare.com
Ardeypharm, Cz. See *Ardeypharm, Ger.*
Ardeypharm, Ger. Ardeypharm GmbH, Loerfeldstr. 20, 58313 Herdecke, Germany.
url: www.ardeypharm.de
Ardeypharm, Hung. See *Ardeypharm, Ger.*
Ardez, Cz. Ardez Pharma sro, Praha, Czech Republic.
Ardix, Fr. Ardix Médical, 27 rue du Pont, 92200 Neuilly-sur-Seine, France.
Ares, Mex. See *Psicofarma, Mex.*
Ares, Pol. Ares Trading SA, Oddział w Polsce, al. Jana Pawła II 34/10, 00-141 Warsaw, Poland.
Areu, Spain. Areu, Ctra Madrid Valencia, Km 23.5, Arganda del Rey, 28500 Madrid, Spain.
Arex, Venez. Arex Technology, Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.
Argenfarma, Arg. Lab. Argenfarma S.R.L., LLavallol 2649, 1417 Buenos Aires, Argentina.
Argiletz, Fr. Argiletz SA, 14 route d'Echampeu, 77440 Lizy-sur-Ourcq, France.
url: www.argiletz.com
ARI, Austral. ARI, Division of ANSTO, Private Mail Bag 1, Menai, NSW 2234, Australia.
url: www.ansto.gov.au
Arion, Arg. Lab. Arion S.R.L., Almafuerte 96, 2900 San Nicolas, Buenos Aires, Argentina.
Aristo, India. Aristo Pharmaceuticals Ltd, 23-A Shah Industrial Estate, Off Veea Desai Rd, Andheri (W), Mumbai 400 053, India.
url: www.aristopharma.org
Ariston, Arg. Química Ariston S.A.C.I.F., O'Connor 550/5, 1707 V. Sarmiento, Buenos Aires, Argentina.
Ariston, Braz. Ariston Industrias Químicas e Farm. Ltda, Rua Adherbal Stresser 84, 05566-000 São Paulo, SP, Brazil.
Aristopharma, Hong Kong. See *Sincerity, Hong Kong.*
Arjun, UK. Arjun Products Ltd, 2 Lonsdale Rd, Bilston, West Midlands, WV14 7AE, UK.
Arko, Ger. Arko Pharma GmbH, Bajuwarenring 12, 82041 Oberhaching, Germany.
url: www.arkopharma.com
Arkochim, Spain. Arkochim España, Meneses 2, 28045 Madrid, Spain.
url: www.arkochim.es
Arkofarm, Ital. Arkofarm S.r.l., Via Limone Piemonte 13/D, 18039 Ventimiglia (IM), Italy.
url: www.arkopharma-italia.com
Arkomedika, Fr. See *Arkopharma, Fr.*
Arkopharma, Belg. Arkopharma, Edisonlaan 13, 1300 Wavre, Belgium.
url: www.arkopharma.be
Arkopharma, Fr. Laboratoires Arkopharma, B.P. 28, 06511 Carros cdx, France.
url: www.arkopharma.com
Arkopharma, Hong Kong. See *Primal, Hong Kong.*
Arkopharma, Israel. See *Guri, Israel.*
Arkopharma, Switz. See *Naturpharma, Switz.*

Arkopharma, UK. Arkopharma UK Ltd, 6 Redlands Centre, Redlands, Coulsden, Surrey, CR5 2HT, UK.
url: www.arkopharma.com
Arla, Fin. Oy Arla Foods AB, PL 91, 00401 Helsinki, Finland.
Arlex, Mex. Arlex de México, S.A.deC.V., Puerto Acapulco No.35, Col. Piloto, Deleg. Alvaro Obregon, 01290 Mexico D.F., Mexico.
Arlor, Fr. Lab Arlor, 92-94 avenue Jean-Baptiste-Lebas, 59051 Roubaix cdx 1, France.
url: www.alpharegul.com
Armour, USA. See *CSL Behring, USA.*
Armoxindo, Indon. Armoxindo Farma PT, Jl Arjuna No 28, Tanjung Duren, Jakarta, Indonesia.
Armstrong, Arg. Lab. Armstrong S.A.C.I.F., Joaquin V. Gonzalez 653, 1407 Buenos Aires, Argentina.
Armstrong, Mex. Armstrong Laboratorios de Mexico S.A. de C.V., Perifirico Sur No. 6677-1er Piso, Col. Ejidos de Tepepan, Deleg. Xochimilco, 16018 Mexico D.F., Mexico.
url: www.lab-armstrong.com.mx
Aroli-Aromes, Fr. Aroli-Aromes Ligeriens Jean d'Aveze, 2 rue Georget, 37000 Tours, France.
Aroma, Turk. Aroma İlaç Sanayi Ltd. Şti., Abdi İpekçi Cad., Özel İdare İş Merakezi K:2 No. 201, Bayrampaşa, İstanbul, Turkey.
Aroma Life, Israel. Aroma Life, Hagefen 84, Moshav Gimzu 73130, Israel.
Arriani, Gr. Arriani Pharmaceuticals SA, 85 Lavriou Ave, 190 02 Peania, Athens, Greece.
Arrow, Austral. Arrow Pharmaceuticals Ltd, P.O. Box 397, Surry Hills, NSW 2010, Australia.
url: www.arrowpharma.com
Arrow, Braz. Arrow Farmacêutica SA, Rua Barão de Petrópolis 311, 20251061 Rio de Janeiro, Rio de Janeiro, Brazil.
Arrow, Cz. See *Arrow, UK.*
Arrow, Denm. Arrow Pharma ApS, Hovedgaden 41, 2970 Horsholm, Denmark.
Arrow, Fr. Arrow, France.
Arrow, Hong Kong. See *LCH, Hong Kong.*
Arrow, Hung. See *Arrow, UK.*
Arrow, Swed. Arrow Läkemedel AB, Nybrogatan 59, 114 40 Stockholm, Sweden.
Arrow, UK. Arrow Generics Ltd, Unit 2 Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK.
Ars Vitae, Switz. Ars Vitae AG, Weingartenstrasse 9, 8803 Ruschilkon, Switzerland.
Arsmedendi, Gr. Arsmedendi, Valaoritou 7, 152 32 Chalandri, Greece.
Artecef, Neth. Artecef BV, Schepenveld 41, 3890 BB Zeewolde, Netherlands.
url: www.artecef.nl
Artegodan, Ger. Artegodan GmbH, Wendlandstr. 1, 29439 Luchow, Germany.
Artesan, Cz. See *Artesan, Ger.*
Artesan, Ger. Artesan Pharma GmbH & Co. KG, Wendlandstr. 1, 29439 Luchow, Germany.
url: www.artesan.de
Arteva, Ger. Arteva Pharma GmbH, Leutstettenerstr. 10, 82131 Gauting, Germany.
Artex, NZ. Artex Ltd, P.O. Box 249, Waipukurau, New Zealand.
Arthropharm, Austral. Arthropharm P/L, 111 Bronte Rd, Bondi Junction, NSW 2022, Australia.
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Artis, Spain. See *Novartis, Spain.*
Artsana, Ital. Artsana S.p.A., Via Saldarini Catelli 1, 22070 Grandate (CO), Italy.
Artu, Neth. Artu Biologicals Europe BV, Vijzelweg 11, 8243 PM Lelystad, Netherlands.
Arun, UK. Arun Pharmaceuticals Ltd, Unit 37, Woolmer Way, Bordon, Hampshire, GU35 9QE, UK.
A.S., UK. A.S. Pharma Ltd, P.O. Box 181, Polegate, East Sussex, BN26 6WD, UK.
url: www.aspharma.co.uk
ASAC, Spain. A.S.A.C. Pharma, Sagitario 14, 03006 Alicante, Spain.
url: www.asac.net
Asahi, Jpn. Asahi Chemical Industry Co. Ltd, 9-1 Kanda Mitoshirocho, Chiyoda-ku, Tokyo 101-8481, Japan.
url: www.asahi-kasei.co.jp
Ascend, USA. Ascend Therapeutics Inc., 607 Herndon Pkwy, Suite 210, Herndon, VA 20170, USA.
url: www.ascendtherapeutics.com
Ascende Medz, Philipp. Ascende Medz Phils Inc., Suite 2207 Antel Global Corporate Ctr, Julia Vargas Ave, Ortigas Ctr, Pasig City, Philippines.
Ascent, USA. Ascent Pediatrics Inc., 187 Ballardvale St, Suite B125, Wilmington, MA 01887, USA.
url: www.ascentpediatrics.com
Asche, Cz. Asche AG, Nitranská 24/1258, 130 00 Prague 3, Czech Republic.
Asche, Ger. See *Asche Chiesi, Ger.*
Asche Chiesi, Ger. Asche Chiesi GmbH, Gasstr. 6, 22761 Hamburg, Germany.
url: www.chiesigroup.com
Ascher, USA. B.F. Ascher & Co., 15501 W 109th St, Lenexa, KS 66219, USA.
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Asens, Spain. Asens, Alava 61, 08005 Barcelona, Spain.
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Aset, Turk. See *Sanovel, Turk.*
Ashbourne, UK. Ashbourne Pharmaceuticals Ltd, The Drummonds, Spring Hill Office Park, Harborough Rd, Pitsford, Northampton, NN6 9AA, UK.
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Asia Pacific, Hong Kong. See *Pharmalink, Hong Kong.*
Asia Pharma, Philipp. See *Corbridge, Philipp.*
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Aspen, Hong Kong. See *Primal, Hong Kong.*
Aspen, NZ. See *Healthcare Logistics, NZ.*
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Aspen Consumer, S.Afr. See *Aspen, S.Afr.*
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Associated National Brokerage, Canad. Associated National Brokerage Inc., 120 Harry Walker Parkway N, Newmarket, Ontario, L3Y 7B2, Canada.
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Assos, Turk. Assos İlaç San ve. Tic. Ltd. Şti., Acibadem Cad., Erdem Sok. No. 2/12, Axibadem, İstanbul, Turkey.
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Asta Medica, Fin. See *Viatria, Swed.*
Asta Medica, Hong Kong. See *Unico, Hong Kong.*
Asta Medica, Indon. Asta Medica, Indonesia.
Asta Medica, Irl. See *Viatris, UK.*
Asta Medica, Israel. See *Megapharm, Israel.*
Asta Medica, Ital. See *Viatris, Ital.*
Asta Medica, Malaysia. See *JDH, Malaysia,* and *Zuellig, Malaysia.*
Asta Medica, NZ. See *NZ Medical & Scientific, NZ.*
Asta Medica, Singapore. See *JDH, Singapore.*
Asta Medica, Switz. See *Viatris, Switz.*
Asta Medica, Thai. See *Zuellig, Thai.*
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Astellas, Fin. See *Algol, Fin.*
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Astellas, Philipp. See *Zuellig, Philipp.*
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Astra, Israel. See *Teva, Israel.*
Astra, Mex. See *AstraZeneca, Mex.*
Astra, Port. See *AstraZeneca, Port.*
Astra, Spain. See *AstraZeneca, Spain.*
Astra, Swed. See *AstraZeneca, Swed.*
Astra, USA. See *AstraZeneca, USA.*
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Astrapin, Ger. See *Hameln, Ger.*
Astrapin, Philipp. See *PharmAsia, Philipp.*
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Atafarm, Turk. See *Atabay, Turk.*
Atenea, Spain. See *AstraZeneca, Spain.*
Athena Neurosciences, USA. See *Elan, USA.*
Athenstaedt, Cz. See *Athenstaedt, Ger.*

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Atlas, Canad. Laboratoire Atlas, 900 Blvd des Sciences, Suite 200, St-Leonard, Quebec, H1H 1H1, Canada.

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Atrix, Denm. See *Meda, Denm.*

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Atrix, Neth. See *Atrix, Ger.*

Atrix, Port. See *Atrix, Ger.*

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Aurantis, Braz. See *Biochimico, Braz.*

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Auriga, Hong Kong. See *Primal, Hong Kong.*

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Aurobindo, Philipp. See *Pharmawealth, Philipp.*

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Austroplant, Cz. See *Schwabe, Cz.*

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Aveflor, Pol. See *Salus, Pol.*

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Aventis, Belg. See *Sanofi-Aventis, Belg.*

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Aventis, Venez. See *Sanofi-Aventis, Venez.*

Aventis Behring, Arg. See *Aventis, Arg.*

Aventis Behring, Austria. See *Aventis, Austria.*

Aventis Behring, Denm. See *Aventis Behring, Swed.*

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Aventis Behring, Ger. Aventis Behring GmbH, Postfach: 1230, 35002 Marburg (Lahn), Germany.
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Aventis Behring, Hong Kong. Aventis Behring Asia Pacific Ltd, Unit 1208-1208, 12/F K Wah Ctr, 191 Java Rd, North Point, Hong Kong.

Aventis Behring, Irl. See *Sanofi-Aventis, Irl.*

Aventis Behring, Israel. See *Mediline, Israel.*

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Aventis Behring, Norw. See *Aventis Behring, Swed.*

Aventis Behring, Pol. See *Sanofi-Aventis, Pol.*

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Aventis Behring, UK. See *ZLB, UK.*

Aventis Behring, USA. See *CSL Behring, USA.*

Aventis Pasteur, Arg. See *Aventis, Arg.*

Aventis Pasteur, Austral. Aventis Pasteur P/L, P.O. Box 7025, Baulkham Hills Business Centre, NSW 2153, Australia.
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Aventis Pasteur, Austria. Aventis Pasteur GmBH, Richard-Strauss-Strasse 33, A-1230 Vienna, Austria.
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Aventis Pasteur, Belg. See *Sanofi Pasteur, Belg.*

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Aventis Pasteur, Fin. See *Aventis Pasteur, Denm.*

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Aventis Pasteur, Ger. Aventis Pasteur MSD GmbH, Paul-Ehrlich-Str. 1, 69181 Leimen, Germany.
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Aventis Pasteur, Hong Kong. See *Aventis, Hong Kong.*

Aventis Pasteur, Irl. See *Sanofi Pasteur, Irl.*

Aventis Pasteur, Israel. See *Sanofi-Aventis, Israel.*

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Aventis Pasteur, Malaysia. See *Aventis, Malaysia.*

Aventis Pasteur, Mex. See *Aventis, Mex.*

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Aventis Pasteur, Norw. See *Sanofi Pasteur, Belg.*

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Aventis Pasteur, Spain. See *Sanofi Pasteur, Spain.*

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Aventis Pasteur, Thai. Aventis Pasteur (Thailand) Ltd, 4 Fl, VTT I Building, 3195/9 Rama IV Rd, Klong Toey, Bangkok 10110, Thailand.
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Aventis Pasteur, Turk. See *Sanofi-Aventis, Turk.*

Aventis Pasteur, UK. See *Sanofi Pasteur, UK.*

Aventis Pasteur, USA. See *Sanofi Pasteur, USA.*

Averroes, Malaysia. Averroes Pharmaceuticals Sdn Bhd, 11E Level 5, Block 1, Worldwide Business Ctr, Jln 13/50 Section 13, 40300 Shah Alam, Selangor, Malaysia.

Aveva, Canad. See *Aveva, USA.*

Aveva, USA. Aveva Drug Delivery Systems Inc., 3250 Commerce Parkway, Miramar, Florida, 33025, USA.

Avgerinos, Gr. AVGERINOS ChR., Greece.

Avon, Canad. Avon Canada Inc., 5500 Trans Canada Hwy, Pointe-Claire, Quebec, H9R 1B6, Canada.

Awareness, Canad. Awareness Corp., 210-9087B-198th Street, Langley, British Columbia, V1M 3B1, Canada.

AWD, Cz. See *AWD, Ger.*

AWD, Ger. AWD.pharma GmbH & Co. KG, Leipziger Str. 7-13, 01097 Dresden, Germany.
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AWD, Hung. See *AWD, Ger.*

AWD, Neth. See *AWD, Ger.*

AWD, Pol. See *Pliva Krakow, Pol.*

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Axcan, Canad. Axcan Pharma Inc., 597 Laurier Blvd, Mont St-Hilaire, Quebec, J3H 6C4, Canada.

Axcan, Cz. See *Axcan, Neth.*

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Axcan, Ger. See *Axcan, Fr.*

Axcan, Hong Kong. See *Silroc, Hong Kong.*

Axcan, Hung. Axcan, Hungary.

Axcan, Israel. See *Megapharm, Israel.*

Axcan, Neth. Axcan Pharma International BV, Engelenkampstraat 72, 6131 JJ Sittard, Netherlands.

Axcan, Pol. See *Czet, Pol.*

Axcan, Port. See *Axcan, Neth.*

Axcan, Singapore. See *Summit, Singapore.*

Axcan, Thai. See *Diethelm, Thai.*

Axcan, USA. Axcan Scandipharm, 22 Inverness Center Pkwy, Suite 310, Birmingham, AL 35242, USA.
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Axofarma, Spain. See *Lundbeck, Spain.*

Axxess, Canad. Axxess Pharma Inc., Unit 105, 20 Valleywood Drive, Markham, Ontario, L3R 6G1, Canada.

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Ayrton, Denm. See *Pharmasol, UK.*

Ayrton, Neth. See *Ayrton, UK.*

Ayrton, UK. Ayrton Saunders Ltd, Ayrton House, Commerce Way, Parliament Business Park, Liverpool, Merseyside, L8 7BA, UK.
url: www.ayrtons.com

A-Z, Philipp. A-Z Market Enterprise Developers Inc., Philippines.

AZ, Port. AZ Farma Produtos Farmacêuticos Lda, Rua Humberto Madeira 7, Valejas, 2745-663 Barcarena, Portugal.

Aza, Austral. See *Lilly, Austral.*

Azevedos, Port. Laboratórios Azevedos, SA, Estrada Nacional 117-2, 2614-503 Amadora, Portugal.

Aziende, Israel. Aziende, Israel.

Azupharma, Cz. See *Azupharma, Ger.*

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url: www.azurpharma.com

BA Farma, Port. Laboratorio B.A. Farma, Lda, R. Professor Sousa da Câmara 207/211, 1070-803 Lisbon, Portugal.

Bach, UK. Bach Flower Remedies Ltd, 1D Gilray, Diss, Norfolk, IP22 4EU, UK.
url: www.bach-flowers.co.uk

Bacon, Arg. Lab. Bacon, Uruguay 136, 1603 Villa Martelli, Buenos Aires, Argentina.

Bad Heilbrunner, Ger. Bad Heilbrunner Naturheilmittel GmbH & Co., Am Krebsenbach 5-7, 83670 Bad Heilbrunn, Germany.
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Bago, Arg. Laboratorios Bagó S.A., Bernardo de Irigoyen 248, 1072 Buenos Aires, Argentina.
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Bago, Singapore. See *Zyfas, Singapore.*

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Bailly, Fr. Laboratoires Bailly SPEAB, 60 rue Pierre-Charron, 75008 Paris, France.

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url: www.vesselvite.com

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Baker Cummins, USA. See *Ivax, USA.*

Baker Norton, USA. See *Ivax, USA.*

Bal, Thai. See *Cosma, Thai.*

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Baldacci, Rus. See *CSC, Rus.*

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Balneopharm, Ger. See *Hanosan, Ger.*
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Bangkok Lab & Cosmetic, Hong Kong. See *T-Boma, Hong Kong.*
Bangkok Lab & Cosmetic, Thai. See *Bangkok Drug, Thai.*
Banner, Malaysia. See *IDS, Malaysia.*
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Barcino, Spain. Barcino, Tuset 1, 08006 Barcelona, Spain.
Bard, Hong Kong. See *US Summit, Hong Kong.*
Bard, UK. Bard Ltd, Forest House, Brighton Rd, Crawley, West Sussex, RH11 9BP, UK.
url: www.crbard.com
Baren-Apotheke, Switz. Bären-Apotheke AG, Kalkbreitestrasse 131, 8003 Zurich, Switzerland.
Barnes Hind, Arg. See *Maurino, Arg.*
Barnes Hind, NZ. See *Allergan, NZ.*
Barr, USA. Barr Laboratories Inc., 2 Quaker Rd, Pomona, NY 01970, USA.
url: www.barrlabs.com
Barre-National, USA. See *Alpharma, USA.*
Barrenne, Braz. Barrenne Indústria Farmacêutica Ltda, Rua Antunes Maciel 86, São Cristovao, 20940-010 Rio de Janeiro, RJ, Brazil.
url: www.barrene.com.br
Barrier Therapeutics, Belg. Barrier Therapeutics NV, Cipalstraat 3, 2440 Geel, Belgium.
Barrier Therapeutics, Neth. See *Barrier Therapeutics, Belg.*
Barrier Therapeutics, Port. See *Barrier Therapeutics, Belg.*
Barrier Therapeutics, USA. Barrier Therapeutics, 600 College Rd East, Suite 3200, Princeton, NJ 08540-6697, USA.
url: www.barriertherapeutics.com
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Bartlett, S.Afr. VJ Bartlett, South Africa.
Bartor Pharmacal, USA. Bartor Pharmacal Co., 70 High St, Rye, NY 10580, USA.
Basel, Turk. Basel İlaç Sanayi ve Ticaret A.Ş., General Ali Rıza Gürcan Cad., Merter İş Merkezi No. 2 91/B, Tozkorporan Merter, İstanbul, 34010, Turkey.
url: www.baselilac.com.tr
Basi, Port. Laboratorios Basi, R.do do Padrão 98, 3000-312 Coimbra, Portugal.
Basic, Philipp. Basic Pharmaceutical Corp., BPC Bldg, 38 Barasoain St, Little Baguio, San Juan, Metro Manila, Philippines.
Basics, Ger. Basics GmbH, Hemmelrather Weg 201, 51377 Leverkusen, Germany.
url: www.basics.de
Bastian, Ger. Bastian-Werk GmbH, August-Exter-Str. 4, 81245 Munich, Germany.
url: www.bastian-werk.de
Bausch & Lomb, Arg. Lab. Bausch & Lomb Argentina S.R.L., Av. Montevideo 160, 1019 Buenos Aires, Argentina.
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Bausch & Lomb, Austral. Bausch & Lomb (Australia) P/L, Level 4, 113 Wicks Rd, North Ryde, NSW 2113, Australia.
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Bausch & Lomb, Belg. Bausch & Lomb, Regent Building, Uitbreidingsstraat 46, 2600 Antwerp, Belgium.
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Bausch & Lomb, Braz. Bausch & Lomb (BL) Indústria Otica Ltda, Rua Dona Alzira 139, 91110010 Porto Alegre, Rio Grande do Sul, Brazil.
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Bausch & Lomb, Canad. Bausch & Lomb Canada Inc., 3762 Fourteenth Ave, 2nd Floor, Markham, Ontario, L3R 0G7, Canada.
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Bausch & Lomb, Hong Kong. Bausch & Lomb (Hong Kong) Ltd, 26/F City Plaza 1, Taikoo Shing, Hong Kong.
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Bausch & Lomb, Malaysia. See *Apex, Malaysia.*
Bausch & Lomb, Mex. Laboratorio Bausch & Lomb Mexico SA de CV, Av. Santa Fe 505 Piso 6, 5349 Cuajimalpa Cruz Manca Santa Fe, Mexico DF, Mexico.
Bausch & Lomb, NZ. Bausch & Lomb New Zealand Ltd, P.O. Box 24-138, Royal Oak, Auckland, New Zealand.
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Bausch & Lomb, Philipp. See *Croma, Philipp.*
Bausch & Lomb, Pol. Bausch & Lomb Polska Sp. zo.o., ul. Związkowa 20, 04-522 Warsaw, Poland.
url: www.bausch.com.pl
Bausch & Lomb, Port. Bausch & Lomb SA, Av. do Forte 3, Edifício Suécia IV, Piso 0 Esq., 2795-504 Carnaxide, Portugal.
Bausch & Lomb, Rus. Bausch & Lomb, 1st Floor, 1-2 bld., 6 Shtuzovaya emb., 113114 Moscow, Russia.
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Bausch & Lomb, S.Afr. Bausch & Lomb (SA) (Pty) Ltd, P.O. Box 5435, Rivonia 2128, South Africa.
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Bausch & Lomb, Singapore. See *Diethelm, Singapore.*
Bausch & Lomb, Spain. Bausch & Lomb Espana S.A., Avda Valdeparra 4, Alcobendas, 28109 Madrid, Spain.
url: www.bausch.com
Bausch & Lomb, Switz. Bausch & Lomb Swiss AG, Sumpfstrasse 3, 6312 Steinhausen, Switzerland.
Bausch & Lomb, Thai. See *Zuellig, Thai.*
Bausch & Lomb, UK. Bausch & Lomb UK Ltd, 106-114 London Rd, Kingston-upon-Thames, Surrey, KT2 6TN, UK.
url: www.bausch.com
Bausch & Lomb, USA. Bausch & Lomb Pharmaceuticals, 8500 Hidden River Parkway, Tampa, FL 33637, USA.
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Baxter, Arg. See *Baxter Immuno, Arg.*
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Baxter, Braz. Baxter Hospitalar Ltda, Rua Eng. Francisco Pitta Brito 779, 04753-080 São Paulo Santo Amaro, SP, Brazil.
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Baxter, Indon. See *Darya-Varia, Indon.*
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Baxter, Israel. See *Teva, Israel.*
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Baxter, Jpn. Baxter Ltd, 4 Banchi, 6 Bancho, Chiyoda-ku, Tokyo 102-8468, Japan.
Baxter, Malaysia. See *United Italian, Malaysia.*
Baxter, Mex. Baxter, S.A de C.V., Insurgentes Sur 1196, Col. del Valle, 03200 Mexico D.F., Mexico.
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Baxter, Philipp. Baxter Healthcare Phils Inc., 19/F Wynsum Corp.Plaza, Emerald Ave, Pasig City, Philippines.
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Baxter, Port. Baxter, Lda, Urbanização Industrial Cabra Figa, Estrada Nacional 249/4, Lote 3, Cabra Figa, 2735 Rio de Mouro, Portugal.
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Baxter, Rus. See *Serono, Rus.*
Baxter, Singapore. See *United Italian, Singapore.*
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Baxter, Venez. Baxter de Venezuela C.A., Calle 9 Edif, Siete, Urb. La Urbina, Caracas, Venezuela.
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Baxter Anaesthesia, UK. See *Baxter, UK.*
Baxter BioScience, Ger. Baxter Deutschland GmbH BioScience, Im Breitspiel 13, 69126 Heidelberg, Germany.
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Baxter BioScience, Turk. See *Eczacibasi-Baxter, Turk.*
Baxter BioScience, UK. Baxter BioScience, Wallingford Rd, Compton, Newbury, Berkshire, RG20 7QW, UK.
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Baxter Immuno, Arg. Baxter Immuno S.A., Entre Rios 1632, 1636 Olivos, Buenos Aires, Argentina.
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Baxter Oncology, Cz. See *Baxter, Cz.*
Baxter Oncology, Fr. See *Baxter, Fr.*
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Baxter Oncology, Israel. See *Teva, Israel.*
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Baxter-Hyland, Hong Kong. See *Baxter, Hong Kong.*
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Bayer, Mex. Bayer de Mexico S.A. de C.V., Division Farmaceutica, Blvd.M. de Cervantes Saavedra 259, Col. Ampl. Granada, 11520 Mexico D.F., Mexico.
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Bayer, Neth. Bayer BV, Energieweg 1, 3641 RT Mijdrecht, Netherlands.
url: www.bayer.com
Bayer, Norw. Bayer AS, Drammensv. 147 B, Postboks 14, 0212 Oslo, Norway.
url: www.bayer.no
Bayer, NZ. Bayer New Zealand Ltd, P.O. Box 2825, Auckland, New Zealand.
url: www.bayer.co.nz
Bayer, Philipp. Bayer Philippines Inc., Cecilia Araneta-Yulo Ave, Canlubang Industrial Estate, Canlubang, Calamba, Laguna, Philippines.
Bayer, Pol. Bayer Polska Sp. zo.o., al. Jerozolimskie 158, 02-326 Warsaw, Poland.
url: www.bayer.com.pl
Bayer, Port. Bayer Portugal, SA, Apartado 666, 2795 Carnaxide, Portugal.
url: www.bayer.com
Bayer, Rus. Bayer A/O Russia, Bolshoi Trekhgorny per. 1/20, 123022 Moscow, Russia.
url: www.bayer.com
Bayer, S.Afr. Bayer (Pty) Ltd, P.O. Box 143, Isando 1600, South Africa.
url: www.bayer.co.za
Bayer, Singapore. See *Zuellig, Singapore.*
Bayer, Spain. Bayer Hispania S.L., Pau Claris 196, 08037 Barcelona, Spain.
url: www.bayer.es
Bayer, Swed. Bayer AB, Box 5237, 402 24 Göteborg, Sweden.
url: www.bayer.se
Bayer, Switz. Bayer (Schweiz) AG, Pharma, Postfach, Grubenstrasse 6, 8045 Zurich, Switzerland.
url: www.bayer.ch
Bayer, Thai. Bayer Thai Co. Ltd, 130/1 North Sathorn Rd, Silom, Bangrak, Bangkok 10500, Thailand.
url: www.bayer.co.th
Bayer, Turk. Bayer Tük Kimya San. Ltd. Şti., Çakmak Mah., Balkan Cad. No:53, Ümraniye, İstanbul, 34770, Turkey.
url: www.bayer.com.tr
Bayer, UK. Bayer plc, Bayer Schering Pharma, Bayer House, Strawberry Hill, Newbury, Berkshire, RG13 1JA, UK.
url: www.bayer.co.uk
Bayer, USA. Bayer HealthCare Pharmaceuticals, 400 Morgan Lane, West Haven, CT 06516-4175, USA.
url: www.bayerus.com
Bayer, Venez. Bayer de Venezuela C.A., Av. Tamanaco - Torre Bayer, Urb. El Rosal, Caracas, Venezuela.
url: www.bayer.com
Bayer Biological, Hong Kong. See *LCH, Hong Kong.*
Bayer Consumer, Arg. See *Bayer, Arg.*
Bayer Consumer, Austral. See *Bayer, Austral.*
Bayer Consumer, Canad. See *Bayer, Canad.*
Bayer Consumer, Malaysia. See *Bayer, Malaysia.*
Bayer Consumer, Mex. See *Bayer, Mex.*
Bayer Consumer, Rus. See *Bayer, Rus.*
Bayer Consumer, UK. See *Bayer, UK.*
Bayer Consumer, USA. Bayer Consumer Care Division, 36 Columbia Rd, P.O. Box 1910, Morristown, NJ 07962-1910, USA.
url: www.bayerus.com; www.consumercare.bayer.com
Bayer Diagnostici, Ital. See *Bayer, Ital.*
Bayer Diagnostics, Fr. Bayer Diagnostics, Tour Horizon, 52 quai de Dion Bouton, 92807 Puteaux cdx, France.
url: www.bayerdiag.com
Bayer Diagnostics, Irl. See *Bayer, Irl.*
Bayer Diagnostics, Mex. Bayer de Mexico S.A. de C.V., Division Diagnosticos, Av. Coyoacan 1553, Col del Valle, 03100 Mexico D.F., Mexico.
url: www.bayerdiag.com
Bayer Diagnostics, UK. See *Bayer, UK.*
Bayer Healthcare, Singapore. Bayer (South East Asia) Pte Ltd, Pharmaceutical & OTC Division, 9 Benoi Sector, S 629844, Singapore.
url: www.bayer.com

Bayer Sante, Fr. Bayer Santé Familiale, 33 rue de l'Industrie, 74240 Gaillard, France.
url: www.bayer.fr
Bayer Schering, Cz. See *Bayer, Cz.*
Bayer Schering, Hung. Bayer Schering Pharma Magyarország, Hungary.
url: www.schering.hu
Bayer Schering, Malaysia. See *Bayer, Malaysia.*
Bayer Schering, Port. See *Bayer, Port.*
BayHealth, Port. BayHealth Comercialização de Produtos Farmacêuticos Unipessoal Lda, Rua da Quinta do Pinheiro 5, 2794-003 Carnaxide, Portugal.
Bayhealth, Spain. See *Bayer, Spain.*
Bayropharm, Spain. See *Bayer, Spain.*
BB, Cz. BB Pharma as, Kovriginova 1416/6, 147 00 Praha 4, Czech Republic.
BBI, UK. BBI Healthcare, Unit A Kestrel Way, Garngoch Industrial Estate, Gorseinon, Swansea, SA4 9WN, UK.
BB-NCIPD, Philipp. See *Global, Philipp.*
BCM, UK. BCM Ltd, Dio First 114, Nottingham, Nottinghamshire, NG90 2PR, UK.
BCP, Philipp. BCP Dermatological Corp., Dela Paz Bldg, 1570 Dapitan St, Sampaloc, Manila, Philippines.
BDF, Mex. See *Beiersdorf, Mex.*
BDH, India. BDH Industries Ltd, Nair Baug, Akurli Rd, Kandivli (E), Mumbai 400 101, India.
BDI, USA. BDI Pharmaceuticals, Inc., 9700 North Michigan Rd, Carmel, IN 46220, USA.
url: www.bdi-marketing.com
Beach, USA. Beach Pharmaceuticals, 201 Delaware St, Greenville, SC 29605, USA.
Beaco, Hung. Beaco Bt, Retek u 32, 1024 Budapest, Hungary.
Beacon, UK. Beacon Pharmaceuticals Ltd, 85 High St, Tunbridge Wells, Kent, TN1 1YG, UK.
url: www.beaconpharma.co.uk
Beacons, Hong Kong. See *Mekim, Hong Kong,* and *Unipharm, Hong Kong.*
Beacons, Singapore. Beacons Pharmaceuticals Pte Ltd, 21 Chin Bee Ave, S 619942, Singapore.
url: www.beacons.com.sg
Beaubour, Fr. Beaubour Nutrition, ZI La Canterie, B.P. 38, 37800 Sainte-Maure-de-Touraine, France.
url: www.beaubour.com
Beaufour, Cz. See *Beaufour, Fr.*
Beaufour, Fr. Beaufour Ipsen Pharma, 24 rue Erlanger, 75781 Paris cdx 16, France.
url: www.beaufour-ipsen.com
Beaufour, Switz. See *Uhlmann-Eyraud, Switz.*
Beaufour Ipsen, Pol. See *Ipsen, Pol.*
Beaufour-Ipsen, Cz. Beaufour Ipsen International, Střední 57/7, 162 00 Prague 6, Czech Republic.
Beaufour-Ipsen, Hong Kong. See *IDS, Hong Kong.*
Beaufour-Ipsen, Hung. See *Europharm, Hung.*
Beaufour-Ipsen, Malaysia. See *Antah, Malaysia.*
Beaufour-Ipsen, Rus. Beaufour Ipsen International SNC, Mosenka Park Tower, Taganskaya ul. 19, 109004 Moscow, Russia.
url: www.ipsen.com
Beaufour-Ipsen, Singapore. See *Emerging Pharma, Singapore.*
Beaufour-Ipsen, Switz. See *Uhlmann-Eyraud, Switz.*
Beaufour-Ipsen, Thai. See *Pacific, Thai.*
Beckman, Canad. See *Beckman, USA.*
Beckman, USA. Beckman Coulter Inc, 4300 North Harbour Bvld, P.O. Box 3100, Fullerton, CA 92834-3100, USA.
url: www.beckmancoulter.com
Beckmann, Ger. Dr Beckmann Pharma, Moosdorfstr. 1, 82229 Seefeld, Germany.
url: www.drbeckmann.de
Becton Dickinson, USA. Becton Dickinson & Co., 1 Becton Drive, Franklin Lakes, NJ 07417, USA.
url: www.bd.com
Bedford, USA. Bedford Laboratories, a Boehringer Ingelheim Company, 300 Northfield Rd, Bedford, OH 44146, USA.
url: www.bedfordlabs.com
Beecham, Port. See *GSK, Port.*
Beecham, Spain. See *GSK, Spain.*
Beethoven, Ger. Beethoven-Pharma Dr Wiemann GmbH, Steinthalstr. 1, 90455 Nurnberg, Germany.
Befelka, Ger. Befelka-Arzneimittel, Parkstr. 6 B, 49080 Osnabruck, Germany.
Behrens, Venez. Laboratorio Behrens C.A., Industria Farmacéutica Nacional, calle Real de Chapellín, Edif. Behrens, Caracas, Venezuela.
url: www.labbehrens.com
Beiersdorf, Arg. Beiersdorf S.A., Triunvirato 2902, 1427 Buenos Aires, Argentina.
url: www.beiersdorf.com
Beiersdorf, Austral. Beiersdorf Australia Ltd, P.O. Box 139, North Ryde, NSW 2113, Australia.
url: www.beiersdorf.com.au
Beiersdorf, Austria. Beiersdorf GmbH, Laxenburger Strasse 151, A-1101 Vienna, Austria.
url: www.beiersdorf.com
Beiersdorf, Belg. Beiersdorf NV SA, Industrielaan 30, B-1070 Brussels, Belgium.
url: www.beiersdorf.be
Beiersdorf, Canad. See *Smith & Nephew, Canad.*
Beiersdorf, Chile. Beiersdorf SA, Lo Espejo 501, Maipu, Santiago, Chile.
Beiersdorf, Cz. Beiersdorf sro, Prague, Czech Republic.
Beiersdorf, Ger. Beiersdorf AG, Unnastr. 48, 20245 Hamburg, Germany.
url: www.beiersdorf.de
Beiersdorf, Gr. Beiersdorf, Ag. Nektariou 2, 153 44 Yerakas, Greece.
Beiersdorf, Hung. Beiersdorf Kft, Tartsay Vilmos u 3, 1126 Budapest, Hungary.
Beiersdorf, Irl. Beiersdorf Ireland Ltd, First Floor, Block 8, St John's Court, Santry, Dublin 9, Ireland.
url: www.beiersdorf.ie
Beiersdorf, Mex. Beiersdorf Mexico S.A. de C.V., Poniente 116 No. 509, Col. Industrial Vallejo, 02300 Mexico D.F., Mexico.
Beiersdorf, Port. Beiersdorf Portuguesa, Lda, Rua Soeiro Pereira Gomes 59, 2746-952 Queluz, Portugal.
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Beiersdorf, Spain. Beiersdorf, Ctra Mataro-Granollers Km 5.4, Argentona, 08310 Barcelona, Spain.
url: www.beiersdorf.com
Beiersdorf, Switz. Beiersdorf AG, Aliothstrasse 40, 4142 Münchenstein, Switzerland.
url: www.beiersdorf.com
Beiersdorf, Thai. Beiersdorf (Thailand) Co. Ltd, 12 Fl, Sathorn Thani Building 1, 90/30-33 North Sathorn Rd, Silom, Bangrak, Bangkok 10500, Thailand.
url: www.beiersdorf.com
Beiersdorf, UK. Beiersdorf UK Ltd, 2010 Solihull Parkway, Birmingham Business Park, Birmingham, B37 7YS, UK.
url: www.beiersdorf.com
Beiersdorf, USA. Beiersdorf Inc., Wilton Corporate Center, 187 Danbury Road, Wilton, CT 06897, USA.
url: www.beiersdorf.com
Beiersdorf, Venez. Beiersdorf S.A., Avenida Francisco de Miranda, Edificio Parque Cristal, Torre Este, piso 14 oficina 14A, Los Palos Grandes, Caracas, Venezuela.
url: www.beiersdorf.com
Beige, S.Afr. See *Brunel, S.Afr.*
Bell, India. Bell Pharma, 75/C Government Industrial Estate, Kandivli (W), Mumbai 400 067, India.
Bell, UK. Bell, Sons & Co. (Druggists), P.O. Box 62, Tanhouse Lane, Widnes, Cheshire, WA8 0SA, UK.
url: www.bells-healthcare.com
Bellwether, Austral. Bellwether, Australia.
Belmac, Spain. Belmac, C/Teide No 4, Planta Baja, Parque Empresarial La Marina, San Sebastian de los Reyes, 28700 Madrid, Spain.
url: www.belmac.com
Belpharma, Belg. See *Bournonville, Belg.*
Belupo, Cz. See *Podravka, Cz.*
Belupo, Rus. Belupo, Lomonosovskii 38, kv 71-72, 119330 Moscow, Russia.
url: www.belupo-dd.ru
Belvedere, Canad. Belvedere International Inc., 5675 Keaton Cres., Mississauga, Ontario, L5R 3G3, Canada.
Ben Venue, Rus. See *AstraZeneca, Rus.*
Bencard, Ger. Bencard Allergie GmbH, Messerschmittstr 4, 80992 Munich, Germany.
url: www.bencard.de
Bene, Cz. See *Bene, Ger.*
Bene, Ger. bene-Arzneimittel GmbH, Herterichstr. 1, 81479 Munich, Germany.
url: www.bene-gmbh.de
Bene, Hung. See *Keri, Hung.*
Bene, Malaysia. See *Mederis, Malaysia.*
Bene, Pol. See *Miralex, Pol.*
Bene-Chemie, Hong Kong. See *Universal, Hong Kong.*
Benecor, Philipp. See *Diethelm, Philipp.*
Benedetti, Ital. Benedetti S.p.A., Vicolo de' Bacchettoni 3, 51100 Pistoia (PT), Italy.
Benefoot, UK. Benefoot UK Ltd, Branson Court, Branson St, Manchester, M40 7FP, UK.
Benitol, Arg. Laboratorios Benitol S.A.C.I., Felipe Vallese 3340/44, 1407 Buenos Aires, Argentina.
url: www.laboratoriosbenitol.com
Bennett, Gr. Bennett Farmakevtiki AE, K Korela 15 & Parnithos, 145 64 N Kifisia, Greece.
Bennett, UK. Bennett Natural Products, Enterprise House, Richmond Hill, Wigan, Lancashire, WN5 8AA, UK.
url: www.healthremedies.co.uk
Bennetts, S.Afr. Bennetts, P.O. Box 76076, Wendywood 2144, South Africa.
url: www.colic.co.za
Bentley, Cz. See *Bentley, Irl.*
Bentley, Irl. Bentley Pharmaceuticals Ireland Ltd, 25/28 North Wall Quay, Dublin 1, Ireland.
Berenguer Infale, Spain. See *Almirall, Spain.*
Beres, Hung. Béres Gyógyszergyár Rt, Szépvölgyi u 135, 1037 Budapest, Hungary.
Beres, Rus. Beres Pharmaceuticals Co. Ltd, Krasnaya Presnya ul. 1-7, Moscow, Russia.
Bergamo, Braz. Lab. Quím. Farmacêutico Bergamo Ltda, Rua Rafael de Marco 43, 06765-000 Taboao da Serra, SP, Brazil.
Bergamon, Ital. Bergamon S.r.l., Via Farini 5, 00185 Rome, Italy.
url: www.bergamon.it
Bergen Brunswig, USA. See *AmerisourceBergen, USA.*
Berk, Cz. See *Glynn, Cz.*
Berk, Turk. Berk İlaç İthalat ve Pazarlama A.Şti., Abc Yolu, Abc Plaza, Istinye, İstanbul, 80860, Turkey.
url: www.berkilac.com
Berk, UK. See *Teva, UK.*
Berko, Turk. Berko İlaç ve Kimya Sanayi Ltd. Şti., Yeni Çamlıca Mah. Baraj Yolu, Cad. Özgür Sok. No:16, Y. Dudullu-Ümraniye, İstanbul, Turkey.
url: www.berko.com.tr
Berlex, Canad. Berlex Canada Inc., 334 Avro Ave, Pointe-Claire, Quebec, H9R 5W5, Canada.
url: www.berlex.ca
Berlex, Port. Berlex Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.
Berlex, USA. See *Bayer, USA.*
Berlico Mulia, Indon. Berlico Mulia Farma, Jl Juwangen Kalasan Km 10.6, Tromol Pos No 8, 55571 Yogyakarta, DI Yogyakarta, Indonesia.
Berlifarma, Port. Berlifarma Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.
Berlimed, Braz. See *Schering, Braz.*
Berlimed, Port. Berlimed Especialidades Farmacêuticas Lda, Estrada Nacional 249, Km 15, 2725-397 Mem-Martins, Portugal.
Berlin, Hong Kong. See *Ebewe, Hong Kong.*
Berlin Pharm, Rus. Berlin-Pharma ZAO Moscow, ul. Kashirskoe 22-3, Str. 3, 115201 Moscow, Russia.
url: www.berlin-chemie.ru
Berlin Pharm, Singapore. See *Polymedic, Singapore.*
Berlin Pharm, Thai. Berlin Pharmaceutical Industry Co. Ltd, 359 New Rd, Bangkok 10100, Thailand.
url: www.berlinpharm.com
Berlin-Chemie, Cz. Berlin-Chemie Menarini Group, Komarková 27, 148 00 Prague 4, Czech Republic.
Berlin-Chemie, Ger. Berlin-Chemie AG, Glienicker Weg 125, 12489 Berlin, Germany.
url: www.berlin-chemie.de
Berlin-Chemie, Hung. Berlin-Chemie Képviselet, Váci út 113, 1138 Budapest, Hungary.
Berlin-Chemie, Pol. Berlin-Chemie/Menarini Polska Sp. zo.o., ul. Cybernetyki 7, 02-677 Warsaw, Poland.
url: www.menarini.pl
Berlin-Chemie, Rus. See *Berlin Pharm, Rus.*
Berlipharm, Irl. See *Clissmann, Irl.*
Berlipharm, Neth. Berlipharm BV, Van Houten Industriepark 1, 1381 MZ Weesp, Netherlands.
Berlis, Switz. Berlis AG 704 Blegistrasse 3, 6341 Baar, Switzerland.
Berman, Mex. Berman Laboratorios S.A. de C.V., Laboratoristas No. 46, Col. Iztapalapa Sifon, 09400 Mexico D.F., Mexico.
Berna, Canad. See *Berna, USA.*
Berna, Cz. See *Berna, Switz.*
Berna, Denm. See *Cortec, Denm.*
Berna, Fin. See *SBL, Swed.*
Berna, Hong Kong. See *Keller, Hong Kong.*
Berna, Indon. Berna Biotech Korea Corp., 501A Graha Bumiputra, Jl Asia Afrika No 141-149, Bandung 40112, Indonesia.
url: www.bernabiotech.co.kr
Berna, Ital. Istituto Sieroterapico Berna S.r.l., Via Bellinzona 39, 22100 Como, Italy.
Berna, Malaysia. See *Diethelm, Malaysia.*
Berna, Neth. See *Berna, Ital.*
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Berna, NZ. See *Pharmabroker, NZ.*
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Berna, Pol. See *Biomed Krakow, Pol.*
Berna, Port. See *Vieira, Port.*
Berna, Singapore. See *Diethelm, Singapore.*
Berna, Spain. Berna, P Castellana 163, 28046 Madrid, Spain.
url: www.bernabiotech.es
Berna, Switz. Berna Biotech AG, Rehhagstrasse 79, 3018 Berne, Switzerland.
Berna, Thai. See *Diethelm, Thai.*
Berna, Turk. C/o Yeni Şark Ecza Deposu A.Ş., Balmumcu, Barbaros Bulvan, Hoşsohbet Sok. 2, Beşiktaş, İstanbul, Turkey.
url: www.bernabiotech.com
Berna, USA. Berna Products Corp., 4216 Ponce de Leon Blvd, Coral Gables, FL 33146, USA.
url: www.bernaproducts.com
Bernabo, Arg. Laboratorios Bernabo SA, Terrada 2346, 1416 Buenos Aires, Argentina.
Bernauer, Switz. Bernauer & Co, 6052 Hergiswil, Switzerland.
Berner, Fin. Berner Oy, Sahaajankatu 24, 00810 Helsinki, Finland.
Bernofarm, Indon. Bernofarm PT, Komp Harmoni Plaza, Blok J No 3-4, Jl Suryopranoto, 10130 Jakarta Pusat, DKI Jaya, Indonesia.
Berren, Fin. Berren Oy, Pohjoinen Hesperiankatu 13 B 15, 00260 Helsinki, Finland.
Bersan, Ital. Bersan Cosmetica Ipoallergenica S.r.l., Via delle Pervinche 10, 00100 Rome, Italy.
url: www.bersan.it
Berta, Ital. Berta S.r.l., Via Andrea Doria 7, 20124 Milan, Italy.
Bertek, USA. Bertek Pharmaceuticals Inc, 781 Chestnut Ridge Rd, Morgantown, WV 26505, USA.
url: www.bertek.com
Bescansa, Spain. Bescansa, Pl. Inds. Tambre-via Pasteur 8, Santiago de Compostela, 15890 La Coruna, Spain.
Besins, Belg. Besins Distribution Belgium, rue Villain XIIII 53-55, 1000 Brussels, Belgium.
url: www.besins.be
Besins, Cz. See *Besins, Fr.*
Besins, Denm. See *Schering, Denm.*
Besins, Fr. Laboratoires Besins International, 13 rue Perier, 92120 Montrouge, France.
Besins, Ger. See *Kade, Ger.*
Besins, Hong Kong. See *Bi Asian Pacific, Hong Kong.*
Besins, Hung. Besins, Hungary.
Besins, Israel. See *CTS, Israel.*
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Besins, Norw. See *Schering, Swed.*
Besins, Port. See *Besins, Fr.*
Besins, Rus. See *FIC, Rus.*
Besins, Singapore. See *Pharmed, Singapore.*
Besins, Thai. See *BJC, Thai.*
Besins, UK. See *Besins, Fr.*
Besins International, Israel. See *CTS, Israel.*
Besins-Iscovesco, Malaysia. See *Wellchem, Malaysia.*
Best, Mex. Laboratorios Best S.A. de C.V., Municipio Libre No. 199, Col. Benito Juarez Portales, 03300 Mexico D.F., Mexico.
Beta, Arg. Laboratorios Beta S.A., Av. San Juan 2266, 1232 Buenos Aires, Argentina.
url: www.betalab.com.ar
Beta, Canad. Beta Brands, 100 Cumberland Ave, Hamilton, Ontario, L8M 1Z1, Canada.
Beta, Ital. Laboratorio Biologico Chemioterapico Beta S.r.l., Via IV Novembre 171/3, 25080 Prevalle, Italy.
Beta, Spain. See *AstraZeneca, Spain.*
Beta, USA. Beta Dermaceuticals, P.O. Box 691106, San Antonio, TX 78269-1106, USA.
url: www.beta-derm.com
Beta Healthcare, UK. Beta Healthcare, Standard House, Prospect Place, Lenton, Nottingham, Nottinghamshire, NG7 1RX, UK.
Be-Tabs, S.Afr. Be-Tabs Pharmaceuticals (Pty) Ltd, P.O. Box 43486, Industria 2042, South Africa.
url: www.be-tabs.co.za
Betamadrileno, Spain. Betamadrileño, Area Empresarial Andalucia, Sector 4 Parcela 28, Getafe, 28906 madrid, Spain.
Betapharm, Ger. betapharm Arzneimittel GmbH, Kobelweg 95, 86156 Augsburg, Germany.
url: www.betapharm.de
Beutlich, USA. Beutlich Pharmaceuticals, 1541 Shields Drive, Waukegan, IL 60085, USA.
url: www.beutlich.com
Bevo, Gr. Bevo, 104 38 Athens, Greece.
Bexal, Spain. Bexal Farmaceutica, C/ Osa Mayor n: 4, Edificio Osa Mayor, Oficina B, Aravaca, 28023 Madrid, Spain.
url: www.bexal.es
Beximco, Singapore. See *Advanced, Singapore.*
Bharat, Philipp. See *Pharmawealth, Philipp.*
BHR, UK. BHR Pharmaceuticals Ltd, 41 Centenary Business Centre, Hammond Close, Attleborough Fields, Nuneaton, Warkwickshire, CV11 6RY, UK.
url: www.bhr.co.uk
BI, Gr. See *Boehringer Ingelheim, Gr.*
Bi Asian Pacific, Hong Kong. Bi Asian Pacific Ltd, Flat B, 22/F, Tak Lee Commercial Building, 113-117 Wan Chai Rd, Wanchai, Hong Kong.
Biagini, Cz. See *Kedrion, Ital.*
Bial, Port. Laboratorios Bial (Portela & Co., SA), Av da Siderurgia Nacional, Apartado 19, 4745-457 São Mamede do Coronado, Portugal.
url: www.bial.com
Bial, Spain. Bial-Industrial Farmaceutica, Alameda de Urquijo 27, Bilbao, 48008 Vizcaya, Spain.
url: www.bial.es
Bialfar, Port. See *Bial, Port.*
Bialport, Port. See *Bial, Port.*
Biara, Port. Biara Produtos Farmacêuticos Lda, Rua Ramalho Ortigão 45 A, 1070-228 Lisbon, Portugal.
Bichsel, Switz. Laboratorium Dr G Bichsel AG, Bahnhofstrasse 5a, 3800 Interlaken, Switzerland.
Bieffe, Cz. See *Bieffe, Ital.*
Bieffe, Ital. Bieffe Medital S.p.A., Via Nuova Provinciale, 23034 Grosotto (SO), Italy.
Bieffe, Spain. See *Baxter, Spain.*
Biem, Turk. Biem İlaç, 57 Sokak No:19/1, Emek, İstanbul, Turkey.
url: www.biemilac.com.tr
Bier, Ital. Bier Farmaceutici di A di Finizio Sas, Via Cupa Capodichino 19, 80144 Naples, Italy.
url: www.bierfarmaceutici.it
Biex, Irl. See *Helsinn Birex, Irl.*
Bifarma, Ital. Bifarma Fitoterapici di Bignardi Sergio, Via Pallia 5, 20139 Milan, Italy.
Bilim, Thai. See *JDH Borneo, Thai.*
Bilim, Turk. Bilim İlaç San. ve Tic A.Ş., Ayazaga Koyu Yolu No:6, Maslak, İstanbul, 34398, Turkey.
url: www.bilimpharma.com
Billev, Hung. Billev, Hungary.
Billiet, Arg. Lab. Billiet & Cma. S.R.L., Soler 3564, 1425 Buenos Aires, Argentina.
Binesa, Spain. See *Pfizer, Spain.*
Binnofarm, Rus. See *Moskhimfarm, Rus.*

Bintang Toedjoe, Indon. Bintang Toedjoe PT, Jl Jend A Yani 2, Pulo Mas, 13210 Jakarta, Indonesia.
Bio Farma, Malaysia. See *Propharm, Malaysia.*
Bio Farma, Thai. See *Biogenetech, Thai.*
Bio Merieux, UK. Bio Merieux UK, Grafton Way, Basingstoke, Hampshire, RG22 6HY, UK.
url: www.biomerieux.com
Bio Minerals, Philipp. See *Zuellig, Philipp.*
Bio Portugal, Port. Bioportugal Quimico Farmacêutica Lda, Alameda Fernão Lopes 19 E, Miraflores, 1495-135 Algés, Portugal.
Bio Products, Malaysia. See *Germax, Malaysia.*
Bio Sidus, Thai. See *BJC, Thai.*
Bio Vita, Canad. Bio Vita, 1212 Louvain Ouest, Montreal, Quebec, H4N 1G5, Canada.
Bio2, Fr. Laboratoires Bio2, 99 bvd des Belges, 69006 Lyon, France.
url: www.bio2labo.com
Biobasal, Cz. See *Biobasal, Switz.*
Biobasal, Switz. Biobasal AG, Eulerstrasse 55, 4003 Basle, Switzerland.
Biobras, Braz. See *Novo Nordisk, Braz.*
BioCalth, UK. BioCalth International (UK) Ltd., Airdale Business Centre, Millennium Road, Skipton, North Yorkshire, BD23 2TZ, UK.
url: www.biocalth.co.uk
Biocel, Turk. Biocel, Turkey.
Bioceuticals, UK. Bioceuticals Ltd, 26 Zennor Rd, London, SW12 0PS, UK.
url: www.bioceuticals.co.uk
Biochefa, Pol. Biochefa Farnaceutyczny Zakład Naukowo-Produkcyjny, ul. Kasztanowa 3, 41-205 Sosnowiec, Poland.
url: www.biochefa.pl
Biochem, Gr. Biochem Diagnostics S.A., 6 Zisimopoulou Str. & Sygrou Ave, 175 64 P. Faliro, Greece.
url: www.biochem.gr
Biochem, India. Biochem Pharmaceutical Industries, Aidun Building, John Crasto Lane, Mumbai 400 002, India.
url: www.biochemgroup.com
Biochemie, Austria. Biochemie GmbH, Brunner Strasse 59, A-1235 Vienna, Austria.
url: www.biochemie.com
Biochemie, Cz. Biochemie Austria, Ulice 1. pluku 17, 186 00 Prague 8, Czech Republic.
url: www.biochemie-generics.cz
Biochemie, Hong Kong. See *Unipharm, Hong Kong.*
Biochemie, Hung. See *Novartis, Hung.*
Biochemie, Indon. See *Anugerah Pharmindo, Indon.*
Biochemie, Malaysia. Biochemie Marketing Office, LiFung Centre, Lot 6, Persiaran Perusahan, Seksyen 23, Kawasan Perusahaan Shah Alam, 40300 Shah Alam, Selangor, Malaysia.
url: www.biochemie.com
Biochemie, NZ. See *CSL, NZ.*
Biochemie, Singapore. See *FP, Singapore.*
Biochemie, Thai. See *Novartis, Thai.*
Biochimici, Ital. Biochimici PSN S.p.A., Via Viadagola 30, 40050 Quarto Inferiore (BO), Italy.
Biochimico, Braz. Instituto Biochimico Ltda, Rod. Presidente Dutra km 310, 27580-000 Rio de Janeiro, RJ, Brazil.
Biocide, S.Afr. Biocide Ltd, P.O. Box 33, 236 Sir Lowry Rd, Woodstock 7915, South Africa.
Bioclon, Mex. Laboratorios Bioclon S.A. de C.V., Calz. de Tlalpan 4687, Coyoacan Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.bioclon.com.mx
Bioclones, S.Afr. Bioclones (Pty) Ltd, P.O. Box 784351, Sandton 2146, South Africa.
url: www.bioclones.co.za
Biocodex, Cz. See *Biocodex, Fr.*
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Biocodex, Fr. Laboratoires Biocodex, 19 rue Barbès, 92126 Montrouge cdx, France.
Biocodex, Hong Kong. See *Primal, Hong Kong.*
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Biocodex, USA. Biocodex, 300 North Mill St, Cresswell, OR 97426, USA.
Biocom, Fr. Laboratoires Biocom, 44 bd Saint-Jacques, 75014 Paris, France.
Bioconcepts, Austral. BioConcepts Pty Ltd, P.O. Box 1492, Eagle Farm, BC Qld 4009, Australia.
Bioconcepts, UK. Bioconcepts Ltd, P.O. Box 15, Havant, Hampshire, PO9 1RQ, UK.
url: www.bioconcepts.co.uk
Biocontrol, Arg. Biocontrol S.A., Fraga 1504, 1427 Buenos Aires, Argentina.
Biocrom, Arg. Lab. Biocrom Esp. Med. S.A., Luis Viale 965, 1416 Buenos Aires, Argentina.
Biocumed, Arg. Lab. Biocumed S.A., Av. J. B. Justo 2781, 1414 Buenos Aires, Argentina.
Biocur, Ger. Biocur Arzneimittel GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany.
url: www.biocur.de
Biocure, Ital. Biocure S.r.l., Via Durazzo 5, 20134 Milan, Italy.
Bioderma, Fr. Bioderma, 75 cours Albert-Thomas, 69447 Lyon cdx 03, France.
url: www.bioderma.com
Bioderma, Ital. Bioderma Italia Srl, P.zza Cadorna 10, 20123 Milan, Italy.
Bioderma, Venez. Laboratorios Bioderma (Dermabel S.A.), Calle los Manguitos, Torre Mega III, Piso 3, Of. 3D Urb. Las Palmas, Caracas, Venezuela.
Bio-Diat, Cz. See *Bio-Diat, Ger.*
Bio-Diat, Ger. Bio-Diät-Berlin GmbH, Selerweg 43-45, 12169 Berlin, Germany.
url: www.bio-diaet-berlin.de
Bio-Diet, Israel. Bio-Diet, Israel.
Biodim, Fr. Biodim, 17 rue de l'Ancienne Mairie, 92100 Boulogne-Billiancourt, France.
Biodiphar, Belg. Biodiphar SA, Rue des Trois Arbres 16a, 1180 Brussels, Belgium.
url: www.biodiphar.be
Biodue, Ital. Biodue S.r.l., Via Benvenuto Cellini 63/69, 50020 Loc. Sambuca Val di Pesa (FI), Italy.
url: www.pharcos.com
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Bioenvision, Port. See *Bioenvision, UK.*
Bioenvision, UK. Bioenvision Ltd, 11-12 Charles II St, Savanah House, London, SW1Y 4QU, UK.
Bioes, Fr. Laboratoires Bioes, 38 bd Henri-Sellier, 92156 Suresnes cdx, France.
url: www.bioes.fr
Bioethical, Ital. Bioethical S.r.l., Via Cadore 7, 26015 Soresina (CR), Italy.
Bioextra, Hung. Bioextra Kft, Bibor u 10, 1149 Budapest, Hungary.
Biofarm, Cz. See *Biofarm, Pol.*
Biofarm, Pol. Biofarm Sp. zo.o., ul. Wałbrzyska 13, 60-198 Poznań, Poland.
url: www.biofarm.pl
Biofarm, Rus. See *Marvel, Rus.*
Biofarma, Braz. Biofarma Farmacêutica Ltda, Prof. Roldao de Barros 271/79, 04823-010 São Paulo, SP, Brazil.
Biofarma, Mex. Biofarma Natural CMD SA de CV, Industria Hulera 97 Fracc. Indust., 45130 Zapopan Norte Zapopan, Jalisco, Mexico.
Biofarma, Turk. Biofarma İlaç San. Ltd. Şti., Samandira Baldesi, Veysel Karani Mah. No:48, Kartal, İstanbul, 81470, Turkey.
url: www.biofarma.com.tr
Biofarma, Venez. Laboratorio Biofarma C.A., Av. Rio Caura Torre Humboldt Piso 11, Oficina 1107, Prados del Este, Caracas 1080, Venezuela.
BioFemme, Philipp. BioFemme Inc. (Unilab Womens Healthcare), 2/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Philippines.
Biofilm, USA. Biofilm Inc., 3225 Executive Ridge 1707 Vista, CA 92081, USA.
url: www.astroglide.com
Bio-Fizik, Turk. Bio-Fizik Medical, Meşrutiyet Cad. No: 29/23, Kizilay, Ankara, Turkey.
Bioforce, Ger. Bioforce GmbH, Bruhlstr. 15, 78465 Constance, Germany.
url: www.bioforce.de
Bioforce, Switz. Bioforce AG, Postfach 76, 9325 Roggwil/TG, Switzerland.
url: www.bioforce.ch
Bioforce, UK. Bioforce UK Ltd, 2 Brewster Place, Irvine, Ayrshire, KA11 5DD, UK.
url: www.bioforce.co.uk
BioForm, USA. BioForm Medical, 1875 S Grant St, Suite 110, San Mateo, CA 94402, USA.
url: www.bioform.com
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Biogal, Israel. See *Teva, Israel.*
Biogal, Pol. See *Salus, Pol.*
Biogal, Rus. See *Teva, Rus.*
Biogalenic, Venez. Laboratorios Biogalenic C.A., Calle Bernardo Smilak, Edif. Jayor, Piso 1, San Martin, Caracas, Venezuela.
url: www.biogalenic.com
Biogalenica, Spain. Biogalenica, Ramon Trias Fargas 7-11 Ed, Marina Village, 08005 Barcelona, Spain.
Biogal-Teva, Hung. Biogal-Teva Pharma Rt, Róbert Károly krt 66, 1134 Budapest, Hungary.
Biogam, Arg. Biogam Argentina S.A., Av. Jujuy 1152, 1229 Buenos Aires, Argentina.
url: www.biogam-argentina.com
Biogam, Switz. See *Kart, Switz.,* and *Serolab, Switz.*
Biogaran, Fr. Biogaran, 15 bd Charles-de-Gaulle, 92707 Colombes cdx, France.
Biogaran, S.Afr. See *Servier, S.Afr.*
Bio-Garten, Austria. Bio-Garten GmbH, Triesterstrasse 14/1, A-2351 Wiener Neudorf, Austria.
Biogen, Austral. Biogen P/L, Suite 2601, Level 26, 100 Miller St, North Sydney, NSW 2060, Australia.
url: www.biogen.com
Biogen, Austria. See *Biogen, Fr.*
Biogen, Belg. Biogen Idec Belgium NV/SA, Regus Parc Atrium, 11000 Brussels, Belgium.
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Biogen, Canad. Biogen Idec Canada Inc., 3 Robert Speck Pkwy, Suite 300, Mississauga, Ontario, L4Z 2G5, Canada.
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Biogen, Cz. See *Biogen, Neth.*
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Biogen, Fin. Biogen Idec Finland Oy, Äyritie 12, 01510 Vantaa, Finland.
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Biogen, Hung. Biogen, Hungary.
Biogen, Irl. See *Biogen, UK.*
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Biogen, Norw. Biogen Idec Norway AS, Karenslyst alle 8b, 0278 Oslo, Norway.
url: www.biogen.com
Biogen, NZ. See *CSL, NZ.*
Biogen, Pol. See *Richter, Pol.*
Biogen, Port. Biogen Idec Portugal Sociedade Farmacêutica Unipessoal Lda, Av. Duque d'Avila 185, Floor 8, 1050-082 Lisbon, Portugal.
url: www.biogenidec.com
Biogen, Rus. See *Gedeon Richter, Rus.*
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url: www.biogenidec.com
Biogen, Swed. BiogenIdec Sweden AB, Kanalvägen 1 A, plan 2, 194 61 Upplands Väsby, Sweden.
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Bio-Gen, Turk. Bio-Gen İlaç San. Ltd. Şti., Bosna Hersek Cad. No:32/2, Emek, Ankara, 06510, Turkey.
url: www.bio-gen.net
Biogen, UK. Biogen Idec Ltd, Thames House, Foundation Park, Maidenhead, Berkshire, SL6 3UD, UK.
url: www.biogen.com
Biogen, USA. Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, USA.
url: www.biogenidec.com
Biogen Dompe, Switz. Dompé-Biogen AG, Landis + Gry-Strasse 3, 6300 Zug, Switzerland.
url: www.biogen.ch
Biogena, Ital. Valetudo S.r.l., Divisione Biogena, Via Ghiaie 6, 24030 Presezzo (BG), Italy.
Biogenetech, Thai. Biogenetech Co. Ltd, Biopex Building, 749/12, Soi Watchannal, Off Soi Pradoo Sathupradit Rd, Bangphongphang, Yannawa, Bangkok 10120, Thailand.
BioGenex, USA. BioGenex Laboratories, 4600 Norris Canyon Rd, San Ramon, CA 94583, USA.
url: www.biogenex.com
Bioglan, Austral. Bioglan Ltd, 8/10 Yalgar Rd, Yalgar Business Park, Kirrawee, NSW 2232, Australia.
url: www.bioglan.com.au
Bioglan, Denm. See *Bioglan, Swed.*
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Bioglan, Ger. Bioglan Pharma GmbH, Robert-Bosch-Str. 6, 35398 Giessen, Germany.
url: www.bioglan.de
Bioglan, Hong Kong. See *Keller, Hong Kong.*
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Bioglan, Malaysia. See *United Italian, Malaysia.*
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Bioglan, Swed. Bioglan AB, Box 50310, 202 13 Malmö, Sweden.
url: www.bioglan.com
Bioglan, Thai. See *Hua, Thai.*
Bioglan, UK. See *Centrapharm, UK.*
Bioglan, USA. See *Bradley, USA.*
Bio-Health, UK. Bio-Health Ltd, Culpeper Close, Medway City Estate, Rochester, Kent, ME2 4HU, UK.
url: www.bio-health.co.uk
Biohorm, Spain. See *Uriach, Spain.*
Bioiberica, Spain. Bioiberica, Pl. Francesc Macia 7, 08029 Barcelona, Spain.
url: www.bioiberica.com
Bioimmun, Ger. BioImmunPharma GmbH, Im Dammwald 27, 61381 Friedrichsdorf, Germany.
url: www.bioimmun.de
Bioindustria, Ital. See *Pfizer, Ital.*
Biokanol, Ger. Biokanol Pharma GmbH, Kehler Str. 7, 76437 Rastatt, Germany.
url: www.biokanol.de
Bio-Kem, Turk. Bio-Kem Laboratuar Malzemeleri Sanayi & Ticaret Ltd STI, Millet Caddesi, Feriha Apartmani, 64/5 Findikzade, 34093 Fatih İstanbul, Turkey.
url: www.bio-kem.com
Biokhimik, Rus. Biokhimik, Vasenko St 15a, 430030 Saransk, Russia.
url: www.biohim.moris.ru
Biokosma, Fr. Lab Biokosma France, 2 rue des Lilas, 39004 Lons-le-Saunier cdx, France.
Biol, Arg. Inst. Biolsgico Arg. S.A.I.C., J. E. Uriburu 153, 1027 Buenos Aires, Argentina.
Biolab, Hong Kong. See *Mekim, Hong Kong.*
Biolab, Malaysia. See *Medispec, Malaysia.*
Biolab, NZ. Biolab Scientific, P.O. Box 102-922, North Shore Mail Centre, Auckland, New Zealand.
url: www.biolabgroup.com
Biolab, Philipp. See *Cathay, Philipp.*
Biolab, Singapore. See *Indrugco, Singapore.*
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Biolab Sanus, Braz. Biolab Sanus Farmacêutica Ltda, Av. dos Bandeirantes 5386, Planalto Paulista, 04071-900 São Paulo, SP, Brazil.
url: www.biolabfarma.com.br
Biolac, Swed. Biolac AB, Box 22057, 250 22 Helsingborg, Sweden.
url: www.biolac.se
Biolatina, Chile. Biolatina Chile SA, San Sebastian 2807, Las Condes, Santiago, Chile.
BioLife, Ger. Bio.Life Pharma GmbH, Haubachstr. 33, 10585 Berlin, Germany.
Biolink, Philipp. Biolink Pharma, Unit 1207 Pres Tower Cond, 81 Timog Ave, Quezon City, Philippines.
Biolitec, Belg. See *Biolitec, Irl.*
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Biolitec, Denm. See *Biolitec, UK.*
Biolitec, Ger. See *Biolitec, UK.*
Biolitec, Irl. Biolitec Pharma Ireland Ltd, United Drug House, Magna Drive, Magna Business Park, Citywest Rd, Dublin 24, Ireland.
url: www.biolitec.com
Biolitec, Neth. See *Biolitec, UK.*
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Biolitec, UK. Biolitec Pharma Ltd, Research Avenue South, Herriot Watt Research Park, Edinburgh, EH14 4AP, UK.
url: www.biolitec.com
Biologia, Braz. Laboratório Brasileiro de Biologia Ltda, Rua Allan Kardec 66, 20710-230 Rio de Janeiro, RJ, Brazil.
Biological E, India. Biological E. Ltd, 18/1&3, Azamabad, Hyderabad 500 020, India.
url: www.biologicale.com
Biologici Italia, Ital. Biologici Italia Laboratories S.r.l., Via Cavour 41/3, 20026 Novate Milanese (MI), Italy.
Biologiques de l'Ile-de-France, Fr. See *Medix, Fr.*
BioMarin, Cz. See *BioMarin, UK.*
BioMarin, Fr. BioMarin, France.
BioMarin, Port. BioMarin Europe Ltd, Portugal.
url: www.biomarinpharm.com
BioMarin, UK. BioMarin Europe Ltd, Axtell House, 23-24 Warwick St, London, W1B 5NQ, UK.
url: www.biomarinpharm.com
BioMarin, USA. BioMarin Pharmaceutical Inc., 105 Digital Drive Novato, CA 94949, USA.
Biomatrix, Israel. See *Genzyme, Israel.*
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Biomed, Austral. Biomed Australia Pty Ltd., Unit 3, 9 Packard Ave, Castle Hill, NSW 2154, Australia.
Biomed, NZ. Biomed Ltd, P.O. Box 44-069, Pt Chevalier, Auckland, New Zealand.
Biomed, Spain. Biomed, Aragon 178, Entreplanta, Palma de Mallorca, 07008 Mallorca, Spain.
Biomed, Switz. Biomed AG, Uberlandstrasse 199, Postfach, 8600 Dubendorf 1, Switzerland.
url: www.biomed.ch
Biomed Krakow, Pol. Biomed-Kraków Instytut Biotechnologii Surowic i Szczepionek, al. Sosnowa 8, 30-224 Kraków, Poland.
url: www.biomed.pl
Biomed Lublin, Pol. Biomed Lublin, Biomed Wytwórnia Surowic i Szczepionek Sp. zo.o., ul. Uniwersytecka 10, 20-029 Lublin, Poland.
url: www.biomed.lublin.pl
Biomed Warszawa, Pol. Biomed Warszawa, Biomed Wytwórnia Surowic i Szczepionek, ul. Chełmska 30/34, 00-725 Warsaw, Poland.
url: www.biomed.waw.pl
Biomedica, Cz. Biomedica sro, Prague, Czech Republic.
Biomedica, Hong Kong. See *Trendful, Hong Kong.*
Biomedica, Ital. Biomedica Foscama Industria Chimico Farmaceutica S.p.A., Via Morolense 87, 03013 Ferentino (FR), Italy.
url: www.biomedicafoscama.com
Biomedica, Thai. See *Osotspa, Thai.*
Biomedica-Chemica, Gr. Biomedica-Chemica A.E., G. Lyra 25, 145 64 K. Kifisia, Greece.
Biomedis, Hong Kong. See *Unam, Hong Kong.*
Biomedis, Indon. See *Medifarma, Indon.*
Biomedis, Malaysia. See *Unam, Malaysia.*
Biomedis, Philipp. Biomedis Inc., Greenfields Bldg No 1, 750 Shaw Blvd, Mandaluyong City, Philippines.
Biomedis, Singapore. See *Far East, Singapore.*
Biomedis, Thai. See *Olic, Thai.*
Biomedis Oncology, Philipp. See *Biomedis, Philipp.*
Biomeks, Turk. Biomeks İlaç San. Ltd. Şti., Ulucanlar Caddesi, Ses Sokak, No:2/1-2-3, Cebeci, Ankara, 06340, Turkey.
url: www.biomeks.com
Biomep, Mex. Biomep SA de CV, Providencia 622, 3100 Benito Juarez del Valle, Mexico.
Biomerica, USA. Biomerica Inc., 1533 Monrovia Ave, Newport Beach, CA 92663, USA.
url: www.biomerica.com
Bio-Merieux, Hong Kong. See *Primal, Hong Kong.*
Bio-Merieux, USA. bioMerieux Inc., 100 Rodolphe St, Durham, NC 27712, USA.
url: www.biomerieux-usa.com
Biomet, Austral. Biomet Australia Ltd, 4/6-8 Byfield St, North Ryde, NSW 2113, Australia.
url: www.biomet.com

Biomet, Belg. Biomet Belgium BVBA, Fotografielann 5, 2610 Wilrijk, Belgium.
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Biomet, Fin. Biomet Finland Oy, Vattuniemenranta 2, 00210 Helsinki, Finland.

Biomet, Ger. Biomet Deutschland GmbH, Gustav-Krone-Str. 2, 14167 Berlin, Germany.
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Biomet, Singapore. See *Zuellig, Singapore.*

Biomet, Switz. Biomet Orthopaedics Swizterland GmbH, Gewerbezone Widalmi 12, 3216 Ried b Kerzers FR, Switzerland.
url: www.biometeurope.com

Biomet, UK. Biomet UK Ltd, Waterton Industrial Estate, Bridgend, South Wales, CF31 3XA, UK.
url: www.biometmerck.co.uk

Biomet Merck, Denm. Biomet Merck ApS, Hattingvej 7, 8700 Horsens, Denmark.
url: www.biometmerck.dk

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Biomet Merck, UK. See *Biomet, UK.*

Biomin, Cz. Biomin as, Czech Republic.

Biomo, Ger. biomo Pharma GmbH, Lendersbergstrasse 86, 53721 Siegburg, Germany.

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Bionax, Malaysia. See *Diethelm, Malaysia,* and *JDH, Malaysia.*

Bionax, Singapore. Bionax Singapore Pte Ltd, 99 Bukit Timah Rd, Alfa Centre 03-06, S 229835, Singapore.

Bionax, Thai. Bionax (Thailand) Ltd, 10 Fl, Unit A, Lake Rajada Office Complex, 193/35 New Rachadapisek Rd, Kwaeng Klongtoey, Khet Klongtoey, Bangkok 10110, Thailand.

Bioniche, Canad. Bioniche Pharma, 275 Labrosse Ave, Pointe-Claire, Quebec, H9R 1A3, Canada.
url: www.bioniche.com

Bioniche Teoranta, Singapore. See *Wellchem, Singapore.*

Bionorica, Austria. See *Bionorica, Ger.*

Bionorica, Cz. See *Schwabe, Cz.*

Bionorica, Ger. Bionorica AG, Kerschensteinerstr. 11-15, 92318 Neumarkt/Opf, Germany.
url: www.bionorica.de

Bionorica, Hong Kong. See *Jacobson, Hong Kong.*

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Bionorica, Switz. See *Biomed, Switz.*

Bionorica, Thai. See *Zuellig, Thai.*

Bionutra, Singapore. See *Zuellig, Singapore.*

Bionutre, Arg. Laboratorio Bionutre SRL, Lavalle 1145, 2000 Rosario, Santa Fe, Argentina.

Bio-Oil Research, Irl. See *Allphar, Irl.*

BioPartners, Cz. See *BioPartners, Ger.*

BioPartners, Ger. BioPartners GmbH, Eisenstrasse 3, 65428 Russelsheim, Germany.

BioPartners, Port. See *BioPartners, Ger.*

Biopas, Venez. Laboratorios Biopas S.A., Calle 10, Ef. Vizcaya, Torre B Piso 3, La Urbina, Caracas, Venezuela.

Biopat, Spain. See *MSD, Spain.*

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Biopharm, Hong Kong. See *Great Eastern, Hong Kong,* and *Mekim, Hong Kong.*

Biopharm, Philipp. See *PNF, Philipp.*

Biopharm, Rus. See *Marvel, Rus.*

Biopharm, Thai. Biopharm Chemicals Co. Ltd, 7 Fl, Bio House, 55 Sukhumvit 39, Bangkok 10110, Thailand.
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Biophausia, Denm. BioPhausia A/S, Gydevang 39-41, 3450 Allerød, Denmark.
url: www.biophausia.se

Biophausia, Ger. See *Biophausia, Swed.*

Biophausia, Neth. See *Biophausia, Swed.*

Biophausia, Norw. See *Biophausia, Swed.*

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Biophytarom, Fr. Laboratoires Biophytarom, Cap 18, 43 rue de l'Evangile, 75886 Paris cdx 18, France.

Biopin, Rus. Biopin Pharma OOO, Nevskii Prospekt 82, pom. 1, 191025 Saint Petersburg, Russia.
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Bioplanta, Ger. Bioplanta Arzneimittel GmbH, Bahnhofstr. 5, 76275 Ettlingen, Germany.

Biopolymer, Philipp. See *Keller, Philipp.*

Bioport, USA. BioPort Corp., 3500 N Mlk Jr Blvd, Lansing, MI 48906-9910, USA.
url: www.bioport.com

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Bioprogress, Ital. Bioprogress S.p.A., Via Aurelia 58, 00100 Rome, Italy.

Bioprojet, Fr. Bioprojet Pharma, 9 rue Rameau, 75002 Paris, France.

Bioquest, Ger. BioQuest GmbH, Holtystr. 19, 30171 Hannover, Germany.
url: www.bioquest-web.com

Bioquimed, Mex. Laboratorio Médico Biológico SA de CV, Reforma 9, 4400 Coyoacán Atlántida, Mexico.

Bioquimico, Arg. Lab. Bioquímico Argentino (LBA Farma) S.R.L., Irala 1575, 1164 Buenos Aires, Argentina.
url: www.lbafarma.com.ar

Bioreance, Fr. Bioreance Laboratoires, 220 bvd de la République, 92210 Saint-Cloud, France.
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Bioren, Switz. Bioren SA, 4 rue des îles, 2108 Couvet, Switzerland.

Biores, Ital. Biores Italia S.r.l., Via Vittorio Grassi 13, 00155 Rome, Italy.

Bioresearch, Mex. Bioresearch de Mexico S.A. de C.V., Rio Totolica 15-A, 53370 Naucalpan de Juarez, Mexico.
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Bioresearch, Spain. See *Abbott, Spain.*

Biorex, UK. Biorex Laboratories Ltd, 2 Crossfield Chambers, Gladbeck Way, Enfield, Middlesex, EN2 7HT, UK.

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Biorga, Hong Kong. See *CNW, Hong Kong.*

Biosano, Chile. Laboratorios Biosano SA, Aeropuerto 9941, Cerrillos, Santiago, Chile.

Bio-Sante, Canad. Les Laboratoires Bio-Santé, 3564 Griffith St, St-Laurent, Quebec, H4C 1A7, Canada.

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BioSaude, Port. BioSaúde Produtos Farmacêuticos Lda, Av. José Malhoa, Edifício Malhoa Plaza 2, Piso Escritório 2.2, 1070-325 Lisbon, Portugal.

Bioscience, Philipp. See *Baxter, Philipp.*

Bioscience, Thai. Bioscience Co. Ltd, 4/15 Moo 5 Rama II Rd, Samae-Dam, Bangkhuntien, Bangkok 10150, Thailand.

Biosel, Turk. Biosel İlaç San. ve Tic. A.Ş., Akbaba Köyü, Fener Cad. No:117, Beykoz, İstanbul, 81660, Turkey.
url: www.biosel.com.tr

Bio-Sen, Turk. Bio-Sen, Turkey.

Bioser (Βιοσερ), Gr. See *Vioser, Gr.*

Biosintetica, Braz. Laboratórios Biosintetica Ltda, Av das Nações Unidas 22.428, Predio 30, 04795-916 São Paulo, SP, Brazil.
url: www.biosintetica.com.br

Biosintex, Arg. Biosintex, Salom 657, 1277 Buenos Aires, Argentina.

Biosis, Philipp. Biosis Pharmaceutical Phils, Inc., Suite 303, GJ Bldg, 385 Quezon Ave, Quezon City, Philippines.

Biospray, Gr. Biospray S.A., Favierou 39, Greece.
url: www.biospray.gr

Biostam (Βιοσταμ), Gr. VIOSTAM K.MPOUGIA & SIA OE, Papadiamantopoulou 66, 157 71 Zografou, Greece.

Bio-Strath, Cz. Bio-Strath AG, Czech Republic.

Bio-Strath, Switz. Bio-Strath AG, Muhlebachstrasse 25, 8032 Zurich, Switzerland.

Biosyn, Cz. See *Biosyn, Ger.*

Biosyn, Ger. biosyn Arzneimittel GmbH, Schorndorfer Str. 32, 70734 Fellbach, Germany.
url: www.biosyn.de

Biosyn, Neth. See *Biosyn, Ger.*

Biosyn, Switz. See *Medinova, Switz.*

Biosynthesis, Gr. Biosynthesis, Parnithos 116, 136 71 Athens, Greece.

Biosynthesis, Rus. Biosynthesis ZAO, Friendship ul. 4, 440033 Penza, Russia.

Biotal, Pol. Biotal, ul. Opolska 3, 44-100 Gliwice, Poland.
url: www.maga-biotal.pl

Biotech, Austral. See *Milton, Austral.*

Biotech, Rus. Biotech, Bolshoi pr-t P.S. 29A, 197198 St Petersburg, Russia.

Biotech, S.Afr. Biotech Laboratories (Pty) Ltd, P.O. Box 7115, Johannesburg 2000, South Africa.
url: www.biotech.co.za

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Bio-Tech, USA. Bio-Tech Pharmacal, P.O. Box 1992, Fayetteville, AR 72702, USA.
url: www.bio-tech-pharm.com

Biotech, Venez. Laboratorios Biotech C.A., Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.
url: www.biotech.com.ve

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Biotechnology, Israel. Biotechnology General Israel Ltd, Kiryat Weisman, Rehovot 76326, Israel.

Biotecnoquimica, Venez. Laboratorio Biotecnoquímica, Calle 10 con 5 Edif. Walpirema, Piso 1, La Urbina, Caracas, Venezuela.
url: www.biotecnoquimica.com

Biotehnos, Rus. See *Rompharm, Rus.*

Biotek, NZ. See *In Vitro, NZ.*

Biotek, Turk. Biotek İlaçlari, Akkavak Sok. No:6, Nişantaşi, İstanbul, Turkey.

Biotel, USA. Biotel Corporation, 366 Madison Ave 1506, New York, NY 10017, USA.

Biotenk, Arg. Laboratorio Farmaceutico Biotenk S.A., Zuvirma 5747, 1439 Buenos Aires, Argentina.
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Biotest, Austria. Biotest Pharmazeutika GmbH, Einsiedlergasse 58, Postfach 8, A-1053 Vienna, Austria.
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Biotest, Cz. See *Reg, Cz.*

Biotest, Ger. Biotest Pharma GmbH, Landsteinerstr. 3-5, 63303 Dreieich, Germany.
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Biotest, Gr. Biotest, Kyprion Agoniston 25, 151 26 Marousi, Greece.

Biotest, Hong Kong. See *Chong Lap, Hong Kong.*

Biotest, Hung. Biotest Hungária Kft, Beregszasz út 55/b, 1118 Budapest, Hungary.

Biotest, Israel. See *Margalit, Israel.*

Biotest, Ital. Biotest Italia S.r.l., Via L. da Vinci 43, 20090 Trezzano sul Naviglio (MI), Italy.
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Biotest, Malaysia. See *Lazuli, Malaysia.*

Biotest, Neth. See *Biotest, Ger.*

Biotest, Pol. See *Nobipharm, Pol.*

Biotest, Port. See *Boehringer Ingelheim, Port.*

Biotest, Singapore. See *Eschol, Singapore.*

Biotest, Switz. Biotest (Schweiz) AG, Schutzenstrasse 17, 5102 Rupperswil, Switzerland.
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Biotest, Thai. See *Charoen, Thai.*

Biotest, Turk. See *Kansuk, Turk.*

Biothera, Belg. See *AstraZeneca, Belg.*

Biotherapie, Fr. See *Expanscience, Fr.*

Biotherm, Canad. Biotherm Canada, 2115 Crescent St, Montreal, Quebec, H3G 2C1, Canada.

Biotika, Cz. Biotika Bohemia sro, Kovriginová 1416/6, 147 00 Prague 4, Czech Republic.

Biotiki, Rus. Biotiki, Luganskaya St 9, Moscow, Russia.

Biotime, Canad. See *Abbott, Canad.*

Bioton, Pol. Bioton Sp. zo.o., ul. Starościńska 5, 02-516 Warsaw, Poland.
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Biotoscana, Chile. Biotoscana Farma SA, Carmen Covarrubias 271, Ñuñoa, Santiago, Chile.

Biotrends, Gr. BIOTRENDS, Vor Ipeirou 65, 146 71 N. Erythraia, Greece.

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Biovail, Canad. Biovail Pharmaceuticals, 7150 Mississauga Rd, Mississauga, Ontario, L5N 8M5, Canada.
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Biovail, Denm. See *Gea, Denm.*

Biovail, USA. Biovail Pharmaceuticals Inc., 700 Route 202/206 North, Bridgewater, NJ 08807, USA.
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Bio-Ved, Singapore. See *MD, Singapore.*

Biovena, Pol. See *Actavis, Pol.,* and *Bioton, Pol.*

Biovicent, Ger. Biovicent GmbH, Heidelberger Str. 57a, 68519 Viernheim, Germany.

Biovital, Austral. Biovital Pty Ltd, 24/10 Yalgar Road, Kirrawee, NSW 2232, Australia.

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url: www.biovitrum.com

Biovitrum, Norw. Biovitrum AB, CJ Hambros plass 2 C, 0164 Oslo, Norway.

Biovitrum, Swed. Biovitrum AB, Plasma Products, 112 76 Stockholm, Sweden.
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Bipharma, Hong Kong. See *US Summit, Hong Kong.*

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url: www.birchlabs.com

Bird, USA. Bird Products Corp., 1100 Bird Center Drive, Palm Springs, CA 92262, USA.
url: www.viasyscriticalcare.com

Biscova, Ger. Biscova-Arzneimittel, Fuhrenkamp 7, 29559 Wrestedt/Stederdorf, Germany.

Bitelab, Fin. Bitelab Oy, Paloheinäntie 62 b A, 00670 Helsinki, Finland.
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Bittermedizin, Ger. Bittermedizin Arzneimittel Vertriebs-GmbH, Taku-Fort-Str. 20, 81827 Munich, Germany.
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Bittner, Pol. Bittner Pharma International Sp. zo.o., ul. Dąbrowskiego 247/249, 92-232 Łódź, Poland.
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Bittner, Rus. See *Herbs Trading, Rus.*

Bivea, Fr. Bivea SARL, 3 place du Chaperon-Rouge, 33600 Pessac, France.
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BJC, Thai. BJC Trading Co Ltd, 99 Soi Rubia, Sukhumvit 42 Rd, Bangkok 10110, Thailand.
url: www.bjc.co.th

Blackhall, Irl. Blackhall Pharmaceutical Distributors Ltd, Saucertown, Swords, Dublin, Ireland.
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Blackhawk, Canad. Blackhawk Indian Remedy Co., 2639 Thompson Drive, Kamloops, British Columbia, V2C 4L5, Canada.

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Blaine, USA. Blaine Pharmaceuticals Co. Inc., 1717 Dixie Highway, Suite 700, Fort Wright, KY 41011, USA.
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Blair, USA. See *Purdue Frederick, USA.*

Blairex, Canad. See *Blairex, USA.*

Blairex, USA. Blairex Labs Inc., 1600 Brain Drive, P.O. Box 2127, Columbus, IN 47202-2127, USA.
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Blake, UK. Thomas Blake & Co., The Byre House, Fearby, Nr Masham, North Yorkshire, HG4 4NF, UK.
url: www.veilcover.com

Blansett, USA. Blansett Pharmacal Co., Inc., P.O. Box 638, North Little Rock, AR 72115, USA.
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Blau, Pol. Blau Farma Sp. zo.o., ul. Jutrzenki 94, 02-230 Warsaw, Poland.
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Blausiegel, Braz. Blausiegel Indústria e Comércio Ltda, Rodovia Raposo Tavares km 30.5 no.2833, 06705-030 Cotia Barro Branco, SP, Brazil.
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Bledina, Fr. Bledina SA, B.P. 432, 69654 Villefranche-sur-Saône cdx, France.
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Bles, Canad. Bles Chemicals Inc., 8-60 Pacific Court, London, Ontario, N5V 3K4, Canada.

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Blis, NZ. Blis Technologies, P.O. Box 1229, Level 4, 31 Waring Taylor St, Wellington, New Zealand.
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Blistex, Hong Kong. See *Mekim, Hong Kong.*

Blistex, Israel. See *Mediline, Israel.*

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Block, Austria. See *GSK, Austria.*

Block, Canad. See *GSK Consumer, Canad.*

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Bloem Beheer, Neth. Bloem Beheer BV, Papierbaan 50a, 9672 BH Winschoten, Netherlands.

Blooming Fields, Philipp. Blooming Fields Phils, Inc., 6/F Textron Bldg, 168 Luna Mencias St, San Juan, Metro Manila, Philippines.

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Blue Cross, Philipp. Blue Cross Pharmaceutical Phils, Inc., Unit 2102, Tektite East Tower, PSEC, Ortigas Center, Pasig City, Philippines.

Blue Ocean, UK. Blue Ocean Sales Brokers, Cams Hall Estate, Fareham, Hampshire, PO16 8UU, UK.

Blue Sky, Philipp. Blue Sky Trading Co. Inc., Blue Sky Building, 416 Dasmariñas St, Binondo, Manila, Philippines.

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BMS, Austral. Bristol-Myers Squibb, Division of Bristol-Myers Australia P/L, P.O. Box 39, Noble Park, VIC 3174, Australia.
url: www.bmsa.com.au

BMS, Austria. Bristol-Myers Squibb GmbH, Columbusgasse 4, A-1100 Vienna, Austria.
url: www.b-ms.at

BMS, Belg. Bristol-Myers Squibb Belgium SA, Parc de l'Alliance, Avenue de Finlande, 8, 1420 Braine-l'Alleud, Belgium.
url: www.bms.be

BMS, Braz. Bristol-Myers Squibb Farmacêutica Ltda, Rua Carlos Gomes 924, 04743-903 São Paulo, SP, Brazil.
url: www.bristol.com.br

BMS, Canad. Bristol-Myers Squibb Canada Inc., 2365 Cote-de-Liesse Rd, Montreal, Quebec, H4N 2M7, Canada.
url: www.bms.com

BMS, Chile. Bristol-Myers Squibb, Av. Pte. Balmaceda 2174, Santiago, Chile.

BMS, Cz. Bristol-Myers Squibb sro, Lazarská 6, 120 00 Prague 2, Czech Republic.
url: www.b-ms.cz

BMS, Denm. Bristol-Myers Squibb, Lyngby Hovedgade 98, 2800 Lyngby, Denmark.
url: www.bms.com

BMS, Fin. Oy Bristol-Myers Squibb (Finland) AB, Metsänneidonkuja 8, 02130 Espoo, Finland.
url: www.bmsfinland.com

BMS, Fr. Bristol-Myers Squibb, 3 rue Joseph-Monier, 92506 Rueill-Malmaison cdx, France.
url: www.bms.com

BMS, Ger. Bristol-Myers Squibb GmbH, Sapporobogen 6-8, 80809 Munich, Germany.
url: www.b-ms.de

BMS, Gr. Bristol-Myers Squibb, 102 Tatoiou Ave, 146 71 N. Erythrea, Greece.
url: www.bms.gr; www.bms.com

BMS, Hong Kong. Bristol-Myers Squibb (Hong Kong) Ltd, Unit 3001-2, 30/F, New York Life Tower, Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
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BMS, Hung. Bristol-Myers Squibb Gyógyszerkereskedelmi Kft, Szabadság tér 7, 1054 Budapest, Hungary.

BMS, Indon. Bristol-Myers Squibb, Tamara Ctr Bldg, 10th Fl, Jl Jend Sudirman Kav 24, 12920 Jakarta, DKI Jaya, Indonesia.

BMS, Irl. Bristol-Myers Squibb Pharmaceuticals, Watery Lane, Swords, Co. Dublin, Ireland.
url: www.bmsireland.ie

BMS, Israel. Bristol-Myers Squibb Ltd, P.O. Box 3311, Petach Tikva, Israel.
url: www.bms.com

BMS, Ital. Bristol-Myers Squibb S.r.l., Via Virgilio Maroso 50, 00142 Rome, Italy.
url: www.bms.it

BMS, Jpn. See *Bristol, Jpn.*

BMS, Malaysia. Bristol-Myers Squibb (Malaysia) Sdn Bhd, 16th Floor, Menara Lien Hoe, 8 Persiaran Tropicana, 47410 Petaling Jaya, Selangor, Malaysia.
url: www.bms.com

BMS, Mex. Bristol-Myers Squibb de Mexico S. de R.L. de C.V., Av. Revolución No. 1267, Col. Tlacopac, Deleg. A. Obregón, 01040 Mexico D.F., Mexico.
url: www.bms.com.mx

BMS, Neth. Bristol-Myers Squibb, Vijzelmolenlaan 9, 3447 GX Woerden, Netherlands.
url: www.bms.com

BMS, Norw. Bristol-Myers Squibb Norway Ltd, Veritasv. 26, Postboks 464, 1323 Hovik, Norway.
url: www.bms.no

BMS, NZ. Bristol-Myers Squibb, P.O. Box 62663, Central Park, Aukland, New Zealand.
url: www.bms.com

BMS, Philipp. Bristol-Myers Squibb (Phil) Inc., 2309 Don Chino Roces Ave, Makati City, Philippines.

BMS, Pol. Bristol-Myers Squibb Services Sp. zo.o., al. Armii Ludowej 26, 00-609 Warsaw, Poland.
url: www.b-ms.pl

BMS, Port. Bristol-Myers Squibb Farmacêutica Portuguesa, Lda, Edifício Fernão de Magalhães, Quinta da Fonte, 2780-730 Paço de Arcos, Portugal.
url: www.bms.com

BMS, Rus. Bristol-Myers Squibb, Trekhprudny per 9, korp 1b, 103001 Moscow, Russia.
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BMS, S.Afr. Bristol-Myers Squibb (Pty) Ltd, P.O. Box 1408, Bedfordview, 2008 Johannesburg, South Africa.
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BMS, Singapore. Bristol-Myers Squibb (S) Pte Ltd, 66 East Coast Rd, 05-00, S 428778, Singapore.
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BMS, Spain. Bristol Myers Squibb España, Campus Empresarial Jose Ma Churruca, Almansa 101, 28040 Madrid, Spain.
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BMS, Switz. Bristol-Myers Squibb AG, Neuhofstrasse 6, 6340 Baar, Switzerland.
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BMS, Thai. Bristol-Myers Squibb (Thailand) Ltd, Bristol-Myers Squibb Building, 10/10-11 Srinakarin Rd, Bangplee, Samutprakarn 10540, Thailand.
url: www.bms.com

BMS, Turk. Bristol-Myers Squibb İlaçlari Ltd. Şti., Buyukdere Cad. Meydan Sok, Plaza Spring Giz. K:8, Maslak, İstanbul, 80670, Turkey.
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BMS, UK. Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge Business Park, Sanderson Rd, Uxbridge, Middlesex, UB8 1DH, UK.
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BMS, USA. Bristol-Myers Squibb, P.O. Box 4500, Princeton, NJ 08543-4500, USA.
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BMS, Venez. Bristol-Myers Squibb de Venezuela S.A., Calle Bernardette-Edif. Bristol-Myers Squibb, Los Cortijos de Lourdes, Aptd. Postal 61173, Caracas 1060-A, Venezuela.
url: www.bms.com.ve

BMS Oncology, USA. See *BMS, USA.*

BNS, Austria. BNS PharmavertriebsgesmbH, Lemböckgasse 49, A-1230 Vienna, Austria.

BOC, UK. BOC Gases, The Priestley Centre, 10 Priestley Rd, Surrey Research Park, Surrey, GU2 7XY, UK.
url: www.boc.com

Boca, USA. Boca Pharmacal Inc., 6601 Lyons Rd, Coconut Creek, FL 33073, USA.
url: www.bocamedicalproducts.com

Bochemie, Cz. Bochemie as, Bohumín, Czech Republic.

Bock, Ger. Bock-Pharma GmbH, Odenwaldstr. 2, 64646 Heppenheim, Germany.
url: www.bock-pharma.com

Bode, Ger. Bode Chemie Hamburg, Melanchthonstr. 27, 22525 Hamburg, Germany.
url: www.bode-chemie.de

Bode, Indon. See *Tempo Scan Pacific, Indon.*

Bode, Neth. See *Bode, Ger.*

Bodene, S.Afr. See *Fresenius Kabi, S.Afr.*

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Body Spring, Ital. See *Angelini, Ital.*

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Boehringer Ingelheim, Israel. See *Teva, Israel.*

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url: www.boehringer-ingelheim.no

Boehringer Ingelheim, NZ. Boehringer Ingelheim (NZ) Ltd, 47 Druces Rd, Wiri, Manukau City, Auckland, New Zealand.
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Boehringer Ingelheim, Singapore. See *Diethelm, Singapore.*

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Boehringer Ingelheim Consumer, USA. See *Boehringer Ingelheim, USA.*

Boehringer Ingelheim Promeco, Mex. See *Boehringer Ingelheim, Mex.*

Boehringer Ingelheim Self Medication, UK. See *Boehringer Ingelheim, UK.*

Boehringer Mannheim, Israel. See *Teva, Israel.*

Boehringer Mannheim, Port. See *Roche, Port.*

Boehringer Mannheim, USA. See *Roche, USA.*

Boehringer Mannheim Diagnostics, USA. See *Roche, USA.*

Boffi, Ital. Eredi di Antonio Boffi S.n.c., Via Lorenzo Magalotti 6, 00197 Rome, Italy.

Bohm, Spain. Bohm, Molina Seca 23 Plg. Cobo Calleja, Fuenlabrada, 28947 Madrid, Spain.
url: www.lab-bohm.com

BOI, Spain. See *Merck, Spain.*

Boie, Philipp. Boie Inc., 520 Alabang-Zapote Rd, Almanza 1, Las Piñas City, Philippines.
url: www.boie.com.ph

Boileau & Boyd, Irl. See *Allphar, Irl.*

Boiron, Austral. See *Boiron, Fr.*

Boiron, Canad. Boiron Canada Inc., 816 Guimond St, Longueil, Quebec, J4G 1T5, Canada.
url: www.boiron.ca

Boiron, Cz. Boiron CZ sro, Vlková 40, 130 00 Prague 3, Czech Republic.

Boiron, Fr. Boiron, 20 rue de la Liberation, 69110 Sainte-Foy-les-Lyon, France.
url: www.boiron.fr

Boiron, Neth. See *Boiron, Fr.*

Boiron, Port. See *Prisfar, Port.*

Boiron, Switz. See *Serolab, Switz.*

Bolder, Cz. See *Bolder, Ger.*

Bolder, Ger. Bolder Arzneimittel GmbH & Co. KG, Koblenzer Str. 65, 50968 Cologne, Germany.
url: www.bolder.de

Bolder, Hong Kong. See *Mekim, Hong Kong.*

Bonafarma, Port. See *Jaba, Port.*

Bonamedis, Switz. Bonamedis GmbH, Haldenstrasse 27, 8427 Rorbas, Switzerland.

Bonapace, Thai. Bonapace, Thailand.

Bonimed, Pol. Bonimed Laboratorium Medycyny Naturalnej, ul. Stawowa 23, 34-300 Żywiec, Poland.
url: www.bonimed.ig.pl

Boniscontro & Gazzone, Ital. Laboratorio Prodotti Farmaceutici Boniscontro & Gazzone S.r.l., Via Tiburtina 1004, 00100 Rome, Italy.

Boots, Austral. See *Boots Healthcare, Austral.*

Boots, Denm. See *Novartis, Denm.*

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Boots, Fr. See *Knoll, Fr.*

Boots, Ger. See *Kanoldt, Ger.*

Boots, Hong Kong. See *Keller, Hong Kong.*

Boots, Israel. See *Teva, Israel.*

Boots, Philipp. The Boots Company (Phils) Inc., 22/F Equitable Bank Tower, 8751 Paseo de Roxas, Makati City, Philippines.

Boots, Pol. Boots Healthcare, ul. Chłodna 51, 00-867 Warsaw, Poland.

Boots, Rus. Boots Healthcare (CIS) Ltd, Tverskaya ul. 16/2, et. 7, Moscow, Russia.

Boots, Singapore. The Boots Company (Far East) Pte Ltd, 180-B Bencoolen St, 09-03 The Bencoolen, S 189648, Singapore.

Boots, Switz. See *Doetsch, Grether, Switz.*

Boots, Thai. See *Olic, Thai.*

Boots, UK. Boots the Chemists, Thane Rd, D90 East FO8, Nottingham, NG90 1BS, UK.
url: www.boots.com

Boots, USA. See *Abbott, USA.*

Boots Healthcare, Austral. Boots Healthcare Australia P/L, Locked Bag 2067, North Ryde, NSW 1670, Australia.
url: www.skinexpert.net

Boots Healthcare, Austria. See *Boots Healthcare, Ger.*

Boots Healthcare, Belg. Boots Healthcare NV/SA, Koningin Astridlaan 164, 1780 Wemmel, Belgium.
url: www.bootshealthcare.be

Boots Healthcare, Canad. Boots Healthcare USA Inc., 1680 Tech Ave, Mississauga, Ontario, L4W 5S9, Canada.

Boots Healthcare, Cz. Boots Healthcare CEE Ltd, Sokolovská 84-86, 180 00 Prague 8, Czech Republic.
url: www.skinexpert.net

Boots Healthcare, Fr. Laboratoires Boots Healthcare, 35 rue Baudin, 92300 Lavallois-Perret, France.
url: www.skinexpert.net

Boots Healthcare, Ger. Boots Healthcare Deutschland GmbH, Amsinckstr. 67, 20097 Hamburg, Germany.
url: www.bhd.de

Boots Healthcare, Irl. Boots Healthcare Ltd, Parkview House, Beech Hill Office Campus, Clonskeagh, Dublin 4, Ireland.
url: www.skinexpert.net

Boots Healthcare, Ital. Boots Healthcare S.p.A., Via Tarantelli 13/15, 22076 Mozzate (CO), Italy.
url: www.skinexpert.net

Boots Healthcare, Malaysia. Boots Trading (Malaysia) Sdn Bhd, Level 4, Wisma Samudra, 1 Jln Kontraktor U1/14, Hicom-Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia.
url: www.skinexpert.net

Boots Healthcare, Neth. Boots Healthcare BV, Gooimeer 6-26, 1411 DD Naarden, Netherlands.
url: www.skinexpert.net

Boots Healthcare, NZ. Boots Healthcare New Zealand Ltd, P.O. Box 27-341, Wellington 1, New Zealand.
url: www.skinexpert.net

Boots Healthcare, Port. Boots Healthcare Portugal, Lda, Av. Duque d'Ávila, 185, 1050-082 Lisbon, Portugal.
url: www.skinexpert.net

Boots Healthcare, S.Afr. Boots Healthcare (SA) (Pty) Ltd, 20 Zulberg Close, Building A, Entrance 2, Johannesburg 2198, South Africa.
url: www.skinexpert.net

Boots Healthcare, Spain. Boots Healthcare, Doctor Zamenhof 36 Dup 2, 28027 Madrid, Spain.
url: www.bootshealthcare.es

Boots Healthcare, Switz. Boots Healthcare (Switzerland) AG, Hermal, Untermuli 11, 6300 Zug, Switzerland.
url: www.skinexpert.net

Boots Piramal, India. See *Nicholas Piramal, India.*

Borer, Thai. Borer Chemie.

Borg, UK. Borg Medicare Ltd, P.O. Box 99, Hitchin, Hertfordshire, SG5 2GF, UK.

Boryung, Thai. See *Masu, Thai.*

Bosch, Philipp. See *Clinbaxy, Philipp.*

Bosnalek, Rus. See *Bosnalijek, Rus.*

Bosnalijek, Rus. Bosnalijek Pharmaceuticals, ul. Dimitria Ulianova 16, korp. 2, kv. 321, 117292 Moscow, Russia.
url: www.bosnalijek.com

Botanica, NZ. Botanica, New Zealand Pharmacology Ltd, P.O. Box 32128, Christchurch, New Zealand.
url: www.botanica.co.nz

Bottger, Ger. Böttger GmbH, Paulsborner Str. 2, 10709 Berlin, Germany.

Bouchara, Fr. See *Bouchara-Recordati, Fr.*

Bouchara, Rus. See *FIC, Rus.*

Bouchara, Singapore. See *Pharmacon, Singapore.*

Bouchara, Switz. See *Interdelta, Switz.*

Bouchara-Recordati, Fr. Laboratoires Bouchara-Recordati, 68 rue Marjolin, 92302 Levallois-Perret, France.

Bouchara-Recordati, Hong Kong. See *Rich Plan, Hong Kong.*

Boucher & Muir, Austral. Boucher & Muir P/L, P.O. Box 333, North Sydney, NSW 2059, Australia.
url: www.bnmgroup.com

Boucher & Muir, NZ. Boucher & Muir New Zealand, Level 14 Forsythe Barr Tower, 55-56 Shortland St, Auckland, New Zealand.

Bouhon, Ger. Apotheker Walter Bouhon GmbH & Co. KG, Walter-Bouhan-Str 4, 90427 Nurnberg, Germany.
url: www.freioel.de

Bournonville, Belg. Bournonville Eumedica SA/NV, W. Churchill Av. 67, 1180 Brussels, Belgium.
url: www.belpharma.com

Bournonville, Neth. Bournonville Pharma BV, Nassaulaan 13, 2514 JS Den Haag, Netherlands.
url: www.belpharma.com

Bouty, Ital. Bouty SpA, V.le Casiraghi 471, 20099 Sesto S Giovanni (MI), Italy.

Bouwer Bartlett, S.Afr. 512 The Granger, 40 Beach Rd, Granger Bay, Cape Town, South Africa.
url: www.bouwerbartlett.co.za

Bouzen, Arg. Bouzen S.A.C.,I.F.A.F., Calle 36 No. 165/67, 1900 La Plata, Buenos Aires, Argentina.
url: www.bouzensa.com.ar

Bowman, USA. Bowman Pharmaceuticals Inc., 119 Schroyer Ave SW, Canton, OH 44702, USA.

Boyle, USA. Boyle & Co. Pharmaceuticals, 1613 Chelsea Rd, San Marino, CA 91108, USA.

BPC, UK. The Bolton Pharmaceutical 100 Ltd (BPC 100 Ltd), 2 Chapel Drive, Ambrosden, Oxfordshire, OX25 2RS, UK.

BPL, India. BPL Pharmaceuticals Pvt Ltd, 380/82 Sankersett Rd, Sankersett Smriti, Chira Bazar, Mumbai 400 002, India.

BPL, Israel. See *Kamada, Israel.*

BPL, Singapore. See *JDH, Singapore.*

BPL, Thai. See *BJC, Thai.*

BPL, UK. Bio Products Laboratory, Dagger Lane, Elstree, Hertfordshire, WD6 3BX, UK.
url: www.bpl.co.uk

BPL-Meizler, Braz. See *Meizler, Braz.*

BPR, Ital. BPR International S.r.l., Via Q Sella 4, 20121 Milan (MI), Italy.

BPRL, Singapore. See *Zyfas, Singapore.*

BR Pharmaceuticals, UK. BR Pharmaceuticals Ltd, Clayton Wood Close, West Park Ring Rd, Leeds, West Yorkshire, LS16 6QE, UK.
url: www.brpharmaceuticals.co.uk

Bracco, Austria. See *Bracco, Ital.*

Bracco, Canad. Bracco Diagnostics Inc, Suite 103, Unit 11, 2600 Skymark Avenue, Mississauga, Ontario, L4W 5B2, Canada.
url: www.bracco.com

Bracco, Cz. See *Bracco, Ital.*

Bracco, Denm. See *Astra Tech, Denm.*

Bracco, Hung. See *Ewopharma, Hung.*

Bracco, Israel. See *Dexxon, Israel.*

Bracco, Ital. Bracco S.p.A., Via E. Folli 50, 20134 Milan, Italy.
url: www.bracco.com

Bracco, Neth. Bracco International BV, Strawinskylaan 3051, 1077 ZX Amsterdam, Netherlands.

Bracco, Norw. See *Astra Tech, Norw.*

Bracco, Port. See *Dario Correia, Port.*

Bracco, Switz. Bracco Suisse SA, C.P. 1764, 6850 Mendrisio, Switzerland.

Bracco, UK. Bracco UK Ltd, Bracco House, Mercury Park, Wycombe Lane, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.
url: www.bracco.com

Bracco, USA. Bracco Diagnostics, 107 College Road East, Princeton, NJ 08540, USA.
url: www.bracco.com

Bracey, UK. Bracey's Pharmaceuticals, 209 Menlove Ave, Liverpool, Merseyside, L18 3EF, UK.
url: www.odaban.com

Bradley, Canad. Bradley Pharmaceuticals Inc., 1031 Meyerside Drive, Unit 12, Mississauga, Ontario, L5T 2H5, Canada.

Bradley, Singapore. See *Pan-Malayan, Singapore.*

Bradley, USA. Bradley Pharmaceuticals, 383 Route 46 West, Fairfield, NJ 07004-2402, USA.
url: www.bradpharm.com

Brady, Austria. Brady C. KG, Hörlgasse 5, 1090 Wien, Austria.
url: www.brady.co.at

Bragafarm, Port. Bragafarm Promoção de Medicamentos Lda, Parque Industrial do Seixal, 2840-069 Paio Pires, Portugal.

Bragg, UK. J L Bragg (Ipswich) Ltd, 34 Boss Hall Rd, Ipswich, Suffolk, IP1 5BN, UK.
url: www.charcoal.uk.com

Braintree, Canad. See *Source, Canad.*

Braintree, USA. Braintree Laboratories Inc., 60 Columbian St West, P.O. Box 850929, Braintree, MA 02185-0929, USA.
url: www.braintreelabs.com

Brainware, S.Afr. Brainware Compu (Pty) Ltd, 476 Kings Highway, Lynnwood, Pretoria, South Africa.

Brands Worldwide, Austral. Brands Worldwide, 205 Victoria St, Beaconsfield, NSW 2015, Australia.
url: www.brandsworldwide.com.au

Brandt, Switz. See *Uhlmann-Eyraud, Switz.*

Brasmedica, Braz. Brasmedica S.A. Industrias Farmacêuticas, Avenida Miguel Stefano 2278, 04301-002 São Paulo, SP, Brazil.

Brassora, Arg. Brassora SA, Estados Unidos 609, 1101 Capital, Argentina.

Brasterapica, Braz. Brasterapica Indústria Farmacêutica Ltda, Rua Bela Cintra 299 7 andar, 01415-002 São Paulo, SP, Brazil.
url: www.brasterapica.com.br

Brauer, Austral. Brauer Natural Medicine P/L, P.O. Box 234, Tanunda, SA 5352, Australia.
url: www.brauer.com.au

Braun, Arg. B. Braun Medical S.A., J. E. Uriburu 663 Pso. 7, 1027 Buenos Aires, Argentina.
url: www.bbraun.com

Braun, Austral. B Braun Australia P/L, Norwest Business Park, 17 Lexington Drive, Bella Vista, NSW 2153, Australia.
url: www.bbraun.com.au

Braun, Austria. Braun Austria GmbH, In den Langackern 5, A-2344 Maria Enzersdorf, Austria.
url: www.bbraun.com

Braun, Belg. B. Braun Medical NV/SA, Woluwelaan 140 B, 1831 Diegem, Belgium.
url: www.bbraun.be

Braun, Chile. B Braun Medical SA, Calle Nueva 5319, Conchalf, Santiago, Chile.

Braun, Cz. B Braun Medical sro, Cigánková 1861, 148 00 Prague 11, Czech Republic.
url: www.bbraun.cz

Braun, Denm. B Braun Medical A/S, Halmtorvet 29, 1700 Copenhagen V, Denmark.
url: www.bbraun.com

Braun, Fin. B. Braun Medical Oy, Huopalahdentie 24, 00350 Helsinki, Finland.
url: www.bbraun.com

Braun, Fr. B Braun Medical SA, 204 av du Mal-Juin, B.P. 331, 92107 Boulogne cdx, France.
url: www.bbraun.fr

Braun, Ger. B. Braun Melsungen AG, Carl-Braun-Str. 1, 34212 Melsungen, Germany.
url: www.bbraun.de

Braun, Hong Kong. B Braun Medical (HK) Ltd, 13-14/F Henan Bldg, 90 Jaffe Rd, Wanchai, Hong Kong.
url: www.bbraun.com.hk

Braun, Hung. B Braun Medical Kft, Felhévizi u 3-5, 1023 Budapest, Hungary.

Braun, Indon. See *Buminusantara, Indon.*

Braun, Israel. See *Teva, Israel.*

Braun, Ital. B. Braun Milano S.p.A., Via V. da Seregno 14, 20161 Milan, Italy.
url: www.bbraun.com

Braun, Neth. See *Braun, Ger.*

Braun, Norw. B. Braun Medical A/S, Kjernasv 13 B, 3142 Vestskogen, Norway.
url: www.bbraun.com

Braun, Philipp. See *Pharmawealth, Philipp.*

Braun, Pol. B Braun, Aesculap Chifa Sp. zo.o., ul. Tysiąclecia 14, 64-300 Nowy Tomyśl, Poland.
url: www.chifa.pl

Braun, Port. B. Braun Medical, Lda, Estrada Consiglieri Pedroso 80, Queluz Park, Queluz de Baixo, 2745-533 Barcarena, Portugal.
url: www.bbraun.com

Braun, S.Afr. B Braun (Pty) Ltd, P.O. Box 1787, Randburg 2125, South Africa.
url: www.bbraun.co.za

Braun, Singapore. B Braun Singapore Pte Ltd, 460 Alexandra Rd, 34-03 PSA Building, S 119963, Singapore.
url: www.bbraun.com.sg

Braun, Spain. Braun Medical, Ctra Tarrasa 121, Rubi, 08191 Barcelona, Spain.
url: www.bbraun.com

Braun, Swed. B. Braun Medical AB, Box 110, 182 12 Danderyd, Sweden.
url: www.bbraun.com

Braun, Switz. B. Braun Medical AG, Hospital Care, Postfach, 6020 Emmenbrucke, Switzerland.
url: www.bbraun.ch

Braun, Thai. B Braun (Thailand) Ltd, 12 Fl, Q-House Ploenchit Building, 598 Ploenchit Rd, Lumpini Pathumwan, Bangkok 10330, Thailand.
url: www.bbraun.co.th

Braun, Turk. B.Braun İlaç Tiscaret Şti., Universite Mahallesi, Civan Sokak, No: 15/2, Avcilar, İstanbul, 34850, Turkey.
url: www.bbraun.com

Braun, UK. B. Braun Medical Ltd, Thorncliffe Park Industrial Estate, Chapeltown, Sheffield, South Yorkshire, S35 2PW, UK.
url: www.bbraun.co.uk

Braun, USA. B. Braun Medical, 1601 Wallace Drive, Suite 150, Carrollton, TX 75006, USA.
url: www.bbraunusa.com

Braun Melsungen, Ital. See *Braun, Ital.*

Bray, UK. Bray Health & Leisure (Solport Ltd), 1 Regal Way, Faringdon, Oxfordshire, SN7 7BX, UK.
url: www.bray.co.uk

Breckenridge, USA. Breckenridge Pharmaceutical Inc, 1141 South Rogers Circle, Suite 3, Boca Raton, FL 33487, USA.
url: www.breckenridgepharma.com

Bregenzer, Austria. Herbert Bregenzer, Am Damm 20, A-6820 Frastanz, Austria.

Brel, Philipp. Brel Pharmaceutical Inc., Suite 709, National Life Insurance Building, 6762 Ayala Ave, Makati City, Philippines.

Brench, Ger. Brench Pharma AG, Siegesstr. 26, 80802 Munich, Germany.
url: www.brench.de

Brenntag, Denm. Brenntag Disinfection, Gl Strandv. 16, 2990 Niva, Denmark.
url: www.brenntag-nordic.com

Brenntag, Norw. See *Brenntag, Denm.*

Bride, Cz. See *Bride, Fr.*

Bride, Fr. Laboratoires Bride, 263 c av de Laon, 51100 Reims, France.

Bride, Hung. See *PDP, Hung.*

Bright Future, Hong Kong. Bright Future Pharmaceutical Laboratories Ltd, BF Pharmaceutical Ctr, 8 Wang Fu St, Yuen Long Industrial Estate, Yuen Long, N.T., Hong Kong.

Brighton, USA. Brighton Pharmaceuticals, 201 Shannon Oaks Circle 200, Cary, NC 27511, USA.

Brimms, Israel. See *Trima, Israel.*

Bripharm, Irl. See *Astellas, Irl.*

Bristol, Canad. See *BMS, Canad.*

Bristol, Jpn. Bristol Pharmaceuticals K.K., 6-5-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 163-1328, Japan.

Bristol, USA. See *BMS, USA.*

Bristol-Myers, Spain. See *BMS, Spain.*

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Britannia Health, UK. See *Britannia Pharmaceuticals, UK.*

Britannia Pharmaceuticals, Irl. See *Clonmel, Irl.*

Britannia Pharmaceuticals, UK. Britannia Pharmaceuticals Ltd, 41-51 Brighton Rd, Redhill, Surrey, RH1 6YS, UK.
url: www.britannia-pharm.co.uk

BritHealth, UK. See *Cintas, UK.*

British Dispensary, Thai. British Dispensary, 272 Moo 1 Soi Pattanasuk, Teparak Rd, Samutprakarn 10270, Thailand.

British Pharmaceuticals, Austral. See *Organon, Austral.*

Brocades, Singapore. See *Indrugco, Singapore.*

Brookstone, USA. Brookstone Pharmaceuticals LLC, 9005 Westside Parkway, Alpharetta, GA 30004, USA.
url: www.brookstonepharma.com

Bros, Gr. Bros E.P.E., Avgis & Galinis 15, 145 64 Nea Kifissia, Greece.

Brothier, Fr. Laboratoires Brothier, 41 rue de Neuilly, 92000 Nanterre, France.
url: www.brothier.com

Brovar, S.Afr. Brovar S & P (Pty) Ltd, South Africa.

Brown & Burk, India. Brown & Burk Pharmaceuticals Ltd, 303, A Wing, Queen's Corner Apartments, Bangalore 560 001, India.

Brown & Burk, Malaysia. See *Zyfas, Malaysia.*

Brown & Burk, Philipp. See *Brel, Philipp.,* and *Medhaus, Philipp.*

Bruluagsa, Mex. Bruluagsa SA de CV, Calle 18, Lote 10, Manzana 23 2 sec. Pqu, 50450 Atlacomulco, Estado de Mexico, Mexico.

Bruluart, Mex. Importadora y Manufacturera Bruluart SA, Geranios 9, 54940 Tultitlan San Fco. Chilpan, Estado de Mexico, Mexico.

Brum, Spain. Laboratorios Brum, Quevedo 4, Oviedo, 33012 Asturias, Spain.
url: www.laboratoriosbrum.com

Brunel, S.Afr. Brunel Laboratories (Pty) Ltd, P.O. Box 23103, Innesdale 0031, South Africa.

Bruno, Ital. Bruno Farmaceutici S.p.A., Via delle Ande 15, 00100 Rome, Italy.

Bruschettini, Ital. Bruschettini S.r.l., Via Isonzo 6, 16147 Genoa, Italy.
url: www.bruschettini.com

Bryan, USA. Bryan Corp., 4 Plympton St., Woburn, MA 01801, USA.
url: www.bryancorporation.com

bsa, Fr. bsa (Lab), BP 432, 69654 Villefranche-sur-Saône cdx, France.

BSM, Austria. BSM Diagnostica GesmbH, Alser Strasse 25, A-1080 Vienna, Austria.

BSN, Austral. BSN Medical, 211 Wellington Rd, Clayton, Vic 3168, Australia.
url: www.bsnmedical.com

BSN, Fr. See *Smith & Nephew, Fr.*

BSN, Ital. BSN Medical, Viale Colleoni 17, 20041 Agrate Brianza (MI), Italy.

BSSAA, UK. British Snoring & Sleep Apnoea Association Ltd, 2nd Floor Suite, 52 Albert Rd North, Reigate, Surrey, RH2 9EL, UK.
url: www.britishsnoring.co.uk

Bucaneve, Ital. Bucaneve Medicinali S.r.l., Via Sercognani 15, 20156 Milan, Italy.

Bucca, Spain. Bucca, Juan Alvarez Mendizabal 43, 28008 Madrid, Spain.

Buchrucker, Austria. Laboratorium Buchrucker, Aschacherstrasse 1, A-4100 Ottensheim, Austria.

Buckley, Canad. W.K. Buckley Ltd, 5230 Orbitor Drive, Mississauga, Ontario, L4W 5G7, Canada.
url: www.buckleys.com

Budapharma, Hung. Budapharma Kft, Kevélyhegyi u 15/a, 1028 Budapest, Hungary.

Bullivants, Austral. Bullivants, Campus Pharmacy, The University of Queensland, Union Building, St. Lucia, QLD 4067, Australia.
url: www.campuspharmacy.com.au

Buminusantara, Indon. Buminusantara bestari Perkasa, Rukan Blok B No 21, Graha Cempaka Mas, Jl Letjen Suprapto Sumur Batu, 10640 Jakarta, Indonesia.

Bunker, Braz. Bunker Indústria Farmacêutica Ltda, Rua Anibal dos Anjos Carvalho 212, 04810-050 São Paulo, SP, Brazil.

Burel, USA. Burel Pharmaceuticals, 464 Church Rd, Suite 100, Madison, MS 39110, USA.
url: www.burelpharmaceuticals.com

Burnshield, Israel. Burnshield, Israel.

Bushnell, India. Walter Bushnell Ltd, Pragati Bhavan, 2nd Floor, Jai Singh Rd, New Delhi 110 001, India.

Bustillos, Mex. Laboratorios Bustillos, S.A. de C.V., Manuel Dublan No. 40, Col. Tacubaya, Deleg. Miguel Hidalgo, 11800 Mexico D.F., Mexico.

Busto, Spain. Busto, Paseo Del Deleite S/N, Aranjuez, Madrid, Spain.

Butler, Ger. John O Butler GmbH, Beyerbachstr. 1, 65830 Kriftel, Germany.
url: www.jbutler.com

Buxton, Arg. Laboratorios Buxton SA, Santos Dumont 4671, 1427 Buenos Aires, Argentina.

Byk, Arg. Byk Argentina S.A., Tronador 4890, 1430 Buenos Aires, Argentina.

Byk, Austria. Byk Österreich Pharma GmbH, Ketzergasse 200, A-1235 Vienna, Austria.

Byk, Belg. See *Altana, Belg.*

Byk, Cz. Byk Česká republika sro, Novodvorská 994/138, 142 21 Prague 4, Czech Republic.

Byk, Neth. Byk Nederland BV, Weerenweg 29, 1161 AG Zwanenburg, Netherlands.

Byk, Port. See *Altana, Port.*

Byk Gulden, Ger. See *Altana, Ger.*

Byk Gulden, Ital. Byk Gulden Italia S.p.A., Via Giotto 1, 20032 Cormano (MI), Italy.

Byk Gulden, Mex. See *Altana, Mex.*

Byk Gulden, Singapore. See *Pacific Biosciences, Singapore.*

Byk Madaus, S.Afr. See *Altana, S.Afr.*

Byk Tosse, Ger. See *Altana, Ger.*

Bykomed, Port. See *Altana, Port.*

BYS, Philipp. See *Health Vision, Philipp.,* and *Lantaka, Philipp.*

C & L, Hong Kong. C & L Pharmaceutical Ltd, Unit A-C, 19/F Flourish Food Manufactory Ctr, 18 Tai Lee St, Yuen Long, N.T., Hong Kong.
url: www.candl.com.hk

C & M, USA. See *Genesis, USA.*

C & RF, Ital. C&RF S.r.l., Via Trinacria 11, 95030 Tremestieri Etneo (CT), Italy.

Cabassi, Ital. Cabassi & Giuriati S.p.A., Via Uruguay 20/22, Z.I. Padua, 35127 Padua, Italy.
url: www.cabassi-giuriati.it

Caber, Ital. Farmaceutici Caber S.p.A., Viale Citta d'Europa 681, 00144 Rome, Italy.

Cablon, Neth. Cablon medical BV, Klepelhoek 11, 3833 GZ Leusden, Netherlands.

Cabuchi, Arg. Lab. Cabuchi S.A., Tucuman esq. San Juan, 5220 Jesus Marma, Cordoba, Argentina.

CaDiGroup, Ital. Ca.Di.Group S.r.l., Via Pieve Tesino 75, 00124 Rome, Italy.
url: www.cadigroup.it

Cadila, Cz. Cadila Healthcare Ltd, Strmy vrch 119, 159 00 Prague 5, Czech Republic.
url: www.cadilapharma.com

Cadila, India. See *Zydus, India.*

Cadila, Malaysia. See *Zyfas, Malaysia.*

Cadila, Philipp. See *Brel, Philipp.*

Cadila, Rus. Cadilla Healthcare Ltd, Gubkina ul. 14, Of. 39, 117312 Moscow, Russia.
url: www.cadilapharma.com

Cadila, Singapore. See *Uni, Singapore.*

Cadila, Thai. See *Pharmaland, Thai.*

Cadila Pharma, India. Cadila Pharmaceuticals Ltd, Cadila Corporate Campus, Sarkhej-Dholka Rd, Bhat, Ahmedabad 382 210, India.
url: www.cadilapharma.com

Cady, Ital. Cady Paris by Caselli Alda, Vicolo della Neve 7, 40123 Bologna, Italy.

Caesaro, Austria. Caesaro Med GmbH, Raidenstrasse 46, A-4060 Leonding, Austria.

Cafar, Venez. CAFAR (Compania Anonima Farmaceutica), Avenida M. Perez Pisanti, Sector Industrial Los 3 puentes, Urb. El Tambor Los Teques, Caracas, Venezuela.
url: www.cafar.com.ve

CAF-DCF, Belg. CAF-DCF CV, De Tyraslaan 109, 1120 Brussels, Belgium.
url: www.caf-dcf.redcross.be

CAG, Fr. C.A.G. Pharma, 8 rue de la Source, 92310 Sèvres, France.
url: www.cagpharma.com

Cagdas, Turk. Çağdaş Eczacılar Labotatuvan San. ve Tic. A.Ş., 1649 Sok. No:15, Bayraklı, İzmir, Turkey.
url: www.cagdasecza.com.tr

Caif, Arg. Compaña Argentina de Invest. Farmaceuticas SA, Solvs 1702, 1134 Buenos Aires, Argentina.

Caldeira & Marques, Port. Caldeira & Marques, Lda, Rua 25 de Abril, Lote 32-B, Brandoa, 2650-061 Amadora, Portugal.

Caldeira & Metelo, Port. Caldeira & Metelo, Lda, Rua 25 de Abril, Lote 26, loja, Brandoa, 2650-061 Amadora, Portugal.

Calea, Austria. Calea Austria Healthcare GmbH, Estermannstrasse 17, A-4020 Linz, Austria.

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California Department of Health, USA. California Department of Health, USA.

California Scientific, Arg. California Scientific Argentina SA, Belgrano 3380, Mar del Plata, (B7600GKZ), Pcia. de Buenos Aires, Argentina.
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Calmic, USA. See *Wellcome, USA.*
Calmoseptine, Philipp. See *Metro, Philipp.*
Calmoseptine, USA. Calmoseptine Inc., 16602 Burke Lane, Huntington Beach, CA 92647, USA.
url: www.calmoseptine.com
Calox, Venez. Laboratorios Calox C.A., Av. Don Diego Cisneros Edificio Calox, Los Ruices, Apartado 62483, Caracas 1071, Venezuela.
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Cal-White, USA. Cal-White Mineral Co., P.O. Box 7890, Klamath Falls, OR 97602, USA.
Cambridge, Irl. Cambridge Laboratories (Ireland) Ltd, Alexandra House, The Sweepstakes, Ballsbridge, Dublin 4, Ireland.
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Cambridge, UK. Cambridge Laboratories, Deltic House, Kingfisher Way, Silverlink Business Park, Wallsend, Tyne & Wear, NE28 9NX, UK.
url: www.camb-labs.com
Cambridge Healthcare, UK. See *Typharm, UK.*
Camden, Singapore. See *Advanced, Singapore.*
Camps, Spain. Camps, Planeta 39, 08012 Barcelona, Spain.
Campus, Swed. Campus Pharma AB, Svärdvägen 13, 182 33 Danderyd, Sweden.
url: www.campuspharma.se
Cana, Gr. Cana S.A., 446 Irakliou Ave, 141 22 Iraklio Attikis, Greece.
url: www.cana.gr
Canadian Custom Packaging, Canad. Canadian Custom Packaging Co., 333 Rimrock Rd, Toronto, Ontario, M3J 3J9, Canada.
Can-Am Care, USA. Can Am Care Corp., 3780 Mansell Rd, Suite T-50, Alpharetta, GA 30022, USA.
url: www.canamcare.com
Canderm, Canad. Canderm Pharma, 5353 Thimens Blvd, Saint-Laurent, Quebec, H4R 2H4, Canada.
Candioli, Ital. Istituto Candioli Profilattico & Farmaceutico S.p.A., Via Manzoni 2, 10092 Beinasco (TO), Italy.
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Cangene, Canad. Cangene Corporation, 104 Chancellor Matheson Rd, Winnipeg, Manitoba, R3T 5Y3, Canada.
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Cangene, Gr. Cangene, Greece.
Cangene, Hong Kong. See *Hind Wing, Hong Kong.*
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Cangene, Philipp. See *GenAsia, Philipp.*
Cangene, Port. See *Cangene, UK.*
Cangene, UK. Cangene Europe Ltd, Parkshot House, 5 Kew Rd, Richmond, Surrey, TW9 2PR, UK.
Cankat, Turk. Cankat İlaç Ltd. Şti., Erciyes İşyerleri Sitesi 4. Cad. No:16, Macunköy, Ankara, 06370, Turkey.
url: www.cankat.com.tr
Canonne, Braz. Laboratório Canonne Ltda, Avenida Canal do Anil 1263, 22765-430 Rio de Janeiro, RJ, Brazil.
Can-Sel, Turk. Can-Sel, Turkey.
Cansin, Turk. Cansın İlaç Ltd. Şti., Süleyman Sırrı Sokak No:16/ 5, Yenişehir, Ankara, Turkey.
url: www.cansinmed.com
Cantabria, Spain. Cantabria, Arequipa 1, 28043 Madrid, Spain.
Cantassium Co., UK. The Cantassium Company, Larkhill Farm, Putney, UK.
Canyon, Cz. See *Canyon, UK.*
Canyon, Neth. See *Canyon, UK.*
Canyon, Port. See *Canyon, UK.*
Canyon, UK. Canyon Pharmaceuticals Ltd, 20-22 Bedford Row, London, WC1R 4JS, UK.
Capellon, USA. Capellon Pharmaceuticals Inc., 7509 Flagstone St, Fort Worth, TX 76118, USA.
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Capilares, Spain. Productos Capilares, Lopez Bravo 78, Plg. Ind. Villalonquejar, 09080 Burgos, Spain.
Capo Sole, Ital. Capo Sole S.r.l., Via Edison 60, 20019 Settimo Milanese (MI), Italy.
Caprifarmindo, Indon. Caprifarmindo, Komplek Industri Cimarene No 8, Padalarang, Bandung, Indonesia.
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Caps, S.Afr. Caps Pharmaceuticals (SA) (Pty) Ltd, P.O. Box 2801, Johannesburg 2000, South Africa.
Capsifar, Port. Capsifar - Comércio de Produtos Químico-Farmacêuticos Lda, Rua de Santa Rita, Lote 3, Loja Esq., 2765-281 São João do Estoril, Cascais, Portugal.
Caraco, USA. Caraco Pharmaceutical Labs, 1150 Elijah McCoy Drive, Detroit, MI 48202, USA.
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Caraderm, Irl. Caraderm Ltd, 6 Pine Valley, Rostrevor, Co. Down, BT34 3DE, Ireland.
Carbel, Mex. Grupo Carbel S.A. de C.V., Temistocles 96, Polanco Chapultepec, 11550 Mexico D.F., Mexico.
Cardinal, Hong Kong. See *Star, Hong Kong.*
Cardinal, Philipp. See *Crisdy-Na, Philipp., MG, Philipp.,* and *More, Philipp.*
Cardinal Health, USA. Cardinal Health Inc., 7000 Cardinal Place, Dublin, OH 43017, USA.
url: www.cardinal-health.com
Careiatrics, Arg. Careiatrics S.A., Dorrego 331, 1414 Buenos Aires, Argentina.
Carinopharm, Austria. See *Carinopharm, Ger.*
Carinopharm, Ger. Carinopharm GmbH, Rochusstr. 175-177, 53123 Bonn, Germany.
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Carlo Erba OTC, Ital. See *Pharmacia, Ital.*
Carlson, USA. J.R. Carlson Laboratories Inc., 15 College Drive, Arlington Heights, IL 60004-1985, USA.
url: www.carlsonlabs.com
Carme, USA. See *Senetek, USA.*
Carnation, USA. See *Nestle, USA.*
Carnot, Mex. Carnot Laboratorios, Productos Cientificos, S.A. de C.V., Nicolas San Juan No.1046, Col del Valle, 03100 Mexico D.F., Mexico.
Carnrick, USA. See *Elan, USA.*
Carolina, USA. Carolina Medical Products Co., P.O. Box 147, Farmville, NC 27828, USA.
url: www.carolinamedical.com
Carrare, Fr. Laboratoires Carrare, 1 rue Frederic-Bastiat, 75008 Paris, France.
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Carrington, USA. Carrington Labs, 2001 Walnut Hill Lane, Irving, TX 75038, USA.
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Carter, Austral. Carter Products (Australia) P/L, 1/108 Old Pittwater Road, Brookvale, NSW 2100, Australia.
Carter, NZ. See *Wilson, NZ.*
Carter, UK. Carter Products Ltd, Wear Bay Rd, Folkestone, Kent, CT19 6PG, UK.
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Carter Horner, Canad. Carter Horner Inc., 6600 Kitimat Rd, Mississauga, Ontario, L5N 1L9, Canada.
Carter Horner, Hong Kong. See *US Summit, Hong Kong.*
Carter Horner, Thai. See *US Summit, Thai.*
Carter-Horner, Philipp. See *Zenaust, Philipp.*
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Carter-Wallace, UK. See *Carter, UK.*
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Cartilade, Arg. Cartilade Arg. Farmacia Maure S.R.L., Av. Cabildo 499, 1426 Buenos Aires, Argentina.
Casana, Indon. Casana, Indonesia.
Casasco, Arg. Lab. Casasco S.A.I.C., Carabobo 22, 1406 Buenos Aires, Argentina.
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Casel, Turk. Casel İlaç San. ve Tic. Ltd. Şti., Nadide Sk. No:5, Merter, İstanbul, Turkey.
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Casen Fleet, Port. See *Casen Fleet, Spain.*
Casen Fleet, Spain. Casen Fleet, Autovia de Logrono Km 13.3, Utebo, 50180 Zaragoza, Spain.
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Casimiro & Moreira, Port. Casimiro & Moreira Lda, Rua das Água Férreas 50 A/P 3.5, 4440 Valongo, Portugal.
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Cassella-med, Cz. See *Cassella-med, Ger.*
Cassella-med, Ger. Cassella-med GmbH & Co. KG, Gereonsmuhlengasse 1, 50670 Cologne, Germany.
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Catalysis, Arg. Catalysis Argentina S.A., Av. Raul S. Ortiz 1277, 1414 Buenos Aires, Argentina.
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Cathay, Philipp. The Cathay Drug Co. Inc., 2/F Vernida I Cond, 120 Amorsolo St, Legaspi Vill, Makati City, Philippines.
Cavalheiro, Port. See *Confar, Port.*
Cazi, Braz. Cazi Química Farmacêutica Indústria e Comércio Ltda, Rua Antônio Lopes 17, 06600-000 Jandira, SP, Brazil.
CCD, Fr. Laboratoires CCD, 60 rue Pierre-Charron, 75008 Paris, France.
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CCM, Hong Kong. See *Zuellig, Hong Kong.*
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CCM, Malaysia. See *Upha, Malaysia.*
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CCS, Swed. CCS Clean Chemical Sweden AB, Tunavägen 277 B, 781 73 Borlänge, Sweden.
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Ceccarelli, Ital. Ceccarelli Farmaceutici S.r.l., Via G. Caponsacchi 31, 50126 Florence, Italy.
Cedar Health, UK. Cedar Health Ltd, Pepper Rd, Bramhall Moor Lane, Hazel Grove, Stockport, Cheshire, SK7 5BW, UK.
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Cedona, Neth. Cedona Pharmaceuticals BV, Netherlands.
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Celgene, Fr. Celgene, 6/8 Blvd Haussmann, 75009 Paris, France.
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Cell Pharm, Port. See *Cell Pharm, Ger.*
Cell Therapeutics, Austria. See *Cell Therapeutics, UK.*
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url: www.ctiseattle.com
Cell Therapeutics, Neth. See *Cell Therapeutics, UK.*
Cell Therapeutics, Spain. See *Cell Therapeutics, UK.*
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Cellegy, Singapore. See *Steward Cross, Singapore.*
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url: www.celltechgroup.com
Celltech, Fr. Laboratoires Celltech Pharma, 6 pl Boulnois, 75017 Paris, France.
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Celltech, Ger. Celltech Pharma GmbH & Co. KG, Bamlerstra. 1 B, 45141 Essen, Germany.
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Celltech, Irl. See *United Drug, Irl.*
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Celltech, Spain. Celltech Pharma, Montalban 5, 2 Izda, 28014 Madrid, Spain.
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Celltech, USA. Celltech Pharmaceuticals Co., 755 Jefferson Rd, Rochester, NY 14623, USA.
url: www.celltechgroup.com
CellTran, UK. CellTran Ltd, The Innovation Centre, 217 Portobello, Sheffield, S1 4DP, UK.
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Celon, Pol. Celon Pharma Sp. zo.o., ul. Ogrodowa 2 a, 05-092 Łomianki Kiełpin, Poland.
Celsus, Philipp. Celsus Pharmaceuticals Phils, Inc., 115 Scout Ralios St, Cor 11th Jamboree St, Quezon City, Philippines.
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Cem, Turk. Cem Farma İlaç Ltd. Şti., Sağlık 1 Sok. No: 36/7, Yenişehir, Ankara, Turkey.
url: www.cemfarma.com.tr
Cenci, USA. HR Cenci Labs Inc., 152 North Broadway St, Fresno, CA 93701, USA.
CeNeS, UK. CeNeS Ltd, Compass House, Vision Park, Chivers Way, Histon, Cambridgeshire, CB4 9ZR, UK.
url: www.cenes.co.uk
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Centaur, India. Centaur Laboratories Pvt Ltd, 279 New Ashirwad No. 5, Ram Mandir Rd, Goregaon West, Mumbai 400 104, India.
url: www.centaurpharma.com
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Centeon, Ital. See *Aventis Behring, Ital.*
Centeon, Pol. Centeon Pharma GmbH Oddział w Warszawie, al. Jerozolimskie 183, 02-486 Warsaw, Poland.
Centeon, USA. See *CSL Behring, USA.*
Center, Israel. See *Rekah, Israel.*
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Centocor, Hung. See *Centocor, Neth.*
Centocor, Israel. See *Lilly, Israel.*
Centocor, Neth. Centocor Europe BV, Einsteinweg 101, 2333 CB Leiden, Netherlands.
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Centocor, Norw. See *Lilly, Norw.*
Centocor, Pol. See *Lilly, Pol.*
Centocor, Rus. See *Centocor, Neth.*
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Centrafarm, Neth. Centrafarm Services BV, Nieuwe Donk 9, 4879 AC Etten-Leur, Netherlands.
Central, Thai. Central Poly Trading Co. Ltd, 100/261 Moo 3, Saima Muang, Nonthaburi 11000, Thailand.
Central Clinical, Pol. See *SecFarm, Pol.*
Central Pharmaceuticals, USA. See *Schwarz, USA.*
Centrapharm, Belg. See *Sandipro, Belg.*
Centrapharm, UK. See *Derma, UK.*
Centrix, USA. Centrix Pharmaceutical Inc., 31 Inverness Center Parkway, Suite 270, Birmingham, AL 35242, USA.
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Centrofarma, Port. Centrofarma Indústria e Comércio de Produtos Farmacêuticos Unipessoal Lda, R. da Quinta do Pinheiro 5, 2794-003 Carnaxide, Portugal.
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url: www.centurion.com.tr
Centurion, USA. Centurion Labs LLC, 4700 Caldwell Mill Rd, Birmingham, AL 35234, USA.
url: www.centurionlabs.com
Century, Canad. See *Century, USA.*
Century, USA. Century Pharmaceuticals Inc., 10377 Hague Rd, Indianapolis, IN 46256-3399, USA.
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Cephalon, Austria. See *Cephalon, Ger.,* and *Cephalon, UK.*
Cephalon, Cz. See *Cephalon, Fr.*
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Cephalon, Fr. Cephalon France, 20 rue Charles-Martigny, 94700 Maisons-Alfort, France.
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Cephalon, Irl. See *Cephalon, UK.*
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Cephalon, Norw. See *Swedish Orphan, Norw.*
Cephalon, Port. See *Cephalon, Fr.*
Cephalon, Switz. See *Globopharm, Switz.*
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Cephalon, USA. Cephalon Inc., 41 Moores Rd, Frazer, PA 19355, USA.
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Cesra, Cz. See *Cesra, Ger.*
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Cesra, Pol. See *Solpharm, Pol.*
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Cetin, Turk. Cetin, Turkey.
Cetus, Arg. Lab. Cetus S.R.L., Querandmes 4275, 1183 Buenos Aires, Argentina.
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Ceuta, UK. Ceuta Healthcare Ltd, Hill House, 41 Richmond Hill, Bournemouth, Dorset, BH2 6HS, UK.
url: www.ceuta-healthcare.co.uk
Ceutical, Hong Kong. Ceutical Trading Co. Ltd, Rm 24, 12/F, Goldfield Industrial Ctr, 1 Sui Wo Rd, Fo Tan, Shatin, N.T., Hong Kong.

Cevallos, Arg. Lab. Cevallos Salud S.R.L., Zapiola 2836/40, 1428 Buenos Aires, Argentina.

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Chaix et du Marais, Fr. Ste des Laboratoires Chaix et du Marais, 7 rue Labie, 75017 Paris, France.
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Chance, Pol. Chance Spółka Jawna Zakład Produkcji Farmaceutycznej, Pieńków 11, 05-152 Czosnów, Poland.
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Charoen Bhaesaj, Malaysia. See *Propharm, Malaysia.*

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Chatfield Laboratories, UK. Chatfield Laboratories, Kramer Mews, London, SW5 9JL, UK.

Chattem, Canad. Chattem (Canada) Inc., 2220 Argentia Rd, Mississauga, Ontario, L5N 2K7, Canada.

Chattem, Ger. See *Chattem, UK.*

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Chattem, UK. Chattem UK Ltd, Guerry House, Ringway Centre, Edison Rd, Basingstoke, Hampshire, RG21 2YH, UK.

Chattem, USA. Chattem Consumer Products, 1715 West 38th St, Chattanooga, TN 37409, USA.
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Chauvin, Belg. See *Bausch & Lomb, Belg.*

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url: www.bausch.com

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Chauvin, Thai. See *Neopharm, Thai.*

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Chefaro, Cz. See *Chefaro, Neth.*

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Chefaro, Israel. See *Neopharm, Israel.*

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Chefaro, Neth. Chefaro Nederland BV, Keileweg 8, 3029 BS Rotterdam, Netherlands.
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Chefaro, Port. Chefaro Portuguesa Distribuição de Produtos Farmacêuticos Unipessoal Lda, Av. Tomaz Ribeiro 43, Edificio Neopark, Bloco 1-4 A, 2795-574 Carnaxide, Portugal.

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Chefaro, UK. Chefaro UK Ltd, 1 Tower Close, St Peters Industrial Park, Huntingdon, Cambridgeshire, PE29 7DH, UK.
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Chefaro Ardeval, Fr. Laboratoires Chefaro-Ardeval, 2-4 rue de Chaintron, 92542 Montrouge cdx, France.

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Chemedica, Hong Kong. TRB Chemedica Hong Kong Ltd, Rm 2104, 21/F CC Wu Building, 302-8 Hennessy Rd, Wanchai, Hong Kong.
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Chemedica, Thai. TRB Chemedica (Thailand) Ltd, No 66, Q House Asoke Bldg, 14 Fl, Sukhumvit 21 Rd, North Klongtoey Subdistrict, Wattana District, Bangkok 10110, Thailand.

Chemedica, UK. TRB Chemedica UK Ltd, 14 Brindley Court, Lymedale Business Park, Newcastle-under-Lyme, Staffordshire, ST5B 9QA, UK.

Chemi, Ital. Chemi SpA, Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy.

Chemical, Fr. Chemical Farma, 131 av du Général-de-Gaulle, 92200 Neuilly-sur-Seine, France.

Chemical Research, Pol. Chemical Research, ul. Grunwaldzka 102, 80-244 Gdańsk, Poland.

Chemidex, Irl. See *Allphar, Irl.*

Chemidex, UK. Chemidex Pharma Ltd, Chemidex House, Egham Business Village, Crabtree Rd, Egham, Surrey, TW20 8RB, UK.
url: www.chemidex.co.uk

Cheminova, Rus. Cheminova LLC (Russia), Floor 7, 24 D Smolnaya ul., 125445 Moscow, Russia.
url: www.cheminova.com

Cheminova, Spain. Cheminova, Almansa 105, No. 20, 28040 Madrid, Spain.
url: www.cheminova.com

Chemipal, Israel. Chemipal, P.O. Box 8111, Netanya 42293, Israel.
url: www.chemipal.co.il

Chemipharma, Gr. Iasis Chemipharma A.E., Agiou Konstantinou 40, 151 242 Maroussi, Greece.

Chemists Own, Austral. Chemists Own Pty Ltd, P.O. Box 105, Ingleburn, NSW 1890, Australia.
url: www.chemistsown.com.au

Chemo, Cz. See *Chemo, Spain.*

Chemo, Neth. See *Chemo, Spain.*

Chemo, Spain. Chemo Iberica SA, Gran Via Carlos III 98, 7a, 08028 Barcelona, Spain.
url: www.chemoiberica.com

Chemomedica, Austria. Chemomedica Medizintechnik und Arzneimittel GmbH, Wipplingerstrasse 19, A-1013 Vienna, Austria.

Chemopharma, Chile. See *Sanitas, Chile.*

Chemopharma, Cz. Chemopharma as, Ústí nad Labem, Czech Republic.

Chemo-Pharma, India. Chemo-Pharma Labs Ltd, Empire House, 214 D. N. Road, Fort, Mumbai 400 001, India.

Chemotrade, Cz. Chemotrade sro, Mala Štěpánská 15, 120 00 Prague 2, Czech Republic.

Chephasaar, Ger. Chephasaar, Chem.-pharm. Fabrik GmbH, Muhlstr. 50, 66386 St Ingbert, Germany.
url: www.chephasaar.de

Chephasaar, Pol. See *MIP, Pol.*

Cheplapharm, Ger. Cheplapharm Arzneimittel GmbH, Bahnhofstr 1a, 17498 Mesekenhagen, Germany.
url: www.cheplapharm.de

Chesebrough-Pond's, USA. See *Unilever, USA.*

Chester, Canad. See *Technilab, Canad.*

Chew, Thai. Chew Brothers & Co. Ltd Part, 1561/3 Petchburi Rd, New Extension, Makason, Bangkok 10310, Thailand.

Chi Sheng, Thai. See *Charoen, Thai.*

Chibret, Ger. See *MSD, Ger.*

Chibret, Port. See *MSD, Port.*

Chibret, Spain. See *MSD, Spain.*

Chiesi, Cz. See *Medicom, Cz.*

Chiesi, Fr. Chiesi SA, Imm. le Doublon, bat B, 11 av. Dubonnet, 92400 Courbevoie, France.
url: www.chiesigroup.com

Chiesi, Gr. Chiesi Hellas S.A., 1 Pentelis Ave, 152 35 Vrilissia, Greece.
url: www.chiesigroup.com

Chiesi, Hong Kong. See *CNW, Hong Kong.*

Chiesi, Hung. See *Torrex, Hung.*

Chiesi, Ital. Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43100 Parma, Italy.
url: www.chiesigroup.com

Chiesi, Malaysia. See *Germax, Malaysia.*

Chiesi, Neth. See *Multipharma, Neth.*

Chiesi, Pol. See *Torrex, Pol.*

Chiesi, Port. See *Chiesi, Ital.*

Chiesi, Rus. See *Pharmaregie, Rus.*

Chiesi, Singapore. See *JDH, Singapore.*

Chiesi, Spain. Chiesi España, Berlin 38-48, 7 planta, 08029 Barcelona, Spain.
url: www.chiesigroup.com

Chiesi, Switz. Chiesi SA, Via Franscini 17, 6900 Lugano, Switzerland.
url: www.chiesigroup.com

Chiesi, Thai. See *Pacific, Thai.*

Chilton, USA. Chilton Labs Inc., 299B Fairfield Ave, Fairfield, NJ 07004, USA.

Chimicor, Fr. See *Chimicor, Ital.*

Chimicor, Ital. Chimicor S.r.l., Via Nosellare 12, 36028 Rossano Veneto, Italy.
url: www.chimicor.it

China Chem & Pharma, Thai. See *Charoen, Thai.*

Chinoin, Cz. See *Sanofi Synthelabo, Cz.*

Chinoin, Hung. Chinoin Pharmaceutical and Chemical Works Ltd, P.O. Box 110, 1325 Budapest, Hungary.

Chinoin, Mex. Chinoin, Productos Farmaceuticos, S.A. de C.V., Lago Tanganica No. 18, Col. Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.

Chinoin, Pol. See *Sanofi-Aventis, Pol.*

Chinoin, Rus. See *Sanofi-Aventis, Rus.*

Chinosolfabrik, Ger. Chinosolfabrik (Zweigniederlassung der Riedel-de Haen AG), Wunstorfer Str. 40, 30926 Seelze, Germany.
url: www.chinosol.de

Chinta, Thai. See *Square, Thai.*

ChiRhoClin, USA. ChiRhoClin Inc., 4000 Blackburn Lane, Suite 270, Burtonsville, MD 20866, USA.
url: www.chirhoclin.com

Chiron, Belg. See *Chiron, Neth.*

Chiron, Canad. Chiron Canada Ltd, 3300 Côte-Vertu Bvld, Suite 403, St. Laurent, Quebec, H4R 2B7, Canada.
url: www.chiron.com

Chiron, Cz. See *Medicom, Cz.*

Chiron, Denm. See *Orphan, Denm.*

Chiron, Fr. Chiron France, 10 rue Chevreul, 92150 Suresnes, France.
url: www.chiron.com

Chiron, Ger. Chiron GmbH, Linprunstr. 16, 80335 Munich, Germany.
url: www.chiron.com

Chiron, Hong Kong. See *Honbase, Hong Kong.*

Chiron, Hung. See *Chiron Behring, Hung.*

Chiron, Irl. See *Allphar, Irl.,* and *United Drug, Irl.*

Chiron, Israel. See *Concept, Israel.*

Chiron, Ital. Chiron Italia S.r.l., Via Cimarosa 4, 20144 Milan, Italy.

Chiron, Neth. Chiron BV, Paasheuvelweg 30, 1105 BJ Amsterdam Zuidoost, Netherlands.
url: www.chiron.com

Chiron, Norw. See *Swedish Orphan, Norw.*

Chiron, Pol. See *Medagro, Pol.*

Chiron, Singapore. See *Pacific Biosciences, Singapore,* and *Sime Darby, Singapore.*

Chiron, Spain. Chiron Iberia, Edificio Dublin, Parque Emp. San Fernando, San Fernando de Henares, 28831 Madrid, Spain.
url: www.chiron.com

Chiron, Swed. See *Chiron Vaccines, Ital.*

Chiron, Thai. See *Biogenetech, Thai.*

Chiron, Turk. See *Novartis, Turk.*

Chiron, UK. See *Novartis, UK.*

Chiron, USA. Chiron Therapeutics, 4560 Horton St, Emeryville, CA 94608-2916, USA.
url: www.chiron.com

Chiron Behring, Ger. Chiron Behring GmbH & Co, Emil-von-Behring-Str. 76, 35041 Marburg, Germany.
url: www.chiron-behring.de

Chiron Behring, Hung. Chiron Behring GmbH & Co, Pf 732/21, 1388 Budapest 62, Hungary.

Chiron Behring, Israel. See *Mediline, Israel.*

Chiron Behring, Malaysia. See *Chiron Behring, Ger.*

Chiron Behring, Norw. See *Chiron Behring, Ger.*

Chiron Behring, Pol. See *Imed, Pol.*

Chiron Vaccin, Fr. See *Chiron, Fr.*

Chiron Vaccines, Ger. See *Chiron Behring, Ger.*

Chiron Vaccines, Hong Kong. See *IDS, Hong Kong.*

Chiron Vaccines, Irl. See *Allphar, Irl.*

Chiron Vaccines, Ital. Chiron Vaccines, Divisione Chiron S.r.l., Via Fiorentina 1, 53100 Siena, Italy.
url: www.chiron.com

Chiron Vaccines, Neth. See *Novartis Vaccines, UK.*

Chiron Vaccines, Philipp. See *Marketlink, Philipp.*

Chiron Vaccines, Thai. See *Biogenetech, Thai.*

Chiron Vaccines, UK. See *Novartis Vaccines, UK.*

Chitin, Hong Kong. See *Trinity, Hong Kong.*

Choay, Israel. See *Promedico, Israel.*

Choay, Port. See *Sanofi Synthelabo, Port.*

Chobet, Arg. Soubeiran Chobet S.R.L., Ibera 5055, 1431 Buenos Aires, Argentina.

Chong Kun Dang, Ital. Chong Kun Dang Italia S.p.A., Fraz. Domodossolina, 28651 Borgo S Giovanni (LO), Italy.

Chong Lap, Hong Kong. Chong Lap (HK) Co. Ltd, Unit 715-6, Lippo Sun Plaza, 28 Canton Rd, Tsim Sha Tsui, Kowloon, Hong Kong.

Choongwae, Hong Kong. See *Vantone, Hong Kong.*

Choongwae, Kor. Choongwae Pharma Corp., Sindehbahng-1 Dong, Dongjahk-Gu, Seoul 156-010, Korea.
url: www.choongwae.com

Choongwae, Philipp. See *Endure, Philipp.*

Choongwae, Singapore. See *Kyowa, Singapore.*

Chowgule, India. Chowgule & Co. (Hind) Ltd, Malhotra House, Opposite GPO, Walchand Hirachand Marg, Mumbai 400 001, India.

CHR, Ger. C.H.R. Heim Arzneimittel GmbH, Elisabethenstr. 34, 64283 Darmstadt, Germany.

Chrisana, Switz. Chrisana GmbH, Ruggenstrasse 31, 8903 Birmensdorf, Switzerland.
url: www.chrisana.ch

Chrispa (Χρισπα), Gr. Chrispa Alfa Pharma A.E., Andr. Leon-Menandrou 58, 104 32 Athens, Greece.

Christiaens, Belg. See *Nycomed, Belg.*

Christo, Hong Kong. Christo Pharmaceuticals Ltd, Blk A-D, 14/F, Stage 2, Superluck Industrial Ctr, 57 Sha Tsui Rd, Tsuen Wan, N.T., Hong Kong.

Chugai, Denm. See *Aventis, Denm.*

Chugai, Fr. Laboratoires Chugai Pharma France, Immeuble Lafayette, La Défense 5, 2 place des Vosges, Paris-LA Défense cdx, France.
url: www.chugai.fr

Chugai, Ger. Chugai Pharma Marketing Ltd, Lyoner Str. 15, 60528 Frankfurt/Main, Germany.
url: www.chugaipharma.de

Chugai, Hong Kong. See *Fandasy, Hong Kong,* and *Tai Tong, Hong Kong.*

Chugai, Irl. See *Chugai, UK.*

Chugai, Jpn. Chugai Pharmaceutical Co. Ltd, 2-1-9 Kyobashi, Chuo-ku, Tokyo 104-8301, Japan.
url: www.chugai-pharm.co.jp

Chugai, Norw. See *Aventis, Norw.*

Chugai, Thai. See *Siam Pharm, Thai.*

Chugai, UK. Chugai Pharma UK, Mulliner House, Flanders Rd, Turnham Green, London, W4 1NN, UK.
url: www.chugai.co.uk

Church, Mex. Church & Dwight SRL de CV, Calz. de las Armas 110, 54080 Fracc. las Armas, Estado de Mexico, Mexico.

Church & Dwight, Austral. Church & Dwight Australia Pty Ltd, Unit 1, 108 Old Pittwater Rd, Brookvale, NSW 2100, Australia.

Church & Dwight, Canad. Church & Dwight Canada Corp., 635 Secretariat Court, Mississauga, Ontario, L5S 0A5.

CI, Austria. CI Pharma Arzneimittel Handels GmbH, A-1180 Vienna, Austria.

Ci & Di, Ital. Ci & Di S.r.l., Via Merlo 1, 20122 Milan, Italy.

Ciba, USA. See *Novartis, USA.*

Ciba Consumer, USA. See *Novartis, USA.*

Ciba Vision, Arg. See *Novartis, Arg.*

Ciba Vision, Austral. Ciba Vision Australia P/L, Private Bag 100, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.cibavision.com.au

Ciba Vision, Braz. See *Novartis, Braz.*

Ciba Vision, Canad. See *Novartis, Canad.*

Ciba Vision, Cz. See *Novartis, Cz.*

Ciba Vision, Israel. See *Promedico, Israel.*

Ciba Vision, Ital. Ciba Vision S.r.l., gruppo Novartis, Via Enrico Mattei 17, 30020 Marcon (VE), Italy.
url: www.cibavision.it

Ciba Vision, NZ. See *Novartis, NZ.*

Ciba Vision, Port. See *Novartis, Port.*

Ciba Vision, Rus. See *Novartis Ophthalmics, Rus.*

Ciba Vision, Switz. See *Novartis Ophthalmics, Switz.*

Ciba Vision, Thai. See *Zuellig, Thai.*

Ciba Vision, USA. See *Novartis Ophthalmics, USA.*

Ciba-Geigy, USA. See *Novartis, USA.*

Cibran, Braz. Companhia Brasileira de Antibioticos Cibran, Rua da Quitanda 3, 4 andar, 20011-030 Rio de Janeiro, RJ, Brazil.

Ciclum, Port. Ciclum Farma Unipessoal Lda, R Alfredo da Silva 16, 2610-016 Amadora, Portugal.

Ciclum, Spain. Ciclum Farma, Doctor Zamenhof 38, 28027 Madrid, Spain.

CICSA, Mex. Compañia Internacional de Comercio SA de CV, Monzón 184, 9860 Iztapalapa Cerro de la Estrella, Mexico.

Ciech, Rus. Ciech AO, Kutuzovski Prospekt 7/14, Korp. 5, kv. 11-12, 121248 Moscow, Russia.
url: www.ciech.ru

Cielle, Ital. Farma Cielle S.r.l., Via Michele Amari 15, 90139 Palermo, Italy.

CIF, Braz. Companhia Industrial Farmacêutica, Rua Figueira de Melo 301, 20941-001 Rio de Janeiro, RJ, Brazil.
url: www.cif-farmaceutica.com.br

Cifarma, Braz. Cifarma Cientifica Farmacêutica Ltda, Av. das Industrias 3651, 33040-130 Belo Horizonte, MG, Brazil.
url: www.cifarma.com.br

Cilag, Cz. See *Janssen-Cilag, Cz.*

Cilag, Hong Kong. See *Janssen, Hong Kong,* and *Keller, Hong Kong.*

Cilag, Mex. Cilag de Mexico S.A. de C.V., Miguel Angel de Quevedo No. 247, Col. Romero de Terreros, Deleg. Coyoacan, 04310 Mexico D.F., Mexico.

Cilag, Philipp. See *Zuellig, Philipp.*

Cilag, Rus. See *Janssen-Cilag, Rus.*

Cimed, Braz. Cimed Indústria de Medicamentos Ltda, Rua Engenheiro Prudente 119, 01550-000 São Paulo Vila Monumento, SP, Brazil.
url: www.cimed.ind.br

Cimex, Cz. See *Swisspharma, Cz.*

Cimex, Hong Kong. See *LCH, Hong Kong.*

Cimex, Switz. Cimex AG Pharmazeutika, Birsweg 2, 4253 Liesberg, Switzerland.
Cimprich, Cz. Pharm Dr Ivan Cimprich, Karlovy Vary, Czech Republic.
Cinetic, Arg. Cinetic Laboratories Argentina S.A., Av. Triunvirato 2734/6, 1427 Buenos Aires, Argentina.
Cinfa, Spain. Cinfa, Olaz-Chipi 10, Poligono Areta, Huarte-Pamplona, 31620 Navarra, Spain.
url: www.cinfa.com
Cintas, UK. Cintas Pharma, a division of BritHealth Limited, Business & Technology Centre, Bessemer Drive, Stevenage, Hertfordshire, SG1 2DX, UK.
url: www.pharmalicensing.com
Cipan, Port. Cipan, Companhia Industrial Produtora de Antibioticos SA, Vala do Carregado, Apartado 60, 2600-733 Castanheira do Ribatejo, Portugal.
url: www.cipan.pt
Cipharmed, Fr. Cipharmed (Lab), 11 bd Émile-Augier, 75016 Paris, France.
Cipla, Austral. Cipla GenPharm Australia Pty Ltd, Kaybank Plaza, 33 Scarborough St, Southport, Qld 4215, Australia.
Cipla, Cz. See *CZ, Cz.*
Cipla, Hong Kong. See *Lifetech, Hong Kong.*
Cipla, India. Cipla Ltd, Mumbai Central, Mumbai 400 008, India.
url: www.cipla.com
Cipla, Israel. See *Margalit, Israel.*
Cipla, Malaysia. See *Antah, Malaysia.*
Cipla, Philipp. See *Pharmawealth, Philipp.*
Cipla, S.Afr. See *Cipla-Medpro, S.Afr.*
Cipla, Thai. See *Neopharm, Thai.*
Cipla, Venez. See *PG, Venez.*
Cipla-Medpro, S.Afr. Cipla-Medpro (Pty) Ltd, Rosen Heights, Rosen Park, Bellville 7530, South Africa.
url: www.ciplamedpro.co.za
Circle, USA. Circle Pharmaceuticals Inc., 6788 Hawthorn Park Drive, Indianapolis, IN 46220, USA.
CIS, Cz. See *CIS, Fr.*
CIS, Fr. CIS bio International, B.P. 32, 91192 Gif-sur-Yvette cdx, France.
url: www.cisbiointernational.fr
CIS, Hung. See *CIS, Fr.*
CIS, Neth. See *CIS, Fr.*
CIS, Port. See *CIS, Fr.*
CIS, Spain. CIS España, Prim 5, 28004 Madrid, Spain.
Citomed, Rus. Citomed ZAO, Muchnojj per. 2, 191023 Saint Petersburg, Russia.
CJ, Thai. See *BJC, Thai.*, and *RX, Thai.*
CKD, Philipp. See *Endure, Philipp.*, and *Largen, Philipp.*
Clairol, Canad. See *Procter & Gamble, Canad.*
Clarben, Port. See *Clarben, Spain.*
Clarben, Spain. Clarben, Vallermoso 28, 28015 Madrid, Spain.
url: www.clarben.com
Clariana, Spain. Clariana Pico, Ctra Carlet Valencia Km 0.5, Carlet, 46240 Valencia, Spain.
Clarins, Canad. Clarins, 4757 Poirier Blvd, St-Laurent, Quebec, H4R 2A4, Canada.
Clay Park, USA. Clay-Park Labs Inc., 1700 Bathgate Ave, Bronx, NY 10457, USA.
url: www.claypark.com
Clement, Fr. See *Clement-Thekan, Fr.*
Clement Thionville, Fr. Laboratoires Clément-Thionville, 6 rue Joffre, B.P. 60028, 57101 Thionville cdx, France.
Clement-Thekan, Fr. Laboratoires Clément-Thékan, 2-4 rue Chaintron, B.P. 850, 92542 Montrouge cdx, France.
Climax, Braz. Laboratório Climax S.A., Rua Joaquim Tavora 822, 04015-011 São Paulo, SP, Brazil.
Clinbaxy, Philipp. Clinbaxy Intl, Inc., 1139-1141 Rizal Ave, Cor Mayhaligue St, Sta Cruz, Manila, Philippines.
CliniMed, UK. CliniMed Ltd, Cavell House, Knaves Beech Way, Loudwater, High Wycombe, Buckinghamshire, HP10 9QY, UK.
url: www.clinimed.co.uk
Clinique, Canad. Clinique Laboratories, 121 Bloor St E, Toronto, Ontario, M4W 3N5, Canada.
Clintec, Austria. See *Baxter, Fr.*
Clintec, Belg. See *Baxter, Belg.*
Clintec, Cz. See *Nestle, Fr.*
Clintec, Denm. See *Baxter, Denm.*
Clintec, Israel. See *Teva, Israel.*
Clintec, Neth. See *Nestle, Fr.*
Clintec, USA. See *Baxter, USA.*
Clintex, Port. See *Labesfal, Port.*
Clissmann, Irl. HE Clissmann, 72 Heather Rd, Dublin 18, Ireland.
url: www.clissmann.com
Clonmel, Irl. Clonmel Healthcare Ltd, Waterford Rd, Clonmel, Co. Tipperary, Ireland.
url: www.clonmel-health.ie
CMM Medicor, Rus. CMM Medicor, The Centre of Modern Medicine Ltd, Ul. Alexeya Aviridova 15/3, 121374 Moscow, Russia.
url: www.galavit.ru
CMS, Switz. CMS Control & Monitoring Systems GmbH, Huslerstrasse 30, 5453 Remetschwill, Switzerland.
CMS-Dental, Denm. CMS-Dental ApS, Wildersgade 55, 1408 Copenhagen K, Denmark.
CNN, Philipp. CNN Generics Distribution Inc., Rm 210, Lawyers Coop Bldg, 459 Quezon Ave, Cor Banawe, Quezon City, Philippines.
CNS, Austral. CNS Pharma Pty Ltd, Level 4, Deutsche Bank Place, Corner Hunter and Phillip Streets, Sydney, NSW 2000, Australia.
CNW, Hong Kong. CNW (Hong Kong) Ltd, Rm 606, 6/F, Fo Tan Industrial Ctr, 26-28 Au Pui Wan St, Fo Tan, Shatin, N.T., Hong Kong.
url: www.cnwhk.com
Co Ord-Med, Hung. Co Ord-Med Információs Iroda, Csaba u 7/a II/1, 1122 Budapest, Hungary.
Cobalt, Canad. Cobalt Pharmaceuticals Inc., 6500 Kitimat Rd, Mississauga, Ontario, L5N 2B8, Canada.
Codal Synto, Hong Kong. See *CNW, Hong Kong, Hong Tai Hong, Hong Kong,* and *Star, Hong Kong.*
Codal Synto, Malaysia. See *Propharm, Malaysia.*
Codal Synto, Thai. See *Star, Thai.*
Codali, Belg. Codali SA, Ave Henri Dunant 31, 1140 Brussels, Belgium.
url: www.codali.be
Codan Triplus, Swed. Codan Triplus AB, Smorhalevägen 11, 434 42 Kungsbacka, Sweden.
url: www.codantriplus.se
Codepharma, Fr. Lab Codepharma, 80-82 rue Gallieni, 92100 Boulogne-Billancourt, France.
Codifar, Port. Codifar, Cooperativa Distribuidora Farmaceutica CRL, Av. Marechal Gomes da Costa 19, 1800-255 Lisbon, Portugal.
Codifra, Fr. Laboratoires Codifra, 18 av. Dutarte, 78150 de Chesney, France.
Codilab, Port. Codilab, Indústria e Comércio de Produtos Farmacêuticos SA, Av. Marechal Gomes da Costa 19, 1800-255 Lisbon, Portugal.
Coel, Pol. Wytwórnia Euceryny Laboratorium Farmaceutyczne Coel SJ, ul. Wł Żeleńskiego 45, 31-353 Kraków, Poland.
url: www.coel.krakow.pl
Cofasa, Venez. Laboratorios Cofasa S.A., Urbanización Industrial Lebrún, Edificio Cofasa, 4to. Piso, Caracas, Venezuela.
url: www.laboratoriocofasa.com
Coffey, Irl. Coffey Healthcare Ltd, 4 Finglas Business Centre, Jamestown Rd, Dublin 11, Ireland.
url: www.coffeyhealthcare.com
Colfarm, Pol. Zakłady Farmazeutyczne Colfarm SA, ul. Wojska Polksiego 3, 39-300 Mielec, Poland.
url: www.colfarm.pl
Colgate, Arg. See *Colgate-Palmolive, Arg.*
Colgate, Gr. Colgate-Palmolive Hellas, Piraeus, Greece.
url: www.colgate.com
Colgate Oral, USA. Colgate Oral Pharmaceuticals, 1 Colgate Way, Canton, MA 02021, USA.
url: www.colgateprofessional.com
Colgate Oral Care, Austral. Colgate Oral Care, P.O. Box 3964, Sydney, NSW 2001, Australia.
url: www.colgate.com
Colgate Palmolive, Port. Colgate Palmolive Unipessoal Lda, Rua Mário Castelhano no 1, Queluz de Baixo, 2730-120 Barcarena, Portugal.
Colgate-Hoyt, USA. See *Colgate-Palmolive, USA.*
Colgate-Palmolive, Arg. Colgate-Palmolive Argentina S.A., Av. Antartida Argentina 2269, 1836 Llavallol, Buenos Aires, Argentina.
url: www.colgate.com
Colgate-Palmolive, Austral. See *Colgate Oral Care, Austral.*
Colgate-Palmolive, Austria. See *Colgate-Palmolive, Ger.*
Colgate-Palmolive, Canad. Colgate Palmolive Canada, 99 Vanderhoof Ave, Toronto, Ontario, M4G 2H6, Canada.
url: www.colgate.com
Colgate-Palmolive, Denm. Colgate Palmolive A/S, Postbox 93, 2600 Glostrup, Denmark.
url: www.colgate.com
Colgate-Palmolive, Fin. See *Colgate-Palmolive, Denm.*
Colgate-Palmolive, Fr. Colgate-Palmolive, 55 bd de la Mission-Marchand, 92401 Courbevoie cdx, France.
Colgate-Palmolive, Ger. Colgate-Palmolive GmbH, Liebigstr 2-20, 22113 Hamburg, Germany.
url: www.colgate.de
Colgate-Palmolive, Ital. Colgate Palmolive Italia S.r.l., Divisione Oral Pharmaceuticals, Via Giorgione 59/63, 00147 Rome, Italy.
url: www.colgate.com
Colgate-Palmolive, Neth. Colgate-Palmolive Nederland BV, 1382 LV Weesp, Netherlands.
Colgate-Palmolive, Norw. See *Colgate-Palmolive, Denm.*
Colgate-Palmolive, Swed. See *Colgate-Palmolive, Denm.*
Colgate-Palmolive, Switz. Colgate-Palmolive AG, Zurcherstrasse 68, 8800 Thalwill, Switzerland.
url: www.colgate.ch
Colgate-Palmolive, UK. Colgate-Palmolive Ltd, Guilford Business Park, Middleton Rd, Guildford, Surrey, GU2 5LZ, UK.
url: www.colgate-palmolive.co.uk
Colgate-Palmolive, USA. Colgate-Palmolive Co., 300 Park Ave, New York, NY 10022, USA.
url: www.colgate.com
Colin, Belg. Colin Laboratoires NV, Rue Trou-du-Loup 50, 4670 Blegny, Belgium.
Coll, Spain. Coll Farma, Napoles 166, 08013 Barcelona, Spain.
Collagen, Austral. Collagen Biomedical P/L, Unit 1, Chullora Central, Chullora, NSW 2190, Australia.
Collagen, Ger. Collagen Aesthetics, Hansaallee 201, 40549 Dusseldorf, Germany.
url: www.collagen.de
Collagen Aesthetics, NZ. Collagen Aesthetics Ltd, P.O. Box 25-556, St. Heliers, Auckland, New Zealand.
CollaGenex, Neth. See *CollaGenex, UK.*
CollaGenex, UK. CollaGenex International Ltd, The Old Stable Block, 7 Buttermarket, Thame, Oxfordshire, OX9 3EW, UK.
url: www.collagenex.com
CollaGenex, USA. CollaGenex Pharmaceuticals Inc., 41 University Drive, Newtown, PA 18940, USA.
url: www.collagenex.com
Collect, Braz. Collect Importação e Comércio Ltda, Brazil.
Collett, Fin. Collett Pharma Finland Oy, Äyritie 12 B, 01510 Vantaa, Finland.
Collins, Mex. Productos Farmaceuticos Collins S.A. de C.V., Cipres No. 1677, Col. del Fresno, 44900 Guadalajara, Jalisco, Mexico.
url: www.collins.com.mx
Collins Elixir, UK. Collins Elixir Co., P.O. Box 33, Kingsbridge, Devon, TQ7 1YQ, UK.
Coloplast, Arg. Coloplast de Argentina S.A., Hipylito Bouchart 547, Piso 13, 1106 Buenos Aires, Argentina.
url: www.coloplast.com
Coloplast, Fr. Laboratoires Coloplast, 58 rue Roger-Salengro, Peripole 126, 94126 Fontenay-sous-Bois cdx, France.
url: www.coloplast.fr
Coloplast, Ger. Coloplast GmbH, Kuehnstr. 75, 22045 Hamburg, Germany.
Coloplast, S.Afr. Coloplast A/S, Van Reenens Rd, Woodmead Office Park, 20 Stirrup Lane, Woodmead Ext. 14, Sandton, South Africa.
url: www.coloplast.com
Coloplast, UK. Coloplast Ltd, Peterborough Business Park, Peterborough, Cambridgeshire, PE2 0FX, UK.
url: www.coloplast.co.uk
Coloplast, USA. Coloplast Corp., 1955 West Oak Circle, Marietta, GA 30062-2249, USA.
url: www.us.coloplast.com
Columbia, Arg. Laboratorios Columbia de Argentina SA, Cervantes 2950, Buenos Aires, Argentina.
Columbia, Canad. Columbia Laboratories Canada Inc., 600 Peter Morand Cres., Suite 140, Ottawa, Ontario, K1G 5Z3, Canada.
Columbia, Mex. Laboratorios Columbia, S.A. de C.V., Calz. del Hueso No. 160, Col. Ejido de Santa Ursula Coapa, Deleg. Coyoacan, 04850 Mexico D.F., Mexico.
Columbia, S.Afr. Columbia Pharmaceuticals (Pty) Ltd, P.O. Box 7026, Bonaero Park 1622, South Africa.
Columbia, USA. Columbia Laboratories Inc., 354 Eisenhower Parkway, Second Floor, Plaza 1, Livingston, NY 07039, USA.
url: www.columbialabs.com
Combe, Arg. Lab. Combe Argentina SRL, Pola 2249/51, 1440 Buenos Aires, Argentina.
Combe, Canad. See *Combe, USA.*
Combe, Ger. Combe Pharma Ltd, Rheinstr. 219, 76532 Baden-Baden, Germany.
url: www.combe-pharma.de
Combe, Israel. See *Mediline, Israel.*
Combe, Ital. Combe Italia S.r.l., Via G C Procaccini 41, 20154 Milan, Italy.
Combe, Spain. Combe Europa, Orense 58, 28020 Madrid, Spain.
Combe, UK. Combe International Ltd, 4th Floor, AMP House, Dingwell Rd, Croydon, Surrey, CR9 2AU, UK.
url: www.combe.com
Combe, USA. Combe Inc., 1101 Westchester Ave, White Plains, NY 10604, USA.
url: www.combe.com
Combino, Spain. Combino Pharm, Fructuos Gelabert 6-8, Sant Joan Despi, 08024 Barcelona, Spain.
url: www.combino-pharm.es
Combiphar, Indon. Combiphar PT, Graha Atrium Lt 14, Jl Senen Raya No 135, 10160 Jakarta Pusat, DKI Jaya, Indonesia.
Combustin, Ger. Combustin Pharm. Präparate GmbH, Offinger Str. 7, 88525 Hailtingen/Bussen, Germany.
Commerce, USA. See *Del, USA.*
Commonwealth Serum, Hong Kong. See *LCH, Hong Kong.*
Community Pharmacy, Thai. Community Pharmacy Public Co. Ltd, 96/17 Moo 13, Khubon Rd, Kannayao, Bangkok 10230, Thailand.
url: www.cophar.com
Complutense, Spain. Centro PET Complutense SA, C/Manuel Bartolome Cossio 10, 28040 Madrid, Spain.
url: www.petmadrid.com
Compu, S.Afr. CompuPharm (Pty) Ltd, P.O. Box 30599, Sunnyside 0132, South Africa.
Concept, India. Concept Pharmaceuticals Ltd, 167 C.S.T. Rd, Santacruz (E), Mumbai 400 098, India.
Concept, Israel. Concept for Pharmacy Ltd, P.O. Box 2105, Kfar Sava 44643, Israel.
url: www.concept-rx.co.il
Concord, UK. See *Archimedes, UK.*
Concordia, Mex. Laboratorios Concordia S.A. de C.V., Ejército Nacional 579, 8 Piso, Miguel Hidalgo Ampliación Granada, 11520 México D.F., Mexico.
Condrugs, Thai. Condrugs International Co. Ltd, 51/507-508 Drive-in Square, Soi 1, Ladprao Rd, Klongjan, Bangkapi, Bangkok 10240, Thailand.
Confab, Hong Kong. See *Pan-Well, Hong Kong.*
Confar, Port. Confar, Lda, Rua Sebastião e Silva 25, Zona Industrial de Massama, 2745-838 Queluz, Portugal.
Conforma, Belg. Conforma, Belgium.
Connaught, NZ. See *CSL, NZ.*
Connetics, USA. Connetics, 3160 Porter Drive, Palo Alto, CA 94304, USA.
url: www.connetics.com
Consolidated Chemicals, Irl. See *Whelehan, Irl.*
Consupharma, Mex. Consupharma SA de CV, Pico de Verapaz 435 Piso 2, Tlalpan Jardines de Montana, 14210 Mexico D.F., Mexico.
url: www.consupharma.com
Continental, Cz. See *Continental Pharma, Belg.*
Continental, Spain. Continental Farmaceutica, Spain.
Continental, USA. Continental Consumer Products, 770 Forest, Suite B, Birmingham, MI 48009, USA.
Continental Ethicals, S.Afr. Continental Ethicals (Division of S.A. Druggists Ltd), 1 Corlett Drive, Illovo, Johanesburg 2196, South Africa.
Continental Pharma, Belg. Continental Pharma Inc., Tervurenlaan 270-272 bte 24, 1150 Brussels, Belgium.
Continental Pharma, Thai. See *Union Medical, Thai.*
Continentales, Mex. Farmacos Continentales S.A. de C.V., Mexico.
Continental-Pharm, Thai. Continental-Pharm Co Ltd, 85/5 Soi Prachoomporn, Chaengwattana Rd, Laksi, Bangkok, Thailand.
Contract Pharmacal, USA. Contract Pharmacal Corporation, 135 Adams Avenue, Hauppauge, NY 11788, USA.
url: www.contractpharmacal.com
Contragest, Ger. Contragest GmbH, Kelsterbacher Str. 28, 64546 Walldorf, Germany.
url: www.contragest.de
Controlled Therapeutics, Pol. See *Medagro, Pol.*
Convatec, Arg. See *BMS, Arg.*
Convatec, Austral. Convatec Australia, Division of Bristol-Myers Squibb, Level 1, 352 Welling Road, Mulgrave, VIC 3170, Australia.
url: www.convatec.com
Convatec, Canad. Convatec Canada, 555 Dr Frederick Philips St, Suite 110, St-Laurent, Quebec, H4M 2X4, Canada.
url: www.convatec.com
Convatec, Fr. See *BMS, Fr.*
Convatec, Irl. See *BMS, Irl.*
Convatec, Israel. See *Philtel, Israel.*
Convatec, Ital. See *BMS, Ital.*
Convatec, Port. See *BMS, Port.*
Convatec, UK. Convatec Ltd, Harrington House, Milton Rd, Ickenham, Uxbridge, Middlesex, UB10 1DE, UK.
url: www.convatec.com
Convatec, USA. ConvaTec, P.O. Box 5254, Princeton, NJ 08543-5245, USA.
url: www.convatec.com
Cook-Waite, USA. See *Kodak, USA.*
Coop. Farm., Ital. Cooperativa Farmaceutica Soc. (CoFa Farmaceutici), Via Passione 8, 20122 Milan, Italy.
Cooper, Fr. Coopération Pharmaceutique Française, 77020 Melun cdx, France.
Cooper (Κοπερ), Gr. KOPER AE, Aristovoulou 64, 118 53 Attikis, Greece.
Cooper, USA. Cooper Surgical, 95 Corporate Drive, Trumbull, CT 06611, USA.
Cooperation Pharmaceutique, Fr. See *Cooper, Fr.*
Copernico, Ital. Copernico Farmaceutici S.r.l., Viale Etiopia 8, 00100 Rome, Italy.
Cophar, Switz. Cophar SA, Route de Moncor 10, 1752 Villars-sur-Glâne, Switzerland.
Co-Pharma, UK. Co-Pharma Ltd, Unit 4, Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD1 8SS, UK.
url: www.co-pharma.co.uk
Copley, USA. See *Teva, USA.*
Copyfarm, Denm. Copyfarm A/S, Energivej 15, 5260 Odense S, Denmark.
Coradol, Ger. Coradol-Pharma GmbH, Ludwig-Erhard-Str. 10, 50129 Bergheim, Germany.
url: www.coradol.de
Coraltis, Israel. Coraltis Ltd, P.O. Box 168, Rosh Haayin 48091, Israel.
corax, Ger. corax pharma GmbH, Lendersbergstr. 86, 53721 Siegburg, Germany.
Corax, Neth. See *corax, Ger.*
Corbridge, Philipp. Corbridge Group Phils, Inc., 5/F Jater Bldg, 118 West Ave, Quezon City, Philippines.
Cordoba, Arg. Lab. Córdoba S.A., Rmo Negro 655, 6270 Huinca Renanco, Córdoba, Argentina.

Coria, USA. Coria Laboratories, 3909 Hulen St, Fort Worth, TX 76107, USA.

Corifel, Switz. Corifel SA, Via Clemente Maraini 9, 6907 Lugano 7, Switzerland.

Corixa, USA. Corixa Corp., 1900 9th Ave., Suite 1100, Seattle, WA 98104, USA.
url: www.corixa.com

Cork, Singapore. Cork International Pte Ltd, 20 Toh Guan Rd, 08-02 Accord Distri Centre, S 608839, Singapore.

Corman, Ital. Corman S.p.A., Via Sciesaa 10, 20084 Lacchiarella (MI), Italy.
url: www.corman.it

CORNE, Mex. Corporacion Operadora de Representaciónes y Negocios S.A. de C.V. (CORNE), Dr Vertis 894, Col. Narvarte, 3020 México D.F., Mexico.

Cornelli, Ital. Cornelli Consulting Sas, Corso Indipendenza 1, 20129 Milan, Italy.
url: www.cornelliconsulting.it

Cornerstone, USA. Cornerstone Biopharma Inc., 200 Regency Parkway, Suite 255, Cary, NC 27511, USA.
url: www.cornerstonebiopharma.com

Coronet, Indon. Coronet Crown PT, Jl Kupang Indah VIII No 9, 60225 Surabaya, Jawa Timur, Indonesia.

Corsa, Indon. Corsa Industries Ltd PT, Jl KS Tubun IIC/30, Jakarta, DKI Jaya, Indonesia.

Corsalud, Venez. Corporacion de Salud C.A., Av. J. M. Vargas, Edif. Artico Piso 1 Oficina 15B, Sta. Fe Norte Caracas, Caracas, Venezuela.

Cortec, Denm. Cortec Medical A/S, St Kongensgade 69, 1264 Copenhagen K, Denmark.
url: www.cortec.com

Cortecs, Irl. See *Provalis, UK.*

Cortex, Ital. Cortex Italia S.r.l., Via Vigoni 3, 20122 Milan, Italy.

Corypharma, Ital. Corypharma S.r.l., Via Bellagamba s.n., 60035 Jesi (AN), Italy.

Cos Farma, Ital. Cos-Farma S.r.l., Via di Portonaccio 23/B, 00159 Rome, Italy.

Cosan, Switz. Cosan GmbH, Chriesbaumstrasse 2, 8604 Volketswil ZH, Switzerland.

Cosma, Thai. Cosma Medical Co Ltd, 48 Soi Samarnchant-Barbos, Sukhumvit 42 Rd, Phrakanong, Klongtoey, Bangkok 10110, Thailand.

Cosmair, Canad. See *L'Oreal, Canad.*

Cosmea, Denm. Cosmea ACO A/S, Slotsmarken 18, 2970 Horsholm, Denmark.
url: www.cosmea.dk

Cosmetique Active, Switz. Cosmétique Active (Suisse) SA, Industriestrasse 9, 5432 Neuenhof., Switzerland.

Cosmetique Active, UK. Cosmetique Active (UK) Ltd, 255 Hammersmith Rd, London, W6 8AZ, UK.

Cosmo, Ital. Cosmo Pharmaceutical Solution & REsearch SpA, Via C Colombo 1, 20020 Lainate (MI), Italy.
url: www.comsospa.it

Cosmochema, Ger. Cosmochema Dr H.-H. Reckeweg GmbH, Dr Reckeweg-Str. 2-4, 76532 Baden-Baden, Germany.
url: www.cosmochema.de

Cosmofarma, Port. Cosmofarma, Lda (Laboratórios Cosmos), Rua Arco do Carvalhão 14, 1070 Lisbon, Portugal.

Cosmopharm, Gr. Cosmopharm E.P.E., Kazarma Korinthou, P.O. Box 42, 201 00 Korinthos, Greece.

Costec, Arg. Costec S.R.L. Esp. Dermatocosméticas, Av. Corrientes 1296 Piso 7 Dto.76, 1043 Buenos Aires, Argentina.

Cotek, Singapore. See *Zuellig, Singapore.*

CoTherix, USA. CoTherix Inc., 5000 Shoreline Court, Suite 101, South San Francisco, CA 94080, USA.
url: www.cotherix.com

Coup, Gr. Coup O.E., Ag. Varvaras 53, 172 35 Dafni, Greece.

Couzian, Fr. Laboratoires Gabriel Couzian, 1018 av. Tassigny, 71000 Macon, France.

Covan, S.Afr. See *Adcock Ingram, S.Afr.*

Cow & Gate, Irl. See *Nutricia, Irl.*

Cow & Gate, Israel. See *Guri, Israel.*

Cow & Gate, UK. See *Nutricia Clinical, UK.*

Cowik, Pol. Hurtownia Farmaceutyczna Cowik Sp. zo.o., ul. Powązkowska 59/151, 01-728 Warsaw, Poland.

Cox, Hong Kong. See *Unipharm, Hong Kong.*

Cox, Singapore. See *Pharmed, Singapore,* and *Sime Darby, Singapore.*

CP, Cz. See *Wockhardt, UK.*

CP, Israel. See *Propharm, Israel.*

CP Pharma, Switz. CP Pharma (Schweiz) AG, Emil Frey-Strasse 85, Postfach 922, 4142 Münchenstein 1, Switzerland.
url: www.cppharma.ch

CP Pharmaceuticals, Hong Kong. See *Vantone, Hong Kong.*

CP Pharmaceuticals, Irl. See *Wockhardt, UK.*

CP Pharmaceuticals, UK. See *Wockhardt, UK.*

CPH, Port. Companhia Portuguesa Higiene, SA, Rua dos Bem Lembrados 141, Manique, 2645-471 Alcabideche, Portugal.

Craveri, Arg. Craveri S.A.I.C., Arengreen 830, 1405 Buenos Aires, Argentina.
url: www.craveri.com.ar

Crawford, Cz. See *Crawford, UK.*

Crawford, UK. Crawford Pharmaceuticals, Furtho House, 20 Towcester Rd, Old Stratford, Milton Keynes, Buckinghamshire, MK19 6AQ, UK.
url: www.crawfordpharms.co.uk

Crealko, Arg. Crealko S.A., Paraguay 610 Piso 19, 1428 Buenos Aires, Argentina.

Creative Brands, Austral. Creative Brands P/L, 30 Bando Road, Springvale, VIC 3171, Australia.

Crefar, Port. Crefar, Lda, Rua da Madalena 171, 1149-032 Lisbon, Portugal.

Crinex, Fr. Laboratoires Crinex, B.P. 337, 92541 Montrouge cdx, France.

Crinos, Ital. Crinos S.p.A., Via Pavia 6, 20136 Milan, Italy.

Crinos, Pol. See *Medagro, Pol.*

Cris Flower, Ital. Cris Flower International S.n.c., Via Livorno 61, 00162 Rome, Italy.
url: www.crisflower.com

Crisdy-Na, Philipp. Crisdy-Na Drug Corp., G-Seven Sons & Co Bldg, 5/F 646 Muelle de Binondo, Estraude St, Binondo, Manila, Philippines.

Cristalfarma, Ital. See *Mediolanum, Ital.*

Cristalia, Braz. Cristalia Produtos Químicos Farmacêuticos Ltda, Av. Paoletti 363, 13970000 Itapira, SP, Brazil.
url: www.cristalia.com.br

Critical Therapeutics, USA. Critical Therapeutics, 60 Westview St, Lexington, MA 02421, USA.
url: www.criticaltherapeutics.com

Croma, Austria. Croma-Pharma GmbH, Industriezeile 6, A-2100 Leobendorf, Austria.

Croma, Philipp. Croma Medic Inc., Alegria Bldg, 2229 Don Chino Roces Ave, Makati City, Philippines.

Crombie, NZ. Crombie and Price, P.O. Box 121, Oamaru, New Zealand.
url: www.crombie-price.co.nz

Crookes Healthcare, UK. Crookes Healthcare Ltd, D6 Building, Nottingham, Nottinghamshire, NG90 6BH, UK.
url: www.crookes.co.uk

Crosslands, India. See *Ranbaxy, India.*

Crown, S.Afr. Crown Laboratories Ltd, P.O. Box 100187, Moreleta Plaza 0167, South Africa.

Crown, USA. Crown Laboratories Inc., P.O. Box 1425, Johnson City, TN 37605, USA.
url: www.crownlaboratories.com

Cruciani, Ital. Cruciani - Prodotti Crual Srl, Via Edoardo Scarfoglio 5, 00159 Rome, Italy.
url: www.crual.it

Cruz, Spain. Fernandez de la Cruz, Crta Sevilla Malaga Km 5.6, Alcalá de Guadaira, 41500 Seville, Spain.

Cryopharma, Mex. Cryopharma, Pizzard y Salud, KM 22.5 Carretera Guadalajara Morelia, Jalisco Zuniga, 45640 Guadalajara, Jalisco, Mexico.

CS, Fr. Laboratoires CS Dermatologie, 35 rue d'Artois, 75008 Paris, France.

CS, Hong Kong. See *Keller, Hong Kong.*

CS, Port. CS Portugal, Lda, Rua João de Deus 32, Venda Nova, 2700-488 Amadora, Portugal.

CSC, Austria. CSC Pharmaceuticals Handels-GmbH, Gewerbestrasse 18-20, A-2102 Bisamberg, Austria.

CSC, Cz. CSC Praha sro, Pernerová 32/10, 180 00 Prague 8, Czech Republic.

CSC, Ger. CSC Pharmaceuticals Germany GmbH, Sieker Landstr. 126, 22143 Hamburg, Germany.
url: www.csc-pharma.de

CSC, Hung. CSC Pharmaceuticals Llc Magyarországi Kereskedelmi Képviselete, Kakukk u 43, 1121 Budapest, Hungary.

CSC, Rus. CSC Ltd, Kashirskoe Highway 23, 115478 Moscow, Russia.

CSL, Austral. CSL Ltd, 45 Poplar Road, Parkville, VIC 3052, Australia.
url: www.csl.com.au

CSL, Braz. CSL Behring Com. de Prods. Farmacêuticos Ltda, Rua Olimpíadas 194, 5 andar, 04551-000 Vila Olimpia São Paulo, Brazil.

CSL, Cz. See *CSL, Ger.*

CSL, Denm. CSL Denmark ApS, Fruebjergvej 3, 2100 Copenhagen 0, Denmark.

CSL, Ger. CSL Behring GmbH, Philipp-Reis-Strasse 2, 65795 Hattersheim am Main, Germany.
url: www.cslbehring.de

CSL, Hung. CSL Behring, Hungary.

CSL, Malaysia. See *United Italian, Malaysia.*

CSL, NZ. CSL (NZ) Ltd, P.O. Box 62590, Central Park, Auckland 6, New Zealand.
url: www.csl.com.au

CSL, Port. See *CSL, Spain.*

CSL, Spain. CSL Behring, Av. Paisos Catalans 34, Esplugues de Llobregat, Barcelona 08950, Portugal.
url: www.cslbehring.es

CSL, UK. CSL Behring UK Ltd, Hayworth House, Market Place, Haywards Heath, West Sussex, RH16 1DB, UK.
url: www.cslbehring.co.uk

CSL, USA. CSL Biotherapies, P.O. Box 60446, 1020 First Ave, King of Prussia, PA 19406, USA.
url: www.cslbiotherapies-us.com

CSL Behring, Canad. CSL Behring Canada Inc., 1460 44 Metcalfe St, Ottawa, Ontario, KLP 6L5, Canada.

CSL Behring, USA. CSL Behring, P.O. Box 61501, 1020 First Ave, King of Prussia, PA 19406, USA.
url: www.cslbehring-us.com

CSL Biotherapies, Austral. CSL Biotherapies, 45 Poplar Rd, Parkville, Vic 3052, Australia.
url: www.cslbiotherapies.com.au

CSP, Fr. CSP, 76 av. du Midi, B.P. 77, 63802 Cournon cdx, France.

CT, Cz. See *CT, Ger.*

CT, Ger. ct-Arzneimittel GmbH, Lengeder Str. 42A, 13407 Berlin, Germany.
url: www.ct-berlin.de

CT, Ital. C.T., Laboratorio Farmaceutico S.r.l., Via D. Alighieri 69-71, 18038 San Remo (IM), Italy.

CT, Philipp. See *PharmAsia, Philipp.*

CT, Rus. See *Ratiopharm, Rus.*

CTI, Israel. See *CTS, Israel.*

CTS, Hong Kong. See *DKSH, Hong Kong.*

CTS, Israel. C.T.S. Chemical Industries Ltd, 4 Haharosh St, P.O.Box 10, Hod-Hasharon 45240, Israel.
url: www.cts.co.il

CTS, Rus. See *Lefnin, Rus.*

Cubist, Israel. See *Medison, Israel.*

Cubist, USA. Cubist Pharmaceuticals, 65 Hayden Ave., Lexington, MA 02421, USA.
url: www.cubist.com

Cullen & Davison, Irl. Cullen & Davison Ltd, Killenaule Rd, Fethard, Co Tipperary, Ireland.

Cullen & Davison, UK. See *Cullen & Davison, Irl.*

Culver, Austral. Alberto Culver (Aust) P/L, P.O. Box 253, Parramatta, NSW 2150, Australia.

Cumberland, USA. Cumberland Swan Holdings Inc., 1 Swan Drive, Smyrna, TN 37167, USA.
url: www.cumberlandswan.com

Cupal, UK. See *SSL, UK.*

Cuprocept, S.Afr. Cuprocept SA, P.O. Box 400, New Germany 3620, South Africa.

Curacel, Austral. Curacel International P/L, Suite 14, 1645 Ipswich Rd, Rocklea, QLD 4106, Australia.
url: www.curacel.com.au

Curaden, Ital. Curaden Healthcare srl, Via Don Vercesi 18, 20152 Milan, Italy.

Curagita, Cz. See *Curagita, Ger.*

Curagita, Ger. Curagita AG, Ringstr. 19 B, 69115 Heidelberg, Germany.

Curamed, Ger. CuraMED Pharma GmbH, Pforzheimer Str. 5, 76227 Karlsruhe, Germany.

Curaprox, UK. Curaprox UK Ltd, Unit 11, Harvard Industrial Estate, Kimbolton, Cambridgeshire, PE23 0NJ, UK.

Curasan, Austria. See *Curasan, Ger.*

Curasan, Ger. curasan AG, Lindigstr. 4, 63801 Kleinostheim, Germany.
url: www.curasan.de

Curatis, Ger. Curatis Pharma GmbH, Karl-Wiechert-Allee 76, 30625 Hannover, Germany.
url: www.curatis-pharma.de

Curex, Israel. Curex, P.O. Box 8366, New Industry Area, Netanya, Israel.

Curtis, Pol. Curtis Healthcare Sp. zo.o., ul. Żeromskiego 9, 60-544 Poznań, Poland.
url: www.curtish.com.pl

Cusi, Singapore. See *Pharmaforte, Singapore.*

Cusi, Venez. See *Leti, Venez.*

Cuxson, Gerrard, Canad. See *Cuxson, Gerrard, UK.*

Cuxson, Gerrard, UK. Cuxson, Gerrard & Co. Ltd, 125 Broadwell Rd, Oldbury, Warley, West Midlands, B69 3BF, UK.
url: www.cuxsongerrard.com

CV Therapeutics, USA. CV THerapeutics Inc., 3172 Porter Drive, Palo Alto, CA 94304, USA.
url: www.cvt.com

Cybermed, Austria. CBM Cybermed AG & Co. KEG, Postfach 50, A-3402 Klosterneuburg, Austria.

Cyclomedica, Irl. Cyclomedica Europe, Ulysses House, Foley St, Dublin, Ireland.
url: www.cylopharm.com

Cyclomedica, Port. See *Cyclomedica, Irl.*

Cynergen, Indon. Cynergen Health, Indonesia.
url: www.cynergenhealth.com

Cyntfarm, Pol. Cyntfarm Sp. zo.o., ul. Grunwaldzka 27, 05-800 Pruszków, Poland.
url: www.cyntfarm.com.pl

Cypress, USA. Cypress Pharmaceutical, 135 Industrial Blvd, Madison, MS 39110, USA.
url: www.cypressrx.com

Cypros, USA. See *Questcor, USA.*

CytoChemia, Ger. CytoChemia AG, Im Burgerstock 7, 79241 Ihringen, Germany.
url: www.cytochemia.de

Cytogen, Cz. See *Cytogen, USA.*

Cytogen, Israel. See *Megapharm, Israel.*

Cytogen, USA. Cytogen Corp., 600 College Rd East, Suite 3100, Princeton, NJ 08540, USA.
url: www.cytogen.com

Cytosol, Israel. See *Tzamal, Israel.*

Cytosol, USA. Cytosol Ophthalmics, 1325 William White Pl. NE, Lanoir, NC 28645, USA.
url: www.cytosol.com

CZ, Cz. CZ Pharma sro, Zeleny pruh 95/97, 140 00 Prague 4, Czech Republic.

Czet, Pol. Czet Pharma Inc. Sp. zo.o. Przedstawicielstwo w Polsce, ul. Belwederska 26/30, 00-585 Warsaw, Poland.
url: www.czetpharma.com.pl

Cziher, Hung. Cziher Hungary Kft, Kosztolányi D tér 8, 1114 Budapest, Hungary.

D & M, Chile. D & M Pharma SA, Los Conquistadores 2178, Providencia, Santiago, Chile.

DAB, Swed. DAB Dental AB, Box 423, 194 04 Upplands Väsby, Sweden.
url: www.dabdental.se

Dabur, Hung. Dabur Oncology Kft, Victor Hugo 45, 1132 Budapest, Hungary.

Dabur, India. Dabur Pharmaceuticals Ltd, Kaushambi, Ghaziabad 201 010, India.
url: www.dabur.com

Dabur, Philipp. Dabur Pharma Ltd, 19/F Philamlife Tower, 8767 Paseo de Roxas, Makati City, Philippines.

Dabur, Thai. See *Bioscience, Thai.*

Daehan, Singapore. See *Uni, Singapore.*

Daewon, Hong Kong. See *Ebewe, Hong Kong.*

Daewoo, Thai. See *Pharmaland, Thai.*

Daewoong, Singapore. See *Pharmaforte, Singapore.*

Daewoong, Thai. See *JDH Borneo, Thai.*

Dafra, Belg. Dafra Pharma NV, Slachthuisstraat 30/7, 2300 Turnhout, Belgium.
url: www.dafra.be

Dagra, Neth. Dagra-Pharma BV, Verrijn Stuartweg 60, 1112 AX Diemen, Netherlands.

Daiichi, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Daiichi, Indon. See *Kalbe, Indon.,* and *Otto, Indon.*

Daiichi, Jpn. Daiichi Pharmaceutical Co. Ltd, 1-8 Koami-cho Nihonbashi, Chuo-ku, Tokyo 103-8541, Japan.
url: www.daiichipharm.co.jp

Daiichi, Malaysia. See *Kyowa, Malaysia.*

Daiichi, Singapore. See *Kyowa, Singapore.*

Daiichi, Thai. Daiichi Pharmaceutical (Thailand) Ltd, 10 Fl, Boonmitr Building, Silom Rd, Bangkok 10500, Thailand.

Daiichi, USA. Daiichi Pharmaceutical Corp., 11 Phillips Parkway, Montvale, NJ 07645-1810, USA.
url: www.daiichius.com

Daiichi Sankyo, Fr. Daiichi Sankyo France SAS, 1 rue Eugène-et-Armand-Peugeot, 92500 Rueil-Malmaison, France.
url: www.daiichi-sankyo.fr

Daiichi Sankyo, Jpn. Daiichi Sankyo Co. Ltd, 3-5-1 Hihombashi-Honcho, Chuo-ku, Tokyo 103-8426, Japan.
url: www.daiichisankyo.co.jp

Daiichi Sankyo, Port. Daiichi Sankyo Portugal Lda, Lagoas Park, Edifício 11, 2740-270 Porto Salvo, Portugal.

Daiichi Sankyo, UK. Daiichi-Sankyo UK Ltd, Chiltern Place, Chalfont Park, Gerrards Cross, Buckinghamshire, SL9 0BG, UK.
url: www.daiichi-sankyo.co.uk

Daiichi Sankyo, USA. Daiichi Sankyo, Two Hilton Court, Parsippany, NJ 07054, USA.
url: www.sankyopharma.com

Dainippon, Jpn. Dainippon Sumitomo Pharmaceutical Co. Ltd, 2-6-8 Dosho-machi, Chuo-ku, Osaka 541-8524, Japan.
url: www.ds-pharma.co.jp

Daito, Jpn. Daito Corp., 326 Yokamachi, Toyamashi, Toyama 939-8221, Japan.
url: www.daitonet.co.jp

Dakota, Austral. Dakota Pharmaceuticals, 16 Byfield Street, North Ryde, NSW 2113, Australia.

Dakota, Cz. See *Dakota, Fr.*

Dakota, Fr. Laboratoires Dakota Pharm, 22 av. Galilée, 92350 Le Plessis-Robinson, France.

Dalkhimfarm, Rus. See *Masterlek, Rus.*

Dallas, Arg. Lab. Dallas S.A., Av. Cabildo 86, Piso 7 Of.702/4, 1426 Buenos Aires, Argentina.

Dal-Vita, Austral. Dal-Vita Products Australia P/L, P.O. Box 477, Manly, NSW 1165, Australia.

Damor, Ital. Farmaceutici Damor S.p.A., Via E Scaglione 27, 80145 Naples, Italy.

Danco, USA. Danco Laboratories, P.O. Box 4816, New York, NY 10185, USA.
url: www.earlyoptionpill.com

Danene, S.Afr. Danene Pharmaceuticals Pty Ltd, Unit 1-A-1, Persequor Close, 49 De Havilland Crescent, Persequor Technopark, Pretoria, South Africa.
url: www.danene.co.za

Danes, Arg. Lab. Danes Internacional, Division Grunenthal Argentina, Rivadavia 954 Piso 2, 1002 Buenos Aires, Argentina.

Daniels, USA. See *Jones, USA.*

Danipharm, Denm. Danipharm A/S, Englandsvej 350-356, 2770 Kastrup, Denmark.

Danipharm, Hong Kong. Danipharm Medic Team (Asia Pacific) Ltd, Unit 8-9, 31/F Clifford Ctr, 782 Cheung Sha Wan Rd, Kowloon, Hong Kong.
url: www.danipharm.com

Dankos, Indon. Dankos Indonesia PT, Enseval Bldg, Jl Letjend Suprapto, Cempaka Putih, 10510 Jakarta, DKI Jaya, Indonesia.

Dankos, Malaysia. See *Zyfas, Malaysia.*

Dankos, Philipp. See *Lakeside, Philipp.*

Dankos, Singapore. See *Zyfas, Singapore.*

Dankos, Thai. Dankos, Thailand.

Danlex, Philipp. Danlex Research Lab. Inc., 701 Bayview Intl Tower II, Roxas Blvd, Manila, Philippines.

Danpac, Indon. Danpac Pharma PT, Komplek Apartemen Permata Executive Lt 2, Jl Pos Pengumben, Raya Kelapa Dua, 11550 Jakarta, DKI Jaya, Indonesia.

Dansk, Israel. See *Promedico, Israel.*

Dansk Droge, Pol. See *Amis, Pol.*

Dansk Droge, Rus. See *Sanofi-Aventis, Rus.*

Dansk-Flama, Braz. Dansk-Flama Instituto de Fisiologia Aplicada, Rua Barão de Petrópolis 311, Rio Comprido, 20251-061 Rio de Janeiro, Brazil.

Danval, Spain. See *Servier, Spain.*

Dapha, Philipp. See *New Smart, Philipp.*

Daquimed, Port. Daquimed SA, Rua Dr. Afonso Cordeiro 194 - 1, 4450-001 Matosinhos, Portugal.
url: www.daquimed.com

Dar Al Dawa, Hong Kong. See *Primal, Hong Kong.*

Darier, Mex. Laboratorios Dermatologicos Darier S.A. de C.V., Av. Insurgentes sur 3579 Torre 3, Piso 8, M Hidalgo La Joya Olimpica, 14020 Mexico D.F., Mexico.
url: www.darier.com.mx

Dario Correia, Port. Dario Correia, Lda, Rua Duque de Palmela 25, 1250 Lisbon, Portugal.

Darnica, Pol. See *Alfpol, Pol.*

Darou Pakhsh, Rus. Darou Pakhsh Moscow, Dmitriya Ulyanova St 16/2, of. 69, 117292 Moscow, Russia.

Darrow, Braz. Darrow Laboratórios S.A., Rua Marques de Olinda 69, 22251-040 Rio de Janeiro, RJ, Brazil.

Dartmouth, USA. Dartmouth Pharmaceuticals Inc., 38 Church Ave, Wareham, MA 02751, USA.
url: www.ilovemynails.com

Darya-Varia, Indon. Darya-Varia Laboratoria PT, Graha Darya Varua 2/F, Jl Melawai Raya No 93, Kebayoran Baru, 12130 Jakarta, DKI Jaya, Indonesia.

Daudt, Braz. Laboratório Daudt Oliveira Ltda, Rua Simões da Mota 57, 21540-100 Rio de Janeiro, RJ, Brazil.
url: www.odontis.com.br

Davi, Port. Dávi Farmacêutica, Lda, Estrada da Barrosa, Elospark, Arm. 8, Algueirão, 2725-193 Mem Martins, Portugal.

David, India. Albert David Ltd, 15 Chittaranjan Ave, Kolkata 700 072, India.
url: www.albertdavidindia.com

Davis, Spain. See *Pfizer, Spain.*

Davur, Spain. Davur S.L., Teide 4, Parque Empresarial la Marina, San Sebastian de los Reyes, 28700 Madrid, Spain.
url: www.davur.com

Day, Ital. Day Farma S.a.s. di Franco Tovecci & C, Via Alessandro Manzoni 227, 80100 Naples, Italy.

Dayton, USA. Dayton Laboratories Inc., 7760 NW 56th St, Miami, FL 33166, USA.

DB, Fr. Laboratoires DB Pharma, 1 bis, rue du Cdt-Rivière, 94210 La Varenne-St-Hilaire, France.

DB, Switz. See *Uhlmann-Eyraud, Switz.*

DBL, Indon. See *Tempo Scan Pacific, Indon.*

DBL, NZ. See *Baxter, NZ.*

DBV, Fr. DBV Technologies, 88 av du Général-Leclerc, 92100 Boulogne-Billancourt, France.
url: www.diallertest.com; www.dbv-technologies.com

DC Labs, Canad. DC Labs Ltd, 795 Pharmacy Ave, Toronto, Ontario, M1L 3K2, Canada.

DCF, Port. Dermo Cosmética Farmacêutica Lda, Portugal.

DDD, Austria. See *delta pronatura, Ger.*

DDD, Hong Kong. See *Trinity, Hong Kong.*

DDD, Israel. See *Chemipal, Israel.*

DDD, Malaysia. See *People's, Malaysia.*

DDD, Singapore. See *Indrugco, Singapore.*

DDD, UK. DDD Ltd, 94 Rickmansworth Rd, Watford, Hertfordshire, WD1 7JJ, UK.
url: www.dddgroup.co.uk

DDSA Pharmaceuticals, UK. DDSA Pharmaceuticals Ltd, 310 Old Brompton Rd, London, SW5 9JQ, UK.

De Angeli, Ital. Istituto De Angeli Ph S.p.A., Via Lorenzini 8, 20139 Milan, Italy.

De Mayo, Braz. De Mayo Industrias Químicas e Farmacêuticas Ltda, Rua Barão de Petrópolis 109, 20251-061 Rio de Janeiro, RJ, Brazil.

De Salute, Ital. De Salute S.r.l., Via Cadore 7, 26015 Soresina (CR), Italy.

De Witt, Austria. See *De Witt, UK.*

De Witt, Denm. See *Ferring, Denm.*

De Witt, Hung. E C De Witt & Co Ltd, Hungary.

De Witt, Irl. See *Mayrs, Irl.*

De Witt, Neth. See *De Witt, UK.*

De Witt, Norw. See *Ferring, Norw.*

De Witt, NZ. See *Regional Health, NZ.*

De Witt, Pol. See *Ferring, Pol.*

De Witt, Port. See *De Witt, UK.*

De Witt, UK. E.C. De Witt & Co. Ltd, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS, UK.
url: www.ecdewitt.co.uk

Deafarma, Ital. Deafarma Srl, P.zza L Cadorna 11, 20123 Milan, Italy.

Debioclinic, Fr. Debioclinic SA, 2 rue du Nouveau Bercy, 94220 Charenton-le-Pont, France.
url: www.debiopharm.com

Debioclinic, Swed. See *Debioclinic, Fr.*

Deca, Ital. Laboratorio Chimico Deca S.r.l., Via Balzaretti 17, 20133 Milan, Italy.

Decafarma, Port. Decafarma Comércio de Produtos Farmacêuticos Lda, Rua Armindo Rodrigues 9-A, 1600-414 Lisbon, Portugal.

Declimed, Ger. See *Desitin, Ger.*

Decomed, Port. Decomed Farmacêutica, Lda, Rua Sebastião e Silva 56, 2745-838 Massama, Portugal.

Decrox, Spain. Decrox, Crta Sevilla Malaga Km 5.6, 41500 Alcala de Guadaira, Seville, Spain.

Dee, UK. Dee Pharmaceuticals Ltd, Office 3K6 Redwither Tower, Redwither Business Centre, Wrexham, Clwyd, LL13 9XT, UK.

Defiante, Neth. Defiante, Netherlands.

Defiante, Port. Defiante Farmacêutica Lda, Rua dos Ferreiros 260, 9000-082 Funchal, Madeira.

Defuen, Arg. Defuen S.A., Av. Dorrego 331, 1414 Buenos Aires, Argentina.

DeGa, Philipp. DeGa International Pharma Corp., Rm 314 Common Goal Tower, Finance cor. Industry St, Madrigal Business Park, Alabang, Muntinlupa City, Philippines.

Degorts, Mex. Degort's Chemical S.A. de C.V., Alhambra No. 310, Benito Juarez Portales, 03300 Mexico D.F., Mexico.

Degussa, UK. Degussa Ltd, Winterton House, Winterton Way, Macclesfield, Cheshire, SK11 0LP, UK.
url: www.degussa.com

Dekaz, Gr. Dekaz Ltd, 43 Thermopilon Str, Vrilissia 152 35, Greece.
url: www.dekaz.gr

Deklerht, USA. Deklerht, USA.

Del, Canad. Del Pharmaceutics (Canada) Inc., 316 Bayview Drive, Barrie, Ontario, L4N 3V7, Canada.

Del, USA. Del Pharmaceuticals Inc., 726 EAB Plaza, P.O. Box 9357, Uniondale, NY 11553, USA.
url: www.dellabs.com

Del Bel, Arg. Lab. Del Bel S.R.L., Avellaneda 1523, 5000 Cordoba, Argentina.

Del Saz & Filippini, Ital. Farmaceutici Del Saz & Filippini S.r.l., Via Dei Pestagalli 7, 20138 Milan, Italy.

Del Sol, Arg. Laboratorio Drogueria Del Sol SRL, Barragán 457, 1408 Buenos Aires, Argentina.

Delagrange, Indon. See *Soho, Indon.*

Delagrange, Port. See *Infar, Port.*

Delamac, Austral. Delamac Pharmaceuticals P/L, Suite 1/14 Hill Street, Spring Hill, Qld 4000, Australia.

Delattre-Hemapurine, Belg. Delattre-Hemapurine, Belgium.

Delegant, Gr. Delegant, Greece.

Delfi, Singapore. Delfi Singapore Pte Ltd, 7 Gul Circle 02-01/06, Keppel DistriCentre, S-629563, Singapore.

Delicias, Mex. Delicias S.A. de C.V., Productos Alimenticios, Apartado Postal No. 376, Zona Industrial, 31000 Chihuahua, Mexico.

Delmont, USA. Delmont Laboratories Inc., 715 Harvard Ave, P.O. Box 269, Swarthmore, PA 19081, USA.
url: www.delmont.com

Del-Ray, USA. See *Crown, USA.*

Delta, Arg. Delta Farma S.A., Bacacay 1820/22, 1406 Buenos Aires, Argentina.

Delta, Braz. Instituto Terapeutico Delta Ltda, Rua Engenheiro Guilherme Cristiano Frendez 827, 03477-000 São Paulo, SP, Brazil.

Delta, Fr. Laboratoires Delta Pharm, B.P. 27, 22170 Chatelaudren, France.

Delta, Irl. Delta Laboratories Ltd, 26 Airfield Court, Dublin 4, Ireland.

Delta, Port. Laboratórios Delta, Lda, Rua Direita de Massamá 148, 2745-751 Queluz, Portugal.
url: www.delta.pt

Delta, Singapore. See *Green Cross, Singapore.*

Delta BKB, Ital. Delta BKB S.r.l., V.le Emilio Po 224, 41100 Modena, Italy.

delta pronatura, Ger. delta pronatura Dr. Krauss & Dr. Beckmann GmbH & Co. KG, Kurt-Schumacher-Ring 15-17, 63329 Egelsbach, Germany.
url: www.delta-pronatura.de

Delta West, Malaysia. See *Pfizer, Malaysia.*

Deltapharm, Hong Kong. DeltaPharm Ltd, Flat D, 22/F, Boldwin Building, 16-18 Wah Sing St, Kwai Hing, Tsuen Wan, N.T., Hong Kong.

DeltaSelect, Cz. See *Reg, Cz.*

DeltaSelect, Ger. DeltaSelect GmbH, Benzstr. 5, 72793 Pfullingen, Germany.
url: www.deltaselect.de

DeltaSelect, Hung. See *DeltaSelect, Ger.*

DeltaSelect, Singapore. DeltaSelect, Singapore.

Dem, Turk. Dem İlaç Ltd. Şti., İkbaliye Mah. Acıbadem Cad. No: 56, Kadıköy, İstanbul, Turkey.
url: www.demilac.com

Demo, Gr. Demo Abee, 21 KM Athens - Lamia, 145 65 Krioneri, Greece.
url: www.demo.gr

Demo, Philipp. See *PharmAsia, Philipp.*

Demo, Thai. See *Pharmaland, Thai.*

Democal, Switz. Democal AG, Postfach 1045, 1701 Fribourg-Moncor, Switzerland.
url: www.democal.ch

Denamed, Norw. Denamed AS, Strømsv. 48, 2010 Strømmen, Norway.
url: www.denamed.no

Dendron, UK. See *DDD, UK.*

Dendy, Austral. Dendy Pharmaceuticals P/L, 44 Cromer St, East Brighton, VIC 3187, Australia.

Denk, Cz. See *Denk, Ger.*

Denk, Ger. E Denk OHG, Munich, Germany.

Denk, Hong Kong. See *Star, Hong Kong,* and *Universal, Hong Kong.*

Denk, Singapore. See *Luen Wah, Singapore.*

Denk, Thai. See *Sriprasit, Thai.*

Denolin, Belg. Denolin SA, Rue des Goujons 152, 1070 Brussels, Belgium.

Denorex, Canad. See *Denorex, USA.*

Denorex, USA. The Denorex Co., 3510 North Lake Creek Drive, Jackson, Wyoming 83001, USA.

Densmore, Fr. Laboratoires Densmore, 7 rue d emillo, BP 486, MC 98012, Monaco.

Dent, USA. See *Grandpa Brands, USA.*

Dentaid, Chile. Laboratorios Dentaid SA, Camino de la Colina 1432, Huechuraba, Santiago, Chile.

Dentaid, Spain. Dentaid, Parque Tecno del Valle, Ronda Can Fatjo 10, Cerdanyola, 08290 Barcelona, Spain.
url: www.dentaid.es

Dental Health Products, UK. See *Intrapharm, UK.*

Dental Warehouse, S.Afr. Dental Warehouse (Pty) Ltd, Private Bag X8, Wendywood 2144, South Africa.
url: www.dentalwarehouse.co.za

Dental-Kosmetik, Ger. Dental-Kosmetik GmbH, Katharinestr. 4, 01099 Dresden, Germany.
url: www.dental-kosmetik.de

Dentinox, Cz. See *Dentinox, Ger.*

Dentinox, Ger. Dentinox Gesellschaft für Pharmazeutische Präparate Lenk & Schuppan, Nunsdorfer Ring 19, 12277 Berlin, Germany.
url: www.dentinox.de

Dentinox, Hung. See *Penta, Hung.*

Dentinox, Pol. See *Miralex, Pol.*

Dentirol, Swed. Dentirol AB, Box 24046, 400 22 Göteborg, Sweden.
url: www.dentirol.se

Dentox, UK. Dentox Ltd, P.O. Box 1195, Warwickshire, CV35 0ZY, UK.
url: www.brushtox.co.uk

Dentsply, Austral. Dentsply (Australia) P/L, 11-21 Gilby Road, Mt. Waverley, VIC 3149, Australia.
url: www.dentsply.com.au

Dentsply, Denm. See *Dentsply, UK.*

Dentsply, Fin. See *Tamro, Fin.*

Dentsply, Fr. Dentsply France, 17 rue Michael-Faraday, 78180 Montigny-le-Bretonneux, France.
url: www.dentsply.fr

Dentsply, Ger. Dentsply DeTrey GmbH, De-Trey-Strasse 1, 78467 Constance, Germany.
url: www.dentsply.de

Dentsply, Ital. Dentsply Italia S.r.l., Via A Cavaglieri 26, 00100 Rome, Italy.
url: www.dentsply.it

Dentsply, Neth. See *Dentsply, UK.*

Dentsply, Norw. See *Dentsply, UK.*

Dentsply, NZ. Dentsply NZ, 58 Richard Pearse Drive, Auckland, New Zealand.
url: www.dentsply.com

Dentsply, Port. See *Dentsply, Ger.*

Dentsply, Swed. Dentsply Ltd, Box 2024, 128 21 Skarpnäck, Sweden.
url: www.dentsply.com

Dentsply, UK. Dentsply Ltd, Hamm Moor Lane, Addlestone, Weybridge, Surrey, KT15 2SE, UK.
url: www.dentsply.co.uk

Denver, Arg. Denver Farma S.A., Natalio Querido 2285, 1605 Munro, Buenos Aires, Argentina.

Dep, Canad. Dep Corporation, 5045 Orbitor Dr., Bldg 7, Suite 300, Mississauga, Ontario, L4W 4Y4, Canada.

DEP, USA. DEP Corp., 2101 East Via Arado, Rancho Dominguez, CA 90220, USA.

Depofarma, Ital. Depofarma S.r.l., Via Guindazzi 44/54, 80040 Pollena Trocchia (NA), Italy.

Depomed, USA. Depomed, 1360 O'Brien Dr, Menlo Park, CA 94025-1436, USA.
url: www.depomedinc.com

Deproco, UK. Deproco UK Ltd, Units R & S, Orchard Business Centre, St. Barnabas Close, Allington, Maidstone, Kent, ME16 0JZ, UK.
url: www.septodont.co.uk

DePuy, Ger. DePuy Orthopädie GmbH, a Johnson & Johnson Company, Mellinweg 16, 66280 Sulzbach, Germany.
url: www.jnjgateway.com

DePuy, UK. DePuy International Ltd, St Anthonys Rd, Leeds, West Yorkshire, LS11 8DT, UK.

Derek, Singapore. Derek Marketing Pte Ltd, Block 221 Henderson Rd, 05-11 Henderson Building, S 159557, Singapore.

Dergam, Fr. Laboratoires Dergam, 50 rue de Charonne, 75011 Paris, France.
url: www.dergam.com

Derma, UK. Derma UK Ltd, ARC Progress, Mill Lane, Stotford, Bedfordshire, SG5 4NY, UK.
url: www.derma.co.uk

Dermaclin, Mex. Dermaclin S.A. de C.V., Rebsamen 747, Col. Narvarte, 03020 Mexico D.F., Mexico.

Dermadolin, Turk. Dermadolin Üretim ve Pazarlama, Gürsel Mah. 28, Nisan Cad. No: 33/B, Kağıthane, İstanbul, 33400, Turkey.

Dermal, Israel. See *Trupharm, Israel.*

Dermal Laboratories, Irl. See *Fulcrum, Irl.*

Dermal Laboratories, UK. Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Hertfordshire, SG4 7QR, UK.
url: www.dermal.co.uk

Dermapharm, Austria. Dermapharm GmbH, Türkenstrasse 25/12, A-1090 Vienna, Austria.

Dermapharm, Ger. Dermapharm AG, Luise-Ullrich-Strasse 6, 82031 Grunwald, Germany.
url: www.dermapharm.de

Dermapharm, Neth. See *Dermapharm, Ger.*

Dermapharm, Switz. Dermapharm AG, Bösch 104, 6331 Hunenberg, Switzerland.
url: www.dermapharm.ch

Derma-Rx, Hong Kong. See *Dermatech, Hong Kong.*

Dermatech, Austral. Dermatech Laboratories, Unit 19, 167 Prospect Highway, Seven Hills, NSW 2147, Australia.
url: www.dermatech.com.au

Dermatech, Hong Kong. Dermatech Co, 13/F SB Commercial Building, 478 Nathan Rd, Kowloon, Hong Kong.
url: www.dermatech.com.hk

Dermatech, NZ. See *Dermatech, Austral.*

Dermatech, Philipp. See *Zenaust, Philipp.*

Dermatech, Singapore. See *Sime Darby, Singapore.*

Dermik, Canad. Dermik Laboratories Canada Inc., 6205 Airport Rd, Building B, Suite 100, Mississauga, Ontario, L4V 1E1, Canada.
url: www.dermik.com

Dermik, Hong Kong. See *Ebewe, Hong Kong.*

Dermik, Israel. See *Mediline, Israel.*

Dermik, Singapore. See *JDH, Singapore.*

Dermik, USA. See *Sanofi-Aventis, USA.*

DermoDuemila, Ital. DermoDuemila Srl, P.le F.il Macedone 140, 00124 Casalpalocco (RM), Italy.

Dermofarm, Spain. Dermofarm, Can Sant Joan, Rubi, 08191 Barcelona, Spain.
url: www.dermofarm.com

Dermofarma, Ital. Dermofarma Italia S.r.l., Via Beata Francesca 10, 83100 Avellino, Italy.

Dermol, USA. Dermol Pharmaceuticals Inc., 3807 Roswell Rd, Marietta, GA 30062, USA.

Dermophil Indien, Fr. Laboratoires du Dermophil Indien, B.P. 9, 61600 La Ferte-Mace, France.

Dermoprog, Ital. Dermoprog S.r.l., V.le Gorizia 25, 00100 Rome, Italy.

Dermoteca, Port. Dermoteca, SA, Estrada Nacional 117, 2720 Alfragide, Portugal.

Dermpharma, Philipp. Dermpharma Inc., 2266 Aurora Blvd, Pasay City, Philippines.

Dermtek, Canad. Dermtek Pharmaceuticals Ltd, 1600 Trans-Canada Highway, Suite 200, Dorval, Quebec, H9P 1H7, Canada.
url: www.reversa.ca

Desarrollo, Spain. Desarrollo Farma y Cosmeticos, Pa de la Castellana 143, 28046 Madrid, Spain.

Desatnik, S.Afr. MI Desatnik, P.O. Box 39359, Booysens 2041, South Africa.

Desitin, Cz. Desitin Arzneimittel SRN, Opletalová 25, P.O. Box 112, 111 21 Prague 1, Czech Republic.

Desitin, Denm. Desitin Pharma A/S, Havnegade 55, 1058 Copenhagen K, Denmark.
url: www.desitin.dk

Desitin, Fin. See *Algol, Fin.*

Desitin, Ger. Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany.
url: www.desitin.de

Desitin, Hung. Desitin Pharma Kft, Maros u 12/B IV em., 1122 Budapest, Hungary.

Desitin, Israel. See *Megapharm, Israel.*

Desitin, Neth. See *Byk, Neth.*

Desitin, Norw. Desitin Pharma A/S, Niels Leuchsv. 99, 1359 Eiksmarka, Norway.
url: www.desitin.no

Desitin, Pol. See *Ewopharma, Pol.*

Desitin, Swed. Desitin Pharma AB, Box 2064, 431 02 Mölndal, Sweden.
url: www.desitinpharma.se

Desitin, Switz. Desitin-Pharma GmbH, Gestadeckplatz 2, 4410 Liestal, Switzerland.
url: www.desitin.ch

Desma, Ger. Desma GmbH, Rheinallee 122, 55120 Mainz, Germany.

Desma, Pol. See *Desma, Ger.*

Desma, Port. See *Desma, Spain.*

Desma, Spain. Desma Laboratorio Farmaceutico, Cuatro Amigos 7, 28029 Madrid, Spain.
url: www.desmapharma.com

Desma, Switz. Desma Healthcare BV, Corso San Gottardo 32, 6830 Chiasso, Switzerland.

Desopharmex, Switz. Desopharmex AG, Muttenzerstrasse 107, 4133 Pratteln 1, Switzerland.

Desra, Turk. Desra, Turkey.

Dessau, Cz. See *Dessau, Ger.*

Dessau, Ger. See *Riemser, Ger.*

Deston, USA. See *Trx Pharma, USA.*

Detsaves (Ντετσαβες), Gr. NTETSAVES G. S. & SIA E.E., Kapodistriou 42, 104 32 Athens, Greece.

Deutsch Chinesische, Hong Kong. Deutsch Chinesische Apotheke (Maple Inc.), 809, Wellborne Commercial Ctr, 8 Java Rd, North Point, Hong Kong.

Deutsche, Chile. See *Sanofi Synthelabo, Chile.*

Deva, Fr. Deva (Lab), B.P. 3, 38880 Autrans, France.
url: www.lab-deva.com

Deva, Turk. Deva Holding İlaç Grubu, Büyükdere Cad. No:199/A, Levent, İstanbul, 80640 4., Turkey.
url: www.devaholding.com.tr

Deverge, Ital. Devergè Medicina e Medicalizzazione S.r.l., C.so Casale 206, 10132 Turin, Italy.

Devesa, Ger. Devesa Dr Reingraber GmbH & Co. KG, Heinkelstr. 8a, 76461 Muggensturm, Germany.
url: www.devesa.de
Devries, Israel. Devries & Co. Ltd, 51 Ahad Ha'am St, Tel Aviv 65206, Israel.
DeVriMed, Neth. DeVriMed, Sterappel 10, 9076 LD St Annaparochie, Netherlands.
Dex Biotec, Switz. Dex Biotec GmbH, Dorfstrasse 38, 8706 Meilen, Switzerland.
Dexa, Hong Kong. See *Health Alliance, Hong Kong.*
Dexa, Indon. Dexa Medica Pharm & Chem PT, Jl RS Fatmawati Versil No 33, (Apotik Cilandak) 2/F, Jakarta Selatan, DKI Jaya, Indonesia.
Dexa, Philipp. Dexa Medica Representative Office, Medical Plaza Bldg, Unit 1911, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.
Dexa, Pol. See *Cowik, Pol.*
Dexa, Singapore. See *Apotheca, Singapore,* and *JDH, Singapore.*
Dexcel, Denm. See *Vitaflo, Denm.*
Dexcel, Hung. See *Pro-Pharma, Hung.*
Dexcel, Israel. See *Dexxon, Israel.*
Dexcel, Neth. See *Dexcel, UK.*
Dexcel, Norw. See *Dexcel, UK.*
Dexcel, Port. See *Dexcel, UK.*
Dexcel, UK. Dexcel Pharma Ltd, 1 Cottesbrooke Park, Heartlands Business Park, Daventry, Northamptonshire, NN11 5YI, UK.
url: www.dexcel.com
DexGen, USA. DexGen Pharmaceuticals Inc., P.O. Box 675, Manasquan, NJ 08736, USA.
url: www.dexgen.com
Dexo, Fr. Laboratoires Dexo, 179 bureaux de la Colline, 92213 Saint-Cloud cdx, France.
Dexo, Port. See *Dexo, Fr.*
Dexo, Switz. See *Actipharm, Switz.,* and *Uhlmann-Eyraud, Switz.*
Dexo, USA. Dexo Pharma, 4424 W 24th Pl., Lawrence, KS 66047, USA.
Dexter, Arg. Dexter S.A.C.I. (Int'l), Humahuaca 4065, 1192 Buenos Aires, Argentina.
Dexter, Spain. Dexter Farmaceutica, Avda Virgen de Montserrat 215, 08026 Barcelona, Spain.
Dexxon, Israel. Dexxon, P.O. Box 50, Hadera 38100, Israel.
url: www.dexxon.co.il
Dexxon, Philipp. See *PharmAsia, Philipp.*
Dey, USA. Dey LP, 2751 Napa Valley Corporate Drive, Napa, CA 94558, USA.
url: www.deyinc.com
Dey's, India. Dey's Medical Stores (Manufacturing) Ltd, 62 Bondel Rd, Kolkata 700 087, India.
url: www.deysmedicallimited.com
DHA, Hong Kong. See *US Summit, Hong Kong.*
DHA, Malaysia. See *JDH, Malaysia.*
DHA, Singapore. Drug Houses of Australia (Asia) Pte Ltd, 2 Chia Ping Rd, 09-00 Haw Par Tiger Balm Building, S 619968, Singapore.
url: www.dha.com.sg
DHN, Fr. Laboratoires DHN, Nutrition Clinique, Le Haut-Montigne, 35370 Torce, France.
DHP, UK. DHP Healthcare Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QS, UK.
DHU, Cz. See *DHU, Ger.*
DHU, Ger. Deutsche Homöopathie-Union, Ottostr. 24, 76227 Karlsruhe, Germany.
url: www.dhu.de
DHU, Malaysia. See *Antah, Malaysia.*
DHU, Rus. See *German Homoeopathic, Rus.*
DHU, Spain. Laboratorios DHU Ibérica, S.A., Pol Ind Francolm Parcela 3, Nave 1-2, Apartado de Correos 1082, 43006 Tarragona, Spain.
url: www.dhu.es
Diaco, Ital. Laboratori Diaco Biomedicali S.p.A., Via Flavia 124, 34147 Trieste, Italy.
Diafarm, Rus. See *Akti-M, Rus.*
Diafarm, Spain. Diafarm, Avda Arraona 119-123, Barbera del Valles, 08210 Barcelona, Spain.
url: www.diafarm.es
Dial, Canad. The Dial Corporation, 3515 Quilter Court, Burlington, Ontario, L7M 3C3, Canada.
Diamedica, Venez. Laboratorio Diamédica, Av. Abraham Lincoln con Calle Olimpo, Torre Domus Piso 19, Sabana Grande, Caracas, Venezuela.
url: www.diamedica.com.ve
Diamo, Switz. DiaMo Narcotics GmbH, Postfach 30, 3613 Steffisburg, Switzerland.
Diamond, Philipp. Diamond Laboratories Inc., No 8 Feria Rd, Commonwealth Ave, Diliman, Quezon City, Philippines.
Diapit, Gr. DIAPIT, Ag. Konstantinou 6, 104 31 Athens, Greece.
Diatide, USA. See *Berlex, USA.*
Diatos, Fr. Diatos SA, 166 blvd du Montparnasse, 75014 Paris, France.
Diatos, Port. See *Diatos, Fr.*
Diatos, UK. See *Diatos, Fr.*
Diba, Mex. Laboratorios Diba, S.A. de C.V., Escorza No. 728, 44190 Guadalajara, Jalisco, Mexico.
url: www.dibafarma.com
Dibropharm, Ger. Dibropharm GmbH Distribution & Co. KG, Kleine-Dollen-Str. 5, 76532 Baden-Baden, Germany.
Dicamed, Swed. Dicamed AB, Djupdalsvägen 24, 192 51 Sollentuna, Sweden.
url: www.dicamed.se
Dickinson, USA. Dickinson Brands Inc., 31 East High St, East Hampton, CT 06424, USA.
url: www.witchhazel.com
Dicofar, Arg. Laboratorio Dicofar SRL, Fray Cayetano Rodriguez 3520, 1702 Ciudadela, Buenos Aires, Argentina.
Dicofarm, Ital. Dicofarm S.p.A., Via Vitorchiano 151, 00100 Rome, Italy.
url: www.dicofarm.it
Dieckmann, Ger. See *MSD, Ger.*
Diedenhofen, Thai. See *Oui Heng, Thai.*
Diele, Fr. Diele Distripharma, 18 av Albert-Einstein, 93152 Le Blanc-Mesnil cdx, France.
Diepharmex, Fr. Laboratoires Diepharmex, 26 rue de l'Industrie, 92400 Corbevoie, France.
Diet Erba, NZ. See *NZ Distributors, NZ.*
Dietaroma, Fr. Diétaroma SA, B.P. 4, 69240 Bourg de Thizy, France.
Dietary Foods, UK. Dietary Foods Ltd, Cumberland House, Brook Street, Soham, Cambridgeshire, CB7 5BA, UK.
url: www.dietaryfoods.co.uk
Dieterba, Ital. Dieterba, Via Migliara 45, 04100 Latina, Italy.
Diethelm, Malaysia. Diethelm Malaysia Sdn Bhd, 74 Jln Universiti, 46700 Petaling Jaya, Selangor, Malaysia.
url: www.diethelmkeller.com
Diethelm, Philipp. Diethelm Phils Inc., Brgy Mamplasan, Binan, Laguna, Philippines.
Diethelm, Singapore. Diethelm Singapore Pte Ltd, 34 Boon Leat Terrace, S 119866, Singapore.
url: www.diethelm.com.sg
Diethelm, Thai. Diethelm & Co. Ltd, Pharmaceutical Division, 280 New Rd, Bangkok 10100, Thailand.
url: www.diethelmpharma-thailand.com
Difa, Ital. Difa-Cooper S.p.A., Via Milano 160, 21042 Caronno Pertusella (VA), Italy.
Difass, Ital. Difass Industria Farmaceutica Dietetica SA, Via dei Casetti 25, 47893 Borgomaggiore, San Marino, Italy.
Diffucap, Braz. Diffucap-Chemobras Quim Farm Ltda, Rua Goias 1232, 21380-010 Rio de Janeiro, RJ, Brazil.
Digestive Care, USA. Digestive Care Inc., 1120 Win Drive, Bethlehem, PA 18017-7059, USA.
url: www.digestivecare.com
Dimethaid, Canad. Dimethaid Health Care Ltd, 1405 Denison St, Markham, Ontario, L3R 5V2, Canada.
url: www.dimethaid.com
Dimethaid, Ger. Dimethaid GmbH, Vor dem Schlosstor 9, 39164 Wanzleben, Germany.
url: www.dimethaid.de
Dimethaid, Port. See *Dimethaid, UK.*
Dimethaid, UK. Dimethaid UK Ltd, Spectrum House, 20-26 Cursitor St, London, EC4A 1HY, UK.
url: www.dimethaid.com
Dimportex, Spain. Dimportex, Deba Bahi 67, 08026 Barcelona, Spain.
Dinafarma, Braz. Laboratório Dinafarma Ltda, Avenida Major Alvim 155, 12942550 Atibaia, SP, Brazil.
Dincsa, Turk. Dinçsa Ilaç Sanayi ve Ticaret AS, I Organize Sanayi Bolgesi, Avar Cad. No 2, Sincan/Ankara, Turkey.
url: www.dincsa.com
Dinctas, Turk. Dinçtaş İlaç San. A.Ş., Mithatpasa Cad.No: 49/15, Kızılay, Ankara, 06420, Turkey.
Diomed, UK. See *Dermal Laboratories, UK.*
Dioptic, Canad. Dioptic Laboratories, Division of Akorn Pharmaceuticals Canada Ltd, 1405 Denison St, Markham, Ontario, L3R 5V2, Canada.
url: www.dioptic.com
Dioptra, Rus. Dioptra ZAO, Miklukho-Maklaya 16/10, 117871 Moscow, Russia.
Dipa, Indon. Dipa Pharmalab Intersains, Jl Kebon Jeruk Raya No 66, 11530 Jakarta, DKI Jaya, Indonesia.
Dirinco, Neth. Dirinco BV, Saffierborch 14, 5241 LN Rosmalen, Netherlands.
url: www.dirinco.com
Discotrade, Israel. See *Dexxon, Israel.*
Discovery, UK. Discovery Pharmaceuticals, The Old Vicarage, Market Place, Castle Donnington, Derbyshire, DE74 2JB, UK.
url: www.discoverypharma.co.uk
Discus, USA. Discus dental Inc., 8550 Higuera St, Culver City, CA 90232, USA.
url: www.discusdental.com
Dismed, S.Afr. Dismed Pharmaceutical Pty Ltd, Unit A3, Tilbury Business Park, Midbrand, 1685, South Africa.
Dispensapharm, Canad. See *Pfizer, Canad.*
Disperga, Austria. Dr C Szalagyl Disperga GmbH, Josefstadter Strasse 43, A-1080 Vienna, Austria.
Dispolab, Arg. Dispolab Farmaceutica Argentina SA, Libertad 976, Piso 2 B, Buenos Aires, Argentina.
Dispolab, Chile. Dispolab Farmaceutica SA, Santa Victoria 213, Providencia, Santiago, Chile.
Disprofarma, Arg. Disprofarma S.A., Virrey Cevallos 1643, 1135 Buenos Aires, Argentina.
url: www.disprofarma.com.ar
Disprovent, Arg. Disprovent S.A., Cervantes 2950, 1417 Buenos Aires, Argentina.
Dissolvurol, Mon. Laboratoires Dissolvurol, Le Concorde, 11 rue du Gabian, MC 98000, Monaco.
Dista, Spain. See *Lilly, Spain.*
Dista, Switz. See *Lilly, Switz.*
Dista, USA. See *Lilly, USA.*
Distri B3, Fr. Laboratoires Distri B3, rue Max Planck, Technopole de Chateau-Gombert, 13013 Marseille, France.
url: www.distrib3.com
Distrifarma, Port. Distrifarma, SA, Condomínio Industrial Queluz Park, Estrada Consiglieri Pedroso 80 Lote 3, Queluz de Baixo, 2745-553 Barcarena, Portugal.
Distriphar, UK. See *Sanofi-Aventis, UK.*
Distriquimica, Spain. See *Esteve, Spain.*
Divapharma, Cz. See *Divapharma, Ger.*
Divapharma, Ger. Divapharma-Knufinke Arzneimittel-werk GmbH, 12274 Berlin, Germany.
url: www.divapharm-knufinke.de
Divapharma, Hung. See *Bayer, Hung.*
Divapharma, Pol. See *Nepentes, Pol.*
Diviser Aquilea, Spain. See *Aquilea, Spain.*
Dixon-Shane, USA. See *RS, USA.*
DJ, USA. See *Biovail, USA.*
Djaya Bima Agung, Indon. See *Leiras, Indon.*
DKSH, Hong Kong. DKSH Hong Kong Ltd, 23/F Tower A, Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
url: www.dksh.com
DKSH, Indon. DKSH Healthcare, PT DKSH Tunggal, Suite 2206 22nd Floor, Menara Jamsostek Jalan, Jendral Gatot Subroto No 38, 12710 Jakarta, DKI Jakarta, Indonesia.
url: www.dksh.com
DKT, Philipp. DKT Philippines Inc., Suite 801 The Linden Suites, No 37 San MIguel Ave, Ortigas Ctr, Pasig City, Philippines.
DM, Braz. DM Indústria Farmacêutica Ltda, Av. Piracema 155, 06460-030 Barueri, SP, Brazil.
DMG, Ger. DMG Chemisch-Pharmazeutische Fabrik GmbH, Postfach: 530104, 22531 Hamburg, Germany.
DMG, Ital. DMG Italia S.r.l., Via Campello sul Clitunno 34, 00100 Rome, Italy.
DMS, Ital. DMS Farmaceutici SpA, Via Provinciale per Lecco 78, 22038 Travernerio (CO), Italy.
DNA, Mex. DNA Pharmaceuticals SA de CV, Blvd Avila Camacho 92-A Piso 12 PH, 53500 Naucalpan el Conde, Estado de Mexico, Mexico.
DNR, Arg. Laboratorio DNR Farma SRL, Hipolito Vieytes 147, 1603 Villa Martelli, Buenos Aires, Argentina.
Doak, Hong Kong. See *International Medical, Hong Kong.*
Doak, USA. See *Bradley, USA.*
DOC, Ital. DOC Generici S.r.l., Via Manuzio 7, 20124 Milan, Italy.
Docmed, S.Afr. Docmed, South Africa.
Docpharm, Ger. Docpharm Arzneimittelvertrieb GmbH & Co. KGaA, Reetzstr. 83, 76327 Pfinztal, Germany.
url: www.docpharm.de
Docpharma, Belg. Docpharma, 3001 Heverlee, Belgium.
url: www.docpharma.be
Docta, Spain. Docta, Gran Via de les Corts, Catalanes 774, 08013 Barcelona, Spain.
Doctum, Gr. Doctum Pharmaceutical S.A., K. T. Giokaris & Co., Marko Lulu 1 oxil km, 190 02 Peania Attiki, Greece.
Doetsch, Grether, Switz. Doetsch Grether AG, 4002 Basle, Switzerland.
url: www.doetschgrether.ch
Dolhay, Hung. Dolhay Klinika, Domoszló utja 18, 1037 Budapest, Hungary.
Dolisos, Belg. Dolisos SA, Rue Carli 5, 1140 Brussels, Belgium.
Dolisos, Canad. Dolisos, 1400 Hocquart St, St-Bruno, Quebec, J3V 6E1, Canada.
url: www.dolisos.ca
Dolisos, Cz. See *Boiron, Cz.*
Dolisos, Fr. See *Boiron, Fr.*
Dolisos, Ital. Laboratoires Dolisos Italia S.r.l., Via Pontina Vecchia km 34,200, 00040 Ardea (Rome), Italy.
url: www.dolisos.it
Dollder, Venez. Especialidades Dollder, Av. José María Vargas, Torre El Colegio, Piso 13, Santa Fé Norte, Caracas, Venezuela.
url: www.dollder.com
Dolorgiet, Cz. See *ProMed, Cz.*
Dolorgiet, Denm. See *Actavis, Denm.*
Dolorgiet, Ger. Dolorgiet GmbH & Co. KG, Otto-von-Guericke-Str. 1, 53757 St. Augustin/Bonn, Germany.
Dolorgiet, Hung. See *Budapharma, Hung.*
Dolorgiet, Neth. See *Dolorgiet, Ger.*
Dolorgiet, Pol. See *ProMed, Pol.*
Dolorgiet, Rus. See *Pro.Med, Rus.*
Dom, Spain. See *Salvat, Spain.*
Domestic, Rus. Domestic Medicines ZAO, Generala Dorokhova ul., d. 18, 119530 Moscow, Russia.
Dominguez, Arg. Lab. Dominguez S.A., Av. La Plata 2552, 1437 Buenos Aires, Argentina.
Dominion, Canad. See *Pharmascience, Canad.*
Dominion, India. Dominion Chemical Industries Ltd, Hosur Rd, Bommanahalli, Bangalore 560 068, India.
Dompe, Cz. See *Dompe, Ital.*
Dompe, Hung. Dompe, Hungary.
Dompe, Ital. Dompè Farmaceutici S.p.A., Via San Martino 12-12/A, 20122 Milan, Italy.
url: www.dompe.it
Dompe, Neth. See *Dompe, Ital.*
Dompe, Philipp. See *Metro, Philipp.*
Dompe, Pol. See *Perffarma, Pol.*
Dompe, Port. See *Dompe, Ital.*
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Dompe Biotec, Ital. See *Dompe, Ital.*
Dompe Biotec, Neth. See *Dompe, Ital.*
Doms-Adrian, Cz. See *Bouchara-Recordati, Fr.*
Don, Israel. See *Manon, Israel.*
Donell, USA. Donell Inc., 501 Fifth Ave, Suite 1214, New York, NY 10017, USA.
url: www.cxproducts.com
Donell DerMedex, USA. See *Donell, USA.*
Dong, Singapore. See *Pharmaforte, Singapore.*
Dong Kook, Hong Kong. See *CNW, Hong Kong.*
Dong Kook, Singapore. See *Polymedic, Singapore.*
Dong Kook, Thai. See *Charoen, Thai.*
Dong Wha, Philipp. See *Pharmazel, Philipp.*
Dong-A, Philipp. See *Metro, Philipp.*
Donini, Ital. Donini S.r.l., Via Ecce Homo 18, 37054 Nogara (VR), Italy.
Donmed, S.Afr. See *Organon, S.Afr.*
DORC, Neth. Dutch Ophthalmic Research Center International, Scheijdelveweg 2, 3214 VN Zuidland, Netherlands.
url: www.dorc.nl
Dormer, Canad. Dormer Laboratories Inc., 91 Kelfield St, Unit 5, Rexdale, Ontario, M9W 5A3, Canada.
url: www.dormer.com
Dorom, Ital. Dorom S.r.l., Via le G Richard 7, 20143 Milan, Italy.
Dorwest, UK. Dorwest Herbs Ltd, Shipton Gorge, Bridport, Dorset, DT6 4LP, UK.
url: www.dorwest.co.uk
Dosa, Arg. Lab. Dosa S.A., Girardot 1369, 1427 Buenos Aires, Argentina.
Doskar, Austria. Doskar Mag. Martin Pharm. Produkte, Schottenring 14, A-1010 Vienna, Austria.
Dossier, Neth. Dossier BV, Waardsedijk Oost 8, 3417 XJ Montfoort, Netherlands.
Douglas, Austral. Douglas Pharmaceuticals Australia Ltd, P.O. Box 7004, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.douglas.com.au
Douglas, Hong Kong. See *Hind Wing, Hong Kong.*
Douglas, Israel. See *Taro, Israel.*
Douglas, Malaysia. See *Schmidt, Malaysia.*
Douglas, NZ. Douglas Pharmaceuticals Ltd, P.O. Box 45-027, Auckland, New Zealand.
url: www.douglas.co.nz
Douglas, Singapore. See *Grafton, Singapore.*
Douglas, Thai. See *JDH Borneo, Thai.*
Dovalle, Braz. Farmoterapica Dovalle Indústria Química Farmacêutica Ltda, Rodovia SC 438 Km 3, 88701970 Tubarao, SC, Brazil.
Dow, USA. See *Bertek, USA.*
DP-Medica, Switz. DP-Medica SA, Pharmazeutische Produkte, Case postale 238, Fribourg, Switzerland.
DPS, Pol. DPS Pharma, Przedstawicielstwo w Polsce, ul. Balaton 9 A, 01-971 Warsaw, Poland.
Dr Janssen, Ger. Dr. Werner Janssen Nachf. Chem.-pharm. Produkte GmbH, Grenzstr. 2, 53340 Meckenheim, Germany.
Dr P, Ger. Dr. P. Medizinische Dienste by Dr. Panzer GmbH, Kieler Str. 2, 12163 Berlin, Germany.
url: www.lary-phary.com
Drac, Switz. Drac AG, Hauptgasse 29, 3280 Murten, Switzerland.
Drag, Chile. Drag Pharma Invetec SA, Las Dalias 3193, Macul, Santiago, Chile.
Dragenopharm, Israel. See *Taro, Israel.*
Drawer, Arg. Lab. Drawer S.A., Dorrego 127, 1878 Quilmes, Buenos Aires, Argentina.
Draximage, Canad. Draximage, 16751 Trans-Canada Highway, Kirkland, Quebec, H9H 4J4, Canada.
url: www.draximage.com
Draximage, Neth. See *Draximage, UK.*
Draximage, UK. Draximage (UK) Ltd, 5 Old Bailey, London, EC4M 7BA, UK.
Draximage, USA. See *Draximage, Canad.*
Draxis, Canad. Draxis Health Inc., 6870 Goreway Dr, Mississauga, Ontario, L4V 1P1, Canada.
DRD, Gr. D.R.D. EPE, Ag. Lavras 111, 111 41 Athens, Greece.
Dreluso, Ger. Dreluso Pharmazeutika, Dr Elten & Sohn GmbH, Marktplatz 5, 31840 Hessisch Oldendorf, Germany.
url: www.dreluso.de
Dresden, Cz. See *Asta Medica, Cz.*
Dresden, Ger. Arzneimittelwerk Dresden GmbH, Meissner Str. 35, 01445 Radebeul, Germany.
Dresden, Pol. See *Pliva Krakow, Pol.*
Driburg, Arg. Laboratorio Driburg Company SA, Warnes 3112, 1636 Vicente Lopez Olivos, Buenos Aires, Argentina.
Drogsan, Turk. Drogsan Doğa Kaynaklı İlaç-Hammaddeleri San. ve Tic. A.Ş., Oğuzlar Mah. 56. Sok 7/3, Balgat, Ankara, 06520, Turkey.
url: www.drogsan.com
Droreth, Israel. Matzkel I Droreth Ltd, 17 Lilienblum St, Tel Aviv 65132, Israel.
url: www.droreth.com

Drossapharm, Ger. Drossapharm GmbH, Weiler Str. 19-21, 79540 Lorrach, Germany.
url: www.drossapharm.com
Drossapharm, Israel. See *Gilco, Israel.*
Drossapharm, Switz. Drossapharm SA, Postfach 2660, 4002 Basle, Switzerland.
url: www.drossapharm.ch
Drovepat, Venez. Drovepat S.A., Av. Lecuna esq. de Velsquez 12-07 Planta Alta, Urb. Santa Rosalia Caracas, Caracas, Venezuela.
Drug Research, Ital. D.R. Drug Research S.r.l., Via F Turati 3, 22036 Erba (CO), Italy.
Drug Research, Singapore. See *Zyfas, Singapore.*
Drugtech, Chile. Laboratorio Drugtech, Av. Pedro de Valdivia 428, Providencia, Santiago, Chile.
Druide, Canad. Laboratoires Druide Inc., 154 Oneida Dr, Pointe-Claire, Quebec, H9R 1A8, Canada.
url: www.druide.ca
Du Pont, Cz. See *Torrex, Cz.*
Du Pont, Fr. See *BMS, Fr.*
Du Pont, Hong Kong. See *Keller, Hong Kong.*
Du Pont, Irl. See *United Drug, Irl.*
Du Pont, Israel. See *Teva, Israel.*
Du Pont, Singapore. See *Boots, Singapore.*
Du Pont, USA. See *BMS, USA.*
Duchesnay, Canad. Duchesnay Inc., 2925 Industrial Blvd, Laval, Quebec, H7L 3W9, Canada.
url: www.duchesnay.com
Ducray, Fr. See *Pierre Fabre, Fr.*
Ducto, Braz. Lab. Ducto Ind. Farm. Ltda, Rua VPR 3 Quadra 2-A, Modulos 20/21 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.ducto.com.br
Dumex, Malaysia. Dumex (Malaysia) Sdn Bhd, 1 Jln 205, 46050 Petaling Jaya, Selangor, Malaysia.
url: www.youngnutrition.net
Dumex, NZ. See *CSL, NZ.*
Dumex, Philipp. Dumex Philippines Inc., 3/F IDC Bldg, E Rodriguez Jr Ave, Bo Ugong Norte Libis, Quezon City, Philippines.
Dumex, Singapore. Dumex, Representative Office, 9 Third Lok Yang Rd, S 628004, Singapore.
url: www.dumex.com.sg
Dumex, Switz. See *Dumex-Alpharma, Switz.*
Dumex-Alpharma, Switz. See *Medinova, Switz.*
Dumex-Alpharma, Thai. See *Stada, Thai.*
Dumont, Arg. Quím. Dumont Freres S.R.L., Saladillo 2452/68, 1440 Buenos Aires, Argentina.
Dunar, Spain. Dunar, Arequipa 1, 28043 Madrid, Spain.
Duncan, Arg. Laboratorios Duncan S.A., Av. San Martmn 6340/42, 1419 Buenos Aires, Argentina.
url: www.duncanbioquim.com.ar
Duncan, Hong Kong. See *Pan-Well, Hong Kong.*
Duncan, Philipp. Duncan Pharmaceuticals Inc., 2266 Don Chino Roces Ave, Makati City, Philippines.
Duncan, Flockhart, Irl. See *GSK, Irl.*
Dunhall, USA. Dunhall Pharmaceuticals Inc., Highway 59N, P.O. Box 100, Gravette, AR 72736, USA.
Dunner, Switz. Dr Dünner SA, Artherstrassec 60, 6405 Immensee, Switzerland.
Duomed, Switz. Duomed AG, 9533 Kirchberg, Switzerland.
Duopharm, Ger. Duopharm GmbH, Grassingerstr. 9, 83043 Bad Aibling, Germany.
url: www.duopharm.de
Duopharma, Hong Kong. See *Weston, Hong Kong.*
Duopharma, Malaysia. Duopharma Malaysia Sdn Bhd, Lot 2599 Jalan Seruling 59, Kaw 3, Taman Klang Jaya, 41200 Klang, Selangor, Malaysia.
url: www.duopharma.com.my
Duopharma, Philipp. Duopharma Trade (Phils) Inc., Skrene Properties Bldg, 3759 Cuenca cor Emilia St, Palanan, Makati City, Philippines.
Duphar, NZ. See *Solvay, NZ.*
Duphar Nezel, Spain. See *Solvay, Spain.*
Duphar-Interfran, Thai. See *Union Medical, Thai.*
Dupomar, Arg. Dupomar S.A.C.I.F., Venezuela 174, 1095 Buenos Aires, Argentina.
Dura, USA. See *Elan, USA.*
Duramed, USA. See *Barr, USA.*
Durascan, Denm. DuraScan Medical Products AS, C F Tietgens Boulevard 40, 5220 Odense S, Denmark.
url: www.durascan.com
Durban, Spain. Durban, Santos Zarate 20, 04004 Almeria, Spain.
Durbin, UK. Durbin Plc, 180 Northolt Rd, South Harrow, Middlesex, HA2 0LT, UK.
url: www.durbin.co.uk
Durex, Canad. Durex Canada, Division of SSL Canada Inc., 100 Courtland Ave, Concord, Ontario, L4K 3T6, Canada.
url: www.durex.com
Durex, USA. Durex Consumer Products, 3585 Engineering Drive, Suite 200, Norcross, GA 30092-2820, USA.
url: www.durex.com
DUSA, USA. DUSA Pharmaceuticals Inc., 25 Upton Drive, Wilmington, MA 01887, USA.
url: www.dusapharma.com
Dutch Lady, Malaysia. Dutch Lady Milk Industries Bhd, 13 Jln Semangat, 46200 Petaling Jaya, Selangor, Malaysia.
Dutch Ophthalmic, USA. Dutch Ophthalmic USA, One Little River Rd, P.O. Box 968, Kingston, NH 03848, USA.
url: www.dorc.nl
Dutec, Austral. Dutec Diagnostics P/L, P.O. Box 79, Croydon, NSW 2132, Australia.
Dyckerhoff, Ger. Dyckerhoff Pharma GmbH & Co., Robert-Perthel-Str. 49, 50739 Cologne, Germany.
url: www.dyckerhoff-pharma.de
DYN, Israel. DYN Diagnostics, Ha'eshel 7, 3063 Caesarea Industrial Park, Israel.
url: www.dyn.co.il
Dynacren, Ital. Dynacren Laboratorio Farmaceutico del Dott. A. Francioni e di M. Gerosa S.r.l., Via P Nenni 12, Loc Malpensa, 28053 Castelletto Ticino (NO), Italy.
url: www.dynacren.it
Dynamic, Philipp. Pharma Dynamic Inc., 2/F PDI Bldg, 71 Maysilo St, Mandaluyong City, Philippines.
Dynamit, Austria. Dynamit Nobel Wien GmbH, A-8813 St Lamprecht, Austria.
Dynasty, Philipp. Dynasty Pharmaceuticals, 2432 Legarda St, Sampaloc, Manila, Philippines.
Dyntec, Cz. Dyntec sro, Terezín, Czech Republic.
Dzwon, India. Dzwon Remedies, 75/C Government Industrial Estate, Kandivli West, Mumbai 400 067, India.
e5, USA. e5 Pharma LLC, 3550 NW 126th Ave, Coral Springs, FL 33065, USA.
url: www.e5pharma.com
Eadriex, Philipp. Eadriex Pharmaceuticals Phils Inc., 147 Scout Railos, Kamuning, Quezon City, Philippines.
Eagle, Austral. Eagle Pharmaceuticals P/L, P.O. Box 927, Castle Hill, NSW 1765, Australia.
url: www.eaglepharmaceuticals.com.au
East India Pharma, India. East India Pharmaceutical Works Ltd, 6 Little Russel St, Kolkata 700 071, India.
Eastern Pharmaceuticals, Irl. See *Intra Pharma, Irl.*
Eastern Pharmaceuticals, UK. Eastern Pharmaceuticals Ltd, Coomb House, St. Johns Rd, Isleworth, Middlesex, TW7 6NA, UK.
url: www.eastern-pharmaceuticals.co.uk
e+b, Austria. See *e+b, Ger.*
e+b, Ger. e+b GmbH & Co. Pharma KG, Emil-Kemmer-Str. 33, 96103 Hallstadt, Germany.
e+b, Hung. e+b, Hungary.
Ebedent, Gr. Ebedent, 4 Themistokleous, 106 78 Athens, Greece.
url: www.ebedent.gr
Eberth, Denm. See *Alternova, Denm.*
Eberth, Ger. Dr. Friedrich Eberth Arzneimittel, Hohenburger Str. 39, 92289 Ursensollen, Germany.
url: www.eberth.de
Eberth, Switz. See *Uhlmann-Eyraud, Switz.*
Ebewe, Austria. Ebewe Pharma GmbH Nfg KG, Mondseestrasse 11, A-4866 Unterach am Attersee, Austria.
url: www.ebewe.com
Ebewe, Cz. See *Avalanche, Cz.*
Ebewe, Ger. See *Ebewe, Austria.*
Ebewe, Hong Kong. Ebewe Pharma (ASIA) Ltd, 8/F Eastwood Ctr, 5 A Kung Ngam Village Rd, Shaukeiwan, Hong Kong.
Ebewe, Hung. See *Medico Uno, Hung.*
Ebewe, Israel. Ebewe, Israel.
Ebewe, Pol. Ebewe Pharma GmbH Nfg. KG Sp.k., Przedstawicielstwo w Polsce, ul. Hauke-Bosaka 16a, 01-540 Warsaw, Poland.
url: www.ebewe.com
Ebewe, Rus. Ebewe Pharma GmbH Nfg.KG, 3-II Samotchnyi, per D3, st 2, 127473 Moscow, Russia.
url: www.ebewe.ru
Ebewe, Thai. See *Schumit, Thai.*
Ebi, Switz. Ebi-Pharm AG, Lindachstrasse 8c, 3038 Kirchlindach, Switzerland.
url: www.ebipharm.ch
EBN, Fr. EBN (Lab), B.P. 84, 68310 Wittelsheim, France.
url: www.ebnlab.com
Ebos, NZ. Ebos Group Ltd, P.O. Box 411, Christchurch, New Zealand.
url: www.ebos.co.nz
Echo, Ital. Echo S.r.l., Via O Rinuccini 40, 50144 Florence, Italy.
EciFarma, Chile. EciFarma SA, Carmen Covarrubias 271, Nunoa, Santiago, Chile.
Eco, S.Afr. Eco Pharmaceuticals (Pty) Ltd, South Africa.
Ecobi, Hong Kong. See *Rich Plan, Hong Kong.*
Ecobi, Ital. Farmaceutici Ecobi s.a.s., Via E. Bazzano 26, 16019 Ronco Scrivia (GE), Italy.
Ecobrands, UK. Ecobrands Ltd, 3 Adam & Eve Mews, London, W8 6UG, UK.
url: www.ecobrands.com
Ecofarm, Ital. Ecofarm Group Srl, Via F Vezzani 99/r, 16159 Genoa Rivarolo, Italy.
Ecolab, Austria. Ecolab GmbH, Erdbergstrasse 29, A-1030 Vienna, Austria.
Ecolab, Ger. Ecolab Deutschland GmbH, Reisholzer Werftstr. 38-42, 40589 Dusseldorf, Germany.
Ecolab, Ital. Henkel Ecolab S.p.A., Via Morozzo Della Rocca 6, 20123 Milan, Italy.
Ecolab, Neth. Ecolab BV, Edisonbaan 9-11, 3439 MN Nieuwegein, Netherlands.
Eco-Med-Poll, Cz. Eco-Med-Poll Prague, Na vlastni pudě, 102 00 Prague 2, Czech Republic.
Econo Med, USA. Econo Med Pharmaceuticals Inc., 4305 Sartin Rd, Burlington, NC 27217-7522, USA.
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Econophar, Belg. Econophar s.a.r.l., Rue Anatole France 119, 1030 Brussels, Belgium.
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Ecosol, Switz. Ecosol AG, Hinterbergstrasse 24, 6330 Cham, Switzerland.
url: www.ecosol.ch
ECR, USA. ECR Pharmaceuticals, P.O. Box 71600, Richmond, VA 23255, USA.
url: www.ecrpharmaceuticals.com
Ecupharma, Ital. Ecupharma S.r.l., Via Mazzini 20, 20123 Milan, Italy.
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Eczacibasi, Rus. Eczacibasi Ilac Sanayi, Mal. Lubyanka ul. 16/4/11, 1, pod. 3, 101000 Moscow, Russia.
Eczacibasi, Turk. Eczacıbaşı İlaç A.Ş., Büyükdere Cad., Ali Kaya Sok. No:7, Levent, İstanbul, 80640 1., Turkey.
url: www.eis.com.tr
Eczacibasi-Baxter, Turk. Eczacıbaşı-Baxter Hastane Ürünleri San. ve Tic. A.Ş., Ayazağa Cendere Yolu No: 19, Şişli, İstanbul, Turkey.
url: www.eczacibasi-baxter.com.tr
Eczane, Arg. Lab. Eczane Pharma S.A., Laprida 43, 1870 Avellaneda, Buenos Aires, Argentina.
Eden, S.Afr. See *Boots Healthcare, S.Afr.*
Ederka, Mex. Farmaceuticos Ederka S.A. de C.V., Calle 3 Num. 1, Fracc. Ind. Benito Juarez, 76130 Queretaro Qro, Mexico.
Edigen, Spain. Edigen, Chile 8-2a planta, oficina 203, Las Matas, 28290 Madrid, Spain.
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Edmond, Denm. See *Pharmacuro, Denm.*
Edmond, Port. See *Edmond Pharma, Ital.*
Edmond Pharma, Ital. Edmond Pharma S.r.l., Via dei Giovi 131, 20037 Paderno Dugnano (MI), Italy.
Edol, Port. Edol, SA, Av 25 de Abril 6-6A, Linda-a-Velha, 2795-195 Linda-a-Velha, Portugal.
Edwards, Austria. See *Edwards, Ger.*
Edwards, Ger. Edwards Lifesciences Germany GmbH, D85716-Unterschleissheim, Germany.
Edwards, Spain. Edwards Lifesciences, Avda Juan de la Cierva 27, Paterna, 46980 Valencia, Spain.
url: www.edwards.com
Edwards, USA. Edwards Pharmaceuticals Inc., 111 Mulberry St, Ripley, MS 38663, USA.
Edwards Lifesciences, USA. Edwards Lifesciences, One Edwards Way, Irvine, CA 92614, USA.
url: www.edwards.com
Efamol, Austral. Efamol Ltd, P.O. Box 6745, Baulkham Hills BC, NSW 2153, Australia.
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Efamol, UK. See *Nutricia Clinical, UK.*
Efarmes, Spain. See *Lacer, Spain.*
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Effik, Fr. Laboratoires Effik, Burospace, 91571 Bievres cdx, France.
url: www.effik.com
Effik, Ital. Effik Italia S.p.A., Via A Lincoln 7/a, 20092 Cinisello Balsamo (MI), Italy.
Effik, Port. Laboratórios Effik Sociedade Unipessoal Lda, Rua Consiglieri Pedroso No 123, Queluz de Baixo, 2730-065 Barcarena, Portugal.
Effik, Spain. Effik, Antonio de Cabezon 27 5, Planta Ed Alfa Laval, 28034 Madrid, Spain.
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EGIS, Hung. EGIS Pharmaceuticals, Hungária krt 179-187, 1146 Budapest, Hungary.
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Egis, Neth. See *Egis, UK.*
Egis, Philipp. See *PharmAsia, Philipp.*
Egis, Pol. Egis Polska Sp. zo.o., ul. Powązkowska 44 c, 01-755 Warsaw, Poland.
url: www.egis.pl
Egis, Rus. Egis Pharmaceuticals Ltd, Krasnaya Presnya ul. 1-7, Of. 560, 123242 Moscow, Russia.
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Egis, Thai. See *Medline, Thai.*
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Ego, Austral. Ego Pharmaceuticals P/L, 21-31 Malcolm Rd, Braeside, VIC 3195, Australia.
url: www.egopharm.com.au
Ego, Hong Kong. See *Lision Hong, Hong Kong.*
Ego, Malaysia. See *Somedico, Malaysia.*
Ego, NZ. See *Douglas, NZ.*
Ego, Singapore. See *Grafton, Singapore.*
Ehrenhofer, Austria. Dr. F. Ehrenhöfer GmbH, Triester Strasse 36, A-2620 Neunkirchen, Austria.
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Eight, Spain. Eight Farmaceutica, Javier del Quinto 6, 28043 Madrid, Spain.
Eiken, Jpn. Eiken Chemical Co. Ltd, 5-26-20 Oji, Kita-ku, Tokyo 114-0002, Japan.
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Eisai, Ger. Eisai GmbH, Lyoner Str. 36, 60528 Frankfurt, Germany.
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Eisai, Hong Kong. Eisai (Hong Kong) Co. Ltd, Rm 2008, Fortress Tower, 250 King's Rd, North Point, Hong Kong.
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Eisai, Hung. See *Eisai, UK.*
Eisai, Indon. Eisai Indonesia PT, Ratu Plaza Tower (Office) 11/F, Jl Jend Sudirman No 9, 10270 Jakarta, DKI Jaya, Indonesia.
Eisai, Irl. See *Eisai, UK.*
Eisai, Jpn. Eisai Co. Ltd, 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan.
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Eisai, Neth. See *Eisai, UK.*
Eisai, Philipp. HI-Eisai Pharmaceutical Inc., 20/F Multinational Bancorporation Ctr, 6805 Ayala Ave, Makati City, Philippines.
Eisai, Port. See *Eisai, UK.*
Eisai, Rus. See *Janssen-Cilag, Rus.*
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EL, Philipp. See *Cathay, Philipp.*, and *Celsus, Philipp.*
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Eladon, UK. Eladon Ltd, P.O. Box 111, Bangor, Gwynedd, LL57 1ZB, UK.
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Elaiapharm, Switz. See *Interdelta, Switz.*
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Elan, Cz. See *Elan, Irl.*
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Elan, Ger. Elan Pharma GmbH, Rosenkavalierplatz 8, 81925 Munich, Germany.
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Elan, Hung. Elan, Hungary.
Elan, Irl. Elan Pharma (Ireland) Ltd, Monksland, Athlone, Co. Westmeath, Ireland.
url: www.elan-pharma.ie
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Elan, UK. Elan Pharma Ltd, Abel Smith House, Gunnels Wood Rd, Stevenage, Hertfordshire, SG1 2FG, UK.
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Elan, USA. Elan Phamaceuticals, 7475 Lusk Blvd, San Diego, CA 92121, USA.
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Elanda, Pol. Elanda Zakład Produkcji Środków Farmaceutycznych, ul. Sportowa 9, 97-340 Rozprza, Poland.
url: www.elanda.pl
Elder, India. Elder Pharmaceuticals Ltd, Elder House, C-9 Dalia Industrial Estate off New Link Rd, Andheri West, Mumbai 400 053, India.
Elea, Arg. Laboratorio Elea S.A.C.I.F.y.A., Sanabria 2353 Piso 1, 1417 Buenos Aires, Argentina.
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Elea, Mex. Laboratorios Elea México SA de CV, Marcelo 9, 3100 Benito Juárez del Valle, Mexico.
Electra-Box, Fin. Electra-Box Pharma Oy, Ojamonharjuntie 21, 08100 Lohja, Finland.
url: www.electrabox.com
Electra-Box, Swed. Electra-Box Pharma AB, Box 2035, 135 02 Tyreso, Sweden.
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Electramed, Irl. Electramed Ltd, U2 Kinsealy Business Park, Kinsealy, Co. Dublin, Ireland.
url: www.electramed.ie
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url: www.elisium.com.ar
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Ellem, Swed. Ellem Läkemedel AB, Svärdvägen 13, 182 12 Danderyd, Sweden.
url: www.ellem.nu
Elmor, Venez. Laboratorios Elmor S.A., Av. Eugenio Mendoza, Centro Letonia, Piso 16, La Castellana, Apartado Postal 80444, Caracas 1062, Venezuela.
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Elofar, Braz. Laboratório Farmacêutico Elofar Ltda, Rua Tereza Cristina 85, 88075-970 Florianopolis, SC, Brazil.
Elpen (Ελπεν), Gr. Elpen A.E., 95 Marathonos Ave, 190 09 Pikermi, Greece.
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Elpen, Singapore. See *Green Cross, Singapore.*
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Elvetium, Arg. Elvetium S.A., Catulo Castillo 2437, 1261 Buenos Aires, Argentina.
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Embil, Philipp. See *Zuellig, Philipp.*
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Embil, Turk. Embil İlaç Ltd. Şti., P. K. 226, Şişli, İstanbul, Turkey.
url: www.embli.com
Emcure, Thai. See *Pharmadica, Thai.*
Emerging Pharma, Malaysia. Emerging Pharma Sdn Bhd, Phileo Damansara II, Lot 3A03, Block B, No 15, Jln 16/11, Off Jln Damansara, 46350 Petaling Jaya, Selangor, Malaysia.
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Emerging Pharma, Singapore. See *Sime Darby, Singapore.*
Emo-Farm, Pol. EMO-Farm Sp. zo.o., ul. Łódzka 157, 95-054 Ksawerów k/Łodzi, Poland.
url: www.emo-farm.pl
Emonta, Austria. Emonta Pharma GmbH, Weidelstrasse 21, A-1100 Vienna, Austria.
Emonta, Switz. Emonta GmbH, Unt Rebberg-weg 123, 4153 Reinach, Switzerland.
Empresa de Nutricion, Arg. Empresa de Nutrición Argentina SRL, Florida 1595, 8003 Bahía Blanca, Buenos Aires, Argentina.
EMS, Braz. EMS Ind. Farmacêutica Ltda, Rodovia SP 101, Km 08, 13186-481 Hortolandia, SP, Brazil.
url: www.ems.com.br
Enaleni, S.Afr. Enaleni Pharmaceuticals, P.O.Box 32003, Mobeni 4060, South Africa.
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Enapharm, Swed. Enapharm AB, Box 30, 745 21 Enköping, Sweden.
Encysive, Cz. See *Encysive, UK.*
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Encysive, UK. Encysive (UK) Ltd, Alder Castle House, 10 Noble St, London, EC2V 7QJ, UK.
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Endo, USA. Endo Pharmaceuticals Inc., 110 Endo Bvld, Chadds Ford, PA 19317, USA.
url: www.endo.com
Endurance, USA. Endurance Products Co., P.O. Box 230489, Tigard, OR 97223, USA.
url: www.endur.com
Endure, Philipp. Endure Medical Inc., 17A Belvedere Tower, San Miguel Ave, Ortigas Complex, Pasig City, Philippines.
Energon, Gr. Energon Farmakevtiki, Dilou 13, 121 34 Peristeri, Greece.
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Engelhard, Ger. Engelhard Arzneimittel GmbH & Co. KG, Herzbergstr. 3, 61138 Niederdorfelden, Germany.
url: www.engelhard-am.de
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Enila, Braz. Laboratório Enila S.A., Rua Viúva Cláudio 355, 20970-030 Rio de Janeiro, RJ, Brazil.
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url: www.ensinger.de
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Enturia, UK. Enturia Ltd, Reigate Place, 43 London Rd, Reigate, Surrey, RH2 9PW, UK.
Enviroderm, USA. EnviroDerm Pharmaceuticals Inc., 46 Christa McAuliffe Bvld, Plymouth, MA 02360, USA.
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Enzimas, Arg. Enzimas S.A., San Rafael 1950, 6700 Lujan, Buenos Aires, Argentina.
Enzon, Canad. See *Enzon, USA.*
Enzon, USA. Enzon, Inc., 685 Route 202/206, Bridgewater, NJ 08807, USA.
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Enzpharma, NZ. eNZpharma Ltd, 27a Cambrai Ave, Mt Roskill, Auckland, New Zealand.
Enzypharm, Austria. Enzypharm GmbH, Piaristengasse 29, A-1080 Vienna, Austria.
Eon, USA. Eon Labs Inc., 1999 Marcus Ave., Lake Success, NY 11042, USA.
url: www.eonlabs.com
E-Pharma, Ital. E-Pharma Trento, Via Provina 2, 38040 Ravina (TN), Italy.
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Epicaris, Arg. Lab. Epicaris S.A., Av. Piedrabuena 4190, 1439 Buenos Aires, Argentina.
Epiderm, UK. Epiderm Ltd, Wass Lane, Sotby, Market Rasen, LN8 5LH, UK.
url: www.covermark.com
Epien, USA. Epien Medical Inc., 4225 White Bear Pkwy, Suite 600, St Paul, MN 55110, USA.
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EpiPharm, Austral. EpiPharm Pty Ltd, Level 13, 1 Collins St, Melbourne, Vic 3000, Australia.
Epsilon, Spain. See *AstraZeneca, Spain.*
Equazen, Hong Kong. See *Silroc, Hong Kong.*
Equilibre Attitude, Fr. Laboratoires Equilibre Attitude, B.P. 289, 06227 Vallauris cdx, France.
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Equity, S.Afr. Equity Pharmaceuticals (Pty) Ltd, 1 Petunia St, Bryanston 1600, South Africa.
ERA, Denm. ERA Medical ApS, Storeholm 25, 2670 Greve, Denmark.
Erbiode, Austria. Erbiode Pharma Service GmbH, Steindorf 65, A-5570 Mauterndorf, Austria.
Erempharma, Fr. Laboratoires Erempharma, 75 rue Bayen, 75017 Paris, France.
Erfa, Belg. Erfa SA, Rue des Cultivateurs 25, 1040 Brussels, Belgium.
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Erfa, Canad. Erfa Canada Inc., 4545 Sherbrooke St W, Westmont, Quebec, H3Z 1E8, Canada.
url: www.erfa.net
Erfar, Gr. Erfar Pharmaceutical Laboratories, Altani, 153 44 Pallini, Greece.
Ergha, Irl. See *Helsinn Birex, Irl.*
Eriochem, Arg. Eriochem SA, Ruta 12 Km 452 (16.5), 3100 Parana Avellaneda, Entre Rios, Argentina.
Erjean, Fr. Laboratoires Erjean, 9 rue de Sébastopol, B.P. 867, 31015 Toulouse cdx 6, France.
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url: www.erkim-ilac.com.tr
Erkimya, Turk. Erkimya İlaç San. ve Tic. Ltd. Şti., İzzettin Çalişlar Cad. No: 42/3, Bahçelievler, İstanbul, 34590, Turkey.
Erlimpex, Indon. Erlimpex PT, Jl Sultan Agung 83, 50232 Semarang, Jawa Tengah, Indonesia.
Ern, Spain. Laboratorios Ern S.A., C/ Pedro IV 499, 08020 Barcelona, Spain.
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Ernest Jackson, UK. Ernest Jackson & Co. Ltd, 29 High St, Crediton, Devon, EX17 3AP, UK.
url: www.ejackson.co.uk
Erol, Swed. Erol AB, Box 95, 274 22 Skurup, Sweden.
Errekappa, Ital. Errekappa Euroterapici S.p.A., Via C. Menotti 1/A, 20129 Milan, Italy.
Escaned, Spain. Escaned, Tomas Breton 46, 28045 Madrid, Spain.
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Esfar, Port. Laboratórios Esfar, SA, Rua da Escola de Medicina Veterinária 15-17, 1049-029 Lisbon, Portugal.
ESI, USA. See *Wyeth, USA.*
Esme, Arg. Lab. Esme S.A.I.C., Uriarte 1686, 1414 Buenos Aires, Argentina.
Esoform, Ital. Esoform S.p.A., Viale del Lavoro 10, 45100 Rovigo, Italy.
ESP, Canad. See *ESP, USA.*
ESP, USA. ESP Pharma Inc., 2035 Lincoln Highway, Suite 2150, Edison, NJ 08817, USA.
url: www.esppharma.com
Esparma, Cz. See *Techmed, Cz.*
Esparma, Ger. esparma GmbH, Lange Gohren 3, 39171 Osterweddingen, Germany.
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Esparma, Rus. Esparma, Leninskii pr-t 148, Of 123-124, 119571 Moscow, Russia.
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Espe, Austria. Espe HandelsGmbH, Marokkanergasse 9/8, A-1030 Vienna, Austria.
Espe, Cz. See *3M Espe, Ger.*
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Espe, Switz. Espe AG, Baumackerstrasse 46, Postfach 8360, 8050 Zurich, Switzerland.

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Esplanade, Austria. Esplanade-Apotheke, Esplanade 18, A-4820 Bad Ischl, Austria.
Esprit, USA. Esprit Pharma, Two Tower Center Blvd, East Brunswick, NJ 08816, USA.
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Esro, Switz. Esro SA, Bohnirainstrasse 13, 8800 Thalwil, Switzerland.
url: www.esro.ch
Essenpharma, Philipp. Essenpharma Inc., 3/F Dr Floro Noza Brosas, Medical Foundation Clinic, 7418 Santillan St, Pasay Rd, Makati City, Philippines.
Essential, NZ. Simply Essential 2000 Ltd, 2 Kamura St., Karitane, Otago, New Zealand.
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Essential Dental, NZ. The Essential Dental Co Ltd, 3 Arawa St, Grafton, Auckland, New Zealand.
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Essex, Austral. See *Schering-Plough, Austral.*
Essex, Chile. See *Schering-Plough, Chile.*
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Essex, Philipp. Essex Pharmaceuticals Inc., 12/F San Miguel Properties Ctr, St Francis St, Ortigas Ctr, Mandaluyong City, Philippines.
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Essex, Switz. Essex Chemie AG, Weystrasse 20, 6000 Lucerne 6, Switzerland.
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Esteve, Port. Esteve Farma Lda, Av do Forte 3, Edifício Suécia II, Piso 4A, 2794-044 Carnaxide, Portugal.
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Ethex, USA. Ethex Corp., 10888 Metro Court, St Louis, MO 63043-2413, USA.
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Ethica, Indon. Ethica Industri Farmasi PT, Jl Pulo Gadung 6, Kawasan Industri Pulo Gadung, 13290 Jakarta Timur, DKI Jaya, Indonesia.
Ethicare, Austral. Ethicare Pharmaceuticals P/L, 32 Success Crescent, Salter Point, WA 6952, Australia.
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Ethypharm, Austria. See *Ethypharm, Fr.*
Ethypharm, Cz. See *ProMed, Cz.*
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Eu Rho, Ger. Eu Rho OTC Pharma GmbH, Kamen Karree 32-34, 59174 Kamen, Germany.
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Eulite, Neth. Eulite BV, Beatrixlaan 4, 5531 HB Bladel, Netherlands.
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Eumedica, Neth. See *Bournonville, Belg.*
Eumedica, Switz. Eumedica Pharmaceuticals (Schweiz) AG, Peter Merian-Strasse 54, 4002 Basle, Switzerland.
url: www.eumedica.com
Eumedica, UK. See *Eumedica, Belg.*
Euphar, Ital. Euphar Group S.r.l., Via Gandine 4/6, 29100 Piacenza, Italy.
Eupharmed, Ital. EuPharmed Srl, Via Yser 8, 00100 Rome, Italy.
Eureco, Neth. Eureco-Pharma BV, Van Polanenweg 2, 2921 LT Krimpen A/D Ijssel, Netherlands.
Eurim, Ger. Eurim-Pharm GmbH, Am Ganslehen 4-6, 83451 Piding, Germany.
Euro Nippon Kayaku, Pol. See *JKC, Pol.*
Euro OTC, Ger. Euro OTC Pharma GmbH, Edisonstr. 6, 59199 Bönen, Germany.
Euro Registratie, Neth. Euro Registratie Collectief BV, Van der Giessenweg 5, 2921 LP Krimpen A/D Ijssel, Netherlands.
EuroAsia, Philipp. EuroAsia Pharmaceuticals Inc., 3/F Eurochem Bldg, Cor. Rd 1, Mindanao Ave, Quezon City, Philippines.
EuroCept, Belg. See *EuroCept, Neth.*
EuroCept, Neth. EuroCept BV, Kortenhoefsedijk 86a, 1241 LS Kortenhoef, Netherlands.
EuroCept, Norw. See *EuroCept, Neth.*
Euroderm, Arg. Euroderm Laboratorios S.R.L., Emilio Mitre 1790/94, 1424 Buenos Aires, Argentina.
Euroderm, Ital. Euroderm S.r.l., V.le Italia 147, 19126 La Spezia, Italy.
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Euroderm OTC, Ital. Euroderm OTC SpA, Via IV Novembre 54, 20019 Settimo Milanese (MI), Italy.
Euroderm-RDC, Ital. Euroderm-RDC S.p.A., P.le Aquileia 8, 20144 Milan (MI), Italy.
Eurodrug, Hong Kong. Eurodrug Laboratories Ltd, Rm 903, 625 Kings Rd, North Point, Hong Kong.
Eurodrug, Hung. See *Keri, Hung.*
Eurodrug, Malaysia. See *Apex, Malaysia.*
Eurodrug, Mex. Eurodrug Laboratories de México SA de CV, Yucatán 88, 6700 Roma, Mexico.
Eurodrug, Philipp. See *Croma, Philipp.*
Eurodrug, Singapore. See *JDH, Singapore.*
Eurodrug, Thai. Eurodrug, 8B Fl, Ocean Tower 1, 170 New Ratchapisek Rd, Sukumvit 16 Klongtoey, Bangkok 10110, Thailand.
Euroexim, Spain. Euroexim, C/Emilio Munoz 15, 28037 Madrid, Spain.
Eurofarma, Braz. Eurofarma Laboratórios Ltda, Rua Barão do Triunfo 1440, 04602-005 São Paulo, SP, Brazil.
url: www.eurofarmalaboratorio.com.br
Eurofarmaco, Ital. Eurofarmaco S.r.l., Via Aurelia 58, 00100 Rome, Italy.
Eurogen, Neth. See *Eurogen, UK.*
Eurogen, UK. EuroGen Pharmaceuticals Ltd, Ist Floor Eagle House, Montpelier Drive, Cheltenham, Gloucestershire, GL50 1TA, UK.
Eurogenerics, Belg. Eurogenerics SA, Esplanade Heysel bte 22, 1020 Brussels, Belgium.
url: www.eurogenerics.be
EuroHealth, Philipp. EuroHealth Care Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.
Eurolab, Arg. Lab. Eurolab Div. Nutricional (Grupo Eurofar SRL), Av. Juan de Garay 3881, 1256 Buenos Aires, Argentina.
Euro-Labor, Port. See *Grunenthal, Port.*
Euro-Med, Indon. See *Euro-Med, Philipp.*
Euromed, Ital. Euromed S.r.l., Via A Gentileschi 26, 80126 Naples, Italy.
url: www.euromed.it
Euro-Med, Philipp. Euro-Med Laboratories Phil. Inc., 1000 United Nations Ave, Cor San Marcelino St, Manila, Philippines.
Euromedex, Fr. Laboratoires Euromedex, 24 rue des Tuileries, B.P. 74684, Souffelweyersheim, 67458 Mundolschein cdx, France.
url: www.euromedex.com
Euromex, Mex. Laboratorios Euromex S.A. de C.V., Unicornio No. 142, Col. Prado Churubusco, 04230 Mexico D.F., Mexico.
Europe Biofarm, Rus. NPO Europe Biofarm ZAO, Poddubnogo ul. 33a, 400040 Volgograd, Russia.
European Community, Rus. C European Community C Ltd, Kashirskoe ul. 24, 115478 Moscow, Russia.
Europharm, Austria. Europharm, Jochen-Rindt-Strasse 23, A-1230 Vienna, Austria.
Europharm, Hong Kong. Europharm Laboratories Co. Ltd, 12-14 Dai Wang St, Tai Po Industrial Estate, Tai Po, N.T., Hong Kong.
url: www.europharm.com.hk
Europharm, Hung. Europharm Trade Kft, Kővirózsa út 5, 1163 Budapest, Hungary.

Euro-Pharma, Ital. Euro-Pharma S.r.l., Corso Tassoni 25, 10143 Turin, Italy.
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Europharma, Ital. Europharma S.r.l., Via Pergolesi 194, 41100 Modena, Italy.
Europharma, Spain. See *Boehringer Ingelheim, Spain.*
Europhta, Mon. Laboratoires Europhta, Le Concorde, 11 rue du Gabian, MC 98000, Monaco.
Europlant Phytofarm, Pol. Europlant Phytofarm Sp. zo.o., ul. Św. Michała 43, 61-119 Poznań, Poland.
url: www.europlant.com.pl
Eurospital, Ital. Eurospital S.p.A., Via Flavia 122, 34147 Trieste, Italy.
Eurosup, Ital. Eurosup, Via Novara 4, 27030 Castello d'Agogna, Italy.
url: www.eurosup.com
Eurovita, Malaysia. See *JDH, Malaysia.*
Eurovita, Thai. See *Diethelm, Thai.*
Eurowest, Philipp. See *Basic, Philipp.*
EUSA, Port. See *EUSA, UK.*
EUSA, UK. EUSA Pharma, Building 3, Arlington Business Park, Whittle Way, Stevenage, Hertfordshire, SG1 2FP, UK.
url: www.eusapharma.com
Eutherapie, Belg. See *Servier, Belg.*
Eutherapie, Fr. Euthérapie, 27 rue du Pont, 92200 Neuilly-sur-Seine cdx, France.
Evans, Fin. See *Oriola, Fin.*
Evans, Irl. See *Novartis, UK.*
Evans, Israel. See *Novartis, Israel.*
Evans, Norw. See *Mericon, Norw.*
Evans Medical, Israel. See *Novartis, Israel.*
Evans Vaccines, Switz. See *Lifebiotech, Switz.*
Evaux, Fr. Évaux Laboratoires, 67 av de la République, 23110 Évaux-les-Bains, France.
url: www.evaux-laboratoires.fr
Everett, USA. Everett Laboratories Inc., 29 Spring St, West Orange, NJ 07052, USA.
url: www.everettlabs.com
Evers, Ger. Pharmazeutische Fabrik Evers & Co. GmbH, Siemensstr. 4, 25421 Pinneberg, Germany.
url: www.pharmaevers.de
Evers, Indon. See *Pharos, Indon.*
Evers, Thai. See *Sriprasit, Thai.*
Eversil, Braz. Eversil Produtos Farmacêuticos Indústria e Comércio Ltda, Rua Agostinho Teixeira de Lima 344, 04826-230 São Paulo, SP, Brazil.
url: www.eversil.com.br
Everton, USA. See *Trx Pharma, USA.*
Evisco, Ger. Evisco-Pharma, Klosterplatz 6, 87509 Immenstadt, Germany.
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Ewopharma, Hung. Ewopharma AG Képviselet, Gyorskocsi u 12 II/3, 1011 Budapest, Hungary.
Ewopharma, Pol. Ewopharma AG Spółka zo.o., ul. Świętokrzyska 36 m 16, 00-116 Warsaw, Poland.
Exbio, Cz. Exbio Praha as, Videňská 1083, 142 00 Prague 4, Czech Republic.
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Excelentia, Arg. Laboratorios Excelentia S.A., Santo Domingo 4088, 1437 Buenos Aires, Argentina.
Excelvision, Israel. See *Resdevco, Israel.*
Exel, Belg. See *Nycomed, Belg.*
Exelgyn, Denm. See *Exelgyn, Swed.*
Exelgyn, Fin. See *Exelgyn, Swed.*
Exelgyn, Fr. Exelgyn, 6 rue Christophe-Colomb, 75008 Paris, France.
Exelgyn, Gr. See *Exelgyn, Fr.*
Exelgyn, Israel. See *Lapidot, Israel.*
Exelgyn, Norw. See *Exelgyn, Swed.*
Exelgyn, Swed. Exelgyn, Box 1343, 181 25 Lidingo, Sweden.
Exelgyn, UK. Exelgyn Laboratories, P.O. Box 4511, Henley-on-Thames, Oxfordshire, RG9 5ZQ, UK.
Exir, Rus. See *Darou Pakhsh, Rus.*
Expanpharm, Fr. Laboratoires Expanpharm International, 60 rue Fessart, 92100 Boulogne, France.
Expanpharm, Switz. See *Uhlmann-Eyraud, Switz.*
Expanscience, Fr. Laboratoires Expanscience, 10 av. de l'Arche, 92400 Courbevoie, France.
url: www.expanscience.com
Expanscience, Pol. See *Medagro, Pol.*
Expanscience, Rus. See *CSC, Rus.*
Expanscience, Spain. Expanscience, Pol. Ind. Los Olivos, Adaptación 33, Getafe, 28906 Madrid, Spain.
url: www.mustela.com
Experimental Production, Rus. See *Veropharm, Rus.*
Expomedica, Port. Expomédica Sociedade Exportadora Importadora de Material Médico Lda, Av. 5 de Outubro 89 -1, 1050-050 Lisbon, Portugal.
url: www.expomedica.pt
Express Care, NZ. Express Care Direct, New Zealand.
Exterius, Ger. Exterius Health Care GmbH, Robert-Koch-Str. 2, 51674 Wiehl, Germany.
Extractum, Cz. See *Extractum, Hung.*
Extractum, Hung. Extractum Pharma Rt, Fóti út 56, 1047 Budapest, Hungary.
url: www.expharma.hu
Exxe, Ital. Exxe Srl, Via Breda 120, 20126 Milan, Italy.
url: www.exxe.it
Eyetech, USA. Eyetech, 3 Times Square, 12th Floor, New York, NY 10036, USA.
url: www.eyetech.com
E-Z-EM, Belg. See *E-Z-EM, Neth.*
E-Z-EM, Canad. E-Z-EM Canada Inc., 11 065 L-H Lafontaine, Anjou, Quebec, H1J 2Z4, Canada.
url: www.ezemcanada.com
E-Z-EM, Cz. See *E-Z-EM, UK.*
E-Z-EM, Hung. See *Amersham Health, Hung.*
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E-Z-EM, Neth. See *Rooster, Neth.*
E-Z-EM, Port. See *Martins & Fernandes, Port.*
E-Z-EM, UK. E-Z-EM Ltd, Avonbury Business Park, Howes Lane, Bicester, Oxfordshire, OX26 2UA, UK.
url: www.ezem.com
F5 Profas, Spain. F5 Profas, Ed Indubuilding Goico, Via Los Poblados 17, 28033 Madrid, Spain.
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Fabra, Arg. Lab. Fabra S.R.L., Carlos Villate 5271, 1605 Munro, Buenos Aires, Argentina.
Fabrigen, Canad. Fabrigen Inc., P.O. Box 507, Pierrefonds, Quebec, H9H 4M6, Canada.
Face, Ital. Face Laboratori Farmaceutici SpA, Via Sardorella 43, 16152 Genova, Italy.
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url: www.faes.es
Fagron, Neth. Fagron Pharmaceuticals bv, Hoogeveenenweg 210, 2913 LV Nieuwerkerk A/D Ijssel, Netherlands.
Fahrenheit, Indon. See *Pratapa Nirmala, Indon.*
Fahrenheit, Philipp. See *PNF, Philipp.*
Fako, Turk. Fako İlaçari A.Ş., Büyükdere Cad. No: 205, Levent, İstanbul, 80650 4., Turkey.
url: www.fako.com.tr
Falk, Cz. See *Ewopharma, Cz.*
Falk, Denm. See *Meda, Denm.*
Falk, Ger. Dr. Falk Pharma GmbH, Leinenweberstr. 5, 79108 Freiburg, Germany.
url: www.drfalkpharma.de
Falk, Hong Kong. See *Jacobson, Hong Kong.*
Falk, Hung. See *Medical Consulting, Hung.*
Falk, Indon. See *Darya-Varia, Indon.*
Falk, Irl. See *Falk, UK.*
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Falk, Philipp. See *Zuellig, Philipp.*
Falk, Pol. See *Ewopharma, Pol.*
Falk, Port. Dr. Falk Pharma Portugal Lda, Av. José Gomes Ferreira 11, Edifício Atlas II - 3 Piso, Sala 33, Miraflores, 1495-139 Algés, Portugal.
Falk, Singapore. See *JDH, Singapore.*
Falk, Spain. See *Falk, Ger.*
Falk, Thai. See *Zuellig, Thai.*
Falk, UK. Dr Falk Pharma UK Ltd, Bourne End Business, Cores End Rd, Bourne End, Buckinghamshire, SL8 5AS, UK.
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Famac, Ital. Lab. Famac, Cosmetologia Scientifica, Via G Ripamonti 9, 20136 Milan, Italy.
Famar, Gr. Famar S.A., 63 Ag. Demetriou Str., 174 56 Alimos, Greece.
url: www.famar.gr
Family Health, Rus. Family Health ZAO, Bolshaya Serpukhovskaya st. 60, 113093 Moscow, Russia.
url: www.familyhealth.ru
Family Planning Sales, UK. Family Planning Sales Ltd, 28 Kelburne Rd, Cowley, Oxford, Oxfordshire, OX4 3SZ, UK.
Famy, Philipp. See *DKT, Philipp.*
Fandasy, Hong Kong. Fandasy Co. Ltd, Unit A, 18/F Federal Ctr, 77 Sheung On St, Chaiwan, Hong Kong.
Fapromed, Arg. Fapromed S.A., Gral. M.A. Rodrmguez 2830, 1416 Buenos Aires, Argentina.
Far East, Singapore. Far East Drug Co (Pte) Ltd, 1 Sophia Rd, 08-01 Peace Centre, S 228149, Singapore.
Far East, Thai. Far East Pharmaceutical Ltd Part, 92/1-2 Lanluang Rd, Bangkok 10100, Thailand.
Faran, Gr. Faran Laboratories S.A., Achaias & Troizinias, 145 64 N. Kifisia, Greece.
url: www.faran.gr
Farbo, Ital. Farbo s.n.c. del dott. Donato Mele & C., Via Stelvio 12/18, 20021 Ospiate di Bollate (MI), Italy.
Farchim, Cz. See *Farchim, Switz.*
Farchim, Switz. Farchim SA, ZI de Planchy, Bulle, Switzerland.
Farco, Austria. See *Farco, Ger.*
Farco, Cz. See *Farco, Ger.*
Farco, Denm. See *Tjellesen, Denm.*
Farco, Ger. Farco-Pharma GmbH Pharmazeutische Präparate, Mathias-Bruggen-Str. 82, 50829 Cologne, Germany.
url: www.farco-pharma.de
Farco, Hong Kong. See *Sincerity, Hong Kong.*
Farco, Hung. See *Co Ord-Med, Hung.*
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Farco, Israel. See *CTS, Israel.*
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Farco, Rus. See *Invar, Rus.*
Farcoral, Mex. Profesional Medica Farcoral S.A. de C.V., Circuito Norte No. 28, Unidad Guadalupe, 72560 Puebla, Mexico.
Fardi, Port. See *Fardi, Spain.*
Fardi, Spain. Fardi, Grassot 16, 08025 Barcelona, Spain.
url: www.fardi.es
Fargim, Ital. Far.g.im S.r.l., Via Cervignano 29, 95129 Catania, Italy.
Fargin, Port. See *Tecnifar, Port.*
Faria, Braz. Laboratório Farmacêutico Faria Ltda, Rua Coronel Delfino Nonato de Faria 151, Sta Tereza, 36020-170 Juiz de Fora, MG, Brazil.
Fariberica, Port. Faribérica, SA, Estrada da Luz 90 - 9 D/E, 1600-160 Lisbon, Portugal.
Farlab, Port. Farlab Comercio e Representações Lda, Zona Industria da Portelinha APTDO 2050, Av. Associação Comercial e Ind de Gondomar 390/410, 4510-688 Famzeres, Portugal.
Farma, Venez. Grupo Farma S.A., Av. Principal, Los Ruices, Edif. Farma, Urb. Los Ruices, Caracas 1071, Venezuela.
url: www.grupofarma.com
Farma Energy, Ital. Farma Energy, Via Polia 36/38, 00100 Rome, Italy.
url: www.farmaenergy.com
Farma Lepori, Spain. Farma Lepori, Osi 7-9, 08034 Barcelona, Spain.
url: www.farmalepori.com
Farmabraz, Braz. Farmabraz Beta Atalaia Farmacêutica Ltda, Rua Com. João C. de Almeida 36, 20770-100 Rio de Janeiro, RJ, Brazil.
Farmacelsia, Spain. Farmacelsia, Ramallosa S/N, Teo, 15883 Coruna, Spain.
url: www.ifelaboratorios.com
Farmaceutica H, Mex. Farmacéutica Hispanoamericana SA de CV, Lago Iseo 184, 11320 Anahuac, Mexico.
Farmachimici, Ital. Farmachimici S.r.l., Via Mercanti 36, 84121 Salerno, Italy.
url: www.farmachimici.it
Farmaco, Mex. Laboratorio de Productos Farmaceuticos y Biologicos Farmaco S.A., Jaime Nuno No. 112, Col. Guadalupe Inn, 01020 Mexico D.F., Mexico.
Farmaco, Pol. Farmaco, ul. Polarna 14, 93-465 Łódź, Poland.
Farmacologico Milanese, Ital. Laboratorio Farmacologico Milanese S.r.l., Via Monterosso 273, 21042 Caronno Pertusella (VA), Italy.
Farmacom, Pol. See *Grunenthal, Pol.,* and *Pliva Krakow, Pol.*
Farmacoope, Port. Farmacoope Cooperativa Nacional das Farmácias CRL, Travess de Santa Catarina 8, 1200-403 Lisbon, Portugal.
Farmacox, Port. Farmacox Companhia Farmacêutica Lda, Quinta da Fonte, Edifício Vasco sa Gama 19, Porto Salvo, 2770-192 Paço de Arcos, Portugal.
Farmades, Ital. Farmades S.p.A., Via di Tor Cervara 282, 00155 Rome, Italy.
Farmaervas, Braz. Laboratório Farmaervas Ltda, Rua Saldanha Marinho 161, 3055020 São Paulo, São Paulo, Brazil.
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Farmaka, Ital. Farmaka S.r.l., Via Vetreria 1, 22070 Grandate (CO), Italy.
url: www.farmaka.it
Farmakochimiki, Gr. Botonia Farmakochimiki A.E., Pigasou 18, 151 25 Marousi, Greece.
Farmakor, Rus. Farmakor ZAO, Kamennoostrovskij prosp., d. 67, a/ja 76, 197022 Saint Petersburg, Russia.
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Farmal, Pol. Wytwórnia Farmaceutyczna Farmal, ul. Rycerska 2/33, 42-500 Będzin, Poland.
Farmalab, Braz. Farmalab Industrias Químicas e Farmacêuticas Ltda, Av. BrigADEIRO Faria Lima 1811, 12° andar, 01451-001 São Paulo, SP, Brazil.
url: www.farmalabchiesi.com.br
Farmalex, Gr. Farmalex S.A., 15-17 Anast Tsocha, 115 10 Athens, Greece.
Farmalider, Spain. Farmalider, C/ Aragoneses 9, Alcobendas, 28100 Madrid, Spain.
Farmalight, Port. Farmalight, Lda, Rua Padre Américo 18, Escritório 1, 1600-548 Lisbon, Portugal.
url: www.farmalight.pt
Farmaline, Thai. Farmaline Co. Ltd, 48 Soi Urupong 1, Rama 6 Rd, Rajthevee, Bangkok 10400, Thailand.
Farmamust, Gr. Farmamust Epe, Plateia Pantazopoulou 7, GR-10443 Kolonos Attikis, Greece.
Farmanic, Gr. Farmanic, Fylis 137, 134 51 Kamatero, Greece.
Farmanova, Ital. Farmanova AFM S.r.l., Via Flaminia 287 Sc. A. int.10, 00100 Rome, Italy.
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Farmapol, Pol. Zakład Chemiczno-Farmaceutyczny Farmapol Sp. zo.o., ul. Św. Wojciech 29, 61-749 Poznań, Poland.
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Farmaprojects, Neth. See *Farmaprojects, Spain.*
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url: www.farmaprojects.es
Farma-Projekt, Pol. Farma-Projekt Sp. zo.o., ul. Salwatorska 14, 30-109 Kraków, Poland.
url: www.farmaprojekt.pl
Farmasa, Braz. Laboratório Americano de Farmacoterapia S/A, Rua Nova York 245, 04560-908 São Paulo, SP, Brazil.
url: www.farmasa.com.br
Farmasa, Mex. Laboratorios Farmasa, S.A. de C.V., Bufalo No. 27, Col. del Valle, 03100 Mexico D.F., Mexico.
Farmasan, Ger. Farmasan Arzneimittel GmbH & Co., Pforzheimer Str. 5, 76227 Karlsruhe, Germany.
Farmasan, Thai. See *JDH Borneo, Thai.*
Farmasierra, Spain. Farmasierra S.A., Ctra de Irun Km 26.2, San Sebastian de Los Reyes, 28100 Madrid, Spain.
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Farmasix, Port. Farmasix Produtos Farmacêuticos Sociedade Unipessoal Lda, Quinta da Fonte, Edifício Vasco da Gama 19, 2770-192 Paço de Arcos, Portugal.
Farmasoft, Rus. See *Pharmasoft, Rus.*
Farmasur, Spain. Farmasur, Pol Store C/H 28-A, 41008 Seville, Spain.
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Farma-Tek, Turk. Farma-Tek İlaç Ltd. Şti., Kısıklı Cad., Oymacı Sok. No: 16/A, Altunizade, İstanbul, 34662, Turkey.
url: www.farma-tek.com
Farmatrading, Port. Farmatrading, Lda, Travessa de Santa Catarina no 18, 1200-403 Lisbon, Portugal.
Farmatre, Ital. Farma 3 S.r.l., Via Solferino 42, 20036 Meda (MI), Italy.
Farmaurino, Ital. Farmaurino Srl, Via Giovanni Porzio 4, CDN Isola A/7, Scala B, 80100 Naples (NA), Italy.
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Farmed, Turk. Farmed İlaç Ltd. Şti., Şenlik Mah, Yeşil Ada Sok. No:5 K: 1, Florya, İstanbul, Turkey.
url: www.farmed.com.tr
Farmedia, Gr. Farmedia S.A., 22 Athinas & Apollonos str, 153 44 Gerakas, Greece.
url: www.farmedia.gr
Farmedica, Braz. Farmedica Indústria Farmacêutica Ltda, Avenida Automovel Clube 1140, 25565-000 João de Meriti, RJ, Brazil.
Farmex, Gr. See *Pharmex (Φαρμεξ), Gr.*
Farmigea, Ital. Farmigea Industria Chimico Farmaceutica S.p.A., Via G. Oliva n. 8, 56121 Ospedaletto-Pisa, Italy.
url: www.farmigea.it
Farmila, Cz. See *Rephachem, Cz.*
Farmila, Ital. Farmila-Thea Farmaceutici S.p.A., Via E. Fermi 50, 20019 Settimo Milanese (MI), Italy.
url: www.farmila.it
Farmilia, Gr. Farmilia Inc., Favierou 48, 104 38 Athens, Greece.
Farmina, Pol. Farmina Sp. zo.o., ul. Lipska 44, 30-721 Kraków, Poland.
url: www.farmina.pl
Farminvest, Ital. Farminvest S.p.A., Strada Vicinale dei Moretti, 10090 Ivrea (TO), Italy.
Farmion, Braz. Farmion Laboratório Brasileiro de Farmacologia Ltda, Avenida Celso dos Santos 579, 04658-240 São Paulo, SP, Brazil.
Farmitalia, Cz. See *Pharmacia, Ital.*
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Farmoquimica, Braz. Farmoquimica S.A., Av. Luis Carlos Prestes 410, 22775-055 Rio de Janeiro, RJ, Brazil.
url: www.fqm.com.br
Farmorcore, Port. Laboratórios Farmorcore, SA, Quinta da Francelha de Cima, 2685 Prior-Velho, Portugal.
Farmoterapia, Arg. Farmoterapia Internacional S.R.L., Alvear 231 Piso 1 of.1, 1640 Martinez, Buenos Aires, Argentina.
Farmoz, Port. Farmoz Sociedade Técnico Medicinal S.A., Rua Professor Henrique de Barros, Edifício Sagres 3 A, 2685-338 Prior Velho, Portugal.
Farmstandart, Rus. Farmstandart, Dolgoprudnyjj g., Likhachevskijj pr. d. 5, 141700 Moscow, Russia.
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Faromed, Austria. Faromed GmbH, Johann Straussgasse 7/5, A-1040 Vienna, Austria.

Fascino, Thai. Fascino Pharmacy Groups, 99 Moo 2 Tumbon Bangtoey, Aumpeur Sampharn, Nakornphathom 73210, Thailand.
url: www.fascino.co.th

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Fatol, Austria. See *Fatol, Ger.*

Fatol, Cz. See *Fatol, Ger.*

Fatol, Ger. Fatol Arzneimittel GmbH, Robert-Koch-Str., 66578 Schiffweiler, Germany.
url: www.fatol.de

Fatol, Hong Kong. See *Mekim, Hong Kong.*

Faulding, Austral. See *Mayne, Austral.*

Faulding, Fr. Faulding Pharmaceuticals SA, 93 Rue Magenta, 92600 Asnières, France.
url: www.maynepharma.com

Faulding, Israel. See *Tzamal, Israel.*

Faulding, Port. Faulding Farmacêutica, Lda, Rua Amália Rodrigues, lote 4, 2750-228 Cascais, Portugal.
url: www.maynegroup.com

Faulding, Singapore. See *Mayne, Singapore.*

Faulding, USA. See *Mayne, USA.*

Faulding Consumer, Austral. See *Mayne, Austral.*

Fawns & McAllan, Austral. See *Sigma, Austral.*

Fawns & McAllan, Hong Kong. See *LCH, Hong Kong.*

FD, Ital. FD Farmaceutici S.r.l., Via Castello 15, 29019 San Giorgio Piacentino (PC), Italy.

FDC, India. FDC Ltd, 142-48 S.V. Rd, Jogeshwari (West), Mumbai 400 102, India.
url: www.fdcindia.com

FDC, Thai. See *Kaspa, Thai.*

Febena, Ger. Febena Pharma GmbH, Oskar-Jager-Str. 115, 50825 Cologne, Germany.
url: www.febena.de

Fecofar, Arg. Fed. Arg. de Coop. Farm., Av. Pte. Peron 2742, 1754 San Justo, Buenos Aires, Argentina.

Federfarma, Ital. FederFARMA.CO SpA, Viale Piceno 6, 20129 Milan, Italy.

Feldhoff, Ger. W. Feldhoff & Comp. Arzneimittel GmbH, Hans-C.-Wirz-Str. 2, 99867 Gotha, Germany.

Felgentrager, Cz. See *Felgentrager, Ger.*

Felgentrager, Ger. Dr. Felgenträger & Co. Öko-chem. und Pharma GmbH, Zerbster Str. 7a, 06862 Rodleben, Germany.
url: www.dr-felgentraeger.de

Felgentrager, Pol. See *Felgentrager, Ger.*

Felo, Denm. Felo ApS, Jeshojvej 12, 4700 Naestved, Denmark.

Felton, Austral. Felton, Grimwade & Bickford P/L, P.O. Box 74, Oakleigh South, VIC 3167, Australia.
url: www.fgb.com.au

Femi Agran, Israel. Femi Agran, Israel.

Fenton, UK. Fenton Pharmaceuticals Ltd, 4J Portman Mansions, Chiltern St, London, W1M 1LF, UK.

Ferakon, Gr. Ferakon EPE (Φερακον ΕΠΕ), Menandrou 85, 104 38 Athens, Greece.

Ferel, Port. Ferel Comércio e Representação Lda, Portugal.

Ferlito, Ital. Ferlito Farmaceutici, Divisione Palmares S.p.A., Via E Ramarini 31-33, 00016 Monterotondo Scalo (RM), Italy.
url: www.ferlitofarmaceutici.it

Ferlux, Fr. Ferlux SA, 24 av. d'Aubiere, B.P. 151, 63804 Cournon d'Auvergne cdx, France.
url: www.ferlux.com

Fermenta Biotech, Rus. See *Transatlantic, Rus.*

Fermon, Spain. Fermon, Alfonso Alcocer 7, Badalona, 08918 Barcelona, Spain.

Ferndale, Hong Kong. See *US Summit, Hong Kong.*

Ferndale, UK. Ferndale Pharmaceuticals Ltd, Unit 605, Thorp Arch Estate, Wetherby, West Yorkshire, LS23 7BJ, UK.
url: www.ferndalepharma.co.uk

Ferndale, USA. Ferndale Laboratories Inc., 780 West Eight Mile Rd, Ferndale, MI 48220, USA.
url: www.ferndalelabs.com

Ferol, Hung. Ferol Kft, Czobor u 53, 1147 Budapest, Hungary.

Feron, Rus. Feron OOO, Volokolamskoe sh. 73, 123424 Moscow, Russia.

Ferraz, Lynce, Port. Ferraz, Lynce, SA, Rua Consiglieri Pedroso 123, Queluz de Baixo, 2730-056 Barcarena, Portugal.

Ferrer, Hong Kong. See *Keller, Hong Kong.*

Ferrer, Indon. See *Darya-Varia, Indon.*

Ferrer, Malaysia. See *Wellmex, Malaysia.*

Ferrer, Philipp. See *Metro, Philipp.,* and *Patriot, Philipp.*

Ferrer, Port. Ferrer Azevedos SA, Edificio Azevedos, Estrada Nacional 117-2, 2724-503 Amadora, Portugal.

Ferrer, Rus. See *Egis, Rus.*

Ferrer, Singapore. See *Pharmacon, Singapore.*

Ferrer, Spain. Ferrer Farma, Edifici L'illa, Diagonal 549. 5a planta, 08029 Barcelona, Spain.
url: www.ferrergrupo.com

Ferrer, Thai. See *Pacific, Thai.*

Ferrer-Novag, Mex. See *Novag, Mex.*

Ferrier, Fr. See *Arkopharma, Fr.*

Ferring, Arg. Ferring S.A., Venezuela 174, 1095 Buenos Aires, Argentina.
url: www.ferring.com

Ferring, Austral. Ferring Pharmaceuticals P/L, Suite 2B, Level 2, 802 Pacific Highway, Gordon, NSW 2072, Australia.
url: www.ferring.com

Ferring, Austria. Ferring Arzneimittel GmbH, Wienerbergstrasse 11, A-1100 Vienna, Austria.
url: www.ferring.com

Ferring, Belg. Ferring SA, Hopmarkt 9 bus 3, 9300 Aalst, Belgium.
url: www.ferring.com

Ferring, Braz. Laboratórios Ferring Ltda, Praca São Marcos 624 1-andar, Vila Ida, 05455-050 São Paulo, SP, Brazil.
url: www.ferring.com

Ferring, Canad. Ferring Inc., 200 Yorkland Blvd, Suite 800, Toronto, Ontario, M2J 5C1, Canada.
url: www.ferring.com

Ferring, Chile. See *Recalcine, Chile.*

Ferring, Cz. Ferring-Léčiva as, K Rybníku 475, 252 42 Jesenice u Prahy, Czech Republic.
url: www.ferring.cz

Ferring, Denm. Ferring Laegemidler A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark.
url: www.ferring.dk

Ferring, Fin. Ferringlääkkeet Oy, Tähdenlennonkuja 1, PL 23, 02241 Espoo, Finland.
url: www.ferring.com

Ferring, Fr. Laboratoires Ferring SAS, 7 rue Jean-Baptiste-Clement, 94250 Gentilly, France.
url: www.ferring.com

Ferring, Ger. Ferring Arzneimittel GmbH, Wittland 11, 24109 Kiel, Germany.
url: www.ferring.de

Ferring, Gr. Ferring EPE, 42 Kapodistriou St, 10432 Athens, Greece.
url: www.ferring.com

Ferring, Hong Kong. Ferring Pharmaceuticals Ltd, Unit A, 9/F Garment Ctr, 576-586 Castle Peak Rd, Kowloon, Hong Kong.

Ferring, Hung. Ferring GmbH Gyógyszerkereskedelmi Képviselet, Szekszárdi út 10/b, 1138 Budapest, Hungary.

Ferring, India. Ferring Pharmaceuticals Pvt Ltd, 403/404 Sigma, 4th Floor, Technology St, Central Ave, Hiranandani Gardens, Powai, Mumbai 400 076, India.
url: www.ferring.com

Ferring, Irl. See *United Drug, Irl.*

Ferring, Israel. See *Lapidot, Israel.*

Ferring, Ital. Ferring S.p.A., Via Senigallia 18/2, 20161 Milan, Italy.
url: www.ferring.com

Ferring, Malaysia. See *United Italian, Malaysia.*

Ferring, Mex. Ferring S.A. de C.V., Av. Nemesio Diez Riega Mza. 2 Lote 15, Col. Parque Industrial Cerrillo II, 52000 Lerma, Mexico.
url: www.ferring.com

Ferring, Neth. Ferring BV, Postbus 184, 2130 AD Hoofddorp, Netherlands.
url: www.ferring.nl

Ferring, Norw. Ferring Legemidler AS, Postboks 4445 Nydalen, 0403 Oslo, Norway.
url: www.ferring.com

Ferring, NZ. See *Pharmaco, NZ.*

Ferring, Philipp. See *Diethelm, Philipp.*

Ferring, Pol. Ferring Pharmaceuticals BV Sp. zo.o., przedstawicielstwo w Polsce, ul. Królowej Marysieńki 11/4, 02-954 Warsaw, Poland.
url: www.ferringpl.com.pl

Ferring, Port. Ferring Portuguesa, Lda, Rua Professor Henrique de Barros, Edifício Sagres, 8 - Sala A, 2685-338 Prior Velho, Portugal.
url: www.ferring.com

Ferring, Rus. Ferring Pharmaceuticals B.V., Karmanitskii per. 9, 119002 Moscow, Russia.
url: www.ferring.ru

Ferring, S.Afr. Ferring (Pty) Ltd, P.O. Box 14358, Clubview 0014, South Africa.
url: www.ferring.com

Ferring, Singapore. See *United Italian, Singapore.*

Ferring, Spain. Ferring, Saturno 1, Edificio Saturno, Pozuelo de Alarcon, 28224 Madrid, Spain.
url: www.ferring.com

Ferring, Swed. Ferring AB, Box 4041, 203 11 Malmö, Sweden.
url: www.ferring.se

Ferring, Switz. Ferring SA, Industriestrasse 50a, 8304 Wallisellen, Switzerland.
url: www.ferring.com

Ferring, Thai. See *Pacific, Thai.*

Ferring, UK. Ferring Pharmaceuticals UK, The Courtyard, Waterside Drive, Langley, Berkshire, SL3 6EZ, UK.
url: www.ferring.com

Ferring, USA. Ferring Pharmaceuticals Inc., 400 Rella Bvld, Suffern, NY 10901, USA.
url: www.ferringusa.com

Ferro, Arg. Lab. Ferro, Av. Mate de Luna 4333, 4000 S.M. de Tucuman, Tucuman, Argentina.

Ferron, Indon. Ferron Par PT, Gedung Graha Elnusa Lt 3, Jl TB Simatupang Kav 1B, Jakarta Selatan, DKI Jaya, Indonesia.

Ferrosan, Cz. Ferrosan A/S, Rostislavová 11, 140 00 Prague 4, Czech Republic.

Ferrosan, Denm. Ferrosan A/S, Sydmarken 1-5, 2860 Søborg, Denmark.
url: www.ferrosan.com

Ferrosan, Fin. Oy Ferrosan AB, Kutojantie 11, 02630 Espoo, Finland.
url: www.ferrosan.fi

Ferrosan, Fr. Laboratoires Ferrosan, 64 rue Pierre-Charron, 75008 Paris, France.
url: www.imedeen.fr

Ferrosan, Pol. Ferrosan Poland Sp. zo.o., ul. Włodarzewska 45 D, 02-384 Warsaw, Poland.
url: www.ferrosan.com.pl

Ferrosan, Rus. Ferrosan A/S, Novy Arbat ul. 7, 119019 Moscow, Russia.
url: www.ferrosan.ru

Fertin, Denm. See *Meda, Denm.*

Fertin, Norw. See *Meda, Norw.*

FHC, Port. FHC Farmacêutica Lda, Parque Industrial de Mortágua, Lote 2, 3450-232 Mortágua, Portugal.

Fher, Ital. Fher, Divisione della Boehringer Ingelheim, Casella Postale, 50100 Florence, Italy.

Fher, Spain. See *Boehringer Ingelheim, Spain.*

Fibertone, USA. See *Marlyn, USA.*

FIC, Rus. FIC Medical, Krasnopresnenskaya nab. 12, Gostinitsa International-2, Of. 742, 123610 Moscow, Russia.
url: www.aha.ru

Fides, Ger. See *FidesLine, Ger.*

Fides Ecopharma, Spain. See *Rottapharm, Spain.*

FidesLine, Ger. FidesLine Biologische Heilmittel Heel GmbH, Dr.-Reckeweg-Str. 2-4, 76532 Baden-Baden, Germany.
url: www.fides.de

Fidex, Arg. Prod. Farm. Fidex S.A., Gral. Savio Ruta 88 Km 9.5, 7601 Batan Mar del Plata, Buenos Aires, Argentina.
url: www.fidexsa.com.ar

Fidia, Cz. See *Glynn, Cz.*

Fidia, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Fidia, Hung. See *CSC, Hung.*

Fidia, Indon. See *Combiphar, Indon.*

Fidia, Ital. Fidia Farmaceutici S.p.A., Via Ponte della Fabbrica 3/A, 35031 Abano Terme (Padua), Italy.

Fidia, Malaysia. See *Somedico, Malaysia.*

Fidia, Neth. See *Fidia, Ital.*

Fidia, Pol. See *Pharm Supply, Pol.*

Fidia, Thai. See *Diethelm, Thai.*

Fielding, USA. See *Novavax, USA.*

Filadams, Philipp. Filadams Pharma Inc., 37 Mapagkumbaba, Cor Matipid St, Sikatuna Vill, Quezon City, Philippines.

Filaxis, Arg. Laboratorios Filaxis S.A., Carlos Pellegrini 1023, Piso 7, 1009 Buenos Aires, Argentina.
url: www.filaxis.com

Filiz, Turk. Filiz Ecza Deposu Tic. Ltd. Şti., 2 Cad. 81, Sok. No: 12/1, Öveçler, İstanbul, Turkey.

Filofarm, Pol. Farmaceutyczna Spółdzielnia Pracy Filofarm, ul. Pułaskiego 39, 85-619 Bydgoszcz, Poland.
url: www.filofarm.com.pl

Filorga, Fr. Laboratoires Filorga, 18 rue de Miromesnil, 75008 Paris, France.
url: www.filorga.com

Fimo, Ital. F.I.M.O. S.r.l. Fabbrica Italiana Materiale Odontotecnico e Odontoiatrico, Via Edolo 40, 20125 Milan, Italy.

Finadiet, Arg. Finadiet S.A.C.I.F.I. Esp. Med., Hipolito Yrigoyen 3771, 1208 Buenos Aires, Argentina.
url: www.finadiet.com.ar

Finderm, Ital. Finderm Farmaceutici S.r.l. di Scaccia Fabbio e C., V.le Alcide de Gasperi 165, 95100 Catania, Italy.

Finmedical, Ital. Finmedical S.r.l., Vicolo de Bacchettoni 1a, 51100 Pistoia, Italy.

Finn Vita, Chile. Laboratorio Finn Vita SA, Los Conquistadores 2178, Providencia, Santiago, Chile.

Fiori, Ital. Dr F & C Fiori S.n.c., Corso San Maurizio 35, 10124 Turin, Italy.

FIRMA, Ital. FIRMA-Fabbr. Ital. Ritrov. Medic. Aff. S.p.A., Via di Scandicci 37, 50143 Florence, Italy.

First Horizon, USA. First Horizon Pharmaceutical Corp., 6195 Shiloh Rd, Alpharetta, GA 30005, USA.
url: www.firsthorizonpharm.com

Firstpharm, S.Afr. FirstPharm Pharmaceuticals (Pty) Ltd, P.O. Box 22544, KwaZulu-Natal, Glenashley 4022, South Africa.
url: www.firstpharm.co.za

Fischer, Israel. Fischer Pharmaceuticals Ltd, P.O. Box 39071, Tel Aviv 61390, Israel.
url: www.dr-fischer.com

Fischer, USA. Fischer Pharmaceuticals Inc., 7040 W Palmetto Park Rd 4, Suite 606, Boca Raton, FL 33433-3407, USA.
url: www.dr-fischer.com

Fisher, Neth. Dr Fisher Farma BV, Vijzelweg 32, 8243 PM Lelystad, Netherlands.

Fisiopharma, Cz. See *Fisiopharma, Ital.*

Fisiopharma, Ital. Fisiopharma S.r.l., Via Carnevali 116, 20158 Milan, Italy.

Fisons, USA. See *Celltech, USA.*

Fitobucaneve, Ital. Fitobucaneve S.r.l., Via Galvani 25/27, 20018 Sedriano (MI), Italy.

Fitolife, Ital. Laboratorio Fitolife S.r.l., Via Domiziana km 55, 80072 Arco Felice Pozzuoli (NA), Italy.
url: www.fitolife.it

Flamel, Fr. Flamel Technologies, Avenue Gustave Eiffel, 33608 Pessac Cedex, France.

Flamel, Neth. See *Flamel, Fr.*

Flamel, Port. See *Flamel, Fr.*

Flanders, USA. Flanders Inc., P.O. Box 80428, Charleston, SC 29416, USA.
url: www.flandersbuttocksointment.com

Fleet, Austral. C.B. Fleet Co. (Australia) P/L, P.O. Box 716, Braeside, VIC 3195, Australia.
url: www.ozpages.com/cbfleet

Fleet, Hong Kong. See *IDS, Hong Kong.*

Fleet, Malaysia. See *United Italian, Malaysia.*

Fleet, NZ. See *Baxter, NZ.*

Fleet, Philipp. See *Blooming Fields, Philipp.*

Fleet, Singapore. See *JDH, Singapore.*

Fleet, USA. C.B. Fleet Co. Inc., 4615 Murray Pl., P.O. Box 11349, Lynchburg, VA 24506, USA.
url: www.cbfleet.com

Fleet-Dewitt, Hong Kong. See *JDH, Hong Kong.*

Fleming, USA. Fleming & Co., 1733 Gilsinn Lane, Fenton, MO 63026, USA.
url: www.flemingcompany.com

Flex-Power, USA. Flex-Power, 1563 Solano Ave, P.O. Box 171, Berkeley, CA 94706, USA.
url: www.flexpower.com

Flora, Canad. Flora Mfg & Dist. Ltd, 7400 Fraser Park Drive, Burnaby, BC, V5J 5B9, Canada.

Florabio, Ger. Florabio GmbH, Muhlstr. 5-7, 71106 Magstadt, Germany.

Florafaun, Austral. Florafaun P/L, 16 Pearl Street, Sorrento, WA 6020, Australia.
url: www.florafaun.com.au

Flordis, Austral. Flordis Pty Ltd, Level 2, 3 Carlingford Rd, Epping, NSW 2121, Australia.
url: www.flordis.com.au

Florida, Arg. Drogueria Florida S.R.L., Franklin D. Roosevelt 3430/2, 1430 Buenos Aires, Argentina.

Floris, Israel. Floris, Misgav 20179, Israel.

Florizel, UK. Florizel Ltd, P.O. Box 138, Stevenage, Hertfordshire, SG2 8YN, UK.

Fluoritab, USA. Fluoritab Corp., P.O. Box 507, Temperance, MI 48182-0507, USA.

Flupal, Venez. Laboratorios Flupal C.A., Parcelamiento Industrial La Fe Parcel a Nro. B23, Macarao, Caracas 1000 A, Venezuela.

Flynn, Irl. See *Flynn, UK.*

Flynn, UK. Flynn Pharma Ltd, 2nd Floor, The Maltings, Bridge St, Hitchin, Hertfordshire, SG5 2DE, UK.

Focus, Hung. Focus, Hungary.

Focus, UK. Focus Pharmaceuticals Ltd, 5 Faraday Court, First Avenue, Centrum 100, Burton-upon-Trent, Staffordshire, DE14 2WX, UK.
url: www.focuspharmaceuticals.co.uk

Fonte, Switz. Fonte SA, Via Guiseppe Cattori 1, 6601 Locarno, Switzerland.
url: www.fontelocarno.ch

Fontelabor, Port. Fontelabor Produtos Farmacêuticos Lda, Quinta da Fonte, Edifício Vasco da Gama 19, Porto Salvo, 2780-730 Paco de Arcos, Portugal.

Fonten, Ital. Fonten Farmaceutici S.r.l., Via dei Castelli Romani 22, 00040 Pomezia (RM), Italy.

Fonterra, Indon. Fonterra Brands Indonesia PT, Jl Casablanca Kav 18, Wisma Staco Lt 15, Jakarta 12870, Indonesia.

Fonterra, Malaysia. Fonterra Brands (Malaysia) Sdn Bhd, Lot 12 Subang Hi-Tech Industrial Park, Batu Tiga, 40300 Shah Alam, Selangor, Malaysia.

Fonterra, Philipp. Fonterra Brands (Phils) Inc., 19/F Cyber One Tower, 11 Eastwood Ave, Eastwood City Cyber Park, Libis, Quezon City, Philippines.

Fontovit, Braz. Fontovit Laboratórios Ltda, Rua Antônio das Chagas 862, 04714-001 São Paulo, Brazil.
url: www.fontovit.com.br

Foramen, Philipp. See *Biolink, Philipp., Interhealthcare, Philipp.,* and *Solvang, Philipp.*

Ford Medical, UK. Ford Medical Associates Ltd, 8 Wyndham Way, Orchard Heights, Ashford, Kent, TN25 4PZ, UK.
url: www.fordmedical.co.uk

Forder, Arg. Forder Lab. Esp. Dermatologicas, Rivadavia 5747 Piso 5 Dto.A, 1406 Cdad., Buenos Aires, Argentina.

Forest, Hung. See *Repharma, Hung.*

Forest, Irl. See *Forest Laboratories, UK.*

Forest Laboratories, Cz. See *Forest Laboratories, UK.*

Forest Laboratories, Hong Kong. See *Hind Wing, Hong Kong,* and *Suburfarm, Hong Kong.*

Forest Laboratories, Pol. See *Nepentes, Pol.*

Forest Laboratories, Port. See *Forest Laboratories, UK.*

Forest Laboratories, UK. Forest Laboratories Europe, Bourne Rd, Bexley, Kent, DA5 1NX, UK.
url: www.forestlabs.com

Forest Laboratories, USA. Forest Laboratories Inc., 909 Third Ave, New York, NY 10022, USA.
url: www.frx.com

Forest Pharmaceuticals, USA. Forest Pharmaceuticals Inc., 13600 Shoreline Drive, St. Louis, MO 63045, USA.
url: www.forestpharm.com

Forley, UK. See *Goldshield, UK.*

Formenti, Cz. See *Formenti, Ital.*

Formenti, Hung. See *CSC, Hung.*

Formenti, Ital. Farmaceutici Formenti S.p.A., Via Correggio 43, 20149 Milan, Italy.

Formenti, Pol. See *Medagro, Pol.*

Formula, NZ. Formula Products, P.O. Box 36-443, Northcote, Auckland, New Zealand.

Fornet, Fr. Laboratoires Fornet, 7/13 bd Paul-Emile-Victor, 92200 Neuilly-sur-Seine, France.

Forster, Ger. Dr Förster GmbH, Odenwaldstr. 15, 63263 Neu-Isenburg, Germany.
url: www.drfoerster.de

Fortbenton, Arg. Lab. Fortbenton Co. S.A., Escalada 133, 1407 Buenos Aires, Argentina.
url: www.fortbenton.com.ar

Forte, USA. See *Eon, USA.*

Fortune, Hong Kong. Fortune Pharmacal Co. Ltd, 14A/F Zung Fu Industrial Bldg, 1067 King's Rd, Hong Kong.

Forum, Hung. See *Ferol, Hung.*

Forum, Neth. See *Britannia Pharmaceuticals, UK.*

Forum, Port. Forum Products Ltd, Portugal.

Fouchard, Chile. Laboratorio Fouchard SA, Monsenor Felix Cabrera 42, Of. 1, Providencia, Santiago, Chile.

Fougera, USA. E. Fougera Co., 60 Baylis Rd, Melville, NY 11747, USA.
url: www.fougera.com

Fournier, Austral. Fournier Laboratories, Level 4, Suite 7, 35 Spring St, 2022 Bondi Junction, NSW, Australia.

Fournier, Belg. Fournier Pharma SA, Rue des Trois Arbres 16b, 1180 Brussels, Belgium.
url: www.groupe-fournier.com

Fournier, Canad. Fournier Pharma Inc., 1010 Sherbrooke St W, 19th Floor, Montreal, Quebec, H3A 2R7, Canada.
url: www.fournierpharma.com

Fournier, Cz. Fournier Laboratoires, Norbertov 130/3, 162 00 Prague 6, Czech Republic.
url: www.groupe-fournier.fr

Fournier, Fr. Laboratoires Fournier SA, 153 rue de Buzenval, 92380 Garches, France.
url: www.groupe-fournier.com

Fournier, Ger. Fournier Pharma GmbH, Justus-von-Liebig Str. 16, 66280 Sulzbach, Germany.
url: www.groupe-fournier.com

Fournier, Gr. Fournier Hellas, 7 Granikou Str., 151 25 Marousi, Greece.
url: www.groupe-fournier.com

Fournier, Hong Kong. See *Wing Wai, Hong Kong,* and *Zuellig, Hong Kong.*

Fournier, Hung. Fournier Hungary Kft, Kapás u 38, 1123 Budapest, Hungary.

Fournier, Indon. Laboratories Fournier PT, Jl Tanah Abang II 37, 10160 Jakarta, Indonesia.

Fournier, Irl. Fournier Laboratories Ireland Ltd, Anngrove, Carrigtwohill, Co. Cork, Ireland.
url: www.groupe-fournier.com

Fournier, Ital. Fournier Farma S.p.A., Palazzo Caravaggio, Via Cassanese 224, 20090 Segrate (MI), Italy.
url: www.groupe-fournier.com

Fournier, Malaysia. See *Zuellig, Malaysia.*

Fournier, Philipp. Laboratoires Fournier Phils Inc., G/F Port Royale Place, 118 Rada St, Legaspi Vill, Makati City, Philippines.

Fournier, Pol. Fournier Polska Sp. zo.o, ul. Grzybowska 80/82, 00-844 Warsaw, Poland.
url: www.fournier.pl

Fournier, Port. Fournier Farmacêutica Portugal, Lda, Av Eng. Duarte Pacheco, Amoreiras, Torre 2 - 14B, 1070-102 Lisbon, Portugal.
url: www.groupe-fournier.com

Fournier, Rus. See *Beaufour-Ipsen, Rus.*

Fournier, Switz. See *Globopharm, Switz.*

Fournier, Thai. See *Pacific, Thai.*

Fournier, Turk. Fournier Laboratuan Tic. Ltd. Şti., A. Adnan Saygun Cad. 58, A Block Daire : 1 Ulus, Beşiktaş, İstanbul, 80600, Turkey.
url: www.groupe-fournier.com

Fournier, UK. See *Solvay, UK.*

Fournier SA, Spain. Fournier SA, Ce Euronova 3, Rda Poniente 16, Tres Cantos, 28760 Madrid, Spain.
url: www.fournierpharma.com

Fourtts, Singapore. See *Zyfas, Singapore.*

Fox, UK. Charles H Fox Ltd, 22 Tavistock St, Covent Garden, London, WC2E 7PY, UK.
url: www.charlesfox.co.uk

FP, Singapore. F.P. Marketing (S'Pore) Pte Ltd, 5 Pereira Rd, 04-03 Asiawide Industrial Building, S 368025, Singapore.

Framingham, Arg. Framingham Pharma SRL, Agoero 363, 1171 Buenos Aires, Argentina.

Francia, Ital. Francia Farmaceutici Industria Farmaco Biologica S.r.l., Via dei Pestagalli 7, 20138 Milan, Italy.

Franco-Indian, India. Franco-Indian Pharmaceuticals Ltd, 20 Dr E Moses Rd, Mumbai 400 011, India.
url: www.francoindian.com

Franconpharm, Ger. franconpharm Arzneimittel GmbH, Alexandrinenstr. 1, 96450 Coburg, Germany.

Frandiet, Fr. Frandiet SA, ZA des Savines, 101 rue Marc-Seguin, B.P. 315, 07503 Guilherand-Granges cdx, France.

Frankin, Hong Kong. Frankin Pharmaceutical Lab., 15/F China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.

Frasca, Arg. Laboratorios Frasca S.R.L., B. Blanca 1660, 1407 Buenos Aires, Argentina.

Freeda, USA. Freeda Vitamins Inc., 36 East 41st St, New York, NY 10017, USA.
url: www.freedavitamins.com

Fresenius, Belg. See *Fresenius Kabi, Belg.*

Fresenius, Hong Kong. See *Fresenius Kabi, Hong Kong.*

Fresenius, Israel. See *Genmedix, Israel,* and *Promedico, Israel.*

Fresenius, Switz. See *Fresenius Kabi, Switz.*

Fresenius Biotech, Cz. See *Fresenius Kabi, Ger.*

Fresenius Biotech, Thai. See *Natural Media, Thai.*

Fresenius Hemocare, Singapore. See *Diethelm, Singapore.*

Fresenius Hemocare, Thai. See *Natural Media, Thai.*

Fresenius Kabi, Arg. Fresenius Kabi Argentina S.A., Lavalleja 1214, 1414 Buenos Aires, Argentina.
url: www.fresenius-kabi.com

Fresenius Kabi, Austria. Fresenius Kabi Austria GmbH, Hafnerstrasse 36, A-8055 Graz, Austria.
url: www.fresenius-kabi.at

Fresenius Kabi, Belg. Fresenius Kabi SA, Molenberglei 7, 2627 Schelle, Belgium.
url: www.fresenius-kabi.com

Fresenius Kabi, Chile. Lab. Fresenius Kabi Chile Ltda, Calle Nueva 1661 F, Huechuraba, Chile.

Fresenius Kabi, Cz. Fresenius Kabi sro, Křenová 1, 162 00 Prague 6, Czech Republic.

Fresenius Kabi, Denm. Fresenius Kabi, Bredgade 71, 1260 Copenhagen K, Denmark.
url: www.fresenius-kabi.com

Fresenius Kabi, Fin. Fresenius Kabi AB, Rajatorpantie 41 C, 01640 Vantaa, Finland.
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Fresenius Kabi, Fr. Fresenius Kabi France, 5 place du Marivel, 92316 Sèvres cdx, France.
url: www.fresenius-kabi.com

Fresenius Kabi, Ger. Fresenius Kabi Deutschland GmbH, Else-Kroner-Str. 1, 61352 Bad Homburg v. d. H., Germany.
url: www.fresenius.de

Fresenius Kabi, Gr. Fresenius Kabi Hellas A.E., 354 Messoghion Ave, 153 41 Agia Paraskevi, Greece.
url: www.fresenius-kabi.com

Fresenius Kabi, Hong Kong. Fresenius Kabi Hong Kong Ltd, Rm 5101-23, 51/F Sun Hung Kai Ctr, 30 Harbour Rd, Wanchai, Hong Kong.
url: www.fresenius-kabi.com

Fresenius Kabi, Hung. Fresenius Kabi Hungary Kft, Lajos u 48-66 E ep. I. em, 1036 Budapest, Hungary.

Fresenius Kabi, Indon. Fresenius Kabi PT, Ariobimo Sentral Bldg Lt 11, Jl HR Rasuna Said, Kav X-2 Kav 5, Kuningan, Jakarta, Indonesia.

Fresenius Kabi, Irl. Fresenius Kabi Ireland, Unit 3B, Fingal Bay Business Park, Balbriggan, Co. Dublin, Ireland.
url: www.fresenius-kabi.com

Fresenius Kabi, Ital. Fresenius Kabi Italia S.p.A., Via Camagre 41, 37063 Isola della Scala (VR), Italy.
url: www.fresenius-kabi.com

Fresenius Kabi, Malaysia. See *Antah, Malaysia.*

Fresenius Kabi, Mex. Laboratorios Frenesius Kabi Mexico S.A. de C.V., Paseo del Norte 5300, Km 12.5 Zapopan, San Juan de Oco, 45010 Guadalajara, Jalisco, Mexico.
url: www.freseniuskabi.com.mx

Fresenius Kabi, Neth. Fresenius Kabi, Netherlands.

Fresenius Kabi, Norw. Fresenius Kabi Norge AS, Markedsavd., Gjerdrumsv. 12, 0486 Oslo, Norway.
url: www.fresenius-kabi.com

Fresenius Kabi, NZ. See *Baxter, NZ.*

Fresenius Kabi, Philipp. Fresenius Kabi Phils Inc., 16/F Equitable Bank Tower, 8751 Paseo de Roxas, Makati City, Philippines.

Fresenius Kabi, Pol. Fresenius Kabi Polska Sp. zo.o., ul. Hrubieszowska 2, Crown Tower, 01-209 Warsaw, Poland.
url: www.freseniuskabi.com

Fresenius Kabi, Port. Fresenius Kabi Pharma Portugal, Lda, Avenida do Forte 3, Edifício Suécia III, 2795-504 Carnaxide, Portugal.
url: www.fresenius-kabi.com

Fresenius Kabi, Rus. See *Pfizer, Rus.*

Fresenius Kabi, S.Afr. Fresenius Kabi, P.O. Box 4156, Halfway House, South Africa.
url: www.fresenius-kabi.co.za

Fresenius Kabi, Singapore. See *Diethelm, Singapore.*

Fresenius Kabi, Spain. Fresenius Kabi España, Marina 16-18, Pl 17, Torre Mapfre-Villa Olimpica, 08005 Barcelona, Spain.
url: www.fresenius-kabi.com

Fresenius Kabi, Swed. Fresenius Kabi, Rapsgatan 7, 751 74 Uppsala, Sweden.
url: www.fresenius-kabi.se

Fresenius Kabi, Switz. Fresenius Kabi (Schweiz) AG, Spichermatt 30, 6371 Stans, Switzerland.
url: www.fresenius-kabi.com

Fresenius Kabi, Thai. Fresenius Kabi Thailand Ltd, The Millennia Building, 2403-4, 24th Floor, 62 Lungsuan Road, Lumpini, Patumwan, Bangkok 10330, Thailand.
url: www.fresenius-kabi.com

Fresenius Kabi, Turk. Fresenius Kabi İlaç Sanayi ve Ticaret Ltd. Şti., Eski Buyukdere Cad, Ayazaga Yolu No: 7 GIZ 2000 Plaza Kat: 4, Maslak, İstanbul, Turkey.
url: www.fresenius-kabi.com

Fresenius Kabi, UK. Fresenius Kabi Ltd, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, UK.
url: www.fresenius-kabi.co.uk

Fresenius Medical, Austral. Fresenius Medical Care Australia P/L, 305 Woodpark Rd, Smithfield, NSW 2164, Australia.
url: www.fmc-ag.com

Fresenius Medical, Austria. See *Fresenius Kabi, Ger.*
url: www.fmc-ag.com

Fresenius Medical, Cz. Fresenius Medical Care sro, Lužna 591, 160 00 Prague 6, Czech Republic.

Fresenius Medical, Denm. Fresenius Medical Care Danmark A/S, Herstedvang 14, 2620 Albertslund, Denmark.
url: www.fmc-ag.com

Fresenius Medical, Fin. Fresenius Medical Care Suomi Oy, Vattuniemenranta 2, 00210 Helsinki, Finland.
url: www.freseniussuomi.fi

Fresenius Medical, Ger. See *Fresenius Kabi, Ger.*

Fresenius Medical, Hung. Fresenius Medical Care Magyarország Egeszegugyi Kft, Csévi köz 7/b, 1025 Budapest, Hungary.

Fresenius Medical, Neth. Fresenius Medical Care Nederland BV, Vimmerik 22, 5253 CB Nieuwkuijk, Netherlands.

Fresenius Medical, Pol. Fresenius Medical Care, ul. Krzywa 13, 60-118 Poznań, Poland.

Fresenius Medical, Port. Fresenius Medical Care, Lda, Rua da Boaviagem 35, Lugar de Crestins, Moreira, 4470 MAIA, Portugal.
url: www.fmc-ag.com

Fresenius Medical, Spain. Fresenius Medical Care, Ctra Vallderiolf Km 0.4, La Roca Del Valles, 08430 Barcelona, Spain.
url: www.fmc-ag.com

Fresenius Medical, Swed. Fresenius Medical Care Sverige AB, Djupdalsvägen 24, 192 51 Sollentuna, Sweden.

Fresenius Medical, Switz. See *Fresenius Kabi, Switz.*

Fresenius Medical, USA. Fresenius Medical Care North America, 95 Hayden Ave, Lexington, MA 02420, USA.
url: www.fmcna.com

Fresh Ones, Arg. Distribuidora Fresh ones S.A., Las Heras 4857, 1603 Villa Martelli, Buenos Aires, Argentina.

Frezyderm, Gr. Frezyderm, Menandrou 75, 104 37 Athens, Greece.

Friesland, Hong Kong. See *Keller, Hong Kong.*

Friesland, Malaysia. See *Dutch Lady, Malaysia.*

Friesland, Singapore. See *Diethelm, Singapore.*

Frik, Turk. Dr. F. Frik İlaç San. ve Tic. Ltd. Şti., Aydınevler Mah. Sanayi cad. No: 22, Küçükyalı, İstanbul, 34854, Turkey.
url: www.frik.com.tr

Frisian Flag, Indon. Frisian Flag, Jl Raya Bogo Km 5, Pasar Rebo, 13760 Jakarta, Indonesia.

Frisocare, Hong Kong. See *Keller, Hong Kong.*

Frosst, Spain. See *MSD, Spain.*

Fruit of the Earth, Canad. Fruit of the Earth, 6090 White Hart Lane, Mississauga, Ontario, L5R 3Y4, Canada.

Fuca, Fr. Laboratoires Fuca, 1 bis, rue de Plaisance, 94732 Nogent-sur-Marne cdx, France.

Fucus, Arg. Laboratorio Farmaciutico Argentino S.A., Santiago del Estero 3117, 1640 Martinez, Buenos Aires, Argentina.

Fuji, Jpn. Fuji Chemical Industry Co Ltd, 55 Yokohoonji, Kamiichi-machi, Toyama-Pref. 930-0397, Japan.

Fujimoto, Jpn. Fujimoto Pharmaceutical Corp., 1-3-40 Nishi-Otsuka, Matsubara, Osaka 580-8514, Japan.
url: www.fujimoto-pharm.co.jp

Fujisawa, Austria. Fujisawa GmbH, Linzerstrasse 221/E0.2, A-1140 Vienna, Austria.
url: www.fujisawa.at

Fujisawa, Belg. Fujisawa Belgian Branch, Sint-Maartenstraat 12A, 3000 Leuven, Belgium.
url: www.fujisawa.be

Fujisawa, Chile. See *Pharma Investi, Chile.*

Fujisawa, Denm. Fujisawa Scandinavia AB, Carlsbergvej 24, 3400 Hillerød, Denmark.
url: www.fujisawaeurope.com

Fujisawa, Ger. Fujisawa Deutschland GmbH, Berg-am-Laim-Str. 129, 81673 Munich, Germany.
url: www.fujisawa-deutschland.de

Fujisawa, Hong Kong. Fujisawa Pharmaceuticals (China) Co Ltd, Suite 708-09, 7/F Prudential Tower, The Gateway, Harbour City, Kowloon, Hong Kong.
url: www.fujisawa.com

Fujisawa, Hung. See *Pro-Pharma, Hung.*

Fujisawa, Israel. See *Teva, Israel.*

Fujisawa, Jpn. Fujisawa Pharmaceutical Co. Ltd, 4-7 Doshomachi 3-chome, Chuo-ku, Osaka 541-8514, Japan.
url: www.fujisawa.co.jp

Fujisawa, Philipp. See *Zuellig, Philipp.*

Fujisawa, Switz. See *Astellas, Switz.*

Fujisawa, Thai. See *BJC, Thai.*

Fujisawa, USA. See *Astellas, USA.*

Fulcrum, Irl. Fulcrum Medical Marketing, Cahill May Roberts, Pharmapark, Chapelizod, Dublin 20, Ireland.
url: www.fulcrummarketing.ie

Fulford, India. Fulford (India) Ltd, Eureka Towers, Mindspace, Link Rd, Malad (West), Mumbai 400 064, India.

Fulton, Ital. Fulton Medicinali S.p.A., Via Marconi 28/9, 20020 Arese, Italy.
url: www.fulton.it

Fumedica, Ger. Fumedica GmbH, Industriestr. 40, 44628 Herne, Germany.
url: www.fumedica.de

Fumouze, Fr. Laboratoires Fumouze, Le Malesherbes, 110-114 rue Victor-Hugo, 92303 Levallois-Perret cdx, France.

Fumouze, Hong Kong. See *Trinity, Hong Kong.*

Fumouze, Israel. See *Naveh, Israel.*

Fumouze, Malaysia. See *Apex, Malaysia.*

Fumouze, Singapore. See *Pan-Malayan, Singapore.*

Funcke, Cz. Pharma Funcke, Czech Republic.

Funk, Spain. See *Almirall, Spain.*

Funke, Cz. See *Funke, Ger.*

Funke, Ger. Pharma Funke GmbH, Oberhausen, Germany.

Fuso, Hong Kong. See *Hing Ah, Hong Kong,* and *Primal, Hong Kong.*

Fuso, Jpn. Fuso Pharmaceutical Industries Ltd, 2-3-11 Morinomiya, Joto-ku, Osaka 536-8523, Japan.

Fustery, Mex. See *Ivax, Mex.*

G & W, USA. G & W Laboratories Inc., 111 Coolidge St, South Plainfield, NJ 07080-3895, USA.
url: www.gwlabs.com

G Pharm, Fr. Laboratoires G Pharm SAS, 34980 Saint-Clément-de-Rivière, France.

GA, Gr. GA Pharmaceuticals S.A., Agisilaou 46, 173 41 Athens, Greece.
url: www.gap.gr

GABA, Belg. See *GABA, Neth.*

GABA, Cz. See *GABA, Switz.*

GABA, Fin. See *GABA, Switz.*

GABA, Fr. Laboratoires GABA, 86 rue du Dome, 92514 Boulogne cdx, France.
url: www.gaba.com

GABA, Ger. GABA GmbH, Berner Weg 7, 79539 Lorrach, Germany.
url: www.gaba-dent.de

GABA, Neth. GABA BV, Bolderweg 1, 1332 AX Almere, Netherlands.
url: www.gaba-bv.nl

GABA, Port. See *GABA, Ger.*

GABA, Switz. GABA AG, Pharmazeutische und kosmetische Praparate, Grabetsmattweg, 4106 Therwil, Switzerland.
url: www.gaba.ch

Gabriel, Gr. Gabriel Health Ltd, 14 Gr. Kousidi, 15772 Athens, Greece.

Gache, Venez. Productos Gache S.A., Calle La Industria, Ed. Lemar P.B., Urb. Palo Verde, Caracas, Venezuela.

Gador, Arg. Gador S.A., Darwin 429, 1414 Buenos Aires, Argentina.
url: www.gador.com.ar

Gahler, Canad. Gahler Enterprises Ltd, 3655 Bonneville Pl, Burnaby, British Colombia, V3N 4S9, Canada.

Gaily, Hong Kong. Gaily Pharmaceutical Co Ltd, Rm 1307, 13/F Leader Ind Ctr, 57-59 Au Pui Wan St, Fo Tan, NT, Hong Kong.

Gal, Pol. Sepcjalistyczne Przedsiębiorstwo Rolno-Przetwórcze Gal, ul. Krótka 4, 61-012 Poznań, Poland.
url: www.gal.com.pl

Galactopharm, Ger. Galactopharm Hans Sanders, Sudstr. 10, 49751 Sogel, Germany.
url: www.galactopharm.de

Galagen, USA. See *Hormel, USA.*

Galderma, Arg. Galderma Argentina S.A., Av Juramento 1775, Piso 3, 1428 Ed. Juramento Plaza, Buenos Aires, Argentina.
url: www.galderma.com.ar

Galderma, Austral. Galderma Australia P/L, P.O. Box 502, Frenchs Forest, NSW 2086, Australia.
url: www.galderma.com

Galderma, Belg. Galderma Belgilux SA, Fountain Business Centre Bornem, Gebouw 5, bus 205, Van Kerckhovenstraat 110, 2880 Bornem, Belgium.
url: www.galderma.com

Galderma, Braz. Galderma Brasil Ltda, Av. Nações Unidas, 18001, 6th Floor, Vila Almeida, 04795-100 São Paulo, SP, Brazil.
url: www.galderma.com

Galderma, Canad. Galderma Canada Inc., 7300 Warden Ave, Suite 210, Markham, Ontario, L3R 9Z6, Canada.
url: www.galderma.com

Galderma, Chile. Galderma Chile Laboratorios Ltda, Europa 2066, Providencia, Santiago, Chile.

Galderma, Cz. See *Galderma, Fr.*

Galderma, Denm. Galderma Svenska, c/o Regus House, Lars Bjørnsstraede 3, 1454 Copenhagen K, Denmark.
url: www.galderma.com

Galderma, Fin. Galderma Nordic AB, Mannerheimintie 12 B, 00100 Helsinki, Finland.
url: www.galderma.com

Galderma, Fr. Laboratoires Galderma, Tour Europlaza, La Défense 4, 20 av. Andre-Prothin, 92927 La Défense cdx, France.
url: www.galderma.com

Galderma, Ger. Galderma Laboratorium GmbH, Munzinger Str. 5, 79111 Freiburg i. Br., Germany.
url: www.galderma.de

Galderma, Hong Kong. Galderma Hong Kong Ltd, Unit 1303, 13/F CRE Building, 303 Hennessy Rd, Wanchai, Hong Kong.
url: www.galderma.com

Galderma, Hung. See *Ewopharma, Hung.*

Galderma, India. Galderma (India) Pvt Ltd, 23 Steelmade Industrial Estate, 2nd Floor, Marol Village, Andheri (E), Mumbai 400 059, India.
url: www.galderma.com

Galderma, Irl. See *Allphar, Irl.*

Galderma, Israel. See *Luxembourg, Israel.*

Galderma, Ital. Galderma Italia S.p.A., C. Dir. Colleoni Pal. Sirio 3, 20041 Agrate Brianza (MI), Italy.
url: www.galderma.com

Galderma, Malaysia. See *Summit, Malaysia.*

Galderma, Mex. Galderma Mexico S.A. de C.V., Jose Maria Ibarraran No. 20, Col. San Jose Insurgentes, 03900 Mexico D.F., Mexico.
url: www.galderma.com.mx

Galderma, Neth. Galderma S.A., Avelingen-West 5, 4202 MS Gorinchem, Netherlands.
url: www.galderma.com

Galderma, Norw. Galderma Nordic AB, c/o Regus, Ibsenkvartalet, CJ Hambros plass 2 C, 0164 Oslo, Norway.
url: www.galderma.com

Galderma, NZ. See *Pacific, NZ.*

Galderma, Philipp. Galderma Philippines, Unit 2802, 28/F Atlanta Ctr, 31 Annapolis St, Greenhills, San Juan, Metro Manila, Philippines.

Galderma, Pol. Galderma Polska Sp. zo.o., ul. Łączyny 4, 02-820 Warsaw, Poland.

Galderma, Port. Laboratórios Galderma, SA, Av Duque d'Ávila 185, 1050-082 Lisbon, Portugal.
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Galderma, Rus. Galderma SA, Strominskiy pereulok, 6, 107076 Moscow, Russia.
url: www.galderma.com

Galderma, S.Afr. Galderma Laboratories SA (Pty) Ltd, P.O. Box 71150, Bryanston 2021, South Africa.
url: www.galderma.com

Galderma, Singapore. See *Summit, Singapore.*

Galderma, Spain. Galderma, C/ Agustin de Foxa 29 - 6 pl, 28036 Madrid, Spain.
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Galderma, Swed. Galderma Nordic AB, Box 15028, 167 15 Bromma, Sweden.
url: www.galderma.com

Galderma, Switz. Galderma SA, Zugerstrasse 8, 6330 Cham, Switzerland.
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Galderma, Thai. See *US Summit, Thai.*

Galderma, UK. Galderma (UK) Ltd, Meridien House, 69-71 Clarendon Rd, Watford, Hertfordshire, WD17 1DS, UK.
url: www.galderma.com

Galderma, USA. Galderma Laboratories Inc., 14501 North Freeway, Fort Worth, TX 76177, USA.
url: www.galdermausa.com

Galderma, Venez. Laboratorios Galderma Venezuela S.A., Av. Lima con Paseo Colón, Edificio Polar (Nestle), Piso 14, Oficina 14A, Plaza Venezuela Los Caobos, Caracas, Venezuela.
url: www.galderma.com.ve

Galen, Canad. See *Pfizer, Canad.*

Galen, Ger. Galenpharma, GmbH, Wittland 13, 24109 Kiel, Germany.

Galen, Irl. See *Allphar, Irl.*

Galen, Mex. See *Probiomed, Mex.*

Galen, Neth. See *Galen, UK.*

Galen, Port. See *Galen, UK.*

Galen, Turk. Galen İlaç San A.Ş., Barbaros Mah, Evren Cad. Çim Sok. No: 54 Balmumcu, Kadıköy, İstanbul, 81100, Turkey.

Galen, UK. Galen Ltd, Seagoe Industrial Estate, Craigavon, Northern Ireland, BT63 5UA, UK.
url: www.galen.co.uk

Galena, Cz. See *Ivax, Cz.*

Galena, Pol. Farmaceutyczna Spółdzielnia Pracy Galena, ul. Krucza 62, 50-984 Wrocław, Poland.
url: www.galena.pl

Galena, Rus. See *Ivax, Rus.*

Galena, Thai. See *SPB, Thai.*

Galenica, Gr. Galenica A.E., 2 Achilleos St., 104 37 Athens, Greece.
url: www.galenica.gr

Galenica, Hung. Galenica, Hold u. 16/D, 8200 Veszprém, Hungary.
url: www.galenica.hu

Galenika, Ger. See *Hetterich, Ger.*

Galenika, Hung. See *Inex, Hung.*

Galenium, Indon. Galenium Pharmasia Laboratories PT, Jl Aditiawarman No 67, Kebayoran Baru, 12160 Jakarta Selatan, Indonesia.

Galenium, Malaysia. See *Germax, Malaysia.*

Galeno, Venez. Galeno Química C.A., 4ta.Transv., Edif.Centro Ind. de Boleita-Piso 1, Urb. Boleita Sur Caracas, Caracas, Venezuela.

Galenogal, Braz. See *Hertz, Braz.*

Galenowe Olsztyn, Pol. Laboratorium Galenowe Olsztyn Sp. zo.o., ul. Spółdzielcza 25 A, 11-001 Dywity, Poland.
url: www.labgal.com.pl

Galenus, Gr. Galenus Pharmaceuticals SA, Jean Moreas 33, Halandri, Greece.
url: www.galenus.gr

Galenus, Pol. Farmaceutyczno-Chemiczna Spółdzielnia Pracy Galenus, ul. Senatorska 36, 00-095 Warsaw, Poland.
url: www.fp.com.pl/galenus

Galephar, Fr. Laboratoires Galéphar, ZI de Krafft, bat B, 67150 Erstein, France.

Galephar, Switz. Galéphar SA, rue de l'Eglise 5, 1146 Mollens, Switzerland.
url: www.galephar.net

Galepharma, Turk. Galepharma Medikal Elektronik Tic. Ltd. Şti., Meşrutiye Cad. No: 10/23, Bakanliklar, Ankara, Turkey.

Galex, Cz. Galex, Czech Republic.

Gallia, Braz. Gallia Farmacêutica Ltda, Av. Montese 840, 31565-150 Belo Horizonte, MG, Brazil.

Gallia, Fr. Laboratoires Gallia, B.P. 432, 69654 Villefranche-sur-Saône cdx, France.

Gallivit, Fr. Gallivit France (Lab), 12 rue du Quatre-Septembre, 75002 Paris, France.

Galmed, Cz. Galmed as, Ostrava, Czech Republic.

Galpharm, UK. GalPharm International Ltd, Hugh House, Galpharm Way, Upper Cliffe Rd, Dodworth Business Park, Dodworth, Barnsley, South Yorkshire, S75 3SP, UK.
url: www.galpharm.co.uk

Galpharma, Israel. See *Luxembourg, Israel.*

Gambar, Ital. Laboratori Gambar S.r.l., Via Bolognola 45, 00138 Rome, Italy.

Gambro, Cz. See *Gambro, Swed.*

Gambro, Denm. Gambro A/S, Jydekrogen 8, 2625 Vallensbaek, Denmark.
url: www.gambro.com

Gambro, Fin. Oy Gambro AB, Sahaajankatu 24, PL 30, 00811 Helsinki, Finland.
url: www.gambro.com

Gambro, Hung. Gambro Egeszsegugyi Szolgaltato es Kereskedelmi Kft, Diósárok u 5, 1125 Budapest, Hungary.

Gambro, Israel. See *Teva, Israel.*

Gambro, Neth. See *Gambro, Swed.*

Gambro, Port. See *Gambro, Swed.*

Gambro, Spain. Gambro, Avda de la Industria 16, Coslada, 28820 Madrid, Spain.
url: www.gambro.com

Gambro, Swed. Gambro, Box 10101, 220 10 Lund, Sweden.
url: www.gambro.se

Gambro, USA. Gambro Healthcare International, 10810 W Collins Ave, Lakewood, CO 80215-4498, USA.
url: www.gambrohealthcare.com

Gamida-Medequip, Israel. Gamida-Medequip Ltd, 54 Harei Yehuda St, Savyon 56530, Israel.

Ganassini, Fr. Istituto Ganassini, 124 bd Haussmann, 75008 Paris, France.
url: www.ganassini.fr

Ganassini, Ital. Istituto Ganassini S.p.A. di Ricerche Biochimiche, Via Gaggia 16, 20139 Milan, Italy.
url: www.ganassini.it

Gandhour, Fr. Laboratoires Gandhour, 1 bis, rue de Plaisance, 94732 Nogent-sur-Marne cdx, France.

Gap, Gr. See *GA, Gr.*

GAR, Singapore. See *Innomed, Singapore.*

Garant, Ital. Laboratorio Chimico Garant S.r.l., Via Melchiorre Gioia 47, 20124 Milan, Italy.

Garden House, Arg. Lab. Garden House S.A., Estomba 1058/60, 1427 Buenos Aires, Argentina.

Garec, S.Afr. Garec Pharmaceuticals, P.O. Box 1123, Halfway House 1685, South Africa.

Garnier, UK. Laboratoires Garnier, Golden Ltd, 255 Hammersmith Rd, London, W6 8AZ, UK.
url: www.garnier.com

Gaschler, Ger. Pharma-Laboratorium S.M. Gaschler GmbH, Oeschlanderweg 17a, 88131 Lindau, Germany.

Gastroenterologicos, Mex. Gastroenterológicos S.A. de C.V., Viena 56, Del Carmen Coyoacan, 04100 Mexico D.F., Mexico.

Gate, USA. See *Teva, USA.*

Gattefosse, Hong Kong. See *Great Liaison, Hong Kong.*

Gautier, Arg. Lab. Gautier S.A. Argentina, Terrada 1270, 1416 Buenos Aires, Argentina.

Gayoso, Spain. Gayoso, Ctar M-300 Km 29.92, 28802 Alcala de Henares, Madrid, Spain.
url: www.laboratorios-gayoso.com

GBF, Philipp. GBF Pharma & Medical Supplies, GBF Bldg, D' Garden, Bago Aplaya, Talomo District, Davao City, Philippines.

GC, Venez. Laboratorio Generico de Calidad GC, Av. 20 Puente Restaurador a Río, Edif. Pulmobronk, Parroquia Sta. Teresa, Caracas, Venezuela.

GD, Ital. GD Tecnologie Interdisciplinari Farmaceutiche S.r.l., Via Augusto Gaudenzi 29, 00163 Rome, Italy.
url: www.gditalia.biz

GE, Belg. GE Healthcare SA, Koningin Astridlaan 49, 1780 Wemmel, Belgium.
url: www.gehealthcare.com

GE, Cz. GE Healthcare (South Central Europe) Handels GmbH, Vyskocilova 1422/1a, 140 28 Praha 4, Czech Republic.

GE, Ger. GE Medical Systems Accessories & Supplies GmbH, Falkenried 88, 20251 Hamburg, Germany.
url: www.medimex.de

GE, Gr. GE Health Care, Kyprou 156 & Kon/poleos 91, 164 51 Argyroupoli, Greece.

GE, Port. Satis - GE Healthcare, Edifício Ramazzotti, Av. do Forte 6-6A, 2790-072 Carnaxide, Portugal.

GE Healthcare, Neth. GE Healthcare BV, Cygne Centre, 5612 AP Eindhoven, Netherlands.

GE Healthcare, NZ. See *Amersham, NZ.*

GE Healthcare, USA. See *Amersham Biosciences, USA.*

Gea, Denm. A/S GEA, Kanalholmen 8-12, 2650 Hvidovre, Denmark.
url: www.hexal.dk

Gea, Fin. Oy Gea AB, Rajatorpantie 41, 01640 Vantaa, Finland.
url: www.gea-pharm.fi

Gea, Norw. GEA Farmaceutisk Fabrik AS, Stortorvet 10, 0155 Oslo, Norway.
url: www.gea-pharm.com

Gea, Pol. See *Hexal, Pol.*

Gea, Swed. GEA Farmaceutisk Fabrik AB, Berga Allé 1 E, 254 52 Helsingborg, Sweden.
url: www.gea-pharm.se

Gea, Switz. See *Ecosol, Switz.*

Gebauer, Canad. See *Gebauer, USA.*

Gebauer, Hong Kong. See *Vantone, Hong Kong.*

Gebauer, USA. Gebauer Co., 4444 East 153rd St., Cleveland, OH 44128, USA.
url: www.gebauerco.com

Gebro, Austria. Gebro Pharma GmbH, A-6391 Fieberbrunn, Austria.
url: www.gebro.com

Gebro, Cz. See *Gebro, Austria.*

Gebro, Hung. See *Sager, Hung.*

Gebro, Spain. Gebro Pharma, C/ Monestir 23, 08034 Barcelona, Spain.
url: www.gebro.com

Gebro, Switz. Gebro Pharma SA, Postfach 397, 4410 Liestal, Switzerland.
url: www.gebro.com

Gedeon Richter, Cz. Gedeon Richter AT, Italská 13, 120 00 Prague 2, Czech Republic.
url: www.richtergedeon.cz

Gedeon Richter, Hong Kong. See *Mekim, Hong Kong.*

Gedeon Richter, Hung. Gedeon Richter Rt, Gyömrői út 19-21, 1103 Budapest, Hungary.

Gedeon Richter, Israel. See *Trima, Israel.*

Gedeon Richter, Malaysia. See *Pahang, Malaysia.*

Gedeon Richter, Rus. Gedeon Richter, Krasnaya Presnya ul. 1-7, 123242 Moscow, Russia.
url: www.g-richter.ru

Gedeon Richter, Singapore. See *Sime Darby, Singapore.*

Gedeon Richter, Thai. See *Medline, Thai.*

Gedis, Ital. Gedis S.r.l., Via Vezzolano 15, 10153 Turin, Italy.

Geigy, USA. See *Novartis, USA.*

Geistlich, Hung. See *SATCO, Hung.*

Geistlich, Irl. Geistlich Pharma, 36 Lower Stephen Street, Dublin 2, Ireland.
url: www.geistlich.com

Geistlich, Singapore. See *Diethelm, Singapore.*

Geistlich, Switz. Geistlich-Pharma AG, 6110 Wolhusen, Switzerland.
url: www.geistlich.ch

Geistlich, UK. Geistlich Pharma, Newton Bank, Long Lane, Chester, Cheshire, CH2 3PF, UK.
url: www.geistlich.co.uk

Gelcaps, Mex. Gelcaps Exp. de Mexico SA de CV, Circuito Centro Civico 27, 53100 Naucalpan de Juarez Ciudad Satel, Estado de Mexico, Mexico.

Gelos, Cz. See *Gelos, Spain.*

Gelos, Port. See *Gelos, Spain.*

Gelos, Spain. Gelos, Joan XXIII 10, Esplugues de Llobregat, 08950 Barcelona, Spain.
url: www.gelos.es

Gelpharma, Mex. Gelpharma SA de CV, Priv. Agustin Gutierrez 125, 3340 General Anaya, Mexico DF, Mexico.

Gemardi, Thai. See *Diethelm, Thai.*

Gemballa, Braz. Laboratórios Gemballa Ltda, Avenida Sete de Setembro 50, 89160-000 Rio do Sul, SC, Brazil.

Gemelli, Denm. Gemelli A/S, Nybrovej 110, 2800 Lyngby, Denmark.

Gemepe, Arg. Lab. GeMePe S.A., Jovellanos 886, 1267 Buenos Aires, Argentina.
url: www.gemepe.com.ar

Gemi, Pol. Przedsiębiorstwo Produkcji Farmaceutycznej Gemi, ul. Mickiewicza 36, 05-480 Karczew k/ Otwocka, Poland.
url: www.gemi.pl

Geminis, Arg. Géminis S.A., Flora 582, 1706 Haedo, Buenos Aires, Argentina.

Gen, Turk. Gen İlaç ve Sağlık Ürünleri San. ve Tic. Ltd. Şti., Hal Yolu Caddesi Bay Plaza, No: 5 K: 5, İçerenköy, İstanbul, Turkey.
url: www.gen-ilac.com

GenAsia, Philipp. GenAsia Biotech L L Corp., UG 41, Cityland Pioneer, 128 Pioneer St, Mandaluyong City, Philippines.

Genbay, Turk. Genbay, Turkey.

GenDerm, USA. See *Medicis, USA.*

Genedec, Port. Genedec Medicamentos Genéricos Lda, Rua Sebastião e Silva 56, 2745-838 Massamá, Portugal.

Genentech, Rus. See *Roche, Rus.*

Genentech, USA. Genentech Inc., 1 DNA Way, South San Francisco, CA 94080-4990, USA.
url: www.gene.com

Genepharm, Cz. See *Genepharm, Gr.*

Genepharm, Gr. Genepharma Group A.E., 18 km Marathon Ave, 153 51 Pallini, Greece.
url: www.genepharm.gr

General Dietary, UK. General Dietary Ltd, P.O. Box 38, Kingston-upon-Thames, Surrey, KT2 7YP, UK.

General Drug, Philipp. See *United Home, Philipp.*

General Drugs, Thai. General Drugs House Co. Ltd, 2-4 Soi Lard Prao 82, Bangkok 10310, Thailand.
url: www.gdh.co.th

General Drugs House, Philipp. See *GBF, Philipp.*

General Electric, Chile. General Electric Inc., Alcántara 200 Piso 11, Las Condes, Santiago, Chile.

General Nutrition, Canad. General Nutrition Canada, 6299 Airport Td, Ste 201, Mississauga, Ontario, L4V 1N3, Canada.

General Topics, Ital. General Topics S.r.l., Località Santigaro 32, 25010 San Felice (BS), Italy.

Generfarma, Spain. Generfarma, Los Centelles 7, 46006 Valencia, Spain.

Genericon, Austria. Genericon Pharma GmbH, Schlossplatz 1, A-8502 Lannach, Austria.

Genericon, Cz. Genericon sro, Anny Letenské 1108/15, 120 00 Praha 2, Czech Republic.

Generics, Cz. See *Merck, Cz.*

Generics, Denm. See *NM, Denm.*

Generics, Hung. See *Merck, Hung.*

Generics, Israel. See *Genmedix, Israel.*

Generics, Pol. See *Merck, Pol.*

Generics, UK. Generics (UK) Ltd, Albany Gate, Drakes Lane, Potters Bar, Hertfordshire, EN6 1AG, UK.
url: www.generics.uk.com

Generics Pharmacal, Philipp. See *Filadams, Philipp.*

Generis, Port. Generis Farmacêutica SA, Rua José Galhardo 3, 1750-131 Lisbon, Portugal.
url: www.generis.pt

Generix, S.Afr. Generix International SA (Pty) Ltd, Cnr Pooke and Ester Roads, Athlone, Industria, Cape Town, South Africa.

Genesis, Gr. Genesis Pharma S.A., 24 Fillelinon St., 152 32 Chalandri, Greece.
url: www.genesispharma.com

Genesis, Philipp. Genesis Pharma Inc., 77 Branches Ext, Mendoza Vill, Proj 8, Quezon City, Philippines.

Genesis, Turk. Genesis İlaç ve Sağlık Ürünleri A.Ş., Sadıkoğlu İş Merkezi-I, D:44, Hasanpaşa, İstanbul, 34722, Turkey.
url: www.Genesis.gen.tr

Genesis, USA. Genesis Pharmaceuticals, 1721 Maplelane Ave, Hazel Park, MI 48030, USA.
url: www.genesispharm.com

Genetic, Ital. Genetic SpA, Via della Monica 26, 84083 Castel San Giorgio (SA), Italy.

Genetics Institute, Austria. See *Baxter BioScience, Ger.*

Genetics Institute, USA. Genetics Institute, 35 Cambridge Park Drive, Cambridge, MA 02140, USA.
url: www.genetics.com

Geneva, USA. See *Novartis, USA.*

Genevrier, Fr. Laboratoires Génévrier, B.P. 47, 06901 Sophia Antipolis cdx, France.

Genevrier, Singapore. See *Pan-Malayan, Singapore.*

Genexo, Pol. Genexo Sp. zo.o., ul. Śmiała 51, 01-526 Warsaw, Poland.
url: www.genexo.pl

Geni, Spain. Geni, Belanes 12, 28043 Madrid, Spain.

Genmedix, Israel. Genmedix Ltd, P.O. Box 8500, New Industrial Zone, Netanya, Israel.
url: www.merck.de

Geno, India. Geno Pharmaceuticals Ltd, Pharmaceutical Complex, Karaswada, Mapusa, Goa 403 507, India.
url: www.genopharma.com

Genom, Braz. Genom Farmacêutica Ltda, Av. Ceci 820, 06460-120 Barueri, SP, Brazil.

Genop, S.Afr. Genop Healthcare (Pty) Ltd, P.O. Box 3911, Halfway House 1685, South Africa.
url: www.genophealthcare.co.za

Genopharm, Fr. Laboratoires Genopharm, Parc de l'Esplanade, 10 rue Enrico-Fermi, Saint-Thibault-des-Vignes, 77462 Lagny-sur-Marne cdx, France.

Genosis, UK. Genosis plc, Suite 1, 2nd Floor, 1 Crown Square, Woking, Surrey, GU21 6HR, UK.
url: www.genosis.co.uk

Genovate, Thai. See *Charoen, Thai.*

Genpharm, Canad. Genpharm Inc., 37 Advance Rd, Etobicoke, Ontario, M8Z 2S6, Canada.
url: www.genpharm.ca

Genpharm, Israel. See *Genmedix, Israel.*

Genpharm, S.Afr. Genpharm Pharmaceuticals CC, P.O. Box 607, Rivonia 2128, South Africa.

Genpharm, USA. See *Medarex, USA.*

Genser, Arg. Alimentos Genser S.A., Cucha Cucha 2548, 1416 Buenos Aires, Argentina.
url: www.genser.com.ar

Gensia, USA. See *Teva, USA.*

Genta, USA. Genta Inc., 2 Connell Drive, Berkeley Heights, NJ 07922, USA.
url: www.genta.com
Gentek, Venez. See *Leti, Venez.*
Gentex, USA. Gentex Pharma LLC, USA.
url: www.gengtexpharma.com
Genthon, Hong Kong. See *International Medical, Hong Kong.*
Gentili, Ital. Istituto Gentili S.p.A., Via Mazzini 112, 56125 Pisa, Italy.
Genus, UK. Genus Pharmaceuticals Ltd, 65 London Rd, Newbury, Berkshire, RG14 1JN, UK.
url: www.genuspharma.com
Genzyme, Arg. Genzyme de Argentina SA, Fondo de la Legua 161, 1667 Boulogne sur Mer, Buenos Aires, Argentina.
Genzyme, Austral. Genzyme Australasia P/L, P.O. Box 6207, Baulkham Hills Business Centre, Baulkham Hills, NSW 2153, Australia.
url: www.genzyme.com.au
Genzyme, Austria. See *Genzyme, Neth.*
Genzyme, Belg. Genzyme Belgium, Ikaroslaan 53, 1930 Zaventem, Belgium.
url: www.genzyme.com
Genzyme, Canad. Genzyme Canada Inc., 800-2700 Matheson Bvld E, East Tower, Mississauga, Ontario, L4W 4V9, Canada.
url: www.genzyme.com
Genzyme, Cz. See *Genzyme, UK.*
Genzyme, Denm. Genzyme A/S, Islands Brygge 57 st tv, 2300 Copenhagen S, Denmark.
url: www.genzyme.com
Genzyme, Fin. See *Genzyme, Denm.*
Genzyme, Fr. Genzyme SAS, ZI des Beaux Soleils 9, Chaussée Jules César, Bat 2, BP 225 Osny, 95523 Cergy-Pontoise Cedex, France.
url: www.genzyme.fr
Genzyme, Ger. Genzyme GmbH, Siemensstr. 5 b, 63263 Neu-Isenberg, Germany.
url: www.genzyme.de
Genzyme, Gr. Genzyme Hellas LLC, 599 Vouliagmenis Ave, 164 52 Argyroupoli, Greece.
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Genzyme, Hong Kong. See *IDS, Hong Kong, Naturest, Hong Kong, Vantone, Hong Kong,* and *Zuellig, Hong Kong.*
Genzyme, Hung. Genzyme Europe BV Képviselet, Apor Vilmos ter 25-26, 1124 Budapest, Hungary.
url: www.genzyme.com
Genzyme, Irl. See *Genzyme, UK.*
Genzyme, Israel. Genzyme Israel Ltd, P.O. Box 1188, Kfar Saba, Israel.
url: www.genzyme.co.il
Genzyme, Ital. Genzyme S.r.l., Via Scaglia Est 144, 41100 Modena, Italy.
url: www.genzyme.com
Genzyme, Jpn. Genzyme Tokyo, 9F, Ichigaya-Tokyu Bldg., 4-2-1 Kudan-Kita, Chiyoda-ku, Tokyo 102-0073, Japan.
url: www.genzyme.co.jp
Genzyme, Malaysia. Genzyme Malaysia Sdn Bhd, Unit E305 East Wing Metropolitan Square, Jln PJU 8/1, Bandar Damansara Perdana, 47820 Petaling Jaya, Selangor, Malaysia.
Genzyme, Neth. Genzyme BV, Gooimeer 10, 1411 DD Naarden, Netherlands.
url: www.genzyme.com
Genzyme, Norw. See *Genzyme, Denm.*
Genzyme, Pol. Genzyme Polska, al. Stanów Zjednoczonych 61a, 04-028 Warsaw, Poland.
url: www.genzyme.com
Genzyme, Port. Genzyme Portugal SA, Tagus-park, Edifício Ciencia II, 2, Sala 2D, 2740-120 Porto Salvo, Portugal.
Genzyme, Singapore. See *Pharmacon, Singapore.*
Genzyme, Spain. Genzyme, Damian Sanchez Lopez 3, San Sebastian de los Reyes, 28700 Madrid, Spain.
url: www.genzyme.com
Genzyme, Swed. See *Genzyme, Denm.*
Genzyme, Switz. Genzyme GmbH, Zugerstrasse 72, 6340 Baar, Switzerland.
url: www.genzyme.com
Genzyme, Turk. Genzyme Turkey Ltd, Suleyman Seba Caddesi, BJK Plaza A98 Besiktas, İstanbul 34357, Turkey.
url: www.genzyme.com
Genzyme, UK. Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford, Oxfordshire, OX4 2SU, UK.
url: www.genzyme.co.uk
Genzyme, USA. Genzyme Corp., 500 Kendall St, Cambridge, MA 02142, USA.
url: www.genzyme.com
Genzyme Biosurgery, Thai. See *BJC, Thai.*
Geofman, Philipp. See *Clinbaxy, Philipp.*
Geolab, Braz. Geolab Indústria Farmacêutica Ltda, VP 1B Quadra 8 Mod. 01 a 08, 75133600 Anapolis, Goias, Brazil.
Gepepharm, Ger. gepepharm GmbH, Lendersbergstr. 86, 53721 Siegburg, Germany.
Gerard, Denm. See *NM, Denm.*
Gerard, Irl. Gerard Laboratories, U36 Baldoyle Industrial Estate, Grange Rd, Baldoyle, Dublin 13, Ireland.
Gerard, Israel. See *Genmedix, Israel.*
Gerard, Norw. See *Norgesfarma, Norw.*
Gerber, Mex. Productos Gerber S.A. de C.V., Epigmenio Gonzalez No. 59, Col. Industrial, 76150 Queretaro, Qro, Mexico.
url: www.gerber.com.mx
Gerbex, Canad. Gerbex Inc. Produits, 331 Principale St, St-Thomas d'Aquin, Quebec, J0H 2A0, Canada.
Gerda, Fr. Laboratoires Gerda, 6 rue Childebert, 69002 Lyon, France.
Geriatric Pharm. Corp., USA. See *Shire, USA.*
Geritrex, USA. Geritrex Corp., 144 Kingsbridge Rd East, Mt Vernon, NY 10550, USA.
url: www.geritrex.com
Gerlach, Ger. Eduard Gerlach GmbH, Backerstr. 4-8, 32312 Lübbecke, Germany.
German Homoeopathic, Rus. German Homoeopathic, Vernadskogo pr-t 105, corp. 2, 119526 Moscow, Russia.
German Remedies, India. German Remedies Ltd, Shivsagar Estate 'A', Dr Annie Besant Rd, Worli, Mumbai 400 018, India.
url: www.germanremedies.com
Germandre, Fr. Germandre (Lab), 9 faubourg d'Antraigues, 07600 Vals-les-Bains, France.
Germania, Austria. Germania Pharmazeutika GmbH, Schuselkagasse 8, A-1150 Vienna, Austria.
Germax, Malaysia. Germax Sdn Bhd, P.O. Box 6514, Kampung Tunku, 47307 Petaling Jaya, Selangor, Malaysia.
Germiphene, Canad. Germiphene Corporation, 1379 Colborne St E, P.O. Box 1748, Brantford, Ontario, N3T 5V7, Canada.
Germiphene, Israel. Germiphene, Israel.
Germo, Ital. Germo S.p.A., Via Giotto 19/21, 20032 Cormano (MI), Italy.
url: www.germo.it
Gerolimatos (Γερολυματος), Gr. See *Gerolymatos, Gr.*
Gerolymatos, Gr. Gerolymatos PN AEVE, 13 Asklipiou Str., 145 68 Kryoneri Athens, Greece.
url: www.gerolymatos.gr
Gerolymatos, Hong Kong. See *Primal, Hong Kong.*
Geropharm, Rus. Geropharm OOO, Ordinarnaya, d.12, 197136 Saint-Petersburg, Russia.
url: www.geropharm.ru
Gerot, Austria. Gerot-Pharmazeutika GmbH, Arnethgasse 3, A-1160 Vienna, Austria.
Gerot, Cz. See *Horna, Cz.*
Gerot, Hung. Gerot Pharmazeutika Magyarországi Közvetlen Kereskedelmi Képviselet, Bajcsy-Zsilinszky út 12, 1051 Budapest, Hungary.
Gerot, Malaysia. See *Germax, Malaysia.*
Gerot, Neth. See *Gerot, Austria.*
Gerot, Pol. Gerot Pharmazeutika GmbH Sp. zo.o., Przedstawicielstwo w Polsce, al. Jana Pawła II 61, 01-031 Warsaw, Poland.
url: www.gerot.pl
Gerot, Rus. See *Lannacher, Rus.*
Gerot, Singapore. See *Green Cross, Singapore.*
Gerot, Switz. See *Orion, Switz.*
Gervasi, Spain. Gervasi Farmacia, C/Juan XXIII 15-19, 08950 Brcelona, Spain.
GES, Spain. GES Genrécos Españoles, Colquide 6, Portal 2 Oficina F, Las Rozas, 28230 Madrid, Spain.
Gestafarma, Port. Sociedade Farmacêutica Gestafarma, Lda, Rua Dr. Álvaro de Castro 65-7, 1600-058 Lisbon, Portugal.
Getz, Philipp. Getz Pharma Pakistan (Pvt) Ltd, 5/F Ortigas Bldg, Ortigas Ave, Pasig City, Philippines.
Geyer, Braz. Geyer Medicamentos SA, Rua Pelotas 280, 90220-110 Porto Alegre, RS, Brazil.
url: www.geyermed.com.br
Geymonat, Ital. Geymonat S.p.A., Via S. Anna 2, 03012 Anagni (FR), Italy.
Geymonat, Switz. See *Lucchini, Switz.*
Gezzi, Arg. Lab E J Gezzi SRL, 14 de Julio 855 OB Dto. 2, 1427 Buenos Aires, Argentina.
GFC, Mex. Comercial GFC SA de CV, Blvd Juan A de Torres 220, 37360 Leon Gto Vibar, Mexico.
GfE, Ger. GfE Medizintecknik GmbH, Hofener Str 45, 90431 Nürnberg, Germany.
url: www.gfe-online.de
GFR, Canad. GFR Pharma Ltd, 11450 201 A St, Maple Ridge, British Colombia, V2X 0Y4, Canada.
Ghimas, Ital. Ghimas S.p.A., Via R. Fucini 2, 40033 Casalecchio di Reno (BO), Italy.
url: www.ghimas.com
GHP, Thai. General Hospital Products Public Co. Ltd, 75/1 Rama VI Rd, Bangkok 10400, Thailand.
Giempi, Venez. Laboratorios Giempi C.A., Calle Bolívar, Ed. Giempi, Urb. La Trinidad, Caracas 1081, Venezuela.
url: www.giempi.com
GiEnne, Ital. GiEnne Pharma S.p.A., Groupe Therabel, Via Lorenteggio 270/A, 20152 Milan, Italy.
Gifrer Barbezat, Fr. Laboratoires Gifrer Barbezat, 4-10 rue Paul Bert, BP 165, 69153 Decines cdx, France.
url: www.gifrer.fr
Gil, USA. Gil Pharmaceutical, USA.
url: www.gilpharmaceutical.com
Gilbert, Cz. See *Gilbert, Fr.*
Gilbert, Fr. Laboratoires Gilbert, av. du Général-de-Gaulle, B.P.115, 14204 Hérouville-Saint-Clair cdx, France.
url: www.groupebatteur.fr
Gilco, Israel. Gilco Pharm Ltd, 12 Hayekev St., Rishon LeZiyon 75497, Israel.
Gilead, Austral. Gilead Sciences Pty Ltd, Unit 2, 41 Stamford Rd, Oakleigh, VIC 3166, Australia.
url: www.gilead.com
Gilead, Austria. See *Gilead, UK.*
Gilead, Canad. Gilead Sciences Canada Inc., Vancouver, Canada.
url: www.gilead.com
Gilead, Chile. See *Pharma Investi, Chile.*
Gilead, Cz. See *Gilead, UK.*
Gilead, Denm. See *Orphan, Denm.*
Gilead, Fr. Gilead Sciences, 100 Avenue de Suffren, 75015 Paris, France.
url: www.gilead.com
Gilead, Ger. Gilead Sciences GmbH, Fraunhoferstr. 17, 82152 Martinsried/Planegg, Germany.
url: www.gilead-sciences.de
Gilead, Gr. Gilead Sciences, Inc., 2 Rizountos & Thrakis Str., Helliniko, 167 77 Athens, Greece.
url: www.gilead.com
Gilead, Hong Kong. See *IDS, Hong Kong.*
Gilead, Hung. See *Gilead, UK.*
Gilead, Irl. See *Gilead, UK.*
Gilead, Ital. Gilead Sciences S.r.l., Via Marostica 1, 20146 Milan, Italy.
url: www.gilead.com
Gilead, Neth. Gilead Sciences BV, Postbus 1054, 1300 BB Almere, Netherlands.
url: www.gilead.nl
Gilead, Norw. See *Swedish Orphan, Norw.*
Gilead, NZ. See *Baxter, NZ.*
Gilead, Pol. See *Medagro, Pol.*
Gilead, Port. Gilead Sciences Lda, Campo Grande 28 7A, 1700-093 Lisbon, Portugal.
Gilead, Rus. Gilead Sciences, Dmitriya Ulyanova ul. 16, korp. 2, of. 184-185, 117292 Moscow, Russia.
url: www.gilead.com
Gilead, Singapore. See *IDS, Singapore.*
Gilead, Spain. Gilead Sciences S.L., Agustin de Foxa 27, Planta 11, 28036 Madrid, Spain.
url: www.gilead.com
Gilead, Thai. See *Siam Pharm, Thai.*
Gilead, UK. Gilead Sciences Ltd, The Flowers Building, Granta Park, Abington, Cambridge, Cambridgeshire, CB1 6GT, UK.
url: www.gilead.com
Gilead, USA. Gilead Sciences Inc., 333 Lakeside Drive, Foster City, CA 94404, USA.
url: www.gilead.com
Gillette, Arg. Gillette Argentina, Gdor. Ugarte 3561, 1605 Munro, Buenos Aires, Argentina.
Gillette, Belg. See *Procter & Gamble, Belg.*
Gillette, Ital. Gillette Group Italy, Business Unit Braun, Oral Care SpA, Via Pirelli 18, 20124 Milan (MI), Italy.
Gillette, Neth. Gillette Nederland BV, Visseringlaan 20, Rijswijk, Netherlands.
Giovanardi, Ital. Giovanardi Farmaceutici S.n.c. del Dr Benito Giovanardi e Figli, Via Sapeto 28, 16131 Genoa, Italy.
url: www.giovanardi.net
Gisand, Switz. Gisand AG, Schlaflistrasse 14, 3013 Berne, Switzerland.
Giscard, Arg. Lab. Gastón Giscard S.R.L., Rivadavia 4178 Piso 1 Dto.A, 1205 Buenos Aires, Argentina.
Giuliani, Ital. Giuliani S.p.A., Via Palagi 2, 20129 Milan, Italy.
Giulini, Israel. See *Gramse, Israel.*
Glades, USA. Glades Pharmaceuticals, 6340 Sugarloaf Parkway, Duluth, GA 30097, USA.
url: www.glades.com
Glaxo, Jpn. See *GSK, Jpn.*
Glaxo, USA. See *GSK, USA.*
Glaxo Allen, Ital. See *GSK, Ital.*
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Glaxo Wellcome, USA. See *GSK, USA.*
Glenbrook, USA. See *Sanofi-Aventis, USA.*
Glenmark, India. Glenmark Pharmaceuticals Ltd, 801-813, 8th Floor, Mahalaxmi Chambers, 22 Bhulabhai Desai Rd, Mumbai 400 026, India.
url: www.glenmarkpharma.com
Glenmark, Malaysia. Glenmark Pharmaceuticals Ltd, 21-6-1, Jln 3/50, Diamond Square Business Ctr, Off Jln Gombak, 53000 Kuala Lumpur, Malaysia.
Glenmark, Philipp. Glenmark Philippines Inc., Unit 1105, 11/F Prestige Tower, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.
Glenmark, Rus. Glenmark Pharmaceuticals Ltd, Kaluzhskaya Ploshad. 1, Office 271, 119047 Moscow, Russia.
url: www.glenmarkcis.com
Glenmark, Singapore. See *Uni, Singapore.*
Glenmark, Thai. See *Union Medical, Thai.*
Glenwood, Austria. See *Glenwood, Ger.*
Glenwood, Canad. Glenwood Laboratories Canada Ltd, 2406 Speers Rd, Oakville, Ontario, L6L 5M2, Canada.
Glenwood, Ger. Glenwood GmbH, Riedener Weg 23, 82319 Starnberg, Germany.
url: www.glenwood.de
Glenwood, UK. Glenwood Laboratories Ltd, Jenkins Dale, Chatham, Kent, ME4 5RD, UK.
Glenwood, USA. Glenwood Inc., 111 Cedar Lane, Englewood, NJ 07631, USA.
url: www.glenwood-llc.com
Global, Philip. Global Business Xpress Service Inc., Unit 8D, Lansbergh Place, 170 Tomas Morato, Quezon City, Philippines.
Global, USA. Global Pharmaceuticals Inc., 3735 Castor Ave, Philadelphia, PA 19124, USA.
url: www.globalphar.com
Global Eramas, Indon. See *Tempo Scan Pacific, Indon.*
Globalpharma, Ital. Globalpharma Srl, Via B Croce 26, 00142 Rome (RM), Italy.
Globo, Braz. Laboratório Globo Ltda, Av. Montese 840, 31565-150 Belo Horizonte, MG, Brazil.
Globopharm, Switz. Globopharm AG, Seestrasse 200, 8700 Kusnacht, Switzerland.
url: www.globopharm.ch
Gloria, Ital. Gloria Maglieria Elastica Srl, Via Diaz 7, 22017 Menaggio (CO), Italy.
Glynn, Cz. Glynn Brothers Chemicals Prague sro, K Betani 1092/19, 148 00 Prague 4, Czech Republic.
url: www.gbc-prague.cz
GM, USA. GM Pharmaceuticals, 912 W Randol Mill Rd, Arlington, TX 76012, USA.
GMP, Indon. Global Multi Pharmalab (GMP) PT, Kawasan Industri Terboyo, Kav A 20-23, Jl Raya Kaligawe KM 6, 50118 Semarang, Indonesia.
GNLD, Austral. GNLD International P/L, P.O. Box 419, Beenleigh, Qld 4207, Australia.
url: www.gnld.com.au
GNR, Ital. GNR S.p.A., Largo Umberto Boccioni 1, 21040 Origgio (Va), Italy.
GNR, Port. See *Agostinho, Port.*
Gobbi, Arg. Lab. Gobbi Novag S.A., F. Onsari 498, 1875 Wilde, Buenos Aires, Argentina.
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Godecke, Ger. See *Pfizer, Ger.*
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Goemar, Philipp. See *Powermist, Philipp.*
Gojo, Canad. See *Gojo, USA.*
Gojo, USA. Gojo Industries Inc., P.O. Box 991, Akron, OH 44309-0991, USA.
url: www.gojo.com
Golaz, Switz. Laboratoire Golaz SA, Case postale 1067, 1701 Fribourg-Moncor, Switzerland.
Golden Neo-Life, Canad. Golden Neo-Life Diamite International Ltd, 3 400 Britannia Rd East, Mississauga, Ontario, L4Z 1X9, Canada.
Goldline, USA. See *Ivax, USA.*
Goldmed, Pol. Goldmed Sp. zo.o., ul. Jakuba Kubickiego 19/15, 02-954 Warsaw, Poland.
url: www.sebamed.pl
Goldplus, Singapore. Goldplus Universal Pte Ltd, 8 Kaki Bukit Rd 2, 02-19/20 Ruby Warehouse Complex, S 417841, Singapore.
Goldschmidt, Switz. See *Desopharmex, Switz.*
Goldshield, Austral. Goldshield Healthcare (Australia), 118-124 Willoughby Rd, Crows Nest, NSW 2065, Australia.
Goldshield, Denm. See *Goldshield, UK.*
Goldshield, Fin. See *Goldshield, UK.*
Goldshield, Ger. See *Nordend, Ger.*
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Goldshield, Irl. See *Allphar, Irl.*
Goldshield, Israel. See *Pharmateam, Israel.*
Goldshield, Neth. See *Goldshield, UK.*
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Goldshield, Singapore. See *Orient, Singapore.*
Goldshield, Spain. Goldshield Pharmaceuticals Ltd, C/ Virgen Del Rosario 34A, 28220 Madrid, Spain.
Goldshield, Swed. See *Goldshield, UK.*
Goldshield, Thai. See *SPB, Thai.*
Goldshield, UK. Goldshield Pharmaceuticals Ltd, NLA Tower, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.
url: www.goldshieldplc.com
Gomenol, Fr. Laboratoires du Gomenol, 48 rue des Petites-Écuries, 75010 Paris, France.
Goodfellow, Philipp. Goodfellow Marketing & Sales, Unit 1500 Jollibee Plaza Bldg, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.
Goodwill, Hung. Goodwill Pharma Kft, Széher út 21/b, 1021 Budapest, Hungary.
Goodys, USA. See *GSK Consumer, USA.*
Gordon, Arg. Lab. Gordon S.A.C.I.F.I.A., Malvinas Argentinas 3311, 1644 Victoria, Buenos Aires, Argentina.
Gordon, USA. Gordon Laboratories, 6801 Ludlow St, Upper Darby, PA 19082-2408, USA.
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Gosnii, Rus. See *SSRI, Rus.*
Gothaplast, Ger. Gothaplast Verbandpflasterfabrik GmbH, Postfach: 100132, 99851 Gotha/Thuringen, Germany.
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Gothia, Norw. Gothia Medical AS, Gjerdrumsv. 12, 0484 Oslo, Norway.
Gothia, Swed. Gothia Läkemedel AB, Bolshedens Industriväg 20, 427 50 Billdal, Sweden.
Gouka, Neth. Apotheek Gouka, Groenelaan 111, 3114 CE Schiedam, Netherlands.

Goulart, Braz. Laboratórios Goulart S.A., Rua Aguape 56, Parada de Lucas, 21010-080 Rio de Janeiro, Brazil.

GP, UK. See *Derma, UK.*

GPL, Switz. GPL Ginsana Products Lugano SA, Tochterunternehmen der Pharmaton SA, Postfach, 6903 Lugano, Switzerland.
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Graceway, USA. Graceway Pharmaceuticals LLC, 340 Edgemont Ave, Suite 500, Bristol, TN 37620, USA.
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Gracia, Indon. Gracia Pharmindo PT, Kawasan Industri Dwipapuri, Blok M-30, Jl Raya Rancaekek Km 24.5, 45364 Bandung, Indonesia.

Graf Fruttasan, Switz. Graf Fruttasan AG, Untere Etzmatten 16, 4467 Rothenfluh/BL, Switzerland.
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Grafton, Singapore. Grafton Pharmasia Pte Ltd, 66 Tannery Lane, 01-05A Sindo Building, S 347805, Singapore.
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Grafton, UK. Grafton International, Relay Business Park, Tamworth, Staffordshire, B77 5PT, UK.
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Gramon, Arg. Laboratorios Gramón, Intendente Amaro Avalos 4208, 1605 Munro, Buenos Aires, Argentina.
url: www.gramon.com.ar

Gramon-Bago, Urug. Gramón-Bagó de Uruguay S.A., Av. Joaquín Suárez 3359, Montevideo, 11.700, Uruguay.
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Gramse, Israel. Gramse Pharmaceuticals Ltd, P.O Box 528, New Industrial Park, Yokneam 20692, Israel.
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Granado, Braz. Casa Granado Lab. Farmacias e Drogarias S.A., Travessa do Comércio 17, 20010-080 Rio de Janeiro, RJ, Brazil.
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Grandel, Ger. Dr Grandel GmbH, Pfladergasse 7-13, 86150 Augsburg, Germany.
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Grandel-Synpharma, Ger. See *Grandel, Ger.*

Grandpa Brands, USA. Grandpa Brands Co., 1820 Airport Exchange Bvld, Erlanger, KY 41018, USA.
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Grands Espaces, Fr. Les Grands Espaces Thérapeutiques, B.P. 6054, 34030 Montpellier cdx 01, France.

Granions, Mon. Laboratoires des Granions, 7 rue de l'Industrie, MC 98000, Monaco.

Grans Remedy, NZ. See *Essential, NZ.*

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Grasler, Ger. gräsler pharma GmbH, Brunnleitenstr. 3, 82284 Grafrath, Germany.

Gray, Arg. Prod. Farmaciuticos Dr. Gray S.A.C.I., Thames 372 Piso 1, 1414 Buenos Aires, Argentina.

Gray, USA. See *Purdue Frederick, USA.*

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Great Year, Hong Kong. Great Year Trading Co. Ltd, 18/F, 80 Gloucester Rd, Wanchai, Hong Kong.

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Green Cross, Hong Kong. See *Sunny Plaza, Hong Kong.*

Green Cross, Malaysia. See *Propharm, Malaysia.*

Green Cross, Philip. See *Vizcarra, Philipp.*

Green Cross, Singapore. Green Cross Pte Ltd, 63 Hillview Ave, 07-06 Lam Soon Industrial Building, S 669569, Singapore.

Green Cross, Thai. See *Diethelm, Thai.*

Green Cross Guangzhou, Singapore. See *Grifols, Singapore.*

Green Leaf, Philipp. Green Leaf Herbals Inc., 57, 11th St, New Manila, Quezon City, Philippines.

Green Turtle Bay Vitamin Co., USA. The Green Turtle Bay Vitamin Co., P.O. Box 642, Summit, NJ 07902, USA.
url: www.energywave.com

Greenpharma, Braz. Greenpharma Química e Farmacêutica Ltda, Quadra 2-A Modulos 32/35 DAIA, 75133-600 Anapolis, GO, Brazil.
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Grifols, Ger. Grifols Deutschland GmbH, Siemensstr. 18, 63225 Langen, Germany.
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Grifols, Hong Kong. See *Great Year, Hong Kong,* and *Keller, Hong Kong.*

Grifols, Hung. See *Inthera, Hung.*

Grifols, Indon. See *Tempo Scan Pacific, Indon.*

Grifols, Israel. See *DYN, Israel.*

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Grifols, Philipp. See *Diethelm, Philipp.*

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Grimberg, Israel. Grimberg, Israel.

Grin, Mex. Laboratorios Grin S.A. de C.V., Rodriguez Saro 630, Col. Del Valle, 03100 Mexico D.F., Mexico.
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Grindeks, Hung. See *Medi-Zone, Hung.*

Grindex, Cz. Grindex, Czech Republic.

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Grossmann, Hong Kong. See *Kai Cheong, Hong Kong.*

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Grunenthal, Cz. See *Chemotrade, Cz.*

Grunenthal, Denm. See *Norpharma, Denm.,* and *Pfizer, Denm.*

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Grunenthal, Hung. See *Biogal-Teva, Hung.*

Grunenthal, Indon. See *Pharos, Indon.*

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Grunenthal, Mex. Grünenthal de Mexico S.A. de C.V., Periferico Sur No. 6677, Col. Ejidos de Tepepan, Deleg. Xochimilco, 16018 Mexico D.F., Mexico.
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Grunenthal, Neth. See *Byk, Neth.*

Grunenthal, Norw. See *Pharmacia, Norw.*

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Grunenthal, Singapore. See *Zuellig, Singapore.*

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Grunwalder, Ger. Grüwalder Gesundheitsprodukte GmbH, Ruhlandstrasse 5, 83646 Bad Tolz, Germany.
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Gry, Ger. Gry-Pharma GmbH, Kandelstr. 10, 79199 Kirchzarten, Germany.

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GSK, Braz. GlaxoSmithKline Brasil Ltda, Estrada dos Bandeirantes 8464, 22783-110 Rio de Janeiro, RJ, Brazil.
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GSK, Mex. GlaxoSmithKline Mexico S.A. de C.V., Calz. Mexico-Xochimilco No. 4900, Deleg. Tlalpan San Lorenzo Huipulco, 14370 Mexico D.F., Mexico.
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GSK, Port. GlaxoSmithKline Lda, Rua Dr. António Loureiro Borges 3, Arquiparque, Miraflores, 1495-131 Algés, Portugal.
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GSK Consumer, Austria. See *GSK, Austria.*

GSK Consumer, Belg. See *GSK, Belg.*

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GSK Consumer, Cz. See *GSK, Cz.*

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GSK Consumer, Venez. See *GSK, Venez.*
GSK Sante, Fr. See *GSK, Fr.*
Guardian, Indon. Guardian Pharmatama PT, Green Ville Maisonette, Blok FA 18-19, Green Ville, Jakarta Barat, DKI Jaya, Indonesia.
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Guidotti, Gr. See *Menarini, Gr.*
Guidotti, Hung. See *Berlin-Chemie, Hung.*
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Guidotti, Pol. See *Berlin-Chemie, Pol.*
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Gulf, Malaysia. See *Averroes, Malaysia.*
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Gynea, Spain. Gynea Laboratorios, Avda Cataluna 127 B, 08184 Palau-Solita i Plegamans, Barcelona, Spain.
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Gynetics, USA. Gynetics Inc., 3371 Route One, Suitre 200, Lawrenceville, NJ 08648, USA.
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Gynopharm, Chile. See *Recalcine, Chile.*
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url: www.hal-allergy.com
Halal, UK. Halal Pharmaceuticals Ltd, 7 Oxford St, Manchester, M1 4WX, UK.
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url: www.haller.ind.br
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url: www.hameln-pharmaceuticals.com
Hameln, Thai. See *JDH Borneo, Thai.*
Hamilton, Austral. Hamilton Pharmaceuticals P/L, P.O. Box 7, Adelaide, SA 5001, Australia.
url: www.hamiltonlabs.com.au
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Hamilton, Singapore. See *IDS, Singapore.*
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url: www.hand-prod.com.pl
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Hanosan, Ger. Hanosan GmbH, Hanosanstr. 1, 30826 Garbsen, Germany.
url: www.hanosan.de
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Hanseler, Switz. Hänseler AG, Industriestrasse 35, 9100 Herisau, Switzerland.
url: www.haenseler.ch
Hapra, Cz. Hapra sro, Myslbeková 25, 169 00 Prague 6, Czech Republic.
Harbin, Thai. See *Top, Thai.*
Hardis, Ital. Hardis SpA, SS bis 7 km 19.5, 80029 San Antimo, Italy.
Hargell, Canad. Hargell Ltd, 5050 Dufferin St, Suite 108, North York, Ontario, M3H 5T5, Canada.
Harley Street Supplies, UK. Harley Street Supplies Ltd, 29 Westfields Ave, London, SW13 0AT, UK.
Harn, Thai. Harn Thai Pharma Ltd, 2121 New Petchburi Rd, Bangkok 10320, Thailand.
url: www.harnthai.com
Harpers, Malaysia. Harpers Trading (Malaysia) Sdn Bhd, Lot 14 Jalan Bersatu 13/4, 46200 Petaling Jaya, Malaysia.
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Harras-Curarina, Cz. See *Horna, Cz.*
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url: www.harraspharma.de
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Hartmann, Fr. Laboratoires Paul Hartmann, 18 rue des Goumiers, 67730 Châtenois, France.
url: www.hartmann-online.com
Harvard, USA. The Harvard Drug Group LLC, 31778 Enterprise Dr, Livonia, MI 48150, USA.
url: www.harvardlink.com
Harvest, USA. Harvest Pharmaceuticals Inc., P.O. Box 3586, Radford, VA 24143, USA.
url: www.harvestpharmaceuticals.com
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Harvey-Scruton, UK. Harvey-Scruton Ltd, 4 Barker Lane, York, North Yorkshire, YO1 6JR, UK.
Hasco-Lek, Pol. Przedsiębiorstwo Produkcji Farmaceutycznej Haco-Lek, ul. Żmigrodzka 242 E, 51-131 Wrocław, Poland.
url: www.hasco-lek.pl
Hassle, Swed. Hässle Läkemedel AB, 431 83 Mölndal, Sweden.
url: www.astrazeneca.se
Hauck, USA. See *Shire, USA.*
Haupt, Israel. See *Margalit, Israel.*
Hausmann, Irl. See *Clonmel, Irl.*
Hautel, Arg. Hautel S.A., Warnes 829 Dto. A, 1414 Buenos Aires, Argentina.
Haw Par, Austral. See *Haw Par, Singapore.*
Haw Par, Canad. Haw Par Corp. Ltd, P.O. Box 4129, Vancouver, British Columbia, V6B 3Z6, Canada.
Haw Par, Singapore. Haw Par Healthcare Ltd, 401 Commonwealth Drive, 03-03 Haw Par Technocentre, Singapore 149598, Singapore.
url: www.tigerbalm.com
Hawgreen, UK. Hawgreen Ltd, The Maltings, 2nd Floor, Bridge St, Hatfield, Hertfordshire, AL10 8ZP, UK.
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HB, Braz. H.B. Farma Laboratórios Ltda, Av. Eugenio Borges 1060, 24751-000 São Gonçalo, RJ, Brazil.
HCP, Gr. HCP AE (S. Stavropoulou), Sarantaporou 57, 121 31 Peristeri, Greece.
Health & Diet Food Co., UK. Health & Diet Food Co. Ltd, Vitality House, 6 Avenue, Centrum 100, Burton-on-Trent, Staffordshire, DE14 2WP, UK.
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Health Alliance, Hong Kong. Health Alliance International Co. Ltd, Unit 1302-03, SUP Tower, 75 King's Rd, North Point, Hong Kong.
Health Care Products, USA. See *Hi-Tech, USA.*
Health Chemical, Hong Kong. See *Sun Hing, Hong Kong.*
Health Enterprise, Hong Kong. J Health Enterprise, Unit 1606, 16/F, 113 Argyle St, Mongkok, Kowloon, Hong Kong.
url: www.biogaia.com
Health Imports, UK. Health Imports Ltd, Binbrook Mill, Young Street, Bradford, West Yorkshire, BD8 9RE, UK.
Health Perception, UK. Health Perception Ltd, Lakeside Business Park, Swan Lane, Sandhurst, Berkshire, GU47 9DN, UK.
url: www.health-perception.co.uk
Health Saver, Philipp. Health Saver Pharmaceuticals, Philippines.
Health Vision, Hong Kong. Health Vision Enterprise Ltd, Rm 2504, K Wah Ctr, 191 Java Rd, North Point, Hong Kong.
Health Vision, Philipp. Health Vision Pharma-cel, Bldg 3022 Zambales Highway, Upper QB, Subic Bay Freeport Zone, Olongapo City, Philippines.
HealthAid, UK. HealthAid Ltd, HealthAid House, Marlborough Hill, Harrow, Middlesex, HA1 1UD, UK.
url: www.healthaid.co.uk
Health-Care, Gr. See *HCP, Gr.*
Healthcare Brands, Cz. See *Healthcare Brands, UK.*
Healthcare Brands, UK. Healthcare Brands International Ltd, 56 Queen Anne St, London, W1G 8LA, UK.
Healthcare Innovations, UK. Healthcare Innovations, 930 High Rd, London, N12 9RT, UK.
Healthcare Logistics, NZ. Healthcare Logistics, 58 Richard Pearse Drive, Airport Oaks, Auckland, New Zealand.
Healtheries, NZ. Healtheries of New Zealand Ltd, P.O. Box 22 045, Otahuhu, Auckland, New Zealand.
url: www.healtheries.co.nz
Healthfirst, USA. Healthfirst Corp., 22316 70th Ave W, Unit A, Mountlake Terrace, WA 98043, USA.
url: www.healthfirst.com
Healthline, USA. Healthline Laboratories Inc., 2805 Danbar Dr., Green Bay, WI 54313, USA.
Healthpoint, USA. Healthpoint Medical, 3909 Hulen St., Fort Worth, TX 76107, USA.
url: www.healthpoint.com
Healthypharm, Neth. Healthypharm BV, Nieuwe Donk 9, 4879 AC Etten-Leur, Netherlands.
Heber, Thai. See *Pharmadica, Thai.*
Hebert, Canad. Distribution L Hébert, 15260 Notre-Dame St E, Montreal, Quebec, H1A 1W6, Canada.
Hebron, Braz. Hebron S.A. Indústria Química e Farmacêutica, Rua Ribeiro de Brito 573, 6 andar, 51021-310 Recife, PE, Brazil.
url: www.hebron.com.br
Heca, Neth. Heca BV, Industrieweg 24, Postbus 39, 7957 SG De Wijk, Netherlands.
Heck, Switz. Heck Pharma SA, Studenmatt 9, 1791 Courtaman, Switzerland.
Hedat, Pol. Przedsiębiorstwo Handlowe Hedat SJ, ul. Wrocławska 13, 05-071 Sulejówek, Poland.
url: www.hedat.pl
Heel, Belg. Heel Belgium NV, Booiebos 25, B-9031 Drongen, Belgium.
Heel, Cz. See *Peithner, Cz.*
Heel, Ger. Biologische Heilmittel Heel GmbH, Dr.-Reckeweg-Str. 2-4, 76532 Baden-Baden, Germany.
url: www.heel.de
Heel, Neth. See *Heel, Belg.*
Heel, S.Afr. Heel South Africe (Pty) Ltd, Linbro Business Park, 5 Galaxy Ave, Sandton 2199, South Africa.
url: www.heel.com
Heel, USA. Heel Inc., P.O. Box 11280, Albuquerque, NM 87192-0280, USA.
url: www.heelusa.com
Hefa, Ger. See *Sanavita, Ger.*
Heinimann, Switz. Heico U Heinimann, Schitterstrasse 11, 9413 Oberegg, Switzerland.
Heinz, UK. H.J. Heinz Co. Ltd, South Building, Hayes Park, Hayes, Middlesex, UB4 8AL, UK.
url: www.heinz.co.uk
Heinz-Wattie, NZ. Heinz-Wattie's Australasia Ltd, P.O. Box 439, Hastings, New Zealand.
url: www.watties.co.nz
Helago, Ger. Helago-Pharma GmbH, Rheinallee 11, 53173 Bonn, Germany.
url: www.helago.de
Helapet, UK. Helapet Ltd, Circle Business Centre, Blackburn Rd, Houghton Regis, Bedfordshire, LU5 5DD, UK.
url: www.helapet.co.uk
Helena, Canad. See *Helena, USA.*
Helena, USA. Helena Laboratories, 1530 Lindbergh Dr, P.O. Box 752, Beaumont, TX 77707, USA.
url: www.helena.com
Helfarma, Port. Helfarma, Lda, Rua João Chagas 53, 1495-072 Algés, Portugal.
Heliopharma, Hung. See *Medipharma, Hung.*
Helios, UK. Helios Healthcare Ltd, P.O. Box 203, Hitchin, Hertfordshire, SG5 2ZQ, UK.
Helixor, Ger. Helixor Heilmittel GmbH & Co., Fischermuhle 1, 72348 Rosenfeld, Germany.
url: www.helixor.de
Helm, Port. Helm Produtos Químicos Lda, Estrada Nacional No 10, Km 140,260, 2695-066 Bobadela LRS, Portugal.
Help, Gr. Help E.P.E., Evag.Zekkas-Balaoritou 4, Athyens, 144 52 Metamorfosi, Greece.
Help, Pol. See *Blubit, Pol.*
Helsinn, Hong Kong. See *Zuellig, Hong Kong.*
Helsinn, Port. Helsinn, Lda, Estrada Nacional 249/4 (Km 1.6), Abrunheira, Apartado 155, 2710-901 Sintra, Portugal.
Helsinn Birex, Hung. See *Helsinn Birex, Irl.*
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Helsinn Birex, Irl. Helsinn Birex Pharmaceuticals Ltd, Damastown, Mulhuddart, Dublin 15, Ireland.
url: www.helsinn.com
Helsinn Birex, Neth. See *Helsinn Birex, Irl.*
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Helvepharm, Switz. Helvepharm AG, Walzmuhlestrasse 60, 8500 Frauenfeld, Switzerland.
url: www.helvepharm.ch
Helvetia, Cz. Helvetia Pharma as, Slezská 949/32, 120 00 Praha 2, Czech Republic.
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url: www.hamatilac.com.tr
HemispheRx, USA. HemispheRx, 1 Penn Center, 1617 John F Kennedy Blvd, Philadelphia, PA 19103, USA.
url: www.hemispherx.net
Hemoderivados, Arg. U.N.C. Hemoderivados, Av. Valparaiso SN, 5000 Cordoba, Argentina.
url: www.unc-hemoderivados.com
Hemofarm, Rus. Hemofarm Koncern A.D., Trifonovskaya ul. 45 b, 129272 Moscow, Russia.
url: www.hemofarm.ru
Hemopharm, Ger. Hemopharm GmbH, Konigsteiner Str. 2, 61350 Bad Homburg v. d. H., Germany.
url: www.hemopharm.de
Henkel, Austria. Henkel Austria GmbH, Erdbergstrasse 29, A-1030 Vienna, Austria.
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Hennig, Ger. Hennig Arzneimittel GmbH & Co. KG, Liebigstr. 1-2, 65439 Florsheim am Main, Germany.
url: www.hennig-am.de
Henning, Ger. Henning Berlin Arzneimittel GmbH, Potsdamer Str. 8, 10785 Berlin, Germany.
url: www.henning.de
Henning, Hung. Dr Henning, Hungary.
Henning, Israel. Henning, Israel.
Henning Walldorf, Ger. Dr. Georg Friedrich Henning, Chemische Fabrik Walldorf GmbH, Robert-Bosch-Str. 62, 69190 Walldorf, Germany.
Hepacholan, Braz. Laboratório Hepacholan S.A., Av. Manoel Monteiro de Araújo 1051, Vila Jaguara, 05113-020 São Paulo, SP, Brazil.
Hepatoum, Fr. Laboratoires Hépatoum, B.P. 5, 03270 Saint-Yorre, France.
Heptafarma, Port. Heptafarma Companhia Farmacêutica Sociedade Unipessoal Lda, Quinta da Fonte, Edificio Vasco da Gama 19, Porto Salvo, 2770-192 Paç de Arcos, Portugal.
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url: www.herbastudio.pl
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url: www.herbal-concepts.co.uk
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Herbal Laboratories, UK. Herbal Laboratories Ltd, Malew House, 21 Malew St., Castletown, Isle Of Man, IM9 1AD, UK.
url: www.herballaboratories.com
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Herbamed, Switz. Herbamed AG, Untere Au, 9055 Buhler, Switzerland.
url: www.herbamed.ch
Herbapol Krakow, Pol. Krakowskie Zakłady Zielarskie Herbapol SA, ul. K Chałupnika 14, 310462 Kraków, Poland.
url: www.herbapol.krakow.pl
Herbapol Lodz, Pol. See *Herbapol Lublin, Pol.*
Herbapol Lublin, Pol. Herbapol-Lublin SA, ul. Diamentowa 25, 20-954 Lublin, Poland.
url: www.herbapol.com.pl
Herbapol Poznan, Pol. Poznańskie Zakłady Zielarskie Herbapol SA, ul. Towarowa 47/51, 61-896 Poznań, Poland.
url: www.herbapol.poznan.pl

Herbapol Pruszkow, Pol. Warszawskie Zakłady Zielarskie Herbapol, ul. Ołowkowa 54, 05-800 Pruszków, Poland.
url: www.herbapol.waw.pl

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url: www.herbapol.pl

Herbarium, Braz. Herbarium Laboratório Botanico Ltda, Rua Maua 838, 80030-200 Curitiba, PR, Brazil.
url: www.herbarium.com.br

Herbaxt, Fr. Laboratoires Herbaxt, Z.I. Nord, bat 5, 77200 Torcy, France.

Herbcare, Philipp. Herbcare Corp., PDC Compound, Pilar Vill, Las Piñas City, Philippines.

Herbes Universelles, Canad. Herbes Universelles, 7, 70e Ave O, Blainville, Quebec, J7C 1R7, Canada.

Herbion, Rus. Herbion Pakistan PVT Ltd, Miklukho-Maklaya ul. 8, str. 3, 117198 Moscow, Russia.
url: www.herbion.com

Herbrand, Ger. Dr Herbrand KG, Brambachstr. 31, 77723 Gengenbach, Germany.
url: www.herbrand-pharma.de

Herbs & Nature, Philipp. Herbs & Nature Corp., Unit G10-B, Regalia Park Tower, P Tuazon Ave, Cubao, Quezon City, Philippines.

Herbs Trading, Rus. Herbs Trading GmbH, Novinskii boulevard, d.3, str. 1, 121099 Moscow, Russia.
url: www.bittner.ru

Herchemie, Austria. Herchemie, Hasnerstrasse 7, A-9020 Klagenfurt, Austria.

Heremco, Gr. Heremco, Deligiorgi 49, 104 37 Athens, Greece.

Heritage, Canad. Heritage Brands, 120 Harry Walker Parkway N, Newmarket, Ontario, L3Y 7B2, Canada.

Heritage Consumer, USA. Heritage Consumer Products, 141 South Ave, Suite 2, Fanwood, NJ 07023, USA.

Hermal, Austria. See *Hermal, Ger.*

Hermal, Cz. See *Boots Healthcare, Cz.*

Hermal, Ger. Hermal Kurt Herrmann GmbH & Co., Scholtzstr. 3, 21465 Reinbek, Germany.
url: www.hermal.de

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Hermes, Ger. Hermes Arzneimittel GmbH, Georg-Kalb-Str. 5-8, 82049 Grosshesselohe/München, Germany.
url: www.hermes-arzneimittel.de

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Hermes, Port. See *Hermes, Ger.*

Hero, Switz. Hero, Postfach, 5600 Lenzburg, Switzerland.

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Herron, Austral. Herron Pharmaceuticals P/L, P.O. Box 95, Brisbane Market, QLD 4106, Australia.
url: www.herron.com.au

Hertz, Braz. Kley Hertz SA, Rua Comendador Azevedo 224, 90220-150 Porto Alegre, Rio Grande do Sul, Brazil.
url: www.grupohertz.com

Hetero, India. Hetero Healthcare Ltd, A-201/202 Dipti Classic, 32/34 W T Suren Rd, Andheri (East), Mumbai 400 093, India.

Hetterich, Ger. Chemische Fabrik Dr. Hetterich GmbH & Co. KG, Gebhardtstr. 5, 90762 Furth/Bayern, Germany.
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Heumann, Ger. Heumann Pharma GmbH, Sudwestpark 50, 90449 Nürnberg, Germany.
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Hevert, Ger. Hevert-Arzneimittel GmbH & Co. KG, In der Weiherwiese 1, 55569 Nussbaum, Germany.
url: www.hevert.de

Hexa, Arg. Lab. Hexa-Medinova S.A., Helguera 254/58, 1406 Buenos Aires, Argentina.

Hexal, Arg. Hexal Argentina S.A., Paseo Colyn 221 Piso 7, 1063 Buenos Aires, Argentina.
url: www.hexal.com.ar

Hexal, Austral. Hexal Australia P/L, Level 4, Suite 1-6, 100 Harris St, Pyrmont, NSW 2009, Australia.
url: www.hexal.com.au

Hexal, Austria. Hexal Pharma GmbH, Wilhelminenstrasse 91/II F, A-1160 Vienna, Austria.
url: www.hexal.at

Hexal, Braz. Hexal do Brasil Ltda, Av. Itaborai 1425, 04135-001 São Paulo, SP, Brazil.
url: www.hexal.com.br

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Hexal, Denm. Hexal A/S, Kanalholmen 8-12, 2650 Hvidovre, Denmark.
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Hexal, Ger. Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany.
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Hexal, Gr. Hexal Hellas, L. Parnithos 189, 136 71 Acharnes, Greece.

Hexal, Hung. Hexal Hungária Kft, Tímár u 20, 1034 Budapest, Hungary.
url: www.hexal.hu

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Hexal, Mex. Laboratories Hexal S.A. de C.V., Calle Candelaria 186, Col. Atlantida, Deleg. Coyoacan, 04370 Mexico D.F., Mexico.
url: www.hexal.com.mx

Hexal, Neth. Hexal BV, Pastoorslaan 28, 2182 BX Hillegom, Netherlands.

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Hexal, Pol. Hexal Polska Sp. zo.o., ul. Domaniewska 50 C, 02-672 Warsaw, Poland.
url: www.hexal.com.pl

Hexal, Rus. Hexal AG, 3, ul. Kulneva, 121170 Moscow, Russia.
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Hexpharm, Indon. Hexpharm Jaya PT, Gedung Sapta Mulia Lt 3, Jl Rawa Gelam V Kav OR No 3B, Kawasan Industri Pulo Gadung, 13820 Jakarta Timur, DKI Jaya, Indonesia.

Heyl, Cz. See *Heyl, Ger.*

Heyl, Ger. Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Goerzallee 253, 14167 Berlin, Germany.
url: www.heyl-berlin.de

Heyl, USA. Heyltx Corp., 925 S Mason Rd, Katy, TX 77450, USA.
url: www.heyltex.com

Higate, Arg. Higaté Medical Argentina, Av. Eva Peron 3052, 1650 San Marten Villa Libertad, Buenos Aires, Argentina.

High Chemical, USA. High Chemical Co., 3901-A Nebraska St, Levittown, PA 19056, USA.
url: www.sarapin.com

Hikma, Cz. Hikma Pharmaceuticals, Czech Republic.

Hikma, Neth. See *Hikma, Port.*

Hikma, Port. Hikma Farmacêutica (Portugal), Lda, Estrada do Rio da Mo 8, 8A e 8B Fervença, 2705-906 Terrugem SNT, Portugal.
url: www.hikma.com

Hikma, Rus. See *Gedeon Richter, Rus.*

Hilarys, Canad. Hilary's Distribution Ltd, 145 Idema Rd, Markham, Ontario, L3R 1A9, Canada.

Hill, Canad. Hill Dermaceuticals Inc., Mississauga, Ontario, L4X 2X6, Canada.

Hill, USA. Hill Dermaceuticals Inc., 2650 S. Mellonville Ave, Sanford, FL 32773-9311, USA.
url: www.hillderm.com

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Hillestad, USA. Hillestad Pharmaceuticals, 178 US Highway 51 N, P.O. Box 1700, Woodruff, WI 54569-1700, USA.
url: www.hillestadlabs.com

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Himalaya Herbal, Malaysia. Himalaya Herbal Healthcare, Malaysia.
url: www.himalayahealthcare.com

Himmel, USA. Himmel Pharmaceuticals Inc., P.O. Box 5479, Lake Worth, FL 33466, USA.

Hind Wing, Hong Kong. Hind Wing Co. Ltd, Unit No 1103B, 11/F, Block B, Seaview Estate, 2-8 Watson Rd, North Point, Hong Kong.

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Hing Yip, Hong Kong. Hing Yip Medicine Co., 2/F, Lo Ko House, 133 Gloucester Rd, Hong Kong.

Hisamitsu, Cz. See *Hisamitsu, UK.*

Hisamitsu, Hong Kong. See *DKSH, Hong Kong.*

Hisamitsu, Jpn. Hisamitsu Seiyaku, 408 Daikanmachi, Tashiro, Tosu, Saga 841-8686, Japan.
url: www.hisamitsu.co.jp

Hisamitsu, Malaysia. See *Sime Darby, Malaysia.*

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Hisamitsu, UK. Hisamitsu UK Ltd, 500 Chiswick High Rd, London, W4 5RG, UK.
url: www.hisamitsu.co.jp

Hisamitsu, USA. Hisamitsu America Inc., 3528 Torrance Blvd, Suite 112, Torrance, CA 90503, USA.
url: www.salonpas.us

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Hi-Tech, USA. Hi-Tech Pharmacal, 369 Bayview Ave, Amityville, NY 11701, USA.
url: www.hitechpharm.com

Hizon, Philipp. See *Metro, Philipp.*

HK Pharma, UK. HK Pharma Ltd, P.O. Box 105, Hitchin, Hertfordshire, SG5 2GG, UK.

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HMA, Arg. H Medical Argentina SA, Int. Tomkinson 1750, 1642 San Isidro, Buenos Aires, Argentina.

Hobein, Ger. Dr. Hobein & Co. Nachf. GmbH Arzneimittel, Grenzstr. 2, 53340 Meckenheim, Germany.
url: www.eubos.de

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Hobein, Malaysia. Hobein, Malaysia.

Hochland, Israel. Hochland, Israel.

Hochstetter, Chile. Laboratorios Hochstetter SA, Dardignac 6, Santiago, Chile.

Hoe, Malaysia. Hoe Pharmaceuticals Sdn Bhd, Suite 8.01, 8th Fl, Menara IGB, Mid Valley City, Lingkaran Syed Putra, 59200 Kuala Lumpur, Wilayah Persekutuan, Malaysia.
url: www.hoepharma.com.my

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Hoeveler, Austria. Hoeveler Mag. & Co. GmbH, Mosham 40, A-4943 Geinberg, Austria.

Hofmann, Austria. Hofmann Pharma GmbH & Co. KG, St Oswaldweg 20, A-5081 Anif, Austria.

Hofmann, Chile. Droguería Hofmann SAC, Los Gobelinos 2507, Renca, Santoago, Chile.

Hofmann & Sommer, Ger. Hofmann & Sommer GmbH & Co. KG, Lindenstr. 11, 07426 Konigsee, Germany.
url: www.hofmannundsommer.de

Hogil, USA. Hogil Pharmaceutical Corporation, 235 Mamaroneck Ave, Suite 202, White Plains, NY 10605, USA.
url: www.hogil.com

Holista, Canad. Holista Health Corp, PO Box 57525, Coquitlam, British Columbia, V3K 5Y9, Canada.
url: www.holistahealth.com

Holistica, Fr. Laboratoires Holistica International, 465 chemin des Jalassières, 13510 Eguilles, France.
url: www.holistica.fr

Hollborn, Ger. Dr K Hollborn & Sohne GmbH & Co. KG, Brahestr. 13, 04347 Leipzig, Germany.
url: www.hollborn.de

Holley-Cotec, China. Beijing Holley-Cotec Pharmaceuticals Co Ltd, Room 1601, Full Tower,, No 9 Dong san Huan Zhong Road, Chaoyang District, Beijing, 100020, China.
url: www.cotecxin.com

Hollister, Canad. Hollister Ltd, 95 Mary St, Aurora, Ontario, L4G 1G3, Canada.
url: www.hollister.com

Hollister-Stier, USA. Hollister-Stier Laboratories LLC, 3525 N. Regal, Spokane, WA 99207, USA.
url: www.hollister-stier.com

Holsten, Ger. Holsten Pharma GmbH, Im Burgerstock 7, 79241 Ihringen, Germany.
url: www.holstenpharma.de

Home, Port. See *Wyeth Consumer, Port.*

Home Diagnostics, USA. Home Diagnostics Inc., 2300 NW 55th Court, Fort Lauderdale, FL 33309, USA.
url: www.homediagnosticsinc.com

Homeocan, Canad. Homéocan, 3025, boul. de l'Assomption, Montreal, Quebec, H1N 2H2, Canada.
url: www.homeocan.ca

Homeofarm, Pol. Laboratorium Farmaceutyczne Homeofarm Sp. zo.o., ul Jagiellońska 44, 80-366 Gdańsk, Poland.
url: www.homeofarm.pl

Homeosyn, Ital. Homeosyn Italia Srl, P.zza Cesare de Cupis 15, 00155 Rome, Italy.

Homme de Fer, Fr. Laboratoires de l'Homme de Fer, 2 pl. de l'Homme de Fer, 67000 Strasbourg, France.

Hommel, Ger. Hommel Pharma GmbH & Co. KG, Rohrkamp 26, 59348 Luedinghausen, Germany.
url: www.hommel-pharma.com

Honbase, Hong Kong. Honbase Trading Ltd, Unit 10, 27/F Metropole Square, 2 On Yui St, Sui Lek Yuen, Shatin, NT, Hong Kong.

Hong Kong Medical, Hong Kong. Hong Kong Medical Supplies Ltd, 7/F China Aerospace Centre, 143 Hoi Bun Rd, Kwun Tong, Hong Kong.

Hong Tai Hong, Hong Kong. Hong Tai Hong, Rua de Almirante, Costa Cabral No 68, 1/F, Flat B, Edificio Sun Flat, Macau.

Hope, USA. Hope Pharmaceuticals, 8260 E Gelding Drive, Suite 104, Scottsdale, AZ 85260, USA.
url: www.hopepharm.com

HorFerVit, Ger. HorFerVit Pharma GmbH, H.-Brockmann Str. 81, 26131 Oldenburg, Germany.
url: www.horfervit.de

Horizon, USA. See *First Horizon, USA.*

Hormel, Hong Kong. See *IDS, Hong Kong.*

Hormel, Israel. See *Megapharm, Israel.*

Hormel, Singapore. See *JDH, Singapore.*

Hormel, USA. Hormel HelathLabs Inc., 3000 Tremont Rd, Savannah, GA 31405, USA.
url: www.hormelhealthlabs.com

Hormona, Mex. Laboratorios Hormona S.A. de C.V., Blvd. M. Avila Camacho No.470, Col. San Andres Atoto, 53500 Naucalpan de Juarez, Mexico.

Hormosan, Ger. Hormosan Pharma GmbH, Wilhelmshöher Str. 106, 60389 Frankfurt/Main, Germany.
url: www.hormosan.de

Horna, Cz. Horna Business Service, Narcisová 2/850, 106 00 Prague 10, Czech Republic.

Hosbon, Spain. Hosbon, Ronda General Mitre 72-74, 08017 Barcelona, Spain.

Hospal, Spain. Hospal, Napoles 249, 08001 Barcelona, Spain.
url: www.hospal.es

Hospira, Canad. Hospira Healthcare Corp., 600 1111 Dr Frederik-Philips Blvd, Saint-Laurent, Quebec, H4M 2X6, Canada.

Hospira, Cz. See *Hospira, Neth.*

Hospira, Irl. See *Hospira, UK.*

Hospira, Ital. Hospira SpA, Via Fosse Ardeatine 2, 20060 Liscate (MI), Italy.

Hospira, Malaysia. Hospira Malaysia Sdn Bhd, Suite 201 1st Fl Wisma Glomac 3, Kompleks Kelana Centre Point, Jln SS 7/19, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.hospira.com

Hospira, Neth. Hospira Enterprises BV, Taurusavenue 19-21, 2132 LS Hoofddorp, Netherlands.

Hospira, Port. See *Hospira, Neth.*

Hospira, Rus. See *Abbott, Rus.*

Hospira, Spain. Hospira, Consuegra 7, 28036 Madrid, Spain.
url: www.hospira.es

Hospira, UK. Hospira Ltd, Asmec Centre, Merlin Rd, Brunel, Theale, Berkshire, RG7 4AB, UK.
url: www.hospira.co.uk

Hospira, USA. Hospira Inc., Lake Forest, Illinois, USA.
url: www.hospira.com

Hospital Line, Gr. Hospital Line, K Palama 36, 143 43 Halkidona, Greece.

Hospithera, Belg. SA Hospithera NV, Rue de la Petite Ile, 1070 Brussels, Belgium.
url: www.hospithera.com

Hovid, Hong Kong. See *Wellgo, Hong Kong.*

Hovid, Malaysia. Hovid Sdn Bhd, 121 Jalan Kuala Kangsar, 30010 Ipoh, Perak, Malaysia.
url: www.hovid.com

Hovid, Philipp. Hovid, Unit 306 AIC Gold Tower Cond., Emerald Ave, Ortigas Ctr, Pasig City, Philippines.
url: www.hovid.com

Hovid, Singapore. See *Goldplus, Singapore.*

Howmedica, Cz. See *Howmedica, Irl.*

Howmedica, Denm. See *Stryker, Swed.*

Howmedica, Irl. Howmedica International Inc., Raheen Industrial Estate, Limerick, Ireland.

Howmedica, Neth. See *Howmedica, Irl.*

Howmedica, NZ. See *Howmedica, UK.*

Howmedica, Port. See *Howmedica, Irl.*

Howmedica, Spain. See *Stryker, Spain.*

Howmedica, UK. Howmedica International Ltd, 622 Western Ave, Park Royal, London, W3 0TF, UK.

Hoyer, Ger. Hoyer-Madaus GmbH & Co. KG, Alfred-Nobel-Str. 10, 40789 Monheim, Germany.
url: www.hoyer-madaus.de

HPB, Rus. State Institute of Highly Pure Biopreparations, Pudozhskaya St 7, 197110 Saint Petersburg, Russia.
url: www.hpb-spb.com

HPC, Switz. HPC Harras Pharma Curarina, Worbstrasse 221, 3073 Gumligen, Switzerland.

HPP, Hong Kong. Hong Kong Puis Pharmaceuticals Co Ltd, Rm 1303-4, 13/F Kwang Tung Prov Bang Bldg, 587-9 Nathan Rd, Kowloon, Hong Kong.

HRA, Cz. See *HRA, Fr.*

HRA, Denm. See *Nycomed, Denm.*

HRA, Fin. See *Tamro, Fin.*

HRA, Fr. Laboratoires HRA Pharma, 19 rue Frederick-Lemaitre, 75020 Paris, France.
url: www.hra-pharma.com

HRA, Ger. See *HRA, Fr.*

HRA, Neth. See *HRA, Fr.*

HRA, Norw. See *Nycomed, Norw.*

HRA, Pol. mip18r.

HRA, Spain. See *HRA, Fr.*

HRA, UK. See *HRA, Fr.*

HSL, NZ. Health Support Ltd, P.O. Box 44 027, Point Chevalier, Auckland, New Zealand.
url: www.healthsupport.co.nz

HSPMM, Rus. See *Teva, Rus.*

Hua, Thai. B L Hua & Co. Ltd, 2 Somdej Chaopraya Rd, Klongsan, Bangkok 10600, Thailand.

Hua Shin, Philipp. See *New Smart, Philipp.*

Hub, India. See *Aventis, India.*

Hubert, UK. Hubert A.C. Thomas & Co., Burry Port, Carmarthenshire, SA16 0TB, UK.

Hubner, Cz. Hubner, Czech Republic.

Hubner, Fin. See *Oriola, Fin.*

Huckaby, USA. Huckaby Pharmacal Inc., 11802 Brinley Ave, Suite 201, Louisville, KY 40243, USA.

Hudson, USA. Hudson Corp., 90 Orville Drive, Bohemia, NY 11716, USA.

Hugh Source, Hong Kong. Hugh Source (International) Ltd, Rm 1312 New East Ocean Centre, 9 Science Museum Rd, Tsim Sha Tsui East, Kowloon, Hong Kong.
url: www.btxa.com

Human, Cz. See *Humanpharma, Hung.*

Human, Hung. See *Humanpharma, Hung.*

Human, Philipp. See *PharmAsia, Philipp.*

Humana, Ital. Humana Italia S.p.A., Via R Boscovich 55, 20124 Milan, Italy.
url: www.humana.it

Humana, Pol. See *DPS, Pol.*

Humanpharma, Hung. Humanpharma Gyógyszergyártó Kft, Táncsics Mihály út 82, 2100 Gödöllő, Hungary.
url: www.human.hu

Humco, USA. Humco Holdings Group Inc., 7400 Alumax Drive, Texarkana, TX 75501, USA.
url: www.humco.com

Hungaro-Gen, Hung. Hungaro-Gen Kft, Budai Nagy Antal u. 3 I/3, 1137 Budapest, Hungary.
url: www.hungaro-genkft-c.cegbongeszo.hu

Huntley, UK. Huntley Pharmaceuticals Ltd, P.O. Box 2752, Marlborough, Wiltshire, SN8 1ZH, UK.
url: www.huntley-pharma.co.uk

Husler, Switz. Franz Hüsler AG, Pharmazeutische Präparate, Chriesbaumstrasse 6, 8604 Volketswil, Switzerland.

Husnu, Turk. See *Bilim, Turk.*

HWS OTC, Austria. HWS-OTC-Service GmbH, Steindorf 65, A-5570 Mauterndorf, Austria.

Hyde, Canad. Hyde Pharmaceuticals, 20 Lewis St, Fort Erie, Ontario, L2A 5M6, Canada.

Hyde, S.Afr. Hyde Pharmaceuticals (Pty) Ltd, 80 Bonza Bay Rd, Beacon Bay 5241, South Africa.

Hydration, Singapore. See *MBD, Singapore.*

Hyland, USA. See *Baxter-Hyland, USA.*

Hylands, Canad. Hylands Homeopathic Canada, 381-A, route 139, Sutton, Quebec, J0E 2K0, Canada.

Hyperion, Rus. See *Rompharm, Rus.*

Hypoguard, Irl. See *Hypoguard, UK.*

Hypoguard, UK. Hypoguard (UK) Ltd, Dock Lane, Melton, Woodbridge, Suffolk, IP12 1PE, UK.
url: www.hypoguard.com

Hyrex, USA. Hyrex Pharmaceuticals, 3494 Democrat Rd, P.O. Box 18385, Memphis, TN 38118-0385, USA.

I Farmacologia, Spain. See *Schwarz, Spain.*

IAE, Philipp. IAE Pharmaceuticals Corp., 25 Kabignayan St, Cor Banawe, Quezon City, Philippines.

Iamatica, Gr. Iamatica, Chalandriou 6A, 153 43 Ag. Paraskevi, Greece.

Iapharm, Gr. IAPHARM, 54 Menandrou Str., 104 31 Athens, Greece.
url: www.iapharm.gr

Iasis, Gr. See *Chemipharma, Gr.*

Iason, Austria. Iason Labormedizin GmbH & Co KG, Feldkirchnerstrasse 4, A-8054 Graz, Austria.

Iason, Cz. See *Iason, Austria.*

Iason, Neth. See *Iason, Austria.*

Iator, Gr. Iator, Sorou 4, 151 25 Marousi, Greece.

IBA, Pol. See *Bioton, Pol.*

IBC, Ital. Istituto Biologico Chemioterapico SpA, Via Crescentino 25, 10154 Turin, Italy.
url: www.abcfarmaceutici.it

Ibefar, Braz. Ibefar Inst. Brasileiro de Esp. Ftcas. Ltda, Rua Franca Pinto 1357, 04016-035 São Paulo, Brazil.

Ibfarma, Braz. Ibfarma Indústria de Biotecnologia Farm. Ltda, Via Aratu QD 10, Lote 01-CIA, 43700-000 Simões Filho, BA, Brazil.

IBI, Cz. IBI sro, Myslbeková 25, 169 00 Prague 6, Czech Republic.

IBI, Ital. Istituto Biochimico Italiano Giovanni Lorenzini S.p.A., Via Tucidide 56, Torre 6, 20134 Milan, Italy.
url: www.ibi-lorenzini.com

IBI International, Cz. IBI International sro, Sokolovská 24, 186 00 Prague 8, Czech Republic.

Ibirn, Ital. Istituto Bioterapico Nazionale S.r.l., Via V. Grassi 9/11/13/15, 00155 Rome, Italy.

IBIS, UK. IBIS Products, Stevenage, Hertfordshire, SG1 4QG, UK.

IBN, Ital. IBN Istituto Biologico Nazionale S.r.l., Viale Citta d'Europa 681, 00144 Rome, Italy.

IBSA, Cz. See *IBI, Cz.*

IBSA, Denm. See *Meda, Denm.*

IBSA, Hong Kong. See *Mekim, Hong Kong.*

IBSA, Hung. IBSA Pharma Kft, Fodor u 54/b, 1124 Budapest, Hungary.

IBSA, Ital. Ibsa Farmaceutici Italia S.r.l., Vian Emilia 99 Frazione San Grato, 26900 Lodi, Italy.
url: www.ibsa.it

IBSA, Malaysia. See *Sun, Malaysia.*

IBSA, Neth. See *IBSA, Switz.*

IBSA, Philipp. See *Sonix, Philipp.*

IBSA, Port. See *IBSA, Ital.*

IBSA, Switz. Institut Biochimique SA, Via del Piano, 6915 Pambio-Noranco, Switzerland.
url: www.ibsa.ch

Icaro, Spain. See *AstraZeneca, Spain.*

ICC, Israel. See *Rekah, Israel.*

Ichthyol, Austria. See *Ichthyol, Ger.*

Ichthyol, Ger. Ichthyol-Gesellschaft Cordes, Hermanni & Co. (GmbH & Co.) KG, Sportallee 85, 22335 Hamburg, Germany.
url: www.ichthyol.de

Ichthyol, Switz. See *Medinova, Switz.*

ICI, India. ICI India Ltd, Ennore Express Highway, Ennore, Chennai 600 057, India.
url: www.icipharms.com

ICIM, Ital. ICIM International S.r.l., Via Peloritana 28, 20024 Garbagnate Milanese (MI), Italy.

ICM, Singapore. ICM, Integrated Contract Manufacturing Pte Ltd, 26 Kallang Place, 05-17, S 339157, Singapore.
url: www.icmpharma.com.sg

ICN, Arg. ICN ARG S.A.I.C. y F., Teodoro Vilardebo 2855/65, 1417 Buenos Aires, Argentina.
url: www.icnpharm.com

ICN, Austral. ICN Pharmaceuticals Australasia Pty Ltd, 85 Saint Hilliers Rd, Auburn, NSW 2144, Australia.

ICN, Austria. ICN Pharmaceuticals Austria GmbH, Michael-Pracher-Strasse 25A/7, A-5020 Salzburg, Austria.
url: www.icnpharm.com

ICN, Belg. ICN Biomedicals, Doornveld 10, 1731 Asse-Relegem, Belgium.
url: www.icnpharm.com

ICN, Braz. ICN Farmacêutica Ltda, Rua Geraldo Flausino Gomez 61, andar 10, 04575-060 São Paulo, SP, Brazil.
url: www.icnpharm.com

ICN, Canad. ICN Canada Ltd, 1956 Bourdon St, Montreal, Quebec, H4M 1V1, Canada.
url: www.icncanada.com

ICN, Cz. ICN Czech Republic as, Truhlářská 13-15, 110 00 Prague 1, Czech Republic.
url: www.icnpharm.cz

ICN, Denm. See *Medilink, Denm.*

ICN, Fin. See *ICN, Neth.*

ICN, Fr. ICN Pharmaceuticals France SA, 4 rue Jean-Rostand, Parc Club, 91893 Orsay cdx, France.
url: www.icnpharm.com

ICN, Ger. ICN Pharmaceuticals Germany GmbH, Bolongarostr. 82-84, 65929 Frankfurt/Main, Germany.
url: www.icnpharm.com

ICN, Hong Kong. See *JDH, Hong Kong.*

ICN, Hung. ICN Magyarország Rt, Csatárka u 82-84, 1025 Budapest, Hungary.

ICN, Irl. See *Allphar, Irl.*

ICN, Israel. See *Devries, Israel.*

ICN, Ital. ICN Pharmaceuticals Italy S.r.l., Via G.B. Pirelli 20, 20124 Milan, Italy.
url: www.icnpharm.com

ICN, Malaysia. See *JDH, Malaysia,* and *Pharmaforte, Malaysia.*

ICN, Mex. ICN Farmaceutica S.A de C.V, Blvd Manuel Avila Camacho 40, P.20 T.Es, Miguel Hidalgo Lomas de Chapulte, 11000 Mexico D.F, Mexico.
url: www.icnpharm.com

ICN, Neth. ICN Pharmaceuticals Holland BV, Stephensonstraat 45, 2723 RM Zoetermeer, Netherlands.
url: www.icnpharm.com

ICN, Norw. See *Medilink, Denm.*

ICN, NZ. See *Pacific, NZ.*

ICN, Pol. ICN Polfa Rzeszów SA, Biuro Marketingu i Sprzedaży, ul. Szucha 13/15, 00-580 Warsaw, Poland.
url: www.polfa.com.pl

ICN, Port. ICN Portugal Lda, Avenida Marechal Gomes da Costa 19, 1804-806 Lisbon, Portugal.
url: www.icnpharm.com

ICN, Rus. See *Valeant, Rus.*

ICN, Singapore. See *JDH, Singapore.*

ICN, Spain. See *Valeant, Spain.*

ICN, Switz. ICN Pharmaceuticals Switzerland AG, Ruhrbergstrasse 21, 4127 Birsfelden, Switzerland.
url: www.icnpharm.com

ICN, Thai. See *Diethelm, Thai.*

ICN, UK. See *Valeant, UK.*

ICN, USA. See *Valeant, USA.*

Icon, Philipp. Icon Pharma Corp., 1211 Medical Plaza, Ortigas Bldg, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.

ID Biomedical, Canad. ID Biomedical Corp. of Quebec, 525 Cartier Blvd West, Laval, Quebec, H7V 3S8, Canada.

Idaman, Malaysia. Idaman Pharma Sdn Bhd, 66 Jalan 1/27F, Pusat Bandar Wangsa Maju, 53300 Kuala Lumpur, Malaysia.
url: www.idamanpharma.com

Ideal, Fr. Idéal, 65 rue Alexandre-Dumas, B.P. 53, 69513 Vaulx-en-Velin cdx, France.
url: www.ideal.fr

Ideal Health, UK. Ideal Health Group Ltd, The Common, Potten End, Berkhamstead, Hertfordshire, HP4 2QF, UK.

IDEC, USA. See *Biogen, USA.*

Ideco, Ital. Ideco Srl, Via L Braille 18, 39100 Bolzano, Italy.

Iderne, Fr. Laboratoires Michel Iderne, Parc d'activités Rosenmeer, 67560 Rosheim, France.

IDI, Ital. IDI Farmaceutici S.p.A., Via dei Castelli Romani 83/85, 00040 Pomezia (Rome), Italy.

IDIS, Neth. See *IDIS, UK.*

IDIS, UK. IDIS World Medicines, Millbank House, 171-185 Ewell Rd, Surbiton, Surrey, KT6 6AX, UK.
url: www.idis.co.uk

Ido, Fr. Laboratoires Ido, 13 rue Commines, 75003 Paris, France.

Idol, Thai. See *JDH Borneo, Thai.*

IDS, Hong Kong. IDS (Hong Kong) Ltd Healthcare Division, 14/F LiFung Ctr, 2 On Ping St, Siu Lek Yuen, Shatin, NT, Hong Kong.
url: www.idsmarketing.com

IDS, Malaysia. IDS Marketing, LiFung Centre, Lot 6 Persiaran Perusahaan Seksyen 23, 40300 Shah Alam, Selangor, Malaysia.
url: www.idsmarketing.com

IDS, Singapore. IDS Marketing, Pharmaceutical Division, 279 Jalan Ahmad Ibrahim, 03-01, S-639938, Singapore.

IDS, Thai. IDS Marketing (Thailand) Ltd, 505 Moo 2, Bangpa-in Industrial Estate, Udom Sorayudh Rd, Tambol Klongjig, Amphur Bangpa-in, Ayudhaya 13160, Thailand.
url: www.idsmarketing.com

IEPSA, S.Afr. IEPSA (Pty) Ltd, P.O. Box 36482, Menlo Park 0102, South Africa.
url: www.iepsa.co.za

IFA, Mex. See *Investigacion, Mex.*

Ifarm, Pol. Instytut Farmaceutyczny, ul. Rydygiera 8, 01-793 Warsaw, Poland.
url: www.ifarm.waw.pl

Ifars, Indon. Ifars Pharmaceutical Laboratories PT, Jl Raya Solo-SRagen Km 14.9, Karang Anyar Solo, 57762 Jawa, Indonesia.

IFET, Gr. I.F.E.T. (Institute of Pharmaceutical Research and Technology S.A.), 18th Km of Marathonos Ave, 153 44 Pallini, Greece.
url: www.ifet.gr

IFET (ΙΦΕΤ), Gr. See *IFET, Gr.*

IFI, Ital. Istituto Farmacoterapico Italiano S.p.A., Via Paolo Frisi 23, 00100 Rome, Italy.

Ifusa, Mex. Laboratorios Ifusa S.A., Francisco Lorenzana 20, Col. San Rafael, Deleg. Cuauhtemoc, 06470 Mexico D.F., Mexico.

IG, Malaysia. See *Medidata, Malaysia,* and *Pharmaniaga, Malaysia.*

Igefarma, Braz. See *Theraskin, Braz.*

IIP, Ger. Institut für Industrielle Pharmazie F & E GmbH, Benzstrasse 2a, 63741 Aschaffenburg, Germany.
url: www.iip-gmbh.de

IIP, Port. See *IIP, Ger.*

Ikapharmindo, Indon. Ikapharmindo Putramas PT, Jl Pulo Gadung Raya No 29, Kawasan Industri Pulo Gadung, 13930 Jakarta, DKI Jaya, Indonesia.

Ikx, Arg. Ikx Cosmetica, Av. Cordoba 2348, (C1120AAG) Capital Federal, Argentina.
url: www.cosmeticaikx.com.ar

Ildong, Philipp. See *Metro, Philipp.*

Ilex, Austria. See *Ilex, UK.*

Ilex, Denm. See *Schering, Denm.*

Ilex, Norw. See *Schering, Norw.*

Ilex, UK. Ilex Pharmaceuticals Ltd, 1-3 Frederick Sanger Rd, Surrey Research Park, Guildford, Surrey, GU2 7YD, UK.
url: www.ilexonc.com

Iliafarm, Gr. Iliafarm (Ιλιαφαρμ), Levadeias 5, 144 52 Metamorfosi, Greece.

Il-ko, Turk. See *Bilim, Turk.*

Illa, Ger. ILLA Healthcare GmbH, Burgermeister-Seidl-Str. 8, 82515 Wolfratshausen, Germany.
url: www.illa-healthcare.com

Iller, Ger. Iller Pharma GmbH, Max-Planck-Str. 7, 89257 Illertissen, Germany.
url: www.docsalbe.de

Ilsan, Turk. Ilsan Hexal İlaç Ltd. Şti., Gebze Plastikçiler Org. San. Böl., Atatürk Blv. 9. Cad. No: 1, Gebze, Kocaeli, Turkey.
url: www.ilsan.com.tr

IMA, Braz. Instituto de Medicamentos e Alergia IMA Ltda, Rua Araujo Leitao 193, 20715-310 Rio de Janeiro, RJ, Brazil.

ImaRx, USA. ImaRx Therapeutics Inc., 1730 E River Rd, Suite 200, Tucson, AZ 85718, USA.
url: www.imarx.com

Imed, Pol. Imed Poland Sp. zo.o., ul. Duchnicka 3, 01-796 Warsaw, Poland.
url: www.imed.com.pl

Imeks, Malaysia. Imeks Pharma Sdn Bhd, 2 Jln 6/33B, MWE Commercial Park Kepong, 52000 Kuala Lumpur, Wilaya Persekutuan, Malaysia.

Imgroma, Neth. Imgroma BV, Aldebert van Scharnlaan 170 A-2, 6224 JX Maastricht, Netherlands.

Imi, Denm. Imi Pharma A/S, Literbuen 9, 2740 Skovlunde, Denmark.

Immapharma, Rus. Immapharma OOO, Gamalei ul. 18, 123098 Moscow, Russia.
url: www.immapharma.ru

Immodal, Austria. Immodal Pharmaka GmbH, Bundesstrasse 44, A-6111 Volders, Austria.

Immuno, Austria. See *Baxter, Austria.*

Immuno, Braz. Immuno Prod. Biologicos e Químicos Ltda, Rua Adolfo Lutz 82, 22451-120 Rio de Janeiro, RJ, Brazil.

Immuno, Hong Kong. See *Mekim, Hong Kong.*

Immuno, Israel. See *Teva, Israel.*

Immuno, Neth. Immuno BV, Brasem 51, 4941 SE Raamsdonksveer, Netherlands.

Immuno, USA. See *Baxter-Hyland, USA.*

Immunomedics, Cz. See *Immunomedics, Ger.*

Immunomedics, Ger. Immunomedics Europe, Otto-Roehm-Str. 69, 64293 Darmstadt, Germany.
url: www.immunomedics.com

Immunomedics, Neth. See *Immunomedics, Ger.*

Immunomedics, Port. See *Immunomedics, Ger.*

Immunomedics, UK. See *Immunomedics, Ger.*

Immunomedics, USA. Immunomedics, 300 American Rd, Morris Plains, NJ 07950, USA.
url: www.immunomedics.com

Immunotec, Canad. Immunotec Research, 292 Adrien-Patenaude, Vaudreuil-Dorion, Quebec, J7V 5V5, Canada.

Immunotec, USA. See *Immunotec, Canad.*

IMO, Ital. Istituto di Medicina Omeopatica S.p.A., Via Vincenzo Monti 6, 20123 Milan, Italy.
url: www.omeoimo.it

Imperial, Hong Kong. See *Unam, Hong Kong.*

Imperial, Malaysia. See *Unam, Malaysia.*

Imperial, Philipp. LR Imperial Inc., 2/F Bonaventure Plaza, Ortigas Ave, Greenhills, San Juan, Philippines.

Imperial, Singapore. See *Far East, Singapore.*

Impilo, S.Afr. Impilo Drugs (Pty) Ltd, P.O. Box 3322, Sundumbili 4491, South Africa.

IMS, Ital. International Medical Service S.r.l., Via Lauretina 169, 00040 Pomezia (RM), Italy.
url: www.imsonline.it

IMS, USA. See *Celltech, USA.*

Imtix, Cz. See *Imtix, Fr.*

Imtix, Fr. Imtix-SangStat, 58 av Debourg, B.P. 7055, 69348 Lyon cdx 07, France.
url: www.sangstat.fr

Imtix, Ital. IMTIX-Sangstat S.r.l., Via Winckelmann 2, 20146 Milan, Italy.
url: www.sangstat.com

Imtix Sangstat, Israel. See *Medison, Israel.*

Imuna, Cz. Imuna sp, Jarkovska 17, Šarišske Michal'any, Slovenia.

Imunomedica, Cz. Imunomedica as, Chuderov 118, 400 11 Ústí nad Labem, Czech Republic.
url: www.imunomedica.cz

Imvi, Arg. Lab. Imvi S.A. (Div. Humana), Olazabal 1665/71, 1428 Buenos Aires, Argentina.
url: www.imvi.com.ar

In Vitro, NZ. In Vitro Technologies, P.O. Box 14-323, Panmure, New Zealand.
url: www.invitro.co.nz

Inamed, Singapore. See *Pharmacon, Singapore.*

Inamed, USA. Inamed Health, 5540 Ekwill St, Santa Barbara, CA 93111, USA.
url: www.inamed.com

Inava, Fr. See *Pierre Fabre, Fr.*

Inca, Ger. Inca-Pharm GmbH, Rochusstrasse 175-177, 53123 Bonn, Germany.
url: www.inca-pharm.com

Incaico, Arg. Lab. Incaico SA, Montiel 156, 1408 Buenos Aires, Argentina.

Inco Veritas, Pol. Inco Veritas SA o/Góra Kalwaria GCHG, ul. Towarowa 8, 05-530 Góra Kalwaria, Poland.
url: www.inco-veritas.com.pl

Inde, Spain. Inde Farma Comercial, Agustin Querol 6 1 A, 28014 Madrid, Spain.

Indeco, Arg. Laboratorio Indeco S.A., Jose Marmol 1924, 1602 Florida, Buenos Aires, Argentina.

Indevus, Canad. See *Indevus, USA.*

Indevus, Malaysia. See *Diethelm, Malaysia.*

Indevus, USA. Indevus Pharmaceuticals Inc., 99 Hayden Ave, Suite 200, Lexington, MA 02421, USA.
url: www.indevus.com

Indian Drugs, India. Indian Drugs & Pharmaceuticals Ltd, IDPL Complex, Dundahera, Delhi-Gurgaon Rd, Gurgaon 122 001, India.

Indochina Healthcare, Thai. Indochina Healthcare Ltd, 23 Fl Olympia Thai Tower, 444 Ratchadapisek Rd, Samsennok Huay Kwang, Bangkok 10320, Thailand.

Indoco, India. Indoco Remedies Ltd, Indoco House, 166 CST Rd, Santacruz (East), Mumbai 400 098, India.
url: www.indoco.com

Indoco, Thai. See *Union Medical, Thai.*

Indofarma, Pol. See *Cowik, Pol.*

Indra Sakti, Indon. Indra Sakti Pharma PT, Jl Cilosari No 25, 10330 Jakarta, DKI Jaya, Indonesia.

Indrugco, Singapore. Indrugco Pte Ltd, 221 Henderson Rd, 07-20 Henderson Building, S 159557, Singapore.
url: www.indrugco.com

Inex, Hung. Inex-Intherexport, Dozsa Gyorgy út 92/a, 1068 Budapest, Hungary.

Inexfa, Spain. Inexfa, Ctra Nacional 340, Km 28, Orihuela, 03300 Alicante, Spain.

Infabra, Braz. Infabra Indústria Farmacêutica Brasileira Ltda, Av. das Americas 8.445 Conj.803, 22793-080 Rio de Janeiro, RJ, Brazil.
url: www.infabra.com.br

INFAI, Switz. INFAI CH GmbH, Bahnhofstrasse 29, 9470 Buchs, Switzerland.
url: www.infai.de

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Infarmed, Belg. Infarmed bvba, Stationsstraat 27, 3570 Alken, Belgium.
url: www.infarmed.be

Infectopharm, Austria. See *Infectopharm, Ger.*

Infectopharm, Cz. See *Infectopharm, Ger.*

Infectopharm, Ger. Infectopharm Arzneimittel und Consilium GmbH, Von-Humboldt-Str. 1, 64646 Heppenheim, Germany.
url: www.infectopharm.com

Infinity, Venez. Infinity Pharma XXI, C.A., Esq. Puente Restaurador, Edif. Puente Restaurador, Santa Teresa, 1010-A Caracas, Venezuela.
Infirmarius-Rovit, Ger. Pharmazeutische Fabrik Infirmarius-Rovit GmbH, Eislinger Str. 66, 73084 Salach, Germany.
url: www.infirmarius-rovit.de
Infosint, Ital. Infosint S.p.A., C. Dir. Colleoni, Pal. Pegaso 2, 20041 Agrate Brianza (MI), Italy.
Infusia, Cz. Infusia as Hořátev, Post Box 13, 289 12 Sadská, Czech Republic.
url: www.infusia.cz
Inga, India. Inga Laboratories Pvt Ltd, Mahakali Rd, Andheri East, Mumbai 400 093, India.
Inga, Malaysia. See *Pahang, Malaysia.*
Ingen, Fr. Lab. Ingen, Sogaris 203, 94654 Rungis cdx, France.
Ingens, Arg. Laboratorios Ingens S.A., Fraga 1401, 1427 Buenos Aires, Argentina.
Ingers, Cz. Ingers Industrial Solutions sro, Brno, Czech Republic.
Inibsa, Port. Laboratórios Inibsa, SA, Sintra Business Park, Zona Industrial da Abrunheira, Edifício 1 - 2, 2710-089 Sintra, Portugal.
url: www.inibsa.com
Inibsa, Spain. Inibsa, Ctra Sabadell Granollers Km 14.5, Llissa de Vall, 08185 Barcelona, Spain.
url: www.inibsa.com
Inkeysa, Spain. Inkeysa, Juan XXIII 15, Esplugas de Llobregat, 08950 Barcelona, Spain.
url: www.inkeysa.es
Inkine, USA. InKine Pharmaceutical Company Inc., 1787 Sentry Pkwy, West Bldg 18, Suite 440, Blue Bell, PA 19422, USA.
url: www.inkine.com
Inmark, Indon. Inmark, Indonesia.
Inmunolab, Arg. Lab. Inmunolab S.A., Paysand 1928, 1416 Buenos Aires, Argentina.
Innocoll, Cz. See *Innocoll, Irl.*
Innocoll, Hung. See *Innocoll, Irl.*
Innocoll, Irl. Innocoll Pharmaceuticals, Dublin Rd, Athlone, County Westmeath, Ireland.
url: www.innocoll-pharma.com
Innoderm, Philipp. Innoderm Inc., Metro Pharma Bldg, 600 Shaw Blvd, Pasig City, Philippines.
Innoledge, Hong Kong. Innoledge International Ltd, 31 Mau Po Village, Clear Water Bay, Hong Kong.
url: www.innoledge.com
Innomed, Singapore. Innomed, Singapore.
Innopharm, Malaysia. See *Zyfas, Malaysia.*
Innopharm, Singapore. See *Zyfas, Singapore.*
Innotech, Cz. See *Innotech, Fr.*
Innotech, Denm. See *Meda, Denm.*
Innotech, Fr. Laboratoires Innotech International, Sté du groupe Innothéra, 7-9 av Francois-Vincent-Raspail, B.P. 32, 94111 Arcueil cdx, France.
url: www.innotechinternational.fr
Innotech, Hong Kong. See *Wing Wai, Hong Kong.*
Innotech, Hung. See *Ubepharm, Hung.*
Innotech, Neth. See *Innotech, Fr.*
Innotech, Norw. See *Meda, Norw.*
Innotech, Port. See *Confar, Port.*
Innotech, Rus. Innotech International, Group Innothera, Pokhodnyi pr-d 4, str. 7a, Business Centre Tushino et. 3, Of. 7, 125373 Moscow, Russia.
Innotech, Singapore. See *Indrugco, Singapore.*
Innothera, Cz. See *Innothera, Fr.*
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url: www.innothera.com
Innothera, Neth. See *Innothera, Fr.*
Innothera, Pol. See *Ipsen, Pol.,* and *Fournier, Pol.*
Innothera, Rus. See *Innotech, Rus.*
Innothera, Switz. See *Interlabo, Switz.*
Innova, Ital. See *Recordati, Ital.*
InnoVisions, USA. Innovisions Inc., USA.
InnoZen, USA. InnoZen Inc., 6429 Independence Ave, Woodland Hills, CA 91367, USA.
url: www.innozen.com
INO Therapeutics, Cz. See *INO Therapeutics, Swed.*
INO Therapeutics, Neth. See *INO Therapeutics, Swed.*
INO Therapeutics, Pol. See *Linde Gaz, Pol.*
INO Therapeutics, Port. See *INO Therapeutics, Swed.*
INO Therapeutics, Spain. INO Therapeutics, Genova 17, 02800 Madrid, Spain.
url: www.inotherapeutics.com
INO Therapeutics, Swed. INO Therapeutics AB, S-181 81 Lidingo, Sweden.
INO Therapeutics, USA. INO Therapeutics Inc., 6th State Route 173, Clinton, NJ 08809, USA.
url: www.inotherapeutics.com
Inogen, Austral. Inogen Pharmaceuticals, Australia.
url: www.genflex.com.au
Inova, Ger. Inova-Global GbR H & S Klein, Kaiserstr. 127, 51145 Cologne, Germany.
url: www.inovaglobal.de
Inpa, Gr. INPA S.A., 154 Kifisias Str., 151 26 Athens, Greece.
url: www.inpa-gr.com
Inpharzam, Switz. See *Zambon, Switz.*
INQ, Braz. Instituto Nacional de Quimioterapia Ltda, Rua Antônio Foster 85, 04760-040 São Paulo, SP, Brazil.
Inquifave, Venez. Inquifave S.A., Qta. La Trinidad, Av.Roosevelt Los Castacos, Urb. El Cementerio, Caracas, Venezuela.
Insight, Canad. See *Associated National Brokerage, Canad.*
Insight, USA. Insight Pharmaceuticals Corp., 1170 Wheeler Way, Suite 150, Langhorne, PA 19047-1749, USA.
Insmed, USA. Insmed Inc., 4851 Lake Brook Drive, Glen Allen, VA 23060, USA.
url: www.insmed.com
Inspire, USA. Inspire Pharmaceuticals Inc., 4222 Emperor Bvld, Suite 200, Durham, NC 27703, USA.
url: www.inspirepharm.com
Institute for Molecular Genetics, Rus. See *Pik, Rus.*
Institute of Immunology, Philipp. See *Global, Philipp.*
Instituto Tecnologico PET, Port. See *Complutense, Spain.*
Insurrir, Ger. Insurrir AG, Brückenstr. 2, 67551 Worms, Germany.
url: www.insurrir.de
Intas, India. Intas Pharmaceuticals Ltd, Chinubhai Center, Off Nehru Bridge, Ashram Rd, Ahmedabad -80 009, India.
url: www.intaspharma.com
Intas, Philipp. See *Pharmawealth, Philipp.*
Intas, Thai. See *Union Medical, Thai.*
Integra, Philipp. Integra Pharma Inc., Unit 3001-88 Corporate Ctr, cor Sedeño & Valero Sts, Salcedo Vill, Makati City, Philippines.
Integrated Pharmaceutical, Philipp. Integrated Pharmaceutical Inc., 416 Dasmariñas St, Binondo, Manila, Philippines.
Integrity, USA. See *Xanodyne, USA.*
Intelpharm, Rus. Intelpharm Corp., Kostina St 4, 603000 Lower Novgorod, Russia.
url: www.intelpharm.ru
Intendis, Braz. Intendis do Brasil Farmacêutica Ltda, Av. Alfredo Egidio de S Aranha 374/84, 7 andar, 04726-170 São Paulo, Brazil.
Intendis, Cz. See *Intendis, Ger.*
Intendis, Denm. See *Schering, Denm.*
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url: www.intendis.fr
Intendis, Ger. Intendis Dermatologie GmbH, Max-Dohrn-Str. 10, 10589 Berlin, Germany.
url: www.intendis.de
Intendis, Hung. See *Bayer Schering, Hung.*
Intendis, Ital. Intendis, Via E Schering 21, 20090 Segrate (MI), Italy.
url: www.intendis.it
Intendis, Mex. Intendis Mexicana SA de CV, Calzada Mexico Xochimilco 5019, 14370 Huipulco del Tlalpan San Lorenzo, Mexico DF, Mexico.
Intendis, Norw. See *Schering, Norw.*
Intendis, Pol. Intendis Polska Sp. zo.o., ul. Migdałowa 4, 02-796 Warsaw, Poland.
url: www.intendis.com
Intendis, Port. Intendis Portugal Sociedade Unipessoal Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.
Intendis, Rus. See *Intendis, Ger.*
Intendis, Singapore. See *Zuellig, Singapore.*
Intendis, Spain. Intendis Pharma, C/Mendez Alvaro 55, 28045 Madrid, Spain.
Inter, Venez. Inter-Farmacéutica, Calle Londres e/ Calles Nueva York y Trinidad, Edif. IUS Piso 3 Of. 3-2, Urb. Las Mercedes, Caracas, Venezuela.
Interbat, Indon. Interbat PT, Jl Mampang, Prapatan Raya No 81, 12790 Jakarta, Indonesia.
Interbelle, Arg. Interbelle Cosmetic S.A., Sanabria 2353 Piso 1, 1417 Buenos Aires, Argentina.
Interbial, Port. See *Bial, Port.*
Intercare, NZ. InterCare Corp. Ltd, P.O. Box 18446, Glen Innes, Auckland, New Zealand.
Interchemia, Cz. Interchemia Praha sro, Šafaříková 3/456, 120 00 Prague 2, Czech Republic.
Interdelta, Switz. Interdelta SA, Case postale 791, 1701 Fribourg, Switzerland.
Interfarma, Port. Interfarma Produtos Quimicos e Farmacêuticos Lda, Rua Dr Antonio Loureiro Borges 2, Arquiparque - Miraflores, 1495-131 Alges, Portugal.
Interferon Sciences, USA. See *HemispheRx, USA.*
Interhealthcare, Philipp. INTERHEALTHcare Pharmaceuticals Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.
Interko, Turk. Interko, Turkey.
Interlabo, Switz. Interlabo SA, Case postale 8, 42/44 rue Prevost-Martin, 1211 Geneva 9, Switzerland.
Interlink, Philipp. Interlink Pharma Mktg Corp., Unit G-52 South Star Plaza, South Superhighway, Bangkal, Makati City, Philippines.
Interlogim, Neth. Interlogim Pharma Service BV, Beeldschermweg 6B, 3821 AH Amersfoort, Netherlands.
Intermed, Gr. See *Unipharma, Gr.*
InterMed, NZ. InterMed Medical Ltd, P.O. Box 33-268, Takapuna, Auckland, New Zealand.
InterMed, Philipp. InterMed Marketing Phils Inc., Suite 709, 7/F Common Goal Tower, Finance cor Industry St, Madrigal Business Park, Ayala Alabang, Muntinlupa City, Philippines.
Intermedica, Switz. Intermedica SA, Pharmazeutische Produkte, Boulevard de Perolles 17, Case postale 238, 1701 Fribourg, Switzerland.
Intermune, Neth. See *Intermune, UK.*
Intermune, Singapore. Intermune, Singapore.
Intermune, UK. InterMune Europe Ltd, Thames House, London, SE18 6NZ, UK.
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International Apex, Philipp. International Apex Pharmaceuticals, Unit 17-A Belvedere Tower, San Miguel Ave, Ortigas Complex, Pasig City, Philippines.
International Dermatologicals, Canad. International Dermatologicals Inc., 1940 Lonsdale Ave, Suite 217A, Vancouver, British Columbia, V7M 2K2, Canada.
International Ethical, USA. International Ethical Labs, 1021 Americo Miranda Ave., Reparto Metropolitano, Rio Piedras, PR 00921, Puerto Rico.
url: www.intetlab.com
International Lab Tech, USA. International Laboratory Technology Corp, 3389 Sheridan St, Suite 149, Hollywood, FL 33021, USA.
International Medical, Hong Kong. International Medical Co. Ltd, Unit 715, 7/F, Block B, Seaview Estate, 2-8 Watson Rd, North Point, Hong Kong.
url: www.timc.com.hk
International Pharmaceuticals, Thai. International Pharmaceuticals Ltd, 38/2 Sukhumvit 63 (Soi Ekamal), Kwaeng Prakanong Nua, Khet Wattana, Bangkok 10110, Thailand.
Interpharm, Austria. Interpharm GmbH, Effingergasse 21, A-1160 Vienna, Austria.
url: www.interpharm.at
Interpharma, Chile. Interpharma SA, Camino a Melipilla 6873, Cerrillos, Santiago, Chile.
Interpharma, Spain. Interpharma, Santa Rosa 6, Santa Coloma de Gramanet, 08921 Barcelona, Spain.
url: www.interpharma.es
Interphil, Hong Kong. See *US Summit, Hong Kong.*
Intersan, Ger. Intersan GmbH, Einsteinstr. 30, 76275 Ettlingen, Germany.
Intersan, Switz. See *Uhlmann-Eyraud, Switz.*
Intersero, Ger. Intersero GmbH, Am Klingenweg 13, 65396 Walluf, Germany.
url: www.intersero.de
Intertrade, Gr. Intertrade Dental, Levkis 111, 145 68 Krioneri, Greece.
INTES, Ital. See *Alfa Intes, Ital.*
Inthera, Hung. Inthera Kft, Háros u 103, 1222 Budapest, Hungary.
Intra, Venez. Laboratorios Intra S.A., Av. Principal 50-75, Barrio Los Estanques Maracaibo, Zulia, Venezuela.
Intra Pharma, Irl. See *United Drug, Irl.*
Intramed, Gr. Intramed, Sardeon 2, 172 37 Ymittos, Greece.
Intramed, S.Afr. Intramed (Pty) Ltd, 6 Gibaud Rd, Port Elizabeth 6001, South Africa.
Intrapharm, Irl. See *United Drug, Irl.*
Intrapharm, UK. Intrapharm Laboratories Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QS, UK.
url: www.intrapharmlabs.com
Intsel, Fr. Laboratoires Intsel Chimos, Technopolis, 145 rue J.-J. Rousseau, 92138 Issy-les-Moulineaux cdx, France.
url: www.intselchimos.com
Invamed, USA. See *Geneva, USA.*
Invar, Rus. Invar OOO, 53a Strelkovoi Divizii ul. 6/9, 410710 Saratov, Russia.
url: www.invar.ru
Inverdia, Swed. Inverdia AB, Vretenvägen 8, 171 54 Solna, Sweden.
url: www.inverdia.com
Inverni della Beffa, Ital. See *Sanofi Synthelabo, Ital.*
Investi, Arg. Investi Farma S.A., Lisandro de la Torre 2160, 1440 Buenos Aires, Argentina.
Investigacion, Mex. Investigación Farmacéutica (IFA) S.A. de C.V, Calle 13-E No. 5 CIVAC, 62500 Jiutepec Morelos, Mexico.
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Investigaciones Filosoficas y Cientificas, Mex. Investigaciones Filosoficas y Cientificas S.A. de C.V., Tlacote No. 128, 76230 Juriquilla, Queretaro, Mexico.
Invicta, Spain. See *Pfizer, Spain.*
Iocom, UK. Iocom (UK) Ltd, Hope Mill, Skipton Rd, Barnoldswick, Lancashire, BB18 6EN, UK.
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Iodosan, Ital. See *GSK Consumer, Ital.*
Iolab, Israel. See *Concept, Israel.*
Iolab, USA. See *Novartis Ophthalmics, USA.*
Ioltech, Fr. Laboratoires Ioltech, av. Paul-Langevin, B.P. 5, 17053 La Rochelle cdx 9, France.
url: www.ioltech.com
Ioltech, Ger. Ioltech Deutschland GmbH, eine Unternehmen der Carl Zeiss Meditec AG, Kurfürsten Anlage 36, 69115 Heidelberg, Germany.
url: www.ioltech.com
Ioltech, Port. See *Ioltech, Fr.*
Iomed, Hong Kong. See *Pan-Well, Hong Kong.*
Iomed, USA. See *Iopharm, USA.*
Ion, USA. Ion Laboratories Inc., 7431 Pebble Drive, Fort Worth, TX 76118, USA.
Ionion, Gr. IONIAN Pharma Ltd, 15-17 Sarantapichou, 114 71 Athens, Greece.
url: www.biotest.com
Ionios (Ιονιος), Gr. See *Ionion, Gr.*
Iopharm, USA. Iopharm, 7509 Flagstone St., Ft Worth, TX 76118, USA.
Ioquin, Austral. See *Alcon, Austral.*
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IPA, Ital. International Pharmaceuticals Associated S.r.l., Via del Casale Cavallari 53, 00100 Rome, Italy.
Ipca, India. Ipca Laboratories Ltd, 63-E Kandivli Industrial Estate, Kandivli (W), Mumbai 400 067, India.
url: www.ipca-labs.com
IPCA, Malaysia. See *Zyfas, Malaysia.*
Ipca, Rus. Ipca Laboratories Ltd, Obroucheva ul. 4, korp. 3, of. 159-160, 119421 Moscow, Russia.
url: www.ipcalabs.com
IPCA, Singapore. See *Zyfas, Singapore.*
Ipex, Ger. See *Ipex, Swed.*
Ipex, Norw. See *Ipex, Swed.*
Ipex, Swed. Ipex Medical AB, Box 120, 182 12 Danderyd, Sweden.
url: www.ipex.se
IPFI, Ital. IPFI Industria Farmaceutica S.r.l., Via Egadi 7, 20144 Milan, Italy.
Iphym, Fr. Laboratoires Iphym, chemin de la Sereine, 01700 Beynost, France.
url: www.iphym.com
IPI, Indon. See *Tempo Scan Pacific, Indon.*
IPI, Port. I.P.I. Portugal Lda, Av. de Berne No 30-4 B, 1050-042 Lisbon, Portugal.
IPR, Rus. See *AstraZeneca, Rus.*
IPRAD, Fr. Laboratoires IPRAD, 42-52 rue de l'Aqueduc, 75010 Paris, France.
IPRAD-Sante, Fr. IPRAD-Santé, 221 rue Lafayette, 75010 Paris, France.
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url: www.ipsfarma.es
Ipsen, Austral. Ipsen Pty Ltd, Suite 42, Waverley Business Centre, 21 Aristoc Rd, Glen Waverley, VIC 3150, Australia.
url: www.beaufour-ipsen.com
Ipsen, Belg. Ipsen NV, Guldensporenpark 87, 9820 Merelbeke, Belgium.
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Ipsen, Cz. See *Beaufour, Fr.*
Ipsen, Denm. Ipsen Scandinavia A/S, Park Allé 292, 2605 Brøndby, Denmark.
Ipsen, Fin. See *Ipsen, Denm.*
Ipsen, Ger. Ipsen Pharma GmbH, Einsteinstr. 30, 76275 Ettlingen, Germany.
url: www.ipsen-pharma.de
Ipsen, Gr. Ipsen EpE, 63 AG. Dimitriou St., 174 56 Alimos, Greece.
url: www.ipsen.com
Ipsen, Irl. Ipsen Pharmaceuticals Ltd, 7 Upper Leeson St, Dublin 4, Ireland.
url: www.ipsen.ie
Ipsen, Israel. See *Medison, Israel.*
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Ipsen, Norw. See *Ipsen, Denm.*
Ipsen, NZ. See *NZ Medical & Scientific, NZ.*
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Ipsen, Port. Ipsen Portugal, SA, Rua General Ferreira Martins, Alameda Fernão Lopes 16-11, Miraflores, 1495-136 Algés, Portugal.
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Ipsen, Swed. See *Ipsen, Denm.*
Ipsen, Switz. See *Globopharm, Switz.*
Ipsen, Thai. See *Pacific, Thai.*
Ipsen, UK. Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK.
url: www.ipsen.co.uk
Ipsen, USA. Ipsen Inc., 27 Maple St., Milford, MA 01757-3650, USA.
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Ipso, Ital. Ipso-Pharma S.r.l., Via San Rocco 6, 85033 Episcopia (PZ), Italy.
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IQFA, Mex. Industrias Químico Farmaceuticas Americanas S.A. de C.V., Lago Peypus No. 215, Col. Anahuac, Deleg. Miguel Hidalgo, 11320 Mexico D.F., Mexico.

Iquinosa, Spain. See *Faes, Spain.*

Irex, Fr. Laboratoires Irex, Groupe Sanofi-Synthélabo, 11 rue Salomon-de-Rothschild, 92150 Suresnes, France.

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Irisfarma, Spain. See *Lilly, Spain.*

Irmed, Ital. Istituto Ricerche Mediche S.r.l., Via della Consortia 17, 37127 Verona-Avesa, Italy.

Iromedica, Rus. See *Santa, Rus.*

Iromedica, Switz. Iromedica AG, Haggenstrasse 45, 9014 St Gallen, Switzerland.
url: www.iromedica.ch

ISA, Arg. Instituto Seroterapico Argentino S.A.I.C., Av. Larrazabal 1848, 1440 Buenos Aires, Argentina.
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Iscotec, Neth. See *Iscotec, Swed.*

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ISI, Cz. See *ISI, Ital.*

ISI, Ital. See *Kedrion, Ital.*

Isis, Cz. See *Alpharma-Isis, Ger.*

Island, Pol. Island Przedsiębiorstwo Handlowe Eksport-Import, ul. Chwarznieńska 192 C, 81-602 Gdynia, Poland.

Iso, Ger. Iso-Arzneimittel GmbH & Co. KG, Bunsenstr. 6-10, 76275 Ettlingen, Germany.
url: www.iso-arznei.de

Isodisnatura, Fr. Isodinatura, 107 quai du Docteur-Dervaux, 92600 Asnières-sur-Seine, France.
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Isomed, Port. See *Isomed, Spain.*

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Isopharm, Hong Kong. See *CNW, Hong Kong.*

Isramedcom, Israel. Isramedcom Ltd, 1 Ha'omanut St, Poleg Industrial Park, Netanya 42504, Israel.

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url: www.istavision.com

Istanbul, Turk. İstanbul İlaç San. ve Tic. A.Ş., Okmeydani Mahmut Şevket Paşa Mah., Mithat Paşa Cad. Keser Sok. No: 1/3, Şişli, İstanbul, Turkey.
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Istar, NZ. Istar Ltd, 8 Braithwaite St, Karori, Wellington, New Zealand.

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Italfarmaco, Cz. See *Italfarmaco, Ital.*

Italfarmaco, Gr. Italfarmaco Hellas A.E., 183 Syngrou & Saldeon, 171 21 N. Smyrni, Greece.
url: www.italfarmaco.gr

Italfarmaco, Ital. Italfarmaco S.p.A., Viale Fulvio Testi 330, 20100 Milan, Italy.
url: www.italfarmaco.it

Italfarmaco, Pol. mmp35l.

Italfarmaco, Port. Italfarmaco Farma Produtos Farmacêuticis Lda, Rua Consiglieri Pedroso 123, Queluz de Baixo, 2745-557 Barcarena, Portugal.

Italfarmaco, Rus. Italfarmaco, Glazovskii per. 7, Of. 12, 119002 Moscow, Russia.

Italfarmaco, Spain. Italfarmaco, San Rafael 3, Alcobendas, 28100 Madrid, Spain.
url: www.itfsp.com

Italmex, Mex. Italmex S.A., Calz. de Tlalpan Num. 3218, Col. Ejido Santa Ursula Coapa, Deleg. Coyoacan, 04910 Mexico D.F., Mexico.
url: www.italmex.com.mx

Italzama, Ital. Italzama, Via Lucio Coilio 15, 00122 Lido di Ostia Ponente, Italy.

ITBS, Hong Kong. See *Universal, Hong Kong.*

ITF, Chile. Lab. ITF Farma Chile SA, Encomenderos 161, Of. 3 B, Las Condes, Santiago, Chile.

ITF, Gr. See *Italfarmaco, Gr.*

ITF, Port. ITF Farma Lda, Rua Consiglieri Pedroso no 123, Queluz de Baixo, 2745-557 Barcarena, Portugal.
url: www.italfarmaco.it

Ivax, Arg. Ivax Argentina SA, JJ Castelli 6701, 1605 Munro, Buenos Aires, Argentina.

Ivax, Canad. See *Ivax, USA.*

Ivax, Cz. Ivax-CR as, Pod Habrovou 3, 152 00 Prague 5, Czech Republic.
url: www.ivax.cz

Ivax, Denm. See *Ivax, Swed.*

Ivax, Fin. Ivax Finland Oy, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.ivax.fi

Ivax, Fr. Ivax SAS, 15 rue del'Hôtel, 92522 Neuilly-sur-Seine, France.
url: www.ivax.com

Ivax, Ger. Ivax Pharma GmbH, Hellersbergstr. 11, 41460 Neuss, Germany.

Ivax, Hong Kong. See *Hong Kong Medical, Hong Kong,* and *International Medical, Hong Kong.*

Ivax, Hung. Ivax-CR a s Közvetlen Kereskedelmi Képviselet, Berlini út 47-49, 1045 Budapest, Hungary.

Ivax, Irl. IVAX Ireland, Unit 301, Waterford Industrial Estate, Waterford, Ireland.
url: www.ivax.co.uk

Ivax, Malaysia. See *Averroes, Malaysia.*

Ivax, Mex. Ivax Pharmaceuticals Mexico S.A. de C.V., Calz de Hueso 859, Ex-Hacienda Coapa, 14100 Mexico D.F., Mexico.
url: www.ivax.com

Ivax, Neth. Ivax Farma bv, Tolnasingel 3, 2411 PV Bodegraven, Netherlands.

Ivax, Norw. Ivax, Postboks 688 Skøyen, 0214 Oslo, Norway.
url: www.ivax.com

Ivax, Pol. See *Teva, Pol.*

Ivax, Rus. Ivax AC, Dmitrovskii per. 9, Business-Centre Stoleshniki, et. 5, 103031 Moscow, Russia.
url: www.ivax.com

Ivax, S.Afr. Ivax, South Africa.

Ivax, Singapore. See *FP, Singapore,* and *Green Cross, Singapore.*

Ivax, Swed. IVAX Scandinavia AB, Box 386, 111 73 Stockholm, Sweden.
url: www.ivax.se

Ivax, Thai. See *BJC, Thai.*

Ivax, UK. See *Teva, UK.*

Ivax, USA. Ivax Pharmaceuticals Inc., 4400 Biscayne Blvd, Miami, FL 33137, USA.
url: www.ivaxpharmaceuticals.com

IVF, Switz. IVF Hartmann AG, 8212 Neuhausen am Rheinfall, Switzerland.

Ivoclar, NZ. Ivoclar Vivadent Ltd, 12 Omega St, Albany, Auckland, New Zealand.

IVP, Ital. Istituto Vaccinogeno Pozzi S.r.l., Via Petriccio 27, 53100 Siena, Italy.

Ivy Corp, USA. Ivy Corporation, P.O. Box 596, W. Caldwell, NJ 07006, USA.

Izotop, Hung. Institute of Isotopes Co Ltd, P.O. Box 851, 1535 Budapest, Hungary.
url: www.izotop.hu

Jaapharm, Canad. Jaapharm Canada Inc., 200 Trowers Rd, Unit 1, Woodbridge, Ontario, L4L 5Z7, Canada.

Jaba, Port. Jaba Farmacêutica, SA, Rua da Tapada Grande, Abrunheira, 2711-901 Sintra, Portugal.
url: www.jaba.pt

Jaba Recordati, Port. See *Jaba, Port.*

Jacobsen, Denm. Jacobsen Pharma AS, Vemmingbund Strandvej 111, 6310 Broager, Denmark.

Jacobsen, Neth. See *Jacobsen, Denm.*

Jacobson, Hong Kong. Jacobson Medical (Hong Kong) Ltd, 15/F China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.

Jacobus, USA. Jacobus Pharmaceutical Co. Inc., 37 Cleveland Lane, P.O. Box 5290, Princeton, NJ 08540, USA.

Jacoby, Austria. Jacoby Pharmazeutika AG, Teichweg 2, A-5400 Hallein-Kaltenhausen, Austria.

Jadran, Rus. Jadran Galenski Laboratorij d.d., Lomonosovskii prospekt 38, pod. 1, of. 3, 119330 Moscow, Russia.
url: www.jadran.ru

Jagson, India. Jagson Pal Pharmaceuticals Ltd, P.O. Box 4545, New Dehli 110 049, India.

Jaka, Rus. See *Jaka-80, Rus.*

Jaka-80, Rus. Jaka-80, Skornyazhnyi per. 7, korp. 2, kv. 8, 107078 Moscow, Russia.
url: www.jaka80.com.mk

Jaldes, Fr. Laboratoires Jaldes, 10 ac de Poussan, B.P. 30, 34770 Gigean cdx, France.

Jamieson, Canad. Jamieson Laboratories, 4025 Rhodes Drive, Windsor, Ontario, N8W 5B5, Canada.

Jamieson, Hong Kong. See *Universal, Hong Kong.*

Jamieson, Philipp. See *One Pharma, Philipp.*

Jamp, Canad. Jamp Pharma Corp., Suite 203, 1380 Newton, Boucherville, Quebec, J4B 5H2, Canada.

Janpharm, S.Afr. Janpharm (Pty) Ltd, 15th Rd, Halfway House 1685, South Africa.

Janssen, Hong Kong. Janssen Pharmaceutica, Unit 1302-1307, Tower 1, Grand Century Place, 193 Prince Edward Rd West, Mongkok, Kowloon, Hong Kong.
url: www.janssenpharmaceutica.com

Janssen, Jpn. Janssen Pharmaceutical K.K, 3-5-2 Nishi-kanda, Chiyoda-ku, Tokyo 101-0065, Japan.
url: www.janssen.co.jp

Janssen, Mex. See *Janssen-Cilag, Mex.*

Janssen, Philipp. See *Johnson & Johnson, Philipp.*

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Janssen, Rus. See *Janssen-Cilag, Rus.*

Janssen, Thai. See *Janssen-Cilag, Thai.*

Janssen, USA. Janssen Pharmaceutical Inc., 1125 Trenton-Harbourton Road, Titusville, NJ 08560-0200, USA.
url: www.janssen.com

Janssen-Cilag, Arg. Janssen-Cilag Farmaceutica S.A., Mendoza 1259, 1428 Buenos Aires, Argentina.
url: www.janssen-cilag.com

Janssen-Cilag, Austral. Janssen-Cilag P/L, Locked Bag 2070, North Ryde, NSW 1670, Australia.
url: www.janssen-cilag.com

Janssen-Cilag, Austria. Janssen-Cilag Pharma Vertrieb GmbH, Pfarrgasse 75, A-1232 Vienna, Austria.
url: www.janssen-cilag.at

Janssen-Cilag, Belg. Janssen-Cilag SA, Roderveldlaan 1, 2600 Berchem, Belgium.
url: www.janssen-cilag.be

Janssen-Cilag, Braz. Janssen-Cilag Farmacêutica Ltda, Rua Gerivatiba 207, 11 andar, 5501900 São Paulo, SP, Brazil.
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Janssen-Cilag, Chile. See *Grunenthal, Chile.*

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Janssen-Cilag, Fin. Janssen-Cilag Oy, Metsänneidonkuja 8, 02130 Espoo, Finland.
url: www.janssen-cilag.com

Janssen-Cilag, Fr. Janssen-Cilag SA, 1 rue Camille-Desmoulins, 92787 Issy-les-Moulineaux cdx 9, France.
url: www.janssen-cilag.fr

Janssen-Cilag, Ger. Janssen-Cilag GmbH, Raiffeisenstr. 8, 41470 Neuss, Germany.
url: www.janssen-cilag.de

Janssen-Cilag, Gr. Janssen-Cilag Pharmaceutical S.A.C.I., 56 Eirinis Ave, 151 21 Pefki, Greece.
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Janssen-Cilag, Hung. Janssen-Cilag, Metropole Center, Hun utca 2, 1135 Budapest, Hungary.

Janssen-Cilag, India. Janssen-Cilag, India.

Janssen-Cilag, Indon. Janssen-Cilag, Division of Johnson & Johnson, Indonesia Mampang Park Office 3/F, Jl Mampang Prapatan Raya No 1, 12790 Jakarta Selatan, DKI Jaya, Indonesia.

Janssen-Cilag, Irl. Janssen-Cilag Ltd, Block B, Ground Floor, Liffey Valley Office Park, Quarryvale, Co. Dublin, Ireland.
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Janssen-Cilag, Ital. Janssen-Cilag S.p.A., Via Michelangelo Buonarroti 23, 20093 Cologno Monzese (MI), Italy.
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Janssen-Cilag, Malaysia. See *Zuellig, Malaysia.*

Janssen-Cilag, Mex. Janssen Cilag S.A. de C.V., Canoa No. 79, Col. Tizapan, Alvaro Obregon, 01090 Mexico D.F., Mexico.
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Janssen-Cilag, Neth. Janssen-Cilag BV, Dr. Paul Janssenweg 150, 5026 RH Tilburg, Netherlands.
url: www.janssen-cilag.nl

Janssen-Cilag, Norw. Janssen-Cilag AS, Hoffsveien 1 D, 0214 Oslo, Norway.
url: www.janssen-cilag.no

Janssen-Cilag, NZ. Janssen-Cilag Pty Ltd, P.O. Box 9222, Newmarket, Auckland, New Zealand.
url: www.janssen-cilag.com

Janssen-Cilag, Pol. Janssen-Cilag Polska Sp. zo.o., ul. Szyszkowa 20, 02-285 Warsaw, Poland.
url: www.janssen-cilag.pl

Janssen-Cilag, Port. Janssen Cilag Farmacêutica, Lda, Rue Consiglieri Pedroso 69 A/B, Queluz de Baixo, 2734-503 Barcarena, Portugal.
url: www.janssen-cilag.com

Janssen-Cilag, Rus. Janssen-Cilag, 43 Bolshaya Tulkaya ul., 113191 Moscow, Russia.
url: www.janssen-cilag.com

Janssen-Cilag, S.Afr. Janssen-Cilag (Pty) Ltd, P.O. Box 785939, Sandton 2146, South Africa.
url: www.janssen-cilag.co.za

Janssen-Cilag, Singapore. Janssen-Cilag, A Division of Johnson & Johnson Pte Ltd, 2 International Business Park, 07-01 Tower One, The Strategy, S 609930, Singapore.
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Janssen-Cilag, Spain. Janssen-Cilag, Paseo de las Doce Estrellas 5-7, Campo de Naciones, 28042 Madrid, Spain.
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url: www.janssen-cilag.se

Janssen-Cilag, Switz. Janssen-Cilag AG, Sihlbruggstrasse 111, 6341 Baar, Switzerland.
url: www.janssen-cilag.ch

Janssen-Cilag, Thai. Janssen-Cilag Ltd, 106 Moo 4, Lad Krabang Industrial Estate, Chalongkrung Rd, Kwaeng Lamplatew, Khet Lad Krabang, Bangkok 10520, Thailand.
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Janssen-Cilag, Turk. Janssen-Cilag, Cumhuriyet Cad., Gürsel Plaza No: 99 K: 4, Kavacik-Beykoz, İstanbul, 81610, Turkey.
url: www.janssen-cilag.com

Janssen-Cilag, UK. Janssen-Cilag Ltd, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK.
url: www.janssen-cilag.co.uk

Janssen-Cilag, Venez. Janssen-Cilag Venezuela, P.O. Box No. 19146, Quinta Crespo, Caracas 1010-A, Venezuela.
url: www.janssen-cilag.com

Janssen-Ortho, Canad. Janssen-Ortho Inc., 19 Green Belt Drive, Toronto, Ontario, M3C 1L9, Canada.
url: www.janssen-ortho.com

Japan Tobacco, Jpn. Japan Tobacco Inc., 2-2-1 Toranomon, Minato-ku, Tokyo 105-8422, Japan.
url: www.jti.co.jp

JAV, Thai. J.A.V. Pharmar Co. Ltd, 1848 soi Jaransaibitwong, 65 Jaransanitwong Rd, Bangbamru, Bangplad, Bangkok 10700, Thailand.

Javelin, UK. Javelin Pharmaceuticals, Compass House, Vision Park, Histon, Cambridge, CB4 9AD, UK.
url: www.javelinpharmaceuticals.com

Jaymac, USA. Jaymac Pharmaceuticals, 49 South Service Rd, Sunset, LA 70584, USA.

Jazz, USA. Jazz Pharmaceuticals Inc., 3180 Porter Drive, Palo Alto, CA 94304, USA.
url: www.jazzpharma.com

JB Chemicals, Thai. See *Union Medical, Thai.*

JB Williams, USA. J. B. Williams Co. Inc., 65 Harriston Road, Glen Rock, NJ 07452-3317, USA.

JC Healthcare, Israel. See *Johnson & Johnson, Israel.*

JC Healthcare, Ital. See *Janssen-Cilag, Ital.*

JDH, Hong Kong. See *IDS, Hong Kong.*

JDH, Malaysia. JDH Pharmaceutical Sdn Bhd, LiFung Centre, Lot 6, Persiaran Perusahaan Seksyen 23, Kawasan Perusahaan Shah Alam, 40300 Shah Alam, Selangor, Malaysia.

JDH, Singapore. JDH Pharmaceutical Division, 279 Jalan Ahmad Ibrahim, 03-01, S 639938, Singapore.

JDH Borneo, Thai. JDH Borneo (Thailand) Ltd, 2160/1 Ramkhamhaeng Rd, Hua Mark, Bangkapi, Bangkok 10240, Thailand.

JE IL, Singapore. See *Pharmaforte, Singapore.*

Jean-Marie, Hong Kong. Jean-Marie Pharmacal Co. Ltd, 1/F, GMP Ctr, 12 Dai Fu St, Tai Po Industrial Estate, Tai Po, N.T., Hong Kong.
url: www.jmp.com.hk

Jean-Marie, Philipp. See *Rutti, Philipp.*

Jelfa, Cz. See *Polfa Ciech, Cz.*

Jelfa, Hung. See *Polcommerce, Hung.*

Jelfa, Pol. Przedsiębiorstwo Farmaceutyczne Jelfa SA, ul. Wincentego Pola 21, 58-500 Jelenia Góra, Poland.
url: www.jelfa.com.pl

Jelfa, Rus. Pharmaceuticals Works Jelfa SA, Prospekt Mira, Dom 74, str. 1, kv. 92, 129041 Moscow, Russia.
url: www.jelfa.ru

Jemo-Pharm, Pol. See *Hedat, Pol.*

Jenapharm, Cz. See *Schering, Cz.*

Jenapharm, Ger. Jenapharm GmbH & Co. KG, Otto-Schott-Str. 15, 07745 Jena, Germany.
url: www.jenapharm.de

Jenapharm, Hong Kong. See *Jacobson, Hong Kong.*

Jenapharm, Hung. See *Jenapharm, Ger.*

Jenapharm, Malaysia. See *Imeks, Malaysia.*

Jenapharm, Pol. See *Schering, Pol.*

Jenapharm, Rus. See *Schering, Rus.*

Jenapharm, Thai. See *BJC, Thai.*

Jengimiel, Venez. Jengimiel C.A., Calle Capitolio, Edificio Indelca, piso 3, local E, Boleita Sur, Caracas, Venezuela.
url: www.jengimiel.com

Jenson, Gr. Jenson, Greece.

Jergens, USA. Andrew Jergens Co., 2535 Spring Grove Ave, Cincinnati, OH 45214-1773, USA.
url: www.jergens.com

Jessup, UK. Jessup Marketing, 27 Old Gloucester St, London, WC1N 3XX, UK.
url: www.jessup.co.uk

Jewim, Philipp. See *NextChem, Philipp.*

JHC Healthcare, UK. JHC Healthcare Ltd, The Maltings, Bridge St, Hitchin, Hertfordshire, SG5 2DE, UK.

JHP, USA. JHP Pharmaceuticals LLC, Morris Corporate Centre 2, One Upper Pond Rd, Building 2, 3rd Floor, Parsippany, NJ 07054, USA.
url: www.jhppharma.com

Jin Yang, Hong Kong. See *Ebewe, Hong Kong.*

Jin Yang, Malaysia. See *Propharm, Malaysia.*

Jin Yang, Singapore. See *Polymedic, Singapore.*

J&J-Merck, USA. See *Johnson & Johnson, USA,* and *Merck, USA.*

JKC, Pol. JKC Consultancy, ul. Julianowska 34 lok.43, 05-500 Piaseczno, Poland.

JMI, USA. See *Jones, USA.*

Jodquellen, Ger. Jodquellen AG, Ludwigstr. 14, 83646 Bad Tolz, Germany.
url: www.alpamare.de

Jofadel, Braz. Jofadel Ind. Farmacêutica S.A., Av. Jose da Frota Vasconcelos 100, 37062-500 Varginha, MG, Brazil.
url: www.jofadel.com.br

Jofrain, Mex. Establecimientos Jofrain S.A. de C.V., Calzada de Tlalpan 2621, Coyoacan Xotepingo, 04610 Mexico D.F., Mexico.
url: www.jofrain.com.mx

Johanser, Ger. St. Johanser Naturmittelvertrieb GmbH, Starnberger Str. 15, 82131 Gauting, Germany.
url: www.st-johanser.de

Johnson, Canad. S.C. Johnson and Son Ltd, 1 Webster St, P.O. Box 250, Brantford, Ontario, N3T 5R1, Canada.

Johnson & Johnson, Arg. Johnson & Johnson de Argentina S.A.C. e I., Mendoza 1259 Piso 1, 1428 Buenos Aires, Argentina.
url: www.jnjarg.com

Johnson & Johnson, Austral. Johnson & Johnson Medical P/L, P.O. Box 134, North Ryde, NSW 2113, Australia.
url: www.jnjgateway.com

Johnson & Johnson, Braz. Johnson e Johnson Indústria e Comércio Ltda, Rua Gerivativa 207, 05501-900 São Paulo, SP, Brazil.
url: www.jnjgateway.com

Johnson & Johnson, Canad. Johnson & Johnson/Merck Consumer Pharmaceuticals of Canada, 890 Woodlawn Rd W, Guelph, Ontario, N1K 1A5, Canada.
url: www.jnjgateway.com

Johnson & Johnson, Cz. Johnson & Johnson Medical, Karla Engliše 3201/6, 150 00 Praha 5, Smíchov, Czech Republic.
url: www.jnjcz.cz

Johnson & Johnson, Fr. See *Ethicon, Fr.*

Johnson & Johnson, Ger. Johnson & Johnson GmbH, Kaiserswerther Str 270, 40474 Dusseldorf, Germany.
url: www.pcr-gmbh.de

Johnson & Johnson, Hong Kong. See *Jacobson, Hong Kong.*

Johnson & Johnson, Hung. Johnson & Johnson Kft, Tó Park, West Gate Business Park, 2045 Törökbálint, Hungary.

Johnson & Johnson, Irl. Johnson & Johnson (Ireland) Ltd, Airton Rd, Tallaght, Dublin 24, Ireland.
url: www.jnjgateway.com

Johnson & Johnson, Israel. Johnson & Johnson, Kibbutz Shefayim, Israel.
url: www.jnjgateway.com

Johnson & Johnson, Ital. Johnson & Johnson Divisione Farmacia S.p.A., 00040 S. Palomba, Pomezia (Rome), Italy.
url: www.jnjgateway.com

Johnson & Johnson, Neth. Johnson & Johnson Medical BV, Computerweg 14, Amersfoort, Netherlands.

Johnson & Johnson, NZ. Johnson & Johnson (NZ) Ltd, P.O. Box 97-561, Wiri, South Auckland, New Zealand.
url: www.jnjgateway.com

Johnson & Johnson, Philipp. Johnson & Johnson, Edison Rd, Barrio Ibayo 1700, Parañaque City, Philippines.

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Johnson & Johnson, Singapore. See *Diethelm, Singapore.*

Johnson & Johnson, Spain. Johnson Johnson, Paseo de las Doce Estrellas, 5-7, 28042 Madrid, Spain.
url: www.jnjgateway.com

Johnson & Johnson, Thai. Johnson & Johnson (Thailand) Co. Ltd, 106 Moo 4 Lat Krabang, Industrial Estate, Chalongkrung Rd, Lumplatew, Lat Krabang, Bangkok 10520, Thailand.
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Johnson & Johnson, UK. Johnson & Johnson Ltd, Foundation Park, Rocksborough Way, Maidenhead, Berkshire, SL6 3UG, UK.
url: www.jnjgateway.com

Johnson & Johnson, USA. Johnson & Johnson Consumer Products Co., 199 Grandview Rd, Skillman, NJ 08558-9418, USA.
url: www.jnj.com

Johnson & Johnson, Venez. Johnson & Johnson de Venezuela S.A., Av. Rómulo Gallegos, Edif. Johnson & Johnson Piso 8, Los Dos Caminos, Caracas 1070, Venezuela.
url: www.jnjgateway.com

Johnson & Johnson Consumer, Belg. Johnson & Johnson Consumer SA, Eikelenbergstraat 20, 1700 Dilbeek, Belgium.
url: www.jnjgateway.com

Johnson & Johnson Consumer, Fr. See *Ethicon, Fr.*

Johnson & Johnson Medical, Arg. Johnson & Johnson Medical S.A., Monsecor Magliano 3061, 1642 San Isidro, Buenos Aires, Argentina.
url: www.jnj.com

Johnson & Johnson Medical, Fr. See *Ethicon, Fr.*

Johnson & Johnson Medical, UK. Johnson & Johnson Medical, Coronation Rd, Ascot, Berkshire, SL5 9EY, UK.
url: www.jnjgateway.com

Johnson & Johnson Medical, USA. Johnson & Johnson Medical Inc., 1 Johnson & Johnson Plaza, New Brunswick, NJ 08933, USA.
url: www.jnj.com

Johnson & Johnson MSD Consumer, UK. Johnson & Johnson MSD Consumer Pharmaceuticals, Enterprise House, Station Rd, Loudwater, High Wycombe, Buckinghamshire, HP10 9UF, UK.
url: www.jnjmsd.co.uk

Johnson Wax, USA. S.C. Johnson Wax, 1525 Howe St, Racine, WI 53403-5011, USA.
url: www.scjohnsonwax.com

Jolly-Jatel, Fr. Laboratoires Jolly-Jatel, 28 av. Carnot, 78100 Saint-Germain-en-Laye, France.

Jones, USA. See *King, USA.*

Jorba, Spain. Jorba, Josefa Valcarcel 30, 28027 Madrid, Spain.

Josper, Braz. Josper Farmacêutica Ltda, Rua Prudente de Morais 1010, 25065240 Duque de Caxias, Rio de Janeiro, Brazil.

Joyson, Singapore. Joyson Pte Ltd, 1 Upper Aljunied Link, Block A 05-06, Joo Seng Warehouse, S-367901, Singapore.
url: www.joyson.com

JP, Braz. JP Indústria Farmacêutica SA, Avenida Pres. Castelo Branco 999, 14095-000 Ribierao Preto, SP, Brazil.
url: www.jpfarma.com.br

JRalph, Philipp. See *One Pharma, Philipp.*

JSJ, USA. JSJ Pharmaceuticals, 3655 Route 202, Suite 116, Doylestown, PA 18901, USA.

Jugoremedia, Rus. See *Jaka-80, Rus.*

Jukunda, Ger. Jukunda Naturarzneimittel Dr Ludwig Schmitt GmbH & Co. KG, Hofmarkstr. 35, 82152 Planegg, Germany.
url: www.jukunda.de

Julphar, UAE. Gulf Pharmaceutical Industries, Julphar, P.O. Box 997, Ras Al Khaimah, United Arab Emirates.
url: www.julphar.com

Jumont, Philipp. Le Jumont Pharmaceuticals, Suite 502 West Trade Ctr, 132 West Ave, Quezon City, Philippines.

Juste, Spain. Juste, Juan Ignacio Luca de Tena, 8, 28027 Madrid, Spain.
url: www.juste.es

Justesa Imagen, Arg. Justesa Imagen Argentina S.A., Viamonte 1328 Piso 9, 1053 Buenos Aires, Argentina.

Justright, Philipp. Justright Pharmaceuticals, 2163 Menadro St, Pandacan, Manila, Philippines.

Juta, Ger. Juta Pharma GmbH, Gutenbergstr. 13, 24941 Flensburg, Germany.
url: www.jutapharma.de

Juventus, Spain. Juventus, Julian Camarillo 37, 28037 Madrid, Spain.

Juvex, Fr. Laboratoires Juvex, B.P. 11, 36110 Levroux, France.

K2 Pharmacare, Chile. See *Recalcine, Chile.*

Kabi Pharmacia, Cz. See *Fresenius Kabi, Cz.*

Kabi Pharmacia, USA. See *Pfizer, USA.*

Kabivitrum, USA. See *Pfizer, USA.*

Kade, Ger. Dr Kade Pharmazeutische Fabrik GmbH, Rigistr. 2, 12277 Berlin, Germany.
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Kade, Hong Kong. Kade, Hong Kong.

Kade, Hung. Dr Kade Pharma, Szirtes út 2/a, 1016 Budapest, Hungary.

Kade, Philipp. See *Metro, Philipp.*

Kade, Pol. Dr Kade, Kadefarm Sp. zo.o., ul. Bułgarska 65 a, 60-320 Poznań, Poland.
url: www.kadefarm.pl

Kade, Rus. See *Esparma, Rus.*

Kade, Thai. See *Hua, Thai.*

Kafetzis, Gr. Kafetzis, Greece.

Kai Cheong, Hong Kong. Kai Cheong Medical Co Ltd, Unit 1001, Tower 1, Harbour Ctr, 1 Hok Cheung St, Hunghom, Kowloon, Hong Kong.

Kaken, Jpn. Kaken Pharmaceutical Co. Ltd, 2-28-8 Honkomagome, Bunkyo-ku, Tokyo 113-8650, Japan.
url: www.kaken.co.jp

Kaketsuken, Thai. See *BJC, Thai.*

Kalbe, Indon. Kalbe Farma PT, Kawasan Industri Delta Silicon, Jl M H Tharmin Blok A3-1, Lippo Cikarang, 12550 Bekasi, Jawa Barat, Indonesia.

Kalbe, Philipp. See *Lakeside, Philipp.*

Kalbe, Singapore. See *Apotheca, Singapore,* and *Sime Darby, Singapore.*

Kalisterra, Fr. Kalisterra, Batiment B, B.P. 54, 217 chemin du Grand-Revoyet, 69230 Saint-Genis Laval, France.

Kamada, Hong Kong. See *Gaily, Hong Kong.*

Kamada, Israel. Kamada Ltd, Kiryat Weizmann, Rehovot, Israel.
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Kameliya, Rus. Kameliya NPP OOO, Gostinichnyi prospekt d. 6, korp. 2, 127106 Moscow, Russia.
url: www.kamelia.ru

Kamp, Arg. Distribuidor Kamp Dental S.R.L., Av. Roque Saenz Peca 825 Piso 4 of.45, 1035 Buenos Aires, Argentina.

Kampel Martian, Arg. Lab. Kampel Martian S.A., Av. del Libertador 6550, 5 piso, 1428 Buenos Aires, Argentina.
url: www.kampelmartian.com

Kanion, Israel. See *Chemipal, Israel.*

Kanoldt, Ger. Kanoldt Arzneimittel GmbH, Karl-Zeiss-Ring 3, 85737 Ismaning, Germany.

Kanonfarma, Rus. Kanonfarma Prodakshn ZAO, Barrikadnaya ul., 8/5 A, 123242 Moscow, Russia.
url: www.canonpharma.ru

Kansuk, Turk. Kansuk Laboratuvan San. ve. Tic. A.Ş., Beşyol Mah., Eski Londra Asfaltı No:4, Sefaköy, İstanbul, 34620, Turkey.
url: www.kansuk.com

Kappin, UK. Kappin Ltd, Cunard Rd, Park Royal, London, NW10 6PN, UK.

Karicare, NZ. See *Nutricia, NZ.*

Karnataka, Philipp. See *Pharmawealth, Philipp.*

Karr, Switz. Karr Dental AG, Zugerstrasse 56, 8810 Horgen, Switzerland.
url: www.karrdental.ch

Karrer, Ger. Hans Karrer GmbH, Messerschmittring 54, 86343 Konigsbrunn, Germany.
url: www.hans-karrer.de

Kart, Switz. Laboratoires Kart SA, En Budron A 16, 1052 Le Mont-sur-Lausanne, Switzerland.

Kaspa, Thai. Kaspa Pharmaceutical (Thailand) Co Ltd, 261/452 Jaransanitwong Rd, Soi 29/1, Bangkoknoi, Bangkok 10700, Thailand.
url: www.kaspapharma.com

Katadyn, Fr. Katadyn France (Lab), 5 rue Gallice, 38100 Grenoble, France.
url: www.katadyn.fr

Katadyn, Switz. Katadyn Produkte AG, Wasseraufbereitung, Birkenweg 4, 8304 Wallisellen, Switzerland.

Kato, Pol. kato Sp. zo.o., ul Marszałkowska 138/82, 00-004 Warsaw, Poland.
url: www.kato.pl

Katsagonis, Gr. Katsagonis, Greece.

Katsoupas, Gr. Ch. Katsoupas (Ant. Kouskos O.E.), 48 Socratous Str., 104 31 Athens, Greece.

Kattwiga, Ger. Pharm. Fabrik Kattwiga GmbH, Zur Grenze 30, 48529 Nordhorn, Germany.
url: www.kattwiga.de

Katwijk, Neth. Katwijk Pharma BV, Archimideseweg 2, 2333 CN Leiden, Netherlands.

Katwijk, Philipp. See *Ascende Medz, Philipp.*

Kay, Canad. Mary Kay Cosmetics Ltd, 2020 Meadowvale Blvd, Mississauga, Ontario, L5N 6Y2, Canada.

Kayaku, Cz. See *Kayaku, Jpn.*

Kayaku, Hong Kong. See *Main Life, Hong Kong.*

Kayaku, Hung. See *Cziher, Hung.*

Kayaku, Indon. See *Kalbe, Indon.*

Kayaku, Jpn. Nippon Kayaku Co. Ltd, 1-11-2 Fujimi, Chiyoda-ku, Tokyo 102-8172, Japan.
url: www.nipponkayaku.co.jp

Kayaku, Malaysia. See *JDH, Malaysia.*

Kayaku, Philipp. See *Zuellig, Philipp.*

Kayaku, Singapore. See *JDH, Singapore.*

Kayaku, Thai. See *Masu, Thai.*

KBR, Ital. K.B.R. S.r.l. Kroton Biologic Researches, Corso Vittorio Emanuele 73, 88074 Crotone (KR), Italy.

Kedrion, Arg. See *Scott-Cassara, Arg.*

Kedrion, Ital. Kedrion S.p.A., Localita ai Conti Barga, 55020 Castelvecchio Pascoli (LU), Italy.

Kedrion, Port. See *Kedrion, Ital.*

Kedrion, Rus. See *Riace, Rus.*

Kedrion, Thai. See *Biogenetech, Thai.*

Kee, India. Kee Pharma Ltd, A-1 Community Centre, Naraina Industrial Area, Phase II, New Delhi 110028, India.
url: www.keepharma.com

Keene, USA. Keene Pharmaceuticals Inc., P.O. Box 7, Keene, TX 76059-0007, USA.

Kela, Belg. Kela Veterinaria, Industriepark West 68, B-9100 Sint-Niklass, Belgium.

Kelemata, Ital. Kelemata S.p.A., Via S Quintino 28, 10121 Turin, Italy.

Keller, Hong Kong. Edward Keller Ltd, 21/F Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
url: www.dksh.com

Keller, Philipp. Edward Keller (Phils) Inc., Camelray Industrial Park 1, Canlubang, Calamba, Laguna, Philippines.

Kemifar, Ital. Kemifar Srl, Viale F Borromeo 4, 20017 Rho (MI), Italy.
url: www.kemifar.com

Kemifarma, Denm. Kemifarma Holdings ApS, Jaegersborg Allé 51, 2920 Charlottenlund, Denmark.
url: www.kemifarma.dk

Kemiprogress, Ital. Kemiprogress S.r.l., Via Aurelia 58, 00100 Rome, Italy.

Kemopharm, Thai. Kemopharm Thailand Co. Ltd, 138 Soi Indamara 18, Vibhavadi Rangsit Rd, Bangkok 10400, Thailand.

Kendall, USA. Kendall Health Care Products, 15 Hampshire St, Mansfield, MA 02048, USA.
url: www.kendallhq.com

Kendall McGaw, USA. See *Braun, USA.*

Kendrick, Mex. Laboratorios Kendrick, S.A. de C.V., Paseo de los Laureles No. 458-205, Col. Bosques de las Lomas, Deleg. Cuajimalpa, 05120 Mexico D.F., Mexico.
url: www.kendrick.com.mx

Kener, Mex. Laboratorios Kener S.A. de C.V., Calderon de la Barca No. 27, Col. Polanco, Deleg. Miguel Hidalgo, 11560 Mexico D.F, Mexico.
url: www.kener.com.mx

Kenfarma, Spain. Kenfarma, Ctra de Rubi 90-100, Sant Cugat del Valles, 28002 Barcelona, Spain.

Kent, UK. Kent Pharmaceuticals Ltd, Wotton Rd, Ashford, Kent, TN23 6LL, UK.
url: www.kentpharm.co.uk

Kenwood, Hong Kong. See *International Medical, Hong Kong.*

Kenwood, USA. See *Bradley, USA.*

Kenyaku, Hong Kong. See *Ebewe, Hong Kong.*

Kenyaku, Thai. See *Asian TJD, Thai.,* and *Schumit, Thai.*

Kerapharm, Fr. Kerapharm, 123 bureaux de la Colline, 92213 St-Cloud cdx, France.

Keri, Cz. See *Keri, Hung.*

Keri, Hung. Keri Pharma Kft, Bartha Boldizsár, 4032 Debrecen, Hungary.

Keri, Neth. See *Keri, Hung.*

Kern, Spain. Kern Pharma, Venus 72, Pol Ind Colon II, Terrassa, 08228 Barcelona, Spain.
url: www.kernpharma.es

Kern, Switz. E Kern AG, Pharmazeutische Kraut-erspezialitäten, Hauptstrasse 23, 8867 Niederumen, Switzerland.

Kernpharm, Neth. Kernpharm BV, Rooseveltlaan 6, 5466 AB Veghel, Netherlands.

KerrHawe, Switz. KerrHawe SA, P.O. Box 268, 6934 Bioggio, Switzerland.
url: www.kerrhawe.com

Keryos, Ital. Keryos SpA, P.zza della Repubblica 28, 20124 Milan, Italy.

Kestrel, UK. Kestrel Healthcare Ltd, Ashfield House, Resolution Rd, Ashby de la Zouch, Leicestershire, LE65 1HW, UK.

Keton, Mex. Laboratorios Keton de Mexico S.A. de C.V., Lago Xochimilco No. 65, Col. Anahuac, Deleg. Miguel Hidalgo, 11320 Mexico D.F., Mexico.

Keun Wha, Philipp. See *Endure, Philipp.*

Key, Arg. Key Pharma S.A., Av. San Martmn 1750, 1602 Florida, Buenos Aires, Argentina.

Key, Austral. Key Pharmaceuticals P/L, P.O. Box 121, Concord West, NSW 2138, Australia.
url: www.keypharm.com.au

Key, Canad. See *Schering, Canad.*

Key, Chile. Key Company SA, Panamericana Norte 5369, Santiago, Chile.

Key, Israel. See *Luxembourg, Israel.*

Key, Spain. Key Pharma, P Castellana 143, 28046 Madrid, Spain.

Key, USA. See *Schering-Plough, USA.*

Key Oncologics, S.Afr. Key Oncologics, 171 Katherine Rd, Building 1, Sandton, South Africa.
url: www.keyoncologics.co.za

Key Sun, Austral. Key Sun Laboratories, 2/10 Ponderpsa Parade, Warriewood, NSW 2102, Australia.

Keyerson, Mex. Casa Keyerson S.A. de C.V., Calzada del hueso 160, Ej. Sta.Ursula Coapa, 04850 Mexico D.F., Mexico.

Keymen, Turk. Keymen, Turkey.

KG, Ital. KG Italia S.r.l., Via Volturno 10/12, 50019 Sesto Fiorentino (FI), Italy.

Khandelwal, India. Khandelwal Laboratories Ltd, 79/87 D. Lad Path, Mumbai 400 033, India.
url: www.khandelwallab.com

Khandelwal, Philipp. See *Pharmasan, Philipp.*

Kibion, Cz. See *Kibion, Swed.*

Kibion, Swed. Kibion AB, Kungsgatan 109, 751 05 Uppsala, Sweden.
url: www.kibion.se

Kiehls, USA. Kiehl's, New York, NY 10014, USA.
url: www.kiehls.com

Kimberly-Clark, USA. Kimberly-Clark Health Care, 1400 Holcomb Bridge Rd, Roswell, GO 30076, USA.
url: www.kchealthcare.com

Kimia, Indon. Kimia Farma PT, Jl 15 Oktober No 58, Dili, Timor Timur, Indonesia.

Kimiceg, Venez. Laboratorios Kimiceg C.A., Urb. Montalbán, Centro Comercial Uslar, Torre de Oficinas, Piso 7, Caracas, Venezuela.
url: www.kimiceg.com.ve

Kin, Spain. Laboratorios Kin S.A., Ciudad de Granada 123, 08018 Barcelona, Spain.
url: www.labkinonline.es

Kinder, Braz. Laboratório Kinder Ltda, Rua VPR 1 Quadra 2-A, Modulo 5 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.kinder.ind.br

King, Irl. King Pharmaceuticals Ltd, Donegal St, Ballybofey, County Donegal, Ireland.

King, UK. See *King, Irl.*

King, USA. King Pharmaceuticals Inc., 501 Fifth St, Bristol, TN 37620, USA.
url: www.kingpharm.com

Kingswood, USA. Kingswood Laboratories Inc., 10375 Hague Rd, Indianapolis, IN 46256, USA.

Kirby, Arg. See *Schering-Plough, Arg.*

Kireen, Malaysia. Kireen Pharmaceutical Sdn Bhd, 9 Jalan Kempas 4, Taman Perindustrian, Tampoi Indah, 81200 Johor Bahru, Johor, Malaysia.

Kirin, Hong Kong. Kirin Pharmaceutical (Asia) Co Ltd, Unit 1002C-D, 10/F Admiralty Centre Tower 1, 18 Harcourt Rd, Admiralty, Hong Kong.
url: www.kirinholdings.co.jp

Kirin, Jpn. Kirin Brewery Co. Ltd, Pharmaceutical Division, 6-26-1 Jingu-mae, Shibuya-ku, Tokyo 150-8011, Japan.
url: www.kirin.co.jp

Kirkman, USA. Kirkman Labs Inc., 6400 SW Rosewood, Lake Oswego, OR 97035, USA.
url: www.kirkmanlabs.com
Kissei, Hong Kong. See *Hing Ah, Hong Kong,* and *Main Life, Hong Kong.*
Kissei, Jpn. Kissei Pharmaceutical Co. Ltd, 19-48 Yoshino, Matsumoto, Nagano 399-8710, Japan.
url: www.kissei.co.jp
Kite, Gr. Kite Hellas E.P.E, 166 Ionias Ave, Greece.
url: www.kite.gr
Kite (Κιτε), Gr. See *Kite, Gr.*
Kivema, Israel. Kivema Ltd, 33 Hachoresh St, Kfar Shmaryahu 46910, Israel.
Kiwi, Neth. Kiwi Farm BV, Haven 215F, 22252 EZ Katwijk, Netherlands.
Kiwi, USA. Kiwi Brands Inc., 447 Old Swede Rd, Douglassville, PA 19518-1239, USA.
KK, UK. KK Toiletries Ltd, 2 Westgate, Skelmersdale, Lancashire, WN8 8AZ, UK.
url: www.kktoiletries.co.uk
Klein, Ger. Dr Gustav Klein, Steinenfeld 3, 77736 Zell am Harmersbach, Germany.
url: www.klein-phytopharma.de
Kleva, Gr. Kleva Ltd, 189 Parnithos Ave, Athens, 136 71 Acharnes, Greece.
url: www.kleva.gr
Kleva, Singapore. See *Green Cross, Singapore.*
Klever, Ger. F. W. Klever GmbH, Hauptstr. 20, 84168 Aham/Ndb., Germany.
url: www.klever-ballistol.de
KLI, USA. KLI Corp., 1119 Third Ave SW, Carmel, IN 46032, USA.
url: www.entertainers-secret.com
Klinge, Ger. See *Fujisawa, Ger.*
Klinge, Irl. See *Astellas, Irl.*
Klinge, Switz. Klinge Pharma AG, Bachstrasse 10, 8280 Kreuzlingen, Switzerland.
Klinger, Braz. Laboratórios Klinger do Brasil Ltda, Rua Assahy 45, Rudge Ramos, 09633-010 São Bernardo do Campo, SP, Brazil.
url: www.labklinger.com.br
Klinos, Venez. Laboratorios Klinos C.A., 2da. Avenida de Campo Alegre, Torre Credival, Mezzanina, Chacao, Caracas 1060, Venezuela.
Klonal, Arg. Lab. Klonal, Lamadrid esq. T. de Alvear, 1878 Quilmes, Buenos Aires, Argentina.
Klorane, Fr. Laboratoires Klorane, Les Cauquillous, B.P. 100, 81506 Lavaur cdx, France.
Kloster, S.Afr. Kloster Pharmaceuticals (Pty) Ltd, P.O. Box 2734, Paarl 7620, South Africa.
Klosterfrau, Austria. Maria Clementine Martin Klosterfrau GmbH, Doerenkampgasse 11, A-1105 Vienna, Austria.
Klosterfrau, Cz. See *Klosterfrau, Ger.*
Klosterfrau, Ger. Maria Clementine Martin Klosterfrau Vertriebsgesellschaft mbH, 50606 Cologne, Germany.
url: www.klosterfrau.de
Klosterfrau, Hung. See *Klosterfrau, Ger.*
Klosterfrau, Pol. See *Nepentes, Pol.*
Klus, Switz. Klus-Apotheke AG, Hegibachstrasse 102, 8032 Zurich, Switzerland.
Kneipp, Cz. See *Kneipp, Ger.*
Kneipp, Ger. Kneipp-Werke, 97064 Wurzburg, Germany.
url: www.kneip.de
Kneipp, Switz. Kneipp (Schweiz) GmbH, Schwarzackerstrasse 2, 8304 Wallisellen, Switzerland.
url: www.kneipp-schweiz.ch
Knobel, Switz. Dr med G Knobel AG, Bahnhofstrasse 9, 8730 Uznach, Switzerland.
Knoll, Braz. Knoll SA Produtos Químicos e Farmacêuticos, Estrada dos Bandeirantes 2400, 27710-104 Rio de Janeiro, RJ, Brazil.
Knoll, Cz. Knoll sro, Šafránková 3, 155 00 Prague 5, Czech Republic.
url: www.knoll.cz
Knoll, Fr. See *Abbott, Fr.*
Knoll, Ger. See *Abbott, Ger.*
Knoll, India. See *Abbott, India.*
Knoll, Mex. Química Knoll de Mexico S.A. de C.V., La Candelaria No.186, Col. Atlantida, Deleg. Coyoacan, 04370 Mexico D.F., Mexico.
Knoll, Neth. Knoll BV, Hettenheuvelweg 41-43, 1101 BM Amsterdam, Netherlands.
Knoll, Port. Knoll Lusitana, Lda, Rua Alfredo da Silva 3 C/D, 1300-040 Lisbon, Portugal.
Knoll, Rus. See *Abbott, Rus.*
Knoll, S.Afr. See *Abbott, S.Afr.*
Knoll, Switz. See *Abbott, Switz.*
Knoll, USA. See *Abbott, USA.*
Knop, Chile. Laboratorio Esp. Med. Knop Ltda, Av. Lib. Bdo. O'higgins 1671, Santiago, Chile.
Kobayashi, Jpn. Kobayashi Pharmaceutical Co. Ltd, 40306 Doshomachi, Chuo-ku, Osaka 541-0045, Japan.
url: www.kobayashi.co.jp
Kobayashi, Thai. See *Charoen, Thai.*
Kocak, Turk. Koçak Farma İlaç A.Ş., Bağlarbaşi Gazi Cad. No:64/66, Üsküdar, İstanbul, Turkey.
url: www.kocakilac.com
Kocsel, Turk. See *Onko, Turk.*
Kodak, USA. Kodak Dental, 343 State St, Rochester, NY 14650, USA.
url: www.kodak.com
koGen, UK. See *Galen, UK.*
Kohler, Austria. Dr Köhler Pharma GmbH, Steckhovengasse 17, A-1130 Vienna, Austria.
Kohler, Cz. See *Reg, Cz.*
Kohler, Ger. Dr Franz Köhler Chemie GmbH, Neue Bergstr. 3-7, 64665 Alsbach-Hahnlein, Germany.
url: www.koehler-chemie.de
Kohler, Hung. See *Kohler, Ger.*
Kohler-Pharma, Ger. Köhler Pharma GmbH, Neue Bergstr. 3-7, 64665 Alsbach, Germany.
Kolassa, Austria. Dr. Kolassa & Merz GmbH, Gastgebgasse 5-13, A-1230 Vienna, Austria.
Komedic, Malaysia. Komedic Sdn Bhd, 4 Jln PJS 11/14, Bandar Sunway, 46150 Petaling Jaya, Selangor, Malaysia.
Kondon, USA. Kondon Manufacturing, Croswell, MI 48422, USA.
Koni-Cofarm, Chile. Laboratorio Koni-Cofarm SA, Crescente Errazuriz 2077, Nunoa, Santiago, Chile.
Konimex, Indon. Konimex PT, Jl K H Wahid Haysim No 162, Jakarta, DKI Jaya, Indonesia.
Konpharma, Ital. Konpharma Srl, Via Pietro della Valle 1, 00193 Rome (RM), Italy.
Konsuma, Venez. See *Farma, Venez.*
Konsyl, Israel. See *Pharmateam, Israel.*
Konsyl, USA. Konsyl Pharmaceuticals, 8050 Industrial Park Rd, Easton, MD 21601, USA.
url: www.konsyl.com
Kora, Irl. KoRa Healthcare, Frans Maas House, Swords Business Park, Swords, County Dublin, Ireland.
url: www.kora-health.ie
Kora, UK. See *Kora, Irl.*
Korangi, Port. Korangi S.A., Parque Empresarial Primóvel Edifício A1, r/c Albarraque, 2635-595 Rio de Mouro, Portugal.
Korea Pharma, Singapore. See *Pharma 2000, Singapore,* and *Pharmaforte, Singapore.*
Korea United, Philipp. See *Qualimed, Philipp.*
Korea United, Singapore. See *Kyowa, Singapore,* and *Ziwell, Singapore.*
Korean Drug, Singapore. See *Ziwell, Singapore.*
Korean Ginseng, Philipp. See *Psalmstre, Philipp.*
Korean United, Malaysia. See *Kyowa, Malaysia.*
Korhispana, Spain. Korhispana, PSJ Can Politic 17 3, Hospitalet de Llobregat, 08907 Barcelona, Spain.
url: www.korhispana.com
KOS, USA. Kos Pharmaceutics Inc., 1 Cedar Brook Drive, Cranberry, NJ 08512-3618, USA.
url: www.kospharm.com
Kosmidis, Gr. Kosmidis, Greece.
Kotor, Fr. Kotor Pharma (Lab), ZI Toulon-Est, 809 av de Draguignan, B.P. 49, 83087 Toulon cdx 9, France.
url: www.kotorpharma.com
Kotra, Hong Kong. See *Deltapharm, Hong Kong,* and *Hind Wing, Hong Kong.*
Kotra, Malaysia. Kotra Pharma (M) Sdn Bhd, No. 1 Jln TTC 12, Cheng Industrial Estate, 75250 Melaka, Melaka, Malaysia.
url: www.kotrapharma.com
Kottas-Heldenberg, Austria. Kottas-Heldenberg Mag. R.u. Sohn, Bauernmarkt 24, A-1014 Vienna, Austria.
Kowa, Jpn. Kowa Co. Ltd, 3-4-14 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8433, Japan.
url: www.kowa.co.jp
Kozmed, Turk. Kozmed, Tesvikiye Cad. Alhambra, Apt No. 178 K4 D5, Nisantasi Sisli, 34365 İstanbul, Turkey.
url: www.kozmed.com
Kramer, Philipp. Kramer Pharmaceutical Corp., 60 Cambridge St, Cubao, Quezon City, Philippines.
Kramer, USA. Kramer Laboratories Inc., 8778 SW 8th St, Miami, FL 33174-9990, USA.
url: www.kramerlabs.com
Kremers-Urban, USA. Kremers Urban, P.O. Box 427, Mequon, WI 53092, USA.
Kreussler, Cz. See *IBI International, Cz.*
Kreussler, Denm. See *Felo, Denm.*
Kreussler, Fin. See *Tamro, Fin.*
Kreussler, Fr. Laboratoire Kreussler Pharma, 2 rue de la Haye, Le Dome, B.P. 10901, 95731 Roissy-Charles-de-Gaulle cdx, France.
url: www.kreussler.fr
Kreussler, Ger. Chemische Fabrik Kreussler & Co. GmbH, Rheingaustr. 87-93, 65203 Wiesbaden, Germany.
url: www.kreussler-pharma.de
Kreussler, Hung. See *Repharma, Hung.*
Kreussler, Pol. See *Biotal, Pol.*
Kreussler, Switz. See *Globopharm, Switz.*
Kreussler, Thai. See *Berlin Pharm, Thai.*
Krewel, Ger. Krewel Meuselbach GmbH, Krewelstr. 2, 53783 Eitorf, Germany.
url: www.krewel-meuselbach.de
Krewel, Switz. See *Lubapharm, Switz.*
Krewel Meuselbach, Cz. Krewel Meuselbach GmbH, Nam. gen. Kutlvašra 6, 140 00 Prague 4, Czech Republic.
Krewel Meuselbach, Pol. Krewel Meuselbach GmbH, Przedstawicielstwo w Polsce, ul. Odyńca 63/24, 02-644 Warsaw, Poland.
Kring, Neth. Vereniging Kring Apothekers Nederland, Parallelweg 151, 5223 AR 'S-Hertogenbosch, Netherlands.
KRKA, Cz. KRKA Slovinsko, Mezibranská 7, 110 00 Prague 1, Czech Republic.
KRKA, Hong Kong. See *Unipharm, Hong Kong.*
KRKA, Hung. KRKA, Királyhágó u 5/a, 1126 Budapest, Hungary.
KRKA, Irl. KRKA Pharma Dublin, 1 Stokes Place, Dublin 2, Ireland.
KRKA, Neth. See *KRKA, Irl.*
KRKA, Pol. Krka Polska Sp. zo.o., ul. Równoległa 5, 02-235 Warsaw, Poland.
url: www.krkapolska.pl
KRKA, Port. KRKA Farmacêutica Unipessoal Lda, Portugal.
KRKA, Rus. KRKA d.d., ul. 2-ya Zvenigorodskaya, d. 13, Str. 41, et. 5, 125009 Moscow, Russia.
url: www.krka.ru
KRKA, Singapore. See *Uni, Singapore.*
Krolton, Arg. Krolton, Labopharma Pharmaceutical Group SA, Balboa 351, 1427 Buenos Aires, Argentina.
Kropf, Switz. Dr A & M Kropf, Promenade, 3780 Gstaad, Switzerland.
Krotex, Pol. Krotex Poland Sp. zo.o., ul. Rydygiera 8 bl. 18, 01-793 Warsaw, Poland.
url: www.krotex.com.pl
Krugher, Ital. See *KG, Ital.*
Krugmann, Ger. See *Mundipharma, Ger.*
Kuhnil, Thai. See *Medline, Thai.*
Kunzle, Switz. Krauterpfarrer Kunzle AG, 6573 Magadino, Switzerland.
Kur und Stadtapotheke, Austria. Kur- und Stadtapotheke, Oberer Stadtplatz 5, A-6060 Hall in Tirol, Austria.
Kuraray, Jpn. Kuraray Co. Ltd, Shin-Hankyu Bldg, 1-12-39 Umeda, Kita-ku, Osaka 530-8611, Japan.
url: www.kuraray.co.jp
Kurtsan, Turk. Kurtsan İlaçları A.Ş., Keresteciler Sitesi, Kasim Sok. No: 63, Merter, İstanbul, 34010, Turkey.
url: www.kurtsan.com.tr
KV, Malaysia. See *Apex, Malaysia.*
KV, Singapore. See *Pan-Malayan, Singapore.*
KV, USA. K.V. Pharmaceutical Co., 2503 S Hanley Rd, St Lois, MO 63144, USA.
url: www.kvpharmaceutical.com
Kwizda, Austria. Kwizda Pharma GmbH, Effingergasse 21, A-1160 Vienna, Austria.
url: www.kwizda.at
Kwizda, Cz. See *Horna, Cz.*
Kwizda, Ger. Kwizda Pharma GmbH & Co KG, Rüdesheimer Str. 15, 80686 Munich, Germany.
url: www.kwizda.at
Kwizda, Hung. See *Medico Uno, Hung.*
Kwizda, Pol. See *Hand-Prod, Pol.*
Kyorin, Jpn. Kyorin Pharmaceutical Co. Ltd, 2-5 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8311, Japan.
url: www.kyorin-pharm.co.jp
Kyorin, Thai. Kyorin.
Kyowa, Hong Kong. See *Tai Tong, Hong Kong.*
Kyowa, Jpn. Kyowa Hakko Kogyo Co. Ltd, 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan.
url: www.kyowa.co.jp
Kyowa, Malaysia. Kyowa Hakko (Malaysia) Sdn Bhd, 20 Jln SS 19/5, 47500 Subang Jaya, Selangor, Malaysia.
url: www.kyowa.co.jp
Kyowa, Singapore. Kyowa Hakko Industry (S) Pte Ltd, 260 Orchard Rd, The Heeren 12-04, S 238855, Singapore.
url: www.kyowa-asean.com
Kyowa, Thai. Kyowa Hakko (Thailand) Ltd, 101/11 Srinakarin Rd, Suanluang, Bangkok 10250, Thailand.
url: www.kyowa-asean.com
Kyowa, UK. Kyowa Hakko (UK) Ltd, 258 Bath Rd, Slough, Berkshire, SL1 4DX, UK.
url: www.kyowa-asean.com
Kyowa Hakko, Philipp. See *Eisai, Philipp.*
LA, Arg. Lab. Austral S.A., Av. Olascoaga 951, 8300 Neuquen, Argentina.
Lab, Port. Laboratórios Lab, Lda, Rua Escola de Medicina Veterinária 15-17, 1049-029 Lisbon, Portugal.
Lab Francais du Fractionnement, Fr. Lab Français du Fractionnement et des Biotechnologies, 3 av des Tropiques, B.P. 305, Les Ulis, 91958 Courtaboeuf cdx, France.
Lab Francais du Fractionnement, Neth. See *Lab Francais du Fractionnement, Fr.*
Labatec, Switz. Labatec-Pharma SA, Case postale 62, 31 rue du Cardinal-Journet, 1217 Meyrin 2, Switzerland.
Labcatal, Fr. Laboratoires Labcatal, 7 rue Roger-Salengro, B.P. 305, 92541 Montrouge cdx, France.
url: www.labactal.fr
Labcorp, USA. Laboratory Corporation of America, 840 Research Parkway, Suite 102, Oklahoma City, OK 73104, USA.
url: www.labcorp.com
Labesfal, Port. Labesfal, SA, Campo de Besteiros, 3465-051 Campo de Besteiros, Portugal.
Labialfarma, Port. Labialfarma, Laboratório de Biologia Alimentar e Farmacêutica Lda, Felgueira, 3450-336 Sobral, Mortágua, Portugal.
Labima, Belg. Labima SA, Ave Van Volxem 328, 1190 Brussels, Belgium.
Labinca, Arg. Labinca S.A., Cramer 4130, 1429 Buenos Aires, Argentina.
Labitec, Spain. Labitec, Lope de Rueda 46, 28009 Madrid, Spain.
Labocean, Fr. Laboratoires Labocean, ZI de Kerjean, 56500 Locmine, France.
Labochem, Cz. See *Labochem, Gr.*
Labochem, Gr. Labochem Ltd, 1 Aristonikou str., 116 36 Athens, Greece.
Labocor, Port. Labocor, Lda, Largo Cidade de Vittoria 7, 2750 Cascais, Portugal.
Labofarm, Pol. Innowacyjno-Wdrożeniowe Laboratorium Farmaceutyczne Labofarm, ul. Lublichowska 176 b, 83-200 Straogard Gdański, Poland.
url: www.labofarm.com.pl
Labomed, Chile. Instituto Farmaceutico Labomed SA, Lira 278, Santiago, Chile.
Labor, Pol. Farmaceutyczno-Chemiczna Spółdzielna Pracy Labor, ul. Długosza 49, 56-162 Wrocław, Poland.
url: www.labor.com.pl
Laboratories for Applied Biology, Irl. See *Boileau & Boyd, Irl.*
Laboratories for Applied Biology, Malaysia. See *Sime Darby, Malaysia.*
Laboratories for Applied Biology, Singapore. See *Sime Darby, Singapore.*
Laboratories for Applied Biology, UK. Laboratories for Applied Biology Ltd, 91 Amhurst Park, London, N16 5DR, UK.
url: www.cerumol.com
Laboratorio Farm., Israel. See *Premopharm, Israel.*
Laboratorios Chile, Chile. Laboratorios Chile SA, Av. Marathon 1315, Nunoa, Santiago, Chile.
Laborest, Ital. See *Pharma-Natura, Ital.*
Labormed, Rus. See *Rompharm, Rus.*
Labortecne, Braz. Labortecne Ltda, Av. Agamenon Magalhães 180, Vila Popular, 532030-010 Olinda, PE, Brazil.
url: www.labortecne.com.br
Laborterapia, Port. Laborterapia Produtos Farmaceuticos SA, Taguspark, Edificio Inovacao II, Sala 421, 2700 Oeiras, Portugal.
Lacefa, Arg. Lab. Lacefa S.A.I.C.A., Ladines 2263/7, 1419 Buenos Aires, Argentina.
Lacer, Hong Kong. See *CNW, Hong Kong.*
Lacer, Port. See *Lacer, Spain.*
Lacer, Spain. Lacer, Sardenya 350, 08025 Barcelona, Spain.
url: www.lacer.es
Lachema, Cz. See *Pliva, Cz.*
Lachema, Rus. See *Pliva, Rus.*
Lachifarma, Ital. Lachifarma S.r.l., Laboratorio Chimico Farmaceutico Salentino, S.S. 16, Zona Industriale, 73010 Zollino (LE), Italy.
url: www.lachifarma.com
Laclede, Singapore. See *MBD, Singapore.*
Laclede, USA. Laclede Inc., 2030 East University Drive, Rancho Dominguez, CA 90220, USA.
url: www.laclede.com
Lacoer, Ger. See *Laves, Ger.*
Lacteol, Switz. See *Uhlmann-Eyraud, Switz.*
Laetitia, Ger. Laetitia Naturprodukte Vertriebs GmbH, Elsasser Str. 4-6, 81667 Munich, Germany.
url: www.bitterstern.de
Lafage, Arg. Lab. Lafage S.R.L., J. E. Uriburu 61, 1027 Buenos Aires, Argentina.
Lafare, Ital. Laboratorio Farmaceutico Reggiano S.r.l., Via S.B. Cozzolino 77, 80056 Ercolano Resina (NA), Italy.
Lafarmen, Arg. Lafarmen S.A., Rioja 2163/69, 5500 Mendoza, Argentina.
Lafayette, Philipp. Lafayette Pharmaceutical Lab. Inc., 132, 13th Ave, Cubao, Quezon city, Philippines.
Lafayette, USA. See *Mallinckrodt-Baker, USA.*
Lafedar, Arg. Lafedar, Lab. Federales Argentinos S.A., Valentmn Torra 4880, 3100 Entre Rios, Argentina.
url: www.lafedar.com
Lafi, Chile. See *Recalcine, Chile.*
Lafit, Braz. Lafit Laboratórios Fitoterapico Ltda, Rua Isaias de Andrade e Souza 645, 38307-070 Ituiutaba, MG, Brazil.
Lafon, Belg. See *Lafon, Fr.*
Lafon, Fr. Laboratoires Lafon, 19 av. du Professeur Cadiot, B.P. 22, 94701 Maisons-Alfort cdx, France.
Lafon, Hong Kong. See *Worldwide, Hong Kong.*
Lafon, Israel. See *Medison, Israel.*
Lafran, Fr. Laboratoires Lafran, 1 rte des Stains, 94387 Bonneuil-sur-Marne cdx, France.
Lagamed, S.Afr. See *Aspen, S.Afr.*
Lagap, Neth. BV Lagap BNL, Stormsweg 25, 2921 LZ Krimpen A/D Ijssel, Netherlands.
Lagap, Switz. Lagap SA, Via San Gottardo 9, 6943 Vezia, Switzerland.
Lagap, UK. See *Novartis, UK.*
Lagepha, Belg. Lagepha, Belgium.
Lagos, Arg. Lagos Laboratorios Argentina S.R.L., Jorge Newbery 1829, 1426 Buenos Aires, Argentina.
url: www.lagoslab.com.ar
Lainco, Spain. Lainco, Avda Bizet 8-12, Pol. Ind. Can Jardi, Rubi, 08191 Barcelona, Spain.
url: www.lainco.es
Lake, USA. See *Wisconsin Pharmacal, USA.*
Lakeside, Mex. Lakeside de Mexico S.A. de C.V., Carr. Mexico Toluca 2822, Lomas de Bezares, 11000 Mexico D.F., Mexico.
Lakeside, Philipp. Lakeside Pharmaceuticals Phils Inc., Unit 304, APC Bldg, 1186 Quezon Ave, Quezon City, Philippines.
Lalco, Canad. See *Nobel, Canad.*
Lallemand, Pol. See *Merck, Pol.*
Lam Thong, Thai. See *March, Thai.*

Lamberts Healthcare, UK. Lamberts Healthcare Ltd, Century Place, Tunbridge Wells, Kent, TN2 3BE, UK.
url: www.lambertshealthcare.co.uk

Lamda (Λαμδα), Gr. Lamda Pharmaceutical A.E., 6 Thermopylon Str., 152 33 Chalandri, Greece.

Lampugnani, Ital. Lampugnani Farmaceutici S.p.A., Via Gramsci 4, 20014 Nerviano (Milan), Italy.

Lamsa, Arg. Laboratorio Argentino de Medicamentos SA, El Calden S/N, 6360 Gral. Pico, La Pampa, Argentina.

Lancome, Canad. See *L'Oreal, Canad.*

Lander, Canad. Lander Co. Canada Ltd, 275 Finchdene Square, Scarborough, Ontario, M1X 1C7, Canada.

Landson, Indon. Landson, PT Pertiwi Agung Pharmaceutical Industries Ltd, Gedung Mensa II Lantai 2, Jl H R Rasuna Said Kav B-35, Kuningan, 12910 Jakarta, Indonesia.
url: www.landson.co.id

Landson, Malaysia. See *Zyfas, Malaysia.*

Landson, Singapore. See *Zyfas, Singapore.*

Landsteiner, Mex. Landsteiner Scientific SA de CV, Periferico sur 4124 T.II Zafiro P.8, 1900 Ex-Rancho de Anzaldo, Mexico DF, Mexico.

Lane, Pol. See *Amis, Pol.*

Lane, UK. G.R. Lane Health Products Ltd, Sisson Rd, Gloucester, GL1 3QB, UK.
url: www.laneshealth.com

Lannacher, Austria. Lannacher Heilmittel GmbH, Schlossplatz 1, A-8502 Lannach, Austria.

Lannacher, Cz. See *Horna, Cz.*

Lannacher, Denm. See *Nordic Drugs, Denm.*

Lannacher, Israel. See *Taro, Israel.*

Lannacher, Norw. See *Nordic, Swed.*

Lannacher, Pol. Lannacher Heilmittel GmbH Sp. zo.o., Przedstawicielstwo w Polsce, al. Jana Pawła II 61, 00-031 Warsaw, Poland.

Lannacher, Rus. Lannacher Heilmittel GmbH, B. Sukharevskaya pl. 16/18, pod. 3, et. 9, 103045 Moscow, Russia.

Lannett, USA. Lannett Co., Inc., 9000 State Rd, Philadelphia, PA 19136, USA.
url: www.lannett.com

Lanpharm, Arg. Lab. Lanpharm SA, J E Uriburu 61, 1027 Buenos Aires, Argentina.

Lans, Rus. Lans, Russia.

Lantaka, Philipp. Lantaka Distributors Corp., Unit 228 Cityland 9, Dela Rosa St Condominium, 7648 Dela Rosa St, Makati City, Philippines.

Lantheus, USA. Lantheus Medical Imaging Inc., Bldg 200-2, 331 Treble Cove Rd, N Billerica, MA 01862, USA.
url: www.lantheus.com

Lapapharm (Λαπαφαρμ), Gr. Lapapharm Inc., 73 Menandrou Str., 104 37 Athens, Greece.

Laphal, Cz. See *Laphal, Fr.*

Laphal, Fr. Laphal Industrie, Avenue de Provence, 13190 Allauch cdx, France.
url: www.laphal.com

Laphal, Hong Kong. See *C & L, Hong Kong,* and *Wing Wai, Hong Kong.*

Laphi, Fr. See *PPDH, Fr.*

Lapi, Indon. Lapi PT, Jl Gedong Panjang No 32, 11240 Jakarta, Indonesia.

Lapidot, Israel. A. Lapidot Pharmaceuticals Ltd, 8 Ha'shita St, Industry Park, Caesaria 38900, Israel.
url: www.lapidot.com

Lapreven, Venez. Laboratorio Lapreven S.A., Centro Comercial Bello Monte, Piso 8 Of. 8B y 8C, Caracas, Venezuela.

Laquifa, Port. Laquifa Laboratórios S.A., Rua Alfredo da Silva 3C, 1300-040 Lisbon, Portugal.

Largen, Philipp. Largen Med Inc., 1604 Antel Global Bldg, J Vargas St, Ortigas Center, Pasig City, Philippines.

Larken, USA. Larken Laboratories, 148 Weisenberger Rd, Madison, MS 39110, USA.

Larkhall Laboratories, UK. Larkhall Laboratories, Forest Road, Charlbury, Chipping Norton, Oxon, OX7 3HH, UK.

Laser, USA. Laser Inc., 2200 W 97th Place, P.O. Box 905, Crown Point, IN 46307, USA.

Latinofarma, Braz. Latinofarma Indistrias Farmacêuticas Ltda, Rua Dr Tomas Sepe 489, 6711270 Jardim da Gloria Cotia, São Paulo, Brazil.

Lauria, Arg. Lauria, Merlino & Cía. S.C., Av. La Plata 340/44, 1235 Buenos Aires, Argentina.

Laus, Spain. See *Novartis, Spain.*

Lavena, Rus. See *Sopharma, Rus.*

Laves, Ger. Laves-Arzneimittel GmbH, Barbarastr. 14, 30952 Ronnenberg, Germany.
url: www.laves-pharma.de

Lavipharm, Gr. Lavipharm Group, Agias Marinas St, 190 02 Peania Attica, Greece.
url: www.lavipharm.gr

Lavipharm, Israel. See *Megapharm, Israel.*

Layton, USA. Layton Bioscience Inc., 709 E Evelyn Ave, Sunnyvale, CA 94086, USA.
url: www.laytonbio.com

Lazar, Arg. Laboratorio Dr. Lazar & Cia. S.A., Av. Velez Sarsfield 5855, 1605 Carapachay, Buenos Aires, Argentina.
url: www.lazar.com.ar

Lazuli, Malaysia. Lazuli Sdn Bhd, 18 Jln SS 5 A/9, 47301 Petaling Jaya, Selangor, Malaysia.

LBS, Malaysia. See *Antah, Malaysia.*

LBS, Thai. LBS Laboratory Ltd Part, 602 Soi Phanichanant, Sukhumvit 71 Rd, Bangkok 10110, Thailand.
url: www.lbslab.com

LCA, Belg. LCA, Belgium.

LCA, Fr. Laboratoire LCA, 9 allée Promethée, 28000 Chartres, France.

LCH, Hong Kong. Luen Cheong Hong Ltd, 25/F, 200 Gloucester Rd, Wanchai, Hong Kong.

LDA, Arg. Lab. LDA SA, Alcaraz 5294, 1407 Buenos Aires, Argentina.

LDP, Rus. Laboratoire de Development Pharmaceutique, Nikolskaya ul. 19, of. 9, 109012 Moscow, Russia.

LDPSA, Fr. LDPSA, 38 rue Bassano, 7508 Paris, France.

Leader, Hong Kong. Leader Pharmaceutical & Cosmetic Co. Ltd, 2/F, 42 Hankow Rd, Kowloon, Hong Kong.

Lebeh, USA. Lebeh, USA.

Leciva, Cz. Lečiva as, U Kabelorny 130, 10237 Prague 10, Czech Republic.
url: www.leciva.cz

Leciva, Hung. See *Leciva, Cz.*

Leciva, Rus. Leciva ZAO, Prechistenka 40/2,, Bld.1, Gate 2, 5th floor, 113054 Moscow, Russia.

Lectec, USA. LecTec Corp., 5616 Lincoln Dr., Edina, MN 952933-2291, USA.
url: www.lectec.com

LED, Fr. Laboratoires d'Evolution Dermatologique, 7 rue d'Aguesseau, 75008 Paris, France.

Lederle, Cz. See *Wyeth, Cz.*

Lederle, Ger. See *Wyeth, Ger.*

Lederle, Hong Kong. See *Wyeth, Hong Kong.*

Lederle, Indon. See *Wyeth, Indon.*

Lederle, Israel. See *Neopharm, Israel.*

Lederle, NZ. See *Wyeth, NZ.*

Lederle, Switz. See *AHP, Switz.*

Lederle, USA. See *Wyeth, USA.*

Lee, USA. Lee Pharmaceuticals, 1434 Santa Anita Ave., South El Monte, CA 91733, USA.
url: www.leepharmaceuticals.com

Lee-Adams, Canad. Lee-Adams Laboratories, 611 Royalmount Ave, Montreal, Quebec, H4P 2T4, Canada.

Leeming, USA. See *Pfizer, USA.*

Lefnin, Rus. Lefnin OOO, Stasovoi ul. 2-B, 117071 Moscow, Russia.
url: www.lefnin.ru

Legrand, Braz. See *EMS, Braz.*

Legras, Fr. Laboratoires Legras, 114 Bis, rue Michel-Ange, 75016 Paris, France.

Lehning, Canad. See *Lehning, Fr.*

Lehning, Cz. See *Lehning, Fr.*

Lehning, Fr. Laboratoires Lehning, 1-3 rue du Petit-Marais, 57640 Sainte-Barbe, France.
url: www.lehning.com

Leidapharm, Neth. Leidapharm BV, Archimedesweg 2, 2333 CN Leiden, Netherlands.

Leiras, Cz. See *Leiras, Fin.*

Leiras, Denm. See *Nycomed, Denm.*

Leiras, Fin. Oy Leiras Finland AB, PL 1406, 00101 Helsinki, Finland.
url: www.leiras.fi

Leiras, Indon. See *Dexa, Indon.*

Leiras, Israel. See *Perrigo, Israel.*

Leiras, Singapore. See *MBD, Singapore.*

Leitner, USA. Leitner Pharmaceuticals, 340 Edgemont Ave, Ste 300, Bristol, Tennessee 37620, USA.
url: www.leitnerpharmaceuticals.com

LEK, Austria. LEK Ljubiljana Holding GmbH, Steckhovengasse 2/5, A-1130 Vienna, Austria.

Lek, Cz. Lek Pharma sro, Jeseniová 30, 130 00 Prague 3, Czech Republic.

Lek, Hong Kong. See *Hind Wing, Hong Kong.*

Lek, Hung. Lek, Verovskova 57, 1526 Ljubljana, Slovenia.

Lek, Pol. Lek Polska Sp. zo.o., ul. Domaniewska 50 C, 02-672 Warsaw, Poland.
url: www.lek.com.pl

Lek, Rus. Lek, Starokonyushennyi per. 10/10 str. 1, 119002 Moscow, Russia.

Lek, Singapore. See *FP, Singapore.*

Lek, Thai. See *RX, Thai.*

Lek-Am, Pol. Przedsiębiorstwo Farmaceutyczne Lek-Am Sp. zo.o., ul. Podwale 23, 00-261 Warsaw, Poland.
url: www.lekam.pl

Leki Natury, Pol. Przedsiębiorstwo Farmaceutyczne Leki Natury, ul. Zielona 30, 08-500 Ryki, Poland.

Lekkhim-Kharkov, Rus. See *Citomed, Rus.*

Lekko, Rus. See *Masterlek, Rus.*

Leksir, Rus. Leksir, Krylatskie kholmy St 30, corp. 9, 121614 Moscow, Russia.
url: www.filtrum.ru

Lema, Philipp. Lema Pharmaceuticals Inc., Suite 201 Menchavez Bldg, Escario St, Cebu City, Philippines.

Lemax, Arg. Lemax Laboratorios SRL, Neuquin 923, 1752 Lomas del Mirador, Buenos Aires, Argentina.

Lemery, Cz. See *Medicom, Cz.*

Lemery, Mex. Lemery S.A. de C.V., Calle 1 No. 5-A Interior 101, Mabuel Avila Camacho, 11610 Mexico D.F., Mexico.

Lemery, Rus. See *Sicor, Rus.*

Lemery, Thai. See *Pharmaland, Thai.*

Lemmon, USA. See *Teva, USA.*

Lemoine, Fr. Laboratoires Lemoine, Imm le Doublon, bat B, 11 av. Dubonnet, 92400 Courbevoie, France.

Lennod, USA. Lennod, USA.

Lennon, Austral. Lennon Healthcare Research PL, 1 Camelot Place, St Ives, NSW 2075, Australia.

Lennon, S.Afr. See *Aspen, S.Afr.*

Lensa, Spain. Lensa, Potosi 2-4, 08030 Barcelona, Spain.

Leo, Austria. Leo Pharma GesellschafftmbH, Mariahilfer Strasse 123/4.OG, A-1060 Vienna, Austria.
url: www.leopharma.com

Leo, Belg. Leo Pharma SA, Sneeuwbeslaan 20, 2610 Wilrijk, Belgium.
url: www.leo-pharma.be

Leo, Canad. Leo Pharma Inc., 123 Commerce Valley Dr. E, Suite 400, Thornhill, Ontario, L3T 7W8, Canada.
url: www.leopharma.ca

Leo, Cz. See *Leo, Denm.*

Leo, Denm. Leo Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark.
url: www.leo-pharma.com

Leo, Fin. Leo Pharma Oy, Äyritie 12 B, 01510 Vantaa, Finland.
url: www.leo-pharma.fi

Leo, Fr. Laboratoires Leo, B.P. 311, 78054 St-Quentin-Yvelines cdx, France.
url: www.leo-pharma.com/fr

Leo, Ger. Leo Pharma GmbH, Frankfurter Str. 233, A3, 63263 Neu-Isenburg, Germany.
url: www.leo-pharma.de

Leo, Gr. Leo Pharmaceutical Products Hellas Ltd., 30 Vas. Georgiou & Mikras Asias, 152 33 Calandri, Greece.
url: www.leo-pharma.gr

Leo (Λεο), Gr. See *Leo, Gr.*

Leo, Hong Kong. See *Keller, Hong Kong.*

Leo, Hung. See *Medicine & Business, Hung.*

Leo, Indon. See *Darya-Varia, Indon.*

Leo, Irl. Leo Laboratories Ltd, 285 Cashel Rd, Dublin 12, Ireland.
url: www.leo.ie

Leo, Israel. See *Dexxon, Israel.*

Leo, Malaysia. See *Diethelm, Malaysia,* and *Summit, Malaysia.*

Leo, Neth. Leo Pharma BV, Hoge Mossen 16-20, 4822 NH Breda, Netherlands.
url: www.leopharma.com

Leo, Norw. Leo Pharma AS, Postboks 193 Lilleaker, 0216 Oslo, Norway.
url: www.leo.no

Leo, NZ. See *CSL, NZ.*

Leo, Philipp. See *Zuellig, Philipp.*

Leo, Pol. See *Perffarma, Pol.*

Leo, Port. Leo-Farmaceuticos, Lda, Av das Nações Unidas 27, 1600-531 Lisbon, Portugal.
url: www.leopharma.com

Leo, Rus. See *Onyx, Rus.*

Leo, Singapore. Leo Pharma Singapore, 6A Maju Ave, S 556684, Singapore.
url: www.leopharma.com

Leo, Spain. Leo Pharma, Marina 16-18, 08005 Barcelona, Spain.
url: www.farmacusi.es

Leo, Swed. Leo Pharma AB, Box 404, 201 24 Malmö, Sweden.
url: www.leo.se

Leo, Switz. Leo Pharmaceutical Products Sarath Ltd, Eichwatt 5, Postfach 1154, 8105 Regensdorf-Watt, Switzerland.
url: www.leopharma.com

Leo, Thai. See *Olic, Thai.*

Leo, UK. Leo Pharma, Longwick Rd, Princes Risborough, Buckinghamshire, HP27 9RR, UK.
url: www.leo-pharma.co.uk

Leopold, Austria. Leopold Pharma GmbH, Hafnerstrasse 36, A-8055 Graz, Austria.

Leopold, Cz. See *Leopold, Austria.*

Leovan, Gr. Leovan M. Aedn & Cia EE, 22 Argonayton Str., 167 77 Elliniko, Greece.

Lepetit, Ital. See *Aventis, Ital.*

Lepori, Port. See *Angelini, Port.*

Lero, Fr. Léro, 65 bd du Mal-de-Lattre-de-Tassigny, 92150 Suresnes, France.

Leros, Cz. Leros sro, U Narodni galerie 460, 156 15 Prague 5, Czech Republic.
url: www.leros.cz

Lersan, Arg. See *Pharmos, Arg.*

Les 3 Chenes, Ital. Les 3 Chenes Italia Srl, Viale Gozzadini 19, 40124 Bologna (BO), Italy.

Lesourd, Fr. Laboratoires Gabriel Lesourd, 6 rue Ste-Isaure, 75018 Paris, France.

Lesvi, Spain. See *Vita, Spain.*

Leti, Ger. Leti Pharma GmbH, Mannesmannstr. 4, 58455 Witten, Germany.
url: www.leti.de

Leti, Spain. Laboratorios Leti, Gran Via de las Corts Catalanes 184, 08038 Barcelona, Spain.
url: www.leti.com

Leti, Venez. Laboratorio Leti S.A.V., 2a Av., Parcela 3, Manzana J Edif. Leti, Guarenas, Caracas, Venezuela.
url: www.leti.com.ve

Leti Gentek, Venez. See *Leti, Venez.*

Leurquin, Fr. Laboratoires Leurquin Mediolanum, 68/88 rue Ampere, 93330 Neuilly-sur-Marne, France.
url: www.mediolanum-farma.com

Leurquin, Hong Kong. See *Innoledge, Hong Kong.*

Leurquin, Switz. See *Uhlmann-Eyraud, Switz.*

Leurquin Mediolanum, Hung. See *Ubepharm, Hung.*

Lever, UK. Lever Faberge, 3 St James Rd, Kingston-upon-Thames, Surrey, KT1 2BA, UK.
url: www.leverfaberge.co.uk

Levofarma, Ital. See *Uno, Ital.*

Lewison, Philipp. Lewison Pharmaceuticals Corp., 88 Teresa Bldg, 15th Ave, Murphy, Cubao, Quezon City, Philippines.

Lexis, USA. Lexis Laboratories, P.O. Box 202887, Austin, TX 78720, USA.

Lexon, UK. Lexon (UK) Ltd, 18 Oxleasow Rd, East Moons Moat, Redditch, Worcestershire, B98 0RE, UK.
url: www.lexonuk.com

Leyh, Ger. Leyh Pharma GmbH, Gewerbegebeit Baierstal, 98596 Trusetal, Germany.

LFB, Fr. LFB Biomedicaments, 3 av des Tropiques, B.P. 305, Les Ulis, 91958 Courtaboeuf cdx, France.
url: www.lfb.fr

LFB, Port. See *LFB, Fr.*

LG, Philipp. See *Zuellig, Philipp.*

LG, Pol. See *Sanofi-Aventis, Pol.*

LG Chem, Thai. See *Aventis Pasteur, Thai.*

LG Life Sciences, India. LG Life Sciences India Pvt Ltd, LG House, AB-3 Safdarjung Enclave, New Delhi 110029, India.

LG Life Sciences, Malaysia. See *Duopharma, Malaysia.*

LG Life Sciences, Thai. See *Novatec, Thai.*

LG Pharm, Hong Kong. See *Hind Wing, Hong Kong.*

Li Chung Yun, Canad. Li Chung Yun Co., 5 13550 77th Ave, Surrey, British Colombia, V3W 6Y3, Canada.

Liade, Spain. See *Abbott, Spain.*

Liba, Turk. Liba Laboratuvarları A.Ş., Otağtepe Cad. No: 5, Kavacık, İstanbul, 81610, Turkey.

Libbs, Braz. Libbs Farmacêutica Ltda, Rua Josef Kryss 250, 01140-050 São Paulo, SP, Brazil.
url: www.libbs.com.br

LIBP, Hong Kong. See *Hugh Source, Hong Kong.*

Libra, S.Afr. Libra, South Africa.

Librapharm, Spain. See *Grunenthal, Spain.*

Lichtenstein, Cz. See *Lichtenstein, Ger.*

Lichtenstein, Ger. Lichtenstein Pharmazeutica GmbH & Co., Industriestrasse 26, 56218 Mulheim-Karlich, Germany.
url: www.lichtenstein-pharma.de

Lichtwer, Canad. Lichtwer Pharma, 145 Idema Road, Markham, Ontario, L3R 1A9, Canada.
url: www.lichtwer.de

Lichtwer, Cz. See *Lichtwer, Ger.*

Lichtwer, Ger. Lichtwer Pharma AG, Wallenroder Str. 8-10, 13435 Berlin, Germany.
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Lichtwer, Neth. See *Lichtwer, Ger.*

Lichtwer, Switz. See *Adroka, Switz.*

Lichtwer, UK. Lichtwer Pharma UK, Regency House, Mere Park, Dedmere Rd, Marlow, Buckinghamshire, SL7 1FJ, UK.
url: www.lichtwer.co.uk

Liconsa, Cz. See *Liconsa, Spain.*

Liconsa, Port. See *Liconsa, Spain.*

Liconsa, Spain. Liconsa S.A., Gran Via de Carlos III, 98 - 7, 08028 Barcelona, Spain.
url: www.liconsa.com

Liebermann, Ger. Pharma Liebermann GmbH, Hauptstr. 27, 89423 Gundelfingen/Do., Germany.
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Lierac, Fr. Laboratoires Liérac, 35 av Franklin-Roosevelt, 75008 Paris, France.

LIFAERP, Braz. Lab. Indl. Farm. Assoc. de Ens. de Ribeirao Preto, Av. Costabile Romano 2201 Bl. J, 14096-380 Ribeirao Preto, SP, Brazil.

Life, Ger. Life Pharma GmbH, Frigenstr. 5, 67065 Ludwigshafen, Germany.

Life, Israel. See *Rekah, Israel.*

Life Essence, UK. Life Essence Ltd, 24 St Clairs Rd, Croydon, Surrey, CR0 5NE, UK.

Life Plus, UK. Life Plus Europe Ltd, Little End Rd, Eaton Socon, Cambridgeshire, PE19 8JH, UK.
url: www.lifeplus.com

Lifebiotech, Switz. LifeBiotech AG, Gattikerstrasse 5, Postfach, 8029 Zurich, Switzerland.

Lifepharma, Ital. Lifepharma S.p.A., Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy.

Lifeplan, UK. Lifeplan Products, Elizabethan Way, Lutterworth, Leicestershire, LE17 4ND, UK.
url: www.lifeplan.co.uk

Liferpal, Mex. Liferpal MD, S.A. de C.V., Refineria No. 1266, Col. Alamo Industrial, 44490 Guadalajara, Jalisco, Mexico.

Lifescan, Canad. Lifescan Canada, 4170 Still Creek Drive, Suite 234, Burnaby, British Columbia, V5C 6C6, Canada.
url: www.lifescancanada.com

Lifescan, Fr. Laboratoires Lifescan, Division d'Ortho-Clinical Diagnostics, 1 rue Camille-Desmoulins, TSA 40007, 92787 Issy-les-Moulineaux cdx 9, France.
url: www.lifescanfrance.com

Lifescan, Irl. See *Fulcrum, Irl.*
Lifescan, Ital. See *Ortho, Ital.*
Lifescan, Port. See *Johnson & Johnson, Port.*
Lifescan, USA. Lifescan, 1000 Gibraltar, Milpitas, CA 95035-6312, USA.
url: www.lifescan.com
Lifesign, USA. LifeSign LLC, P.O. Box 218, Somerset, NJ 08875-0218, USA.
url: www.lifesignmed.com
Lifetech, Hong Kong. Lifetech Enterprises Inc., Suite 3808, New World Tower, 18 Queen's Rd Central, Hong Kong.
url: www.lifetechgroup.com
Ligand, Denm. See *Zeneus, Denm.*
Ligand, Hung. Ligand, Hungary.
Ligand, Neth. See *Ligand, UK.*
Ligand, UK. Ligand Pharmaceuticals UK Ltd, 108 High St, Crawley, West Sussex, RH10 1BB, UK.
Li-il, Ger. Li-iL GmbH Arzneimittel, Leipziger Str. 300, 01139 Dresden, Germany.
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Lilly, Arg. Eli Lilly Interamerica Inc., Av. Scalabrini Ortiz 3333 5 Piso, 1425 Buenos Aires, Argentina.
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Lilly, Fin. Oy Eli Lilly Finland AB, Rajatorpantie 41 C 3. krs, PL 16, 01641 Vantaa, Finland.
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Lilly, Ger. Lilly Deutschland GmbH, Saalburgstr. 153, 61350 Bad Homburg, Germany.
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Lilly, Jpn. Eli Lilly Japan K.K., 7-1-5 Isogami-dori, Chuo-ku Kobe, Hyago 651-0086, Japan.
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Lilly, Mex. Eli Lilly y Compania de Mexico S.A. de C.V., Calz de Tlalpan No. 2024, Col Campestre Churubusco, Deleg. Coyoacan, 04200 Mexico D.F., Mexico.
url: www.lilly.com.mx
Lilly, Neth. Eli Lilly Nederland, Grootschlag 1-5, 3991 RA Houten, Netherlands.
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Lilly, Thai. See *Diethelm, Thai.*
Lilly, Turk. Lilly İlaç Tic. Ltd. Şti., Kısıklı Cad., Kuşbakışı Sok. No: 6 Rainbow Plaza K: 3, Altunizade, İstanbul, 81180, Turkey.
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Lincoln, UK. Lincoln Medical Ltd, 13 Boathouse Meadow Business Park, Cherry Orchard Lane, Salisbury, Wiltshire, SP2 7LD, UK.
Lincoln Medical, Pol. See *Biomed Krakow, Pol.*
Linde, UK. Linde Gas UK Ltd, Johnson's Bridge Rd, Church Lane, West Bromwich, West Midlands, B71 1LG, UK.
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Linde Gaz, Pol. Linde Gaz Polska Sp. zo.o., al. Jana Pawła II 41a, 31-864 Kraków, Poland.
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Linderma, UK. Linderma Ltd, Canon Bridge House, Canon Bridge, Madley, Herefordshire, HR2 9JF, UK.
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Lindopharm, Ger. Lindopharm GmbH, Neustr. 82, 40721 Hilden, Germany.
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Lindopharm, Israel. Lindopharm, Israel.
Lineafarm, Spain. Lineafarm, Spain.
Linfar, Arg. Laboratorios Linfar S.R.L., Emilio Casas Ocampo 2838, 5009 Altos de San Martin, Cordoba, Argentina.
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Link, Fr. Link, France.
Link, Irl. See *Intra Pharma, Irl.*
Link, NZ. Link Pharmaceuticals, Level 20, ASB Bank Centre, 135 Albert St, Auckland, New Zealand.
Link, UK. See *Archimedes, UK.*
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Lipha, Indon. See *Ikapharmindo, Indon.*
Lipha, Switz. See *Merck, Switz.*
Lipha Sante, Fr. See *Merck-Lipha, Fr.*
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Lipomed, Denm. See *Lipomed, Ger.*
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Lipomed, Port. See *Lipomed, Ger.*
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Lipomed, UK. See *Lipomed, Ger.*
Liposome Company, Austria. See *Wyeth Lederle, Austria.*
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Lisapharm, Israel. See *Premopharm, Israel.*
Lisapharma, Hong Kong. See *Mekim, Hong Kong.*
Lisapharma, Hung. See *Medico Uno, Hung.*
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Lisapharma, Malaysia. See *Zyfas, Malaysia.*
Lisapharma, Pol. See *Imed, Pol.*
Lisapharma, Singapore. See *Zyfas, Singapore.*
Lisapharma, Thai. See *Charoen, Thai.*, and *SPB, Thai.*
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Lloyd, Philipp. See *Randril, Philipp.*, and *Vitalink, Philipp.*
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Lofarma, Hung. See *Lofarma, Ital.*
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Loges, Hong Kong. See *Lision Hong, Hong Kong.*
Logogen, Spain. See *Italfarmaco, Spain.*
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Longshunrong, Philipp. See *Goodfellow, Philipp.*
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Loprofar, Braz. See *Lopes, Braz.*
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Loren, Mex. Laboratorios Farmaceuticos Loren S.A. de C.V., Km. 91 Carr. Federal Mexico-Puebla, Corredor Industrial Quetzalcoatl, 74160 Huejotzingo, Pue, Mexico.
Lorex, Denm. See *Pharmacia, Denm.*
Lorvic, Canad. See *Prof. Pharm. Corp., Canad.*
Lorvic, USA. See *Young, USA.*
Lotus, Malaysia. See *Zuellig, Malaysia.*
Lotus, USA. See *Harvest, USA.*
Loyal Advance, Hong Kong. Loyal Advance Ltd, 8/F, B2-B4 Tsing Yi Industrial Ctr, Phase 1, Tsing Yi Island, N.T., Hong Kong.
LPB, Ital. LPB Istituto Farmaceutico S.p.A., Largo Umberto Boccioni 1, 21040 Origgio (VA), Italy.
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LRC, Israel. See *Promedico, Israel.*
LSI, USA. LSI America Corp., 4732 Twin Valley Drive, Austin, TX 78731-3537, USA.
url: www.ondrox.com
LSP, Thai. Lerd Singh Pharmaceutical Fact Ltd Part, 922 Sukhumvit 50, Prakanong, Klongtoey, Bangkok 10250, Thailand.
LTS, Israel. See *Teva, Israel.*
Luar, Arg. Química Luar S.R.L., Angel Carranza 1946, 1414 Buenos Aires, Argentina.
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Lucchini, Switz. Laboratoire Lucchini SA, Case postale 1214, 1211 Geneva 26, Switzerland.
Luchon, Fr. Laboratoires de Luchon, 22 bd Dardenne, 31110 Luchon, France.
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Ludwig, Singapore. See *Apotheca, Singapore.*
Luen Wah, Malaysia. Luen Wah Medical Co Sdn Bhd, No. 43-G & 43-1F The Highway Centre, Jln 51/205, 46050 Petaling Jaya, Selangor, Malaysia.
Luen Wah, Singapore. Luen Wah Medical Co (S) Pte Ltd, 40 North Canal Rd, S 059296, Singapore.
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Lundbeck, Malaysia. See *JDH, Malaysia.*
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Lundbeck, NZ. See *Zuellig, NZ.*
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Lundbeck, Thai. See *Hua, Thai.*

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Luper, Braz. Luper Indústria Farmacêutica Ltda, Rua Doutor Clementino 608, 03059-030 São Paulo, SP, Brazil.
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Lupin, Cz. See *Lupin, India.*

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Lupin, USA. Lupin Pharmaceuticals Inc., Harborplace Tower, 111 South Calvert St., 21st floor, Baltimore, MD 21202, USA.
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Lusal, Port. Lusal Produção Quimico-Farmacêutico Luso-Alemã Lda, Estrada Nacional 249, Km 15, 2725-397 Mem Martins, Portugal.

Lusalfarma, Port. See *Lusal, Port.*

Lusofarmaco, Cz. See *Lusofarmaco, Ital.*

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Lusofarmaco, Port. See *GSK, Port.*

Lusofarmaco, Rus. See *Berlin Pharm, Rus.*

Lusomedicamenta, Port. Lusomedicamenta Sociedade Técnica Farmacêutica SA, Estrada Consiglieri Pedroso 69 B, Queluz de Baixo, 2730-055 Barcarena, Portugal.
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Lusoterapia, Port. Lusoterapia Sociedade de Comércio de Produtos Quimico Farmacêuticos Lda, Av. António Augusto de Aguiar 128, 1069-133 Lisbon, Portugal.

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Lyempf, Indon. See *Tempo Scan Pacific, Indon.*

Lyka, Rus. See *Reddy, Rus.*

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Lyofin, Gr. Lyofin, Greece.

Lyron, Switz. Lyron AG, Postfach 3538, 4002 Basle, Switzerland.

Lysi, Pol. See *Island, Pol.*

Lysoform, Ger. Lysoform Dr. Hans Rosemann GmbH, Kaiser-Wilhelm-Str. 133, 12247 Berlin, Germany.
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M & H, Malaysia. See *Germax, Malaysia.*

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Maabarot, Israel. See *Trima, Israel.*

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Macarthur, Austral. See *Roche, Austral.*

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Mack, Malaysia. See *Summit, Malaysia.*

Mack, Pol. See *Mack, Illert., Ger.*

Mack, Rus. See *Ebewe, Rus.,* and *Pfizer, Rus.*

Mack, Singapore. See *Summit, Singapore.*

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Mack, Illert., Ger. See *Pfizer, Ger.*

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Madaus, Norw. See *Meda, Norw.*

Madaus, Philipp. See *Zuellig, Philipp.*

Madaus, Pol. Madaus AG, Przedstawicielstwo w Polsce, ul. Rumiana 65, 02-956 Warsaw, Poland.
url: www.madaus.pl

Madaus, Port. Madaus Farma Portugal Unipessoal Lda, Av. D João II, Lote 1.02.1 D 2, 1990-090 Lisbon, Portugal.

Madaus, Spain. Madaus, FOC 68-82, 08038 Barcelona, Spain.
url: www.madaus.es

Madaus, Switz. See *Zeller, Switz.*

Madaus, Thai. See *Oui Heng, Thai.*

Maeil, Hong Kong. Maeil HK, 17A China Trade Ctr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.
url: www.maeil.com.hk

Maelor, UK. Maelor Pharmaceuticals Ltd, Office Village, Chester Business Park, Chester, CH4 9QZ, UK.
url: www.maelor.plc.uk

Maersk, UK. See *Unomedical, UK.*

Maffioli, Ital. Prodotti Dott. Maffioli S.a.s. di A. Labruzzo & C., Via Firenze 38, 20060 Trezzano Rosa (MI), Italy.

Magis, Ital. Magis Farmaceutici S.p.A., Via Cacciamali 34-36-38, Zona Ind. (Loc. Noce), 25125 Brescia, Italy.

Magistra, Switz. Laboratoires Magistra SA, 28 Chemin du Grand-Puits, Case postale 122, 1217 Meyrin 2/Geneva, Switzerland.

Magna, USA. MAGNA Pharmaceuticals Inc., 11802 Brinley Ave, Suite 201, Louisville, KY 40243, USA.
url: www.magnaweb.com

Magnapharma, Pol. Magnapharma Sp. zo.o., ul. Turystyczna 3, 91-615 Łódź, Poland.
url: www.magnapharma.com.pl

Magno-Humphries, USA. Magno-Humphries Laboratories Inc., 8800 S.W. Commercial St, Tigard, OR 97223, USA.
url: www.magno-humphries.com

Mahakam Beta, Indon. Mahakam Beta Farma/Mundipharma, Jl Pulo Kambing II No 20, Kawasan Industri Pulogadung, 13930 Jakarta Timur, DKI Jaya, Indonesia.

Mahakam Beta, Malaysia. See *Somedico, Malaysia.*

Mahdeen, Canad. Mahdeen Mediceuticals, Division of Canmax Laboratories, 6600 Kennedy Rd, 4, Mississauga, Ontario, L5T 2M9, Canada.

Maigal, Arg. Lab. Maigal Corp., 12 de Octubre 1725, 1416 Buenos Aires, Argentina.

Main Life, Hong Kong. Main Life Corp. Ltd, 9/F, Winning Ctr, 46-48 Wyndham St Central, Hong Kong.

Majestic, Canad. See *Majestic, USA.*

Majestic, USA. Majestic Drug Company Inc., 4996 Main St, P.O.Box 490, South Fallsberg, NY 12779, USA.
url: www.majesticdrug.com

Major, USA. See *Harvard, USA.*

Makara, Austria. Makara Pharm GmbH, A-6234 Brandenberg 19C, Austria.

Makiz-Pharma, Rus. Makiz-Pharma ZAO, Avtomobilnyi pr., d. 6, 109029 Moscow, Russia.

Makros, Braz. Makros Indústria Farmacêutica Ltda, Rua Riachuelo 410, 20230-013 Rio de Janeiro, RJ, Brazil.

Malam, UK. Malam Laboratories Ltd, 37 Oakwood Rise, Heaton, Bolton, BL1 5EE, UK.

Malayan, Singapore. See *Luen Wah, Singapore.*

Malaysia Chemist, Singapore. Malaysia Chemist Pte Ltd, 104 Boon Keng Rd, 04-01, S 339775, Singapore.
url: www.malchem.com

Malesci, Ital. Malesci Istituto Farmacobiologico S.p.A., Via Lungo l'Ema 7, 50012 Bagno a Ripoli (FI), Italy.
url: www.malesci.it

Mallard, USA. See *Shire, USA.*

Mallinckrodt, Arg. Mallinckrodt Medical Argentina Ltda, Av. Cyrdoba 1345 Piso 7, 1055 Buenos Aires, Argentina.
url: www.mallinckrodt.com

Mallinckrodt, Austral. Mallinckrodt Australia, Trading as Tyco Healthcare P/L, Unit 4, 310 Ferntree Gully Road, Notting Hill, VIC 3168, Australia.
url: www.mallinckrodt.com

Mallinckrodt, Austria. Mallinckrodt Medical GmbH, Im Campus 21, Europaring F09402, A-2345 Brunn am Gebirge, Austria.
url: www.tycohealthcare.com

Mallinckrodt, Cz. Mallinkrodt Medical, Czech Republic.

Mallinckrodt, Neth. Mallinckrodt Medical BV, Westerduinweg 3, 1755 Le Petten, Netherlands.

Mallinckrodt, Port. See *Tyco, Port.*

Mallinckrodt, UK. Mallinckrodt Medical UK Ltd, 10 Talisman Business Centre, London Rd, Bicester, Oxfordshire, OX6 0JX, UK.
url: www.mallinckrodt.com

Mallinckrodt, USA. Mallinckrodt Pharmaceuticals, 675 McDonnell Blvd, Hazelwood, MO 63042, USA.
url: www.mallinckrodt.com

Mallinckrodt-Baker, USA. Mallinckrodt-Baker Inc., 222 Red School Lane, Phillipsburg, NJ 08865, USA.
url: www.mallbaker.com

Mallix, Philipp. See *Am-Europharma, Philipp.*

Malpharm, Hong Kong. See *International Medical, Hong Kong.*

Mandri, Spain. Mandri, Pau Claris 182, 08037 Barcelona, Spain.

Manetti Roberts, Ital. L. Manetti H. Roberts & C. SpA, Via Baldanzese 177, 50041 Calenzano (FI), Italy.

Manix, Philipp. DB Manix International Inc., 67 Scout Fuentebella St, Tomas Morato, Quezon City, Philippines.

Mann, Cz. See *Mann, Ger.*

Mann, Ger. Dr Gerhard Mann, Chem.-pharm. Fabrik GmbH, Brunsbutteler Damm 165-73, 13581 Berlin, Germany.
url: www.mannpharma.de

Mann, Hung. See *Chauvin Ankerpharm, Hung.*

Mann, Irl. See *Pharma-Global, Irl.*

Mann, Malaysia. See *People's, Malaysia.*

Mann, Pol. See *Bausch & Lomb, Pol.*

Mann, Rus. See *Bausch & Lomb, Rus.*

Mann, Singapore. See *Indrugco, Singapore.*

Mann, Thai. See *Zuellig, Thai.*

Manne, USA. Manne, P.O. Box 825, Johns Island, SC 29457, USA.

Manon, Israel. Manon Ltd, P.O. Box 3905, Tel Aviv, Israel.

Manor, UK. Manor Drug Co. (Nottingham) Ltd., Manor House, Merlin Way, Quarry Hill Rd, Ilkeston, Derbyshire, DE7 4RA, UK.
url: www.manorpharmacy.co.uk

Mantecorp, Braz. Mantecorp Indústria Quimica e Farmacêutica Ltda, Rua Antonio das Chagas 1623, 2 andar, 04714-002 São Paulo, Brazil.

Manuell, Mex. Laboratorios Manuell, S.A., Jarcieria 237 Eq.con Plomeros, Col Morelos, Deleg. Venustiano Carranza, 15270 Mexico D.F., Mexico.
url: www.manuell.com

Manx, UK. Manx Pharma Ltd, Manx House, Spectrum Business Estate, Bircholt Rd, Maidstone, Kent, ME15 9YP, UK.
url: www.manxhealthcare.com

Mar, Arg. Laboratorios Mar S.A., Av. Gaona 3875, 1407 Buenos Aires, Argentina.

Marano, Ital. Marano Benito, Via E Vittorini, Villa Scalea, 90147 Palermo, Italy.

Marcel, Mex. Laboratorios Marcel S.A. de C.V., Calzada Gonzalez Gallo 1707, Jalisco, 44870 Guadalajara, Mexico.

Marcelle, Canad. Groupe Marcelle Inc., 9200 Côte de Liesse, Lachine, Quebec, H8T 1A1, Canada.

March, Thai. March Pharmaceuticals Co. Ltd, 655 Praditmanutham Rd, Wangthonglang, Bangkok 10310, Thailand.

Marching, Hong Kong. MPL, Marching Pharmaceutical Ltd, Units 2,4,8-12, 9/F Block B Vigor Ind Bldg, 14-20 Cheung Tat Rd, Tsing Yi, Hong Kong.
url: www.marching.com.hk

Marcmed, Pol. Przedsiębiorstwo Produkcyjno-Handlowe Marcmed, ul. Zamenhofa 29-31, 20-453 Lublin, Poland.
url: www.marcmed.pl

Marco, Austral. Marco D'Polo Importing & Merchandising, 12 Lancaster St, Ingleburn, NSW 2565, Australia.

Marco Viti, Ital. Marco Viti Farmaceutici S.p.A., Via Mentana 38, 36100 Vicenza (VI), Italy.

Marcofina, Hong Kong. See *C & L, Hong Kong.*

Marel, Neth. Marel BV, Leiden, Netherlands.

Marfarma, Ital. Marfarma Holding SpA, Via Balestrieri 6, 20154 Milan (MI), Italy.

Margalit, Israel. Margalit, P.O. Box 16666, Tel Aviv 61166, Israel.

Marien, Austria. See *Marien, Ger.*

Marien, Ger. Marien-Apotheke Prien am Chiemsee, Marktplatz 10, 83209 Prien, Germany.
url: www.marien-prien.de

Marin, USA. AG Marin Pharmaceuticals, 1730 N W 79th Avenue, Miami, FL 33126, USA.

Marinex, Pol. Marinex International, ul. Placowa 4, 93-446 Łódź, Poland.
url: www.marinex.com.pl

Marion Merrell, Pol. See *Sanofi-Aventis, Pol.*

Marion Merrell Dow, USA. See *Sanofi-Aventis, USA.*

Marjan, Braz. Marjan Indústria e Comércio Ltda, Rua Gibraltar 165, 04755-070 São Paulo, SP, Brazil.
url: www.marjan.com.br

Marketlink, Philipp. Marketlink International Corp., 4/F The Taipan Place, Emerald Ave, Ortigas Ctr, Pasig City, Philippines.

Markos-Mefar, Ital. Markos-Mefar SpA, Via dei Prati 62, 25073 Bovezzo (BS), Italy.

Marlborough Pharmaceuticals, UK. Marlborough Pharmaceuticals, P.O. Box 2957, Marlborough, Wiltshire, SN8 1WS, UK.

Marlin, USA. Marlin Industries, P.O. Box 560, Grover Beach, CA 93483-0560, USA.

Marlop, USA. Marlop Pharmaceuticals Inc., 230 Marshall St., Elizabeth, NY 07206, USA.

Marlyn, Hong Kong. See *Great Liaison, Hong Kong.*

Marlyn, USA. Marlyn Nutraceuticals Inc., 4404 E. Ellwood, Phoenix, AZ 85040, USA.
url: www.naturally.com

Marmir, Pol. Marmir Sp. zo.o., ul. Witomińska 10, 81-311 Gdynia, Poland.

Marnel, USA. Marnel Pharmaceuticals Inc., 206 Luke Drive, Lafayette, LA 70506, USA.

Mars, Philipp. See *Pasteur, Philipp.*

Mars, UK. Mars Ltd, Dundee Rd, Slough, Berkshire, SL1 4JX, UK.

Martin, Arg. Drogueria Martin S.A., Roque Perez 2543, 1430 Buenos Aires, Argentina.

Martin, Cz. See *Martin-Johnson & Johnson, Fr.*

Martin, Pol. See *Janssen-Cilag, Pol.*

Martin, Spain. B Martin Pharma, Ochandiano 10, 28023 Madrid, Spain.

Martin, Switz. See *Uhlmann-Eyraud, Switz.*

Martin & Harris, India. Martin & Harris, India.

Martindale, Hong Kong. See *LCH, Hong Kong.*

Martindale Pharmaceuticals, UK. Martindale Pharmaceuticals Ltd, Hubert Rd, Brentwood, Essex, CM14 4LZ, UK.
url: www.martindalepharma.co.uk

Martinez Llenas, Spain. Martinez Llenas, Afueras del Barrio de Santa Ines S/N, La Roca del Valles, 08430 Barcelona, Spain.

Martin-Johnson & Johnson, Fr. Laboratoires Martin-Johnson & Johnson-MSD, 1 rue Camille-Desmoulins, TSA 20005, 92797 Issy-les-Moulineaux cdx 9, France.
url: www.proktos.com

Martins & Fernandes, Port. A. Martins & Fernandes, SA, Rua Raul Mesnier du Ponsard 4-B, 1750-243 Lisbon, Portugal.

Martyn, S.Afr. A Martyn Sentinel Drug Store, 128 Smith St, Durban, South Africa.

Maruho, Jpn. Maruho Co. Ltd, 1-5-22 Nakatsu, Kita-ku, Osaka 531-0071, Japan.

Maruishi, Jpn. Maruishi Pharmaceutical Co. Ltd, 2-4-2 Imazunaka, Tsurumi-ku, Osaka 538-0042, Japan.

Maruko, Jpn. Maruko Pharmaceutical Co. Ltd, 5-17 Kodama 1-Chome, Nishi-ku, Nagoya 451-0066, Japan.
url: www.maruko-pharm.co.jp

Marvecs, Ital. Marvecs Services Srl, Via Paracelso 26, 20041 Agrate Brianza, Italy.

Marvel, Rus. Marvel Farm, 3-i Krasnoselskii per. 19, str. 4, et. 5, 107140 Moscow, Russia.

Masa, Thai. Masa Lab Co. Ltd, 50/25 Soi Thongpan 2, Takham Rd, Bangkunthien, Bangkok 10150, Thailand.

Mascia Brunelli, Ital. Mascia Brunelli S.p.A., Viale Monza 272, 20128 Milan, Italy.

Mason, USA. Mason Pharmaceuticals Inc., 4425 Jamboree, Suite 250, Newport Beach, CA 92660, USA.

Masta, UK. Masta Ltd, Moorfield Rd, Yeadon, Leeds, West Yorkshire, LS19 7BN, UK.
url: www.masta.org

Mastelli, Ital. Mastelli S.r.l., Via Bussana Vecchia 32, 18032 San Remo (IM), Italy.
url: www.mastelli.com

Master, Chile. Laboratorio Farmaceutico Master SA, Av. Irarrazaval 2821, Torre A, Of. 1001, Santiago, Chile.

Master Pharma, Ital. Master Pharma S.r.l., Via G Chiesi 1, 43100 Parma, Italy.

Masterlek, Rus. Masterlek ZAO, 1-a Volkonskii per. d.11, Str. 2, 103473 Moscow, Russia.
url: www.masterlek.ru

Masters, Pol. See *Miralex, Pol.*

Masters, UK. Masters Pharmaceutical Ltd, Masters House, 5 Sandridge Close, Harrow, Middlesex, HA1 1TW, UK.
url: www.mastersint.com
Masu, Thai. Masu Co Ltd, 9 Fl, MBK Tower, 444 Phayathai Rd, Bangkok 10330, Thailand.
Materfarma, Port. Materfarma Produtos Farmacêuticos SA, Edifício Botânico, Rua do Campo Alegre 1306 - 3, Sala 310, 4150-174 Porto, Portugal.
Matrix, USA. See *Chiron, USA.*
Mauermann, Cz. See *Mauermann, Ger.*
Mauermann, Ger. Mauermann-Arzneimittel, Franz Mauermann oHG, Heinrich-Knote-Str. 2, 82343 Pocking, Germany.
Maurinho, Arg. Laboratorio Mauriño Hnos, 9 de Julio 245, 1708 Moron, Buenos Aires, Argentina.
Maurino, Arg. Laboratorio Maurino Hnos., 9 de Julio 245, 1708 Moron, Buenos Aires, Argentina.
Mavena, Ger. Mavena GmbH, Haubachstrasse 33, 10585 Berlin, Germany.
url: www.mavena.com
Mavena, Switz. Mavena Health Care AG, Haselstrasse 1, 5401 Baden, Switzerland.
url: www.mavena.com
Maver, Chile. Laboratorios Maver SA, Emilio Vaisse 574, Providencia, Santiago, Chile.
Maver, Mex. Productos Maver S.A. de C.V., Av. Oleoducto No. 2804, Fracc. Industrial El Alamo, 44490 Tlaquepaque, Jalisco, Mexico.
Mavi, Ital. Mavi Sud S.r.l., V.le dell'Industria 1, 04011 Aprilia (LT), Italy.
url: www.mavicosmetics.it
Mavi, Mex. Productos Mavi S.A. de C.V., Osa Menor 197, Col. Prado Churubusco, Deleg. Coyoacan, 04230 Mexico D.F., Mexico.
Max Farma, Ital. See *Uno, Ital.*
Maxfarma, Spain. Maxfarma, Salamanca 13, 28020 Madrid, Spain.
Maxi, Thai. Maxi Medical Drug (Mahavej), 27 Paholyothin 41, Bangkok 10900, Thailand.
Maxim, Thai. Maxim Intercontinental Ltd Part, 640/56-57 Petchburi 22 Rd, Rajthevi, Bangkok 10400, Thailand.
Maxmedic, Ger. MaxMedic Pharma GmbH & Co. KG, Amalienstr. 71, 80799 Munich, Germany.
url: www.maxmedic.de
May & Baker, UK. See *Sanofi-Aventis, UK.*
Mayne, Austral. Mayne Pharma P/L, Level 6, 390 St Kilda Road, Melbourne, VIC 3004, Australia.
url: www.maynegroup.com
Mayne, Belg. Mayne Pharmaceuticals SA, Rue de Trois Arbres 16, 1180 Brussels, Belgium.
url: www.maynepharma.com
Mayne, Canad. Mayne Pharma (Canada) Inc., 18100 aut. Transcanadienne, Montreal, Quebec, H9J 4A1, Canada.
Mayne, Cz. See *Mayne, UK.*
Mayne, Denm. Mayne Pharma Danmark, Universitetsparken 7, 4000 Roskilde, Denmark.
Mayne, Fin. See *Berren, Fin.*
Mayne, Hong Kong. Mayne Pharma (HK) Ltd, Unit 3A, 16/F Eastwood Ctr, 5A Kung Ngam Village Rd, Shaukeiwan, Hong Kong.
url: www.maynepharma.com
Mayne, Irl. Mayne Pharma (Ireland) Ltd, Unit 31A, Ravensrock Rd, Sandyford Industrial Estate, Foxrock, Dublin 18, Ireland.
url: www.maynepharma.com
Mayne, Ital. Mayne Pharma (Italia) gia Faulding Farmaceutici Srl, Via Fiorelli 12, 80121 Naples, Italy.
Mayne, Malaysia. Mayne Pharma (Malaysia) Sdn Bhd, Suite 201, 1st Fl, Wisma Glomac 3, Kompleks Kelana Centre Point, Jln SS 7/19, 47301 Petaling Jaya, Selangor, Malaysia.
url: www.maynepharma.com
Mayne, Mex. Mayne Pharma Mexico SA de CV, Av. Insurgentes sur 800 Piso 8, 3100 Del Valle, Mexico DF, Mexico.
Mayne, NZ. Mayne Pharma Pty Ltd, P.O. Box 17055, Karori, Wellington, New Zealand.
Mayne, Port. Mayne Pharma (Portugal) Lda, Rua Amália Rodrigues 240, 2750-228 Cascais, Portugal.
Mayne, Singapore. Mayne Pharma (Sea) Pte Ltd, 70 Bendemeer Rd, 04-02 Hiap Huat House, S 339940, Singapore.
url: www.maynegroup.com
Mayne, Spain. Mayne Pharma, Alberto Alcocer 7, 28036 Madrid, Spain.
url: www.maynepharma.com
Mayne, Swed. Mayne Pharma (Nordic)AB, Box 34 116, 100 26 Stockholm, Sweden.
url: www.maynegroup.com
Mayne, Thai. See *Indochina Healthcare, Thai.*
Mayne, UK. Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK.
url: www.maynepharma.com
Mayne, USA. Mayne Pharma (USA) Inc., 650 From Rd, Mack-Cali Centre II, Second Floor, Paramus, NJ 07652, USA.
url: www.us.maynepharma.com
Mayo, Mex. Laboratorios Mayo S.A. de C.V., Av. Hidalgo 1337, 44160 Guadalajara, Jalisco, Mexico.
Mayoly Spindler, Pol. See *Perffarma, Pol.*
Mayoly-Spindler, Cz. See *Mayoly-Spindler, Fr.*
Mayoly-Spindler, Fr. Laboratoires Mayoly-Spindler, 6 av de l'Europe, 78400 Chatou, France.
Mayoly-Spindler, Malaysia. See *Antah, Malaysia.*
Mayoly-Spindler, Mex. Mayoly Spindler de Mexico SA de CV, Búfalo 27 Piso 1, 3100 Benito Juárez del Valle, Mexico.
Mayoly-Spindler, Rus. See *Pro.Med, Rus.*
Mayoly-Spindler, Singapore. See *Polymedic, Singapore.*
Mayoly-Spindler, Switz. See *Uhlmann-Eyraud, Switz.*
Mayoly-Spindler, Thai. See *Charoen, Thai.*
Maypo, Mex. Farmacéuticos Maypo SA de CV, Mexico.
Mayrhofer, Austria. Mayrhofer Pharmazeutika, Melissenweg 15, A-4021 Linz, Austria.
Mayrs, Irl. David Mayrs Ltd, Broombridge Industrial Estate, Dublin 11, Ireland.
MBD, Singapore. MBD Marketing (S) Pte Ltd, 371 Beach Rd, 03-30 KeyPoint, S 199597, Singapore.
MBP, Ger. Medical Biomaterial Products GmbH, Lederstr. 7, 19306 Neustadt-Glewe, Germany.
url: www.mbp-gmbh.de
MC, Ital. MC S.r.l. Off. Prod. Presidi Medico Chirurgici, S.S. 106, 89040 Portigliola (RC), Italy.
McCaughey, Canad. McCaughet Consumer Products Management Inc., 3228 South Service Rd, Suite 203, Burlington, Ontario, L7N 3H8, Canada.
url: www.mcprti.com
McGaw, USA. See *Braun, USA.*
McGhan, Ger. McGhan Medical GmbH, Hansaallee 201, 40549 Dusseldorf, Germany.
url: www.mcghan.com
McGhan, Hong Kong. See *Onstrong, Hong Kong.*
McGloin, Austral. J. McGloin P/L, P.O. Box 294, Kings Grove, NSW 2208, Australia.
McGuff, USA. McGuff Pharmaceuticals Inc., 2921 W. MacArthur Blvd, Santa Ana, CA 92704, USA.
url: www.mcguffpharmaceuticals.com
McHenry, USA. McHenry Labs Inc., 1402 Caldwell Lane, Smithville, TX 78957, USA.
url: www.ora5.com
McNeil, Cz. See *McNeil, UK.*
McNeil, Fr. McNeil, France.
McNeil, Ger. McNeil GmbH & Co OHG, Rhöndorfer Str. 80, 53604 Bad Honnef, Germany.
url: www.mcneil-pharma.de
McNeil, Hong Kong. See *Jacobson, Hong Kong,* and *Janssen, Hong Kong.*
McNeil, Ital. McNeil Srl, Via M Buonarroti 23, 20093 Cologno Monzese (MI), Italy.
McNeil, Neth. McNeil BV, Dr Paul Janssenweg 150, 5026 RH Tilburg, Netherlands.
McNeil, Spain. McNeil Iberica, Antigua Ctra Barcelona Km 32.800, Alcalá de Henares, 28805 Madrid, Spain.
McNeil, UK. McNeil Ltd, Enterprise House, Station Rd, Loudwater, High Wycombe, Buckinghamshire, HP10 9UF, UK.
McNeil, USA. RA McNeil Co, 1210 E Dallas Rd, Chattanooga, TN 37405, USA.
McNeil Consumer, Canad. McNeil Consumer Healthcare, 890 Woodlawn Rd W., Guelph, Ontario, N1K 1A5, Canada.
url: www.mcneilcanada.com
McNeil Consumer, USA. McNeil Consumer & Specialty Pharmaceuticals, Camp Hill Rd, Fort Washington, PA 19034, USA.
url: www.tylenol.com
McNeil Pharmaceutical, USA. See *Ortho McNeil, USA.*
MCR, USA. MCR American Pharmaceuticals, 16206 Flight Path Drive, Brooksville, FL 34604, USA.
url: www.mcramerican.com
MD, Singapore. MD Pharmaceuticals Pte Ltd, 896 Dunearn Rd, 04-03 Sime Darby Centre, S 589472, Singapore.
MD Vision, Fr. MD Vision, ZA Les-Hauts-de-Lafourcade, 32201 Gimont, France.
MDA, Austral. MDA Pharma, 28 Park St, Mona Vale, NSW 2103, Australia.
MDE, UK. MDE Diagnostic Ltd, The Surrey Technology Centre, Surrey, GU2 7YG, UK.
url: www.mdediagnostic.co.uk
MDI, S.Afr. MDI, South Africa.
MDM, Fr. MDM, 9 rue Brezin, 75014 Paris, France.
MDM, Ital. MDM S.p.A., Via Volturno 29/B, 20052 Monza (MI), Italy.
url: www.mdmspa.com
MDR, USA. MDR Fitness Corp., 14101 NW 4th St, Sunrise, FL 33325, USA.
url: www.mdr.com
MDS, Belg. MDS Nordion SA, Zoning Industriel, Ave de l'Espérance, 6220 Fleurus, Belgium.
url: www.mds.nordion.com
MDS, Cz. See *MDS, Belg.*
MDS, Neth. See *MDS, Belg.*
MDS, Port. See *MDS, Belg.*
MDS Diagnostics, NZ. MDS Diagnostics, P.O. Box 24-162, Royal Oak, Auckland, New Zealand.
url: www.mdsdiagnostics.com
ME Pharmaceuticals, USA. ME Pharmaceuticals Inc., 2800 Southeast Parkway, Richmond, IN 47374, USA.
Mead Johnson, Austral. See *BMS, Austral.*
Mead Johnson, Braz. See *BMS, Braz.*
Mead Johnson, Chile. See *BMS, Chile.*
Mead Johnson, Fr. See *BMS, Fr.*
Mead Johnson, Gr. See *BMS, Gr.*
Mead Johnson, Hong Kong. See *BMS, Hong Kong.*
Mead Johnson, Indon. Mead Johnson Nutritional Division, Tamara Ctr 11/F, Jl Jend Sudiman Kav 24, 12920 Jakarta, DKI Jaya, Indonesia.
Mead Johnson, Irl. See *BMS, Irl.*
Mead Johnson, Israel. See *BMS, Israel.*
Mead Johnson, Ital. See *BMS, Ital.*
Mead Johnson, Malaysia. See *Diethelm, Malaysia.*
Mead Johnson, NZ. See *BMS, NZ.*
Mead Johnson, Philipp. Mead Johnson (Phil) Inc., 2309 Pasong Tamo Ext, Makati City, Philippines.
Mead Johnson, Pol. See *BMS, Pol.*
Mead Johnson, Port. See *BMS, Port.*
Mead Johnson, Singapore. See *Diethelm, Singapore.*
Mead Johnson, Venez. See *BMS, Venez.*
Mead Johnson Nutritionals, Canad. Mead Johnson Nutritionals, Division of Bristol-Myers Squibb Canada Inc., 333 Preston Ave, Suite 700, Ottawa, Ontario, K1S 5N4, Canada.
url: www.meadjohnson.ca
Mead Johnson Nutritionals, Fin. Mead Johnson Nutritionals, Metsänneidonkuja 8, 02130 Espoo, Finland.
url: www.meadjohnson.nu
Mead Johnson Nutritionals, Thai. See *BMS, Thai.*
Mead Johnson Nutritionals, UK. See *BMS, UK.*
Mead Johnson Nutritionals, USA. Mead Johnson Nutritionals, 2400 W Lloyd Expressway, Evansville, IN 47721-0001, USA.
url: www.meadjohnson.com
Meadow, UK. Meadow Laboratories, 18 Avenue Rd, Chadwell Heath, Romford, Essex, RM6 4JF, UK.
Mebo, Thai. See *Diethelm, Thai.*
Meckel, Ger. Meckel-Spenglersan GmbH, Steinfeldweg 13, 77815 Buhl, Germany.
url: www.spenglersan.de
Mecom, Rus. See *Abdi, Rus.*
Mecom, Turk. See *Abdi, Turk.*
Mecosin, Indon. Mecosin Indonesia PT, Jl Palmerah Utr 14-A, 11480 Jakarta, Indonesia.
Med, Turk. Med-İlaç San. ve Tic. A.Ş., Bankalar Cad. Bozkurt Han 19/4, Karaköy, İstanbul, 34420, Turkey.
url: www.medilac.com.tr
Med Immune, Hong Kong. See *Abbott, Hong Kong.*
Med. Prod. Panam., USA. Medical Products Panamericana Inc., 647 W Flagler St, Miami, FL 33130, USA.
Meda, Belg. Meda Pharma, Chaussée de la Hulpe 166, B-1170 Brussels, Belgium.
url: www.medapharma.be
Meda, Cz. Meda Pharma sro, Kodaòská 1441/46, 100 10 Praha 10, Czech Republic.
url: www.meda.se
Meda, Denm. Meda AS, Solvang 8, 3450 Allerod, Denmark.
url: www.meda.dk
Meda, Fin. Meda Oy, Lemminkäisenkatu 32, 20520 Turku, Finland.
url: www.meda.fi
Meda, Fr. Meda Pharma, 25 bd Amiral-Bruix, 75116 Paris, France.
url: www.meda.se
Meda, Ger. Meda GmbH, Otto-von-Guericke-Ring 9, 65205 Wiesbaden, Germany.
Meda, Gr. See *Meda, Swed.*
Meda, Hung. Meda Pharma Hungary Kft, Váci ú 91, 1139 Budapest, Hungary.
url: www.medapharma.com
Meda, Irl. See *Meda, UK.*
Meda, Neth. See *Meda, Swed.*
Meda, Norw. Meda A/S, Bjerkas Industriomrade, 3470 Slemmestad, Norway.
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Meda, Pol. Meda Pharmaceuticals Sp. zo.o., al. Jana Pawła II 15, 00-828 Warsaw, Poland.
Meda, Port. Meda Pharma - Produtos Farmacêuticos S.A., Ruo do Centro Cultural 13, 1749-066 Lisbon, Portugal.
Meda, Spain. See *Meda, Swed.*
Meda, Swed. Meda AB, Box 906, 170 09 Solna, Sweden.
url: www.meda.se
Meda, Switz. Meda Pharma GmbH, Hegnaustrasse 60, 8602 Wangen, Switzerland.
url: www.meda.se
Meda, Thai. See *Zuellig, Thai.*
Meda, UK. Meda Pharmaceuticals, Building 2000, Beach Drive, Cambridge Research Park, Cambridge, Cambridgeshire, CB5 9PD, UK.
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Medac, Arg. Medac Farmaceutica S.A., Heredia 553, Buenos Aires, Argentina.
Medac, Austria. See *Medac, Ger.*
Medac, Cz. See *Medac, Ger.*
Medac, Denm. See *Medac, Swed.*
Medac, Fin. Medac, Jorvas High Tech Center, Hirsalantie 11, 02420 Kirkkonummi, Finland.
url: www.medac.se
Medac, Ger. medac Gesellschaft für klinische Spezialpräparate mbH, Theaterstr. 6, 22880 Wedel, Germany.
url: www.medac.de
Medac, Gr. See *Biochem, Gr.*
Medac, Hung. See *Medac, Ger.*
Medac, Neth. See *Medac, Ger.*
Medac, Norw. See *Medac, Swed.*
Medac, Pol. medac GmbH Sp. zo.o., Przedstawicielstwo w Polsce, ul. Władysława 14, 02-066 Warsaw, Poland.
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Medac, Port. See *Medac, Ger.*
Medac, Rus. See *Schering, Rus.*
Medac, Spain. See *Medac, Ger.*
Medac, Swed. Medac, Box 120, 432 23 Varberg, Sweden.
url: www.medac.se
Medac, UK. Medac UK, 13 Lynedoch Crescent, Glasgow, G36 6EQ, UK.
Medacta, Ital. Medacta Italia Srl, Via G Stephenson 94, 20157 Milan, Italy.
Medagro, Pol. Medagro International Sp. zo.o., ul. Podleśna 83, 05-552 Łazy, Poland.
url: www.medagro.com.pl
Medana, Cz. See *Medana, Pol.*
Medana, Pol. Medana Pharma Terpol Group SA, ul. Warcka 3, 98-200 Sieradz, Poland.
url: www.terpol.pl
Medana, Rus. See *Polpharma, Rus.*
Medarex, USA. Medarex Inc., 707 State Rd, Princeton, NJ 08540, USA.
url: www.medarex.com
Med-Care, Turk. Med-Care Kimya San. ve Tic. Ltd. Şti., Gümüşsuyu Dümen Sok., Gümüşpalas Apt. No: 1/6, Taksim, İstanbul, 80090, Turkey.
Medchem, S.Afr. Medchem Pharmaceuticals (Pty) Ltd, P.O. Box 36014, Menlo Park 0102, South Africa.
Medco, USA. Medco Laboratories Inc., P.O. Box 864, Sioux City, IA 51102-0864, USA.
url: www.medcolab.com
Medconsult, NZ. Medconsult Services Ltd, P.O. Box 35-927, Browns Bay, Auckland, New Zealand.
Medcor, Neth. Medcor Pharmaceuticals BV, Ketelmeerstraat 142-144, 8226 JX Lelystad, Netherlands.
Med-Derm, USA. See *Crown, USA.*
Medea, Spain. See *Reig Jofre, Spain.*
Medeca, Swed. Medeca Pharma AB, Box 24005, 750 24 Uppsala, Sweden.
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Medefield, Austral. Medefield P/L, 6 Gundah Rd, Mt Kuring-Gai, NSW 2080, Australia.
Medela, Canad. Medela Canada Inc., 4090B Sladeview Cres., Unit 2, Mississauga, Ontario, L5L 5Y5, Canada.
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Medentech, Israel. See *Concept, Israel.*
Mederis, Malaysia. Mederis Sdn Bhd, c7-8 Megan Ave 1, 189 Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia.
url: www.mederis.com.my
Medestea, Ital. Medestea Reasearch & Production S.r.l., Via Ribes, 10010 Colleretto Giacosa, Italy.
Medeus, Malaysia. See *Summit, Malaysia.*
Medeus, Spain. See *Zeneus, Spain.*
Medeva, Cz. See *Celltech, UK.*
Medeva, Israel. See *Margalit, Israel.*
Medevale, Cz. Medevale Pharmaservices Ltd, Czech Republic.
Medex, Cz. Medex Praha, Radlická 61, 150 00 Prague 5, Czech Republic.
Medexus, Canad. Medexus Inc., 7895 Tranmere Dr, Unit 4, Mississauga, Ontario, L5S 1V9, Canada.
url: www.medexus.ca
MedGen, Philipp. See *MG, Philipp.*
Medgenix, Belg. Medgenix Benelux SA, Vliegveld 21, 8560 Wevelgem, Belgium.
Medhaus, Philipp. Medhaus Pharma Inc., 139 K 1st St, Kamuning, Quezon City, Philippines.
Medhouse, Swed. Medhouse AB, Upplandsgatan 2B, 111 23 Stockholm, Sweden.
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Medi Challenge, S.Afr. Medi Challenge (Pty) Ltd, 1st Floor, Barvic House North, 4 Burke St., Kensington B, Randburg 2125, South Africa.
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Medialyse, Cz. See *Medialyse, Gr.*
Medialyse, Gr. Medialyse SA, 38 Sorou Str, 15125 Marousi, Greece.
Mediam, Fr. Mediam, 46 rue Desire Verhaege, 59155 Faches-Thumenil, France.
Mediam, Neth. See *Mediam, Fr.*
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Medibase, Ital. Medibase S.r.l., Via della Selva 4, 59021 Vaiano (PO), Italy.
url: www.medibase.it
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Medibios, India. Medibios Labs. Pvt Ltd, 107 Mangalam, Kulupwadi, Mumbai 400 066, India.
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Medibrands, Israel. Medibrands, P.O. Box 531, Yokneam 20692, Israel.
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Medic, Braz. Medic Industrial Farmacêutica Ltda, Rua Conselheiro Mayrink 362, 20960-140 Rio de Janeiro, RJ, Brazil.
Medic, Denm. Medic Team a/s, Blokken 31 (postboks 193), 3460 Birkerød, Denmark.
url: www.medic-team.dk
Medic, NZ. Medic Corp. Ltd, Private Bag, Lower Hutt, Wellington, New Zealand.

Medica, Arg. Cosmética Médica, Carabobo 13, 1406 Buenos Aires, Argentina.

Medica, NZ. Medica Pacifica Ltd, P.O.Box 24-421, Royal Oak, Auckland, New Zealand.
url: www.medica.co.nz

Medica Korea, Hong Kong. See *Ebewe, Hong Kong.*

Medica Korea, Malaysia. See *Zyfas, Malaysia.*

Medica Korea, Philipp. See *Metro, Philipp.*

Medica Korea, Singapore. See *Zyfas, Singapore.*

Medica Pedia, Philipp. See *Zuellig, Philipp.*

Medic+Aid, Philipp. Medi+Aid Distributors Inc., 202 Elco Bldg, E Rodriguez Ave, Quezon City, Philippines.

Medical, Arg. Química Medical Arg. S.A.C.I., Int. Amaro Avalos 4208, 1605 Munro, Buenos Aires, Argentina.

Medical, Port. See *Gestafarma, Port.*

Medical, Spain. Medical, Manuel Concha Ruiz 1, 14012 Cordoba, Spain.
url: www.laboratoriosmedical.com

Medical Consulting, Hung. Medical Consulting Ltd, Hunfalvy u 8, 1015 Budapest, Hungary.

Medical Developments, Austral. Medical Developments Australia P/L, 7/56 Smith Rd, Springvale, VIC 3171, Australia.

Medical Diagnostics, UK. See *MDE, UK.*

Medical Industries, Austral. Medical Industries Australia P/L, 148-52 Regent St, Redfern, NSW 2016, Australia.
url: www.medind.com.au

Medical Instruments, Switz. Medical Instruments Corp., P.O. Box 706, 4502 Solothurn, Switzerland.

Medical Nutrition, USA. Medical NUtrition, 10 West Forest Ave, Englewood, NJ 07531, USA.
url: www.pbsnutrition.com

Medical Ophthalmics, USA. Medical Ophthalmics Inc., 40146 U.S. Hwy 19 N, Tarpon Springs, FL 34689, USA.
url: www.medicalophthalmics.com

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Medical Supply, Thai. Medical Supply Co. Ltd, 101 Sribumpen Rd, Yannawa, Bangkok 10120, Thailand.

Medicaland, Port. Medicaland Lda, Av. de Roma 30, 3 Dto, 1000-266 Lisbon, Portugal.

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Medicalia, Spain. Medicalia, Recoletos 19, 28000 1 Madrid, Spain.

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Medican, Canad. Medican Pharma Inc., 1120 Victoria St N, Suite 203, Kitchener, Ontario, N2B 3T2, Canada.

Medicap, Hong Kong. See *IDS, Hong Kong.*

Medicap, Rus. See *Mega, Rus.*

Medicap, Thai. See *Neopharm, Thai.*

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Medice, Hung. See *Medice, Ger.*

Medice, Neth. See *Medice, Ger.*

Medichem, Hong Kong. See *Unam, Hong Kong.*

Medichem, Indon. See *Medifarma, Indon.*

Medichem, Malaysia. See *Unam, Malaysia.*

Medichem, Philipp. Medichem Pharmaceuticals Inc., 6/F Dynavision Bldg, Rada St, Legaspi Vill, Makati City, Philippines.

Medichem, Singapore. See *Far East, Singapore.*

Medichemie, Switz. Medichemie AG, Bruhlstrasse 50, 4107 Ettingen, Switzerland.

MedicHerb, UK. See *Schwabe, UK.*

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Medicine & Business, Hung. Medicine & Busines Kft, Zrinyi u 21, 1039 Budapest, Hungary.

Medicine Products, Thai. See *Medicine Supply, Thai.*

Medicine Supply, Thai. Medicine Supply Co. Ltd, 77/11 Moo 4, Petchkasem Rd, Thatamnak, Nakhonchaisri, Nakhonpathom 73120, Thailand.

Medicines Company, Denm. See *Nycomed, Denm.*

Medicines Company, Gr. The Medicines Company, Greece.

Medicines Company, Hung. See *Medicines Company, UK.*

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Medicines Company, UK. The Medicines Company, Suite B, Park House, 11 Milton Park, Abingdon, Oxfordshire, OX14 4RS, UK.
url: www.themedicinescompany.com

Medicines Company, USA. The Medicines Company, 8 Campus Drive, Parsippany, NJ 07054, USA.
url: www.themedicinescompany.com

Medicis, Canad. Medicis Canada Ltd, 355 McCaffrey St, St-Laurent, Quebec, H4T 1Z7, Canada.

Medicis, USA. Medicis Pharmaceutical Corp., 8125 N Hayden Dr., Scottsdale, AZ 85258-2463, USA.
url: www.medicis.com

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Medico-Biological Laboratories, UK. Medico-Biological Laboratories Ltd, Kingsend House, 44 Kingsend, Ruislip, Middlesex, HA4 7DA, UK.

Medicom, Cz. Medicom International sro, Pateřni 7, 635 00 Brno - Bystrc, Czech Republic.

Medicom, Neth. See *Medicom, UK.*

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Medicone, USA. Medicone Co., USA.

Medicopharm, Austria. Medicopharm Dr H Sorgo GmbH, Thimiggasse 25, A-1180 Vienna, Austria.

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Medidata, Malaysia. Medidata Sdn Bhd, 36 Jln PJS 8/6, Sunway Mentari, 46150 Petaling Jaya, Selangor, Malaysia.

Mediderm, Chile. See *Recalcine, Chile.*

Medifarm, Turk. Medifarm, Turkey.

Medifarm, Venez. Medifarm, C.A. Inversiones y Representaciones, C.C.Caroni-Modulo B11 Av. Caurimare, Colinas de Bello Monte, Caracas, Venezuela.

Medifarm A-Derm, Venez. See *Medifarm, Venez.*

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Medifarm Ducray, Venez. See *Medifarm, Venez.*

Medifarma, Indon. Medifarma Lab Inc. PT, Jl Rawagelam V Blok L Kav 11-13, Kawasan Industri Pulogadung, 13920 Jakarta Timur, DKI Jaya, Indonesia.

Medifarma, Mex. Grupo Medifarma S.A. de C.V., Cuanconte No. 7, Col. San Gregorio, Atlapulco Xochimilico, 16600 Mexico D.F., Mexico.

Medifive, Thai. Medifive Pharma Co. Ltd, 51/465-466 Drive-in Square, Soi 3 Ladprao Rd, Klongjan, Bangkok 10240, Thailand.

Medifood, Ital. Medifood Italia S.r.l., Via Balbi 31/1, 16126 Genoa, Italy.
url: www.medifoodonline.com

Medifront, Fin. Medifront Oy, Tykistokatu 6 B, 20520 Turku, Finland.
url: www.medifront.fi

Medigivor, Venez. Corporación Medigivor C.A., Av Ppal Bello Campo, Quinta Alcira N. 83, Chacao 1060, Caracas, Venezuela.

Medihealth, Mex. See *Rhein, Mex.*

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Mediherb, Austral. Mediherb P/L, P.O. Box 713, Warwick, QLD 4370, Australia.
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Medihoney, Austral. Medihoney Pty Ltd, 399 Archerfield Rd, Richlands, 4077 QLD, Australia.
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Medika, Ger. Medika Lizenz Pharmaz. Präparate, Am Alten Weg 20, 82041 Oberhaching, Germany.

Medika, Switz. Medika AG, Industriestrasse 111, 4147 Aesch, Switzerland.
url: www.medika.ch

Medikem, Fr. Laboratoires Medikem, Le Cyrano, Rue Rageneau, B.P. 517, 24100 Bergerac, France.

Medikon, Indon. Medikon Prima Laboratories PT, Jl Talib I No 26, 11140 Jakarta Barat, DKI Jaya, Indonesia.

Medilab, Spain. See *Italfarmaco, Spain.*

Medilat, Gr. Medilat, L. Alexandras 117, 114 75 Athens, Greece.

Mediline, Israel. See *Medibrands, Israel.*

Medilink, Denm. Medilink A/S, Somandshvile Park 1 A, 2960 Rungsted Kyst, Denmark.

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Medilusa, Port. Medilusa Comércio e Indústria de Especialidades Farmacêuticas Lda, Rua Duarte Galvão 13 R/C Esq., 1500-252 Lisbon, Portugal.

Medimar, Gr. Medimar Ltd, 13 Kifisias, 54 655 Thessalonica, Greece.
url: www.medimar.gr

MediMar, UK. See *TK, UK.*

Medimfoods, Venez. Medimfoods Representaciones C.A., Zona Industrial - 2da, Avenida Diag. a Lab. Leti, Edificio Farvenca Guarenas, Caracas, Venezuela.

Medimmune, Denm. See *Schering-Plough, Denm.*

MedImmune, Neth. MedImmune Oncology Inc., Lagelandseweg 78, 6545 CG Nijmegen, Netherlands.

Medimmune, Norw. See *Swedish Orphan, Norw.*

Medimmune, USA. Medimmune Inc., 1 MedImmune Way, Gaithersburg, MD 20878, USA.
url: www.medimmune.com

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Medimpex, Denm. See *Schering, Denm.*

Medimpex, Fr. Medimpex SA, 1-3 rue Caumartin, 75009 Paris, France.

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Medimpex, UK. Medimpex UK Ltd, 127 Shirland Rd, London, W9 2EP, UK.
url: www.medimpexuk.com

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Medimport, Mex. Laboratorios Medimport S.A. de C.V., Via Lactea No. 29, Coyoacan Prado Churubusco, 04230 Mexico D.F., Mexico.

Medimprove, Hung. Medimprove Bt, Dalmady Győző u 12, 1182 Budapest, Hungary.

Mediner, Hung. Mediner Kft, Nagy Lajos király tér 5 I/11, 4032 Debrecen, Hungary.

Medinfar, Port. Laboratório Medinfar, SA, Rua Manuel Ribeiro da Pavia 1 - 1, Venda Nova, 2700-547 Amadora, Portugal.
url: www.medinfar.pt

Medinova, Hong Kong. See *Great Liaison, Hong Kong.*

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Medinova, Singapore. See *Diethelm, Singapore.*

Medinova, Spain. Medinova, C/Collado Mediano S/N, Las Rozas, 28230 Madrid, Spain.

Medinova, Switz. Medinova AG, Eggbuhlstrasse 14, 8052 Zurich, Switzerland.

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Medinteg, Venez. Medinteg C.A., Calle Perez Pisante c/J Juan Diaz Ed. Sani, Piso 2, U.I. Los Tres Puentes Los Teques, Miranda, Venezuela.

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Mediphar, Venez. Mediphar C.A., Calle 3B. Edificio Escachia, Piso 3. Local 3C, La Urbina, Caracas, Venezuela.
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Medipharm, Chile. Medipharm SA, Carrion 1398, Independencia, Santiago, Chile.

Medipharma, Arg. Laboratorios Medipharma S.A., Calle 143 1435 e/61 y 62, 1900 La Plata, Buenos Aires, Argentina.
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Medipharma, Ger. Medipharma Homburg GmbH, Michelinstr. 10, 66424 Homburg, Germany.

Medipharma, Hong Kong. Medipharma Ltd, Hong Kong, Unit 2409, Tsuen Wan Industrial Ctr, 220-248 Texaco Rd, Tsuen Wan, N.T., Hong Kong.

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Medi-Physics, USA. See *Amersham Biosciences, USA.*

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Mediplus, UK. Mediplus Ltd, Unit 7, Cressex Business Park, The Gateway Centre, Coronation Rd, High Wycombe, Buckinghamshire, HP12 3SU, UK.
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Mediquest, Singapore. Mediquest Pte Ltd, 1557 Keppel Rd, 03-02, Inchcape Marketing Building, S-089066, Singapore.

Medi-Radiopharma, Cz. See *Medi-Radiopharma, Hung.*

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Medirex, Port. Medirex Pharma Lda, Rua Manuel Lemos Peixoto 12-B, 2610-110 Alfragide Amadora, Portugal.

Medi-Rx, Philipp. Medi-Rx Inc., 11 Mindanao Ave, Pag-asa, Quezon City, Philippines.

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url: www.delta.is

Medis, Israel. Pharma Medis Co. Ltd, P.O. Box 2820, Holon, Israel.

Medisa, Switz. Medisa AG, Riedstrasse 1, 6330 Cham, Switzerland.

Medisense, Austral. MediSense Products, Abbott Diagnostics Division, 666 Doncaster Rd, Doncaster, VIC 3108, Australia.
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Medisense, UK. See *Abbott, UK.*

Medisint, Ital. Medisint S.r.l., Via Settala 10, 20124 Milan, Italy.

Medison, Israel. Medison Pharma Ltd, P.O. Box 7090, Petach Tikva 49170, Israel.
url: www.medison.co.il

Medisource, Irl. Medisource Ltd, Unit 11, Southern Cross Business Park, Bray, Co. Wicklow, Ireland.
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Medispec, Malaysia. Medispec (M) Sdn Bhd, No 55 & 57 Lorong Sempadan 2, Off Boundary Rd, 11400 Ayer Itam, Penang, Malaysia.
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Medisys, Philipp. Medisys Pharma Inc., 2003 Pres. Quirino Ave, Pandacan, Manila, Philippines.

Meditec, Israel. See *Sam-On, Israel.*

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Meditop, Hung. Meditop Gyógyszeripari Kft, Ady Endre u 1, 2097 Pilisborosjenő, Hungary.
url: www.meditop.hu

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Mediwhite, Ital. Mediwhite Srl, Via del Forte Bravetta 98, 00100 Rome, Italy.

Medix, Fr. Laboratoires Médix, 18 rue Saint-Mathieu, 78550 Houdan, France.

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Medix, Spain. Medix, Alcalá 431, 28027 Madrid, Spain.
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Medi-Zone, Hung. Medi-Zone Pharma Kft, Lovas u 13, 1012 Budapest, Hungary.

Medley, Braz. Medley S.A. Indústria Farmacêutica, Rua Macedo Costa 55, Jardim Santa Genebra, 13080-010 Campinas, SP, Brazil.
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url: www.mlgl.co.uk

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url: www.medochemie.ru

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Medogar, Israel. Medogar, P.O. Box 49170, Petach Tikva 7003, Israel.
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Medopharm, Ger. Medopharm Arzneimittel GmbH & Co. KG, Grunwalderstr. 22, 79098 Freiburg, Germany.
url: www.medopharm.de

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Medosan, Ital. Medosan S.r.l., Industrie Biochimiche Riunite, Via di Cancelliera 12, 00040 Cecchina (RM), Italy.

Medphano, Ger. medphano Arzneimittel GmbH, Maienbergstr. 10, 15562 Rudersdorf, Germany.
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Medpointe, USA. MedPointe Healthcare Inc., 265 Davidson Ave, Suite 300, Somerset, NJ 08873-4120, USA.
url: www.medpointeinc.com

Medpro, S.Afr. See *Cipla-Medpro, S.Afr.*

Medra, Austria. Medra Handels-GmbH, Gastgebgasse 5-13, A-1230 Vienna, Austria.

Medra, NZ. Medra Services, P.O. Box 115, Fielding, New Zealand.

Medreich, Hong Kong. Medreich Far East Ltd, 27/F, 211 Johnston Rd, Wanchai, Hong Kong.
url: www.medreich.com

Medsan, Turk. Medsan İthalat-İhracat İlaç San. ve Tic. A.Ş., Adnan Saygun Cad. No: 8/6, Yenişehir, Ankara, Turkey.
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Medserve, Switz. medServe GmbH, Wollerauerstrasse 60, 8834 Schindellegi, Switzerland.

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Mega Lifesciences, Philipp. Mega Lifesciences Pty Ltd, Unit 4B, 4/F Eurovilla II Bldg, 118 VA Rufino St, Legaspi Vill, Makati City, Philippines.
Mega Lifesciences, Singapore. See *Mega Lifesciences, Thai.*
Mega Lifesciences, Thai. Mega Lifesciences Pty Ltd, 120 Moo 11 Asia Center Bldg, 9th Fl, Bangna-Trad Rd, Bangna, Bangkok 10260, Thailand.
url: www.megawecare.com
Mega Vitamin, Austral. Mega Vitamin Laboratories P/L, 5 Tahlee St, Burwood, NSW 2134, Australia.
Megafyt-R, Cz. Megafyt-R sro, Vrané nad Vltavou, Czech Republic.
Megahealth, Chile. See *Recalcine, Chile.*
Megapha, Singapore. Megapha Pte Ltd, 12 Arumugam Rd, 04-08A Cheng Chwee Huat Industrial Building, S 409958, Singapore.
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Megat, Venez. See *Leti, Venez.*
Meiji, Hong Kong. See *Main Life, Hong Kong.*
Meiji, Indon. Meiji Indonesia PT, Jl Tanah Abang II No 4, 10160 Jakarta Pusat, DKI Jaya, Indonesia.
Meiji, Jpn. Meiji Seika Kaisha Ltd, 2-4-16 Kyobashi, Chuo-ku, Tokyo 104-8002, Japan.
url: www.meiji.co.jp
Meiji, Malaysia. See *Somedico, Malaysia.*
Meiji, Singapore. See *Pharma 2000, Singapore.*
Meiji, Thai. Thai Meiji Pharmaceutical Co. Ltd, 8 Fl, Regent House, 183 Rajdamri Rd, Bangkok 10330, Thailand.
Meizler, Braz. Meizler SA, Alameda Jura 149, Alphaville, 06455-010 Barueri, SP, Brazil.
url: www.meizler.com.br
Mekim, Hong Kong. Mekim Ltd, Room 905, Harbour Centre Tower 2, 8 Hok Cheung St, Hunghom, Kowloon, Hong Kong.
url: www.mekim.com
Mekos, Denm. See *Vitaflo, Denm.*
Mekos, Port. See *Mekos, Denm.*
Melisana, Belg. Melisana SA, Ave du Four à Briques 1, 1140 Brussels, Belgium.
url: www.melisana.be
Melisana, Switz. Melisana AG, Ankerstrasse 53, Postfach, 8026 Zurich, Switzerland.
Mellin, Ital. Mellin, Div. Dietetica Star, Via Matteotti 142, 20041 Agrate Brianza (MI), Italy.
Melora, Port. Melora Portuguesa Produtos Farmacêuticos e Cosméticos Lda, Av. Estados Unidos da América 97, 12 Esq, 1700-167 Lisbon, Portugal.
Memsep, Cz. Memsep sro, Strakonická 1134/13, 150 00 Prague 5, Czech Republic.
Menarini, Arg. Laboratorios Menarini Argentina S.A., Girardot 1689, 1427 Buenos Aires, Argentina.
url: www.menarini.com
Menarini, Austria. See *Menarini, Ital.*
Menarini, Belg. Menarini Benelux SA, Belgicastraat 4, 1930 Zaventem, Belgium.
url: www.menarini.com
Menarini, Cz. See *Berlin-Chemie, Cz.*
Menarini, Fin. Berlin-Chemie Menarini Finland Oy, Rajatorpantie 41 C, 01640 Vantaa, Finland.
Menarini, Fr. Menarini France, 1 rue du Jura, Silic 528, 94633 Rungis cdx, France.
url: www.menarini.com
Menarini, Gr. Menarini Hellas S.A., Constantinoupouleous & Dambergis 7, 104 45 Athens, Greece.
url: www.menarini.com
Menarini, Hong Kong. See *Mekim, Hong Kong.*
Menarini, Hung. See *Berlin-Chemie, Hung.*
Menarini, Indon. See *Dexa, Indon.,* and *Sanbe, Indon.*
Menarini, Irl. A. Menarini Pharmaceuticals Ireland Ltd, 72 York Rd, Dun Laoghaire, Dublin, Ireland.
url: www.menarini.com
Menarini, Ital. A. Menarini Industrie Farmaceutiche Riunite S.r.l., Via Sette Santi 3, 50131 Florence, Italy.
url: www.menarini.com
Menarini, Malaysia. See *Pharmaforte, Malaysia.*
Menarini, Neth. Menarini Farma Nederland, De Bleek 17, 3447 GV Woerden, Netherlands.
url: www.menarini.com
Menarini, Port. A. Menarini Portugal, Farmacêutica SA, Quinta da Fonte, Edificio D Manuel I Piso 2A, Rua dos Malhões 1, 2770-071 Paç de Arcos, Portugal.
url: www.menarini.com
Menarini, Rus. BC Menarini Pharma GmbH, ul. Shabolovka 31, Str. B, 3rd Floor, 115998 Moscow, Russia.
url: www.menarini.com/mondo/russia.htm
Menarini, Singapore. See *Pharmaforte, Singapore.*
Menarini, Spain. Menarini, Alfonso XII 587, Badalona, 08918 Barcelona, Spain.
url: www.menarini.es
Menarini, Swed. Menarini, Sweden.
url: www.menarini.com
Menarini, Switz. A Menarini AG, Eggbuhlstrasse 14, 8026 Zurich, Switzerland.
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Menarini, Thai. See *Biopharm, Thai.*
Menarini, UK. A Menarini Pharma UK srl, Menarini House, Mercury Park, Wycombe Lane, Woburn Green, Buckinghamshire, HP10 0HH, UK.
url: www.menarini.com
Menarini Diagnostics, Fr. A. Menarini Diagnostics, 16 rue Georges-Besse, Silic 46, 92182 Antony cdx, France.
url: www.menarini.fr
Menarini Diagnostics, Port. A. Menarini Diagnósticos Lda, Estrada Nacional 249, Lote 4 - 1, Aboboda, 2785-000 S. Domingos de Rana, Portugal.
Menarini Diagnostics, UK. A. Menarini Diagnostics, Wharfedale Rd, Winnersh, Workingham, Berkshire, RG41 5RA, UK.
url: www.menarini.com
Mendelejeff, Ital. Stabilimento Chimico Farmaceutico Mendelejeff S.r.l., Via Aurelia 58, 00100 Rome, Italy.
Menley & James, USA. Menley & James Laboratories Inc., 100 Tournament Drive, Suite 210, Horsham, PA 19044-3697, USA.
Mennen, USA. See *Colgate-Palmolive, USA.*
Mentholatum, Austral. Mentholatum Australasia P/L, P.O. Box 398, Mulgrave North, VIC 3170, Australia.
url: www.mentholatum.com.au
Mentholatum, Canad. Mentholatum Co. of Canada Ltd, 20 Lewis St, Fort Erie, Ontario, L2A 5M6, Canada.
url: www.mentholatum.ca
Mentholatum, Cz. See *Mentholatum, UK.*
Mentholatum, Hong Kong. Mentholatum Asia Pacific Ltd, 1616-21 Tower 2, Grand Central Plaza, 138 Shatin Rural Committee Rd, Shatin, Hong Kong.
url: www.mentholatum.com.hk
Mentholatum, Hung. Mentholatum, Hungary.
Mentholatum, Israel. See *Mediline, Israel.*
Mentholatum, Pol. See *Nepentes, Pol.*
Mentholatum, S.Afr. Mentholatum South Africa (Pty) Ltd, 80 Bonza Bay Rd, Beacon Bay 5241, South Africa.
url: www.mentholatum.com
Mentholatum, Singapore. See *Diethelm, Singapore.*
Mentholatum, UK. The Mentholatum Co. Ltd, 1 Redwood Ave, Peel Park Campus, East Kilbride, Glasgow, G74 5PF, UK.
url: www.mentholatum.co.uk
Mentholatum, USA. Mentholatum Inc., 707 Sterling Dr., Orchard Park, NY 14127, USA.
url: www.mentholatum.com
Mentiterm, Gr. Mentiterm Farmakeftiki EPE, Greece.
Mento, Turk. Mento, Turkey.
Mepha, Braz. Mepha Inv. Des. e Fab. Farm. Ltda, Est. dos Bandeirantes 4015, 22775-112 Rio de Janeiro, RJ, Brazil.
Mepha, Cz. See *Medimport, Cz.*
Mepha, Hong Kong. See *Ceutical, Hong Kong.*
Mepha, Hung. See *Pharmarex, Hung.*
Mepha, Indon. See *Sunthi Sepuri, Indon.*
Mepha, Israel. See *Gilco, Israel.*
Mepha, Malaysia. See *JDH, Malaysia,* and *Mepharm, Malaysia.*
Mepha, Pol. Mepha Polska Sp. zo.o., ul. Zbożowa 22 H, 20-827 Lublin, Poland.
Mepha, Port. Mepha, Lda, R. Elias Garcia 28 C, Venda Nova, Apartado 6617, 2701-355 Amadora, Portugal.
url: www.mepha.pt
Mepha, Singapore. See *Megapha, Singapore.*
Mepha, Switz. Mepha Pharma AG, Postfach 445, 4147 Aesch/BL, Switzerland.
url: www.mepha.ch
Mepha, Thai. See *Amcron, Thai.*
Mepharm, Malaysia. Mepharm (Malaysia) Sdn Bhd, 15 Jln USJ 1/19, Taman Subang Permal, 47600 Subang Jaya, Selangor, Malaysia.
Mepro, Chile. See *Merck, Chile.*
Meprofarm, Indon. Meprofarm PT, Jl Soekamo Hatta 789, Km 11, Gedebage, 40294 Bandung, Jawa Barat, Indonesia.
Mercian, Cz. See *Mercian, Jpn.*
Mercian, Jpn. Mercian Corporation, Tokyo, Japan.
Merck, Arg. Merck Química Argentina S.A.I.C., Panamericana Plaza Tronador 4890 Piso 5, 1430 Buenos Aires, Argentina.
url: www.merck.com.ar
Merck, Austria. Merck GmbH, Zimbagasse 5, A-1147 Vienna, Austria.
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Merck, Belg. Merck SA, Brusselsesteenweg 288, 3090 Overijse, Belgium.
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Merck, Braz. Merck S.A. Industrias Químicas, Estrada dos Bandeirantes 1099, 22710-571 Rio de Janeiro, RJ, Brazil.
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Merck, Chile. Merck Química Chilena Ltda, Francisco de Paula Taforo 1981, Nunoa, Santiago, Chile.
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Merck, Denm. See *Biomet Merck, Denm.,* and *Nordic Drugs, Denm.*
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Merck, Ger. Merck KGaA, Frankfurter Str. 250, 64271 Darmstadt, Germany.
url: www.medizinpartner.de
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Merck, Hong Kong. Merck Pharmaceutical Ltd, Unit 10-12, 22/F, Paul Y. Ctr, 51 Hung To Rd, Kwan Tung, Hong Kong.
Merck, Hung. Merck Kft, Budafoki út 209/a, 1117 Budapest, Hungary.
Merck, India. Merck (India) Ltd, Shiv Sagar Estate 'A', Dr Annie Besant Rd, Worli, Mumbai 400 018, India.
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Merck, Indon. Merck Indonesia PT, Jl Raya Desa Gedong 8, Pasar Rebo, 13760 Jakarta, DKI Jaya, Indonesia.
Merck, Irl. See *MSD, Irl.*
Merck, Israel. See *Neopharm, Israel.*
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Merck, Malaysia. Merck (Malaysia) Sdn Bhd, 4 Jln U1/26, Section U1, Hicom Glenmarie Industrial Park, 40150 Shah Alam, Selangor, Malaysia.
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Merck, Mex. Merck S.A. de C.V., Calle 5 Num 7, 53370 Naucalpan de Juarez, Mexico.
url: www.merck.com.mx
Merck, Neth. Merck Nederland BV, Basisweg 34, 1043 AP Amsterdam, Netherlands.
url: www.merck.nl
Merck, Norw. See *Biomet Merck, Norw.*
Merck, Philipp. Merck Inc., 24/F GT Tower Intl, 6613 Ayala Ave, cor HV dela Costa St, Salcedo Vill, Makati City, Philippines.
Merck, Pol. Merck Sp. zo.o., ul. Aleje Jerozolimskie 178, 02-486 Warsaw, Poland.
url: www.merck.com.pl
Merck, Port. Merck Genéricos Lda, Rua Alfredo da Silva 3-C, Apartado 3185, 1300-040 Lisbon, Portugal.
url: www.merck.pt
Merck, Rus. See *Nycomed, Rus.*
Merck, S.Afr. Merck Pharmaceuticals (Pty) Ltd, P.O. Box 1998, Halfway House 1685, South Africa.
url: www.merck.com
Merck, Singapore. Merck Pte Ltd, Merck Serono Division, 3 International Business Park, 02-01 Nordic European Centre, S 609927, Singapore.
url: www.merck.com.sg
Merck, Spain. Merck Farma Química, Poligono Merck, Mollet del Valles, 08100 Barcelona, Spain.
url: www.merck.es
Merck, Swed. Merck AB, Pharma Division, Box 23033, 10435 Stockholm, Sweden.
url: www.merck.se
Merck, Switz. Merck (Schweiz) AG, Ruchligstrasse 20, 8953 Dietikon, Switzerland.
url: www.merck.ch
Merck, Thai. Merck Ltd, 19 Fl, Emporium Tower, 622 Sukhumvit Rd, Klongton Klongtoey, Bangkok 10110, Thailand.
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Merck, Turk. Merck İlaç Ecza ve Kimya Tic. Ltd. Şti., Balabandere Cad. No: 2-4, İstinye, İstanbul, 34460, Turkey.
url: www.merck.com.tr
Merck, UK. E. Merck Pharmaceuticals Ltd, Harrier House, High St, West Drayton, Middlesex, UB7 7QG, UK.
url: www.merckpharma.co.uk
Merck, USA. Merck & Co., 1 Merck Dr, White House Station, NJ 08889-1000, USA.
url: www.merck.com
Merck, Venez. Merck S.A., Hans Neumann Ed.Corimon p3, Los Cortijos de Lou., Caracas, Venezuela.
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Merck Bago, Braz. See *Merck, Braz.*
Merck Consumer, Singapore. See *Zuellig, Singapore.*
Merck Consumer, UK. See *Seven Seas, UK.*
Merck dura, Ger. Merck dura GmbH, Postfach: 100635, 64206 Darmstadt, Germany.
url: www.merck-dura.de
Merck Frosst, Canad. Merck Frosst Canada Ltd, P.O. Box 1005, Pointe-Claire, Dorval, Quebec, H9R 4P8, Canada.
url: www.merckfrosst.com
Merck Generiques, Fr. Merck Génériques (Lab), 34 rue Saint-Romain, 69359 Lyon cdx 08, France.
Merck Lipha Sante, Pol. See *Merck, Pol.*
Merck Medication Familiale, Fr. Merck Médication Familiale, 18 C boulevard Winston-Churchill, 21070 Dijon, France.
Merck Sante, Denm. See *Nycomed, Denm.*
Merck Sante, Hong Kong. See *Merck, Hong Kong.*
Merck Sante, Pol. See *Merck, Pol.*
Merck Selbstmedikation, Ger. Merck Selbstmedikation GmbH, Rosslerstrasse 96, 64293 Darmstadt, Germany.
url: www.merckselbstmedikation.de
Merck Serono, UK. Merck Serono, Bedfont Cross, Stanwell Rd, Feltham, Middlesex, TW14 8NX, UK.
Merckle, Cz. See *Ratiopharm, Cz.*
Merckle, Ger. Merckle GmbH, Graf-Arco-Str. 3, 89079 Ulm, Germany.
url: www.merckle.de
Merckle, Rus. See *Ratiopharm, Rus.*
Merck-Lipha, Fr. Merck Lipha Santé, 37 rue St-Romain, 69008 Lyon, France.
url: www.mercksante.fr
Merck-Lipha, Hong Kong. See *Merck, Hong Kong.*
Merck-Lipha, Switz. See *Actipharm, Switz.*
Merck-Theramex, Hong Kong. See *Hind Wing, Hong Kong,* and *Zuellig, Hong Kong.*
Mercury, Philipp. Mercury Drug Corp., 7 Mercury Ave, cor E Rodriguez Jr Ave, Bagumbayan 1110, Quezon City, Philippines.
Meretek, USA. Meretek Diagnostics Inc., 2655 Crescent Drive, Suite C, Lafayette, CO 80026, USA.
url: www.meretek.com
Mergers Drugfil, Philipp. Mergers Drugfil Corp/ Han Seo Pharm, 6/F Golden Rock Bldg, 168 Salcedo St, Legaspi Vill, Makati City, Philippines.
Mericon, Norw. Mericon AS, Postboks 1865 Gulset, 3705 Skien, Norway.
Mericon, USA. Mericon Industries Inc., 8819 N Pioneer Rd, Peoria, IL 61615, USA.
url: www.mericon-industries.com
Meridian, Israel. See *Teva, Israel.*
Meridian, S.Afr. Meridian Pharma, division of Elttab Pharmaceuticals, South Africa.
Meridian, USA. See *King, USA.*
Merind, India. See *Wockhardt, India.*
Merisant, Arg. Merisant Argentina S.R.L., Dardo Rocha 2754 Piso 2 of.2, 1640 Martinez, Buenos Aires, Argentina.
url: www.merisant.com
Merisant, Canad. Merisant Co., 2655 North Sheridan Way, Suite 105, Mississauga, Ontario, L5K 2P8, Canada.
Merisant, Thai. See *Diethelm, Thai.*
Merit, USA. Merit Pharmaceuticals, 2611 San Fernando Rd, Los Angeles, CA 90065, USA.
url: www.meritpharm.com
Merkez, Turk. Merkez Laboratuvarı İlaç San. ve Tic. A.Ş., Çamlık Mah. Ayça Sok. No: 4, Taşdelen, Ümraniye, İstanbul, Turkey.
url: www.merkezlab.com
Mer-National, S.Afr. See *Adcock Ingram, S.Afr.*
Mersifarma, Indon. Mersifarma Tirmaku Mercusana PT, Jl Raya Pasar Minggu Km 18/17, 12510 Jakarta Selatan, DKI Jaya, Indonesia.
Mert, Turk. Mert İlaç San. ve Tic. A.Ş, Hastane Mahallesi Yassı Ören Cadessi, Nakkaş Yolu Hadımköy, İstanbul, Turkey.
url: mertpharma.com
Mertens, Arg. Mertens S.A. Esp. Medicinales, Av. Montes de Oca 1731, 1271 Buenos Aires, Argentina.
Merz, Austria. See *Merz, Ger.*
Merz, Cz. See *Merck, Cz.,* and *Naturprodukt, Cz.*
Merz, Fin. See *Tamro, Fin.*
Merz, Ger. Merz Pharmaceuticals GmbH, Eckenheimer Landstr. 100, 60318 Frankfurt (Main), Germany.
url: www.merz.de
Merz, Hong Kong. See *Weston, Hong Kong.*
Merz, Hung. See *Merz, Ger.*
Merz, Indon. See *Combiphar, Indon.*
Merz, Israel. See *Megapharm, Israel.*
Merz, Malaysia. See *Germax, Malaysia,* and *Summit, Malaysia.*
Merz, Mex. Merz Pharma de Mexico SA de CV, Av. Insurgentes sur 3579 Torre 3 Piso 2, 14020 M Hidalgo la Joya Olimpica, Mexico DF, Mexico.
Merz, Neth. See *Aventis, Neth.*
Merz, Philipp. See *Croma, Philipp.,* and *Zuellig, Philipp.*
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Merz, Rus. Merz Pharma GmbH & Co KGaA, Jamskogo Polja 1-ja ul. d. 9/13,, Of. 503, 125124 Moscow, Russia.
url: www.merz.ru
Merz, Singapore. See *Green Cross, Singapore,* and *Pharma 2000, Singapore.*
Merz, Switz. Merz Pharma (Schweiz) AG, Postfach, 4123 Allschwil, Switzerland.
url: www.merz.ch
Merz, UK. Merz Pharma UK Ltd, 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire, WD6 3SR, UK.
url: www.merzpharma.co.uk
Merz, USA. Merz Pharmaceuticals, P.O. Box 18806, Greensboro, NC 27419, USA.
url: www.merzusa.com
Merz Consumer, Ger. See *Merz, Ger.*
Messer Griesheim, Austria. Messer Griesheim Austria, Gumpoldskirchen, Austria.
Messer Griesheim, Cz. See *Messer Griesheim, Austria.*
Meta, Canad. Meta Pharmaceuticals, 155 Orenda Rd, Brantford, Ontario, L6W 1W3, Canada.
Meta Fackler, Ger. meta Biologische Heilmittel Fackler KG, Philipp-Reis-Str. 3, 31832 Springe, Germany.
url: www.metafackler.de
Metabolic Solutions, USA. Metabolic Solutions Inc., 460 Amherst St, Nashua, NH 03063, USA.
url: www.metsol.com
Metanoia, Fr. Métanoïa, 2 allee Albert-Caquot, 51686 Reims cdx 2, France.

Metapharma, Canad. See *Meta, Canad.*
Metapharma, Ital. Metapharma S.p.A., Viale delle Dalie 26, 00042 Anzio (RM), Italy.
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Methapharm, USA. Methapharm Inc., 117722 West Sample Rd, Suite 101, Coral Springs, FL 33065, USA.
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Metiska, Indon. Metiska Farma PT, Jl Raya Kebayoran Lama No 557, 12220 Jakarta, DKI Jaya, Indonesia.
Metochem, Austria. Metochem-Pharma GmbH, Jochen-Rindt-Strasse 23, A-1230 Vienna, Austria.
Metochem, Cz. See *Metochem, Austria.*
Metrika, USA. Metrika Inc., 510 Oakmead Parkway, Sunnyvale, CA 94085-4022, USA.
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Metro, Philipp. Metro Drug Distribution, Mañalac Ave, Sta Maria Indl Estate, Bagumbayan, Bicutan, Taguig, Metro Manila, Philippines.
Metropolitan, Philipp. Metropolitan Pharmaceutical Products, Philippines.
Met-Rx, USA. MET-Rx Engineered Nutrition, 90 Orville Drive, Bohemia, NY 11716, USA.
url: www.metrx.com
Metz, Philipp. Metz Pharmaceuticals Inc., 27 Sct Bayoran, South Triangle, Quezon City, Philippines.
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Mexin, India. Mexin Medicaments Pvt Ltd, 142-AB Government Industrial Estate, Kandivli (W), Mumbai 400 067, India.
Meyer, Venez. Meyer Productos Terapéuticos S.A., Urb. Ind. Boleíta Norte Calle E, Edif. Meyer, Aptdo. 70008, Caracas 1071-A, Venezuela.
url: www.meyer.com.ve
Meyer Alian, Venez. See *Meyer, Venez.*
Meyer Nature, Venez. See *Meyer, Venez.*
Meyer Zall, S.Afr. Meyer Zall Laboratories (Pty) Ltd, Innovation & Research Building, Nelson Mandela Metropolitan University, Saasveld Road, George 6529, South Africa.
url: www.mzl.co.za
Meyer-Haake, Ger. Meyer-Haake Medical Innovations, Am Joseph 9, 61273 Wehrheim, Germany.
url: www.meyer-haake.de
Meyers, Philipp. Meyers Pharm (Phil) Inc., 176 Roosevelt Ave, San Francisco del Monte, Quezon City, Philippines.
Mezina, Fin. Mezina Oy, Harmaaparrankuja 1, PL 301, 02101 Espoo, Finland.
MG, Philipp. MG Prime Pharmaceuticals Inc., G/F Richmack Bldg, 72 Mindanao Ave, Proj. 6, Quezon City, Philippines.
MGI, Hong Kong. See *Jacobson, Hong Kong.*
MGI, Israel. See *Megapharm, Israel.*
MGI, Malaysia. See *Diethelm, Malaysia.*
MGI, USA. MGI Pharma Inc., 5775 West Old Shakopee Rd, Suite 100, Bloomington, MN 55437-3174, USA.
url: www.mgipharma.com
MH Consulting, Cz. MH Consulting sro, Praha, Czech Republic.
Miba, Ital. Miba Prodotti Chimici e Farmaceutici S.p.A., Via Falzarego 8, 20021 Ospiate di Bollate (MI), Italy.
Mibe, Ger. Mibe GmbH Arzneimittel, Münchener Str. 15, 06796 Brehna, Germany.
Mibe, Neth. See *Mibe, Ger.*
Michallik, Ger. Fritz Osk. Michallik GmbH & Co., Kisslingweg 60, 75417 Mühlacker, Germany.
url: www.michallik.com
Mickan, Ger. Mickan Arzneimittel GmbH, Industriestr. 5, 76189 Karlsruhe, Germany.
url: www.mickan.de
Micro, India. Micro Labs Ltd, 3 Queens Rd, Bangalore 560 001, India.
url: www.microlabsltd.com
Micro, Mex. Micro Pharmaceuticals México S de RL de CV, Guillermo González Camarena 900 Ed Pza S, 1210 Torre B pso 6 Sta De Ctro Ccial, Mexico.
Micro, Philipp. See *Brel, Philipp.*
Micro, S.Afr. Micro, South Africa.
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Microfarm, Pol. Przedsiębiorstwo Produkcyjno-Handlowe Microfarm SC, ul. Krakusa 7, 30-535 Kraków, Poland.
Microgen, Rus. NPO Microgen FGUP, Zubovskii bul'var, d. 4, 119021 Moscow, Russia.
url: www.microgen.ru
Micron, USA. Micron Technology Inc., 800 S Federal Way, Boise, ID 83707, USA.
url: www.micron.com
Microsules, Arg. Microsules Argentina SA, Hipolito Yrigoyen 3771, 1208 Buenos Aires, Argentina.
url: www.microsules.com.ar
Microsules Bernabo, Arg. Microsules y Bernabo S.A., Terrada 2346, 1416 Buenos Aires, Argentina.
url: www.microsulesybernabo.com.ar
Midax, Ital. Midax Italia S.r.l., Via Piave 5, 35010 San Pietro in Gu (PD), Italy.
Middlebrook, USA. Middlebrook Pharmaceuticals, 20425 Seneca Meadows Parkway, Germantown, MD 20876, USA.
url: www.advancispharm.com
Midlothian, USA. Midlothian Laboratories, 5323 Perimeter Parkway Ct., Montgomery, AL 36116-5125, USA.
url: www.midlothianlabs.com
Midro, Ger. Midro Lörrach GmbH, Barenfelser Str. 7, 79539 Lörrach, Germany.
url: www.midro.de
Midro, Israel. See *Promedico, Israel.*
Midro, Switz. Midro Vertrieb AG, Uferstrasse 90, 4019 Basle, Switzerland.
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Milance, USA. Milance, USA.
Milano, Thai. Milano Lab Ltd Part, 62 Soi Latphrao 94, Bangkok 10310, Thailand.
Miles, Ital. See *Bayer Diagnostici, Ital.*
Miles, UK. The Miles Group, Fitzwilliam House, 84 Fitzwilliam St, Huddersfield, West Yorkshire, HD1 5BB, UK.
Miles, USA. See *Bayer, USA.*
Miles Consumer Healthcare, USA. See *Bayer, USA.*
Milex, Canad. See *Milex, USA.*
Milex, USA. Milex Products Inc., 350 Randy Rd, Suite 2, Carol Dtraen, IL 60188-1813, USA.
url: www.milexproducts.com
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Millenium, USA. Millenium Pharmaceuticals Inc., 40 Landsdowne St., Cambridge, MA 02139, USA.
url: www.mlnm.com
Miller, USA. Miller Pharmacal Group Inc., 350 Randy Rd, Suite 2, Carol Stream, IL 601881831, USA.
url: www.millerpharmacal.com
Millet Roux, Braz. Produtos Farmacêuticos Millet Roux Ltda, Praia de Botafogo 440, 25 andar, 22250-040 Rio de Janeiro, RJ, Brazil.
url: www.milletroux.com.br
Millet-Franklin, Arg. Laboratorios Millet-Franklin S.A., Thames 121 Piso 1 of. 2, 1609 Boulogne, Buenos Aires, Argentina.
url: www.milletfranklin.com
Millimed, Thai. Millimed Co Ltd, 193 Moo 1 Suksawad Rd, Pakklongbangprakort, Phra Samutchedi, Samutprakarn 10290, Thailand.
url: www.millimedthailand.com
Milmet, India. See *Sun, India.*
Milo, Spain. Milo, Pol Ind Centrovia, C/ Los Angeles 60, La Muela, 50196 Zaragoza, Spain.
url: www.laboratoriosmilo.com
Milte, Ital. Milte Italia S.p.A., Via Tadino 29/A, 20124 Milan, Italy.
url: www.milte.it
Milton, Austral. Milton Pharmaceuticals P/L, 100 Antimony St, Carole Park, QLD 4300, Australia.
url: www.miltonpharma.com
Milupa, Austria. Milupa GmbH, Postfach 2, A-5412 Puch, Austria.
Milupa, Cz. See *Milupa, Austria.*
Milupa, Fr. Milupa, 4 rue Joseph-Monier, 92859 Rueil-Malmaison cdx, France.
Milupa, Irl. See *Nutricia, Irl.*
Milupa, Ital. Milupa S.p.A., Via Lepetit 8, 20020 Lainate (MI), Italy.
Milupa, Pol. See *Nutricia, Pol.*
Milupa, Port. Milupa Portuguesa, Lda, Zona Industrial, 2790-076 Carnaxide, Portugal.
Milupa, Switz. Milupa SA, 1564 Domdidier, Switzerland.
url: www.milupa.ch
Milupa, UK. Milupa Ltd, Division of Nutricia, Newmarket Ave, White Horse Business Park, Trowbridge, Wiltshire, BA14 0XQ, UK.
url: www.milupa4hcps.co.uk
Milve, Rus. See *Sopharma, Rus.*
Minancora, Braz. Minancora & Cia Ltda, Rua do Principe 461, 89201-001 Joinville, SC, Brazil.
url: www.minancora.com.br
Minerva, Gr. Minerva Pharmaceutical S.A., 132 Kiffisou Ave, 121 33 Peristeri, Greece.
url: www.minervapharm.gr
Minerva (Μινερβα), Gr. See *Minerva, Gr.*
Ministry of Defence, UK. Ministry of Defence, Whitehall, London, SW1 2HB, UK.
Minorock Mandiri, Indon. Minorock Mandiri PT, Jl Kelapa Dua 69, 16951 Jakarta, Indonesia.
Minrad, USA. Minrad Inc., 847 Main St., Buffalo, NY 14203, USA.
url: www.minrad.com
Minskinterkaps, Belarus. Minskinterkaps UP, Inzhenernaya St. 26, 220075 Minsk, Belarus.
url: www.mic.by
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Mintlab, Chile. Mintlab Co SA, Nueva Andres Bello 1940, Independencia, Santiago, Chile.
MIP, Ger. MIP Pharma GmbH, Kirkeler Str. 41, 66440 Blieskastel, Germany.
url: www.mip-pharma.de
MIP, Pol. MIP Pharma Polska Sp. zo.o., ul. Orzechowa 5, 80-175 Gdańsk, Poland.
Mipharm, Ital. Mipharm S.p.A., Via B Quaranta 12, 20141 Milan, Italy.
url: www.mipharm.it
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Miralex, Pol. Miralex Sp. zo.o., ul. Św. Szczepana 25, 61-465 Poznań, Poland.
url: www.miralex.pl
Mirren, S.Afr. Mirren (Pty) Ltd, P.O. Box 87607, Houghton 2041, South Africa.
url: www.mirren.co.za
Misemer, USA. See *Edwards, USA.*
Mission, Austral. Mission Pharmacal Australia Pty Ltd., Level 2, 294 New South Head Road, Double Bay, NSW 2028, Australia.
url: www.missionpharmacal.com.au
Mission Pharmacal, Hong Kong. See *International Medical, Hong Kong.*
Mission Pharmacal, Malaysia. See *Somedico, Malaysia.*
Mission Pharmacal, Singapore. See *Pharma 2000, Singapore.*
Mission Pharmacal, USA. Mission Pharmacal Co., 10999 IH 10 West, Suite 1000, San Antonio, TX 78230-1355, USA.
url: www.missionpharmacal.com
MIT, Ger. MIT Gesundheit GmbH, Flutstr. 74, 47533 Kleeve, Germany.
url: www.mit-gesundheit.com
Mita, Hong Kong. Mita Pharmaceutical Co. Ltd, Rm 1208, 12/F, Phase 1, Metro Ctr, 32 Lam Hing St, Kowloon Bay, Kowloon, Hong Kong.
Mithra, Belg. Mithra Pharmaceuticals NV, Rue sur les Foulons 1, 4000 Liège, Belgium.
url: www.mithra.be
Mitim, Ital. Mitim S.r.l., Via Rodi 27, 25126 Brescia, Italy.
Mitsubishi, Jpn. See *Mitsubishi-Tokyo, Jpn.*
Mitsubishi, Malaysia. See *Summit, Malaysia.*
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Mitsubishi, Pol. Mitsubishi Corp., al. Jerozolimski 65/79, 00-697 Warsaw, Poland.
Mitsubishi, Thai. See *Diethelm, Thai.*
Mitsubishi, UK. Mitsubishi Pharma Europe Ltd, Jupiter House, London, EC21 1BR, UK.
Mitsubishi-Tanabe, Jpn. Mitsubishi Tanabe Pharma, 3-2-10-cho, Chuo-ku, Osaka Doshomachi, Japan.
url: www.mt-pharma.co.jp
Mitsubishi-Tokyo, Hong Kong. See *Hing Ah, Hong Kong.*
Mitsubishi-Tokyo, Jpn. Mitsubishi-Tokyo Pharmaceuticals Inc., 2-6 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8405, Japan.
url: www.m-pharma.co.jp
Mitsui, Jpn. Mitsui Seiyaku, Asahi Building, 3-12-2 Nihonbashi, Chuo-ku, Tokyo, Japan.
Miyarisan, Jpn. Miyarisan Pharmaceutical Co., Ltd, 1-10-3 Kaminakazato, Kita-ku, Tokyo 114-0016, Japan.
url: www.miyarisan.com
Mizar, Spain. See *Novartis, Spain.*
MJ Biopharm, Thai. See *Pharmaland, Thai.*
ML, Neth. See *ML Laboratories, UK.*
ML Laboratories, UK. ML Laboratories Plc, Blaby Hall, Church St, Blaby, Leicestershire, LE8 4FA, UK.
url: www.mllabs.co.uk
MM, India. M.M. Labs., Mahalaxmi Chambers, 22 Bhulabhai Desai Rd, Mumbai 400 026, India.
Mochida, Jpn. Mochida Pharmaceutical Co. Ltd, 1-7 Yotsuya, Shinjuku-ku, Tokyo 160-8515, Japan.
url: www.mochide.co.jp
Modi-Mundipharma, India. Modi-Mundipharma Ltd, 1400 Modi Tower, 98 Nehru Place, New Delhi 110 019, India.
url: www.modigroup.com
Molar, UK. Molar Ltd, The Close, West End, Wedmore, Somerset, MS28 4BN, UK.
url: www.molar.ltd.uk
Molex Ayus, Indon. Molex Ayus Pharmaceutical, Gedung Sinar Astri Lt IV, Jl Ir H Juanda No 5c, 10120 Jakarta, DKI Jaya, Indonesia.
Molimin, Ger. Molimin Arzneimittel GmbH, Emil-Kemmer-Str. 33, 96103 Hallstadt, Germany.
Molnlycke, Austral. Molnlycke Health Care Pty Ltd, Building 1 Ground Floor, 14 Aquatic Drive, Frenchs Forest, NSW 2086, Australia.
Molnlycke, Belg. Mölnlycke Health Care NV, Posthoflei 5, bus 7, B-2600 Berchem, Belgium.
url: www.molnlycke.com
Molnlycke, Canad. Molnlycke Health Care, 2010 Winston Park Dr., Suite 100, Oakville, Ontario, L6H 5R7, Canada.
url: www.tendra.com
Molnlycke, Fr. Laboratoires Mölnlycke Health Care, ZAC du Moulin, av Clement-Ader, B.P. 42, 59118 Wambrechies cdx, France.
url: www.molnlycke.net
Molnlycke, Ger. Mölnlycke Health Care GmbH, Max-Planck Str. 15, 40699 Erkrath, Germany.
url: www.molnlycke.net; www.tendra.com
Molnlycke, Ital. Molnlycke Health Care srl, Via Marsala 40/c, 21013 Gallarate (VA), Italy.
url: www.molnlycke.net
Molnlycke, UK. Mölnlycke Healthcare Ltd, The Arenson Centre, Arenson Way, Dunstable, Bedfordshire, LU5 5UL, UK.
url: www.molnlycke.net
Molteni, Cz. See *Molteni, Ital.*
Molteni, Ital. L. Molteni & C. dei F.lli Alitti S.p.A., S.S. 67, Fraz. Granatieri, 50018 Scandicci (FI), Italy.
Molteni, Pol. Molteni Farmaceutici Polska Sp. zo.o., ul. Obrońców Modlina 3, 30-733 Kraków, Poland.
url: www.molteni.com.pl
Molteni, Port. See *Molteni, Ital.*
Molteni, Rus. See *Reddy, Rus.*
Molypharma, Spain. Molypharma, Avda. Dr. Severo Ochoa 37, 4i, Alcobendas, 28100 Madrid, Spain.
url: www.molypharma.es
Mona Lisa, Israel. See *Hackmey, Israel.*
Monarch, Canad. See *King, USA.*
Monarch, Cz. See *Monarch, Irl.*
Monarch, Hung. Monarch, Hungary.
Monarch, Irl. Monarch Pharmaceuticals Ireland Ltd, 25-28 North Wall Quay, Dublin 1, Ireland.
Monarch, Port. See *Monarch, Irl.*
Monarch, USA. See *King, USA.*
Monchpharma, Ger. Mönchpharma Arzneimittel GmbH, Genhulsen 35, 41179 Mönchengladbach, Germany.
Monico, Ital. Monico S.p.A., Via Ponte di Pietra 7, 30175 Mestre (VE), Italy.
Monik, Spain. Monik, Avda de la Playa 1, Conil de la Frontera, 11140 Cadiz, Spain.
Monin, Fr. Laboratoires Monin-Chanteaud, Parc Euromedecine II, rue de la Valsière, 34099 Montpellier cdx 5, France.
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Monsanto, Ital. Monsanto Italiana S.p.A., Via Walter Tobagi 8, 20089 Peschiera Borromeo (MI), Italy.
Monsanto, Port. See *Pharmacia, Port.*
Monserrat, Arg. Monserrat y Eclair S.A., Virrey Cevallos 1625/7, 1135 Buenos Aires, Argentina.
Montavit, Austria. Montavit GmbH, Salzbergstrasse 96, A-6060 Absam, Austria.
url: www.montavit.com
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Montavit, Thai. Montavit, Thailand.
Monte Verde, Arg. Monte Verde SA, Cabildo 86, Piso 4, Buenos Aires, Argentina.
Montebello, Fr. Montebello France SA, av.des Noelles, B.P. 216, 44505 La Baule cdx, France.
Montefarmaco, Cz. See *Montefarmaco, Ital.*
Montefarmaco, Ital. Montefarmaco S.p.A., Via G. Galilei 7, 20016 Pero (MI), Italy.
url: www.montefarmaco.com
Monticello, USA. Monticello Drug Co., 1604 Stockton St, Jacksonville, FL 32204-4524, USA.
url: www.monticellocompanies.com
Montpellier, Arg. See *Disprofarma, Arg.*
Montpellier, Rus. See *Bago, Rus.*
Montrose, Cz. See *Montrose, UK.*
Montrose, UK. Montrose Fine Chemical Co Ltd, Irvine, UK.
Moore, USA. Moore Medical Corp., P.O. Box 1500, New Britain, CT 06050-1500, USA.
url: www.mooremedical.com
Morado, Ital. Morado S.p.A., Via Cacciamali 36, 25125 Brescia, Italy.
More, Philipp. SV More Pharma Corp., 5/F SV More Group Corp Center, 16 Sct Tuazon cor Roces Ave, Quezon City, Philippines.
Moreno, Port. Farmácia Moreno, Sociedade Unipessoal Lda, Lg. São Domingos 44, 4050-545 Porto, Portugal.
Morgan, Ital. Morgan Srl, Via Divisione Folgore 46, 36100 Vicenza (VI), Italy.
url: www.morganpharma.it
Morinaga, Indon. See *Sanghiang, Indon.*
Morishita, Philipp. Morishita-Seggs Pharmaceuticals Inc., 782 San Rafael St, Mandaluyong City, Philippines.
Morningside, UK. Morningside Healthcare Ltd, 115 Narborough Rd, Leicester, Lesicestershire, LE3 0PA, UK.
Morrith, Spain. See *GSK, Spain.*
Morton Grove, USA. Morton Grove Pharmaceuticals Inc., 6451 West Main St, Morton Grove, IL 60053, USA.
url: www.mgp-online.com
Morton Salt, USA. Morton Salt, 123 N Wacker Dr., Chicago, IL 60606-1597, USA.
url: www.mortonsalt.com
Mosi-Guard, UK. Mosi-Guard International Ltd, Moorfield Rd, Yeadon, Leeds, West Yorkshire, LS19 7BN, UK.
url: www.mosiguard.com
Moskhimfarm, Rus. Moskhimfarmpreparaty Fgup Im. N.A. Semashko, Rusakovskaja ul., d. 19, 107113 Moscow, Russia.
Mothersoy, USA. MotherSOY Inc., 424 S Kentucky Ave, Evansville, IN 47714, USA.
url: www.mothersoy.com
Motima, Fr. Laboratoires Motima, 19 rue de Passy, 75016 Paris, France.
Movianto, UK. Movianto UK Ltd, 1 Progress Park, Bedford, MK42 9XE, UK.
url: www.movianto.com
MPM, UK. MPM, UK.
MPM, USA. MPM Medical Inc., 2301 Crown Ct, Irving, TX 75038, USA.
url: www.mpmmedicalinc.com
MPS, Austral. MPS Laboratories (Australia) P/L, 8 Kinane Street, Brighton, VIC 3186, Australia.
MR Pharma, Ger. MR Pharma GmbH, Waldstrasse 30, D-22889 Tangstedt, Germany.
MR Pharma, Neth. See *MR Pharma, Ger.*

MSD, Arg. Merck Sharp & Dohme (Arg.) Inc., Av. del Libertador 1410, 1638 Vicente Lopez, Buenos Aires, Argentina.
url: www.msd.com.ar

MSD, Austral. Merck Sharp & Dohme (Australia) P/L, P.O. Box 79, Granville, NSW 2142, Australia.
url: www.msd-australia.com.au

MSD, Austria. Merck Sharp & Dohme GmbH, Donau-City Strasse 6, A-1220 Vienna, Austria.
url: www.msd-austria.com

MSD, Belg. Merck Sharp & Dohme B.V., Chaussée de Waterloo 1135, 1180 Brussels, Belgium.
url: www.msd-belgium.be

MSD, Braz. Merck Sharp & Dohme Farma Ltda, Rua Alexandre Dumas 2510, 04717-004 São Paulo, SP, Brazil.
url: www.msd-brazil.com

MSD, Chile. Merck Sharp & Dohme, Av. Americo Vespucio Sur 100, Of. 401, Las Condes, Santiago, Chile.

MSD, Cz. Merck Sharp & Dohme, Křenová 5, 160 00 Prague 6, Czech Republic.

MSD, Denm. Merck Sharp & Dohme, Smedeland 8, 2600 Glostrup, Denmark.
url: www.msk.dk

MSD, Fin. Suomen MSD Oy, PL 46, 02151 Espoo, Finland.
url: www.msd-finland.com

MSD, Ger. MSD Sharp & Dohme GmbH, Lindenplatz 1, 85540 Haar, Germany.
url: www.msd.de

MSD, Hong Kong. Merck Sharp & Dohme (Asia) Ltd, 26/F Caroline Ctr, Lee Gardens Two, 28 Yun Ping Rd, Causeway Bay, Hong Kong.
url: www.msd.com.hk

MSD, Hung. Merck Sharp & Dohme Kft, Tartsay Vilmos u 14, 1126 Budapest, Hungary.

MSD, Indon. Merck Sharp & Dohme, Wisma BNI 46, 27th Fl, Jl Jend Sudirman Kav 1, 10220 Jakarta, DKI Jaya, Indonesia.

MSD, Irl. Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.
url: www.msd.ie

MSD, Israel. MSD Israel, P.O. Box 7121, Petach Tikva, Israel.
url: www.mercksharpdohme.com

MSD, Ital. Merck Sharp & Dohme (Italia) S.p.A., Via G. Fabbroni 6, 00100 Rome, Italy.
url: www.msd-italia.com

MSD, Malaysia. Merck Sharp & Dohme Malaysia, 15th Floor Menara Merias, 1 Jln 19/3, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.mercksharpdohme.com

MSD, Mex. Merck Sharp & Dohme de Mexico S.A. de C.V., Av. Division del Norte No. 3377, Col. Xotepingo, Deleg. Coyoacan, 04610 Mexico D.F., Mexico.
url: www.msd.com.mx

MSD, Neth. Merck Sharp & Dohme BV, Postbus 581, 2003 PC Haarlem, Netherlands.
url: www.msd.nl

MSD, Norw. MSD (Norge) A/S, Solbakken 1, Postboks 458 Brakeroya, 3002 Drammen, Norway.
url: www.msd.no

MSD, NZ. Merck Sharp & Dohme (NZ) Ltd, 109 Carlton Gore Road, Newmarket, Auckland, New Zealand.
url: www.msd.co.nz

MSD, Philipp. Merck Sharp & Dohme, 26/F Philamlife Tower, 8767 Paseo de Roxas, Makati City, Philippines.

MSD, Pol. MSD Polska Sp. zo.o., ul. Chłodna 51, 00-867 Warsaw, Poland.

MSD, Port. Merck Sharp & Dohme, Lda, Edifício Vasco da Gama 19, Quinta da Fonte, Porto Salvo, 2770-192 Paç de Arcos, Portugal.
url: www.msd.pt

MSD, Rus. Merck Sharp & Dohme Idea, Berezhkovskaya nab. 2, Gostinista Slavonic/Radisson, 121095 Moscow, Russia.
url: www.msd.ru

MSD, S.Afr. Merck Sharp & Dohme (Pty) Ltd, Private Bag 3, Halfway House 1685, South Africa.
url: www.mercksharpdohme.com

MSD, Singapore. Merck Sharp & Dohme (IA) Corp, Singapore Branch, 300 Beach Road, 13-02 The Concourse, S 199555, Singapore.
url: www.msd-singapore.com

MSD, Spain. Merck Sharp & Dohme S.A., Josefa Valcarcel 38, 28027 Madrid, Spain.
url: www.msd.es

MSD, Swed. Merck Sharp & Dohme (Sweden) AB, Box 7125, 192 07 Sollentuna, Sweden.
url: www.msd.se

MSD, Switz. Merck Sharp & Dohme-Chibret SA, Niederlassung von Merck & Co., Inc., USA, Schaffhauserstrasse 136, Postfach, 8152 Glattbrugg, Switzerland.
url: www.msd.ch

MSD, Thai. See *BLH, Thai.*

MSD, Turk. See *Merck, Turk.*

MSD, UK. Merck Sharp & Dohme Ltd, Hertford Rd, Hoddesdon, Hertfordshire, EN11 9BU, UK.
url: www.msd-uk.com

MSD, USA. See *Merck, USA.*

MSD, Venez. Merck Sharp & Dohme de Venezuela, Av. Principal de los Cortijos de Lourdes, Centro Empresarial Senderos P.I - Los C.Lourde, Caracas, Venezuela.
url: www.msd.com.ve

MSD Chibropharm, Ger. See *MSD, Ger.*

MSD-Chibret, Fr. Laboratoires Merck Sharp & Dohme-Chibret, 3 ave Hoche, 75114 Paris cdx 08, France.
url: www.mercksharpdohme.com

MTF, Gr. MTF, Greece.

Mucos, Austria. Mucos Emulsions-GmbH, Leberstrasse 96, A-1110 Vienna, Austria.

Mucos, Cz. Mucos Pharma CZ sro, Uhřiněveská 448, 252 43 Průhonice, Czech Republic.
url: www.mucos.cz

Mucos, Ger. Mucos Pharma GmbH & Co., Malvenweg 2, 82538 Geretsried, Germany.
url: www.mucos.de

Mucos, Hung. See *PannonPharma, Hung.*

Mucos, Rus. Mucos Pharma GMbH & Co, Kashirskoe sh. 34A, 115522 Moscow, Russia.

Mucos, Venez. Casa de Representación Mucos de Venezuela S.A., Calle San Ernesto, Quinta Mucos, Sect. Sorocaima, La Trinidad, Baruta, Caracas, Venezuela.
url: www.mucos.de

Mugi, Indon. Mugi Laboratories PT, Jl PLN No 99, Duren Tiga, 12760 Jakarta, Indonesia.

Muir Hutchinson, NZ. See *UCB, Austral.*

Mulda, Turk. Mulda Koll Şti., Bomonti, Güvenç Sok. No: 11/4, Şişli, İstanbul, Turkey.

Muller Goppingen, Ger. Chemisch-Pharmazeutische Fabrik Göppingen Carl Müller, Apotheker, GmbH & Co. KG, Bahnhofstr. 33-35 & 40, 73033 Goppingen, Germany.
url: www.mueller-goeppingen.de

Muller Goppingen, Indon. See *Darya-Varia, Indon.*

Multicare, Philipp. Multicare Pharmaceuticals Phils Inc., 26/F Rufino Tower, 6784 Ayala Ave, Makati City, Philippines.
url: www.multicare.com.ph

Multichem, NZ. Multichem, Private Bag 93527, Takapuna, Auckland, New Zealand.
url: www.multichem.co.nz

Multilab, Braz. Multilab Ind. e Com. Prods. Farmacêuticos Ltda, RS 401 Km 30 No. 1009, 96700-000 São Jeronimo, RS, Brazil.
url: www.multilab.com.br

Multilan, Israel. See *Neopharm, Israel.*

Multipharma, Neth. Multipharma BV, Postbus 216, 1380 AE Weesp, Netherlands.
url: www.multipharma.nl

Multi-Pro, Canad. Distributions Multi-Pro Inc., 8480 Champ d'eau, St-Leonard, Quebec, H1P 1Y3, Canada.

Mundipharma, Austral. Mundipharma, P.O. Box 5214, Sydney, NSW 2001, Australia.
url: www.mundipharma.com

Mundipharma, Austria. Mundipharma GmbH, Apollogasse 16-18, A-1072 Vienna, Austria.
url: www.mundipharma.co.uk

Mundipharma, Belg. Mundipharma, Campus Mechelen, Schaliënhoevedree, 2800 Mechelen, Belgium.

Mundipharma, Cz. Mundipharma GmbH, Turisticka 36, 621 00 Brno, Czech Republic.

Mundipharma, Fin. Mundipharma Oy, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.mundipharma.com

Mundipharma, Fr. Mundipharma, 42 rue d'Aguesseau, 92100 Boulogne-Billancourt, France.
url: www.mundipharma.com

Mundipharma, Ger. Mundipharma GmbH, Mundipharma Str. 2, 65549 Limburg (Lahn), Germany.
url: www.mundipharma.de

Mundipharma, Hong Kong. See *Jacobson, Hong Kong.*

Mundipharma, Hung. See *Extractum, Hung.*

Mundipharma, Indon. See *Mahakam Beta, Indon.*

Mundipharma, Irl. Mundipharma Pharmaceutical Co., 54 Fitzwilliam Square, Dublin 2, Ireland.

Mundipharma, Ital. Mundipharma Pharmaceuticals Srl, Via G Serbelloni 4, 20122 Milan, Italy.

Mundipharma, Malaysia. See *Diethelm, Malaysia.*

Mundipharma, Neth. Mundipharma Pharmaceuticals BV, Astronaut 36, 3824 MJ Amersfoort, Netherlands.

Mundipharma, Norw. mundipharma AS, Postboks 218, 1326 Lysaker, Norway.
url: www.mundipharma.com

Mundipharma, Philipp. Mundipharma Distribution GmbH (Philippine Branch), Unit 201 The Taipan Place, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Mundipharma, Pol. Mundipharma Polska Sp. zo.o., ul. Poleckzi 12, 02-822 Warsaw, Poland.
url: www.mundipharma.com.pl

Mundipharma, Port. Mundipharma Farmacêutica Lda, Edifício Atrium Saldanha, Praca Duque de Saldanha 106, Lisbon 1050-094, Portugal.

Mundipharma, Singapore. See *Cork, Singapore.*

Mundipharma, Spain. Mundipharma Pharmaceuticals, Via de Los Poblados, 1 Ed. Alvento Planta, Baja, 28033 Madrid, Spain.
url: www.mundipharma.co.uk

Mundipharma, Swed. Mundipharma AB, Mölndalsvägen 26, 412 63 Göteborg, Sweden.
url: www.mundipharma.se

Mundipharma, Switz. Mundipharma Medical Co, St Alban-Rheinweg 74, 4020 Basle, Switzerland.
url: www.mundipharma.ch

Mundipharma, Thai. See *JDH Borneo, Thai.*

Munir, Turk. Münir Şahin İlaç San. ve Tic. A.Ş., Çavuşoğlu Mah. Sanayii Cad. No: 22, Kartal, İstanbul, 81430, Turkey.
url: www.munirsahin.com

Munro, UK. Munro Wholesale Medical Supplies Ltd, 10 Stroud Rd, Kelvin Industrial Estate, East Kilbride, G75 0YA, UK.

Murdock, USA. See *Natures Way, USA.*

Muro, Israel. See *Megapharm, Israel.*

Muro, USA. Muro Pharmaceutical Inc., 890 East St, Tewksbury, MA 01876-1496, USA.
url: www.muropharm.com

Musa, Braz. Laboratório Musa Rodolpho Jordano Ltda, Rua Pedra Dourada 110, Zona Industrial de Jacarepagua, 22780-082 Rio de Janeiro, Brazil.
url: www.labmusa.com.br

Muskus, Venez. C Muskus S.A., Calle San Mateo, Quinta Manedor Piso 2, Sorocaima La Trinidad 1010, Caracas, Venezuela.

Myadec, Austral. Myadec, Australia.

Mylan, USA. Mylan Laboratories Inc., 1500 Corporate Drive, Suite 400, Canonsburg, PA 15317, USA.
url: www.mylan.com

Mylange, Fr. Laboratoires Mylange, 69 rue Pasteur, 62300 Lens, France.

Myogen, Irl. See *Allphar, Irl.*

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Myra, Thai. See *Olic, Thai.*

Myung In, Singapore. See *Ziwell, Singapore.*

MZ, S.Afr. See *Meyer Zall, S.Afr.*

MZL, S.Afr. MZL Investments, Private Bag X4, Hout Bay 7872, South Africa.

Nabi, USA. Nabi Biopharmaceuticals, 5800 Park of Commerce Blvd NW, Boca Raton, FL 33487, USA.
url: www.nabi.com

Nabiqasim, Philipp. See *EuroAsia, Philipp.*, and *Patriot, Philipp.*

Nabros, Rus. See *Nizhpharm, Rus.*

Nadeau, Canad. See *Technilab, Canad.*

Nadinola, Canad. See *Hargell, Canad.*

Naf, Arg. Lab. Naf S.A., Fco. Acuca de Figueroa 886 Piso 1, 1180 Buenos Aires, Argentina.

Nafar, Mex. Nafar Laboratorios SA de CV, Justo Sierra 933, 45235 Zapopan Agua Blanca Indust., Jalisco, Mexico.

Nagor, UK. Nagor Ltd, P.O. Box 21, Douglas, Isle of Man, IM99 1AX, UK.
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Naina, Singapore. Naina Mohamed & Sons Pte Ltd, 1 Ubi Crescent, 05-04 Number One Building, S 408563, Singapore.

Nakorn, Thai. See *TNP, Thai.*, and *V & V, Thai.*

Nakornpatana, Thai. Nakornpatana Pharm Co. Ltd, 495, 601/5-8 Soi Suthiporn, Prachasongkroh Rd, Dindaeng, Bangkok 10400, Thailand.

Naltek, Canad. Naltek, Canada.

NAM, Ger. NAM Neukönigsförder Arzneimittel GmbH, Moorweg Strasse 35, 26197 Grossenkneten, Germany.
url: www.nam.de

NAM, Ital. Natura Alma Mater Srl, Via Tre Settembre 178/c, 47891 Dogana San Marino, Italy.

Napp, Hong Kong. See *Jacobson, Hong Kong.*

Napp, Irl. See *Mundipharma, Irl.*

Napp, Port. See *Napp, UK.*

Napp, UK. Napp Pharmaceuticals Ltd, Cambridge Science Park, Milton Rd, Cambridge, Cambridgeshire, CB4 0GW, UK.
url: www.napp.co.uk

Narval, Spain. Narval Pharma S.A., Travesma de los Castaqos 2, Monteprmncipe, 28668 Madrid, Spain.
url: www.narvalpharma.com

Nasmark, Canad. Nasmark Inc., 5650 Tomken Rd, Unit 12, Mississauga, Ontario, L4W 4P1, Canada.

Nastech, Israel. See *Tzamal, Israel.*

Nat Druggists, S.Afr. National Druggists (Pty) Ltd, P.O. Box 3253, Durban 4000, South Africa.

Natal Bioproducts, S.Afr. Natal Bioproducts Institute, Private Bag X9043, Pinetown 3600, South Africa.
url: www.nbi-kzn.org.za

Natco, India. Natco Pharma Ltd, Natco House, Road No 2, Banjara Hills, Hyderabad 500033, India.

Nathura, Ital. Nathura Srl, Via Meucci 14, 42027 Montecchio Emilia (RE), Italy.
url: www.nathura.com

National Blood Centre, Thai. National Blood Centre, Thai Red Cross Society, Thailand.

National Care, Canad. National Care Products, 251 Saulteaux Crescent, Winnipeg, Manitoba, R3J 3C7, Canada.

National Diagnostic, Austral. National Diagnostic Products (Australia) P/L, 7-9 Merriwa St, Gordon, NSW 2072, Australia.
url: www.biodiagnostics.com

National Vitamin, USA. National Vitamin Co. Inc., 2075 West Scranton Ave, Porterville, CA 93257, USA.
url: www.nationalvitamin.com

Natiris, Venez. Laboratorios Natiri's C.A., Calle 25 entre carrera 21 y 22, Piso 5 Ctro Comercial, Cosmo Barquisimeto, Lara, Venezuela.

Natrahealth, UK. Natrahealth Ltd, Omicron House, Fircroft Way, Edenbridge, Kent, TN8 6EL, UK.
url: www.natrahealth.com

Natrapharm, Philipp. Natrapharm Inc., The Patriot Bldg, Km 18 West Service Rd, South Luzon Expressway, Parañaque City, Philippines.

Natren, USA. Natren Inc., 3105 Willow Lane, Westlake Village, CA 91361, USA.
url: www.natren.com

Nattermann, Ger. See *Cassella-med, Ger.*

Nattermann, Pol. See *Sanofi-Aventis, Pol.*

Nattermann, Rus. See *Sanofi-Aventis, Rus.*

Natufarma, Arg. Lab. Natufarma, Av. Cordoba 1745, 3080 Esperanza, Santa Fe, Argentina.
url: www.natufarma.com.ar

Natumin, Pol. See *Krotex, Pol.*

Natur Produkt, Pol. Natur Produkt Zdrovit Sp. zo.o., ul. Nocznickiego 31, 01-918 Warsaw, Poland.
url: www.naturprodukt.pl

Natural Factors, Canad. Natural Factors Nutritional Products Ltd, 3655 Bonneville Place, Burnaby, British Colombia, V3N 4S9, Canada.

Natural Life, Arg. Natural Life S.A., Tucuman 3516, 1189 Buenos Aires, Argentina.

Natural Media, Thai. Natural Media Co. Ltd, 68/1 Yenakas 2, Chongnonsee, Yannawa, Bangkok 10120, Thailand.

Natural San, Arg. Natural San SRL, Loyola 465, 1414 Buenos Aires, Argentina.

Natural Touch, UK. Natural Touch Ltd, 7 Dragoon House, Hussar Court, Brambles Farm, Waterlooville, Hampshire, PO7 7SE, UK.

Naturale, Philipp. Naturale Laboratories Inc., 73 Sct Fernandez St, Brgy Laging Handa, Quezon City, Philippines.

Naturarzneimittel, Ger. Naturarzneimittel Regneri GmbH & Co. KG, Carl-Zeiss-Str. 4, 76275 Ettlingen, Germany.

Nature's Bounty, USA. Nature's Bounty Inc., P.O. Box 801612, Boca Raton, FL 33481, USA.
url: www.nbty.com

Natures Sunshine, Canad. See *Natures Sunshine, USA.*

Natures Sunshine, USA. Nature's Sunshine Products Inc., 1655 N Main St, Spanish Fork, Utah, 84660-1007, USA.

Nature's Way, Philipp. See *Sonix, Philipp.*

Natures Way, USA. Nature's Way, 10 Mountain Springs Parkway, Springville, UT 84663, USA.
url: www.naturesway.com

Naturest, Hong Kong. Naturest Co. Ltd, Suite 2508, Bank of America Tower, 12 Harcourt Rd Central, Hong Kong.

Naturex, Mex. See *Maver, Mex.*

Naturissima, Venez. Productos Naturissima de Venezuela, Calle del Arenal Edif. Biotech, Urb. La Trinidad, Caracas, Venezuela.

Naturland, Cz. Naturland Czech Republic sro, Kartouzská 4/200, 15 000 Prague 5, Czech Republic.

Naturland, Hung. Naturland, Csillagvirág u 8, 1106 Budapest, Hungary.

Naturmed, Ital. Naturmed 2000 S.r.l., Via Prov.le 33 (Resid. Oasi), 19030 Castelnuovo Magra (SP), Italy.

Naturopathica, Austral. Naturopathica, P.O. Box 7096, Sydney, NSW 2001, Australia.
url: www.naturopathica.com.au

Naturopathica, UK. Naturopathica Ltd, Lloyds Court, Suite 307, 1 Goodmans Yard, London, E1 8AT, UK.
url: www.skindoctors.co.uk

Naturpharma, Switz. Naturpharma SA, 5d route des Jeunes, Case postale 8, 1211 Geneva 26, Switzerland.

Naturprodukt, Cz. Naturprodukt CZ sro, Mládežnická 9, 736 01 Havířov, Czech Republic.
url: www.naturpro.cz

Naturprodukt, Hung. Naturprodukt Kft, DEPO Pf: 8, 2046 Törökbálint, Hungary.

Naturwaren, Cz. Naturwaren OHG, Czech Republic.

Naturwaren, Ital. Naturwaren Italia S.r.l., Via Galvani 33, 39100 Bolzano, Italy.

Natysal, Spain. Naytsal, C/ Molino 2, Meco, 28880 Madrid, Spain.
url: www.natysal.com

Navamedic, Cz. See *Navamedic, Norw.*

Navamedic, Norw. Navamedic ASA, Vollsveien 13 C, P.O. Box 438, 1327 Lysaker, Norway.
url: www.navamedic.com

Navamedic, Port. See *Navamedic, Norw.*

Naveh, Israel. Naveh Pharmacy, Yad Harutzim 19, Netanya, Israel.

NBF, Ital. N.B.F. Italia S.r.l., Corso di Porta Vittoria 14, 20122 Milan, Italy.

NBI, S.Afr. See *Natal Bioproducts, S.Afr.*

NBZ, India. NBZ-Pharma Ltd, R-905 MIDC, Rabale, Navi Mumbai 400 701, India.

NCSN, Ital. NCSN Farmaceutici S.r.l., Via Svetonio 15, 00100 Rome, Italy.

Neat Feat, NZ. Neat Feat Products Ltd, P.O. Box 65-256, Mairangi Bay, Auckland, New Zealand.
url: www.neatfeat.co.nz

Nebo, Denm. See *Salfarm, Denm.*

Nebo, Hong Kong. See *Zuellig, Hong Kong.*

Nebo, Norw. See *Andersen, Norw.*

Nebo, Philipp. See *A-Z, Philipp.*

Nebo, Thai. See *Natural Media, Thai.*

Nebo, Venez. See *PG, Venez.*

Neckerman, Braz. Neckerman Indústria Farmacêutica Ltda, Rua das Perobeiras 157, 05879-470 São Paulo, SP, Brazil.

Nederlands Vaccin Instituut, Neth. Het Nederlands Vaccin Instituut, Antonie van Leeuwenhoeklaan 9-11, Postbus 457, 3720 AL Bilthoven, Netherlands.
url: www.nvi-vaccin.nl

Nefa, Turk. Nefa İlaç Gıda Sağlık ve Kozmetik Ürünleri San. Tic. A.Ş., Darülaceze Cad., Perpa Ticaret Merkezi B Blok. K:11 No: 1746, Okmeydani, İstanbul, Turkey.
url: www.nefa.com.tr

Nefox, Spain. See *Pfizer, Spain.*

Nefro, Austria. Nefro Pharma Grosshandelsgmbh, An der Landesbahn 2-4, A-2100 Korneuburg, Austria.

Negma, Belg. See *Vitalpharma, Belg.*

Negma, Fr. Laboratoires Negma-Lerads, Imm Strasbourg, av de l'Europe, Toussus-le-Noble, 78771 Magny-les-Hameaux cdx, France.

Negma, Hung. See *Ubepharm, Hung.*

Negma, Israel. See *Pharmateam, Israel.*

Neiadas (Νειαδας), Gr. See *Niadas, Gr.*

Neitum, Fr. Neitum (Lab), 43 rue des Hérideaux, 69008 Lyon, France.

Nella, UK. Nella Pharmaceutical Products Ltd, Kincraig Court, Kincraig Rd, Blackpool, Lancashire, FY2 0FY, UK.

Nelson, UK. A Nelson & Co. Ltd, Broadheath House, 83 Parkside, London, SW19 5LP, UK.
url: www.nelsonshomoeopathy.co.uk

Neo Dermos, Arg. Neo Dermos S.R.L., Francisco Bilbao 1927, 1406 Buenos Aires, Argentina.

Neo Laboratories, UK. See *Alinter, UK.*

Neo Quimica, Braz. Laboratório Neo Química Comércio e Indústria Ltda, Rua VPR 1 Quadra 2-A, Modulo 4 DAIA, 75133-600 Anapolis, GO, Brazil.
url: www.neoquimica.com.br

Neocorp, Ger. Neocorp AG, Am Weidenbach 6, 82362 Weilheim, Germany.
url: www.neocorp.de

Neo-Farmaceutica, Port. Neo-Farmacêutica, Lda, Avenida D João II, 1990-090 Lisbon, Portugal.
url: www.neo-farmaceutica.pt

Neolab, Canad. Neolab, 5476 Upper Lachine Rd, Montreal, Quebec, H4A 2A4, Canada.

Neolab, UK. Neolab Ltd., 57 High St, Odiham, Hampshire, RG29 1LF, UK.

Neopharm, Israel. Neopharm Ltd, 8 Hashiloach St, P.O. Box 7063, Petach Tikva 49170, Israel.
url: www.neopharmisrael.com

Neopharm, Thai. Neopharm Co. Ltd, 13/10 Moo 15, Talingchan-Suphanburi, Bangmaenang, Bangyai, Nonthaburi 11140, Thailand.
url: www.neopharms.com

Neopharma, Denm. See *Neopharma, Swed.*

Neopharma, Ger. Neopharma GmbH & Co. KG, Kirchstr. 10, 83229 Aschau i. Chiemgau, Germany.

Neopharma, Hung. Neopharma, Hungary.

Neo-Pharma, India. Neo-Pharma Pvt Ltd, Kasturi Building, 5th Floor, J. Tata Rd, Mumbai 400 020, India.

Neopharma, Swed. NeoPharma AB, Fyrisborgsgatan 3, Box 22, 751 03 Uppsala, Sweden.
url: www.neopharma.se

Neopharma, Venez. Comercializadora Neopharma de Venezuela C.A., Av Fco Miranda e Av Elice y C La Joya, Ctro P Miranda, Piso 4 Of. 4-B Chacao, 1010-A Caracas, Venezuela.

Neopharmed, Ital. Neopharmed S.p.A., Via Vitorchiano 151, 00100 Rome, Italy.
url: www.neopharmed.it

Neovita, Braz. Instituto Farmoterapico Neovita Ltda, Rua Dr. Rodrigues Santana 80, 20910-240 Rio de Janeiro, RJ, Brazil.

Neovita, Ital. Neovita S.a.s. di G. Pirotta & C., Via Solferino 4, 21040 Uboldo (VA), Italy.

Nepalm, Fr. Laboratoires Nepalm Sarl, 136 bis, av des Frères-Lumière, 69008 Lyon, France.

Nepentes, Pol. Nepentes Sp. zo.o., ul. Gwiaździsta 69 F, 01-651 Warsaw, Poland.
url: www.nepentes.com.pl

Nephron, USA. Nephron Pharmaceuticals Corp., 4121 SW 34th St, Orlando, FL 32811, USA.
url: www.nephronpharm.com

Nephro-Tech, USA. Nephro-Tech, Inc., P.O. Box 16106, Shawnee, KS 66203, USA.
url: www.nephrotech.com

Nes, Israel. Nes, Israel.

Nestle, Arg. Nestlé Argentina S.A., Av. del Libertador 1855, 1836 Vicente Lopez, Buenos Aires, Argentina.
url: www.nestle.com.ar

Nestle, Austral. Nestle Australia Ltd, 1 Homebush Bay Drive, Rhodes, NSW 2138, Australia.
url: www.nestle.com.au

Nestle, Braz. Nestle Indl. e. Coml. Ltda, Av. das Nações Unidas 12495, 04578-902 São Paulo, SP, Brazil.
url: www.nestle.com.br

Nestle, Canad. Nestle Canada Inc., 25 Sheppard Ave W, North York, Ontario, M2N 6S8, Canada.
url: www.nestle.ca

Nestle, Cz. Nestlé Food sro, Prague, Czech Republic.

Nestle, Fin. Suomen Nestlé Oy, Huopalahdentie 24, 00350 Helsinki, Finland.
url: www.nestle.fi

Nestle, Fr. Nestlé, 7 bd Pierre-Carle, B.P. 900, Noisiel, 77446 Marne-la-Vallée cdx 2, France.
url: www.nestle.fr

Nestle, Hong Kong. Nestle Hong Kong Ltd, 28/F, PCCW Tower, Taikoo Place, 979 King's Rd, Quarry Bay, Hong Kong.
url: www.nestle.com

Nestle, Indon. Nestlé Indonesia PT, Arkadia Office Park, Jl Let Jend TB, Simatupang Kav 88, 12520 Jakarta, DKI Jaya, Indonesia.

Nestle, Israel. See *Megapharm, Israel.*

Nestle, Ital. Nestlè Italiana S.p.A., Viale G. Richard 5, 20143 Milan, Italy.
url: www.nestle.it

Nestle, Malaysia. Nestle (Malaysia) Bhd, Nestle House, 4, Lorong Pesiaran, 46918 Petaling Jaya, Selangor, Malaysia.
url: www.nestle.com.my

Nestle, Mex. Nestle Mexico S.A. de C.V., Av Ejercito Nacional No. 453, Col. Granada, Deleg. Miguel Hidalgo, 11520 Mexico D.F., Mexico.
url: www.nestle.com.mx

Nestle, Philip. Nestlé Philippines Inc., 31 Plaza Drive, Rockwell Ctr, Makati City, Philippines.

Nestle, Port. Nestlé Portugal, SA, Rua Alexandre Herculano 8-8A, 2799-554 Linda-a-Velha, Portugal.
url: www.nestle.pt

Nestle, Rus. Nestle Food OOO, Paveletskaya pl. 2, Sr.1, 115054 Moscow, Russia.
url: www.nestle.ru

Nestle, Singapore. Nestle Singapore (Pte) Ltd, 200 Cantonment Rd, 03-01 Southpoint, S 089763, Singapore.

Nestle, Switz. Nestlé Suisse AG, Case postale 352, 1800 Vevey, Switzerland.
url: www.nestle.ch

Nestle, Thai. See *Zuellig, Thai.*
url: www.nestle.com

Nestle, UK. Nestlé Clinical Nutrition Ltd, St George's House, Park Lane, Croydon, Surrey, CR9 1NR, UK.
url: www.nestleclinical.co.uk

Nestle, USA. Nestle Clinical Nutrition, 800 North Brand Blvd, Glendale, CA 91203, USA.
url: www.nestle.com

Nestle, Venez. Nestle Venezuela S.A., Edificio Polar, Plaza Venezuela, Apartado 3367, Caracas 1010-A, Venezuela.
url: www.nestle.com.ve

Nestle Clinical, Irl. See *Baxter, Irl.*

Nestmann, Cz. Nestmann, Czech Republic.

Nettopharma, Denm. See *Nycomed, Denm.*

Network Health & Beauty, UK. Network Health & Beauty, Network House, Lynchford Lane, Farnborough, Hampshire, GU14 6JF, UK.
url: www.networkhb.com

Neuraxpharm, Ger. neuraxpharm Arzneimittel GmbH & Co. KG, Elisabeth-Selbert-Str. 23, 40764 Langenfeld, Germany.

Neurogard, Spain. See *MSD, Spain.*

NeuroGenesis, USA. NeuroGenesis/Matrix Tech. Inc., 120 Park Ave, League City, TX 77573, USA.
url: www.neurogenesis.com

Neuropharma, Arg. Neuropharma, Pringles 10 Piso 3, 1183 Buenos Aires, Argentina.

Neusc, Spain. Neusc, Ctra S. Hipolit KM 1, C/Sau 1, Gurb-Vic, 08503 Barcelona, Spain.

Neutrogena, Fr. See *Ethicon, Fr.*

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Neutrogena, Philip. See *Johnson & Johnson, Philipp.*

Neutrogena, UK. See *Johnson & Johnson, UK.*

Neutrogena, USA. Neutrogena Corp., 5760 W 96th St, Los Angeles, CA 90045-5595, USA.
url: www.neutrogena.com

Neutrogena Dermatologicals, USA. See *Neutrogena, USA.*

Neutron Technology, USA. See *Micron, USA.*

Nevada, Swed. Nevada Pharma AB, Wallingatan 18, 111 24 Stockholm, Sweden.
url: www.nevadapharma.se

Neves, Port. Laboratório J. Neves, Lda, Parque Industrial do Seixal, 2840-069 Paio Pires, Portugal.

Nevzat, Turk. Mustafa Nevzat İlaç San. A.Ş., Pak İş Merkezi, Prof. Dr. Bülent Tarcan Sok. No: 5/1, Gayrettepe, İstanbul, 34349, Turkey.
url: www.mn.com.tr

New England Nuclear, Austria. New England Nuclear, Vienna, Austria.

New Farma, Ital. New Farma Soc. Coop. a.r.l., Via Guglielmino 62/D, 95030 Tremestieri (CT), Italy.

New Pharma, Venez. New Pharma C.A., Av. Bolívar Quinta Francelis, Piso 1 Oficina 6, El Paraíso 1020, Caracas, Venezuela.

New Research, Ital. New Research S.r.l., P.za Don Luigi Sturzo 34, 04011 Aprilia (LT), Italy.

New River, USA. See *Shire, USA.*

New Smart, Philipp. New Smart Formulae Trading Corp., Room 505, Cedar Executive Bldg II, 26 Timog Ave cor Sct Tobias St, Quezon City, Philippines.

New Ulros, Ital. New Ulros S.r.l., Via delle Industrie 40, 35020 Albignasego (PD), Italy.
url: www.newulros.com

New Vision, Canad. New Vision Nutritionals Co., 3140 14th Ave NE, Suite 1, Calgary, Alberta, T2A 6J4, Canada.

NewFaDem, Ital. New.Fa.Dem. Srl Farmaceutici e Chimici, Via Ferrovie dello Stato 1, 80014 Giugliano (NA), Italy.

Newport, Irl. Newport Pharmaceuticals Ltd, Frank Maas House, Swords Business Park, Swords, Co. Dublin, Ireland.
url: www.newport-pharma.com

Newport, Philip. See *Marketlink, Philipp.*

Nexis, Spain. Nexis Farmaceutica, Principe de Vergara 112, 28001 Madrid, Spain.
url: www.nexisfarmaceutica.com

Nexmed, Hong Kong. Nexmed (Asia) Ltd, Rm 2208, 22/F Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.

Nexo, Arg. Laboratorio Nexo Pharmaceutical Group SA, Ponferrada 285, 1708 Moron, Buenos Aires, Argentina.

Nexstar, Austral. See *Gilead, Austral.*

Nexstar, Israel. See *Neopharm, Israel.*

Nexstar, Rus. See *Gilead, Rus.*

Nexstar, USA. See *Gilead, USA.*

NextChem, Philipp. NextChemical Enterprises, Rm 409 Integrated Professionals Office Bldg, 14 Quezon Ave, Quezon City, Philippines.

NHS, Fr. NHS, 1-7 rue du Jura, Silic 528, 94633 Rungis cdx, France.

Niadas, Gr. Niadas & Sons S.A., P.O.Box 59, 190 02 Paiania, Greece.

Niagara, Canad. Niagara Pharmaceuticals Inc., 60 Innovation Dr, Flamborough, Ontario, L9H 7P3, Canada.

Nice Pak, Austral. Nice Pak Products, 2-4 Sullivan St, Moorabbin, Vic 3189, Australia.
url: www.nicepak.com.au

Niche, Denm. Niche Pharma, Tvedangen 225, 2730 Herlev, Denmark.

Niche, Irl. Niche Generics Ltd, Unit 5, Baldoyle Industrial Estate, Dublin 13, Ireland.
url: www.nichegenerics.com

Niche, Singapore. See *Pharma 2000, Singapore.*

Niche, USA. Niche Pharmaceuticals Inc, 200 N Oak St, P.O. Box 449, Roanoake, TX 76262, USA.
url: www.niche-inc.com

Nicholas, Indon. Nicholas Laboratories PT, Jl Pulobuaran Raya, Block FF 12A, Kawasan Industri Pulo Gadung, 13930 Jakarta, Indonesia.

Nicholas Piramal, India. Nicholas Piramal India Ltd, 100 Centre Point, Dr. Ambedkar Rd, Parel, Mumbai 400 012, India.
url: www.nicholaspiramal.com

Nicobrand, Denm. See *UCB, Denm.*

Nicobrand, Neth. See *Nicobrand, UK.*

Nicobrand, Norw. See *UCB, Norw.*

Nicobrand, UK. Nicobrand Ltd, 189 Castleroe Rd, Coleraine, BT51 3RP, UK.

Nida, Singapore. See *Advanced, Singapore.*

Niddapharm, Ger. NIDDApharm GmbH, Konrad-Adenauer-Allee 8-10, 61118 Bad Vilbel, Germany.
url: www.niddapharm.de

Niedermaier, Ger. Dr Niedermaier GmbH, Taufkirchner Str. 59, 85662 Hohenbrunn bei Munich, Germany.
url: www.niedermaier-pharma.de

Nigy, Fr. Laboratoires Nigy, 6 av de l'Europe, B.P. 51, 78401 Chatou cdx, France.

Nigy, Singapore. See *Polymedic, Singapore.*

Nihon, Jpn. Nihon Pharmaceutical Co. Ltd, 9-8 Higashikanda 1-chome, Chiyoda-ku, Tokyo 101-0031, Japan.

Nikken, Jpn. Nikken Chemicals Co., Ltd, 5-4-14 Tsukiji, Chuo-ku, Tokyo 104-8448, Japan.

Nikken, Malaysia. See *Pharmaforte, Malaysia.*

Nikken, Thai. See *Masu, Thai.*

Nikkho, Braz. Química E Farmacêutica Nikkho do Brasil Ltda, Rua Jaime Perdigao 431-435, 21920-240 Ilha do Governador, RJ, Brazil.

Nikolakopoulos, Gr. A. Nikolakopoulos & Co. O.E, 115 Galatsiou Ave, 111 46 Athens, Greece.

Nikolakopoulos (Νικολακοπουλος), Gr. See *Nikolakopoulos, Gr.*

Nion, USA. Nion Corp., 15501 First St, Irwindale, CA 91706, USA.

Nitecs, Austral. Nitecs P/L, 4 Donald Street, Carlingford, NSW 2118, Australia.

Ni-The, Gr. Ni-The N. A. The Ophilis & Sons Ltd, 52 Psychari, 111 41 Athens, Greece.

NitroMed, USA. NitroMed Inc., 125 Spring St, Lexington, MA 02421, USA.

Nitto Denko, Jpn. Nitto Denko Corp., 2-5-25 Umeda, Kita-ku, Osaka 530-0001, Japan.
url: www.nitto.com

Niverpharm, Fr. Laboratoires Niverpharm, ZI des Taupières, rue Francis-Garnier, 58000 Nevers, France.

Nixoderm, Malaysia. See *Summit, Malaysia.*

Nizhpharm, Rus. Nizhpharm OAO, 7 Salganskaya ul., GSP-459, 603950 Nizhny Novgorod, Russia.
url: www.nizhpharm.com

Nizpharm, Rus. See *Nizhpharm, Rus.*

NM, Denm. NM Pharma A/S, Overgaden neden Vandet 7, 1414 Copenhagen K, Denmark.

NM, Swed. See *Pfizer, Swed.*

Nnodum, USA. Nnodum Corp., P.O. Box 19725, Cincinnati, OH 45219, USA.
url: www.zikspain.com

Nobel, Canad. Nobel Pharm Enrg, 2615 pl. Chasse, Montreal, Quebec, H1Y 2C3, Canada.

Nobel, Ital. Nobel Farmaceutici S.r.l., Via Tirbutina 1004, 00156 Rome, Italy.

Nobel, Turk. Nobel İlaç San. ve Tic. A.Ş., Barbaros Bulvarı No: 76-78, Beşiktaş, İstanbul, 34353, Turkey.
url: www.nobel.com.tr

Nobipharm, Pol. Nobipharm Sp. zo.o., ul. Rydygiera 8, 01-793 Warsaw, Poland.
url: www.nobipharm.pol.pl

Noel, India. Noel, India.

Nogues, Fr. Laboratoires Noguès, 43 rue de Neuilly, 92000 Nanterre, France.

Nogues, Switz. See *Uhlmann-Eyraud, Switz.*

Noir, India. Noir Pharmaceuticals Pvt Ltd, 380/82 J. Sankersett Rd, Sankersett Smriti, Chira Bazar, Mumbai 00 020, India.

Nolt, Arg. Nolt SA, Cervipo 4671 Piso 4'I C, 1425 Buenos Aires, Argentina.

Nolver, Venez. Nolver C.A., Mult.Empres.Este-To.Libertador Nucleo A, Pso.3-Of.32-A, Chacao, Caracas, Venezuela.

Nomax, USA. Nomax Inc., 40 North Rock Hill Rd, St Louis, MO 63119, USA.
url: www.nomax.com

Noos, Ital. Noos S.r.l., Via Campello S/Clitunno 34/1, 00181 Rome, Italy.

Nordend, Ger. Nordend-Apotheke Dr. Wolfgang Hotz, Friedrich-Ebert-Platz 17, 64289 Darmstadt, Germany.

Nordiatech, Denm. NorDiaTech A/S, Baldersbuen 29 F, 2640 Hedehusene, Denmark.
url: www.nordiatech.dk

Nordic, Fr. Nordic Pharma, France.

Nordic, Neth. Nordic Pharma BV, Tolweg 15, 3741 LM Baarn, Netherlands.
url: www.nordicpharma.nl

Nordic, Swed. Nordic Drugs AB, Box 300 35, 200 61 Limhamn, Sweden.
url: www.nordicdrugs.se

Nordic, UK. Nordic Pharma UK Ltd, Abbey House, Arlington Business Park, Theale, Reading, Berkshire, RG7 4SA, UK.
url: www.nordicpharmagroup.com

Nordic Drugs, Denm. Nordic Drugs, Halmtorvet 29, 1700 Copenhagen V, Denmark.
url: www.nordicdrugs.se

Nordic Drugs, Fin. Nordic Drugs AB, PL 16, 02241 Espoo, Finland.
url: www.nordicdrugs.se

Nordic Drugs, Norw. See *Nordic, Swed.*

Nordin, Mex. Química Franco Mexicana Nordin S.A. de C.V., Paseo Lomas Atlas No. 292, Col. Lomas del Valle, 45120 Zapopan, Jal., Mexico.
url: www.nordin.com.mx

Nordion, Neth. See *MDS, Belg.*

Nordmark, Cz. See *Nordmark, Ger.*

Nordmark, Ger. Nordmark Arzneimittel GmbH & Co. KG, Pinnauallee 4, 25436 Uetersen, Germany.
url: www.nordmark-pharma.de

Nordmark, Indon. See *Tunggal Idaman, Indon.*

Nordmark, Singapore. See *Indrugco, Singapore.*

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NordMedica, Denm. NordMedica A/S, Bredgade 41, 1, 1260 Copenhagen K, Denmark.
url: www.nordmedica.com

NordMedica, Swed. See *NordMedica, Denm.*

Norgesfarma, Norw. Norgesfarma AS, Skarersletta 45, Postboks 198, 1471 Lorenskog, Norway.

Norgine, Austral. Norgine P/L, 3/14 Rodborough Road, Frenchs Forest, NSW 2086, Australia.
url: www.norgine.com

Norgine, Austria. Norgine Pharma GmbH, Haidestrasse 4, A-1110 Vienna, Austria.
url: www.norgine.com

Norgine, Belg. Norgine SA, Haasrode Research Park, Romeinsestraat 10, 3001 Heverlee, Belgium.
url: www.norgine.com

Norgine, Cz. See *Norgine, Fr.*

Norgine, Denm. See *Biolac, Swed.*

Norgine, Fr. Laboratoires Norgine Pharma, 23 av. de Neuilly, 75116 Paris, France.
url: www.norgine.com

Norgine, Ger. Norgine GmbH, Im Schwarzenborn 4, 35041 Marburg, Germany.
url: www.norgine.de

Norgine, Hong Kong. See *Treasure Mountain, Hong Kong.*

Norgine, Irl. See *United Drug, Irl.*

Norgine, Ital. Norgine Italia S.r.l., Via Prina 15, 20154 Milan (MI), Italy.
url: www.norgine.com

Norgine, Malaysia. See *Apex, Malaysia.*

Norgine, Neth. Norgine BV, Hogehilweg 7, 1101 CA Amsterdam Zuid-Oost, Netherlands.
url: www.norgine.com

Norgine, Norw. See *Andersen, Norw.*

Norgine, NZ. See *CSL, NZ.*

Norgine, Philipp. See *Zuellig, Philipp.*

Norgine, Port. See *Norgine, Fr.*

Norgine, S.Afr. Norgine (Pty) Ltd, P.O. Box 781247, Gauteng, Sandton 2146, South Africa.
url: www.norgine.com

Norgine, Singapore. See *Grafton, Singapore.*

Norgine, Spain. Norgine de España, Maudes, 51 8 Pl., 28003 Madrid, Spain.
url: www.norgine.com

Norgine, Switz. Norgine AG, Neue Bahnhofstrasse 160, 4132 Muttenz, Switzerland.
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Norgine, Thai. See *Zuellig, Thai.*

Norgine, UK. Norgine Pharmaceuticals Ltd, Chaplin House, Moorhall Rd, Harefield, Uxbridge, Middlesex, UB9 6NS, UK.
url: www.norgine.com

Noriega, Spain. Noriega, Spain.

Noristan, S.Afr. See *Sanofi-Aventis, S.Afr.*

Norit, Austria. See *Vemedia, Neth.*

Norit, Cz. See *Solvay, Neth.*

Norit, Israel. See *Droreth, Israel.*

Norit, Neth. Norit Nederland B.V., P.O. Box 105, Nijverheidsweg Noord 72, 3800 AC Amersfoort, Netherlands.
url: www.norit.com

Norit, Port. See *Norit, Neth.*

Norma (Νορμα), Gr. Norma Greece A.E., Menandrou 54, 103 31 Athens, Greece.
url: www.normahellas.gr

Norma, UK. See *Alinter, UK.*

Normal, Port. Laboratório Normal, Lda, Rua do Centro Empresarial, Edifício 8, Quinta da Beloura, 2710-444 Sintra, Portugal.

Norman, Canad. See *Norman, USA.*

Norman, USA. Merle Norman Cosmetics, 9130 Bellanca Ave, Los Angeles, CA 90045, USA.

Normon, Port. Laboratórios Normon SA, Rua Mouzinho da Silveira 10, 1250-167 Lisbon, Portugal.

Normon, Spain. Normon S.A., Ronda de Valdecarrizo 6, Tres Cantos, 28760 Madrid, Spain.
url: www.normon.com

Norpharm, Irl. Norpharm Ltd, 26 Laurence St, Drogheda, County Louth, Ireland.

Norpharm, Neth. See *Norpharm, Irl.*

Norpharma, Denm. Norpharma A/S, Slotsmarken 15, 2970 Hørsholm, Denmark.
url: www.norpharma.dk

Norpharma, Pol. See *Mundipharma, Pol.*

Norstar, USA. Norstar Consumer Products, 5517 Ninety-fifth Ave, Kenosha, WI 53144, USA.
url: www.norstarcpc.com

Northfield, Philipp. See *Biolink, Philipp.*

Northia, Arg. Esp. Medicinales Northia S.A.C.I.F.I.A., Madero 135, 1408 Buenos Aires, Argentina.

Norton, Cz. See *Ivax, Irl.*

Norton, Denm. See *Pharmacodane, Denm.*

Norton, Hung. See *Norton Healthcare, UK.*

Norton, Israel. See *Promedico, Israel.*

Norton, Neth. See *Ivax, UK.*

Norton, NZ. See *Airflow, NZ.*

Norton, Pol. See *Teva, Pol.*

Norton, Rus. See *Ivax, Rus.*

Norton, S.Afr. See *Ivax, S.Afr.*

Norton Healthcare, Denm. See *United Nordic, Denm.*

Norton Healthcare, Singapore. See *FP, Singapore*, and *Green Cross, Singapore.*

Norton Healthcare, UK. See *Ivax, UK.*

Norwood, Canad. Norwood Packaging Ltd, 8519-132nd St, R.R. 4, Surrey, British Columbia, V3W 4N8, Canada.

Noster, Neth. See *Noster, Swed.*

Noster, Port. See *Noster, Swed.*

Noster, Swed. Noster System AB, Baggansgatan 25, S-111 31 Stockholm, Sweden.

Nostrum, Port. Sociedade Nostrum, Lda, Rua da Escola de Medicina Veterinária, 15/17, 1049-029 Lisbon, Portugal.

Nostrum, Spain. See *Pfizer, Spain.*

Nourypharma, Ger. See *Organon, Ger.*

Nova, Port. Nova AZ Comercialização Produtos Farmacêuticos Lda, Portugal.

Nova Argentia, Arg. Nova Argentia SA, Alvaro Barros 1113, 1838 Luis Guillon, Buenos Aires, Argentina.

Nova Argentia, Ital. Nova Argentia Industria Farmaceutica S.r.l., Via G. Pascoli 1, 20064 Gorgonzola (MI), Italy.

Novag, Mex. Novag Infancia S.A. de C.V., Claz. de Tlalpan No. 3417, Col. Sta. Ursula Coapa-Coyoacan, 04650 Mexico D.F., Mexico.

Novag, Spain. See *Ferrer, Spain.*

Novagen, Gr. Novagen Pharmaceuticals, Souri 6 & Korinthou, 144 51 Athens, Greece.

Novalac, Malaysia. See *Harpers, Malaysia.*

Novalac, Singapore. See *Delfi, Singapore.*

Novapharm, Venez. See *Farma, Venez.*

Novapharma, Venez. Novapharma S.A., Av. Principal de los Ruices Edif. Pharma, Urb. Los Ruices, Caracas, Venezuela.

Novaquimica, Braz. Novaquimica Sigma Pharma-Nature's Plus Ltda, Rodovia SP101 (Campinas a Monte Mor) Km 08, 13186-481 Hortolandia, SP, Brazil.

Novara, Arg. Laboratorios Novara SRL, Pje Blanque 1130, 2000 Rosario, Santa Fe, Argentina.

Novartis, Arg. Novartis Argentina S.A., Ramallo 1851, 1429 Buenos Aires, Argentina.
url: www.ar.novartis.com

Novartis, Austral. Novartis Pharmaceuticals P/L, P.O. Box 101, North Ryde, NSW 1670, Australia.
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Novartis, Austria. Novartis Pharma GmbH, Brunner Strasse 59, A-1230 Vienna, Austria.
url: www.at.novartis.com

Novartis, Belg. Novartis Pharma SA, Telecom Gardens, Medialaan 40 bus 1, 1800 Vilvoorde, Belgium.
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Novartis, Braz. Novartis Biociencias S.A., Avenida Professor Vicente Rao 90/120, Predio 156 3° ander, 04706-900 São Paulo, SP, Brazil.
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Novartis, Canad. Novartis Pharmaceuticals Canada Inc., 385 Bouchard Blvd, Dorval, Quebec, H9S 1A9, Canada.
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Novartis, Chile. Laboratorio Novartis Chile SA, Francisco meneses 1980, Nunoa, Santiago, Chile.

Novartis, Cz. Novartis Czech Republic sro, V Olšinach 75, 100 00 Prague 10, Czech Republic.
url: www.novartis.cz

Novartis, Denm. Novartis Healthcare AS, Lyngbyvej 172, 2100 Copenhagen O, Denmark.
url: www.novartis.dk

Novartis, Fin. Novartis Finland Oy, Metsänneidonkuja 10, 02130 Espoo, Finland.
url: www.novartis.fi

Novartis, Fr. Novartis Pharma SAS, 2-4 rue Lionel-Terray, 92500 Rueil-Malmaison, France.
url: www.fr.novartis.com

Novartis, Ger. Novartis Pharma GmbH, Roonstr. 25, 90429 Nürnberg, Germany.
url: www.novartispharma.de

Novartis, Gr. Novartis (Hellas) A.E.B.E., 12o chlm. Ethnikis Odou Athinon-Lamias, 144 51 Metamorfosi, Greece.
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Novartis, Hong Kong. Novartis Pharmaceuticals (HK) Ltd, 37/F Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
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Novartis, Hung. Novartis Hungária Kft, Bartók Béla út 43-47, 1114 Budapest, Hungary.

Novartis, India. Novartis India Ltd, Pharmaceutical Division, 6th Floor, Royal Insurance Building, 14 J. Tata Road, Mumbai 400 020, India.
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Novartis, Irl. Novartis Ireland Ltd, Beech House, Beech Hill Office Campus, Clonskeagh, Dublin 4, Ireland.
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Novartis, Israel. Novartis Ltd, Hasivim 23, Petach Tikva, Israel.
url: www.novartis.com

Novartis, Ital. Novartis Farma S.p.A., Largo Umberto Boccioni 1, 21040 Origgio (VA), Italy.
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Novartis, Jpn. Novartis Pharma K.K., 4-17-30 Nishi-Azabu, Minato-ku, Tokyo 106-8618, Japan.
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Novartis, Malaysia. Novartis Corporation (Malaysia) Sdn Bhd, Lot 9, Jln 26/1, Seksyen 26, Kawasan Perindustrian Hicom, 40400 Shah Alam, Selangor, Malaysia.
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Novartis, Mex. Novartis Farmaceutica S.A. de C.V., Calz. de Tlalpan No. 1779, Col. San Diego Churubusco, Deleg. Coyoacan, 04120 Mexico D.F., Mexico.
url: www.mx.novartis.com

Novartis, Neth. Novartis Pharma BV, Postbus 241, 6800 LZ Arnhem, Netherlands.
url: www.novartis.nl

Novartis, Norw. Novartis Norge AS, Brynsalleen 4, Postboks 237 Okern, 0510 Oslo, Norway.
url: www.novartis.no

Novartis, NZ. Novartis New Zealand Ltd, Private Bag 19-999, Avondale, Auckland, New Zealand.
url: www.novartis.com

Novartis, Philipp. Novartis Healthcare Phils Inc., 5/F Asian Reinsurance Bldg, Cor Salcedo & Gamboa St, Legaspi Vill, Makati City, Philippines.

Novartis, Pol. Novartis Poland Sp. zo.o., al. Witosa 31, 00-710 Warsaw, Poland.
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Novartis, Port. Novartis Farma, SA, Rua do Centro Empresarial, Edifício 8, Quinta da Beloura, 2710-444 Sintra, Portugal.
url: www.novartis.com

Novartis, Rus. Zao Novetis Parma AG, B. Palashevski Pereulok 15/A, 103104 Moscow, Russia.
url: www.novartis.ru

Novartis, S.Afr. Novartis South Africa (Pty) Ltd, P.O. Box 92, ZA-Kempton Park, Isando 1600, South Africa.
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Novartis, Singapore. Novartis (Singapore) Pte Ltd, Pharmaceutical Division, 10 Hoe Chiang Road, 09-05/06 Keppel Towers, S 089315, Singapore.
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Novartis, Spain. Novartis Farmaceutica, Gran Via Corts Catalanes 764, 08013 Barcelona, Spain.
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Novartis, Swed. Novartis Sverige AB, Box 1150, 183 11 Täby, Sweden.
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Novartis, Switz. Novartis Pharma Schweiz AG, Monbijoustrasse 118, Postfach, 3001 Berne, Switzerland.
url: www.novartis.ch

Novartis, Thai. Novartis (Thailand) Ltd, 159/30 Vibhavadi Rangsit Rd, Laksi, Bangkok 10210, Thailand.
url: www.th.novartis.com

Novartis, Turk. Novartis İlaç Ltd. Şti., Barbaros Bulvarı No: 83, Beşiktaş, İstanbul, Turkey.
url: www.novartis.com.tr

Novartis, UK. Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 5SG, UK.
url: www.novartis.co.uk

Novartis, USA. Novartis Pharmaceuticals Corp., One Health Plaza, East Hanover, NJ 07936-1080, USA.
url: www.pharma.us.novartis.com

Novartis, Venez. Novartis de Venezuela S.A., 3ra. Transversal de Los Ruices Edif. Novartis, (68097) Los Ruices, Caracas, Venezuela.
url: www.novartis.com

Novartis Consumer, Arg. See *Novartis, Arg.*

Novartis Consumer, Austral. Novartis Consumer Health Australasia P/L, P.O. Box 4499, Mulgrave, VIC 3170, Australia.
url: www.novartisnutrition.com

Novartis Consumer, Austria. See *Gebro, Austria.*

Novartis Consumer, Belg. See *Novartis, Belg.*

Novartis Consumer, Canad. Novartis Consumer Health Canada Inc., 2233 Argentia Rd, Suite 205, Mississauga, Ontario, L5N 2X7, Canada.
url: www.ca.novartis.com

Novartis Consumer, Cz. See *Novartis, Cz.*

Novartis Consumer, Ger. Novartis Consumer Health GmbH, Zielstattstr. 40, 81379 Munich, Germany.
url: www.novartis-consumerhealth.de

Novartis Consumer, Hong Kong. See *Novartis, Hong Kong.*

Novartis Consumer, Hung. See *Novartis, Hung.*

Novartis Consumer, Irl. See *Novartis, Irl.*

Novartis Consumer, Israel. See *Novartis, Israel.*

Novartis Consumer, Ital. See *Novartis, Ital.*

Novartis Consumer, Malaysia. See *Novartis, Malaysia.*

Novartis Consumer, Neth. Novartis Consumer Health Benelux, Postbus 2014, 4800 CA Breda, Netherlands.
url: www.novartis.nl

Novartis Consumer, NZ. See *Novartis, NZ.*

Novartis Consumer, Pol. Novartis Poland Sp. zo.o.. Consumer Health OTC, ul. Bokserska 66, 02-690 Warsaw, Poland.
url: www.novartis.pl

Novartis Consumer, Port. Novartis Consumer Health, Lda, Av Poeta Mistral 2-2, 1069-172 Lisbon, Portugal.
url: www.consumer-health.novartis.com

Novartis Consumer, Rus. Novartis Consumer Health S.A., B. Palashevskii per. d.15, 123104 Moscow, Russia.
url: www.novartis.ru

Novartis Consumer, S.Afr. See *Novartis, S.Afr.*

Novartis Consumer, Spain. Novartis Consumer Health S.A., Marina 206, 08013 Barcelona, Spain.
url: www.novartisconsumerhealth.es

Novartis Consumer, Switz. Novartis Consumer Health Schweiz AG, Monbijoustrasse 118, 3001 Berne, Switzerland.
url: www.novartis-consumer-health.ch

Novartis Consumer, UK. Novartis Consumer Health, Wimblehurst Rd, Horsham, West Sussex, RH12 4AB, UK.
url: www.novartis.co.uk

Novartis Consumer, USA. Novartis Consumer Health Inc., 200 Kimball Drive, Parsippany, NJ 07054-0622, USA.
url: www.novartis.com

Novartis Nutrition, Canad. Novartis Nutrition Corporation, 2233 Argentia Road, Suite 205, West Tower, Mississauga, Ontario, L5N 2X7, Canada.
url: www.ca.novartis.com

Novartis Nutrition, Cz. See *Novartis, Cz.*

Novartis Nutrition, Fr. Laboratoires Novartis Nutrition, B.P. 29, 31250 Revel, France.
url: www.novartisnutrition.com

Novartis Nutrition, Hong Kong. See *Novartis, Hong Kong.*

Novartis Nutrition, Singapore. See *Zuellig, Singapore.*

Novartis Nutrition, USA. Novartis Nutrition Corp., 1600 Utica Ave. South, Suite 600, St. Louis Park, MN 55416, USA.
url: www.novartisnutrition.com

Novartis Ophthalmics, Arg. See *Novartis, Arg.*

Novartis Ophthalmics, Austral. See *Novartis, Austral.*

Novartis Ophthalmics, Braz. See *Novartis, Braz.*

Novartis Ophthalmics, Canad. See *Novartis, Canad.*

Novartis Ophthalmics, Cz. See *Novartis, Cz.*

Novartis Ophthalmics, Fr. See *Novartis, Fr.*

Novartis Ophthalmics, Ger. See *Novartis, Ger.*

Novartis Ophthalmics, Hong Kong. See *Novartis, Hong Kong.*

Novartis Ophthalmics, Hung. See *Novartis, Hung.*

Novartis Ophthalmics, Malaysia. See *Novartis, Malaysia.*

Novartis Ophthalmics, Rus. Novartis Ophthalmics, Krasnoproletarskaya, d.2/4, str.16, 103006 Moscow, Russia.
url: www.novartis.ru

Novartis Ophthalmics, Singapore. See *Novartis, Singapore.*

Novartis Ophthalmics, Swed. See *Novartis, Swed.*

Novartis Ophthalmics, Switz. See *Novartis, Switz.*

Novartis Ophthalmics, UK. See *Novartis, UK.*

Novartis Ophthalmics, USA. Novartis Ophthalmics Inc., 11695 Johns Creek Parkway, Duluth, GA 30097, USA.
url: www.novartis.com

Novartis OTC, Singapore. Novartis (Singapore) Pte Ltd OTC Division, 491B River Valley Rd, 14-04 Valley Point, S-248373, Singapore.

Novartis Sante, Fr. Novartis Santé Familiale SA, 14 bd Richelieu, B.P. 440, 92845 Rueil-Malmaison cdx, France.

Novartis Vaccines, Cz. See *Novartis, Cz.*

Novartis Vaccines, Hung. See *Novartis, Hung.*

Novartis Vaccines, Port. See *Novartis, Port.*

Novartis Vaccines, Singapore. See *Novartis, Singapore.*

Novartis Vaccines, UK. Novartis Vaccines, Symphony House, Robert Robinson Ave, The Oxford Science Park, Oxford, Oxfordshire, OX4 4GA, UK.
url: www.chironvaccines.com

Novartis Vaccines, USA. See *Novartis, USA.*

Novasorel, Ital. Novasorel Srl, Via del Corno 12, 40069 Zola Predosa (BO), Italy.

Novatec, Thai. Novatec Healthcare Co Ltd, 8 Fl, Yada Bldg, 58 Silom Rd, Bangrak, Bangkok 10500, Thailand.

Novavax, USA. Novavax Inc., 508 Lapp Rd, Malvern, PA 19355, USA.
url: www.novavax.com

Novaxo, Fr. Laboratoires Novaxo, 100 rte de Versailles, 78163 Marly-le-Roi cdx, France.

Novel, Ital. Novel OTC S.r.l., Via M. Bandello 4/2, 20123 Milan, Italy.

Novell, Hong Kong. See *CNW, Hong Kong*, and *Hong Tai Hong, Hong Kong.*

Novell, Indon. Novell Pharmaceutical PT, Jl Limo No 42 AB, Permata Hijau Senayan, 12220 Jakarta, Indonesia.

Noven, USA. Noven Pharmaceuticals, 11960 SW 144th St, Miami, FL 33186, USA.
url: www.noven.com

Noventis, Cz. Noventis sro, Filmová 174, 761 79 Zlín, Czech Republic.

Noventure, Spain. Noventure, C/Gran Capitan 2-4, 08034 Barcelona, Spain.

Novex, Fr. Novex, France.

Novexal, Gr. Novexal Hellas Ltd, Ag. Dimitriou 25, 17455 Kalamaki, Greece.
url: www.hexal.de

Novipharm, Austria. Novipharm GmbH, Klagenfurter Strasse 164, A-9210 Portschach, Austria.

Novis, Gr. Novis, Karistou 30, 144 51 Metamorfosi, Greece.

Novo Nordisk, Arg. Novo Nordisk Pharma Argentina S.A., Av. Del Libertador 14099, 1640 Martinez, Buenos Aires, Argentina.
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Novo Nordisk, Austral. Novo Nordisk Pharmaceuticals P/L, Level 3/21 Solent Circuit, Baulkham Hills, NSW 2153, Australia.
url: www.novonordisk.com.au

Novo Nordisk, Austria. Novo-Nordisk Pharma GmbH, Erdbrgstrasse 52-60/3/16, A-1030 Vienna, Austria.
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Novo Nordisk, Belg. Novo Nordisk Pharma SA, Blvd International 55, 1070 Brussels, Belgium.
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Novo Nordisk, Braz. Novo Nordisk Farmacêutica do Brasil Ltda, Av. Francisco Matarazzo 1.500, 12/14 andar, 05001-400 São Paulo, SP, Brazil.
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Novo Nordisk, Canad. Novo Nordisk Canada Inc., 2700 Matheson Blvd E, 3rd Floor, West Tower, Mississauga, Ontario, L4W 4V9, Canada.
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Novo Nordisk, Denm. See *Novo Nordisk, Swed.*

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Novo Nordisk, Hong Kong. Novo Nordisk Hong Kong Ltd, Unit 507, 5/F, Trade Square, 681 Cheung Sha Wan Rd, Kowloon, Hong Kong.
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Novo Nordisk, Hung. Novo Nordisk Hungária Kft, Felsőzöldmáli út 35, 1025 Budapest, Hungary.
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Novo Nordisk, Indon. Novo Nordisk Indonesia, Perkantoran Hisau Arkadia, Tower B, Penthouse Fl, Jl TB Simatupang Kav 88, 12520 Jakarta, Indonesia.

Novo Nordisk, Irl. Novo-Nordisk Pharmaceuticals Ltd, 3/4 Upper Pembroke St, Dublin 2, Ireland.
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Novo Nordisk, Israel. Novo Nordisk Ltd, 20 Hataas St, Kfar Saba 44425, Israel.
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Novo Nordisk, Ital. Novo Nordisk Farmaceutici S.p.A., Via Elio Vitorini 129, 00144 Rome (RM), Italy.
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Novo Nordisk, Jpn. Novo Nordisk Pharma Ltd, 5-7 Nihonbashi Ohdenma-cho, Chuo-ku, Tokyo 103-8575, Japan.
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Novo Nordisk, Malaysia. Novo Nordisk Pharma (Malaysia) Sdn Bhd, Suite 5.07, Level 5, Wisma KT, 14 Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
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Novo Nordisk, NZ. Novo Nordisk Pharmaceuticals Ltd, 58 Richard Pearse Drive, Airport Oaks, Mangere, New Zealand.
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Novo Nordisk, Singapore. See *JDH, Singapore.*

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Novo Nordisk, Turk. Novo Nordisk Sağlick Ürünleri Tic. Ltd. Şti., Nispetiye Cad., Akmerkez E-3 Blok Kat:7, Etiler, İstanbul, Turkey.
url: www.novoturk.com

Novo Nordisk, UK. Novo Nordisk Pharmaceuticals Ltd, Novo Nordisk House, Broadfield Park, Brighton Rd, Pease Pottage, Crawley, West Sussex, RH11 9RT, UK.
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Novo Nordisk, USA. Novo Nordisk Pharmaceuticals Inc., 100 College Rd West, Princeton, NJ 08540, USA.
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Novocol, USA. See *Septodont, USA.*

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Novolog, Israel. Novolog, Israel.

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Novopharm, Hong Kong. See *Primal, Hong Kong.*

Novopharm, Philipp. See *Diethelm, Philipp.*

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Novopharm, Singapore. See *Green Cross, Singapore.*

Novosibkhimfarm, Rus. See *Domestic, Rus.*

Novum, Belg. Novum Pharma s.p.r.l., Xavier de Cocklaan 66 bus 3, 9830 Sint-Martins-Latem, Belgium.

Novum, Mex. Novum Pharma SA de CV, Blvd Juan A de Torres 220-2, 37353 León, Gto Vibar, Mexico.

Novum, Neth. Novum Pharma BV, Van Panhuysstraat 47, 2203 JP Noordwijk, Netherlands.

Novyphar, Belg. Novyphar, Belgium.

NPBI, Neth. NPBI, Burgemeester Haspelslaan 15, 1181 NB Amstelveen, Netherlands.

NPC, Fr. Laboratoires NPC, 01290 Saint-André-d'Huiriat, France.

Nucare, UK. Nucare Plc, 494-496 Honeypot Lane, Stanmore, Middlesex, HA7 1JH, UK.
url: www.nucare.co.uk

Nucitec, Mex. Nucitec SA de CV, Hacienda de Jaltengo 13, 14350 Prado Coapa, Mexico DF, Mexico.

Nucleopharm, Arg. Nucleopharm SRL, Av. Remedios 5341/49, 1440 Buenos Aires, Argentina.

Nucleus, Iceland. Nucleus ehf, Box 55, Nasustanes, 116 Reykjavik, Iceland.

Nucleus, Neth. See *Nucleus, Iceland.*

Nucliber, Spain. Nucliber S.A., Hierro 9, 28045 Madrid, Spain.
url: www.nucliber.com

Nucro-Technics, Canad. Nucro-Technics, 2000 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.
url: www.nucro-technics.com

Nufarindo, Indon. Nufarindo Pharma Lab, Mangkang Kulon Km 16.5 Kec Tugu, 50155 Semarang, Jawa Tengah, Indonesia.

Nu-Life, Canad. Nu-Life Nutrition Ltd, 68 Leek Crescent, Richmond Hill, Ontario, L4B 1H1, Canada.

Numark, Canad. See *Numark, USA.*

Numark, UK. Numark Management Ltd, 5/6 Fairway Court, Amber Close, Tamworth Business Park, Tamworth, Staffordshire, B77 4RP, UK.
url: www.numarkpharmacists.com

Numark, USA. Numark Laboratories Inc., 164 North Field Ave, Edison, NJ 08818, USA.
url: www.numarklabs.com

Numil, Turk. Numil Gıda Ürünleri San. ve Tic. A.Ş., Yapi Kredi Plaza B Blok, K:9 No: 24, Levent, İstanbul, 80620, Turkey.
url: www.nutricia.com.tr

Nuova Signorini, Ital. Nuova Signorini G & C Sas, Via Pozzo Castello 1/A, 47843 Misano Adriatico (RN), Italy.
url: www.nuovasignorini.com

Nuovo ISM, Ital. Nuovo Istituto Sieroterapico Milanese S.r.l., Barga, Castelvecchio Pascoli (LU), Italy.

Nupel, Spain. Laboratorios Asociados Nupel S.L., Rua Carpinteiros 25, 27003 Lugo, Spain.

Nu-Pharm, Canad. Nu-Pharm Inc., 50 Mural St, Units 1 & 2, Richmond Hill, Ontario, L4B 1E4, Canada.

Nupharma, Thai. Nupharma & Healthcare Co Ltd, 18 Soi Plubpla, Thungmongkorn Rd, Talingchan, Thailand.

Nutergia, Fr. Laboratoires Nutergia, B.P. 52, 12700 Capdenac, France.
url: www.nutergia.fr

NutraCea, USA. NutraCea, 1261 Hawks Flight Court, El Dorado Hills, CA 95762, USA.
url: www.nutracea.com

Nutraceuticals, UK. Nutraceuticals Ltd, Wortley House, 16 Eastbourne Rd, Hornsea, East Yorkshire, HU18 1QS, UK.
url: www.calciumclear.com

Nutralife, UK. Nutralife UK Ltd, Omicron House, Fircroft Way, Edenbridge, Kent, TN8 6EL, UK.

Nutraloric, USA. Nutraloric, 350 N Lantana, Unit G1, Camarillo, CA 93010, USA.

Nutramax, USA. NutraMax Laboratories Inc., 208 Lakeside Bvld, Edgewood, MD 21040, USA.
url: www.nutramaxlabs.com

Nutrasweet, NZ. Nutrasweet Consumer Products, P.O. Box 3872, Auckland, New Zealand.
url: www.nutrasweet.com

Nutravite, Canad. Nutravite, 1470 Leathead Rd, Unit 2, Kelowna, British Columbia, V1X 7J6, Canada.
url: www.nutravite.com

Nutri Gizindo, Indon. Nutri Gizindo Nusantara PT, Jl Jelambar Slt II 4, Jakarta 11460, Indonesia.

Nutrichem Diat, Cz. Nutrichem Diat.

Nutricia, Austral. Nutricia Australia P/L, 14-16 Brookhallow Avenue, Baulkham Hills, NSW 2153, Australia.
url: www.nutricia.com

Nutricia, Canad. Nutricia Canada Inc., 35 Webster St, Suite 103, Kentville, Nova Scotia, B4N 1N4, Canada.
url: www.nutriciacanada.com

Nutricia, Cz. Nutricia as, Pod Višňovkou 25, 142 01 Prague 4, Czech Republic.

Nutricia, Fin. Nutricia Oy, Linnankatu 26 A, 20100 Turku, Finland.
url: www.nutricia.fi

Nutricia, Fr. Nutricia, 4 rue Joseph-Monier, 92859 Rueil-Malmaison cdx, France.
url: www.nutricia.fr

Nutricia, Hong Kong. Nutricia (Asia-Pacific) Ltd, Suite 1505, 15/F Harcourt House, 39 Gloucester Rd, Wanchai, Hong Kong.
url: www.nutricia.com

Nutricia, Indon. Nutricia Indonesia PT, Menara Jamsostek Lt 19, Jl Gatot 4 Subroto Kav 38, 12930 Jakarta, Indonesia.

Nutricia, Irl. Nutricia Ireland Ltd, Deansgrange Business Park, Deansgrange, Co. Dublin, Ireland.
url: www.nutricia.com

Nutricia, Ital. Nutricia S.p.A., Via Lepetit 8, 20020 Lainate (MI), Italy.
url: www.nutricia.it

Nutricia, Mex. Nutricionales American S.A. de C.V., Iglesia 2, Torre E Desp. 601, Col. Tizapan de San Angel, 01090 Mexico D.F., Mexico.
url: www.nutricia.com

Nutricia, NZ. Nutricia New Zealand, P.O. Box 62523, Central Park, Auckland 6, New Zealand.
url: www.nutricia.com

Nutricia, Pol. Nutricia Polska Sp. zo.o., ul. Poselska 29, 03-931 Warsaw, Poland.
url: www.nutricia.com.pl

Nutricia, Port. Nutricia Portugal. Lda, Rua da Fraternidade Oerária, 2794-024 Carnaxide, Portugal.
url: www.nutricia.pt

Nutricia, Thai. See *BJC, Thai.*

Nutricia, Turk. See *Numil, Turk.*

Nutricia, Venez. See *Klinos, Venez.*

Nutricia Clinical, Fin. Nutricia Clinical Oy, Linnankatu 26 A, 20100 Turku, Finland.
url: www.nutricia.fi

Nutricia Clinical, UK. Nutricia Clinical Care, Nutricia Ltd, Newmarket Ave, White Horse Business Park, Trowbridge, Wiltshire, BA14 0XQ, UK.
url: www.nutricia-clinical-care.co.uk

Nutricia Dietary, UK. See *Nutricia Clinical, UK.*

Nutricia-Bago, Arg. Nutricia-Bagó S.A., Marcelo T de Alvear 590 Piso 1, 1058 Buenos Aires, Argentina.
url: www.nutricia-bago.com.ar

Nutricia-Loma Lindar, USA. See *Nutricia, Mex.*

Nutricional, Arg. Nutricional Argentina SRL, Av. Pueyrredon 924, Piso 3 F, 1032 Buenos Aires, Argentina.

Nutricorp, Canad. Nutricorp International, 4025 Rhodes Drive, Windsor, Ontario, N8W 5B5, Canada.

Nutridiver, Spain. Nutridiver SL, C/del Pont Reixat 5, 08960 Sant Just Desvern, Barcelona, Spain.

Nutrifar, Ital. Nutrifar S.r.l., Via Andreis 74, 25015 Desenzano Del Garda (BS), Italy.

Nutrifarma, Turk. Nutrifarma Sağlıck Ürün ve Hizm. A.Ş., Büyükdere Cad., Nurol Plaza No:71 K:19, Maslak, İstanbul, 80870, Turkey.
url: www.nutrifarma.com.tr

Nutrilab, Braz. See *Farmoquimica, Braz.*

Nutrimed, Fr. Nutrimed Medic System, 6/10 rue Mirabeau, 75016 Paris, France.

Nutrimed, Switz. Nutrimed AG, Pharmazeutische und diatetische Produkte, Spalenvorstadt 34, 4051 Basle, Switzerland.
url: www.nutrimed.ch

Nutripharm, USA. Nutripharm Laboratories Inc., Salem Industrial Park, Building 5, Lebanon, NJ 08833, USA.

Nutrisante, Fr. Nutrisanté (Lab), Parc d'activité Sud Loire, BP 1211, 85612 Montaigu cdx, France.
url: www.nutrisante.fr

Nutrisoy, USA. See *Mothersoy, USA.*

Nutrition & Sante, Ital. Nutrition & Santé SpA, L.go Umberto Boccioni 1, 21040 Origgio (VA), Italy.

Nutrition 21, USA. Nutrition 21, 4 Manhattanville Rd, Purchase, NY 10577, USA.
url: www.nutrition21.com

Nutri-Well, Hong Kong. See *Winsor, Hong Kong.*

Nuvia, Fr. Nuvia (Lab), 92 bvd Flandrin, 75116 Paris, France.
url: www.lovamine.fr

Nycomed, Arg. Nycomed Argentina, Adolfo Alsina 2954, 1205 Buenos Aires, Argentina.
url: www.nycomed.com

Nycomed, Austria. Nycomed Austria GmbH, St Peter-Strasse 25, A-4020 Linz, Austria.

Nycomed, Belg. Nycomed Christiaens, Chris Juliam, Gentsesteenweg 615, 1080 Brussels, Belgium.
url: www.nycomed.be

Nycomed, Braz. Nycomed Pharma Ltda, Rua do Estilo Barrocco 721, 04709-011 São Paulo, Brazil.

Nycomed, Cz. Nycomed sro, Novodvorská 994/138, 142 21 Praha 4, Czech Republic.

Nycomed, Denm. Nycomed Danmark A/S, Langebjerg 1, 4000 Roskilde, Denmark.
url: www.nycomed.dk

Nycomed, Fin. See *Oriola, Fin.*

Nycomed, Fr. Nycomed France SAS, 140 av. Jean Lolive, 93695 Pantin cdx, France.

Nycomed, Ger. Nycomed Pharma GmbH, Edisonstr. 16, 85716 Unterschleissheim, Germany.
url: www.nycomed.de

Nycomed, Gr. Nycomed Hellas, Kifissias 196, 152 31 Halandri, Greece.
url: www.nycomed.com

Nycomed, Hong Kong. See *IDS, Hong Kong.*

Nycomed, Hung. Nycomed Kft, Konkoly Thege Miklós út 29-33, 1121 Budapest, Hungary.

Nycomed, Irl. See *Newport, Irl.*

Nycomed, Israel. See *Medison, Israel.*

Nycomed, Ital. See *Amersham, Ital.*

Nycomed, Neth. Nycomed BV, Nikkelstraat 5, 4823 AE Breda, Netherlands.
url: www.nycomed.nl

Nycomed, Norw. Nycomed Pharma AS, Drammensv. 852, Postboks 205, 1372 Asker, Norway.
url: www.nycomed.no

Nycomed, Pol. Nycomed Polska Sp. zo.o., ul. Dworkowa 3, 00-784 Warsaw, Poland.

Nycomed, Port. See *Nycomed, Denm.*

Nycomed, Rus. Nycomed Pharma AS, Central Office, Timura Frunze ul. 24, 119021 Moscow, Russia.
url: www.nycomed.ru

Nycomed, Singapore. See *FP, Singapore.*

Nycomed, Spain. See *Amersham, Spain.*

Nycomed, Swed. Nycomed AB, Box 1215, 181 24 Lidingo, Sweden.
url: www.nycomed.se

Nycomed, Switz. Nycomed AG, Moosacherstrasse 14, Au, 8820 Wadenswil, Switzerland.
url: www.nycomed.ch

Nycomed, Thai. See *Shiwa, Thai.*

Nycomed, UK. Nycomed UK Ltd, 3 Globside Business Park, Fieldhouse Lane, Marlow, Buckinghamshire, SL7 1HZ, UK.

Nycomed, USA. See *Amersham Biosciences, USA.*

Nycomed Amersham, UK. See *Amersham, UK.*

Nycomed Imaging, Canad. See *Amersham, Canad.*

NZ Distributors, NZ. New Zealand Distributors Ltd, P.O. BOX 41014, St Lukes, Auckland, New Zealand.

NZ Medical & Scientific, NZ. New Zealand Medical & Scientific Ltd, P.O. Box 24-138, Royal Oak, Auckland, New Zealand.
url: www.nzms.co.nz

Oakhurst, USA. Oakhurst Co., 3000 Hempstead Turnpike, Levittown, NY 11756, USA.
url: www.omedicine.com

OBA, Denm. OBA Pharma ApS, Kronprinsessegade 26 A (postboks 117), 1004 Copenhagen K, Denmark.

Obagi, Indon. Obagi Indonesia PT, Jl Gunawarman 45, 12180 Jakarta, Indonesia.
url: www.obagi.sg

Oberlin, Fr. See *UPSA Conseil, Fr.*

Obex, NZ. Obex Medical Ltd, 303 Manukau Rd, P.O. Box 26511, Epsom, Auckland, New Zealand.
url: www.obex.co.nz

Oboi, Philipp. See *Pharmawealth, Philipp.*

Obolenskoe, Rus. See *Domestic, Rus.*

Ocean Nutrition, Canad. Ocean Nutrition Canada Ltd, 101 Research Drive, Dartmouth, Nova Scotia, B2Y 4T6, Canada.

OCFZP, Pol. OCFZP Biostymulator International Trading Co. Sp. zo.o., ul. Ks. Łysika 6 B, 46-300 Olesno, Poland.

Oclassen, USA. See *Watson, USA.*

Octafarma, Mex. Octafarma SA de CV, Calzada de Mexico Tacuba 1419, 11230 M Hidalgo Nueva Argentina, Mexico DF, Mexico.

Octapharma, Austral. Octapharma Australia Pty Ltd, Jones Bay Wharf, 42/26-32 Pirrama Rd, Pyrmont, NSW 2009, Australia.

Octapharma, Austria. Octapharma Pharmazeutika, Oberlaaer Strasse 235, A-1100 Vienna, Austria.
url: www.octapharma.com

Octapharma, Belg. Octapharma SA, Rue de Stalle 63, 1180 Brussels, Belgium.
url: www.octapharma.com

Octapharma, Cz. See *Octapharma, Austria.*

Octapharma, Denm. Octapharma Nordic AB, Naesseslottet, Dronninggårds Allé 136, 2840 Holte, Denmark.

Octapharma, Fin. Octapharma AB, Myyrmaentie 2 B, 01600 Vantaa, Finland.
url: www.octapharma.com

Octapharma, Fr. Laboratoires Octapharma SA, 70-72 rue du Maréchal-Foch, B.P. 33, 67381 Lingolsheim, France.
url: www.octapharma.com

Octapharma, Ger. Octapharma Vertrieb von Plasmaderivaten GmbH, Bahnhofstr. 43, 40764 Langenfeld, Germany.
url: www.octapharma.de

Octapharma, Gr. Octapharma Hellas S.A., 60 Poseidonos Ave, 166 75 Glyfada, Greece.
url: www.octapharma.gr

Octapharma, Hong Kong. See *Weston, Hong Kong.*

Octapharma, Hung. Octapharma Képviselet, Harcsa u 2, 1023 Budapest, Hungary.

Octapharma, Mex. Octapharma SA de CV, Calzada de México Tacuba 1419, 11230 M Hidalgo Nueva Argentina, Mexico.

Octapharma, Neth. Octapharma, Netherlands.

Octapharma, Norw. Octapharma AS, Furubakken, 2090 Hurdal, Norway.
url: www.octapharma.com

Octapharma, NZ. Octapharma New Zealand Ltd, Lumley Centre, 88 Shortland St, Auckland, New Zealand.

Octapharma, Port. Octapharma Produtos Farmacêuticos Lda, Rua da Graca 14, 1170-169 Lisbon, Portugal.

Octapharma, Rus. Octapharma, Smolensk pl. 3, 121099 Moscow, Russia.

Octapharma, Spain. Octapharma S.A., Diego Garcia, Parque Empresarial de San Fernando, Av. Castilla 2, 28830 Madrid, Spain.
url: www.octapharma.es

Octapharma, Swed. Octapharma AB, Nordenflychtsvägen 55, 112 75 Stockholm, Sweden.
url: www.octapharma.com

Octapharma, Switz. Octapharma AG, Seidenstrasse 2, Postfach 239, 8853 Lachen, Switzerland.
url: www.octapharma.com

Octapharma, Thai. See *Hua, Thai.*

Octapharma, UK. Octapharma Ltd, 6 Elm Court, Copse Drive, Coventry, CV5 9RG, UK.
url: www.octapharma.com

Octapharma, USA. Octapharma USA, Inc., 5885 Trinity Parkway, Suite 350, Centreville, VA 20170, USA.
url: www.octapharmausa.com

Ocumed, USA. OcuMed Inc., 1307 W. Fillmore, Chicago, IL 60607, USA.
url: www.ocumed.com

Ocusoft, USA. Cynacon/OCuSOFT, 5311 Ave N, P.O. Box 429, Richmond, TX 77406-0429, USA.
url: www.ocusoft.com

Odan, Canad. Odan Laboratories Ltd, 255 Hymus Bvld, Pointe-Claire, Quebec, H9R 1G6, Canada.
url: www.odanlab.com

Odin, Spain. See *AstraZeneca, Spain.*

Odontomed, Braz. Laboratório Odontomed Indústria e Comércio Ltda, Avenida Bosque da Saúde 1088, 04142-081 São Paulo, SP, Brazil.

Odontopharm, Switz. Odontopharm AG, Engestrasse 23, 3012 Bern, Switzerland.

Odyssey, USA. Odyssey Pharmaceuticals Inc, 200 Park Ave., Florham Park, NJ 07932, USA.
url: www.odysseypharm.com

Oenobiol, Fr. Laboratoires Oenobiol, 59 bd Exelmans, 75781 Paris cdx 16, France.
url: www.oenobiol.com

OEP, Philipp. OEP Philippines Inc., Rm 606 Sedcco 1 Bldg, Cor Rada & Legaspi Sts, Legaspi Vill, Makati City, Philippines.

Ofar, Arg. Dist. Ofar S.A., Salom 651, 1277 Buenos Aires, Argentina.

OFF, Ital. Officina Farmaceutica Fiorentina S.r.l. Istituto Biochimico, Quart. Varignano 12-14, 55049 Viareggio (Lucca), Italy.

Offenbach, Mex. Offenbach Mexicana S.A. de C.V., Cda. del Rosedal 3, Col. Reforma Social, 11650 Mexico D.F., Mexico.

Ofimex, Mex. See *Aventis, Mex.*

Oftalder, Port. See *Edol, Port.*

Oftalmi, Venez. Laboratorios L.O. Oftalmi C.A., Edificio Santo Domingo, Calle 6, Zona Industrial La Urbina, Apto 66285, Caracas 1061-A, Venezuela.
url: www.oftalmi.com

Ogera, Switz. Ogera AG, Lerzenstrasse 18, 8953 Dietikon, Switzerland.

Ogna, Ital. Giovanni Ogna & Figli S.p.A., Via Figini 41, 20053 Muggio (MI), Italy.
url: www.ogna.it

Ohara, Jpn. Ohara Chemical Industries Ltd, 43-1 Oharaichiba, Koka-cho, Koka-gun, Shiga 520-3433, Japan.

Ohara, Philipp. See *Crisdy-Na, Philipp.*

Ohmeda, USA. See *Baxter, USA.*

Ohropax, Switz. See *Uhlmann-Eyraud, Switz.*

OJG, Belg. See *Novum, Belg.*

Okasa, Thai. See *IDS, Thai.*

Olan-Kemed, Thai. Olan-Kemed Co. Ltd, 176 Ladprao Rd, Bangkok 10900, Thailand.

Olbas, Ger. See *Schoenenberger, Ger.*

Olgunsoy, Turk. Olgunsoy İlaç ve Kozmetik Sanayi A.Ş., 4152 Sok. No: 31, Karabağlar, İzmir, Turkey.
url: www.olgunsoy.com

Olic, Thai. Olic (Thailand) Ltd, 280 New Rd, Bangkok 10100, Thailand.
url: www.olic-thailand.com

Olinka, Neth. See *Olinka, UK.*

Olinka, UK. Olinka UK Ltd, 38/40 Chamberlayne Rd, London, NW10 3JE, UK.

Olvos, Gr. OLVOS SCIENCE A.E., Achilleos 2, 104 37 Athens, Greece.

OM, Cz. See *Pharmedial, Cz.*

OM, Hong Kong. See *Primal, Hong Kong.*

OM, Hung. OM Hungária Kft, Mandula köz 6, 2089 Telki, Hungary.

OM, Indon. See *Corsa, Indon.*

OM, Malaysia. See *Pharmaforte, Malaysia.*

OM, Philipp. See *Zuellig, Philipp.*

OM, Pol. See *Pharmbos, Pol.*

OM, Port. OM Portuguesa, SA, Rua da Indústria no 2, Quinta Grande, 2720-302 Alfragide, Portugal.
url: www.ompharma.com

OM, Rus. See *Grunenthal, Rus.*

OM, Switz. OM Pharma, 22 rue du Bois-du-Lan, 1217 Meyrin 2/Geneva, Switzerland.
url: www.ompharma.com

Ombrelle, Canad. Ombrelle Canada, 4895 Hickmore, Montreal, Quebec, H4T 1K5, Canada.

Omedir, Arg. Laboratorios Omedir S.A., Corvalan 1983/85, 1440 Buenos Aires, Argentina.

Omega, Arg. Esp. Medicinales Omega, Serrano 985, 1414 Buenos Aires, Argentina.

Omega, Belg. Omega Pharma, Industriepark De Prijkels, Venecoweg 26, 9810 Nazareth, Belgium.
url: www.omega-pharma.be

Omega, Canad. Omega Laboratories Ltd, 11177 Hamon St, Montreal, Quebec, H3M 3A2, Canada.
url: www.omegalaboratory.com

Omega, Fr. Omega Pharma SA, Rue Chaintron 2/4, B.P. 850, 92120 Montrouge, France.

Omega, Gr. Omega Pharma Hellas, 19o chlm. Ethn. Odou Athinon-Lamias, 146 71 N Erithraia, Greece.

Omega, Irl. Omega Diagnostics Ireland Ltd, Unit A6, Southern Cross Business Park, Boghall Rd, Bray, Co. Wicklow, Ireland.
url: www.omegairl.com

Omega, Spain. See *Almirall, Spain.*

Omega Rex, Pol. Omega Rex, ul. Instalatorów 9, 02-237 Warsaw, Poland.

Omegin, Ger. Omegin Dr Schmidgall GmbH & Co. KG, Industriepark 210, 78244 Gottmadingen, Germany.
url: www.omegin.de

Omeofarma, Ital. Omeofarma S.r.l., Via di Morena 12/a, 00043 Ciampino (Rome), Italy.

Omicron, Arg. Laboratorio Omicron SA, Calle 23 Esquina Calle 66, 1651 San Martin Villa Zagela, Buenos Aires, Argentina.

Omida, Switz. Omida AG, Homoopathische Heilmittel, Erlistrasse 2, 6403 Kussnacht a.R., Switzerland.

OMJ, Hong Kong. See *Keller, Hong Kong.*

Omni, UK. Omni Nutraceuticals Ltd, 8 St. Thomas Place, Cambridgeshire Business Park, Ely, Cambridgeshire, CB7 4EX, UK.
url: www.omninutra.co.uk

Omnii, USA. Omnii Oral Pharmaceuticals, 1500 N Florida Mango Rd, Suite 1, West Palm Beach, FL 33409, USA.
url: www.omniipharma.com

Omnimed, S.Afr. See *Braun, S.Afr.*

Omninvest, Hung. Omninvest, P.O. Box 112, 1506 Budapest, Hungary.
url: www.omninvest.hu

Omni-Protech, India. Omni-Protech Drugs Pvt Ltd, C-4, 13 Functional Elec. Est., Bhosari, Pune 411 026, India.

OmniVision, Denm. See *OmniVision, Swed.*

OmniVision, Ger. OmniVision GmbH, Lindbergstr. 7, 82178 Puchheim, Germany.
url: www.omnivision-pharma.com

OmniVision, Norw. See *OmniVision, Swed.*

OmniVision, Swed. OmniVision AB, Svärdvägen 11C, SE-182 33 Danderyd, Sweden.

OmniVision, Switz. OmniVision AG, Zentralstrasse 100, 8212 Neuhausen am Rheinfall, Switzerland.

Omrix, Belg. Omrix Biopharmaceuticals SA, Waterloo Rd Center, Chaussee de Waterloo 200, 1640 Rhode-St-Genese, Belgium.
url: www.omrix.com

Omrix, Ger. See *Omrix, Belg.*

Omrix, Israel. Omrix Biopharmaceuticals Ltd, MDA Blood Center, Tel Hashomer Hospital, Tel Aviv 52621, Israel.
url: www.omrix.com

Omrix, Neth. See *Omrix, Belg.*

Omrix, Port. See *Omrix, Belg.*

One Drop Only, Ger. One Drop Only Chem.-pharm.-Vertriebs-GmbH, Stieffring 14, 13627 Berlin, Germany.
url: www.onedroponly.de

One Pharma, Philipp. One Pharma Co Inc., A Liwanag cor G Diaz St, BFRV Classic 1, Las Piñas City, Philippines.
url: www.onepharma.com.ph

Onko, Turk. Onko & Koçsel İlaçlari, Koşuyolu Cad. No: 102, Kadiköy, İstanbul, 34718, Turkey.
url: www.onkokocsel.com

Onkoworks, Ger. Onkoworks Gesellschaft zur Herstellung und Vertrieb onkologischer Spezialpräparate mbH, Schallbruch 5, 42781 Haan/Rhid., Germany.
url: www.onkoworks.de

Ono, Jpn. Ono Pharmaceutical Co. Ltd, 2-1-5 Doshomachi, Chuo-ku, Osaka 541-8526, Japan.
url: www.ono.co.jp

Onset, USA. Onset Therapeutics, 400 Highland Corporate Drive, Cumberland, RI 02864, USA.
url: www.onsettx.com

Onstrong, Hong Kong. Onstrong Ltd, Rm B, 11/F, Bright Growth Medical Ctr, 335 Nathan Rd, Kowloon, Hong Kong.

Ony, Israel. See *Rafa, Israel.*

Onyx, Rus. Onyx Farma, Grokholskii per. 13, str. 2, 129010 Moscow, Russia.

OP, Ital. OP Pharma Srl, Via Torino 51, 20123 Milan, Italy.

Opakim, Turk. Opakim, Turkey.

Opco, Denm. Opco Pharma A/S, Messingvej 54, 8900 Randers, Denmark.
url: www.opco.dk

Openfar, Spain. Openfar, C/Collado Mediano SN, 28230 Las Rozas, Madrid, Spain.

Opfermann, Ger. Opfermann Arzneimittel GmbH, Robert-Koch-Str. 2, 51674 Wiehl, Germany.
url: www.opfermann.de

Ophtapharma, Canad. Ophtapharma Canada Inc., 1100 Cremazie E, Suite 708, Montreal, Quebec, H2P 2X2, Canada.

Ophtha, Denm. Ophtha A/S, Halmtorvet 29, 1700 Copenhagen V, Denmark.
url: www.ophtha.dk

Ophtha, Norw. See *Ophtha, Denm.*

Ophthalmic Laboratories, Austral. Ophthalmic Laboratories P/L, 41 Sydenham Rd, Brookvale, NSW 2100, Australia.

OPi, Canad. See *OPi, Fr.*

OPi, Cz. See *OPi, Fr.*

OPi, Fr. OPi SA, 3 allee des Sequioas, 69760 Limonest, France.

OPi, Neth. See *OPi, Fr.*

OPi, UK. OPi Ltd, Aston House, York Rd, Maidenhead, Berkshire, SL6 1SF, UK.

Opocalcium, Fr. Laboratoires de l'Opocalcium, 20 rue Louis-Charles-Vernin, 77190 Dammarie-les-Lys, France.

Opopharma, Switz. Opopharma SA, Kirchgasse 42, 8001 Zurich, Switzerland.

Optident, UK. Optident Dental Products, International Development Centre, Valley Drive, Ilkley, West Yorkshire, LS29 8PB, UK.
url: www.optident.co.uk

Optik, Turk. Optik Medikal İlaç Ltd. Şti., Valikonaği Cad. No: 173, B Blok N: 5, Nişantaşi, İstanbul, 80220, Turkey.
url: www.optikmedikal.com

Optikem, USA. Optikem International Inc., 2172 S Jason St, Denver, CO 80223, USA.

Optima, Ger. Optima Pharmazeutische GmbH, Schäfflerstr. 7, 85368 Moosburg, Germany.
url: www.optimapharma.de

Optima, UK. Optima Health Ltd, 47/48 St Mary St, Cardiff, South Glamorgan, CF10 1AD, UK.
url: www.optimah.com

Optimapharma, Canad. See *Taro, Canad.*

Optimed, Ger. Optimed Pharma GmbH, Alfred-Nobel-Str. 5, 50226 Frechen, Germany.
url: www.optimed-pharma.de

Optimox, USA. Optimox Corp., P.O. Box 3378, Suite 406, Torrance, CA 90510-3378, USA.
url: www.optimox.com

Optopics, USA. Optopics, USA.

Optrex, India. Optrex, India.

Optrex, Malaysia. See *Boots Healthcare, Malaysia.*

Optrex, Singapore. See *Boots, Singapore.*

Opus, S.Afr. Opus Pharmaceuticals (Pty) Ltd, P.O.Box 78618, Sandton 2146, South Africa.

Opus, UK. See *Trinity, UK.*

Opus Materia, Gr. Opus Materia, Palaiologou 33, 175 64 P. Faliro, Greece.

OPW, Ger. See *Altana, Ger.*

Oral-B, Arg. See *Gillette, Arg.*

Oral-B, Austral. Oral-B Laboratories P/L, 5 Caribbean Drive, Scoresby, VIC 3179, Australia.
url: www.oralb.com

Oral-B, Canad. Oral-B Laboratories Ltd, 4 Robert Speck Parkway, Suite 1000, Mississauga, Ontario, L4Z 4C5, Canada.
url: www.oralb.com

Oral-B, Ital. Oral-B Laboratories, Gillette Group Italy S.p.A., Business Unit Braun-Oral Care, Via Pirelli 18, 20124 Milan, Italy.
url: www.oralb.com

Oral-B, USA. Braun Oral-B Consumer Services, 1 Gillette Park, South Boston, MA 02127-1096, USA.
url: www.oralb.com

Oraldent, UK. Oraldent Ltd, Unit 11, Harvard Industrial Estate, Kimbolton, Cambridgeshire, PE28 0NJ, UK.
url: www.oraldent.co.uk

Oramon, Ger. Oramon Arzneimittel GmbH, Mittelstr. 18, 88471 Laupheim, Germany.

Oramon, Neth. See *Oramon, Ger.*

Oramon, Pol. See *Solpharm, Pol.*

Orapharma, Neth. Orapharma Europe Inc., Professor JH Bavincklaan 7, 1183 AT Amstelveen, Netherlands.

Orapharma, Port. See *Orapharma, Neth.*

OraPharma, USA. OraPharma Inc., 732 Louis Dr., Warminster, PA 18974, USA.
url: www.orapharma.com

Orbis Consumer, UK. See *Kappin, UK.*

Orbus, Canad. Orbus Pharma Inc., 20 Konrad Crescent, Markham, Ontario, L3R 8T4, Canada.

Orchid, Hong Kong. See *Mekim, Hong Kong.*

Orchid, India. Orchid, India.

Orchid, Philipp. See *PharmAsia, Philipp.*

Ordesa, Ital. Ordesa Logistica Srl, Via Andrea Doria 48/B, 20124 Milan (MI), Italy.
url: www.ordesa.it

Ordesa, Spain. Ordesa, Ctra del Prat 9-11, Sant Boi de Llobregat, 08830 Barcelona, Spain.
url: www.ordesa.es

Or-Dov, Austral. Or-Dov Pharmaceuticals P/L, P.O. Box 172, Doncaster, VIC 3108, Australia.

Orexo, Denm. See *Orexo, Swed.*

Orexo, Swed. Orexo AB, Box 303, 751 05 Upsala, Sweden.
url: www.orexo.com

Organifar, Venez. Organifar S.A., Av. Rómulo Gallegos, Torre Samán Piso 4 Ofic. A-4, (1071) Los Dos Caminos, Caracas, Venezuela.

Organon, Arg. Organon Argentina SA, Sucre 865, 1428 Buenos Aires, Argentina.
url: www.organon.com.ar

Organon, Austral. Organon (Australia) P/L, Private Bag 25, Lane Cove, NSW 2066, Australia.
url: www.organon.com

Organon, Austria. Organon GmbH, Siebenbrunnengasse 21/D/IV, A-1050 Vienna, Austria.
url: www.organon.at

Organon, Belg. Organon SA, Crown Building, Chaussee de la Hulpe 166, 1170 Brussels, Belgium.
url: www.organon.be

Organon, Braz. See *Akzo, Braz.*

Organon, Canad. Organon Canada Ltd, 200 Consillium Place, Suite 700, Scarborough, Ontario, M1H 3E4, Canada.
url: www.organon.ca

Organon, Chile. Organon Chile Ltda, Loreley 1582, La Reina, Santiago, Chile.

Organon, Cz. Organon sro, Pobřežni 3, 186 00 Prague 8, Czech Republic.
url: www.organon.cz

Organon, Denm. Organon AS, Literbuen 9, 2740 Skovlunde, Denmark.
url: www.organon.dk

Organon, Fin. Oy Organon AB, Maistraatinportti 2, PL 101, 00241 Helsinki, Finland.
url: www.organon.fi

Organon, Fr. Organon, 10 rue Godefroy, 92821 Puteaux cdx, France.
url: www.organon.fr

Organon, Ger. Organon GmbH, Mittenheimer Strasse 62, 85764 Oberschleissheim, Germany.
url: www.organon.de

Organon, Gr. Organon Hellas S.A., P.O. Box 73892, 167 77 Elliniko, Greece.
url: www.organon.gr

Organon (Oργανον), Gr. See *Organon, Gr.*

Organon, Hong Kong. Organon (HK) Ltd, 27/F, 88 Hing Fat St, Causeway Bay, Hong Kong.
url: www.organon.com

Organon, Hung. Organon Hungary kereskedelmi Kft, Róbert Károly krt 64-66 III em, 1134 Budapest, Hungary.
url: www.organon.hu

Organon, India. Organon (India) Ltd, Nishuvi House, 75 Dr Annie Besant Rd, Worli, Mumbai, India.

Organon, Indon. Organon Indonesia PT, Jl R C Veteran-Bintaro, Kebayoran Lama, 12330 Jakarta, Indonesia.

Organon, Irl. See *United Drug, Irl.*

Organon, Israel. See *Neopharm, Israel.*

Organon, Ital. Organon Italia S.p.A., Via Ostilia 15, 00100 Rome, Italy.
url: www.organon.it

Organon, Jpn. Nippon Organon K.K., 5-90 Tomobuchi-cho 1-chome, Miyakojima-ku, Osaka City 534-0016, Japan.
url: www.organon.jp

Organon, Malaysia. Organon (M) Sdn Bhd, Level 4, Building A, Paremba Square, Saujana Resort, Seksyen U2, 40150 Shah Alam, Selangor, Malaysia.
url: www.organon.com

Organon, Mex. Organon Mexicana S.A. de C.V., Calz. de Camarones No.134, Col. San Salvador Xochimanca, Deleg. Azcapotzalco, 02870 Mexico D.F., Mexico.
url: www.organon.com.mx

Organon, Neth. Organon Nederland BV, Griekenweg 25, 5342 PX Oss, Netherlands.
url: www.organon.nl

Organon, Norw. Organon AS, Johan Drengsrudsv. 52, Postboks 324, 1372 Asker, Norway.
url: www.organon.no

Organon, NZ. See *Pharmaco, NZ.*

Organon, Philipp. Organon Philippines Inc., 5/F Feliza Bldg, 108 VA Rufino St, Legaspi Vill, MCPO Box 2003, Makati City, Philippines.

Organon, Pol. Organon Polska Sp. zo.o., ul. Poleckzi 21, 02-822 Warsaw, Poland.
url: www.organon.com.pl

Organon, Port. Organon Portuguesa, Lda, Av. Conde Valbom 30, 1069-037 Lisbon, Portugal.
url: www.organon.pt

Organon, Rus. Organon, Smolnaya ul. 24d, 125445 Moscow, Russia.
url: www.organon.ru

Organon, S.Afr. Organon Pharmaceuticals, P.O. Box 75907, Gardenview 2047, South Africa.
url: www.organon.co.za

Organon, Singapore. See *Zuellig, Singapore.*

Organon, Spain. Organon Española, Ctra de Hospitalet 147-149, Ed Amsterdam, Citypark, R Del Dalt, Cornella de Llobregat, 08940 Barcelona, Spain.
url: www.organon.es

Organon, Swed. Organon AB, Fiskhamnsgatan 6A, 414 58 Göteborg, Sweden.
url: www.organon.se

Organon, Switz. Organon SA, Churerstrasse 158, 8808 Pfaffikon/SZ, Switzerland.
url: www.organon.ch

Organon, Thai. Organon (Thailand) Ltd, 14 Fl, Ploenchit Center Building, 2 Sukhumvit Rd, Klongtoey, Bangkok 10110, Thailand.

Organon, Turk. Organon İlaçlari A.Ş., Mahir İz-Cad. No. 21, Altunizade, İstanbul, 81270, Turkey.
url: www.organon.com.tr

Organon, UK. Organon Laboratories Ltd, Cambridge Science Park, Milton Rd, Cambridge, CB4 0FL, UK.
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Organon, USA. Organon Inc., 56 Livingston Ave, Roseland, NJ 07068, USA.
url: www.organon-usa.com
Organon, Venez. Organon Venezolana, S.A., Apartado Postal 549, Caracas 1010-A, Venezuela.
url: www.organon.com.ve
Organon Teknika, Canad. See *Organon, Canad.*
Organon Teknika, Irl. See *United Drug, Irl.*
Organon Teknika, USA. See *Bio-Merieux, USA.*
Orient, Hong Kong. Orient Europharma, Rm 1711, 17/F Olympia Plaza, 225 King's Rd, North Point, Hong Kong.
Orient, Malaysia. Orient Europharma (M) Sdn Bhd, 33 Jln U1/30, Section U1, 40150 Shah Alam, Selangor, Malaysia.
Orient, Singapore. Orient Europharm Pte Ltd, 1 Sophia Rd, 04-12 Peace Centre, S 228149, Singapore.
Oriental, Arg. Oriental Farmaceutica I.C.I.F.A., G. Cossio 6160, 1408 Buenos Aires, Argentina.
Oriental, Philipp. See *Endure, Philipp.*
Oriola, Fin. Oriola Oy, PL 8, 02101 Espoo, Finland.
url: www.oriola.com
Orion, Austral. Orion Laboratories P/L, 85 Briggs St, Welshpool, WA 6106, Australia.
url: www.orion.net.au
Orion, Austria. See *Orion, Fin.*
Orion, Cz. Orion Pharma sro, Zeleny pruh 95/97, 140 00 Prague 4, Czech Republic.
url: www.orionpharma.cz
Orion, Denm. Orion Pharma A/S, Mollevej 9A, 2990 Niva, Denmark.
url: www.orionpharma.dk
Orion, Fin. Orion-yhtymä Oyj, Kalkkipellontie 2, 02601 Espoo, Finland.
url: www.orionpharma.com
Orion, Ger. Orion Pharma GmbH, Notkestr. 9, 22607 Hamburg, Germany.
url: www.orionpharma.com
Orion, Hong Kong. See *Treasure Mountain, Hong Kong.*
Orion, Hung. Orion Pharma Kft, Xenter 13 Irodaház, 1139 Budapest, Hungary.
url: www.orion.fi
Orion, Irl. See *Allphar, Irl.*
Orion, Israel. See *Genmedix, Israel,* and *Rafa, Israel.*
Orion, Malaysia. See *Apex, Malaysia.*
Orion, Neth. See *Orion, Fin.*
Orion, Norw. Orion Pharma AS, Ulvenv 84, Postboks 52 Okern, 0508 Oslo, Norway.
url: www.orionpharma.no
Orion, NZ. See *Zuellig, NZ,* and *St Ives, NZ.*
Orion, Pol. Orion Oyj SA, Przedstawicielstwo w Polsce, ul. Parandowskiego 19, 01-699 Warsaw, Poland.
Orion, Port. See *Orion, Fin.*
Orion, Rus. Orion Corporation, Orion Pharma, Lyusinovskaya ul. 36, et. 7, 113093 Moscow, Russia.
url: www.orionpharma.ru
Orion, Singapore. See *Pharmacon, Singapore.*
Orion, Swed. Orion Pharma AB, Box 334, 192 30 Sollentuna, Sweden.
url: www.orionpharma.se
Orion, Switz. Orion Pharma AG, Untermuli 11, 6300 Zug, Switzerland.
url: www.orionpharma.ch
Orion, Thai. See *Harn, Thai.*
Orion, UK. Orion Pharma UK Ltd, 1st Floor Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, UK.
url: www.orionpharma.com
Orion, USA. See *Lifesign, USA.*
Ormed, Ger. ORMED GmbH & Co KG, Merzhauser Str. 112, 79100 Freiburg, Germany.
url: www.ormed.de
Orna, Turk. Orna İlaç San. ve Tic Ltd., Çavuşbaşi Cad. Yayabeyi Sok., Arın İş Mer. No.11, Kavacık, İstanbul, Turkey.
Oro, Turk. Oro İlaçlari Ltd. Şti., Girne Mahallesi, Narlıdere Cad. No: 19 K: 3, Maltepe, İstanbul, 81550, Turkey.
Orpha-Devel, Austria. Orpha-Devel Handels- und Vertriebs GmbH, Wintergasse 85/1b, A-3002 Purkersdorf, Austria.
Orpha-Devel, Cz. See *Orpha-Devel, Austria.*
Orphan, Austral. Orphan Australia P/L, 48 Kangan Drive, Berwick, VIC 3806, Australia.
url: www.orphan.com.au
Orphan, Belg. Orphan Europe Benelux BVBA, Koning Albert I Laan 48, 1780 Wemmel, Belgium.
Orphan, Denm. Swedish Orphan AS, Wilders Plads, Bygning V, 1403 Copenhagen K, Denmark.
url: www.swedishorphan.com
Orphan, Fin. Oy Swedish Orphan AB, Rajatorpantie 41C, 01640 Vantaa, Finland.
url: www.swedishorphan.com
Orphan, Fr. Orphan Europe SARL, Imm Le Guillaumet, 92046 Paris-La Défense, France.
url: www.orphan-europe.com
Orphan, Ger. Orphan Europe (Germany) GmbH, Max-Planck-Str. 6, 63128 Dietzenbach, Germany.
url: www.orphan-europe.com
Orphan, Hung. See *Orphan, Ger.*
Orphan, Ital. Orphan Europe Italy S.r.l., Via Cellini 11, 20090 Segrate (MI), Italy.
url: www.orphan-europe.com
Orphan, Neth. See *Swedish Orphan, Swed.*
Orphan, Pol. Orphan Europe (Germany) GmbH, Przedstawicielstwo w Polsce, ul. Czereśniowa 98, 02-456 Warsaw, Poland.
url: www.orphan-europe.com
Orphan, Spain. Orphan Europe, Gran Via de les Corts Catalanes 649, Despacho No 1, 08010 Barcelona, Spain.
url: www.orphan-europe.com
Orphan, UK. Orphan Europe (UK) Ltd, Isis House, 43 Station Rd, Henley-on-Thames, Oxfordshire, RG9 1AT, UK.
url: www.orphan-europe.com
Orphan, USA. Orphan Pharmaceuticals USA, 1101 Kermit Drive, Suite 600, Nashville, TN 37217, USA.
url: www.swedishorphan.com
Orphan Europe, Cz. See *Orphan, Fr.*
Orphan Europe, Port. See *Orphan, Spain.*
Orphan Medical, Canad. See *Orphan Medical, USA.*
Orphan Medical, Israel. See *Tzamal, Israel.*
Orphan Medical, USA. Orphan Medical Inc., 13911 Ridgedale Drive, Suite 250, Minnetonka, MN 55305, USA.
url: www.orphan.com
Orravan, Spain. See *Reig Jofre, Spain.*
Orsade, Spain. Orsade, Avda Virgen de Montserrat 221, 08026 Barcelona, Spain.
Ortec, USA. Ortec International Inc., 9920 Kenmore Blvd, Akron, OH 44314, USA.
url: www.cortecinternational.com
Ortega, USA. Ortega, USA.
Ortho, Hong Kong. See *Janssen, Hong Kong,* and *Jacobson, Hong Kong.*
Ortho, Hung. See *Johnson & Johnson, Hung.*
Ortho, Israel. See *CTS, Israel.*
Ortho, Ital. Ortho Clinical Diagnostics S.p.A., Div. LifeScan Italia, Via Chiese 74, 20126 Milan, Italy.
Ortho, Venez. See *Johnson & Johnson, Venez.*
Ortho Biotech, UK. See *Janssen-Cilag, UK.*
Ortho Biotech, USA. Ortho Biotech L.P., 430 Route 22 East, P.O. Box 6914, Bridgewater, NJ 08807-0914, USA.
url: www.orthobiotech.com
Ortho Dermatological, USA. See *Ortho Neutrogena, USA.*
Ortho Diagnostic, Belg. Ortho-Clinical Diagnostic SA, Antwerpsesteenweg 19-21, 2340 Beerse, Belgium.
Ortho Diagnostic, USA. Ortho-Clinical Diagnostic Inc., 100 Indigo Creek Dr., Rochester, NJ 14626, USA.
url: www.orthoclinical.com
Ortho McNeil, USA. Ortho McNeil Pharmaceutical Inc., 1000 Route 202, P.O. Box 300, Raritan, NJ 08869-0602, USA.
url: www.ortho-mcneil.com
Ortho Neutrogena, USA. OrthoNeutrogena, a Division of Ortho-McNeil Pharmaceutocals Inc., 199 Grandview Rd, Skillman, NJ 08558, USA.
url: www.orthoneutrogena.com
Ortho Pharmaceutical, USA. See *Ortho McNeil, USA.*
Orthodontiki (Ορθοδοντικη), Gr. Orthodontiki, Proxenou Koromila 36, 546 22 Thessaloniki, Greece.
Ortis, Ital. Ortis Laboratoires, Viale dell'Appennino 441, 47100 Forlì, Italy.
Ortomed, Neth. Ortomed BV, Postbus 1081, 3330 CB Zwijndrecht, Netherlands.
url: www.ortomed.nl
Ortoquimica, Braz. Ortoquimica Ind. Químico Farmacêutica Ltda, Av. Magalhães de Castro 800, 05502-001 São Paulo, SP, Brazil.
Orva, Turk. Orva İlaç San. ve Tic A.Ş., Atatürk Organize Sanayi, Bölgesi 100010 Sok. No: 10, Çiğli, İzmir, 35620, Turkey.
Oryx, Canad. See *Cobalt, Canad.*
Osaka University, Cz. See *Osaka University, Jpn.*
Osaka University, Jpn. The Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan.
Oscient, USA. Oscient Pharmaceuticals, 1000 Winter Street, Suite 2200, Waltham, MA 02154, USA.
url: www.oscient.com
Osler, Fr. Laboratoires Osler, 42 rue Monge, 75005 Paris, France.
Osorio de Moraes, Braz. Laboratórios Osorio de Moraes Ltda, Avenida Cardeal Eugenio Pacelli 2281, 32210-001 Contagem, MG, Brazil.
Osoth, Thai. Osoth Inter Laboratories, 757/10 Soi Pradoo 1, Sathupradit 8 Rd, Bangpongpang, Yannawa, Bangkok 10120, Thailand.
Osotspa, Thai. Osotspa Co. Ltd, 2100 Ram Khamhaeng Rd, Hua Mark, Bangkapi, Bangkok 10240, Thailand.
Osteohealth, USA. See *Luitpold, USA.*
OTC, Spain. OTC Iberica, C/Monturiol, 2, Poligono Ind. Sur, 08026 Barcelona, Spain.
url: www.otciberica.com
OTC, Switz. OTC Pharma SA, Windeggstrasse 16, 8867 Niederurnen, Switzerland.
OTC Concepts, UK. OTC Concepts Ltd, 2 Park St, Woburn, Milton Keynes, Buckinghamshire, MK17 9PG, UK.
OTL, Denm. See *OTL, Fr.*
OTL, Fin. See *OTL, Fr.*
OTL, Fr. OTL Pharma SA, 15 rue de Turbigo, 75002 Paris, France.
url: www.otl-pharma.com
OTL, Neth. See *OTL, Fr.*
OTL, Port. See *OTL, Fr.*
OTL, Spain. See *OTL, Fr.*
Otosan, Ital. Otosan, Via degli Scavi 32, 47100 Forlì, Italy.
url: www.otosan.com
Otsira, India. See *Aristo, India.*
Otsuka, Denm. See *BMS, Denm.*
Otsuka, Hong Kong. Otsuka Pharmaceutical (HK) Ltd, Rm 1401, Phase 1, Ming An Plaza, 8 Sunning Rd, Causeway Bay, Hong Kong.
url: www.otsuka.com
Otsuka, Hung. See *Otsuka, UK.*
Otsuka, Indon. Otsuka Indonesia PT, Perkantoran Hijau Arkadia, Jl TB Simatupang Kav 88, 10330 Jakarta Selatan, DKI Jaya, Indonesia.
Otsuka, Jpn. Otsuka Pharmaceutical Co. Ltd, 2-9 Kanda-Tsukasa-cho, Chiyoda-ku, Tokyo 101-8535, Japan.
url: www.otsuka.co.jp
Otsuka, Malaysia. See *Luen Wah, Malaysia.*
Otsuka, Neth. See *Otsuka, UK.*
Otsuka, Norw. See *BMS, Norw.*
Otsuka, Philipp. Otsuka, 3/F King's Court II Bldg, Don Chino Roces Ave, Makati City, Philippines.
Otsuka, Port. See *Otsuka, UK.*
Otsuka, Singapore. See *Luen Wah, Singapore.*
Otsuka, Spain. Otsuka Pharmaceutical, Provenza 388, 08025 Barcelona, Spain.
url: www.otsuka-europe.com
Otsuka, Thai. See *Zuellig, Thai.*
Otsuka, UK. Otsuka Pharmaceutical (UK) Ltd, BSI Tower, 389 Chiswick High Rd, London, W6 8DW, UK.
url: www.otsuka-europe.com
Otsuka, USA. Otsuka America Pharmaceutical Inc, 2440 Research Blvd, Rockville, MD 20850, USA.
url: www.otsuka.com
Otto, Indon. Otto Pharmaceutical Industries Ltd, Gedung Mensa I, Lantai 1, Jl H R Rasuna Said Kav B-34, 12940 Kuningan, Jawa Barat, Indonesia.
Ottolenghi, Ital. Dr. Ottolenghi & C. S.r.l., Via Cuneo 5, 10028 Trofarello (TO), Italy.
url: www.ottolenghi.it
OTW, Ger. OTW-Naturarzneimittel Regneri GmbH & Co KG, Carl-Zeiss-Str. 4, 76275 Ettlingen, Germany.
Oui Heng, Thai. Oui Heng Import Co. Ltd, 46, 46/2 Soi Charansanitwongs 40, Charansanwitwongs Rd, Bangkok 10700, Thailand.
Outdoor Recreations, USA. Outdoor Recreations, USA.
Ovation, Canad. See *Ovation, USA.*
Ovation, Cz. See *Ovation, Irl.*
Ovation, Denm. See *Orphan, Denm.*
Ovation, Irl. Ovation Healthcare International Ltd, 1 Setanta Place, Dublin 2, Ireland.
Ovation, Port. See *Ovation, Irl.*
Ovation, USA. Ovation Pharmaceuticals Inc., Four Parkway North, Deerfield, IL 60015, USA.
url: www.ovationpharma.com
Ovelle, Irl. Ovelle Ltd, Industrial Estate, Coes Rd, Dundalk, Co. Louth, Ireland.
url: www.ovelle.com
Overfarma, Port. Overfarma Lda, Av. Dr. Fernando Ricardo Ribeiro Leitão 18-R/c dto, Massamá, 2745-771 Queluz, Portugal.
Overseas, India. Overseas Health Care Pvt Ltd, P.O. Box 25, Phillaur 144410, India.
Oxford Laboratories, Rus. Oxford Laboratories, 26-t Bakinskikh Komissarov ul. 9, on. 117, 119571 Moscow, Russia.
Oxford Nutrition, UK. Oxford Nutrition Ltd, Unit 5 Western Units, Pottery Rd, Bovey Tracey, TQ13 9JJ, UK.
url: www.nutrinox.com
Oxo, Port. See *Dimethaid, Ger.*
Oxo, Switz. See *Doetsch, Grether, Switz.*
Oxo, Thai. Oxo Chemie (Thailand) Co. Ltd, 6 Fl, Asoke Towers Com Building, 213/14-15 Sukhumvit 21 Rd, Klongtoey Nua, Watana, Bangkok 10110, Thailand.
url: www.oxochemie.com
Oxochemie, Indon. See *Pharos, Indon.*
Ozaki, Mex. Comercializadora Ozaki SA de CV, Playa Cuyutlan 261, 8810 Iztacalco Reform. Iztlaccihuatl, Mexico.
Ozon, Rus. Ozon, g Zhigulevsk, Pesochnaya St 11, 445350 Samarskaya, Russia.
Ozone, Cz. Ozone Laboratories Czech sro, Biskupský Dvùr 2095/8, 110 00 Praha, Czech Republic.
url: www.ozonelaboratories.cz
Ozone, Hung. Ozone Laboratories, Szent László tér 6/2/5, 1105 Budapest, Hungary.
url: www.ozonelaboratories.hu
Pabiance, Hung. See *Polcommerce, Hung.*
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Pacific, Hong Kong. See *LCH, Hong Kong.*
Pacific, Israel. See *Genmedix, Israel.*
Pacific, Malaysia. See *Ziwell, Malaysia.*
Pacific, NZ. Pacific Pharmaceuticals Co. Ltd, P.O. Box 11-183, Ellerslie, Auckland, New Zealand.
Pacific, Philipp. Pacific Pharmaceutical Generics Inc., R-303 Lawyers Coop Bldg, 459 Quezon Ave cor Banawe, Quezon City, Philippines.
Pacific, Singapore. See *Ziwell, Singapore,* and *Zuellig, Singapore.*
Pacific, Thai. Pacific Healthcare (Thailand) Co. Ltd, 229/1 South Sathorn Rd, Bangkok 10120, Thailand.
url: www.phc.co.th
Pacific Biosciences, Singapore. Pacific Biosciences Pte Ltd, 101 Thomson Rd, 16-05 United Square, S 307591, Singapore.
url: www.pacbios.com
Paddock, USA. Paddock Laboratories Inc., 3940 Quebec Ave North, Minneapolis, MN 55427, USA.
url: www.paddocklabs.com
Padia, Ger. Pädia Arzneimittel GmbH, Gruhlstr. 3, 50374 Erftstadt, Germany.
url: www.paedia.de
Padma, Switz. Padma AG, Wiesenstrasse 5, 8603 Schwerzenbach, Switzerland.
url: www.padma.com
Padro, Spain. See *Novartis, Spain.*
Paedpharm, Austral. Paedpharm P/L, P.O. Box 6533, East Perth, WA 6892, Australia.
url: www.paedpharm.com.au
Paesel, Ger. Paesel & Lorei GmbH & Co. Hauptniederlassung, Freihafen 8, 47138 Duisburg, Germany.
url: www.paesel-lorei.de
Pahang, Malaysia. Pahang Pharmacy Sdn Bhd, Lot 5979, Jln Teratai, Off Jln Meru, 41050 Klang, Selangor, Malaysia.
Paines & Byrne, Irl. See *Paines & Byrne, UK.*
Paines & Byrne, NZ. See *NZ Medical & Scientific, NZ.*
Paines & Byrne, Thai. See *Union Medical, Thai.*
Paines & Byrne, UK. Paines & Byrne Ltd, Lovett House, Lovett Rd, Staines, Middlesex, TW18 3AZ, UK.
Pal Midwest, USA. Pal Midwest Ltd, P.O. Box 624, Rockford, IL 61101, USA.
Paladin, Canad. Paladin Laboratories Inc., 6111 Royalmount Ave, Suite 102, Montreal, Quebec, H4T 2T4, Canada.
url: www.paladin-labs.com
Palisades, USA. See *Glenwood, USA.*
Palmares, Ital. See *Ferlito, Ital.*
Palmer, Malaysia. See *Propharm, Malaysia.*
Pal-Pak, USA. Pal-Pak Inc., 1201 LIberty St, P.O. Box 299, Allentown, PA 18105, USA.
Pamex, Irl. Pamex Ltd, First Floor, 14 Moneen Business Park, Castlebar, Co. Mayo, Ireland.
url: www.pamex.ie
Pamlab, USA. See *Pan American, USA.*
Pampa, Pol. Pampa Laboratorium Farmaceutyczno-Kosmetyczne, ul. Kościuszki 24, 05-500 Piaseczno, Poland.
url: www.pampa.com.pl
Pan American, USA. Pan American Laboratories, P.O. Box 8950, Mandeville, LA 70470-8950, USA.
url: www.pamlab.com
Pan Quimica, Spain. Pan Química Farmaceutica, Rufino Gonzalez 50, 28037 Madrid, Spain.
Panacea, India. Panacea Biotec Ltd, B-1 Extn. A-27., Mohan Co-op. Industrial Estate, Mathura Rd, New Delhi 110 044, India.
url: www.panacea-biotec.com
Panalab, Arg. Lab. Panalab S.A. Argentina, Av. Del Libertador 6250 Piso 2, 1428 Buenos Aires, Argentina.
Panax, Switz. Panax Import, F Ruckstuhl & Co., Bergtalweg 2a, 9500 Wil, Switzerland.
Panderma, Austria. Panderma Arzneimittel GmbH, Braunlichgasse 40-42, A-2700 Wiener Neustadt, Austria.
Pangaoshou, Philipp. See *Spring Vine, Philipp.*
Pangeo, Israel. See *Mediline, Israel.*
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Panpharma, Hong Kong. See *Universal, Hong Kong.*
Panpharma, Philipp. Panpharma-Meinz Pharmaceuticals Corp., 10/F Feliza Bldg, VA Rufino St, Legaspi Vill, Makati City, Philippines.
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Pantofarma, Spain. See *Almirall, Spain.*
Panvifarm, Gr. Panvifarm, Chalkokondyli 19, 104 32 Athens, Greece.
Pan-Well, Hong Kong. Pan-Well Trading Co., 4/F, Flat D, Goldfield Bldg, 42-44 Connaught Rd West, Hong Kong.
Panzera, Ital. Farmaceutici G.B. Panzera S.r.l., Via de Sanctis 71, 20141 Milan, Italy.

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Paracelsia, Port. Paracélsia Indústria Farmacêutica SA, Rua Antero de Quentel 639, 4200-068 Porto, Portugal.
Paradise, Canad. Paradise Promotions Ltd, 13 George St, Novar, Ontario, P0A 1R0, Canada.
Parafarm, Pol. Parafarm SC, ul. Stolarska 1/3 m 42, 97-200 Tomaszów Mazowiecki, Poland.
url: www.parafarm.cfp.pl
Paragerm, Fr. Laboratoires Paragerm, ZI 3 rue, B.P. 68, 06511 Carros cdx, France.
Paragerm, Indon. Paragerm, Indonesia.
Parggon, Mex. Laboratorios Parggon S.A. de C.V., Av. Vallarta 7000, Zapopan San Juan de Ocotan, 45019 Jalisco, Mexico.
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Parke, Davis, Arg. See *Pfizer, Arg.*
Parke, Davis, Austria. Parke-Davis GmbH, Brunner Strasse 81, A-1230 Vienna, Austria.
Parke, Davis, Belg. See *Pfizer, Belg.*
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Parke, Davis, Ital. Parke Davis S.p.A., Via C. Colombo 1, 20020 Lainate (Milan), Italy.
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Parke, Davis, USA. See *Pfizer, USA.*
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Parkfields, UK. Parkfields Sterile Supply Unit, Pond Lane, Parkfields, Wolverhampton, West Midlands, WV2 1HL, UK.
Parma, Hung. Parma Produkt Gyógyszergyártó Kft, Uzsoki u 36/a, 1145 Budapest, Hungary.
Parmed, USA. Parmed Pharmaceuticals Inc., 4220 Hyde Park Blvd, Niagara Falls, NY 14305, USA.
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Parnell, Canad. See *Parnell, USA.*
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Parsenn, Switz. Parsenn-Produkte AG, Abt. Pharmazeutik, Klus, 7240 Kublis, Switzerland.
Parthenon, USA. Parthenon Inc., 3311 West 2400 South, Salt Lake City, UT 84119, USA.
url: www.parthenoninc.com
Pasadena, USA. See *Taylor, USA.*
Pascal, USA. Pascal Co. Inc., P.O. Box 1478, Bellevue, WA 98009-1478, USA.
url: www.pascaldental.com
Pascoe, Ger. Pascoe Pharmazeutische Präparate GmbH, Schiffenberger Weg 55, 35394 Giessen, Germany.
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Pascual, Hong Kong. See *Yik Kwan, Hong Kong.*
Pascual, Philipp. Pascual Laboratories Inc., L & I Building, 817 EDSA, South Triangle, Quezon City, Philippines.
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Passauer, Ger. Herbert J Passauer GmbH & Co. KG, Ebersstrasse 56, 10827 Berlin, Germany.
Passion for Life, Singapore. See *Pan-Malayan, Singapore.*
Passion for Life, UK. Passion for Life Healthcare Ltd, 55 High St., Epsom, Surrey, KT19 8DH, UK.
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Pasteur, Chile. Laboratorios Pasteur Ltda, Ignacio Serrano 568, Concepción, Santiago, Chile.
Pasteur, Philipp. Pasteur Pharmaceutical Sales, G/F SGS Foundation Bldg, 1335 G Araneta Ave, Sta Mesa Heights, Quezon City, Philippines.
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Patheon, Rus. See *Novartis Consumer, Rus.*
Pathogenesis, USA. See *Chiron, USA.*
Patriot, Philipp. Patriot Pharmaceuticals Corp., The Patriot Bldg, Km 18 West Service Rd, South Luzon Expressway, Parañaque City, Philippines.
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PDN, Hong Kong. See *Universal, Hong Kong.*
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Peckforton, UK. Peckforton Pharmaceuticals Ltd, Crewe Hall, Crewe, Cheshire, CW1 6UL, UK.
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Pediapharm, Chile. See *Recalcine, Chile.*
Pediapharma, Philipp. Pediapharma Inc., Penthouse 4, Landsdale Tower, 86 Mother Ignacia Ave, Quezon City, Philippines.
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Pediatrica, Indon. See *Medifarma, Indon.*
Pediatrica, Malaysia. See *Unam, Malaysia.*
Pediatrica, Philipp. Pediatrica Inc., 3/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.
Pediatrica, Singapore. See *Far East, Singapore.*
Pediatrica, Thai. See *Olic, Thai.*
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Peithner, Cz. Dr Peithner Prag sro, Čestmírova 1, 140 00 Prague 4, Czech Republic.
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Peking-Boell, Ger. Peking Royal Jelly Deutschland BOELL HandelsKontor, Am Kirchberg 3, 86666 Burgheim, Germany.
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Penederm, Canad. See *Pharmascience, Canad.*
Penederm, USA. See *Bertek, USA.*
Penmix, Singapore. See *Pharmaforte, Singapore.*
Penmix, Thai. See *Cosma, Thai.*
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Pennex, Israel. See *Gramse, Israel.*
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Peptos, Rus. Peptos Pharma, Miklukho-Maklaja ul., d. 16/10, 117997 Moscow, Russia.
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Perez Gimenez, Spain. See *Calmante Vitaminado, Spain.*
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Perivita, Neth. See *Perivita, Norw.*
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Permamed, Pol. See *Magnapharma, Pol.*
Permamed, Switz. Permamed AG, Ringstrasse 29, Postfach 360, 4106 Therwil, Switzerland.
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Permark, S.Afr. See *Boots Healthcare, S.Afr.*
Permatec, Arg. Permatec Laboratorio Medicinal SA, Combate de los Pozos 336, 1080 Buenos Aires, Argentina.
Pern, UK. Pern Consumer Products Ltd, Quantum House, Hobson Industrial Estate, Burnopfield, County Durham, NE16 6EA, UK.
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Perrigo, Canad. See *Perrigo, USA.*
Perrigo, Israel. Perrigo Ltd, 29 Lehi Street, Bnei Brak 51200, Israel.
url: www.perrigo.com
Perrigo, Pol. See *Omega Rex, Pol.*
Perrigo, UK. Perrigo, Wrafton Laboratories Ltd., Wrafton, Braunton, Devon, EX33 2DL, UK.
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Perryment, Neth. See *Perryment, UK.*
Perryment, UK. Perryment Ltd, 42-46 High St, Esher, Surrey, KT10 9QY, UK.
Person & Covey, Canad. See *Seaford, Canad.*
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Personal Care, USA. Personal Care Group Inc., 225 Summit Ave, Montvale, NJ 07645-1574, USA.
Personal Products, USA. Personal Products Company, 199 Grandview Rd, Skillman, NJ 08558, USA.
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Pertussin, USA. Pertussin Laboratories, USA.
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Petsiavas (Πετσιαβας), Gr. See *Petsiavas, Gr.*
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Pfizer, Fin. Pfizer Oy, PL 36, 00331 Helsinki, Finland.
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Pfizer, Israel. Pfizer Pharmaceuticals Ltd, 9 Shenkar St, Herzliya Pituah 46725, Israel.
url: www.pfizer.com
Pfizer, Ital. Pfizer Italiana S.r.l., Via Valbondione 113, 00188 Rome, Italy.
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Pfizer, Jpn. Pfizer Pharmaceutical Inc., 2-1-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 163-0461, Japan.
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Pfizer, NZ. Pfizer Laboratories Ltd, Level 3, Pfizer House, 14 Normanby Rd, Mt Eden, Auckland, New Zealand.
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Pfizer, Philipp. Pfizer Inc., 23/F Ayala Life-FGU Ctr, 6811 Ayala Ave, Makati City, Philippines.
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Pfizer, Swed. Pfizer AB, Box 501, 183 25 Täby, Sweden.
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Pfizer, Turk. Pfizer İlaçlari Ltd. Şti., Muallim Naci Cad., Bostan Çikmazı No: 3, Ortaköy, İstanbul, 34347, Turkey.
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Pfizer Consumer, Austral. See *Pfizer, Austral.*
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Pfleger, Ger. Dr R. Pfleger Chemische Fabrik GmbH, 96045 Bamberg, Germany.
url: www.dr-pfleger.de
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Pfluger, Ger. Homöopathisches Laboratorium A. Pflüger GmbH, Bielefelder Str. 17, 33378 Rheda-Wiedenbruck, Germany.
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PG, Venez. Pharmaceutical Group PG, C.A., Av Venezuela con Humboldt, CC El Recreo, Trre Sur, Caracas, Venezuela.
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Pharlab, Braz. Pharlab Indústria Farmacêutica Ltda, Rua São Francisco 1300, 35590-000 Lagoa da Prata, MG, Brazil.
Pharm Supply, Pol. Pharm Supply AG, ul. Marconich 2 m 9, 02-954 Warsaw, Poland.
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Pharma & Co, Austria. Pharma & Co Handel GmbH, Stephansplatz 8A/6, A-1010 Vienna, Austria.
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Pharma 2000, Singapore. Pharma 2000 Pte Ltd, 59 Ubi Ave 1, 07-11 Bizlink Centre, S 408938, Singapore.
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Pharma Clal, Israel. Pharma-Clal Ltd, 21 Lehi St, Bnei Brak 51200, Israel.
Pharma Dynamics, S.Afr. Pharma Dynamics (Pty) Ltd, P.O.Box 30958, Tokai 7966, South Africa.
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Pharma Nord, Fin. Oy Pharma Nord AB, Rajatorpantie 41 C, 01640 Vantaa, Finland.
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Pharma Nord, Irl. See *Electramed, Irl.*
Pharma Nord, Malaysia. See *Sun, Malaysia.*
Pharma Nord, Norw. Pharma Nord Norge AS, Syretarnet 25, 3048 Drammen, Norway.
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Pharma Nord, Port. See *Pharma Nord, Denm.*
Pharma Nord, Thai. See *Biogenetech, Thai.*
Pharma Nord, UK. Pharma Nord UK Ltd, Telford Court, Morpeth, Northumberland, NE61 2DB, UK.
url: www.pharmanord.com
Pharma Nutria, Philipp. See *More, Philipp.*
Pharma Patent, Hung. Pharma Patent Kft, Szentlászlói út 44, 2000 Szentendre, Hungary.
Pharma Tek, USA. See *X-Gen, USA.*
Pharma Wernigerode, Rus. See *Queisser, Rus.*
Pharmabiotics, Chile. See *Recalcine, Chile.*
Pharmabroker, NZ. Pharmabroker Sales Ltd, P.O. Box 302 234, North Harbour Postal Centre, Auckland, New Zealand.
Pharmacard, Switz. Pharmacard Family Astral AG, 7 rue Pedro Maylan, 1211 Geneva 17, Switzerland.
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Pharmacare, Hong Kong. See *Suburfarm, Hong Kong.*
Pharmacare, Malaysia. See *Medidata, Malaysia.*
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Pharmacare, Singapore. See *IDS, Singapore.*
Pharmaceutical Co, India. The Pharmaceutical Co of India, Arun Chambers, J. Dadajee Rd, Tardeo, Mumbai 400 034, India.
Pharmaceutical Enterprises, S.Afr. Pharmaceutical Enterprises (Pty) Ltd, Howards Drive, Pinelands, Howard Place 7405, South Africa.
Pharmaceutical Specialties, USA. Pharmaceutical Specialties Inc., P.O. Box 6298, Rochester, MN 55903-6298, USA.
url: www.psico.com
Pharmachem, UK. M & A Pharmachem Ltd, Allenby Laboratories, Wigan Rd, Westhoughton, Bolton, BL6 2LA, UK.
url: www.mapharmachem.co.uk
Pharmachemie, Belg. Pharmachemie, Laarstraat 16, 2610 Wilrijk, Belgium.
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Pharmachemie, Denm. See *Pharmachemie, Neth.*
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Pharmachemie, Hong Kong. See *US Summit, Hong Kong.*
Pharmachemie, Indon. Pharmachemie, Indonesia.
Pharmachemie, Israel. See *Teva, Israel.*
Pharmachemie, Malaysia. See *United Italian, Malaysia.*
Pharmachemie, Neth. Pharmachemie BV, Swensweg 5, 2031 GA Haarlem, Netherlands.
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Pharmachemie, Philipp. See *Marketlink, Philipp.,* and *Metro, Philipp.*
Pharmachemie, Port. See *Pharmachemie, Neth.*
Pharmachemie, S.Afr. Pharmachemie (Pty) Ltd, P.O. Box 7115, Johannesburg 2000, South Africa.
Pharmachemie, Singapore. See *FP, Singapore.*
Pharmachemie, Thai. See *Pacific, Thai.*
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Pharmachim, Cz. See *Pharmachim, Bulg.*
Pharmachim, Hung. See *Agrichem, Hung.*
Pharmachim, Rus. See *Sopharma, Rus.*
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Pharmacia, Arg. See *Pfizer, Arg.*
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Pharmacia, Belg. See *Pfizer, Belg.*
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Pharmacia, Denm. See *Pfizer, Denm.*
Pharmacia, Fin. See *Pfizer, Fin.*
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Pharmacia, Hung. See *Pfizer, Hung.*
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Pharmacia, Irl. See *Pfizer, Irl.*
Pharmacia, Israel. See *Perrigo, Israel.*
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Pharmacia, NZ. See *Pfizer, NZ.*
Pharmacia, Pol. See *Pfizer, Pol.*
Pharmacia, Port. See *Pfizer, Port.*
Pharmacia, Rus. See *Pfizer, Rus.*
Pharmacia, S.Afr. See *Pfizer, S.Afr.*
Pharmacia, Singapore. Pharmacia Singapore Pte Ltd, 101 Thomson Rd, 31-04/05 United Square, S 307591, Singapore.
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Pharmacia, Spain. See *Pfizer, Spain.*
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Pharmacia, Switz. See *Pfizer, Switz.*
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Pharmacia, UK. See *Pfizer, UK.*
Pharmacia, USA. See *Pfizer, USA.*
Pharmacia, Venez. See *Pfizer, Venez.*
Pharmacia Upjohn, Israel. See *Perrigo, Israel.*
Pharmacia Upjohn, Ital. See *Pharmacia, Ital.*
Pharmacia Upjohn, Mex. See *Pfizer, Mex.*
Pharmacia Upjohn, Port. See *Pharmacia, Port.*
Pharmacia Upjohn, Rus. See *Pfizer, Rus.*
Pharmacia Upjohn, Switz. See *Pharmacia, Switz.*
Pharmacia Upjohn, USA. See *Pfizer, USA.*
Pharmacia-Upjohn, Gr. See *Pfizer, Gr.*
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Pharmacodane, Norw. See *Pharmacodane, Denm.*
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Pharmacosmos, Port. See *Pharmacosmos, Denm.*
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Pharmador, S.Afr. See *Protea, S.Afr.*
Pharmadorf, Arg. PharmaDorf SA, Virrey Loreto 3878, 1427 Buenos Aires, Argentina.
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Pharmagen, Turk. See *Sanofi-Aventis, Turk.*
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Pharmagenus, Spain. See *Uriach, Spain.*
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Pharma-Global, Irl. See *United Drug, Irl.*
Pharma-Global, UK. See *Nucare, UK.*
Pharmahex, Philipp. See *Blooming Fields, Philipp.*
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Pharmakin Korea, Venez. See *Pharmakin, Venez.*
Pharmakochimiki (Φαρμακοχημικη), Gr. See *Farmakochimiki, Gr.*
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Pharmalink, Ger. See *Pharmalink, Swed.*
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Pharmalink, Neth. See *Pharmalink, Swed.*
Pharmalink, Philipp. See *Zuellig, Philipp.*
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Pharmanex, USA. Pharmanex Inc., 74 West Center, Provo, UT 84601, USA.
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Pharmaniaga, Malaysia. Pharmaniaga Marketing Sdn Bhd, P.O. Box 2030, Pusat Business Bukit Raja, 40800 Shah Alam, Selangor, Malaysia.
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Pharmanik (Φαρμανικ), Gr. See *Farmanic, Gr.*
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Pharmarex, Hung. Pharmarex Fejleszto es Kereskedelmi Kft, Arboc u 6 IV em, 1133 Budapest, Hungary.

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Pharmasant, Thai. See *Central, Thai.*

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Pharmascience, Hong Kong. See *Hind Wing, Hong Kong,* and *Jacobson, Hong Kong.*

Pharmascience, Malaysia. See *Ranbaxy, Malaysia.*

Pharmascience, Singapore. See *JDH, Singapore.*

Pharmasearch, Irl. Pharmasearch Ltd, IDA Industrial Estate, Dublin Rd, County Loghrea, Ireland.

Pharmasearch, Neth. See *Pharmasearch, Irl.*

Pharmasearch, Port. See *Pharmasearch, Irl.*

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Pharmaselect, Cz. See *Pharmaselect, Austria.*

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Pharmaserve, Singapore. See *Polymedic, Singapore.*

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Pharmasol, Rus. See *Janssen-Cilag, Rus.*

Pharmasol, Singapore. See *Joyson, Singapore.*

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Pharmaspec, Philipp. Pharmaspec NA Inc., 3/F Hizon Bldg, 29 Quezon Ave, Quezon City, Philippines.

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Pharmatel, NZ. See *Bamford, NZ.*

Pharmaten (Φαρματεν), Gr. See *Pharmathen, Gr.*

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Pharmathen, Hong Kong. See *Health Alliance, Hong Kong.*

Pharmathen, Philipp. See *Ascende Medz, Philipp.*

Pharmaton, Cz. See *Boehringer Ingelheim, Cz.*

Pharmaton, Indon. See *Boehringer Ingelheim, Indon.*

Pharmaton, Israel. See *Pharmashalom, Israel.*

Pharmaton, Malaysia. See *Boehringer Ingelheim, Malaysia.*

Pharmaton, NZ. Pharmaton, New Zealand.

Pharmaton, Rus. See *Boehringer Ingelheim, Rus.*

Pharmaton, S.Afr. See *Swisspharm, S.Afr.*

Pharmaton, Singapore. See *Diethelm, Singapore.*

Pharmaton, Switz. Pharmaton SA, 6934 Bioggio, Switzerland.

Pharmaton, Thai. See *Boehringer Ingelheim, Thai.*

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Pharmavit, Cz. See *BMS, Cz.*

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Pharmax, Singapore. See *Naina, Singapore.*

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Pharmazam, Spain. See *Zambon, Spain.*

Pharmazel, Philipp. Pharmazel Inc., Philippines.

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Pharmion, Norw. See *Pharmion, Denm.*

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Pharmonta, Ger. See *Pharmonta, Austria.*

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Pharmout, Port. Pharmout Farmacêutica Internacional Lda, Rua da Quinta das Romeiras 104 - 7, 1495-236 Algés, Portugal.

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Pharmygiene, Rus. See *FIC, Rus.*

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Philopharm, Rus. See *Queisser, Rus.*

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Phoenix, Austria. Phoenix Arzneiwarengrosshandlung GmbH, Albert Schweitzer Gasse 3, A-1140 Vienna, Austria.

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Phoenix, Irl. See *Fulcrum, Irl.*

Phoenix, Philipp. Phoenix Pharmaceuticals Inc., Asian Mansion II, G/F No 3, 108 Dela Rosa St, Legaspi Vill, Makati City, Philippines.

Phoenix-Elea, Arg. See *Phoenix, Arg.*

Phoinix Pharm (Φοινιξ Φαρμ), Gr. FOINIX FARM EPE, Anavrytis 5, 111 43 Athens, Greece.

Phonix, Ger. Phönix Laboratorium GmbH, Benzstr. 10, 71149 Bondorf, Germany.
url: www.phoenix-laboratorium.de

Phos-Kola, Braz. Laboratório Phos-Kola Ltda, Rua das Laranjeiras 984, 49010-000 Aracaju, SE, Brazil.

Photocure, Denm. See *Photocure, Norw.*

Photocure, Fin. See *Photocure, Norw.*

Photocure, Norw. PhotoCure ASA, Hoffsvein 48, 0377 Oslo, Norway.
url: www.photocure.com

Photocure, Swed. See *Photocure, Norw.*

Photocure, USA. PhotoCure ASA, 161 Washington St, Conshohocken, PA 19428, USA.

PH&T, Gr. PH&T, Greece.

PHT, Ital. PHT Pharma Srl, Via V Monti 56, 20123 Milan, Italy.

Physicians Science & Nature, USA. Physicians Science & Nature, USA.

Phyto Kemo, Indon. Phyto Kemo Agung Farma PT, Jl Mesjid No 90, Susukan-Pasar Rebo, 13750 Jakarta Timur, Indonesia.
url: www.phytokemo.com

Phytobiolab, Fr. Lab Phytobiolab, 9 allée de Corrèze, 31770 Colomiers, France.

Phytodiet, Fr. Laboratoires Phytodiet, B.P. 68012, 57028 Metz cdx 01, France.

Phytofarm Kleka, Pol. See *Europlant Phytofarm, Pol.*

Phytologic, Austral. Phytologic Pty Ltd, 1-7 Doody St, Alexandria, NSW 2015, Australia.

Phytomed, Switz. Phytomed AG, Tschamerie 25, 3415 Hasle/Burgdorf, Switzerland.

Phytomedica, Fr. Laboratoires Phytomedica, ZI Les Milles, B.P. 5000, Parc d'activités de Pichaury, 13791 Aix-en-Provence cdx 3, France.
url: www.phytomedica-labo.com

Phytomedicine, Austral. Phytomedicine P/L, P.O. Box 1995, Dee Why, NSW 2099, Australia.
url: www.phytomedicine.com.au

Phytopharma, Switz. Phytopharma SA, Chemin des Golettes 4a, 1666 Grandvillard, Switzerland.
url: www.phytopharma.ch

Phytosolba, Fr. Laboratoires Phytosolba, 89 rue Salvador-Allende, 95870 Bezons, France.

Phytotec, Hung. Phytotec Hungária Kft, Lotz Károly u 3, 1026 Budapest, Hungary.

Piam, Ital. Vecchi & C. Piam di G. Assereto, E. Maragliano e C. S.a.p.a., Via Padre G. Semeria 5, 16131 Genoa, Italy.
url: www.piamfarmaceutici.com

Piam, Singapore. See *Zyfas, Singapore.*

Picharn, Thai. Picharn c/o The Picharn Co. Ltd, 53/43 Soi Amornphan 5, Viphavadi-Rangsit Rd, Jatujak, Bangkok 10900, Thailand.

Pickles, UK. J. Pickles & Sons, Beech House, 62 High St, Knaresborough, North Yorkshire, HG5 0EA, UK.
url: www.jpickleshealthcare.com

Picot, Fr. Laboratoires des Produits Picot, 189 quai Lucien-Lheureux, B.P. 83, 62102 Calais cdx, France.
url: www.picot.fr

Picot, Switz. See *Ridupharm, Switz.*

Piemont, Ital. Piemont-Farm Srl, Via Cirie 8, 10099 San Mauro (TO), Italy.

Pierre Fabre, Arg. Pierre Fabre Argentina S.A., Marcelo T de Alvear 684, piso 7, 1058 Buenos Aires, Argentina.
url: www.pierre-fabre.com.ar

Pierre Fabre, Austral. Pierre Fabre Medicament Australia Pty Ltd., Parkview Business Centre, 1 Maitland Place, Baulkham Hills, NSW 2153, Australia.
url: www.pierre-fabre.com

Pierre Fabre, Austria. See *Pierre Fabre, Fr.*

Pierre Fabre, Belg. See *Nycomed, Belg.*

Pierre Fabre, Canad. Pierre Fabre Pharma Canada Inc., 1400 Marie-Victorin, Suite 207, St-Bruno-de-Montarville, Quebec, J3V 6B9, Canada.

Pierre Fabre, Cz. Pierre Fabre Medicament sro, Radimová 36, 160 00 Prague 6, Czech Republic.

Pierre Fabre, Denm. See *Pierre Fabre, Swed.*

Pierre Fabre, Fin. See *Algol, Fin.*

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Pierre Fabre, Ger. Pierre Fabre Pharma GmbH, Jechtinger Str. 13, 79111 Freiburg, Germany.
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Pierre Fabre, Gr. Pierre Fabre Hellas A.E., Pontou 64, 115 27 Athens, Greece.
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Pierre Fabre, Hong Kong. See *Orient, Hong Kong.*

Pierre Fabre, Hung. See *Ewopharma, Hung.*

Pierre Fabre, Indon. See *Darya-Varia, Indon.*

Pierre Fabre, Israel. See *Mediline, Israel.*

Pierre Fabre, Ital. Pierre Fabre Italia S.p.A., Via G.G. Winckelmann 1, 20146 Milan, Italy.
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Pierre Fabre, Malaysia. See *Orient, Malaysia.*

Pierre Fabre, Mex. Pierre Fabre Farma de Mexico S.A. de C.V., Blvd Manuel Avila Camacho 191, Piso 4 In, Polanco Los Morales, 11510 Mexico D.F., Mexico.
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Pierre Fabre, Neth. Pierre Fabre Benelux, Ijsselburcht 4, 6825 BP Arnhem, Netherlands.
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Pierre Fabre, Norw. See *Pierre Fabre, Swed.*

Pierre Fabre, Philipp. See *Zuellig, Philipp.*

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Pierre Fabre, Port. Pierre Fabre Médicament Portugal, Lda, Rua Rodrigo da Fonseca 178 - 2 Esq, 1099-067 Lisbon, Portugal.
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Pierre Fabre, Rus. Pierre Fabre Medicament, Usacheva ul. 33, 119048 Moscow, Russia.
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Pierre Fabre, S.Afr. See *Pierre Fabre, Fr.*

Pierre Fabre, Singapore. See *Orient, Singapore.*

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Pierre Fabre, Swed. Pierre Fabre Pharma Norden AB, Box 349, 191 47 Sollentuna, Sweden.
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Pierre Fabre, Thai. See *BJC, Thai.*

Pierre Fabre, Turk. See *Sanofi-Aventis, Turk.*

Pierre Fabre, UK. Pierre Fabre Ltd, Hyde Abbey House, 23 Hyde St, Winchester, Hampshire, SO23 7DR, UK.
url: www.pierre-fabre.com

Pierre Fabre, USA. See *Genesis, USA.*

Pierre Fabre Dermatologie, Cz. See *Pierre Fabre, Cz.*

Pierre Fabre Dermatologie, Pol. See *Pierre Fabre, Pol.*

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Pierre Fabre Dermo-Cosmetique, Arg. See *Pierre Fabre, Arg.*

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Pierre Fabre Oral Care, Arg. See *Pierre Fabre, Arg.*

Pierre Fabre Sante, Arg. See *Pierre Fabre, Arg.*

Pierre Fabre Sante, Fr. See *Pierre Fabre, Fr.*

Pierre Fabre Sante, Singapore. See *Summit, Singapore.*

Pierrel, Ital. Pierrel Farmaceutici S.p.A., Via Revere 16, 20123 Milan, Italy.
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Pietrasanta, Ital. Pietrasanta Pharma S.r.l., Loc. S. Rocchino, 55054 Massarosa (LU), Italy.
url: www.pietrasantapharma.it

Piette, Thai. See *International Pharmaceuticals, Thai.*

Pik, Rus. Pik-Farma OOO, Gasheka ul. 7, Of. 320, 129010 Moscow, Russia.
url: www.pikfarma.ru

Pilkington Barnes-Hind, USA. See *Wesley, USA.*

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url: www.pinewood.ie

Pinewood, Neth. See *Pinewood, Irl.*

Pinewood, UK. See *Pinewood, Irl.*

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Pint, Cz. See *Pint, Austria.*
Pint, Hung. See *WI Pharma, Hung.*
Pint, Israel. See *Gilco, Israel.*
Pionneau, Fr. Laboratoires Pionneau, 33870 Vayres, France.
Piramal, India. See *Nicholas Piramal, India.*
Pirri, Canad. Pirri Pharma Canada Inc., 1001 Victoria Square, Block E, 8th Floor, Montreal, Quebec, H2Z 2B7, Canada.
Pirri, Hong Kong. See *C & L, Hong Kong.*
Pisa, Mex. Laboratorios Pisa S.A. de C.V., Miguel Angel de Quevedo 555, Coyoacan Romeros de Terreros, 4310 Mexico D.F., Mexico.
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Pizarro, Braz. Pizarro Farmacêutica Ltda, Rua Lino Coutinho 1568, 04207-002 São Paulo Ipiranga, SP, Brazil.
Pizzard, Mex. Laboratorios Pizzard S.A. de C.V., Km 22.5 Carretera Guadalajara, Guadalajara Morelia Tlaj. Zuniga, 45640 Jalisco, Mexico.
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Plan, Switz. Laboratoires Plan SA, Chemin de la Verseuse 1, Case postale 208, 1219 Aire-Geneva, Switzerland.
Plantamed, Ger. See *Bionorica, Ger.*
Plantes et Medecines, Fr. Laboratoires Plantes et Médecines, Le Payrat, 46000 Cahors, France.
Plantina, Ger. Plantina Biologische Arzneimittel AG, Jochbergweg 1, 82418 Murnau, Germany.
url: www.plantina.de
Plants, Ital. Plants, Laboratorio della Dott.ssa Luisa Coletta, Viaria C, Zona Industriale, 98040 Giammoro (ME), Italy.
Plasmon, Ital. Plasmon Dietetici Alimentari S.p.A., Via Cascina Bel Casule 7, 20141 Milan, Italy.
Plastchim, Rus. See *Sopharma, Rus.*
Plasti-Esteril, Mex. Plasti-Esteril SA de CV, Av. Ing. Salvador Sanchez 9, 50450 Atlacomulco Pq. Ind. Atlacomulco, Estado de Mexico, Mexico.
Plata, Arg. Lab. Pharma del Plata S.R.L., Valentin Torra 5450, 3100 Pque.Ind.G. Belgrano, Entre Rios, Argentina.
Playtex, Canad. Playtex Ltd, 6363 Northam Drive, Mississauga, Ontario, L4V 1N5, Canada.
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Pliva, Hung. Pliva d d Magyarországi Kereskedelmi Képviselete, Galagonya u 5, 1036 Budapest, Hungary.
Pliva, Irl. See *United Drug, Irl.*
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Pliva, Rus. Pliva AO, Novocheremushkinskaya ul. 61, 117418 Moscow, Russia.
url: www.pliva.ru
Pliva, Spain. See *Edigen, Spain.*
Pliva, UK. Pliva Pharma Ltd, Vision House, Bedford Rd, Petersfield, Hampshire, GU32 3QB, UK.
url: www.pliva.co.uk
Pliva Krakow, Pol. Pliva Kraków, Zakłady Farmaceutyczne Spółka Akcyjna, ul. Mogilska 80, 31-546 Kraków, Poland.
url: www.pliva.pl
Pliva Lachema, Pol. See *Pliva Krakow, Pol.*
Pliva-Lachema, Cz. Pliva-Lachema as, Karásek 1, Brno 621 33, Czech Republic.
Plough, Port. See *Schering-Plough, Port.*
Plumbland, Arg. Plumbland Holdings Ltd, Paraguay 914 Piso 8 A, 1057 Buenos Aires, Argentina.
Plurilab, Port. Plurilab Produtos Farmacêuticos e Dietéticos Lda, Portugal.
Plurisystem, Ital. Plurisystem S.a.s. di Arippa Lionello & C., Via F Vezzani 99r, 16159 Genova-Rivarolo, Italy.
Plus, Gr. Plus Farmakevtiki, Greece.
Plusandex, Venez. Laboratorios Plusandex, C.A., Parque Industrial El Vigía, Calle A, entre Calle 1 y 2, Edif. Plusandex, El Vigía, Merida, Venezuela.
url: www.plusandex.com
Plymouth Pharmaceuticals, USA. Plymouth Pharmaceuticals, P.O. Box 702418, Tulsa, OK 74170-2418, USA.
url: www.plymouthpharmaceuticals.com
PMC, Austral. See *AstraZeneca, Austral.*
PMG, Chile. PMG SA, Rosario sur 91 Of. 304, Las Condes, Santiago, Chile.
PMP, Turk. PMP İlaç Pazarlama Danışmanlık ve Tic. Ltd. A.Ş., Gardenya Plaza 3 K: 15 D: 73, Ataşehir, İstanbul, 81120, Turkey.
PMR, Singapore. PMR Associates, 791 North Bridge Rd, S 198759, Singapore.
url: www.pom.com.sg
PNF, Philipp. PNF Pharmaceutical Inc., Skrene Properties Bldg, 3759 Cuenca cor Emillia St, Palanan, Makati City, Philippines.
Podravka, Cz. Podravka International sro, Ul. Františka Kadlece 572/16, 180 00 Prague 8, Czech Republic.
url: www.belupo.hr
Poehlmann, Ger. Dr Poehlmann & Co. GmbH, Postfach: 1365, 58303 Herdecke, Germany.
Poen, Arg. Lab. Poen S.A.C.I.F.I., Fray Justo Sarmiento 2350, 1636 Olivos, Buenos Aires, Argentina.
url: www.poen.net.ar
Poen, Chile. Laboratorio Poen, Av. Andres Bello 1495, Providencia, Santiago, Chile.
Pohl, Cz. See *Merck, Cz.*
Pohl, Denm. See *Pohl, Ger.*
Pohl, Ger. G. Pohl-Boskamp GmbH & Co., Kieler Str. 11, 25551 Hohenlockstedt, Germany.
url: www.pohl-boskamp.com
Pohl, Hong Kong. See *Health Vision, Hong Kong.*
Pohl, Israel. See *Megapharm, Israel.*
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Pohl-Boskamp, Swed. G Pohl-Boskamp GmbH & Co, Saltholsgatan 44, 426 76 Västra Frölunda, Sweden.
Point of Care Diagnostics, NZ. Point of Care Diagnostics, New Zealand.
Poirier, Fr. Laboratoires Pharm. Poirier, ZA La Haute-Limougere, B.P. 24, 37230 Fondettes, France.
Polcommerce, Hung. Polcommerce Kft a Ciech, Polfa Ltd képviselője, Ötvös János u 1-3, 1021 Budapest, Hungary.
Polfa, Cz. See *Polfa Ciech, Cz.*
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Polfa Ciech, Cz. Polfa Ciech AS, Francouzská 2, byt 5, 120 00 Prague 2, Czech Republic.
Polfa Grodzisk, Pol. Grodziskie Zakłady Farmaceutyczne Polfa, ul. Poniatowskiego 5, 05-825 Grodzisk Mazowiecki, Poland.
url: www.polfa-grodzisk.com.pl
Polfa Kutno, Pol. Kutnowskie Zakłady Farmaceutyczne Polfa SA, Biuro w Warszawie, ul. Domaniewska 50 a, 02-672 Warsaw, Poland.
url: www.polfakutno.pl
Polfa Lodz, Pol. Zakłady Farmaceutyczne Polfa-Łódź SA, ul. Drewnowska 43/55, 91-002 Łódź, Poland.
url: www.polfa-lodz.com.pl
Polfa Pabianice, Pol. Pabianickie Zakłady Farmaceutyczne Polfa SA, ul. Piłsudskiego 5, 95-200 Pabianice, Poland.
url: www.polfa.pabianice.pl
Polfa Tarchomin, Pol. Tarchomińskie Zakłady Farmaceutyczne Polfa SA, ul. Aleksandra Fleminga 2, 03-176 Warsaw, Poland.
url: www.polfa-tarchomin.com.pl
Polfa Warszawa, Pol. Warszawskie Zakłady Farmaceutyczne Polfa SA, ul. Karolkowa 22/24, 01-207 Warsaw, Poland.
url: www.polfawar.com.pl
Polfarmex, Pol. Polfarmex SA, ul. Józefów 9, 99-300 Kutno, Poland.
url: www.polfarmex.com.pl
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Polidis, Fr. Ste Polidis, 7 rue Gallieni, 92500 Rueil-Malmaison, France.
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Polifarma, Ital. Polifarma S.p.A., Via Tor Sapienza 138, 00155 Rome, Italy.
Polifarma, Turk. See *Aroma, Turk.*
Polinac, Venez. Laboratorios Politecnicos Nacionales C.A., Cipreses a Hoyo 109-11, Pso.1 Edif. El Viejo, Urb. Sta. Rosalía Caracas, Caracas, Venezuela.
Polipharm, Thai. Polipharm Co. Ltd, 109 Mu 12 Bangna-Trat Rd, Bangpleeyai, Bangplee, Samutprakan 10540, Thailand.
url: www.polipharm.com
Polisan, Rus. Polisan, Ligovskii etc. 112, 191119 Saint Petersburg, Russia.
url: www.polysan.ru
Polisorb, Rus. Polisorb, g Kopeisk, Tomskaya St 14, 456652 Chelyabinskaya obl, Russia.
Polive, Fr. Laboratoires Polivé SNC, 19-23 bd Georges-Clemenceau, 92400 Courbevoie, France.
Pol-Nil, Cz. See *Pol-Nil, Pol.*
Pol-Nil, Pol. Pol-Nil SA, ul. Annopol 6A, 03-236 Varšava, Poland.
Polon, Pol. Łódzkie Przedsiębiorstwo Farmaceutyczne Polon Sp. zo.o., ul. Pojezierska 99, 91-342 Łódź, Poland.
url: www.polon-farm.com.pl
Polpharma, Cz. See *Polfa Ciech, Cz.*
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Polpharma, Rus. Polpharma SA, Kantemirovskaya ul. 58, Of. 7037, 115477 Moscow, Russia.
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Polychronus, Gr. Polychronus, Greece.
Polydan, Rus. Polydan NPFP OOO, Mamonovskii per. 6, of. 10, 123001 Moscow, Russia.
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Polymer Technology, USA. See *Bausch & Lomb, USA.*
Polypharm, Ger. Polypharm GmbH, Bad Nauheimer Str. 4, 64289 Darmstadt, Germany.
Ponce, Venez. Ponce & Benzo Sucesores C.A., Edificio Ponce & Benzo, 2da. Avenida, Urb. Santa Eduvigis, Caracas, Venezuela.
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Pond's, Philipp. See *DKT, Philipp.*
Pond's, Thai. Pond's Chemical Thailand ROP, 79 MU 4 Ramindra Rd, Bangkhen, Bangkok 10220, Thailand.
Pond's Chemical, Singapore. See *Wellchem, Singapore.*
Portal, USA. Portal Pharmaceutical, 67E Mendez Vigo, Mayaguez, PR 00680, Puerto Rico.
Portex, UK. Portex Ltd, Boundary Rd, Hythe, Kent, CT21 6JL, UK.
url: www.portex.com
Porton, Israel. See *Medogar, Israel.*
Pose, Thai. Pose Health Care Ltd, 99/1 Soi Ramintra 107, Ramintra Rd, Kannayao, Bangkok 10230, Thailand.
Potter's, UK. Potters (Herbal Supplies) Ltd, 1 Botanic Court, Martland Park, Wigan, WN5 0JZ, UK.
url: www.pottersherbals.co.uk
Pound International, UK. Pound International Ltd, 109 Baker St, London, W1M 1FE, UK.
Powermist, Philipp. Powermist Pharma Corp., Suite 2601 Medical Plaza Ortigas, San Miguel Ave, Ortigas Ctr, Pasig City, Philippines.
Pozitron, Hung. Pozitron Diagnosztika Kft, Hunyadi János út 9, 1117 Budapest, Hungary.
PP Lab, Thai. See *Picharn, Thai.*
PPDH, Fr. PPDH SA, 247 bis rue des Pyrenees, 75020 Paris, France.
Praecis, USA. Praecis Pharmaceuticals Inc., 830 Winter St, Waltham, MA 02451-1420, USA.
url: www.praecis.com
Prafa, Indon. Prafa Pharin PT, Graha Darya-Varia 2/F, Jl Melawai Raya No 93, 12910 Jakarta, DKI Jaya, Indonesia.
Prasco, USA. Prasco Laboratories, 7155 E Kemper Rd, Cincinnati, OH 45249, USA.
url: www.prascolabs.com
Prasfarma, Spain. See *Almirall, Spain.*
Pratapa Nirmala, Indon. Pratapa Nirmala PT, Jl Raden Saleh Raya 4, 10430 Jakarta, DKI Jaya, Indonesia.
Prater, Chile. Laboratorio Prater SA, Av. P Aguirre Cerda 5291, Cerrillos, Santiago, Chile.
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Prats, Spain. Prats, Travesera del Dalt 44, 08024 Barcelona, Spain.
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Precimex, Mex. Precimex S.A. de C.V., Calderón de la Barca 27, Miguel Hidalgo Palmas Polanco, 11560 Mexico DF, Mexico.
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Pred, Fr. Laboratoires Pred, Bâtiment 6, 79 av Aristide Briand, 94118 Arcueil cdx, France.
url: www.pred.fr
Premia, UK. Premia Cosmetics Ltd, UK.
url: www.premiacos.com
Premier, Irl. Premier Medical Ltd, Dromin, Kilmallock, Co. Limerick, Ireland.
Premier, S.Afr. See *Sandoz, S.Afr.*
Premier, Thai. Premier Pharma Supply Co Ltd, 62/340 Moo, 5 Terdphrakiat Rd, Watchalaw, Bangkruay, Nonthaburi 11130, Thailand.
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Presselin, Ger. Presselin-Arzneimittel GmbH & Co. KG, Heinkelstr. 8a, 76461 Muggensturm, Germany.
url: www.presselin.de
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Prestwick, Canad. Prestwick Pharmaceuticals Canada Inc., 4 Innovation Drive, Dundas, Ontario, L9H 7P3, Canada.
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url: www.hemoccult.com
Preventys, Fr. Laboratoires Preventys, 9 Chemin du Roc-Fleuri, 13100 Aix-en-Provence, France.
Prieto, Arg. Laboratorios Prieto S.A., Maza 1869/73, 1240 Buenos Aires, Argentina.
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Primal, Hong Kong. Primal Chemical Co. Ltd, Flat A, 7/F, Hoi Bun Industrial Bldg, 6 Wing Yip St, Kwun Tong, Kowloon, Hong Kong.
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Prime, Singapore. See *Uni, Singapore.*
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Primera, Philipp. Primera Pharma Corp., 3/F JGS Bldg, 30 Scout Tuason St, Diliman, Quezon City, Philippines.
url: www.primerapharma.com
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Princeps, Ital. Princeps Srl, Via Donatori de Sangue snc, 12026 Piasco (CN), Italy.
url: www.alpiflor.com
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Principle Healthcare, UK. Principle Healthare Ltd., Airedale Business Centre, Millennium Road, Skipton, North Yorkshire, BD23 2TZ, UK.
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Prisfar, Port. Prisfar, SA, Rua Antero de Quentel 629, 4200-068 Porto, Portugal.
url: www.prisfar.pt
Pro Concepta, Switz. Pro Concepta Zug AG, Lindenstrasse 12, 6341 Baar/Zug, Switzerland.
url: www.proconcepta.ch
Pro Doc, Canad. Pro Doc Limitée, 2925 Industrial Blvd, Laval, Quebec, H7L 3W9, Canada.
Pro Medica, Swed. See *Schering-Plough, Swed.*
Pro Task, Thai. Pro Task Co. Ltd, 1201/45 Ladprao 94, Wangthonglaang, Bangkok 10310, Thailand.
Pro Vaccine, Switz. Pro Vaccine AG, Lindenstrasse 12, Linden-Park, 41 Baar/Zug, Switzerland.
url: www.provaccine.ch
Probifasa, Mex. Probifasa S.A. de C.V., Calz. Mexico-Tacuba No. 1419, Col Argentina Pte., Deleg. Miguel Hidalgo, 11230 Mexico D.F., Mexico.
Probiomed, Mex. Probiomed, S.A. de C.V., San Esteban 88, Azcapotzalco Santo Tomas, 2020 Mexico D.F., Mexico.
url: www.probiomed.com.mx
Probios, Port. Probios, Lda, Rua João Chagas 53-A, Escritório 201, 1495-072 Algés, Portugal.
url: www.almirallprodesfarma.com
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Procare, Austral. See *Biovital, Austral.*
Proceane, Fr. Laboratoires Proceane Ressources Marines, B.P. 88, 44503 La Baule cdx, France.
url: www.proceane.com
Procter & Gamble, Arg. Procter & Gamble Interamericanos Inc., Suipacha 664 Piso 2, 1008 Buenos Aires, Argentina.
url: www.pg.com
Procter & Gamble, Austral. Procter & Gamble Australia P/L, Locked Bag 75, Parramatta, NSW 2124, Australia.
url: www.pg.com
Procter & Gamble, Austria. Procter & Gamble Austria GmbH, Guglgasse 7-9, A-1030 Vienna, Austria.
url: www.pg.com
Procter & Gamble, Belg. Procter & Gamble Pharmaceuticals SA, Temselaan 100, 1853 Strombeek-Bever, Belgium.
url: www.pgpharma.com
Procter & Gamble, Braz. Procter & Gamble do Brasil S.A., Av. Maria Coelho Aguiar 251, Bloco E-Andares 4./5, Jd São Luiz, 05805-000 Paulo, SP, Brazil.
url: www.procter.com.br
Procter & Gamble, Canad. Procter & Gamble Inc., P.O. Box 355, Station A, Toronto, Ontario, M5W 1C5, Canada.
url: www.pg.com
Procter & Gamble, Cz. See *Procter & Gamble, Ger.*
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Procter & Gamble, Fr. Procter & Gamble Pharmaceuticals France, 96 av Charles-de-Gaulle, 92201 Neuilly-sur-Seine cdx, France.
url: www.fr.pg.com
Procter & Gamble, Ger. Procter & Gamble Pharmaceuticals Germany GmbH, Dr-Otto-Rohm Str 2-4, 64331 Weiterstadt, Germany.
url: www.procterundgamble.de
Procter & Gamble, Hong Kong. See *Keller, Hong Kong.*

Procter & Gamble, Hung. Procter & Gamble Pharmaceuticals, Váci út 35, 1135 Budapest, Hungary.

Procter & Gamble, Irl. See *Procter & Gamble (H&B Care), UK.*

Procter & Gamble, Israel. See *Neopharm, Israel.*

Procter & Gamble, Ital. Procter & Gamble Srl, Viale C Pavese 385, 00100 Rome, Italy.
url: www.pg.com

Procter & Gamble, Mex. Procter & Gamble de Mexico S.A. de C.V., Loma Florida 32, Lomas de Vistahermosa, Del. Cuajimalpa, 05100 Mexico D.F., Mexico.
url: www.pg.com.mx

Procter & Gamble, Neth. Procter & Gamble Pharmaceuticals, Watermanweg 100, 3067 GG Rotterdam, Netherlands.
url: www.pg.com

Procter & Gamble, Norw. See *Roche, Norw.*

Procter & Gamble, NZ. Procter & Gamble NPD, Inc., 7th Floor, Acer Building, 10-12 Scotia Place, Auckland, New Zealand.
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Procter & Gamble, Pol. Procter & Gamble Operations Polska Sp. zo.o., ul. Zabraniecka 20, 03-872 Warsaw, Poland.
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Procter & Gamble, Port. Procter & Gamble Portugal Produtos de Consumo, Higiene e Saúde SA, Edifício Álvares Cabral, Quinta da Fonte, Estrada de Paço d'Arcos 85, 2780 Porto Salvo Oeiras, Portugal.

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Procter & Gamble, Swed. Procter & Gamble Nordic Inc., filial Sverige, Box 273 03, 102 54 Stockholm, Sweden.
url: www.procter.se

Procter & Gamble, Switz. Procter & Gamble AG, 47 rue de Saint-Georges, 1213 Petit-Lancy 1, Switzerland.
url: www.pg.com

Procter & Gamble, UK. Procter & Gamble Pharmaceuticals UK Ltd, Rusham Park Technical Centre, Whitehall Lane, Egham, Surrey, TW20 9NW, UK.
url: www.uk.pg.com

Procter & Gamble, USA. Procter & Gamble, 1 or 2, Procter & Gamble Plaza, Cincinnati, OH 45201, USA.
url: www.pg.com

Procter & Gamble, Venez. Procter & Gamble de Venezuela C.A., Edificio P&G, Calle Altagracia, Urb Sorocaima 30, sector La Trinidad, Caracas 1080, Venezuela.
url: www.pg.com

Procter & Gamble (H&B Care), UK. Procter & Gamble (Health & Beauty Care) Ltd, The Heights, Brooklands, Weybridge, Surrey, KT13 0XP, UK.
url: www.uk.pg.com

ProCyte, USA. ProCyte Corp., 8511 154th Ave NE, Bldg A, Redmond, WA 98052-3557, USA.
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Prodava, Arg. Lab. Prodava S.A., Raulies 1970/8, 1427 Buenos Aires, Argentina.

Prodemdis, Canad. Prodemdis Enr., 4355 Sir Wilfrid Laurier Blvd, St-Hubert, Quebec, J3Y 3X3, Canada.
url: www.confab.ca

Prodes, Hung. See *PDP, Hung.*

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Prodotti, Braz. Prodotti Laboratório Farmacêutico Ltda, Avenida João Dias 1084, Santo Amaro, 04724-001 São Paulo, SP, Brazil.

Produfarma, Port. Produfarma, Lda, Estrada de Benfica 403-B, 1500-077 Lisbon, Portugal.

Produits Dentaires, Switz. Produits Dentaires SA, 18 rue des Bosquets, 1800 Vevey, Switzerland.
url: www.pdsa.ch

Proel, Gr. Proel S.A., Dilou 9, 121 34 Peristeri, Greece.
url: www.proel.gr

Proethic, USA. ProEthic Pharmaceuticals Inc., 5331 Perimeter Parkway Court, Montgomery, AL 36116, USA.
url: www.proethic.com

Prof. Pharm. Corp., Canad. Professional Pharmaceutical Corporation, 9200 Cote-de-Liesse Blvd, Lachine, Quebec, H8T 1A1, Canada.

Profarb, Braz. Profarb Ltda, Rua Paschoal Bernardino 25, 36880-000 Muriae, MG, Brazil.

Profarm, Pol. Przedsiębiorstwo Produkcji Farmaceutyczno-Kosmetyczne Profarm, ul. Słupska 18, 84-300 Lębork, Poland.

Profarma, Cz. Profarma sro, Liberecká 20, 466 01 Jablonec nad Nisou, Czech Republic.
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Profarma, Thai. See *International Pharmaceuticals, Thai.*

Profile, UK. Profile Therapeutics plc, Heath Place, Bognor Regis, West Sussex, PO22 9SL, UK.
url: www.profilepharma.com

Proge, Ital. Proge Farm S.r.l., Via Croce 4, 28065 Cerano (NO), Italy.

Progen, Ital. Progen Srl, Via Farfisa 18, 60021 Camerano (AN), Italy.
url: www.progen.org

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Pro-Health, NZ. Pro-Health Products Ltd, P.O. Box 28-545, Remuera, Auckland, New Zealand.
url: www.nicobrevin.com

Prohealth, Philipp. Prohealth Pharma Phils Inc., Suite 2603C, 26/F East Wing Tektite Tower, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Prolab, Pol. Farmaceutyczne Przeds. Produkcyjno-Analityczno-Handlowe Prolab Halkiewicz i Ratajczyk Sp.J, ul. Przemysłowa 3, Praterek, 89-100 Nakło n/Notecią, Poland.
url: www.prolab.tpi.pl

Promeco, Mex. See *Boehringer Ingelheim, Mex.*

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Promed, Ger. See *AstraZeneca, Ger.*

Promed, Indon. Promedrahardjo PT Farmasi Industri, Jl Raya Siliwangi-Sundawenang, ParungKuda-Sukabumi, Jawa Barat, Indonesia.

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Promed, Rus. Promed Exports, Shosse Entusiastov, 7, 111102 Moscow, Russia.
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Pro.Med, Rus. Pro.Med CS Praha a.s., 7-ya Kozhukhovskaya St 15, Str. 1, 109193 Moscow, Russia.

Promedica, Ital. See *Chiesi, Ital.*

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Promedico, Israel. ProMedico Ltd, 4 Baltimor St, Petach Tikva 49510, Israel.
url: www.promedico.co.il

Promefarm, Ital. Promefarm S.r.l., Corso Indipendenza 6, 20129 Milan, Italy.

Prometheus, USA. Prometheus Laboratories Inc., 5739 Pacific Center Blvd, San Diego, CA 92121-4203, USA.
url: www.prometheuslabs.com

Prometic, USA. ProMetic BioSciences Inc., 155 Willowbrooke Blvd, Suite 460, Wayne, NJ 07470, USA.
url: www.prometic.com

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Pronova, Norw. Pronova Biocare AS, Lysaker Torg 8, N-1324 Lysaker, Norway.

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Pronova, USA. Pronova Corp., P.O. Box 144281, Coral Gables, FL 33114, USA.
url: www.pronovacorp.com

Pronovo, Turk. Pronovo, Turkey.

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Propharm, Israel. Propharm, P.O. Box 4066, Zichron Yaacov, Israel.

Propharm, Malaysia. Propharm (M) Sdn Bhd, 640-A, 4th Mile, Ipoh Rd, 51200 Kuala Lumpur, Wilayah Persekutuan, Malaysia.

Propharma, Denm. Propharma A/S, Industrivaenget 18, 4622 Havdrup, Denmark.
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Pro-Pharma, Hung. Pro-Pharma, Berlini út 47-49, 1045 Budapest, Hungary.

Pro-Pharma, USA. Pro-Pharma, USA.

Propharma, USA. Propharma, 7760 NW 56th St, Miami, FL 33166, USA.

Proreo, Switz. Proreo Pharma AG, Rebgasse 2, 4410 Liestal, Switzerland.
url: www.proreopharma.com

Prosan, Hong Kong. See *CNW, Hong Kong.*

Prosel, Philipp. Prosel Pharma Inc., Unit 26B, 26/F Chatham House Cond, Va Rufino cor. Valero Sts, Salcedo Village, Makati City, Philippines.

Prospa, Ital. Prospa Italia S.r.l., Via Modica 6, 20143 Milan (MI), Italy.

Prospa, Port. Prospa, SA, Rua do Proletariado 15C, 2790-138 Carnaxide, Portugal.

ProStrakan, Cz. See *ProStrakan, UK.*

ProStrakan, Fr. ProStrakan Pharma, 15 rue de Turbigo, 75002 Paris, France.
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ProStrakan, Gr. See *Anabiosis, Gr.*

ProStrakan, Port. See *ProStrakan, UK.*

ProStrakan, Swed. ProStrakan AB, Gaijersgatan 2, 216 18 Malmö, Sweden.
url: www.prostrakan.com

ProStrakan, UK. ProStrakan Group Ltd, Buckholm Mill, Buckholm Mill Brae, Galashiels, Scotland, TD1 2HB, UK.
url: www.strakan.com

Protea, S.Afr. Protea Pharm (Pty) Ltd, P.O. Box 553, Isando 1600, South Africa.

Protec, UK. Protec Health International Ltd, P.O. Box 137, Cirencester, Gloucestershire, GL7 5YW, UK.

Proteika, Fr. Proteika SA, Lab de Dietetique Medicale, 2 av des Noelles, B.P. 216, 44505 La Baule cdx, France.
url: www.proteika.com

Protein, Mex. Protein S.A. de C.V., Damas 120, Benito Juarez San Jose Insurgente, 3900 Mexico DF, Mexico.

Protherics, USA. Protherics Inc., 5214 Maryland Way, Suite 405, Brentwood, TN 37027, USA.
url: www.protherics.com

Protidiet, Fr. Protidiet, ZAE Migelane, B.P. 10, 33650 Saucats, France.
url: www.protidiet.com

Protiforme, Fr. Protiforme, 49 av. de la Motte-Picquet, 75015 Paris, France.
url: www.protiforme.net

Protina, Cz. See *Protina, Ger.*

Protina, Ger. Protina Pharmazeutische Gesellschaft mbH, Adalperostr. 90, 85737 Ismaning, Germany.
url: www.protina.de

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Proula, Venez. Proula Medicamentos, Av. 3 No. 29 Edif. Eva, 2do. Piso, Merida, Venezuela.
url: www.proulamed.com

Provalis, Irl. See *Provalis, UK.*

Provalis, UK. Provalis Healthcare, Newtech Square, Deeside Industrial Park, Deeside, Flintshire, CH5 2NT, UK.
url: www.provalis.co.uk

Provefarma, Arg. Laboratorio Provefarma SA, Calle 4 e/5 y 7, 3017 Sauce Viejo, Santa Fe, Argentina.

Provit, Mex. Provit S.A. de C.V., Nino Artillero No. 500, C.U. Independencia, 50070 Toluca, Mexico.

Provita, Austria. Provita Pharma GmbH, Seidengasse 33-35, A-1070 Vienna, Austria.

Provita, Ital. Provita Industria Farmaceutica S.r.l., Via Dora 7, 00198 Rome, Italy.

PRX, USA. See *Par, USA.*

PS, Ital. PS Pharma Srl, Via della Tenuta di Torrenova 142 Sc.A, 00133 Rome, Italy.

Psalmstre, Philipp. Psalmstre Enterprises, 5/F JMJ Bldg, P Sanchez, cor P Antonio Sts, Sta Mesa, Manila, Philippines.

PSI, Belg. PSI, Belgium.

PSI, Ital. Programmi Sanitari Integrati Srl, Via G Lanza 3, 20121 Milan, Italy.

Psicofarma, Mex. Laboratorio Psicofarma S.A. de C.V., Calz. de Tlalpan No. 4369, Col. Toriello Guerra, 14050 Mexico D.F., Mexico.
url: www.psicofarma.com.mx

PSM, NZ. PSM Healthcare Ltd, P.O. Box 76-401, Manukau City, Auckland, New Zealand.
url: www.psm.co.n

Psorimed, Switz. Psorimed AG, Postfach, 5401 Baden, Switzerland.

Puebla, Arg. Lab. Puebla S.R.L., Andres Lamas 2427, 5009 Barrio Escobar, Cordoba, Argentina.

Puerto Galiano, Spain. Puerto Galiano, Calle 'S', 4, Parque Europolis, Las Rozas, 28230 Madrid, Spain.
url: www.puertogaliano.com

Pulitzer, Ital. Pulitzer Italiana S.r.l., Via Tiburtina 1004, 00100 Rome, Italy.

Pulmobronk, Venez. Laboratorios del Pulmobronk, C.A., Av. P. Los Ruices, Ed. Monaca Torre Sur. P.5. Of.1, Caracas 1841, Venezuela.

Pulmomed, Rus. Pulmomed ZAO, Leninskii prospekt 33, korp. 3, et. 3, 117071 Moscow, Russia.
url: www.pulmomed.ru

Pulsion, Ger. Pulsion Medical Systems GmbH, Stahlgruberring 28, 81829 Munich, Germany.
url: www.pulsion.de

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Purdue, Canad. Purdue Pharma, 575 Granite Court, Pickering, Ontario, L1W 3W8, Canada.

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Purdue Frederick, USA. The Purdue Frederick Co., One Stamford Forum, 201 Tresser Blvd, Stamford, CT 06901-3431, USA.
url: www.pharma.com

Purissimus, Arg. Purissimus S.A., Juan F.Segum 4635, 1425 Buenos Aires, Argentina.
url: www.purissimus.com

Puritan Quartz, Thai. Puritan Quartz.

Purity Health, Canad. Purity Health Products, a division of Sunopta Inc., 6 Commerce Crescent, Acton, Ontario, L7J 2X3, Canada.

Purity Life, Canad. Purity Life Health Products, 6 Commerce Cres., Acton, Ontario, L7J 2X3, Canada.
url: www.puritylife.com

Purna, Belg. Purna Pharmaceuticals NV, Rijksweg 17, 2870 Puurs, Belgium.
url: www.purna.be

Pynogin, UK. Pynogin GmbH, Gee Lawson Distribution Centre, Unit 15 South Nottingham & Wilford Industrial Estate, Wilford, Nottingham, Nottinghamshire, NG11 7EP, UK.

Pyridam, Indon. Pyridam Indonesia PT, Jl Kemandoran 8 No 16, Grogol Utara, 12210 Jakarta Selatan, DKI Jaya, Indonesia.

Q Pharma, Spain. Laboratorios Q Pharma S.L., Portugal 23, 03003 Alicante, Spain.
url: www.q-pharma.net

Qestmed, S.Afr. Qestmed Ltd, Unit 2, Gazelle Place, Corporate Park, Old Pretoria Main Rd, Midrand 1685, South Africa.

QHP, USA. Quality Health Products Inc., P.O. Box 433, Indiana, PA 15701, USA.
url: www.qhpinc.com

QLT, Canad. QLT Inc., 887 Great Northern Way, Vancouver, BC, V5T 4T5, Canada.
url: www.qltinc.com

QLT, USA. QLT USA Inc., 2579 Midpoint Drive, Fort Collins, CO 80525, USA.
url: www.qltinc.com

Q-Med, Ital. Q-Med ICT Srl, Via Mario Borsa 11, 26845 Codogno (LO), Italy.

Q-Med, Singapore. Q-Med, Singapore.

Q-Med, UK. Q-Med (UK) Ltd, Castle Court, 41 London Rd, Reigate, Surrey, RH2 9RJ, UK.

Q-Med, USA. Q-Med Scandinavia Inc., 103 Carnegie Center, Suite 301, Princeton, NJ 08540, USA.
url: www.deflux.com

Q-Pharm, Ger. Q-Pharm AG, Bismarckallee 14-16, 23795 Bad Segeberg, Germany.
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Q-Pharma, Arg. Laboratorios Q-Pharma Argentina SA, Av. Chorroarin 710, Buenos Aires, Argentina.

QSA, Cz. See *QSA, Ger.*

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Qualicare, Switz. Qualicare AG, Florenz-Strasse 7, 4142 Münchenstein, Switzerland.
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Qualifarma, Ital. Qualifarma, Via Roma 22, 29010 Vernasca (PC), Italy.
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Qualimed, Philipp. Qualimed Pharma Inc., Unit 1001, 10/F Centerpoint Bldg, Gamet St cor Julia Vargas Ave, Ortigas Ctr, Pasig City, Philippines.

Qualiphar, Belg. Qualiphar SA, Rijksweg 9, 2880 Bornem, Belgium.
url: www.qualiphar.be

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Qualitec, Spain. Qualitec Farma Europe S.L., C/ Segre 28, 28002 Madrid, Spain.
url: www.qualitec-europa.com

Qualitest, USA. Qualitest Products Inc., 130 Vintage Drive, Huntsville, AL 35811, USA.

Quality, Hong Kong. Quality Pharmaceutical Laboratory Ltd, 21/F, 23/F Mai On Industrial Bldg, 19-21 Kung Yip St, Kwai Chung NT, Hong Kong.

Quality Formulations, USA. Quality Formulations Laboratories Inc., 110 Pennsylvania Ave., Paterson, NJ 07503, USA.
url: www.qualityformulations.com

Quantum, USA. Quantum Pharmics Ltd, USA.

Quatromed, S.Afr. Quatromed, 10 Lindley St., Bethlehem 9700, South Africa.

Queisser, Cz. See *Queisser, Ger.*

Queisser, Ger. Queisser Pharma GmbH & Co., Schleswiger Str. 74, 24941 Flensburg, Germany.
url: www.queisser.de

Queisser, Pol. Queisser Pharma Polconsult, Przedstawicielstwo w Polsce, ul. Kubickiego 17 m 9, 02-954 Warsaw, Poland.
url: www.queisser.pl

Queisser, Rus. Queisser Pharma GmbH.& Co., Lyusinovskaya ul. 36, Of. 73, 113093 Moscow, Russia.
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Quest, UK. Quest Vitamins Ltd, 8 Venture Way, Aston Science Park, Birmingham, B7 4AP, UK.
url: www.questvitamins.co.uk

Questcor, USA. Questcor Pharmaceuticals Inc., 3260 Whipple Rd, Union City, CA 94578, USA.
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Quidel, USA. Quidel Corp., 10165 McKellar Court, San Diego, CA 92121, USA.
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Quidnovi, Ital. Quidnovi SpA, Via Ferrarese 156/8, 40128 Bologna (BO), Italy.
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Quies, Fr. Laboratoires Quies, 4 rue Ambroise-Croizat, 91120 Palaiseau, France.

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Quimica y Farmacia, Mex. Química y Farmacia, S.A. de C.V., Av. Insurgentes sur 619 Desp 602, Benito Juarez Napoles, 3810 Mexico D.F., Mexico.

Quimifar, Spain. Químifar, Comadran 37, Pol Ind Can Salvatella, Barbera del Valles, 08210 Barcelona, Spain.
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Quimioterapica, Braz. Quimioterapica Brasileira Ltda, Rua São Januario 712, Tubalina, 38400-410 Uberlandia, MG, Brazil.

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Quinnova, USA. Quinnova Pharmaceuticals, 301 S State St, Suite N001, Newton, PA 18940, USA.
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Quinoderm, Hong Kong. See *Mekim, Hong Kong.*
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Quintessa, USA. Quintessa Corp., P.O. Box 808, Lancaster, CA 93584, USA.
Quiraus, Port. Quiraus Comércio Produtos Quimicos e Tecnologia Farmacêutica Lda, Av. Salvador Allende 12 - 1, 2780-163 Oeiras, Portugal.
Quixtar, Canad. Quixtar Canada Corp., 375 Exeter Rd, London, Ontario, N5Y 5V6, Canada.
Ra, Turk. Ra Tıbbi Cihazlar San. ve Tic. A.Ş., Nenehatun Cad., No: 103/7-8, Gaziosmanpaşa, Ankara, 06700, Turkey.
Rabi & Solabo, Fr. Laboratoires Rabi & Solabo, 67 rue Voltaire, 92150 Suresnes, France.
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Radyum, Turk. Radyum Laboratuvan İlaç San. ve Tic. A.Ş., Fevzipaşa Bulvan, Yeni Han No: 49/ K: 3, Çankaya, İzmir, Turkey.
Rafa, Israel. Rafa Laboratories Ltd, Hamarpeh St 5, P.O. Box 405, Jerusalem 91003, Israel.
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Raffo, Chile. Laboratorios Raffo SA, Simon Bolivar2183, Nunoa, Santiago, Chile.
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Ram, USA. See *Bradley, USA.*
Ramini, Ital. Ramini S.p.A., Via di Vallerano 96, 00100 Rome, Italy.
url: www.raminispa.com
Ramon Sala, Spain. See *Reig Jofre, Spain.*
RAN, Ger. R.A.N. Novesia AG Arzneimittel, Hurtgener Str. 6, 41464 Neuss/Rhein, Germany.
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Ranbaxy, Austral. Ranbaxy Australia Pty Ltd, Suite 4.02, Building D, Level 4, 12-24 Talavera Rd, North Ryde, 2113 NSW, Australia.
url: www.ranbaxy.com
Ranbaxy, Braz. Ranbaxy S.P. Medicamentos Ltda, Avenida das Americas 1155, Sala 1201 a 1204, Barra da Tijuca, 22631-000 Rio de Janeiro, RJ, Brazil.
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Ranbaxy, Cz. See *Interchemia, Cz.*
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Ranbaxy, Hong Kong. See *Hind Wing, Hong Kong.*
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Ranbaxy, Malaysia. Ranbaxy (Malaysia) Sdn Bhd, Box #8, Wisma Selangor Dredging, 5th Floor, South Block, 142-A Jalan Ampang, 50450 Kuala Lumpur, Kuala Lumpur, Malaysia.
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Ranbaxy, Mex. Ranbaxy Laboratories Ltd, Av. Paseo de las Palmas 239-103, 11000 Lomas de Chapultepec, Mexico.
Ranbaxy, Philipp. See *Aldril, Philipp., Medhaus, Philipp.,* and *Randril, Philipp.*
Ranbaxy, Pol. Ranbaxy (Poland) Sp. zo.o., ul. Kubickiego 11, 02-954 Warsaw, Poland.
url: www.ranbaxy.com.pl
Ranbaxy, Rus. Ranbaxy Laboratories Ltd, Techno Park, Office Centre, 45-48 Russian Exhibition Centre, Prospekt Mira, 129223 Moscow, Russia.
url: www.ranbaxy.com
Ranbaxy, S.Afr. Ranbaxy (SA) (Pty) Ltd, Third Floor, Outspan House, 1006 Lenchen Avenue North, Centurion, Pretoria, South Africa.
url: www.ranbaxy.com
Ranbaxy, Singapore. See *Zyfas, Singapore.*
Ranbaxy, Spain. Laboratorios Ranbaxy S.L., Paseo de Gracia 9, 7th floor, 08007 Barcelona, Spain.
url: www.ranbaxy.com
Ranbaxy, Thai. Ranbaxy Unichem Co. Ltd, 3 Fl, Rm 314-8, Phayathai Building, 31 Phayathai Rd, Rajathevi, Bangkok 10400, Thailand.
url: www.ranbaxy.com
Ranbaxy, UK. Ranbaxy (UK) Ltd, Consolidated Pneumatic House, 6th Floor, 97-107 Uxbridge Rd, Ealing, London, W5 5TL, UK.
url: www.ranbaxy.com
Ranbaxy, USA. Ranbaxy Pharmaceuticals Inc., 600 College Rd E, Suite 2100, Princeton, NJ 08540, USA.
url: www.ranbaxy.com
Randall, Mex. Randall Laboratories, S.A de C.V., Lago Rodolfo No. 58, M Hidalgo Granada, 11520 Mexico D.F., Mexico.
Randi, Israel. Randi, 5 Plotiski St, Rishon Lezion, Israel.
Randob, USA. Randob Laboratories Ltd, 6 Walnut St., P.O. Box 440, Cornwall, NY 12518, USA.
Randril, Philipp. Randril International Co. Inc., Unit 2205-A, 22/F West Tower, PSEC Exchange Rd, Ortigas Ctr, Pasig City, Philippines.
Ransom, UK. William Ransom & Sons plc, Alexander House, 40A Wilbury Way, Hitchin, Hertfordshire, SG4 0AP, UK.
url: www.williamransom.com
Rappai, Switz. Dr F. Rappai Pharmazeutika, Postfach, 8952 Schlieren-Zürich, Switzerland.
url: www.rappai.ch
Raptakos, India. Raptakos Brett & Co. Ltd, 47 Dr Annie Besant Rd, Worli, Mumbai 400 025, India.
Raptakos, Thai. See *Union Medical, Thai.*
Rare Disease Therapeutics, USA. Rare Disease Therapeutics, 1101 Kermit Drive, Suite 608, Nashville, TN 37217, USA.
url: www.raretx.com
Ratiopharm, Austria. Ratiopharm Arzneimittel Vertriebs-GmbH, Albert-Schweitzer-Gasse 3, A-1140 Vienna, Austria.
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Ratiopharm, Belg. ratiopharm Belgium nv, Sint Lambertusstraat 141, B-1200 Brussels, Belgium.
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Ratiopharm, Canad. Ratiopharm, 6975 Creditview Rd, Unit 5, Mississauga, Ontario, L5N 8E9, Canada.
url: www.ratiopharm.ca
Ratiopharm, Cz. Ratiopharm CZ sro, Bělehradská 54, 120 00 Prague 2, Czech Republic.
Ratiopharm, Fin. ratiopharm Oy, PL 67, 02631 Espoo, Finland.
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Ratiopharm, Ger. ratiopharm GmbH, Graf-Arco-Str. 3, 89079 Ulm/Donautal, Germany.
url: www.ratiopharm.de
Ratiopharm, Hong Kong. See *CNW, Hong Kong,* and *Hong Tai Hong, Hong Kong.*
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Ratiopharm, Neth. See *Ratiopharm, Ger.*
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Ratiopharm, Port. Ratiopharm, Lda, Edifício Tejo, 6 piso, Rua Quinta do Pinheiro, 2790-143 Carnaxide, Portugal.
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Ratiopharm, UK. Ratiopharm UK Ltd, 5 Jackson Close, Grove Rd, Cosham, Portsmouth, Hampshire, PO6 1UP, UK.
url: www.ratiopharm.co.uk
Ravensberg, Ger. Ravensberg GmbH, Schneckenburgstr. 46, 78467 Constance, Germany.
Rayere, Mex. Farmaceuticos Rayere S.A., Alambra 621, Benito Juarez Portales, 03300 Mexico D.F., Mexico.
Raymos, Arg. Lab. Raymos S.A.I.C., Vuelta de Obligado 2775, 1428 Buenos Aires, Argentina.
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Raza, Hong Kong. See *Ebewe, Hong Kong.*
Raza, Malaysia. Raza Manufacturing Bhd, 11A Jln P/1, Kawasan Perusahaan Bangi, 43650 Bandar Baru Bangi, Selangor, Malaysia.
RCA, Ital. Ricerca Cosmetica Avanzata S.r.l., Zona Industriale Loc. Penitro, 04023 Formia (LT), Italy.
R&D, USA. See *Watson, USA.*
RDC, Ital. See *Euroderm-RDC, Ital.*
Realdyme, Fr. Sté Réaldyme, 28700 Garancières-en-Beauce, France.
Reall, Switz. Medical Concepts Reall-YS S.á.r.l, Ave Villardin 22, 1009 Pully, Switzerland.
Reanal, Hung. Reanal Finomvegyszergyar Rt, Telepes u 53, 1147 Budapest, Hungary.
Recalcine, Chile. Laboratorios Recalcine SA, San Eugenio 567, Santiago, Chile.
Reccius, Chile. Laboratrios Reccius Ltda, Pucara 5326, Nunoa, Santiago, Chile.
Recherche Botanique, Fr. Laboratoires de Recherche Botanique, 9 av. Guy-Petit, 64200 Biarritz, France.
url: www.lrb.fr
Recip, Denm. See *Medic, Denm.*
Recip, Fin. See *Algol, Fin.*
Recip, Neth. See *Recip, Swed.*
Recip, Norw. See *Nycomed, Norw.*
Recip, Port. See *Recip, Swed.*
Recip, Swed. Recip AB, Bränningevägen 12, 120 54 Årsta, Sweden.
url: www.recip.se
Reckeweg, Cz. See *Reckeweg, Ger.*
Reckeweg, Ger. Pharmazeutische Fabrik Dr. Reckeweg & Co. GmbH, Berliner Ring 32, 64625 Bensheim, Germany.
url: www.reckeweg.de
Reckeweg, Neth. See *Reckeweg, Ger.*
Reckitt & Colman, Arg. Reckitt & Colman Arg. S.A., Avda. Pueyrredon 2446 Pso. 2, 1118 Buenos Aires, Argentina.
Reckitt & Colman, Austral. See *Reckitt Benckiser, Austral.*
Reckitt & Colman, Belg. See *Reckitt Benckiser, Belg.*
Reckitt & Colman, Cz. See *Reckitt Benckiser, UK.*
Reckitt & Colman, USA. See *Reckitt Benckiser, USA.*
Reckitt Benckiser, Austral. Reckitt Benckiser Pharmaceuticals, P.O. Box 138, West Ryde, NSW 2114, Australia.
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Reckitt Benckiser, Cz. See *Reckitt Benckiser, UK.*
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Reckitt Benckiser, Norw. See *Nycomed, Norw.*
Reckitt Benckiser, NZ. Reckitt Benckiser Pharmaceuticals, Private Bag 93121, Henderson, Auckland, New Zealand.
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Reckitt Benckiser, Pol. See *Boots, Pol.*
Reckitt Benckiser, Port. Reckitt Benckiser Healthcare Lda, Rua D Cristovão da Gama No 1 - 1 C/D, 1400-113 Lisbon, Portugal.
Reckitt Benckiser, S.Afr. Reckitt Benckiser Pharmaceuticals (Pty) Ltd, P.O. Box 164, Isando 1600, South Africa.
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Reckitt Benckiser, Singapore. See *Zuellig, Singapore.*
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Recofarma, Ital. See *Recordati, Ital.*
Recon, Singapore. See *Zyfas, Singapore.*
Recordati, Cz. See *Recordati, Ital.*
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Recordati, Hong Kong. See *Unico, Hong Kong.*
Recordati, Ital. Recordati Industria Chimica e Farmaceutica S.p.a., Via Civitali 1, 20148 Milan, Italy.
Recordati, Malaysia. See *Summit, Malaysia.*
Recordati, Pol. See *Fournier, Pol.*
Recordati, Singapore. See *MD, Singapore,* and *Orient, Singapore.*
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url: www.recordati.it
Recordati, UK. Recordati Pharmaceuticals Ltd, Knyvett House, The Causeway, Staines, Middlesex, TW18 3BA, UK.
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Reddy, Hung. Reddy, Hungary.
Reddy, Malaysia. See *Pahang, Malaysia,* and *Zyfas, Malaysia.*
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Reddy, S.Afr. Dr Reddy's Laboratories (Pty) Ltd, 3rd Floor, TA Bank Building, 160 Jan Smuts Ave, Rosebank, 2196, South Africa.
Reddy, Singapore. See *Zyfas, Singapore.*
Reddy, Thai. See *Neopharm, Thai.*
Reddy, USA. Dr Reddy's Laboratories Inc., 200 Somerset Corporate Bvld, Building II, Bridgewater, NJ 08807, USA.
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Reddy's, India. Dr. Reddy's Laboratories Ltd, 7-1-27 Ameerpet, Hyderabad 500 016, India.
url: www.drreddys.com
Redi-Products, USA. See *Aplicare, USA.*
Redken, Canad. See *L'Oreal, Canad.*
Reed & Carnrick, USA. See *Schwarz, USA.*
Reedco, USA. See *GSK Consumer, USA.*
Reese, USA. Reese Pharmaceutical Co. Inc., 10617 Frank Ave, Cleveland, OH 44106, USA.
url: www.reesechemical.com
Reg, Cz. Reg-Pharm sro, Fialková 45, 106 00 Prague 10, Czech Republic.
Rega, Port. Rega Farma Promoção de Produtos Farmacêuticos SA, Rua João Chagas 53, Piso 3, 1495-764 Cruz Quebrada, Portugal.
Regal, Canad. Regal Pharmaceuticals, Division of Bradcan Corp., 900 Harrington Court, Burlington, Ontario, L7N 3N4, Canada.
Regenaplex, Ger. Regenaplex Homöopathische Komplexmittel, Robert-Bosch-Str. 3, 78467 Constance, Germany.
url: www.regenaplex.de
Regeneron, USA. Regeneron Pharmaceuticals, 777 Old Saw Mill River Rd, Tarrytown, NY 10591, USA.
url: www.regeneron.com
Regent, Canad. See *Regent, USA.*
Regent, Switz. See *Globopharm, Switz.*
Regent, USA. Regent Medical Americsa LLC, 250 3585 Engineering Drive, Norcross, Georgia, 30092, USA.
Regent Medical, Norw. See *Molnlycke, UK.*
Regent Medical, Swed. See *Molnlycke, UK.*
Regent Medical, UK. See *Molnlycke, UK.*
Regime, Canad. Regime Industries Ltd, 205 20050 Stewart Crescent, Maple Ridge, British Colombia, V2X 0T4, Canada.
Regina, UK. Regina Health Ltd, NLA Tower, 12-16 Addiscombe Rd, Croydon, Surrey, CR0 0XT, UK.
url: www.reginahealthcare.com
Regiomedica, Cz. See *Regiomedica, Ger.*
Regiomedica, Ger. Regiomedica GmbH, Teichstrasse 66, D-79539 Lorrach, Germany.
Regiomedica, Neth. See *Regiomedica, Ger.*
Regional Health, Austral. Regional Health Care Products Group, Medi-Consumables P/L, 3-11 Primrose Ave, Rosebery, NSW 2018, Australia.
url: www.rhcg.com.au
Regional Health, NZ. Regional Health Ltd, P.O. Box 101-104, North Shore Mail Centre, Auckland, New Zealand.
url: www.regional.co.nz
Regius, Braz. Laboratório Regius Ltda, Rua Doutor Ramiro D'Avila 57, 90620-050 Porto Alegre, RS, Brazil.
Reig Jofre, Spain. Reig Jofre, Gran Capitan 10, Sant Joan Despi, 08970 Barcelona, Spain.
url: www.reigjofre.com
Rekah, Israel. Rekah Ltd, P.O. Bos 25, Azor 58190, Israel.
url: www.rekah.co.il
Relax, Ital. Relax Health Care S.r.l., Corso Sempione 36, 20154 Milan, Italy.
Relax, UK. Relax UK Ltd, Temple House, 2 Barbour Gardens, Colchester, Essex, CO2 9SA, UK.
url: www.dontbugmepatch.co.uk
Reliant, USA. Reliant, 110 Allen Rd, Liberty Corner, NJ 07938, USA.
url: www.reliantrx.com
Relyo, Gr. Relyo Hellas A.E., Favierou 48, 104 38 Athens, Greece.
Remedica, Hong Kong. See *Ebewe, Hong Kong,* and *Primal, Hong Kong.*
Remedica, Malaysia. See *JDH, Malaysia.*
Remedica, Philipp. See *Corbridge, Philipp.*
Remedica, Singapore. See *JDH, Singapore.*
Remedica, Thai. See *Pharmadica, Thai.*
Remedina, Gr. Remedina, Gounari 23 and Areos, 134 51 Kamatero Attiki, Greece.
Remek, Gr. Remek S.A., 3 Koleti Str., 144 52 Metamorfosi, Greece.
Remexa, Mex. Representaciones Mex-America S.A. de C.V.,, Diagonal 20 de Noviembre No. 264, Col. Obrera, Deleg. Cuauhtemoc, 06800 Mexico D.F., Mexico.
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Remidex, India. Remidex Pharma Pvt Ltd, B-249/250 Industrial Estate, Peenya II Stage, Bangalore 560 058, India.
Renapharma, Norw. Renapharma, Postboks 8664, 7452 Trondheim, Norway.
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Renapharma, Swed. Renapharma AB, Box 938, 751 09 Uppsala, Sweden.
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Renaudin, Fr. Laboratoires Renaudin, ZA Errobi, 64250 Itxassou, France.
Rendell, NZ. See *NZ Medical & Scientific, NZ.*
Rendell, UK. W.J. Rendell Ltd, Ickleford Manor, Hitchin, Hertfordshire, SG5 3XE, UK.
Rentschler, Austria. See *Rentschler, Ger.*
Rentschler, Cz. See *Rentschler, Ger.*
Rentschler, Ger. Dr. Rentschler Arzneimittel GmbH & Co., Mittelstr. 18, 88471 Laupheim, Germany.
url: www.rentschler.de

Rentschler, Singapore. See *PMR, Singapore.*
Repha, Ger. Repha GmbH Biologische Arzneimittel, Alt-Godshorn 87, 30855 Langenhagen, Germany.
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Repharma, Hung. Repharma Kft, Victor Hugo u 35 V/36, 1132 Budapest, Hungary.
RepliGen, USA. RepliGen Corp., 41 Seyon St., Building 1, Suite 100, Waltham, MA 02453, USA.
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Reprefar, Port. See *Pierre Fabre, Port.*
Republic, USA. Republic Drug Co., 175 Great Arrow, Suite 4, Buffalo, NY 14207, USA.
Requa, USA. Requa Inc., 540 Barnum Ave., P.O. Box 2348, Bridgeport, CT 06608, USA.
url: www.requa.com
Resdevco, Israel. Resdevco Ltd, P.O. Box 3338, Jerusalem, Israel.
Research Foundation, Philipp. See *Zuellig, Philipp.*
Research Industries Corp., USA. See *Edwards Lifesciences, USA.*
Resinag, Israel. See *Promedico, Israel.*
Resinag, Switz. Resinag AG, Grienbachstrasse 17, 6300 Zug, Switzerland.
Resource Medical, UK. ReSource Medical UK Ltd, 187 Manchester Rd, Thornton Lodge, Huddersfield, HD1 3JG, UK.
url: www.resource-medical.co.uk
Respa, USA. Respa Pharmaceuticals Inc., P.O. Box 88222, Carol Stream, IL 60188, USA.
Restan, S.Afr. See *Novartis, S.Afr.*
Retrain, Spain. Retrain, Alfonso XII 587, Badalona, 08912 Barcelona, Spain.
Retterspitz, Ger. Retterspitz GmbH, Laufer Str. 17-19, 90571 Schwaig, Germany.
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Reuabuen, USA. See *Novartis, USA.*
Reuffer, Mex. Reuffer Laboratorios S.A. de C.V., Juan de Dios Arias 78, Cuauhtemoc Vista Alegre, 06860 Mexico D.F., Mexico.
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Rex, NZ. Rex Medical, P.O. Box 23-025, Papatoetoe, Auckland, New Zealand.
Rexcel, India. See *Ranbaxy, India.*
Rextar, India. See *Ranbaxy, India.*
Rez, Cz. Ústav jaderneho vyzkumu Řež as, Řež u Prahy, Czech Republic.
Rhein, Mex. Siegfried Rhein S.A. de C.V., Bosque de Alisos 47-B Piso 3, Cuajimalpa Bosques de las Lomas, 5120 Mexico D.F., Mexico.
Rhodia, Israel. Rhodia Israel Ltd, P.O. Box 8443, Netanya, Israel.
Rhodiapharm, Canad. Rhodiapharm Inc., 2150 St Elzear Blvd W, Laval, Quebec, H7L 4A8, Canada.
Rhone-Poulenc Aventis, Ital. See *Aventis, Ital.*
Rhone-Poulenc Rorer, Austria. See *Aventis, Austria.*
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Rhone-Poulenc Rorer, Pol. See *Sanofi-Aventis, Pol.*
Rhone-Poulenc Rorer, Rus. See *Sanofi-Aventis, Rus.*
Rhone-Poulenc Rorer, USA. See *Sanofi-Aventis, USA.*
Riace, Rus. Farma Riace, Vysheslavcev 2-jj per., d. 17, 127018 Moscow, Russia.
url: www.pharmariace.ru
Ribex, Ital. See *Pfizer, Ital.*
Ribosepharm, Ger. ribosepharm GmbH, Berg-am-Laim-Str. 127, 81673 Munich, Germany.
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RiC, Pol. Przedsiębiorstwo Farmaceutyczne RiC, ul. Cybernetyki 11, 02-677 Warsaw, Poland.
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Ricerfarma, Malaysia. See *Pharmaniaga, Malaysia.*
Rich Plan, Hong Kong. Rich Plan International Ltd, Flat 9, 16/F, Block C, Wah Lok Industrial Ctr, 31-41 Shan Mei St, Fotan, Shatin, N.T., Hong Kong.
Richard, Fr. Laboratoires Richard, rue du Progrès, ZI des Reys de Saulce, 26270 Saulce-sur-Rhone, France.
Richardson-Vicks, USA. See *Procter & Gamble, USA.*
Richardson-Vicks Personal Care, USA. See *Procter & Gamble, USA.*
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Richmond, Arg. Lab. Richmond, Av. Elcano 4938, 1427 Buenos Aires, Argentina.
Richter, Austria. Richter Pharma, Feldgasse 19, A-4600 Wels, Austria.
Richter, Philipp. See *PharmAsia, Philipp.*
Richter, Pol. Richter Gedeon Ltd SA, Przedstawicielstwo w Polsce, ul. Królowej Marysieńki 70, 02-954 Warsaw, Poland.
url: www.gedeonrichter.pl
Richwood, USA. See *Shire, USA.*
Ricola, Canad. Ricola, Canada.
RID, USA. R.I.D. Inc., 609 N Mednik Ave, Los Angeles, CA 90022-1320, USA.
Rider, Chile. Laboratorios Rider SA, Placer 1348, Santiago, Chile.
Ridupharm, Switz. Ridupharm, Emil Frey-Strasse 99, 4142 Münchenstein, Switzerland.
Riel, Austria. Riel GmbH & Co. KG, Gasselberg 53-54, A-8564 Krottendorf-Gaisfeld, Austria.
Riemser, Cz. See *Riemser, Ger.*
Riemser, Ger. Riemser Arzneimittel AG, An der Wiek 7, 17493 Greifswald/Insel Riems, Germany.
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Rimafar, Spain. See *Belmac, Spain.*
Rimsa, Mex. Rimsa, Representaciones e Investigaciones Medicas S.A. de C.V., Av. Acoxpa No. 464, Prado Coapa, Deleg. Tlapan Fracc., 14350 Mexico D.F., Mexico.
url: www.gruporimsa.com.mx
Rising Pharmaceuticals, USA. Rising Pharmaceuticals Inc., 3 Pearl Court, Suite A/B, Allendale, NJ 07401, USA.
url: www.risingpharma.com
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Ritter, Ger. Walter Ritter GmbH & Co., Spaldingstr. 110 B, 20097 Hamburg, Germany.
url: www.walterritter.de
Ritter, Hong Kong. See *IDS, Hong Kong, Mekim, Hong Kong,* and *Suburfarm, Hong Kong.*
Ritter, Malaysia. See *JDH, Malaysia.*
Ritter, Singapore. See *JDH, Singapore.*
Ritter, Thai. See *Osotspa, Thai.*
Rius, Spain. Rius Garriga, Pujadas 95, 08005 Barcelona, Spain.
Riva, Canad. Laboratoire Riva Inc., 660 Industrial Blvd, Blainville, Quebec, J7C 3V4, Canada.
Rivadis, Fr. Laboratoires Rivadis, B.P. 111, ZI de Louzy, 79103 Thouars cdx, France.
url: www.labo-rivadis.fr
River Foods, Austral. River Foods, 1/3 Macquarie Drive, Thomastown, VIC 3074, Australia.
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Rivers Edge, USA. River's Edge Pharmaceutical, Suwanee, GA 30024, USA.
Rivex, Canad. Rivex Pharma Inc., 3-305 Industrial Parkway S, Aurora, Ontario, L4G 6X7, Canada.
Rivex Ophthalmics, Canad. See *Rivex, Canad.*
Riviera, Austria. Riviera Handelsgesellschaft.m.b.h., Penzingerstrasse 54, A-1140 Vienna, Austria.
Riviera, Cz. See *Riviera, Austria.*
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Roberts, Israel. See *Medison, Israel,* and *Pharmateam, Israel.*
Roberts, USA. See *Shire, USA.*
Roberts & Sheppey, UK. Roberts & Sheppey (Melrose) Ltd, Manor Farm House, Ickford, Aylesbury, Buckinghamshire, HP18 9JB, UK.
url: www.melrose-skincare.co.uk
Robins, Hong Kong. See *US Summit, Hong Kong.*
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url: www.robinsoncare.com
Robugen, Ger. Robugen GmbH Pharmazeutische Fabrik, Alleenstr. 22-6, 73730 Esslingen, Germany.
url: www.robugen.de
Robugen, Hong Kong. See *Mekim, Hong Kong.*
RoC, Fr. See *Johnson & Johnson Medical, Fr.*
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Roche, Arg. Productos Roche S.A.Q. e I., Ruta 9 Km 34, 1610 Ricardo Rojas Tigre, Buenos Aires, Argentina.
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Roche, Austral. Roche Products P/L, P.O. Box 255, Dee Why, NSW 2099, Australia.
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Roche, Austria. Roche Austria GmbH, Engelhorngasse 3, A-1211 Vienna, Austria.
url: www.roche.at
Roche, Belg. Roche SA/NV, Rue Dante 75, 1070 Brussels, Belgium.
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Roche, Braz. Produtos Roche Químicos e Farmacêuticos S.A., Avenida Engenheiro Billings 1729, 05321-900 São Paulo, SP, Brazil.
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Roche, Canad. Hoffmann-La Roche Ltd, 2455 Meadowpine Blvd, Mississauga, Ontario, L5N 6L7, Canada.
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Roche, Denm. Roche A/S, Industriholmen 59, 2650 Hvidovre, Denmark.
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Roche, Indon. Roche Indonesia PT, Gedung Artha Graha 21-23 Fl, Sudirman Central Business District Lot 25, Jl Jend Sudirman Kav 52-53, 12190 Jakarta, DKI Jaya, Indonesia.
Roche, Irl. Roche Pharmaceuticals (Ireland) Ltd, 3004 Lake Drive, City West, Naas Rd, Dublin 24, Ireland.
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Roche, Mex. Grupo Roche Syntex de Mixico, S.A. de C.V., Carr. Mexico-Toluca 2822, Miguel Hidalgo Lomas de Bezares, 11000 Mexico D.F., Mexico.
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Roche, Norw. Roche Norge AS, Kristoffer Robinsv. 13, Postboks 41 Haugenstua, 0915 Oslo, Norway.
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Roche, NZ. Roche Products (New Zealand) Ltd, P.O. Box 12-492, Penrose, Auckland, New Zealand.
url: www.roche.co.nz
Roche, Philipp. Roche (Phils) Inc., 2252 Don Chino Roces Ave, Makati City, Philippines.
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Roche, Port. Roche Farmacêutica Química, Lda, Estrada Nacional 249, 2720-413 Amadora, Portugal.
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Roche, Turk. Roche Müstahzarlan San. A.Ş., Mecidiyeköy Yolu No: 102, Mecidiyeköy Şişli, İstanbul, 34387, Turkey.
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Roche, USA. Roche Pharmaceuticals, 340 Kingsland St, Nutley, NJ 07110-1199, USA.
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Roche Diagnostics, NZ. Roche Diagnostics NZ Ltd, P.O. Box 62-089, Auckland, New Zealand.
url: www.roche-diagnostics.com
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Roche-Posay, Irl. La Roche-Posay Cosmetique Active, Styne House, Upper Hatch St., Dublin 8, Ireland.
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Roche-Posay, USA. La Roche-Posay Laboratoire Pharmaceutique, 112 Madison Ave, 12th Floor, New York, NY 10016, USA.
url: www.laroche-posay.com
Roddensers, Philipp. Roddensers Pharmaceuticals, R 2030 VV Soliven Shopping Complex, EDSA, Greenhills, San Juan, Metro Manila, Philippines.
Rodisma, Ger. Rodisma-Med Pharma GmbH, Kölner Str. 48, 51149 Cologne, Germany.
url: www.rodisma.de
Rodleben, Cz. See *UCB, Cz.*
Rodleben, Ger. Rodleben Pharma GmbH, Am Waldchen 19, 06862 Rosslau, Germany.
Rodlen, USA. Rodlen Laboratories, Subsidiary of Winston Laboratories Inc., 100 Fairway Drive, Ste 134, Vernon Hills, IL 60061, USA.
url: www.winstonlabs.com
Roehr, Philipp. See *Biolink, Philipp.*
Roemmers, Arg. Roemmers S.A.I.C.F., Fray Justo Sarmiento 2350, 1636 Olivos, Buenos Aires, Argentina.
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Roerig, Chile. See *Pfizer, Chile.*

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Rogers, Canad. Rogers Pharmaceuticals Ltd, 330 Marwood Drive, Unit 4, Oshawa, Ontario, L1H 8B4, Canada.
Roha, Ger. roha Arzneimittel GmbH, Rockwinkeler Heerstr. 100, 28355 Bremen, Germany.
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Roha, Hong Kong. See *Hind Wing, Hong Kong.*
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Rohto-Mentholatum, Thai. Rohto-Mentholatum (Thailand) Ltd, 5 Fl, Q House Bldg, 38 Convent Rd, Silom Bangrak, Bangkok 10500, Thailand.
Roi Surya, Indon. Roi Surya Prima PT, Jl Kapas Krampung 57, Surabaya, Jawa Timur, Indonesia.
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Rolmex, Canad. Rolmex International Inc., 1351 rue Gay-Lussac, Boucherville, Quebec, J4B7K1, Canada.
Romark, USA. Romark Laboratories, 3000 Bayport Drive, Suite 200, Tampa, FL 33607, USA.
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Rompharm, Rus. Rompharm, Leninskii prospekt 32, et. 3, 119991 Moscow, Russia.
url: www.rompharm.ru
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Ronnet, Arg. Ronnet Laboratoires S.A., Jose Enrique Rodo 5940, Buenos Aires, Argentina.
Rontag, Arg. Lab. Rontag S.A., Arcos 2626, 1428 Buenos Aires, Argentina.
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Rosa-Phytopharma, Fr. Laboratoires Rosa-Phytopharma, 68 rue Jean-Jaques-Rousseau, 75001 Paris, France.
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Rosch & Handel, Austria. Rösch & Handel, Gudrunstrasse 150, A-1100 Vienna, Austria.
Rosco, Denm. A/S Rosco, Farmaceutisk Industri, Taastrupgaardsvej 30, 2630 Taastrup, Denmark.
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Rosell, Canad. Institut Rosell Inc., 8380 Blvd Saint-Laurent, Montreal, Quebec, H2P 2M6, Canada.
Rosell, Cz. Institut Rosell, Czech Republic.
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Rosemont, UK. Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite St, Leeds, West Yorkshire, LS11 9XE, UK.
url: www.rosemontpharma.com
Rosen, Ger. Rosen Pharma GmbH, Kirkeler Str. 41, 66440 Blieskastel, Germany.
Rosken, Hong Kong. See *Suburfarm, Hong Kong.*
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Ross, USA. Ross Products, Division of Abbott Laboratories Inc., 625 Cleveland Ave, Columbus, OH 43215, USA.
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Rossendorf, Cz. Verein für Kenverfahrenstechnik und Analytik Rossendorf EV, Czech Republic.
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url: www.rotexmedica.com
Rotexmedica, Malaysia. See *Duopharma, Malaysia.*
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Rotexmedica, Singapore. See *CCM, Singapore.*
Roth, Austria. G Roth & Söhne Pharmazeutische Präparate GmbH, Wagnerstrasse 29, A-2371 Hinterbruhl, Austria.
Rothpharma, Austria. See *Roth, Austria.*
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Rotop, Ger. Rotop Pharmaka AG, Bautzner Landstr. 45, 01454 Radeberg, Germany.
url: www.rotop-pharmaka.de
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Rottapharm, Fin. See *Algol, Fin.*
Rottapharm, Fr. Laboratoires Rottapharm, 83-85 bd Vincent-Auriol, 75013 Paris, France.
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Rottapharm, Gr. Rottapharm, Greece.
Rottapharm, Hung. See *CSC, Hung.*
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Rottapharm, Neth. See *Rottapharm, Irl.*
Rottapharm, Pol. Rottapharm, Poland.
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Roux-Ocefa, Arg. Lab. Roux-Ocefa S.A., Montevideo 79/81, 1019 Buenos Aires, Argentina.
Rovi, Port. Laboratórios Farmacêuticos Rovi SA, Av. Defensores de Chaves 15 - 5 B, 1000-109 Lisbon, Portugal.
Rovi, Spain. Rovi, Julian Camarillo 35, 28037 Madrid, Spain.
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Rowa, Ger. Rowa Wagner GmbH & Co. KG Arzneimittelfabrik, Frankenforster Str. 77, 51427 Bergisch Gladbach, Germany.
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Rowa, Hong Kong. See *Jacobson, Hong Kong.*
Rowa, Hung. See *SATCO, Hung.*
Rowa, Irl. Rowa Pharmaceuticals Ltd, Bantry, Co. Cork, Ireland.
url: www.rowa.ie
Rowa, Israel. See *Megapharm, Israel.*
Rowa, Malaysia. See *JDH, Malaysia.*
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Roxane, USA. Roxane Laboratories Inc., a Subsidiary of Boehringer Ingelheim, P.O. Box 16532, Columbus, OH 43216, USA.
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Royton, Braz. Royton Química Farmacêutica Ltda, Avenida Doutor Cardoso de Melo 1318, 04548-004 São Paulo, SP, Brazil.
url: www.royton.com.br
RPF, Ital. Ricerca, Produzione e Commercializzazione di Prodotti Farmaceutici e Cosmetici Srl, Via Grottole 80/B, 81020 Castel Morrone (CE), Italy.
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url: www.rspharma.com
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Rubiepharm, Ger. RubiePharm Vertriebs GmbH, Brüder-Grimm-Str. 121, 36396 Steinau an der Strasse, Germany.
url: www.rubiepharm.de
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url: www.ruhrpharm.de
Rutti, Philipp. WM Rutti Inc., 75 Retiro cor Ipo St, La Loma, Quezon City, Philippines.
RW, Canad. RW Packaging Ltd, 200 Omand's Creek Blvd, Winnipeg, Mannitoba, R2R 1V7, Canada.
RX, Hong Kong. RX Co, Hong Kong.
RX, Thai. RX Company Ltd, 93/90 Soi Prachanukul 2, Ratchadapisek Rd, Bangsue, Bangkok 10800, Thailand.
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url: www.ryepharmaceuticals.com
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url: www.sabapharm.com
Sabex, Canad. Sabex Inc., 145 Jules-Leger St, Boucherville, Quebec, J4B 7K8, Canada.
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url: www.sabiluc.fr
Sabona, Ger. Sabona GmbH, Gutenbergstr. 1, 83052 Bruckmühl, Germany.
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url: www.saborapharm.fi
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url: www.salitine.de
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Salmon, Switz. Salmon Pharma, St Jakobs-Strasse 110, Postfach, 4002 Basle, Switzerland.
Salonpas, UK. Salonpas (UK) Ltd, Unit B, 32a Eveline Rd, Mitchum, Surrey, CR4 3LE, UK.
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url: www.salusint.com.pl
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Salusif, Port. Salusif, Lda, Rua do Centro Cultural 10 r/c, 1700 Lisbon, Portugal.
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Salvat, Spain. Salvat, Gall 30-36, Esplugas de Llobregat, 08950 Barcelona, Spain.
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url: www.samarthpharma.com
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Samjin, Singapore. See *Zyfas, Singapore.*
Samnam, Singapore. See *Pharmaforte, Singapore.*
Sam-On, Israel. Meditec/Sam-On Ltd, P.O. Box 1224, Bat-Yam 59602, Israel.
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Samyang, Singapore. See *Emerging Pharma, Singapore.*
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Sanbe, Philipp. See *Endure, Philipp.*
Sancor, Arg. Sancor Coop. Unidas Ltdas, Tacuari 202 Piso 3, 1071 Buenos Aires, Argentina.
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Sandersons, UK. Sandersons (Chemists) Ltd, 37 Oakwood Rise, Heaton, Bolton, BL1 5EE, UK.
Sandipro, Belg. See *Nycomed, Belg.*
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Sandoz, Austria. See *Novartis, Austria.*
Sandoz, Belg. See *Novartis, Belg.*
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Sandoz, Denm. See *Novartis, Denm.*
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Sandoz, Gr. See *Novartis, Gr.*
Sandoz, Hung. See *Novartis, Hung.*
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Sandoz, Ital. See *Novartis, Ital.*
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Sandoz, Neth. See *Novartis, Neth.*
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Sandoz, Philipp. See *Novartis, Philipp.*
Sandoz, Pol. See *Lek, Pol.*
Sandoz, Port. See *Novartis, Port.*
Sandoz, Rus. See *Sanofi-Aventis, Rus.*
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Sandoz, Singapore. See *FP, Singapore.*
Sandoz, Spain. See *Novartis, Spain.*
Sandoz, Swed. See *Novartis, Swed.*
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Sandoz, Thai. See *Novartis, Thai.*
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Sandoz, USA. See *Novartis, USA.*
Sandoz, Venez. See *Novartis, Venez.*
Sandoz Nutrition, USA. See *Novartis Nutrition, USA.*
Sanfer, Mex. Laboratorios Sanfer S.A. de C.V., Calz. de Tlalpan No. 550, Col. Moderna, Deleg. Benito Juarez, 03510 Mexico D.F., Mexico.
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Sang-A, Malaysia. See *Sun, Malaysia.*
Sang-A, Singapore. See *Emerging Pharma, Singapore.*

Sang-A Pharm, Singapore. See *Sime Darby, Singapore.*
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Sangstat, Malaysia. See *Summit, Malaysia.*
Sangstat, Singapore. See *Summit, Singapore.*
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Sanico, Switz. See *Uhlmann-Eyraud, Switz.*
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Sanitas, Port. See *Menarini, Port.*
Sankyo, Austral. See *Pharmacia, Austral.*
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Sankyo, Cz. See *IBI International, Cz.*
Sankyo, Denm. See *Gea, Denm.*
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Sankyo, Fr. See *Fornet, Fr.*
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Sankyo, Hong Kong. See *Hing Ah, Hong Kong,* and *Keller, Hong Kong.*
Sankyo, Hung. See *Budapharma, Hung.*
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Sanochemia, Cz. See *Sanochemia, Austria.*
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Sanochemia, Hung. See *Sanochemia, Ger.*
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Sanochemica, Neth. See *Sanochemica, Austria.*
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Sanofi, Denm. See *Sanofi Synthelabo, Denm.*
Sanofi, Irl. See *Sanofi-Aventis, Irl.*
Sanofi, Neth. See *Sanofi Synthelabo, Neth.*
Sanofi, Switz. See *Sanofi Synthelabo, Switz.*
Sanofi, USA. See *Sanofi-Aventis, USA.*
Sanofi BMS, Norw. See *Sanofi-Aventis, Norw.*
Sanofi Omnimed, S.Afr. See *Omnimed, S.Afr.*
Sanofi Pasteur, Arg. See *Sanofi Synthelabo, Arg.*
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Sanofi Pasteur, Denm. See *Sanofi Synthelabo, Denm.*
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Sanofi Pasteur, Hong Kong. See *Sanofi-Aventis, Hong Kong.*
Sanofi Pasteur, Hung. See *Sanofi-Aventis, Hung.*
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Sanofi Pasteur, Neth. See *Sanofi Pasteur, Belg.*
Sanofi Pasteur, Norw. See *Sanofi Synthelabo, Norw.*
Sanofi Pasteur, Pol. See *Aventis Pasteur, Pol.*
Sanofi Pasteur, Port. Sanofi Pasteur MSD S.A., Estrada de Alfragide 67, Lote F Sul, Piso 2 - Alfrapark, 2610-008 Amadora, Portugal.
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Sanofi Pasteur, Venez. See *Sanofi-Aventis, Venez.*
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Sanofi Synthelabo, Gr. See *Sanofi-Aventis, Gr.*
Sanofi Synthelabo, Hong Kong. See *Sanofi-Aventis, Hong Kong.*
Sanofi Synthelabo, Hung. See *Sanofi-Aventis, Hung.*
Sanofi Synthelabo, Indon. See *Sanofi-Aventis, Indon.*
Sanofi Synthelabo, Irl. See *Sanofi-Aventis, Irl.*
Sanofi Synthelabo, Israel. See *CTS, Israel.*
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Sanofi Synthelabo, NZ. See *Sanofi-Aventis, NZ.*
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Sanofi Synthelabo, Port. See *Sanofi-Aventis, Port.*
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Sanofi Torrent, India. See *Torrent, India.*
Sanofi Winthrop, Denm. See *Sanofi Synthelabo, Denm.*
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Sanova, Denm. See *Tjellesen, Denm.*
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Sanquin, Neth. Sanquin, Plesmanlaan 125, 1066 CX Amsterdam, Netherlands.
Sanquin, Port. See *Sanquin, Neth.*
Sant Gall, Arg. Sant Gall Friburg Q.C.I., Av. Brasil 3131/3, 1260 Buenos Aires, Argentina.
Santa, Gr. SANTA N. MPALANOS ABEE, Leof. Dimokratias 145, 136 71 Acharnes, Greece.

Santa, Rus. Santa OOO, a/ya 100, 119311 Moscow, Russia.

Santa, Turk. Santa Farma İlaç San. A.Ş., Okmeydanı Boruçiçeği Sok. No: 20, Şişli, İstanbul, 34382, Turkey.
url: www.santafarma.com

Santarus, USA. Santarus, Inc., 10590 West Ocean Air Drive, Suite 200, San Diego, CA 92130, USA.
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Sante Naturelle, Canad. Santé Naturelle (AG) Ltée, 369 Charles Péguy, La Prairie, Quebec, J5R 3E8, Canada.
url: www.santenaturelle.ca

Santen, Cz. Santen Oy, Business Centre Chronos, Vaclavske nam 66, 110 00 Prague 1, Czech Republic.

Santen, Denm. Santen, Kongeleddet 1, 2920 Charlottenlund, Denmark.
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Santen, Fin. Santen Oy, Niittyhaankatu 20, PL 33, 33721 Tampere, Finland.
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Santen, Ger. Santen GmbH, Industriestrasse 1, 82110 Germering, Germany.
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Santen, Hong Kong. See *Hong Kong Medical, Hong Kong,* and *Leader, Hong Kong.*

Santen, Hung. See *Llogo, Hung.*

Santen, Indon. See *Ferron, Indon.*

Santen, Jpn. Santen Pharmaceutical Co Ltd, 3-9-19 Shimoshinjo, Higashi-Yodogawa-ku, Osaka 533-8651, Japan.
url: www.santen.co.jp

Santen, Neth. See *Santen, Fin.*

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Santen, Philipp. See *Croma, Philipp.*

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Santen, Port. See *Santen, Swed.*

Santen, Rus. Santen AO, Mytnaya ul. 1, pod. 1, et. 6, 117049 Moscow, Russia.
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Santen, Singapore. See *JDH, Singapore.*

Santen, Swed. Santen Pharma AB, Solna torg 3, 171 45 Solna, Sweden.
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Santen, Thai. See *Greater Pharma, Thai.,* and *Oui Heng, Thai.*

Santen, USA. Santen Inc., 555 Gateway Drive, Napa, CA 94558, USA.
url: www.santeninc.com

Santiveri, Spain. Santiveri, Encuny 8, 08038 Barcelona, Spain.
url: www.santiveri.es

Sanum-Kehlbeck, Ger. Sanum-Kehlbeck GmbH & Co. KG, Hasseler Steinweg 9-12, 27318 Hoya, Germany.
url: www.sanum.com

Sanus, Gr. Sanus, Greece.

Sanval, Braz. Sanval Comércio e Indústria Ltda, Rua Lagrange 401, 04761-050 São Paulo, SP, Brazil.
url: www.sanval.com.br

Sanwa, Jpn. Sanwa Kagaku Kenkyusho Co Ltd, 35 Higashi-Sotobori-cho, Higashi-ku, Nagoya 461-8631, Japan.
url: www.skk-net.com

Sapos, Hung. Sapos, Hungary.

Saprochi, Israel. See *Meditrend, Israel.*

Saprochi, Switz. Saprochi SA, Chemin de la Cretaux, Case postale 327, 1196 Gland/VD, Switzerland.
url: www.saprochi.ch

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Satis, Port. Satis Radioisótopos e Protecções contra Sobretensões Eléctricas Lda, Av. do Forte 4, 2795-502 Carnaxide, Portugal.

Sato, Thai. See *Diethelm, Thai.*

Satori, Fr. Laboratoires Satori International, Parc d'activite de Limonest, 540 allée des Hêtres, 69760 Limonest, France.
url: www.satori-international.fr

Sauter, Austral. See *Roche, Austral.*

Savage, USA. See *Altana, USA.*

Saval, Chile. Laboratorios Saval SA, Avenida Presidente Eduardo Frei Montalva 4600, Santiago, Chile.
url: www.saval.cl

Savant, Arg. Savant Pharm SA, Ruta Nacional Nro 19 Km. 204, Cordoba, Argentina.

Savi, Mex. Savi Distribuciones SA de CV, Mayas 10, 53150 Naucalpan Sta. Cruz Acatlan, Mexico DF, Mexico.

Savient, USA. Savient Pharmaceuticals Inc., One Tower Center, 14th Floor, East Brunswick, NJ 08816, USA.
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Savoma, Ital. Savoma Medicinali S.p.A., Via Baganza 2/A, 43100 Parma, Italy.

Savoy, Singapore. See *Polymedic, Singapore.*

Say, Turk. Say İlaç San. ve Tic. Ltd. A.Ş., Bağdat Cad., Göker Apt. No: 314, D: 2, Caddebostan, İstanbul, Turkey.

SBL, Cz. See *SBL, Swed.*

SBL, Denm. See *Pasteur Merieux, Denm.*

SBL, Fin. See *SBL, Swed.*

SBL, Neth. See *SBL, Swed.*

SBL, Norw. SBL Vaccin Norge, C. J. Hansensv. 3 A, 2007 Kjeller, Norway.
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SBL, Port. See *SBL, Swed.*

SBL, Swed. SBL Vaccin AB, Lundagatan 2, 105 21 Stockholm, Sweden.
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SC Terapia, Pol. SC Terapia, Poland.

Scaglietti, Ital. Scaglietti Srl, Via Tagliamento n 6, 41050 Montale Rangone (MO), Italy.

Scan Lab, Thai. See *Harn, Thai.*

Scan-Anida, Pol. Scan-Anida Sp. zo.o., ul. Motyla 26, 30-733 Kraków, Poland.
url: www.scananida.com.pl

Scand Pharm, Swed. Scandinavian Pharmaceuticals-Generics AB, Box 23033, 104 35 Stockholm, Sweden.
url: www.scandpharm.se

Scandimed, Swed. ScandiMed, Forskaregatan 1, 275 37 Sjöbo, Sweden.
url: www.bonecement.com

Scandinavian Health Care, Norw. Scandinavian Health Care AS, Grini Naeringspark 1, 1361 Østerås, Norway.
url: www.shc.no

Scandinavian Laboratories, Pol. See *Marinex, Pol.*

Scandinavian Natural Health & Beauty, USA. Scandinavian Natural Health & Beauty Products Inc., 13 North Seventh St, Perkasie, PA 18944, USA.
url: www.scandinaviannaturals.com

Scandipharm, Israel. See *Megapharm, Israel.*

Scandipharm, USA. See *Axcan, USA.*

Scanpharm, Cz. See *Scanpharm, Denm.*

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Scanpharm, Hong Kong. See *Winsor, Hong Kong.*

Scanpharm, Philipp. See *Phoenix, Philipp.*

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Schaper & Brummer, Austria. See *Schaper & Brummer, Ger.*

Schaper & Brummer, Cz. See *Schaper & Brummer, Ger.*

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Schaper & Brummer, Malaysia. See *JDH, Malaysia.*

Schaper & Brummer, Pol. See *Zymella, Pol.*

Schaper & Brummer, Singapore. See *Bionax, Singapore.*

Schaper & Brummer, Thai. See *Diethelm, Thai.*

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Scheffler, Cz. See *Scheffler, Ger.*

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Schein, USA. See *Watson, USA.*

Scherax, Ger. See *Alk-Scherax, Ger.*

Scherer, Cz. See *Theramex, Mon.*

Scherer, Hong Kong. See *Atlantic, Hong Kong, Star, Hong Kong,* and *Winsor, Hong Kong.*

Scherer, Hung. Scherer, Hungary.

Scherer, Indon. See *Pharos, Indon.*

Scherer, Malaysia. See *Zuellig, Malaysia.*

Scherer, Philipp. See *Meyers, Philipp.,* and *Philusa, Philipp.*

Scherer, Singapore. See *Luen Wah, Singapore.*

Scherer, Thai. See *Kemopharm, Thai., Osotspa, Thai., Sriprasit, Thai.,* and *Star, Thai.*

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Schering, Indon. See *Bayer, Indon.*

Schering, Irl. See *Clissmann, Irl.*

Schering, Israel. See *Perrigo, Israel.*

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Schering, Malaysia. See *Zuellig, Malaysia.*

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Schering, UK. See *Bayer, UK.*

Schering, USA. See *Schering-Plough, USA.*

Schering, Venez. Schering de Venezuela S.A., Segunda Avenida de Campo Alegre, Edif. Torre Cari Pisos 1, 2 y 3, Apartado 66802, Caracas 1061-A, Venezuela.
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Schering-Plough, Austria. See *Aesca, Austria.*

Schering-Plough, Belg. Schering-Plough SA, Rue de Stalle 67, 1180 Brussels, Belgium.
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Schering-Plough, Hong Kong. Schering-Plough, Division of SOL Ltd, 17/F Chinachem Exchange Square, 1 Hoi Wan St, Quarry Bay, Hong Kong.
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Schering-Plough, Hung. Schering-Plough Central East AG Magyarországi Kereskedelmi Képviselet, Váci út 35 II emelet, 1134 Budapest, Hungary.

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Schering-Plough, Irl. See *Pfizer, Irl.*

Schering-Plough, Israel. See *Trading, Israel.*

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Schering-Plough, Singapore. See *Zuellig, Singapore.*

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Schiapparelli Searle, USA. See *SCS, USA.*

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Schmid, Israel. Schmid, Israel.

Schmid, USA. See *Durex, USA.*

Schmidgall, Austria. Dr A & L Schmidgall, Wolfganggasse 45-7, A-1121 Vienna, Austria.
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Schmidgall, Cz. See *Schmidgall, Austria.*

Schmidgall, Hung. See *Penta, Hung.*

Schmidgall, Pol. See *Goldmed, Pol.*

Schmidgall, Rus. See *Santa, Rus.*

Schmidt, Malaysia. Schmidt Biomedtech Sdn Bhd, 5/F Wisma Domain, No 18A, Lot 318, Jln 51A/223, 46100 Petaling Jaya, Selangor, Malaysia.
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Schoenenberger, Ger. Walther Schoenenberger GmbH & Co. KG, Muhlstr. 5-7, 71106 Magstadt, Germany.

Scholl, Canad. See *Schering-Plough, Canad.*

Scholl, Hung. See *SSL, Hung.*

Scholl, Israel. See *Dexxon, Israel.*

Schonenberger, Switz. Schönenberger Pharma AG, Schachenstrasse 24, 5012 Schonenwerd, Switzerland.

Schoning-Berlin, Ger. Schöning Pharmazeutische Präparate GmbH & Co. KG, Porschestr. 22-24, 12107 Berlin, Germany.
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Schuck, Ger. Schuck GmbH, Industriestr. 11, 90571 Schwaig b. Nürnberg, Germany.
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Schuco, UK. Schuco International Ltd, Challenge House, 1 Lyndhurst Ave, London, N12 0NE, UK.
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Schulke & Mayr, Austria. Schülke & Mayr GmbH, Zieglergasse 8/3, A-1070 Vienna, Austria.
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Schulke & Mayr, Ger. Schülke & Mayr GmbH, Robert-Koch-Str. 1, 22851 Norderstedt, Germany.
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Schulke & Mayr, Switz. Schülke & Mayr AG, Obere Zaune 12, 8001 Zurich, Switzerland.
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Schulke & Mayr, Thai. See *Diethelm, Thai.*

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Schwabe, Hung. See *Schwabe, Ger.*

Schwabe, Malaysia. See *Antah, Malaysia.*

Schwabe, Neth. See *VSM, Neth.*

Schwabe, Philipp. See *Zuellig, Philipp.*

Schwabe, Pol. See *Medagro, Pol.*

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Schwabe, Singapore. See *MD, Singapore.*

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Schwarz, Denm. See *Erol, Swed.*

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Schwarz, Irl. See *Allphar, Irl.*

Schwarz, Israel. See *Medis, Israel.*

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Schwarz, Malaysia. See *Ranbaxy, Malaysia.*

Schwarz, Norw. See *Andersen, Norw.,* and *Meda, Norw.*

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url: www.schwarzpharmaasia.com

Schwarz, Pol. Schwarz Pharma Sp. zo.o., ul. Dolna 21, 05-092 Łomianki, Poland.
url: www.schwarzpharma.pl

Schwarz, Rus. Schwarz Pharma AG, Usacheva ul. 33/2, str. 5, 119048 Moscow, Russia.
url: www.schwarzpharma.com

Schwarz, Singapore. See *Zyfas, Singapore.*

Schwarz, Spain. Schwarz Pharma Spain, Paseo de la Castellana, 141, Pl. 15, 28046 Madrid, Spain.
url: www.schwarzpharma.es

Schwarz, Switz. See *Globopharm, Switz.*

Schwarz, Thai. See *BJC, Thai.*

Schwarz, UK. Schwarz Pharma Ltd, Schwarz House, East St, Chesham, Buckinghamshire, HP5 1DG, UK.
url: www.schwarzpharma.co.uk

Schwarz, USA. Schwarz Pharma Inc., 6140 W Executive Drive, Mequon, WI 53092, USA.
url: www.schwarzusa.com

Schwarzhaupt, Austria. See *Schwarzhaupt, Ger.*

Schwarzhaupt, Ger. Kommanditgesellschaft Schwarzhaupt GmbH & Co., Sachsenring 37-47, 50677 Cologne, Germany.
url: www.schwarzhaupt-arznei.de

Schwarzhaupt, Thai. See *Pacific, Thai.*

Schwarzkopf, Canad. See *Dep, Canad.*

Schwarzwalder, Ger. Schwarzwälder Natur-Heilmittel, Marktplatz 4, 93183 Kallmunz, Germany.

Schworer, Ger. Pharma Schwörer GmbH, Goethestr. 29, 69257 Wiesenbach, Germany.
url: www.pharma-schwoerer.de

Schwulst, S.Afr. See *Alliance, S.Afr.*

SciClone, Hong Kong. SciClone Pharmaceuticals International Ltd, Rm 3401A Windsor House, 311 Gloucester Rd, Causeway Bay, Hong Kong.
url: www.sciclone.com

SciClone, Indon. See *Tempo Scan Pacific, Indon.*

Sciclone, Ital. Sciclone Pharmaceuticals Italy S.r.l., Via Lisbona 11, 00100 Rome, Italy.

Sciclone, Malaysia. See *Diethelm, Malaysia.*

SciClone, Philipp. See *Zuellig, Philipp.*

Sciclone, Singapore. See *Zuellig, Singapore.*

Sciclone, Thai. See *Diethelm, Thai.*

Scidia, Arg. Scidia, Argentina.

Sciele, USA. Sciele Pharma Inc., Five Concourse Parkway, Suite 1800, Atlanta, GA 30328, USA.
url: www.sciele.com

Sciencex, Fr. Laboratoires Sciencex, 1 rue Edmond-Guillout, 75015 Paris, France.

Scientific Hospital Supplies, Austral. Scientific Hospital Supplies, 14-16 Brookhollow Avenue, Norwest Business Park, Baulkham Hills, NSW 2153, Australia.

Scientific Hospital Supplies, Irl. See *Nutricia, Irl.*

Scientific Hospital Supplies, Israel. See *Megapharm, Israel.*

Scientific Hospital Supplies, NZ. See *Nutricia, NZ.*

Scientific Hospital Supplies, UK. See *SHS, UK.*

Scigen, Austral. SciGen Ltd, Level 7, 2 Bligh St, Sydney, NSW 2000, Australia.
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Scigen, Hong Kong. See *Zuellig, Hong Kong.*

SciGen, Philipp. SciGen Ltd, 2/F Metro Drug Inc. Bldg, Manalac Ave, Bagumbayan, Taguig, Metro Manila, Philippines.

Scigen, Singapore. SciGen Pte Ltd, 14 Science Park drive, 04-01A The Maxwell, S 118226, Singapore.
url: www.scigen.com.au

Scios, USA. Scios Inc., 6500 Paseo Padre Parkway, Fremont, CA 94555, USA.
url: www.sciosinc.com

Scipharm, S.Afr. Scipharm Ltd, P.O. Box 13119, Vorna Valley 1686, South Africa.
url: www.scientificgroup.com

Sclavo, Israel. See *Promedico, Israel.*

Scot, Israel. See *Trupharm, Israel.*

Scotia, Cz. See *Scotia, UK.*

Scotia, Irl. See *Scotia, UK.*

Scotia, UK. Scotia Pharmaceuticals Ltd, Scotia House, Castle Business Park, Stirling, Stirlingshire, FK9 4TZ, UK.

Scott, Canad. See *Lander, Canad.*

Scott-Cassara, Arg. Scott-Cassara, Gaona 4302, 1407 Buenos Aires, Argentina.

Scot-Tussin, USA. Scot-Tussin Pharmacal Co. Inc., 32 West Hamden Rd, P.O. Box 8217, Cranston, RI 02920-0217, USA.
url: www.scot-tussin.com

SCS, USA. See *Sanofi-Aventis, USA.*

SDA, USA. SDA Laboratories, 280 Railroad Ave, Greenwich, CT 06830, USA.

SDR, USA. SDR Pharmaceuticals Inc., 27 Mountain View Drive, Andover, NJ 07821, USA.
url: www.sdrpharma.com

SEA Pharm, Thai. SEA Pharm Co Ltd, 20/20 Moo 3, Sammuang, Lardbualuang, Pranakornsriayutthaya 13230, Thailand.

Sea-Band, UK. Sea-Band Ltd, Lancaster Rd, Hinckley, Leicestershire, LE10 0AW, UK.
url: www.sea-band.com

Seaford, Canad. Seaford Pharmaceuticals Inc., 1530 Drew Rd, Unit 28, Mississauga, Ontario, L5S 1W8, Canada.
url: www.seaford.ca

Searle, Braz. See *Pharmacia, Braz.*

Searle, Cz. See *Pharmacia, Cz.*

Searle, Israel. See *Perrigo, Israel.*

Searle, Neth. See *Pharmacia, Neth.*

Searle, Pol. See *Pfizer, Pol.*

Searle, Rus. See *Pfizer, Rus.*

Searle, S.Afr. See *Pfizer, S.Afr.*

Searle, USA. See *Pfizer, USA.*

Seatrace, USA. Seatrace Pharmaceuticals, P.O. Box 7200, Gadsden, AL 35906, USA.

Sebapharma, Hong Kong. See *Mekim, Hong Kong.*

Sebapharma, Thai. See *Oui Heng, Thai.*

Seber, Port. Seber Portuguesa Farmacêutica, SA, Rua Norberto de Oliveira 1-5, 2620-111 Póvoa de St Adrião, Portugal.

SecFarm, Pol. SecFarm Sp. zo.o., ul. Korkowa 120, 04-502 Warsaw, Poland.

Se-cure, Singapore. See *Age D'or, Singapore.*

Sedabel, Braz. Laboratório Sedabel Ltda, Rodovia Washington Luiz 1308 Km 4.5, 25085-000 Duque de Caxias, RJ, Brazil.
url: www.sedabel.com.br

Sedar, Braz. Sedar Indústria Farmacêutica Ltda, Rodovia BR 101 Sul Km 18, Distr. Ind. dos Prazeres, 50950-000 Recife, PE, Brazil.

SEDR, Israel. See *Rafa, Israel.*

Sefarma, Ital. Sefarma S.r.l., Via Robert Koch 1.2, 20152 Milan, Italy.

Segix, Ital. Segix Italia S.r.l., Via del Mare 36, 00040 Pomezia (RM), Italy.
url: www.segixitalia.it

Seid, Spain. Seid, Ctra Sabadell Granollers Km 15, Llissa de Vall, 08185 Barcelona, Spain.
url: www.lab-seid.com

Seiko Eiyo, Hong Kong. See *Primal, Hong Kong.*

Sekpharma, S.Afr. See *Sekunjalo, S.Afr.*

Sekunjalo, S.Afr. Sekunjalo Healthcare, Sekunjalo House, Block F The Terraces, Steenberg Office Park, Tokal, Cape Town, 7945, South Africa.
url: www.sekunjalo.com

Selen, Turk. Selen, Turkey.

Selena, Swed. See *Selena Fournier, Swed.*

Selena Fournier, Denm. See *Ipex, Swed.*

Selena Fournier, Norw. See *Ipex, Swed.*

Selena Fournier, Swed. Selena Fournier AB, Box 1266, 172 25 Sundbyberg, Sweden.
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Selenium Pharma, Hung. Selenium Pharma Kft, Berényi u 8, 1016 Budapest, Hungary.

Self-Care Products, UK. Self-Care Products Ltd, 30 Sycamore Rd, Amersham, Buckinghamshire, HP6 5DR, UK.

Sella, Ital. Sella A. Lab. Chim. Farm. S.r.l., Via Vicenza 67, 36015 Schio (Vicenza), Italy.
url: www.sellafarmaceutici.it

Selmag, Switz. Selmag-Weibel, Bergackerweg 8, 3054 Schupfen/BE, Switzerland.

Selvi, Ital. Selvi Laboratorio Bioterapico S.p.A., Via Procoio 28, 00065 Fiano Romano (RM), Italy.

Selz, Ger. Pharma Selz GmbH, Leininger Ring 65a, 67278 Bockenheim, Germany.
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Semper, Fin. See *Arla, Fin.*

Seneca, USA. See *Beach, USA.*

Senese, Ital. Industria Farmaceutica Galenica Senese S.r.l., Via Cassia Nord 351, 53014 Monteroni d'Arbia (SI), Italy.

Senetek, USA. Senetek plc, 620 Airpark Rd, Napa, CA 94558, USA.
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Seng, Hong Kong. See *Health Alliance, Hong Kong.*

Seng, Thai. See *Sang, Thai.*

Senju, Jpn. Senju Pharmaceutical Co. Ltd, 2-5-8 Hiranomachi, Chuo-ku, Osaka 541-0046, Japan.

Senju, Pol. See *Mitsubishi, Pol.*

Senosiain, Mex. Laboratorios Senosiain S.A. de C.V., Andres Bello 45 Piso 10,20,21, Col. Chapultepec, Miguel Hidalgo, 11560 Mexico D.F., Mexico.

Sensomed, Philipp. Sensomed Phils Inc., Unit 1508 Orient Square Bldg, 26 F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

Seoul Pharma, Singapore. See *Pharmaforte, Singapore.*

Sepracor, USA. Sepracor, 84 Waterford Drive, Marlborough, MA 01752, USA.
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Septa, Spain. Septa Chemifarma, Sierra Guadarrama 11, Pol. Ind. 2, San Fernando de Henares, 28850 Madrid, Spain.

Septodont, Austral. Specialites Septodont Pty Ltd., P.O. Box 288, Emu Plains, NSW 2750, Australia.

Septodont, Cz. See *Septodont, Fr.*

Septodont, Denm. See *CMS-Dental, Denm.*

Septodont, Fin. See *Sirowa, Fin.*

Septodont, Fr. Specialites Septodont, Saint-Maur des Fosses, France.

Septodont, Norw. See *Denamed, Norw.*

Septodont, Port. See *Septodont, Fr.*

Septodont, Switz. See *Odontopharm, Switz.*

Septodont, USA. Septodont Inc., 245-C Quigley Blvd, New Castle, DE 19720, USA.
url: www.septodontinc.com

Sequus, Austria. See *Three Rivers, USA.*

Sequus, Israel. See *Gamida-Medequip, Israel.*

Sequus, Spain. See *Three Rivers, USA.*

Sequus, USA. See *Alza, USA.*

Serag-Weissner, Cz. See *Serag-Wiessner, Ger.*

Serag-Wiessner, Ger. Serag-Wiessner KG, Zum Kugelfang 8-12, 95119 Naila, Germany.
url: www.serag-wiessner.de

SERB, Fr. Laboratoires SERB, 53 rue Villiers de l'Isle Adam, 75020 Paris, France.
url: www.serb-labo.com

Serch, Arg. Lab. Serch S.R.L., Av. Arturo Illia 668, 1706 Haedo, Buenos Aires, Argentina.

Serdex, Indon. See *Corsa, Indon.*

Serdex, Thai. See *Pacific, Thai.*

Serdia, India. Serdia Pharmaceuticals (India) Ltd, Serdia House, Off Dr S.S. Rao Rd, Parel, Mumbai 400 012, India.

Sermedica, Port. Sermédica Especialidades Farmacêuticas Lda, Av. Antonio Augusto de Aguiar 128, 1069-133 Lisbon, Portugal.

Sermmitr, Thai. Sermmitr c/o The Sermmitr Co. Ltd, 82, 84 Arkarn 2, Ratchamnoen Ave, Bangkok 10200, Thailand.

Serolab, Switz. Serolab SA, CP 43, 1618 Châtel-St-Denis, Switzerland.
url: www.serolab.ch

Serono, Arg. Serono Argentina S.A., Thames 158, 1642 San Isidro, Buenos Aires, Argentina.
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Serono, Austral. Serono Australia P/L, Allambie Grove Business Park, 4/25 Frenchs Forest Rd (East), Frenchs Forest, NSW 2086, Australia.
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Serono, Austria. Serono Austria GmbH, Wiederhofergasse 3/24, A-1090 Vienna, Austria.
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Serono, Belg. Serono Benelux SA, Heysel Esplanade b11, 1020 Brussels, Belgium.
url: www.serono.com

Serono, Braz. Serono Produtos Farmacêuticos Ltda, Rua Dr Eduardo de Souza Aranha 387, 11° andar, 04543-121 São Paulo, SP, Brazil.
url: www.serono.com.br

Serono, Canad. Serono Canada Inc., 1075 North Service Rd, Suite 100, Oakville, Ontario, L6M 2G2, Canada.
url: www.serono-canada.com

Serono, Cz. Serono Pharma Services sro, Betlemská 1, 110 00 Prague 1, Czech Republic.
url: www.ares-serono.com

Serono, Denm. Serono Nordic, Aarhusgade 88, 7, 2100 Copenhagen O, Denmark.
url: www.serono.com

Serono, Fin. Serono Nordic, Rajatorpantie 41 B, 01640 Vantaa, Finland.
url: www.serono.com

Serono, Fr. Laboratoires Serono, L'Arche du Parc, 738 rue Yves-Kermen, 92658 Boulogne cdx, France.
url: www.serono.com

Serono, Ger. Serono Pharma GmbH, Freisinger Str. 5, 85716 Unterschleissheim, Germany.
url: www.serono.com

Serono, Gr. Serono Hellas A.E., 3-5 Konitsis St., 151 25 Marousi, Greece.
url: www.serono.gr

Serono, Hong Kong. Serono Hong Kong Ltd, Rm 2004-6, 20/F, Alliance Building, 130-136 Connaught Rd Central, Hong Kong.
url: www.serono.com

Serono, Hung. See *Pharma-Marketing, Hung.*

Serono, Indon. See *DKSH, Indon.*

Serono, Irl. See *Allphar, Irl.*

Serono, Israel. See *ASI, Israel.*

Serono, Ital. Industria Farmaceutica Serono S.p.A., Via Casilina 125, 00176 Rome, Italy.
url: www.serono.it

Serono, Malaysia. See *Antah, Malaysia.*

Serono, Mex. Serono de Mexico S.A. de C.V., Av. Insurgentes Sur No. 1898 Piso 16, Colonia Florida, 01030 Mexico D.F., Mexico.
url: www.serono.com

Serono, Neth. Serono Benelux, Alexanderstraat 3-5, 2514 TJ The Hague, Netherlands.
url: www.serono.com

Serono, Norw. Serono Nordic AB, Luhrtoppen 2, 1470 Lorenskog, Norway.
url: www.serono.com

Serono, NZ. See *Douglas, NZ.*

Serono, Philipp. See *Diethelm, Philipp.*

Serono, Pol. See *Ares, Pol.*

Serono, Port. Serono, Lda, Rua Tierno Galvan 16B, 16 piso-Esc.1, 1070-274 Lisbon, Portugal.
url: www.serono.com

Serono, Rus. Serono Pharma International, Usievicha ul. 20, Building 1, Business Centre Sokol Plaza, 125190 Moscow, Russia.
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Serono, S.Afr. Serono South Africa (Pty) Ltd, P.O. Box 1877, Fourways 2055, South Africa.
url: www.serono.com

Serono, Singapore. See *Grafton, Singapore.*

Serono, Spain. Serono, Maria de Molina 40, 28006 Madrid, Spain.
url: www.serono.com

Serono, Swed. Serono Nordic AB, Box 1803, 171 21 Solna, Sweden.
url: www.serono.com

Serono, Switz. Serono Pharma Schweiz, Steinhauserstrasse 74, 6305 Zug, Switzerland.
url: www.serono.com

Serono, Thai. Serono Thailand Co. Ltd, 889, 25 Fl, Thai CC Tower, Room 253, South Sathorn Rd, Yannawa, Sathorn, Bangkok 10120, Thailand.
url: www.serono.com

Serono, Turk. Serono İlaç Paz. ve Tic. A.Ş., Kayışdağği Cad., Karaman Çiftiği Yolu Kar Plaza Blok No: 45, K: 7, İçerenköy, İstanbul, 81120, Turkey.
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Serono, UK. Serono UK Ltd, Bedfont Cross, Stanwell Rd, Feltham, Middlesex, TW14 8NX, UK.
url: www.serono.com

Serono, USA. Serono Laboratories Inc., One Technology Place, Rockland, MA 02370, USA.
url: www.seronousa.com

Serono, Venez. Serono de Venezuela S.A., Avenida Venezuela con Calle Mohedano, Edificio Torre Centuria, Piso 3, Oficinas 3-A y 3-B, Urbanización El Rosal, Caracas 1060, Venezuela.
url: www.serono.com

Serotherapeutisches, Austria. Serotherapeutisches Institut, Richard-Strauss-Strasse 33, A-1232 Vienna, Austria.

Seroyal, Canad. Seroyal International Inc., 44 E Beaver Creek Rd, Unit 17, Richmond Hill, Ontario, L4B 1G8, Canada.

SERP, Mon. SERP, le Triton, 5 rue du Gabian, MC 98000, Monaco.

Serra Pamies, Hong Kong. See *Hind Wing, Hong Kong.*

Serra Pamies, Spain. Serra Pamies, Ctra de Castellvell 24, Reus, 43206 Tarragona, Spain.
url: www.lsp.es

Serral, Mex. Serral S.A. de C.V., Adolfo Prieto No. 1009, Col. del Valle, Deleg. Benito Juarez, 03100 Mexico D.F., Mexico.
url: www.serral.com.mx

Serranita, Arg. La Serranita, Lab. de Esp. Medic. y Cosmet., Calle 49 3752, 1653 Villa Ballester, Buenos Aires, Argentina.

Sertex, Arg. Laboratorio Sertex S.R.L., Brown 2862, 2000 Rosario, Santa Fe, Argentina.
url: www.rosario.com.ar/sertex/

Serum Institute, India. Serum Institute of India Ltd, 501 Dalamal Tower, 211 Nariman Point, Mumbai 400 021, India.
url: www.seruminstitute.com

Serum-Werk Bernburg, Ger. Serumwerk Bernburg AG, Hallesche Landstr. 105 b, 06406 Bernburg, Germany.
url: www.serum-werk.de

Serum-Werk Bernburg, Rus. Serumwerk Bernburg AG, Glavpochtampt, a/ya 370, 101000 Moscow, Russia.
url: www.serumwerk.com

Servier, Arg. Servier Argentina S.A., Av. Belgrano 1480, 1093 Buenos Aires, Argentina.
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Servier, Austral. Servier Laboratories (Australia) P/L, P.O. Box 196, Hawthorn, VIC 3122, Australia.
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Servier, Austria. Servier Pharma GmbH, Mariahilfe Strasse 20/5, A-1070 Vienna, Austria.
url: www.servier.com

Servier, Belg. Servier Benelux SA, Riverside Business Park, Blvd International 57, 1070 Brussels, Belgium.
url: www.servier.com

Servier, Braz. Servier Do Brasil Ltda, Rua Mario Piragibe 23, Lins de Vasconcelos, 20720-320 Rio de Janeiro, RJ, Brazil.
url: www.servier.com.br

Servier, Canad. Servier Canada Inc., 235 blvd Armand-Frappier, Laval, Quebec, H7V 4A7, Canada.
url: www.servier.com

Servier, Chile. See *Grunenthal, Chile.*

Servier, Cz. Servier sro, Sladkovského nám 1, 130 00 Prague 3, Czech Republic.

Servier, Denm. Servier Danmark A/S, Roskildevej 39 A, 2000 Frederiksberg, Denmark.
url: www.servier.com

Servier, Fin. Servier Finland Oy, Vanhankyläntie 44 C, PL 157, 04401 Järvenpää, Finland.
url: www.servier.com

Servier, Fr. Laboratoires Servier, 22 rue Garnier, 92200 Neuilly-sur-Seine, France.
url: www.servier.com

Servier, Ger. Servier Deutschland GmbH, Westendstr. 170, 80686 Munich, Germany.
url: www.servier.de

Servier, Gr. Servier Greece E.P.E, L. Synggrou 181, 171 21 N. Smyrni, Greece.
url: www.servier.com

Servier, Hong Kong. Servier Hong Kong Ltd, Rm 1901, 19/F The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong.

Servier, Hung. Servier Hungária Kft, Váci út 1-3, 1062 Budapest, Hungary.

Servier, Indon. Les Laboratoires Servier (PT Parvico Bersaudara), Menara Kadin Indonesia 18/Fl, Jl HR Rasuna Said X-5 Kav 2-3, 12950 Jakarta, Indonesia.

Servier, Irl. Servier Laboratories (Ireland) Ltd, Block 2, West Pier Business Campus, Old Dunleary Road, Dun Laoghaire, Co. Dublin, Ireland.
url: www.servier.ie

Servier, Israel. See *Teva, Israel.*

Servier, Ital. Servier Italia S.p.A., Via Luca Passi 85, 00166 Rome, Italy.
url: www.servier.com

Servier, Malaysia. See *Zuellig, Malaysia.*

Servier, Mex. Laboratorios Servier Mexico SA de CV, Paseo de las Palmas 830 PH, 11000 Lomas de Chapultepec, Mexico DF, Mexico.

Servier, Neth. Servier Nederland BV, Einsteinweg 82, 2333 CD Leiden, Netherlands.
url: www.servier.com

Servier, NZ. Servier Laboratories (NZ) Ltd, 2nd Floor, 29 Union St., Auckland, New Zealand.
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Servier, Philipp. Servier Phils Inc., Orion Bldg, No 2 Orion cor Mercedes St, Bel-Air, Makati City, Philippines.

Servier, Pol. Servier Polska Sp. zo.o., ul. Jana Kazimierza 10, 01-248 Warsaw, Poland.
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Servier, Port. Servier Portugal, Lda, Av António Agusto de Aguiar 128, 1069-133 Lisbon, Portugal.
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Servier, Rus. Laboratory Servier, Paveletskaya pl. 2, str. 3, 113054 Moscow, Russia.
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Servier, S.Afr. Servier Laboratories (SA) (Pty) Ltd, P.O. Box 930, Rivonia 2128, South Africa.
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Servier, Singapore. Servier (S) Pte Ltd, 510 Thomson Rd, 09-02 SLF Building, S 298135, Singapore.
url: www.servier.com

Servier, Spain. Servier, Avda de Madronos 33, 28043 Madrid, Spain.
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Servier, Swed. See *Servier, Denm.*

Servier, Switz. Servier (Suisse) SA, 10 rue de la Bergère, 1242 Satigny, Switzerland.
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Servier, Thai. Servier (Thailand) Ltd, 15 Fl, Ploenchit Center Building, 2 Sukhumvit Rd, Klongtoey, Bangkok 10110, Thailand.
url: www.servier.com

Servier, Turk. Servier İlaç ve Araştırma A.Ş., Maslak Giz Kule Meydan Sok. No: 28 K: 22-23, Medidiköy, İstanbul, 80650, Turkey.
url: www.servier.com

Servier, UK. Servier Laboratories Ltd, Wexham Springs, Framewood Rd, Wexham, Slough, Buckinghamshire, SL3 6RJ, UK.
url: www.servier.co.uk

Servier, Venez. Laboratorios Servier S.A., Final Calle Vargas, Edif.Ctro. Berimer Nivel Mezanina, Caracas, Venezuela.
url: www.servier.com

Servipharm, Hong Kong. See *Unipharm, Hong Kong.*

Servipharm, Israel. Servipharm, Israel.

Servipharm, Malaysia. See *JDH, Malaysia.*

Sesderma, Spain. Sesderma, Poligono Industrial de Rafelbunol, C/ Massamagrell 3, Rafelbunol, 46138 Valencia, Spain.
url: www.sesderma.com

Setfarma, Port. Setfarma Distribuição e Comercialização de Produtos de Saúde Lda, Rua Bombeiros Voluntários Dafundo 1, 1495-714 Cruz Quebrada, Portugal.

Seton, Cz. See *SSL, UK.*

Seton, Israel. See *Pharmateam, Israel.*

Seton, Neth. See *SSL, UK.*

Seton, Pol. See *SSL, Pol.*

Seton Scholl, Austral. See *SSL, Austral.*

Sevapharma, Cz. Sevapharma as, Korunní 108, 101 03 Prague 10, Czech Republic.
url: www.sevapharma.cz

Seven Seas, Hong Kong. See *Zuellig, Hong Kong.*

Seven Seas, Irl. Seven Seas (Ireland) Ltd, 7 The Anchorage, Charlotte Quay, Dublin 4, Ireland.
url: www.sevenseas.ie

Seven Seas, Singapore. See *Zuellig, Singapore.*

Seven Seas, UK. Seven Seas Ltd, Hedon Rd, Marfleet, Hull, HU9 5NJ, UK.
url: www.seven-seas.ltd.uk

Seven Stars, Thai. See *Charoen, Thai.*

Sevene, Fr. Sevene Pharma, Mazet Pailhès, 30170 Monoblet, France.

Sevens, Gr. SEVENS LTD, Alkmanous 53, 115 28 Ilissia, Greece.

Seviton, Switz. Seviton Schwitzerland Naturprodukte GmbH, Schwitzengelstrasse 36, 6342 Baar, Switzerland.
url: www.seviton.ch

Seyer, USA. Seyer Pharmatec Inc., P.O. Box 9270, Caguas, PR 00725, Puerto Rico.
url: www.spharmatec.com

SF, Ital. SF Group srl, Via Di Fioranello 186, 00134 Rome (RM), Italy.

SFD, Port. Sociedade Farmaçêutica de Desenvolvimento, Lda, Rua Duque d'Ávila no 193, 1050-082 Lisbon, Portugal.

SGS Biopharma, Belg. SGS Biopharma, Vieux Chemin du Pote, 1301 Wavre, Belgium.
url: www.sgsbiopharma.com

Shaklee, Canad. Shaklee Canada Inc., 952 Century Dr, Burlington, Ontario, L7L 5P2, Canada.
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Shalpharm, Israel. See *Rekah, Israel.*

Shandong Kexing, Philipp. See *Goodfellow, Philipp.*

Shanghai RAAS, Thai. See *Charoen, Thai.*

Shanghai Yanan, Thai. See *Premier, Thai.*

Shanta, India. Shanta Biotechnics Pvt Ltd, 3rd Floor, Serene Chambers, Road No.7, Banjara Hills, Hyderabad 500 021, India.
url: www.shanthabiotech.com

Shantha, Philipp. See *Medtest, Philipp.*

Shantys, UK. Shanty's Ltd, 3-4 Coppen Rd, Dagenham, Essex, RM8 1HU, UK.
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Shchelkovskii, Rus. See *Masterlek, Rus.*

Shenzhen, Philipp. See *Dynasty, Philipp.*

Shepa, Gr. SHEPA OE, Veranzerou 33, 104 32 Athens, Greece.

Sherman, USA. Sherman Pharmaceuticals Inc., P.O. Box 1377, Mandeville, LA 70470-1377, USA.

Sherwood, USA. See *Kendall, USA.*

Shield, Irl. Shield Health Ltd, Unit 1, Thompson Business Park, Clane, Co. Kildare, Ireland.
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Shigaken, Singapore. See *Luen Wah, Singapore.*

Shin Poong, Malaysia. See *Zyfas, Malaysia.*

Shin Poong, Philipp. Phil Shin Poong Pharma Inc., Unit 1110 Cityland Shaw Tower, Shaw Blvd cor St Francis St, Mandaluyong City, Philippines.

Shin Poong, Singapore. See *Zyfas, Singapore.*

Shinyaku, Hong Kong. See *Hing Ah, Hong Kong.*

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Shinyaku, Malaysia. See *Wellchem, Malaysia.*

Shinyaku, Philipp. See *Marketlink, Philipp.*

Shinyaku, Singapore. See *Wellchem, Singapore.*

Shinyaku, Thai. See *Asian TJD, Thai.*

Shionogi, Jpn. Shionogi & Co. Ltd, 3-1-8 Doshomachi, Chuo-ku, Osaka 541-0045, Japan.
url: www.shionogi.co.jp

Shionogi, USA. Shionogi USA Inc., 100 Campus Drive, Florham Park, NJ 07932, USA.
url: www.shionogiusa.com

Shire, Canad. See *Shire Biochem, Canad.*

Shire, Cz. See *Shire, UK.*

Shire, Denm. See *Meda, Denm.*

Shire, Fr. Shire France, 160 rue de Paris, 92771 Boulogne-Billancourt, France.
url: www.shire.com

Shire, Ger. Shire Deutschland GmbH & Co. KG, Siegburger Str. 126, 50679 Cologne, Germany.
url: www.shire.com

Shire, Hong Kong. See *IDS, Hong Kong.*

Shire, Hung. See *Shire, UK.*

Shire, Irl. Shire Pharmaceuticals Ireland Ltd, 5 Riverwalk, Citywest Business Campus, Dublin 24, Ireland.
url: www.shire.com

Shire, Ital. Shire Italia S.p.A., Via Provinciale Lucchese 70, 50019 Sesto Fiorentino (FI), Italy.
url: www.shire.com

Shire, Malaysia. See *JDH, Malaysia.*

Shire, Neth. See *Shire, UK.*

Shire, Norw. See *Meda, Norw.*

Shire, Philipp. See *GenAsia, Philipp.*

Shire, Port. See *Shire, Spain.*

Shire, Singapore. See *JDH, Singapore.*

Shire, Spain. Shire Pharmaceuticals Iberica, Paseo Pintor Rosales 40, Bajo Izda, 28008 Madrid, Spain.
url: www.shire.com

Shire, UK. Shire Pharmaceuticals Ltd, Hampshire International Business Park, Chineham, Basingstoke, Hampshire, RG24 8EP, UK.
url: www.shire.com

Shire, USA. Shire Pharmaceuticals, 725 Chesterbrook Blvd, Wayne, PA 19087-5637, USA.
url: www.shire.com

Shire Biochem, Canad. Shire Biochem Inc., 275 Armand-Frappier Bvld, Laval, Quebec, H7V 4A7, Canada.
url: www.shire.com

Shire Biologics, Canad. Shire Biologics, Division of Shire Biochem Inc., 2323 Parc Technologique Bvld, Sainte-Foy, Quebec, G1P 4R8, Canada.

Shire Richwood, USA. See *Shire, USA.*

Shiseido, Canad. Shiseido Canada Inc., 60 Leek Crescent, Richmond Hill, Ontario, L4B 1H1, Canada.

Shiwa, Thai. Shiwa Chemicals Co. Ltd, 34/1 Sukhumvit 39, (Soi Prompong), Bangkok 10110, Thailand.

Shoppers Drug Mart, Canad. Shoppers Drug Mart, 225 Yorkland Blvd, Willowdale, Ontario, M2J 4Y7, Canada.

Shou Chan, Philipp. See *New Smart, Philipp.*

Shreya, India. Shreya Life Sciences Pvt Ltd, Shreya House 301/A, Pereira Hill Rd, Andheri (E), Mumbai 400099, India.

Shreya, Rus. See *Biofarm, Rus.*

SHS, Cz. See *SHS, UK.*

SHS, Fr. SHS International Ltd, 4 passage St-Antoine, 92508 Rueil-Malmaison, France.
url: www.shsweb.co.uk

SHS, Israel. See *Megapharm, Israel.*

SHS, Singapore. See *Pharma 2000, Singapore.*

SHS, UK. SHS International Ltd, 100 Wavertree Boulevard, Liverpool, Merseyside, L7 9PT, UK.
url: www.shsweb.co.uk

SHS, USA. SHS North America/Scientific Hospital Supplies, P.O. Box 117, Gaithersburg, MD 20884, USA.
url: www.shsna.com

SHS Nutricia, UK. See *SHS, UK.*

Siam Bheasach, Malaysia. See *Luen Wah, Malaysia.*

Siam Bheasach, Thai. See *Siam Pharm, Thai.*

Siam Medicare, Thai. Siam Medicare Co. Ltd, 77/37 Soi Senanikom 1, Phaholyothin Rd, Bangkok 10900, Thailand.

Siam Pharm, Thai. Siam Pharmaceutical Co. Ltd, 171/1 Soi Choke Chai Ruammitr, Vibhavadi-Rangsit Rd, Bangkok 10900, Thailand.

Siar, Ital. Siar Pharma Prodotti chimico-farmaceutici Srl, Via G Verdi 33, 20060 Bussero (MI), Italy.

Sicomed, Hong Kong. See *Hong Kong Medical, Hong Kong.*

Sicomed, Rus. See *Rompharm, Rus.*

Sicor, Rus. Sicor Europe SA, Leningradskii prospekt 37a, k. 14, Business-centre Zapadny Most, 125167 Moscow, Russia.
url: www.sicor.com

Sicor, USA. See *Teva, USA.*

Sidefarma, Port. Sidefarma SA, Rua da Guine 26, 2689-514 Prior Velho, Portugal.

Sidefarma, Thai. See *Zuellig, Thai.*

Sidepal, Braz. Sidepal Industrial e Comercial Ltda, Av. Nova Cumbica 920/30, 7231000 Guarulhos, SP, Brazil.
url: www.sidepal.com.br

Sidmak, India. Sidmak Laboratories (India) Ltd, National Highway No.8, Abrama, Valsad 396 001, India.
url: www.sidmak.com

Sidone, Braz. Sidone Indústria e Comércio Ltda., Rua São Francisco Xavier 930, 38412-080 Uberlandia, MG, Brazil.

Sidroga, Switz. Sidroga AG, Postfach, 4800 Zofingen, Switzerland.
url: www.sidroga.com

Sidus, Arg. Laboratorios Sidus S.A., Av. del Libertador 742, 1638 Vicente Lopez, Buenos Aires, Argentina.
url: www.sidus.com.ar

Siegfried, Cz. See *Siegfried, Switz.*

Siegfried, Switz. Siegfried CMS AG, 4800 Zofingen, Switzerland.

Siegfried, Thai. See *Diethelm, Thai.*

Siemens, Canad. See *Siemens, USA.*

Siemens, Ger. Siemens & Co., Heilwasser und Quellenprodukte des Staatsbades Bad Ems GmbH & Co. KG, Arzbacher Str. 78, 56130 Bad Ems, Germany.
url: www.emser.de

Siemens, Switz. See *Ecosol, Switz.*

Siemens, USA. Siemens Medical Solutions, 511 Benedict Ave, Tarrytown, NY 10591, USA.

Sifa, Turk. Şifa Kimya İlaç Kozmetik San. ve Tic. A.Ş., 2. Organize Sanayi Bölgesi, Kırım Cad. No:15 Selçuklu, Selçuklu, Konya, Turkey.
url: www.sifakimya.com

Sifar, Turk. Sifar İlaçları Tic. ve San. A.Ş., Dr. Faruk Ayanoğlu Cad. No: 26 D: 1, Fenerbahçe, İstanbul, 34726, Turkey.
url: www.sifar.com.tr

Sifarma, Ital. Sifarma S.p.A., Via Brunelleschi 12, 20146 Milan, Italy.
url: www.sifarma.it

Sifauman, Port. Sifauman Especialidades Farmacêuticas Lda, Portugal.

SIFFRA, Ital. SIFFRA Farmaceutici Srl, Via Pontida 1/a, 20025 Legnano (MI), Italy.
url: www.siffra.it

Sifi, Canad. Sifi America Inc., 708 1100 Cremazie Est, Montreal, Quebec, H2P 2X2, Canada.

SIFI, Cz. See *SIFI, Ital.*

SIFI, Ital. Società Industria Farmaceutica Italiana S.p.A., Via Ercole Patti 36, 95025 Lavinao-Aci S. Antonio (CY), Italy.

SIFI, Rus. See *Schering-Plough, Rus.*, and *Zambon, Rus.*

SIFI, Singapore. See *Green Cross, Singapore.*

Sigma, Arg. Laboratorios Sigma, Chaco 667, 5000 Cordoba Capital, Argentina.

Sigma, Austral. Sigma Pharmaceuticals P/L, 96 Merrindale Drive, Croydon, VIC 3136, Australia.
url: www.sigmaco.com.au

Sigma, Braz. See *Novaquimica, Braz.*

Sigma, Hong Kong. See *GSK, Hong Kong.*

Sigma, India. Sigma Laboratories Ltd, 18 Subhash Rd, Vile Parle (E), Mumbai 400 057, India.
url: www.sigmalab.com

Sigma, NZ. See *Zuellig, NZ.*

Sigma, Philipp. See *Zenaust, Philipp.*

Sigma, UK. Sigma Chemical Co. Ltd, 1 Colonial Way, North Watford Industrial Estate, North Watford, Hertfordshire, WD2 4PJ, UK.
url: www.sigpharm.co.uk

Sigmapharm, Austria. Sigmapharm Arzneimittel GmbH & Co KG, Leystrasse 129, A-1204 Viena, Austria.
url: www.sigmapharm.at

Sigmapharm, Hung. Sigmapharm, Dunadűlő u 33, 1212 Budapest, Hungary.

Sigmapharm, Switz. See *Ridupharm, Switz.*

Sigma-Tau, Canad. Sigma-Tau Pharmaceuticals Inc., 200 Ellesmere Rd, Unit 16, Scarborough, Ontario, M1H 2W4, Canada.
url: www.sigma-tau.com

Sigma-Tau, Cz. See *Sigma-Tau, Ital.*

Sigma-Tau, Fr. Sigma-Tau France, 5 av. de Verdun, 94202 Ivry sur Seine, France.
url: www.sigma-tau.it

Sigma-Tau, Ger. Sigma-Tau Arzneimittel GmbH, Shadowstr. 44, 40212 Dusseldorf, Germany.
url: www.sigma-tau.it

Sigma-Tau, Hong Kong. See *Keller, Hong Kong,* and *Sino-Asia, Hong Kong.*

Sigma-Tau, Hung. Sigma-Tau, Hungary.

Sigma-Tau, Ital. Sigma Tau S.p.A., Via Pontina Km. 30,400, 00040 Pomezia (Rome), Italy.
url: www.sigma-tau.it

Sigma-Tau, Neth. Sigma-Tau Ethifarma B.V., Postbus 10072, 9400 CB Assen, Netherlands.
url: www.sigma-tau.it

Sigma-Tau, Philipp. See *Diethelm, Philipp.*

Sigma-Tau, Rus. See *Riace, Rus.*

Sigma-Tau, Spain. Sigma Tau Espana, Poligono Azque, Apt. do 1144, Alcalá de Henares, 28815 Madrid, Spain.
url: www.sigma-tau.com

Sigma-Tau, Switz. Sigma-Tau Pharma AG, Luzernerstrasse 2, 4800 Zofingen, Switzerland.
url: www.sigma-tau.ch

Sigma-Tau, USA. Sigma-Tau Pharmaceuticals Inc., 800 S Frederick Ave, Suite 300, Gaithersburg, MD 20877, USA.
url: www.sigmatau.com

Silanes, Mex. Laboratorios Silanes S.A. de C.V., Amores No. 1304, Col. del Valle, Deleg. Benito Juarez, 03100 Mexico D.F., Mexico.
url: www.silanes.com.mx

Silarx, USA. Silarx Pharmaceuticals Inc., 19 West St, Spring Valley, NY 10977, USA.
url: www.silarx.com

Silesia, Chile. Laboratorios Silesia SA, Av. Chile Espana 325, Santiago, Chile.

Silom, Thai. Silom Medical Co. Ltd, 35/3 Suparaj Soi 1, Phaholyothin Rd, Samsennai, Bangkok 10400, Thailand.

Silroc, Hong Kong. Silroc International (HK) Ltd, Unit C, 5/F, Skyline Tower, 18 Tong Mi Rd, Mongkok, Kowloon, Hong Kong.

Silva, Venez. Laboratorios Silco, Silva & Cía., Sucs. S.A., Paraderos a Venus 221, Caracas, Venezuela.

Silvestre, Braz. Silvestre Labs. Química & Farmacêutica Ltda., Av. Vinte e Quatro S/N, 21941-590 Rio de Janeiro, RJ, Brazil.
url: www.silvestrelabs.com.br

Simac, Neth. Simac Diagnostica BV, Plesmanstraat 59, 3905 KZ Veenendaal, Netherlands.

Simaport, Port. Simaport Comércio de Produtos Médico-Dentários Lda, Rua Prof. Henrique de Barros, Edifício Sagres 1 A, 2685-338 Prior Velho, Portugal.

Sime Darby, Malaysia. Sime Darby Marketing Sdn Bhd, F-F10, Mezzanine F1, Lot PT 11101, Kompleks Sime Darby, Jln Kewajipan, 47600 Subang Jaya, Selangor, Malaysia.

Sime Darby, Singapore. Sime Darby Marketing, A Division of Sime Darby Singapore Ltd, 896 Dunearn Rd, 04-03 Sime Darby Centre, S 589472, Singapore.

Simesa, Ital. Simesa S.p.A., Via F. Sforza Palazzo Galileo, 20080 Basiglio (MI), Italy.

Simoes, Braz. Laboratório Simões Ltda, Rua Pereira de Almeida 102, 20260-100 Rio de Janeiro, RJ, Brazil.

Simons, Ger. Georg Simons GmbH, Bunsenstr. 1, 82152 Planegg/Martinsried, Germany.
url: www.simons.de

Sin Sin, Philipp. See *Philusa, Philipp.*

Sincerity, Hong Kong. Sincerity (Asia) Co. Ltd, 1/F, Blk E, Nam Pak Hong Bldg, 24 Bonham Strand W, Hong Kong.

Sinclair, Irl. See *Pinewood, Irl.*

Sinclair, Ital. Sinclair Srl, Viale Restelli 29, Milan, Italy.
url: www.sinclairpharma.com

Sinclair, UK. Sinclair Pharmaceuticals Ltd, Borough Rd, Godalming, Surrey, GU7 2AB, UK.
url: www.sinclairpharma.com

Sindan, Hung. S C Sindan, Hungary.

Sindan, Pol. Sindan, ul. Puławska 314, 02-818 Warsaw, Poland.
url: www.sindan.pl

Singer, Switz. Pharma-Singer AG, Windeggstrasse 2, 8867 Niederurnen, Switzerland.
url: www.perskindol.ch

Sino-Asia, Hong Kong. Sino-Asia Pharmaceutical Supplies Ltd, 1 Fung Fai Terrace, 1 Village Rd, Happy Valley, Hong Kong.

Sintactica, Ital. Sintactica S.r.l., Strada Padana Superiore 1, 20060 Cassina de' Pecchi (MI), Italy.
url: www.sintactica.it

Sinterapico, Braz. Laboratório Sinterapico Industrial e Farmacêutico Ltda, Rua Olegario Cunha Lobo 25, 12940-000 Atibaia, SP, Brazil.

Sintesina, Arg. Sintesina S.A., Av. Pte. Arturo Illia 4194, 1613 Los Polvorines, Buenos Aires, Argentina.

Sintetica, Switz. Sintetica SA, Via Penate 5, casella postale 1764, 6850 Mendrisio, Switzerland.

Sintez, Rus. Sintez OAO, Tverskaya ul. 20, Of. 530, 125009 Moscow, Russia.
url: www.sintezmos.narod.ru

Sintofarma, Braz. Laboratórios Sintofarma S.A., Rua Sergipe 120, 01243-000 São Paulo, SP, Brazil.

Sipaco, Port. Sipaco Internacional, Avda 5 de Outubro 267,6, 01600 Lisbon, Portugal.

Sipaco, Spain. See *Sipaco, Port.*

Siphar, Switz. Siphar SA, Casella postale 32, 6814 Cadempino, Switzerland.

SIRC, Singapore. See *Zyfas, Singapore.*

Sirius, USA. Sirius Laboratories Inc., 100 Fairway Drive, Suite 130, Vernon Hills, IL 60061, USA.
url: www.siriuslabs.com

Sirowa, Fin. Sirowa Helsinki, Rajatorpantie 41 C, 01640 Vantaa, Finland.

Sirton, Ital. Sirton Pharmaceuticals SpA, Piazza XX Settembre 2, 22079 Villa Guardia (CO), Italy.

Sirval, Ital. Società Italiana Ritrovati Val Srl, Via Maloia 8, 20158 Milan, Italy.

Sistas, Turk. Sistaş İlaç San. A.Ş., Nafiz Gürman Mah., Turunçlu Sok. No: 17 A Blok, Merter, İstanbul, Turkey.
url: www.sistasilac.com

Sisu, Canad. Sisu Enterprises Co Inc., 104A-3430 Brighton Ave, Burnaby, British Columbia, V5A 3H4, Canada.
url: www.sisuhealth.com

SIT, Cz. See *SIT, Ital.*

SIT, Denm. See *SIT, Ital.*

SIT, Fin. See *SIT, Ital.*

SIT, Hung. See *SIT, Ital.*

SIT, Ital. Specialità Igienico Terapeutiche S.r.l., C.so Cavour 70, 27035 Mede (Pavia), Italy.

Siu Guan, Malaysia. See *Averroes, Malaysia.*

Sivaderm, Arg. Lab. Sivaderm S.A., Sarmiento 2171 Pso. 8 Dto.A, 1044 Buenos Aires, Argentina.
url: www.sivaderm.com

Sixtem, Ital. Sixtem Life Srl, Via Adige 34, 50019 Sesto Fiorentino (FI), Italy.

SJ Pharm, USA. SJ Pharmaceuticals, 4587 Damascus Rd, Memphis, TN 38118, USA.
url: www.sjpharmacal.com

SJA, Gr. S.J.A PHARM, Arkoleon 11, 104 45 Athens, Greece.

SK, Kor. SK Chemicals, 948-1 Daechi 3-dong, Gangnam-gu, Seoul (135-283), Korea.
url: www.skchemicals.com

SK, Philipp. See *Metro, Philipp.*

SK, Singapore. See *Wellchem, Singapore.*

Skills, Ital. Skills in Farmacia S.r.l., Piazza Buonarroti 32, 20145 Milan, Italy.
url: www.skillsfarmacia.it

SkinMedica, USA. SkinMedica Inc., 5909 Sea Lion Place, Ste H, Carlsbad, CA 92008, USA.
url: www.skinmedica.com

Skye, USA. SkyePharma Inc., 10450 Science Center Drive, San Diego, CA 92121, USA.
url: www.skyepharma.com

Skyepharma, Denm. See *Norpharma, Denm.*

Skyepharma, Neth. See *Skyepharma, UK.*

Skyepharma, Norw. See *Mundipharma, Norw.*

SkyePharma, Pol. See *Mundipharma, Pol.*

Skyepharma, UK. SkyePharma plc, 105 Piccadilly, London, W1V 9FN, UK.

SLE, Israel. Salomon, Levin, & Elstein Ltd, P.O. Box 8077, Kiryat Nordau, Netanya, Israel.

SL-Farma, Hung. SL-Farma Hungary Kft, Pasaréti út 79 I/1, 1026 Budapest, Hungary.

Slovakofarma, Cz. Slovakofarma sro, Machová 18, 120 00 Prague 2, Czech Republic.

Slovakofarma, Singapore. See *Sime Darby, Singapore.*

Slovakofarma, Thai. See *Medline, Thai.*

SM, Philipp. See *PNF, Philipp.*

SM, Thai. SM Pharmaceutcal Co. Ltd, 82, 84 Arkarn 2, Ratchdamnoen Ave, Bangkok 10200, Thailand.

SM, Venez. Laboratorio Farmaceutico S.M. C.A., Av. 59-A N99 L20 Circun.2 Apdo. 552, Cab El Sajarito Maracaibo, Zulia, Venezuela.

SMA Nutrition, Irl. See *Wyeth, UK.*

SMA Nutrition, UK. See *Wyeth, UK.*

Smaller, Spain. See *ASAC, Spain.*

SMB, Belg. Laboratoires S.M.B. SA, Rue de la Pastorale 26-28, 1080 Brussels, Belgium.
url: www.smb.be

SMB, Chile. Laboratorios SMB Farma SA, Av. Bulnes 377, Dpto 305, Santiago, Chile.

SMB, Port. See *SMB, Belg.*

SMB, Singapore. See *Pan-Malayan, Singapore.*

SMB, Thai. See *Berlin Pharm, Thai.*

Smetana, Austria. See *EF-EM-ES, Austria.*

Smith, Hung. See *Abbott, Hung.*

Smith & Nephew, Austral. Smith & Nephew P/L, 315 Ferntree Gully Road, Mt Waverley, VIC 3149, Australia.
url: www.smith-nephew.com

Smith & Nephew, Austria. See *Smith & Nephew Healthcare, UK.*

Smith & Nephew, Belg. See *GSK, Belg.*

Smith & Nephew, Canad. Smith & Nephew Inc., 4707 Levy St, St-Laurent, Quebec, H4R 2P9, Canada.
url: www.smith-nephew.com

Smith & Nephew, Denm. Smith & Nephew A/S, Naerum Hovedgade 2, 2850 Naerum, Denmark.
url: www.smith-nephew.com

Smith & Nephew, Fin. Smith & Nephew Oy, Ayritie 12 C, 01510 Vantaa, Finland.
url: www.smith-nephew.com

Smith & Nephew, Fr. Smith & Nephew SA, 25 bd Alexandre-Oyon, 72019 Le Mans cdx 2, France.
url: www.smith-nephew.com

Smith & Nephew, Ger. Smith & Nephew GmbH, Max-Planck-Str. 1-3, 34253 Lohfelden, Germany.
url: www.smith-nephew.de

Smith & Nephew, Hong Kong. Smith & Nephew Ltd, Units 813-816, 8/F Delta House, 3 On Yiu St, Shatin, N.T., Hong Kong.
url: www.smith-nephew.com

Smith & Nephew, Irl. Smith & Nephew Medical, Carraig Court, George's Ave, Blackrock, Co. Dublin, Ireland.
url: www.smith-nephew.com

Smith & Nephew, Ital. Smith & Nephew S.r.l., Viale Colleoni 13, 20041 Agrate Brianza (MI), Italy.
url: www.smith-nephew.com

Smith & Nephew, Malaysia. See *Zuellig, Malaysia.*

Smith & Nephew, Neth. See *GSK, Neth.*

Smith & Nephew, Norw. Smith & Nephew AS, Postboks 224, 1379 Nesbru, Norway.
url: www.smith-nephew.com

Smith & Nephew, NZ. Smith & Nephew Ltd, P.O. Box 442, Auckland, New Zealand.
url: www.smith-nephew.com

Smith & Nephew, Philipp. See *GenAsia, Philipp.*

Smith & Nephew, Port. See *Smith & Nephew Healthcare, UK.*

Smith & Nephew, S.Afr. Smith & Nephew Pharmaceuticals (Pty) Ltd, P.O. Box 92, Pinetown 3600, South Africa.
url: www.smith-nephew.com

Smith & Nephew, Singapore. See *Zuellig, Singapore.*

Smith & Nephew, Spain. Smith Nephew, Fructous Gelabert 2-4, Sant Joan Despi, 08970 Barcelona, Spain.
url: www.smith-nephew.com

Smith & Nephew, Swed. Smith & Nephew AB, Box 143, 431 22 Mölndal, Sweden.
url: www.smith-nephew.se

Smith & Nephew, Switz. Smith & Nephew AG, Glutz Blotzheim-Strasse 1, 4502 Solothurn, Switzerland.
url: www.smith-nephew.ch

Smith & Nephew, Thai. Smith & Nephew Ltd, 344/3 Soi Rongrien Yepun, Rama IX Rd, Bangapi, Huay Kwang, Bangkok 10320, Thailand.
url: www.smith-nephew.com

Smith & Nephew, UK. See *Smith & Nephew Healthcare, UK.*

Smith & Nephew, USA. Smith & Nephew United, 11775 Starkey Rd, Largo, FL 33773-1970, USA.
url: www.smith-nephew.com

Smith & Nephew Healthcare, UK. Smith & Nephew Healthcare Ltd, Healthcare House, Goulton St, Hull, HU3 4DJ, UK.
url: www.smith-nephew.com

Smith & Nephew SoloPak, USA. See *SoloPak, USA.*

Smith Kline & French, Port. See *GSK, Port.*

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SmithKline Beecham, Spain. See *GSK, Spain.*

SmithKline Beecham, Switz. See *GSK, Switz.*

SmithKline Beecham, USA. See *GSK, USA.*

SmithKline Beecham Consumer, Irl. See *GSK, Irl.*

SmithKline Beecham Consumer, Switz. See *GSK, Switz.*

SmithKline Beecham Consumer, USA. See *GSK Consumer, USA.*

SmithKline Diagnostics, USA. See *Beckman, USA.*

SMTL, UK. Surgical Materials Testing Laboratory, Princess of Wales Hospital, Coity Rd, Bridgend, Mid Glamorgan, CF31 1RQ, UK.
url: www.smtl.co.uk

SNBTS, UK. Scottish National Blood Transfusion Service, Protein Fractionation Centre, 21 Ellen's Glen Rd, Edinburgh, EH17 7QT, UK.
url: www.scotblood.co.uk

Snow Brand, Hong Kong. Snow Brand Hong Kong Co Ltd, Hong Kong.

Socobom, Belg. Socobom, Louisalaan 149 bus 24, 1050 Brussels, Belgium.
url: www.socobom.com

Socofar, Port. Socofar - Sociedade Comercial de Especialidades Farmacêutics S.A., Rua Padre Luis Aparicio 3, 1150 Lisbon, Portugal.

Socopharm, Fr. Laboratoires Socopharm, Chemin de Marcy, 58800 Corbigny, France.

Sodhan, Turk. Sodhan Aşi ve Kan. Ürünleri, Libya Cad. Becerikli Sok. No: 13/1-2, Kocatepe, Ankara, Turkey.
url: www.sodhan.com

Sodia, Fr. Laboratoires Sodia, av. Robert Schuman, 51100 Reims, France.

Sodilac, Fr. Sodilac, 176 av. Charles-de-Gaulle, 92522 Neuilly-sur-Seine cdx, France.

Sofar, Ital. Sofar Farmaceutici S.p.A., Via Firenze 40, 20060 Trezzano Rosa (MI), Italy.
url: www.sofarfarm.it

Sofex, Port. Sofex Farmacêutica, Lda, Rua Sebastião e Silva 25, Zona Industrial de Massamá, 2745-838 Queluz, Portugal.

Sofibel, Fr. See *Fumouze, Fr.*

SofLens, S.Afr. See *Bausch & Lomb, S.Afr.*

Sofus, Swed. Sofus Pharma AB, Frosundaviks allé 15, 169 70 Solna, Sweden.

Sogefin, Ital. Sogefin Srl, Via Bianca Visconti 9, 62023 Fermo (AP), Italy.

Soho, Indon. Soho Industri Pharmasi PT, Jl Pulo Gadung No 5, Kawasan Industri Pulo Gadung, 13920 Jakarta Timur, DKI Jaya, Indonesia.

Sojar, Arg. Sojar S.A., Velez Sarsfield 870, 2013 Rosario, Santa Fe, Argentina.

Solar, Canad. Solar Cosmetics Labs Inc, 6845 Rexwood Rd, Unit 3-5, Mississauga, Ontario, L4V 1S5, Canada.

Solara, Mex. Solara Farmaceutica SA de CV, Av Paseo de las Palmas 330 PB, 11000 Lomas de Chapultepec, Mexico DF, Mexico.

Solas, Indon. Solas PT, Jl Industri No 18, Cimareme-Padalarang, 40553 Bandung, Jawa Barat, Indonesia.

Solco, Austria. Solco Pharma Austria GmbH, Michael Pacher Strasse 25A/7, A-5020 Salzburg, Austria.

Solco, Cz. See *ICN, Cz.*

Solco, Hong Kong. See *Kai Cheong, Hong Kong.*

Solco, Indon. See *Pharos, Indon.*

Solco, Ital. Solco, Italy.

Solco, Rus. See *Valeant, Rus.*

Solco, Switz. Solco Basel SA, Ruhrbergstrasse 21, 4127 Birsfelden, Switzerland.
url: www.solco.ch

Solco, Thai. See *Diethelm, Thai.*

Soldan, Ger. Dr. C. Soldan GmbH, Herderstr. 5-9, 90427 Nürnberg, Germany.
url: www.soldan.com

Solea, Ital. Solea S.a.s., Via Cassoli 22, 42100 Reggio Emilia, Italy.

Solfran, Mex. Laboratorios Solfran S.A., Altos Hornos No. 2721, Fracc. Ind. el Alamo, 45590 Tlaquepaque, Jalisco, Mexico.

Solgar, UK. See *Boots, UK.*
url: www.solgar.co.uk

Solgar, USA. Solgar Vitamin Co. Inc., 500 Willow Tree Rd, Leonia, NJ 07605, USA.
url: www.solgar.com

Soll (Σωλλ), Gr. SOLL ELLAS AE, 17o chlm. L. Staton, 190 04 Spata, Greece.

Solmer, Switz. Solmer SA, Postfach 100, 6976 Castagnola-Suisse, Switzerland.

SoloPak, USA. SoloPak Pharmaceuticals Inc., 1845 Tonne Rd, Elk Grove Village, IL 60007-5125, USA.

Solpharm, Pol. Solpharm, ul. Zwycięzców 42/93, 03-938 Warsaw, Poland.
url: www.solpharm.pl

Solpro, Mex. Solpro S.A. de C.V., Ciruelos No. 137, Local 26, Centro Comercial El Pinar, Jurica, 76100 Queretaro, Mexico.
url: www.solpro.com.mx

Solus, India. See *Ranbaxy, India.*

Solvang, Philipp. Solvang Pharma Inc., 238 Tomas Morato Ave, South Triangle, Quezon City, Philippines.

Solvay, Austral. Solvay Pharmaceuticals, Division of Solvay Biosciences P/L, Locked Bag 1070, Pymble, NSW 2073, Australia.
url: www.solvaypharmaceuticals.com

Solvay, Austria. Solvay Pharma GmbH, Donaustrasse 106, A-3400 Klosterneuburg, Austria.
url: www.solvaypharma.at

Solvay, Belg. Solvay Pharma & Cie S.N.C., Blue Planet Building, Ave Bourgemestre E. Demunter 3, 1090 Brussels, Belgium.
url: www.solvaypharmaceuticals.com

Solvay, Braz. Solvay Farma Ltda, Rua Sergipe 120, 1243000 São Paulo, São Paulo, Brazil.

Solvay, Canad. Solvay Pharma Inc., 60 Columbia Way, Suite 102, Markham, Ontario, L3R 0C9, Canada.
url: www.solvaypharmaceuticals.com

Solvay, Cz. Solvay Pharma sro, Bieblová 19, 150 00 Prague 5, Czech Republic.

Solvay, Denm. Solvay Pharma ApS, Hørkaer 28, 2730 Herlev, Denmark.
url: www.solvay-pharma.dk

Solvay, Fin. See *Algol, Fin.*

Solvay, Fr. Solvay Pharma, 42 rue Rouget-de-Lisle, B.P. 22, 92151 Suresnes cdx, France.
url: www.solvaypharmaceuticals.com

Solvay, Ger. Solvay Arzneimittel GmbH, Hans-Böckler-Allee 20, 30173 Hannover, Germany.
url: www.solvay-arzneimittel.de

Solvay, Gr. Solvay Pharma M.E.P.E., Agiou Dimitriou 63, 174 56 Alimos, Greece.
url: www.solvay.com

Solvay, Hong Kong. See *Keller, Hong Kong.*

Solvay, Hung. Solvay Pharma Kft, Hegyalja út 100/a, 1112 Budapest, Hungary.
url: www.solvaypharma.hu

Solvay, India. Solvay Pharma India Ltd, Suraj Prakash, 1st floor, 86 Shankar Ghanekar Marg, Prabhadevi, Mumbai 400 025, India.
url: www.solvaypharmaceuticals.com

Solvay, Indon. Solvay Pharma Indonesia PT, Wisma 46 Kota BNI Lt 12.01, Jl Jend Sudirman Kav 1, 10220 Jakarta, DKI Jaya, Indonesia.

Solvay, Irl. Solvay Healthcare Ltd, Belgard Rd, Tallaght, Dublin 24, Ireland.
url: www.solvaypharmaceuticals.com

Solvay, Israel. See *Perrigo, Israel.*

Solvay, Ital. Solvay Pharma S.p.A., Via della Liberta 30, 10095 Grugliasco (TO), Italy.
url: www.solvaypharmaceuticals.com

Solvay, Malaysia. See *Zuellig, Malaysia.*

Solvay, Neth. Solvay Pharma BV, C J Van Houtenlaan 36, 1381 CP Weesp, Netherlands.
url: www.solvaypharmaceuticals.com

Solvay, Norw. Solvay Pharma AS, Hamang Terrasse 55, Postboks 248, 1301 Sandvika, Norway.
url: www.solvay.no

Solvay, NZ. Solvay Interox (N-Z) Ltd, P.O. Box 62-005, Mt Wellington, Auckland, New Zealand.
url: www.solvay.com

Solvay, Philipp. Solvay Pharma Inc. Philippines, 6/F Port Royal Place, 118 Rada St, Legaspi Vill, Makati City, Philippines.

Solvay, Pol. Solvay Pharmaceuticals GmbH (Sp. zo.o.), Przedstawicielstwo w Polsce, ul. Orzycka 6, 02-695 Warsaw, Poland.
url: www.solvaypharma.pl

Solvay, Port. Solvayfarma, Lda, Av. Marechal Gomes da Costa 33, 1800-255 Lisbon, Portugal.
url: www.solvaypharmaceuticals.com

Solvay, Rus. Solvay Pharma GmbH, Vavilova ul. 24, et. 5, 119991 Moscow, Russia.
url: www.solvay-pharma.ru

Solvay, S.Afr. Solvay Pharma (Pty) Ltd, P.O. Box 5278, halfway House 1685, South Africa.
url: www.solvaypharmaceuticals.com

Solvay, Singapore. See *Sime Darby, Singapore.*

Solvay, Spain. Solvay Pharma, Avda Diagonal 507-509, 08029 Barcelona, Spain.
url: www.solvaypharma.es

Solvay, Swed. Solvay Pharma AB, Sisjö Kullegata 8, 421 32 Västra Frölunda, Sweden.
url: www.solvaypharmaceuticals.com

Solvay, Switz. Solvay Pharma AG, Untermattweg 8, 3027 Bern, Switzerland.
url: www.solvaypharmaceuticals.com

Solvay, Thai. See *BJC, Thai.*

Solvay, UK. Solvay Healthcare, Mansbridge Rd, West End, Southampton, Hampshire, SO18 3JD, UK.
url: www.solvayhealthcare.co.uk

Solvay, USA. Solvay Pharmaceuticals Inc., 901 Sawyer Road, Marietta, GA 30062, USA.
url: www.solvaypharmaceuticals-us.com

Soma, Braz. See *Theraskin, Braz.*

Soma, Switz. Soma Pharma AG, Soma Medical, Ruessenstrasse 5A, 6340 Baar, Switzerland.
url: www.somapharm.com

Somedico, Malaysia. Somedico Sdn Bhd, 68 Jln SS 21/39, Damansara Utama, 47400 Petaling Jaya, Selangor, Malaysia.

Somerset, USA. Somerset Pharmaceuticals Inc., 2202 NW Shore Blvd, Suite 450, Tampa, FL 33607, USA.
url: www.somersetpharm.com

Sommerville, UK. Marie Sommerville Health Ltd, 69 Alexander Ave, Eaglesham, Glasgow, G76 0DS, UK.

Sonix, Philipp. Sonix Pharmaceuticals Inc., Unit 2207, 88 Corporate Ctr, Sedeno cor Valero Sts, Salcedo Vill, Makati City, Philippines.

Sons, Mex. Laboratorios Química Son's S.A. de C.V., Av. 23 Poniente No. 2302-A, 72410 Puebla, Pue., Mexico.

Sooft, Ital. Sooft Italia Srl, C.da Molino 17, 63025 Montegiorgio, Italy.
url: www.sooft.it

Sopharma, Bulg. Sopharma Pharmaceuticals, 16 Iliensko Shosse Str., 1220 Sofia, Bulgaria.
url: www.sopharma.bg

Sopharma, Pol. Sopharma Poland Sp. zo.o., ul. Szyszkowa 58, 02-285 Warsaw, Poland.

Sopharma, Rus. Sopharma AO, Taganskaya ul. 19, et. 10, 109147 Moscow, Russia.
url: www.sopharma.bg

Sopherion, Canad. See *Sopherion, USA.*

Sopherion, USA. Sopherion Therapeutics Inc., 200 104 Carnegie Centre, Princeton, NJ 08540, USA.

Sophia, Mex. Laboratorios Sophia S.A. de C.V., Poniente 44 2702, Azcapotzalco, Xochimanca, 2870 Mexico D.F., Mexico.
url: www.sophia.com.mx

Soprolin, Fr. Laboratoires Soprolin Sarl, 27 rue du Bedat, B.P. 116, 47203 Marmande cdx, France.
url: www.supro.tm.fr

Soraya, Pol. Soraya SA - Cederroth International, ul. Polna 21, 05-250 Radzymin, Poland.
url: www.pharbio.pl

Sorgente della Vita, Switz. Sorgente della Vita SA, 6648 Minusio, Switzerland.

Soria Natural, Spain. Soria Natural, Pol Ind La Sacea 1, Garray, 42162 Soria, Spain.
url: www.sorianatural.es

Sorin, Spain. Sorin Biomedica Espana S.A., Avda. Cerdanyola 75-77, Sant Cugat del Valles, 08190 Barcelona, Spain.
url: www.sorin-cid.com

Sorin-Maxim, Fr. Laboratoires Sorin-Maxim, rue Claude-Bernard, 12700 Capdenac, France.

SoSe, Gr. SoSe, Greece.

SoSe, Ital. So.Se. Pharm S.r.l., Via dei Castelli Romani 22, 00040 Pomezia (Rome), Italy.
url: www.sosepharm.com

Sotex, Rus. Sotex ZAO, Kashirskoe sh. 22, korp. 4, 115201 Moscow, Russia.
url: www.sotex.ru

Source, Canad. Source Medical Corp., 60 International Bvld, Toronto, Ontario, M9W 6J2, Canada.

Sovedis, Fr. Laboratoires Sovedis, 9 av. d'Arromanches, 94100 Saint-Maur des Fosses, France.

Sovereign, UK. See *Waymade, UK.*

SP, Denm. See *Schering-Plough, Denm.*

SPA, Cz. See *Medicom, Cz.*

SPA, Ital. Società Prodotti Antibiotici S.p.A., Via Biella 8, 20143 Milan, Italy.

SPA, Philipp. See *Zuellig, Philipp.*

SPA, Pol. See *Medagro, Pol.*

Spagyros, Switz. Spagyros AG, Tannackerstrasse 7, 3073 Gumlingen, Switzerland.

Spaly, Spain. See *Lilly, Spain.*

Sparks, NZ. David Sparks Ltd, P.O. Box 83-122, Edmonton, Auckland, New Zealand.

SPB, Rus. Farmacevticheskaja Fabrika SPB OAO, Moiseenko ul., d. 24A, 191144 Saint Petersburg, Russia.

SPB, Thai. S.P.B. Pharma Co. Ltd, Apt 14B, Sathorn Park Place, 27/44 South Sathorn, Sathorn, Bangkok 10120, Thailand.

Special Product's Line, Ital. Special Product's Line SpA, Via Campobello 15, 00040 Pomezia (RM), Italy.

Specifar, Cz. See *Specifar, Gr.*

Specifar, Gr. Specifar Pharmaceuticals S.A., 1, 28 Octovriou str., 123 51 Ag. Varvara, Greece.
url: www.specifar.gr

Specifar (Σπεσιφαρ), Gr. See *Specifar, Gr.*

Specpharm, S.Afr. See *Enaleni, S.Afr.*

Spectropharm, Canad. Spectropharm Dermatology, 6870 Goreway Drive, Mississauga, Ontario, L4V 1P1, Canada.

Spectrum, UK. Spectrum Thea, Fernbank House, Springwood Way, Macclesfield, Cheshire, SK10 2XA, UK.

Spedrog, Arg. Spedrog Caillon S.A.I.y C., Alte. Fco. J. Segui 2106, 1416 Buenos Aires, Argentina.

Spefar, Venez. Laboratorios Spefar Venezolanos S.A., Calle Las Piedritas, Zona Industrial de la Trinidad, Edif. Spefar, Caracas, Venezuela.
url: www.spefar.com.ve

SpePharm, UK. SpePharm UK Ltd, 28A New Yatt Rd, Witney, Oxfordshire, OX28 1NZ, UK.
url: www.spepharm.com

Speywood, Cz. See *Speywood, UK.*

Speywood, UK. Speywood Laboratories Ltd, Unit 9, Ash Rd, Wrexham Industrial Estate, Wrexham, Clwyd, LL13 9QS, UK.

Speywood, USA. See *Ipsen, USA.*

Spineda, Arg. Spineda, Pérez y Hnos. Y Cia SRL, Zado 3735, 1431 Villa Urquiza, Buenos Aires, Argentina.

Spirig, Cz. See *Spirig, Switz.*

Spirig, Fr. Laboratoires Spirig SA, 109 bd d'Haussonville, 54000 Nancy, France.
url: www.laboratoires-spirig.com

Spirig, Singapore. See *Summit, Singapore.*

Spirig, Switz. Spirig Pharma AG, Postfach 111, 4622 Egerkingen, Switzerland.

Spiromed, Hung. Spiromed Co. Ltd, Kaptárkö u 2, 1118 Budapest, Hungary.

Spitzner, Ger. W. Spitzner, Arzneimittelfabrik GmbH, Bunsenstr. 6-10, 76275 Ettlingen, Germany.
url: www.spitzner.de

Spofa, Cz. Spofa as, Poděbradská 5, 180 47 Prague 9, Czech Republic.

Spring Vine, Philipp. Spring Vine Herbal Trading, 1154 CM Recto Ave, Sta Cruz, Manila, Philippines.

Spyfarma, Spain. Laboratorios Spyfarma S.A., Ctra Sevilla Malaga Km 5.5 Km, Alcalá de Guadaira, 41500 Seville, Spain.
url: www.spyfarma.com

Square, Malaysia. See *Medispec, Malaysia.*

Square, Philipp. See *Lerna, Philipp.*

Square, Thai. Pharma Square Co. Ltd, 5 Fortune Town, 4 Fl, Rm 22-26, Ratchadapisek Rd, Bangkok 103320, Thailand.

Squibb, Canad. See *BMS, Canad.*

Squibb, Spain. See *BMS, Spain.*

Squibb, USA. See *BMS, USA.*

Squibb Diagnostics, USA. See *BMS, USA.*

Sri Jay, Rus. See *Astellas, Rus.*

Sriprasit, Thai. Sriprasit Dispensary R O P, 617 Charoen Rath Rd, Klongsarn, Bangkok 10600, Thailand.
url: www.sriprasit.com

SSI, Pol. Statens Serum Insituit Polska, ul. Grójecka 22/24 m 53, 02-021 Warsaw, Poland.

SSI, Swed. SSI Sverige, Carlsgatan 12A, Slagthuset, 211 20 Malmö, Sweden.

SSL, Austral. SSL International, 225 Beach Rd, Mordilloc, VIC 3195, Australia.
url: www.sslaustralia.com.au

SSL, Cz. See *SSL, UK.*

SSL, Fr. SSL Healthcare France SA, 49 av Georges-Pompidou, 92593 Levallois-Perret cdx, France.
url: www.ssl-international.com

SSL, Hong Kong. See *JDH, Hong Kong.*

SSL, Hung. SSL Magyarország Kft, Váci út 95, 1139 Budapest, Hungary.
url: www.ssl-international.com

SSL, Irl. SSL Healthcare Ireland Ltd, A10, Calmont Park, Ballymount, Dublin 12, Ireland.
url: www.ssl-international.com

SSL, Ital. SSL Healthcare Italia S.p.A., Via M. E. Lepido 178/5, 40132 Bologna, Italy.
url: www.ssl-international.com

SSL, Malaysia. See *Zuellig, Malaysia.*

SSL, Neth. SSL Healthcare Nederland BV, De Weegschaal, 5215 MN 'S Hertogenbosch, Netherlands.
url: www.ssl-international.com

SSL, NZ. SSL New Zealand Ltd, c/-54 Carbine Rd, Mount Wellington, Auckland, New Zealand.
url: www.ssl-international.com

SSL, Pol. SSL Healthcare Polska Sp. zo.o., ul. Szturmowa 2 a, 02-678 Warsaw, Poland.
url: www.ssl-international.com

SSL, Switz. SSL Healthcare Schweiz AG, Rheinstrasse 81, 4133 Pratteln, Switzerland.
url: www.ssl-international.com

SSL, Thai. See *Diethelm, Thai.*

SSL, UK. SSL International plc, 35 New Bridge St., London, EC4V 6BW, UK.
url: www.ssl-international.com

SSM, Turk. SSM Steril Sağlık Malzemeleri San. ve Tic. A.Ş., Katip Salih Sok. No:6, Kosuyolu, İstanbul, 34718, Turkey.
url: www.steril.com

SSRI, Rus. State Scientific-Research Institute for Specially Pure Biological Products, Pudozhskaya ul. 7, 197110 Saint Petersburg, Russia.

ST, Thai. ST Pharma, 1937/16 Soi Ramkamhaeng 21, Banhkapi, Bangkok 10240, Thailand.

St Ives, NZ. St Ives Medical, P.O. Box 65-069, Auckland, New Zealand.

St Laurent, Canad. St Laurent Laboratoire, 1010 Berlier St, Laval, Quebec, H7L 3R9, Canada.

Stada, Austria. Stada Arzneimittel GmbH, Heiligenstadter Strasse 52/2/8, A-1190 Vienna, Austria.
url: www.stada.at

Stada, Cz. Stada Pharma International os, Hnevkovská 58, 148 00 Prague 4, Czech Republic.

Stada, Denm. See *Pharmacodane, Denm.*

Stada, Ger. Stada GmbH, Stadastr. 2-18, 61118 Bad Vilbel, Germany.
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Stada, Hong Kong. Stada Pharmaceuticals (Asia) Ltd, 2513-2516 Paul Y Ctr, 51 Hung To Rd, Kwun Tong, Hong Kong.
url: www.stada.de

Stada, Hung. See *Biogal-Teva, Hung.*

Stada, Malaysia. See *Antah, Malaysia.*

Stada, Neth. See *Stada, Ger.*

Stada, Philipp. See *Croma, Philipp.*

Stada, Pol. Stada Pharma International GmbH Sp. zo.o. Oddział w Polsce, ul. Kubickiego 17 m 28, 02-954 Warsaw, Poland.
url: www.stada.de

Stada, Port. Stada Lda, Quinta da Fonte, Edifício D Amelia, Piso 1 Ala B, 2770-229 Paço de Arcos, Portugal.

Stada, Rus. Stada Pharma International, Leninskii prospekt 113/1, Of. D 403, 117198 Moscow, Russia.
url: www.stada.com

Stada, Singapore. See *JDH, Singapore.*

Stada, Spain. Laboratorio Stada S.L., Frederic Mompou 5, Sant Just Desvern, 08960 Barcelona, Spain.
url: www.stada.es

Stada, Swed. Stadapharm AB, Adelgatan 11, 211 22 Malmö, Sweden.

Stada, Thai. Stada Asiatic Co. Ltd, 41/18 Rama III Rd, Chongnonsee, Yannawa, Bangkok 10120, Thailand.

Stada, USA. STADA Pharmaceuticals Inc., 5 Cedar Brook Drive, Cranbury, NJ 08512, USA.
url: www.stadausa.com

Stadmed, India. Stadmed Pvt Ltd, AA-21 Sector-I, Salt Lake City, Kolkata 700 064, India.
url: www.evolutionindia.com

Stafford-Miller, Austral. Stafford Miller Ltd, P.O. Box 406, North Ryde, NSW 1670, Australia.

Stafford-Miller, Braz. See *GSK, Braz.*

Stafford-Miller, Hong Kong. See *Trinity, Hong Kong.*

Stafford-Miller, Irl. See *Intra Pharma, Irl.*

Stafford-Miller, Israel. See *CTS, Israel.*

Stafford-Miller, Ital. See *GSK Consumer, Ital.*

Stafford-Miller, Norw. See *Meda, Norw.*

Stafford-Miller, NZ. See *GSK, NZ.*

Stafford-Miller, Port. See *GSK, Port.*

Stafford-Miller, Switz. See *Doetsch, Grether, Switz.*

Stafford-Miller, UK. See *GSK, UK.*

Stalder, Philipp. See *BCP, Philipp.*

Stallergenes, Belg. Stallergenes Belgium SA, Chaussée de Louvain 277, 1410 Waterloo, Belgium.
url: www.stallergenes.com

Stallergenes, Cz. See *Stallergenes, Fr.*

Stallergenes, Fr. Stallergènes SA, 6 rue Alexis-de-Tocqueville, 92183 Antony cdx, France.
url: www.stallergenes.fr

Stallergenes, Ger. Stallergenes GmbH & Co KG, Carl-Friedrich-Gauss-Str. 50, 47475 Kamp-Lintfort, Germany.
url: www.stallergenes.de

Stallergenes, Ital. Stallergenes Italia S.r.l., Viale Certosa 191 Ang. Via Tribulo 2, 20151 Milan, Italy.

Stallergenes, Pol. See *Ewopharma, Pol.*

Stallergenes, Switz. See *Trimedal, Switz.*

Stancare, India. See *Ranbaxy, India.*

Standard, Philipp. See *Pharmawealth, Philipp.*

Standard Chem & Pharm, Thai. See *Union Medical, Thai.*

Standard Drug, USA. Standard Drug Company, 1279 N 7th St, Riverton, IL 62561, USA.

Stanley, Canad. Stanley Pharmaceuticals Ltd, Division of Vita Health Products Ltd, 150 Beghin Ave, Winnipeg, Manitoba, R2J 3W2, Canada.

Stanley, Israel. See *Manon, Israel.*

Star, Hong Kong. Star Medical Supplies Ltd, Unit E, 1/F Hop Hing Industrial Bldg, 704 Castle Peak Rd, Lai Chi Kok, Kowloon, Hong Kong.

Star, Thai. Star Lab Co. Ltd, 542 Vipavadi Rangsit Rd, Din Dang, Bangkok 10400, Thailand.

Star, USA. Star Pharmaceuticals Inc., 1881 W. State Road 84, Suite 101, Fort Lauderdale, FL 33315, USA.
url: www.starpharm.com

Stark, Ger. H. C. Stark GmbH Chemische Fabrik, Schneckenburgstr. 46, 78467 Constance, Germany.

Statens Serum Institut, Denm. Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark.
url: www.ssi.dk

Statens Serum Institut, Fin. See *Statens Serum Institut, Denm.*

Statens Serum Institut, Norw. See *SSI, Swed.*

Staufen, Ger. Staufen-Pharma GmbH & Co., Bahnhofstr. 35, 73033 Goppingen, Germany.
url: www.staufen-pharma.de

Stauffacher, Switz. Stauffacher Apotheke, Dr Langer AG, Birmensdorferstrasse 1, 8004 Zurich, Switzerland.

STD, Cz. See *STD Pharmaceutical Products, UK.*

STD, Hung. See *Vicis, Hung.*

STD, Irl. See *STD Pharmaceutical Products, UK.*

STD Pharmaceutical Products, UK. STD Pharmaceutical Products Ltd, Plough Lane, Hereford, Herefordshire, HR4 0EL, UK.
url: www.stdpharm.co.uk

Stegropharm, Ger. StegroPharm Arzneimittel GmbH, St.-Johann-Str. 8, 80999 Munich, Germany.

Steierl, Ger. Steierl Pharma GmbH, Muhlfelder Str. 48, 82211 Herrsching, Germany.
url: www.steierl.de

Steigerwald, Cz. See *Steigerwald, Ger.*

Steigerwald, Ger. Steigerwald Arzneimittelwerk GmbH, Havelstr. 5, 64295 Darmstadt, Germany.
url: www.steigerwald.de

Steigerwald, Pol. See *Amis, Pol.*

Steigerwald, Switz. See *Hanseler, Switz.*

Steinbach, Philipp. Steinbach Products Inc., 151 San Francisco St, Brgy Plainview, Mandaluyong City, Philippines.

Steiner, Ger. Steiner & Co. Deutsche Arzneimittel Gesellschaft, Ostpreussendamm 72/74, 12207 Berlin, Germany.
url: www.steinerarznei-berlin.de

Stella, Belg. See *Lohmann, Belg.*

Stella, Canad. Stella Pharmaceutical Canada Inc., 407-220 Duncan Mill Rd, Don Mills, Ontario, M3B 3J5, Canada.
url: www.nutribar.com

Stellar, Canad. Stellar International Inc., Stellar Healthcare, 82 Wellington St S, Suite 201, London, Ontario, N6B 2K3, Canada.
url: www.stellarint.com

Stellar, USA. See *Star, USA.*

Stendhal, Mex. Especificos Stendhal SA de CV, Carretera Picacho Ajusco 130-303, 14390 Tlalpan Jardines en Montana, Mexico DF, Mexico.

Step, Arg. Step Argentina S.A., Saenz 314, 1832 Lomas de Zamora, Buenos Aires, Argentina.

Stephar, Neth. Stephar BV, van Giesenweg 5, 2921 LN Krimpen aan den Ijssel, Netherlands.

Sterfil, India. Sterfil Laboratories, 101 Sterling Chambers, Mogra Village Lane, Andheri (E), Mumbai 400 069, India.

SteriMax, Canad. SteriMax Inc., Suite 3, 2740 Matheson Blvd East, Mississauga, Ontario, L4W 4X3, Canada.

SteriPharm, Fr. SteriPharm France Sarl, 4 rue des Bonnes-Gens, 67000 Strasbourg, France.
url: www.steripharm.biz

Steris, USA. Steris Laboratories Inc., 620 N 51st Ave, Phoenix, AZ 85043, USA.

Sterling, India. Sterling Lab., 57 Sipcot Industrial Complex, Hosur 635 126, India.

Sterling, Indon. Sterling Products Indonesia PT, Graha Paramitha 5/F, Jl Denpasar Raya Blok D II, HR Rasuna Said, Kuningan, 12950 Jakarta, DKI Jaya, Indonesia.

Sterling, USA. See *Sterling Health, USA.*

Sterling Health, Spain. See *GSK, Spain.*

Sterling Health, USA. See *Bayer, USA.*

Stern, Ger. See *AstraZeneca, Ger.*

Sterop, Belg. Sterop, Avenue de Scheut 46-50, 1070 Brussels, Belgium.
url: www.sterop.be

Sterwin, UK. See *Sanofi-Aventis, UK.*

Stetifarm, Venez. See *Leti, Venez.*

Steward Cross, Singapore. Steward Cross Pte Ltd, 801 Lor 7 Toa Payoh, Wearnes Technology Annexe Building, 01-00, S 319319, Singapore.
url: www.stewardcross.com

Stewart Jackson, USA. See *SJ Pharm, USA.*

Stichting, Cz. See *Stichting, Neth.*

Stichting, Neth. Stichting Registratiebeheer, Soest, Netherlands.

Stiefel, Arg. Stiefel Argentina S.A., Av. Federico Lacroze 3194, 1426 Buenos Aires, Argentina.
url: www.stiefel.com

Stiefel, Austral. Stiefel Laboratories P/L, Unit 2, 10 Salisbury Road, Castle Hill, NSW 2154, Australia.
url: www.stiefel.com

Stiefel, Belg. See *Stiefel, Ger.*

Stiefel, Braz. Laboratórios Stiefel Ltda, Rua João Cavalheiros Salem 1081/1301, 07243-580 Guarulhos, SP, Brazil.
url: www.stiefel.com.br

Stiefel, Canad. Stiefel Canada Inc., 6635 Henri-Bourassa Blvd W, Montreal, Quebec, H4R 1E1, Canada.
url: www.stiefel.ca

Stiefel, Chile. Laboratorios Stiefel de Chile y Cia Ltda, Av. Americo Vespucio 1220, Penalolen, Santiago, 693 25 60, Chile.
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Stiefel, Cz. Stiefel Laboratories sro, Pod Špitálem 1355, 156 00 Prague 5, Czech Republic.

Stiefel, Denm. Stiefel Laboratories (Nordic) ApS, Havnegade 39, 1058 København K, Denmark.
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Stiefel, Fin. See *Bitelab, Fin.*

Stiefel, Fr. Laboratoires Stiefel (France), 6 Av. de l'Imperatrice Josephine, 92500 Reuil-Malmaison, France.
url: www.stiefel.com

Stiefel, Ger. Stiefel Laboratorium GmbH, Mühlheimer Str. 231, 63075 Offenbach am Main, Germany.
url: www.stiefel-gmbh.de

Stiefel, Hong Kong. Stiefel Laboratories (Hong Kong) Ltd, 601B, 6F, Tower 2, Cheung Sha Wan Plaza, 833 Cheung Sha Wan Rd, Kowloon, Hong Kong.
url: www.stiefel.com

Stiefel, Hung. See *Mediner, Hung.*

Stiefel, Indon. Stiefel Laboratories Pte Ltd, Graha Atrium Building 11th Floor, Jalan Senen Raya No 135, 10410 Jakarta Pusat, Indonesia.
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Stiefel, Irl. See *Allphar, Irl.*

Stiefel, Israel. See *Perrigo, Israel.*

Stiefel, Ital. Stiefel Laboratories S.r.l., Via Calabria 15, 20090 Redecesio di Segrate (MI), Italy.
url: www.stiefel.com

Stiefel, Malaysia. See *Diethelm, Malaysia.*

Stiefel, Mex. Stiefel Mexicana S.A. de C.V., Av. Uno No. 63, Col. San Pedro de los Pinos, Delegación Benito Juárez, 03800 Mexico D.F., Mexico.
url: www.stiefel.com

Stiefel, Neth. See *Bipharma, Neth.*

Stiefel, Norw. See *Scandinavian Health Care, Norw.*

Stiefel, NZ. See *Sparks, NZ.*

Stiefel, Philipp. Stiefel Philippines Inc., Suite 1604 West Tower, Philippine Stock Exchange Ctr, Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Stiefel, Pol. Stiefel Polska Sp. zo.o., ul. Kamionkowska 51, 03-812 Warsaw, Poland.
url: www.stiefel.com

Stiefel, Port. Laboratórios Farmacêuticos Stiefel (Portugal), Lda, Av Maria Lamas, Lote 19, Bloco D, Piso 2, Serra das Minas, 2735 Rio de Mouro, Portugal.
url: www.stiefel.com

Stiefel, S.Afr. Stiefel Laboratories SA (Pty) Ltd, P. O. Box 12657, Clubview, Pretoria 0014, South Africa.
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Stiefel, Singapore. Stiefel Laboratories (Pte) Ltd, 103 Gul Circle, S 629589, Singapore.

Stiefel, Spain. Stiefel, Coto de Donana 11-13 Area, Andalucia Sector 1, Pinto, 28320 Madrid, Spain.
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Stiefel, Thai. Stiefel Laboratories (Thailand) Ltd, 33 Fl, Phaholyothin Place Building, 408/143 Phaholylothin Rd, Samsenni Phayathal, Bangkok 10400, Thailand.
url: www.stiefel.com

Stiefel, UK. Stiefel Laboratories (UK) Ltd, Holtspur Lane, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0AU, UK.
url: www.stiefel.co.uk

Stiefel, USA. Stiefel Laboratories Inc., 255 Alhambra Circle, Coral Gables, FL 33134, USA.
url: www.stiefel.com

Stiefel, Venez. Laboratorios Stiefel de Venezuela S.A., Avenida Francisco de Miranda, Centro Seguros La Paz, Piso 3, Of. E-32-F, Boleita Sur, Caracas, Venezuela.
url: www.stiefel.com

STOM, Ital. STOM Srl, Via G Verdi 46, 03043 Cassino (FR), Italy.

Stomygen, Ital. Gruppo Stomygen S.r.l., Via F. Jorini 69, 00149 Rome, Italy.
url: www.stomygen.com

Stonebridge, USA. Stonebridge Pharmaceuticals, 6340 Sugarloaf Pkwy, Suite 400, Duluth, GA 30097, USA.
url: www.stonebridgepharma.com

Storz, Israel. See *Isramedcom, Israel.*

Stragen, Cz. See *Stragen, Denm.*

Stragen, Denm. Stragen Nordic A/S, Mollehaven 8, 4040 Jyllinge, Denmark.
url: www.stragennordic.com

Stragen, Hung. See *Stragen, Denm.*

Stragen, Pol. See *Schwarz, Pol.*

Stragen, Switz. Stragen Pharma SA, 3 rue de Senger, 1211 Geneva 4, Switzerland.
url: www.stragen.ch

Stragen, UK. Stragen UK Ltd, Castle Court, 41 London Rd, Reigate, Surrey, UK.

Strakan, Irl. See *ProStrakan, UK.*

Strakan, Singapore. See *Orient, Singapore.*

Strakan, UK. See *ProStrakan, UK.*

Strallhofer, Austria. Mag. Dr. Till Strallhofer, St-Veit-Gasse 56, A-1130 Vienna, Austria.

Strand, Malaysia. See *Pharmaniaga, Malaysia.*

Strathmann, Ger. Strathmann AG & Co., Sellhopsweg 1, 22459 Hamburg, Germany.
url: www.strathmann.de

Strathmann, Hung. Strathmann Ag & Co Képviselete, Ipoly u 5/f, 1133 Budapest, Hungary.

Stratus, USA. Stratus Pharmaceuticals Inc., 14377 SW 142nd St, P.O. Box 4632, Miami, FL 33186, USA.
url: www.stratuspharmaceuticals.com

Streger, Mex. Streger S.A., Km. 8 Antigua Carretera Xalapa-Coatepec, 91500 Consolapa-Coatepec, Veracruz, Mexico.

Streuli, Philipp. See *Interlink, Philipp.*

Streuli, Switz. G. Streuli & Co. AG, 8730 Uznach, Switzerland.

Strickland, Canad. See *Hargell, Canad.*

Strides, Philipp. See *Medhaus, Philipp.*

Stroder, Ital. Ist. Farmaco Biologico Stroder S.r.l., Via di Ripoli 207/V, 50126 Florence, Italy.

Stryker, Gr. Stryker Hellas EPE, 455 Messogion Ave, 153 43 Athens, Greece.
url: www.stryker.gr

Stryker, Ital. Stryker Italia Srl, Via Ghisalba 158, 00188 Rome, Italy.

Stryker, Spain. Stryker Howmedica Iberica, Manuel Tovar 35, 28034 Madrid, Spain.
url: www.stryker.es

Stryker, Swed. Stryker AB, Krossvarksgatan 3 (Box 60048), S-21 610 Malmö, Sweden.

Stuart, Port. Stuart Produtos Farmacêuticos Lda, Rua Humberto Madeira 7, Valejas, 2745-663 Barcarena, Portugal.

Stuart, USA. See *AstraZeneca, USA.*

Stulln, Ger. Pharma Stulln GmbH, Werksstr. 3, 92551 Stulln, Germany.
url: www.pharmastulln.de

Sturtevant, USA. The F.C. Sturtevant Company, P.O. Box 607, Bronxville, NY 10708, USA.
url: www.columbiapowder.com

Suan, Gr. Suan, Greece.

Substipharm, Fr. Laboratoires Substipharm, 264 rue du Fbg-St-Honore, 75008 Paris, France.
url: www.substipharm.com

Suburfarm, Hong Kong. Suburfarm Investment & Trading Co. Ltd, Medical Health Care Division, Unit 7A-B, 39/F Cable TV Tower, 9 Hoi Shing Rd, Tsuen Wan, N.T., Hong Kong.

Sudmedica, Ger. Südmedica GmbH, Ehrwalder Str. 21, 81377 Munich, Germany.

Sudo, Singapore. See *Pharma 2000, Singapore.*

Su-Heung, Philipp. See *Biolink, Philipp.*

Sulphur Zdroj, Pol. Przedsiębiorstwo Faraceutyczne Sulphur Zdrój Exim, ul. J Rokosza 18, 28-100 Busko Zdrój, Poland.
url: www.busko-zdroj.sulphur.com.pl

Sumitomo, Hong Kong. See *Main Life, Hong Kong.*

Sumitomo, Jpn. See *Dainippon, Jpn.*

Sumitomo, Rus. See *AstraZeneca, Rus.*

Summers, USA. Summers Laboratories Inc., 103 G.P. Clement Dr., Collegeville, PA 19426-2044, USA.
url: www.sumlab.com

Summit, Malaysia. Summit Co (M) Sdn Bhd, Lot 6, Jln 19/1, 46300 Petaling Jaya, Selangor, Malaysia.
url: www.ussummit.com.my

Summit, Singapore. Summit Company (S) Ltd, 10 Pandan Crescent, 02-05 UE Tech Park, S 128466, Singapore.
url: www.ussummit.com.sg

Summit, USA. See *Novartis, USA.*

Sun, Canad. Sun Pharmaceutical Industries Inc., 1111 Flint Rd, Unit 23, Downsview, Ontario, M3J 3C7, Canada.

Sun, India. Sun Pharmaceutical Industries Ltd, Acme Plaza, Andheri Kurla Rd, Andheri (E), Mumbai 400 059, India.
url: www.sunpharma.com

Sun, Malaysia. Sun Pharmaceutical, 512, Block E, Phileo Damansara 1, Jln 16/11, 46350 Petaling Jaya, Selangor, Malaysia.

Sun, Mex. Sun Pharma de México SA de CV, Margaritas 17-A, 1030 Florida, Mexico.

Sun, Rus. Sun Pharmaceutical Industries Ltd, Profsoyuznaya ul. 57, Of. 722, 117420 Moscow, Russia.
url: www.sunpharma.ru

Sun, Thai. See *Pharmaland, Thai.*

Sun Hing, Hong Kong. Sun Hing Pharmaceutical Co. Ltd, Rm 1012, Blk 3, Nan Fung Ind City, 18 Tin Hau Rd, Tuen Mun, N.T., Hong Kong.

Sun Ventures, Rus. Sun Ventures OOO, Rustaveli ul. 14, Str. 6, 127254 Moscow, Russia.

Sundown, Venez. See *Medimfoods, Venez.*

Sun-Farm, Pol. Sun-Farm Sp. zo.o., Człekówka 75, 05-340 Kołbiel, Poland.

Sunny Plaza, Hong Kong. Sunny Plaza Ltd, 704, 7/F Kwai Hung Holdings Ctr, 89 Kings Rd, North Point, Hong Kong.

Sunpab, Philipp. Sunpab Health Care Products Phils Inc., 202 Elco Bldg, E Rodriguez Sr Ave, Quezon City, Philippines.

Sunrise, Austral. Sunrise Nutrition P/L, P.O. Box 355, Deepdene DC, VIC 3103, Australia.

Sunspot, Austral. Sunspot Products P/L, Level 3, Suite 303, 20 Bungan St, Mona Vale, NSW 2103, Australia.
url: www.sunspot.com.au

Sunspot, Hong Kong. See *Treasure Mountain, Hong Kong.*

Sunstar, Jpn. Sunstar Inc., 3-1 Asahi-machi, Takatsuki City, Osaka 569-1195, Japan.

Sunstar, UK. Sunstar, The Old Hatchery, Blind Lane, Bedale, North Yorkshire, DL8 1BW, UK.
url: www.jp.sunstar.com

Sunthi Sepuri, Indon. Sunthi Sepuri Indonesia PT, Jl Jend Sudirman Kav 7-8, 10220 Jakarta, Indonesia.

Sunward, Hong Kong. See *Primal, Hong Kong.*

Sunward, Malaysia. Sunward Pharmaceutical Sdn Bhd, 9 Jln Kempas 4, Taman Perindustrian, Tampoi Indah, 81200 Tampoi, Johor, Malaysia.

Sunward, Philipp. See *Primera, Philipp.*

Sunward, Singapore. Sunward Pharmaceutical Pte Ltd, 11 Wan Lee Rd, Jurong, S 627943, Singapore.

Super Mayoreo Naturista, Mex. Super Mayoreo Naturista S.A. de C.V., Calle 3 No. 13 Local 4, Fracc. Industrial Alce Blanco, Naucalpan de Juarez, 53370 Mexico D.F., Mexico.
url: www.smn.com.mx

Super Nutrition, Canad. Super Nutrition Ltd, 1804 West 4th Ave, Vancouver, British Colombia, V6J 1M3, Canada.

SuperGen, Canad. See *SuperGen, USA.*

SuperGen, USA. SuperGen Inc., 4140 Dublin Blvd, Suite 200, Dublin, CA 94568, USA.
url: www.supergen.com

Superlife, Mex. Superlife SA de CV, Gabriel Mancera 242, 3100 Bénito Juárez del Valle, Mexico.

Support, Braz. Support Produtos Nutricionais Ltda, Vincente Pinzon 173, 2 andar, 04547-130 São Paulo, Brazil.

Supra Ferbindo, Indon. Supra Ferbindo Farma PT, Jl HR Rasuna Said Kav 10-11, Ged Bina Mulia II Lt 6, 12950 Jakarta, Indonesia.

Surge, Philipp. See *EuroAsia, Philipp.*

Surgicraft, UK. Surgicraft Ltd, 8 Padgets Lane, Clews South Moons Moat, Redditch, Worcestershire, B98 7ST, UK.
url: www.surgicraft.co.uk

Surgimed, Venez. Laboratorio Surgimed, Av. F.Solano con Los Manguitos Piso 5 Of.13, Resid. Libertador, Caracas, Venezuela.

Survival, Arg. Lab. Survival SRL, Castillo 1531, 1414 Buenos Aires, Argentina.

Survival Technology, USA. See *King, USA.*

Surya Dermato, Indon. Surya Dermato Medica (SDM) Lab PT, Jl Paseban Raya 21, 60293 Jakarta Pusat, DKI Jaya, Indonesia.

Sussex, UK. Sussex Pharmaceutical Ltd, Charlwoods Rd, East Grinstead, Sussex, RH19 2HL, UK.

Sustime, Philipp. See *Primera, Philipp.*

Sutton, Canad. HJ Sutton Industries Ltd, 8701 Jane St, Unit C, Vaughan, Ontario, L4K 2M6, Canada.

Svizera, India. Svizera Healthcare, 18 Subhash Rd, Vile Parle (E), Mumbai 400 057, India.
url: www.svizerahealth.com

SVR, Fr. Laboratoires SVR Cosmétologie Médicale, ZAC de la Tremblaie, rue de la Mare-a-Blot, 91220 Le Plessis-Pâté, France.

SVR, Ital. Laboritoires SVR-ZAC La Tremblaie, Via dei Cybo 5, 20100 Milan, Italy.

SVUS, Cz. SVUS Pharma as, Hradec Králové, Czech Republic.

Swedish Orphan, Cz. See *Swedish Orphan, Swed.*

Swedish Orphan, Irl. See *Fulcrum, Irl.*

Swedish Orphan, Norw. Swedish Orphan AS, Trollasv. 6, 1414 Trollasen, Norway.
url: www.swedishorphan.com

Swedish Orphan, Port. Swedish Orphan International AB, Centro Empresarial Torres de Lisboa, Rua Tomas da Fonseca, Torre G, 1 Piso, 1600-209 Lisbon, Portugal.

Swedish Orphan, Swed. Swedish Orphan AB, Drottninggatan 98, 111 60 Stockholm, Sweden.
url: www.swedishorphan.com

Swedish Orphan, UK. Swedish Orphan International Ltd, Trinity House, Cambridge Business Park, Cowley Rd, Cambridge, CB4 0WZ, UK.
url: www.swedishorphan.com

Swedpharm, Chile. Lab. Swedpharm, Monseñor Felix Cabrera 41 Of. 1, Providencia, Santiago, Chile.

Swiss Bio, Malaysia. Swiss Bio Pharma Sdn Bhd, 2nd Fl, Blk E, No 10, Jln Bersatu 13/4, 46200 Petaling Jaya, Selangor, Malaysia.

Swiss Herbal, Canad. Swiss Herbal Remedies Ltd, 35 Leek Cres, Richmond Hill, Ontario, L4B 4C2, Canada.
url: www.swissherbal.com

Swiss Pharm, Thai. See *Pharmadica, Thai.*

Swiss Pharma, Philipp. See *Metro, Philipp.*, and *PharmAsia, Philipp.*

Swisshealth, UK. SwissHealth, P.O. Box 34104, London, NW10 7FD, UK.
url: www.swisshealth.com

Swisspharm, S.Afr. See *Altana, S.Afr.*

Swisspharma, Cz. Swisspharma sro, Koněvová 141, 130 00 Prague 3, Czech Republic.

Sydenham, Philipp. See *Scheeling, Philipp.*

Sylak, Swed. Sylak AB, Datavägen 29, 436 32 Askim, Sweden.

Sylk, UK. Sylk Ltd, P.O. Box 340, Rickmansworth, Hertfordshire, WD3 5WD, UK.

Symbiopharm, Ger. SymbioPharm GmbH, Auf den Luppen, 35745 Herborn-Horbach, Germany.
url: www.symbiopharm.de

SymbioPharm, Hung. See *Symbiopharm, Ger.*

SymPhar, Neth. See *SymPhar Pol.*

SymPhar, Pol. SymPhar Sp. zo.o., ul. Grójecka 186/516, 02-390 Warsaw, Poland.

Synapse, Irl. Synapse Medical, Unit 12, Keypoint Business Park, Rosemount Business Park Drive, Ballycoolin Rd, Dublin 11, Ireland.
url: www.synapsemedical.ie

Synco, Hong Kong. Synco (HK) Ltd, Blk D, 3/F, Sun View Industrial Bldg, 3 On Yip St, Chaiwan, Hong Kong.
url: www.synco-pharma.com

Syncom, India. Syncom, India.

Syner, Ger. Syner-Medica GmbH, Cappeler Gleiche 8, 35043 Marburg, Germany.

Synergia, Fr. Laboratoires Synergia, B.P. 345, 42015 Saint Etienne Cedex 2, France.
url: www.synergia-ltd.com

Syner-Med, UK. Syner-Med (Pharmaceutical Products) Ltd, Beech House, 840 Brighton Rd, Purley, Surrey, CR8 2BH, UK.
url: www.syner-med.com

Synmedic, Switz. Synmedic AG, Gerhardstrasse 1, Postfach, 8036 Zurich, Switzerland.
url: www.synmedic.ch

Synmosa, Singapore. See *Zyfas, Singapore.*

Synpharma, Switz. Synpharma AG, Postfach, 9240 Uzwil, Switzerland.

Syntetic, Denm. A/S Syntetic, Danisco Cultor, Edwin Rahrs Vej 38, 8220 Brabrand, Denmark.

Syntex, Cz. See *Roche, Canad.*

Syntex, Indon. See *Darya-Varia, Indon.*

Syntex, Mex. Syntex S.A. de C.V., Cerrada de Bezares 9, Miguel Hidalgo Lomas de Bezares, 11910 Mexico D.F., Mexico.

Syntex, USA. See *Roche, USA.*

Synteza, Pol. Przedsiębiorstwo Farmaceutyczno-Chemiczne Synteza Sp zo.o., ul. Św. Michał 67/71, 60-594 Poznań, Poland.
url: www.synteza.com

Synthelabo, Israel. See *Mediline, Israel.*

Synthelabo, Port. See *Sanofi Synthelabo, Port.*

Synthelabo, Switz. See *Sanofi Synthelabo, Switz.*

Synthesis, Rus. Synthesis ZAO, Constitution prospekt 7, 640008 Kurgan, Russia.

Synthon, Cz. See *Synthon, Spain.*

Synthon, Spain. Synthon Hispania S.L., Castello 1, Poligono Las Salinas, 08830 Sant Boi de Llobregat, Spain.
url: www.synthon.es

Synthon, USA. Synthon Pharmaceuticals Ltd, 9000 Development Drive, P.O.Box 110487, Research Triangle Park, NC 27709, USA.
url: www.synthon.com

Syosset, USA. Syosset Laboratories Inc., 150 Eileen Way, Syosset, NY 11791, USA.

Syrio, Ital. Syrio Pharma SpA, Via C Hajech 10, 20129 Milan, Italy.

Systopic, India. Systopic Laboratories Ltd, 101 Pragati Chamber, Commercial Complex, Ranjit Nagar, New Dehli 110 008, India.
url: www.systopic.com

Syxyl, Ger. Syxyl GmbH & Co. KG, Gereonsmühlengasse 5, 50670 Cologne, Germany.

Szama, Arg. Lab. Szama S.A., Lafuente 161, 1406 Buenos Aires, Argentina.
url: www.szama.com

T Man, Thai. T Man Pharma Ltd, Part, 101/2 Soi Moungsakul, Bangkuntian, Bangkok 10150, Thailand.
url: www.tmanpharma.com
T3A Pharma, Hung. See *Beaco, Hung.*
Tablets, India. Tablets (India) Ltd, Jhaver Centre, IV Floor, 72 Marshalls Road, Chennai 600 008, India.
url: www.tabletsindia.com
Tack Fung, Hong Kong. Tack Fung Medical Supplies Co., Rm 504, Tien Cheung Hong Bldg, 77-81 Jervois St Central, Hong Kong.
Taco, Ger. Taco-GmbH, Chem.-Pharm. Fabrik, Alte Heerstr. 76, 53757 St. Augustin, Germany.
TAD, Cz. See *KRKA, Cz.*
TAD, Denm. See *Copyfarm, Denm.*
TAD, Ger. TAD Pharma GmbH, Heinz-Lohmann-Str. 5, 27472 Cuxhaven, Germany.
url: www.tad.de
TAD, Ital. TAD Pharma Italia Srl, Via Felice Casati 16, 20124 Milan (MI), Italy.
url: www.tadph.com
TAD, Neth. See *TAD, Ger.*
TAD, Port. See *TAD, Ger.*
Taejoon, Singapore. See *Pharmaforte, Singapore.*
Tafarm, Gr. Tafarm, Christianoupoleos 108, 111 46 Galatsi, Greece.
Tafir, Spain. Tafir, Trifon Pedrero 4-6, 28019 Madrid, Spain.
Tai Guk, Singapore. See *Polymedic, Singapore.*
Tai Tong, Hong Kong. Tai Tong Co. Ltd, Rm 901-902, Alliance Bldg, 130-136 Connaught Rd Central, Hong Kong.
Tai Yu, Philipp. See *Cathay, Philipp., Endure, Philipp.,* and *Medicamenta, Philipp.*
Taiho, Jpn. Taiho Pharmaceutical Co. Ltd, 1-27 Kanda-Nishiki-cho, Chiyoda-ku, Tokyo 101-8444, Japan.
url: www.taiho.co.jp
Taiho, Malaysia. See *Luen Wah, Malaysia.*
Taiho, Rus. See *Grindex, Rus.*
Taiho, Singapore. See *Luen Wah, Singapore.*
Taisho, Jpn. Taisho Pharmaceutical Co. Ltd, 3-24-1 Takada, Toshima-ku, Tokyo 170-8633, Japan.
url: www.taisho.co.jp
Taisho, Malaysia. See *Diethelm, Malaysia.*
Taiwan Biotech, Malaysia. See *Averroes, Malaysia.*
Taiwan Biotech, Philipp. See *New Smart, Philipp.,* and *Pharmawealth, Philipp.*
Takeda, Austria. Takeda Pharma GmbH, Seidengasse 33-35/4, A-1070 Vienna, Austria.
url: www.takeda.com
Takeda, Cz. See *Medicom, Cz.*
Takeda, Denm. See *Lilly, Denm.*
Takeda, Fr. Laboratoires Takeda, 15 quai de Dion-Bouton, 92816 Puteaux cdx, France.
url: www.takeda.com
Takeda, Ger. Takeda Pharma GmbH, Viktoriaallee 3-5, 52066 Aachen, Germany.
url: www.takeda.de
Takeda, Hong Kong. Takeda Chemical Industries Ltd, Unit 1801-2, 18/F Fook Lee Commercial Ctr, Town Place, 33 Lockhart Rd, Wanchai, Hong Kong.
url: www.takeda.com
Takeda, Indon. Takeda Indonesia PT, Mashil Tower 15/F, Jl Jend Sudirman Kav 25, 12920 Jakarta, DKI Jaya, Indonesia.
Takeda, Israel. See *Promedico, Israel.*
Takeda, Ital. Takeda Italia Farmaceutici S.p.A., Via Elio Vittorini 129, 00144 Rome, Italy.
url: www.takeda.com
Takeda, Jpn. Takeda Chemical Industries Ltd, 4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645, Japan.
url: www.takeda.com
Takeda, Malaysia. See *Luen Wah, Malaysia,* and *Zuellig, Malaysia.*
Takeda, Neth. See *Takeda, UK.*
Takeda, Norw. See *Lilly, Norw.*
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Takeda, Port. See *Takeda, UK.*
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Takeda, Spain. See *Takeda, UK.*
Takeda, Switz. Takeda Pharma AG, Alpenblickstrasse 26, 8853 Lachen, Switzerland.
url: www.takeda.ch
Takeda, Thai. Takeda (Thailand) Ltd, 12A Fl, Si Ayutthaya Building, Si Ayutthaya Rd, 487/1 Ratchathewi, Bangkok 10400, Thailand.
url: www.takeda.com
Takeda, UK. Takeda UK Ltd, Takeda House, The Mercury Centre, Wycombe Lane, Wooburn Green, High Wycombe, Buckinghamshire, HP10 0HH, UK.
url: www.takeda.co.uk
Takeda, USA. Takeda Pharmaceuticals America, 475 Half Day Rd, Suite 500, Lincolnshire, IL 60069, USA.
url: www.takedapharm.com
Talcris, Arg. Talcris S.A., Congreso 2160 PB. A, 1428 Buenos Aires, Argentina.
Talecris, Canad. See *Talecris, USA.*
Talecris, Rus. See *Talecris, USA.*
Talecris, USA. Talecris Biotherapeutics, P.O.Box 110526, 4101 Research Commons, 79 TW Alexander Drive, Research Triangle Park, North Carolina 27709, USA.
url: www.talecris.com
Talinn, Cz. Talinn Farmaatsiatehase AS, Czech Republic.
Tallin, Pol. Tallin Pharmaceutical Plant, Poland.
Tallinn, Rus. See *BMS, Rus.*
Tamar, Israel. Tamar Marketing, Rishon-Lezion 75652, Israel.
Tamro, Fin. Tamro Distribution/Pharmakon, Rajatorpantie 41 B, PL 11, 01640 Vantaa, Finland.
Tanabe, Hong Kong. See *Primal, Hong Kong.*
Tanabe, Indon. Tanabe Indonesia PT, Jl Tanah Abang III No 8, 10160 Jakarta Pusat, DKI Jaya, Indonesia.
Tanabe, Jpn. See *Mitsubishi-Tokyo, Jpn.*
Tanabe, Malaysia. See *Pharmaforte, Malaysia.*
Tanabe, Singapore. See *Pharmaforte, Singapore.*
Tanabe, Thai. See *Wellchem, Thai.*
Tanki, Arg. Tanki S.A., Erezcano 3161, 1437 Buenos Aires, Argentina.
Tanning Research, Canad. Tanning Research Labs, 108 Newbold Court, London, Ontario, N6E 1Z7, Canada.
Tanning Research, USA. Tanning Research Labs Inc., P.O. Box 265111, Daytone Beach, FL 32126-5111, USA.
url: www.htropic.com
Tanta, Canad. Tanta Pharmaceuticals Inc., 1009 Burns St East, Whitby, Ontario, L1N 6A6, Canada.
TAP, Canad. See *Abbott, Canad.*
TAP, USA. TAP Pharmaceutical Products Inc., 675 North Field Drive, Lake Forest, IL 60045, USA.
url: www.tap.com
Taphlan, Switz. See *Serolab, Switz.*
Tarbis, Spain. See *Ferrer, Spain.*
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Tarchomin, Rus. Tarchomin Pharmaceutical Works Polfa S.A., Sr. Pereyaslavskaya ul. 13, str. 2, 129110 Moscow, Russia.
Target, Gr. Target Pharma, Menandrou 54, 104 31 Athens, Greece.
Tarmac, USA. Tarmac Products Inc., 13295 NW 107th Ave, Hialeah Gardens, FL 33018, USA.
url: www.tarmacproducts.com
Taro, Canad. Taro Pharmaceuticals Inc., 130 East Drive, Bramalea, Ontario, L6T 1C3, Canada.
url: www.taro.ca
Taro, Israel. Taro Pharmaceutical International, 14 Hakitor St, P.O. Box 10347, Haifa Bay 26110, Israel.
url: www.taro.co.il
Taro, Thai. See *Union Medical, Thai.*
Taro, UK. Taro Pharmaceuticals (UK) Ltd, 1st Floor, Prince of Wales House, 3 Bluecoats Ave, Hertfordshire, SG14 1PB, UK.
url: www.taropharma.co.uk
Taro, USA. Taro Pharmaceuticals USA Inc., 5 Skyline Drive, Hawthorne, NY 10532-9998, USA.
url: www.tarousa.com
Taro Consumer, USA. See *Taro, USA.*
Tatkhimfarmpreparaty, Rus. Tatkhimfarmpreparaty, Kazan, Belomorskaya St 260, 420091 Tatarstan, Russia.
Tau, Spain. See *AstraZeneca, Spain.*
Tauret, Cz. Tauret sro, 140 00 Praha 4, Czech Republic.
Taurus, Ger. Taurus Pharma GmbH, Benzstr. 11, 61352 Bad Homburg, Germany.
url: www.tauruspharma.de
Taxandria, Neth. Taxandria Pharmaceutica BV, Postbus 90241, 5000 LV Tilburg, Netherlands.
Taylor, USA. See *Akorn, USA.*
Taymed, Turk. Taymed Sağlıck Ürünleri Tic. Ltd. A.Ş., Büyükdere Cad., Çayırçimen Sok. Emlak Kredi Blokları A 1 Blok K: 2 D: 11, Levent, İstanbul, Turkey.
url: www.taymed.com.tr
T-Boma, Hong Kong. Trenton-Boma Ltd, Rm 1901, Clifford Centre, 782 Cheung Sha Wan Rd, Kowloon, Hong Kong.
TC Pharma-Chem, Thai. TC Pharma-Chem Co Ltd, 488 Soi Chalermsook, Phaholyotin Rd, Ladyao, Jatujak, Bangkok 10900, Thailand.
url: www.tcpharmachem.com
Team Medica, Switz. Team Medica AG, Postfach, Baarerstrasse 10, 6304 Zug, Switzerland.
Teamm, USA. See *Accentia, USA.*
Tecefarma, Spain. See *Menarini, Spain.*
Techmed, Cz. Techmed sro, 664 55 Moutnice 37, Czech Republic.
Technikon, S.Afr. Technikon Laboratories, P.O. Box 150, Maraisburg 1700, South Africa.
url: www.techlab.co.za
Technilab, Canad. See *Ratiopharm, Canad.*
Technilab, Hong Kong. See *Hind Wing, Hong Kong.*
Technilab, Malaysia. See *Mepharm, Malaysia.*
Technilab, Pol. See *Czet, Pol.,* and *Pharmix, Pol.*
Technipro, Austral. Technipro Marketing P/L, 13 Bourke St, North Parramatta, NSW 2150, Australia.
url: www.geocities.com/technipro_australia
Technobio, Mex. Technobio SA de CV, Sur 101 B 216, 9090 Iztapalapa Héroes de Churubusco, Mexico.
Technomedservis, Rus. Technomedservis, Voroncovskaja ul. 23, 109147 Moscow, Russia.
Technopharm, Irl. Technopharm Compounding Ltd, Unit 2, 88/89 Furze Rd, Sandyford Industrial Estate, Dublin 18, Ireland.
url: www.technopharm.com
Technostic, Austral. Technostic Consulting Pty Ltd, 6735 Cutrock Rd, Lisarow, NSW 2250, Australia.
Teclapharm, Ger. Teclapharm GmbH, Heilgenthalar Str. 4, 21335 Luneburg, Germany.
url: www.teclapharm.de
Tecnifar, Port. Tecnifar, SA, Rua Tierno Galvan, Torre 3, 12 Piso, 1099-036 Lisbon, Portugal.
Tecnimede, Port. Tecnimede, SA, Rua Prof. Henrique de Barros, Edifício Sagres, 5B, 2685-338 Prior Velho, Portugal.
url: www.grupo-tm.com
Tecnimede, Spain. Tecnimede Espana, Avda. Pio XII, 92, Edificio URAL A, Planta 16, Puerta 4, 28036 Madrid, Spain.
url: www.grupotecnimede.com
Tecnobio, Spain. See *Almirall, Spain.*
Tecnofarma, Chile. Tecnofarma SA, Las Violetas 2169, Santiago, Chile.
Tecnofarma, Mex. Tecnofarma S.A. de C.V., Azafran No. 123, Col. Granjas Mexico, 08400 Mexico D.F., Mexico.
url: www.tecnofarma.com.mx
Tecnonat, Arg. Tecnonat S.A., 24 de Noviembre 368, 1170 Buenos Aires, Argentina.
url: www.tecnonat.com
Tec-O-Pharm, Israel. Tec-O-Pharm, P.O. Box 45054, Jerusalem 91450, Israel.
url: www.toplibra.co.il
Tedec Meiji, Israel. See *Trima, Israel.*
Tedec Meiji, Port. Tedec Meiji Farma SA Sucursal, Av. António Augusto de Aguiar 163, 5 Dto, 1050--14 Lisbon, Portugal.
Tedec Meiji, Spain. Tedec Meiji Farma, Ctra M-300, Km 30.5, Alcalá de Henares, 28820 Madrid, Spain.
url: www.tedecmeiji.com
Teguhsindo, Indon. Teguhsindo Lestaritama, Jl Kebayoran Lama No 557, 12220 Jakarta, DKI Jaya, Indonesia.
Teijin, Hong Kong. See *Hind Wing, Hong Kong.*
Teijin, Indon. See *Dipa, Indon.*
Teijin, Jpn. Teijin Ltd, 2-1-1 Uchisaiwai-cho, Chiyoda-ku, Tokyo 100-8585, Japan.
url: www.teijin.co.jp
Teijin, Philipp. See *Croma, Philipp.*
Teijin, Singapore. See *Pharmacon, Singapore.*
Teijin, Thai. See *BJC, Thai.*
Teikoku, Jpn. Teikoku Hormone Mfg Co. Ltd, 2-5-1 Shibaura, Minato-ku, Tokyo 108-8532, Japan.
url: www.teikoku-hormone.co.jp
Teikoku Seiyaku, Jpn. Teikoku Seiyaku Co. Ltd, 567 Sanbonmatsu, Ochi-cho, Okawa-gun, Kagawa 769-2695, Japan.
Tek, Thai. See *Neopharm, Thai.*
Tek, Turk. See *Farma-Tek, Turk.*
Teka, Turk. Teka Teknik Cihazlar San. ve Tic. A.Ş., Altan Erbulak Sok. No: 3, Mecidiyeköy, İstanbul, 80300, Turkey.
url: www.tekateknik.com.tr
Teknofarma, Ital. Teknofarma S.p.A., Strada Comunale da Bertolla alla Abbadia di Stura 14, 10156 Turin, Italy.
Teleflex, Ital. Teleflex Medical Srl, Via Torino 5, 20039 Varedo (MI), Italy.
url: www.teleflexmedical.com
Telluride, USA. Telluride Pharm. Corp, 300 Valley Rd, Hillsborough, NJ 08844-4656, USA.
url: www.tellpharm.com
Tema, S.Afr. Tema Medical (Pty) Ltd, P.O. Box 3467, Cramerview 2060, South Africa.
Temapharm, Cz. See *Temapharm, Pol.*
Temapharm, Pol. Temapharm Sp zoo, Varšava, Poland.
Temis, Arg. Lab. Temis Lostaló S.A., Zepita 3178, 1285 Buenos Aires, Argentina.
url: www.temislostalo.com.ar
Temmentec, Cz. See *Henkel, Austria.*
Temmler, Cz. See *Temmler, Ger.*
Temmler, Denm. See *Kemifarma, Denm.*
Temmler, Ger. Temmler Pharma GmbH & Co. KG, Temmlerstr. 2, 35039 Marburg/Lahn, Germany.
url: www.temmler.de
Temmler, Israel. See *Megapharm, Israel.*
Temmler, Port. See *Confar, Port.*
Temmler, Thai. See *JDH Borneo, Thai.*
Tempo Scan Pacific, Indon. Tempo Scan Pacific PT, Gedung Bina Mulia II, Jl HR Rasuna Said Kav 11, 12950 Jakarta, DKI Jaya, Indonesia.
Tempo Scan Pacific, Malaysia. See *Wellmex, Malaysia.*
Tems, Turk. Tems, Turkey.
Tender, Canad. Tender Corp. Canada, P.O. Box 31018, Barrie, Ontario, L4M 5A5, Canada.
url: www.tendercorp.com
Tender, Cz. Tender Corporation, Czech Republic.
Tender, Israel. See *Meditrend, Israel.*
Tentan, Switz. Tentan AG, Brunnliweg 16, 4433 Ramlinsburg, Switzerland.
url: www.tentan.ch
Teofarma, Belg. See *Teofarma, Ital.*
Teofarma, Fr. See *Teofarma, Ital.*
Teofarma, Ger. See *Teofarma, Ital.*
Teofarma, Gr. Teofarma, Ag Dimitriou 63, 174 56 Alimos, Greece.
Teofarma, Hung. See *Teofarma, Ital.*
Teofarma, Ital. Teofarma, Via F.lli Cervi 8, I-27010 Valle Salimbene (PV), Italy.
url: www.teofarma.it
Teofarma, Neth. Teofarma, Netherlands.
Teofarma, Port. Teofarma srl, c/o Indiconta, Rua Domingos Sequeira 27, 1350-119 Lisbon, Portugal.
Teofarma, Spain. See *Teofarma, Ital.*
Teofarma, UK. See *Teofarma, Ital.*
Teomed, Switz. Teomed AG, Tumigerstrasse 71, Postfach 20, 8606 Greifensee, Switzerland.
url: www.teomed.ch
Terapeutico, Ital. Laboratorio Terapeutico M.R. S.r.l., Via Domenico Veneziano 13, 50143 Florence, Italy.
url: www.mr-online.it
Terapia, Cz. See *Terapia, Roum.*
Terapia, Hung. See *Medico Uno, Hung.*
Terapia, Roum. The Terapia Medicinal Drugs Enterprise, Cluj-Napoca, Roumania.
Terapia, Rus. See *Akrikhin, Rus.*
Teravix, Port. Teravix, Lda, Av António Augusto de Aguiar 128, 1050 Lisbon, Portugal.
Tercica, USA. Tercica, 2000 Sierra Point Parkway, Brisbane, CA 94005, USA.
url: www.tercica.com
Terme di Salsomaggiore, Ital. Terme di Salsomaggiore S.p.A., Via Roma 9, 43039 Salsomaggiore Terme (Parma), Italy.
Terme di Tabiano, Ital. Termi di Tabiano SpA, Viale Alle Terme 32, 43030 Tabiano (PR), Italy.
url: www.termeditabiano.it
Terme Sirmione, Ital. Terme Sirmione S.p.A., Piazza Virgillio 1, 25010 Colombare di Sirmione (BS), Italy.
url: www.termedisirmione.com
Terra, Turk. Terra İlaç ve Kimya Sanayi Tic. A.Ş., Bulgurlu Mah., Alemdağ Cad. Masaldan İş Merkezi No: 46 B Blok K: 3, Üsküdar, İstanbul, Turkey.
url: www.terrailac.com.tr
Terra-Bio, Ger. Terra-Bio-Chemie GmbH, Lindenbergstr. 5, 79199 Kirchzarten, Germany.
url: www.terra-bio.de
Terrafor, Fr. Laboratoires Terrafor, B.P. 62, 76302 Sotteville-les-Rouen cdx, France.
url: www.terrafor.com
Terramedic, Philipp. Terramedic Inc., ENE Industrial Complex, Brgy San Antonio, San Pedro, Laguna, Philippines.
Terrapharm, Austria. Terrapharm Pharm. Produktions- und Handels-GmbH, Braunlichgasse 40-42, A-2700 Wiener Neustadt, Austria.
Tetesept, Ger. tetesept Pharma GmbH, Marschnerstr. 10, 60318 Frankfurt, Germany.
url: www.merz.de
Tetra, Israel. Tetra Pharm, 1 Azrieli Center, Round Bldg, 24 floor, Tel Aviv 67021, Israel.
url: www.sebocalm.co.il
Tetrafarm, Arg. Laboratorios Tetrafarm SA, Calle 15 1547, 1884 Berazategui, Buenos Aires, Argentina.
Teuto, Braz. Laboratório Teuto-Brasileiro Ltda, VP 7-D Modulo 11 Quadra 13, 75133-600 Anapolis, GO, Brazil.
url: www.teutointernational.com
Teva, Belg. Teva Belgium, Laarstraat 16, 2610 Wilrijk, Belgium.
url: www.tevabelgium.be
Teva, Canad. Teva Neuroscience G.P.-S.E.N.C., 999 de Maisonneuve W, Suite 550, Montreal, Quebec, H3A 3L4, Canada.
url: www.tevaneuroscience.com
Teva, Cz. Teva Pharmaceuticals CR sro, Andrysková 21, 636 00 Brno, Czech Republic.
url: www.teva.cz
Teva, Denm. See *Aventis, Denm.*
Teva, Ger. TEVA Generics GmbH, Kandelstrasse 10, 79199 Kirchzarten, Germany.
url: www.teva-generics.de
Teva, Hong Kong. See *International Medical, Hong Kong,* and *Primal, Hong Kong.*
Teva, Hung. See *Biogal-Teva, Hung.*
Teva, Israel. Teva Pharmaceuticals Ind. Ltd, P.O. Box 8077, Kiryat Nordau, Netanya, Israel.
url: www.tevapharm.com
Teva, Ital. Teva Pharma Italia S.r.l., V.le G. Richard 7, 20143 Milan, Italy.
url: www.tevapharm.com
Teva, Neth. Teva Pharma BV, Industrieweg 23, Mijdrecht, Netherlands.
Teva, Norw. See *Aventis, Norw.*
Teva, Philipp. See *Diethelm, Philipp.*
Teva, Pol. See *Lundbeck, Pol.,* and *Sanofi-Aventis, Pol.*
Teva, Port. Teva Pharma Produtos Farmacêuticos Lda, Lagoas Park, Edifício 1, Piso 3, 2740-264 Porto Salvo, Portugal.
Teva, Rus. Teva Pharmaceutical Industries Ltd., Nauchny proezd 8, of. 226, 117246 Moscow, Russia.
url: www.teva.ru
Teva, S.Afr. Teva Pharmaceuticals (Pty) Ltd, P.O.Box 1590, Ruimsig, Roodepoort, Gauteng 1732, South Africa.
url: www.tevapharm.com
Teva, Singapore. See *Green Cross, Singapore.*
Teva, Spain. Teva Genericos Espanola S.L., Guzman El Bueno 133, Edificio Britannia 4 A, 28003 Madrid, Spain.
url: www.tevaeurope.com
Teva, Swed. Teva Sweden AB, Sundstorget 2, 251 10 Helsingborg, Sweden.
url: www.teva.se
Teva, Thai. See *RX, Thai.,* and *Union Medical, Thai.*
Teva, UK. Teva UK Ltd, Building V, The London Road Campus, London Road, Harlow, Essex, CM17 9LP, UK.
url: www.tevapharm.com

Teva, USA. Teva Pharmaceuticals USA, 1090 Horsham Rd, North Wales, PA 19454-1090, USA.
url: www.tevausa.com

Teva Tuteur, Arg. Teva Tuteur S.A., Encarnación Ezcurra 365, Piso 3, Puerto Madero, Buenos Aires, Argentina.
url: www.tevatuteur.com.ar

Texinfine, Fr. Texinfine, 60 rue Duguesclin, 69466 Lyon cdx 06, France.

Textilease, USA. Textilease Medique Products, 900 Lively Blvd, Wood Dale, IL 60191, USA.

Thai Otsuka, Thai. Thai Otsuka Pharmaceutical Co. Ltd, 11 Fl, Regent House Building, 183 Rajdamri Rd, Khwang Lumpini, Khet Pathumwan, Bangkok 10330, Thailand.
url: www.thai-otsuka.co.th

Thaipharmed, Thai. See *ST, Thai.*

Thaler, Switz. JR Thaler, 9000 St-Gall, Switzerland.

Thalgo, Fr. Lab Thalgo Nutrition, Domaine des Châtaigniers, 83520 Roquebrune-sur-Argens, France.
url: www.thalgo.com

Thames, USA. See *Taro, USA.*

The Forty-Two, Thai. See *Siam Medicare, Thai.*

Thea, Belg. Thea Pharma NV SA, Jan Broeckaertlaan 18/11, B-9230 Wetteren, Belgium.
url: www.thea.be

Thea, Fr. Laboratoires Théa, 12 rue Louis-Bleriot, 63016 Clermont-Ferrand cdx 2, France.
url: www.laboratoires-thea.fr

Thea, Ger. See *Thea, Fr.*

Thea, Hong Kong. See *Silroc, Hong Kong.*

Thea, Ital. Thea Farmaceutici S.r.l., Via Gioberti 1, 20123 Milan, Italy.

Thea, Neth. See *Thea, Fr.*

Thea, Philipp. See *Croma, Philipp.*

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Thea, Port. See *Thea, Fr.*

Thea, Spain. Thea, PG Sant Joan 91, 08007 Barcelona, Spain.

Thea, Switz. Théa Pharma SA, Webergasse 45, 8200 Schaffhausen, Switzerland.

Theiss Naturwaren, Pol. See *Natur Produkt, Pol.*

Themis, India. Themis Pharmaceuticals Ltd, 38 Suren Rd, Andheri (E), Mumbai 400 093, India.

Themis Chemicals, India. Themis Chemicals Ltd, 11/12 Udyognagar Industrial Estate, S.V. Rd, Goregaon (W), Mumbai 400 062, India.

Theodoridis, Gr. Theodoridis, Greece.

Therabel, Belg. Therabel Pharma SA, Rue Egide Van Ophem 108, 1180 Brussels, Belgium.
url: www.therabel.com

Therabel, Fr. Laboratoires Thérabel Lucien Pharma, 123 rue Jules-Guesde, 92309 Levallois-Perret cdx, France.
url: www.therabel.com

Therabel, Ital. Therabel Pharma S.p.A., Via Lorenteggio 270/a, 20152 Milan, Italy.
url: www.therabel.com

Therabel, Neth. Therabel Pharma NV, Westblaak 89, 3012 KG Rotterdam, Netherlands.

Therabel, Port. See *Therabel, Neth.*

Therakos, Fr. See *Therakos, UK.*

Therakos, UK. Therakos Inc. Europe, Coronation Rd, Ascot, Berkshire, SL5 9EY, UK.
url: www.therakos.com

Therakos, USA. Therakos Inc., 437 Creamery Way, Exton, PA 19341, USA.
url: www.therakos.com

Theralab, Canad. See *E-Z-EM, Canad.*

Theramed, Canad. Theramed Corp., 6891 Edwards Bvld, Mississauga, Ontario, L5T 2T9, Canada.
url: www.theramed.com

Theramex, Cz. See *Theramex, Mon.*

Theramex, Ital. Theramex S.p.A., Via Mancinelli 11, 20131 Milan, Italy.
url: www.theramex.it

Theramex, Mon. Laboratoires Théramex, 6 av. Prince-Héréditaire-Albert, B.P. 59, MC 98007, Monaco.
url: www.mercksante.fr

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Therapharma, Hong Kong. See *Unam, Hong Kong.*

Therapharma, Philipp. Therapharma Inc., 3/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.

Therapharma, Thai. See *Olic, Thai.*

Theraplix, Fr. See *Aventis, Fr.*

TheraSelect, Ger. TheraSelect GmbH, Emil-von-Behring Strasse 76, 35041 Marburg, Germany.
url: www.plasmaselect.de

TheraSelect, Port. See *TheraSelect, Ger.*

Theraskin, Braz. Theraskin, Marginal Direita da Anchieta Km 13.3, 09883-000 São Bernardo do Compo, SP, Brazil.
url: www.theraskin.com.br

Therasophia, Fr. Therasophia, 630 route des Dolines, 06560 Valbonne, France.
url: www.therasophia.com

Theratech, Fr. Laboratoires Theratech, 6 rue Dubais, 27000 Evreux, France.

Theriaca, Ital. Theriaca S.r.l., Palazzina C Int. 2, Via Pietroantonio Micheli 78, 00100 Rome, Italy.

Ther-Rx, USA. Ther-Rx Corp., 1 Corporate Woods Drive, Bridgeton, MO 63044, USA.
url: www.ther-rx.com

Therval, Fr. Therval Medical, 29 rue du Pont, 92200 Neuilly-sur-Seine, France.

Thiemann, Ger. See *Celltech, Ger.*

Thompson, UK. Thompson Medical Co. Ltd, Riding Court, Riding Court Rd, Datchet, Slough, Berkshire, SL3 9JT, UK.

Thompson, USA. See *Chattem, USA.*

Thomson, Austral. Richard Thomson P/L, Unit 2, 109 Vanessa Street, Kingsgrove, NSW 2208, Australia.

Thornton & Ross, Irl. See *Allphar, Irl.*

Thornton & Ross, UK. Thornton & Ross Ltd, Linthwaite Laboratories, Huddersfield, West Yorkshire, HD7 5QH, UK.
url: www.thorntonross.com

Three Rivers, Malaysia. See *Summit, Malaysia.*

Three Rivers, USA. Three Rivers Pharmaceuticals, 312 Commerce Park Drive, Cranberry Township, Pennsylvania 16066, USA.
url: www.3riverspharma.com

Thuna, Canad. Thuna Herbal Remedies Ltd, 298 Danforth Ave, Toronto, Ontario, M4K 1N6, Canada.

Thursday, Austral. Thursday Plantation laboratories Ltd, Pacific Highway, Gallen's Road, Ballina, NSW 2478, Australia.
url: www.thursdayplantation.com.au

Tiber, USA. Tiber Laboratories, 5400 Laurel Sprongs Pkwy, Suite 503, Suwanee, GA 30024, USA.
url: www.tiberlabs.com

Tibotec, USA. See *Ortho Biotech, USA.*

Tiefenbacher, Ger. Alfred Tiefenbacher GmbH & Co KG, Van der Smisse Strasse 1, 22767 Hamburg, Germany.

Tiefenbacher, Neth. See *Tiefenbacher, Ger.*

Tiger, Cz. See *DHA, Singapore.*

Tillomed, UK. Tillomed Laboratories Ltd, 3 Howard Rd, Eaton Socon, St Neots, Cambridgeshire, PE19 3ET, UK.
url: www.tillomed.com

Tillotts, Hong Kong. See *Associated Medical, Hong Kong.*

Tillotts, Irl. Tillotts Pharma Ltd, 25 Sandyford Office Park, Dublin 18, Ireland.
url: www.tillotts.com

Tillotts, Israel. See *Tradis-Gat, Israel.*

Tillotts, NZ. See *Baxter, NZ.*

Tillotts, Singapore. See *Wellchem, Singapore.*

Tillotts, Switz. Tillotts Pharma AG, Hauptstrasse 27, 4417 Ziefen, Switzerland.
url: www.tillotts.com

Tillotts, Thai. See *Union Medical, Thai.*

Tilman, Belg. Tilman SA/NV, Zoning Industriel 15, 5377 Baillonville, Belgium.
url: www.tilman.be

Tilman, Hong Kong. See *Sincerity, Hong Kong.*

Time-Cap, USA. Time-Cap Labs Inc., 7 Michael Ave, Farmingdale, NY 11735, USA.
url: www.timecaplabs.com

Timm, Neth. Timm Health Care BV, Tinbergenlaan 1, 3401 MT Ijsselstein, Netherlands.

Tipomark, Ital. Tipomark S.r.l., Via Andrea Appiani 12, 20121 Milan, Italy.

Tiroler, Austria. Tiroler Steinölwerke OHG, A-6213 Pertisau am Achensee, Austria.

Tisane Provencale, Switz. See *Uhlmann-Eyraud, Switz.*

Titan, Turk. Titan, Turkey.

Titanpharma, Ital. Titanpharma Farmaceutici, Via N di Galasso 21, 47899 Galazzano (San Marino), Italy.

Tjellesen, Denm. E. Tjellesen A/S, Blokken 81, 3460 Birkerød, Denmark.
url: www.e-tjellesen.com

TK, UK. TK Diagnostics, 65 High St, Wheatley, Oxford, Oxfordshire, OX33 1XT, UK.
url: www.tk-diagnostics.com

TKT, Austria. See *TKT, Swed.*

TKT, Belg. See *Shire, UK.*

TKT, Denm. TKT Europe-5S, Naesseslottet, Dronninggårds Allé 136, 2840 Holte, Denmark.
url: www.tkt5s.com

TKT, Fr. See *TKT, Swed.*

TKT, Ger. TKT Europe 5 S GmbH, Am Weissen Berg 21, 96193 Wachenroth, Germany.
url: www.tkt5s.com

TKT, Gr. TKT, Greece.

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TKT, Ital. TKT Europe-5S Srl, Via Carducci 5, 20123 Milan, Italy.

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TKT, Spain. See *Shire, Spain.*

TKT, Swed. TKT Europe-5S AB, Rinkebyvdgen 11 B, 182 36 Danderyd, Sweden.
url: www.tkt5s.com

TMCi, Philipp. See *InterMed, Philipp.*

TNP, Thai. TNP Health Care Co. Ltd, 94/7 Soi Yimprakrob, Ngamwongwan Rd, Nonthaburi 11000, Thailand.
url: www.thainakorn.com

TO-Chemicals, Thai. TO-Chemicals (1979) Ltd, 280 Soi Sabai Jai, Suthisarn Rd, Bangkok 10320, Thailand.
url: www.tochemicals.com

Tocogino, Mex. Laboratorios Tocogino S.A. de C.V., Chihuahua No. 185, Col. Roma, 06700 Mexico D.F., Mexico.
url: www.cosmos2.net/tocogino

Togal, Ger. Togal-Werk AG, Ismaninger Str.105, 81675 Munich, Germany.
url: www.togal.de

Togal, Neth. See *Togal, Ger.*

Togal, Switz. Togal-Werk SA, Via Val Gersa 4, 6900 Lugano-Massagno, Switzerland.

Toho, Hong Kong. See *Primal, Hong Kong.*

Toho, Thai. See *Diethelm, Thai.*

Tolmann, Philipp. JM Tolmann Laboratories Inc., 95 North Zuzuarregui St, Diliman, Quezon City, Philippines.

Tomnus, Braz. Tomnus Química e Farmacêutica Ltda, Rua: Came 482, 03121-020 São Paulo Mooca, SP, Brazil.

Tonipharm, Fr. Laboratoires Tonipharm, 3 rue des 4-Cheminées, 92514 Boulogne cdx, France.

Top, Thai. Top Pharma Supply Co Ltd, 62/257 Moo 5 Terdphrakiat Rd, Watchalaw, Bangkruay, Nonthaburi 11130, Thailand.

Topfer, Ger. Töpfer GmbH, Heisingerstr. 6, 87463 Dietmannsried, Germany.
url: www.toepfer-gmbh.de

Topgen, Belg. Topgen ESV, Etienne Demunterlaan 1, Bus 8, 1090 Brussels, Belgium.

Topmed, Belg. Topmed, Belgium.

TopoTarget, Cz. See *TopoTarget, Denm.*

TopoTarget, Denm. TopoTarget A/S, Symbion Science Park, Fruebjergvej 3, 2100 Copenhagen, Denmark.
url: www.topotarget.com

TopoTarget, Gr. TopoTarget, Greece.

TopoTarget, UK. TopoTarget UK Ltd, 87A Milton Park, Abingdon, Oxfordshire, OX14 4RY, UK.
url: www.topotarget.com

TopoTarget, USA. TopoTarget USA Inc., 100 Enterprise Drive, Rockaway, NJ 07866, USA.
url: www.topotarget.com

Toprak, Turk. Toprak İlaç ve Kimyevi Maddeler San. Tic. A.Ş., Toprak Center, Ihlamur Yıldız Cad. No:10, B Blok Kat: A, Beşiktaş, İstanbul, 34353, Turkey.
url: www.toprakilac.com.tr

Toray, Jpn. Toray Industries Inc., 2-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo 103-8666, Japan.

Torbet, Cz. See *Typharm, UK.*

Torbet, Irl. See *Allphar, Irl.*

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Torbet Laboratories, UK. See *Typharm, UK.*

Torii, Jpn. Torii Pharmaceutical Co. Ltd, 3-3-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan.

Torlan, Spain. Laboratorios Torlan S.A., Ctra Barcelona 135-B, Cerdenola del Valles, 08290 Barcelona, Spain.
url: www.torlan.es

Torrens, Spain. Torrens, Camino del Hospital S/N, Olesa de Bonevalls, 08739 Barcelona, Spain.

Torrent, Braz. Torrent do Brasil Ltda, Rua Florida 1738, 5th floor,, 04565-001 São Paulo, SP, Brazil.
url: www.torrent.com.br

Torrent, Cz. See *Glynn, Cz.*

Torrent, Ger. Torrent Pharma GmbH, Gregor-Umhof-Strasse 11, D-76694 Forst, Germany.

Torrent, India. Torrent Pharmaceuticals Ltd, Torrent House, Off Ashram Rd, Ahmedabad 380 009, India.
url: www.torrent-india.com

Torrent, Neth. See *Torrent, Ger.*

Torrent, Philipp. Torrent Pharma Philippines Inc., Unit 401-C ITC Building, 337 Sen Gil Puyat, Makati City, Philippines.

Torrent, Pol. See *Pliva Krakow, Pol.*

Torrent, Rus. Torrent Pharmaceuticals Ltd, Novocheremushkinskaya St 61, 117418 Moscow, Russia.

Torrent, Singapore. See *Zyfas, Singapore.*

Torrent, Thai. See *Union Medical, Thai.*

Torrex, Austria. Torrex Pharma GmbH, Lange Gasse 76/12, A-1080 Vienna, Austria.

Torrex, Cz. Torrex Pharma sro, Na Květnici 33, 140 00 Prague 4, Czech Republic.

Torrex, Hung. Torrex Pharma Kft, Petőfi Sandor u 12, 1052 Budapest, Hungary.

Torrex, Pol. Torrex Chiesi Polska Sp. zo.o., ul. Biała 3 p 321, 00-895 Warsaw, Poland.
url: www.torrex-chiesi.pl

Torrex Chiesi, Cz. Torrex Chiesi Cz sro, Na Květnici 33, Praha 4, Czech Republic.

Torrex Chiesi, Hung. Torrex Chiesi Kft, Kristóf tér 4, III/1-3, H-1052 Budapest, Hungary.

Tosara, UK. See *Forest Laboratories, UK.*

Tosi, Hong Kong. See *Sincerity, Hong Kong.*

Tosi, Ital. Tosi Farmaceutici sas di Silvana Tosi & C, Via Mattei 24, 28100 Novara, Italy.

Toulade, Fr. Laboratoires Toulade, av. du Docteur-Aubry, 76280 Criquetot-L'Esneval, France.

Towa, Philipp. See *Crisdy-Na, Philipp.*

Tower, Canad. See *Tower, USA.*

Tower, USA. Tower Laboratories, 8 Essex Industrial Park Rd, Centerbrook, Connecticut, 06409, USA.

Toyama, Jpn. Toyama Chemical Co., Ltd, 3-2-5 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.
url: www.toyama-chemical.co.jp

Toyo, Hong Kong. See *Hing Yip, Hong Kong.*

TP, Thai. TP Drug Lab Co. Ltd, 67 Sukhumvit 62, Prakanong, Bangkok 10250, Thailand.

Trading, Israel. Trading Pharma A.G., P.O.Box 7012, Petach Tikva 49170, Israel.

Tradiphar, Fr. Laboratoires Tradiphar, 176 rue de l'Arbrisseau, 59000 Lille, France.
url: www.tradiphar.com

Tradis-Gat, Israel. Tradis-Gat, P.O. Box 7775, Petach Tikva, Israel.

Trahan, Thai. See *Diethelm, Thai.*

Tramedico, Belg. Tramedico SA, Europark-Oost 34, PB 50, 9100 Sint-Niklaas, Belgium.
url: www.tramedico.be

Tramedico, Neth. Tramedico BV, Postbus 192, 1380 AD Weesp, Netherlands.
url: www.tramedico.nl

Trans Canaderm, Canad. See *Stiefel, Canad.*

Trans Dermal, Austral. Trans Dermal Pharmaceuticals Pty Ltd, Level 10, St Martins Tower, 31 Market St, Sydney, NSW 2000, Australia.

Transatlantic, Rus. Transatlantic International, Ulof Palme ul. 1, Section 5, 119590 Moscow, Russia.
url: www.transatlantic.ru

Transdermal, UK. Transdermal Ltd, Grimwade Ave, Croydon, Surrey, CR0 5DJ, UK.

Transfarma, Philipp. See *Metro, Philipp.*

Transfarma, Thai. Transfarma Ltd, 6 Fl, Ploenchit Center, 2 Sukhumvit Rd, Kwaeng, Klongtoey, Bangkok 10110, Thailand.

Transpen, UK. Transpen Marketing Ltd, Office 3, Roe Lee Industrial Estate, Whalley New Rd, Blackburn, Lancashire, BB1 9SU, UK.
url: www.acustat.co.uk

Travel-Safe, UK. Travel-Safe Products Ltd, Hippodrome House, Birchett Rd, Aldershot, Hampshire, GU11 1LZ, UK.
url: www.travsafe.com

TRB, Arg. TRB Pharma S.A., Plaza 939, 1427 Buenos Aires, Argentina.

TRB, Braz. TRB Pharma Indústria Química e Farmacêutica Ltda, Av. Giuseppina V. Di Napoli 1100, 13086-550 Campinas, SP, Brazil.
url: www.trbpharma.com.br

TRB, Cz. See *TRB, Arg.*

TRB, Indon. TRB, Indonesia.

TRB, Singapore. See *Pharma 2000, Singapore.*

Treasure Mountain, Hong Kong. Treasure Mountain Development Co. Ltd, 19/F Chit Lee Commercial Bldg, 30-36 Shaukeiwan Rd, Hong Kong.
url: www.tmdcl.com.hk

Treiner, USA. Treiner Co, USA.

Trendful, Hong Kong. Trendful Development Ltd, Room 1217 China Merchants Tower, Shun Tak Ctr, 168-200 Connaught Rd Central, Hong Kong.

Trenka, Austria. F Trenka Chemisch-Pharmazeutische Fabrik GmbH, Goldeggassee 5, A-1040 Vienna, Austria.

Trenka, Israel. See *Tetra, Israel.*

Trenka, Malaysia. See *Antah, Malaysia.*

Trenker, Belg. Laboratoires Pharmaceutiques Trenker SA, Ave Dolez 480-482, 1180 Brussels, Belgium.
url: www.trenker.be

Trenker, Hong Kong. See *Europharm, Hong Kong.*

Trenker, Thai. See *JAV, Thai.*

Treupha, Switz. Treupha SA, Zurcherstrasse 59, 5401 Baden, Switzerland.
url: www.treupha.ch

Tri Tec, USA. Tri Tec Labs, 1000 Robins Rd, Lynchburg, VA 24504-3558, USA.

Triangle, USA. See *Tri Tec, USA.*

Trianon, Canad. Trianon Laboratories Inc., 660 Industriel Blvd, Blainville, Quebec, J7C 3V4, Canada.

Triax, USA. Triax Pharmaceuticals LLC, 20 Commerce Drive, Suite 232, Cranford, NJ 07016-3599, USA.
url: www.triaxpharma.com

Tribest, S.Afr. Tribest Products, P.O. Box 7286, Roggebaai, Cape Town 8012, South Africa.

Tridoss, India. Tridoss Labs Pvt Ltd, 167 Readymoney Terrace, 2nd Floor, Dr A B Rd, Worli, Mumbai 400018, India.

Trigon, Hung. Trigon Biotechnologiai Rt, Hőgyes Endre utca 4, 1092 Budapest, Hungary.

Trillium, Canad. Trillium Health Care Products Inc., 2337 Parkdale Ave, Brockville, Ontario, K6V 5W5, Canada.

Trima, Cz. See *Trima, Israel.*

Trima, Hong Kong. See *Gaily, Hong Kong.*

Trima, Israel. Trima, Kibbutz Ma'abarot 40230, Israel.
url: www.trima.co.il

Trima, Singapore. See *Green Cross, Singapore.*

Trima, Thai. See *Union Medical, Thai.*

Tri-Med, USA. See *Kimberly-Clark, USA.*

Trimedal, Switz. Trimedal AG, Postfach 114, 8306 Bruttisellen, Switzerland.
url: www.trimedal.ch

Trimen, USA. Trimen Inc., P.O. Box 309, New Oxford, PA 17350, USA.
url: www.trimen.com

Trinity, Hong Kong. Trinity Trading Co. Ltd, Unit 7A-B, 39/F Cable TV Tower, 9 Hoi Shing Rd, Tsuen Wan, N.T., Hong Kong.

Trinity, Irl. See *Trinity, UK.*

Trinity, UK. Trinity Chiesi Pharmaceuticals Ltd, Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY, UK.
url: www.trinity-chiesi.co.uk

Triomed, S.Afr. See *Aspen, S.Afr.*

Tripharma, Rus. See *Abdi, Rus.*

Tripharma, Turk. See *Abdi, Turk.*

Triton, Canad. Triton Pharma Inc., 31 B 665 Millway Ave, Concord, Ontario, L4K 3T8, Canada.

Triton, USA. Triton Consumer Products, Inc., 561 West Golf, Arlington Heights, IL 60005, USA.
url: www.tritonconsumerproducts.com

Troika, Venez. See *PG, Venez.*

Troikaa, India. Troikaa Pharmaceuticals Ltd, Om Towers, Satellite Rd, Ahmedabad 380 015, India.
url: www.troikaa.com

Trommsdorf, Hung. See *Afamia, Hung.*

Trommsdorff, Cz. See *R-mark, Cz.*

Trommsdorff, Ger. Trommsdorff GmbH & Co. KG Arzneimittel, Trommsdorffstr. 2-6, 52477 Alsdorf, Germany.
url: www.trommsdorff.de

Trophic, Canad. Trophic Canada Ltd, 260 Okanagan Ave East, Penticton, British Colombia, V2A 3J7, Canada.

Tropica Mas, Indon. Tropica Mas Pharmaceuticals PT, Jl A Yeni, Komplek Pertamina Patra II, No 20, 10510 Jakarta, DKI Jaya, Indonesia.

Tropon, Ger. Tropon GmbH, Neurather Ring 1, 51063 Cologne, Germany.
url: www.tropon.de

Tropon, Indon. See *Soho, Indon.*

Trupharm, Israel. Trupharm, P.O. Box 8105, Netanya, Israel.

Truw, Ger. Truw Arzneimittel Vertriebs GmbH, Ziethenstr. 8, 33330 Gutersloh, Germany.
url: www.truw.de

Truxton, USA. C.O. Truxton Inc., 136 Harding Ave, Bellmawr, NJ 08099, USA.

Trx Pharma, USA. TRx Pharma, Quadrangle IV Suite 100, 6340 Quadrangle Drive, Chapel Hill, NC 27517, USA.
url: www.trxpharma.com

Tryon, USA. Tryon Laboratories, 27368 Via Industria, Temecula, CA 92590, USA.

TS, Ital. Farmacetici T.S. S.r.l., Via M. G. dell'Unita 2, 00046 Grottaferrata (Rome), Italy.

Tshepo, S.Afr. Tshepo Pharmaceuticals (Pty) Ltd, Block 1 Atterbury Estates, 19 Frikkie de Beer St, Menlyn, Pretoria, South Africa.

TSNKB, Rus. TSNKB, Russia.

Tsumura, Cz. See *Tsumura, Jpn.*

Tsumura, Jpn. Tsumura & Co., 12-7 Nibancho, Chiyoda-ku, Tokyo 102-8422, Japan.
url: www.tsumura.co.jp

TTK, India. TTK Healthcare Ltd, 91 Santhome High Road, Chennai 600 028, India.

TTN, Thai. TTN Thitiratsanon Co. Ltd, 157/9 Prannok Rd, Siriraj Bangkoknoi, Bangkok 10700, Thailand.

Tubilux, Ital. Tubilux Pharma S.p.A., Via Costarica 20/22, 00040 Pomezia (RM), Italy.

Tubilux, Port. See *Davi, Port.*

Tum, Turk. Tum Ekip İlaç A.Ş., Bayraktar Bulvan, Beyit Sok. No:26 Y. Dudullu, Ümraniye, İstanbul, 34775, Turkey.
url: www.tumekip.com.tr

Tungfa, Philipp. See *New Smart, Philipp.*

Tunggal Idaman, Indon. Tunggal Idaman Abdi PT, Jl Jend A Yani No 7, 13230 Jakarta Timur, DKI Jaya, Indonesia.

Turgut, Turk. See *Abdi, Turk.*

Turimed, Switz. Turimed SA, Hertistrasse 8, 8304 Wallisellen, Switzerland.

Tussin, Ger. Tussin Pharma GmbH, Menchestr. 22 A, 35274 Kirchhain, Germany.

Tutogen, Ger. Tutogen Medical GmbH, Industriestr. 6, 91077 Neunkirchen a. Br., Germany.
url: www.tutogen.de

Twardy, Ger. Astrid Twardy GmbH, Liebigstr. 18, 65439 Florsheim/Main, Germany.
url: www.twardy.de

Tyco, Canad. Tyco Healthcare, 7500 Trans-Canada Hwy, Pointe-Claire, Quebec, H9R 5H8, Canada.
url: www.tyco.com

Tyco, Cz. See *Tyco, Ger.*

Tyco, Denm. Tyco Healthcare Danmark, Langebrogade 6 E, 4, 1411 Copenhagen K, Denmark.
url: www.tycohealthcare.com

Tyco, Fin. Tyco Healthcare Finland Oy, Koydenpunojankatu 2 D, PL 340, 00181 Helsinki, Finland.
url: www.tycohealthcare.com

Tyco, Ger. Tyco Healthcare Deutschland GmbH, Gewerbepark 1, 93333 Neustadt/Donau, Germany.
url: www.tycohealth.de

Tyco, Hung. Tyco Healthcare Magyarország Képviselet, Karinthy Frigyes u 9 IV/1, 1117 Budapest, Hungary.

Tyco, Ital. Tyco Healthcare Italia SpA, Via Rivoltana 2/D, 20090 Segrate (MI), Italy.
url: www.tycohealthcare.it

Tyco, Norw. Tyco Healthcare Norge AS, Lensmannslia 1, 1386 Asker, Norway.

Tyco, Port. Tyco Healthcare Portugal Lda, Estrada do Outeiro de Polima, Lote 10, 1 Piso, Abóboda, 2785-521 S. Domingos de Rana, Portugal.
url: www.tycohealthcare.com

Tyco, Spain. Tyco Healthcare Spain S.L., Fructuos Gelabert 6, 8a Planta, Sant Joan Despi, 08970 Barcelona, Spain.
url: www.tycohealthcare.com

Tyco, Swed. Tyco Healthcare Norden AB, Box 397, 581 04 Linköping, Sweden.
url: www.tycohealthcare.com

Tyco, UK. Tyco Healthcare, 154 Fareham Rd, Gosport, Hampshire, PO13 0AS, UK.
url: www.tycohealthcare.co.uk

Tymofarm, Pol. PRP Tymofarm Witold Brzosko Magdalena Brzosko, ul. Willowa 8.10, 00-790 Warsaw, Poland.
url: www.tymofarm.pl

Tynor, Philipp. See *Zuellig, Philipp.*

Typen, Arg. Typen S.A.I.C.F., Colombres 257, 1177 Buenos Aires, Argentina.

Typharm, UK. Typharm Ltd, 14D Wendover Rd, Rackheath Industrial Estate, Norwich, Norfolk, NR13 6LH, UK.
url: www.typharm.com

Tyrol, Austria. Tyrol Pharma GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria.

Tyson, USA. Tyson Nutraceuticals Inc., 3535 Lomita Blvd, Unit A, Torrance, CA 90505, USA.
url: www.tysonnutraceuticals.com

Tzamal, Israel. Tzamal Pharma Ltd, 20 Hamgshimim St, P.O. Box 7004, Kiryat Matalon, Petach Tikva, Israel.
url: www.tzamal-medical.co.il

UAD, USA. See *Forest Laboratories, USA.*

UAP, Indon. See *Medifarma, Indon.*

UAS, Philipp. See *Zenaust, Philipp.*

UB, Switz. UB Interpharm SA, 36 av Cardinal-Mermillod, 1227 Carouge/GE, Switzerland.

Ubepharm, Hung. Ubepharm, Bodor u 8 I/6, 1138 Budapest, Hungary.

UCB, Austral. UCB Pharma, A Division of UCB Australia P/L, 19 Potter St, Carigieburn, VIC 3064, Australia.
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UCB, Austria. UCB Pharma GmbH, Brunnerstrasse 73/5, A-1210 Vienna, Austria.
url: www.ucbpharma.com

UCB, Belg. UCB Pharma SA, Route de Lennik 437, 1070 Brussels, Belgium.
url: www.pharma.ucb-group.com

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UCB, Fin. UCB Pharma Oy Finland, Malminkaari 5, 00700 Helsinki, Finland.
url: www.ucbpharma.com

UCB, Fr. UCB Pharma S.A., 21 rue de Neuilly, 92003 Nanterre, France.
url: www.ucbpharma.com

UCB, Ger. UCB GmbH, Huttenstr. 205, 50170 Kerpen, Germany.
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UCB, Gr. UCB Pharma A.E., 580 Vouliagmenis Ave, 164 52 Argiroupoli, Greece.
url: www.ucb-group.com

UCB, Hong Kong. UCB Pharma Ltd, Unit 1002-03, 10/F Guangdong Finance Building, 88 Connaught Rd West, Hong Kong.
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UCB, Hung. UCB Magyarország Kft, Hűvösvölgyi út 54, 1021 Budapest, Hungary.

UCB, India. UCB India Pvt Ltd, VIP House, 1st Floor, 88C Old Prabhadevi Rd, Mumbai 400 025, India.
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UCB, Indon. See *Darya-Varia, Indon.*

UCB, Irl. See *United Drug, Irl.*

UCB, Ital. UCB Pharma S.p.A., Via Praglia 15, 10044 Pianezza (TO), Italy.
url: www.ucbpharma.com

UCB, Jpn. UCB Japan Co. Ltd, 2-2 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan.
url: www.ucbpharma.com

UCB, Malaysia. UCB Asia Pacific Sdn Bhd, Suite 3.08, 3rd floor, Wisma Academy, 4A, Jln 19/1, 46300 Petaling jaya, Selangor, Malaysia.
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UCB, Mex. UCB de Mexico S.A. de C.V., Homero No. 440, Piso 7, Col. Chapultepec Morales, 11570 Mexico D.F., Mexico.
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UCB, Neth. UCB Pharma BV, Druivenstraat 5, 4816 KB Breda, Netherlands.
url: www.ucbpharma.com

UCB, Norw. UCB Pharma AS, Brynsv. 96, 1352 Kolsas, Norway.
url: www.ucb.be

UCB, NZ. See *UCB, Austral.*

UCB, Philipp. UCB Philippines Inc., 9/F Salcedo Towers, 169 HV dela Costa St, Salcedo Village, Makati City, Philippines.

UCB, Pol. UCB Pharma Sp. zo.o., ul. Kruczkowskiego 8, 00-380 Warsaw, Poland.
url: www.ucb.de

UCB, Port. UCB, Lda, Rua Gregório Lopes, Lote 1597, 1400-195 Lisbon, Portugal.
url: www.ucbpharma.com

UCB, Rus. See *Pliva, Rus.*

UCB, S.Afr. UCB SA (Pty) Ltd, P.O. Box 31036, Braamfontein 2017, South Africa.
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UCB, Singapore. UCB Singapore Pte Ltd, 100 Beach Rd, 34-01/02 Shaw Towers, S 189702, Singapore.
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UCB, Spain. UCB Pharma, Avenida de Barcelona 239, Molins de Rei, 08750 Barcelona, Spain.
url: www.ucbpharma.com

UCB, Swed. UCB Pharma AB (Sweden), Murmansgatan 126 A, 212 25 Malmö, Sweden.
url: www.ucbpharma.com

UCB, Switz. UCB-Pharma AG, 10 ch. de Croix-Blanche, 1630 Bulle, Switzerland.
url: www.ucbpharma.com

UCB, Thai. UCB Pharma (Thailand) Ltd, 27 Fl, Panjathani Tower, 127/32 Nonsee Rd, Yannawa, Bangkok 10120, Thailand.
url: www.ucb-group.com

UCB, Turk. UCB Pharma A.Ş., Cemil Topuzlu Cad., İş Bankasi Bloklan D Blok K: 4 D: 7, Fenerbahçe, İstanbul, 81030, Turkey.
url: www.pharma.ucb-group.com

UCB, UK. UCB Pharma Ltd, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK.
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UCB, USA. UCB Pharma Inc., 1950 Lake Park Drive, Smyrna, GA 30080, USA.
url: www.ucb-group.com

UCI, Braz. UCI-Farma Indústria Farmacêutica Ltda, Rua Cruzeiro 374, 09725-310 São Bernardo do Campo, SP, Brazil.
url: www.uci-farma.com.br

Ucyclyd, USA. See *Medicis, USA.*

UDL, USA. UDL Laboratories Inc., 1718 Northrock Court, Rockford, IL 61103, USA.
url: www.udllabs.com

Ufavita, Rus. Ufavita, Ufimskii Vitamin Works OAO, Letnikovskaya ul. 10, str. 7, et. 2, 115114 Moscow, Russia.
url: www.ufavita.ru

UFSA, Turk. See *Ulagay, Turk.*

Uhlmann-Eyraud, Switz. F. Uhlmann-Eyraud SA, 28 chemin du Grand-Puits, 1217 Meyrin 2/Geneva, Switzerland.

Ulagay, Turk. İ.E. Ulagay İlaç San. ve Tic. A.Ş., Davutpaşa Cad. No: 12, Topkapı, İstanbul, 34473, Turkey.
url: www.ieulagay.com.tr

Ulkar, Turk. See *Nobel, Turk.*

Ulmer, USA. Ulmer Pharmacal Co., 1614 Industry Ave, P.O. Box 408, Park Rapids, MN 56470, USA.
url: www.lobanaproducts.com

Ultra, Mex. Ultra Laboratorios SA de CV, Av. Doctor R Michel 2920, 44490 Guadalajara Pque. Ind. El Alamo, Jalisco, Mexico.

Ultrapharm, UK. Ultrapharm Ltd, Centenary Business Park, Henley-on-Thames, Oxfordshire, RG9 1DS, UK.
url: www.gfdiet.com

Ultratech, India. Ultratech India Ltd, 113 J K Chambers, Sector 17, Vashi, Mumbai, India.
url: www.ultratechindia.com

Umeda, Philipp. See *DKT, Philipp.*

Umeda, Thai. Umeda Co Ltd, 26/18-21 Ram-Indra Rd, Bangkok 10230, Thailand.
url: www.umeda.co.th

Unam, Hong Kong. Unam Corp Ltd, 7/F Chiu Lung Bldg, 25 Chiu Lung St Central, Hong Kong.

Unam, Malaysia. Unam Corporation (M) Sdn Bhd, 11th Floor, Menara ING, 84 Jln Raja Chulan, 50200 Kuala Lumpur, Kuala Lumpur, Malaysia.

Undra, Mex. Undra, Mexico.

Uni, Singapore. Uni Drug House Pte Ltd, 61 Kaki Bukit Ave 1, 05-31 Shunli Industrial Park, S 417943, Singapore.

Unia, Pol. Zakłady Farmaceutyczne Unia Spółdzielnia Pracy, ul. Chłodna 56/60, 00-872 Warsaw, Poland.
url: www.uniapharm.pl

Uniao Quimica, Braz. União Química Farmacêutica Nacional S.A., Avenida dos Bandeirantes 5386, 04071-900 São Paulo, SP, Brazil.
url: www.uniaoquimica.com.br

Unibios, Spain. Unibios, Spain.

Unichem, India. Unichem Laboratories Ltd, Prabhat Estate, S.V. Rd, Jogeshwari (W), Mumbai 400 102, India.
url: www.unichemindia.com

Unichem, Malaysia. See *Antah, Malaysia.*

Unichem, Rus. See *Transatlantic, Rus.*

Unichem, Singapore. See *Uni, Singapore.*

Unichem, UK. Unichem Ltd, Unichem House, Cox Lane, Chessington, Surrey, KT9 1SN, UK.
url: www.unichem.co.uk

Unicity, Singapore. Unicity Singapore Pte Ltd, 530 Lorong 6 Toa Payoh, 02-06 HDB Hub, Singapore 310530, Singapore.
url: www.unicitynetwork.com.sg

Unico, Hong Kong. Unico Health Care Products Ltd, Rm 1007, Tower B Seaview Estate, 2-8 Watson Rd, North Point, Hong Kong.
url: www.unicohk.com

Unico, USA. Unico Inc., 1830 2nd Ave N, Lake Worth, FL 33461, USA.

Unicure, India. Unicure Remedies Pvt Ltd, F/25 Industrial Estate, Gorwa, Vadodara 390 016, India.
url: www.unicurepharma.com

Uniderm, Israel. See *Promedico, Israel.*

Uniderm, Ital. Uniderm Farmaceutici S.r.l., Ple F. il Macedone 140, 00124 Casalpalocco (RM), Italy.
url: www.uniderm.it

Unifa, Port. See *CPH, Port.*

Unifarm, Ital. Unifarm S.p.A., Via Provina 3, 38040 Ravina (TN), Italy.

Unigene, Port. See *Unigene, UK.*

Unigene, UK. Unigene UK Ltd, 191 Sparrows Herne, Bushey Heath, Hertfordshire, WD23 1AJ, UK.

Unigreg, Irl. See *Unigreg, UK.*

Unigreg, UK. Unigreg Ltd, Enterprise House, 181-9 Garth Rd, Morden, Surrey, SM4 4LL, UK.
url: www.unigreg.com

Unilab, Hung. Unilab, Hungary.

Unilab, Malaysia. See *Diethelm, Malaysia.*

Unilab, Philipp. Unilab Nutritionals Inc., 4/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.

Unilever, Canad. Unilever, 160 Bloor St. E, Suite 300, Toronto, Ontario, M4W 3W3, Canada.

Unilever, USA. Unilever HPC, 33 Benedict Place, Greenwich, CT 06830, USA.
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Unilfarma, Port. See *Boehringer Ingelheim, Port.*

Unimed, Cz. Unimed Bohemia sro, U Dvora 25, 779 00 Olomouc, Czech Republic.

Unimed, India. Unimed Technologies Pvt Ltd, Synergy House, Subhanpura, Gorwa Rd, Vadodara 390 016, India.

Unimed, Israel. See *Megapharm, Israel.*

Unimed, USA. See *Solvay, USA.*

Unimedic, Swed. Unimedic AB, Box 91, 864 21 Matfors, Sweden.
url: www.unimedic.se

Unimex, Philipp. Unimex Inc., 1104 Shaw Towers, Shaw Blvd cor St Francis St, Mandaluyong City, Philippines.

Union, Singapore. Union Chem & Pharm, Singapore.

Union Drug, Thai. Union Drug Laboratories Co Ltd, 2601 Sukhumvit Rd, Bangjak, Prakanong, Bangkok 10260, Thailand.

Union Health, Ital. Union Health Srl, Via Roccamandolfi 1, 00100 Rome, Italy.

Union Medical, Thai. Union Medical (Thailand) Co. Ltd, 513/199-200 Jaransanitwong Rd, Soi 37 Bangkoknoi, Bangkok 10700, Thailand.
url: www.unionmedical.co.th

Unipack, Austria. Unipack GmbH, Braunlichgasse 40-42, A-2700 Wiener Neustadt, Austria.

Unipath, Canad. See *Unipath, UK.*

Unipath, Israel. See *Perrigo, Israel.*

Unipath, Ital. Unipath Div. Unilever Italia SpA, Via Nino Bonnet 10, 20154 Milan, Italy.

Unipath, UK. Unipath Ltd, Priory Business Park, Bedford, Bedfordshire, MK44 3UP, UK.
url: www.unipath.com

Unipath, USA. Unipath Diagnostics Co., 47 Hulfish St, Suite 400, Princeton, NJ 08542, USA.
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Unipharm, Hong Kong. Unipharm Trading Co., Rm 634-635, Nan Fung Ctr, 264-298 Castle Peak Rd, Tsuen Wan, N.T., Hong Kong.

Unipharm, Israel. Unipharm Ltd, P.O. Box 21429, Tel Aviv, Israel.
url: www.unipharm.co.il

Unipharm, Mex. Unipharm de Mexico SA de CV, Tamarindos XV-A Lote 10 y 11, 91697 Veracruz C Ind. Bruno Pagliai, Veracruz, Mexico.

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Unipharm, Rus. Unipharm Inc., Khokhlovskii per. 13, str. 1, 109028 Moscow, Russia.
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Unipharm, Singapore. See *Green Cross, Singapore.*

Unipharm, Turk. Unipharm İlaç San. ve Tic. A.Ş., Gursel Mah. İlkem Sok. No: 5/1-2, Kağıthane, İstanbul, 80270, Turkey.

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Unipharma, Spain. Unipharma, Mino 8, 08022 Barcelona, Spain.
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Unipharma, Switz. Unipharma SA, Via Pian Scairolo 6, 6917 Barbengo, Switzerland.
url: www.unipharma.ch

Unique, India. Unique Pharmaceutical Laboratories, Neelam Centre, B Wing, 4th floor, Hind Cycle Rd, Worli, Mumbai 400 025, India.
url: www.uniquepharma.com

Unique, Rus. Unique Pharmaceutical Laboratories, Sadovaya-Kudrinskaya ul. 3, 123242 Moscow, Russia.

Unique, Singapore. See *Uni, Singapore,* and *United Italian, Singapore.*

Unique, Venez. See *PG, Venez.*

Uni-Sankyo, India. Uni-Sankyo Ltd, 392 Sagar Society, Plot 84, Road No. 2, Banjara Hills, Hyderabad 500 034, India.
url: www.pubergen.com

Unison, Hong Kong. See *Health Alliance, Hong Kong.*

Unison, Malaysia. See *Pahang, Malaysia.*

Unison, Philipp. See *Justright, Philipp.*

Unison, Singapore. See *Age D'or, Singapore.*

Unison, Thai. Unison Laboratories Co. Ltd, 160 Soi Onnuch, Sukhumvit Rd, Ladkrabang, Bangkok 10520, Thailand.
url: www.unisonlab.com

United, Canad. United Industries, Canada.

United American, Hong Kong. See *Unam, Hong Kong.*

United American, Malaysia. See *Unam, Malaysia.*

United American, Philipp. United American Pharmaceuticals Inc., 2/F Greenfield Bldg, 750 Shaw Blvd, Mandaluyong City, Philippines.

United American, Singapore. See *Far East, Singapore.*

United American, Thai. See *Olic, Thai.*

United Drug, Irl. United Drug, United Drug House, Belgard Rd, Tallaght, Dublin 24, Ireland.
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United Home, Philipp. United Home Products, 66 Unied St, Mandaluyong City, Philippines.

United Italian, Malaysia. United Italian Trading (M) Sdn Bhd, No 1, 1st Floor, The Highway Centre, Jln 51/205, 46050 Petaling Jaya, Selangor, Malaysia.
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United Italian, Singapore. United Italian Trading Corp Pte Ltd, 65 Upper Paya Lebar Rd, 06-03 Guang Ming Industrial Building, S 534817, Singapore.

United Lab, Malaysia. See *Diethelm, Malaysia.*

United Laboratories, Philipp. United Laboratories, 66 United St, Mandaluyong City, Philippines.

United Medical, Braz. United Medical Ltda, Rua Jesuino Arruda 769, 9 andar, 04532-082 São Paulo, SP, Brazil.

United Nordic, Denm. United Nordic Pharma A/S, Hammervej 7, 2970 Hørsholm, Denmark.

United Pharma, Pol. See *Farma-Projekt, Pol.*

United Research, USA. United Research Laboratories, 1100 Orthodox St, Philadelphia, PA 19124, USA.
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United Therapeutics, Cz. See *United Therapeutics, UK.*

United Therapeutics, Israel. See *Rafa, Israel.*

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Universal, Hong Kong. Universal Pharmaceutical Lab Ltd, Eastern Ctr, G/F & 1/F, Unit 1-5, 1065 King's Rd, Quarry Bay, Hong Kong.

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Upha, Indon. See *Nutri Gizindo, Indon.*

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Upha, Singapore. See *FP, Singapore,* and *Zuellig, Singapore.*

Upjohn, USA. See *Pfizer, USA.*

UPSA, Cz. See *UPSA, Fr.*

UPSA, Fr. Laboratoires UPSA, La Grande Arche Nord, 92044 Paris-La Défense cdx, France.

Upsa, Ital. Upsa S.r.l., Via Virgillio Maroso 50, 00100 Rome, Italy.

UPSA, Neth. See *UPSA, Fr.*

UPSA, Switz. See *Upsamedica, Switz.*

UPSA Conseil, Fr. See *BMS, Fr.*

Upsamedica, Ital. See *Upsa, Ital.*

Upsamedica, Switz. Upsamedica SA, Neuhofstrasse 6, 6341 Baar, Switzerland.
url: www.bms.ch

Upsher Smith, Israel. See *Meditrend, Israel.*

Upsher-Smith, USA. Upsher-Smith Laboratories Inc., 14905 23rd Ave North, Minneapolis, MN 55447, USA.
url: www.upsher-smith.com

Upsifarma, Port. Upsifarma, Lda, S. Domingos à Lapa 8, Letra H, 1200-835 Lisbon, Portugal.

Uragme, Ital. Uragme, Via A. Vivaldi 9, 00100 Rome, Italy.

Urbion, Spain. Urbion Farma, Avda Portugal, Parcela 85 Pol Allendeduero, Aranada de Duero, 09400 Burgos, Spain.

Urgo, Belg. See *Fournier, Belg.*

Urgo, Cz. See *Urgo, Fr.*

Urgo, Fr. Laboratoires Urgo, B.P. 157, 42 rue de Longvic, 21300 Chenove, France.
url: www.urgo.fr

Urgo, Ger. See *Fournier, Ger.*

Urgo, Israel. See *Perrigo, Israel.*

Urgo, Pol. See *Imed, Pol.*

Uriach, Cz. See *Uriach, Spain.*

Uriach, Hung. J Uriach & Cia, Hungary.

Uriach, Pol. See *Medagro, Pol.*

Uriach, Singapore. See *IDS, Singapore.*

Uriach, Spain. Uriach, Avdaa. Cami Real 51-57, Pol. Industrial Riera de Caldes, Palau-Solita i Plegamans, 08184 Barcelona, Spain.
url: www.uriach.com

Uriach Aquilea OTC, Spain. See *Uriach, Spain.*

Uriage, Fr. Laboratoires Dermatologiques Uriage, 98 av de la Republique, 92400 Courbevoie, France.
url: www.labo-uriage.com

URL, USA. United Research Laboratories, 1100 Orthodox St, Philadelphia, PA 19124, USA.
url: www.urlmutual.com

Urocor, USA. See *Labcorp, USA.*

URPAC, Fr. See *Beaufour, Fr.*

Ursapharm, Belg. See *Ursapharm, Neth.*

Ursapharm, Cz. Ursapharm sro, Hradešín - skladový areál, 281 72 Přišimasy, Czech Republic.

Ursapharm, Ger. Ursapharm Arzneimittel GmbH & Co. KG, Industriestr., 66129 Saarbrucken, Germany.
url: www.ursapharm.de

Ursapharm, Israel. See *Kivema, Israel.*

Ursapharm, Malaysia. See *Pharmaforte, Malaysia.*

Ursapharm, Neth. Ursapharm Benelux BV, Postbus 376, 3770 AJ Barneveld, Netherlands.
url: www.ursapharm.nl

Ursapharm, Pol. Ursapharm Arzneimittel, Farm-Production Adam Członkowski, ul. Żywiczna 7, 05-092 Łomianki, Poland.
url: www.ursapharm.de

Ursapharm, Rus. See *Santen, Rus.*

Ursapharm, Switz. Ursapharm Schweiz GmbH, Froheimstrasse 2, 9325 Roggwill, Switzerland.

US Bioscience, USA. US Bioscience Inc., 26111 Miles Rd, Cleveland, OH 44128, USA.
url: www.usbio.com

US Food & Pharmaceuticals, USA. US Food & Pharmaceuticals, 313 West Beltline Highway, Suite 184, Madison, WI 53713, USA.

US Pharmaceutical, USA. US Pharmaceutical Corp., 2401-C Mellon Court, Decatur, GA 30035, USA.
url: www.uspharmaceuticalcorp.com

US Pharmacia, Pol. US Pharmacia Sp. zo.o., ul. Puławska 435 A, 02-801 Warsaw, Poland.
url: www.usp.pl

US Summit, Hong Kong. U.S. Summit Co. Ltd, Unit A, 32/F, Manulife Tower, 169 Electric Rd, North Point, Hong Kong.
url: www.ussummit.com.hk

US Summit, Thai. US Summit Corp (Overseas), 52/184 Sukhapibai 3 Rd, Huamark, Bangkapi, Bangkok 10240, Thailand.

US Surgical, USA. Unites States Surgical Corp., 150 Glover Ave, Norwalk, CT06856, USA.
url: www.ussurg.com

Usana, Canad. See *USANA, USA.*

Usana, Hong Kong. Usana Hong Kong Ltd, Unit 2504-06, 25/F, World Trade Centre, 280 Gloucester Rd, Causeway Bay, Hong Kong.

Usana, Malaysia. Usana Health Sciences (UHS) Essential Health (Malaysia) Sdn Bhd, M.01 & M.02 Menara Axis, 2 Jln 51A/223, 46100 Petaling Jaya, Selangor, Malaysia.
url: www.usana.com

Usana, Mex. Usana México SA de CV, Blvd Manuel Avila Camacho 138 Piso 3 Lo, 11000 Lomas de Chapultepec, Mexico.

Usana, Singapore. Usana, Singapore.

USANA, USA. USANA, Inc., 3838 West Parkway Blvd, Salt Lake City, UT 84120, USA.
url: www.usana.com

USB, Pol. See *Schering-Plough, Pol.*

USV, India. USV Ltd, B.S. Devshi Marg, Govandi, Mumbai 400 088, India.
url: www.usvindia.com

USV, Israel. See *Mediline, Israel.*

USV, Singapore. See *Zyfas, Singapore.*

Utandningstester, Denm. See *Utandningstester, Swed.*

Utandningstester, Swed. Utandningstester i Sverige AB, Södra vägen 53, 412 54 Göteborg, Sweden.
url: www.utandningstester.se

Utopian, Thai. Utopian Co. Ltd, 602 Moo 3, Teparak Rd, Muang, Samuthprakarn 10270, Thailand.

Uzdrowisko Ciechocinek, Pol. Przedsiębiorstwo Uzdrowisko Ciechocinek SA, ul. Kościuszki 10, 87-720 Ciechocinek, Poland.

V & V, Thai. V & V Bangkok, 94/7 Soi Yimprakrob, Ngamwongwan, Nonthaburi, Thailand.

VAAS, Ital. VAAS S.r.l., Via Siena 268, 47032 Capocolle di Bertinoro (FO), Italy.

Vaccina, S.Afr. Vaccina CC, P.O. Box 75804, Gardenview 2047, South Africa.

Vaillant, Ital. Laboratori Italiani Vaillant S.r.l., Via Cavalieri V. Veneto 241, 21040 Cislago (VA), Italy.

Vakcina, Hung. Vakcina Kft, Rákóczi u 64, 3636 Sajógalgóc, Hungary.

Valda, Ital. See *GSK Consumer, Ital.*

Valdecasas, Mex. Laboratorios Valdecasas S.A., Av. Insurgentes Sur No. 4058, Deleg. Tlalpan, 14430 Mexico D.F., Mexico.

Valeant, Arg. Valeant Argentina SA, Av. Int. Tomkinson 2054, 1642 San Isidro, Argentina.

Valeant, Austral. See *ICN, Austral.*

Valeant, Braz. Valeant Farmacêutica do Brasil Ltda, Rua Geraldo Flausino Gomes 61, 10 andar, 04575-060 São Paulo, Brazil.

Valeant, Canad. Valeant Canada Ltd, 4787 rue Lévy, Montreal, Quebec, H4R 2P9, Canada.

Valeant, Cz. Valeant Czech Pharma sro, Truhlářská 1104/13 1103/15, 110 00 Praha 1, Czech Republic.

Valeant, Denm. See *Medilink, Denm.*

Valeant, Fin. See *Medilink, Denm.*

Valeant, Ger. Valeant Pharmaceuticals Germany GmbH, Düsseldorfer Str. 40 A, 65760 Eschborn, Germany.
url: www.valeant.com

Valeant, Gr. Valeant, Greece.

Valeant, Hong Kong. See *IDS, Hong Kong.*

Valeant, Hung. Valeant Pharma Magyarország Kft, Csatárka út 82-84, 1025 Budapest, Hungary.
url: www.valeant.com

Valeant, Indon. See *Combiphar, Indon.*

Valeant, Irl. See *Allphar, Irl.*

Valeant, Malaysia. See *IDS, Malaysia.*

Valeant, Mex. Valeant Pharmaceuticals Inter., SA de VC, Blvd Avila Camacho 40 P.20 T Esmeralda, 11000 Lomas de Chapultepec, Mexico.

Valeant, Neth. See *Valeant, UK.*

Valeant, Philipp. Valeant Pharmaceuticals (Philippines) Inc., Unit 1901-B West Tower, Tektite Bldg, Phil. Stock Exchange Rd, Ortigas Ctr, Pasig City, Philippines.

Valeant, Pol. See *ICN, Pol.*

Valeant, Port. See *Valeant, Spain.*

Valeant, Rus. Valeant Pharmaceuticals International, 1st Tverskaya-Vamskaya, 23, Building 1, Parus Business Center, Moscow, Russia.
url: www.valeant.com

Valeant, Singapore. See *JDH, Singapore.*

Valeant, Spain. Valeant Pharmaceuticals Iberica S.A., Muntaner 239-253, Atico, Barcelona, Spain.
url: www.valeant.com

Valeant, Switz. Valeant Pharmaceuticals Switzerland GmbH, Ruhrbergstrasse 21, 4127 Birsfelden, Switzerland.
url: www.valeant.com

Valeant, UK. Valeant Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire, RG24 8WG, UK.
url: www.valeant.com

Valeant, USA. Valeant Pharmaceuticals Inc., 3300 Hyland Drive, Costa Mesa, CA 92626, USA.
url: www.valeant.com

Valeas, Cz. See *Valeas, Ital.*

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Valens, Ital. Farma Valens S.r.l., Via Passopomo 5, 95101 Snata Venerina (CT), Italy.

Valeo, Canad. Valeo Pharma Inc., 16 667 Hymus Blvd, Kirkland, Quebec, H9H 4R9, Canada.

Valeras, USA. Valeras, USA.

Valetudo, Ital. Valetudo Divisione Biogena Srl, Via Ghiaie 6, 24030 Presezzo (BG), Italy.

Validus, USA. Validus Pharmaceuticals Inc., 2001 Route 46 East, Suite 310, Parsippany, NJ 07054, USA.
url: www.validuspharma.com

Valio, Fin. Valio Oy, Meijeritie 6, PL 10, 00039 Valio, Finland.

Valma, Chile. Laboratorio Valma Ltda, Miguel de Atero 2883, Santiago, Chile.

ValMed, USA. ValMed Inc., 15280 NW 79th Court, Suite 109, First Floor, Miami Lakes, FL 33016, USA.
url: www.valmed.com

Valmor, Venez. Laboratorios Valmor C.A., Av. Fco. de Miranda, Edif. Easo Torre Norte P.1 Of. E, El Rosal, Caracas, Venezuela.
url: www.valmorca.com.ve

Valomed, Spain. See *Italfarmaco, Spain.*

Valuge, Arg. Valuge S.A., Cuyo 2870, 1640 Martinez, Buenos Aires, Argentina.

Vamsler, Philipp. Vamsler Phils Inc., 141 Scout de Guia St, Quezon City, Philippines.

Vana, Thai. Vana Corp Ltd, 2038 Sukhumvit Rd, Bangkok 10260, Thailand.
url: www.atlantic-lab.com

Vanden Bogaerde, Belg. Vanden Bogaerde SA, Avenue de l'Araucaria 34/2-3, 1020 Brussels, Belgium.

Vangard, USA. Vangard Labs Inc., P.O. Box 1268, Glasgow, KY 42142-1268, USA.

Vannier, Arg. Lab. Vannier S.A., H. Irigoyen 2321 5to Piso, 1089 Buenos Aires, Argentina.

Vantone, Hong Kong. Vantone Medical Supplies Co. Ltd, Flat J, 10/F International Industrial Ctr, 2-8 Kwei Tei St, Fotan, N.T., Hong Kong.

Vardhaman, India. Vardhaman Remedies Pvt Ltd, Plot No J-102, MIDC Industrial Area, Boisar, Thane 401 506, India.

Vargas, Venez. Laboratorios Vargas S.A., Las Piedras a Puente Restaurador, Edif. Vargas, Caracas, Venezuela.

Varifarma, Arg. Lab. Varifarma S.A., Ernesto de las Carreras 2469, 1643 Beccar, Buenos Aires, Argentina.

Varipharm, Ger. See *MSD, Ger.*

Vatring, USA. Vatring Pharmaceuticals, 225 North 11th St, Wytheville, VA 24382, USA.
url: www.vatring.net

Vaxines, Philipp. Vaxines Trading Inc., Blk 13, Lot 3B M Consing St, BF Resort Vill, Talon 2, Las Piñas City, Philippines.

Vebas, Ital. Vebas S.r.l., Via Benaco 1/3, 20098 San Giuliano Milanese (MI), Italy.

Vecchi, Malaysia. See *Zyfas, Malaysia.*

Vectem, Spain. Vectem, Wagner 22, Pol Ind Can Jardi, Rubi, 08191 Barcelona, Spain.
url: www.vectem.com

Veda, Fr. See *Zambon, Fr.*

Vedim, Fr. Laboratoires Vedim Pharma, 7 rue Diderot, 92003 Nanterre, France.

Vedim, Ger. See *UCB, Ger.*

Vedim, Pol. See *UCB, Pol.*

Vedim, Port. Vedim Pharma, Lda, Rua Carlos Calisto 4-B, 1400-043 Lisbon, Portugal.

Vedim, Spain. See *UCB, Spain.*

Vegal, Spain. Vegal Farmaceutica, Tramontana 44, Pozuelo de Alarcon, 28223 Madrid, Spain.

Vegebom, Fr. Laboratoires Vegebom SA, 174 quai de Jemmapes, 75010 Paris, France.
url: www.vegebom.com

Vegetal, Ital. Vegetal Progress S.r.l., Località Novero 8, 10070 Devesi di Cirie (TO), Italy.
url: www.vegetal-progress.it

Veinfar, Arg. Veinfar, Esp. Medicinales Larjan, Av. Piedrabuena 4190, 1439 Buenos Aires, Argentina.
url: www.veinfar.com.ar

Velin, Denm. Velin-Pharma A/S, 66 Kongevejen, 3480 Fredensborg, Denmark.

Velin, Neth. See *Velin, Denm.*

Velka, Gr. Velka Hellas A.E., 12 Korinthou Str., 154 51 N. Psychiko, Greece.

Veltipharm, Gr. Veltipharm, Deligiorgi 55-59, 104 37 Athens, Greece.

Vemedia, Belg. ABC Chemicals Vemedia, Parc Industriel 19, 1440 Wauthier-Braine, Belgium.
url: www.abc-chemicals.com

Vemedia, Neth. See *Solvay, Neth.*

Vendiz, Philipp. vendiz Pharmaceuticals Inc., 116 Esteban Abada St, Loyola Heights, Quezon City, Philippines.

Vent-3, Arg. Lab. Vent-3 SRL, Juan D. Jufre 4820, 5014 Secc. 4a Bo. Jose I Diaz, Cordoba, Argentina.

Ventaglio, Chile. Laboratorios Ventaglio LTDA, Tobalaba 155 Of. 1001, Providencia, Santiago, Chile.

Ventiv, Hung. Ventiv Health Magyarország Kft, Hovat u 14-24, 1027 Budapest, Hungary.

Veracity, USA. Veracity Pharmaceuticals Inc., 6601 Lyons Rd, Coconut Creek, FL 33073, USA.
url: www.veracitypharma.com

Veresne, Arg. Veresne SA, Santiago del Estero 286 Piso 3 Of. 2, 1075 Buenos Aires, Argentina.

Verheilen, Philipp. See *PrimeDrug, Philipp.*

Veripalvelu, Fin. Suomen Punainen Risti Veripalvelu, Kivihaantie 7, 00310 Helsinki, Finland.
url: www.veripalvelu.redcross.fi

Verisfield, Gr. Verisfield (UK) Ltd, 14 Kerassountos Str, GR-115 28 Athens, Greece.
url: www.verisfield.gr

Verla, Ger. Verla-Pharm, Arzneimittelfabrik, Apotheker H.J.v. Ehrlich GmbH & Co. KG, Hauptstr. 98, 82327 Tutzing, Germany.
url: www.verla.de

Verla, Hung. See *Verla, Ger.*

Verla, Switz. See *Biomed, Switz.*

Verman, Fin. Oy Verman AB, Vanhankyläntie 44 B, PL 152, 04401 Järvenpää, Finland.
url: www.verman.fi

Veron, Ger. Veron Pharma Vertriebs-GmbH, Neuweg 30, 67697 Otterberg, Germany.
url: www.veronpharma.de

Veropharm, Rus. Veropharm ZAO, Bolshaya Pochtovaya ul. 36, 105082 Moscow, Russia.
url: www.veropharm.ru

Versapharm, USA. VersaPharm Inc., 1775 West Oak Parkway, Suite 800, Marietta, GA 30062-2260, USA.
url: www.versapharm.com

Vertical, USA. Vertical Pharmaceuticals Inc., 3 Kellogg Court, Suite 19, Edison, NJ 08817, USA.
url: www.verticalpharma.com

Verum, USA. See *Victory, USA.*

Vesale, Belg. Vesale, Belgium.

Vesco, Thai. See *TC Pharma-Chem, Thai.*

Vetco, USA. Vetco Pharmaceuticals, 105 Baylis Rd, Second Floor, Melville, NY 11747-1155, USA.

Vezedes, Fr. Vézédès Sarl, 9 quai de Rotterdam, 68110 Illzach, France.

VHB, India. VHB Pharmaceuticals Pvt Ltd, 40-B/1 Shankar Smruti, Sir Bhalchandra Rd, Dadar (E), Mumbai 400 014, India.
url: www.vhbgroup.com

Viamedica, Spain. Viamedica, Po de Recoletos 19, 28001 Madrid, Spain.

Vianex (Βιανεξ), Gr. Vianex S.A., Tatoiou Str., 18th Km Lamia National Rd, 146 10 Nea Erythrea, Greece.
url: www.vianex.gr

Viatria, Swed. Viatria AB, Kemistvägen 17, 183 79 Täby, Sweden.

Viatris, Austria. Viatris Pharma GmbH, Liesinger Flur-Gasse 2C, A-1230 Vienna, Austria.
url: www.viatris.at

Viatris, Belg. Viatris SA/NV, Chaussee de la Hulpe 166, Terhulpsesteenweg, 1000 Brussels, Belgium.
url: www.viatris.be

Viatris, Cz. See *Meda, Cz.*

Viatris, Denm. See *AstraZeneca, Denm.*
Viatris, Fr. Viatris, Av J.F. Kennedy, 33701 Mérignac cdx, France.
url: www.viatris.fr
Viatris, Ger. VIATRIS GmbH & Co. KG, Weismullerstr. 45, 60314 Frankfurt a.M., Germany.
url: www.viatris.de
Viatris, Gr. See *Meda, Swed.*
Viatris, Hong Kong. See *Health Vision, Hong Kong.*
Viatris, Hung. See *Meda, Hung.*
Viatris, Ital. Viatris S.p.A., Viale Brenta 18, 20139 Milan, Italy.
url: www.viatris.com
Viatris, Neth. Viatris BV, Verrijn Stuartweg 60, 1112 AX Diemen, Netherlands.
url: www.viatris.nl
Viatris, Norw. See *Santen, Norw.*
Viatris, Pol. See *Pliva Krakow, Pol.*
Viatris, Port. Viatris Farmacêutica SA, Rua do Centro Cultural 13, 1749-066 Lisbon, Portugal.
url: www.viatris.pt
Viatris, Rus. See *Pliva, Rus.*
Viatris, Spain. Viatris Pharmaceuticals S.A.U., Avenida de Castilla 2, Edificio Berlmn - 2a Planta, San Fernando de Henares, 28830 Madrid, Spain.
url: www.viatris.com
Viatris, Switz. VIATRIS GmbH, Hegnaustrasse 60, 8602 Wangen, Switzerland.
url: www.viatris.ch
Viatris, UK. See *Meda, UK.*
Vican, Gr. Vican, Ermou 1, 144 52 Metamorfosi, Greece.
Vichy, Canad. See *L'Oreal, Canad.*
Vichy, Fr. Laboratoires Vichy, Cosmétique Active France, Le Doublon, bat A, 11 av. Dubonnet, 92407 Courbevoie cdx, France.
url: www.vichy.fr
Vichy, USA. Vichy LLC, Fifth Ave, New York, NY10017, USA.
url: www.vichy.com
Vicis, Hung. Vicis Pharma Kft, Kapás u 11-15, Buda Business Center, 1027 Budapest, Hungary.
Vickmans, Hong Kong. Vickmans Laboratories Ltd, 2/F China Trade Cyr, 122-124 Wai Yip St, Kwun Tong, Kowloon, Hong Kong.
Victory, USA. Victory Pharmaceuticals, 12707 High Bluff Drive, Suite 200, San Diego, CA 92130, USA.
Victus, Venez. Victus de Venezuela C.A., Av Fco de Miranda, Ctro de Seguros La Paz, Piso 3, Ala Oeste Boleita Sur, Caracas, Venezuela.
Vida, Hong Kong. Vida Laboratories Ltd, Unit 919 Vanta Industrial Ctr, 21 Tai Lin Pai Rd, Kwai Chung, N.T., Hong Kong.
url: www.vidalab.com
Vida, Port. See *Atral, Port.*
Vieira, Port. Raul Vieira, Lda, Rua dos Correeiros 41, 1100 Lisbon, Portugal.
Vifor, Cz. See *Vifor, Switz.*
Vifor, Denm. See *Renapharma, Swed.*
Vifor, Fin. See *Sairaalapalvelu, Fin.*
Vifor, Hong Kong. See *Hong Kong Medical, Hong Kong.*
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Vifor, Port. See *Ferraz, Lynce, Port.,* and *Confar, Port.*
Vifor, Singapore. See *Baxter, Singapore.*
Vifor, Switz. Vifor SA, Route de Moncor 10, 1752 Villars-sur-Glâne, Switzerland.
url: www.vifor.ch
Vifor, Thai. See *Diethelm, Thai.*
Vifor International, Switz. Vifor (International) AG, Pharmazeutische Spezialitäten, Rechenstrasse 37, Postfach, 9001 St Gallen, Switzerland.
url: www.vifor.com
Vilar, Rus. Farm Vilar ZAO, Grina ul. 7, 117216 Moscow, Russia.
url: www.farmvilar.ru
Vilco, Gr. Vilco S.A., 11-15 Aristotelous Str., 104 32 Athens, Greece.
url: www.vilco.gr
Vinas, Spain. Viñas, Provenza 386, 08025 Barcelona, Spain.
Vincenti, Venez. Laboratorios Vincenti C.A., Urb. Industrial Santa Cruz, Calle Roma, Edif., Centro Proa, Piso 2 Guarenas, Caracas, Venezuela.
url: www.vincentilab.com
Vinci, Spain. See *Pfizer, Spain.*
Vindex, USA. Vindex Pharmaceuticals, Cordova, TN 38088, USA.
url: www.vindexpharm.com
Vingmed, Norw. Vingmed AS, Fjordv. 1, Postboks 374, 1363 Hovik, Norway.
url: www.vitaline.com
Viofar, Gr. Viofar E.P.E, Ethn. Antistaseos and triphilias 76A, 136 71 Acharnai, Greece.
Vioser, Gr. Vioser A.E., Kanari 5, 141 22 N. Heraklion, Greece.
url: www.bioser.gr
Vipharm, Pol. Vipharm SA, ul. Przewoźników 11, 03-691 Warsaw, Poland.
url: www.vipharm.pl
Vir, Spain. Industria Química Farmaceutica Vir, Laguna 42-44, Pol In Urtinsa II, Alcorcon, 28923 Madrid, Spain.
Viranative, Swed. ViraNative AB, Box 7979, 907 19 Umea, Sweden.
Virco, Canad. Virco Pharmaceuticals (Canada) Co., 30 St Clair Ave W, Suite 400, Toronto, Ontario, M4V 3A1, Canada.
Virgo, Philipp. Virgo Pharmaceutical Lab, Virgo Bldg, 270 N S Amoranto Ave, Sta Mesa Hts, Quezon City, Philippines.
ViroPharma, USA. ViroPharma Inc., 397 Eagleview Blvd, Exton, PA 19341, USA.
url: www.viropharma.com
Vis, Pol. Zakłady Chemiczno-Farmaceutyczne Visz Sp. zo.o., ul. Krawiecka 3, 41-902 Bytom, Poland.
url: www.vis-farm.pl
Visfarm, Spain. See *Novartis, Spain.*
Vision, Canad. See *Vision, USA.*
Vision, USA. Vision Pharmaceuticals Inc., Mitchell, SD 57301, USA.
url: www.visionpharm.com
Visiontech, Arg. Visiontech, Division Oftalmologica de Latinmarket SA, Moreno 1401/05, 1093 Buenos Aires, Argentina.
Vistakon, USA. Vistakon Pharmaceuticals LLC,
url: www.vistakonpharmaceutical.com
Vistapharm, USA. VistaPharm, 2224 Cahaba Valley Drive, Suite B3, Birmingham, AL 35242, USA.
url: www.vistapharm.com
Visufarma, Ital. Visufarma S.r.l., Via Canino 21, 00191 Rome, Italy.
Vita, Ital. See *Sanofi Synthelabo OTC, Ital.*
Vita, Port. See *Vita, Spain.*
Vita, Spain. Grupo Vita/Vita Cientifica S.L., Avda de Barcelona 69, Sant Juan Despi, 08970 Barcelona, Spain.
url: www.grupovita.es
Vita, Venez. Laboratorios Vita, Av.Principal Mari Perez, Edif. Vita, Mari Perez Caracas, Caracas, Venezuela.
Vita Green, Hong Kong. Vita Green Health Products Co Ltd, Rm 1005 Manning House, 48 Queens Rd Central, Hong Kong.
url: www.vitagreen.com
Vita Health, Canad. Vita Health Products Inc., 150 Beghin Ave, Winnipeg, Manitoba, R2J 3W2, Canada.
url: www.vitahealth.ca
Vita Health, Malaysia. See *Medispec, Malaysia,* and *Zuellig, Malaysia.*
Vita Health, Singapore. Vita Health Laboratories Pte Ltd, 371 Beach Rd, Keypoint 20-01/07, S 199597, Singapore.
Vita Health, Switz. Vita Health Care AG, 3177 Laupen, Switzerland.
Vita Healthcare, UK. Vita Healthcare Ltd, Palladium House, 1-4 Argyll St, London, W1V 2LD, UK.
Vita Pharm, Canad. Vita Pharm Canada Ltd, 2835 Kew Dr., Windsor, Ontario, N8T 3B7, Canada.
Vitabalans, Cz. See *Vitabalans, Fin.*
Vitabalans, Fin. Vitabalans Oy, Varastokatu 8, 13500 Hämeenlinna, Finland.
url: www.vitabalans.fi
Vitabalans, Hung. See *Vitabalans, Fin.*
Vitabiotics, Cz. See *Vitabiotics, UK.*
Vitabiotics, Hong Kong. See *Mekim, Hong Kong.*
Vitabiotics, Hung. Vitabiotics, Hungary.
Vitabiotics, Indon. Vitabiotics Utama Indonesia PT, Jl Pemuda No 44, 13220 Jakarta Timur, DKI Jaya, Indonesia.
Vitabiotics, Irl. See *Allphar, Irl.*
Vitabiotics, Philipp. See *Endure, Philipp.*
Vitabiotics, UK. Vitabiotics Ltd, 1 Apsley Way, London, NW2 7HF, UK.
url: www.vitabiotics.com
Vitae, Mex. Vitae Laboratorios S.A. de C.V., Euclides No. 3214, Fracc. Vallarta San Jorge, 44690 Guadalajara, Jalisco, Mexico.
Vitafarma, Spain. Vitafarma, C/Florida 29, Hernani, 20120 Guipuzcoa, Spain.
url: www.vitafarma.es
Vitaflo, Denm. Vitaflo Scandinavia AB, Boks 144, 3400 Hillerød, Denmark.
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Vitaflo, Irl. See *Allphar, Irl.*
Vitaflo, Norw. Vitaflo Norge, Carl Kjelsensv. 38, 0874 Oslo, Norway.
Vitaflo, Swed. Vitaflo Scandinavia AB, Box 53063, 400 14 Göteborg, Sweden.
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Vitaflo, UK. Vitaflo Ltd, 11 Century Building, Brunswick Business Park, Liverpool, Merseyside, L3 4BL, UK.
url: www.vitaflo.co.uk
Vitaglow, Austral. See *Blackmores, Austral.*
Vitalia, UK. Vitalia Health Ltd, P.O. Box 2492, Marlow, Buckinghamshire, SL7 2WW, UK.
url: www.vitalia-health.co.uk
Vitaline, Fin. See *Sairaalapalvelu, Fin.*
Vitaline, Irl. See *Vitaline, UK.*
Vitaline, Norw. See *Vingmed, Norw.*
Vitaline, Swed. Vitaline Scandinavia AB, Box 938, 751 09 Uppsala, Sweden.
Vitaline, UK. Vitaline Pharmaceuticals UK Ltd, 8 Ridge Way, Drakes Drive, Crendon Business Park, Long Crendon, Buckinghamshire, HP18 9BF, UK.
Vitaline, USA. Vitaline Corp., 9 Monroe Parkway, Suite 250, Lake Oswego, OR 97035, USA.
url: www.vitaline.com
Vitalink, Philipp. Vitalink Health Products Inc., 103 Scout de Guia, cor Tomas Morato Ave, Quezon City, Philippines.
Vitality, Canad. Vitality Products Inc., 8585 123rd St, Surrey, British Colombia, V3W 6E2, Canada.
Vitality, USA. See *Pamlab, USA.*
Vitalpharma, Belg. Vitalpharma SA, Drie bomenstraat 16, 1180 Brussels, Belgium.
Vitamed, Israel. Vitamed Ltd, P.O. Box 114, Binyamina 30550, Israel.
Vitamed, Pol. Hurtownia Farmaceutyczna Vitamed, ul. Ostrowskiego 24, 97-213 Smardzewice, Poland.
Vitamed, Turk. Vitamed, Turkey.
Vitamedica, Irl. Vitamedica Europe Ltd, Unit 34, 11 Dublin, Ireland.
Vitamedica, Neth. See *Vitamedica, Irl.*
Vitamex, Pol. See *Ferrosan, Pol.*
Vitapan, Braz. Vitapan Indústria Farmacêutica Ltda, Rua VPR 01 Qd. 2-A-Mod.1 DAIA, 75133600 Anapolis, Goias, Brazil.
Vitaplex, Austral. Vitaplex Products, P.O. Box 270, Gymea, NSW 2227, Australia.
Vitaresearch, Ger. Vitaresearch, Dynamostr. 13, 68165 Mannheim, Germany.
url: www.vitaresearch.com
Vitarum, Arg. Vitarum, Ayacucho 153, Piso 1 B, 5000 Cordoba, Argentina.
Vitasan, Austria. Vitasan GmbH, Teichweg 2, A-5400 Hallein, Austria.
Vitelle, Austral. See *Mayne, Austral.*
Viternat, Braz. Viternat Laboratórios Ltda, Av Dr Luis Arrobas Martins 759, 04781-001 São Paulo, SP, Brazil.
Vitorgan, Ger. vitOrgan Arzneimittel GmbH, Brunnweisenstr. 21, 73760 Ostfildern, Germany.
url: www.vitorgan.de
Vitoria, Port. Laboratórios Vitória, SA, Rua Elias Garcia 28, Venda Nova, 2700-327 Amadora, Portugal.
Vitrolife, Swed. Vitrolife AB, Mölndalsvägen 30, 412 63 Göteborg, Sweden.
url: www.vitrolife.com
Vivalife, Port. Vivalife Laboratórios Lda, Rotunda Nuno R. Santos, 2685 Portela de Sacavim, Portugal.
Vivance, Fr. Vivance SA, La maison blanche, 71570 Romaneche-Thorins, France.
url: www.punchpower.com
Vivax, Cz. Vivax, Czech Republic.
Vivax, Venez. Vivax Pharmaceuticals, Final calle Vargas Torre Este, Piso 2 Ed.Ctro.Berimer, Urb. Boleita Norte, Caracas, Venezuela.
Vivax Colmed, Venez. See *Vivax, Venez.*
Vivax Gynopharm, Venez. See *Vivax, Venez.*
Vivax Optipharm, Venez. See *Vivax, Venez.*
Viviar, Spain. Viviar, Pol Ind Pista de Ademuz, Autov Valencia-Liria Km 9.4, Paterna, 46980 Valencia, Spain.
Vivipharma, Ital. Vivipharma SA, Via Guardia del Consiglio 15, 47891 Galazzano (RSM), San Marino, Italy.
url: www.vivipharma.com
Vivus, USA. Vivus Inc, 1172 Castro St, Mountain View, CA 94040, USA.
url: www.vivus.com
Vizcarra, Philipp. Vizcarra Pharmaceutical Inc., Segundina Bldg, 464 United Nations Ave, Ermita, Manila, Philippines.
Vocate, Gr. Vocate A.E., Gounari 150, 166 74 Glyfada, Greece.
url: www.vocate.gr
Voco, Cz. See *Voco, Ger.*
Voco, Denm. See *Voco, Ger.*
Voco, Ger. Voco GmbH, Postfach: 767, 27457 Cuxhaven, Germany.
url: www.voco.de
Voco, Pol. See *Voco, Ger.*
Voigt, Switz. Voigt Industrie Services AG, Hofstrasse 50, 8590 Romanshorn 1, Switzerland.
Volchem, Ital. Volchem Srl, Via E Dandolo 14, 35010 Grossa di Gazzo (PD), Italy.
url: www.volchem.com
Volta, Chile. Laboratorio Volta Ltda, Jose Miguel Carrera 14-A Complejo Ind., Los Libertadores Colina, Santiago, Chile.
Vomelin, Hung. Vomelin Bt, Róna u 103/b, 1149 Budapest, Hungary.
Vonnace, Philipp. Vonnace Pharmaceuticals Corp, 2/F Teresa Bldg 15th Ave, Murphy, Cubao, Quezon City, Philippines.
Vortech, USA. Vortech Pharmaceuticals, 6851 Chase Rd, Dearborn, MI 48126, USA.
Voyage, Fr. Laboratoires Pharma Voyage, 29 av. de la Gare, 78310 Coignières, France.
VP, Spain. VP Pharma Baru, Valle de Tobalina Nave 3, 16 Madrid, Spain.
Vramed, Rus. See *Sopharma, Rus.*
VRI BioMedical, Austral. VRI BioMedical Ltd, Suite G9, 1 Central Ave, Australian Technology Park, Eveleigh, NSW 1430, Australia.
url: www.vribiomedical.com.au
VSM, Belg. VSM Belgium, Prins Boudewijnlaan 17 unit 7, 2550 Kontich, Belgium.
url: www.vsm.nl
VSM, Neth. VSM Geneesmiddelen BV, Postbus 9321, 1800 GH Alkmaar, Netherlands.
url: www.vsm.nl
Wabosan, Austria. Wabosan Arzneimittelvertriebs GmbH, Anton Anderer Platz 6, A-1210 Vienna, Austria.
Wagner, Hung. Wagner Pharmafax Kft, Gyógyszer Business Center, Kassai u 56-58/b, 1041 Budapest, Hungary.
Wakamoto, Hong Kong. See *Tai Tong, Hong Kong.*
Wakamoto, Jpn. Wakamoto Pharmaceutical Co. Ltd, 1-5-3 Nihonbashi-Muromachi, Chuo-ku, Tokyo 103-8330, Japan.
url: www.wakamoto-pharm .co.jp
Wakefield, USA. See *Ivax, USA.*
Wala, Ger. Wala Heilmittel GmbH, Bosslerweg 2, 73087 Bad Boll/Eckwalden, Germany.
url: www.walaarzneimittel.de
Wala, Switz. Wala Schweiz GmbH, Waghausgasse 3, 3011 Berne, Switzerland.
Waldheim, Austria. See *Sanochemia, Austria.*
Walker, Arg. Laboratorio Walker S.R.L., E. Zeballos 249, 2000 Rosario, Santa Fe, Argentina.
url: www.laboratoriowalker.com.ar
Walker Pharmacal, USA. Walker Pharmacal, 4200 Laclede Ave, St Louis, MO 63108, USA.
Wallace, India. Wallace Pharmaceuticals Ltd, 101/2 Floral Deck Plaza, Off Central MIDC Rd, Andheri (East), Mumbai 400 093, India.
url: www.wallacepharma.net
Wallace, USA. See *Carter-Wallace, USA.*
Wallace Mfg Chem., UK. See *Alinter, UK.*
Wallis, UK. Wallis Laboratory, Laporte Way, Luton, Bedfordshire, LU4 8WL, UK.
Walmark, Cz. Walmark a.s., Oldrichovice 44, Trinec, Czech Republic.
Walsh, USA. Walsh Dohmen, USA.
Wampole, Canad. Wampole Brands Inc., 5950 Cote-de-Liesse, Montreal, Quebec, H4T 1E2, Canada.
Wampole, USA. Wampole Laboratories, 2 Research Way, Princeton, NJ 08540, USA.
url: www.wampolelabs.com
Wandel, Mex. Farmacéutica Wandel SA de CV, Conkal MZ 391 Lt 1, 14200 Tlalpan Ejidos de Padierna, Mexico.
Wander, India. Wander Ltd, Plot No. 21, Sector-19, Kopri Rd, Vashi, Navi Mumbai 400 703, India.
url: www.wanderonline.com
Wander, Philipp. See *Zuellig, Philipp.*
Wander, Port. Sociedade de Produtos Farmacêuticos Wander Lda, Rua do Centro Empresarial, Edifício 8, Quinta da Beloura, 2710-444 Sintra, Portugal.
Wander Health Care, Switz. Wander AG, Fabrikstrasse 10, 3176 Neuenegg, Switzerland.
url: www.wander.ch
Warner Chilcott, Canad. See *Warner Chilcott, USA.*
Warner Chilcott, USA. Warner Chilcott Laboratories, 100 Enterprise Drive, Rockaway, NJ 07866, USA.
url: www.warnerchilcott.com
Warner-Lambert, Austral. See *Pfizer, Austral.*
Warner-Lambert, Ital. See *Pfizer, Ital.*
Warner-Lambert, Mex. See *Pfizer, Mex.*
Warner-Lambert, USA. See *Pfizer, USA.*
Warner-Wellcome, USA. See *Warner-Lambert, USA.*
Warsaw-Polfa, Rus. Warsaw Pharmaceutical Work Polfa, Kutuzovskii prospekt 13, kv. 84/85, 121248 Moscow, Russia.
Wassen, Ital. Wassen Italia S.r.l., Via Canova 25, 20145 Milan, Italy.
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Wassen, UK. Wassen International Ltd, 14 The Mole Business Park, Leatherhead, Surrey, KT22 7BA, UK.
url: www.wassen.com
Wassermann, Ital. Alfa Wassermann S.p.A., Contrada Sant'Emidio, 65020 Alanno (PE), Italy.
Wassermann, Malaysia. See *Antah, Malaysia, Emerging Pharma, Malaysia,* and *Zyfas, Malaysia.*
Wassermann, Philipp. See *Corbridge, Philipp.*
Watkins, Canad. See *Watkins, USA.*
Watkins, USA. Watkins Inc., 150 Liberty St, Winona, Minnesota, 55987-0570, USA.
Watson, USA. Watson Pharmaceuticals Inc., 311 Bonnie Circle, Corona, CA 91720, USA.
url: www.watsonpharm.com
Waymade, UK. Waymade Healthcare plc, Sovereign House, Miles Gray Rd, Basildon, Essex, SS14 3FR, UK.
url: www.waymadehealthcare.plc.uk
Waymar, Canad. Waymar Pharmaceuticals Inc., 330 Marwood Drive, Unit 4, Oshawa, Ontario, L1H 8B4, Canada.
WE, USA. WE Pharmaceuticals Inc, P.O. Box 1142, Ramona, CA 92065, USA.
url: www.wepharma.com
Wearnes, Malaysia. See *Apex, Malaysia.*
Weber & Weber, Ger. Weber & Weber GmbH & Co. KG, Herrschinger Str. 33, 82266 Inning/Ammersee, Germany.
url: www.weber-weber.de
Wedgewood, USA. Wedgewood Pharmacy, 405 Heron Drive, Suite 200, Swedesboro, NJ 08085, USA.
url: www.wedgewoodpharmacy.com

Weifa, Norw. Weifa AS, Hausmannsg. 6, Postboks 9113 Grönland, 0133 Oslo, Norway.
url: www.weifa.no
Weifa, Thai. See *Harn, Thai.*
Weimer, Thai. See *Schumit, Thai.*
Welcker-Lyster, Canad. See *Ratiopharm, Canad.*
Weleda, Austria. Weleda GmbH & Co. KG, Hosenedelgasse 27, A-1220 Vienna, Austria.
url: www.weleda.at
Weleda, Fr. Laboratoires Weleda, 9 rue Eugene-Jung, 68330 Huningue, France.
url: www.weleda.com
Weleda, Ger. Weleda AG-Heilmittelbetriebe, Mohlerstr. 3-5, 73525 Schwabisch Gmund, Germany.
url: www.weleda.de
Weleda, Neth. Weleda Nederland BV, Platinastraat 161, 2718 SR Zoetermeer, Netherlands.
Weleda, S.Afr. See *Pharma-Natura, S.Afr.*
Weleda, Switz. Weleda AG, Stollenrain 11, 4144 Arlesheim, Switzerland.
url: www.weleda.ch
Weleda, UK. Weleda (UK) Ltd, Heanor Rd, Ilkeston, Derbyshire, DE7 8DR, UK.
url: www.weleda.co.uk
Welfide, Malaysia. See *Antah, Malaysia.*
Welfide, Singapore. See *Alpha Therapeutic, Singapore.*
Wellchem, Malaysia. Syarikat Wellchem Sdn Bdh, 928-929 Jln 17/38, 46400 Petaling Jaya, Selangor, Malaysia.
url: www.wellchem.com
Wellchem, Singapore. Wellchem Pharmaceuticals Pte Ltd, 221 Henderson Rd, 04-15 Henderson Building, S 159557, Singapore.
url: www.wellchem.com
Wellchem, Thai. Wellchem Pharmaceutical Co. Ltd, 99/287-288 Nonsee Rd, Yannawa, Bangkok 10120, Thailand.
Wellcome, Irl. See *GSK, Irl.*
Wellcome, Israel. See *GSK, Israel.*
Wellcome, Port. See *GSK, Port.*
Wellcome, Spain. See *GSK, Spain.*
Wellcome, USA. See *GSK, USA.*
Wellgo, Hong Kong. Wellgo Pharmaceutical Co. Ltd, Unit 03-08, 22/F Millenium City, 378 Kwun Tong Rd, Kwun Tong, Kowloon, Hong Kong.
Wellhealth, Philipp. See *Ad-Drugstel, Philipp.*
Wellmex, Malaysia. Wellmex Sdn Bhd, 23-26 Jln Bidara 1, Taman Bidara, 68100 Batu Caves, Selangor, Malaysia.
Wellpharma, Ital. Wellpharma Srl, Piazza Sempione 5, 20145 Milan (MI), Italy.
Wellspring, Canad. Wellspring Pharmaceuticals Canada Corp., 400 Iroquois Shore Rd, Oakville, Ontario, L6H 1M5, Canada.
url: www.wellspringpharm.com
Wellspring, USA. Wellspring Pharmaceutical Corp., 9040 Town Center Parkway, Suite 205, Bradenton, FL 34202, USA.
url: www.wellspringpharm.com
Welt, Arg. Lab. Welt S.A.I.C., Tronador 3030/2, 1430 Buenos Aires, Argentina.
Welti, Switz. Dr Heinz Welti AG, Althofstrasse 12, 5432 Neuenhof, Switzerland.
Weltrap, Arg. Lab. Weltrap S.A., Balcarce 1072, 2000 Rosario, Santa Fe, Argentina.
Weluga, Hong Kong. mfh12x; mth1k.
Wenig, Austria. Mr J W Wenig GmbH, Van der Nullgasse 22, A-1100 Vienna, Austria.
Wermar, Mex. Wermar Pharmaceuticals SA de CV, Enrique Gonzalez Martinez 200, 6400 Cuauhtemoc Sta. Maria la Ribera, Mexico DF, Mexico.
Wernigerode, Cz. See *Wernigerode, Ger.*
Wernigerode, Ger. Pharma Wernigerode GmbH, Dornbergsweg 35, 38855 Wernigerode/Harz, Germany.
url: www.pharmawernigerode.de
Wernigerode, Rus. See *Queisser, Rus.*
Wescrib, Philipp. Wescrib Co, 2 San Diego St, Canumay, Valenzuela City, Philippines.
Wesley, USA. Wesley Pharmacal Inc., 114 Railroad Drive, Ivyland, PA 18974, USA.
WestCan, Canad. See *Vita Health, Canad.*
West-Coast, Thai. See *Union Medical, Thai.*
Western Medical, USA. Western Medical Supply Inc., USA.
url: www.westernmedicalsupply.com
Westlake, USA. Westlake Laboratories Inc., 24700 Center Ridge Rd, Cleveland, OH 44145, USA.
url: www.westlake-labs.com
Westmont, Hong Kong. See *Unam, Hong Kong.*
Westmont, Indon. See *Westmont, Philipp.*
Westmont, Malaysia. See *Unam, Malaysia.*
Westmont, Philipp. Westmont Pharmaceuticals Inc., 4/F Bonaventura Plaza, Ortigas Ave, Greenhills, San Juan, Metro Manila, Philippines.
Westmont, Singapore. See *Far East, Singapore.*
Westmont, Thai. See *Olic, Thai.*
Weston, Hong Kong. Weston Pharmaceutical Ltd, Unit 26, 8/F Tower A, Southmark, 11 Yip Hing St, Wong Chuk Hang, Hong Kong.
Westward, USA. West-Ward Pharmaceutical Corp., 465 Industrial Way West, Eatontown, NJ 07724, USA.
Westwood, USA. See *BMS, USA.*
Westwood-Squibb, Canad. See *BMS, Canad.*
Westwood-Squibb, USA. See *BMS, USA.*

Whelehan, Irl. Whelehan Group, T.P. Whelehan, 3 Northern Cross Business Park, Finglas, Dublin 11, Ireland.
url: www.tpwhelehan.ie
White, Arg. White Pharma S.A., Av. San Martmn 1750, 1602, Florida, Buenos Aires, Argentina.
Whitehall, Austral. Whitehall Laboratories Australia P/L, Private Mailbag 1, Punchbowl, NSW 2196, Australia.
Whitehall, Braz. See *Wyeth, Braz.*
Whitehall, Fr. Whitehall, 80 av du Général-de-Gaulle, 92031 Paris-La Défense cdx, France.
Whitehall, Irl. See *Wyeth, Irl.*
Whitehall, Israel. See *Neopharm, Israel.*
Whitehall, Ital. Whitehall Italia S.p.A., Via Puccini 3, 20121 Milan, Italy.
Whitehall, NZ. Whitehall, P.O. Box 12736, Penrose, Auckland, New Zealand.
Whitehall, Pol. See *Wyeth, Pol.*
Whitehall, Thai. Whitehall Thailand, 23 Fl, Silom Complex Building, 191 Silom Rd, Bangkok 10500, Thailand.
Whitehall, USA. See *Wyeth Consumer, USA.*
Whitehall Consumer, Austral. Whitehall Consumer Healthcare Pty Ltd, 17-19 Solent Circuit, Norwest Business Park, Baulkham Hills, NSW 2153, Australia.
Whitehall Consumer, NZ. See *Whitehall, NZ.*
Whitehall-Much, Ger. Whitehall-Much GmbH, Regina-Protmann-Str. 16, 48159 Münster, Germany.
url: www.whitehall-much.de
Whitehall-Robins, Canad. Whitehall-Robins Inc., 5975 Whittle Rd, Mississauga, Ontario, L4Z 3M6, Canada.
Whitehall-Robins, Switz. Whitehall-Robins AG, Grafenauweg 10, 6301 Zug 7, Switzerland.
Whitehall-Robins, USA. See *Wyeth Consumer, USA.*
WI Pharma, Hung. WI Pharma Kft, Miskolci u 50, 1147 Budapest, Hungary.
Wick, Ger. Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Sulzbacher Str. 40, 65824 Schwalbach, Germany.
url: www.wickpharma.de
Widatra Bhakti, Indon. Widatra Bhakti PT, Wisma Tugu Raden Saleh 6th Floor, Jln Raden Saleh No 44, 10330 Jakarta, Indonesia.
url: www.widatra.com
Widmer, Austria. Louis Widmer GmbH, Itzlinger Hauptstrasse 34, A-5020 Salzburg, Austria.
Widmer, Belg. Louis Widmer NV, Haverheidelaan 9, 9140 Temse, Belgium.
Widmer, Cz. See *Widmer, Switz.*
Widmer, Fin. Louis Widmer Oy, Sömäisten rantatie 29, 00580 Helsinki, Finland.
Widmer, Ger. Louis Widmer GmbH, Grossmattstr. 11, 79618 Rheinfelden, Germany.
url: www.louis-widmer.com
Widmer, Neth. See *Widmer, Belg.*
Widmer, Philipp. See *Zuellig, Philipp.*
Widmer, Switz. Dermatologica Widmer, Laboratoires Louis Widmer AG, 8952 Schlieren, Switzerland.
Wiedemann, Ger. Wiedemann Pharma GmbH, Pilotyweg 14, 82541 Munsing, Germany.
url: www.wiedemann-pharma.de
Wierhom, Arg. Wierhom Pharma S.A., Arismendi 2441, 1427 Buenos Aires, Argentina.
Wild, Switz. Dr Wild & Co. AG, Lange Gasse 4, 4002 Basle, Switzerland.
url: www.wild-pharma.com
Will Pharma, Neth. Will Pharma BV, Wilgenlaan 5, 1161 JK Zwanenburg, Netherlands.
Williams, USA. Williams Laboratories Inc., 5 Anngina Drive, Unit B, Enfield, CT 06082, USA.
url: www.williamlabs.com
Will-Pharma, Belg. Will-Pharma SA, Rue du Manil 80, 1301 Wavre, Belgium.
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Will-Pharma, Neth. Will-Pharma BV, Wilgenlaan 5, 1161 JK Zwanenburg, Netherlands.
Willpharma, Thai. See *BJC, Thai.*
Willvonseder, Austria. Willvonseder & Marchesani, Heinrich-v-Buol-Gasse 45, A-1211 Vienna, Austria.
Wilson, NZ. Wilson Consumer Products Ltd, P.O. Box 105-125, Auckland, New Zealand.
url: www.wilson.co.nz
Wing Wai, Hong Kong. Wing Wai Trading Co., Unit E, 2/F Freder Ctr, 3 Mok Cheong St, Kowloon, Hong Kong.
Win-Medicare, India. See *Modi-Mundipharma, India.*
Win-Medicare, Thai. See *Union Medical, Thai.*
Winsor, Hong Kong. Winsor & Co., Rm 1707-1707A, Wu Sang House, 655 Nathan Rd, Kowloon, Hong Kong.
Winthrop, Cz. See *Sanofi Synthelabo, Cz.*
Winthrop, Fr. See *Sanofi-Aventis, Fr.*
Winthrop, Ger. Winthrop Arzneimittel GmbH, Industriestr. 10, 82256 Fürstenfeldbruck, Germany.
url: www.winthrop.de
Winthrop, Pol. See *Sanofi-Aventis, Pol.*
Winthrop, Port. See *Sanofi-Aventis, Port.*
Winthrop, UK. See *Sanofi-Aventis, UK.*
Winthrop Consumer, USA. See *Bayer Consumer, USA.*

Winzer, Ger. Dr Winzer Pharma GmbH, Brunsbutteler Damm 165-173, 13581 Berlin, Germany.
url: www.drwinzer.de
Wisconsin Pharmacal, USA. Wisconsin Pharmacal Co., 1 Pharmacal Way, Jackson, WI 53037, USA.
url: www.pharmacalway.com
Wise, UK. Wise Pharmaceuticals Ltd, Unit 7, Hani Wells Business Park, Hardicker St, Manchester, M19 2RB, UK.
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WL, Fin. WL-Medical Oy, Karvaamokuja 4, 00380 Helsinki, Finland.
url: www.wl-medical.fi
WN, Canad. WN Pharmaceuticals Ltd, 2000 Brigantine Drive, Coquitlam, British Colombia, V3K 7B5, Canada.
Wockhardt, Hung. See *PDP, Hung.*
Wockhardt, India. Wockhardt Ltd, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.
url: www.wockhardtin.com
Wockhardt, Rus. Wockhardt Ltd, 26 Bakinskikh komissarov ul. 9, Of. 87, 119571 Moscow, Russia.
Wockhardt, UK. Wockhardt UK Ltd, Ash Rd North, Wrexham Industrial Estate, Wrexham, Clwyd, LL13 9UF, UK.
url: www.wockhardt.co.uk
Woelm, Ger. Woelm Pharma GmbH & Co., Rhondorfer Str. 80, 53604 Bad Honnef, Germany.
url: www.woelm.com
Woelm, Israel. See *CTS, Israel.*
Wolff, Austria. See *Wolff, Ger.*
Wolff, Cz. See *Hapra, Cz.*
Wolff, Denm. See *Leo, Swed.*
Wolff, Ger. Dr. August Wolff Arzneimittel GmbH & Co., Sudbrackstr. 56, 33611 Bielefeld, Germany.
url: www.wolff-arzneimittel.de
Wolff, Hung. See *Medimprove, Hung.*
Wolff, Malaysia. See *Summit, Malaysia.*
Wolff, Neth. See *Wolff, Ger.*
Wolff, Pol. See *Solpharm, Pol.*
Wolff, Port. See *Wolff, Ger.*
Wolfs, Belg. Wolfs SA, Industriepark West 68, 9100 Sint-Niklaas, Belgium.
Women First, USA. Women First Healthcare Inc., 5355 Mira Sorrento Pl., Suite 700, San Diego, CA 92121, USA.
url: www.womenfirst.com
Woods, Austral. H.W. Woods P/L, P.O. Box 1005, Huntingdale, VIC 3166, Australia.
Woodward, USA. Woodward Laboratories, Inc., 125-B Columbia, Aliso Viejo, CA 92656-1458, USA.
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World Markets, Pol. World Markets Sp. zo.o., ul. Olecka 23, 04-980 Warsaw, Poland.
World Pioneer, Hong Kong. World Pioneer Ltd, Rm 3509 AIA Tower, 183 Electric Rd, North Point, Hong Kong.
Worldwide, Hong Kong. Worldwide Resources Pharmaceutical Ltd, Unit 20-21, 15/F Goldfield Industrial Ctr, 1 Sui Wo Rd, Fotan, Shatin, Hong Kong.
Worwag, Cz. Wörwag Pharma GmbH & Co, Slezská 509, 500 03 Hradec Králové, Czech Republic.
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Worwag, Ger. Wörwag Pharma GmbH & Co. KG, Calwer Str. 7, 71034 Böblingen, Germany.
url: www.woerwagpharma.de
Worwag, Hong Kong. See *Jacobson, Hong Kong.*
Worwag, Hung. Wörwag Pharma Képviselet, Zöldkő út 9/b, 1025 Budapest, Hungary.
Worwag, Pol. Wörwag Pharma Spółka Komandytowa, Przedstawicielstwo w Polsce, ul. Fasolowa 45 m 43, 02-482 Warsaw, Poland.
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Worwag, Port. See *Worwag, Ger.*
Worwag, Rus. Wörwag Pharma GmbH, Varshavskoe Shosse, 125 ZH, 11 floor, 117545 Moscow a/ya 43, Russia.
url: www.woerwagpharma.ru
Wrapsa, S.Afr. Wrapsa Packaging & Manufacturing (Pty) Ltd, P.O. Box 7779, Centurion 0046, South Africa.
url: www.wrapsa.co.za
WraSer, USA. WraSer Pharmaceuticals, 148 Weisenberger Rd, Suite D, Madison, MS 39130, USA.
url: www.wraser.com
Wrigley, USA. Wm. Wrigley Jr. Co., P.O. Box 3900, Peoria, IL 61614, USA.
url: www.wrigley.com
Wunderpharm, Arg. Laboratorio Wunderpharm S.R.L., Remedios 5322, 1440 Buenos Aires, Argentina.
Wyeth, Arg. See *Wyeth-Whitehall, Arg.*
Wyeth, Austral. Wyeth Pharmaceuticals, Division of Wyeth Australia P/L, Locked Bag 5002, Baulkham Hills BC, NSW 2153, Australia.
url: www.wyeth.com.au
Wyeth, Belg. Wyeth, Division of AHP Pharma, Parc Scientifique Einstein, Rue du Bosquet 15, 1348 Louvain-la-Neuve, Belgium.
url: www.wyeth.be
Wyeth, Braz. Laboratórios Wyeth-Whitehall Ltda, Rua Alexandre Dumas 2200, 5th Floor, 04717-004 São Paulo, SP, Brazil.
url: www.wyeth.com.br

Wyeth, Canad. Wyeth Canada, 1025 Marcel Laurin Blvd, St-Laurent, Quebec, H4R 1J6, Canada.
url: www.wyeth.com
Wyeth, Chile. Laboratorios Wyeth Inc., Los Tres Antonios 2526, Santiago, Chile.
Wyeth, Cz. Wyeth Whitehall Czech sro, Novodvorská 994, 142 21 Prague 4, Czech Republic.
Wyeth, Denm. See *Wyeth Lederle, Denm.*
Wyeth, Fin. Wyeth, Rajatorpantie 41 C, 01640 Vantaa, Finland.
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Wyeth, Fr. See *Wyeth Lederle, Fr.*
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Wyeth, Gr. Wyeth Hellas, 126 Kyprou Ave, 164 52 Argyroupolis, Greece.
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Wyeth, Hung. Wyeth Whitehall Kft, Lajos u 78, 1036 Budapest, Hungary.
Wyeth, India. See *Wyeth Lederle, India.*
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url: www.wyeth.ie
Wyeth, Israel. See *Dexxon, Israel*, and *Neopharm, Israel.*
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Wyeth, Neth. Wyeth Pharmaceuticals BV, Planetenweg 99, 2132 HL Hoofddorp, Netherlands.
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Wyeth Consumer, Arg. See *Wyeth-Whitehall, Arg.*
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Wyeth Consumer, Hong Kong. Wyeth (Hong Kong) Ltd Consumer Healthcare, Rm 1401-1404, 14/F CC Wu Bldg, 302-308 Hennessy Rd, Wanchai, Hong Kong.
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Wyeth Lederle, Belg. See *Wyeth, Belg.*
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Wyeth Lederle, Hung. See *Wyeth, Hung.*
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Wyeth Lederle, Neth. See *Wyeth, Neth.*
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Wyeth Nutrition, Indon. See *Wyeth, Indon.*
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Wyeth-Ayerst, USA. See *Wyeth, USA.*
Wyeth-Whitehall, Arg. Wyeth-Whitehall S.A., Ing. Enrique Butty 275, 1001 Buenos Aires, Argentina.
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Xepa-Soul Pattinson, Malaysia. Xepa-Soul Pattinson (M) Sdn Bhd, 1-5 Cheng Industrial Estate, 75250 Melaka, Malaysia.
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Xepa-Soul Pattinson, Singapore. See *Grafton, Singapore.*
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X-Gen, USA. X-Gen Pharmaceuticals Inc., P.O. Box 445, Big Flats, NY 14814, USA.
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Ximena Polanco, Chile. Laboratorio Ximena Polanco, Dresden 4640, Santiago, Chile.
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Yalacta, Fr. Laboratoires Yalacta, 97 rue du Général Moulin, 14050 Caen cdx, France.
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Yamanouchi, Neth. See *Astellas, Neth.*
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Yes, Neth. See *Yes, Ger.*
YF Chem, Thai. See *Sriprasit, Thai.*
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Yoo Young, Philipp. See *International Apex, Philipp.*
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Young Again Nutrients, USA. Young Again Nutrients, The Woodlands Center, P.O. Box 8234, Spring, TX 77387-8234, USA.
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Young Again Products, USA. Young Again Products Inc., 3608-B Oleander Drive 310, Wilmington, NC 28403, USA.
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Youngflex, Canad. Youngflex Manufacturing Inc., 60 Granton Drive, Unit 6, Richmond Hill, Ontario, L4B 1H7, Canada.
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YSS, Philipp. See *Cathay, Philipp.*
Yu Sheng, Singapore. See *Polymedic, Singapore.*
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Yung Shin, Thai. See *Far East, Thai.*
Yungjin, Philipp. See *Endure, Philipp.*
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Zak, Austria. Zak-Pharma Dienstleistung GmbH, A-1130 Vienna, Austria.
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Zambon, Cz. See *Zambon, Ital.*
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Zambon, Ger. Zambon GmbH, Heinrich-Hertz-Str. 13, 50170 Kerpen, Germany.
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Zambon, Hong Kong. Zambon (HK) Ltd, Rm 4109-4110, 41/F China Resources Bldg, 26 Harbour Rd, Wanchai, Hong Kong.
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Zambon, Malaysia. See *Emerging Pharma, Malaysia.*
Zambon, Neth. Zambon Nederland BV, Algolweg 9 A, 3821 BG Amersfoort, Netherlands.
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Zambon, Philipp. See *Cathay, Philipp.*
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Zambon, Switz. Zambon Svizzera SA, Via Industria 13, Casella postale 200, 6814 Cadempino, Switzerland.
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Zambon, Thai. See *SM, Thai.*
Zanfel, USA. Zanfel Laboratories Inc., P.O. Box 349, Moreton, IL 61550, USA.
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Zekides, Gr. See *Biospray, Gr.*
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Zellaforte, Switz. Zellaforte Vertriebsanstalt, Austrasse 52, FL-9490 Vaduz, Switzerland.
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Zen, Israel. Zen, Israel.
Zenaust, Philipp. Zenaust Pharma Inc., 67 West Capitol Drive, Kapitolyo, Pasig City, Metro Manila, Philippines.
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Zeneus, Fin. See *Zeneus, Denm.*
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Zeneus, Hong Kong. See *Jacobson, Hong Kong.*
Zeneus, Hung. See *Cephalon, Fr.*
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Zeneus, Neth. See *Zeneus, UK.*
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Zenith, UK. Zenith Pharmaceuticals Ltd, P.O. Box 85, Abingdon, Oxfordshire, OX14 3UA, UK.
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Zenith Goldline, USA. See *Ivax, USA.*
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Zentiva, Hung. Zentiva Hu KFT, Népfürdo utca 22, 1138 Budapest, Hungary.
Zentiva, Philipp. See *PharmAsia, Philipp.*
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Zeroderma, UK. Zeroderma Ltd, The Manor House, Victor Barns, Northampton Rd, Brixworth, Northamptonshire, NN6 9DQ, UK.
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Ziaja, Pol. Ziaja Ltd Zakład Produkcji Leków Sp. zo.o., ul. Jesienna 9, 80-298 Gdańsk, Poland.
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Zila, Port. See *Zila, UK.*
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ZLB, Fin. See *Veripalvelu, Fin.*
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Zoki, Thai. See *Asian TJD, Thai.*

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Zydus Cadila, Thai. See *Pharmaland, Thai.*

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Zymo, USA. ZymoGenetics Inc., 1201 Eastlake Ave East, Seattle, Washington 98102-3702, USA.
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Zynova, Philipp. Zynova Pharmaceuticals Inc., Unit 18B, 9 Strata 2000 Bldg, F Ortigas Jr Rd, Ortigas Ctr, Pasig City, Philippines.

General Index

Entries cover drugs (by monograph title, other approved names, synonyms, and chemical names), diseases (by disease treatment review title and associated terms), and proprietary preparations (by proprietary or brand name). They are arranged alphabetically in word-by-word order. Page references give both the page and column number as in 476·1, where 476 represents the page number and the figure 1 indicates that the entry will be found in column 1 of that page. There is no column number when the entry is in a table.

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